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# Metabolic syndrome and the progression of knee osteoarthritis on MRI

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SUMMARY

*Objective:* Metabolic osteoarthritis (OA) is one of the proposed clinical phenotypes defined by the existence of metabolic syndrome (MetS). This study aimed to (1) investigate whether MetS and its components are associated with progression of knee OA magnetic resonance imaging (MRI) features, and (2) to evaluate the interaction of MetS with menopause and progression of MRI features.
*Method:* 682 women from the Rotterdam Study who participated in a sub-study with knee MRI data available and 5-year follow-up were included. Tibiofemoral (TF) and patellofemoral (PF) OA features were assessed with the MRI Osteoarthritis Knee Score. MetS was quantified by the MetS severity Z-score. Generalized estimating equations were used to evaluate associations between MetS and menopausal transition and progression of MRI features.
*Results:* MetS severity at baseline was associated with progression of osteophytes in all compartments, bone marrow lesions (BMLs) in the PF compartment, and cartilage defects in the medial TF compartment. Waist circumference was associated with progression of osteophytes in all compartments and cartilage defects in the medial TF compartment. High-density lipoprotein (HDL)-cholesterol levels were associated with progression of osteophytes in the medial and lateral TF compartment and glucose levels with osteophytes in the PF and medial TF compartment. No interactions were found between MetS with menopausal transition and MRI features.
*Conclusion:* Women with higher MetS severity at baseline showed progression of osteophytes, BMLs, and cartilage defects, indicating more structural knee OA progression after 5 years. Further studies are required to understand whether targeting MetS components may prevent the progression of structural knee OA in women.



## Introduction

Metabolic syndrome-associated osteoarthritis (OA) is one of the proposed clinical phenotypes that define individuals with obesity and metabolic syndrome (MetS)[1]. After age 50, the prevalence of OA in women increases more quickly compared to men, suggesting a role of menopause in the progression of OA[2]. The menopausal transition is accompanied by the emergence of many features of MetS, including increased central body fat, increased pro-inflammatory markers[3,4], a more atherogenic lipid profile, as well as increased glucose and insulin levels[5]. Since MetS is a major public health problem[6], it is important to understand the potential mechanism underlying the association between MetS and OA progression.

MetS is a clustering of abdominal obesity combined with a higher prevalence of other metabolic diseases (i.e., diabetes type 2, insulin resistance, hypertension, and dyslipidemia)[1]. Although it is now well established that obesity, due to mechanical overload exerted on the joints, is a risk factor for OA[7], less is known on the

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metabolic aspects of obesity. Multiple reviews investigating the association of MetS with knee OA have produced conflicting findings[8–11]. A meta-analysis of observational studies, showed that MetS increases the risk for both clinical and structural knee OA[8]. Other reviews, however, have not identified an association[9] or an increased risk[10] of knee OA due to MetS. Interestingly, sex-stratified analysis suggests that MetS is associated with a higher risk of knee OA in women, but not in men[10]. Menopause is associated with a 60% increased risk of MetS[12]. Therefore, it could be hypothesized that the changes in inflammatory and metabolic factors, due to menopause, may explain why MetS is a risk factor for knee OA development in women and not in men.

It is important to identify the components of MetS that should be targeted in therapies to prevent progression of knee OA. This requires a better understanding of how women with MetS are at higher risk of knee OA progression. For example, in a longitudinal study investigating the individual MetS components, MetS and low high-density lipoprotein (HDL) were independently associated with medial compartment cartilage volume loss and bone marrow lesion (BML) size increase in both men and women[13]. Other studies reported that high waist circumference (WC) was the only metabolic component out of five that was strongly associated with knee OA in women[14,15]. Furthermore, in a 10-year follow-up study an association between the number of components of MetS and increased incidence of radiographic and symptomatic knee OA was found in both men and women[16]. However, in most cases, there was no association after adjustment for body mass index (BMI)[14,16]. This may be explained by the mediated effect of BMI on the relationship between MetS and its components and worse knee pain trajectories[17]. The strong role of obesity either through abnormal joint loading or metabolic inflammation, or a combination of both, may mask the association between other components of MetS, such as WC, with knee OA[18]. It should be taken into consideration that BMI is highly correlated to abdominal obesity[19], which is the most prevalent component of MetS[20], and that BMI ignores the contribution of fat and muscle to body mass[21]. The inconsistent findings may be caused by the heterogeneity of both knee OA and MetS and influenced by the adjustments for risk factors, including BMI. Hence, more research needs to be undertaken before the association between MetS and knee OA in women is more clearly understood.

Longitudinal studies on the association of MetS and progression of knee OA are scarce, and no study has examined female-specific pathways involved in MetS components and MRI-defined structural change of knee OA. Therefore, this study aimed to investigate whether MetS and the individual components of MetS are associated with the progression of features of knee OA assessed by MRI over a 5 years follow-up period among women in the general population. The second aim was to evaluate the interaction of MetS with menopausal transition and the progression of MRI features.

## Method

### *Study population*

This study included 682 women who participated in a knee MRI sub-study of the third sub-cohort ($N = 3932$) of the Rotterdam Study (RS-III), an ongoing prospective cohort study. Details of the study design of the RS have been published elsewhere[22]. In brief, participants were interviewed at home followed by two visits to the research facility for additional interviewing, and laboratory and clinical assessment at baseline (RS-III-1). A follow-up visit (RS-III-2) took place four–six years after the baseline visit. After their study visit for RS-III-1, 891 women participated in a knee MRI sub-study to investigate early signs of knee OA, where additional knee-specific baseline and 5-year follow-up measurements were performed (See Supplementary Table S1 for the timeline)[23]. We excluded participants ($n = 209$) with no MRI at follow-up, resulting in 682 participants.

The RS has been approved by the Medical Ethics Committee of the Erasmus MC (MEC02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, 1071272-159521-PG). All participants provided written informed consent.

### *Data collection*

Measurements were assessed at four time points. The average time interval between the two baseline and two follow-up measurements was 14 and 8 months, respectively.

### *Clinical assessment*

Systolic and diastolic blood pressure (BP) was measured using a random-zero sphygmomanometer on the right arm. BMI was calculated based on weight in kilograms divided by height in meters squared (kg/m$^2$). WC was measured at the level midway between the lower rib margin and the iliac crest. Hip circumference (HC) was measured at the point yielding the maximum circumference over the buttocks. The waist–hip ratio (WHR) was calculated by dividing WC by HC.

### *Laboratory assessment*

Fasting blood samples were collected using venipuncture. Serum HDL-cholesterol, triglycerides, glucose, and estradiol levels were determined using standard techniques.

### *Questionnaire*

Education level was defined as primary education (primary), lower/intermediate general education or lower vocational education (lower), intermediate vocational education or higher general education (further), or higher vocational education or university (higher). The name, dosage, and indication of the medication participants used in the past week were recorded. Smoking was categorized as currently smoking and not currently smoking. Among current smokers, the number of cigarettes smoked per day was assessed. The number of glasses of alcohol per day was converted to grams per day and categorized as light (<15 g/day), moderate (15–29.9 g/day), and heavy (≥30 g/day) drinking. Physical activity was assessed using the LASA Physical Activity Questionnaire (LAPAQ) and expressed in MET hours/week[24]. Postmenopausal women were defined as women who reported an absence of menstrual periods for 12 months, including women reporting menopause after a natural menstrual period, after therapy or operation before the age of 50 years that might have led to menopause. Two menopausal transition categories were defined as (1) transition from perimenopause to postmenopause and (2) peri- or postmenopause at baseline and follow-up. The right and/or left knee was considered to have pain if the participants answered “yes” to “do you have pain in and/or around the knee?”.

### *Radiographic measurements*

Weight-bearing anteroposterior radiographs of the extended knee were obtained with a centered position of the patella[25]. Knee alignment was measured at the medial angle formed by the femur and tibia (FT angle). Three alignment categories were defined as normal alignment (182–184°), valgus alignment (>184°), and varus alignment (<182°)[26].

### *MRI acquisition and interpretation*

Participants underwent bilateral knee MRI at baseline and follow-up on a 1.5-T MRI scanner (Signa Excite 2, General Electric

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Healthcare, Milwaukee, Wisconsin) with an eight-channel cardiac coil to image both knees simultaneously (See Supplementary File S2). All scans were semi-quantitatively scored by two trained readers using the MRI Osteoarthritis Knee Score (MOAKS)[27]. For this study, cartilage defects, osteophytes, BMLs, effusion-synovitis, and Hoffa-synovitis were reported. A cartilage score of ≥1 (0 = none; 1 = <10%; 2 = 10–75%; 3 = >75% of sub-region of cartilage surface area) was considered as having cartilage defects. Osteophytes (0 = absent; 1 = small; 2 = medium; 3 = large) and BMLs (0 = none; 1 = <33%; 2 = 33–66%; and >66% of sub-regional volume) were indicated present when grade ≥1. Effusion-synovitis (0 = none; 1 = small; 2 = medium; 3 = large) and Hoffa-synovitis (0 = normal; 1 = mild; 2 = moderate; 3 = severe) were indicated present when grade ≥2. The presence of a horizontal, vertical, complex, or root tear was considered as having a meniscal tear.

### *MetS classification*

Using the consensus definition incorporating International Diabetes Federation (IDF), American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI)[28], a diagnosis of MetS was made when at least three of the following five conditions were met.

1. Abdominal obesity: elevated WC (≥80 cm).
2. Dyslipidemia: elevated triglycerides (≥150 mg/dL).
3. Dyslipidemia: reduced HDL-cholesterol (<50 mg/dL).
4. Hypertension: elevated BP (systolic ≥130 and/or diastolic ≥85 mmHg) or antihypertensive drug treatment.
5. Hyperglycemia: elevated fasting glucose (≥100 mg/dL) or drug treatment for elevated glucose.

A continuous MetS severity z-score (z-MetS) was calculated using the following five components: WC, triglycerides, HDL-cholesterol, systolic BP, and glucose[29]. The equation for non-Hispanic white women was used, as they most closely reflect the cohort population: $\text{zMetS} = -7.2591 + 0.254 \times \text{wc} - 0.0120 \times \text{HDL}\left(\frac{\text{mg}}{\text{dL}}\right) + 0.0075 \times \text{systolic bp} + 0.5800 \times \ln\left(\text{triglycerides}\left(\frac{\text{mg}}{\text{dL}}\right)\right) + 0.0203 \times \text{fasting glucose}\left(\frac{\text{mg}}{\text{dL}}\right)$. The resultant score can be interpreted as a z-score with higher scores representing an increased severity of MetS. The change in z-MetS score is defined as z-MetS at follow-up minus z-MetS at baseline.

### *MRI knee OA definition*

The MOAKS subregions were combined to define three articular compartments: patellofemoral (PF) (patella and femoral trochlea), medial tibiofemoral (TF) (medial femoral condyle: central and posterior; medial tibia plateau: anterior, central, and posterior), and lateral TF (lateral femoral condyle: central and posterior; lateral tibia plateau: anterior, central, and posterior). The articular features were individually assessed in the three compartments. In addition, a definition for the identification of PF and medial and lateral TF OA on MRI based on the presence of the individual features was used[30]. To evaluate the change in cartilage defects, osteophytes, and BMLs, a definition for the identification of subregional OA progression score was used (See Supplementary Table S3 for the definitions of the change of MOAKS features)[31]. For effusion- and Hoffa-synovitis, the difference between baseline and follow-up scores was calculated. No change and improvement were combined because there were only a few improvement scores, resulting in a dichotomized score of no change or improvement vs progression.

### *Statistical analysis*

Descriptive statistics were applied to describe the participant characteristics at baseline. Pearson's correlation coefficient was calculated to analyse the association between BMI and WC. 284 women had serum estradiol levels below the lower limit of detection (18.40 pmol/L), therefore estradiol was grouped in tertiles in which women with undetectable levels were included in the lowest tertile.

To account for the clustering of knees (two knees included per participant) at subject level, the generalized estimating equations (GEE) approach was utilized. First, in model one the association between MRI features and z-MetS at baseline was assessed. Then, in model two the association between the change in MRI features and the change in z-MetS and z-MetS at baseline was analysed. Only the MRI features that were statistically significantly associated ($P < 0.05$) with the change in z-MetS or z-MetS at baseline in model two were used in models three and four. In model three the association between the change in MRI features and the individual MetS components at baseline was assessed. Finally, in multivariable GEE model four, the association between the change in MRI features and the interaction between z-MetS at baseline and change in menopausal status were assessed. Model four included z-MetS at baseline, change in menopausal status, and the interaction term, and was adjusted for tertiles of estradiol levels at baseline. All models were adjusted for age, with additional adjustments for BMI, knee alignment, and meniscal tears in a separate model.

GEE models were computed using an exchangeable working correlation matrix structure with a binomial probability distribution and a logit link. An exchangeable correlation matrix should mean that the relation between the left and right knees of the same subjects is assumed to be equally correlated. All GEE models used robust standard error estimation. Adjusted odds ratios (OR) with corresponding 95% confidence interval (CI) were reported. GEE analyses were performed using RStudio (R Foundation for Statistical Computing, Vienna, Austria) with the geepack package[32].

## Results

The baseline characteristics are presented in Table I. A total of 682 participants were included, of whom 196 (28.74%) had MetS. At baseline, participants with MetS had a higher BMI, were more often diabetic, were lower educated, and had a lower physical activity pattern compared to participants without MetS. The correlation coefficients between BMI and WC at baseline and follow-up were 0.88 and 0.89, respectively.

### *Association between z-MetS at baseline and MRI features at baseline*

A higher z-MetS score at baseline was associated with all PF MRI features (see Table II). Moreover, a higher z-MetS was associated with the presence of osteophytes in the medial and lateral TF compartment and with the presence of effusion-synovitis. A higher z-MetS score was associated with the presence of PF and medial and lateral TF OA. After adjustment for BMI, knee alignment, and meniscal tears at baseline, z-MetS at baseline remained associated with PF OA (1.64 (1.25–2.14)), but not with medial and lateral TF OA or with the MRI features at baseline.

### *Association between z-MetS at baseline with the change in z-MetS and the change in MRI features*

A higher z-MetS score at baseline was associated with progression of osteophytes and BMLs in the PF compartment (see

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| Characteristics | Total ($N = 682$) | No MetS* ($n = 486$) | MetS* ($n = 196$) |
|---|---|---|---|
| Age, years | 53.33 (3.77) | 53.15 (3.74) | 53.76 (3.81) |
| Height, cm | 165.39 (6.05) | 165.55 (6.01) | 164.99 (6.13) |
| Weight, kg | 73.46 (13.26) | 70.23 (11.42) | 81.47 (14.11) |
| Waist–hip ratio[a] (median [IQR]) | 0.82 [0.78, 0.86] | 0.80 [0.76, 0.84] | 0.86 [0.82, 0.90] |
| BMI, kg/m$^2$ | 26.84 (4.60) | 25.61 (3.86) | 29.91 (4.85) |
| Education level, *n* (%) | | | |
| Primary | 46 (6.8) | 29 (6.0) | 17 (8.8) |
| Lower | 266 (39.2) | 176 (36.2) | 90 (46.6) |
| Further | 178 (26.2) | 130 (26.7) | 48 (24.9) |
| Higher | 189 (27.8) | 151 (31.1) | 38 (19.7) |
| Smoking, *n* (%) | 159 (23.4) | 116 (23.9) | 43 (22.1) |
| Cigarettes per day† | 14.56 (7.50)[1] | 14.38 (7.39) | 15.03 (7.84) |
| Alcohol intake, *n* (%) | | | |
| Light, <15 g/day | 577 (85.1) | 412 (85.1) | 165 (85.1) |
| Moderate, 15–29.9 g/day | 91 (13.4) | 64 (13.2) | 27 (13.9) |
| Heavy, ≥30 g/day | 10 (1.5) | 8 (1.7) | 2 (1.0) |
| Diabetes, *n* (%) | 17 (2.5) | 3 (0.6) | 14 (7.2) |
| Postmenopausal, *n* (%) | 438 (64.2) | 308 (63.4) | 130 (66.3) |
| Estradiol, pmol/l[b] (median [IQR]) | 30.89 [18.35, 88.04] | 27.75 [18.35, 95.20] | 37.00 [18.35, 77.94] |
| Physical activity, MET h/w[c] | 60.81 (48.60) | 63.48 (48.97) | 53.30 (46.88) |
| z-MetS[d] (median [IQR]) | −0.32 [−0.78, 0.18] | −0.58 [−0.97, −0.24] | 0.48 [0.11, 0.96] |
| MetS components | | | |
| Waist circumference, cm[e] | 87.55 (11.70) | 84.20 (9.89) | 95.73 (11.77) |
| Triglycerides, mmol/l (median [IQR]) | 1.11 [0.84, 1.55] | 0.98 [0.78, 1.23] | 1.71 [1.29, 2.24] |
| HDL-Cholesterol, mmol/l | 1.62 (0.45) | 1.76 (0.42) | 1.29 (0.33) |
| Hypertension, *n* (%) | 312 (45.7) | 171 (35.2) | 141 (71.9) |
| Glucose, mmol/l (median [IQR]) | 5.10 [4.80, 5.50] | 5.00 [4.70, 5.30] | 5.60 [5.18, 6.00] |
| Current knee pain, *n* (%) | | | |
| Left | 81 (11.9) | 54 (11.1) | 27 (13.8) |
| Right | 100 (14.7) | 68 (14.0) | 32 (16.3) |
| Knee alignment left, *n* (%)[f] | | | |
| Normal alignment | 211 (31.5) | 135 (28.4) | 76 (39.2) |
| Valgus alignment | 48 (7.2) | 32 (6.7) | 16 (8.2) |
| Varus alignment | 411 (61.3) | 309 (64.9) | 102 (52.6) |
| Knee alignment right, *n* (%)[g] | | | |
| Normal alignment | 244 (36.4) | 164 (34.5) | 80 (41.2) |
| Valgus alignment | 92 (13.7) | 59 (12.4) | 33 (17.0) |
| Varus alignment | 334 (49.9) | 253 (53.2) | 81 (41.8) |
| Meniscal tear, *n* (%) | | | |
| Left | 54 (7.9) | 39 (8.0) | 15 (7.7) |
| Right | 64 (9.4) | 48 (9.9) | 16 (8.2) |

Values are mean (SD) unless otherwise stated. Abbreviations: MetS, metabolic syndrome; BMI, body mass index; MET h/w, metabolic equivalent of task hours/week; z-Mets, MetS severity z-score; HDL, high-density lipoprotein.
Number of missing values >10: [a]21, [b]29, [c]136, [d]32, [e]21, [f]12, [g]12.
* The MetS consensus definition incorporating IDF and AHA/NHLBI was used.
† Average number of cigarettes smoked per day of current cigarette smokers ([1]143).

**Table I**

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Characteristics of the study population stratified by metabolic syndrome at baseline

Table III). In the medial TF compartment, a higher z-MetS at baseline was associated with progression of cartilage defects and osteophytes, but the change in z-MetS was only associated with progression of cartilage defects. In the lateral TF compartment, a higher z-MetS score at baseline was associated with progression of osteophytes. The change in z-MetS was not associated with the change in MRI features in the PF or lateral TF compartment. The change in effusion- and Hoffa-synovitis had no association with z-MetS score at baseline or the change in z-MetS. After additional adjustment for BMI, knee alignment, and meniscal tears at baseline, z-MetS at baseline remained only associated with the progression of BMLs in the PF compartment (1.28 (1.01–1.61)). After these adjustments, z-MetS at baseline and the change in z-MetS was no longer associated with the change in MRI features.

*Association between MetS components at baseline and the change in MRI features*

WC at baseline was associated with progression of osteophytes in all compartments and with cartilage defects in the medial TF compartment (see Table IV). HDL-cholesterol was associated with progression of osteophytes in the medial and lateral TF compartment. Glucose levels were associated with osteophytes in the PF and medial TF compartment. After additional adjustment for BMI, knee alignment, and meniscal tears at baseline, glucose levels remained associated with osteophytes in the PF compartment (1.16 (1.00, 1.34)), HDL-cholesterol with osteophytes in the medial TF compartment (1.62 (1.02, 2.56)), as well as HDL-cholesterol (1.93 (1.08, 3.48)) with osteophytes in the lateral TF compartment.

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| | Absent | | Present | | z-MetS Baseline |
|---|---|---|---|---|---|
| | Knees, *n* | Mean (SD) | Knees, *n* | Mean (SD) | OR (95% CI) age-adjusted |
| PF OA | 1227 | −0.26 (0.82) | 47 | 0.22 (1.30) | **1.52 (1.24, 1.86)** |
| Cartilage defects | 916 | −0.31 (0.77) | 358 | −0.06 (0.99) | **1.35 (1.14, 1.61)** |
| Osteophytes | 1137 | −0.29 (0.77) | 136 | 0.23 (1.21) | **1.73 (1.39, 2.16)** |
| BMLs | 698 | −0.31 (0.79) | 579 | −0.16 (0.90) | **1.22 (1.03, 1.44)** |
| TF medial OA | 1180 | −0.28 (0.81) | 96 | 0.22 (1.03) | **1.62 (1.19, 2.20)** |
| Cartilage defects | 1063 | −0.25 (0.85) | 211 | −0.16 (0.79) | 1.07 (0.89, 1.29) |
| Osteophytes | 1118 | −0.30 (0.75) | 155 | 0.21 (1.25) | **1.76 (1.41, 2.20)** |
| BMLs | 960 | −0.27 (0.83) | 317 | −0.16 (0.88) | 1.12 (0.95, 1.32) |
| TF lateral OA | 1237 | −0.25 (0.81) | 40 | 0.14 (1.41) | **1.43 (1.11, 1.85)** |
| Cartilage defects | 1161 | −0.25 (0.82) | 113 | −0.13 (1.03) | 1.11 (0.89, 1.40) |
| Osteophytes | 1187 | −0.27 (0.78) | 85 | 0.23 (1.41) | **1.61 (1.28, 2.04)** |
| BMLs | 1084 | −0.25 (0.82) | 193 | −0.18 (0.94) | 1.07 (0.88, 1.29) |
| Effusion-synovitis | 1159 | −0.26 (0.79) | 115 | 0.02 (1.23) | **1.35 (1.06, 1.70)** |
| Hoffa-synovitis | 1223 | −0.23 (0.85) | 50 | −0.36 (0.67) | 0.79 (0.53, 1.16) |

Odds ratios (ORs) and 95% confidence intervals (CIs) with statistically significant associations shown bolded. Abbreviations: z-MetS, metabolic syndrome z-score; PF, patellofemoral; TF, tibiofemoral; BMLs, bone marrow lesions.

**Table II**

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Baseline z-MetS scores stratified by the presence or absence of PF, medial and lateral TF OA, and the MRI features at baseline

*Association between z-MetS at baseline with the change in menopausal status and the change in MRI features*

During the follow-up period, 193 (79.1%) out of 244 women (7 unknown) who were perimenopausal at baseline became postmenopausal. 502 (79.6%) out of 631 women that were postmenopausal at follow-up reported menopause after a natural menopause period. See Supplementary Table S4 for z-MetS values at baseline and change of z-MetS scores stratified by menopausal transition. None of the z-MetS at baseline−menopausal transition interactions were associated with the change in MRI features (see Table V).

## Discussion

This study investigated the association between MetS and the progression of knee OA MRI features in middle-aged women. A higher MetS severity at baseline was associated with the progression of osteophytes in all compartments, BMLs in the PF compartment, and cartilage defects in the medial TF compartment. WC was associated with the progression of osteophytes in all compartments and cartilage in the medial TF compartment. HDL-cholesterol levels were associated with the progression of osteophytes in the medial and lateral TF and glucose levels were associated with the progression of osteophytes in the PF and medial TF compartment. No interaction effects were found between MetS severity and menopausal transition with MRI features.

Our results imply that women with a higher MetS severity may be more susceptible to structural progression of knee OA than women with lower MetS severity. The presence and progression of osteophytes had the most consistent and strongest association with MetS severity at baseline in all compartments. These results are in line with other research that found that people with MetS had higher osteophyte scores in the patella, trochlea, and medial tibia compared to an active lean group[33]. Synovial macrophages play an important role in osteophyte formation by the production of growth factors[34]. This suggest that an increase in low-grade inflammation may lead to activation of macrophages resulting in an increased presence of osteophytes. Alternatively, the association between MetS and osteophytes could be explained by the fact that osteophytes are highly correlated with malalignment[35]. Malalignment, especially in combination with a high BMI, is a known risk factor for the development and progression of knee OA[26,36]. Therefore, women with MetS who are more often overweight or obese may be at a higher risk for the development and progression of osteophytes than women without MetS. The truth likely lies somewhere in the middle where the combined presence of low-grade inflammation and mechanical overload increases the risk of progression of osteophytes.

There is some evidence to suggest that BMLs are an indicator of subsequent joint degeneration since BMLs predict progression of OA reflected by greater cartilage loss[37–39]. Although MetS was associated with the prevalence and progression of BMLs in the PF compartment, this was not the case in the TF compartment. Subchondral bone is highly vascularized and it is therefore thought that BMLs may be the consequence of vascular pathology, indicating a role of serum lipids[40]. In contrast to earlier findings[13,41], however, we found no evidence of an association between low HDL-cholesterol and hypertriglyceridemia with BMLs. When interpreting these results it is important to bear in mind that it is still unclear under what conditions a BML is classified as an OA-related BML. Additionally, traumatic BMLs (e.g., anterior cruciate ligament (ACL) tears) often resolve within months after an injury[42] while non-traumatic BMLs can be present for months to years[43]. Therefore, these conflicting results could be explained by the fluctuating nature of BMLs which makes it difficult to assess relationships between MetS and OA-related BML progression.

Synovitis is a risk factor for incident knee OA[44] and is associated with worsening of structural OA[45]. While one study found no difference in effusion-synovitis in a MetS group compared to an active lean group[33], other research indicated that overweight and obese women with effusion-synovitis had increased odds for incident radiographic OA, but not in men[46]. We observed that the presence of effusion-synovitis, but not Hoffa-synovitis, was associated with a

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| | z-MetS Baseline | | | | | Δz-MetS | | |
|---|---|---|---|---|---|---|---|---|
| | No change and improvement | | Progression | | | No change and improvement | Progression | |
| | Knees, *n* | Mean (SD) | Knees, *n* | Mean (SD) | OR (95% CI) age-adjusted | Mean (SD) | Mean (SD) | OR (95% CI) age-adjusted |
| PF | | | | | | | | |
| Cartilage defects | 976 | −0.28 (0.77) | 267 | −0.13 (1.02) | 1.15 (0.94, 1.42) | 0.15 (0.48) | 0.09 (0.76) | 0.89 (0.65, 1.22) |
| Osteophytes | 1098 | −0.29 (0.76) | 143 | 0.08 (1.21) | **1.54 (1.21, 1.96)** | 0.15 (0.49) | 0.07 (0.87) | 1.04 (0.77, 1.41) |
| BMLs | 917 | −0.28 (0.76) | 322 | −0.15 (0.99) | **1.20 (1.00, 1.42)** | 0.15 (0.49) | 0.12 (0.69) | 1.00 (0.78, 1.28) |
| TF medial | | | | | | | | |
| Cartilage defects | 1122 | −0.26 (0.83) | 121 | −0.08 (0.79) | **1.35 (1.08, 1.69)** | 0.13 (0.56) | 0.24 (0.50) | **1.56 (1.15, 2.10)** |
| Osteophytes | 1079 | −0.28 (0.76) | 161 | 0.01 (1.18) | **1.39 (1.10, 1.77)** | 0.15 (0.49) | 0.10 (0.86) | 1.05 (0.75, 1.48) |
| BMLs | 1072 | −0.26 (0.83) | 167 | −0.17 (0.84) | 1.07 (0.87, 1.32) | 0.14 (0.56) | 0.11 (0.51) | 0.94 (0.71, 1.24) |
| TF lateral | | | | | | | | |
| Cartilage defects | 1157 | −0.25 (0.85) | 86 | −0.22 (0.61) | 1.05 (0.82, 1.36) | 0.13 (0.55) | 0.22 (0.51) | 1.32 (0.83, 2.10) |
| Osteophytes | 1129 | −0.28 (0.77) | 110 | 0.10 (1.26) | **1.44 (1.10, 1.88)** | 0.15 (0.49) | 0.04 (1.00) | 0.95 (0.64, 1.40) |
| BMLs | 1157 | −0.25 (0.84) | 82 | −0.27 (0.67) | 0.97 (0.76, 1.26) | 0.14 (0.56) | 0.18 (0.47) | 1.15 (0.76, 1.74) |
| Effusion-synovitis | 1121 | −0.25 (0.81) | 117 | −0.22 (1.03) | 0.99 (0.78, 1.25) | 0.14 (0.52) | 0.12 (0.78) | 0.91 (0.61, 1.36) |
| Hoffa-synovitis | 1145 | −0.26 (0.80) | 92 | −0.14 (1.17) | 1.10 (0.84, 1.45) | 0.14 (0.53) | 0.09 (0.82) | 0.90 (0.62, 1.30) |

Odds ratios (ORs) and 95% confidence intervals (CIs) with statistically significant associations shown bolded. Abbreviations: z-MetS, metabolic syndrome z-score; PF, patellofemoral; TF, tibiofemoral; BMLs, bone marrow lesions.

**Table III**

Osteoarthritis and Cartilage

z-MetS at baseline and change in z-MetS scores stratified by the change in MRI features

| | PF | | TF medial | | TF lateral |
|---|---|---|---|---|---|
| | Osteophytes | BMLs | Cartilage defects | Osteophytes | Osteophytes |
| WC, cm | **1.03 (1.01, 1.05)** | 0.99 (0.98, 1.01) | **1.03 (1.01, 1.05)** | **1.03 (1.01, 1.05)** | **1.03 (1.01, 1.05)** |
| Triglycerides, mmol/l | 1.02 (0.75, 1.37) | 1.18 (0.92, 1.50) | 0.85 (0.56, 1.28) | 1.08 (0.84, 1.38) | 1.26 (0.96, 1.65) |
| HDL-cholesterol, mmol/l | 1.25 (0.72, 2.17) | 0.88 (0.61, 1.26) | 0.92 (0.55, 1.54) | **1.62 (1.04, 2.51)** | **1.93 (1.10, 3.37)** |
| Glucose, mmol/l | **1.19 (1.03, 1.38)** | 1.12 (0.99, 1.26) | 0.94 (0.79, 1.11) | **1.16 (1.01, 1.34)** | 1.13 (0.97, 1.32) |
| Hypertension, *n* | 1.01 (0.66, 1.53) | 0.88 (0.67, 1.16) | 1.16 (0.77, 1.75) | 1.08 (0.74, 1.59) | 1.19 (0.74, 1.93) |

Odds ratios (ORs) and 95% confidence intervals (CIs) with statistically significant associations shown bolded. Abbreviations: MetS, metabolic syndrome; PF, patellofemoral; TF, tibiofemoral; BML, bone marrow lesions; WC, waist circumference; HDL, high-density lipoprotein.

* Only the MRI features that were associated (*P*-value <0.05) with the change in z-MetS or z-MetS at baseline (model 2) were analysed.

**Table IV**

Osteoarthritis and Cartilage

Age-adjusted association between MetS components at baseline with the change in MRI features*

higher MetS severity at baseline. It has been suggested that more than mild synovitis is required before it can affect structural progression[45]. Although only a few women had moderate-to-severe synovitis, cartilage defects in the PF compartment were associated with MetS severity at baseline. In addition, cartilage progression in the medial TF compartment was associated with the change in MetS severity. This may suggest a link between MetS severity, the presence of joint effusion-synovitis, and progression of cartilage defects. More research needs to be undertaken to understand whether synovitis may mediate the effect of cartilage loss. Further work is required to investigate whether women with MetS have more synovitis, ideally using contrast-enhanced MRI for detecting synovitis[47], and therefore are at higher risk of radiographic OA than women without MetS.

Against our expectation, no interaction between menopausal transition with MetS and MRI features was found. Findings from a recent review indicate how hormones, including estrogens, and other sex-related factors influence OA progression and development, for instance by increased muscle mass loss and bone loss[48]. Our results are likely to be influenced by the high number of women in the study who were postmenopausal at baseline. Since only a few women became postmenopausal during the follow-up period, the current study population may not have been suitable to assess the role of menopause. Moreover, the large confidence intervals of the interaction terms do not rule out the possibility of an association between MetS with menopause and the progression of OA. In addition, estradiol levels were only available at baseline, therefore we could not adjust for changes in estradiol levels. Since

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| | PF | | TF medial | | TF lateral |
|---|---|---|---|---|---|
| | Osteophytes | BMLs | Cartilage | Osteophytes | Osteophytes |
| Baseline z-MetS × menopausal transition | 1.45 (0.76, 2.78) | 0.73 (0.48, 1.10) | 1.14 (0.61, 2.15) | 1.14 (0.61, 2.15) | 0.66 (0.27, 1.60) |

Odds ratios (ORs) and 95% confidence intervals (CIs). Abbreviations: z-MetS, metabolic syndrome z-score; PF, patellofemoral; TF, tibiofemoral; BMLs, bone marrow lesions.

* Only the MRI features that were associated (*P*-value <0.05) with the change in z-MetS or z-MetS at baseline (model 2) were analysed.

**Table V**

Osteoarthritis and Cartilage

Age- and estradiol tertiles-adjusted association between z-MetS at baseline with the change in menopausal status and the change in MRI features*

more women develop OA after the age of 50, it is important to investigate how hormonal changes during menopausal transition results in metabolic changes that affect OA progression to help develop sex-specific OA treatments.

Progression of cartilage defects in the medial TF compartment was the only feature that was associated with the change in MetS severity. However, after adjustment for the potential mechanical confounders of BMI, meniscal tears, and knee alignment at baseline, there was no association between the change in MetS severity with the progression of MRI features. Although on average MetS severity increased, the changes were small, which may explain the absence of an association between changes in MetS severity and progression of other MRI features. Since BMI ignores the contribution of fat and muscle to body mass, questions have been raised about whether BMI adjustment is justified when studying MetS[18]. Among the MetS components, HDL-cholesterol level was associated with the progression of osteophytes in the lateral and medial TF compartment. Unfortunately, none of the studies investigating the association between HDL cholesterol and OA analysed osteophyte progression. WC was most often associated with the progression of MRI features, suggesting an important role of abdominal obesity in OA progression. In addition, sensitivity analysis in women with a BMI above 30 demonstrated similar results (data not presented). MetS severity at baseline (except for progression of cartilage in the medial TF compartment) and the change in MetS severity remained associated with the progression of the MRI features in women with a BMI above 30. Therefore, considering the high correlation of BMI with WC, it was decided to present the age-adjusted analyses with additional adjustments for BMI, meniscal tears, and knee alignment. Intervention studies that target weight loss should look beyond BMI and also consider the sex differences with regard to BMI and body composition[49,50].

While there are several strengths to this study, including the longitudinal design, MRI-defined progression, and a continuous MetS z-score, there are limitations as well. First, participants were allowed to enrol in the knee-specific sub-study after participants' initial study visit for the cohort, resulting in a time interval between the measurements of the metabolic components and knee-specific outcomes. Although some MRI features are known to fluctuate over time, the changes in MetS severity over time were small, therefore we expect the time differences to be of little impact. An additional uncontrolled factor is the possible effect of ligament tears on the progression of knee OA. The z-MetS severity score was calculated using an equation that is specific for non-Hispanic women. Although no data was available on the ethnicity of the parent, 84.6% of the participants had four grandparents that were non-Hispanic. Finally, although 219 women were excluded from the analysis due to missing MRI data at follow-up, there was no difference in baseline characteristics compared to the 682 women included in the analysis (See Supplementary Table S5).

## Conclusion

MetS severity was associated with progression of osteophytes in all compartments, BMLs in the PF compartment, and cartilage defects in the medial TF compartment, although baseline BMI, meniscal tears, and knee alignment remain confounders. Collectively, these findings suggest that women who have higher MetS severity may potentially be at risk for more structural knee OA progression. Further research should be undertaken to investigate the role of menopause in OA progression. Intervention studies are required that target MetS components, with a primary focus on abdominal obesity, to investigate whether reducing these indicators of MetS severity prevents the progression of structural knee OA in women.

## Patient consent for publication

Not required.

## Data availability statement

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (datamanagement.ergo@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

## Author contributions

All authors (NJ, EM, DS, EO, JvM, MvM, SB-Z) contributed to the conception and design of the article, as well as analysis and interpretation of data. The article was written by NJ. All other authors (EM, DS, EO, JvM, MvM, SB-Z) critically revised and edited the manuscript draft and approved the final manuscript.

## Competing interests

None declared.

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**Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2023.02.003.

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