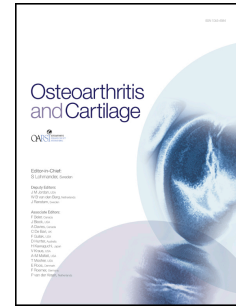


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TITLE PAGE**Longitudinal association between foot and ankle symptoms and worsening of symptomatic radiographic knee osteoarthritis: data from the osteoarthritis initiative**

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ABSTRACT

Objective To assess whether foot and/or ankle symptoms are associated with an increased risk of worsening of knee pain and radiographic change in people with knee osteoarthritis (OA).

Methods The presence and laterality of foot/ankle symptoms were recorded at baseline in 1368 participants from the Osteoarthritis Initiative with symptomatic radiographic knee OA. Knee pain severity (measured using the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale) and minimum medial tibiofemoral joint space (minJSW) width measured on x-ray were assessed yearly over the subsequent four years. Associations between foot/ankle symptoms and worsening of (i) knee pain, and (ii) both knee pain and minJSW (i.e. symptomatic radiographic knee OA) were assessed using logistic regression.

Results Foot/ankle symptoms in either foot/ankle significantly increased the odds of knee pain worsening (adjusted OR 1.54, 95% CI 1.25 to 1.91). Laterality analysis showed ipsilateral (adjusted OR 1.50, 95% CI 1.07 to 2.10), contralateral (adjusted OR 1.44, 95% CI 1.02 to 2.06) and bilateral foot/ankle symptoms (adjusted OR 1.61, 95% CI 1.22 to 2.13) were all associated with knee pain worsening in the follow up period. There was no association between foot/ankle symptoms and worsening of symptomatic radiographic knee OA.

Conclusion The presence of foot/ankle symptoms in people with symptomatic radiographic knee OA was associated with increased risk of knee pain worsening, but not worsening of symptomatic radiographic knee OA, over the subsequent four years. Future studies should investigate whether treatment of foot/ankle symptoms reduces the risk of knee pain worsening in people with knee OA.

Key words: Knee Osteoarthritis, Arthritis, Epidemiology, Foot, Ankle, Pain

ACCEPTED MANUSCRIPT

Knee osteoarthritis (OA) is a major public health problem that causes substantial pain, physical dysfunction and impaired quality-of-life. There is no cure for knee OA and the disease often progresses to advanced stages. Although there is a discordance between knee pain and joint deterioration¹, both are drivers of costly joint replacement surgery². Therefore, it is important to identify risk factors that are associated with the worsening of knee symptoms, with and without concurrent structural deterioration, in an attempt to prevent disease progression.

Researchers have identified a number of risk factors for the worsening of knee OA symptoms and structure, such as age, ethnicity and malalignment^{3,4}, however modifiable risk factors are required to prevent progression to advanced disease and/or surgery. To date, the strongest known modifiable risk factors for worsening of knee pain in people with knee OA are a higher body mass index (BMI) and infrapatellar fat pad or intercondylar synovitis⁴, whilst a recent meta-analysis identified greater knee pain at baseline as the only modifiable risk factor associated with structural progression³. Although these risk factors are potentially modifiable, weight loss interventions have poor compliance and limited long-term success⁵ and the remaining risk factors are likely to be symptoms or sequelae of OA and thus it is unclear whether targeted treatment would slow disease progression.

A potential risk factor for worsening knee OA that has not been investigated is foot/ankle symptoms. Concurrent symptoms at the foot, ankle and knee occur more often than any other multi-joint pain presentation, and their co-occurrence substantially increases the risk of problems with walking, standing and rising from sitting compared to single- and other multi-joint symptoms⁶. In people with knee OA, cross-sectional studies have shown that the presence of

foot/ankle symptoms is also associated with worse knee symptoms, health-related quality-of-life, depressive symptoms and functional abilities⁷. More recently, our longitudinal study showed that foot/ankle symptoms are an independent risk factor for developing knee OA in people free of the disease but at risk⁸. Potential mechanisms linking foot/ankle symptoms and incident knee OA, such as foot pronation, inappropriate footwear or widespread pain⁸, may also increase the risk for worsening in those with OA. However, as incident disease is a different phenomenon to worsening OA and risk factors may not be consistent across both, it is necessary to separately establish the association of foot/ankle symptoms with worsening OA. This is important as worse knee pain and greater radiographic severity are predictors of progression to arthroplasty². Knowledge of risk factors in those with knee OA can provide insight into why the disease progresses in some individuals but not others and help identify potential new treatment targets for future clinical trials¹⁰. Therefore, the aim of this study was to investigate whether the presence of foot/ankle symptoms at baseline is associated with an increased risk of worsening of (i) knee pain, and (ii) both knee pain and radiographic change, in people with symptomatic radiographic knee OA.

METHODS

Study population

Data were obtained from the Osteoarthritis Initiative (OAI), an online and publically available database (<http://www.oai.ecsf.edu/>). The OAI is a prospective multi-centre cohort study of 4796 participants aged between 45-79 years who have existing knee OA, or who are considered at-risk of the disease. The participants were recruited from four sites throughout the United States including Baltimore, Maryland; Columbus, Ohio; Pittsburgh, Pennsylvania; and Pawtucket,

Rhode Island. The institutional review board at each site approved all protocols and procedures and all participants provided informed consent. Further details regarding the wider OAI study protocols can be found online¹¹. Our study included OAI participants with established symptomatic radiographic knee OA (n=1368), defined as both knee symptoms (pain, aching or stiffness in and around the knee on most days of the month for at least one month in the previous year¹²) and radiographic evidence of knee OA (Kellgren and Lawrence [KL] grade ≥ 2) in at least one knee. If knee OA was present in both knees then both were included in the analyses.

Demographic characteristics and covariates

Demographic characteristics collected included age, sex and race (White, Black/African American or Asian/other non-white). Covariates included BMI, baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, depression measured using the Centre for Epidemiological Studies Depression Scale (CES-D)¹³, worst baseline KL grade, baseline minimum medial tibiofemoral joint space width (minJSW), baseline tibial rim distance (defined as the distance between the anterior or posterior margin of the tibia, and the tibial margin of the joint space), and comorbidities assessed using the questionnaire version of the Charlson comorbidity index (CCI)¹⁴. The CCI derives a weighted score based on the presence or absence of 14 different comorbidities such as stroke, diabetes, asthma, and kidney failure, amongst others, and we dichotomised the cohort into those with ‘no comorbidities’ (CCI=0) and those with ‘one or more comorbidities’ (CCI ≥ 1) based on the total CCI score. Data on individual comorbidities is provided in supplementary Table 1. For descriptive purposes, we also classified participants as obese ($>30 \text{ kg/m}^2$), overweight (≥ 25 and $\leq 30 \text{ kg/m}^2$) or healthy weight (<25

kg/m²), Scores on the CES-D were summed and a score of ≥ 16 was used to indicate significant depressive symptoms¹³.

Foot/ankle symptoms

Self-reported foot/ankle symptoms were recorded for each of the left and right feet at baseline.

Foot/ankle symptoms were defined as pain, aching or stiffness in the foot and/or ankle on more than half of the days during the past 30 days, consistent with previously published definitions^{6, 15}.

We classified participants as having or not having foot/ankle symptoms, as well as classifying foot/ankle symptoms as ipsilateral, contralateral or bilateral relative to the affected knee.

Outcomes

We investigated worsening of (i) knee pain and; (ii) both knee pain and radiographic knee OA.

Knee pain severity was determined using the WOMAC pain subscale at baseline and the 12, 24, 36 and 48 month follow-up visits¹⁶. The WOMAC pain subscale is comprised of five items and responses are recorded on a 5-point Likert scale. Scores were summed (range of 0-20) and

converted to a 0-100 normalised scale, with higher scores indicating worse pain. We defined

knee pain worsening as an increase of at least 9 points on the 0-100 WOMAC pain scale from baseline at any of the subsequent follow up visits, based on previously published smallest

detectable difference values^{17, 18}, and consistent with recent definitions used by others

investigating risk factors for symptomatic progression in knee OA¹⁹. People with a baseline

WOMAC pain score >91 (and thus unable to worsen according to this definition) were excluded

from these analyses.

To assess worsening of radiographic knee OA, weightbearing fixed-flexion posteroanterior radiographs of each knee were taken at baseline and at the 12, 24, 36 and 48 month visits. Radiographs were read centrally and automated software was used to identify the tibial and femoral margins of the knee joint from digitised copies of the radiographs²⁰. To determine the minJSW, the software measured the smallest distance between the tibia and the femur in the medial knee joint compartment in millimeters. Worsening of radiographic knee OA was defined as a medial tibiofemoral minJSW decrease of ≥ 0.7 mm from baseline, based on the Osteoarthritis Research Society International and Outcome Measures in Rheumatology minimal detectable difference cut-off value²¹. People with a baseline minJSW score of < 0.7 mm (and thus unable to worsen according to this definition) were also excluded from this analysis. A detailed outline of participant inclusion for each of the two aims is presented in Figure 1.

Statistical analysis

Descriptive characteristics of all variables at baseline were calculated according to the presence or absence of foot/ankle symptoms. Between-group differences were assessed using χ -squared tests, analysis of variance, Wilcoxon rank-sum or Kruskal-Wallis rank tests as appropriate.

To investigate whether foot/ankle symptoms were associated with worsening of knee pain (aim 1) and worsening of symptomatic radiographic knee OA (aim 2) over the subsequent four years, we used logistic regression models with the presence of foot/ankle symptoms (yes/no) as a binary explanatory variable. Models were fitted using generalized estimating equations to account for the correlation between left and right knees within participants. Models were performed unadjusted, as well as adjusted for baseline covariates determined *a priori*. The

covariates included in the adjusted model for aim 1 were age, sex, BMI, WOMAC pain at baseline, race, depression, worst baseline KL grade, and Charlson Comorbidity index (dichotomised), as these factors are known to be associated with both foot/ankle symptoms and knee OA. Models for aim 2 were also adjusted for the covariates included in the model for aim 1, with baseline minJSW and baseline tibial rim distance also included.

Unadjusted and adjusted analyses were then repeated to investigate the association between ipsilateral, contralateral and bilateral foot/ankle symptoms at baseline and the worsening of knee pain and worsening of symptomatic radiographic knee OA. Logistic regression models were again fitted using generalized estimating equations to adjust for clustering of knees within participants. Significance was set at $p\text{-value} \leq 0.05$ and Stata v12 (Stata Corporation, College Station, TX, USA) was used for all statistical analyses.

RESULTS

Sample characteristics

Four participants were excluded due to having a baseline WOMAC pain score of >91 in at least one knee, leaving data from 1364 participants. For aim 2, an additional 95 participants with $\text{minJSW} < 0.7\text{mm}$ were excluded, as were 130 participants with missing minJSW, leaving 1139 participants for aim 2 analyses. People with foot/ankle symptoms were more likely to be female ($p < 0.001$), younger ($p = 0.038$), have a higher BMI ($p = 0.001$) and to report more comorbidities ($p = 0.016$), worse WOMAC knee pain score ($p < 0.001$) and more depressive symptoms ($p < 0.001$) at baseline than those without foot/ankle symptoms. There were no differences in race, worst KL

grade, or minJSW at baseline between those with and without foot/ankle symptoms. Data are presented in Table 1.

Worsening of knee pain

Of the 2596 knees from 1319 participants analysed, 1,280 knees from 910 participants worsened (Table 2). See Supplementary Table 2 for the distribution of knees and participants who reported pain worsening at one time point and those who reported sustained pain worsening. The presence of symptoms in any foot/ankle at baseline was significantly associated with knee pain worsening (adjusted OR 1.54, 95% CI 1.25 to 1.91). Analyses of foot/ankle symptom laterality showed that ipsilateral (adjusted OR 1.50, 95% CI 1.07 to 2.10), contralateral (adjusted OR 1.44, 95% CI 1.02 to 2.06) and bilateral foot/ankle symptoms (adjusted OR 1.61, 95% CI 1.22 to 2.13) all significantly increased the odds for knee pain worsening in the follow up period.

Worsening of symptomatic radiographic knee OA

Of the 2005 knees from 1033 people analysed, 305 knees from 262 participants had worsening of both knee pain and minJSW (Table 3). See Supplementary Table 2 for the distribution of knees and participants who had worsening of both knee pain and minJSW at one time point and those who had sustained pain and minJSW worsening. The presence of symptoms in any foot/ankle at baseline was not significantly associated with worsening of these outcomes. Likewise, analysis based on foot/ankle symptoms laterality also revealed no significant associations between foot/ankle symptoms and worsening of both knee pain and minJSW.

DISCUSSION

In this study, people with knee OA who also had foot/ankle symptoms were more likely to experience clinically relevant worsening of their knee pain at some time in the subsequent four years than people with knee OA but without foot/ankle symptoms. Risk for knee pain worsening increased regardless of foot/ankle symptom laterality. There were no longitudinal associations between symptoms in any foot/ankle and worsening of symptomatic radiographic knee OA.

The association between knee pain progression and foot/ankle symptoms regardless of laterality may be explained by a number of mechanisms. For example, foot pronation is associated with foot pain²², and people with existing knee OA have been shown to walk with greater foot pronation²³, potentially to allow the foot to be plantigrade to compensate for knee varus. Thus, given that foot pronation causes greater internal tibial rotation^{24,25}, this may increase rotational stress on the tibiofemoral joint and peri-articular structures²⁶, exacerbating existing knee pain in people with knee OA. Ipsilateral and contralateral foot pronation have also been shown to increase the knee adduction moment²⁴, and a higher knee adduction moment is also associated with greater knee pain in people with established knee OA²⁷. Alternatively, associations between multiple pain locations, such as the foot and knee, may be an epiphenomenon due to an unmeasured shared risk factor such as fibromyalgia, pain catastrophizing, a multi-joint pain phenotype or generalised form of OA²⁸. The similar odds ratios for the association between foot/ankle symptoms on the ipsilateral and contralateral limbs, and worsening of knee pain, provide some support for this theory. Finally, certain styles of footwear, such as high heels, are associated with a greater likelihood of foot problems²⁹ and abnormal knee biomechanics³⁰ known to increase the risk of knee pain in older adults³¹.

Although foot/ankle symptoms were associated with worsening of knee pain, there was no longitudinal association with worsening of both knee pain and minJSW. This may be because the participants who experienced this outcome were a smaller subset (n=79) of those who had knee pain worsening, and thus the model may not have had enough power to detect a relationship. Alternatively, it is possible that our measure of radiographic progression (minJSW) recorded using x-ray was not sensitive enough to detect structural deterioration³². The use of MRI measures may be more suitable to detect longitudinal joint changes not evident on x-ray. There is some support for this from a recent study that found having a greater number of painful sites (including at the foot) predicted knee cartilage loss on MRI in people aged between 50 and 80 years³³.

Our findings add support to the scant previous literature investigating associations between foot/ankle and knee OA symptoms. Symptoms at these two sites have previously been shown to be the most prevalent multi-joint pain pattern, and to be associated with greater functional limitations, than the co-occurrence of pain at the knee and any other joint⁶. In a cross-sectional study using OAI data, we showed that knee OA patients with concurrent foot/ankle symptoms reported worse knee pain and other OA symptoms, in addition to worse general health and functional measures, than knee OA patients without foot/ankle symptoms⁷. Our recent longitudinal study reported that foot/ankle symptoms are a risk factor for developing knee OA symptoms and symptomatic radiographic knee OA over the subsequent four years in people at-risk of the disease³⁴. Interestingly, this previous study found that bilateral and contralateral foot/ankle symptoms, but not ipsilateral foot/ankle symptoms, increased the risk of developing these outcomes. In contrast, we found associations between knee pain worsening and foot/ankle

symptoms regardless of laterality in the current study. This might suggest that different mechanisms underpin the associations in incident versus worsening OA.

Some limitations may have influenced the findings of our study. Firstly, foot/ankle symptoms were self-reported and were only required to be present in the previous 30 days. Although this is consistent with the most widely used definitions of foot/ankle pain and/or symptoms¹⁵, a clinical foot assessment or more detailed foot pain questionnaire, such as the Manchester Foot Pain and Disability Index³⁵ (which rates a number of different aspects of foot pain and functional limitations), may have yielded different results. Secondly, participants were included based on the presence of knee symptoms, but as there was no minimum WOMAC pain score requirement in our inclusion criteria, it is possible our analyses included people who did not report any measureable knee pain. Further, knee pain worsening was only required to be present at one of the follow up visits, so our analyses included both people whose knee pain worsened temporarily at a single time-point as well as those with sustained pain worsening. Thirdly, potential mechanistic data such as foot/ankle osteoarthritis, foot posture or dynamic foot function were not recorded in the OAI dataset and therefore we were unable to include these variables in our analyses. Finally, dichotomising data such as we did with BMI and Charlson comorbidity index can also leave residual confounding³⁶. However when we repeated the analyses using fractional polynomials to model the continuous scores for these covariates, we found no strong evidence of this (see Table 3 in the supplementary analyses).

In summary, this study found that people with knee OA who report foot/ankle symptoms are at an increased risk of knee pain worsening compared to people without foot/ankle symptoms over

the subsequent four years. However, foot/ankle symptoms were not associated with worsening of symptomatic radiographic knee OA. These findings are important given that knee pain worsening has been shown to be an independent predictor of future knee joint replacement surgery³⁷. Furthermore, both general³⁸ and specific³⁹⁻⁴² causes of foot pain can be treated using simple conservative interventions, suggesting foot/ankle symptoms may be a modifiable risk factor for knee OA pain worsening. Future research should investigate whether treating foot/ankle symptoms in people with knee OA reduces worsening of knee pain in this population.

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AUTHOR CONTRIBUTIONS

All authors were involved in conception and design of the study, or in acquisition analysis and interpretation of data, and in revising it critically for important intellectual content. All authors approved the final version to be published. Dr. Paterson takes responsibility for the integrity of of the work as a whole, from inception to finished article.

Conception and design. Paterson, Kasza, Hinman, Hunter, Bennell.

Analysis and interpretation of data. Paterson, Kasza, Hunter, Hinman, Menz, Peat, Bennell.

Drafting of the article. Paterson, Bennell.

Critical revision of the article for important intellectual content. Paterson, Kasza, Hunter, Hinman, Menz, Peat, Bennell.

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CONFLICT OF INTEREST

No authors report competing interests.

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TABLES

Table 1. Baseline characteristics of participants according to the presence of foot/ankle symptoms. One participant had missing foot/ankle symptoms status at baseline. Values are N (%) unless otherwise indicated.

Characteristic	Missing (n)	No foot/ankle symptoms(n=1013)	Any foot/ankle symptoms (n=351)	P value [†]
Sex	0			<0.001
Male		477 (47.1)	113 (32.2)	
Female		536 (52.9)	238 (67.8)	
Mean (SD) age (years)	0	61.6 (9.1)	60.6 (8.6)	0.038
Race:	1			0.106
Asian and other non-white		33 (3.3)	8 (2.3)	
White/Caucasian		723 (71.4)	234 (66.9)	
Black/African American		257 (25.4)	108 (30.9)	
Comorbidities:	0			0.016
0		711 (70.2)	222 (63.2)	
≥1		302 (29.8)	129 (36.8)	

Foot/ankle symptoms and knee OA

Median (IQR) BMI kg/m ²	3	29.4 (26.4, 33.0)	31 (27.3, 34.5)	<0.001
BMI categories:	3			0.001
Healthy weight (BMI <25 kg/m ²)		151 (15.0)	29 (8.3)	
Overweight (BMI 25-30 kg/m ²)		393 (38.9)	126 (35.9)	
Obese (BMI >30 kg/m ²)		466 (46.1)	196 (55.8)	
Worst KL grade*	0			0.080
0		0 (0)	0 (0)	
1		0 (0)	0 (0)	
2		441 (43.5)	173 (49.3)	
3		402 (39.7)	134 (38.2)	
4		170 (16.8)	44 (12.5)	
Median (IQR) highest WOMAC pain score*	0	25 (10, 40)	35 (20, 50)	<0.001
Mean (SD) minimum JSW (mm)*	1	3.3 (1.6)	3.4 (1.4)	0.278

Depression	22		<0.001
No		889 (89.1)	271 (78.8)
Yes		109 (10.9)	73 (21.2)

SD, standard deviation; IQR, interquartile range; BMI, body mass index; KL, Kellgren Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; JSW, joint space width.

* Baseline values (worst value across knees for each participant)

† P-values from chi-squared test for binary and categorical variables, Wilcoxon rank-sum or Kruskal-Wallis rank tests for variables presented as median (IQR), and analysis of variance tests for variables presented as mean (SD).

Table 2. Logistic regression analyses for the risk of the worsening of knee pain during the four-year follow up period. Logistic regression models fit using generalised estimating equations to account for the clustering of knees within participants.

Laterality of foot/ankle symptoms	Total number of knees	No knee pain worsening N (%)	Knee pain worsening N (%)	Risk for knee pain worsening			
				Unadjusted OR (95% CI)	P value	Adjusted [†] OR (95% CI)	P value
No symptoms (ref)	1933	1021 (77.6)	912 (71.3)	1		1	
Any side	663	295 (22.4)	368 (28.8)	1.36 (1.12 to 1.65)	0.002	1.54 (1.25 to 1.91)	<0.001
Ipsilateral	157	71 (5.4)	86 (6.7)	1.33 (0.96 to 1.84)	0.089	1.50 (1.07 to 2.10)	0.017
Contralateral	154	67 (5.1)	87 (6.8)	1.44 (1.03 to 1.99)	0.030	1.44 (1.02 to 2.06)	0.038
Bilateral	352	157 (11.9)	195 (15.2)	1.35 (1.05 to 1.73)	0.019	1.61 (1.22 to 2.13)	<0.001

OR, odds ratios; CI, confidence intervals.

[†] Adjusted for age, sex, BMI, WOMAC pain at baseline, race, depression, Charlson Comorbidity index (dichotomised), and worst baseline KL grade.

Table 3. Logistic regression analyses for the risk of the worsening of knee pain and minJSW during the four-year follow up period. Models fit using generalized estimating equations to account for the clustering of knees within participants.

Laterality of foot/ankle symptoms	Total number of knees	No knee pain or minJSW worsening N (%)	Knee pain and minJSW worsening N (%)	Risk for knee pain and minJSW worsening			
				Unadjusted OR (95% CI)	P value	Adjusted [†] OR (95% CI)	P value
No symptoms (ref)	1513	1287 (75.7)	226 (74.1)	1		1	
Any side	492	413 (24.3)	79 (25.9)	1.06 (0.79 to 1.42)	0.69	1.09 (0.80 to 1.49)	0.58
Ipsilateral	106	89 (5.2)	17 (5.6)	1.11 (0.65 to 1.88)	0.70	1.07 (0.62 to 1.87)	0.81
Contralateral	104	83 (4.9)	21 (6.9)	1.35 (0.82 to 2.23)	0.23	1.43 (0.86 to 2.40)	0.17
Bilateral	282	241 (14.2)	41 (13.4)	0.94 (0.63 to 1.40)	0.77	0.97 (0.64 to 1.48)	0.90

OA, osteoarthritis; minJSW, minimal medial tibiofemoral joint space width; OR, odds ratios; CI, confidence intervals.

† Adjusted for age, sex, BMI, WOMAC pain at baseline, race, depression, Charlson Comorbidity index (dichotomised), worst baseline KL grade, baseline minJSW and baseline tibial rim distance.

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FIGURE REFERENCES

Figure 1. Flowchart for participant inclusion and exclusion.

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