

## ORIGINAL ARTICLE

# Central sensitization as a determinant of patients' benefit from total hip and knee replacement

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## Funding sources

This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (RP-PG-0407-10070). The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The research team acknowledges the support of the NIHR, through the Comprehensive Clinical Research Network.

## Conflicts of interest

None declared.

## Accepted for publication

18 July 2016

doi:10.1002/ejp.929

## Abstract

**Background:** Discrepancies exist between osteoarthritic joint changes and pain severity before and after total hip (THR) and knee (TKR) replacement. This study investigated whether the interaction between pre-operative widespread hyperalgesia and severity of radiographic osteoarthritis (OA) was associated with pain severity before and after joint replacement.

**Methods:** Data were analysed from 232 patients receiving THR and 241 receiving TKR. Pain was assessed pre-operatively and at 12 months post-operatively using the WOMAC Pain Scale. Widespread hyperalgesia was assessed through forearm pressure pain thresholds (PPTs). Radiographic OA was evaluated using the Kellgren and Lawrence scheme. Statistical analysis was conducted using multilevel models, and adjusted for confounding variables.

**Results:** *Pre-operative:* In knee patients, there was weak evidence that the effect of PPTs on pain severity was greater in patients with more severe OA (Grade 3 OA:  $\beta = 0.96$  vs. Grade 4:  $\beta = 4.03$ ), indicating that in these patients higher PPTs (less widespread hyperalgesia) was associated with less severe pain. In hip patients, the effect of PPTs on pain did not differ with radiographic OA (Grade 3 OA:  $\beta = 3.95$  vs. Grade 4:  $\beta = 3.67$ ).

*Post-operative:* There was weak evidence that knee patients with less severe OA who had greater widespread hyperalgesia benefitted less from surgery (Grade 3 OA:  $\beta = 2.28$ ; 95% CI  $-1.69$  to  $6.25$ ). Conversely, there was weak evidence that hip patients with more severe OA who had greater widespread hyperalgesia benefitted more from surgery (Grade 4 OA:  $\beta = -2.92$ ; 95% CI  $-6.58$  to  $0.74$ ).

**Conclusions:** Widespread sensitization may be a determinant of how much patients benefit from joint replacement, but the effect varies by joint and severity of structural joint changes.

**Significance:** Pre-operative widespread hyperalgesia and radiographic osteoarthritis (OA) severity may influence how much patients benefit from joint replacement. Patients undergoing knee replacement with less severe OA and greater widespread hyperalgesia benefitted less from surgery than patients with less hyperalgesia. Patients undergoing hip replacement with more severe OA and greater widespread hyperalgesia benefitted more than patients with less hyperalgesia.

## 1. Introduction

Assessment and diagnosis of osteoarthritis (OA) commonly involves radiographs to visualize structural joint changes. However, radiographic results do not always correlate with symptoms, and there is discordance between pain severity and radiographic OA severity. Research has demonstrated that some patients experience little pain in the presence of severe structural joint changes, whereas other patients report severe pain with milder structural joint changes (Bedson and Croft, 2008). The severity of radiographic OA has been found to explain <20% of the variance in pain intensity (Murphy et al., 2011). The aetiology of this discordance is likely multifactorial, as pain severity can be influenced by numerous factors including psychological status (Finan et al., 2013), peripheral causes of pain including bone marrow lesions, knee effusions and soft tissue lesions (Felson, 2005), and central-mediated changes in pain processing (Finan et al., 2013; Goode et al., 2014).

The severity of structural joint changes as assessed by x-ray (radiographic OA) has been associated with long-term pain outcomes in patients following joint replacement. Studies report that patients with less severe structural joint changes prior to surgery are more likely to report chronic pain post-operatively (Dowsey et al., 2012, 2016; Valdes et al., 2012). Understanding this inverse relationship between radiographic OA and pain after joint replacement may partly help to explain why 10% of patients receiving total hip replacement (THR) and 20% of patients receiving total knee replacement (TKR) report unfavourable long-term pain outcomes (Beswick et al., 2012).

One possible factor contributing to the relationships between radiographic OA and pain severity before and after joint replacement is central sensitization. This refers to changes in central pain processing that occur when large amounts of peripheral noxious input lead to hyperexcitability of neurones and amplification of pain signalling. Reduced pain thresholds at a body site distant to the painful joint, known as widespread hyperalgesia, is one indication of the presence of central sensitization and can be assessed experimentally using Quantitative Sensory Testing (QST). Central sensitization is common in patients with OA (Suokas et al., 2012) and pain severity is associated with QST findings (Arendt-Nielsen et al., 2010). Patients with high pain severity and less severe radiographic OA have been found to report greater abnormalities in central pain processing than patients with less pain and more severe

radiographic OA (Finan et al., 2013). Preliminary research suggests that central sensitization may be associated with outcomes after joint replacement (Lundblad et al., 2008; Wylde et al., 2013). In light of this, the aims of this study were to investigate whether pre-operative widespread hyperalgesia, radiographic OA, and the interaction between these two factors were associated with: (1) Pre-operative pain severity; and (2) Change in pain severity from pre-operative to 12 months post-operative, that is, how much pain relief patients gained from joint replacement.

## 2. Patients and methods

The data analysed were from the Arthroplasty Pain Experience (APEX) trials. The published protocol and clinical results paper for the APEX trials provides full details of the research design and findings (Wylde et al., 2011a, 2015a). Briefly, these double-blind, single-centre, randomized controlled trials aimed to investigate the effect of local anaesthetic wound infiltration on pain severity at 12 months after joint replacement. Between 2009 and 2012, 322 patients undergoing THR and 316 patients undergoing TKR were recruited. Inclusion criteria were waiting for a primary unilateral THR or TKR for OA. Exclusion criteria were inability to provide informed consent or complete questionnaires and medical co-morbidity precluding use of spinal anaesthesia, regional blocks or strong analgesics post-operatively. The APEX trials were approved by Southampton and South West Hampshire Research Ethics Committee (09/H0504/94) and all participants provided informed, written consent.

### 2.2 Measurements

#### 2.2.1 Exposures

*2.2.1.1 Widespread hyperalgesia.* Pre-operative widespread hyperalgesia was assessed using QST, a non-invasive method which measures participants' responses to external stimuli of controlled intensity. The measurement of pressure pain thresholds (PPTs) using a digital algometer was chosen because it is quick and easy to perform in a clinical setting, has demonstrated good short-term reliability in patients with OA (Wylde et al., 2011b), and is a sensitive method for evaluating pain sensitization (Suokas et al., 2012). A digital algometer (Somedic, Horby, Sweden) with a 1 cm probe was used to assess pre-operative PPTs at the volar forearm. Force was applied at a constant rate

of 10 kPa/s and participants were instructed to say 'stop' as soon as the sensation of pressure became the first sensation of pain. PPTs can be interpreted as lower values representing increased widespread hyperalgesia. Pressure algometry was repeated three times, and the position of the algometer was altered slightly each time to avoid sensitization of the test area. PPT used in the analyses was based on the mean of the three PPT measurements, and then standardized across the population using a z-transformation. Results are the interpreted per standard deviation increase in PPT.

**2.2.1.2 Radiographic OA severity.** The degree of structural joint damage was graded on pre-operative anteroposterior and lateral radiographs using the Kellgren and Lawrence (K&L) scheme (Kellgren and Lawrence, 1957). This scheme assesses OA severity based on the degree of osteophyte formation and cartilage degeneration (as measured by joint space narrowing), with scores ranging from 0 (no joint damage) to 4 (severe joint damage). Patients with a K&L grade of  $\leq 2$  (5 knee patients and 14 hip patients) were excluded from these analyses because of the small numbers. Radiographs were graded by one observer (AO). Interobserver reliability was assessed by a second observer (PD) grading a random sample of 26 hip OA radiographs and 28 knee OA radiographs and agreement was good (Hip: unweighted kappa 0.70, agreement 84.6%; Knee: unweighted kappa 0.61; agreement 78.6%).

### 2.2.2 Outcomes

Patient-reported pain severity in the replaced joint was assessed pre-operatively and at 12 months post-operatively using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Pain scale (Bellamy et al., 1988). Total scores were transformed to a 0–100 scale (worst to best).

### 2.2.3 Confounding variables

This analysis involved analysing data from the APEX trials as a cohort study, and therefore adjustment was required to control for confounding factors. In addition, analyses that used post-intervention data were adjusted for allocation to the trial intervention (randomization) to ensure that any treatment effect from the intervention did not bias the results (Martin et al., 2010; Black et al., 2014). Confounding factors that were adjusted for were age at recruitment, gender, cohabitation (living alone or not alone),

employment status (retired or not retired), educational attainment (education to before or after normal school leaving age) and body mass index (BMI).

### 2.3 Statistical analysis

All analyses were performed separately for hip and knee patients. Participant characteristics and outcome measures are reported as means, standard deviations (SD), median and interquartile cut-points for continuous measures. Frequencies were used to describe categorical variables.

A multilevel model was used to simultaneously investigate the effect of PPT and OA grade on pre-operative pain severity and change in pain severity from pre- to post-operative. In this approach, the effect of the exposure variable(s) on pre-operative pain was not modelled directly. Instead, this effect was investigated by the inclusion of an interaction between the pre-operative measurement occasion and the exposure variable(s). In addition, the effect of the exposure(s) on change in pain was modelled by the inclusion of an (two way) interaction between the exposure variable(s) and time. Furthermore, to investigate any interactions between PPT and OA grade on pre-operative pain and change in pain, three-way interactions between the measurement occasion, PPT and OA grade were used. This approach allowed the investigation of the effect of PPT and OA grade on the amount of pain relief that patients gained from joint replacement, while appropriately adjusting for the effect of the exposures on pre-operative pain.

Four models with pre-operative pain and change in pain severity with surgery as outcomes were constructed. Model 1 investigated the association between OA grade and pain. Model 2 investigated the association between PPT and pain. Model 3 investigated two associations (1) the association between OA and pain adjusted for PPT; and (2) the association between PPT and pain adjusted for OA. Model 4 investigated the interaction between PPT and OA grade and the impact on pain. The models described above were first minimally adjusted for age, gender and randomization and then more completely adjusted for age, gender, randomization, cohabitation, employment status, education and BMI.

All models were fitted using iterative generalized least squares in MLwiN (Rasbash et al., 2009) using Stata's `runmlwin` command (Leckie and Charlton, 2013).

### 3. Results

#### 3.1 Participants

WOMAC Pain scores at 12 months post-operative were available for 281 patients receiving TKR and 273 patients receiving THR. After exclusion of patients with incomplete covariate information, including confounding variables, 232 patients receiving THR and 241 receiving TKR were included in the analysis. Patients not included in the analysis were broadly similar to those included in the analysis (Supporting Information Tables S1 and S2). The mean age of participants included in the analysis was 66 (SD 10) in the hip cohort and 69 (SD 9) in the knee cohort. The percentage of female patients was slightly higher than male patients (56% women in the hip cohort and 53% in the knee cohort). Demographic and clinical characteristics of participants are presented in Tables 1 and 2.

#### 3.2 Association of PPTs and radiographic OA with pre-operative pain severity

##### 3.2.1 Hip OA

Results are presented in Table 3. There was no evidence of an association between pre-operative pain severity and OA grade (Pre-operative model 1). A higher PPT, indicating less widespread hyperalgesia, was significantly associated with a higher WOMAC Pain score, that is, less pre-operative pain (Pre-operative model 2). A SD increase in standardized PPT resulted in nearly a 4 point higher score on the WOMAC Pain Scale. Adjusting the association between pre-operative pain severity and PPT by OA

**Table 1** Demographic characteristics of patients undergoing total hip replacement and total knee replacement.

		Hips (n = 232)	Knees (n = 241)
Randomization	Standard care	113 (49%)	120 (50%)
	Intervention	119 (51%)	121 (50%)
Sex	Male	101 (44%)	113 (47%)
	Female	131 (56%)	128 (53%)
Retired	Not retired	91 (39%)	65 (27%)
	Retired	141 (61%)	176 (73%)
Cohabitation	Alone	50 (22%)	69 (29%)
	Not alone	182 (78%)	172 (71%)
Education	Before normal school leaving age	155 (67%)	184 (76%)
	After normal school leaving age	77 (33%)	57 (24%)

grade resulted in a very modest attenuation of the results. Similarly, adjusting the association between pre-operative pain severity and OA grade by PPT resulted in a modest attenuation of the results (Pre-operative model 3). The effect of PPT on pre-operative pain severity was similar in patients with Grade 3 and 4 OA, that is, no interaction between PPT and OA grade (Pre-operative model 4). There was little difference between the effects when analyses were more fully adjusted for socio-demographic factors.

##### 3.2.2 Knee OA

Results are presented in Table 4. Pre-operative pain was significantly less severe in patients with Grade 4 OA (Pre-operative model 1), and on average patients with Grade 4 OA had a 5 point higher (better) WOMAC Pain Score than patients with Grade 3 OA. Higher PPTs were significantly associated with less severe pre-operative pain (Pre-operative model 2), with a SD increase in standardized PPT resulting in nearly a 3-point better score on the WOMAC Pain Scale. Adjusting the association between pre-operative pain severity and PPTs by OA grade and vice versa resulted in a very modest attenuation of the results (Pre-operative model 3). There was a weak suggestion of an interaction between pre-operative pain severity, PPT and OA grade (Pre-operative model 4). While the interaction was not nominally significant ( $p > 0.05$ ), the association between pre-operative pain severity and PPT in patients with Grade 4 OA was approximately four times greater than in patients with Grade 3 OA, indicating that as PPT increases, pain severity decreases.

#### 3.3 Association of PPTs and radiographic OA with post-operative pain outcomes

##### 3.3.1 Total hip replacement

Results are presented in Table 3. There was weak evidence of an association of radiographic OA with change in pain (Post-operative model 1). Patients with Grade 4 OA had an approximately 4.5 unit greater change in WOMAC Pain score than patients with Grade 3 OA, although the evidence was weak. There was no evidence of an association between PPT and change in pain severity between pre and post-surgery (Post-operative model 2). Adjusting the association between pain and PPT by OA grade and vice versa resulted in a very modest attenuation of the results (Post-operative model 3). The effect of PPTs on change in pain severity differed by OA grade (Post-operative model 4). There was weak evidence

**Table 2** Descriptive statistics for patients undergoing total hip and total knee replacement.

	Time	Measure	Mean (SD)	IQR (25, 50, 75)
Hips ( <i>n</i> = 232)	Pre	PPT mean <sup>a</sup>	212.40 (97.64)	(138.16, 193.33, 266.66)
		PPT SD <sup>b</sup>	39.25 (32.89)	(16.34, 29.70, 53.73)
		BMI	29.18 (5.62)	(25.65, 27.96, 32.07)
		Age	66.37 (10.22)	(59.50, 66.00, 73.00)
		WOMAC Pain score	43.83 (18.37)	(30.00, 45.00, 55.00)
Knees ( <i>n</i> = 241)	Pre	WOMAC Pain score	90.46 (15.28)	(85.00, 95.00, 100.00)
		PPT mean <sup>a</sup>	203.13 (103.45)	(31.67, 180.33, 248)
		PPT SD <sup>b</sup>	32.97 (25.96)	(16.37, 27.22, 40.51)
		BMI	32.55 (6.29)	(28.03, 31.85, 36.25)
		Age	68.93 (8.66)	(63.00, 70.00, 75.00)
	Post	WOMAC Pain score	42.78 (16.68)	(35.00, 45.00, 55.00)
		WOMAC Pain score	80.21 (21.45)	(65.00, 85.00, 100.00)

<sup>a</sup>Mean average pressure pain thresholds (PPT) across the three replicates.

<sup>b</sup>Mean average PPT standard deviation across the three replicates.

**Table 3** Longitudinal regression analyses of pre-operative pain severity and post-operative change in pain severity, Kellgren and Lawrence osteoarthritis (OA) grade and pressure pain thresholds (PPTs) in patients undergoing total hip replacement (*n* = 232).

Model	Exposure	Adjusted	Pre-operative pain			Change in pain from pre-operative to post-operative			Model interaction <i>p</i> -value*
			$\beta$	(95 CI)	<i>p</i> -value	$\beta$	(95 CI)	<i>p</i> -value	
1	OA	Minimal	-2.17	(-6.92, 2.57)	0.369	4.54	(-1.27, 10.35)	0.126	
2	PPT	Minimal	3.85	(1.54, 6.16)	0.001	-1.33	(-4.19, 1.54)	0.364	
3	OA	Minimal + PPT	-1.82	(-6.49, 2.84)	0.443	4.41	(-1.41, 10.22)	0.138	
	PPT	Minimal + OA	3.78	(1.47, 6.09)	0.001	-1.17	(-4.03, 1.69)	0.422	
4	OA	Minimal + PPT	-1.74	(-6.42, 2.95)	0.468	4.77	(-1.04, 10.57)	0.108	
	PPT & Grade 3 OA	Minimal	3.96	(0.35, 7.57)	0.032	1.50	(-3.01, 6.01)	0.514	
	PPT & Grade 4 OA	Minimal	3.61	(0.63, 6.58)	0.017	-2.92	(-6.58, 0.73)	0.117	0.054
1	OA	Full	-1.46	(-6.01, 3.09)	0.529	4.54	(-1.27, 10.35)	0.126	
2	PPT	Full	3.87	(1.66, 6.07)	0.001	-1.33	(-4.19, 1.54)	0.363	
3	OA	Full + PPT	-1.07	(-5.53, 3.38)	0.637	4.41	(-1.40, 10.23)	0.137	
	PPT	Full + OA	3.82	(1.61, 6.02)	0.001	-1.17	(-4.03, 1.69)	0.423	
4	OA	Full + PPT	-1.03	(-5.50, 3.44)	0.651	4.77	(-1.03, 10.58)	0.107	
	PPT & Grade 3 OA	Full	3.95	(0.51, 7.40)	0.024	1.51	(-3.00, 6.01)	0.513	
	PPT & Grade 4 OA	Full	3.67	(0.84, 6.51)	0.011	-2.92	(-6.58, 0.74)	0.118	0.052

Minimal adjustment = age, gender and randomization.

Full adjustment = Minimal adjustment + cohabitation, employment status, educational attainment and BMI.

\*Model interaction *p*-value represents the improvement of fit by the introduction of the interaction between PPT and OA grade in both the pre-operative, and post-operative change analysis.

Exposures = OA (Kellgren and Lawrence Grade 4 vs. Grade 3), PPT (pressure pain threshold on a standardized scale, with higher values indicating less pain sensitivity).

Regression coefficients = adjusted mean difference (or change), with increasing values indicating less pain on the WOMAC Pain scale.

that patients in the Grade 4 OA group with higher PPTs benefitted less from surgery (decreased change in WOMAC Pain score) than those with lower PPTs. In contrast, there was little evidence of an association between PPTs and change in pain severity in patients with Grade 3 OA.

### 3.3.2 Total knee replacement

Results are presented Table 4. There was little evidence of a difference in change in pain severity

following surgery in patients with Grade 3 and 4 OA (Post-operative model 1). Similarly, there was no association between change in pain severity and PPTs (Post-operative model 2), and adjusting this association between pain severity and PPTs by OA grade and vice versa had little effect (Post-operative model 3). There was weak evidence of a differential effect of PPT by OA grade on change in pain severity following surgery (Post-operative model 4). Results suggested weak evidence of a positive association between PPTs and change in pain severity in patients

**Table 4** Longitudinal regression analyses of pre-operative pain severity and post-operative change in pain severity, Kellgren and Lawrence osteoarthritis (OA) grade and pressure pain thresholds (PPTs) in patients undergoing total knee replacement ( $n = 241$ ).

Model	Exposure	Adjusted	Pre-operative pain			Change in pain from pre-operative to post-operative			Model interaction $p$ -value*
			$\beta$	(95 CI)	$p$ -value	$\beta$	(95 CI)	$p$ -value	
1	OA	Minimal	5.10	(1.08, 9.13)	0.013	3.05	(-2.15, 8.24)	0.250	
2	PPT	Minimal	2.83	(0.72, 4.94)	0.009	0.18	(-2.39, 2.75)	0.891	
3	OA	Minimal + PPT	4.97	(1.00, 8.94)	0.014	3.05	(-2.15, 8.25)	0.250	
	PPT	Minimal + OA	2.76	(0.67, 4.84)	0.009	0.16	(-2.41, 2.73)	0.902	
4	OA	Minimal + PPT	4.98	(1.03, 8.93)	0.014	3.03	(-2.14, 8.21)	0.251	
	PPT & Grade 3 OA	Minimal	1.03	(-2.10, 4.15)	0.520	2.28	(-1.69, 6.25)	0.261	
	PPT & Grade 4 OA	Minimal	3.96	(1.33, 6.59)	0.003	-1.34	(-4.69, 2.01)	0.432	0.242
1	OA	Full	5.40	(1.41, 9.40)	0.008	3.04	(-2.15, 8.24)	0.251	
2	PPT	Full	2.82	(0.76, 4.88)	0.007	0.18	(-2.39, 2.75)	0.891	
3	OA	Full + PPT	5.30	(1.37, 9.24)	0.008	3.05	(-2.15, 8.24)	0.250	
	PPT	Full + OA	2.77	(0.74, 4.80)	0.008	0.16	(-2.41, 2.73)	0.903	
4	OA	Full + PPT	5.33	(1.41, 9.25)	0.008	3.03	(-2.14, 8.21)	0.251	
	PPT & Grade 3 OA	Full	0.96	(-2.08, 4.01)	0.536	2.28	(-1.69, 6.25)	0.260	
	PPT & Grade 4 OA	Full	4.03	(1.45, 6.61)	0.002	-1.34	(-4.69, 2.00)	0.431	0.220

Minimal adjustment = age, gender and randomization.

Full adjustment = Minimal adjustment + cohabitation, employment status, educational attainment and BMI.

\*Model interaction  $p$ -value represents represent the improvement of fit by the introduction of the interaction between PPT and OA grade in both the pre-operative, and post-operative change analysis. Exposures = OA (Kellgren and Lawrence Grade 4 vs. Grade 3), PPT (pressure pain threshold on a standardized scale, with higher values indicating less pain sensitivity).

Regression coefficients = adjusted mean difference (or change), with increasing values indicating less pain on the WOMAC Pain scale.

with Grade 3 OA, suggesting that patients with higher PPTs benefitted more from surgery (increased change in WOMAC Pain score) than those with lower PPTs. In contrast, there was little evidence of an association between PPTs and change in pain severity in patients with Grade 4 OA.

#### 4. Discussion

This exploratory study has a number of potentially important findings that provide insight into the associations between central sensitization, radiographic OA and pain severity in patients undergoing joint replacement. No association was found between radiographic OA and pain severity in patients waiting for THR, and an inverse relationship in patients waiting for TKR. There was some evidence that patients with less severe hip OA reported less improvement in pain by 12 months after surgery. Confirming our previous findings about central sensitization and pain severity (Wylde et al., 2015c), more widespread hyperalgesia were associated with more severe pain pre-operatively, but not with change in pain from pre- to post-surgery. Interestingly, analysis of the interaction between radiographic OA, PPTs and pain severity revealed further complexities. The pre-operative data indicated that patients with more severe radiographic knee OA

who had more widespread hyperalgesia reported more severe pain. The longitudinal analysis revealed there was weak evidence that patients with less severe knee OA and more widespread hyperalgesia responded less favourably to surgery than those with less widespread hyperalgesia. Conversely, there was weak evidence for patients with more severe hip OA and more widespread hyperalgesia to respond better to surgery than patients with less widespread hyperalgesia. Reasons for these conflicting results are unclear, but they suggest that central sensitization may be a determinant of how much patients benefit from joint replacement, although this varies by joint and the severity of structural joint changes. Further work is needed to elucidate the reasons for these differences, but these initial findings highlight the importance of considering hip and knee OA as separate diseases.

As expected, there was a lack of concordance between pre-operative pain severity and radiographic OA. In agreement with previous research (Dowsey et al., 2016), no association was found between pre-operative pain severity and radiographic OA in patients waiting for THR. However, in patients waiting for TKR, an inverse relationship was observed, with less severe OA associated with more severe pre-operative pain. This finding differs from an earlier study which found no association between

radiographic knee OA and pre-operative pain severity (Dowsey et al., 2012). The differences between the two studies may lie partly in the differing methods of pain assessment. Our study confirmed the noted discordance between radiographic OA and pain severity in patients waiting for joint replacement, and additionally suggests an inverse relationship between pain severity and radiographic knee OA.

Analyses of the relationship between PPTs and pain severity revealed that widespread hyperalgesia was associated with more severe pain before joint replacement. Previous research has also reported similar associations, as well as associations between pre-operative widespread hyperalgesia and pain after joint replacement (Lundblad et al., 2008; Arendt-Nielsen et al., 2010; Neogi et al., 2013; Wylde et al., 2013). However, our previous work demonstrated that pre-operative widespread hyperalgesia was not associated with the amount of pain relief that patients gain from joint replacement (Wylde et al., 2015c). Our further analyses produced novel findings suggesting that the relationship between widespread hyperalgesia and pain is influenced by radiographic OA severity. A previous study found that radiographic OA status did not modify the relationship between PPTs and self-reported symptoms (Goode et al., 2014). Although our findings were similar for patients with hip OA, there was weak evidence that patients with Grade 4 OA who had more widespread hyperalgesia reported greater pre-operative pain. In our longitudinal analysis of radiographic OA and change in pain with surgery, we found different results in patients undergoing THR and TKR. There was some weak evidence TKR patients with less severe OA and more widespread hyperalgesia responded less favourably to surgery than those with less widespread hyperalgesia. This suggests that central sensitization may be a determinant of gaining less benefit from TKR. However, there was weak evidence that THR patients with more severe OA and more widespread hyperalgesia to respond better to surgery than patients with less widespread hyperalgesia. These findings appear somewhat counter-intuitive, suggesting a beneficial effect of central sensitization on improvement in pain after THR for patients with severe OA. It is also important to note that these findings provided only weak evidence and should therefore be interpreted with caution. However, if confirmed in future studies, the reasons for these findings warrant further investigation.

Strengths of the study include the longitudinal study design, large sample size, use of robust measures of widespread hyperalgesia and pain, stratification of analysis by OA grade and comprehensive approach to statistical analysis which allowed the analysis of pre-operative pain and change in pain with surgery. However, it is important to consider the limitations when interpreting the findings. This analysis was exploratory in nature and conducted on an existing data set and therefore the study was not powered for this analysis. Although we adjusted the analyses for demographic and socioeconomic variables, other factors are known to influence the pain experience and could have been controlled for such as depression and anxiety. Also we did not collect information on the treatments that participants received after joint replacement, which could have influenced pain outcomes at 12 months. Our outcome of interest was pain severity, and while we used a validated tool to assess this, pain severity is only one dimension of the patients' experience of pain and it is important to acknowledge that there are many other important pain outcomes, such as pain-related distress and pain interference (Wylde et al., 2015b). Similarly, the assessment of PPTs is only one method by which to measure changes in central pain modulation, and research assessing parameters such as temporal summation or conditioned pain modulation may further add to the knowledge of pain mechanisms in the context of OA and joint replacement (Yarnitsky et al., 2008; Petersen et al., 2015).

In summary, although our previous work found no effect of pre-operative widespread hyperalgesia on the amount of pain relief that patients gain from joint replacement (Wylde et al., 2015c), analysis stratified by OA grade suggests that there is a trend that widespread pain sensitization reduces the amount of pain relief that patients with less severe OA gain from TKR. Previous research has found that patients with less severe OA experience less benefit from joint replacement, and it has been proposed that this may be because factors beyond structural joint changes, such as central sensitization, are contributing to pain severity in these patients (Valdes et al., 2012). Our findings provide evidence, albeit weak, for this hypothesis in patients undergoing TKR, but not THR. As this is the first study to investigate the interaction of PPTs and radiographic OA on benefit gained after joint replacement, reasons for these conflicting findings between patients undergoing THR and TKR are unclear and further research is needed to confirm these findings and provide further

insight into potential mechanistic pathways. However, these findings could have important clinical implications, through identifying the potential for stratified treatment of pain in patients undergoing joint replacement.

### Author contributions

V.W., R.G.H., P.D. and A.W.B. were involved in the design, management and delivery of the study. V.W. and A.S. performed the statistical analyses. V.W. and A.S. drafted the manuscript and all authors revised it critically for important intellectual content. All authors gave final approval for the version to be submitted. A.W.B. takes responsibility for the integrity of the work as a whole, from inception to finished article.

### Acknowledgements

The authors thank all patients and staff at Southmead Hospital who were involved in the APEX trials. Particular thanks go to the following consultant orthopaedic surgeon and anaesthetists: Gordon Bannister, John Church, Steve Eastaugh-Waring, Alan Gibson, William Harries, Paul Harvie, Katherine Jenkins, Michael Kelly, Nick Koehli, John Leigh, Sanchit Mehendale, Ronelle Mouton, Andrew Porteous and Jason Webb. The authors also thank the following people who were involved in data collection: Debbie Delgado, Louise Hawkins, Cindy Mann, Leigh Morrison, Dave Rea, Jenny Tyler and Connie Jamera. The team also thank Erik Lenguerrand for his contribution to data cleaning and management.

### Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 1983.

### References

Arendt-Nielsen, L., Nie, H., Laursen, M.B., Laursen, B.S., Madeleine, P., Simonsen, O.H., Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain* 149, 573–581.

Bedson, J., Croft, P.R. (2008). The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskelet Disord* 9, 116.

Bellamy, N., Buchanan, W.W., Goldsmith, C.H., Campbell, J., Stitt, L.W. (1988). Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 15, 1833–1840.

Beswick, A.D., Wylde, V., Goberman-Hill, R., Blom, A., Dieppe, P. (2012). What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic

review of prospective studies in unselected patients. *BMJ Open* 2, e000435.

Black, J.A., Sharp, S.J., Wareham, N.J., Sandbaek, A., Rutten, G.E., Lauritzen, T., Khunti, K., Davies, M.J., Borch-Johnsen, K., Griffin, S.J., Simmons, R.K. (2014). Change in cardiovascular risk factors following early diagnosis of type 2 diabetes: A cohort analysis of a cluster-randomised trial. *Br J Gen Pract* 64, e208–e216.

Dowsey, M.M., Nikpour, M., Dieppe, P., Choong, P.F.M. (2012). Associations between pre-operative radiographic changes and outcomes after total knee joint replacement for osteoarthritis. *Osteoarthritis Cartilage* 20, 1095–1102.

Dowsey, M.M., Nikpour, M., Dieppe, P., Choong, P.F. (2016). Associations between pre-operative radiographic osteoarthritis severity and pain and function after total hip replacement: Radiographic OA severity predicts function after THR. *Clin Rheumatol* 35, 183–9.

Felson, D.T. (2005). The sources of pain in knee osteoarthritis. *Curr Opin Rheumatol* 17, 624–628.

Finan, P.H., Buenaver, L.F., Bounds, S.C., Hussain, S., Park, R.J., Haque, U.J., Campbell, C.M., Haythornthwaite, J.A., Edwards, R.R., Smith, M.T. (2013). Discordance between pain and radiographic severity in knee osteoarthritis: Findings from quantitative sensory testing of central sensitization. *Arthritis Rheum* 65, 363–372.

Goode, A.P., Shi, X.A., Gracely, R.H., Renner, J.B., Jordan, J.M. (2014). Associations between pressure-pain threshold, symptoms, and radiographic knee and hip osteoarthritis: The Johnston county osteoarthritis project. *Arthritis Care Res* 66, 1513–1519.

Kellgren, J.H., Lawrence, J.S. (1957). Radiological assessment of osteoarthritis. *Ann Rheum Dis* 16, 494–502.

Leckie, G., Charlton, C. (2013). runmlwin – A program to run the MLwiN multilevel modelling software from within Stata. *J Stat Softw* 52, 1–40.

Lundblad, H., Kreicbergs, A., Jansson, K.A. (2008). Prediction of persistent pain after total knee replacement for osteoarthritis. *J Bone Joint Surg* 90-B, 166–171.

Martin, R.M., Kramer, M.S., Dahhou, M., Platt, R.W., Patel, R., Bogdanovich, N., Matush, L., Davey Smith, G., Promotion of Breastfeeding Intervention Trial Study Group (2010). Do gastrointestinal tract infections in infancy increase blood pressure in childhood? A cohort study. *J Epidemiol Community Health*, 64, 1068–1073.

Murphy, S.L., Lyden, A.K., Phillips, K., Clauw, D.J., Williams, D.A. (2011). Association between pain, radiographic severity, and centrally-mediated symptoms in women with knee osteoarthritis. *Arthritis Care Res* 63, 1543–1549.

Neogi, T., Frey-Law, L., Scholz, J., Niu, J., Arendt-Nielsen, L., Woolf, C., Nevitt, M., Bradley, L., Felson, D.T., For the Multicenter Osteoarthritis Study (2013). Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: Trait or state? *Ann Rheum Dis* 74, 682–688.

Petersen, K.K., Arendt-Nielsen, L., Simonsen, O., Wilder-Smith, O., Laursen, M.B. (2015). Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain* 156, 55–61.

Rashbash, J., Charlton, C., Browne, W., Healey, M., Cameron, B. (2009). MLwiN Version 2.24. Centre for Multilevel Modelling, University of Bristol.

Suokas, A.K., Walsh, D.A., McWilliams, D.F., Condon, L., Moreton, B., Wylde, V., Arendt-Nielsen, L., Zhang, W. (2012). Quantitative sensory testing in painful osteoarthritis: A systematic review and meta-analysis. *Osteoarthritis Cartilage* 20, 1075–1085.

Valdes, A.M., Doherty, S.A., Zhang, W., Muir, K.R., Maciewicz, R.A., Doherty, M. (2012). Inverse relationship between preoperative radiographic severity and postoperative pain in patients with osteoarthritis who have undergone total joint arthroplasty. *Semin Arthritis Rheum* 41, 568–575.

Wylde, V., Goberman-Hill, R., Horwood, J., Beswick, A., Noble, S., Brookes, S., Smith, A.J., Pyke, M., Dieppe, P., Blom, A.W. (2011a). The effect of local anaesthetic wound infiltration on chronic pain after lower limb joint replacement: A protocol for a



- double-blind randomised controlled trial. *BMC Musculoskelet Disord* 12, 53.
- Wylde, V., Palmer, S., Learmonth, I.D., Dieppe, P. (2011b). Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. *Osteoarthritis Cartilage* 19, 655–658.
- Wylde, V., Palmer, S., Learmonth, I., Dieppe, P. (2013). The association between pre-operative pain sensitisation and chronic pain after knee replacement: An exploratory study. *Osteoarthritis Cartilage* 21, 1253–1256.
- Wylde, V., Lenguerrand, E., Gooberman-Hill, R., Beswick, A., Marques, E., Noble, S., Horwood, J., Pyke, M., Dieppe, P., Blow, A. (2015a). The effect of local anaesthetic infiltration on chronic post-surgical pain after total hip and knee replacement: The APEX randomised controlled trials. *Pain* 156, 1161–1170.
- Wylde, V., Mackichan, F., Bruce, J., Gooberman-Hill, R. (2015b). Assessment of chronic post-surgical pain after knee replacement: Development of a core outcome set. *Eur J Pain* 19, 611–620.
- Wylde, V., Sayers, A., Lenguerrand, E., Gooberman-Hill, R., Pyke, M., Beswick, A., Dieppe, P., Blom, A.W. (2015c). Pre-operative widespread pain sensitisation and chronic pain after hip and knee replacement: A cohort analysis. *Pain* 156, 47–54.
- Yarnitsky, D., Crispel, Y., Eisenberg, E., Granovsky, Y., Ben-Nun, A., Sprecher, E., Best, L.-A., Granot, M. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain* 138, 22–28.

## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Table S1.** Demographic and clinical characteristics of patients undergoing total hip replacement ( $n = 90$ ) and total knee replacement ( $n = 75$ ) not included in the analysis because of missing data.

**Table S2.** Descriptive statistics for patients undergoing total hip replacement ( $n = 90$ ) and total knee replacement ( $n = 75$ ) not included in the analysis because of missing data.