

# 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

### **Authors:**

Marius Henriksen\*, Mark Creaby, Hans Lund, Carsten Juhl, Robin Christensen

### **\*Contact person:**

Dr Marius Henriksen

Senior Researcher, PT, MSc, PhD.

The Parker Institute: Clinical Motor Function Laboratory

Copenhagen University Hospital, Frederiksberg

Nordre Fasanvej 57

DK-2000 Copenhagen F

Denmark

Email: [marius.henriksen@regionh.dk](mailto:marius.henriksen@regionh.dk)

Fax: +45 3816 4159

# **ABSTRACT**

## **Background**

XXXXXXX

## **Objectives**

XXXXXXX

## **Search methods**

XXXXX

## **Selection criteria**

XXXXX

## **Data collection and analysis**

XXXX

## **Results**

XXXXXX

## **Authors' conclusions**

XXXXXX

# 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

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.

# 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: WOMMS/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 (mm<sup>3</sup>), bone marrow lesion area/volume (mm<sup>2</sup>/mm<sup>3</sup>), 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?

- . 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.

## 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

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).

## **ACKNOWLEDGEMENTS**

This study was supported by grants from The Oak Foundation, XXX, and Frederiksberg Hospital.

We wish to acknowledge XXX.

## REFERENCES

- (1) Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008 Jan;58(1):26-35.
- (2) Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1987 Aug;30(8):914-8.
- (3) Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81(9):646-56.
- (4) Aspden RM. Osteoarthritis: a problem of growth not decay? *Rheumatology (Oxford)* 2008 Oct;47(10):1452-60.
- (5) Sequeira MM, Rickenbach M, Wietlisbach V, Tullen B, Schutz Y. Physical activity assessment using a pedometer and its comparison with a questionnaire in a large population survey. *Am J Epidemiol* 1995 Nov 1;142(9):989-99.
- (6) Henriksen M, Simonsen EB, Alkjaer T, Lund H, Graven-Nielsen T, Danneskiold-Samsøe B, et al. Increased joint loads during walking - A consequence of pain relief in knee osteoarthritis. *Knee* 2006 Sep 28;13:445-50.
- (7) Zhao D, Banks SA, Mitchell KH, D'Lima DD, Colwell CW, Jr., Fregly BJ. Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. *J Orthop Res* 2007 Jun;25(6):789-97.
- (8) Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. *J Orthop Res* 1991 Jan;9(1):113-9.
- (9) Boyer KA, Angst MS, Asay J, Giori NJ, Andriacchi TP. Sensitivity of gait parameters to the effects of anti-inflammatory and opioid treatments in knee osteoarthritis patients. *J Orthop Res* 2011 Dec 16.
- (10) Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. *Ann Rheum Dis* 2002 Jul;61(7):617-22.
- (11) Shrader MW, Draganich LF, Pottenger LA, Piotrowski GA. Effects of knee pain relief in osteoarthritis on gait and stair-stepping. *Clin Orthop* 2004 Apr;421:188-93.
- (12) Schnitzer TJ, Popovich JM, Andersson GB, Andriacchi TP. Effect of piroxicam on gait in patients with osteoarthritis of the knee. *Arthritis Rheum* 1993 Sep;36(9):1207-13.
- (13) Hurwitz DE, Sharma L, Andriacchi TP. Effect of knee pain on joint loading in patients with osteoarthritis. *Curr Opin Rheumatol* 1999 Sep;11(5):422-6.

- (14) Hill AB. The environment and disease: Association or causation? Proc R Soc Med 1965 May;58:295-300.
- (15) Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997 Apr;24(4):799-802.
- (16) Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986 Aug;29(8):1039-49.
- (17) Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
- (18) Khan K, ter Riet G, Popay J, Nixon J, Kleijnen J. STAGE II – Conducting the review. PHASE 5 – Study quality assessment. 2001
- (19) Schunemann H, Hill S, Guyatt G, Akl EA, Ahmed F. The GRADE approach and Bradford Hill's criteria for causation. J Epidemiol Community Health 2011 May;65(5):392-5.