

## Examining sex differences in knee pain: the Multicenter Osteoarthritis Study



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### SUMMARY

**Objective:** To determine whether women experience greater knee pain severity than men at equivalent levels of radiographic knee osteoarthritis (OA).

**Design and methods:** A cross-sectional analysis of 2712 individuals (60% women) without knee replacement or a recent steroid injection. Sex differences in pain severity at each Kellgren–Lawrence (KL) grade were assessed by knee using visual analog scale (VAS) scale and Western Ontario and McMaster Universities Arthritis Index (WOMAC) with and without adjustment for age, analgesic use, Body mass index (BMI), clinic site, comorbid conditions, depression score, education, race, and widespread pain (WSP) using generalized estimating equations. Effect sizes (Cohen's *d*) were also calculated. Analyses were repeated in those with and without patellofemoral OA (PFOA).

**Results:** Women reported higher VAS pain at all KL grades in unadjusted analyses ( $d = 0.21$ – $0.31$ ,  $P < 0.0001$ – $0.0038$ ) and in analyses adjusted for all covariates except WSP ( $d = 0.16$ – $0.22$ ,  $P < 0.0001$ – $0.0472$ ). Pain severity differences further decreased with adjustment for WSP ( $d = 0.10$ – $0.18$ ) and were significant for KL grade  $\leq 2$  ( $P = 0.0015$ ) and 2 ( $P = 0.0200$ ). Presence compared with absence of WSP was associated with significantly greater knee pain at all KL grades ( $d = 0.32$ – $0.52$ ,  $P < 0.0001$ – $0.0008$ ). In knees with PFOA, VAS pain severity sex differences were greater at each KL grade ( $d = 0.45$ – $0.62$ ,  $P = 0.0006$ – $0.0030$ ) and remained significant for all KL grades in adjusted analyses ( $d = 0.31$ – $0.57$ ,  $P = 0.0013$ – $0.0361$ ). Results using WOMAC were similar.

**Conclusions:** Women reported greater knee pain than men regardless of KL grade, though effect sizes were generally small. These differences increased in the presence of PFOA. The strong contribution of WSP to sex differences in knee pain suggests that central sensitivity plays a role in these differences.

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### Introduction

Women are at greater risk for developing knee osteoarthritis (OA)<sup>1,2</sup> compared with men, particularly those over 50 years of age<sup>2</sup>. Women with OA have also been found to have greater levels of knee pain and lower function<sup>3–6</sup>. However, a greater prevalence of radiographic knee OA in women<sup>7,8</sup> could account for sex differences in knee pain and function<sup>3,4</sup>. Few studies have examined the degree to which the symptoms of knee OA differ between men and women after accounting for the degree of radiographic severity.

In addition to OA, several chronic musculoskeletal pain conditions are overrepresented in women such as temporomandibular disorders, headaches, and fibromyalgia<sup>9</sup>, all of which are generally thought to involve central sensitization. Indeed, the term, “central sensitivity syndromes”<sup>10</sup> has been coined to represent a number of these frequently comorbid chronic pain conditions that may share altered central pain processing<sup>11</sup>. The predominance of women with central sensitivity syndrome diseases might suggest that women are at greater risk for enhanced pain related to central sensitization than men.

Experimental pain studies of sex differences in pain sensitivity in healthy subjects, however, have produced somewhat inconclusive results. A meta-analysis found generally greater pain sensitivity in women than men for pain threshold and tolerance to a

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variety of noxious stimuli, with mean effect sizes ranging from  $d = 0.09$  to  $0.82$ <sup>12</sup>. In contrast, a recent review of the literature concluded little additional evidence is available to support clear sex differences in acute pain sensitivity<sup>9</sup>. Others have suggested women may be more susceptible to centrally-mediated pain than men, since they show greater temporal summation to heat pain<sup>13</sup> and greater referred pain in response to intramuscular experimental pain<sup>14</sup>, and less conditioned pain modulation<sup>15</sup>. However, clinical studies of knee OA have been lacking in their explicit examination of sex differences in pain sensitivity, likely in part due to the inherently confounding issue of disease severity.

Thus, the primary purpose of this study was to examine whether women exhibit greater pain than men despite similar levels of radiographic knee OA, using a large epidemiological study of adults with or at risk for knee OA. Our secondary aim was to define the role of widespread pain (WSP) in men and women, as an indication of the presence of heightened “central sensitivity”.

## Methods

### Study sample

For this cross-sectional analysis, data from the baseline examination of the Multicenter Osteoarthritis Study (MOST) were utilized. MOST is an observational study that enrolled 3026 community-dwelling adults aged 50–79 years with knee OA or known risk factors for knee OA including age, female sex, overweight, and history of knee symptoms, knee injury and/or surgery. Participants were from Iowa City, IA, and Birmingham, AL or the surrounding communities. The study design and participant eligibility has been described previously<sup>16</sup>. Participants who had a steroid injection in the past year or with a history of total knee replacement were excluded from this study (Fig. 1). The MOST study was approved by the institutional review boards at the University of Iowa; University of Alabama, Birmingham; University of

California, San Francisco; and Boston University Medical Center. All participants provided written, informed consent.

### Assessments

#### Analgesic use

Participants provided information on analgesic medication (salicylate, non-steroidal anti-inflammatory drug (NSAID), opioid and “other” analgesic that included acetaminophen and other analgesics and antipyretics) use through an interviewer-administered questionnaire at the clinic visit. Participants were asked whether medications were used on an intermittent or regular basis. Analyses controlled for regular use of analgesic medications.

#### Anthropometric measures

Body mass index (BMI,  $\text{kg/m}^2$ ) was calculated from weight in kilograms divided by the square of the height in meters (Stadiometer, Holtain, Wales, UK), as measured by trained and certified staff at the clinic visit.

#### Comorbid conditions

Participants completed the Charlson Comorbidity Index, a validated classification system of comorbid conditions<sup>17</sup>. Responses were categorized as none, one, and two or more comorbid conditions.

#### Depressive symptoms score

The Center for Epidemiologic Studies Depression Scale (CES-D)<sup>18</sup> was utilized as an indicator of depressive symptoms. The instrument includes 20 items which query participants' feelings over the past 7 days. A score of 16 or greater has been used as an indicator of depression<sup>19</sup>.

#### Education

Participants provided information on the highest grade or year of school completed. Responses were categorized into one of three categories: less than high school education, completion of high school and at least some college.

#### Knee radiographs

Weight-bearing, fixed-flexion posteroanterior and lateral radiographs of the knees were obtained at baseline according to the MOST radiograph protocol as previously described<sup>20</sup>. Each participant's radiographs were scored by two independent readers (an experienced academically-based musculoskeletal radiologist and a rheumatologist experienced in study reading) according to Kellgren–Lawrence (KL) scale at the tibiofemoral joint. Participants who attended both the baseline MOST visit and a follow-up visit had their baseline radiographs evaluated for the presence of patellofemoral (PF) OA. Their PFOA status was indicated as present if there was an osteophyte grade  $\geq 2$  or if there was an osteophyte grade  $\geq 1$  plus presence of PF joint space narrowing (JSN)  $\geq 2$  or sclerosis  $\geq 2$  or cysts  $\geq 2$ <sup>21</sup>.

#### Pain

We used two assessments to characterize knee-specific pain. Average knee pain over the past 30 days was assessed on a 0–100 mm visual analog scale (VAS), with anchors of 0 indicating ‘no pain’ and 100 indicating ‘pain as bad as it could be’ for each knee. Pain during activities (i.e., walking, standing, stairs) was assessed using a subset of questions from the Western Ontario and McMaster Universities Arthritis Index (WOMAC pain) for each knee. This subscale comprises five items with responses that range from no (0) to extreme (4) pain with a possible total score of 20. Higher scores on the WOMAC indicate greater pain. WOMAC scores were

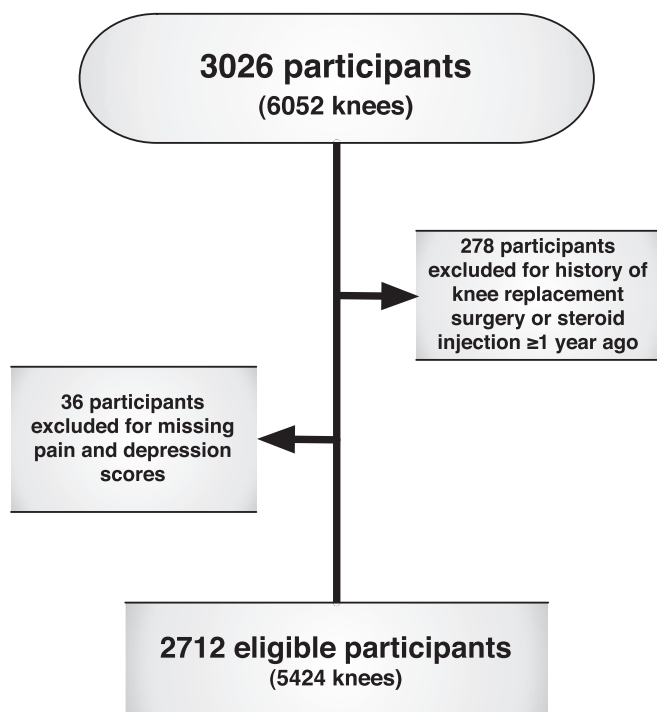


Fig. 1. Participant inclusion diagram.

also rescaled to a range of 0–100% for analyses. Differences in pain severity between men and women were evaluated according to effect sizes as well as whether differences were clinically important (minimal clinically important differences (MCID)). The MCID utilized in this study was a difference of  $\geq 6\%$  of the maximal score<sup>22,23</sup>. This corresponded to six points for VAS and rescaled WOMAC pain.

### WSP

WSP was ascertained using a homunculus. It was defined using American College of Rheumatology 1990 classification criteria<sup>24</sup>. WSP was considered present if participants reported pain in all five regions of the body including axial pain, pain both above and below the waist and pain on both the right and left sides of the body.

### Statistical methods

Participant characteristics were summarized with frequencies and means for both the eligible study cohort and those excluded. Comparisons between men and women as well as between the eligible and excluded participants for each covariate were assessed using *t*-tests for continuous and chi-square tests for categorical variables.

Histograms of knee pain severity and results of normality tests (Shapiro–Wilk, Kolmogorov–Smirnov) revealed knee pain severity did not follow a normal distribution. The knee was the basic unit of analysis with each participant providing two knees. Knee-specific pain assessments were compared between men and women using generalized estimating equations to control for the covariance between knees in the same subject and stratified by the radiographic severity of each knee: KL grade <2, 2, 3, and 4. This method may also be used on data that are clustered and do not follow a normal distribution. Differences in knee pain severity were compared between men and women with the following models: Model (1) unadjusted estimate; Model (2) adjusted for age, BMI (kg/m<sup>2</sup>), comorbidities (none, one, two or more), CES-D score, clinic site, educational level, frequent use of pain medications, and race; Model (3) Model 2 further adjusted for the presence of WSP. All analyses were adjusted for KL grade of the contralateral knee. We also examined whether PFOA status had an impact on sex differences in pain severity in sub-analyses. These analyses were conducted separately because the severity of PFOA was not graded. PFOA was defined as present or absent. All except for 376 knees from eligible participants met criteria for evaluation of PFOA status. The same analyses (Model 1, Model 2 and Model 3) were repeated in knees with and without PFOA separately. Adjusted and unadjusted least square (LS) means, 95% confidence intervals (CIs) and Standard Error (SE) for all analyses and standardized effect sizes (Cohen's *d*, positive = greater pain in women) were computed. Effect sizes were defined as small (*d* = 0.2), medium (*d* = 0.5) or large (*d* = 0.8)<sup>25</sup>.

LS means are defined as the linear combination of the estimated effects from a linear model. Analyses were completed using the statistical software SAS Version 9.3 (SAS Institute Inc., Cary, NC) and significance was set at an alpha level of 0.05 throughout.

### Results

A total of 2712 subjects (5424 knees) were included in the current study (Fig. 1). The proportion of men and women did not significantly differ between those excluded due to knee replacement surgery, steroid injection in the past year or missing pain or covariate data (*n* = 314) and those included. However, the excluded cohort tended to be slightly older (mean  $\pm$  SD: 65.3  $\pm$  7.9 vs 62.2  $\pm$  8.1 years, *P* < 0.0001), have a slightly higher BMI (32.5  $\pm$  6.6 vs 30.5  $\pm$  5.9 kg/m<sup>2</sup>, *P* < 0.0001), more comorbid conditions (20.1%

**Table 1**

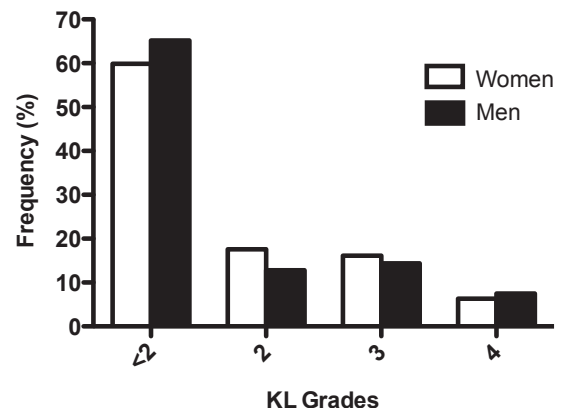
Characteristics of women compared with men (mean  $\pm$  SD or % as indicated)

Characteristic	Women ( <i>n</i> = 1618)	Men ( <i>n</i> = 1094)	<i>P</i> -value
Age at baseline (years)	62.3 $\pm$ 7.9	62.0 $\pm$ 8.3	0.48
BMI (kg/m <sup>2</sup> )	30.6 $\pm$ 6.3	30.4 $\pm$ 5.1	0.27
Race (% Caucasian)	83.7%	85.3%	0.26
Education (% > high school)	41.2%	50.9%	<0.0001
Site (% University of Iowa)	51.5%	49.8%	0.38
WSP %	56.2%	40.4%	<0.0001
CES-D score $\geq$ 16 (%)	13.5%	7.9%	<0.0001
Comorbidities (% $\geq$ 1 reported)	12.2%	13.2%	0.39
Bilateral knee OA (%)	29.2%	22.3%	<0.0001
PFOA (%)	22.2%	18.0%	0.0089
Salicylate use (%)	34.5%	46.7%	<0.0001
NSAID use (%)	25.0%	17.3%	<0.0001
Opioid use (%)	3.5%	2.7%	0.29
Other analgesic use (%)	8.8%	4.9%	0.0001

vs 12.6% with  $\geq 2$  comorbid conditions, *P* < 0.0001), had a greater percentage with WSP (55.1% vs 49.9%, *P* < 0.0001), and less education (35.0% vs 45.1% with  $\geq$  high school education, *P* = 0.0006) than those included.

Within the included study cohort, more women than men reported depressive symptoms, WSP, and had bilateral radiographic knee OA and PFOA (Table 1). Analgesic medication use differed between men and women with a greater percentage of men reporting frequent salicylate analgesic use and a greater percentage of women used NSAIDs (Table 1). The distribution of men and women with knees at each KL grade was significantly different (*P* < 0.0001) with a higher proportion of women's knees with radiographic knee OA (40.0% KL  $\geq 2$ ) than men (34.8% KL  $\geq 2$ ), particularly with KL grade = 2 (Fig. 2, 17.6% vs 12.8%). There were 376 out of the eligible 5424 knees (6.9% of eligible knees) missing information about PFOA status. Participants not missing PFOA data were similar in characteristics to those included in the primary analyses. For example, there were no significant differences in age, BMI, percent with bilateral knee OA, percent with at least two comorbid conditions, percent with a CES-D score indicating depressive symptoms, percent with a level of education greater than high school, percent with frequent medication use, percent with WSP or percent women.

For those missing PFOA information compared with those not missing PFOA information, age and percent women did not significantly differ, BMI was slightly greater (mean  $\pm$  SD: 31.4  $\pm$  6.2 vs 30.5  $\pm$  5.8, *P* = 0.0380), percent with WSP was greater (58.8% vs 55.1%, *P* = 0.0110) and percent with more than a high school education was lower (36.4% vs 45.7%, *P* = 0.0447).



**Fig. 2.** Frequency of knees by KL grade in women and men.

**Table II**  
Estimated differences (LS mean  $\pm$  SE, 95% CI, *P*-value) in pain levels in knees between women and men by KL grade

KL grade	Unadjusted*		Adjusted†		Adjusted‡	
<b>VAS pain (0–100)</b>						
KL < 2 ( <i>n</i> = 3365)	4.2 $\pm$ 0.7 (2.8–5.7)	<0.0001	3.3 $\pm$ 0.7 (1.9–4.6)	<0.0001	2.1 $\pm$ 0.7 (0.8–3.5)	0.0015
KL = 2 ( <i>n</i> = 852)	5.3 $\pm$ 1.6 (2.1–8.5)	0.0015	4.6 $\pm$ 1.5 (1.6–7.6)	0.0036	3.5 $\pm$ 1.5 (0.6–6.4)	0.0200
KL = 3 ( <i>n</i> = 838)	6.4 $\pm$ 1.8 (2.9–10.0)	0.0004	4.2 $\pm$ 1.7 (0.8–7.5)	0.0151	3.2 $\pm$ 1.7 (–0.1–6.6)	0.0566
KL = 4 ( <i>n</i> = 369)	7.6 $\pm$ 2.6 (2.5–12.7)	0.0038	5.0 $\pm$ 2.5 (0.1–9.9)	0.0472	4.4 $\pm$ 2.5 (–0.5–9.3)	0.0792
<b>WOMAC pain (0–100%)</b>						
KL < 2 ( <i>n</i> = 3365)	3.6 $\pm$ 0.6 (2.3–4.9)	<0.0001	2.6 $\pm$ 0.6 (1.4–3.7)	<0.0001	1.5 $\pm$ 0.6 (0.3–2.6)	0.0115
KL = 2 ( <i>n</i> = 852)	4.8 $\pm$ 1.4 (2.1–7.5)	0.0007	4.2 $\pm$ 1.3 (1.6–6.7)	0.0016	3.1 $\pm$ 1.2 (0.7–5.6)	0.0128
KL = 3 ( <i>n</i> = 838)	6.0 $\pm$ 1.5 (3.0–9.1)	0.0001	3.9 $\pm$ 1.4 (1.1–6.7)	0.0059	2.8 $\pm$ 1.4 (0.1–5.6)	0.0436
KL = 4 ( <i>n</i> = 369)	3.9 $\pm$ 2.1 (–0.1–8.0)	0.0605	1.3 $\pm$ 1.9 (–2.5–5.1)	0.4932	0.8 $\pm$ 2.0 (–3.0–4.7)	0.6699

\* Adjusted for contralateral knee KL grade.

† Adjusted for age, BMI, depression score, education, clinic site, race, comorbid conditions and analgesic medication use.

‡ Further adjusted for presence of WSP.

### VAS pain

Women consistently reported greater or equal knee pain compared with men at each KL grade as shown in Table II. In unadjusted analyses (Model 1), pain was greater in women than men at each KL grade, but only clinically significant for KL grades  $\geq 3$ . The associated effect sizes for differences were small and ranged from 0.2 (KL grades  $\leq 2$ ) to 0.3 (KL grades  $\geq 3$ ). After adjusting for covariates (Model 2), sex differences in VAS pain remained significantly higher in women than in men for all KL grades. In addition, adjustment for WSP (Model 3) reduced the differences in pain levels between men and women such that differences only remained significant for KL grades  $\leq 2$ . At all KL grades, presence of WSP (Model 3) was associated with greater pain severity with mean VAS pain scores 7.5–10.7 higher than in those without WSP ( $P < 0.0001$  for KL grades  $< 2$ –3 and  $P = 0.0008$  for KL grade 4). There was a significant interaction between sex and presence of WSP ( $3.0 \pm 1.4$ , 95% CI = 0.3–5.6,  $P = 0.0288$ ) such that pain severity was significantly greater in women with WSP compared with men with WSP.

### WOMAC pain

Analyses repeated using WOMAC pain were similar to those using VAS pain (Table II). However, in unadjusted (Model 1) and adjusted analyses (model 2), differences in pain severity were not statistically or clinically significant for KL grade 4.

### Subanalyses in knees with PFOA data

In knees with PFOA, women reported pain of greater severity for all KL grades in unadjusted analyses (Model 1) for VAS pain and for

all KL grades  $< 4$  for WOMAC pain. Adjusted models (Models 2 and 3) slightly reduced the estimated differences though they remained statistically significant for all KL grades for VAS pain (Table III) and all KL grades  $< 4$  for WOMAC pain (Table IV). In most cases, statistically significant differences also met or exceeded clinically important differences. Effect sizes for unadjusted analyses of PFOA were much higher than for the analyses of TFOA data. For VAS pain, effect sizes were moderate (KL grades  $< 2$  and 4 = 0.5 and KL grade 2 = 0.6) or small (KL grade 3 = 0.4). For WOMAC pain, effect sizes were also moderate (KL grades 2 and 3 = 0.5) or small (KL grade  $< 2$  = 0.4, KL grade 4 = 0.3).

In knees without PFOA, however, statistically significant differences were only present in knees with a KL grade  $< 2$ , KL grade = 2 (WOMAC only) or KL grade = 3 in unadjusted analyses (Model 1). In adjusted analyses (Models 2 and 3), differences remained statistically significant for KL grade  $< 2$  (i.e., no evidence of radiographic TFOA or PFOA). Sex differences in VAS pain scores for knees without PFOA are shown in Table III by KL grade while differences in WOMAC pain are shown in Table IV. In all cases, where statistically significant, differences among knees without PFOA were small and did not meet the cut-offs for clinical significance. In addition, all effect sizes were  $\leq 0.2$ .

### Discussion

The main results of this study showed that women generally reported greater pain at all KL grades compared with men, especially in the presence of PFOA. These sex differences also were found prior to the onset of radiographic knee OA (TFOA KL grade  $< 2$ ) and were present regardless of adjustment for covariates in knees without PF or TFOA. Indeed, Maleki-Fischbach and Jordan<sup>26</sup> suggested that more studies need to specifically examine sex

**Table III**  
Estimated differences (LS mean  $\pm$  SE, 95% CI, *P*-value) in VAS pain levels (0–100) between women and men by KL grade in knees with PFOA and without PFOA

KL grade	Unadjusted*		Adjusted†		Adjusted‡	
<b>+ PFOA</b>						
KL < 2 ( <i>n</i> = 160)	9.2 $\pm$ 2.9 (3.6–14.8)	0.0025	8.9 $\pm$ 3.0 (3.1–14.7)	0.0048	7.1 $\pm$ 2.9 (1.5–12.7)	0.0184
KL = 2 ( <i>n</i> = 248)	12.2 $\pm$ 3.1 (6.1–18.4)	0.0006	15.1 $\pm$ 3.0 (9.2–21.1)	<0.0001	11.5 $\pm$ 3.2 (5.2–17.8)	0.0013
KL = 3 ( <i>n</i> = 238)	10.8 $\pm$ 3.3 (4.4–17.3)	0.0018	8.3 $\pm$ 3.1 (2.2–14.4)	0.0085	7.0 $\pm$ 3.1 (1.0–13.0)	0.0251
KL = 4 ( <i>n</i> = 179)	11.4 $\pm$ 3.7 (4.2–18.6)	0.0030	8.9 $\pm$ 3.6 (1.9–16.0)	0.0165	8.0 $\pm$ 3.7 (0.7–15.3)	0.0361
<b>– PFOA</b>						
KL < 2 ( <i>n</i> = 3205)	3.9 $\pm$ 0.7 (2.5–5.4)	<0.0001	3.0 $\pm$ 0.7 (1.6–4.3)	<0.0001	1.9 $\pm$ 0.7 (0.5–3.2)	0.0062
KL = 2 ( <i>n</i> = 604)	3.0 $\pm$ 1.9 (–0.6–6.7)	0.1072	1.9 $\pm$ 1.7 (–1.5–5.3)	0.2868	1.5 $\pm$ 1.7 (–1.8–4.8)	0.3725
KL = 3 ( <i>n</i> = 600)	5.2 $\pm$ 2.1 (1.1–9.3)	0.0144	2.5 $\pm$ 2.0 (–1.4–6.4)	0.2021	1.8 $\pm$ 2.0 (–2.1–5.7)	0.3621
KL = 4 ( <i>n</i> = 190)	5.3 $\pm$ 3.5 (–1.6–12.2)	0.1383	2.4 $\pm$ 3.2 (–4.0–8.6)	0.4727	1.8 $\pm$ 3.1 (–4.3–7.9)	0.5619

\* Adjusted for contralateral knee KL grade and PFOA status.

† Adjusted for age, BMI, depression score, education, clinic site, race, comorbid conditions and analgesic medication use.

‡ Further adjusted for presence of WSP.

**Table IV**  
Estimated differences (LS mean  $\pm$  SE, 95% CI, *P*-value) in WOMAC pain levels (0–100%) between women and men by KL grade in knees with PFOA and without PFOA

KL grade	Unadjusted*		Adjusted†		Adjusted‡	
<b>+ PFOA</b>						
KL < 2 ( <i>n</i> = 160)	6.2 $\pm$ 2.6 (1.2–11.2)	0.0185	5.3 $\pm$ 2.5 (0.4–10.1)	0.0408	3.9 $\pm$ 2.5 (–0.9–8.7)	0.1282
KL = 2 ( <i>n</i> = 248)	9.3 $\pm$ 2.7 (4.1–14.6)	0.0019	12.3 $\pm$ 2.5 (7.5–17.2)	<0.0001	8.9 $\pm$ 2.6 (3.8–14.0)	0.0019
KL = 3 ( <i>n</i> = 238)	9.8 $\pm$ 2.9 (4.2–15.4)	0.0013	7.6 $\pm$ 2.8 (2.2–13.0)	0.0075	6.3 $\pm$ 2.8 (0.9–11.7)	0.0269
KL = 4 ( <i>n</i> = 179)	5.2 $\pm$ 2.7 (–0.01–10.4)	0.0537	3.5 $\pm$ 2.5 (–1.5–8.4)	0.1808	2.8 $\pm$ 2.7 (–2.4–8.0)	0.3026
<b>– PFOA</b>						
KL < 2 ( <i>n</i> = 3205)	3.5 $\pm$ 0.7 (2.2–4.7)	<0.0001	2.4 $\pm$ 0.6 (1.2–3.6)	<0.0001	1.4 $\pm$ 0.6 (0.2–2.5)	0.0214
KL = 2 ( <i>n</i> = 604)	3.1 $\pm$ 1.6 (0.05–6.2)	0.0484	1.9 $\pm$ 1.5 (–1.0–4.8)	0.2086	1.5 $\pm$ 1.4 (–1.3–4.3)	0.2868
KL = 3 ( <i>n</i> = 600)	4.9 $\pm$ 1.8 (1.4–8.4)	0.0064	2.4 $\pm$ 1.6 (–0.7–5.6)	0.1384	1.4 $\pm$ 1.6 (–1.7–4.5)	0.3681
KL = 4 ( <i>n</i> = 190)	3.2 $\pm$ 2.8 (–2.4–8.7)	0.2716	0.5 $\pm$ 2.6 (–4.6–5.6)	0.8460	0.1 $\pm$ 2.5 (–4.9–5.0)	0.9836

\* Adjusted for contralateral knee KL grade and PFOA status.

† Adjusted for age, BMI, depression score, education, clinic site, race, comorbid conditions and analgesic medication use.

‡ Further adjusted for presence of WSP.

differences in various assessments of OA, and whether risk factors for OA act similarly in both men and women, rather than simply controlling for sex.

Our results are consistent with previous findings. In one large cohort study, a greater proportion of women had symptomatic knee OA than men, when stratifying by knee OA grade<sup>27</sup>. Similarly, in a Korean population, symptom severity was greater in women compared with men at the same KL grade, with the exception of KL grade 3<sup>28</sup>. However, that particular KL grade comparison was likely underpowered. In a study conducted in the Netherlands, Schiphof *et al.* found being female was a significant risk factor for knee pain, but the increased risk for women was not KL grade specific<sup>29</sup>. In a study involving adults scheduled for knee replacement surgery, women were found to have greater pain intensity during movement and pain sensitivity compared with men<sup>6</sup>. Lastly, in a study of older adults with knee pain, men were found to have a higher incidence of radiographic disease<sup>30</sup>, suggesting women had similar pain despite less severe disease. Our findings further expand on these previous studies by considering PFOA and covariates that may account for sex differences, radiographic status of the contralateral knee, and study of a larger sample size. While gender-related pain changes have been observed when considering either TFOA or PFOA, few studies have attempted to consider both variables in the same study. Thus, in addition to the large sample size, this study uniquely considered the presence of PFOA in addition to KL grade when evaluating sex differences.

Results from the main analyses in our study in knees with radiographic TFOA showed that sex differences in knee pain severity were largely explained by BMI, depressive symptoms, comorbid conditions, socioeconomic status, and, especially, presence of WSP. However, significant differences generally remained following adjustment for all covariates for KL grades <4, suggesting additional unmeasured factors may contribute to knee pain severity differences between men and women at these particular grades. For example, KL grade 2 corresponds with presence of osteophytes while KL grade 3 corresponds with the onset of JSN which was found to have a stronger association with knee pain than osteophytes in a large cohort study<sup>31</sup>. Though not detectable by radiography, JSN may reflect loss of cartilage as well as features associated with knee pain such as meniscal extrusion<sup>32,33</sup>. However, we found estimates for differences in knee pain severity between women and men were slightly lower for KL grade 3 than for KL grade 2. In our study, sex differences were typically the least pronounced at the highest KL grade (KL grade 4). In those cases, the underlying nociceptive input from the damaged knees may override other factors contributing to the heterogeneous pain experience, such as multiple psychosocial, experimental, genetic, and neurochemical variables that can influence sex differences in both clinical and experimental pain perception<sup>34</sup>.

The largest differences we observed for pain severity were in knees with PFOA. This is consistent with previous data that show PFOA is an important contributor to knee pain<sup>35,36</sup>. It has also been suggested that risk factors for TFOA and PFOA may differ<sup>37,38</sup>, which could explain why WSP had a more significant effect on pain severity differences between men and women with TFOA than in knees with both PFOA and TFOA. Thus, our findings support evaluation of the PF joint in addition to the more commonly evaluated TF joint in studies of knee OA and knee pain.

The reasons for the sex differences in knee OA and knee OA symptoms have yet to be fully elucidated. It has been suggested that sex differences in hormones, body composition, psychosocial characteristics, knee structure and neural processing may play a role. Several studies have examined the role of estrogens on knee OA. While results support a contribution to knee OA<sup>39–41</sup>, the evidence is not definitive. BMI has been found to be highly predictive of both knee OA<sup>42,43</sup> and knee pain<sup>44</sup> and, similar to our study, BMI is generally greater in women than in men. Psychosocial characteristics such as depression may also contribute. For example, it has been reported that women have higher rates of depression<sup>45</sup>, which has also been associated with pain<sup>46</sup>. In addition, structural differences between men and women, including cartilage thickness, volume, and joint surface area have been documented<sup>47–49</sup>.

The evidence for the role of central sensitization in various pain conditions is growing. While WSP is not a measure of central sensitivity, it is believed to involve centrally-mediated processes<sup>50</sup>. Our hypothesis, that presence of WSP would be associated with greater knee pain for each radiographic knee OA severity level was supported. We also found a higher proportion of women than men with some degree of WSP at baseline. Since women may be more susceptible to centrally-mediated pain than men<sup>13–15</sup>, a proportion of the observed sex differences in those with OA could be a result of centrally-mediated mechanisms. However, presence of WSP did not appear to explain sex differences in pain severity in knees with PFOA.

Our findings should be interpreted in light of the following limitations. First, we categorized individuals by radiographic tibiofemoral KL grades and presence/absence of PFOA, though these grades cannot fully represent differences in peripheral joint disease, such as synovitis or other pathologies, that may further contribute to sex differences. In addition, categorization of knees by presence or absence of PFOA was less precise than grading structural changes at the PF joint and it is possible that women may have had more severe PFOA than men in our study, but this could not be determined from the available data. Despite our less precise assessment of the PF joint, we found differences in pain severity between men and women with PFOA were clinically significant for all KL grades for VAS pain and all KL grades <4 for

WOMAC pain. We found the magnitude of the sex-differences in pain, though significant, to be relatively small for TFOA. In particular, these differences required relatively large sample sizes to be adequately powered, especially for knees with KL grades <2. This is likely one of the reasons this issue has not been well characterized in previous studies. Lastly, this analysis evaluated sex differences in knee pain, controlling for radiographic severity, but did not include measures of central sensitization. Future studies further examining whether these observed sex differences could be explained by sex differences in central pain modulation would be desirable. However, this information advances our general understanding of sex differences in knee pain due to OA, which may assist in the care of individual patients despite the relatively small overall mean effect size. That is, numerous factors likely contribute to pain variability, but greater pain in women, even after controlling for numerous confounding variables, was consistently observed.

In summary, women report greater knee pain than men despite similar levels of radiographic knee OA. Thus, a disparity in disease impact for knee OA between men and women was observed, and exists prior to the onset of radiographic knee OA. However, sex differences were in part ameliorated by considering the presence of PF knee OA; supporting that the PF joint, in addition to the TF joint, should be included in future studies of knee pain. The strong association between pain severity and presence of WSP suggests that central sensitivity may be one component contributing to the observed sex differences.

#### Author contributions

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#### Competing interest statement

The authors have no professional relationships with companies or manufacturers who will benefit from the results of the present study.

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