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Review Article

Occupational Exposure to Knee Loading and the Risk of Osteoarthritis of the Knee: A Systematic Review and a Dose-Response Meta-Analysis

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ABSTRACT

Background: Osteoarthritis of the knee is considered to be related to knee straining activities at work. The objective of this review is to assess the exposure dose-response relation between kneeling or squatting, lifting, and climbing stairs at work, and knee osteoarthritis.
Methods: We included cohort and case–control studies. For each study that reported enough data, we calculated the odds ratio (OR) per 5,000 hours of cumulative kneeling and per 100,000 kg of cumulative lifting. We pooled these incremental ORs in a random effects meta-analysis.
Results: We included 15 studies (2 cohort and 13 case–control studies) of which nine assessed risks in more than two exposure categories. We considered all but one study at high risk of bias. The incremental OR per 5,000 hours of kneeling was 1.26 (95% confidence interval 1.17–1.35, 5 studies, moderate quality evidence) for a log-linear exposure dose-response model. For lifting, there was no exposure dose-response per 100,000 kg of lifetime lifting (OR 1.00, 95% confidence interval 1.00–1.01). For climbing, an exposure dose-response could not be calculated.
Conclusion: There is moderate quality evidence that longer cumulative exposure to kneeling or squatting at work leads to a higher risk of osteoarthritis of the knee. For other exposure, there was no exposure dose-response or there were insufficient data to establish this. More reliable exposure measurements would increase the quality of the evidence.

1. Introduction

Degenerative diseases of the knee, such as osteoarthritis, are prevalent. In the general American adult population, the prevalence was estimated at 14% which increases to 19% in those over 45 years of age and to 40% in those over 60 years of age [1]. While several risk factors have been identified, the causes of knee osteoarthritis are not well established. Age, obesity, and being overweight (body mass index, > 26), work-related activities, playing sports at high levels, and malalignment of the knee joint are the most prominent risk factors [1–4]. There is probably also a genetic component and evidence suggests sex as a possible risk factor, with studies reporting higher prevalence of knee osteoarthritis in women over the age of 45 years [1].

The limited number of treatment options, after the condition sets in, predominately consists of nonsteroidal anti-inflammatory drugs to reduce the pain and weight management to reduce mechanical stress. Finally, with advanced disease, total knee replacement is an option [3,5]. Combined with the irreversibility of the disease, it underscores the importance of preventative measures.

Work-related physical activities, which increase pressure on the joint, are considered a risk factor by many authors. High mechanical stress at the knee joint due to kneeling, squatting, lifting, and climbing stairs indicate these occupational activities as a risk factor. This has also been concluded in a considerable number of systematic reviews of studies that evaluated the risk of knee osteoarthritis as a result of occupational activities [6–9]. However, none of these systematic reviews has looked at the exposure dose-response relationship. In

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general, the existence of an exposure dose-response relation is considered an important argument to infer causality [10,11].

Therefore the objective of this review is to assess the exposure dose-response relation between kneeling or squatting, lifting, and climbing stairs at work and knee osteoarthritis.

2. Material and methods

We developed an *a priori* protocol following standard Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance which is available here: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019646.

We included prospective cohort and case–control studies in participants with knee-loading exposure at work compared to those with lower or no exposure and that measured the risk or severity of knee osteoarthritis. We excluded professional athletes, as knee problems for athletes may be injury-related. We included studies that measured exposure to knee loading by self-reports or observations of tasks that involve the following activities: working in kneeling/squatting positions, lifting weights, or climbing stairs/ladders. Studies with job titles as the only measurement of exposure were excluded in order to reduce measurement bias. Because age is strongly related to the onset and worsening of knee osteoarthritis, we included studies only if they had taken age differences between groups into account.

We searched Embase, Web of Science, and Medline through PubMed (strategy available in Appendix I) using a sensitive search strategy consisting of appropriate words for exposure and outcome until May 1, 2015. First, we searched for systematic reviews on heavy workload and knee osteoarthritis. We used the reviews to locate the primary studies. Then we searched for primary studies since the publication of the latest review up until July 1, 2015.

We included studies that used incidence of knee osteoarthritis measured with X-ray, arthroscopy, or a physician's diagnosis. We excluded studies that used biomarkers and proxy measures, as these may not represent the actual health outcome. We included severity outcomes based on appropriate imaging techniques (e.g., X-ray) or validated scales.

Study selection and data extraction were done in duplicate (CM, RR, AK, PK) and then compared. If there was no consensus after discussion, a third reviewer (JV) resolved disagreements [12]. Data on the following study characteristics were extracted: design, funding, data source, time span, confounders, participants (source, demographics, inclusion/exclusion criteria, numbers recruited), exposure (type, measure, technique, categories), outcome (name, definition, measuring technique), and study results [number of participants analyzed, mean/standard deviations, adjusted/crude risk and odds ratios (ORs), mean difference, standard error, *p* values].

We adapted a checklist for assessing the quality of observational studies as developed by Shamliyan et al [13]. We first formulated an ideal study assessing the effect of occupational knee load on knee osteoarthritis, and then based upon deviation from the ideal model, determined risk of bias for each study. Risk of bias was considered most important for the following items: assessment of exposure, assessment of the outcome, confounders, attrition, and errors in the analysis. A more detailed description of the risk of bias assessment can be found in Appendix II.

If a study had a high risk of bias in one or more of the important domains, we labelled it overall as a study with a high risk of bias. We applied a sensitivity analysis to distinguish between studies with high and low risk of bias.

We included studies of any language and publication status, in order to avoid language and publication bias. To assess if publication bias in the included studies still could have influenced our results, we inspected a funnel plot and applied Egger's test.

We pooled studies with similar participant characteristics, exposure, and outcome measures. We considered the effect of knee loading similar for participants with all kinds of occupations. We considered all exposures to one type of knee straining occupational activity as similar, for example, all exposure that involved climbing stairs. We made a combined category of kneeling and/or squatting because studies did not separate these exposures very well. We assessed statistical heterogeneity by means of the I^2 statistic and considered values up to 25% as low, 25–75% as moderate, and above 75% as high degrees of heterogeneity.

For the data-synthesis we used three complementary approaches to explore the exposure response relationship.

First, a meta-analysis of ORs of lowest versus highest exposure categories was conducted with the general inverse variance method using a random effects model with the RevMan program (version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark). For this, we combined studies using log ORs and standard error of the lowest versus the highest exposure categories as provided in the articles by the authors. We calculated the standard error from the 95% confidence intervals (CIs) reported in the articles.

Next, we prepared the data, from those studies that reported more than two exposure categories, to perform a meta-analysis of incremental ORs per unit of exposure. Studies reported different exposure dose-response analyses. They usually divided the exposure dose in varying self-selected categories and provided ORs per category. To be able to calculate an exposure dose-response per study, we followed the following procedure as described by Il'yasova et al [14]. First, for each study we transformed the exposure data to a similar metric that in our view best reflected cumulative exposure and that was available from most studies. We defined exposure as lifetime hours for kneeling, the lifetime number of kilos for lifting, and the lifetime number of flights of stairs for climbing. Where we could not transform the results to these metrics, the studies could not be included in the dose-response meta-analysis. Then, again for each study, we assigned one exposure dose per category reported in the study. For this, we took the midpoint between the upper and lower boundary of each exposure category. This midpoint was then the exposure dose that was associated with the risk in that category. Next, we employed the Generalized Least Squares for trend estimation (GLST) regression technique as described by Orsini et al [15] and implemented in STATA (Release 12 ed.; StataCorp, College Station, TX, USA) to calculate the dose-response curve for that study, which is represented by the incremental OR per unit of exposure. Since the results of this calculation can be expressed for any unit of increase, we had to choose a meaningful exposure dose increase for the reporting. With meaningful, we mean a biologically meaningful exposure dose, because this could be a plausible amount of exposure to achieve an effect of mechanical stress on the knee. For kneeling we choose 5,000 hours, which is approximately equivalent to 5 years of 4 hour exposure per workday as a meaningful unit of exposure. For lifting, we choose 100,000 kilos. For climbing, we intended to do this for the number of stairs climbed, but since there were not enough data to do an analysis, we refrained from doing so. Finally, we combined the incremental ORs obtained for study in a random effects meta-analysis with the RevMan program as described above to obtain an overall pooled risk estimate.

Third, to test which type of exposure dose-response model, linear or quadratic, fitted the data best, we also used the meta-regression model as implemented in a web-based R-version written by Crippa and Orsini (https://cran.r-project.org/web/packages/dosresmeta/index.html) [15,42].

We used sensitivity analysis to test the influence of various assumptions about the exposure dose and to test the effect of adjustment for confounding. Based on existing literature, we decided on four important confounders for the relationship between knee load and osteoarthritis: age, sex, body mass index, and injuries. We further analyzed subgroups of sex (male versus female) and for the time period of the study (published before 2000, 2001–2005, 2006–2010, 2011–2015). To assess the quality of the evidence, we adapted the GRADE approach that divides the quality of the evidence in four levels: high, moderate, low, and very low quality [11]. We started the rating at high quality for cohort studies and at moderate quality for case–control studies, because the case–control design is inherently more subject to bias. GRADE considers first five dimensions of the total body of evidence: limitations in the study, consistency, directness, precision, and publication bias. The quality of the evidence can be downgraded with one or more levels if any of these dimensions are problematic. Next, GRADE considers three dimensions that can be used to upgrade the quality of the evidence: dose-response relation, large effect size, and confounding works towards the null.

3. Results

3.1. Search

The search yielded 286 references to systematic reviews of which we selected 50 to be read full-text, because they potentially could fulfil our inclusion criteria. Of these, 24 reviews fulfilled our inclusion criteria. These reviews contained 38 primary studies that we again assessed full-text for inclusion. Articles that were in foreign languages such as German, Chinese, and Spanish were assessed by native speakers. This resulted in 17 included publications. The search for primary studies after the date of the latest systematic review did not yield any additional studies. Three publications reported on the same study [16–18]. Thus, we had 15 studies that fulfilled our inclusion criteria. Excluded studies are listed in Appendix III. Five studies reported the results for male and female gender separately. We included these as separate study-arms in the analyses which is denoted with -f- or -m- after the study id. Therefore, of the 15 included studies, we have 20 study-arms in the analyses.

3.2. Study characteristics

Thirteen studies had a case–control design [16,19–30] and two were prospective cohort studies [31,32] (Table 1). On average, the case–control studies included 583 participants (range 74–1,316) and the cohort studies included 274 participants (range, 105–424) in the analysis. Studies were mainly from Europe ($n = 11$). Two were from Japan and one each from China and Morocco.

Two studies included only females [21,30] and two other studies only males [16,29]. In studies that included both females and males, the percentage of males was 52% [27], 36% [32], 28% [20], and 27% [26]. One study included both sexes but did not report how many males or females were included [28]. One study did not report any information about the sex of the participants [31].

All case–control studies reported that they used controls matched with the age of cases. The exact age band, within which the matching took place, was reported in four studies and was at most 5 years wide. Seven of the eleven studies that did not report the age band reported the mean age or the age range and this showed a good agreement between cases and controls. Two studies did not report on age [24,32].

3.3. Outcomes

The case–control studies defined the outcome in cases based on a cut-off on the Kellgren and Lawrence scale of $\geq$ Grade 2 ($n = 2$), $\geq$ Grade 3 ($n = 5$), as minimal visible changes on the radiograph ($n = 2$), or as knee prosthetic surgery ($n = 4$). One cohort study defined new cases of knee osteoarthritis as those that were symptom- and sign-free at baseline, but that had signs of knee osteoarthritis on the radiograph at follow-up [32]. The other cohort defined cases as those with progression of joint space narrowing on the radiograph [31].

3.4. Exposures measurements

All of the included studies reported the exposure to occupational activities as kneeling, squatting, lifting, or climbing or combinations thereof. Only two studies reported a definition of the activities themselves.

3.4.1. Kneeling or squatting

Eight studies reported kneeling and squatting as kneeling only or squatting only. Four studies combined the exposure to kneeling and squatting, and one study combined kneeling, squatting, and crawling. Two studies did not report on kneeling or squatting.

3.4.2. Lifting

All but two studies measured the exposure to lifting only, heavy lifting only, or lifting and carrying.

3.4.3. Climbing

Nine studies evaluated the exposure to climbing (of stairs, of stairs or ladders, and of stairs, ladders, or flights of stairs). Six studies did not report on any form of climbing.

3.4.4. Other exposure combinations

One study [28] measured the exposure to lifting, carrying, and climbing together as light (walking, sitting, and carrying), medium (lifting with bent knees and carrying, climbing ladders or stairs with or without carrying), or heavy knee moments (activities with additional jumping with or without carrying extra load). One study combined kneeling and lifting into one exposure [32].

3.5. Exposure dose

Occupational exposure to the activities kneeling, squatting, and climbing was measured as two exposure categories (yes/no) in six studies, and as more than two exposure categories in nine studies allowing for a dose-response analysis (Table 1). The exposure to lifting was measured as yes/no categories in six studies and as more than two categories in nine studies, allowing for the calculation of a dose-response relation. For climbing stairs, there were four studies that had more than two exposure categories.

3.5.1. Kneeling and/or squatting

The definition of no exposure or the lowest reference exposure for kneeling varied. It was defined as 0 minutes per total working life time [27], < 30 minutes per working day [20], < 1 hour per working day [24,26,29,30], rarely or almost never [22], and as < 15 years doing work that involves kneeling for > 1 hour a day [21]. Studies reported squatting in a similar manner, except in Sandmark 2000, where no exposure to “squatting or knee bending” was defined as < 2 minutes in work life for women or 0 minutes in work life for men [27].

3.5.2. Lifting

Studies reported the lowest exposure for lifting as zero tons per work life [23], as “no lifting and carrying” [16], “no regular lifting” [25], as a working life long sum of 0–4 kg for women and 0–107 kg for men [27], lifting only objects < 10 kg [24], lifting between 5 kg and 20 kg [22], < 25 kg [20,26,29,30], < 1 year in work involving lifting > 25 kg > 10 times per week [33], or as < 24 years doing work that involved lifting [21]. One study measured the exposure to “lifting heavy objects” as “low, medium, and high” but neither reported the cut-off points nor the measure [31].

Table 1
Characteristics of included studies ($N = 15$)

Study ID	Country	Study period	n Participants	Occupation	Age (y) (mean ± sd/range)	Gender (% male)	Outcome measure	Exposure measures	Exposure measurement technique	≥ 2 Exposure categories
Case–control studies										
Coggon 2000	UK	1995–1998	1,036	nr	47–93	40%, separate analysis for males/ females	Surgery (listed for surgery graded according to KL scale)	K or S, Cst or Cfl or Cl, L	Interview	K or S, Cst or Cfl or Cl, L
Cooper 1994	UK	nr	327	Various	72.7 ± ?/55–90	28%	3 or 4 on KL scale	K, S, Cst, HL	Interview	No
Dawson 2003	UK	nr	111	nr	50–70	0%	Surgery (listed for knee replacement surgery)	K, S, L	Interview	K, S, L
Elsner 1996	Germany	1989–1993	383	various	Males: 58% > 55 y Females: 59% > 55 y	57%, separate analysis for males/ females	Changes observed in radiographs	K, S, HL	Questionnaire	No
Klussmann 2010	Germany	2006–2010	1,270	nr	Females: cases 59.6 ± 9.8, controls 54.8 ± 11.8 Males: cases 57.1 ± 11.2, controls 50.9 ± 12.7	41%, separate analysis for males/ females	≥ 2 on KL scale or outer bridge scale ≥ 3	K or S, Cst, L or Car	Questionnaire & interview	K or S, L or Car
Lau 2000	China (Hong-Kong)	1998	1,316	nr	nr	25%, separate analysis for males/females	3 or 4 on KL scale	K, S, Cst, L > 10 kg, L > 50 kg	Interview using standardized & structured questionnaire	L > 10 kg, L > 50 kg
Manninen 2002	Finland	1992–1993	805	nr	Males: cases 67.5 ± 5.7 controls: 67.2 ± 5.6 Females: cases 69.2 ± 5.4, controls 67.1 ± 5.6	20%, separate analysis for males/ females	Surgery (undergone knee arthroplasty)	K or S, Cst, L	Telephone interview	K or S, Cst, L
Mounach 2008	Morocco	2005–2006	190	Various	Cases 59.7 ± 8.5/37–76, controls 59.7 ± 8.5	27%	≥ 3 on KL scale	K, S, Cst, HL	Questionnaire	No
Seidler 2008	Germany	nr	622	Various	25–70	100%	> 2 on KL scale	K or S, L or Car	Interview	K or S, L or Car
Sandmark 2000	Sweden	1994	1,173	nr	nr	52%	Surgery (if leads to a knee prosthetic surgery)	K, S or Kb, Cst, L	Questionnaire	K, S or Kb, Cst, L
Sahlström 1997	Sweden	nr	729	nr	Males: 77 ± ?/52–96 Females: 72 ± ?/47–96	nr	Changes observed in radiographs	Knee moments	Questionnaire	No
Yoshimura 2004	Japan	nr	186	Various	Cases & controls 73.3 ± 9.8	0%	≥ 3 on KL scale	K, S, Cst, HL	Interview translated from Coggon 2000	No
Yoshimura 2006	Japan	nr	74	Various	Cases 70.0 ± 6.6, controls 70.1 ± 7.0	100%	≥ 3 on KL scale	K, S, Cst, L	Interview translated from Coggon 2000	No
Cohort Studies										
Schouten 1992	Netherlands	1988	105	nr	23% > 60	nr	Changes observed in radiographs	K or S or Cr, HL	Questionnaire	K or S or Cr, HL
Zhang 2011	UK	1996–2008	424	nr	nr	36%	nr	K or L	Questionnaire	K or L

C, climbing; Car, carrying; Cfl, climbing flights; Cl, climbing ladders; Cr, crawling; Cst, climbing stairs; HL, heavy lifting; K, kneeling; L, lifting; nr, not reported; S = squatting.

Table 2
Risk of bias in case control studies of knee osteoarthritis incidence for six domains and overall per study. Low = low risk of bias, high = high risk of bias, unclear = unclear risk of bias

Category/CC study ID	Coggon 2000	Cooper 1994	Elsner 1996	Lau 2000	Manninen 2002	Seidler 2008	Sandmark 2000	Klussmann 2010	Mounach 2008	Dawson 2003	Sahlström 1997	Yoshimura 2004	Yoshimura 2006
Funding & conflict of interest	Low	High	High	Low	Unclear	High	Unclear	Low	High	Unclear	High	Unclear	Unclear
Outcome assessment	Low	Low	High	High	Unclear	Low	High	Low	High	High	Low	Unclear	Unclear
Exposure assessment	High	Low	High	Low	Low	Low	Low	High	High	High	High	High	High
Confounding factors	Low	Low	High	High	Low	Low	Low	Low	Low	High	High	High	Unclear
Attrition bias	Low	High	High	High	High	Low	Low	Low	High	High	Low	High	High
Analysis	Low	Low	Low	High	Low	Low	High	Low	High	Low	High	High	High
Overall	High	High	High	High	High	Low	High	High	High	High	High	High	High

3.5.3. Climbing

The lowest or reference exposure to climbing was expressed as < 10 flights of stairs [20], < 15 flights [24], < 30 steps per day [29,30], < 50 steps per day [26], < 166 steps per lifetime for women and < 103 steps per lifetime for men [27], < 1 year in work that involves climbing ladders or stairs > 30 times a day [19], or "not at all or very little" ($n = 1$) [25].

3.6. Risk of bias in studies

There was one case–control study that scored a low risk of bias for all important domains [16]. Overall, this left us with almost all case–control studies at a high risk of bias (Table 2). The domains that were most at risk of bias were those for exposure assessment, outcome assessment, and attrition bias. Most studies were at low risk of bias for the adjustment of confounding and appropriate analysis technique. The risk of bias in both cohort studies was high because of poor assessment of the exposure and the high number of nonrespondents in both (Table 3). We give a more detailed analysis of the risk of bias in Appendix II.

3.7. Effects of the exposures

3.7.1. Exposed versus unexposed workers

3.7.1.1. Kneeling or squatting versus no kneeling or squatting. A meta-analysis of 12 case–control studies that measured exposure to knee loading at work resulted in an OR of 1.70 with a 95% CI of 1.35–2.13 with moderate heterogeneity ($I^2 = 49\%$) of the results across studies (Fig. 1). One study could not be included because it did not report the results [29]. The funnel plot with the effect sizes plotted against 1/variance of the studies revealed that small studies with null results or positive effects are missing in the left lower quadrant of Fig. 2. Egger's test resulted in a significant coefficient of bias ($\beta = 2.25$, $p = 0.033$).

3.7.1.2. Lifting versus no lifting. A meta-analysis of 11 case–control studies that measured lifting showed an OR of 1.69 (95% CI 1.43–2.00, $I^2 = 51\%$) for exposed versus nonexposed workers. One study and one study arm of another study could not be included in the meta-analysis due to missing data [23,29].

Table 3
Risk of bias in cohort studies of knee osteoarthritis incidence for six domains and overall per study

Category/cohort study ID	Schouten 1992	Zhang 2011
Funding & conflict of interest	Unclear	Unclear
Outcome assessment	Low	Low
Exposure assessment	High	High
Confounding factors	Low	Low
Attrition bias	High	High
Analysis	Low	Unclear
Overall	High	High

High, high risk of bias, Low, low risk of bias, Unclear, unclear risk of bias.

3.7.1.3. Climbing versus no climbing. A meta-analysis of seven studies measuring climbing yielded an OR of 1.55 (95% CI 1.25–1.91, $I^2 = 68\%$) for exposed versus nonexposed workers. Two studies could not be included in the meta-analysis [23,29].

3.7.2. Exposure versus no exposure in cohort studies

One cohort study, which combined kneeling, squatting, and crawling, reported a nonsignificant OR of 0.31 (95% CI 0.09–1.04) for workers that kneeled, squatted, or crawled compared to workers that did not [31]. The other study combined the exposure to kneeling and lifting and found an OR of 1.35 (95% CI 1.05–1.73) for exposed versus unexposed workers [32].

3.8. Dose-response analysis

3.8.1. Kneeling or squatting

The meta-analysis of the risk per 5,000 hours of lifetime kneeling or squatting at work of the case–control studies yielded an OR of 1.26 (95% CI 1.17–1.35) with no heterogeneity across study results (Fig. 3). This means a 26% increase in the risk of knee osteoarthritis per 5,000 hours increase of kneeling or squatting.

We could not pool the data for cohort studies, as only one study reported results for more than two exposure categories (low, medium, and high), but did not report the exact doses for the categories.

In the sensitivity analysis, the risk of knee osteoarthritis was not different for female workers (OR = 1.28, 95% CI 1.15–1.42) as compared to males (OR = 1.25, 95% CI 1.11–1.40).

In the sensitivity analysis, assumptions for the lowest possible exposure level indicated an OR of 1.33 (95% CI 1.22–1.33) and this did not differ substantially from the highest possible exposure level, which yielded an OR of 1.22 (95% CI 1.15–1.30).

Out of three exposure models (linear with logRR, splines, and quadratic), the quadratic model fitted the data the best (Fig. 4). The risk appeared to peak at around 24,500 lifetime hours of kneeling at work with a maximum OR of 2.56 (95% CI 1.27–5.37) and then remained at about the same level.

The funnel plot and the Egger test for publication bias across studies ($n = 8$) did not reveal strong bias with a nonsignificant bias coefficient ($\beta = 1.70$, $p = 0.255$).

The overall quality of the evidence for the exposure dose-response for kneeling according to GRADE was moderate.

3.8.2. Lifting

Three case–control studies reported more than two exposure categories for lifting. We performed a dose-response analysis with two studies with four study arms [19,25] which yielded a pooled OR of 1.00 (95% CI 1.00–1.01) per 100,000 kilos of lifetime lifting (Fig. 5). The studies that reported the dose as kilogram hours per

Study or subgroup	log(odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI	Year
Cooper 1994b	1.22378	0.49641	3.9%	3.40 (1.29, 9.00)	1994
Elsner 1996m	0.78846	0.40752	5.0%	2.20 (0.99, 4.89)	1996
Elsner 1996f	0.78846	0.76347	2.0%	2.20 (0.49, 9.82)	1996
Lau 2000f	-0.10536	0.19724	9.6%	0.90 (0.61, 1.32)	2000
Coggon 2000m	0.53063	0.44464	4.5%	1.70 (0.71, 4.06)	2000
Coggon 2000f	1.16315	0.71125	2.2%	3.20 (0.79, 12.90)	2000
Lau 2000m	0.33647	0.26781	7.8%	1.40 (0.83, 2.37)	2000
Sandmark 2000f	0.40547	0.25021	8.2%	1.50 (0.92, 2.45)	2000
Sandmark 2000m	0.74194	0.21874	9.0%	2.10 (1.37, 3.22)	2000
Manninen 2002f	0.59333	0.24935	8.2%	1.81 (1.11, 2.95)	2002
Manninen 2002m	0.51879	0.47691	4.1%	1.68 (0.66, 4.28)	2002
Dawson 2003f	1.43031	0.6106	2.8%	4.18 (1.26, 13.83)	2003
Yoshimura 2004f	-0.13926	0.30393	7.0%	0.87 (0.48, 1.58)	2004
Seidler 2008m	0.87547	0.38626	5.4%	2.40 (1.13, 5.12)	2008
Mounach 2008b	-0.28768	0.34337	6.2%	0.75 (0.38, 1.47)	2008
Klussmann 2010f	0.92426	0.31714	6.7%	2.52 (1.35, 4.69)	2010
Klussmann 2010m	0.90422	0.28563	7.4%	2.47 (1.41, 4.32)	2010
Total (95% CI)			**100.0%**	**1.70 (1.35, 2.13)**	

Heterogeneity: Tau² = 0.10; Chi² = 31.51, df = 16 ($p = 0.01$); I² = 49%
Test for overall effect: Z = 4.54 ($p < 0.00001$)

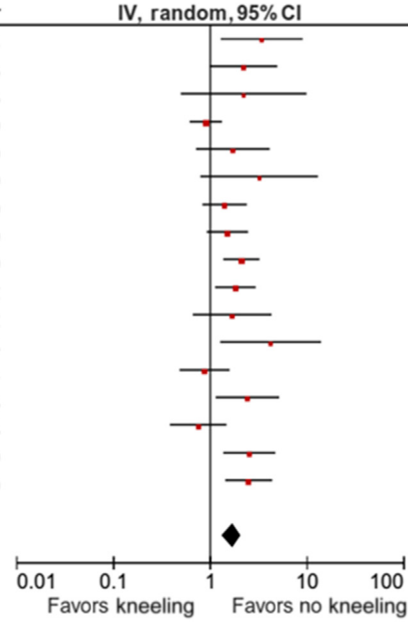

Fig. 1. Forest plot of case control studies of kneeling or squatting (yes/no) and knee osteoarthritis ($n = 12$); b = both sexes, f = female, m = male. CI, confidence interval; SE, standard error.

lifetime used "sometimes" as a cut-off point, or did not report the number of kilograms lifted. Therefore, they could not be included in the dose-response analysis because the data could not be transformed into a reliable dose as kilograms lifted per lifetime [16,21,23]. None of the studies showed a clear dose-response with incremental ORs varying from 0.99 to 1.01. Because of the low number of studies, publication bias could not be assessed. GRADE assessment yielded a low quality of evidence rating. We started at moderate quality and we downgraded with one level because of high risk of bias and there were no reasons to upgrade.

3.8.3. *Climbing stairs*

As no study reported sufficient information to calculate a dose for climbing stairs, no dose-response analysis could be performed.

4. Discussion

The odds for developing knee osteoarthritis in workers that reported kneeling or squatting at work (yes/no) was 1.70 times greater (95% CI 1.35–2.13) than the odds for workers that reported

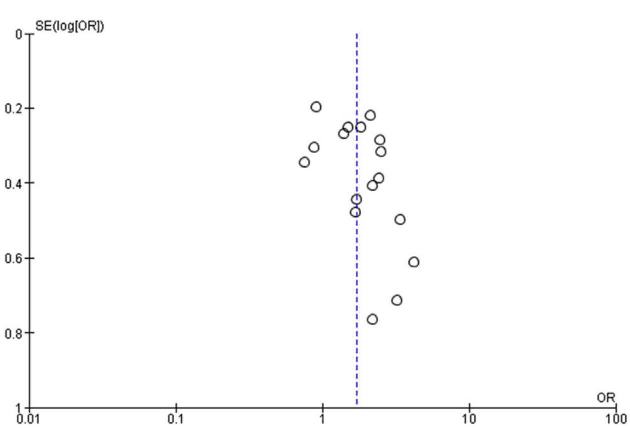

Fig. 2. Funnel plot of kneeling studies (yes/no) against precision (1/variance). OR, odds ratio; SE, standard error.

not kneeling or squatting at work, but there was a significant risk for publication bias in these results. However, the dose-response analysis of eight study arms yielded an OR of 1.26 (95% CI 1.17–1.35) per additional 5,000 lifetime hours of kneeling or squatting at work. The quadratic model that fitted the data better showed a similar risk increase per 5,000 hours of exposure, but after a total of 24,500 hours the incremental risk decreased somewhat. The quality of the evidence was moderate for these studies and the dose-response outcome and there was no indication of publication bias in these results. The meta-analyses for the dichotomous exposure (yes versus no) to lifting and climbing resulted in similar risk estimates as for kneeling. The linear dose-response analysis for lifting showed no risk increase per 100,000 kilos lifted at work (OR 1.00, 95% CI 1.00–1.01). A dose-response analysis was not possible for exposure to climbing. The quality of the evidence was rated as low for lifting. The results were robust to sensitivity analyses for assumptions that we had to make to estimate the exposure doses.

4.1. *Strengths and limitations of the review*

We conducted the review according to an *a priori* formulated and published protocol preventing changing the question or the methods based on the data found. We applied strict inclusion criteria to include more precise studies and exclude unclear exposures. We prevented language bias by including studies in languages other than English. Therefore, we believe that we included all available good quality studies.

To our knowledge, this is the first time the nature of this relationship has been explored and our findings should be tested in future studies. The magnitude of effect of kneeling in our study was comparable with that of obesity reported in a recent meta-analysis [34]. This analysis showed that being overweight (body mass index of 25.0–29.9 kg/m^2) resulted in an OR of 2.45 (95% CI 1.88–3.20) based on 11 studies.

It may be that we overestimated the effect size for being exposed compared to no/minimal exposure because of the lack of negative findings, especially in small studies, as indicated in the funnel plot. However, we did not find an indication of publication

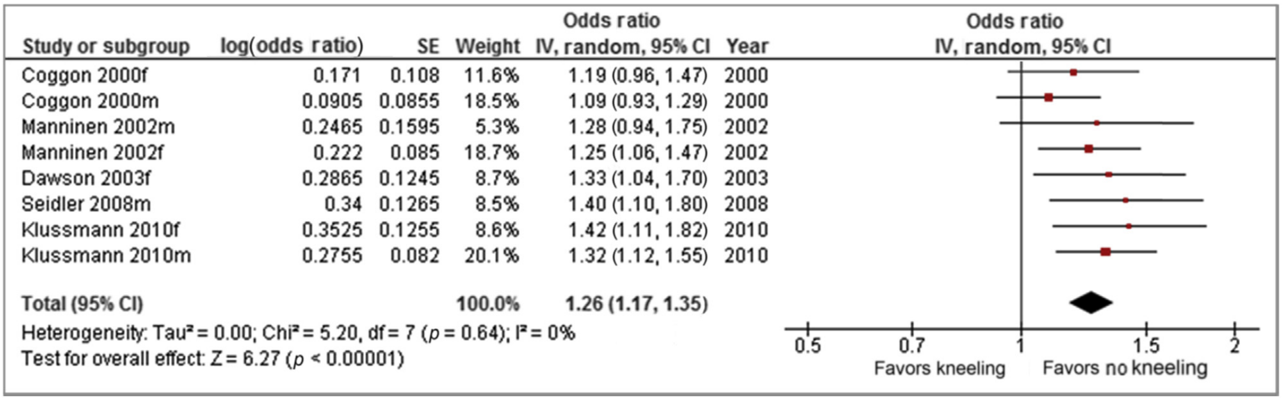

Fig. 3. Forest plot of odds ratios (ORs) for the risk of knee osteoarthritis due to exposure to incremental units of 5,000 hours of kneeling at work in case–control study arms ($n = 8$), f = female, m = male. CI, confidence interval; SE, standard error.

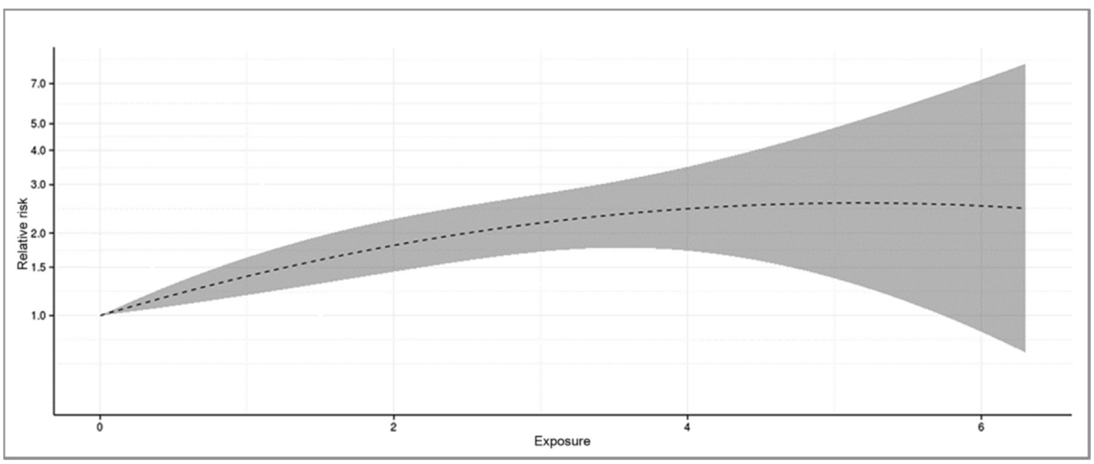

Fig. 4. Quadratic exposure dose-response function for kneeling or squatting and knee osteoarthritis from meta-regression of case–control studies ($n = 8$) with 95% confidence limit in gray shades. Unit of exposure is 5,000 hours of kneeling or squatting at work.

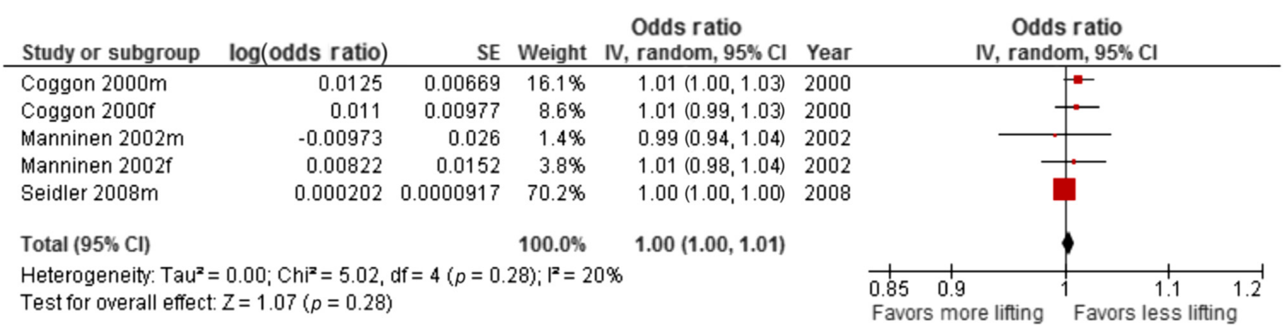

Fig. 5. Forest plot of odds ratios (ORs) for the risk of knee osteoarthritis due to exposure to incremental units of 100,000 kg lifetime lifting at work in case–control study arms ($n = 5$). CI, confidence interval; f, female, m, male. SE, standard error.

bias in the funnel plot of the studies that allowed for an estimation of the exposure dose-response association.

We do not know of any other exposure dose-response analysis. The main assumption in a dose-response meta-analysis is that about the nature of the relation between the exposure and the risk. We tested not only a linear relationship, but also quadratic function and relationship based on splines. In the absence of prior evidence, we made *a priori* assumptions about a biologically plausible exposure dose. We had to estimate doses in studies and sometimes make assumptions. We checked the influence of our assumptions with sensitivity analyses based on best and worst case scenarios. Even though there were differences between these scenarios, the direction and magnitude of the effect size remained similar.

Overall, the risk of bias in most studies was high. All studies relied on self-reports to measure exposure retrospectively over a period of 35–60 years, making recall bias likely. Only two studies [16,23] adjusted for other occupational knee straining activities when estimating the effect of a specific exposure, which could explain why the results for different exposures across studies were similar.

We excluded three studies because they used a Job Exposure Matrix (JEM). We excluded these because they were not based on objective measurements and there is no evidence that expert judgments are a valid measure of exposure [35]. One of these studies [36] developed a JEM based on self-report measurements from a study included in this review [19]. The other two JEM studies used expert ratings to assign an exposure dose category to a job title [37,38]. All three JEM studies found some relation between knee load and osteoarthritis but none calculated a dose response. Therefore, the exclusion of these studies would not have an effect on our conclusions.

4.2. Implications for practice

The increased risk of osteoarthritis by 26% in workers with > 5,000 hours of kneeling/squatting exposure warrants prevention efforts in all occupations involving these activities. Floor layers of sand-cement bound screed floors kneel or squat a large part of their working time. A recent study showed that kneeling time decreased when using a self-propelled or a manually moved machine compared to the traditional way of floor laying while working on their knees [39] and while changing the floor technology [40]. Reducing the time workers are kneeling is also beneficial after knee arthritis has occurred and increases the chances of return to work [41].

4.3. Implications for research

In future studies, to prevent recall bias, researchers should use more objective measurements of exposure, such as direct logged hours of an activity or objective knee angle measurements, with longitudinal follow-up. Given the publication bias in the low versus highest exposure analysis, studies with more workers are needed. Case–control studies should include at least 384 cases and 384 controls. The preventive effect of knee cushioning, aids, and spacing of activities should be further evaluated in controlled trials and well-designed case–control studies.

Conflicts of interest

None of the authors had a conflict of interest to declare.

Acknowledgments

This project was commissioned by the Danish Work Environment Fund based on an international tender, but the funder had no influence on the analysis or the reporting of the results. The quality of the study was assured by means of peer-review.

Appendix I

Search strategy

I. Search for reviews	
PubMed: 03.05.2015	
#1	"workload"[MeSH Terms] OR "workload"[All Fields] OR ("work"[All Fields] AND "load"[All Fields]) OR "work load"[All Fields]
#2	"physical"[All Fields] OR kneeling[All Fields] OR kneel*[tw] OR squatting[All Fields] OR squatt*[tw] OR crawling [All Fields] OR crawl*[tw] OR lifting[Mesh Terms] OR lifting[All Fields] OR lift*[tw] OR ladders[All Fields] OR stairs [All Fields]
#3	miner*[tw] OR Millwright*[tw] OR industr*[tw] OR (oil[All Fields] AND ("Rig"[Journal] OR "rig"[All Fields])) OR pick*[tw] OR boilermaker*[tw] OR installer*[tw] OR landscaper*[tw] OR pipefitter*[tw] OR migrant*[tw] OR "mechanics"[MeSH Terms] OR "mechanics"[tw] OR (("motor vehicles"[MeSH Terms] OR ("motor"[tw] AND "vehicles"[tw]) OR "motor vehicles"[tw] OR "truck"[tw]) AND driver*[tw]) OR (refinery[tw] AND operator[tw]) OR machine*[tw] OR electric*[tw] OR repair*[tw] OR farm*[tw] OR "maintenance" [MeSH Terms] OR "maintenance"[tw] OR "wood"[MeSH Terms] OR "wood"[tw] OR concrete[tw] OR (brick*[tw] AND (layer[tw] OR mason[tw])) OR plumber*[tw] OR "asphalt"[Supplementary Concept] OR "asphalt"[tw] OR rock*[tw] OR (Sheet[tw] AND ("metals"[MeSH Terms] OR "metals"[tw] OR "metal"[tw])) OR Seam*[tw] OR fisherm*[tw] OR waitress*[tw] OR construct*[tw] OR "floors and floorcoverings"[MeSH Terms] OR ("floors"[tw] AND "floorcoverings"[tw]) OR "floors and floorcoverings"[tw] OR (floor*[tw] AND lay*[tw])
#4	"work"[MeSH Terms] OR "work"[All Fields] OR "occupations"[MeSH Terms] OR "occupations"[All Fields] OR "occupation"[All Fields] OR works*[tw] OR work'*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupation*[tw] OR "manpower"[Subheading] OR "manpower"[All Fields]
#5	(#2 OR #3) AND #4
#6	#1 OR #5
#7	"knee"[MeSH Terms] OR "knee"[All Fields] OR "knee joint"[MeSH Terms] OR ("knee"[All Fields] AND "joint"[All Fields]) OR "knee joint"[All Fields] OR "lower extremity"[MeSH Terms] OR ("lower"[All Fields] AND "extremity"[All Fields]) OR "lower extremity"[All Fields] OR ("lower"[All Fields] AND "limb"[All Fields]) OR "lower limb"[All Fields]
#8	("osteoarthritis, knee"[MeSH Terms] OR "osteoarthritis"[All Fields] OR "arthritis"[MeSH Terms] OR "arthritis"[All Fields] OR "arthrosis"[tw]) OR (meniscus[All Fields] OR meniscal[All Fields]) OR "bursitis"[MeSH Terms] OR "bursitis"[All Fields]
#9	#6 AND #7 AND #8
#10	"meta-analysis as topic"[MeSH Terms] OR meta-analysis[pt] OR meta-analysis[tiab] OR review[pt] OR review[tiab] NOT (letter[pt] OR editorial[pt] OR comment[pt]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])
#11	#9 AND #10
Embase (embase.com): 06.05.2015	
#1	'workload'/de OR 'workload' OR 'work load' OR (work AND load) OR work NEAR/5 load
#2	'physical' OR kneeling OR kneel* OR squatting OR squatt* OR crawling OR crawl* OR 'lifting effort'/de OR 'lifting effort' OR lifting OR ladder* OR stairs

(continued on next page)

(*continued*)

#3	miner* OR millwright* OR industr* OR (oil AND ('rig':jt OR 'rig')) OR pick* OR boilermaker* OR installer* OR landscaper* OR pipefitter* OR migrant* OR 'mechanics'/de OR 'mechanics' OR 'motor vehicle'/de OR 'motor' NEAR/3 'vehicles' OR 'motor vehicles' OR 'truck' NEAR/3 driver* OR refinery NEAR/3 operator* OR machine* OR electric* OR repair* OR farm* OR 'device maintenance'/de OR 'maintenance' OR 'wood'/de OR 'wood' OR concrete OR (brick* AND (layer OR mason)) OR plumber* OR 'asphalt'/de OR 'asphalt' OR rock* OR (sheet AND ('metals' OR 'metal'/de OR 'metal')) OR seam* OR fisherm* OR waitress* OR construct* OR 'building'/de OR ('floors' AND 'floorcoverings') OR 'floors and floorcoverings' OR floor* NEAR/5 lay*
#4	'work'/de OR 'work' OR 'occupation'/de OR 'occupation' OR occupation OR occupations OR work* OR 'manpower'/de OR 'manpower' OR manpower
#5	#2 OR #3
#6	#4 AND #5
#7	#1 OR #6
#8	'knee'/de OR 'knee' OR 'knee joint' OR ('knee' AND 'joint') OR 'leg'/de OR 'leg' OR 'lower extremity' OR ('lower' AND 'extremity') OR 'lower' NEAR/1 'limb' OR 'lower limb'
#9	'knee osteoarthritis'/de OR 'knee osteoarthritis' OR 'osteoarthritis' OR 'arthritis'/de OR 'arthritis' OR 'arthrosis' OR meniscus OR meniscal OR 'bursitis'/de OR 'bursitis'
#10	#7 AND #8 AND #9
#11	'meta analysis (topic)'/de OR 'meta analysis':it OR review:it OR review:ab,ti NOT (letter:it OR editorial:it OR comment:it)
#12	#10 AND #11
#13	#12 NOT ([animals]/lim NOT [humans]/lim)
#14	#13 AND [embase]/lim
#15	#14 NOT [medline]/lim
Web of Science 06.05.2015	
#1	TS=("workload" OR "work load" OR (work AND load) OR (work NEAR load)) Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#2	TS=("physical" OR kneeling OR kneel* OR squatting OR squatt* OR crawling OR crawl* OR "lifting effort" OR lifting OR ladder* OR stairs) Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#3	TS=(miner* OR millwright* OR industr* OR (oil AND "rig") OR pick* OR boilermaker* OR installer* OR landscaper* OR pipefitter* OR migrant* OR "mechanics" OR ("motor" NEAR "vehicles") OR "motor vehicles" OR ("truck" NEAR driver*) OR (refinery NEAR operator*) OR machine* OR electric* OR repair* OR farm* OR "maintenance" OR "wood" OR concrete OR ((brick*) AND (layer OR mason)) OR plumber* OR "asphalt" OR rock* OR ((sheet) AND ("metals" OR "metal")) OR seam* OR fisherm* OR waitress* OR construct* OR "building" OR (("floors") AND ("floorcoverings")) OR "floors and floorcoverings" OR (floor* NEAR lay*)) Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#4	TS=("'work" OR "occupation" OR occupation OR occupations OR work* OR "manpower" OR manpower) Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#5	#2 OR #3 Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#6	#4 AND #5 Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#7	#1 OR #6 Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#8	TS=("knee" OR "knee joint" OR ("knee" AND "joint") OR "leg" OR "lower extremity" OR ("lower" AND "extremity") OR ("lower" NEAR "limb") OR "lower limb") Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#9	TS=("knee osteoarthritis" OR "osteoarthritis"' OR "arthritis" OR "arthrosis" OR meniscus OR meniscal OR "bursitis") Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#10	#7 AND #8 AND #9 Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#11	TS=("meta analysis" OR "review") Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#12	TI=("review") Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#13	#11 OR #12 Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years
#14	#10 AND #12 Indexes = SCI-EXPANDED, SSCI, A&HCI Timespan = All years

II. Search for primary studies

PubMed: 08.09.2015 (same as earlier search excluding review filter and including 2011 publication time limit)	
#1	"workload"[MeSH Terms] OR "workload"[All Fields] OR ("work"[All Fields] AND "load"[All Fields]) OR "work load"[All Fields]
#2	"physical"[All Fields] OR kneeling[All Fields] OR kneel*[tw] OR squatting[All Fields] OR squatt*[tw] OR crawling[All Fields] OR crawl*[tw] OR lifting[Mesh Terms] OR lifting[All Fields] OR lift*[tw] OR ladders[All Fields] OR stairs[All Fields]

(*continued*)

#3	miner*[tw] OR Millwright*[tw] OR industr*[tw] OR (oil[All Fields] AND ("Rig"[Journal] OR "rig"[All Fields])) OR pick*[tw] OR boilermaker*[tw] OR installer*[tw] OR landscaper*[tw] OR pipefitter*[tw] OR migrant*[tw] OR "mechanics"[MeSH Terms] OR "mechanics"[tw] OR (("motor vehicles"[MeSH Terms] OR ("motor"[tw] AND "vehicles"[tw]) OR "motor vehicles"[tw] OR "truck"[tw]) AND driver*[tw]) OR (refinery[tw] AND operator[tw]) OR machine*[tw] OR electric*[tw] OR repair*[tw] OR farm*[tw] OR "maintenance" [MeSH Terms] OR "maintenance"[tw] OR "wood"[MeSH Terms] OR "wood"[tw] OR concrete[tw] OR (brick*[tw] AND (layer[tw] OR mason[tw])) OR plumber*[tw] OR "asphalt"[Supplementary Concept] OR "asphalt"[tw] OR rock*[tw] OR (Sheet[tw] AND ("metals"[MeSH Terms] OR "metals"[tw] OR "metal"[tw])) OR Seam*[tw] OR fisherm*[tw] OR waitress*[tw] OR construct*[tw] OR "floors and floorcoverings"[MeSH Terms] OR ("floors"[tw] AND "floorcoverings"[tw]) OR "floors and floorcoverings"[tw] OR (floor*[tw] AND lay*[tw])
#4	"work"[MeSH Terms] OR "work"[All Fields] OR "occupations"[MeSH Terms] OR "occupations"[All Fields] OR "occupation"[All Fields] OR works*[tw] OR work'*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupation*[tw] OR "manpower"[Subheading] OR "manpower"[All Fields]
#5	(#2 OR #3) AND #4
#6	#1 OR #5
#7	"knee"[MeSH Terms] OR "knee"[All Fields] OR "knee joint"[MeSH Terms] OR ("knee"[All Fields] AND "joint"[All Fields]) OR "knee joint"[All Fields] OR "lower extremity"[MeSH Terms] OR ("lower"[All Fields] AND "extremity"[All Fields]) OR "lower extremity"[All Fields] OR ("lower"[All Fields] AND "limb"[All Fields]) OR "lower limb"[All Fields]
#8	("osteoarthritis, knee"[MeSH Terms] OR "osteoarthritis"[All Fields] OR "arthritis"[MeSH Terms] OR "arthritis"[All Fields] OR "arthrosis"[tw]) OR (meniscus[All Fields] OR meniscal[All Fields]) OR "bursitis"[MeSH Terms] OR "bursitis"[All Fields]
#9	#6 AND #7 AND #8
#10	("2011"[Date - Publication]: "3000"[Date - Publication])
#11	#9 AND #10
Embase (embase.com): 08.09.2015 (same as earlier search excluding review filter and including 2011 publication time limit)	
#1	'workload'/de OR 'workload' OR 'work load' OR (work AND load) OR work NEAR/5 load
#2	'physical' OR kneeling OR kneel* OR squatting OR squatt* OR crawling OR crawl* OR 'lifting effort'/de OR 'lifting effort' OR lifting OR ladder* OR stairs
#3	miner* OR millwright* OR industr* OR (oil AND ('rig':jt OR 'rig')) OR pick* OR boilermaker* OR installer* OR landscaper* OR pipefitter* OR migrant* OR 'mechanics'/de OR 'mechanics' OR 'motor vehicle'/de OR 'motor' NEAR/3 'vehicles' OR 'motor vehicles' OR 'truck' NEAR/3 driver* OR refinery NEAR/3 operator* OR machine* OR electric* OR repair* OR farm* OR 'device maintenance'/de OR 'maintenance' OR 'wood'/de OR 'wood' OR concrete OR (brick* AND (layer OR mason)) OR plumber* OR 'asphalt'/de OR 'asphalt' OR rock* OR (sheet AND ('metals' OR 'metal'/de OR 'metal')) OR seam* OR fisherm* OR waitress* OR construct* OR 'building'/de OR ('floors' AND 'floorcoverings') OR 'floors and floorcoverings' OR floor* NEAR/5 lay*
#4	'work'/de OR 'work' OR 'occupation'/de OR 'occupation' OR occupation OR occupations OR work* OR 'manpower'/de OR 'manpower' OR manpower
#5	#2 OR #3
#6	#4 AND #5
#7	#1 OR #6
#8	'knee'/de OR 'knee' OR 'knee joint' OR ('knee' AND 'joint') OR 'leg'/de OR 'leg' OR 'lower extremity' OR ('lower' AND 'extremity') OR 'lower' NEAR/1 'limb' OR 'lower limb'
#9	'knee osteoarthritis'/de OR 'knee osteoarthritis' OR 'osteoarthritis' OR 'arthritis'/de OR 'arthritis' OR 'arthrosis' OR meniscus OR meniscal OR 'bursitis'/de OR 'bursitis'
#10	#7 AND #8 AND #9
#11	#10 NOT ([animals]/lim NOT [humans]/lim)
#12	#11 AND [embase]/lim
#13	#12 NOT [medline]/lim

Appendix II

Detailed risk of bias assessment. The detailed risk of bias items are aggregated into six domains of risk of bias, listed at the bottom and explained in the methods section of the article. The bottom row provides the aggregation of the domains at study level

RoB Sub-domains	Study ID														
	Coggon 2000	Cooper 1994	Elsner 1996	Lau 2000	Manninen 2002	Seidler 2008	Sandmark 2000	Klussmann 2010	Mounach 2008	Dawson 2003	Sahlström 1997	Schouten 1992	Yoshimura 2004	Yoshimura 2006	Zhang 2011
Funding source of study:	Low	Low	Low	Low	?	High	Low	Low	?	Low	Low	Low	Low	Low	Low
role of funding organization in data analysis & interpretations of the results:	?	Low	?	Low	?	Low	Low	Low	?	Low	Low	?	?	?	?
Conflict of interest	?	?	?	Low	?	Low	?	Low	?	?	?	?	?	?	Low
Source of outcome data	Low	Low	Low	Low	?	Low	Low	Low	Low	Low	Low	Low	?	?	Low
Severity, degree of the symptoms of the condition	Low	na	na	na	na	na	na	Low	na	High for cases, low for controls	na	Low	na	?	Low
Validation of outcome measurements	Low	Low	High	High	?	Low	High	Low	High	High for cases, low for controls	Low	Low	?	?	Low
Definition of the exposure – general	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	?	Low	Low	Low	Low
Definition of the exposure – length of exposure	Low	Low	High	Low	Low	Low	Low	Low	Low	High	?	High	Low	Low	High
Measure the exposure – Intensity/dose of exposure	High	High	High	Low	Low	Low	Low	Low, except for climbing stairs = high	High	High	?	?	High	High	High
Source to measure exposure	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Measurement methods used for exposure assessment	High	High	High	High	High	High	High	High	High	High	High	High	High	High	High
Masking of investigators	?	Low	?	?	?	?	?	High	?	?	Low	?	?	?	?
Reliability of exposure estimates – prospective studies	na	na	na	na	na	na	na	na	na	na	na	High	na	na	High
Reliability – case–control studies	?	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	na	Low	Low	na
Confounding factors Osteoarthritis/meniscal lesion	Low	Low	High	High (k, s, L 50 kg+) low (c, L > 10 kg)	Low	Low	Low	Low	Low	High	?	Low	High	?	Low
Confounding factors Bursitis	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Measuring of confounding factors	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Cohort studies – Loss of follow-up	na	na	na	na	na	na	na	na	na	na	na	High	na	na	High
Case–control studies - Non response	Low	High	High	?	High	Low	Low	Low	?	High	Low	na	High	High	na
Analysis of the study – Methods to reduce research specific bias	Low	Low	Low	High: K, S/low: Cl & L 10 kg	Low	Low	High	Low	High	Low	High (logistic regression only)	Low	High	?	?
Dose response analysis	Low	High	High	High: Cl, K, S/low: L	Low	Low	High	Low	High	Low	High	Low	High	?	?
Reporting of the tested hypothesis	Low	Low	Low	High	Low	Low	Low	High	High	Low	High	Low	Low	High	High
Precision of the estimates	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	?	Low
Sample size justification	?	?	?	High	?	Low	?	Low	?	High	?	?	?	?	High
1) Funding & conflict of interest	Low	High	High	Low	?	High	?	Low	High	?	High	?	?	?	?
2) Adequate diagnosis of outcome	Low	Low	High	High	?	Low	High	Low	High	High	Low	Low	?	?	Low
3) Adequate ascertainment of exposure	High	Low	High	Low	Low	Low	Low	High	High	High	High	High	High	High	High
4) Confounding factors	Low	Low	High	High	Low	Low	Low	Low	Low	High	High	Low		?	Low
5) Attrition bias	Low	High	High	High	High	Low	Low	Low	High	High	Low	High	High	High	High
6) Analysis of the study	Low	Low	Low	High	Low	Low	High	Low	High	Low	High	Low	High	High	?
all 6 categories	High	High	High	High	High	Low	High	High	High	High	High	High	High	High	High

High, high risk of bias; Low, low risk of bias; na, not applicable because not assessed in the study; ?, unclear risk of bias.

Appendix III

Excluded studies

Study ID	Reason for exclusion
Aghili 2012	Outcome musculoskeletal disorder
Allen 2012	Cross-sectional study
Apold 2014	Physical activities measured as sedentary, moderate, intermediate & intensive, classification system does not enable a specification of our activities of interest
Bieleman 2013	Outcome not of interest (work participation)
Chen 2007	Cross-sectional study, no OA, bursitis, or ML outcome (pain only)
Cheng 2000	Leisure time physical activity (not occupational knee load)
Cooper 2000	No occupational knee load exposure measurements
D'Souza 2008	Cross-sectional study (survey data)
Du 2005	Cross-sectional study, no occupational exposure
Enderlein 1989	Job title only
Ezzat 2012	Cross-sectional study
Felson 1991	Use of job classification system based on experts' rating, inclusion in the discussion section.
Gholami 2015	Cross-sectional prevalence of cases
Hart 1999	No physical workload, not age adjusted
Herquelot 2015	No OA, B, ML specific outcome (pain)
Hwang 2012	Job title only (no JEM), outcome meniscal lesions
Ingham 2011	No OA, bursitis or ML outcome (pain)
Jacobs 2014	No primary study
Jensen 2015	Cross-sectional study, job title only
Jones 2007	Not OA, bursitis or ML outcome (outcome knee pain only, not measured if knee pain is OA/B/ML)
Jonnsson 2015	Job title only
Kohatsu 1990	Crude exposure measurement does not enable differentiation between exposure/no exposure to kneeling, squatting, climbing, or lifting, no occupational tasks or activities measured, general occupational exposure classified as light, medium, heavy
Le Manach 2012	Cross-sectional study, bursitis
Martin 2013	Use of job exposure matrix based on subjective measures from 2 other studies (both of which are included), inclusion in discussion section
Muraki 2011	Cross-sectional study
Namali 2011	Cross-sectional design
Ratzlaff 2012	Cross-sectional design, analysis of joint force exposure,
Sigurdardottir 2013	Same study population as Johnsson 2015
Toivanen 2010	Crude exposure measurement does not enable differentiation between exposure & no exposure (to kneeling, squatting, climbing, or lifting)
Vingard 1992	Exposure measurement based on job titles only
Von Nauwald 1986	Job title only

JEM, Job Exposure Matrix; ML, Meniscal Lesion; OA, osteoarthritis.

References

[1] Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26–35.

[2] Visser AW, de Mutsert R, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 2015;74:1842–7.

[3] Hiligsmann M, Cooper C, Guillemin F, Hochberg MC, Tugwell P, Arden N, Berenbaum F, Boers M, Boonen A, Branco JC, Maria-Luisa B, Bruyère O, Gasparik A, Kanis JA, Kvien TK, Martel-Pelletier J, Pelletier JP, Pinedo-Villanueva R, Pinto D, Reiter-Niesert S, Rizzoli R, Rovati LC, Severens JL, Silverman S, Reginster JY. A reference case for economic evaluations in osteoarthritis: An expert consensus article from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum 2014;44:271–82.

[4] Gouttebarge V, Inklaar H, Backx F, Kerkhoffs G. Prevalence of osteoarthritis in former elite athletes: a systematic overview of the recent literature. Rheumatol Int 2015;35:405–18.

[5] Tanaka R, Ozawa J, Kito N, Moriyama H. Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil 2013;27:1059–71.

[6] McWilliams DF, Leeb BF, Muthuri SG, Doherty M, Zhang W. Occupational risk factors for osteoarthritis of the knee: a meta-analysis. Osteoarthritis Cartilage 2011;19:829–39.

[7] Palmer KT. Occupational activities and osteoarthritis of the knee. Br Med Bull 2012;102:147–70.

[8] Jensen LK. Knee osteoarthritis: influence of work involving heavy lifting, kneeling, climbing stairs or ladders, or kneeling/squatting combined with heavy lifting. Occup Environ Med 2008;65:72–89.

[9] Jensen LK, Eenberg W. Occupation as a risk factor for knee disorders. Scand J Work Environ Health 1996;22:165–75.

[10] Verbeek J. When work is related to disease, what establishes evidence for a causal relation? Saf Health Work 2012;3:110–6.

[11] Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.

[12] Cochrane Handbook for Systematic Reviews of Interventions [Internet]. The Cochrane Collaboration. 2011. Available from: www.cochrane-handbook.org.

[13] Shamliyan T, Kane RL, Ansari MT, Raman G, Berkman ND, Grant M, Janes G, Maglione M, Moher D, Nasser M, Robinson KA, Segal JB, Tsouros S. Development of the quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: pilot study of new checklists. Agency for Healthcare Research and Quality; 2011. Methods Research Report. AHRQ Publication No. 11-EHC008-EF.

[14] Il'yasova D, Hertz-Picciotto I, Peters U, Berlin JA, Poole C. Choice of exposure scores for categorical regression in meta-analysis: a case study of a common problem. Cancer Causes Control 2005;16:383–8.

[15] Orsini N, Bellocco R, Greenland S. Generalize least squares for trend estimation of summarized dose-response data. The Stata Journal 2006;6:40–57.

[16] Seidler A, Bolm-Audorff U, Abolmaali N, Elsner G. The role of cumulative physical work load in symptomatic knee osteoarthritis - a case-control study in Germany. J Occup Med Toxicol 2008;3:14.

[17] Seidler A, Bolm-Audorff U, Abolmaali N, Elsner G. Correction: The role of cumulative physical work load in symptomatic knee osteoarthritis - a case-control study in Germany (Seidler et al. 2008). J Occup Med Toxicol 2012;7:21.

[18] Vrezas I, Elsner G, Bolm-Audorff U, Abolmaali N, Seidler A. Case-control study of knee osteoarthritis and lifestyle factors considering their interaction with physical workload. Int Arch Occup Environ Health 2010;83:291–300.

[19] Coggon D, Croft P, Kellingray S, Barrett D, McLaren M, Cooper C. Occupational physical activities and osteoarthritis of the knee. Arthritis Rheum 2000;43:1443–9.

[20] Cooper C, McAlindon T, Coggon D, Egger P, Dieppe P. Occupational activity and osteoarthritis of the knee. Ann Rheum Dis 1994;53:90–3.
[21] Dawson J, Juszczak E, Thorogood M, Marks SA, Dodd C, Fitzpatrick R. An investigation of risk factors for symptomatic osteoarthritis of the knee in women using a life course approach. J Epidemiol Community Health 2003;57:823–30.
[22] Elsner G, Nienhaus A, Beck W. [Knee joint arthroses and work-related factors]. Soz Praventivmed 1996;41:98–106.
[23] Klussmann A, Gebhardt H, Nubling M, Liebers F, Quiros Perea E, Cordier W, von Engelhardt LV, Schubert M, Dávid A, Bouillon B, Rieger MA. Individual and occupational risk factors for knee osteoarthritis: results of a case-control study in Germany. Arthritis Res Ther 2010;12:R88.
[24] Lau EC, Cooper C, Lam D, Chan VN, Tsang KK, Sham A. Factors associated with osteoarthritis of the hip and knee in Hong Kong Chinese: obesity, joint injury, and occupational activities. Am J Epidemiol 2000;152:855–62.
[25] Manninen P, Heliovaara M, Riihimaki H, Suoma-Iainen O. Physical workload and the risk of severe knee osteoarthritis. Scand J Work Environ Health 2002;28:25–32.
[26] Mounach A, Nouijai A, Ghozlani I, Ghazi M, Achemlal L, Bezza A, El Maghraoui A. Risk factors for knee osteoarthritis in Morocco. A case control study. Clin Rheumatol 2008;27:323–6.
[27] Sandmark H, Hogstedt C, Vingard E. Primary osteoarthrosis of the knee in men and women as a result of lifelong physical load from work. Scand J Work Environ Health 2000;26:20–5.
[28] Sahlstrom A, Montgomery F. Risk analysis of occupational factors influencing the development of arthrosis of the knee. Eur J Epidemiol 1997;13:675–9.
[29] Yoshimura N, Kinoshita H, Hori N, Nishioka T, Ryujin M, Mantani Y, Miyake M, Takeshita T, Ichinose M, Yoshiida M, Oka H, Kawaguchi H, Nakamura K, Cooper C. Risk factors for knee osteoarthritis in Japanese men: a case-control study. Mod Rheumatol 2006;16:24–9.
[30] Yoshimura N, Nishioka S, Kinoshita H, Hori N, Nishioka T, Ryujin M, Mantani Y, Miyake M, Coggon D, Cooper C. Risk factors for knee osteoarthritis in Japanese women: heavy weight, previous joint injuries, and occupational activities. J Rheumatol 2004;31:157–62.
[31] Schouten JS, van den Ouweland FA, Valkenburg HA. A 12 year follow up study in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. Ann Rheum Dis 1992;51:932–7.
[32] Zhang W, McWilliams DF, Ingham SL, Doherty SA, Muthuri S, Muir KR, Doherty M. Nottingham knee osteoarthritis risk prediction models. Ann Rheum Dis 2011;70:1599–604.
[33] Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, Dieppe PA. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995–1000.
[34] Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ Open 2015;5:e007568.
[35] van der Beek AJ, Frings-Dresen MH. Assessment of mechanical exposure in ergonomic epidemiology. Occup Environ Med 1998;55:291–9.
[36] Martin KR, Kuh D, Harris TB, Guralnik JM, Coggon D, Wills AK. Body mass index, occupational activity, and leisure-time physical activity: an exploration of risk factors and modifiers for knee osteoarthritis in the 1946 British birth cohort. BMC Musculoskelet Disord 2013;14:219.
[37] Felson DT, Hannan MT, Naimark A, Berkeley J, Gordon G, Wilson PW, Anderson J. Occupational physical demands, knee bending, and knee osteoarthritis: results from the Framingham Study. J Rheumatol 1991;18:1587–92.
[38] Riyazi N, Rosendaal FR, Slagboom E, Kroon HM, Breedveld FC, Kloppenburg M. Risk factors in familial osteoarthritis: the GARP sibling study. Osteoarthritis Cartilage 2008;16:654–9.
[39] Visser S, van der Molen HF, Kuijer PP, Sluiter JK, Frings-Dresen MH. Stand up: comparison of two electrical screed levelling machines to reduce the work demands for the knees and low back among floor layers. Ergonomics 2016:1–8.
[40] Visser S, van der Molen HF, Kuijer PP, van Holland BJ, Frings-Dresen MH. Evaluation of two working methods for screed floor layers on musculoskeletal complaints, work demands and workload. Ergonomics 2013;56:69–78.
[41] Kievit AJ, van Geenen RC, Kuijer PP, Pahlplatz TM, Blankevoort L, Schafroth MU. Total knee arthroplasty and the unforeseen impact on return to work: a cross-sectional multicenter survey. J Arthroplasty 2014;29:1163–8.
[42] Crippa A, Orsini N. Multivariate dose-response meta-analysis: the dosresmeta R package. J Stat Softw 2016;72. http://dx.doi.org/10.18637/jss.v072.c01. CodeSnippet1.