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Pre-operative pressure pain thresholds do not meaningfully explain satisfaction or improvement in pain after knee replacement: a cohort study

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SUMMARY

Objectives: Pain sensitization could be a risk factor for poor outcomes after knee replacement surgery (KR) for knee osteoarthritis (KOA). We aimed to evaluate the association between pre-operative central and peripheral pain sensitization measured using a digital pressure algometer and KR outcomes.
Methods: Consecutive patients with severe KOA listed for KR were recruited. Sociodemographic and symptoms data were collected prior to surgery. Pre-operative pressure pain thresholds (PPTs) were measured using a digital pressure algometer at the index knee and forearm. Patient satisfaction at 6 and 12 months after KR was assessed using a 4-point Likert scale, and dichotomized to satisfied and dissatisfied to KR. Western Ontario and McMaster Universities Index (WOMAC) Pain and function was assessed. The associations between pre-operative PPTs with KR outcomes at 6 and 12 months were evaluated.
Results: Of the 243 patients recruited, response rate at 6 and 12 months were 95.5% and 96.7%. The dissatisfaction rates were 8.2% and 5.1% at 6 and 12 months. There was no statistically significant association between pre-operative index knee or forearm PPTs and patient satisfaction. PPTs measured at the knee, but not the forearm, were weakly associated with change in the WOMAC pain score at 12 months, after adjustment for confounding factors.
Conclusion: Pre-operative central sensitization, measured by handheld digital algometry, was not statistically significantly associated with satisfaction or change in pain after KR. Pre-operative peripheral sensitization was associated with change in pain symptoms after KR; however, this association was weak and unlikely to be a meaningful predictor of KR outcome in clinical practice.

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Introduction

Knee osteoarthritis (KOA) is one of the leading causes of disability worldwide, and knee replacement surgery (KR) is the only treatment that can effectively relieve pain and restore function for patients with severe KOA. The volume of KR has increased over the past decade[1,2], and the demand for primary KR has been projected to grow[2]. However, up to 20% of patients reported little or no improvement in pain after surgery[3], which can

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have a significant negative impact on patients as well as the society[4].

The reasons why some patients do not respond to KR are poorly understood, although the aetiology is likely to be multifactorial[5]. Traditional sociodemographic factors such as age, gender and body mass index (BMI) cannot fully explain the variation in response[6,7]. Patients with KOA have central pain sensitization represented by lower pain thresholds[8–10], that may potentially predict chronic pain after KR[11–14]. The concept of pain sensitization is characterized by pronounced changes in joint nociceptors and the nociceptive processing in the spinal cord, as well as the supraspinal cord levels such as the brainstem, thalamus and cerebral cortex that process emotion and fear[15]. These changes have been implicated as part of the pathogenesis of chronic pain in KOA[16].

Pain sensitization is traditionally measured in a research context using quantitative sensory testing (QST). A number of different QST techniques are available but may have limited utility in a clinical setting due to expense, non-transportable equipment and a high technical level of skills required to administer and interpret the tests. Measurement of pressure pain thresholds (PPTs), using a digital algometer, is an inexpensive and simple method of QST, thereby increasing its potential for use in a clinical context. Preliminary studies on KOA patients have demonstrated the validity and reliability of PPT measurement[17].

Although KR is primarily performed to relieve chronic pain, patient satisfaction is a key outcome to assess after elective procedures. Satisfaction is also one of the core domain set endorsed by the Outcome Measures in Rheumatology (OMERACT)-Total joint replacement working group, to be reported in every clinical trial[18]. Satisfaction is a multidimensional construct, stretching beyond pain relief and functional improvement to encompass many different factors related to a person's psychological status, experience and expectations[19]. However, patient satisfaction after KR is a less well studied concept compared to pain relief and functional improvement[20,21]. Symptomatic relief and satisfaction may not be equivalent[22,23]. Factors related to inadequate pain relief were reported to be different among patients with different levels of satisfaction[24]. Among those moderately dissatisfied, local sensitization and tenderness were associated with persistent pain; in the most dissatisfied, pain was associated with instability, stiffness and negative social support. This also suggests satisfaction is a separate domain from pain relief. Better understanding of psychosocial and neural factors that explain patient satisfaction could inform future work to design interventions to improve patients' experiences and satisfaction with elective KR surgery.

Pain sensitization represents a concept of distorted pain processing from peripheral to the cerebral level. People with anxiety[25] and depression[26] have altered sensitivity to different experimental painful stimulus compared to healthy controls. People with experimentally induced temporary optimistic state have lower pain ratings during a cold pressure task[27]. In addition, associations have been found between pain tolerance with social functioning[28], bonding and attachment[29], which were also correlated with variation in μ-opioid receptor viability on function brain magnetic resonance imaging. Endogenous endorphin and the μ-opioid receptor system that are known for their roles in pain control are increasingly recognized to have pivotal roles in generating positive emotion, reducing stress reaction, and maintenance of cognitive functions. Therefore, we hypothesize that pain sensitization may have a direct or indirect impact upon both pain and satisfaction outcomes after KR. In this prospective cohort study, we aimed to evaluate the association between pre-operative pain sensitization measured by a digital pressure algometer, and patient satisfaction and change in pain after KR in an Asian population.

Methods

Patient and study design

From June to November 2015, 249 consecutive patients with severe KOA listed for KR were recruited at the Pre-admission Assessment Centre of Singapore General Hospital (SGH). Questionnaires and PPT assessments were completed 1–2 weeks prior to surgery. The study protocol was approved by the Singhealth Central Institution Review Board (CIRB Ref 2014/2010), and all patients provided informed, written consent before participation. This report adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations[30].

We excluded patients enlisted for KR for other diagnosis and revision surgery; and patients with cognitive impairment or dementia established by the short portable mental status questionnaire[31]. Sociodemographic variables, including age, gender, ethnicities, education level, occupation, and smoking habit were collected prior to surgery. All patient-reported outcomes were available in English and Simplified Chinese and were self-administered by patients in either language of patients' choice. Comorbidities were collected using the Functional Comorbidity index[32]. Body weight and height were measured. The severity of KOA in the index knee on radiography was assessed by the Kellgren–Lawrence grading[33]. Index knee was defined as the knee listed for KR, and the dominant knee in case of bilateral KR. One trained researcher (ZXL) graded the radiographs and a second researcher (YYL) independently graded 30% of radiographs for inter-rater reliability. Both researchers were blinded to the clinical data of patients at the time of scoring. The intra-class correlation coefficient (ICC) of KL grading was 0.86 (95% confidence interval, CI: 0.76–0.91).

Pressure pain threshold assessment

Pre-operative PPTs of each patient was measured using a handheld digital algometer (Somedic AB, Sweden) on the day of recruitment. PPTs were measured at two body sites: the index knee and the right forearm. These body sites were chosen to provide evidence of peripheral sensitization (index knee) and central sensitization (forearm). Peripheral sensitization was assessed at the medial joint line of the index knee (PPT knee). Central sensitization was assessed at the mid-point between the wrist and elbow of the volar aspect of right forearm (PPT forearm). All recruited patients were pain-free in their right forearm at time of assessment. A standardized protocol was adopted with multiple video conferences with the original research team[17]. One trained designated staff (SQX) performed all PPT measurements to minimize measurement variability. A 1 cm^2 probe was held perpendicular to the skin and pressure was applied at a constant rate of 10 kPa/s. The patients were instructed to say “stop” at the very first sensation of pain, at which point the PPT reading was recorded. A total of three readings were taken at each site, with the average of the last two taken to increase reliability. The position of the algometer on the skin was altered very slightly between each reading to avoid sensitization of the test area.

Repeat PPT measurements were taken for 25 patients on the day of KR surgery (median 9 days from the first PPT measurements, range 2–16 days) for test–retest reliability evaluation. The ICC (95% CI) of PPT forearm and PPT knee were 0.80 (0.64–0.91) and 0.72 (0.48–0.86), respectively.

Knee symptom evaluation

Pain, stiffness and physical function of the knee were measured using the self-administered Western Ontario and McMaster

Universities Index (WOMAC)[34]. A score for each subscale was calculated and transformed into a 0–100 scale; with a higher score indicate worst symptoms. Pain in the left and right knee was assessed separately using the WOMAC pain scale. Patients completed the WOMAC index prior to surgery and at 6 and 12 months after surgery.

Other pre-operative evaluations

Patients self-reported yes/no to having pain in nine body sites (neck, lower back, left and right shoulder/elbow or hand, the non-index knee, left and right hip, left and right ankle or foot) and responses were summed to produce a count of the number of painful body sites. Symptoms of anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS)[35]. Self-efficacy was assessed using the Pain Self-efficacy questionnaire[36], which has been shown to predict functional outcomes after KR[37]. The 10-item Pain Self-efficacy questionnaire assesses how confidently patients can cope with their daily lives, despite the knee pain. Total scores ranged from 0 to 60, with a higher score indicate better self-efficacy. Patients' expectations of KR were evaluated by asking about expected pain after recovery from surgery (not at all painful through to very painful), and expected limitations in everyday activities after recovery from surgery (not limited at all through to greatly limited). The mean scores of the above ranged from 1 to 3.5, with a lower score indicating higher expectations[38].

Outcome of KR surgery

The outcomes of KR were collected by administrating questionnaires over the telephone at 6 and 12 months after KR. One trained telephone interviewer, who identified herself as independent from the surgical team, collected all post-operative outcomes. She explained to participants that their responses would be stored anonymously and not directly fed back to the surgeons. To assess satisfaction, participants were asked “How would you rate your overall satisfaction with the surgery?” with responses on a 4-point Likert scale (very satisfied/somewhat satisfied/somewhat dissatisfied/very dissatisfied)[39,40]. The aim was to assess satisfaction with the result of the intervention, rather than the process of care. Percentage changes in WOMAC pain scores were also calculated using WOMAC pain at 6 or 12 months minus baseline WOMAC pain, divided by baseline WOMAC pain. Lower (and negative) values indicated greater improvement in pain.

Patients' perspectives on their outcome were explored with two questions: “How do you rate the improvement in 1) pain and 2) functional ability of the knee that you had surgery? (no change or worsen/slightly better/a great deal better/completely resolved or restored).

Statistical analysis

Patient dissatisfied to KR were defined as those reported overall satisfaction as somewhat dissatisfied and very dissatisfied. We assumed the dissatisfaction rate to KR to be 10% based on previous data from our center[41], and postulated an odd ratio (OR) of 3.5 for PPTs in predicting dissatisfaction after KR. This OR was a conservative estimate based on a study that reported an OR of 9 for pain threshold measured by an electric stimulator in predicting KR outcomes[11]. We assumed the multi-collinearity between the pain threshold measurement and other demographic variables to be moderate (a multiple R2 of 50%, or equivalently a Variance inflation Factor of 2), and the standard deviation (SD) of PPT measurement to be 86 units. Based on these assumptions and specifying the margin of error to be 1% of the postulated OR, the required sample size was 116 patients. We therefore initially aimed to recruit at least 180 patients to account for 30% loss to follow up. During our study, more data was published showing a smaller effect size than the initial data, and therefore we made the decision to recruit as many patients as possible within the planned recruitment period.

Analysis was performed using IBM SPSS statistic package, version 23. All variables were reported as means, standard deviations or median, interquartile range for parametric and non-parametric continuous measures; and as frequencies for categorical variables. Independent pre-operative variables were compared between patients who were satisfied/dissatisfied with KR at 6 months and 12 months after surgery using Mann–Whitney *U* test for continuous variables and chi-square test for categorical variables. As most independent variables were not normally distributed, non-parametric test was used for consistency. Generalized linear regression models were used to estimate the associations of baseline variables with non-responders to KR and the percentage change in WOMAC pain at 6 and 12 months after surgery respectively. The percentage change of WOMAC pain at 6 and 12 months were reflected (maximum value plus one minus the percentage change) and then squared to achieve normality in the multivariable analyses. We assessed a minimally sufficient set of confounding variables using directed acyclic graphs (DAG) visual representations of possible causal assumptions (DAGitty v2.3)[42] that minimize bias for the total effect of PPT on change on WOMAC pain[43]. We repeated the regression models with adjustment of the minimal sufficient set based on the DAG analysis. Following standard practice, *P* values of <0.05 were taken as statistically significant.

We explored the associations of baseline variables with persistent pain after KR. Persistent pain post-KR was defined as patients answering “no change or worsen” or “slightly better” to “How do you rate the improvement in pain” at 6 and 12 months after KR.

Results

Of the 249 patients who were approached prior to surgery, 243 were eligible and consented to participate (Fig. 1). Outcomes data were collected from 232 patients (95.5%) at 6 months and 235 patients (96.7%) at 12 months. Pre-operative characteristics of participants are provided in Table I. The mean age of participants was 66 years, 79% were female and 82% were Chinese. The high female: male ratio of participants in this study is consistent with data from numerous large Asian registries and cohorts[44–47]. The majority (95%) of patients underwent total knee replacement (TKR), with 5% of patients having a unicompartmental knee replacement (UKR). The majority of patients had moderate to severe KOA on radiographs, and moderate knee symptoms. There was no statistically significant difference between patients satisfied and dissatisfied to KR in terms of pre-operative characteristics except that dissatisfied patients had statistically significant worse WOMAC pain and function and more painful body sites.

At 6 and 12 months, 8.2% and 5.1% of patients were “very dissatisfied” or “somewhat dissatisfied” with the outcome of their KR. However, among those reported "satisfied", there was a sizable proportion of patients reported slight or no improvement in terms of pain (33.5%) and function (40.6%) at 6 months, with similar results at 12 months after KR (Table II). Only a minority of patients reported complete resolution of pain (11.3%), and unrestricted functional ability (7.1%) at 6 months.

The distribution of baseline PPT forearm and knee as stratified by satisfaction and pain improvement at 6 months are shown in Fig. 2, and the detailed scores for all time-points were summarized in Supplementary Table 1.

In the univariable analysis, there was high correlation between PPT forearm and PPT knee (Spearman's Rho (r) = 0.579, $P < 0.001$),

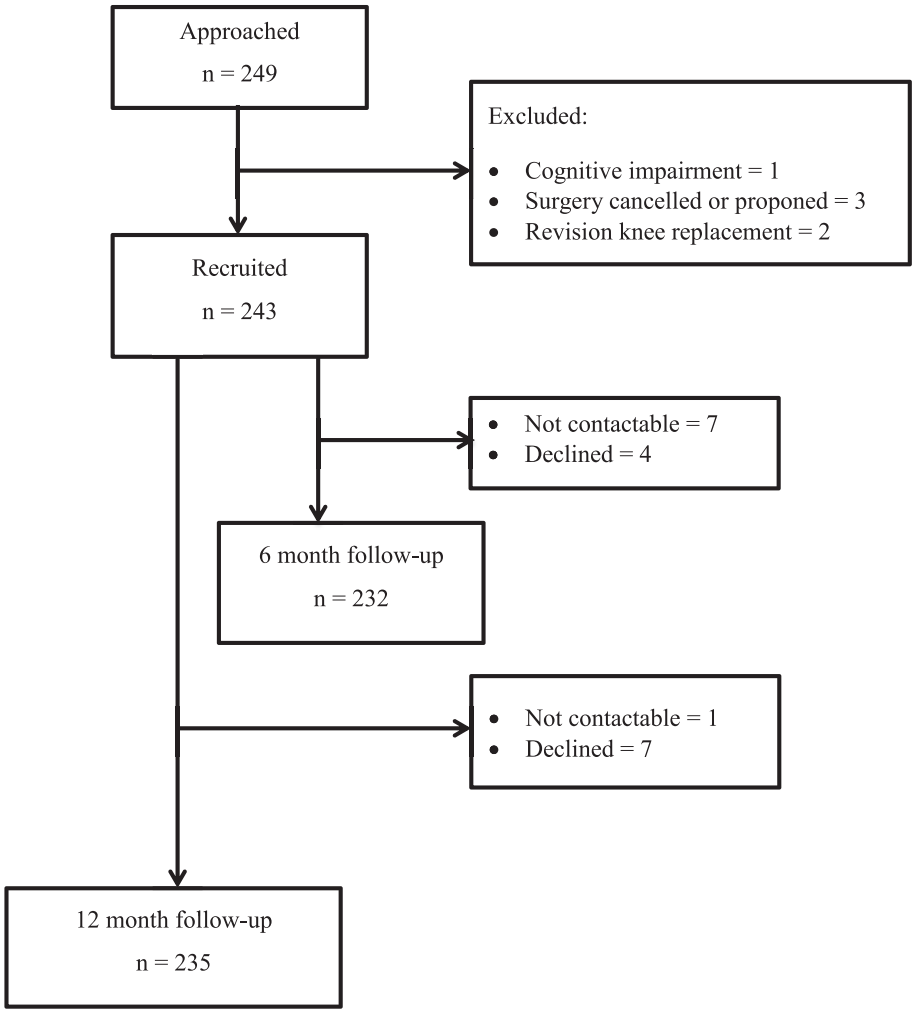

Fig. 1. Flow diagram of the study.

but not for PPTs with baseline WOMAC pain (PPT forearm $r = -0.108$, $P = 0.089$; PPT knee $r = -0.104$, $P = 0.100$). In the multivariable analysis, the number of painful body sites, pre-operative WOMAC pain scores and percentage change in WOMAC pain scores were associated with non-responders at 6 months (Table III). Self-efficacy, pre-operative WOMAC pain scores and percentage change in WOMAC pain scores were associated with non-responders at 12 months. In a model without percentage change in WOMAC pain and function (as they may be mediators rather than true confounders), not enough empirical evidence was found to claim any association between PPT arm or knee with satisfaction (all $P > 0.05$).

In addition, we did not find any statistical evidence of association between PPT forearm and change in WOMAC outcomes. However, there was empirical evidence of association of PPT knee with percentage change in WOMAC pain at 6 months and 12 months, after adjustment for age, gender and BMI. After adjustment for all other variables including baseline WOMAC scores, PPT knee was statistically significantly associated with percentage change in WOMAC pain at 12 months (Table IV).

We constructed empirical DAG (Supplementary Fig. 1) that may explain possible causal effect of PPT on change of WOMAC pain, and a minimally sufficient adjustment set included the following variables: KL grading, anxiety, depression, expectation, number of painful body sites and pain. Repeated regression models with adjustment of the minimally sufficient adjustment set did not materially change the result (Supplementary Table 2). PPT knee was statistically significantly associated with change in WOMAC pain at 12 months, while no association was noted between PPT arm and change in pain.

We explored possible influence of radiographic severity of KOA with PPT knee but noted no statistically significant interaction between radiographic severity of KOA with PPT measured at both knee and forearm for change in WOMAC outcomes (data not shown).

In the exploratory multivariable analysis for persistent pain after KR, there were 39.7% and 27.9% of patients who did not have major pain improvement at 6 and 12 months after KR. There was no empirical evidence to claim any association between PPTs at both sites with persistent pain (Supplementary Table 3).

Discussion

The overall dissatisfaction rate to KR in this study was relatively low. The key driver for dissatisfaction was less improvement in WOMAC pain. There was statistically significant association between number of painful body sites and non-responder status, suggesting that the presence of widespread pain may have a negative impact on KR outcomes. However, there was not enough empirical evidence to claim association between PPT forearm, as a

Table I
Baseline characteristics of recruited patients ($n = 243$)

	Total ($n = 243$)	Satisfied at 6 month ($n = 212$)	Dissatisfied at 6 month ($n = 20$)	*P*
Age*	66.0 (8.3)	66.1 (8.4)	66.3 (6.9)	0.954
Female, *n* (%)	191 (78.6)	168 (79.2)	14 (70.0)	0.336
Ethnicity				
Chinese, *n* (%)	200 (82.3)	176 (83.0)	15 (75.0)	
Non-Chinese, *n* (%)	43 (17.7)	36 (17.0)	5 (25.0)	0.369
Education				
None	33 (13.6)	29 (13.7)	3 (15.0)	
Primary	96 (39.5)	85 (40.1)	8 (40.0)	
Secondary and above	114 (46.9)	98 (46.2)	9 (45.0)	0.986
Working, *n* (%)	76 (31.3)	66 (31.1)	7 (35.0)	0.722
Ever smoker, *n* (%)	26 (10)	21 (9.9)	3 (15.0)	0.511
Current smoker, *n* (%)	11 (4.5)	10 (4.7)	1 (5.0)	0.955
Living alone, *n* (%)	17 (7)	14 (6.6)	1 (5.0)	0.780
Surgery type				
TKR	231 (95.1)	202 (95.3)	19 (95.0)	
UKA	12 (4.9)	10 (4.7)	1 (5.0)	0.995
Bilateral	13 (5.3)	13 (6.2)	0	
Unilateral	230 (94.7)	211 (98.6)	21 (100)	0.096
Radiography of index knee				
KL1	1 (0.4)	0	0	
KL2	12 (5.1)	10 (4.7)	1 (5.0)	
KL3	98 (41.9)	82 (38.7)	10 (50.0)	
KL4	123 (52.6)	113 (53.3)	8 (40.0)	0.542
Missing	9 (3.7)	7 (3.3)	1 (5.0)	
BMI†	27.9 (5.5)	27.8 (5.4)	28.5 (6.8)	0.892
No. of comorbidities†	2.0 (1.0)	2.0 (1.0)	2.0 (1.8)	0.376
No. of painful body sites with pain†	1.0 (2.0)	1.0 (1.0)	1.0 (2.5)	0.108
Years of pain in index knee†	3.0 (3.0)	3.0 (3.0)	3.0 (1.8)	0.942
Baseline WOMAC pain (0–100)†	40.0 (20.0)	35.0 (25.0)	50.0 (37.5)	0.003
Baseline WOMAC function (0–100)†	30.9 (25.0)	29.4 (23.5)	42.6 (34.6)	0.005
6 month WOMAC pain (0–100)†	10.0 (20.0)	5.0 (15.0)	40.0 (28.8)	<0.0001
6 month WOMAC function (0–100)†	10.3 (12.9)	8.8 (11.8)	44.9 (32.0)	<0.0001
% change in WOMAC pain	−77.4 (−50.0)	−80.0 (−47.1)	−24.0 (82.5)	<0.0001
% change in WOMAC function	−66.7 (51.2)	−68.3 (−48.6)	−12.8 (49.2)	<0.0001
HADS anxiety (0–21)†	2.0 (3.0)	2.0 (3.0)	3.0 (4.5)	0.053
HADS depression (0–21)†	2.5 (3.0)	2.0 (3.0)	3.5 (4.5)	0.074
Self-efficacy (0–60)†	47.0 (10.0)	47.0 (9.0)	42.5 (12.8)	0.028
Baseline PPT forearm, kPa†	171.5 (110.0)	171.8 (117.9)	167.8 (97.9)	0.080
Baseline PPT knee, kPa†	175.0 (121.0)	173.5 (122.5)	132.8 (111.0)	0.260

BMI = body mass index; No. = number; TKR = total knee replacement surgery; UKR = uni-compartmental knee replacement surgery; KL = Kellgren-Lawrence grading of tibiofemoral joint on radiograph of index knee; WOMAC = Western Ontario and McMaster Universities Index; HADS = hospital anxiety and depression scale; PPT = pressure pain threshold.
* Mean (SD).
† Median (Interquartile range).

Table II
Patients' perspectives of index knee condition 6 and 12 months after KR

		6 months	12 months
Patients satisfied	Total, *n* (%)	212 (91.4)	223 (94.9)
	Improvement in pain (%)		
	No change or worsening pain	0.5	0
	Slightly better	33.0	22.9
	A great deal better	55.2	74.4
	Pain completely absent	11.3	2.7
	Improvement in functional ability (%)		
	No change or worsening functional ability	0.5	0
	Slightly better	40.1	27.8
	A great deal better	52.4	70.9
	Functional ability completely unrestricted	7.1	1.3
Patients dissatisfied	Total, *n* (%)	20 (8.6)	12 (5.1)
	Improvement in pain (%)		
	No change or worsening pain	45.0	66.7
	Slightly better	50.0	33.3
	A great deal better	5.0	0
	Pain completely absent	0	0
	Improvement in functional ability (%)		
	No change or worsening functional ability	40.0	66.7
	Slightly better	55.0	33.3
	A great deal better	5.0	0
	Functional ability completely unrestricted	0	0

surrogate of pre-operative central sensitization, and satisfaction or pain outcomes after KR. PPT knee as a surrogate of peripheral sensitization was empirically found to be weakly associated with percentage change in WOMAC pain at 6 and 12 months after adjustment for confounding factors. The differences in baseline PPT forearm and knee for patients endorsing satisfied vs dissatisfied were not statistically significant and had overlapping confidence intervals. Our current study adds to the literature by reporting lack of statistically significant evidence of association between pre-operative central sensitization, assessed using PPTs, and satisfaction or change in pain scores after KR, thereby implying that pre-operative central sensitization may not bring meaningful utility in predicting TKR outcomes.

Strengths of this study include its relatively large sample size, high follow up rates, and the use of validated outcome measures. Pain sensitization was assessed through measuring pain thresholds, which have been shown to have good test–retest reliability[17]. To minimize variability of PPT measurement, one designated staff personnel was tasked to do the measurement and have achieved good test–retest reliability for the measurements. The unique strength of our study is that it is the first to evaluate the association between pre-operative pain sensitizations and satisfaction outcomes of KR, together with various psychosocial factors. Satisfaction to KR stretches beyond pain relief and functional improvement

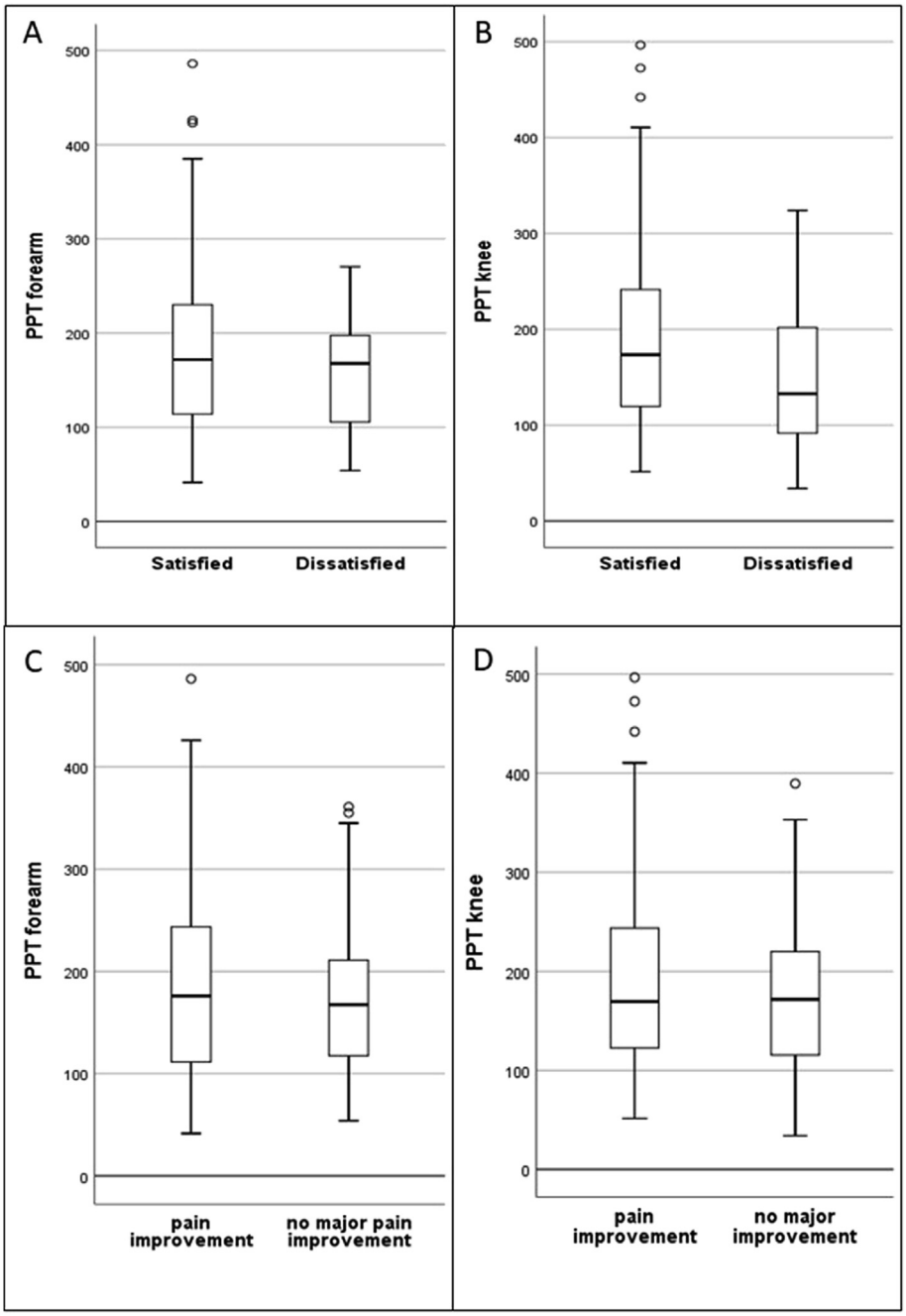

Fig. 2. Box plot of baseline PPT forearm and knee. A. Baseline PPT forearm as stratified by satisfaction at 6 months. B. Baseline PPT knee as stratified by satisfaction at 6 months. C. Baseline PPT forearm as stratified by pain improvement at 6 months. D. Baseline PPT knee as stratified by pain improvement at 6 months.

to encompass many different factors related to a person's experience and expectation before and after KR[19,20]. It is also the first Asian study to evaluate whether pre-operative measures of pain sensitization are associated with the outcome of KR. Patients from different counties and different races have different expectations regarding KR[48,49]. Our study sample is also representative of the local population undergoing KR with a similar gender mix, age range and ethnicity as reported by a KR clinical pathway database[41,45].

There are a number of limitations of our study that should be considered when interpreting the results. The overall aim was to investigate the association of PPT with satisfaction and change in pain outcomes, which cannot be interpreted as causative effect. The risk estimates for co-variates in the statistical model should not be interpreted as directly comparable. The interpretation of the empirical DAG and minimally sufficient set of confounders rely on the robustness of the empirical graph and cannot assess effect modification due to interactions or correlations between variables. There was minimal variability in the radiographic severity of OA among participants (41.9% KL grade 3 and 52.6 % KL grade 4) and therefore the findings of this exploratory analysis should be interpreted with caution. Although we collected data on a number of potential predictors of outcomes, other factors which may affect KR outcome, such as pain catastrophizing and fulfillment of expectations were not included in our analysis[50]. Nevertheless, we adjusted for key confounding factors such as age, gender, BMI,

Table III
Multivariable analysis for variables associated with overall dissatisfaction at 6 month and 12 month

	Dissatisfaction at 6 month			Dissatisfaction at 12 month		
	Relative risk	95% CI	*P*	Relative risk	95% CI	*P*
Age	1.091	0.972; 1.224	0.140	0.882	0.684; 1.136	0.330
Gender						
Male	2.592	0.152; 44.077	0.510	3.409	0.140; 83.194	0.452
Female	1.00		–	1.00		–
Education						
Primary or below	0.749	0.098; 5.755	0.781	3.042	0.104; 89.378	0.519
Secondary or above	1.00		–	1.00		–
Radiography						
KL 2–3	0.235	0.019; 2.897	0.259	5.669	0.503; 63.835	0.160
KL 4	1.00		–	1.00		–
BMI, kg/m^2	0.861	0.678; 1.094	0.220	1.093	0.814; 1.466	0.555
No. of comorbidity	0.769	0.230; 2.573	0.670	2.131	0.650; 6.982	0.211
No. painful body sites	2.114	1.009; 4.432	*0.047*	1.714	0.656; 4.476	0.271
Anxiety	0.720	0.431; 1.204	0.210	3.218	0.929; 11.139	0.065
Depression	1.177	0.725; 1.911	0.509	0.651	0.262; 1.616	0.354
Self-efficacy	0.957	0.855; 1.072	0.447	1.315	1.028; 1.682	*0.030*
Expectation	3.775	0.262; 54.443	0.329	0.941	0.079; 11.254	0.961
PPT knee	0.999	0.983; 1.016	0.947	1.007	0.983; 1.031	0.590
PPT forearm	0.994	0.979; 1.009	0.406	1.002	0.986; 1.018	0.808
WOMAC pain baseline	1.294	1.079; 1.552	*0.005*	1.306	1.041; 1.639	*0.021*
WOMAC function baseline	0.919	0.811; 1.040	0.181	0.965	0.832; 1.118	0.634
% change in WOMAC pain	1.122	1.045; 1.204	*0.001*	1.074	1.023; 1.127	*0.004*
% change in WOMAC function	1.020	0.991; 1.050	0.177	1.072	1.014; 1.133	*0.014*

BMI = body mass index; No. = number; WOMAC = Western Ontario and McMaster Universities Index; PPT = pressure pain threshold.
Note: The interpretations of risk estimates of different variables are not directly comparable.

Table IV
Multivariable analysis for variables associated with percentage change in WOMAC pain at 6 month and 12 month

	% Change in WOMAC pain At 6 month			% Change in WOMAC pain At 12 month		
	Regression coefficient*	95% CI	*P*	Regression coefficient*	95% CI	*P*
Age	83.595	−91.958; 259.149	0.351	60.522	−161.777; 282.820	0.594
Gender						
Male	−2050.670	−5481.190; 1379.850	0.241	−3362.842	−7717.745; 992.062	0.130
Female	Ref	–	–	Ref		–
Education						
Primary or below	371.679	−2317.746; 3061.103	0.786	−267.879	−3680.137; 3144.378	0.878
Secondary or above	Ref	–	–	Ref		–
Radiography						
KL 2–3	−2982.181	−5607.348; −357.014	*0.026*	407.356	−2931.880; 3746.593	0.811
KL 4	Ref	–	–			
BMI, kg/m^2	−39.986	−336.551; 256.579	0.792	342.264	−39.947; 724.476	0.079
No. of comorbidity	510.013	−842.817; 1862.843	0.460	−713.270	−2437.686; 1011.146	0.418
No. painful body sites	39.447	−1030.474; 1109.368	0.942	−457.292	−1816.568; 901.985	0.510
Anxiety	−66.617	−678.135; 544.900	0.831	−94.234	−881.406; 692.937	0.814
Depression	−106.394	−783.805; 571.017	0.758	−133.464	−977.308; 710.381	0.757
Self-efficacy	31.684	−124.100; 187.468	0.690	62.669	−135.124; 260.462	0.535
Expectation	1372.739	−1515.197; 4260.676	0.352	−310.065	−3982.647; 3362.517	0.869
PPT knee	18.063	−1.369; 37.494	0.068	31.793	6.985; 56.602	*0.012*
PPT forearm	−.629	−18.742; 17.484	0.946	−11.447	−34.428; 11.534	0.329
WOMAC pain baseline	196.129	85.733; 306.524	*<0.001*	349.989	209.888; 490.091	*<0.001*
WOMAC function baseline	−111.444	−225.508; 2.620	0.055	−153.478	−297.513; −9.442	*0.037*

No. = number; BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Index; PPT = pressure pain threshold; KL = Kellgren-Lawrence grading of tibiofemoral joint on radiograph of index knee.
* The interpretations of risk estimates of different variables are not directly comparable.

baseline WOMAC pain and various psychological factors. We did not control for analgesic use prior to PPT measurements, which may affect pain perception assessments. Also this study only evaluated a single static QST parameter, and further research is needed to build on preliminary research that suggests that dynamic QST parameters may be associated with outcome after KR[51].

Some patients with KOA have been shown to have pain sensitization both at peripheral and central levels[8,9,52–54], and this may be one of the underlying reasons for persistent pain after KR[11]. The measure of pain sensitization has been explored using various methods, such as pain at rest and QST. Of all the somatosensory changes in KOA, pressure hyperalgesia has been found to be the most prevalent[55], and reliable[17]. Significant associations between PPTs and pain at baseline have been described in some studies[8,53,56], but not all[57], including ours. The limited number of studies that have examined the association between pre-operative PPTs and KR outcomes reported conflicting results regarding the use of PPT in predicting joint replacement outcomes[11,51,57,58]. Pre-operative pain sensitization that measured a low pain threshold to electrical stimulus was found to be statistically significantly associated with persistent pain after KR[11]. Another study showed that PPT measured at forearm predicts post KR movement pain but

not pain on rest[58]. A post hoc analysis of patients recruited to two clinical trials have found that pre-operative PPTs were not predictive of the amount of pain relief that patients gain from joint replacement surgery[57]. However, subsequent subgroup analysis revealed that KOA patients with less severe radiographic damage and who had greater widespread hyperalgesia benefitted less from surgery[59]. This suggests that the effect of pain sensitization may affect joint replacement surgery outcomes, but may vary according to the severity of OA.

The finding of the current study has several clinical and methodological implications. For the clinical aspect, although central sensitization was not statistically significantly associated with changes in either satisfaction or pain symptoms outcomes after controlling for several sociodemographic and psychological factors, peripheral sensitization was empirically found to have weak association with the percentage change in WOMAC pain after surgery. Normalization of the pre-operative pain-processing abnormalities after surgery has been demonstrated in some studies[12,54], suggesting that these abnormalities may be maintained by peripheral nociceptive inputs. Of note is that although there was statistically significant association between PPT knee and change in pain outcomes, a *P*-value <0.05 does not necessarily imply clinical relevance[60]. Indeed, the distribution of baseline PPT forearm and knee between patients who reported diverging satisfaction and pain improvement outcomes had overlapping confidence intervals. Given the small differences in PPT between satisfaction groups, the development of a cut-off of PPT that predicts KR outcomes would be impossible. For the methodological aspect, the associations of PPT knee with satisfaction and change in pain symptoms were small compared to the OR of 9.0 that was reported in a previous study[11]. With this small effect size and the low dissatisfaction rate of 5–9%, the sample size in this study was under-powered to demonstrate a statistically significant association between PPTs and KR outcomes, despite a large sample size comparable to similar studies. Our findings, however, are consistent with a previous study[57], providing further evidence that PPTs, measured using a handheld digital algometer, have little predictive value to preoperatively identify non-responders to KR, for both satisfaction and pain outcomes. A recent study in Denmark has explored various methods of measuring preoperative pain sensitization and KR outcome. The study found that central sensitization measured using a computer-controlled cuff algometer placed on the upper leg which assesses deep somatic tissue pain sensitivity, predicted postoperative pain relief after KR[51]. In the same study, widespread pain sensitization measured by cuff and handheld algometry derived different sensory profiles that had different predictive values for postoperative outcomes. Other pain sensitization mechanisms such as temporal summation of pain (facilitated pain responses to repeated painful stimulation)[8,56], and conditioned pain modulation (central inhibition of pain pathway)[54,56] were found to be abnormal in KOA patients compared to healthy controls. These modalities may be useful QST tools for pre-operatively predicting KR outcomes. Mounting evidence have shown that central sensitization is present in some patients with KOA, however, further research is needed to identify the mechanism underlying chronic pain in KOA and better measurement modalities that may predict KR outcomes. Research incorporating multimodal sensory testing could provide further elucidation on the mechanisms contributing to chronic pain after KR.

Our study found that over one-third of the patients still reported little or no improvement in pain and function at 6 months after surgery. These figures remained similar at 12 months after surgery, by which time outcomes plateau and little further improvement in pain can be expected. Previous studies have found that some patients with residual symptoms report high satisfaction with their outcomes[22,23] reflecting that satisfaction is a different or boarder concept than pain relief. The key factors reported to be associated with satisfaction include degree of improvement in pain and function, and patient expectations[20,21]. Other important factors include depression and pain in other body parts[21]. Among patients with differing level of satisfaction, inadequate pain relief may be driven by different factors. In a recent study, peripheral sensitization was found to be associated with inadequate pain relief among patients with less dissatisfaction, but not among those most dissatisfied[24]. The factors related to inadequate pain relief may be different in patients with different levels of satisfaction. Reporting of satisfaction with KR outcomes can vary depending on the level of responses, the context, expectations of patients and the satisfaction domain being assessed[6]. For example, patients can be satisfied with pain relief, but not satisfied with their ability to perform leisure activities[61]. Our study observed that a high proportion of satisfied patients reported little improvement of pain and function, and the reasons for this warrants further investigation.

Conclusion

Pre-operative central sensitization measured by handheld digital algometry was found to be not statistically significantly associated with satisfaction or improvement in pain after KR. On the other hand, there was some statistical evidence of association between pre-operative peripheral sensitization and change in pain symptoms after KR; however, since this association was rather weak, it is unlikely to be a meaningful predictor of KR outcome to be used in clinical practice.

Author contributions

YYL, BC, JT, VW and PD conceptualized and designed the study; YYL, SQX, ZL, SBW, HCC, and WY acquired the data; YYL, QF and BC performed the data analysis; all authors interpreted the data; YYL, ZL, QF and VW drafted the manuscript; all authors critically revised and approved the final version of manuscript. All authors take responsibility for the integrity of the work as a whole.

Conflict of interest

None of the authors (YYL, ZL, QF, VW, SQX, SJY, NNL, HCC, WY, MHT, BC, SBW, PD, JT) have any financial disclosures or notable competing interests.

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Supplementary data

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References

1. Cram P, Lu X, Kates SL, Singh JA, Li Y, Wolf BR. Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991–2010. JAMA 2012;308:1227–36.

2. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Jt Surg Am Vol 2007;89:780–5.
3. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. 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 2012;2:e000435.
4. Jeffery AE, Wylde V, Blom AW, Horwood JP. "It's there and I'm stuck with it": patients' experiences of chronic pain following total knee replacement surgery. Arthritis Care Res 2011;63:286–92.
5. Toms AD, Mandalia V, Haigh R, Hopwood B. The management of patients with painful total knee replacement. J Bone Jt Surg Br Vol 2009;91:143–50.
6. Wylde V, Dieppe P, Hewlett S, Learmonth ID. Total knee replacement: is it really an effective procedure for all? Knee 2007;14:417–23.
7. Judge A, Arden NK, Cooper C, Kassim Javaid M, Carr AJ, Field RE, *et al*. Predictors of outcomes of total knee replacement surgery. Rheumatology 2012;51:1804–13.
8. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, *et al*. Sensitization in patients with painful knee osteoarthritis. Pain 2010;149:573–81.
9. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23:1043–56.
10. Suokas AK, Walsh DA, McWilliams DF, Condon L, Moreton B, Wylde V, *et al*. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2012;20:1075–85.
11. Lundblad H, Kreicbergs A, Jansson KA. Prediction of persistent pain after total knee replacement for osteoarthritis. J Bone Jt Surg Br Vol 2008;90-B:166–71.
12. Kosek E, Ordeberg G. Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatment. Eur J Pain 2000;4:229–38.
13. Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. Pain 2011;152:566–72.
14. Wylde V, Palmer S, Learmonth ID, Dieppe P. The association between pre-operative pain sensitisation and chronic pain after knee replacement: an exploratory study. Osteoarthritis Cartilage 2013;21:1253–6.
15. Kulkarni B, Bentley DE, Elliott R, Julyan PJ, Boger E, Watson A, *et al*. Arthritic pain is processed in brain areas concerned with emotions and fear. Arthritis Rheum 2007;56:1345–54.
16. Schaible HG. Mechanisms of chronic pain in osteoarthritis. Curr Rheumatol Rep 2012;14:549–56.
17. Wylde V, Palmer S, Learmonth ID, Dieppe P. Test-retest reliability of quantitative sensory testing in knee osteoarthritis and healthy participants. Osteoarthritis Cartilage 2011;19:655–8.
18. Singh JA, Dowsey MM, Dohm M, Goodman SM, Leong AL, Scholte Voshaar M, *et al*. Achieving consensus on total joint replacement trial outcome reporting using the OMERACT filter: endorsement of the final core domain set for total hip and total knee replacement trials for endstage arthritis. J Rheumatol 2017;44:1723–6.
19. Dunbar MJ, Richardson G, Robertsson O. I can't get no satisfaction after my total knee replacement: rhymes and reasons. Bone Jt J 2013;95-B(11 Suppl A):148–52.
20. Choi YJ, Ra HJ. Patient satisfaction after total knee arthroplasty. Knee Surg Relat Res 2016;28:1–15.
21. Gunaratne R, Pratt DN, Banda J, Fick DP, Khan RJK, Robertson BW. Patient dissatisfaction following total knee arthroplasty: a systematic review of the literature. J Arthroplasty 2017;32:3854–60.
22. Parvizi J, Nunley RM, Berend KR, Lombardi Jr AV, Ruh EL, Clohisy JC, *et al*. High level of residual symptoms in young patients after total knee arthroplasty. Clin Orthop Relat Res 2014;472:133–7.
23. Kim TK, Kwon SK, Kang YG, Chang CB, Seong SC. Functional disabilities and satisfaction after total knee arthroplasty in female Asian patients. J Arthroplasty 2010;25:458–64. e1–2.
24. Howells N, Murray J, Wylde V, Dieppe P, Blom A. Persistent pain after knee replacement: do factors associated with pain vary with degree of patient dissatisfaction? Osteoarthritis Cartilage 2016;24:2061–8.
25. Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. Pain 2000;84:65–75.
26. Thompson T, Correll CU, Gallop K, Vancampfort D, Stubbs B. Is pain perception altered in people with depression? A systematic review and meta-analysis of experimental pain research. J Pain Off J Am Pain Soc 2016;17:1257–72.
27. Hanssen MM, Peters ML, Vlaeyen JW, Meevissen YM, Vancleef LM. Optimism lowers pain: evidence of the causal status and underlying mechanisms. Pain 2013;154:53–8.
28. Johnson KV, Dunbar RI. Pain tolerance predicts human social network size. Sci Rep 2016;6:25267.
29. Nummenmaa L, Manninen S, Tuominen L, Hirvonen J, Kalliokoski KK, Nuutila P, *et al*. Adult attachment style is associated with cerebral mu-opioid receptor availability in humans. Hum Brain Mapp 2015;36:3621–8.
30. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007;4:e297.
31. Smyer MA, Hofland BF, Jonas EA. Validity study of the short portable mental status questionnaire for the elderly. J Am Geriatr Soc 1979;27:263–9.
32. Groll DL, To T, Bombardier C, Wright JG. The development of a comorbidity index with physical function as the outcome. J Clin Epidemiol 2005;58:595–602.
33. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
34. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. 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 1988;15:1833–40.
35. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
36. Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. Eur J Pain 2007;11:153–63.
37. Wylde V, Dixon S, Blom AW. The role of preoperative self-efficacy in predicting outcome after total knee replacement. Muscoskel Care 2012;10:110–8.
38. Mannion AF, Kampfen S, Munzinger U, Kramers-de Quervain I. The role of patient expectations in predicting outcome after total knee arthroplasty. Arthritis Res Ther 2009;11:R139.
39. Mahomed N, Gandhi R, Daltroy L, Katz JN. The self-administered patient satisfaction scale for primary hip and knee arthroplasty. Arthritis 2011;2011:591253.
40. Wylde V, Learmonth I, Potter A, Bettinson K, Lingard E. Patient-reported outcomes after fixed- versus mobile-bearing total knee replacement: a multi-centre randomised controlled trial

using the Kinemax total knee replacement. J Bone Jt Surg Br Vol 2008;90:1172–9.
41. Huang Y, Lee M, Chong HC, Ning Y, Lo NN, Yeo SJ. Reasons and factors behind post-total knee arthroplasty dissatisfaction in an Asian population. Ann Acad Med 2017;46:303–9.
42. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology 2011;22:745.
43. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol 2008;8:70.
44. Ko Y, Narayanasamy S, Wee HL, Lo NN, Yeo SJ, Yang KY, *et al.* Health-related quality of life after total knee replacement or unicompartmental knee arthroplasty in an urban Asian population. Value Health 2011;14:322–8.
45. Xu GG, Sathappan SS, Jaipaul J, Chan SP, Lai CH. A review of clinical pathway data of 1663 total knee arthroplasties in a tertiary institution in Singapore. Ann Acad Med 2008;37:924–8.
46. Leung YY, Ang LW, Thumboo J, Wang R, Yuan JM, Koh WP. Cigarette smoking and risk of total knee replacement for severe osteoarthritis among Chinese in Singapore–the Singapore Chinese health study. Osteoarthritis Cartilage 2014;22:764–70.
47. Kumar A, Tsai WC, Tan TS, Kung PT, Chiu LT, Ku MC. Temporal trends in primary and revision total knee and hip replacement in Taiwan. J Chin Med Assoc 2015;78:538–44.
48. Lingard EA, Sledge CB, Learmonth ID. Patient expectations regarding total knee arthroplasty: differences among the United States, United Kingdom, and Australia. J Bone Jt Surg Am 2006;88:1201–7.
49. Groeneveld PW, Kwoh CK, Mor MK, Appelt CJ, Geng M, Gutierrez JC, *et al.* Racial differences in expectations of joint replacement surgery outcomes. Arthritis Rheum 2008;59:730–7.
50. Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. Br J Anaesth 2015;114:551–61.
51. Petersen KK, Graven-Nielsen T, Simonsen O, Laursen MB, Arendt-Nielsen L. Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. Pain 2016;157:1400–6.
52. Imamura M, Imamura ST, Kaziyama HH, Targino RA, Hsing WT, de Souza LP, *et al.* Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum 2008;59:1424–31.
53. Neogi T, Frey-Law L, Scholz J, Niu J, Arendt-Nielsen L, Woolf C, *et al.* Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? Ann Rheum Dis 2015;74:682–8.
54. Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis Rheum 2012;64:2907–16.
55. Wylde V, Palmer S, Learmonth ID, Dieppe P. Somatosensory abnormalities in knee OA. Rheumatology 2012;51:535–43.
56. Arendt-Nielsen L, Egsgaard LL, Petersen KK, Eskehave TN, Graven-Nielsen T, Hoeck HC, *et al.* A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. Eur J Pain 2015;19:1406–17.
57. Wylde V, Sayers A, Lenguerrand E, Gooberman-Hill R, Pyke M, Beswick AD, *et al.* Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. Pain 2015;156:47–54.
58. Rakel BA, Blodgett NP, Bridget Zimmerman M, Logsden-Sackett N, Clark C, Noiseux N, *et al.* Predictors of postoperative movement and resting pain following total knee replacement. Pain 2012;153:2192–203.
59. Wylde V, Sayers A, Odutola A, Gooberman-Hill R, Dieppe P, Blom AW. Central sensitization as a determinant of patients' benefit from total hip and knee replacement. Eur J Pain 2017;21:357–65.
60. Wasserstein RL, Lazar NA. The ASA's statement on P-values: context, process, and purpose. Am Stat 2016;70:129–33.
61. Wright RJ, Sledge CB, Poss R, Ewald FC, Walsh ME, Lingard EA. Patient-reported outcome and survivorship after Kinemax total knee arthroplasty. J Bone Jt Surg Am Vol 2004;86-A:2464–70.