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# Presence of Magnetic Resonance Imaging–Defined Inflammation Particularly in Overweight and Obese Women Increases Risk of Radiographic Knee Osteoarthritis: The POMA Study

Frank W. Roemer,[1] Ali Guermazi,[2] Michael J. Hannon,[3] Tomoko Fujii,[3] Patrick Omoumi,[4] David J. Hunter,[5] Felix Eckstein,[6] and C. Kent Kwoh[3]

**Objective.** The present study was undertaken to assess whether the odds for incident radiographic osteoarthritis (OA) differ between men and women in regard to body mass index (BMI) and inflammatory magnetic resonance imaging (MRI) markers 1 and 2 years prior, and whether the presence of inflammation on MRI differs between normal-weight and overweight/obese individuals who develop radiographic OA up to 4 years prior.

**Methods.** We studied 355 knees from the Osteoarthritis Initiative study that developed incident radiographic OA and 355 matched controls. MRIs were read for effusion-synovitis and Hoffa-synovitis for up to 4 consecutive annual time points. Subjects were classified as normal-weight (BMI <25), overweight (BMI ≥25 and <30), or obese (BMI ≥30). Conditional logistic regression was used to assess odds of incident radiographic OA for effusion-synovitis and Hoffa-synovitis at 1 and 2 years prior to radiographic OA incidence (i.e., "P-1" and "P-2") considering BMI category. Bivariate logistic regression was used to assess odds of inflammation for cases only.

**Results.** One hundred seventy-eight (25.1%) participants were normal weight, 283 (39.9%) overweight, and 249 (35.1%) obese. At P-2, being overweight with Hoffa-synovitis, which had an odds ratio [OR] of 3.26 (95% confidence interval [95% CI] 1.39–7.65), or effusion-synovitis (OR 3.56 [95% CI 1.45–8.75]) was associated with greater odds of incident radiographic OA in women. For those with incident radiographic OA, there were no increased odds of synovitis in the overweight/obese subgroup for most time points, but increased odds for effusion-synovitis were observed at P-2 (OR 2.21 [95% CI 1.11–4.43]).

**Conclusion.** Presence of inflammatory markers seems to play a role especially in overweight women, while obese women have increased odds for radiographic OA also in the absence of these markers.

## INTRODUCTION

Obesity is one of the key risk factors for the development of knee osteoarthritis (OA) (1). Associations linking OA development to components of the so-called metabolic syndrome beyond obesity have been suggested. These include chronic low-grade inflammation, a feature shared by OA and metabolic disorders that may contribute to the genesis of both (2,3). While studies

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[1]Frank W. Roemer, MD: Boston University School of Medicine, Boston, Massachusetts, and Friedrich-Alexander University Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [2]Ali Guermazi, MD, PhD: Boston University School of Medicine, Boston, Massachusetts, and VA Boston Healthcare System, West Roxbury, Massachusetts; [3]Michael J. Hannon, MA (current address: Pinney Associates, Pittsburgh, Pennsylvania), Tomoko Fujii, MS, MPH (current address: The University of Tokyo, Tokyo, Japan), C. Kent Kwoh, MD (current address: University of Arizona College of Medicine, Tucson): University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [4]Patrick Omoumi, MS, PhD: Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [5]David J. Hunter, MBBS, PhD: Royal North Shore Hospital and Institute of Bone and University of Sydney, Sydney, New South Wales, Australia; [6]Felix Eckstein, MD: Paracelsus Medical University Salzburg and Nuremberg, Salzburg, Austria, and Chondrometrics, Ainring, Germany.

**SIGNIFICANCE & INNOVATIONS**

- In women, being overweight with Hoffa-synovitis and being overweight or obese with effusion-synovitis increases odds for incident radiographic osteoarthritis (OA) 2 years later.
- Presence of effusion-synovitis increases odds for incident radiographic OA in overweight and obese women but not in men.
- For individuals who develop incident radiographic OA, increased odds for effusion-synovitis were observed 2 years prior (odds ratio 2.21 [95% confidence interval 1.11–4.43]).
- Both mechanical load and inflammation seem to have a role in OA incidence for overweight and obese women, while for men the role of inflammation in conjunction with high body mass index seems to be less relevant.

have reported that the metabolic syndrome is clearly associated with increased risk of knee OA (4), a recent meta-analysis suggested that this may only be indirect, and that there was insufficient evidence that the metabolic syndrome was associated with incident knee OA independent of body mass index (BMI) (5).

Beyond proinflammatory systemic factors, local intraarticular adipose tissues such as Hoffa's fat pad produce inflammatory and catabolic mediators that may contribute to OA pathogenesis (6). Further, it is unclear whether women and men show differences regarding the presence of metabolic syndrome and incident knee OA. While one study did not report any sex-specific differences (3), others have highlighted that inflammation and metabolic syndrome may have a larger impact on OA incidence in women compared to men (7). We hypothesize that individuals with high body mass index (BMI) and local inflammation as assessed by magnetic resonance imaging (MRI), considered as surrogates for some of the components of the metabolic syndrome (8), may be at increased odds for incident knee OA, and that overweight and obese individuals are at increased odds for exhibiting signs of local joint inflammation as assessed by MRI up to 4 years prior to the incidence of radiographic OA.

The aims of this study were as follows: to assess whether odds for incident radiographic OA differ between men and women in regard to BMI and inflammatory MRI markers 1 and 2 years prior to radiographic OA incidence using a matched case–control sample of subjects who developed or did not develop incident radiographic OA; and to analyze whether odds of presence of MRI features of inflammation such as effusion-synovitis (effusion) and Hoffa-synovitis (synovitis) differ between normal-weight, and overweight/obese individuals who develop incident radiographic OA over a period of up to 4 years prior.

## MATERIALS AND METHODS

**The Osteoarthritis Initiative (OAI).** The OAI is a longitudinal cohort study designed to identify biomarkers of the onset and/or progression of knee OA. Both knees of 4,796 participants were studied using 3T MRI and fixed-flexion radiography at baseline, 12, 24, 36, and 48 months of follow-up (9). The institutional review boards at each of the sites approved the study, and all participants gave informed consent.

**Radiography.** OAI knee radiographs were acquired using the posteroanterior fixed-flexion weight-bearing protocol using a positioning frame. Kellgren/Lawrence (K/L) grade was determined by central readings of baseline serial fixed-flexion knee radiographs (10).

**Case and control knee selection.** Cases were defined as study participants who had at least 1 knee that developed incident radiographic OA during the 4 years of follow-up. Incident radiographic OA was defined as the first occurrence of radiographic findings compatible with OA (K/L grade of ≥2 on the posteroanterior view based on central readings) during the course of study. This time point was called P0, with P-1 being defined as the time point 1 year before radiographic OA was detected, P-2 defined as 2 years prior, P-3 three years prior, and P-4 four years prior to when incident radiographic OA was read. All participants fulfilling the case definition were included. An identical number of control knees were selected from knees that did not develop incident radiographic OA during the study period. The controls were matched to case knees according to K/L grade, sex, age (within 5 years), and contralateral knee OA status (i.e., K/L grade = 0, 1, or 2+ in the other knee). Each case was matched to those who were at risk at the time of case occurrence and those with available images at relevant time points, whether this was at 12, 24, 36, or 48 months of follow-up. Both cases and control

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Address correspondence to Frank W. Roemer, MD, Adjunct Professor of Radiology, Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, FGH Building, 3rd floor, 820 Harrison Avenue, Boston, MA 02118. Email: froemer@bu.edu.

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knees were either K/L grade 0 or 1 at baseline based on central readings. Only 1 knee per subject was used as a case knee. A flow chart of the inclusion of cases and controls is included as Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24568.

**MRI acquisition and assessment.** MRI of both knees was performed on identical 3T systems (Siemens Trio) at the 4 OAI clinical sites. The OAI pulse sequence protocol and the sequence parameters have been published in detail (9).

Two musculoskeletal radiologists with 11 (FWR) and 14 (AG) years' experience of semiquantitative assessment of knee OA at the time of reading, blinded to clinical data and case–control status, read the MRIs according to the MRI OA Knee Score system (11). Baseline and follow-up MRIs were read with the chronological order known to the readers. Diffuse hyperintense signal on the sagittal intermediate-weighted fat-suppressed sequence in the intercondylar region of Hoffa's fat pad were scored from 0 to 3 as a surrogate for synovial thickening, termed Hoffa-synovitis (i.e., synovitis). The degree of hyperintensity was assessed according to the following grades: 0 = normal, 1 = mild, 2 = moderate, and 3 = severe. Joint effusion (also called effusion-synovitis, as it is not possible to discern joint fluid from synovial thickening on non–contrast-enhanced MRI) was graded from 0 to 3 in terms of the estimated maximal distention of the synovial cavity (i.e., effusion) as follows: grade 0 = none, grade 1 = small, grade 2 = medium, and grade 3 = large (11,12). Examples of the different grades of Hoffa-synovitis and effusion-synovitis are presented in Figure 1. Detailed reliability data of MRI assessment are presented in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24568.

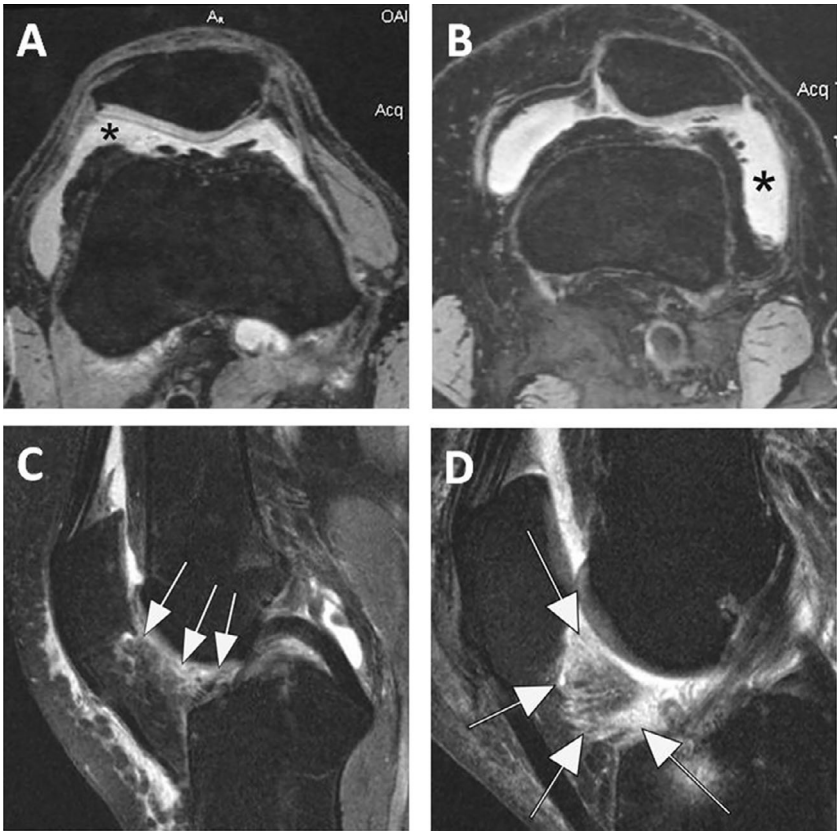


**Figure 1.** Magnetic resonance imaging (MRI) markers of inflammation in osteoarthritis (OA). Fluid-sensitive sequences are capable of delineating intraarticular joint fluid. However, a distinction between true joint effusion and synovial thickening is not possible, as both are visualized as a hyperintense signal within the joint cavity. For this reason, the term effusion-synovitis was introduced, which in the MRI OA Knee Score system is scored based on the distension of the joint capsule and is graded from 0 to 3 in terms of the estimated maximal distention of the synovial cavity, with 0 = normal, grade 1 = <33% of maximum potential distention, grade 2 = 33–66% of maximum potential distention, and grade 3 = >66% of maximum potential distention. Axial dual-echo steady-state MRI shows grade 2 effusion-synovitis (**asterisk**) (**A**) and grade 3 effusion-synovitis (**asterisk**) (**B**). In addition, signal changes in Hoffa's fat pad are commonly used as a surrogate for synovitis on non–contrast-enhanced MRI. Although synovitis can only be visualized directly on contrast-enhanced sequences, it has been shown that Hoffa's signal changes are a sensitive but nonspecific surrogate of synovitis (**C**). Sagittal intermediate-weighted fat-suppressed MRI shows a discrete ill-defined hyperintense signal alteration in Hoffa's fat pad consistent with grade 2 Hoffa-synovitis (**arrows**) (**D**). Severe, grade 3 signal alterations almost occupying the entire fat pad are seen in this image (**arrows**).

**Table 1.** Demographic characteristics of the sample*

| | Cases (n = 355) | Controls (n = 355) | *P* |
|---|---|---|---|
| Age, mean ± SD years | 60.1 ± 8.6 | 60.0 ± 8.4 | NA |
| BMI, mean ± SD kg/m$^2$ | 28.9 ± 4.5 | 27.7 ± 4.4 | 0.0003 |
| WOMAC knee pain score, mean ± SD† | 2.6 ± 3.3 | 1.4 ± 2.5 | <0.0001 |
| WOMAC functioning score, mean ± SD† | 8.4 ± 10.8 | 4.3 ± 7.8 | <0.0001 |
| Sex | | | NA |
| Female | 237 (66.8) | 237 (66.8) | |
| Male | 118 (33.2) | 118 (33.2) | |
| BMI, kg/m$^2$ | | | 0.0032 |
| Normal/underweight | 70 (19.7) | 108 (30.4) | |
| Overweight | 147 (41.4) | 136 (38.3) | |
| Obese | 138 (38.9) | 111 (31.3) | |
| Race | | | 0.2143 |
| White | 283 (79.7) | 299 (84.2) | |
| African American | 61 (17.2) | 47 (13.2) | |
| Asian | 6 (1.7) | 2 (0.6) | |
| Other | 5 (1.4) | 7 (2) | |
| K/L grade | | | NA |
| 0 | 133 (37.5) | 133 (37.5) | |
| 1 | 222 (62.5) | 222 (62.5) | |
| Knee injury at OAI baseline‡ | 136 (38.3) | 70 (19.7) | <0.0001 |
| Knee surgery at OAI baseline§ | 54 (15.2) | 24 (6.8) | 0.0004 |

* Values are the number (%) unless indicated otherwise. *P* values for differences by Fisher's exact test for categorical variables and *t*-tests for ordinal variables were not calculated for variables used in matching. BMI = body mass index; K/L = Kellgren/Lawrence; NA = not applicable; OAI = Osteoarthritis Initiative; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† WOMAC knee pain is on a scale of 1 to 20, and WOMAC functioning of 1 to 96, with higher values representing more pain/less functioning.
‡ Knee injury defined as 1 inhibiting ability to walk for at least 2 days.
§ Knee surgery includes arthroscopy.

**Statistical analysis.** Subjects were classified as normal weight (BMI <25 kg/m$^2$), overweight (BMI ≥25 kg/m$^2$ and <30 kg/m$^2$), or obese (BMI ≥30 kg/m$^2$) at OAI enrollment. In the case–control design part of the study, conditional logistic regression was used to assess the risk of incident radiographic OA stratified by presence of synovitis and effusion focusing on the time points P-1 and P-2 only. Presence of synovitis and effusion was defined as "any," i.e., knees that exhibited grades 1–3 of synovitis or effusion on MRI. The time points P-3 and P-4 were not considered, as low numbers did not allow meaningful interpretation of the interactions (for P-3 only, 59 cases, and for P-4 only, 53 cases were available). For the case–control analysis, stratification by sex was undertaken, and BMI, synovitis, and effusion or the interaction were used as exposure variables. First, the bivariate associations of radiographic OA and the different synovitis and effusion categories and BMI were estimated. After this initial analysis, the risk of radiographic OA for the interaction of BMI and effusion/synovitis was examined. The category of normal weight, especially in men, was sufficiently uncommon that we used the overweight category as the referent for the BMI analysis because it was the norm.

Bivariate logistic regression was used to assess the odds of the presence of synovitis and effusion at time points P-1, P-2, P-3, P-4, and baseline in subjects who developed radiographic OA (i.e., only cases), comparing overweight and obese subjects combined to subjects of normal weight as the reference. We considered a 2-tailed *P* value of less than 0.05 as statistically significant. All statistical calculations were performed using Stata/IC, version 11.2, for Windows and SAS, version 9.3.

## RESULTS

A total of 355 case knees and 355 matched control knees were included. Participants had a mean ± SD age of 60.2 ± 8.6 years; 66.8% were female. Cases had a slightly higher BMI compared to controls (28.9 kg/m$^2$ versus 27.7 kg/m$^2$; *P* = 0.0003). No significant differences with regard to ethnicity between cases and controls were observed (84% of the subjects were White). The case-defining visit of radiographic OA incidence was 12 months for 119 knees (33.5%), 24 months for 83 knees (23.4%), 36 months for 103 knees (29.0%), and 48 months for 50 knees (14.1%). In total, 178 (25.1% of all study participants; n = 138 [77.5%] women) participants were normal weight, 283 (39.9% of all study participants; n = 166 [58.7%] women) were overweight, and 249 (35.1% of all study participants; n = 170 [68.3%] women) were obese at baseline. Details of demographic characteristics regarding cases and controls are presented in Table 1.

Regarding the interaction of BMI with synovitis and effusion, using overweight women and men without synovitis or effusion

as the reference, obesity without synovitis was associated with greater odds of radiographic OA in women at P-2, with an odds ratio (OR) of 2.87 (95% confidence interval [95% CI] 1.21–6.83), as was being overweight with synovitis (OR 3.26 [95% CI 1.39–7.65]). Being obese with synovitis was not associated with increased odds at P-2. For men, there were no combinations of synovitis and BMI that were associated with increased odds of radiographic OA compared to those being overweight without synovitis at P-2. Furthermore, being overweight with joint effusion at P-2 was associated with increased OA odds in women (OR 3.56 [95% CI 1.45–8.75]), an association also observed in women who were obese (OR 3.46 [95% CI 1.38–8.72]).

At P-1 and combining all BMI categories, having any synovitis or any effusion was associated with increased odds of radiographic OA in both men and women. Further, presence of synovitis was associated with incident radiographic OA in overweight and obese women and men, with the latter association also seen for men of normal weight, which was not the case for women of normal weight. Positive associations of effusion with incident OA were only seen in overweight (OR 3.14 [95% CI 1.55–6.36]) and obese women (OR 3.03 [95% CI 1.50–6.15]) but not women of normal weight or in men. Table 2 gives a detailed overview of these results regarding the interactions between BMI, sex, and severity of inflammation at P-2 and P-1.

For those knees that developed radiographic OA, there were no increased odds of synovitis in the combined overweight/obese (i.e., categories combined) BMI subgroup compared to the normal-weight subgroup at any of the 4 time

**Table 2.** Odds for developing radiographic osteoarthritis (OA) at Osteoarthritis Initiative (OAI) visits year 2 (P-2) or year 1 (P-1) prior to the case-defining visit in matched cases and controls*

| | P-2 | | | | | P-1 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All, no. (%) | Men, no. (%) | Men, OR (95% CI) (n = 136) | Women, no. (%) | Women, OR (95% CI) (n = 300) | All, no. (%) | Men, no. (%) | Men, OR (95% CI) (n = 224) | Women, no. (%) | Women, OR (95% CI) (n = 436) |
| Normal weight | 116 (26.6) | 21 (15.4) | 1.32 (0.42–4.15) | 95 (31.7) | 0.57 (0.31–1.04) | 166 (25.2) | 38 (17.0) | 0.96 (0.44–2.10) | 128 (29.4) | 0.52 (0.31–0.87) |
| Overweight | 169 (38.8) | 63 (46.3) | Ref. | 106 (35.3) | Ref. | 264 (40.0) | 114 (50.9) | Ref. | 150 (34.4) | Ref. |
| Obese | 151 (34.6) | 52 (38.24) | 0.89 (0.44–1.78) | 99 (33.0) | 1.3 (0.77–2.43) | 230 (34.8) | 72 (32.1) | 0.92 (0.52–1.64) | 158 (36.2) | 1.44 (0.89–2.35) |
| No synovitis | 221 (50.7) | 59 (43.4) | Ref. | 162 (54.0) | Ref. | 337 (51.1) | 99 (44.4) | Ref. | 238 (54.6) | Ref. |
| Synovitis | 215 (49.3) | 77 (56.6) | 1.79 (0.91–3.50) | 138 (46.0) | 1.75 (1.05–2.91)† | 322 (48.9) | 124 (55.6) | 3.62 (1.94–6.74)† | 198 (45.4) | 1.97 (1.29–3.01)† |
| No effusion | 234 (53.7) | 72 (52.9) | Ref. | 162 (54.0) | Ref. | 338 (51.2) | 107 (47.8) | Ref. | 231 (53.0) | Ref. |
| Effusion | 202 (46.3) | 64 (47.1) | 0.75 (0.36–1.59) | 138 (46.0) | 2.88 (1.64–5.03) | 322 (48.8) | 117 (52.2) | 1.88 (1.05–3.37)† | 205 (47.0) | 2.89 (1.87–4.47)† |
| No synovitis, BMI normal | 66 (15.1) | 11 (8.1) | 1.45 (0.31–6.77) | 55 (18.3) | 0.67 (0.29–1.59) | 91 (13.8) | 18 (8.1) | 1.57 (0.42–5.81) | 73 (16.7) | 0.75 (0.35 1.59) |
| No synovitis, BMI overweight | 84 (19.3) | 25 (18.4) | Ref. | 59 (19.7) | Ref. | 130 (19.7) | 47 (21.1) | Ref. | 83 (19.0) | Ref. |
| No synovitis, BMI obese | 71 (16.3) | 23 (16.9) | 1.03 (0.31–3.42) | 48 (16.0) | 2.87 (1.21–6.83)† | 116 (17.6) | 34 (15.2) | 1.63 (0.58–4.57) | 82 (18.8) | 2.30 (1.17–4.56)† |
| Synovitis, BMI normal | 50 (11.5) | 10 (7.4) | 3.25 (0.69–15.29) | 40 (13.3) | 1.52 (0.61–3.77) | 74 (11.2) | 19 (8.5) | 4.10 (1.46–11.55)† | 55 (12.6) | 1.23 (0.57–2.64) |
| Synovitis, BMI overweight | 85 (19.5) | 38 (27.9) | 1.99 (0.66–6.00) | 47 (15.7) | 3.26 (1.39–7.65)† | 134 (20.3) | 67 (30.0) | 5.69 (2.06–15.67)† | 67 (15.4) | 3.66 (1.74–7.69)† |
| Synovitis, BMI obese | 80 (18.3) | 29 (21.3) | 1.63 (0.58–4.60) | 51 (17.0) | 1.86 (0.80–4.34) | 114 (17.3) | 38 (17.0) | 3.72 (1.39–9.98)† | 76 (17.4) | 2.71 (1.24–5.92)† |
| No effusion, BMI normal | 69 (15.8) | 15 (11.0) | 3.86 (0.83 18.05) | 54 (18.0) | 0.68 (0.28–1.63) | 105 (15.9) | 26 (11.6) | 1.00 (0.35–2.86) | 79 (18.1) | 0.50 (0.23–1.09) |
| No effusion, BMI overweight | 92 (21.1) | 31 (22.8) | Ref. | 61 (20.3) | Ref. | 125 (18.9) | 46 (20.5) | Ref. | 79 (18.1) | Ref. |
| No effusion, BMI obese | 73 (16.7) | 26 (19.1) | 1.41 (0.46 4.33) | 47 (15.7) | 1.16 (0.50–2.67) | 108 (16.4) | 35 (15.6) | 0.61 (0.25–1.51) | 73 (16.7) | 1.71 (0.85–3.47) |
| Effusion, BMI normal | 47 (10.8) | 6 (4.4) | 0.00 (0.00–0.00)‡ | 41 (13.7) | 1.30 (0.51–3.30) | 61 (9.2) | 12 (5.4) | 1.75 (0.46–6.58) | 49 (11.2) | 1.78 (0.81–3.89) |
| Effusion, BMI overweight | 77 (17.7) | 32 (23.5) | 1.64 (0.53–5.12) | 45 (15.0) | 3.56 (1.45–8.75)† | 139 (21.1) | 68 (30.4) | 1.41 (0.60–3.30) | 71 (16.3) | 3.14 (1.55–6.36)† |
| Effusion, BMI obese | 78 (17.9) | 26 (19.1) | 1.10 (0.36–3.37) | 52 (17.3) | 3.46 (1.38–8.72)† | 122 (18.5) | 37 (16.5) | 1.94 (0.77–4.86) | 85 (19.5) | 3.03 (1.50–6.15)† |

* 95% CI = 95% confidence interval; BMI = body mass index; OR = odds ratio; P-1 = OAI visit 1 year prior to the case-defining visit when incident radiographic OA was diagnosed/read; P-2 = OAI visit 2 years prior to the case-defining visit when incident radiographic OA was diagnosed/read; Ref. = reference.
† Statistically significant at $P < 0.05$.
‡ No case knees in this category.

points prior to the case visit or the baseline visit. However, being overweight/obese was associated with an increased odds of effusion at P-2 (OR 2.21 [95% CI 1.11–4.43]). Though not statistically significant, increased odds for effusion were also observed for the visit P-1 (OR 1.68 [95% CI 0.98–2.88]). Table 3 presents details for the case knees and associated odds for synovitis or effusion at several time points prior to the incidence of radiographic OA.

## DISCUSSION

The presence of synovitis increased the odds of developing radiographic OA in overweight women at the time point 2 years before radiographic OA was detected, while obese women had an increased risk for radiographic OA also without synovitis. At the time point of 1 year prior to OA incidence, we observed increased odds for incident radiographic OA in overweight and obese women with presence of joint effusion, but not in men. At the same time point, increased odds for radiographic OA incidence were seen in both overweight and obese women and men in the presence of synovitis, but not for normal-weight women with synovitis, suggesting that the presence of effusion seems to play a role particularly in overweight or obese women. In knees that developed radiographic OA, increased odds of effusion were observed for the combined overweight/obese group at P-2 but not for Hoffa-synovitis or any of the other time points, suggesting a possible link between high BMI, presence of joint effusion, and radiographic OA development 2 years later.

While the role of body weight and knee radiographic OA incidence is well established, its interactions with local

**Table 3.** Risk for Hoffa-synovitis and effusion-synovitis in case knees that developed incident radiographic osteoarthritis (OA) based on baseline body mass index (BMI) status for different Osteoarthritis Initiative (OAI) visits, with normal weight participants as the reference (Ref.)*

| OAI visit prior to incident radiographic OA and BMI status | No synovitis/ effusion | Yes synovitis/ effusion | OR (95% CI) | *P* |
|---|---|---|---|---|
| Synovitis (any) | | | | |
| P-1 | | | | |
| Normal (n = 63) | 28 | 35 | Ref. | |
| Overweight (n = 266) | 106 | 160 | 1.21 (0.68–2.15) | 0.52 |
| P-2 | | | | |
| Normal (n = 48) | 22 | 26 | Ref. | |
| Overweight (n = 177) | 78 | 99 | 1.07 (0.54–2.13) | 0.84 |
| P-3 | | | | |
| Normal (n = 38) | 21 | 17 | Ref. | |
| Overweight (n = 112) | 53 | 59 | 1.38 (0.63–3.00) | 0.42 |
| P-4 | | | | |
| Normal (n = 13) | 6 | 7 | Ref. | |
| Overweight (n = 37) | 18 | 19 | 0.90 (0.23–3.51) | 0.89 |
| Baseline | | | | |
| Normal (n = 69) | 35 | 34 | Ref. | |
| Overweight (n = 285) | 128 | 157 | 1.26 (0.73–2.19) | 0.41 |
| Effusion (any) | | | | |
| P-1 | | | | |
| Normal (n = 64) | 33 | 31 | Ref. | |
| Overweight (n = 266) | 103 | 163 | 1.68 (0.98–2.88) | 0.06 |
| P-2 | | | | |
| Normal (n = 48) | 30 | 18 | Ref. | |
| Overweight (n = 177) | 76 | 101 | 2.21 (1.11–4.43)† | 0.02 |
| P-3 | | | | |
| Normal (n = 38) | 25 | 13 | Ref. | |
| Overweight (n = 112) | 55 | 57 | 1.99 (0.91–4.38) | 0.09 |
| P-4 | | | | |
| Normal (n = 13) | 7 | 6 | Ref. | |
| Overweight (n = 37) | 17 | 20 | 1.37 (0.36–5.22) | 0.64 |
| Baseline | | | | |
| Normal (n = 70) | 42 | 28 | Ref. | |
| Overweight (n = 285) | 139 | 146 | 1.58 (0.93–2.68) | 0.09 |

* Values are the number unless indicated otherwise. Ref. is normal weight (BMI <25 kg/m$^2$). Overweight and obese subgroups are combined. 95% CI = 95% confidence interval; OR = odds ratio; P-1 = OAI visit 1 year prior to the case-defining visit (when radiographic OA incidence was diagnosed/read); P-2 = OAI visit 2 years prior to the case-defining visit (when radiographic OA incidence was diagnosed/read); P-3 = OAI visit 3 years prior to the case-defining visit (when radiographic OA incidence was diagnosed/read); P-4 = OAI visit 4 years prior to the case-defining visit (when radiographic OA incidence was diagnosed/read).
† Statistically significant at $P < 0.05$.

inflammation have been less clear (1). Reported associations between obesity and OA development also for non–weight-bearing joints suggest a more complex interaction beyond increased biomechanical loading. In a population-based cohort study, it has been reported that metabolic syndrome may be prevalent in 59% of patients with knee OA and in 23% of those without (13). Conversely, Niu et al found in a population-based study that among women, abdominal obesity and high blood pressure were associated with incident radiographic OA, but metabolic syndrome was not (3). We have shown previously a strong association between the presence of joint inflammatory markers based on MRI and subsequent radiographic OA incidence, and this current work expands this, taking also into account sex and BMI differences (14). The fact that 2 years prior to radiographic OA incidence, obesity in women without synovitis exhibited increased risk for radiographic OA, as did being overweight with synovitis, but that obesity with synovitis did not, was not an expected finding. We can only speculate that potentially in obese individuals other factors, including direct results of increased loading due to higher BMI resulting in structural changes like bone marrow alterations, cartilage damage, or meniscal lesions and extrusion, may be more relevant than inflammatory manifestations such as effusion or synovitis.

Concerning the second part of our analysis focusing on cases only regarding prevalence of inflammatory markers in the different subgroups, we found that up to 4 years prior to radiographic OA incidence, in general, the combined overweight/obese subgroup did not show significantly increased rates of local inflammation, with the exception of effusion 2 years prior to radiographic OA incidence, while at 1 year prior, the association was close to being significant. A recent study also from the OAI reported a significantly greater prevalence and severity of synovial inflammation imaging biomarkers in knees of overweight and obese participants compared to those that have normal weight (15). In contrast to our study, however, almost 20% of included subjects exhibited radiographic OA grades 2 and 3, and for those without radiographic OA, it is not known how many developed radiographic OA at later time points. Thus, we speculate based on our findings that for case knees only (i.e., for those that developed radiographic OA), other factors beyond obesity, including local structural damage such as meniscal or cartilage lesions, may have additional impact on the presence of synovial inflammation, thus diluting possible impact of increased BMI.

We acknowledge that in this exploratory study we did not analyze subjects with defined metabolic syndrome, as we only analyzed interactions of BMI and MRI markers of inflammation, which limits extrapolation of our findings to patients with metabolic syndrome (3). An additional limitation of our study includes the absence of information on symptomatic OA. We do not know if subjects who developed radiographic OA also developed symptoms, and if subjects developed symptoms prior to the diagnosis of radiographic OA. Furthermore, the OAI study does not include contrast-enhanced MRI sequences, the gold standard for synovitis assessment (16). However, we used an established surrogate for whole-joint synovitis that has been used in multiple studies applying MRI (11). Inter- and intrareader agreement was almost perfect for effusion grading, but only substantial for synovitis assessment, which is a limitation and likely reflects the nonspecificity of non–contrast-enhanced MRI (17).

In conclusion, the presence of MRI-defined Hoffa-synovitis seems to play a role for incident radiographic OA development, especially in overweight women, whereas obese women have increased odds for radiographic OA even in the absence of Hoffa-synovitis. Presence of joint effusion has an impact on radiographic OA development particularly in overweight and obese women but not men. Being overweight/obese increased odds for joint effusion in the knees that developed incident radiographic OA at time points 1 and 2 years prior. These results suggest that both mechanical load and inflammation have a role in OA incidence for overweight and obese women, while for men, the role of inflammation in conjunction with high BMI appears to be less relevant.

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## 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 submitted for publication. Dr. Roemer 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.** Roemer, Guermazi, Hannon, Fujii, Hunter, Eckstein, Kwoh.

**Acquisition of data.** Roemer, Guermazi, Fujii, Kwoh.

**Analysis and interpretation of data.** Roemer, Guermazi, Hannon, Fujii, Omoumi, Hunter, Eckstein, Kwoh.

## ADDITIONAL DISCLOSURES

Author Hannon is currently an employee of Pinney Associates but was employed by the University of Pittsburgh during the time the study was conducted. Author Eckstein is an employee of Chondrometrics.

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