

Rest Pain and Movement-Evoked Pain as Unique Constructs in Hip and Knee Replacements

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Objective. There is limited information about the extent to which the association between preoperative and chronic postoperative pain is mediated via pain-on-movement or pain-at-rest. We explored these associations in patients undergoing total hip replacement (THR) and total knee replacement (TKR).

Methods. A total of 322 and 316 patients receiving THR and TKR, respectively, were recruited into a single-center UK cohort (Arthroplasty Pain Experience) study. Preoperative, acute postoperative, and 12-month pain severity was measured using self-reported pain instruments. The association between preoperative/acute pain and chronic postoperative pain was investigated using structural equation modeling (SEM).

Results. Patients with high levels of preoperative pain were more likely to report chronic pain after THR ($\beta = 0.195$, $P = 0.02$) and TKR ($\beta = 0.749$, $P < 0.0001$). Acute postoperative pain-on-movement was not associated with chronic pain after TKR or THR after adjusting for preoperative pain; however, acute pain-at-rest was associated with chronic pain after THR ($\beta = 0.20$, $P < 0.0002$) but not TKR after adjusting for preoperative pain. Analysis of pain-at-rest and pain-on-movement highlighted differences between THR and TKR patients. Chronic pain-at-rest after THR was weakly associated with pain-at-rest during the preoperative ($\beta = 0.11$, $P = 0.068$) and acute postoperative period ($\beta = 0.21$, $P < 0.0001$). In contrast, chronic pain-on-movement after TKR was strongly associated with the severity of pain-on-movement during the preoperative period ($\beta = 0.51$, $P = 0.001$).

Conclusion. SEM illustrated the different patterns of association between measures of pain over time in patients undergoing THR and TKR for osteoarthritis. These findings highlight the importance of future work that explores the mechanisms underlying pain-on-movement and pain-at-rest.

INTRODUCTION

Osteoarthritis (OA) of the hip and knee is characterized by pain and reduced mobility. In 2012, 76,448 total hip replacements (THRs) and 76,497 total knee replacements (TKRs) were performed in England and Wales (1). Joint

replacement can be a successful operation for providing pain relief and improving function; however, pain after surgery is common. On the first postoperative day, approximately 50% of patients report moderate or severe pain in their replaced joint (2). In the longer term, 7–23% of THR patients and 10–34% of TKR patients report moderate to severe pain following surgery (3). Chronic postsurgical pain can be distressing (4) and has a considerable socioeconomic cost (5).

Understanding why and predicting which patients are likely to experience chronic pain following surgery may facilitate the development of effective interventions that reduce chronic pain postsurgery. Previous studies have indicated that there is an association between preoperative pain and long-term pain in joint replacement following surgery (6), and that severe acute postsurgical pain is associated with chronic postsurgical pain in a wide variety of surgical disciplines (7). However, we are currently unaware of any study that has formally explored the mediating effect of acute postsurgical pain between preoperative pain and chronic long-term pain following total joint replacement.

Furthermore, within the surgical literature, there is a growing recognition of the importance of distinguishing

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Significance & Innovations

- Using structural equation modeling, we have highlighted the very different patterns of pain in patients undergoing total hip replacement (THR) and total knee replacement (TKR).
- The association between preoperative pain and chronic pain measured at 12 months is 5 times as strong in patients undergoing TKR compared to THR.
- Preoperative pain-on-movement is the strongest predictor of chronic pain-on-movement at 12 months in patients undergoing TKR. Whereas preoperative pain-at-rest is weakly predictive of chronic pain-at-rest at 12 months in patients undergoing THR.

between pain-at-rest and pain-on-movement due to differing mechanistic pathways and clinical implications, such as differential effectiveness of pharmacologic therapies and impact on functional recovery (8,9). It has therefore been argued that the assessment of acute postoperative pain-on-movement is more important than assessing pain-at-rest because of the potential for interference with postoperative mobilization (10). In the context of OA, pain-on-movement is often more severe than pain-at-rest (11) and has an earlier onset in the disease course. However, the mediating pathways between preoperative, acute postoperative, and chronic postoperative pain-at-rest and pain-on-movement remain unclear.

The aim of this analysis was to formally explore and understand the associations between preoperative pain, acute postsurgical pain, and chronic postsurgical pain after THR and TKR, comparing the differences between pain-at-rest and pain-on-movement.

PATIENTS AND METHODS

Between 2009 and 2012, 322 and 316 patients undergoing THR and TKR, respectively, were recruited into 2 double-blind, single-center, randomized controlled trials that compared local anesthetic wound infiltration for reducing chronic pain after joint replacement. The design of the Arthroplasty Pain Experience (APEX) trials has been reported previously (12). Briefly, the inclusion criteria were being listed for a primary unilateral THR or TKR for OA. Exclusion criteria included inability to provide informed consent or complete questionnaires, and medical comorbidity precluding use of spinal anesthesia, regional blocks, and strong analgesics postoperatively. The primary outcome was pain severity in the replaced joint at 12 months postoperative, measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale (13).

The APEX trials were registered as an International Standardized Randomized Controlled Trial (96095682), approved by Southampton and South West Hampshire Research Ethics Committee (09/H0504/94), and all participants provided informed written consent.

Measurements. *Exposures/mediators.* The primary exposures of interest were preoperative pain, measured 6 weeks prior to surgery, and acute postsurgical pain, measured on postoperative days 1, 2, and 3.

Preoperative pain was measured using a self-completed WOMAC pain scale. The WOMAC pain scale is a 5-item validated questionnaire that assesses joint pain severity when 1) walking, 2) using stairs, 3) sitting or lying, 4) standing upright, and 5) in bed (13,14). Response options were recorded on a 5-point ordered response scale, the average score of the 5 items was transformed to a 0–100 scale (extreme pain to no pain). The score was also divided into subcomponents of weight-bearing pain (pain-on-movement [walking, using stairs, and standing upright items]) and non-weight-bearing pain (pain-at-rest [sitting or lying and bed items]) (15).

Acute postsurgical pain was measured on postoperative days 1, 2, and 3 using a 10-cm visual analog scale (VAS). Patients were asked to “indicate the intensity of your present hip/knee pain . . .” ranging from “no pain” to “worst possible pain,” either “at rest” or “on movement.” Pain was measured at rest and on movement at 8:00 AM, 12:00 PM, and 5:00 PM daily for 3 days postsurgery. For simplicity and to aid convergence, the VAS results were recoded into ordinal responses ranging between 0 and 10, and the mean VAS scores at rest and on movement across the 3 postoperative days were also calculated.

Outcome and confounding variables. Chronic postsurgical pain was assessed using the WOMAC pain scale at 12 months after surgery (14).

Confounding factors that were adjusted for in the analyses included sex and socioeconomic status, which included employment status, cohabitation (living alone), and educational attainment (\leq age 16 years or $>$ age 16 years). These factors were adjusted for using the prerequisite knowledge (16) based on literature that suggests that demographics (17) and socioeconomic status (18,19) influence patient-reported outcomes after joint replacement. In addition, as the APEX trials were analyzed as cohort data, all analyses were adjusted for the treatment participants received in the trial (20,21).

Modeling strategy. Given the large difference in the prevalence of hip and knee OA (22) and varied genetic etiology (23), we a priori chose to analyze the data of patients undergoing THR and TKR separately. In order to compare the results between patients groups (THR and TKR), we fitted 6 different incremental models to illustrate the effect of the different exposures on chronic pain measured at 12 months postoperative, adjusting for confounding variables and potential mediators. The exposures of interest in models 1 to 6 are 1) preoperative pain, 2) acute postoperative pain-on-movement, 3) acute postoperative pain-at-rest, 4) preoperative pain adjusted for acute postoperative pain-on-movement, 5) preoperative pain adjusted for acute postoperative pain-at-rest, and 6) preoperative pain adjusted for acute postoperative pain-on-movement and pain-at-rest. Models 1, 2, and 3 are interpreted as the total effect of the exposure associated with pain severity at 12 months postoperative independent of confounding variables (randomization, education, cohabitation, employment, and

sex), whereas models 4, 5, and 6 are interpreted as the direct effect of preoperative pain independent of acute pain-on-movement (model 4), acute pain-at-rest (model 5), and both acute pain-at-rest and pain-on-movement (model 6), in addition to the confounding variables listed previously.

In order to further understand the difference between models of total effect and in/direct effects, we investigated the mediating pathways between preoperative and chronic postoperative pain via acute postoperative pain using structural equation modeling (SEM). These analyses are fully adjusted for all other variables in the model. All models were additionally adjusted for trial arm, sex, and socioeconomic status.

Statistical methods. *Descriptive statistics.* Population characteristics and outcome measures are reported as means, SDs, and interquartile cut points for continuous measures and frequencies for categorical variables. The frequencies of responses, by item, for the pre- and postoperative WOMAC pain scores are presented in Supplementary Table 1 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>). Means, SDs, and interquartile cut points for VAS scores for postoperative days 1, 2 and 3, by 8:00 AM, 12:00 PM, and 5:00 PM are presented in Supplementary Table 2 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>).

Confirmatory factor analysis (CFA) and SEM approach. Prior to fitting full structural equation models we investigated the factor structure of the WOMAC pain questionnaire using CFA.

SEM was adopted for 3 reasons: 1) it provides a framework to conduct mediation analyses, i.e., the investigation of the in/direct effects of preoperative pain on chronic pain and indirectly via acute pain-on-movement or acute pain-at-rest, 2) it allows multi-item pain instruments (e.g., WOMAC pain scale or repeated VAS pain scales) to be investigated without simple aggregation of scores, and 3) effects of interest can be estimated in the presence of missing data under the missing at random assumption using maximum likelihood with missing values (24).

Interpreting SEM models. Results from SEMs are interpreted with respect to the latent constructs (preoperative pain, acute pain-on-movement, acute pain-at-rest, and chronic pain). In addition, the results are interpreted on the same scale as the scores were originally measured; specifically, the WOMAC pain scale is a 5-point scale, and the acute pain-on-movement and acute pain-at-rest are 10-point scales. Results (β coefficients) are interpreted per unit increase in the latent exposure and its association with the latent outcome, where the latent outcome or exposures represent a weighted combination of each item on the composite pain scale of interest. In addition, SEM models do not require complete data and can be estimated under the missing at random assumption. Therefore, results are interpreted with respect to all individuals who entered the study opposed to those with only complete data.

Multiple latent variable analyses. In addition to using a single latent variable model of pain preoperatively and at

Table 1. Demographic characteristics of hip and knee patients*

| | THR patients | | | TKR patients | | |
|------------------|--------------|------|---------|--------------|------|---------|
| | No. | % | Missing | No. | % | Missing |
| Randomized to... | | | | | | |
| Standard care | 159 | 49.4 | | 159 | 50.3 | |
| Intervention | 163 | 50.6 | 0 | 157 | 49.7 | 0 |
| Sex | | | | | | |
| Male | 133 | 41.3 | | 150 | 47.5 | |
| Female | 189 | 58.7 | 0 | 166 | 52.5 | 0 |
| Employment | | | | | | |
| Unemployed | 195 | 65.4 | | 220 | 76.9 | |
| Employed | 103 | 34.6 | 24 | 66 | 23.1 | 30 |
| Retirement | | | | | | |
| Not retired | 133 | 41.3 | | 98 | 31.0 | |
| Retired | 189 | 58.7 | 0 | 218 | 69.0 | 0 |
| Cohabitation | | | | | | |
| Alone | 74 | 24.2 | | 84 | 28.3 | |
| Not alone | 232 | 75.8 | 16 | 213 | 71.7 | 19 |
| Education | | | | | | |
| ≤age 16 years | 208 | 67.8 | | 224 | 76.2 | |
| >age 16 years | 99 | 32.2 | 15 | 70 | 23.8 | 22 |

* THR = total hip replacement; TKR = total knee replacement.

12-months postoperatively, further analyses were conducted by grouping items in the preoperative/postoperative WOMAC assessment more strongly associated with acute pain-on-movement and acute pain-at-rest. This subdivision enables the 2 main constructs of the WOMAC pain scale to be investigated simultaneously and mutually adjusted for one another.

All analyses were conducted in Stata, version 13.1, and THR and TKR patients were analyzed separately. All *P* values are reported unadjusted for multiple comparisons.

RESULTS

Descriptive data. A total of 321 THR and 316 TKR patients completed a preoperative WOMAC pain scale and were included in the analyses. Baseline characteristics of participants are provided in Table 1. There was a higher percentage of females than males (59% versus 41%) undergoing THR, and a more equal percentage of females and males undergoing TKR (53% versus 47%). Patients undergoing THR had a mean \pm SD age of 66.2 ± 10.9 years, which was slightly younger than TKR patients at 69.1 ± 18.6 years. The majority of both cohorts was educated up to age 16 years (68% for THR patients, 76% for TKR patients), and a large proportion of patients were retired. Preoperative WOMAC pain scores were very similar between THR and TKR patients (Table 2).

During the acute postsurgical phase, VAS pain-on-movement and pain-at-rest scales were well completed (86% movement and 89% rest in patients undergoing THR, and 91% movement and 92% rest in patients undergoing TKR); however, lower completion rates were observed on postoperative day 3 (Table 2). At 12 months the WOMAC pain scale was completed by 283 THR patients (88%) and 277 TKR patients (88%). On average, THR patients had less pain than

Table 2. Descriptive statistics for preoperative and postoperative WOMAC pain scores and VAS for acute postoperative pain on-movement and at rest*

| Measure | THR | | | | | TKR | | | | |
|--------------------------|-----|---------------|------|------|-------|-----|---------------|------|------|-------|
| | No. | Mean ± SD | 25 | 50 | 75 | No. | Mean ± SD | 25 | 50 | 75 |
| Preoperative WOMAC pain | 321 | 42.48 ± 18.51 | 30.0 | 40.0 | 55.0 | 316 | 42.47 ± 16.70 | 30.0 | 45.0 | 55.0 |
| On movement (VAS) | | | | | | | | | | |
| Day 1 | 301 | 5.78 ± 2.32 | 4.0 | 5.7 | 7.7 | 279 | 6.21 ± 2.37 | 5.0 | 6.3 | 8.0 |
| Day 2 | 295 | 4.59 ± 2.52 | 2.3 | 4.5 | 6.7 | 284 | 5.89 ± 2.38 | 4.2 | 6.0 | 7.7 |
| Day 3 | 271 | 3.90 ± 2.38 | 2.0 | 3.3 | 6.0 | 260 | 4.70 ± 2.48 | 2.7 | 5.0 | 6.3 |
| 3-day average | 305 | 4.03 ± 1.79 | 2.7 | 3.9 | 5.2 | 290 | 4.94 ± 2.01 | 3.3 | 5.1 | 6.2 |
| At rest (VAS) | | | | | | | | | | |
| Day 1 | 301 | 3.15 ± 2.00 | 1.7 | 2.7 | 4.3 | 280 | 4.39 ± 2.28 | 2.7 | 4.3 | 6.0 |
| Day 2 | 296 | 2.40 ± 1.85 | 1.0 | 1.8 | 3.4 | 284 | 3.98 ± 2.36 | 2.0 | 4.0 | 5.7 |
| Day 3 | 271 | 2.07 ± 1.71 | 1.0 | 1.3 | 2.7 | 260 | 3.04 ± 2.12 | 1.0 | 2.7 | 4.3 |
| 3-day average | 299 | 2.72 ± 1.73 | 1.3 | 2.3 | 3.8 | 288 | 3.88 ± 2.10 | 2.1 | 3.7 | 5.2 |
| Postoperative WOMAC pain | 283 | 88.99 ± 16.85 | 85.0 | 95.0 | 100.0 | 277 | 79.77 ± 21.22 | 65.0 | 85.0 | 100.0 |

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = visual analog scale; THR = total hip replacement; TKR = total knee replacement.

TKR patients (Table 2). At 12-months postoperative, 5% of patients with THR and 12% of patients with TKR reported severe/extreme pain, defined as a WOMAC pain score of ≤50, and 46% of patients with THR and 30% of patients with TKR reported no pain (WOMAC pain score of 100).

A detailed breakdown of the frequency of responses to pre- and postoperative WOMAC items is listed in Supple-

mentary Table 1 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>).

Descriptive statistics of acute postoperative pain by time and day of data collection and nonresponse are shown in Supplementary Table 2; further nonresponse data of acute pain-at-rest and pain-on-movement and

Table 3. SEM analysis of preoperative and acute pain and postoperative pain, using a single latent variable model of the WOMAC pain score in hip and knee patients*

| Model | Exposure | Adjusted | β | SE | 95% CI | P | Likelihood | Model DoF |
|-------|--------------------|-----------------------------------|---------|-------|---------------|--------|------------|-----------|
| THR | | | | | | | | |
| 1 | Preoperative WOMAC | Confounders | 0.195 | 0.084 | 0.030, 0.360 | 0.0206 | -3951.0 | 64 |
| 2 | VAS move | Confounders | 0.085 | 0.034 | 0.018, 0.153 | 0.0135 | -7013.0 | 83 |
| 3 | VAS rest | Confounders | 0.190 | 0.046 | 0.099, 0.281 | 0.0000 | -6758.9 | 83 |
| 4 | Preoperative WOMAC | Confounders + VAS move | 0.170 | 0.085 | 0.004, 0.336 | 0.0442 | -8887.9 | 107 |
| 5 | Preoperative WOMAC | Confounders + VAS rest | 0.142 | 0.083 | -0.020, 0.305 | 0.0856 | -8634.5 | 107 |
| 6 | Preoperative WOMAC | Confounders + VAS move + VAS rest | 0.152 | 0.083 | -0.011, 0.315 | 0.0675 | -13482.4 | 151 |
| TKR | | | | | | | | |
| 1 | Preoperative WOMAC | Confounders | 0.749 | 0.126 | 0.502, 0.996 | 0.0000 | -3992.0 | 64 |
| 2 | VAS move | Confounders | 0.140 | 0.044 | 0.054, 0.226 | 0.0014 | -7114.8 | 83 |
| 3 | VAS rest | Confounders | 0.222 | 0.058 | 0.109, 0.336 | 0.0001 | -7091.3 | 83 |
| 4 | Preoperative WOMAC | Confounders + VAS rest | 0.697 | 0.127 | 0.448, 0.946 | 0.0000 | -8843.9 | 107 |
| 5 | Preoperative WOMAC | Confounders + VAS move | 0.654 | 0.133 | 0.393, 0.915 | 0.0000 | -8816.1 | 107 |
| 6 | Preoperative WOMAC | Confounders + VAS move + VAS rest | 0.638 | 0.149 | 0.346, 0.930 | 0.0000 | -13534.3 | 151 |

* P values in structural equation modeling (SEM) models are based on z-distributions. Confounding variables include trial randomization, education, cohabitation, employment, and sex. SEM analyses are based on one latent variable analyses of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain items, which range from 1-5 (extreme pain to no pain); SEM models are estimated using maximum likelihood with missing values, which assumes missing data are missing at random, given other covariates. Acute pain-on-movement and pain-on-rest are modeled using a latent variable approach, where the 3 daily assessments (8:00 AM, 12:00 PM, and 5:00 PM) on days 1, 2, and 3 are used to model the acute pain-on-movement/pain-at-rest latent variables. 95% CI = 95% confidence interval; THR = total hip replacement; VAS = visual analog scale; move = pain-on-movement; rest = pain-at-rest; TKR = total knee replacement.

number of missing items are reported in Supplementary Table 3.

Supplementary Table 4 shows descriptive statistics of preoperative WOMAC score by 12-month postoperative WOMAC completion status. The proportion of individuals who did not complete the study had similar demographic characteristics to those who did complete the primary outcome measure.

CFA. The factor loadings prior to surgery in patients undergoing THR suggest that WOMAC items 3 and 4 are more similar to each other than items 1, 2, and 5 (i.e., factor loadings <1). This loading pattern tentatively indicated that there may be more similarities between weight-bearing (pain-on-movement) questions than non-weight-bearing questions (pain-at-rest). Similarly, the factor loading of items 3 and 4 in patients undergoing TKR are substantially elevated in comparisons to items 1, 2, and 5. A 2-factor model (pain-on-movement and pain-at-rest) resulted in a substantially improved fit in patients undergoing THR ($P = 0.02$) and TKR ($P < 0.0001$). Unsurprisingly, each factor is moderately correlated; however, there is still significant variability between the factors (for CFA factor loadings and correlations, see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>).

SEM analysis. Using an SEM approach, the association between preoperative WOMAC pain and chronic WOMAC pain, adjusted for confounding factors, was investigated (Table 3). In minimally adjusted analyses, preoperative WOMAC pain scores were associated with 12-month postoperative WOMAC pain scores in both THR and TKR patients. A 1-unit increase in the WOMAC latent variable preoperatively was associated with a 0.19- and 0.75-unit increase in the WOMAC pain at 12-months in THR and TKR patients, respectively (Table 3). In TKR patients, the minimally adjusted association was nearly 4 times as large in comparison to THR patients (model 1, THR versus TKR). Acute pain-on-movement and acute pain-at-rest following surgery were also associated with chronic WOMAC pain at 12-months in both THR and TKR patients (models 2 and 3, THR and TKR) (Table 3), with a slightly stronger association observed with acute pain-at-rest compared to acute pain-on-movement in both THR and TKR patients (model 2 versus 3, THR and TKR) (Table 3).

Furthermore, the association between preoperative WOMAC pain and chronic WOMAC pain was attenuated following adjustment for acute pain, pain-on-movement or pain-at-rest (models 4, 5, and 6). The association in THR patients was mildly attenuated and the confidence interval of the association overlapped zero ($P = 0.0675$). However, there was a stronger attenuation of the association in TKR but, despite this, results remained strongly significant, suggesting a stronger mediating effect of acute pain in TKR patients compared to THR patients (Table 3). By comparing models using likelihood ratio tests, it is clear that model fit is improved following the adjustment of both acute pain-at-rest and acute pain-on-movement.

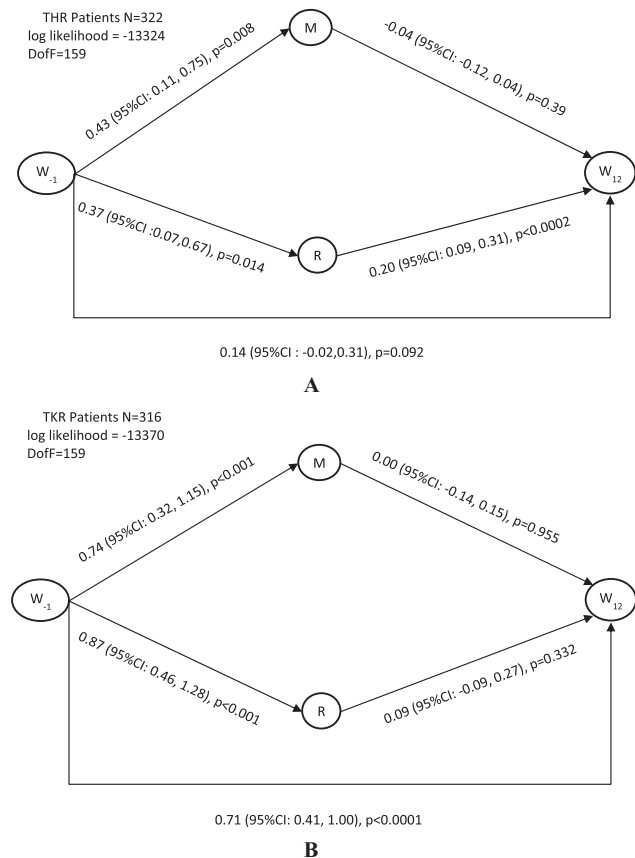


Figure 1. Structural equation model (SEM) of the association between latent variables preoperative WOMAC (W_{-1}), acute postoperative pain-on-movement (M), acute pain-at-rest (R), and postoperative WOMAC (W_{12}) in total hip replacement (THR) patients (A) and total knee replacement (TKR) patients (B). Arrows indicate direction of effects, coefficients are in the natural units of the measurement scales, and P values are based on z -distribution. Models are estimated using maximum likelihood allowing for missing values. Full SEM models, including confirmatory factor analysis, are presented in Supplementary Figures 2 and 3 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>). 95% CI = 95% confidence interval.

Mediation analysis. Single latent variable WOMAC. Using the WOMAC score as a single latent variable (i.e., no distinction between preoperative and 12-month postoperative pain-on-movement or pain-at-rest), the association between preoperative pain, acute pain-on-movement/pain-at-rest, and chronic pain was investigated. Figures 1A and 1B illustrate the proposed associations between latent variables for the THR and TKR patients, respectively. The item factor loadings are presented in Supplementary Figures 2 and 3 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>).

The WOMAC single latent variable models differ from those presented in Table 3 by allowing preoperative pain to influence acute pain-on-movement and acute pain-at-rest. In THR patients, the direct effect of preoperative pain on chronic pain is slightly attenuated in comparison to model 6 shown in Table 3, with only a minor increase in the width of the confidence interval. This model also

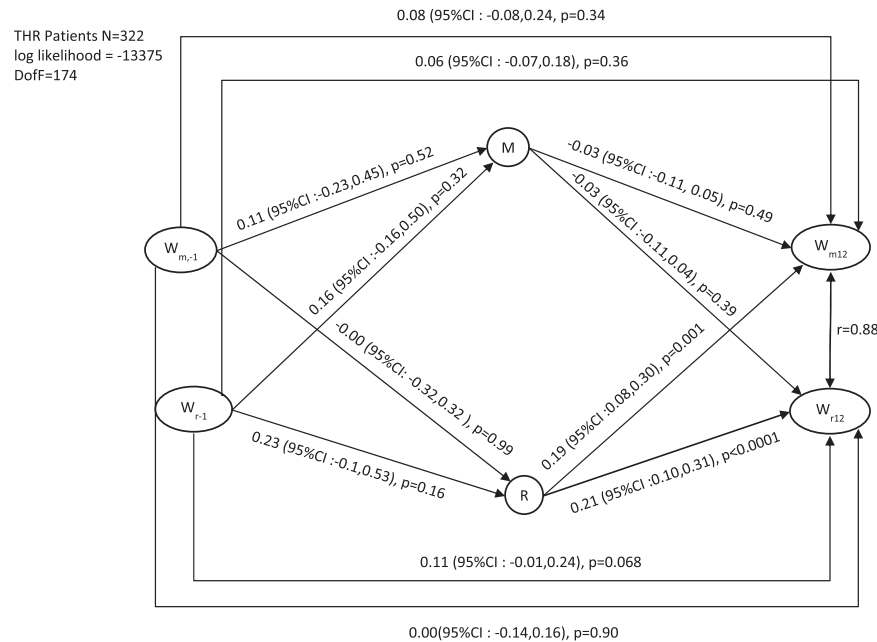


Figure 2. Structural equation model (SEM) of the association between latent variables preoperative WOMAC pain-on-movement ($W_{m,-1}$), preoperative WOMAC pain-at-rest ($W_{r,-1}$), acute postoperative pain-on-movement (M), acute pain-at-rest (R), postoperative WOMAC pain-on-movement (W_{m12}), and postoperative WOMAC pain-at-rest (W_{r12}) in total hip replacement (THR) patients. Single-headed arrows indicate direction of effects, coefficients are in the natural units of the measurement scales, and P values are based on z -distribution. Arrow between W_{m12} and W_{r12} indicates correlation coefficient. Models are estimated using maximum likelihood allowing for missing values. Full SEM models, including confirmatory factor analysis, are presented in Supplementary Figure 4 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>). 95% CI = 95% confidence interval.

highlights that the attenuation observed in the fully adjusted model (model 6) versus a less adjusted model (model 1, Table 3) is primarily a result of the indirect association between acute pain-at-rest and pain at 12 months (Figure 1A), and not the association between acute pain-on-movement and pain at 12 months.

The pattern of results in TKR patients is somewhat less clear. The strong direct association between preoperative pain is somewhat enhanced by allowing for the effect of preoperative pain on acute pain (Table 3, model 6 versus Figure 1B). However, the minor attenuation observed in comparison to model 1 (Table 3) is principally occurring via the indirect association via acute pain-at-rest and not pain-on-movement.

Two latent variable WOMAC. Using the WOMAC score as a two latent variable pain model, i.e., distinguishing between pain-on-movement and pain-at-rest both pre- and postoperatively, the effects of preoperative pain (at rest/on movement) was investigated with acute pain-on-movement/acute pain-at-rest and chronic pain (at rest/on movement). Figures 2 and 3 illustrate the path models and direction of effects between latent variables for the THR and TKR patients, respectively. The item factor loadings have been omitted for clarity, and Supplementary Figures 4 and 5 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>) present the full models with factor loadings.

In THR patients, the two latent variable SEM approach clearly shows that the majority of the association previously seen in the single latent variable model between preoperative and chronic pain is mediated directly via preoperative pain-at-rest, with little effect of indirect pathways or directly via preoperative pain-on-movement. However, an independent association of acute pain-at-rest is weakly positively associated with both chronic pain-on-movement and pain-at-rest. Despite the marginal associations observed in patients undergoing THR, there is very strong evidence to support a two latent variable model in comparison to the single latent variable model (likelihood ratio test: 15df, $P < 0.0001$).

In TKR patients, the results are quite different, and the two latent variable model highlights that the strongest association is primarily between preoperative pain-on-movement and chronic pain-on-movement. Preoperative pain-at-rest is also associated with chronic pain-at-rest, and acute pain-at-rest is also associated with chronic pain-at-rest, but not chronic pain-on-movement.

In Figure 1B, the strong associations between preoperative pain and acute pain-on-movement/pain-at-rest are clarified, demonstrating that preoperative pain-on-movement is more strongly associated with chronic pain-at-rest or pain-on-movement, in comparison to preoperative pain-at-rest, which is weakly associated with acute pain-at-rest.

There is very strong evidence to support a two latent variable SEM model in comparison to a single latent vari-

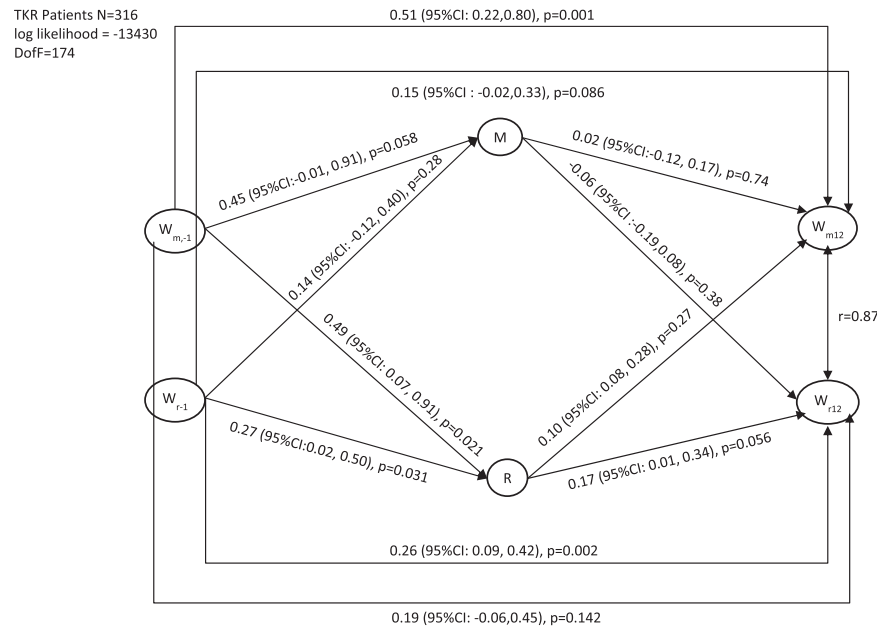


Figure 3. Structural equation model (SEM) of the association between latent variables: preoperative WOMAC pain-on-movement ($W_{m,-1}$), preoperative WOMAC pain-at-rest ($W_{r,-1}$), acute postoperative pain-on-movement (M), acute pain-at-rest (R), postoperative WOMAC pain-on-movement ($W_{m,12}$), and postoperative WOMAC pain-at-rest ($W_{r,12}$) in total knee replacement (TKR) patients. Arrows indicate direction of effects, coefficients are in the natural units of the measurement scales, and P values are based on z -distribution. Arrow between $W_{m,12}$ and $W_{r,12}$ indicates correlation coefficient. Models are estimated using maximum likelihood allowing for missing values. Full SEM models, including confirmatory factor analysis, are presented in Supplementary Figure 5 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>). 95% CI = 95% confidence interval.

able model in patients undergoing TKR (likelihood ratio test; 15df, $P < 0.0001$).

There was no evidence of significant indirect effects in either THR or TKR patients, despite significant intermediate paths.

DISCUSSION

Using an SEM approach in a cohort of patients undergoing THR ($n = 321$) and TKR ($n = 316$), we have compared and contrasted associations between measures of pain over time. This highlighted important differences between patients with hip and knee OA undergoing joint replacement. In particular, the different contributions of pain-at-rest and pain-on-movement to chronic postsurgical pain were marked. Chronic pain after THR was moderately associated with pain-at-rest during the preoperative and acute postoperative period. In contrast, chronic pain after TKR was predominately associated with the severity of pain-on-movement during the preoperative period. These findings allude to different patterns of pain mechanisms within hip and knee OA, and highlight the importance of future work to identify the sources and potential treatment options for these different diseases.

Within both a clinical and research setting, there is often the assumption that hip and knee OA are the same disease. Treatment and management guidelines often treat

them as the same disease (25,26) and they are often analyzed together in research studies (27–29). However, differences between hip and knee OA are evident in terms of epidemiology, risk factors, structural joint changes, and outcomes after surgery (3,30–34). Our study adds to the literature by demonstrating potentially important differences in pain mechanisms between the 2 diseases in relation to the associations of pain-at-rest and pain-on-movement to chronic pain after joint replacement. Whereas pain-at-rest was associated with chronic pain after THR, pain-on-movement was more strongly associated with chronic pain after TKR. This could potentially reflect differences in underlying pain mechanisms. In OA, there are 2 main peripheral sources of pain: subchondral bone pressure and inflammation. Research suggests that subchondral bone pressure is more associated with pain-at-rest (35) and inflammation is more associated with pain-on-movement (36). Therefore, it could be hypothesized that subchondral bone pressure may be the more important pain mechanism in hip OA, whereas inflammation may be more important in knee OA.

Furthermore, the lack of any significant indirect effect between preoperative pain, acute postoperative pain, and chronic postoperative pain suggests that there is likely to be limited utility in attempting to interrupt the pain pathway in the acute postoperative setting, and while acute postoperative pain is associated with chronic postoperative pain, eliminating acute postoperative pain will not be

a panacea. Improving pain management strategies that are targeted preoperatively may prove more efficacious, as they will modify direct effects, especially when attempting to minimize pain-at-rest in patients undergoing THR and pain-on-movement in patients undergoing TKR. Whether minimizing preoperative pain via analgesics or operating earlier in the life-course of patients with OA will prove more effective in minimizing the number of individuals with chronic pain is unclear. Furthermore, the consequences of operating earlier in patients with OA are unclear and may lead to increased prosthesis revision rates later in life.

Strengths of this research include the long-term postoperative followup, use of validated outcome measures to assess pain, good rates of data collection for the outcome measures, and the robust comparisons between patients undergoing THR and TKR. Our sample population is representative of the population undergoing THR and TKR as a whole with a similar disease profile, sex mix, and age range as reported by the National Joint Registry of England and Wales (1) and, therefore, we believe our results to be generalizable. In addition, the use of SEM provides a simple method to estimate the effects of interest in the presence of missing data under the missing at random assumption, using full information maximum likelihood, as suggested by the comparison of baseline characteristics by completion status (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22656/abstract>).

It is important to acknowledge the study limitations when interpreting the results. While the study is a prospective cohort that has many advantages over cross-sectional studies, the results may still be influenced by residual unmeasured confounding and should be interpreted with caution; further research is needed to investigate the mechanistic pathways behind our observed associations using robust research designs. Despite the use of the same validated pain assessment tool (WOMAC) preoperatively and at 12 months following surgery, the assessment of acute postsurgical pain used VAS, and therefore the differences observed may be in part due to the variation in pain assessment tools. However, we are not aware of a pain assessment tool that has been validated for use in all 3 settings. Additionally, there are many factors that can influence pain, and while theoretically we could have accounted for more of these in our analyses, such as psychosocial factors, model convergence becomes difficult. Therefore, we controlled for key confounding variables that we believe are not on the causal pathway, including demographic and socioeconomic factors. Similarly, while it is technically possible to specify a model that formally compares the size of effects between THR and TKR, practically this is not possible as models do not converge. It is also important to note that while SEM provides a simple model that is useful in helping us interpret the data, other models may be equally as valid. Finally, using a continuous link function between the WOMAC items and latent variables may violate the assumptions of SEM; specifically, errors of the latent variables may not be truly Gaussian (24).

Our findings have a number of clinical implications and directions for future research. They provide further evidence that hip and knee OA are different diseases and respond differently to joint replacement. As such, future research studies should analyze data on hip and knee patients separately. We have also demonstrated that pain-at-rest and pain-on-movement differ in hip and knee patients. This highlights the importance of distinguishing between these 2 types of pain in research studies, and the need to explore if this distinction can improve the poor ability of statistical models to predict which patients are at risk of developing chronic postsurgical pain (37). There is also a need for further research to understand the pain mechanisms driving these different associations and to investigate whether interventions have different effects in hip and knee OA. There is some existing evidence that pharmacologic therapies target pain-at-rest and pain-on-movement differently (38,39), and the potential implications of this for improving the efficacy of treatment for hip and knee OA warrant further investigation.

In conclusion, our findings highlight the different and complex pain pathways in THR and TKR patients and how there is still considerable scope to improve long-term pain outcomes. Further insight into the mechanisms underlying pain-on-movement and pain-at-rest in hip and knee OA could be valuable in improving treatment for patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Mr. Sayers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Sayers, Dieppe.

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