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## Psychological factors and their relation to osteoarthritis pain

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### Abstract

**Objective**—We assessed associations between mental health and osteoarthritis (OA) pain

**Methods**—Two hundred and sixty-six subjects with hip and/or knee OA from the Longitudinal Examination of Arthritis Pain (LEAP) study were interviewed weekly for 12 weeks, measuring WOMAC pain subscale and 5-item Mental Health Inventory (MHI-5).

We examined associations between MHI-5 and its change, divided into quartiles, to WOMAC pain and its change (occurring one week later) using linear regression, adjusting for age, sex, body mass index, medication use. Generalized estimating equations were used to account for repeated measurements correlation. We also assessed the relation of MHI-5 to the risk of pain flare using conditional logistic regression in a case crossover study.

**Results**—Seventy-five men and 191 women were included. Mean age was 65.0, mean BMI 31.5. 82% had knee as their primary site. The mean WOMAC score was 2.93 in the quartile with the highest MHI-5 as compared with a mean WOMAC of 4.57 in the quartile with the lowest MHI-5 (p for trend across quartiles <0.001). In the case crossover analysis (91 subjects), periods with the worst MHI-5 quartile had 2.1 times the odds of a pain flare the subsequent week as compared to periods with the best MHI-5 quartile (p<0.001).

**Conclusion**—We demonstrate an association between worsened measures of mental health and OA pain and risk of pain flares. General mental health is a modifiable component of health and may represent a new avenue for prevention of OA pain flares.

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## Key Indexing Terms

osteoarthritis; pain; mental health

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## Introduction

Osteoarthritis (OA) is a common and debilitating disease, affecting approximately 12% of those between 25 and 74 years of age (1), with almost 27 million adults in the U.S. having clinical OA of any joint (2). This condition is associated with the vast majority of hip and knee replacement surgeries and costs to society approach \$15 billion per year in the U.S.(3).

For the majority of patients, pain in OA is episodic in nature. In the Boston Osteoarthritis Study, 39% of those with radiographic knee OA as well as pain on most days during any month in the previous year had Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain scores that varied from little or no pain to severe pain measured at 3 different time points over three years (4). Further, pain intensity levels appear to vary within an individual over both long periods as well as short periods(5), ascribed by patients variously to such factors as the weather, activity levels, and medication use. There has been very little work done on characterizing or describing short-term variations in pain level in OA(6), and the origins of pain in those with radiographic OA are not well understood.

Pain itself is a complicated condition with a multitude of components and pitfalls in measurement. The experience of pain is generated or modified by nociception, neuropathic symptoms, psychological and personality factors, genetic influences, past painful experiences, comorbid conditions, and expectations related to future pain(7-12). Furthermore, measurement of pain is made difficult by a variety of only partially understood variables, including subjects' desire to please interviewers, high levels of recall bias, confounding by poor physical function(13), confusion over which dimension of pain is being measured by questions which do not define frequency or periodicity of pain, and idiosyncratic subject reporting styles. We have tried to eliminate some of the between-subject problems in pain measurement by employing a case crossover analysis where case and control periods are compared within a single subject.

Depression is also a common condition, has a prevalence of 16% among elderly persons(14,15), and has an impact on disability levels comparable to other important diseases such as heart disease and hypertension(16). Psychological well-being has been significantly associated with disability in patients with OA(17), and anxiety has been found to be associated with knee pain in women(18-20). Modification of depression has also been demonstrated to affect arthritis pain levels (21). There is no longitudinal study to date that has examined fluctuations in OA pain and their relation to changes in general mental health.

The Longitudinal Examination of Arthritis Pain (LEAP) Study investigated the relationship between self-rated pain fluctuations on a weekly basis and health outcomes including healthcare resource use in adults treated for osteoarthritis of the hip and/or knee(22). We used detailed information on mental health factors from these weekly telephone interviews to examine the role of these factors in fluctuations of OA pain.

## MATERIALS AND METHODS

A detailed description of the LEAP study has been published elsewhere (22). In brief, patients in the LEAP study were enrolled from primary care as well as rheumatology practices across the United States, with clinical diagnoses of hip or knee OA as assessed by

their own physicians. The LEAP study recruited patients by identifying sites across the US with high numbers of OA patients. Posters were displayed at the practices, and both practices and patients were paid for recruitment and for participation. The subjects participated in telephone interviews at intervals of approximately one week for up to 12 weeks, during which they responded to questions about their OA pain, psychological state, as well as a variety of other questions. Medication use was collected by recording the number of days of the previous week subjects had used either prescription or over-the-counter medications to treat their pain.

### **Pain Assessment**

The outcome measure was the WOMAC pain subscale score (0-10 scale). This scale represents worse pain at the higher end of the scale, and was assessed by the question “Thinking about the pain you felt in your <signal joint> because of your OA during the last week. Please rate your pain on a scale of 0 (no pain) to 10 (extreme pain). How much pain do you have... Walking on a flat surface? Going up or down stairs? At night while lying in bed? Sitting or lying? Standing upright?” The total score out of 50 was normalized to a 0-10 scale for this analysis. The WOMAC was measured at baseline and at weekly intervals, and in each case a weekly average was obtained.

### **Mental Health Status Assessment**

The Mental Health Index-5 (MHI-5) was collected weekly in the LEAP study. The MHI-5 measures general mental health(23,24) and assesses general mood or affect and positive well-being. It has also been found valid for use in screening for mood disorders(25). We have reported raw scores in this paper (scale 5-30) and higher scores indicate better mental health while lower scores indicate worse mental health. Questions in the MHI-5 take the form of “During the past week, how much of the time were you a happy person?” with answers in a 6 point Likert scale ranging from “all of the time” to “none of the time”. The MHI-5 is a validated(23) measure of general mental health.

### **Statistical Analysis**

We excluded data from the analysis where the time interval between two consecutive interviews was greater than 8 days in order to understand the short term relation between mental health and pain. We also performed similar sub-analyses limited to either shorter or longer time frames. Analyses were performed using SAS statistical software, version 9.1 (SAS Institute, Inc.).

We examined associations between MHI-5 and its change to WOMAC pain occurring one week later. We divided baseline MHI-5 and change from baseline to the value one week prior to the WOMAC score under question into quartiles. For the MHI-5 there is no generally agreed-upon or clinically validated cutpoint for a case of common mental disorder. Various studies have used different methodologies in British, German and Dutch populations to arrive at cutpoints that vary from 60 to 76 on a normalized scale in a non-HIV population(24-26). We took the cutpoint for high prevalence of mental health problems established by Hoeymans at 72 (or 23 points on the raw scale we use) as our cutpoint, and the first quartile in our study corresponds to MHI-5 values which fall below this number. Thus, our analyses reflected four quartiles, the first of which comprised those MHI-5 values representing a population with a high prevalence of mental health problems and the other three representing three ordinal categories within a population of subjects with MHI-5 values that are associated with low prevalence of mental health problems.

In a multiple linear regression model we adjusted for age, sex, body mass index, and prescription and over-the-counter pain medication use (defined as whether the subject used

prescription/over-the-counter medication to treat pain during the previous week, and if so, how many days each type was used). The dependent variable was WOMAC pain and the independent variables were quartiles of baseline MHI-5 score and change of MHI-5 score. We used generalized estimating equations to account for correlated data of repeated measurements within a subject.

We also conducted a case crossover study to assess the relation of general mental health to the risk of pain flare one week later, using a conditional logistic regression model. Specifically, we used each weekly time point for each subject as the unit of analysis. We defined a “pain flare” (or “case period”) as an interview where the subject reported a WOMAC score in the highest thirty percent of all WOMAC scores. We defined a “control period” as an interview where the subject reported a WOMAC score in the lowest seventy percent of all WOMAC scores. Only subjects who had at least one case period and at least one control period were included in this analysis.

## RESULTS

Three hundred and three subjects were screened in the LEAP study, 288 were enrolled, 9 subjects had no pain information collected, and 7 had only one visit with pain information recorded. A further 6 subjects had greater than 8 days duration between all visits, and these subjects were not included in the analysis. Restricting the analyses to visits where the prior visit was 8 days or less distant eliminated 14% of the total visits and allowed for maintenance of close proximity between putative predictors and the WOMAC pain outcome. Also, a small number of subjects (23) had individual visits that were apparently filled out with reference to the pain in a different joint than their “signal joint”; these visits were eliminated from the analyses.

Two hundred and sixty-six subjects were included in the analysis group, all of whom carried a clinical diagnosis of OA of the hip or knee or both, as ascertained by the original LEAP investigators. 67% of the subjects were recruited in rheumatology clinics and 33% from general practice clinics. Of these subjects, 75 were men and 191 women, with a mean age of 65.0 (SD±8.5) and mean BMI of 31.5 (SD±7.4) (see Table 1). 82% of the subjects had OA with the knee defined as their primary site, while 18% defined the hip as their primary site. OA in the signal joint was confirmed by radiograph in 80% of the subjects, while 20% did not have radiographs available. The range of WOMAC scores was wide and varied from 0.2 to 9.6, with a mean for the entire group of 3.8 (±2.2). Mean MHI-5 was 25.1 (±4.0). As described by Hutchings(22), the majority of participants completed the majority of repeated measurements, with the mean number of follow-ups completed being 10.7 out of a possible 12 and 82% of participants completing 10 or more interviews.

### GEE Results

As shown in Table 2 and Figure 1, better baseline mental health was associated with less pain as compared with worse baseline mental health (adjusted mean WOMAC score 2.93 for the highest quartile of MHI-5 as compared with 4.57 for the lowest quartile;  $p$  for trend<0.001). Change of MHI-5 from baseline values was also associated with change in WOMAC pain (Table 2 and Figure 2). The greatest improvement from baseline in mental health was associated with better WOMAC scores as compared with the quartile with the greatest worsening in mental health from baseline, with an adjusted mean WOMAC score 3.53 for the highest MHI-5 quartile as compared with 4.06 for the lowest quartile ( $p$  for trend<0.001). We found similar results in the same analyses limited to time frames longer or shorter than 8 days (data not shown).

### Case Crossover Results

Ninety-one subjects, who were the only subjects out of the overall 266 who had both at least one case period and at least one control period, were included in the case crossover analysis. The demographic characteristics of these subjects were similar to the overall group (Table 1). The WOMAC range for control periods was 0.2-4.9 and for case periods was 5.0-9.6, with a mean WOMAC score of 4.5 ( $\pm 1.8$ ), and mean MHI-5 of 24.7 ( $\pm 4.0$ ).

General mental health was associated with the risk of pain flare. As shown in Table 3, when subjects had the worst MHI-5 scores the odds of a pain flare the subsequent week were 2.11 times higher than when the same subjects were in periods with the best MHI-5 scores ( $p < 0.001$ ).

### DISCUSSION

In summary, worse baseline mental health is associated with worse OA knee pain in a cross-sectional analysis. Furthermore, improvement in mental health from baseline is associated with reduction in pain of OA. Lastly, the risk of a pain flare is increased by worsened mental health in the week prior to the flare. These three basic findings support a strong association and possibly predictive relation between mental health and OA pain.

The rationale for examining the mental health factors and their relation to pain in OA is multifold. First, it is clear that the etiology of OA pain is not well understood, and that both peripheral and central neuronal abnormalities of function may play a part(27). Given the importance of the central nervous system in understanding pain, and the known relation between depression or other components of mental health and intrinsic neuronal function, psychological factors become prime suspects as mediators of the experience of pain.

Second, pain in a variety of other conditions has been found to be associated with psychological state, and treatment with antidepressants has been found to alleviate pain. Tricyclic antidepressants have been demonstrated in small trials to be effective at reducing pain in rheumatoid arthritis patients(28-30), but have not achieved widespread use for treatment of that disease, given the development of disease-modifying drugs for that condition; at present there are no available disease-modifying treatments for OA. Three recent meta-analyses of anti-depressant treatment for fibromyalgia have all supported the likelihood of a modest effect on pain with tricyclics(31-33), but duloxetine has demonstrated a significant and repeated effect on tender points and measures of pain in randomized, controlled clinical trials(34,35).

Lastly, there has been some preliminary evidence that treatment of depression, a powerful factor in mental health, can affect pain in OA. Lin et al.(21) found a significant reduction in OA pain with enhancement of treatment for coexistent depression in OA patients.

Our study carries the inherent strengths of the original LEAP data. These include the first weekly independent measurements of pain and mental health in a cohort of OA patients to our knowledge. Other strengths include a plausible time frame for a causal relationship between predictor and outcome of approximately one week, convincing trends in the data that appear stable, and a case crossover analysis which demonstrates a persuasive relation to pain flares in a manner which eliminates questions of genetic, experiential, and neuronal differences between subjects. Furthermore, the differences across groups in mental health in LEAP are large. Nettles et al.(36) state that "a change of more than 10 points [in a normalized scale of the MHI-5] was considered a significant change in mood"; a change of 10 points in the Nettles paper corresponds to a change of 2.5 points on the raw MHI-5 scale

we use in this paper, which is much smaller than the change values we observed in the LEAP study.

There are also significant limitations in our study. These include combining hip and knee OA subjects into one cohort. Our most significant limitation, however, is intrinsic to the study of pain and mental health in any setting: it is quite difficult to address the spectre of reverse causality in these data. It may be true, as we have found, that mental health affects pain levels in OA. It seems intuitively true, however, that pain in OA affects mental health, and to disentangle this relationship is daunting. For example, although we have separated the independent variable from the outcome by one week in these analyses, it still may be the case that subjects have a premonition of pain they will experience the next week which could affect their mental health. Although we have tried to establish the mental health variable as predictive in our analysis, this does not negate the possibility that reverse causality plays a significant role in the results.

It may be that ultimately the question of causality is academic. There may be an iterative process at work, with an ongoing stream of OA pain and related worsened mental health that feeds back on itself over time. Certainly the cross-sectional association we have found is consistent with such a picture. It is worth considering whether entering that process at any point with a therapeutic intervention related to mental health will have the capability to abort the circular pain process. The relationship of pain to mental health may be mediated in part by a variety of factors, including social isolation, sleep changes, and changes in physical activity. We were not able to look at these questions given the information collected in the LEAP study.

In conclusion, we have shown that worse or worsening mental health precedes reporting of worse OA-related pain and OA pain flares. With the paucity of effective interventions for OA pain and the toxicities of some in common use, mental health may represent a new therapeutic target for OA pain, with potential significant opportunities for both patients and physicians.

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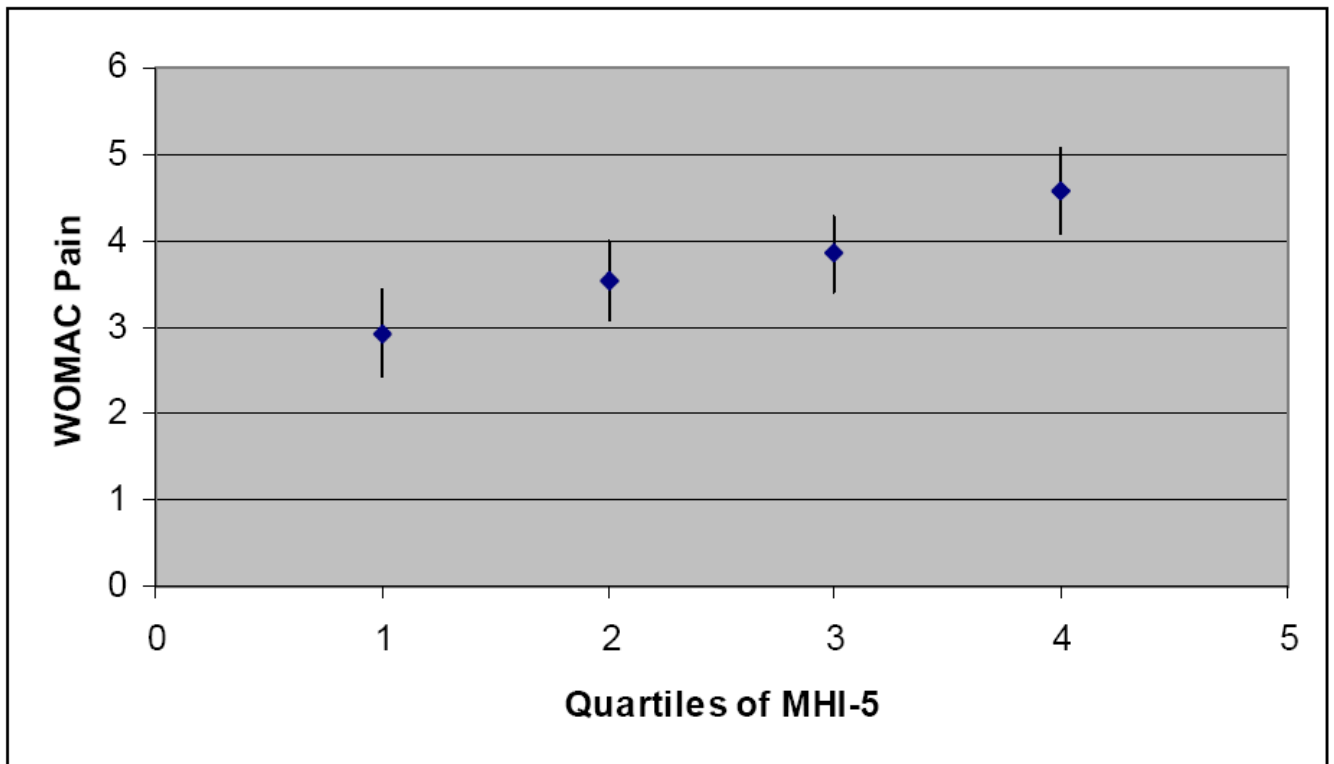
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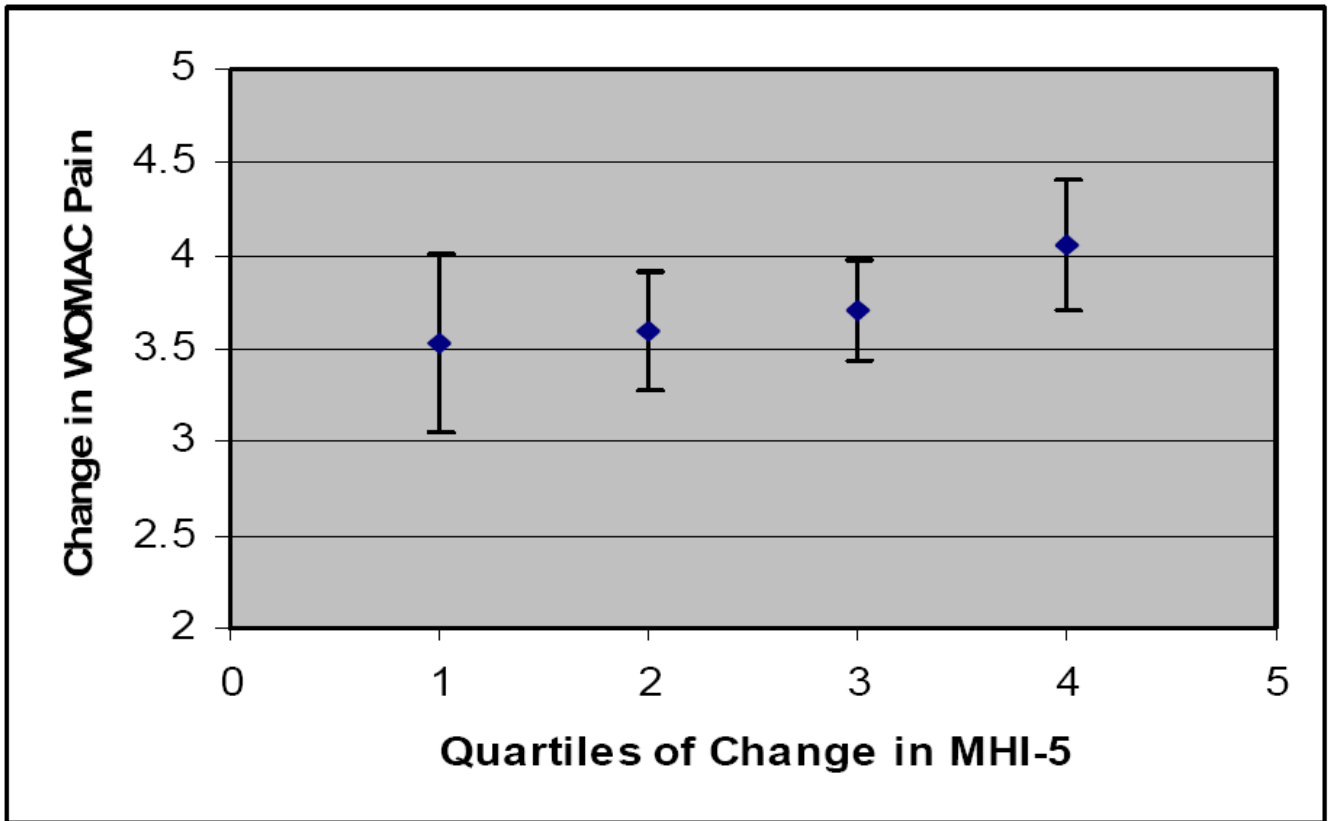
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**Figure 1.**

Baseline MHI-5 in quartiles with mean WOMAC pain, adjusted for age, sex, BMI, and medication use.  $p$  for trend  $<0.001$ . The first quartile is those with the best mental health, while the fourth quartile represents those with the worst mental health. Error bars represent 95% confidence intervals.



**Figure 2.** Change in MHI-5 with mean change in WOMAC pain, adjusted for age, sex, BMI, and medication use.  $p$  for trend  $<0.001$ . Error bars represent 95% confidence intervals.

**Table 1**

## Subject Characteristics

Characteristic	Subjects (n=266)	Case-crossover Subjects (n=91)
Age, years [mean (SD)]	65(±8.5)	65(±8.8)
Female [n (%)]	191 (71)	72 (79)
BMI, kg/m <sup>2</sup> [mean (SD)]	31.5 (±7.4)	31.4 (±8.8)
Race – Non-Hispanic White	89%	89%
Race – African-American	6%	8%
Race – Other	5%	3%
Knee as primary site [n (%)]	216 (82)	71 (78)
Hip as primary site [n (%)]	50 (18)	20 (22)
WOMAC range	0.2-9.6	0.2-4.9 (control periods) 5.0-9.6 (case periods)
WOMAC [mean(SD)]	3.8 (±2.2)	4.5 (±1.8)
MHI-5 [mean (SD)]	25.1 (±4.0)	24.7 (±4.0)

**Table 2**

Relation of MHI-5 and its change to pain intensity, adjusted for age, sex, BMI, and medication use (linear regression model)

MHI-5	N Observations	Adjusted Mean WOMAC Pain
<b>Baseline MHI-5 Values</b>		
28-30	53	2.93
26-27	67	3.54
23-25	75	3.86
13-22	68	4.57
<b>P for trend</b>		<0.001
<b>Change of MHI-5</b>		
3-14 (improved)	448	3.53
1-2	517	3.59
0-0	556	3.71
(-13) – (-1) (worsened)	526	4.06
<b>P for trend</b>		<0.001

**Table 3**

MHI-5 and its relation to pain flares (case crossover analysis). Adjusted for medication use.

MHI-5 Quartile Range	N Case Periods	N Control Periods	Unadjusted Odds Ratio	Adjusted Odds Ratio
28-30 (ref)	77	143	1.00	1.00
26-27	68	89	1.18	1.19
23-25	89	86	2.05	1.95
13-22	102	95	2.01	2.11
<b>P for trend</b>			0.002	<0.001