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Metabolic Syndrome and Osteoarthritis Distribution in the Hand Joints: A Propensity Score Matching Analysis From the Osteoarthritis Initiative

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ABSTRACT. ***Objective.*** To investigate the metabolic syndrome (MetS) association with radiographic and symptomatic hand osteoarthritis (HOA).

Methods. Using 1:2 propensity score matching for relevant confounders, we included 2509 participants (896 MetS positive and 1613 MetS negative) from the Osteoarthritis Initiative dataset. MetS and its components, according to the International Diabetes Federation criteria, were extracted from baseline data, and included hypertension, abdominal obesity, dyslipidemia, and diabetes. We scored distinct hand joints based on the modified Kellgren-Lawrence (mKL) grade of baseline radiographs, with HOA defined as mKL ≥ 2. In the cross-sectional analysis, we investigated the association between MetS and its components with radiographic HOA and the presence of nodal and erosive HOA phenotypes using regression models. In the longitudinal analysis, we performed Cox regression analysis for hand pain incidence in follow-up visits.

Results. MetS was associated with higher odds of radiographic HOA, including the number of joints with OA (OR 1.32, 95% CI 1.08–1.62), the sum of joints mKLs (OR 2.42, 95% CI 1.24–4.71), mainly in distal interphalangeal joints (DIPs) and proximal interphalangeal joints (PIPs; OR 1.52, 95% CI 1.08–2.14 and OR 1.38, 95% CI 1.09–1.75, respectively), but not metacarpophalangeal (MCP) and first carpometacarpal (CMC1) joints. Hand pain incidence during follow-up was higher with MetS presence (HR 1.25, 95% CI 1.07–1.47). The erosive HOA phenotype and joints' nodal involvement were more frequent with MetS (OR 1.40, 95% CI 1.01–1.97 and OR 1.28, 95% CI 1.02–1.60, respectively).

Conclusion. MetS, a potentially modifiable risk factor, is associated with radiographic DIP and PIP OA and longitudinal hand pain incidence while sparing MCPs and CMC1s. Nodal and erosive HOA phenotypes are associated with MetS, suggestive of possible distinct pathophysiology.

Key Indexing Terms: erosive osteoarthritis, hand, metabolic syndrome, nodal osteoarthritis, Osteoarthritis Initiative, propensity score matching

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The hand joints are commonly affected by osteoarthritis (OA), with an approximately 40% occurrence rate in the general population.[1] It has been shown that symptomatic hand OA (HOA) limits daily functional activities and can compromise social life, especially in the elderly population.[2] While the exact etiology of HOA is not well understood, it is thought to present in heterogeneous phenotypes according to its underlying etiology, risk factors, and associated pathophysiology.[3,4] Since no disease-modifying OA drug has been proven effective for HOA,[5] a better understanding of HOA phenotypes and any associated "modifiable" risk factors is essential to improve treatment outcomes.[3,6]

Metabolic risk factors have been associated with OA in peripheral joints such as the knee, hip,[7] and, less unanimously, hand joints[8,9,10,11] and are considered potentially modifiable OA risk factors.[6,12,13] While there is no unified definition for metabolic syndrome (MetS), a combination of known metabolic risk factors such as abdominal (i.e., central) obesity, dyslipidemia, hypertension, and diabetes are commonly included in the MetS criteria.[14,15]

Compared to other peripheral joints, the previous reports on the association between MetS and HOA have been less consistent.[10,11,12,16,17] This could be a result of the following: (1) aggregate analysis of all hand joint groups rather than distinct evaluations of individual hand joints, which could have specific pathophysiology and risk factors;[18,19,20,21] (2) study design (longitudinal vs cross-sectional); (3) different definitions of HOA (clinical/symptomatic vs radiographic HOA); (4) study populations and prevalence of relevant comorbid conditions; and perhaps most importantly, (5) relevant confounders not being appropriately addressed. Thus, using a propensity score (PS) matched design, on a large cohort of participants from the Osteoarthritis Initiative (OAI) dataset, we aimed to investigate the association MetS with the radiographic distribution of HOA among each distinct joint group of the hand at baseline and the pain outcome in follow-up examinations. We also assessed the association of MetS with different HOA phenotypes.

METHODS

Study population and design. We used data from the publicly available OAI database. OAI is a multicenter, ongoing cohort study (OAI protocol details are available at https://nda.nih.gov/oai/study-details). In brief, men and women between ages 45 to 79 years from all ethnic groups were included. Participants with physician-diagnosed inflammatory arthritis, with endstage forms of knee OA, or unable to undergo magnetic resonance imaging (MRI) examination were excluded. Participants who met the selection criteria but were unwilling to participate were considered as recruitment failures.

From a total of 4796 OAI participants, the ones with unavailable baseline hand radiographs (n = 92) and undetermined assessment of either of the MetS components at the baseline visit (n = 32) were excluded from the study, and a total of 4672 participants were included in the PS matching analysis (Figure 1). We performed a cross-sectional assessment of radiographic HOA grading and HOA phenotypes and while using a cohort design, we assessed the longitudinal incidence of hand pain.

Assessment of MetS. Similar to the previous relevant OAI studies on MetS, we defined MetS presence and components according to the International Diabetes Federation criteria,[14] at the baseline visit. Hypertension was defined as ≥ 130 mmHg systolic blood pressure (BP) or ≥ 85 mmHg diastolic BP at the baseline physical examination or being on BP-lowering medication, indicated in the assessment participants' medication inventory form (MIF) at baseline visit. Diabetes was indicated by self-reported diabetes or the presence of antidiabetic medications in the MIFs. Dyslipidemia was defined as using lipid-lowering medications as indicated in the participants' MIF at baseline. Abdominal obesity was defined as a waist circumference of ≥ 94 cm in men and ≥ 80 cm in women on physical examination.[14] Participants with abdominal obesity and at least 2 of the other components (dyslipidemia, diabetes, and hypertension) were regarded as MetS positive (MetS+).

Cross-sectional assessment of radiographic HOA. Baseline posteroanterior radiographs of the dominant or left hand (in case of ambidexterity) were obtained from the OAI dataset (including 2196 right-handed, 146 left-handed, and 31 participants with ambidexterity). Because the radiographic HOA gradings were not publicly available in OAI dataset, in this study, a trained musculoskeletal radiologist (with 7 yrs of experience), unaware of any subject's demographics, assessed all radiographs. The severity of radiographic HOA was assessed in the distal interphalangeal joints (DIPs) and proximal interphalangeal joints (PIPs), and the thumb interphalangeal (IP), metacarpophalangeal (MCP), and first carpometacarpal (CMC1 or thumb base) joints. Modified Kellgren–Lawrence (mKL) grading was used[22] (Supplementary Table 1, available from the authors upon request) with radiographic HOA in a joint defined as mKL ≥ 2. The main radiographic dependent variables included the highest mKL grade between the assessed joints (maximum mKL), the total number of joints with OA, and the summation of mKL of all assessed joints (mKL sum). Moreover, all hand joints were evaluated for the presence of erosive HOA, a subtype of HOA, defined as Verbruggen-Veys erosive or remodeled phase[23] in ≥ 1 joint in participants with HOA. The mKL grading system has been shown to have good reliability and intraclass correlation coefficient (ICC) in previous studies.[24] For our assessment, we have previously evaluated the reader's reliability with the concordance with an expert reader,[25] and results showed a good concordance for the sum of mKL scores. Moreover, our results showed an ICC of 0.88 (95% CI 0.80–0.93).

Longitudinal assessment of hand pain incidence outcome. Hand pain was defined as an affirmative answer to the question, "Have you felt hand/finger pain, aching or stiffness more than half the days, in the past 30 days?" OAI participants responded to this question in baseline assessment and at 6 OAI follow-up visits (yrs 1, 2, 3, 4, 6, and 8). A potential barrier for an accurate evaluation of temporal features of pain is the fluctuating nature of HOA pain and lack of reliability for patient-reported outcome measures at multiple follow-ups such as binary reports for the presence of hand pain.[26] Therefore, similar to other validated measures of pain incidence in OA,[27] we have indicated pain incidence as a positive response to the above question, not in its first occurrence, but when the pain was reported consecutively at ≥ 2 visits. Considering that participants without HOA at baseline radiograph may develop HOA in later follow-up visits, both participant groups with and without HOA at baseline were included in the longitudinal assessment of hand pain incidence.

Assessment of HOA phenotypes. At baseline physical examination, the OAI trained medical staff assessed the presence of Heberden nodes (HNs) in the DIP joints on the second to fifth digits of both hands, and subjects with at least 1 HN were categorized as having "nodal HOA." Participants with at least 1 joint with evident erosion were indexed as having an "erosive HOA" phenotype.

Statistical analyses. To explore the possible confounders with available data in the OAI project, we used a direct acyclic graph for the presentation of potential confounders[28] on the mutual HOA and MetS risk factors, according to previously published metaanalyses[29,30] (Supplementary Figure 1, available from the authors upon request). Potential confounders included age (yrs), sex (man/woman), race (White/non-White), educational level, BMI (quartiles), smoking (never smoked, past smoker, < 14 cigarettes/day, ≥ 14 cigarettes/day), alcohol consumption (none, < 1, 1–3, 4–7, 8–14, and ≥ 15 units/week), level of physical activity according to physical activity for elderly score questionnaire, and daily lifting of heavy objects with hands

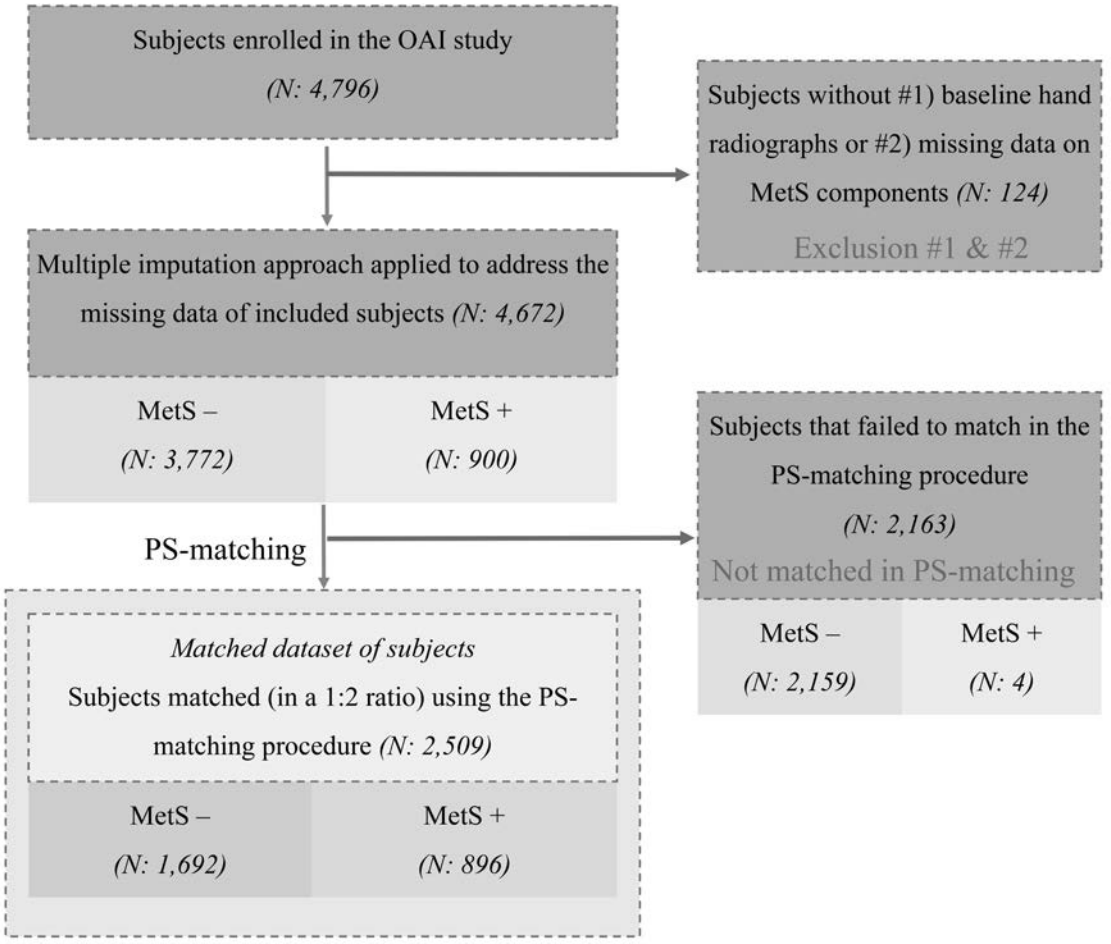

Figure 1. Flowchart of study participants. MetS: metabolic syndrome; MetS−: metabolic syndrome negative; MetS+: metabolic syndrome positive; mKL OAI: Osteoarthritis Initiative; PS: propensity score.

(yes/no). These variables were included in both multiple imputations and PS matching methods (explained below).

Considering that excluding the missing data in the analysis may lead to biased estimates,[31] we used multiple imputation methods to estimate missing values in the confounding variables (< 1.3% of data, detail presented in Supplementary Data and Supplementary Table 2, available from the authors upon request). After we imputed the missing data, we further matched subjects for the presence of MetS+ and MetS negative (MetS−) using the 1:2 PS matching with the nearest-neighbor method and a caliper of 0.1 in the logistic regression model. The deviation of variables between groups was evaluated using the standardized mean difference (SMD), with a value of ≥ 0.1 indicated as an imbalance.[32]

Logistic and linear regression models were used to investigate the association between HOA status (dependent variables) and the presence of MetS (primary independent variable). Linear regression models were used to assess numeric dependent variables (sum of mKL in hand or hand joint groups and sum of hand joints with OA). ORs were calculated by the exponential transformation of β coefficients for ease of presentation and interpretation. All models were adjusted for the PS of the participants. We further assessed the collective influence of multiple components of MetS using the number of metabolic risk factors in a dose-response manner (0–4) and as the independent variable. Since the independent variable here (number of metabolic risk factors) differed from the exposure variable in PS matching (presence of MetS), we further adjusted the model for all variables included in the PS matching model.

After checking and confirming assumptions of proportional hazards, linear covariate relationships, and lack of independence, Cox proportional hazard was used to assess longitudinal incidence in the hand pain while considering adjustment for PS and clusters of matched participants in the model.

The open-source R software version 3.6.2 (lme4, lmerTest, MASS, haven, survival, MatchIt, mice, and tableone packages; R Foundation for Statistical Computing) was used for statistical analysis.

Sensitivity analysis. We assessed the sensitivity of the results to removing imputed data and using an alternative definition of MetS (National Cholesterol Education Program Adult Treatment Panel III definition).[15]

Ethics. The medical ethics review boards of the University of California, San Francisco (approval number 10-00532), and the 4 clinical centers of the OAI project recognized the project as Health Insurance Portability and Accountability Act compliant. Subjects gave informed consent before participating in the OAI project.

RESULTS

Characteristics of study participants. After PS matching, a total of 2509 participants (1613 MetS+ and 896 matched MetS−) were included in the study (Table 1). Both MetS+ and MetS− matched groups had an average age of approximately 64.5 (SD 8.5) years, and approximately 55% of them were women, with proper balance for all the PS matched variables (SMD < 0.100).

Table 1. Baseline characteristics of the study population before and after PSM according to the presence of MetS, defined by IDF criteria.

	All OAI Subjects			Matched Subjects		
	MetS− n = 3772	MetS+ n = 900	SMD[a]	MetS− n = 1613	MetS+ n = 896	SMD
Variables included in the PSM model						
Age, yrs, mean (SD)	60.27 (9.11)	65.00 (8.48)	**0.537**	64.14 (8.67)	64.96 (8.48)	0.096
Women, n (%)	2236 (59.3)	491 (54.6)	0.095	914 (56.7)	490 (54.7)	0.040
Non-White race[b], n (%)	718 (19.0)	248 (27.6)	**0.203**	408 (25.3)	245 (27.3)	0.047
BMI, kg/m^2, mean (SD)	28.11 (4.79)	30.72 (4.43)	**0.565**	30.27 (4.44)	30.69 (4.42)	0.094
Educational level, n (%)	–	–	**0.246**	–	–	0.045
High school graduate or less	565 (15.0)	205 (22.8)	–	338 (21.0)	204 (22.8)	–
College graduate or unfinished college education	1685 (44.7)	419 (46.6)	–	758 (47.0)	416 (46.4)	–
Graduate degree or unfinished graduate school	1522 (40.3)	276 (30.7)	–	517 (32.1)	276 (30.8)	–
Alcohol use, drinks/week, n (%)	–	–	**0.206**	–	–	0.043
None	694 (18.4)	223 (24.8)	–	376 (23.3)	222 (24.8)	–
< 1	1415 (37.5)	332 (36.9)	–	612 (37.9)	329 (36.7)	–
1–3	593 (15.7)	99 (11.0)	–	182 (11.3)	99 (11.0)	–
4–7	574 (15.2)	119 (13.2)	–	221 (13.7)	119 (13.3)	–
8–14	338 (9.0)	78 (8.7)	–	141 (8.7)	78 (8.7)	–
15+	158 (4.2)	49 (5.4)	–	81 (5.0)	49 (5.5)	–
Smoking, n (%)	–	–	**0.124**	–	–	0.019
Never smoked	2039 (54.1)	439 (48.8)	–	788 (48.9)	436 (48.7)	–
Past smoker	1481 (39.3)	403 (44.8)	–	726 (45.0)	402 (44.9)	–
Smoker < 14 cigarettes/d	145 (3.8)	39 (4.3)	–	64 (4.0)	39 (4.4)	–
Smoker ≥ 14 cigarettes/d	107 (2.8)	19 (2.1)	–	35 (2.2)	19 (2.1)	–
PASE score, mean (SD)	165.57 (83.09)	140.89 (75.84)	**0.310**	143.81 (75.20)	141.18 (75.87)	0.035
Lift objects > 25 lbs most days, n (%)	1378 (36.5)	323 (35.9)	0.013	578 (35.8)	323 (36.0)	0.004
Variables not included in the PSM model						
Pain in the hands[c], n (%)	2933 (77.8)	667 (74.1)	0.085	1236 (76.6)	665 (74.2)	0.056
Presence of HNs, n (%)	2281 (60.5)	584 (64.9)	0.091	1002 (62.1)	581 (64.8)	0.057
No. of HNs, mean (SD)	2.29 (2.62)	2.68 (2.78)	**0.147**	2.41 (2.66)	2.69 (2.79)	0.102
Hand OA[d], n (%)	–	–	**0.252**	–	–	0.123
Erosive hand OA	171 (4.5)	63 (7.0)	–	81 (5.0)	63 (7.0)	–
No hand OA	2373 (62.9)	456 (50.7)	–	903 (56.0)	453 (50.6)	–
Non-erosive hand OA	1228 (32.6)	381 (42.3)	–	629 (39.0)	380 (42.4)	–
Hypertension[e], n (%)	1353 (35.9)	862 (95.8)	**1.629**	728 (45.1)	858 (95.8)	1.334
Diabetes mellitus[e], n (%)	40 (1.1)	322 (36.7)	**1.022**	23 (1.5)	319 (36.5)	0.999
Dyslipidemia[e], n (%)	503 (13.3)	795 (88.3)	**2.268**	250 (15.5)	793 (88.5)	2.140
Abdominal obesity[e], n (%)	3105 (84.4)	900 (100.0)	**0.608**	1485 (93.2)	896 (100.0)	0.383

Values in bold are representative of a statistically significant imbalance. Quantitative variables are shown as mean (SD), and qualitative variables are shown as n (%). [a]Significant difference for SMD was defined as ≥ 0.1. [b]Race of participants was categorized as White and non-White, considering the small number of participants in each non-White race group. [c] The hand pain in the baseline visit was defined as a positive answer to the question, "Have you felt hand/finger pain, aching, or stiffness more than half the days, in the past 30 days?" [d] Hand OA was defined as ≥ 1 joint with mKL ≥ 2, and erosive OA was defined as ≥ 1 joint with the presence of Verbruggen-Veys erosive or remodeled phase in hand radiographs in subjects with hand OA. [e] Components of MetS defined by IDF were defined as (1) hypertension: ≥ 130 mmHg systolic BP or ≥ 85 mmHg diastolic BP at baseline physical examination or on BP-lowering medication indicated in the medication history; (2) diabetes: self-reported diabetes or use of oral or injectable antidiabetic medications indicated in the participant's medication history; (3) dyslipidemia: use of lipid-lowering medications indicated in the participant's medication history; and (4) abdominal obesity: waist circumference of ≥ 94 cm in men and ≥ 80 cm in women. According to the IDF criteria, MetS is defined as abdominal obesity and at least 2 of hypertension, dyslipidemia, and diabetes. BP: blood pressure; HN: Heberden node; IDF: International Diabetes Federation; MetS: metabolic syndrome; mKL: modified Kellgren-Lawrence; OA: osteoarthritis; OAI: Osteoarthritis Initiative; PASE: Physical Activity Scale for the Elderly; PSM: propensity score matching; SMD: standardized mean difference.

Association of MetS and cross-sectional HOA measures and involved joints. The presence of MetS was associated with a higher number of hand joints with radiographic HOA (OR 1.32, 95% CI 1.08–1.62; Table 2). Further, the presence of MetS was associated with the mKL sum score (OR 2.42, 95% CI 1.24–4.71) and maximum mKL in hand joints (OR 1.21, 95% CI 1.05–1.40). The collective influence of multiple MetS components, examined using the number of metabolic risk factors, showed similar results in a dose-response fashion (Table 2).

Further, assessment of HOA status separately in PIP, DIP, MCP, and CMC1 joints showed that the presence of MetS was associated with the total number of DIP joints with HOA

Table 2. Association of hand OA status with the presence of MetS and the number of present MetS components, defined by IDF, in PS matched study subjects.

Hand OA Status	Mean (SD) or n (%)		OR[a] (95% CI) n = 2509 Independent Variable	
Radiographic Assessment of Hand Joints	MetS−, n = 1613	MetS+, n = 896	MetS Presence	No. of MetS Components
Sum of hand joints mKL grades[b]	7.38 (8.13)	8.56 (8.63)	**2.42 (1.24–4.71)**	**1.93 (1.42–2.63)**
Total no. of hand joints with OA (mKL ≥ 2)[b]	1.76 (2.43)	2.11 (2.65)	**1.32 (1.08–1.62)**	**1.21 (1.10–1.33)**
Maximum mKL grade in hand joints	–	–	**1.21 (1.05–1.40)**	**1.17 (1.08–1.26)**
Grade 0	505 (31.3)	239 (26.7)	–	–
Grade 1	400 (24.8)	216 (24.1)	–	–
Grade 2	396 (24.6)	218 (24.3)	–	–
Grade 3	139 (8.6)	104 (11.6)	–	–
Grade 4	173 (10.7)	119 (13.3)	–	–
Sum of PIP joints mKL grades[b]	1.68 (2.85)	2.07 (3.05)	**1.38 (1.09–1.75)**	**1.25 (1.12–1.40)**
No. of PIP joints with OA (mKL ≥ 2)[b]	0.49 (1.05)	0.63 (1.17)	**1.13 (1.03–1.23)**	**1.08 (1.03–1.12)**
Sum of DIP joints mKL grades[b]	3.33 (4.10)	3.85 (4.38)	**1.52 (1.08–2.14)**	**1.36 (1.16–1.60)**
No. of DIP joints with OA (mKL ≥ 2)[b]	0.98 (1.44)	1.17 (1.54)	**1.15 (1.02–1.30)**	**1.10 (1.04–1.17)**
Sum of IP joints (DIPs and PIPs) mKL grades[b]	5.83 (6.98)	6.86 (7.45)	**2.27 (1.28–4.05)**	**1.80 (1.38–2.35)**
No. of IP joints with OA (mKL ≥ 2)[b]	1.93 (2.62)	2.30 (2.84)	**1.33 (1.07–1.65)**	**1.23 (1.11–1.36)**
Sum of MCP joints mKL grades[b]	0.59 (1.44)	0.67 (1.54)	1.04 (0.92–1.17)	1.05 (0.99–1.11)
No. of MCP joints with OA (mKL ≥ 2)[b]	0.17 (0.51)	0.19 (0.56)	1.01 (0.97–1.05)	1.02 (1.00–1.04)
CMC1 mKL grade	–	–	1.00 (0.86–1.17)	1.02 (0.93–1.10)
Grade 0	854 (53.2)	468 (52.5)	–	–
Grade 1	261 (16.3)	134 (15.0)	–	–
Grade 2	278 (17.3)	165 (18.5)	–	–
Grade 3	105 (6.5)	55 (6.2)	–	–
Grade 4	106 (6.6)	69 (7.7)	–	–
Presence of erosive OA	81 (5.0)	63 (7.0)	**1.40 (1.01–1.97)**	**1.29 (1.06–1.57)**
Total no. of hand joints with erosive OA[b]	0.09 (0.47)	0.12 (0.52)	1.03 (0.99–1.07)	1.02 (1.00–1.05)
Presence of nodal OA	1002 (62.1)	581 (64.8)	1.09 (0.92–1.29)	1.07 (0.97–1.17)
Total no. of hand joints with nodal OA[b]	2.41 (2.66)	2.69 (2.79)	**1.28 (1.02–1.60)**	**1.17 (1.06–1.30)**
Symptomatic assessment of hand joints				
Baseline: self-reported pain in the hands[c]	1236 (76.6)	665 (74.2)	0.89 (0.74–1.08)	0.94 (0.85–1.04)
Longitudinal: hand pain incidence (Cox model)			HR (95%CI)	
			1.25 (1.07-1.47)	**1.17 (1.08-1.27)**

Values in bold values are statistically significant. Logistic (binary or ordered) and linear regression models were used. The independent variables included (1) presence of MetS, defined according to the IDF criteria of abdominal obesity and at least 2 of hypertension, dyslipidemia, and diabetes; and (2) the number of MetS components ranging from 0 to 4. All models were adjusted for the matched study participants' PS, and models with the number of MetS components as the independent variable were adjusted for all variables included in the PS match. [a] ORs were calculated by the exponential transformation of β coefficients for ease of presentation and interpretation. [b] Linear regression models were used to assess numeric continuous dependent variables, including the sum of mKL in hand or hand joint groups and the sum of hand joints with OA. [c] Hand pain was defined as a positive answer to the question, "Have you felt hand/finger pain, aching or stiffness more than half the days, in the past 30 days?" CMC1: carpometacarpal; DIP: distal interphalangeal; IDF: International Diabetes Federation; IP: interphalangeal; MCP: metacarpophalangeal; MetS: metabolic syndrome; mKL: modified Kellgren-Lawrence; OA: osteoarthritis; PIP: proximal interphalangeal; PS: propensity score.

and the mKL sum in DIPs (OR 1.15, 95% CI 1.02–1.30, and OR 1.52, 95% CI 1.08–2.14, respectively) and PIPs (number of joints with OA: OR 1.13, 95% CI 1.03–1.23 and mKL sum OR 1.38, 95% CI 1.09–1.75), but not MCPs and CMC1s.

Evaluation of MetS association with HOA phenotypes showed that MetS presence is associated with greater odds of erosive HOA (OR 1.40, 95% CI 1.01–1.97) and a nonsignificant trend toward a higher number of joints with erosion (OR 1.03, 95% CI 0.99–1.07). While the association of MetS with the presence of nodal HOA was not significant itself, there was a greater number of joints with nodal HOA with MetS presence (OR 1.28, 95% CI 1.02–1.60). With each additional MetS component, a greater number of hand joints presented with erosive (OR 1.02, 95% CI 1.00–1.05) and nodal HOA (OR 1.17, 95% CI 1.06–1.30; Table 2).

Association of MetS and cross-sectional and longitudinal hand pain. While there was no association between the presence of MetS and hand pain in the baseline visit, survival analysis on 8-year follow-up of hand pain showed a significantly higher incidence of hand pain in MetS+ participants (HR 1.25, 95% CI 1.07–1.47) or with the presence of each additional MetS component (HR 1.17, 95% CI 1.08–1.27, Table 2).

Sensitivity analysis results. Sensitivity analysis showed that our results were not sensitive to excluding imputed data or changing MetS criteria (Supplementary Table 3 and Supplementary Table 4, available from the authors upon request).

DISCUSSION

Using a PS matched sample of the OAI dataset, we found that the presence of MetS was associated with a higher odds of incidence of hand pain and radiographic structural damage of HOA. We have further shown that MCP and thumb base joints are spared in this association, and MetS co-occurs with erosive and nodal HOA phenotypes presentation.

The majority of the previous studies on MetS and OA association have focused on knee OA and have reported a greater odds of knee OA progression associated with MetS.[7,33,34] It has been suggested that in the knee, OA mechanical and weight-bearing stress (as a result of obesity) is a significant risk factor, whereas in hands, as nonweight-bearing joints, systemic effects of MetS (sometimes referred to as "metainflammation")[35] may provide a risk for OA development.[12,30,36] Compared to knee OA, there has been less consistency among the results of studies on the association between MetS and HOA, which may be partly a result of the complexity of the design and the presence of confounding covariates. While several studies have suggested a greater HOA prevalence in patients with MetS,[12,16,17,37] several others have reported no significant association with the presence of MetS and HOA incidence or progression.[8,9,10,11] These conflicting results can be attributed to inconsistent definitions and criteria for MetS determinations and, most importantly, lack of optimal integration of pertinent confounding variables in the statistical models (neither used PS matching or other relevant statistical methods in their observational studies).

Most prior studies on MetS did not assess HOA individually among the distinct hand joint groups[13,37] or excluded MCP and thumb base joints from their analysis.[11] Among the few prior studies that did include MCP and thumb base joints, while Dahaghin, *et al* reported a significant association between MetS and HOA presence in DIP, PIP, and MCP joints but not thumb base OA,[16] Marshall, *et al* found no association between MetS and susceptibility of HOA in either of hand joint groups.[10] It has been suggested that the involvement of the MCPs and especially the thumb base joints is less related to systemic risk factors such as hyperlipidemia, diabetes, obesity, and more commonly related to hand overuse or trauma.[10,20] The frequent involvement of the IP joints in the systemic presentations of OA such as nodal, generalized, or erosive OA phenotypes, rather than phenotypes associated with localized etiologies (e.g., posttraumatic OA)[18,19,21] emphasizes the possible susceptibility of IP joints to systemic risk factors, in line with our observations.

Inflammatory joint changes are repeatedly reported in both the erosive or nodal HOA phenotypes, as evidenced by central and marginal erosions, synovitis, tenosynovitis, and effusions in MRI assessments[3] and increased vascularization in Doppler imaging.[38] In particular, erosive HOA has been suggested to represent metabolically driven pathophysiology associated with low-grade inflammation,[39] a mutual finding with MetS pathophysiology.[12,30,36] On the other hand, metabolic risk factors (e.g., obesity, hypertension, and dyslipidemia) were more prevalent in community-dwelling patients with erosive HOA than in patients with nonerosive HOA.[39] In line with previous studies, we have shown an association between erosive HOA and selected metabolic risk factors.[10,40] However, several studies found no significant association between MetS itself and erosive HOA, which has been partly attributed to small sample sizes.[10,11] Future metaanalyses may help to overcome this limitation.

Similar to our findings on the association of the number of HNs with MetS, 1 previous study has investigated the potential risk factors in HOA according to the presence of HN phenotypes and found an association between the presence of diabetes and increased radiographic HOA progression, only in subjects with nodal HOA.[10] Despite no unified criteria to define HOA phenotypes, HNs are considered the hallmark of "generalized OA."[41] Metabolic risk factors are known to be more prevalent in patients with generalized OA.[42] We have previously shown that the use of statins as lipid-lowering drugs can be protective against knee OA progression, only in patients who are HN+ and not HN–.[43] Consistent with the literature's overall evidence, HNs are slightly more prevalent in MetS+ than MetS– participants prior to matching.[6,41,44,45] These can further propose a clinically important biomarker role of HNs for the systemic presentation of metabolic OA risk factors.[6] However, our cross-sectional observational results need to be confirmed by longitudinal studies as causal inference has the potential to bias in cross-sectional assessment.

The main strengths of our observational study compared to previous relevant reports include a large number of participants analyzed from the well-known OAI cohort, the use of an extended 8-year follow-up period for symptoms, PS matched design to address covariate overlap between exposure groups to avoid extrapolation, and considering heterogeneity in the HOA phenotypes and distribution.

Our study has several limitations. First, the OAI dataset is aimed and longitudinally collected to investigate the association of physical, imaging-derived, or laboratory-based biomarkers with knee OA development and progression. Therefore, OAI inclusion/exclusion criteria are tailored for this specific aim, and any posthoc analysis on this dataset would be susceptible to selection bias. We tried to address this possible nonrandom subject selection using the PS matching method. Second, the OAI dataset lacks serum lipid profile and plasma glucose and glycosylated hemoglobin measurements. Therefore, these components of MetS were assessed by self-report and medication history, which are neither as specific as laboratory assessment nor can differentiate controlled and poorly controlled patients. Previous studies have reported acceptable reliability of self-reported assessment for diabetes (indexed in our study with both self-reported and medication history), but lower reliability for dyslipidemia,[46,47] for which we did not use self-reported data and only used medication history as a proven sensitive method.[48] Since compared to laboratory measurements, our approach has acceptable positive predictive value but lower negative predictive value, this limitation could drive our results through null and would not cause a significant positive association. Third, different criteria suggested for MetS may influence the generalizability of our results. However, sensitivity analysis results showed that our results were not sensitive to changes in the used criteria. Fourth, our radiographic assessment included

only cross-sectional radiographs of the dominant hand in each participant, which is more susceptible to confounding bias than longitudinal designs. The PS matching method is a well-recognized statistical method that potentially can minimize the risk of confounding variables;[49] however, as one of the frequently reported limitations of the PS matching, there would be a residual risk of confounding effect regarding the variables not included in the PS matching model (unknown risk factors or the ones with unavailable data).[50] Moreover, the inclusion of participants' dominant hand would bold the mechanical HOA risk factors over systemic/metabolic factors. However, this would have mitigated the MetS–HOA association and would not cause the observed positive association. Fifth, HOA symptoms were assessed using yes/no questions as the only measure available on the OAI dataset, with no quantification of pain level. We tried to improve the reliability of assessment using temporal variations in pain, similar to other validated measures of pain incidence in OA.[27] While a survival model may not be optimal for evaluation of fluctuating outcomes like pain, it may be a better fit for the symptomatic pain incidence data that we evaluated. Finally, we could not identify the duration and severity of MetS and its components in the OAI dataset, increasing the probability of Neiman bias,[51] (i.e., patients with severe MetS may have died and not enrolled in our sample). However, unlike our findings, this bias would drive the association through the null and make it look less severe.

In conclusion, while considering possible confounders in a matched design, our study confirms the association of MetS as a potentially "modifiable risk factor" with radiographic and symptomatic HOA, in IP joints, in persons with or at risk of knee OA. Longitudinal studies can investigate the potential role of MetS as a modifiable risk factor for HOA in specific HOA phenotypes with HNs or erosions. Future mechanistic and experimental studies are warranted to elucidate the causal relationship of this association.

DATA SHARING POLICY

The deidentified clinical and demographic information of subjects is publicly available at the OAI project data repository (https://oai.nih.gov). The dataset of hand radiograph readings and the R codes used in this work are available from the corresponding author upon reasonable request.

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