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Review

Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis

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SUMMARY

Osteoarthritis (OA) is a leading cause of pain and disability and leads to a reduced quality of life. The aim was to determine the current evidence on risk factors for onset of knee pain/OA in those aged 50 and over. A systematic review and meta-analysis was conducted of cohort studies for risk factors for the onset of knee pain. Two authors screened abstracts and papers and completed data extraction. Where possible, pooled odds ratios (OR) were calculated via random effects meta-analysis and population attributable fractions (PAFs) derived. 6554 papers were identified and after screening 46 studies were included. The main factors associated with onset of knee pain were being overweight (pooled OR 1.98, 95% confidence intervals (CI) 1.57–2.20), obesity (pooled OR 2.66 95% CI 2.15–3.28), female gender (pooled OR 1.68, 95% CI 1.37–2.07), previous knee injury (pooled OR 2.83, 95% CI 1.91–4.19). Hand OA (pooled OR 1.30, 95% CI 0.90–1.87) was found to be non-significant. Smoking was found not to be a statistically significant risk or protective factor (pooled OR 0.92, 95% CI 0.83–1.01). PAFs indicated that in patients with new onset of knee pain 5.1% of cases were due to previous knee injury and 24.6% related to being overweight or obese. Clinicians can use the identified risk factors to identify and manage patients at risk of developing or increasing knee pain. Obesity in particular needs to be a major target for prevention of development of knee pain. More research is needed into a number of potential risk factors.

Introduction

Osteoarthritis (OA) is a serious joint disease that leads to a reduced quality of life. In 2003, OA was the sixth leading cause of disability worldwide, and has been estimated to rise to the fourth leading cause by 2020[1]. A 2004 study carried out in a general population estimated that the prevalence of symptomatic OA in those aged 60 and above was 9.6% in men and 18% in women[2]. Approximately 25% of adults aged over 55 report at least one episode of knee pain each year, which is likely to reflect underlying OA[3]. OA is commonly presented in general practice, over 7 years an estimated 13% of older adults receive a diagnosis of OA[4].

A systematic review and meta-analysis assessing observational studies up to January 2008 identified a set of factors for which there was consistent evidence for their association with onset of knee OA[5]. These factors were obesity, hand OA, previous knee trauma, older age and female gender. However there was limited evidence regarding the importance of co-morbidities such as depression, occupational and physical activities, and socio-demographic factors such as social class.

The objective of this systematic review and meta-analysis was to determine the current evidence on risk factors for onset of knee pain/OA in those aged 50 and over. The review concentrated on non-clinical risk factors such as body mass index (BMI) and age. Some of these risk factors can be modified at an individual patient level in order to minimise the risk of developing knee OA or knee pain and therefore lead to an increased quality of life for patients. A further aim was therefore to estimate the individual contribution of identified risk factors to the population level of onset of knee OA.

Methods

Phase 1 – Systematic review and meta-analysis

Search strategy and study selection

A search of studies published between the start of each database and December 2012 was conducted using bibliographic databases, including MEDLINE, EMBASE, CINAHL and AMED. Search terms

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included terms for knee OA/pain combined with terms for incidence. Appendix A shows the full search strategy for MEDLINE and AMED.

Cohort studies were included if they had the outcome of onset of knee pain/OA, described symptomatically or radiographically. We excluded case–control studies as they are more prone to selection bias and are often considered as delivering less reliable evidence[6]. In our previous review, conclusions from cohort and case–control studies were generally consistent with each other but case–control studies gave larger effect sizes[5]. In the current review, studies were included if the mean age of participants at follow-up was 50 or above in order to ascertain risk factors that were relevant to older adults. As in the previous review, risk factors assessed were demographic, socio-economic, co-morbidity related and patient determined, such as weight, age, gender and previous knee injury. Studies that defined onset of knee problems in terms of total knee replacement (TKR) or other surgical interventions were excluded, as were the studies that treated such interventions as a risk factor for onset of knee pain or OA. Surgery is usually the most definitive intervention for severe OA and is unlikely to relate to the original onset of knee pain/OA. Studies relating to inflammatory arthritis, such as rheumatoid arthritis, were also excluded as the pathophysiological process involved is different to OA and therefore has different risk factors. Appendix B shows full inclusion and exclusion criteria. A flow chart of the study selection is shown in Fig. 1.

Two authors independently reviewed all identified abstracts, with a third author reviewing those where a consensus had not been reached. Two authors then assessed all remaining papers for inclusion in the final review. Disagreements were resolved by consensus.

Data extraction

Odds ratios (OR) for the association of each potential risk factor with knee pain were extracted (or calculated where information allowed) from each paper included in the final review. Symptomatic OA was usually diagnosed clinically using patient reported symptoms of pain, stiffness or reduced function. Radiographic based OA was based either on an increasing Kellgren Lawrence (K/L) score or a K/L score of 2 or more.

Where more than one paper included data from the same study, the results from the longest follow-up or the most recently published paper were included. If studies presented both unadjusted

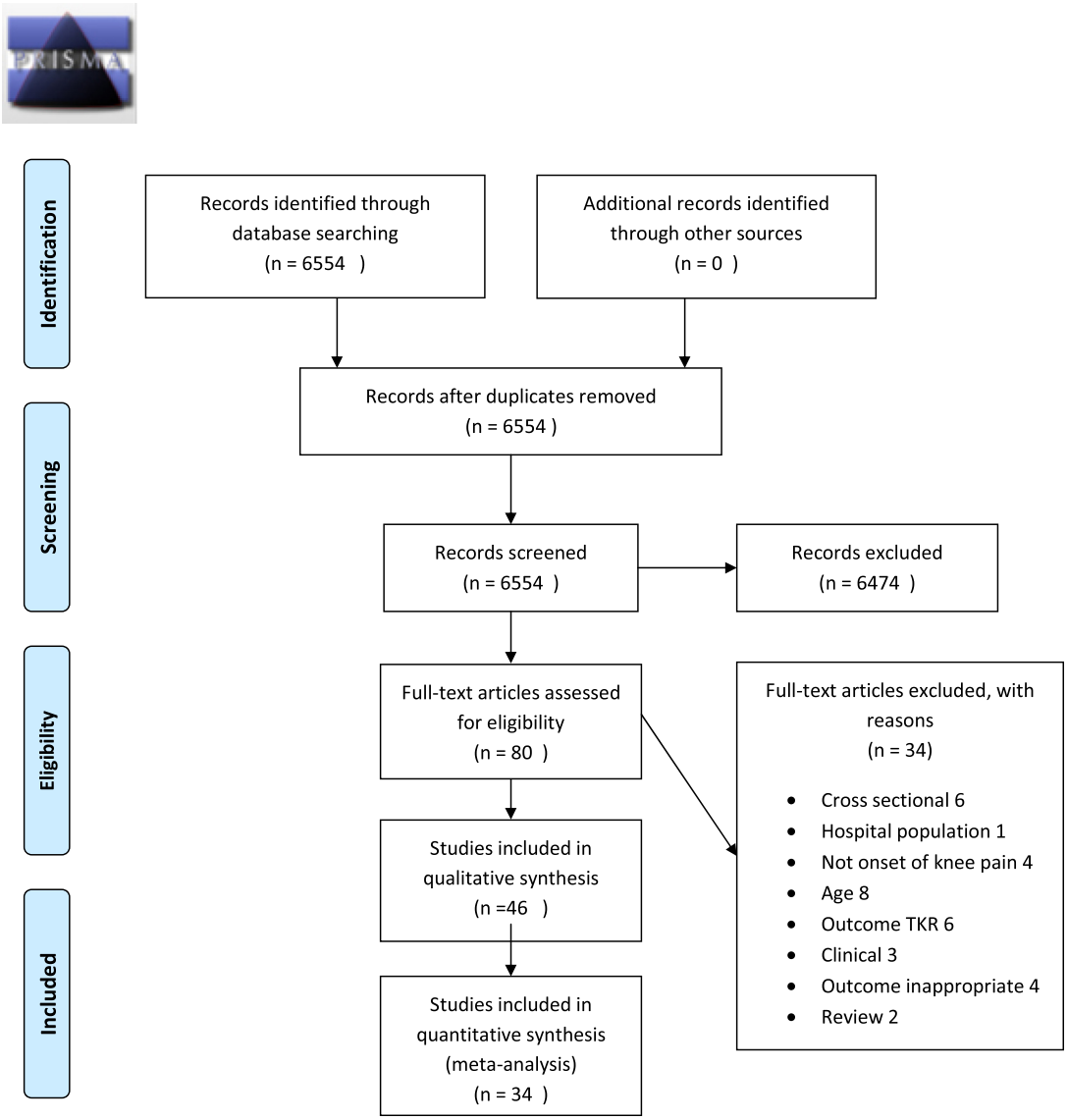

Fig. 1. Flow diagram for: Current evidence on risk factors for knee OA in older adults: a systematic review and meta-analysis.

ORs and ORs adjusted for potential confounders, adjusted ORs were used.

Meta-analysis

Where risk factors had consistent definitions across studies and effect estimates were reported in a similar fashion, meta-analyses were conducted to obtain pooled estimates and associated 95% confidence intervals (CI). The I^2 statistic was calculated to assess the proportion of total variance accounted for by heterogeneity between studies[7]. DerSimonian and Laird random effects models[8] were then used to calculate the pooled OR as significant heterogeneity was present between studies for each risk factor.

For the purpose of this review, overweight was defined as a BMI of 25–30 and obesity as a BMI over 30. If BMI was analysed on a continuous scale, then unit effect sizes were converted to that per five units to reflect comparison of an overweight BMI of 28 against a normal BMI of 23, and also to per 10 units to allow comparison of an obese BMI of 33 against a normal BMI.

Where possible results for people who currently smoked were compared with those for people who never smoked. If this was not possible, we compared people who had a previous smoking history to those with none. If studies had assessed the effect of heaviness of smoking, we used the estimated effect for light/moderate smoking compared with no smoking.

The previous review[4] showed that weighting studies by their methodological quality did not alter the conclusions, or greatly alter the pooled estimates; therefore we did not assess the methodological quality of studies for this review.

Phase 2 – Population attributable fractions (PAFs)

To illustrate the contribution of the main risk factors on knee pain/OA, the second phase of the study mapped the pooled effect size estimates for modifiable factors obtained in the meta-analyses onto data collected from a previous cohort study to determine PAFs for knee OA in the general population. PAFs allow estimation of the proportion of new cases of knee pain/OA in the population that could be avoided if the risk factor was removed, essentially therefore the proportion of new cases related to the risk factor.

The Knee Pain Screening Tool (KNEST) study was a prospective cohort study in North Staffordshire, UK. A baseline questionnaire was sent to all patients aged 50 and over registered at three general practices. Participants who responded to the baseline questionnaire were also sent a 3 year questionnaire. The study was approved by the North Staffordshire Local Research Ethics Committee.

Full details of the study have been given elsewhere. The questionnaire included the KNEST, a validated measure, which includes a question on knee pain (whether the respondent has had pain in or around the knee in the last year) and whether they have ever had a knee injury which required consultation with a GP[8,9].

Self-reported height and weight at baseline were used to determine BMI.

Of the 8995 people sent a baseline questionnaire, 6792 (adjusted response 77%) responded. Of these 6792 subjects, 5784 were still registered at the practices at follow-up and hence sent a follow-up questionnaire. 3907 (adjusted response 68%) responded and answered the KNEST knee pain question at both baseline and follow-up[8,9].

PAFs for onset of knee OA at 3 years were determined using logistic regression modelling[10] among those KNEST participants that reported no knee pain at baseline. The model was initially used to calculate the probability of onset of knee OA for each KNEST participant using their actual status (present or absent) on each risk factor and applying as the regression coefficients the log of the pooled odds ratio estimates for that risk factor obtained in the meta-analysis.

The sum of these probabilities (N_1) across participants equates to the predicted level of onset of knee OA in the population based on the actual prevalence of the risk factors in the KNEST population. The model was then repeated with the risk factor of interest coded as absent for all participants and the predicted number of cases determined by again summing the participants' probabilities (N_2). The PAF for each risk factor was then calculated as: $(N_1 - N_2)/N_1 \times 100$.

Stata 12.1 was used for all statistical analyses[11].

Results

Phase 1 – Systematic review and meta-analysis

Study characteristics

6554 papers were identified using the search strategy. 6474 were excluded at title and abstract screening and 34 after reading the papers in full. In total, 46 papers were included in this review with 34 included in the meta-analysis.

Study results

Meta-analysis was performed for five risk factors where a sufficient number of studies reported findings. These were: BMI, where three pooled OR's were calculated (overweight, obese, overweight or obese), female gender, smoking, previous knee injury and the presence of hand OA/Heberden's nodes. Table I gives the pooled OR's obtained from the random effects meta-analyses.

Overweight

In total, 23 cohort studies in 23 papers reported on being overweight[12–34]. The studies consistently demonstrated being overweight was a risk factor for the onset of knee OA, though there was considerable heterogeneity present among the results reported ($I^2 = 98.8\%$). The OR for being overweight as calculated from one study[18] was unusually high (OR 16.9, 95%CI 12.1–23.5), hence was excluded from the meta-analysis. The pooled OR of the remaining twenty-two studies was 1.98 (95% CI 1.57–2.20). One study suggested that gain in weight was directly correlated with an increasing risk of knee OA[14]. One study compared the risk of being overweight on developing knee OA to that of developing hip OA and found the association between being overweight and the development of hip OA was weaker[35].

Obesity

Twenty-three cohort studies investigated obesity as a risk factor for onset of knee OA[12–26,28–34,36]. One of these studies[18] was excluded from the meta-analysis as the implied OR for obesity was 285. Among the remaining 22 studies, there was a large amount of heterogeneity between the study findings ($I^2 = 98.7\%$), however all

Table I
Pooled ORs for association of commonly studied risk factors with knee OA

Risk factor	No of studies	Total no of participants	Pooled OR	Lower CI	Upper CI	*I* squared
Overweight	22	398,251	1.98	1.57	2.2	98.8
Obesity	22	401,119	2.66	2.15	3.28	98.7
Overweight or obese	25	415,613	2.10	1.82	2.42	99.2
Previous knee injury	13	27,326	2.83	1.91	4.19	89.1
Female gender	11	28,133	1.68	1.37	2.07	72.5
Hand OA	6	5232	1.30	0.90	1.87	54.7
Smoking	13	362,061	0.92	0.83	1.01	43.6

studies were generally consistent in reporting being obese as a risk factor for the onset of knee OA. The pooled OR of the 22 studies was 2.66 (95% CI 2.15–3.28). This pooled estimate demonstrates that obesity has a slightly larger effect on onset of knee OA than being overweight.

Overweight OR obese

Twenty-six cohort studies reported results, or could have such results deduced, on assessing the effect of being either overweight or obese (BMI over 25)[12–26,28–35,37–39]. One such study[18] was excluded from the meta-analysis as the deduced OR for being overweight or obese was 69. The I^2 among the remaining twenty-five studies was 99.2% and the resulting pooled OR was 2.10 (CI 1.82–2.42) showing an increased risk of knee OA in those overweight or obese (Fig. 2).

Previous knee injury

Thirteen cohort studies were included in the meta-analysis of previous knee injury as a risk factor for the onset of knee OA[9,13–15,17,18,21,23,31,32,37,40,41] with only one showing that those with previous knee injury had a lower, though non-significant risk of developing knee OA[14]. The other studies all showed increased risk of knee OA with a prior injury. The extent of heterogeneity present between findings reported was considerable ($I^2 = 89.1\%$) and the pooled OR was 2.83 (95% CI 1.91–4.19) (Fig. 3).

Female gender

Eleven cohort studies assessed female gender as a potential risk factor[9,12,14–16,21,23,24,26,31,34], (other studies used it as an adjustment factor without reporting its effect estimates). One paper did not include enough information to be included in the meta-analysis[32]. There was consistent evidence that females were at higher risk of knee OA. I^2 was 72.5% and pooled OR was 1.68 (95% CI 1.37– 2.07).

Hand OA/Heberden's nodes

Hand OA, usually diagnosed clinically by the presence of Heberden's nodes, was assessed as a risk factor by six cohort studies[14,17,24,34,37,42]. The extent of heterogeneity was moderate and on border of significance at the 5% level ($I^2 = 54.7$). The pooled OR of 1.30 (95% CI 0.90–1.87) indicated that hand OA may potentially be a risk factor for knee OA.

Smoking

Fourteen studies assessed smoking as a potential risk factor[13,14,17,19,20,23,24,26,28,31,34,38,43,44]. One was not included in the meta-analysis as it measured smoking differently to the other papers[44]. The pooled OR of 0.92 (95% CI 0.83–1.01, $I^2 = 43.6$) suggests that overall smoking is not associated with knee OA.

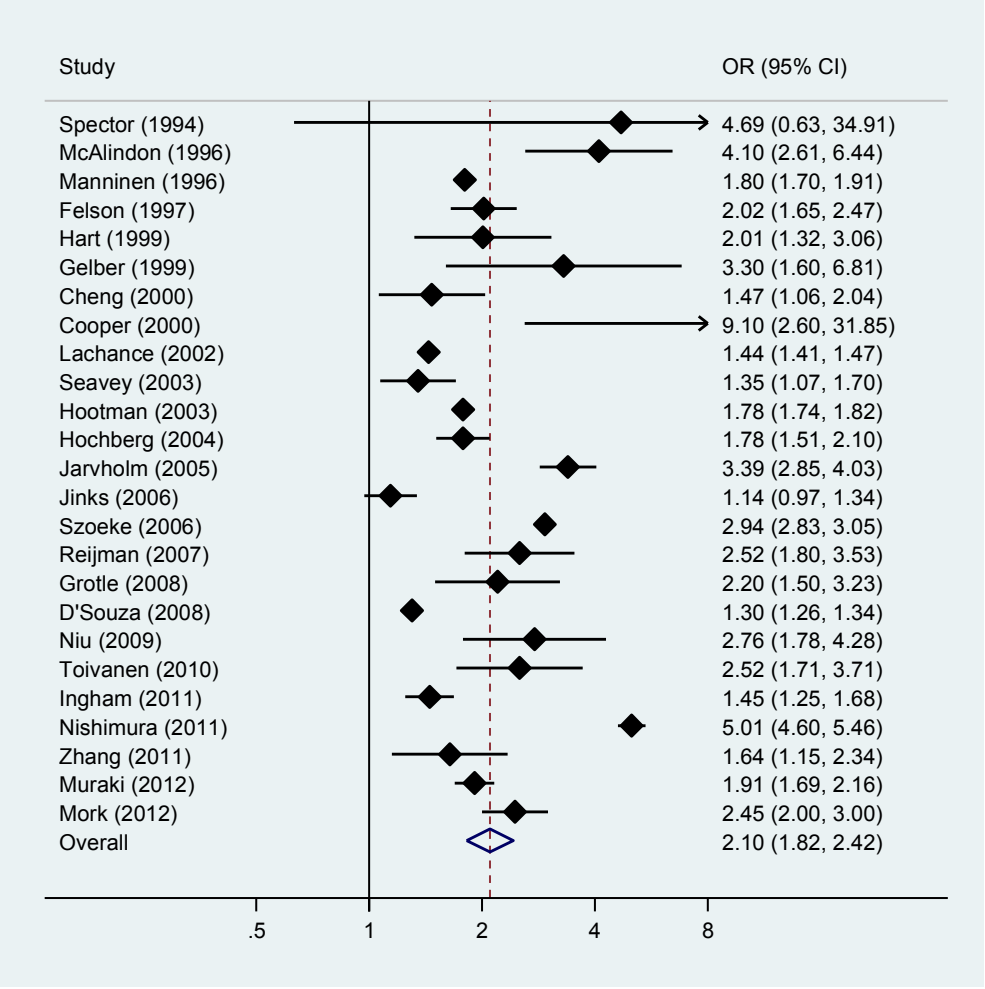

Fig. 2. Forest Plot of association of overweight or obese with knee OA. Pooled OR 2.10; 95% CI 1.82–2.42 $I^2 = 98.9\%$.

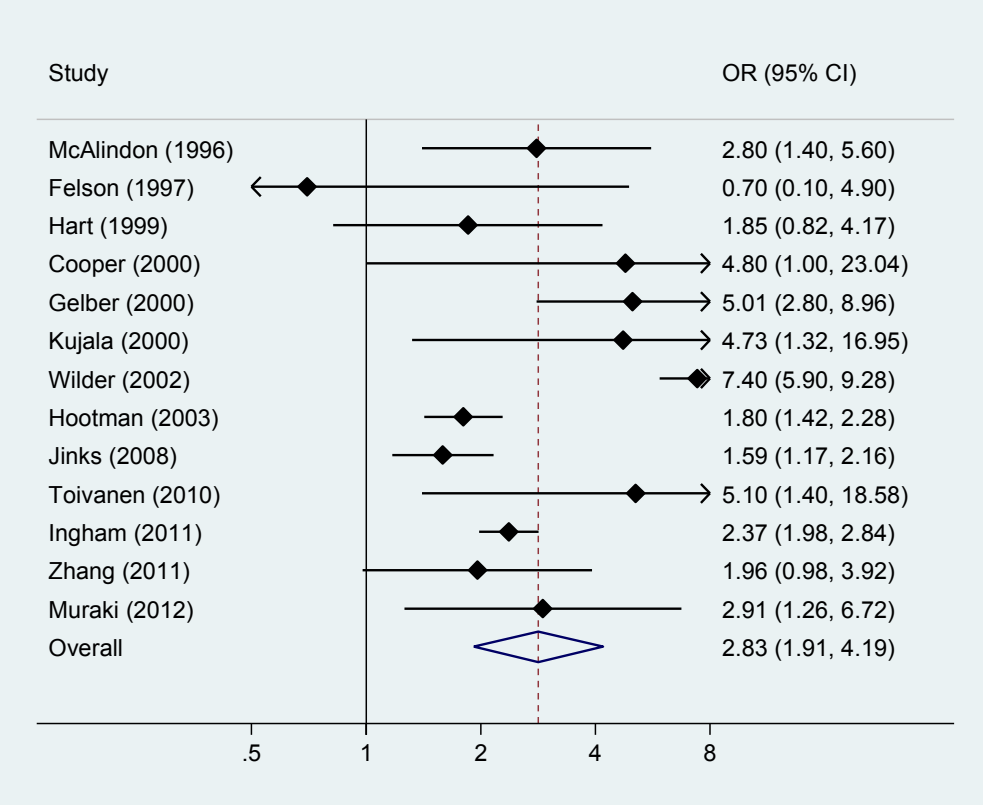

Fig. 3. Forest Plot of association of previous knee injury with knee OA. Pooled OR 2.83; 95% CI 1.91, 4.19 $I^2 = 89.1\%$.

Increasing age

Nineteen studies assessed increasing age as a risk factor for knee OA[9,12,13,15–17,19–21,23,24,26,28,31,32,34,38,45,46]. Creating a pooled OR was not possible as the studies used a range of different age categorisations. They were generally in agreement that increasing age was a significant risk factor for onset of knee OA. Jarvholm *et al.* suggested a 'non-linear' relationship between age and knee OA incidence with a sharp increase in incidence between the ages of 50 and 75 in male patients but limited increase above age 75[20]. Another study agreed with this and suggested that a 'levelling off or decline' occurred after the age of 80[46].

Occupational risks

Occupational activities were also discussed in several cohort studies. Having a heavy physical workload was investigated by two studies[26,31], but both found it to be non-significant.

Kneeling was investigated by four studies[18,21,32,34] and found to be significantly related to knee OA by three[18,21,32], suggesting that it is an important element of physical work that can be classed as a risk factor for knee pain and knee OA. Lifting was also assessed by three studies[21,32,34] and was significantly related to knee OA by one[32]. One study assessed farming and construction work and found that both were significant risk factors for knee OA[47]. One study found a non-significant relationship of bending with knee OA[48]. In summary, it would appear that individuals who are exposed to certain physically demanding activities in their daily working lives may be at an increased risk of developing knee pain and knee OA.

Physical activity

High levels of physical activity were assessed by sixteen studies[13–15,17,18,22,26,31,34,37,38,45,49–52]. Three papers showed a statistically significant relationship between high levels of physical activity or intense physical activity such as long-distance running and the development of knee OA[14,37,50]. One study suggested that it was habitual physical activity which created the greatest risk meaning that those with more varied exercise routines had less risk of developing knee OA[14] and another only found an increased risk of developing knee OA in those who ran 20 miles or more each week[38]. All other papers discussed a theoretical risk but did not demonstrate significant results. Referring back to our inclusion criteria, we only looked at studies discussing the general population so these results do not include athletes or professional sportsmen. One study suggested that higher levels of physical activity were associated with knee OA in younger men (aged 20–49) but not in men older than 50 or in women[38].

Co-morbidities

Two studies[26,36] concluded that cardiovascular disease such as hypertension or ischaemic heart disease are risk factors and one of those also suggested that respiratory illness could contribute[36]. However Mork *et al.* suggest that a sedentary lifestyle exacerbated by knee pain/OA could make such co-morbidities worse, hence a dual association[22] with the knee OA and the co-morbidity accelerating the progression of each other.

Depression was studied in three studies[9,26,53] and two of these found a statistically significant link with knee OA[9,26]. Experiencing unspecified pain elsewhere in the body was also found to be significant by two papers.[9,21]

Oestrogen

Four papers investigated the effect of oestrogen. Some suggested that ingestion of oestrogen, predominantly in the form of

Hormone Replacement Therapy, may offer some protection against knee OA[17,28,32,51], and three papers proposed that patients who had a hysterectomy, therefore had less endogenous oestrogen exposure, were more likely to develop knee OA[17,39,54]. However, none of the associations were statistically significant. Hart *et al.* presented findings that current oestrogen use may play a protective effect against women developing knee OA[17].

Education and household income

Jorgensen *et al.* assessed level of education and their findings suggest that even a basic education may be associated with reduced risk of developing knee OA[55] however, this is not supported by two other studies that assessed education level[9,26].

Three papers assessed whether having a higher household income or a professional job is associated with a reduced risk of developing knee OA[9,17,55], with two reporting significant results[17,55].

Other

Several other risk factors were also discussed by a small number of studies.

Poor self-evaluation of health[9,53] was proposed as a potential risk factor but statistically no association was demonstrated. There was also no association found between alcohol use and knee pain[23]. One study found that being hyper-mobile could be protective[56].

One study found that those who had been married, divorced or widowed were statistically more likely to have knee pain and knee OA rather than those who were unmarried and that having children was a statistically significant risk factor[55]. Another study considered the association of cohabiting status with knee OA but did not demonstrate any statistical significance[9].

Results phase 2 – PAFs

We calculated PAFs for being overweight or obese and having previous knee injury as these were the two strongest modifiable risk factors, had a pooled OR obtained from the meta-analysis, and had available information in the KNEST study. Table II shows the list of PAFs calculated.

The PAFs indicates that for an estimated 5.1% of new knee pain/OA patients, this is related to a previous injury. An estimated 17.3% of new cases of knee pain is related to obesity and 24.6% to being overweight or obese.

Discussion

This systematic review aimed to provide up-dated evidence on the risk factors for developing knee pain/OA among older adults. The findings are timely due to the 2014 update to the NICE OA guidelines for managing OA in adults[57]. Since the publication of our last review (studies up to January 2008)[5], there has been further evidence to support the effect of previously known risk factors of increased BMI, previous knee injury, age, being female and hand OA. The conclusion that there is no association of smoking with onset of knee OA remained when adding more recent literature. Quantitative pooling of results was feasible for five risk factors; all except smoking and Heberden's nodes were found to have a significant effect on development of knee OA. Individual study effect size estimates for smoking tended to suggest there may be a negative association with onset of knee OA, however only one such study showed a significant relationship. The pooling of results showed non-significant association.

Table II
PAFs for overweight, obesity and previous knee injury for onset of knee pain

Risk factor	PAF
Injury	5.1%
Obesity	17.3%
Overweight or obese	24.6%

The findings of this review together with NICE Osteoarthritis guidelines (2014) emphasise the continued importance of weight loss as a management option for OA[57]. Our calculated PAF values demonstrate that 24.6% of cases of onset of knee pain could be attributed to being either overweight or obese. According to the National Joint Registry, 90,842 TKR's took place in 2012, an increase of 7.3% in number of procedures from 2011[58]. Primary TKR plus 5 years of follow-up care is estimated to cost £7458 per patient[59]. This means that the financial implications of severe knee OA are significant for the National Health Service.

Health care professionals sometimes have difficulty in discussing weight issues with patients with OA[60], a recent study found that people with OA are still more likely to receive pharmacological treatments than non pharmacological treatments (including weight loss advice)[61]. A recent Cochrane review on the effectiveness of interventions to change health care professionals behaviour to promote weight reduction did not provide firm conclusions[62] leaving a gap in knowledge about how to address this problem. The need for training to address barriers to health professionals providing support and advice has previously been highlighted[63] and new approaches to support clinicians to discuss weight loss strategies with patients are urgently required. Finally, recent research adds to the complexity by highlighting the interplay between pain, biomechanics and weight loss, thereby requiring interventions to take account of multiple factors[64].

There is increasing but still low levels of evidence that certain occupational activities such as kneeling, high levels of physical activity, farming and construction work, and comorbid conditions such as depression or cardiovascular disease are risk factors for knee OA. High levels of physical activity appear to increase risk of knee OA where patients undertake habitual and repetitive motion, whereas in comparison those who undertake a less intense exercise pattern do not appear to have increased risk. In comparison it can be concluded that having a sedentary lifestyle increases the risk of excess bodyweight and associated co-morbidities therefore a patients should try to vary their exercise and create an element of balance between high-impact and repetitive motion and lower impact exercise.

A limited number of studies investigating socio-economic status such as household income or having a professional job found these attributes to be protective of developing knee OA.

Case-control studies were excluded from this review. Including them may have added to the evidence on certain risk factors but they are generally regarded as representing a lower level of evidence given particularly the potential of selection bias in choosing controls. Our previous review suggested including case–control studies would not have altered our conclusions although case-controls studies, unlike cohort studies, did suggest smoking had a negative association with knee OA, and they also tended to give increased strengths of associations. We did not assess quality of the studies, again because in our previous review accounting for quality of studies made no difference to our findings. We also excluded non-English language papers as part of our exclusion criteria, which means that potentially there could be additional studies which were missed. We used the I^2 statistic to calculate heterogeneity, which was moderate for hand OA and high for all other risk factors therefore despite using random effects meta-analysis some caution is needed in interpreting the pooled ORs.

Given the size and scope of this review, it was not possible to cover all potential risk factors for knee OA. For example, this systematic review does not consider risk factors such as low muscle strength or mal-alignment.

In phase 2 of our study we could not calculate PAFs for hand OA as this was not included in the KNEST study. The definition of knee pain was self-reported and may not reflect radiographic OA but it is likely that knee pain in the elderly is related to OA. Use of a larger more comprehensive dataset would have been beneficial to calculate impact numbers for these risk factors, and this may be addressed in a different study. It is also important to note that there are different ways of estimating PAFs, all of which may result in slightly different estimates[65]. However the PAFs determined here give an idea of how much of new knee pain may be related to obesity, overweight and previous injury.

In conclusion, this review has identified several risk factors for the development of knee pain and knee OA in older adults. The results of this review can be used clinically to help healthcare professionals identify and manage patients at risk of developing or increasing knee OA. Some, such as weight, can be targeted clinically in order to reduce the number of patients who suffer from knee OA. Patients with other risk factors such as previous knee injury, age and female gender can be managed to reduce progression of the condition. There is however limited evidence regarding factors such as the influence of co-morbidities, and socio-economic status and therefore further research needs to focus on these risk factors rather than those for which extensive evidence already exists.

Contributions

CJ, KJ, and MB conceived the study. VS, MB and JJ performed the searches. VS, MB, CJ and KJ extracted the data. VS and MB performed the analyses. All authors contributed to the interpretation of the findings. VS drafted the paper and all authors critically revised it and approved the final manuscript.

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Consortium

The funders played no involvement in the study.

Competing interests

None.

Appendix A. Search Strategy for MEDLINE

Search Strategy.

Medline & AMED.

Prognosis search filter (maximise sensitivity) – http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx.

Searches	Results
1	exp Osteoarthritis/
2	knee$1.mp.
3	1 and 2
4	(knee$ adj3 (osteoarthr$ or pain$ or disab$5)).mp.
5	3 or 4
6	incidence.sh. or exp mortality/or follow-up studies.sh. or prognos$.tw. or predict$.tw. or course.tw.
7	risk$.tw.
8	6 or 7
8	5 and 8

Search 12/12/12.

Appendix B. Inclusion and Exclusion Criteria

Inclusion Criteria.

- English language
- Quantitative studies: cohort 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+ or age stratified analysis with 50+ strata
- Risk factors must be demographic, socio-economic, comorbid, previous knee events (for example injury) and other patient determined factors
- Primary care population

Exclusion Criteria.

- Knee pain related to other musculoskeletal conditions e.g., rheumatoid arthritis, rheumatism
- Studies whose outcome is a total knee replacement or studies of patients following total knee replacements.
- Animal studies
- Clinical risk factors or outcome including proprioception, muscle strength, joint alignment, cartilage loss
- Conference abstracts
- Not an original study (e.g., editorial or literature review)
- Not English language
- Case–control or cross sectional studies
- Studies in those with previous trauma/injury without general population comparator group

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