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Metabolic syndrome, radiographic osteoarthritis progression and chronic pain of the knee among men and women from the general population: The Rotterdam study

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ABSTRACT

Objective: Although a relationship between osteoarthritis and components of metabolic syndrome (MetS) has been suggested, most of the results have been cross-sectional. We, therefore, aimed to investigate the sex-specific longitudinal association of (components of) MetS with progression of radiographic osteoarthritis and chronic pain in the knee joints in a large prospective cohort.

Method: In the large population-based Rotterdam study of up to 6,138 individuals, median follow-up time 5.7 (IQR 5.5) years, we examined the relation between MetS and its components (abdominal obesity, high triglycerides, low high-density lipoprotein, elevated blood pressure, and type 2 diabetes) with the progression of osteoarthritis using generalized estimating equations, generalized linear models and competing risk analysis. Analyses were stratified for sex. Covariates adjusted for: age, smoking, alcohol use, education, sub-cohort, baseline K/L grade, months between radiographs and BMI.

Results: The presence of MetS (37.6 % in men, 39 % in women) and elevated blood pressure was associated with an increased risk of knee osteoarthritis progression in both men and women. MetS was associated with an increased risk of incident chronic knee pain (CKP) in men. In addition, abdominal obesity and high triglycerides showed higher riskfor incidence of CKP in men,but not in women. The associations were attenuated and no longer significant after BMI-adjustment, except for the association of MetS and high triglycerides with incidence of CKP in men that stayed significant (OR 1.04, 95 %CI 1.00–1.07 for MetS and OR 1.04, 95 %CI 1.01–1.07 for high triglycerides).

Conclusion: Metabolic syndrome and individual metabolic components, such as abdominal obesity and elevated blood pressure, were associated with radiographic progression of knee OA in both men and women, but not independent of BMI. Metabolic syndrome and high triglycerides were associated with incidence of CKP only in men.

Introduction

Osteoarthritis (OA) is a highly prevalent joint disorder estimated to affect over 35 % of adults over 60 years of age [1–3]. It is a leading cause of pain and disability, especially in women, and is associated with increased morbidity and mortality [4]. The frequency of osteoarthritis is increasing fast, mainly caused by the aging of the population, and the accelerated prevalence of obesity, which is the primary risk factor for knee OA [2,5,6].

The association between OA and obesity is thought to be due, in part, to mechanical overload exerted on the joints. However, there is a growing body of evidence that OA is a metabolic disease, as body mass

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index (BMI) is also associated with non-weight bearing joints, such as hand OA [7]. The state of obesity is associated with several metabolic changes in the individual, such as altered glucose and lipid metabolism. These metabolic changes tend to co-occur in individuals and are reffered to as metabolic syndrome (MetS).

Evidence suggests the existence of a distinct form of OA, called metabolic OA, which is linked to obesity-related factors such as increased glucose levels and dyslipidaemia [8,9]. However, conclusive evidence for the existence of metabolic OA is still lacking and also which component of MetS is involved. One of the most prominent components of MetS, hyperglycaemia and/or type 2 diabetes (T2D) has been implicated as a key factor in the pathophysiology of OA [10–12]. Similarly, MetS and its components have been associated with various OA outcomes [13,14]. Moreover, the metabolic OA-type is thought to be more prominent in females. Sex differences have been noted in the prevalence and clinical representation of MetS, more specifically in fat distribution and adipocyte function [15].

Clear evidence for a causal effect of MetS on OA is still lacking. Cross-sectional studies [16,17] found a positive association between MetS and Knee OA, but this disappeared after adjustments for weight or BMI (if applied). Prospective studies can provide more insight into the causal relationship. A recent meta-analysis found evidence to support MetS as an independent risk factor of incident Knee OA in women but not in men. The authors identified five studies with adjustment for BMI [18]. Four out of the five studies examined incident total knee replacements as the outcome, while there was only one prospective study examining radiographic progression in knee OA [19]. The longitudinal ROAD study with 3-year follow-up [20] was not included in this meta-analysis because instead of waist circumference BMI $\geq$25 was used as one of the metabolic factors and therefore the authors did not adjust for BMI in their analyses. In their study, Yoshimura et al., were able to show that accumulating a larger number of the components of metabolic syndrome was associated with incidence and progression of knee OA.

Moreover, there is conflicting evidence for an association between T2D and OA. The most recent systematic review and meta-analysis showed that positive associations mostly came from cross-sectional studies, while case-control and prospective studies showed no or negative associations [21].

Despite pain being the main symptom taken into account for diagnosing OA at the clinic and what patients care most about, there are only a few studies that investigated the association of MetS and metabolic components with pain outcomes. One study showed that abdominal obesity, low serum levels of HDL, high levels of serum triglycerides and presence of MetS were all significantly associated with a "moderate" pain trajectory [22]. In a sample of middle-aged adults, there was a significant positive association between MetS and knee symptoms [23]. However, another recent study [24], found no associations between MetS or its individual components with worse knee symptoms after adjustment for BMI. Therefore, similar to radiographic knee OA, more evidence is needed to clearly assess the evidence for an association between metabolic factors and pain.

Since data on the structural progression of OA and pain symptoms concerning metabolic determinants are scarce, there is a strong need for large longitudinal studies. Therefore, in this study, we aimed to examine the sex-specific relationship between MetS, its components and progression of ROA and prevalent and incident chronic pain specifically in the knee, using large prospective cohort data.

Materials and methods

Study population

This study was embedded within the Rotterdam Study (RS), an ongoing prospective population-based cohort study of Dutch individuals living in the Ommoord district of Rotterdam in the Netherlands, which consists of multiple sub-cohorts [25]. All people of a certain age (depending on the cohort) who lived in Ommoord and were registered in the municipal register were invited to participate [26]. The first cohort, RS-I, consisted of individuals aged 55 or older. Baseline measurements were collected from 1990 to 1993 for 7983 participants (RS-I). The second cohort started in 2000 with similar recruitment criteria (RS-II cohort, $N = 3011$). The third cohort was recruited in 2006 by the inclusion of individuals aged 45 and older (RS-III cohort, $N = 3932$). The 3 sub-cohorts and corresponding sample sizes are illustrated in Fig. 1. The overall response rate in the RS was 72 %. Follow-up data were collected at follow-up visits every ~3–5 years. The participants are followed for a variety of diseases that are frequent in the elderly to investigate determinants of disease occurrence and progression. Baseline and follow-up data including information on health profile, biometric measurements, medical history, medication usage, serum samples and radiographs were obtained through structured home interviews and visits to the research centre.

The present study includes participants for whom baseline exposure data, pain questionnaires and radiographs of knees at both baselines and at least one follow-up visit were available and assessed for OA and chronic pain. We included participants from visits 3, 4 and 5 of RS-I (1997–2008), visits 1, 2 and 3 of RS-II (2000–2012) and visits 1 and 2 of RS-III (2006–2014). (Fig. 1).Important to note is that RS participants were not specifically selected for radiographs when included in the original cohort.

The RS has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. The approval has been renewed every 5 years (MEC 02.1015). All participants provided written informed consent for participation in the RS. An overview of the RS cohorts is found in Fig. 1 and more details on participants included in this study are found in the corresponding flowcharts as **Supplementary Figs. S1and S2**.

Metabolic syndrome (MetS) and components

MetS was assessed according to the consensus definition of the International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) in 2009 [27]. A MetS diagnosis required a minimum of 3 out of the 5 components to be present (Fig. 2). Individuals who did not meet the criteria of having at least 3 measurements are controls. Blood samples and information on fasting status were acquired during participant visits to the research centre.

Prevalent T2D was defined following the current WHO guidelines as a fasting blood glucose of $\geq$7.0 mmol/L, if fasting blood samples were unavailable non-fasting blood glucose of $\geq$11.1 mmol/L, or the use of glucose-lowering medication [28]. Information on the use of glucose-lowering medication was acquired through both structured home interviews and linkage to pharmacy dispensing records. Blood samples and information on fasting status were acquired during participant visits to the research centre.

Blood pressure (BP) was measured at the research center by a trained research assistant at the right upper arm using a random-zero sphygmomanometer after the participant had been sitting quietly for $\geq$5 min. Systolic BP was recorded at the appearance of sounds (first-phase Korotkoff) and diastolic BP at the disappearance of sounds (fifth-phase Korotkoff). Systolic and diastolic BP were calculated as the average of the 2 measurements. Hypertension was defined as a systolic BP $\geq$140 mm Hg, a diastolic BP $\geq$90 mm Hg, or the use of antihypertensive medication. At the research center, a physician ascertained the indication for which the medication had been prescribed.

Serum total cholesterol was measured in a nonfasting blood sample by using an automated enzymatic method. For further details on measurement protocol, detailed information can be found in the Rotterdam Study design, objectives and main findings regular paper published along the years [25,26,29–34].

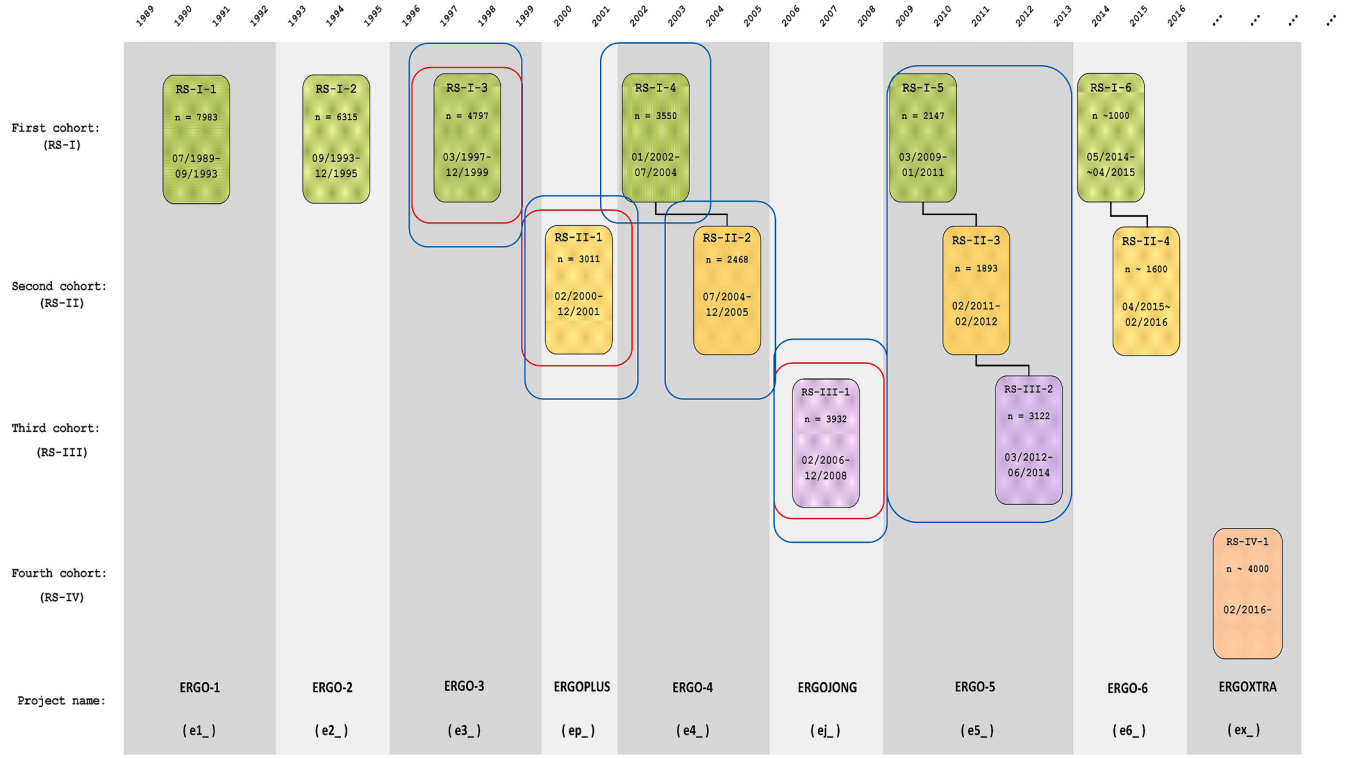

Fig. 1. Overview of the Rotterdam Study cohorts. For the present study we used data on osteoarthritis assessed by X-ray at visits RS-I- 3, 4, 5, RS-II- 1, 2, 3 and RS-III-1, 2 (in blue frame) and the exposures/metabolic factors assessed at visits RS-I-3, RS-II-1 and RS-III-1 (in red frame). Figure was adapted from article published by Hofman et al., 2015 under license CC BY 4.0 (http://creativecommons.org/licenses/by/4.0).

	Men	Women
Waist circumference	≥94 cm	≥80 cm
HDL-Cholesterol	< 40 mg/dl (1.03 mmol/l) or lipid-lowering medication use	< 50 mg/dl (1.29 mmol/l) or lipid-lowering medication use
Triglycerides	≥150 mg/dl (1.7 mmol/l or lipid-lowering medication use	
Blood pressure	SBP≥130 mm Hg or DBP≥85 mm Hg or antihypertensive medication use	
Fasting blood glucose	≥ 100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes	

Fig. 2. Metabolic syndrome components.

Radiographic OA progression

Knee radiographs were taken with the knee and patella in an extended and central position respectively. Radiographic OA was assessed by observers blinded for clinical and demographic data [35].

As currently there is no consensus on what constitutes progression of radiographic OA, we used a definition that combines both incident and progressive OA as previous studies in RS [36,37].

Progression of OA in knee joints was defined as a Kellgren-Lawrence (KL)-grade of 0 or 1 at baseline and a KL-grade 2–4 or total joint replacement (TJR) at follow-up, or an increase of the KL-grade of 1 or more for joints with a baseline KL-grade of 2 or higher. Knee joints with KL-grade 4 or TJR at baseline were excluded from the analysis.

Chronic joint pain assessment

During the home interview, participants were asked about current musculoskeletal pain in the knees using a dichotomous variable (yes/no). If present, a more specific question on whether they experienced pain or stiffness in the knee was posed (yes/no). If the answer was positive, the duration of this pain was recorded. **Chronic knee pain (CKP)** was defined as pain or stiffness in the knee for more than 3 months. **Incident CKP** was defined as the development of CKP at follow-up in persons who did not have CKP at first visit. Controls were free of pain in all the joints.

Potential confounders

Analyses of radiographic knee OA were adjusted for age, smoking, alcohol consumption, educational attainment, baseline KL score, subcohort and months between radiographs. Adjustment for months between radiographs was done because there were participants who had an average of ~5 years while other participants ~10 years between X-ray measurements. We maximized the number of participants, included in our sex-stratified analysis, with available X-ray data at baseline and at least 1 follow-up X-ray measurement. Adjustment for baseline KL score was done to account for the increased chance of developing/progressing when having a higher KL score at baseline X-ray measurement, **Supplementary Table S1.** [38]. Additionally, we expanded all models by adding body mass index (BMI) to verify if the associations are independent of this strong risk factor. BMI was computed from

measurements of height and weight (kg/m2) taken during visits to the research center. BMI is a measure of weight (kg) corrected for surface area (m2). In this study we approached adjustment for BMI from a biological perspective to correct body weight for surface area. Using BMI increases the precision of the weight measurement taking into account the variability of weight explained by differences in body surface. Baseline information on age, current cigarette smoking (yes/no), alcohol consumption (no/any consumption) and educational attainment (primary, lower, intermediate and higher [39], were collected from participants using questionnaires during structured home interviews. Depression was assessed based on the Center for Epidemiological Studies Depression scale (CES-D) [40]. This self-reporting scale of depressive symptoms gives a score between 0 and 80.

Statistical analysis

Our primary analyses consisted of multivariate logistic regression models to assess the relation between MetS and each of its components separately with ROA progression. For radiographic knee OA, correlations between right and left extremity in individuals were taken into account with the use of generalized estimating equations (GEE). For chronic knee pain analyses we used generalized linear regressions (GLM). All analyses were stratified by sex to observe potential sex differences in the associations. Odds ratios (OR) accompanied by 95 % confidence intervals (CI) for progression of ROA were calculated for each joint type using the absence of OA progression as reference and adjusted for the potential confounders and other influencing factors.

Subsequently, we performed a competing risk analysis where we compared the cumulative incidence estimates for knee OA progression concerning diabetes taking death and lost to follow-up as a competing risk into account. The objective of this analysis was to understand the reason behind the inverse association between T2D and knee OA progression using GEE model. In short, we fitted the competing risk regression (CRR) [41], developed by Fine and Gray, which considers the effect of predictors on the sub-hazard function (cumulative incidence function) accounting for the presence of competing risks [42]. We report the effect estimates as sub-hazard ratios(SHR) accompanied by 95 %CI. Programming for CRR is publicly available using the statistical software R, *cmprsk* package (version 4.0.5, http://www.r-project.org).

Sensitivity analyses

For sensitivity analyses, we also adjusted for total physical activity. We repeated the analyses by excluding the people having total joint replacement at follow-up (which might constitute a more symptomatic progression than structural progression). For radiographic knee OA, we also performed the same analysis restricting cases to only incident knee OA.

We further stratified by the mean for age (<65 and ≥65 years old), BMI (<27 and ≥27 kg/m^2), and follow-up time (<100 and ≥100 months). We also repeated the analyses after excluding participants who changed exposure status in MetS and its components during follow-up.

In a separate analysis, we performed a threshold effect analysis using sex-specific quartiles of the MetS components and adjusted for the same covariates as in our primary analysis.

All statistical analyses were performed in R version 4.0.5 [43] using *geepack* (GEE analysis) and *cmprsk* (analysis of competing risks) packages. Statistical significance was defined as $p < 0.05$.

Results

Of the total 6138 participants with longitudinal knee radiographs and exposure data, 2379 (38 %) had MetS at baseline according to our criteria, 37.6 % in men and 39 % in women. In our study sample, 3606 participants have been at the 1st follow-up and 2532 have been at least at the 2nd follow-up. The median (IQR) follow-up time is 5.7 (5.5) years. The mean (SD) age of the population at baseline was 63.6 (8.06) years. Participants with MetS had at baseline on average higher BMI and lower education attainment (Table 1). A separate sample of 2,777men and 3,263women was eligible for the analysis of chonic knee pain (CKP) (Table 2).

Radiographic progression of knee OA

From the 6138 participants, we had information on 12,276 knees for our GEE analysis. After exclusion of missing data on covariates, 12,031 knees were included for progression analyses, 10,959 knees were free of ROA at baseline (KL<2), and 1072 had a KL≥2. A total of 1155 (9.6 %) knees showed OA progression during follow-up (more details on numbers of knees with various KL grades at baseline and how many of those progressed can be found in **Supplementary Table S1**). We observed that abdominal obesity and elevated blood pressure (BP) were associated with progression of ROA in the initial multivariate analysis in both men and women (Table 3), while MetS only reached significance in men, and a trend towards higher risk was seen in women albeit not reaching significance. After BMI-adjustment, there is a high risk estimate, suggestive of a possible association, however not reaching significance in both sexes.

In the BMI-adjusted analyses, T2D was inversely associated with

Table 1
Characteristics of the study population in our analyses of the radiographic knee OA progression.

	Males		Females	
	No metabolic syndrome (1675)	Metabolic syndrome (1010)	No metabolic syndrome (2137)	Metabolic syndrome (1369)
Age, years	63.5 ± 8.1	63.5 ± 7.76	62.7 ± 8.04	64.8 ± 8.12
BMI, kg/m2	26 ± 3.12	28.4 ± 3.51	26.2 ± 4.15	28.8 ± 4.45
Waist circumference, cm	95 ± 9.12	102 ± 9.29	85.9 ± 11.1	94 ± 11.1
Triglycerides, mmol/L	1.23 ± 0.472	2.03 ± 1.15	1.14 ± 0.39	1.85 ± 0.832
HDL-cholesterol, mmol/L	1.36 ± 0.305	1.1 ± 0.283	1.71 ± 0.378	1.32 ± 0.358
Systolic blood pressure, mmHg	137 ± 19.7	145 ± 19.1	133 ± 20.3	143 ± 19.9
Diastolic blood pressure, mmHg	78.6 ± 10.7	82.1 ± 11.3	76.5 ± 10.8	79.2 ± 11.3
Fasting blood glucose, mmol/L	5.52 ± 0.706	6.34 ± 1.86	5.32 ± 0.602	5.99 ± 1.46
Smoking, %	259 (17.8)	207 (16.9)	369 (18.4)	263 (18.1)
Alcohol consumption, %	1363 (93.8)	1135 (92.5)	1737 (86.5)	1163 (80.2)
Education level, % primary	109 (7.5)	89 (7.25)	198 (9.87)	223 (15.4)
lower	377 (25.9)	373 (30.4)	1031 (51.4)	764 (52.7)
intermediate	544 (37.4)	471 (38.4)	483 (24.1)	328 (22.6)
higher	423 (29.1)	294 (24)	295 (14.7)	136 (9.37)
Abdominal obesity, %	728 (50.1)	1054 (85.9)	1322 (65.9)	1349 (93)
High triglycerides, %	126 (8.67)	943 (76.9)	165 (8.22)	1205 (83)
Low HDL cholesterol, %	169 (11.6)	1040 (84.8)	136 (6.78)	1167 (80.4)
Elevated BP, %	909 (62.6)	1137 (92.7)	1146 (57.1)	1296 (89.3)
Type 2 Diabetes, %	28 (1.93)	299 (24.4)	18 (0.897)	260 (17.9)

Categorical variables are displayed as count (%). Continuous variables are presented as mean ± SD.
Abbreviations: BMI - body mass index, HDL - high-density lipoproteins, BP - blood pressure.

Table 2
Characteristics of the study population in our analyses of chronic knee pain.

	Males		Females	
	No metabolic syndrome (1476)	Metabolic syndrome (1301)	No metabolic syndrome (1862)	Metabolic syndrome (1401)
Age, years	64.39 (9.52)	64.41 (8.94)	63.46 (9.68)	66.13 (9.28)
BMI, kg/m2	25.84 (3.18)	28.27 (3.67)	26.32 (4.35)	28.95 (4.56)
Waist circumference, cm	94.88 (9.41)	102.40 (9.48)	86.42 (11.49)	94.90 (11.34)
Triglycerides, mmol/L	1.23 (0.47)	2.03 (1.14)	1.15 (0.38)	1.91 (0.87)
HDL-cholesterol, mmol/L	1.37 (0.32)	1.09 (0.28)	1.70 (0.38)	1.31 (0.34)
Systolic blood pressure, mmHg	137.03 (20.39)	145.82 (19.75)	134.24 (21.52)	144.19 (20.61)
Diastolic blood pressure, mmHg	78.27 (11.27)	81.78 (11.53)	77.10 (11.24)	79.28 (11.38)
Fasting blood glucose, mmol/L	5.53 (0.72)	6.38 (1.90)	5.31 (0.61)	6.10 (1.61)
Smoking, %	280 (19.0)	241 (18.5)	350 (18.8)	251 (17.9)
Alcohol consumption, %	1368 (92.8)	1169 (89.9)	1585 (85.2)	1084 (77.4)
Education level, % primary	124 (8.4)	109 (8.4)	219 (11.8)	236 (16.9)
lower	383 (26.0)	397 (30.6)	916 (49.4)	714 (51.3)
intermediate	541 (36.7)	478 (36.8)	439 (23.7)	317 (22.8)
higher	425 (28.9)	314 (24.2)	279 (15.1)	126 (9.0)
Abdominal obesity, %	718 (49.5)	1101 (85.9)	1256 (69.0)	1314 (94.9)
High triglycerides, %	170 (11.9)	1091 (84.1)	124 (6.8)	1122 (80.4)
Low HDL cholesterol, %	126 (8.7)	997 (77.0)	162 (8.7)	1140 (81.4)
Elevated BP, %	922 (62.6)	1220 (93.8)	1115 (60.1)	1268 (90.7)
Type 2 Diabetes, %	39 (2.6)	337 (25.9)	17 (0.9)	288 (20.6)
Depression, %	1476 (53.2)	1301 (46.8)	1862 (57.1)	1401 (42.9)

ROA progression in men, OR 0.66, 95 %CI 0.44–0.99, and although not significant, the same direction was seen in women, OR 0.85, 95 %CI 0.63–1.15 (Table 3). The competing risk analysis show similar results for T2D (**Supplementary Table S2**), a significant lower risk for knee OA progression, sub-hazard ratio (SHR) 0.46, 95 %CI 0.30–0.70 in men and SHR 0.75, 95 %CI 0.56–1.01 in women, while there are significant positive associations with the competing event, SHR 1.84, 95 %CI 1.59–2.14 in men and SHR 1.68, 95 %CI 1.42–2.00 in women. We obtained similar results from the Cox pH and cause-specific hazard (CSH) models (**Supplementary Table S2**). Thus, participants with T2D were more likely to be lost to follow-up or die (**Supplementary Fig. S5**). In addition, our study population is on average healthier with lower prevalences of the metabolic factors compared to the population lost to follow-up (**Supplementary Table S3).** Briefly, earlier death or loss to follow-up lead to fewer participants remaining at risk of developing or progressing to knee OA and therefore may mask the true effect of T2D on knee OA progression.

Additionally adjusting for physical activity did not change our results. When we stratified by the mean of age, BMI, and follow-up time (**Supplementary Table S4**), we did not observe significant effect modification by these variables. In addition, after excluding participants who changed exposure status on MetS, its components and T2D during follow-up, our results remained consistent (**Supplementary Table S5**). Similarly, after the exclusion of participants with a TJR at follow-up, our results did not change (**Supplementary Table S6**). When restricting our analyses to incident knee OA we obtained similar results (**Supplementary Table S7**).

To examine the existence of possible threshold effects which has been suggested before [19,44], we analysed sex-specific quartiles of each MetS component for risk of knee OA progression. Except for sex-specific quartiles of BP, none of the other components showed threshold effects. We observed that the upper 3 quartiles of systolic BP (SBP) had a higher risk for progression in both men and women (**Supplementary Fig. S4**). These results were slightly attenuated after BMI-adjustment and were no longer significant. For diastolic BP (DBP) we saw an association for upper quartiles 2–4 against 1 with knee OA progression in men (OR 1.46, 95 %CI 1.06–2.01), which became borderline significant after BMI-adjustment (OR 1.31, 95 %CI 0.948–1.82).

Chronic knee pain (CKP)

In females, elevated BP and T2D were associated with lower risk of CKP prevalence irrespective of BMI adjustment (**Supplementary Table S8**). In contrast, in males MetS and high triglycerides were associated with higher CKP incidence independently of BMI (Table 4). No associations were found in the females between MetS or its individual components with incident CKP..

Discussion

We here show results from, to our knowledge, the largest prospective study up to now examining the relationship between MetS and its components with structural and symptomatic OA in the knee joint. Our study showed no association of MetS with progression of ROA independently from BMI. There was an indication of an inverse relation between T2D and progression of knee OA even after BMI adjustment, albeit only significant in men. Among the separate MetS components, elevated SBP was associated with an increased risk for radiographic knee OA progression in both men and women, but this association disappeared after BMI-adjustment. Regarding CKP, our study revealed that MetS and high triglycerides are associated with incidence of CKP in men, but not in women.Our study shows no evidence for possible sex differences in the relationship between MetS, its components and radiographic knee OA. However, there is an indication for sex differences in the relationship between MetS, its components and CKP.

Sex differences in the relationship between (components of) MetS and OA have not been thoroughly investigated yet. Two prospective studies looked at sex differences in the association between (components of) MetS and OA outcomes for the knee [13,19], one study for the hip [13] and one for the hand joint [7]. One of the studies [13] found MetS significantly associated with a slightly higher risk of severe knee OA in women compared to men, which disappeared after BMI-adjustment, and no association was observed for severe hip OA. In our larger study, we did not find evidence of sex differences in the association between MetS, its components and radiographic knee OA. However, contrary to our expectation, we found significant associations for MetS and high triglycerides with CKP incidence in males but not females. This is in contrast to data from the literature, where some studies suggest females having a higher risk of developing pain symptoms in the presence of MetS [22,45,46].

Previous studies have identified hypertension as a potential risk factor for incidence or progression of OA independent of BMI [14,19,47]. Data from the Framingham study suggest that high DBP increases the risk of radiographic progression of OA in the knee [19] and elevated BP increases the risk in hand [44]. In our study, higher SBP was significantly associated with higher odds of radiographic progression of knee OA. After BMI-adjustment, however, the association disappeared, suggesting that BMI drives the association between elevated SBP and progression of knee OA. Our analyses involving incident CKP did not reveal a clear link between BP and CKP incidence.

In line with several previous cohort studies, we found that prevalent

Table 3
Associations of metabolic syndrome, diabetes with radiographic knee OA.

	Males					Females				
	No. of knees	Progressive ROA, no. (%)	Crude model	Model 1	Model 2	No. of knees	Progressive ROA, no. (%)	Crude model	Model 1	Model 2
Metabolic syndrome										
no	2845	178 (6.3)	1	1	1	3947	413 (10)	1	1	1
yes	2411	199 (8.3)	1.35 (1.05 - 1.73)	1.39 (1.08 - 1.79)	1.11 (0.85 - 1.43)	2828	365 (13)	1.26 (1.06 - 1.5)	1.14 (0.95 - 1.37)	0.88 (0.73 - 1.07)
Abdominal obesity										
no	1685	76 (4.5)	1	1	1	1446	87 (6)	1	1	1
yes	3483	297 (8.5)	1.99 (1.46 - 2.71)	1.89 (1.38 - 2.59)	1.2 (0.84 - 1.73)	5232	686 (13)	2.36 (1.8 - 3.08)	2 (1.53 - 2.62)	1.08 (0.80 - 1.46)
High triglycerides										
no	2794	206 (7.4)	1	1	1	4118	469 (11)	1	1	1
yes	2378	166 (7.6)	0.95 (0.74 - 1.22)	1.09 (0.84 - 1.4)	0.94 (0.73 - 1.22)	2543	299 (12)	1.03 (0.86 - 1.23)	1.00 (0.83 - 1.2)	0.87 (0.72 - 1.05)
Low HDL										
no	3103	214 (6.9)	1	1	1	4102	453 (11)	1	1	1
yes	2105	160 (7.6)	1.1 (0.86 - 1.42)	1.17 (0.91 - 1.51)	1.03 (0.79 - 1.33)	2673	325 (12)	1.11 (0.93 - 1.32)	1.1 (0.92 - 1.32)	0.94 (0.78 - 1.13)
Elevated BP										
no	1239	62 (5)	1	1	1	1982	162 (8.2)	1	1	1
yes	4005	315 (7.9)	1.62 (1.17 - 2.25)	1.47 (1.05 - 2.05)	1.21 (0.86 - 1.7)	4777	612 (13)	1.65 (1.33 - 2.04)	1.31 (1.04 - 1.63)	1.02 (0.81 - 1.29)
Type 2 Diabetes										
no	4615	332 (7.2)	1	1	1	6232	697 (11)	1	1	1
yes	641	45 (7)	0.96 (0.66 - 1.41)	0.87 (0.59 - 1.27)	0.66 (0.44 - 0.99)	543	81 (15)	1.39 (1.05 - 1.84)	1.19 (0.88 - 1.59)	0.85 (0.63 - 1.15)

Abbreviations: ROA - radiographic osteoarthritis, HDL - high-density lipoproteins, BP - blood pressure.
Values indicate OR (95% CI).
Model 1: Adjusted for age, smoking, alcohol use, education, sub-cohort, baseline K/L grade and months between radiographs.
Model 2: Model 1 additionally adjusted for BMI.

Table 4
Associations of metabolic syndrome, diabetes with incident chronic knee pain (CKP).

Incident Chronic Knee Pain	Males			Females		
	Crude model	Model 1	Model 2	Crude model	Model 1	Model 2
Metabolic syndrome	1.05* (1.02, 1.09)	1.06* (1.02, 1.09)	1.04* (1.01, 1.07)	1.02 (0.99, 1.06)	1.02 (0.98, 1.06)	1.00 (0.96, 1.04)
Abdominal obesity	1.06* (1.03, 1.10)	1.06* (1.03, 1.10)	1.04 (0.99, 1.08)	1.05* (1.01, 1.09)	1.05 (1.00, 1.09)	1.00 (0.95, 1.05)
High triglycerides	1.05* (1.02, 1.08)	1.05* (1.02, 1.08)	1.04* (1.01, 1.07)	1.00 (0.97, 1.04)	1.01 (0.96, 1.05)	0.99 (0.95, 1.03)
Low HDL	1.02 (0.99, 1.05)	1.03 (0.99, 1.06)	1.02 (0.98, 1.05)	1.02 (0.98, 1.05)	1.02 (0.98, 1.06)	1.00 (0.96, 1.04)
Elevated BP	1.00 (0.97, 1.04)	1.00 (0.96, 1.04)	0.99 (0.95, 1.02)	1.03 (0.99, 1.07)	1.02 (0.97, 1.06)	1.00 (0.95, 1.04)
Type 2 Diabetes	1.04 (0.99, 1.09)	1.04 (0.99, 1.09)	1.02 (0.97, 1.07)	1.01 (0.95, 1.07)	1.02 (0.94, 1.09)	0.99 (0.92, 1.06)

* $p < 0.05$
Abbreviations: OA - osteoarthritis, HDL - high-density lipoproteins, BP - blood pressure.
Values indicate OR (95% CI).
Model 1: Adjusted for age, sub-cohort, months of follow-up, baseline K/L grade, depression score and years since menopause (in females)
Model 2: Model 1 additionally adjusted for BMI.

T2D led to lower odds of knee OA progression. In the Multicenter OA study (MOST), and the Framingham Offspring cohort lower risks of incident knee OA were found in participants with T2D and high serum glucose, respectively [19,48]. Despite taking competing risks into account, our results from secondary analyses showed the same apparent inverse relationship between OA and T2D. This result could be due to the higher risk of dying or of being lost to follow-up for people with diabetes, before they would have progression of knee OA stage.Therefore, in the alive and followed-up participants, we are not able to correctly quantify the relation between OA and diabetes in our study population, and this leads to an apparent protective effect of diabetes on OA. This may also apply to other studies showing a similar protective effect. In long-term studies of elderly populations, such as the Rotterdam Study, participants often develop multiple comorbidities. Thus, many participants are lost to follow-up or die before diagnosis or study completion, as they cannot attend follow-up assessments.As a consequence, only the healthy survivors remain included in longitudinal analyses and these constitute the group at risk for OA progression.

Strengths and limitations

First, to our knowledge, this is the largest longitudinal study up to date assessing the effect of MetS and its components on the progression of ROA with prospective data on the knee, hip and hand joints. Second, the comprehensive phenotyping of the Rotterdam Study, allowed us to control for multiple confounders and present sex-specific associations.

Third, as there is currently no consensus on how to define OA progression, studies often employ incident OA using radiographic or self-reported pain measures or "hard" outcome events such as TJR as outcomes. In our analyses of knee and hip OA, we opted for a compound measure that combined both newly occurring OA and progression from prevalent OA, thus capturing the maximum amount of OA progression cases. Still, the use of the KL grading system leaves much to be desired for it is insensitive to small changes [49]. Lastly, the adjustment for BMI is a well-known dilemma in epidemiologic studies of OA. One always wonders whether or not it is appropriate to adjust for BMI. This issue exists because the inclusion of BMI as a covariate does drive whether or not many of the associations are statistically significant or not. Important to note, BMI has been shown to be an important risk factor for knee OA and it is thus important to evaluate possible metabolic risk factors also independent from the effect of this strong risk factor. Therefore, we chose to present our results both with and without the adjustment for BMI, leaving it up to the reader to derive his own conclusions.

A limitation of this study was the lack of adjustment for previous joint injuries of participants which further limited our ability to adjust for risk factors relating to mechanical force [50]. Similar to other epidemiological studies, radiologic examination and MetS classification happened simultaneously at baseline. As a consequence, the duration of exposure before baseline was unknown in our study leading to potential misclassification bias [51]. Only participants who were healthy enough to visit the research centre at follow-up were included in this study. As MetS and T2D are associated with higher mortality and comorbidities such selection may have introduced additional bias through a healthy survivor bias, leading to underestimation of the risks of OA progression [51–53]. Another limitation is related to pain symptom assessment which was questionnaire based and evidently a more objective measure would provide us with more robust results.

Conclusions

This study revealed that MetS and individual metabolic components, such as abdominal obesity and elevated blood pressure, are associated with radiographic progression of knee OA in both men and women, but not independent of BMI, suggesting that the associations are mainly driven by high BMI. In addition, MetS and high triglycerides were associated with incidence of CKP in men, but not in women.

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Patient and public involvement

Patients and the General Public will be informed of the results through the dedicated website of Artrose Gezond (https://artrosegezond.nl/), ZonMw (https://zonmw.nl), and via the Erasmus MC Rotterdam Osteoarthritis Research (ROAR) twitter account (@roar_NL).

Data sharing statement

Rotterdam Study data can be made available to interested researchers upon request. Requests can be directed to data manager Frank J.A. van Rooij (f.vanrooij@erasmusmc.nl) or visit the following website for more information https://www.ergo-onderzoek.nl/contact. We are unable to place data in a public repository due to legal and ethical restraints. Sharing of individual participant data was not included in the informed consent of the study, and there is potential risk of revealing participants' identities as it is not possible to completely anonymize the data.

CRediT authorship contribution statement

I.A. Szilagyi: Conceptualization, Methodology, Formal analysis, Data curation, Visualization, Writing – original draft, Writing – review & editing. **N.L. Nguyen:** Conceptualization, Methodology, Formal analysis, Data curation, Visualization, Writing – original draft. **C.G. Boer:** Conceptualization, Methodology, Data curation, Writing – review & editing. **D. Schiphof:** Conceptualization, Methodology, Data curation, Investigation, Writing – review & editing. **F. Ahmadizar:** Methodology, Data curation, Investigation, Writing – review & editing. **M. Kavousi:** Methodology, Data curation, Investigation, Writing – review & editing. **S.M.A. Bierma-Zeinstra:** Conceptualization, Methodology, Investigation, Resources, Data curation, Supervision, Project administration, Writing – review & editing, Funding acquisition. **J.B.J. van Meurs:** Conceptualization, Methodology, Investigation, Resources, Data curation, Supervision, Project administration, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

S.M.A. Bierma-Zeinstra declares doing consultancy for Pfizer (tanezumab) and reports grants from The Netherlands Organisation for Health Research and Development (ZonMw), Dutch Arthritis Association, Foreum. The remaining authors declare no competing financial interests. All authors declare no nonfinancial conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152544.

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