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C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study

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Summary

Objective: To explore the relationships between C-reactive protein (CRP), metabolic syndrome (MetS) and incidence of severe knee or hip osteoarthritis (OA) in a prospective study.

Methods: A population-based cohort ($n = 5171$, mean age 57.5 ± 5.9 years) was examined between 1991 and 1994. Data was collected on lifestyle habits, measures of overweight, blood pressure as well as high-density lipoprotein (HDL) cholesterol, triglycerides, glucose and CRP measured with high-sensitive methods. Incidence of severe OA, defined as arthroplasty due to knee or hip OA, was monitored over 12 years of follow-up, in relation to CRP levels and presence of the MetS according to the adult treatment panel III-national cholesterol education program (ATPIII–NCEP) definition.

Results: A total of 120 participants had severe hip OA and 89 had knee OA during the follow-up. After adjustment for age, sex, smoking, physical activity and CRP, presence of MetS was associated with significantly increased risk of knee OA (relative risk [RR]: 2.1, 95% confidence interval [CI]: 1.3–3.3). However, this relationship was attenuated and non-significant after adjustment for body mass index (BMI) (RR: 1.1, 95% CI: 0.7–1.8). MetS was not significantly associated with incidence of hip OA. In women, CRP was associated with knee OA in the age-adjusted analysis. However, there was no significant relationship between CRP and incidence of knee or hip OA after risk factor adjustments.

Conclusion: The increased incidence of knee OA in participants with the MetS was largely explained by increased BMI. CRP was not associated with incidence of knee or hip OA when possible confounding factors were taken into account.

Key words: Osteoarthritis, Epidemiology, C-reactive protein, Metabolic syndrome.

Introduction

Several studies have shown that individuals with obesity or overweight have increased risk of osteoarthritis (OA) in the knee[1–7]. Although the role of obesity for the development of OA in the hip is less clear, several large prospective population studies have suggested that obesity also is associated with hip OA[8–12]. The pathogenic mechanisms underlying this association are debated, and several hypotheses have been proposed[13–16]. There is general agreement that biomechanics and increased dynamic loading of the joint are involved, but it was suggested that other factors associated with obesity could contribute to the increased incidence of OA.

Obesity, hypertension, dyslipidemia, diabetes and insulin resistance tend to cluster into the so-called metabolic syndrome (MetS)[17]. These risk factors are more prevalent in patients with OA[18]. Elevated plasma level of C-reactive protein (CRP), a marker of low-grade systemic inflammation, is another factor frequently found in obese individuals. Increased circulating levels of CRP have been associated with prevalent and progressive knee and hip OA[19–23] and hand OA[24,25], although it was pointed out that blood CRP levels also are influenced by race, sex, body mass index (BMI), and co-morbidities[26]. It has been proposed that systemic inflammation, possibly in combination with diabetes or insulin resistance, could increase the damage of the cartilage and impair the reparative processes[15]. Low-grade systemic inflammation could thus be an etiological link between obesity and OA, with a possible contribution of locally produced factors produced by adipose tissue[27]. Obesity and the MetS could also be associated with OA through atherogeneic effects of the metabolic factors, resulting in microvascular changes in the subchondral bone[14].

The purpose of this study was to explore whether CRP or the components of the MetS are associated with severe OA defined as arthroplasty due to knee or hip OA, and whether this is independent of BMI.

Methods

The Malmö Diet and Cancer (MDC) study is a population-based cohort established between 1991 and 1996 ($n = 28,466$). The overall participation rate was approximately 41%. Characteristics of all participants and non-participants have been reported[28]. The study cohort was representative of the underlying population with respect to the prevalence of, e.g., overweight

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and smoking, while the mortality rate was higher in non-participants[28]. A random 50% of those who entered the MDC cohort between November 1991 and February 1994, and who were born between 1926 and 1945 ($n = 12,445$), were invited to take part in a study on the epidemiology of carotid artery disease[29] (Fig. 1). Age range was 46–68 years (mean 57.5, standard deviation [SD] 5.9). A total of 6103 participants were recruited for the ultrasound examination. In order to arrange for blood sampling under standardized conditions, these individuals were rescheduled for a second visit that took place a mean of 8 months later. Of the 6103 participants, 557 (9.3%) did not return for blood sampling. Another 352 individuals were excluded because of incomplete data for CRP or variables defining the MetS. Individuals with history of surgery for knee or hip OA ($n = 23$ and $n = 30$, respectively) were excluded. After all exclusions, 5171 participants remained for the analysis of knee OA and 5164 for the analysis of hip OA. The Ethics Committee at Lund University approved the project.

LIFESTYLE HABITS

Assessment of smoking habits and leisure time physical activity has been described[29,30]. In short, smoking was categorized into nonsmokers (i.e., never smokers and ex-smokers) and current smokers (i.e., occasional and regular smokers). Information about smoking was missing for 114 (2.2%) of the participants. Physical activity was assessed by 18 questions about physical activities in different seasons. The activities were added up to a score, based on the intensity and time spent on each activity. The score was categorized into sex-specific quartiles when used in the analysis[30].

PHYSICAL EXAMINATION

Blood pressure (mmHg) was measured once in supine position after 10 min of rest. Weight (kg) and height (m) were measured with the participants wearing light indoor clothing and without shoes. The waist circumference (cm) was measured at the level of the umbilicus.

LABORATORY ANALYSES

After an overnight fast, blood samples were drawn for the determination of serum lipids and whole blood glucose. Samples were analyzed by standard methods at the Department of Clinical Chemistry, Malmö University Hospital. Blood glucose was determined by a routine hexokinase method. Triglycerides and total cholesterol were determined on a DAX 48 automatic analyser with use of reagents and calibrators from the supplier of the instrument (Bayer AB, Göteborg, Sweden). High-density lipoprotein (HDL) cholesterol was determined by the same procedure as used for total cholesterol but after precipitation of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) with dextran sulfate[31]. CRP was analyzed with high-sensitive methods in frozen plasma gathered at the baseline examination. Tina-quant CRP latex high-sensitivity assay (Roche Diagnostics, Basel, Switzerland) was used on an ADVIA 1650 Chemistry System (Bayer Healthcare, Tarrytown, NY, USA). CRP was categorized into low (<1 mg/L), intermediate (1–3 mg/L) and high levels (≥3 mg/L)[32].

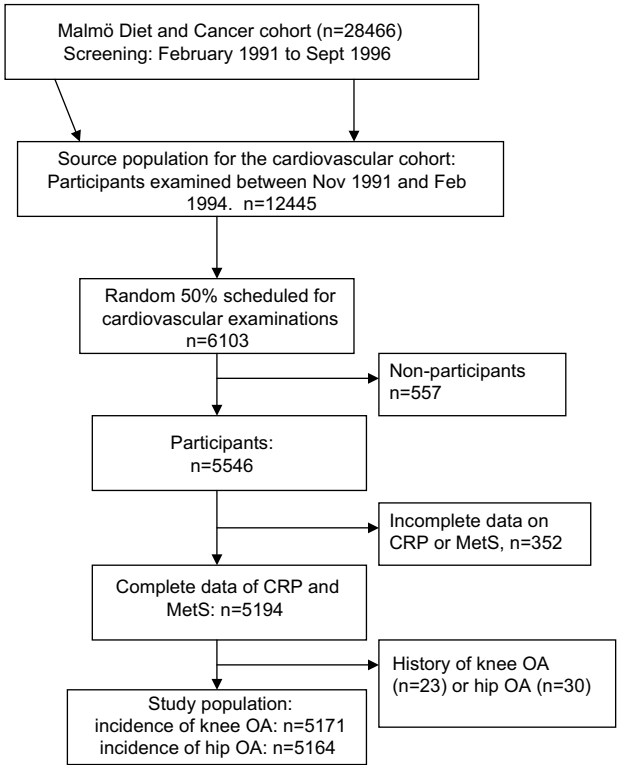

Fig. 1. Flow chart of the study population.

DEFINITIONS OF THE MetS

The NCEP–ATPIII definition was used[17]. The MetS is defined as presence of any three components out of five, i.e., high waist circumference (≥102/88 cm for men/women), low HDL (<1.03/1.29 mmol/L for men/women or lipid-lowering medication), hypertension (≥130/85 mmHg or treatment for hypertension), hyperglycemia (fasting plasma glucose ≥5.6 mmol/L) and hypertriglyceridemia (≥1.7 mmol/L or treatment).

DEFINITION OF KNEE AND HIP OA

Knee OA was defined as a first knee arthroplasty or high tibial osteotomy (procedures coded 8424, 8423, 8428, 8010, 8199 or NGB09, NGB19, NGB29, NGB39, NGB49, NGB99 and NGK59)[33], in combination with a diagnosis of OA (715 or M17 according to ICD-9 and ICD-10, respectively). Only the first event was counted for patients with more than one knee arthroplasty.

Hip OA was defined as a first hip arthroplasty (procedures coded 8414, 8010, NFB09, NFB19, NFB29, NFB39, NFB49 and NFB99) in combination with a diagnosis of hip OA (715 or M16 according to ICD-9 and ICD-10, respectively). Patients with more than one hip arthroplasty were only counted once. Cases specifically coded as primary OA constituted 97% and 89% of all knees and hips included, respectively.

The follow-up times were calculated separately for knee and hip OA. All participants were followed until the first OA surgery, emigration from Sweden, death or December 31, 2005, whichever came first. Information on knee and hip arthroplasty for OA and mortality were based on record linkage with the Swedish Hospital Discharge Register and the Swedish Causes of Death Register. Individuals who moved out of Sweden were censored at the day of emigration.

STATISTICAL METHODS

One-way analysis of variance (ANOVA) and Pearsons' χ^2 were used to compare the occurrence of risk factors in individuals with and without knee or hip OA during the follow-up period. Cox proportional hazards model was used to explore the relationships between MetS or categories of CRP, respectively, and incidence of knee or hip OA, and to adjust these relationships for confounding factors. Age and BMI were modeled as continuous variables and the quartiles of physical activity were modeled as an ordinal variable. Sex and the components of MetS were modeled as dichotomous variables. Three categories of CRP were used in the multivariate analysis. Tolerance was calculated in order to estimate the degree of collinearity between the independent variables. Tolerance values below 0.20 have been suggested to indicate collinearity problems[34]. P-values < 0.05 were considered statistically significant.

Results

KNEE OA

During the mean follow-up of 12.4 years, 89 participants (30 men and 59 women) had arthroplasty ($n = 80$) or high tibial osteotomy ($n = 9$) due to knee OA. Waist circumference, BMI and age were higher in participants who subsequently had knee OA, and prevalence of hyperglycemia was higher (Table I). In women, a significant relationship was observed between the categories of CRP and subsequent knee OA. In men, BMI was the only risk factor with significant differences between those with and without knee OA during the follow-up.

HIP OA

A total of 120 participants (40 men and 80 women) had hip arthroplasty during the follow-up. Age, BMI and waist circumference were higher in all cases and in female cases

(Table II). Although not significantly, female cases with hip OA had higher baseline CRP levels compared to controls. Only age showed a statistically significant difference between cases and controls in men.

MULTIVARIATE ANALYSIS

The relationship between CRP, MetS and incidence of knee and hip OA is presented in Table III, with adjustments in three models. The MetS was associated with increased incidence of knee OA after adjustments for age and sex (RR: 2.29, 95% CI: 1.5−3.5) and in the age-adjusted analysis of women (RR: 2.90, 95% CI: 1.7−4.9). These relationships remained significant after adjustments for smoking, physical activity and CRP. However, after adjustments for BMI at baseline, the relationship between MetS and incidence of knee OA was attenuated and non-significant. Of the risk factors in Model 3, only age (RR per year: 1.07, 95% CI: 1.03−1.12) and BMI (RR per 1 kg/m^2: 1.18, 95% CI: 1.12−1.23) were significantly associated with knee OA. Tolerance in Model 3 was 0.73 for BMI, 0.79 for MetS and above 0.87 for all other variables.

Age (RR per year: 1.09, 95% CI: 1.05−1.12) and BMI (RR per 1 kg/m^2: 1.08, 95% CI: 1.03−1.14) were significantly associated with incidence of hip OA in the final model (Model 3). Neither MetS nor CRP was associated with hip OA in the multivariate analysis (Table III).

INDIVIDUAL COMPONENTS OF THE MetS

The components of the MetS were individually adjusted for confounding factors in the multivariate analysis (Table IV). Except for waist, none of the MetS components were associated with knee OA in the final model. However, both high waist circumference (RR: 2.16, 95% CI: 1.2−4.0, $P = 0.014$) and BMI (RR per 1 kg/m^2: 1.13, 95% CI: 1.06−1.20, $P < 0.001$) were independently associated with incidence of knee OA after adjustments for other risk factors (Table IV, Model 3). Tolerance of this regression model was 0.53 for BMI, 0.58 for waist and above 0.86 for all other risk factors, indicating an acceptable degree of collinearity.

Except for waist (RR: 1.8, 95% CI: 1.2−2.7), none of the individual MetS components were associated with incidence of hip OA after adjustment for age and sex. After adjustments for age, sex, smoking, physical activity and CRP, high waist circumference (RR: 1.7, 95% CI: 1.1−2.6) was still associated with hip OA. This relationship was not significant after further adjustments for BMI (RR for high waist: 1.1, 95% CI: 0.6−2.0, $P = 0.693$).

Discussion

Relationships between obesity and OA in the knee or hip have been reported from many studies. It has been proposed that metabolic risk factors and systemic low-grade inflammation, which often is increased in obesity, could contribute to this relationship[13−15]. This prospective population-based study confirmed that high BMI or waist circumference is associated with incidence of severe knee or hip OA defined as the combination of diagnosis of knee or hip OA with arthroplasty. In the univariate analysis, women who developed severe knee OA had higher prevalence of the MetS, hypertension, hyperglycemia and high CRP (>3 mg/L) than women without OA during follow-up. However, these relationships were attenuated and non-significant when BMI was taken into account in the multivariate analysis.

Several studies have reported relationships between CRP and various features of OA. CRP was shown to be associated with the extent and severity of knee OA, knee pain or markers of local synovial inflammation, and with knee OA progression[19−23,35,36]. In contrast, our results suggest that the increased incidence of OA in individuals with elevated CRP is largely explained by increased body mass. The adipose tissue is an important source of various proinflammatory cytokines, which could stimulate the hepatic production of CRP and other acute phase proteins[37,38]. Obesity is an important determinant of high CRP levels[39].

Our results suggest that systemic inflammation *per se* is of little importance for incidence of OA, at least in presence of overweight or obesity. We cannot exclude a role for local inflammation associated with excess adipose tissue in the joint. In the present study, blood for the high-sensitive CRP assay was sampled several years before OA surgery. It is possible that CRP better reflects occurrence and progression of OA in patients with established disease, than

Table I
Distribution of risk factors at baseline in participants with and without severe knee OA during follow-up

Knee OA	All		Men		Women	
	Yes	No	Yes	No	Yes	No
N	89	5082	30	2115	59	2967
Age (year)	59.7 ± 5.3†	57.6 ± 6.0	59.5 ± 5.0	57.7 ± 6.0	59.9 ± 5.5†	57.5 ± 5.9
BMI (kg/m^2)	28.9 ± 4.6‡	25.7 ± 3.9	28.2 ± 4.1‡	26.2 ± 3.5	29.3 ± 4.7‡	26.4 ± 4.1
Smokers (%)	18.4	22.3	28.6	23.0	13.6	21.7
MetS (%)	39.3‡	21.9	36.7	28.1	40.7‡	17.5
Waist (≥102/88 cm) (%)	44.9‡	15.2	30.0	17.4	52.5‡	13.7
Low HDL (%)	31.5	30.8	23.3	31.3	35.6	30.5
Hypertriglyceridemia (%)	28.1	22.1	30.0	29.5	27.1	16.9
Hypertension (%)	88.8	79.9	86.7	85.2	89.8*	76.1
Hyperglycemia (%)	29.2†	15.9	33.3	22.0	27.1‡	11.5
CRP						
Geometric mean (mg/L)	1.62	1.40	1.35	1.42	1.77§	1.39
<1 mg/L (%)	29.2	37.2	43.3	35.8	22.0	38.2
1−3 mg/L (%)	44.9	39.9	36.7	41.0	49.2	39.1
>3 mg/L (%)	25.8	22.9	20.0	23.2	28.8*	22.7

Age and BMI are presented as mean ± SD. Other risk factors are presented as proportions (%). *$P < 0.050$, †$P < 0.010$, ‡$P < 0.001$ for knee OA yes vs no and §$P = 0.078$.

Table II
Distribution of risk factors at baseline in participants with and without severe hip OA during follow-up

Hip OA	All		Men		Women	
	Yes	No	Yes	No	Yes	No
N	120	5044	40	2100	80	2944
Age (year)	60.0 ± 5.1‡	57.5 ± 6.0	59.9 ± 5.1*	57.7 ± 6.0	60.0 ± 5.1‡	57.5 ± 5.9
BMI (kg/m^2)	27.1 ± 4.2‡	25.8 ± 3.9	26.7 ± 3.3	26.2 ± 3.5	27.3 ± 4.7‡	25.4 ± 4.1
Smokers (%)	20.3	22.2	15.0	23.3	23.1	21.4
MetS (%)	22.5	22.2	25.0	28.2	21.3	18.0
Waist (≥102/88 cm) (%)	25.0†	15.6	22.5	17.5	26.3†	14.2
Low HDL (%)	25.8	31.0	20.0	31.4	28.8	30.7
Hypertriglyceridemia (%)	20.0	22.2	25.0	29.4	17.5	17.1
Hypertension (%)	86.7	79.9	92.5	85.0	83.8	76.2
Hyperglycemia (%)	13.3	16.2	12.5	22.4	13.8	11.8
CRP						
Geometric mean (mg/L)	1.64	1.40	1.47	1.42	1.73**	1.38
<1 mg/L (%)	29.2	37.3	32.5	36.0	27.5	38.1
1–3 mg/L (%)	45.8	39.9	47.5	40.8	45.0	39.2
>3 mg/L (%)	25.0	22.9	20.0	23.1	27.5§	22.7

Age and BMI are presented as mean ± SD. Other risk factors are presented as proportions (%). *$P < 0.050$, †$P < 0.010$, ‡$P < 0.001$ for hip OA yes vs no and **$P = 0.060$, §$P = 0.074$.

the risk of developing OA in a population-based setting. Elevated CRP has been associated with prevalence of radiologically confirmed[21] or symptomatic OA[20,24,25], degree of symptoms[35,36] and progression of disease in participants with OA[22]. In support of the present results, a population-based study reported that the relationships between radiographically determined knee and hip OA and CRP were greatly attenuated and non-significant after adjustments for BMI[26]. To our knowledge, there are no previous studies of CRP and incidence of knee or hip OA in apparently healthy individuals.

A strong correlation or collinearity between BMI and MetS or CRP could cause problems in separating the effects of these risk factors in the multivariate models. However, the relationships between BMI and the other risk factors were not strong enough to produce this problem. We calculated

Table III
Multivariate analysis of CRP and MetS in relation to incidence of severe knee and hip OA

	Age and sex*	Model 2	Model 3
Knee OA			
All			
MetS (yes vs no)	2.3 (1.5–3.5)	2.1 (1.3–3.3)	1.1 (0.7–1.8)
CRP (1–3 vs <1 mg/L)	1.4 (0.8–2.2)	1.2 (0.7–2.0)	0.9 (0.5–1.5)
CRP (≥3 vs <1 mg/L)	1.4 (0.8–2.4)	1.2 (0.6–2.1)	0.7 (0.4–1.2)
Men			
MetS (yes vs no)	1.5 (0.7–3.1)	1.4 (0.6–3.1)	0.6 (0.2–1.5)
CRP (1–3 vs <1 mg/L)	0.7 (0.3–1.5)	0.5 (0.2–1.2)	0.4 (0.2–0.9)
CRP (≥3 vs <1 mg/L)	0.7 (0.3–1.8)	0.6 (0.2–1.6)	0.4 (0.1–1.1)
Women			
MetS (yes vs no)	2.9 (1.7–4.9)	2.5 (1.5–4.4)	1.4 (0.8–2.6)
CRP (1–3 vs <1 mg/L)	2.1 (1.1–4.0)	1.8 (0.9–3.5)	1.4 (0.7–2.7)
CRP (≥3 vs <1 mg/L)	2.1 (1.03–4.4)	1.6 (0.7–3.3)	0.9 (0.4–1.9)
Hip OA			
All			
MetS (yes vs no)	1.0 (0.6–1.5)	1.0 (0.6–1.5)	0.7 (0.4–1.2)
CRP (1–3 vs <1 mg/L)	1.4 (0.9–2.2)	1.4 (0.9–2.2)	1.3 (0.8–2.0)
CRP (≥3 vs <1 mg/L)	1.4 (0.8–2.3)	1.4 (0.8–2.3)	1.1 (0.6–1.9)
Men			
MetS (yes vs no)	0.8 (0.4–1.7)	0.9 (0.4–1.8)	0.7 (0.3–1.6)
CRP (1–3 vs <1 mg/L)	1.2 (0.6–2.5)	1.4 (0.7–2.9)	1.3 (0.6–2.7)
CRP (≥3 vs <1 mg/L)	0.9 (0.4–2.2)	1.2 (0.5–3.1)	1.1 (0.4–2.8)
Women			
MetS (yes vs no)	1.1 (0.6–1.9)	1.0 (0.6–1.7)	0.7 (0.4–1.3)
CRP (1–3 vs <1 mg/L)	1.5 (0.9–2.5)	1.5 (0.9–2.6)	1.3 (0.8–2.3)
CRP (≥3 vs <1 mg/L)	1.6 (0.9–2.9)	1.5 (0.8–2.8)	1.1 (0.6–2.2)

*Model 1: MetS and CRP individually adjusted for age and sex when appropriate. Model 2: age, sex (all participants), smoking, CRP, physical activity, MetS. Model 3: Model 2 + BMI at the baseline examination.

Data are presented as relative risks (95% CI) for individuals with the risk factor.

Table IV
Multivariate analysis of components of the MetS in relation to incidence of severe knee and hip OA

	Age and sex*	Model 2	Model 3
Knee OA			
Waist (≥102/88 cm) (%)	4.5 (3.0–6.8)	4.7 (3.0–7.4)	2.2 (1.2–4.0)
Low HDL (%)	1.0 (0.6–1.6)	0.9 (0.6–1.5)	0.7 (0.4–1.1)
Hypertriglyceridemia (%)	1.4 (0.9–2.2)	1.3 (0.8–2.1)	0.9 (0.5–1.5)
Hypertension (%)	1.7 (0.9–3.4)	1.6 (0.8–3.2)	1.3 (0.6–2.5)
Hyperglycemia (%)	2.3 (1.5–3.7)	2.2 (1.4–3.6)	1.4 (0.9–2.4)
Hip OA			
Waist (≥102/88 cm) (%)	1.8 (1.2–2.7)	1.7 (1.1–2.6)	1.1 (0.6–2.0)
Low HDL (%)	0.8 (0.5–1.1)	0.7 (0.5–1.1)	0.7 (0.4–1.0)
Hypertriglyceridemia (%)	0.9 (0.6–1.4)	0.9 (0.5–1.4)	0.7 (0.5–1.2)
Hypertension (%)	1.4 (0.8–2.4)	1.4 (0.8–2.4)	1.3 (0.7–2.2)
Hyperglycemia (%)	0.8 (0.5–1.4)	0.8 (0.5–1.4)	0.7 (0.4–1.2)

Model 2: adjusted for age, sex, smoking, physical activity and CRP (<1 mg/L, 1–3 mg/L and ≥3 mg/L). Model 3: +BMI at the baseline examination.

*Relative risks of knee OA (95% CI) for individuals with the risk factor, adjusted for age and sex.

the tolerance values for the multivariate models to determine the degree of collinearity between the independent variables. When all covariates were entered into the final model (Model 3), tolerance for MetS was still 0.79, which means that 79% of the variance of MetS was unique for that variable and only 21% could be explained by all other independent variables. It was suggested that tolerance values below 0.20 should be regarded as potential collinearity problems[34]. Hence, BMI is not so closely linked to the MetS that one might expect.

The components of the MetS are well-known atherosclerotic risk factors. Diabetes, which is an important comorbid condition of the MetS, is associated with arteriosclerosis in the large and small arteries. Prevalence of atherosclerotic risk factors is high in individuals with OA[18], and it has been proposed that vascular pathology of subchondral small vessels could play an etiological role in the development of OA. This hypothesis was not supported by the present results. It is also noteworthy that smoking, which is strongly associated with atherosclerosis and endothelial dysfunction[40], also was unrelated to the incidence of severe OA when BMI was taken into account. Our results are partially concordant with the population-based study by Dahaghin *et al.*[41], who did not find any independent relationship between hypertension or blood lipids and hand OA.

The participants of this cohort were almost exclusively Caucasian, and much of the relationships between MetS and cardiovascular disease (CVD) are based on studies from Asian or Afro-American populations[42]. However, it was shown that CRP and the metabolic risk factors are associated with CVD also in the present Caucasian cohort[43]. We cannot rule out that absence of significant findings could be explained by limited statistical power in the present study.

Total arthroplasty or high tibial osteotomy of the knee or arthroplasty of the hip due to OA was used to define OA in the present study. Other studies have used different OA definitions, e.g., knee or hip arthroplasty without a confirmed diagnosis, radiographic criteria, symptom criteria, or OA defined by self-reported diagnosis. The relationship between these different OA definitions is uncertain, and their relationship with inflammation and cardiovascular risk factors may not be the same. While the definition of arthroplasty or osteotomy due to OA will only identify a minority of the very large OA population, it has the advantage of an unambiguous connection with disease burden of OA and being available in reliable national registries.

The Swedish hospital discharge register was used for case-retrieval. This register covers all Swedish hospitals. A validation study estimated that this register includes at least 95% of all primary knee and hip arthroplasties and that the diagnostic misclassification was about 5% for hip replacements[44]. Primary OA was the diagnosis for more than 85% of all primary knee arthroplasties and more than 75% of all primary hip arthroplasties in Sweden during the follow-up period. We therefore believe that the bias in the present study due to misclassification of OA is small, and likely nondifferential.

The decision to surgically treat a patient with OA is influenced by other factors than the severity of symptoms and radiographic signs[45]. Of particular relevance to studies using arthroplasty as an outcome is the possibility of a healthy patient selection bias in the decision to perform an arthroplasty. Obesity is associated with cardiovascular disease, which hypothetically could reduce the probability of arthroplasty. On the other hand, obesity could be associated with worse symptoms, which could increase the probability of being selected for surgery. We have previously observed that the relationships between measures of overweight and arthroplasty for OA remain following exclusion of participants with self-reported significant co-morbidities at the baseline examination[12]. This would argue against a healthy patient selection bias influencing our results. However, the presence and effects of such patient selection bias are very difficult to explore and we cannot completely rule it out.

We conclude that the increased incidence of knee OA in participants with the MetS is mainly explained by increased BMI in these individuals. In this prospective population-based study, CRP was not associated with incidence of knee or hip OA when possible confounding factors were taken into account.

Conflict of interest

Gunnar Engström, Jan Rollof and Maria Gerhardsson de Verdier are employed as senior scientists by AstraZeneca R&D. There are no other potential conflicts of interest.

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