Title

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The association of slow gait speed with trajectories of worsening depressive symptoms in knee osteoarthritis: An observational study

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Abstract

Background—The purpose of this study was to investigate the association of slow gait speed, defined as walking slower than what is necessary for the community with trajectories of depressive symptoms over 7 years among people with or at high risk of knee OA.

Methods—Using data from the Osteoarthritis Initiative, we described trajectories of depressive symptoms measured annually with the Center for Epidemiologic Studies Depression Scale (CES-D). We categorized speed during a 20-meter walk < 1.2 m/s as 'slow gait speed'. We used a group-based method (PROC TRAJ) to agnostically identify homogeneous clusters of depressive symptom trajectories. We then examined the association of slow gait speed with depressive symptom trajectories using multinomial logistic regression adjusted for potential confounders.

Results—From the 3939 participants included (age 61.4 ± 9.2, BMI 28.4 ± 4.7, 58% women, 63% college degree), we identified five trajectories. The first three were stable over time and included 74% of the sample. The remainder had worsening depressive symptoms over time. Slow gait speed was associated with 2.0 times the odds of having the worst depressive symptoms trajectory compared those without slow gait speed.

Conclusion—Slow gait speed may represent important risk factor for worsening depressive symptoms over time in people with or at high risk of knee OA, and may signal the need for rehabilitation.

Introduction

Depressive symptoms have a wide variety of negative influences on health including increased risk of mortality, over medication, and poor treatment adherence.(1–3) As a result, the presence of depressive symptoms may worsen pain and hinder therapeutic efforts for people with knee osteoarthritis (OA).(4) Depressive symptoms are common in people with self-reported arthritis and often emerge following the development of functional limitation,

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such as difficulty walking or climbing stairs.(5) However, no empirical data to supports this hypothesis in knee OA. In particular, little is known about trajectories of depressive symptoms and what specific types of functional limitation may be associated with worsening depressive symptom trajectories over time.

One important daily functional activity highly relevant to adults is the ability to walk at speeds necessary for mobility and navigation in the community. Walking ≥ 1.2 m/s is a minimum speed necessary to cross streets using timed signals.(6) Thus, the ability to walk at or above 1.2 m/s is a reasonable proxy for the ability to navigate independently in the community. Conversely, walking < 1.2 m/s may represent difficulty walking in the community and/or the need for help from others. This may, in turn, limit the ability for adults to be independent in the community and participate in may types of activities. It is known that the development or worsening of disability is a risk factor for the development of major depressive symptoms.(7) However, it is unclear to what extent difficulty walking in the community, in and of itself, is associated with subsequent worsening of depressive symptoms.

Therefore, the purpose of our study was to describe trajectories of depressive symptoms over 7 years and to investigate the association of slow gait speed, as a proxy for difficulty walking in the community, with subsequent depressive symptom trajectories in people with or at high risk of knee OA. Because depression itself is a risk factor for subsequent worsening of depression,(8) we focused on people who initially had no or low levels of depressive symptoms.

Methods

Study Sample

The Osteoarthritis Initiative (OAI) is an ongoing longitudinal cohort study of the risk factors and natural history of OA. Adults between 45 to 79 years of age at enrollment who had or were at high risk of knee OA were recruited from four clinical sites: Baltimore MD, Pittsburgh PA, Pawtucket RI, and Columbus OH. Detail regarding the rationale and approach for the OAI can be found at http://www.oai.ucsf.edu/datarelease/About.asp. Briefly, OAI recruited two primary sub cohorts. One had symptomatic knee OA at baseline and the other did not but was at high risk based on the presence of risk factors associated with the development of symptomatic knee OA. Increased risk was identified from age-specific criteria for established risk factors including knee symptoms in the past 12 months(9), being overweight from gender-specific cut-points(9–11), knee injury causing difficulty walking for at least one week(9, 12, 13), any knee surgery history(10, 14), family history of a total knee replacement(15, 16), Heberden's nodes(9, 17), or repetitive knee bending at work or outside of work(18, 19). People were excluded who had rheumatoid or inflammatory arthritis, end-stage disease defined as severe joint space narrowing in both knees at baseline, or bilateral total knee replacements, positive pregnancy test, or used ambulatory aids other then a cane. Institutional Review Board approval was obtained from all sites for the parent OAI study.

Study Outcome

Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D),(20) which includes 20 items experienced during the past week with item scores ranging from 0 (rarely or none of the time) to 3 (most or all of the time). Items that are positively worded are reverse coded. The CES-D summary score ranges from 0 to 60 with higher scores representing a higher likelihood of psychological distress. Specifically a score ≥ 16 was used to define possible depression.(20) The CES-D was assessed annually after baseline visit, and we used CES-D data up to the 84-month visit.

For our study, we included study participants without a high level of depressive symptoms at baseline, defined by a CES-D score < 16.(20)

Study Exposures

We measured gait speed during a 20-meter walk at the baseline OAI visit. For the 20-meter walk, participants were instructed to walk at a usual pace from a starting point to an orange cone 20 meters away. Timing started with the first step after the starting line and ended after the first step over the finishing line using a stopwatch. We slow gait speed as < 1.2 meters/second (m/s), the minimum speed necessary to cross streets at timed cross walks.(6)

Potential confounders

The following factors were considered as potential confounders (based on their association with function in previous studies(22–24)) and were ascertained by interview, questionnaire, and/or direct measurement as appropriate at the baseline OAI visit: Age, sex, BMI, race (non-White vs. White), comorbidities (≥ 1 vs none, measured from the modified Charlson comorbidity index)(25), education (< college degree vs. ≥ college degree), radiographic knee OA, and intensity of knee pain (0–10 VAS scale).

Radiographic knee osteoarthritis (ROA) was assessed from weight-bearing posteroanterior and lateral fixed flexion radiographic evaluations of both knees(26). Radiographs were independently graded twice among three expert readers (Two rheumatologists and a musculoskeletal radiologist) for joint space narrowing and osteophytes in the tibiofemoral joint according to Kellgren and Lawrence (KL) criteria (grades 0–4)(27). Any disagreements were adjudicated among all three expert readers to reach consensus.

Knee pain intensity was rated on an ordinal scale ranging from “0” to “10” with “0” representing “No pain” and “10” being “Pain as bad as you can imagine”.(28, 29) Participants were asked to rate the worst pain in each knee over the last 7 days.

Lower body pain was measured from self-report. Study participants who marked the presence of pain at the foot, ankle, or hip on a homunculus were classified as having lower body pain.

Analysis

We included study participants who did not have a high level of depressive symptoms (CES-D < 16) at baseline and who had a minimum of two follow-up time points for a total of at

least 3 visits in order to provide an adequate number of data points for trajectory analyses.(30, 31) We compared characteristics for those meeting study inclusion criteria at baseline who did and did not have at least two follow-up visits, i.e. were and were not included in the analytic dataset. We also compared characteristics for those with and without the CES-D at baseline.

We identified trajectories of depressive symptoms by first determining the number of trajectory groups using a group based trajectory model (PROC TRAJ).(32) We used Bayesian Information Criterion (BIC) to select the optimal number of trajectory groups, i.e., the number of trajectory groups was varied until the best-fitting model was obtained as indicated by the BIC.(33) In addition, we required the smallest trajectory group to include ≥ 5% of the subjects from the sample in order to provide a meaningful and pragmatic description of patterns of change from a clinical perspective. We modeled intercept only, linear, quadratic, or cubic polynomial terms. We used the posterior probabilities of group membership from each individual to assess the fit of the model, which was provided by the PROC TRAJ macro. High probability of membership into a single group represents a good model fit.

Next, we examined the association of slow gait speed with trajectories of depressive symptoms as a multilevel categorical outcome using multinomial logistic regression. Study subjects were classified as having a healthy gait speed (≥ 1.2 m/s) or slow gait speed(<1.2 m/s). We calculated odds ratios (OR) and 95% confidence intervals (95% CI) of membership in each trajectory group with the group with least depressive symptoms as reference. We also calculated OR and 95% CI for potential adjusted for potential confounders.

Given that the association of gait speed with depressive symptoms may differ among those with major depressive symptoms at baseline, we repeated all analyses including all study participants regardless of CES-D scores at baseline.

Results

Of the 4796 study participants in OAI, 65 did not have CES-D scores at baseline, 480 had a CES-D score ≥ 16 at baseline, and 312 had fewer than two follow-up visits, resulting in an analytic sample of n=3939. The average age of the analytic sample was 61.4 years, 58% were women, and the average CES-D score at baseline was 4.8. Table 1. Compared with those included in the analytic dataset, subjects with less than two follow-up visits were more likely to be non-White, and have less than a college education, more depressive symptoms, have comorbid conditions, higher BMI, and higher intensity of knee pain at baseline. Supplemental Table 1. We found similar differences among those with and without CES-D scores at baseline. Supplemental Table 2.

We identified five trajectories over 84 months. Figure 1. The first three trajectories ‘No Depressive Symptoms’, ‘Mild Depressive Symptoms’, and ‘Mild/Moderate Depressive Symptoms’ included 16%, 30%, and 27% of participants, respectively. These trajectories were characterized by little to no change in depressive symptoms over 84 months and were shaped with time-intercept only polynomial orders. The remainder of study participants had

worsening of either moderate or severe depressive symptoms. Nineteen percent were on a 'worsening moderate depressive symptoms' trajectory starting with a mean CES-D score (sd) of 7.8 (3.9) increasing to 10.9 (5.6) by the 84-month visit. Eight percent were on a 'worsening severe depressive symptoms' trajectory starting with a mean CES-D score (sd) of 9.7 (3.9) and ending with a score of 17.8 (8.8), on average. These trajectories were shaped with quadratic polynomial orders. The posterior probability of allocating each study participant into the group trajectories was ≥ 0.91, indicating that there was a 91% probability on average of each individual's trajectory fitting the respective group trajectory.

As shown in Table 1, age, sex, and race at baseline where evenly distributed among depressive symptom trajectory groups. For those on the worsening severe depressive symptom trajectory, there was a lower proportion of people at baseline with a college education and a healthy weight (BMI < 25), and a higher proportion with comorbidity, obesity (BMI ≥ 30), ROA, and more depressive symptoms and knee pain.

The proportion of study participants with a healthy gait speed,, i.e., > 1.2 m/s at baseline, decreased with worse trajectory groups, while the proportion of those with slow gait speed increased with worse trajectory groups. Table 2 Slow gait speed at baseline was associated with 2.1 times the odds of a having a trajectory of worsening severe depressive symptoms compared with those with no limitation in walking, (Adjusted OR 2.1, 95% CI [1.4, 2.9]. Including all participants regardless of CES-D at baseline, we found similar results. Table 3

Discussion

We found slow gait speed to be significantly associated with a subsequent trajectory of increasing depressive symptoms among people with or at high risk of knee OA. People with a gait speed consistent with difficulty walking in the community were almost twice as likely to have a trajectory of increasing depressive symptoms compared with those with no difficulty walking. These findings provide empirical evidence that slow gait speed may be a risk factor for subsequent worsening of depressive symptoms in people with or at high risk of knee OA.

Whether it is walking ability *per se* or participation restriction in the community caused by difficulty walking that leads to the increased risk of worsening depressive symptoms is unknown. General limitations in function due to knee pain have been shown to precede the emergence of depressive symptoms.(5) Additionally, more limitations are associated with greater depressive symptoms in arthritis.(34) Walking limitations may also create difficulties in participating important daily life activities, which then leads to increases in depressive symptoms. For example, Parmelee and colleges reported in a cross-sectional study that the ability perform discretionary activities, e.g., working on hobbies or visiting friends or relatives at their home, was associated with fewer depressive symptoms in older adults with knee OA.(36) Katz and colleagues reported similar results in people with rheumatoid arthritis (RA).(1) It is possible that slow gait limits the ability of individuals to engage in these types of valued activities.

Slow gait has been shown in other studies to be a risk factor for functional limitation and disability,(21, 37) which may also compromise independence. Loss of independence may affect mood because it changes self-identity through its impact on social roles. Gignac and colleagues reported that adults with OA had only low to moderate satisfaction with the way they were able to perform social roles; less satisfaction with role performance was associated with depression.(38, 39) Loss of independence may also lead to social isolation. Social isolation and loneliness have demonstrated strong relationships to depression.(40, 41)

It is important to highlight that the ability to walk is a modifiable characteristic for adults and responsive to exercise interventions, such as strength training or supervised walking programs. Exercise is known to have a moderate and statistically significant effect to improve physical function in people with knee OA.(43) Furthermore, exercise has been shown to have moderate positive clinical effect to reduce depressive symptoms in adults.(44) Even for people with existing major depression, exercise is effective to improve physical function in older adults.(45) These findings highlight the clinical importance of referring people with knee OA who start to have difficulty walking in the community or at home for rehabilitation, such as physical therapy.

We find it noteworthy that there were unique trajectories of depressive symptoms among people with or at risk of knee OA in the OAI. Previous longitudinal studies of patterns of depressive symptoms in RA have shown little change from baseline measures over 8 years.(46) We found two trajectories of worsening depressive symptoms over time for people with or at high risk of knee OA. There was a strong correlation between baseline depressive symptoms and subsequent trajectories; those with higher baseline CES-D scores tended to be in a trajectory of worsening. This phenomenon has been observed in the other physiological measures, such as blood pressure in adults(47), knee cartilage loss among people with osteoarthritis,(48) and gait speed trajectories for older adults.(49) An analogy of a “horse-racing” effect has been proposed to explain this phenomenon; one would expect the fast horses to be out in front at any given time point.(50) Thus, people with more depressive symptoms do not “start” worse depressive symptoms at the beginning of a longitudinal study, but rather were in a trajectory of worsening well before the start of the study.

There are several limitations to our study. First, we did not directly measure the ability to walk in the community, but inferred this from a measure of gait speed during a 20-meter timed walk. There is possibility that people with slow gait speeds during the observed timed walk may still be able to walk without difficulty in the community. However, we believe these thresholds were reasonable given previous literature linking 1.2 m/s to the ability to walk across timed cross-walks(51). Second, there was greater loss to follow-up with the worsening severe and moderate depressive symptom trajectories, 25% and 17%, respectively, compared with those with no and mild depressive symptoms trajectories, 13% and 14%, respectively. Hence, it is possible that the trajectories may be conservative estimates of actual worsening over time. From an analytical perspective, loss to follow-up is mitigated since the trajectory analyses requires as few as three study visits. Third, the consequence of depressive symptom trajectory groups with subsequent meaningful health outcomes is unclear. We do find it noteworthy, however, that the mean CES-D value for the worst trajectory group was above the 16-point threshold for major depressive symptoms by

the 24-month follow-up visit. In addition, even sub-threshold depressive symptoms can have negative health and psychological effects.(52) Hence, it is highly possible that the trajectory groups do have clinical significance. Fourth, study participants may have already been on a trajectory of worsening prior to our study baseline since we included those with a score < 16 at baseline. Therefore, it is premature to definitively conclude that the ability to walk in the home and community is associated with depressive symptom trajectories.

We tested only one pathway in the relationship between poor functioning and depression. It is likely, though, that the relationship between functional limitation and depressive symptoms form a vicious cycle, with declines in one prospectively reciprocating with more decline on the other. As an example, in a previous analysis, we found that depression was a risk factor for a trajectory of functional decline.(53)

Nevertheless, our longitudinal findings provide preliminary support that the inability to walk at a speed necessary for the home and community at baseline is associated with subsequent worsening of depressive symptoms.

Despite these limitations, our study has several strengths. First, we employed a performance-based measure of walking ability that is less likely to be confounded by psychological well-being than a self-reported measure of physical function. Second, we utilized longitudinal data over 7 years from a well-characterized OA cohort study, the Osteoarthritis Initiative. This study provides a large sample size with standardized measures of physical function and depressive symptoms.

To conclude, we found that slow gait speed may be a risk factor for worsening depressive symptoms among people with or at risk of knee OA. Clinicians may consider risk-stratifying patients who report the onset of difficulty walking to receive rehabilitation, which may mitigate worsening of both depressive symptoms and functional limitation over time. Psychological counseling to cope with loss or to develop strategies for maintaining important life activities may also be helpful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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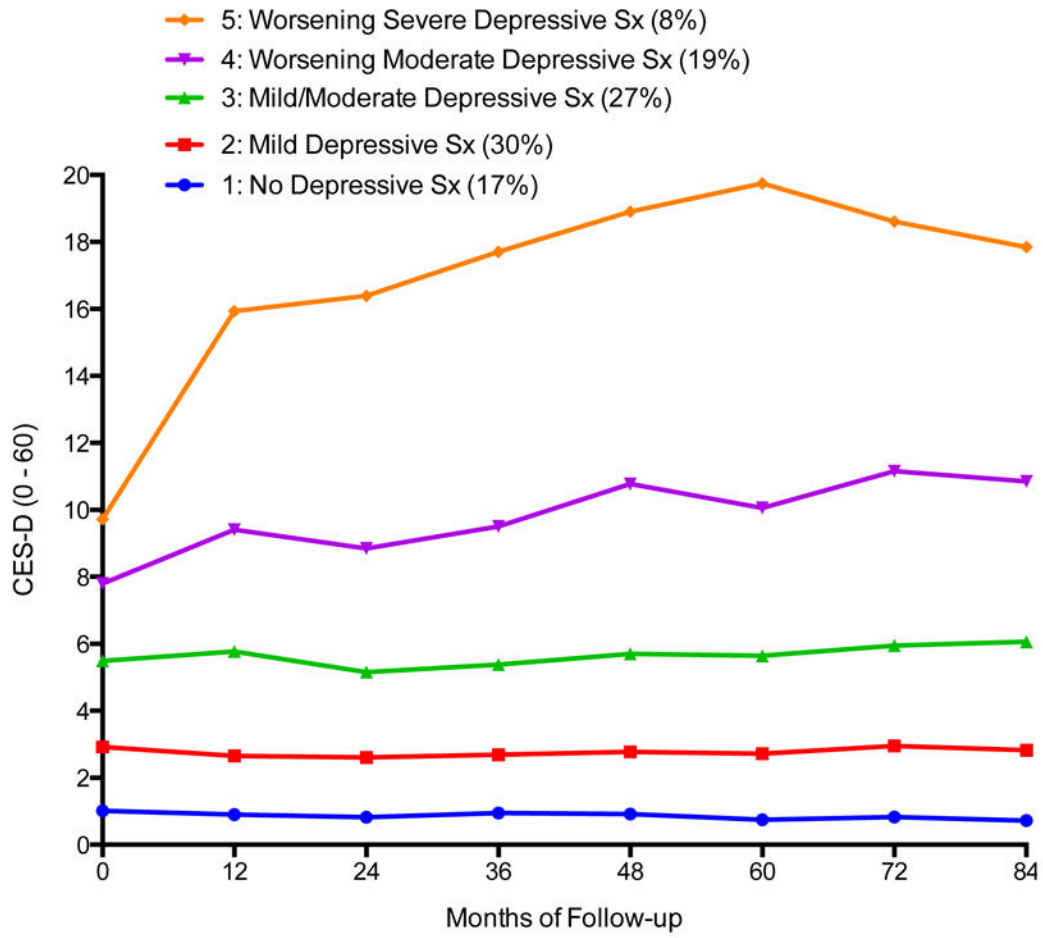
Significance and Innovation

- Functional limitation, in general, is associated with subsequent worsening of depressive symptoms. However, it is unclear to what extent slow gait speed, defined as walking less than a speed necessary for the community may be associated with a trajectory of worsening depressive symptoms.
- We found slow gait speed was associated with higher risk of membership in a trajectory of worsening depressive symptoms.
- We believe our findings highlight the clinical importance of referring people with knee OA who start to exhibit slow gait speed for rehabilitation, such as physical therapy, to mitigate such loss and risk of future depressive symptoms.



Trajectory Groups	0	12	24	36	48	60	72	84
Worsening Severe Depressive Sx (n)	303	279	270	265	261	236	228	226
Worsening Moderate Depressive Sx (n)	743	708	676	671	677	657	618	623
Mild/Moderate Depressive Sx (n)	1074	1025	1021	991	985	946	912	914
Mild Depressive Sx (n)	1172	1112	1106	1088	1096	1048	1015	1012
No Depressive Sx (n)	647	627	623	606	613	581	569	564

Figure 1.
Trajectories of depressive symptoms (n=3939)

Table 1

Characteristics at baseline for all study participants (n=3939) and within trajectory groups.

Subject characteristic at baseline	All Study Participants (n=3939)	No depressive symptoms (n=647)	Mild depressive symptoms (n=1172)	Mild/Moderate depressive symptoms (n=1074)	Worsening moderate depressive symptoms (n=743)	Worsening severe depressive symptoms (n=303)
Age [Mean (sd; min-max)]	61.4 (9.2; 45–79)	60.5 (8.7; 45–79)	61.0 (8.9;45–79)	62.0 (9.2; 45–79)	62.2 (9.5; 45–79)	60.5 (9.7; 45–79)
Women [%]	58	50	57	57	62	64
White [%]	83	87	84	81	79	81
College graduate [%]	63	74	68	61	55	52
Depressive symptoms (CES-D) [Mean (sd; min-max)]	4.8 (4.1; 0–15)	1.0 (1.4, 0–7)	2.9 (2.5, 0–14)	5.5 (3.4, 0–15)	7.8 (3.9, 0–15)	9.7 (3.9, 0–15)
At least 1 comorbidity [%]	23	15	20	24	27	30
Mean BMI [kg/m^2] [Mean (sd; min-max)]	28.4 (4.7; 17.6–48.7)	27.5 (4.4; 17.7–42.0)	28.2 (4.6; 18.4–47.4)	28.6 (4.8; 17.8–46.8)	28.7 (4.8; 18.1–48.7)	29.6 (4.9; 17.6–44.3)
Healthy weight (< 25) [%]	25	30	26	24	23	16
Overweight (25 to 30) [%]	40	43	41	38	40	38
Obese (≥ 30) [%]	35	27	34	38	38	46
ROA [%]	56	49	54	60	58	58
Knee pain in the last 30 days [0–10] [Mean (sd; min-max)]	3.1 (2.6; 0–10)	2.4 (2.4, 0–10)	2.9 (2.6, 0–10)	3.2 (2.6; 0–10)	3.6 (2.7; 0–10)	4.1 (2.9; 0–10)

Table 2

Association of slow gait speed with depressive symptoms trajectory groups with CES-D < 16 at baseline. Unadjusted and Adjusted* Odds Ratio (OR) and 95% Confidence Interval (CI). Gait speed was categorized as >1.2 m/s, healthy gait speed; < 1.2 m/s, slow gait speed.

		Unadjusted OR [95% CI]	Adjusted OR [95% CI]
Trajectory Group	**Slow gait speed[%]**	**Slow gait speed vs Healthy gait speed**	**Slow gait speed vs Healthy gait speed**
No depressive symptoms (n=647)	15.3	1.0 Ref	1.0 Ref
Mild depressive symptoms (n=1172)	22.0	1.6 [1.2, 2.0]	1.3 [1.0, 1.7]
Mild/Moderate depressive symptoms (n=1074)	26.6	2.0 [1.6, 2.6]	1.4 [1.1, 1.9]
Worsening moderate depressive symptoms (n=743)	32.4	2.7 [2.0, 3.5]	1.8 [1.3, 2.4]
Worsening severe depressive symptoms (n=303)	34.8	2.9 [2.1, 4.1]	2.0 [1.4, 2.9]

*Adjusted for age, sex, BMI, comorbidity, race, education, radiographic knee OA, knee pain intensity, and lower-body pain.

Table 3

Association of slow gait speed with depressive symptoms trajectory groups with all study participants with CES-D scores at baseline. Unadjusted and Adjusted* Odds Ratio (OR) and 95% Confidence Interval (CI). Gait speed was categorized as >1.2 m/s, healthy gait speed; < 1.2 m/s, slow gait speed.

		Unadjusted OR [95% CI]	Adjusted OR [95% CI]
Trajectory Group	**Difficulty walking at a community speed[%]**	**Slow gait speed vs Healthy gait speed**	**Slow gait speed vs Healthy gait speed**
No depressive symptoms (n=916)	16.3	1.0 Ref	1.0 Ref
Mild depressive symptoms (n=1403)	23.4	1.5 [1.3, 1.9]	1.4 [1.1, 1.7]
Mild/Moderate depressive symptoms (n=1138)	29.3	2.1 [1.7, 2.6]	1.6 [1.3, 2.1]
Worsening moderate depressive symptoms (n=654)	37.2	3.0 [2.4, 3.9]	2.1 [1.6, 2.7]
Worsening severe depressive symptoms (n=225)	45.8	4.3 [3.2, 6.0]	3.1 [2.2, 4.4]

*Adjusted for age, sex, BMI, comorbidity, race, education, radiographic knee OA, knee pain intensity, and lower-body pain.