Osteoarthritis and Cartilage (2010) **18,** 24–33

doi:10.1016/j.joca.2009.08.010

Osteoarthritis and Cartilage

Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis

M. Blagojevic†*, C. Jinks†, A. Jeffery‡ and K. P. Jordan†
† *Arthritis Research Campaign National Primary Care Centre, Keele University, Staffordshire, England, United Kingdom*
‡ *Quintiles, Berkshire, United Kingdom*

Summary

Objective: Knee osteoarthritis (OA) is common in older adults. Determination of risk factors for onset of knee OA may help in its prevention. The objective of this systematic review, and meta-analysis, was to determine the current evidence on risk factors for knee OA.

Design: A systematic literature search was carried out for cohort and case–control studies evaluating the association of demographic, comorbid, and other patient-determined factors with onset of knee OA. A scoring tool was developed to assess the quality of studies. Heterogeneity of studies was examined. Where possible studies were pooled to give an overall estimate of the association of factors with onset of knee OA.

Results: Of the 2233 studies screened, 85 were eventually included in the review. Study quality tended to be moderate. The main factors consistently associated with knee OA were obesity (pooled OR 2.63, 95% CI 2.28–3.05), previous knee trauma (pooled OR 3.86, 95% CI 2.61–5.70), hand OA (pooled OR 1.49, 95% CI 1.05–2.10), female gender (pooled OR 1.84 95% CI 1.32–2.55) and older age. Smoking appeared to have a moderate protective effect, however this was not evident once the analysis was restricted to cohort studies only.

Conclusions: Whilst certain factors have been extensively reviewed (for example, body mass index), more longitudinal studies are needed to investigate the association of physical occupational and other patient-determined factors with future knee OA. The quality of such studies also needs to be improved. However, there are identifiable factors which can be targeted for prevention of disabling knee pain.

Key words: Osteoarthritis, Knee, Knee pain, Incidence, Risk factors, Systematic review, Meta-analysis.

Introduction

Symptomatic (self-reported knee pain) and radiographic osteoarthritis (OA) of the knee are common in the older age groups. The knee is the site most affected by joint pain in older adults where it is usually attributed to OA in this age-group[1,2]. Up to a half of people aged 50 and over report having knee pain during the course of a year, and a quarter have severe and disabling knee pain[3]. Development of knee pain can herald a substantial and persistent reduction in the ability to undertake everyday activities[4,5]. The high prevalence of knee OA, and its impact on physical functioning and quality of life, means that identifying approaches to prevention should be a public health priority.

There have been no comprehensive systematic reviews of risk factors for onset of knee OA (defined either symptomatically or radiographically). Despite the plethora of studies which have investigated risk factors for knee OA, a recent review of reviews found only four systematic reviews on risk factors for knee OA, three of which examined physical workload and one on oestrogen replacement therapy[6]. The authors concluded by stating there were no systematic reviews available on risk factors for knee OA, such as injury and overweight, despite a number of primary research studies examining them.

In order to assess the current evidence on risk factors for the incidence of knee pain or knee OA in the elderly, we have carried out a systematic review and meta-analysis. We have concentrated on demographic, comorbid, previous knee events and other patient-determined factors which can be easily measured in a non-clinical setting.

*Address correspondence and reprint requests to: Milisa Blagojevic, Arthritis Research Campaign National Primary Care Centre, Keele University, Staffordshire ST55BG, United Kingdom. Tel: 44-01782-734711; Fax: 44-91782-733911; E-mail: m.blagojevic@keele.ac.uk
Received 24 February 2009; revision accepted 1 August 2009.

Methods

SEARCH STRATEGY AND STUDY SELECTION

Computerised bibliographic databases were searched for studies published between 1960 and third January 2008. The databases searched were MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature Database (CINAHL), and the Allied and Complementary Medicine Database (AMED). Other websites searched included the Cochrane Library, National Institute for Clinical Excellence, National Electronic Library for Health – musculoskeletal specialist library, Arthritis Research Campaign, Arthritis Care, Arthritis and Musculoskeletal Alliance, and Arthritis Foundation (US) National Office.

Searches were made in the titles, abstracts and keywords for combinations of the following terms: knee, OA, pain, disab*, risk, prognos*, predict*, cohort*, prospective. The full search strategy is available on the journal's website.

The list of references of all identified relevant studies were also searched. No contact was attempted with authors. The criteria for selection are presented in Table I.

Table I
Criteria for selection of studies in review

Inclusion criteria
English language
Quantitative studies: prospective cohort studies or retrospective case−control studies
Outcome of onset of knee OA, knee pain, knee disability or physical limitations relating to knee or radiographic knee OA
Mean age at follow-up of 50 plus or age-stratified analysis with 50+ strata
Risk factors must be demographic, socio-economic, comorbid, previous knee events (e.g., injury, operation), and other patient-determined factors
Exclusion criteria
Knee pain related to other musculoskeletal conditions e.g., rheumatoid arthritis, rheumatism
Animal studies
Studies on amputees
Clinical risk factors or outcome including proprioception, muscle strength, alignment, cartilage loss
Conference abstracts
Not an original study (e.g., editorial or literature review)
Non English language
Cross-sectional studies
Studies in those with previous trauma/injury without general population comparator group

Cross-sectional studies (which could only determine associations) were excluded. In order to obtain risk factors applicable to the older age group where OA is the most likely reason for knee pain, the mean age of the population at follow-up time point had to be 50 years or greater for inclusion. Initially three of the four authors reviewed all identified abstracts to assess possible eligibility. Disagreements were resolved by consensus. Two of the four authors then reviewed all remaining papers to assess whether they should be included in the final review. Again disagreement was resolved by consensus.

METHODOLOGICAL QUALITY

To assess the methodological quality of the included papers, a quality assessment tool, adapted from Mallen *et al.*[7] and Van Dijk *et al.*[8] was used (Table II).

One point was allocated if a criterion was met. No points were awarded if the criterion was not met or there was not enough information to say whether the criterion was met. The quality tool covered issues relating to both internal and external validity. In order to ensure studies allowed for a reasonable level of confounding, studies which examined at least two factors from at least two of the following domains (knee-related, general health, demographic) were awarded a point[9,10]. All studies were scored by MB and by one of KJ and CJ using a standardised electronic form. After the first 10 papers were reviewed, consistency of scoring was checked. For each study, a total quality score was calculated by summing up all rated items (maximum score 14 points). All three reviewers discussed and resolved disagreements through consensus. The intraclass correlation coefficient (2, 1)[11] was used to determine level of reliability in quality scores between the first and second reviewers.

DATA EXTRACTION

Effect sizes (odds ratios, relative risks or hazard ratios) were extracted or calculated from original studies where this was possible. Many studies reported effect sizes for men and women separately and these subgroups were merged *via* inverse variance pooling before entering the meta-analysis. That is, the gender effects were weighted based on the relative variance of effect size in the two gender groups. There was a considerable variation in the reported outcomes and the terminology used to describe knee OA, but they generally fell into symptomatic or radiographic (or both) groups.

We accepted the original definitions of symptomatic or radiographic from each paper. Symptomatic OA was generally based on patient's self-report of their knee problems, typically of pain although occasionally this also included stiffness or functional problems. Radiographic OA was generally based on a Kellgren and Lawrence (K/L) score of 2 or more. If OA was defined based on both self-report and radiographic evidence, then we classified it as being both symptomatic and radiographic-based.

When several radiographic outcomes for the incidence of knee OA were provided, those based on the increase in K/L score were used. When results on both the incidence of knee OA and incidence of severe knee OA are reported, the former was used.

For risk factors that were included in more than one paper from the same study, the results from the paper reporting the longest follow up were included in the meta-analysis, or if follow-up length was the same, the most recently published paper was included.

Table II
Quality assessment tool and number (%) of studies achieving each criteria

Criteria	*n* (%) of studies achieving criteria
Clearly defined and appropriate study objective	82 (97)
Prospective study design	40 (47)
Inclusion and exclusion criteria are clear and appropriate	60 (71)
Representative sample e.g., general population sample should not exclude subgroups	27 (32)
All subjects aged 50 or over at follow-up	37 (44)
Sample size calculation given or $\geq$20 subjects per variable included in multivariate analysis	75 (88)
Appropriate and validated outcome measure	69 (81)
Two prognostic factors used from each of at least two domains of knee-related, general health and demographic[9,10]	33 (39)
Length of follow-up $\geq$36 months	45 (53)
Baseline response $\geq$70%	19 (22)
Loss and dropout at follow-up $<$25%	17 (20)
Adequate description and discussion of drop-outs	22 (26)
Appropriate analysis	73 (86)
Adjusted results given with CI (if appropriate)	75 (88)

META-ANALYSIS

For risk factors that had a consistent definition and where results were reported in a similar fashion across several studies, a meta-analysis was performed to obtain a pooled estimate of the size of the risk factor.

The Cochran *Q* statistic was derived to assess the presence of heterogeneity in studies assessing the same risk factor. A small number of studies considered each risk factor, hence we assumed heterogeneity up to a two-sided *P*-value of 0.05. Also, the I^2 statistic was computed, representing the proportion of total variation in study estimates that is accounted for by heterogeneity[12]. For risk factors where studies could be considered homogenous, meta-analysis using a fixed-effects (no significant inter-study variation) model based on the inverse variance approach was used. Otherwise the random-effects approach of DerSimonian and Laird[13] was employed. A pooled effect size weighted by the quality score was also determined.

Where random-effects meta-analysis was performed, possible sources of heterogeneity in effect sizes were investigated. The log odds ratio for the study was used as the dependent variable and study characteristics entered as the independent variables in separate meta-regressions. Sources of potential heterogeneity explored were quality score, recentness of publication (defined as year of publication pre-2001 or 2001 onwards), study type (prospective cohort vs case–control/retrospective) and definition of knee OA (radiographic vs symptomatic or symptomatic + radiographic). A sensitivity analysis was then performed by stratifying the meta-analysis by study design (cohort or case–control) to further assess the impact of type of design on effect sizes.

For body mass index (BMI), normal BMI was defined as <25, overweight as 25–30 and obesity as >30. For studies where BMI was analysed on the continuous scale, effect sizes were converted to be per five units to reflect overweight BMI of 28 against a normal BMI of 23, and per 10 units to reflect an obese BMI of 33 against a normal BMI. In a further analysis where possible, overweight and obese categories were combined weighting for the category size.

For smoking, pooled odds ratio (ORs) were based on current smoking against never smoked, or ever smoked against never if no separation was made between current and ex-smoking. Where results were analysed by heaviness of smoking, the results for light/moderate smoking compared to none were used.

Funnel plots, which plot the log of the effect size against the log standard error of the effect size, were used to assess publication bias. Symmetry of funnel plots was tested using Egger's test[14], establishing statistical significance at $P < 0.05$.

Results

STUDY CHARACTERISTICS

Two thousand two hundred and thirty three articles were identified using our search strategy, 1780 were excluded at abstract stage. Finally, 85 papers were included in this review (see Appendix). The intraclass correlation coefficient showed satisfactory reliability between the first and second reviewers (0.66; 95% CI 0.52, 0.77). The mean quality score was 8.08 (S.D. 2.18, range 2–14). Fifty six (66%) studies scored ≥8, but only 19 (22%) scored ≥10. There was no difference in quality score between those studies published more recently (2001 onwards) to those published earlier (mean difference 0.3; 95% CI −0.6, 1.3). Table II details the number of studies meeting each criterion. Baseline response of at least 70% (22% of studies achieved this criteria), loss to follow-up of less than 25% (20%) and adequate discussion of dropout (26%) were the main areas of poor quality. 86% of all prospective studies had a follow up greater than 36 months.

Forty two (49%) studies were prospective studies. Fifty one (60%) studies used a radiological definition of knee OA as their outcome, 8 (9%) used only a symptomatic definition of knee OA and the remainder used a combination of the two. Thirty two (38%) studies were from the USA, 45 (53%) from Europe and the rest from elsewhere.

STUDY RESULTS

For five factors (BMI, previous knee injury, smoking, gender, and Heberden's nodes/hand OA), a pooled OR was determined. All the risk factors showed substantial heterogeneity between studies, hence random-effects models rather than fixed effects were used to pool the ORs across all studies. In each case, the pooled OR weighted for quality score was similar, though generally with narrower confidence intervals, to that for the random-effects model weighted by the inverse variance method (Table III). The latter is reported below.

As judged by Egger's test, there was no evidence of publication bias being present at 5% significance level for any of the factors apart from gender ($P = 0.022$).

BMI

Thirty six papers reported on BMI[15–50]. Nine studies combined overweight or obesity and 11 gave results on a continuous scale. Three papers were from the same study so only one[22] of these was included in the meta-analysis. All studies assessing BMI showed being overweight and obese to be risk factors for future knee problems, although the size of the effects varied ($I^2 = 99\%$ for overweight; 97% for obesity). The random-effects pooled odds ratio for being overweight compared to normal weight was 2.18 (95% CI 1.86, 2.55); for obesity compared to normal weight it was 2.63 (2.28, 3.05); and for overweight or obese compared to normal weight it was 2.96 (2.56, 3.43). One study also found that increasing from normal to overweight during adult life may give a slightly higher risk of developing knee OA leading to arthroplasty than being constantly overweight during adult life[36]. Another study found that among women at an elevated risk of OA due to high BMI, weight loss decreased this risk substantially[34].

Figure 1 shows the variation in odds ratios across studies for obesity. For studies reporting gender-specific results, effect sizes tended to be slightly larger for females than males whilst the meta-regression results suggested some evidence that effects of obesity were slightly larger when the knee OA was defined radiographically ($P = 0.05$), and for case–control studies ($P = 0.008$). Restricting the meta-analysis to cohort studies only led to a slight reduction in the pooled effect sizes but no change in overall conclusions.

Three further studies found highest body weight in the past to be a significant risk factor for knee OA, however the studies lacked height adjustments hence were excluded from the meta-analysis[51,52,54].

PREVIOUS KNEE INJURY

Of the 16 studies investigating previous knee injury, all but two concluded that it was an important risk factor[19–23,25,26,30,31,33,48,51–55]. There was a large amount of heterogeneity ($I^2 = 88\%$) in study effect size estimates and the random-effects pooled OR was 3.86 (95% CI 2.61, 5.70). Meta-regression did not show any factors which explained any of the heterogeneity. Performing the meta-analysis on cohort studies only gave a slightly lower pooled OR: 3.17 (95% CI 1.67, 6.03; $n = 8$).

SMOKING

The categorisation of smoking varied and where possible currently smoking vs never was used as the contrast of interest. There was mixed evidence for smoking[15,18,19,22,27,30,33,37,40,43,44,48,50,54,56–59], with the 18

Table III
Pooled odds ratios for most commonly investigated risk factors

Factor	No. of papers	No. of subjects*	*P*-value for heterogeneity	I^2	Random-effects pooled OR (95% CI)	Pooled OR weighted by score (95% CI)
BMI						
Overweight						
Case–control	8	8702	<0.001	96.1%	2.22 (1.78, 2.77)	2.59 (2.23, 3.00)
Cohort	15	630,824	<0.001	98.9%	2.13 (1.71, 2.64)	1.96 (1.79, 2.14)
Overall	23	639,526	<0.001	98.5%	2.18 (1.86, 2.55)	2.13 (1.98, 2.30)
Obese						
Case–control	5	4530	<0.001	92.9%	4.25 (3.15, 5.73)	5.54 (4.34, 7.09)
Cohort	12	342,258	<0.001	95.1%	2.22 (1.91, 2.57)	2.37 (2.13, 2.64)
Overall	17	346,788	<0.001	96.7%	2.63 (2.28, 3.05)	2.89 (2.61, 3.20)
Overweight/obese						
Case–control	10	6751	<0.001	93.3%	3.79 (3.02, 4.75)	4.56 (3.72, 5.59)
Cohort	16	346,330	<0.001	98.9%	2.60 (2.14, 3.17)	2.66 (2.26, 3.17)
Overall	26	353,081	<0.001	98.6%	2.96 (2.56, 3.43)	3.16 (2.78, 3.59)
Previous knee injury						
Case–control	8	6313	<0.001	83.9%	4.58 (2.71, 7.74)	4.70 (3.47, 6.36)
Cohort	8	10,433	<0.001	91.1%	3.17 (1.67, 6.03)	2.76 (1.82, 4.20)
Overall	16	16,746	<0.001	87.8%	3.86 (2.61, 5.70)	3.48 (2.65, 4.57)
Smoking						
Case–control	8	7047	0.805	0%	0.60 (0.51, 0.71)	0.66 (0.53, 0.83)
Cohort	10	337,700	0.161	30.9%	0.97 (0.88, 1.07)	0.98 (0.86, 1.13)
Overall	18	344,747	<0.001	60.9%	0.84 (0.74, 0.95)	0.84 (0.74, 0.94)
Gender						
Case–control	2	2488	0.454	0%	1.86 (1.35, 2.56)	1.83 (1.33, 2.52)
Cohort	6	7865	<0.001	88.5%	1.85 (1.23, 2.77)	1.93 (1.61, 2.32)
Overall	8	10,353	<0.001	85.3%	1.84 (1.32, 2.55)	1.91 (1.63, 2.24)
Heberden's nodes						
Case–control	4	3207	0.001	81.6%	1.41 (0.80, 2.47)	1.40 (1.08, 1.81)
Cohort	4	2902	0.176	39.3%	1.55 (1.01, 2.40)	1.71 (1.14, 2.54)
Overall	8	6109	0.003	67.1%	1.49 (1.05, 2.10)	1.58 (1.21, 2.05)

*There was a large prospective study[40], which included 320,192 subjects in the analysis, hence difference between number of patients in case–control and cohort studies for certain factors is increased.

studies varying between having no effect on future knee problems and a protective effect (Fig. 2).

The pooled OR suggested a small protective effect of smoking (0.84; 95% CI 0.74, 0.95). Meta-regression suggested case–control studies ($P < 0.001$) and studies with knee pain defined radiographically ($P = 0.003$) showed a greater protective effect.

However, ignoring case–control studies, the pooled OR was 0.97 (95% CI 0.88, 1.07; $n = 10$), suggesting that no protective effect of smoking was found when restricting the analysis to cohort studies only.

GENDER

Gender was often used as an adjustment factor and gender-specific effect estimates were rarely reported. Therefore, some caution is needed as this review of gender as a risk factor necessarily does not include all studies which used it. However, in the nine studies that reported the gender effect size[17,22–24,43,45,60–62], there was general agreement that females were more likely to develop knee problems than males (pooled OR 1.84, 95% CI 1.32, 2.55). One paper was excluded from the meta-analysis[60], in order to avoid duplication of papers from the same study. This was consistent with higher incidence rates of knee OA in women than men in a study set in primarily blue-collar workers in the USA[63].

Results remained almost unchanged when the meta-analysis was performed on cohort studies only.

HEBERDEN'S NODES/HAND OA

Five of the eight studies evaluating Heberden's nodes and/or hand OA suggested this was a risk factor for future knee problems[18,22,25,26,30,33,45,64]. The pooled OR was 1.49 (95% CI 1.05, 2.10) and no factors were identified in the meta-regression that could account for substantial heterogeneity ($I^2 = 67\%$).

Including cohort studies only in the meta-analysis did not change the findings.

AGE

It was not possible to pool the effect sizes for age due to different categorisations of age-groups and differing age ranges between the 15 studies which reported results[17,19,23,24,27,35,37,43,45,50,57,61–63,65]. A number of studies assumed the effect of age on knee pain was linear. As with gender, a number of studies adjusted for age without giving the age effect size. All studies showed increasing age to be a risk factor although studies tended not to explore the very old. One study which detailed age-specific incidence rates of knee OA showed increased incidence

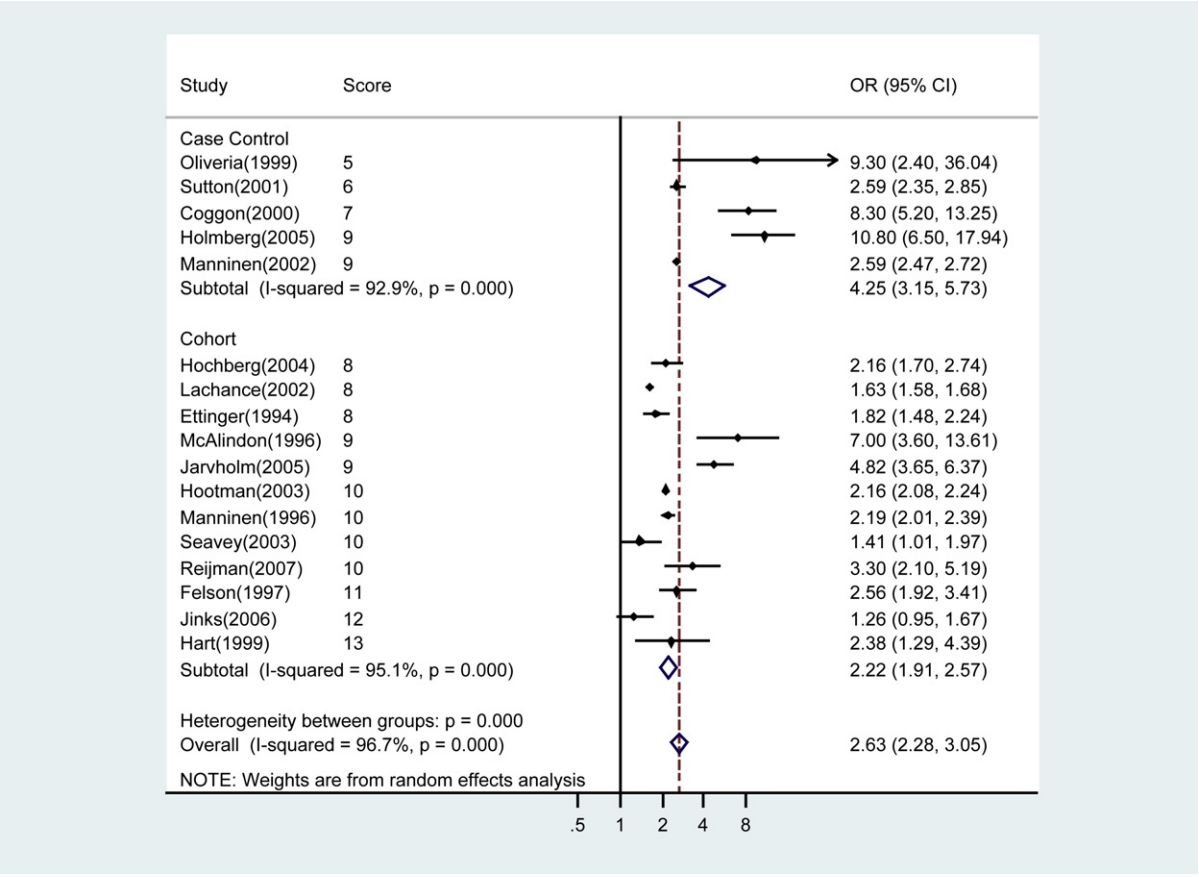


Fig. 1. Forest plot of effect of obesity on onset of knee OA.

with age before levelling off around age 80, although the number of subjects were small in the older age group[63].

OCCUPATIONAL ACTIVITIES

Five papers looked at the effect of general occupational physical workload/stress and gave mixed results[20,43,52,57,66]. These were generally case–control studies, although the few prospective studies provided similar findings.

Specific activities examined in the studies suggested from limited evidence a protective effect of sitting (>2 h per day)[25,42,45,51,66]. There was some evidence of an increased risk for excessive kneeling[18,20,25,31,45,51,66–68], squatting[25,51,66–68], climbing steps[20,25,51,54,66,67], standing (>2 h per day)[20,25,45,51,66] and lifting[18,20,25,45,51,54]. One paper investigated effects of jobs requiring knee bending and found it to be a significant risk factor[69]. There was little evidence of an association of future knee problems with either excessive driving[20,25,51] or walking[20,21,25,30,33,45,51,54]. There was some evidence that specific occupations were risk factors for knee pain, for example, farming[66,70–72], construction work[66,72] and physical education teaching[73].

PHYSICAL ACTIVITY/EXERCISE

Whilst many studies examined physical activity, running and exercise, definitions varied[19–22,26,27,30,33,35,45,57,74–83]. This led to mixed evidence on its effect. Higher quality scores studies, which tended to be cohort studies, generally suggested an increased risk of knee OA in those who exercise more regularly or intensely. Studies looking specifically at sportsmen/women (e.g., soccer players, weight lifters) reported a higher risk in these groups[31,65,83–86], with one small lower quality study being the exception[87].

OESTROGEN USE

Six studies suggested oestrogen use to be protective, though non-significant, factor[18,30,50,59,88,89]. One case–control study suggested it was a reasonably strong risk factor[44].

ORAL CONTRACEPTIVES

The three studies examining oral contraceptive use indicated there was unlikely to be an association with onset of knee OA[18,44,59].

BONE MINERAL DENSITY (BMD)

There was a consistent strong association of increased BMD being related to onset of knee OA in the three studies that investigated this risk factor in women[92–94].

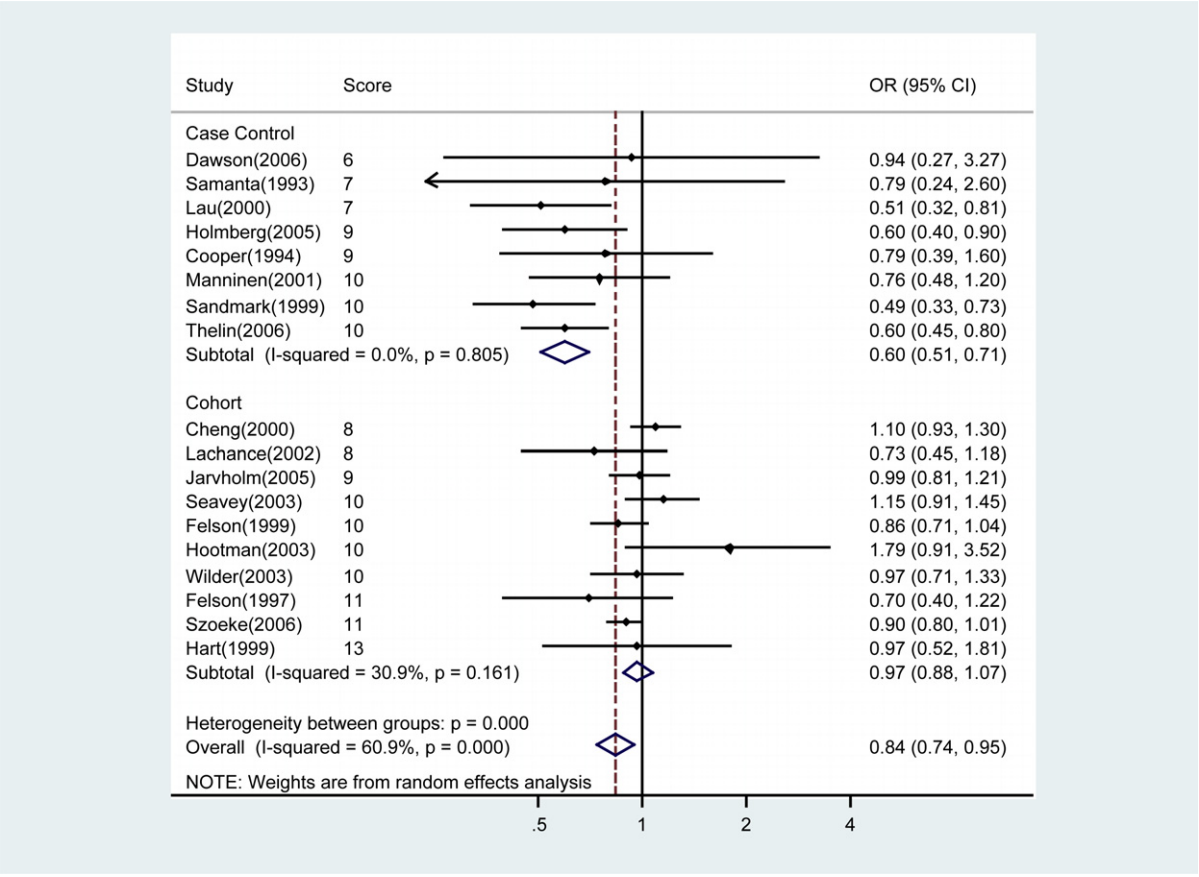


Fig. 2. Forest plot of effect of smoking on onset of knee OA.

HYSTERECTOMY

The three studies which evaluated hysterectomy as a risk factor were consistent in suggesting there may be a modest association of hysterectomy with onset of knee OA, although all three results were non-significant[30,59,90].

HYPERTENSION

There was mixed evidence of the association of hypertension with onset of knee OA with two cohort studies investigating it showing a significant positive association[39,43] and one case–control study revealing no significant effect of hypertension[33].

DEPRESSION/MENTAL HEALTH

There is some limited evidence from two studies that depression or poor mental health is a risk factor for onset of symptomatic knee OA[43,91].

MENISCECTOMY

Three related studies comparing those who had undergone meniscetomy up to 22 years previously to a control group showed an increased risk of knee OA in the operated group[95–97].

OTHER FACTORS

Other, albeit high (score ≥ 9) quality studies evaluated hypermobility (protective)[98], education (no association)[43] and social class (professional ranks had higher risk)[30]. However, more evidence is needed for all these factors. Independent of BMD, a study in women suggested a prior fracture led to a decreased risk of onset of knee OA[94]. People with index finger shorter than the ring finger had an increased risk of knee OA in one further study[99].

Discussion

This systematic review and meta-analysis indicates increased BMI, previous knee injury, presence of Heberden's nodes/hand OA, female gender, older age, intensive physical activity, certain physical occupational activities (e.g., kneeling, squatting) and increased BMD to be risk factors for the onset of knee OA in older adults. There is some limited evidence to suggest poor mental health and hysterectomy may also be linked to onset of knee OA. Oestrogen use generally appeared to have protective, though insignificant, effect on OA onset. Sitting for more than 2 h a day seems to decrease the risk of incident knee OA. However, there were a number of factors for which the evidence is too limited to be able to ascertain its strength of association with onset of knee OA.

Pooling results from case–control and cohort studies suggested smoking may decrease the risk of incident knee OA. However, this result was not apparent when restricting the analysis to cohort studies and, hence, may not be a true effect. Some studies have suggested that smoking may delay cartilage destruction[22,56]. However, the possibility of a protective effect of smoking needs to be investigated further as there appears to be no current clear biological explanation.

There was a suggestion of some publication bias for gender, therefore some caution is needed on the conclusions for gender. A number of studies adjusted for gender without reporting the relationship of gender to onset of knee OA and it may be that these were less likely to show an effect of gender.

Whilst certain factors have been extensively reviewed (e.g., BMI), more longitudinal studies are needed to investigate the association of comorbid, occupational, and socio-demographic factors with future knee OA. In our recent prospective study, published after the final date for inclusion into this review, we also found depression to be a risk factor for onset of knee pain[12].

The quality of studies could be improved in future by paying particular attention to maximising response and follow-up rates and ensuring potential confounders (such as the factors identified here) are also measured.

We have not distinguished between knee pain and knee OA as in the older age group the majority of knee pain is attributed to OA. However there is evidence to suggest that the effects of obesity and smoking are greater when knee OA is defined radiographically.

Comparison of our findings with that investigating risk factors for onset of hip OA suggest that risk factors are similar, with obesity, and certain occupational and sporting activities also found to be related to onset of hip OA, and oestrogen possibly showing a protective effect[8].

Our review does have some limitations. Our quality scoring tool was developed by combining two previous methods, and has not been rigorously tested. However, we did find satisfactory reliability between the first and second reviewers. Also it weights each quality item equally which may not be appropriate. However, it is of interest to note that the pooled ORs weighted by quality score were similar to random-effects pooled ORs weighted by inverse variance. Part of our future methodological work will involve methods of weighting by individual quality items as well as methods weighting for inverse of the variances and quality scores jointly.

Our meta-analysis was limited by the small number of studies for most risk factors. Similarly, detection of sources of heterogeneity was hindered by the same problem. This led to a lack of power for conducting analyses to study sources of heterogeneity and therefore can only give a guide to reasons for heterogeneity.

Cohort and case–control studies were generally consistent in their direction of findings (except for smoking), although case–control studies tended to give larger effect sizes.

We have not assessed in detail the effect of different definitions of the risk factors across the studies, simply due to the extent of variability and the small number of studies investigating each risk factor. This was particularly true for physical activity and so we have not attempted to perform a meta-analysis for this potential risk factor. We have also not allowed for different follow-up periods again because the prospective studies varied in their follow-up period, and the case–control studies had longer, but also varied recall periods. The degree of adjustment for confounding variables also varied from study to study. Hence the pooled risk estimates calculated in the meta-analysis here may include some confounding of the true relationship between risk factors and knee OA. An example of this may be the relationship of smoking status with BMI, as current smoking has been shown to be related to a lower BMI[100]. Not all studies examining smoking reported adjusting for BMI.

It would therefore be of interest to investigate any evidence of interactions between risk factors, for example effects of smoking in obese vs non-obese individuals, however due to insufficient number of studies reporting such detailed findings, it was not possible to pursue this.

We only searched for English language articles and restricted our search of risk factors to those which are patient-determined, socio-demographic, previous knee events or comorbid conditions. That is, those factors which are more easily identifiable in the general population. This excludes clinical factors such as cartilage loss and genetic markers.

This review is concerned with onset of knee OA, and it is possible that the risk factors for progression are different. Belo *et al.* performed a systematic review of progression of knee OA using 37 studies published up to the end of 2003[101]. In contrast to this review, they concluded that gender and previous knee injury were not related to progression. Their main determinants were generalised OA and level of hyaluronic acid. Van Dijk *et al.* suggested that BMI and older age were risk factors for worsening functioning in knee OA, and no association was concluded for gender, physical activity, and comorbidity[10].

The implications of this review are that there are factors which are easily identifiable and therefore patients with these risk factors can be targeted for prevention of disabling knee pain. In particular, targeting obesity, those with knee injury and those with hand OA would be beneficial. Treatment of comorbidities like depression and hypertension may also reduce risk of future knee problems.

Conflict of interest

There is no conflict of interest and the paper has not been submitted elsewhere.

Acknowledgements

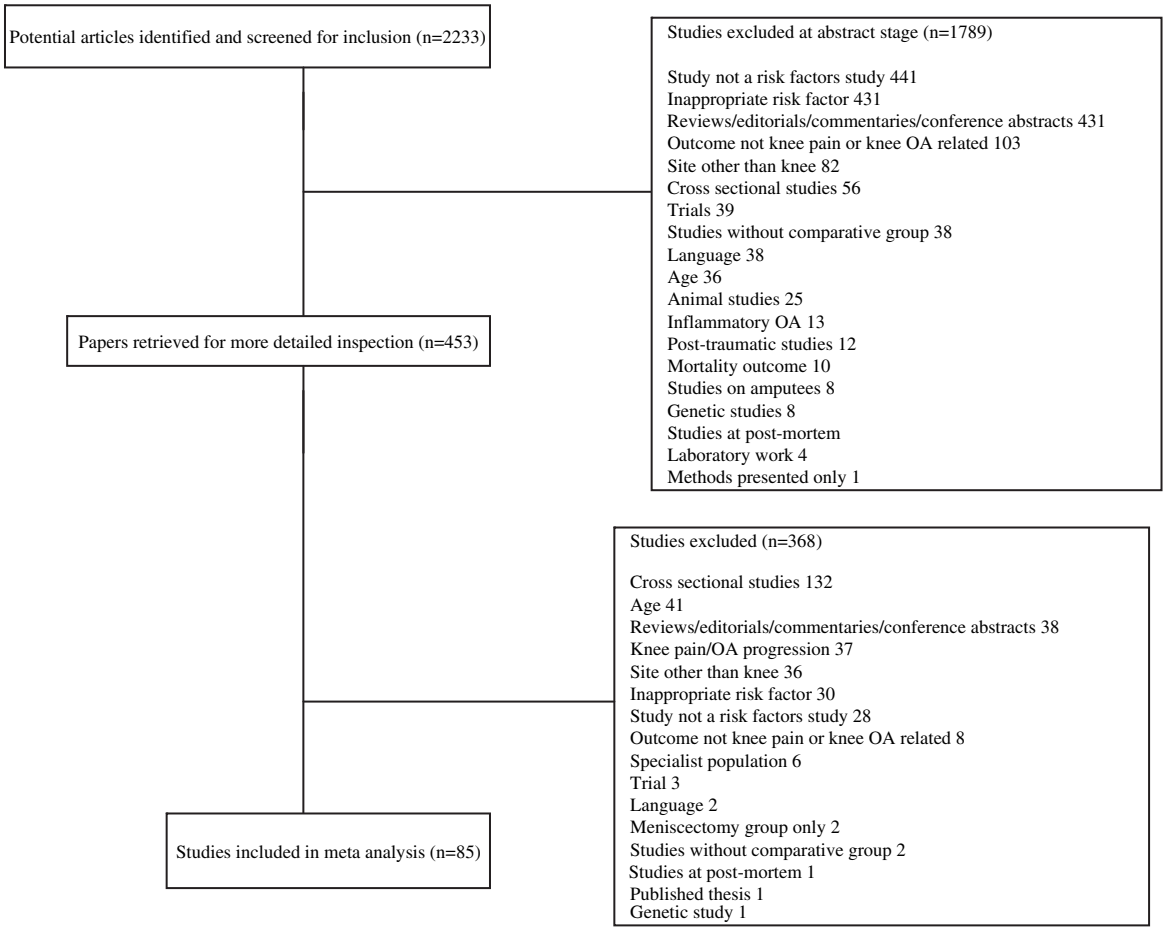
The study was funded by a UK Department of Health Public Health Initiative, which had no involvement in the study design, collection, analysis and interpretation of data, writing of the manuscript or in the decision to submit the manuscript for publication. We would like to thank Professor Peter Croft and Dr Mark Porcheret for their comments on a draft version of the paper.

Supplementary material

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.joca.2009.08.010.

Appendix

Flow chart for study selection



References

1. Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, *et al*. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. Ann Rheum Dis 1998;57: 649–55.
2. Thomas E, Peat G, Harris L, Wilkie R, Croft PR. The prevalence of pain and pain interference in a general population of older adults: cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). Pain 2004;110:361–8.
3. Jinks C, Jordan K, Ong BN, Croft P. A brief screening tool for knee pain in primary care (KNEST). 2. Results from a survey in the general population aged 50 and over. Rheumatology (Oxford) 2004;43:55–61.
4. Jinks C, Jordan K, Croft P. Osteoarthritis as a public health problem: the impact of developing knee pain on physical function in adults living in the community: (KNEST 3). Rheumatology 2007;46:877–81.
5. Donald IP, Foy C. A longitudinal study of joint pain in older people. Rheumatology (Oxford) 2004;43:1256–60.
6. Bierma-Zeinstra SM, Koes BW. Risk factors and prognostic factors of hip and knee osteoarthritis. Nat Clin Pract Rheumatol 2007;3:78–85.
7. Mallen CD, Peat G, Thomas E, Dunn KM, Croft PR. Prognostic factors for musculoskeletal pain in primary care: a systematic review. Br J Gen Pract 2007;57:655–61.
8. Van Dijk GM, Dekker J, Veenhof C, van den Ende CH. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. Arthritis Rheum 2006;55:779–85.
9. Jordan K, Jinks C, Croft P. A prospective study of the consulting behaviour of older people with knee pain. Br J Gen Pract 2006;56: 269–76.
10. Jinks C, Jordan KP, Blagojevic M, Croft P. Predictors of onset and progression of knee pain in adults living in the community. A prospective study. Rheumatology (Oxford) 2008;47:368–74.
11. Shrout PE, Fleiss JL. Intraclass correlations – uses in assessing rater reliability. Psychol Bull 1979;86:420–8.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
15. Holmberg S, Thelin A, Thelin N. Knee osteoarthritis and body mass index: a population-based case–control study. Scand J Rheumatol 2005;34:59–64.
16. Harms S, Larson R, Sahmoun AE, Beal JR. Obesity increases the likelihood of total joint replacement surgery among younger adults. Int Orthop 2007;31:23–6.
17. Hochberg M, Lethbridge C, Tobin J. Bone mineral density and osteoarthritis: data from the Baltimore Longitudinal Study of Aging. Osteoarthritis Cartilage 2004;12:S45–8.
18. 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.

19. Hootman J, Macera C, Helmick C, Blair S. Influence of physical activity-related joint stress on the risk of self-reported hip/knee osteoarthritis: a new method to quantify physical activity. Prev Med 2003;36: 636–44.
20. Manninen P, Heliövaara M, Riihimäki H, Suoma I. Physical workload and the risk of severe knee osteoarthritis. Scand J Work Environ Health 2002;28:25–32.
21. Sutton AJ, Muir KR, Mockett S, Fentem P. A case–control study to investigate the relation between low and moderate levels of physical activity and osteoarthritis of the knee using data collected as part of the Allied Dunbar National Fitness Survey. Ann Rheum Dis 2001;60: 756–64.
22. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, *et al*. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997;40:728–33.
23. McAlindon T, Zhang Y, Hannan M, Naimark A, Weissman B, Castelli W, *et al*. Are risk factors for patellofemoral and tibiofemoral knee osteoarthritis different? J Rheumatol 1996;23:332–7.
24. Manninen P, Riihimäki H, Heliövaara M, Mäkelä P. Overweight, gender and knee osteoarthritis. Int J Obes Relat Metab Disord 1996;20: 595–7.
25. 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.
26. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, *et al*. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995–1000.
27. Cheng Y, Macera CA, Davis DR, Ainsworth BE, Troped PJ, Blair SN. Physical activity and self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor? J Clin Epidemiol 2000;53:315–22.
28. Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. Am J Med 1999;107:542–8.
29. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology (Cambridge, Mass) 1999;10:161–6.
30. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum 1999;42:17–24.
31. Kujala UM, Kettunen J, Paananen H, Aalto T, Battié MC, Impivaara O, *et al*. Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. Arthritis Rheum 1995;38:539–46.
32. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. Ann Rheum Dis 1994;53:565–8.
33. Cooper C, McAlindon T, Snow S, Vines K, Young P, Kirwan J, *et al*. Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: differences between medial tibiofemoral and patellofemoral disease. J Rheumatol 1994;21:307–13.
34. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med 1992;116:535–9.
35. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med 1988;109:18–24.
36. Manninen P, Riihimaki H, Heliövaara M, Suomalainen O. Weight changes and the risk of knee osteoarthritis requiring arthroplasty. Ann Rheum Dis 2004;63(11):1434–7.
37. Lachance L, Sowers MF, Jamadar D, Hochberg M. The natural history of emergent osteoarthritis of the knee in women. Osteoarthritis Cartilage 2002;10:849–54.
38. Shiozaki H, Koga Y, Omori G, Tamaki M. Obesity and osteoarthritis of the knee in women: results from the Matsudai Knee Osteoarthritis Survey. Knee 1999;6:189–92.
39. Ettinger WH, Davis MA, Neuhaus JM, Mallon KP. Long-term physical functioning in persons with knee osteoarthritis from NHANES I: effects of comorbid medical conditions. J Clin Epidemiol 1994;47:809–15.
40. Järvholm B, Lewold S, Malchau H, Vingard E. Age, bodyweight, smoking habits and the risk of severe osteoarthritis in the hip and knee in men. Eur J Epidemiol 2005;20:537–42.
41. Kohatsu ND, Schurman DJ. Risk factors for the development of osteoarthrosis of the knee. Clin Orthop Relat Res 1990;261:242–6.
42. Sahlstrom A, Montgomery F. Risk analysis of occupational factors influencing the development of arthrosis of the knee. Eur J Epidemiol 1997;13:675–9.
43. Seavey WG, Kurata JH, Cohen RD. Risk factors for incident self-reported arthritis in a 20 year followup of the Alameda County Study Cohort. J Rheumatol 2003;30:2103–11.
44. Sandmark H, Hogstedt C, Lewold S, Vingσrd E. Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. Ann Rheum Dis 1999;58:151–5.
45. D'Souza JC, Werner AW, Keyserling WM, Gillespie B, Rabourn R, Ulin S, *et al*. Occupational activities and knee osteoarthritis: an analysis of the third National Health and Nutrition Examination Survey (NHANES III) using expert ratings of job categories. Am J Ind Med 2008;51:37–46.
46. Liu B, Balkwill A, Banks E, Cooper C, Green J, Beral V. Relationship of height, weight and body mass index to the risk of hip and knee replacements in middle-aged women. Rheumatology 2007; 46:861–7.
47. Reijman M, Pols HAP, Bergink AP, Hazes JMW, Belo JN, Lievense A, *et al*. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis 2007;66:158–62.
48. Thelin N, Holmberg S, Thelin A. Knee injuries account for the sports-related increased risk of knee osteoarthritis. Scand J Med Sci Sports 2006;16:329–33.
49. Jinks C, Jordan K, Croft P. Disabling knee pain – another consequence of obesity: results from a prospective cohort study. BMC Public Health 2006;6:258.
50. Szoeke CE, Cicuttini FM, Guthrie JR, Clark MS, Dennerstein L. Factors affecting the prevalence of osteoarthritis in healthy middle-aged women: data from the longitudinal Melbourne Women's Midlife Health Project. Bone 2006;39:1149–55.
51. Yoshimura N, Nishioka S, Kinoshita H, Hori N, Nishioka T, Ryujin M, *et al*. Risk factors for knee osteoarthritis in Japanese women: heavy weight, previous joint injuries, and occupational activities. J Rheumatol 2004;31:157–62.
52. Yoshimura N, Kinoshita H, Hori N, Nishioka T, Ryujin M, Mantani Y, *et al*. Risk factors for knee osteoarthritis in Japanese men: a case–control study. Mod Rheumatol 2006;16:24–9.
53. Wilder FV, Hall BJ, Barrett Jr JP, Lemrow NB. History of acute knee injury and osteoarthritis of the knee: a prospective epidemiological assessment. The Clearwater Osteoarthritis Study. Osteoarthritis Cartilage 2002;10:611–6.
54. 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.
55. Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. Ann Intern Med 2000;133:321–8.
56. Wilder FV, Hall BJ, Barrett JP. Smoking and osteoarthritis: is there an association? The Clearwater Osteoarthritis Study. Osteoarthritis Cartilage 2003;11:29–35.
57. Manninen P, Riihimaki H, Heliovaara M, Suomalainen O. Physical exercise and risk of severe knee osteoarthritis requiring arthroplasty. Rheumatology (Oxford) 2001;40:432–7.
58. Felson DT, Anderson JJ, Naimark A, Hannan MT, Kannel WB, Meenan R. Does smoking protect against osteoarthritis? Arthritis Rheum 1989;32:166–72.
59. Samanta A, Jones A, Regan M, Wilson S, Doherty M. Is osteoarthritis in women affected by hormonal changes or smoking? Br J Rheumatol 1993;32:366–70.
60. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, *et al*. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1995;38:1500–5.
61. Borrero S, Kwoh CK, Sartorius J, Ibrahim SA. Brief report: gender and total knee/hip arthroplasty utilization rate in the VA system. J Gen Intern Med 2006;21(Suppl 3):S54–7.
62. Soeroso J, Dans LF, Amarillo ML, Santoso GH, Kalim H. Risk factors of symptomatic osteoarthritis of the knee at a hospital in Indonesia. APLAR J Rheumatol 2005;8:106–13.
63. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 1995;38: 1134–41.
64. Dahaghin S, Bierma Z, Reijman M, Pols HAP, Hazes JMW, Koes BW. Does hand osteoarthritis predict future hip or knee osteoarthritis? Arthritis Rheum 2005;52:3520–7.
65. Deacon A, Bennell K, Kiss ZS, Crossley K, Brukner P. Osteoarthritis of the knee in retired, elite Australian Rules footballers. Med J Aust 1997; 166:187–90.
66. Sandmark H, Hogstedt C, Vingσrd 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.
67. Cooper C, McAlindon T, Coggon D, Egger P, Dieppe P. Occupational activity and osteoarthritis of the knee. Ann Rheum Dis 1994;53:90–3.
68. Tangtrakulwanich B, Chongsuvivatwong V, Geater AF. Associations between floor activities and knee osteoarthritis in Thai Buddhist monks: the Songkhla study. J Med Assoc Thailand 2006;89:1902–8.
69. Felson DT, Hannan MT, Naimark A, Berkeley J, Gordon G, Wilson PW, *et al*. Occupational physical demands, knee bending, and knee osteoarthritis: results from the Framingham Study. J Rheumatol 1991;18: 1587–92.

70. Holmberg S, Thelin A, Thelin N. Is there an increased risk of knee osteoarthritis among farmers? A population-based case–control study. Int Arch Occup Environ Health 2004;77:345–50.
71. Holmberg S, Stiernström E, Thelin A, Svärdsudd K. Musculoskeletal symptoms among farmers and non-farmers: a population-based study. Int J Occup Environ Health 2002;8:339–45.
72. Vingσrd E, Alfredsson L, Goldie I, Hogstedt C. Occupation and osteoarthrosis of the hip and knee: a register-based cohort study. Int J Epidemiol 1991;20:1025–31.
73. Sandmark H. Musculoskeletal dysfunction in physical education teachers. Occup Environ Med 2000;57:673–7.
74. Felson DT, Nui J, Clancy M, Sack B, Aliabadi P, Zhang Y. Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: the Framingham Study. Arthritis Rheum 2007;57:6–12.
75. Konradsen L, Hansen EM, Sondergaard L. Long distance running and osteoarthrosis. Am J Sports Med 1990;18:379–81.
76. Panush RS, Schmidt C, Caldwell JR, Edwards NL, Longley S, Yonker R, *et al*. Is running associated with degenerative joint disease? J Am Med Assoc 1986;255:1152–4.
77. Sohn RS, Micheli LJ. The effect of running on the pathogenesis of osteoarthritis of the hips and knees. Clin Orthop Relat Res 1985;198: 106–9.
78. Kujala UM, Sarna S, Kaprio J, Koskenvuo M, Karjalainen J. Heart attacks and lower-limb function in master endurance athletes. Med Sci Sports Exerc 1999;31:1041–6.
79. Rogers LQ, Macera CA, Hootman JM, Ainsworth BE, Blairi SN. The association between joint stress from physical activity and self-reported osteoarthritis: an analysis of the Cooper Clinic data. Osteoarthritis Cartilage 2002;10:617–22.
80. McAlindon TE, Wilson PW, Aliabadi P, Weissman B, Felson DT. Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham Study. Am J Med 1999; 106:151–7.
81. Imeokparia RL, Barrett JP, Arrieta MI, Leaverton PE, Wilson AA, Hall BJ, *et al*. Physical activity as a risk factor for osteoarthritis of the knee. Ann Epidemiol 1994;4:221–30.
82. Hannan MT, Felson DT, Anderson JJ, Naimark A. Habitual physical activity is not associated with knee osteoarthritis: the Framingham Study. J Rheumatol 1993;20:704–9.
83. Sandmark H, Vingσrd E. Sports and risk for severe osteoarthrosis of the knee. Scand J Med Sci Sports 1999;9:279–84.
84. Spector TD, Harris PA, Hart DJ, Cicuttini FM, Nandra D, Etherington J, *et al*. Risk of osteoarthritis associated with long-term weight-bearing sports: a radiologic survey of the hips and knees in female ex-athletes and population controls. Arthritis Rheum 1996;39:988–95.
85. Roos H, Lindberg H, GΣrdsell P, Lohmander LS, Wingstrand H. The prevalence of gonarthrosis and its relation to meniscectomy in former soccer players. Am J Sports Med 1994;22:219–22.
86. Kettunen JA, Kujala UM, Kaprio J, Koskenvuo M, Sarna S. Lower-limb function among former elite male athletes. Am J Sports Med 2001;29:2–8.
87. Klunder KB, Rud B, Hansen J. Osteoarthritis of the hip and knee joint in retired football players. Acta Orthop Scand 1980;51:925–7.
88. Hannan MT, Felson DT, Anderson JJ, Naimark A, Kannel WB. Estrogen use and radiographic osteoarthritis of the knee in women. The Framingham Osteoarthritis Study. Arthritis Rheum 1990;33:525–32.
89. Zhang YQ, McAlindon TE, Hannan MT, Chaisson CE, Klein R, Wilson PWF, *et al*. Estrogen replacement therapy and worsening of radiographic knee osteoarthritis. Arthritis Rheum 1998;41:1867–73.
90. Spector TD, Hart DJ, Brown P, Almeyda J, Dacre JE, Doyle DV, *et al*. Frequency of osteoarthritis in hysterectomized women. J Rheumatol 1991;18:1877–83.
91. Palmer KT, Reading I, Calnan M, Linaker C, Coggon D. Does knee pain in the community behave like a regional pain syndrome? Prospective cohort study of incidence and persistence. Ann Rheum Dis 2007;66:1190–4.
92. Zhang Y, Hannan MT, Chaisson CE, McAlindon TE, Evans SR, Aliabadi P, *et al*. Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. J Rheumatol 2000;27:1032–7.
93. Bergink AP, Uitterlinden AG, van L, Hofman A, Verhaar J, Pols HAP. Bone mineral density and vertebral fracture history are associated with incident and progressive radiographic knee osteoarthritis in elderly men and women: the Rotterdam Study. Bone 2005;37:446–56.
94. Hart DJ, Cronin C, Daniels M, Worthy T, Doyle DV, Spector TD. The relationship of bone density and fracture to incident and progressive radiographic osteoarthritis of the knee: the Chingford Study. Arthritis Rheum 2002;46:92–9.
95. Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. Arthritis Rheum 2004;50:2811–9.
96. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. Arthritis Rheum 2003;48:2178–87.
97. Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. Arthritis Rheum 1998;41:687–93.
98. Dolan A, Hart D, Doyle DV, Grahame R, Spector T. The relationship of joint hypermobility, bone mineral density, and osteoarthritis in the general population: the Chingford Study. J Rheumatol 2003;30:799–803.
99. Zhang W, Robertson J, Doherty S, Liu JJ, Maciewicz RA, Muir KR, *et al*. Index to ring finger length ratio and the risk of osteoarthritis. Arthritis Rheum 2007;58:137–44.
100. Molarius A, Seidell JC, Kuulasmaa K, Dobson AJ, Sans S. Smoking and relative body weight: an international perspective from the WHO MONICA Project. J Epidemiol Community Health 1997;51: 252–60.
101. Belo JN, Berger MY, Reijman M, Koes BW, Bierma-Zeinstra SM. Prognostic factors of progression of osteoarthritis of the knee: a systematic review of observational studies. Arthritis Rheum 2007;57:13–26.