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

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Strengths and limitations of this study

- This systematic review and meta-analysis will offer comprehensive understanding of the association between work-related psychosocial factors and inflammatory markers.
- The review will include a range of work-related psychosocial factors, and focus on inflammatory markers as an aggregated cluster.
- The review will only include prospective studies to ensure stronger evidence.
- The findings of this review may be useful for assessing chronic inflammation as a risk factor for cardiovascular disease (CVD) in the workplace, and determining future approaches for CVD prevention.
- Depending on the results, limitations may be confounding factors that might not have been adjusted for in the selected studies and low generalizability.

Abstract

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

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

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

TRIAL REGISTRATION NUMBER: PROSPERO CRD42018081553 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=81553).

Introduction

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

Chronic inflammation has been suggested as a potential mediator for the development of CVD.[14] Several previous studies reported associations between adverse work-related psychosocial factors and increased levels of inflammatory markers. Inflammatory markers, including C-reactive protein (CRP),[15-20] interleukin-6 (IL-6),[20 21] and tumor necrosis factor (TNF-α), are implicated in coordinating atherosclerosis.[22] Previous meta-analyses[23,24] identified associations between psychosocial factors and inflammatory markers, but findings from these studies were not stable because of heterogeneity in methods (e.g., the 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 work-related psychosocial factors may affect the flexibility and balance of the immune system. Although some meta-analyses investigated inflammatory markers in relation to psychological stress[23-26] and unemployment,[27] few systematic reviews or meta-analysis have been conducted regarding the associations between work-related psychosocial factors and inflammatory markers. A previous systematic review of 56 studies by Nakata[28] 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, −0.05; p<0.001).[13] These previous systematic reviews and meta-analyses included cross-sectional studies. However, pooled associations between work-related psychosocial factors and inflammatory markers derived from prospective studies may provide more reliable evidence.

This study aims to conduct a comprehensive systematic review and meta-analysis of the effects of work-related psychosocial factors on inflammatory markers, based on published prospective studies. Our hypothesis is that adverse work-related psychosocial factors would increase inflammatory markers. Moreover, we will identify the work-related psychological factors that have the strongest associations with specific inflammatory markers.

Methods and analysis

Study design

This study protocol for a systematic review and meta-analysis of prospective studies follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guideline.[29] Future findings will be reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.[30] This study protocol was registered with PROSPERO (CRD42018081553).

Eligibility criteria

Participants, exposures, comparisons, and outcomes (PECO) of the studies included in this systematic review and meta-analysis will be defined as follows: (P) inclusion of all workers, (E) presence of adverse psychosocial factors at work, (C) absence of adverse psychosocial factors at work, and (O) increased inflammatory markers. Target participants are all employed workers of participating companies. There will be no exclusion criteria related to employment status, job type, and shift type. The study exposures (adverse psychosocial factors at work) will include a range of task and organizational characteristics, work conditions, and workplace interactions,[31] including job strain, low social support, effort-reward imbalance, organizational injustice, and low workplace social capital. Long working hours and shift work will also be included as target exposures. Inflammatory markers will include those that were investigated in terms of associations with psychosocial factors at work in previous studies, including CRP, IL-6, and TNF-α.

Eligibility criteria for study selection are studies that: 1) were conducted to evaluate associations between psychosocial factors at work and inflammatory markers; 2) used longitudinal or prospective cohort designs; 3) were conducted among workers; 4) provided sufficient data for calculating coefficients between psychosocial factors at work and inflammatory markers (γ, β), odds ratios (ORs),

relative risks (RRs), or hazard ratios (HRs) with standard errors (SEs) or 95% CIs; 5) were published as original articles in English or Japanese; and 6) were published up to the end of 2017.

Information sources, search strategy, and data management

A systematic search of published studies will be conducted using electronic databases: PubMed (MEDLINE), EMBASE, PsycINFO/PsycARTICLES, and the Japan Medical Abstracts Society. Search terms will include words related to the PECO of eligible published studies. The proposed search strategy is shown in Appendix 1. All identified studies will be managed in a Microsoft® Excel file (Washington, US). Before the study selection process, duplicated citations in the Excel file will be excluded by KW. Decisions on all studies will be recorded.

Study selection process

First, 14 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT) will independently conduct screening of identified titles and abstracts, according to the eligibility criteria. Second, we will obtain full texts of all eligible studies. In the full text review phase, the studies will be reviewed using a standardized form for assessing eligibility for inclusion in this review. Any disagreements will be settled in discussion among all authors until consensus is reached. We will directly contact corresponding authors of eligible studies if the results of the publication are unclear and may be related to multiple interpretations, or the results reported in the publication did not show data relevant to our study analysis. The reasons for excluding studies will be recorded. A flow chart will be prepared that shows the entire review process.

Data collection

Data will be extracted independently from the included studies by 14 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT) using a standardized data extraction form. Any disagreement or inconsistencies will be resolved by consultation and consensus among all authors. Collected data will include: year of publication, country where the study was conducted, numbers of participants included at baseline and in the analysis, sampling framework, participants' demographic characteristics (i.e., mean age, sex proportions, and employment status), length of follow-up, follow-up rate,

exposure and comparison variables (adverse psychosocial factors at work), outcome variables (inflammatory markers), number and proportion of participants with increased levels of inflammatory markers or mean scores and variances/standard deviations of markers, and sufficient data for calculating the coefficients (β, γ), ORs, RRs, or HRs with SEs/95% CIs for the association between adverse psychosocial factors at work and inflammatory markers. When the included studies report multiple measures of association, we will preferentially select measures of association adjusted by demographic (e.g., age, sex, education, and marital status) and lifestyle variables (e.g., smoking, physical activity, and sleep). Measures of association adjusted for other adverse psychosocial factors at work and/or inflammatory markers will not be adopted to avoid over-adjustment. Sex-stratified coefficients will be selected if those were the only reported results. Any missing data from the studies will be obtained by contacting the relevant research team.

Assessment of study quality

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

Data synthesis and statistical methods

The included studies will be statistically synthesized in a meta-analysis to estimate pooled coefficients and 95% CIs, stratified by the types of measures of association (β, γ, OR, RR, and HR). When the included studies report ORs, RRs, or HRs, we will calculate log-transformed ORs, RRs, or HRs, and estimate SEs based on 95% CIs. These parameters will be used in the meta-analysis and for examining publication bias using a funnel plot and Egger's test.[34,35] We will use a random effects model[36] to summarize the results using R version 3.4.1 with the "meta" and "metafor" packages.[37] The results will be presented in a

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

Subgroup and sensitivity analyses will also be conducted to compare the results across subgroups or under specific conditions when sufficient heterogeneity is detected. Major grouping characteristics will include types of exposures and outcomes, participants' demographic characteristics (e.g., sex, age, employment status, occupational groups), and study quality. Any subgroup differences will be reported, and our findings will be explained by considering these differences. When trends are observed between pooled associations and any grouping characteristics, meta-regression will be conducted using the "metareg" function of R. A sensitivity analysis may be conducted for included studies with a NOS score indicating high quality (≥7). All collected data and analyzed results will be deposited by the corresponding author and available for external reviewers and readers upon request.

Patient and Public Involvement statement

Any patients and or study participants were not involved in this study because this is the study protocol for the systematic review and meta-analysis.

Ethics and dissemination

This study does not require ethical approval because the systematic review and meta-analysis will be based on previously published studies. The results will be submitted for publication in a scientific peer-reviewed journal, according to the MOOSE guideline.[30]

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Competing interests

The author(s) declare that they have no competing interests.

Strengths and limitations

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

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

Authors' contributions

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

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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

	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 study) OR (prospective cohort study) OR (prospective studies) OR (follow-up studies) OR (observational stud*))
EMBASE, PsycINFO/ PsycARTICLES	(employe* OR manag* OR colleague* OR worksit* OR “work” OR works* OR work* OR worka* OR worke* OR workg* OR worki* OR workl* OR workp* OR occupant* OR company* OR offic* OR busines* OR workplace) AND (("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) 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 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 (prospective studies) OR (follow-up studies) OR (observational stud*))
Japan Medical Abstracts Society	(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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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 #
ADMINISTRATIVE INFORMATION			
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
INTRODUCTION			
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
METHODS			
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. 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^2, 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.**

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

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Primary Subject Heading:	Occupational and environmental medicine
Secondary Subject Heading:	Immunology (including allergy)
Keywords:	Inflammation, Psychosocial factors at work, Cardiology < INTERNAL MEDICINE, Occupational health, Workplace, MENTAL HEALTH

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

Authors

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*HE and KW made equal contributions to this study.

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Word count: 2,016 words

Abstract

INTRODUCTION: Chronic inflammation may be a mediator for the development of cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders. Meta-analytic associations between work-related psychosocial factors and inflammatory markers have shown that work-related psychosocial factors could affect the flexibility and balance of the immune system. However, few systematic reviews or meta-analyses have investigated the association between work-related psychosocial factors and inflammatory markers. Based on prospective studies, the present investigation will conduct a comprehensive systematic review and meta-analysis of the association between work-related psychosocial factors and inflammatory markers.

METHODS AND ANALYSIS: The systematic review and meta-analysis will include published studies identified from electronic databases (PubMed, EMBASE, PsycINFO, PsycARTICLES, Web of Science and Japan Medical Abstracts Society) according to recommendations of the Meta-analysis of Observational Studies in Epidemiology guideline. Inclusion criteria are studies that did the following: examined associations between work-related psychosocial factors and increased inflammatory markers; used longitudinal or prospective cohort designs; were conducted among workers; provided sufficient data for calculating odds ratios or relative risk with 95% confidence intervals; were published as original articles in English or Japanese; and were published up to the end of 2017. Study selection, data extraction, quality assessment, and statistical syntheses will be conducted by 14 investigators. Any inconsistencies or disagreements will be resolved through discussion. The quality of studies will be evaluated using the Risk of Bias Assessment Tool for Nonrandomized Studies.

ETHICS AND DISSEMINATION: The investigation study will be based on published studies, so ethics approval is not required. The results of this study will be submitted for publication in a scientific peer-reviewed journal. The findings may be useful for assessing risk factors for increased inflammatory markers in the workplace and determining future approaches for preventing CVD, metabolic diseases, and psychotic and neurodegenerative disorders.

TRIAL REGISTRATION NUMBER: PROSPERO CRD42018081553 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=81553).

Strengths and limitations of this study

- This systematic review and meta-analysis will offer comprehensive understanding of the association between work-related psychosocial factors and inflammatory markers.
- The review will include a range of work-related psychosocial factors and focus on inflammatory markers.
- To ensure stronger evidence, the review will include only prospective studies.
- The findings of this review may be useful for assessing chronic inflammation as a risk factor for cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders in the workplace as well as for determining future approaches for preventing CVD, metabolic diseases, and psychotic and neurodegenerative disorders.
- Depending on the results, limitations could be confounding factors that may not have been adjusted for in the selected studies as well as low generalizability.

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,[1-5] effort-reward imbalance,[6] organizational justice,[7-9] and workplace social capital[10]; there is a major focus on work stress.[2] These factors may affect cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders through such mechanisms as prolonged overactivation and dysregulation of the autonomic nervous system and the hypothalamus-pituitary-adrenal cortex axis.[11-13]

Chronic inflammation has been suggested as a potential mediator for the development of CVD, metabolic diseases, and psychotic and neurodegenerative disorders.[14-18] Several studies have reported associations between adverse work-related psychosocial factors and increased levels of inflammatory markers. Inflammatory markers, including C-reactive protein (CRP),[19-24] interleukin-6 (IL-6),[24 25] and tumor necrosis factor (TNF-α), have been implicated in coordinating atherosclerosis.[26] Previous meta-analyses[27 28] 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[27-30] and unemployment[31]; 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[32] 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).[13] These systematic reviews and meta-analyses included cross-sectional studies. However, pooled associations between work-related psychosocial factors and inflammatory markers derived from

prospective studies may provide more reliable evidence.

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

METHODS AND ANALYSIS

Study design

This study protocol for a systematic review and meta-analysis of prospective studies follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guideline.[33] Future findings will be reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.[34] This study protocol was registered with PROSPERO (CRD42018081553).

Eligibility criteria

Participants, exposures, comparisons, and outcomes (PECO) of the studies included in this systematic review and meta-analysis will be defined as follows: (P) inclusion of all workers; (E) presence of adverse psychosocial factors at work; (C) absence of adverse psychosocial factors at work; and (O) increased inflammatory markers. Target participants will all be employees of participating companies. There will be no exclusion criteria related to employment status, job type, or shift type. The study exposures (adverse psychosocial factors at work) will include a range of task and organizational characteristics and work conditions,[35] such as job strain,[1-5] low social support, effort-reward imbalance,[6] organizational injustice,[7-9] and low workplace social capital.[10] Long working hours and shift work will also be included as target exposures. Inflammatory markers will include those investigated in terms of association with psychosocial factors at work in previous studies, including CRP, IL-6, and TNF-α.

Eligibility criteria for selection are the following studies that (1) were

conducted to evaluate associations between psychosocial factors at work and inflammatory markers; (2) used longitudinal or prospective cohort designs; (3) were conducted among workers; (4) provided sufficient data for calculating coefficients of associations between psychosocial factors at work and inflammatory markers (γ, β), odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with standard errors (SEs) or 95% CIs; (5) were published as original articles in English or Japanese; and (6) were published up to the end of 2017.

Information sources, search strategy, and data management

A systematic search of published studies will be conducted using electronic databases: PubMed (MEDLINE), EMBASE, PsycINFO, PsycARTICLES, Web of Science, and the Japan Medical Abstracts Society. Search terms will include words related to the PECO of eligible published studies. The proposed search strategy appears in Appendix 1. All identified studies will be managed in a Microsoft Excel file (WA, US). Before the study selection process, duplicated citations in the Excel file will be excluded by KW. Decisions on all studies will be recorded.

Study selection process

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

Data extraction

Data will be extracted independently from the included studies by 14 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT) working in pairs using a standardized data extraction form. The data will be distributed according to the investigators' capacity. Any discrepancies or inconsistencies in the assessment will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached. The extracted data will include the following: year of publication; country where the study was conducted; number of participants at baseline and in the analysis; sampling framework; participants' demographic characteristics (i.e., mean age, sex proportions, and employment status); length of follow-up; follow-up rate; exposure and comparison variables (adverse psychosocial factors at work); outcome variables (inflammatory markers); number and proportion of participants with increased levels of inflammatory markers or mean scores and variances or standard deviations of markers; and sufficient data for calculating the coefficients (β, γ), ORs, RRs, or HRs with SEs or 95% CIs for the association between adverse psychosocial factors at work and inflammatory markers. If the included studies report multiple measures of association, we will attempt to select measures of association adjusted by demographic variables (e.g., age, sex, education, and marital status). If the studies report measures of association adjusted by lifestyle variables (e.g., smoking, physical activity, and sleep), we will as far as possible extract measures both with and without adjustment for lifestyle variables. To avoid over-adjustment, measures of association adjusted for other adverse psychosocial factors at work or inflammatory markers will not be adopted. Sex-stratified coefficients will be selected if they are the only reported results. Any missing data from the studies will be obtained by contacting the relevant research team.

Assessment of study quality

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

The risk of bias for each domain is classified as low, high, or unclear risk. The number of papers assessed by each investigator will depend on their capacity. Any discrepancies in quality assessment among the investigators will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached.

Data synthesis and statistical methods

The included studies will be statistically synthesized in a meta-analysis to estimate pooled coefficients and 95% CIs, stratified by types of measures of association (β, γ, OR, RR, and HR). If the included studies report ORs, RRs, or HRs, we will calculate log-transformed ORs, RRs, or HRs and determine SEs based on 95% CIs. These parameters will be used in the meta-analysis and for examining publication bias by means of a funnel plot and Egger's test with statistical software, R version 3.4.1.[38 39] We will employ a random-effects model[40] to summarize the results using R version 3.4.1 with the "meta" and "metafor" packages.[41]

For the main analysis, we will synthesize all types of psychosocial factors at work in the random-effects model. The results will be presented in a narrative format if a meta-analysis is not appropriate or possible, e.g., if only two or fewer studies are eligible and included in the study. Heterogeneity will be assessed using the chi-square test with Cochran's Q statistic, which is calculated by I^2 values,[42] assuming that I^2 values of 25%, 50%, and 75% indicate low, medium, and high heterogeneity, respectively.

Subgroup and sensitivity analyses will be conducted to compare the results across subgroups or under specific conditions when sufficient heterogeneity is detected. Major possible grouping characteristics will include types of exposure and outcome, participants' demographic characteristics (e.g., sex, age, employment status, occupational groups), and study quality. Any subgroup differences will be reported, and our findings will be explained by considering these differences. Results with and without adjustment for lifestyle variables will be compared in another sensitivity analysis. If trends are observed between pooled associations and any grouping characteristics, meta-regression will be conducted using the "metareg" function of R. A sensitivity analysis may be conducted for included studies where the RoBANS is classified as low risk. All extracted data and analyzed results will be deposited by the corresponding author and made available for external reviewers and readers upon request.

Patient and public involvement statement

This study will not involve any patients or study participants: this study protocol is for a systematic review and meta-analysis.

Ethics and dissemination

This study does not require ethical approval because the systematic review and meta-analysis will be based on previously published studies. The results will be submitted for publication in a scientific peer-reviewed journal, according to the MOOSE guideline.[34]

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Competing Interests

The authors declare that they have no competing interests.

Strengths and limitations

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

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

Authors' contributions

HE, KW, NK, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, KT, ASh, and AT made substantial contributions to the conception and design of the study, writing the protocol and revising it critically for important intellectual content, and

approving the final version to be published. All authors will be involved in the entire study process (i.e., data extraction, assessment, and synthesis).

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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*)
EMBASE, PsycINFO/ PsycARTICLES, Web of Science	(employe* OR manag* OR colleague* OR worksit* OR “work” OR works* OR work* OR worka* OR worke* OR workg* OR worki* OR workl* OR workp* OR occupant* OR company* OR offic* OR busines* OR workplace) AND (("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)

	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*)
Japan Medical Abstracts Society	(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 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 ソーシャルキャピタル 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 OR 症例対照研究 OR 疫学研究 OR 後向き研究)

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	Sipsma 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	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.		KW	HE	○	×	×

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 #
ADMINISTRATIVE INFORMATION			
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
INTRODUCTION			
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
METHODS			
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 τ)	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.**

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

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

Authors

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Abstract

INTRODUCTION: Chronic inflammation may be a mediator for the development of cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders. Meta-analytic associations between work-related psychosocial factors and inflammatory markers have shown that work-related psychosocial factors could affect the flexibility and balance of the immune system. However, few systematic reviews or meta-analyses have investigated the association between work-related psychosocial factors and inflammatory markers. Based on prospective studies, the present investigation will conduct a comprehensive systematic review and meta-analysis of the association between work-related psychosocial factors and inflammatory markers.

METHODS AND ANALYSIS: The systematic review and meta-analysis will include published studies identified from electronic databases (PubMed, EMBASE, PsycINFO, PsycARTICLES, Web of Science and Japan Medical Abstracts Society) according to recommendations of the Meta-analysis of Observational Studies in Epidemiology guideline. Inclusion criteria are studies that did the following: examined associations between work-related psychosocial factors and increased inflammatory markers; used longitudinal or prospective cohort designs; were conducted among workers; provided sufficient data for calculating odds ratios or relative risk with 95% confidence intervals; were published as original articles in English or Japanese; and were published up to the end of 2017. Study selection, data extraction, quality assessment, and statistical syntheses will be conducted by 14 investigators. Any inconsistencies or disagreements will be resolved through discussion. The quality of studies will be evaluated using the Risk of Bias Assessment Tool for Nonrandomized Studies.

ETHICS AND DISSEMINATION: The investigation study will be based on published studies, so ethics approval is not required. The results of this study will be submitted for publication in a scientific peer-reviewed journal. The findings may be useful for assessing risk factors for increased inflammatory markers in the workplace and determining future approaches for preventing CVD, metabolic diseases, and psychotic and neurodegenerative disorders.

TRIAL REGISTRATION NUMBER: PROSPERO CRD42018081553 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=81553).

Strengths and limitations of this study

- This systematic review and meta-analysis will offer comprehensive understanding of the association between work-related psychosocial factors and inflammatory markers.
- The review will include a range of work-related psychosocial factors and focus on inflammatory markers.
- To ensure stronger evidence, the review will include only prospective studies.
- The findings of this review may be useful for assessing chronic inflammation as a risk factor for cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders in the workplace as well as for determining future approaches for preventing CVD, metabolic diseases, and psychotic and neurodegenerative disorders.
- Depending on the results, limitations could be confounding factors that may not have been adjusted for in the selected studies as well as low generalizability.

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,[1-5] effort-reward imbalance,[6] organizational justice,[7-9] and workplace social capital[10]; there is a major focus on work stress.[2] These factors may affect cardiovascular disease (CVD), metabolic diseases, and psychotic and neurodegenerative disorders through such mechanisms as prolonged overactivation and dysregulation of the autonomic nervous system and the hypothalamus-pituitary-adrenal cortex axis.[11-13]

Chronic inflammation has been suggested as a potential mediator for the development of CVD, metabolic diseases, and psychotic and neurodegenerative disorders.[14-18] Several studies have reported associations between adverse work-related psychosocial factors and increased levels of inflammatory markers. Inflammatory markers, including C-reactive protein (CRP),[19-24] interleukin-6 (IL-6),[24 25] and tumor necrosis factor (TNF-α), have been implicated in coordinating atherosclerosis.[26] Previous meta-analyses[27 28] 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[27-30] and unemployment[31]; 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[32] 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).[13] These systematic reviews and meta-analyses included cross-sectional studies. However, pooled associations between work-related psychosocial factors and inflammatory markers derived from

prospective studies may provide more reliable evidence.

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

METHODS AND ANALYSIS

Study design

This study protocol for a systematic review and meta-analysis of prospective studies follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guideline.[33] Future findings will be reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.[34] This study protocol was registered with PROSPERO (CRD42018081553).

Eligibility criteria

Participants, exposures, comparisons, and outcomes (PECO) of the studies included in this systematic review and meta-analysis will be defined as follows: (P) inclusion of all workers; (E) presence of adverse psychosocial factors at work; (C) absence of adverse psychosocial factors at work; and (O) increased inflammatory markers. Target participants will all be employees of participating companies. There will be no exclusion criteria related to employment status, job type, or shift type. The study exposures (adverse psychosocial factors at work) will include a range of task and organizational characteristics and work conditions,[35] such as job strain,[1-5] low social support, effort-reward imbalance,[6] organizational injustice,[7-9] and low workplace social capital.[10] Long working hours and shift work will also be included as target exposures. Inflammatory markers will include those investigated in terms of association with psychosocial factors at work in previous studies, including CRP, IL-6, and TNF-α.

Eligibility criteria for selection are the following studies that (1) were

conducted to evaluate associations between psychosocial factors at work and inflammatory markers; (2) used longitudinal or prospective cohort designs; (3) were conducted among workers; (4) provided sufficient data for calculating coefficients of associations between psychosocial factors at work and inflammatory markers (γ, β), odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with standard errors (SEs) or 95% CIs; (5) were published as original articles in English or Japanese; and (6) were published up to the end of 2017.

Information sources, search strategy, and data management

A systematic search of published studies will be conducted using electronic databases: PubMed (MEDLINE), EMBASE, PsycINFO, PsycARTICLES, Web of Science, and the Japan Medical Abstracts Society. Search terms will include words related to the PECO of eligible published studies. The proposed search strategy appears in Appendix 1. All identified studies will be managed in a Microsoft Excel file (WA, US). Before the study selection process, duplicated citations in the Excel file will be excluded by KW. Decisions on all studies will be recorded.

Study selection process

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

Data extraction

Data will be extracted independently from the included studies by 14 investigators (HE, KW, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, and KT) working in pairs using a standardized data extraction form. The data will be distributed according to the investigators' capacity. Any discrepancies or inconsistencies in the assessment will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached. The extracted data will include the following: year of publication; country where the study was conducted; number of participants at baseline and in the analysis; sampling framework; participants' demographic characteristics (i.e., mean age, sex proportions, and employment status); length of follow-up; follow-up rate; exposure and comparison variables (adverse psychosocial factors at work); outcome variables (inflammatory markers); number and proportion of participants with increased levels of inflammatory markers or mean scores and variances or standard deviations of markers; and sufficient data for calculating the coefficients (β, γ), ORs, RRs, or HRs with SEs or 95% CIs for the association between adverse psychosocial factors at work and inflammatory markers. If the included studies report multiple measures of association, we will attempt to select measures of association adjusted by demographic variables (e.g., age, sex, education, and marital status). If the studies report measures of association adjusted by lifestyle variables (e.g., smoking, physical activity, and sleep), we will as far as possible extract measures both with and without adjustment for lifestyle variables. To avoid over-adjustment, measures of association adjusted for other adverse psychosocial factors at work or inflammatory markers will not be adopted. Sex-stratified coefficients will be selected if they are the only reported results. Any missing data from the studies will be obtained by contacting the relevant research team.

Assessment of study quality

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

The risk of bias for each domain is classified as low, high, or unclear risk. The number of papers assessed by each investigator will depend on their capacity. Any discrepancies in quality assessment among the investigators will be recorded and the inter-rater reliability determined; such matters will be discussed among all the investigators until consensus is reached.

Data synthesis and statistical methods

The included studies will be statistically synthesized in a meta-analysis to estimate pooled coefficients and 95% CIs, stratified by types of measures of association (β, γ, OR, RR, and HR). If the included studies report ORs, RRs, or HRs, we will calculate log-transformed ORs, RRs, or HRs and determine SEs based on 95% CIs. These parameters will be used in the meta-analysis and for examining publication bias by means of a funnel plot and Egger's test with statistical software, R version 3.4.1.[38 39] We will employ a random-effects model[40] to summarize the results using R version 3.4.1 with the "meta" and "metafor" packages.[41]

For the main analysis, we will synthesize all types of psychosocial factors at work in the random-effects model. The results will be presented in a narrative format if a meta-analysis is not appropriate or possible, e.g., if only two or fewer studies are eligible and included in the study. Heterogeneity will be assessed using the chi-square test with Cochran's Q statistic, which is calculated by I^2 values,[42] assuming that I^2 values of 25%, 50%, and 75% indicate low, medium, and high heterogeneity, respectively.

Subgroup and sensitivity analyses will be conducted to compare the results across subgroups or under specific conditions when sufficient heterogeneity is detected. Major possible grouping characteristics will include types of exposure and outcome, participants' demographic characteristics (e.g., sex, age, employment status, occupational groups), and study quality. Any subgroup differences will be reported, and our findings will be explained by considering these differences. Results with and without adjustment for lifestyle variables will be compared in another sensitivity analysis. If trends are observed between pooled associations and any grouping characteristics, meta-regression will be conducted using the "metareg" function of R. A sensitivity analysis may be conducted for included studies where the RoBANS is classified as low risk. All extracted data and analyzed results will be deposited by the corresponding author and made available for external reviewers and readers upon request.

Patient and public involvement statement

This study will not involve any patients or study participants: this study protocol is for a systematic review and meta-analysis.

Ethics and dissemination

This study does not require ethical approval because the systematic review and meta-analysis will be based on previously published studies. The results will be submitted for publication in a scientific peer-reviewed journal, according to the MOOSE guideline.[34]

Funding

This work is supported by the Work-related Diseases Clinical Research Grant 2016 (160701-01) from the Ministry of Health, Labour and Welfare, Japan. The funder has no role in study design, data extraction and analysis, decision to publish, or preparation of the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

Strengths and limitations

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

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

Authors' contributions

HE, KW, NK, EA, HA, YA, AI, RI, MI, KI, YK, NN, YO, ASa, KT, ASh, and AT made substantial contributions to the conception and design of the study, writing the protocol and revising it critically for important intellectual content, and

approving the final version to be published. All authors will be involved in the entire study process (i.e., data extraction, assessment, and synthesis).

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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*)
EMBASE, PsycINFO/ PsycARTICLES, Web of Science	(employe* OR manag* OR colleague* OR worksit* OR “work” OR works* OR work* OR worka* OR worke* OR workg* OR worki* OR workl* OR workp* OR occupant* OR company* OR offic* OR busines* OR workplace) AND (("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)

	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*)
Japan Medical Abstracts Society	(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 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 ソーシャルキャピタル 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 OR 症例対照研究 OR 疫学研究 OR 後向き研究)

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	Sipsma 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	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.		KW	HE	○	×	×

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 #
ADMINISTRATIVE INFORMATION			
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
INTRODUCTION			
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
METHODS			
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 τ)	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.**

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