Osteoarthritis and Cartilage 30 (2022) 381–394

Osteoarthritis and Cartilage

Review

Are biomechanics during gait associated with the structural disease onset and progression of lower limb osteoarthritis? A systematic review and meta-analysis

N. D'Souza † *, J. Charlton ‡ §, J. Grayson †, S. Kobayashi †, L. Hutchison †, M. Hunt § ||, M. Simic †

† *The Discipline of Physiotherapy, Faculty of Medicine and Health, University of Sydney, Australia*
‡ *Graduate Programs in Rehabilitation Sciences, Faculty of Medicine, University of British Columbia, Canada*
§ *Motion Analysis and Biofeedback Laboratory, University of British Columbia, Canada*
|| *Department of Physical Therapy, Faculty of Medicine, University of British Columbia, Canada*

ARTICLE INFO

Article history:
Received 9 May 2021
Accepted 23 October 2021

Keywords:
Osteoarthritis
Biomechanics
Disease progression
Disease onset
Gait
Risk factors

SUMMARY

Objective: To evaluate if gait biomechanics are associated with increased risk of structurally diagnosed disease onset or progression of lower limb osteoarthritis (OA).
Method: A systematic review of Medline and Embase was conducted from inception to July 2021. Two reviewers independently screened records, extracted data and assessed risk of bias. Included studies reported gait biomechanics at baseline, and either structural imaging or joint replacement occurrence in the lower limb at follow-up. The primary outcome was the Odds Ratio (OR) (95% confidence interval (CI)) of the association between biomechanics and structural OA outcomes with data pooled for meta-analysis.
Results: Twenty-three studies reporting 25 different biomechanical metrics and 11 OA imaging outcomes were included (quality scores ranged 12–20/21). Twenty studies investigated knee OA progression; three studies investigated knee OA onset. Two studies investigated hip OA progression. 91% of studies reported a significant association between at least one biomechanical variable and OA onset or progression. There was an association between frontal plane biomechanics with medial tibiofemoral and hip OA progression and sagittal plane biomechanics with patellofemoral OA progression. Meta-analyses demonstrated increased odds of medial tibiofemoral OA progression with greater baseline peak knee adduction moment (KAM) (OR: 1.88 [95%CI: 1.08, 3.29]) and varus thrust presence (OR: 1.97 [95%CI: 1.32, 2.96]).
Conclusion: Evidence suggests that certain gait biomechanics are associated with an increased odds of OA onset and progression in the knee, and progression in the hip.
Registration number: PROSPERO CRD42019133920

Introduction

Osteoarthritis (OA) is characterised by structural changes, such as bone marrow lesions (BMLs), osteophytes, cartilage loss and symptoms including pain and functional deficits[1]. OA is a leading contributor to disability worldwide[2] and associated with considerable economic burden[3]. To reduce this burden, understanding of modifiable risk factors of disease onset and/or progression is needed. A key emerging risk factor is theorised to be the loading environment of weight-bearing joints[4].

In-vivo animal studies have shown a link between compressive joint loading and structural changes, which may contribute to increased OA onset and progression risk[5]. Articular cartilage and subchondral bone have significant capacity to withstand load and remodel in response[6]. However, excessive compressive loading beyond a threshold may overwhelm the ability of the cartilage and

* Address correspondence and reprint requests to: N. D'Souza, Faculty of Medicine and Health, The University of Sydney, Susan Wakil Health Building, D 18 Western Avenue, Camperdown NSW 2006, Australia. Tel.: 61-2-8627-6970.
E-mail addresses: n.dsouza@sydney.edu.au (N. D'Souza), jesse.charlton@ubc.ca (J. Charlton), jane.grayson@sydney.edu.au (J. Grayson), sarah.kobayashi@sydney.edu.au (S. Kobayashi), lhut9413@uni.sydney.edu.au (L. Hutchison), michael.hunt@ubc.ca (M. Hunt), milena.simic@sydney.edu.au (M. Simic).

https://doi.org/10.1016/j.joca.2021.10.010
1063-4584/

subchondral bone to adapt, potentially causing tissue failure[6,7]. Shear loading (transverse and medio-lateral forces) is also proposed to contribute to osteoarthritic changes by compromising cartilage integrity[8]. Excessive compressive or shear forces are therefore hypothesised to surpass the threshold of tissue capacity and can result in load being shifted to infrequently loaded joint areas[4].

Joint loads are estimated non-invasively via three-dimensional (3D) gait analysis[9,10]. For example, the external knee adduction moment (KAM) acts to rotate the tibia with respect to the femur in the frontal plane, and is widely considered a valid[11] and reliable[12] proxy measure of medial to lateral knee joint load distribution during gait. Research alludes to an association between higher baseline KAM magnitudes during gait and greater odds of knee OA progression over time, with reported odds ratios (OR) of 1.3 [95%CI: 0.86, 1.98][13] and 6.46 [95%CI: 2.40, 17.45][14]. Significant associations between gait biomechanical metrics at baseline and OA progression at follow-up have also been reported in people with hip OA. A recent study suggests that hip joint loading patterns, such as cumulative hip frontal plane moment, may be associated with hip OA progression[15]. Differences in gait biomechanics have also been identified between people with ankle OA and healthy controls, possibly alluding to increased risk of OA changes.[16]

A comprehensive systematic evaluation of gait biomechanics at baseline and the association with subsequent OA onset and progression in lower limb weight-bearing joints is needed due to the potentially modifiable nature of gait. One systematic review, published in 2014[17], aimed to study if the KAM biomechanical metric is associated with higher risk of knee OA progression. The authors did not find a significant association between higher KAM and OA progression, potentially due to the small number of studies ($k = 4$) and large variability in findings. Since 2014, additional studies have been conducted examining the relationship between KAM variables and knee OA progression[18,19], and further studies have suggested that other biomechanical metrics may also be relevant for knee OA pathology, such as knee flexion moment (KFM)[20] and varus thrust presence[21]. Further, the focus of the previous review[17] was knee OA progression and one biomechanical metric, and did not provide data on OA outcomes at other lower limb joints or evaluate OA onset. This research is important as biomechanical metrics hypothesised to be associated with loading[22], are modifiable through certain interventions, including braces[23], orthoses[24], gait aids[25], and gait modification strategies.[26]

Given the emerging research, a systematic and comprehensive risk evaluation is required for the hip, knee, and ankle joints. This review aims to determine and quantify if gait biomechanical metrics are associated with the onset or progression of structural OA changes in the major lower limb joints, defined by imaging-based changes or joint replacement occurrence.

Methods

Data sources and searches

We searched two electronic databases, Medline and Embase from inception to 12/07/2021. Key terms included “Osteoarthritis”, “Biomechanics/gait”, “Knee/Hip/Ankle”, “Disease onset/progression” and terms referring to OA structural changes (Appendix A). The search was restricted to humans, with no restriction on language, age, race, or geographical location. A bibliographic and citation search of included studies was conducted. This review was registered prospectively (Prospero CRD42019133920).

Inclusion/exclusion criteria

Studies

Studies were eligible if they were longitudinal and reported OA structural outcomes assessed through either imaging (e.g., radiographs or MRI: Magnetic Resonance Imaging) changes between baseline and follow-up or joint replacement surgery occurrence after baseline. Dissertations, conference proceedings, abstract, case studies, intervention studies with no observation/control group, and reviews (systematic or narrative) were excluded. Studies with participants who had history of knee/hip replacement prior to baseline, inflammatory arthritis, or neurological conditions affecting gait at baseline were excluded.

Exposure and outcome

All included studies reported gait biomechanics including kinetic, kinematic, and spatiotemporal metrics. The following terminology will be used throughout this review: we defined “*biomechanical metrics*” as umbrella kinetic, kinematic, or spatiotemporal measurements in the frontal, sagittal and transverse planes (e.g., KAM and hip flexion angle). We used the term “*biomechanical variables*” to define these metrics at specific timepoints in the gait cycle (e.g., early stance peak KAM, or midstance hip flexion angle). Lower limb biomechanical metrics derived from marker-based motion capture, two-dimensional (2-d) videography, or pressure-sensing mats were extracted. Studies exclusively investigating static alignment or non-gait biomechanical metrics were excluded. Studies defined disease onset as any OA structural changes detected on imaging via semi-quantitative and quantitative scales from imaging-defined healthy joints at baseline. Studies defined lower limb OA progression as worsening of OA features on imaging, or the occurrence of joint replacement surgery. Occurrence of joint replacement surgery was chosen as an acceptable OA progression outcome as structural OA worsening on imaging over time has shown to predict the need for joint replacement surgery, inclusive of joint space narrowing (JSN) seen on radiographs[27] and changes in cartilage volume and BMLs seen on MRI.[28]

Inclusion determination

All records were initially screened by title and abstract. Full-texts of relevant records were obtained and screened to determine eligibility. Two reviewers independently screened, and a third independent reviewer was available to resolve disagreements.

Risk of bias

Risk of bias was evaluated independently by two reviewers (ND, JC) with disagreements resolved by a third reviewer (JG). Quality was assessed using the risk of bias tool reported in Chapple *et al.*[29], specifically designed for the assessment of OA prognostic studies (Appendix B). The tool contains 20 items divided into 4 subscales: study participation, study attrition, measurement and data presentation, and analysis and presentation of results. Each item was scored 0 (poor quality) or 1 (good quality), with a total score range of 0–21. We modified item N to have two separate points: one for blinding of the assessors and one for the use of standardised procedures for reading imaging or joint replacement occurrence. In reference to study attrition, studies were scored as “unable to determine” if they did not report the initial baseline sample of participants and only included participants who had follow-up data.

Quality of evidence

Two reviewers (ND, JC) independently assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for prognostic factors[30].

Four items: study limitations, inconsistency, indirectness, imprecision, and publication bias were evaluated to grade the overall quality of evidence for meta-analyses with ≥3 studies. Disagreements were resolved by a third reviewer (MS).

Data extraction and synthesis

Using a standardised template, two reviewers (ND, JC) independently extracted the following data: affected joint, baseline condition (healthy or OA), recruitment, participant characteristics, inclusion/exclusion, biomechanical assessment method, OA onset and progression definition, study design and attrition rate. The primary value extracted was the Odds Ratio (OR) (95%CI: 95% confidence interval) of the association between biomechanical variables and OA onset/progression. If this was unavailable, baseline biomechanical variables were extracted, which included mean (standard deviation (SD)) for the progression and non-progression subgroups or the reported regression coefficients. If a study only provided baseline biomechanical variables through graphs, data were extracted through the Webplot digitiser[31]. In this instance, baseline variables were entered into Comprehensive Meta-Analysis software which converted the values into an OR point estimate (95% CI).

Meta-analyses were performed for all biomechanical variables which could be grouped according to the consistent joint, plane of motion, direction/torque, and time/phase of the gait cycle. Analyses were conducted on all available outcomes of disease progression for the same biomechanical variable. If the data from the same cohort was presented in two studies, meta-analysis was conducted using the study reporting either the largest sample size and/or reported adjusted odds ratios. Heterogeneity was determined by evaluating the similarity in study methods (including imaging outcomes, follow-up times, and cohort similarities) as well as the I^2 statistic (<40% suggesting low heterogeneity)[32]. Given that included studies in the meta-analyses had increased heterogeneity due to varying follow-up periods, I^2 >40% and sample sizes, we used a random effects model for all analyses. Sensitivity analyses were conducted separately for outcomes by modes of imaging (radiographic and MRI), then grouped further for the specific

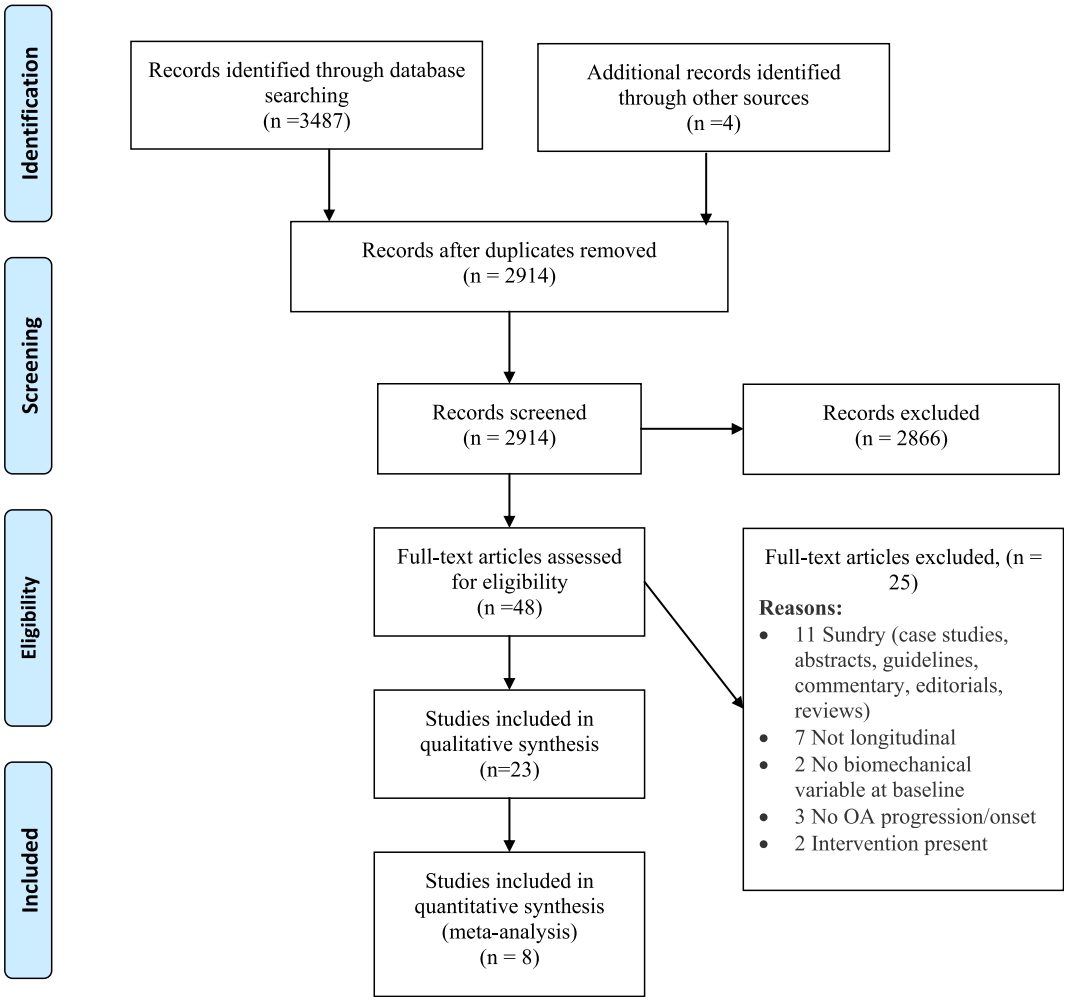

Fig. 1

PRISMA.

Study	Lower limb region	Sample size (% F)	%Attrition (follow-up time)	Age Mean (SD) unless otherwise stated	BMI Mean (SD) unless otherwise stated	Participant characteristics	Biomechanical assessment	Outcome	Baseline OA severity (KL) (%)-unless otherwise stated	Onset/ progression definition	Adjustment of results (ORs unless otherwise stated)
Knee Osteoarthritis											
Bennell *et al.*, 2011[13] Australia	Medial tibiofemoral	144 (56%)	Unable to determine attrition (12 months)	64.4 (8)	28.6 (4.5)	Community dwellings, sub-study (no Rx) of a previous RCT Age >50 Y, pain >3/ 10 VAS, KL 2–3.	3D Gait Analysis	MRI	Grade II = 53% Grade III = 7%	Progression: BML- Increase of 1 from a described semi-quantitative scale	Adjusted for age, gender, body mass index, MRI machine, static knee alignment, treatment group and baseline tibiofemoral cartilage defect score or BML scores
Brisson *et al.*, 2017[34] Canada	Medial tibial	64 (NR)	17% (Mean SD follow-up: 2.56 (0.51))	61 (6.9)	28.5 (5.7)	Rheumatology/ Orthopaedic offices. Between age 40–70 with OA diagnosis according to ACR criteria.	3D Gait Analysis	MRI	Grade 1-II = 4% Grade II = 35% Grade III = 35% Grade IV = 27%	Progression: Change in cartilage morphology	Adjusted for Age, sex, BMI and baseline medial tibial cartilage volume
Brisson & Gatti *et al.*, 2021[48] Canada	Medial tibiofemoral	47 (83%)	Unable to detemine attrition (Mean SD follow-up: 2.57 (0.53))	61.1 (6.8)	28.8 (5.8)	Rheumatology/ orthopaedic offices (convenience sample). Diagnosis of OA as per ACR criteria. KL grade ≥2	3D Gait Analysis	MRI	Grade II = 38% Grade III = 38% Grade IV = 23%	Progression: Annual change in cartilage volume	Age, height, BMI and gait speed
Chang *et al.*, 2017[35] USA	Patellofemoral joint	250 (77%)	18% (24 months)	64.2 (10)	28.4 (5.7)	From the MAK 3 study -Community dwelling definite osteophyte presence.	3D Gait Analysis	MRI	Grade 0 = 4% Grade I = 18% Grade II = 48% Grade III = 14% Grade IV = 15%	Progression: Any one full grade increase in WORMS score	Adjusted for age, sex, gait speed, and PF disease severity
Chang *et al.*, 2015[19] USA	Medial tibiofemoral	250 (77%)	18% (24 months)	64.2 (10)	28.4 (5.7)	From the MAK 3 study Community dwelling, definite osteophyte presence.	3D Gait Analysis	MRI	Reported for knees: Grade 0 = 4% Grade I = 18% Grade II = 48 % Grade III = 14 % Grade IV = 15%	Progression: Any one full grade increase in WORMS score	Adjusted for gait speed, age, gender, KL grade, knee pain severity, and medication use
Chang *et al.*, 2004[36] USA	Medial tibiofemoral	237 (73%)	6% (18 months)	68 (10.7)	30 (6)	Subset of MAK study Community dwellings with osteophyte presence.	2D Video cameras	X-RAY	Not provided	Progression: Any worsening joint space width (OARSI atlas)	Adjusted for age, sex, BMI, and pain severity
Chang *et al.*, 2005[37] USA	Medial tibiofemoral	57 (63%)	Unable to determine attrition (18 months)	67 (8.7)	29 (4.1)	Subset of MAK study Community dwellings with osteophyte presence.	3D Gait Analysis	X-RAY	Mild OA (no JSN) = 72% Moderate OA (not severe) = 28%	Progression: Any worsening in the grade of joint space width (OARSI atlas)	Adjusted for age, sex, knee pain, physical activity (PASE), knee OA severity
Chang *et al.*, 2007[38] USA	Medial tibiofemoral	56 (59%)	Unable to determine attrition (18 months)	66.6 (8.6)	29 (4.2)	Subset of MAK study Community dwellings with osteophyte presence.	3D Gait Analysis	X-RAY	Grade II = 71% Grade III = 29%	Progression: Any worsening in the radiographic medial joint space (OARSI atlas)	Adjusted for age, gender, BMI, knee pain severity and baseline disease severity

Chehab *et al.*, 2014[39] USA	Medial tibiofemoral	16 (62%)	61% (Mean follow- up (SD): 4.7 (0.6))	60.1 (9.4)	28.3 (4.5)	Recruited from a previous cohort (Community and Veterans affairs. Age >40 years, X-ray diagnosed medial knee OA; KL $\geq$ 1)	3D Gait Analysis	MRI	Grade I = 25% Grade II = 31% Grade III = 38% Grade IV = 6%	Progression: Change in cartilage thickness	Standardised coefficients
Costello *et al.*, 2020[44] Canada ⊖	Medial tibiofemoral	49 (Radiographic outcome: PG: 18% NPG: 38% TKA outcome: PG: 31% NPG: 31%)	Unable to determine attrition (Follow-up in years (Radiographic: NPG: 7.3 (2.3) years PG: 6.8 (2.2) years TKA: NPG: 7.3 (2.0) years PG: 5.9 (2.6) years)	Radiographic outcome: NPG: 18% PG: 38% TKA outcome: NPG: 31% PG: 31%	Radographic outcome: NPG: 30.5 (5.6) PG: 32.4 (5.3) TKA outcome: NPG: 32.1 (6.0) PG: 30.7 (3.0)	Retrospective secondary analysis of data from participants. Recruited from community and orthopaedic offices. Participants should have functional ability to jog 5 m, walk a city block and climb stairs.	3D Gait Analysis	Radiographic JSN and TKA occurrence	Radiographic outcome: (n) Grade 1 = 6 Grade 2 = 17 Grade 3 = 26 Grade 4: = 0 TKA outcome: Grade 1 = 6 Grade 2 = 17 Grade 3 = 26 Grade 4 = 0	Progression: Structural outcome: one grade or greater increase in radiographic medial JSN from baseline. OR occurrence of TKA.	Unadjusted (PC scores and discrete metrics)
Davis *et al.*, 2019[18] Canada ⊖	Medial tibiofemoral	52 PG: 33% NPG: 58%	8% (Mean follow-up (SD): 2.97 (0.4))	PG: 61.3 (6.3) NPG: 54.1 (7.4)	PG: 29.7 (5.4) NPG: 28.9 (4.7)	Community-Orthopaedic and sports medicine clinics Self-reported ability to walk a city block, jog 5 m, walk upstairs. KL grade 1-3	3D Gait Analysis	X-RAY	PG:(n): Grade 0 = 1 Grade I = 5 Grade II = 4 Grade III = 0 NPG:(n): Grade I = 2 Grade II = 24 Grade III = 12 Grade IV = 0	Progression: OARSI-OMERACT Progression defined as one grade increase in medial joint space narrowing	Unadjusted
Erhart-Hledik *et al.*, 2021[47] USA	Medial tibiofemoral	38 (55%)	31% (Mean follow-up (SD): 7.1 (2.3))	56.5 (6.3)	25 (4.4)	Convenience sample recruited from 104 healthy individuals previously tested in studies (studies not specified). No diagnosis of knee OA, BMI <35 kg/m^2	3D Gait Analysis	MRI	N/A = healthy individuals at baseline	Onset: Change in cartilage thickness from baseline to follow-up. Diagnosis of OA: KL $\geq$ 2	Unstandardised coefficients
Favre *et al.*, 2016[40] USA	Medial tibiofemoral	16 (63%)	62% (Mean follow-up (SD): 4.7 (0.6))	59 (9)	29.1 (4.1)	Recruited from a previous cohort (Orthopaedic clinic, community Age >40)	3D Gait Analysis	MRI	KL (0–4) Reported as mean (SD): 2.1 (1.1)	Progression: Change in cartilage thickness	Adjusted for age, gender, BMI, walking speed, K/L grade and pain.
Hart *et al.*, 2020[45] USA	Patellofemoral and medial tibiofemoral	1,089 (62%)	Unable to determine attrition (24 months)	66.9 (7.5)	29.6 (4.7)	Recruited from the MOST Study. Independent walking ability	Pressure walkway	MRI	Not provided	Progression: Increase in WORMS score >1 from 60 to 84 months to follow-up. Within grade WORMS score changes were also considered indicative of worsening.	Risk ratios adjusted for age, BMI and previous injury/ surgery.

(*continued on next page*)

Table I (*continued*)

Study	Lower limb region	Sample size (% F)	%Attrition (follow-up time)	Age Mean (SD) unless otherwise stated	BMI Mean (SD) unless otherwise stated	Participant characteristics	Biomechanical assessment	Outcome	Baseline OA severity (KL) (%)-unless otherwise stated	Onset/ progression definition	Adjustment of results (ORs unless otherwise stated)
Hatfield *et al.*, 2015[41] Canada ⊖	Medial Tibiofemoral	80 (PG: 27%) (NPG: 32%)	33% (TKA: 4 (3) years No TKA: 8 (2) years)	PG: 60.2 (9.3) NPG: 57.9 (7.3)	PG: 30.9 (4.7) NPG: 31.5 (6.2)	Recruited from orthopaedic offices. Moderate clinical and radiographic OA. Able to jog 5 m, to walk a city block, able to climb stairs.	3D Gait Analysis	TKA occurrence	Median value provided Grade 3 for both TKA and no TKA groups.	Progression: TKA	PC scores- (alignment, K/L score, JSN score, WOMAC total score, WOMAC pain score, age, sex, and mass)
Mahmoudian *et al.*, 2017[46] Belgium	Medial tibiofemoral	47 (100%)	Unable to determine attrition (2 years)	68 (0.9)	21.17 (0.7)	Recruited from the University hospital, > 57 years.	3D Gait Analysis	MRI	KL 0 = 22% KL 1 = 36% KL 2 = 2% KL 3 = 13%	Progression: BLOKS scoring: change in the number of BMLs, cumulative scores for size and % of full thickness lesions.	Unstandardsied coefficients
Miyazaki *et al.*, 2002[14] Japan	Medial tibiofemoral	106 (81%)	30% (6 years)	69.9 (7.8)	24.5 (3.2)	Recruited from Orthopaedic Offices. Age >50 Medial knee pain in daily activities, varus alignment	3D Gait Analysis	X-RAY	Grade I = 20% Grade II = 25% Grade III = 34% Grade IV = 21%	Progression: One or more grade narrowing of the joint space and osteophyte formation (KL grading)	Adjusted for age, sex, pain score, mechanical axis and joint space width.
Sharma *et al.*, 2017[42] USA	Medial tibiofemoral	4,796 (59%)	Final sample size not specific (84 months (IQ range: 60 −84))	61.2 (0.2)	28.6 (4.8)	Participants were recruited from the OAI. Ages of 45−79	2D Video Camera	X-RAY	Not provided	Onset and progression: Increased (partial or whole grade) in KL grade or JSN	Adjusted for age, sex, BMI and pain on the (WOMAC) pain subscale
Stefanik *et al.*, 2016[43] USA	Patellofemoral joint	2,330 (62%)	55% (24 months)	66.9 (7.5)	29.6 (4.7)	Recruited as part of the MOST Study. Independent walking ability, no aid or knee brace	Pressure walkway	MRI	Not provided	Progression: WORMS Score worsening	Adjusted for age, BMI, leg length, and tibiofemoral joint structural damage
Teng *et al.*, 2015[33] USA	Patellofemoral joint	84 (67%)	27% (12 months)	51.3 (9.9)	24.4 (2.2)	Recruited from the community. Age >35 years. Radiographic signs of OA.	3D Gait Analysis	MRI	Not provided	Progression: WORMS Score increase of 1 grade.	Adjusted for age, sex, body mass index, and presence of baseline PF joint OA
Wink *et al.*, 2017[21] USA ⊖	Medial tibiofemoral	2,768 With thrust (50%) No thrust (68%)	64% (24 months)	With thrust: 67.4 (7.6) No thrust: 66.4 (7.5)	With thrust: 29.8 (4.9) No thrust: 29.3 (4.7)	Participants were part of the MOST Study. Independent walking ability	2D Video cameras	MRI	With thrust: Grade II = 16% Grade III = 23% Grade IV = 6%	Onset (incidence BML): BML score increase WORMS score >2 Progression: Worsening of a whole grade in BML Worsening of the WORMS score (from baseline)	Adjusted for age, sex, race, BMI, clinic site and baseline KL grade

Table I

Study characteristics

Hip Osteoarthritis											
Kumar *et al.*, 2018[49] USA⊕	Hip	57 (PG: 59% NPG:37%)	0% (18 months)	PG: 52 (11.8) NPG: 44.1 (13.4)	PG: 24 (3.6) NPG: 24 (2.6)	Participants were recruited from the community KL 2 or 3.	3D Gait Analysis	MRI	NPG: Grade 0 = 37% Grade I = 40% Grade II = 17% Grade III = 7% PG: Grade 0 = 9% Grade 1 = 41% Grade II = 23% Grade III = 27%	Progression: Any change in scores from SHOMRI	Adjusted for age, sex, BMI, presence of OA at baseline
Tateuchi *et al.*, 2017[15] Japan	Hip	50 (100%)	0% (12 months)	47.4 (10.7)	Not provided	Recruited from the department of Orthopaedic surgery Kyoto University. Ability to walk without assistive devices	3D Gait Analysis	X-Ray	Minimum JSW at baseline: NPG:3.7 (1.4) mm PG: 2.9 (1.4) mm	Progression Reduction of 0.5 mm/year in JSW	Adjusted for age, gender, body weight, and minimum JSW (mm)

ACR = American college of rheumatology; BLOKS = Boston Leeds osteoarthritis knee score; BML = bone marrow lesions; BMI = body mass index; JSW = joint space width; K/L = Kellgren Lawrence; MAK = mechanical factors in arthritis of the knee; MOST = multicentre osteoarthritis study; MRI = magnetic resonance imaging; NR = not reported; OARSI-OMERACT = osteoarthritis research society international (OARSI)- outcome measures in rheumatology (OMERACT); PASE = physical activity scale for the elderly; PF = patellofemoral joint; Rx = intervention group; RCT = randomised controlled trial; SHOMRI = scoring hip osteoarthritis with MRI; TKA = total knee athroplasty; VAS = visual analog scale; WORMS = whole-organ MRI scoring; WOMAC = western Ontario and Mcmaster universities arthritis index.
⊕: Studies did not provide overall summary scores for Age, BMI, %female, therefore mean (SD) for subgroups were reported.

Osteoarthritis and Cartilage

outcome of disease progression (e.g.: joint space narrowing (JSN), BMLs). For meta-analyses where <3 studies were available, results are reported in Appendix C. Reported biomechanical metrics not included in a meta-analysis were presented in table format and reported during the narrative synthesis. Overall, a narrative summary of the number of studies reporting biomechanical metrics and the number of studies with positive, negative or no associations to OA pathology are provided for each joint.

Results

Our search yielded 2,914 independent records, of which 48 were retained for full-text screening, and 23 studies met the eligibility criteria for final inclusion (Fig. 1). Of the included studies, 21 evaluated the relationship between biomechanical metrics and knee OA[13,14,18,19,21,33–48], two of the hip[15,49], and no study reported biomechanical metrics associated with ankle OA. Twenty-two studies (14 cohorts) investigated OA disease progression, and two of these studies (separate cohorts)[21,42], also investigated knee OA disease onset. An additional study only investigated knee OA onset[47]. Baseline participant characteristics of included studies are reported in Table I.

All studies recruited participants from either community dwellings or orthopaedic offices. Sample sizes varied between 16[39,40] and 4796,[42] with most studies having a greater proportion of female participants. Follow-up assessments ranged from 12[13,15,33] to 95 months[41] after baseline. A total of 25 unique biomechanical metrics were evaluated using 3D motion analysis ($k = 18$)[13–15,18,19,33–35,37–41,44,46–49], 2-d video analysis ($k = 3$)[21,36,42] and pressure platforms ($k = 2$)[43,45]. For OA structural outcomes, 14 studies conducted MRI evaluations, 8 studies used radiographic evaluations and two studies reported progression by total knee arthroplasty (TKA)[41,44] at follow-up. Imaging outcomes included a range of measures across varying compartments of the relevant joint, including BMLs[13,19,21,43], cartilage thickness loss[19,39,40,47], cartilage volume loss[13,34,48], cartilage damage[19,43], cartilage defects[13], joint space width[15,37], JSN[18,38,42,44], Kellgren and Lawrence (KL) grade worsening[14,42], change in Boston Leeds Osteoarthritis Knee Score (BLOKS)[46], Hip Osteoarthritis with MRI (SHOMRI) scores[49], and Whole Organ MRI- Scoring scores (WORMS) worsening.[33,35,36,45]

Risk of bias

Study quality ranged from 12 to 20 points out of a maximum 21, and a mean (SD) score of 16.78 (2.55) (Table II). Studies performed strongly ($k = 15$) with regards to measurement, and data presentation as well as analysis and presentation of results. Majority of studies had appropriate representation of the OA population, with the study setting/baseline characteristics adequately described. Biomechanical metrics were clearly defined, and structural imaging outcomes used reliable scoring systems with blinded assessors. Seven studies[13,37,38,44–46,48] only reported participants with follow-up data and thus attrition was not possible to determine.

Synthesis of results

Table III provides a summary of confirmed associations between baseline biomechanics and OA onset or progression risk. All but two studies[34,46] (91%) reported at least one significant association between a biomechanical variable at baseline and OA disease onset or progression. Eighteen studies found an association between higher values of baseline gait biomechanics and OA progression in the knee and hip, signifying an increased risk of OA progression[13–15,18,19,21,33,35,36,38–42,44,45,48,49]. Two studies also

Study	Study Participation (out of 4)	Study Attrition (out of 3)	Measurement and Data Presentation (out of 9)	Analysis and Presentation of Results (out of 5)	Overall Score (out of 21)
Bennell *et al.*, 2011[13]	3	Unable to determine	9	5	17
Brisson *et al.*, 2017[34]	3	3	8	4	18
Brisson *et al.* & Gatti, 2021[48]	2	Unable to determine	8	2	12
Chang *et al.*, 2017[35]	3	3	9	4	19
Chang *et al.*, 2015[19]	3	3	9	5	20
Chang *et al.*, 2004[36]	3	3	9	4	19
Chang *et al.*, 2005[37]	3	Unable to determine	9	5	17
Chang *et al.*, 2007[38]	3	Unable to determine	9	5	17
Chehab *et al.*, 2014[39]	3	2	8	4	17
Costello *et al.*, 2020[44]	4	Unable to determine	8	1	13
Davis *et al.*, 2019[18]	2	3	9	1	15
Erhart-Hledik *et al.*, 2021[47]	3	2	7	2	14
Favre *et al.*, 2016[40]	3	2	7	4	16
Hart *et al.*, 2020[45]	3	Unable to determine	6	5	14
Hatfield *et al.*, 2015[41]	3	2	6	3	14
Kumar *et al.*, 2018[49]	3	3	9	5	20
Mahmoudian *et al.*, 2017[46]	2	Unable to determine	6	4	12
Miyazaki *et al.*, 2002[14]	3	2	8	5	18
Sharma *et al.*, 2017[42]	3	2	9	5	19
Stefanik *et al.*, 2016[43]	3	2	8	5	18
Tateuchi *et al.*, 2017[15]	3	3	9	5	20
Teng *et al.*, 2015[33]	3	2	9	5	19
Wink *et al.*, 2017[21]	3	2	8	5	18

Table II

Osteoarthritis and Cartilage

Risk of bias

found significant associations between baseline biomechanics and knee OA onset[21,47]. Three studies[37,38,43] found a negative association between higher values of hip adduction moment, toe-out angle and step length (observed in one quintile) with the risk of OA progression in the knee, suggesting a potentially protective association with OA structural progression.

Appendix D represents all reported biomechanical metrics and variables and their associations with OA disease onset and/or progression. A total of 25 biomechanical metrics were studied for the hip and knee joints, out of which 83 biomechanical variables were evaluated during specific gait cycle time-points.

The majority of evidence supported an association between frontal, sagittal and transverse plane lower limb joint biomechanics and knee OA progression. For OA onset and progression in the medial tibiofemoral joint and individual regions within this compartment, positive associations were found with peak KAM values (5/8 cohorts), higher peak KAM[14,19,38,47], higher early stance peak KAM[18,39], KAM impulse ($k = 2/4$)[13,19], presence of varus thrust ($k = 3/3$)[21,36,42], and knee transverse plane moment ($k = 2/3$)[18,44] observed through structural worsening. For the patellofemoral joint, two studies investigated and reported positive associations for dynamic joint stiffness[35], late stance peak KFM and KFM impulse in the second half of stance[33]. For the hip joint, hip flexion angle[49] and cumulative frontal plane moment[15] were associated with hip OA progression in one study each.

Results of meta-analyses

Due to variability of biomechanics and OA outcomes reported, meta-analyses could only be conducted on three biomechanical variables and their association with OA disease progression in the medial tibiofemoral joint. These included peak KAM, KAM impulse and varus thrust. For the KAM variable, three studies reported peak KAM[13,14,19] and two reported early stance peak KAM[18,44]. As the peak KAM frequently occurs during early stance[50], we thought it was relevant to pool these studies for meta-analysis. The GRADE quality of evidence for all main analyses are shown in Table IV.

Greater magnitudes of early stance peak KAM were associated with increased odds of overall OA progression in the medial tibiofemoral joint (OR: 1.88 [95%CI: 1.08,3.29]; $k = 5$; average follow-up = 45months; $n = 601$; $I^2 = 73\%$, Fig. 2, low quality evidence) as determined by medial tibiofemoral BMLs, cartilage damage, cartilage defects, KL grade worsening and medial tibiofemoral JSN. Greater magnitudes of early stance peak KAM were associated with increased odds of radiographically-defined OA progression in the medial tibiofemoral joint (OR:3.53 [95%CI: 1.47, 8.48]; $k = 3$; average follow-up = 64 months; $n = 207$; $I^2 = 46\%$, Fig. 3, moderate quality evidence). Varus thrust presence was associated with increased odds of overall OA disease progression in the medial tibiofemoral joint (OR: 1.97 [95%CI: 1.32, 2.96]; $k = 3$; average follow-up = 54 months; $n = 8{,}059$; $I^2 = 76\%$, Fig. 4, moderate quality evidence).

Findings from sensitivity analyses with <3 studies are reported in Appendix C. For early stance peak KAM, positive associations remained for MRI- defined BMLs (OR: 1.30 [95%CI: 1.02,1.66]; $k = 2$; average follow-up = 18 months; $n = 394$), but not for medial tibiofemoral JSN and cartilage damage or defects in the medial tibiofemoral joint. For KAM impulse, positive associations remained for increased medial tibiofemoral BMLs size (OR: 2.07 [95%CI: 1.17,3.68]; $k = 2$; average follow-up = 18 months; $n = 394$),

Study	Lower limb region	Biomechanical variables/metrics associated with onset and/or progression	Positive association with OA progression	Negative association with OA progression	Positive association with OA onset
Bennell *et al.*, 2011[13]	Medial tibial	KAM impulse	✓		
Brisson *et al.*, 2017[34]	Medial tibial	Peak KAM	o	o	o
		KAM impulse	o	o	o
Brisson & Gatti *et al.*, 2021[48]	Medial tibiofemoral	Medial contact force peak	✓		
Chang *et al.*, 2017[35]	Patellofemoral	Knee sagittal dynamic joint stiffness (DJS)	✓		
Chang *et al.*, 2015[19]	Regions of the medial tibial and femoral weight-bearing surface	Peak KAM	✓		
		KAM impulse	✓		
Chang *et al.*, 2004[36]	Medial tibiofemoral	Varus thrust	✓		
Chang *et al.*, 2005[37]	Medial tibiofemoral	External hip adduction moment		✓	
Chang *et al.*, 2007[38]	Medial tibiofemoral	Toe-out angle		✓	
		Early stance peak KAM	✓		
Chehab *et al.*, 2014[39]	Medial-lateral (femoral and tibial regions)	Early stance peak KAM	✓		
		Peak KFM	✓		
		Walking speed	✓		
Costello *et al.*, 2020[44]	Medial tibiofemoral	Midstance KAM	✓		
		Midstance KRM	✓		
Davis *et al.*, 2019[18]	Medial tibiofemoral	Early stance peak KAM	✓		
		Range of KRM throughout stance	✓		
Erhart-Hledik *et al.*, 2021[47]	Medial tibial	Knee extension moment			✓
		Peak KAM			✓
Favre *et al.*, 2016[40]	Medial tibial and femoral	Maximum knee flexion angle during heel strike and midstance	✓		
		Maximum anterior- posterior displacement of the femur during heel strike and swing	✓		
Hart *et al.*, 2020[45]	Patellofemoral Medial tibiofemoral	Step rate	✓		
Hatfield *et al.*, 2015[41]	Knee	Early-mid stance KAM difference in magnitude	✓		
		KAM overall magnitude	✓		
		Knee flexion/extension moment difference	✓		
		Hip adduction angle	✓		
		Ankle flexion angle (stance to swing difference)	✓		
		Ankle flexion moment (early-mid stance dorsiflexion magnitude)	✓		
		Ankle rotation moment (early-late stance difference)	✓		
Kumar *et al.*, 2017[49]	Hip	Early stance peak hip flexion angle	✓		
Mahmoudian *et al.*, 2017[46]	Knee	Knee adduction angle	o	o	o
Miyazaki *et al.*, 2002[14]	Medial tibiofemoral	Peak KAM	✓		
Sharma *et al.*, 2017[42]	Medial tibiofemoral	Varus thrust	✓		
Stefanik *et al.*, 2016[43]	Patellofemoral	Second largest step length quintile		✓	
Tateuchi *et al.*, 2017[15]	Medial Hip	Cumulative frontal hip joint moment	✓		
Teng *et al.*, 2015[33]	Patellofemoral	Late stance peak KFM	✓		
		Late stance KFM impulse	✓		
Wink *et al.*, 2017[21]	Medial tibiofemoral	Varus thrust	✓		✓

KAM = knee adduction moment; KFM = knee flexion moment; KRM = knee rotation moment.
✓ = association.
o = no association identified.

Table III

Osteoarthritis and Cartilage

Summary of the confirmed associations between baseline biomechanical metrics and variables with risk of OA onset or progression in the lower limb regions

but not for cartilage damage or defects. For the onset of medial tibiofemoral joint OA, varus thrust presence was not associated (OR: 1.08 [95%CI: 0.86,1.36]; $k = 2$ studies; average follow-up = 72 months; $n = 7{,}822$).

Discussion

This systematic review confirms that gait biomechanics are associated with increased odds of OA progression in the hip and

Biomechanical metric/variable	Outcome	Participants (n)	Number of studies	OR (95% CI)	Risk of bias (study limitations)	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
Early stance peak KAM*	Medial tibiofemoral progression	601	5[13,14,18,19,44]	1.88 (1.08, 3.29)	Serious limitations	Serious limitations	No serious limitations	No serious limitations	Publication bias detected	Low quality
Early stance peak KAM†	Radiographic outcomes of medial tibiofemoral progression	207	3[14,18,44]	3.53 (1.47, 8.48)	Serious limitations	Serious limitations	No serious limitations	No serious limitations	Publication bias undetected	Moderate quality
Varus thrust‡	Medial tibiofemoral progression	8,059	3[21,36,42]	1.97 (1.32, 2.96)	No serious limitations	Serious limitations	No serious limitations	No serious limitations	Publication bias undetected	Moderate quality

Overall quality of evidence.

* There is low quality evidence to suggest that early stance peak KAM was associated with increased odds of medial tibiofemoral OA progression. There was risk of bias present in the assessment of individual studies, and increased incosistency/heterogenity in the meta-analysis. There was dispersion in the sample sizes and therefore, publication bias was detected.

† There is moderate quality evidence to suggest that early stance peak KAM was associated with increased odds of radiographic outcomes of medial tibiofemoral OA progression. There was risk of bias present in individual studies, and moderate inconsistency present in the meta-analsysis. However, the exposure and outcome methods were relavant to the clinical OA population. Whilst publication bias was difficult to assess due to the small number of studies, we decided that there was low bias present as the studies assessed other prognostic factors.

‡ There is moderate quality evidence to suggest that varus thrust is associated with increased odds of medial tibiofermoral OA progression. The meta-analysis had a moderate-large effect size, with individual studies having low risk of bias in the assessment. The prognostic factor and imaging outcome were also relevant to the clinical OA population. It was difficult to assess for publication bias given the small number of studies, however, the studies were dispersed and additional secondary analyses were conducted in large samples, therefore publication bias was undetected.

Table IV

Osteoarthritis and Cartilage

GRADE summary of findings

knee joints over time. Results confirm that higher early stance peak KAM is associated with 1.88 greater odds of OA progression in the medial tibiofemoral joint ($k = 5$; $n = 601$; low quality evidence). We also identified that people who exhibited varus thrust had 1.97 greater odds of medial tibiofemoral OA progression ($n = 8,059$). Our review also suggests associations between biomechanics and OA progression in the hip and patellofemoral joints.

Meta-analyses demonstrated that peak KAM, KAM impulse and varus thrust were positively associated with OA disease progression. The previous review by Henriksen *et al.*[17], found no significant association between peak KAM and medial tibiofemoral OA progression (OR: 1.90 [95%CI:0.85, 4.25]). The pooled meta-analysis for this previous review included a study[51] which had an active intervention present after baseline, and therefore was excluded from our review. Since 2014, additional studies have investigated the KAM[18,19,34,39,41,44,47], and our meta-analysis ($k = 5$) concluded that peak KAM was positively associated with OA progression in the medial tibiofemoral joint (low-quality evidence). Due to diversity in the KAM variables reported, our meta-analyses were limited to only include five studies. Overall, seven cohorts (9 out of 10 studies) which investigated the KAM variables found a greater risk of knee OA onset[47] and progression[13,14,18,19,38,39,41,44] with higher KAM values. The KAM impulse considers the magnitude and duration of the KAM over stance and may represent a better indicator of medial tibiofemoral joint loading. Whilst we identified a positive association between KAM impulse and 2.07 greater odds of worsening BMLs in the medial tibiofemoral joint, as only two studies were pooled, the strength of the predictive relationship is uncertain. Greater OA progression odds due to higher KAM values is supported by Trepcyznski *et al.*[52], where medial to lateral loading imbalance was correlated with increased medial compressive forces in individuals who later underwent TKA.

Our meta-analysis of low-quality evidence indicates that higher peak KAM values were associated with 1.88 increased odds of medial tibiofemoral OA progression, with the association size varying between studies. This may be due to follow-up time variability, or sensitivity of imaging outcomes. For instance, larger OR's were reported where follow-up time was greater than 24 months (OR range = 4.3–6.4)[14,18], in comparison to a 12 month follow-up[13] (OR: 1.31 [95%CI: 0.86,1.98]). It is also important to consider variability in baseline KAM metrics across studies, as studies[14,18,38] that generally reported higher KAM values in participants also identified larger OR's. In this instance, developing a sensitivity threshold value for peak KAM may help identify individuals at greater risk of OA progression. Miyazaki *et al.*[14], demonstrated that a peak KAM threshold of 5% BW*Ht was 80% sensitive to detecting OA progression over 6 years[14]. As this was the only study to provide a threshold, further studies are needed to confirm threshold values for evaluating OA progression risk. The variability in findings may also be explained by 1) different imaging methods, 2) different joint regions examined, 3) different joint structures (e.g., cartilage defects, BMLs), 4) variability in the imaging outcomes used and 5) time-frames to detect structural changes. For instance, Chang *et al.*[19], found associations between higher peak KAM values with cartilage loss in the subregions of the knee but did not find an association for the medial tibiofemoral joint as a whole. Further research using standardised imaging outcome measurements are needed to quantify the size of the increased odds more accurately.

Varus thrust is proposed to acutely increase medial tibiofemoral loading via an abrupt lateral shift of the knee during stance, followed by return to a less varus alignment during swing[53] and is associated with structural OA progression. Our meta-analysis ($k = 3$)[21,36,42] of moderate quality evidence demonstrated a positive

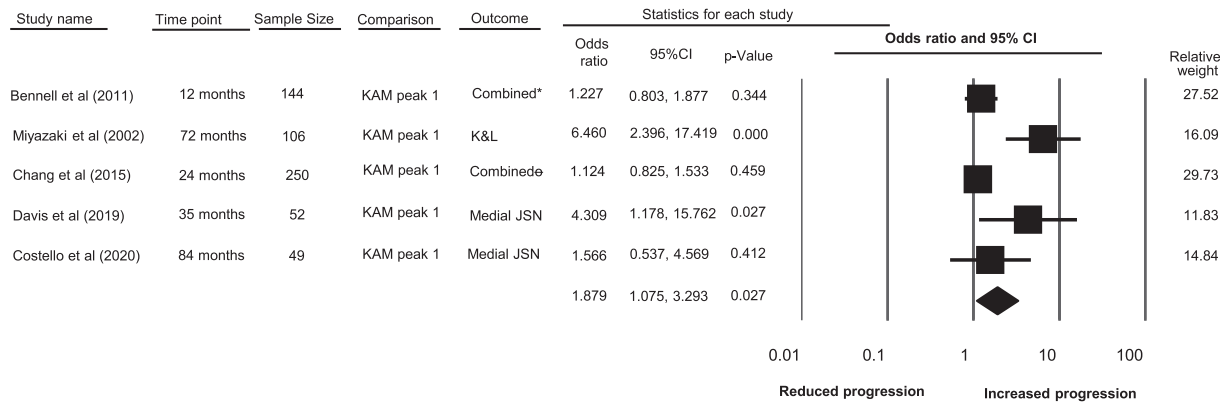

Fig. 2

Osteoarthritis and Cartilage

Meta-analysis for the association between early stance peak KAM and medial tibiofemoral OA progression. * = bone marrow lesions and cartilage damage; Combined ɵ = bone marrow lesions and cartilage defects; JSN = joint space narrowing; KAM = knee adduction moment; KL= Kellgren Lawrence grade.

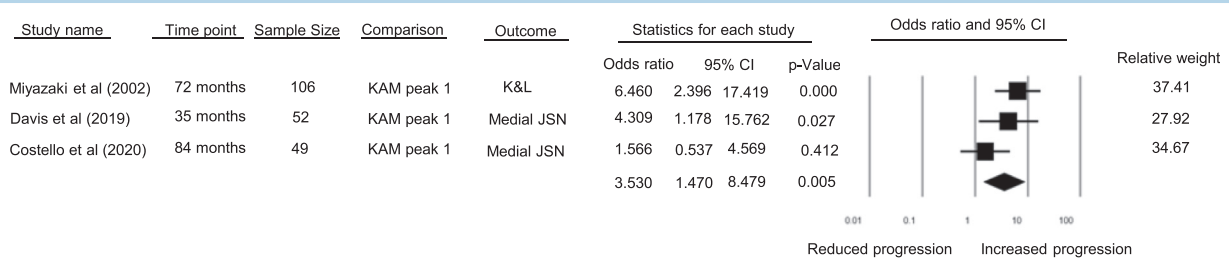

Fig. 3

Osteoarthritis and Cartilage

Meta-analysis for the association between early stance peak KAM and radiographic outcomes of medial tibiofemoral OA progression. JSN = Joint space narrowing; KAM = knee adduction moment; K&L = Kellgren Lawrence grade.

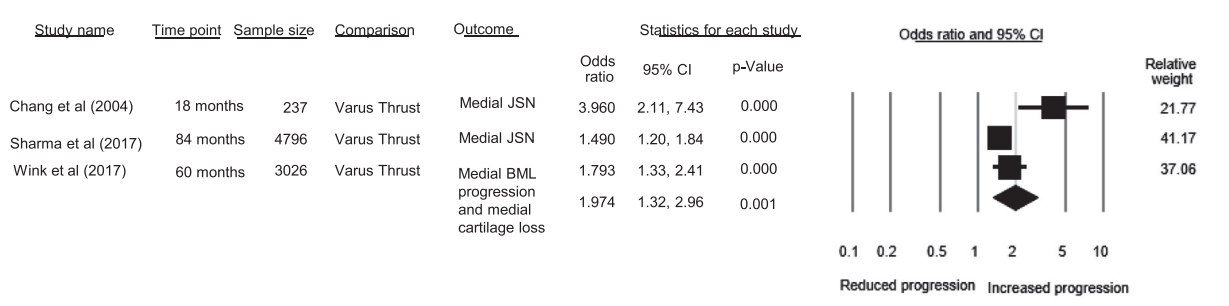

Fig. 4

Osteoarthritis and Cartilage

Meta-analysis for the association between varus thrust and medial tibiofemoral OA progression. BML = bone marrow lesions; JSN = joint space narrowing.

association between varus thrust and increased medial tibiofemoral loading with a 97% increased odds for medial tibiofemoral OA progression. These studies visually identified, and dichotomously categorised varus thrust (present or absent). Two of these studies[21,42] investigated the association between varus thrust and disease onset with differential results. Wink *et al.*[21], used MRI outcomes to define disease onset and confirmed an association between varus thrust and presence of BMLs in the medial tibiofemoral joint over 24 months, though the same was not found for other imaging outcomes[21]. Sharma *et al.*[42], used radiographic assessment and defined disease onset as incident KL grade $\geq$2 and found no association with disease onset over 84 months. As the studies used different imaging tools to assess and define disease onset, it was difficult to combine these results. The WORMS scoring tool used in Wink *et al.*[21], may be more sensitive to detecting presence of BMLs[21], as opposed to identifying a whole-grade change in KL grading in Sharma *et al.*[42],. Further studies using a standardised imaging tool are required to determine if an association exists between varus thrust presence and knee OA onset.

Sagittal and transverse plane biomechanical metrics were also found to be associated with increased risk of medial tibiofemoral OA progression; however, data could not be pooled for meta-analyses due to the small number of findings. Three studies evaluated transverse plane metrics and two of these[18,44] found an association between midstance knee rotation moment (KRM)[44] and KRM range[18] with medial tibiofemoral JSN. This supports findings from *in vitro* studies which demonstrate shear loading and the negative effect on cartilage integrity[8]. Of the four studies which investigated sagittal plane kinetics for the medial tibiofemoral joint[19,39,41,44], one study[39] found an association between KFM and cartilage loss and the other[41] with progression to TKA. For sagittal plane kinematics, one study[40] identified an association between maximum knee flexion angle and increased femoral anterior-posterior displacement with medial tibiofemoral OA progression, suggesting that kinematic changes in heel strike and midstance may increase medial knee contact forces[40]. Future studies should investigate the associations of sagittal and transverse plane biomechanics with medial tibiofemoral OA progression.

For patellofemoral OA, four studies[33,35,43,45] found associations between biomechanical metrics and patellofemoral OA progression. Two studies[33,35] investigated knee sagittal plane metrics, and found KFM[33] and dynamic joint stiffness[35] to be associated with patellofemoral progression. It has been postulated that a higher KFM is associated with increased patellofemoral joint reaction forces[54] which may contribute to patellofemoral joint disease progression. Two additional studies[43,45] also investigated spatio-temporal metrics and found that a lower step rate was associated with lateral patellofemoral OA progression[45] whilst a larger step length may have protective effects, however this was only identified in the second largest step length quintile and therefore possibly a chance finding[43]. As patellofemoral joint OA is largely prevalent (present in more than half of individuals with knee OA)[55], a need exists for additional longitudinal studies.

Only two studies[15,49] reported sagittal and frontal plane hip biomechanics, with hip OA progression. Tateuchi *et al.*[15], investigated physical activity and kinetics, and found associations between cumulative frontal plane moment (product of moment impulse and number of steps per day), and worsening in medial hip JSW. Theoretically, repetitive loading during gait may accelerate hip OA progression through increased joint loading exposure, potentially resulting in chondrocyte damage[56]. However, as this was the only longitudinal study investigating cumulative loading as a risk factor, results need to be replicated before strong conclusions can be drawn.

There are several strengths to this review. Firstly, we conducted a comprehensive search for biomechanical metrics associated with both onset and progression of OA in all major lower limb joints. As previous research focuses largely on medial tibiofemoral joint OA, our review demonstrates other biomechanical variables associated with the hip and patellofemoral joint, though more studies are needed. Secondly, we followed PRISMA guidelines and had two reviewers independently perform screening, data-extraction and risk of bias evaluation using a valid assessment tool. Thirdly, we followed a rigorous meta-analysis plan, particularly relevant due to the variability of reported structural imaging outcomes. Some limitations need consideration when interpreting the results of this review. After extensive search strategy piloting, we chose to conduct the search in only two databases, therefore, it is possible that additional eligible studies were not identified. This was decided because extensive pilot searches of additional databases (CINAHL, Scopus and AMED) yielded no additionally relevant studies, with predominantly studies pertaining to genetics and biochemistry. Our study was limited to meta-analyses of only three biomechanical variables, despite 83 biomechanical variables and 11 imaging outcomes reported across the included studies. Future research should focus on developing standardised procedures for the conduct and reporting of biomechanical variables (e.g., specific time-points, normalization) as well as standardised imaging definitions of OA onset and progression (e.g., imaging methods, time-frames, quantification methods).

The extensive results generated in this review is important in understanding the key role gait biomechanics may play as biomarkers for lower limb OA onset and progression, with 91% of studies confirming risk of OA onset or progression. We found an association between higher KAM variables and varus thrust with medial tibiofemoral OA progression in 11 out of 12 studies. There was also evidence for biomechanics as a potential risk factor for hip and patellofemoral OA progression. For future research, we need large, high quality longitudinal studies to confirm our findings for the hip and knee and investigate the association of gait biomechanics with onset/progression of ankle OA. Given the potentially modifiable nature of biomechanical risk factors[26], clinical trials are required to see if altering these risk factors can slow OA progression.

Conflict of interest

Nicole D'Souza: There are no financial or personal interest that could have potentially and inappropriate influence the integrity of the work in this manuscript to disclose by the author.

Jesse Charlton: There are no financial or personal interest that could have potentially and inappropriate influence the integrity of the work in this manuscript to disclose by the author.

Jane Grayson: There are no financial or personal interest that could have potentially and inappropriate influence the integrity of the work in this manuscript to disclose by the author.

Sarah Kobayashi: There are no financial or personal interest that could have potentially and inappropriate influence the integrity of the work in this manuscript to disclose by the author.

Laura Hutchison: There are no financial or personal interest that could have potentially and inappropriate influence the integrity of the work in this manuscript to disclose by the author.

Michael Hunt: There are no financial or personal interest that could have potentially and inappropriate influence the integrity of the work in this manuscript to disclose by the author.

Milena Simic: There are no financial or personal interest that could have potentially and inappropriate influence the integrity of the work in this manuscript to disclose by the author.

Funding
A. Prof. Milena Simic is supported by the University of Sydney's SOAR fellowship. Nicole D'Souza is supported by the Westmead Charitable Trust, Allied Health Career Development grant Jesse Charlton and Michael Hunt are supported by the Canadian Institutes of Health Research. Laura Hutchison is supported by the Arthritis Australia National Research Program Scholarship, Funded by Arthritis Western Australia.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2021.10.010.

References

1. Hunter DJ. Osteoarthritis. Best Pract Res Clin Rheumatol 2011;25(6):801–14.
2. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(9995):743–800.
3. Kingsbury SR, Gross HJ, Isherwood G, Conaghan PG. Osteoarthritis in Europe: impact on health status, work productivity and use of pharmacotherapies in five European countries. Rheumatology 2014;53(5):937–47.
4. Andriacchi T, Mündermann A, Smith R, Alexander E, Dyrby C, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Ann Biomed Eng 2004;32(3):447–57.
5. Ko FC, Dragomir C, Plumb DA, Goldring SR, Wright TM, Goldring MB, van der Meulen MC. In vivo cyclic compression causes cartilage degeneration and subchondral bone changes in mouse tibiae. Arthritis Rheum 2013;65(6):1569–78.
6. Stewart HL, Kawcak CE. The importance of subchondral bone in the pathophysiology of osteoarthritis. Frontiers In Veterinary Science 2018;5:178.
7. Simon SR, Radin EL, Paul IL, Rose RM. The response of joints to impact loading — II in vivo behavior of subchondral bone. J Biomech 1972;5(3):267–72.
8. Lee MS, Trindade MCD, Ikenoue T, Schurman DJ, Goodman SB, Smith RL. Effects of shear stress on nitric oxide and matrix protein gene expression in human osteoarthritic chondrocytes in vitro. J Orthop Res 2002;20(3):556–61.
9. Favre J, Jolles BM. Gait analysis of patients with knee osteoarthritis highlights a pathological mechanical pathway and provides a basis for therapeutic interventions. EFORT Open Reviews 2016;1(10):368–74.
10. Cappozzo A, Della Croce U, Leardini A, Chiari L. Human movement analysis using stereophotogrammetry: Part 1: theoretical background. Gait Posture 2005;21(2):186–96.
11. Kutzner I, Trepczynski A, Heller MO, Bergmann G. Knee adduction moment and medial contact force–facts about their correlation during gait. PLoS One 2013;8(12):81036.
12. Birmingham T, Hunt M, Jones I, Jenkyn T, Giffin J. Test-retest reliability of the peak knee adduction moment during walking in patients with medial compartment knee osteoarthritis. Arthritis Care Res 2007;57(6):1012–7.
13. Bennell KL, Bowles K-A, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis 2011;70:1770–4.
14. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis 2002;61(7):617–61722.
15. Tateuchi H, Koyama Y, Akiyama H, Goto K, So K, Kuroda Y, *et al*. Daily cumulative hip moment is associated with radiographic progression of secondary hip osteoarthritis. Osteoarthritis Cartilage 2017;25(8):1291–8.
16. Queen R. Directing clinical care using lower extremity biomechanics in patients with ankle osteoarthritis and ankle arthroplasty. J Orthop Res 2017;35(11):2345–55.
17. Henriksen M, Creaby MW, Lund H, Juhl C, Christensen R. Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials. BMJ Open 2014;4(7), 005368.
18. Davis EM, Hubley-Kozey CL, Landry SC, Ikeda DM, Stanish WD, Astephen Wilson JL. Longitudinal evidence links joint level mechanics and muscle activation patterns to 3-year medial joint space narrowing. Clin BioMech 2019;61:233–9.
19. Chang AH, Moisio KC, Chmiel JS, Eckstein F, Guermazi A, Prasad PV, *et al*. External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. Osteoarthritis Cartilage 2015;23(7):1099–106.
20. Creaby MW. It's not all about the knee adduction moment: the role of the knee flexion moment in medial knee joint loading. Osteoarthritis Cartilage 2015;23(7):1038–40.
21. Wink AE, Gross KD, Brown CA, Guermazi A, Roemer F, Niu J, *et al*. Varus thrust during walking and the risk of incident and worsening medial tibiofemoral MRI lesions: the Multicenter Osteoarthritis Study. Osteoarthritis Cartilage 2017;25(6):839–45.
22. Bowling FL, Reeves ND. Conservative biomechanical strategies for knee osteoarthritis. Nat Rev Rheumatol 2011;7(2):113–22.
23. Jones RK, Nester CJ, Richards JD, Kim WY, Johnson DS, Jari S, *et al*. A comparison of the biomechanical effects of valgus knee braces and lateral wedged insoles in patients with knee osteoarthritis. Gait Posture 2012;37(3):368–72.
24. Maly MR, Culham EG, Costigan PA. Static and dynamic biomechanics of foot orthoses in people with medial compartment knee osteoarthritis. Clin BioMech 2002;17(8):603–10.
25. Simic M, Bennell KL, Hunt MA, Wrigley TV, Hinman RS. Contralateral cane use and knee joint load in people with medial knee osteoarthritis: the effect of varying body weight support. Osteoarthritis Cartilage 2011;19(11):1330–7.
26. Simic M, Hinman RS, Wrigley TV, Bennell KL, Hunt MA. Gait modification strategies for altering medial knee joint load: a systematic review. Arthritis Care Res 2011;63(3):405–26.
27. Bruyere O, Richy F, Reginster JY. Three year joint space narrowing predicts long term incidence of knee surgery in patients with osteoarthritis: an eight year prospective follow up study. Ann Rheum Dis 2005;64(12):1727–30.
28. Tanamas SK, Wluka AE, Pelletier J-P, Pelletier JM, Abram F, Berry PA, *et al*. Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. Rheumatology 2010;49(12):2413–9.
29. Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. Arthritis Care Res 2011;63(8):1115–25.
30. Foroutan F, Guyatt G, Zuk V, Vandvik PO, Alba AC, Mustafa R, *et al*. GRADE Guidelines 28: use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. J Clin Epidemiol 2020;121:62–70.

31. Rohatgi A. WebPlotDigitizer 2020, https://automeris.io/WebPlotDigitizer/.
32. Higgins JPT. In: Cochrane Handbook for Systematic Reviews of Interventions. 2nd edn. Hoboken, NJ: Wiley-Blackwell; 2019.
33. Teng H-L, Macleod TD, Link TM, Majumdar S, Souza RB. Higher knee flexion moment during the second half of the stance phase of gait is associated with the progression of osteoarthritis of the patellofemoral joint on magnetic resonance imaging. J Orthop Sports Phys Ther 2015;45(9):656–64.
34. Brisson NM, Wiebenga EG, Stratford PW, Beattie KA, Totterman S, Tamez-Peña JG, *et al.* Baseline knee adduction moment interacts with body mass index to predict loss of medial tibial cartilage volume over 2.5 years in knee Osteoarthritis. J Orthop Res 2017;35(11):2476–83.
35. Chang AH, Chmiel JS, Almagor O, Guermazi A, Prasad PV, Moisio KC, *et al.* Association of baseline knee sagittal dynamic joint stiffness during gait and 2-year patellofemoral cartilage damage worsening in knee osteoarthritis. Osteoarthritis Cartilage 2017;25(2):242–8.
36. Chang A, Hayes K, Dunlop D, Hurwitz D, Song J, Cahue S, *et al.* Thrust during ambulation and the progression of knee osteoarthritis. Arthritis Rheum 2004;50(12):3897–903.
37. Chang A, Hayes K, Dunlop D, Song J, Hurwitz D, Cahue S, *et al.* Hip abduction moment and protection against medial tibiofemoral osteoarthritis progression. Arthritis Rheum 2005;52(11):3515–9.
38. Chang A, Hurwitz D, Dunlop D, Song J, Cahue S, Hayes K, *et al.* The relationship between toe-out angle during gait and progression of medial tibiofemoral osteoarthritis. Ann Rheum Dis 2007;66(10):1271–5.
39. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis Cartilage 2014;22(11):1833–9.
40. Favre J, Erhart-Hledik JC, Chehab EF, Andriacchi TP. Baseline ambulatory knee kinematics are associated with changes in cartilage thickness in osteoarthritic patients over 5 years. J Biomech 2016;49(9):1859–64.
41. Hatfield GL, Stanish WD, Hubley-Kozey CL. Three-dimensional biomechanical gait characteristics at baseline are associated with progression to total knee arthroplasty. Arthritis Care Res 2015;67(7):1004–14.
42. Sharma L, Chang AH, Jackson RD, Nevitt M, Moisio KC, Hochberg M, *et al.* Varus thrust and incident and progressive knee osteoarthritis. Arthritis & Rheumatology 2017;69(11):2136–43.
43. Stefanik JJ, Gross KD, Guermazi A, Felson DT, Roemer FW, Niu J, *et al.* Relation of step length to magnetic resonance imaging–detected structural damage in the patellofemoral joint: the multicenter osteoarthritis study. Arthritis Care Res 2016;68(6):776–83.
44. Costello KE, Astephen Wilson JL, Stanish WD, Urquhart N, Hubley-Kozey CL. Differences in baseline joint moments and muscle activation patterns associated with knee osteoarthritis progression when defined using a clinical versus a structural outcome. J Appl Biomech 2020;36(1):1–51.
45. Hart HF, Gross KD, Crossley KM, Barton CJ, Felson DT, Guermazi A, *et al.* Step rate and worsening of patellofemoral and tibiofemoral joint osteoarthritis in women and men: the multicenter osteoarthritis study. Arthritis Care Res 2020;72(1):107–13.
46. Mahmoudian A, van Dien JH, Bruijn SM, Baert IAC, Faber GS, Luyten FP, *et al.* Dynamic and static knee alignment at baseline predict structural abnormalities on MRI associated with medial compartment knee osteoarthritis after 2 years. Gait Posture 2017;57:46–51.
47. Erhart-Hledik JC, Chehab EF, Asay JL, Favre J, Chu CR, Andriacchi TP. Longitudinal changes in tibial and femoral cartilage thickness are associated with baseline ambulatory kinetics and cartilage oligomeric matrix protein (COMP) measures in an asymptomatic aging population. Osteoarthritis Cartilage 2021;29(5):687–96.
48. Brisson NM, Gatti AA, Damm P, Duda GN, Maly MR. Association of machine learning based predictions of medial knee contact force with cartilage loss over 2.5 years in knee osteoarthritis. Arthritis & Rheumatology 2021;73(9):1638–45.
49. Kumar D, Wyatt C, Lee S, Okazaki N, Chiba K, Link TM, *et al.* Sagittal plane walking patterns are related to MRI changes over 18-months in people with and without mild-moderate hip osteoarthritis. J Orthop Res 2018;36(5):1472–7.
50. Simic M, Hunt MA, Bennell KL, Hinman RS, Wrigley TV. Trunk lean gait modification and knee joint load in people with medial knee osteoarthritis: the effect of varying trunk lean angles. Arthritis Care Res 2012;64(10):1545–53.
51. Woollard JD, Gil AB, Sparto P, Kwoh CK, Piva SR, Farrokhi S, *et al.* Change in knee cartilage volume in individuals completing a therapeutic exercise program for knee osteoarthritis. J Orthop Sports Phys Ther 2011;41(10):708–22.
52. Trepczynski A, Kutzner I, Bergmann G, Taylor WR, Heller MO. Modulation of the relationship between external knee adduction moments and medial joint contact forces across subjects and activities. Arthritis & Rheumatology 2014;66(5):1218–27.
53. Issa S, Sharma L. Epidemiology of osteoarthritis: an update. Curr Rheumatol Rep 2006;8(1):7–15.
54. Loudon JK. Biomechanics and pathomechanics of the patellofemoral joint. Int J Sports Phys Ther 2016;11(6):820–30.
55. Kobayashi S, Pappas E, Fransen M, Refshauge K, Simic M. The prevalence of patellofemoral osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2016;24(10):1697–707.
56. Tateuchi H, Koyama Y, Tsukagoshi R, Akiyama H, Goto K, So K, *et al.* Associations of radiographic degeneration and pain with daily cumulative hip loading in patients with secondary hip osteoarthritis. J Orthop Res 2016;34(11):1977–83.