Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies

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ABSTRACT

Objectives: Obesity is suggested to be a risk factor for knee osteoarthritis (OA). This meta-analysis aimed to examine the relationship between body mass index (BMI) and the risk of knee OA in published prospective studies.

Design: Meta-analysis.

Studies reviewed: An extensive literature review was performed, and relevant studies published in English were retrieved from the computerised databases MEDLINE, EMBASE and Cochrane.

Methods: The effect estimate (RR or HR) and its 95% CI are investigated on the basis of the evaluation of differences of knee OR risk in overweight or obesity versus those with normal weight. Category-specific risk estimates were further transformed into estimates of the RR in terms of per increase of 5 in BMI by using the generalised least-squares method for trend estimation. Studies were independently reviewed by two investigators. Subgroup analysis was performed. Heterogeneity and publication bias were assessed. Data from eligible studies were extracted, and the meta-analysis was performed using the STATA software V.12.0.

Results: 14 studies were finally included in the analysis. The results showed that overweight and obesity were significantly associated with higher knee OA risks of 2.45 (95% CI 1.88 to 3.20, p<0.001) and 4.55 (95% CI 2.90 to 7.13, p<0.001), respectively. The risk of knee OA increases by 35% (95% CI 1.18 to 1.53, p<0.001) with a 5 kg/m² increase in BMI. Subgroup analysis showed that obesity was an independent predictor of knee OA risk regardless of the study country, sample size, gender proportion of participants, duration of follow-up, presence of adjusted knee injury and assessed study quality above or below an NOS score of 8. No publication bias was detected.

Conclusions: Obesity was a robust risk factor for knee OA. Professionals should take a possible weight reduction into account for the treatment of knee OA whenever a patient is significantly overweight.

INTRODUCTION

Knee osteoarthritis (OA), which is a degenerative disease, is the most common form of arthritis in the knee.1 Knee OA is related to ageing, articular cartilage obesity, fatigue, trauma, joint congenital abnormalities and joint deformities caused by many factors such as degradation of injury, under joint margins and subchondral bone reactive hyperplasia.2 Clinical manifestations of knee OA are slow development of joint pain, tenderness, stiffness, joint swelling, limited mobility and joint deformities. There were 20 million individuals suffering from knee OA in the USA, and this figure is expected to double over the next two decades.3 4 Knee pain was reported by up to a half of the individuals aged over 50, among which severe and disabling knee pain accounted for approximately 50%.5 The high prevalence and substantial impact on quality of life of knee OA calls for more high-quality studies assessing adiposity using parameters on body mass index only.

Strengths and limitations of this study

- We applied random-effect models based on the heterogeneity of the true effects distribution, which avoided the bias of overstating the precision of findings in fixed-effects models.
- A limitation of the current study was the small number of studies involved, with limited numbers of participants. This reflected the paucity of high-quality clinical trials that addressed this research topic.
- We conclude that all patients with osteoarthritis should be treated with caution. There is still a considerable need for more high-quality studies assessing adiposity using parameters on body mass index only.
individuals have 1.5 to 2 times the risk of developing knee OA as their leaner counterparts.10 Fowler-Brown found that a 5 kg/m² increase in BMI was associated with a 32% increase in the probability of OA, and leptin contributed approximately half of the total effect of obesity on knee OA.7 Within a meta-analysis of risk factors for the onset of knee OA, obesity (OR=2.63, 95% CI 2.28 to 3.05) was found to be associated with knee OA. However, although this meta-analysis included both cohort and case–control studies, data on subgroup analysis were not available.11

This study systematically combined existing prospective studies that investigating the association of obesity and risk of knee OA to identify the true effect sizes. This study used a random-effect meta-analysis following the MOOSE guidelines12 for observational studies and the QUORUM guidelines for clinical trials.13

MATERIALS AND METHODS
Search strategy for identifying studies
An in-depth literature search was performed using the keywords ‘obesity’ OR ‘weight’ OR ‘body weight’ OR ‘body mass’ OR ‘body mass index’ OR ‘anthropometric’ OR ‘anthropometry’ OR ‘adiposity’ AND (‘arthritis’ OR ‘osteoarthritis’ OR ‘OA’) in various combinations. The computerised databases PubMed, EMBASE and Cochrane were searched to identify eligible studies in English-language journals before August 2014. We also searched the relevant references in the retrieved studies and reviewed articles from the bibliographic database. The corresponding authors in some studies were contacted for more information beyond that in their published articles.

Article selection criteria
All prospective studies that explored the association of obesity and risk of knee OA were considered eligible for the analysis. Two investigators (Zheng Huaqing and Chen Changhong) independently assessed the articles for relevance. Articles that met the following criteria were excluded: (1) cross-sectional studies; (2) a standardised effect size could not be calculated. (3) BMI were categorised according to the WHO (normal weight: BMI of less than 23.0 kg/m²; overweight: 23.0–24.9 kg/m² of BMI; obese: over 30.0 kg/m² of BMI; Asian criteria (normal weight: BMI of less than 23.0 kg/m²; overweight: 23.0–24.9 kg/m² of BMI; obese: over 25.0 kg/m² of BMI) of the elderly.14 It was because this meta-analysis was performed mainly using the data from published studies that the need for institutional review board approval was waived.

Quality assessment and data abstraction
The Newcastle-Ottawa-Scale (NOS)15 was used to assess the quality of each article. The NOS contains eight items, categorised into three dimensions including selection, comparability and, depending on the study type, outcome (cohort studies). For each item, a series of response options was provided. A star system was used to allow a semi-quantitative assessment of study quality, such that the highest quality studies were awarded a maximum of one star for each item with the exception of the item related to comparability that allowed the assignment of two stars. The NOS ranges between zero and nine stars.

All articles were first de-identified (article title, author names, journal name and year of publication) before selection. The abstracts of the articles were independently reviewed by two of the authors (Zheng Huaqing and Chen Changhong). The data were filtered and input into a standard electronic form. Any discrepancies were resolved by discussion until a consensus was reached. If there was no consensus, the principal investigator (Zheng Huaqing) would make the final decision on the eligibility of the study and data extraction.

Statistical analyses
Data management and analysis were performed by using the STATA software (V12.0; Stata Corporation, College Station, Texas, USA). We examined the relationship between BMI and the risk of knee OA on the basis of the effect estimate (RR or HR) and its 95% CI published in each study. A random-effects model was used to calculate summary RRs and 95% CIs for overweight or obesity compared to normal weight individuals. We then transformed category-specific risk estimates into estimates of the RR associated with every 5 kg/m² increase in body mass index (BMI) by using the generalised least-squares method for trend estimation. These estimates were calculated assuming the presence of a linear relationship between the natural logarithm of the RR and increasing BMI. The value assigned to each BMI category was the midpoint for closed categories and the median for open

Figure 1 Flow chart describing the article selection process. BMI, body mass index.
Table 1  Baseline characteristics of studies included in the systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Age at baseline</th>
<th>Percentage male</th>
<th>Knee OA cases</th>
<th>Follow-up (year)</th>
<th>Covariates in fully adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grotle et al</td>
<td>Norway</td>
<td>Cohort</td>
<td>1854</td>
<td>24–76</td>
<td>43.7%</td>
<td>114</td>
<td>10.0</td>
<td>Age, gender, work type, leisure time activities</td>
</tr>
<tr>
<td>Hart et al</td>
<td>UK</td>
<td>Cohort</td>
<td>715</td>
<td>54.1</td>
<td>0</td>
<td>95</td>
<td>4.0</td>
<td>Hysterectomy, ERT, smoking, physical activity, knee pain and social class</td>
</tr>
<tr>
<td>Cooper et al</td>
<td>UK</td>
<td>Cohort</td>
<td>346</td>
<td>&gt;55.0</td>
<td>26.3</td>
<td>45</td>
<td>5.1</td>
<td>Age and sex</td>
</tr>
<tr>
<td>Reijman et al</td>
<td>Netherlands</td>
<td>Cohort</td>
<td>1372</td>
<td>&gt;55.0</td>
<td>–</td>
<td>75</td>
<td>6.6</td>
<td>Age, sex and follow-up time</td>
</tr>
<tr>
<td>Järvholm et al</td>
<td>Sweden</td>
<td>Cohort</td>
<td>320</td>
<td>15–67</td>
<td>100%</td>
<td>502</td>
<td>12.0</td>
<td>Age and smoking</td>
</tr>
<tr>
<td>Niu et al</td>
<td>USA</td>
<td>Cohort</td>
<td>2623</td>
<td>62.4</td>
<td>40%</td>
<td>163</td>
<td>2.5</td>
<td>Age, gender, race, bone mineral density and knee injury</td>
</tr>
<tr>
<td>Liu et al</td>
<td>UK</td>
<td>Cohort</td>
<td>490532</td>
<td>50–69</td>
<td>0</td>
<td>974</td>
<td>2.9</td>
<td>Age, region of recruitment, deprivation index</td>
</tr>
<tr>
<td>Wang et al</td>
<td>Australia</td>
<td>Cohort</td>
<td>41528</td>
<td>25–75</td>
<td>41.1%</td>
<td>541</td>
<td>5.0</td>
<td>Age, gender, country of birth and education</td>
</tr>
<tr>
<td>Toivanen et al</td>
<td>Finland</td>
<td>Cohort</td>
<td>823</td>
<td>&gt;30</td>
<td>44.8%</td>
<td>94</td>
<td>22.0</td>
<td>Age, gender</td>
</tr>
<tr>
<td>Lohmander et al</td>
<td>Sweden</td>
<td>Cohort</td>
<td>27960</td>
<td>45–73</td>
<td>39.4%</td>
<td>471</td>
<td>11.0</td>
<td>Age, gender, smoking and physical activity</td>
</tr>
<tr>
<td>Felson et al</td>
<td>USA</td>
<td>Cohort</td>
<td>598</td>
<td>63.7</td>
<td>36.3%</td>
<td>93</td>
<td>8.0</td>
<td>Age, gender, smoking, physical activity, knee injury and weight change</td>
</tr>
<tr>
<td>Hochberg et al</td>
<td>USA</td>
<td>Cohort</td>
<td>437</td>
<td>&gt;20</td>
<td>68.2%</td>
<td>–</td>
<td>4.0</td>
<td>Age, gender and smoking</td>
</tr>
<tr>
<td>Manninen et al</td>
<td>Finland</td>
<td>Cohort</td>
<td>6647</td>
<td>40–64</td>
<td>–</td>
<td>126</td>
<td>10.0</td>
<td>None</td>
</tr>
<tr>
<td>Shiozaki et al</td>
<td>Japan</td>
<td>Cohort</td>
<td>1191</td>
<td>40–65</td>
<td>0</td>
<td>–</td>
<td>14.0</td>
<td>Physical exercise and knee injury</td>
</tr>
</tbody>
</table>

ERT, estrogen replacement therapy; NOS, Newcastle-Ottawa-Scale; OA, osteoarthritis.
categories (assuming a normal distribution for BMI). We combined the RRs for each 5 kg/m² increase in BMI by using a random-effect meta-analysis.

The measure of heterogeneity was evaluated by using $I^2$, which was used to assess the percentage of the total variation from all studies to define the heterogeneity. A high value for $I^2$ indicates heterogeneity. $I^2$ values of 25%, 50% and 75% correspond to cut-off points for low, moderate and high degrees of heterogeneity. Publication bias was evaluated by using Egger’s test in this statistical analysis. Funnel plots for the incidence of knee OA were visually inspected.

Subgroup analyses were conducted to investigate the impact of the study country, sample size, gender proportion of participants, duration of follow-up, presence of adjusted knee injury and assessed study quality above or below an NOS score of 8 on the pooled effect sizes. We also performed a sensitivity analysis by removing each individual study from the meta-analysis in order to study the influence on the meta-analysis of each study. All reported p values were 2-sided, and p values <0.05 were considered statistically significant for all included studies.

RESULTS

A total of 972 abstracts were initially selected through database search and citation tracking, and 926 articles were excluded because they failed to meet the criteria. For the remaining 46 articles, 7 were affiliate study, 12 did not have comparison data of different BMI groups and 13 had no desirable outcomes to calculate effect sizes. The results of the study-selection process are shown in figure 1. In addition, the baseline characteristics and NOS score of the 14 articles selected for our analysis are shown in table 1.

In these 14 prospective studies, 12 were conducted in western countries and 2 were conducted in the Asia-Pacific region. The proportion of males ranged from 0% to 100%; however, the proportion of gender was not a significant predictor of the effect size in this study. Overweight and obesity were significantly associated with higher knee OA risks of 2.45 (95% CI 1.88 to 3.20, p<0.001, figure 2) and 4.55 (95% CI 2.90 to 7.13, p<0.001, figure 3), respectively. The risk of knee OA increases by 35% (RR: 1.35; 95% CI 1.18 to 1.53, p<0.001) with a 5 kg/m² increase in BMI, which is shown in figure 4. Subgroup analysis showed that the conclusions were consistent with overall analysis based on predefined factors (table 2).

Significant heterogeneity was found in the models of overweight versus normal weight ($I^2=86.1\%$, p<0.001), obesity versus normal weight ($I^2=94.8\%$, p<0.001) and the increase of knee OA with a 5 kg/m² increase in BMI ($I^2=99.3\%$, p<0.001). Sensitivity analyses were performed for each of the outcomes. No study crossed zero, and removing any study would have no effect on the pooled WMD (data not shown).

Publication bias was examined by using funnel plots and Egger’s regression test, and results indicated that there was no significant publication bias (p>0.05) in the outcomes of this meta-analysis. Consequently, unpublished data were not evaluated further.
Figure 3  Forest plot for the aggregate risk of knee osteoarthritis for obesity versus normal weight.

Figure 4  Forest plot for the aggregate risk of knee osteoarthritis with the increase of a 5 kg/m² of body mass index.
DISCUSSION
The aim of this meta-analysis was to review relevant prospective literatures in order to identify the risk of being overweight or obese for knee OA. On the basis of the search strategy and inclusion criteria, a total of 14 original studies were selected and assessed. Pooled RR showed that being overweight or obese was approximately 2.5 and 4.6 times more likely to have knee OA than having normal weight. The risk of knee OA increases by 35% with a 5 kg/m² increase in BMI. Furthermore, obesity was an independent predictor of knee OA risk regardless of the study country, sample size, gender proportion of participants, duration of follow-up, presence of adjusted knee injury and assessed study quality above or below an NOS score of 8. Subgroup analysis showed that the study country and gender proportion were not significant predictors of the effect sizes in this study.

The findings in this meta-analysis of obesity as a robust risk factor for knee OA were consistent with previous studies. Manninen et al. found that increasing from normal weight to overweight during adult life might slightly increase the risk of developing knee OA leading to arthroplasty compared with being constantly overweight during adult life. In a 12-year cohort study, weight loss decreased the high risk of OA due to high

### Table 2  Subgroup analyses

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of study</th>
<th>RR and 95% CI</th>
<th>p Value</th>
<th>Heterogeneity (%)</th>
<th>p Value for heterogeneity</th>
<th>p Value for interaction test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>9</td>
<td>1.30 (1.11 to 1.53)</td>
<td>0.001</td>
<td>99.5</td>
<td>&lt;0.001</td>
<td>0.524</td>
</tr>
<tr>
<td>USA or other countries</td>
<td>5</td>
<td>1.44 (1.10 to 1.89)</td>
<td>0.007</td>
<td>97.2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1000</td>
<td>9</td>
<td>1.35 (1.20 to 1.52)</td>
<td>&lt;0.001</td>
<td>98.2</td>
<td>&lt;0.001</td>
<td>0.582</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>5</td>
<td>1.28 (1.10 to 1.48)</td>
<td>0.001</td>
<td>87.8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Per cent male (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>2</td>
<td>1.24 (1.12 to 1.37)</td>
<td>&lt;0.001</td>
<td>14.1</td>
<td>0.281</td>
<td>0.383</td>
</tr>
<tr>
<td>&lt;60</td>
<td>10</td>
<td>1.35 (1.15 to 1.59)</td>
<td>&lt;0.001</td>
<td>99.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 years or greater</td>
<td>6</td>
<td>1.25 (1.11 to 1.40)</td>
<td>&lt;0.001</td>
<td>97.0</td>
<td>&lt;0.001</td>
<td>0.203</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>8</td>
<td>1.41 (1.22 to 1.63)</td>
<td>&lt;0.001</td>
<td>97.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Adjusted knee injury</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>1.19 (1.10 to 1.29)</td>
<td>&lt;0.001</td>
<td>60.8</td>
<td>0.054</td>
<td>0.086</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>1.39 (1.18 to 1.62)</td>
<td>&lt;0.001</td>
<td>99.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Study quality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 or 9</td>
<td>6</td>
<td>1.36 (1.11 to 1.66)</td>
<td>0.003</td>
<td>99.7</td>
<td>&lt;0.001</td>
<td>0.535</td>
</tr>
<tr>
<td>&lt;8</td>
<td>8</td>
<td>1.27 (1.17 to 1.37)</td>
<td>&lt;0.001</td>
<td>72.5</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5  Funnel plot for the assessment of publication bias.
BMI among women. Fowler-Brown (2014) measured BMI in 653 community dwelling adults aged above 70 years, and found that a 5 kg/m^2 increase in BMI was associated with a 32% increase in the probability of knee OA, and at the same time, a 200 pM increase in serum leptin was associated with an increase of 11% in the probability of knee OA. These findings suggested the shared pathogenetic role for metabolic factors with knee OA. The possible mechanism might involve adipokines such as leptin which contributed approximately half of the total effect of obesity on knee OA.32

According to the findings from our systematic meta-analysis, it is valuable for physicians and policymakers to take obesity as one of the most important risks of knee OA into consideration. The Osteoarthritis Research Society International (OARSI) guidelines strongly recommended that overweight patients with OA with lower limb OA lost weight and maintained a lower weight level.33 We applied random-effect models based on the heterogeneity of the true effects distribution, which avoided the bias of overstating the precision of findings in fixed-effects models. A limitation of the current study was the small number of studies involved, with limited numbers of participants. This reflected the paucity of high-quality clinical trials that addressed this research topic. Generalising the conclusions from this study to all patients with OA should be performed with caution, and there is still a considerable need for more high-quality studies assessing adiposity using parameters beyond BMI only.

In summary, this meta-analysis confirmed that obesity was a robust risk factor for knee OA. Professionals who treat knee OA should accept a possible weight reduction in mind whenever a patient is significantly overweight.

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