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Psychological and pain sensitisation characteristics are associated with patellofemoral osteoarthritis symptoms: The Multicenter Osteoarthritis Study

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CONFLICTS OF INTEREST

A. Guermazi is the President and shareholder of Boston Imaging Core Lab (BICL), LLC, and consultant to Pfizer, MerckSerono, GE, TissueGene, OrthoTrophix, AstraZeneca and Sanofi. F. Roemer is a CMO and shareholder of BICL, LLC.

Abstract

Objective: Determine the relation of symptomatic and structural features of patellofemoral osteoarthritis (PFOA) to psychological characteristics and measures of pain sensitisation, in older adults with or at risk of knee OA.

Methods: 1112 participants from the Multicenter Osteoarthritis Study were included (713 females; mean±SD age 66.8±7.6 years, body mass index 29.5±4.8 kg/m^2). Participants were grouped based on presence of PFOA symptoms (anterior knee pain and pain on stairs) and MRI PFOA (full-thickness cartilage lesion with bone marrow lesion): (i) PF symptoms with MRI PFOA; (ii) PF symptoms without MRI PFOA; (iii) MRI PFOA without PF symptoms; and (iv) no PF symptoms or MRI PFOA (no PFOA). Relation of PFOA classification to depressive symptoms, catastrophizing, temporal summation (TS) and pressure pain thresholds (PPTs) was evaluated using logistic (categorical variables) and linear regression (continuous variables).

Results: Compared with no PFOA, those with PF symptoms with or without MRI PFOA had significantly greater odds of depressive symptoms, catastrophising and patellar TS (odds ratios 1.5–2.01), and those with PF symptoms without MRI PFOA had significantly greater odds of wrist TS (1.66). Males with PF symptoms without MRI PFOA had significantly lower PPT at the patella compared with not PFOA and those with MRI PFOA only (no symptoms). There were no significant differences at the wrist for males, or the patella or wrist for females.

Conclusion: Persons with PFOA symptoms, regardless of MRI PFOA status, are more likely to demonstrate depressive symptoms, catastrophizing and TS. Males with PFOA symptoms without MRI PFOA demonstrate local hyperalgesia.

Keywords

Knee; osteoarthritis; pain; magnetic resonance imaging

Patellofemoral osteoarthritis (PFOA) is a distinct and important subgroup of knee OA, resulting in pain around or behind the patella during weight bearing activities (e.g. squatting, stair ambulation) (1). The PF joint is frequently the first knee joint compartment affected by OA, and the presence of isolated symptomatic PFOA increases the risk of an individual developing OA in their tibiofemoral (TF) joint (2). Radiographic and MRI features of PFOA have a stronger association with pain and disability than those in the TF joint (1). Importantly, PFOA tends to affect younger people than TFOA. Radiographic evidence of PFOA is present in 24% of adults with PF pain aged 26–50 years (3), and 55% with PF pain aged 40–50 years (4). Thus, the impact of symptomatic PFOA is likely to have substantial effects across occupational tasks, domestic and parenting duties, and physical activity, for a longer proportion of the lifespan.

Preliminary studies suggest that PFOA may be a sequela of PF pain in adolescence and younger adults (5). The two conditions share similar symptoms, impairments, and biomechanical characteristics (6). As the identity and evidence for PFOA has developed, studies have focused on characterising the biomechanical features of the condition (7), and evaluating the effects of biomechanical interventions (e.g. bracing, taping, exercise, manual therapy) (8, 9). However, findings in similar populations indicate that non-mechanical

features may also contribute to PFOA symptoms and function. Younger adults with PF pain demonstrate psychological impairments that are related to pain and function (10, 11). Similarly, older adults with knee OA have increased risk of developing depression compared with people without OA (12).

Beyond psychological factors, other non-mechanical factors that have been increasingly studied in OA are neurobiological alterations in pain signalling that can influence the pain experience. One such mechanism is pain sensitization, which reflects facilitation in peripheral or central nociceptive signalling (i.e., peripheral and central sensitization, respectively). Measures of pain sensitisation (lower pressure pain threshold, presence of mechanical temporal summation) have been associated with greater pain severity in older adults with knee OA, though whether there are differences between TF and PFOA as not been studied to date (13)(14). Of note, younger adults with PF pain also have lower pressure pain thresholds at local and remote sites compared to pain-free controls, indicating the presence of mechanical hyperalgesia (15, 16), likely reflecting peripheral sensitization. Taken together, these findings suggest that people with PFOA may also demonstrate psychological impairments and pain sensitisation, which may affect their response to traditional mechanical interventions. Although a recent study found no statistical differences in pressure pain threshold between people with PFOA and controls (17), their small sample size warrants further investigation of pain sensitisation measures in this population. Without understanding contributions to PFOA symptoms beyond biomechanical aspects of the disease, a large burden of symptoms may remain unaddressed for those with PFOA.

The aim of this study was to determine whether symptomatic and structural features of PFOA are related to psychological characteristics and measures of pain sensitisation, in older adults with or at risk of knee OA.

MATERIALS AND METHODS

Participants

The Multicenter Osteoarthritis Study (MOST) is a NIH-funded longitudinal cohort of 3026 people with or at risk of knee OA. The study design has been outlined in detail previously (18). Briefly, participants aged 50–79 years (at baseline) were recruited from Iowa City, Iowa and Birmingham, Alabama (USA), and standardised measures collected at baseline and 15, 30, 60, 72, and 84 months. Ethical approval was obtained from the institutional reviews boards of the University of Iowa (#201511711), University of Alabama at Birmingham (#000329007), University of California, San Francisco (UCSF) (#10–00500), and Boston University Medical Center (#H-32956).

This cross-sectional analysis utilised data from the MOST 60-month visit, at which time measures relevant to this study were obtained.

Pain measures

Two measures from the MOST participants were used to define the presence of PF-related symptoms. These were selected based on consensus-based criteria (1, 7). A knee pain map was used to identify painful areas around the knee. Participants were asked to mark on the

map where they experienced their knee pain when it was painful, and could select multiple areas if appropriate. Anterior knee pain was defined as present if participants marked the area corresponding to the peripatellar region, regardless of whether other areas were also marked (19).

Participants also completed the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (20). We used the item relating to pain during stair climbing (item 2), which was rated on a 5-point Likert scale (none, mild, moderate, severe, extreme). Pain during stairs was deemed to be present if participants rated experiencing pain during stairs that was at least mild in severity (19).

Participants were then classified as having PF-related symptoms if they had both the presence of anterior knee pain (knee pain map) and at least mild pain on stairs (WOMAC pain item 2).

Magnetic resonance imaging (MRI)

Participants underwent 1.0T extremity MRI of both knees (OrthOneTM, ONI Medical Systems, Wilmington MA), using a phased-array knee coil. Fat-suppressed fast spin echo proton density (PD) weighted sequences were acquired in two planes: (i) sagittal (repetition time (TR) 4800 ms, TE 35 ms, 3 mm slice thickness, 0 mm interslice gap, 32 slices, 288 × 192 matrix, 140 mm^2 field of view (FOV), echo train length 8); and (ii) axial (TR 4680 ms, TE 13 ms, 3 mm slice thickness, 0 mm interslice gap, 20 slices, 288 × 192 matrix, 140 mm^2 FOV, echo train length 8). A short tau inversion recovery (STIR) sequence was also acquired in the coronal plane (TR 6650 ms, TE 15 ms, TI 100 ms, 3 mm slice thickness, 0 mm interslice gap, 28 slices, 256 × 192 matrix, 140 mm^2 FOV, echo train length 8).

For reading of MRIs, one knee of each participant was randomly selected. All MRIs were scored semi-quantitatively by two trained and experienced musculoskeletal radiologists (AG, FWR), using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) (21). WORMS divides the patella, femur, and tibia into 14 subregions, including four PF subregions (medial and lateral patella; medial and lateral trochlea [anterior femur]). Full thickness cartilage loss was defined as WORMS scores of 2.5 (full thickness focal defect <1cm in greatest width), 5 (multiple areas of full-thickness loss, of grade 2.5) or 6 (diffuse [≥75% of the region) full-thickness loss) (22). The presence of a bone marrow lesion (BML) was defined as a WORMS score of ≥1 (bone marrow lesion of any size) (22). Inter-rater reliability was adequate for cartilage (weighted kappa 0.73) and BMLs (0.67) (23).

Participants were classified as having PFOA on MRI if they had both a full-thickness cartilage lesion and a bone marrow lesion in the PF joint (23).

Classification of symptomatic and structural PFOA

Participants were classified into one of four separate PFOA groups, based on the presence of PF symptoms and MRI PFOA: (i) PF symptoms with MRI PFOA; (ii) PF symptoms (no MRI PFOA as defined above); (iii) MRI PFOA (no PF symptoms); and (iv) no PFOA (i.e. no PF symptoms or MRI PFOA).

Psychological variables

Participants completed the Centre for Epidemiological Studies Depression Scale (CES-D) (24) and Coping Strategies Questionnaire (CSQ) (25). The CES-D was dichotomized to indicate the presence (≥16) or absence (<16) of depressive symptoms (26). We used a single item (item 3) from the CSQ to represent pain catastrophising: "*when I feel pain I feel it's terrible and that it's never going to get any better*". Responses were dichotomized to indicate the presence (≥1) or absence (0) of pain catastrophizing.

Quantitative sensory testing

Quantitative sensory testing (QST) comprising mechanical temporal summation (TS) and pressure pain threshold (PPT) was performed at the patella and at the wrist. Specifically, the stimuli were applied over the midpoint of the patella (bilaterally), and distally over the dorsal aspect of the distal radioulnar joint (right side unless contraindicated). Participants were positioned in supine for measurement of patellar TS and PPT, and were seated with their test forearm resting on a flat surface for the wrist TS and PPT measures. QST procedures in the MOST cohort have been detailed previously (13).

TS was assessed using a 60g von Frey filament (Aalborg University, Denmark). Participants were asked to rate the pain experienced during four baseline stimulations over the test site to obtain a baseline score (0–10 numerical rating scale; higher scores indicate worse pain). The monofilament stimulus was then applied over the test site for 30 seconds, at a rate of 1 Hz. Participants rated their pain again immediately after the repeated stimulus, and 15 seconds after cessation. Temporal summation was defined as being present if participants reported increased pain after the test stimulus, compared with baseline. Test-retest reliability (14 days) for temporal summation was κ 0.61 (13).

PPT was measured over each test site using a hand-held algometer with a $1cm^2$ rubber tip (FDIX25, Wagner Instruments, Greenwich, CT, USA). Pressure was applied at a rate of 0.5kg/s. Participants were instructed to indicate when the pressure first changed to slight pain. Three repetitions were recorded at each site (kg/cm^2). The average of three repetitions was calculated for each site for use in further analyses, with lower PPT values indicating greater mechanical pain sensitivity. Test-retest reliability for PPT ranged from 0.85 to 0.90 (intraclass correlation coefficients) (13).

Statistical analysis

We evaluated the relation of the four PFOA categories (based on PF symptoms and MRI PFOA defined above) to the outcomes of interest using logistic regression for those outcomes that were dichotomous (presence of depressive symptoms, pain catastrophizing, and TS); the referent group in all analyses was the group with no PF symptoms or MRI PFOA (no PFOA). Because PPT ranges differ among men and women (27), the mean PPT for each of the four categories were assessed separately for males and females using linear regression. All analyses were adjusted for age, sex (except for PPT analyses), body mass index (BMI) and MRI features of TFOA (presence of full thickness cartilage lesions, presence of one marrow lesions). Sensitivity analyses were performed, where groups were collapsed into those with and without PF pain (irrespective of the presence or absence of

MRI features). Analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

RESULTS

1112 participants (713 [64%] females) were included in the current study (Figure 1). The mean [SD] age and BMI were 66.8 [7.6] years and 29.5 [4.8] kg/m^2, respectively. Participant characteristics are presented in Table 1.

Psychological variables

Compared with the reference group (no PFOA), those with PF symptoms with MRI PFOA had significantly greater odds of having depressive symptoms (OR 2.01, 95% CI 1.13 to 3.56) (Figure 2; Supplementary Table 1). Participants with PF symptoms (no MRI PFOA) also had significantly greater odds of depressive symptoms (OR 1.79, 95% CI 1.04 to 3.09), compared with the reference group. Participants who had MRI PFOA but no symptoms were not significantly different than the reference group.

For pain catastrophizing, those with PF symptoms with MRI PFOA (OR 1.5, 95% CI 1.03 to 2.19) and those with PF symptoms alone (OR 1.79, 95% CI 1.26 to 2.54) had significantly greater odds of pain catastrophizing, compared with the reference group (Figure 2; Supplementary Table 1). There was no significant difference in odds of pain catastrophizing for participants with MRI PFOA without PF symptoms, and the reference group.

Quantitative sensory tests

Compared with the reference group (no PFOA), participants with PF symptoms with MRI PFOA had significantly greater odds of demonstrating temporal summation over the patella (OR 1.71, 95% CI 1.15 to 2.53), but not at the wrist (Figure 2; Supplementary Table 1). Participants with PF symptoms only (no MRI PFOA) had significantly greater odds of demonstrating temporal summation at both the patella (OR 1.96, 95% CI 1.37 to 2.80) and the wrist (OR 1.66, 95% CI 1.16 to 2.37). There were no significant differences in odds of temporal summation for those with MRI PFOA alone (no PF symptoms).

Group means and 95% CIs for PPT at the patella and wrist are presented in Figure 3 and Supplementary Table 2, stratified by sex. Males with PF symptoms only (no MRI PFOA) had significantly lower PPT at the patella compared to those with MRI PFOA only (mean difference −1.32 kg/cm^2, 95% CI −2.43 to −0.22) and compared to those with the group with no PFOA (mean difference −1.37 kg/cm^2, 95% CI −2.36 to −0.38). There were no significant differences in PPT at the wrist. For females, there were no significant between-group differences at the patella or wrist.

Sensitivity analyses

Compared with those without PF symptoms (regardless of MRI PFOA status), those with PF symptoms (also regardless of MRI PFOA status) had 2.12 (95% CI 1.38, 3.27), 1.55 (1.18, 2.03), 1.53 (1.16, 2.03), and 1.92 (1.45, 2.54) times the odds of having depressive

symptoms, catastrophizing, temporal summation at the wrist, and temporal summation at the patella, respectively.

Males with PF symptoms had significantly lower PPT at the patella compared to those without symptoms (mean difference −0.92 kg/cm^2, 95% CI −1.52 to −0.31), but differences were not significant at the wrist (mean difference −0.39 kg/cm^2, 95% CI −0.8 to 0.03). There were no significant differences between females with and without PF symptoms for PPT at the patella (mean difference −0.21 kg/cm^2, 95% CI −0.51 to 0.09) or wrist (mean difference −0.06 kg/cm^2, 95% CI −0.24 to 0.12).

DISCUSSION

We found that people with PF symptoms, with or without MRI PFOA, have greater odds of depressive symptoms, pain catastrophizing, and local mechanical TS, compared to people without PF symptoms or MRI PFOA. Those with PF symptoms only (no MRI PFOA) also had greater odds of mechanical TS at the wrist, compared to people with no PFOA. We found sex-specific between-group differences for PPT. Males with PF symptoms only (no MRI PFOA) had significantly lower PPT at the patella compared to those with MRI PFOA only, and compared to those with no PFOA, although no differences were found at the wrist. However, no significant between-group differences in PPT were found for females.

Taken together, our findings demonstrate the presence of psychological impairment, local hyperalgesia and symptom amplification in people with symptomatic features of PFOA, as well as more widespread symptom amplification. This is irrespective of whether structural PFOA (defined as a full-thickness cartilage lesion with BML in the PFJ) is present on MRI, particularly as those with PF symptoms only (without MRI PFOA) demonstrated findings consistent with sensitisation. This suggests that it is PF symptoms and not structural changes that are largely associated with the presence of these features. Our findings in PFOA are consistent with Neogi et al (13), who evaluated TS and PPT in people with radiographic TFOA (with or without PFOA) in the same MOST cohort. The relevance of imaging features of OA in the knee has been questioned by multiple studies, given the discordance between structural features and symptoms of pain and function (28). The literature is characterised by studies that both support and negate a relationship between MRI OA and pain (29), while studies also highlight that a large proportion of asymptomatic people have features of knee OA on x-ray and MRI (30). Nevertheless, our findings highlight the primary importance of the symptoms of PFOA, as well as their consideration in assessment and management of patients.

Although depressive symptoms and catastrophising have not been previously identified in PFOA, our findings regarding these characteristics are consistent with previous studies in similar musculoskeletal populations. Depressive symptoms have been identified in knee OA and patellofemoral pain populations (10–12). Catastrophising has been demonstrated in younger adults with patellofemoral pain (11). While the cross-sectional nature of our study precludes inference of causality, our findings do suggest that psychological impairments are present in people with symptomatic features of PFOA. It is important that health professionals who manage people with PFOA are cognisant of this, and refer for appropriate

management as indicated. It is also important for future studies to establish whether there are other psychological characteristics associated with this population, such as anxiety and kinesiophobia (10).

Within our cohort, individuals with PF symptoms also demonstrated increased temporal summation at both local and remote sites. While it is logical that local temporal summation would be associated with the presence of pain locally at the knee, particularly a chronic pain condition such as PFOA, increased temporal summation at a remote site (the wrist) may suggest central sensitisation, though we did not find differences in hyperalgesia at the wrist. Our findings suggest that temporal summation and pressure pain threshold provide different information, and that temporal summation may be a characteristic of the individual (i.e. trait), rather than a result of the presence of PFOA pain (state), consistent with conclusions of Neogi et al (13).

It is unsurprising that local hyperalgesia was present in our cohort, as it is a feature in people with knee OA (14) and those with patellofemoral pain (15, 16). What is novel is that we found that this was only the case in males and not females. Males with PF symptoms only had significantly lower PPT over the patella, even when compared to those with combined PF symptoms and MRI PFOA. The reasons for this are unclear, but do reinforce that it is symptoms driving observed differences, rather than structure (13). This raises the question that reported between-group differences in PPT observed in prior studies are related to sex, which has not previously been considered separately. This may explain findings of Bartholomew et al (17), who reported no differences in PPT between a mixed-sex cohort of people with PFOA and controls. Because of differences in PPT between sexes (27), we considered male and female PPT separately. Sex-specific subgroups of PFOA should be explored further in future studies evaluating pain sensitisation.

Our findings provide important preliminary information regarding psychological factors and pain sensitisation in older adults with symptoms of PFOA, which might plausibly influence the management of people with PFOA, and inform design of future studies. Most notably, our findings suggest that psychological and pain characteristics should be considered when assessing and managing people with PFOA. Assessment of pain sensitisation may help consider further mechanism-based management approaches as more treatments become available. Exploration of how psychological characteristics and pain sensitisation are associated with and predictive of symptoms and function in those with PFOA is warranted to gain prognostic insights, and further support for consideration of pain phenotyping. Finally, given our findings that depressive symptoms, pain catastrophising and pain sensitisation are related to PF symptoms, these factors should be investigated for their ability to predict treatment response.

Inferences from this study should be made bearing in mind some potential limitations. Although we diagnosed PFOA using consensus-based criteria available in the MOST cohort, diagnosis of PFOA would typically involve additional criteria (e.g. crepitus, physical examination to exclude other sources of knee pain) (1, 8, 9). The MOST cohort consists of older adults with or at risk of knee OA, who present with particular characteristics (e.g. high BMI). Thus, findings of this study may not apply to younger adults with PFOA, or those

with lower BMI. Furthermore, there were limitations regarding the specific variables available. For example, our evaluation of psychological variables was limited to depressive symptoms and pain catastrophising. Based on findings in knee OA and younger adults with patellofemoral pain, evaluation as to whether other psychological characteristics such as anxiety and fear of movement are also features of PFOA is warranted. We also acknowledge that there are multiple ways in which MRI PFOA can be defined. From systematic review findings highlighting the high prevalence of individual structural features (e.g. cartilage lesions, bone marrow lesions) in asymptomatic people (30), we chose to define PFOA as the combination of a full-thickness cartilage lesion with co-existing bone marrow lesion (23). This was based on our previous findings in 26–50 year old adults with persistent PF pain, where we found a high prevalence of partial thickness lesions and osteophytes in pain-free controls, and that PFOA defined as combined full-thickness cartilage lesion with a bone marrow lesion was better able to differentiate PF pain from controls (3). However, we acknowledge that other features of PFOA may be related to symptoms (e.g. synovitis, effusion), which should be explored in future studies.

In conclusion, people with PFOA symptoms, with or without structural features of PFOA, are more likely to demonstrate psychological impairments (depressive symptoms, catastrophizing) and pain sensitisation (temporal summation), compared with asymptomatic people with no MRI PFOA. Sex-specific differences were observed for PPT. Further exploration of how psychological characteristics and pain sensitisation are associated with and predictive of symptoms and function in those with PFOA is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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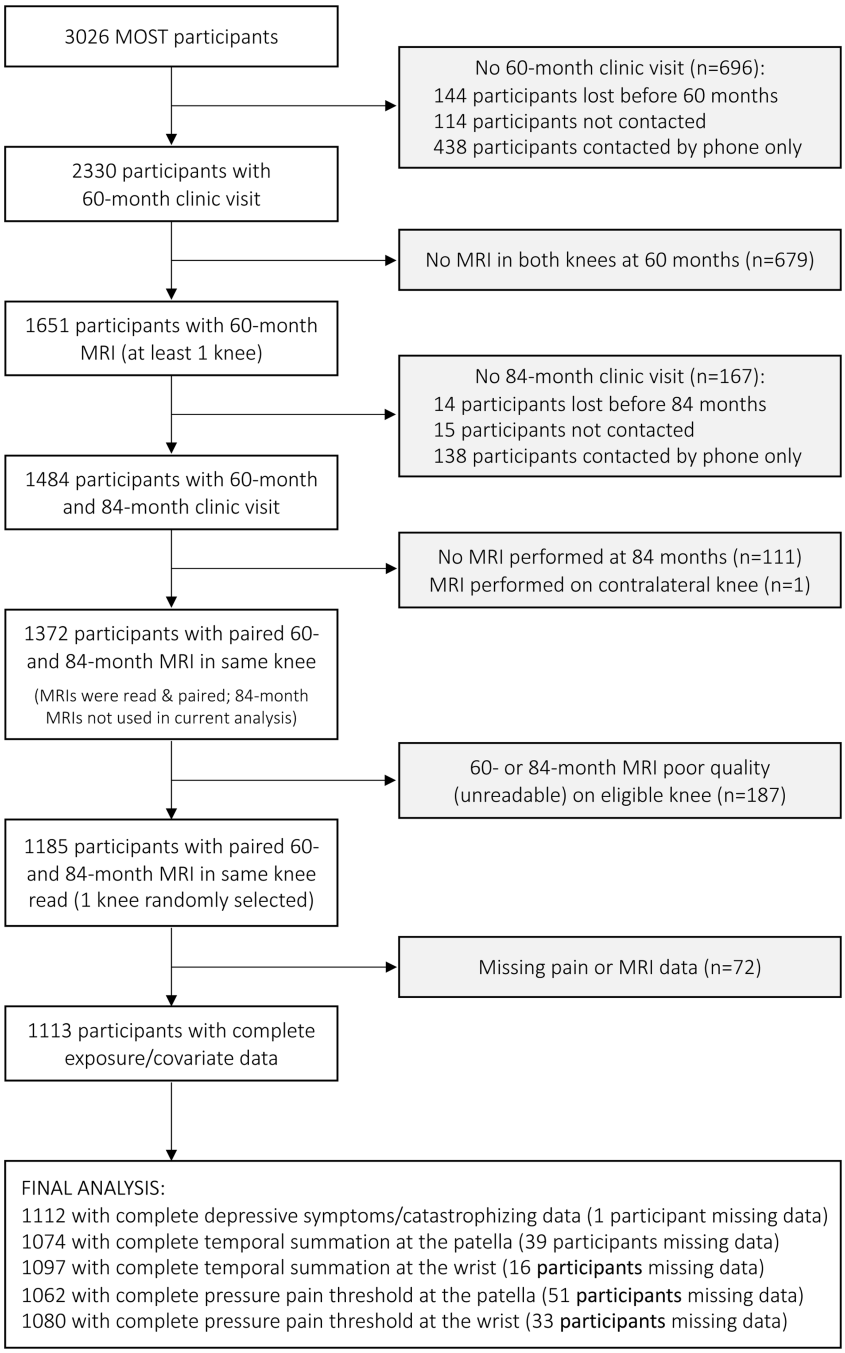

Figure 1.
Flow chart of participants included in the analysis.

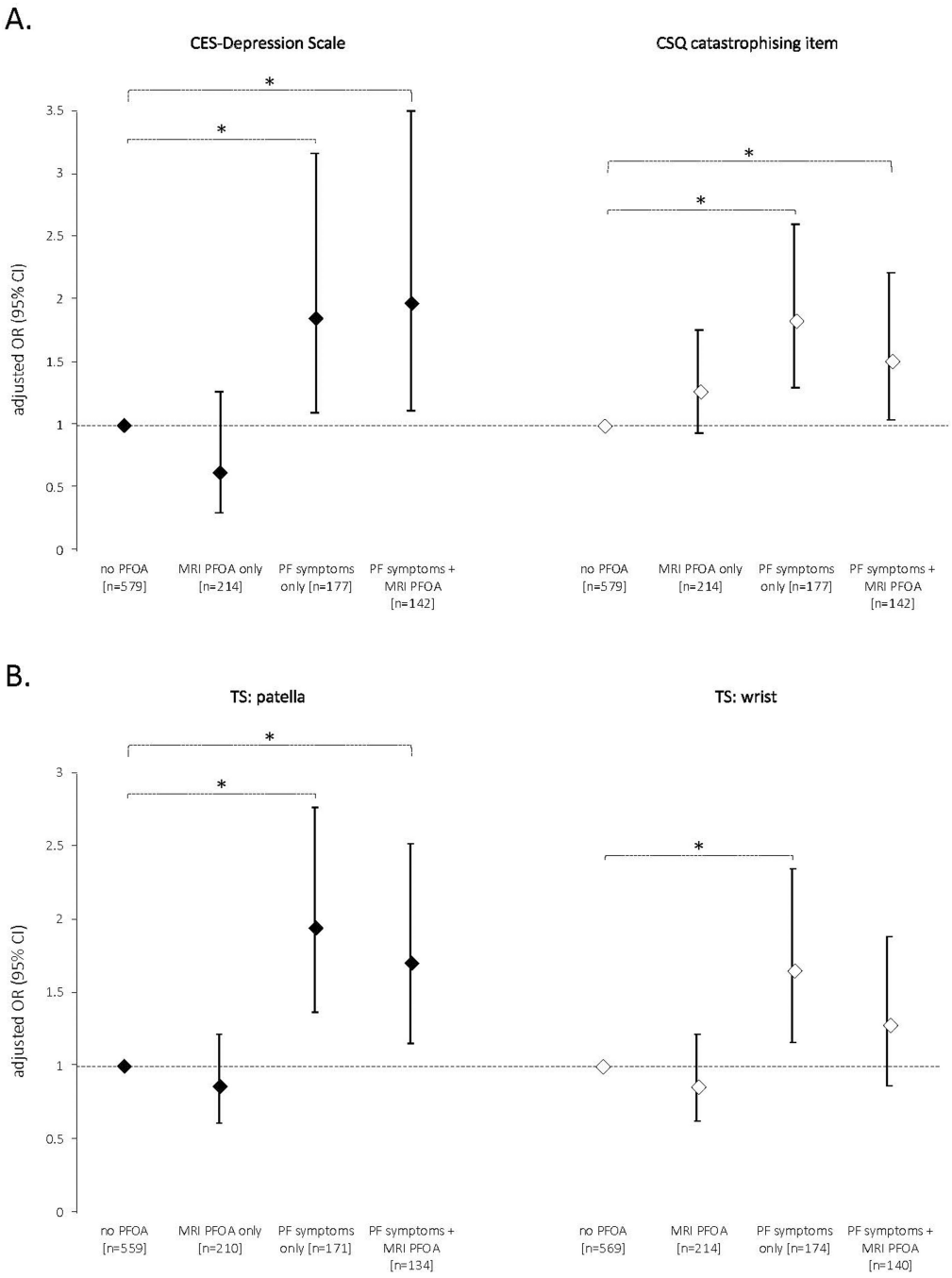

Figure 2.

Adjusted odds ratios (with 95% confidence intervals) for the CED-Depression Scale (black diamonds) and catastrophising item of the Coping Strategies Questionnaire (white diamonds) (panel A), and for temporal summation at the patella (black diamonds) and wrist (white diamonds) (panel B), for each PFOA group (adjusted for age, sex, body mass index, tibiofemoral osteoarthritis; reference group = no pain or MRI OA).

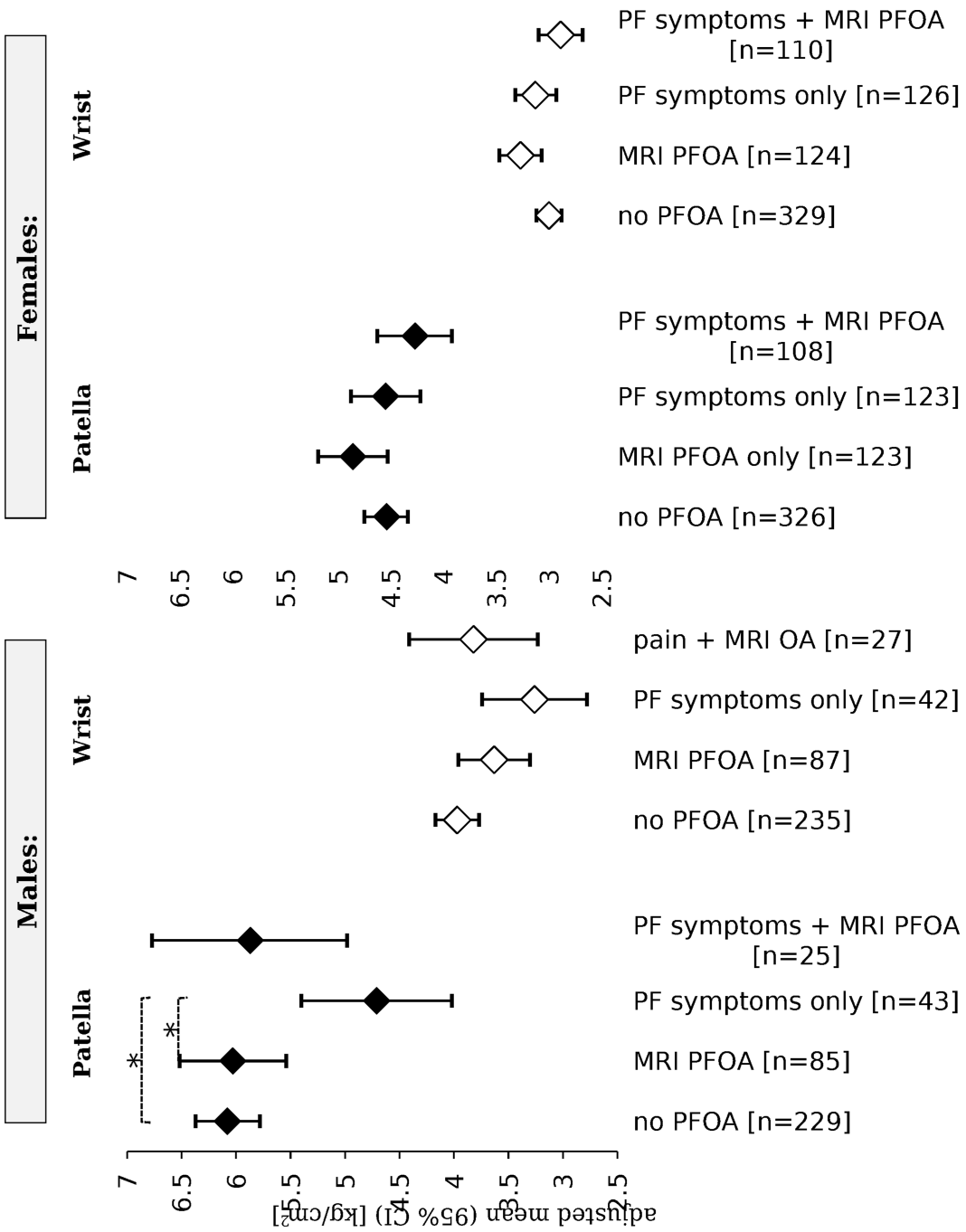

Figure 3.

Adjusted means (with 95% confidence intervals) for pressure pain threshold at the patella (black diamonds) and wrist (white diamonds), for each PFOA group, stratified by sex (adjusted for age, body mass index, tibiofemoral osteoarthritis).

Table 1.

Participant characteristics. Values are mean (SD) unless otherwise specified.

	PF symptoms + MRI PFOA (n=142)	PF symptoms only (no MRI PFOA) (n=177)	MRI PFOA only (no PF symptoms) (n=214)	No PFOA (n=579)	Total cohort (n=1112^)
Age, years	67.4 (7.4)	65.8 (7.5)	67.5 (7.6)	66.7 (7.6)	66.8 (7.6)
Number (%) of females	28 (19.7)	44 (24.9)	88 (41.1)	239 (41.3)	713 (64)
Body mass index, kg/m^2	30.7 (4.5)	30.2 (5.3)	29.9 (4.6)	28.9 (4.7)	29.5 (4.8)
Number (%) with depressive symptoms	22 (15.5)	25 (14.1)	10 (4.7)	42 (7.3)	99 (8.9)
Number (%) with catastrophizing	78 (54.9)	102 (57.6)	103 (48.1)	238 (41.1)	521 (46.9)
Number (%) with temporal summation at the patella*	63 (47.0)	84 (49.1)	66 (31.4)	193 (34.5)	406 (37.8)
Number (%) with temporal summation at the wrist*	57 (40.7)	80 (46.0)	70 (32.7)	204 (35.9)	411 (37.5)
PPT Patella, kg*	4.5 (2.0)	4.6 (2.0)	5.3 (2.2)	5.2 (2.2)	5.04 (2.1)
PPT Wrist, kg*	3.1 (1.2)	3.2 (1.3)	3.4 (1.3)	3.4 (1.4)	3.33 (1.4)
Number (%) with patellofemoral pain	142 (100)	177 (100)	0 (0)	0 (0)	319 (28.7)
Number (%) with patellofemoral full thickness cartilage lesion	142 (100)	14 (7.9)	214 (100)	42 (7.3)	412 (37.1)
Number (%) with patellofemoral bone marrow lesion	142 (100)	88 (49.7)	214 (100)	233 (40.2)	677 (60.9)
Number (%) with tibiofemoral full thickness cartilage lesion	50 (35.2)	74 (41.8)	90 (42.1)	167 (28.8)	381 (34.3)
Number (%) with tibiofemoral bone marrow lesion	68 (47.9)	92 (52.0)	112 (52.3)	229 (39.6)	501 (45.1)

^ sample size lower than total cohort due to missing data. See figure 1 for details.