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## The independent effect of pain in one versus two knees on the presence of low physical function: The MOST Study

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### Abstract

While knee pain severity is thought to greatly impact function, the additional contribution of pain in one versus two knees is not known. We examined the relation between unilateral versus bilateral pain with low physical functioning at baseline and at 30 months while accounting for knee pain severity.

The Multicenter Osteoarthritis Study (MOST) is a cohort study of people who have or are at high risk for knee OA. We defined low physical function as WOMAC PF scores  $\geq 28/68$ , consistent with poor functional outcome. Incidence and improvement from low physical function were defined as scores that declined below and improved above this threshold at 30 months. We examined the association between pain in one or two knees with low physical function with risk ratios adjusting for known confounders.

Of the 2069 subjects (Age  $63 \pm 8$  yrs, BMI  $31 \pm 6$  kg/m<sup>2</sup>, female 63%), the prevalence of low physical functioning was 50% lower among persons with unilateral pain compared with those with bilateral pain [adj PR 0.5 (95% CI 0.4-0.7)]. Of those without low physical functioning at baseline, the risk of incidence at 30 months was 30% less for unilateral pain compared with bilateral pain [adj RR 0.7 (95% CI 0.5-1.0)]. Of those with low physical functioning at baseline, the risk of improvement was 1.7 times more likely for unilateral pain compared with bilateral pain [adj RR 1.7 (95% CI 1.3-2.2)].

The presence of pain in one versus two knees provides important information regarding present and future physical functioning.

### Introduction

Knee osteoarthritis (OA) is the most common type of arthritis and is the leading cause of difficulty with physical functioning compared with any other chronic disease<sup>1, 2</sup>. An estimated 7 million people or 2.8% of the US population have difficulty with physical functioning attributable to arthritis, and this is expected to increase to 11.6 million or 3.6% by the year 2023, resulting in a tremendous public health burden. Knee OA causes knee pain<sup>4</sup>, which is thought to be a leading cause of difficulty with physical functioning, such as limitations with walking and getting up from a chair<sup>5-7</sup>.

Clinically, the severity of knee pain is thought to be one of the strongest factors influencing limitations in physical function, with little attention paid to whether one knee versus two knees have pain. For instance, high pain severity can limit the ability to walk or climb stairs regardless if pain is in one or both knees. As a consequence, physical therapists and other clinicians commonly focus on and treat the more painful of the two knees with the expectation that improvement in physical function will follow. However, future functional ability is also likely influenced by whether or not pain is in one or two knees. For instance, those with one painful knee can compensate to successfully complete functional tasks, such as walking with an assistive device, or climbing stairs one step at a time. Hence, these persons may be more likely to have better physical function outcomes in the future compared with those with pain in both knees.

Researchers have assumed pain severity plays a more dominant role in physical function than whether pain is in one or both knees, as demonstrated in the methods investigators typically employ to examine the relation of knee-specific pain with person-specific physical function measures. These methods include using the worse knee as a reference for pain, termed the 'index knee' and ignoring the other less or non-painful knee<sup>8-10</sup>, or utilizing questionnaires which do not differentiate between pain in one or both knees<sup>11-15</sup>. The assumption with these methods is that information on the more painful knee or pain severity alone is sufficient to understand the pain-function relationship.

Previous literature supports the notion that persons with two painful knees are more likely to have difficulty with physical function compared with those with one painful knee<sup>16, 17</sup>. However, it is noteworthy that these studies were conducted cross-sectionally in the general population and not one that was specific to persons with knee OA. Furthermore, these studies did not account for knee pain severity nor examined how such pain at baseline may influence function longitudinally.

Thus, we believe a study of the association of pain in one or both knees with physical function at baseline and longitudinally while accounting for knee pain severity among persons with knee OA is needed and pertinent to both clinicians and researchers. We are particularly interested in a state of significant limitation within a broad range of daily activities, which we term low physical function and measure with a self-report questionnaire, the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) physical function scale, examining 17 different activities<sup>18</sup>. The specific purpose of our study is to examine whether persons with unilateral knee pain at baseline have a similar risk of low physical function at baseline and at 30 months compared with those with bilateral knee pain, independent of knee pain severity.

## Patients and Methods

### Study Sample

A detailed description of recruitment and sampling for MOST has been published elsewhere<sup>19</sup>. In brief, we used data from the Multicenter Osteoarthritis (MOST) study, a large multicenter prospective cohort study of 3026 community-dwelling persons who had or who were at high risk of developing symptomatic knee osteoarthritis (OA) at baseline. Participants were defined as being at risk of developing knee OA based on known risk factors, including older age, female gender, previous knee injury or operation, and high body weight. Subjects aged 50 to 79 years were recruited from Birmingham, Alabama and Iowa City, Iowa. Baseline assessments took place between May 2003 and March 2005, and follow-up assessments 30 months later. The MOST study protocol was approved by the institutional review boards at the University of Iowa, University of California, San Francisco, University of Alabama at Birmingham, and Boston University Medical Center.

For the present study, our sample consisted of persons who had at least one knee with a minimal degree of knee pain, defined as a baseline pain score on the visual analogue scale (VAS) of at least a 10 (with 0 -100 as endpoints where 0 is no pain). We did not use the WOMAC pain score to define painful knees due to its high correlation with the outcome, WOMAC physical function<sup>20</sup>. We anticipated that subjects undergoing a new knee or hip replacement would likely improve in function; hence we excluded these persons from analyses. Persons with existing joint replacements at baseline were included in analyses.

### Study Variables

**Exposure variable**—We categorized all eligible subjects as having unilateral or bilateral knee pain. Persons with one knee with a VAS of at least 10 or greater were classified as having unilateral pain, while those with two knees with a VAS of at least 10 or greater were classified as having bilateral pain.

**Outcome variable**—We defined low physical functioning as scores of at least 28/68 and greater on the WOMAC physical function scale<sup>18</sup>, which is consistent with a previous definition of poor functional outcome for persons with knee OA<sup>8</sup>, and within a range of scores reported for persons awaiting total knee replacement<sup>21</sup>. Persons reaching a score of 28/68 report having at least slight to moderate difficulty in all 17 tasks from the WOMAC physical function scale, or severe to extreme difficulty in 7 to 9 tasks.

### Statistical Analysis

At baseline, subjects with scores of at least 28/68 were classified as having prevalent low physical functioning. Persons without low physical functioning at baseline who declined below this threshold at 30 months were classified as having incident low physical functioning, while persons with low physical functioning at baseline who improved above these thresholds at 30 months were classified as having improvement from low physical functioning.

We examined the relationship of pain in one versus two knees with the presence of low physical function at baseline (prevalence), and the occurrence of new low physical function (incidence) and improvement from initially having had low physical function at 30 months (improvement). Given the strong association between knee pain severity and physical function<sup>22, 23</sup>, we first performed analyses stratified by knee pain severity, followed by combining all subjects' data. Subjects with a VAS range of 10-39/100 were divided into a mild knee pain group, and those with a VAS range of  $\geq 40/100$  into a moderate/severe pain group. Those with two painful knees were categorized according to the more painful knee. In addition, we adjusted for knee pain severity as a continuous variable (VAS) to account for differences in pain within pain severity strata. For persons with bilateral pain, we used data from the knee with more pain. We assessed the relation of one versus two painful knees with each outcome by computing prevalence and risk ratios using regression methods with a log-link function and robust standard errors<sup>24</sup>. All analyses were adjusted for the following potential confounders based on existing evidence linking them to function<sup>6, 8, 19, 25-27</sup>: age, sex (male/female), race (Caucasian, other), BMI risk of significant depressive symptomatology (CES-D  $\geq 16$ , yes/no)<sup>28</sup>, low back, hip, or foot pain presence (yes/no), comorbidities measured with the Charlson comorbidity index<sup>29</sup> (none,  $\geq 1$ ), and knee pain severity (VAS).

### Results

Of the 3026 subjects from the MOST study, 941 had VAS pain less than 10/100 in both knees and 16 were missing WOMAC physical function, leaving 2069 for baseline analyses. Subject characteristics are listed in Table 1. The mean age and BMI of subjects was 62.6 years, and 31.1 kg/m<sup>2</sup>, respectively. A majority of subjects were female (63%), Caucasian (83%), and did

not have any comorbidities (63%). At 30 months, 262 had missing data or did not complete the follow up visit, leaving 1807 for the 30-month analyses. Those missing (n=262) were older (63.1 vs 62.5 years [missing vs returning]), had a higher BMI (32.5 vs 31.1), and were less likely to be Caucasian (69% vs 83%), have depressive symptoms (28% vs 16%), and have more than one comorbidity (45% vs 37%) compared with persons returning at 30 months. There was no difference in the distribution of sex, nor in the presence of pain at the low back, hip, or foot.

At baseline, 545 (25%) of participants had low physical functioning. Among those with mild pain, persons with pain in one knee were 70% less likely to have low physical function compared with those with pain in both knees [adjusted prevalence ratio (adj PR) 0.3 (95% CI 0.1-0.5)]. Among those with moderate/severe pain, a similar number of persons with pain in one and two knees had low physical function present [adj PR 0.9 (95% CI 0.8-1.1)]. Among all persons (mild and moderate/severe pain), those with unilateral pain were 50% less likely to have low physical functioning than those with bilateral pain [adj PR 0.5 (95% CI 0.3-0.7)]. See Table 2.

At 30 months, 176 (13%) of 1380 participants developed low physical functioning. Persons with mild pain in one knee were 30% less likely to have incident low physical function at 30 months compared with those with pain in both knees [adjusted risk ratio (adj RR) 0.7 (95% CI 0.5-1.0)]. We found a similar effect for persons with moderate/severe pain, though this effect was not statistically significant [adj RR 0.7 (95% CI 0.4-1.2)]. Among all persons, those with unilateral pain were 30% less likely to develop low physical functioning [adj RR 0.7 (95% CI 0.5-1.0)]. See Table 3.

By 30 months 175 (41%) of 427 persons improved and no longer had low physical functioning. For persons with mild and moderate/severe pain at baseline, those with pain in one knee were 1.8 and 1.6 times, respectively, more likely to no longer have low physical function at 30 months, compared with those with pain in both knees [adj RR 2.0 (95% CI 1.2-3.0) and 1.6 (95% CI 1.3-2.0)]. Among all persons, those with unilateral pain were 1.7 times more likely to no longer have low physical functioning compared with those with bilateral pain [adj RR 1.7 (95% CI 1.3-2.2)] See Table 4.

## Discussion

We found the presence of low physical function at baseline and at follow-up to be different among persons with pain in one versus two knees, after adjusting for knee pain severity. Specifically, at baseline persons with pain in one knee were less likely to have low physical functioning compared with persons with two painful knees. At follow-up, persons with pain in one knee were less likely to have low physical function and were more likely to improve from low physical functioning compared with those who had pain in both knees, after accounting for pain severity and other potential confounders. These results suggest that the likelihood for change in functioning is not solely based on pain severity of the worst knee, but also whether pain involvement is in one or both knees.

Is it clinically plausible that persons with unilateral pain have a better functional outlook compared with those with bilateral pain? One possible reason why this may occur is that persons with unilateral pain can compensate with the non-painful lower limb during functional activities. Furthermore, persons with unilateral pain could use an assistive device, such as a cane, to minimize pain during functional activities, which would not be as effective in reducing pain for those with bilateral pain. These points may aid the ability to avoid poor functional outcomes over time in persons with one versus two painful knees.

The relation of knee pain with physical function is complex. Our findings confirm that pain location (one versus two knees) is an important factor to consider. However pain location is not sufficient to fully understand why persons with knee pain may functionally decline or improve. In particular, previous literature has highlighted pain severity playing a substantial role in changes in physical functioning<sup>22, 23</sup>. We found this to be consistent in our study with more decline and less improvement in physical function for persons with moderate/severe knee pain compared with those with mild knee pain. These findings support the notion that severity of knee pain is an important determinant of function<sup>8, 14</sup>, and underscores the need to account for pain severity when examining the relationship between unilateral versus bilateral pain with physical functioning.

There are some limitations to our study. First, we examined pain only measured at baseline. Thus, it remains unclear how changes in unilateral versus bilateral pain over time co-vary with changes in function. Nonetheless, we found baseline pain to be associated with physical function two and a half years later, which suggests that a single time-point assessment does have value. Second, we estimated a reasonable definition for low physical function given that no cutoff has been established in the literature. We performed a sensitivity analysis using cutoffs of low physical functioning ranging from 25 to 34/68 for WOMAC physical function and found similar results. As mentioned previously, our cut-off was consistent with previously published literature, and represents moderate to severe difficulties across multiple activities. Third, we assessed physical function using only one instrument, WOMAC physical function. Performance measures can also be employed to measure function. However, our purpose was to evaluate a broad range of functional tasks, which is better accomplished using self-report of a variety of tasks rather than a performance measure of one particular task. Lastly, our cohort included both persons with and without knee OA. We repeated our analyses including only those with radiographic knee OA and found similar results.

In summary, we find it noteworthy that the location of pain in one versus two knees at baseline was relevant for changes in function 30 months later. Our findings support the notion that clinicians focus on therapy directed at both knees, not just the more painful knee. From a research perspective, it may not be sufficient enough to employ an index or reference knee approach when examining the relationship between knee-specific and person-specific outcomes. Rather, the presence of unilateral versus bilateral pain should be noted in addition to pain severity to improve the ability to evaluate pain-function relationships. This especially may be pertinent when studying physical functioning longitudinally.

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**Table 1**

Summary baseline characteristics of the study sample

|                                     | <b>All subjects<br/>N=2069</b> | <b>Unilateral<br/>N=760</b> | <b>Bilateral<br/>N= 1309</b> |
|-------------------------------------|--------------------------------|-----------------------------|------------------------------|
| Age in years [Mean (sd)]            | 62.6 (8.2)                     | 62.4 (8.0)                  | 62.8 (8.2)                   |
| Female [n (%)]                      | 1306 (63)                      | 425 (56)                    | 881 (67)                     |
| Caucasian [n (%)]                   | 1676 (81)                      | 654 (86)                    | 1022 (78)                    |
| BMI* [kg/m] [Mean (sd)]             | 31.2 (6.3)                     | 30.3 (5.9)                  | 31.8 (6.5)                   |
| CES-D <sup>†</sup> ≥16 [n (%)]      | 348 (17)                       | 810(11)                     | 268 (21)                     |
| Low back, hip, or foot pain [n (%)] | 1714 (83)                      | 586 (77)                    | 1128 (86)                    |
| No Comorbidity [n (%)]              | 1290 (62)                      | 498 (66)                    | 792 (61)                     |
| ROA at the knee [n (%)]             | 1279 (65)                      | 442 (62)                    | 837 (67)                     |

\* BMI = Body Mass Index

<sup>†</sup> CES-D= Center for Epidemiologic Studies Depression Scale



Relation of bilateral and unilateral knee pain among those with mild and moderate/severe pain at baseline to prevalence of low physical functioning.<sup>§</sup>

**Table 2**

|                                  | Baseline VAS*<br>(0-100)<br>[mean (sd)] | Baseline<br>WOMAC <sup>†</sup><br>(0-68)<br>[mean (sd)] | Low physical<br>functioning <sup>‡</sup> / total<br>number of subjects | %  | Prevalence<br>Ratio [95% CI] |
|----------------------------------|---|---|--|----|------------------------------|
| <u>Mild Knee pain</u>            |   |   |  |    |                              |
| Bilateral                        | 23.4 (8.4)                              | 16.3 (8.5)  | 63/666   | 10 | 1.0 Ref                      |
| Unilateral                       | 18.7 (8.2)                              | 11.9 (7.7)  | 15/588   | 3  | 0.3 [0.1-0.5]                |
| <u>Moderate/Severe Knee pain</u> |   |   |  |    |                              |
| Bilateral                        | 59.9 (16.9)                             | 30.5 (10.9)   | 386/643  | 60 | 1.0 Ref                      |
| Unilateral                       | 56.6 (16.2)                             | 26.8 (11.4)   | 81/172   | 47 | 0.9 [0.8-1.1]                |
| Overall                          |   |   |  |    |                              |
| Bilateral                        | 41.3 (22.6)                             | 23.3 (12.1)   | 449/1309   | 34 | 1.0 Ref                      |
| Unilateral                       | 27.3 (19.0)                             | 15.3 (10.7)   | 96/760   | 13 | 0.5 [0.3-0.7]                |

\* VAS=Visual Analogue Scale for knee pain severity

<sup>†</sup> WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index

<sup>‡</sup> Defined as WOMAC physical function scores of 28 and greater.

<sup>§</sup> Adjusted for age, sex, race, BMI, depressive symptoms, pain elsewhere, comorbidity, and pain severity.

Relation of bilateral and unilateral knee pain among those with mild and moderate/severe pain at baseline to incidence of low physical functioning.<sup>§</sup>

Table 3

|                                  | Baseline VAS*<br>(0-100)<br>[mean (sd)] | Baseline WOMAC <sup>†</sup><br>(0-68)<br>[mean (sd)] | Change in WOMAC over 30 months<br>[mean (sd)] | Incidence of low physical functioning <sup>‡</sup> / total number of subjects | %  | Prevalence Ratio [95% CI] |
|----------------------------------|---|--|---|---|----|---------------------------|
| <u>Mild Knee pain</u>            |   |  |   |   |    |                           |
| Bilateral                        | 22.7 (8.4)                              | 14.5 (7.0)   | 0.8 (8.8)                                     | 65/551  | 12 | 1.0 Ref                   |
| Unilateral                       | 18.6 (8.1)                              | 11.2 (7.0)   | 0.4 (9.0)                                     | 37/524  | 7  | 0.7 [0.5-1.0]             |
| <u>Moderate/Severe Knee pain</u> |   |  |   |   |    |                           |
| Bilateral                        | 53.2 (14.0)                             | 20.0 (5.6)   | 0.7 (10.5)                                    | 60/227  | 26 | 1.0 Ref                   |
| Unilateral                       | 51.7 (12.8)                             | 18.6 (6.6)   | -0.8 (11.5)                                   | 14/78   | 18 | 0.7 [0.4-1.2]             |
| <u>Overall</u>                   |   |  |   |   |    |                           |
| Bilateral                        | 31.6 (17.3)                             | 16.1 (7.1)   | 0.8 (9.3)                                     | 125/778   | 16 | 1.0 Ref                   |
| Unilateral                       | 22.9 (14.2)                             | 12.1 (7.4)   | 0.2 (9.4)                                     | 51/602  | 9  | 0.7 [0.5-1.0]             |

\* VAS=Visual Analogue Scale for knee pain severity

<sup>†</sup> WOMAC PF = Western Ontario and McMaster's University Osteoarthritis Index Physical Function Scale

<sup>‡</sup> Defined as persons with WOMAC physical function scores of 28 and greater at 30 months but not at baseline.

<sup>§</sup> Adjusted for age, sex, race, BMI, depressive symptoms, pain elsewhere, comorbidity, and pain severity.

**Table 4**

Relation of bilateral and unilateral knee pain among those with mild and moderate/severe pain at baseline to improvement from low physical functioning.<sup>§</sup>

|                                  | Baseline VAS* (0-100) [mean (sd)] | Baseline WOMAC† (0-68) [mean (sd)] | Change in WOMAC over 30 months [mean (sd)] | Improvement from low physical functioning‡ / total number of subjects | Risk Ratio [95% CI] |
|----------------------------------|-----------------------------------|------------------------------------|--|---|---------------------|
| <u>Mild Knee pain</u>            |                                   |                                    |  |   |                     |
| Bilateral                        | 28.2 (7.9)                        | 32.2 (3.5)                         | -5.8 (11.7)                                | 21/49   | 36 1.0 Ref          |
| Unilateral                       | 22.7 (10.3)                       | 31.4 (3.9)                         | -12.1 (12.3)                               | 10/12   | 83 1.8 [1.1-2.9]    |
| <u>Moderate/Severe Knee pain</u> |                                   |                                    |  |   |                     |
| Bilateral                        | 64.5 (17.0)                       | 37.2 (7.3)                         | -5.6 (11.7)                                | 106/305   | 35 1.0 Ref          |
| Unilateral                       | 60.4 (17.3)                       | 34.9 (6.0)                         | -12.5 (13.7)                               | 38/61   | 62 1.6 [1.2-2.1]    |
| <u>Overall</u>                   |                                   |                                    |  |   |                     |
| Bilateral                        | 59.5 (20.4)                       | 36.5 (7.1)                         | -5.6 (11.7)                                | 127/354   | 36 1.0 Ref          |
| Unilateral                       | 54.2 (21.6)                       | 34.3 (5.8)                         | -12.4 (13.3)                               | 48/73   | 65 1.7 [1.3-2.2]    |

\* VAS=Visual Analogue Scale for knee pain severity

† WOMAC PF = Western Ontario and McMaster's University Osteoarthritis Index Physical Function Scale

‡ Defined as persons with WOMAC physical function scores of 28 and greater at baseline but not at 30 months.

§ Adjusted for age, sex, race, BMI, depressive symptoms, pain elsewhere, comorbidity, and pain severity.