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The Association of Metabolic Syndrome and Obesity With Clinical Hip Osteoarthritis in the Study of Osteoporotic Fractures and the Osteoporotic Fractures in Men Study Cohorts

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Objective. Metabolic dysregulation frequently co-occurs with obesity, which has been shown to be a risk factor for lower extremity osteoarthritis (OA). We evaluated the association between metabolic syndrome (MetS), alone and in combination with obesity, and hip OA.

Methods. In two parallel cross-sectional analyses, we studied 403 women from the Study of Osteoporotic Fractures (SOF) and 2354 men from the Osteoporotic Fractures in Men (MrOS) study. We used multivariable logistic regression to evaluate associations of obesity (body mass index ≥ 30 kg/m^2) and/or MetS (three of five National Cholesterol Education Program Adult Treatment Panel III criteria) with clinical hip OA, defined as a modified Croft score of 2 or more or total hip replacement, and pain or limited range of motion. Our analysis adjusted for demographics.

Results. Approximately 3.5% of SOF women and 5.4% of MrOS men had clinical hip OA. Among women, obesity was not associated with hip OA, yet those with MetS had a 365% higher odds of hip OA (95% CI: 1.37-15.83). Among men, those who had obesity had a 115% higher odds of hip OA (95% CI: 1.39-3.32), yet MetS was not associated with hip OA. There was no interaction between MetS, obesity, and hip OA in either women or men.

Conclusion. In women, but not in men, MetS was associated with hip OA. In men, but not in women, obesity was associated with hip OA. These findings suggest that mechanical effects of obesity may predominate in the pathogenesis of hip OA in men, whereas metabolic effects predominate in women.

INTRODUCTION

Lower extremity osteoarthritis (OA) causes pain, impaired mobility, and diminished ability to perform activities of daily living, collectively leading to a reduced individual quality of life and significant societal burden (1). OA affects approximately 27 million Americans, and the prevalence of hip OA in particular has been estimated to be 9.2% (2) among those older than 45 years of age. Obesity, defined as a body mass index (BMI) of greater than or equal to 30 kg/m^2, affects more than 35% of American adults (3) and has been recognized as one of the strongest modifiable risk factors for lower extremity OA. Higher BMI is strongly associated with knee OA (4), but the association between BMI and hip OA has been

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less consistent, with several studies demonstrating null associations (5–10).

Historically, the increased risk of lower extremity OA conferred by obesity was thought to be due to a mechanical load effect leading to cartilage breakdown. Studies reporting an association of obesity with non–weight-bearing hand joints suggested, however, that metabolic effects of increased adiposity may also be involved (11). The exact mechanism by which metabolic factors contribute to the pathogenesis of OA is not known. Some have proposed that adipose tissue releases systemic factors, including adipokines such as leptin, adiponectin, resistin, and visfatin/nicotinamide phosphoribosyltransferase, that may contribute to cartilage degradation as well as cause local synovitis perpetuating the damage (12).

Dysregulation of plasma adipokines, including those that have been implicated in cartilage degradation, is a key feature of metabolic syndrome (MetS) (13). MetS is a state of chronic low-grade inflammation that confers an increased risk for cardiovascular disease and mortality (13). Although obesity is frequently associated with MetS, some individuals with obesity have normal metabolic profiles. Conversely, not all individuals who have MetS have obesity. In particular, epidemiologic studies have identified a subgroup of metabolically healthy individuals with obesity, who constitute 31.7% of Americans, who have an elevated BMI but do not demonstrate features of metabolic dysregulation. A subgroup of approximately 23.5% of Americans, who instead display metabolic profiles typically associated with obesity but are of normal weight (14), have also been identified. The identification of these different obesity phenotypes suggests that metabolic adiposity and elevated BMI can and should be evaluated as distinct risk factors, as it is not known whether individuals with MetS alone have the same risk as those with elevated BMI alone, or how either of these populations compare to individuals who exhibit both metabolic dysregulation and elevated BMI.

Thus, the recognition that MetS can occur independently of increased BMI suggests a novel hypothesis that MetS may modify the association of obesity and OA. To this end, several studies have demonstrated an association between MetS and knee OA (15–17). However, the only two studies of MetS and hip OA (18,19) used total hip replacement status as a proxy for severe OA, and neither showed a significant association with MetS. Because obesity and medical comorbidities including those that comprise MetS may be considered relative contraindications for elective total hip replacement, joint replacement status may underestimate the overall prevalence of OA and selectively underestimate both MetS and obesity among individuals with total joint replacement.

The purpose of this study was to examine effects of obesity, MetS, and the interaction of MetS and obesity on hip OA as defined by radiographic findings and clinical symptoms. Because previous work has shown sex differences both in the prevalence of hip OA (20–22) as well as in obesity and metabolic homeostasis (23–25), this study was performed in parallel on separate cohorts of men and women. Our initial hypotheses were twofold: 1) that obesity would be associated with hip OA in both cohorts and 2) that the association between obesity and hip OA would be modified by MetS.

MATERIALS AND METHODS

Study participants and populations. The Study of Osteoporotic Fractures (SOF) and Osteoporotic Fractures in Men (MrOS) study are community-based cohort studies in the United States designed to assess risk factors for osteoporotic fractures.

The SOF cohort enrolled 9704 women between October 1986 and October 1988 from four clinical sites: Baltimore, MD; Pittsburgh, PA; Minneapolis, MN; and Portland, OR (26). To be eligible, women had to be 65 years of age or older, ambulatory, and without bilateral hip replacements. Non-white women were also excluded from the original cohort because of low incidence of hip fracture. Participants included in this analysis were taken from the 5685 women with available pelvic radiographs at the baseline visit. We then excluded 25 participants without recorded BMI and 789 participants without documented clinical hip examination. Of the remaining participants, 403 had available laboratory measures as part of the fracture and stroke ancillary studies required for the determination of MetS status. Compared to the 4469 SOF participants without laboratory measures available, this subset of 403 women was 0.6 years older, had a 2.8% higher prevalence of diabetes, and were similar in prevalent hip OA and anthropometry.

The MrOS cohort enrolled 5994 community-dwelling, ambulatory men between March 2000 and April 2002, who were 65 years of age or older across six of the following clinical sites: Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA (27). Participants were eligible if they could walk without assistance, did not have bilateral hip replacements at the time of the study, were able to provide self-reported data, lived near one of the clinical study sites, did not have medical conditions that would result in imminent death, and were able to understand and sign an informed consent. Participants included in this analysis were taken from the 4215 individuals with digitized pelvic radiographs obtained at visit 2, which occurred between March 2005 and May 2006. These men represented 93% of the 4530 visit 2 attendees. Although hip radiographs were not available until visit 2, the data were treated in a cross-sectional fashion, covering a period of 6 years from March 2000 to May 2006. We excluded 2 participants without recorded BMI, 471 participants without laboratory values, 171 participants without documented clinical hip examination, and 4 participants with problems preventing interpretation of their radiographs. An additional 1213 participants did not have waist circumference data required for the determination of MetS

analyses as only men who were participants of the ancillary sleep study had available waist circumference measures, yielding a sample of 2354 participants. The sleep study visit data were obtained between December 2003 and March 2005, within the period between the baseline and visit 2. There was no significant difference between the 1213 participants who did not have available waist circumference measures and this subset of 2354 men with respect to other anthropometric measures, prevalent hip OA, or demographics.

Institutional review board approval was obtained at all participating sites in each study, and all participants provided written informed consent.

Assessment of population characteristics. Characteristics for both SOF and MrOS participants were ascertained at the baseline visit unless otherwise specified. Age, race and ethnicity, education, past medical history, medication use, and instrumental activities of daily living impairment were determined by self-administered questionnaire. Height on Harpenden stadiometer, weight by standard balance beam or digital scales, waist circumference (measured at baseline in SOF and at sleep visit 1 in MrOS), and supine (SOF) or sitting (MrOS) blood pressure were measured using standard protocols. BMI was calculated as kg/m^2.

Morning phlebotomy was performed to obtain serum plasma for biochemical measures, including high-density lipoprotein (HDL), triglycerides, and glucose. In SOF, HDL and triglycerides were measured by assays at the Endocrine Sciences laboratory on two subsets of patients: 400 women in the Fracture Study (28) and 490 women in the stroke case-control study (29). In MrOS, HDL (coefficient of variation [CV]: 2.39%) and triglycerides (CV: 3.03%) were measured using a Roche COBAS Integra 800 automated analyzer on previously thawed serum. Fasting glucose was not measured in SOF. In MrOS, fasting glucose was quantitatively measured enzymatically on a Hitachi 917 Autoanalyzer with an interassay CV of less than 3%.

Walking speed to complete a 6-m course and hip pain and internal rotation were assessed by a trained clinical examiner. In SOF, examination of hip pain and range of motion and internal rotation did not occur until the year 2 clinic visit (January 1989-December 1990), approximately 2 years after the baseline x-rays were taken (October 1986-October 1988). In SOF, bone mineral density as assessed by single photon absorptiometry of the os calcis was used. Details of the bone density measurements have been described previously (30). Total hip bone mineral density was assessed by dual-energy x-ray absorptiometry scan in MrOS.

Radiography and hip OA definition. In SOF, supine anteroposterior pelvic radiographs were obtained with the hips in 15 to 30 degrees of internal rotation at the baseline visit. In MrOS, standing pelvic radiographs were obtained using a standardized footmat with toes internally rotated 15 degrees and the

x-ray beam positioned two inches above the pubic symphysis at visit 2.

In SOF and MrOS, hip radiographs were read for the following individual radiographic features of OA: joint space narrowing, osteophyte formation, cysts, and femoral head deformity. A summary grade for radiographic hip OA severity of 0 to 4 on the modified Croft score was assigned to each hip as has been described previously (31). All radiographs were read by the primary reader (NEL) who was blinded to the participants' clinical characteristics. The reliability of these radiographic methods has previously been published, and the interrater reliability for radiograph readings with a summary grade of 2 or more was good ($\kappa = 0.65$) (30,31,32).

Hips were considered to have clinically significant hip OA if a summary grade of 2 or more was present and the participant had either documented hip pain or internal rotation limited to below the lower quartile for the population. No participants in the SOF analytic sample had total hip replacement at baseline. In the MrOS population, of which some participants in the analytic sample had total hip replacement, total hip replacement was included as a proxy for clinically significant hip OA. As has been described previously (33), all total hip replacements performed for management of hip fractures prior to visit 2 were excluded.

MetS definition. MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) guidelines (34). In addition, treatment of the conditions associated with MetS was considered as a surrogate for the defining criterion because appropriate medical treatment should normalize serum laboratory values. Specifically, in SOF, the defining levels used for this study were as follows:

1. Waist circumference greater than 88 cm,
2. Triglycerides of 150 mg/dl or more,
3. HDL less than 50 mg/dl,
4. Blood pressure of 130/85 or more or use of a thiazide diuretic, and
5. Diagnosed diabetes (the NCEP-ATPIII criterion uses a fasting glucose ≥110 mg/dl, but fasting glucose was not available in SOF).

In MrOS, the defining levels used for this study were as follows:

1. Waist circumference greater than 102 cm,
2. Triglycerides 150 mg/dl or more or use of gemfibrozil,
3. HDL less than 40 mg/dl,
4. Blood pressure of 130/85 or more or use of a thiazide diuretic, calcium channel blocker, Angiotensiconverting enzyme (ACE) inhibitor, or angiotensin receptor blocker, and
5. Fasting glucose of 110 mg/dl or more or use of an oral hypoglycemic or insulin.

For both SOF and MrOS, participants meeting any three of the five criteria were considered to have MetS.

Statistical methods. To compare subjects with and without clinical hip OA, *t*-tests or Wilcoxon rank sum tests for continuous variables, depending on distributions, and χ^2 tests for categorical variables were used. Logistic regression with sequential models was used to assess the association of obesity and MetS with hip OA. Model 1 was the unadjusted association. Model 2 was adjusted for age and race (in MrOS only). Model 3 included the covariates from model 2 and was adjusted for the nonprimary explanatory variable (eg, MetS in the obesity analysis and obesity in MetS).

To analyze the interaction between MetS and obesity, an interaction term between MetS and obesity was included in the fully adjusted model.

Two-sided *P* values of less than 0.05 were considered statistically significant. All analyses were performed using SPSS version 28.0.1.1.

RESULTS

Participant characteristics. The prevalence of OA was 3.5% in 403 women from SOF and 5.4% in 2354 men from MrOS. The mean participant age was 71.2 ± 4.8 years in SOF and 72.6 ± 5.3 years in MrOS. Among women in SOF, those with hip OA had a higher os calcis bone mineral density

and a lower HDL as compared to those without hip OA (Table 1). In MrOS, men with clinical hip OA had higher weight, BMI, waist circumference, and corrected total hip bone mineral density as compared to those without clinical hip OA (Table 2). Men with hip OA also had impaired physical function as indicated by a slower walking speed and a higher number of impairments in instrumental activities of daily living. Men with hip OA were more likely to report use of nonsteroidal antiinflammatory drugs and corticosteroids. No significant difference was found in age, education, race, height, blood pressure, history of diabetes, or use of bisphosphonates among participants with versus without hip OA in either women in SOF or men in MrOS.

Obesity and clinical hip OA. Approximately 21.8% of women in SOF and 20.6% of men in MrOS had obesity (BMI ≥30). Women who did not have obesity had a similar prevalence of clinical hip OA (3.5%) as compared to those who had obesity (3.4%). Among women in SOF, obesity was not significantly associated with hip OA in unadjusted or fully adjusted analysis (odd ratio [OR]: 0.53; 95% CI: 0.14-2.09) (Table 3). Additional analysis of BMI as a continuous variable with hip OA in women did not demonstrate any significant association (data not shown). Obesity was also not significantly associated with radiographic

Table 1. The Study of Osteoporotic Fractures baseline participant characteristics by clinical hip OA status

Characteristic	N	No clinical hip OA (n = 389)	Clinical hip OA (n = 14)	*P* value
Age, y (mean ± SD)	403	71.2 ± 4.8	70.6 ± 3.0	0.67
Education, % graduated high school	403	77.6	78.6	0.93
Race, % White	402	100	100	—
Height, cm (mean ± SD)	399	159.2 ± 5.6	159.3 ± 5.9	0.97
Weight, kg (mean ± SD)	397	67.4 ± 11.5	69.4 ± 14.0	0.54
BMI, kg/m^2 (mean ± SD)	403	26.6 ± 4.3	27.4 ± 6.1	0.50
Obesity, % with BMI ≥30	403	21.8	21.4	0.97
Metabolic syndrome, % Yes	403	39.3	71.4	0.016*
Waist circumference, cm (mean ± SD)	403	83.7 ± 10.4	86.1 ± 15.8	0.41
Systolic blood pressure, mm Hg (mean ± SD)	403	142.0 ± 18.5	147.9 ± 22.2	0.25
Medication use, %				
Corticosteroid use (Yes)	403	12.3	7.1	0.56
NSAID use (Yes)	403	5.4	0	0.37
Medical comorbidities, %				
Diabetes (Yes)	403	7.7	14.3	0.37
Walking speed, m/s (mean ± SD)	403	1.3 ± 0.3	1.2 ± 0.2	0.23
Number of IADL impairments[a]	403	0.4 ± 0.9	0.7 ± 1.1	0.28
Os calcis BMD, g/cm^2 (mean ± SD)	402	0.4 ± 0.1	0.5 ± 0.1	0.009*
Laboratory measurements, mg/dl				
Triglycerides (median, (25th, 75th percentile))	403	145.0 (104, 208)	167.0 (121.0, 261.3)	0.231
HDL (median, (25th, 75th percentile))	403	52.0 (43.0, 60.0)	41.5 (35.0, 48.0)	0.004*

Note: Clinical hip OA was defined as a modified Croft score of 2 or more and either documented hip pain or internal rotation limited to below the lower quartile for the population. For normally distributed continuous variables, mean and SD with *P* value from Student's *t*-test are provided. For categorical variables, percentages are provided. For continuous variables that were not normally distributed, the median and interquartile range with *P* value from Mann-Whitney U test are provided.
Abbreviations: BMD, bone mineral density; BMI, body mass index; HDL, high-density lipoprotein; IADL, instrumental activities of daily living; NSAID, nonsteroidal antiinflammatory drug; OA, osteoarthritis.
[a]The number of IADL impairments is defined as the number of the following five activities that the woman has any difficulty performing: 1) walking 2 or 3 blocks outside on level ground, 2) climbing up 10 steps, 3) preparing meals, 4) doing heavy housework, or 5) shopping for groceries or clothes.
*Indicates statistical significance at *P* < 0.05.

Table 2. The Osteoporotic Fractures in Men study baseline participant characteristics by clinical hip OA status

Characteristic	N	No clinical hip OA (n = 2234)	Clinical hip OA (n = 120)	P value
Age, y (mean ± SD)	2354	72.5 ± 5.3	73.2 ± 5.1	0.20
Education, % graduated high school	2354	94.8	95.0	0.91
Race, % White	2354	91.0	92.5	0.57
Height, cm (mean ± SD)	2354	174.6 ± 6.7	175.5 ± 6.0	0.12
Weight, kg (mean ± SD)	2354	83.3 ± 12.6	88.3 ± 13.5	<0.001*
BMI, kg/m^2 (mean ± SD)	2354	27.3 ± 3.7	28.6 ± 3.9	<0.001*
Obesity, % with BMI ≥30	2354	20.0	31.7	0.002*
Metabolic syndrome, % (Yes)	2354	39.9	40.0	0.988
Waist circumference, cm (mean ± SD)	2354	99.5 ± 10.8	103.7 ± 11.2	<0.001*
Systolic blood pressure, mm Hg (mean ± SD)	2354	139.9 ± 18.5	139.6 ± 19.2	0.88
Medication use, %				
Corticosteroid use (Yes)	2256	1.5	4.4	0.02*
NSAID use (Yes)	2256	14.1	21.9	0.02*
Bisphosphonate use (Yes)	2198	1.4	1.8	0.76
Medical comorbidities, %				
Diabetes (Yes)	2354	8.5	9.2	0.81
Myocardial infarction (Yes)	2354	12.1	15.0	0.34
Walking speed, m/s (mean ± SD)	2352	1.3 ± 0.2	1.2 ± 0.2	<0.001*
Number of IADL impairments[a]	2353	0.2 ± 0.6	0.5 ± 1.1	<0.001*
Corrected total hip BMD, g/cm^2 (mean ± SD)	2354	0.97 ± 0.1	1.00 ± 0.1	0.006*
Laboratory measurements, mg/dl, median				
Triglycerides (median, (25th, 75th percentile))	2354	123.0 (90.0, 178.0)	120.0 (92.0, 161.5)	0.42
HDL (median, (25th, 75th percentile))	2354	47.0 (39.0, 57.0)	47.0 (39.0, 57.0)	0.96
Glucose (median (25th, 75th percentile))	1990	99.0 (93.0, 108.0)	102.0 (94.3, 109.0)	0.12

Note: Clinical hip OA was defined as total hip replacement or a modified Croft score of 2 or more and either documented hip pain or internal rotation limited to below the lower quartile for the population. For categorical variables, percentages are provided. For normally distributed continuous variables, mean and SD and P value from Student's *t*-test are provided. For continuous variables that were not normally distributed, the median and interquartile range and P value from Mann-Whitney U test are provided.
Abbreviations: BMD, bone mineral density; BMI, body mass index; HDL, high-density lipoprotein; IADL, instrumental activities of daily living; NSAID, nonsteroidal antiinflammatory drug; OA, osteoarthritis.
[a]The number of IADL impairments is defined as the number of the following five activities that the man has any difficulty performing: 1) walking 2 or 3 blocks outside on level ground, 2) climbing up 10 steps, 3) preparing meals, 4) doing heavy housework, or 5) shopping for groceries or clothes.
*Indicates statistical significance at $P < 0.05$.

hip OA in unadjusted or fully adjusted analysis (OR: 0.98; 95% CI: 0.88-1.08).

Men who had obesity had a higher prevalence of clinical hip OA (8.5%) as compared to men who did not have obesity (4.4%). Among men in MrOS, obesity was associated with 115% higher odds of having hip OA after adjustment for age, race, and MetS (OR: 2.15; 95% CI: 1.39-3.32) (Table 4). Obesity was associated with 59% higher odds of having radiographic hip OA in fully adjusted analysis (OR: 1.59; 95% CI: 1.17-2.17).

MetS and clinical hip OA. Approximately 40.4% of women in SOF and 39.9% of men in MrOS met the definition of MetS. Women who did not have MetS had a lower prevalence of clinical hip OA (1.7%) as compared to those with MetS (6.1%). Among women in SOF, those who had MetS had 365% higher odds of having clinical hip OA (OR: 4.65; 95% CI: 1.37-15.83) in fully adjusted analysis (Table 5). Women in SOF with MetS also demonstrated higher odds of radiographic hip OA as compared to those without MetS, although this

Table 3. Unadjusted and sequentially adjusted odds ratios for the association of obesity (BMI ≥30) with clinical and radiographic hip OA in the Study of Osteoporotic Fractures

		Obesity (BMI ≥30) odds ratio (95% CI)	
	N	Prevalent clinical hip OA	Prevalent radiographic hip OA
No. obesity/No. hip OA		3/14	11/19
Base model 1 (unadjusted)	403	0.98 (0.27-3.58)	0.95 (0.31-2.95)
Model 2 (age adjusted)	403	0.96 (0.26-3.52)	0.94 (0.30-2.90)
Model 3 (adjusted for age, MetS [yes/no])	403	0.53 (0.14-2.09)	0.98 (0.88-1.08)

Abbreviations: BMI, body mass index; MetS, metabolic syndrome; OA, osteoarthritis.

Table 4. Unadjusted and sequentially adjusted odds ratios for the association of obesity defined as BMI ≥30 with clinical and radiographic hip osteoarthritis or total hip replacement in the Osteoporotic Fractures in Men study

	N	Obesity (BMI ≥30) odds ratio (95% CI)	
		Prevalent clinical hip OA or THR	Prevalent radiographic hip OA or THR
No. obesity/No. hip OA		38/120	77/282
Base model 1 (unadjusted)	2354	1.86 (1.25-2.77)*	1.54 (1.16-2.04)*
Model 2 (age and race adjusted)	2354	1.97 (1.31-2.94)*	1.51 (1.14-2.01)*
Model 3 (adjusted for age, race, and MetS)	2354	2.15 (1.39-3.32)*	1.59 (1.17-2.17)*

Abbreviations: BMI, body mass index; MetS, metabolic syndrome; OA, osteoarthritis; THR, total hip replacement.
*$P < 0.05$.

association was not statistically significant (OR: 2.40; 95% CI: 0.90-6.43).

Men who had MetS had the same prevalence of clinical hip OA as compared to men who did not have MetS (5.1%). There was no significant association between MetS and either clinical hip OA (OR: 0.81; 95% CI: 0.54-1.21) or radiographic hip OA (OR: 1.03; 95% CI: 0.78-1.35) among men in MrOS (Table 6).

Association and interaction between obesity and MetS. Among women in SOF, there was a higher prevalence of MetS among those who had obesity (72.7%) as compared to those who did not have obesity (31.4%; $P < 0.001$). Similarly, among men in MrOS, there was a higher prevalence of MetS among those who had obesity (72.5%) as compared to those who did not have obesity (31.5%) ($P < 0.001$).

There was no significant interaction between MetS and obesity on hip OA in either cohort in fully adjusted analysis (women in SOF: $P_{interaction} = 0.99$; men in MrOS: $P_{interaction} = 0.30$; Figure 1).

DISCUSSION

In this study of older community-dwelling persons, MetS defined according to the NCEP-ATPIII criteria was associated with clinical hip OA in older women but not in men. Conversely, obesity was not associated with clinical hip OA in older women, but obesity was associated with 115% higher odds of clinical hip OA in older men. MetS did not modify the association between obesity and clinical hip OA among either women or men.

These results are consistent with previous studies demonstrating a modest association between BMI and hip OA (15–17,35–37). The absence of a significant association among women suggests that sex-related differences may exist in the odds conferred by obesity and may explain why no significant association was shown in prior studies with populations of women only (10) or those combining men and women (6,38).

Interestingly, the reverse relationship was seen with MetS. Despite a much smaller sample size for whom metabolic data were available, women demonstrated 365% higher odds of clinical hip OA in association with MetS, whereas in men there was no association between MetS and clinical hip OA. These findings suggest that the association between MetS and hip OA may be stronger in women than men. Although some studies have shown an association between knee OA and MetS (39), ours is the first to suggest a significant association of MetS with hip OA in women. This novel finding may be underscored by the fact that clinical hip OA, rather than total hip replacement status, was assessed in our study (18,19). Some previous studies used total hip arthroplasty status alone as a surrogate for OA, which likely underestimates the prevalence of OA, particularly for women (21), providing a plausible explanation for the disparate results.

Our results suggest that among men, the mechanical component of obesity as indicated by elevated BMI appears to predominate. The relative importance of the mechanical aspect of increased adiposity in men may be because of the sex-related differential distribution of mass. Women tend to have increased fat

Table 5. Unadjusted and sequentially adjusted odds ratios for the association of MetS with clinical and radiographic hip osteoarthritis in the Study of Osteoporotic Fractures

	N	MetS odds ratio (95% CI)	
		Prevalent clinical hip OA	Prevalent radiographic hip OA
No. MetS/No. hip OA		10/14	11/19
Base model 1 (unadjusted)	403	3.86 (1.19-12.52)*	2.10 (0.83-5.34)
Model 2 (age adjusted)	403	3.91 (1.20-12.72)*	2.13 (0.83-5.41)
Model 3 (adjusted for age and obesity [yes/no])	403	4.65 (1.37-15.83)*	2.40 (0.90-6.43)

Abbreviations: MetS, metabolic syndrome; OA, osteoarthritis.
*$P < 0.05$.

Table 6. Unadjusted and sequentially adjusted odds ratios for the association of MetS with clinical and radiographic hip osteoarthritis or total hip replacement in the Osteoporotic Fractures in Men study

	N	MetS odds ratio (95% CI)	
		Prevalent clinical hip OA or THR	Prevalent radiographic hip OA or THR
No. obesity/No. hip OA		48/120	120/282
Base model 1 (unadjusted)	2354	1.00 (0.69-1.46)	0.88 (0.69-1.14)
Model 2 (age and race adjusted)	2354	1.03 (0.70-1.49)	0.85 (0.66-1.10)
Model 3 (adjusted for age, race, and MetS)	2354	0.81 (0.54-1.21)	1.03 (0.78-1.35)

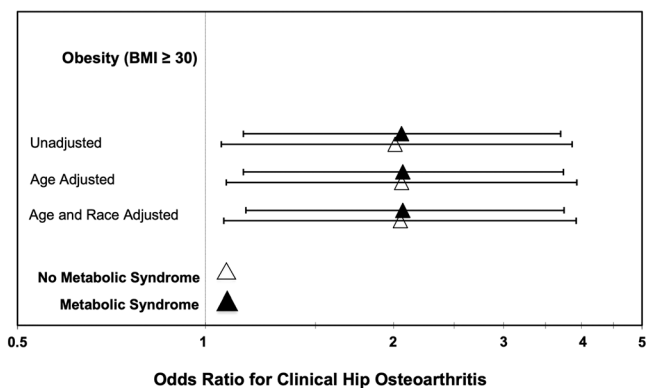Abbreviations: MetS, metabolic syndrome; OA, osteoarthritis; THR, total hip replacement.

mass in the femoral and gluteal regions (40,41) that would not be expected to increase compressive load on the hip joint as much as the abdominal adiposity observed in men. This might also explain why increased waist circumference, which is an indicator of abdominal obesity, was associated with hip OA in men in univariate analyses (data not shown). Alternatively, because elevated BMI may also be accompanied by higher muscle mass (42,43), it is possible that elevated BMI increases muscle force across the hip. However, as this was a cross-sectional study design, it is also possible that the presence of clinical hip OA resulted in decreased activity, which then led to higher body mass. Future studies are needed to clarify the effect of regional body mass distribution and composition on hip OA risk.

The association of higher BMI with hip OA among men in the present study (OR: 2.15) is relatively modest compared to reported ORs for obesity and knee OA (OR: 2.63-4.55) (4,40,41,44). One explanation may be that hip geometry plays a more important role in altering hip joint biomechanics than mechanical load from increased adiposity alone. Hip deformities, including cam lesions and acetabular dysplasia, have been associated with increased risk of hip OA (45). It is possible that more subtle variations in hip morphometry also contribute to hip OA.

Although higher BMI did not appear to be associated with hip OA among women, as noted earlier, there was an association

Figure 1. Odds ratios for the association of obesity with clinical hip OA in the Osteoporotic Fractures in Men study, stratified by MetS status. BMI, body mass index; MetS, metabolic syndrome; OA, osteoarthritis.

between MetS and hip OA in this cohort. One possible explanation for this may relate to sex differences in mass composition. Women tend to have a higher percentage of fat mass than men of the same BMI (46). Because fat weighs less than an equivalent volume of lean mass, a woman may have a relatively subtle change in her calculated BMI but have a large change in the amount of body fat and, therefore, the metabolic factors secreted by that increased adipose tissue. Thus, women may be more likely to experience metabolic rather than mechanical effects of adiposity on hip OA. This is consistent with prior work demonstrating that women more frequently present with polyarticular osteoarthrosis, which is more likely to be related to systemic disease (22).

This study has several limitations. First, being a cross-sectional study, causal inference is not possible. A longitudinal study of hip OA would allow us to determine a temporal association between obesity and hip OA that was observed in the present study among older men and between MetS and hip OA that was observed among older women. As noted earlier, it is possible that the hip OA resulted in pain and decreased activity, which subsequently resulted in increased BMI in men or MetS in women. Second, the limited number of women in SOF with serum measurements required for the determination of MetS resulted in a very small number of participants with clinical hip OA (n = 14). This severely limited the power of the study to detect associations between obesity and MetS and hip OA, as well as for evaluating the interaction between MetS and obesity in this cohort. This subgroup of women with metabolic measurements were only minimally older with a slightly higher prevalence of diabetes and did not differ from the larger cohort in the prevalence of hip OA or anthropometry. Thus, they were likely similar to the larger cohort, even though the results were not definitively generalizable to the original cohort. In a larger analytic sample, it is possible that a weaker association between obesity and hip OA could be detected for which this study was insufficiently powered to detect. Similarly, in MrOS, a large number of participants were excluded due to lack of available waist circumference measurement, such that it is unclear whether the findings of this study are definitively generalizable to the larger cohort. Of note, however, we found no difference between the subset of men with available waist circumference measures as compared to those without with

respect to other anthropometric measures, prevalent hip OA, or demographics, suggesting that the subset of men included in the study were likely similar to the larger cohort.

Third, with regard to MetS, we also note that our definition of MetS treated each of the MetS criteria with equal importance. Clinically, it is possible that the different components of MetS may have variable contributions to hip OA. For example, diabetes may play a more significant role in producing an inflammatory milieu, which predisposes to hip OA, than does hypertension.

Fourth, the cross-sectional period for our main analyses covered 4 years in SOF and 6 years in MrOS. This is a limitation of retrospective data use because the measures of interest were not all available at a single visit and there were no suitable proxy variables at the same visit. However, during this 4- to 6-year window of time, there is typically minimal progression in radiographic hip OA or obesity status (31). Additionally, we note that the size of the analytic cohort for SOF women was modest, resulting in limited power as evidenced by the wide CI for the estimated association. The findings in this study should, therefore, be confirmed in other cohorts with larger analytic sample sizes. Finally, we note that several risk factors that contribute to hip OA were not available in these cohorts. Important risk factors include antecedent hip injury, congenital hip dysplasia, and occupations resulting in increased impact or repetitive injury to the hip. Although we have no reason to suspect that these risk factors would present at different prevalences between MetS and metabolically normal participants, or between participants with obesity and those without obesity, additional studies are needed to explore these risk factors in greater detail.

The major strength of this study is the use of two well-characterized community-based cohorts of older men and women in parallel. The radiographs used in this study were read by expert readers, and these reads have been evaluated for reliability and used in previous studies (30–32). We also introduced a clinically meaningful definition of hip OA, which required not only radiographic findings consistent with hip OA but also symptoms of either hip pain or limited internal rotation. This definition of hip OA makes the results of this study more generalizable to the typical hip patient with OA seen in medical practice, as many patients with radiographic OA alone do not experience symptoms (47) and would only be identified incidentally in radiographs obtained for other purposes. We performed secondary analyses using only the radiographic OA definition, and these yielded the same results but with smaller or nonsignificant effect sizes, which is consistent with the idea that the clinical hip OA definition identifies a more homogenous group of individuals with more severe hip OA. Additionally, previous studies of hip OA and MetS have used total hip replacement status as a surrogate measure (18,19), which may have underestimated the outcome prevalence because not all patients who have hip OA elect to undergo arthroplasty.

In summary, the types of adiposity may have different contributions to hip OA among women and men. Among older women in SOF, MetS was associated with clinical hip OA, whereas obesity was not. In contrast, among older men in MrOS, obesity was associated with clinical hip OA, whereas MetS was not. Further studies are needed to characterize the differences in men and women and possible dependence of hip OA pathogenesis on regional distribution and mass composition effects of adiposity.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Karen Y. Cheng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Cheng, Nevitt, Lane, Hughes-Austin.
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