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Statistical Approaches to Evaluating the Effect of Risk Factors on the Pain of Knee Osteoarthritis in Longitudinal Studies

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Abstract

Purpose of review—We describe commonly used measures of knee pain in longitudinal studies and review various analytic approaches to evaluating the effect of a risk factor on each type of pain measure.

Recent findings—In longitudinal epidemiologic studies of knee pain, frequent knee pain and activity-related pain severity are the most commonly used measures for pain. Various analytic approaches have been used to evaluate the effect of a risk factor on each type of pain measure. Analytic approaches utilized include the generalized estimating equations model and the mixed-effects linear regression model for pain severity assessed as a continuous outcome variable; the mixed-effects logistic regression model and conditional logistic regression model for pain exacerbation measured as a dichotomous outcome variable; and a mixed-effects regression model, stratified proportional odds model, and a multi-state transition model for pain severity measured as an ordinal outcome variable.

Summary—Compared with cross-sectional studies, longitudinal studies allow investigators to assess the effect of change in a risk factor of interest on change in risk of knee pain or change in pain severity. With appropriate analysis methods investigators are able to minimize potential confounders that differ among individuals or knees but which do not vary over time within a person or knee.

Keywords

Longitudinal study; pain; knee osteoarthritis; statistical modeling

Introduction

Osteoarthritis (OA) is the most common joint disorder and the leading cause of disability in the elderly (1,2). Symptomatic knee OA occurs in approximately 37% of persons aged 60 years or older (3). Pain from knee OA is a key symptom in the decision to seek medical care and an important antecedent to disability (4). Most previous studies have focused on risk factors for radiographic knee OA. Factors that differentiate symptomatic knee OA from asymptomatic radiographic disease are still largely unknown.

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Pain is a subjective experience that is unique to the individual. Many factors, including genetic predisposition (5,6), prior experience (7,8), idiosyncratic appraisals (9), expectations (10,11), current mood status (12), and socio-cultural environment (13-15) influence an individual's response to painful stimuli. Unless these factors are measured and controlled, studies that aim to evaluate the effect of a particular risk factor on knee pain by comparing groups of individuals are susceptible to residual confounding bias (16).

While pain in knee OA is commonly chronic, it is not necessarily constant. Clinically, physicians often notice that patients with knee OA experience episodes of recurrent pain or pain exacerbation over the course of the disease. The pain from knee OA typically worsens with use of the involved joint, and decreases or is relieved with rest (17). Such pain patterns are also observed in epidemiologic studies (18)(19,20). These findings indicate that pain fluctuates in knee OA and suggest that factors that vary over time may play roles in pain from knee OA. Assessing the dynamic relation of risk factors to knee pain in longitudinal studies poses significant methodological challenges.

In this paper we first describe several commonly used measures of knee pain in longitudinal studies. We then review various analytic approaches to evaluating the effect of a risk factor on each type of pain measure. To illustrate these methods, we examine the relation of a psychological measure and its change to knee pain severity (either as a continuous scale or in ordinal order) as well as to the risk of knee pain exacerbation (or “flare”) using data from the Longitudinal Examination of Arthritis Pain (LEAP) Study (20).

Assessment of Knee Pain

Several measurements of knee pain have been used in epidemiologic studies. The most commonly used measures of knee pain include frequent knee pain and activity-related pain severity.

a. Frequent knee pain

Subjects are asked to characterize their knee symptoms on most days, often over a specified time period (*e.g.*, the previous 30 days). For example, in the Framingham Osteoarthritis Study, Multicenter Osteoarthritis Study, and Osteoarthritis Initiative, subjects were asked the following question: “During the past 30 days, have you had pain, aching, or stiffness in your knee on most days?” A positive response to the question is considered to indicate the presence of frequent knee pain; a negative response is considered to indicate the absence of frequent knee pain(21,22). Most studies have collected such information for each knee separately.

b. Pain Severity

The most commonly-used instruments to assess knee pain severity are the Western Ontario McMaster Universities (WOMAC) pain subscale score (23) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain subscale (24). More recently, OARSI/OMERACT developed a new OA pain tool, *i.e.*, the measure of Intermittent and Constant Osteoarthritis Pain (ICOAP)(25). The ICOAP is comprised of 11 questions on constant (five items, range of subscale from 0-20) as well as intermittent pain (six items, range of subscale from 0-24) for the seven days prior to questioning.

The Data Set: The Longitudinal Examination of Arthritis Pain (LEAP) Study

A detailed description of the LEAP study has been published elsewhere (20). In brief, subjects in the LEAP study were enrolled from across the US, and had a clinical diagnosis of hip or knee OA or both as assessed by their own physicians. The subjects responded to questions

about their OA pain and state of mental health in weekly telephone interviews for up to 12 weeks.

a. Assessment of Knee Pain

Subjects were asked to identify one knee (“signal knee”) that had more severe pain at the baseline visit and to rate knee pain severity over the prior seven days with the WOMAC instrument (Pain Subscale) at baseline and at subsequent weekly interviews. The total score out of 50 was normalized to a 0-10 scale for the analysis.

b. Mental Health Status Assessment

The Mental Health Index-5 (MHI-5) (26) was collected weekly in the LEAP study. The MHI-5 measures general mental health and assesses general mood or affect and positive well-being. The total score ranges from 5-30 with the higher score indicating better mental health. We divided baseline MHI-5 and change from baseline to the value one week prior to the WOMAC score into quartiles. The ranges of MHI-5 at the baseline examination for each quartile were: 13-22, 23-25, 26-27, and 28-30.

Analysis Methods for Knee Pain Severity as a Continuous Outcome Variable

Two commonly used statistical models to examine the association between a risk factor and a continuous outcome variable in longitudinal studies are GEE and mixed-effects linear regression models. GEE models the marginal distribution of repeated observed outcomes as a function of risk factors while accounting for the dependence of the repeated outcome variable by assuming a certain working correlation structure. It can be written as the following:

$$Y_{ij} = \beta_0 + \beta_b x_{i0} + \beta_w (x_{i(j-1)} - x_{i0}) + \gamma CF_{i(j-1)} + \varepsilon_{ij}, i=1, 2, \dots, n; j=1, \dots, n_i \quad (1)$$

where: Y is the observed measurement of the outcome variable (*e.g.*, WOMAC knee pain); x is the risk factor of interest (*e.g.*, MHI-5); and CF represents potential confounders. Index i indicates the i^{th} subject ($i=1, 2, \dots, n$); index j indicates j^{th} follow-up visit ($j=1, 2, \dots, n_i$) with 0 indicating the baseline visit; $(x_{i(j-1)} - x_{i0})$ represents the change of the risk factor assessed at $(j-1)^{\text{th}}$ follow-up visit from that of baseline visit. β_b estimates an association of risk factor x with outcome variable Y between subjects, *i.e.*, an average difference in outcome variable Y when comparing subjects for whom the values of x differed by one unit. Regression coefficient β_w represents a within-subject association between change in risk factor x and change in value of outcome variable Y , *i.e.*, by decomposition of $x_{i(j-1)}$, we would be able to estimate the expected change in outcome variable Y per unit change in x for a given subject.

An alternative approach is the mixed-effects linear regression model. This model allows either the intercept, or the regression coefficients, or both to vary between subjects. For example, one can write the mixed-effects linear regression model with random-intercepts as the following:

$$Y_{ij} = \beta_{0i} + \beta_b x_{i0} + \beta_w (x_{i(j-1)} - x_{i0}) + \gamma CF_{i(j-1)} + \varepsilon_{ij}, i=1, 2, \dots, n; j=1, 2, \dots, n_i \quad (2)$$

where: β_{0i} has a normal distribution with mean β_0 and variance σ_v^2 , representing subject-specific effect due to unknown factors. The interpretations of β_b and β_w are the same as those described in the GEE model. When the outcome is a continuous variable, a mixed-effects model with random-intercepts can be considered to be a marginal model, and the effect estimates from the mixed-effects linear model with a random intercept are almost identical to those from the GEE approach (27).

We examined the association of baseline MHI-5 and its change with WOMAC pain adjusting for age, sex, body mass index (BMI), and use of pain medication among subjects in the LEAP study using both GEE (28) and the mixed-effects linear regression models, respectively.

Table 1 shows the parameter estimates, standard errors, and p-values for trends from the GEE and mixed-effects linear regression models with random intercepts. Both models showed that subjects with better mental health status (*i.e.*, higher MHI-5 scores) had lower severity of knee pain than those with worse mental health status. Changes in mental health status were also strongly associated with changes in severity of knee pain. In both models the estimates and standard errors were nearly identical.

Analysis Methods for Knee Pain as a Dichotomized Outcome Variable

Frequent knee pain, a dichotomous variable, is commonly used to assess the presence of knee pain. Sometimes when pain severity (*e.g.*, WOMAC) is also collected in a study, its distribution may not be normal. It is often a challenge to normalize a skewed distribution when a large proportion of subjects have a pain score of 0. In this case, one may consider grouping the WOMAC pain score into categories.

For the purposes of illustration, we divided the WOMAC pain score in the LEAP study into two categories: pain “exacerbation (or flare)” and “no exacerbation (or no flare).” Specifically, we defined a subject as experiencing a pain exacerbation (or “flare”) if he/she reported a WOMAC score of ≥ 5 (range 0-10) at the scheduled telephone interview, a score corresponding to the highest 30% of all WOMAC scores; a score of <5 was defined as a “no flare” for that scheduled interview. Of 202 subjects who have baseline and at least one follow-up data on both MHI-5 and WOMAC pain score, 96 (47.5%) did not experience pain flare, 17 (8.4%) experienced one pain flare, 15 (7.4%) experienced two pain flares, and 76 (36.6%) reported 3 or more pain flares.

Assuming subject-specific intercepts follow a normal distribution we can write the mixed-effects logistic regression model as the following:

$$\log \left[\frac{\Pr(Y_{ij}=1)}{1 - \Pr(Y_{ij}=1)} \right] = \beta_{0i} + \beta_b x_{i0} + \beta_w (x_{i(j-1)} - x_{i0}) + \gamma CF_{i(j-1)}, i=1, 2, \dots, n; j=1, 2, \dots, n_i \quad (3)$$

where: $\beta_{0i} \sim N(\beta_0, \sigma_v^2)$

The notations in the formula are the same as those for the continuous outcome variable except that outcome variable Y here represents the observed binary variable (*i.e.*, pain flare). β_b and β_w are the estimates of the between-subject and within-subject effects of MHI-5 on the occurrence of pain flare, respectively.

In longitudinal studies some biological specimens (*e.g.*, blood) or images (*e.g.*, magnetic resonance images) may be collected repeatedly from all participants. The cost of analyzing these specimens or images for all subjects is often formidable when the sample size is large. If the research question focuses on whether changes in biological features indicated by these specimens or images are associated with the risk of pain fluctuation, we may consider conducting a self-matched case-control study, akin to a case-crossover study, to test the study hypothesis. Only subjects (or knees) that experienced knee pain during at least one, but not all, scheduled visits are included. This type of study not only greatly reduces the cost of the study,

but also minimizes the selection bias as well as potential confounding bias varying between subjects or knees.

In both study designs one can use either a conditional logistic regression model or a mixed-effects logistic regression model to analyze data.

The conditional logistic regression model can be written follows:

$$\log \left[\frac{\Pr(Y_{ij}=1)}{1 - \Pr(Y_{ij}=1)} \right] = \beta_{0i} + \beta_w x_{i(j-1)} + \gamma CF_{i(j-1)}, i=1, 2, \dots, n; j=1, 2, \dots, n_i \quad (4)$$

The conditional likelihood approach eliminates nuisance parameters β_{0i} by conditioning on their sufficient statistics.

We examined the association between MHI-5 and its change with the risk of pain flare among participants in the LEAP study using both a mixed-effects logistic regression model and a conditional logistic regression model (28). As shown in Table 2, while subjects with poor mental health status were more likely to experience pain flare than those with better mental health status (between-subject association), the effect estimates were likely to be confounded by other uncontrolled confounders. On the other hand, changes in MHI-5 were strongly associated with the risk of knee pain flare (*i.e.*, within-subject association): risk of pain flare increased 3-fold when mental health status worsened from the best category (28-30) to the worst one (13-22). When limiting the analysis to 74 subjects who experienced knee pain flare during at least one, but not all, telephone interviews, the results from the conditional logistic regression model and mixed-effects logistic regression model were comparable.

Analysis Methods for Severity of Knee Pain as an Ordinal Outcome Variable

Sometimes a large proportion of subjects' WOMAC scores are 0, and there is no appropriate data transformation approach that can make the data symmetric enough to even remotely resemble a normal distribution. In such a case, conventional linear regression models are inappropriate because of the violation of the normality assumption. Although we can dichotomize WOMAC scores to address this problem, the information on degree of pain severity is essentially lost in doing this. To overcome such a problem, one may consider categorizing the pain severity into an ordinal scale (*e.g.*, no pain, mild pain, moderate pain, and severe pain).

Several analytical methods are available for analyzing this type of data, including mixed-effects proportional odds regression models, stratified proportional odds regression models by amalgamating conditional likelihoods (29), and multistate transition models. The mixed-effects proportional odds model for an ordinal outcome variable from a longitudinal study can be written as the following:

$$\log \left[\frac{\Pr(Y_{ij} \geq k)}{1 - \Pr(Y_{ij} \geq k)} \right] = \gamma_k + \beta_{0i} + \beta_b x_{i0} + \beta_w (x_{i(j-1)} - x_{i0}) + \gamma CF_{i(j-1)}, i=1, 2, \dots, n; j=1, 2, \dots, n_i; k=1, 2, \dots, K-1 \quad (5)$$

where: $\gamma_1 > \gamma_2 > \dots > \gamma_{K-1}$, $\Pr(Y_{ij} \geq 0) = 1$ and $\beta_{0i} \sim N(\beta_0, \sigma_v^2)$.

However, the classical conditioning techniques do not apply to ordinal data when the stratified proportional odds model is assumed. Bharmar *et al* proposed fitting a stratified proportional

odds model by amalgamating conditional likelihoods. Specifically, one could collapse the K -category ordinal outcome variable ($k=0,1,\dots,K-1$) into all possible binary scale (*i.e.*, $\geq k$, $< k$) and obtain a robust sandwich estimate for the variance of the effect estimate using the conditional likelihood approach (29).

$$\log \left[\frac{\Pr(Y_{ij} \geq k)}{1 - \Pr(Y_{ij} \geq k)} \right] = \beta_{0ki} + \beta_w X_{i(j-1)} + \gamma CF_{i(j-1)}, i=1, 2, \dots, n; j=1, 2, \dots, n; k=1, 2, \dots, K-1 \quad (6)$$

where: $\gamma_1 > \gamma_2 > \dots > \gamma_{K-1}$, $\Pr(Y_{ij} \geq 0) = 1$ and $\beta_{0ki} = \gamma_k + \beta_{0i}$. By amalgamating conditional likelihood we can then eliminate nuisance parameters β_{0ki} .

The multistate transition model is a semi-parametric survival model that models the transition intensity function (*i.e.* hazard function) between disease transitions from one state to another with its covariates. As depicted in Figure 1 the disease state (*e.g.*, pain severity category) of a subject at a particular time point can be classified as one of K distinct ordinal states and a “transition” occurs when disease state changes between two adjacent time points.

The transition intensity function λ_{zz}^* , for transition from state z to state z^* at time t is a Cox proportional hazards model $\lambda_{zz}^*(t/z, X_i) = \lambda_{0zz}^*(t) \exp^{X_i(t)\beta_{zz}^*}$, where: $X_i(t)$ represents the covariates of subject i at time t , β_{zz}^* is the coefficient specific to transition z to z^* . The exponential estimate of coefficient β_{zz}^* is the relative risk transitioning from disease state z to z^* for a unit change by the covariate $X_i(t)$. Using multistate transition model, Zhang et al examined the association between psychological factor and transition of pain severity (30).

As shown in Table 3, subjects with poor mental health status were more likely to have experienced more severe pain than those with better mental health status (between-subject association), this association is likely to be affected by potential confounders. At the same time changes in mental health status were strongly associated with risk of change in pain severity (*i.e.*, within-subject association). For example, when subjects' MHI-5 worsened from the best category (28-30) to the worst one (13-23) the risk of knee pain severity increased by almost 2-fold. Interestingly, the effect estimates generated from both mixed-effects proportional odds regression model and stratified proportional odds model are very similar.

Table 4 presents the results from the multistate transition model. In this analysis, we divided knee pain severity into tertile groups: none/mild pain (WOMAC score: 0-2.2), moderate pain (WOMAC score: 2.3-4.9), and severe pain (WOMAC score: 5.0-10). After adjusting for age, sex, BMI, and pain medication use, improvement of mental health status was associated with a lower risk of pain worsening (all of the upper triangle of Table 4), whereas deterioration in mental health status was associated with an increased risk of pain worsening (all of the lower triangle of Table 4). For every 5-unit improvement in MHI-5, the risk of pain worsening by one category (*i.e.*, from none/mild to moderate pain, or from moderate to severe) decreased by 10% (RR= 0.9), and the risk of pain worsening by two categories (*i.e.*, from none/mild to severe pain) decreased by more than 50% (RR= 0.5). On the other hand, for every 5-unit improvement in MHI-5, the risk of pain improvement by one category (*i.e.*, from moderate to none/mild) increased by 50% (RR= 1.5), and the risk of pain alleviation by two categories (*i.e.*, from severe to none/mild) more than doubled (RR= 2.1).

Conclusion

In this paper we have described several statistical approaches to analyzing longitudinal data on knee pain and used a real epidemiologic dataset to illustrate the application of each method. Compared with cross-sectional studies, longitudinal studies allow the investigator to assess the

effect of change in a factor of interest on change in risk of knee pain or pain severity; thus the investigator can assert greater confidence in making a causal inference for the effect of the risk factor. Also, when assessing the effect of changes in a factor of interest on the risk of pain or pain severity over time, each individual can serve as his/her own control, thereby reducing the effect of potential confounders that may differ among individuals but which do not vary over time within a person.

When pain is assessed as a dichotomous or ordinal outcome variable, both conditional logistic regression and mixed-effects regression models often generate comparable effect estimates. However, the within-subject effect in a mixed-effect model may be biased if the distribution of the intercept is mis-specified, especially when each subject only provides outcome data from a very few time points. Unlike a conditional logistic regression model, in a mixed-effect model one can assess both between-subject and within-subject associations of a risk factor of interest with pain occurrence.

Finally, in some studies, pain occurrence or pain severity is assessed on both knees at multiple time points. In these situations, more advanced statistical methods are required to handle the multilevel data.

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References

1. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635–46. [PubMed: 11033593]
2. Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994;84:351–8. [PubMed: 8129049]
3. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. *Arthritis Rheum* 2007;58:26–35. [PubMed: 18163497]
4. Hadler NM. Knee pain is the malady—not osteoarthritis. *Ann Intern Med* 1992;116:598–9. [PubMed: 1543316]
5. Zubieta JK, Smith YR, Bueller JA, et al. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science* 2001;293:311–5. [PubMed: 11452128]
6. Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. *Proc Natl Acad Sci U S A* 1999;96:7744–51. [PubMed: 10393892]
7. Vase L, Riley JL 3rd, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 2002;99:443–52. [PubMed: 12406519]
8. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain* 2006;124:126–33. [PubMed: 16701952]
9. Dworkin, SF.; Sherman, JJ. Relying on objective and subjective measures of chronic pain: Guidelines for use and interpretation. In: Turk, DC.; Melzack, R., editors. *Handbook of Pain Assessment*. Guilford Press; New York: 2001. p. 619–38.
10. Fields HL. Pain modulation: expectation, opioid analgesia and virtual pain. *Prog Brain Res* 2000;122:245–53. [PubMed: 10737063]
11. Wager TD. Expectations and anxiety as mediators of placebo effects in pain. *Pain* 2005;115:225–6. [PubMed: 15911149]
12. Villemure C, Slotnick BM, Bushnell MC. Effects of odors on pain perception: deciphering the roles of emotion and attention. *Pain* 2003;106:101–8. [PubMed: 14581116]

13. Giardino ND, Jensen MP, Turner JA, et al. Social environment moderates the association between catastrophizing and pain among persons with a spinal cord injury. *Pain* 2003;106:19–25. [PubMed: 14581106]
14. Gamsa A. Is emotional disturbance a precipitator or a consequence of chronic pain? *Pain* 1990;42:183–95. [PubMed: 2247316]
15. Deshields TL, Tait RC, Gfeller JD, et al. Relationship between social desirability and self-report in chronic pain patients. *Clin J Pain* 1995;11:189–93. [PubMed: 8535037]
- 16*. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *Am J Epidemiol* 2007;166:646–55. [PubMed: 17615092]
17. Cannon, GW. Osteoarthritis, B. Clinical Features. Arthritis Foundation; Atlanta: 2001.
18. Felson DT, Zhang Y, Hannan MT, et al. The incidence and natural history of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1995;38:1500–5. [PubMed: 7575700]
- 19**. Gooberman-Hill R, Woolhead G, Mackichan F, et al. Assessing chronic joint pain: lessons from a focus group study. *Arthritis Rheum* 2007;57:666–71. [PubMed: 17471543]
- 20*. Hutchings A, Calloway M, Choy E, et al. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. *The Journal of rheumatology* 2007;34:2291–300. [PubMed: 17937461]
21. Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis and rheumatism* 1987;30:914–8. [PubMed: 3632732]
22. Zhang Y, Xu L, Nevitt MC, et al. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing Osteoarthritis Study. *Arthritis and rheumatism* 2001;44:2065–71. [PubMed: 11592368]
23. Bellamy N, Buchanan WW, Goldsmith CH, et al. 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. [PubMed: 3068365]
24. Roos EM, Roos HP, Lohmander LS, et al. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88–96. [PubMed: 9699158]
25. Hawker GA, Davis AM, French MR, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2008;16:409–14.
26. Berwick DM, Murphy JM, Goldman PA, et al. Performance of a five-item mental health screening test. *Med Care* 1991;29:169–76. [PubMed: 1994148]
27. Twisk, JWR. Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide. Cambridge University Press; 2003.
- 28*. Wise B, Wang N, Niu J, et al. Psychological factors and their relation with osteoarthritis pain flares. *Arthritis Rheum* 2007;56:s122.
- 29**. Mukherjee B, Ahn J, Liu I, et al. Fitting stratified proportional odds models by amalgamating conditional likelihoods. *Statistics in medicine* 2008;27:4950–71. [PubMed: 18618428]
- 30**. Zhang B, Lin H, Hunter DJ, et al. A Multistate Transition Model for Osteoarthritis Pain Change. *Communications in Statistics – Theory and Methods*. In press.

Figure 1.
A Multistate Transition Model

Table 1

Association between MHI-5 and its change to pain severity among 202 participants of LEAP Study

MHI-5 Categories	Difference in Mean (SE)WOMAC Pain *	
	GEE	Mixed Model
Between-subject association		
28-30	0 (reference)	0 (reference)
26-27	0.92 (0.39)	0.92 (0.38)
23-25	0.95 (0.37)	0.95 (0.39)
13-22	1.82 (0.37)	1.82 (0.38)
P for trend	<0.001	<0.001
Within-subject Association		
28-30	0 (reference)	0 (reference)
26-27	0.20 (0.10)	0.20 (0.08)
23-25	0.24 (0.12)	0.24 (0.10)
13-22	0.49 (0.17)	0.49 (0.11)
P for trend	<0.001	<0.001

* adjusted for age, sex, BMI, and pain medication use.

Table 2

Association between MHI-5 and its change and pain flare among participants of LEAP Study

MHI-5 categories	Mixed-effects logistic regression models		Conditional logistic regression model***
	Model 1*	Model 2**	
	OR (95% CI)	OR (95% CI)	OR (95% CI)
	Between-subject Association		
28-30	1.0 (Reference)	1.0 (Reference)	Not applicable
26-27	4.0 (0.6, 27.4)	2.3 (0.7, 7.5)	
23-25	5.4 (0.8, 36.0)	2.2 (0.7, 7.0)	
13-22	28.3 (4.6, 173)	2.5 (0.9, 7.4)	
P for trend	<0.001	0.036	
	Within-subject Association		
28-30	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
26-27	1.6 (0.8, 3.1)	1.6 (0.8, 3.2)	1.7 (0.83, 3.60)
23-25	2.3(1.0, 4.9)	2.0 (1.0, 4.3)	2.3 (1.01, 5.15)
13-22	3.0 (1.2, 7.0)	2.2 (1.0, 4.8)	2.3 (0.93, 5.61)
P for trend	<0.001	0.008	< 0.002

* adjusting for age, sex, BMI, and pain medication use among 202 participants

** adjusting for age, sex, BMI, and pain medication use among 74 participants

*** adjusting for pain medication use among 74 subjects

Table 3

Association between MHI-5 and its change and pain severity categories among participants of LEAP Study

MHI-5 categories	Mixed-effects logistic regression models		Stratified logistic regression model***
	Model 1*	Model 2**	
	OR (95% CI)	OR (95% CI)	OR (95% CI)
	Between-subject Association		
28-30	1.0 (Reference)	1.0 (Reference)	Not applicable
26-27	6.8 (1.2, 37.5)	3.0 (0.9, 10.6)	
23-25	5.7 (1.0, 31.3)	3.1 (0.9, 10.5)	
13-22	37.5 (7.1, 199)	5.8 (1.8, 19.0)	
P for trend	<0.001	0.005	
	Within-subject Association		
28-30	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
26-27	1.6 (1.0, 2.5)	1.6 (1.0, 2.6)	1.6 (1.0, 2.6)
23-25	1.4 (0.8, 2.3)	1.4 (0.8, 2.4)	1.4 (0.8, 2.4)
13-22	2.2 (1.2, 4.2)	2.1 (1.1, 4.1)	2.1 (1.1, 4.0)
P for trend	0.003	0.010	<0.001

* adjusting for age, sex, BMI, and pain medication use among 202 participants

** adjusting for age, sex, BMI, and pain medication use among 135 participants

*** adjusting for pain medication use among 135 subjects

Table 4

Relative Risk of Transition of Pain Severity per 5-Unit Increase in MHI-5 Score With permission from [30]*
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5-unit increase in MHI-5 score			
From	To		
	No/mild pain	Moderate Pain	Severe Pain
No/mild pain	1.0	0.9 (95% CI: 0.8, 1.1) p=0.02	0.5 (95% CI: 0.3,0.9) p=0.032
Moderate Pain	1.5 (95% CI: 1.2-1.8) P<0.0001	1.0	0.9 (95% CI: 0.8-1.1) p=0.02
Severe Pain	2.1 (95% CI: 0.9-5.1) p=0.098	1.5 (95% CI: 1.2, 1.8) P<0.0001	1.0