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BIOMECHANICAL FACTORS ASSOCIATED WITH THE DEVELOPMENT OF KNEE OSTEOARTHRITIS: PROTOCOL FOR A SYSTEMATIC REVIEW AND META-ANALYSIS.

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ABSTRACT

Introduction: Osteoarthritis is one of the most common causes of pain and disability, with knee osteoarthritis (KOA) being the most prevalent. Adverse biomechanics may play a role in the development of KOA. We have defined biomechanical factors as joint related factors that interact with the forces, moments and kinematics in and around a synovial joint. Although a number of studies and systematic reviews have been performed to assess the association of various factors with the development of KOA, a comprehensive overview of biomechanical factors associated with the development of KOA is not available. Such an overview might help to identify persons at high risk of developing KOA due to adverse biomechanics and to improve prevention strategies. Additionally, the results of this review can be used to increase patient knowledge. Finally, this review will identify gaps in the literature, which helps to set the agenda for future biomechanical studies. The aim of this review is 1) to identify biomechanical factors that are associated with (the development of) KOA, and 2) to identify the impact of other relevant risk factors on this association.

Methods and analysis: Cohort, cross sectional and case-control studies investigating the association of a biomechanical factor with (the development of) KOA are included. MEDLINE, EMBASE, CINAHL and SPORTDiscus are searched from their inception until August 2015. Two reviewers independently screen articles obtained by the search for eligibility, extract data and score risk of bias. Quality of evidence is evaluated. Meta-analysis using random effects model is applied in each of the biomechanical factors, if possible.

Ethics and dissemination: This systematic review and meta-analysis does not require ethical approval. The results of this systematic review and meta-analysis will

be disseminated through publications in peer-reviewed journals, presentations at (inter)national conferences and patient information.

PROSPERO registration number: CRD42015025092.

ARTICLE SUMMARY

Article focus

- This article describes a protocol for a systematic review and meta-analysis to identify biomechanical factors that are associated with the development of knee osteoarthritis (KOA).
- The impact of relevant risk factors (i.e. high BMI, female gender, history of previous knee injury and higher age) on this association is also assessed in this systematic review and meta-analysis.

Key messages

- The primary goal of this systematic review and meta-analysis is to give an overview of biomechanical factors that are associated with the development of KOA.
- This may be used to identify persons at high risk of developing KOA.

Strengths and limitations of this study

- To our knowledge, this is the first article to give an overview of biomechanical factors associated with the development of KOA.
- This review does not assess the mechanism of how the biomechanical factors are related to the development of KOA.
- This is a protocol article. Results of the systematic review and meta-analysis will be published in a different article.

INTRODUCTION

Osteoarthritis is one of the leading causes of pain and activity limitations, which often affects the knee joint.[1] Currently, no cure for osteoarthritis is available, and the exact pathogenesis remains unknown.[2-4] Many studies have been performed to identify factors that are associated with the development of knee osteoarthritis (KOA).[2, 5, 6]

A recent systematic review showed that several risk factors were associated with the development of knee pain or KOA in those aged 50 and over, although this review did not consider biomechanical factors.[7] We have defined biomechanical factors as joint related factors that interact with the forces, moments and kinematics in and around a synovial joint. Biomechanical factors can be divided in four main biomechanical impairments relevant to KOA, i.e. skeletal malalignment, impaired proprioception, muscle dysfunction and laxity (see Table 1). Skeletal malalignment refers to abnormal alignment of or deformity within the knee joint. Impaired proprioception refers to a deterioration of the senses of knee joint position and movement. Muscle dysfunction refers to a loss of muscle strength, or muscle weakness, to loss of muscle endurance and to changed muscle activation patterns for the muscles that act on the knee joint. Laxity refers to a loss of passive joint stabilisation due to the inability of passive structures in and around the knee (knee ligaments, cruciate ligaments, capsule) to provide an adequate counterbalance to the mechanical forces acting upon the knee during activity. These biomechanical impairments might impact on the load of the knee. Abnormal loading is associated with imbalances that may eventually lead to KOA.[8] Next to biomechanical factors, other risk factors (e.g. high body mass index (BMI), female gender, history of previous knee injury and higher age) have been shown to be associated with the

development of KOA.[7] Thus the development of KOA might depend on a combination of biomechanical factors and other risk factors.

Table 1. Biomechanical impairments and risk factors relevant to the development of KOA, subdivision, and measurement.

	Impairment/risk factor	Subdivision	Measurement
Abnormal loading			Moments, KRF, KCF
	Skeletal malalignment	Static	Leg alignment (HKA), passive ROM, Q-angle
		Dynamic	Thrust, active ROM
	Muscular dysfunction	Muscular	Strength, HQ-ratio
		Neurologic	Activation pattern, RFD, co-contraction, co-activation
	Impaired proprioception	Joint position sense	Error, accuracy
		Joint movement sense	Threshold
	Laxity	Anterior-posterior	Tibial translation
		Varus-valgus	Tibial transalation, joint angle, torque
	High BMI	Categorical*	e.g. obese, BMI > 30
		Continuous	BMI
	Gender	Categorical*	Male, female

Previous knee injury[§]	Categorical[*]	e.g. ligament rupture, meniscal lesion, tibia plateau fracture
Age	Categorical[*]	e.g. middle aged, elderly
	Continuous	Age

[*]comparable categorical risk factors will be grouped in analyses, based on decision by the two reviewers [§] studies should not be influenced by rehabilitation or surgical treatment. KOA: knee osteoarthritis, BMI: body mass index, KRF: knee reaction force, KCF: knee contact force, HKA: hip-knee-ankle-angle, ROM: range of motion, RFD: rate of force development.

The relationship between biomechanical factors and the development of KOA has been indicated in several biomechanical studies and systematic reviews, but there is no systematic review available that contains an overview of all available evidence of the influence of biomechanical factors on the development of KOA.[9-12] Such an overview may be used to identify persons at high risk of developing KOA. Several strategies like physical therapy, knee braces or insoles might prevent the development of KOA in those persons by interacting on the biomechanical factors. In addition, an overview provides information that can be used to base the rationale behind strategies to prevent the development of KOA on, to inform patients about biomechanical risk factors for KOA and to identify the focus of future biomechanical and clinical studies.

Objectives

The aim of this review is 1) to identify biomechanical factors that are associated with (the development of) KOA, and 2) to identify the impact of other relevant risk factors on this association. Therefore the proposed systematic review will answer the following questions:

1. Which biomechanical factors are associated with (the development of) KOA?
2. Is the association of these biomechanical factors with (the development of) KOA mediated by other risk factors for KOA (i.e. high BMI, female gender, history of previous knee injury and higher age)?

METHODS AND ANALYSIS

This review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) at the National Institute for Health Research and Center for Reviews and Dissemination (CRD) at the University of York (registration number: CRD42015025092).[13] This systematic review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) guidance.[14] The systematic review will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance.[15]

Studies are selected according to the criteria outlined below.

Type of studies

Studies are eligible if they are cohort, cross sectional or case-control studies. The cohort studies can either be prospective or retrospective. All cohort studies should have a follow-up period of at least one year. Studies should not be influenced by rehabilitation or surgical treatment.

Type of participants

Included studies are cohort studies examining participants who might develop KOA, and case-control and cross sectional studies that include both participants with KOA and healthy controls. Participants have KOA if one of the criteria described in Table 2, or an outcome measure related to the criteria, is fulfilled. Both primary and secondary KOA is eligible. Participants can have osteoarthritis in one or both knees, although data should be analysed for only one knee, in order to examine independent associations with KOA. Studies examining participants with both osteoarthritis of the

hip and the knee are only included if separate data of participants with KOA is available. Studies examining participants already having KOA at baseline (cohort studies) or studies examining 'healthy' controls having KOA in either the index or the contralateral knee (cross sectional or case-control studies) according to aforementioned criteria are excluded. Studies examining participants with osteoarthritis in the patellofemoral joint only are excluded. Only data regarding tibiofemoral osteoarthritis is used. Cohort studies examining incidence of KOA in other populations (e.g., rheumatoid arthritis, hypermobility) are included, although only data regarding KOA is used.

Table 2. Criteria of osteoarthritis, and hierarchy of definitions (ranking: *A* (high) - *J* (low)).

A	Clinical KOA	According to clinical ACR criteria
B	Radiological KOA	Kellgren and Lawrence grade ≥ 2, or grade ≥2 /osteophytes, or Ahlback grade > 1
C	Radiological KOA	OARSI atlas criteria: sum of osteophytes or JSN ≥grade 2, or grade 1 JSN in combination with grade 1 osteophyte
D	Clinical KOA	Knee pain and ≥ 50 years old
E	Radiological KOA	Radiographic signs*; only if the authors report the participants to have KOA
F	Surgery due to KOA§	Arthroscopy used to describe KOA
G	Surgery due to KOA§	Osteotomy due to KOA
H	Surgery due to KOA§	Total knee replacement due to KOA
I	KOA defined by MRI	KOA signs on MRI; only if the authors report the participants to have KOA
J	Clinical KOA	Participants report to have KOA diagnosed by physician

*e.g., osteophytes, cartilage damage, joint space narrowing, bone marrow oedema, §only as outcome measure of cohort study. KOA: knee osteoarthritis, ACR: American College of Rheumatology, OARSI: Osteoarthritis Research Society International, JSN: joint space narrowing, MRI: Magnetic Resonance Imaging.

Type of biomechanical factors

Studies exploring the association of a biomechanical factor with (the development of) KOA are reviewed. The biomechanical factors are grouped into one group referring to abnormal loading and four main biomechanical impairments relevant to KOA (see Table 1). Table 1 also describes frequently used ways to measure biomechanical factors. The possible inclusion of measurements of biomechanical factors not listed in Table 1 will be discussed by the reviewers (JT, ADI). Only biomechanical factors directly related to the knee joint are taken into account. Joint angles during activities are excluded due to limited reliability of these measurements. Measurements of moments, knee reaction forces and knee contact forces are included as measurements of abnormal loading, in contrast to measurements of ground reaction forces and centre of pressure, because only the first give a comprehensive estimate of the loading of the knee. The influence of risk factors on the association of biomechanical factors with (the development of) KOA is also reviewed. Studies that only explore non-biomechanical risk factors are excluded from this review.

Types of outcome measure

KOA in included studies can be defined by subjective or objective estimates. Subjective estimates are KOA based on clinical criteria (see Table 2). Objectives estimates are KOA based on radiological, MRI or surgical criteria (see Table 2).

Publication year and language

There is no restriction on publication year and language.

Sources and search strategy

The following databases are searched from their inception until August 2015: MEDLINE via Pubmed, EMBASE via OVID, CINAHL (including preCINAHL) via EBSCO, and SPORTDiscus via EBSCO. Reference lists from included studies and identified relevant reviews, textbooks and clinical guidelines are searched for relevant references. A citation search is performed on highly relevant studies. Experts in the field are asked for relevant references to ensure literature saturation.

Literature search strategies are developed using subject headings (MeSH) and text words related to osteoarthritis, biomechanical factors and study types. Search terms from other relevant reviews are identified and are complemented with additional terms for biomechanical factors. The MEDLINE search strategy is included in Appendix 1 and is adjusted in order to apply it to other databases.

Study inclusion and exclusion criteria

The inclusion criteria are:

- The study assesses the association of a biomechanical factor with the development of KOA, and possibly the impact of other risk factors on this association.
- A biomechanical factor is a knee joint related factor that interacts with the forces, moments and kinematics in and around a synovial joint.
- The study is a cohort study:
    - Participants developing KOA and participants not developing KOA.

or

- The study is a case-control study or cross sectional study:

- Participants with and without KOA.

The exclusion criteria are:

- The study includes only participants with patellofemoral osteoarthritis.
- The study does not distinguish between hip osteoarthritis and KOA.
- The study is influenced by rehabilitation or surgical treatment.

Data management

References from all searches are uploaded into EndNote (X7) bibliographic software (Thompson Reuters, Philadelphia, Pennsylvania, USA). Duplicates are removed with the SRA-DM (Systematic Review Assistant-Deduplication Module).[16] Remaining duplicates are removed with EndNote duplicate removal and manually by screening for duplicates while the list of references is sorted alphabetically based on author. All full text files are stored in EndNote. For all studies reviewed in full text, a form regarding eligibility criteria check is stored. Data from included studies is entered into a data extraction form in Microsoft Excel. If a meta-analysis is eligible, the data is transferred to STATA software (V13.0 or later, StataCorp LP) to do statistical analysis.

Selection process

Two members of the study team (JT, ADI) independently screen titles and abstracts of the studies obtained by the search strategy. The full text of any study is obtained if it was judged eligible by at least one of the reviewers. Then, the two reviewers use a standardized form to select studies eligible for inclusion in the review. Consensus on inclusion is reached by discussion. Reasons for excluding studies based on the full text are recorded. When more than one study is based on the same population and

contains the same information with respect to the association at issue, only one study is included. This is based on the following order; 1) the publication with the largest sample size, 2) the most recent publication, or 3) the study that examined KOA using the highest ranked outcome measure. Hierarchy of the definitions is described later at "Data items, outcomes and hierarchy" and in Table 2. If studies of the same study population present different information with respect to the association at issue, both studies are included. A PRISMA-flowchart is completed to summarise the process. Neither of the review authors is blinded to the journal titles or to the study authors or institutions.[17]

Data collection process

Two reviewers (JT, ADI) independently extract data from the included studies using a customised form, piloted prior to use. Consensus on extracted data is reached by discussion, and conflictive data extraction is discussed with a third member of the study team (CJ or HL).

Data items, outcomes and hierarchy

Data items that are extracted from included studies are described in Table 3. Table 3 shows that in cohort studies preferably the number of participants developing KOA and not developing KOA, and the number of participants exposed and not exposed to the biomechanical factor are extracted. In cross sectional or case-control studies, preferably the number of participants with and without KOA, and the number of participants exposed and not exposed to the biomechanical factor are extracted. If this is not available, mean values for the biomechanical factors or odds ratios are extracted, respectively. The same data extraction and analyses are performed for

biomechanical factors and other risk factors. Therefore, in the following paragraphs only biomechanical factors are mentioned. The hierarchy for definitions of KOA is based on comprehensiveness of the definition and the use in clinical practise (see Table 2, ranking: A - J). Symptomatic KOA is based on the American College of Rheumatology criteria.[18] Radiographic KOA is based on radiological atlases (e.g. the Kellgren and Lawrence (K/L) Classification).[19, 20] In addition, physicians or authors can state that participants have KOA. The hierarchy is used for study selection if more than one study examines the same population and for data extraction in studies using two or more outcome measures of KOA. For the latter, only data regarding the highest ranked outcome measure is extracted.

Table 3. Data extraction.

All studies	
First author	Age (mean±SD)
Year of publication	BMI (mean±SD)
Study design	Definition of KOA used
Duration of follow-up[1]	Definition of BF used
Number of participants	Definition of RF used[*]
Gender (% female)	No. of participants developing KOA[1] or with KOA[2]
Cohort studies	*Case-control or cross sectional studies*
No. of participants developing KOA - exposed to BF/RF	No. of participants with KOA – exposed to BF/RF
No. of participants *not* developing KOA	No. of controls - exposed to BF/RF

– exposed to BF/RF	
No. of participants developing KOA - *not* exposed to BF/RF	No. of participants with KOA – *not* exposed to BF/RF
No. of participants *not* developing KOA - *not* exposed to BF/RF	No. of controls – *not* exposed to BF/RF
or	
Mean±SD of biomechanical factor within participants developing KOA	Mean±SD of biomechanical factor within participants with KOA
Mean±SD of biomechanical factor within participants *not* developing KOA	Mean±SD of biomechanical factor within controls
or	
Odds ratios for the association between BF/RF and the development of KOA	Odds ratios for the association between BF/RF and KOA

Preferably the numbers of participants are extracted. If these are not available, mean values for the biomechanical or risk factor, or odds ratios are extracted, respectively. *if eligible, [1]for cohort studies, [2] for case-control and cross sectional studies. SD: standard deviation, KOA: knee osteoarthritis, BF: biomechanical factor, RF: risk factor.

Risk of bias in individual studies

Risk of bias for each included study is scored independently by two reviewers (JT, ADI). Consensus on conflicting scores is reached by discussion. The Quality In Prognostic Studies (QUIPS) tool is used.[21] Six areas of potential study biases are assessed: study participation, study attrition, prognostic factor measurement, study

confounding, outcome measurement, and statistical analysis and reporting. Risk of bias for study participation is the likelihood that the relationship between the prognostic factor and the outcome is different for participants and eligible non-participants. Risk of bias for study attrition is the likelihood that the relationship between the prognostic factor and the outcome is different for completing and non-completing participants. Risk of bias for prognostic factor measurement is related to differential measurement of the prognostic factor related to the level of outcome. Risk of bias for study confounding is the effect of the prognostic factor being distorted by another factor that is related to the prognostic factor and outcome. Risk of bias for outcome measurement is related to differential measurement of outcome related to the baseline level of the prognostic factor. Risk of bias for statistical analysis and reporting is the risk of bias whether the statistical analysis is dependent on KOA status and the exposure to the biomechanical factor or not, and whether the presentation of results differs between KOA status and exposure. Study attrition is not applicable for cross sectional and case-control studies, thus is only rated in cohort studies. Studies are classified as being of high-quality if all study biases are assessed to have a low or moderate risk of bias. Studies with a high risk of bias for at least one study bias are defined as low-quality studies. A summary statement regarding the quality of the included studies included is reported in the results section.

Assessment of publication bias

It is assumed that biomechanical projects indicating no association between a biomechanical factor and (the development of) KOA are likely to not be published. Therefore, funnel plots are used to show the OR on the x-axis against the sample size on the y-axis for each biomechanical factor.

Data synthesis

Data is grouped by the category abnormal loading and the main biomechanical impairments. Subsequently, data is grouped per subdivision of biomechanical impairments, as shown in table 1, and per study design (i.e. cohort studies vs. a combination of cross sectional and case-control studies). Biomechanical factors studied in more than one study per study design are subjected to meta-analyses. Meta-analyses are applied on the OR of developing KOA in participants who are exposed to the biomechanical factor of interest (cohort studies), or the OR of the biomechanical factor being present in participants with KOA compared to the control group (cross sectional or case-control studies). Random effects model (Mantel Haenszel method) is used, as large clinical heterogeneity is expected due to the variation in the definition of KOA and biomechanical factors. Meta regression analyses are applied to assess the summary effect measure of multiple biomechanical factors. This is also used to assess the impact of other risk factors, and combinations of other risk factors, on the association of biomechanical factors with (the development of) KOA. A forest plot is made for each biomechanical factor and for combinations of biomechanical factors and other risk factors.

Heterogeneity between studies combined in one meta-analysis is examined with standard Q-tests, and calculated as the I^2 statistics, measuring the proportion of inconsistency in the summary effect measure due to between-study heterogeneity.[22, 23]

If any substantial heterogeneity is identified through analysis of Chi^2 and I^2 statistics, subgroup and sensitivity analyses are performed. These are only performed if at least three studies are included in the meta-analysis. Subgroup analyses are used to explore

possible sources of heterogeneity. Subgroups are based on the outcome definition used, i.e. objective (radiological, MRI and surgical criteria) or subjective estimates (clinical criteria). Subgroups are also identified based on the ways to measure the biomechanical factor and the duration of follow-up (cohort studies). Sensitivity analyses are done based on risk of bias. If sensitivity analyses appear to influence the findings of the review, this is reported and discussed in the 'Discussion' section.

Confidence in cumulative estimate

The quality of evidence is evaluated for the association of the category abnormal loading and each subdivision of a biomechanical impairment with the (development of) KOA, because this relates to different assessment strategies for clinicians and healthcare providers. The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) framework adapted for prognostic studies is used.[24] Factors that may decrease the quality level of evidence are phase of investigation, study limitations, inconsistency, indirectness, imprecision and publication bias. Factors that may increase the quality level of evidence are moderate or large effect size and exposure-response gradient. It is proposed to base the starting point for the quality level of evidence on phase of investigation. This is not applicable for cross sectional and case-control studies. Therefore the starting point for these studies is low. Quality level of evidence is determined as high, moderate, low, or very low and is reported in the summary of findings table. Quality of evidence is also assessed for combinations of biomechanical factors and risk factors that are examined in meta-analyses.

An algorithm is developed that can be used by healthcare providers to identify the biomechanical risk factors which are present in persons at high risk of developing

KOA.[25] Biomechanical factors are divided into categories base on study type (longitudinal and cross sectional/case-control studies) and base of evidence. Evidence is based on a significant meta-analysis, a longitudinal or cross sectional/case-control study with a significant finding, an insignificant meta-analysis, or on a longitudinal or cross sectional/case-control study with insignificant findings. This results in different categories within the algorithm; must consider (significant meta-analysis), maybe consider (study with significant finding), do not consider (insignificant meta-analysis) and not currently clinically relevant (study with insignificant findings).

DISCUSSION

To our knowledge, this is the first review that gives an overview of the existing evidence of biomechanical factors that are associated with the development of KOA. Findings may be used to improve identification of persons at high risk of developing KOA, which gives the opportunity to aim to prevent the development of KOA. In addition, the overview can be used to provide the rationale behind strategies to prevent the development of KOA. This may lead to both the improvement of existing strategies and the development of new strategies. Also, the information can improve the patients' understanding of the development of KOA, and therefore increase patient empowerment. Furthermore the results of this review should identify the gaps in the literature, which should direct future biomechanical studies.

This systematic review and meta-analysis protocol does not require ethical approval. The results of this systematic review and meta-analysis will be disseminated via publications in peer-reviewed journals, presentations at (inter)national conferences and patient information.

Contributions

JT is the guarantor. JT, ADI, CJ, JD, MS and HL drafted the protocol. JT, ADI, CJ and HL contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. JT and HL developed the search strategy. JT, CJ and HL provided statistical expertise. All authors read, provided feedback and approved the final protocol.

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Competing interests statement

The authors do not have any financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

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TABLES

Table 1. Biomechanical impairments and risk factors relevant to the development of KOA, subdivision, and measurement.

	Impairment/risk factor	Subdivision	Measurement
Abnormal loading			Moments, KRF, KCF
	Skeletal malalignment	Static	Leg alignment (HKA), passive ROM, Q-angle
		Dynamic	Thrust, active ROM
	Muscular dysfunction	Muscular	Strength, HQ-ratio
		Neurologic	Activation pattern, RFD, co-contraction, co-activation
	Impaired proprioception	Joint position sense	Error, accuracy
		Joint movement sense	Threshold
	Laxity	Anterior-posterior	Tibial translation
		Varus-valgus	Tibial transalation, joint angle, torque
	High BMI	Categorical*	e.g. obese, BMI > 30
		Continuous	BMI
	Gender	Categorical*	Male, female
	Previous knee injury§	Categorical*	e.g. ligament rupture, meniscal lesion, tibia

		plateau fracture
Age	Categorical*	e.g. middle aged, elderly
	Continuous	Age

*comparable categorical risk factors will be grouped in analyses, based on decision by the two reviewers § studies should not be influenced by rehabilitation or surgical treatment. KOA: knee osteoarthritis, BMI: body mass index, KRF: knee reaction force, KCF: knee contact force, HKA: hip-knee-ankle-angle, ROM: range of motion, RFD: rate of force development.

Table 2. Criteria of osteoarthritis, and hierarchy of definitions (ranking: *A* (high) - *J* (low)).

A	Clinical KOA	According to clinical ACR criteria
B	Radiological KOA	Kellgren and Lawrence grade ≥ 2, or grade ≥2 /osteophytes, or Ahlback grade > 1
C	Radiological KOA	OARSI atlas criteria: sum of osteophytes or JSN ≥grade 2, or grade 1 JSN in combination with grade 1 osteophyte
D	Clinical KOA	Knee pain and ≥ 50 years old
E	Radiological KOA	Radiographic signs*; only if the authors report the participants to have KOA
F	Surgery due to KOA§	Arthroscopy used to describe KOA
G	Surgery due to KOA§	Osteotomy due to KOA
H	Surgery due to KOA§	Total knee replacement due to KOA
I	KOA defined by MRI	KOA signs on MRI; only if the authors report the participants to have KOA
J	Clinical KOA	Participants report to have KOA diagnosed by physician

*e.g., osteophytes, cartilage damage, joint space narrowing, bone marrow oedema, §only as outcome measure of cohort study. KOA: knee osteoarthritis, ACR: American College of Rheumatology, OARSI: Osteoarthritis Research Society International, JSN: joint space narrowing, MRI: Magnetic Resonance Imaging.

Table 3. Data extraction.

All studies	
First author	Age (mean±SD)
Year of publication	BMI (mean±SD)
Study design	Definition of KOA used
Duration of follow-up[1]	Definition of BF used
Number of participants	Definition of RF used[*]
Gender (% female)	No. of participants developing KOA[1] or with KOA[2]
Cohort studies	*Case-control or cross sectional studies*
No. of participants developing KOA - exposed to BF/RF	No. of participants with KOA – exposed to BF/RF
No. of participants *not* developing KOA – exposed to BF/RF	No. of controls - exposed to BF/RF
No. of participants developing KOA - *not* exposed to BF/RF	No. of participants with KOA – *not* exposed to BF/RF
No. of participants *not* developing KOA - *not* exposed to BF/RF	No. of controls – *not* exposed to BF/RF
or	
Mean±SD of biomechanical factor within participants developing KOA	Mean±SD of biomechanical factor within participants with KOA
Mean±SD of biomechanical factor within participants *not* developing KOA	Mean±SD of biomechanical factor within controls
or	
Odds ratios for the association between	Odds ratios for the association between

BF/RF and the development of KOA BF/RF and KOA

Preferably the numbers of participants are extracted. If these are not available, mean values for the biomechanical or risk factor, or odds ratios are extracted, respectively. *if eligible, [1]for cohort studies, [2] for case-control and cross sectional studies. SD: standard deviation, KOA: knee osteoarthritis, BF: biomechanical factor, RF: risk factor.

APPENDIX 1

Medline search strategy

(((((((gonarthros*[Tiab]) OR gonarthrit* [Tiab])) OR ((((((“knee” [MeSH]) OR “knee Joint” [MeSH]) OR knee[Tiab]) OR tibiofemoral [Tiab])) AND ((((((“osteoarthritis” [MeSH]) OR osteoarthrit* [Tiab]) OR osteoarthros* [Tiab]) OR degenerative arthr* [Tiab]) OR arthrosis [Tiab]) OR arthroses [Tiab])))) AND ((“Bone Malalignment”[MeSH]) OR “Pressure”[MeSH:noexp]) OR “Leg Length Inequality”[MeSH]) OR “Genu varum”[MeSH]) OR “Genu valgum”[MeSH]) OR “Contracture”[MeSH]) OR alignment [Title]) OR malalignment [Tiab]) OR adduct*[Tiab]) OR abduct*[Tiab]) OR varu*[Tiab]) OR valgu*[Tiab]) OR valga*[Tiab]) OR vara*[Tiab]) OR hip knee ankle angle[Tiab]) OR mechanic*[Title]) OR mechano*[Title]) OR anatomic* axis[Tiab]) OR compression[Tiab]) OR load*[Tiab]) OR Torque[Tiab]) OR moment[Tiab]) OR force[Tiab]) OR genu recurvatum[Tiab]) OR q angle[Tiab]) OR contracture[Tiab]) OR joint stiffness[Tiab]) OR malformation[Tiab]) OR weight-bearing[Tiab]) OR leg length inequality[TIAB]) OR foot position[Tiab]) OR geometry[Tiab]) OR offset[Tiab]) OR shaft[Tiab]) OR lever arm[Tiab])) OR ((((((((((((((((((((((“Proprioception”[MeSH]) OR “Feedback, Sensory”[MeSH]) OR “Motion Perception”[MeSH]) OR propriocep*[Tiab]) OR sensory motor system[Tiab]) OR sensory motor function[Tiab]) OR neuromuscular control[Tiab]) OR kinesthesia[Tiab]) OR sensory feedback[Tiab]) OR joint position sense[Tiab]) OR sense of position[Tiab]) OR sensation of movement[Tiab]) OR sense of effort[Tiab]) OR movement sense[Tiab]) OR force sense[Tiab]) OR position sense[Tiab]) OR motion sensation[Tiab]) OR force sensation[Tiab]) OR movement registration[Tiab]) OR movement detection[Tiab]) OR force reproduction[Tiab]) OR movement reproduction[Tiab]) OR active movement[Tiab]) OR passive movement[Tiab]) OR motion perception[Tiab])) OR ((((((((((“Muscle Strength”[MeSH]) OR “Muscular Atrophy”[MeSH]) OR “Muscle Weakness”[MeSH]) OR Muscle Weakness[Tiab]) OR muscle dysfunction[Tiab]) OR muscle inhibition[Tiab]) OR co-contraction[Tiab]) OR muscle strength[Tiab]) OR muscle endurance[Tiab]) OR angular velocity[Tiab]) OR psychomotor performance[Tiab])) OR ((((((“Joint Instability”[MeSH]) OR hypermobil*[Tiab]) OR laxity[Tiab]) OR instabil*[Tiab]) OR stability[Tiab]) OR unstable[Tiab])) OR ((((((“Mechanical Processes”[MeSH]) OR “Biomechanical Phenomena”[MeSH]) OR biomechan*[Tiab]) OR kinetic*[title]) OR kinematic*[title]) OR walking pattern[Tiab]))) AND ((((((((((((((((((((((((((“Cohort Studies”[MeSH]) OR cohort [Tiab]) OR longitudinal [Tiab]) OR prospective [Tiab]) OR retrospective [Tiab]) OR explorative [Tiab]) OR concurrent [Tiab]) OR incidence [Tiab]) OR follow-up[Tiab]) OR followup[Tiab]) OR “Cross-Sectional Studies”[MeSH]) OR cross-sectional [Tiab]) OR prevalence [Tiab]) OR disease frequency [Tiab]) OR “Case-Control Studies”[MeSH]) OR case-control [Tiab]) OR case-comparison [Tiab]) OR case-compeer [Tiab]) OR case-referent [Tiab]) OR case-base [Tiab]) OR risk factors[Tiab]) OR “causality”[MeSH]) OR causality[Tiab]) OR predisposing[Tiab]) OR prognos*[Tiab])

APPENDIX 1

Medline search strategy

(((((((gonarthros*[Tiab]) OR gonarthrit* [Tiab])) OR ((((((“knee” [MeSH]) OR “knee Joint” [MeSH]) OR knee[Tiab]) OR tibiofemoral [Tiab])) AND ((((((“osteoarthritis” [MeSH]) OR osteoarthrit* [Tiab]) OR osteoarthros* [Tiab]) OR degenerative arthr* [Tiab]) OR arthrosis [Tiab]) OR arthroses [Tiab])))) AND ((“Bone Malalignment”[MeSH]) OR “Pressure”[MeSH:noexp]) OR “Leg Length Inequality”[MeSH]) OR “Genu varum”[MeSH]) OR “Genu valgum”[MeSH]) OR “Contracture”[MeSH]) OR alignment [Title]) OR malalignment [Tiab]) OR adduct*[Tiab]) OR abduct*[Tiab]) OR varu*[Tiab]) OR valgu*[Tiab]) OR valga*[Tiab]) OR vara*[Tiab]) OR hip knee ankle angle[Tiab]) OR mechanic*[Title]) OR mechano*[Title]) OR anatomic* axis[Tiab]) OR compression[Tiab]) OR load*[Tiab]) OR Torque[Tiab]) OR moment[Tiab]) OR force[Tiab]) OR genu recurvatum[Tiab]) OR q angle[Tiab]) OR contracture[Tiab]) OR joint stiffness[Tiab]) OR malformation[Tiab]) OR weight-bearing[Tiab]) OR leg length inequality[TIAB]) OR foot position[Tiab]) OR geometry[Tiab]) OR offset[Tiab]) OR shaft[Tiab]) OR lever arm[Tiab])) OR ((((((((((((((((((((((“Proprioception”[MeSH]) OR “Feedback, Sensory”[MeSH]) OR “Motion Perception”[MeSH]) OR propriocep*[Tiab]) OR sensory motor system[Tiab]) OR sensory motor function[Tiab]) OR neuromuscular control[Tiab]) OR kinesthesia[Tiab]) OR sensory feedback[Tiab]) OR joint position sense[Tiab]) OR sense of position[Tiab]) OR sensation of movement[Tiab]) OR sense of effort[Tiab]) OR movement sense[Tiab]) OR force sense[Tiab]) OR position sense[Tiab]) OR motion sensation[Tiab]) OR force sensation[Tiab]) OR movement registration[Tiab]) OR movement detection[Tiab]) OR force reproduction[Tiab]) OR movement reproduction[Tiab]) OR active movement[Tiab]) OR passive movement[Tiab]) OR motion perception[Tiab])) OR ((((((((((“Muscle Strength”[MeSH]) OR “Muscular Atrophy”[MeSH]) OR “Muscle Weakness”[MeSH]) OR Muscle Weakness[Tiab]) OR muscle dysfunction[Tiab]) OR muscle inhibition[Tiab]) OR co-contraction[Tiab]) OR muscle strength[Tiab]) OR muscle endurance[Tiab]) OR angular velocity[Tiab]) OR psychomotor performance[Tiab])) OR ((((((“Joint Instability”[MeSH]) OR hypermobil*[Tiab]) OR laxity[Tiab]) OR instabil*[Tiab]) OR stability[Tiab]) OR unstable[Tiab])) OR ((((((“Mechanical Processes”[MeSH]) OR “Biomechanical Phenomena”[MeSH]) OR biomechan*[Tiab]) OR kinetic*[title]) OR kinematic*[title]) OR walking pattern[Tiab])))) AND ((((((((((((((((((((((((((“Cohort Studies”[MeSH]) OR cohort [Tiab]) OR longitudinal [Tiab]) OR prospective [Tiab]) OR retrospective [Tiab]) OR explorative [Tiab]) OR concurrent [Tiab]) OR incidence [Tiab]) OR follow-up[Tiab]) OR followup[Tiab]) OR “Cross-Sectional Studies”[MeSH]) OR cross-sectional [Tiab]) OR prevalence [Tiab]) OR disease frequency [Tiab]) OR “Case-Control Studies”[MeSH]) OR case-control [Tiab]) OR case-comparison [Tiab]) OR case-compeer [Tiab]) OR case-referent [Tiab]) OR case-base [Tiab]) OR risk factors[Tiab]) OR “causality”[MeSH]) OR causality[Tiab]) OR predisposing[Tiab]) OR prognos*[Tiab])

Section and topic	Check Manuscript	Item No	Checklist item
Administrative information			
Title:			
Identification	yes	1a	Identify the report as a protocol of a systematic review
Update	n/a	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	yes	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	yes	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	yes	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	n/a	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	yes	5a	Indicate sources of financial or other support for the review
Sponsor	yes	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	yes	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
Introduction			
Rationale	yes	6	Describe the rationale for the review in the context of what is already known
Objectives	yes	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
Methods			
Eligibility criteria	yes	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	yes	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	yes	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:			
Data management	yes	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	yes	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	yes	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	yes	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	yes	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	yes	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	yes	15a	Describe criteria under which study data will be quantitatively synthesised
	yes	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)
	yes	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	yes	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	yes	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	yes	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

yes: fulfilled

no: not fulfilled

n/a: not applicable

BMJ Open

Biomechanical factors associated with the development of tibiofemoral knee osteoarthritis: protocol for a systematic review and meta-analysis.

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BIOMECHANICAL FACTORS ASSOCIATED WITH THE DEVELOPMENT OF TIBIOFEMORAL KNEE OSTEOARTHRITIS: PROTOCOL FOR A SYSTEMATIC REVIEW AND META-ANALYSIS.

AUTHORS

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Key words: systematic review, meta-analysis, osteoarthritis, biomechanics, development.

Word count: 3466

Tables: 3

Figures: -

Appendixes: 1

ABSTRACT

Introduction: Altered biomechanics, increased joint loading, and tissue damage might be related in a vicious cycle within the development of knee osteoarthritis (KOA). We have defined biomechanical factors as joint-related factors that interact with the forces, moments and kinematics in and around a synovial joint. Although a number of studies and systematic reviews have been performed to assess the association of various factors with the development of KOA, a comprehensive overview focusing on biomechanical factors that are associated with the development of KOA is not available. The aim of this review is 1) to identify biomechanical factors that are associated with (the development of) KOA, and 2) to identify the impact of other relevant risk factors on this association.

Methods and analysis: Cohort, cross sectional and case-control studies investigating the association of a biomechanical factor with (the development of) KOA will be included. MEDLINE, EMBASE, CINAHL and SPORTDiscus will be searched from their inception until August 2015. Two reviewers will independently screen articles obtained by the search for eligibility, extract data and score risk of bias. Quality of evidence will be evaluated. Meta-analysis using random effects model will be applied in each of the biomechanical factors, if possible.

Ethics and dissemination: This systematic review and meta-analysis does not require ethical approval. The results of this systematic review and meta-analysis will be disseminated through publications in peer-reviewed journals and presentations at (inter)national conferences.

PROSPERO registration number: CRD42015025092.

ARTICLE SUMMARY

Strengths and limitations of this study

- To our knowledge, performing this review will result in the first article giving an overview of the existing evidence of biomechanical factors that are associated with the development of KOA.
- This review does not assess the mechanism of how the biomechanical factors are related to the development of KOA.
- This is a protocol article. Results of the systematic review and meta-analysis will be published in a different article.

INTRODUCTION

The aetiology of osteoarthritis is known to be both biological and mechanical.[1] Although the sequence is unknown, increased joint loading and altered biomechanics might lead to tissue damage. This might deteriorate into structural changes, potentially with symptoms of osteoarthritis such as pain and activity limitations. In turn, structural changes might lead to further altered biomechanics, forming a vicious cycle.

A recent systematic review showed that several other risk factors, such as age, gender, BMI and previous knee injury, were associated with the development of knee pain or knee osteoarthritis in those aged 50 and over.[2] In an editorial acompanying this review, Zhang suggested that a systematic review and meta-analysis in biomechanical risk factors should also be performed.[3] We have defined biomechanical factors as joint-related factors that interact with the forces, moments and kinematics in and around the knee joint. Current research into biomechanical factors focuses on four main biomechanical impairments relevant to tibiofemoral knee osteoarthritis (KOA), i.e. skeletal malalignment, impaired proprioception, muscle dysfunction and laxity (see Table 1). Skeletal malalignment refers to abnormal alignment of or deformity within the knee joint. Valgus and varus malalignment might lead to increased loads in the lateral and medial compartment of the tibiofemoral joint respectively, and thus a possible increased risk for the development of KOA. Impaired proprioception refers to a deterioration of the senses of knee joint position and movement, or a primary neurological defect. This might lead to more excessive movements, decreased stabilization during stance and decreased coordination of complex movement systems and precise knee joint motions. Deterioration of those three functions of knee proprioception might lead to increased joint loading and structural changes.[4] Muscle

dysfunction refers to a loss of muscle strength, or muscle weakness, to loss of muscle endurance and to changed muscle activation patterns for the muscles that act on the knee joint. It is suggested that the knee extensors protect the joint during loading and movement, by absorbing shocks and stabilizing the knee.[5] On the contrary, higher strength could also lead to higher loads in the knee joint, because of joint space narrowing induced by muscle strength. Laxity refers to a loss of passive joint stabilisation due to the inability of passive structures in and around the knee (knee ligaments, cruciate ligaments, capsule) to provide an adequate counterbalance to the mechanical forces acting upon the knee during activity. For example, lateral laxity allows the lateral femoral condyle to "lift of" the tibial plateau, which increases the medial joint loading.[6] Laxity may adversely affect other biomechanical factors.[7] Alteration in these four biomechanical impairments will impact on the loading of the knee. Abnormal loading is associated with imbalances that may eventually lead to KOA.[8] Within the development of KOA biomechanical factors and other risk factors will interact with each other. For example gender is associated with malalignment and previous knee injury has been shown to increase laxity. Although it is not possible to reduce the risk to develop KOA based on other risk factors, it might be possible to reduce the additional risk of the biomechanical factors by preventive strategies (eg knee braces, insoles or physical therapy).

Table 1. Biomechanical impairments and risk factors relevant to the development of KOA, subdivision, and measurement.

	Impairment/risk factor	Subdivision	Measurement
Abnormal loading			Moments, KRF, KCF, thrust
	Skeletal malalignment		Leg alignment (e.g. HKA), Q-angle
	Muscular dysfunction	Muscular	Strength, HQ-ratio
		Neurologic	Activation pattern, RFD, co-contraction, co-activation
	Impaired proprioception	Joint position sense	Error, accuracy
		Joint movement sense	Threshold
	Laxity	Anterior-posterior	Tibial translation
		Varus-valgus	Tibial transalation, joint angle, torque
	High BMI	Categorical*	e.g. obese, BMI > 30
		Continuous	BMI
	Gender	Categorical*	Male, female
	Previous knee injury§	Categorical*	e.g. ligament rupture, meniscal lesion, tibia plateau fracture
	Age	Categorical*	e.g. middle aged, elderly

	Continuous	Age

*comparable categorical risk factors will be grouped in analyses, based on decision by the two reviewers § studies should not be influenced by rehabilitation or surgical treatment. KOA: knee osteoarthritis, BMI: body mass index, KRF: knee reaction force, KCF: knee contact force, HKA: hip-knee-ankle-angle, RFD: rate of force development.

The relationship between biomechanical factors and the development of KOA has been indicated in several biomechanical studies and systematic reviews, but there is no systematic review available that contains an overview of all available evidence of the influence of particularly biomechanical factors on the development of KOA.[5, 9-11] Although each biomechancial factor will be assessed with several different methods and most studies most probably have a cross sectional study design, we expect to be able to give an overview of biomechancial factors that are associated with (the development of) KOA. Such an overview may be used to identify persons at high risk of developing KOA. Several strategies like physical therapy, knee braces or insoles might prevent the development of KOA in those persons by interacting on the biomechanical factors. In addition, an overview provides information that can be used to base the rationale behind strategies to prevent the development of KOA on and to identify the focus of future biomechanical and clinical studies.

Objectives

The aim of this review is 1) to identify biomechanical factors that are associated with (the development of) KOA, and 2) to identify the impact of other relevant risk factors on this association. Therefore the proposed systematic review will answer the following questions:

1. Which biomechanical factors are associated with (the development of) KOA?
2. Is the association of these biomechanical factors with (the development of) KOA mediated by other risk factors for KOA (i.e. high BMI, female gender, history of previous knee injury and higher age)?

METHODS AND ANALYSIS

This review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) at the National Institute for Health Research and Center for Reviews and Dissemination (CRD) at the University of York (registration number: CRD42015025092).[12] This systematic review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) guidance.[13] The systematic review will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance.[14]

Studies will be selected according to the criteria outlined below.

Type of studies

Studies will be eligible if they are cohort, cross sectional or case-control studies. The cohort studies can either be prospective or retrospective. All cohort studies should have a follow-up period of at least one year. Studies should not be influenced by rehabilitation or surgical treatment.

Type of participants

Included studies will be cohort studies examining participants who do not have KOA at baseline but who have KOA at the follow-up measurement and participants who do not have KOA at both baseline and follow-up. Those two groups will be referred to as 'developing KOA' and 'not developing KOA'. Other included studies will be case-control and cross sectional studies that include both participants with KOA and healthy controls. Participants have KOA if one of the criteria described in Table 2, or an outcome measure related to the criteria, is fulfilled. Both idiopathic and secondary

KOA is eligible. Participants can have osteoarthritis in one or both knees, although data should be analysed for only one knee, in order to examine independent associations with KOA. Studies examining participants with both osteoarthritis of the hip and the knee will only be included if separate data of participants with KOA is available. Studies examining participants already having KOA at baseline (cohort studies) or studies examining 'healthy' controls having KOA in either the index or the contralateral knee (cross sectional or case-control studies) according to aforementioned criteria will be excluded. Studies examining participants with osteoarthritis in the patellofemoral joint only will be excluded. Data regarding patellofemoral osteoarthritis will not be used, and we will exclude data of individuals stated to have a combination of patellofemoral and tibiofemoral osteoarthritis. Cohort studies examining incidence of KOA in other populations (e.g., rheumatoid arthritis, hypermobility) will be included, although only data regarding KOA will be used.

Table 2. Criteria of osteoarthritis, and hierarchy of definitions (ranking: *A* (high) - *J* (low)).

A	Clinical KOA	According to clinical ACR criteria
B	Radiological KOA	Kellgren and Lawrence grade ≥ 2, or grade ≥2 /osteophytes, or Ahlback grade ≥ 1
C	Radiological KOA	OARSI atlas criteria: sum of osteophytes or JSN ≥grade 2, or grade 1 JSN in combination with grade 1 osteophyte
D	Clinical KOA	Knee pain and ≥ 50 years old
E	Radiological KOA	Radiographic signs*; only if the authors report the participants to have KOA
F	Surgery due to KOA§	Arthroscopy used to describe KOA
G	Surgery due to KOA§	Osteotomy due to KOA
H	Surgery due to KOA§	Total knee replacement due to KOA
I	KOA defined by MRI	KOA signs on MRI; only if the authors report the participants to have KOA
J	Clinical KOA	Participants report to have KOA diagnosed by physician

*e.g., osteophytes, cartilage damage, joint space narrowing, bone marrow oedema, §only as outcome measure of cohort study. KOA: knee osteoarthritis, ACR: American College of Rheumatology, OARSI: Osteoarthritis Research Society International, JSN: joint space narrowing, MRI: Magnetic Resonance Imaging.

Type of biomechanical factors

Studies exploring the association of a biomechanical factor with (the development of) KOA will be reviewed. The biomechanical factors will be grouped into one group referring to abnormal loading and four main biomechanical impairments relevant to KOA (see Table 1). Table 1 also describes frequently used ways to measure biomechanical factors. The possible inclusion of measurements of biomechanical factors not listed in Table 1 will be discussed by the reviewers (JT, ADI). Only biomechanical factors directly related to the knee joint will be taken into account. Joint angles during activities will be excluded due to limited reliability of these measurements. Measurements of moments, knee reaction forces and knee contact forces will be included as measurements of abnormal loading, in contrast to measurements of ground reaction forces and centre of pressure, because only the first give a comprehensive estimate of the loading of the knee. The influence of other risk factors on the association of biomechanical factors with (the development of) KOA will also be reviewed. Studies that only explore non-biomechanical risk factors will be excluded from this review.

Types of outcome measure

KOA in included studies can be defined by clinical, radiological, MRI or surgical criteria (see Table 2).

Publication year and language

There will be no restriction on publication year and language.

Sources and search strategy

The following databases will be searched from their inception until August 2015: MEDLINE via Pubmed, EMBASE via OVID, CINAHL (including preCINAHL) via EBSCO, and SPORTDiscus via EBSCO. Reference lists from included studies and identified relevant reviews, textbooks and clinical guidelines will be searched for relevant references. A citation search will be performed on highly relevant studies. Experts in the field will be asked for relevant references to ensure literature saturation.

Literature search strategies will be developed using subject headings (MeSH) and text words related to osteoarthritis, biomechanical factors and study types. Search terms from other relevant reviews will be identified and will be complemented with additional terms for biomechanical factors. The MEDLINE search strategy is included in Appendix 1 and will be adjusted in order to apply it to other databases.

Study inclusion and exclusion criteria

The inclusion criteria will be:

- The study assesses the association of a biomechanical factor with the development of KOA, and possibly the impact of other risk factors on this association.
- KOA is defined as tibiofemoral osteoarthritis, either idiopathic or secondary.
- A biomechanical factor is a knee joint-related factor that interacts with the forces, moments and kinematics in and around the knee joint.
- The study is a cohort study:

- Participants who do not have KOA at baseline but who have KOA at the follow-up measurement and participants who do not have KOA at both baseline and follow-up.

or

- The study is a case-control study or cross sectional study:
  - Participants with and without KOA.

The exclusion criteria will be:

- The study includes only participants with patellofemoral osteoarthritis.
- The study does not distinguish between hip osteoarthritis and KOA.
- The study is influenced by rehabilitation or surgical treatment.

Data management

References from all searches will be uploaded into EndNote (X7) bibliographic software (Thompson Reuters, Philadelphia, Pennsylvania, USA). Duplicates will be removed with the SRA-DM (Systematic Review Assistant-Deduplication Module).[15] Remaining duplicates will be removed with EndNote duplicate removal and manually by screening for duplicates while the list of references will be sorted alphabetically based on author. All full text files will be stored in EndNote. For all studies reviewed in full text, a form regarding eligibility criteria check will be stored. Data from included studies will be entered into a data extraction form in Microsoft Excel. If a meta-analysis is eligible, the data will be transferred to STATA software (V13.0 or later, StataCorp LP) to do statistical analysis.

Selection process

Two members of the study team (JT, ADI) will independently screen titles and abstracts of the studies obtained by the search strategy. The full text of any study will be obtained if it was judged eligible by at least one of the reviewers. Then, the two reviewers will use a standardized form to select studies eligible for inclusion in the review. Consensus on inclusion will be reached by discussion. Reasons for excluding studies based on the full text will be recorded. When more than one study is based on the same population and contains the same information with respect to the association at issue, only one study will be included. This will be based on the following order; 1) the publication with the largest sample size, 2) the most recent publication, or 3) the study that examined KOA using the highest ranked outcome measure. Hierarchy of the definitions is described later at "Data items, outcomes and hierarchy" and in Table 2. If studies of the same study population present different information with respect to the association at issue, both studies will be included. A PRISMA-flowchart will be completed to summarise the process. Neither of the review authors will be blinded to the journal titles or to the study authors or institutions.[16]

Data collection process

Two reviewers (JT, ADI) will independently extract data from the included studies using a customised form, piloted prior to use. Consensus on extracted data will be reached by discussion, and conflictive data extraction will be discussed with a third member of the study team (CJ or HL).

Data items, outcomes and hierarchy

Data items that will be extracted from included studies are described in Table 3. Table

3 shows that in cohort studies preferably the number of participants developing KOA and not developing KOA, and the number of participants exposed and not exposed to the biomechanical factor will be extracted. In cross sectional or case-control studies, preferably the number of participants with and without KOA, and the number of participants exposed and not exposed to the biomechanical factor will be extracted. If this is not available, mean values for the biomechanical factors or odds ratios will be extracted, respectively. The same data extraction and analyses will be performed for biomechanical factors and other risk factors. Therefore, in the following paragraphs only biomechanical factors will be mentioned. The hierarchy for definitions of KOA is based on comprehensiveness of the definition and the use in clinical practise (see Table 2, ranking: A - J). Symptomatic KOA is based on the American College of Rheumatology criteria.[17] Radiographic KOA is based on radiological atlases (e.g. the Kellgren and Lawrence (K/L) Classification).[18, 19] In addition, physicians or authors can state that participants have KOA. The hierarchy will be used for study selection if more than one study examines the same population and for data extraction in studies using two or more outcome measures of KOA. For the latter, only data regarding the highest ranked outcome measure will be extracted.

Table 3. Data extraction.

All studies	
First author	Age (mean±SD)
Year of publication	BMI (mean±SD)
Study design	Definition of KOA used
Duration of follow-up[1]	Definition of BF used
Number of participants	Definition of RF used[*]
Gender (% female)	No. of participants developing KOA[1] or with KOA[2]
Cohort studies	*Case-control or cross sectional studies*
No. of participants developing KOA - exposed to BF/RF	No. of participants with KOA – exposed to BF/RF
No. of participants *not* developing KOA – exposed to BF/RF	No. of controls - exposed to BF/RF
No. of participants developing KOA - *not* exposed to BF/RF	No. of participants with KOA – *not* exposed to BF/RF
No. of participants *not* developing KOA - *not* exposed to BF/RF	No. of controls – *not* exposed to BF/RF
or	
Mean±SD of biomechanical factor within participants developing KOA	Mean±SD of biomechanical factor within participants with KOA
Mean±SD of biomechanical factor within participants *not* developing KOA	Mean±SD of biomechanical factor within controls
or	
Odds ratios for the association between	Odds ratios for the association between

Preferably the numbers of participants are extracted. If these are not available, mean values for the biomechanical or risk factor, or odds ratios are extracted, respectively. *if eligible, [1]for cohort studies, [2] for case-control and cross sectional studies. SD: standard deviation, KOA: knee osteoarthritis, BF: biomechanical factor, RF: risk factor.

Risk of bias in individual studies

Risk of bias for each included study will be scored independently by two reviewers (JT, ADI). Consensus on conflicting scores will be reached by discussion. The Quality In Prognostic Studies (QUIPS) tool will be used.[20] Six areas of potential study biases will be assessed: study participation, study attrition, prognostic factor measurement, study confounding, outcome measurement, and statistical analysis and reporting. Risk of bias for study participation is the likelihood that the relationship between the prognostic factor and the outcome is different for participants and eligible non-participants. Risk of bias for study attrition is the likelihood that the relationship between the prognostic factor and the outcome is different for completing and non-completing participants. Risk of bias for prognostic factor measurement is related to differential measurement of the prognostic factor related to the level of outcome. Risk of bias for study confounding is the effect of the prognostic factor being distorted by another factor that is related to the prognostic factor and outcome. Risk of bias for outcome measurement is related to differential measurement of outcome related to the baseline level of the prognostic factor. Risk of bias for statistical analysis and reporting is the risk of bias whether the statistical analysis is

dependent on KOA status and the exposure to the biomechanical factor or not, and whether the presentation of results differs between KOA status and exposure. Study attrition is not applicable for cross sectional and case-control studies, thus will only be rated in cohort studies. Studies will be classified as being of high-quality if all study biases are assessed to have a low or moderate risk of bias. Studies with a high risk of bias for at least one study bias will be defined as low-quality studies. A summary statement regarding the quality of the included studies will be reported in the results section.

Assessment of publication bias

It is assumed that biomechanical projects indicating no association between a biomechanical factor and (the development of) KOA are likely to not be published. Therefore, funnel plots will be used to show the OR on the x-axis against the sample size on the y-axis for each biomechanical factor.

Data synthesis

Data will be grouped by the category abnormal loading and the main biomechanical impairments. Subsequently, data will be grouped per subdivision of biomechanical impairments, as shown in table 1, and per study design (i.e. cohort studies vs. a combination of cross sectional and case-control studies). Biomechanical factors studied in more than one study per study design will be subjected to meta-analyses. Meta-analyses will be applied on the OR of developing KOA in participants who are exposed to the biomechanical factor of interest (cohort studies), or the OR of the biomechanical factor being present in participants with KOA compared to the control group (cross sectional or case-control studies). Random effects model (Mantel

Haenszel method) will be used, as large clinical heterogeneity is expected due to the variation in the definition of KOA and biomechanical factors. Meta-regression analyses using study-level risk factors as covariates in a multivariate regression analysis can be used to explore the impact of different biomechanical factors.[21] The impact of the biomechanical factors will be assessed by fitting multiple restricted maximum likelihood-based (REML) meta-regression models.[22, 23] A priori, we defined a relevant covariate (biomechanical or other risk factor) as one that would decrease the between study variance (estimated as tau-squared ($\boldsymbol{\tau}^2$), as a consequence of the inclusion in the meta-regression analysis.[24] Meta regression analysis will also be used to assess the impact of other risk factors, combinations of other risk factors, including interactions between risk factors, on the association of biomechanical factors with (the development of) KOA. A forest plot will be made for each biomechanical factor and for combinations of biomechanical factors and other risk factors.

Heterogeneity between studies combined in one meta-analysis will be examined with standard Q-tests, and will be calculated as the I^2 statistics, measuring the proportion of inconsistency in the summary effect measure due to between-study heterogeneity.[25, 26]

If any substantial heterogeneity will be identified through analysis of Chi^2 and I^2 statistics, subgroup and sensitivity analyses will be performed. These will only be performed if at least three studies are included in the meta-analysis. Subgroup analyses will be used to explore possible sources of heterogeneity. Subgroups will be based on the outcome definition used, i.e. clinical, radiological, MRI and surgical criteria. Subgroups will also be identified based on the ways to measure the biomechanical factor and the duration of follow-up (cohort studies). Other subgroups

will be tibiofemoral osteoarthritis and general knee osteoarthritis, and medial and lateral tibiofemoral osteoarthritis. Sensitivity analyses will be done based on risk of bias. If sensitivity analyses appear to influence the findings of the review, this will be reported and discussed in the 'Discussion' section.

Confidence in cumulative estimate

The quality of evidence will be evaluated for the association of the category abnormal loading and each subdivision of a biomechanical impairment with the (development of) KOA, because this relates to different assessment strategies for clinicians and healthcare providers. The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) framework adapted for prognostic studies will be used.[27] Factors that may decrease the quality level of evidence are phase of investigation, study limitations, inconsistency, indirectness, imprecision and publication bias. Factors that may increase the quality level of evidence are moderate or large effect size and exposure-response gradient. It is proposed to base the starting point for the quality level of evidence on phase of investigation. This is not applicable for cross sectional and case-control studies. Therefore the starting point for these studies will be low. Quality level of evidence will be determined as high, moderate, low, or very low and will be reported in the summary of findings table. Quality of evidence will also be assessed for combinations of biomechanical factors and risk factors that will be examined in meta-analyses.

An algorithm will be developed that can be used by healthcare providers to identify the biomechanical risk factors which are present in persons at high risk of developing KOA.[28] Biomechanical factors will be divided into categories base on study type (longitudinal and cross sectional/case-control studies) and base of evidence. Evidence

will be based on a significant meta-analysis, a longitudinal or cross sectional/case-control study with a significant finding, an insignificant meta-analysis, or on a longitudinal or cross sectional/case-control study with insignificant findings. This results in different categories within the algorithm; must consider (significant meta-analysis), maybe consider (study with significant finding), do not consider (insignificant meta-analysis) and not currently clinically relevant (study with insignificant findings).

ETHICS AND DISSEMINATION

This article describes the framework for a systematic review and meta-analysis into the association of biomechanical factors with the development of knee osteoarthritis. To our knowledge, performing this will result in the first review that gives an overview of the existing evidence of biomechanical factors that are associated with the development of KOA. This systematic review and meta-analysis protocol does not require ethical approval. The results of this systematic review and meta-analysis will be disseminated via publications in peer-reviewed journals, presentations at (inter)national conferences and patient information.

Contributions

JT is the guarantor. JT, ADI, CJ, JD, MS and HL drafted the protocol. JT, ADI, CJ and HL contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. JT and HL developed the search strategy. JT, CJ and HL provided statistical expertise. All authors read, provided feedback and approved the final protocol.

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Competing interests statement

The authors do not have any financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

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TABLES

Table 1. Biomechanical impairments and risk factors relevant to the development of KOA, subdivision, and measurement.

	Impairment/risk factor	Subdivision	Measurement
Abnormal loading			Moments, KRF, KCF, thrust
	Skeletal malalignment		Leg alignment (e.g. HKA), Q-angle
	Muscular dysfunction	Muscular	Strength, HQ-ratio
		Neurologic	Activation pattern, RFD, co-contraction, co-activation
	Impaired proprioception	Joint position sense	Error, accuracy
		Joint movement sense	Threshold
	Laxity	Anterior-posterior	Tibial translation
		Varus-valgus	Tibial transalation, joint angle, torque
	High BMI	Categorical*	e.g. obese, BMI > 30
		Continuous	BMI
	Gender	Categorical*	Male, female
	Previous knee injury§	Categorical*	e.g. ligament rupture, meniscal lesion, tibia plateau fracture

Age	Categorical*	e.g. middle aged, elderly
	Continuous	Age

*comparable categorical risk factors will be grouped in analyses, based on decision by the two reviewers § studies should not be influenced by rehabilitation or surgical treatment. KOA: knee osteoarthritis, BMI: body mass index, KRF: knee reaction force, KCF: knee contact force, HKA: hip-knee-ankle-angle, RFD: rate of force development.

Table 2. Criteria of osteoarthritis, and hierarchy of definitions (ranking: *A* (high) - *J* (low)).

A	Clinical KOA	According to clinical ACR criteria
B	Radiological KOA	Kellgren and Lawrence grade ≥ 2, or grade ≥2 /osteophytes, or Ahlback grade ≥ 1
C	Radiological KOA	OARSI atlas criteria: sum of osteophytes or JSN ≥grade 2, or grade 1 JSN in combination with grade 1 osteophyte
D	Clinical KOA	Knee pain and ≥ 50 years old
E	Radiological KOA	Radiographic signs*; only if the authors report the participants to have KOA
F	Surgery due to KOA§	Arthroscopy used to describe KOA
G	Surgery due to KOA§	Osteotomy due to KOA
H	Surgery due to KOA§	Total knee replacement due to KOA
I	KOA defined by MRI	KOA signs on MRI; only if the authors report the participants to have KOA
J	Clinical KOA	Participants report to have KOA diagnosed by physician

*e.g., osteophytes, cartilage damage, joint space narrowing, bone marrow oedema, §only as outcome measure of cohort study. KOA: knee osteoarthritis, ACR: American College of Rheumatology, OARSI: Osteoarthritis Research Society International, JSN: joint space narrowing, MRI: Magnetic Resonance Imaging.

Table 3. Data extraction.

All studies	
First author	Age (mean±SD)
Year of publication	BMI (mean±SD)
Study design	Definition of KOA used
Duration of follow-up[1]	Definition of BF used
Number of participants	Definition of RF used[*]
Gender (% female)	No. of participants developing KOA[1] or with KOA[2]
Cohort studies	*Case-control or cross sectional studies*
No. of participants developing KOA - exposed to BF/RF	No. of participants with KOA – exposed to BF/RF
No. of participants *not* developing KOA – exposed to BF/RF	No. of controls - exposed to BF/RF
No. of participants developing KOA - *not* exposed to BF/RF	No. of participants with KOA – *not* exposed to BF/RF
No. of participants *not* developing KOA - *not* exposed to BF/RF	No. of controls – *not* exposed to BF/RF
or	
Mean±SD of biomechanical factor within participants developing KOA	Mean±SD of biomechanical factor within participants with KOA
Mean±SD of biomechanical factor within participants *not* developing KOA	Mean±SD of biomechanical factor within controls
or	
Odds ratios for the association between	Odds ratios for the association between

BF/RF and the development of KOA	BF/RF and KOA

Preferably the numbers of participants are extracted. If these are not available, mean values for the biomechanical or risk factor, or odds ratios are extracted, respectively. *if eligible, [1]for cohort studies, [2] for case-control and cross sectional studies. SD: standard deviation, KOA: knee osteoarthritis, BF: biomechanical factor, RF: risk factor.

1

APPENDIX 1

Medline search strategy

(((((((gonarthros*[Tiab]) OR gonarthrit* [Tiab])) OR ((((((“knee” [MeSH]) OR “knee Joint” [MeSH]) OR knee[Tiab]) OR tibiofemoral [Tiab])) AND ((((((“osteoarthritis” [MeSH]) OR osteoarthrit* [Tiab]) OR osteoarthros* [Tiab]) OR degenerative arthr* [Tiab]) OR arthrosis [Tiab]) OR arthroses [Tiab])))))
AND
((((((((((((((((((((((((((((((((((((((“Bone Malalignment”[MeSH]) OR “Pressure”[MeSH:noexp]) OR “Leg Length Inequality”[MeSH]) OR “Genu varum”[MeSH]) OR “Genu valgum”[MeSH]) OR “Contracture”[MeSH]) OR alignment [Title]) OR malalignment [Tiab]) OR adduct*[Tiab]) OR abduct*[Tiab]) OR varu*[Tiab]) OR valgu*[Tiab]) OR valga*[Tiab]) OR vara*[Tiab]) OR hip knee ankle angle[Tiab]) OR mechanic*[Title]) OR mechano*[Title]) OR anatomic* axis[Tiab]) OR compression[Tiab]) OR load*[Tiab]) OR Torque[Tiab]) OR moment[Tiab]) OR force[Tiab]) OR genu recurvatum[Tiab]) OR q angle[Tiab]) OR contracture[Tiab]) OR joint stiffness[Tiab]) OR malformation[Tiab]) OR weight-bearing[Tiab]) OR leg length inequality[TIAB]) OR foot position[Tiab]) OR geometry[Tiab]) OR offset[Tiab]) OR shaft[Tiab]) OR lever arm[Tiab]))
OR
((((((((((((((((((((((“Proprioception”[MeSH]) OR “Feedback, Sensory”[MeSH]) OR “Motion Perception”[MeSH]) OR propriocep*[Tiab]) OR sensory motor system[Tiab]) OR sensory motor function[Tiab]) OR neuromuscular control[Tiab]) OR kinesthesia[Tiab]) OR sensory feedback[Tiab]) OR joint position sense[Tiab]) OR sense of position[Tiab]) OR sensation of movement[Tiab]) OR sense of effort[Tiab]) OR movement sense[Tiab]) OR force sense[Tiab]) OR position sense[Tiab]) OR motion sensation[Tiab]) OR force sensation[Tiab]) OR movement registration[Tiab]) OR movement detection[Tiab]) OR force reproduction[Tiab]) OR movement reproduction[Tiab]) OR active movement[Tiab]) OR passive movement[Tiab]) OR motion perception[Tiab]))
OR
((((((((((“Muscle Strength”[MeSH]) OR “Muscular Atrophy”[MeSH]) OR “Muscle Weakness”[MeSH]) OR Muscle Weakness[Tiab]) OR muscle dysfunction[Tiab]) OR muscle inhibition[Tiab]) OR co-contraction[Tiab]) OR muscle strength[Tiab]) OR muscle endurance[Tiab]) OR angular velocity[Tiab]) OR psychomotor performance[Tiab]))
OR
((((((“Joint Instability”[MeSH]) OR hypermobil*[Tiab]) OR laxity[Tiab]) OR instabil*[Tiab]) OR stability[Tiab]) OR unstable[Tiab]))
OR
((((((“Mechanical Processes”[MeSH]) OR “Biomechanical Phenomena”[MeSH]) OR biomechan*[Tiab]) OR kinetic*[title]) OR kinematic*[title]) OR walking pattern[Tiab])))
AND
((((((((((((((((((((((“Cohort Studies”[MeSH]) OR cohort [Tiab]) OR longitudinal [Tiab]) OR prospective [Tiab]) OR retrospective [Tiab]) OR explorative [Tiab]) OR concurrent [Tiab]) OR incidence [Tiab]) OR follow-up[Tiab]) OR followup[Tiab]) OR “Cross-Sectional Studies”[MeSH]) OR cross-sectional [Tiab]) OR prevalence [Tiab]) OR disease frequency [Tiab]) OR “Case-Control Studies”[MeSH]) OR case-

control [Tiab]) OR case-comparison [Tiab]) OR case-compeer [Tiab]) OR case-referent [Tiab]) OR case-base [Tiab]) OR risk factors[Tiab]) OR "causality"[MeSH]) OR causality[Tiab]) OR predisposing[Tiab]) OR prognos*[Tiab])

Section and topic	Check Manuscript	Page Manuscript	Item No	Checklist item
Administrative information				
Title:				
Identification	yes	1	1a	Identify the report as a protocol of a systematic review
Update	n/a	n/a	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	yes	3/10	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:				
Contact	yes	1/2	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	yes	24	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	n/a	n/a	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:				
Sources	yes	24	5a	Indicate sources of financial or other support for the review
Sponsor	yes	24	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	yes	24	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
Introduction				
Rationale	yes	5-8	6	Describe the rationale for the review in the context of what is already known
Objectives	yes	9	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions comparators, and outcomes (PICO)
Methods				
Eligibility criteria	yes	10-13	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such a years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	yes	14	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers o other grey literature sources) with planned dates of coverage
Search strategy	yes	33/34 (appendix 1)	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:				
Data management	yes	15	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	yes	16	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of review (that is, screening, eligibility and inclusion in meta-analysis)

Data collection process	yes	16	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate) any processes for obtaining and confirming data from investigators
Data items	yes	16/17	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	yes	16/17	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcome with rationale
Risk of bias in individual studies	yes	19	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	yes	20-22	15a	Describe criteria under which study data will be quantitatively synthesised
	yes	20-22	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data an methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ
	yes	20-22	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	yes	20-22	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	yes	20	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within
Confidence in cumulative evidence	yes	22-23	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

yes: fulfilled

no: not fulfilled

n/a: not applicable