



Associations Between Calcaneal Enthesophytes and Osteoarthritis of the Hands and Feet

Journal:	<i>Arthritis Care and Research</i>
Manuscript ID	Draft
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Menz, Hylton; La Trobe University, Musculoskeletal Research Centre, Faculty of Health Sciences Marshall, Michelle; Keele University, Arthritis Research UK Primary Care Centre, Primary Care Sciences Thomas, Martin; Keele University, Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences Rathod, Trishna; Keele University, Research Institute for Primary Care & Health Sciences Peat, George; Keele University, Research Institute for Primary Care & Health Sciences Roddy, Edward; Keele University, Arthritis Research UK Primary Care Centre
Key Words: Please choose key words for your manuscript. Choosing the best match of the journal's keywords to your work will likely result in better match to reviewers with expertise in your interest area. It may also help to speed the review process.:	Osteoarthritis, Foot, Hand, Enthesophytes
Optional Terms: You have the option to add additional key words that are not on the journal's list to more specifically categorize your submission.:	

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Associations Between Calcaneal Enthesophytes and Osteoarthritis of the Hands and Feet

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Declaration of interests: none.

Funding: This work was funded by an Arthritis Research UK Programme Grant (18174) and service support through West Midlands North CLRN. HBM is currently a National Health and Medical Research Council of Australia Senior Research Fellow (ID: 1135995). MJT is currently supported by an Integrated Clinical Academic Programme Clinical Lectureship from the National Institute for Health Research (NIHR) and Health Education England (HEE) (ICA-CL-2016-02-014).

Abstract

Objective. To examine associations between calcaneal enthesophytes and osteoarthritis (OA) in the hands and feet, in order to provide insights into the role of biomechanical and systemic processes in the development of OA.

Methods. Adults aged ≥ 50 years registered with four general practices were mailed a Health Survey. Responders reporting foot pain within the last 12 months underwent a detailed assessment which included hand and foot radiographs. Calcaneal enthesophytes (plantar and posterior) and OA features (osteophytes and joint space narrowing) were documented. Associations between enthesophytes and hand and foot OA (including OA phenotypes and OA features at individual joints) were explored using generalised estimating equations, adjusting for age, sex and body mass index.

Results. Data were available from 532 participants (298 women, mean [SD] age 64.9 [8.4] years). Calcaneal enthesophytes were not associated with hand OA phenotypes or OA at individual hand joints. In contrast, plantar calcaneal enthesophytes were positively associated with polyarticular foot OA (odds ratio [OR] 1.80, 95% confidence interval [CI] 1.02 – 3.17). When individual foot joints were examined, posterior enthesophytes were associated with talonavicular joint OA (OR 1.58, 95% CI 1.02 – 2.44) and plantar enthesophytes were associated with 1st metatarsophalangeal joint OA (OR 0.67, 95% CI 0.49 – 0.98) and navicular-cuneiform joint OA (OR 2.30, 95% CI 1.40 – 3.79). Patterns of association were similar for osteophytes and joint space narrowing.

Conclusion. Calcaneal enthesophytes are more strongly associated with foot OA than hand OA. The pattern of association is suggestive of a local, biomechanical rather than systemic bone-forming process.

Key words: enthesophytes, osteoarthritis, foot, hand

Significance and Innovations

- Calcaneal enthesophytes are more strongly associated with foot osteoarthritis (OA) than hand OA
- Patterns of association are similar for osteophytes and joint space narrowing
- These findings suggest that calcaneal enthesophytes represent a local, biomechanical rather than systemic bone-forming process

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3 Entheses are sites of attachment of tendons, ligaments, fascia or articular capsules to bone
4 (1). When entheses are exposed to metabolic, inflammatory, traumatic or degenerative
5 processes, pathological bone formation may occur, resulting in the development of
6 enthesophytes (bony spurs) (2). Several systemic conditions are associated with
7 enthesophytes, including psoriatic arthritis (3), rheumatoid arthritis (4) and diffuse
8 idiopathic skeletal hyperostosis (5). However, enthesophytes may also develop in response
9 to local mechanical stresses (6, 7), and their prevalence, particularly at the foot, increases
10 with age and body mass index (8).
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19 Enthesophytes are also frequently observed in osteoarthritis (OA) (4, 9-11), although their
20 role in the pathophysiology of OA remains uncertain. Examinations of skeletal remains have
21 reported strong associations between generalised enthesophytes and osteophyte formation in
22 the upper and lower limbs (12, 13), suggesting that enthesophytes may be indicative of a
23 systemic 'bone-forming' phenotype of OA. This is supported by studies demonstrating
24 strong associations between high bone mass, osteophytes and enthesophytes (14, 15). In
25 contrast, only weak associations have been found between hand enthesophytes and hand
26 (16) and knee (17) OA, which suggests that hand enthesophytes may develop in response to
27 local biomechanical factors rather than a systemic bone formation process.
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36 Examining associations between calcaneal enthesophytes and features of OA at local (foot)
37 and remote (hand) sites may provide a useful model for evaluating the relative role of
38 systemic and biomechanical processes in the development of OA. If enthesophytes are
39 indicative of a systemic bone-forming process, one would expect to observe similar
40 associations with OA at the hand and foot, and stronger associations with osteophytes than
41 joint space narrowing. In contrast, if enthesophytes reflect local mechanical stresses,
42 stronger associations might be observed between calcaneal enthesophytes and foot OA
43 compared to hand OA. Therefore, the objective of this study was to examine the
44 associations between calcaneal enthesophytes (plantar and posterior) and OA features (both
45 osteophytes and joint space narrowing) in joints of the hands and feet.
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MATERIALS AND METHODS

Study design

Data were collected via a population-based health survey and research assessment clinic as part of the Clinical Assessment Study of the Foot (18). Adults aged 50 years and over registered with four general practices were invited to take part in the study, irrespective of consultation for foot pain or problems. Ethical approval was obtained from Coventry Research Ethics Committee (reference number: 10/H1210/5).

Data collection

All eligible participants were mailed a Health Survey questionnaire that gathered information on demographic and social characteristics and general health. Participants who reported pain in and around the foot in the past 12 months and provided written consent to further contact were invited to attend a research clinic where radiographs were obtained from both hands and feet according to standardised protocols (18, 19). All films were graded by a single reader (MM) with previously documented intra-rater reliability (20, 21). For the hands, dorso-palmar views were obtained (20), and graded for the presence and severity of OA using the Kellgren and Lawrence (K&L) grading system. Standardised scoring was completed for 11 joints in each hand and wrist: the distal interphalangeal (DIP), proximal interphalangeal (PIP), the thumb interphalangeal (IP), the first carpometacarpal (CMC) and the trapezioscapoid (TS) joints. Radiographic OA for an individual hand joint was defined as the presence of K&L ≥ 2 . Three hand OA phenotypes were documented as described previously: generalised hand OA (defined as K&L ≥ 2 in ≥ 1 DIPJ and ≥ 1 PIPJ and ≥ 1 first CMCJ across either hand), thumb base OA (defined as K&L ≥ 2 in first CMCJ in either hand), and IPJ OA (defined as K&L ≥ 2 in ≥ 2 IPJ [rays 2–5] across either hand) (22).

For the feet, weightbearing dorso-plantar and lateral views were obtained, and osteophytes and joint space narrowing at the first metatarsophalangeal (MTP), first and second cuneometatarsal (CM), navicular-cuneiform (NC) and talo-navicular (TN) joints were graded (0–3) according to a validated atlas (23). Radiographic OA at each individual joint was defined as a score of 2 or more for osteophytes or joint space narrowing on either dorso-plantar or lateral views, and two foot OA phenotypes (first MTP OA and polyarticular

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3 foot OA) were documented as previously described (24). Plantar and posterior calcaneal
4 enthesophytes were documented from lateral x-rays as absent (score = 0), small (score = 1),
5 moderate (score = 2) or severe (score = 3) using standard atlas images (Figure 1), and then
6 dichotomised as possible (score = 0 or 1) or definite (score = 2 or 3). To establish inter-rater
7 reliability of enthesophyte scoring, HBM and MM independently scored 120 lateral
8 radiographs (60 right foot, 60 left foot). Reliability was excellent for both plantar and
9 posterior enthesophytes (quadratic weighted kappa 0.82, 95% CI 0.76 – 0.89; percentage
10 agreement 94% and 0.79, 95% CI 0.70 – 0.88; 94%, respectively).
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18 **Statistical analysis**

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21 All analyses were conducted using SPSS Version 22 (IBM Corporation, Armonk, NY).
22 Person-level associations between enthesophytes and hand and foot OA phenotypes were
23 explored using logistic regression. Individual joint associations between enthesophytes and
24 OA features (OA case definition, osteophytes and joint space narrowing) in each hand and
25 foot joint were explored using generalised estimating equations to account for the
26 correlation between measurements obtained from the right and left limbs in the participant.
27 Age, sex and body mass index were considered to be confounding variables and were
28 adjusted for in all analyses. Odds ratios with 95% confidence intervals are presented and
29 statistical significance was determined as $p < 0.05$.
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39 **RESULTS**

40 **Study population**

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43 As previously reported, a total of 5,109 completed Health Survey questionnaires were
44 received (adjusted response 56%) (21). Of these, 1,635 individuals who reported pain in and
45 around the foot in the past 12 months and provided written consent to further contact were
46 invited to the research assessment clinic and 560 attended. Individuals with inflammatory
47 arthritis (n=24) were excluded, and complete hand and foot radiographs were unavailable
48 for 4 participants, leaving a total of 532 eligible participants for this analysis (298 women
49 and 234 men, mean [SD] age 64.9 [8.4] years, mean [SD] body mass index 30.4 [5.6]
50 kg/m²).
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Prevalence of enthesophytes and OA features

Posterior enthesophytes were present in 174 feet (16%) and plantar enthesophytes were present in 283 feet (27%). The prevalence of hand OA phenotypes was as follows: no hand OA (n=250 participants, 47%), generalised hand OA (n=46, 9%), thumb base OA (n=227, 43%) and IPJ OA (n=137, 26%). The prevalence of foot OA phenotypes was as follows: no or minimal foot OA (n=340 participants, 64%), isolated 1st MTPJ OA (n=115, 22%) and polyarticular foot OA (n=77, 14%).

Associations between calcaneal enthesophytes and hand and foot OA phenotypes

Table 1 reports the person-level associations between calcaneal enthesophytes and foot and hand OA phenotypes. Odds ratios (ORs) ranged from 0.69 to 1.80. There was a reduced odds of having a plantar enthesophyte in those with thumb base OA (OR 0.69, 95% confidence interval [CI] 0.46 – 1.03, although not reaching statistical significance), and an increased odds of having a plantar enthesophyte in those with polyarticular foot OA (OR 1.80, 95% CI 1.02 – 3.17, $p<0.05$).

Associations between calcaneal enthesophytes and hand OA

Table 2 reports individual joint associations between calcaneal enthesophytes and hand OA. ORs ranged from 0.25 to 1.70, but the confidence intervals were wide. There were no significant associations between enthesophytes and hand OA features, with the exception of plantar enthesophytes being negatively associated with joint space narrowing of the middle finger DIPJ (OR 0.25, 95% CI 0.10 – 0.65, $p<0.05$).

Associations between calcaneal enthesophytes and foot OA

Table 3 reports individual joint associations between calcaneal enthesophytes and foot OA. ORs ranged from 0.41 to 3.12. Posterior enthesophytes were significantly associated with OA of the TNJ (OR 1.58, 95% CI 1.02 – 2.44, $p<0.05$) and osteophytes of the TNJ (OR 1.63, 95%CI 1.03 – 2.58, $p<0.05$), while plantar enthesophytes were significantly associated with OA of the 1st MTPJ (OR 0.67, 95% CI 0.48 – 0.94, $p<0.05$) and NCJ (OR 2.30, 95% CI 1.40 – 3.79, $p<0.01$), osteophytes of the 1st MTPJ (OR 0.69, 95% CI 0.49 – 0.98, $p<0.05$)

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3 and NCJ (OR 3.12, 95%CI 1.67 – 5.85, $p<001$), and joint space narrowing of the NCJ (OR
4 2.56, 95% CI 1.39 – 4.74, $p<0.01$).
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7 8 **DISCUSSION** 9

10 The objective of this study was to examine associations between calcaneal enthesophytes
11 and osteoarthritis (OA) in the hands and feet, in order to provide insights into the role of
12 biomechanical and systemic processes in the development of OA. We found that calcaneal
13 enthesophytes were not associated with any hand OA phenotype or with the case definition
14 of OA at individual hand joints. In contrast, plantar calcaneal enthesophytes were associated
15 with the polyarticular foot OA phenotype and with OA features at several individual foot
16 joints. Taken together, these findings suggest that calcaneal enthesophytes may result from a
17 local, biomechanical process rather than a systemic ‘bone forming’ process.
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25 Our findings are inconsistent with those of Rogers et al (12, 13), who reported strong
26 associations between generalised enthesophytes and osteophytes in the upper and lower
27 limbs in skeletal remains. However, it has been argued that differentiating between
28 osteophytes and enthesophytes may be difficult in such specimens, and the inability to
29 accurately determine the age of the specimens may have led to confounding (25). Indeed,
30 subsequent studies that adjusted for age reported no association between hand enthesophytes
31 and bone marrow lesions at the knee (17), no or weak associations between enthesophytes
32 and osteophytes in the hand (16, 26), and no association between calcaneal enthesophytes
33 and upper or lower limb OA (11). Our findings are similar and suggest that although
34 enthesophytes and osteophytes frequently coexist, they may be initiated by different
35 processes.
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46 Osteophytes develop through a process of chondrocyte hypertrophy and endochondral
47 ossification, resulting in deposition of bone in the periosteum. Although this pathway is
48 thought to be initiated by both mechanical and biochemical stimuli, observations of cartilage
49 formation in the periosteum of immobilised joints suggest that mechanical stresses are not
50 essential for osteophyte development (27). Enthesophytes also develop in response to
51 endochondral ossification and may therefore have a similar pathophysiology to osteophytes.
52 However, calcaneal enthesophytes in particular may be more responsive to mechanical
53 stimuli due to the weightbearing function of the foot. Indeed, histological studies suggest
54 that calcaneal enthesophytes increase the surface area of the interface between tendon and
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3 bone, and may therefore be an adaptive mechanism to protect the enthesis from excessive
4 mechanical loading (6, 28).
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8 We found several associations between calcaneal enthesophytes and OA features in foot
9 joints that may be indicative of a local, mechanical aetiology. First, posterior calcaneal
10 enthesophytes, which are thought to result from increased tensile forces in the Achilles
11 tendon (28), were positively associated with talonavicular joint OA. The talonavicular joint
12 is a ball and socket joint that moves in concert with the subtalar/ankle joint complex and has
13 a significant dorsiflexion component (29). In the presence of OA, it is likely that the
14 available range of dorsiflexion at the talonavicular joint is decreased, thereby leading to
15 greater tension in the Achilles tendon as the tibia moves over the foot during the propulsive
16 phase of gait. Second, plantar enthesophytes were positively associated with the
17 polyarticular foot OA phenotype and OA affecting the navicular-cuneiform joint. OA
18 affecting the midfoot joints has been associated with pronated ('flat') foot type (30, 31),
19 which is in turn associated with increased traction of the insertion of the plantar fascia into
20 the calcaneal enthesis (32). Finally, the negative association between plantar enthesophytes
21 and 1st MTPJ OA may also be related to the role of foot posture, as while plantar
22 enthesophytes are positively associated with pronated foot posture (33, 34), 1st MTPJ OA is
23 not (35).
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38 Strengths of our study include the population-based sample and the use of standardised
39 imaging and assessment for both the hands and feet. However, our findings need to be
40 interpreted in the context of several limitations. First, the overall response to the postal
41 health survey questionnaire from which the clinical sample was derived was lower than
42 expected. However, responders to the questionnaire did not differ greatly from the mailed
43 population (21). Second, we did not have access to knee radiographs in this population,
44 which would have enabled more direct comparisons to previous studies (14, 15, 17) and
45 provided an additional remote site to examine these associations. Third, our use of
46 radiographs did not enable us to identify the precise location of the calcaneal enthesophytes.
47 Although posterior enthesophytes are most commonly located within the Achilles tendon,
48 plantar enthesophytes are more variable, and may develop within intrinsic muscles and
49 loose connective tissue as well as within the plantar fascia itself (36). Finally, our
50 interpretation of the possible mechanical links between enthesophytes and OA in the foot is
51 inherently speculative and requires confirmation with biomechanical assessment techniques.
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5 In summary, our study has shown that calcaneal enthesophytes are more strongly associated
6 with foot OA than hand OA and have similar associations with osteophytes and joint space
7 narrowing. This pattern of association suggests that calcaneal enthesophytes primarily result
8 from a local, biomechanical process rather than a systemic 'bone forming' process. Future
9 investigations incorporating observations of osteophytes and enthesophytes from multiple
10 joints are required to provide further insights into the relative role of systemic and
11 biomechanical processes in the pathophysiology of OA.
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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Menz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Menz, Marshall, Thomas, Peat, Roddy.

Acquisition of data. Marshall, Thomas, Roddy.

Analysis and interpretation of data. Menz, Marshall, Thomas, Rathod-Mistry, Peat, Roddy

ACKNOWLEDGEMENTS

We would like to thank the administrative, health informatics and research nurse teams of Keele University's Arthritis Research UK Primary Care Centre, the staff of the participating general practices and the Haywood Hospital, particularly Dr Jackie Saklatvala, Carole Jackson and the radiographers at the Department of Radiology. We would like to acknowledge the contributions of Linda Hargreaves, Gillian Levey, Liz Mason, Dr Jennifer Pearson, Julie Taylor and Dr Laurence Wood to data collection.

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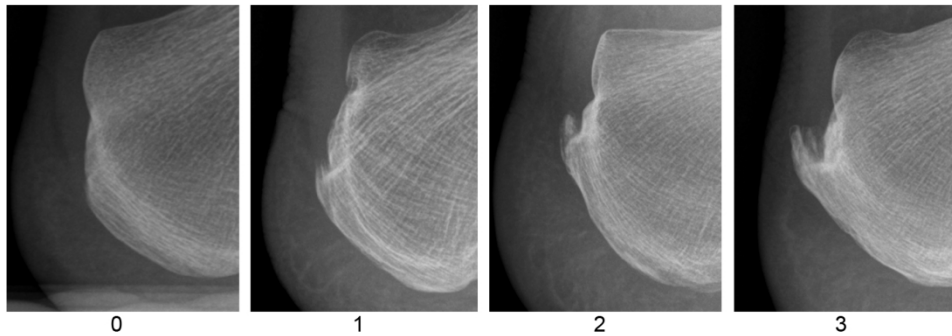
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3 **Figure legends**
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6 **Figure 1.** Standardised images used to identify presence of posterior and plantar calcaneal
7 enthesophytes. Enthesophytes were considered to be definitely present if a score of 2 or
8 above was documented.
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For Peer Review Only

Posterior calcaneal enthesophytes



Plantar calcaneal enthesophytes

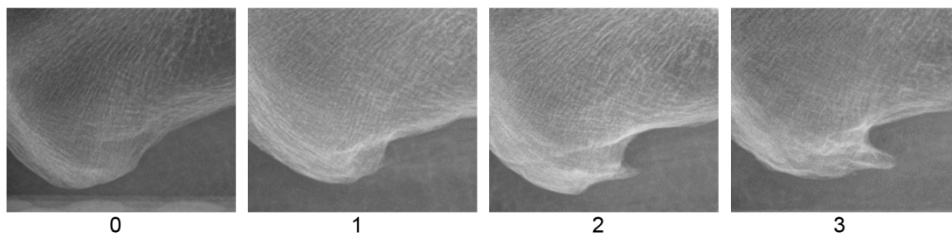


Figure 1. Standardised images used to identify presence of posterior and plantar calcaneal enthesophytes. Enthesophytes were considered to be definitely present if a score of 2 or above was documented.

Table 1. Associations between hand OA phenotypes, foot OA phenotypes and enthesophytes.¹ Data are odds ratios (95% confidence intervals).

	Posterior enthesophyte	Plantar enthesophyte
Hand OA ²		
Generalised	0.75 (0.33 – 1.71)	0.93 (0.45 – 1.91)
Thumb base	1.06 (0.70 – 1.62)	0.69 (0.46 – 1.03)
IPJ	1.16 (0.72 – 1.89)	1.02 (0.65 – 1.61)
Foot OA ³		
1 st MTPJ	1.08 (0.65 – 1.78)	0.93 (0.58 – 1.50)
Polyarticular	1.30 (0.71 – 2.36)	1.80 (1.02 – 3.17)*

Notes:

¹ analysis at person level, logistic regression adjusted for age, sex and body mass index

² overlapping hand OA phenotypes from Marshall et al (22). Reference category is no hand OA or other two phenotypes

³ discrete foot OA phenotypes from Rathod et al (24). Reference category is no or minimal foot OA

* $p < 0.05$

Table 2. Associations between enthesophytes and OA in each hand joint.¹ Data are odds ratios (95% confidence intervals).

	Posterior enthesophytes			Plantar enthesophytes		
	OA ²	OP ²	JSN ²	OA ²	OP ²	JSN ²
Little finger DIPJ	1.10 (0.68 – 1.78)	0.86 (0.29 – 2.54)	0.74 (0.34 – 1.62)	0.81 (0.55 – 1.20)	0.62 (0.34 – 1.14)	0.88 (0.49 – 1.60)
Ring finger DIPJ	1.05 (0.51 – 2.14)	1.61 (0.66 – 3.93)	0.83 (0.33 – 2.09)	0.89 (0.49 – 1.61)	0.85 (0.33 – 2.18)	0.49 (0.21 – 1.14)
Middle finger DIPJ	0.92 (0.53 – 1.63)	0.92 (0.46 – 1.84)	0.42 (0.17 – 1.03)	0.76 (0.46 – 1.25)	0.71 (0.40 – 1.28)	0.25 (0.10 – 0.65)*
Index finger DIPJ	0.88 (0.55 – 1.39)	0.90 (0.51 – 1.56)	0.72 (0.36 – 1.43)	1.12 (0.77 – 1.63)	0.93 (0.50 – 1.73)	0.82 (0.40 – 1.66)
Little finger PIPJ	0.99 (0.47 – 2.09)	0.73 (0.12 – 4.38)	0.62 (0.07 – 5.43)	1.35 (0.72 – 2.54)	0.58 (0.09 – 3.55)	0.44 (0.05 – 3.88)
Ring finger PIPJ	0.28 (0.04 – 1.96)	NC	0.51 (0.05 – 5.72)	0.35 (0.10 – 1.13)	0.27 (0.03 – 2.54)	1.02 (0.40 – 2.58)
Middle finger PIPJ	0.88 (0.40 – 1.95)	NC	0.70 (0.15 – 3.23)	0.81 (0.40 – 1.65)	NC	0.96 (0.31 – 3.03)
Index finger PIPJ	0.71 (0.35 – 1.43)	1.70 (0.55 – 5.24)	0.70 (0.15 – 3.23)	1.19 (0.68 – 2.09)	0.78 (0.24 – 2.52)	0.96 (0.31 – 3.03)
Thumb IPJ	1.05 (0.68 – 1.63)	NC	NC	0.81 (0.54 – 1.23)	NC	NC
CMCJ	0.92 (0.61 – 1.40)	0.96 (0.55 – 1.67)	0.70 (0.32 – 1.57)	0.88 (0.64 – 1.21)	1.20 (0.79 – 1.84)	0.63 (0.33 – 1.21)
TSJ	1.02 (0.51 – 2.03)	NC	NC	1.07 (0.61 – 1.88)	NC	NC

Notes:

¹ analysis at the hand level, generalised estimating equations adjusted for age, sex and body mass index² osteoarthritis (OA), osteophyte (OP) and joint space narrowing (JSN) according to Kellgren and Lawrence score ≥ 2 * $p < 0.05$

NC: not calculable due to insufficient cell count

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Table 3. Associations between enthesophytes and OA in each foot joint.¹ Data are odds ratios (95% confidence intervals).

	Posterior enthesophytes			Plantar enthesophytes		
	OA ²	OP ³	JSN ⁴	OA ²	OP ³	JSN ⁴
1 st MTPJ	0.75 (0.51 – 1.11)	0.73 (0.49 – 1.07)	0.86 (0.50 – 1.48)	0.67 (0.48 – 0.94)*	0.69 (0.49 – 0.98)*	1.02 (0.61 – 1.69)
1 st CMJ	0.70 (0.31 – 1.59)	0.84 (0.34 – 2.05)	0.41 (0.09 – 1.83)	1.28 (0.71 – 2.31)	1.17 (0.52 – 2.64)	1.33 (0.61 – 2.94)
2 nd CMJ	1.03 (0.64 – 1.65)	1.14 (0.60 – 2.17)	0.92 (0.54 – 1.58)	1.41 (0.95 – 2.09)	1.26 (0.72 – 2.22)	1.44 (0.93 – 2.21)
NCJ	1.09 (0.56 – 2.12)	1.49 (0.74 – 3.00)	0.76 (0.32 – 1.83)	2.30 (1.40 – 3.79)**	3.12 (1.67 – 5.85)**	2.56 (1.39 – 4.74)**
TNJ	1.58 (1.02 – 2.44)*	1.63 (1.03 – 2.58)*	1.33 (0.54 – 3.27)	1.15 (0.78 – 1.70)	1.15 (0.76 – 1.73)	1.27 (0.70 – 2.32)

Notes:
¹ analysis at the foot level, generalised estimating equations adjusted for age, sex and body mass index
² osteoarthritis case definition using Menz et al (23) atlas
³ osteophyte score of ≥2 using Menz et al (23) atlas
⁴ joint space narrowing score of ≥2 using Menz et al (23) atlas
* $p < 0.05$, ** $p < 0.01$