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Dynamic Effects of Depressive Symptoms on Osteoarthritis Knee Pain

Alan M. Rathbun, PhD, MPH*,

Post-Doctoral Fellow, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD 21201

Elizabeth A. Stuart, PhD,

Professor of Mental Health, Biostatistics, and Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205

Michelle Shardell, PhD,

Staff Scientist Statistician, Translational Gerontology Branch, National Institute on Aging, Baltimore, MD 21224

Michelle S. Yau, PhD, MPH,

Post-Doctoral Fellow, Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School, Boston, MA 02131

Mona Baumgarten, PhD, and

Professor of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD 21201

Marc C. Hochberg, MD, MPH

Professor of Medicine and Epidemiology and Public Health, Head of the Division of Rheumatology and Clinical Immunology, Vice Chair of the Department of Medicine, University of Maryland School of Medicine, Baltimore, MD 21201

Abstract

Objective—To estimate the dynamic causal effects of depressive symptoms on osteoarthritis (OA) knee pain.

Methods—Marginal structural models were used to examine dynamic associations between depressive symptoms and pain over 48 months among older adults (n=2,287) with radiographic knee OA (Kellgren-Lawrence grade=2 or 3) in the Osteoarthritis Initiative. Depressive symptoms

*Corresponding Author: Alan M. Rathbun, PhD, MPH, University of Maryland School of Medicine, 660 W. Redwood Street, Howard Hall Suite 200, Baltimore, MD 21201; Phone: (410) 706-5151; Fax: (410) 706-4433; arathbun@som.umaryland.edu.

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AUTHOR CONTRIBUTIONS

All authors were involved in the drafting of the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Alan M. Rathbun 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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at each annual visit were assessed (threshold = 16) using the Center for Epidemiological Studies Depression Scale. OA knee pain was measured using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale rescaled to range from 0 to 100.

Results—Depressive symptoms at each visit were generally not associated with greater OA knee pain at subsequent time points. Causal mean differences in WOMAC pain score comparing depressed to non-depressed ranged from 1.78 (95% confidence interval [CI]: -0.73, 4.30) to 2.58 (95% CI: 0.23, 4.93) within the first and fourth years, and the depressive symptoms by time interaction was not statistically significant ($P=0.94$). However, there was a statistically significant dose-response relationship between the persistence of depressive symptoms and OA knee pain severity ($P=0.002$). Causal mean differences in WOMAC pain score comparing depressed to non-depressed were 0.89 (95% CI: -0.17, 1.96) for one visit with depressive symptoms, 2.35 (95% CI: 0.64, 4.06) for two visits with depressive symptoms, and 3.57 (95% CI: 0.43, 6.71) for three visits with depressive symptoms.

Conclusion—The causal effect of depressive symptoms on OA knee pain does not change over time, but pain severity significantly increases with the persistence of depressed mood.

Osteoarthritis (OA) is the most prevalent inflammatory joint disorder that affects approximately 27 million Americans and is a prominent cause of pain and functional disability in community-dwelling older adults (1). Depressive symptoms are a common comorbidity that occur in approximately 20% of persons suffering from OA, which is more than double the prevalence in the general United States population (2,3). Consequences of depressive symptoms in OA patients include reduced quality of life, greater use of healthcare resources, and increased mortality rate (4,5). Moreover, co-occurring depression in OA patients leads to greater medical costs: approximately \$4,400 (\$13,684 vs. \$9,284) per patient per year (6). In addition to the detrimental effects on overall health and well-being, depression exacerbates OA symptoms and complicates a condition that is inherently difficult to manage.

Among patients with rheumatologist-diagnosed OA, research has generally shown that depressive symptoms are predictive of elevations in future pain, which may affect multiple downstream facets of disease progression and treatment (7–10). If depression intensifies the perception and experience of pain, then the comorbidity may indirectly lead to increases in functional disability (10,11). Given the discordance between the severity of structural pathology of OA and symptoms, current treatment is primarily focused on pain management, with available options being weight loss, patient education, analgesics, physical therapy, and eventually, surgery (12–14). Depressive symptoms are also associated with an increased odds of inadequate pain relief during analgesic treatment and significantly higher pain ratings after total knee replacement (15,16). Despite the meaningful effect of depressive symptoms on the experience of OA knee pain, the condition is under-recognized by treating rheumatologists and not prioritized during clinical care (14,17).

The bidirectional relationship between depressive symptoms and pain in patients with musculoskeletal disorders has been well established in the research literature; changes in pain predict elevations in the future severity of depressive symptoms, and changes in depressive symptoms are associated with greater subsequent pain severity (18). However,

existing research has not recognized that depressive symptoms and musculoskeletal pain may cumulatively affect each other as condition-specific symptoms change over time (Figure 1). The proposed conceptual framework implies that OA knee pain and other time-varying confounders affect depressive symptoms at the same time point and also future follow-up visits. Conversely, depressive symptoms affect the likelihood of future depressed mood and the experience of pain and other time-varying confounders at subsequent follow-up visits. OA knee pain and other time-varying confounders also exhibit intra-person clustering, where current values are affected by the previous severity or status within each construct. Controlling for time-varying confounders using standard regression approaches when evaluating the cumulative effect of dynamic exposures can lead to biased effect estimates (19).

Depressive symptoms are dynamic, and prior depressive illness modifies the experience of current depressed mood. Depressive illness onset occurring earlier in life predicts future depressive symptoms that manifest with greater intensity and frequency (20). However, research in patients with rheumatologist-diagnosed OA has operationalized depression using static, time-invariant definitions, and no studies have evaluated how the persistence of depressive symptoms cumulatively affect the experience of musculoskeletal pain (7–10,18). Standard design approaches are ill-suited to evaluate complex causal relationships in which current exposure is affected by prior exposure, prior outcome, and other time-dependent confounders (21). Many studies assessing causal relationships using observational data in psychological research employ structural equation modeling (SEM) (22). However, there are limitations associated with SEM, which was not specifically designed to assess the cumulative effects of time-varying exposures in epidemiological analyses (21,23).

Marginal structural models (MSMs) were explicitly developed for the purpose of examining the effects of time-varying exposures (21). Thus, the objective of this study was to estimate the dynamic causal effects of depressive symptoms on OA knee pain using MSMs. It was hypothesized that (1) the causal effect of depressive symptoms on OA knee pain would increase over time and (2) the persistence of depressed mood would be associated with more severe OA knee pain.

PATIENTS AND METHODS

Study Data and Sample

The Osteoarthritis Initiative (OAI) is a longitudinal study of knee health. Participants who had or were at high risk for symptomatic radiographic knee OA in one or both knees were enrolled at one of four clinical sites between February 2004 and May 2006. Recruitment yielded a racially diverse sample of 4,796 men and women between the ages of 45 and 79 years (24). Institutional review boards at each OAI clinical site and the OAI data coordinating center approved the OAI study. Data from baseline and four annual follow-up visits were used (enrollees dataset 22, kXR SQ reading (BU) 0.7, and clinical datasets 0.2.2, 1.2.1, 3.2.1, 5.2.1, and 6.2.2). The median time to recovery from a depressive episode is between 6 and 12 months, and four years provided sufficient time for fluctuations between depressed and non-depressed states and multiple occurrences of depressive symptoms (25). The analytic sample included participants (N=2,432) with established radiographic disease,

defined as a Kellgren-Lawrence grade of two or three in one or both knees at study enrollment (Figure 2). To avoid ceiling effects on OA knee pain, subjects with end-stage OA disease or with evidence of total knee replacement at enrollment were excluded. For participants with radiographic evidence of OA in both knees, only the knee from the dominant leg was used, which was assigned with an algorithm: (1) leg used to kick a ball; (2) dominant hand if ambidextrous legs or missing dominant leg data; (3) right leg if missing data on dominant leg or hand. The sample was further restricted to participants (n=2,287) with complete baseline data.

Depressive Symptoms

Depressive symptoms were measured at each time point using the long-form 20-Item Center for Epidemiological Studies Depression (CES-D) Scale (26). The CES-D has been demonstrated to be a valid and reliable measure of depressive symptoms among individuals with arthritis pain and older adults with multiple chronic conditions (27,28). The presence of depressive symptoms at each annual visit was classified using the recommended CES-D screening threshold of 16 (26). Although depressive symptoms occur on a severity continuum, they were dichotomized to provide an easily interpretable estimate (e.g., causal mean difference) and enhance the clinical utility of the results. Persistence of depressive symptoms for each subject at a given time point t was operationalized as the total number of prior visits to the current observation at which the participant was classified as depressed.

Knee Pain

Knee pain was measured using the Western Ontario and McMaster Universities Arthritis (WOMAC; Likert version 3.1) Index (29). The WOMAC is a valid and responsive questionnaire that provides information on OA symptoms: joint stiffness, pain, and functional disability (29). The pain subscale of the WOMAC includes 5 items scored on a Likert scale resulting in a score ranging from 0 to 20, where higher values are indicative of more severe OA knee pain (29). The pain subscale was rescaled by multiplying the original values by a factor of 5 so the distribution of scores ranged from 0 to 100 and the results could easily be interpreted in the context of a clinically meaningful difference. The minimum perceptible clinical improvement in WOMAC pain is approximately 9.7 units on the rescaled measure (30). Subjects were right censored at the first instance of missing outcome data.

Potential Confounders

Covariates were selected a priori based on literature review. Time-invariant variables measured only at the baseline visit were age (years), sex, race (White, African American, other), education (high school graduate, college graduate, post-graduate degree), marital status (married, widowed, divorced, separated, never married), employment status (employed or unemployed), insurance status (insured or uninsured), smoking (never, former, current), alcohol consumption (none, minimal, moderate), comorbidity assessed using the composite Charlson index comprised of 22 different comorbid conditions (31), and radiographic disease severity evaluated by medial compartment joint space narrowing (32). Time-varying confounders that were measured at every data collection time point were: physical activity using the Physical Activity Scale for the Elderly (33); body mass index

(BMI); use of analgesics including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or opioid analgesics during the previous 30 days; history of knee injury as indicated by a limited ability to walk for at least two days; and WOMAC pain subscale (29). The last observation was carried forward in instances of missing values for time-varying covariates (34).

Statistical Analysis

Participant characteristics at study enrollment were compared between depressed and non-depressed subjects. For continuous variables, means and standard deviations were estimated and *t*-tests were used to evaluate differences between those with and without depressive symptoms. Frequencies and percentages were calculated for categorical variables and chi-square tests were used to test for differences between the depressed and non-depressed.

MSMs were the primary method of analysis because the hypothesized relationships involved time-varying confounders. MSMs use inverse probability of exposure and censoring weights to adjust for time-varying confounders (in addition to selection bias due to censorship) that may simultaneously be confounding variables and mediators on the causal pathway between exposure and outcome (21). MSMs use two models: a model predicting the probability of exposure at each time point and a structural model of outcomes that is fit using weights generated from the exposure model. Rather than modeling the association between observed exposures and observed outcomes, which cannot be interpreted causally, this method models the relationship between exposures and their corresponding potential outcomes (35). MSMs yield unbiased estimates conditional on five (some untestable) assumptions: exchangeability, positivity, consistency, correct model specification, and no measurement error (21). Exchangeability implies no unmeasured confounding; positivity assumes there are both unexposed and exposed persons at all levels of the confounders; and consistency assumes a subject's counterfactual outcome is their observed outcome under their observed exposure history (36).

Two primary analyses were performed: (1) an evaluation of depressive symptoms as a lagged time-varying binary variable to determine if their causal effect on OA knee pain changed over time; and (2) an assessment of the association between persistence of depressive symptoms as a lagged time-varying cumulative categorical variable and OA knee pain. The models for the first analysis fit with a lagged time-varying binary variable tested the depressive symptoms by follow-up time interaction, and time-specific causal mean differences in OA knee pain and the corresponding time-specific changes and differences-in-change between the depressed and non-depressed were estimated. The models for the second analysis fit with a lagged time-varying cumulative categorical variable estimated causal mean differences in OA knee pain associated with the total number of annual visits with depressive symptoms relative to participants with no depressive symptoms. All statistical tests were two sided and significance was set at an alpha level of 0.05 for structural outcome models. Analyses were conducted using Stata (Version 13.1, Stata Corp, College Station, Texas, USA).

To calculate exposure weights, pooled logistic regression models were used to estimate the probability of depressive symptoms at each follow-up visit conditional on time-invariant and

time-varying confounders (37). Exploratory analyses were used to determine appropriate functional forms for continuous covariates using locally weighted scatter plot smoothing curves. Stabilized weights were used to improve MSM performance; the inverse of the conditional probability of having depressive symptoms at each time point was stabilized with the estimated exposure probability given time-invariant confounders (21). The time-specific stabilized exposure weights were used in the first analysis assessing depressive symptoms as a lagged time-varying binary variable. The estimated exposure probabilities were multiplied across visits for the second analysis assessing the association between persistence of depressive symptoms as a lagged time-varying cumulative categorical variable and OA knee pain, such that an individual's observation at a given time point was weighted by the inverse probability of having the exposure history he or she had up to that time point.

Inverse probability of censoring weights were used to account for any potential selection bias arising from differential attrition between depressed and non-depressed participants (21). Censoring weights were calculated in the same manner as described for the cumulative exposure weights, except that the primary exposure variable was included as a covariate in numerator and denominator pooled logistic regression models (37). The final stabilized weights for both analyses were the product of the exposure weights and censoring weights at each time point (21). Appropriate diagnostic assessments for inverse probability weights in MSMs were also used, which included evaluations of underlying theoretical assumptions (e.g., positivity) (36). The inverse probability weights were used in weighted linear models to estimate the relationship between depressive symptoms as a (1) lagged time-varying binary variable and a (2) lagged time-varying categorical variable and the outcome of interest (OA knee pain). MSMs were fit using an independent working correlation matrix; robust standard errors were estimated to account for the clustering of observations within patients (37). Sensitivity analyses are described in the Appendix.

RESULTS

Sample Characteristics

Depressed individuals (n=225) at enrollment were more likely to be younger, female, non-white, and divorced, separated, or never married (Table 1). Depressive symptoms at baseline were also associated with lower socioeconomic status, more current smoking, and less alcohol consumption. Non-depressed participants had lower BMI, less comorbidity, lower analgesic use, and less OA knee pain than depressed participants. Censorship due to missing outcome data resulted in 54 subjects being censored at the first follow-up visit, 121 subjects being censored at the second follow-up visit, 89 subjects being censored at the third follow-up visit, and 48 subjects being censored at the fourth follow-up visit (Figure 2).

Depressive Symptoms and OA Knee Pain

Among non-censored participants, 216 subjects at year one had prior depressive symptoms at baseline, 217 subjects at year two had prior depressive symptoms at year one, 206 subjects at year three had prior depressive symptoms at year two, and 199 subjects at year four had prior depressive symptoms at year three (Table 2). Depressive symptoms at each time point were generally not associated with greater OA knee pain at the next annual follow-up visit.

Mean differences in WOMAC pain score between depressed and non-depressed ranged from 1.78 (95% confidence interval [CI]: -0.73, 4.30) at year one to 2.58 (95% CI: 0.23, 4.93) at year four. Changes in WOMAC pain score among the depressed were 0.96 (95% CI: -2.24, 4.16) between year one and year two, -0.57 (95% CI: -3.35, 2.20) between year two and year three, and 0.94 (95% CI: -2.41, 4.29) between year three and year four (Figure 3). Among the non-depressed, change in WOMAC pain score was 0.79 (95% CI: -0.02, 1.60) between year one and year two, and there was little variation in change thereafter. The depressive symptoms by time interaction was not statistically significant ($P=0.94$).

Persistence of Depressive Symptoms and OA Knee Pain

After four years of follow-up in non-censored participants, 196 subjects had one prior visit with depressive symptoms, 90 subjects had two prior visits with depressive symptoms, 56 subjects had three prior visits with depressive symptoms, and 48 subjects had four prior visits with depressive symptoms (Figure 2). There was generally a dose-response relationship between the number of annual visits with depressive symptoms and mean differences in OA knee pain during follow-up. Depressed participants had higher average WOMAC pain scores ($P=0.002$) compared to the non-depressed that increased with increasing persistence of depressive symptoms: 0.89 (95% CI: -0.17, 1.96) for those with one annual visit with depressive symptoms, 2.35 (95% CI: 0.64, 4.06) for those with two annual visits with depressive symptoms, and 3.57 (95% CI: 0.43, 6.71) for those with three annual visits with depressive symptoms (Table 3). However, subjects classified as depressed at every time point had an average estimated pain score that was 2.61 (95% CI: -2.26, 7.50) units greater than the non-depressed.

Sensitivity Analyses

Multivariable GEEs (Table S1, Figure S1, and Table S2) adjusted for time-varying confounders concurrent with depressive symptoms and MSMs (Table S3 and Table S4) adjusted for time-varying confounders lagged to depressive symptoms yielded estimates similar to the primary results.

DISCUSSION

This study used longitudinal data from a large, well-characterized cohort of individuals with radiographically confirmed knee OA to investigate the causal effect of depressive symptoms and persistence of depressed mood on OA knee pain. The presence of depressive symptoms meeting threshold criteria at each time point was generally associated with small, non-significant increases in pain at subsequent follow-up visits, and the causal effect of depressive symptoms on OA knee pain did not change over time. However, with the exception of those classified with depressive symptoms at every time point, there was a dose-response relationship indicating that OA knee pain increased significantly with increasing persistence of depressed mood. These findings suggest that depressive symptoms are prospectively associated with a uniform effect on OA knee pain that increases linearly with the number of annual visits at which a subject is classified as depressed.

Depressive symptoms at a single time point were only associated with statistically greater OA knee pain during the last follow-up interval. These results diverge from prior studies demonstrating statistically significant associations between depressive symptoms and pain in OA (7–10) and research showing that changes in depression are associated with subsequent increases in musculoskeletal pain (18). Prior OAI research has shown that baseline depressive symptoms are a robust predictor of worsening pain, but effect sizes were small, and an appreciable degree of persistence is necessary to have a meaningful impact on OA symptoms (9). Evidence indicates that OAI participants with radiographic disease experience very little change in OA knee pain, and therefore, have minimal longitudinal variability in their OA symptoms (38). Knee OA is better characterized by constant pain rather than worsening symptoms, which may contribute to the small magnitude of the associations. Studies yielding larger estimates than the current study of the association between depressive symptoms and OA knee pain have also had shorter intervals between the outcome assessments (7–9,18). Previous studies imply that with a closer temporal ordering between depression and arthritis symptoms the magnitude of the association increases, and with assessments at yearly intervals, the current study may underestimate the association between depressive symptoms and OA knee pain (39,40). Also, antidepressants are associated with a greater probability of depressed mood and less severe pain, but their use was not evaluated in the OAI, and without adjusting for this potential time-varying confounder structural outcome models may yield smaller effect estimates (24). Although the effect sizes in this study are small, the results need to be interpreted within the design and characteristics of the OAI cohort.

Persistence of depressed mood was significantly associated with worse OA knee pain, and the magnitude of the association increased with increasing number of annual visits with depressive symptoms, except when present at all visits. The time to recovery from a major depressive episode is generally between six and twelve months (25). In this study, at the fourth annual assessment approximately 50% of non-censored depressed participants (194/390) had two or more visits at which they had been classified with depressive symptoms. Prior depressive illness, life stress, and medical comorbidity are risk factors for persistence of depressed mood, and consequently, many subjects with depressive symptoms may have experienced chronic major depressive disorder, defined as depressive episodes lasting longer than 24 months (20,41). Our results imply that pain severity increases with increasing persistence of depressed mood, except in those classified with depressive symptoms at every time point. Participants with depressive symptoms at all visits may have had a more extensive depression history and a depressive illness onset occurring prior to study enrollment than participants classified as depressed at fewer time points (20). Thus, the causal attribution of depressive symptoms may have manifested before entry into the cohort among those depressed at all annual visits, resulting in a smaller marginal effect compared to depressed subjects with three annual visits classified with depressive symptoms.

Our findings highlight the contribution of depressive symptoms to patients' experience of OA knee pain, which is particularly important due to the implications for clinical care (14). Approximately 50% of OA patients with depressed mood do not seek care from a mental health care provider, and 30% with diagnosed major depressive disorder do not use

antidepressants (42,43). Combination therapy using anti-depressants and psychotherapy is utilized by as few as 19% of OA patients who suffer from major depressive disorder (43). This under-treatment may lead to more frequent and more severe depressive symptoms which, in turn, causes more intense and persistent OA knee pain. As a consequence, depressive symptoms among persons with knee OA may be an important contributor to poor analgesic treatment response and post-surgical outcomes (15,16). Patient-reported OA symptoms also form the basis for clinical decisions regarding surgical intervention, and depressed mood could be responsible, in part, for the approximately 31% of OA patients who are inappropriately selected to undergo total knee arthroplasty (44). Experimental studies have consistently shown that unimodal treatment strategies are ineffective, and approaches that target both chronic physical disease and depression could lead to improvements in both the primary condition and its sequelae (45,46). This study underscores the need for recognition and treatment of depression as part of OA intervention and pain management strategies.

The results need to be interpreted in the context of the limitations of this research. Depressive symptoms were measured using a patient-reported questionnaire, which cannot be interpreted as major depressive disorder diagnosed using DSM-V criteria (47). As measured in this study, depression was intended to be representative of the core symptom (i.e., depressed mood) of the disorder rather than a clinical diagnosis. The categorization of depressive symptoms could have resulted in measurement error, which can reduce statistical power and induce residual confounding (48,49). Also, the validity of the estimates is contingent upon the models being correctly specified, no confounding by unmeasured factors, and that there were depressed and non-depressed participants at all levels of confounders (36). These limitations are mitigated by the study's strengths. The multi-site prospective design provided a heterogeneous sample of participants with radiographically confirmed knee OA based on consensus readings by experienced musculoskeletal radiologists (24). OAI data include comprehensive longitudinal measures of radiographic disease severity, OA symptoms, and other sociodemographic and clinical characteristics that allowed to control for a variety of potential confounders. The results were robust to various types of adjustment and consistent across different modeling methods. This study is the first to examine the causal effect of the presence and persistence of depressive symptoms on OA knee pain using modern epidemiological methods.

In summary, the causal effect of depressive symptoms on OA knee pain does not change over time, however, pain severity significantly increases with increasing persistence of depressed mood. The most recent OA clinical care guidelines focus on the management of arthritis symptoms but also now consider modifiable factors that contribute to patients' experience of their illness (13). Given that structural disease decline in OA is progressive and irreversible, the results of our study underscore the necessity for developing alternative disease management strategies that can be integrated into routine rheumatology practice. There is a need for interventions that target modifiable factors such as depression in OA patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE & INNOVATION

- Causal effect of depressive symptoms on OA knee pain does not change over time
- OA knee pain increases with increasing persistence of depressed mood
- Findings highlight the need for depression treatment and management to improve OA knee pain

Figure 1.

Directed acyclic graph illustrating the hypothesized causal relationships between depressive symptoms, time-varying confounders, and OA knee pain; subscripts i and t refer to the i^{th} participant at time point t , respectively.

Figure 2.

Study sample flow diagram. CES-D: Center for Epidemiological Studies Depression Scale; K-L: Kellgren-Lawrence; OAI: Osteoarthritis Initiative; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 3.

Time-specific changes in WOMAC pain score among the (A) depressed and (B) non-depressed. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; Y1-Y2: Year one to year two; Y2-Y3: Year two to year three; Y3-Y4: Year three to year four. Time-invariant confounders from study baseline: age, sex, race, marital Status, education, employment, health insurance, smoking, alcohol consumption, Charlson comorbidity, and JSN grade. Time-varying confounders concurrent to depressive symptoms: PASE score, BMI, acetaminophen, opioids, NSAIDs, knee injury, and WOMAC pain score.

Table 1

Baseline characteristics of the study sample (n=2,287).

Variable	Depressed (n=225)		Non-depressed (n=2062)		P Value
Age (m, SD)	59.6	8.9	62.8	8.9	<0.001
Female (n, %)	151	67.1	1203	58.3%	0.011
Race (n, %)					
White	137	60.9	1638	79.4%	0.001
African American	78	34.7	380	18.4%	
Other	10	4.4	44	2.1%	
Marital Status (n, %)					<0.001
Married	94	41.8	1404	68.1%	
Widowed	30	13.3	182	8.8%	
Divorced	50	22.2	287	13.9%	
Separated	9	4.0	29	1.4%	
Never Married	42	18.7	160	7.8%	
Education (n, %)					<0.001
High School	146	64.9	820	39.8%	
College Graduate	47	20.9	614	29.8%	
Post-Graduate Degree	32	14.2	628	30.5%	
Employed (n, %)	128	56.9	1232	59.8%	0.407
Health Insurance (n, %)	200	88.9	2017	97.8%	<0.001
Smoking (n, %)					<0.001
Never	114	50.7	1108	53.7%	
Current	29	12.9	107	5.2%	
Former	82	36.4	847	41.1%	
Alcohol Consumption (n, %)					0.013
None	60	26.7	396	19.2	
Moderate	152	67.6	1480	71.8	
Heavy	13	5.8	186	9.0	
PASE Score (m, SD)	151.7	84.9	157.2	80.5	0.336
BMI (m, SD)	31.1	5.2	29.5	4.7	<0.001

Variable	Depressed (n=225)	Non-depressed (n=2062)	P Value
Charlson Comorbidity (m, SD)	0.6	0.4	0.8
Acetaminophen (n, %)	42	208	10.1
Opioids (n, %)	18	48	2.3
NSAIDs (n, %)	102	684	33.2
Knee Injury (n, %)	88	702	34.0
JSN Grade (n, %)			0.129
0	81	780	37.8
1	74	758	36.8
2	70	524	25.4
WOMAC Pain Score (m, SD)	26.2	23.0	13.5
		16.2	<0.001

BMI: Body mass index; JSN: Joint space narrowing; NSAIDs: Non-steroidal anti-inflammatory drugs; PASE: Physical Activity Scale for the Elderly; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Table 2

Mean differences in pain score (0–100) at each follow-up visit by presence of depressive symptoms from the previous visit over four years of follow-up.

Time Interval	Number of Visits with Depressive Symptoms	Number of Visits with no Depressive Symptoms	WOMAC Pain Score	95% CI	P Value
Y0-Y1	216	2017	1.78	−0.73, 4.30	0.165
Y1-Y2	217	1895	1.95	0.01, 3.89	0.05
Y2-Y3	206	1817	1.54	−0.62, 3.70	0.162
Y3-Y4	199	1776	2.58	0.23, 4.93	0.031

CI: Confidence Interval; WOMAC: Western Ontario and McMaster Universities Arthritis Index; Y0-Y1: Year 0 to year 1; Y1-Y2: Year 1 to year 2; Y2-Y3: Year 2 to year 3; Y3-Y4: Year 3 to year 4.

Time-invariant confounders from study baseline: age, sex, race, marital status, education, employment, health insurance, smoking, alcohol consumption, Charlson comorbidity, and JSN grade.

Time-varying confounders concurrent to depressive symptoms: PASE score, BMI, acetaminophen, opioids, NSAIDs, knee injury, and WOMAC pain score.

Table 3

Mean differences in WOMAC pain score (0–100) by number of annual visits with depressive symptoms over four years of follow-up.

Number of Annual Visits With Depressive Symptoms	Mean WOMAC Pain Score	95% CI	Mean Difference	95% CI	P Value
0	13.17	12.87, 13.46	REF	REF	REF
1	14.07	13.06, 15.07	0.89	−0.17, 1.96	0.099
2	15.52	13.86, 17.19	2.35	0.64, 4.06	0.007
3	16.74	13.63, 19.86	3.57	0.43, 6.71	0.026
4	15.79	10.92, 20.65	2.61	−2.26, 7.50	0.294

CI: Confidence Interval; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Time-invariant confounders from study baseline: age, sex, race, marital status, education, employment, health insurance, smoking, alcohol consumption, Charlson comorbidity, and JSN grade.

Time-varying confounders concurrent to depressive symptoms: PASE score, BMI, acetaminophen, opioids, NSAIDs, knee injury, and WOMAC pain score.