

**Blagojevic M, Jinks C, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis and Cartilage 2010;18:24-33.**

Design Systematic review and meta-analysis of observational studies

Purpose of study: to assess current evidence on risk factors for the incidence of knee pain and OA in the elderly

Search strategy:

- Databases included MEDLINE, EMBASE, CINAHL, the Cochrane Library, the National Electronic Library for Health, and other databases through January 2008
- Two authors reviewed articles for whether they met inclusion criteria which were:
  - o English language
  - o Prospective cohort or retrospective case-control studies
    - Cross-sectional studies were excluded
  - o Mean age of subjects was 50 or older
  - o Outcome was onset of knee OA, knee pain, knee disability, or physical limitations relating to symptomatic knee or radiographic knee OA
  - o Risk factors were demographic, socio-economic, comorbid, previous knee events such as surgery or injury, and other patient-determined factors
- Exclusion criteria were
  - o Knee pain related to other conditions such as rheumatoid arthritis
  - o Amputee studies or animal studies
  - o Literature reviews or conference abstracts
  - o Clinical risk factors or outcome including proprioception, muscle strength, knee alignment, or cartilage loss
  - o Studies of subjects with previous injury but without a general population comparison group
- Methodological quality was assessed with an instrument which awarded points on numerous criteria including
  - o Clearly defined study objective
  - o Prospective design
  - o Inclusion and exclusion criteria clear and appropriate
  - o Representative sample of general population
  - o All subjects age at least 50 at start of followup
  - o Appropriate and validated outcome measure
  - o Analyses adjusted for confounders such as knee-related, general health, or demographic factors
  - o Length of followup at least 36 months
  - o Baseline response at least 70%
  - o Less than 25% dropout

- Adequate description of dropouts
- Appropriate analysis
- Adjusted results given with confidence intervals (CI) where appropriate, such as a 95% CI

#### Definition of main risk factors and estimates of their effects

- For BMI, normal was defined as less than 25, overweight was 25 to 30, and obese was over 30
- For smoking, categories were based on current smoker versus never smoker, ever smoker versus never smoker, and light/moderate versus heavy smoking
- Meta-analysis was done on the pooled odds ratios (OR), and in anticipation of heterogeneity between studies, sources of heterogeneity were examined, including study quality, recentness of publication (pre 2001 versus since 2001), study type (case-control versus cohort), and definition of knee OA (radiographic versus symptomatic)

#### Results:

- 2233 studies were identified using the search strategy in all databases, and 85 studies were included in the review
  - 42 studies were prospective
  - 51 used a radiological definition of knee OA, a used only a symptomatic definition, and the remaining studies used a combination of both
  - 38 studies were done in the USA, 45 in Europe, and the rest from elsewhere
- A pooled OR was estimated for five factors: BMI, smoking gender, previous knee injury, and hand OA with Heberden's nodes
- All risk factors showed substantial heterogeneity, and random-effects meta-analysis models were used for the pooled OR
- 36 studies reported on BMI, and all 36 reported that increased BMI was a risk factor for knee OA, although the results were highly heterogeneous due to some studies showing much larger odds ratios than others
  - The pooled OR for obesity was estimated from 17 studies, 5 case-control and 12 cohort studies
    - The pooled OR from the case-control studies was larger (OR=4.25, 95% Ci 3.15 to 5.73) than for the cohort studies (2.22, 95% CI 1.91 to 2.57)
    - When the pooled OR was weighted by quality score, the results were very similar for obesity
  - The pooled OR for overweight (not obese) versus normal BMI was somewhat smaller than for obesity (2.22 from the case-control and 2.13 from the cohort studies)

- Previous knee injury was investigated in 16 studies, and all but two concluded it was an important risk factor; the pooled OR was 3.86 (95% CI from 2.61 to 5.70); when restricted to cohort studies, the pooled OR was similar but with wider confidence intervals due to having only 8 studies (OR=3.17, 95% CI 1.67 to 6.03)
- Smoking had variable OR for OA, and the pooled OR from 18 studies appeared to show a protective effect of smoking (OR=0.84, 95% CI 0.74 to 0.95), but when the analysis was restricted to cohort studies, no effect of smoking was found
- Gender was reported for 9 studies, and women were somewhat more likely than men to have OA (OR=1.84, 95% CI 1.32 to 2.55)
- Hand OA with Heberden's nodes suggested that hand OA was associated with future knee problems (OR 1.49, 95% CI 1.05 to 2.10)
- Occupational activities were reported to be associated with OA in several studies, but OR were not pooled and the authors did not report the magnitude of the effect sizes
  - o Climbing steps, standing more than two hours per day, excessive kneeling or squatting, knee bending, and lifting were reported to be risk factors for OA, but walking and excessive driving were not associated with OA
  - o Farming and construction work were risk factors for knee pain, but again pooled OR were not reported by the authors
- Other factors were included in the systematic review, such as physical activity, estrogen use, contraceptive use, bone mineral density, hypertension, hysterectomy, and depression, but pooled odds ratios were not reported for these variables, even though several (increased physical activity, older age, and increased bone density) were said to be associated with increased risk of OA

#### Authors' conclusions:

- Knee OA is more common in people with obesity and overweight than in people of normal weight with BMI less than 25
- A history of knee injury is associated with an increased risk of knee OA
- Hand OA is associated with an increased incidence of knee OA
- Study quality was an unclear influence on the estimate of risk factors; most of the analyses which took study quality into account yielded similar odds ratios for the relationship between risk factors and knee OA
- This study was concerned with the occurrence of knee OA and not with its progression, for which the risk factors could be different
- Targeting obesity, knee injury, and hand OA could be beneficial for patients at risk of knee OA

#### Comments:

- Even though the heterogeneity of the meta-analysis was very large for increased BMI and knee OA, the studies were unanimous in reporting that both overweight and

- obesity were associated with an increased risk of knee OA, and the heterogeneity arose from some studies reporting very large odds ratios (on the order of 7 to 10) while others were on the order of 2 to 3
- The characteristics of knee injury associated with knee OA were not given in any detail, but are likely to be highly heterogeneous
  - Many of the results for risk factors of interest are reported in narrative form rather than quantitatively; for example, increased bone mineral density was reported in three studies to be associated with increased risk of knee OA, but this is not elaborated upon
  - The pooled OR for hand OA was modest in magnitude (OR=1.49), and may represent a similar pathophysiologic process rather than being a modifiable risk factor for knee OA; it may be more of a marker than a causative factor for the knee

Assessment: adequate meta-analysis with strong evidence of increased BMI as a significant risk factor for the occurrence of onset of knee OA, and for previous knee injury as a significant risk factor for OA, and for hand OA as a significant marker of risk for knee OA