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Review article

WHO/ILO work-related burden of disease and injury: Protocol for systematic reviews of exposure to long working hours and of the effect of exposure to long working hours on stroke

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ABSTRACT

Background: The World Health Organization (WHO) and the International Labour Organization (ILO) are developing a joint methodology for estimating the national and global work-related burden of disease and injury (WHO/ILO joint methodology), with contributions from a large network of experts. In this paper, we present the protocol for two systematic reviews of parameters for estimating the number of deaths and disability-adjusted life years from stroke attributable to exposure to long working hours, to inform the development of the WHO/ILO joint methodology.

Objectives: We aim to systematically review studies on occupational exposure to long working hours (called Systematic Review 1 in the protocol) and systematically review and meta-analyse estimates of the effect of long working hours on stroke (called Systematic Review 2), applying the Navigation Guide systematic review

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methodology as an organizing framework, conducting both systematic reviews in tandem and in a harmonized way.

Data sources: Separately for Systematic Reviews 1 and 2, we will search electronic academic databases for potentially relevant records from published and unpublished studies, including Medline, EMBASE, Web of Science, CISDOC and PsychINFO. We will also search electronic grey literature databases, Internet search engines and organizational websites; hand-search reference list of previous systematic reviews and included study records; and consult additional experts.

Study eligibility and criteria: We will include working-age (≥15 years) workers in the formal and informal economy in any WHO and/or ILO Member State, but exclude children (< 15 years) and unpaid domestic workers. For Systematic Review 1, we will include quantitative prevalence studies of relevant levels of occupational exposure to long working hours (i.e. 35–40, 41–48, 49–54 and ≥55 h/week) stratified by country, sex, age and industrial sector or occupation, in the years 2005–2018. For Systematic Review 2, we will include randomized controlled trials, cohort studies, case-control studies and other non-randomized intervention studies with an estimate of the relative effect of a relevant level of long working hours on the incidence of or mortality due to stroke, compared with the theoretical minimum risk exposure level (i.e. 35–40 h/week).

Study appraisal and synthesis methods: At least two review authors will independently screen titles and abstracts against the eligibility criteria at a first stage and full texts of potentially eligible records at a second stage, followed by extraction of data from qualifying studies. At least two review authors will assess risk of bias and the quality of evidence, using the most suited tools currently available. For Systematic Review 2, if feasible, we will combine relative risks using meta-analysis. We will report results using the guidelines for accurate and transparent health estimates reporting (GATHER) for Systematic Review 1 and the preferred reporting items for systematic reviews and meta-analyses guidelines (PRISMA) for Systematic Review 2.

PROSPERO registration number: CRD42017060124.

1. Background

The World Health Organization (WHO) and the International Labour Organization (ILO) are developing a joint methodology for estimating the work-related burden of disease and injury (WHO/ILO joint methodology) (Ryder, 2017). The organizations plan to estimate the numbers of deaths and disability-adjusted life years (DALYs) that are attributable to selected occupational risk factors for the year 2015. The WHO/ILO joint methodology will be based on already existing WHO and ILO methodologies for estimating the burden of disease for selected occupational risk factors (International Labour Organization, 2014; Pruss-Ustun et al., 2017). It will expand existing methodologies with estimation of the burden of several prioritized additional pairs of occupational risk factors and health outcomes. For this purpose, population attributable fractions (Murray et al., 2004) – the proportional reduction in burden from the health outcome achieved by a reduction of exposure to the risk factor to zero – will be calculated for each additional risk factor-outcome pair, and these fractions will be applied to the total disease burden envelopes for the health outcome from the WHO *Global Health Estimates* (World Health Organization, 2017).

The WHO/ILO joint methodology will include a methodology for estimating the burden of stroke from occupational exposure to long working hours if feasible, as one additional prioritized risk factor-outcome pair. To optimize parameters used in estimation models, a systematic review is required of studies on the prevalence of exposure to long working hours ('Systematic Review 1'), as well as a second systematic review and meta-analysis of studies with estimates of the effect of exposure to long working hours on stroke ('Systematic Review 2'). In the current paper, we present the protocol for these two systematic reviews in parallel to presenting systematic review protocols on other additional risk factor-outcome pairs elsewhere (Hulshof et al., submitted; John et al., submitted; Li et al., accepted; Mandrioli et al., in press; Pachito et al., submitted; Rugulies et al., submitted; Teixeira et al., submitted; Tenkate et al., submitted). To our knowledge, this is the first systematic review protocol of its kind. The WHO/ILO joint estimation methodology and the burden of disease estimates are separate from these systematic reviews, and they will be described and reported elsewhere.

We refer separately to Systematic Reviews 1 and 2, because the two systematic reviews address different objectives and therefore require different methodologies. The two systematic reviews will, however, be harmonized and conducted in tandem. This will ensure that – in the later development of the methodology for estimating the burden of disease from this risk factor–outcome pair – the parameters on the risk factor prevalence are optimally matched with the parameters from studies on the effect of the risk factor on the designated outcome. The findings from Systematic Reviews 1 and 2 will be reported in two distinct journal articles. For all four protocols in the series with long working hours as the risk factor, one Systematic Review 1 will be published.

1.1. Rationale

In the context of growing size and aging of the world's population, the global burden of stroke is increasing dramatically (Mukherjee and Patil, 2011), with 16.9 million people suffering a stroke each year and a global incidence of 258/100,000/year (Bejot et al., 2016). To consider the feasibility of estimating the burden of stroke due to exposure to long working hours, and to ensure that potential estimates of burden of disease are reported in adherence with the guidelines for accurate and transparent health estimates reporting (GATHER) (Stevens et al., 2016), WHO and ILO require a systematic review of studies on the prevalence of relevant levels of exposure to long working hours (Systematic Review 1), as well as a systematic review and meta-analysis of studies with estimates of the relative effect of exposure to long work hours on the incidence of and mortality from stroke, compared with the theoretical minimum risk exposure level (Systematic Review 2). The theoretical minimum risk exposure level is the exposure level that would result in the lowest possible population risk, even if it is not feasible to attain this exposure level in practice (Murray et al., 2004). These data and effect estimates should be tailored to serve as parameters for estimating the burden of stroke from exposure to long working hours in the WHO/ILO joint methodology.

Several studies have suggested a potential association of exposure to long working hours with increased risks of cardiovascular diseases in general (Virtanen et al., 2012) and coronary heart disease and stroke specifically (Kang et al., 2012; Kivimaki et al., 2015a). The only previous systematic review on the effect of exposure to long working hours on stroke that we are aware of was published in 2015, covered evidence and data up to August 2014 and included one published study and several unpublished studies (Kivimaki et al., 2015a). It found a dose–response association, with relative risk estimates for stroke of 1.10

(95% CI 0.94–1.28; p = 0.24) for study participants working 41–48 h/week; 1.27 (1.03–1.56; p = 0.03) for those working 49–54 h/week; and 1.33 (1.11–1.61; p = 0.002) for those working ≥55 h/week, compared with participants working standard hours (p for trend < 0.0001). However, our Systematic Review 1 will be the – to the best of our knowledge – first systematic review of prevalence studies of exposure to long working hours, and Systematic Review 2 will expand the scope of the existing systematic review (Kivimaki et al., 2015a) by covering evidence from studies published up to May 2018.

Work in the informal economy may lead to different exposures and exposure effects than does work in the formal economy. The informal economy is defined as "all economic activities by workers and economic units that are – in law or in practice – not covered or insufficiently covered by formal arrangements," but excluding "illicit activities, in particular the provision of services or the production, sale, possession or use of goods forbidden by law, including the illicit production and trafficking of drugs, the illicit manufacturing of and trafficking in firearms, trafficking in persons, and money laundering, as defined in the relevant international treaties" (104th International Labour Conference, 2015). Therefore, we consider in both systematic reviews the formality of the economy reported in included studies.

1.2. Description of the risk factor

The definition of the risk factor, the risk factor levels and the theoretical minimum risk exposure level are presented in Table 1. Long working hours are defined as any working hours (both in main and secondary jobs) exceeding standard working hours, i.e. working hours of ≥41 h/week. Based on results from earlier studies on long working hours and health endpoints (Kivimaki et al., 2015a; Kivimaki and Kawachi, 2015; Kivimaki et al., 2015b; Virtanen et al., 2012), the preferred four exposure level categories for our review are 35–40, 41–48, 49–54 and ≥55 h/week, allowing calculations of potential dose-response associations. If the studies provide the preferred exposure categories, we will use the preferred exposure categories, if they provide other exposure categories, we will use the other exposure categories, as long as exposure exceeds 40 h/week.

The theoretical minimum risk exposure is standard working hours defined as 35–40 h/week. We acknowledge that it is possible that the theoretical minimum risk exposure might be lower than standard working hours, but we have to exclude working hours < 35 h/week, because studies indicate that a proportion of individuals working less than standard hours do so because of existing health problems (Kivimaki et al., 2015c; Virtanen et al., 2012). Thus, this exposure concerns full-time workers in the formal and informal economy. In other words, individuals working less than standard hours might belong to a health-selected group or a group concerned with family care and therefore cannot serve as comparators. Consequently, if a study used as the reference group individuals working less than standard hours or a combination of individuals working standard hours and individuals working less than standard hours, it will be excluded from the review and meta-analysis. The category 35–40 h/week is the reference group used in many large studies and previous systematic reviews (Bejot et al., 2016; Stevens et al., 2016; Virtanen et al., 2012). Since the theoretical minimum risk exposure level is usually set empirically based on the causal epidemiological evidence, we will change the assumed level as evidence suggests.

If several studies report exposure levels differing from the standard levels we define here, then, if possible, we will convert the reported levels to the standard levels and, if not possible, we will report analyses on these alternate exposure levels as supplementary information in the systematic reviews. In the latter case, our protocol will be updated to reflect our new analyses.

Table 2
ICD-10 codes and disease and health problems covered by the WHO burden of disease category *II.H.4 Stroke* and their inclusion in this review.

ICD-10 code	Disease or health problem	Included in this review
I60	Subarachnoid haemorrhage	Yes
I61	Intracerebral haemorrhage	Yes
I62	Other nontraumatic intracranial haemorrhage	Yes
I63	Cerebral infarction	Yes
I64	Stroke, not specified as haemorrhage or infarction	Yes
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	Yes
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction	Yes
I67	Other cerebrovascular diseases	Yes
I68	Cerebrovascular disorders in diseases classified elsewhere	Yes
I69	Sequelae of cerebrovascular disease	Yes

1.3. Description of the outcome

The WHO *Global Health Estimates* group outcomes into standard burden of disease categories (World Health Organization, 2017), based on standard codes from the *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10) (World Health Organization, 2015). The relevant WHO *Global Health Estimates* category for this systematic review is "*II.H.4 Stroke*" (World Health Organization, 2017). In line with the WIIO *Global IHealth Estimates*, we define the health outcome covered in Systematic Review 2 as stroke, defined as conditions with ICD-10 codes I60 to I69 (Table 2). We will consider prevalence of, incidence of and mortality from stroke. Table 2 presents for each disease or health problem included in the WHO *Global Health Estimates* category its inclusion in this review. This review covers all the relevant WHO *Global Health Estimates* categories.

1.4. How the risk factor may impact the outcome

Fig. 1 presents the logic model for our systematic review of the causal relationship between exposure to long working hours and stroke. This logic model is an *a priori*, process-oriented one (Rehfuess et al., 2017) that seeks to capture the complexity of the risk factor–outcome causal relationship (Anderson et al., 2011).

Based on knowledge of previous research on long working hours and stroke, we assume that the effect of long working hours on stroke could be modified by country (or WHO region), sex, age, industrial sector, occupation, and formality of the economy. Confounding should

Table 1
Definitions of the risk factor, risk factor levels and the minimum risk exposure level.

	Definition
Risk factor	Long working hours (including those spent in secondary jobs), defined as working hours > 40 h/week, i.e. working hours exceeding standard working hours (35–40 h/week).
Risk factor levels	Preferable exposure categories are 35–40, 41–48, 49–54 and ≥55 h/week. However, whether we can use these categories will depend on the information provided in the studies. If the preferable exposure categories are not available, we will use the exposure categories provided by the studies as long as these exposure categories exceed 40 h/week.
Theoretical minimum risk exposure level	Standard working hours defined as working hours of 35–40 h/week.

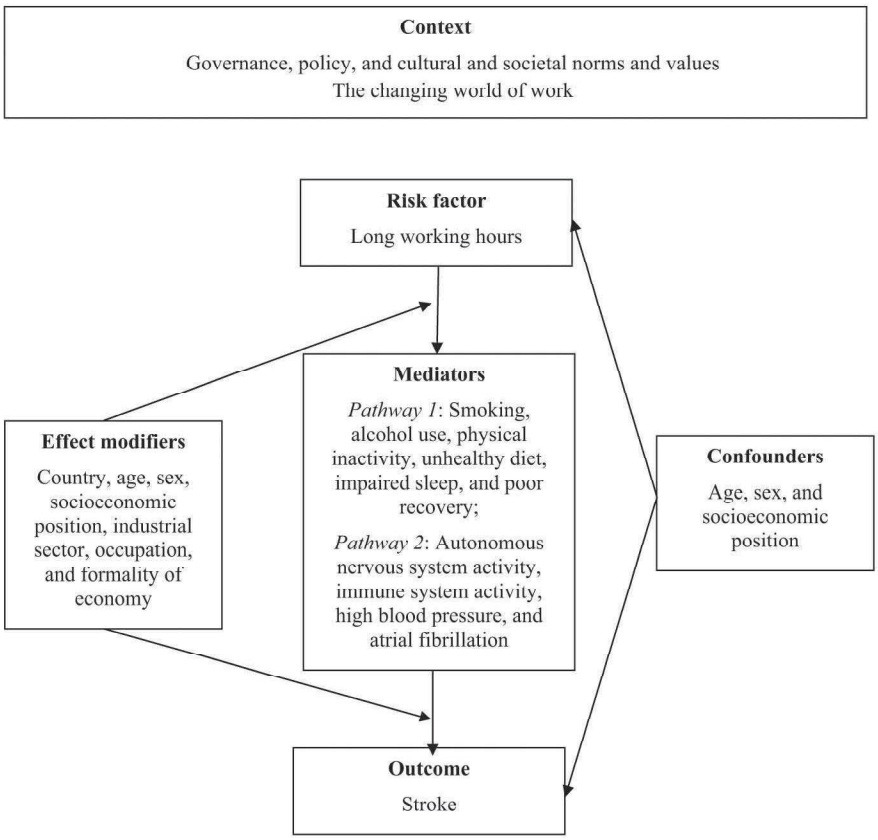

Fig. 1. Logic model of the possible causal relationship between long working hours and stroke.

be considered by, at least, age, sex, and an indicator of socioeconomic position (e.g. income, education or occupational grade). Exceptions are accepted for studies whose study samples were homogenous (such as men only) or who conducted subgroup analyses (such as sex-specific analyses).

Several variables may mediate the effects of this exposure on disease risk through two major pathways. The first one concerns behavioural responses that result in an increase in health-adverse behaviours, such as tobacco smoking, high alcohol consumption, unhealthy diet and physical inactivity. These behaviours are established risk factors of stroke (Taris et al., 2011; Virtanen et al., 2015). Moreover, impaired sleep and poor recovery resulting from this exposure increase the risk of stroke (Sonnentag et al., 2017; Virtanen et al., 2009). Chronic psychosocial stress responses define a second pathway mediating the effects of exposure on stroke. According to established physiological evidence, recurrent high effort (exposure) results in continued activation of the autonomic nervous/immune systems and associated stress axes, the sympatho-adrenal medullary and the hypothalamic-pituitary adrenal axes, with excessive release of stress hormones (adrenalin, noradrenalin and cortisol) (Chandola et al., 2010; Jarczok et al., 2013; Nakata, 2012). In the longer run, this recurrent activation exceeds the regulatory capacity of the cardiovascular system, thus triggering functional dysregulations (e.g. sustained high blood pressure) and structural lesions (e.g. atherogenesis in coronary vessels) (Kivimaki and Steptoe, 2018).

Working long hours may have a direct influence on stroke through a physiological response. In fact, chronic psychosocial stress was shown to activate structures in the prefrontal cortex and limbic system stimulating abnormal levels of stress hormones, as well as arousing the sympathetic and vagal tone via the hypothalamic-pituitary-adrenal and sympatho-adrenal medullary axes (Steptoe and Kivimaki, 2012, 2013). These reactions may alter a range of endocrine, immune and inflammatory biomarkers with adverse effects on the cardiovascular system, such as high blood pressure (Hayashi et al., 1996), other cardiometabolic risk factors (McEwen, 1998a, 1998b) and growth of carotid intima-media thickness (Krause et al., 2009).

2. Objectives

1. Systematic Review 1: To systematically review quantitative studies of any design on the prevalence of relevant levels of exposure to long working hours in the years 2005–2018 among the working-age population, disaggregated by country, sex, age and industrial sector or occupation. Systematic Review 1 will be conducted in a co-ordinated fashion across all four review groups that examine long working hours with regard to health endpoints (i.e. ischaemic heart disease (Li et al., in press), stroke, depression (Rugulies et al., submitted) and alcohol use (Pachito et al., submitted), led by GS.
2. Systematic Review 2: To systematically review and meta-analyse randomized controlled trials, cohort studies, case-control studies and other non-randomized intervention studies including estimates of the relative effect of a relevant level of occupational exposure to long working hours on stroke in any year among the working-age population, compared with the minimum risk exposure level of 35–40 h/week.

3. Methods

We will apply the *Navigation Guide* (Woodruff and Sutton, 2014) methodology for systematic reviews in environmental and occupational health as our guiding methodological framework, wherever feasible. The guide applies established systematic review methods from clinical medicine, including standard Cochrane Collaboration methods for systematic reviews of interventions, to the field of environmental and occupational health to ensure systematic and rigorous evidence synthesis on environmental and occupational risk factors that reduces bias

and maximizes transparency (Woodruff and Sutton, 2014). The need for further methodological development and refinement of the relatively novel *Navigation Guide* has been acknowledged (Woodruff and Sutton, 2014).

Systematic Review 1 may not map well to the *Navigation Guide* framework (Fig. 1 on page 1009 in (Lam et al., 2016c)), which is tailored to hazard identification and risk assessment. Nevertheless, steps 1–6 for the stream on human data can be applied to systematically review exposure to risk factors. Systematic Review 2 maps more closely to the *Navigation Guide* framework, and we will conduct steps 1–6 for the stream on human data, but not conduct any steps for the stream on non-human data, although we will briefly summarize narratively the evidence from non-human data that we are aware of.

We have registered the protocol in PROSPERO under CRD42017060124. This protocol adheres with the preferred reporting items for systematic review and meta-analysis protocols statement (PRISMA-P) (Moher et al., 2015; Shamseer et al., 2015), with the abstract adhering with the reporting items for systematic reviews in journal and conference abstracts (PRISMA-A) (Beller et al., 2013). Any modification of the methods stated in the present protocol will be registered in PROSPERO and reported in the systematic review itself. Systematic Review 1 will be reported according to the GATHER guidelines (Stevens et al., 2016), and Systematic Review 2 will be reported according to the preferred reporting items for systematic review and meta-analysis statement (PRISMA) (Liberati et al., 2009). Our reporting of the parameters for estimating the burden of stroke from occupational exposure to long working hours in the systematic review will adhere with the requirements of the GATHER guidelines (Stevens et al., 2016), because the WHO/ILO burden of disease estimates that may be produced consecutive to the systematic review must also adhere to these reporting guidelines.

3.1. Systematic Review 1

3.1.1. Eligibility criteria

The population, exposure, comparator and outcome (PECO) criteria (Liberati et al., 2009) are described below.

3.1.1.1. Types of populations. We will include studies of the working-age population (≥15 years) in the formal and informal economy. Studies of children (aged < 15 years) and unpaid domestic workers will be excluded. Participants residing in any WHO and/or ILO Member State and any industrial setting or occupation will be included. We note that occupational exposure to long working hours may potentially have further population reach (e.g. across generations for workers of reproductive age) and acknowledge that the scope of our systematic reviews will not be able capture these populations and impacts on them. Appendix A provides a complete, but briefer overview of the PECO criteria.

3.1.1.2. Types of exposures. We will include studies that define long working hours in accordance with our standard definition (Table 1). We will prioritize measures of the total number of hours worked, including in both of: main and secondary jobs, self-employment and salaried employment and informal and formal jobs. Cumulative exposure may be the most relevant exposure metric in theory, but we will here prioritize a non-cumulative exposure metric in practice, because we believe that global exposure data on agreed cumulative exposure measures do not currently exist. We will include all studies where long working hours were measured, whether objectively (e.g. by means of time recording technology), or subjectively, including studies that used measurements by experts (e.g. scientists with subject matter expertise) and self-reports by the worker or workplace administrator or manager. If a study presents both objective and subjective measurements, then we will prioritize objective measurements. We will include studies with measures from any data source, including registry data.

We will include studies on the prevalence of occupational exposure to the risk factor, if it is disaggregated by country, sex (two categories: female, male), age group (ideally in 5-year age bands, such as 20–24 years) and industrial sector (e.g. *International Standard Industrial Classification of All Economic Activities, Revision 4* [ISIC Rev. 4]) (United Nations, 2008) or occupation (as defined, for example, by the *International Standard Classification of Occupations 1988* [ISCO-88] (International Labour Organization, 1987) or *2008* [ISCO-08] (International Labour Organization, 2012)). Criteria may be revised in order to identify optimal data disaggregation to enable subsequent estimation of the burden of disease.

We shall include studies with exposure data for the years 2005 to 31st May 2018. For optimal modelling of exposure, WHO and ILO require exposure data up to 2018, because recent data points help better estimate time trends, especially where data points may be sparse. The additional rationale for this data collection window is that the WHO and ILO aim to estimate burden of disease in the year 2015, and we believe that the lag time from exposure to outcome will not exceed 10 years; so in their models, the organizations can use the exposure data from as early as 2005 to determine the burden of stroke 10 years later in 2015. To make a conclusive judgment on the best lag time to apply in the model, we will summarize the existing body of evidence on the lag time between exposure to long working hours and stroke in the review.

Both objective and subjective measures will be included. If both subjective and objective measures are presented, then we will prioritize objective ones. Studies with measures from any data source, including registries, will be eligible. The exposure parameter should match the one used in Systematic Review 2 or can be converted to match it.

3.1.1.3. Types of comparators. There will be no comparator, because we will review risk factor prevalence only.

3.1.1.4. Types of outcomes. Exposure to the occupational risk factor (i.e. long working hours).

3.1.1.5. Types of studies. This systematic review will include quantitative studies of any design, including cross-sectional studies. These studies must be representative of the relevant industrial sector, relevant occupational group or the national population. We will exclude qualitative, modelling, and case studies, as well as non-original studies without quantitative data (e.g. letters, commentaries and perspectives).

Study records written in any language will be included. If a study record is written in a language other than those spoken by the authors of this review or those of other reviews (Hulshof et al., submitted; John et al., submitted; Li et al., accepted; Mandrioli et al., in press; Pachito et al., submitted; Rugulies et al., submitted; Teixeira et al., submitted; Tenkate et al., submitted) in the series (i.e. Arabic, Bulgarian, Chinese, Danish, Dutch, English, French, Finnish, German, Hungarian, Italian, Japanese, Norwegian, Portuguese, Russian, Spanish and Swedish), it will be translated into English. Published and unpublished studies will be included.

Studies conducted using unethical practices will be excluded from the review.

3.1.1.6. Types of effect measures. We will include studies with a measure of the prevalence of a relevant level of exposure to long working hours.

3.1.2. Information sources and search

3.1.2.1. Electronic academic databases. We (DG, JP and GS) will at a minimum search the following seven electronic academic databases:

1. Ovid Medline with Daily Update (2005 to 31st May 2018).
2. PubMed (2005 to 31st May 2018).

3. EMBASE (2005 to 31st May 2018).
4. Scopus (2005 to 31st May 2018).
5. Web of Science (2005 to 31st May 2018).
6. CISDOC (2005 to 31st May 2012).
7. PsychInfo (2005 to 31st May 2018).

The Ovid Medline search strategy for Systematic Review 1 is presented in Appendix B. We will perform searches in electronic databases operated in the English language using a search strategy in the English language. Consequently, study records that do not report essential information (i.e. title and abstract) in English will not be captured. We will adapt the search syntax to suit the other electronic academic and grey literature databases. When we are nearing completion of the review, we will search the PubMed database for the most recent publications (e.g., e-publications ahead of print) over the last six months. Any deviation from the proposed search strategy in the actual search strategy will be documented.

3.1.2.2. Electronic grey literature databases. AD, DG, JP, and GS will at a minimum search the two following electronic academic databases:

1. OpenGrey (http://www.opengrey.eu/)
2. Grey Literature Report (http://greylit.org/).

3.1.2.3. Internet search engines. We (AD, DG, JP and GS) will also search the Google (www.google.com/) and GoogleScholar (www.google.com/scholar/) Internet search engines and screen the first 100 hits for potentially relevant records.

3.1.2.4. Organizational websites. The websites of the following six international organizations and national government departments will be searched by AD, DG, JP and GS:

1. International Labour Organization (www.ilo.org/).
2. World Health Organization (www.who.int).
3. European Agency for Safety and Health at Work (https://osha.europa.eu/en).
4. Eurostat (www.ec.europa.eu/eurostat/web/main/home).
5. China National Knowledge Infrastructure (http://www.cnki.net/).
6. Finnish Institute of Occupational Health (https://www.ttl.fi/en/).
7. United States National Institute of Occupational Safety and Health (NIOSH) of the United States of America, using the NIOSH data and statistics gateway (https://www.cdc.gov/niosh/data/).

3.1.2.5. Hand-searching and expert consultation. AD, DG, JP, and GS will hand-search for potentially eligible studies in:

- Reference list of previous systematic reviews.
- Reference list of all study records of all included studies.
- Study records published over the past 24 months in the three peer-reviewed academic journals from which we obtain the largest number of included studies.
- Study records that have cited an included study record (identified in Web of Science citation database).
- Collections of the review authors.

Additional experts will be contacted with a list of included studies and study records, with the request to identify potentially eligible additional ones.

3.1.3. Study selection

Study selection will be carried out with Covidence (Babineau, 2014; Covidence systematic review software) and/or the Rayyan Systematic Reviews Web App (Ouzzani et al., 2016). All study records identified in the search will be downloaded and duplicates will be identified and deleted. Afterwards, at least two review authors (out of: BAE, DG, JP and ES), working in pairs, will independently screen against eligibility criteria titles and abstracts (step 1) and then full texts of potentially relevant records (step 2). A third review author (AD, LM or GS) will resolve any disagreements between the pairs of study selectors. If a study record identified in the literature search was authored by a review author assigned to study selection or if an assigned review author was involved in the study, then the record will be re-assigned to another review author for study selection. In the systematic review, we will document the study selection in a flow chart, as per GATHER guidelines (Stevens et al., 2016).

3.1.4. Data extraction and data items

A data extraction form will be developed and piloted until there is convergence and agreement among data extractors. At a minimum, two review authors (out of: BAE, ES and LMH) will independently extract the data on exposure to long working hours, disaggregated by country, sex, age and industrial sector or occupation. A third review author (GS) will resolve conflicting extractions. At a minimum, we will extract data on study characteristics (including study authors, study year, study country, participants, exposure and outcome), study design (including study type and measurements of the risk factor), risk of bias (including missing data, as indicated by response rate and other measures) and study context. The estimates of the proportion of the population exposed to the occupational risk factor from included studies will be entered into and managed with, the Review Manager, Version 5.3 (RevMan 5.3) (2014) or DistillerSR (EvidencePartner, 2017) softwares.

We will also extract data on potential conflict of interest in included studies, including the financial disclosures and funding sources of each author and their affiliated organization. We will use a modification of a previous method to identify and assess undisclosed financial interests (Forsyth et al., 2014). Where no financial disclosure/conflict of interest is provided, we will search declarations of interest both in other records from this study published in the 36 months prior to the included study record and in other publicly available repositories (Drazen et al., 2010a; Drazen et al., 2010b).

We will request missing data from the principal study author by email or phone, using the contact details provided in the principal study record. If no response is received, we will follow up twice via email, at two and four weeks.

3.1.5. Risk of bias assessment

Generally agreed methods (i.e. framework plus tool) for assessing risk of bias do not exist for systematic reviews of input data for health estimates (The GATHER Working Group, 2016), for burden of disease studies, of prevalence studies in general (Munn et al., 2014), and those of prevalence studies of occupational and/or environmental risk factors specifically (Krauth et al., 2013; Mandrioli and Silbergeld, 2016; Vandenberg et al., 2016). None of the five standard risk of bias assessment methods in occupational and environmental health systematic reviews (Rooney et al., 2016) is applicable to assessing prevalence studies. The *Navigation Guide* does not support checklist approaches, such as (Hoy et al., 2012; Munn et al., 2014), for assessing risk of bias in prevalence studies.

We will use a modified version of the *Navigation Guide* risk of bias tool (Lam et al., 2016c) that we developed specifically for Systematic Review 1 (Appendix C). We will assess risk of bias on the levels of the individual study and the entire body of evidence. As per our preliminary tool, we will assess risk of bias along five domains: (i) selection bias; (ii) performance bias; (iii) misclassification bias; (iv) conflict of interest; and (v) other biases. Risk of bias will be: "low"; "probably low"; "probably high"; "high" or "not applicable". To judge the risk of bias in each domain, we will apply our *a priori* instructions (Appendix C).

All risk of bias assessors (BE, DG, ES, LM and GS) will trial the tool until they synchronize their understanding and application of each risk of bias domain, considerations and criteria for ratings. At least two

study authors (out of: BE, DG, ES, and LM) will then independently judge the risk of bias for each study by outcome, and a third author (GS) will resolve any conflicting judgments. We will present the findings of our risk of bias assessment for each eligible study in a standard 'Risk of bias' table (Higgins et al., 2011). Our risk of bias assessment for the entire body of evidence will be presented in a standard 'Risk of bias summary' figure (Higgins et al., 2011).

3.1.6. Synthesis of results

We will neither produce any summary measures, nor synthesise the evidence quantitatively. The included evidence will be presented in what could be described as an 'evidence map'. All included data points from included studies will be presented, together with meta-data on the study design, number of participants, characteristics of population, setting, and exposure measurement of the data point.

3.1.7. Quality of evidence assessment

There is no agreed method for assessing quality of evidence in systematic reviews of the prevalence of occupational and/or environmental risk factors. We will adopt/adapt from the latest *Navigation Guide* instructions for grading (Lam et al., 2016c), including criteria (Appendix D). We will downgrade for the following five reasons from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach: (i) risk of bias; (ii) inconsistency; (iii) indirectness; (iv) imprecision; and (v) publication bias (Guyatt et al., 2011; Schünemann et al., 2011). We will grade the evidence, using the three *Navigation Guide* quality of evidence ratings: "high", "moderate" and "low" (Lam et al., 2016c). Within each of the relevant reasons for downgrading, we will rate any concern per reason as "none", "serious" or "very serious". We will start at "high" for non-randomized studies and will downgrade for no concern by nil, for a serious concern by one grade (−1), and for a very serious concern by two grades (−2). We will not up-grade or down-grade the quality of evidence for the three other reasons normally considered in GRADE assessments (i.e. large effect, dose-response and plausible residual confounding and bias), because we consider them irrelevant for prevalence estimates.

All quality of evidence assessors (BAE, ES, LMH and DG) will trial the application of our instructions and criteria for quality of evidence assessment until their understanding and application is synchronized. At least two review authors (ES and LMH) will independently judge the quality of evidence for the entire body of evidence by outcome. A third review author (GS) will resolve any conflicting judgments. In the systematic review, for each outcome, we will present our assessments of the risk for each GRADE domain, as well as an overall GRADE rating.

3.1.8. Strength of evidence assessment

To our knowledge, no agreed method exists for rating strength of evidence in systematic reviews of prevalence studies. We (AD and GS) will rate the strength of the evidence for use as input data for estimating national-level exposure to the risk factor. Our rating will be based on a combination of the following four criteria: (i) quality of the entire body of evidence; (ii) population coverage of evidence (WHO regions and countries); (iii) confidence in the entire body of evidence; and (iv) other compelling attributes of the evidence that may influence certainty. We will rate the strength of the evidence as either "potentially sufficient" or "potentially inadequate" for use as input data (Appendix E).

3.2. Systematic Review 2

3.2.1. Eligibility criteria

The PECO (Liberati et al., 2009) criteria are described below.

3.2.1.1. Types of populations. We will include studies of the working-age population (≥15 years) in the formal and informal economy. Studies of children (aged < 15 years) and unpaid domestic workers will be excluded. Participants residing in any WHO and/or ILO Member State and any industrial setting or occupational group will be included. We note that occupational exposure to long working hours may potentially have further population reach (e.g. across generations for workers of reproductive age) and acknowledge that the scope of our systematic reviews will not be able capture these populations and impacts on them. Appendix F provides a complete, but briefer overview of the PECO criteria.

3.2.1.2. Types of exposures. We will include studies that define long working hours in accordance with our standard definition (Table 1). We will again prioritize measures of the total number of hours worked, including in both of: main and secondary jobs, self-employment and salaried employment and informal and formal jobs. We will include all studies where long working hours were measured, whether objectively (e.g. by means of time recording technology), or subjectively, including studies that used measurements by experts (e.g. scientists with subject matter expertise) and self-reports by the worker or workplace administrator or manager. If a study presents both objective and subjective measurements, then we will prioritize objective measurements. We will include studies with measures from any data source, including registry data.

3.2.1.3. Types of comparators. The included comparator will be participants exposed to the theoretical minimum risk exposure level (Table 1). We will exclude all other comparators.

3.2.1.4. Types of outcomes. We will include studies that define stroke in accordance with our standard definition of this outcome (Table 2). Eligible measurements must include a diagnosis of stroke that is well documented by administrative data or imaging. Measurements by questionnaire only will be excluded.

We will include both first-ever stroke and no record of stroke treatment > 10 years before baseline. Recurrent strokes will be excluded.

The following measurements of stroke will be regarded as eligible:

i) Diagnosis by a physician with imaging.
ii) Hospital discharge records.
iii) Other relevant administrative data (e.g. records of sickness absence or disability).
iv) Medically certified cause of death.

All other measure will be excluded from this systematic review.

Only objective measurements of stroke will be eligible, and subjective stroke measurements will be ineligible.

3.2.1.5. Types of studies. We will include studies that investigate the effect of long working hours on stroke for any years. Eligible study designs will be randomized controlled trials (including parallel-group, cluster, cross-over and factorial trials), cohort studies (both prospective and retrospective), case-control studies and other non-randomized intervention studies (including quasi-randomized controlled trials, controlled before-after studies and interrupted time series studies). We included a broader set of observational study designs than is commonly included, because a recent augmented Cochrane Review of complex interventions identified valuable additional studies using such a broader set of study designs (Arditi et al., 2016). As we have an interest in quantifying risk and not in qualitative assessment of hazard (Barroga and Kojima, 2013), we will exclude all other study designs (e.g. uncontrolled before-and-after, cross-sectional, qualitative, modelling, case and non-original studies).

Records published in any year and any language will be included. Again, the search will be conducted using English language terms, so that records published in any language that present essential information (i.e. title and abstract) in English will be included. If a record is written in a language other than those spoken by the authors of this

review or those of other reviews in the series (Hulshof et al., submitted; John et al., submitted; Li et al., accepted; Mandrioli et al., in press; Pachito et al., submitted; Rugulies et al., submitted; Teixeira et al., submitted; Tenkate et al., submitted), then the record will be translated into English. Published and unpublished studies will be included. Studies conducted using unethical practices will be excluded.

3.2.1.6. Types of effect measures. We will include measures of the relative effect of a relevant level of long working hours on the risk of developing or dying from stroke, compared with the theoretical minimum risk exposure level. Effect estimates of prevalence measures only will be excluded. We will include relative effect measures such as risk ratios and odds ratios for mortality measures and hazard ratios for incidence measures (e.g. developed or died from stroke). Measures of absolute effects will be excluded (e.g. mean differences in risks or odds). Measures of absolute effects (e.g. mean differences in risks or odds) will be converted into relative effect measures, but if conversion is impossible, they will be excluded. To ensure comparability of effect estimates and facilitate meta-analysis, if a study presents an odds ratio, then we will convert it into a risk ratio, if possible, using the guidance provided in the Cochrane Collaboration's handbook for systematic reviews of interventions (Higgins and Green, 2011).

As shown in our logic model (Fig. 1), we *a priori* consider the following variables to be potential effect modifiers of the effect of long working hours on stroke: country, age, sex, industrial sector, occupational group and formality of employment. We consider age, sex, working and employment conditions, and socio-economic position to be potential confounders. Potential mediators are: autonomous nervous system activity, immune system activity, smoking, alcohol use, physical inactivity, unhealthy diet, impaired sleep, poor recovery, high blood pressure, and atrial fibrillation.

If a study presents estimates for the effect from two or more alternative models that have been adjusted for different variables, then we will systematically prioritize the estimate from the model that we consider best adjusted, applying the lists of confounders and mediators identified in our logic model (Fig. 1). We will prioritize estimates from models adjusted for more potential confounders over those from models adjusted for fewer. For example, if a study presents estimates from a crude, unadjusted model (Model A), a model adjusted for one potential confounder (Model B) and a model adjusted for two potential confounders (Model C), then we will prioritize the estimate from Model C. We will prioritize estimates from models unadjusted for mediators over those from models that adjusted for mediators, because adjustment for mediators can introduce bias. For example, if Model A has been adjusted for two confounders, and Model B has been adjusted for the same two confounders and a potential mediator, then we will choose the estimate from Model A. We prioritize estimates from models that can adjust for time-varying confounders that are at the same time also mediators, such as marginal structural models (Pega et al., 2016), over estimates from models that can only adjust for time-varying confounders, such as fixed-effects models (Gunasekara et al., 2014), over estimates from models that cannot adjust for time-varying confounding. If a study presents effect estimates from two or more potentially eligible models, then we will explain specifically why we prioritized the selected model.

3.2.2. Information sources and search

3.2.2.1. Electronic academic databases. At a minimum, we (AD, DG, JP and GS) will search the eight following electronic academic databases:

1. International Clinical Trials Register Platform (to May 31st 2018).
2. Ovid MEDLINE with Daily Update (1946 to May 31st 2018).
3. PubMed (1946 to May 31st 2018).
4. EMBASE (1947 to May 31st 2018).
5. Scopus (1788 to May 31st 2018).
6. Web of Science (1945 to May 31st 2018).
7. CISDOC (1901 to 2012).
8. PsychInfo (1880 to May 31st 2018).

The Ovid Medline search strategy for Systematic Review 2 is presented in Appendix G. To identify studies on stroke, we have adopted or adapted several search terms or strings used in a recent Cochrane Review on Cerebrolysin for acute ischaemic stroke (Ziganshina et al., 2016). We will perform searches in electronic databases operated in the English language using a search strategy in the English language. We (GS, DG and JP) will adapt the search syntax to suit the other electronic academic and grey literature databases. When we are nearing completion of the review, we will search the PubMed database for the most recent publications (e.g., e-publications ahead of print) over the last six months. Any deviation from the proposed search strategy in the actual search strategy will be documented.

3.2.2.2. Electronic grey literature databases. At a minimum, we (AD, DG, JP and GS) will search the two following two electronic academic databases:

1. OpenGrey (http://www.opengrey.eu/)
2. Grey Literature Report (http://greylit.org/).

3.2.2.3. Internet search engines. We (AD, DG, JP and GS) will also search the Google (www.google.com/) and GoogleScholar (www.google.com/scholar/) Internet search engines and screen the first 100 hits for potentially relevant records.

3.2.2.4. Organizational websites. The websites of the seven following international organizations and national government departments will be searched for both systematic reviews by AD, DG, JP and GS:

1. International Labour Organization (www.ilo.org/).
2. World Health Organization (www.who.int).
3. European Agency for Safety and Health at Work (https://osha.europa.eu/en).
4. Eurostat (www.ec.europa.eu/eurostat/web/main/home).
5. China National Knowledge Infrastructure (http://www.cnki.net/).
6. Finnish Institute of Occupational Health (https://www.ttl.fi/en/).
7. United States National Institute of Occupational Safety and Health (NIOSH) of the United States of America, using the NIOSH data and statistics gateway (https://www.cdc.gov/niosh/data/).

3.2.2.5. Hand-searching and expert consultation. We (AD, DG, JP and GS) will hand-search for potentially eligible studies in:

- Reference list of previous systematic reviews.
- Reference list of all included study records.
- Study records published over the past 24 months in the three peer-reviewed academic journals with the largest number of included studies.
- Study records that have cited the included studies (identified in Web of Science citation database).
- Collections of the review authors.

Additional experts will be contacted with a list of included studies, with the request to identify potentially eligible additional studies.

3.2.3. Study selection

Study selection will be carried out with Covidence or the Rayyan Systematic Reviews Web App (Ouzzani et al., 2016). All study records identified in the search will be downloaded and duplicates will be identified and deleted. Afterwards, at least two review authors (out of: MB, FB, CDT, CD, BAE, DG, AM, LMH, AO, FPi, MR, YR, ES and AT), working in pairs, will independently screen titles and abstracts (step 1) and then full texts (step 2) of potentially relevant records. A third

review author (out of: AD, GS and SI) will resolve any disagreements between the two review authors. If a study record identified in the literature search was authored by a review author assigned to study selection or if an assigned review author was involved the study, then the record will be re-assigned to another review author for study selection. The study selection will be documented in a flow chart in the systematic review, as per PRISMA guidelines (Liberati et al., 2009).

3.2.4. Data extraction and data items

A data extraction form will be developed and trialled until data extractors reach convergence and agreement. At a minimum, two review authors (out of: LMH, AM, MR, AD, and GS) will extract data on study characteristics (including study authors, study year, study country, participants, exposure and outcome), study design (including summary of study design, comparator, epidemiological models used and effect estimate measure), risk of bias (including selection bias, reporting bias, confounding, and reverse causation) and study context (e.g. data on contemporaneous exposure to other occupational risk factors potentially relevant for deaths or other health loss from stroke.) A third review author (SI) will resolve conflicts in data extraction. Data will be entered into and managed with the Review Manager, Version 5.3 (RevMan 5.3) (2014) or DistillerSR (EvidencePartner, 2017) softwares, but the Health Assessment Workspace Collaborative (HAWC) (Shapiro, 2014; Shapiro, 2015) may also be used in parallel or to prepare data for entry into RevMan 5.3.

We will also extract data on potential conflict of interest in included studies. For each author and affiliated organization of each included study record, we will extract their financial disclosures and funding sources. We will use a modification of a previous method to identify and assess undisclosed financial interest of authors (Forsyth et al., 2014). Where no financial disclosure or conflict of interest statements are available, we will search the name of all authors in other study records gathered for this study and published in the prior 36 months and in other publicly available declarations of interests (Drazen et al., 2010a; Drazen et al., 2010b).

We will request missing data from the principal study author by email or phone, using the contact details provided in the principal study record. If we do not receive a positive response from the study author, we will send follow-up emails twice, at two and four weeks.

3.2.5. Risk of bias assessment

Standard risk of bias tools do not exist for systematic reviews for hazard identification in occupational and environmental health, nor for risk assessment. The five methods specifically developed for occupational and environmental health are for either or both hazard identification and risk assessment, and they differ substantially in the types of studies (randomized, observational and/or simulation studies) and data (e.g. human, animal and/or in vitro) they seek to assess (Rooney et al., 2016). However, all five methods, including the *Navigation Guide* (Lam et al., 2016c), assess risk of bias in human studies similarly (Rooney et al., 2016).

The *Navigation Guide* was specifically developed to translate the rigor and transparency of systematic review methods applied in the clinical sciences to the evidence stream and decision context of environmental health (Woodruff and Sutton, 2014), which includes workplace environment exposures and associated health outcomes. The guide is our overall organizing framework, and we will also apply its risk of bias assessment method in Systematic Review 2. The *Navigation Guide* risk of bias assessment method builds on the standard risk of bias assessment methods of the Cochrane Collaboration (Higgins et al., 2011) and the US Agency for Healthcare Research and Quality (Viswanathan et al., 2008). Some further refinements of the *Navigation Guide* method may be warranted (Goodman et al., 2017), but it has been successfully applied in several completed and ongoing systematic reviews (Johnson et al., 2016; Johnson et al., 2014; Koustas et al., 2014; Lam et al., 2016a; Lam et al., 2014; Lam et al., 2017; Lam et al., 2016b; Vesterinen et al., 2014; Vesterinen et al., 2015). In our application of the *Navigation Guide* method, we will draw heavily on one of its latest versions, as presented in the protocol for an ongoing systematic review (Lam et al., 2016d; Lam et al., 2016c). Should a more suitable method become available, we may switch to it.

We will assess risk of bias on the levels of the individual study and the entire body of evidence. The nine risk of bias domains included in the *Navigation Guide* method for human studies are: (i) source population representation; (ii) blinding; (iii) exposure assessment; (iv) outcome assessment; (v) confounding; (vi) incomplete outcome data; (vii) selective outcome reporting; (viii) conflict of interest; and (ix) other sources of bias. While two of the earlier case studies of the *Navigation Guide* did not utilize outcome assessment as a risk of bias domain for studies of human data (Johnson et al., 2014; Koustas et al., 2014; Lam et al., 2014; Vesterinen et al., 2014), all of the subsequent reviews have included this domain (Johnson et al., 2016; Lam et al., 2016a; Lam et al., 2017; Lam et al., 2016b; Lam et al., 2016d; Lam et al., 2016c). Risk of bias or confounding ratings will be: "low"; "probably low"; "probably high"; "high" or "not applicable" (Lam et al., 2016d). To judge the risk of bias in each domain, we will apply *a priori* instructions (Appendix H), which we have adopted or adapted from an ongoing *Navigation Guide* systematic review (Lam et al., 2016d). For example, a study will be assessed as carrying "low" risk of bias from source population representation, if we judge the source population to be described in sufficient detail (including eligibility criteria, recruitment, enrollment, participation and loss to follow up) and the distribution and characteristics of the study sample to indicate minimal or no risk of selection effects. The risk of bias at study level will be determined by the worst rating in any bias domain for any outcome. For example, if a study is rated as "probably high" risk of bias in one domain for one outcome and "low" risk of bias in all other domains for the outcome and in all domains for all other outcomes, the study will be rated as having a "probably high" risk of bias overall.

All risk of bias assessors (CD, FB and DG) will jointly trial the application of the risk of bias criteria until they have synchronized their understanding and application of these criteria. At least two study authors (out of: CD, FB and DG) will independently judge the risk of bias for each study by outcome. Where individual assessments differ, a third author (AD, GS or SI) will resolve the conflict. In the systematic review, for each included study, we will report our study-level risk of bias assessment by domain in a standard 'Risk of bias' table (Higgins et al., 2011). For the entire body of evidence, we will present the study-level risk of bias assessments in a 'Risk of bias summary' figure (Higgins et al., 2011).

3.2.6. Synthesis of results

We will conduct meta-analyses separately for estimates of the effect on incidence and mortality. If we find two or more studies with an eligible effect estimate, two or more review authors (out of: AD, SI, AO and YR) will independently investigate the clinical heterogeneity of the studies in terms of participants (including country, sex, age and industrial sector or occupation), level of risk factor exposure, comparator and outcomes. If we find that effect estimates differ considerably by country, sex and/or age, or a combination of these, then we will synthesise evidence for the relevant populations defined by country, sex and/or age, or combination thereof. Differences by country could include or be expanded to include differences by country group (e.g. WHO region or World Bank income group). If we find that effect estimates are clinically homogenous across countries, sexes and age groups, then we will combine studies from all of these populations into one pooled effect estimate that could be applied across all combinations of countries, sexes and age groups in the WHO/ILO joint methodology.

If we judge two or more studies for the relevant combination of country, sex and age group, or combination thereof, to be sufficiently clinically homogenous to potentially be combined quantitatively using quantitative meta-analysis, then we will test the statistical

heterogeneity of the studies using the I^2 statistic (Figueroa, 2014). If two or more clinically homogenous studies are found to be sufficiently homogenous statistically to be combined in a meta-analysis, we will pool the risk ratios of the studies in a quantitative meta-analysis, using the inverse variance method with a random effects model to account for cross-study heterogeneity (Figueroa, 2014). The meta-analysis will be conducted in RevMan 5.3, but the data for entry into these programmes may be prepared using another recognized statistical analysis programme, such as Stata. We will neither quantitatively combine data from studies with different designs (e.g. combining cohort studies with case-controls studies), nor unadjusted and adjusted models. We will only combine studies that we judge to have a minimum acceptable level of adjustment for confounders. If quantitative synthesis is not feasible, then we will synthesise the study findings narratively and identify the estimates that we judged to be the highest quality evidence available.

3.2.7. Additional analyses

If we source micro-data on exposure, outcome and potential confounding variables, we may conduct meta-regressions to adjust optimally for potential confounders.

If there is evidence for differences in effect estimates by country, sex, age, industrial sector and/or occupation, or by a combination of these variables, then we will conduct subgroup analyses by the relevant variable or combination of variables, as feasible. Where both studies on workers in the informal economy and in the formal economy are included, then we will conduct sub-group analyses by formality of economy. Findings of these subgroup analyses, if any, will be used as parameters for estimating burden of disease specifically for relevant populations defined by these variables. We will also conduct subgroup analyses by study design (e.g. randomized controlled trials versus cohort studies versus case-control studies).

We will perform sensitivity analyses that will include only studies judged to be of "low" or "probably low" risk of bias from conflict of interest; judged to be of "low" or "probably low" risk of bias; and with documented or approximated ICD-10 diagnostic codes. Finally, depending on the available data, ischaemic (I63), haemorrhagic (I60 and I61) and transient (I65 and I66) stroke will be analysed separately. We may also conduct a sensitivity analysis using an alternative meta-analytic model, namely the inverse variance heterogeneity (IVhet) model.

3.2.8. Quality of evidence assessment

We will assess quality of evidence using a modified version of the *Navigation Guide* quality of evidence assessment tool (Lam et al., 2016d). The tool is based on the GRADE approach (Guyatt et al., 2011; Schünemann et al., 2011) adapted specifically to systematic reviews in occupational and environmental health (Morgan et al., 2016). Should a more suitable method become available, we may switch to it.

Working in pairs, we (MB, FB, CDT, CD, BAE, DG, AM, LMH, AO, FP, MR, YR, ES and AT) will assess quality of evidence for the entire body of evidence by outcome, with any disagreements resolved by a third review author (AD, GS or SI). We will adopt or adapt the latest *Navigation Guide* instructions (Appendix D) for grading the quality of evidence (Lam et al., 2016d). We will downgrade the quality of evidence for the following five GRADE reasons: (i) risk of bias; (ii) inconsistency; (iii) indirectness; (iv) imprecision; and (v) publication bias. If our systematic review includes ten or more studies, we will generate a funnel plot to judge concerns on publication bias. If it includes nine or fewer studies, we will judge the risk of publication bias qualitatively. To assess risk of bias from selective reporting, protocols of included studies, if any, will be screened to identify instances of selective reporting.

We will grade the evidence, using the three *Navigation Guide* standard quality of evidence ratings: "high", "moderate" and "low" (Lam et al., 2016d). Within each of the relevant domains, we will rate the concern for the quality of evidence, using the ratings "none", "serious" and "very serious". As per *Navigation Guide*, we will start at "high" for randomized studies and "moderate" for observational studies. Quality will be downgrade for no concern by nil grades (0), for a serious concern by one grade (−1) and for a very serious concern by two grades (−2). We will up-grade the quality of evidence for the following other reasons: large effect, dose-response and plausible residual confounding and bias. For example, if we have a serious concern for risk of bias in a body of evidence consisting of observational studies (−1), but no other concerns, and there are no reasons for upgrading, then we will downgrade its quality of evidence by one grade from "moderate" to "low".

3.2.9. Strength of evidence assessment

We will apply the standard *Navigation Guide* methodology (Lam et al., 2016c) to rate the strength of the evidence. The rating will be based on a combination of the following four criteria: (i) quality of the body of evidence; (ii) direction of the effect; (iii) confidence in the effect; and (iv) other compelling attributes of the data that may influence our certainty. The ratings for strength of evidence for the effect of long working hours on stroke will be "sufficient evidence of toxicity/harmfulness", "limited of toxicity/harmfulness", "inadequate of toxicity/harmfulness" and "evidence of lack of toxicity/harmfulness" (Appendix I).

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Author contributions

IDI, NL, FPe and APÜ had the idea for the systematic review. IDI, NL, FPe and YU gathered the review team. FPe led and all authors contributed to the development of the standard methodology for all systematic reviews in the series. FPe led and all authors contributed to the development and writing of the standard template for all protocols in the series. AD, SI and GS are the lead reviewers of this systematic review. AD, CDT, DG, SI and GS wrote the first draft of this protocol, using the protocol template prepared by FPe, and MB, FB, CD, BAE, AM, LMH, AO, JP, FPe, FPi, APÜ, MR, YR, AT and YU made substantial contributions to revisions of the manuscript. The search strategy was developed and piloted by DG, JP and GS in collaboration with a research librarian. FPe and GS are experts in epidemiology, AD and SI are experts in occupational psychosocial risk factors and cardiovascular diseases, and FPe and JP are experts in systematic review methodology. FPe coordinated all inputs from WHO, ILO and external experts and ensured consistency across the systematic reviews of the series. AD, SI and GS are the guarantors of the systematic reviews.

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Conflict of interest

None declared.

Appendices. Supplementary data

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Obesity Comorbidity/Etiology and Pathophysiology

Work-related psychosocial factors and metabolic syndrome onset among workers: a systematic review and meta-analysis

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Summary

Background: Work-related psychosocial factors have been associated with metabolic syndrome. However, no systematic reviews or meta-analyses have evaluated this association.

Methods: A systematic literature search was conducted, using PubMed, Embase, PsycINFO, PsycARTICLES and the Japan Medical Abstracts Society. Eligible studies included those that examined the previously mentioned association; had a longitudinal or prospective cohort design; were conducted among workers; provided sufficient data for calculating odds ratios, relative risks or hazard ratios with 95% confidence intervals; were original articles in English or Japanese; and were published no later than 2016. Study characteristics, exposure and outcome variables and association measures of studies were extracted by the investigators independently.

Results: Among 4,664 identified studies, 8 were eligible for review and meta-analysis. The pooled risk of adverse work-related stress on metabolic syndrome onset was significant and positive (RR = 1.47; 95% CI, 1.22–1.78). Sensitivity analyses limiting only the effects of job strain and shift work also indicated a significant positive relationship (RR = 1.75; 95% CI, 1.09–2.79; and RR = 1.59; 95% CI, 1.00–2.54, P = 0.049 respectively).

Conclusion: This study reveals a strong positive association between work-related psychosocial factors and an elevated risk of metabolic syndrome onset. The effects of job strain and shift work on metabolic syndrome appear to be significant.

Keywords: metabolic syndrome, psychosocial, worker, workplace.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE, Meta-Analysis of Observational Studies in Epidemiology; WHO, World Health Organization; IDF, International Diabetes Foundation; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; OR, odds ratio; RR, relative risk; HR, hazard ratio; CI, confidence interval; NOS, Newcastle–Ottawa Quality Assessment Scale; SE, standard error; DCS model, job demand-control-support model.

Introduction

Metabolic syndrome, a cluster of medical conditions including multiple risk factors for cardiovascular disease and type 2 diabetes, is characterized by comorbidity of abdominal obesity, high blood glucose or insulin resistance, hypertension, dyslipidaemia and microalbuminuria (1–5). Metabolic syndrome has been associated with cardiovascular diseases onset (3), increased cancer risks (6), a low health-related quality of life (7) and all-cause mortality (8,9). While some variations by demographic variables and ethnicity exist, the prevalence of metabolic syndrome is high (10–14), and it is thus recognized as an important public health target worldwide.

Work-related psychosocial factors have been associated with cardiovascular health (15–18). Job demands and job control (19), effort-reward imbalance (20), organizational justice (21) and social support from supervisors and colleagues (22) have been linked to cardiovascular disease onset. Shift work (23,24) and long working hours (25–29) were also reported to heighten the risk of cardiovascular disease. Previous systematic reviews and meta-analyses have established that these factors were associated with the individual components of metabolic syndrome, such as blood pressure and hypertension (30,31), weight gain and obesity (32,33), as well as blood glucose and impaired glucose tolerance (34), but were insignificant for blood lipids and dyslipidaemia (34,35).

However, only two systematic reviews and/or meta-analyses (36,37) were conducted regarding the relationship between work-related psychosocial factors and metabolic syndrome, as defined by international clinical criteria (1–5). A systematic review of 39 prospective studies conducted by Bergmann et al. (36) found a positive association between chronic psychosocial stressors and metabolic syndrome. However, they combined studies of both working and non-working populations, included both metabolic syndrome and each component of metabolic syndrome as outcomes and adopted general stressors as exposures, but without statistically synthesizing the association. The other systematic review and meta-analysis (37) investigated an association using night shift work only as an exposure, and combined prospective, retrospective and cross-sectional studies. Thus, a further systematic review and meta-analysis is indispensable to understand and integrate existing evidence regarding the association between work-related psychosocial factors and metabolic syndrome onset.

This study aimed to evaluate published prospective studies to investigate whether adverse work-related psychosocial factors were associated with an elevated risk of metabolic syndrome. This study is the first systematic review and meta-analysis to analyse this association among the working population. Its finding would offer the strongest evidence at present because the study targeted only prospective studies and would be clearest to answer whether the association is significant.

Methods

Study design

This systematic review and meta-analysis of prospective cohort studies followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (38) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (39). The study protocol, explained elsewhere (40), was registered at PROSPERO (CRD42016039096).

Data sources and searches

A systematic search was conducted in May 2017 using PubMed, Embase, PsycINFO, PsycARTICLES and the Japan Medical Abstracts Society databases, focusing on published studies up to 2016.

Search terms were preliminarily developed by two investigators (KI and AT) and discussed and agreed upon by all authors. These terms, explained elsewhere (40), included key words related to the participants, exposures, comparisons and outcomes (PECO) of the studies to be included. The PECO were defined as follows: (P) inclusion of all workers, (E) presence of adverse work-related psychosocial factors, (C) absence of adverse work-related psychosocial factors and (O) metabolic syndrome onset. We targeted all employed workers as participants, regardless of employment status, job type or shift type. The work-related psychosocial factors included a variety of task and organizational characteristics, work conditions and workplace interactions (41). The diagnostic standards for metabolic syndrome were defined by several international institutions (1–5): the World Health Organization (WHO), International Diabetes Foundation (IDF), National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI).

Eligibility criteria

Eligible studies were those that (1) were conducted to evaluate the association between work-related psychosocial factors and metabolic syndrome onset; (2) used a longitudinal or prospective cohort design; (3) were conducted among workers; (4) provided sufficient data for calculating odds ratios (ORs), relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs); (5) were published as original articles in English or Japanese; and (6) were published up to 2016. Work-related psychosocial factors and

metabolic syndrome were defined based on the PECO of this study.

Study selection

All identified studies were managed within a Microsoft® Excel (Washington, USA) file. Prior to screening the studies, duplicate studies were excluded by one of the investigators (KI). Afterwards, nine investigators (KW, A Sakuraya, KI, EA, YA, HE, YK, NN and HA) independently reviewed the titles and abstracts according to the eligibility criteria (first screening). Studies that clearly did not meet the criteria were excluded at this phase, and the others (studies that met the criteria and those wherein we could not assess the criteria according to the title and abstract) proceeded to a full-text review. When the investigators disagreed on the eligibility during the full-text review, the disagreements were settled by consensus of all authors. The reasons for excluding particular studies were recorded at the full-text review phase.

Data extraction and quality assessment

Information from each of the included studies was extracted by one of the nine investigators, using a standardized data extraction form. Information included study characteristics, exposure and outcome variables and association measures of work-related psychosocial factors and metabolic syndrome onset. After extraction, information was confirmed by discussion among all authors to reach a consensus in data collection. If the studies did not list this information and/or contained unclear information, we contacted the corresponding authors to seek clarification.

Study characteristics

The year of publication, country where the study was conducted, number of participants at baselines and analyses, sampling framework (population, community or worksite based), participant characteristics, number of outcome events, length of follow-up and follow-up rate were collected.

Exposure and outcome variables

Information on exposure variables (i.e. adverse work-related psychosocial factors), diagnostic criteria for metabolic syndrome and information on a comparison group (i.e. absence of adverse work-related psychosocial factors) were also collected.

Association measures

We collected ORs, RRs or HRs (hereafter called RRs) with 95% CIs for the association between work-related psychosocial factors and metabolic syndrome onset. When multiple RRs were reported in the included studies, we selected RRs adjusted by demographic variables (e.g. age, sex, education and marital status) and lifestyle variables (e.g. smoking, physical activity and sleep). Other association measures were not adopted, due to over-adjustment. Sex-stratified RRs were selected if those were the only reported measures of association.

For each included study, the nine investigators independently assessed study quality using the Newcastle-Ottawa Quality Assessment Scale (NOS) (42), which evaluates cohort studies based on eight items categorized into three groups: (1) selection of the study cases, (2) comparability of the population and (3) ascertainment of whether the exposure or outcome included any risk of bias (i.e. selection bias or bias from loss to follow-up). The NOS is scored from 0 to 9, and studies with scores ≥ 7 are considered as high quality (43). Discrepancy in quality assessment among the investigators was solved by discussion and consensus among all authors.

Data synthesis and analysis

For the main analysis to estimate the pooled risk of work-related psychosocial factors related to metabolic syndrome, the extracted RRs were subjected to a random-effects model meta-analysis (44), using Stata version 12 (LightStone®, Tokyo, Japan). Heterogeneity was assessed using the χ^2 test on Cochran's Q statistic, which was calculated into I^2 values (45), assuming that I^2 values of 25, 50 and 75% indicated low, medium and high heterogeneity respectively. Prior to the analysis, we calculated log-transformed RRs and their standard errors (SEs) based on the 95% CIs. If included studies reported RRs between the presence of *protective* work-related psychosocial factors and metabolic syndrome onset, their log-transformed associations were reverse-coded. Publication bias was examined by drawing a funnel plot and conducting Egger's test.

Sensitivity analyses were conducted for studies that scored as high quality in the NOS (≥ 7) and that reported relevant SEs based on the funnel plot. Subgroup meta-analyses were also conducted separately for types of work-related psychosocial factors.

Changes to the protocol

After protocol registration at PROSPERO, the search terms for the Japan Medical Abstracts Society were changed to more concise and compatible Japanese translations from English terms, the details of which are described in Appendix Table A1. The MOOSE checklist was used in addition to the PRISMA checklist as the reporting checklist after protocol registration, because this study is the meta-analysis for observational studies.

Results

Selected studies

A flow chart of the study selection process is shown in Fig. 1. The initial search of the five databases identified 4,821 records. After removing 157 duplicates, 4,664 records were included in the first screening, after which 4,646 records were excluded and 18 records proceeded to full-text screening. Subsequently, 10 studies that did not meet the criteria for participant (N = 2), exposure (N = 2), outcome (N = 2), association measures (N = 1) and study design (N = 3) were excluded. Finally, 8 studies (45–52) were included in the qualitative review and meta-analysis.

Study characteristics

Characteristics of the eight prospective cohort studies (46–53) are shown in Table 1. Six of them were

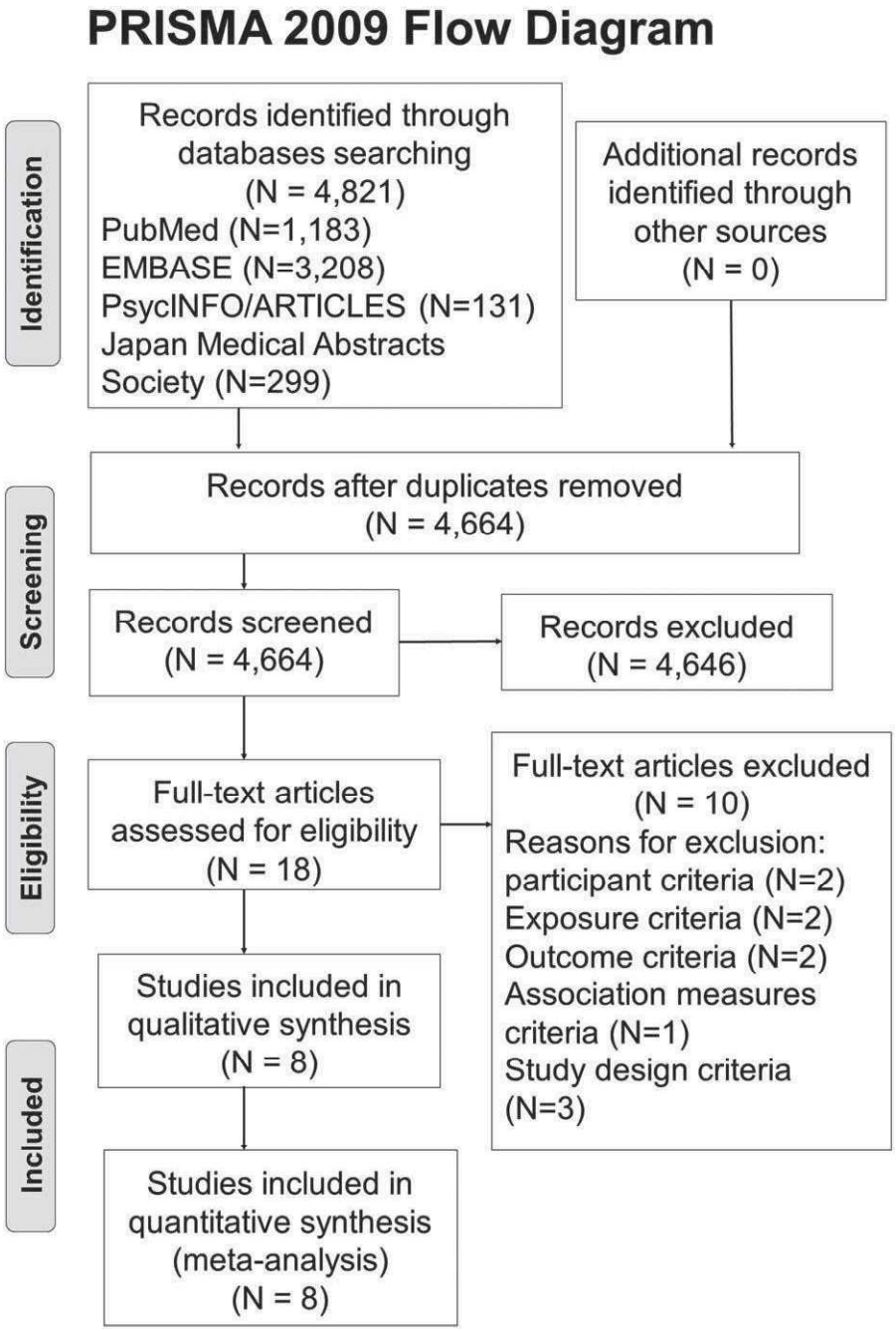

Figure 1 PRISMA flow diagram. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Studies included in the systematic review and meta-analysis ($N = 8$)

First author (year), country	Baseline no.	Men	Women	No. for analysis	Men	Women	Recruitment	Participants	Exposure	Comparison	Outcome standards	No. of outcome events	F-U	F-U rate	Study quality[†]
1. Garbarino (2015) (46), ITA	290	290	0	220	220	0	Workplace	Police officers	'High stress' persons Job strain (D/C > 1) or effort-reward imbalance (E/R > 1)	Not 'high stress' persons	IDF or NCEP-ATP III	27	5 years	81.0%	8
2. Pimenta (2015) (47), ESP	11,950	N/A	N/A	6,845	2,486	4,359	University	University graduates who were currently working	Working hours 25–39 h/week 40–49 h/week ≥50 h/week	>0–24 h/week	IDF and AHA/NHLBI	409	8.3 years	57.3%	6
3. Kawada (2014) (48), JPN	1,677	1,677	0	1,653	1,653	0	Workplace	Workers in a manufacturing company	Shift work Two-shift work Three-shift work	Daytime shift work	NCEP-ATP III	260	3 years	100.0%	6
4. Edwards (2012) (49), USA	2,914	1,390	1,524	2,550	1,233	1,347	Population	Black and white men and women	High job strain	Low job strain	NCEP-ATP III	202	5 years	88.5%	7
5. Gimeno (2010) (50), GBR	9,618	6,468	3,150	6,321	4,398	1,923	Workplace	All office staffs in London, England, in civil service departments	High level of justice	Low level of justice	NCEP-ATP III and AHA/NHLBI	1,068	14 years	65.7%	7
6. Pietroiusti (2010) (51), ITA	770	N/A	N/A	624	N/A	N/A	Workplace	Nurses in three large hospitals	Night shift work	Daytime shift work	NCEP-ATP III and AHA/NHLBI	42	4 years	81.0%	5
7. De Bacquer (2009) (52), BEL	N/A	N/A	N/A	1,529	1,529	0	Workplace	Workers from nine large Belgian companies	High job strain Shift work	Low job strain Not shift work	IDF	364	6.6 years	88.0%	6
8. Chandola (2006) (53), GBR	10,308	N/A	N/A	6,600	4,662	1,938	Workplace	Employees in civil service departments	Iso-strain	Not iso-strain	NCEP-ATP III	562	14 years	N/A	6

F-U, follow-up; D/C, demands/control; E/R, effort/reward; IDF, International Diabetes Foundation; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; N/A, not available.

[†]Study quality was assessed using the Newcastle–Ottawa Quality Assessment Scale

conducted in Italy, Spain, the UK and Belgium (46,47,50–53); one in Japan (48); and the other one in the USA (49). The number of workers who participated was 290–11,950 at baselines and 220–6,845 at the analyses. Six of the studies recruited participants from workplace-based sampling, targeting police officers (48), workers in private companies (48,52), civil servants (50,53) and hospital nurses (51). Work-related psychosocial factors adopted were job strain or iso-strain (N = 4) (46,49,52,53), effort-reward imbalance (N = 1) (46), organizational justice (N = 1) (50), shift work (N = 3) (48,51,52) and working hours (N = 1) (47). The standard diagnoses for metabolic syndrome were those used by the IDF (5) (N = 3) (46,47,52), the NCEP (3) (N = 6) (46,48–52) and the AHA/NHLBI (4) (N = 3) (47,50,51). The length of follow-up was 3–14 years, while the follow-up rate was 65.7–100.0%. Study quality scores by the NOS ranged from 5 to 8; only three studies scored as high quality (≥7) (46,49,50).

Results of individual studies

The 12 RRs reported in the eight studies are shown in Table 2. Three of the studies reported significant positive associations between adverse work-related psychosocial factors and metabolic syndrome onset (46,51,53); one reported insignificant associations (47), and four reported mixed results (48–50,52).

Garbarino et al. (46) indicated the elevated risk for metabolic syndrome onset among male police officers who scored as having 'high stress', which was identified if their demands/control (D/C) or effort/reward (E/R) ratios were >1.00. These variables consistently indicated significant positive associations with metabolic syndrome onset in both crude (OR = 3.29; 95% CI, 1.44–7.54) and fully adjusted models (OR = 2.68; 95% CI, 1.08–6.70). The association between the job demand-control-support model (DCS model) and metabolic syndrome onset was also investigated by Edwards et al. (49), De Bacquer et al. (52) and Chandola et al. (53) Two of these studies (49,52) used high job strain (a combination of high job demands and low job control) as the exposure and low job strain as the comparison, based on median scores of job demands and control among each population. The results for the associations were insignificant among male workers (HR = 1.80; 95% CI, 0.90–3.60 and OR = 0.96; 95% CI, 0.69–1.33) but significant and positive among female workers (HR = 2.20; 95% CI, 1.00–4.60). Chandola et al. (53) used iso-strain as the exposure, which was the lowest third of work social support, in addition to high job strain. They indicated a dose–response association between iso-strain and metabolic syndrome onset and found that participants who experienced iso-strain three or more times during follow-up (14 years) were especially at high risk for metabolic syndrome onset (OR = 2.29; 95% CI, 1.27–4.12). Gimeno et al. (50) investigated the protective effect of organizational justice at work and indicated that male workers who were in the highest third for justice at work were significantly less likely to have metabolic syndrome (HR = 0.75; 95% CI, 0.63–0.89), although this was not the case for female workers (HR = 0.88; 95% CI, 0.67–1.17).

The effect of shift work was investigated in three studies (48,51,52). Kawada et al. (48) measured self-reported shift work as two-shift (starting at 06:30 or 15:00 hours) and three-shift work (starting at 06:30, 14:30 or 22:30 hours) among Japanese male workers in a car-manufacturing company, compared with the daytime shift (08:00–17:00 hours). Pietroiusti et al. (51) defined night-shift work as working at least an average of four nights per month, in comparison with the daytime shift (07:00–21:00 hours). Additionally, De Bacquer et al. (52) reported on the effect of OR shift work on metabolic syndrome and job strain. These three studies consistently indicated significant positive associations, except between three-shift work and metabolic syndrome onset in Kawada *et al.*'s study (50) (OR = 0.72; 95% CI, 0.37–1.41).

Another study investigated the effects of working hours as the exposures for metabolic syndrome onset. Pimenta et al. (47) conducted a prospective cohort study among university graduates working in Spain and reported that ≥50 working hours/week was significantly associated with metabolic syndrome onset, compared with <24 working hours in the crude model (RR = 1.85; 95% CI, 1.21–2.83), but insignificant in the adjusted model (RR = 1.33; 95% CI, 0.82–2.15).

Meta-analysis

The main result of the random-effects model meta-analysis from 12 RRs in the eight studies is shown in Fig. 2. The estimated pooled RR was significantly positive (RR = 1.47; 95% CI, 1.22–1.78). The heterogeneity was medium and statistically significant (I^2 = 58·7%, p = 0.005). According to a funnel plot for the log-transformed RRs and their SEs among the eight studies, one of the studies (51) reported an extremely large RR and SE, while Egger's test was not significant (p = 0.154, Fig. 3).

Based on the funnel plot of the main results, we conducted sensitivity analysis for the seven studies, excluding that by Pietroiusti et al. (51) The estimated pooled RR from 11 RRs of the seven studies was also positive and significant (RR = 1.39; 95% CI, 1.18–1.63). Meanwhile, both heterogeneity (I^2 = 43·7%, p = 0.059) and the result of Egger's test (p = 0.392) were insignificant. The other sensitivity analysis for the three studies scored as high quality (46,49,50), also resulting in a significant positive association (RR = 1.40; 95% CI, 1.16–1.70). When we excluded one of the studies (50,53) from the same cohort study (the Whitehall II study),

Table 2 Measures of association between work-related psychosocial factors and metabolic syndrome (*N* = 8)

First author (year), country	Sex	Comparison	Crude or adjusted	RR [log RR]	95% CI (low)	95% CI (high)	Source
1. Garbarino (2015), ITA	Men	High stress vs. not high stress	Demographic and lifestyle	2.68 [0.99]	1.08 [0.08]	6.70 [1.90]	Table 3, p. 7
2. Pimenta (2015), ESP	Men and women	Working hours, ≥50 vs. >0–24 h/week	Demographic and lifestyle	1.33 [0.29]	0.82 [−0.20]	2.15 [0.77]	Table 2, p. 686
3. Kawada (2014), JPN	Men	Two-shift work vs. daytime shift	Demographic, lifestyle and components of MetS	1.43 [0.36]	1.05 [0.05]	1.95 [0.67]	Table 3, p. 58
3. Kawada (2014), JPN	Men	Three-shift work vs. daytime shift		0.72 [−0.33]	0.37 [−0.99]	1.41 [0.34]	
4. Edwards (2012), USA	Men	High strain vs. low strain	Demographic, lifestyle and depression	1.80 [0.59]	0.90 [−0.11]	3.60 [1.28]	Table 3, p. 1451
4. Edwards (2012), USA	Women	High strain vs. low strain		2.20 [0.79]	1.00 [0.00]	4.60 [1.53]	
5. Gimeno (2010), GBR	Men	Low level of justice vs. high level of justice*	Demographic	1.33 [0.29]	1.12 [0.12]	1.59 [0.46]	Table 2, p. 259
5. Gimeno (2010), GBR	Women	Low level of justice vs. high level of justice*		1.20 [0.19]	0.89 [−0.11]	1.61 [0.48]	
6. Pietroiusti (2010), ITA	Men and women	Night shift vs. daytime shift	Demographic and lifestyle	5.10 [1.63]	2.15 [0.77]	12.11 [2.49]	Table 3, p. 56
7. De Bacquer (2009), BEL	Men	High job strain vs. low job strain	Age	0.96 [−0.04]	0.69 [−0.37]	1.33 [0.29]	Table 2, p. 851
7. De Bacquer (2009), BEL	Men	Shift work vs. not shift work		1.65 [0.50]	1.25 [0.22]	2.18 [0.78]	
8. Chandola (2006), GBR	Men and women	Iso-strain vs. not iso-strain	Demographic and lifestyle	2.29 [0.83]	1.27 [0.24]	4.12 [1.42]	Table 3, p. 3

R, relative risk; log RR, log-transformed RR; CI, confidence interval; MetS, metabolic syndrome.
*The reference group was reversed into the adverse work-related psychosocial factor (low level of justice), and RRs were also reversed.

the significance of the pooled RRs did not change: RR = 1.60; 95% CI, 1.22–2.08 when excluding Gimeno et al. (50); RR = 1.42; 95% CI, 1.18–1.72 when excluding Chandola et al. (53).

We conducted two subgroup analyses, stratifying work-related psychosocial factors into job strain (5 RRs from the four studies) (46,49,52,53) and shift work (4 RRs from the three studies) (48,51,52). The pooled RR between job

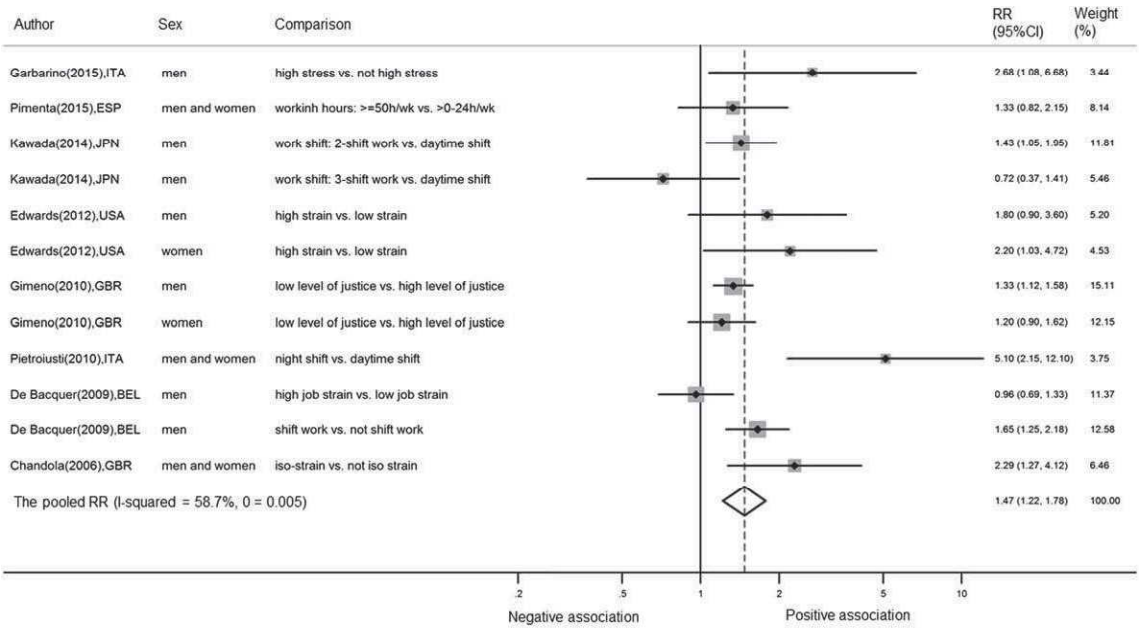

Figure 2 Work-related psychosocial factors and relative risks of metabolic syndrome for eight studies: a random-effect model. [Colour figure can be viewed at wileyonlinelibrary.com]

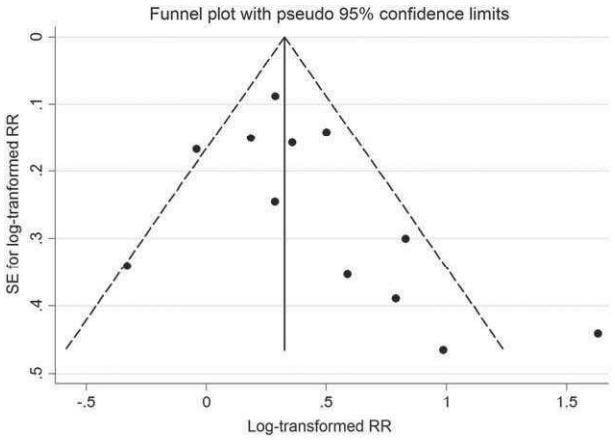

Figure 3 Funnel plot for log-transformed relative risks of metabolic syndrome associated with work-related psychosocial factors and standard errors for eight studies.

strain and metabolic syndrome onset was positive and significant (RR = 1.75; 95% CI, 1.09–2.79). The pooled association between shift work and metabolic syndrome was slightly weaker than that for job strain but was also positive and significant (RR = 1.59; 95% CI, 1.00–2.54, $p = 0.049$).

Discussion

The pooled positive associations between work-related psychosocial factors and metabolic syndrome onset were consistently significant in the main, sensitivity and subgroup analyses. Adverse work-related psychosocial factors may elevate the risk of metabolic syndrome by 1.4 times. This latest finding is consistent with previous studies (36,37) and represents the strongest evidence at present to suggest the influence of work-related psychosocial factors on metabolic syndrome. This association is useful in interpreting the high prevalence of metabolic syndrome in the working population and understanding the pathways for future onsets of cardiovascular disease and/or type 2 diabetes.

The possible mechanisms of this association can be explained by both neuroendocrine and behavioural indicators. The most frequent one is the direct effect of psychosocial stressors on the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (54,55). In this pathway, stressful psychosocial factors cause increased cortisol levels, followed by increased insulin resistance, then visceral fat accumulation through binding of cortisol with glucocorticoid receptors, with abdominal obesity as the endpoint (56). Moreover, activation of the HPA axis can inhibit the secretion of sex steroids and growth hormones, which has the same consequence with cortisol. Simultaneously, activation of the sympathetic nervous system can produce synergic effects with secretion of cortisol, epinephrine and norepinephrine, which may lead to hypertension. Another possible pathway by which work stress leads to metabolic syndrome involves inflammatory processes (57,58). Inflammatory markers, such as cytokines and C-reactive proteins, have been positively associated with metabolic syndrome and are powerful activators of the HPA axis (56,59).

Biological pathways may be mediated by unhealthy behaviours: dietary habits, smoking and physical inactivity (60,61). Changes in dietary habits or energy intake might be explained by the mechanism that glucocorticoid secretion caused by cortisol weakens the efficacy of the leptin system, resulting in 'stress eating' and energy imbalance (54,55). Physical inactivity can also be caused by stressors like job strain and effort-reward imbalance through fatigue in leisure time (62,63). Although most of the included studies did adjust for the effects of health-related behaviours (drinking, smoking and physical inactivity) at baseline, few studies controlled for energy intake and eating behaviour, and changes in health-related behaviours over the course of follow-up (53). Therefore, these indirect effects on metabolic syndrome occur and should be further investigated for a clearer understanding of causality.

Among the associations between specific kinds of psychosocial factors and metabolic syndrome, those involving job strain/iso-strain and shift work were repeatedly investigated and significantly associated with metabolic syndrome. A previous study (37) reported almost the same RR (1.57) as our study for shift work (1.59). Thus, the adverse effects of these two factors on metabolic syndrome may be valid. Among other psychosocial work environments, the effort-reward imbalance model and organizational justice might also impact metabolic syndrome. These factors may play a role not only in damaging the pathological pathways but also protecting and decreasing HPA axis deregulation (50) on metabolic syndrome. Meanwhile, we could not confirm a clear association between long working hours and metabolic syndrome onset. Pimenta et al. (47) claimed that the shortage of longitudinal studies and limited areas of the study fields (most studies were conducted in Japan, where *karoshi* is well recognized) might make the association less clear. Evidence of kind-specific, work-related psychosocial factor associations with metabolic syndrome should be sought in future research. Specific mechanisms for each work-related psychosocial factor are also unknown. However, both biological and behavioural pathways may exist for every association (36). Furthermore, shift work can cause changes in melatonin secretion and circadian rhythms and deterioration of sleep quality (37,51,52,63,65). This pathway might be specific for shift work.

This study had several limitations. First, some studies have reported low follow-up rates, resulting in underestimation of effect size: workers under adverse psychosocial factors at work were more likely to be sick or absent. Second, heterogeneity in diagnostic standards for metabolic syndrome, work-related psychosocial factors and cut-off points

for adversity of exposures may result in the underestimation of the pooled association and make the interpretation difficult. Third, possible confounders that were not adjusted in the included studies may cause confounding bias, such as socioeconomic status and comorbidity of mental health disorders. Some subgroup effects should also be tested in the future, such as gender. Although this study could not investigate sex-stratified associations due to a shortage of sex-stratified results, differences in hormone functions may be important variables (56,57). Fourth, we used the NOS for the assessment of study quality and risk of bias, which did not include several important aspects suggested recently (e.g. conflicts of interest) (66). Finally, the findings are not generalizable for other populations, countries and work-related psychosocial factors that were not investigated in the included studies (e.g. role of stress, mobbing at work or social capital in the workplace) (67–69).

This study revealed a strong positive association between adverse work-related psychosocial factors and elevated risk of metabolic syndrome onset. The effects of job strain and shift work on metabolic syndrome may be valid. Future studies should investigate the effects of other psychosocial factors at work and among specific subgroups such as sex, age and ethnicity. Furthermore, mediation analyses are necessary to explain potential mechanisms between these factors and metabolic syndrome, using biological and behavioural indicators.

Conflict of interest statement

No conflict of interest was declared.

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Appendix

Table A1 Changes to the protocol: Search terms used for the Japan Medical Abstracts Society

Database	Search terms
Before (registered terms for the protocol)	(("心理的ストレス"/TH or "Stress, Psychological"/AL) or ("社会的支援"/TH or "Social Support"/AL) or ("職務満足度"/TH or "Job Satisfaction"/AL) or ("勤務体制"/TH or "Work Schedule Tolerance"/AL) or ("従業員の勤務評価"/TH or "Employee Performance Appraisal"/AL) or ("従業員の苦情"/TH or "Employee Grievances"/AL) or "Social Justice/psychology"/AL or ("人員削減"/TH or "Personnel Downsizing"/AL) or ("スタッフ開発"/TH or "Staff Development"/AL) or ("組織の文化"/TH or "Organizational Culture"/AL) or ("いじめ"/TH or "Bullying"/AL) or ("偏見"/TH or "Prejudice"/AL) or ("社会的差別"/TH or "Social Discrimination"/AL) or ("人間関係"/TH or "Interpersonal Relations"/AL) or "Communication/psychology"/AL) OR (("メカニカルストレス"/TH or "Stress, Mechanical"/AL) or ("挙上(力学)"/TH or "Lifting"/AL) or ("患者の移動と持ち上げ"/TH or "Moving and Lifting Patients"/AL) or ("体重負荷"/TH or "Weight-Bearing"/AL) or ("生体力学的現象"/TH or "Biomechanics"/AL) or ("労作"/TH or "Physical Exertion"/AL) or ("機械的ねじれ"/TH or "Torsion, Mechanical"/AL) or ("姿勢バランス"/TH or "Postural Balance"/AL) or ("歩行運動"/TH or "Walking"/AL) or ("生体機能回復"/TH or "Recovery of Function"/AL) or ("リラクゼーション"/TH or "Relaxation"/AL) or (static/AL and (姿勢/TH or posture/AL)) or (awkward/AL and (姿勢/TH or posture/AL)) or (dynamic/AL and (姿勢/TH or posture/AL)) or (static/AL and (労働/TH or work/AL)) or (dynamic/AL and load*/AL) or lift*/AL or carry*/AL or hold*/AL or pull*/AL or drag*/AL or push*/AL or ((マニュアル/TH or manual/AL) and ("ハンドリング(心理学)"/TH or handling/AL)) or force*/AL or biomechanic*/AL or walking*/AL or (postural/AL and (姿勢バランス/TH or balance/AL)) or flexion*/AL or extension*/AL or turning/AL or sitting/AL or kneeling/AL or squatting/AL or twisting/AL or bending/AL or reaching/AL or standing/AL or sedentary/AL or (repetitive/AL and movement*/AL) or (monotonous/AL and (労働/TH or work/AL)) or (リラクゼーション/TH or relaxation/AL) or (recovery/AL and of/AL and function/AL) or (physical/AL and demand*/AL) or (physically/AL and demand*/AL)) OR (psychosocial/AL or (job/AL and (捻挫/TH or strain/AL)) or ((労働/TH or work/AL) and (捻挫/TH or strain/AL)) or ((労働/TH or work/AL) and demand*/AL) or (job/AL and demand*/AL) or (high/AL and demand*/AL) or (low/AL and control/AL) or (lack/AL and of/AL and control/AL) or ((労働/TH or work/AL) and control/AL) or (job/AL and control/AL) or (decision/AL and latitude/AL) or ((労働/TH or work/AL) and influence*/AL) or (demand/AL and resource*/AL) or ((労作/TH or effort/AL) and reward*/AL) or ((時間/TH or time/AL) and pressure*/AL) or recuperation*/AL or ((労働/TH or work/AL) and overload*/AL) or ((労働/TH or work/AL) and over-load*/AL) or recovery/AL or ("コーピング(心理学)"/TH or coping/AL) or ((労働/TH or work/AL) and (適性/TH or ability/AL)) or (social/AL and support/AL) or (support/AL and system*/AL) or (social/AL and network*/AL) or (emotional/AL and support/AL) or (interpersonal/AL and relation*/AL) or interaction*/AL or justice*/AL or injustice*/AL or (job/AL and (個人的満足/TH or satisfaction/AL)) or ((労働/TH or work/AL) and (個人的満足/TH or satisfaction/AL)) or (退屈/TH or boredom/AL) or (skill/AL and discretion*/AL) or (staff/AL and development/AL) or (社会的差別/TH or discrimination/AL) or harass*/AL or (work-place/AL and conflict*/AL) or ((職場/TH or workplace/AL) and violen*/AL) or (work-place/AL and violen*/AL) or (いじめ/TH or bullying/AL) or (年齢差別/TH or ageism/AL) or (同性愛嫌悪/TH or homophobia/AL) or (人種差別/TH or racism/AL) or (性差別/TH or sexism/AL) or victimization*/AL or (silent/AL and workplace*/AL) or ((社会的役割/TH or role/AL) and ambiguity/AL) or role-conflict*/AL or work-role*/AL or (working/AL and hour*/AL) or (working/AL and (時間/TH or time/AL)) or (day-time/AL) or (nighttime/ AL) or (shift/AL and work*/AL) or ((労働/TH or work/AL) and shift*/AL) or (temporary/AL and (労働/TH or work/AL)) or fulltime/ AL or

(*Continues*)

Table A1 (Continued)

Database	Search terms
	part-time/AL or (flexible/AL and work*/AL) or (organizational/AL and change/AL) or (organisational/AL and change/AL) or (lean/AL and (経済学/TH or production/AL)) or (job/AL and security/AL) or (job/AL and insecurity/AL)) AND (("メタボリックシンドローム"/TH or "Metabolic syndrome"/AL) or ("インスリン抵抗性"/TH or "Insulin resistance"/AL) or ("メタボリックシンドローム"/TH or "Metabolic syndrome X"/AL) or "Cardio-metabolic syndrome"/AL or "Reaven's syndrome"/AL) AND ((longitudinal/AL and study/AL) or (prospective/AL and cohort/AL and study/AL) or (PROSPECTIVE/AL and STUDIES/AL) or (FOLLOWUP/ AL and STUDIES/AL) or (observational/AL and stud*/AL))
After (used terms)	((メカニカルストレス/TH or 機械的ストレス/AL) or 持ちあげ/AL or 患者の移動/AL or 患者の持ち上げ/AL or (体重負荷/TH or 荷重負荷/AL) or (体重負荷/TH or 体重負荷/AL) or (生体力学的現象/TH or 生物力学/AL) or (労作/TH or 労作/AL) or (機械的ねじれ/TH or 機械的ねじれ/AL) or (姿勢/TH or 姿勢/AL) or (姿勢バランス/TH or バランス/AL) or (歩行運動/TH or ウォーキング/AL) or (歩行/TH or 歩行/AL) or 機能的回復/AL or (リラクゼーション/TH or リラクセーション/AL) or 静的姿勢/AL or 窮屈な姿勢/AL or 動的姿勢/AL or 静的労働/AL or 動的負荷/AL or 持ちあげ/AL or 運搬/AL or 抱え込み/AL or 引き/AL or 引きずり/AL or 押し/AL or 手作業/AL or 力/AL or (生体力学的現象/TH or 生物力学/AL) or (歩行運動/TH or ウォーキング/AL) or (歩行/TH or 歩行/AL) or (姿勢/TH or 姿勢/AL) or (姿勢バランス/TH or バランス/AL) or 屈曲/AL or 伸長/AL or 拡張/AL or (回転/TH or 回転/AL) or (座位/TH or 座位/AL) or 座り/AL or 膝曲げ/AL or スクワット/AL or より合わせ/AL or 曲げ/AL or 伸ばし/AL or (立位/TH or 立位/AL) or (座位/TH or 座位/AL) or 反復運動/AL or 単調動作/AL or 単調な仕事/AL or (リラクゼーション/TH or リラクセーション/AL) or 機能的回復/AL or 身体的負荷/AL or 身体的/AL or 負荷/AL) AND ((心理的ストレス/TH or 心理的ストレス/AL) or (社会的支援/TH or ソーシャルサポート/AL) or (職務満足度/TH or 仕事の満足度/AL) or 仕事のストレス耐性/AL or 従業員のパフォーマンス評価/AL or 従業員の抗議/AL or (社会的正義/AL and (心理学/TH or 心理学/AL)) or (人員削減/TH or 人員削減/AL) or 従業員教育/AL or (組織の文化/TH or 組織文化/AL) or (いじめ/TH or いじめ/AL) or (偏見/TH or 偏見/AL) or (社会的差別/TH or 社会的差別/AL) or (人間関係/TH or 対人関係/AL) or ((コミュニケーション/TH or コミュニケーション/AL) and (心理学/TH or 心理学/AL))) and (心理社会的/AL or 仕事のストレイン/AL or (職業性ストレス/TH or 仕事のストレス/AL) or 仕事の要求度/AL or 高い要求度/AL or 低いコントロール/AL or コントロールの欠如/AL or 仕事のコントロール/AL or 裁量の範囲/AL or 仕事の影響/AL or 要求度資源/AL or 努力報酬/AL or 時間的切迫/AL or 病気からの回復/AL or 療養/AL or 仕事の負担/AL or 回復/AL or ("コーピング(心理学)"/TH or コーピング/AL) or 対処/AL or 職務能力/AL or (社会的支援/TH or 社会的支援/AL) or (社会的支援/TH or ソーシャルサポート/AL) or 支援システム/AL or サポートシステム/AL or 社会的ネットワークOR/AL and ソーシャルネットワーク/AL or 情緒的支援/AL or (精神的援助/TH or 情緒的サポート/AL) or (人間関係/TH or 対人関係/AL) or (人間関係/TH or 人間関係/AL) or 対人交流/AL or 相互作用/AL or 公正/AL or 不公正/AL or 職務満足感/AL or (退屈/TH or 退屈/AL) or 技能の幅/AL or 職員研修/AL or (社会的差別/TH or 差別/AL) or 嫌がらせ/AL or 職場の葛藤/AL or 職場の暴力/AL or (いじめ/TH or いじめ/AL) or (年齢差別/TH or 年齢差別/AL) or 同性愛差別/AL or (人種差別/TH or 人種差別/AL) or (性差別/TH or 性差別/AL) or (虐待/TH or 虐待/AL) or 静かな職場/AL or 役割曖昧さ/AL or 役割葛藤/AL or 仕事での役割/AL or (労働時間/TH or 労働時間/AL) or (労働時間/TH or 勤務時間/AL) or 日中/AL or 夜間/AL or シフト業務/AL or (交代制勤務/TH or 交代勤務/AL) or 時間差勤務/AL or 臨時業務/AL or フルタイム/AL or パートタイム/AL or フレックス制度/AL or (組織改革/TH or 組織改革/AL) or 組織再編/AL or リーン生産/AL or トヨタ生産方式/AL or 安定雇用/AL or 不安定雇用/AL) and ((メタボリックシンドローム/TH or メタボリック症候群/AL) or メタボリックシンドローム/AL or (インスリン抵抗性/TH or インスリン抵抗性/AL) or シンドロームX/AL or 心臓代謝症候群/AL or Reaven症候群/AL) and ((縦断研究/TH or 縦断研究/AL) or 前向きコホート研究/AL or (前向き研究/TH or 前向き研究/AL) or (追跡研究/TH or 追跡研究/AL) or (追跡研究/TH or フォーア研究/AL) or (観察研究/TH or 観察研究/AL)) and (DT=1900:2016) and (LA=日本語) and (PT=原著論文)

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Review article

WHO/ILO work-related burden of disease and injury: Protocol for systematic reviews of exposure to long working hours and of the effect of exposure to long working hours on ischaemic heart disease☆

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ABSTRACT

Background: The World Health Organization (WHO) and the International Labour Organization (ILO) are developing a joint methodology for estimating the national and global work-related burden of disease and injury (WHO/ILO joint methodology), with contributions from a large network of experts. In this paper, we present the protocol for two systematic reviews of parameters for estimating the number of deaths and disability-adjusted life years of ischaemic heart disease from exposure to long working hours, to inform the development of the WHO/ILO joint methodology.

Objectives: We aim to systematically review studies on occupational exposure to long working hours (Systematic Review 1) and systematically review and meta-analyse estimates of the effect of long working hours on ischaemic heart disease (Systematic Review 2), applying the Navigation Guide systematic review methodology as an organizing framework. The selection of both, the exposure and the health outcome is justified by substantial scientific evidence on adverse effects of long working hours on ischaemic heart disease risk.

Data sources: Separately for Systematic Reviews 1 and 2, we will search electronic academic databases for potentially relevant records from published and unpublished studies, Medline, EMBASE, Web of Science, CISDOC and PsychINFO. We will also search electronic grey literature databases, Internet search engines and organizational websites; hand-search reference list of previous systematic reviews and included study records; and consult additional experts.

Study eligibility and criteria: We will include working-age (≥15 years) workers in the formal and informal economy in any WHO and/or ILO Member State, but exclude children (< 15 years) and unpaid domestic workers. For Systematic Review 1, we will include quantitative prevalence studies of relevant levels of exposure to long working hours (i.e. 35–40, 41–48, 49–54 and ≥55 h/week) stratified by country, sex, age and industrial sector or occupation. For Systematic Review 2, we

☆ Systematic review protocol

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will include randomized controlled trials, cohort studies, case-control studies and other non-randomized intervention studies with an estimate of the relative effect of relevant level(s) of long working hours on the prevalence of, incidence of or mortality from ischaemic heart disease, compared with the theoretical minimum risk exposure level (i.e. 35–40 h/week).

Study appraisal and synthesis methods: At least two review authors will independently screen titles and abstracts against the eligibility criteria at a first stage and full texts of potentially eligible records at a second stage, followed by extraction of data from qualifying studies. At least two review authors will assess risk of bias and the quality of evidence, using the most suited tools currently available. For Systematic Review 2, if feasible, we will combine relative risks using meta-analysis. We will report results using the guidelines for accurate and transparent health estimates reporting (GATHER) for Systematic Review 1 and the preferred reporting items for systematic reviews and meta-analyses guidelines (PRISMA) for Systematic Review 2.

PROSPERO registration number: CRD42017084243.

1. Background

The World Health Organization (WHO) and the International Labour Organization (ILO) are developing a joint methodology for estimating the work-related burden of disease and injury (WHO/ILO joint methodology) (Ryder, 2017). The organizations plan to estimate the numbers of deaths and disability-adjusted life years (DALYs) that are attributable to selected occupational risk factors, in the first place for the year 2015. The WHO/ILO joint methodology will be based on already existing WHO and ILO methodologies for estimating the burden of disease for selected occupational risk factors (Pruss-Ustun et al., 2017; International Labour Organization, 2014). It will expand existing methodologies with estimation of the burden of several prioritized additional pairs of occupational risk factors and health outcomes. For this purpose, population attributable fractions (Murray et al., 2004) – the proportional reduction in burden from the health outcome achieved by a reduction of exposure to the theoretical minimum risk exposure level – will be calculated for each additional risk factor-outcome pair, and these fractions will be applied to the total disease burden envelopes for the health outcome from the *WHO Global Health Estimates* (World Health Organization, 2017).

The WHO/ILO joint methodology may include a methodology for estimating the burden of ischaemic heart disease from occupational exposure to long work hours if feasible, as one additional prioritized risk factor-outcome pair. To optimize parameters used in estimation models, a systematic review is required of studies on the prevalence of exposure to long working hours ('Systematic Review 1'), as well as a second systematic review and meta-analysis of studies with estimates of the effect of exposure to long work hours on ischaemic heart disease ('Systematic Review 2'). In the current paper, we present the protocol for these two systematic reviews, in parallel to presenting systematic review protocols on other additional risk factor-outcome pairs elsewhere (Descatha et al., 2018; Hulshof et al., 2018; John et al., 2018; Mandrioli et al., 2018; Pachito et al., 2018; Rugulies et al., 2018; Teixeira et al., 2018; Tenkate et al., 2018). To our knowledge, this is the first systematic review protocol of its kind. The WHO/ILO joint estimation methodology and the burden of disease estimates are separate from these systematic reviews, and they will be described and reported elsewhere.

We refer separately to Systematic Reviews 1 and 2, because the two systematic reviews address different objectives and therefore require different methodologies. The two systematic reviews will, however, be harmonized and conducted in tandem. This will ensure that – in the later development of the methodology for estimating the burden of disease from this risk factor–outcome pair – the parameters on the risk factor prevalence are optimally matched with the parameters from studies on the effect of the risk factor on the designated outcome. The findings from Systematic Reviews 1 and 2 will be reported in two distinct journal articles. For all four protocols in the series with long working hours as the risk factor, (Descatha et al., 2018; Pachito et al., 2018; Rugulies et al., 2018) one Systematic Review 1 will be published.

1.1. Rationale

To consider the feasibility of estimating the burden of ischaemic heart disease due to exposure to long working hours, and to ensure that potential estimates of burden of ischaemic heart disease are reported in adherence with the guidelines for accurate and transparent health estimates reporting (GATHER) (Stevens et al., 2016), WHO and ILO require a systematic review of studies on the prevalence of relevant levels of exposure to long working hours (Systematic Review 1), as well as a systematic review and meta-analysis with estimates of the relative effect of exposure to long work hours on the prevalence of, incidence of and mortality from ischaemic heart disease, compared with the theoretical minimum risk exposure level (Systematic Review 2). The theoretical minimum risk exposure level is the exposure level that would result in the lowest possible population risk, even if it is not feasible to attainable this exposure level in practice (Murray et al., 2004). These data and effect estimates should be tailored to serve as parameters for estimating the burden of ischaemic heart disease from exposure to long work hours in the WHO/ILO joint methodology.

Our research will substantially extend the current body of systematic review evidence. A 2012 systematic review and meta-analysis on the effect of exposure with long working hours on cardiovascular disease, which included five cohort studies and six case-control studies published up to September 2011, reported a pooled odds ratio of 1.37, with a 95% confidence interval (CI) of 1.11–1.70 (Kang et al., 2012). A second systematic review on the effect of long working hours on ischaemic heart disease published in 2012 included four prospective studies and seven case-control studies published between 1966 and 19 January 2011. For the prospective studies, the authors reported a pooled relative risk of 1.39 (95% CI: 1.12–1.72) and for the case-control studies a pooled relative risk of 2.43 (95% CI: 1.81–3.26) (Virtanen et al., 2012). Finally, a third systematic review and meta-analysis published in 2015 of 24 cohort studies (including 20 unpublished studies) in Europe, the USA and Australia up to 20 August 2014 found a relative risk of 1.13 (95% CI: 1.02–1.26) for the effect of long working hours (≥ 55 h/week) on ischaemic heart disease (Kivimaki et al., 2015a). However, our Systematic Review 1 will be the – to the best of our knowledge – first systematic review of prevalence studies of exposure to long working hours, and Systematic Review 2 will expand the scope of the existing systematic review evidence by covering evidence from studies published up to 31 May 2018.

Work in the informal economy may lead to different exposures and exposure effects than does work in the formal economy. The informal economy is defined as "all economic activities by workers and economic units that are – in law or in practice – not covered or insufficiently covered by formal arrangements", but excluding "illicit activities, in particular the provision of services or the production, sale, possession or use of goods forbidden by law, including the illicit production and trafficking of drugs, the illicit manufacturing of and trafficking in firearms, trafficking in persons and money laundering, as defined in the relevant international treaties" (Anon, 2015). Consequently, formality of work (informal vs. formal) may be an effect modifier of the effect of long working hours on ischaemic heart disease. Therefore, we consider in both systematic reviews the formality of the economy reported in included studies.

1.2. Description of the risk factor

The definition of the risk factor, the risk factor levels and the

theoretical minimum risk exposure level are presented in Table 1. Long working hours are defined as any working hours exceeding standard working hours, i.e. working hours of ≥41 h/week. Based on results from earlier studies on long working hours and health endpoints, (Kivimaki et al., 2015a; Kivimaki et al., 2015b; Virtanen et al., 2015) the preferred four exposure level categories for our review are 35–40, 41–48, 49–54 and ≥55 h/week. This will allow calculating estimates both for large exposure contrast (i.e. comparing the theoretical minimal exposure to ≥55 h/week) and for potential dose-response associations (i.e. comparing the theoretical minimal exposure to all other exposure categories). If the studies provide the preferred exposure level categories, we will use these categories, but if they provide other exposure categories, we will use the other exposure categories, as long as exposure exceeds 40 h/week.

The theoretical minimum risk exposure is standard working hours defined as 35–40 h/week. We acknowledge that it is possible that the theoretical minimum risk exposure might be lower than standard working hours, but we have to exclude working hours ≤35 h/week, because studies indicate that a proportion of individuals working less than standard hours do so because of existing health problems (Virtanen et al., 2012; Kivimaki et al., 2015b). Thus, this exposure concerns full-time workers in the formal and informal economy. In other words, individuals working less than standard hours might belong to a health-selected group or a group concerned with family care and therefore cannot serve as comparators. Consequently, if a study used as the reference group individuals working less than standard hours or a combination of individuals working standard hours and individuals working less than standard hours, it will be excluded from the systematic review and meta-analysis. The category 35–40 h/week is the reference group used in many large studies and previous systematic reviews (Kang et al., 2012; Virtanen et al., 2012). Since the theoretical minimum risk exposure level is usually set empirically based on the causal epidemiological evidence, we will change the assumed level as evidence suggests.

If several studies report exposure levels differing from the standard levels we define here, then, if possible, we will convert the reported levels to the standard levels and, if not possible, we will report analyses on these alternate exposure levels as supplementary information in the systematic reviews. In the latter case, our protocol will be updated to reflect our new analyses.

1.3. Description of the outcome

The WHO *Global Health Estimates* group outcomes into standard burden of disease categories (World Health Organization, 2017), based on standard codes from the *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10) (World Health Organization, 2015). The relevant WHO *Global Health Estimates* category for this systematic review is "*II.H.2 Ischaemic heart disease*" (World Health Organization, 2017). In line with the WHO *Global Health Estimates*, we define the health outcome covered in Systematic Review 2 as ischaemic heart disease, defined as conditions with ICD-10 codes I120 to I125 (Table 2). We will consider prevalence of, incidence of and mortality from ischaemic heart disease. Table 2 presents for each disease or health problem included in the WHO *Global Health Estimates* category the inclusion in this review. This review covers all the relevant WHO *Global Health Estimates* categories.

Table 2
ICD-10 codes and disease and health problems covered by the WHO burden of disease category *II.H.2 Ischaemic heart disease* and their inclusion in this review.

ICD-10 code	Disease or health problem	Included in this systematic review
I20	Angina pectoris	Yes
I21	Acute myocardial infarction	Yes
I22	Subsequent myocardial infarction	Yes
I23	Certain current complications following acute myocardial infarction	Yes
I24	Other acute ischaemic heart diseases	Yes
I25	Chronic ischaemic heart disease	Yes

1.4. How the risk factor may impact the outcome

Fig. 1 presents the logic model for our systematic review of the causal relationship between exposure to long working hours and ischaemic heart diseases. This logic model is an *a priori*, process-orientated one (Rehfuess et al., 2017) that seeks to capture the complexity of the risk factor–outcome causal relationship (Anderson et al., 2011a).

Theoretically, distinct social contexts in labour market are likely to exacerbate or mitigate the effect of exposure to long working hours on ischaemic heart disease risk. While empirical tests of this assumption are not available, these contexts can exert a direct effect on working hours. Evidence suggests that economic globalization drives people around the world to work longer hours (Lee et al., 2007).

Based on knowledge of previous research on long working hours and ischaemic heart disease, (Kivimaki et al., 2015a; Kivimaki et al., 2015b; Virtanen et al., 2015) we assume that the effect of exposure to long working hours on ischaemic heart disease could be modified by country (or WHO region), sex, age, industrial sector, occupation and formality of the economy. Confounding should be considered by, at least, age, sex and socioeconomic position (e.g. income, education or occupational grade). Exceptions are accepted for studies whose study samples were homogenous (such as men only) or that conducted sensitivity analyses to test the presence of confounding (such as sex-disaggregated analyses that can help identify confounding by sex).

Several variables may mediate the effects of this exposure on disease risk through two major pathways. The first one concerns behavioural responses that result in an increase in health-adverse behaviours, such as cigarette smoking, high alcohol consumption, unhealthy diet and physical inactivity. These behaviours are established risk factors of ischaemic heart disease (Virtanen et al., 2015; Taris et al., 2011). Moreover, impaired sleep and poor recovery resulting from this exposure increase the risk of ischaemic heart disease (Virtanen et al., 2009; Sonnentag et al., 2017). Chronic psychosocial stress responses define a second pathway mediating the effects of exposure on ischaemic heart disease. According to established physiological evidence, recurrent high effort (exposure) results in continued activation of the autonomic nervous/immune systems and associated stress axes, the sympatho-adrenal medullary and the hypothalamic-pituitary adrenal

Table 1
Definitions of the risk factor, risk factor levels and the minimum risk exposure level.

	Definition
Risk factor	Long working hours (including those spent in secondary jobs), defined as working hours > 40 h/week, i.e. working hours exceeding standard working hours (35–40 h/week).
Risk factor levels	Preferable exposure categories are 35–40, 41–48, 49–54 and ≥55 h/week. However, whether we can use these categories will depend on the information provided in the studies. If the preferable exposure categories are not available we will use the exposure categories provided by the studies as long as these exposure categories exceed 40 h/week.
Theoretical minimum risk exposure level	Standard working hours defined as working hours of 35–40 h/week.

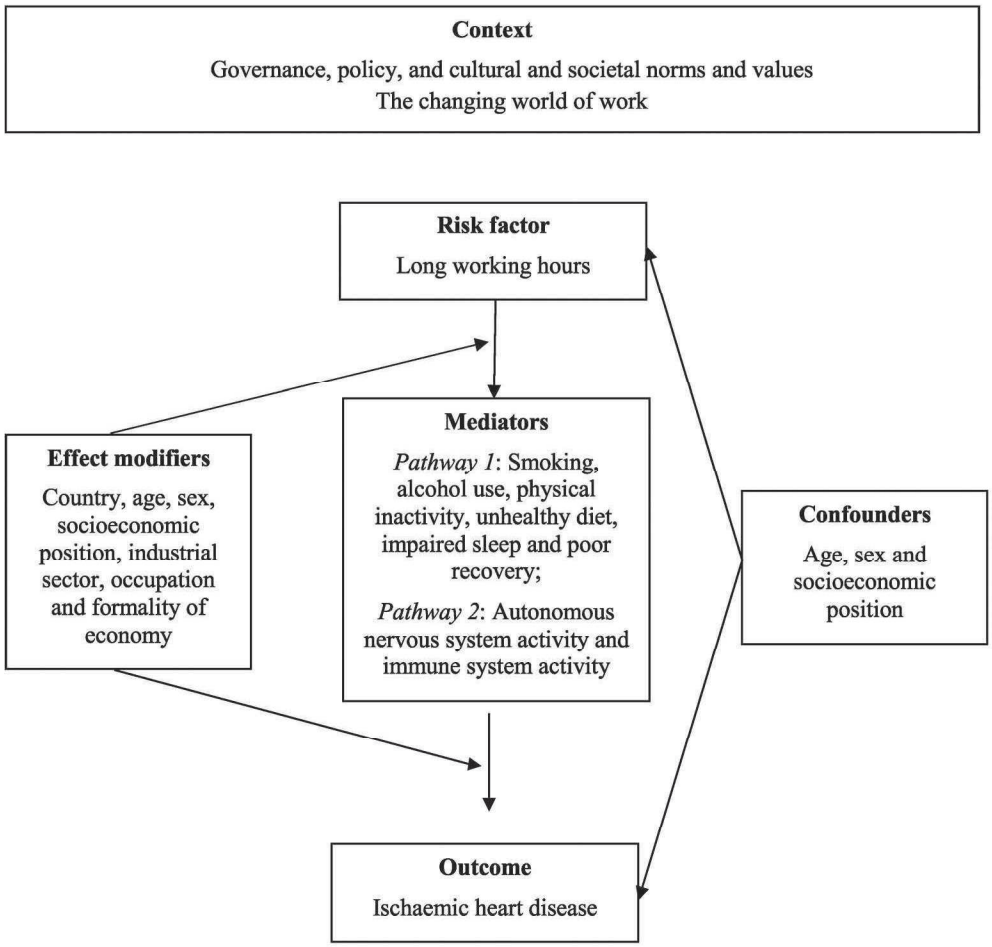

Fig. 1. Logic model of the causal relationship between long working hours and ischaemic heart disease.

axes, with excessive release of respective stress hormones (i.e. adrenalin, noradrenalin and cortisol) (Chandola et al., 2010; Jarczok et al., 2013; Nakata, 2012). In the longer run, this recurrent activation exceeds the regulatory capacity of the cardiovascular system, thus triggering functional dysregulations (e.g. sustained high blood pressure) and structural lesions (e.g. atherogenesis in coronary vessels) (Kivimaki and Steptoe, 2018).

In addition to epidemiological, clinical and experimental evidence suggesting that chronic psychosocial stress (including that from working long hours) presents a risk factor of ischaemic heart disease, there is indirect evidence on its causal role from animal studies. In classical experiments with cynomolgus macaques a direct effect of exposure to a chronic psychosocial stressor on growth of atherosclerotic plaques in coronary vessels was demonstrated, and this process was prevented by administration of beta-adrenergic blocking agents (Kaplan and Manuck, 1994).

2. Objectives

1. Systematic Review 1: To systematically review quantitative studies of any design on the prevalence of relevant levels of exposure to long working hours in the years 2005 to 2018 among the working-age population, disaggregated by country, sex, age and industrial sector or occupation. Systematic Review 1 will be conducted in a coordinated fashion across all four review groups that examine long working hours with regard to health endpoints (i.e. ischaemic heart disease, stroke (Descatha et al., 2018), depression (Rugulies et al., 2018) and alcohol use (Pachito et al., 2018)), led by GS and with JL being the focal point from the working group on long working hours and ischaemic heart disease.
2. Systematic Review 2: To systematically review and meta-analyse randomized controlled studies, cohort studies, case-control studies and other non-randomized intervention studies including working-age workers (Population) exposed to long working hours (Exposure), compared with workers with the minimum theoretical risk exposure level of 35–40 h/week (Comparator), in order to estimate the relative effect on ischaemic heart disease (Outcome).

3. Methods

We will apply the *Navigation Guide* (Woodruff and Sutton, 2014) methodology for systematic reviews in environmental and occupational health as our guiding methodological framework, wherever feasible. The guide applies established systematic review methods from clinical medicine, including standard Cochrane Collaboration methods for systematic reviews of interventions, to the field of environmental and occupational health to ensure systematic and rigorous evidence synthesis on environmental and occupational risk factors that reduces bias and maximizes transparency (Woodruff and Sutton, 2014). The need for further methodological development and refinement of the relatively novel *Navigation Guide* has been acknowledged (Woodruff and Sutton, 2014).

Systematic Review 1 may not map well to the *Navigation Guide* framework (Fig. 1 on page 1009 in (Lam et al., 2016a)), which is tailored to hazard identification and risk assessment. Nevertheless, steps 1–6 for the stream on human data can be applied to systematically review exposure to risk factors. Systematic Review 2 maps more closely to the *Navigation Guide* framework (Lam et al., 2016a), and we will

conduct steps 1–6 for the stream on human data, but not conduct any steps for the stream on non-human data, although we will briefly summarize narratively the evidence from non-human data that we are aware of.

We have registered the protocol in PROSPERO under CRD42017084243. This protocol adheres with the preferred reporting items for systematic review and meta-analysis protocols statement (PRISMA-P) (Moher et al., 2015; Shamseer et al., 2015), with the abstract adhering with the reporting items for systematic reviews in journal and conference abstracts (PRISMA-A) (Beller et al., 2013). Any modification of the methods stated in the present protocol will be registered in PROSPERO and reported in the systematic review itself. Systematic Review 1 will be reported according to the GATHER guidelines (Stevens et al., 2016), and Systematic Review 2 will be reported according to the preferred reporting items for systematic review and meta-analysis statement (PRISMA) (Liberati et al., 2009). Our reporting of the parameters for estimating the burden of ischaemic heart disease to long working hours in the systematic review will adhere with the requirements of the GATHER guidelines (Stevens et al., 2016), because the WHO/ILO burden of disease estimates that may be produced consecutive to the systematic review must also adhere to these reporting guidelines.

3.1. Systematic review 1

3.1.1. Eligibility criteria

The population, exposure, comparator and outcome (PECO) criteria (Liberati et al., 2009) are described below.

3.1.1.1. Types of populations. We will include studies of working-age (≥15 years) workers in the formal and informal economy. Studies of children (aged < 15 years) and unpaid domestic workers will be excluded. Participants residing in any WHO and/or ILO Member State and any industrial setting or occupation will be included. We note that occupational exposure to long working hours may potentially have further population reach (e.g. across generations for workers of reproductive age) and acknowledge that the scope of our systematic reviews will not be able capture these populations and impacts on them. Appendix A provides a complete, but briefer overview of the PECO criteria.

3.1.1.2. Types of exposures. We will include studies that define long working hours in accordance with our standard definition (Table 1). We will prioritize measures of the total number of hours worked, including in both of: main and secondary jobs, self-employment and salaried employment and informal and formal jobs. Cumulative exposure may be the most relevant exposure metric in theory, but we will prioritize a non-cumulative exposure metric in practice, because we believe that global exposure data on agreed cumulative exposure measures do not currently exist. We will include all studies where long working hours were measured, whether objectively (e.g. by means of time recording technology) or subjectively, including studies that used measurements by experts (e.g. scientists with subject matter expertise) and self-reports by the worker or workplace administrator or manager. If a study presents both objective and subjective measurements, then we will prioritize objective measurements. We will include studies with measures from any data source, including registry data.

We will include studies on the prevalence of occupational exposure to the risk factor, if it is disaggregated by country, sex (two categories: female, male), age group (ideally in 5-year age bands, such as 20–24 years) and industrial sector (e.g. *International Standard Industrial Classification of All Economic Activities, Revision 4* [ISIC Rev. 4] (United Nations, 2008)) or occupation (as defined, for example, by the *International Standard Classification of Occupations 1988* [ISCO-88] (International Labour Organization, 1987) or *2008* [ISCO-08] (International Labour Organization, 2012)). Criteria may be revised in order to identify optimal data disaggregation to enable subsequent estimation of the burden of disease.

We shall include studies with exposure data for the years 2005 to 31 May 2018. For optimal modelling of exposure, WHO and ILO require exposure data up to 2018, because recent data points help better estimate time trends, especially where data points may be sparse. The additional rationale for this data collection window is that WHO and ILO aim to estimate burden of disease in the year 2015, and we believe that the lag time from exposure to outcome will not exceed 10 years; so in their models, the organizations can use the exposure data from as early as 2005 to determine the burden of ischaemic heart disease 10 years later in 2015. To make a conclusive judgment on the best lag time to apply in the model, we will summarize the existing body of evidence on the lag time between exposure to long working hours and ischaemic heart disease in the review.

The exposure parameter should match the one used in Systematic Review 2 or can be converted to match it.

3.1.1.3. Types of comparators. There will be no comparator, because we will review risk factor prevalence only.

3.1.1.4. Types of outcomes. Exposure to the occupational risk factor (i.e. long working hours).

3.1.1.5. Types of studies. This systematic review will include quantitative studies of any design, including cross-sectional studies. These studies must be representative of the relevant industrial sector, relevant occupational group or the national population. We will exclude qualitative, modelling and case studies, as well as non-original studies without quantitative data (e.g. letters, commentaries and perspectives).

Study records written in any language will be included. If a study record is written in a language other than those spoken by the authors of this review or those of other reviews (Descatha et al., 2018; Hulshof et al., 2018; John et al., 2018; Mandrioli et al., 2018; Pachito et al., 2018; Rugulies et al., 2018; Teixeira et al., 2018; Tenkate et al., 2018) in the series (i.e. Arabic, Bulgarian, Chinese, Danish, Dutch, English, French, Finnish, German, Hungarian, Italian, Japanese, Norwegian, Portuguese, Russian, Spanish, Swedish and Thai), it will be translated into English. Published and unpublished studies will be included.

Studies conducted using unethical practices will be excluded from the review.

3.1.1.6. Types of effect measures. We will include studies with a measure of the prevalence of a relevant level of exposure to long working hours.

3.1.2. Information sources and search

3.1.2.1. Electronic academic databases. We (DG and DP) will at a minimum search the following seven electronic academic databases:

1. Ovid Medline with Daily Update (2005 to 31 May 2018).
2. PubMed (2005 to 31 May 2018).
3. EMBASE (2005 to 31 May 2018).
4. Scopus (2005 to 31 May 2018).
5. Web of Science (2005 to 31 May 2018).
6. CISDOC (2005 to 31 May 2012).
7. PsychInfo (2005 to 31 May 2018).

The Ovid Medline search strategy for Systematic Review 1 is presented in Appendix B. We will perform searches in electronic databases operated in the English language using a search strategy in the English language. Consequently, study records that do not report essential information (i.e. title and abstract) in English will not be captured. We will adapt the search syntax to suit the other electronic academic and grey literature databases. When we are nearing completion of the

review, we will search the PubMed database for the most recent publications (e.g., e-publications ahead of print) over the last six months. Any deviation from the proposed search strategy in the actual search strategy will be documented.

3.1.2.2. Electronic grey literature databases. We (GS and AT) will at a minimum search the two following electronic academic databases:

1. OpenGrey (http://www.opengrey.eu/).
2. Grey Literature Report (http://greylit.org/).

3.1.2.3. Internet search engines. We (GS and MMF) will also search the Google (www.google.com/) and Google Scholar (www.google.com/scholar/) Internet search engines and screen the first 100 hits for potentially relevant records.

3.1.2.4. Organizational websites. The websites of the seven following international organizations and national government departments will be searched by AD, DG, JP and GS:

1. International Labour Organization (www.ilo.org/).
2. World Health Organization (www.who.int).
3. European Agency for Safety and Health at Work (https://osha.europa.eu/en).
4. Eurostat (www.ec.europa.eu/eurostat/web/main/home).
5. China National Knowledge Infrastructure (http://www.cnki.net/).
6. Finnish Institute of Occupational Health (https://www.ttl.fi/en/).
7. United States National Institute of Occupational Safety and Health (NIOSH) of the United States of America, using the NIOSH data and statistics gateway (https://www.cdc.gov/niosh/data/).

3.1.2.5. Hand-searching and expert consultation. AD, DG, JP and GS will hand-search for potentially eligible studies in:

1. Reference list of previous systematic reviews.
2. Reference list of all study records of all included studies.
3. Study records published over the past 24 months in the three peer-reviewed academic journals from which we obtain the largest number of included studies.
4. Study records that have cited an included study record (identified in Web of Science citation database).
5. Collections of the review authors.

Additional experts will be contacted with a list of included studies and study records, with the request to identify potentially eligible additional ones.

3.1.3. Study selection

Study selection will be carried out with Covidence (Babineau, 2014) and/or the Rayyan Systematic Reviews Web App (Ouzzani et al., 2016). All study records identified in the search will be downloaded and duplicates will be identified and deleted. Afterwards, at least two review authors (AD and KS) will independently screen against eligibility criteria the titles and abstracts (step 1) and then full texts of potentially relevant records (step 2). A third review author (GS) will resolve any disagreements between the study selectors. If a study record identified in the literature search was authored by a review author assigned to study selection or if an assigned review author was involved in the study, then the record will be re-assigned to another review author for study selection. In the systematic review, we will document the study selection in a flow chart, as per GATHER guidelines (Stevens et al., 2016).

3.1.4. Data extraction and data items

A data extraction form will be developed and piloted until there is convergence and agreement among data extractors. At a minimum, two review authors (out of: BAE, ES and LMH) will independently extract the data on exposure to long working hours, disaggregated by country, sex, age and industrial sector or occupation. A third review author (GS) will resolve conflicting extractions. At a minimum, we will extract data on study characteristics (including study authors, study year, study country, participants and exposure), study design (including study type and measurements of the risk factor), risk of bias (including missing data, as indicated by response rate and other measures) and study context. The estimates of the proportion of the population exposed to the occupational risk factor from included studies will be entered into and managed with the Review Manager, Version 5.3 (RevMan 5.3) (Anon, 2014) or DistillerSR (EvidencePartner, 2017) software.

We will also extract data on potential conflict of interest in included studies, including the financial disclosures and funding sources of each author and their affiliated organization. We will use a modification of a previous method to identify and assess undisclosed financial interests (Forsyth et al., 2014). Where no financial disclosure/conflict of interest is provided, we will search declarations of interest both in other records from this study published in the 36 months prior to the included study record and in other publicly available repositories (Drazen et al., 2010a; Drazen et al., 2010b).

We will request missing data from the principal study author by email or phone, using the contact details provided in the principal study record. If no response is received, we will follow up twice via email, at two and four weeks.

3.1.5. Risk of bias assessment

Generally agreed methods (i.e. framework plus tool) for assessing risk of bias do not exist for systematic reviews of input data for health estimates (The GATHER Working Group, 2016), for burden of disease studies, of prevalence studies in general (Munn et al., 2014) and of prevalence studies of occupational and/or environmental risk factors specifically (Krauth et al., 2013; Mandrioli and Silbergeld, 2016; Vandenberg et al., 2016). None of the five standard risk of bias assessment methods in systematic reviews (Rooney et al., 2016) are applicable to assessing prevalence studies. The *Navigation Guide* does not support checklist approaches, such as (Munn et al., 2014; Hoy et al., 2012) for assessing risk of bias in prevalence studies.

We will use a modified version of the *Navigation Guide* risk of bias tool (Lam et al., 2016a) that we developed specifically for Systematic Review 1 (Appendix C). We will assess risk of bias on the levels of the individual study and the entire body of evidence. As per our preliminary tool, we will assess risk of bias along five domains: (i) selection bias; (ii) performance bias; (iii) misclassification bias; (iv) conflict of interest; and (v) other biases. Risk of bias will be: "low"; "probably low"; "probably high"; "high" or "not applicable". To judge the risk of bias in each domain, we will apply our *a priori* instructions (Appendix C).

All risk of bias assessors (BAE, DG, LMH and GS) will trial the tool until they synchronize their understanding and application of each risk of bias domain, considerations and criteria for ratings. At least two study authors (out of: BAE, DG and LMH) will then independently judge the risk of bias for each study by outcome, and a third author (GS) will resolve any conflicting judgments. We will present the findings of our risk of bias assessment for each eligible study in a standard 'Risk of bias' table (Higgins et al., 2011). Our risk of bias assessment for the entire body of evidence will be presented in a standard 'Risk of bias summary' figure (Higgins et al., 2011).

3.1.6. Synthesis of results

We will neither produce any summary measures, nor synthesise the evidence quantitatively. The included evidence will be presented in what could be described as an 'evidence map'. All included data points from included studies will be presented, together with meta-data on the study design, number of participants, characteristics of population, setting and exposure measurement of the data point.

3.1.7. Quality of evidence assessment

There is no agreed method for assessing quality of evidence in systematic reviews of the prevalence of occupational and/or environmental risk factors. We will adopt or adapt from the latest *Navigation Guide* instructions for grading (Lam et al., 2016a), including criteria (Appendix D). We will downgrade for the following five reasons from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach: (i) risk of bias; (ii) inconsistency; (iii) indirectness; (iv) imprecision; and (v) publication bias (Schünemann et al., 2011). We will grade the evidence, using the three *Navigation Guide* quality of evidence ratings: "high", "moderate" and "low" (Lam et al., 2016a). Within each of the relevant reasons for downgrading, we will rate any concern per reason as "none", "serious" or "very serious". We will start at "high" for non-randomized studies and will downgrade for no concern by nil, for a serious concern by one grade (−1) and for a very serious concern by two grades (−2). We will not up-grade or down-grade the quality of evidence for the three other reasons normally considered in GRADE assessments (i.e. large effect, dose-response and plausible residual confounding and bias), because we consider them irrelevant for prevalence estimates.

All quality of evidence assessors (BAE, LMH and DG) will trial the application of our instructions and criteria for quality of evidence assessment until their understanding and application is synchronized. At least two review authors (LMH and DG) will independently judge the quality of evidence for the entire body of evidence by outcome. A third review author (GS) will resolve any conflicting judgments. In the systematic review, for each outcome, we will present our assessments for each GRADE domain, as well as an overall GRADE rating.

3.1.8. Strength of evidence assessment

To our knowledge, no agreed method exists for rating strength of evidence in systematic reviews of prevalence studies. We (AD and GS) will rate the strength of the evidence for use as input data for estimating national-level exposure to the risk factor. Our rating will be based on a combination of the following four criteria: (i) quality of the entire body of evidence; (ii) population coverage of evidence (WHO regions and countries); (iii) confidence in the entire body of evidence; and (iv) other compelling attributes of the evidence that may influence certainty. We will rate the strength of the evidence as either "potentially sufficient" or "potentially inadequate" for use as input data (Appendix E).

3.2. Systematic Review 2

3.2.1. Eligibility criteria

The PECO (Liberati et al., 2009) criteria are described below.

3.2.1.1. Types of populations. We will include studies of working-age (≥15 years) workers in the formal and informal economy. Studies of children (aged < 15 years) and unpaid domestic workers will be excluded. Participants residing in any WHO and/or ILO Member State and any industrial setting or occupational group will be included. We note that occupational exposure to long working hours may potentially have further population reach (e.g. across generations for workers of reproductive age) and acknowledge that the scope of our systematic reviews will not be able capture these populations and impacts on them. Appendix F provides a complete, but briefer overview of the PECO criteria.

3.2.1.2. Types of exposures. We will include studies that define long working hours in accordance with our standard definition (Table 1). We will again prioritize measures of the total number of hours worked, including in both of: main and secondary jobs, self-employment and salaried employment and informal and formal jobs. We will include all studies where long working hours were measured, whether objectively (e.g. by means of time recording technology), or subjectively, including studies that used measurements by experts (e.g. scientists with subject matter expertise) and self-reports by the worker or workplace administrator or manager. If a study presents both objective and subjective measurements, then we will prioritize the objective measurements. We will include studies with measurements from any data source, including registry data.

3.2.1.3. Types of comparators. The included comparator will be participants exposed to the theoretical minimum risk exposure level (Table 1). We will exclude all other comparators.

3.2.1.4. Types of outcomes. We will include studies that define ischaemic heart disease in accordance with our standard definition of this outcome (Table 2). Other coronary-related unspecific symptoms (e.g. chest pain) will be excluded. We expect that most studies examining exposure to long working hours and its effect on ischaemic heart disease have documented ICD-10 diagnostic codes. In the remaining cases, methods that approximate ICD-10 criteria will ascertain ischaemic heart disease.

The following measurements of ischaemic heart disease will be regarded as eligible:

i. Diagnosis by a physician with imaging.
ii. Hospital discharge records.
iii. Other relevant administrative data (e.g. records of sickness absence or disability).
iv. Medically certified cause of death.

All other measures will be excluded from this systematic review.

Objective and subjective measures of the outcome will be eligible. If a study presents both objective and subjective measurements, then we will prioritize the objective ones.

3.2.1.5. Types of studies. We will include studies that investigate the effect of long working hours on ischaemic heart disease for any years. Eligible study designs will be randomized controlled trials (including parallel-group, cluster, cross-over and factorial trials), cohort studies (both prospective and retrospective), case-control studies and other non-randomized intervention studies (including quasi-randomized controlled trials, controlled before-after studies and interrupted time series studies). We included a broader set of observational study designs than is commonly included, because a recent augmented Cochrane Review of complex interventions identified valuable additional studies using such a broader set of study designs (Arditi et al., 2016). As we have an interest in quantifying risk and not in qualitative assessment of hazard (Barroga and Kojima, 2013), we will exclude all other study designs (e.g. uncontrolled before-and-after, cross-sectional, qualitative, modelling, case and non-original studies).

Records published in any language will be included. Again, the search will be conducted using English language terms, so that records published in any language that present essential information (i.e. title and abstract) in English will be included. If a record is written in a language other than those spoken by the authors of this review or those of other reviews in the series (Descatha et al., 2018; Hulshof et al., 2018; John et al., 2018; Mandrioli et al., 2018; Pachito et al., 2018; Rugulies et al., 2018; Teixeira et al., 2018; Tenkate et al., 2018), then the record will be translated into English. Published and unpublished studies will be included.

Studies conducted using unethical practices will be excluded (e.g. studies that delibrately exposed humans to a known risk factor to human health).

3.2.1.6. Types of effect measures. We will include measures of the relative effect of a relevant level of long working hours on the risk of having, developing or dying from ischaemic heart disease, compared with the theoretical minimum risk exposure level. Included relative

effect measures are risk ratios and odds ratios for prevalence and mortality measures and hazard ratios for incidence measures (e.g., developed or died from ischaemic heart disease). Measures of absolute effects (e.g. mean differences in risks or odds) will be converted into relative effect measures, but if conversion is impossible, they will be excluded. To ensure comparability of effect estimates and facilitate meta-analysis, if a study presents an odds ratio, then we will convert it into a risk ratio, if possible, using the guidance provided in the Cochrane Collaboration's handbook for systematic reviews of interventions (Higgins and Green, 2011).

As shown in our logic framework (Fig. 1), we *a priori* consider the following variables to be potential effect modifiers of the effect of long working hours on ischaemic heart disease: country, age, sex, industrial sector, occupation and formality of employment. We consider age, sex and socio-economic position to be potential confounders. Potential mediators are: tobacco smoking, alcohol use, physical inactivity, unhealthy diet, impaired sleep, poor recovery, autonomous nervous system activity and immune system activity.

If a study presents estimates for the effect from two or more alternative models that have been adjusted for different variables, then we will systematically prioritize the estimate from the model that we consider best adjusted, applying the lists of confounders and mediators identified in our logic model (Fig. 1). We will prioritize estimates from models adjusted for more potential confounders over those from models adjusted for fewer. For example, if a study presents estimates from a crude, unadjusted model (Model A), a model adjusted for one potential confounder (Model B) and a model adjusted for two potential confounders (Model C), then we will prioritize the estimate from Model C. We will prioritize estimates from models unadjusted for mediators over those from models that adjusted for mediators, because adjustment for mediators can introduce bias. For example, if Model A has been adjusted for two confounders and Model B has been adjusted for the same two confounders and a potential mediator, then we will choose the estimate from Model A over that from Model B. We prioritize estimates from models that can adjust for time-varying confounders that are at the same time also mediators, such as marginal structural models (Pega et al., 2016) over estimates from models that can only adjust for time-varying confounders, such as fixed-effects models, (Gunasekara et al., 2014), over estimates from models that cannot adjust for time-varying confounding. If a study presents effect estimates from two or more potentially eligible models, then we will explain specifically why we prioritized the selected model.

3.2.2. Information sources and search

3.2.2.1. Electronic academic databases. At a minimum, we (CB, EC and PL) will search the eight following electronic academic databases:

1. International Clinical Trials Register Platform (to 31 May 2018).
2. Ovid MEDLINE with Daily Update (1946 to 31 May 2018).
3. PubMed (1946 to 31 May 2018).
4. EMBASE (1947 to 31 May 2018).
5. Scopus (1788 to 31 May 2018).
6. Web of Science (1945 to 31 May 2018).
7. CISDOC (1901 to 2012).
8. PsychInfo (1880 to 31 May 2018).

The Ovid Medline search strategy for Systematic Review 2 is presented in Appendix G. We will perform searches in electronic databases operated in the English language using a search strategy in the English language. We will adapt the search syntax to suit the other electronic academic and grey literature databases. When we are nearing completion of the review, we will search the PubMed database for the most recent publications (e.g., e-publications ahead of print) over the last six months. Any deviation from the proposed search strategy in the actual search strategy will be documented.

3.2.2.2. Electronic grey literature databases. At a minimum, we (GS and AT) will search the two following two electronic academic databases:

1. OpenGrey (http://www.opengrey.eu/).
2. Grey Literature Report (http://greylit.org/).

3.2.2.3. Internet search engines. We (GS and MMF) will also search the Google (www.google.com/) and Google Scholar (www.google.com/scholar/) Internet search engines and screen the first 100 hits for potentially relevant records.

3.2.2.4. Organizational websites. The websites of the seven following international organizations and national government departments will be searched for both systematic reviews by GS and HP:

1. International Labour Organization (www.ilo.org/).
2. World Health Organization (www.who.int).
3. European Agency for Safety and Health at Work (https://osha.europa.eu/en).
4. Eurostat (www.ec.europa.eu/eurostat/web/main/home).
5. China National Knowledge Infrastructure (http://www.cnki.net/).
6. Finnish Institute of Occupational Health (https://www.ttl.fi/en/).
7. United States National Institute of Occupational Safety and Health (NIOSH) of the United States of America, using the NIOSH data and statistics gateway (https://www.cdc.gov/niosh/data/).

3.2.2.5. Hand-searching and expert consultation. We (GS and JL) will hand-search for potentially eligible studies in:

- Reference list of previous systematic reviews.
- Reference list of all included study records.
- Study records published over the past 24 months in the three peer-reviewed academic journals with the largest number of included studies.
- Study records that have cited the included studies (identified in Web of Science citation database).
- Collections of the review authors.

Additional experts will be contacted with a list of included studies, with the request to identify potentially eligible additional studies.

3.2.3. Study selection

Study selection will be carried out with the Rayyan Systematic Reviews Web App (Ouzzani et al., 2016). All study records identified in the search will be downloaded and duplicates will be identified and deleted. Afterwards, at least two review authors (PLS and JL) will independently screen titles and abstracts (step 1) and then full texts (step 2) of potentially relevant records. A third review author (JS) will resolve any disagreements between the two review authors. If a study record identified in the literature search was authored by a review author assigned to study selection or if an assigned review author was involved the study, then the record will be re-assigned to another review author for study selection. The study selection will be documented in a flow chart in the systematic review, as per PRISMA guidelines (Liberati et al., 2009).

3.2.4. Data extraction and data items

A data extraction form will be developed and trialled until data extractors reach convergence and agreement. At a minimum, two review authors (RR and JL) will extract data on study characteristics (including study authors, study year, study country, participants, exposure and outcome), study type (including study design, comparator, epidemiological models used and effect estimate measure), risk of bias (including selection bias, reporting bias, confounding and reverse causation) and study context (e.g. data on contemporaneous exposure to other occupational risk factors potentially relevant for deaths or

other health loss from ischaemic heart disease). A third review author (JS) will resolve conflicts in data extraction. Data will be entered into and managed with the Review Manager, Version 5.3 (RevMan 5.3) (Anon, 2014) or DistillerSR (EvidencePartner, 2017) software, but the Health Assessment Workspace Collaborative (HAWC) (Shapiro, 2013) may also be used in parallel or to prepare data for entry into RevMan 5.3.

We will also extract data on potential conflict of interest in included studies. For each author and affiliated organization of each included study record, we will extract their financial disclosures and funding sources. We will use a modification of a previous method to identify and assess undisclosed financial interest of authors (Forsyth et al., 2014). Where no financial disclosure or conflict of interest statements are available, we will search the name of all authors in other study records gathered for this study and published in the prior 36 months and in other publicly available declarations of interests (Drazen et al., 2010a; Drazen et al., 2010b).

We will request missing data from the principal study author by email or phone, using the contact details provided in the principal study record. If we do not receive a positive response from the study author, we will send follow-up emails twice, at two and four weeks.

3.2.5. Risk of bias assessment

Standard risk of bias tools do not exist for systematic reviews for hazard identification in occupational and environmental health, nor for risk assessment. The five methods specifically developed for occupational and environmental health are for either or both hazard identification and risk assessment, and they differ substantially in the types of studies (randomized, observational and/or simulation studies) and data (e.g. human, animal and/or *in vitro*) they seek to assess (Rooney et al., 2016). However, all five methods, including the *Navigation Guide* one (Lam et al., 2016a), assess risk of bias in human studies similarly (Rooney et al., 2016).

The *Navigation Guide* was specifically developed to translate the rigor and transparency of systematic review methods applied in the clinical sciences to the evidence stream and decision context of environmental health (Woodruff and Sutton, 2014), which includes workplace environment exposures and associated health outcomes. The guide is our overall organizing framework, and we will also apply its risk of bias assessment method in Systematic Review 2. The *Navigation Guide* risk of bias assessment method builds on the standard risk of bias assessment methods of the Cochrane Collaboration (Higgins et al., 2011) and the US Agency for Healthcare Research and Quality (Viswanathan et al., 2008). Some further refinements of the *Navigation Guide* method may be warranted (Goodman et al., 2017), but it has been successfully applied in several completed and ongoing systematic reviews (Johnson et al., 2014; Koustas et al., 2014; Lam et al., 2014; Vesterinen et al., 2014; Johnson et al., 2016; Lam et al., 2016b; Lam et al., 2017; Lam et al., 2016c). In our application of the *Navigation Guide* method, we will draw heavily on one of its latest versions, as presented in the protocol for an ongoing systematic review (Lam et al., 2016a). Should a more suitable method become available, we may switch to it.

We will assess risk of bias on the individual study level and on the body of evidence overall. The nine risk of bias domains included in the *Navigation Guide* method for human studies are: (i) source population representation; (ii) blinding; (iii) exposure assessment; (iv) outcome assessment; (v) confounding; (vi) incomplete outcome data; (vii) selective outcome reporting; (viii) conflict of interest; and (ix) other sources of bias. While two of the earlier case studies of the *Navigation Guide* did not utilize outcome assessment as a risk of bias domain for studies of human data (Johnson et al., 2014; Koustas et al., 2014; Lam et al., 2014; Vesterinen et al., 2014), all of the subsequent reviews have included this domain (Lam et al., 2016a; Johnson et al., 2016; Lam et al., 2016b; Lam et al., 2017; Lam et al., 2016c). Risk of bias or confounding ratings will be: "low"; "probably low"; "probably high"; "high"; or "not applicable" (Lam et al., 2016a). To judge the risk of bias in each domain, we will apply *a priori* instructions (Appendix H), which we have adopted or adapted from an ongoing *Navigation Guide* systematic review (Lam et al., 2016a). For example, a study will be assessed as carrying "low" risk of bias from source population representation, if we judge the source population to be described in sufficient detail (including eligibility criteria, recruitment, enrollment, participation and loss to follow up) and the distribution and characteristics of the study sample to indicate minimal or no risk of selection effects. The risk of bias at study level will be determined by the worst rating in any bias domain for any outcome. For example, if a study is rated as "probably high" risk of bias in one domain for one outcome and "low" risk of bias in all other domains for the outcome and in all domains for all other outcomes, the study will be rated as having a "probably high" risk of bias overall.

All risk of bias assessors (EC, AT and PL) will jointly trial the application of the risk of bias criteria until they have synchronized their understanding and application of these criteria. At least two study authors (EC and AT) will independently judge the risk of bias for each study by outcome. Where individual assessments differ, a third author (PL) will resolve the conflict. In the systematic review, for each included study, we will report our study-level risk of bias assessment by domain in a standard 'Risk of bias' table (Higgins et al., 2011). For the entire body of evidence, we will present the study-level risk of bias assessments in a 'Risk of bias summary' figure (Higgins et al., 2011).

3.2.6. Synthesis of results

We will conduct meta-analyses separately for estimates of the effect on prevalence, incidence and mortality. If we find two or more studies with an eligible effect estimate, two or more review authors (JS and JL) will independently investigate the clinical heterogeneity of the studies in terms of study type, participants (including country, sex, age and industrial sector or occupation), level of risk factor exposure, comparator and outcomes. If we find that effect estimates differ considerably by country, sex and/or age or a combination of these, then we will synthesise evidence for the relevant populations defined by country, sex and/or age or combination thereof. Differences by country could include or be expanded to include differences by country group (e.g. WHO region or World Bank income group). If we find that effect estimates are clinically homogenous across countries, sexes and age groups, then we will combine studies from all of these populations into one pooled effect estimate that could be applied across all combinations of countries, sexes and age groups in the WHO/ILO joint methodology.

If we judge two or more studies for the relevant combination of country, sex and age group or combination thereof, to be sufficiently clinically homogenous to potentially be combined quantitatively using quantitative meta-analysis, then we will test the statistical heterogeneity of the studies using the I^2 statistic (Figueroa, 2014). If two or more clinically homogenous studies are found to be sufficiently homogenous statistically to be combined in a meta-analysis, we will pool the risk ratios of the studies in a quantitative meta-analysis, using the inverse variance method with a random effects model to account for cross-study heterogeneity (Figueroa, 2014). The meta-analysis will be conducted in RevMan 5.3 (Anon, 2014), but the data for entry into these programmes may be prepared using another recognized statistical analysis programme, such as Stata. We will neither quantitatively combine data from studies with different designs (e.g. combining cohort studies with case-controls studies), nor unadjusted and adjusted models. We will only combine studies that we judge to have a minimum acceptable level of adjustment for confounders. If quantitative synthesis is not feasible, then we will synthesise the study findings narratively and identify the estimates that we judged to be the highest quality evidence available.

3.2.7. Additional analyses

If we source micro-data on exposure, outcome and potential confounding variables, we may conduct meta-regressions to adjust

optimally for potential confounders.

If there is evidence for differences in effect estimates by country, sex, age, industrial sector and/or occupation or by a combination of these variables, then we will conduct subgroup analyses by the relevant variable or combination of variables, as feasible. Where both studies on workers in the informal economy and in the formal economy are included, then we will conduct sub-group analyses by formality of economy. Findings of these subgroup analyses, if any, will be used as parameters for estimating burden of disease specifically for relevant populations defined by these variables. We will also conduct subgroup analyses by study design (e.g. randomized controlled trials versus cohort studies versus case-control studies).

We will perform sensitivity analyses that will include only studies judged to be of "low" or "probably low" risk of bias from conflict of interest; judged to be of "low" or "probably low" risk of bias; and with documented or approximated ICD-10 diagnostic codes. We may also conduct a sensitivity analysis using an alternative meta-analytic model, namely the inverse variance heterogeneity (IVhet) model (Doi et al., 2017).

3.2.8. Quality of evidence assessment

We will assess quality of evidence using a modified version of the *Navigation Guide* quality of evidence assessment tool (Lam et al., 2016a). The tool is based on the GRADE approach (Schünemann et al., 2011), adapted specifically to systematic reviews in occupational and environmental health (Morgan et al., 2016). Should a more suitable method become available, we may switch to it.

At least two review authors (JS and JL) will assess quality of evidence for the entire body of evidence by outcome, with any disagreements resolved by a third review author. We will adopt or adapt the latest *Navigation Guide* instructions (Appendix D) for grading the quality of evidence (Lam et al., 2016a). We will downgrade the quality of evidence for the following five GRADE reasons: (i) risk of bias; (ii) inconsistency; (iii) indirectness; (iv) imprecision; and (v) publication bias. If our systematic review includes ten or more studies, we will generate a funnel plot to judge concerns on publication bias. If it includes nine or fewer studies, we will judge the risk of publication bias qualitatively. To assess risk of bias from selective reporting, protocols of included studies, if any, will be screened to identify instances of selective reporting.

We will grade the evidence, using the three *Navigation Guide* standard quality of evidence ratings: "high", "moderate" and "low" (Lam et al., 2016a). Within each of the relevant domains, we will rate the concern for the quality of evidence, using the ratings "none", "serious" and "very serious". As per *Navigation Guide*, we will start at "high" for randomized studies and "moderate" for observational studies (Lam et al., 2016a). Quality will be downgrade for no concern by nil grades (0), for a serious concern by one grade (−1) and for a very serious concern by two grades (−2). We will up-grade the quality of evidence for the following other reasons: large effect, dose-response and plausible residual confounding and bias. For example, if we have a serious concern for risk of bias in a body of evidence consisting of observational studies (−1), but no other concerns and there are no reasons for upgrading, then we will downgrade its quality of evidence by one grade from "moderate" to "low".

3.2.9. Strength of evidence assessment

We will apply the standard *Navigation Guide* methodology (Lam et al., 2016a) to rate the strength of the evidence. The rating will be based on a combination of the following four criteria: (i) quality of the body of evidence; (ii) direction of the effect; (iii) confidence in the effect; and (iv) other compelling attributes of the data that may influence our certainty. The ratings for strength of evidence for the effect of long working hours on ischaemic heart disease will be "sufficient evidence of toxicity/harmfulness", "limited of toxicity/harmfulness", "inadequate of toxicity/harmfulness" and "evidence of lack of toxicity/harmfulness" (Appendix I).

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Author contributions

IDI, NL, FP and APU had the idea for the systematic review. IDI, NL, FP and YU gathered the review team. FP led and all authors contributed to the development of the standard methodology for all systematic reviews in the series. FP led and all authors contributed to the development and writing of the standard template for all protocols in the series. JL and JS are the lead reviewers of this systematic review. JL and JS wrote the first draft of this protocol, using the protocol template prepared by FP; and CB, EC, MMF, PL, JL, FP, HP, RR, JS, PLS, AT and YU made substantial contributions to the revisions of the manuscript. The search strategy was mainly developed and piloted by DP, GS and JL. JL, FP and JS are experts in epidemiology, JL and JS are experts in occupational psychosocial risk factors and cardiovascular diseases and FP is an expert in systematic review methodology. FP coordinated all inputs from World Health Organization, International Labour Organization and external experts and ensured consistency across the systematic reviews of the series. JL and JS are the guarantors of the systematic review.

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Conflict of interest

None declared.

Appendices. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.06.022.

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Association of workplace social capital with psychological distress: results from a longitudinal multilevel analysis of the J-HOPE Study

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ABSTRACT

Objectives Workplace social capital (WSC) is increasingly recognised as a social contextual determinant of workers' mental health, but longitudinal data are sparse. We aimed to evaluate the impact of changes in unit-level WSC on psychological distress among Japanese employees using a prospective multilevel repeated-measures design.

Participants and study design We conducted a 2-year prospective cohort study with 1,944 men and 786 women aged 18–65 years. Participants worked at two manufacturing worksites in Japan and were free from mental illness from the first to third study waves. We used a three-level multilevel regression design to evaluate the prospective association of unit-level WSC with individual-level psychological distress. WSC was measured using a validated six-item instrument and individual-level psychological distress with the Kessler Psychological Distress Scale (K6).

Results The null model indicated a significant degree of between-work unit variation in psychological distress (intraclass correlation=0.1%, p<0.001). In the full model, each SD increase in unit-level WSC was associated with 0.69 point improvement in K6 scores (95% CI −1.12 to −0.26).

Conclusions This prospective study builds on existing knowledge by showing an association between unit-level WSC and modest improvements in mental health among employees in Japan. We recommend that WSC is considered alongside other contextual influences when assessing employees' mental health risks.

Strengths and limitations of this study

- ► A strength of our study is that we evaluated the impact of a change in work unit social capital on changes in individual workers' psychological distress (first differences design).
- ► The use of a self-administered questionnaire to assess both exposures and outcome might have produced common method bias.
- ► The generalisability of the results is uncertain, because workplace social capital depends on the prevailing norm and culture of an organisation and the sample for this study was drawn from a single company.

INTRODUCTION

Social capital is defined as resources accessed by individuals as a result of their membership of a network or group.[1] Workplace social capital (WSC) has attracted increased attention as a potentially important organisational/contextual influence on workers' mental health.[1] A previous study from Finland demonstrated an association between WSC and various mental health indicators.[2] Employees' mental health has also emerged as a critical concern in recent years.[3]

The pathways linking social capital to health outcomes vary by level of analysis.[1] In this paper, we have focused on social capital as a group-level construct. Group-level WSC can bring benefits to individuals, probably through increased emotional support and respect from co-workers, which can reduce psychophysiological stress responses to physically strenuous jobs.[4]

Four cross-sectional and six longitudinal studies have investigated the association between WSC and mental illness.[5–14] A 4-year prospective study demonstrated the impact of changes in individual-level WSC on changes in mental health.[11] Another 5-year prospective multilevel study found that organisational-level WSC was not associated with mental health problems.[9] However, that study assessed unit-level WSC at baseline only and did not update exposure during follow-up.[9] Therefore, the impact of a *change* in unit-level WSC on a worker's psychological distress remains unknown. For example, employees' perceptions of WSC as well as the association between social capital and psychological distress may fluctuate with the business cycle.[15 16]

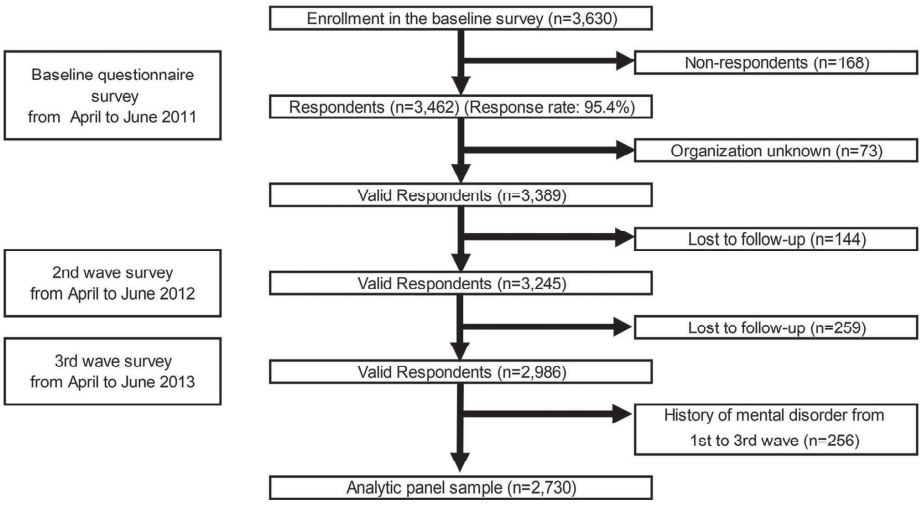

Figure 1 Flow of participants for the study sample (n=2730).

In this study, we constructed a multilevel analysis using three levels (repeated measurements of psychological distress nested within individual employees, then work units) to evaluate the impact of a *change* in unit-level WSC on individual workers' psychological distress. We used panel data from three waves of the Japanese Study of Health, Occupation, and Psychosocial Factors Related Equity (J-HOPE), an occupational cohort study on social class and health in Japan that involved 21 work units.

METHODS

Participants and study design

Written consent was obtained from participants.

This study was conducted as part of J-HOPE, a large-scale workplace-based prospective study involving around 10,000 workers in Japan.[11 17] We used data from the baseline, second and third wave surveys for 1 of the 12 participating J-HOPE sites, based on the availability of exposure data (ie, unit-level information). A detailed flow chart of the study sample is shown in figure 1. We conducted a 2-year prospective cohort study with workers aged 18–65 years (n=3,630) at two manufacturing sites operated by an electrical components company in the Osaka region of Japan. All employees at the two sites were invited to participate in the J-HOPE baseline survey, conducted from April to June 2011. The second and third waves were conducted from April to June 2012 and from April to June 2013. Data were collected using a self-administered questionnaire that included items about psychosocial factors, and demographic and lifestyle characteristics. The original sample included 3,462 respondents in the first wave; 3,344 in the second wave (follow-up rate 95.8%); and 3,179 in the third wave (follow-up rate 88.1%). We excluded participants who did not participate in all three survey waves and anyone who reported a history of mental disorder in any of the three survey waves. This resulted in a sample of 2730 employees for the analysis. The analysis was conducted with the J-HOPE data set as on 22 December 2016. 'Work unit' at the two manufacturing sites was defined by division, of which there were 21.

We compared the baseline characteristics of the study population (n=3,462) with those lost to follow-up (n=694). At baseline, there were no significant differences between the two groups by sex, weekly working hours, annual family income, chronic diseases, smoking status, body mass index (BMI), job strain or psychological distress. However, workers lost to follow-up were older, had a higher occupational status, worked in units with a higher proportion of employees with higher education, drank alcohol more often and reported higher levels of physical exercise.

Dependent variable: psychological distress

Psychological distress was assessed using the Kessler Psychological Distress Scale (K6). The K6 was originally developed as a screening instrument for non-specific psychological distress and serious mental illness. Its internal reliability and validity have been documented.[18] The K6 consists of a six-item battery asking how frequently respondents had experienced symptoms of psychological distress in the past 30 days. Responses range from '0' (none of the time) to '4' (all of the time), with total scores ranging from 0 to 24. The K6 has been translated into Japanese, and the Japanese version has been validated.[19] In this sample, Cronbach's α coefficients for K6 were 0.88 in the first wave, 0.89 in the second wave and 0.89 in the third wave.

Independent variable: WSC

WSC was the main independent variable of interest. To assess this, we used a validated six-item instrument to measure bonding WSC, with each item scored on a four-point Likert Scale: 1: strongly disagree, 2: disagree, 3: agree, 4: strongly agree. The responses were summed, resulting in individual WSC scores from 6 to 24 with

higher scores indicating higher WSC. The internal consistency of the scale was acceptably high in each survey, with Cronbach's α coefficients for the six-item WSC scale of 0.89 in the first wave, 0.90 in the second wave and 0.90 in the third wave. The items in the measure are: 'People keep each other informed about work-related issues in the work unit', 'We have a 'we are together' attitude', 'People feel understood and accepted by each other', 'In our workplace, there is an atmosphere of helping each other', 'In our workplace, we trust each other', and 'Our workplace is a place of laughter and smiles'. The WSC scale has acceptable reliability and validity, described in detail elsewhere.[20] In brief, the scale includes items relevant to bonding WSC to measure the network, trust and reciprocity aspects of the concepts.

Unit-level WSC (level 3) was calculated as the mean of individual (level 1) responses from co-workers in the same work unit. To avoid multicollinearity, we orthogonalised individual-level and unit-level WSC by mean-centring; that is, by subtracting unit-level values (average of individual-level responses) from individual-level values.

Measurement of covariates

The demographic and lifestyle characteristics that were measured based on previous studies about the risk factor for psychological distress were sex, age, education,[21] BMI,[22] job strain,[23] occupation,[24] employment contract,[25] weekly working hours,[26] annual family income,[27] chronic medical illness,[28] smoking status,[29] frequency of alcohol drinking[30] and physical exercise.[31] Employment contract and work-unit information were obtained from the company. BMI was calculated from health check-up results by dividing weight (kg) by the square of height (m^2). We used the Job Content Questionnaire to measure psychological demands and decision latitude.[32] The psychological demand scale has five items, including 'Work fast' and 'Work hard' (response range: 12–48), and the decision latitude scale consists of nine items, including 'Learn new things' and 'Repetitive work' (response range: 24–96). Cronbach's α coefficients for psychological demands and decision latitude were, respectively, 0.67 and 0.82 in the first wave, 0.69 and 0.81 in the second wave, and 0.70 and 0.81 in the third wave. Based on a previous study,[33] we defined job strain as the ratio of psychological demands score ×2 to the decision latitude score, expressed as a continuous variable. Age, BMI and job strain were expressed as continuous variables. Educational attainment was categorised into five groups: 11 years or less, 12–13 years, 14–15 years, 16–17 years and 18 years or more spent in education. We classified occupation based on the International Standard Classification of Occupations, which is based on skill level and skill specialisation.[34] Participants chose one of nine options: (1) managers; (2) professionals; (3) technicians and associate professionals; (4) clerical support workers; (5) service and sales workers; (6) craft and related trade workers; (7) plant and machine operators and assemblers; (8) armed forces occupations; and (9) others. Responses were divided into four categories: managers, non-manual workers (professionals, technicians and associate professionals, clerical support workers, and service and sales workers), manual workers (craft and related trade workers, plant and machine operators and assemblers, and armed forces occupations) and others. Employment contract was categorised as regular or part-time. Weekly working hours were categorised as: ≤30 hours, 31–40 hours, 41–50 hours, 51–60 hours and ≥61 hours per week. Study participants were asked to indicate their annual family income from six income bands: (1) less than 3 million yen; (2) 3–5 million yen; (3) 5–8 million yen; (4) 8–10 million yen; (5) 10–15 million yen; and (6) more than 15 million yen. Past history or current experience of chronic physical conditions was assessed by multiple choice. Conditions included hypertension, diabetes mellitus, hyperlipidaemia, stroke, myocardial infarction and cancer. Smoking status was categorised as never smoked, former smoker or current smoker. Frequency of alcohol drinking was classified as does not drink, drinks but not everyday or drinks every day. Physical exercise was classified as no exercise, light exercise more than once a week, heavy exercise once or twice a week, or heavy exercise more than three times a week. We defined 'light exercise' as exercise that did not produce shortness of breath or elevated heart rate, and 'heavy exercise' as exercise causing shortness of breath and elevated heart rate.

Statistical analysis

Multilevel modelling was performed by considering the association between different levels, with time nested within individuals, then within workplace. By adding a random part in the analysis, the technique accounts for dependence between different levels, allowing the intercept coefficients to vary among different work units. Variance partition coefficient (VPC) was used to estimate the proportion of total variance in K6 scores attributable to the work unit.

We estimated a null model that included only a random intercept and allowed us to estimate the intraclass correlation coefficient (ICC(1)).[35 36] ICC(1) was 4.0% ($p<0.001$) in the first wave, 3.5% ($p<0.001$) in the second wave and 4.0% ($p<0.001$) in the third wave, indicating significant variance in individual WSCs between work units.

We also used a within-group agreement index (r_{wg}) to measure the validity of individual responses. The r_{wg} is calculated by comparing an observed group variance with an expected random variance.[37 38] A higher r_{wg} indicates that social capital may be treated as a contextual phenomenon and supports the aggregation of unit members' perception of the phenomenon to form the derived variable. The r_{wg} of WSC in work units was 0.67–0.82 in the first wave, 0.66–0.89 in the second wave and 0.79–0.92 in the third wave. An r_{wg} over 0.7 supports homogeneity in perceptions of the phenomenon.[39]

The longitudinal analysis was performed with time (at level 1), individuals (at level 2) and work unit (at level 3).

Three models were run, with the cumulative measure of K6 regressed on work units in the empty model (model 0), with individual-level WSC and all individual-level variables included in model 1, with a full model including all individual-level and work unit-level variables and work unit-level WSC and workplace size included in model 1 as random-effects parts (model 2). We standardised all explanatory variables before inclusion in the multilevel analysis.

To address potential bias resulting from missing data, we used multiple imputation by the Markov Chain Monte Carlo method assuming that data were missing at random for explanatory variables and covariates. We created 50 imputed data sets and combined each analysis result using the STATA command 'mi estimate.' All analyses were performed with STATA V.14.0 (STATA). We defined statistical significance as a two-sided p value<0.05.

Patient and public involvement

No participants were involved in developing the research question, outcome measures and overall design of the study. Due to participant anonymity, we are unable to disseminate the results of the research directly to study participants.

RESULTS

Table 1 summarises the participants' characteristics. The majority of the participants were male (71.2%) and the mean age was 38.8 years (SD=10.9) (table 1). The largest occupational group was manual workers. About 80% of our sample was employed full time and about 30% worked 41–50 hours per week in the time between the first and third surveys.

Table 2 shows the workplace characteristics. The mean unit-level social capital was 16.3 (SD=2.8) to 17.1 (SD=0.5 and 0.8) in the first survey, 16.1 (SD=2.1) to 17.3 (SD=0.2) in the second survey and 16.4 (SD=0.0) to 17.4 (SD=1.0) in the third survey.

Table 3 shows the three-level hierarchical regression results. The null model indicated a significant amount of variation in psychological distress between workplaces (ICC=0.1%, p<0.001). Random effects in the initial empty model showed that 50.5% of the average variation in psychological distress was attributed to clustering by individuals over time, while 0.1% was attributed to clustering by work units over time. In model 1, individual-level WSC showed a significant association with psychological distress (coefficient = −0.83; 95% CI −0.92 to −0.73). In model 2, the VPC at the work unit level was 6.9%. Unit-level WSC was significantly related to change in psychological distress (coefficient = −0.69; 95% CI −1.12 to −0.26). This equated to an average improvement in K6 scores of roughly 0.69 points over 3 years for every SD change in unit-level WSC. Similarly, individual-level WSC was significantly related to psychological distress (coefficient = −0.84; 95% CI −0.94 to −0.74). In summary, the

Table 1 Characteristics of eligible participants in each survey wave (2011–2013) (n=2,730)

Characteristics	First survey	Second survey	Third survey
Sex			
Male	1,944 (71.2)		
Female	786 (28.8)		
Age, years (SD)	38.8 (10.9)		
Education (years), n (%)			
11 or less	43 (1.6)	43 (1.6)	39 (1.4)
12–13	1,608 (58.9)	1,621 (59.4)	1,579 (57.8)
14–15	502 (18.4)	497(18.2)	473 (17.3)
16–17	324 (11.9)	326 (11.9)	314 (11.5)
18 or more	193 (7.1)	198 (7.3)	180 (6.6)
Missing	60 (2.2)	45 (1.6)	145 (5.3)
WSC, mean (SD)	16.9 (3.3)	17.1 (3.0)	17.0 (3.1)
Psychological distress, mean (SD)	5.4 (4.4)	4.2 (4.2)	4.2 (4.2)
BMI, mean (SD)	22.8 (3.6)	22.9 (3.6)	23.0 (3.7)
Job strain, mean (SD)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)
Occupation, n (%)			
Manager	219 (8.0)	244 (8.9)	249 (9.1)
Non-manual worker	694 (25.4)	701 (25.7)	656 (24.0)
Manual worker	1,275 (46.7)	1,211 (44.4)	1,197 (43.8)
Others	446 (16.3)	494 (18.1)	481 (17.6)
Missing	96 (3.5)	80 (2.9)	147 (5.4)
Employment contract, n (%)			
Regular employee	2,228 (81.6)	2,225 (81.5)	2,130 (78.0)
Part-time employee	502 (18.4)	492 (18.0)	492 (18.0)
Missing	0 (0.0)	13 (0.5)	108 (4.0)
Weekly working hours, n (%)			
30 or less	616 (22.6)	554 (20.3)	514 (18.8)
31–40	589 (21.6)	806 (29.5)	695 (25.5)
41–50	905 (33.2)	838 (30.7)	872 (31.9)
51–60	427 (15.6)	343 (12.6)	401 (14.7)
61 or more	136 (5.0)	128 (4.7)	119 (4.4)
Missing	57 (2.1)	61 (2.2)	129 (4.7)
Annual family income (million yen), n (%)			
<3	357 (13.1)	313 (11.5)	318 (11.6)
3–5	675 (24.7)	775 (28.4)	695 (25.5)
5–8	1,066 (39.0)	1,021 (37.4)	998 (36.6)
8–10	348 (12.7)	316 (11.6)	314 (11.5)
10–15	193 (7.1)	194 (7.1)	172 (6.3)
15+	21 (0.8)	21 (0.8)	21 (0.8)
Missing	70 (2.6)	90 (3.3)	212 (7.8)
Chronic disease			
No	2,109 (77.3)	2,164 (79.3)	2,081 (76.2)
Yes	371 (13.6)	435 (15.9)	448 (16.4)
Missing	250 (9.2)	131 (4.8)	20 1(7.4)

Continued

Table 1 Continued

Characteristics	First survey	Second survey	Third survey
Smoking status, n (%)			
Never	1,574 (57.7)	1,552 (56.8)	1,495 (54.8)
Former	231 (8.5)	224 (8.2)	243 (8.9)
Current	894 (32.7)	909 (33.3)	874 (32.0)
Missing	31 (1.1)	45 (1.6)	118 (4.3)
Frequency of alcohol drinking, n (%)			
None	1,316 (48.2)	1,290 (47.3)	1,291 (47.3)
Sometimes	825 (30.2)	810 (29.7)	783 (28.7)
Everyday	560 (20.5)	588 (21.5)	540 (19.8)
Missing	29 (1.1)	42 (1.5)	116 (4.2)
Physical exercise, n (%)			
None	1,872 (68.6)	1,771 (64.9)	1,771 (64.9)
Light exercise more than once a week	487 (17.8)	554 (20.3)	511 (18.7)
Heavy exercise once or twice a week	240 (8.8)	251 (9.2)	224 (8.2)
Heavy exercise more than three times a week	46 (1.7)	80 (2.9)	73 (2.7)
Missing	85 (3.1)	74 (2.7)	151 (5.5)

BMI, body mass index; WSC, workplace social capital.

longitudinal analysis showed that unit-level WSC was associated with mental health over a 3-year period.

DISCUSSION

Our prospective study sought to contribute to the discussion on WSC and health by analysing the contextual influence of unit-level WSC on individual psychological distress across a 3-year period. Our findings suggested that unit-level WSC had a slightly favourable impact on individuals' psychological distress (ICC=0.1% in the null model). The impact of unit-level WSC on an individual's psychological distress (coefficient = −0.69; 95% CI −1.12 to −0.26) was about three quaters that of individual-level WSC (coefficient=−0.84; 95% CI −0.94 to −0.74), and the same as that of job strain (coefficient=0.62; 95% CI 0.53 to 0.72). However, unit-level WSC was comparable with the impact of occupation (coefficient = −0.19; 95% CI −0.31 to −0.07), chronic disease (coefficient=0.14; 95% CI 0.03 to 0.25) and annual familial income (coefficient = −0.24; 95% CI −0.35 to −0.13). These findings emphasise the contextual importance of unit-level WSC for workers' psychological distress.

To our knowledge, this is the first study of its kind to examine the influence of unit-level and individual-level WSC on psychological distress, using a multilevel prospective repeated-measures design. The only previously published study on this topic found that a higher perception of WSC among workers was associated with lower ORs for antidepressant treatment and physician-diagnosed depression.[9] However, the study found that unit-level WSC was not associated with depression outcomes after controlling for individual perceptions.[9] An explanation for these divergent results might be cultural differences in the workplace. Bonding social capital is particularly important in Japanese workplaces, because Japanese culture has a group orientation. Altruism, teamwork and group cohesiveness are emphasised in Japanese society, and individual identity is often subsumed within social group identity.[40 41]

In our crude analyses, the ICC for social capital was only 0.1%, indicating that a substantial proportion of the variance of individual social capital is between work units. This is quite low compared with the previous studies.[4 9 39 42] The reason for this discrepancy may be the number of work units and the repeated-measures design. Smaller number of individual employees per work units may show larger ICCs (number of participants/number of work units) such as 32,053/2,182,[4] 9,524/1,522,[39] and 2,043/260.[42] No previous studies have used the repeated measures of psychological distress.[4 9 39 42] The repeated measures may decrease ICC, which indicates the amount of variation in psychological distress between workplaces. The VPC at the work unit level was 6.9% which was in line with previous studies.[4 9 39 42]

Table 2 Workplace characteristics and workplace social capital (n=21)

Workplace size	First survey					Second survey					Third survey				
				r_{wg}					r_{wg}					r_{wg}	
	n	Mean	SD	Max	Min	n	Mean	SD	Max	Min	n	Mean	SD	Max	Min
10–50	5	16.3	2.8	0.82	0.67	5	16.1	2.1	0.82	0.66	6	16.6	1.8	0.91	0.79
50–99	5	17.1	0.8	0.82	0.72	3	17.1	0.8	0.89	0.86	3	17.4	1.0	0.91	0.80
100–199	5	17.1	0.5	0.82	0.78	6	17.0	0.6	0.87	0.81	7	17.2	0.4	0.88	0.81
200–299	2	16.7	0.5	0.80	0.77	3	17.3	0.2	0.86	0.82	3	17.2	0.1	0.84	0.82
≥300	4	16.8	0.3	0.80	0.76	4	17.0	0.3	0.86	0.81	2	16.4	0.0	0.83	0.80
Total	21	16.9	0.6			21	17.0	0.6			21	17.0	0.6		

r_{wg}, within-group agreement index.

Table 3 Associations between work unit-level/individual-level social capital and K6

Estimates	Model 0 Coefficient (95% CI)	Model 1 Coefficient (95% CI)	Model 2 Coefficient (95% CI)
Intercept	4.57 (4.41 to 4.73)	4.55 (4.36 to 4.74)	4.65 (4.17 to 4.99)
Work unit level			
Workplace social capital			–0.69 (–1.12 to –0.26)
Workplace size			0.09 (–0.22 to 0.41)
Individual level fixed effects			
Workplace social capital		-0.83 (–0.92 to –0.73)	–0.84 (–0.94 to –0.74)
Sex		0.13 (–0.06 to 0.32)	0.14 (–0.06 to 0.33)
Age		–0.63(–0.78 to–0.48)	–0.58 (–0.73 to –0.43)
Educational attainment		–0.18 (–0.31 to –0.04)	–0.17 (–0.31 to –0.03)
Occupation		–0.19 (–0.31 to –0.07)	–0.19 (–0.31 to –0.07)
Employment contract		–0.30 (–0.50 to –0.11)	–0.34 (–0.54 to –0.14)
Weekly working hours		0.03 (–0.08 to 0.15)	0.04 (–0.08 to 0.15)
Annual familial income		–0.23 (–0.34 to –0.12)	–0.24 (–0.35 to –0.13)
Chronic disease		0.14 (0.03 to 0.25)	0.14 (0.03 to 0.25)
Smoking status		–0.04 (–0.17 to 0.08)	–0.05 (–0.18 to 0.07)
Frequency of alcohol drinking		–0.01 (–0.13 to 0.10)	–0.02 (–0.14 to 0.09)
Physical exercise		–0.09 (–0.18 to 0.01)	–0.07(–0.17 to 0.02)
BMI		–0.04 (–0.16 to 0.09)	–0.03(–0.15 to 0.10)
Job strain		0.64 (0.54 to 0.74)	0.62 (0.53 to 0.72)
Random effects			
Work unit level variance	0.13	0.27	0.88
Workplace social capital			0.43
Workplace size			0.49
Individual level variance	3.08	2.75	2.76
Time level variance	3.05	2.96	2.92
VPC workplace	0.1%	0.4%	6.9%
VPC individual	50.5%	46.2%	45.1%
VPC time	49.4%	53.4%	50.3%

BMI, body mass index; K6, Kessler Psychological Distress Scale; VPC, variance partition coefficient.

The concepts of workplace social support and WSC are related.[1] For example, a workplace with high social cohesion and solidarity (ie, high social capital) is likely to be one where employees receive social support from their co-workers and supervisors.[1] There are, however, some significant differences between the concepts. Workplace social support is a resource that *individual* workers can access.[1] Even in the same workplace, there may be inequalities in receipt of social support, that is, some workers will receive more than others. WSC, however, is a property of the *workplace*, not the individual.[43 44] In our multilevel analysis, we aggregated workers' perceptions about cohesion and solidarity up to the work unit level. WSC is therefore a group-level concept and distinct from individual reports of social support.

Unit-level WSC can be hypothesised to influence employees' psychological distress in several ways. Kawachi and Berkman[1] set out several mechanisms by which group-level social capital exerted a contextual effect on individual health, including: (1) Reciprocity and mutual support. (2) Informal social control and the maintenance of group norms. (3) Collective efficacy. This might be because in a more cohesive workplace, it is easier to achieve coordination and cooperation among employees,[45] which might reduce employees' psychological distress. Another potential explanation is that workplaces in which workers have similar values about workplace norms and intervene when these norms are violated are believed to collectively discourage antisocial behaviour. Workplace collective efficacy may be associated with fewer problem behaviours that lead to workers' mental health problems. However, WSC may also have a 'dark side' in Japanese workplaces in terms of employee health.[46] High cohesion of a unit as indicated by high WSC might be associated with more

bullying of those who do not 'fit' in the organisational culture. It has also been reported that depression is contagious across social networks.[47]

Unit-level variation of WSC was significant. In the workplace, managers may play an important role in boosting unit-level WSC. Previous community-based intervention studies suggested that work unit social activities may strengthen WSC.[48 49] Examples of interventions to promote WSC include scheduling athletic competitions (undokai) within the company, and social activities such as weekend corporate retreats (shain-ryoko) and cherry blossom viewing picnic parties (hanami).

This study had some limitations. First, the use of a self-administered questionnaire to assess both exposures and outcomes might have produced common method bias. This possibility was reduced in the multilevel analysis because each worker was assigned the *average* value of all workers in the same unit. Second, the generalisability of our results is unclear, because WSC depends on the prevailing norm and culture of an organisation and the sample for this study was drawn from a single company. Third, the definition of 'workplace' is ambiguous, and the questionnaire did not specify the organisational unit in detail. It is therefore possible that different participants interpreted the question differently. Fourth, although we controlled for a range of individual-level and unit-level covariates, we cannot rule out bias from unmeasured confounding. Fifth, there may be other social and economic factors that should have been considered. Workplace bullying plays a significant role in mediating the association between psychosocial factors and psychological distress.[50 51] Economic crises may also have a potential additional negative impact on workers' mental health.[52–54] In Japan, suicide as a result of psychological distress was a significant public health concern for working-aged men after the 'bubble economy' collapsed.[24] These social and economic conditions in Japan may therefore affect the association between organisational psychosocial factors such as WSC and individual mental health. Sixth, we cannot reject the possibility of 'reverse causation' between WSC and psychological distress on the basis of our study design, since the changes in exposure and outcome were assessed simultaneously.

Our study has several strengths, including the large sample of Japanese employees, and the use of a new statistical method, a multilevel analysis using three levels (repeated measurements of psychological distress nested within individual employees, then work units). Based on these analyses, our study provides a new research insight into the contextual effect of WSC on employees' mental health.

CONCLUSIONS

This prospective study adds to previous research by showing that WSC is associated with improvement in mental health among employees. WSC appears to have a contextual effect on employees' mental health. We recommend that unit-level WSC is considered alongside other known contextual influences on the mental health of workers. To prevent mental health problems in subordinates, work unit managers might have a role in boosting WSC, such as organising athletic competitions within the company and social activities (eg, weekend corporate retreats and cherry blossom viewing picnic parties).

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Contributors HE performed the statistical analysis and drafted the manuscript. AT and AI conceived and conducted the study. IK and HH conceived the study and helped to draft the manuscript. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The study aims and protocol were reviewed by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (No. 2772), the Kitasato University Medical Ethics Organization (B12-103), and the Ethics Committee of the University of Occupational and Environmental Health, Japan (No. 10-004).

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Data sharing statement Because the data are still in process to transfer to a data archiving organisation, the ad hoc committee chaired by Prof Akizumi Tsutsumi is taking care of this role. Data are from the occupational cohort study on social class and health conducted in Japan (Japanese Study of Health, Occupation, and Psychosocial Factors Related Equity: J-HOPE) whose authors may be contacted at akizumi@kitasato-u.ac.jp.

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Original

Mental health of working-age populations in Japan who provide nursing care for a person at home: A cross-sectional analysis

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Abstract: Objectives: This study investigated potential associations between having a person in need of nursing care at home and psychological distress amongst the Japanese working population, using a nationally representative sample. **Methods:** We extracted data from the 2013 Comprehensive Survey of Living Conditions conducted by the Ministry of Health, Labour and Welfare of Japan. The original survey was conducted amongst 295,367 households in 5,530 randomly selected municipalities. We analyzed participants aged 25-65 years who headed a household. The original questionnaire included questions about the specific qualifications required to receive long-term care insurance benefits, about psychological distress (measured using the K6 scale), and other covariates. If a family contained a member in need of nursing care at home, the person who headed that household was recognized as the participant who had a person in need of nursing care at home. Multiple logistic regression analysis was conducted to investigate the association between having a person in need of nursing care at home and psychological distress. **Results:** A total of 36,193 men and 2,765 women were included in the analysis, 2.9% of whom had a person in need of nursing care at home. Statistical analysis revealed an association between having a care-requiring older relative at home and psychological distress (odds ratio: 1.40, 95% confidence interval: 1.01-1.93). **Conclusions:** Having a person in need of nursing care at home appears to be positively correlated with worsening mental health of working populations in Japan.
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Key words: Caregivers, Cross-sectional studies, Mental health, Working age population

Introduction

In Japan, care for frail, older adults is largely shouldered by that person's family[1)]. Moreover, traditionally the majority of family caregivers have been nonworking spouses, daughters, or daughters-in-law of the older adults in need of care[1)]. The burden on family members who provide that care is considerable, and poses a crucial problem[2)]: caregivers for older people have been found to be more likely than non-caregivers to experience physical and psychological burdens, and to suffer from anxiety and depression[3-7)].

A recent trend shows an increasing number of primary caregivers who maintain their paid employment because they have no one else to provide care. This reality is part of the ramifications of fewer family members per household in Japan[8)]. Adverse effects seen in such caregivers include lethargy, tiredness and lack of concentration, anxiousness about work-related responsibilities at work, and stress induced by trying to manage the often incompatible roles of worker and caregiver, each with its own conflicting demands and expectations[9)]. To date, only one Japan-based study has investigated the association between caregivers' mental health and caring for older relatives; this was conducted among workers at three sites in a Japanese prefecture[10)]. The authors of that study reported that workers who were caring for older relatives had a significantly increased risk of depression[10)]. The association between caring for older relatives and poor mental

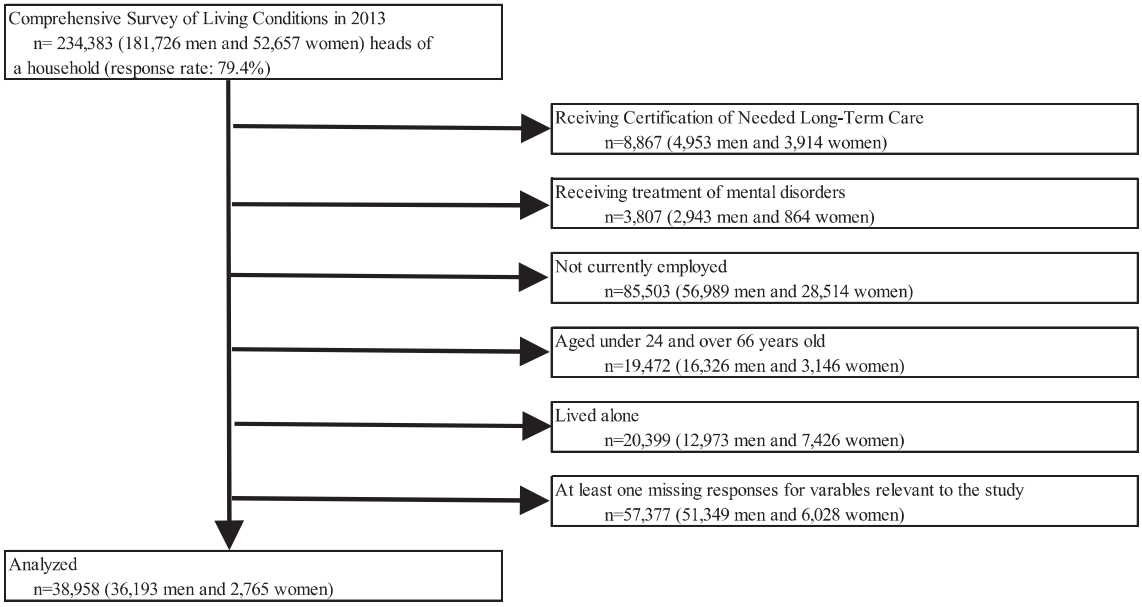

Fig. 1. Flow chart of this study sample

health necessitates examining a nationally representative sample using demographic or occupational variables for adjustment.

Like Japan, other Asian countries also face nationally unprecedented situations in their rapidly growing elderly populations. Because of this rapid increase and the shortage of standardized institutional solutions for long-term care in Asian countries[11-14], working caregivers will presumably be increasingly called upon to provide home care for disabled older adults. The Japanese experience in arranging work-life balance between employment outside the home and nursing care in the home could beneficially contribute to other Asian countries.

This cross-sectional study aimed to investigate the association between workers' mental health and having a person in need of nursing care at home. The study used a nationally representative sample of the Japanese population derived from the nationwide 2013 Comprehensive Survey of Living Conditions, which was conducted by the Ministry of Health, Labour and Welfare of Japan.

Participants and Methods

Data collection

The survey, which covered households and household members nationwide, was conducted in June-July 2013. Participants were chosen from randomly selected areas throughout Japan and given two self-administered questionnaires: one on the household and one on their health. The two questionnaires were distributed to 295,367 households located in 5,530 areas selected randomly from areas of the 2010 Population Census. Members of 234,383 households (response rate: 79.4%) completed the questionnaires, which were collected by survey staff. In the present study, participants were excluded who: had received certification of needing long-term care; were receiving treatment for mental disorders; did not work; were younger than 24 or older than 66 years old; lived alone; or had at least one missing response for variables relevant to the study. The flow of the data collection is presented in Fig. 1. The final analysis was conducted using data on 38,958 participants who were currently employed, were head of a household, whose earnings supported their family, and were aged 25-65 years. This sample comprised 36,193 men and 2,765 women.

We obtained permission to use certain data from the 2013 Comprehensive Survey of Living Conditions for purposes other than those originally intended by the Ministry of Health, Labour and Welfare.

Measures

1) Having a person in need of nursing care at home

Under the Japanese long-term care insurance scheme, individuals certified by the municipal government as needing care or support are eligible to receive insurance benefits. For the household questionnaire, each participant was asked to respond to a question about the specific qualifications for which a household member was receiving long-term care insurance benefits. All respondents were issued a family identification code and, based on this, we were able to delineate the participants into families. If a family contained a member in need of nursing care at home, the person who headed the household was deemed the participant who had a person in need of nursing care at home.

2) Psychological distress

The health questionnaire incorporated the Kessler Psychological Distress Scale (K6) for acquiring data on mental health[15]. The K6 has been translated into Japanese and has shown acceptable internal consistency, reliability, and validity[16]. The scale has been shown to have effectively detected major depression and dysthymia in accordance with the established Diagnostic and Statistical Manual of Mental Disorders-IV criteria[16]. It comprises six items, and measures the extent of psychological distress using a five-point response scale ranging from 0 (none of the time) to 4 (all of the time). Total scores range from 0 to 24, with a higher score indicating proportionally greater distress. In line with the recommended K6 cutoff point, participants with total scores of ≥13 (13-24) were defined as having serious mental illness, while a score of 0-12 suggested no mental illness[16,17].

3) Other covariates and demographic characteristics

Questions in the survey covered basic demographic information. The household questionnaire assessed age, sex, educational attainment, number of family members at home, occupation, employment status, company size, and weekly working hours; the health questionnaire measured sleeping time, smoking status, and frequency of drinking alcohol. Age was classified into the following groups: 25-29, 30-39, 40-49, 50-59, and 60-64 years. Weekly working hours were categorized into the following ranges: ≤ 20, 21-30, 31-40, 41-50, 51-60, and ≥61. The number of family members at home was delineated as 2, 3, 4, 5, and ≥6. Participants were each asked to answer questions about their highest level of educational attainment, choosing from: elementary or junior high school; high school; vocational college; junior college; university; or graduate school. For employment status, they chose from: permanent; regular part-time; casual part-time; temporary; full-time fixed-term contract; post-retirement fixed-term contract; and other. For occupation (i.e., type of job), they chose from: management; professional and technical work, including teaching, health care, and research; office administrator; sales; service; security; agriculture and fishery; manufacturing; transportation or machine operator; construction; cleaning, packing, and operator; other; and unknown. For company size (i.e., the total number of employees in the person's company, including headquarters, branch offices, and factories), they chose from: 1-4; 5-29; 30-99; 100-299; 300-499; 500-999; 1,000-4,999; ≥ 5,000; or unspecified size if employed in a civil service office. For sleeping time, they chose from: <5; 5-6; 6-7; 7-8; 8-9; or >9 hours per night. For smoking status, they chose from: everyday; sometimes; quit smoking for >1 month; or never smoked. For frequency of drinking alcohol, they chose from: everyday; 5-6 days/week; 3-4 days/week; 1-2 days/week; 1-3 days/month; hardly drink; quit drinking; or never drank. Educational attainment was dichotomized into ≤ 12 years or >12 years. Employment status was dichotomized into regular employee or non-regular employee. Occupation was classified into six groups based on previous studies[18,19]: professional or technician; manager; office administrator; sales or service worker; production worker (i.e., manual laborer), including transportation and communications, and production process and related occupations; and other (if occupation was not classifiable). In line with a previous study[19], company size was classified into 1-29, 30-299, 300-999, and ≥1,000 employees, with reference to the definition of small- and medium-sized companies as per Japan's Small and Medium-sized Enterprise Basic Act. Civil service offices were classified as a separate category, irrespective of size, because the original survey did not request that information. Frequency of drinking alcohol was classified into three groups: every day, sometimes, or never.

Statistical analysis

We tested associations between the studied variables and psychological distress using a Chi-square test. We investigated the demographic characteristics of each variable in relation to psychological distress with the following items as an example: Having a person in need of nursing care at home; male; 30-39 years old; 31-40 weekly working hours; two family members at home; <12 years educational attainment; non-regular employee; manager; smallest company size (1-29 employees); 6-7 hours of sleeping time per night; smoking every day; and drinking alcohol every day. With these, the odds ratio (OR) and 95% confidence interval (CI) of psychological distress were estimated for other categories of each characteristic in a series of logistic regression analyses. We first performed the analysis with adjustment for sex and age, and then fully adjusted for sex, age, weekly working hours, number of family members at home, educational attainment, employment status, occupation, company size, sleeping time, smoking status, and frequency of drinking alcohol. We showed the demographic characteristics of the survey respondents who had a person in need of nursing care at home. All analyses were performed using Stata 14 (StataCorp, College Station, TX), with statistical significance set at $p < 0.05$.

Ethics statement

This study involved a retrospective analysis of data that had already been obtained through a national survey. As we did not use any personally identifiable information, and based on existing regulations in Japan, ethical approval was not required.

Results

Table 1 shows the associations between the studied variables and psychological distress. The portion of survey respondents who reported having a person in need of

Table 1. Demographic, occupational, and lifestyle characteristics by psychological distress (n=38,958)

	Psychological distress				
	Low (K6≤12) n=37,671		High (K6≥13) n=1,287		*p* value[a]
	n	(%)	n	(%)	
Sex					
Male	35,067	(96.9)	1,126	(3.1)	<0.001
Female	2,604	(94.2)	161	(5.8)	
Age					
25-29	1,443	(95.7)	65	(4.3)	<0.001
30-39	8,513	(95.8)	378	(4.2)	
40-49	11,444	(96.4)	428	(3.6)	
50-59	10,836	(97.0)	339	(3.0)	
60-65	5,435	(98.6)	77	(1.4)	
Having a person in need of nursing care at home					
No	36,589	(96.7)	1,243	(3.3)	0.250
Yes	1,082	(96.1)	44	(3.9)	
Weekly working hours					
Less than 20	927	(95.0)	49	(5.0)	<0.001
20-30	1,260	(96.1)	51	(3.9)	
31-40	11,283	(96.8)	368	(3.2)	
41-50	14,494	(97.0)	446	(3.0)	
51-60	6,338	(96.9)	200	(3.1)	
More than 61	3,369	(95.1)	173	(4.9)	
Number of family members at home					
2	10,054	(96.4)	379	(3.6)	0.040
3	10,984	(96.6)	391	(3.4)	
4	11,349	(97.1)	340	(2.9)	
5	3,892	(96.8)	129	(3.2)	
More than 6	1,392	(96.3)	48	(3.7)	
Educational attainment					
Less than 12	18,131	(96.6)	630	(3.4)	0.562
More than 12	19,540	(96.8)	657	(3.2)	
Employment status					
Regular employee	32,150	(96.7)	1,084	(3.3)	0.266
Non-regular employee	5,521	(96.5)	203	(3.5)	
Occupation					
Managers	4,519	(97.7)	105	(2.3)	<0.001
Professionals and technicians	11,005	(96.6)	392	(3.4)	
Clerks	4,255	(96.3)	165	(3.7)	
Sales and service workers	7,924	(96.5)	289	(3.5)	
Production workers	9,134	(96.8)	299	(3.2)	
Others	834	(95.8)	37	(4.2)	
Company size (number of employees)					
1-29	7,150	(96.6)	255	(3.4)	0.379
30-299	11,272	(96.6)	403	(3.4)	
300-999	5,537	(96.8)	181	(3.2)	
1000 or more	9,760	(96.7)	332	(3.3)	
Civil service	3,952	(97.2)	116	(2.8)	

Table 1. (continued)

	Psychological distress				
	Low (K6≤12) n=37,671		High (K6≥13) n=1,287		*p* value[a]
	n	(%)	n	(%)	
Sleeping time					
Less than 5 hours	2,744	(90.1)	302	(9.9)	<0.001
5-6 hour	11,945	(96.5)	433	(3.5)	
6-7 hour	13,766	(97.8)	310	(2.2)	
7-8 hour	7,276	(97.8)	162	(2.2)	
8-9 hour	1,630	(97.1)	49	(2.9)	
More than 9	310	(90.9)	31	(9.1)	
Smoking status					
Smokes everyday	12,954	(96.5)	468	(3.5)	0.194
Smokes sometimes	817	(95.9)	35	(4.1)	
Ex-smoker	3,812	(97.0)	119	(3.0)	
Non-smoker	20,088	(96.8)	665	(3.2)	
Frequency of alcohol consumption					
Everyday	11,240	(96.6)	393	(3.4)	<0.001
Sometimes	13,657	(97.4)	371	(2.6)	
Never	12,774	(96.1)	523	(3.9)	

[a] Chi-square.

Table 2. Presence of having an older person receiving long-term care at home and psychological distress (n=38,958)

		Odds ratio (95% confidence interval)			
		Model 1[a]		Model 2[b]	
Have an older relative requiring care at home					
	No	1.00		1.00	
	Yes	1.56	(1.14-2.13)*	1.40	(1.01-1.93)*

[a]Adjusted for age and sex
[b]The fully adjusted logistic regression model is adjusted for sex, age, weekly working hours, number of family at home, educational attainment, employment status, occupation, company size, sleeping time, smoking status, and frequency of drinking alcohol
*p<0.05

nursing care at home was 2.9%. The following groups had significantly higher proportions of participants suffering from psychological distress: female, younger, the shortest and longest weekly working hours, smallest family size, "other" occupation, the shortest and longest sleeping times, and no alcohol consumption.

Table 2 shows the results of multiple logistic regression analysis. This revealed a strong correlation between psychological distress and being an employed worker with a person in need of nursing care at home (OR: 1.40, 95% CI: 1.01-1.93).

Table 3 shows the demographic characteristics of the survey respondents who reported having a person in need of nursing care at home. As Table 3 indicates, the following groups had higher proportions of participants suffering from psychological distress: female, 25-29, 40-49 and 50-59 years old, fewer than 5 hours and more than 9 hours of sleeping time per night, and no alcohol consumption.

Table 3. Demographic, occupational, and lifestyle characteristics among employees who have an older relative requiring care at home by psychological distress (n=1,126)

	Psychological distress			
	Low stress (K6≤12) n=1,082		High stress (K6≥13) n=44	
	n	(%)	n	(%)
Sex				
Male	1,018	(96.4)	38	(3.6)
Female	64	(91.4)	6	(8.6)
Age				
25-29	5	(83.3)	1	(16.7)
30-39	41	(100)	0	(0)
40-49	148	(93.1)	11	(6.9)
50-59	534	(95.4)	26	(4.6)
60-65	354	(98.3)	6	(1.7)
Weekly working hours				
Less than 20	41	(97.6)	1	(2.4)
20-30	59	(100)	0	(0)
31-40	420	(95.9)	18	(4.1)
41-50	366	(97.1)	11	(2.9)
51-60	129	(92.1)	11	(7.9)
More than 61	67	(95.7)	3	(4.3)
Number of family members at home				
2	148	(95.5)	7	(4.5)
3	312	(96.9)	10	(3.1)
4	251	(97.7)	6	(2.3)
5	209	(94.6)	12	(5.4)
More than 6	162	(94.7)	9	(5.3)
Educational attainment				
Less than 12	646	(95.4)	31	(4.6)
More than 12	436	(97.1)	13	(2.9)
Employment status				
Regular employee	811	(95.6)	37	(4.4)
Non-regular employee	271	(97.5)	7	(2.5)
Occupation				
Managers	166	(97.7)	4	(2.3)
Professionals and technicians	259	(96.6)	9	(3.4)
Clerks	95	(94.1)	6	(5.9)
Sales and service workers	218	(96.9)	7	(3.1)
Production workers	317	(95.2)	16	(4.8)
Others	27	(93.1)	2	(6.9)
Company size (number of employees)				
1-29	279	(96.5)	10	(3.5)
30-299	357	(95.0)	19	(5.0)
300-999	120	(96.8)	4	(3.2)
1000 or more	206	(97.2)	6	(2.8)
Civil service	120	(96.0)	5	(4.0)

Table 3. (continued)

	Psychological distress			
	Low stress (K6≤12) n=1,082		High stress (K6≥13) n=44	
	n	(%)	n	(%)
Sleeping time				
less than 5 hours	79	(92.9)	6	(7.1)
5-6 hour	270	(95.7)	12	(4.3)
6-7 hour	309	(97.5)	8	(2.5)
7-8 hour	261	(97.8)	6	(2.2)
8-9 hour	100	(95.2)	5	(4.8)
more than 9	63	(90.0)	7	(10.0)
Smoking status				
Smokes everyday	302	(97.1)	9	(2.9)
Smokes sometimes	10	(83.3)	2	(16.7)
Ex-smoker	124	(96.9)	4	(3.1)
Non-smoker	646	(95.7)	29	(4.3)
Frequency of alcohol consumption				
Everyday	364	(97.9)	8	(2.1)
Sometimes	298	(97.4)	8	2.6)
Never	420	(93.8)	28	(6.2)

Discussion

The present study investigated potential associations between psychological distress and having a person in need of nursing care at home among the Japanese working population. Around 3% of survey respondents reported having a person in need of nursing care at home. This subgroup experienced significantly higher levels of psychological distress when compared with participants who did not have a person at home in need of nursing care. Among the respondents who reported having a person in need of nursing care at home, psychological distress was most prevalent in those who were young and/or female.

The results suggest that having a person in need of nursing care at home may affect the mental health of working populations in Japan. Providing nursing care at home can be time-consuming and is associated with physical and psychological burdens. Indeed, previous research has reported an association between caregiving and depression[3-7,10]. In Japan, among people who had left their job and were caring for older relatives, 25.3% of men and 32.8% of women indicated that stress caused by caregiving was a reason for leaving their job[1]. To reduce workers' care-related stress and prevent them from leaving their jobs, companies in Japan should consider promoting a balance of work and caregiving of older relatives for their employees.

Young and female respondents were more likely to suffer psychological distress than other groups, which is consistent with previous studies[20-23]. Arguably, young female caregivers are more likely than older female caregivers to be working and/or caring for children in the home. Especially in Japanese society, females tend to bear the majority of the child care and housekeeping responsibilities, even when employed outside the home[24]; this situation is specifically linked to gender and age differences in experiences and perceptions of psychological distress. To reduce the number of people who leave or change their jobs, interventions such as stress management and the provision of information about work-care balance for female and young workers may be effective. Also, it should be noted that the sample size of some sex and age groups is small, which might be a source of bias. Further studies are needed to evaluate psychological conditions among women and younger populations by using a larger sample of participants.

Given Japan's aging society and the continued surge in the population of older adults requiring care, it is possible that the number of workers caring for older relatives at home may also increase. When such workers obtain support from their workplace colleagues and/or supervisors, the workers tend to adjust their working hours to allow

them to continue providing care[25]. Occupational health professionals may consider advising on how to adjust working environments to mitigate the impacts that this form of home caregiving can have on workers' mental health.

As of 2017, the total Japanese population was 126.7 million, which included 35 million aged ≥65 years (27.6%) and 17.3 million aged ≥75 years (13.7%)[26]. Japan is the global front-runner of super-aged societies[27]. To maintain the employment rate in Japan, people should be prevented as much as possible from leaving their jobs because of nursing care duties at home. The development of stress management programs for employees who must also fulfill home nursing care for elderly people might be an effective way of helping them retain their paying jobs while also reducing the risk of declining mental health.

There are a few potential limitations of the current study. Firstly, given that this was a cross-sectional investigation, it was not possible to determine causality. Longitudinal studies can be pursued to rectify this. Secondly, the target population of this study was heads of households. Since the head of a household conceivably has the most responsibility within their family, they may feel more stressed than the other household members. Thus, our results may not be generalizable to working populations in other situations. Thirdly, further studies are needed to evaluate whether other confounding factors may provide possible mechanisms for the observed attenuation in the association between having a person in need of nursing care at home and psychological distress amongst the Japanese working population. For example, spousal status (i.e., dual earner or single earner) or being a parent of small children may also play a significant mediating role. Finally, there are additional psychosocial factors in the workplace to consider (e.g., job demands, job control, and support of colleagues and supervisors), which might be important mediators of the association between workers' mental health and their provision of home care for an older relative. These variables should be examined in future research.

Conclusions

This study found that having a person in need of nursing care at home appears to be positively correlated with worsening mental health in working populations in Japan.

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