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Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials

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ABSTRACT

Objective: We performed a systematic review, meta-analysis, and causation analysis to assess the evidence supporting a causal link between knee joint loading during walking and structural knee OA progression.

Design: Systematic review, meta-analysis, and application of Bradford Hill's criteria for causation.

Data Sources: We searched MEDLINE, Scopus, AMED, CINAHL, and SportsDiscus for prospective cohort studies and randomised controlled trials (RCTs) from 1950 through October 2013.

Study eligibility criteria: We selected cohort studies and RCTs in which estimates of knee joint loading during walking were used to predict structural knee OA progression assessed by X-ray or MRI.

Data analyses: Meta-analysis was performed to estimate the combined odds ratio (OR) for structural disease progression with higher baseline loading. The likelihood of a causal link between knee joint loading and OA progression was assessed from cohort studies using the Bradford Hill guidelines to derive a 0-4 causation score based on four criteria and examined for confirmation in RCTs.

Results: Of 1,078 potentially eligible articles, 5 prospective cohort studies were included. The studies included a total of 452 patients relating joint loading to disease progression over 12-72 months. There were very serious limitations associated with the methodological quality of the included studies. The combined OR for disease progression was 1.90 (95% CI: 0.85 to 4.25; I-squared = 77%) for each one-unit increment in baseline knee loading. The combined causation score was 0, indicating no causal association between knee loading and knee OA progression. No RCTs were found to confirm or refute the findings from the cohort studies.

Conclusions: There is very limited and low quality evidence to support for a causal link between knee joint loading during walking and structural progression of knee OA.

PROSPERO registration no.: CRD42012003253.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We performed the first systematic evaluation of the evidence for a causal link between mechanical loading of the knee during walking and structural progression of knee osteoarthritis.
- This systematic review, meta-analysis and causation analysis finds very limited evidence of a causal link between knee joint loading during walking and structural progression of knee osteoarthritis.
- Few studies were included in the meta-analysis since only a small number of studies have been conducted. Further research is needed.

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis affecting a large part of the population, and is a major cause of illness and disability.[1, 2] The knee joint is most frequently affected,[3] and due to the knee's crucial role in independent ambulation, knee OA leads to considerable disability affecting the individual's participation in society and independent living. Because no cure is available and so many people are affected, health care costs associated with knee OA are enormous—even higher than for more high-profile diseases such as diabetes, cancer, and cardiovascular diseases.[4] With its prevalence on the rise, knee OA poses a substantial socioeconomic and public health burden.

Walking is the most common form of human locomotion, and most people walk every day, resulting in millions of steps per year. Biomechanical loading on the knee joint during walking is estimated to exceed 2-3 times body weight;[5] thus, knee joint loading is unavoidable component of an independent lifestyle. One widely accepted theory is that higher knee joint loading during walking is causally linked with accelerated structural knee OA progression.[6-8] In accordance with this theory, unloading is advocated in an attempt to slow or halt disease progression.[9] Unspecific measures of high joint loading, such as excess body mass and Body-Mass Index (BMI), have been associated with OA development,[10, 11] and obesity is believed to act mainly through high mechanical loads,[12] although systemic effects have also been indicated.[13] However higher body mass does not necessarily lead to higher joint loading during walking,[14] and more specific measures of joint loading are necessary to apply.

Objective estimates of joint loading during walking can be obtained by 3-dimensional gait analysis. Typically, the knee adduction moment (KAM) or biomechanical modeling of compression forces is used. The KAM has been of particular interest because it reflects the

medial to lateral joint load distribution,[15] with good face validity with respect to the relative prevalence of medial, as opposed to lateral compartment, tibiofemoral knee OA.[16] Despite its common usage, a recent systematic review did not find consistent evidence that the KAM differs between those with and without knee OA.[17]

The relationship between knee joint loading during walking and knee OA has been a focus of knee OA-related biomechanical research for 10-20 years. Studies reveal that symptomatic treatment of knee OA results in increases in knee joint loads during walking,[5, 18-20] which are unwanted according to the hypothesised structural consequences of increased joint loading. This may generate confusion among researchers, clinicians, and patients, who are interested in this information to aid them in prevention, palliation, and treatment strategies. Establishing causal relationships between modifiable factors, such as knee joint loading, and disease specific measures, such as structural disease progression, is imperative in the generation of effective strategies.

Seminal epidemiological work by Hill proposed a set of criteria (the Bradford Hill criteria) to systematically evaluate the existence of a causal link between an exposure and a health outcome.[21] These criteria have been previously employed to demonstrate the causal link between smoking and lung cancer,[22] and between dietary factors and coronary heart disease,[23] and have the capacity to evaluate the link between knee joint loading and structural knee OA progression.

Therefore the objectives of this study were 1) to systematically evaluate the evidence supporting a causal link between exposure to knee joint loading during walking and structural progression of knee OA using the Bradford Hill criteria, and 2) to determine which knee joint load variables had been studied sufficiently in RCTs and found to support the findings of prospective cohort studies.

METHODS

Methods of the study search strategy, inclusion criteria, and data analysis were pre-specified in a protocol (supplementary file) and pre-registered (PROSPERO 2012:CRD42012003253).

We searched MEDLINE, Scopus, AMED, CINAHL, and SportsDiscus for prospective cohort studies and RCTs from 1950 through October 2013. Search strategies are available as a supplementary file. The reference lists of the retrieved articles were also searched for additional cohort studies and RCTs. Two reviewers (MH and MC) independently assessed study eligibility. Excluded studies and reasons for exclusion were recorded. Disagreement was resolved by discussion and consensus. We included original full-length articles pertaining to the association between knee joint loading during walking, measured by 3-dimensional gait analysis, and structural disease progression assessed quantitatively or semi-quantitatively by X-ray or MRI. We considered only studies that included subjects diagnosed with knee OA that were followed for at least 1 year (necessary because of the sensitivity of imaging and slow disease progression[24]). Cohort studies had to include estimates of knee joint loading during walking at baseline and imaging-based assessment of structural disease progression. Clinical trials had to be randomised and compare image-based structural disease progression between different knee joint loading interventions (e.g. increase vs. decrease), placebo or control.

Data extraction and analysis

The following data were extracted from the studies: 1) Study design; 2) Country of origin; 3) Number of subjects; 4) Characteristics of the subjects; 5) Type of knee joint loading estimate; 6) Magnitudes of the estimate; 7) Description of the interventions (if any); and 8)

Structural disease progression outcome (i.e., semi-quantitative or quantitative measures on x-ray and/or MRI).

For prospective cohort studies, we extracted estimates of the association between baseline knee joint loading and structural disease progression from baseline to follow-up. A progression group is typically compared to a nonprogression group at baseline and the results are typically reported as odds ratios (OR) for disease progression for a one-unit higher baseline knee joint loading. If no OR were reported, we either calculated it from the reported data (if possible), or contacted the study authors requesting the OR. For the RCTs we aimed to compare relative risks of structural disease progression between knee joint loading modification and control groups.

The individual study results were combined in a random effects meta-analysis model using Review Manager.[25] Heterogeneity between trials was assessed using the standard Q-test statistic (testing the hypothesis of homogeneity), and we present the I^2 value, which can be interpreted as the percentage of total variation across the studies due to heterogeneity.[26] Stratified (meta-regression) analyses were performed using SAS software (version 9.2), applying a restricted maximum likelihood (REML) method to estimate the between-study variance and the combined OR.

Methodological quality and Risk of Bias assessment

The methodological quality of the cohort studies were assessed using a published check list.[27] Two of the authors (MH and MWC) assessed this individually and judged each criterion to be “Adequately described”, “Unclear”, or “Inadequately described”. Disagreement was resolved by discussion. If an included study was authored by one or more of the current authors, a third reviewer (HL) was asked to perform a quality assessment. One quality

assessment item was omitted (“*Was a dose-response relationship between exposure and outcome demonstrated?*”) because this item relates to the findings of the study, not the methodological quality and assessment of dose-response forms part of the Bradford Hill criteria for causation (see below). Overall extent of risk of bias and methodological quality within each study was assessed using the GRADE approach to evaluate study limitations.[28]

Evaluation of evidence for causality

A modified algorithm of the Bradford Hill criteria was used to systematically evaluate the evidence of a causal link between knee joint loading during walking and structural progression of knee OA. The following criteria were used in the review of the cohort studies and given a score of 1 (criterion satisfied) or 0 (criterion not satisfied):

1. *Strength of association.* Associations quantified as a pooled OR ≥ 5.0 , with lower 95% CI above 2.0, and statistically significant ($P < 0.05$); in the expected direction was defined as “strong association.” “Moderate association” is defined as any statistically significant pooled OR ($P < 0.05$). A statistically non-significant pooled OR was defined as “no association.”
2. *Consistency across studies.* An association requires replication in other studies. Consistency is defined as $\geq 75\%$ of associations being strong or moderate.
3. *Temporality.* Refers to temporal relationship of association between exposure and outcome; exposure has to precede outcome. It is difficult to ensure temporal correctness because study subjects are assumed to walk daily and are therefore exposed to knee joint loading throughout observation periods. We retained this criterion because temporality is necessary to infer causation; absence of temporal relationship between exposure and outcome precludes a causal link. Our analysis accepted studies with a temporally correct

design defined as baseline knee joint loading related to disease progression over time from that baseline. The temporality criterion was satisfied when temporal correctness was accepted in $\geq 75\%$ of the included studies.

4. *Biological gradient.* When rate of progression increases (or decreases) incrementally as dose of exposure increases; provides strong evidence of causal relationship. This criterion is satisfied when $\geq 75\%$ of tests for a trend pertaining to structural progression outcomes are statistically significant in the expected direction for knee joint loading.

These 4 criteria scores were used to derive one causation score for each knee joint loading variable. The scores were computed as the unweighted sum of the scores from each of the above criteria, for a possible range of 0 to 4. A score of 4 is considered strong evidence of a cause-and-effect relationship. A score of 3 is deemed to indicate moderate evidence. A score of 2 or less is considered weak evidence of causation.

A fifth criterion, *experimental evidence*, was used to examine whether the evidence from the prospective cohort studies was consistent with that from RCTs. Experimental evidence enhances the probability of causation, and may be used to up- or down-grade the calculated causation score.

The following 4 criteria were omitted:

Coherence. Causation is more likely if what is observed is supported by and in agreement with the natural history of the disease. This criterion is usually applied when the outcome is assessed by surrogate outcomes. This criterion is omitted because it is satisfied by default, because imaging modalities are surrogate outcomes.

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4 *Plausibility* relates to the assessment of whether the association is plausible or not. This
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6 criterion is omitted because of the highly subjective nature of this criterion.
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9 *Specificity* relates to the specific response to the exposure. This criterion is omitted because
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11 OA is a multi-structure disease; an association between knee joint loading and disease
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13 progression in multiple structures does not preclude a possible causal relationship.
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15 *Analogy* relates to the possibility that existing similar association can support causation (e.g.,
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17 does the same association exist for hip or hand OA? If so, causation may be supported). This
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19 criterion is omitted because this review focuses specifically on knee OA.
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RESULTS

The search yielded 1,078 potentially eligible studies (Figure 1; references available as a supplementary file). Of those, we included 5 prospective cohort studies published between 2002 and 2013 and involving a total of 452 patients with knee OA[29-33] and 0 RCTs . Study characteristics are summarised in **Table 1**.

Table 1.
Summary of the characteristics of the included studies.

Author (year) country	Knee loading variable	Structural progression measure		Follow-up time	Number of patients (total/progressors/non-progressors)	Females (%)	Ref.
Miyazaki et al. (2002) Japan	Peak KAM (unit:%BW×HT)	≥1 grade according to Altman atlas	sq x-ray	72 months	74/42/32	78%	[30]
Chang et al. (2007) USA	Peak KAM (unit:%BW×HT)	≥1 grade according to Altman atlas	sq x-ray	18 months	56 (64 ^a)/41/15	59%	[31] [34] ^a
Bennell et al. (2011) Australia	Peak KAM (unit:%BW×HT)	≥1 grade medial tibiofemoral cartilage defects	sq MRI	12 months	138/45/93	56%	[29]
	KAM impulse (unit:%BW×HT)	Cartilage volume loss (mm ³)	q MRI		144/n.a./n.a.		
Woollard et al. (2011) USA	Peak KAM (unit:Nm/kg) ^b	Cartilage Volume loss (mm ³)	q MRI	12 months	13/6/7	23%	[32]
Henriksen et al. (2013) Denmark	Peak overall knee compression force (unit: N)	Cartilage loss	sq MRI	12 months	157/n.a./n.a.	89%	[33]
				Median: 12 months	Totals: 452/134/147	Mean: 67%	
BW; Body Weight; HT: Height; Sq: semi-quantitative grading, q: quantitative. ^a Upon request, the authors forwarded a conference abstract with additional data based on 64 subjects. The number of progressors/non-progressors not available from that abstract. ^b We converted the data into %BW×HT after requesting body weight and height data from the authors.							

Four cohort studies[29-32] focused on the same knee joint loading estimate: the peak KAM. In these studies, peak KAM was assessed at baseline and related to structural medial

disease progression assessed after a median of 15 months from that baseline (12-72 months). In one study,[29] the baseline KAM impulse (area under the curve) was also related to medial disease progression. In the fifth study,[33] overall knee compression loading was used as load exposure.

Two studies[30, 31] defined structural disease progression as any worsening in semi-quantitative radiographic medial joint space grade [35]. One study[32] defined structural disease progression as any loss of medial femoral cartilage volume (quantitative MRI) above a measurement error previously established. In on study[33] structural disease progression was assessed from semi-quantitative grading of tibiofemoral cartilage loss and bone marrow lesions. In one study[29] structural progression was assessed semi-quantitatively as medial tibiofemoral cartilage loss and medial tibiofemoral bone marrow lesions, and quantitatively as medial tibial cartilage volume loss. For the meta-analysis, we extracted the association (OR) between peak KAM and semi-quantitative progression in medial tibiofemoral cartilage loss. No ORs were available for the association between KAM and cartilage volume loss because both were continuous variables. However, the linear regression analysis was extracted for the assessment of the biological gradient criteria.

ORs were not reported in 3 studies,[31-33] but in[32] individual patient data were reported and an OR was calculated. We contacted the authors of,[31] asking them to provide an OR if possible. The authors returned a conference abstract including an OR published 4 years prior to the article.[34] The abstract included 64 patients in contrast to the 57 patients included in.[31] The authors could not account for the different number of subjects between the full paper and conference abstract. One study[33] grouped subjects based on changes in joint loading following weight loss (increased vs. reduced loads). There were no between group differences in structural disease progression. Due to the use of an intervention (weight

loss), it was not appropriate to extract OR for baseline loading.

The ORs for structural disease progression ranged from 0.40 to 6.46 for each unit higher baseline peak KAM magnitudes. From the random effects model, the combined OR was estimated to 1.90 (95% CI 0.85 to 4.25). The confidence in this estimate was downgraded due to heterogeneity ($I^2=77\%$). **Figure 2** summarises the individual and pooled estimates.

In [29] the OR for progression of bone marrow lesions was 1.31 (95% CI 0.86 to 1.98) with every unit increment in baseline peak KAM; ORs for progression of cartilage defects and bone marrow lesions were 0.42 (95% CI 0.12 to 1.48) and 1.8 (95% CI 0.63 to 5.17), respectively, with every unit increment in baseline KAM impulse.

One or more criteria were limited in the assessments of risk of selection, detection, and attrition biases. Individual risk assessments are presented in appendix 1. Across the studies, the comparability of the groups at baseline was generally inadequately or unclearly described (selection bias). Also, descriptions of how reliably the joint load exposures were ascertained were not included in 4 of the 5 of the studies (detection bias), and group differences in loss of subjects were not accounted for (attrition bias). The discrepancy in subject numbers in reports from one cohort [31, 34], induced a high risk of selection and attrition bias. **Table 2** presents summaries of the quality assessment. Agreement between quality raters was good ($\kappa = 0.73$ (95% CI: 0.48:0.97)).

Table 2.

Summary of the quality assessment (risk of bias).

Bias type	Quality criteria	Miyazaki et al.[30]	Chang et al.[31, 34]	Bennell et al.[29]	Woollard et al.[32]	Henriksen et al.[33]
Selection	Were the descriptions of the groups and the distribution of prognostic factors sufficient?	A	I	I	A	A
	Were the groups assembled at a similar point in their disease progression?	A	I	I	A	A
	Were the groups comparable on all important confounding factors?	I	I	I	U	A
Detection	Was the joint load estimate reliably ascertained?	U	U	U	U	I
	Was adequate adjustment made for the effects of these confounding variables?	A	I	A	I	I
	Was outcome assessment blind to exposure status?	A	A	I	I	A
	Was follow-up long enough for the outcomes to occur?	A	A	A	A	A
	What proportion of the cohort was followed-up?*	U	A	U	A	A
Attrition	Were dropout rates and reasons for drop-out similar across groups?	I	I	I	A	A
Overall risk of bias		Very serious limitations	Very serious limitations	Very serious limitations	Very serious limitations	Very serious limitations
Methodological quality		low	low	low	low	low
A, Adequately described; U, Unclear; I, Inadequately described. * Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate= <50% ^a Risk of bias within studies is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).						

The non-significant combined OR indicates no association between knee joint load during walking and structural disease progression. Thus, a score of 0 in the *Strength of Association* criterion was assigned. The associations were not consistently replicated (50%), resulting in a score of 0 in the *Consistency* criterion. This finding was further supported by the heterogeneity between the studies ($I^2=77\%$; **Figure 2**), and the discrepancies between

baseline peak KAM magnitudes among progressors and nonprogressors across the cohorts (Figure 3). Temporal correctness was accepted in one cohort.[30] After requesting additional information from the authors of one cohort study,[31] we discovered that the article reports only part of the study. The additional information retrieved,[34] showed that the study consisted of 3 measurements taken every 18 months. Joint space and Kellgren-Lawrence grades (x-rays) were recorded at all 3 time points, whereas the KAM was obtained at time points 2 and 3 (18 and 36 months). KAM at time point 2 (18 months) was associated with structural disease progression from 18 to 36 months and structural disease progression from time point 1 to 2 (baseline to 18 months) was associated with increased KAM from 18 to 36 months.[34] Thus temporally correctness can not be assigned to the observed associations in this study, and the overall *Temporality* criterion was not satisfied (a 0 score). *Biological Gradient* was investigated in one cohort[29] that showed no positive association between baseline peak KAM and loss of medial tibial cartilage volume over 12 months, resulting in a score of 0. Consequently, the causation score based on the included cohort studies was 0 for the association between peak KAM during walking and structural disease progression in patients with knee OA (Table 3).

Table 3.

Bradford Hill criteria and the causation score for the identified knee joint loading exposures.

Knee joint load exposure	Strength ^a Summary or OR (95%CI)	Consistency ^b No (%)	Temporality ^c No (%)	Biological gradient ^d No (%)	Causation score (No. of criteria met)
Peak KAM	1.90 (0.85-4.25)	2/4 (50%)	1/4 (25%)	0/4 (0%)	0
KAM impulse	0.42 (0.12-1.48) ^e	- ^f	0/1 (0%)	1/1 (100%)	- ^g
Peak overall compression	No group difference	- ^f	1/1 (100%)	0/1 (0%)	- ^g

^a Strong association is defined as a pooled OR ≥ 5 with lower 95% CI excluding 2.0. Moderate association is any statistically significant association.

^b Consistency is defined as $\geq 75\%$ of associations showing strong or moderate associations

^c In cohort studies it is difficult if not impossible to ensure temporal correctness because subjects in the studies are expected to walk daily and therefore are exposed to knee joint loading throughout the observation period. In the present analysis, the temporality criterion is satisfied in studies that relate baseline knee joint loading exposures to disease progression over time from that baseline and demonstrate a statistically significant association with structural disease progression.

^d Biological gradient is defined as demonstrated when the rate of progression increases (or decreases) incrementally as dose of exposure increases.

^e Estimate based on one cohort study[29] assessing baseline KAM impulse to progression of cartilage defects assessed by semi-quantitative grading of MRI.

^f Consistency not possible to assess with only one cohort.

^g Causality score not calculated because only one study available.

For the KAM impulse and overall knee compression loading, only one study was available for each exposure,[29, 33] and therefore no causation scores were calculated for these loading exposures.

As the systematic literature search did not identify any RCTs, the findings from the cohort studies can neither be confirmed nor refuted by experimental evidence. Hence the fifth criterion, could not be used to up- or down-grade the causation scores.

DISCUSSION

This review is the first to systematically assess—using systematic review, meta-analysis and the Bradford Hill criteria for evidence for causality—whether a causal link exists between knee joint loading during walking and structural disease progression of knee OA. The systematic literature search identified five prospective cohort studies focusing on three estimates of knee joint loading: the peak KAM, KAM impulse, and overall tibiofemoral compression force. Using a predefined algorithm, a causation score of 0 was reached, indicating no causal link between knee joint loading during walking and structural progression of knee OA. Further, no experimental data from RCTs exist to support or oppose the findings from the cohort studies. One of the prospective cohort studies[33] compared increased vs. decreased loads, without demonstrating differences in structural disease progression opposing a causal link.

Indirectly supporting the present findings, a longitudinal randomised trial comparing laterally wedged insoles (previously demonstrated to reduce loading[36, 37]) with placebo insoles, showed no group differences in structural disease progression.[38] While that study seemingly provided experimental evidence, no joint load exposure data were included to document the assertion that joint loadings were in fact reduced in the “wedged insole” group. Thus, the study did not fulfill the criteria for inclusion in this review. On the other hand, the null outcome is supported by the results in,[33] included in this review showing neither detrimental effects of increased loading nor beneficial effects of decreased loading over 12 months in a group of knee OA patients.

The quality assessment of the included studies showed high risks of selection, detection, and attrition biases (**Table 3**). An important precondition for valid results in cohort studies is that groups should be comparable at baseline. Unless the groups are balanced for relevant

baseline characteristics, differences in structural disease progression cannot confidently be attributed to the effects of interest (joint loads during walking). The included studies revealed significant inadequacies when assessing the comparability of the groups on relevant baseline characteristics, leading to prognostic imbalance. Four of the 5 cohort studies did not report how reliably the joint loading estimates were ascertained (detection bias), which could influence the individual results. Further, the loss of subjects at follow-up in 2 of the 5 cohort studies was beyond 20%, with the dropout rates and reasons for dropout across groups not adequately accounted for (attrition bias). Finally, the discrepant numbers of subjects presented in different reports from the same cohort[31, 34] introduced a serious risk of bias and low confidence in the results. The overall low methodological quality of the included studies gives little confidence in the reported estimates of causation.

Despite the shortage of studies reporting a causal link between joint loading and structural disease progression, the conjectured relationship underlies the rationale for many clinical efforts to reduce knee loading during walking in attempts to retard disease progression. Weight loss, insoles, modified footwear, strengthening exercises, knee braces, and gait modifications have been suggested as means to lower knee joint loads and thus slow structural disease progression through mechanical pathways,[39-44] with effects yet to be proven. The rationale for such efforts is diluted by the present results, not only by the low causality score, but also by the inconsistency across studies in the loading magnitudes between individuals that progress and those that do not. **Figure 3** illustrates that patients with a certain baseline peak KAM magnitude in one study progress, whereas patients with similar baseline peak KAM magnitudes in other studies do not progress. These differences in knee joint loading magnitudes between studies may be due to differences in gait analysis protocols across the involved gait labs, for example in the selection of reference frame

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4 convention for the calculation of the KAM[45] and footwear condition.[42] However,
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6 including diversity of measures of the same variable can strengthen the confidence in the
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8 results of a systematic review.
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10 The results from the included studies exhibited a high degree of heterogeneity (I^2 from
11 the meta-analysis) (**Figure 2**). The two cohorts with significant OR[30, 31, 34] both used
12 radiography as the structural outcome assessment, whereas the studies reporting
13 nonsignificant ORs used MRI.[29, 32] Further, the two studies reporting significant
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15 associations had longer follow-up periods (72 and 18 months), whereas the studies without
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17 significant associations assessed disease progression after 12 months. This concurrence of
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19 follow-up time and imaging modality precludes conclusions about whether the differences in
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21 results are based on follow-up time or imaging modality. Radiography is the current clinical
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23 gold standard for assessing structural disease progression, but it has low temporal sensitivity,
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25 making long follow-up times necessary. MRI—with its shorter temporal sensitivity—is
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27 possibly the more promising tool for assessing single structures and should be used in studies
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29 with longer follow-up times. The total number of patients was 452 in five cohorts. That is a
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31 very small number of patients when considering the large population and when compared to
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33 similar reviews in other chronic diseases. For instance, a recent review of the causal
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35 relationship between dietary factors and coronary heart disease included several millions
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37 individuals in 361 cohorts and a multitude of dietary exposures.[23]
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47 Our study has strengths because we undertook several measures to minimise bias,
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49 restricting our review to studies with the strongest causal inference (cohort studies and
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51 RCTs), conducted independent assessments of study eligibility, and using predefined criteria
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53 to evaluate causation and methodological quality. We may be criticised for using arbitrary OR
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55 cut-offs to define strong and moderate association, but identifying the true cut-off for defining
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clinically meaningful OR values is impossible in a field that has so few longitudinal studies to consult. Also, the causality score omitted several of the original criteria, yet the applied method was pre-specified. We may also be criticised for analysing any image-based structural deterioration, rather than separating the analyses in x-ray and MRI-based assessments. However, the analysis plans were also pre-specified, without prior knowledge of the number of studies and specifics of the outcomes.

Current guidelines on interpretation of data from observational studies and data combined from repeated observational studies (with a reasonable internal validity) would correspond to confidence in the estimate's being "Low-quality evidence", but could be upgraded if there is great confidence in the estimates and the effects are large.[46] However, the present analysis revealed a large inconsistency among study results, poor precision of the combined analysis, and low methodological quality. Thus, we downgraded further to "*very low quality evidence*". The inconsistency of the available studies may limit the appropriateness of meta-analyses, yet support the overall conclusion of this systematic literature review.

In conclusion, our systematic review, meta-analyses, and application of Bradford Hill's criteria for causation indicates no causal link between estimates of knee joint loading during walking and structural progression of knee OA. Future large well designed prospective cohorts with subsequent confirmation from randomised trials are strongly recommended. The current study findings question the rationale behind clinical efforts to reduce knee joint loading during walking as such efforts are currently supported by very low-quality evidence showing no causal link between knee joint loading during walking and progression of knee OA.

COMPETING INTEREST

None declared.

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AUTHOR CONTRIBUTIONS

MH, MWC, HL, CJ, and RC were responsible for study concept and design. RC and MH supervised the study. HL and CJ performed the literature search. MH and MWC acquired the data, which was analysed and interpreted by MH, MWC, CJ, HL, and RC. MH drafted the manuscript, which was critically revised for important intellectual content by MWC, HL, CJ, and RC. RC did the statistical analysis. MH is the guarantor.

ETHICAL APPROVAL

Not required.

DATA SHARING

Details of the literature search, the search results, and reasons for exclusion are available from the corresponding author at robin.christensen@frh.regionh.dk.

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FIGURE LEGENDS

Figure 1

Flowchart of the literature selection process.

Figure 2

Forest plot of the individual ORs of structural disease progression with every increment in baseline peak knee adduction moment. Weights are from a random effects analysis. Individual and pooled estimates are shown with 95% confidence intervals.

Figure 3

The mean baseline KAM knee joint load exposures in patients with and without structural disease progression from the four individual cohorts. Note the overlap between progressors and non-progressors in the different studies. Error bars: 95% CI.

SUPPLEMENTARY FILES

- 1: Study protocol
- 2: Literature search protocol
- 3: List of the literature found

Appendix 1
CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by publication year]

Miyazaki et al. 2002		
Methods	Prospective cohort study	
Participants	74 patients with medial knee OA	
Joint load exposure	External knee adduction moment during walking assessed at baseline	
Structural knee OA progression outcome	Joint space narrowing grade based on Altman atlas of osteoarthritis. Dichotomous grouping (“progrsors”/”non-progrsors”) based on at least one grade worsening over the observation period.	
Observation period	72 months	
Quality assessment (risk of bias)		
Quality criteria	Authors’ judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Adequate	Tables adequately presenting relevant information about subjects.
Are the groups assembled at a similar point in their disease progression?	Adequate	Quote: “... the number of patients with each radiographic scale (K/L grade and joint space narrowing scale) was similar in the two groups.”
Is a potential knee joint loading parameter reliably ascertained?	Unclear	There is no mentioning of reliability assessment or reference.
Were the groups comparable on all important confounding factors?	Inadequate	Quote: “However, there were some significant differences at entry between the groups.” Comment:
Was there adequate adjustment for the effects of these confounding variables?	Adequate	The analyses were adequately adjusted (multivariable logistic regression).
Was outcome assessment blind to exposure status?	Adequate	Quote: “All radiographs were evaluated by an experienced reader who was unaware of all other data.”
Was follow-up long enough for the outcomes to occur?	Adequate	Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Unclear	32 out of a total of 106 (~30%) were lost to follow up.
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Inadequate	Not described. The exposure for those that were lost to follow up was higher than those who completed the study as “non-progrsors”.
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate= <50%
^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

Chang et al. 2007 & Sharma et al. 2003*

Methods	Prospective cohort study	
Participants	57 patients with knee OA (64 patients in abstract) from the MAK cohort (300+ patients).	
Joint load exposure	External knee adduction moment during walking assessed at baseline	
Structural knee OA progression outcome	Joint space narrowing grade based on Altman atlas of osteoarthritis. Dichotomous grouping ("progressing knees"/"non-progressing knees") based on at least one grade worsening over the observation period.	
Observation period	18 months	
Quality assessment (risk of bias)		
Quality criteria	Authors' judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Inadequate	There are no descriptions of the groups, except for the toe-out angle and knee adduction moment.
Are the groups assembled at a similar point in their disease progression?	Inadequate	Not described. Only the distribution of K/L in the full sample is given. The structural disease progression outcome (Altman) is not presented at baseline.
Is a potential knee joint loading parameter reliably ascertained?	Unclear	There is no reliability assessment or reference to previous work.
Were the groups comparable on all important confounding factors?	Inadequate	Not described.
Was there adequate adjustment for the effects of these confounding variables?	Adequate	In the conference abstract there were statistical adjustments for age, gender, BMI, pain, radiographic disease severity (K/L), and varus alignment.
Was outcome assessment blind to exposure status?	Adequate	Quote: "The knee x-ray reader was blinded to the gait analysis data"
Was follow-up long enough for the outcomes to occur?	Adequate	Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Adequate	This study included 57 at baseline and 56 at follow-up. Note: The underlying MAK cohort is 300+ patients no description of how the gait subgroup was selected
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Inadequate	The conference abstract (Sharma et al. 2003) included 64 patients in contrast to the 57 patients included in the article (Chang et al. 2007). The authors could not account for the different numbers of subjects.
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

* Conference abstract based on the study.

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate = <50%

^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

Bennell et al. 2011

Methods	Prospective cohort study
Participants	144 patients with medial knee OA
Joint load exposure	External knee adduction moment during walking assessed at baseline
Structural knee OA progression outcome	Progression of 1 or more grades in bone marrow lesions and cartilage defects assessed by semi-quantitative evaluation of MRI scans. Loss in medial tibial cartilage volume assessed from manual segmentation of MRI scans.
Observation period	12 months

Quality assessment (risk of bias)

Quality criteria	Authors' judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Inadequate	There are no descriptions of the groups that progress in BMLs and cartilage defects.
Are the groups assembled at a similar point in their disease progression?	Inadequate	Not described.
Is a potential knee joint loading parameter reliably ascertained?	Unclear	There is no reliability assessment or reference to previous work.
Were the groups comparable on all important confounding factors?	Inadequate	Not described.
Was there adequate adjustment for the effects of these confounding variables?	Adequate	There were statistical adjustments for age, gender, BMI, MRI machine, alignment, baseline values, and treatment group.
Was outcome assessment blind to exposure status?	Inadequate	Not described.
Was follow-up long enough for the outcomes to occur?	Adequate	Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Unclear	200 enrolled in the underlying study. 144 (72%) had complete data sets.
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Inadequate	Not described.
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate= <50%

^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

Woollard et al. 2011

Methods	Prospective cohort study	
Participants	13 patients with knee OA	
Joint load exposure	External knee adduction moment during walking assessed at baseline	
Structural knee OA progression outcome	Loss of tibiofemoral cartilage volume. Dichotomous grouping ("progressing knees"/"non-progressing knees") based on a cartilage loss greater than measurement error over the observation period.	
Observation period	12 months	
Quality assessment (risk of bias)		
Quality criteria	Authors' judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Adequate	Individual patient data is presented according to group structure.
Are the groups assembled at a similar point in their disease progression?	Adequate	Progressors had more severe radiographic disease at baseline (K/L 3 vs. 2), but similar cartilage volumes at baseline (primary outcome).
Is a potential knee joint loading parameter reliably ascertained?	Unclear	There is no reliability assessment or reference to previous work.
Were the groups comparable on all important confounding factors?	Unclear	Progressors had more severe radiographic disease, BMI and lower age; but comparable on gender, WOMAC (all domains) and alignment.
Was there adequate adjustment for the effects of these confounding variables?	Inadequate	The sample was too small for adjustments of the estimates.
Was outcome assessment blind to exposure status?	Inadequate	Not described.
Was follow-up long enough for the outcomes to occur?	Adequate	Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Adequate	15 invited. 1 lost; 1 excluded.
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Adequate	Only 1 dropout.
Extent of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate = <50%

^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

Henriksen et al. 2013

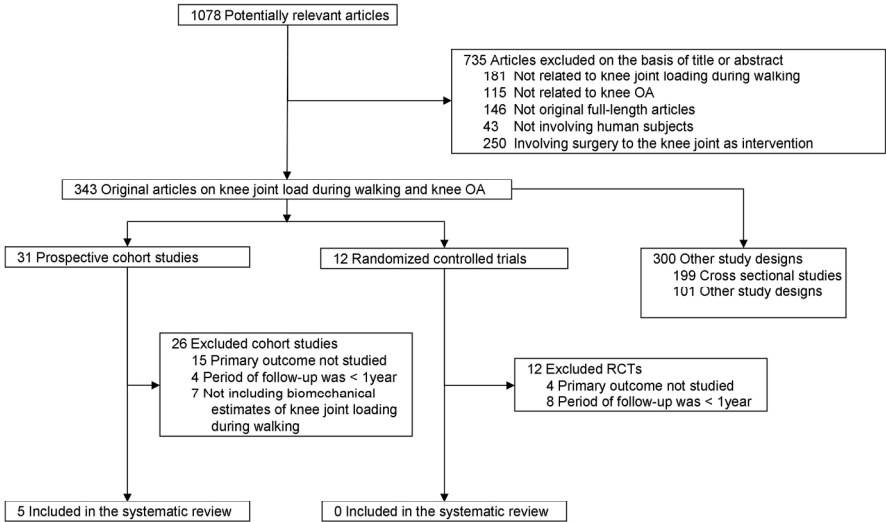
Methods	Secondary data analysis from a randomized trial	
Participants	157 patients with knee OA and a BMI >30 kg/m ²	
Joint load exposure	Change in peak knee joint compression force during walking over the 4 months prior to the 12 month observation period	
Structural knee OA progression outcome	Boston Leeds Knee Osteoarthritis Score (BLOKS) for tibiofemoral cartilage loss and bone marrow lesions	
Observation period	12 months	
Quality assessment (risk of bias)		
Quality criteria	Authors' judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Adequate	Comment: Demographic, primary outcome and secondary outcome data separated by group are provided in Table 1.
Are the groups assembled at a similar point in their disease progression?	Adequate	Quotation: "There were no other statistically significant differences [including in K&L grade and BLOKS measures of tibiofemoral cartilage and bone marrow lesions] between the Unloaders and Loaders at week 16"
Is a potential knee joint loading parameter reliably ascertained?	Adequate	Quotation: "Based on 30 individuals assessed twice separated by one week done prior to the study, intra-class correlation coefficient for the estimation of peak compression force in our lab is 0.91 (95% CI: 0.83 to 0.96)"
Were the groups comparable on all important confounding factors?	Inadequate	Quotations: "Among the Unloaders the ambulatory knee function was not improved from week 0 to week 16, seen as no statistically significant change in walking speed and a reduction in the knee extensor moment" and "...the ambulatory knee function was improved among the Loaders, seen as increases in walking speed and internal knee extensor moment [from week 0 to week 16]" Comment: These quotations highlight a group difference in the change in walking speed, which may influence the change in knee joint loading which was used to assign group membership.
Was there adequate adjustment for the effects of these confounding variables?	Inadequate	Quotation: "Adjusted analysis: We repeated the analysis further including age, sex, week 16 BMI, and the randomization code in the underlying RCT (Diet, Exercise and Control) as covariates." Comment: Analyses were not adjusted for walking speed or change in walking speed.
Was outcome assessment blind to exposure status?	Adequate	Quotation: "All assessors were blinded to the case status."
Was follow-up long enough for the outcomes to occur?	Adequate	Comment: Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Adequate	Quotation: "One year after the weight loss (i.e., at week 68), there were 144 subjects (92%) remaining in the biomechanics sub-cohort, i.e., 13 subjects lost to follow-up"
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Adequate	Quotation: "[participants lost to follow-up] were distributed with 7 (7%) in the Unloader group and 6 (11%) in the Loader group.

		Comment: Reasons for drop out listed in Figure 2.
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

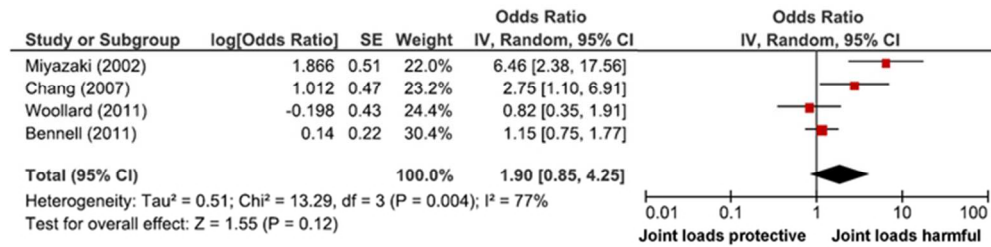
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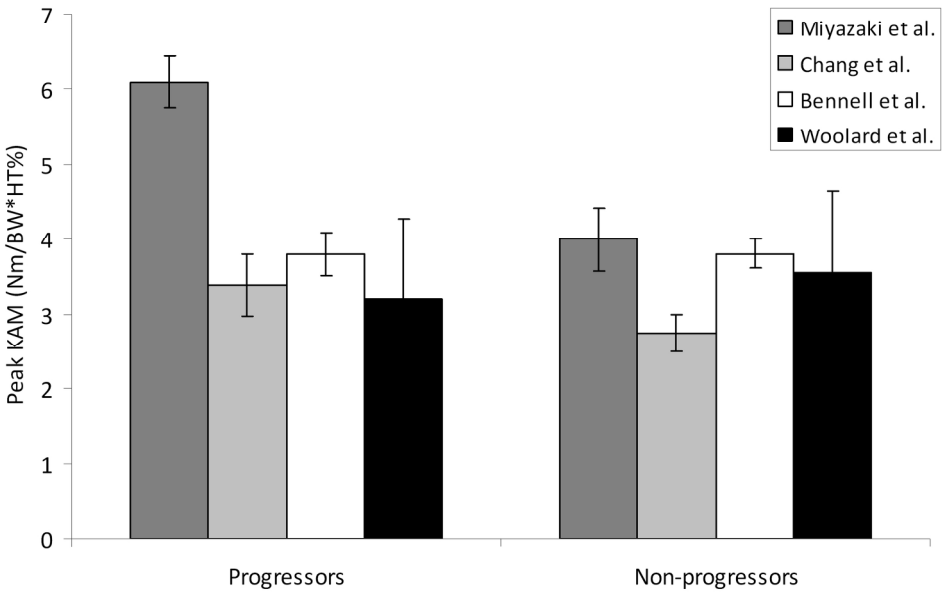
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Flowchart of the literature selection process.
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Forest plot of the individual ORs of structural disease progression with every increment in baseline peak knee adduction moment. Weights are from a random effects analysis. Individual and pooled estimates are shown with 95% confidence intervals.
 62x16mm (300 x 300 DPI)



The mean baseline KAM knee joint load exposures in patients with and without structural disease progression from the four individual cohorts. Note the overlap between progressors and non-progressors in the different studies. Error bars: 95% CI.
190x142mm (300 x 300 DPI)

Causal link between knee joint loading during walking and structural progression of knee osteoarthritis: a systematic review of cohorts and randomized trials

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ABSTRACT

Background

XXXXXXX

Objectives

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Search methods

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Selection criteria

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Data collection and analysis

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Results

XXXXXX

Authors' conclusions

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INTRODUCTION

Description of the condition

Osteoarthritis (OA) is the most common form of arthritis (1) affecting a large part of the population, and is a major cause of disability (2). The incidence and prevalence of OA increase with age (3). Among joints affected by OA, the knee joint is among the most frequently affected (1). Due to the knee's crucial role in independent ambulation knee OA leads to considerable disability affecting the individual's participation in society and independent life style. Pathologically, knee OA is defined as is a progressive structural disorder of the joints primarily characterized by gradual loss of cartilage with concurrent development of osteophytes, meniscal degeneration, bone marrow lesions, synovitis and effusions. The diagnosis is clinical – in the main by the presence of pain - and is most often confirmed by radiography or magnetic resonance imaging (MRI). Symptomatic knee OA is defined as the presence of the radiographic features of OA in combination with symptoms attributable to knee OA. Because no cure is available the burden of morbidity, primary care visits, and health care costs associated with knee OA are enormous and even higher than more high-profile diseases such as diabetes, cancer and cardiovascular diseases (4). Thus knee OA poses a substantial public health burden given its prevalence in the population that continues to rise.

Description of the exposure

Walking is a natural way of moving. Most people walk short distances every day and estimates of steps/day have been reported to be 9300 (women) and 11 900 (men) for young subjects decreasing with age (5), giving approximately between 3.4 and 4.3 million steps/year. With every step the knee joint is loaded, and biomechanical studies estimate the joint loads to exceed 2-3 times body weight (6), and thus knee joint loading is a necessity in independent life style.

While internal forces at joints cannot be measured directly, estimates of joint loads during walking can be obtained non-invasively by means of 3-dimensional gait analysis. Typically, medial tibiofemoral compartment joint loads are estimated using the external knee adduction moment (KAM) as a proxy, because this moment has been shown to be determinative of the medial to

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lateral joint load distribution (7). More detailed biomechanical models have also been used to assess joint loads, in which overall compression forces (i.e., both medial and lateral compartment forces) are estimated based on the summation of joint, muscle, and soft tissue reaction forces (8). More recently, the total reaction moment has been suggested as a measure of overall joint loading during walking (9).

Efforts to reduce the dynamic loads on the knee during walking have been made with the scope to potentially delay or stop structural deterioration. Braces, wedged insoles, exercise, and weight loss are among interventions that have been suggested to have beneficial effects on structural progression of knee OA mainly through mechanical pathways.

How the exposure might work

Knee OA has traditionally been categorized as a “wear and tear” disease, which by definition suggests mechanical factors as being causally involved in both disease initiation and progression. A widely accepted hypothesis is that higher knee joint compression forces and moments during walking are associated with structural knee OA degeneration and changes in knee joint forces and moments must change the distribution, magnitude and direction of forces between and within the joint structures with possible effects on the structural disease progression. Within the knee structural signs of OA commonly occur in weight bearing structures, strengthening the belief that load is involved in knee OA progression. According to the prevailing theories higher loading is believed to accelerate structural progression of knee OA and thus unloading is advocated in an attempt to slow or halt disease progression.

Why it is important to do this review

The relationship between knee joint loads during walking and knee OA has been a focus of research for 10-20 years. The original work of Miyazaki et al. (10) indicating that higher joint loads increase the odds of structural disease progression has stimulated subsequent studies of knee joint loading during walking and knee OA. However, the majority of studies are cross sectional and results of prospective cohort studies and RCTs are discrepant. Results from studies on symptomatic treatment of knee OA paradoxically reveals (presumably) unwanted increase in knee joint loads during walking that were previously suggested to exert detrimental structural effects in

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cohort studies (6;11-13). This may generate confusion among researchers, health care professionals, policy makers, and the population at large who are interested in this information to aid them in knee OA prevention and treatment strategies.

In a classic study, Hill (14) proposed a set of criteria (the Bradford Hill criteria) to evaluate systematically whether a causal link between an exposure of interest and a health outcome exists. These guidelines are used by epidemiologists to test causal hypotheses and have undergone little modification since their original publication. Before advocating that knee joint loadings during walking should be targeted therapeutically, it is necessary to base recommendations on the best available scientific evidence. To address this issue, we conducted a systematic review of the literature examining the association between knee joint loads during walking (hereafter referred to as knee joint load exposures) and structural degeneration in knee osteoarthritis.

Objectives

Our specific objectives are 1) to systematically evaluate the evidence supporting a causal link between exposures to knee joint loadings during walking and progression of structural knee joint degeneration in patients with knee OA using the Bradford Hill criteria; 2) to determine which knee joint load exposures that have been studied sufficiently in RCTs and found to support the findings of prospective cohort studies; and 3) to identify the knee joint load exposures deemed to have insufficient evidence to be conclusive.

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METHODS

Criteria for considering studies for this review

Types of studies

Prospective cohort studies and RCTs.

We only consider studies that follow-up subjects for at least 1 year (according to the OMERACT-III Recommendations for a Core Set of Outcome Measures relating to the sensitivity of imaging and slow disease progression (15)). Cohort studies need to include estimates of joint loading during walking and assessment of disease structural progression. RCTs need to intervene on joint loading and assess the impact on structural disease progression.

Types of participants

The studies must include participants with knee OA diagnosed according to the ACR-criteria (16).

Types of interventions

Clinical trials have to be randomized and compare structural disease progression between different knee joint load exposures (high vs. low or increase vs. decrease), or knee joint load exposures interventions (increase or decrease), placebo or control.

Types of outcome measures

The articles must pertain to the effect of exposure to knee joint loading during walking (e.g. joint moments or estimated joint compression forces from 3-dimensional gait analysis) on structural disease progression assessed by X-ray or MRI.

Outcome measures

Primary – major – outcomes

Structural disease progression assessed by X-ray or MRI.

Semi quantitative assessments:

X-rays: K/L, Ahlback, Altman

MRI: WORMS/BLOKS/MOAKS assessments of cartilage defects, bone marrow lesions, osteophytes, meniscal lesions and extrusions, synovitis, effusion.

Quantitative assessments:

X-rays: Joint space width (mm), alignment (degrees)

MRI: Cartilage thickness (mm), volume (mm³), bone marrow lesion area/volume (mm²/mm³), meniscal extrusions (mm)

Search methods for identification of studies

Electronic searches

We will search MEDLINE, Scopus, AMED, CINAHL and SportsDiscus for prospective cohort studies and RCTs from 1950 through October 2012.

Searching other resources

The reference lists of the retrieved articles will also be scanned for additional cohort studies and RCTs.

Own files for yet unpublished data (e.g. Loader/Unloader manuscript at present in review at A&R, and the knee rotation moment manuscript at present in review at O&C)

Data collection and analysis

Selection of studies

Two of the authors (MH and MC) will independently assess study eligibility. Excluded studies and reasons for exclusion will be listed, and disagreement is resolved by discussion and consensus.

Data extraction and management

The following data will be extracted from the selected studies

1. Study design (cohort study or RCT)
2. Country of origin
3. Number of participants
4. Demographic characteristics of the participants (ie age sex, BMI etc)

5. Disease specific characteristics of the participants (ie baseline symptoms (pain, function etc), radiographic disease severity (ie baseline Kellgren-Lawrence, Ahlback, Altman etc), knee joint alignment etc)
6. Knee joint load exposure assessment tool (ie, joint moment, compression force etc)
7. Knee joint load exposure magnitude
8. Description of the interventions (RCTs)
9. Structural disease outcomes (ie, semi-quantitative or quantitative measures on x-ray and/or MRI)

For the prospective cohort studies, data will be extracted on the estimates of the association between knee joint load exposure and structural disease progression. The cohort studies typically report prediction of structural degeneration based on baseline knee joint load exposure. The higher knee joint load exposure is compared with the lower knee joint load exposure and the results are reported as odds ratios (OR) or relative risks (RR) for each structural disease progression outcome. P-values for trends, where available, will be used to evaluate dose-response relationships.

For the RCTs we compare RRs of structural disease progression between knee joint load exposure modification and control groups.

Assessment of risk of bias in included studies

The Cochrane Collaboration’s tool for assessing risk of bias in randomized trials will apply for these particular studies (17). Risk of bias in cohort studies will be assessed in accordance with recommendations from the Center for Reviews and Dissemination at the University of York (18):

- . Is there sufficient description of the groups and the distribution of prognostic factors?
- . Are the groups assembled at a similar point in their disease progression?
- . Is the intervention/treatment reliably ascertained?
- . Were the groups comparable on all important confounding factors?
- . Was there adequate adjustment for the effects of these confounding variables?

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- . Was a dose-response relationship between intervention/joint load exposure and outcome demonstrated?
- . Was outcome assessment blind to exposure status?
- . Was follow-up long enough for the outcomes to occur?
- . What proportion of the cohort was followed-up?
- . Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Measures of treatment effect (summary measures)

We will calculate or convert the observed likelihood of progression into odds ratios (ORs) with 95% confidence intervals for each study.

Assessment of heterogeneity

We will examine heterogeneity between trials with a standard Q-test statistic (testing the hypothesis of homogeneity), and present the I^2 value, which can be interpreted as the percentage of total variation across several studies due to heterogeneity.

Data synthesis

Combining results of studies

To combine the individual study results we did meta-analyses using SAS software (version 9.2), applying a restricted maximum likelihood (REML) method to estimate the between study variance and the combined OR.

Subgroup analysis and investigation of heterogeneity

We will explore whether different types of measures for joint loading can explain some of the variation in the odds of joint deterioration.

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APPLICATION OF BRADFORD HILL CRITERIA

An algorithm of the Bradford Hill criteria will be used to systematically evaluate the evidence of a causal relationship between knee joint load exposure and structural progression of knee OA.

The following criteria will be used in the review of the retrieved prospective cohort studies:

1. *Strength of association.* Most important factor. Strong associations is defined as $RR \geq 5.0$, with lower 95% CI excluding 2.0, and statistically significant at $P < 0.05$, and in expected direction. Moderate association is defined as any statistically significant effect.
2. *Consistency across studies.* Finding of an association needs to be replicated in other studies. Consistency of knee joint load exposures is defined as $\geq 75\%$ of associations showing strong or moderate associations with structural progression.
3. *Temporality.* Refers to temporal relationship of association between exposure and outcome; exposure must precede outcome on progression. In prospective cohort studies and RCTs it is difficult (if not impossible) to ensure temporally correctness because participants in studies all are expected to walk on a daily basis and therefore are exposed to the knee joint load exposure throughout the observation periods. Although temporally correctness may be impossible to ensure and it thus could be argued that this criterion should be omitted from the present review, we retain this criterion in our assessment of causality because temporality is necessary (although not sufficiently enough in itself) to infer causation; thus absence of temporal relationship between knee joint load exposure and structural knee OA progression will preclude a causal link.
4. *Biological gradient.* When risk of progression increase (or decrease) incrementally as dose of exposure increases; provides strong evidence of causal relationship.

These 4 criteria are used to derive a causation score for each knee joint load exposure. The score is computed as the unweighted sum of the number of criteria that is met, for a possible range of 0 to 4. A score of 4 is considered strong evidence of a cause-and-effect relationship. A score of 3 is deemed to indicate moderate evidence. A score of 2 or less is considered weak evidence of causation.

A fifth criterion, *experimental evidence*, will be used to examine whether the evidence from the prospective cohort studies is consistent with that from RCTs. Experimental evidence enhances the probability of causation and this analysis may be used to up- or downgrade the computed

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causation score. RCT provide the ideal experimental study design to establish causation where randomization is the leading experimental factor that increases confidence in associations.

The following 4 criteria will be omitted

- *Coherence*. Causation is more likely if what is observed is supported by and in agreement with the natural history of the disease. This criterion is usually applied when the outcome of interest is assessed by surrogate outcomes. In the present review this criterion is omitted because it is already satisfied by default, because structural disease progression is by definition a surrogate marker of the disease.
- *Plausibility* relates to the assessment of whether the association is plausible or not. In the present review we omit this criterion because every relation can be described as plausible given that researchers always will think of an explanation once an association is observed. The knee joint load exposures selected in this review all meet plausibility criteria for probable mechanisms to explain associations.
- *Specificity* relates to the specific response to the exposure. In the present review, this criterion is omitted because the single joint load exposures are intercorrelated as are progression of degeneration in the different structures and tissues in the knee and, consequently association between a single knee joint load exposure and progression in multiple structures in the knee does not preclude a possible causal relationship.
- *Analogy* related to the possibility that existing similar association can support causation, e.g. does the same association exist for hip or hand OA, then causation may be supported. Otherwise the evidence is downgraded. This criterion is omitted because this review focuses on knee OA and because argumentation by analogy largely reflects imagination or experience of the scientist and therefore tends to subjective.

The quality of the evidence will also be communicated as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group: GRADE, presents a framework that describes both criteria for assessing the quality of research evidence and the strength of recommendations that includes considerations arising from the Bradford Hill criteria (19).

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We wish to acknowledge XXX.

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Supplementary file1: Literature Search Strategies

PubMed

1. ((knee[Title/Abstract]) OR joint, knee[MeSH Terms]) OR joints, knee[MeSH Terms]
2. ((osteoarthritis[Title/Abstract]) OR osteoarthrosis[Title/Abstract]) OR osteoarthritis[MeSH Terms]
3. (#1) AND #2
4. (((DiseaseExacerbation[Title/Abstract]) OR disease progression[MeSH Terms]) OR disease progressions[MeSH Terms]) OR disease progression[Title/Abstract]
5. (((radiography[MeSH Terms]) OR radiograph* [Title/Abstract]) OR x-ray*[Title/Abstract]) OR magneticresonance[MeSH Terms]) OR magneticresonance[Title/Abstract]
6. #4 OR #5
7. (((biomechanics[MeSH Terms]) OR biomechanic*[Title/Abstract]) OR gait[Title/Abstract]) OR walking[Title/Abstract]
8. #3 AND #6 AND #7

Scopus

1. knee (Ti-Ab-Key)
2. osteoarthritisOR osteoarthrosis(ti-ab-key)
3. progression OR worsening OR magneticresonance OR radiography OR x-ray (Ti-Ab-Key)
4. biomechanic OR gait OR walking (Ti-Ab-Key)
5. #1 AND #2 AND #3 AND #4

AMED, CINAHL, SportsDiscus

1. TI knee OR AB knee OR SU knee
2. TI osteoarthritis OR AB Osteoarthritis OR SU osteoarthritis OR AB osteoarthrosis
3. TI Progression OR AB Progression
4. TI worsening OR AB worsening
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6. TI radiography OR AB radiography
7. TI magnetic resonance OR AB magnetic resonance
8. #3 OR #4 OR #5 OR #6 OR #7
9. TI biomechanic* OR AB biomechanic*
10. TI gait OR AB gait
11. TI walking OR AB walking
12. #9 OR #10 OR #11
- 13.#1 AND #2 AND #8 AND #12

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 & Suppl. file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7



PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11 + figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12 + table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13 + table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-14 + figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 + figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-15 + Figure 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials

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Secondary Subject Heading:	Evidence based practice, Epidemiology
Keywords:	STATISTICS & RESEARCH METHODS, RHEUMATOLOGY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, EPIDEMIOLOGY

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Manuscripts

Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials

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Keywords: Meta analysis, Osteoarthritis, Gait

ABSTRACT

Objective: We performed a systematic review, meta-analysis, and assessed the evidence supporting a causal link between knee joint loading during walking and structural knee OA progression.

Design: Systematic review, meta-analysis, and application of Bradford Hill's considerations on causation.

Data Sources: We searched MEDLINE, Scopus, AMED, CINAHL, and SportsDiscus for prospective cohort studies and randomised controlled trials (RCTs) from 1950 through October 2013.

Study eligibility criteria: We selected cohort studies and RCTs in which estimates of knee joint loading during walking were used to predict structural knee OA progression assessed by X-ray or MRI.

Data analyses: Meta-analysis was performed to estimate the combined odds ratio (OR) for structural disease progression with higher baseline loading. The likelihood of a causal link between knee joint loading and OA progression was assessed from cohort studies using the Bradford Hill guidelines to derive a 0-4 causation score based on four criteria and examined for confirmation in RCTs.

Results: Of 1,078 potentially eligible articles, 5 prospective cohort studies were included. The studies included a total of 452 patients relating joint loading to disease progression over 12-72 months. There were very serious limitations associated with the methodological quality of the included studies. The combined OR for disease progression was 1.90 (95% CI: 0.85 to 4.25; I-squared = 77%) for each one-unit increment in baseline knee loading. The combined causation score was 0, indicating no causal association between knee loading and knee OA progression. No RCTs were found to confirm or refute the findings from the cohort studies.

Conclusions: There is very limited and low quality evidence to support for a causal link between knee joint loading during walking and structural progression of knee OA.

PROSPERO registration no.: CRD42012003253.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We performed the first systematic evaluation of the evidence for a causal link between mechanical loading of the knee during walking and structural progression of knee osteoarthritis.
- This systematic review, meta-analysis and causation analysis finds very limited evidence of a causal link between knee joint loading during walking and structural progression of knee osteoarthritis.
- Few studies were included in the meta-analysis since only a small number of studies have been conducted. Further research is needed.

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis affecting a large part of the population, and is a major cause of illness and disability.[1, 2] The knee joint is most frequently affected,[3] and due to the knee's crucial role in independent ambulation, knee OA leads to considerable disability affecting the individual's participation in society and independent living. Because no cure is available and so many people are affected, health care costs associated with knee OA are enormous—even higher than for more high-profile diseases such as diabetes, cancer, and cardiovascular diseases.[4] With its prevalence on the rise, knee OA poses a substantial socioeconomic and public health burden.

Walking is the most common form of human locomotion, and most people walk every day, resulting in millions of steps per year. Biomechanical loading on the knee joint during walking is estimated to exceed 2-3 times body weight;[5] thus, knee joint loading is unavoidable component of an independent lifestyle. One widely accepted theory is that higher knee joint loading during walking is causally linked with accelerated structural knee OA progression.[6-8] In accordance with this theory, unloading is advocated in an attempt to slow or halt disease progression.[9] Unspecific measures of high joint loading, such as excess body mass and Body-Mass Index (BMI), have been associated with OA development,[10, 11] and obesity is believed to act mainly through high mechanical loads,[12] although systemic effects have also been indicated.[13] However higher body mass does not necessarily lead to higher joint loading during walking,[14] and more specific measures of joint loading are necessary to apply.

Objective estimates of joint loading during walking can be obtained by 3-dimensional gait analysis. Typically, the knee adduction moment (KAM) or biomechanical modelling of

compression forces is used. The KAM has been of particular interest because it reflects the medial to lateral joint load distribution,[15] with good face validity with respect to the relative prevalence of medial, as opposed to lateral compartment, tibiofemoral knee OA.[16] Despite its common usage, a recent systematic review did not find consistent evidence that the KAM differs between those with and without knee OA.[17]

The relationship between knee joint loading during walking and knee OA has been a focus of knee OA-related biomechanical research for 10-20 years. Studies reveal that symptomatic treatment of knee OA results in increases in knee joint loads during walking,[5, 18-20] which are unwanted according to the hypothesised structural consequences of increased joint loading. This may generate confusion among researchers, clinicians, and patients, who are interested in this information to aid them in prevention, palliation, and treatment strategies. Establishing causal relationships between modifiable factors, such as knee joint loading, and disease specific measures, such as structural disease progression, is imperative in the generation of effective strategies.

Seminal epidemiological work by Hill proposed a set of considerations (the Bradford Hill criteria) to systematically evaluate the existence of a causal link between an exposure and a health outcome.[21] These criteria have been previously employed to demonstrate the causal link between smoking and lung cancer,[22] and between dietary factors and coronary heart disease,[23] and have the capacity to evaluate the link between knee joint loading and structural knee OA progression.

Therefore the objectives of this study were 1) to systematically evaluate the evidence supporting a causal link between exposure to knee joint loading during walking and structural progression of knee OA based on Hill's considerations on causality,[21] and 2) to determine

which knee joint load variables had been studied sufficiently in RCTs and found to support the findings of prospective cohort studies.

METHODS

Methods of the study search strategy, inclusion criteria, and data analysis were pre-specified in a protocol (supplementary file 1) and pre-registered (PROSPERO 2012:CRD42012003253).

We searched MEDLINE, Scopus, AMED, CINAHL, and SportsDiscus for prospective cohort studies and RCTs from 1950 through October 2013. Search strategies are available as a supplementary file 2. The reference lists of the retrieved articles were also searched for additional cohort studies and RCTs. Two reviewers (MH and MC) independently assessed study eligibility. Excluded studies and reasons for exclusion were recorded. Disagreement was resolved by discussion and consensus. We included original full-length articles pertaining to the association between knee joint loading during walking, measured by 3-dimensional gait analysis, and structural disease progression assessed quantitatively or semi-quantitatively by X-ray or MRI. We considered only studies that included subjects diagnosed with knee OA that were followed for at least 1 year (necessary because of the sensitivity of imaging and slow disease progression[24]). Cohort studies had to include estimates of knee joint loading during walking at baseline and imaging-based assessment of structural disease progression. Clinical trials had to be randomised and compare image-based structural disease progression between different knee joint loading interventions (e.g. increase vs. decrease), placebo or control.

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4 **Data extraction and analysis**
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6 The following data were extracted from the studies: 1) Study design; 2) Country of
7 origin; 3) Number of subjects; 4) Characteristics of the subjects; 5) Type of knee joint loading
8 estimate; 6) Magnitudes of the estimate; 7) Description of the interventions (if any); and 8)
9 Structural disease progression outcome (i.e., semi-quantitative or quantitative measures on x-
10 ray and/or MRI).
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12 For prospective cohort studies, we extracted estimates of the association between
13 baseline knee joint loading and structural disease progression from baseline to follow-up. A
14 progression group is typically compared to a nonprogression group at baseline and the results
15 are typically reported as odds ratios (OR) for disease progression for a one-unit higher
16 baseline knee joint loading. If no OR were reported, we either calculated it from the reported
17 data (if possible), or contacted the study authors requesting the OR. For the RCTs we aimed to
18 compare relative risks of structural disease progression between knee joint loading
19 modification and control groups.
20

21 The individual study results (i.e., log OR values and their corresponding standard errors)
22 were combined in a random effects meta-analysis model using the generic inverse variance
23 outcome type in Review Manager.[25] Heterogeneity between trials was assessed using the
24 standard Q-test statistic (testing the hypothesis of homogeneity), and we present the I² value,
25 which can be interpreted as the percentage of total variation across the studies due to
26 heterogeneity.[26]
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52 **Methodological quality and Risk of Bias assessment**
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54 The methodological quality of the cohort studies were assessed using a published check
55 list.[27] Two of the authors (MH and MWC) assessed this individually and judged each
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4 criterion to be “Adequately described”, “Unclear”, or “Inadequately described” –
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6 corresponding to “low risk of bias”, “unclear risk of bias”, and “high risk of bias”, respectively.
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8 Disagreement was resolved by discussion. If an included study was authored by one or more
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10 of the current authors, a third reviewer (HL) was asked to perform a quality assessment. One
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12 quality assessment item was omitted (“*Was a dose-response relationship between exposure and*
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14 *outcome demonstrated?*”) because this item relates to the findings of the study, not the
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16 methodological quality and assessment of dose-response forms part of the Bradford Hill
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18 criteria for causation (see below). Overall extent of risk of bias and methodological quality
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20 within each study was assessed using the GRADE approach to evaluate study limitations.[28]
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27 **Evaluation of evidence for causality**

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29 Based on the Bradford Hill considerations on causality[21] a causation score was developed
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31 and used to systematically evaluate the evidence of a causal link between knee joint loading
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33 during walking and structural progression of knee OA. A similar score has previously been
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35 derived from the Bradford Hill considerations to assess the causal relationship between
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37 dietary factors and coronary heart disease. [23] The following criteria were used in the review
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39 of the cohort studies and given a score of 1 (criterion satisfied) or 0 (criterion not satisfied):
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- 43 1. *Strength of association.* Associations quantified as a pooled OR ≥ 5.0 , with lower 95% CI
44 above 2.0; in the expected direction was defined as “strong association.” “Moderate
45 association” is defined as any statistically significant pooled OR ($P < 0.05$). A statistically
46 non-significant pooled OR was defined as “no association.”
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- 52 2. *Consistency across studies.* An association requires replication in other studies. Consistency
53 is defined as $\geq 75\%$ of associations being strong or moderate.
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3. *Temporality*. Refers to temporal relationship of association between exposure and outcome; exposure has to precede outcome. It is difficult to ensure temporal correctness because study subjects are assumed to walk daily and are therefore exposed to knee joint loading throughout observation periods. We retained this criterion because temporality is necessary to infer causation; absence of temporal relationship between exposure and outcome precludes a causal link. Our analysis accepted studies with a temporally correct design defined as baseline knee joint loading related to disease progression over time from that baseline. The temporality criterion was satisfied when temporal correctness was accepted in $\geq 75\%$ of the included studies.
4. *Biological gradient*. When rate of progression increases (or decreases) incrementally as dose of exposure increases; provides strong evidence of causal relationship. This criterion is satisfied when $\geq 75\%$ of tests for a trend pertaining to structural progression outcomes are statistically significant in the expected direction for knee joint loading.

These 4 criteria scores were used to derive one causation score for each knee joint loading variable. The scores were computed as the unweighted sum of the scores from each of the above criteria, for a possible range of 0 to 4. A score of 4 is considered strong evidence of a cause-and-effect relationship. A score of 3 is deemed to indicate moderate evidence. A score of 2 or less is considered weak evidence of causation.

A fifth criterion, *experimental evidence*, was used to examine whether the evidence from the prospective cohort studies was consistent with that from RCTs. Experimental evidence enhances the probability of causation, and may be used to up- or down-grade the calculated causation score.

The following 4 criteria were omitted:

Coherence. Causation is more likely if what is observed is supported by and in agreement with the natural history of the disease. This criterion is usually applied when the outcome is assessed by surrogate outcomes. This criterion is omitted because it is satisfied by default, because imaging modalities are surrogate outcomes.

Plausibility relates to the assessment of whether the association is plausible or not. This criterion is omitted because of the highly subjective nature of this criterion.

Specificity relates to the specific response to the exposure. This criterion is omitted because OA is a multi-structure disease; an association between knee joint loading and disease progression in multiple structures does not preclude a possible causal relationship.

Analogy relates to the possibility that existing similar association can support causation (e.g., does the same association exist for hip or hand OA? If so, causation may be supported). This criterion is omitted because this review focuses specifically on knee OA.

RESULTS

Study selection and characteristics

The search yielded 1,078 potentially eligible studies (**Figure 1**; references available as a supplementary file 3). Of those, we included 5 prospective cohort studies published between 2002 and 2013 and involving a total of 452 patients with knee OA[29-33] and 0 RCTs. The diagnostic criteria for knee OA used to determine participant inclusion in individual studies varied. The American College of Rheumatology (ACR) criteria[34] were used in one study[32], whereas a combination of clinical and radiographic signs of knee OA was used as criteria in 3 studies[29, 31, 33], and 1 study did not report the diagnostic criteria used [30]. Study characteristics are summarised in **Table 1**.

Table 1.

Summary of the characteristics of the included studies.

Author (year) country	Knee loading variable	Structural progression measure		Follow-up time	Number of patients (total/progressors/non-progressors)	Females (%)	Ref.
Miyazaki et al. (2002) Japan	Peak KAM (unit:%BW×HT)	≥1 grade according to Altman atlas	sq x-ray	72 months	74/42/32	78%	[30]
Chang et al. (2007) USA	Peak KAM (unit:%BW×HT)	≥1 grade according to Altman atlas	sq x-ray	18 months	56 (64 ^a)/41/15	59%	[31] [35] ^a
Bennell et al. (2011) Australia	Peak KAM (unit:%BW×HT)	≥1 grade medial tibiofemoral cartilage defects	sq MRI	12 months	138/45/93	56%	[29]
	KAM impulse (unit:%BW×HT)	Cartilage volume loss (mm ³)	q MRI		144/n.a./n.a.		
Woollard et al. (2011) USA	Peak KAM (unit:Nm/kg) ^b	Cartilage Volume loss (mm ³)	q MRI	12 months	13/6/7	23%	[32]
Henriksen et al. (2013) Denmark	Peak overall knee compression force (unit: N)	Cartilage loss	sq MRI	12 months	157/n.a./n.a.	89%	[33]
				Median: 12 months	Totals: 452/134/147	Mean: 67%	
BW; Body Weight; HT: Height; Sq: semi-quantitative grading, q: quantitative. ^a Upon request, the authors forwarded a conference abstract with additional data based on 64 subjects. The number of progressors/non-progressors not available from that abstract. ^b We converted the data into %BW×HT after requesting body weight and height data from the authors.							

Joint loading and structural progression measures

Four cohort studies[29-32] focused on the same knee joint loading estimate: the peak KAM. In these studies, peak KAM was assessed at baseline and related to structural medial disease progression assessed after a median of 15 months from that baseline (12-72 months). In one study,[29] the baseline KAM impulse (area under the curve) was also related to medial disease progression. In the fifth study,[33] overall knee compression loading was used as load exposure.

Two studies[30, 31] defined structural disease progression as any worsening in semi-

quantitative radiographic medial joint space grade [36]. One study[32] defined structural disease progression as any loss of medial femoral cartilage volume (quantitative MRI) above a measurement error previously established. In on study[33] structural disease progression was assessed from semi-quantitative grading of tibiofemoral cartilage loss and bone marrow lesions. In one study[29] structural progression was assessed semi-quantitatively as medial tibiofemoral cartilage loss and medial tibiofemoral bone marrow lesions, and quantitatively as medial tibial cartilage volume loss. For the meta-analysis, we extracted the association (OR) between peak KAM and semi-quantitative progression in medial tibiofemoral cartilage loss. No ORs were available for the association between KAM and cartilage volume loss because both were continuous variables. However, the linear regression analysis was extracted for the assessment of the biological gradient criteria.

Association between joint loading and progression

ORs were not reported in 3 studies,[31-33] but in[32] individual patient data were reported and an OR was calculated. We contacted the authors of,[31] asking them to provide an OR if possible. The authors returned a conference abstract including an OR published 4 years prior to the article.[35] The abstract included 64 patients in contrast to the 57 patients included in.[31] The authors could not account for the different number of subjects between the full paper and conference abstract. One study[33] grouped subjects based on changes in joint loading following weight loss (increased vs. reduced loads). There were no between group differences in structural disease progression. Due to the use of an intervention (weight loss), it was not appropriate to extract OR for baseline loading.

The ORs for structural disease progression ranged from 0.40 to 6.46 for each unit higher baseline peak KAM magnitudes. From the random effects model, the combined OR was

estimated to 1.90 (95% CI 0.85 to 4.25). The confidence in this estimate was downgraded due to heterogeneity ($I^2=77\%$). **Figure 2** summarises the individual and pooled estimates.

In,[29] the OR for progression of bone marrow lesions was 1.31 (95% CI 0.86 to 1.98) with every unit increment in baseline peak KAM; ORs for progression of cartilage defects and bone marrow lesions were 0.42 (95% CI 0.12 to 1.48) and 1.8 (95% CI 0.63 to 5.17), respectively, with every unit increment in baseline KAM impulse.

Methodological quality of the studies

One or more criteria were limited in the assessments of risk of selection, detection, and attrition biases. Individual risk assessments are presented in appendix A. Across the studies, the comparability of the groups at baseline was generally inadequately or unclearly described (selection bias). Also, descriptions of how reliably the joint load exposures were ascertained were not included in 4 of the 5 of the studies (detection bias), and group differences in loss of subjects were not accounted for (attrition bias). The discrepancy in subject numbers in reports from one cohort[31, 35], induced a high risk of selection and attrition bias. **Table 2** presents summaries of the quality assessment. Agreement between quality raters was good ($\kappa = 0.73$ (95% CI: 0.48:0.97)).

Table 2.
Summary of the quality assessment (risk of bias).

Bias type	Quality criteria	Miyazaki et al.[30]	Chang et al.[31, 35]	Bennell et al.[29]	Woollard et al.[32]	Henriksen et al.[33]
Selection	Were the descriptions of the groups and the distribution of prognostic factors sufficient?	A	I	I	A	A
	Were the groups assembled at a similar point in their disease progression?	A	I	I	A	A
	Were the groups comparable on all important confounding factors?	I	I	I	U	A
Detection	Was the joint load estimate reliably ascertained?	U	U	U	U	I
	Was adequate adjustment made for the effects of these confounding variables?	A	I	A	I	I
	Was outcome assessment blind to exposure status?	A	A	I	I	A
	Was follow-up long enough for the outcomes to occur?	A	A	A	A	A
	What proportion of the cohort was followed-up?*	U	A	U	A	A
Attrition	Were dropout rates and reasons for drop-out similar across groups?	I	I	I	A	A
Overall risk of bias		Very serious limitations; high risk of bias	Very serious limitations; high risk of bias	Very serious limitations; high risk of bias	Very serious limitations; high risk of bias	Very serious limitations; high risk of bias
Methodological quality		low	low	low	low	low
A , Adequately described; U , Unclear; I , Inadequately described. * Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate= <50% ^a Risk of bias within studies is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).						

Causality assessment

The non-significant combined OR indicates no association between knee joint load during walking and structural disease progression. Thus, a score of 0 in the *Strength of Association* criterion was assigned. The associations were not consistently replicated (50%), resulting in a

score of 0 in the *Consistency* criterion. This finding was further supported by the heterogeneity between the studies ($I^2=77\%$; **Figure 2**), and the discrepancies between baseline peak KAM magnitudes among progressors and nonprogressors across the cohorts (**Figure 3**). Temporal correctness was accepted in one cohort.[30] After requesting additional information from the authors of one cohort study,[31] we discovered that the article reports only part of the study. The additional information retrieved,[35] showed that the study consisted of 3 measurements taken every 18 months. Joint space and Kellgren-Lawrence grades (x-rays) were recorded at all 3 time points, whereas the KAM was obtained at time points 2 and 3 (18 and 36 months). KAM at time point 2 (18 months) was associated with structural disease progression from 18 to 36 months and structural disease progression from time point 1 to 2 (baseline to 18 months) was associated with increased KAM from 18 to 36 months.[35] Thus temporally correctness can not be assigned to the observed associations in this study, and the overall *Temporality* criterion was not satisfied (a 0 score). *Biological Gradient* was investigated in one cohort[29] that showed no positive association between baseline peak KAM and loss of medial tibial cartilage volume over 12 months, resulting in a score of 0. Consequently, the causation score based on the included cohort studies was 0 for the association between peak KAM during walking and structural disease progression in patients with knee OA (**Table 3**).

Table 3.

Causation criteria and scores for the identified knee joint loading exposures.

Knee joint load exposure	Strength ^a Summary or OR (95%CI)	Consistency ^b No (%)	Temporality ^c No (%)	Biological gradient ^d No (%)	Causation score (No. of criteria met)
Peak KAM	1.90 (0.85-4.25)	2/4 (50%)	1/4 (25%)	0/4 (0%)	0
KAM impulse	0.42 (0.12-1.48) ^e	- ^f	0/1 (0%)	1/1 (100%)	- ^g
Peak overall compression	No group difference	- ^f	1/1 (100%)	0/1 (0%)	- ^g

^a Strong association is defined as a pooled OR ≥ 5 with lower 95% CI excluding 2.0. Moderate association is any statistically significant association.

^b Consistency is defined as ≥ 75% of associations showing strong or moderate associations

^c In cohort studies it is difficult if not impossible to ensure temporal correctness because subjects in the studies are expected to walk daily and therefore are exposed to knee joint loading throughout the observation period. In the present analysis, the temporality criterion is satisfied in studies that relate baseline knee joint loading exposures to disease progression over time from that baseline and demonstrate a statistically significant association with structural disease progression.

^d Biological gradient is defined as demonstrated when the rate of progression increases (or decreases) incrementally as dose of exposure increases.

^e Estimate based on one cohort study[29] assessing baseline KAM impulse to progression of cartilage defects assessed by semi-quantitative grading of MRI.

^f Consistency not possible to assess with only one cohort.

^g Causality score not calculated because only one study available.

For the KAM impulse and overall knee compression loading, only one study was available for each exposure,[29, 33] and therefore no causation scores were calculated for these loading exposures.

As the systematic literature search did not identify any RCTs, the findings from the cohort studies can neither be confirmed nor refuted by experimental evidence. Hence the fifth criterion, could not be used to up- or down-grade the causation scores.

DISCUSSION

This review is the first to systematically assess—using systematic review, meta-analysis and the Bradford Hill considerations on causality—whether a causal link exists between knee joint loading during walking and structural disease progression of knee OA. The systematic literature search identified five prospective cohort studies focusing on three estimates of knee joint loading: the peak KAM, KAM impulse, and overall tibiofemoral compression force. Using a predefined algorithm, a causation score of 0 was reached, showing that there is no evidence of a causal link between knee joint loading during walking and structural progression of knee OA. Further, no experimental data from RCTs exist to support or oppose the findings from the cohort studies. One of the prospective cohort studies[33] compared increased vs. decreased loads, without demonstrating differences in structural disease progression opposing a causal link.

Indirectly supporting the present findings, a longitudinal randomised trial comparing laterally wedged insoles (previously demonstrated to reduce loading[37, 38]) with placebo insoles, showed no group differences in structural disease progression.[39] While that study seemingly provided experimental evidence, no joint load exposure data were included to document the assertion that joint loadings were in fact reduced in the “wedged insole” group. Thus, the study did not fulfill the criteria for inclusion in this review. A recent meta-analysis on symptomatic effects of laterally wedged insoles showed no beneficial effects over neutral insoles, indicating limited effects of laterally wedged insoles.[40] On the other hand, the null outcome is supported by the results in,[33] included in this review, showing neither detrimental effects of increased loading nor beneficial effects of decreased loading over 12 months in a group of knee OA patients.

The quality assessment of the included studies showed high risks of selection, detection, and attrition biases (**Table 3**). An important precondition for valid results in cohort studies is that groups should be comparable at baseline. Unless the groups are balanced for relevant baseline characteristics, differences in structural disease progression cannot confidently be attributed to the effects of interest (joint loads during walking). The included studies revealed significant inadequacies when assessing the comparability of the groups on relevant baseline characteristics, leading to prognostic imbalance. Four of the 5 cohort studies did not report how reliably the joint loading estimates were ascertained (detection bias), which could influence the individual results. Further, the loss of subjects at follow-up in 2 of the 5 cohort studies was beyond 20%, with the dropout rates and reasons for dropout across groups not adequately accounted for (attrition bias). Finally, the discrepant numbers of subjects presented in different reports from the same cohort[31, 35] introduced a serious risk of bias and low confidence in the results. The overall low methodological quality of the included studies gives little confidence in the reported estimates of causation.

Despite the shortage of studies reporting a causal link between joint loading and structural disease progression, the conjectured relationship underlies the rationale for many clinical efforts to reduce knee loading during walking in attempts to retard disease progression. Weight loss, insoles, modified footwear, strengthening exercises, knee braces, and gait modifications have been suggested as means to lower knee joint loads and thus slow structural disease progression through mechanical pathways,[41-46] with effects yet to be proven. The rationale for such efforts is diluted by the present results, not only by the low causality score, but also by the inconsistency across studies in the loading magnitudes between individuals that progress and those that do not. **Figure 3** illustrates that patients with a certain baseline peak KAM magnitude in one study progress, whereas patients with

similar baseline peak KAM magnitudes in other studies do not progress. These differences in knee joint loading magnitudes between studies may be due to differences in gait analysis protocols across the involved gait labs, for example in the selection of reference frame convention for the calculation of the KAM[47] and footwear condition.[44] However, including diversity of measures of the same variable can strengthen the confidence in the results of a systematic review.

The results from the included studies exhibited a high degree of heterogeneity (I^2 from the meta-analysis) (**Figure 2**). The two cohorts with significant OR[30, 31, 35] both used radiography as the structural outcome assessment, whereas the studies reporting nonsignificant ORs used MRI.[29, 32] Further, the two studies reporting significant associations had longer follow-up periods (72 and 18 months), whereas the studies without significant associations assessed disease progression after 12 months. This concurrence of follow-up time and imaging modality precludes conclusions about whether the differences in results are based on follow-up time or imaging modality. Radiography is the current clinical gold standard for assessing structural disease progression, but it has low temporal sensitivity, making long follow-up times necessary. MRI—with its shorter temporal sensitivity—is possibly the more promising tool for assessing single structures and should be used in studies with longer follow-up times. The total number of patients was 452 in five cohorts. That is a very small number of patients when considering the large population and when compared to similar reviews in other chronic diseases. For instance, a recent review of the causal relationship between dietary factors and coronary heart disease included several millions individuals in 361 cohorts and a multitude of dietary exposures.[23]

Our study has strengths because we undertook several measures to minimise bias, restricting our review to studies with the strongest causal inference (cohort studies and

RCTs), conducted independent assessments of study eligibility, and using predefined criteria to evaluate causation and methodological quality. We may be criticised for using arbitrary OR cut-offs to define strong and moderate association, but identifying the true cut-off for defining clinically meaningful OR values is impossible in a field that has so few longitudinal studies to consult. An important limitation is the causality score that applied. The score is a modification of a previous similar score,[23] thus it has limited empirical evidence to support its validity. Also, the causality score omitted several of the original causation considerations as proposed by Hill,[21] yet the applied method was pre-specified. We may also be criticised for analysing any image-based structural deterioration, rather than separating the analyses in x-ray and MRI-based assessments. However, the analysis plans were also pre-specified, without prior knowledge of the number of studies and specifics of the outcomes.

Current guidelines on interpretation of data from observational studies and data combined from repeated observational studies (with a reasonable internal validity) would correspond to confidence in the estimate's being "Low-quality evidence", but could be upgraded if there is great confidence in the estimates and the effects are large.[48] However, the present analysis revealed a large inconsistency among study results, poor precision of the combined analysis, and low methodological quality. Thus, we downgraded further to "*very low quality evidence*". The inconsistency of the available studies may limit the appropriateness of meta-analyses, yet support the overall conclusion of this systematic literature review.

In conclusion, our systematic review, meta-analyses, and application of Bradford Hill's considerations on causation shows that there is no evidence of a causal link between estimates of knee joint loading during walking and structural progression of knee OA. Future large well designed prospective cohorts with subsequent confirmation from randomised trials are strongly recommended. The current study findings question the rationale behind clinical

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4 efforts to reduce knee joint loading during walking as such efforts are currently supported by
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6 very low-quality evidence showing no causal link between knee joint loading during walking
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8 and progression of knee OA.
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COMPETING INTEREST

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AUTHOR CONTRIBUTIONS

MH, MWC, HL, CJ, and RC were responsible for study concept and design. RC and MH supervised the study. HL and CJ performed the literature search. MH and MWC acquired the data, which was analysed and interpreted by MH, MWC, CJ, HL, and RC. MH drafted the manuscript, which was critically revised for important intellectual content by MWC, HL, CJ, and RC. RC did the statistical analysis. MH is the guarantor.

ETHICAL APPROVAL

Not required.

DATA SHARING

Details of the literature search, the search results, and reasons for exclusion are available from the corresponding author at robin.christensen@frh.regionh.dk.

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FIGURE LEGENDS

Figure 1

Flowchart of the literature selection process.

Figure 2

Forest plot of the individual ORs of structural disease progression with every increment in baseline peak knee adduction moment. Weights are from a random effects analysis. Individual and pooled estimates are shown with 95% confidence intervals.

Figure 3

The mean baseline KAM knee joint load exposures in patients with and without structural disease progression from the four individual cohorts. Note the overlap between progressors and non-progressors in the different studies. Error bars: 95% CI.

SUPPLEMENTARY FILES

- 1: Study protocol
- 2: Literature search protocol
- 3: List of the literature found

Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials

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ABSTRACT

Objective: We performed a systematic review, meta-analysis, and ~~causation analysis to~~ assessed the evidence supporting a causal link between knee joint loading during walking and structural knee OA progression.

Design: Systematic review, meta-analysis, and application of Bradford Hill's ~~criteria for~~ considerations on causation.

Data Sources: We searched MEDLINE, Scopus, AMED, CINAHL, and SportsDiscus for prospective cohort studies and randomised controlled trials (RCTs) from 1950 through October 2013.

Study eligibility criteria: We selected cohort studies and RCTs in which estimates of knee joint loading during walking were used to predict structural knee OA progression assessed by X-ray or MRI.

Data analyses: Meta-analysis was performed to estimate the combined odds ratio (OR) for structural disease progression with higher baseline loading. The likelihood of a causal link between knee joint loading and OA progression was assessed from cohort studies using the Bradford Hill guidelines to derive a 0-4 causation score based on four criteria and examined for confirmation in RCTs.

Results: Of 1,078 potentially eligible articles, 5 prospective cohort studies were included. The studies included a total of 452 patients relating joint loading to disease progression over 12-72 months. There were very serious limitations associated with the methodological quality of the included studies. The combined OR for disease progression was 1.90 (95% CI: 0.85 to 4.25; I-squared = 77%) for each one-unit increment in baseline knee loading. The combined causation score was 0, indicating no causal association between knee loading and knee OA progression. No RCTs were found to confirm or refute the findings from the cohort studies.

Conclusions: There is very limited and low quality evidence to support for a causal link between knee joint loading during walking and structural progression of knee OA.

PROSPERO registration no.: CRD42012003253.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We performed the first systematic evaluation of the evidence for a causal link between mechanical loading of the knee during walking and structural progression of knee osteoarthritis.
- This systematic review, meta-analysis and causation analysis finds very limited evidence of a causal link between knee joint loading during walking and structural progression of knee osteoarthritis.
- Few studies were included in the meta-analysis since only a small number of studies have been conducted. Further research is needed.

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis affecting a large part of the population, and is a major cause of illness and disability.[1, 2] The knee joint is most frequently affected,[3] and due to the knee's crucial role in independent ambulation, knee OA leads to considerable disability affecting the individual's participation in society and independent living. Because no cure is available and so many people are affected, health care costs associated with knee OA are enormous—even higher than for more high-profile diseases such as diabetes, cancer, and cardiovascular diseases.[4] With its prevalence on the rise, knee OA poses a substantial socioeconomic and public health burden.

Walking is the most common form of human locomotion, and most people walk every day, resulting in millions of steps per year. Biomechanical loading on the knee joint during walking is estimated to exceed 2-3 times body weight;[5] thus, knee joint loading is unavoidable component of an independent lifestyle. One widely accepted theory is that higher knee joint loading during walking is causally linked with accelerated structural knee OA progression.[6-8] In accordance with this theory, unloading is advocated in an attempt to slow or halt disease progression.[9] Unspecific measures of high joint loading, such as excess body mass and Body-Mass Index (BMI), have been associated with OA development,[10, 11] and obesity is believed to act mainly through high mechanical loads,[12] although systemic effects have also been indicated.[13] However higher body mass does not necessarily lead to higher joint loading during walking,[14] and more specific measures of joint loading are necessary to apply.

Objective estimates of joint loading during walking can be obtained by 3-dimensional gait analysis. Typically, the knee adduction moment (KAM) or biomechanical modelling of

compression forces is used. The KAM has been of particular interest because it reflects the medial to lateral joint load distribution,[15] with good face validity with respect to the relative prevalence of medial, as opposed to lateral compartment, tibiofemoral knee OA.[16] Despite its common usage, a recent systematic review did not find consistent evidence that the KAM differs between those with and without knee OA.[17]

The relationship between knee joint loading during walking and knee OA has been a focus of knee OA-related biomechanical research for 10-20 years. Studies reveal that symptomatic treatment of knee OA results in increases in knee joint loads during walking,[5, 18-20] which are unwanted according to the hypothesised structural consequences of increased joint loading. This may generate confusion among researchers, clinicians, and patients, who are interested in this information to aid them in prevention, palliation, and treatment strategies. Establishing causal relationships between modifiable factors, such as knee joint loading, and disease specific measures, such as structural disease progression, is imperative in the generation of effective strategies.

Seminal epidemiological work by Hill proposed a set of criteria considerations (the Bradford Hill criteria) to systematically evaluate the existence of a causal link between an exposure and a health outcome.[21] These criteria have been previously employed to demonstrate the causal link between smoking and lung cancer,[22] and between dietary factors and coronary heart disease,[23] and have the capacity to evaluate the link between knee joint loading and structural knee OA progression.

Therefore the objectives of this study were 1) to systematically evaluate the evidence supporting a causal link between exposure to knee joint loading during walking and structural progression of knee OA using based on Hill's considerations on causality, [21] the Bradford Hill

criteria, and 2) to determine which knee joint load variables had been studied sufficiently in RCTs and found to support the findings of prospective cohort studies.

METHODS

Methods of the study search strategy, inclusion criteria, and data analysis were pre-specified in a protocol (supplementary file 1) and pre-registered (PROSPERO 2012:CRD42012003253).

We searched MEDLINE, Scopus, AMED, CINAHL, and SportsDiscus for prospective cohort studies and RCTs from 1950 through October 2013. Search strategies are available as a supplementary file 2. The reference lists of the retrieved articles were also searched for additional cohort studies and RCTs. Two reviewers (MH and MC) independently assessed study eligibility. Excluded studies and reasons for exclusion were recorded. Disagreement was resolved by discussion and consensus. We included original full-length articles pertaining to the association between knee joint loading during walking, measured by 3-dimensional gait analysis, and structural disease progression assessed quantitatively or semi-quantitatively by X-ray or MRI. We considered only studies that included subjects diagnosed with knee OA that were followed for at least 1 year (necessary because of the sensitivity of imaging and slow disease progression[24]). Cohort studies had to include estimates of knee joint loading during walking at baseline and imaging-based assessment of structural disease progression. Clinical trials had to be randomised and compare image-based structural disease progression between different knee joint loading interventions (e.g. increase vs. decrease), placebo or control.

Data extraction and analysis

The following data were extracted from the studies: 1) Study design; 2) Country of origin; 3) Number of subjects; 4) Characteristics of the subjects; 5) Type of knee joint loading estimate; 6) Magnitudes of the estimate; 7) Description of the interventions (if any); and 8) Structural disease progression outcome (i.e., semi-quantitative or quantitative measures on x-ray and/or MRI).

For prospective cohort studies, we extracted estimates of the association between baseline knee joint loading and structural disease progression from baseline to follow-up. A progression group is typically compared to a nonprogression group at baseline and the results are typically reported as odds ratios (OR) for disease progression for a one-unit higher baseline knee joint loading. If no OR were reported, we either calculated it from the reported data (if possible), or contacted the study authors requesting the OR. For the RCTs we aimed to compare relative risks of structural disease progression between knee joint loading modification and control groups.

The individual study results (i.e., log OR values and their corresponding standard errors) were combined in a random effects meta-analysis model using the generic inverse variance outcome type in Review Manager.[25] Heterogeneity between trials was assessed using the standard Q-test statistic (testing the hypothesis of homogeneity), and we present the I² value, which can be interpreted as the percentage of total variation across the studies due to heterogeneity.[26] ~~Stratified (meta-regression) analyses were performed using SAS software (version 9.2), applying a restricted maximum likelihood (REML) method to estimate the between-study variance and the combined OR.~~

Methodological quality and Risk of Bias assessment

The methodological quality of the cohort studies were assessed using a published check list.[27] Two of the authors (MH and MWC) assessed this individually and judged each criterion to be “Adequately described”, “Unclear”, or “Inadequately described” corresponding to “low risk of bias”, “unclear risk of bias”, and “high risk of bias”, respectively. Disagreement was resolved by discussion. If an included study was authored by one or more of the current authors, a third reviewer (HL) was asked to perform a quality assessment. One quality assessment item was omitted (“*Was a dose-response relationship between exposure and outcome demonstrated?*”) because this item relates to the findings of the study, not the methodological quality and assessment of dose-response forms part of the Bradford Hill criteria for causation (see below). Overall extent of risk of bias and methodological quality within each study was assessed using the GRADE approach to evaluate study limitations.[28]

Evaluation of evidence for causality

Based on A modified algorithm of the Bradford Hill criteria considerations on causality[21] a causation score was developed and used to systematically evaluate the evidence of a causal link between knee joint loading during walking and structural progression of knee OA. A similar score has previously been derived from the Bradford Hill considerations to assess the causal relationship between dietary factors and coronary heart disease. [23] The following criteria were used in the review of the cohort studies and given a score of 1 (criterion satisfied) or 0 (criterion not satisfied):

1. *Strength of association.* Associations quantified as a pooled OR ≥ 5.0 , with lower 95% CI above 2.0, and statistically significant ($P < 0.05$); in the expected direction was defined as “strong association.” “Moderate association” is defined as any statistically significant

pooled OR ($P<0.05$). A statistically non-significant pooled OR was defined as “no association.”

2. *Consistency across studies.* An association requires replication in other studies. Consistency is defined as $\geq 75\%$ of associations being strong or moderate.
3. *Temporality.* Refers to temporal relationship of association between exposure and outcome; exposure has to precede outcome. It is difficult to ensure temporal correctness because study subjects are assumed to walk daily and are therefore exposed to knee joint loading throughout observation periods. We retained this criterion because temporality is necessary to infer causation; absence of temporal relationship between exposure and outcome precludes a causal link. Our analysis accepted studies with a temporally correct design defined as baseline knee joint loading related to disease progression over time from that baseline. The temporality criterion was satisfied when temporal correctness was accepted in $\geq 75\%$ of the included studies.
4. *Biological gradient.* When rate of progression increases (or decreases) incrementally as dose of exposure increases; provides strong evidence of causal relationship. This criterion is satisfied when $\geq 75\%$ of tests for a trend pertaining to structural progression outcomes are statistically significant in the expected direction for knee joint loading.

These 4 criteria scores were used to derive one causation score for each knee joint loading variable. The scores were computed as the unweighted sum of the scores from each of the above criteria, for a possible range of 0 to 4. A score of 4 is considered strong evidence of a cause-and-effect relationship. A score of 3 is deemed to indicate moderate evidence. A score of 2 or less is considered weak evidence of causation.

A fifth criterion, *experimental evidence*, was used to examine whether the evidence from the prospective cohort studies was consistent with that from RCTs. Experimental evidence enhances the probability of causation, and may be used to up- or down-grade the calculated causation score.

The following 4 criteria were omitted:

Coherence. Causation is more likely if what is observed is supported by and in agreement with the natural history of the disease. This criterion is usually applied when the outcome is assessed by surrogate outcomes. This criterion is omitted because it is satisfied by default, because imaging modalities are surrogate outcomes.

Plausibility relates to the assessment of whether the association is plausible or not. This criterion is omitted because of the highly subjective nature of this criterion.

Specificity relates to the specific response to the exposure. This criterion is omitted because OA is a multi-structure disease; an association between knee joint loading and disease progression in multiple structures does not preclude a possible causal relationship.

Analogy relates to the possibility that existing similar association can support causation (e.g., does the same association exist for hip or hand OA? If so, causation may be supported). This criterion is omitted because this review focuses specifically on knee OA.

RESULTS

Study selection and characteristics

The search yielded 1,078 potentially eligible studies (**Figure 1**; references available as a supplementary file 3). Of those, we included 5 prospective cohort studies published between 2002 and 2013 and involving a total of 452 patients with knee OA[29-33] and 0 RCTs. The diagnostic criteria for knee OA used to determine participant inclusion in individual studies varied. The American College of Rheumatology (ACR) criteria[34] were used in one study[32], whereas a combination of clinical and radiographic signs of knee OA was used as criteria in 3 studies[29, 31, 33], and 1 study did not report the diagnostic criteria used [30]. Study characteristics are summarised in **Table 1**.

Table 1.

Summary of the characteristics of the included studies.

Author (year) country	Knee loading variable	Structural progression measure		Follow-up time	Number of patients (total/progressors/non-progressors)	Females (%)	Ref.
Miyazaki et al. (2002) Japan	Peak KAM (unit:%BW×HT)	≥1 grade according to Altman atlas	sq x-ray	72 months	74/42/32	78%	[30]
Chang et al. (2007) USA	Peak KAM (unit:%BW×HT)	≥1 grade according to Altman atlas	sq x-ray	18 months	56 (64 ^a)/41/15	59%	[31] [35] ^a
Bennell et al. (2011) Australia	Peak KAM (unit:%BW×HT)	≥1 grade medial tibiofemoral cartilage defects	sq MRI	12 months	138/45/93	56%	[29]
	KAM impulse (unit:%BW×HT)	Cartilage volume loss (mm ³)	q MRI		144/n.a./n.a.		
Woollard et al. (2011) USA	Peak KAM (unit:Nm/kg) ^b	Cartilage Volume loss (mm ³)	q MRI	12 months	13/6/7	23%	[32]
Henriksen et al. (2013) Denmark	Peak overall knee compression force (unit: N)	Cartilage loss	sq MRI	12 months	157/n.a./n.a.	89%	[33]
				Median: 12 months	Totals: 452/134/147	Mean: 67%	
BW; Body Weight; HT: Height; Sq: semi-quantitative grading, q: quantitative. ^a Upon request, the authors forwarded a conference abstract with additional data based on 64 subjects. The number of progressors/non-progressors not available from that abstract. ^b We converted the data into %BW×HT after requesting body weight and height data from the authors.							

Joint loading and structural progression measures

Four cohort studies[29-32] focused on the same knee joint loading estimate: the peak KAM. In these studies, peak KAM was assessed at baseline and related to structural medial disease progression assessed after a median of 15 months from that baseline (12-72 months). In one study,[29] the baseline KAM impulse (area under the curve) was also related to medial disease progression. In the fifth study,[33] overall knee compression loading was used as load exposure.

Two studies[30, 31] defined structural disease progression as any worsening in semi-

quantitative radiographic medial joint space grade [36]. One study[32] defined structural disease progression as any loss of medial femoral cartilage volume (quantitative MRI) above a measurement error previously established. In on study[33] structural disease progression was assessed from semi-quantitative grading of tibiofemoral cartilage loss and bone marrow lesions. In one study[29] structural progression was assessed semi-quantitatively as medial tibiofemoral cartilage loss and medial tibiofemoral bone marrow lesions, and quantitatively as medial tibial cartilage volume loss. For the meta-analysis, we extracted the association (OR) between peak KAM and semi-quantitative progression in medial tibiofemoral cartilage loss. No ORs were available for the association between KAM and cartilage volume loss because both were continuous variables. However, the linear regression analysis was extracted for the assessment of the biological gradient criteria.

Association between joint loading and progression

ORs were not reported in 3 studies,[31-33] but in[32] individual patient data were reported and an OR was calculated. We contacted the authors of,[31] asking them to provide an OR if possible. The authors returned a conference abstract including an OR published 4 years prior to the article.[35] The abstract included 64 patients in contrast to the 57 patients included in.[31] The authors could not account for the different number of subjects between the full paper and conference abstract. One study[33] grouped subjects based on changes in joint loading following weight loss (increased vs. reduced loads). There were no between group differences in structural disease progression. Due to the use of an intervention (weight loss), it was not appropriate to extract OR for baseline loading.

The ORs for structural disease progression ranged from 0.40 to 6.46 for each unit higher baseline peak KAM magnitudes. From the random effects model, the combined OR was

estimated to 1.90 (95% CI 0.85 to 4.25). The confidence in this estimate was downgraded due to heterogeneity ($I^2=77\%$). **Figure 2** summarises the individual and pooled estimates.

In,[29] the OR for progression of bone marrow lesions was 1.31 (95% CI 0.86 to 1.98) with every unit increment in baseline peak KAM; ORs for progression of cartilage defects and bone marrow lesions were 0.42 (95% CI 0.12 to 1.48) and 1.8 (95% CI 0.63 to 5.17), respectively, with every unit increment in baseline KAM impulse.

Methodological quality of the studies

One or more criteria were limited in the assessments of risk of selection, detection, and attrition biases. Individual risk assessments are presented in appendix A. Across the studies, the comparability of the groups at baseline was generally inadequately or unclearly described (selection bias). Also, descriptions of how reliably the joint load exposures were ascertained were not included in 4 of the 5 of the studies (detection bias), and group differences in loss of subjects were not accounted for (attrition bias). The discrepancy in subject numbers in reports from one cohort[31, 35], induced a high risk of selection and attrition bias. **Table 2** presents summaries of the quality assessment. Agreement between quality raters was good ($\kappa = 0.73$ (95% CI: 0.48:0.97)).

Table 2.
Summary of the quality assessment (risk of bias).

Bias type	Quality criteria	Miyazaki et al.[30]	Chang et al.[31, 35]	Bennell et al.[29]	Woollard et al.[32]	Henriksen et al.[33]
Selection	Were the descriptions of the groups and the distribution of prognostic factors sufficient?	A	I	I	A	A
	Were the groups assembled at a similar point in their disease progression?	A	I	I	A	A
	Were the groups comparable on all important confounding factors?	I	I	I	U	A
Detection	Was the joint load estimate reliably ascertained?	U	U	U	U	I
	Was adequate adjustment made for the effects of these confounding variables?	A	I	A	I	I
	Was outcome assessment blind to exposure status?	A	A	I	I	A
	Was follow-up long enough for the outcomes to occur?	A	A	A	A	A
	What proportion of the cohort was followed-up?*	U	A	U	A	A
Attrition	Were dropout rates and reasons for drop-out similar across groups?	I	I	I	A	A
Overall risk of bias		Very serious limitations; high risk of bias	Very serious limitations; high risk of bias	Very serious limitations; high risk of bias	Very serious limitations; high risk of bias	Very serious limitations; high risk of bias
Methodological quality		low	low	low	low	low
A, Adequately described; U, Unclear; I, Inadequately described. * Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate= <50% ^a Risk of bias within studies is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).						

Causality assessment

The non-significant combined OR indicates no association between knee joint load during walking and structural disease progression. Thus, a score of 0 in the *Strength of Association* criterion was assigned. The associations were not consistently replicated (50%), resulting in a

score of 0 in the *Consistency* criterion. This finding was further supported by the heterogeneity between the studies ($I^2=77\%$; **Figure 2**), and the discrepancies between baseline peak KAM magnitudes among progressors and nonprogressors across the cohorts (**Figure 3**). Temporal correctness was accepted in one cohort.[30] After requesting additional information from the authors of one cohort study,[31] we discovered that the article reports only part of the study. The additional information retrieved,[35] showed that the study consisted of 3 measurements taken every 18 months. Joint space and Kellgren-Lawrence grades (x-rays) were recorded at all 3 time points, whereas the KAM was obtained at time points 2 and 3 (18 and 36 months). KAM at time point 2 (18 months) was associated with structural disease progression from 18 to 36 months and structural disease progression from time point 1 to 2 (baseline to 18 months) was associated with increased KAM from 18 to 36 months.[35] Thus temporally correctness can not be assigned to the observed associations in this study, and the overall *Temporality* criterion was not satisfied (a 0 score). *Biological Gradient* was investigated in one cohort[29] that showed no positive association between baseline peak KAM and loss of medial tibial cartilage volume over 12 months, resulting in a score of 0. Consequently, the causation score based on the included cohort studies was 0 for the association between peak KAM during walking and structural disease progression in patients with knee OA (**Table 3**).

Table 3.

~~Bradford Hill~~Causation criteria and ~~the causation~~ scores for the identified knee joint loading exposures.

Knee joint load exposure	Strength ^a Summary or OR (95%CI)	Consistency ^b No (%)	Temporality ^c No (%)	Biological gradient ^d No (%)	Causation score (No. of criteria met)
Peak KAM	1.90 (0.85-4.25)	2/4 (50%)	1/4 (25%)	0/4 (0%)	0
KAM impulse	0.42 (0.12-1.48) ^e	- ^f	0/1 (0%)	1/1 (100%)	- ^g
Peak overall compression	No group difference	- ^f	1/1 (100%)	0/1 (0%)	- ^g

^a Strong association is defined as a pooled OR ≥ 5 with lower 95% CI excluding 2.0. Moderate association is any statistically significant association.
^b Consistency is defined as ≥ 75% of associations showing strong or moderate associations
^c In cohort studies it is difficult if not impossible to ensure temporal correctness because subjects in the studies are expected to walk daily and therefore are exposed to knee joint loading throughout the observation period. In the present analysis, the temporality criterion is satisfied in studies that relate baseline knee joint loading exposures to disease progression over time from that baseline and demonstrate a statistically significant association with structural disease progression.
^d Biological gradient is defined as demonstrated when the rate of progression increases (or decreases) incrementally as dose of exposure increases.
^e Estimate based on one cohort study[29] assessing baseline KAM impulse to progression of cartilage defects assessed by semi-quantitative grading of MRI.
^f Consistency not possible to assess with only one cohort.
^g Causality score not calculated because only one study available.

For the KAM impulse and overall knee compression loading, only one study was available for each exposure,[29, 33] and therefore no causation scores were calculated for these loading exposures.

As the systematic literature search did not identify any RCTs, the findings from the cohort studies can neither be confirmed nor refuted by experimental evidence. Hence the fifth criterion, could not be used to up- or down-grade the causation scores.

DISCUSSION

This review is the first to systematically assess—using systematic review, meta-analysis and the Bradford Hill ~~criteria for~~considerations on evidence for causality—whether a causal link exists between knee joint loading during walking and structural disease progression of knee OA. The systematic literature search identified five prospective cohort studies focusing on three estimates of knee joint loading: the peak KAM, KAM impulse, and overall tibiofemoral compression force. Using a predefined algorithm, a causation score of 0 was reached, ~~indicating showing that there is no evidence of a~~ causal link between knee joint loading during walking and structural progression of knee OA. Further, no experimental data from RCTs exist to support or oppose the findings from the cohort studies. One of the prospective cohort studies[33] compared increased vs. decreased loads, without demonstrating differences in structural disease progression opposing a causal link.

Indirectly supporting the present findings, a longitudinal randomised trial comparing laterally wedged insoles (previously demonstrated to reduce loading[37, 38]) with placebo insoles, showed no group differences in structural disease progression.[39] While that study seemingly provided experimental evidence, no joint load exposure data were included to document the assertion that joint loadings were in fact reduced in the “wedged insole” group. Thus, the study did not fulfill the criteria for inclusion in this review. A recent meta-analysis on symptomatic effects of laterally wedged insoles showed no beneficial effects over neutral insoles, indicating limited effects of laterally wedged insoles.[40] On the other hand, the null outcome is supported by the results in,[33] included in this review, showing neither detrimental effects of increased loading nor beneficial effects of decreased loading over 12 months in a group of knee OA patients.

The quality assessment of the included studies showed high risks of selection, detection, and attrition biases (**Table 3**). An important precondition for valid results in cohort studies is that groups should be comparable at baseline. Unless the groups are balanced for relevant baseline characteristics, differences in structural disease progression cannot confidently be attributed to the effects of interest (joint loads during walking). The included studies revealed significant inadequacies when assessing the comparability of the groups on relevant baseline characteristics, leading to prognostic imbalance. Four of the 5 cohort studies did not report how reliably the joint loading estimates were ascertained (detection bias), which could influence the individual results. Further, the loss of subjects at follow-up in 2 of the 5 cohort studies was beyond 20%, with the dropout rates and reasons for dropout across groups not adequately accounted for (attrition bias). Finally, the discrepant numbers of subjects presented in different reports from the same cohort[31, 35] introduced a serious risk of bias and low confidence in the results. The overall low methodological quality of the included studies gives little confidence in the reported estimates of causation.

Despite the shortage of studies reporting a causal link between joint loading and structural disease progression, the conjectured relationship underlies the rationale for many clinical efforts to reduce knee loading during walking in attempts to retard disease progression. Weight loss, insoles, modified footwear, strengthening exercises, knee braces, and gait modifications have been suggested as means to lower knee joint loads and thus slow structural disease progression through mechanical pathways,[41-46] with effects yet to be proven. The rationale for such efforts is diluted by the present results, not only by the low causality score, but also by the inconsistency across studies in the loading magnitudes between individuals that progress and those that do not. **Figure 3** illustrates that patients with a certain baseline peak KAM magnitude in one study progress, whereas patients with

similar baseline peak KAM magnitudes in other studies do not progress. These differences in knee joint loading magnitudes between studies may be due to differences in gait analysis protocols across the involved gait labs, for example in the selection of reference frame convention for the calculation of the KAM[47] and footwear condition.[44] However, including diversity of measures of the same variable can strengthen the confidence in the results of a systematic review.

The results from the included studies exhibited a high degree of heterogeneity (I^2 from the meta-analysis) (**Figure 2**). The two cohorts with significant OR[30, 31, 35] both used radiography as the structural outcome assessment, whereas the studies reporting nonsignificant ORs used MRI.[29, 32] Further, the two studies reporting significant associations had longer follow-up periods (72 and 18 months), whereas the studies without significant associations assessed disease progression after 12 months. This concurrence of follow-up time and imaging modality precludes conclusions about whether the differences in results are based on follow-up time or imaging modality. Radiography is the current clinical gold standard for assessing structural disease progression, but it has low temporal sensitivity, making long follow-up times necessary. MRI—with its shorter temporal sensitivity—is possibly the more promising tool for assessing single structures and should be used in studies with longer follow-up times. The total number of patients was 452 in five cohorts. That is a very small number of patients when considering the large population and when compared to similar reviews in other chronic diseases. For instance, a recent review of the causal relationship between dietary factors and coronary heart disease included several millions individuals in 361 cohorts and a multitude of dietary exposures.[23]

Our study has strengths because we undertook several measures to minimise bias, restricting our review to studies with the strongest causal inference (cohort studies and

RCTs), conducted independent assessments of study eligibility, and using predefined criteria to evaluate causation and methodological quality. We may be criticised for using arbitrary OR cut-offs to define strong and moderate association, but identifying the true cut-off for defining clinically meaningful OR values is impossible in a field that has so few longitudinal studies to consult. An important limitation is the causality score that applied. The score is a modification of a previous similar score,[23] thus it has limited empirical evidence to support its validity. Also, the causality score omitted several of the original ~~criteria~~ causation considerations as proposed by Hill,[21], yet the applied method was pre-specified. We may also be criticised for analysing any image-based structural deterioration, rather than separating the analyses in x-ray and MRI-based assessments. However, the analysis plans were also pre-specified, without prior knowledge of the number of studies and specifics of the outcomes.

Current guidelines on interpretation of data from observational studies and data combined from repeated observational studies (with a reasonable internal validity) would correspond to confidence in the estimate's being "Low-quality evidence", but could be upgraded if there is great confidence in the estimates and the effects are large.[48] However, the present analysis revealed a large inconsistency among study results, poor precision of the combined analysis, and low methodological quality. Thus, we downgraded further to "*very low quality evidence*". The inconsistency of the available studies may limit the appropriateness of meta-analyses, yet support the overall conclusion of this systematic literature review.

In conclusion, our systematic review, meta-analyses, and application of Bradford Hill's ~~criteria for~~ considerations on causation shows that there is no evidence of a ~~indicates no~~ causal link between estimates of knee joint loading during walking and structural progression of knee OA. Future large well designed prospective cohorts with subsequent confirmation from randomised trials are strongly recommended. The current study findings question the

rationale behind clinical efforts to reduce knee joint loading during walking as such efforts are currently supported by very low-quality evidence showing no causal link between knee joint loading during walking and progression of knee OA.

COMPETING INTEREST

None declared.

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AUTHOR CONTRIBUTIONS

MH, MWC, HL, CJ, and RC were responsible for study concept and design. RC and MH supervised the study. HL and CJ performed the literature search. MH and MWC acquired the data, which was analysed and interpreted by MH, MWC, CJ, HL, and RC. MH drafted the manuscript, which was critically revised for important intellectual content by MWC, HL, CJ, and RC. RC did the statistical analysis. MH is the guarantor.

ETHICAL APPROVAL

Not required.

DATA SHARING

Details of the literature search, the search results, and reasons for exclusion are available from the corresponding author at robin.christensen@frh.regionh.dk.

For peer review only

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FIGURE LEGENDS

Figure 1

Flowchart of the literature selection process.

Figure 2

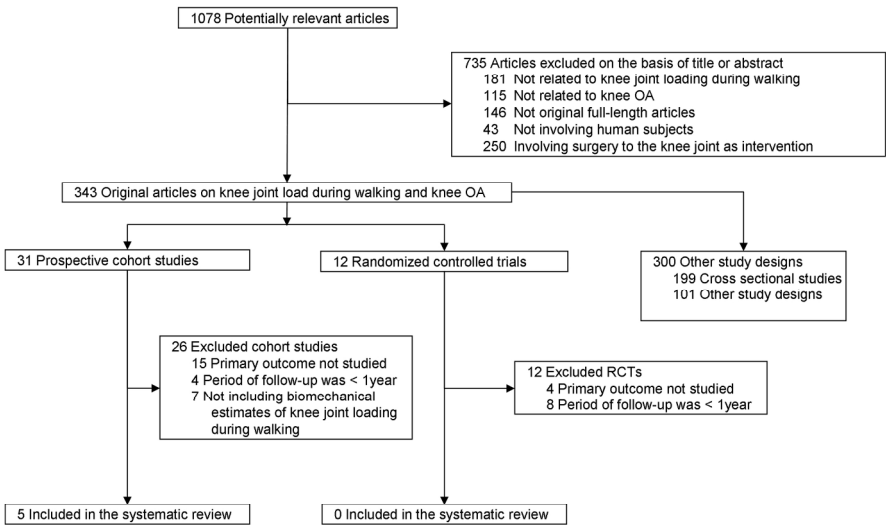
Forest plot of the individual ORs of structural disease progression with every increment in baseline peak knee adduction moment. Weights are from a random effects analysis. Individual and pooled estimates are shown with 95% confidence intervals.

Figure 3

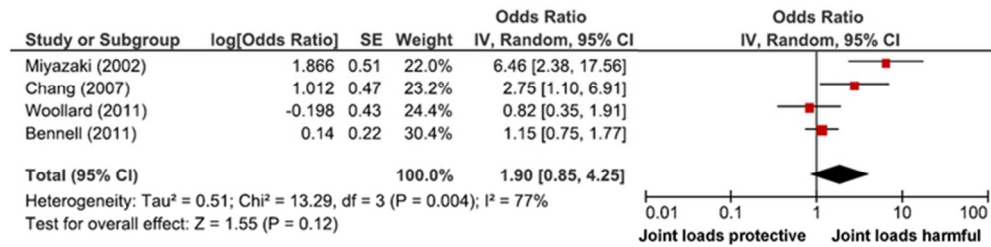
The mean baseline KAM knee joint load exposures in patients with and without structural disease progression from the four individual cohorts. Note the overlap between progressors and non-progressors in the different studies. Error bars: 95% CI.

SUPPLEMENTARY FILES

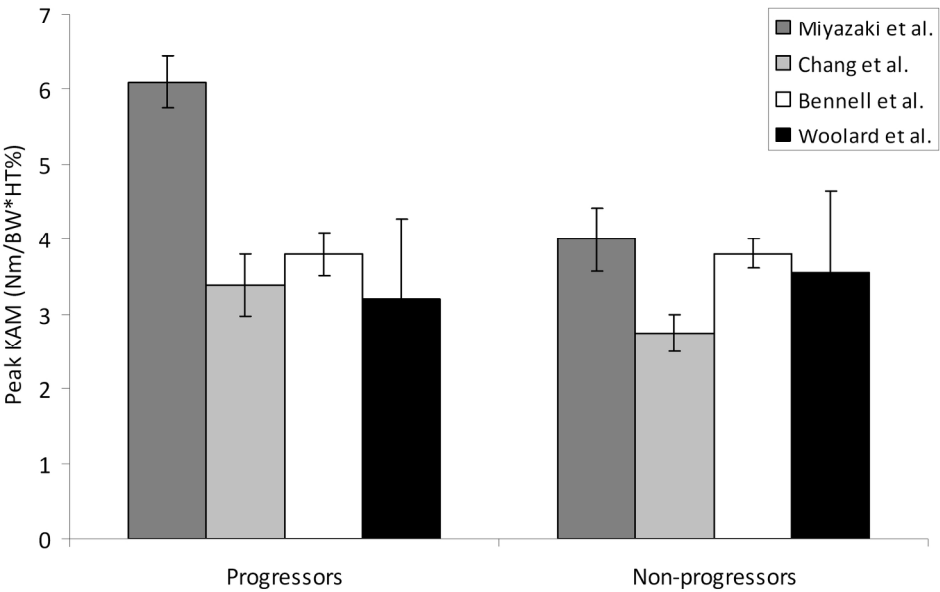
- 1: Study protocol
- 2: Literature search protocol
- 3: List of the literature found



Flowchart of the literature selection process.
190x142mm (300 x 300 DPI)



Forest plot of the individual ORs of structural disease progression with every increment in baseline peak knee adduction moment. Weights are from a random effects analysis. Individual and pooled estimates are shown with 95% confidence intervals.
 62x16mm (300 x 300 DPI)



The mean baseline KAM knee joint load exposures in patients with and without structural disease progression from the four individual cohorts. Note the overlap between progressors and non-progressors in the different studies. Error bars: 95% CI.
190x142mm (300 x 300 DPI)

Appendix A

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by publication year]

Miyazaki et al. 2002

Methods	Prospective cohort study	
Participants	74 patients with medial knee OA	
Joint load exposure	External knee adduction moment during walking assessed at baseline	
Structural knee OA progression outcome	Joint space narrowing grade based on Altman atlas of osteoarthritis. Dichotomous grouping ("progressors"/"non-progressors") based on at least one grade worsening over the observation period.	
Observation period	72 months	
Quality assessment (risk of bias)		
Quality criteria	Authors' judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Adequate	Tables adequately presenting relevant information about subjects.
Are the groups assembled at a similar point in their disease progression?	Adequate	Quote: "... the number of patients with each radiographic scale (K/L grade and joint space narrowing scale) was similar in the two groups."
Is a potential knee joint loading parameter reliably ascertained?	Unclear	There is no mentioning of reliability assessment or reference.
Were the groups comparable on all important confounding factors?	Inadequate	Quote: "However, there were some significant differences at entry between the groups." Comment:
Was there adequate adjustment for the effects of these confounding variables?	Adequate	The analyses were adequately adjusted (multivariable logistic regression).
Was outcome assessment blind to exposure status?	Adequate	Quote: "All radiographs were evaluated by an experienced reader who was unaware of all other data."
Was follow-up long enough for the outcomes to occur?	Adequate	Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Unclear	32 out of a total of 106 (~30%) were lost to follow up.
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Inadequate	Not described. The exposure for those that were lost to follow up was higher than those who completed the study as "non-progressors".
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate = <50%

^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

Chang et al. 2007 & Sharma et al. 2003*

Methods	Prospective cohort study	
Participants	57 patients with knee OA (64 patients in abstract) from the MAK cohort (300+ patients).	
Joint load exposure	External knee adduction moment during walking assessed at baseline	
Structural knee OA progression outcome	Joint space narrowing grade based on Altman atlas of osteoarthritis. Dichotomous grouping (“progressing knees”/“non-progressing knees”) based on at least one grade worsening over the observation period.	
Observation period	18 months	
Quality assessment (risk of bias)		
Quality criteria	Authors’ judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Inadequate	There are no descriptions of the groups, except for the toe-out angle and knee adduction moment.
Are the groups assembled at a similar point in their disease progression?	Inadequate	Not described. Only the distribution of K/L in the full sample is given. The structural disease progression outcome (Altman) is not presented at baseline.
Is a potential knee joint loading parameter reliably ascertained?	Unclear	There is no reliability assessment or reference to previous work.
Were the groups comparable on all important confounding factors?	Inadequate	Not described.
Was there adequate adjustment for the effects of these confounding variables?	Adequate	In the conference abstract there were statistical adjustments for age, gender, BMI, pain, radiographic disease severity (K/L), and varus alignment.
Was outcome assessment blind to exposure status?	Adequate	Quote: “The knee x-ray reader was blinded to the gait analysis data”
Was follow-up long enough for the outcomes to occur?	Adequate	Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Adequate	This study included 57 at baseline and 56 at follow-up. Note: The underlying MAK cohort is 300+ patients no description of how the gait subgroup was selected
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Inadequate	The conference abstract (Sharma et al. 2003) included 64 patients in contrast to the 57 patients included in the article (Chang et al. 2007). The authors could not account for the different numbers of subjects.
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

* Conference abstract based on the study.

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate= <50%

^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

Bennell et al. 2011

Methods	Prospective cohort study	
Participants	144 patients with medial knee OA	
Joint load exposure	External knee adduction moment during walking assessed at baseline	
Structural knee OA progression outcome	Progression of 1 or more grades in bone marrow lesions and cartilage defects assessed by semi-quantitative evaluation of MRI scans. Loss in medial tibial cartilage volume assessed from manual segmentation of MRI scans.	
Observation period	12 months	
Quality assessment (risk of bias)		
Quality criteria	Authors' judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Inadequate	There are no descriptions of the groups that progress in BMLs and cartilage defects.
Are the groups assembled at a similar point in their disease progression?	Inadequate	Not described.
Is a potential knee joint loading parameter reliably ascertained?	Unclear	There is no reliability assessment or reference to previous work.
Were the groups comparable on all important confounding factors?	Inadequate	Not described.
Was there adequate adjustment for the effects of these confounding variables?	Adequate	There were statistical adjustments for age, gender, BMI, MRI machine, alignment, baseline values, and treatment group.
Was outcome assessment blind to exposure status?	Inadequate	Not described.
Was follow-up long enough for the outcomes to occur?	Adequate	Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Unclear	200 enrolled in the underlying study. 144 (72%) had complete data sets.
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Inadequate	Not described.
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate = <50%

^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

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Woollard et al. 2011

Methods	Prospective cohort study
Participants	13 patients with knee OA
Joint load exposure	External knee adduction moment during walking assessed at baseline
Structural knee OA progression outcome	Loss of tibiofemoral cartilage volume. Dichotomous grouping ("progressing knees"/"non-progressing knees") based on a cartilage loss greater than measurement error over the observation period.
Observation period	12 months

Quality assessment (risk of bias)

Quality criteria	Authors' judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Adequate	Individual patient data is presented according to group structure.
Are the groups assembled at a similar point in their disease progression?	Adequate	Progressors had more severe radiographic disease at baseline (K/L 3 vs. 2), but similar cartilage volumes at baseline (primary outcome).
Is a potential knee joint loading parameter reliably ascertained?	Unclear	There is no reliability assessment or reference to previous work.
Were the groups comparable on all important confounding factors?	Unclear	Progressors had more severe radiographic disease, BMI and lower age; but comparable on gender, WOMAC (all domains) and alignment.
Was there adequate adjustment for the effects of these confounding variables?	Inadequate	The sample was too small for adjustments of the estimates.
Was outcome assessment blind to exposure status?	Inadequate	Not described.
Was follow-up long enough for the outcomes to occur?	Adequate	Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Adequate	15 invited. 1 lost; 1 excluded.
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Adequate	Only 1 dropout.
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate = <50%
^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

Henriksen et al. 2013

Methods	Secondary data analysis from a randomized trial	
Participants	157 patients with knee OA and a BMI >30 kg/m ²	
Joint load exposure	Change in peak knee joint compression force during walking over the 4 months prior to the 12 month observation period	
Structural knee OA progression outcome	Boston Leeds Knee Osteoarthritis Score (BLOKS) for tibiofemoral cartilage loss and bone marrow lesions	
Observation period	12 months	
Quality assessment (risk of bias)		
Quality criteria	Authors' judgement	Support for judgement
Sufficient description of the groups and the distribution of prognostic factors?	Adequate	Comment: Demographic, primary outcome and secondary outcome data separated by group are provided in Table 1.
Are the groups assembled at a similar point in their disease progression?	Adequate	Quotation: "There were no other statistically significant differences [including in K&L grade and BLOKS measures of tibiofemoral cartilage and bone marrow lesions] between the Unloaders and Loaders at week 16"
Is a potential knee joint loading parameter reliably ascertained?	Adequate	Quotation: "Based on 30 individuals assessed twice separated by one week done prior to the study, intra-class correlation coefficient for the estimation of peak compression force in our lab is 0.91 (95% CI: 0.83 to 0.96)"
Were the groups comparable on all important confounding factors?	Inadequate	Quotations: "Among the Unloaders the ambulatory knee function was not improved from week 0 to week 16, seen as no statistically significant change in walking speed and a reduction in the knee extensor moment" and "...the ambulatory knee function was improved among the Loaders, seen as increases in walking speed and internal knee extensor moment [from week 0 to week 16]" Comment: These quotations highlight a group difference in the change in walking speed, which may influence the change in knee joint loading which was used to assign group membership.
Was there adequate adjustment for the effects of these confounding variables?	Inadequate	Quotation: "Adjusted analysis: We repeated the analysis further including age, sex, week 16 BMI, and the randomization code in the underlying RCT (Diet, Exercise and Control) as covariates." Comment: Analyses were not adjusted for walking speed or change in walking speed.
Was outcome assessment blind to exposure status?	Adequate	Quotation: "All assessors were blinded to the case status."
Was follow-up long enough for the outcomes to occur?	Adequate	Comment: Satisfied by default, due to inclusion criteria in the present study.
What proportion of the cohort was followed-up? ^a	Adequate	Quotation: "One year after the weight loss (i.e., at week 68), there were 144 subjects (92%) remaining in the biomechanics sub-cohort, i.e., 13 subjects lost to follow-up"
Were drop-out rates and reasons for drop-out similar across exposed and unexposed groups?	Adequate	Quotation: "[participants lost to follow-up] were distributed with 7 (7%) in the Unloader group and 6 (11%) in the Loader group. Comment: Reasons for drop out listed in Figure 2.
Extent of risk of bias in study ^b	Very serious limitation	>1 criterion being inadequately described.
Methodological quality	Low quality	

^a Adequate = follow-up proportion >80%; Unclear 50-80%; Inadequate = <50%

^b Risk of bias is assessed using GRADE's approach to study limitations: No serious limitation defined as all criteria being adequately described (high methodological quality); Serious limitations defined as one criterion being inadequately described or >1 criterion being unclearly described (moderate methodological quality); Very serious limitation defined as >1 criterion being inadequately described (low methodological quality).

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Supplementary file 1: Protocol

Causal link between knee joint loading during walking and structural progression of knee osteoarthritis: a systematic review of cohorts and randomized trials

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ABSTRACT

Background

XXXXXXX

Objectives

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Search methods

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Selection criteria

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Data collection and analysis

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Results

XXXXXX

Authors' conclusions

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INTRODUCTION

Description of the condition

Osteoarthritis (OA) is the most common form of arthritis (1) affecting a large part of the population, and is a major cause of disability (2). The incidence and prevalence of OA increase with age (3). Among joints affected by OA, the knee joint is among the most frequently affected (1). Due to the knee’s crucial role in independent ambulation knee OA leads to considerable disability affecting the individual’s participation in society and independent life style. Pathologically, knee OA is defined as is a progressive structural disorder of the joints primarily characterized by gradual loss of cartilage with concurrent development of osteophytes, meniscal degeneration, bone marrow lesions, synovitis and effusions. The diagnosis is clinical – in the main by the presence of pain - and is most often confirmed by radiography or magnetic resonance imaging (MRI). Symptomatic knee OA is defined as the presence of the radiographic features of OA in combination with symptoms attributable to knee OA. Because no cure is available the burden of morbidity, primary care visits, and health care costs associated with knee OA are enormous and even higher than more high-profile diseases such as diabetes, cancer and cardiovascular diseases (4). Thus knee OA poses a substantial public health burden given its prevalence in the population that continues to rise.

Description of the exposure

Walking is a natural way of moving. Most people walk short distances every day and estimates of steps/day have been reported to be 9300 (women) and 11 900 (men) for young subjects decreasing with age (5), giving approximately between 3.4 and 4.3 million steps/year. With every step the knee joint is loaded, and biomechanical studies estimate the joint loads to exceed 2-3 times body weight (6), and thus knee joint loading is a necessity in independent life style.

While internal forces at joints cannot be measured directly, estimates of joint loads during walking can be obtained non-invasively by means of 3-dimensional gait analysis. Typically, medial tibiofemoral compartment joint loads are estimated using the external knee adduction moment (KAM) as a proxy, because this moment has been shown to be determinative of the medial to

lateral joint load distribution (7). More detailed biomechanical models have also been used to assess joint loads, in which overall compression forces (i.e., both medial and lateral compartment forces) are estimated based on the summation of joint, muscle, and soft tissue reaction forces (8). More recently, the total reaction moment has been suggested as a measure of overall joint loading during walking (9).

Efforts to reduce the dynamic loads on the knee during walking have been made with the scope to potentially delay or stop structural deterioration. Braces, wedged insoles, exercise, and weight loss are among interventions that have been suggested to have beneficial effects on structural progression of knee OA mainly through mechanical pathways.

How the exposure might work

Knee OA has traditionally been categorized as a “wear and tear” disease, which by definition suggests mechanical factors as being causally involved in both disease initiation and progression. A widely accepted hypothesis is that higher knee joint compression forces and moments during walking are associated with structural knee OA degeneration and changes in knee joint forces and moments must change the distribution, magnitude and direction of forces between and within the joint structures with possible effects on the structural disease progression. Within the knee structural signs of OA commonly occur in weight bearing structures, strengthening the belief that load is involved in knee OA progression. According to the prevailing theories higher loading is believed to accelerate structural progression of knee OA and thus unloading is advocated in an attempt to slow or halt disease progression.

Why it is important to do this review

The relationship between knee joint loads during walking and knee OA has been a focus of research for 10-20 years. The original work of Miyazaki et al. (10) indicating that higher joint loads increase the odds of structural disease progression has stimulated subsequent studies of knee joint loading during walking and knee OA. However, the majority of studies are cross sectional and results of prospective cohort studies and RCTs are discrepant. Results from studies on symptomatic treatment of knee OA paradoxically reveals (presumably) unwanted increase in knee joint loads during walking that were previously suggested to exert detrimental structural effects in

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cohort studies (6;11-13). This may generate confusion among researchers, health care professionals, policy makers, and the population at large who are interested in this information to aid them in knee OA prevention and treatment strategies.

In a classic study, Hill (14) proposed a set of criteria (the Bradford Hill criteria) to evaluate systematically whether a causal link between an exposure of interest and a health outcome exists. These guidelines are used by epidemiologists to test causal hypotheses and have undergone little modification since their original publication. Before advocating that knee joint loadings during walking should be targeted therapeutically, it is necessary to base recommendations on the best available scientific evidence. To address this issue, we conducted a systematic review of the literature examining the association between knee joint loads during walking (hereafter referred to as knee joint load exposures) and structural degeneration in knee osteoarthritis.

Objectives

Our specific objectives are 1) to systematically evaluate the evidence supporting a causal link between exposures to knee joint loadings during walking and progression of structural knee joint degeneration in patients with knee OA using the Bradford Hill criteria; 2) to determine which knee joint load exposures that have been studied sufficiently in RCTs and found to support the findings of prospective cohort studies; and 3) to identify the knee joint load exposures deemed to have insufficient evidence to be conclusive.

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METHODS

Criteria for considering studies for this review

Types of studies

Prospective cohort studies and RCTs.

We only consider studies that follow-up subjects for at least 1 year (according to the OMERACT-III Recommendations for a Core Set of Outcome Measures relating to the sensitivity of imaging and slow disease progression (15)). Cohort studies need to include estimates of joint loading during walking and assessment of disease structural progression. RCTs need to intervene on joint loading and assess the impact on structural disease progression.

Types of participants

The studies must include participants with knee OA diagnosed according to the ACR-criteria (16).

Types of interventions

Clinical trials have to be randomized and compare structural disease progression between different knee joint load exposures (high vs. low or increase vs. decrease), or knee joint load exposures interventions (increase or decrease), placebo or control.

Types of outcome measures

The articles must pertain to the effect of exposure to knee joint loading during walking (e.g. joint moments or estimated joint compression forces from 3-dimensional gait analysis) on structural disease progression assessed by X-ray or MRI.

Outcome measures

Primary – major – outcomes

Structural disease progression assessed by X-ray or MRI.

Semi quantitative assessments:

X-rays: K/L, Ahlback, Altman

MRI: WORMS/BLOKS/MOAKS assessments of cartilage defects, bone marrow lesions, osteophytes, meniscal lesions and extrusions, synovitis, effusion.

Quantitative assessments:

X-rays: Joint space width (mm), alignment (degrees)

MRI: Cartilage thickness (mm), volume (mm³), bone marrow lesion area/volume (mm²/mm³), meniscal extrusions (mm)

Search methods for identification of studies

Electronic searches

We will search MEDLINE, Scopus, AMED, CINAHL and SportsDiscus for prospective cohort studies and RCTs from 1950 through October 2012.

Searching other resources

The reference lists of the retrieved articles will also be scanned for additional cohort studies and RCTs.

Own files for yet unpublished data (e.g. Loader/Unloader manuscript at present in review at A&R, and the knee rotation moment manuscript at present in review at O&C)

Data collection and analysis

Selection of studies

Two of the authors (MH and MC) will independently assess study eligibility. Excluded studies and reasons for exclusion will be listed, and disagreement is resolved by discussion and consensus.

Data extraction and management

The following data will be extracted from the selected studies

- 1. Study design (cohort study or RCT)
- 2. Country of origin
- 3. Number of participants
- 4. Demographic characteristics of the participants (ie age sex, BMI etc)

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5. Disease specific characteristics of the participants (ie baseline symptoms (pain, function etc), radiographic disease severity (ie baseline Kellgren-Lawrence, Ahlback, Altman etc), knee joint alignment etc)
6. Knee joint load exposure assessment tool (ie, joint moment, compression force etc)
7. Knee joint load exposure magnitude
8. Description of the interventions (RCTs)
9. Structural disease outcomes (ie, semi-quantitative or quantitative measures on x-ray and/or MRI)

For the prospective cohort studies, data will be extracted on the estimates of the association between knee joint load exposure and structural disease progression. The cohort studies typically report prediction of structural degeneration based on baseline knee joint load exposure. The higher knee joint load exposure is compared with the lower knee joint load exposure and the results are reported as odds ratios (OR) or relative risks (RR) for each structural disease progression outcome. P-values for trends, where available, will be used to evaluate dose-response relationships.

For the RCTs we compare RRs of structural disease progression between knee joint load exposure modification and control groups.

Assessment of risk of bias in included studies

The Cochrane Collaboration's tool for assessing risk of bias in randomized trials will apply for these particular studies (17). Risk of bias in cohort studies will be assessed in accordance with recommendations from the Center for Reviews and Dissemination at the University of York (18):

- . Is there sufficient description of the groups and the distribution of prognostic factors?
- . Are the groups assembled at a similar point in their disease progression?
- . Is the intervention/treatment reliably ascertained?
- . Were the groups comparable on all important confounding factors?
- . Was there adequate adjustment for the effects of these confounding variables?

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- . Was a dose-response relationship between intervention/joint load exposure and outcome demonstrated?
- . Was outcome assessment blind to exposure status?
- . Was follow-up long enough for the outcomes to occur?
- . What proportion of the cohort was followed-up?
- . Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Measures of treatment effect (summary measures)

We will calculate or convert the observed likelihood of progression into odds ratios (ORs) with 95% confidence intervals for each study.

Assessment of heterogeneity

We will examine heterogeneity between trials with a standard Q-test statistic (testing the hypothesis of homogeneity), and present the I^2 value, which can be interpreted as the percentage of total variation across several studies due to heterogeneity.

Data synthesis

Combining results of studies

To combine the individual study results we did meta-analyses using SAS software (version 9.2), applying a restricted maximum likelihood (REML) method to estimate the between study variance and the combined OR.

Subgroup analysis and investigation of heterogeneity

We will explore whether different types of measures for joint loading can explain some of the variation in the odds of joint deterioration.

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APPLICATION OF BRADFORD HILL CRITERIA

An algorithm of the Bradford Hill criteria will be used to systematically evaluate the evidence of a causal relationship between knee joint load exposure and structural progression of knee OA.

The following criteria will be used in the review of the retrieved prospective cohort studies:

1. *Strength of association.* Most important factor. Strong associations is defined as $RR \geq 5.0$, with lower 95% CI excluding 2.0, and statistically significant at $P < 0.05$, and in expected direction. Moderate association is defined as any statistically significant effect.
2. *Consistency across studies.* Finding of an association needs to be replicated in other studies. Consistency of knee joint load exposures is defined as $\geq 75\%$ of associations showing strong or moderate associations with structural progression.
3. *Temporality.* Refers to temporal relationship of association between exposure and outcome; exposure must precede outcome on progression. In prospective cohort studies and RCTs it is difficult (if not impossible) to ensure temporally correctness because participants in studies all are expected to walk on a daily basis and therefore are exposed to the knee joint load exposure throughout the observation periods. Although temporally correctness may be impossible to ensure and it thus could be argued that this criterion should be omitted from the present review, we retain this criterion in our assessment of causality because temporality is necessary (although not sufficiently enough in itself) to infer causation; thus absence of temporal relationship between knee joint load exposure and structural knee OA progression will preclude a causal link.
4. *Biological gradient.* When risk of progression increase (or decrease) incrementally as dose of exposure increases; provides strong evidence of causal relationship.

These 4 criteria are used to derive a causation score for each knee joint load exposure. The score is computed as the unweighted sum of the number of criteria that is met, for a possible range of 0 to 4. A score of 4 is considered strong evidence of a cause-and-effect relationship. A score of 3 is deemed to indicate moderate evidence. A score of 2 or less is considered weak evidence of causation.

A fifth criterion, *experimental evidence*, will be used to examine whether the evidence from the prospective cohort studies is consistent with that from RCTs. Experimental evidence enhances the probability of causation and this analysis may be used to up- or downgrade the computed

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causation score. RCT provide the ideal experimental study design to establish causation where randomization is the leading experimental factor that increases confidence in associations.

The following 4 criteria will be omitted

- *Coherence*. Causation is more likely if what is observed is supported by and in agreement with the natural history of the disease. This criterion is usually applied when the outcome of interest is assessed by surrogate outcomes. In the present review this criterion is omitted because it is already satisfied by default, because structural disease progression is by definition a surrogate marker of the disease.
- *Plausibility* relates to the assessment of whether the association is plausible or not. In the present review we omit this criterion because every relation can be described as plausible given that researchers always will think of an explanation once an association is observed. The knee joint load exposures selected in this review all meet plausibility criteria for probable mechanisms to explain associations.
- *Specificity* relates to the specific response to the exposure. In the present review, this criterion is omitted because the single joint load exposures are intercorrelated as are progression of degeneration in the different structures and tissues in the knee and, consequently association between a single knee joint load exposure and progression in multiple structures in the knee does not preclude a possible causal relationship.
- *Analogy* related to the possibility that existing similar association can support causation, e.g. does the same association exist for hip or hand OA, then causation may be supported. Otherwise the evidence is downgraded. This criterion is omitted because this review focuses on knee OA and because argumentation by analogy largely reflects imagination or experience of the scientist and therefore tends to subjective.

The quality of the evidence will also be communicated as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group: GRADE, presents a framework that describes both criteria for assessing the quality of research evidence and the strength of recommendations that includes considerations arising from the Bradford Hill criteria (19).

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Supplementary file 2: Literature Search Strategies

PubMed

1. ((knee[Title/Abstract]) OR joint, knee[MeSH Terms]) OR joints, knee[MeSH Terms]
2. ((osteoarthritis[Title/Abstract]) OR osteoarthrosis[Title/Abstract]) OR osteoarthritis[MeSH Terms]
3. (#1) AND #2
4. (((DiseaseExacerbation[Title/Abstract]) OR disease progression[MeSH Terms]) OR disease progressions[MeSH Terms]) OR disease progression[Title/Abstract]
5. (((radiography[MeSH Terms]) OR radiograph* [Title/Abstract]) OR x-ray*[Title/Abstract]) OR magneticresonance[MeSH Terms]) OR magneticresonance[Title/Abstract]
6. #4 OR #5
7. (((biomechanics[MeSH Terms]) OR biomechanic*[Title/Abstract]) OR gait[Title/Abstract]) OR walking[Title/Abstract]
8. #3 AND #6 AND #7

Scopus

1. knee (Ti-Ab-Key)
2. osteoarthritisOR osteoarthrosis(ti-ab-key)
3. progression OR worsening OR magneticresonance OR radiography OR x-ray (Ti-Ab-Key)
4. biomechanic OR gait OR walking (Ti-Ab-Key)
5. #1 AND #2 AND #3 AND #4

AMED, CINAHL, SportsDiscus

1. TI knee OR AB knee OR SU knee
2. TI osteoarthritis OR AB Osteoarthritis OR SU osteoarthritis OR AB osteoarthrosis
3. TI Progression OR AB Progression
4. TI worsening OR AB worsening
5. TI x-ray OR AB x-ray
6. TI radiography OR AB radiography
7. TI magnetic resonance OR AB magnetic resonance
8. #3 OR #4 OR #5 OR #6 OR #7
9. TI biomechanic* OR AB biomechanic*
10. TI gait OR AB gait
11. TI walking OR AB walking
12. #9 OR #10 OR #11
- 13.#1 AND #2 AND #8 AND #12

Supplementary file 3: Results of the literature search

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 & Suppl. file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11 + figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12 + table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13 + table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-14 + figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 + figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-15 + Figure 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

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