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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

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