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A systematic review of the sex differences in risk factors for knee osteoarthritis

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Abstract

Objectives: Previous systematic reviews focused on the evidence of common risk factors for knee OA (KOA); however, the effect and strength of association between risk factors and KOA might be different between the two sexes. The aim of the present systematic review was to determine the current evidence on sex differences in the association between risk factors and KOA and their prevalence.

Methods: We searched the following electronic bibliographic databases: MEDLINE (PubMed), EMBASE and Web of Science. A methodological quality assessment was conducted independently by two researchers according to an adapted version of the standardized set of criteria known as the Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS, a star system, was converted to three categories of quality.

Results: In total, 27 studies reported sex-specific risk estimates on several risk factors for KOA. Out of the 22 longitudinal cohort studies (except one nested case–control), 12 were of good quality and 10 were of fair quality. The five cross-sectional studies consisted of one of good, three of fair and one of poor quality. There was an indication of sex differences in risk factors leading to higher risk of KOA: high BMI, alcohol consumption, atherosclerosis and high vitamin E levels in women, and high physical activity, soft drink consumption and abdominal obesity in men. Knee injury, high blood pressure and low step rate seem to affect both women and men.

Conclusion: More good quality studies are needed to assess sex differences in risk factors for KOA, especially for symptomatic/clinical OA.

Keywords: systematic review, risk factors, sex differences, radiographic, symptomatic, clinical, knee OA

Rheumatology key messages

- There is great uncertainty as to whether there are sex differences in the effect of common risk factors for the risk of knee OA.
- Reporting sex-stratified association results can contribute to a better understanding and view of OA.

Introduction

Knee OA (KOA) is one of the most disabling diseases in the elderly population, occurring with a higher prevalence in women [1]. In addition, women over the age of 50 years have twice the risk of developing KOA and are more likely to experience pain and disability compared with men [2]. This difference in risk suggests the possibility of differences existing in the presence and strength of associations of KOA risk factors between men and women.

There have been a number of systematic reviews on risk factors for KOA [3, 4], but none of them looked at sex differences specifically. The most recent systematic review on risk factors and their effects on developing KOA identified several risk factors in older adults [4] such as overweight or obesity, previous knee injury, older age and female gender. Female sex is consistently reported as a risk factor and meta-analytic results from the latest systematic review, using 10 studies, show females at higher risk of KOA with a pooled odds ratio (OR) of 1.7 (95% CI 1.4, 2.1). Despite the increasing evidence pointing towards a higher risk for females of developing KOA, sex was often used only as adjustment factor and sex-specific estimates were rarely reported in previous studies.

However, possible sex differences that might exist in the association between KOA and the other common KOA risk factors have not been thoroughly overviewed yet. Identifying the risk factors that affect women more prominently could help in designing better preventive strategies and in developing sex-specific treatments in the future. In addition, identifying

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the sex-specific risk factors that lead to a significantly higher risk of developing or increasing risk for KOA can be used by healthcare professionals to identify patients in the clinic.

Therefore, the objective of the present systematic review was to determine the current evidence on sex differences in the association between KOA and risk factors. We also assessed the difference among men and women in the prevalence of risk factors when these data were available in the included studies.

Methods

Search strategy and study selection

A search, performed by a medical librarian, between January 2012 and March 2020 was performed in the following electronic bibliographic databases: MEDLINE (PubMed), EMBASE and Web of Science. The search strategy included terms relating to or describing risk factors for KOA (Supplementary Data S1, available at *Rheumatology* online). For the period until 2012, we scanned the included studies in the systematic review published by Silverwood *et al.* in 2015 [4]. Their paper provides a good overview of the risk factors for KOA. We excluded systematic or narrative reviews, meta-analyses, letters, conference abstracts and editorials.

Studies that met the following criteria were included: studies presenting data on prevalence, incidence and progression of structural or clinical tibiofemoral KOA in a human population (including both males and females), in cohort or cross-sectional studies (in the latter case, only when it was clear that the exposure to the risk factor took place before the outcome of KOA), and available in English. The studies reported on at least one known risk factor for KOA; risk factors must be demographic, socio-economic, comorbid health conditions, previous knee events (for example injury) and other factors that are not early signs of the OA disease process (i.e. some imaging/mechanical markers, biomarkers, bone morphology) or possible outcomes including proprioception, muscle mass, muscle strength, joint alignment, cartilage loss will be excluded. We excluded studies on patellofemoral OA, studies of patients following total knee replacements and studies in those with previous trauma/injury without a general population comparator group.

Four independent researchers (I.A.S., J.H.W., J.B.J.v.M., S.M.A.B.-Z.) checked and scanned the titles and abstracts on the above-mentioned criteria according to the method published by Bramer *et al.* [5]. We report the findings of our review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist [6]. The protocol can be found on PROSPERO 2018 CRD42 018109892 (available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018109892).

Quality assessment

A methodological quality assessment on each included article was conducted independently by two researchers, J.H.W. and I.A.S., by scoring the quality of the selected papers according to an adapted version of the standardized set of criteria known as the Newcastle-Ottawa Quality Assessment Scale (NOS) [7] (see Supplementary Data S2 and S3, available at *Rheumatology* online). The NOS, a star system, has been widely used for scoring cohort studies and cross-sectional studies for systematic reviews [8, 9]. We converted to three categories of quality (detailed description in the Supplementary Material, available at *Rheumatology* online) and defined the quality as good (7–8 stars), fair (5–6 stars) and poor (4 stars).

Data extraction

The full texts of selected studies have been subsequently retrieved for detailed inspection. Data of the included studies was extracted by I.A.S. using a pre-defined spreadsheet, including female- and male-specific results with risk estimates and 95% CI.

We classified the studied risk factors in four groups: weight- and height-related, activity-related, comorbidities and markers, and lifestyle-related risk factors. In each table we report on the type of exposure measure, outcome definition, effect sizes (ORs, relative risks or hazard ratios) along with their 95% CI for women and men separately. Due to word count restriction and level of evidence from studies, we decided to only describe good-quality studies in our paper.

Due to a low number of studies on the risk factors and, especially, due to the inconsistencies in exposure measurements we did not perform a meta-analysis and followed the route of a descriptive review, reporting on the current evidence for the investigated risk factors in both men and women. Moreover, we decided to use Z-method to test for statistically significant differences between the two effect estimates in men and women, often used in similar settings, i.e. the work of Schiphof *et al.* (2013) [10] and Szilagyi *et al.* (2022) [11]. For the calculation, we followed the steps described in Chapter 6 of the Cochrane handbook available online: 'Obtaining standard errors from confidence intervals and *P* values: ratio measures' (https://training.cochrane.org/handbook/current/chapter-06#_Ref190817844). The *Z*-test gives a score for testing the null hypothesis that there is no difference between the two groups, by comparing the value of z to the standard normal distribution. A two-sided test with a significance level of 0.05 was used. There is a significant difference in the factor for the specific grade if z is less than -1.96 or if z is >1.96. The results of the *Z*-test are presented in Supplementary Table S2, available at *Rheumatology* online.

Results

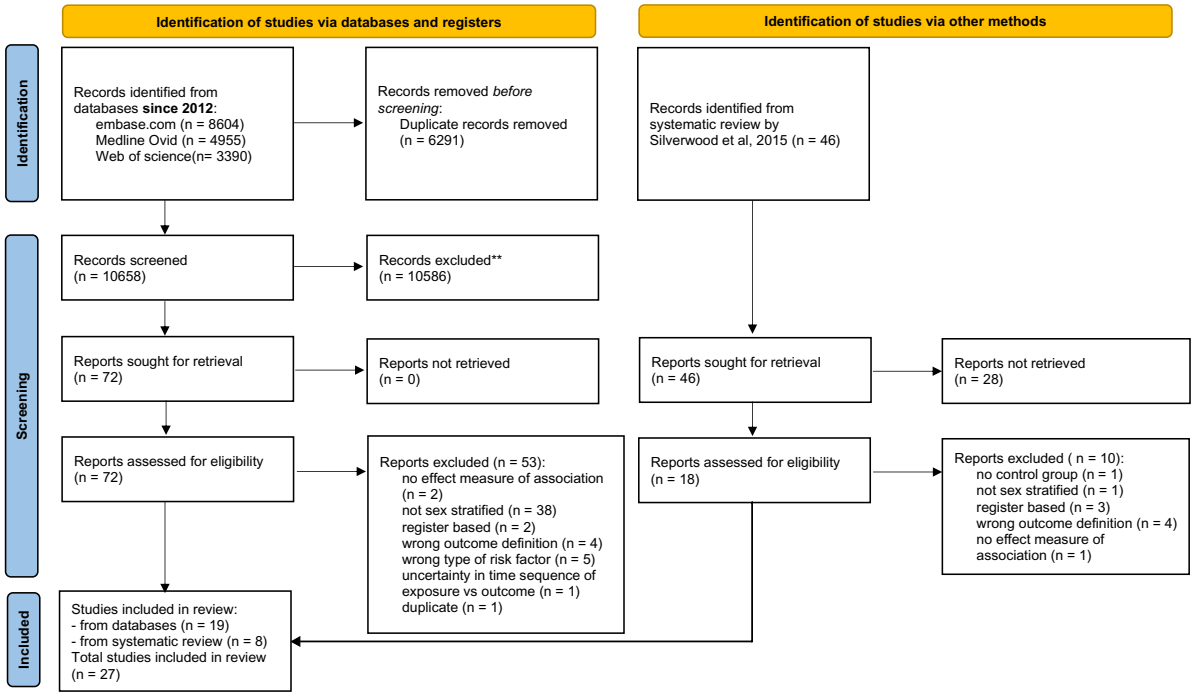
Study characteristics

We found 27 studies reporting sex-specific risk estimates on several risk factors for KOA.

Fig. 1 illustrates the flowchart of the inclusion steps for this systematic review. Our final set of included studies consisted of 22 longitudinal cohort studies (except one nested case–control) and five cross-sectional studies. More than half of the cohort studies were classified as good quality according to NOS quality assessment [12–23], the rest were classified as fair quality [24–33]. Among the five cross-sectional studies one was of good quality [34], three of fair quality [35–37] and one of poor quality [38] as assessed according to the NOS. In Table 1 we show the scores for each component of the NOS quality assessment for the included studies.

Study results

We found 10 studies that investigated the sex-specific associations for weight- and height-related factors with KOA (Table 2), 11 studies for activity-related risk factors (Table 3),



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

Table 1. The quality assessment using the Newcastle-Ottawa Quality Assessment Scale of included studies in the systematic review

Article	Selection			Comparability	Outcome			Total score
	1	2	3	1	1	2	3	
Felson *et al.* (1997) [14]	*	*	*	**	*	*	*	8 (G)
Chaganti *et al.* (2014) [12]	*	*	*	**	*	*	NA	7 (G)
Felson *et al.* (1988) [13]	*	*	*	**	*	*		7 (G)
Hoeven *et al.* (2013) [15]	*	*	*	**	*	*		7 (G)
Hoeven *et al.* (2015) [16]	*	*	*	**	*	*		7 (G)
Lu *et al.* (2013) [17]		*	*	**	*	*	*	7 (G)
Lu *et al.*, (2014) [18]		*	*	**	*	*	*	7 (G)
Mork *et al.* (2012) [19]	*	*	*	**		*	*	7 (G)
Niu *et al.* (2017) [20]	*	*	*	**	*	*		7 (G)
Welling *et al.* (2017) [22]	*	*	*	**	*	0	*	7 (G)
Wilder *et al.* (2002) [23]	*	*		**	*	*	*	7 (G)
Takiguchi *et al.* (2019) [21]	*	*	*	**	*	*		7 (G)
Dahaghin *et al.* (2005) [25]	*	*	*	*	*	*		6 (F)
Eaton *et al.* (2017) [26]	*	*	*	*	*	*		6 (F)
Felson *et al.* (1991) [27]	*	*		**	*	*		6 (F)
Hannan *et al.* (1993) [28]	*	*		**	*	*		6 (F)
Shirinsky *et al.* (2017) [32]		*	*	**	*	*		6 (F)
Culvenor *et al.* (2018) [24]		*	*	**	*	*		6 (F)
Hart *et al.* (2020) [29]		*	*	**	*	*		6 (F)
Misra *et al.*, (2019) [30]		*	*	**	*	*		6 (F)
Rogers-Soeder *et al.* (2020) [31]		*	*	**	*	*		6 (F)
Soutakbar *et al.* (2019) [33]		*	*	**	*	*		6 (F)
McAlindon *et al.* (1996)[a] [34]	*	*	*	**	*	*	–	7 (G)
Martin *et al.* (2013)[a] [35]	*		*	**	*	*	–	6 (F)
Wills *et al.* (2012)[a] [37]	*		*	**	*	*	–	6 (F)
Ratzlaff *et al.* (2012)[a] [36]	*		*	**		*	–	5 (F)
D'Souza *et al.* (2008)[a] [38]	*			*	*	*	–	4 (P)

* : 1 star given; ** : 2 stars given; [a] cross-sectional studies; NA: not available, study is nested case–control study; 0: none of the available answers applied; –: question did not apply for cross-sectional studies; G: good quality; F: fair quality; P: poor quality.

Table 2. Sex-stratified association results of weight- and height-related factors (nine studies) with prevalence/incidence/progression of knee OA

BMI, weight- and height-related risk factors	Outcome[a]	Women	Men	Reference
BMI per 5-unit difference	KL scale	**OR 1.8 (95% CI 1.2, 2.6)**	OR 1.0 (95% CI 0.5, 2.1)	Felson *et al.* (1997) (G)
Most overweight quintile	KL scale	**RR 2.07 (95% CI 1.67, 2.55)**	**RR 1.51 (95% CI 1.14, 1.98)**	Felson *et al.* (1988) (G)
Second overweight quintile	KL scale	**RR 1.44 (95% CI 1.11, 1.86)**	RR 1.0 (95% CI 0.70, 1.41)	Felson *et al.* (1988) (G)
BMI category: 18.5–21.9 (compared with <18.5)	KL scale	HR 1.90 (95% CI 0.82, 4.40)	HR 2.06 (95% CI 0.27, 15.49)	Takiguchi *et al.* (2019) (G)
BMI category: 22.0–24.9 (compared with <18.5)	KL scale	**HR 3.23 (95% CI 1.41, 7.37)**	HR 4.45 (95% CI 0.62, 32.23)	Takiguchi *et al.* (2019) (G)
BMI category: ≥25 (compared with <18.5)	KL scale	**HR 6.03 (95% CI 2.62, 13.87)**	HR 6.91 (95% CI 0.95, 50.18)	Takiguchi *et al.* (2019) (G)
Obese to normal weight	CKP with self-reported physician-diagnosed OA	**RR 4.37 (95% CI 3.01, 6.33)**	**RR 2.78 (95% CI 1.59, 4.84)**	Mork *et al.* (2012) (G)
z-score increase in BMI (models containing both BMI and each activity domain -> OR range)	ACR criteria, prevalence	**OR 1.8 (OR range 1.49–1.92)**	**OR 1.4 (OR range 1.40–1.47)**	Martin *et al.* (2013) (F)
Per *z*-score increase in BMI at age 53 years	ACR criteria, prevalence	**OR 1.89 (95% CI 1.59, 2.24)**	**OR 1.38 (95% CI 1.11, 1.71)**	Wills *et al.* (2012) (F)
BMI, per S.D.	KL scale	**OR 1.43 (95% CI 1.05, 1.93)**	**OR 1.55 (95% CI 1.08, 2.22)**	Culvenor *et al.* (2018) (F)
WHtR, per S.D.	KL scale	OR 1.25 (95% CI 0.77, 2.04)	OR 1.48 (95% CI 0.72, 3.04)	Culvenor *et al.* (2018) (F)
Central (abdominal) obesity, SCF, per S.D.	KL scale	OR 1.21 (95% CI 0.83, 1.75)	OR 1.04 (95% CI 0.70, 1.54)	Culvenor *et al.* (2018) (F)
Peripheral (thigh) adiposity, IMF, per S.D.,	KL scale	OR 1.22 (95% CI 0.86, 1.73)	OR 1.12 (95% CI 0.73, 1.73)	Culvenor *et al.* (2018) (F)
Obese (DXA-derived fat mass) *vs* nonsarcopenic nonobese	KL scale	**RR 2.29 (95% CI 1.64, 3.20)**	**RR 1.73 (95% CI 1.08, 2.78)**	Misra *et al.* (2019) (F)
Sarcopenic obese (DXA-derived fat mass) *vs* nonsarcopenic nonobese	KL scale	**RR 2.09 (95% CI 1.17, 3.73)**	RR 1.74 (95% CI 0.68, 4.46)	Misra *et al.* (2019) (F)
Obese (BMI-defined obesity category) *vs* nonsarcopenic nonobese	KL scale	**RR 1.87 (95% CI 1.37, 2.54)**	**RR 1.92 (95% CI 1.24, 3.00)**	Misra *et al.* (2019) (F)
Sarcopenic obese (BMI-defined obesity category) *vs* nonsarcopenic nonobese	KL scale	RR 1.60 (95% CI 0.93, 2.77)	**RR 2.89 (95% CI 1.49, 5.59)**	Misra *et al.* (2019) (F)
Long-term weight change, kg, 4th quartile (to lowest)	KL scale	HR 1.13 (95% CI 0.66, 1.92)	HR 1.23 (95% CI 0.64, 2.37)	Takiguchi *et al.* (2019) (G)
Birth weight, g, 2500–2999 (compared with <2500)	KL scale	HR 0.82 (95% CI 0.55, 1.22)	HR 1.78 (95% CI 0.88, 3.58)	Takiguchi *et al.* (2019) (G)
Birth weight, g, ≥3000 (compared with <2500)	KL scale	HR 0.70 (95% CI 0.44, 1.13)	HR 1.78 (95% CI 0.84, 3.78)	Takiguchi *et al.* (2019) (G)
Height at age 31 years, highest quartile	ICD code	**HR 1.8 (95% CI 1.0, 3.1)**	**HR 2.5 (95% CI 1.4, 4.5)**	Welling *et al.* (2017) (G)

[a] Outcome was incidence or progression of knee OA unless mentioned otherwise, i.e. 'prevalence'; WHtR waist to hip ratio. Bolded text indicates significant associations. KL: Kellgren & Lawrence system; CKP: chronic knee pain; SCF: subcutaneous fat; IMF: intermuscular fat; HR: hazard ratio; OR: odds ratio; RR: relative risk; G: good quality; F: fair quality.

10 studies for comorbidities and markers (Table 4), and 4 studies for lifestyle risk factors (Table 5). There were 18 studies that looked at radiographic KOA [12–18, 21, 23–27, 29–32, 34], 8 that looked at symptomatic or clinical KOA [19, 20, 22, 28, 35–38] and one study that looked at both structural and symptomatic KOA [33].

From the included studies, 15 out of 27 did not report the sex-specific prevalence of their studied risk factors; however, a great majority of 11 out of the 15 studies provided sufficient data to calculate it. The remaining 12 studies, 5 cross-sectional and 7 longitudinal cohort studies, have reported the sex-specific prevalence for at least one of the studied risk factors. We presented our findings of the sex-specific prevalence for these risk factors in Supplementary Table S1, available at *Rheumatology* online. For the continuous variables we present the mean with S.D. or median (25th–75th).

Weight- and height-related risk factors

A total of eight studies [13, 14, 19, 21, 24, 30, 35, 37] examined BMI, as a continuous variable or categorized (i.e. overweight, obese), as a sex-specific risk factor, of which the majority used the Kellgren & Lawrence system (KL scale) in assessing radiographic KOA [13, 14, 21, 24, 30]. BMI and body composition were examined as exposure in different ways across the studies, including *Z*-scores and cut-offs, which made it impossible to meta-analyse the data. Among the high-quality studies [13, 14, 19, 21], we observed significant associations with higher risk estimates in women

Table 3. Sex-stratified association results of activity-related risk factors (12 studies) with prevalence/incidence/progression of KOA

Activity and related risk factors	Outcome[a]	Women	Men	Reference
Knee injury	KL scale, prevalence	OR 0.7 (95% CI 0.3, 1.7)	**OR 3.7 (95% CI 1.2, 11.3)**	McAlindon *et al.* (1996) (G)
acute knee injury	KL scale	**RR 7.2 (95% CI 5.2, 9.8)**	**RR 8.7 (95% CI 5.9, 12.9)**	Wilder *et al.* (2002) (G)
Physical activity level, 4th quartile (high level) *vs* 1st quartile (sedentary=reference)	KL scale	**OR 3.1 (95% CI 1.1, 8.6)**	**OR 3.8 (95% CI 0.9, 17.3)**	Felson *et al.* (1997) (G)
METs score (/day), highest *vs* lowest quartile	KL scale	HR 0.96 (95% CI 0.65, 1.40)	**HR 1.84 (95% CI 1.10, 3.06)**	Takiguchi *et al.* (2019) (G)
Physical activity, highest *vs* lowest quartile	KL scale	OR 1.42 (95% CI 0.93, 2.17)	**OR 2.37 (95% CI 1.23, 4.54)**	Soutakbar *et al.* (2019) (F)
Physical activity, highest *vs* lowest quartile	KL scale + symptoms	OR 1.61 (95% CI 0.83, 3.11)	OR 1.47 (95% CI 0.55, 3.92)	Soutakbar *et al.* (2019) (F)
High active (PASE ≥200) *vs* moderate/ low active (PASE <200)	KL scale	OR 1.11 (95% CI 0.80, 1.54)	**OR 1.91 (95% CI 1.20, 3.04)**	Soutakbar *et al.* (2019) (F)
High active (PASE ≥200) *vs* moderate/ low active (PASE <200)	KL scale + symptoms	OR 1.12 (95% CI 0.68, 1.82)	OR 1.18 (95% CI 0.56, 2.46)	Soutakbar *et al.* (2019) (F)
Inactive *vs* less active	ACR criteria, prevalence	OR 1.46 (95% CI 0.87, 2.47)	OR 1.77 (95% CI 0.90, 3.48)	Martin *et al.* (2013) (F)
Habitual physical activity during middle age, highest *vs* least active	KL scale + self-reported symptoms	OR 1.09 (95% CI 0.63, 1.90)	OR 1.34 (95% CI 0.66, 2.74)	Hannan *et al.* (1993) (F)
Walking step rate, lowest *vs* highest	MRI			Hart *et al.* (2020) (F)
Lateral		**RR 2.3 (95% CI 1.1, 4.5)**	RR 1.1 (95% CI 0.4, 2.8)	
Medial		RR 1.4 (95% CI 0.8, 2.5)	**RR 2.3 (95% CI 1.2, 4.7)**	
Occupation, ref = office work	KL scale			Takiguchi *et al.* (2019) (G)
Professional or managerial		HR 0.89 (95% CI 0.53, 1.51)	HR 1.41 (95% CI 0.74, 2.72)	
Manual		HR 1.13 (95% CI 0.75, 1.73)	HR 1.65 (95% CI 0.84, 3.24)	
Jobless or housewives		HR 0.75 (95% CI 0.52, 1.09)	HR 1.70 (95% CI 0.77, 3.78)	
Others		HR 1.24 (95% CI 0.49, 3.10)	HR 1.87 (95% CI 0.52, 6.74)	
At least medium physical demands + knee bending	KL scale	OR 2.53 (95% CI 0.82, 7.85)	OR 0.96 (95% CI 0.49, 1.87)	Felson *et al.* (1991) (F)
		OR 0.36 (95% CI 0.09, 1.40)	**OR 2.22 (95% CI 1.38, 3.58)**	
Manual occupation *vs* non-manual occupation	ACR criteria, prevalence	**OR 1.87 (95% CI 1.22, 2.86)**	**OR 2.03 (95% CI 1.19, 3.49)**	Martin *et al.* (2013) (F)
Total knee force: highest quintile	Prevalence[b]	**OR 1.52 (95% CI 1.15, 2.02)**	**OR 1.70 (95% CI 1.06, 2.70)**	Ratzlaff *et al.* (2012) (F)
Occupational knee force: highest quintile	Prevalence[b]	OR 1.37 (95% CI 0.95, 1.98)	OR 1.93 (95% CI 0.95, 3.90)	Ratzlaff *et al.* (2012) (F)
Household knee force: highest quintile	Prevalence[b]	**OR 2.02 (95% CI 1.32, 3.01)**	OR 1.17 (95% CI 0.61–2.24)	Ratzlaff *et al.* (2012) (F)
Sport knee force: highest quintile	Prevalence[b]	OR 0.70 (95% CI 0.46, 1.05)	OR 1.13 (95% CI 0.66, 1.93)	Ratzlaff *et al.* (2012) (F)
Standing, 3rd quartile *vs* 1st quartile	KL scale + self-reported symptoms, prevalence	**OR 2.28 (95% CI 1.09, 4.77)**	OR 1.53 (95% CI 0.66, 3.55)	D'Souza *et al.* (2008) (P)
Kneeling, 4th quartile *vs* 1st quartile	KL scale + self-reported symptoms, prevalence	OR 1.31 (95% CI 0.56, 3.07)	**OR 3.08 (95% CI 1.31, 7.21)**	D'Souza *et al.* (2008) (P)
Heavy lifting, 4th quartile *vs* 1st quartile	KL scale + self-reported symptoms, prevalence	OR 1.40 (95% CI 0.51, 3.82)	**OR 2.72 (95% CI 1.14, 6.50)**	D'Souza *et al.* (2008) (P)

[a] Outcome was incidence or progression of knee OA unless mentioned otherwise, [b] 'health-professional-diagnosed knee OA' and 'pain, aching, or stiffness on most days'; i.e. 'prevalence'. Bolded text indicates significant associations. KL: Kellgren & Lawrence system; HR: hazard ratio; OR: odds ratio; RR: relative risk; G: good quality; F: fair quality; P: poor quality.

Table 4. Sex-stratified association results of comorbidities and markers as risk factors for OA (nine studies) with prevalence/incidence/progression of KOA

Comorbidities and markers	Outcome[a]	Women	Men	Reference
Metabolic syndrome (modified ATP III criteria)	KL scale	RR 0.8 (95% CI 0.5, 1.4)	RR 1.2 (95% CI 0.7, 2.0)	Niu *et al.* (2017) (G)
Abdominal obesity		RR 1.0 (95% CI 0.6, 1.9)	RR 1.7 (95% CI 0.9, 3.1)	
High blood pressure		RR 1.3 (95% CI 0.8, 2.0)	RR 1.3 (95% CI 0.8, 2.1)	
High triglycerides		RR 0.7 (95% CI 0.5, 1.2)	RR 1.2 (95% CI 0.7, 1.9)	
Low HDL		RR 0.7 (95% CI 0.4, 1.2)	RR 1.5 (95% CI 0.9, 2.5)	
Fasting glucose (≥100 mg/dl)		RR 0.9 (95% CI 0.5, 1.5)	RR 0.7 (95% CI 0.4–1.2)	
Metabolic syndrome (modified ATP III criteria)	KL scale + pain	RR 1.1 (95% CI 0.6, 2.0)	RR 1.3 (95% CI 0.6, 2.5)	Niu *et al.* (2017) (G)
Abdominal obesity		RR 1.5 (95% CI 0.8, 2.9)	**RR 2.2 (95% CI 1.0, 4.9)**	
High blood pressure		**RR 1.7 (95% CI 1.0, 3.0)**	**RR 1.8 (95% CI 1.0, 3.4)**	
High triglycerides		RR 1.1 (95% CI 0.6, 1.9)	RR 0.7 (95% CI 0.4, 1.3)	
Low HDL		RR 0.8 (95% CI 0.5, 1.4)	RR 0.8 (95% CI 0.4, 1.5)	
Fasting glucose (≥100 mg/dl)		RR 0.9 (95% CI 0.4, 1.9)	RR 0.8 (95% CI 0.3, 1.7)	
Medication-treated diabetes	KL scale			Shirinsky (2017) (F)
Incidence		OR 0.5 (95% CI 0.14, 1.81)	OR 0.59 (95% CI 0.18, 1.97)	
Progression		OR 0.68 (95% CI 0.42, 1.09)	OR 0.59 (95% CI 0.31, 1.13)	
HOMA-IR (per 1 s.d.)	KL scale	OR 0.80 (95% CI 0.69, 0.94)	OR 1.09 (95% CI 0.89, 1.33)	Rogers-Soeder *et al.* (2020) (F)
Atherosclerosis, intima media thickness	KL scale	**OR 1.7 (95% CI 1.1, 2.7)**	OR 1.3 (95% CI 0.68, 2.36)	Hoeven *et al.* (2013) (G)
Markers atherosclerosis	KL scale			Hoeven *et al.* (2015) (G)
VEGF		OR 1.08 (95% CI 0.93, 1.24)	OR 1.07 (95% CI 0.90, 1.28)	
Coronary artery calcification		OR 1.11 (95% CI 0.95, 1.30)	OR 1.11 (95% CI 0.86, 1.43)	
Plasma levels of CD40L		**OR 1.31 (95% CI 1.08, 1.59)**	OR 1.05 (95% CI 0.80, 1.37)	
Vascular cell adhesion molecule 1		**OR 1.32 (95% CI 1.12, 1.56)**	OR 1.08 (95% CI 0.82, 1.42)	
Skin advanced glycation endproducts	OARSI scale (JSN and JSW)	*P* for linear trend = 0.33	*P* for linear trend = **0.03 for JSN (not JSW)**	Eaton *et al.* (2017) (F)
Vitamin E level	KL scale			Chaganti *et al.* (2014) (G)
Middle *vs* lowest tertile		**OR 2.72 (95% CI 1.04, 7.09)**	OR 0.49 (95% CI 0.17, 1.39)	
Highest *vs* lowest tertile		**OR 3.07 (95% CI 1.24, 7.60)**	OR 0.85 (95% CI 0.35, 2.10)	
Chondrocalcinosis	KL scale	OR 1.1 (95% CI 0.4, 3.0)	OR 1.3 (95% CI 0.3, 6.9)	Felson *et al.* (1997) (G)
Hand OA	KL scale	OR 0.7 (95% CI 0.3, 1.7)	OR 1.7 (95% CI 0.5, 6.0)	Felson *et al.* (1997) (G)
Hand OA	KL scale	OR 1.4	**OR 2.8**	Dahaghin (2005) (F)

[a] Outcome was incidence or progression of knee OA unless mentioned otherwise, i.e. 'prevalence'. Bolded text indicates significant associations. KL: Kellgren & Lawrence system; OR: odds ratio; RR: relative risk; G: good quality; F: fair quality; HDL: high-density lipopotein.

Table 5. Sex-stratified association results for lifestyle-related risk factors (four studies) with prevalence/incidence/progression of knee OA

Lifestyle-related risk factors	Outcome[a]	Women	Men	Reference
Soft drinks (times/week)	OARSI scale (JSW)			Lu *et al.* (2013) (G)
≤1 *vs* none		HR 0.80 (95% CI 0.62, 1.02)	**HR 1.56 (95% CI 1.13, 2.16)**	
2–4 *vs* none		HR 1.09 (95% CI 0.77, 1.54)	**HR 1.55 (95% CI 1.02, 2.35)**	
≥5 *vs* none		HR 0.81 (95% CI 0.52, 1.26)	**HR 2.05 (95% CI 1.32, 3.19)**	
Milk intake (glasses/week)	OARSI scale (JSW)			Lu *et al.* (2014) (G)
≤3		**HR 0.67 (95% CI 0.50, 0.91)**	HR 0.77 (95% CI 0.53, 1.13)	
4–6		HR 0.71 (95% CI 0.50, 1.00)	HR 0.92 (95% CI 0.60, 1.40)	
≥7		**HR 0.56 (95% CI 0.38, 0.81)**	**HR 0.61 (95% CI 0.39, 0.94)**	
Smoking, ref = non-smokers	KL scale			Felson *et al.* (1997) (G)
1–9 cigarettes/day		OR 0.6 (95% CI 0.3, 1.1)	OR 1.2 (95% CI 0.5, 3.3)	
≥10 cigarettes/day		OR 0.5 (95% CI 0.2, 1.2)	OR 0.3 (95% CI 0.1, 1.2)	
Smoking, cigarettes/day	KL scale			Takiguchi *et al.* (2019) (G)
Past smoker *vs* non-smoker		HR 0.79 (95% CI 0.44, 1.43)	HR 1.21 (95% CI 0.78, 1.88)	
1–20		HR 1.08 (95% CI 0.54, 2.18)	HR 0.74 (95% CI 0.33, 1.67)	
≥20		HR 0.61 (95% CI 0.15, 2.46)	HR 0.70 (95% CI 0.36, 1.39)	
Alcohol consumption, g/week	KL scale			Takiguchi *et al.* (2019) (G)
1–149 *vs* none/rarely		**HR 1.49 (95% CI 1.12, 1.99)**	HR 1.11 (95% CI 0.66, 1.88)	
≥150 *vs* none/rarely		HR 1.44 (95% CI 0.80, 2.59)	HR 1.01 (95% CI 0.64, 1.58)	
Coffee consumption, ≥4 (cups/day) *vs* <1	KL scale	HR 1.29 (95% CI 0.64, 2.60)	HR 0.73 (95% CI 0.24, 2.19)	Takiguchi *et al.* (2019) (G)
Green tea consumption, ≥4 (cups/day) *vs* <1	KL scale	HR 0.91 (95% CI 0.52, 1.59)	HR 0.46 (95% CI 0.23, 0.95)	Takiguchi *et al.* (2019) (G)
Education level (ref = Junior high school)	KL scale			Takiguchi *et al.* (2019) (G)
High school		HR 1.00 (95% CI 0.73, 1.37)	HR 0.98 (95% CI 0.65, 1.48)	
Junior college		HR 1.07 (95% CI 0.69, 1.66)	HR 0.71 (95% CI 0.30, 1.65)	
University or higher		HR 0.57 (95% CI 0.20, 1.61)	HR 0.58 (95% CI 0.25, 1.36)	
Household income, yen (ref = 0–2 990 000)	KL scale			Takiguchi *et al.* (2019) (G)
3 000 000–5 990 000		HR 1.13 (95% CI 0.98, 1.30)	HR 0.86 (95% CI 0.57, 1.29)	
6 000 000–8 990 000		HR 1.14 (95% CI 0.85, 1.53)	HR 1.18 (95% CI 0.69, 2.03)	
≥9 000 000		HR 1.47 (95% CI 0.98–2.20)	HR 1.08 (95% CI 0.54, 2.18)	

[a] Outcome was incidence or progression of knee OA unless mentioned otherwise, i.e. 'prevalence'. Bolded text indicates significant associations. KL: Kellgren & Lawrence system; HR: hazard ratio; OR: odds ratio; G: good quality.

compared with men, but there is a marked overlap between the 95% CIs. On the other hand, in one fair quality study, there was a slightly higher risk in men [24].

The prevalence of BMI and obesity across the studies (Supplementary Table S1, available at *Rheumatology* online, $n = 8$ described items) showed similar prevalence without clear sex differences, except one study [36] where prevalence of overweight was higher in men compared with women.

Activity-related risk factors

A total of 12 studies looked at sex differences in the association between activity-related risk factors and KOA (Table 3). Three studies examined injury as a risk factor. No clear pattern of sex differences was seen across the studies. Two studies (good quality) found higher risk estimates in men [23, 34]. We found six studies that examined physical activity (PA) as a risk factor for KOA. Overall, we observed that men had a higher risk estimate compared with women in two good-quality studies [14, 21].

A number of activity-related risk factor were identified that were only reported in few studies, making it difficult to draw conclusions. Among those was step rate, which was shown to affect different compartments in the knee with differential effects in women and men in one study [29]. Finally, no association between different categories of occupation compared with office work were found in a good quality study [21].

Evidence on the contribution of knee force and work activities on KOA is minimal and none of the studies were classified as good quality according to the NOS. One fair-quality study on knee force showed no significant differences between sexes; however, when analysing the components of the total knee force ('a quantitative lifelong joint force from work, sport, and household activity measured in joint loading units') separately, higher household knee force significantly associated with higher odds of symptomatic KOA only in women and not in men [36].

The prevalence of knee injury (Supplementary Table S1, available at *Rheumatology* online, $n = 22$ items described) showed significant associations with higher risk estimates in men compared with women across the studies [23, 29, 33, 34, 36]. Global measures of PA, such as the Metabolic Equivalent of Tasks (METs) and Physical Activity Scale for the Elderly (PASE), showed similar prevalence for men and women. However, when type of work or activity was assessed, these showed sex differences in prevalence.

Comorbidities and markers

Two good-quality studies investigating comorbidities found sex differences in their relation with KOA. One good-quality study investigated metabolic syndrome (MetS) and its components [20]. Among the components, abdominal obesity was significantly associated with higher odds in men when looking at symptomatic KOA, but was not present for radiographic OA. High blood pressure, another MetS component, was associated with higher odds in both men and women in the same study [20].

Atherosclerosis was significantly associated with higher odds of radiographic KOA in females in a good-quality study [15]. In addition, in another study (good quality) from the same authors, two out of four atherosclerosis markers showed significant association with higher odds of radiographic KOA in females compared with men [16].

Other studies investigated an ageing marker and antioxidant nutrients, such as vitamin C and E [12, 26]. One fair-quality study showed a significant association between skin advanced glycation end-products (AGEs) and joint space narrowing (JSN) in men but not in women [26]. Interestingly, a good-quality study examining vitamin C and E levels [12] found that higher vitamin E levels were significantly associated with higher odds of radiographic KOA in women but not in men.

Two studies investigated the association between hand OA and radiographic KOA [14, 25]. Hand OA was associated with higher risk for future radiographic KOA development in women, although the CI was wide, in the fair-quality study [25], but did not associate in the good-quality study [14].

The prevalence estimates from the included studies are presented in Supplementary Table S1, available at *Rheumatology* online ($n = 17$ described items). One study showed slightly higher prevalence in men for MetS and much higher prevalence was observed for the separate components of MetS, except for abdominal obesity, which showed similar prevalence in men and women.

Lifestyle factors

Four studies of good quality focused on the sex differences in the relationship between lifestyle factors and KOA [14, 17, 18, 21]. One of these studies found that consumption of at least one soft drink per week was associated with increased change in joint space width (JSW) compared with no use in men only [17]. When stratified by obesity, a stronger dose–response relationship was found in non-obese men. In obese men, only the highest soft drink level ($\geq$5 times/week) was associated with increased change in JSW (adjusted for baseline KL grade) compared with no use. Takiguchi *et al.* [21] investigated several risk factors for KOA in a large Japanese population; however, only alcohol consumption was significantly associated with radiographic KOA incidence only in women.

The prevalence estimates from the included studies are presented in Supplementary Table S1, available at *Rheumatology* online ($n = 10$ described items). Soft drinks, milk, smoking and alcohol consumption were more prevalent in men, while coffee and tea consumption were slightly more prevalent in women.

Discussion

Our findings show that there is only limited information available on sex differences in risk estimates for KOA and sex-specific prevalence of common risk factors. There is an indication for higher risk of KOA due to high BMI in females irrespective of the KOA definition used in the studies, radiographic, clinical or self-reported KOA. Similarly, atherosclerosis and two markers of atherosclerosis showed higher odds in females. In women, alcohol consumption, while in men, soft drinks consumption and high PA, associated with higher risk of radiographic KOA, and there was no conclusive good-quality evidence for clinical KOA. Abdominal obesity was significantly associated with higher odds in men when using a symptomatic definition of KOA, but was not present for radiographic KOA. There is minimal evidence of sex-specific effect of less commonly investigated risk factors, such as walking step rate, skin AGEs in men and vitamin E in women.

We observed that radiographic KOA was the most used definition of the disease, used in 18 studies, while only 8 studies investigated symptomatic/clinical OA. It is well known that there is a discrepancy between structural and symptomatic aspects in KOA as these do not correlate well [39]. Having pain or stiffness in the knee joint does not imply that structural signs (osteophytes, JSN) are present or the other way around. However, severe symptoms tend to be associated with radiographic findings [40]. Moreover, women tend to have more structural OA (in the knee almost twice as often) [41], and they also experience more pain and disability than men [41]. Therefore, it is plausible that sex-specific factors play a key role in both radiographic and symptomatic KOA, and there may even be some differences in factors between the structural and symptomatic form of KOA. In this review, there were not enough good-quality studies using both definition types to make any observation on this aspect, except for BMI where the sex-specific results did not depend on the outcome definition.

The relationship between PA and KOA is complex and not well understood so far. Our findings show evidence of a marked sex difference in the relationship between PA and radiographic KOA. Higher PA levels were associated with higher risk of radiographic KOA only in men ($P = 0.047$ from Z-test for sex differences in effect estimate, Supplementary Table S2, available at *Rheumatology* online); however, only one [14] of the two good-quality studies [14, 21] and the one fair-quality study [33] adjusted for history of injury, which is a strong risk factor for the development of KOA [42]. No significant association was found for symptomatic KOA [28, 33, 35]. This observed sex difference may partly also be due to differences in the intensity and types of PA in which men and women engage [43]. Women traditionally tend to perform more low- or moderate-intensity PA comprised of walking or domestic work, while men tend to perform on average more high-intensity activities, also reflected in our findings over sex-specific prevalence estimates, which could lead to more and frequent injuries in men (Table 2). Mainly high-intensity PA, as in certain occupations or sports, has been shown to be detrimental to the knee joints and has been linked to the development or progression of OA in the future [38, 44]. To sum up, more research is needed to disentangle this complex relationship between PA and KOA where most probably there is a threshold effect and this threshold might be different for women compared with men. In addition, sports were mostly dominated by men in the past, while nowadays, more and more women enter the field, balancing the proportions of the sexes in the sport field. Therefore, all these results might look quite different in future studies.

While certain risk factors have been fairly well examined by sex-stratified analyses, such as BMI and obesity-related factors, more longitudinal studies are needed to investigate the sex differences in the associations of lifestyle, occupational and comorbid factors with future development and progression of KOA. Through a quick search (Supplementary Data S4, available at *Rheumatology* online), for the period since the final date of inclusion, 1 April 2020, until 2 November 2021, we assessed how many new studies have been published

that may be eligible for this systematic review. We found two studies that performed sex-stratified analysis of risk factors for KOA. One study [45] looked at the association of serum uric acid, a marker of gout, that often coexists with OA in the same patient, and found that baseline and averaged serum uric acid significantly associated with cartilage loss only in female participants after adjustment for possible confounders (OR 0.54, 95% CI 0.30, 0.97 and OR 0.46, 95% CI 0.22, 0.99, respectively). However, a relatively lower prevalence of gout among females was observed, thus they may comprise a different risk group in terms of OA progression. The second study found is our recent prospective study investigating sex differences in risk factors for radiographic KOA. In line with the findings of this systematic review for radiographic KOA, we also found significant sex differences for BMI and PA, although we were not able to adjust for injuries in the latter case [11]. We noted that, overall, there is a need for more good-quality studies to investigate the sex-specific effect of the risk factors on symptomatic/clinical OA.

The present review has some strengths. This is the first systematic review to present the current knowledge on sex differences in risk factors for KOA. The findings of this review bring insight, first, into the level of evidence on sex differences in the association of risk factors for KOA, and secondly, into the sex differences in the prevalence of these risk factors. The low number of high-quality studies on several risk factors hindered us from making strong conclusions about our findings, but we found some risk factors that have potential to be considered for preventive strategies, i.e. high BMI, PA, abdominal obesity, soft drink consumption, walking step rate, skin AGEs and vitamin E levels. Research into sex differences in OA could help in designing better preventive strategies and in developing sex-specific treatments in the future.

Our review has also some limitations. First, due to the small number of studies and inconsistencies in exposure definitions and outcome measures, we refrained from performing a meta-analysis. Secondly, we excluded case–control studies that may have added some evidence to additional risk factors but these are in general regarded as lower level of evidence because there is the potential selection bias in choosing the control group. Thirdly, given the objective of this review, it was not possible to cover all potential risk factors for KOA. We included articles on risk factors that are patient-determined, socio-demographic, previous knee events or comorbid conditions. We excluded studies that investigated risk factors such as low muscle strength or malalignment and clinical factors or outcomes such as cartilage loss and other imaging or genetic markers. Thus, we focused our review on more easily identifiable factors in the general population. Fourth, we did not look at possible differences in results among studies looking at onset compared with progression of KOA. Moreover, we excluded non-English studies, which means that we may have missed additional papers. Finally, it was not very clear from the included studies if these focused on aetiologic (causal factors) or predictive factors. Therefore, in our systematic review we focus on finding which risk factors play a role in sex differences in associations, irrespective of whether these were causal or predictive, for KOA. Since these have different implications, it should be further researched. Our paper is only the first step in assessing the current evidence on factors that may play a role in sex differences for KOA.

Overall, our findings show that possible sex differences may exist in the association between common risk factors and KOA and in the prevalence of these risk factors; therefore, it is crucial to study OA risk factors stratified by sex through good-quality studies to build a comprehensive picture on the effect of risk factors on KOA. Future studies and systematic reviews should also report the sex differences of risk factors for other joints often affected by OA, i.e. hip and hand.

In conclusion, our review shows that there is great uncertainty over whether there are sex differences in the effect of common risk factors for the risk of KOA. Our findings suggest an indication of sex differences in certain risk factors leading to higher risk of KOA: high BMI, alcohol consumption, atherosclerosis and high vitamin E levels in women, and high PA, soft drink consumption and abdominal obesity in men. Based on the current evidence, knee injury, high blood pressure and low step rate affect both women and men. In addition, our review shows that PA and knee injuries are more prevalent in men than women, while BMI shows similar prevalence in the two sexes. The results of this review might be used by healthcare professionals to identify and manage patients at risk of developing or increasing risk for KOA. Some risk factors are easier to target, such as weight loss, while some others may need more strategic implementations, i.e. PA due to its threshold effect. Beside raising awareness, we hope our findings will convince researchers to look into sex differences systematically when investigating risk factors for OA, possibly also in other joints.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

All data generated or analysed during this study are included in this published article and available upon request from the corresponding author.

Contribution statement

All authors contributed substantially to the conception and design of the article. I.A.S. performed the analysis and drafted the initial manuscript. All authors critically revised it for interpretation of results and important intellectual content. All authors approved the final version of the manuscript.

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