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The effect of occupational exposure to ergonomic risk factors on osteoarthritis of hip or knee and selected other musculoskeletal diseases: A systematic review and meta-analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury

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ABSTRACT

Background: The World Health Organization (WHO) and the International Labour Organization (ILO) are developing joint estimates of the work-related burden of disease and injury (WHO/ILO Joint Estimates), with contributions from a large network of experts. Evidence from mechanistic data suggests that occupational exposure to ergonomic risk factors may cause selected other musculoskeletal diseases, other than back or neck pain (MSD) or osteoarthritis of hip or knee (OA). In this paper, we present a systematic review and meta-analysis of parameters for estimating the number of disability-adjusted life years from MSD or OA that are attributable to occupational exposure to ergonomic risk factors, for the development of the WHO/ILO Joint Estimates.

Objectives: We aimed to systematically review and meta-analyse estimates of the effect of occupational exposure to ergonomic risk factors (force exertion, demanding posture, repetitiveness, hand-arm vibration, lifting, kneeling and/or squatting, and climbing) on MSD and OA (two outcomes: prevalence and incidence).

Data sources: We developed and published a protocol, applying the Navigation Guide as an organizing systematic review framework where feasible. We searched electronic academic databases for potentially relevant records from published and unpublished studies, including the International Trials Register, Ovid Medline, EMBASE, and CISDOC. We also searched electronic grey literature databases, Internet search engines and organizational websites; hand-searched reference list of previous systematic reviews and included study records; and consulted additional experts.

Study eligibility and criteria: We included working-age (≥15 years) workers in the formal and informal economy in any WHO and/or ILO Member State but excluded children (<15 years) and unpaid domestic workers. We included randomized controlled trials, cohort studies, case-control studies and other non-randomized intervention studies with an estimate of the effect of occupational exposure to ergonomic risk factors (any exposure to

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force exertion, demanding posture, repetitiveness, hand-arm vibration, lifting, kneeling and/or squatting, and climbing ≥ 2 h/day) compared with no or low exposure to the theoretical minimum risk exposure level (<2 h/day) on the prevalence or incidence of MSD or OA.

Study appraisal and synthesis methods: At least two review authors independently screened 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. Missing data were requested from principal study authors. We combined odds ratios using random-effect meta-analysis. Two or more review authors assessed the risk of bias and the quality of evidence, using Navigation Guide tools adapted to this project.

Results: In total eight studies (4 cohort studies and 4 case control studies) met the inclusion criteria, comprising a total of 2,378,729 participants (1,157,943 females and 1,220,786 males) in 6 countries in 3 WHO regions (Europe, Eastern Mediterranean and Western Pacific). The exposure was measured using self-reports in most studies and with a job exposure matrix in one study and outcome was generally assessed with physician diagnostic records or administrative health data. Across included studies, risk of bias was generally moderate.

Compared with no or low exposure (<2 h per day), any occupational exposure to ergonomic risk factors increased the risk of acquiring MSD (odds ratio (OR) 1.76, 95% confidence interval [CI] 1.14 to 2.72, 4 studies, 2,376,592 participants, I^2 70%); and increased the risk of acquiring OA of knee or hip (OR 2.20, 95% CI 1.42 to 3.40, 3 studies, 1,354 participants, I^2 13%); Subgroup analysis for MSD found evidence for differences by sex, but indicated a difference in study type, where OR was higher among study participants in a case control study compared to study participants in cohort studies.

Conclusions: Overall, for both outcomes, the main body of evidence was assessed as being of low quality. Occupational exposure to ergonomic risk factors increased the risk of acquiring MSD and of acquiring OA of knee or hip. We judged the body of human evidence on the relationship between exposure to occupational ergonomic factors and MSD as "limited evidence of harmfulness" and the relationship between exposure to occupational ergonomic factors and OA also as "limited evidence of harmfulness". These relative risks might perhaps be suitable as input data for WHO/ILO modelling of work-related burden of disease and injury.

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1. Background

The World Health Organization (WHO) and the International Labour Organization (ILO) are finalizing joint estimates of the work-related burden of disease and injury (WHO/ILO Joint Estimates) (Ryder, 2017). The organizations are estimating the numbers of deaths and disability-adjusted life years (DALYs) that are attributable to selected occupational risk factors. The WHO/ILO Joint Estimates is 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 expands these 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 – are being calculated for each additional risk factor-outcome pair, and these fractions are being applied to the total disease burden envelopes for the health outcome from the WHO *Global Health Estimates* for the years 2000–2016 (World Health Organization, 2019).

The WHO/ILO Joint Estimates may include estimates of the burden of selected musculoskeletal diseases other than back or neck pain (MSD) or osteoarthritis of hip or knee (OA) attributable to occupational exposure to ergonomic risk factors if feasible, as one additional prioritized risk factor-outcome pair. To optimize parameters used in estimation models, a systematic review and meta-analysis is required of studies with estimates of the effect of occupational exposure to ergonomic risk factors on MSD or OA (Hulshof et al., 2019). In the current paper, we present this systematic review and meta-analysis. WHO and ILO, supported by a large network of experts, have in parallel also produced a systematic review of studies estimating the prevalence of occupational exposure to ergonomic risk factors (Hulshof et al., 2021) and several other systematic reviews and meta-analyses on other additional risk factor-outcome pairs (Descatha et al., 2018, 2020; Godderis et al., 2018; Hulshof et al., 2019; Li et al., 2018, 2020; Mandrioli et al., 2018; Paulo et al., 2019; Rugulies et al., 2019; Teixeira et al., 2019; Tenkate et al., 2019; Teixeira et al., 2021; Teixeira et al., 2021; Pachito et al., 2021; Pega et al., 2020). To our knowledge, these are the first systematic reviews and meta-analyses conducted specifically for an occupational burden of disease study, including having a pre-published protocol that ensures full transparency (Mandrioli et al., 2018). 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.

1.1. Rationale

To consider the feasibility of estimating the burden of MSD or OA from exposure to occupational ergonomic risk factors, 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 and a meta-analysis of studies with estimates of the relative effect of exposure to occupational ergonomic risk factors on the prevalence or incidence of MSD or OA respectively, compared with the theoretical minimum risk exposure level (presented in this article). The theoretical minimum risk exposure level is the 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 MSD and OA respectively, from exposure to occupational ergonomic risk factors in the WHO/ILO Joint Estimates.

Seven previous systematic reviews have however focused on the evidence on the effect of exposure to one or more of these occupational ergonomic risk factors on one or more selected musculoskeletal diseases of the shoulder (Lievense et al., 2001; van Rijn et al., 2010; van der Molen et al., 2017); elbow (Descatha et al., 2016); hip (Lievense et al., 2001; Jensen, 2008); and knee (Verbeek et al., 2017). These systematic reviews identified the following occupational ergonomic risk factors as relevant.

Regarding OA of the knee, Verbeek et al. (2017) concluded in a meta-analysis of 12 case control studies that measured exposure to kneeling or squatting resulted in a summary OR of 1.7 (95% CI 1.35–2.13, I^2 49%); exposure to lifting (11 studies) in an OR of 1.69 (95% CI 1.43–2.00, I^2 51%); exposure to climbing (seven studies) in an OR of 1.6 (95% CI 1.25–1.91, I^2 68%) and a combination of kneeling and lifting (one study)

in an OR of 1.35 (95% CI 1.05–1.73) (Verbeek et al., 2017).

A recent meta-analysis, based on seven studies, revealed moderate quality evidence for associations between shoulder disorders (M75.1-M75.5) and arm elevation (odds ratio (OR) 1.9, 95% CI 1.47 to 2.47, I^2 31%) and shoulder load, a combined biomechanical exposure measure (OR = 2.0, 95% CI 1.90 to 2.10, I^2 0%) and low to very low evidence for hand force exertion (OR = 1.5, 95% CI 1.25 to 1.87, I^2 66%), and hand-arm vibration (OR = 1.3, 95% CI 1.01 to 1.77, I^2 99%) (van der Molen et al., 2017). Van Rijn et al. (2010) performed a systematic review on the relationship between work-related factors and specific disorders of the shoulder and found in the 17 included studies that repetitive movements of the shoulder, repetitive motion of the hand/wrist of > 2 h/day, hand–arm vibration, and arm elevation showed an association with subacromial impingement syndrome (ORs between: 1.04, 95% CI 1.00–1.07 and 4.7, 95% CI 2.07–10.68), as did upper-arm flexion of ≥ 45° for ≥ 15% of time (OR 2.43, 95% CI 1.04–5.68) and duty cycle of forceful exertions of ≥ 9% time or any duty cycle of forceful pinch (OR 2.66, 95% CI 1.26–5.59) (van Rijn et al., 2010).

Descatha et al. (2016) included in a meta-analysis five prospective studies published between 2001 and 2014 and found a positive association between combined biomechanical exposure involving the wrist and/or elbow and incidence of epicondylitis lateralis (OR 2.6, 95% CI 1.9–3.5) (Descatha et al., 2016). In a systematic review by van Rijn et al. (2009) the associations between force, posture, repetitiveness, hand-arm vibration and a mixture of these exposures and elbow disorders were studied (van Rijn et al., 2009). Handling tools of > 1 kg (ORs of 2.1–3.0), handling loads of > 20 kg at least 10 times/day (OR 2.6) and repetitive movements for > 2 h/day (ORs of 2.8–4.7) were associated with lateral epicondylitis, while handling loads of > 5 kg (2 times/min at minimum of 2 h/day), handling loads of > 20 kg for at least 10 times/day, high hand grip forces for > 1 h/day, repetitive movements for > 2 h/day (ORs of 2.2–3.6) and working with vibrating tools for > 2 h/day (OR 2.2) were all associated with medial epicondylitis.

Jensen (2008) evaluated the association between physical work demands and hip osteoarthritis in 22 included studies and concluded that moderate to strong evidence exists for a relation with heavy lifting (OR ranges between 1.97, 95% CI 1.14–3.4, and 8.5 (95% CI 1.6–45.3) (Jensen, 2008). Furthermore, 13 studies showed a significantly increased risk between farming and hip osteoarthritis, with ORs ranging from 1.9 (95% CI 1.01–3.87) to 12.0 (95% CI 6.7–21.4). Lievense et al. (2001) used a best-evidence synthesis to summarize the results of two retrospective and 14 case-control studies and found moderate evidence for a positive association between previous physical workload and hip osteoarthritis, with ORs ranging from 1.5 (95% CI 0.9–2.5) and 9.3 (95% CI 1.9–44.5) (Lievense et al., 2001). In a subgroup analysis, also ≥ 10 years farming was positively related to hip osteoarthritis.

Work in the informal economy may lead to different exposures and exposure effects than work in the formal economy does. 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" (p. 4) (104th International Labour Conference, 2015). Therefore, we consider the formality of the economy studied in studies included in both systematic reviews.

1.2. Description of the risk factor

The aforementioned seven systematic reviews on the effect of occupational ergonomic risk factors on musculoskeletal diseases of the shoulder (van Rijn et al., 2010; van der Molen et al., 2017); elbow (Descatha et al., 2016); hip osteoarthritis (Lievense et al., 2001; Jensen, 2008); and knee osteoarthritis (Verbeek et al., 2017), and additional documents (Harris and Coggon, 2015); (EWCS, 2017) have identified the seven following types of occupational ergonomic risk factors as being of interest: (i) force exertion (e.g., carrying or moving heavy loads, turn and screw); (ii) demanding posture (e.g. arm elevation, bending and/or twisting); (iii) repetitiveness (e.g., physically repetitive work); (iv) hand-arm vibration; (v) kneeling and/or squatting; (vi) lifting (e.g. lifting heavy loads); and/or (vii) climbing. Therefore, we have reviewed studies on occupational exposure to any (i.e., one or more) of these seven different ergonomic risk factors. The definition of the risk factor, the risk factor levels and the theoretical minimum risk exposure level are presented in Table 1. The WHO Burden of Disease study has previously defined occupational ergonomic risk factors into four categories by occupation, these being background exposure (defined by manager and professionals as occupations); low exposure (clerical and sales workers); moderate exposure (operators and service workers); and high exposure (farmers) (Murray et al., 2004). The Institute of Health Metrics and Evaluation's burden of disease study has defined occupational ergonomic factors for low back and neck pain specifically as "All individuals have the ergonomic factors of clerical and related workers" (p. 1362) (G. B. D. Risk Factors Collaborators, 2017).

1.3. Definition of the outcome

In this systematic review, we will review two outcomes:

1. Any selected other musculoskeletal diseases (MSD), defined as one or more of: shoulder disorders: rotator cuff syndrome, bicipital tendinitis, calcific tendinitis, shoulder impingement, bursitis shoulder; elbow disorders: epicondylitis medialis, epicondylitis lateralis, bursitis elbow; hip disorders: trochanter and other hip bursitis; and knee disorders: chondromalacia patella, meniscus disorders and bursitis knee.
2. Osteoarthritis of the hip or knee (OA).

For the outcomes MSD and OA, only diseases have been included, for which exposure to one or more of the included occupational ergonomic risk factors (Table 1) is considered as a necessary factor for disease development. This selection was mainly based on the information about a possible occupational origin of the selected health outcomes in the seven systematic reviews described above (van der Molen et al., 2017; van Rijn et al., 2010, 2009; Descatha et al., 2016; Jensen, 2008; Lievense et al., 2001; Verbeek et al., 2017), plus additional evidence (Harris and Coggon, 2015).

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*

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

Risk factor	Occupational exposure to ergonomic risk factors (defined as occupational exposure to one or more of: force exertion, demanding posture, repetitive movement, hand-arm vibration, kneeling or squatting, lifting, climbing)
Risk factor level	Two levels: 1. No or low occupational exposure to ergonomic risk factors. 2. Any occupational exposure to ergonomic risk factors. If possible, "any" exposure may be further classified into "moderate" and "high" exposure, preferably based on exposure in terms of level, frequency and/or duration of the exposure.
Theoretical minimum risk exposure level	No occupational exposure to ergonomic risk factors

categories for this systematic review are "*II.M.2. Osteoarthritis*" and "*II.M.5. Other musculoskeletal diseases*" (World Health Organization, 2017). Table 2 presents for each disease or health problem included in the WHO *Global Health Estimates* categories its inclusion in this systematic review. For both categories, this review does not cover 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 reviews of the causal relationship between exposure to occupational ergonomic risk factors and MSD and OA, respectively. This logic model is an *a priori*, process model (Rehfuess et al., 2018) that seeks to capture complexity of the risk factor-outcome causal relationship (Anderson et al., 2011).

Musculoskeletal diseases are multifactorial in origin which means that there may be several etiological risk factors for their onset. Specific potentially relevant pathomechanisms include: posturally induced muscular imbalance, neural pathomechanisms, the 'Cinderella hypothesis' of motor unit recruitment, reperfusion, impaired heat-shock response and stress-induced mitochondrial damage (Forde et al., 2002). Nevertheless, there is currently no clear and circumscriptive understanding of the pathogenesis of work-related musculoskeletal diseases. One postulation is that musculoskeletal diseases result from cumulative micro damage induced by risk factors on cellular and/or tissue level over time.

Table 2
ICD-10 codes and disease and health problems covered by the WHO Global Health Estimates categories "II.M.2. Osteoarthritis" and "II.M.5. Other musculoskeletal diseases" and their inclusion in this systematic review.

ICD-10 code	Disease or health problems (or groups of diseases)	Inclusion in Systematic Review 2
II.M.2. Osteoarthritis		
M15	Polyarthrosis	No
M16	Coxarthrosis [arthrosis of hip]	Yes
M17	Gonarthrosis [arthrosis of knee]	Yes
M18	Arthrosis of first carpometacarpal joint	No
M19	Other arthrosis	No
II.M.5. Other musculoskeletal diseases		
M00	Pyogenic arthritis	No
M02	Reactive arthropathies	No
M08	Juvenile arthritis	No
M11	Other crystal arthropathies	No
M12	Other specific arthropathies	No
M13	Other arthritis	No
M20	Acquired deformities of fingers and toes	No
M21	Other acquired deformities of limbs	No
M22 (except M22.4)	Disorders of patella	No
M22.4	Chondromalacia patellae	Yes
M23 (except M23.0, M23.2, M23.3)	Internal derangement of knee	No
M23.0	Cystic meniscus	Yes
M23.2	Derangement of meniscus due to old tear or injury	Yes
M23.3	Other meniscus derangements	Yes
M23.4	Loose body in knee	Yes
M24	Other specific joint derangements	No
M25	Other joint disorders, not classified	No
M30-36	Systemic connective tissue disorders	No
M40-M43	Deforming dorsopathies	No
M60-M63	Disorders of muscles	No
M70.0 - M70.1	Bursitis & synovitis hand, wrist	Yes
M70.2 - M70.3	Olecranon & other elbow bursitis	Yes
M70.4 - M70.5	Prepatellaris & other knee bursitis	Yes
M70.6 - M70.7	Trochanter & other hip bursitis	Yes
M71-M73	Other bursopathies, fibroblastic disorders, soft tissue disorders in diseases classified elsewhere	No
M75 (except M75.1-M75.5)	Shoulder lesions	No
M75.1	Rotator cuff syndrome	Yes
M75.2	Bicipital tendinitis	Yes
M 75.3	Calcific tendinitis of shoulder	Yes
M75.4	Impingement syndrome of shoulder	Yes
M75.5	Bursitis of shoulder	Yes
M76	Enthesopathies lower limb	No
M77 (except M77.0-M77.1)	Other enthesopathies	No
M77.0	Epicondylitis medialis	Yes
M77.1	Epicondylitis lateralis	Yes
M80-85	Disorders of bone density and structure	No
M86-90	Other osteopathies	No
M91-M94	Chondropathies	No
M95	Other acquired deformities	No
M96	Postprocedural muscluloskeletal disorders	No
M99	Biomechanical lesions, not elsewhere	No

2. Objectives

To systematically review and meta-analyze randomized control trials, cohort studies, case-control studies and other non-randomized intervention studies with estimates of the relative effect of any occupational exposure to ergonomic risk factors on MSD and OA respectively among workers of working age, compared with the minimum risk exposure level of no exposure.

3. Methods

3.1. Developed protocol

The study protocol was registered in PROSPERO (CRD42018102631). This protocol is in accordance with the preferred reporting items for systematic review and meta-analysis protocols statement (PRISMA-P) (Moher et al., 2015; Shamseer et al., 2015). The abstract is in line 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 is reported in the systematic review itself under the section 'Differences between protocol and review'. This systematic review of the effect of exposure to occupational ergonomic risk factors on MSD and OA is reported according to the preferred reporting items for systematic review and meta-analysis statement (PRISMA) (Liberati et al., 2009). Reporting of all parameters for estimating the burden of osteoarthritis, and other musculoskeletal diseases respectively, from occupational exposure to ergonomic risk factors in the systematic reviews will adhere with the requirements of the GATHER guidelines (Stevens et al., 2016), as the WHO/ILO burden of disease estimates produced from the systematic review follow these reporting guidelines.

3.2. Searched literature

3.2.1. Electronic academic databases

We searched the following five electronic academic databases:

1. International Clinical Trials Register Platform (to 6 March 2019).
2. Ovid Medline with Daily Update (1 January 1946 to 6 March 2019).
3. EMBASE (1 January 1947 to 6 March 2019).
4. Web of Science with inclusion of three databases: Science Citation Index Expanded (1900 to 6th March 2019); Social Sciences Citation Index (1 January 1956 to 6 March 2019); Arts and Humanities Citation Index (1 January 1975 to 6 March 2019).
5. OSH UPDATE with inclusion of three databases: CISDOC (1 January 1974 to 6 March 2019); HSELINE (1977 to 6th March 2019); NIOSHTIC-2 (1 January 1977 to 6 March 2018).

The Ovid MEDLINE search strategy was presented in the protocol

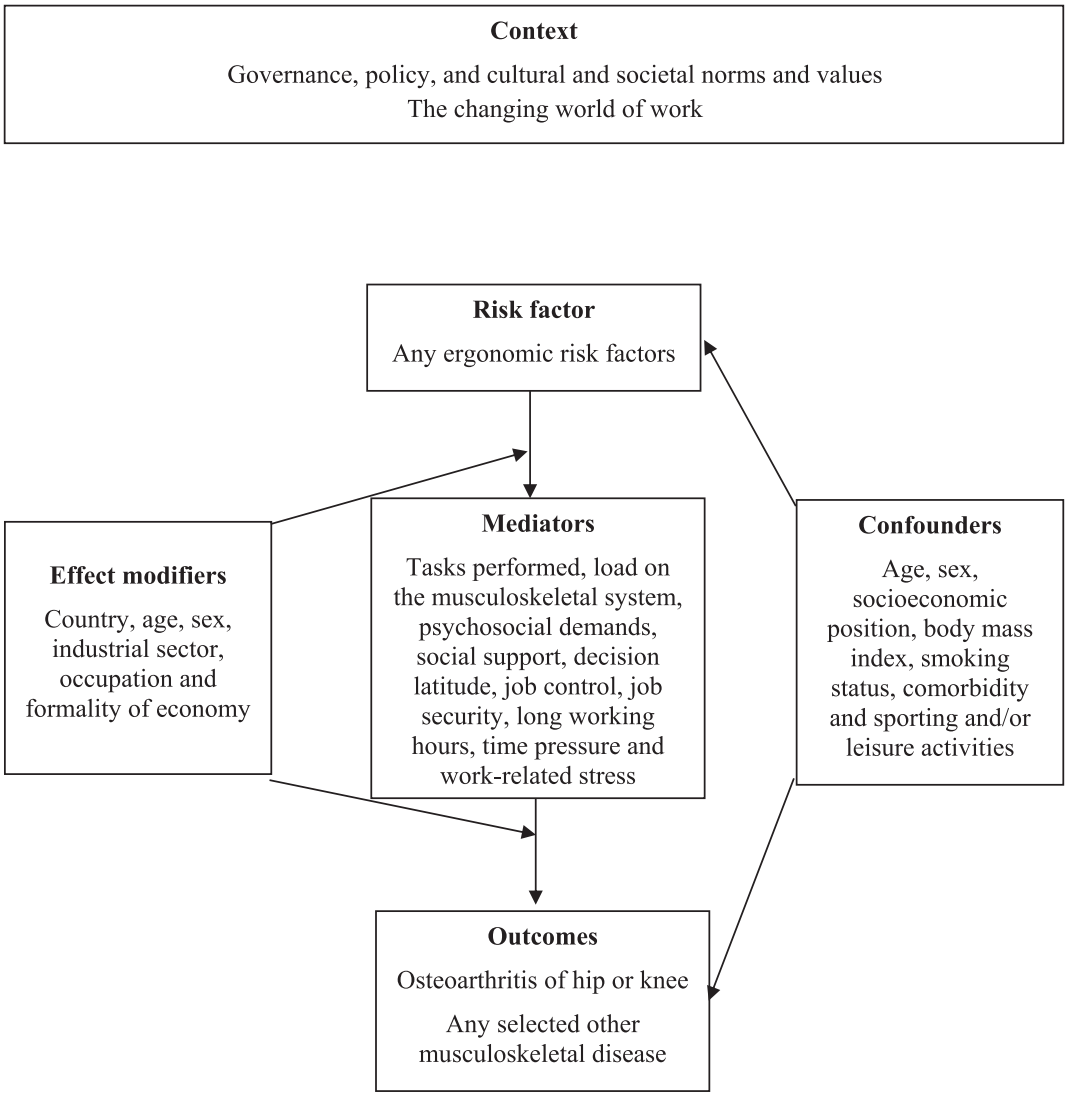

Fig. 1. Logic model of the possible causal relationship between exposure to occupational ergonomic risk factors and osteoarthritis of hip or knee and selected other musculoskeletal diseases.

(Hulshof et al., 2019). The full search strategies for all databases were revised by a clinical librarian/information scientist and the strategies used in Ovid Medline and in EMBASE are presented in Appendix 1 in the Supplementary data. We performed searches in electronic databases operated in the English language using a search strategy also in the English language. Consequently, study records that did not report essential information (i.e. title and abstract) in English were not captured. We have adapted the search syntax to suit the other electronic academic and grey literature databases. Just prior to completion of the review, an additional search of the MEDLINE database was undertaken on 3 March 2020 to capture the most recent publications (e.g., publications ahead of print). No additional studies were identified. Differences between the proposed search strategy and the actual search strategy are documented in Section 7.

3.2.2. Electronic grey literature databases

The following electronic grey literature databases were searched in December 2018:

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

3.2.3. Internet search machines

In addition, we also searched the Google (www.google.com/) and Google Scholar (www.google.com/scholar/) Internet search engines and screened the first 100 hits for potentially relevant records, a strategy used previously in Cochrane Reviews (Pega et al., 2015, 2017).

3.2.4. Organizational websites

The websites of the following nine international organizations and national government departments were searched in the period December 2018 to March 2019:

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. Eurofound (https://www.eurofound.europa.eu/en)
6. China National Knowledge Infrastructure (http://www.cnki.net/).
7. Finnish Institute of Occupational Health (https://www.ttl.fi/en/).
8. United States National Institute of Occupational Safety and Health (NIOSH), using the NIOSH data and statistics gateway (https://www.cdc.gov/niosh/data/).
9. International Ergonomics Association (http://www.iea.cc/).

3.2.5. Hand-searching and expert consultation

Hand-searching for potentially eligible studies was undertaken in:

- Reference lists of previous systematic reviews.
- Reference lists 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 obtained the largest number of included studies (Occup Environ Med; Scand J Work Environ Health; Int Arch Occup Environ Health).
- Study records that have cited an included study record (identified in Web of Science citation database).
- Collections of the review authors.

Additional experts were contacted with a request to identify potentially eligible studies. The Scientific Committee on Musculoskeletal Disorders of the International Commission on Occupational Health and the International Ergonomics Association have been contacted with a request to suggest eligible studies.

3.3. Selected studies

Study selection was carried out with the Covidence software. All records identified in the search were downloaded and duplicates were identified and deleted. Afterwards, pairs of two review authors independently screened titles and abstracts (step 1) and then full texts (step 2) of potentially relevant records. A third review author resolved 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 in the study, the record was re-assigned to another review author for study selection. We present the study selection for both health outcomes in a flow chart, as per PRISMA guidelines (Liberati et al., 2009).

3.3.1. Additional study selection by natural language processing

In order to efficiently identify all instances of the ergonomic risk factors of interest to our research project in the information found in more than two × 18,000 titles and abstracts retrieved by our search strategies, a natural language processing (NLP) method was used. Natural language processing is a subset of artificial intelligence techniques which deals with processing natural language (human language) and extracting the required information. Since our study had precise inclusion criteria as the presence of a number of ergonomic risk factors, we used a regular expression (RegEx or RegExp) technique. Regular expressions are a sequence of characters which represent a search pattern, and have been successfully used for data mining in various fields of medicine (Chen et al., 2019; Sohn et al., 2014). In the case of this systematic review, to search for published papers dealing with vibrations we have employed a regular expression 'vibrat' which would cover all variations of this word, such as vibration, vibrations, vibratory, vibrated, etc. For each of the seven risk factors, regular expressions were developed as presented in Table 3.

References which were originally in Endnote were exported as BibTex and saved as a .txt file. Then, all references were imported into the R programming language using the ***RefManageR*** package (R Core Team, 2019; McLean 2017). The regular expression search strategy was applied to all titles and abstracts and each occurrence of any of the ergonomic risk factors was flagged. Finally, the presence and number of flagged risk factors in the title and abstract was exported to Microsoft Excel together with the original data for further filtering. The regular expression strategy was intentionally developed to result in a high sensitivity to reduce the risk of false negatives.

Table 3
Regular expressions for the seven ergonomic risk factors.

Risk factor	Regular expression(s)
Force exertion (e.g. carrying, turn, screw)	'force', 'exert', 'carry', 'turn', 'screw'
Demanding posture (e.g. arm elevation, twisting)	'postur', 'elevat', 'twist'
Repetitiveness or repetitive work	'repetit', 'repeat'
Hand-arm vibration	'vibrat'
Lifting	'lift'
Kneeling and/or squatting	'kneel', 'squat'
Climbing	'climb'

3.4. Eligibility criteria

The PECO (Morgan et al., 2018) criteria are described below.

3.4.1. Types of populations

We included studies of the working-age population (≥15 years) in the formal and informal economy. Studies of children (aged < 15 years) and unpaid domestic workers were excluded. Participants residing in any WHO and/or ILO Member State and any industrial setting or occupational group were included. Appendix F of our protocol paper provides a briefer overview of the PECO criteria.

3.4.2. Types of exposures

We included studies that define exposure to occupational ergonomic risk factors in accordance with our standard definition (Table 1). We included studies where exposure to occupational ergonomic risk factors was measured, whether objectively (e.g. by means of 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 presented both objective and subjective measurements, then we have prioritized objective measurements. We included studies with measures from any data source, including registry data. Studies from any year were included.

For studies that reported exposure levels differing from our standard levels (Table 1), we converted the reported levels to the standard levels if possible and reported analyses on these alternate exposure levels if possible.

3.4.3. Types of comparators

The included comparator were participants exposed to the theoretical minimum risk exposure level (Table 1). We excluded all other comparators.

3.4.4. Types of outcomes

This systematic review included two outcomes:

1. Has selected other musculoskeletal diseases (MSD).
2. Has osteoarthritis of hip or knee (OA).

We included studies that defined MSD or OA, in accordance with our standard definition of these outcomes (Table 3). We included only include binary measures (present versus not present) of clinically assessed MSD or OA, respectively. Prevalence and incidence of eligible diseases were included, but mortality was excluded.

The following measurements of MSD or OA were regarded as eligible:

i) Diagnosis by a physician.
ii) Hospital admission or discharge records.
iii) Other relevant administrative data (e.g. records of sickness absence or disability).
iv) Registry data of treatment for MSD or OA, respectively.

All other measures were excluded from this systematic review.

We included objective measures of these eligible musculoskeletal diseases (e.g., measured by an occupational health and safety practitioner, such as an occupational physician or nurse, using a validated tool), as well as subjective measures (e.g., measured by a worker). If subjective and objective measures were presented, then we prioritized

objective measures.

3.4.5. Types of studies

We included studies that investigate the effect of exposure to any occupational ergonomic risk factor on MSD or OA for any years. Eligible study designs were 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 excluded 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 were included. Again, the search was conducted using English language terms, so that records published in any language that present essential information (i.e. title and abstract) in English were included. If a record was written in a language other than those spoken by the authors of this review or those of other reviews in the series, then the record was translated into English. Published and unpublished studies were included.

Studies conducted using unethical practices were excluded from the review (e.g., studies that deliberately exposed humans to a known risk factor to human health).

3.4.6. Types of effect measures

We included measures of the relative effect of any exposure to occupational ergonomic risk factors on the prevalence or incidence of MSD or OA respectively, compared with the theoretical minimum risk exposure level of no exposure. Effect estimates of mortality measures were excluded. We include relative effect measures such as risk ratios and odds ratios for prevalence measures and hazard ratios for incidence measures (e.g., developed MSD or OA, respectively). Measures of absolute effects (e.g. mean differences in risks or odds) were converted into relative effect measures, but if conversion was impossible, they were excluded.

As shown in our logic framework (Fig. 1), we *a priori* considered the following variables to be potential effect modifiers of the effect of occupational exposure to ergonomic factors on MSD or OA: country, age, sex, industrial sector, occupational group and formality of employment. We considered age, sex, socioeconomic position, body mass index, smoking status, comorbidity and sporting and/or leisure activities to be potential confounders. Potential mediators are tasks performed, load on the musculoskeletal system, psychosocial demands, social support, decision latitude, job control, job security, long working hours and work-related stress.

If a study presented estimates for the effect from two or more alternative models that have been adjusted for different variables, then we systematically prioritized 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 prioritized estimates from models adjusted for more potential confounders over those from models adjusted for fewer. For example, if a study presented 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 prioritized the estimate from Model C. We prioritized 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 have chosen the estimate from Model A over that from Model B. We prioritized 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 presented effect estimates from two or more potentially eligible models, then we documented specifically why we prioritized the selected model.

3.5. Extracted data

A data extraction form was developed and trialed until data extractors reached convergence and agreement. Pairs of two review authors have extracted 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 health loss from MSD or OA, respectively). A third review author has resolved conflicts in data extraction, if any. Data were entered into and managed with Excel.

We have also extracted data on potential conflict of interest in included studies. For each author and affiliated organization of each included study record, we have extracted their financial disclosures and funding sources. We have used 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 were available, we have searched 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, 2010b).

3.6. Requested missing data

If relevant data were missing, we requested by email or by phone to provide the missing data using the contact details provided in the principal study record. Mostly, missing data were dealing with analysis of exposure to any of the selected risk factors or any of the selected health outcomes. If we did not receive a positive response by study author, a follow-up email was sent at two weeks. On our request, some of the authors performed additional analyses and provided us the requested data. We present a description of additional data, the study author from whom the data were requested, the date of requests sent, the date on which data were received (if any), and a summary of the responses provided by the study authors (Appendix 2 in the Supplementary data).

3.7. Assessed risk of bias

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., 2016a, 2016b, 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 this systematic review. 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., 2016a, 2016b, 2016c; Lam et al., 2017). In our application of the *Navigation Guide* method, we have drawn heavily on one of its latest versions, as presented in the protocol for a systematic review (Lam et al., 2016a, 2016b, 2016c).

We have assessed 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 (Johnson et al., 2016; Lam et al., 2016a, 2016b, 2016c; Lam et al., 2017). Risk of bias or confounding ratings were: "low"; "probably low"; "probably high"; "high" or "not applicable" (Lam et al., 2016a, 2016b, 2016c). To judge the risk of bias in each domain, we have applied *a priori* instructions (Appendix H), which we have adopted or adapted from an ongoing *Navigation Guide* systematic review (Lam et al., 2016a, 2016b, 2016c). For example, a study was be assessed as carrying "low" risk of bias from source population representation, if we judged 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 was determined by the worst rating in any bias domain for any outcome. For example, if a study was 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 have jointly trialed the application of the risk of bias criteria until they have synchronized their understanding and application of the criteria. Pairs of study authors have independently judged the risk of bias for each study by outcome. Where individual assessments differ, a third author has resolved the conflict. For each included study, we have reported 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 present the study-level risk of bias assessments in a 'Risk of bias summary' figure (Higgins et al., 2011).

3.8. Conducted evidence synthesis (including meta-analysis)

If we found two or more studies with an eligible effect estimate (Table 2), two review authors independently investigated 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 found that effect estimates differed considerably by country, sex and/or age, or a combination of these, then we have synthesised 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 found that effect estimates were clinically sufficiently homogenous across countries, sexes and age groups, we have combined 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 Estimates.

If we judged 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, we have tested the statistical heterogeneity of the studies using the I^2 statistic (Woodruff and Sutton, 2014). If two or more clinically homogenous studies were found to be sufficiently homogenous statistically to be combined in a meta-analysis, we have pooled 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 (Woodruff and Sutton, 2014). The meta-analysis was 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 have neither quantitatively combined data from studies with different designs (e.g. cohort studies with case-controls studies), nor unadjusted and adjusted models. We have only combined studies that we judged to have a minimum acceptable level of adjustment for confounders. If quantitative synthesis was not feasible, we have synthesised the study findings narratively and identified the estimates that we judged to be the highest quality evidence available.

3.9. Additional analyses

If there was evidence for differences in effect estimates by country, sex, age, industrial sector and/or occupation, or by a combination of these variables, we have conducted subgroup analyses by the relevant variable or combination of variables, as feasible. 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 have also conducted subgroup analyses by study design (cohort studies versus case-control studies).

3.10. Assessed quality of evidence

We assessed quality of evidence using a modified version of the Navigation Guide quality of evidence assessment tool (Lam et al., 2016a, 2016b, 2016c). 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). We assessed quality of evidence for the entire body of evidence by outcome. We have adopted or adapted the latest Navigation Guide instructions for grading the quality of evidence (Lam et al., 2016a, 2016b, 2016c). We downgraded the quality of evidence for the following five GRADE reasons: (i) risk of bias; (ii) indirectness; (iii) inconsistency; (iv) imprecision; and (v) publication bias. We have judged the risk of publication bias qualitatively. To assess possible risk of bias from selective reporting, protocols of included studies have been screened to identify instances of selective reporting.

We have graded the evidence, using the three Navigation Guide standard quality of evidence ratings: "high", "moderate" and "low" (Lam et al., 2016a, 2016b, 2016c). Within each of the relevant domains, we rated the concern for the quality of evidence, using the ratings "none", "serious" and "very serious". As per Navigation Guide, we start at "high" for randomized studies and "moderate" for observational studies. Quality was downgraded 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 up-graded the quality of evidence for the following other reasons: large effect, dose–response and plausible residual confounding and bias. For example, if we had a serious concern for risk of bias in a body of evidence consisting of observational studies (-1), but no other concerns, and there were no reasons for upgrading, and we downgraded its quality of evidence by one grade from "moderate" to "low".

3.11. Assessed strength of evidence

We have applied the standard Navigation Guide methodology (Lam et al., 2016a, 2016b, 2016c) to rate the strength of the evidence. The

rating was 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 exposure to occupational ergonomic risk factors on MSD and OA respectively, were "sufficient evidence of harmfulness", "limited evidence of harmfulness", "inadequate evidence of harmfulness" and "evidence of lack of harmfulness".

4. Results

4.1. Study selection

Figs. 2a and 2b present the flow diagrams of the study selection for the outcomes MSD and OA respectively.

Of the total of 36,120 individual study records identified in our searches, 18 records from 17 studies fulfilled the eligibility criteria and were included in the systematic review. For the 30 excluded studies that most closely resembled inclusion criteria, the reasons for exclusion are listed in Appendix 1. Of the 18 included studies, eight were included in one or more quantitative meta-analyses.

4.2. Characteristics of included studies

The characteristics of the included studies are summarized in Tables 4a and 4b.

4.2.1. Study type

Half of the included studies were cohort studies (four studies) and the other half were case control studies (four studies). The type of effect estimates most commonly reported was odds ratios (eight studies).

Most studies did adjust for the most important of our pre-specified confounders, no study did not adjust for any of these confounders. The confounders most commonly adjusted for were age and sex. Several studies in addition also adjusted for further potential confounders (Tables 4a and 4b).

4.2.2. Population studied

The included studies captured 2,378,729 workers (1,157,943 females and 1,220,786 males) in total.

Six studies examined both female and male workers, while two studies examined only male workers.

The most commonly studied age groups were those between 20 and 65 years while in the studies on knee or hip osteoarthritis the age groups between 45 and 65 were overrepresented.

By WHO region, most studies examined populations in the European region (six studies from four countries) followed by populations in the Eastern Mediterranean region (one study) and populations in the Western Pacific region (one study). The most commonly studied countries were Germany (two studies) and France (two studies). Most studies

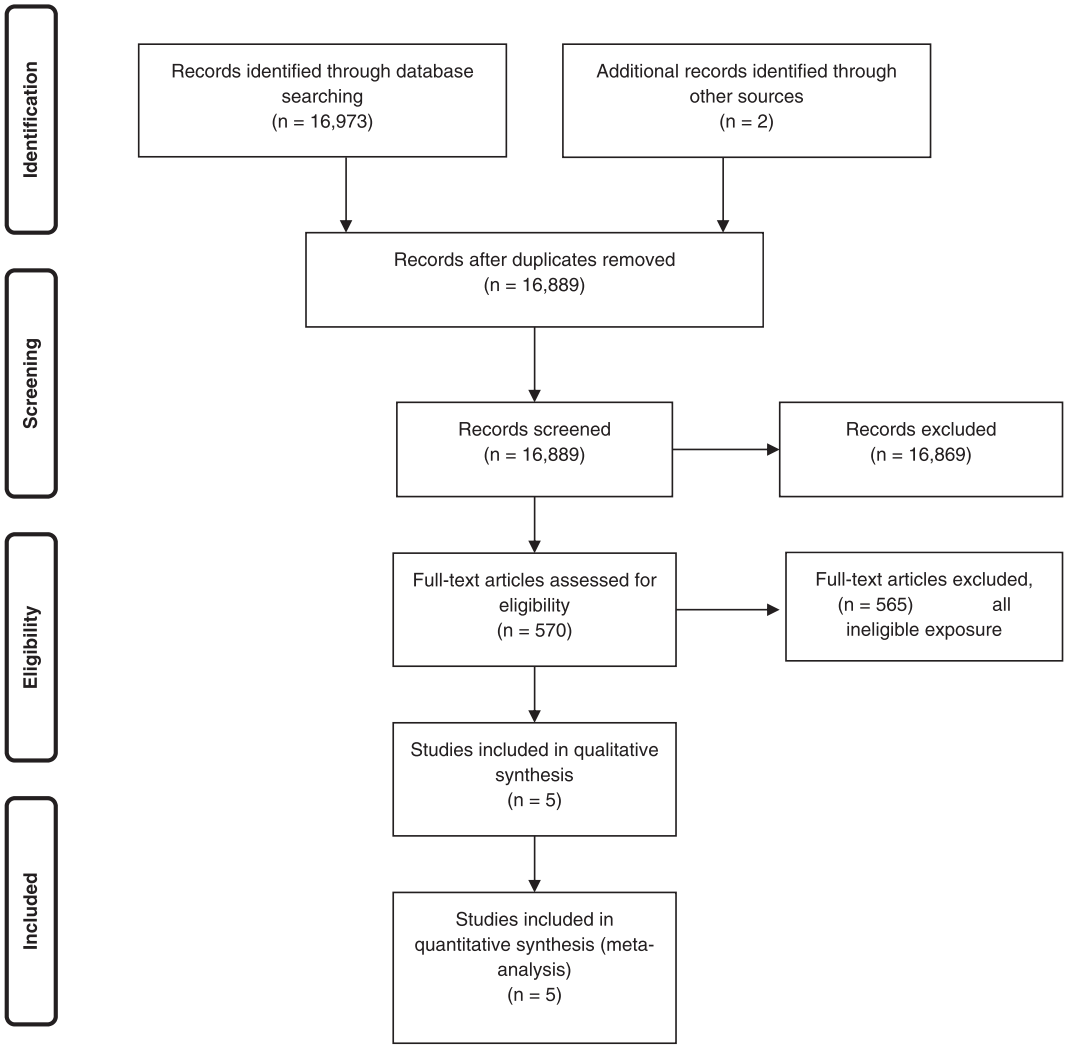

Fig. 2a. Flow diagram of study selection for outcome: selected other musculoskeletal diseases.

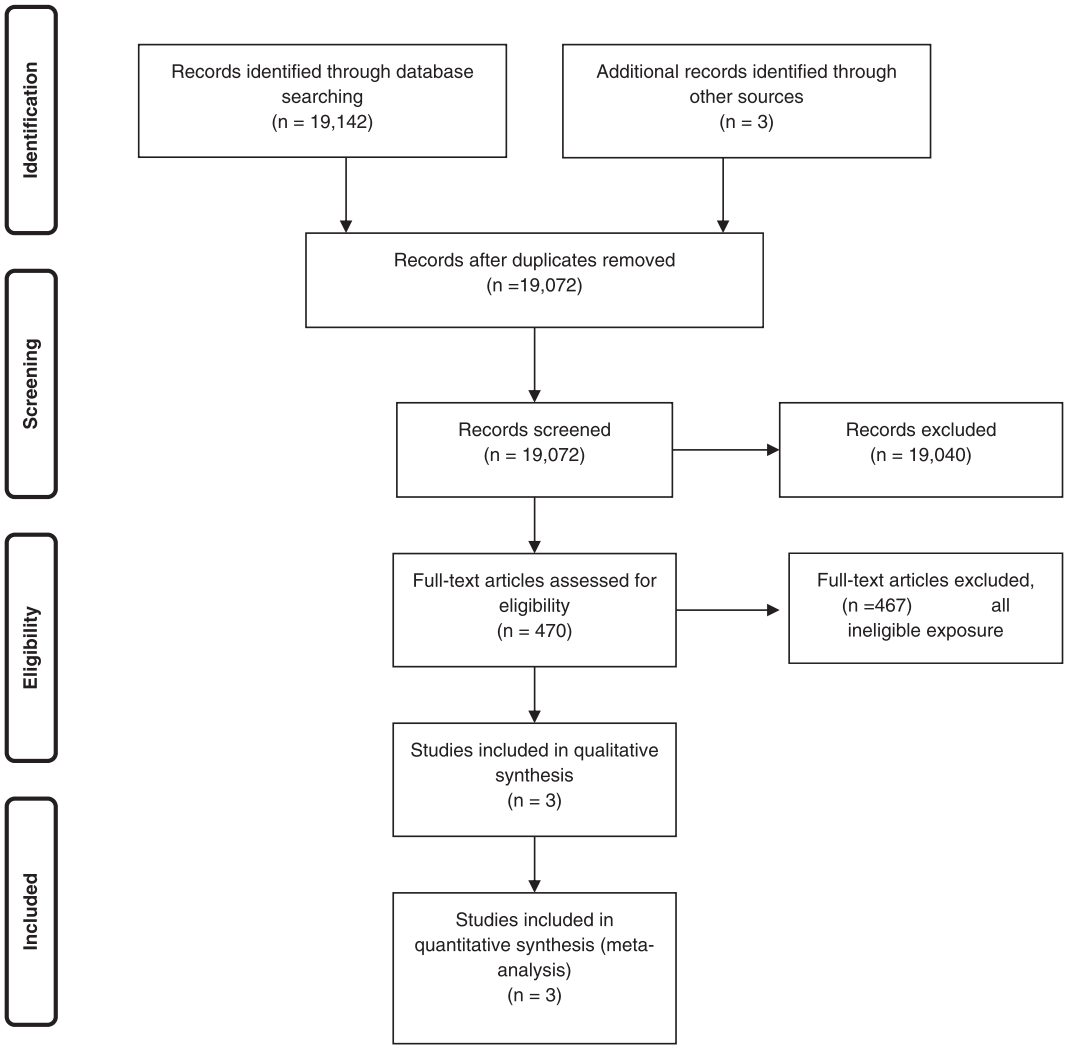

Fig. 2b. Flow diagram of study selection for outcome: knee or hip osteoarthritis.

did not provide detailed quantitative break downs of participants by industrial sectors and occupation, but most studies covered several industrial sectors and occupations.

4.2.3. Exposure studied

Out of a total of eight studies, seven studies measured exposure to the ergonomic risk factors using self-reports by questionnaires or interviews while one study used a job-exposure matrix to measure exposure only indirectly. All studies measured any exposure to at least three out of the seven selected ergonomic risk factors (force exertion, demanding posture, repetitiveness, hand-arm vibration, lifting, kneeling and/or squatting, and climbing).

4.2.4. Comparator studied

The comparator in all studies was no or low exposure to the selected ergonomic risk factors.

4.2.5. Outcomes studied

No studies reported evidence on the outcome of prevalence of MSD or OA.

Five studies reported evidence on the outcome of acquired MSD. Of these, four studies reported evidence on the incidence of several shoulder diseases (supraspinatus tendon lesions, rotator cuff syndrome, subacromial impingement syndrome or chronic shoulder pain), while one study reported evidence on epicondylitis lateralis. Most studies used physician diagnostic records.

Three studies reported evidence on the outcome of acquired OA; two on knee OA and one on hip OA. The outcome was most commonly assessed through physician diagnostic records.

4.3. Risk of bias at individual study level

4.3.1. Acquired other MSD

Tables A4.1–A4.5 in Appendix 4 present the risk of bias in the included studies at individual study level for the outcome 'other MSD' We judged the risk of bias to be low to probably low across studies (Fig. 3).

4.3.1.1. Selection bias. For the cohort studies included in this review we assessed the risk of selection bias to be probably low. Only the cohort study by Herquelot et al. (2013) showed a substantial number of missing cases from the original population. For our purpose the results from the cohort studies by Bodin et al. (2012) and Herquelot et al. (2013) were combined because they originated from the same cohort population. For the only case control study we rated the risk of selection bias as probably low. Although in case control studies the risk of selection bias is often higher compared to cohort studies, this case control study showed an appropriate selection strategy.

4.3.1.2. Performance bias. For the included cohort studies and the case

Table 4a
Characteristics of included studies for outcome: selected other musculoskeletal diseases (MSD).

Study	Study population						Study type				Study context
Study ID	Total number of study participants	Number of female study participants	Country of study population	Geographic location	Industrial sector (ISIC-4 code)	Occupation (ISCO-08)	Age	Study design	Study period (from first data collection to last data collection	Follow-up period (between exposure and outcome)	Latitude and/or seasonality
Miranda 2008	883	58%	Finland	Five regional capitals in Finland	Sample from Finnish adult population ≥ 30 years	Unclear	Mean age 64.2 ± 9.5	Prospective population-based study	1977–80	20 years	N/A
Seidler 2011	783 (483 cases and 300 controls)	Only male	Germany	Region	Many industrial sectors involved	Large range of occupational groups	26–65 years	Case control study	Recruitment period, 2003–2008	Unclear	N/A
Bodin 2012	1456	617	France	Region	Agriculture, Industries, construction, trade and services and temporary employment	Unclear	Mean age, female 38.9, male 38.5	Prospective cohort study	2002–2005 baseline examination 2007–2010 follow-up	5 years	N/A
Herquelot 2013	3231	1350	France	Region	Agriculture, Industries, construction, trade and services and temporary employment	Unclear	< 30: 16.4% 30–44: 54.4% > 45: 29.2%	Prospective repeated measures	April 2002–2005 and 2007–10	5 years	N/A
Dalboge et al. (2014)	2,374,403	48.7%	Denmark	National	Entire Danish working population	–	≤ 35: 17.3% 36–45: 29.3% 46–55: 26% 56–65: 22.7% 66–70: 4.7%	Retrospective cohort study	People alive who lived in Denmark on 31–12-2002; having had employment between 1993 and 2007	At least 5 years full time	N/A

Table 4a. Characteristics of included studies for outcome: selected other musculoskeletal diseases (continued)

Study	Exposure assessment							Co-exposure	Prioritized model		
Study ID	Exposure definition (i.e. how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Levels or intensity of exposure (specify unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors	Are two or more alternative models reported?	Alternative model prioritized/ selected for use in this review	Reason for prioritization/ selection
Miranda 2008	Lifting (yes,no), awkward postures (yes,no), vibration (yes,no), repetitive movement (yes,no), physical workload (sum index of 5 actors)	Individual level	Self-administered baseline questionnaire	Self-report	Yes and no; and sum index of the five factors: 0–5	Lifting: 233; awkward postures: 268; vibration: 73; repetitive movements: 176; sum score: 415	Lifting: 634; awkward postures: 599; vibration: 490; repetitive movements: 691 work paced by machine: 811; sum score 0: 452	Unclear	No	NA	NA
Seidler 2011	Cumulative exposure to work above shoulder level, lifting/ carrying was calculated up to the year of diagnosis (in cases) or to the year of interview (in control subjects).	Individual level	Computeradminis-tered survey	Interview	Prevalence	N = 60	N = 423	Unclear	Yes	Model 2: reported as adjusted OR	Model 2 was adjusted for more potential confounders
Bodin 2012	Workers were defined as exposed if they were exposed	Individual level	Self-administered questionnaire	Question-naires	Working in Biomechanical	N = 577	N = 752	Unclear	Yes	Model 1: multivariate model)	Model 2 contained only the exposure that remained

(*continued on next page*)

Table 4a (*continued*)

	to any of the ergonomic risk factors ≥2h/day)				exposures ≥2 h/ day						statistical significant in backward regression model.
Herquelot 2013	Workers were defined as exposed if they were exposed to any of the ergonomic risk factors ≥ 2h/day	Individual level	Survey and physical examination	Survey and physical examination	Working in Biomechanical exposures ≥2 h/ day	602	822	Unclear	Yes	Multiple imputation	More complete
Dalboge 2014	Shoulder load: any exposure of arm-elevation years, repetition-years, force-years	Individual level	Job Exposure Matrix (JEM)	JEM	Arm elevation years; Repetition years; Force years; HAV years; Shoulder load years	Not explicitely reported	Not explicitely reported	Unclear	No	–	–

Table 4a. Characteristics of included studies for outcome: MSD (continued)

Study	Outcome assessment									Comparator
Study ID	Definition of outcome	ICD code reported for the outcome (if any)?	Method of outcome assessment	Diagnostic assessment method	Specification of outcome	Number of cases with outcome of interest in exposed group	Number of non-cases (i.e. without outcome of interest) in exposed group	Number of cases with outcome of interest in unexposed group	Number of non-cases (i.e. without outcome of interest) in unexposed group	Definition of comparator (define comparator group, including specific level of exposure)
Miranda 2008	Chronic shoulder pain	Unclear	Standard clinical examination protocol and symptoms, and detailed medical records	Standard clinical examination protocol and symptoms, and detailed medical records	Chronic shoulder pain	Lifting: 26; awkward postures: 29; vibration: 13; repetitive movements: 22; sum score: 48	Lifting: 207; awkward postures: 237; vibration: 60; repetitive movements: 154 sum score: 367	Lifting: 37; awkward postures: 34; vibration: 50; repetitive movements: 41; sum score: 15	Lifting: 597; awkward postures: 565; vibration: 440; repetitive movements: 650; sum score: 437	No exposure
Seidler 2011	Supraspinatus tendon	Unclear	Radiologist assessed outcome as diagnosed by MRI	Physician diagnostic record	Supraspinatus tendon lesion	*Lifting/carrying loads ≥20Kg: 270 *Work above shoulder level: 310 *Handheld vibration: 233	*Lifting/carrying loads ≥20Kg : 106 *Work above shoulder level: 108 *Handheld vibration: 56	*Lifting/carrying loads ≥20Kg : 202 *Work above shoulder level: 167 *Handheld vibration: 250	*Lifting/carrying loads ≥20Kg : 185 *Work above shoulder level: 184 *Handheld vibration: 244	No exposure (no lifting ≥20Kg; No work above shoulder level; No handheld vibration)
Bodin 2012	Rotator Cuff Syndrome (RCS)	M 75.1	Unclear	Physician diagnostic record	Rotator Cuff Syndrome (RCS)	Unclear, men=10 women=14	Men=161 women=148	Men=41 women=30	Men=623 women=415	Low/no exposure to repetitive tasks (<4h/ day), repetitive and awkard postures (<2h/day) and hand vibration tools (<2h/ day)
Herquelot 2013	Lateral epicondylitis	M77.1	Physical examination	Physical examination	Pain in lateral elbow region	Unclear	Unclear	Unclear	Unclear	People with no pain on examination
Dalboge 2014	Surgery for subacromial impingement syndrome (SAPS)	M19 or M75.1-M75.9	Surgery for subacromial impingement syndrome	Surgery for subacromial impingement syndrome	Surgery for subacromial impingement syndrome	See original Table 2	Unclear	See Table 2	Unclear	Four different risk factors and a combination of risk factors

Table 4a. Characteristics of included studies for outcome: MSD (continued)

Study	Adjustments of effect estimates in model prioritized by reviewers									Estimate of effect of exposure on outcome		
Study ID	Adjusted for age	Adjusted for sex	Adjusted for socio-economic status	Other potential confounders adjusted for	Adjusted for mediation by:	Adjusted for mediation by:	Adjusted for mediation by:	Other potential mediators adjusted for	Interactions adjusted for	Adjusted for clustering (if any)	Model prioritized by reviewers	Treatment effect measure type	Exposure- or dose–response analysis conducted

(*continued on next page*)

Table 4a (*continued*)

				[Mediator 1]	[Mediator 2]	[Mediator 3]							
Miranda 2008	Yes	Yes	No	Monotonous work; tight work schedule; worries about work, somatisation, BMI, diabetes and physical exercise	No	No	No	Age, gender, work stress, psycho-logical and other factors (e.g. health behaviours). Age and BMI were effect modifiers	No	No	Odds ratio	No	
Seidler 2011	Yes	No	No	Selected model adjusted for age and region	No	No	No	No	No	Model, adjusted odd ratio	Odds ratio	No	
Bodin 2012	Yes	Yes, analysis stratified by sex	No	Psycho-social factors (work pace, co-worker support)						Model II	Odds ratio	No	
Herquelot 2013	No	Analysis done by sex	No	No	No	No	No	No	No	Multi-variate model	Incidence rate ratio	No	
Dalboge 2014	Yes	Yes	No	Region of residence; calendar year at start follow-up	No	No	No	No	No	Model on effect of cumulative occupational physical exposure	Odds ratio	Yes	

control study, the risk of performance bias was assessed as probably low. Information on blinding of study participants and study personnel was not always provided but in most cases, because of the use of primarily questionnaire or administrative data, the possible knowledge of exposure or outcome status could have hardly impacted the results.

4.3.1.3. Detection bias (exposure assessment). For possible detection bias regarding the exposure assessment, the rating is probably high to high. In none of the studies, exposure was measured directly;- it was always self-reported or based on a job-exposure matrix. Therefore, detection bias due to exposure misclassification was mostly rated Probably High. In one study, the case control study by Seidler et al. (2011), it was rated as high, mainly because the additional analysis of the data that was provided by the authors were partly based on a recalculation of cumulative exposure data, averaged over a time period, which may not always reflect adequate exposure assessment.

4.3.1.4. Detection bias (outcome assessment). Detection bias regarding outcome measurement was not seen as a big problem and therefore rated as low to probably low. Most studies used physician diagnostic records, detailed administrative health records or radiological findings related to specific diagnosis or a diagnosis group. For some of the studies specific ICD-codes were reported.

4.3.1.5. Confounding. Possible confounding across the studies was rated as low to probably low. In all studies, the results were presented based on a (multivariable) model to adjust for the most important possible confounders as indicated in our logic model. Adjustment was mostly done for age, sex and socio-economic position and sometimes for other factors like BMI or sporting activities. Appropriate statistical techniques were used for adjustment of confounders.

4.3.1.6. Selection bias (incomplete outcome data). Selection bias due to incomplete outcome data was judged to be low to probably low. In the cohort studies almost all subjects diagnosed with the outcome were analysed at follow up. In one study (Herquelot et al., 2013) multiple imputations were performed for missing data on the follow-up. There is no evidence that this has led to selective reporting of the outcome data.

4.3.1.7. Reporting bias. Selective reporting was not judged as a major issue in the included studies and therefore, this was rated as low to probably low. Although the study protocol of the included studies was not available, it is unlikely that there was selective reporting of outcomes. The outcomes were reported in the results sections of the study records as they had been reported in the abstracts and methods sections in the study record.

4.3.1.8. Conflict of interest. All included studies on MSD did not receive support from a company or other entity with a financial interest in the study findings; were funded by public research agencies or related organizations that were free from commercial interests in the study findings; were authored only by persons who were not affiliated with companies or other entities with vested interests; and/or had no conflict of interest declared by study authors.

4.3.1.9. Other risk of bias. There were no indications for other risk of bias in the included studies and therefore this domain was rated as probably low.

4.3.2. Acquired knee or hip OA

Tables A4.6–A4.8 in Appendix 4 present the risk of bias in the included studies at individual study level for the outcome 'knee or hip OA'. All included studies are case control studies. Although in general, case control studies are regarded as sensitive to a higher risk of bias in comparison to cohort studies, we judged the risk of bias of the included

Table 4b
Characteristics of included studies for outcome: knee or hip osteoarthritis (OA).

Study	Study population							Study type			Study context
Study ID	Total number of study participants	Number of female study participants	Country of study population	Geographic location	Industrial sector (ISIC-4 code)	Occupation (ISCO-08)	Age	Study design	Study period (from first data collection to last data collection	Follow-up period (between exposure and outcome)	Latitude and/or seasonality
Yoshimura 2000	206 (103 cases + 103 controls)	184	Japan	Two health districts in Wakayama Prefecture	Not reported	Not reported	Total: 63.8 ± 10.9; women: 64.1 ± 11; men: 61.0 ± 10	Case control	Not reported	Lifetime history of exposure (since leaving school)	N/A
Seidler et al. (2008)	622 (295 cases + 327 controls)	0	Germany	City of Frankfurt am Main and surrounding places.	Agriculture and mining, Production, Technology Services	See Table 1, 1st column	Mean age cases at initial radiograpy of knee OA: 59.1 ± 8.5; Mean age of population controls at interview: 47.9 ± 12.5.	Case control	unclear	>10 years	N/A
Gholami 2016	526 (263 cases and 263 controls)	363 (194 cases and 169 controls)	Iran	No further information provided	Population-based study. No selection on industrial sector	Unclear	Mean age 56 among cases and 48.8 among controls	Population based case-control study	2004–2005 was the first stage. No further information	No follow-up. A survey in 2004–2005	N/A

Table 4b Characteristics of included studies for outcome: OA (continued)

Study	Exposure assessment							Co-exposure	Prioritized model		
Study ID	Exposure definition (i.e. how was the exposure defined?)	Unit for which exposure was assessed	Mode of exposure data collection	Exposure assessment methods	Levels or intensity of exposure (specify unit)	Number of study participants in exposed group	Number of study participants in unexposed group	Potential co-exposure with other occupational risk factors	Are two or more alternative models reported?	Alternative model prioritized/ selected for use in this review	Reason for prioritization/ selection
Yoshimura 2000	Exposure to lifting, kneeling, squatting, climbing in first job and main job	Individual level	Structured questionnaire	Structured questionnaire	Lifting 25+ kg Kneeling ≥ 1h Squatting ≥1h Climbing ≥ 30 flights of stairs	Lifting: 28 Kneeling: 25 Squatting: 26 Climbing: 25	Lifting: 19 Kneeling: 23 Squatting: 21 Climbing: 25	Sitting ≥ 2h Standing ≥ 2h Driving ≥ 4h Walking ≥ 3 km	No	N/A	N/A
Seidler 2008	Two ways: 1) 1 to 10 yrs. in specific occ. group, >10 yrs. in specific occ. Group 2) cumulative exposure to kneeling/ squatting, lifting/ carrying and their combination	Individual level	Computer-assisted personal interview	Computer-assisted personal interview	≥ 2 h/day, lifting, kneelin/squatting, carrying combined	N = 110	N = 185	Unclear	No	N/A	N/A
Gholami 2016	Squatting (≥1h/ day); kneeling (≥1h/ day); standing (≥2h/ day); walking (≥3h/ day); climbing (≥10 flights/week); carrying/lifting ≥10 kg (≥10 times/week or ≥2h/week)	Individual level	Unclear, self-report	Questionnaire and exam sheet	Squatting (≥1h/ day); kneeling (≥1h/day); standing (≥2h/ day); walking (≥3h/day); climbing (≥10 flights/week carrying/lifting	Numbers in cases and controls: squatting: 57 and 26 Kneeling: 193 and 187 Standing: 218 and 206 Walking: 200 and 180 Climbing: 21- and 39 carrying: 42 and 39	Squatting: 206 and 237 kneeling: 70 and 76 standing: 45 and57 walking: 63 and 83 climbing: 53 and 38 carrying/lifting: 221 and 224	Unclear	No	N/A	N/A

(*continued on next page*)

Table 4b (*continued*)

					≥10 kg (≥10 times/week or ≥2h/week)						

Table 4b Characteristics of included studies for outcome: OA (continued)

Study	Outcome assessment									Comparator
Study ID	Definition of outcome	ICD code reported for the outcome (if any)?	Method of outcome assessment	Diagnostic assessment method	Specification of outcome	Number of cases with outcome of interest in exposed group	Number of non-cases (i.e. without outcome of interest) in exposed group	Number of cases with outcome of interest in unexposed group	Number of non-cases (i.e. without outcome of interest) in unexposed group	Definition of comparator (define comparator group, including specific level of exposure)
Yoshimura 2000	Cases: age > 45 years, listed for total hip arthroplasty due to OA over 1 year	Not reported	Physician diagnosis	Radiographs assessed centrally by single trained observer	Hip OA	See Tables 5 and 6	See Tables 5 and 6	See Tables 5 and 6	See Tables 5 and 6	Low or no exposure to lifting, kneeling, squatting, or climbing
Seidler 2008	Knee OA:To qualify as cases, patients had to have at least grade 2 osteoarthritis according to the reference radiologist's assessment.	Not reported	Physician diagnostic record	Physician diagnostic record	Knee OA	See Tables 1 and 2	See Tables 1 and 2	See Tables 1 and 2	See Tables 1 and 2	Job = reference group: service occupation as main occupation, Activities= reference group: no lifting/carrying, no kneeling/squatting, no lifting/carrying and no kneeling/squatting
Gholami 2016	Knee osteoarthritis	American College Rheumatology (ACR) criteria	Questionnaire and physical examination sheet	ACR criteria	Knee osteoarthritis	Squatting 57, kneeling 193, standing 218, walking 200, climbing 210, carrying/lifting 42	Squatting 26, kneeling 187, standing 206, walking 180, climbing 225, carrying/lifting 39	Squatting 206, kneeling 70, standing 45, walking 63, climbing 53, carrying/lifting 221	Squatting 237, kneeling 76, standing 57, walking 83, climbing 38, carrying/lifting 224	Low or no exposure to squatting, kneeling, standing, walking, climbing and carrying/lifting

Table 4b Characteristics of included studies for outcome: OA (continued)

Study	Adjustments of effect estimates in model prioritized by reviewers										**Estimate of effect of exposure on outcome**		
Study ID	Adjusted for age	Adjusted for sex	Adjusted for socio-economic status	Other potential confounders adjusted for	Adjusted for mediation by: [Mediator 1]	Adjusted for mediation by: [Mediator 2]	Adjusted for mediation by: [Mediator 3]	Other potential mediators adjusted for	Interactions adjusted for	Adjusted for clustering (if any)	Model prioritized by reviewers	Treatment effect measure type	exposure- or dose–response analysis conducted
Yoshimura 2000	Yes (matched)	Yes (matched)	No	Residence, school leaving age, previous knee pain	No	No	No	No	No	No	Conditional logistic regression for matched sets	Odds ratio	For lifting (10+ kg; 25+ kg; 50+ kg)
Seidler 2008	Yes	Yes	No	Region, BMI, jogging/athletics	No	No	No	No	No	No	Model on effect of cumulative occupational exposure to lifting/carrying, kneeling/squatting	Odds ratio	Yes
Gholami 2016	Yes	Yes	Yes, education	Marital status, BMI, smoking, history of knee injury, and the various exposures	No	No	No	No	No	No	Multivariate weighted regression model	Odds ratio	No

studies for this outcome to be low to probably low across the studies (Fig. 3).

4.3.2.1. Selection bias. In two of the three studies selection bias was rated as probably low. In the study by Gholami et al. (2016) it was judged as high, mainly because the study population of cases and controls differed from the eligible population on demographic variables.

4.3.2.2. Performance bias. The risk of performance bias was assessed as probably low. In all included studies, knee or hip OA were radiographically confirmed, according to clear diagnostic criteria and/or to a single trained observer.

4.3.2.3. Detection bias (exposure assessment). Also in the three included studies for this outcome, exposure assessment was based on self-report and therefore detection bias regarding exposure assessment was rated as probably high. In the study by Yoshimura et al. (2000), lifetime history after leaving school of exposure to occupational ergonomic risk factors was asked which may have led to recall bias.

4.3.2.4. Detection bias (outcome assessment). Detection bias regarding outcome measurement leading to possible outcome misclassification was seen as low to probably low. Mostly radiographic confirmation of findings was used based on clear diagnostic criteria (e.g. the American College of Rheumatology (ACR) criteria).

4.3.2.5. Confounding. Possible confounding across the three studies was rated as low to probably low. Results were presented based on a (multivariable) model to adjust for the most important possible confounders as indicated in our logic model. Matching or adjustment was performed for age, sex and socio-economic position and also for other factors like BMI or sporting activities. Appropriate statistical techniques were used for adjustment of confounders.

4.3.2.6. Selection bias (incomplete outcome data). Selection bias due to incomplete outcome data was not seen as a problem across the studies. Outcome data were complete for cases and controls.

4.3.2.7. Reporting bias. Selective reporting was rated as low to probably low across the studies. The outcomes were reported in the results sections of the study records as they had been reported in the abstracts and methods sections in the study.

Conflict of interest

The included studies on OA of hip or knee did not receive support from a company or other entity with a financial interest in the study findings; were funded by public research agencies or related organizations that were free from commercial interests in the study findings; were authored only by persons who were not affiliated with companies or other entities with vested interests; and/or had no conflict of interest declared by study authors.

4.3.2.8. Other risk of bias. Other possible risk of bias was not identified in the included studies, and therefore this was domain was rated as probably low.

4.4. Synthesis of results

4.4.1. Outcome: Acquired other MSD (MSD incidence)

A total of five studies (four cohort studies and one case control study) comprising2,377,375 participants from one WHO region (Europe) reported estimates of the effect of occupational exposure to ergonomic risk factors on other MSD, compared with no or low exposure to ergonomic risk factors. The four cohort studies could be included in a quantitative meta-analysis on prioritized evidence. The results from two studies (Bodin et al., 2012, Herquelot et al., 2013) were based on the same cohort, which both reported on the relationship between exposure to occupational ergonomic risk factors and other MSD (rotator cuff syndrome and epicondylitis lateralis, respectively), and therefore their results have been combined. These studies that we pooled in our meta-analysis were somewhat heterogeneous in the measurement of exposure, but we considered the definition of exposure to still be similar enough to warrant inclusion in the meta-analysis. Compared with no or low exposure, any occupational exposure to ergonomic risk factors increased the risk of acquiring other MSD (OR 1.76, 95% CI 1.14 to 2.72, 4 studies, 2,376,592 participants, I^2 70%; Fig. 4).

A supporting case control study (Seidler et al., 2011) on 783 male workers (483 cases and 300 controls) on occupational exposure to ergonomic risk factors and MSD, in this case shoulder tendon (supraspinatus) lesions, showed an elevated risk for this more specific disorder (OR 4.69, 95% CI 2.10 to 10.47; Fig. 7).

4.4.2. Outcome: Acquired knee or hip OA

Three studies (all case control studies) with a total of 1,354 participants from three different WHO regions (Europe, Eastern Mediterranean, Wester Pacific) reported estimates of the effect of occupational exposure to ergonomic risk factors on knee or hip OA, compared with no or low exposure to ergonomic risk factors. All three studies could be included in a quantitative meta-analysis. These studies that we pooled in our meta-analysis were somewhat heterogeneous in the measurement of exposure, but we considered the definition of exposure to still be homogeneous enough to warrant inclusion in the meta-analysis. Compared with no or low exposure, any occupational exposure to ergonomic risk factors increased the risk of acquiring knee or hip OA (OR 2.20, 95% CI 1.42 to 3.40, 3 studies, 1,354 participants, I^2 13%; Fig. 5).

4.5. Additional analyses

4.5.1. Subgroup analyses

4.5.1.1. By sex. See Fig. 6.

4.5.1.2. By study type. See Fig. 7.

4.6. Quality of evidence

4.6.1. Quality of evidence regarding the outcome MSD

We started at "moderate" for observation studies. The general picture of the cohort studies was that we did have serious concern regarding risk of bias in the prioritized body of evidence, in particular regarding detection bias due to exposure misclassification on this outcome. We judged the overall risk of bias to be moderate, and therefore the quality of evidence was downgraded for this consideration (- 1 level). Exposure data were all based on self-reports or on job exposure matrix data and although they were in general defined clearly in the judgement of the risk of bias this was considered a serious concern. All included studies were carried out in only one WHO region (Europe) which could be considered a risk for indirectness in relation to other WHO regions. However, in contrast to the systematic review on prevalence estimates where we downgraded one level for indirectness, for this review on the relationship between exposure and health outcome, the impact of WHO region was considered to be less significant. Moreover, we did not have any serious concern regarding the quality of evidence on outcome definitions and descriptions. Therefore, following discussion we decided not to downgrade the quality of evidence for indirectness (± 0 levels). We also had no serious concerns regarding inconsistency, in relation to the cohort studies and were sufficiently clinically homogeneous to be combined in a quantitative meta-analysis. Although there is some statistical heterogeneity ($p = 0.03$; $I^2 = 70\%$), the point estimates do not demonstrate wide variability and the confidence intervals show considerable overlap, in particular at the lower boundaries. Therefore,

	Selected other musculoskeletal diseases						*Knee or hip osteoarthritis*		
	Miranda 2008	Bodin 2012	Herquelot 2013	Seidler 2011	Dalboge 2014		Gholami 2016	Seidler 2008	Yoshimura 2000
1. Selection bias?	probably low	probably low	probably low	probably low	low		high	probably low	probably low
2. Performance bias?	probably low	probably low	probably high	probably low	low		probably low	probably low	probably low
3. Detection bias (exposure assessment)?	probably high	probably high	probably high	high	probably high		probably high	probably high	probably high
4. Detection bias (outcome assessment)?	probably low	probably low	probably low	low	low		probably low	low	low
5. Confounding?	low	probably low	low	probably low	low		probably low	probably low	low
6. Selection bias (incomplete outcome data)?	probably low	probably low	probably low	low	low		low	low	low
7. Selective outcome reporting?	probably low	probably low	low	low	low		probably low	low	low
8. Conflict of interest?	low	probably low	probably low	low	low		probably low	low	probably low
9. Other source of bias?	probably low	probably low	probably low	probably low	probably low		probably low	probably low	probably low

Fig. 3. Summary of risk of bias across studies. Acquired other selected musculoskeletal diseases or knee or hip osteoarthritis.

no downgrading of the quality of evidence (± 0 levels) for inconsistency was applied. We had no serious concerns for imprecision, given the relatively narrow CI for the pooled OR, so did not downgrade the quality of evidence for imprecision (± 0 levels). We did not have any serious concerns for publication bias (± 0 levels). We did not upgrade the quality of evidence for a large effect estimate, nor for evidence for consistent dose–response gradients across the studies, or for residual confounding that could increase the confidence. In conclusion, we started to assess the quality of evidence regarding the outcome MSD at the level of "moderate" for observational studies and decided to downgrade with one level. Therefore, we arrived at a final overall rating of "low".

4.6.2. Quality of evidence regarding the outcome OA of knee or hip

As with the previous MSD outcome, we started at "moderate" for observational studies. For the OA outcome we only have three case control studies available which, in general, are thought to possibly lead to a higher risk of bias. From the study limitations for the individual studies and across the studies as summarized in the heat map we did have a serious concern regarding the risk of bias in the body of evidence for this outcome, in particular due to probably high risk of bias for exposure assessment because also here all exposure assessment was based on self-report. Therefore, we regarded the quality of study limitations (risk of bias) as moderate and did downgrade the quality of evidence for risk of bias (- 1 level). We did not have serious concerns for indirectness. In contrast with the studies on MSD, the study data were coming from three different WHO regions (Europe, Easter Mediterranean and Western Pacific). Study populations did not differ from populations at interest and also the exposure definitions or health outcomes did not differ substantially those of primary interest. The quality of evidence was not downgraded for indirectness (± 0 levels). We did not have any serious concerns regarding inconsistency. The included studies were thought to have sufficient clinically homogeneity and the statistical heterogeneity was limited ($p = 0.32$; $I^2 = 13\%$). Also for this outcome, the point estimates do not vary very widely and the confidence intervals show considerable overlap. Therefore, no downgrading of the quality of evidence for inconsistency was considered (± 0 levels). We also had no serious concerns for imprecision, given the sufficiently narrow CI of the pooled OR, and therefore did not downgrade (± 0 levels). We did not have any serious concerns for publication bias (± 0 levels). Comparably to the MSD outcome studies, we did not upgrade the quality of evidence for a large effect estimate, nor for evidence for a consistent dose–response gradient across the studies, or for residual confounding that could increase the confidence. In conclusion, we started to assess the quality of evidence regarding the outcome OA of knee or hip at the starting level of "moderate" for observational studies and decided to downgrade one level for risk of bias. Therefore, we also arrived at a final rating of "low" for this outcome.

4.7. Strength of evidence

According to the protocol, the strength of the evidence was rated based on a combination of four criteria outlined in the Navigation guide: (1) Quality of the entire body of evidence; (2) Direction of the effect estimate; (3) Confidence in the effect estimate; (4) Other compelling attributes.

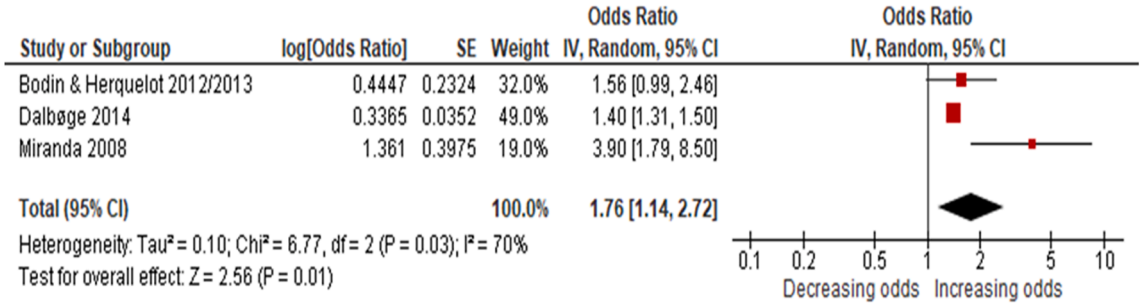

Fig. 4. Forest plot, main meta-analysis of prioritized evidence (cohort studies) on other MSD.

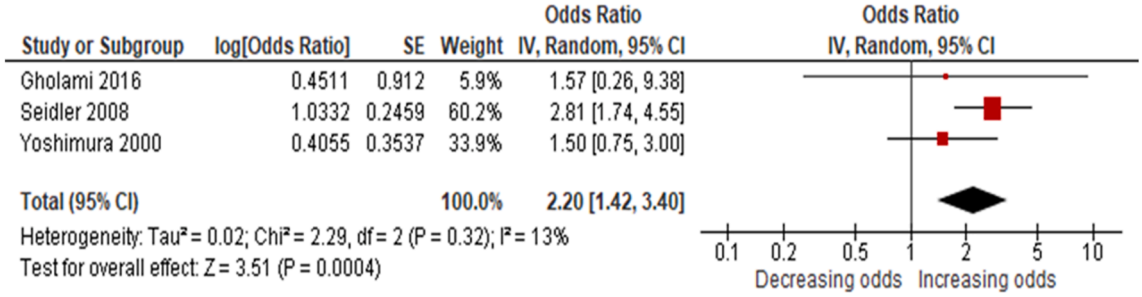

Fig. 5. Forest plot, main meta-analysis of evidence (case-control studies) on knee or hip OA.

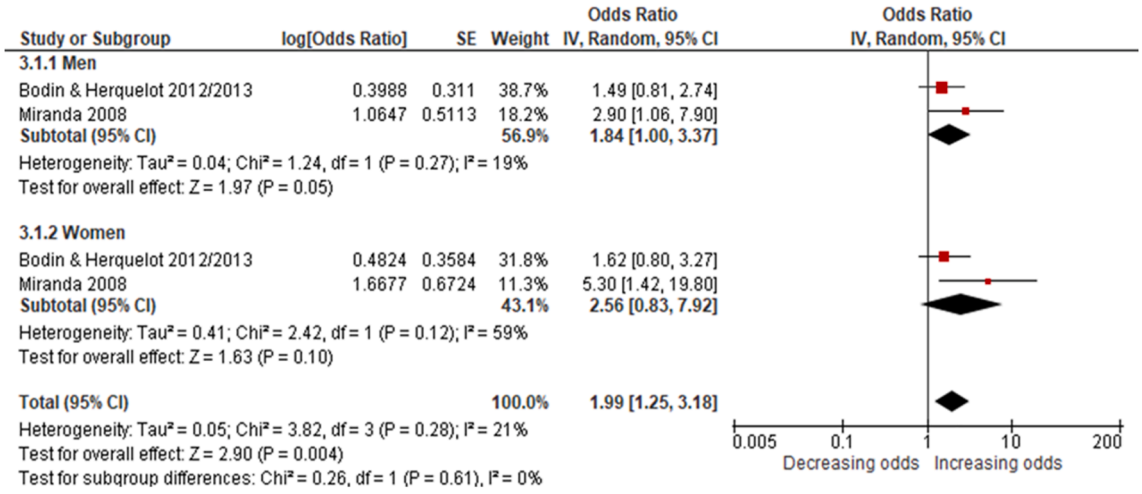

Fig. 6. Subgroup analysis: forest plot of other MSD stratified by sex.

4.7.1. Strength of evidence regarding the outcome MSD

Concerning the size, and quality of the individual cohort studies, it was discussed and agreed that we judge the main body of evidence on the relationship between occupational exposure to physical ergonomic factors and selected other MSD as "limited evidence of harmfulness". The meta-analysis based on four cohort studies, including a large number of participants, and taking into account relevant confounders, documents a moderately increased risk of incident MSD (OR 1.76) with a lower CI beyond 1.0 and a rather narrow CI (1.14–2.72). Overall, across the studies, risk of bias of the cohort studies was regarded moderate, supporting reasonable quality, and the direction of the estimate was similar in all included studies. No study documented a negative effect estimate. There is reasonable confidence in the effect estimate as also a supporting case control study and earlier systematic reviews on the same topic found comparable results.

4.7.2. Strength of evidence regarding the outcome OA of knee or hip

In comparison with the outcome MSD, the number of included studies on OA of knee or hip, was smaller, based on smaller-sized study populations, and consisting of only case control studies, giving lower confidence in the overall quality. Nevertheless, also here a moderately increased odds ratio for OA in exposed populations was found (OR 2.20) with a reasonably narrow CI (1.42–3.40) and a low statistical heterogeneity. The direction of the effect was similar in the studies. Given the moderate risk of bias, and the aforementioned comments regarding the lower confidence in the quality of the body of evidence this leads for this outcome also to the judgement of "limited evidence of harmfulness".

5. Discussion

5.1. Summary of evidence

As shown in the table of summary of findings (Table 5), our

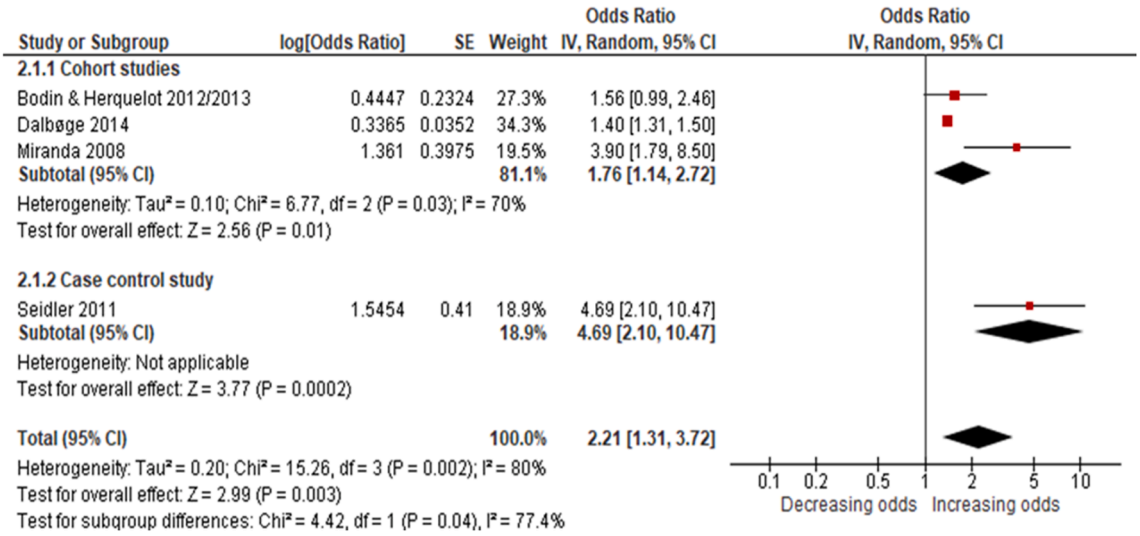

Fig. 7. Subgroup analysis by study type: cohort studies versus case-control studies regarding outcome: other MSD.

systematic review found low quality of evidence for an association between occupational exposure to ergonomic risk factors (force exertion, demanding posture, repetitiveness, hand-arm vibration, lifting, kneeling and/or squatting, and climbing) and the incidence of other MSD, mostly located in the shoulder or elbow. Also low quality of evidence was found for an association between exposure to the aforementioned ergonomic risk factors and OA of knee or hip. Based on the considerations for evaluating the strength of evidence we concluded that, based on human evidence, for other MSD there is limited evidence of harmfulness of exposure to occupational ergonomic risk factors, and also for OA of knee or hip there is limited evidence of harmfulness. Although the reported effects may be modest, due to the widespread and high prevalence estimates of this occupational exposure to ergonomic risk factors, this possible harmfulness warrants attention for preventive occupational health and safety measures.

5.2. Comparison to previous systematic review evidence

Previous systematic reviews on the relationship between ergonomic risk factors and musculoskeletal diseases or osteoarthritis have mostly concentrated on one or only a few ergonomic risk factors and a more specific health outcome, e.g. epicondylitis lateralis, subacromial impingement syndrome, or osteoarthritis of only the knee.

Regarding other MSDs, a systematic review by van Rijn et al. (2010) on the relationship between repetitive movements of the shoulder, repetitive motion of the hand/wrist of > 2 h/day, hand–arm vibration, and arm elevation with with subacromial impingement syndrome revealed an elevated risk (ORs between 1.04 and 4.7). Van der Molen et al. (2017) found moderate quality evidence for associations between shoulder disorders (M75.1-M75.5) and several of 'our' individual ergonomic risk factors with odds ratios, all ranging between 1.5 and 2.0. Descatha et al. (2016) showed a positive association between combined biomechanical exposure involving the wrist and/or elbow and the incidence of epicondylitis lateralis (OR 2.6, 95% CI 1.9–3.5) and an earlier review by van Rijn et al. (2009) on the same health outcome came to comparable results. We think that our review and meta-analysis on other MSD's corroborates this evidence.

With respect to OA, Verbeek et al. (2017) performed a meta-analysis of case control studies on knee osteoarthritis and found for exposure to kneeling or squatting, lifting and climbing all elevated risks with odds ratios varying between 1.4 and 1.7. Moderate to strong evidence for a relationship between heavy lifting and more general physical workload and hip osteoarthritis was reported in previous systematic reviews by Lievense et al (2001), Jensen (2008) and recently Sin et al. (2019). The last authors also revealed an exposure–response relationship for heavy lifting.

Also for this outcome (OA), we think that our systematic review and meta-analysis is well in line with this previous evidence

5.3. Strengths and limitations of this review

5.3.1. Strengths

Our systematic review is part of a larger project with the aim to develop Joint Estimates for estimating the national and global work-related burden of disease and injury (WHO/ILO Joint Estimates), with contributions from a large network of experts. The methodology of the review process was discussed, adapted, accepted and performed according to an intensive and rigorous process that was also presented in a transparent way in a published protocol (Hulshof et al., 2019). To our knowledge, this is the first systematic review and meta-analysis conducted specifically for a global occupational burden of disease due to occupational exposure to ergonomic risk factors, and, as such, it provides a model for future systematic reviews that will help ensure that these global health estimates adhere fully with the *GATHER Guidelines for Accurate and Transparent Health Estimates Reporting* (Stevens et al., 2016).

5.3.2. Limitations

This review has several limitations. First, our searches may have missed studies published in languages other than English. However, we searched many electronic bibliometric and grey literature databases using a comprehensive search strategy and consulted additional experts who also did not identify any additional eligible studies. We have some confidence that we identified most if not all studies eligible for inclusion in our systematic review.

Second, our review is based on a limited number of studies. While previous systematic reviews on the relationship between occupational exposure to ergonomic risk factors and musculoskeletal disorders or osteoarthritis of knee or hip in general were based on a larger number of studies, our rather strict inclusion criteria on exposure (data should be available on exposure to at least five of the seven selected risk factors) and outcome (data on the selected ICD codes should be available, see Table 2) led to the exclusion of all studies in the first round of study selection. Therefore, we have adapted our inclusion criteria regarding exposure and performed a second round of study selection where we included studies with data on at least three of the selected occupational ergonomic risk factors. For this second round of study selection, we have used an additional strategy by using natural language processing with

Table 5
Summary of findings.

Effect of exposure to occupational ergonomic risk factors on other musculoskeletal diseases and osteoarthritis of knee or hip among workers

Population: all workers ≥ 15 years
Settings: all countries and work settings
Exposure: any occupational exposure to selected ergonomic risk factors ≥ 2 h/day
Comparison: no exposure or < 2 h/day

Outcomes	Exposure category	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Navigation Guide quality of evidence rating	Navigation Guide strength of evidence rating for human data	Comments
		Assumed risk Unexposed workers	**Corresponding risk** Exposed worker					
Acquired other MSD (measured with physician diagnostic record or administrative health record)	Occupational exposure to any of the selected ergonomic risk factors ≥ 2 h/day	**440 per 10,000**[a]	**770 per 10,000** (497 to 1118)	**OR 1.76** (1.14 to 2.72)	2,376,592 (4 studies)	⊕⊖⊖ Low	Limited evidence of harmfulness	Better indicated by lower values. Additional evidence from a case control study also showed an elevated risk.
Acquired OA of knee or hip (measured with physician diagnostic record)	Occupational exposure to any of the selected ergonomic risk factors ≥ 2 h/day	**1010 per 10,000**[b]	**1980 per 10,000** (1373 to 2757)	**OR 2.20** (1.42 to 3.40)	1,354 (3 studies)	⊕⊖⊖ Low	Limited evidence of harmfulness	Better indicated by lower values

CI: confidence interval; O**R**: odds ratio

Navigation Guide quality of evidence ratings
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Navigation Guide strength of evidence ratings
Sufficient evidence of toxicity/harmfulness: The available evidence usually includes consistent results from well - designed, well - conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies. For human evidence a positive relationship is observed between exposure and outcome where chance, bias, and confounding, can be ruled out with reasonable confidence.
Limited evidence of toxicity/harmfulness: The available evidence is sufficient to determine the effects of the exposure, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies, the confidence in the effect, or inconsistency of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion. For human evidence a positive relationship is observed between exposure and outcome where chance, bias, and confounding cannot be ruled out with reasonable confidence.
Inadequate evidence of toxicity/harmfulness: Studies permit no conclusion about a toxic effect. The available evidence is insufficient to assess effects of the exposure. Evidence is insufficient because of: the limited number or size of studies, low quality of individual studies, or inconsistency of findings across individual studies. More information may allow an estimation of effects.
Evidence of lack of toxicity/harmfulness: The available evidence includes consistent results from well - designed, well - conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies. For human evidence more than one study showed no effect on the outcome of interest at the full range of exposure levels that humans are known to encounter, where bias and confounding can be ruled out with reasonable confidence. The conclusion is limited to the age at exposure and/or other conditions and levels of exposure studied.

[a] Based on median baseline risks (number of cases in the unexposed groups) in Miranda et al. (2008) and Bodin et al. (2012)/Herquelot et al. (2013).
[b] We extracted the assumed risk from Yoshimura et al. (2000), Peat et al. (2001), Sharma et al. (2006), Quintana et al. (2008), and Verbeek et al. (2017).

regular expressions for the seven ergonomic risk factors. This has led to a (still small) number of potentially eligible studies.

Third, we did not receive requested missing or additional data from a part of the principal study authors that we have contacted. As most of the potentially eligible studies in their published papers did not present data in a way that met our inclusion criterion for exposure definition, i.e. occupational exposure to any of the included ergonomic risk factors, we needed additional data from a substantial part of the potentially eligible studies. For most of these papers, this required additional analysis of the original data. Fortunately, some of the authors responded positively to this request. However, some of the contacted authors indicated that this was not possible or feasible. From some other authors we did not receive any reply. This further limited the number of eligible studies.

Fourth, the relation of work-related factors of physical activities with harm to the human body is a rather complex one. The medical outcomes of this review (selected other MSD and OA) are multifactorial of origin where several risk factors, both work-related and non-work-related may play a role. We have chosen to include only clinically assessed MSD or OA and to exclude (lighter) signs or symptoms of physical load or physical stress. In the included studies, adjustment was made as much as possible for non-work-related risk factors for the outcomes. Nevertheless, it is not absolutely possible to disentangle the influence of occupational physical activities and leisure time physical activity to the full extent. However, recent research suggests that occupational physical activities are of other nature (e.g. often more repetitive or static) and related to other health effects than leisure time physical activity, so it is not possible or sensible to just simply adding or multiplying duration, frequency or intensity of occupational and leisure time physical activities (Holtermann et al., 2019; Coenen et al., 2020). Although this is a very interesting field of discussion and research, this was not the primary purpose of this review.

6. Conclusions

Overall, for both outcomes, the main body of evidence was assessed as being of low quality. Occupational exposure to ergonomic risk factors increased the risk of acquiring MSD and of acquiring OA of knee or hip. We judged the body of evidence on the relationship between exposure to occupational ergonomic factors and MSD as "limited evidence of harmfulness" and the relationship between exposure to occupational

ergonomic factors and OA also as "limited evidence of harmfulness". These relative risks might perhaps be suitable as input data for WHO/ILO modelling of work-related burden of disease and injury.

7. Differences between protocol and systematic review

- Additionally to the study selection process as described in the protocol, we have used a second study selection process by using natural language processing.
- We planned to follow up request for missing data for principal study authors at twice, at two and four weeks after the initial request; in the systematic review we only followed up once, at two weeks after our initial request.
- In the protocol, we planned to convert OR into RR, if possible. To conduct conversion, information on "prevalence of outcome in reference group or baseline risk" is required. However, such information was not available from all included studies. For case-control studies, ORs were reported and were synthesized directly. For cohort studies, also ORs were reported and were used for meta-analyses without any conversion.

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Author contributions

Had the idea for this systematic review: FP, Ivan Ivanov (WHO), Nancy Leppink (ILO)

Selected the lead reviewer and gathered the review teams: FP, Ivan Ivanov, Nancy Leppink

Coordinated the entire series of systematic reviews: FP, Yuka Ujita (ILO)

Were the lead reviewers of this systematic review: CH, MF

Led the design of the systematic review including developed the standard methods: FP

Contributed substantially to the design of the systematic review: All authors

Conducted the search: JD, HM, MF, CH, FP

Selected studies: CC, FM, SM, CHN, JO, KP, PrK, SN, CH, HM, MF, PK

Extracted data: CC, FM, SM, CHN, JO, KP, PrK, SN, CH, HM, MF, PK

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Assessed quality of evidence: CH, HM, PK, SM, CHN, JO, PrK, SN, MF, FP

Developed the standards and wrote the template for all systematic reviews in the series: FP

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Ensured tailoring of the systematic review for WHO/ILO estimation purposes: FP

Ensured harmonization across systematic reviews in the series: FP

Approved the final version of the systematic review to be published: All authors

Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material

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