UCSF

UC San Francisco Previously Published Works

Title

The effect of interactions between BMI and sustained depressive symptoms on knee osteoarthritis over 4 years: data from the osteoarthritis initiative

Permalink

https://escholarship.org/uc/item/8d8322bx

Journal

BMC Musculoskeletal Disorders, 24(1)

ISSN

1471-2474

Authors

Joseph, Gabby B

McCulloch, Charles E

Nevitt, Michael C

et al.

Publication Date

2023

DOI

10.1186/s12891-023-06132-3

RESEARCH

The effect of interactions between BMI and sustained depressive symptoms on knee osteoarthritis over 4 years: data from the osteoarthritis initiative

Gabby B. Joseph[1]*, Charles E. McCulloch[2], Michael C. Nevitt[2], John Lynch[2], Nancy E. Lane[3], Valentina Pedoia[1], Sharmila Majumdar[1] and Thomas M. Link[1]

Abstract

Background To assess the compound effects of BMI and sustained depressive symptoms on changes in knee structure, cartilage composition, and knee pain over 4 years using statistical interaction analyses.

Methods One thousand eight hundred forty-four individuals from the Osteoarthritis Initiative Database were analyzed at baseline and 4-year follow-up. Individuals were categorized according to their BMI and presence of depressive symptoms (based on the Center for Epidemiological Studies Depression Scale (threshold $\geq$ 16)) at baseline and 4-year follow-up. 3T MRI was used to quantify knee cartilage T_2 over 4 years, while radiographs were used to assess joint space narrowing (JSN). Mixed effects models examined the effect of BMI-depressive symptoms interactions on outcomes of cartilage T_2, JSN, and knee pain over 4-years.

Results The BMI-depressive symptoms interaction was significantly associated with knee pain ($p < 0.001$) changes over 4 years, but not with changes in cartilage T_2 ($p = 0.27$). In women, the BMI-depressive symptoms interaction was significantly associated with JSN ($p = 0.01$). In a group-based analysis, participants with obesity and depression had significantly greater 4-year changes in knee pain (coeff.$_{(obesity + depression \ vs. \ no\_obesity + no\_depression)} = 4.09$, 95%CI $= 3.60$–4.58, $p < 0.001$), JSN (coeff. $= 0.60$, 95%CI $= 0.44$–0.77, $p < 0.001$), and cartilage T_2 (coeff. $= 1.09$, 95%CI $= 0.68$–1.49, $p < 0.001$) than participants without depression and normal BMI.

Conclusions The *compound* effects of obesity and depression have greater impact on knee pain and JSN progression compared to what would be expected based on their *individual* effects.

Keywords Depression, Obesity, MRI, Cartilage T_2, JSN

*Correspondence:
Gabby B. Joseph
gabby.joseph@ucsf.edu
[1] Department of Radiology and Biomedical Imaging, University of California, 185 Berry St, Suite 350, San Francisco, CA 94158, USA
[2] Department of Epidemiology and Biostatistics, University of California, San Francisco, USA
[3] Department of Rheumatology, University of California, Davis, USA

Introduction

Osteoarthritis (OA) is a multi-factorial, degenerative joint disease, affecting 10.5% of the US population (from The Institute of Health Metrics Evaluation Global Burden of Disease Tool), causing joint pain and chronic disability [1]. Obesity, which is prevalent in approximately 39.8% of US adults (data from 2015/2016 [2]), and depressive symptoms found in 8.4% of US adults [3]) are two comorbid conditions that are individually associated with

Joseph *et al. BMC Musculoskeletal Disorders*   (2023) 24:27

Page 2 of 11

OA. While many studies have assessed the *individual* effects of obesity and depression on OA [4–11], few have assessed the *compound* effects of these risk factors on knee joint structure, cartilage structure, and symptoms [12].

Obesity and depressive symptoms are two potentially modifiable risk factors for OA [4, 5]. Obesity is associated with increases in knee pain and disability [6], joint space narrowing [7], prevalence of knee cartilage lesions [8], and cartilage biochemical degeneration, which can be analyzed with MRI based T_2 relaxation time measurements that are sensitive to alterations in collagen structure and water content [11]. Moreover, every 5 kg of weight gain increases the risk for OA by 36% (studied in in women aged 45–64, [5]). Depressive symptoms in adults are also associated with increases in joint pain [9] and disability [10], while patterns of osteophyte progression and JSN progression were not found significantly different between depressed and non-depressed individuals over 4 years [13]. However, individuals with mild or moderate-to-severe depression are two or three times more likely to develop knee OA than those without depression [14].

While previous studies have reported associations of both excess body mass and depressive symptoms on symptomatic OA, the knowledge gap on the compound effects of these risk factors on longitudinal changes in cartilage biochemical composition (i.e., MRI knee cartilage T_2) remains to be investigated. Understanding the co-morbid effects of both obesity and depression on OA outcomes could guide patient-specific treatments that concurrently target obesity and depression with an overall goal to slow OA progression. Thus, the purpose of this study was to assess the compound effects of BMI and sustained depressive symptoms on changes in knee structure, cartilage composition, and knee pain over 4 years using statistical interaction analyses. The hypothesis of this study is that individuals with sustained depression have a more progressive course of structural OA and that presence of obesity amplifies this progressive course, more than expected for individual effects alone.

Materials and methods
Subject selection
This study utilized data from the Osteoarthritis Initiative (OAI; https://nda.nih.gov/oai) [15], a multi-center, longitudinal study of individuals aged 45–79 years at enrollment. The OAI dataset includes MRI and radiographic knee images of participants over 8 years. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local institutional review boards of all participating centers (University of Maryland School of Medicine, Ohio State

University, University of Pittsburgh, Memorial Hospital of Rhode Island). In addition, all methods were performed in accordance with the relevant guidelines and regulations the Human Research Protection Program (HRPP) at UC San Francisco.

The present study analyzed participants enrolled in the OAI with the following inclusion criteria: (i) available data on the Center for Epidemiological Studies Depression Scale at the baseline and 4-year follow-up visit, (ii) a baseline Kellgren Lawrence score (KL) ≤ 3 in the right or left knee, (iii) available body mass index (BMI) data at baseline and (iv) either normal BMI (16.9–24.9 kg/m^2) or obese BMI (30–49 kg/m^2) at baseline. The overweight group was excluded to better investigate the effects of obesity in comparison to a normal BMI control cohort (16.9–24.9 kg/m^2). Participants were excluded if their depression symptoms no longer met the threshold between baseline and 4-year follow-up, or participants became depressed (detailed description below) between baseline and 4-year follow-up. Participants with rheumatoid arthritis were also excluded. Based on these criteria, a total of 1844 participants (mean BMI: 28.8 ± 5.90 kg/m^2) were included in this study (Fig. 1) and were categorized into 4 groups: no sustained depressive symptoms (defined below) and normal BMI (16.9–24.9 kg/m^2), $n = 772$; no sustained depressive symptoms and obese BMI (30–49 kg/m^2), $n = 971$; sustained depressive symptoms and normal BMI (16.9–24.9 kg/m^2), $n = 33$; and sustained depressive symptoms and obese BMI (30–49 kg/m^2), $n = 68$.

Depressive symptoms
Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (CES-D) [17] (threshold ≥ 16) at the baseline and 4-year follow-up visit based on previous studies [13]. The CES-D is a 20-item questionnaire that asks individuals how often they experience symptoms associated with depression. This questionnaire has good sensitivity and specificity as well as a high internal consistency [18]. A threshold of ≥ 16 is often recommended as a cutoff when for screening for "clinical depression" [13] based on published studies [13, 16]. Participants with sustained high level of depressive symptoms were defined as those a CES-D score of ≥ 16 at baseline and 4-year follow-up, while participants without sustained depressive symptoms had a CES-D score of < 16 at baseline and 4-year follow-up. Participants with depressive symptoms that were not sustained between baseline (CES-D ≥ 16) and 4-year follow-up (CES-D < 16) or became depressed between baseline (CES-D < 16) and 4-year follow-up (CES-D ≥ 16) were excluded to focus the analysis on participants with or without depressive symptoms at both timepoints.

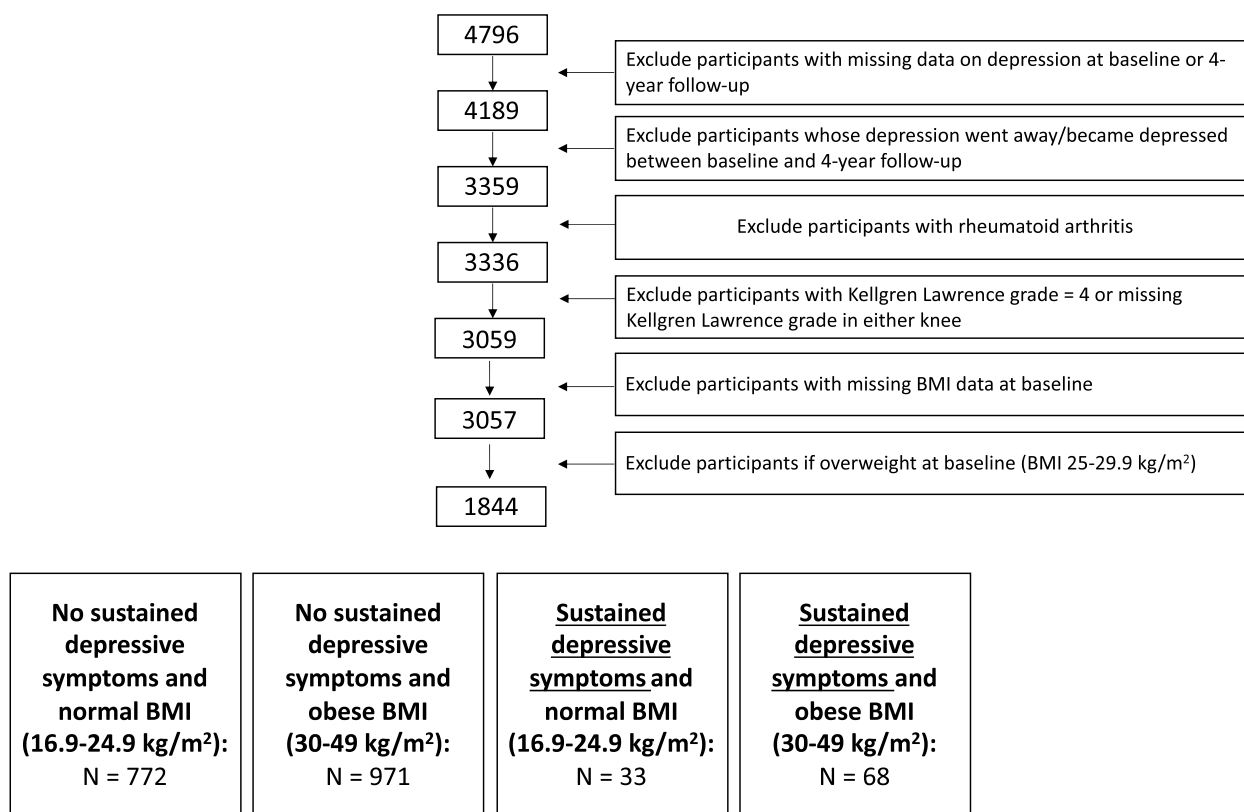Joseph *et al. BMC Musculoskeletal Disorders* (2023) 24:27

Page 3 of 11

Fig. 1 Participant Selection from the OAI. Note that sustained depressive symptoms were defined based on The Center for Epidemiological Studies Depression Scale (threshold ≥16) at the baseline and 4-year follow-up visit [13, 16]

Additional clinical questionnaires

Knee pain was assessed using the *WOMAC (Western Ontario McMaster Universities Osteoarthritis) Index*, a standard questionnaire used to evaluate symptoms related to knee OA, including pain, limited function and stiffness [19]. This questionnaire has three subscales (pain (range: 0 to 20), stiffness (range: 0 to 8), and physical function (range: 0 to 68)) and has been utilized in a number of previous OA studies [20, 21]. The current study focuses on the WOMAC pain subscore; higher scores indicate worse pain.

The participants' physical activity levels were determined using a *Physical Activity Scale for the Elderly (PASE)* with a range of 0 to 400. This is a well-established, reliable, validated questionnaire that has been used to measure physical activity in individuals of similar age to those investigated in the current study [22–25]. The areas of assessment are activities of occupation, household, and leisure activities over a 1 week period.

Radiographs

Standardized bilateral standing posterior-anterior fixed flexion knee radiographs were acquired in all participants in the OAI. For eligibility and to assess baseline disease burden, knee Kellgren Lawrence (KL) gradings [26] were performed at baseline with a score ranging from 0 (none) to 4 (severe). A KL grade of 0 represents definite absence of radiographic changes of OA; grade 1 represents: doubtful joint space narrowing (JSN) and possible osteophytic lipping; grade 2 represents definite osteophytes and possible JSN; grade 3 represents moderate multiple osteophytes, definite JSN and some sclerosis and possible deformity of bone ends; grade 4 represents: large osteophytes, marked JSN, severe sclerosis and definite deformity of bone ends. In addition, JSN (maximum score of the medial and lateral joint sides in each knee) was assessed longitudinally from baseline to 2- and 4-year follow-up [27] based on the OARSI grading scale.

MR imaging acquisition and analyzed parameters
MR imaging acquisition

MR imaging was performed using 3 T MRI scanners (Trio, Siemens, Erlangen, Germany) at four centers (Ohio State University in Columbus, University of Maryland in Baltimore, University of Pittsburgh and Brown University in Rhode Island) as part of the imaging OAI protocol. The following sequence of the right knee were analyzed in this study: sagittal 2D multi-echo (ME) spin-echo

Joseph *et al. BMC Musculoskeletal Disorders*   (2023) 24:27

Page 4 of 11

(SE) sequences for T_2 quantification. The imaging parameters for the MESE T_2 mapping sequence were: TR = 2700 ms, 7 TEs = 10, 20, 30, 40, 50, 60 and 70 ms, in-plane spatial resolution of 0.313 mm × 0.446 mm (0.313 mm × 0.313 mm after reconstruction), slice thickness of 3.0 mm, and 0.5 mm gap. These scanning parameters were optimized based on the OAI MR imaging protocol; additional details on image acquisition parameters have been previously published [15].

Cartilage T_2

MRI cartilage T_2 measurements quantify the composition of the cartilage extracellular matrix, which includes collagen integrity and orientation, as well as water content. Cartilage T_2 measurements of the right knees were quantified at baseline, 2, and 4 years in six regions (medial and lateral tibia, medial and lateral femur, trochlea, and patella). A deep learning-based algorithm with 2D U-Net convolutional neural networks, with high efficacy and precision, was utilized for automatic cartilage segmentation and T_2 quantification as previously described [28, 29]. Briefly, the dataset was randomly split to training, validation, and test sets (65:25:10) and 3D V-Net architecture was used for segmentation. Although the OAI dataset provided images with 7 echoes (TE = 10, 20, 30, 40, 50, 60, 70 ms) for T_2 quantification, the first echo (TE = 10 ms) was not included in the T_2 fitting procedure in order to reduce potential errors resulting from stimulated echoes, and a noise-corrected algorithm was implemented [30, 31]. Average T_2 values for each region were computed and analyzed in this study.

Statistical analysis

Descriptive statistics were performed using a SAS Studio (version 3.8, SAS Institute Inc., Cary, NC, USA) macro program called "Tablen" [32]. Differences in continuous parameters between groups (i.e., age, BMI) were assessed using Kruskal Wallis tests, and differences in categorical parameters between groups (i.e., sex and race) were assessed using Chi-squared tests.

The primary statistical analyses were performed using STATA version 16 software (StataCorp LP, College Station, TX, USA) with significance set to $p < 0.05$. Two types of mixed effects models were performed (described below).

The first set of mixed models *were interaction analyses* to assess whether having both sustained depressive symptoms and obese BMI had a greater effect on knee outcomes (JSN, cartilage T_2, and knee pain) over and above the additive effects of each predictor. The mixed models included a test for statistical interaction between BMI (normal/obese) and sustained depressive symptoms over 4-years (yes/no). All outcomes were treated as continuous variables. First, a model with a triple interaction was coded (interaction between BMI (normal/obese), depression (yes/no) and by time (years), in order to capture BMI-depressive symptoms interactions in the change in the outcome over time. If this interaction was not significant, the model was further simplified by including three double interactions (depression-BMI, depression-time, BMI-time). The interactions reported in this study are between BMI (normal/obese) and sustained depression (yes/no) as none of the interactions for longitudinal change were statistically significant ($p > 0.05$). JSN and cartilage T_2 outcomes were analyzed at baseline, 2 and 4 years, while knee pain outcomes were analyzed annually over 4 years. A random effect for both person and knee were modelled for all outcomes except cartilage T_2. A random effect for only person was modelled for cartilage T_2 outcomes since cartilage T_2 measurements were only obtained in the right knee in the OAI, and thus accounting for two knees was not needed.

The second set of mixed models (that did not include an estimate for and test for an interaction) *were group-based analyses* that investigated the overall differences in outcomes (JSN, cartilage T_2, and knee pain) over all timepoints between participants subdivided into four groups based on baseline BMI (normal/obese) and sustained depression over 4 years (yes/no). The four groups were: no sustained depression and normal BMI (16.9–24.9 kg/m^2), no sustained depression and obese BMI (30–49 kg/m^2), sustained depression and normal BMI (16.9–24.9 kg/m^2), sustained depression and obese BMI (30–49 kg/m^2). The coefficients (which represent the difference in outcomes between each group and the reference group averaged over all timepoints) and *p*-values were derived from these model outputs. These analyses are described as *"group-based"* in the results section.

All mixed effects models were adjusted for age, sex, race, and PASE score. All assumptions for linear mixed models including a normal distribution and independent errors were met.

The outcome variables were designated as primary or exploratory to address potential issues stemming from multiple testing [33]. For cartilage T_2, the primary analyses focused on the average of all regions (medial and lateral tibia, medial and lateral femur, trochlea, and patella). For JSN, the maximum score of the medial and lateral joint sides in each knee was assessed. For the WOMAC score, only the pain subscale was assessed. The remaining outcomes were designated as exploratory.

As a sensitivity analysis, an interaction between BMI-depression-sex was added to each model to assess whether the effects of BMI and depressive symptoms on

outcomes differed by sex. Another sensitivity analysis was performed in participants with KL 0 or 1 in both knees to assess participants without radiographic evidence of OA in either knee. The first sensitivity analysis was included to assess whether the results of the main analyses differed by sex; the second sensitivity analysis was included to assess whether the results held true in participants without radiographic OA.

Results

Participant characteristics

One thousand eight hundred forty-four participants were included in this study; of those 68 had sustained depressive symptoms and obese BMI (30–49 kg/m^2), 33 had sustained depressive symptoms and normal BMI (16.9–24.9 kg/m^2), 971 had no sustained depressive symptoms and obese BMI (30–49 kg/m^2) and 772 had no sustained depressive symptoms and normal BMI (16.9–24.9 kg/m^2). The participant characteristics are listed in Table 1. The average BMI in participants with depressive symptoms and obesity (35.0 ± 3.58 kg/m^2) was greater than that in the other groups (Table 1) including participants with no depressive symptoms and obese BMI (33.4 ± 2.96 kg/m^2, $p < 0.001$). Participants with no depressive symptoms and normal BMI were the eldest (61.2 ± 9.29 years) compared the other groups (age range 58.9–60.4 years, $p = 0.002$). There were significant differences in the PASE score between groups ($p = 0.009$), with the highest PASE score in participants without depressive symptoms and normal BMI (169.0 ± 77.46). There were statistically significant differences in the distribution of race ($p < 0.001$) and KL grade between groups ($p < 0.001$ for both the right and left knees) as shown in Table 1.

Joint space narrowing (JSN)

The test for interaction (Table 2) between sustained depressive symptoms (yes/no) and BMI (normal/obese) on maximum JSN had $p = 0.08$, with the fitted model illustrated in Fig. 2. From the group-based analysis, over 4 years, maximum JSN was significantly greater in participants with *depressive symptoms and an obese BMI* compared to the other groups (Coeff. $_{\text{over 4 years, } no\ depression\ and\ normal\ BMI} = 0.60$, $p < 0.001$, 95%CI = 0.44–0.77; Coeff. $_{\text{over 4 years, no } depression\ and\ obese\ BMI} = 0.25$, $p = 0.002$, 95%CI = 0.09–0.41; Coeff. $_{\text{over 4 years, } depression\ and\ normal\ BMI} = 0.60$, $p < 0.001$, 95%CI = 0.33–0.87. The rates of change in JSN over 4 years between the four participant groups were not significantly different ($p = 0.52$). Table 2 lists the comparisons in JSN over 4 years between all groups compared to a reference group of no depressive symptoms and normal BMI.

WOMAC pain

In the mixed effects regression model with WOMAC pain as an outcome, the interaction between BMI (normal/obese) and sustained depressive symptoms (yes/no) was statistically significant ($p < 0.001$) as shown in Table 2. An illustration of the BMI-depression interaction on WOMAC pain is presented in Fig. 2. From the group-based analysis, over 4 years, the WOMAC pain score was significantly greater in participants with depressive symptoms and obese BMI compared to the other groups (Coeff. $_{\text{over 4 years, } no\ depression\ and\ normal\ BMI} = 4.09$, $p < 0.001$, 95%CI = 3.60–4.58; Coeff. $_{\text{over 4 years, no } depression\ and\ obese\ BMI} = 3.24$, $p < 0.001$, 95%CI = 2.76–3.73; Coeff. $_{\text{over 4 years, } depression\ and\ normal\ BMI} = 3.23$, $p < 0.001$, 95%CI = 2.42–4.05. The rates of change in WOMAC pain over 4-years between the four participant groups were not significantly different ($p = 0.98$). Table 3 lists the comparisons in WOMAC pain over 4 years between all groups compared to a reference group of no depression and normal BMI.

Cartilage T$_2$ measurements

The depression-BMI interaction (Table 2) with average cartilage T$_2$ as an outcome was not statistically significant (Table 2, $p = 0.27$). Average cartilage T$_2$ increased over time in all four groups; however, the rates of change between the four groups were not significantly different (Fig. 1, $p = 0.73$). From the group-based analysis, over 4 years, the T$_2$ was significantly greater in participants with depressive symptoms and obese BMI compared to the other groups (Coeff. $_{\text{over 4 years, } no\ depression\ and\ normal\ BMI} = 1.09$, $p < 0.001$, 95%CI = 0.68–1.49; Coeff. $_{\text{over 4 years, no } depression\ and\ obese\ BMI} = 0.69$, $p = 0.001$, 95%CI = 0.29–1.08; Coeff. $_{\text{over 4 years, } depression\ and\ normal\ BMI} = 0.77$, $p = 0.02$, 95%CI = 0.11–1.44. These results demonstrate that individuals with depressive symptoms and obesity had significant elevations in T$_2$ (over all timepoints) compared to all other groups including individuals without depressive symptoms and without obesity. Table 2 lists the comparisons in cartilage T$_2$ over 4 years between all groups compared to a reference group of no depression and normal BMI. To further examine the differences in cartilage T$_2$ between groups (since the depression-BMI interaction was not statistically significant), an additional exploratory analysis was performed.

Sensitivity analysis: sex differences

In the sensitivity analyses, the BMI-depression-sex interaction was statistically significant for WOMAC pain ($p = 0.02$) and JSN ($p = 0.03$) and was not statistically significant for cartilage T$_2$ ($p = 0.39$) as demonstrated in Table 2. Since these BMI-depression-sex interactions were significant for WOMAC pain and

Joseph *et al. BMC Musculoskeletal Disorders*   (2023) 24:27

Page 6 of 11

Table 1 Participant characteristics at the baseline timepoint. Abbreviations: KL: Kellgren Lawrence, PASE: physical activity scale for the elderly; CES-D: the Center for Epidemiological Studies Depression; JSNmax: maximum joint space narrowing score**.** Note: cartilage T_2 sequences were only acquired in the right knee in the OAI

	No Depression & Normal BMI ($N=772$)	Depression & Normal BMI ($N=33$)	No Depression & Obese ($N=971$)	Depression & Obese ($N=68$)	Total ($N=1844$)	*P*-value
Age (years)						0.0021[1]
Mean (SD)	61.2 (9.29)	58.9 (8.64)	60.1 (8.49)	57.5 (8.30)	60.4 (8.86)	
BMI (kg/m²)						< 0.0001[1]
Mean (SD)	22.8 (1.55)	22.0 (2.19)	33.4 (2.96)	35.0 (3.58)	28.8 (5.90)	
Sex, n (%)						< 0.0001[2]
Male	232 (30.1%)	8 (24.2%)	399 (41.1%)	16 (23.5%)	655 (35.5%)	
Female	540 (69.9%)	25 (75.8%)	572 (58.9%)	52 (76.5%)	1189 (64.5%)	
CES-D scale						< 0.0001[1]
Mean (SD)	4.0 (3.70)	24.9 (9.25)	4.7 (3.94)	23.9 (7.86)	5.5 (6.18)	
WOMAC pain right						< 0.0001[1]
Mean (SD)	1.3 (2.05)	1.9 (3.27)	2.3 (2.91)	5.4 (4.61)	2.0 (2.81)	
WOMAC pain left						< 0.0001[1]
Mean (SD)	1.2 (2.29)	1.9 (3.05)	2.2 (3.20)	5.9 (5.13)	1.9 (3.09)	
Race, n (%)						< 0.0001[2]
0 – Other-non-white	4 (0.5%)	0 (0.0%)	14 (1.4%)	1 (1.5%)	19 (1.0%)	
1 – White or Caucasian	710 (92.1%)	27 (81.8%)	724 (74.6%)	42 (61.8%)	1503 (81.6%)	
2 – Black or African American	41 (5.3%)	5 (15.2%)	230 (23.7%)	25 (36.8%)	301 (16.3%)	
3 - Asian	16 (2.1%)	1 (3.0%)	3 (0.3%)	0 (0.0%)	20 (1.1%)	
Missing	1	0	0	0	1	
KL grade right, n (%)						< 0.0001[2]
0	429 (55.6%)	18 (54.5%)	282 (29.0%)	14 (20.6%)	743 (40.3%)	
1	137 (17.7%)	3 (9.1%)	183 (18.8%)	13 (19.1%)	336 (18.2%)	
2	146 (18.9%)	9 (27.3%)	335 (34.5%)	26 (38.2%)	516 (28.0%)	
3	60 (7.8%)	3 (9.1%)	171 (17.6%)	15 (22.1%)	249 (13.5%)	
KL grade left, n (%)						< 0.0001[2]
0	445 (57.6%)	20 (60.6%)	307 (31.6%)	15 (22.1%)	787 (42.7%)	
1	135 (17.5%)	3 (9.1%)	187 (19.3%)	9 (13.2%)	334 (18.1%)	
2	137 (17.7%)	7 (21.2%)	320 (33.0%)	28 (41.2%)	492 (26.7%)	
3	55 (7.1%)	3 (9.1%)	157 (16.2%)	16 (23.5%)	231 (12.5%)	
PASE						0.0099[1]
Mean (SD)	169.0 (77.46)	142.0 (83.50)	160.7 (85.64)	156.3 (91.98)	163.7 (82.63)	
Mean cartilage T_2 right (ms)						0.0003[1]
Mean (SD)	33.1 (1.95)	33.3 (2.39)	33.3 (1.98)	34.0 (2.17)	33.3 (1.99)	
JSNmax right						< 0.001[1]
Mean (SD)	0.4 (0.62)	0.3 (0.65)	0.7 (0.76)	0.9 (0.76)	0.5 (0.72)	
JSNmax left						< 0.001[1]
Mean (SD)	0.3 (0.60)	0.3 (0.65)	0.6 (0.75)	0.8 (0.80)	0.5 (0.71)	

[1] Kruskal-Wallis *p*-value; [2] Chi-Square *p*-value;

JSN, each respective analysis was subdivided by males and females (Fig. 3). For WOMAC pain, the BMI-depression interaction was significant in females ($p < 0.001$) but was not significant for males ($p = 0.33$). For JSN, the BMI-depression interaction was significant in females ($p = 0.01$) but was not significant for males ($p = 0.35$).

Sensitivity analysis: KL 0/1

Of all the participants included in this study, $n = 865$ had KL grade 0/1 in both knees (of those, 17 had sustained depressive symptoms and obese BMI (30–49 kg/m²), 17 had sustained depressive symptoms and normal BMI (16.9–24.9 kg/m²), 340 had no sustained depressive symptoms and obese BMI (30–49 kg/m²) and 491

Table 2 Interactions between BMI (normal/obese) and sustained depression over 4 years (yes/no) and outcomes (WOMAC pain, JSN, cartilage T_2). An additional interaction between BMI-sustained depression-sex was included to test for sex differences. If significant, the analysis was subdivided by sex. All mixed effects models were adjusted for age, sex, BMI, and race

	WOMAC Pain	JSN	Cartilage T_2
P value for the interaction between BMI and sustained depression	**< 0.001**	0.08	0.27
P value for the interaction between BMI and sustained depression in participants with KL 0/1 in both knees at baseline	**< 0.001**	**0.02**	0.25
P value for the interaction between BMI and sustained depression and sex (male/female)	**0.02**	**0.03**	0.39
P value for the interaction between BMI and sustained depression) in males	0.33	0.35	*
P value for the interaction between BMI and sustained depression in females	**< 0.001**	**0.01**	*

* Note analysis this analysis was not subdivided by males/females since the interaction BMI and sustained depression and sex was not significant
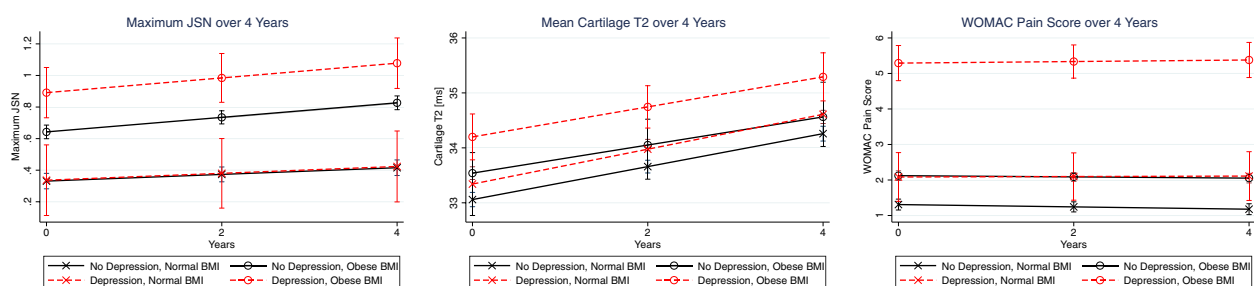

Fig. 2 The graphs (derived from the interaction models) illustrate the longitudinal changes in maximum JSN [range 0 to 3], cartilage T_2 [in ms], and WOMAC pain score [range 0 to 20] over 4 years. The depression-BMI interactions were statistically significant with WOMAC pain ($p < 0.001$). The *p*-value for the depression-BMI interaction on JSN was $p = 0.08$; the interaction was not significant for cartilage T_2 ($p = 0.27$). The figure illustrates that the compound effects of obesity and depression on OA are greater than their individual effects: in all three outcomes, the difference between the normal BMI groups (denoted by X) is less than the obese groups (denoted by O). Thus, the effect of depression is stronger in the obese groups than the normal weight groups

had no sustained depressive symptoms and normal BMI ($16.9–24.9 \, kg/m^2$). In this subset of participants with KL grade 0/1 in both knees, the BMI-depression interaction was statistically significant for WOMAC pain ($p < 0.001$ and JSN ($p = 0.02$), while it was not statistically significant for cartilage T_2 ($p = 0.25$), Table 2. The significant associations found with WOMAC pain outcomes were also found in the primary analysis; however, in this subgroup analysis, JSN outcomes were also statistically significant. These results demonstrate that even in individuals without evidence of radiographic OA (KL 0/1), having sustained depressive symptoms and obesity is associated with joint structure endpoints of increased JSN, as well as increased pain over 4 years.

Discussion

In this study, BMI-depression interactions were significantly associated with greater WOMAC knee pain in all participants, as well as greater JSN in women and participants with KL 0/1 (exploratory analysis) over 4-years. For cartilage T_2, the group-based analysis exhibited that individuals with depressive symptoms and obesity had significant elevations in T_2 compared to all other groups

including individuals without depressive symptoms and without obesity. These results suggest that the compound effects of depression and obesity have greater impact on knee pain and JSN progression compared to what would be expected based on their *individual* effects. Thus, obese individuals with comorbid depression are likely to have worse OA outcomes over 4 years than would be predicted based on the individual effects of depression and obesity.

While many studies have reported the individual effects of both obesity and depression on OA including increased joint pain and disability [6, 9, 10] and increased radiographic degeneration [7, 10], few studies have assessed their combined impact. One study [12], however, reported that patients with obesity and comorbid depression have increased biomarkers of cartilage degradation and bony remodeling as well as worse pain and function over 2 years compared to non-obese individuals and individuals without depression. The results of our study are in agreement with, and complementary to, the results reported by Jacobs et al. [12]: both studies report increased knee pain in participants with obesity and depression, and our study further demonstrates

Joseph *et al. BMC Musculoskeletal Disorders*   (2023) 24:27

Page 8 of 11

Table 3 The associations of BMI/Depression group with WOMAC Pain, maximum JSN and cartilage T_2 [ms]. All mixed effects models were adjusted for age, sex, BMI, and race. Abbreviations: SE: standard error; CI: confidence interval; Coeff: coefficient

	Beta Coeff.	SE	95% CI	P value
Maximum JSN				
No Depression/Normal BMI			Reference	
(N = 772)				
No Depression/Obese BMI	0.35	0.03	0.29–0.42	**< 0.001**
(N = 971)				
Depression/Normal BMI	0.01	0.11	−0.21-0.23	0.90
(N = 33)				
Depression/Obese BMI	0.60	0.08	0.44–0.77	**< 0.001**
(N = 68)				
WOMAC Pain				
No Depression/Normal BMI			Reference	
(N = 772)				
No Depression/Obese BMI	0.84	0.09	0.65–1.03	**< 0.001**
(N = 971)				
Depression/Normal BMI	0.85	0.34	0.17–1.543	**0.01**
(N = 33)				
Depression/Obese BMI	4.09	0.25	3.60–4.58	**< 0.001**
(N = 68)				
Cartilage T_2				
No Depression/Normal BMI			Reference	
(N = 772)				
No Depression/Obese BMI	0.39	0.08	0.24–0.55	**< 0.001**
(N = 971)				
Depression/Normal BMI	0.31	0.28	−0.24-0.87	0.27
(N = 33)				
Depression/Obese BMI	1.09	0.04	0.68–1.49	**< 0.001**
(N = 68)				

increased JSN in a subset of participants (KL 0/1 and females) over 4 years. Collectively, these studies suggest that individuals with comorbid obesity and depressive symptoms have greater progression of symptomatic OA compared to what would be expected based on their *individual* effects.

In addition to the interaction analysis, a further examination of the group-based results is valuable to better understand the effects comorbid obesity and depressive symptoms on OA outcomes. Summarizing the interaction results: the BMI-depression interaction was significant for WOMAC pain ($p < 0.001$), while the interaction effect for JSN was $p = 0.08$ and the interaction effect for cartilage T_2 was $p = 0.27$. Figure 2, which graphically illustrates interactive effects for all outcomes, suggests that there may be a significant interaction observable with cartilage T_2 in a larger sample size especially since interaction analyses are often imprecise [34]. The group-based differences for cartilage T_2 are statistically significant (as described in the results section), and thus support an association between comorbid depression-obesity and

cartilage T_2. Thus, while the interaction analysis for T_2 outcomes was not statistically significant, further studies with larger sample sizes may detect significant associations with comorbid depressive symptoms and obesity.

The results of the sensitivity analyses (exploratory) were consistent with the results in the entire cohort; however, additional significant associations were established in individuals without evidence of radiographic OA, and gender differences were also noted. Of interest, the interaction between depressive symptoms and BMI was significant for JSN outcomes in individuals with KL 0/1 in both knees. These results suggest that despite no evidence of radiographic knee OA, individuals with an obese BMI and depressive symptoms had not only increased knee pain, but also increased JSN loss over 4 years. In the sensitivity analysis subdivided by sex, females with depressive symptoms and obesity were more likely than males to have progression of JSN and knee pain over 4 years. These results may be attributed to evidence that depressive symptoms are more common in women than men [35], and obesity is more common in women than men [36]. In addition, in women, higher Q angles increase joint malalignment and can accelerate loss of cartilage in obese individuals with knee OA [37]. Overall, the severity of radiographic OA and sex may impact the effects of depressive symptoms and obesity on OA outcomes; these are important factors to consider when designing future prospective studies.

The mechanisms responsible for the interrelationships between the comorbid obesity-depression and OA may potentially be related to increased mechanical loading and increased systemic inflammation. Obesity causes increased mechanical loading in the joint including increased compression and external adduction moments during the stance phase of gait, which have been linked to increased bone marrow lesions [38]. Obesity is also associated with increased metabolic inflammation associated with excess adipose tissue and lipids: adipose tissue secretes inflammatory mediators including cytokines and adipokines, creating a systemic environment of increased inflammation, that may lead to OA [39]. In addition to systemic inflammation, localized knee synovitis is associated with obesity, and has been linked to increased cartilage compositional degeneration, joint structure degeneration, and pain [40]. Also, depressive symptoms are associated with systemic inflammation [41], and systemic inflammation creates "a physiological environment that promotes the development of additional inflammatory comorbidities [12]" such as OA. Jacobs et al. reported that cartilage degradation and bone remodeling was evident in a subset of obese patients with comorbid depression, perhaps due to increased inflammation [12]. In addition, several studies have confirmed
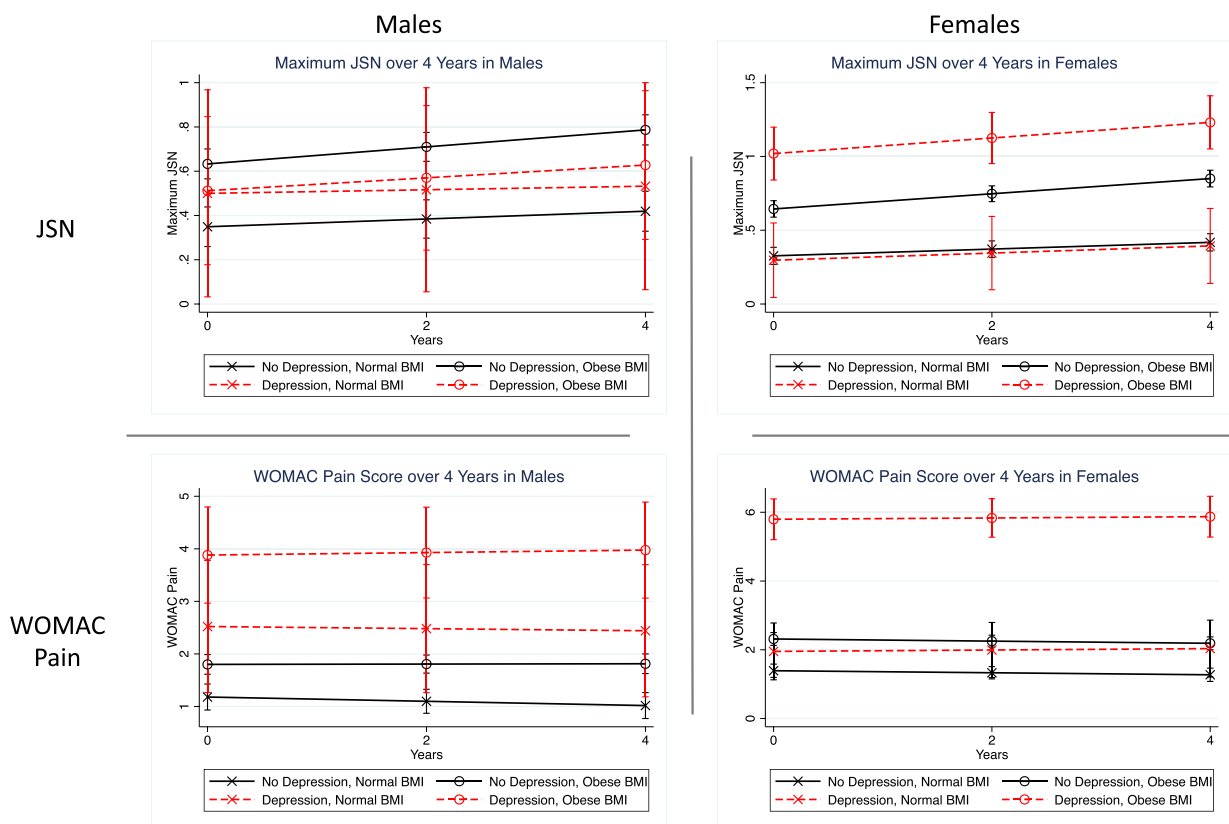
Fig. 3 The BMI-depression-sex interactions were significant for WOMAC pain ($p = 0.02$) and JSN ($p = 0.03$); thus, each respective analysis was subdivided by males and females. For WOMAC pain, the BMI-depression interaction was significant in females ($p < 0.001$) but was not significant for males ($p = 0.33$). For JSN, the BMI-depression interaction was significant in females ($p = 0.01$) but was not significant for males ($p = 0.35$). Note that the range for the JSN score was [0 to 3] and the range for WOMAC pain score was [0 to 20]

"the involvement of inflammation, neurotransmitters, the hypothalamic-pituitary adrenal axis, and cortisol levels in the biological mechanisms of OA and depression [41]" and a genetic component has also been proposed [42]. Overall, we hypothesize that comorbid obesity and depressive symptoms may impact symptomatic knee OA through disrupted mechanical loading patterns and through increased systemic and localized inflammation.

Understanding the interrelationships between obesity, depression and OA will help develop treatment strategies to slow progression of OA. One such potential treatment may be increased physical activity. Since physical activity levels are lower in individuals with both obesity and depression [43], and a lack of physical activity is independently associated with increased inflammation [44], exercise may be a viable treatment option for OA in patients with both obesity and depression. Exercise causes cyclic physiologic mechanical loading and unloading, resulting in anti-inflammatory effects on both systemic and local tissue levels (particularly in adipose tissue and cartilage [43]). In addition, sustained exercise is often prescribed for weight loss [45], with long term decreases mechanical loads on the knee joint. Ultimately, exercise is associated with not only decreases in metabolic and localized inflammation [46] but also decreases in the mechanical burden on joint tissue. Thereby, increased physical activity is potentially a viable treatment for patients with comorbid depression, obesity, and OA.

The primary limitations of this study are its retrospective nature, and the small sample size of participants with sustained depression. While it would be optimal to study a greater number of participants with depression, we analyzed all participants in the OAI that met the requirements of the inclusion/exclusion criteria for this study. In addition, the reasons for a participant's obesity or sustained depression were unknown (no data available in the OAI) and the mechanisms responsible for the associations between depression and joint degeneration were not studied directly; these caveats may be addressed by a future study with a prospective design. The number of statistical analyses performed may raise concerns of multiple testing; to reduce the number of comparisons, we designed the outcomes as primary or exploratory (as described in the statistical

analysis section) [33]. While analyzing cartilage MRI T_{1rho} or other cartilage quantitative measures would be of interest, we were only able to analyze T_2 measurements as only these measurements were provided by the OAI. Despite these limitations, our study also has pertinent strengths, particularly its longitudinal follow-up and quantitative outcomes.

Overall, the results of this study suggest that comorbid obesity and depressive symptoms are associated with progression of symptomatic OA, evidenced by increased knee pain and increased JSN. The compound effects of obesity and depression on OA are greater than their individual effects. Thus, concurrent treatment of obesity and depressive symptoms (potentially through increases in physical activity) may be beneficial when developing individualized non-invasive strategies aimed to slow progression of OA.

Abbreviations

3T	3 Tesla
BMI	Body mass index
Coeff.	Coefficient
CES-D	Center for Epidemiological Studies Depression Scale
DESS	3D dual-echo in steady state
JSN	Joint space narrowing
KL	Kellgren Lawrence
ME	Multi-echo
MRI	Magnetic resonance imaging
OA	Osteoarthritis
OAI	Osteoarthritis initiative
PASE	Physical Activity Scale for the Elderly
SE	Spin echo
TE	Echo time
TR	Relaxation time
WE	Water excitation
WOMAC	Western Ontario McMaster Universities Osteoarthritis

Acknowledgements
Not applicable.

Authors' contributions
Conception design of the work: GBJ, CEM, MCN, JAL, NEL, TML. Acquisition and analysis: GBJ, JAL, CEM, VP. Interpretation of data: GBJ, CEM, MCN, JAL, NEL, VP, SM, TML. Drafting or revision of manuscript: GBJ, CEM, MCN, JAL, NEL, VP, SM, TML. Approval of final manuscript: GBJ, CEM, MCN, JAL, NEL, VP, SM, TML. Personally accountable for the author's own contributions: GBJ, CEM, MCN, JAL, NEL, VP, SM, TML.

Availability of data and materials
The datasets generated and/or analyzed during the current study are available from the Osteoarthritis Initiative (OAI; https://nda.nih.gov/oai).

Declarations

Ethics approval and consent to participate
The OAI participant recruitment obtained ethical approval for participant recruitment and data collection. Informed consent was obtained from all individual participants included in the study. All methods were performed in accordance with the relevant guidelines and regulations the Human Research Protection Program (HRPP) at UC San Francisco.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References
1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380(9859):2163–96.
2. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. NCHS Data Brief. 2017;288:1–8.
3. Prevalence of Major Depressive Episode Among Adults 2022 [Available from: https://www.nimh.nih.gov/health/statistics/major-depression#part_2567.
4. Cohen E, Lee YC. A mechanism-based approach to the management of osteoarthritis pain. Curr Osteoporos Rep. 2015;13(6):399–406.
5. Lementowski PW, Zelicof SB. Obesity and osteoarthritis. Am J Orthop (Belle Mead NJ). 2008;37(3):148–51.
6. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res. 2013;138:185–93.
7. Reijman M, Pols HA, Bergink AP, Hazes JM, Belo JN, Lievense AM, et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam study. Ann Rheum Dis. 2007;66(2):158–62.
8. Laberge MA, Baum T, Virayavanich W, Nardo L, Nevitt MC, Lynch J, et al. Obesity increases the prevalence and severity of focal knee abnormalities diagnosed using 3T MRI in middle-aged subjects--data from the Osteoarthritis Initiative. Skelet Radiol. 2012;41(6):633–41.
9. Kim KW, Han JW, Cho HJ, Chang CB, Park JH, Lee JJ, et al. Association between comorbid depression and osteoarthritis symptom severity in patients with knee osteoarthritis. J Bone Joint Surg Am. 2011;93(6):556–63.
10. Rathbun AM, Schuler MS, Stuart EA, Shardell MD, Yau MS, Gallo JJ, et al. Depression subtypes in individuals with or at risk for symptomatic knee osteoarthritis. Arthritis Care Res. 2020;72(5):669–78.
11. Gersing AS, Schwaiger BJ, Nevitt MC, Zarnowski J, Joseph GB, Feuerriegel G, et al. Weight loss regimen in obese and overweight individuals is associated with reduced cartilage degeneration: 96-month data from the osteoarthritis initiative. Osteoarthr Cartil. 2019;27(6):863–70.
12. Jacobs CA, Vranceanu AM, Thompson KL, Lattermann C. Rapid progression of knee pain and osteoarthritis biomarkers greatest for patients with combined obesity and depression: data from the osteoarthritis initiative. Cartilage. 2020;11(1):38–46.
13. Rathbun AM, Yau MS, Shardell M, Stuart EA, Hochberg MC. Depressive symptoms and structural disease progression in knee osteoarthritis: data from the osteoarthritis initiative. Clin Rheumatol. 2017;36(1):155–63.
14. Wang L, Lu H, Chen H, Jin S, Wang M, Shang S. Development of a model for predicting the 4-year risk of symptomatic knee osteoarthritis in China: a longitudinal cohort study. Arthritis Res Ther. 2021;23(1):65.
15. Peterfy C, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthr Cartil. 2008;16:1433–41.

16. Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck depression inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), geriatric depression scale (GDS), hospital anxiety and depression scale (HADS), and patient health Questionnaire-9 (PHQ-9). Arthritis Care Res. 2011;63(Suppl 11):S454–66.

17. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1(3):385–401.

18. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychol Aging. 1997;12(2):277–87.

19. Bellamy N, Buchanan W, Goldsmith C, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip and knee. J Rheumatol. 1988;15:1833–40.

20. Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. Radiology. 2003;226(2):373–81.

21. Phan CM, Link TM, Blumenkrantz G, Dunn TC, Ries MD, Steinbach LS, et al. MR imaging findings in the follow-up of patients with different stages of knee osteoarthritis and the correlation with clinical symptoms. Eur Radiol. 2006;16:608–18.

22. Stehling C, Lane NE, Nevitt MC, Lynch J, McCulloch CE, Link TM. Subjects with higher physical activity levels have more severe focal knee lesions diagnosed with 3T MRI: analysis of a non-symptomatic cohort of the osteoarthritis initiative. Osteoarthr Cartil. 2010;18(6):776–86.

23. Washburn RA, Ficker JL. Physical activity scale for the elderly (PASE): the relationship with activity measured by a portable accelerometer. J Sports Med Phys Fitness. 1999;39(4):336–40.

24. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. J Clin Epidemiol. 1999;52(7):643–51.

25. Washburn RA, Smith KW, Jette AM, Janney CA. The physical activity scale for the elderly (PASE): development and evaluation. J Clin Epidemiol. 1993;46(2):153–62.

26. Kellgren J, Lawrence J. Radiologic assessment of osteoarthritis. Ann Rheum Dis. 1957;16:494–502.

27. Brandt KD, Fife RS, Braunstein EM, Katz B. Radiographic grading of the severity of knee osteoarthritis: relation of the Kellgren and Lawrence grade to a grade based on joint space narrowing, and correlation with arthroscopic evidence of articular cartilage degeneration. Arthritis Rheum. 1991;34(11):1381–6.

28. Razmjoo A, Caliva F, Lee J, Liu F, Joseph GB, Link TM, et al. T2 analysis of the entire osteoarthritis initiative dataset. J Orthop Res. 2021;39(1):74–85. https://doi.org/10.1002/jor.24811. Epub 2020 Jul 27.

29. Norman B, Pedoia V, Majumdar S. Use of 2D U-net convolutional neural networks for automated cartilage and Meniscus segmentation of knee MR imaging data to determine Relaxometry and morphometry. Radiology. 2018;288(1):177–85.

30. Miller AJ, Joseph PM. The use of power images to perform quantitative analysis on low SNR MR images. Magn Reson Imaging. 1993;11(7):1051–6.

31. Raya J, Dietrich O, Horng A, Weber J, Reiser M, Glaser C. T2 measurement in articular cartilage: impact of the fitting method on accuracy and precision at low SNR. Magn Reson Med. 2010;63(1):181–93.

32. Meyers J. Paper AD-088: demographic table and subgroup summary macro %TABLEN. In: Pharmaceuticals SAS users group conference. San Francisco; 2020. https://www.lexjansen.com/pharmasug/2020/AD/PharmaSUG-2020-AD-088.pdf.

33. Peter Z. Schochet MPR, Inc. Guidelines for Multiple Testing in Impact Evaluations: Technical Methods Report; 2008.

34. Greenland S. Tests for interaction in epidemiologic studies: a review and a study of power. Stat Med. 1983;2(2):243–51.

35. Kuehner C. Why is depression more common among women than among men? Lancet Psychiatry. 2017;4(2):146–58.

36. Garawi F, Devries K, Thorogood N, Uauy R. Global differences between women and men in the prevalence of obesity: is there an association with gender inequality? Eur J Clin Nutr. 2014;68(10):1101–6.

37. Tillman MD, Bauer JA, Cauraugh JH, Trimble MH. Differences in lower extremity alignment between males and females. Potential predisposing factors for knee injury. J Sports Med Phys Fitness. 2005;45(3):355–9.

38. Chen L, Zheng JJY, Li G, Yuan J, Ebert JR, Li H, et al. Pathogenesis and clinical management of obesity-related knee osteoarthritis: impact of mechanical loading. J Orthop Transl. 2020;24:66–75.

39. Urban H, Little CB. The role of fat and inflammation in the pathogenesis and management of osteoarthritis. Rheumatology (Oxford). 2018;57(suppl_4):iv10–21.

40. Kanthawang T, Bodden J, Joseph GB, Lane NE, Nevitt M, McCulloch CE, et al. Obese and overweight individuals have greater knee synovial inflammation and associated structural and cartilage compositional degeneration: data from the osteoarthritis initiative. Skelet Radiol. 2021;50(1):217–29.

41. Wang S-T, Ni G-X. Depression in osteoarthritis: current understanding. Neuropsychiatr Dis Treat. 2022;18:375–89.

42. Barowsky S, Jung JY, Nesbit N, Silberstein M, Fava M, Loggia ML, et al. Cross-disorder genomics data analysis elucidates a shared genetic basis between major depression and osteoarthritis pain. Front Genet. 2021;12:687687.

43. Issa RI, Griffin TM. Pathobiology of obesity and osteoarthritis: integrating biomechanics and inflammation. Pathobiol Aging Age Relat Dis. 2012;2(2012). https://doi.org/10.3402/pba.v2i0.17470.

44. Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature. 2008;454(7203):463–9.

45. Donnelly JE, Smith B, Jacobsen DJ, Kirk E, DuBose K, Hyder M, et al. The role of exercise for weight loss and maintenance. Best Pract Res Clin Gastroenterol. 2004;18(6):1009–29.

46. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011;11(9):607–15.

Publisher's Note