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Association of metabolic syndrome with knee and hand osteoarthritis: a community-based study of women

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ABSTRACT

OBJECTIVE: It is unclear whether the association between osteoarthritis (OA) and metabolic syndrome (MetS) varies with the site of the affected joint and the presence of pain. Our aim was to describe the association between MetS and radiographic OA (ROA) affecting the knee or the hand in the presence or absence of concurrent joint pain.

METHODS: Cross-sectional data of 952 women, aged 45-65 years from the Chingford study, a population-based longitudinal cohort of middle-aged women initiated in 1988-1989 in London (UK), was analysed. MetS was defined using the National Cholesterol Education Program Treatment Panel III criteria. Data was collected on components of MetS: waist circumference, triglycerides, high-density lipoprotein (HDL), blood pressure and blood glucose. The outcome was four knee and hand OA groups: painful ROA, ROA only, pain only and neither ROA nor pain (reference category). Multinomial logistic regression models adjusted for age and body mass index (BMI) were used to evaluate the effect of presence of MetS and its individual components on OA subgroups for knee and hand separately.

RESULTS: 952 eligible women, aged 45-65 years was analysed. A significant association was observed between the presence and the number of MetS with painful knee ROA when adjusted for age; however, this association disappeared when BMI was included in the model. In contrast, the presence and the number of MetS were associated with painful interphalangeal (IPJ) OA after adjusting for both age and BMI. Four out of the five MetS components, including triglycerides, HDL-c, hypertension and glucose, were associated with painful IPJ OA.

CONCLUSIONS: MetS is associated with painful IPJ OA but not with knee OA once BMI is taking into consideration. Further attention to MetS and OA at different sites is needed to understand the metabolic phenotype in OA.

Keywords: Metabolic syndrome, hand, knee, osteoarthritis, pain

1. INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability in the developed world ¹. The natural history of OA is poorly understood; it is recognised as a heterogeneous disease of multifactorial aetiology with shared common radiographic features and symptomatology ^{2,3}.

A higher prevalence of metabolic syndrome (MetS), defined as high waist circumference, dyslipidaemia (low high-density lipoprotein (HDL) and triglyceridaemia), hypertension and insulin resistance, has been reported in patients with OA, even after controlling for identified risk factors such as age, sex and body mass index (BMI) or weight ⁴⁻⁷. Two previous systematic reviews with meta-analyses suggested a strong association between diabetes and OA, independent of weight and BMI^{8,9}. In contrast, a recent systematic review found little evidence to support an association between DM and knee OA and no evidence with hip or hand OA was found¹⁰. A recent meta-analysis demonstrated that hypertension was associated with both radiographic and symptomatic knee OA¹¹, and another systematic review demonstrated an association between dyslipidemia and OA¹².

There is evidence for a relationship between visceral fat tissue^{13,14}, metabolic syndrome (MetS) ¹⁵⁻¹⁷ and OA and this is expected to translate into higher cardiovascular risk¹⁸ and premature mortality.

The association between knee and hand OA with systemic metabolic dysregulation is controversial. Previous studies of MetS and OA focussed on selected groups of individuals with potential confounding by recruitment strategy (often associated with the severity of disease). The Netherlands Epidemiology of Obesity study looked at components of MetS and surrogates of mechanical stress in a general population cohort that over-sampled obese and overweight individuals ¹⁶. This cross-sectional study demonstrated that individuals with MetS were more likely to have hand and knee OA, even after adjusting for age, sex, smoking,

ethnicity and height. In knee OA, this relationship was not significant after adjusting for weight indicating the importance of increased mechanical load on the lower limb joints. Interestingly, the association of MetS and hand OA remained significant even after adjusting for weight.

Most previous studies have focused their attention on lower limb OA and/or radiographic hand OA, however to the best of our knowledge none has studied the association between the accumulation of metabolic factors and painful hand ROA.

The aims of our study were: 1) to assess the association of components of MetS, either singly or additively, with painful and painless ROA affecting two different sites (knee or hand) and, 2) to describe whether this association varies with the site of the affected joint in a community-based cohort of middle-aged women.

2. METHODS

We used cross-sectional data from the Chingford 1000 Women Study, a prospective population-based longitudinal cohort of middle-aged women¹⁹. All women aged 45 or above and registered at a general practice in Chingford (North London, UK) were contacted in 1988-1989 and asked to participate. Out of 1353 women contacted, 1003 (78% response rate) attended the baseline visit. The cohort has been shown to be representative of this group of women in England in terms of basic characteristics, with the exception of a lower rate of current smokers¹⁹⁻²³.

The study was approved by the local ethics committee and written consent was obtained from all participants.

2.1.Exclusion criteria

We excluded women with rheumatoid arthritis (RA) and those who did not have data available on either knee or hand pain and/or radiographic at baseline ($n_{\text{total}}=51$).

2.2.Assessment of joint-specific radiographic OA and pain (outcome)

A physical examination was performed at baseline, with anteroposterior (AP) radiographs of the hands and weight-bearing anteroposterior view (AP) radiographs of the knee. The protocols for radiographic grading and reproducibility for knee and hand ROA have been previously reported ^{22,24}. Women were classified as having knee ROA if they had a Kellgren–Lawrence (K/L) OA grade of ≥ 2 in at least one knee. Hand radiographs were also graded for OA: summary scores of distal and proximal interphalangeal (DIP and PIP) joints were defined as the number of joints with K/L grade ≥ 2 , while hand ROA in any interphalangeal joint (IPJ) was defined as positive if the K/L score in at least one joint was ≥ 2 .

Knee and hand pain was assessed as part of a standardised joint symptom questionnaire administered by a nurse. It contained information on onset, duration (months), and presence (yes/no) for each one of the three following symptoms: pain, stiffness and swelling. Knees and hands were considered to be symptomatic if pain and/or stiffness in the knee or DIP and PIP joints was reported to be present.

The sample was divided into four mutually exclusive subgroups based on the presence or absence of pain and ROA ²⁵:

1. Neither ROA nor pain (Pain–/ROA–; reference category).
2. ROA only (Pain–/ROA+)
3. Pain only (Pain+/ROA–)
4. Painful ROA (Pain+/ROA+: joint(s) with ROA and pain or stiffness affecting the same site)

Women with ROA at one site and pain only at the contralateral site were classified as having ROA-/Pain+ (n=4 and n=3 women for knee and hand, respectively), because we used the ‘highest’ category based on this OA classification.

2.3. Metabolic syndrome (exposure)

MetS was defined according to the Joint Scientific Statement National Cholesterol Education Program III²⁶. Presence of MetS was diagnosed when 3 or more of the following criteria were met: elevated waist circumference (≥ 88 cm), elevated serum triglycerides (≥ 1.7 mmol/L), reduced high-density lipoprotein cholesterol (HDL-c) (< 1.3 mmol/L), hypertension (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg) and elevated fasting blood glucose (≥ 5.6 mmol/L). Women taking medications for dyslipidaemia, hypertension or diabetes were regarded as having dyslipidaemia, hypertension or impaired glucose tolerance, respectively. Systolic and diastolic blood pressure readings were performed using a calibrated sphygmomanometer, and fasting serum samples were taken for estimation of serum lipid profile and blood glucose²³.

2.4. Covariates

The following variables collected at baseline were included in the analysis: age and BMI. They were treated as continuous variables.

2.5. Statistical analysis

Data analysis was performed using Stata software version 13.1 (StataCorp, College Station, Texas). Characteristics for participants were assessed using mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables and relative and absolute values for categorical variables.

To address potential bias and increase precision in this analysis as a result of missing values, multiple imputation was used²⁷. Missing data of some needed variables to calculate number of MetS were observed in 9 (0.9%) to 365 (38.3%) women (see online supplementary file Table

S1). The approach of multiple imputation followed by deletion²⁸ was followed, imputing missing information for all women, but then excluding those with missing data on outcomes. Multivariate imputation by chained equations (MICE) was used which assumes that data are Missing At Random (MAR).

The mechanism of missing data was assumed to be MAR because the underlying values necessary to calculate MetS that were missing for some women are likely to depend on observed data in the Chingford data. The imputation equations included all metabolic components, outcome variables, covariates included in this study, as well as additional variables available on the dataset including menopause status, pain medication, smoking status, alcohol intake, physical activity (times/per week), and occupation (manual/non-manual). Logistic regression was used for the binary variables (individual component of MetS). Two hundred imputed cycles were performed to generate the data set, and the resulting estimates were combined using Rubin's rules. The imputations were assessed by hand (supplementary Tables S2, S3 and S4 compare the distribution and associations with outcome of imputed variables in the imputed data set and the observed data (with no imputation)) and by using graphical methods. Similar results were observed between imputed and observed data sets.

Multinomial logistic regression analysis adjusted for age and then for BMI were conducted to calculate relative-risk ratios (RRR) and 95% confidence intervals (CI) and assess the effect of MetS status, severity of MetS (assessed as the sum of MetS components and analyzed as a continuous variable, range 0–5) and each of its individual components on site-specific OA and pain (knee and hand). 'Neither ROA nor pain' was used as the reference group. Two separate analyses were conducted for knee and hand.

Several sensitivity analyses were conducted. First, a sensitivity analyses was performed to assess a more inclusive cohort, comprising only women without joint pain and K/L=0 as the reference group. A second sensitivity analysis was performed where each subgroup for specific

joint (knee or hand) was adjusted for presence or absence of other OA (knee and/or hand). Third, women with 2 or more affected IPJ joints with K/L grade 2 or higher were classified as having hand ROA. Finally, to examine whether differences in the phenotype of the different hand joints exist²⁹, associations between MetS and hand OA based on the first carpometacarpal joint (CMC) were assessed in isolation.

3. RESULTS

3.1.Participants' characteristics

Of the 1003 eligible women in the Chingford study, 952 (95.0%) women did not have RA and had complete data on knee and hand pain and/or radiographic information (Figure 1).

Demographic and clinical characteristics of included women are shown in Table 1. The median (IQR) age was 54 (49-60) years and the prevalence of MetS among the participants was 11.8%. The most prevalent MetS component was hypertension (57.2%), followed by low HDL-c (19.3%), hypertriglyceridemia (16.6%), high waist circumference (15.7%) and raised fasting glucose (8.3%). The prevalence of painful knee and hand ROA was 7.1% and 12.4% respectively.

Distribution of the five components of MetS by joint-specific ROA and pain group are described in online supplementary file Tables S5 and S6. Overall, hypertension, abnormal waist circumference, triglycerides, HDL-c and fasting glucose (in the context of MetS definition) were higher among women with painful knee and/or hand OA. However, higher waist circumference was significantly different only among knee OA groups and higher level of triglycerides and fasting glucose among IPJ OA groups.

3.2.Association between the presence and the number of MetS components and painful knee and hand ROA

Multinomial logistic regression results on the association between the presence and the number of MetS components on knee and hand OA are displayed in Table 2. Results from age-adjusted analyses indicated that women with MetS had a significantly greater risk of having painful knee ROA than those with neither knee ROA nor knee pain. The RRR (95% CI) for $\geq$ three MetS components vs no MetS components was 4.3 (1.4-12.4). After adjusting for BMI, associations between MetS and painful knee OA were no longer statistically significant (RRR (95% CI): 1.3 (0.4-4.4) and 1.0 (0.7-1.3) for $\geq$ three MetS components vs none components and number of MetS components, respectively).

There were significant associations between the presence and the number of MetS with IPJ OA groups and the association remained after controlling for BMI. Interestingly, RRRs were higher for those with ROA (painful or painless) than the group with knee pain only.

Increase in the number of MetS components resulted in increased risk of painful hand ROA by 50%.

3.3.Association between individual components of MetS and knee and hand OA

The age and BMI adjusted associations between individual components of MetS and painful knee and IPJ ROA are presented in Figure 2 and 3, respectively.

High waist circumference was the only metabolic component significantly associated with higher risk of painful knee ROA ($p<0.001$). However, after adjusting for BMI, this association became nonsignificant (Figure 2).

Hypertriglyceridemia, low HDL-c levels, hypertension and high fasting glucose were correlated with painful IPJ ROA (Figure 3). Among these factors, high fasting glucose had the

strongest correlation with painful IPJ ROA (RRR (95% CI): 3.0 (1.3-7.2)). After adjusting for BMI, all factors remained statistically significant except HDL-c. Waist circumference was the only component that did not show a statistically significant association with painful IPJ ROA (RRR (95% CI): 0.9 (0.5-1.5))

3.4.Sensitivity analyses

No substantial differences in the results were seen after participants with K/L grade =1 were excluded from the reference groups, or after adjusting each model for concurrent OA affecting other examined joints (see Supplementary Table S7). In addition, similar results were found after women were classified as having hand OA if they presented 2 or more affected IPJ joints with a K/L grade of ≥ 2 (see Supplementary Table S7).

After re-running the analysis for CMC OA, no association between number of MetS and any CMC OA groups were found (see Supplementary Table S8).

4. DISCUSSION

This study suggests that MetS is associated with painful knee OA, independent of age, in this community-based cohort of middle-aged women. However, after adjusting for BMI, this association was no longer significant, suggesting that the majority of this association may be explained by higher weight. On the other hand, a statistical association between the presence and number of MetS and painful IPJ ROA was found even after adjusting for age and BMI.

When evaluating the five components of MetS separately, high waist circumference was the only metabolic component strongly associated with knee OA; however, this association became non-significant when BMI was adjusted. Hypertriglyceridaemia, hypertension and raised fasting glucose levels were significantly associated with painful IPJ ROA.

To our knowledge, this is the first community-based study where there has been additional sensitivity analysis adjusting for OA at the other joints (see Supplementary Table 7). A strong independent association between hand OA and the risk of developing knee OA has been reported in a few independent large population based studies³⁰⁻³². This may be due to potential confounding in studies looking at MetS and hand OA without adjusting for presence of OA affecting lower limbs.

Previous studies have shown an association between MetS and knee OA, however the definition of MetS and OA has not been consistent. The majority of studies have focused on an older population and those at higher risk of OA^{15,33}, therefore our findings may not be directly comparable with previous publications. Our findings are consistent with previous studies in middle-age populations that have demonstrated an association between MetS and knee OA, although this was attenuated and not significant after adjustment for BMI^{34,35}.

High BMI is a risk factor for both MetS and OA affecting the knee and the hand; although the association is strongest for knee OA, which would suggest significant role of loading in weight bearing joints⁵.

A previous study has suggested that weight loss is an effective way of reducing the risk of symptomatic knee OA³⁶. A recently published randomised controlled trial showed that brief weight loss interventions offered by GPs in unrelated consultations are cost-effective with patients five times more likely to have lost weight a year later³⁷. As we have demonstrated that the population with MetS is more likely to have knee OA, this group may benefit from targeted weight loss interventions to reduce cardiovascular risk.

The mechanisms underlying the association between metabolic factors and hand OA is unclear. This association between the accumulation of metabolic factors and painful hand ROA has not

previously been reported. Few studies have studied the association between metabolic factors and hand ROA³⁸⁻⁴², however their findings have been contradictory. Strand et. al.^{40,42} did not find any association between MetS and hand ROA after adjusting for age, sex and BMI. Those findings are consistent with the present study for hand ROA without concurrent hand pain. However, association between MetS and painful hand ROA was statistically significant in our analysis (Figure 3). Dahaghi et. al.³⁹ showed that diabetes, hypertension and being overweight were associated with hand OA, which we did not demonstrate (RRR (95% CI): 2.2 (0.9-5.6), 0.9 (0.6-1.5) and 0.8 (0.4-1.6) for high fasting glucose levels, hypertension and high waist circumference, respectively). These discrepancies may be due to differences in the definitions of MetS components, hand OA groups or to the lower prevalence of MetS found in this healthy population (11.8%) or differences in the study population (particularly - mean age and race). In line with our results, Marshall et. al.³⁸ identified an association between selected metabolic factors, principally dyslipidaemia, and the risk of erosive hand ROA in a population sample of symptomatic individuals.

4.1.Strengths and limitations

To our knowledge, no other community-based study has described the patterns of metabolic dysregulation associated with knee and hand OA in middle-aged women. Our group is representative of the general population of this age and gender. Participants were not selected based on symptomatology or radiographic features and this allows us to have a control population (Pain -/ROA -). We used multiple imputation to minimize selection bias and to increase precision²⁷.

Our study has several limitations. First, findings of this study are restricted to middle-age women of Caucasian ethnicity. Second, this study is limited by its cross-sectional design and our analysis does not indicate causality, but suggests that common pathogenic mechanisms

may be involved in women with knee OA, hand OA and MetS. In addition, nowadays a substantial proportion of adults who experiencing pain related to knee or hand OA seek medical advice, therefore it is important for clinicians to be aware of those associations, especially in a view of cardiovascular problems in new users of nonsteroidal medications. Third, our dataset had a relatively high proportion of missing values. The use of a multiple imputation procedure might be preferable in terms of results validity than complete case analysis²⁷. Distributions of the variables with missing data between participants with observed data and those with imputed data were compared and similar results were found, which reinforces our results. Fourth, current knee and hand pain was assessed on a self-reported joint symptoms questionnaire; therefore we cannot verify that joint pain was secondary to OA.. Fifth, some uncontrolled parameters such as physical activity and/or diet may have change since this study started in 1988-1989, therefore, the results may not generalizable to individuals in 2018. However, our findings are consistent with recent studies^{15-17,41} which support that these potential differences may not have any impact on the association between number of MetS and site-specific OA. Sixth, number of women taking lipids or diabetes medication was smaller. Possible explanations for this may be first, women were asking to report their current medication, which may have led to recall and/or desirability bias. Second, the diagnostic criteria for diabetes mellitus and high blood cholesterol were changed in 1997 and 2002, respectively, ^{43,44} such that conservative definitions of serum fasting glucose, triglycerides and HDL ranges were considered. Therefore, some women in this study classified as diabetic or/and with dyslipidemia would not have been diagnosed with the disease in 1989-90.

4.2. Conclusions

In conclusion, data from this study demonstrate that MetS is strongly associated with painful IPJ hand OA when compared to the unaffected group. No association was found for knee OA

when BMI is taking into account. These findings support the concept that OA affecting different joints may have different pathogenic pathways. Further attention to MetS and OA at different sites is needed to understand the metabolic phenotype in OA. These findings have important implications for public health as better control of metabolic factors may further improve quality of life for women of middle age.

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7. REFERENCES

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223.
2. Karsdal MA, Bihlet A, Byrjalsen I, et al. OA phenotypes, rather than disease stage, drive structural progression - identification of structural progressors from 2 phase III randomized clinical studies with symptomatic Knee OA. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2015.
3. Dell'Isola A, Allan R, Smith SL, Marreiros SS, Steultjens M. Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. *BMC musculoskeletal disorders*. 2016;17(1):425.
4. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nature reviews Rheumatology*. 2012;8(12):729-737.
5. Kluzek S, Newton JL, Arden NK. Is osteoarthritis a metabolic disorder? *British medical bulletin*. 2015;115(1):111-121.
6. Wang H, Cheng Y, Shao D, et al. Metabolic Syndrome Increases the Risk for Knee Osteoarthritis: A Meta-Analysis. *Evid Based Complement Alternat Med*. 2016;2016:7242478.
7. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. *Postgraduate medicine*. 2009;121(6):9-20.
8. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. *RMD open*. 2015;1(1):e000077.
9. Williams MF, London DA, Husni EM, Navaneethan S, Kashyap SR. Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis. *Journal of diabetes and its complications*. 2016;30(5):944-950.
10. Dawson LP, Fairley JL, Papandony MC, Hussain SM, Cicuttini FM, Wluka AE. Is abnormal glucose tolerance or diabetes a risk factor for knee, hip, or hand osteoarthritis? A systematic review. *Semin Arthritis Rheum*. 2018.
11. Zhang YM, Wang J, Liu XG. Association between hypertension and risk of knee osteoarthritis: A meta-analysis of observational studies. *Medicine*. 2017;96(32):e7584.
12. Baudart P, Louati K, Marcelli C, Berenbaum F, Sellam J. Association between osteoarthritis and dyslipidaemia: a systematic literature review and meta-analysis. *RMD open*. 2017;3(2):e000442.
13. Belen E, Karaman O, Caliskan G, Atamaner O, Aslan O. An indicator of subclinical cardiovascular disease in patients with primary osteoarthritis: epicardial fat thickness. *International journal of clinical and experimental medicine*. 2015;8(6):9491-9497.
14. Visser AW, Ioan-Facsinay A, de Mutsert R, et al. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study. *Arthritis research & therapy*. 2014;16(1):R19.
15. Yoshimura N, Muraki S, Oka H, et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2012;20(11):1217-1226.
16. Visser AW, de Mutsert R, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Annals of the rheumatic diseases*. 2014.
17. Marshall M, Peat G, Nicholls E, van der Windt D, Myers H, Dziedzic K. Subsets of symptomatic hand osteoarthritis in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical characteristics at baseline and 3-years. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2013;21(11):1674-1684.

18. Calvet J, Orellana C, Larrosa M, et al. High prevalence of cardiovascular co-morbidities in patients with symptomatic knee or hand osteoarthritis. *Scandinavian journal of rheumatology*. 2015;1-4.
19. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *The Journal of rheumatology*. 1993;20(2):331-335.
20. Hart DJ, Spector TD. Cigarette smoking and risk of osteoarthritis in women in the general population: the Chingford study. *Annals of the rheumatic diseases*. 1993;52(2):93-96.
21. Spector TD, Hart DJ, Byrne J, Harris PA, Dacre JE, Doyle DV. Definition of osteoarthritis of the knee for epidemiological studies. *Annals of the rheumatic diseases*. 1993;52(11):790-794.
22. Hart D, Spector T, Egger P, Coggon D, Cooper C. Defining osteoarthritis of the hand for epidemiological studies: the Chingford Study. *Annals of the rheumatic diseases*. 1994;53(4):220-223.
23. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. *The Journal of rheumatology*. 1995;22(6):1118-1123.
24. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. *Arthritis Rheum*. 1999;42(1):17-24.
25. Kluzek S, Sanchez-Santos MT, Leyland KM, et al. Painful knee but not hand osteoarthritis is an independent predictor of mortality over 23 years follow-up of a population-based cohort of middle-aged women. *Annals of the rheumatic diseases*. 2015;75(10):1749-1756.
26. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645.
27. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ (Clinical research ed)*. 2009;338:b2393.
28. von Hippel PT. Regression with Missing Ys: An Improved Strategy for Analyzing Multiply Imputed Data. *Sociological Methodology*. 2007;37:83-117.
29. Kloppenburg M, Kwok WY. Hand osteoarthritis--a heterogeneous disorder. *Nature reviews Rheumatology*. 2011;8(1):22-31.
30. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Annals of the rheumatic diseases*. 2014;73(9):1659-1664.
31. Hirsch R, Lethbridge-Cejku M, Scott WW, Jr., et al. Association of hand and knee osteoarthritis: evidence for a polyarticular disease subset. *Annals of the rheumatic diseases*. 1996;55(1):25-29.
32. Dahaghin S, Bierma-Zeinstra SMA, Reijman M, Pols HAP, Hazes JMW, Koes BW. Does hand osteoarthritis predict future hip or knee osteoarthritis? *Arthritis & Rheumatism*. 2005;52(11):3520-3527.
33. Monira Hussain S, Wang Y, Cicuttini FM, et al. Incidence of total knee and hip replacement for osteoarthritis in relation to the metabolic syndrome and its components: a prospective cohort study. *Semin Arthritis Rheum*. 2014;43(4):429-436.
34. Engstrom G, Gerhardsson de Verdier M, Roloff J, Nilsson PM, Lohmander LS. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*. 2009;17(2):168-173.

35. Niu J, Clancy M, Aliabadi P, Vasani R, Felson DT. Metabolic Syndrome, Its Components, and Knee Osteoarthritis: The Framingham Osteoarthritis Study. *Arthritis Rheumatol*. 2017;69(6):1194-1203.
36. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Annals of internal medicine*. 1992;116(7):535-539.
37. Aveyard P, Lewis A, Tearne S, et al. Screening and brief intervention for obesity in primary care: a parallel, two-arm, randomised trial. *Lancet*. 2016;388(10059):2492-2500.
38. Marshall M, Nicholls E, Kwok WY, et al. Erosive osteoarthritis: a more severe form of radiographic hand osteoarthritis rather than a distinct entity? *Annals of the rheumatic diseases*. 2015;74(1):136-141.
39. Dahaghin S, Bierma-Zeinstra SM, Koes BW, Hazes JM, Pols HA. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam Study. *Annals of the rheumatic diseases*. 2007;66(7):916-920.
40. Strand MP, Neogi T, Niu J, Felson DT, Haugen IK. No association between metabolic syndrome and radiographic hand osteoarthritis: Data from the Framingham study. *Arthritis care & research*. 2017.
41. Tomi AL, Sellam J, Lacombe K, et al. Increased prevalence and severity of radiographic hand osteoarthritis in patients with HIV-1 infection associated with metabolic syndrome: data from the cross-sectional METAFIB-OA study. *Annals of the rheumatic diseases*. 2016;75(12):2101-2107.
42. Strand MP, Neogi T, Niu J, Felson DT, Haugen IK. Association Between Metabolic Syndrome and Radiographic Hand Osteoarthritis: Data From a Community-Based Longitudinal Cohort Study. *Arthritis care & research*. 2018;70(3):469-474.
43. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes care*. 2003;26 Suppl 1:S5-20.
44. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-3421.

TABLES

Table 1. Baseline characteristics of women in the Chingford study

Characteristic	Participants ^a (n=952)
Age (years), median (IQR)	54 (49-60)
BMI (kg/m ²), mean (SD)	25.6 ± 4.3
Waist circumference (cm), mean (SD)	78.0 ± 10.1
High waist circumference (N=943), n (%) ^b	148 (15.7)
Triglycerides (mmol/L), mean (SD)	1.18 ± 0.64
HDL-cholesterol (mmol/L), mean (SD)	1.72 ± 0.45
Lipids medication, n (%)	4 (0.4)
High triglycerides (N=607), n (%) ^b	101 (16.6)
Low HDL-cholesterol (N=587), n (%) ^b	113 (19.3)
SBP (mmHg), mean (SD)	128.3 ± 20.1
DBP (mmHg), mean (SD)	78.6 ± 11.4
BP medication, n (%)	94 (9.9)
Hypertension (N=933), n (%) ^b	534 (57.2)
Glucose (mmol/L), mean (SD)	5.00 ± 0.96
Diabetes medication, n (%)	3 (0.3)
High fasting glucose (N=604), n (%) ^b	50 (8.3)

IQR, interquartile range; BMI, body mass index; SD, standard deviation; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure, RA, rheumatoid arthritis

^aNumber of participants without RA and complete data on both outcome measures.

^bPercentage was calculated using the information available on each individual variable.

High waist circumference: ≥88 cm; high triglycerides: ≥1.7 mmol/L or using lipids medication; low HDL cholesterol: <1.3 mmol/L or using lipids medication; hypertension: ≥130/85 mmHg or currently using antihypertensive medication; high fasting glucose: ≥5.6 mmol/L or currently using anti-diabetic medication

Table 2. Cross-sectional association of presence and number of metabolic syndrome (exposure) with joint-specific pain and ROA (outcome)

Neither ROA nor pain: reference category	<i>Age-adjusted</i>		<i>Age and BMI adjusted</i>	
	RRR (95% CI)	p-value	RRR (95% CI)	p-value
Knee				
<i>Presence of MetS^a (≥ 3 vs. 0)</i>				
ROA only	2.2 (0.8-5.9)	0.139	1.0 (0.3-3.4)	0.996
Pain only	1.5 (0.8-2.6)	0.164	1.1 (0.6-2.2)	0.700
Painful ROA	4.3 (1.4-12.4)	<0.05	1.3 (0.4-4.4)	0.725
<i>Number of MetS^a</i>				
ROA only	1.3 (1.0-1.7)	0.089	1.0 (0.7-1.4)	0.980
Pain only	1.2 (1.0-1.3)	0.051	1.1 (0.9-1.3)	0.379
Painful ROA	1.4 (1.1-1.8)	<0.005	1.0 (0.7-1.3)	0.990
Hand (DIP/PIP joints)				
<i>Presence of MetS^a (≥ 3 vs. 0)</i>				
ROA only	2.2 (0.9-5.0)	0.072	2.0 (0.8-5.4)	0.158
Pain only	0.8 (0.3-1.8)	0.518	0.6 (0.2-1.7)	0.389
Painful ROA	3.9 (1.7-9.2)	<0.005	4.4 (1.7-11.5)	<0.005
<i>Number of MetS^a</i>				
ROA only	1.3 (1.0-1.6)	<0.05	1.3 (1.0-1.7)	0.069
Pain only	0.9 (0.7-1.2)	0.536	0.9 (0.7-1.2)	0.374
Painful ROA	1.4 (1.2-1.8)	<0.005	1.5 (1.2-2.0)	<0.005

OA, Osteoarthritis; MetS, Metabolic syndrome; ROA, radiographic osteoarthritis; RR, relative-risk ratio; CI, confidence intervals; BMI, Body Mass Index

^aMetS components defined by the National Cholesterol Education Program III are as follows: waist circumference: ≥ 88 cm; triglycerides: ≥ 1.7 mmol/L or using lipids medication; HDL cholesterol: < 1.3 mmol/L or using lipids medication; blood pressure: $\geq 130/85$ mmHg or currently using antihypertensive medication; fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.

FIGURE LEGENDS

Figure 1. Flow chart of the study

Figure 2. Cross-sectional association between individual components of MetS* (exposure) and knee painful ROA versus neither ROA nor pain (outcome)

OA, Osteoarthritis; MetS, the Metabolic syndrome; ROA, radiographic osteoarthritis; RR, risk ratios; CI, confidence intervals; HDL-c, high-density lipoprotein cholesterol; BMI, Body Mass Index

*MetS components defined by the National Cholesterol Education Program III are as follows: waist circumference: ≥ 88 cm; triglycerides: ≥ 1.7 mmol/L or using lipids medication; HDL cholesterol: < 1.3 mmol/L or using lipids medication; hypertension: blood pressure $\geq 130/85$ mmHg or currently using antihypertensive medication; fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.

Figure 3. Cross-sectional association between individual components of MetS* (exposure) and hand painful ROA versus neither ROA nor pain (outcome)

OA, Osteoarthritis; MetS, the Metabolic syndrome; ROA, radiographic osteoarthritis; RR, risk ratios; CI, confidence intervals; HDL-c, high-density lipoprotein cholesterol; BMI, Body Mass Index

*MetS components defined by the National Cholesterol Education Program III are as follows: waist circumference: ≥ 88 cm; triglycerides: ≥ 1.7 mmol/L or using lipids medication; HDL cholesterol: < 1.3 mmol/L or using lipids medication; hypertension; blood pressure $\geq 130/85$ mmHg or currently using antihypertensive medication; fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.

SUPPLEMENTARY DATA

Supplemental Table S1. Number (percent) of women with missing data

Characteristic	N=952 ^a
Age	0 (0%)
BMI	0 (0%)
Waist circumference	9 (0.9%)
Triglycerides	345 (36.2%)
HDL-cholesterol	365 (38.3%)
Hypertension	19 (2.0%)
Fasting glucose	348 (36.6%)

BMI, Body Mass Index; HDL, high-density lipoprotein; ROA, Radiographic Osteoarthritis; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; RA, rheumatoid arthritis

^a Women with RA and/or incomplete data on both outcomes (n=952).

Supplemental Table S2. Distribution of MetS* individual components on available/complete cases and imputed data

Characteristic	AC ^a	CC ^b (n=567)	Imputed data ^c (n=952)
			Proportion
High waist circumference (n=943), %	15.7	15.3	15.6
High triglycerides (n=607), %	16.6	16.9	18.4
Low HDL-cholesterol (n=587), %	19.3	19.1	19.8
Hypertension (n=933), %	57.2	52.9	57.2
High fasting glucose (n=604), %	8.3	8.3	9.4

MetS, Metabolic syndrome; AC, available cases; CC, complete cases; HDL, high-density lipoprotein; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

*High waist circumference: ≥ 88 cm; high triglycerides: ≥ 1.7 mmol/L or using lipids medication; low HDL cholesterol: < 1.3 mmol/L or using lipids medication; hypertension: SBP/DBP $\geq 130/85$ mmHg or currently using antihypertensive medication; high fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.

^aWomen with available cases on each individual component of MetS included in the analysis (samples vary depending of each variable)

^bWomen who had complete information on all individual component of MetS and covariates included in the analysis (n=567)

^cImputed data after excluding women with RA and/or incomplete data on both outcomes (n=952).

Supplemental Table S3. Effect size of each individual component of MetS* (Available/Complete cases vs. missing data) with knee OA

Neither ROA nor pain: reference category	AC	CC (n=567)		Imputed data (n=952)	
	Unadjusted RRR (95%CI)	Unadjusted RRR (95%CI)	Age-adjusted RRR (95%CI)	Unadjusted RRR (95%CI)	Age-Adjusted RRR (95%CI)
High WC (n=943)					
ROA only	2.5 (1.4-4.6)	2.5 (1.0-6.3)	2.5 (1.0-6.2)	2.5 (1.4-4.5)	2.2 (1.2-4.1)
Pain only	1.5 (1.0-2.2)	1.2 (0.7-2.0)	1.2 (0.7-2.0)	1.5 (1.0-2.3)	1.5 (1.0-2.2)
Painful OA	4.7 (2.7-8.3)	4.6 (2.3-9.3)	4.4 (2.1-9.1)	4.5 (2.6-8.0)	4.1 (2.3-7.2)
High triglycerides (n=607)					
ROA only	0.9 (0.3-2.7)	0.7 (0.2-2.3)	0.6 (0.2-2.1)	1.1 (0.4-3.1)	0.9 (0.3-2.5)
Pain only	1.3 (0.8-2.1)	1.4 (0.9-2.2)	1.3 (0.8-2.1)	1.3 (0.8-2.0)	1.3 (0.8-2.0)
Painful OA	1.4 (0.6-3.1)	1.3 (0.6-3.0)	1.0 (0.4-2.4)	1.2 (0.6-2.6)	1.0 (0.4-2.1)
Low HDL-c (n=587)					
ROA only	1.3 (0.5-3.2)	1.3 (0.5-3.5)	1.3 (0.5-3.5)	1.4 (0.6-3.4)	1.4 (0.6-3.3)
Pain only	1.1 (0.7-1.7)	1.1 (0.7-1.8)	1.1 (0.7-1.8)	1.1 (0.7-1.7)	1.1 (0.7-1.7)
Painful OA	2.0 (1.0-4.0)	1.9 (0.9-4.0)	1.9 (0.9-4.1)	1.8 (0.9-3.6)	1.8 (0.9-3.6)
Hypertension (n=933)					
ROA only	2.0 (1.2-3.5)	0.8 (0.4-1.8)	0.6 (0.3-1.5)	2.0 (1.2-3.5)	1.4 (0.8-2.5)
Pain only	1.3 (1.0-1.8)	1.3 (0.9-1.9)	1.2 (0.8-1.8)	1.3 (1.0-1.7)	1.3 (0.9-1.8)
Painful OA	2.2 (1.3-3.9)	4.3 (1.9-9.6)	3.0 (1.3-7.1)	2.3 (1.3-4.0)	1.6 (0.9-2.9)
High glucose (n=604)					
ROA only	2.2 (0.7-6.8)	1.0 (0.2-4.7)	1.0 (0.2-4.4)	2.4 (0.8-6.9)	2.1 (0.7-6.1)
Pain only	1.3 (0.6-2.5)	1.2 (0.6-2.4)	1.2 (0.6-2.4)	1.3 (0.7-2.5)	1.3 (0.7-2.5)
Painful OA	2.5 (1.0-6.2)	2.7 (1.1-6.7)	2.3 (0.9-5.8)	2.1 (0.8-5.2)	1.8 (0.7-4.6)

MetS, Metabolic syndrome; OA, Osteoarthritis; AC, available cases; CC, complete cases; IQR, interquartile range; HDL, high-density lipoprotein; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

*High waist circumference: ≥ 88 cm; high triglycerides: ≥ 1.7 mmol/L or using lipids medication; low HDL cholesterol: < 1.3 mmol/L or using lipids medication; hypertension: SBP/DBP $\geq 130/85$ mmHg or currently using antihypertensive medication; high fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.

^aWomen with available cases on each individual component of MetS included in the analysis (samples vary depending of each variable)

^bWomen who had complete information on all individual components of MetS and covariates included in the analysis (n=567)

^cImputed data after excluding women with RA and/or incomplete data on both outcomes (n=952).

Supplemental Table S4. Effect size of each individual component of MetS* (Available/Complete cases vs. missing data) with hand OA

Neither ROA nor pain: reference category	AC	CC (n=567)		Imputed data (n=952)	
	Unadjusted RRR (95%CI)	Unadjusted RRR (95%CI)	Age-adjusted RRR (95%CI)	Unadjusted RRR (95%CI)	Age-Adjusted RRR (95%CI)
High WC (n=943)					
ROA only	1.5 (0.9-2.4)	2.0 (1.0-4.0)	1.9 (0.9-3.9)	1.4 (0.9-2.4)	1.1 (0.7-2.0)
Pain only	0.8 (0.4-1.4)	0.7 (0.3-1.6)	0.7 (0.3-1.6)	0.8 (0.4-1.4)	0.7 (0.4-1.3)
Painful OA	1.4 (0.9-2.4)	1.3 (0.6-2.7)	1.2 (0.6-2.6)	1.4 (0.9-2.4)	1.1 (0.7-1.9)
High triglycerides (n=607)					
ROA only	3.0 (1.6-5.7)	2.6 (1.3-5.1)	2.0 (1.0-4.1)	2.7 (1.4-5.2)	2.1 (1.1-4.3)
Pain only	1.3 (0.6-2.5)	1.2 (0.6-2.5)	1.2 (0.6-2.4)	1.3 (0.6-2.5)	1.2 (0.6-2.4)
Painful OA	3.1 (1.7-5.7)	2.4 (1.3-4.6)	1.8 (0.9-3.6)	3.0 (1.6-5.4)	2.3 (1.2-4.3)
Low HDL-c (n=587)					
ROA only	1.8 (1.0-3.5)	1.8 (0.9-3.5)	1.9 (0.9-3.9)	1.8 (0.9-3.3)	1.8 (0.9-3.5)
Pain only	0.9 (0.5-1.8)	0.9 (0.5-1.9)	0.9 (0.5-1.9)	0.9 (0.5-1.8)	0.9 (0.5-1.8)
Painful OA	1.8 (0.9-3.2)	1.5 (0.8-2.9)	1.7 (0.8-3.3)	1.9 (1.0-3.4)	1.9 (1.0-3.7)
Hypertension (n=933)					
ROA only	1.8 (1.2-2.8)	2.5 (1.3-4.6)	1.1 (0.6-2.3)	1.8 (1.2-2.8)	1.0 (0.6-1.6)
Pain only	0.9 (0.6-1.4)	1.2 (0.7-1.9)	1.0 (0.6-1.8)	0.9 (0.6-1.4)	0.8 (0.5-1.2)
Painful OA	3.2 (2.0-5.1)	4.1 (2.2-7.9)	1.9 (0.9-3.7)	3.2 (2.0-5.1)	1.7 (1.0-2.8)
High glucose (n=604)					
ROA only	3.1 (1.3-6.9)	3.4 (1.5-7.8)	3.2 (1.3-7.9)	2.7 (1.2-6.0)	2.4 (1.0-5.8)
Pain only	0.9 (0.3-2.8)	1.0 (0.3-3.0)	1.0 (0.3-3.0)	0.9 (0.3-2.6)	0.9 (0.3-2.6)
Painful OA	3.7 (1.7-7.8)	3.5 (1.6-7.6)	3.3 (1.4-7.7)	3.4 (1.6-7.1)	3.1 (1.3-7.2)

MetS, Metabolic syndrome; OA, Osteoarthritis; AC, available cases; CC, complete cases; IQR, interquartile range; HDL, high-density lipoprotein; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

*High waist circumference: ≥ 88 cm; high triglycerides: ≥ 1.7 mmol/L or using lipids medication; low HDL cholesterol: < 1.3 mmol/L or using lipids medication; hypertension: SBP/DBP $\geq 130/85$ mmHg or currently using antihypertensive medication; high fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.

^aWomen with available cases on each individual component of MetS included (samples vary depending of each variable)

^bWomen who had complete information on all individual components of MetS and covariates included in the analysis (n=567)

^cImputed data after excluding women with RA and/or incomplete data on both outcomes (n=952).

Supplemental Table S5. Women characteristics across knee status categories (n=952).

Characteristic	Neither ROA nor pain (n=553)	ROA only (n=70)	Pain only (n=261)	Painful ROA (n=68)	p-value
Age, years; median(IQR)	53 (48-59)	58 (51-62)	53 (49-59)	58 (54-62)	<0.001
Missing, n (%)	-	-	-	-	
BMI, kg/m ² , mean $\pm$ SD	25.0 $\pm$ 3.9	27.3 $\pm$ 4.7	25.8 $\pm$ 4.3	28.8 $\pm$ 5.2	<0.005
Missing, n (%)	-	-	-	-	
High waist circumference, n (%)	64 (11.6)	17 (24.3)	42 (16.1)	25 (36.8)	<0.001
Missing, n (%)	3 (0.5)	1 (1.4)	2 (0.8)	3 (4.4)	
High Triglycerides, n (%)	54 (9.8)	4 (5.7)	34 (13.0)	9 (13.2)	0.607
Missing, n (%)	198 (35.8)	41 (58.6)	83 (31.8)	23 (33.8)	
Low HDL-cholesterol, n (%)	62 (11.2)	6 (8.6)	32 (12.3)	13 (19.1)	0.277
Missing, n (%)	206 (37.3)	42 (60.0)	92 (35.3)	25 (36.8)	
Hypertension, n (%)	289 (52.3)	48 (68.6)	149 (57.1)	48 (70.6)	<0.005
Missing, n (%)	7 (1.3)	1 (1.4)	10 (3.8)	1 (1.5)	
High fasting glucose, n (%)	24 (4.3)	4 (5.7)	15 (5.8)	7 (10.3)	0.152
Missing, n (%)	201 (36.4)	41 (58.6)	83 (31.8)	23 (33.8)	

OA, Osteoarthritis; ROA, radiographic osteoarthritis; IQR, interquartile range; SD, standard deviation; HDL, high-density lipoprotein; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

High waist circumference: ≥ 88 cm; high triglycerides: ≥ 1.7 mmol/L or using lipids medication; low HDL cholesterol: < 1.3 mmol/L or using lipids medication; hypertension: SBP/DBP $\geq 130/85$ mmHg or currently using antihypertensive medication; high fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.

Values of p-value refer to differences between pain and ROA groups.

Supplemental Table S6. Women characteristics across hand status categories (n=952).

Characteristic	Neither ROA nor pain (n=604)	ROA only (n=111)	Pain only (n=119)	Painful ROA (n=118)	p-value
Age, years	52 (48-58)	59 (54-62)	53 (49-58)	60 (55-63)	<0.001
Missing, n (%)	-	-	-	-	
BMI, kg/m ²	25.4 ± 4.4	26.4 ± 4.9	25.7 ± 3.8	26.1 ± 4.2	0.103
Missing, n (%)	-	-	-	-	
High waist circumference, n (%)	89 (14.7)	22 (19.8)	14 (11.8)	23 (19.5)	0.177
Missing, n (%)	3 (0.5)	2 (1.8)	1 (0.8)	3 (2.5)	
High Triglycerides, n (%)	53 (8.8)	17 (15.3)	11 (9.2)	20 (17.0)	<0.001
Missing, n (%)	188 (31.1)	55 (50.0)	48 (40.3)	54 (45.8)	
Low HDL-cholesterol, n (%)	70 (11.6)	15 (13.5)	11 (9.2)	17 (14.4)	0.101
Missing, n (%)	202 (33.4)	57 (51.4)	51 (42.9)	55 (46.6)	
Hypertension, n (%)	311 (51.5)	72 (64.9)	59 (49.6)	92 (78.0)	<0.001
Missing, n (%)	14 (2.3)	3 (2.7)	2 (1.7)	0 (0)	
High fasting glucose, n (%)	25 (4.1)	9 (8.1)	4 (3.4)	12 (10.2)	<0.001
Missing, n (%)	189 (31.3)	56 (50.5)	48 (40.3)	55 (46.6)	

OA, Osteoarthritis; ROA, radiographic osteoarthritis; IRQ, interquartile range; SD, standard deviation; HDL, high-density lipoprotein; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

High waist circumference: ≥88 cm; high triglycerides: ≥1.7 mmol/L or using lipids medication; low HDL cholesterol: <1.3 mmol/L or using lipids medication; hypertension: SBP/DBP ≥130/85 mmHg or currently using antihypertensive medication; high fasting glucose: ≥5.6 mmol/L or currently using anti-diabetic medication.

Values of p-value refer to differences between pain and ROA groups.

Supplemental Table S7. Cross-sectional association of number of MetS* (exposure) with joint-specific pain and ROA (outcome)

Neither ROA nor pain: reference category	Knee	Hand
	RRR (95% CI)	RRR (95% CI)
A) Excluding women with K/L grade =1		
<i>Number of MetS</i>		
ROA only	1.0 (0.7-1.4)	1.3 (1.0-1.7)
Pain only	1.1 (0.9-1.3)	0.9 (0.7-1.2)
Painful ROA	1.0 (0.7-1.3)	1.6 (1.2-2.0)
B) Adjusting for OA affecting other joint		
<i>Number of MetS</i>		
ROA only	1.0 (0.7-1.4)	1.3 (1.0-1.7)
Pain only	1.1 (0.9-1.3)	0.9 (0.7-1.1)
Painful ROA	1.0 (0.7-1.3)	1.5 (1.2-2.0)
C) IPJ OA affecting 2 or more joints ^a		
<i>Number of MetS</i>		
ROA only	-	1.1 (0.8-1.6)
Pain only	-	1.0 (0.8-1.2)
Painful ROA	-	1.4 (1.1-1.8)

OA, Osteoarthritis; MetS, the Metabolic syndrome; ROA, radiographic osteoarthritis; RR, risk ratios; CI, confidence intervals; HDL-c, high-density lipoprotein cholesterol.

Adjusted for age and BMI

*MetS components defined by the National Cholesterol Education Program III are as follows: waist circumference: ≥ 88 cm; triglycerides: ≥ 1.7 mmol/L or using lipids medication; HDL cholesterol: < 1.3 mmol/L or using lipids medication; blood pressure: $\geq 130/85$ mmHg or currently using antihypertensive medication; fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.

^aReference category: Women presenting less than 2 IPJ joints affected with a K/L grade of ≥ 2 and without any joint pain.

Supplemental Table S8. Cross-sectional association between number of MetS* (exposure) with CMC pain and ROA (outcome)

Neither ROA nor pain: reference category	CMC	
	RRR (95% CI)	p-value
<i>Number of MetS</i>		
ROA only	0.9 (0.7-1.2)	0.609
Pain only	1.0 (0.7-1.2)	0.726
Painful ROA	0.9 (0.7-1.2)	0.597

CMC, first carpometacarpal; OA, Osteoarthritis; MetS, the Metabolic syndrome; ROA, radiographic osteoarthritis; RR, risk ratios; CI, confidence intervals; HDL-c, high-density lipoprotein cholesterol.

Adjusted for age and BMI

*MetS components defined by the National Cholesterol Education Program III are as follows: waist circumference: ≥ 88 cm; triglycerides: ≥ 1.7 mmol/L or using lipids medication; HDL cholesterol: < 1.3 mmol/L or using lipids medication; blood pressure: $\geq 130/85$ mmHg or currently using antihypertensive medication; fasting glucose: ≥ 5.6 mmol/L or currently using anti-diabetic medication.