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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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A B S T R A C T

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Reviews 1 and 2, we will search electronic academic databases for potentially relevant records from published and unpublished studies, including Medline, EMBASE, Web of Science, CISDOC and PsychINFO.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 WHO *Global Health 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.

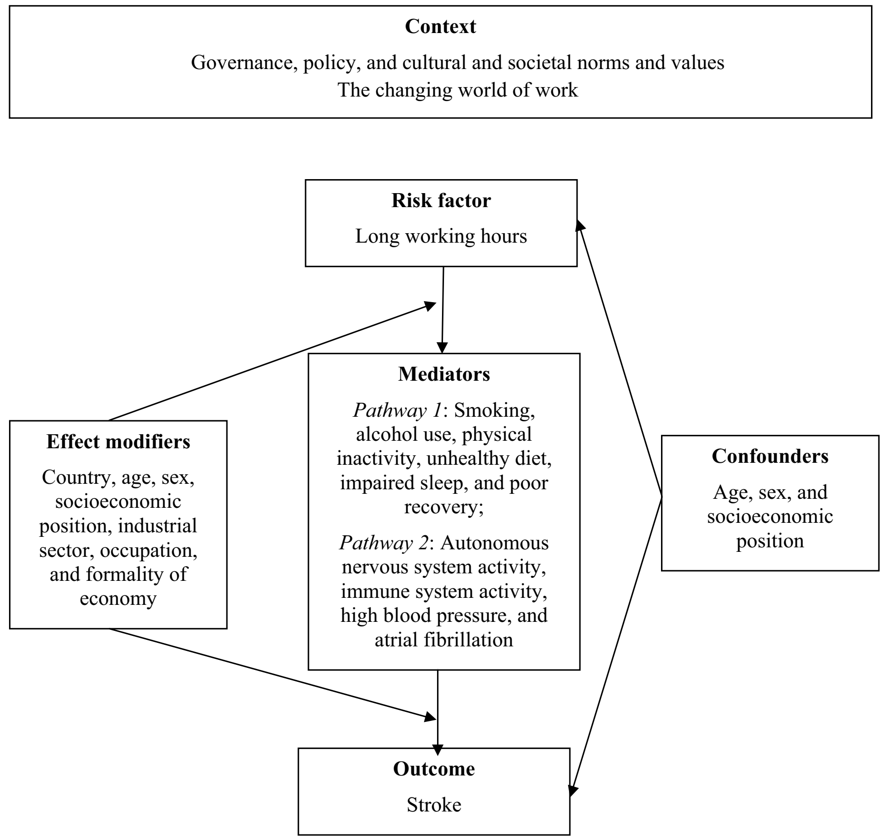

Fig. 1. Logic model of the possible causal relationship between long working hours and stroke.

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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