Metabolic Syndrome and Osteoarthritis Distribution in the Hand Joints: A Propensity-Score Matched Analysis from Osteoarthritis Initiative

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Key Indexing Terms: Metabolic syndrome, Hand, Osteoarthritis.

Conflict of interests: None of the authors have any conflicting personal or financial relationships that could have influenced the results of this study.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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ABSTRACT

Objective

To investigate the metabolic syndrome (MetS) association with radiographic and symptomatic hand osteoarthritis (OA).

Methods

Using 1:2 propensity-score-matching for relevant confounders, we included 2509 ($MetS^{+}$896: $MetS^{-}$1613) participants from the Osteoarthritis Initiative dataset. MetS and its components, according to the International Diabetes Federation criteria, were extracted from baseline data, including hypertension, abdominal obesity, dyslipidemia, and diabetes. We scored distinct hand joints based on modified Kellgren–Lawrence grade (mKL) of baseline radiographs, with OA defined as mKL≥2. In the cross-sectional analysis, we investigated the association between MetS and its components with radiographic hand OA and the presence of nodal and erosive OA 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 hand OA, including the number of joints with OA (odds ratio, 95%confidence interval:1.32, 1.08–1.62), the sum of joints mKLs (2.42, 1.24–4.71), mainly in distal and proximal interphalangeal joints (DIPs:1.52, 1.08–2.14, PIPs:1.38, 1.09–1.75), but not metacarpophalangeal (MCP) and first carpometacarpal (CMC1) joints. Hand pain incidence during follow-up was higher with MetS presence (hazard ratio, 95%CI:1.25, 1.07–

1.47). Erosive hand OA phenotype and joints' nodal involvement were more frequent with MetS (1.40, 1.01–1.97, and 1.28, 1.02–1.60).

Conclusions

MetS, a potentially modifiable risk factor, is associated with radiographic DIP and PIP OA and longitudinal hand pain incidence while sparing MCPs and CMC1. Nodal and erosive OA phenotypes are associated with MetS, suggestive of possible distinct pathophysiology.

KEYWORDS

Metabolic syndrome, Hand, Osteoarthritis Initiative, Propensity-score matching, Nodal Osteoarthritis, Erosive Osteoarthritis.

KEY MESSAGES:

- MetS may be a potentially modifiable risk factor for hand interphalangeal joints OA.
- MetS was associated with radiographic hand IP OA and increased hand pain incidence.
- Nodal and erosive OA phenotypes are associated with the presence of MetS.

1. INTRODUCTION

The hand joints are commonly affected by osteoarthritis (OA), with approximately 40% 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 (DMOAD) has been proven effective for OA,[5] a better understanding of OA phenotypes and any associated "modifiable" risk factors is essential to improve treatment outcomes.[3,6]

Metabolic risk factors have been associated with peripheral joint OA such as the knee, hip,[7], and, less unanimously, hand joints[8-11] 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.[10-12,16,17] It could be due to 1) aggregate analysis of all hand joint groups rather than distinct evaluations of individual hand joints, which could have specific pathophysiology and risk factors. [18-21] 2) study design (longitudinal vs. cross-sectional), 3) different definitions of HOA (clinical/symptomatic versus 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 OA among each

distinct joint group of the hand at baseline and pain outcome in follow-up examinations. We also assessed the association of MetS with different HOA phenotypes.

2. METHODS

2.1. Study Population and Design

We used data from the publicly available OAI database; OAI is a multicenter ongoing cohort study (for the OAI protocol details: https://oai.nih.gov). In brief, Men and Women between ages 45-79 from all ethnic groups were included. Participants with physician-diagnosed inflammatory arthritis, end-stage forms of knee OA, or unable to undergo 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 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, while using a cohort design, we assessed the longitudinal incidence of hand pain.

2.2. Assessment of metabolic syndrome

Similar to the previous relevant OAI studies on MetS, we defined MetS presence and components according to the International Diabetes Federation (IDF) criteria,[14] at the baseline visit; 1) Hypertension was defined as ≥130 mm Hg Systolic blood pressure (BP) or ≥85 mm Hg Diastolic BP at baseline physical examination or being on BP-lowering medication indicated in the assessment participants' medication inventory form (MIF) at baseline visit. 2) Diabetes was indicated by self-reported diabetes or the presence of anti-diabetic medications in the MIFs. 3)

Dyslipidemia was defined as using lipid-lowering medications indicated in the participants' MIF at baseline. 4) Abdominal obesity was assessed by waist circumference of ≥94 cm in men and ≥80 cm in women on physical examination.[14] Participants with abdominal obesity and at least 2/3 of other components (dyslipidemia, diabetes, and hypertension) were regarded as $MetS^{+}$.

2.3. Cross-sectional assessment of radiographic hand OA

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 seven years of experience), unaware of any subject's demographics, assessed all radiographs. The severity of radiographic OA was assessed in the distal and proximal interphalangeal joints (DIPs/PIPs), the thumb interphalangeal, metacarpophalangeal (MCP), and first carpometacarpal (CMC1 or thumb base) joints. Modified Kellgren–Lawrence (mKL) grading was used[22] (Supplementary Table S1) with radiographic OA 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 OA, a subtype of HOA, defined as Verbruggen–Veys erosive or remodeled phase[23] ≥1 joint in participants with HOA. 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% confidence interval (95%CI):0.80–0.93).

2.4. 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 were responded to this question in baseline assessment and six OAI follow-up visits (years 1, 2, 3, 4, 6, and 8). A potential barrier for an accurate evaluation of temporal features of pain is 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 in two or more 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.

2.5. Assessment of Hand OA phenotypes

At baseline physical examination, the trained medical staff of OAI assessed the presence of HNs in the DIP joints on the 2nd–5th digits of both hands, and subjects with at least one Heberden's node (HN) were categorized as having "nodal OA." Participants with at least one joint with evident erosion were indexed as having an "erosive OA" phenotype. All hand joints were evaluated for the presence of erosive OA, a subtype of HOA, defined as Verbruggen–Veys erosive or remodeled phase[23] ≥1 joint in participants with HOA. Verbruggen–Veys grading system has been shown to have good reliability and intraclass correlation coefficient (ICC).[24]

2.6. Statistical analyses

To explore the possible confounders with available data on 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 meta-analyses[29,30] (Supplementary Figure S1) including; age (years), gender (man/woman), race (white/non-white), educational level, body-mass index (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 (PASE) questionnaire, and daily lifting of heavy objects with hands (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 (less than 1.3% of data, detail presented in Supplementary Data S1 and Supplementary Table S2). After we imputed the missing data, we further matched subjects for the presence of metabolic syndrome ($MetS^+$ and $MetS^-$) 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 a 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). Odds ratios (ORs) were calculated by the exponential transformation of beta-coefficients for ease of presentation and interpretation. All models were adjusted for the propensity score 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 propensity score 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) was used for statistical analysis.

2.7. Sensitivity analysis

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

3. RESULTS

3.1. 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 near 64.5 (standard deviation (SD):8.5), and around 55% of them were women with proper balance for all the PS-matched variables (SMD <0.1).

**** Preferred position for Table 1 ****

3.2. Association of MetS and cross-sectional hand OA measures and involved joints

The presence of MetS was associated with a higher number of hand joints with radiographic OA (OR, 95%CI: 1.32, 1.08–1.62) (Table 2). Furthermore, the presence of MetS was associated with the mKL sum score (OR, 95%CI: 2.42, 1.24–4.71) and maximum mKL in hand joints (OR, 95%CI: 1.25, 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 PIPs, DIPs, MCPs, and CMC1 joint showed that the presence of MetS was associated with the total number of joints with OA and the mKL sum in DIPs (OR, 95%CI: 1.15, 1.02–1.30, and OR, 95%CI: 1.52, 1.08–2.14, respectively) and PIPs (number of joints with OA OR, 95%CI: 1.13, 1.03–1.23, and mKL sum OR, 95%CI: 1.38, 1.09–1.75), but not MCPs and CMC1.

Evaluation of MetS association with HOA phenotypes showed that MetS presence is associated with greater odds of erosive HOA (OR, 95%CI: 1.40, 1.01–1.97) and a non-significant trend toward a higher number of joints with erosion (OR, 95%CI: 1.03, 0.99–1.07). While the association of MetS with the presence of Nodal OA was not significant itself, there was a greater

number of joints with nodal OA with the MetS presence (OR, 95%CI: 1.28, 1.02–1.60). With each additional MetS component, a greater number of hand joints presented with erosive (OR, 95%CI: 1.02, 1.00–1.05) and nodal OA (OR, 95%CI: 1.17, 1.06–1.30, Table 2).

**** Preferred position for Table 2 ****

3.3. *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 (hazard ratio (HR), 95%CI: 1.25, 1.07–1.47) or with the presence of each additional MetS component (HR, 95%CI: 1.17, 1.08-1.27, Table 2).

3.4. Sensitivity analysis results

Sensitivity analysis showed that our results were not sensitive to excluding imputed data or changing MetS criteria (Supplementary tables S3 and S4).

DISCUSSION

Using a propensity-score matched sample of the Osteoarthritis Initiative dataset, we found that the presence of metabolic syndrome was associated with a higher odds of incidence of hand pain and radiographic structural damage of hand osteoarthritis. We have further shown that metacarpophalangeal and thumb-base joints are spared in this association, and metabolic syndrome co-occurs with erosive and nodal osteoarthritis 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 hand, as non-weight-bearing joints, systemic effects of MetS (sometimes referred to as "meta-inflammation")[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 due to 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.[8-11] These conflictory 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 OA individually among the distinct hand joint groups [13,37] or excluded MCP and thumb base joints from their analysis.[11] Among 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 OA in either of hand joint groups.[10] It has been suggested that the MCPs and especially thumb base joint are less related to systemic risk factors such as hyperlipidemia, diabetes, obesity, and more commonly related hand overuse or trauma.[10,20] The frequent involvement of interphalangeal joints in the systemic presentations of OA such as nodal, generalized, or erosive OA phenotypes, rather than phenotypes associated with localized etiologies (e.g., post-traumatic OA),[18,19,21] emphasizes on the possible susceptibility of interphalangeal joints to systemic risk factors, in line with our observations.

Inflammatory joint changes are repeatedly reported in both erosive hand OA or nodal OA 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 OA 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 OA than in patients with non-erosive OA.[39] In line with previous studies, we have shown an association of erosive OA with selected metabolic risk factors.[10,40] However, several found no significant association between MetS itself, and erosive OA, which have been partly attributed to small sample sizes.[10,11] Future meta-analysis studies may help to overcome this limitation.

Similar to our findings on the association of the number of HN with MetS, one previous study has investigated the potential risk factors in HOA according to the presence of HNs phenotypes and found an association between the presence of diabetes and increased radiographic HOA progression, only in subjects with nodal OA.[10] Despite no unified criteria to define OA

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 HN^{+} patients and not HNs^{-}.[43] Consistent with the literature's overall evidence, HNs are slightly more prevalent between $MetS^{+}$ than $Mets^{-}$ participants before 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 is 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 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 non-random subject selection using the PS-matching method. Second, the OAI dataset lacks serum lipid profile and plasma glucose/HbA1c 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 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 low 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, and generalized OA 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–OA 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– 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 survival model may not be optimal for evaluation of fluctuating outcomes like pain, it may better fit on 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 metabolic syndrome as a potentially "modifiable risk factor" with hand radiographic and symptomatic osteoarthritis, in interphalangeal joints, in persons with or at risk of or with knee osteoarthritis. Longitudinal studies can investigate metabolic syndrome's potential role as a modifiable risk factor for hand osteoarthritis in specific osteoarthritis phenotypes with Heberden's nodes or erosions. Future mechanistic and experimental studies are warranted to elucidate the causal relationship of this association.

4. ACKNOWLEDGMENTS AND MANUSCRIPT INFORMATION

4.1. *Acknowledgments*

The osteoarthritis initiative, a collaborative project between public and private sectors, includes five contracts N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, and N01-AR-2-2262. This project is conducted by the osteoarthritis initiative project investigators and is financially supported by the National Institutes of Health (NIH). Private funding partners are Merck Research Laboratories, Novartis Pharmaceuticals Corporation, GlaxoSmithKline, and Pfizer, Inc.

In preparing this manuscript, osteoarthritis initiative project publicly available datasets were used. The results of this work do not necessarily reflect the opinions of the osteoarthritis initiative project investigators, the NIH, or the private funding partners.

4.2. *Competing interests*

AG reported that he received funding from MerckSerono, AstraZeneca, Galapagos, Pfizer, Roche, TissueGene (for consultation), and Boston Imaging Core Lab (as the president and stockholder). SD reported that he received funding from Toshiba Medical Systems (for consultation) and grants from GERRAF and Carestream Health (for a clinical trial study). IKH received funding from South-Eastern Norway Health Authority. None of the authors have any conflicting personal or financial relationships that could have influenced the results of this study. Other authors declare that they didn't have any competing interests.

4.3. *Contributors*

All authors participated in the study design, interpreted results, and drafted the manuscript or critically revised it for relevant intellectual content.

4.4. *Funding*

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

4.5. *Patient consent*

Subjects have given informed consent before participating in the Osteoarthritis Initiative (OAI) project.

4.6. *Ethics approval*

The medical ethics review boards of the University of California, San Francisco (Approval Number: 10-00532), and the four clinical centers of osteoarthritis initiative project recognized the project as Health Insurance Portability and Accountability Act (HIPAA)-compliant.

4.7. *Data sharing statement*

The de-identified clinical and demographic information of subjects is publicly available at the osteoarthritis initiative project data repository at 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 requests.

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Figure Legends

Figure 1. Flowchart of study participants.

OAI: Osteoarthritis Initiative, MetS: Metabolic syndrome, PS-matching: Propensity-score matching

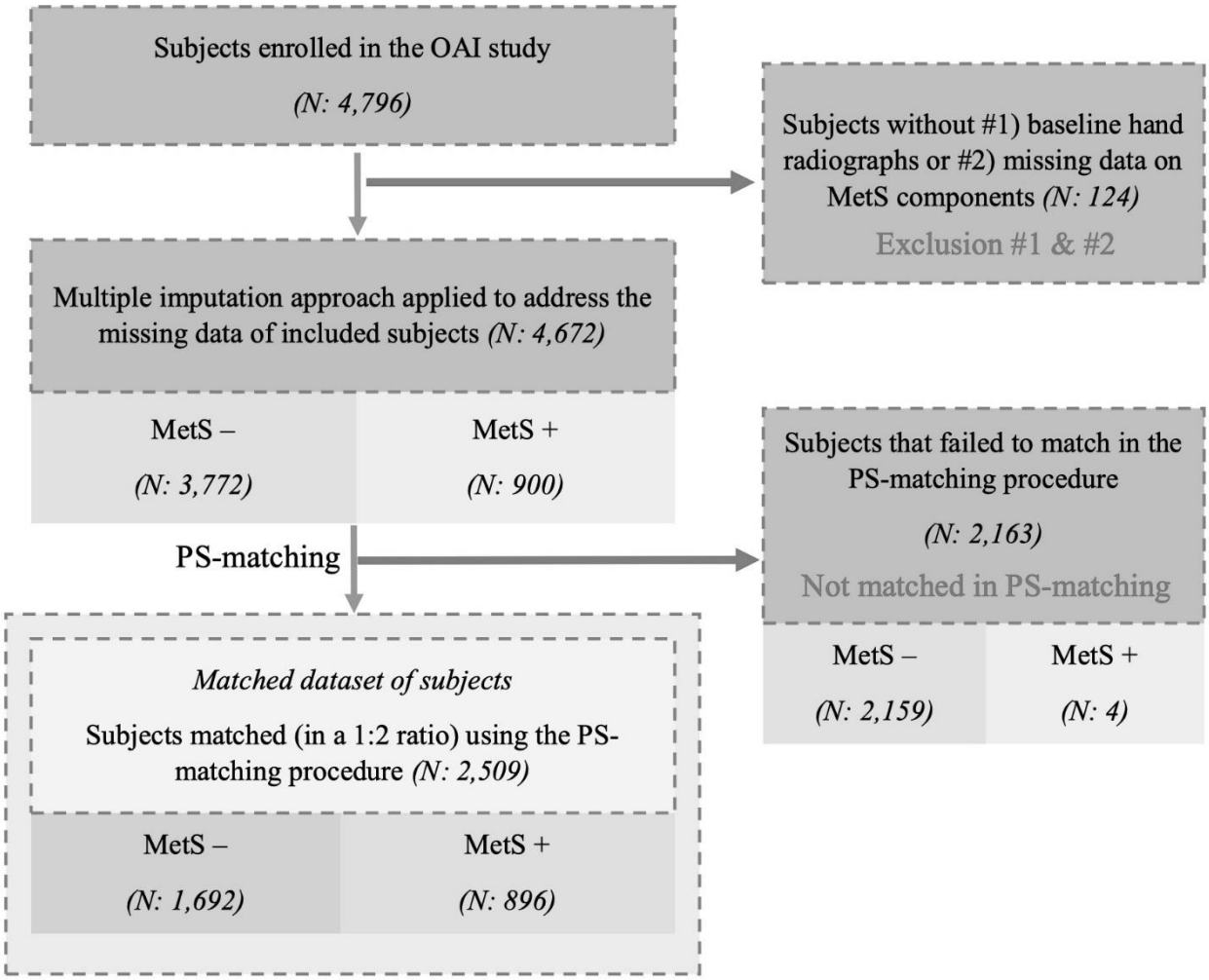

Figure 1. Flowchart of study participants.

OAI: Osteoarthritis Initiative, MetS: Metabolic syndrome, PS-matching: Propensity-score matching

Table 1. Baseline characteristics of the study population before and after propensity score matching according to the presence of metabolic syndrome, defined by international diabetes Federation criteria.

	All OAI subjects			Matched subjects		
	MetS⁻	MetS⁺		MetS⁻	MetS⁺	
	N: 3772	N: 900	SMD	N: 1613	N: 896	SMD
Variables included in the PS matching model						
Age (year) [mean (SD)]	60.27 (9.11)	65.00 (8.48)	**0.537**	64.14 (8.67)	64.96 (8.48)	0.096
No. of women [N (%)]	2236 (59.3)	491 (54.6)	0.095	914 (56.7)	490 (54.7)	0.040
Non-white race [N (%)] †	718 (19.0)	248 (27.6)	**0.203**	408 (25.3)	245 (27.3)	0.047
BMI (kg/m²) [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)	
Collage 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 [N (%)]			**0.206**			0.043
None	694 (18.4)	223 (24.8)		376 (23.3)	222 (24.8)	
<1 drinks/week	1415 (37.5)	332 (36.9)		612 (37.9)	329 (36.7)	
1–3 drinks/week	593 (15.7)	99 (11.0)		182 (11.3)	99 (11.0)	
4–7 drinks/week	574 (15.2)	119 (13.2)		221 (13.7)	119 (13.3)	
8–14 drinks/week	338 (9.0)	78 (8.7)		141 (8.7)	78 (8.7)	
15+ drinks/week	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/day	145 (3.8)	39 (4.3)		64 (4.0)	39 (4.4)	
Smoker ≥ 14 cigarettes/day	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 PS matching model						
Pain in the hands [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 Heberden nodes [mean (SD)]	2.29 (2.62)	2.68 (2.78)	**0.147**	2.41 (2.66)	2.69 (2.79)	**0.102**
Hand OA, type [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 [N (%)]‡	1353 (35.9)	862 (95.8)	**1.629**	728 (45.1)	858 (95.8)	**1.334**
Diabetes Mellitus [N (%)]‡	40 (1.1)	322 (36.7)	**1.022**	23 (1.5)	319 (36.5)	**0.999**
Dyslipidemia [N (%)]‡	503 (13.3)	795 (88.3)	**2.268**	250 (15.5)	793 (88.5)	**2.140**
Abdominal obesity [N (%)]‡	3105 (84.4)	900 (100.0)	**0.608**	1485 (93.2)	896 (100.0)	**0.383**

The baseline characteristics of included participants before and after applying propensity score matching. Quantitative variables are shown in mean (± standard deviation), and qualitative variables are shown in number (% percent). $MetS^{+}$ and $MetS^{-}$ corresponds to subjects with and without metabolic syndrome, respectively. 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?*". Hand OA was defined as ≥ one joint with mKL ≥ two, and erosive OA was defined as ≥ one joint with the presence of Verbruggen–Veys erosive or remodeled phase in hand X-rays in subjects with hand OA. BMI: Body mass index, HN: Heberden's node, MetS: Metabolic Syndrome, OA: Osteoarthritis, PASE: physical activity scale for the elderly, SMD: Standardized mean difference, SD: Standard deviation, N: Number of participants.

* Significant difference for SMD was defined as ≥ 0.1.

† Race of participants was categorized as white and non–white considering the small number of participants in each nonwhite race group.

‡ Components of Metabolic syndrome defined by International Diabetes Federation (IDF) defined as 1) Hypertension: ≥ 130 mm Hg Systolic blood pressure (BP) or ≥ 85 mm Hg at baseline physical examination Diastolic BP or on BP-lowering medication indicated in the medication history 2) Diabetes: Self–reported diabetes or use of oral or injective anti-diabetic medications indicated in the participant's medication history 3) Dyslipidemia: use of lipid-lowering medications indicated in the participant's medication history 4) Abdominal obesity: waist circumference of ≥ 94 cm in men and ≥ 80 cm in women. According to the IDF criteria, MetS defined as; Abdominal obesity and at-least 2/3 of hypertension, dyslipidemia, and diabetes.

Table 2. Association of Hand OA status with the presence of metabolic syndrome and the number of present metabolic syndrome components, defined by international diabetes Federation criteria, in propensity–score-matched study subjects.

Hand OA status	**Descriptive: Mean(SD) / Number(%)**		**OR (95%CI) N:2509 (1613:896)**	
			Independent variable	
Radiographic assessment of hand joints	**MetS⁻ (N:1613)**	**MetS⁺ (N:896)**	**MetS presence**	**Number of MetS components**
Sum of hand joints mKL grades†	7.38 (8.13)	8.56 (8.63)	**2.42 (1.24–4.71**	**1.93 (1.42–2.63)**
Total number of hand joints with OA (mKL≥2) †	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	N:505 (31.3%)	N:239 (26.7%)		
Grade 1	N:400 (24.8%)	N:216 (24.1%)		
Grade 2	N:396 (24.6%)	N:218 (24.3%)		
Grade 3	N:139 (8.6%)	N:104 (11.6%)		
Grade 4	N:173 (10.7%)	N:119 (13.3%)		
Sum of PIP joints mKL grades†	1.68 (2.85)	2.07 (3.05)	**1.38 (1.09–1.75)**	**1.25 (1.12–1.40)**
Number of PIP joints with OA (mKL≥2) †	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†	3.33 (4.10)	3.85 (4.38)	**1.52 (1.08–2.14)**	**1.36 (1.16–1.60)**
Number of DIP joints with OA (mKL≥2) †	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 & PIPs) mKL grades †	5.83 (6.98)	6.86 (7.45)	**2.27 (1.28–4.05)**	**1.80 (1.38–2.35)**
Number of IP joints with OA (mKL≥2) †	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†	0.59 (1.44)	0.67 (1.54)	1.04 (0.92–1.17)	1.05 (0.99–1.11)
Number of MCP joints with OA (mKL≥2) †	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	N:854 (53.2%)	N:468 (52.5%)		
Grade 1	N:261 (16.3%)	N:134 (15.0%)		
Grade 2	N:278 (17.3%)	N:165 (18.5%)		
Grade 3	N:105 (6.5%)	N:55 (6.2%)		
Grade 4	N:106 (6.6%)	N:69 (7.7%)		

Presence of Erosive OA	N:81 (5.0%)	N:63 (7.0%)	**1.40 (1.01–1.97)**	**1.29 (1.06–1.57)**
Total Number of hand joints with Erosive OA†	0.09 (0.47)	0.12 (0.52)	1.03 (0.99–1.07)	**1.02 (1.00–1.05)**
Presence of Nodal OA	N:1002 (62.1%)	N:581 (64.8%)	1.09 (0.92–1.29)	1.07 (0.97–1.17)
Total Number of hand joints with Nodal OA†	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 hand	N:1236 (76.6)	N:665 (74.2)	0.89 (0.74–1.08)	0.94 (0.85–1.04)
Longitudinal: hand pain incidence (Cox model)*			**HR (95%CI), P-value**	
			1.25 (1.07-1.47)	**1.17 (1.08-1.27)**

Logistic (binary or ordered) and linear regression models were used. The independent variables included 1) presence of Metabolic syndrome was defined according to the International Diabetes Federation (IDF) criteria; Abdominal obesity and at least 2/3 of hypertension, dyslipidemia, and diabetes and 2) the number of metabolic syndrome components ranging from 0 to 4. All models were adjusted for the matched study participants' propensity score, and models with the number of MetS components as the independent variable were adjusted for all variables included in the PS-match. Results are presented in odds ratios, 95% confidence interval. 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?*". CI: Confidence interval, CMC1: Carpometacarpal, DIP: Distal interphalangeal, IP: Interphalangeal, mKL: Kellgren–Lawrence, MCP: Metacarpophalangeal, OA: Osteoarthritis, OR: Odds ratio, PIP: Proximal interphalangeal. Bold values indicate statistically significant results.

† 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. Odds ratios were calculated by the exponential transformation of beta–coefficients for ease of presentation and interpretation.