

**ASSOCIATION BETWEEN LOWER LIMB OSTEOARTHRITIS
AND INCIDENCE OF DEPRESSIVE SYMPTOMS:
DATA FROM THE OSTEOARTHRITIS INITIATIVE**

Nicola Veronese, MD^{a,b*}, Brendon Stubbs, PhD^{c,d,e*}, Marco Solmi, MD^{b,f,g}, Toby O Smith, PhD^h,
Marianna Noale, ScDⁱ, Cyrus Cooper, MD^{l,m,n}, Stefania Maggi, MDⁱ

* Veronese and Stubbs are joint first authors.

^a Department of Medicine (DIMED), Geriatrics Division, University of Padova, Italy.

^b Institute of clinical Research and Education in Medicine (IREM), Padova, Italy

^c Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom.

^d Health Service and Population Research Department, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8 AF, United Kingdom.

^e Faculty of Health, Social Care and Education, Anglia Ruskin University, Bishop Hall Lane, Chelmsford CM1 1SQ, UK

^f Department of Neurosciences, University of Padova, Padova, Italy.

^g National Health Care System, Padua Local Unit ULSS 17, Italy.

^h Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, United Kingdom.

ⁱ National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy.

^l Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Nuffield Orthopaedic Centre, University of Oxford, Windmill Road, Oxford, OX3 7LD, UK.

^m MRC Lifecourse Epidemiology Unit, Southampton General Hospital, University of Southampton, Southampton, SO16 6YD, UK.

ⁿ National Institute for Health Research Nutrition Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton General Hospital, Southampton, SO16 6YD, UK.

Corresponding Author:

Nicola Veronese, MD

Department of Medicine - DIMED, Geriatrics Division, University of Padova, Padova, Italy

Via Giustiniani, 2 - 35128 Padova, Italy

Phone: +39 0498218492; Fax: +39 0498211218

Email: ilmannato@gmail.com

ABSTRACT

Background: Osteoarthritis (OA) is associated with a number of medical morbidities. Although the prevalence of depression and depressive symptoms is presumed to be high in people with OA, no prospective comparative study has analyzed its incidence.

Objective: To determine whether OA was associated with an increased odds of developing depressive symptoms.

Design: Longitudinal cohort study (follow-up: four years).

Setting: Data were gathered from the North American Osteoarthritis Initiative (OAI) dataset.

Subjects: People at higher risk developing OA.

Methods: Osteoarthritis diagnosis was defined as the presence of OA at hand, knee, hip, back/neck or other sites at baseline. Depressive symptoms were defined using the 20-item Center for Epidemiologic Studies-Depression (cut-off 16 points) after four years.

Results: 3,491 people without depressive symptoms at baseline were analyzed (1,506 with OA/1,985 without). Using an adjusted logistic regression analysis for 12 potential confounders, people with OA had a similar odds of depressive symptoms at follow-up compared to those without OA (Odds Ratio (OR): 1.26; 95% CI: 0.95-1.67). However, multisite OA (i.e. OA \geq 2 sites; OR: 1.48, 95% CI 1.07-2.05) and the specific presence of hip (OR: 1.72; 95% CI: 1.08-2.73) or knee OA (OR: 1.43; 95% CI: 1.03-1.98) were associated with a greater odds of developing depressive symptoms compared to people without OA.

Conclusions: This is the first study of longitudinal data to demonstrate people with multi-site, hip or knee OA have a greater odds of developing depressive symptoms compared to people without OA. This suggests that OA may be associated with future mental health burden.

Keywords: osteoarthritis; depression; depressive symptoms; epidemiology.

KEY-POINTS

- In cross-sectional studies, osteoarthritis is associated with a higher prevalence of depression and depressive symptoms.
- It is unknown if osteoarthritis could increase the odds of developing depressive symptoms.
- We demonstrated that hip, knee or multi-site osteoarthritis increases the odds of depressive symptoms.

INTRODUCTION

Recent global burden of disease surveys have demonstrated that whilst average life expectancy is rising[1], the number of years people are living with chronic disabilities is also rising. One of the most common causes of years lived with disability are chronic musculoskeletal disorders. [1] Osteoarthritis (OA) accounts for a considerable proportion of this burden[2], with hip and knee OA ranked the 11th highest contributor to global disability.[2] The worldwide prevalence of OA has been estimated to be 10% in men and 20% in women in older people. [2]

A common feature of OA is pain.[3] Pain has been closely linked to incident depression.[4] Pain and depression are also associated with poorer outcomes among people with OA.[5] People with chronic painful conditions are at increased risk of a range of suicidal behaviors.[6] There are a number of reasons that could increase the risk of depression and depressive symptoms in people with OA. For instance, OA is associated with increasing disability and difficulty undertaking activities of daily living,[7] and with lower quality of life.[2] Furthermore, people with OA often engage in less physical activity compared to those without OA [8], whilst lower levels of physical activity is a risk factor for future depression.[9]

Depression and depressive symptoms are seen in a proportion of the OA population. A recent meta-analysis demonstrated that the prevalence of these conditions is approximately 20% in the OA population.[10] The authors acknowledged a lack of comparative studies comparing the prevalence of depression/depressive symptoms in OA compared to non-OA cohorts. It has therefore not been possible to establish if depressive symptoms are more common in people with OA. There has also been an absence of longitudinal studies investigated the incidence of depression and depressive symptoms in this population. [10]

The purpose of this study was to address this limitation and to determine whether: i) people with OA are at greater odds of incident depressive symptoms compared to people without OA; ii) the location of OA (e.g. hand, hip, knee, back/neck) related to the incidence of depressive symptoms; and iii) multisite OA was associated with odds of developing depressive symptoms than single-site presentations.

METHODS

Data source and subjects

All participants in this study were recruited as part of the ongoing, publicly and privately-funded, multicenter Osteoarthritis Initiative (OAI) study, which is available for public access (<http://www.oai.ucsf.edu/>). Patients were recruited from four clinical sites in the US (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. People were eligible if they: i) had knee osteoarthritis and reported knee pain in a 30-day period in the past 12 months; or ii) were at high risk of developing knee OA (e.g. overweight/obese, knee injury/operation, parents/siblings with total knee replacement, frequent knee-bending activities that increase risk, and hand/hip osteoarthritis). All participants provided written informed consent.

The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center, University of California at San Francisco. Specific datasets used were those recorded during baseline and screening evaluations (November 2008) and those evaluating the participants after 48 months.

Exposure

The diagnosis for OA at baseline assessment was self-reported for the most common sites usually affected by OA (knee, hand, hip, back/neck, and other). Through this participant were asked if a doctor, at any time in his/her life, had said that he/she suffers from OA. A summary variable ascertained as the presence of at least one site affected by self-reported OA was then calculated. Multisite OA was defined as the presence of two or more affected sites. Radiological data were available for those with knee OA. Accordingly, a separate analysis was undertaken where knee OA was defined as a combination of self-reported symptoms of pain and stiffness, and radiographical confirmation of OA based on the presence of tibiofemoral osteophytes on a fixed flexion radiograph (as per Osteoarthritis Research Society International atlas grades 1-3, clinical center reading).

Outcomes

The presence of depressive symptoms was derived from the 20-item Center for Epidemiologic Studies-Depression (CES-D) instrument.[11] The range of possible values for this scores is 0 to 60, where higher scores indicate more depressive symptoms.[11] A cut-off of 16 was used for the diagnosis of depressive symptoms. [12]

Covariates

A number of variables were identified from the OAI dataset to explore associations between OA and incident depressive symptoms. These included: (1) physical activity, evaluated using the Physical Activity Scale for the Elderly (PASE), a validated scale for assessing physical activity level in the elderly.[13] The scale covers 12 different activities including: walking, sports and housework, and is scored from 0 upwards, without a maximum score; (2) race was defined as “whites” vs. others; (3) smoking habits as “previous/current” vs. never; (4) educational level was categorized as “degree” vs. others; (5) yearly income as < and missing data vs. $\geq 50,000$ \$; and (6) medical co-morbidities were assessed through the modified Charlson Comorbidity Index (CCI), where higher scores indicate an greater number of morbidities and poorer health.[14] Among the several medical conditions assessed through the CCI, prevalence was reported for the more common diseases associated with OA and depressive symptoms (i.e. fractures, heart failure, heart attack, stroke, chronic obstructive pulmonary disease (COPD), diabetes and cancer).

Statistical analyses

For continuous variables, data normality was assessed using the Kolmogorov-Smirnov test. The data were presented as means and standard deviations (SD) for quantitative measures, and frequency and percentages for discrete variables by OA presence. P-values were calculated for continuous variables using the independent Student T-test and for categorical parameters the chi-square test.

The incidence of depressive symptoms was calculated as the number of new cases per 1000 person-years during the follow-up. The proportional hazards assumption was evaluated by plotting the Schoenfeld residuals versus time. Since this was reported as $p < 0.0001$, a logistic regression analysis, rather than a Cox's proportional hazard models was used. Multivariate logistic binary regression models were constructed using the presence of OA as the exposure and incident depressive symptoms at four-year follow-up as the outcome. The multivariate model included the confounding factors that were significantly different between participants with and without OA at baseline or were significantly associated with incident depressive symptoms at follow-up. Multicollinearity among covariates was assessed through variance inflation factor (VIF), taking a cut-off of 2 as reason for exclusion. No variable was excluded for this reason. The basic model was not adjusted for any confounders, while the fully adjusted model included baseline values of: age (as continuous); gender; race (whites vs. others); Body Mass Index (BMI; as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as \geq or $<$ 50,000\$ and missing data); PASE (as continuous); CCI and baseline CES-D. Changes in CCI during baseline and follow-up evaluations and the onset of new OA cases during the follow-up period were also introduced to the fully-adjusted model. Data of logistic binary analyses were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

On secondary analyses, specific sites affected by OA (categorized as presence of hand, hip, knee, back/neck, or other) and presence of multi-site OA (≥ 2 sites affected by OA) were taken as exposure variables. Participants without OA were taken as the reference throughout these analyses.

To test the robustness of our findings, sensitivity analyses were conducted evaluating the interaction between the presence of self-reported and radiological with clinical diagnosis of OA and selected factors (e.g. age below or more than 65 years, gender, race, education, smoking habits, yearly

income and presence/absence of diseases at baseline) in predicting depressive symptoms at follow-up, without finding any factor significantly influenced our results.

All analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value <0.05.

Declaration of Sources of Funding

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RESULTS

Study participants

At baseline, among 4,796 potentially eligible individuals, 264 were excluded due to missing CES-D data, 462 excluded who had a CES-D ≥ 16 at baseline and a further 579 participants did not return at follow-up evaluation. Accordingly 3,491 participants were eligible for this study. Full details of participant flow are presented in **Figure 1**.

Baseline analyses

The 3,491 participants (1,474 Males/2,017 Females) had a mean age of 61.3 ± 9.1 (range: 45-79) years. At baseline, 1506 people with OA (43.1%) were compared to 1,985 participants without OA.

The baseline characteristics of the OA and non-OA participants are summarized in **Table 1**. The OA participants were more frequently women (62.7 versus 54.1%), white (87.4 versus 80.1%) and older (62.8 ± 8.9 versus 60.0 ± 9.2 years) than those without OA ($p < 0.0001$ for all comparisons). Individuals with OA had higher BMI values, lower physical activity levels, were more frequently smokers and had a higher educational level compared to the non-OA group (**Table 1**). Regarding medical conditions, participants with OA more frequently reported bone fractures and had a higher CCI (**Table 1**). Finally, participants with OA showed significantly higher CES-D score at baseline (5.0 ± 4.1 versus 4.4 ± 3.9 , $p < 0.0001$) compared to without OA.

Follow-up analyses and incident depressive symptoms

After a mean period of 4.2 years, 280 individuals (8.0% of the baseline population) developed depressive symptoms, with an incidence of 26 (95% CI: 0 to 87) new cases per 1,000 person-years. People with OA had an incidence of depressive symptoms of 27 versus 17 new cases per 1,000 persons-years.

The unadjusted analyses demonstrated that people with OA were at an increased odds of depressive symptoms over the four-year follow-up compared to those without (**Table 2**). However, on logistic regression analysis, after adjusting for 12 potential confounders (i.e. age, gender, race, BMI, education, smoking habits, yearly income, PASE score, CCI at baseline and follow-up, CES-D score at baseline, and presence of new onset of OA during follow-up period), demonstrated that having OA at baseline did not significantly increased the odds of depressive symptoms when compared to those without OA (OR=1.26; 95% CI: 0.95-1.67, p=0.25; **Table 2**). These findings were evident also after stratifying for age (≥ 65 years: adjusted OR: 1.33; 95% CI: 0.82-2.14 vs. <65 years: OR: 1.23; 95% CI: 0.86-1.75; p=0.84). Similarly, the CES-D scores at follow-up evaluation were similar between the OA versus and non-OA groups (6.3 ± 6.2 vs. 5.5 ± 6.2 ; p=0.14 adjusted for potential confounders within a generalized linear model).

On multivariate analysis, significant predictors of depressive symptoms were: BMI (one point corresponded to an increase in depressive symptoms of 4% OR: 1.04; 95% CI: 1.00-1.07; p=0.01), baseline CES-D (one point corresponded to an increase in depressive symptoms of 23%; OR: 1.23; 95% CI: 1.19-1.27; p<0.0001) and the onset of co-morbidity during follow-up period (OR: 1.25; 95% CI: 1.08-1.44; p=0.003).

When assessed by specific site, the presence of hip OA (OR: 1.72; 95% CI: 1.08-2.73; p=0.02) and knee OA (OR: 1.43; 95% CI: 1.03-1.98; p=0.03) were associated with an increased odds of depressive symptoms at the follow-up compared to those without (**Table 2**). When radiological/clinical knee OA was used instead of self-reported knee OA, there was a reduction in the strength of association with depressive symptoms, not significant at the p<0.05 level (adjusted OR: 1.32; 95% CI: 0.99-1.78; p=0.06).

People with multi-site OA (i.e. 2 or more sites affected) were at increased odds of incident depressive symptoms compared to those with no OA (OR: 1.48, 95% CI: 1.07-2.05; p=0.03) (**Table 2**).

DISCUSSION

This is the first prospective study to determine the incidence of depressive symptoms in people with OA compared to a non-OA cohort. People with multi-site OA and those with hip and knee OA have a significantly greater odds of developing depressive symptoms compared to those without OA. Significant predictors of developing incident depressive symptoms were higher BMI, higher baseline CES-D scores and the onset of co-morbidities.

The prevalence of depression and depressive symptoms in people with OA has previously been reported as 20%. [10] However, the cross-sectional nature of these studies meant causality could not be determined. Similarly to the increased risk of cardiovascular disease (CVD) in people with OA, we hypothesize that the influence of OA on reducing physical activity and increasing associated obesity may be the mediating pathway to depression.[15–17] Whilst physical activity was not predictive of incident depression, this may be due to the questionable accuracy of self-report measures. [18]Moreover, other risk factors such as CVD are also related to incident depression[19] and are highly prevalent in people with OA.[20] Finally, higher inflammatory markers are frequently evident in people with OA. [21] This may be important in the development of depression and depressive symptoms.[22] People with depression, can have an altered peripheral immune system, with impaired cellular immunity and increased levels of pro-inflammatory cytokines which can influence neurotransmitter metabolism, neuroendocrine function and regional brain activity, all of which are relevant to depression. [22]

Previous literature has demonstrated that people with lower limb OA exhibit a number of barriers to physical activity[23] and many fail to meet recommended physical activity guidelines.[8] In agreement with these observations, our results suggest that hip OA had the strongest association with incident depressive symptoms. Lower levels of physical activity are associated with an increased risk of future incident depression in the general population.[9] Moreover, exercise has a

significant antidepressant effect on people with depression [24]. This therefore provides a further rationale for prescribing exercise for people with OA in addition to its well-documented benefits on pain, strength and function.[25] . Pain and reduced mobility are common features of OA [26,27]. These can become key barriers to physical activity engagement, placing people at greater risk of developing depression [9]. Therefore, people with OA may need additional support to help maintain or increase their physical activity levels and mobility.

The findings should be considered within the limitations of the study. First, the diagnosis of OA was self-reported, except for knee OA. This therefore relies on the individual to accurately recall this information. Second, the diagnosis of depressive symptoms was made only using the CES-D. Whilst the more formal assessment of the American Psychiatric Association' Diagnostic and Statistical Manual [DSM] criteria) was not used, the CES-D used many symptoms defined by the (DSM-V) for a major depressive episode and therefore is justifiable.[28] Third, no information was available to classify the type of pain (articular, neuropathic or other forms), which may be important information for individual's perceived musculoskeletal symptoms and consequently depression.

In conclusion, this study has demonstrated that people with multi-site, hip and knee OA have a significantly greater odds of developing depressive symptoms compared to those without OA. Since the incidence of OA is rising with the ageing population, future trials are indicated to determine whether intervening can reduce the odds of depressive symptoms occurring, thereby improving this population's physical and mental health into later life.

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Table 1. Baseline characteristics classified according to presence or not of osteoarthritis (OA).

Variable	Any site OA (n=1,506)	No OA (n=1,985)	<i>p</i> value*
Age (years)	62.8 (8.9)	60.0 (9.2)	<0.0001
Females (n, %)	944 (62.7)	1073 (54.1)	<0.0001
White race (n, %)	1315 (87.4)	1588 (80.1)	<0.0001
BMI (Kg/m²)	28.6 (4.7)	28.2 (4.7)	0.04
PASE (points)	160.6 (80.4)	167.9 (81.4)	0.008
Smoking (previous/current)	720 (48.0)	857 (43.4)	0.007
Degree (n, %)	534 (35.5)	631 (31.8)	0.03
Yearly income (<50,000 \$)	946 (65.1)	1284 (66.9)	0.27
<i>Medical conditions</i>			
Fractures (n, %)	315 (21.0)	310 (15.7)	<0.0001
Heart attack (n, %)	24 (1.7)	40 (2.2)	0.31
Heart failure (n, %)	27 (1.8)	25 (1.4)	0.88
Stroke (n, %)	45 (3.1)	46 (2.5)	0.34
COPD (n, %)	20 (1.4)	37 (2.0)	0.18
Diabetes (n, %)	97 (6.7)	119 (6.5)	0.89
Cancer (n, %)	81 (5.4)	91 (4.6)	0.31
Charlson co-morbidity score	0.4 (0.8)	0.3 (0.8)	0.01
CES-D (points)	5.0 (4.1)	4.4 (3.9)	<0.0001

Numbers are mean values (and standard deviations) or number (and percentages), as appropriate.

*Unless otherwise specified, *p* values are calculated with an independent Student T-test for continuous and with a chi-square test for categorical variables, respectively.

Abbreviations: BMI: body mass index; CES-D: Center for Epidemiologic Studies Depression Scale; COPD: chronic obstructive pulmonary disease; PASE: physical activity scale for the elderly.

Table 2: Associations between presence of osteoarthritis at the baseline and incident depression.

	<i>No. of events</i>	<i>No. of participants</i>	<i>Unadjusted odds ratio (95%CI)</i>	<i>p – value</i>	<i>Fully-adjusted* Model odds ratio (95%CI)</i>	<i>p –value</i>
No OA**	137	1985	reference		reference	
Presence of OA	143	1506	1.44 (1.12-1.86)	0.005	1.26 (0.95-1.67)	0.10
Hand OA	57	581	1.53 (1.10-2.15)	0.01	1.24 (0.86-1.81)	0.25
Hip OA	32	247	2.07 (1.35-3.16)	0.001	1.72 (1.08-2.73)	0.02
Knee OA	82	783	1.63 (1.21-2.19)	0.001	1.43 (1.03-1.98)	0.03
Back/neck OA	69	610	1.75 (1.28-2.41)	0.001	1.38 (0.97-1.96)	0.07
Other sites OA	35	313	1.75 (1.16-2.62)	0.007	1.39 (0.89-2.16)	0.14
OA at ≥ 2 sites	73	618	1.79 (1.33-2.40)	<0.0001	1.48 (1.07-2.05)	0.03
Radiological/clinical knee OA	165	1891	1.28 (0.99-1.67)	0.06	1.32 (0.99-1.78),	0.06

Unless otherwise specified, data are presented as odds ratios and 95% confidence intervals.

Notes:

* Fully-adjusted model included baseline values of: age (as continuous); gender; race (whites vs. others); body mass index (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as \geq or $<$ 50,000\$ and missing data);

physical activity scale for the elderly (as continuous); Charlson co-morbidity index (as continuous) and its value at follow-up; Center for Epidemiologic Studies Depression Scale (as continuous); presence of new onset of osteoarthritis during follow-up period.

** Those without any presence of osteoarthritis were taken as reference in all analyses.

Figure 1. Cohort flow-chart.

