## Title

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## Journal

Osteoarthritis and cartilage open, 5(1)

## ISSN

2665-9131

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## Publication Date

2023-03-01

## DOI

10.1016/j.ocarto.2022.100331

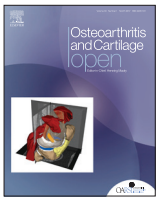
Peer reviewed

Osteoarthritis and Cartilage Open 5 (2023) 100331

Contents lists available at ScienceDirect

Osteoarthritis and Cartilage Open

journal homepage: www.elsevier.com/journals/osteoarthritis-and-cartilage-open/2665-9131



# Do associations with hand OA vary by knee osteoarthritis phenotype? Cross-sectional data from the Multicenter Osteoarthritis Study

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ARTICLE INFO

Handling Editor: H Madry

*Keywords:*
Multi-joint OA
Post-traumatic OA
Pain

ABSTRACT

*Objective:* Osteoarthritis (OA) is highly heterogeneous and has both biomechanical and systemic components that may not have the same etiology. We therefore aimed to identify specific knee OA phenotypes that may be more strongly associated with hand OA to refine the criteria used to define multi-joint OA.
*Design:* We assessed data from the Multicenter Osteoarthritis Study (MOST). We ascertained hand OA from bilateral hand photographs; scores for each joint row were summed to yield an aggregate hand OA score. Knee OA was ascertained from bilateral posteroanterior knee radiographs read for Kellgren-Lawrence grade and individual radiographic features. We tested associations between hand and knee OA with phenotypes including symptomatic OA, hyper- and atrophic knee OA, and one excluding post-traumatic OA. Associations between hand and knee OA were assessed with logistic regression, adjusted for age.
*Results:* We studied 2493 participants with hand and knee OA measures. Median age was 63 years with 57% women. 55% had an aggregate hand OA score $\geq$2; frequency of knee OA phenotypes ranged from 8% to 34%. The age-adjusted odds ratio (OR) was 1.14 (95% confidence interval (CI) = 1.04–1.26) for knee OA per standard deviation of the hand OA aggregate score. Hand OA associations with symptomatic knee OA and knee OA excluding post-traumatic knee OA were OR = 1.16 (95% CI = 1.03–1.31) and OR = 1.21 (95% CI = 1.08–1.35), respectively. No other knee OA phenotype reached statistical significance.
*Conclusions:* Age-adjusted associations between hand and knee OA were modest and were largely similar across knee OA phenotypes.

## 1. Introduction

Osteoarthritis (OA) is the most common form of arthritis in the United States (US) and is projected to affect 67 million US adults by 2030 [1]. It primarily affects the knee, hip, spine, hand, and foot joints of older individuals [2,3] although OA in the hips and knees have the greatest impact on physical functioning and the ability to complete daily activities [4,5]. In 1952, Kellgren and Moore first described the polyarticular involvement of OA at the hands, feet, spine, knees, and hips as a distinct subset of osteoarthritis [6]. Several studies have observed the frequent co-occurrence of OA at the hands, knees, and hips [7–12], and to a lesser extent, the spine [13].

Of the definitions provided for multi-joint OA, hand OA consistently appears as a major component. Studies have shown that persons with hand OA have an increased risk of knee OA and its progression [12,14]. Recent studies show that multi-joint OA has a strong familial component and progresses faster than single site OA [15–17]. While the pathogenesis of knee and hip OA may be largely determined by mechanobiology [18], hand OA as part of a multi-joint OA construct may result from systemic rather than joint-specific biomechanical factors. For example, obesity

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https://doi.org/10.1016/j.ocarto.2022.100331
Received 25 June 2022; Received in revised form 7 December 2022; Accepted 19 December 2022

alters load distributions across the knees [19], which would not necessarily explain the relationship between BMI and hand OA [20]. Additionally, both diabetes and obesity may contribute to erosive hand OA [21].

OA is a highly heterogeneous disease, and it is possible that prior attempts to quantify the association between hand and knee OA may have included different subtypes of OA, some of which reflect only localized and not systemic disease. Efforts to define the multi-joint entity have focused on those with knee OA and investigated what definitions or distributions of hand or other joints best identified those with this entity [22,23]. To our knowledge, no prior studies have examined whether the association with hand OA may differ by knee OA phenotype. For example, individuals with knee injuries may experience damage to joint structures, alterations in joint biomechanics, and increases in joint stress that eventually lead to local, isolated post-traumatic knee OA, while others may develop OA without having a previous injury. Better understanding of how associations with hand OA may differ by knee OA phenotype may help refine the criteria used to define multi-joint OA. We therefore aimed to determine whether associations with hand OA may vary be knee OA phenotype.

## 2. Methods

We assessed data from the Multicenter Osteoarthritis Study (MOST), a longitudinal, prospective, observational study of knee OA in older individuals who have or are at increased risk of developing knee OA based on weight, knee symptoms, or history of knee injuries or operations [24]. The overall aims of MOST were to identify novel biomechanical risk factors, bone and joint structural factors, and nutritional factors associated with incidence and progression of symptomatic and radiographic knee OA. A cohort of 3026 men and women aged 50–79 years was recruited from a community-based sample at two clinical centers, University of Alabama at Birmingham and University of Iowa, comprised of about 20% African Americans and 55% women. Exams began in 2003 and continued with five follow-up examinations at 15, 30, 60, 72, 84, 144, and 168 months. Given the advanced age and large number of individuals with advanced OA and knee replacements in later years of the study, a new cohort of 1525 individuals ages 45–69 years with Kellgren-Lawrence grade (KL) 0, 1, or 2 in the worse affected of the tibiofemoral or patellofemoral compartments in both knees and no continuous and severe pain in either knee was recruited in 2016 (equivalent to the 144-month follow-up visit in the original cohort). The communities sampled and process of recruitment were the same as the original cohort. Those with advanced structural disease (KL $\geq$ 3) or knee replacement, rheumatoid or other inflammatory arthritis, or contraindications to MRI or were unwilling to undergo x-rays or MRIs were excluded. At least a fifth of individuals had to answer 'no' to the questions about 'any knee pain in the past 30 days'.

Bilateral hand photographs were collected for the first time at the 144-month visit. Therefore, analyses were restricted to this timepoint. Participant assessments included in-clinic interviews and at-home self-administered questionnaires. At each clinic visit, participants were assessed for frequent knee pain in each knee defined as pain, aching, or stiffness on most days within the past 30 days. Participants were also asked whether they ever had an injury to the knee (or since the last contact) that limits walking for two or more days or ever had knee surgery (or since the last contact) that may include arthroscopy, meniscectomy, or ligament repair. Participants completed a self-administered questionnaire that included questions about joint pain, aching, and stiffness. Participants that answered 'yes' to having pain, aching, or stiffness in any joints on most days completed a validated standard homunculus [25] to indicate which joints had pain, aching, or stiffness on most days in the past 30 days. Participants who indicated they had pain in the right or left hand were considered to have frequent hand pain. Pain in each body region was used to define musculoskeletal widespread pain (WSP). This entity is defined as the presence of pain in regions above and below the waist, on the right and left sides of the body, and axially [26]. Since we were focused on knee OA phenotypes and knee pain, we did not include knee pain in the definition of WSP (i.e., other lower extremity pain was required). At least three painful joints excluding the knees were needed to meet the definition of WSP.

Hand OA was assessed from bilateral hand photographs using the AGES-Reykjavik scoring atlas, which has been validated against radiographic data [27]. The photos were scored by HJ who developed the atlas. Photographs were scored by an aggregate hand OA score rather than joint by joint as typically done for hand radiographs. Each of the three hand joint groups, distal interphalangeal joints (DIP), proximal interphalangeal joints (PIP) and the first carpometacarpal joint (CMC1) were scored based on a 0–3 scale (0 = unaffected, 1 = possible hand OA, 2 = definite hand OA and 3 = severe hand OA). Here, the emphasis was on severity in each joint group (DIP, PIP, CMC1) with additional considerations for symmetry and typical joints. For the DIP joints, scores of 1 (some evidence of HOA) required definite nodal OA on one side or bilateral suspected OA. Scores of 2 (definite HOA) required bilateral definite nodal OA. Scores of 3 (severe HOA) required bilateral definite OA plus one or more severely affected joints. For the PIP joints, affection of more than one joint was sufficient for a score of 2 (definite HOA). For the CMC1 joints, unilateral severe involvement was sufficient for a score of 3 (severe HOA). Scores were summed across each hand joint group to yield an aggregate score of 0–9. Intra-reader reliability was assessed based on a sample of 48 participants originally read by HJ. Short-term reliability was assessed over a period of 1–2 months and long-term reliability was assessed over a period of 7–8 months. Weighted kappa for the aggregate score was 0.86 (95% CI = 0.80–0.92) for short-term reliability and 0.82 (95% CI = 0.77–0.88) for long-term reliability.

Knee OA was assessed from bilateral posteroanterior knee radiographs read by two readers for KL and individual radiographic features including joint space narrowing grade (JSN) and osteophyte grade (OST) with an adjudication panel composed of three readers if there was disagreement. Knee OA was defined as KL $\geq$ 2 or total joint replacement in one or both knees. Other phenotypes assessed were subsets of knee OA: 1) post-traumatic knee OA (PTOA) defined as KL $\geq$ 2 and history of knee injury that limited walking for 2 or more days or knee surgery in the same knee, 2) knee OA excluding post-traumatic OA, 3) symptomatic knee OA defined as KL $\geq$ 2 and frequent knee pain in the same knee, 4) atrophic knee OA defined as JSN = 1 or 2 and sum of OST $\leq$1 in all compartments [28], and 5) hypertrophic knee OA defined as JSN = 0, 1, or 2 in all compartments and at least one OST $\geq$2 in one or more compartments [28].

Institutional review board approvals were obtained from University of California, San Francisco, Boston University, University of Alabama at Birmingham and The University of Iowa. All participants provided written consent for study participation.

### 2.1. Statistical analyses

We determined the association between the aggregate hand OA score with each knee phenotype using logistic regression, adjusting for age, in a person-level analysis. As part of these primary analyses, we also conducted analyses excluding individuals with a prior history of knee joint injury or surgery, adjusting for age. We then stratified all analyses by gender and median age. We conducted sensitivity analyses removing individuals who had CMC1 only hand OA and refining the hand OA phenotype to an aggregate sum score of symptomatic hand OA, defined when pain, aching, or stiffness was present in the right or left hand as the sum of the row scores. Additional sensitivity analyses were performed by additionally adjusting for WSP. We considered associations that met a *P*-value $<$0.05 statistically significant. All analyses were conducted using SAS 9.4 (Cary, NC).

## 3. Results

A total of 2493 participants had OA measures in all hand and knee joints (Table 1); the median age was 63 years ranging from 45 to 92 years (inter-quartile range (IQR) = 55–68 years) and 57% were women. The proportion of individuals with KL ≥ 2 or total joint replacement in one or both knees was 34%. 13% had PTOA and 8% had symptomatic knee OA. The prevalence of atrophic and hypertrophic OA was 14% and 13%, respectively. 55% had an aggregate hand OA score ≥2.

For each standard deviation (SD) increase in hand OA aggregate score (SD = 1.6), the odds of knee OA increased by 14% (OR = 1.14, 95% CI = 1.04–1.26) (Table 2). After excluding PTOA cases, the age-adjusted association between hand and knee OA was OR = 1.21 (95% CI = 1.08–1.35). We also found a significant association with symptomatic knee OA, where for every SD increase in hand OA aggregate score, the odds of symptomatic knee OA increased by 16% (OR = 1.16, 95% CI = 1.03–1.31). No other association of hand OA with knee OA phenotype reached statistical significance.

We then stratified associations by gender and median age. We found statistically significant age-adjusted associations between hand and knee OA phenotypes in women and older individuals (Table 2). No associations reached statistical significance in men or individuals younger than the median age. We also conducted sensitivity analyses by removing individuals who had isolated thumb base OA and found that associations were comparable to the primary analyses (OR = 1.14, 95% CI = 1.04–1.26). When we defined the hand OA phenotype to an aggregate sum score of symptomatic hand OA (scores summed across rows), findings were largely the same as the primary analyses (Table 3).

We found the strongest association between symptomatic hand OA aggregate score and symptomatic knee OA. For each SD increase in symptomatic hand OA aggregate score (SD = 1.4), the odds of symptomatic knee OA increased by 32% (OR = 1.32, 95% CI = 1.20–1.46) (Table 3). When we stratified analyses by gender and median age, we found similar and statistically significant associations for the relationship between symptomatic hand OA aggregate score and symptomatic knee OA in all strata (Table 3). Additional adjustment for WSP resulted in attenuated odds ratios for all analyses.

**Table 1**
Participant characteristics (n = 2493)[a].

| | |
|---|---|
| Median age (range) in years | 63 (45–92) |
| % Women | 57 |
| Mean aggregate hand OA score (SD) | 1.9 (1.6) |
| % Aggregate hand OA score ≥2 | 55% |
| % Knee OA | 34% |
| % Post-traumatic knee OA | 13% |
| % Symptomatic knee OA | 8% |
| % Atrophic OA | 14% |
| % Hypertrophic OA | 13% |
| % Widespread pain | 33% |

[a] Knee OA=KL ≥ 2 or total joint replacement in one or both knees; post-traumatic knee OA=KL ≥ 2 and history of knee injury that limited walking for 2 or more days or knee surgery in the same knee in one or both knees; symptomatic knee OA=KL ≥ 2 and frequent knee pain in the same knee in one or both knees; atrophic knee OA = JSN 1 or 2 and sum of OST ≤1 in all compartments in one or both knees; hypertrophic knee OA = JSN ≤2 in all compartments and at least one OST ≥2 in at least one compartment in one or both knees; widespread pain = presence of pain in regions above and below the waist, on the right and left sides of the body, and axially.

## 4. Discussion

We found modest age-adjusted associations between hand and knee OA. While knee OA phenotypes that exclude post-traumatic knee OA or focuses on symptomatic knee OA cases provided marginal improvements in the strength of association between hand and knee OA, odds ratios across knee OA phenotypes were largely similar and could be considered in a multi-joint OA construct. Additionally, the age-adjusted associations between hand and knee OA were stronger in women compared to men and older compared to younger individuals, and when assessing symptomatic hand and knee OA. These findings are consistent with known risk factors for multi-joint OA but provide additional insights into more homogenous knee OA phenotypes that may help refine the definition of multi-joint OA.

Studies to date have not always used a clearly stated definition of

**Table 2**
Age-adjusted associations between hand and knee OA.

| | Adjusted OR (95% CI)[a] | | | | |
|---|---|---|---|---|---|
| | Overall | Women | Men | < Median age | ≥ Median age |
| Knee OA | **1.14 (1.04–1.26)** | **1.20 (1.06–1.34)** | 1.03 (0.87–1.22) | 1.05 (0.86–1.29) | **1.19 (1.06–1.32)** |
| Knee OA, excluding PTOA | **1.21 (1.08–1.35)** | **1.25 (1.09–1.43)** | 1.00 (0.80–1.25) | 1.09 (0.85–1.40) | **1.25 (1.10–1.42)** |
| Symptomatic knee OA | **1.16 (1.03–1.31)** | **1.20 (1.04–1.38)** | 1.05 (0.84–1.31) | 1.06 (0.79–1.41) | **1.20 (1.06–1.37)** |
| PTOA | 1.10 (0.97–1.23) | 1.16 (0.99–1.35) | 1.05 (0.86–1.29) | 0.99 (0.73–1.35) | 1.13 (0.99–1.29) |
| Atrophic OA | 1.11 (0.98–1.26) | 1.15 (0.98–1.34) | 1.14 (0.94–1.41) | 1.07 (0.83–1.37) | 1.14 (0.99–1.31) |
| Hypertrophic OA | 1.06 (0.94–1.20) | 1.03 (0.89–1.18) | 1.00 (0.78–1.28) | 0.91 (0.67–1.22) | 1.11 (0.97–1.27) |

[a] Per SD of hand OA aggregate score; knee OA=KL ≥ 2 or total joint replacement in one or both knees; post-traumatic knee OA=KL ≥ 2 and history of knee injury that limited walking for 2 or more days or knee surgery in the same knee in one or both knees; symptomatic knee OA=KL ≥ 2 and frequent knee pain in the same knee in one or both knees; atrophic knee OA = JSN 1 or 2 and sum of OST ≤1 in all compartments in one or both knees; hypertrophic knee OA = JSN ≤2 in all compartments and at least one OST ≥2 in at least one compartment in one or both knees; widespread pain = presence of pain in regions above and below the waist, on the right and left sides of the body, and axially; bolded associations have *P*-values <0.05; median age = 63 years.

**Table 3**
Age-adjusted associations between symptomatic hand OA and symptomatic knee OA.

| | Adjusted OR (95% CI)[a] | | | | |
|---|---|---|---|---|---|
| | Overall | Women | Men | < Median age | ≥ Median age |
| Adjusted for age | **1.32 (1.20–1.46)** | **1.33 (1.18–1.49)** | **1.27 (1.05–1.54)** | **1.38 (1.07–1.80)** | **1.32 (1.19–1.46)** |
| Adjusted for age + WSP | 1.08 (0.99–1.16) | **1.12 (1.01–1.25)** | 0.95 (0.76–1.19) | 1.12 (0.92–1.36) | 1.07 (0.98–1.16) |

[a] Per SD of hand OA aggregate score; knee OA=KL ≥ 2 or total joint replacement in one or both knees; post-traumatic knee OA=KL ≥ 2 and history of knee injury that limited walking for 2 or more days or knee surgery in the same knee in one or both knees; symptomatic knee OA=KL ≥ 2 and frequent knee pain in the same knee in one or both knees; atrophic knee OA = JSN 1 or 2 and sum of OST ≤1 in all compartments in one or both knees; hypertrophic knee OA = JSN ≤2 in all compartments and at least one OST ≥2 in at least one compartment in one or both knees; widespread pain = presence of pain in regions above and below the waist, on the right and left sides of the body, and axially; bolded associations have *P*-values <0.05; WSP = widespread pain; median age = 63 years.

multi-joint OA, and in those studies with a clearly stated definition, at least 15 different definitions of multi-joint OA have been used [29]. Furthermore, many alternative terms have been used, including polyarticular OA, generalized OA and multi- or multiple joint OA. Joint sites included vary widely, but most often included the hands and knees. However, few studies have differentiated post-traumatic from non-traumatic OA. There has only been one study that assessed the relationship between hand OA and knee OA in unoperated and operated knees after unilateral meniscectomy. This study found that those with concomitant hand OA had more frequent and severe knee OA than those with no hand OA in both unoperated and operated knees [30], suggesting that predisposition to multi-site OA may not be differentially related to post-traumatic and non-traumatic OA. Nonetheless, we found that the distinction between post-traumatic and non-traumatic OA may provide stronger associations between hand and knee OA and more homogenous groups for the study of multi-joint OA, particularly in women. Studies of knee OA heritability have shown that heritability estimates are higher in women compared to men [31,32], which may be attributed to the lower prevalence of injury-related damage to the knees in women compared to men. We found that excluding post-traumatic knee OA cases strengthened associations between hand and knee OA in women, but not men. It is possible that the presentation of multi-joint OA may be different in women and men. One potential risk factor that we did not include in the modeling or stratified analyses was BMI, since it may be on the causal pathway and would negate potential associations. Further studies of sex-specific differences in the etiology and presentation of multi-joint OA will be needed.

The inclusion of pain symptoms in previous studies of multi-joint OA is also variable. Some studies only included radiographic OA without consideration for symptomatic or clinical factors, while other studies only assessed symptomatic joints or recruited participants based on pain in a single joint. We found modest age-adjusted associations between hand OA and symptomatic knee OA that like the exclusion of post-traumatic knee OA cases were stronger in women compared to men and in older compared to younger individuals. In sensitivity analyses, we required presence of pain symptoms in both hand and knee OA and found that associations between hand and knee OA were further strengthened and similar across all sex- and age-specific strata. Additional adjustment for WSP yielded null associations, suggesting that WSP may possibly explain the systemic nature underlying multi-joint OA. The evolution of local to WSP may result from systemic increases in central nervous system sensitivity to pain [33]. While WSP does not seem to be associated with incident radiographic or symptomatic knee OA [26], one study found that knee pain may increase the risk of developing WSP [34]. However, no studies have assessed the role of WSP in multi-joint OA. WSP may be a key component to the evolution of multi-joint OA that may reveal novel systemic factors in OA.

Strengths of the study are that we used a large, well-characterized OA cohort with validated measures of OA and pain. However, we were limited to cross-sectional assessments of hand OA using hand photographs. While hand photographs have been validated against hand x-rays [35], this was done in an Icelandic population that may be different from the US population, who tend to be more overweight. This could make it more difficult to visualize the hand nodes and lead to misclassification, which would bias our findings toward the null. The effect sizes found were small, but nonetheless provide insights into potential subgroups that could be further explored in a multi-joint OA construct. While we attempted to remove isolated thumb base OA cases to account for potential mechanical involvement on hand OA, we did not have information on hand injury and could not remove hand OA cases that may be post-traumatic. Also, since hand photographs were only collected at one timepoint and the data were cross-sectional, we cannot rule out the possibility that injury or surgery used to define post-traumatic OA occurred after disease onset. However, in participants that had no history of injury or surgery and no OA at study initiation, most cases who developed OA twelve years later had an injury or surgery that preceded the onset of OA; those who had OA that preceded injury or surgery were few and were not classified as having post-traumatic OA. We also did not assess bilaterality since this was a cross-sectional study and oftentimes those with unilateral disease progress to bilateral disease. We focused on tibiofemoral knee OA but acknowledge that future studies of patellofemoral knee OA may be noteworthy since tibiofemoral and patellofemoral OA may not share the same etiology. Furthermore, our study did not include hip, feet or spine, sites that often are affected by OA. We did include hands and knees, which are the most common joint sites included in a multi-joint phenotype.

In conclusion, we found that age-adjusted associations between hand and knee OA were modest and did not vary dramatically by knee OA phenotype. Exclusion of post-traumatic knee OA or a focus on painful OA suggested possible subgroups, particularly in women and those with widespread pain, that may warrant further investigation to help refine the definition of multi-joint OA. Our study provides new insights into the phenotypes that may be used to define multi-joint OA.

## Author contributions

Conception and design: MSY, DTF. Data acquisition: HJ, JAL, CEL, JCT, MCN, DTF. Analysis and interpretation of the data: MSY, DTF. Drafting of the article: MSY. Critical revision of the article for important intellectual content: all authors. Final approval of the article: all authors. MSY had full access to the study data and takes responsibility for the integrity of the data analysis.

## Funding sources

This study was supported by P30 AR072571 and R01 AR075356. MOST is comprised of four [4] cooperative grants: U01 AG18820 David T. Felson (Boston University); U01 AG18832 James Torner (University of Iowa); U01 AG18947 Cora E. Lewis (University of Alabama at Birmingham); U01 AG19069 Michael C. Nevitt (University of California, San Francisco), funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by MOST study investigators. This manuscript was prepared using MOST Data and does not claim, infer, or imply endorsement by MOST, by the MOST investigators and their respective institutions or by the University of California of the data recipients' use of the data, of the entity or personnel conducting the research, or of any results of the research.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We wish to acknowledge the contributions of the study participants, investigators, and research staff of the MOST Study.

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