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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 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 found [10]. A recent meta-analysis demonstrated that hypertension was associated with both radiographic and symptomatic knee OA [11], and another systematic review demonstrated an association between dyslipidemia and OA [12].

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 risk [18] 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 women[19]. 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 smokers [19-23].

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_{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 III [26]. 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 glucose[23].

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 used[27]. Missing data of some needed variables to calculate number

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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 deletion[28] 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 exist [29], 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 ≥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 ≥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

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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 IJP 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 studies [30-32]. 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 joints[5].

A previous study has suggested that weight loss is an effective way of reducing the risk of symptomatic knee OA[36]. 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 later[37]. 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 ROA [38-42], 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). Dahaghin 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 precision[27].

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 analysis[27]. 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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COMPETING INTERESTS

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CONTRIBUTORS

Authors who made substantial contributions to conception and design, analysis, data

interpretation and drafting and/or revising the article: MTSS, AJ, MG, JLN, NKA and SK.

Authors who made a substantial contribution to acquisition of data: TDS, DH and NKA.

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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

[a]Number of participants without RA and complete data on both outcome measures.

[b]Percentage 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	Age-adjusted		Age and BMI adjusted	
	RRR (95% CI)	**p-value**	**RRR (95% CI)**	**p-value**
Knee				
Presence of MetS[a] (≥3 vs. 0)				
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
Number of MetS[a]				
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)				
Presence of MetS[a] (≥3 vs. 0)				
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**
Number of MetS[a]				
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

[a]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: ≥130/85 mmHg or currently using antihypertensive medication; fasting glucose: ≥5.6 mmol/L or currently using anti-diabetic medication.
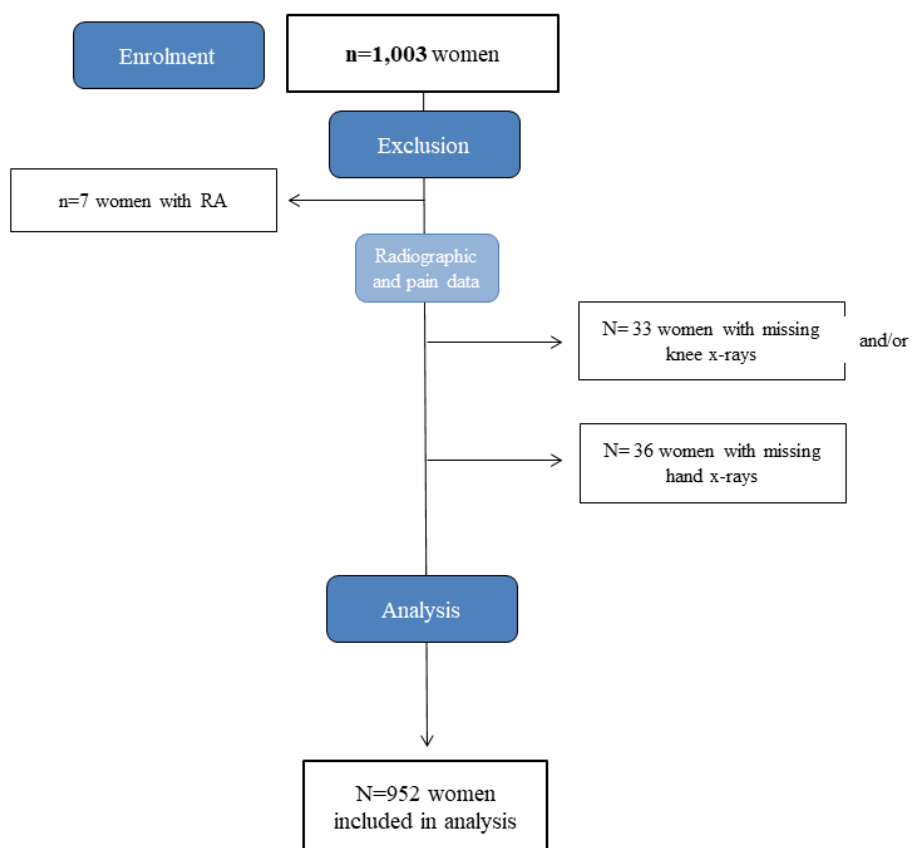
FIGURE LEGENDS

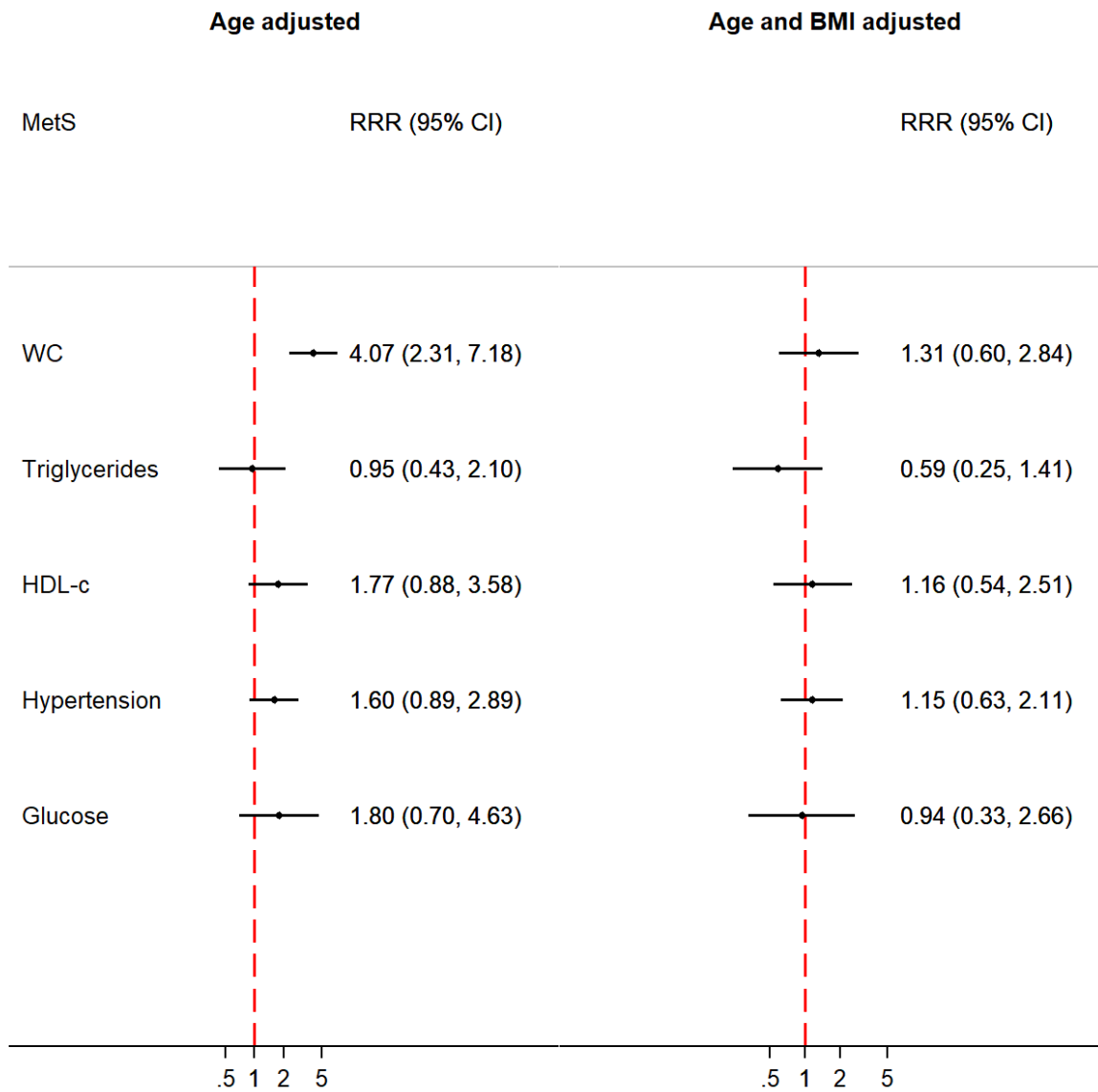**Figure 1.** Flow chart of the study

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≥130/85 mmHg or currently using antihypertensive medication; fasting glucose: ≥5.6 mmol/L or currently using anti-diabetic medication.

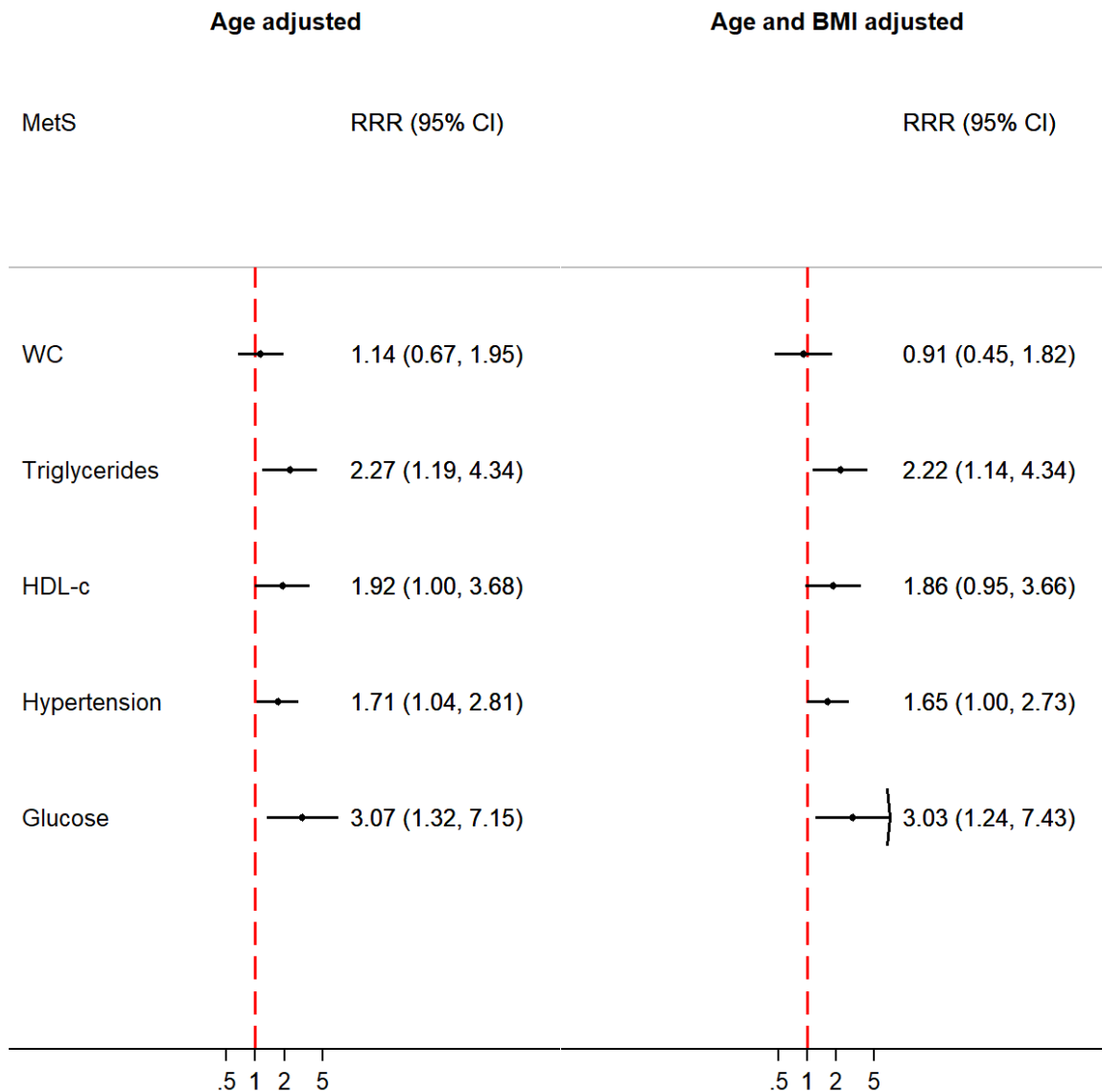| | **Age adjusted** | | **Age and BMI adjusted** | |
MetS		RRR (95% CI)		RRR (95% CI)
WC		1.14 (0.67, 1.95)		0.91 (0.45, 1.82)
Triglycerides		2.27 (1.19, 4.34)		2.22 (1.14, 4.34)
HDL-c		1.92 (1.00, 3.68)		1.86 (0.95, 3.66)
Hypertension		1.71 (1.04, 2.81)		1.65 (1.00, 2.73)
Glucose		3.07 (1.32, 7.15)		3.03 (1.24, 7.43)

.5 1 2 5   .5 1 2 5

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≥130/85 mmHg or currently using antihypertensive medication; fasting glucose: ≥5.6 mmol/L or currently using anti-diabetic medication.