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SUMMARY

Objective: To identify and quantify risk factors for incident knee osteoarthritis (KOA) across the lifespan.
Methods: This systematic review and meta-analysis identified eligible studies from seven electronic databases and three registries. Longitudinal cohort studies or randomised controlled trials evaluating participants who developed incident symptomatic and/or radiographic KOA were included. Two independent reviewers completed data screening and extraction. Estimates were pooled using a random effects model and reported as odds ratio (OR), hazard ratio, or risk ratio and corresponding 95% confidence intervals (95% CI). Grading of Recommendations, Assessment, Development and Evaluation was used to determine the certainty of evidence. Population attributable fractions were calculated, including risk factors significantly associated with radiographic KOA based on the pooled meta-analysis and where we could determine communality scores using existing clinical datasets.
Results: We identified 131 studies evaluating > 150 risk factors. Previous knee injury, older age and high bone mineral density were associated with an increased risk of incident radiographic KOA based on the pooled analysis [OR (95% CI): 2.67 (1.41, 5.05), 1.15 (1.00, 1.33) and 1.82 (1.12, 2.94), respectively], with moderate-to-high certainty. Two risk factors (overweight/obesity and previous knee injury) accounted for 14% of incident radiographic KOA. Other modifiable risk factors, including occupational physical activity, also contribute to radiographic or symptomatic KOA.
Conclusion: Novel strategies addressing known modifiable risk factors including overweight/obesity, knee injuries and occupational physical activity are needed to reduce overall burden of KOA.
Systematic review registration: PROSPERO ID: CRD42023391187

Introduction

Knee osteoarthritis (KOA) is a leading cause of disability.[1,2] The worldwide age-standardised prevalence of KOA was estimated to be 4307 cases (95% Uncertainty Interval: (3845–4913) per 100,000 population).[3] Global estimates point to an increasing prevalence of symptomatic KOA with age, however estimates and certainty of point prevalence vary by age group and country.[4–7] A review estimated global prevalence of approximately 16.0% (95% confidence interval (CI) 14.3–17.8%) in people aged ≥15 years and approximately 22.9% (95% CI 19.8% to 26.1%) in people aged ≥40 years.[4–6] Lifetime risk for symptomatic KOA has been estimated to be as high as 45%.[8] This risk increases to 60.5% in obese individuals compared to normal weight or overweight individuals (30.2% or 46.9%, respectively).[8] Osteoarthritis (OA) is a global public health problem due to increasing rates of obesity and an ageing population, urging the implementation of wide-scale population-level preventive strategies.[9]

A 2015 review summarised the literature on risk factors for the onset of KOA in adults.[10] That hitherto largest review evaluated just 16 risk factors for incident KOA across 46 studies, was published in 2015, excluded studies not published in English and focussed on a cohort aged ≥50 years.[10] It did not provide Grading of Recommendations Assessment, Development and Evaluation (GRADE) ratings for effect estimates and pooled across outcomes and measures of effect, resulting in pooled estimates with high heterogeneity and therefore, unclear clinical applicability. Other published reviews are either narrative, focus on a specific risk factor, such as knee extensor strength[11] or malalignment[12] or do not provide pooled estimates.[13]

A timely update of the evidence is needed to inform KOA prevention and guideline recommendations[14] as several reports have been published since these reviews. Given that prevention of symptomatic and radiographic KOA remains a priority for population health and individual patient care, the aims of this systematic review were to identify and quantify potential risk factors associated with increased or lowered risk of incident KOA and to determine the relative contribution of identified risk factors for incident symptomatic and radiographic KOA across the lifespan.

Methods

This systematic review was registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD42023391187) and the results are reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines.[15]

Search strategy and selection criteria

Searches were conducted in MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, the Chinese National Knowledge Infrastructure and Pan African Clinical Trials Registry], ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform and the European (EU) Clinical Trials Register (www.clinicaltrialsregister.eu) from their inception to June 3, 2024. The MEDLINE search strategy was developed in consultation with a librarian at The University of Sydney. The search strategy syntax was then adjusted for the other databases (Supplemental File 1). The search strategy was supplemented by consultation with content experts and hand searching reference lists of previous reviews.[10–13]

Articles in any language whereby individuals of any age without baseline KOA were considered. Studies needed to define incident KOA and provide quantitative data regarding the risk of incident KOA within the sample(s). Both radiographic and symptomatic/clinical diagnoses of incident KOA (as reported by the studies) were considered.[16] Cohort studies, and randomised controlled trials (RCTs) in which prevention of OA was stipulated as the primary aim and which followed participants to determine incident KOA, were considered. All types of exposures/interventions were eligible. We excluded conference abstracts, case-control or cross-sectional studies, studies which analysed data from < 200 participants,[17] had follow-up of < 1 year, solely included participants with KOA at baseline. Studies were excluded if they assessed knee pain exclusively as a risk factor or assessed KOA using magnetic resonance imaging, as we considered these to be evidence of early-stage OA features.

Citations were exported into EndNote and duplicates were removed. Citations were then imported into Covidence (www.covidence.org) for title, abstract and full text screening[18] by two authors independently (VD, CAS, JZ, IA, SLG, SK). Conflicts were resolved by discussion or by an adjudicator (MLF, DJH).

Data extraction

A custom data extraction form was used which included bibliometric data, study/cohort characteristics, incident KOA assessment and classification, treatment or exposure details and outcome data [odds/risk/hazard ratio (HR) estimates and 95% CIs]. Two authors independently extracted data (VD, CAS, SWN, JZ, IA, SLG, SK) and datasheets were checked for completeness by one author (SWN). Discrepancies were resolved through discussion and a third reviewer (MLF, DJH) was consulted if necessary.

Risk of bias

Risk of bias was assessed independently by two authors (VD, CAS, SWN, JZ, SK, SLG, IA) using the Cochrane Risk of Bias tool (RoB-1) for included RCTs and the Modified Quality In Prognosis Studies (QUIPS)[19] for cohort studies.

Data synthesis and analysis

Following data checking, risk estimates, and 95% CIs were transferred into a separate data extraction sheet for analysis. Meta-analyses were conducted to obtain a pooled risk estimate and corresponding 95% CIs when at least two studies reported on the same risk estimate outcome (odds ratio (OR), risk ratio (RR), hazard ratio (HR)) for a given risk factor, met the following criteria:

(1) Examined the same risk factor and utilised the same measurement approach,
(2) Assessed incident KOA using the same operational outcome (symptomatic or radiographic KOA etc.),
(3) Employed a similar analysis approach (univariate or multivariate),
(4) Had the same unit of analysis (i.e., at the knee or person level).

For pooled analyses, we used adjusted estimates that had adjusted for similar covariates (e.g., age and sex). Random effects meta-analyses were performed using the DerSimonian-Laird method.[20] To account for a small number of studies (< 5), the truncated Knapp-Hartung standard error adjustment was applied to the pooled effect.

Assessment of heterogeneity and bias

Tests of heterogeneity were conducted using the Q statistic. Variability due to between-study heterogeneity was quantified using the I^2 statistic. Where the I^2 statistic indicated high between-study heterogeneity ($I^2 > 50\%$), a sensitivity analysis was performed using the leave-one-out meta-analysis approach to help identify potential sources of heterogeneity. All meta-analyses were conducted using STATA, version 18.0.

The overall certainty of evidence was assessed using a modified GRADE framework.[21] Pooled estimates were assigned a certainty of evidence rating (high, moderate, low, very low). Overall certainty of evidence started at high and was downgraded by one level for: (1) risk of bias; (2) inconsistency; (3) imprecision; (4) publication bias (Supplemental File 2). We did not downgrade for indirectness, as our review encompassed a specific research question and condition. For single cohort studies, overall certainty of evidence started at moderate and was downgraded one level for risk of bias (modified QUIPS rating of high or moderate risk) or imprecision. We used a modified version of the QUIPS tool to assess risk of bias of cohort studies. The six domains considered were: study participation, study attrition, risk factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

Publication bias

Publication bias was assessed when ten or more studies contributed to an effect estimate using the Begg's test.[22]

Population attributable fraction (PAF) calculation

Our PAF calculations included risk factors that were found to be associated with radiographic KOA based on the pooled effect (computed from the adjusted analysis reported in individual studies) and where we

could determine communality scores using existing clinical datasets. There was insufficient data to allow PAF calculations for symptomatic KOA. The RR estimates from multiple studies were pooled using random effects based meta-analysis. The weighted PAF measure was computed using communality-based weights, based on person-level data.

The communality was computed as part of a principal component analysis. A description of the methodology is described in Supplemental File 3. The Osteoarthritis Initiative (OAI) dataset (incidence cohort) was used to compute the communalities of available risk factors, as this dataset is similar to our study context and scope.[23]

Protocol deviations

We present data on KOA only and not hand or hip OA, to avoid potential clinical heterogeneity and support a clear clinical message and recommendations.

Decisions to exclude studies with < 200 participants or follow-up < 1 year were to avoid imprecise estimates due to the heterogeneity of the condition and allow sufficient time to observe our outcome of interest, respectively. We used a modified version of QUIPS instead of the Newcastle-Ottawa scale to assess risk of bias of cohort studies.

Results

Of 14,363 records, 6129 duplicates were removed. A total of 8234 titles and abstracts were screened, full texts of 401 records were inspected and 131 papers were included (Fig. 1). Excluded studies and reasons for exclusion are found in Supplemental File 4.

General characteristics of the included studies

We included 131 studies.[24–154] Two papers reported on the same RCT and population group but over different time points (2.5 and 6–7 years, respectively)[24,25] and 129 were cohort studies, published between 1988 and 2024.[26–154] The most common cohorts included the OAI (n=26),[32,35,40,47,51,55,57,69,71,73,80,87,88,90,99,103,106,121–123,127,134,136,137,142,146] the Multicentre Osteoarthritis Study (MOST) (n=17),[36,38,64,66,72,75,82,90,106,109,114,125,128,129,132,135,146] and the Framingham/Framingham Offspring Cohorts (n=13), all of which were conducted in the USA.[28,49,59,65,68,74,91,94,100,110,131,141,148]

The sample size in the cohort studies ranged from 215[60] to ≥1.7 million.[29] Age of participants ranged from median interquartile range (IQR) 22.8 (20–26)[84] to a mean standard deviation (SD) of 80.7 (5.0)[28] years, with percentages of females ranging from 20%[102] to 100%.[125,141] Ethnicity was uncommonly reported. The average length of follow-up ranged from 1 year[145] to 40 years[74] (Supplemental Files 5 and 6).

Most studies used ORs to report the risk of incident KOA (n=77).[26–28,30–32,35,36,38–41,45,47–50,53–55,57,59,61,62,65–68,70–76,78–81,85–87,90,95,97,98,100,103,106–108,110–112,115,117,122–124,127–129,132–136,138,139,141,143,146,148–150,153,154] Twenty-six cohort studies reported risk of incident KOA using HR (20.8%).[29,33,37,42–44,51,56,58,69,77,83,89,92,93,99,101,105,113,118–120,126,137,142,151] Twenty-one cohort studies reported risk of incident KOA using RR (14.6%).[34,46,52,63,64,82,88,91,94,96,104,109,114,116,121,125,130,131,140,144,147] Five studies used other measures, such as probability estimates or percentages (3.1%).[60,84,102,145,152]

Over half of the studies (n=73, 56.2%) defined incident KOA using radiographic criteria,[26,27,30,32,34,35,39,40,44,45,48–51,54,59–62,67–76,78,80–82,

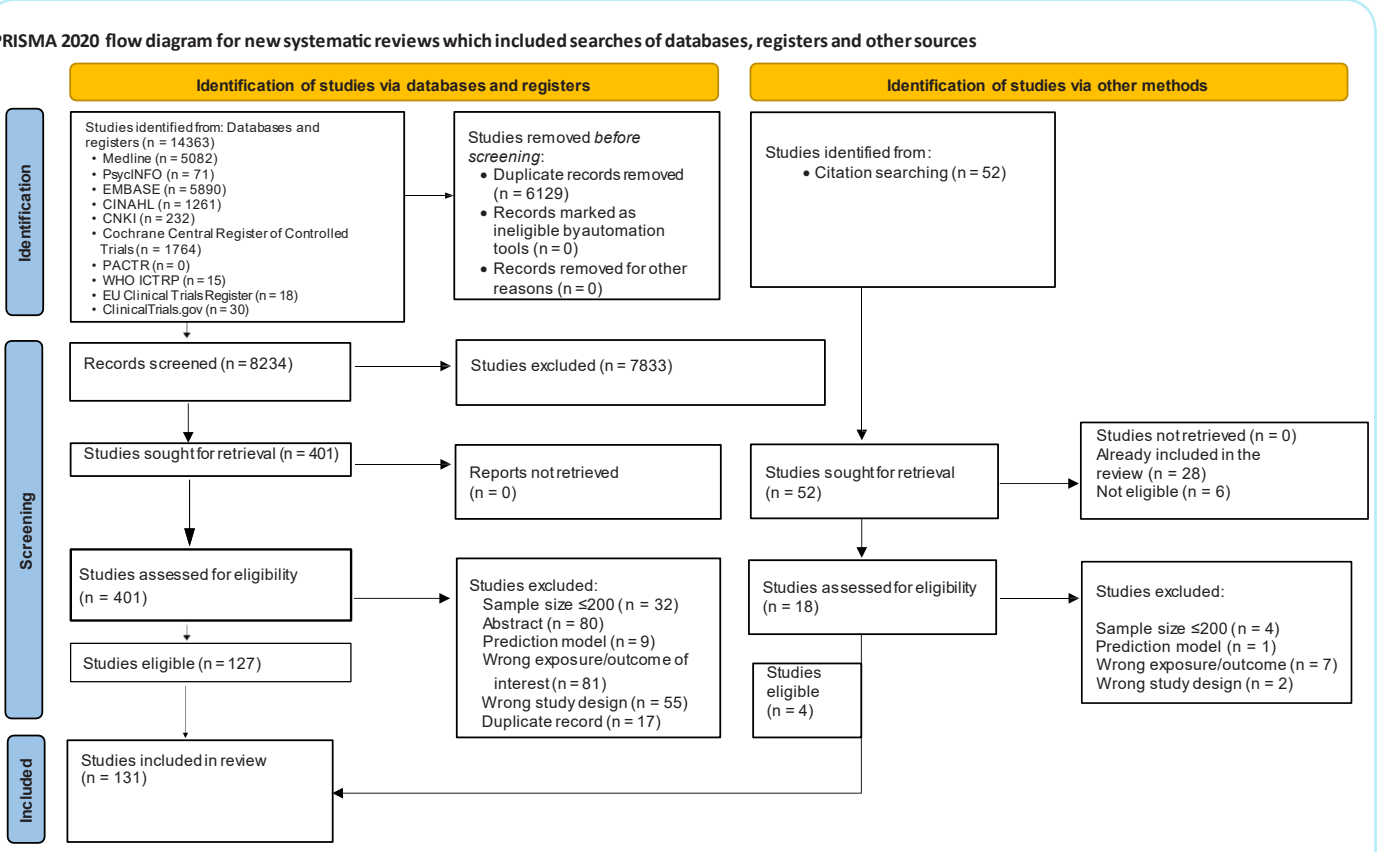

Fig. 1

Osteoarthritis and Cartilage

PRISMA flow diagram.

84,89–94,96,97,100–104,107–112,114,118,120,123–126,129,130,133,135–140,142–144,153

most commonly as Kellgren and Lawrence (KL grade) ≥2. Nine studies reported on symptomatic KOA without evidence of radiographic KOA,[31,37,63,79,85,86,95,116,141] 26 studies reported symptomatic-radiographic KOA[28,36,41,47,55,57,64–66,87,88,99,106,117,119,121,122,127,128,131,132,134,145,146,148,150] and nine used a combination of approaches (self-report, physician diagnosed).[38,43,46,98,105,149,151,152,154] Twelve studies used the International Classification of Disease 9th Revision (ICD-9) or 10th Revision (ICD-10) codes[29,33,42,52,53,56,58,77,83,113,115,147] (Supplemental Files 5 and 6).

Risk of bias of included studies

Of the 129 cohort studies, 90 were appraised as having low risk of bias, 24 had moderate risk of bias and 15 had high risk of bias. Of the two studies which originated from the same RCT, both were low risk of bias (Supplemental Files 7 and 8).

Pooled analysis

Potentially modifiable risk factors (e.g., overweight/obesity, previous knee injury) were considered separately from non-modifiable risk factors (e.g., age, sex). Data extractions for risk estimates are presented in Supplemental Files 9 to 11. Pooling of effect estimates was possible for ten potentially modifiable and non-modifiable risk factors and are presented in Fig. 2, with significant associations demonstrated for five (detailed below). Supplemental Figs. 1–13 present the forest plots, including individual studies.

Over 150 risk factors were reported. Numerous risk factors were associated with a lower incidence of KOA (moderate to low-quality evidence (Fig. 3)). However, most risk factors identified were associated with a higher incidence of KOA (Figs. 4–6).

We present the results from a select number of risk factors where there were sufficiently large sample sizes. Further results are described in the Supplemental File 12. The GRADE ratings are presented in Figs. 3–6.

Potentially modifiable risk factors

Overweight/obesity

Thirty-two studies evaluated body mass index (BMI) as a risk factor for developing incident KOA. Of these, 20 evaluated radiographic KOA and the remaining evaluated symptomatic KOA.

Radiographic KOA

Pooling was possible for five studies,[26,32,81,112,149] which evaluated BMI as a continuous exposure. For every unit increase in BMI, individuals were 17% more likely to develop radiographic KOA (adjusted OR 1.17, 95% CI 1.10, 1.24). The between-study heterogeneity was high (I^2 = 52.9%). Sensitivity analysis excluding one study[149] reduced I^2 to 47.6%, yet the estimate remained similar (aOR 1.19, 95% CI 1.12 1.27) (Fig. 2). For studies unable to be pooled,[45,97,98,111,133] the effect estimates ranged from adjusted odds ratio (aOR) 1.6 (1.0, 2.8)[98] to 18.3 (5.1, 65.1)[111] for individuals who were at least overweight (BMI ≥25 kg/m^2).

Four studies investigated the effect of BMI on RR of incident radiographic KOA.[82,104,109,114] There was a statistically significant association between BMI and medial tibiofemoral OA but not lateral tibiofemoral OA in people who are overweight or obese.[109]

Symptomatic KOA

When repeated measures of BMI were considered across the lifespan in a United Kingdom birth cohort study, the greatest odds of

Risk factor	Effect Measure	Outcome	No studies Reference	Effect estimate	Lower limit	Upper limit	I^2	GRADE
Age	OR	ROA	3 [76,90,112]	1.15	1.00	1.33	89.26	Low
Sex female	OR	ROA	7 [26,32,76,90,110,112,133]	1.93	1.25	2.98	63.52	Low
Sex female	OR	SxOA	2 [79,133]	4.32	0.88	21.12	96.40	Very Low
Sex female	HR	ICD OA	2 [42,59]	1.30	1.07	1.59	0.00	Moderate
Alcohol	OR	ROA	2 [78,133]	0.51	0.25	1.04	83.57	Very Low
BMI Obese	HR	ICD OA	2 [42,59]	3.10	2.45	3.94	0.00	Moderate
BMI Overweight	HR	ICD OA	2 [42,59]	2.02	1.65	2.46	0.00	Moderate
BMI per 1 unit increase	OR	ROA	5 [26,32,81,112,149]	1.17	1.10	1.24	52.87	Low
Femoral neck BMD	OR	ROA	2 [27,50]	1.82	1.12	2.94	31.84	High
Knee Injury	OR	ROA	6 [26,76,78,90,110,111]	2.67	1.41	5.05	27.04	Moderate
Knee Injury	HR	ICD OA	2 [42,113]	3.58	1.54	8.32	79.51	Moderate
Osteoporosis	OR	ROA	2 [112,133]	1.41	0.70	2.86	65.52	Very Low
Physical Activity Q2	OR	ROA	2 [74,110]	1.55	0.82	2.92	50.20	Very Low
Physical Activity Q3	OR	ROA	2 [74,110]	1.54	0.82	2.90	87.60	Very Low
Physical Activity Q4	OR	ROA	2 [74,110]	1.85	0.68	5.03	78.10	Very Low
Smoking	OR	ROA	4 [26,110,112,133]	0.56	0.20	1.58	91.68	Very Low

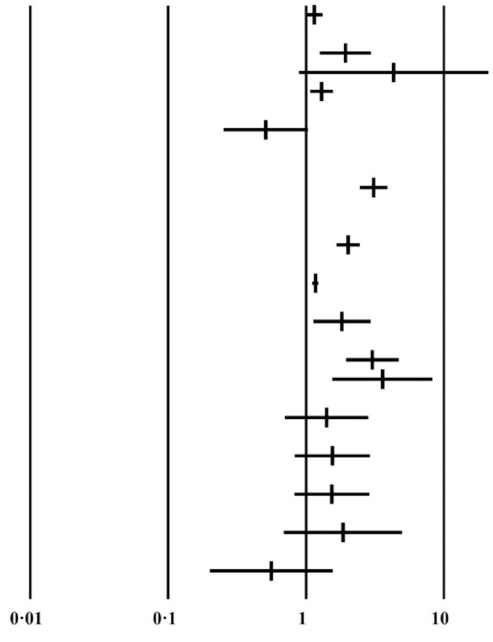

Fig. 2

Osteoarthritis and Cartilage

Meta-analysis results for all pooled studies. Abbreviations: ROA, radiographic osteoarthritis; SxOA, symptomatic osteoarthritis; ICD OA, osteoarthritis defined using International Classification of Disease codes; Q2/Q3/Q4, quartiles of physical activity.

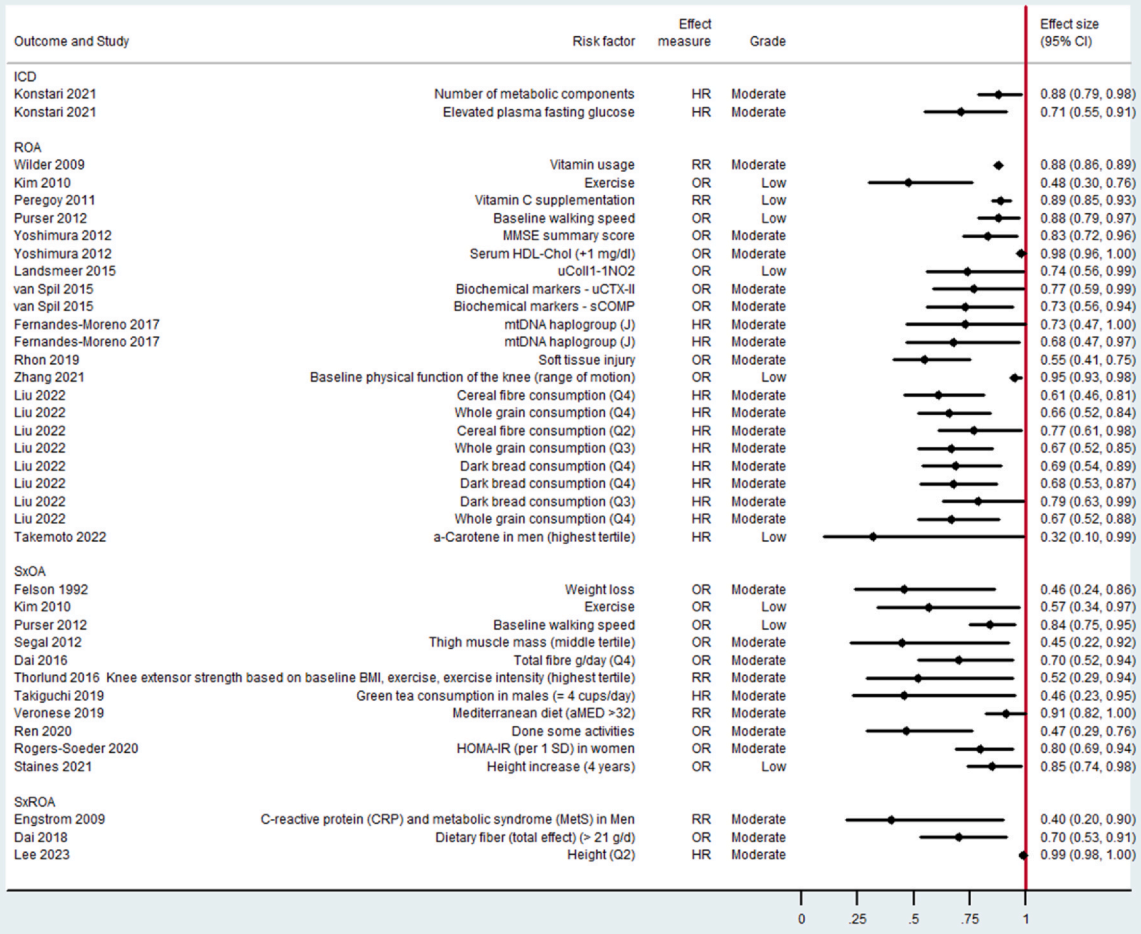

Fig. 3

Osteoarthritis and Cartilage

Risk factors associated with lower incidence of knee OA. *For referent categories, refer to the Supplemental Files 9–11. Abbreviations: ROA, radiographic osteoarthritis; SxOA, symptomatic osteoarthritis; ICD OA, osteoarthritis defined using International Classification of Disease codes; aMED, alternate Mediterranean diet score; HDL, high-density lipoprotein; HOMA-IR, homoeostatic model assessment for insulin; Q2/Q3/Q4, quartiles of fibre consumption; MMSE, Mini-Mental State Examination; mtDNA, mitochondrial DNA.

incident symptomatic KOA was found for high BMI at 43 years of age (aOR 2.64; 95% CI 1.8, 3.87).[85] However, two studies evaluating symptomatic KOA found conflicting results for individuals with BMI ≥25 kg/m^2 in Korean and Chinese adults, with statistically significant results found in the Korean, but not the Chinese cohort.[79,133] One study reporting on HRs found Japanese females and males with BMI ≥25 kg/m^2 were at higher risk of developing incident symptomatic KOA, 4.13 (95% CI 2.15, 7.94) and 7.74 (95% CI 1.07, 55.91) respectively.[93]

Previous knee injury

Eleven studies[28,56,60,76,98,109–111,113,115,144] investigated the impact of previous knee injuries (self-reported injury resulting in impaired function (e.g., inability to walk for ≥2 days))[109] on incident KOA. Most studies investigated anterior cruciate ligament (ACL) injuries with/without meniscus injuries.

Radiographic KOA

Six studies reporting ORs for the association between past knee injury and incident radiographic KOA were pooled and found an almost three-fold increased odds (aOR 2.67 95% CI 1.41, 5.05)[26,76,78,90,110,111] (Fig. 2). Previous knee injury was associated with incident radiographic KOA in both medial and lateral compartments in the MOST and OAI cohorts, the adjusted risk ratio (aRR) ranged from 1.57 (95% CI 1.13, 2.19) to 2.08 (95% CI 1.3, 3.31).

Habitual/Leisure-time physical activity level

Fourteen studies[40,58,65,73,74,89,94,98,99,106,110,127,148,153] reported on leisure-time physical activity using various measures. Two studies reporting ORs were pooled.[74,110] These studies measured physical activity using the Framingham Physical Activity Index. The pooled estimate showed no association between physical activity quartiles and incident radiographic KOA in elderly patients (ranging from

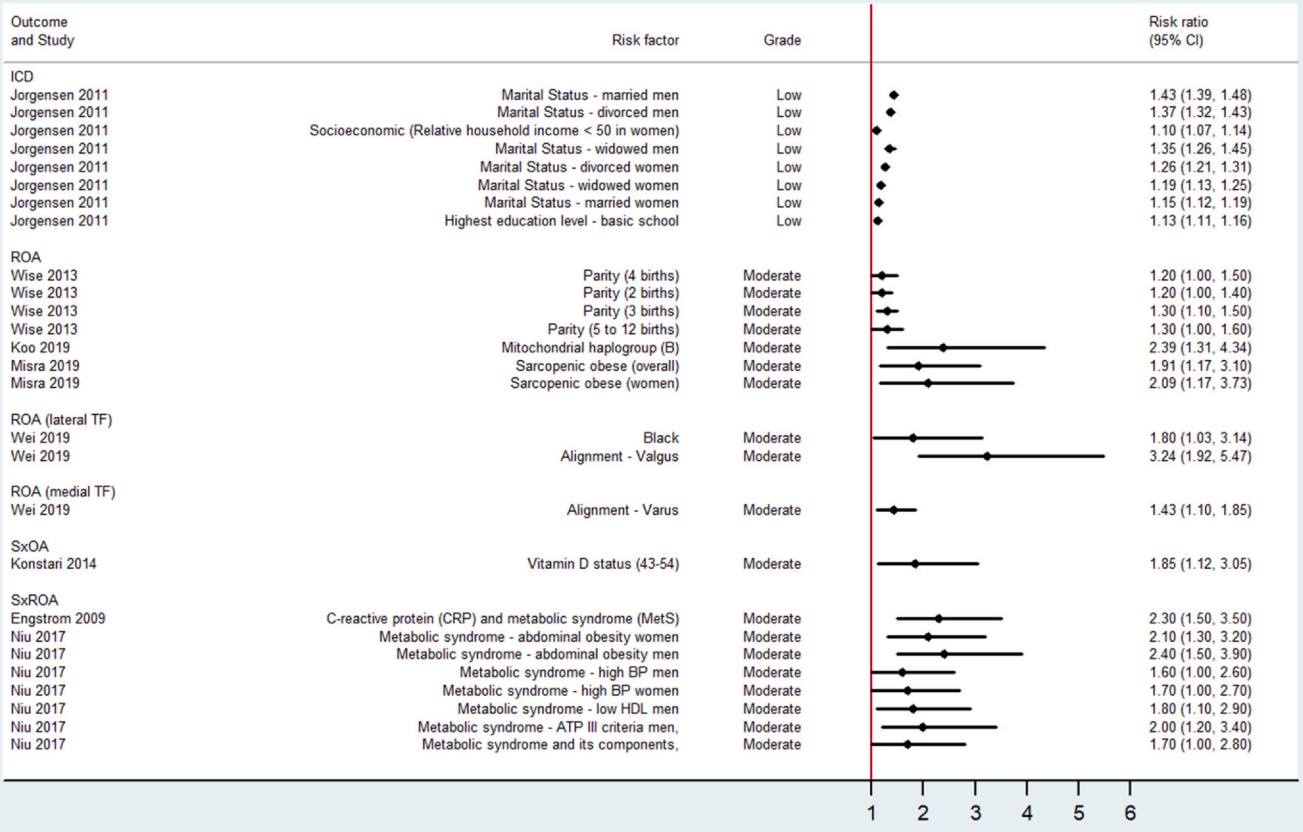

Fig. 4

Osteoarthritis and Cartilage

Risk factors associated with higher incidence of knee OA (relative risk). *For referent categories, refer to Supplemental File 9. Abbreviations: ROA, radiographic osteoarthritis; SxOA, symptomatic osteoarthritis; ICD OA, osteoarthritis defined using International Classification of Disease codes; Q2/Q3/Q4, quartiles of physical activity.

Quartile 1 (sedentary) to Quartile 4 (high levels of leisure-time physical activity) (Fig. 2)).

A further seven studies[40,58,65,89,98,99,106] showed no association between leisure-time physical activity and incident radiographic or symptomatic KOA. Two studies[94,127] found that high levels of leisure-time physical activity in overweight or obese individuals was associated with incident KOA, with one showing that the weight-associated risk for KOA was increased in women with high levels of physical activity; RR 3.6 (1.7 to 7.7) for the heaviest quintile.[94] Similar trends were observed for men. One study showed that football participation, including in the teen years was associated with greater risk of incident radiographic or symptomatic KOA.[73]

Total recreational physical activity and weight bearing physical activity in individuals with low levels of lower-limb muscle mass were found to be associated with incident radiographic KOA; OR 1.20 (1.07, 1.34) and 1.21 (1.09, 1.35) respectively.[153] Heavy levels of daily habitual physical activity (≥ 1 h per day) were found to be associated with incident radiographic KOA in one study (OR), whereas no associations were found between light or moderate levels of daily habitual physical activity (≥ 1 h per day) and incident radiographic KOA.[148]

Occupational physical activity

Nine studies investigated occupational risk factors, including occupational physical activity and their association with KOA.[42,58,80,93,98,100,119,133,146] Eight showed a clear association between occupational physical activity and incident radiographic and/or symptomatic KOA. This included work that required walking while handling materials (compared to jobs mostly involving sitting),[80] and occupations which combine knee bending and physical demands.[100] One study reporting on HRs, did not find an association between type of work (office work, professional, manual, jobless or housewives) and incident symptomatic KOA in a Japanese cohort.[93]

Three studies reported on occupational job category and/or workplace physical activity.[80,133,146] They found that manual work (ranging from light, light manual and heavy), were associated with incident radiographic KOA, symptomatic-radiographic KOA and

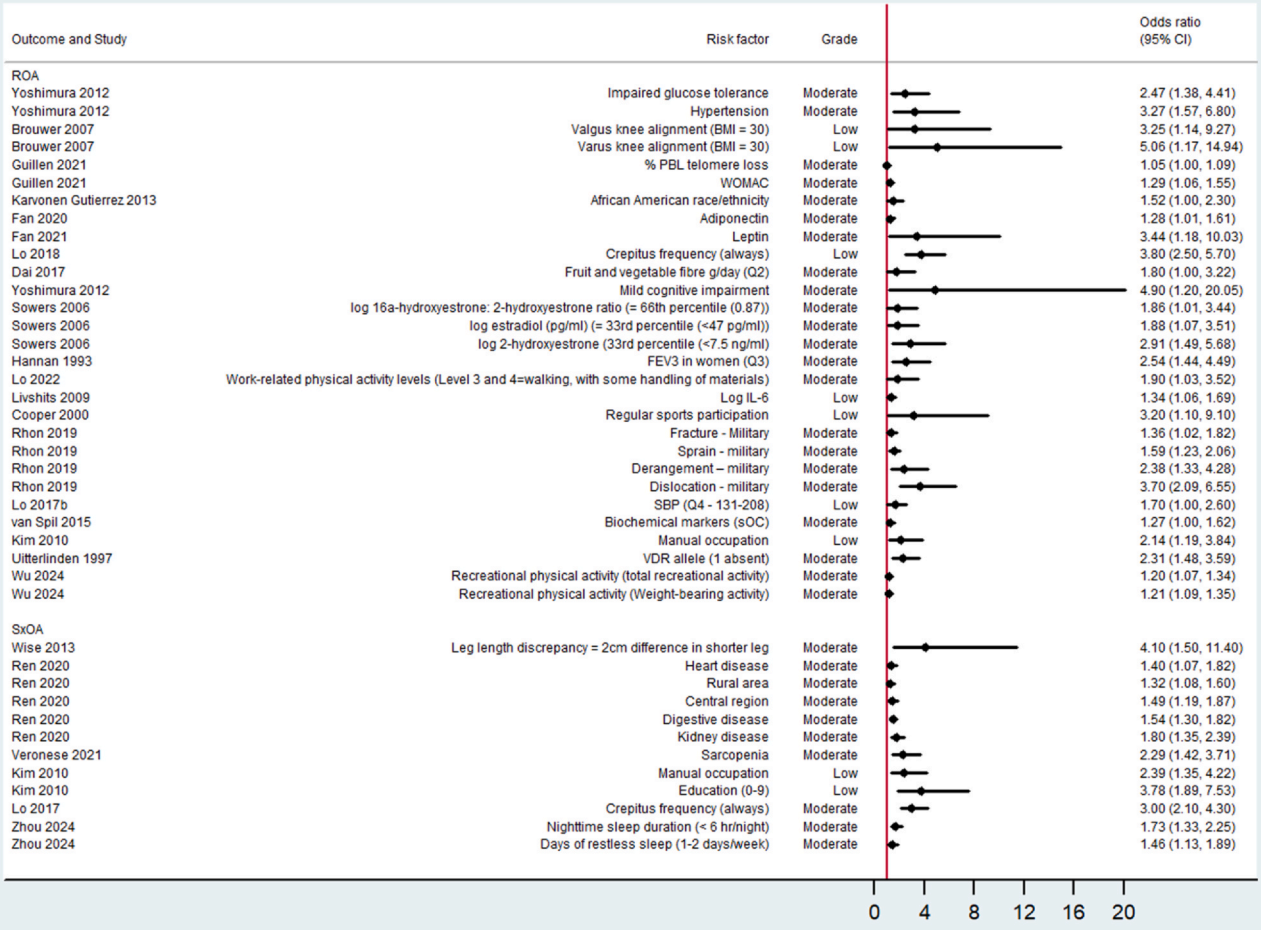

Fig. 5 Osteoarthritis and Cartilage

Risk factors associated with higher incidence of knee OA (odds ratio). *For referent categories, refer to Supplemental File 10. Abbreviations: ROA, radiographic osteoarthritis; SxOA, symptomatic osteoarthritis; ICD OA, osteoarthritis defined using International Classification of Disease codes; TF, tibiofemoral; ATP III, National Cholesterol Education Program Adult Treatment Panel III; BP, blood pressure; HDL, high-density lipoprotein.

symptomatic KOA. Men had a two-fold greater risk of incident radiographic KOA if they engaged in heavy, manual occupations (aRR 2.7 95% CI 1.17, 6.26).[146] However, an association was not seen for women.

Manual handling of loads > 20 kg for ≥13 years, was associated with incident KOA (ICD criteria) (adjusted hazard ratio (aHR) 1.71 95% CI 1.03, 2.85).[58] Another study reported associations between shift work exceeding 20 years and incident radiographic KOA (aHR 1.28 95% CI 1.04, 1.57).[119]

Bone mineral density (BMD)

Three studies reporting on ORs evaluated the association between areal BMD and radiographic KOA.[27,49,50] Pooled results from two studies found an association between higher femoral neck BMD (mean femoral neck BMD ≥1.01 g/cm^2 at baseline) and incident radiographic KOA (aOR 1.82 95% CI 1.12, 2.94). A higher risk of incident radiographic KOA was also reported with the highest quartile of lumbar spine BMD at baseline in one study (mean BMD: 1.32 g/cm^2, aOR 4.7 95% CI 2.1, 10.7).[50]

Non-modifiable risk factors

Sex and gender

Nineteen studies assessed female sex or gender as a potential risk factor for KOA.

Radiographic KOA

Pooled results from seven studies found that females had almost double the odds of developing incident radiographic KOA compared to males (aOR 1.93 95% CI 1.25, 2.98).[26,32,76,90,110,112,133] The between-study heterogeneity was high (I^2 = 63.5%). Sensitivity analysis excluding a study[32] reduced I^2 to 30.4% and the effect remained significant (aOR 2.22, 95% CI 1.62, 3.05) (Fig. 2). Another study reporting on HRs found that males were ~40% less likely to develop incident

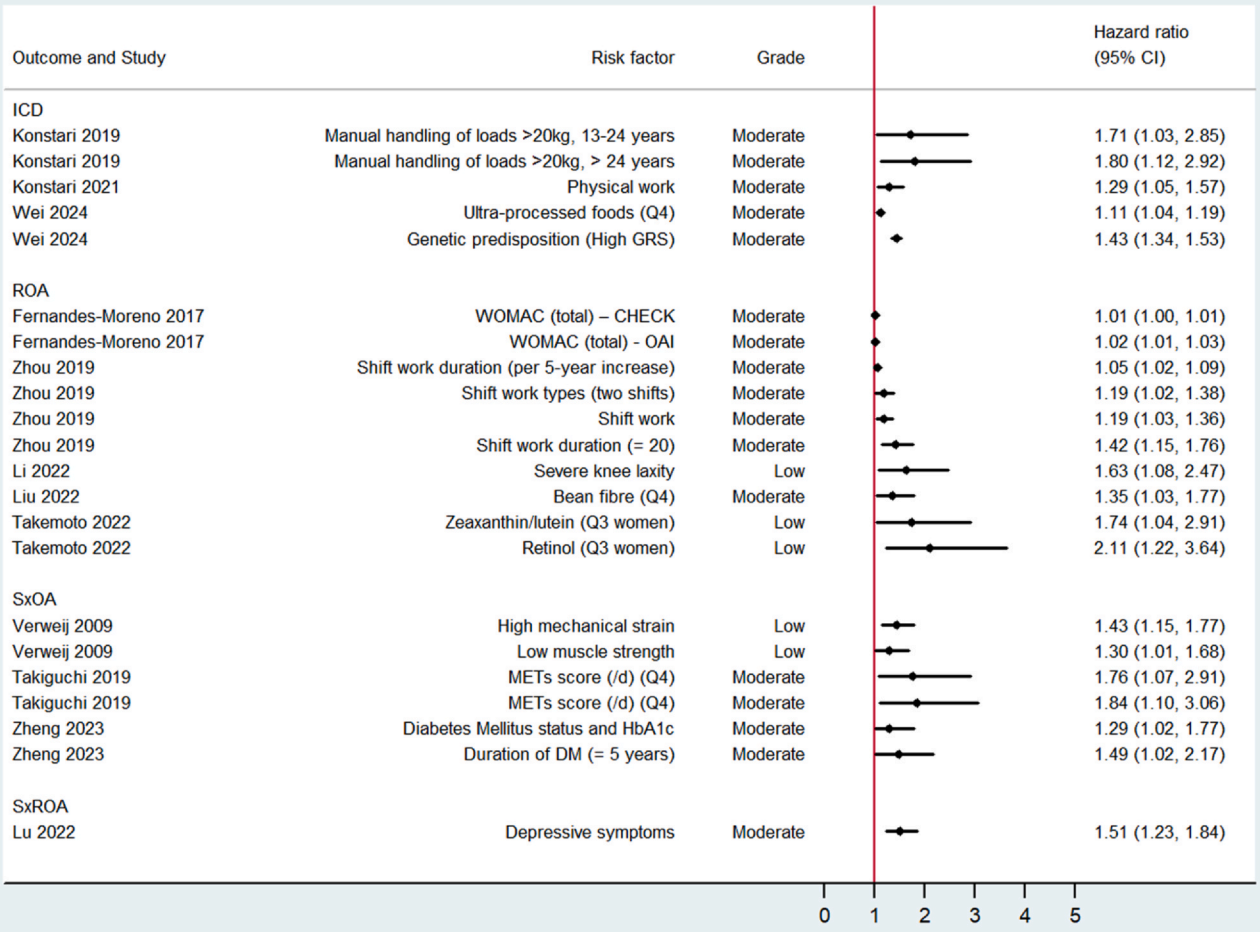

Fig. 6 Osteoarthritis and Cartilage

Risk factors associated with higher incidence of knee OA (hazard ratio). *For referent categories, refer to Supplemental File 11. Abbreviations: ROA, radiographic osteoarthritis; SxOA, symptomatic osteoarthritis; ICD OA, osteoarthritis defined using International Classification of Disease codes; Q2/Q3/Q4, quartiles of physical activity.

radiographic KOA (aHR 0.59 95% CI 0.49, 0.71).[92] Two studies unable to be pooled found female sex was associated with radiographic KOA in the OAI cohort,[92,109] but not in the MOST and the Cohort Hip and Knee (CHECK) cohorts.[92,109]

Symptomatic KOA

The pooled estimate from two studies evaluating symptomatic KOA was not statistically significant.[79,133] Males with uncontrolled diabetes (HbA1C ≥ 7%) were more likely to develop incident symptomatic KOA (aHR 1.62 95% CI 1.08, 2.43), compared to their female counterparts (aHR 1.36 95% CI 0.97, 1.93).[37] One study evaluating RRs found that females had almost double the risk of developing symptomatic KOA (aRR 1.96 95% CI 1.01, 3.82).[131]

Age

Fourteen studies evaluated the association between age and incident KOA.

Radiographic KOA

Three studies reporting on ORs found an association between age and radiographic KOA, with increasing risk as age increased (pooled aOR 1.15 95% CI 1.00, 1.33).[76,90,112] The between-study heterogeneity was high (I^2 = 89.3%). Sensitivity analysis excluding one study[112] reduced the I^2 to 21.8% and the pooled effect remained significant per unit increase in age (aOR 1.06, 95% CI 1.02, 1.10) (Fig. 2). One study reporting on HRs did not find an association between age and incident radiographic KOA.[92]

Three studies reporting RRs found associations between age and radiographic KOA.[94,104,109] In one study, associations between age and radiographic KOA were found for females but not males across all age categories.[94]

Symptomatic KOA

One study reporting on ORs, did not find any association between age and symptomatic KOA across any age category.[79] Two studies reporting on HRs, found conflicting results regarding the association between age and symptomatic KOA. One study found significant

Group	Risk factor for radiographic KOA	Communality	Unweighted PAF	Weighted PAF	Percent weighted PAF
Non-modifiable	Age	–	0.935	–	
	Sex	–	0.413	–	
	Hand OA	–	0.344	–	
	Overall weighted PAF	–	–	–	
Modifiable	Being overweight or obese	0.061	0.119	0.102	77.20
	Previous knee injury	0.045	0.035	0.030	22.80
	Overall weighted PAF	–	–	**0.141**	100

Risk factor definition for computation of PAF: Age - < 50 years vs ≥ 50 years, Sex- female vs male, Hand OA - yes/no, Obesity/overweight - yes vs. no, Previous knee injury - yes vs no.

Table I Osteoarthritis and Cartilage

Principal component analysis/Communality Weighted Population Attributable Fractions for risk factors by modifiable and non-modifiable group.

associations across all comparisons and that females ≥70 years had a higher aHR for developing symptomatic KOA (13.51 95% CI 7.19, 25.4), compared to females aged 60–69 (5.89 95% CI 3.38, 10.25) or females aged 50–59 (3.13 95%CI 1.77, 5.56).[93] Males ≥70 years had a higher aHR for developing symptomatic KOA (7.36 95% CI 2.94, 18.43), compared to males aged 60–69 (5.73 95% CI 2.57, 12.77) or males aged 50–59 (4.07 95% CI 1.80, 9.20).[93] Another study found no associations across all comparisons except in individuals aged < 65 with uncontrolled diabetes (HbA1c ≥ 7%) where an association was seen (1.51 95% CI 1.12, 2.03).[37]

Additional findings

Based on moderate certainty evidence, parity (5–12 births), poor sleep quality, high intake of ultra-processed foods and depressive symptoms were associated with higher risk of incident KOA (symptomatic or radiographic) (Figs. 4–6). Conversely, there was moderate certainty evidence that a mediterranean diet, high dietary fibre and consumption of cereal, dark bread and green tea were associated with lower risk of incident KOA (Fig. 3).

PAF

Table I presents the communality, unweighted and weighted PAFs adjusted for communality.

Fig. 7 shows the life course model of potentially modifiable risk factors for incident radiographic knee OA. Together, two modifiable risk factors (overweight/obesity and previous knee injury) account for 14% of incident radiographic KOA.

Discussion

This review identified > 150 risk factors related to incident radiographic and/or symptomatic KOA. There is high to moderate certainty evidence that overweight/obesity, previous knee injury, higher femoral neck spine BMD and occupational physical activity (e.g., shift work) are associated with an increased risk of radiographic KOA. There is moderate to low certainty evidence that female sex and older age are associated with incident KOA. Pooled estimates show a lack of association between the following risk factors and incident radiographic KOA: smoking, alcohol intake, leisure-time physical activity and osteoporosis (based on low or very low certainty of evidence). Most of the studies evaluated three large cohorts from the USA (OAI, MOST and Framingham). Two modifiable risk factors (overweight/obesity and previous knee injury) accounted for 14% of overall risk of incident radiographic KOA, therefore there are opportunities to quantify the contribution of other risk factors towards incident KOA.

Strengths and limitations of this study

Our evaluation of > 150 risk factors associated with increasing or lowered risk of incident KOA, alongside strength of evidence ratings, provides important guidance for future research. We synthesised the evidence for all reported risk factors for incident KOA without date or language restrictions, making this the most comprehensive review in the field. Our methods were rigorous, in line with best practice standards for conducting systematic reviews. Few studies were conducted outside the USA, and in low- and middle-income countries, limiting the generalisability to global populations. We considered different outcomes (e.g., radiographic, symptomatic KOA) separately, which resulted in greater homogeneity across our pooled analyses and enabled more tailored clinical guidance. This is advantageous as there is heterogeneity in defining both symptomatic and/or radiographic OA[155] and the overlap between the two is limited.

Due to the large heterogeneity in exposures, outcomes, and measures of effect, it was not possible to conduct pooled analyses for all risk factors. Some studies reported large OR estimates with unusually wide CIs, suggesting a sparse data bias. The possibility of confounding cannot be eliminated, given that most studies were observational in nature. Furthermore, we could not assess publication bias for any risk factor as too few studies were included in the pooled analysis.

We could not determine a correlation matrix between all the risk factors found to be associated with incident radiographic KOA based on our pooled analysis, as the available data did not allow. This means the contribution of important risk factors, such as occupational physical activity, could not be accounted for in the PAF analysis. Communality values were calculated based on information about risk factors from a single cohort (OAI), which limits the generalisability of the findings. We were unable to calculate PAF for symptomatic KOA as the available data did not permit. Nevertheless, this is an important clinical question, as radiographic KOA does not consistently relate to symptoms. We excluded studies where there was evidence of MRI structural changes, which meant that earlier studies in children with longer term follow-up were not captured.[156–158]

Finally, it was not possible to determine if the same participants were being reported on in different studies across the OAI, MOST and Framingham cohorts, therefore we cannot exclude potential duplication of participants across studies.

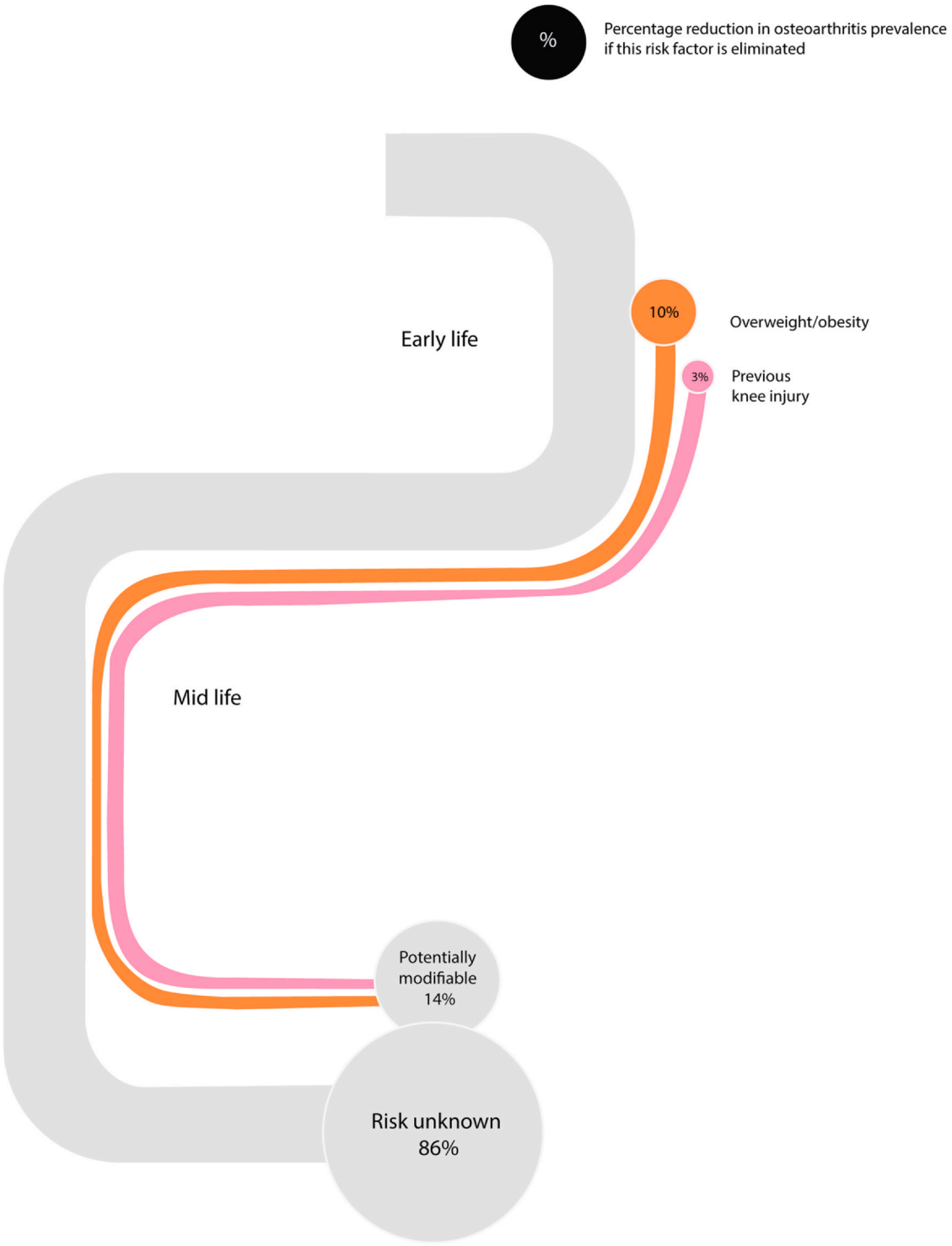

Fig. 7

Osteoarthritis and Cartilage

Life-course model of potentially modifiable risk factors for osteoarthritis across the lifespan.

Nevertheless, we provide more rigorous estimates compared to previous research. For example, the 2015 review[10] did not account for communality (clustering) of risk factors within an individual and reported a larger contribution of obesity and knee injury in the PAF calculations compared to our review.

Meaning of the study and implications

Our review identified moderate quality evidence that modifiable risk factors, including overweight/obesity, previous knee injury and occupational physical activity, are associated with incident KOA and

should be core targets for future preventive strategies. Previous studies have shown no effect of sex on the risk of developing incident KOA,[10] whereas we found that females had a two-fold greater risk of developing incident radiographic KOA, compared to males. However, in individuals with diabetes, males were at greater risk of developing incident KOA than females. Older age was not found to be a strong risk factor for incident KOA, as most incident cases of KOA are likely to be diagnosed at middle age.[159]

Societal interventions are urgently needed to address modifiable risk factors associated with incident KOA, including high intake of ultra-processed foods, poor sleep quality, occupational risks, knee injury and overweight/obesity (particularly in females). This includes targeted interventions to prevent weight gain and obesity and funded physical activity, education and nutrition programs during critical developmental years.[160–162] Given that mid-life obesity is a strong predictor of developing incident KOA, and that obese children and adolescents are five times more likely to be obese in adulthood, it is imperative that these interventions are implemented at an early age.[163]

Our findings reflect the physical activity paradox documented in previous research.[164] There is inconclusive evidence regarding the association between leisure-time physical activity and incident KOA. However, it was measured heterogeneously making it difficult to ascertain the type, dose and frequency of leisure-time physical activity which may be beneficial or adversely associated with incident KOA. Leisure-time physical activity was associated with incident radiographic or symptomatic KOA in individuals with low levels of lower limb muscle mass who engaged in weight-bearing physical activity and in overweight or obese individuals who engaged in heavy physical activity. This suggests that the type of physical activity, and/or the intrinsic capacity of the individual may be important considerations.

Conversely, occupational physical activity was significantly associated with incident radiographic or symptomatic KOA, calling for urgent efforts from workplaces and employers to reduce sedentary work, reduce physical load-bearing, improve strength and help reduce weight in the workforce.[165] Such efforts may have benefits beyond KOA prevention, there may be social, mental health and economic benefits.[164]

There is also a need for multi-component injury prevention interventions and solutions for individuals involved in sporting activities from an early age. ACL injuries are the most prevalent form of knee injury and there is evidence to support injury prevention programs which involve focused strengthening, landing and pivoting techniques.[166]

Future directions

Our data provides a platform to inform risk prediction models for the development of incident KOA. Given the emphasis on leisure-time physical activity in international clinical guidelines for OA prevention,[14] there is a need to resolve the present KOA risk uncertainty in future high quality studies, both for radiographic and symptomatic KOA. However, it is clear that future mitigation strategies need to target occupational physical activity. Government and workplace interventions aimed at reducing sedentary work, heavy manual handling, particularly over prolonged periods, duration of shift work and consumption of ultra-processed foods may prove effective in curbing the risk of incident KOA across the lifespan.

Furthermore, given the focus on non-drug interventions for the prevention and management of KOA, it is worthwhile establishing the longitudinal association of modifiable risk factors such as smoking, alcohol consumption and dietary risk factors (e.g., intake of cereal, dark bread, and green tea) in large, prospective cohort studies.

Our review identified heterogeneity in the definition and classification of KOA, prompting broader discussion for a consensus-based approach on KOA criteria.

There are limited studies on the incidence of KOA in Hispanics, Africans, or Southeast Asians, warranting research in these populations. The role of epigenetic and potentially modifiable genetic factors that may contribute meaningfully to prevention strategies should be explored. A focus on, and funding of, discovery research in addition to implementing community and lifestyle programs can help to reduce the global burden of KOA.

Conclusion

Obesity and previous knee injury together accounted for 14% of the total risk of KOA, urging novel societal strategies and future trials targeting these risk factors to reduce overall disease burden. Efforts addressing occupational risk factors and future research evaluating the association between potentially important risk factors such as leisure-time physical activity and incident KOA are also needed.

Author contributions

All authors contributed to the conception and design of the study, provided critical input on the draft and approved the final version. VD and CAS carried out the search strategy. VD, CAS, JZ, IA, SLG, SK, SWN carried out data extraction and performed risk of bias assessments. Conflicts were resolved by an adjudicator MLF, DJH. VD, CAS and VV carried out data analysis. VD and CAS led the write up of the draft manuscript.

Declarations of interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2025.03.003.

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