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Presence of erosions is not a risk factor for the development of knee OA in a hand OA population: Results from the Framingham OA study

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ABSTRACT

Objective: This study aimed to investigate whether there is a difference in risk of knee OA between individuals with erosive hand osteoarthritis (OA) compared to non-erosive hand OA, and to identify other risk factors for knee OA presence and development in hand OA patients.
Methods: Subjects were selected from the Framingham OA study's Offspring and Community cohorts. Bilateral knee and hand radiographs were scored. Generalized linear models compared knee OA prevalence and incidence rates among hand OA-free, non-erosive and erosive hand OA. Multivariable logistic regression identified risk factors for symptomatic knee OA (presence of hand OA, anatomical location, erosions, number of affected finger joints, radiographic grade changes), adjusted for age, sex and BMI.
Results: In total, 2367 participants were studied. Hand classification (hand OA-free, non-erosive and erosive hand OA) significantly impacted the prevalence of knee OA ($P < 0.0001$). Prevalence rates at baseline were 6.3 %, 17.9 % and 26.8 % for radiographic knee OA and 2.9 %, 9.7 % and 12.7 % for symptomatic knee OA for hand OA-free, non-erosive and erosive hand OA respectively. Post hoc analysis indicated differences were primarily between hand OA-free and hand OA groups ($p < 0.001$), with no significant differences between erosive and non-erosive hand OA ($p = 0.7$ and $p = 0.8$). Overall, hand OA was identified as a risk factor for knee OA development. Presence of erosions did not increase risk, but the number of affected finger joints and changes in Kellgren-Lawrence grade did.
Conclusion: Hand OA is associated with knee OA presence and incidence with no difference in the risk of knee OA between those with non-erosive vs erosive hand OA.

1. Introduction

Osteoarthritis (OA) is one of the most prevalent musculoskeletal disease in the general population. Knees, hips, spine and hands are most often affected [1]. While OA can be generalized and thereby affect different joint sites in one person, the relationship between OA in different anatomical locations remains an area of investigation [2].

Notably, an association between hand and knee OA has been consistently demonstrated in both cross-sectional and cohort studies, with individuals who have hand OA being at higher risk of having or developing knee OA. Furthermore, this association, has been found to be consistent across different knee OA phenotypes [3–8]. Moreover, the progression of hand OA is correlated with radiographic progression in the knee [8]. Importantly, studies indicate that the strength of the association between hand and knee OA increases with disease severity [7,9].

So far, there is lack of consensus on whether erosive hand OA is a distinct disease or a more severe form within the hand OA spectrum [10,11]. Examining the differences between erosive and non-erosive hand OA, as well as their connection to knee OA, is crucial for gaining valuable insights into the broader mechanisms of OA progression and its systemic nature. First it may help elucidate the underlying mechanisms linking OA across joint sites, shedding light on whether erosive changes contribute to this association. Second, it could improve risk stratification for knee OA in individuals with hand OA, particularly in the presence of erosive

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disease. Erosive hand OA is often referred to as a more aggressive form of OA, characterized by its destructive and inflammatory features within the hand [10]. If erosive hand OA is found to be associated with a higher prevalence of knee OA, this might suggest a systemic predisposition to a more severe form of OA that affects multiple joint sites. Understanding this connection could help identify erosive hand OA as a marker for heightened disease activity in OA, influencing both prognosis and therapeutic approaches.

Until now, only one study has investigated the association between erosive hand and knee OA. This particular study revealed an association between erosive hand OA and subchondral attrition in the knee, as observed on MRI. However, it appeared that this association could be attributed to a greater severity of radiographic OA in individuals with erosive disease, rather than solely to the presence of erosions [9]. The primary objective of this study was to investigate the association between erosive hand OA and established radiographic knee OA, with a specific focus on determining whether the association between erosive hand OA and knee OA differs from that of non-erosive hand OA. Our secondary aim was to investigate specific hand OA-related factors as potential risk contributors to the presence and development of knee OA within a population affected by hand OA.

2. Methods

2.1. Subjects

Subjects were selected from the Offspring and Community cohort of the Framingham OA study [12]. Participants were eligible if they had available knee and hand radiographs. The Offspring cohort included offspring of subjects of the original Framingham Heart Study and spouses of these offspring. In this cohort, participants underwent an examination between 1992 and 1995 and returned for follow-up assessments with an average follow-up duration of 8.7 years. Participants from the Offspring cohort were only included if they received hand and knee radiographs at follow-up visit.

The community cohort was recruited from the general population of the town of Framingham using census-tract data and random-digit telephone dialing. Participants underwent an examination between 2002 and 2005, during which both hand and knee radiographs were performed. For analyses of cross-sectional findings or knee OA prevalence both the Offspring and Community cohorts were included. For the longitudinal analysis or knee OA incidence, exclusively the Offspring cohort was used. The Boston University Medical Center Institutional Review Board approved the Framingham OA study and written informed consent was obtained.

2.2. Knee and hand radiographs

Bilateral weight-bearing posteroanterior knee and hand radiographs were acquired at baseline for both the Offspring, and Community cohorts and during follow-up for the Offspring cohort. All knee radiographs were scored by a musculoskeletal radiologist for both cohorts. Hand radiographs from the Offspring cohort were also scored by a musculoskeletal radiologist, while those from the Community cohort were scored by a trained reader with hand OA expertise (IKH) backed by a musculoskeletal radiologist for reliability assessment. All radiographs were scored using the Kellgren-and Lawrence scale (KL) [13].

Presence of knee OA was defined radiographically and clinically on joint level. A knee joint was classified as having radiographic knee OA if the KL score was $\geq$2. Symptomatic knee OA was defined as the presence of radiographic knee OA, as defined previously, combined with the presence of knee pain, aching or stiffness in the same knee. Knee symptoms were present if participants experienced knee pain, aching or stiffness for at least a month within the last 12 months. Hand OA was defined at the subject level. A subject was classified as having radiographic hand OA if the subject had at least one hand joint with KL $\geq$ 2. The assessed hand joints encompassed the bilateral 2nd to 5th distal interphalangeal (DIP) joints, 2nd to 5th proximal interphalangeal (PIP) joints, the interphalangeal joint of the thumb, and the thumb base (including carpometacarpal and scapho-trapezial joints). A subject was classified as having symptomatic hand OA when at least one hand joint with radiographic OA was accompanied by pain, aching or stiffness in the same joint.

2.3. Potential predictors

Several variables were investigated as potential risk factors for the occurrence or progression to symptomatic knee OA, within a population with radiographic and symptomatic hand OA, both cross-sectionally and longitudinally. These factors were selected based on existing literature and through exploratory analyses of the available dataset. The following risk factors were assessed: presence of symptomatic hand OA as defined above, presence of bilateral hand OA (i.e., symptomatic HOA as defined above is present in both hands), presence of thumb base OA (i.e., KL $\geq$ 2 in the carpometacarpal or scapho-trapezial joint), presence of OA at a DIP joint (i.e., KL $\geq$ 2 in one or more DIP joint(s)), presence of OA at a proximal interphalangeal (PIP) joint (i.e., KL $\geq$ 2 in one or more PIP joint(s)), presence of erosive hand OA (i.e., the simultaneous presence of radiographic hand OA and a central erosion in at least one interphalangeal joint), the number of affected finger joints (i.e. joints with KL $\geq$ 2), an increase of one or more units in KL in one or more joint.

2.4. Analysis

Descriptive statistics were performed and crude prevalence and incidence numbers of radiographic and symptomatic knee OA at baseline (Community and Offspring cohort) and after 9 years of follow-up (Offspring cohort) were calculated.

Generalized linear models (GLM) were used to compare prevalence and incidence rates of both radiographic and symptomatic knee OA between three groups: no hand OA, non-erosive hand OA and erosive hand OA. Chi-square tests were used for pairwise comparisons between the three groups. Multivariable logistic regression analysis, adjusting for age, sex and BMI, were used to identify risk factors for knee OA development in a hand OA population both cross-sectionally and longitudinally.

All analyses were performed in SAS version 9.4. A significance level of $\alpha = 0.05$ was used for all statistical testing.

3. Results

In total, 2367 participants from both cohorts were studied, 1293 participants from the offspring cohort and 1074 from the Community cohort. The mean age was 58.9 years (SD 9.9), 56.5 % were female, and the mean BMI was 27.8 (SD 5.3). Radiographic hand OA was present in 49.4 % of the participants. Among them, 85.6 % had non-erosive OA, and 14.3 % had erosive OA. DIP OA was found in 65.4 %, PIP OA in 30.8 %, and thumb base OA in 68.5 % of those with hand OA. Symptomatic hand OA was present in 17.6 % of participants. A comprehensive overview of these descriptive statistics can be found in Table 1.

3.1. Prevalence and incidence of radiographic and symptomatic knee OA

Crude prevalence and incidence numbers for both radiographic and symptomatic knee OA are shown in Tables 2 and 3. At baseline, radiographic OA was found in 19.1 % and 6.3 % (Community and Offspring cohort) and 11.8 and 7.3 (Offspring cohort only) of knees in the radiographic hand OA and the no hand OA population respectively. After 9-years of follow-up, prevalence numbers of radiographic knee OA were slightly higher with 20.5 % and 8.9 % (Offspring cohort only) of knees affected in the radiographic hand OA population and the no hand OA population respectively. When the radiographic hand OA population was divided into non erosive and erosive, radiographic knee OA was seen in

26.8 % of the knees of the erosive hand OA population vs 17.9 % in the non-erosive group for the Community and Offspring cohort combined. For the Offspring only the prevalences were 14 % and 11.5 % in the erosive versus non erosive hand OA population. After 9-years of follow-up, radiographic knee OA was seen in 20.9 % and 20.3 % (Offspring cohort only) of the knees of the erosive and non-erosive hand OA population respectively.

Crude incidence percentages of radiographic knee OA in the offspring cohort were 13.4 % and 5.7 % of the knees respectively in the hand OA and no hand OA population. The incidence of radiographic knee OA was similar in those with erosive and non-erosive hand OA (14.9 % and 13.3 % of the knees respectively). Descriptive statistics of all subgroups is reported in Supplementary tables S1, S2.

3.2. Difference between no hand OA, erosive hand OA and non-erosive hand OA

The GLM analyses revealed a noteworthy overall impact of hand classification (no hand OA, non-erosive hand OA and erosive hand OA) on both the prevalence of radiographic knee OA (F-value 78.38, $P < 0.0001$) and symptomatic knee OA (F-value 47.64, $P < 0.0001$) (Table 4A). The models accounted for 5.83 % and 3.63 % of the variance, respectively, meaning approximately 5.83 % and 3.63 % of the variability in the prevalence of radiographic and symptomatic knee OA respectively can be attributed to different hand classifications.

The GLM models investigating the incidence of knee OA similarly revealed significant outcomes for both radiographic (F-value 9.21, $P < 0.0001$) and symptomatic (F-value 8.53, $p = 0.002$) knee OA. Nevertheless, due to the modest R-squared (R2) values in both models, the associations between hand type and incidence of radiographic and symptomatic knee OA are weak, as only 0.75 % and 0.67 % of the variability in incidence of radiographic and symptomatic knee OA can be attributed to hand classification.

Post hoc pairwise comparisons (Table 4B) showed that the impact of hand OA classification on both the prevalence and incidence of radiographic knee OA was primarily driven by the distinction between individuals with hand OA and those without ($p < 0.001$, $p < 0.001$ for prevalence and $p < 0.001$ and $p = 0.02$ for incidence), rather than between the erosive and non-erosive hand OA subgroups. No significant difference was seen between non-erosive and erosive hand OA group in terms of their association with radiographic knee OA prevalence and incidence respectively ($p = 0.70$, $p = 0.80$). Concerning symptomatic knee OA prevalence, differences were similarly attributed to the divergence between the no hand OA group on one hand and the non-erosive and erosive groups on the other hand ($p < 0.001$). Again, no dissimilarity was observed between the erosive and non-erosive groups ($p = 0.80$). Regarding the incidence of symptomatic knee OA, the disparity was exclusively attributed to the differences between the no hand OA and the non-erosive hand OA group ($p < 0.001$).

Table 1
Baseline demographic and clinical variables of the study participants.

	Framingham Community and offspring cohort N = 2301
Age, mean (SD) years	58.91 (9.9)
Sex (female), n (%)	1300 (56.5)
BMI, mean (SD)	27.8 (5.3)
Radiographic hand OA, (n = patients) (%)[b]	1136 (49.4)
Non-erosive hand OA, (n = patients) (%)	973 (85.6))[a]
Erosive hand OA, n (=patients) (%)[d]	163 (14.3)[a]
DIP OA, n (%)	743 (65.4)[a]
PIP OA, n (%)	350 (30.8)[a]
Thumb base OA, n (%)	730 (68.5)[a]
Symptomatic hand OA (n = patients) (%)[c]	404 (17.6)

Data are mean (standard deviation) or number (%).

[a] This represents number of persons with this form of hand OA (the percent is number with this form of hand OA divided by the total number of subjects with radiographic hand OA.).

[b] Radiographic hand OA (at least one hand joint with KL $\geq$ 2. Assessed hand joints: 2nd to 5th distal interphalangeal (DIP) joints, 2nd to 5th proximal interphalangeal (PIP) joints, the interphalangeal joint of the thumb, and the thumb base (including carpometacarpal and scapho-trapezial joints). Percentage is the percentage on total subjects in the cohort.

[c] Symptomatic hand OA (at least one hand joint with radiographic OA, accompanied by pain, aching or stiffness in the same joint). Percentage is the percentage on total subjects in the cohort.

[d] Erosive hand OA (simultaneous radiographic had OA and a central erosion in at least one IP (DIP and or PIP).

3.3. Risk factors for development of knee OA

The presence of hand OA was identified as a significant predictor for knee OA development, with both radiographic hand OA and symptomatic hand OA yielding predictive odds ratios (OR 1.8 [1.4; 2.4] and odds ratio 1.9 [1.3; 2.7] respectively.

When identifying risk factors within the hand OA population, none of the examined potential variables were identified as risk factors for presence of symptomatic knee OA on a cross-sectional level (Table 5). In the longitudinal analysis, some variables were retained as significant risk factors. Interestingly, among those with hand OA, erosive hand OA did not demonstrate a risk association with symptomatic knee OA (OR 0.89 (0.45; 1.75)). Presence of thumb base OA, DIP and PIP OA also did not show a risk association with symptomatic knee OA development within a hand OA population. However, among those with hand OA, significant associations were found between the number of finger joints affected 1.38 (0.75; 2.51) and increased in KL grade 1.82 (1.14; 2.91), indicating increased risk with a greater number of affected joints and severity of joint involvement, respectively.

4. Discussion

This study suggests that while hand OA overall is associated with knee OA, there is no significant difference between non-erosive and erosive hand OA in terms of their association with OA in the knee. The differences in knee OA prevalence and incidence among erosive, non-erosive and hand OA-free patients, were not attributed to the presence of erosions, but rather to the presence of hand OA itself. Furthermore, presence of erosions was not identified as a risk factor for the development of knee OA in analyses restricted to those with hand OA.

This study confirms the association between hand and knee OA. Moreover, this research highlights that, within a population affected by hand OA, hand OA progression and disease extent serve as risk factors for the development of knee OA. Presence of OA in the DIP, PIP and thumb base joints did not show an increased risk for knee OA development. It is important to note that all of the aforementioned risk factors were exclusively identified in the longitudinal analysis and were not confirmed in the cross-sectional analyses. This suggests the identified risk factors exert latent effects, rather than an immediate influence on knee OA, gradually elevating the risk over time.

To the best of our knowledge, this is the first study investigating the association between erosive hand OA and established radiographic knee OA. One study did explore the association between erosive hand OA and subchondral attrition on MRI, which is a feature of advanced knee OA. This study demonstrated that the positive association between erosive hand OA and subchondral attrition was attributed to a higher degree of radiographic OA in individuals with erosive disease, rather than solely to the presence of erosions itself. Our study results align with this finding.

Oliviero et al. [14] reported higher levels of cytokines (IL-1β, IL-6, IL-8) and metalloproteinases (MMP-1 and MMP-3) in knee OA patients with concomitant radiographic erosive HOA compared to those without erosions. Additionally, the inflammatory mediators IL-1β, IL-6, MMP-1

Table 2
Observed prevalence and incidence of radiographic knee OA in the Framingham Offspring and Community cohorts and subcohorts.

	Overall Framingham cohort (n = 4271 knees)	Offspring cohort (n = 2239 knees)	Hand OA (radiographic) (n = 2085 knees; n = 753 knees offspring only)	No hand OA (radiographic) (n = 2186 knees; n = 700 knees offspring only)	Hand OA (symptomatic) (n = 1748 knees; n = 543 knees offspring only)	No hand OA (symptomatic) (n = 2523 knees; n = 827 knees offspring only)	Erosive hand OA (n = 298 knees; n = 86 knees offspring only)	Non-erosive hand OA population (n = 1748 knees; n = 636 knees offspring only)
Prevalence of radiographic knee OA at baseline (%)	12.6	7.9	Community and offspring: 19.1 Offspring only: 11.8	Community and offspring: 6.3 Offspring only: 7.3	Community and offspring: 20.3 Offspring only: 12.3	Community and offspring: 7.2 Offspring only: 8.8	Community and offspring: 26.8 Offspring only: 14.0	Community and offspring: 17.9 Offspring only: 11.5
Prevalence of radiographic knee OA at 9 years follow-up (%)	–	12.8	20.5	8.9	19.7	6.4	20.9	20.3
Incidence of radiographic knee OA at 9 years follow-up (%)	–	8.1	13.4	5.7	13.0	6.7	14.9	13.3

All values are percentages (%).

Table 3
Observed prevalence and incidence of symptomatic knee OA in the Framingham Offspring and Community cohorts and subcohorts.

	Overall Framingham cohort (n = 4137 knees)	Offspring cohort (n = 2150 knees)	Hand OA population (radiographic) (n = 2024 knees; n = 719 knees offspring only)	No Hand OA population (radiographic) (n = 2113 knees; n = 682 offspring only)	Hand OA population (symptomatic) (n = 1705 knees; n = 524 offspring only)	No Hand OA population (symptomatic) (n = 2432 knees; n = 806 offspring only)	Erosive hand OA population (n = 284 knees; n = 78 offspring only	Non-erosive hand OA population (n = 1714 knees; 621 offspring only)
Prevalence of symptomatic knee OA at baseline (%)	6.4	2.7	Community and offspring: 10.0 Offspring only: 4.6	Community and offspring: 2.9 Offspring only: 5.6	Community and offspring: 11.0 Offspring only: 4.8	Community and offspring: 3.1 Offspring only: 5.5	Community and offspring: 12.7 Offspring only: 3.9	Community and offspring: 9.7 Offspring only: 4.8
Prevalence of symptomatic knee OA at 9 years follow-up (%)	–	5.2	9.2	3.2	8.6	4.1	6.6	9.2
Incidence of symptomatic knee OA at 9 years follow-up (%)	–	4.3	7.6	2.7	6.8	3.5	4.1	7.6

All values are percentages (%).

and MMP-3 were correlated with the number of erosions, suggesting a systemic interplay among hand and knee joints in erosive hand OA patients, compared to those without erosions. This interplay does not entirely align with our findings. However, it is important to note that the patients in the study of Oliviero et al. were hand OA patients with knee effusions while patients without knee OA were not examined. This might suggest that erosive hand OA patients indeed do not have a higher risk of the development of knee OA compared to non-erosive hand OA patients. However, if erosive hand OA patients do develop knee OA, it appears that inflammation in knee joints is elevated compared to those without erosions. Whether erosive osteoarthritis is considered as a separate disease entity or a more severe form of hand OA is still debated in literature [10, 15,16].

Table 4A
Generalized mixed models comparing hand OA type and prevalence/incidence of knee OA.

		F value	Pr > F	R-square
Prevalence	*Symptomatic knee OA*	47.64	<0.001	0.036
	Radiographic knee OA	78.38	<0.001	0.058
Incidence	*Radiographic knee OA*	9.62	<0.001	0.008
	Symptomatic knee OA	8.53	<0.001	0.007

This table presents F-values, associated p-values (Pr > F), and R-squared values for each model.

Table 4B
Pairwise comparisons of prevalence and incidence of radiographic and symptomatic knee OA among hand OA Groups.

Comparison	N (no HOA)	N (Non-erosive HOA)	N (Erosive HOA)	Prevalence *P*-value	Incidence *P*-value
Radiographic knee OA					
No HOA vs non-erosive	1165 (50.65)	973 (42.29)	–	<0.001	<0.001
No HOA vs erosive	1165 (50.65)	–	163 (7.08)	<0.001	0.02
Non-erosive vs erosive	–	973 (42.29)	163 (7.08)	0.7	0.8
Symptomatic knee OA					
No HOA vs non-erosive	1165 (50.65)	973 (42.29)	–	<0.001	<0.001
No HOA vs erosive	1165 (50.65)	–	163 (7.08)	<0.001	0.8
Non-erosive vs erosive	–	973 (42.29)	163 (7.08)	0.8	0.2

This table presents pairwise comparisons of the prevalence and incidence of radiographic and symptomatic knee osteoarthritis (OA) across hand OA groups. All analyses were adjusted for potential confounders, including age, BMI, and sex.

Table 5
Risk factors for the development of symptomatic knee OA in subjects with radiographic and symptomatic hand OA.

Subjects with hand OA N = 1136 participants, 2272 knees	Radiographic hand OA population (odds ratio and 95 % Confidence interval) N = 2272 knees		Symptomatic hand OA population (odds ratio and 95 % Confidence interval) N = 808 knees	
Variable	Cross-sectional analysis	Longitudinal analysis (Offspring only)	Cross-sectional analysis	Longitudinal analysis (Offspring only)
Presence of bilateral hand OA	1.29 (0.28; 5.92)	1.11 (0.58; 2.13)	0.98 (0.20; 4.72)	1.22 (0.57; 2.65)
Presence of thumb base OA	1.65 (0.60; 4.53)	1.33 (0.86; 2.06)	2.11 (0.69; 6.45)	1.59 (1.00; 2.55)
Presence of DIP OA	1.13 (0.37; 3.43)	1.13 (0.69; 1.85)	0.89 (0.23; 3.27)	0.90 (0.48; 1.71)
Presence of PIP OA	0.38 (0.13; 1.16)	1.48 (0.95; 2.32)	0.36 (0.12; 1.05)	1.42 (0.90; 2.26)
Presence of erosive HOA	0.57 (0.12; 2.69)	0.89 (0.45; 1.75)	0.54 (0.12; 2.51)	0.84 (0.42; 1.65)
Number of finger joints affected-continuous[a]	0.90 (0.73; 1.10)	1.07 (0.95; 1.20)	0.89 (0.73; 1.10)	1.17 (1.06; 1.29)
Number of finger joints affected-dichotomous (1 if 3 or more joints have KL $\geq$ 2)[a]	0.75 (0.26; 2.18)	1.33 (0.81; 2.17)	0.72 (0.24; 2.21)	1.84 (1.15; 2.96)
$\geq$ 1 Unit change in KL grade in at least one joint[a]	–	1.71 (0.99; 2.97)	–	1.38 (0.75; 2.51)
$\geq$ 1 Unit change in KL grade in at least two joints[a]	–	1.66 (1.07; 2.59)	–	1.48 (0.91; 2.42)
$\geq$ 1 Unit change in KL grade in at least three joints[a]	–	1.79 (1.63, 2.74)	–	1.82 (1.14; 2.91)

Data are odds ratio (OR) with 95 % confidence interval.
[a] Includes thumb joint.

Several limitations are apparent in this study. Notwithstanding the considerable size of the Framingham cohort in terms of persons with OA, the representation of individuals with erosive hand OA remained quite small. However, the prevalence in our cohort aligns with findings from other studies. For instance, in a Dutch population-based cohort, the prevalence of erosive hand OA in general population was 2.8 % and increased to 5 % and 10.2 % among those with radiographic and symptomatic OA, respectively [17]. Bijsterbosch et al. [18] reported higher prevalences of 10.9 % in the general population and 16 % in the hand OA population. In addition, our study found a percentage of 19.1 and 11.8 % of radiographic knee OA in the hand OA population and a percentage of 12.6 % in the general population. This is in consistent with the 13 % prevalence reported in Europe [19]. It should be noted, however that the prevalence reported in this study is the percentage of affected knees rather than the percentage of participants with knee OA. Despite these comparisons, data on knee OA prevalence within hand OA populations remain scarce. Consequently, these findings need to be replicated in a cohort characterized by a higher proportion of individuals affected with erosive hand OA. In addition, the characteristics of the Framingham cohort in terms of racial and ethnic diversity limit the generalizability of these findings to more diverse populations. These aspects should be taken into consideration in future studies.

In conclusion, this study confirmed an association between hand OA and knee OA. However, it did not find an association between erosive hand OA and knee OA, indicating that the presence of erosions was not identified as a risk factor for the development of knee OA.

Author contributions

Contributions of the authors: TV: study design, interpretation of the data, analysis of the data, drafting of the article, final approval of the manuscript. IH, DF: data collection, study design, interpretation of the data, final approval of the manuscript. RW: study design, final approval of the manuscript. GM,NU: analysis of the data, statistical expertise, final approval of the manuscript.

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Declaration of competing interest

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Appendix A. Supplementary data

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