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# BMJ Open

## Psychosocial factors at work and inflammatory markers: protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022612
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2018
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Keywords:	Inflammation, Psychosocial factors at work, Cardiology < INTERNAL MEDICINE, Occupational health, Workplace, MENTAL HEALTH

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1 **Psychosocial factors at work and inflammatory markers: protocol for a**  
2 **systematic review and meta-analysis**

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6 38 **Word count: 1,819 words**  
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5 39 **Strengths and limitations of this study**

- 6 40 ● This systematic review and meta-analysis will offer comprehensive  
7 41 understanding of the association between work-related psychosocial factors  
8 42 and inflammatory markers.  
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11 43  
12 44 ● The review will include a range of work-related psychosocial factors, and  
13 45 focus on inflammatory markers as an aggregated cluster.  
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15 46  
16 47 ● The review will only include prospective studies to ensure stronger evidence.  
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19 49 ● The findings of this review may be useful for assessing chronic inflammation  
20 50 as a risk factor for cardiovascular disease (CVD) in the workplace, and  
21 51 determining future approaches for CVD prevention.  
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23 52  
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25 53 ● Depending on the results, limitations may be confounding factors that might  
26 54 not have been adjusted for in the selected studies and low generalizability.  
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5 **Abstract**

6 **INTRODUCTION:** Chronic inflammation may be a mediator for the development  
7 of cardiovascular disease (CVD). Meta-analytic associations between  
8 work-related psychosocial factors and inflammatory markers have shown that  
9 work-related psychosocial factors may affect the flexibility and balance of the  
10 immune system. However, few systematic reviews or meta-analyses have  
11 investigated the association between work-related psychosocial factors and  
12 inflammatory markers. This study aims to conduct a comprehensive systematic  
13 review and meta-analysis of the effects of work-related psychosocial factors on  
14 inflammatory markers, based on prospective studies.

15 **METHODS AND ANALYSIS:** The systematic review and meta-analysis will  
16 include published studies identified from electronic databases (PubMed,  
17 EMBASE, PsycINFO, PsycARTICLES, and Japan Medical Abstracts Society)  
18 according to the recommendations of the Meta-analysis of Observational  
19 Studies in Epidemiology guideline. Inclusion criteria are studies that: examined  
20 associations between work-related psychosocial factors and increased  
21 inflammatory markers; used longitudinal or prospective cohort designs; were  
22 conducted among workers; provided sufficient data for calculating odds ratios or  
23 relative risk with 95% confidence intervals; were published as original articles in  
24 English or Japanese; and were published up to the end of 2017. Study selection,  
25 data collection, quality assessment, and statistical syntheses will be conducted  
26 based on discussions among investigators.

27 **ETHICS AND DISSEMINATION:** This study is based on published studies,  
28 meaning ethics approval is not required. The results of this study will be  
29 submitted for publication in a scientific peer-reviewed journal. The findings may  
30 be useful for assessing risk factors for increased inflammatory markers in the  
31 workplace and determining future approaches for CVD prevention.

32 **TRIAL REGISTRATION NUMBER:** PROSPERO CRD42018081553  
33 ([https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?RecordID=81553](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=81553)).  
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## 84 Introduction

85 Most adults spend around half of their waking hours at work, meaning  
86 the workplace is an important setting to promote health and wellbeing.  
87 Increasing attention is being directed to work-related psychosocial factors, with a  
88 major focus on work stress.[1] Work-related psychosocial factors include job  
89 strain,[1-5] effort-reward imbalance,[6] organizational justice,[7-9] and workplace  
90 social capital.[10] These factors affect cardiovascular disease (CVD) or risk  
91 factors for CVD (e.g., body mass index, blood pressure) through mechanisms  
92 such as prolonged overactivation and dysregulation of the autonomic nervous  
93 system and the hypothalamus-pituitary-adrenal cortex axis.[11-13]

94 Chronic inflammation has been suggested as a potential mediator for the  
95 development of CVD.[14] Several previous studies reported associations  
96 between adverse work-related psychosocial factors and increased levels of  
97 inflammatory markers. Inflammatory markers, including C-reactive protein  
98 (CRP),[15-20] interleukin-6 (IL-6),[20 21] and tumor necrosis factor (TNF- $\alpha$ ), are  
99 implicated in coordinating atherosclerosis.[22] Previous meta-analyses[23,24]  
100 identified associations between psychosocial factors and inflammatory markers,  
101 but findings from these studies were not stable because of heterogeneity in  
102 methods (e.g., the conceptualization or measurement of work-related  
103 psychosocial factors, sample compositions, and statistical approaches).

104 Meta-analytic associations between work-related psychosocial factors  
105 and inflammatory markers indicate work-related psychosocial factors may affect  
106 the flexibility and balance of the immune system. Although some meta-analyses  
107 investigated inflammatory markers in relation to psychological stress[23-26] and  
108 unemployment,[27] few systematic reviews or meta-analysis have been  
109 conducted regarding the associations between work-related psychosocial  
110 factors and inflammatory markers. A previous systematic review of 56 studies by  
111 Nakata[28] suggested that work-related psychosocial factors were related to  
112 disrupted immune response. However, that study did not statistically synthesize  
113 the associations. To our knowledge, only one meta-analysis of the association  
114 between effort-reward imbalance and inflammatory markers ( $k=7$ ,  $N=9952$ )  
115 found a negative association with immunity ( $r=-0.09$ , confidence interval [CI]:  
116  $-0.14$ ,  $-0.05$ ;  $p<0.001$ ).[13] These previous systematic reviews and  
117 meta-analyses included cross-sectional studies. However, pooled associations  
118 between work-related psychosocial factors and inflammatory markers derived  
119 from prospective studies may provide more reliable evidence.

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5 120 This study aims to conduct a comprehensive systematic review and  
6 121 meta-analysis of the effects of work-related psychosocial factors on  
7 122 inflammatory markers, based on published prospective studies. Our hypothesis  
8 123 is that adverse work-related psychosocial factors would increase inflammatory  
9 124 markers. Moreover, we will identify the work-related psychological factors that  
10 125 have the strongest associations with specific inflammatory markers.  
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## 15 127 **Methods and analysis**

### 16 128 *Study design*

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18 129 This study protocol for a systematic review and meta-analysis of  
19 130 prospective studies follows the Preferred Reporting Items for Systematic  
20 131 Reviews and Meta-Analysis Protocols guideline.[29] Future findings will be  
21 132 reported according to the Meta-analysis of Observational Studies in  
22 133 Epidemiology (MOOSE) reporting guidelines.[30] This study protocol was  
23 134 registered with PROSPERO (CRD42018081553).  
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### 27 136 *Eligibility criteria*

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29 137 Participants, exposures, comparisons, and outcomes (PECO) of the  
30 138 studies included in this systematic review and meta-analysis will be defined as  
31 139 follows: (P) inclusion of all workers, (E) presence of adverse psychosocial  
32 140 factors at work, (C) absence of adverse psychosocial factors at work, and (O)  
33 141 increased inflammatory markers. Target participants are all employed workers of  
34 142 participating companies. There will be no exclusion criteria related to  
35 143 employment status, job type, and shift type. The study exposures (adverse  
36 144 psychosocial factors at work) will include a range of task and organizational  
37 145 characteristics, work conditions, and workplace interactions,[31] including job  
38 146 strain, low social support, effort-reward imbalance, organizational injustice, and  
39 147 low workplace social capital. Long working hours and shift work will also be  
40 148 included as target exposures. Inflammatory markers will include those that were  
41 149 investigated in terms of associations with psychosocial factors at work in  
42 150 previous studies, including CRP, IL-6, and TNF- $\alpha$ .  
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49 151 Eligibility criteria for study selection are studies that: 1) were conducted to  
50 152 evaluate associations between psychosocial factors at work and inflammatory  
51 153 markers; 2) used longitudinal or prospective cohort designs; 3) were conducted  
52 154 among workers; 4) provided sufficient data for calculating coefficients between  
53 155 psychosocial factors at work and inflammatory markers ( $\gamma$ ,  $\beta$ ), odds ratios (ORs),  
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5 156 relative risks (RRs), or hazard ratios (HRs) with standard errors (SEs) or 95%  
6 157 CIs; 5) were published as original articles in English or Japanese; and 6) were  
7 158 published up to the end of 2017.  
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#### 10 160 *Information sources, search strategy, and data management*

11 161 A systematic search of published studies will be conducted using  
12 162 electronic databases: PubMed (MEDLINE), EMBASE,  
13 163 PsycINFO/PsycARTICLES, and the Japan Medical Abstracts Society. Search  
14 164 terms will include words related to the PECO of eligible published studies. The  
15 165 proposed search strategy is shown in Appendix 1. All identified studies will be  
16 166 managed in a Microsoft® Excel file (Washington, US). Before the study selection  
17 167 process, duplicated citations in the Excel file will be excluded by KW. Decisions  
18 168 on all studies will be recorded.  
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#### 24 170 *Study selection process*

25 171 First, 14 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO,  
26 172 ASa, and KT) will independently conduct screening of identified titles and  
27 173 abstracts, according to the eligibility criteria. Second, we will obtain full texts of  
28 174 all eligible studies. In the full text review phase, the studies will be reviewed  
29 175 using a standardized form for assessing eligibility for inclusion in this review. Any  
30 176 disagreements will be settled in discussion among all authors until consensus is  
31 177 reached. We will directly contact corresponding authors of eligible studies if the  
32 178 results of the publication are unclear and may be related to multiple  
33 179 interpretations, or the results reported in the publication did not show data  
34 180 relevant to our study analysis. The reasons for excluding studies will be recorded.  
35 181 A flow chart will be prepared that shows the entire review process.  
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#### 43 183 *Data collection*

44 184 Data will be extracted independently from the included studies by 14  
45 185 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT)  
46 186 using a standardized data extraction form. Any disagreement or inconsistencies  
47 187 will be resolved by consultation and consensus among all authors. Collected  
48 188 data will include: year of publication, country where the study was conducted,  
49 189 numbers of participants included at baseline and in the analysis, sampling  
50 190 framework, participants' demographic characteristics (i.e., mean age, sex  
51 191 proportions, and employment status), length of follow-up, follow-up rate,  
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5 192 exposure and comparison variables (adverse psychosocial factors at work),  
6 193 outcome variables (inflammatory markers), number and proportion of  
7 194 participants with increased levels of inflammatory markers or mean scores and  
8 195 variances/standard deviations of markers, and sufficient data for calculating the  
9 196 coefficients ( $\beta$ ,  $\gamma$ ), ORs, RRs, or HRs with SEs/95% CIs for the association  
10 197 between adverse psychosocial factors at work and inflammatory markers. When  
11 198 the included studies report multiple measures of association, we will  
12 199 preferentially select measures of association adjusted by demographic (e.g., age,  
13 200 sex, education, and marital status) and lifestyle variables (e.g., smoking,  
14 201 physical activity, and sleep). Measures of association adjusted for other adverse  
15 202 psychosocial factors at work and/or inflammatory markers will not be adopted to  
16 203 avoid over-adjustment. Sex-stratified coefficients will be selected if those were  
17 204 the only reported results. Any missing data from the studies will be obtained by  
18 205 contacting the relevant research team.

#### 26 207 *Assessment of study quality*

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28 208 Fourteen investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO,  
29 209 ASa, and KT) will independently assess the quality of each included study using  
30 210 the Newcastle-Ottawa Quality Assessment Scale (NOS).[32] The NOS  
31 211 evaluates cohort studies based on eight items categorized into three groups: 1)  
32 212 selection of study cases, 2) comparability of the population, and 3)  
33 213 ascertainment of whether the exposures or outcomes included any risk of bias  
34 214 (i.e., selection bias or bias from loss to follow-up). NOS scores range from 0–9,  
35 215 with studies scoring  $\geq 7$  considered high quality.[33] Discrepancies in quality  
36 216 assessment among investigators will be resolved by discussion and consensus  
37 217 among all authors.

#### 43 219 *Data synthesis and statistical methods*

44 220 The included studies will be statistically synthesized in a meta-analysis to  
45 221 estimate pooled coefficients and 95% CIs, stratified by the types of measures of  
46 222 association ( $\beta$ ,  $\gamma$ , OR, RR, and HR). When the included studies report ORs, RRs,  
47 223 or HRs, we will calculate log-transformed ORs, RRs, or HRs, and estimate SEs  
48 224 based on 95% CIs. These parameters will be used in the meta-analysis and for  
49 225 examining publication bias using a funnel plot and Egger's test.[34,35] We will  
50 226 use a random effects model[36] to summarize the results using R version 3.4.1  
51 227 with the "meta" and "metafor" packages.[37] The results will be presented in a

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5 228 narrative format if a meta-analysis is not appropriate or possible. Heterogeneity  
6 229 will be assessed by the chi-square test with Cochran's  $Q$  statistic, which is  
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8 230 calculated by  $I^2$  values,[38] on the assumption that  $I^2$  values of 25%, 50%, and  
9 231 75% indicate low, medium, and high heterogeneity, respectively.

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11 232 Subgroup and sensitivity analyses will also be conducted to compare the  
12 233 results across subgroups or under specific conditions when sufficient  
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14 234 heterogeneity is detected. Major grouping characteristics will include types of  
15 235 exposures and outcomes, participants' demographic characteristics (e.g., sex,  
16 236 age, employment status, occupational groups), and study quality. Any subgroup  
17 237 differences will be reported, and our findings will be explained by considering  
18 238 these differences. When trends are observed between pooled associations and  
19 239 any grouping characteristics, meta-regression will be conducted using the  
20 240 "metareg" function of R. A sensitivity analysis may be conducted for included  
21 241 studies with a NOS score indicating high quality ( $\geq 7$ ). All collected data and  
22 242 analyzed results will be deposited by the corresponding author and available for  
23 243 external reviewers and readers upon request.  
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#### 29 245 *Patient and Public Involvement statement*

30 246 Any patients and or study participants were not involved in this study  
31 247 because this is the study protocol for the systematic review and meta-analysis.  
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#### 35 249 **Ethics and dissemination**

36 250 This study does not require ethical approval because the systematic review and  
37 251 meta-analysis will be based on previously published studies. The results will be  
38 252 submitted for publication in a scientific peer-reviewed journal, according to the  
39 253 MOOSE guideline.[30]  
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#### 43 255 **Funding**

44 256 This study is supported by the Work-related Diseases Clinical Research Grant  
45 257 2016 (160701-01) from the Ministry of Health, Labour and Welfare, Japan. The  
46 258 funder has no role in study design, data collection and analysis, decision to  
47 259 publish, or preparation of the final manuscript.  
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#### 51 261 **Competing interests**

52 262 The author(s) declare that they have no competing interests.  
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## 264 **Strengths and limitations**

265 This systematic review and meta-analysis will be based on prospective studies,  
266 and show the strongest evidence for comprehensive associations between  
267 psychosocial factors at work and inflammatory markers. The findings will  
268 highlight potential mediators and underlying mechanisms for the development of  
269 CVD due to adverse psychosocial factors.

270 There are several likely limitations in this study, including confounding  
271 bias and low generalizability. If selected studies do not report  
272 demographic-adjusted associations, the findings will be distorted by the  
273 unobserved characteristics among the population. In addition, the findings will  
274 not be generalizable to populations that were not included in the selected  
275 studies.

## 277 **Authors' contributions**

278 HE, KW, NK, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, KT, ASH, and AT  
279 made substantial contributions to the conception and design of the study, writing  
280 the protocol and revising it critically for important intellectual content, and  
281 approving the final version to be published. All authors will be involved in the  
282 entire study process (i.e., data collection, assessment, and synthesis).

## 284 **Acknowledgements**

285 We thank Audrey Holmes, MA, from Edanz Group ([www.edanzediting.com/ac](http://www.edanzediting.com/ac))  
286 for editing a draft of this manuscript.

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## Appendix 1. Search terms used for the electronic databases

Database	Search terms
PubMed	(employe*[tw] OR manag*[tw] OR colleague*[tw] OR worksit*[tw] OR “work”[tw] OR works*[tw] OR work’*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupant*[tw] OR company*[tw] OR offic*[tw] OR busines*[tw] OR workplace[mh]) AND (“Stress, Mechanical”[Mesh] OR “Lifting”[Mesh] OR “Moving and Lifting Patients”[Mesh] OR “Weight-Bearing”[Mesh] OR “Biomechanics” OR “Physical Exertion”[Mesh] OR “Torsion, Mechanical”[Mesh] OR “Postural Balance”[Mesh] OR “Walking”[Mesh] OR “Recovery of Function”[Mesh] OR “Relaxation”[Mesh] OR (static[Title/Abstract] AND posture) OR (awkward[Title/Abstract] AND posture) OR (dynamic[Title/Abstract] AND posture) OR static work[Title/Abstract] OR dynamic load*[Title/Abstract] OR lift*[Title/Abstract] OR carry*[Title/Abstract] OR hold*[Title/Abstract] OR pull*[Title/Abstract] OR drag*[Title/Abstract] OR push*[Title/Abstract] OR manual handling[Title/Abstract] OR force*[Title/Abstract] OR biomechanic*[Title/Abstract] OR walking*[Title/Abstract] OR postural balance[Title/Abstract] OR flexion*[Title/Abstract] OR extension*[Title/Abstract] OR turning[Title/Abstract] OR sitting[Title/Abstract] OR kneeling[Title/Abstract] OR squatting[Title/Abstract] OR twisting[Title/Abstract] OR bending[Title/Abstract] OR reaching[Title/Abstract] OR standing[Title/Abstract] OR sedentary[Title/Abstract] OR repetitive movement*[Title/Abstract] OR monotonous work[Title/Abstract] OR relaxation[Title/Abstract] OR recovery of function[Title/Abstract] OR physical demand*[Title/Abstract] OR physically demand*[Title/Abstract]) OR (“Stress, Psychological”[Majr] OR “Social Support”[Majr] OR “Job Satisfaction”[Mesh] OR “Work Schedule Tolerance”[Mesh] OR “Employee Performance Appraisal”[Mesh] OR “Employee Grievances”[Mesh] OR “Social Justice/psychology”[Mesh] OR “Personnel Downsizing”[Mesh] OR “Staff Development”[Mesh] OR “Organizational Culture”[Mesh] OR “Bullying”[Mesh] OR “Prejudice”[Mesh] OR “Social Discrimination”[Mesh] OR “Interpersonal Relations”[Mesh] OR “Communication/psychology”[Mesh]) OR (psychosocial[Title/Abstract] OR job strain[Title/Abstract] OR work strain[Title/Abstract] OR work demand*[Title/Abstract] OR job demand*[Title/Abstract] OR high demand*[Title/Abstract] OR low control[Title/Abstract] OR lack of control[Title/Abstract] OR work control[Title/Abstract] OR job control[Title/Abstract] OR decision latitude[Title/Abstract] OR work influence*[Title/Abstract] OR demand resource*[Title/Abstract] OR effort reward*[Title/Abstract] OR time pressure*[Title/Abstract] OR recuperation*[Title/Abstract] OR work overload*[Title/Abstract] OR work over-load*[Title/Abstract] OR recovery[Title/Abstract] OR coping[Title/Abstract] OR work ability[Title/Abstract] OR social support[Title/Abstract] OR support system*[Title/Abstract] OR social network*[Title/Abstract] OR emotional support[Title/Abstract] OR interpersonal relation*[Title/Abstract] OR interaction*[Title/Abstract] OR justice*[Title/Abstract] OR injustice*[Title/Abstract] OR job satisfaction[Title/Abstract] OR work satisfaction[Title/Abstract] OR boredom[Title/Abstract] OR skill discretion*[Title/Abstract] OR staff development[Title/Abstract] OR discrimination[Title/Abstract] OR harass*[Title/Abstract] OR work-place conflict*[Title/Abstract] OR workplace



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 change[Title/Abstract] OR lean production[Title/Abstract] OR job security[Title/Abstract] OR job insecurity[Title/Abstract]) AND  
 ("inflammation"[MeSH Terms] OR inflammation\*[All Fields]) OR ("immune system"[MeSH Terms] OR "immune system  
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 ("cytokines"[MeSH Terms] OR cytokine\*[All Fields]) OR ("lymphokines"[MeSH Terms] OR lymphokine\*[All Fields]) OR  
 ("chemokines"[MeSH Terms] OR chemokine\*[All Fields]) OR ("monokines"[MeSH Terms] OR monokine\*[All Fields]) OR  
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 ((longitudinal study) OR (prospective cohort study) OR (prospective studies) OR (follow-up studies) OR (observational stud\*))  
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 worki\* OR workl\* OR workp\* OR occupant\* OR company\* OR offic\* OR busines\* OR workplace) AND  
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 Exertion" OR "Torsion, Mechanical" OR "Postural Balance" OR "Walking" OR "Recovery of Function" OR "Relaxation" OR  
 (static AND posture) OR (awkward AND posture) OR (dynamic AND posture) OR (static AND work) OR (dynamic AND load\*)  
 OR lift\* OR carry\* OR hold\* OR pull\* OR drag\* OR push\* OR (manual AND handling) OR force\* OR biomechanic\* OR  
 walking\* OR (postural AND balance) OR flexion\* OR extension\* OR turning OR sitting OR kneeling OR squatting OR twisting  
 OR bending OR reaching OR standing OR sedentary OR (repetitive AND movement\*) OR (monotonous AND work) OR  
 relaxation OR (recovery AND of AND function) OR (physical AND demand\*) OR (physically AND demand\*)) OR ("Stress,  
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 OR "Personnel Downsizing"/exp OR "Personnel Downsizing" OR "Staff Development"/exp OR "Staff Development" OR  
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 "Prejudice"/exp OR "Prejudice" OR "Social Discrimination"/exp OR "Social Discrimination" OR "Interpersonal Relations"/exp OR  
 "Interpersonal Relations" OR "Communication/psychology") OR (psychosocial OR (job AND strain) OR (work AND strain) OR  
 (work AND demand\*) OR (job AND demand\*) OR (high AND demand\*) OR (low AND control) OR (lack AND of AND control)  
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over-load\*) OR recovery OR coping OR (work AND ability) OR (social AND support) OR (support AND system\*) OR (social AND network\*) OR (emotional AND support) OR (interpersonal AND relation\*) OR interaction\* OR justice\* OR injustice\* OR (job AND satisfaction) OR (work AND satisfaction) OR boredom OR (skill AND discretion\*) OR (staff AND development) OR discrimination OR harass\* OR (work-place AND conflict\*) OR (workplace AND violen\*) OR (workplace AND violen\*) OR bullying OR ageism OR homophobia OR racism OR sexism OR victimization\* OR (silent AND workplace\*) OR (role AND ambiguity) OR role-conflict\* OR work-role\* OR (working AND hour\*) OR (working AND time) OR day-time OR night-time OR (shift AND work\*) OR (work AND shift\*) OR (temporary AND work) OR full-time OR part-time OR (flexible AND work\*) OR (organizational AND change) OR (organizational AND change) OR (lean AND production) OR (job AND security) OR (job AND insecurity))) AND  
 (((("inflammation" OR inflammation\*) OR ("immune system" OR "immune system phenomena" OR "immunity" OR "immunology")) OR ("c-reactive protein" OR ("c-reactive" AND protein) OR c-reactive protein OR CRP) OR ("cytokines" OR cytokine\*) OR ("lymphokines" OR lymphokine\*) OR ("chemokines" OR chemokine\*) OR ("monokines" OR monokine\*) OR ("tumor necrosis factor-alpha" OR tumor necrosis factor\* OR ("tumor" AND "necrosis" AND factor\*) OR TNF\*) OR ("interleukins" OR interleukin\* OR IL)) AND  
 ((longitudinal study) OR (prospective cohort study) OR (follow-up studies) OR (observational stud\*)))

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(労働 OR 従業員 OR 社員 OR ワークサンプル OR 同僚 OR 仲間 OR 上司 OR 管理 OR 監督 OR マネージャー OR マネジャー OR 課長 OR 部長 OR 主任 OR 上長 OR 役員 OR チーフ OR リーダー OR 上役 OR 雇い主 OR 雇主 OR 雇用 OR ワークグループ OR 仕事 OR ワーク OR 作業 OR 就労 OR 勤務 OR ワーキング OR 働く OR 職場 OR オフィス OR 研究所 OR 診療所 OR 医院 OR 事業 OR 職業 OR 家業 OR 事務 OR 業務 OR 執務 OR 営業 OR 所業 OR 実業 OR 産業 OR 就業 OR 企業 OR 会社 OR 商会 OR 法人) AND  
 (機械的ストレス OR 持ちあげ OR 患者の移動 OR 患者の持ち上げ OR 荷重負荷 OR 体重負荷 OR 生物力学 OR 労作 OR 機械的ねじれ OR 姿勢 OR バランス OR ウォーキング OR 歩行 OR 機能的回復 OR リラクセーション OR 静的姿勢 OR 窮屈な姿勢 OR 動的姿勢 OR 静的労働 OR 動的負荷 OR 持ちあげ OR 運搬 OR 抱え込み OR 引き OR 引きずり OR 押し OR 手作業 OR 力 OR 生物力学 OR ウォーキング OR 歩行 OR 姿勢 OR バランス OR 屈曲 OR 伸長 OR 拡張 OR 回転 OR 座位 OR 座り OR 膝曲げ OR スクワット OR より合わせ OR 曲げ OR 伸ばし OR 立位 OR 座位 OR 反復運動 OR 単調動作 OR 単調な仕事 OR リラクセーション OR 機能的回復 OR 身体的負荷 OR 身体的 OR 負荷) OR (心理的ストレス OR ソーシャル・サポート OR 仕事の満足度 OR 仕事のストレス耐性 OR 従業員のパフォーマンス評価 OR 従業員の抗議 OR (社会的正義 AND 心理学) OR 人員削減 OR 従業員教育 OR 組織文化 OR いじめ OR 偏見 OR 社会的差別 OR 対人関係 OR (コミュニケーション AND 心理学)) OR (心理社会的 OR 仕事のストレイン OR 仕事のストレス OR 仕事の要求度 OR 高い要求度 OR 低いコントロール OR コントロールの欠如 OR 仕事のコントロール OR 裁量の範囲 OR 仕事の影響 OR 要求度資源 OR 努力報酬 OR 時間的切迫 OR 病気からの回復 OR 療養 OR 仕事の負担 OR 回復 OR コーピング OR 対処 OR

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職務能力 OR 社会的支援 OR ソーシャルサポート OR 支援システム OR サポートシステム OR 社会的ネットワーク OR ソーシャルネットワーク OR 情緒的支援 OR 情緒的サポート OR 対人関係 OR 人間関係 OR 対人交流 OR 相互作用 OR 公正 OR 不公正 OR 職務満足感 OR 退屈 OR 技能の幅 OR 職員研修 OR 差別 OR 嫌がらせ OR 職場の葛藤 OR 職場の暴力 OR いじめ OR 年齢差別 OR 同性愛差別 OR 人種差別 OR 性差別 OR 虐待 OR 静かな職場 OR 役割曖昧さ OR 役割葛藤 OR 仕事での役割 OR 労働時間 OR 勤務時間 OR 日中 OR 夜間 OR シフト業務 OR 交代勤務 OR 時間差勤務 OR 臨時業務 OR フルタイム OR パートタイム OR フレックス制度 OR 組織改革 OR 組織再編 OR リーン生産 OR トヨタ生産方式 OR 安定雇用 OR 不安定雇用) AND  
 (炎症 OR 免疫 OR C反応性 OR CRP OR サイトカイン OR リンホカイン OR ケモカイン OR モノカイン OR 腫瘍壊死性因子 OR TNF OR インターロイキン OR IL) AND  
 (縦断研究 OR 前向きコホート研究 OR 前向き研究 OR 追跡研究 OR フォローアップ研究 OR 観察研究)

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Peer review only

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	On page #
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P.4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P. 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	P. 9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	P. 10
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	P. 5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P. 6
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P. 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P. 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P. 7-8 Appendix 1

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Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P. 7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P. 7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P. 7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P. 7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P. 7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P. 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P. 8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I <sup>2</sup> , Kendall's τ)	P. 8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P. 9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P. 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

# BMJ Open

## Psychosocial factors at work and inflammatory markers: protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022612.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Jun-2018
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<b>Primary Subject Heading</b>:	Occupational and environmental medicine
Secondary Subject Heading:	Immunology (including allergy)
Keywords:	Inflammation, Psychosocial factors at work, Cardiology < INTERNAL MEDICINE, Occupational health, Workplace, MENTAL HEALTH

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1 **Psychosocial factors at work and inflammatory markers: protocol for a**  
2 **systematic review and meta-analysis**

3  
4 **Authors**

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38 **Word count: 2,016 words**

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5 **Abstract**

6 **INTRODUCTION:** Chronic inflammation may be a mediator for the development  
7 of cardiovascular disease (CVD), metabolic diseases, and psychotic and  
8 neurodegenerative disorders. Meta-analytic associations between work-related  
9 psychosocial factors and inflammatory markers have shown that work-related  
10 psychosocial factors could affect the flexibility and balance of the immune  
11 system. However, few systematic reviews or meta-analyses have investigated  
12 the association between work-related psychosocial factors and inflammatory  
13 markers. Based on prospective studies, the present investigation will conduct a  
14 comprehensive systematic review and meta-analysis of the association between  
15 work-related psychosocial factors and inflammatory markers.  
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20 **METHODS AND ANALYSIS:** The systematic review and meta-analysis will  
21 include published studies identified from electronic databases (PubMed,  
22 EMBASE, PsycINFO, PsycARTICLES, Web of Science and Japan Medical  
23 Abstracts Society) according to recommendations of the Meta-analysis of  
24 Observational Studies in Epidemiology guideline. Inclusion criteria are studies  
25 that did the following: examined associations between work-related psychosocial  
26 factors and increased inflammatory markers; used longitudinal or prospective  
27 cohort designs; were conducted among workers; provided sufficient data for  
28 calculating odds ratios or relative risk with 95% confidence intervals; were  
29 published as original articles in English or Japanese; and were published up to  
30 the end of 2017. Study selection, data extraction, quality assessment, and  
31 statistical syntheses will be conducted by 14 investigators. Any inconsistencies  
32 or disagreements will be resolved through discussion. The quality of studies will  
33 be evaluated using the Risk of Bias Assessment Tool for Nonrandomized  
34 Studies.  
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42 **ETHICS AND DISSEMINATION:** The investigation study will be based on  
43 published studies, so ethics approval is not required. The results of this study will  
44 be submitted for publication in a scientific peer-reviewed journal. The findings  
45 may be useful for assessing risk factors for increased inflammatory markers in  
46 the workplace and determining future approaches for preventing CVD, metabolic  
47 diseases, and psychotic and neurodegenerative disorders.  
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50 **TRIAL REGISTRATION NUMBER:** PROSPERO CRD42018081553  
51 ([https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?RecordID=81553](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=81553)).  
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5 74 **Strengths and limitations of this study**

- 6 75 ● This systematic review and meta-analysis will offer comprehensive  
7 76 understanding of the association between work-related psychosocial factors  
8 77 and inflammatory markers.  
9 78  
10 79 ● The review will include a range of work-related psychosocial factors and  
11 80 focus on inflammatory markers.  
12 81  
13 82 ● To ensure stronger evidence, the review will include only prospective  
14 83 studies.  
15 84  
16 85 ● The findings of this review may be useful for assessing chronic inflammation  
17 86 as a risk factor for cardiovascular disease (CVD), metabolic diseases, and  
18 87 psychotic and neurodegenerative disorders in the workplace as well as for  
19 88 determining future approaches for preventing CVD, metabolic diseases, and  
20 89 psychotic and neurodegenerative disorders.  
21 90  
22 91 ● Depending on the results, limitations could be confounding factors that may  
23 92 not have been adjusted for in the selected studies as well as low  
24 93 generalizability.  
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## 94 INTRODUCTION

95 Most adults spend around half of their waking hours at work, and so the  
96 workplace is an important setting to promote health and well-being. Increasing  
97 attention is being directed to work-related psychosocial factors, such as job  
98 strain,<sup>1-5</sup> effort-reward imbalance,<sup>6</sup> organizational justice,<sup>7-9</sup> and workplace social  
99 capital<sup>10</sup>; there is a major focus on work stress.<sup>2</sup> These factors may affect  
100 cardiovascular disease (CVD), metabolic diseases, and psychotic and  
101 neurodegenerative disorders through such mechanisms as prolonged  
102 overactivation and dysregulation of the autonomic nervous system and the  
103 hypothalamus-pituitary-adrenal cortex axis.<sup>11-13</sup>

104 Chronic inflammation has been suggested as a potential mediator for the  
105 development of CVD, metabolic diseases, and psychotic and neurodegenerative  
106 disorders.<sup>14-18</sup> Several studies have reported associations between adverse  
107 work-related psychosocial factors and increased levels of inflammatory markers.  
108 Inflammatory markers, including C-reactive protein (CRP),<sup>19-24</sup> interleukin-6  
109 (IL-6),<sup>24-25</sup> and tumor necrosis factor (TNF- $\alpha$ ), have been implicated in  
110 coordinating atherosclerosis.<sup>26</sup> Previous meta-analyses<sup>27-28</sup> have identified the  
111 associations between psychosocial factors and inflammatory markers; however,  
112 the findings from those studies were not conclusive because of methodological  
113 heterogeneity (e.g., conceptualization or measurement of work-related  
114 psychosocial factors, sample compositions, and statistical approaches).

115 Meta-analytic associations between work-related psychosocial factors  
116 and inflammatory markers indicate that such factors may affect the flexibility and  
117 balance of the immune system. Some meta-analyses have investigated  
118 inflammatory markers in relation to psychological stress<sup>27-30</sup> and  
119 unemployment<sup>31</sup>; however, few systematic reviews or meta-analyses have been  
120 conducted regarding the associations between work-related psychosocial  
121 factors and inflammatory markers. A systematic review of 56 studies by Nakata<sup>32</sup>  
122 suggested that work-related psychosocial factors were related to disrupted  
123 immune response. However, that study did not statistically synthesize the  
124 associations. To our knowledge, only one meta-analysis of the association  
125 between effort-reward imbalance and inflammatory markers ( $k = 7$ ,  $N = 9952$ )  
126 found a negative association with immunity ( $r = -0.09$ ; confidence interval [CI],  
127  $-0.14$  to  $-0.05$ ;  $P < 0.001$ ).<sup>13</sup> These systematic reviews and meta-analyses  
128 included cross-sectional studies. However, pooled associations between  
129 work-related psychosocial factors and inflammatory markers derived from

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5 130 prospective studies may provide more reliable evidence.

6 131 Based on published prospective studies, the present investigation will  
7 132 conduct a comprehensive systematic review and meta-analysis of the  
8 133 associations between work-related psychosocial factors and inflammatory  
9 134 markers. Inflammatory markers will include those that were previously  
10 135 investigated in terms of associations with psychosocial factors at work, including  
11 136 CRP, IL-6, and TNF- $\alpha$ . Our hypothesis is that adverse work-related psychosocial  
12 137 factors would increase inflammatory markers. Moreover, we will identify the  
13 138 work-related psychological factors that have the strongest associations with  
14 139 specific inflammatory markers.  
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## 21 141 **METHODS AND ANALYSIS**

### 22 142 **Study design**

23 143 This study protocol for a systematic review and meta-analysis of  
24 144 prospective studies follows the Preferred Reporting Items for Systematic  
25 145 Reviews and Meta-Analysis Protocols guideline.<sup>33</sup> Future findings will be  
26 146 reported according to the Meta-analysis of Observational Studies in  
27 147 Epidemiology (MOOSE) reporting guidelines.<sup>34</sup> This study protocol was  
28 148 registered with PROSPERO (CRD42018081553).  
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### 34 150 **Eligibility criteria**

35 151 Participants, exposures, comparisons, and outcomes (PECO) of the  
36 152 studies included in this systematic review and meta-analysis will be defined as  
37 153 follows: (P) inclusion of all workers; (E) presence of adverse psychosocial  
38 154 factors at work; (C) absence of adverse psychosocial factors at work; and (O)  
39 155 increased inflammatory markers. Target participants will all be employees of  
40 156 participating companies. There will be no exclusion criteria related to  
41 157 employment status, job type, or shift type. The study exposures (adverse  
42 158 psychosocial factors at work) will include a range of task and organizational  
43 159 characteristics and work conditions,<sup>35</sup> such as job strain,<sup>1-5</sup> low social support,  
44 160 effort-reward imbalance,<sup>6</sup> organizational injustice,<sup>7-9</sup> and low workplace social  
45 161 capital.<sup>10</sup> Long working hours and shift work will also be included as target  
46 162 exposures. Inflammatory markers will include those investigated in terms of  
47 163 association with psychosocial factors at work in previous studies, including CRP,  
48 164 IL-6, and TNF- $\alpha$ .  
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54 165 Eligibility criteria for selection are the following studies that (1) were  
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5 166 conducted to evaluate associations between psychosocial factors at work and  
6 167 inflammatory markers; (2) used longitudinal or prospective cohort designs; (3)  
7 168 were conducted among workers; (4) provided sufficient data for calculating  
8 169 coefficients of associations between psychosocial factors at work and  
9 170 inflammatory markers ( $\gamma$ ,  $\beta$ ), odds ratios (ORs), relative risks (RRs), or hazard  
10 171 ratios (HRs) with standard errors (SEs) or 95% CIs; (5) were published as  
11 172 original articles in English or Japanese; and (6) were published up to the end of  
12 173 2017.  
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### 18 175 **Information sources, search strategy, and data management**

19 176 A systematic search of published studies will be conducted using  
20 177 electronic databases: PubMed (MEDLINE), EMBASE, PsycINFO,  
21 178 PsycARTICLES, Web of Science, and the Japan Medical Abstracts Society.  
22 179 Search terms will include words related to the PECO of eligible published studies.  
23 180 The proposed search strategy appears in Appendix 1. All identified studies will  
24 181 be managed in a Microsoft Excel file (WA, US). Before the study selection  
25 182 process, duplicated citations in the Excel file will be excluded by KW. Decisions  
26 183 on all studies will be recorded.  
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### 32 185 **Study selection process**

33 186 First, following the eligibility criteria, 14 investigators (HE, KW, EA, HA, YA,  
34 187 AI, RI, MI, KI, YK, NN, YO, ASa, and KT) will independently conduct screening of  
35 188 identified titles and abstracts in pairs. Second, we will obtain full texts of all  
36 189 eligible studies. In the full-text review phase, the studies will be examined using  
37 190 a standardized form (Appendix 2) to assess eligibility for inclusion in this review.  
38 191 The number of papers examined by each investigator will depend on the  
39 192 investigator's capacity. Any discrepancies in assessment will be recorded and  
40 193 the inter-rater reliability determined; such matters will be discussed among all  
41 194 the investigators until consensus is reached. We will directly contact the  
42 195 corresponding authors of eligible studies if the results of the publication are  
43 196 unclear and may be related to multiple interpretations or if the reported results  
44 197 did not show data relevant to our study analysis. The reasons for excluding  
45 198 studies will be recorded. A flow chart will be prepared showing the entire review  
46 199 process.  
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### 53 200 54 201 **Data extraction**

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5 202 Data will be extracted independently from the included studies by 14  
6 203 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT)  
7 204 working in pairs using a standardized data extraction form. The data will be  
8 205 distributed according to the investigators' capacity. Any discrepancies or  
9 206 inconsistencies in the assessment will be recorded and the inter-rater reliability  
10 207 determined; such matters will be discussed among all the investigators until  
11 208 consensus is reached. The extracted data will include the following: year of  
12 209 publication; country where the study was conducted; number of participants at  
13 210 baseline and in the analysis; sampling framework; participants' demographic  
14 211 characteristics (i.e., mean age, sex proportions, and employment status); length  
15 212 of follow-up; follow-up rate; exposure and comparison variables (adverse  
16 213 psychosocial factors at work); outcome variables (inflammatory markers);  
17 214 number and proportion of participants with increased levels of inflammatory  
18 215 markers or mean scores and variances or standard deviations of markers; and  
19 216 sufficient data for calculating the coefficients ( $\beta$ ,  $\gamma$ ), ORs, RRs, or HRs with SEs  
20 217 or 95% CIs for the association between adverse psychosocial factors at work  
21 218 and inflammatory markers. If the included studies report multiple measures of  
22 219 association, we will attempt to select measures of association adjusted by  
23 220 demographic variables (e.g., age, sex, education, and marital status). If the  
24 221 studies report measures of association adjusted by lifestyle variables (e.g.,  
25 222 smoking, physical activity, and sleep), we will as far as possible extract  
26 223 measures both with and without adjustment for lifestyle variables. To avoid  
27 224 over-adjustment, measures of association adjusted for other adverse  
28 225 psychosocial factors at work or inflammatory markers will not be adopted.  
29 226 Sex-stratified coefficients will be selected if they are the only reported results.  
30 227 Any missing data from the studies will be obtained by contacting the relevant  
31 228 research team.

### 229 230 **Assessment of study quality**

231 Fourteen investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO,  
232 ASa, and KT) will independently assess in pairs the quality of each included  
233 study using the internationally recognized Risk of Bias Assessment Tool for  
234 Nonrandomized Studies (RoBANS).<sup>36 37</sup> The RoBANS was developed to  
235 determine the risk of bias of non-randomized studies; it comprises six domains:  
236 selection of participants; confounding variables; measurement of exposure;  
237 blinding of outcomes; incomplete outcome data; and selective outcome reporting.



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5 238 The risk of bias for each domain is classified as low, high, or unclear risk. The  
6 239 number of papers assessed by each investigator will depend on their capacity.  
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8 240 Any discrepancies in quality assessment among the investigators will be  
9 241 recorded and the inter-rater reliability determined; such matters will be discussed  
10 242 among all the investigators until consensus is reached.  
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#### 13 244 **Data synthesis and statistical methods**

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15 245 The included studies will be statistically synthesized in a meta-analysis to  
16 246 estimate pooled coefficients and 95% CIs, stratified by types of measures of  
17 247 association ( $\beta$ ,  $\gamma$ , OR, RR, and HR). If the included studies report ORs, RRs, or  
18 248 HRs, we will calculate log-transformed ORs, RRs, or HRs and determine SEs  
19 249 based on 95% CIs. These parameters will be used in the meta-analysis and for  
20 250 examining publication bias by means of a funnel plot and Egger's test with  
21 251 statistical software, R version 3.4.1.<sup>38 39</sup> We will employ a random-effects  
22 252 model<sup>40</sup> to summarize the results using R version 3.4.1 with the "meta" and  
23 253 "metafor" packages.<sup>41</sup>

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27 254 For the main analysis, we will synthesize all types of psychosocial factors  
28 255 at work in the random-effects model. The results will be presented in a narrative  
29 256 format if a meta-analysis is not appropriate or possible, e.g., if only two or fewer  
30 257 studies are eligible and included in the study. Heterogeneity will be assessed  
31 258 using the chi-square test with Cochran's Q statistic, which is calculated by  $I^2$   
32 259 values,<sup>42</sup> assuming that  $I^2$  values of 25%, 50%, and 75% indicate low, medium,  
33 260 and high heterogeneity, respectively.

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37 261 Subgroup and sensitivity analyses will be conducted to compare the  
38 262 results across subgroups or under specific conditions when sufficient  
39 263 heterogeneity is detected. Major possible grouping characteristics will include  
40 264 types of exposure and outcome, participants' demographic characteristics (e.g.,  
41 265 sex, age, employment status, occupational groups), and study quality. Any  
42 266 subgroup differences will be reported, and our findings will be explained by  
43 267 considering these differences. Results with and without adjustment for lifestyle  
44 268 variables will be compared in another sensitivity analysis. If trends are observed  
45 269 between pooled associations and any grouping characteristics, meta-regression  
46 270 will be conducted using the "metareg" function of R. A sensitivity analysis may be  
47 271 conducted for included studies where the RoBANS is classified as low risk. All  
48 272 extracted data and analyzed results will be deposited by the corresponding  
49 273 author and made available for external reviewers and readers upon request.  
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5 2746 275 **Patient and public involvement statement**7  
8 276 This study will not involve any patients or study participants: this study  
9 277 protocol is for a systematic review and meta-analysis.  
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12 279 **Ethics and dissemination**13 280 This study does not require ethical approval because the systematic review and  
14 281 meta-analysis will be based on previously published studies. The results will be  
15 282 submitted for publication in a scientific peer-reviewed journal, according to the  
16 283 MOOSE guideline.<sup>34</sup>  
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20 285 **Funding**21  
22 286 This work is supported by the Work-related Diseases Clinical Research Grant  
23 287 2016 (160701-01) from the Ministry of Health, Labour and Welfare, Japan. The  
24 288 funder has no role in study design, data extraction and analysis, decision to  
25 289 publish, or preparation of the final manuscript.  
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29 291 **Competing Interests**30 292 The authors declare that they have no competing interests.  
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34 294 **Strengths and limitations**35 295 This systematic review and meta-analysis will be based on prospective studies  
36 296 and show the strongest evidence for the associations between psychosocial  
37 297 factors at work and inflammatory markers. The findings will highlight potential  
38 298 mediators and underlying mechanisms for the development of CVD owing to  
39 299 adverse psychosocial factors.  
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42 301 There are several likely limitations in this study, including confounding  
43 302 bias and low generalizability. If selected studies do not report  
44 303 demographic-adjusted associations, the findings will be distorted by the  
45 304 unobserved characteristics among the population. In addition, the findings will  
46 305 not be generalizable to populations not included in the selected studies.  
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50 306 **Authors' contributions**51 307 HE, KW, NK, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, KT, ASH, and AT  
52 308 made substantial contributions to the conception and design of the study, writing  
53 309 the protocol and revising it critically for important intellectual content, and  
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310 approving the final version to be published. All authors will be involved in the  
311 entire study process (i.e., data extraction, assessment, and synthesis).

312

### 313 **Acknowledgements**

314 We thank Audrey Holmes, MA, from Edanz Group ([www.edanzediting.com/ac](http://www.edanzediting.com/ac))  
315 for editing a draft of this manuscript.

316

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## Appendix 1. Search terms used for the electronic databases

Database	Search terms
PubMed	(employe*[tw] OR manag*[tw] OR colleague*[tw] OR worksit*[tw] OR “work”[tw] OR works*[tw] OR work’*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupant*[tw] OR company*[tw] OR offic*[tw] OR busines*[tw] OR workplace[mh]) AND (“Stress, Mechanical”[Mesh] OR “Lifting”[Mesh] OR “Moving and Lifting Patients”[Mesh] OR “Weight-Bearing”[Mesh] OR “Biomechanics” OR “Physical Exertion”[Mesh] OR “Torsion, Mechanical”[Mesh] OR “Postural Balance”[Mesh] OR “Walking”[Mesh] OR “Recovery of Function”[Mesh] OR “Relaxation”[Mesh] OR (static[Title/Abstract] AND posture) OR (awkward[Title/Abstract] AND posture) OR (dynamic[Title/Abstract] AND posture) OR static work[Title/Abstract] OR dynamic load*[Title/Abstract] OR lift*[Title/Abstract] OR carry*[Title/Abstract] OR hold*[Title/Abstract] OR pull*[Title/Abstract] OR drag*[Title/Abstract] OR push*[Title/Abstract] OR manual handling[Title/Abstract] OR force*[Title/Abstract] OR biomechanic*[Title/Abstract] OR walking*[Title/Abstract] OR postural balance[Title/Abstract] OR flexion*[Title/Abstract] OR extension*[Title/Abstract] OR turning[Title/Abstract] OR sitting[Title/Abstract] OR kneeling[Title/Abstract] OR squatting[Title/Abstract] OR twisting[Title/Abstract] OR bending[Title/Abstract] OR reaching[Title/Abstract] OR standing[Title/Abstract] OR sedentary[Title/Abstract] OR repetitive movement*[Title/Abstract] OR monotonous work[Title/Abstract] OR relaxation[Title/Abstract] OR recovery of function[Title/Abstract] OR physical demand*[Title/Abstract] OR physically demand*[Title/Abstract]) OR (“Stress, Psychological”[Majr] OR “Social Support”[Majr] OR “Job Satisfaction”[Mesh] OR “Work Schedule Tolerance”[Mesh] OR “Employee Performance Appraisal”[Mesh] OR “Employee Grievances”[Mesh] OR “Social Justice/psychology”[Mesh] OR “Personnel Downsizing”[Mesh] OR “Staff Development”[Mesh] OR “Organizational Culture”[Mesh] OR “Bullying”[Mesh] OR “Prejudice”[Mesh] OR “Social Discrimination”[Mesh] OR “Interpersonal Relations”[Mesh] OR “Communication/psychology”[Mesh]) OR (psychosocial[Title/Abstract] OR job strain[Title/Abstract] OR work strain[Title/Abstract] OR work demand*[Title/Abstract] OR job demand*[Title/Abstract] OR high demand*[Title/Abstract] OR low control[Title/Abstract] OR lack of control[Title/Abstract] OR work control[Title/Abstract] OR job control[Title/Abstract] OR decision latitude[Title/Abstract] OR work influence*[Title/Abstract] OR demand resource*[Title/Abstract] OR effort reward*[Title/Abstract] OR time pressure*[Title/Abstract] OR recuperation*[Title/Abstract] OR work overload*[Title/Abstract] OR work over-load*[Title/Abstract] OR recovery[Title/Abstract] OR coping[Title/Abstract] OR work ability[Title/Abstract] OR social support[Title/Abstract] OR support system*[Title/Abstract] OR social network*[Title/Abstract] OR emotional support[Title/Abstract] OR interpersonal relation*[Title/Abstract] OR interaction*[Title/Abstract] OR social capital [Title/Abstract] OR justice*[Title/Abstract] OR injustice*[Title/Abstract] OR job satisfaction[Title/Abstract] OR work satisfaction[Title/Abstract] OR boredom[Title/Abstract] OR skill discretion*[Title/Abstract] OR staff development[Title/Abstract] OR discrimination[Title/Abstract] OR harass*[Title/Abstract] OR work-place



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 (("inflammation"[MeSH Terms] OR inflammation\*[All Fields]) OR ("immune system"[MeSH Terms] OR "immune system phenomena"[MeSH Terms] OR "immunity"[All Fields] OR "immunology"[All Fields])) OR ("c-reactive protein"[MeSH Terms] OR ("c-reactive"[All Fields] AND protein[All Fields]) OR c-reactive protein[All Fields] OR CRP[All Fields]) OR ("cytokines"[MeSH Terms] OR cytokine\*[All Fields]) OR ("lymphokines"[MeSH Terms] OR lymphokine\*[All Fields]) OR ("chemokines"[MeSH Terms] OR chemokine\*[All Fields]) OR ("monokines"[MeSH Terms] OR monokine\*[All Fields]) OR ("tumor necrosis factor-alpha"[MeSH Terms] OR tumor necrosis factor\*[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND factor\*[All Fields]) OR TNF\*[All Fields]) OR ("interleukins"[MeSH Terms] OR interleukin\*[All Fields] OR IL[All Fields])) AND  
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OR (work AND control) OR (job AND control) OR (decision AND latitude) OR (work AND influence\*) OR (demand AND resource\*) OR (effort AND reward\*) OR (time AND pressure\*) OR recuperation\* OR (work AND overload\*) OR (work AND over-load\*) OR recovery OR coping OR (work AND ability) OR (social AND support) OR (support AND system\*) OR (social AND network\*) OR (emotional AND support) OR (interpersonal AND relation\*) OR interaction\* OR (social AND capital) OR justice\* OR injustice\* OR (job AND satisfaction) OR (work AND satisfaction) OR boredom OR (skill AND discretion\*) OR (staff AND development) OR discrimination OR harass\* OR (work-place AND conflict\*) OR (workplace AND violen\*) OR (workplace AND violen\*) OR bullying OR ageism OR homophobia OR racism OR sexism OR victimization\* OR (silent AND workplace\*) OR (role AND ambiguity) OR role-conflict\* OR work-role\* OR (working AND hour\*) OR (working AND time) OR day-time OR night-time OR (shift AND work\*) OR (work AND shift\*) OR (temporary AND work) OR full-time OR part-time OR (flexible AND work\*) OR (organizational AND change) OR (organizational AND change) OR (lean AND production) OR (job AND security) OR (job AND insecurity))) AND  
 (((("inflammation" OR inflammation\*) OR ("immune system" OR "immune system phenomena" OR "immunity" OR "immunology")) OR ("c-reactive protein" OR ("c-reactive" AND protein) OR c-reactive protein OR CRP) OR ("cytokines" OR cytokine\*) OR ("lymphokines" OR lymphokine\*) OR ("chemokines" OR chemokine\*) OR ("monokines" OR monokine\*) OR ("tumor necrosis factor-alpha" OR tumor necrosis factor\* OR ("tumor" AND "necrosis" AND factor\*) OR TNF\*) OR ("interleukins" OR interleukin\* OR IL)) AND  
 ((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\*))

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Appendix 2. Standardized form to assess eligibility for inclusion

ID	Database	No	Title	Author name	Source	Abstract	URL	reviewer 1	reviewer 2	Result screening 1	Result screening 2	Result discussion
1	Embase	1	Effect of breastfeeding on postpartum depressive symptoms among adolescent and young adult mothers	Sispa H.L., Ruiz E., Jones K., Magriples U., Kershaw T.,	Journal of Maternal-Fetal and Neonatal Medicine (2018) 31:11 (1442-1447). Date of Publication: 3 Jun 2018	<p>Purpose: To describe the association between breastfeeding and postpartum depressive symptoms among a sample of adolescent and young adult mothers and to determine whether breastfeeding difficulty moderates this association. Materials and methods: Data were derived from a prospective cohort of pregnant adolescent and young adult females (ages 14-21) as they transitioned to parenthood. This analysis uses data collected during pregnancy and at 6 months postpartum among mothers (n = 137) who initiated breastfeeding. Multivariable linear regression was used to adjust for prenatal depressive symptoms and other potential confounders. Results: Postpartum depressive symptoms were not significantly associated with breastfeeding duration or breastfeeding at 6 months. Early breastfeeding difficulty moderated the association between depressive symptoms and breastfeeding at 6 months. Among young mothers who were still breastfeeding at 6 months, those who reported no early breastfeeding difficulties had the lowest depressive scores and those who reported much early breastfeeding difficulty had the highest depressive scores at 6 months. Conclusions: Minimizing challenges with breastfeeding may help improve postpartum mental health among adolescent and young adult mothers. Health care providers should help young pregnant women manage expectations about breastfeeding and ensure that they are linked to appropriate professional breastfeeding support during the early postpartum period.</p>		KW	HE	○	×	×

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	On page #
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P.3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P. 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	P. 10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	P. 10
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	P. 5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P. 6
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P. 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P. 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P. 7-8 Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P. 7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P. 7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P. 7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P. 7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P. 7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P. 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P. 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	P. 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P. 9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P. 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

# BMJ Open

## Psychosocial factors at work and inflammatory markers: protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022612.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Jul-2018
Complete List of Authors:	<p>Eguchi, Hisashi; Kitasato University School of Medicine, Department of Public Health  Watanabe, Kazuhiro; The University of Tokyo, Department of Mental Health, Graduate School of Medicine  Kawakami, Norito; The University of Tokyo, Department of Mental Health  Ando, Emiko; Osaka University, Department of Social and Environmental Health, Division of Environmental Medicine and Population Sciences, Graduate School of Medicine  Arima, Hideaki; The University of Tokyo, Department of Mental Health, Graduate School of Medicine  Asai, Yumi; The University of Tokyo, Department of Mental Health, Graduate School of Medicine  Inoue, Akiomi; Kitasato University School of Medicine, Department of Public Health  Inoue, Reiko; Hitachi Automotive Systems Ltd  Iwanaga, Mai; Graduate School of Medicine, The university of Tokyo, Department of Psychiatric Nursing  Imamura, Kotaro; The University of Tokyo, Department of Mental Health, Graduate School of Medicine  Kobayashi, Yuka; Honda Motor Co., Ltd.  Nishida, Norimitsu; Kyoto Industrial Health Association  Otsuka, Yasumasa; Faculty of Human Sciences, University of Tsukuba  Sakuraya, Asuka; The University of Tokyo, Department of Mental Health, Graduate School of Medicine  Tsuno, Kanami; Wakayama Medical University - Kimiidera Campus, Department of Hygiene, School of Medicine  Shimazu, Akihito; College of Liberal Arts and Sciences, Kitasato University,  Tsutsum, Akizumi; Kitasato University, Department of Public Health</p>
<b>Primary Subject Heading</b>:	Occupational and environmental medicine
Secondary Subject Heading:	Immunology (including allergy)
Keywords:	Inflammation, Psychosocial factors at work, Cardiology < INTERNAL MEDICINE, Occupational health, Workplace, MENTAL HEALTH

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Manuscripts

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1 **Psychosocial factors at work and inflammatory markers: protocol for a**  
2 **systematic review and meta-analysis**

3  
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38 **Word count: 2,016 words**

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5 **Abstract**

6 **INTRODUCTION:** Chronic inflammation may be a mediator for the development  
7 of cardiovascular disease (CVD), metabolic diseases, and psychotic and  
8 neurodegenerative disorders. Meta-analytic associations between work-related  
9 psychosocial factors and inflammatory markers have shown that work-related  
10 psychosocial factors could affect the flexibility and balance of the immune  
11 system. However, few systematic reviews or meta-analyses have investigated  
12 the association between work-related psychosocial factors and inflammatory  
13 markers. Based on prospective studies, the present investigation will conduct a  
14 comprehensive systematic review and meta-analysis of the association between  
15 work-related psychosocial factors and inflammatory markers.  
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20 **METHODS AND ANALYSIS:** The systematic review and meta-analysis will  
21 include published studies identified from electronic databases (PubMed,  
22 EMBASE, PsycINFO, PsycARTICLES, Web of Science and Japan Medical  
23 Abstracts Society) according to recommendations of the Meta-analysis of  
24 Observational Studies in Epidemiology guideline. Inclusion criteria are studies  
25 that did the following: examined associations between work-related psychosocial  
26 factors and increased inflammatory markers; used longitudinal or prospective  
27 cohort designs; were conducted among workers; provided sufficient data for  
28 calculating odds ratios or relative risk with 95% confidence intervals; were  
29 published as original articles in English or Japanese; and were published up to  
30 the end of 2017. Study selection, data extraction, quality assessment, and  
31 statistical syntheses will be conducted by 14 investigators. Any inconsistencies  
32 or disagreements will be resolved through discussion. The quality of studies will  
33 be evaluated using the Risk of Bias Assessment Tool for Nonrandomized  
34 Studies.  
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42 **ETHICS AND DISSEMINATION:** The investigation study will be based on  
43 published studies, so ethics approval is not required. The results of this study will  
44 be submitted for publication in a scientific peer-reviewed journal. The findings  
45 may be useful for assessing risk factors for increased inflammatory markers in  
46 the workplace and determining future approaches for preventing CVD, metabolic  
47 diseases, and psychotic and neurodegenerative disorders.  
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50 **TRIAL REGISTRATION NUMBER:** PROSPERO CRD42018081553  
51 ([https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?RecordID=81553](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=81553)).  
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5 74 **Strengths and limitations of this study**

- 6 75 ● This systematic review and meta-analysis will offer comprehensive  
7 76 understanding of the association between work-related psychosocial factors  
8 77 and inflammatory markers.  
9 78  
10 79 ● The review will include a range of work-related psychosocial factors and  
11 80 focus on inflammatory markers.  
12 81  
13 82 ● To ensure stronger evidence, the review will include only prospective  
14 83 studies.  
15 84  
16 85 ● The findings of this review may be useful for assessing chronic inflammation  
17 86 as a risk factor for cardiovascular disease (CVD), metabolic diseases, and  
18 87 psychotic and neurodegenerative disorders in the workplace as well as for  
19 88 determining future approaches for preventing CVD, metabolic diseases, and  
20 89 psychotic and neurodegenerative disorders.  
21 90  
22 91 ● Depending on the results, limitations could be confounding factors that may  
23 92 not have been adjusted for in the selected studies as well as low  
24 93 generalizability.  
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## INTRODUCTION

Most adults spend around half of their waking hours at work, and so the workplace is an important setting to promote health and well-being. Increasing attention is being directed to work-related psychosocial factors, such as job strain,<sup>1-5</sup> effort-reward imbalance,<sup>6</sup> organizational justice,<sup>7-9</sup> and workplace social capital<sup>10</sup>; there is a major focus on work stress.<sup>2</sup> 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.<sup>11-13</sup>

Chronic inflammation has been suggested as a potential mediator for the development of CVD, metabolic diseases, and psychotic and neurodegenerative disorders.<sup>14-18</sup> Several studies have reported associations between adverse work-related psychosocial factors and increased levels of inflammatory markers. Inflammatory markers, including C-reactive protein (CRP),<sup>19-24</sup> interleukin-6 (IL-6),<sup>24-25</sup> and tumor necrosis factor (TNF- $\alpha$ ), have been implicated in coordinating atherosclerosis.<sup>26</sup> Previous meta-analyses<sup>27-28</sup> have identified the associations between psychosocial factors and inflammatory markers; however, the findings from those studies were not conclusive because of methodological heterogeneity (e.g., conceptualization or measurement of work-related psychosocial factors, sample compositions, and statistical approaches).

Meta-analytic associations between work-related psychosocial factors and inflammatory markers indicate that such factors may affect the flexibility and balance of the immune system. Some meta-analyses have investigated inflammatory markers in relation to psychological stress<sup>27-30</sup> and unemployment<sup>31</sup>; however, few systematic reviews or meta-analyses have been conducted regarding the associations between work-related psychosocial factors and inflammatory markers. A systematic review of 56 studies by Nakata<sup>32</sup> suggested that work-related psychosocial factors were related to disrupted immune response. However, that study did not statistically synthesize the associations. To our knowledge, only one meta-analysis of the association between effort-reward imbalance and inflammatory markers ( $k = 7$ ,  $N = 9952$ ) found a negative association with immunity ( $r = -0.09$ ; confidence interval [CI],  $-0.14$  to  $-0.05$ ;  $P < 0.001$ ).<sup>13</sup> These systematic reviews and meta-analyses included cross-sectional studies. However, pooled associations between work-related psychosocial factors and inflammatory markers derived from

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5 130 prospective studies may provide more reliable evidence.

6 131 Based on published prospective studies, the present investigation will  
7 132 conduct a comprehensive systematic review and meta-analysis of the  
8 133 associations between work-related psychosocial factors and inflammatory  
9 134 markers. Inflammatory markers will include those that were previously  
10 135 investigated in terms of associations with psychosocial factors at work, including  
11 136 CRP, IL-6, and TNF- $\alpha$ . Our hypothesis is that adverse work-related psychosocial  
12 137 factors would increase inflammatory markers. Moreover, we will identify the  
13 138 work-related psychological factors that have the strongest associations with  
14 139 specific inflammatory markers.  
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## 21 141 **METHODS AND ANALYSIS**

### 22 142 **Study design**

23 143 This study protocol for a systematic review and meta-analysis of  
24 144 prospective studies follows the Preferred Reporting Items for Systematic  
25 145 Reviews and Meta-Analysis Protocols guideline.<sup>33</sup> Future findings will be  
26 146 reported according to the Meta-analysis of Observational Studies in  
27 147 Epidemiology (MOOSE) reporting guidelines.<sup>34</sup> This study protocol was  
28 148 registered with PROSPERO (CRD42018081553).  
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### 33 150 **Eligibility criteria**

34 151 Participants, exposures, comparisons, and outcomes (PECO) of the  
35 152 studies included in this systematic review and meta-analysis will be defined as  
36 153 follows: (P) inclusion of all workers; (E) presence of adverse psychosocial  
37 154 factors at work; (C) absence of adverse psychosocial factors at work; and (O)  
38 155 increased inflammatory markers. Target participants will all be employees of  
39 156 participating companies. There will be no exclusion criteria related to  
40 157 employment status, job type, or shift type. The study exposures (adverse  
41 158 psychosocial factors at work) will include a range of task and organizational  
42 159 characteristics and work conditions,<sup>35</sup> such as job strain,<sup>1-5</sup> low social support,  
43 160 effort-reward imbalance,<sup>6</sup> organizational injustice,<sup>7-9</sup> and low workplace social  
44 161 capital.<sup>10</sup> Long working hours and shift work will also be included as target  
45 162 exposures. Inflammatory markers will include those investigated in terms of  
46 163 association with psychosocial factors at work in previous studies, including CRP,  
47 164 IL-6, and TNF- $\alpha$ .  
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54 165 Eligibility criteria for selection are the following studies that (1) were  
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5 166 conducted to evaluate associations between psychosocial factors at work and  
6 167 inflammatory markers; (2) used longitudinal or prospective cohort designs; (3)  
7 168 were conducted among workers; (4) provided sufficient data for calculating  
8 169 coefficients of associations between psychosocial factors at work and  
9 170 inflammatory markers ( $\gamma$ ,  $\beta$ ), odds ratios (ORs), relative risks (RRs), or hazard  
10 171 ratios (HRs) with standard errors (SEs) or 95% CIs; (5) were published as  
11 172 original articles in English or Japanese; and (6) were published up to the end of  
12 173 2017.  
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### 18 175 **Information sources, search strategy, and data management**

19 176 A systematic search of published studies will be conducted using  
20 177 electronic databases: PubMed (MEDLINE), EMBASE, PsycINFO,  
21 178 PsycARTICLES, Web of Science, and the Japan Medical Abstracts Society.  
22 179 Search terms will include words related to the PECO of eligible published studies.  
23 180 The proposed search strategy appears in Appendix 1. All identified studies will  
24 181 be managed in a Microsoft Excel file (WA, US). Before the study selection  
25 182 process, duplicated citations in the Excel file will be excluded by KW. Decisions  
26 183 on all studies will be recorded.  
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### 32 185 **Study selection process**

33 186 First, following the eligibility criteria, 14 investigators (HE, KW, EA, HA, YA,  
34 187 AI, RI, MI, KI, YK, NN, YO, ASa, and KT) will independently conduct screening of  
35 188 identified titles and abstracts in pairs. Second, we will obtain full texts of all  
36 189 eligible studies. In the full-text review phase, the studies will be examined using  
37 190 a standardized form (Appendix 2) to assess eligibility for inclusion in this review.  
38 191 The number of papers examined by each investigator will depend on the  
39 192 investigator's capacity. Any discrepancies in assessment will be recorded and  
40 193 the inter-rater reliability determined; such matters will be discussed among all  
41 194 the investigators until consensus is reached. We will directly contact the  
42 195 corresponding authors of eligible studies if the results of the publication are  
43 196 unclear and may be related to multiple interpretations or if the reported results  
44 197 did not show data relevant to our study analysis. The reasons for excluding  
45 198 studies will be recorded. A flow chart will be prepared showing the entire review  
46 199 process.  
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### 53 200 54 201 **Data extraction**

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5 202 Data will be extracted independently from the included studies by 14  
6 203 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT)  
7 204 working in pairs using a standardized data extraction form. The data will be  
8 205 distributed according to the investigators' capacity. Any discrepancies or  
9 206 inconsistencies in the assessment will be recorded and the inter-rater reliability  
10 207 determined; such matters will be discussed among all the investigators until  
11 208 consensus is reached. The extracted data will include the following: year of  
12 209 publication; country where the study was conducted; number of participants at  
13 210 baseline and in the analysis; sampling framework; participants' demographic  
14 211 characteristics (i.e., mean age, sex proportions, and employment status); length  
15 212 of follow-up; follow-up rate; exposure and comparison variables (adverse  
16 213 psychosocial factors at work); outcome variables (inflammatory markers);  
17 214 number and proportion of participants with increased levels of inflammatory  
18 215 markers or mean scores and variances or standard deviations of markers; and  
19 216 sufficient data for calculating the coefficients ( $\beta$ ,  $\gamma$ ), ORs, RRs, or HRs with SEs  
20 217 or 95% CIs for the association between adverse psychosocial factors at work  
21 218 and inflammatory markers. If the included studies report multiple measures of  
22 219 association, we will attempt to select measures of association adjusted by  
23 220 demographic variables (e.g., age, sex, education, and marital status). If the  
24 221 studies report measures of association adjusted by lifestyle variables (e.g.,  
25 222 smoking, physical activity, and sleep), we will as far as possible extract  
26 223 measures both with and without adjustment for lifestyle variables. To avoid  
27 224 over-adjustment, measures of association adjusted for other adverse  
28 225 psychosocial factors at work or inflammatory markers will not be adopted.  
29 226 Sex-stratified coefficients will be selected if they are the only reported results.  
30 227 Any missing data from the studies will be obtained by contacting the relevant  
31 228 research team.

### 229 230 **Assessment of study quality**

231 Fourteen investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO,  
232 ASa, and KT) will independently assess in pairs the quality of each included  
233 study using the internationally recognized Risk of Bias Assessment Tool for  
234 Nonrandomized Studies (RoBANS).<sup>36 37</sup> The RoBANS was developed to  
235 determine the risk of bias of non-randomized studies; it comprises six domains:  
236 selection of participants; confounding variables; measurement of exposure;  
237 blinding of outcomes; incomplete outcome data; and selective outcome reporting.



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5 238 The risk of bias for each domain is classified as low, high, or unclear risk. The  
6 239 number of papers assessed by each investigator will depend on their capacity.  
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8 240 Any discrepancies in quality assessment among the investigators will be  
9 241 recorded and the inter-rater reliability determined; such matters will be discussed  
10 242 among all the investigators until consensus is reached.  
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#### 13 244 **Data synthesis and statistical methods**

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15 245 The included studies will be statistically synthesized in a meta-analysis to  
16 246 estimate pooled coefficients and 95% CIs, stratified by types of measures of  
17 247 association ( $\beta$ ,  $\gamma$ , OR, RR, and HR). If the included studies report ORs, RRs, or  
18 248 HRs, we will calculate log-transformed ORs, RRs, or HRs and determine SEs  
19 249 based on 95% CIs. These parameters will be used in the meta-analysis and for  
20 250 examining publication bias by means of a funnel plot and Egger's test with  
21 251 statistical software, R version 3.4.1.<sup>38 39</sup> We will employ a random-effects  
22 252 model<sup>40</sup> to summarize the results using R version 3.4.1 with the "meta" and  
23 253 "metafor" packages.<sup>41</sup>

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27 254 For the main analysis, we will synthesize all types of psychosocial factors  
28 255 at work in the random-effects model. The results will be presented in a narrative  
29 256 format if a meta-analysis is not appropriate or possible, e.g., if only two or fewer  
30 257 studies are eligible and included in the study. Heterogeneity will be assessed  
31 258 using the chi-square test with Cochran's Q statistic, which is calculated by  $I^2$   
32 259 values,<sup>42</sup> assuming that  $I^2$  values of 25%, 50%, and 75% indicate low, medium,  
33 260 and high heterogeneity, respectively.

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37 261 Subgroup and sensitivity analyses will be conducted to compare the  
38 262 results across subgroups or under specific conditions when sufficient  
39 263 heterogeneity is detected. Major possible grouping characteristics will include  
40 264 types of exposure and outcome, participants' demographic characteristics (e.g.,  
41 265 sex, age, employment status, occupational groups), and study quality. Any  
42 266 subgroup differences will be reported, and our findings will be explained by  
43 267 considering these differences. Results with and without adjustment for lifestyle  
44 268 variables will be compared in another sensitivity analysis. If trends are observed  
45 269 between pooled associations and any grouping characteristics, meta-regression  
46 270 will be conducted using the "metareg" function of R. A sensitivity analysis may be  
47 271 conducted for included studies where the RoBANS is classified as low risk. All  
48 272 extracted data and analyzed results will be deposited by the corresponding  
49 273 author and made available for external reviewers and readers upon request.  
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5 2746 275 **Patient and public involvement statement**7  
8 276 This study will not involve any patients or study participants: this study  
9 277 protocol is for a systematic review and meta-analysis.  
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12 279 **Ethics and dissemination**13 280 This study does not require ethical approval because the systematic review and  
14 281 meta-analysis will be based on previously published studies. The results will be  
15 282 submitted for publication in a scientific peer-reviewed journal, according to the  
16 283 MOOSE guideline.<sup>34</sup>  
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19 284

20 285 **Funding**21  
22 286 This work is supported by the Work-related Diseases Clinical Research Grant  
23 287 2016 (160701-01) from the Ministry of Health, Labour and Welfare, Japan. The  
24 288 funder has no role in study design, data extraction and analysis, decision to  
25 289 publish, or preparation of the final manuscript.  
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29 291 **Competing Interests**30 292 The authors declare that they have no competing interests.  
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34 294 **Strengths and limitations**35 295 This systematic review and meta-analysis will be based on prospective studies  
36 296 and show the strongest evidence for the associations between psychosocial  
37 297 factors at work and inflammatory markers. The findings will highlight potential  
38 298 mediators and underlying mechanisms for the development of CVD owing to  
39 299 adverse psychosocial factors.  
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42 301 There are several likely limitations in this study, including confounding  
43 302 bias and low generalizability. If selected studies do not report  
44 303 demographic-adjusted associations, the findings will be distorted by the  
45 304 unobserved characteristics among the population. In addition, the findings will  
46 305 not be generalizable to populations not included in the selected studies.  
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50 306 **Authors' contributions**51 307 HE, KW, NK, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, KT, ASH, and AT  
52 308 made substantial contributions to the conception and design of the study, writing  
53 309 the protocol and revising it critically for important intellectual content, and  
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5 310 approving the final version to be published. All authors will be involved in the  
6 311 entire study process (i.e., data extraction, assessment, and synthesis).

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8 312

### 9 313 **Acknowledgements**

10 314 We thank Audrey Holmes, MA, from Edanz Group ([www.edanzediting.com/ac](http://www.edanzediting.com/ac))  
11 315 for editing a draft of this manuscript.

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13 316

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16 319 coronary heart disease: a collaborative meta-analysis of individual  
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## Appendix 1. Search terms used for the electronic databases

Database	Search terms
PubMed	(employe*[tw] OR manag*[tw] OR colleague*[tw] OR worksit*[tw] OR "work"[tw] OR works*[tw] OR work*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupant*[tw] OR company*[tw] OR offic*[tw] OR busines*[tw] OR workplace[mh]) AND ("Stress, Mechanical"[Mesh] OR "Lifting"[Mesh] OR "Moving and Lifting Patients"[Mesh] OR "Weight-Bearing"[Mesh] OR "Biomechanics" OR "Physical Exertion"[Mesh] OR "Torsion, Mechanical"[Mesh] OR "Postural Balance"[Mesh] OR "Walking"[Mesh] OR "Recovery of Function"[Mesh] OR "Relaxation"[Mesh] OR (static[Title/Abstract] AND posture) OR (awkward[Title/Abstract] AND posture) OR (dynamic[Title/Abstract] AND posture) OR static work[Title/Abstract] OR dynamic load*[Title/Abstract] OR lift*[Title/Abstract] OR carry*[Title/Abstract] OR hold*[Title/Abstract] OR pull*[Title/Abstract] OR drag*[Title/Abstract] OR push*[Title/Abstract] OR manual handling[Title/Abstract] OR force*[Title/Abstract] OR biomechanic*[Title/Abstract] OR walking*[Title/Abstract] OR postural balance[Title/Abstract] OR flexion*[Title/Abstract] OR extension*[Title/Abstract] OR turning[Title/Abstract] OR sitting[Title/Abstract] OR kneeling[Title/Abstract] OR squatting[Title/Abstract] OR twisting[Title/Abstract] OR bending[Title/Abstract] OR reaching[Title/Abstract] OR standing[Title/Abstract] OR sedentary[Title/Abstract] OR repetitive movement*[Title/Abstract] OR monotonous work[Title/Abstract] OR relaxation[Title/Abstract] OR recovery of function[Title/Abstract] OR physical demand*[Title/Abstract] OR physically demand*[Title/Abstract]) OR ("Stress, Psychological"[Majr] OR "Social Support"[Majr] OR "Job Satisfaction"[Mesh] OR "Work Schedule Tolerance"[Mesh] OR "Employee Performance Appraisal"[Mesh] OR "Employee Grievances"[Mesh] OR "Social Justice/psychology"[Mesh] OR "Personnel Downsizing"[Mesh] OR "Staff Development"[Mesh] OR "Organizational Culture"[Mesh] OR "Bullying"[Mesh] OR "Prejudice"[Mesh] OR "Social Discrimination"[Mesh] OR "Interpersonal Relations"[Mesh] OR "Communication/psychology"[Mesh]) OR (psychosocial[Title/Abstract] OR job strain[Title/Abstract] OR work strain[Title/Abstract] OR work demand*[Title/Abstract] OR job demand*[Title/Abstract] OR high demand*[Title/Abstract] OR low control[Title/Abstract] OR lack of control[Title/Abstract] OR work control[Title/Abstract] OR job control[Title/Abstract] OR decision latitude[Title/Abstract] OR work influence*[Title/Abstract] OR demand resource*[Title/Abstract] OR effort reward*[Title/Abstract] OR time pressure*[Title/Abstract] OR recuperation*[Title/Abstract] OR work overload*[Title/Abstract] OR work over-load*[Title/Abstract] OR recovery[Title/Abstract] OR coping[Title/Abstract] OR work ability[Title/Abstract] OR social support[Title/Abstract] OR support system*[Title/Abstract] OR social network*[Title/Abstract] OR emotional support[Title/Abstract] OR interpersonal relation*[Title/Abstract] OR interaction*[Title/Abstract] OR social capital [Title/Abstract] OR justice*[Title/Abstract] OR injustice*[Title/Abstract] OR job satisfaction[Title/Abstract] OR work satisfaction[Title/Abstract] OR boredom[Title/Abstract] OR skill discretion*[Title/Abstract] OR staff development[Title/Abstract] OR discrimination[Title/Abstract] OR harass*[Title/Abstract] OR work-place



conflict\*[Title/Abstract] OR workplace violen\*[Title/Abstract] OR work-place violen\*[Title/Abstract] OR bullying[Title/Abstract] OR ageism[Title/Abstract] OR homophobia[Title/Abstract] OR racism[Title/Abstract] OR sexism[Title/Abstract] OR victimization\*[Title/Abstract] OR silent workplace\*[Title/Abstract] OR role ambiguity[Title/Abstract] OR role-conflict\*[Title/Abstract] OR work-role\*[Title/Abstract] OR working hour\*[Title/Abstract] OR working time[Title/Abstract] OR day-time[Title/Abstract] OR night-time[Title/Abstract] OR shift work\*[Title/Abstract] OR work shift\*[Title/Abstract] OR temporary work[Title/Abstract] OR full-time[Title/Abstract] OR part-time[Title/Abstract] OR flexible work\*[Title/Abstract] OR organizational change[Title/Abstract] OR organisational change[Title/Abstract] OR lean production[Title/Abstract] OR job security[Title/Abstract] OR job insecurity[Title/Abstract])) AND  
 (("inflammation"[MeSH Terms] OR inflammation\*[All Fields]) OR ("immune system"[MeSH Terms] OR "immune system phenomena"[MeSH Terms] OR "immunity"[All Fields] OR "immunology"[All Fields])) OR ("c-reactive protein"[MeSH Terms] OR ("c-reactive"[All Fields] AND protein[All Fields]) OR c-reactive protein[All Fields] OR CRP[All Fields]) OR ("cytokines"[MeSH Terms] OR cytokine\*[All Fields]) OR ("lymphokines"[MeSH Terms] OR lymphokine\*[All Fields]) OR ("chemokines"[MeSH Terms] OR chemokine\*[All Fields]) OR ("monokines"[MeSH Terms] OR monokine\*[All Fields]) OR ("tumor necrosis factor-alpha"[MeSH Terms] OR tumor necrosis factor\*[All Fields] OR ("tumor"[All Fields] AND "necrosis"[All Fields] AND factor\*[All Fields]) OR TNF\*[All Fields]) OR ("interleukins"[MeSH Terms] OR interleukin\*[All Fields] OR IL[All Fields])) AND  
 ((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\*)) AND  
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 ("Stress, Mechanical" OR "Lifting" OR "Moving and Lifting Patients" OR "Weight-Bearing" OR "Biomechanics" OR "Physical Exertion" OR "Torsion, Mechanical" OR "Postural Balance" OR "Walking" OR "Recovery of Function" OR "Relaxation" OR (static AND posture) OR (awkward AND posture) OR (dynamic AND posture) OR (static AND work) OR (dynamic AND load\*) OR lift\* OR carry\* OR hold\* OR pull\* OR drag\* OR push\* OR (manual AND handling) OR force\* OR biomechanic\* OR walking\* OR (postural AND balance) OR flexion\* OR extension\* OR turning OR sitting OR kneeling OR squatting OR twisting OR bending OR reaching OR standing OR sedentary OR (repetitive AND movement\*) OR (monotonous AND work) OR relaxation OR (recovery AND of AND function) OR (physical AND demand\*) OR (physically AND demand\*)) OR ("Stress, Psychological"/exp OR "Stress, Psychological" OR "Social Support"/exp OR "Social Support" OR "Job Satisfaction"/exp OR "Job Satisfaction" OR "Work Schedule Tolerance"/exp OR "Work Schedule Tolerance" OR "Employee Performance Appraisal"/exp OR "Employee Performance Appraisal" OR "Employee Grievances"/exp OR "Employee Grievances" OR "Social Justice/psychology" OR "Personnel Downsizing"/exp OR "Personnel Downsizing" OR "Staff Development"/exp OR "Staff Development" OR "Organizational Culture"/exp OR "Organizational Culture" OR "Bullying"/exp OR "Bullying" OR "Prejudice"/exp OR "Prejudice"/exp OR "Prejudice" OR "Social Discrimination"/exp OR "Social Discrimination" OR "Interpersonal Relations"/exp OR "Interpersonal Relations" OR "Communication/psychology") OR (psychosocial OR (job AND strain) OR (work AND strain) OR (work AND demand\*) OR (job AND demand\*) OR (high AND demand\*) OR (low AND control) OR (lack AND of AND control)

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OR (work AND control) OR (job AND control) OR (decision AND latitude) OR (work AND influence\*) OR (demand AND resource\*) OR (effort AND reward\*) OR (time AND pressure\*) OR recuperation\* OR (work AND overload\*) OR (work AND over-load\*) OR recovery OR coping OR (work AND ability) OR (social AND support) OR (support AND system\*) OR (social AND network\*) OR (emotional AND support) OR (interpersonal AND relation\*) OR interaction\* OR (social AND capital) OR justice\* OR injustice\* OR (job AND satisfaction) OR (work AND satisfaction) OR boredom OR (skill AND discretion\*) OR (staff AND development) OR discrimination OR harass\* OR (work-place AND conflict\*) OR (workplace AND violen\*) OR (workplace AND violen\*) OR bullying OR ageism OR homophobia OR racism OR sexism OR victimization\* OR (silent AND workplace\*) OR (role AND ambiguity) OR role-conflict\* OR work-role\* OR (working AND hour\*) OR (working AND time) OR day-time OR night-time OR (shift AND work\*) OR (work AND shift\*) OR (temporary AND work) OR full-time OR part-time OR (flexible AND work\*) OR (organizational AND change) OR (organizational AND change) OR (lean AND production) OR (job AND security) OR (job AND insecurity))) AND  
 (((("inflammation" OR inflammation\*) OR ("immune system" OR "immune system phenomena" OR "immunity" OR "immunology")) OR ("c-reactive protein" OR ("c-reactive" AND protein) OR c-reactive protein OR CRP) OR ("cytokines" OR cytokine\*) OR ("lymphokines" OR lymphokine\*) OR ("chemokines" OR chemokine\*) OR ("monokines" OR monokine\*) OR ("tumor necrosis factor-alpha" OR tumor necrosis factor\* OR ("tumor" AND "necrosis" AND factor\*) OR TNF\*) OR ("interleukins" OR interleukin\* OR IL)) AND  
 ((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\*))

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 Abstracts  
 (労働 OR 従業員 OR 社員 OR ワークサンプル OR 同僚 OR 仲間 OR 上司 OR 管理 OR 監督 OR マネージャー OR マネジャー OR 課長 OR 部長 OR 主任 OR 上長 OR 役員 OR チーフ OR リーダー OR 上役 OR 雇い主 OR 雇主 OR 雇用 OR ワークグループ OR 仕事 OR ワーク OR 作業 OR 就労 OR 勤務 OR ワーキング OR 働く OR 職場 OR オフィス OR 研究所 OR 診療所 OR 医院 OR 事業 OR 職業 OR 家業 OR 事務 OR 業務 OR 執務 OR 営業 OR 所業 OR 実業 OR 産業 OR 就業 OR 企業 OR 会社 OR 商会 OR 法人) AND  
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OR 差別 OR 嫌がらせ OR 職場の葛藤 OR 職場の暴力 OR いじめ OR 年齢差別 OR 同性愛差別 OR 人種差別  
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(縦断研究 OR 前向きコホート研究 OR 前向き研究 OR 追跡研究 OR フォローアップ研究 OR 観察研究 OR 症例  
対照研究 OR 疫学研究 OR 後向き研究)

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Appendix 2. Standardized form to assess eligibility for inclusion

ID	Database	No	Title	Author name	Source	Abstract	URL	reviewer 1	reviewer 2	Result_ screening 1	Result_ screening 2	Result_ discussion
1	Embase	1	Effect of breastfeeding on postpartum depressive symptoms among adolescent and young adult mothers	Sisima H.L., Ruiz E., Jones K., Magriples U., Kershaw T.	Journal of Maternal-Fetal and Neonatal Medicine (2018) 31:11 (1442-1447). Date of Publication: 3 Jun 2018	<p>Purpose: To describe the association between breastfeeding and postpartum depressive symptoms among a sample of adolescent and young adult mothers and to determine whether breastfeeding difficulty moderates this association. Materials and methods: Data were derived from a prospective cohort of pregnant adolescent and young adult females (ages 14-21) as they transitioned to parenthood. This analysis uses data collected during pregnancy and at 6 months postpartum among mothers (n = 137) who initiated breastfeeding. Multivariable linear regression was used to adjust for prenatal depressive symptoms and other potential confounders. Results: Postpartum depressive symptoms were not significantly associated with breastfeeding duration or breastfeeding at 6 months. Early breastfeeding difficulty moderated the association between depressive symptoms and breastfeeding at 6 months. Among young mothers who were still breastfeeding at 6 months, those who reported no early breastfeeding difficulties had the lowest depressive scores and those who reported much early breastfeeding difficulty had the highest depressive scores at 6 months. Conclusions: Minimizing challenges with breastfeeding may help improve postpartum mental health among adolescent and young adult mothers. Health care providers should help young pregnant women manage expectations about breastfeeding and ensure that they are linked to appropriate professional breastfeeding support during the early postpartum period.</p>		KW	HE	○	×	×

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	On page #
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P.3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P. 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	P. 10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	P. 10
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	P. 5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P. 6
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P. 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P. 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P. 7-8 Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P. 7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P. 7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P. 7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P. 7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P. 7-8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P. 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P. 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	P. 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P. 9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P. 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*