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Systematic review and meta analysis

Correlation between pain severity and levels of anxiety and depression in osteoarthritis patients: a systematic review and meta-analysis

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Abstract

Objectives. Osteoarthritis (OA) is a chronic degenerative musculoskeletal disease that causes articular damage and chronic pain, with a prevalence of up to 50% in individuals >60 years of age. Patients suffering from chronic painful conditions, including OA, also frequently report anxiety or depression. A systematic review and meta-analysis were performed to assess the correlation between pain severity and depressive and anxious symptomatology in OA patients.

Methods. A systematic search was conducted using four databases (PubMed, Medline, Scopus, and Web of Science) from inception up to 14 January 2020. We included original articles evaluating pain severity and anxiety and/or depression severity in OA-diagnosed patients. Detailed data were extracted from each study, including patients' characteristics and pain, anxiety, and depression severity. When available, the Pearson correlation coefficient between pain and depression severity and pain and anxiety severity was collected, and a meta-analysis of random effects was applied.

Results. This systematic review included 121 studies, with a total of 38 085 participants. The mean age was 64.3 years old, and the subjects were predominantly female (63%). The most-used scale to evaluate pain severity was the Western Ontario and the McMaster Universities Osteoarthritis Index, while for anxiety and depression, the Hospital Anxiety and Depression Scale was the most used. The meta-analysis showed a moderate positive correlation between pain severity and both anxious ($r = 0.31$, $P < 0.001$) and depressive symptomatology ($r = 0.36$, $P < 0.001$).

Conclusion. Our results demonstrate a significant correlation between pain and depression/anxiety severity in OA patients, highlighting the need for its routine evaluation by clinicians.

Key words: anxiety, depression, joint, osteoarthritis, pain

Rheumatology key messages

- OA patients report low to moderate levels of anxiety and depression, concomitant with pain.
- The severity of pain correlates with the levels of anxiety/depression in OA patients.
- Early screening of mood disorders is crucial for improving OA pain management therapies.

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CLINICAL SCIENCE

Introduction

OA is a chronic musculoskeletal disease characterized by degeneration of articular cartilage and periarticular structures, leading to pain and functional limitations [1]. OA incidence and prevalence increase with age [2], impacting over 50% of the population aged >65 years [3]. Thus, as life expectancy increases, the prevalence and impact of OA are expected to rise. Although any joint can be affected, knee-OA is the most frequent, with a great impact on patients' quality of life, since pain and stiffness in large weight-bearing joints often lead to significant impairments in function and mobility [4].

Current pharmacological pain management therapies include the use of analgesics and NSAIDs [5, 6]. Although these drugs are effective for acute pain, their analgesic capacity weakens in the long term, in addition to causing adverse side effects. Since no effective pharmacological treatment for OA pain is currently available, its impact is substantial both at the individual and societal level [7].Chronic pain and physical dysfunction are key symptoms described by patients with OA [8, 9]. Importantly, as well as leading to physical limitations, OA pain is associated with emotional distress [10], and research shows that ~20% of adults with OA are diagnosed with concomitant depression and/or anxiety, in addition to chronic pain [11, 12]. It is, however, unclear whether these comorbidities precede the OA painful state or are a consequence of chronic pain and associated loss of functioning. Importantly, these psychological factors are often overlooked and undertreated, contributing to a further decrease in the patient's quality of life, adding to the reduction already caused by OA itself and its functional limitations [13]. Finally, as anxiety and depression enhance pain perception [14], a positive feedforward circle is established in which each disorder worsens the other two.

While a recent review has established the co-existence of pain and anxiety and/or depression in OA patients [12], the role of pain intensity in the severity of these psychiatric comorbidities remains unknown. Hence, in this work, we propose to systematically review the literature that quantifies pain, anxiety, and depression symptomatology in osteoarthritic patients, and to assess the correlation between pain and anxiety/depression severity through a meta-analysis.

Methods

This systematic review and meta-analysis were performed following the PRISMA statement for reporting systematic reviews and meta-analyses [15]. This review's protocol was not registered previously to its submission.

Search strategies

A systematic search of the literature was conducted using four electronic databases (PubMed, MEDLINE, Scopus, and Web of Science) from inception up to 14 January 2020. The following combination of search criteria was used: 'osteoarthritis' AND 'pain' AND ('depression' OR 'anxiety').

Eligibility criteria

Articles were included when fulfilling the following criteria: (i) studies performed in clinically diagnosed OA patients, based on the ACR criteria or a combination of clinical and radiological data; (ii) evaluation of pain severity; and (iii) anxious and/or depressive symptomatology using clinically tested and validated scales or (iv) the correlation between these parameters. Exclusion criteria included: (i) non-original articles; (ii) studies performed in animal models; (iii) reports written in a language other than English; (iv) studies with categorical outcome variables; (v) studies evaluating changes in pain and emotions after primary arthroplasty or (vi) in a rheumatic population that did not discriminate an osteoarthritic group.

Study selection

After the removal of duplicates, every study was individually assessed using the inclusion and exclusion criteria to determine eligibility for inclusion in the systematic review and meta-analysis. Publications were first screened based on titles and abstracts, and afterwards the full text was examined. Four researchers carried out the study selection, and disagreements at any stage were resolved through discussion between authors or by consultation with FPR.

Outcome measures

The main outcomes measured were (i) pain severity, (ii) anxious or depressive symptomatology severity and (iii) correlation values between these measures. When outcomes were measured at different time points, only the baseline values were considered.

Data extraction and management

Detailed data were extracted from each study and compiled in a Microsoft Excel spreadsheet by all authors, including the following information: (i) name of the article, (ii) author's names, (iii) year of publication, (iv) the country in which the study took place, (v) study design, (vi) joint(s) affected, (vii) sample size, (viii) participant characteristics (age, gender and BMI) and (iv) outcome measures of pain, depression and anxiety severity (the scale used, range and severity). Results from studies that used the same scale to evaluate the main outcomes were grouped for the calculation of weighted averages.

The meta-analysis was performed using the RevMan 5.3 software. The Pearson correlation coefficients (r) between pain and anxiety severity and/or depressive severity were collected and converted to Fisher-Z values according to the following equation: $Z = 0.5[\ln(1+r) - \ln(1-r)]$. Their respective standard deviations were calculated according to the following equation: $SD = \frac{1}{\sqrt{n-3}}$. The results reported in this work were reconverted to

Pearson correlation coefficients (r) using the equation: $r = \frac{1-e^{-2z}}{1+e^{-2z}}$.

Whenever this data was unavailable, we contacted the authors by email. Taking into account the heterogeneity between studies, a random-effects model was used to aggregate data to promote the generality of the results, as well as a subgroup analysis for the scale used to assess the main outcomes (anxiety/depression).

A leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm that our findings were not driven by any single study.

Assessment of quality

The risk of bias was not assessed, as this review was comprised of different types of studies. The Critical Appraisal Skills Programme (CASP) checklist [16] was used to systematically assess the quality of the randomized controlled trial (RCT) studies included herein. For the appraisal of observational studies (cross-sectional and cohort), the Newcastle–Ottawa Assessment Scale (NOS) [17] was used.

Results

Search results and inclusion

A total of 4474 publication references were initially retrieved. After the removal of 2229 duplicates, 2245 publications were screened based on titles and abstracts, and 279 publications were identified as potentially eligible. After checking the full text for detailed information and data extraction, 121 publications were included in this review and 39 were included in the meta-analysis [18–138]. An additional four articles were excluded as we were informed by the authors they contained duplicate data from others included in this systematic review [139–142]. The summary of the screening process is presented in Fig. 1.

Quality of studies

The Critical Appraisal Skills Programme (CASP) checklist was used to systematically assess the quality of the RCT studies (see Supplementary Table S1, available at *Rheumatology* online). Out of a total of 24 RCT articles, 18 (75%) of the studies were considered good and 6 (25%) of medium quality. All studies addressed a focused issue, and 20 referred to the randomization process used in the assignment of patients to each treatment. In 5 studies, the total sample of patients included was not accounted for upon its conclusion, and all studies treated the groups equally aside from the experimental intervention. The groups were similar at the start of the trial in 19 studies, and in 12 trials the patients, health workers and study personnel were blind to treatment. It was uncertain whether the results could be applied to the local population in 6 studies and if all clinically important outcomes were considered in 3 trials. Only 8 trials appeared to propose an intervention whose benefits surpassed the side effects.

The quality appraisal of observational studies was performed using the Newcastle–Ottawa Assessment Scale (NOS), for a total of 36 cross-sectional and 61 cohort studies (see Supplementary Table S2, available at *Rheumatology* online). Out of a total of 97 articles, 61 were considered of high quality and 36 of medium quality. In 87 studies, the exposed cohort was truly or somewhat representative of the OA population; however, only 14 articles provided a justified and satisfactory justification for the sample size required and used. In all articles, OA diagnosis was performed through secure records or structured interviews, and the outcomes were evaluated through an independent blind assessment. Of the 97 articles, 82 studies controlled for age/sex and 55 for additional factors (e.g. BMI, education and comorbidities). Follow-up was performed in 37 studies, of which in 32 the follow-up time was $\geq$6 months, and in 29 the follow-up rate was $\geq$80%.

Description of the included studies

Approximately 32.8% of the included studies were performed in the USA. The remaining studies comprised a wide range of countries, including Canada (16.0%), the UK (11.2%) and Turkey (8.0%). Regarding study design, 47.2% were cohort studies, 27.2% were cross-sectional studies and 20.8% were RCTs. The description of the studies is presented in Table 1.

Participants

A total of 38 085 patients were included in our analysis. Overall, ~62.8% of the participants were women and 37.2% were men. Six articles did not include data regarding the gender of the participants and were not included in this calculation.

The weighted age average of the participants was 64.3 years old. Six articles did not include data regarding the age of the participants, and seven studies provided only the median value for age and were thus not included in the average age calculation. The weighted BMI average was 28.2 kg/m^2. Forty-eight studies were excluded from the BMI average calculation for not stating the participants' BMI or for providing only the median value.

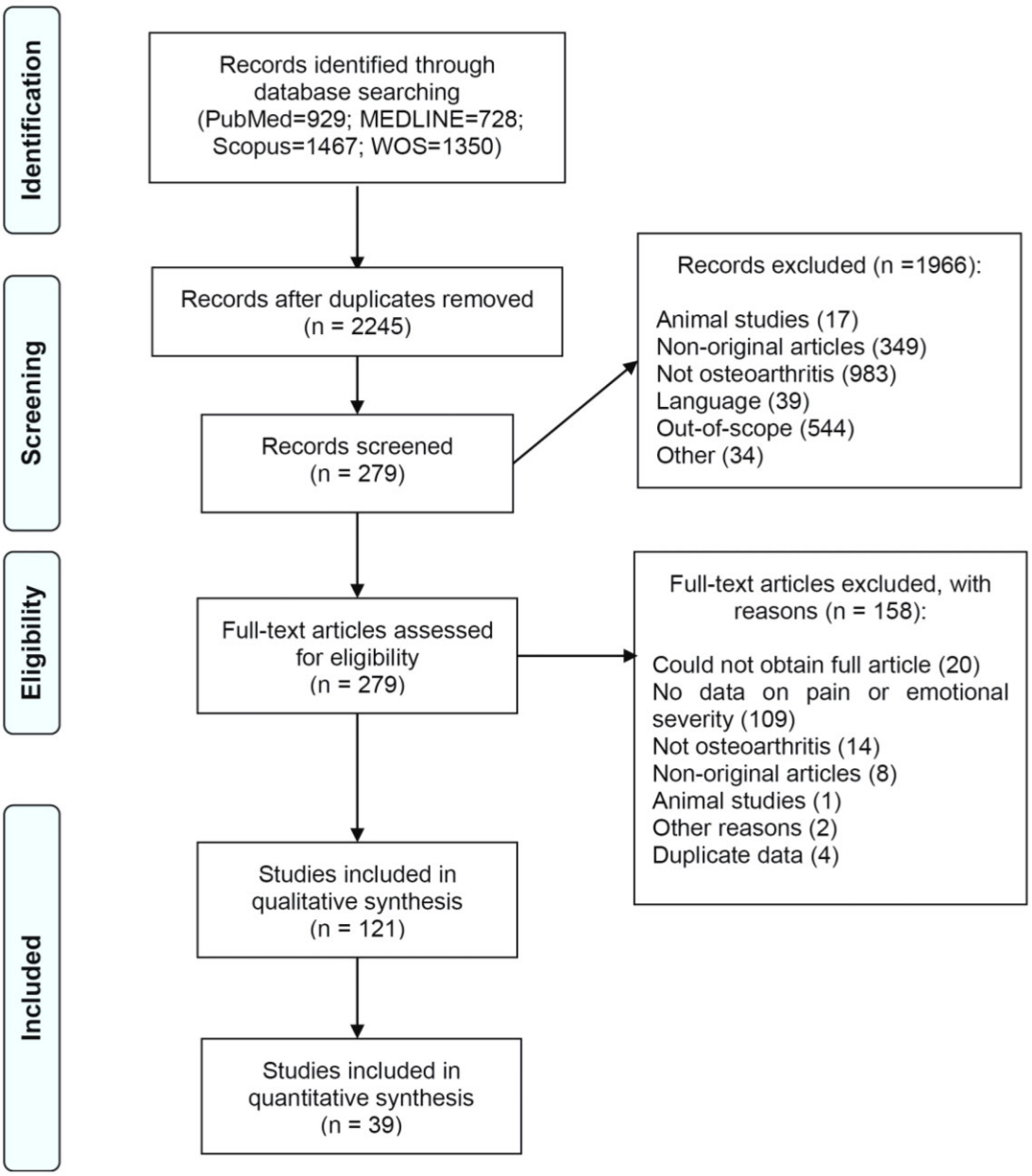
The most frequently affected joint was the knee (64.0%), and, in the remaining cases, the other joints affected included the hip, shoulder, wrist, hand or ankle. In some cases, multiple joints were affected simultaneously.

Assessment of pain severity

To be able to assess and compare the mean values obtained from different scales, we normalized the pain severity data to a range of 0–100 (see Table 2).

The most frequently applied scale used to assess pain severity was the WOMAC Pain subscale, which was used in ~57.8% of studies. The scale range varied between studies, namely from 0–20 to 0–500. After normalization to a range of 0–100, the weighted average

Fig. 1 Flowchart representing the different stages of the selection process



was 40.5 out of 100. Five articles provided the median value and were not included in this calculation.

The Visual Analogue Scale (VAS), a continuous scale range of 0–10 or 0–100, was used in 23.1% of studies. To enable comparison between the results of different reports, data were normalized to a range of 0–100, and the weighted average of pain severity obtained was 38.3 out of 100. One study provided the median value and was not included in this estimate. The Numeric Pain Rating Scale (NRS), ranging from 0 to 10 or 0 to 100, was used in 12.4% of studies, and the normalized pain severity was 58.8 out of 100. One study provided the median value and was not included in this calculation. The Knee injury and Osteoarthritis Outcome Score (KOOS) and Hip dysfunction and Osteoarthritis Outcome Score (HOOS) were used in nine articles, ranging from 0–4 or 0–100, where lower scores indicate more severe pain. After normalization, the weighted mean pain severity value was 51.0 out of 100. The Brief Pain Inventory (BPI), with a range of 0–10, was used in seven studies, and the normalized weighted average of pain intensity obtained with this tool was 48.6 out of 100. The McGill Pain Questionnaire (MPQ) was applied in seven studies, with a range of 0–100, 0–45 or 0–78. After normalizing

Table 1 Characterization of the studies included in the systematic review

Study	Country	Design	Joint(s)	Participants					
				Population	OA diagnosis criteria	Sample	Gender (M/F)	Age	BMI
Strath *et al*., 2020 [19]	USA	RCT	Knee	Clinical cohort	ACR	21	9/12	68.7 (7.1)	26.9 (3.0)
Kilink *et al*., 2019 [45]	Turkey	Cross-sectional	Knee	Clinical cohort	ACR criteria	200	80/120	53.2 (6.0)	27.2 (4.1)
Chen *et al*., 2019 [20]	China	Longitudinal	Knee	Scheduled for IAHA	Clinical/radiological	102	28/74		
Koh *et al*., 2019 [31]	South Korea	RCT	Knee	Scheduled arthroplasty	Clinical/radiological	80	11/69	68.8 (7.6)	
Lenguerrand *et al*., 2019 [44]	UK	RCT	Knee	Scheduled arthroplasty	Clinical/radiological	180	81/99	69 (9)	
Zheng *et al*., 2019 [84]	Australia	RCT	Knee	Clinical cohort	ACR criteria	413	205/208	63.2 (3.6)	29.6 (2.1)
Ahn and Ham, 2019a [18]	South Korea	RCT	Multiple	Clinical cohort	Clinical/radiological	87	10/77	71.3	
Rajapakshe *et al*., 2019 [128]	Canada	Cohort	Ankle	Scheduled arthroplasty	Clinical/radiological	89	35/4		
Ahn *et al*., 2019b [42]	USA	Open label	Knee	Clinical cohort	ACR criteria	20	5/15	61.2 (7.2)	28.3 (8.1)
Akintayo *et al*., 2019 [106]	Nigeria	Cross-sectional	Knee	Clinical cohort	ACR criteria	250	41/109	59.9 (10.6)	30.8 (5.48)
Karp *et al*., 2019 [62]	USA	RCT	Knee	Clinical cohort	Clinical/radiological	99	38/61	71.0 (7.6)	31.49 (8.5)
Gay *et al*., 2019 [95]	France	RCT	Knee	Clinical cohort	ACR criteria	123	22/101	68.1 (6.8)	28.9 (5.1)
Tolk *et al*., 2019 [51]	The Netherlands	Cross-sectional	Knee	Scheduled arthroplasty	Clinical/radiological	204	82/122	68.6 (9.3)	29.0 (5.0)
Aree-Ue *et al*., 2019 [117]	Thailand	Cross-sectional	Knee	Clinical cohort	ACR criteria	200	28/172	71.9 (6.8)	24.6 (4.1)
Power *et al*., 2019 [46]	Canada	Longitudinal	Multiple	Scheduled arthroplasty	Clinical/radiological	747	333/414	65.1 (9.1)	29.5 (6.0)
Perruccio *et al*., 2019 [73]	Canada	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	477	196/279	65.4 (8.9)	30.7 (6.3)
Hasset *et al*., 2018 [55]	USA	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	1448	680/768	62.1 (12.0)	
Nur *et al*., 2018 [57]	Turkey	Cross-sectional	Knee	Clinical cohort	ACR criteria	110	0/110	60.6 (6.1)	31.0 (4.5)
Kornilov *et al*., 2018 [50]	Russia	Longitudinal	Knee	Scheduled arthroplasty	Clinical/radiological	79	4/75	63 (8)	
Hayashi *et al*., 2018 [48]	Japan	Longitudinal	Hip, knee	Scheduled arthroplasty	Clinical/radiological	72	13/59	68.9 (9.6)	24.8 (3.9)
O'moore *et al*., 2018 [47]	Australia	RCT	Knee	Clinical cohort	ACR criteria	69	14/55	59.3 (6.6)	
Power *et al*., 2018 [49]	Canada	Cross-sectional	Hip, knee	Scheduled arthroplasty	Clinical/radiological	843	481/362	65.1 (9.2)	
Yakobov *et al*., 2018 [53]	UK	Longitudinal	Knee	Scheduled arthroplasty	Clinical/radiological	110	41/69	66.9 (8.4)	31.0 (5.0)
Ozkuk *et al*., 2018 [54]	Turkey	RCT	Multiple	Clinical cohort	Clinical/radiological	150	48/102	69.2 (3.6)	29.2 (4.4)
de Koning *et al*., 2018 [56]	Europe	Cohort	Multiple	Clinical cohort	ACR criteria	832	248/584		[a]27.8
Luna *et al*., 2017 [61]	Denmark	Longitudinal	Knee	Scheduled arthroplasty	Clinical/radiological	60	23/37	67 (6)	29.0 (4.9)
Uslu Güvendi *et al*., 2018 [52]	Turkey	RCT	Knee	Clinical cohort	ACR criteria	50	4/56	61.9 (1.5)	31.2 (0.9)
Riddle *et al*., 2017 [58]	USA	Cross-sectional	Knee	Scheduled arthroplasty	Clinical/radiological	384	107/277	63.2 (8.0)	
El Monaem *et al*., 2017 [59]	Egypt	Cohort	Knee	Clinical cohort	ACR criteria	200	40/160	51.9 (7.8)	22.3 (1.2)
Ahn *et al*., 2017 [66]	USA	Cohort	Knee	Clinical cohort	Clinical/radiological	100	38/62	55 (8)	26.4 (4.5)
Tang *et al*., 2017 [68]	USA	Cross-sectional	Multiple	Clinical cohort	Clinical/radiological	367	79/288	72.9 (8.2)	
Lee *et al*., 2017 [60]	USA	Cross-sectional	Knee	Clinical cohort	ACR criteria	80	19/61	60.3 (10.3)	33.0 (7.1)
Marszalek *et al*., 2017 [67]	USA	Cross-sectional	Knee	Clinical cohort	Clinical/radiological	262	81/181	59.8 (10.5)	32.1 (7.4)

(continued)

Table 1 Continued

Study	Country	Design	Joint(s)	Participants					
				Population	OA diagnosis criteria	Sample	Gender (M/F)	Age	BMI
Allen *et al*., 2017 [69]	UK	RCT	Hip, knee	Clinical cohort	ACR criteria	537	397/140	63.3 (9.6)	35.8 (7.4)
Wylde *et al*., 2017 [63]	UK	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	266	97/169		
Askin *et al*., 2017 [70]	USA	Cross-sectional	Knee	Clinical cohort	ACR criteria	60	14/46	56.2 (10.1)	29.82 (4.82)
Hadlandsmyth *et al*., 2017 [64]	USA	Cross-sectional	Knee	Scheduled arthroplasty	Clinical/radiological	346	158/88	62.0 (9.6)	
Shimura *et al*., 2017 [71]	Japan	Cross-sectional	Knee	Clinical cohort	ACR criteria	115	0/115	70.6 (7.5)	24.3 (3.3)
Mallen *et al*., 2017 [65]	UK	RCT	Multiple	Clinical cohort	Clinical/radiological	1412	613/799	65.5 (10.3)	28.6 (3.4)
Pagé *et al*., 2016 [74]	Canada	Longitudinal	Hip	Scheduled arthroplasty	Clinical/radiological	150	79/71	60.0 (9.2)	
Liu *et al*., 2016 [72]	The Netherlands	Cross-sectional	Hand	Clinical cohort	Clinical/radiological	247	30/217	61.6 (8.7)	26.5
Mesci *et al*., 2016 [77]	Turkey	Cross-sectional	Knee	Clinical cohort	ACR criteria	60	14/46	62.9 (10.5)	29.6 (4.9)
Cottam *et al*., 2016 [83]	UK	Cohort	Knee	Clinical cohort	Clinical/radiological	26	12/14	[a]67.5 (54–84)	
Reckziegel *et al*., 2016 [81]	UK	Cross-sectional	Knee	Clinical cohort	Clinical/radiological	14	9/5	64.1 (7.4)	
Hsieh and Lee, 2016 [78]	Taiwan	RCT	Knee	Clinical cohort	ACR criteria	90	20/70	61.5 (10.8)	25.2 (2.7)
Carlesso *et al*., 2016 [79]	Canada	Cohort	Hip, knee	Clinical cohort	Clinical/radiological	462	104/358	76.3 (7.1)	27.8 (5.1)
Waimann *et al*., 2016 [82]	USA	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	212	72/140	65.2 (8.9)	33.1 (6.7)
de Achaval, 2016 [93]	USA	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	236	82/154	65	33 (7)
Lindberg *et al*., 2016	Norway	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	203	64/139	68.2 (9.2)	29.2 (4.8)
Wood *et al*., 2016 [80]	Canada	Cohort	Hip, knee	Scheduled arthroplasty	Clinical/radiological	463	200/263	[a]68 (61–75)	[a]30 (27–34)
Zietek *et al*., 2016 [75]	Poland	Cross-sectional	Multiple	Scheduled arthroplasty	Clinical/radiological	78	30/48	68.3 (9.7)	30.7 (4)
Schroeter *et al*., 2015 [98]	Germany	Cohort	Knee	Clinical cohort	Clinical/radiological	89	42/47	58.9 (11.1)	
Yilmaz *et al*., 2015 [94]	Turkey	RCT	Knee	Clinical cohort	Clinical/radiological	139	0/139	45.7 (5.6)	29.3 (5.2)
Yıldırıım *et al*., 2015 [90]	Turkey	RCT	Knee	Clinical cohort	Clinical/radiological	100	34/66	56.6 (9.8)	30.6 (4.5)
Pagé *et al*., 2015 [87]	Canada	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	173	88/85	62.9 (6.8)	
Mehta *et al*., 2015 [86]	Canada	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	494	171/323	64.9 (10.2)	
Paterson *et al*., 2015 [91]	Australia	Cohort	Knee	OAI Database	Clinical/radiological	1255	544/711	[a]61 (45–77)	[a]30 (23–38)
Driban *et al*., 2015 [89]	USA	Cross-sectional	Knee	Clinical cohort	ACR criteria	204	61/143	60.2 (10.5)	32.8 (7.2)
Mesci *et al*., 2015 [97]	Turkey	Cohort	Knee	Clinical cohort	Clinical/radiological	55	22/33	71.2 (5.2)	28.0 (4.2)
Parmelee *et al*., 2015 [88]	USA	Cohort	Knee	Clinical cohort	Clinical/radiological	367	133/234	67.9 (9.7)	
Chen *et al*., 2015 [96]	Taiwan	Cross-sectional	Multiple	Clinical cohort	Clinical/radiological	192	54/138	[a]70 (42–89)	
Zullig *et al*., 2015 [92]	USA	Cross-sectional	Hip, knee	Clinical cohort	ACR criteria	300	272/78	61.1 (9.2)	33.8 (5.8)
Riddle et al., 2015 [85]	USA	Cohort	Knee	OAI Database with scheduled arthroplasty	Clinical/radiological	254	100/154	67.9 (8.6)	30.0 (4.6)
Goode *et al*., 2014 [101]	USA	Cross-sectional	Multiple	Clinical cohort	Clinical/radiological	1602	525/1077	67.9 (9.0)	31.5 (7.1)
Marcum *et al*., 2014 [99]	USA	Cross-sectional	Knee	Clinical cohort	ACR criteria	190	161/29	66.6 (9.4)	32.4 (6.5)
Kim *et al*., 2014 [103]	South Korea	RCT	Knee	Clinical cohort	ACR criteria	212	33/179	[a]57 (51–62)	24.2 (28)
Sinikallio *et al*., 2014 [102]	Finland	Case–control	Knee	Clinical cohort	Clinical/radiological	111	34/77	63.6 (7.2)	30.0 (6.2)

(continued)

Table 1 Continued

Study	Country	Design	Joint(s)	Participants					
				Population	OA diagnosis criteria	Sample	Gender (M/F)	Age	BMI
Brown *et al*., 2014 [100]	UK	Cross-sectional	Multiple	Clinical cohort	ACR criteria	16		55.0 (8.7)	
Holla *et al*., 2013 [105]	The Netherlands	Cross-sectional	Knee	AOC Database	ACR criteria	294	106/188	61.1 (7.4)	29.2 (5.5)
Weiner *et al*., 2013 [110]	USA	RCT	Knee	Clinical cohort	ACR criteria	190	29/161	66.6 (9.3)	32.4 (6.5)
French *et al*., 2013 [107]	Ireland	RCT	Hip	Clinical cohort	ACR criteria	131	49/84	61.9 (9.9)	
Hochman *et al*., 2013 [111]	Canada	Cohort	Knee	Clinical cohort	Clinical/radiological	36	6/30	60.7 (6.8)	[a]29
McHugh *et al*., 2013 [112]	UK	Cohort	Hip	Scheduled arthroplasty	Clinical/radiological	206	88/118	66.3 (10.4)	27.2 (5.3)
Goodin *et al*., 2013 [108]	USA	Cohort	Knee	Clinical cohort	ACR criteria	140	36/104	56.7 (7.2)	
Gignac *et al*., 2013 [104]	Canada	Cohort	Multiple	Clinical cohort	Clinical/radiological	177	54/123		
Hirschmann *et al*., 2013 [109]	Switzerland	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	110	46/58	70 (11)	29 (6)
Steigerwald *et al*., 2012 [115]	Spain	Open label	Knee	Clinical cohort	ACR criteria	200	65/135	67.4 (10.8)	31.9 (5.9)
Perruccio *et al*., 2012 [113]	Canada	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	494	171/323	64.9	
White *et al*., 2012 [116]	USA	Cross-sectional	Knee	MOST Database	Clinical/radiological	1018	407/611	63.1 (7.8)	31.7 (6.3)
Wylde *et al*., 2012 [118]	UK	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	220	84/136	70 (9)	
Ulus *et al*., 2012 [114]	Turkey	RCT	Knee	Clinical cohort	ACR criteria	40	6/32	60.5 (9.5)	31.3 (4.6)
Hawker *et al*., 2011 [126]	Canada	Cohort	Knee	Clinical cohort	Clinical/radiological	529	114/415	75.4	
Kim *et al*., 2011 [123]	South Korea	Cohort	Knee	Clinical cohort	Clinical/radiological	556	64/492	73.3 (5.6)	25.0 (3.3)
Bearne *et al*., 2011 [122]	UK	RCT	Hip	Clinical cohort	Clinical/radiological	48	14/34	66.0	27.1
Perruccio *et al*., 2011 [121]	Canada	Cohort	Hip, knee	Scheduled arthroplasty	Clinical/radiological	449	180/269	63.5	
Hochman *et al*., 2011 [125]	Canada	Cohort	Knee	Clinical cohort	Clinical/radiological	171	39/132	[a]76 (67–99)	
Riddle *et al*., 2011 [120]	USA	Cohort	Knee	OAI Database	Clinical/radiological	3407	1392/2015	60.6 (9.0)	
Lopez-Olivo *et al*., 2011 [124]	USA	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	241	78/163	65 (9)	
Tonelli *et al*., 2011 [119]	USA	Cohort	Knee	Scheduled arthroplasty	Clinical/radiological	208	70/138	61.8 (9.9)	28.0 (7.2)
Stebbings *et al*., 2010 [133]	UK	Cross-sectional	Hip, knee	Clinical cohort	ACR criteria	103	60/43	66.0 (9.0)	
White *et al*., 2010 [132]	USA	Cross-sectional	Knee	MOST Database	ACR criteria	1801	666/1135	62.7 (8.0)	10.9 (6.0)
Akyol *et al*., 2010 [130]	Turkey	RCT	Knee	Clinical cohort	ACR criteria	40	20/20	57.2 (9.39)	30.7 (4.2)
Riddle *et al*., 2010 [127]	USA	Cohort	Knee	Clinical cohort	Clinical/radiological	283	88/195	63.7	30.5 (6.4)
Gandhi *et al*., 2010 [131]	Canada	Cohort	Hip, knee	Clinical cohort	Clinical/radiological	200	81/119	64.6 (9.5)	28.8 (4.7)
Hawker, *et al*. 2010 [129]	Canada	Cohort	Hip, knee	Clinical cohort	Clinical/radiological	613	137/476	77.8 (6.9)	28.6 (5.8)
Chiou *et al*., 2009 [134]	Taiwan	Cross-sectional	Multiple	Clinical cohort	Clinical/radiological	69	20/49	68.0 (5.5)	
Corsinovi *et al*., 2009 [137]	Italy	RCT	Multiple	Clinical cohort	ACR criteria	111	0/111	78.1 (8.3)	
Morone *et al*., 2009 [136]	USA	Cohort	Knee	Clinical cohort	Clinical/radiological	88	40/48	71.5 (5.4)	
Allen *et al*., 2009 [138]	USA	Cross-sectional	Knee	JCOP Database	Clinical/radiological	1368	486/882	66.6 (10.1)	31.5 (6.8)
Possley *et al*., 2009 [135]	USA	Cohort	Knee	Clinical cohort	Clinical/radiological	105	93/1276	67.1 (8.4)	34.5 (5.9)
Scopaz *et al*., 2009 [21]	USA	Cross-sectional	Knee	Clinical cohort	ACR criteria	182	60/122 591/0	63.9 (8.8)	

(continued)

Table 1 Continued

Study	Country	Design	Joint(s)	Participants					
				Population	OA diagnosis criteria	Sample	Gender (M/F)	Age	BMI
Wang *et al*., 2009 [22]	USA	RCT	Knee	Clinical cohort	ACR criteria	40	10/30	65.0 (7.8	29.9 (4.8)
de Groot *et al*., 2008 [24]	The Netherlands	Cohort	Hip, knee	Scheduled arthroplasty	Clinical/radiological	84	36/48	61.8	29.6 (4.8)
Chen *et al*., 2008 [27]	USA	RCT	Knee	Clinical cohort	ACR criteria	106	30/76	62.8 (9.2)	30.7 (5.1)
Power *et al*., 2008 [25]	Canada	Cohort	Hip, knee	Clinical cohort	Clinical/radiological	46	18/28	72.3 (7.7)	
Sale *et al*., 2008 [26]	Canada	Cross-sectional	Hip, knee	Clinical cohort	Clinical/radiological	1227	299/928	75.1 (7.8)	
Parrish *et al*., 2008 [23]	USA	Cohort	Multiple	Clinical cohort	Clinical/radiological	76	0/76	59.6 (8.1)	
Appelt *et al*., 2007 [32]	USA	Cross-sectional	Hip, knee	Clinical cohort	Clinical/radiological	591	591/0	66.0	
Lange *et al*., 2007 [29]	Australia	Cross-sectional	Knee	Clinical cohort	ACR criteria	41	0/41	63 (9)	33.1 (6.8)
Tsai *et al*., 2007 [30]	China	Cross-sectional	Knee	Clinical cohort	Clinical/radiological	199	63/136	73.4 (5.5)	
Marks, 2007 [33]	USA	Cross-sectional	Knee	Clinical cohort	Clinical/radiological	99	17/82	69.7 (10.1)	29.4 (5.6)
Kalichman *et al*., 2007 [28]	USA	Cohort	Knee	BOKS Database	Clinical/radiological	213	126/87	66.7	31.4
Maly *et al*., 2006 [34]	Canada	Cohort	Knee	Clinical cohort	Clinical/radiological	54	22/32	68.3 (8.7)	28.6 (5.1)
Buszewicz *et al*., 2006 [35]	UK	RCT	Hip, knee	Clinical cohort	Clinical/radiological	812	302/510	68.5 (8.4)	
Sherman *et al*., 2003 [36]	USA	Cohort	Knee	OASIS Database	Clinical/radiological	285	139/146	71.2 (4.6)	
Ibrahim *et al*., 2002 [37]	USA	Cross-sectional	Hip, knee	Clinical cohort	Clinical/radiological	596		65.6 (15.0)	
Creamer *et al*., 2000 [39]	USA	Cohort	Knee	Clinical cohort	ACR criteria	69			31.4 (6.8)
Wilcox *et al*., 2000 [40]	USA	Cohort	Knee	OASIS Database	Clinical/radiological	429	204/225	71.7 (4.9)	29.7 (5.3)
Keefe *et al*., 2000 [38]	USA	Cross-sectional	Knee	Clinical cohort	Clinical/radiological	168	72/96	60.9 (10.7)	
Orbell *et al*., 1998b [41]	UK	Cohort	Hip, knee	Clinical cohort	Clinical/radiological	72	29/43	68.2 (9.0)	
Creamer *et al*., 1998 [43]	USA	Cohort	Knee	Clinical cohort	ACR criteria	58	18/40	65.6 (10.4)	31.8 (6.8)

Results presented as mean (S.D.) or [a]median (range). **AOC**: Amsterdam Osteoarthritis Cohort; **BOKS**: Boston Osteoarthritis of the Knee Study; **JCOP**: Johnston County Osteoarthritis Project; **MOST**: Multicentre Osteoarthritis Study; **OAI**: OA Initiative; **OASIS**: OA Study in Seniors; **RCT**: randomized controlled trial.

Table 2 Outcome measures

Article	Pain scale	Results (0-100)	Anxiety scale	Results	MA	Depression scale	Results	MA
Strath *et al*., 2020 [19]	BPI	91.0 (58.7)				QIDS (0–27)	1.86 (1.07)	$r = 0.253$
	KOOS	80.7 (13.5)						
Kilink *et al*., 2019 [45]	OKS	50.2 (16.8)				BDI (0–63)	11.6 (1.07)	$r = 0.377$
Chen *et al*., 2019 [20]	WOMAC	22.6 (19.9)	STAI (20–80)	20.2 (9.9)	$r = 0.329$	GDS (0–15)	2.75 (2.56)	$r = 0.305$
Koh *et al*., 2019 [31]	BPI	66.5 (9.5)				HAM-D (0–20)	3.1 (2.7)	
	ICOAP	127 (27)						
Lenguerrand *et al*., 2019 [44]	KOOS	39 (20)	HADS (0–21)	[a]6 (3–10)		HADS (0–21)	6 (4–9)	
Zheng *et al*., 2019 [84]	WOMAC	27.3 (17.2)				PHQ-9 (0–27)	3.2 (4.1)	
Ahn and Ham, 2019a [18]	WOMAC	32.5 (18.3)				CES-D (0–60)	19.6 (9.1)	
Rajapakshe *et al*., 2019 [128]	VAS	65.4 (18.8)				PHQ-9 (0–27)	6.1 (5.7)	$r = 0.482$
	AOS	60.5 (19.7)						
	PEG	58 (2.5)						
Ahn *et al*., 2019b [42]	WOMAC	55.2 (25.4)	PROMIS (7–35)	13.5		PROMIS (8–40)	12.3 (7.69)	
	VAS	39.8 (22.0)						
Akintayo *et al*., 2019 [106]	WOMAC	44.2 (19.3)				PHQ-9 (0–27)	4.7 (4.2)	
Karp *et al*., 2019 [62]	NRS	95.2 (41.0)	GAD-7 (0–21)	3.17 (2.68)		PHQ-9 (0–27)	5.6 (2.1)	
Gay *et al*., 2019 [95]	NRS	49.6 (19.9)	HADS (0–21)	8.5 (3.5)	$r = 0.159$	HADS (0–21)	5.8 (3)	$r = 0.038$
	NRS	49.0 (24.0)						
Tolk *et al*., 2019 [51]	OKS	63.2 (10.5)	HADS (0–21)	4.2 (3.3)	$r = 0.085$	HADS (0–21)	4.1 (3.1)	$r = 0.176$
	OKS	63.2 (10.5)						
Aree-Ue *et al*., 2019 [117]	NRS	27.0 (19.7)				GDS (0–15)	4.19 (2.9)	$r = 0.18$
Power *et al*., 2019 [46]	WOMAC	50.9 (16.9)				HADS (0–100)	25.4 (17.0)	
Perruccio *et al*., 2019 [73]	KOOS	56.5 (17.2)			$r = 0.341$	HADS (0–21)	5.0 (2.7)	$r = 0.416$
Hasset *et al*., 2018 [55]	BPI	48.0 (20.6)	HADS (0–21)	5.4 (3.83)		HADS (0–21)	4.8 (3.4)	
Nur *et al*., 2018 [57]	VAS	49.0 (19.0)	HADS (0–21)	7.9 (4.5)		HADS (0–21)	6.9 (3.9)	
Kornilov *et al*., 2018 [50]	BPI	50.0 (20.0)	HADS (0–21)	8.0 (4.0)	$r = 0.242$	HADS (0–21)	6.0 (4.0)	$r = 0.238$
Hayashi *et al*., 2018 [48]	VAS	36.4 (21.1)	HADS (0–21)	5.6 (3.6)	$r = 0.254$	HADS (0–21)	5.6 (3.4)	$r = 0.408$
O'moore *et al*., 2018 [47]	WOMAC	48.6 (18.6)				PHQ-9 (0–27)	13.5 (4.8)	
Power *et al*., 2018 [49]	WOMAC	45.1 (23.1)				HADS (0–100)	25.0 (17.5)	
Yakobov *et al*., 2018 [53]	WOMAC	53.0 (16.5)				PHQ-9 (0–27)	6.8 (7.0)	$r = 0.31$
Ozkuk *et al*., 2018 [54]	VAS	72.9 (16.4)	STAI (20–80)	46.0 (8.7)	$r = 0.285$			
de Koning *et al*., 2018 [56]	WOMAC	[a]15 (10–25)	HADS (0–21)	[a]4 (2–7)		HADS (0–21)	[a]4 (2–7)	
Luna *et al*., 2017 [61]	KOOS	65.0 (16.0)	HADS (0–21)	[a]1 (0–4)		HADS (0–21)	[a]1 (0–4)	
Uslu Güvendi *et al*., 2018 [52]	WOMAC	59.8 (4.5)	HADS (0–21)	5.5 (1.0)		HADS (0–21)	5.5 (1.0)	
Riddle *et al*., 2017 [58]	WOMAC	57.0 (16.8)	GAD-7 (0–21)	5.4 (4.9)	$r = 0.258$	PHQ-8 (0–24)	5.9 (4.9)	$r = 0.291$
El Monaem *et al*., 2017 [59]	WOMAC	78.8 (26.5)				BDI (0–63)	12.8 (12.2)	
	NRS	64.0 (13.3)						
Ahn *et al*., 2017 [66]	WOMAC	31.9 (17.7)				CES-D (0–60)	7.0 (8.7)	$r = 0.54$
	GCPS	45.5 (16.9)						
Tang *et al*., 2017 [68]	GCPS	43.0 (15.0)				CES-D (0–60)	6.7 (5.1)	

(continued)

Table 2 Continued

Article	Pain scale	Results (0-100)	Anxiety scale	Results	MA	Depression scale	Results	MA
Lee *et al*., 2017 [60]	WOMAC	51.9 (19.8)				BDI (0–63)	7.5 (8.5)	
Marszalek *et al*., 2017 [67]	WOMAC	52.2 (19.9)	PROMIS (36–82)	50.1 (8.8)		BDI (0–63)	7.9 (9.1)	
Allen *et al*., 2017 [69]	WOMAC	40.2 (17.7)				PHQ-8 (0–24)	4.6 (4.4)	
Wylde *et al*., 2017 [63]	WOMAC	[a]40 (30–55)	HADS (0–21)	[a]6 (3–9)		HADS (0–21)	[a]5 (3–8)	
	AKSS	[a]40 (31–49)						
Askin *et al*., 2017 [70]	WOMAC	55.4	HADS (0–21)	7.9 (4.1)	$r = 0.479$	HADS (0–21)	9.3 (5.0)	$r = 0.309$
	VAS	53.8						
Hadlandsmyth *et al*., 2017 [64]	NRS	[a]20 (0–50)	STAI (20–80)	[a]33 (26–40)	$r = 0.66$			
Shimura *et al*., 2017 [71]	VAS	52.4 (24.1)				SDS	39.0 (8.3)	$r = 0.22$
	JKOM	45.9 (20.6)						$r = 0.19$
Mallen *et al*., 2017 [65]	NRS	65.1 (21.4)	GAD-7 (0–21)	5.3 (5.7)	$r = 0.35$	PHQ-8	6.1 (6.0)	$r = 0.36$
	GCPS	65.6 (19.4)						
Pagé *et al*., 2016 [74]	WOMAC	46.5 (17.0)	HADS (0–21)	5.6 (3.9)		HADS (0–21)	4.3 (3)	
	PDI	45.1 (20.4)						
Liu *et al*., 2016 [72]	MPQ	43.2 (19.2)	HADS (0–21)	4		HADS (0–21)	2	
Mesci *et al*., 2016 [77]	WOMAC	53.3 (20.2)	HADS (0–21)	7.7 (4.6)		HADS (0–21)	6.3 (3.6)	
	VAS	61.0 (19.0)						
Cottam *et al*., 2016 [83]	VAS	40.2	STAI (20–80)	41.4	$r = 0.392$	BDI (0–63)	7.8	$r = 0.252$
Reckziegel *et al*., 2016 [81]	VAS	29.0 (28.4)	STAI (20–80)	32.2 (9.1)		BDI (0–63)	6.5 (5)	
Hsieh and Lee, 2016 [78]	KOOS	39.1 (16.8)	HADS (0–21)	7.3 (3.8)		HADS (0–21)	7.6 (3.0)	
Carlesso *et al*., 2016 [79]	WOMAC	47.5 (19.8)	HADS (0–21)	3.7 (2.7)	$r = 0.27$	CES-D	11.5 (8.5)	$r = 0.54$
Waimann *et al*., 2016 [82]	WOMAC	54.0 (19.0)	DASS21 (0–21)	3.2 (5.1)		DASS21 (0–21)	3.8 (5.5)	
de Achaval *et al*., 2016 [93]	WOMAC	55.0 (19.0)	DASS21 (0–21)	3 (5)		DASS21 (0–21)	4 (6)	
Lindberg *et al*., 2016	BPI	55.0 (21.0)	HADS (0–21)	4.6 (3.5)		HADS (0–21)	3.5 (3.1)	
Wood *et al*., 2016 [80]	VAS	[a]60 (40–80)	HADS (0–21)	[a]5 (3–8)		HADS (0–21)	[a]6 (3–9)	
Zietek *et al*., 2016 [75]	VAS	30.0 (1.0)	STAI (20–80)					
Schroeter *et al*., 2015 [98]	VAS	60.3 (20.1)				HADS (0–21)	8 (4)	
Yilmaz *et al*., 2015 [94]	VAS	68.1 (27.6)				BDI (0–63)	3.0 (9.4)	$r = 0.52$
Yıldırım *et al*., 2015 [90]	WOMAC	57.0 (21.5)				BDI (0–63)	13.6 (8.9)	
	VAS	24.3 (22.5)						
Pagé *et al*., 2015 [87]	WOMAC	58.5 (20.9)	HADS (0–21)	5.9 (3.5)		HADS (0–21)	4.3 (2.6)	
Mehta *et al*., 2015 [86]	KOOS	41.0 (16.3)				HADS (0–21)	5.3 (3.5)	
Paterson *et al*., 2015 [91]	WOMAC	[a]50 (0–55)				CES-D (0–60)	[a]5 (0–15)	$r = 0.246$
Driban *et al*., 2015 [89]	WOMAC	50.8 (19.7)	PROMIS (36–82)	50.2 (8.9)	$r = 0.20$	BDI	7.6 (8.6)	
						PROMIS (36–82)	48.9 (8.9)	$r = 0.19$
Mesci *et al*., 2015 [97]	WOMAC	60.3 (21.0)				BDI (0–63)	12.9 (7.4)	
	VAS	49.0 (29.5)						
Parmelee *et al*., 2015 [88]	GCPS	48.5 (18.0)				CES-D	9.7 (9.3)	
Chen *et al*., 2015 [96]	WOMAC	[a]21.5 (1.4–84.4)	HADS (0–21)	[a]4 (0–16)		HADS (0–21)	[a]5 (0–16)	
Zullig *et al*., 2015 [92]	WOMAC	51.0 (20.0)				PHQ-8 (0–24)	6.8 (5.4)	
Riddle *et al*., 2015 [85]	KOOS	55.5 (18.2)				CES-D (0–60)	7.3 (6.9)	

(continued)

Table 2 Continued

Article	Pain scale	Results (0-100)	Anxiety scale	Results	MA	Depression scale	Results	MA
Goode *et al.*, 2014 [101]	PPT (Dolorimeter)	90.0 (17.5)				CES-D (0–60)	6.5 (7.4)	
Marcum *et al.*, 2014 [99]	WOMAC	49.5 (17.5)				CES-D (0–60)	12.9 (10.4)	
Kim *et al.*, 2014 [103]	WOMAC	35.4 (18.2)				BDI (0–63)	9.8 (7.2)	
	NRS	57.4 (13.6)						
Sinikallio *et al.*, 2014 [102]	WOMAC	57.0 (13.4)	BAI	8.1 (6.0		BDI (0–63)	5.9 (4.8)	
	NRS	65.0 (17.0)						
Brown *et al.*, 2014 [100]	VAS	41.0 (22.0)	HADS (0–21)	7.5 (3.7		HADS (0–21)	4.3 (3.7)	
Holla *et al.*, 2013 [105]	NRS	50.0 (22.0)				HADS (0–21)	[a]3 (1–6)	
Weiner *et al.*, 2013 [110]	WOMAC	48.7 (17.5)				CES-D (0–60)	12.9 (20.1)	
French *et al.*, 2013 [107]	NRS	57.6 (25.4)	HADS (0–21)	6.1 (4.1	$r = 0.440$	HADS (0–21)	4.7 (3.2)	$r = 0.467$
Hochman *et al.*, 2013 [111]	WOMAC	41.0 (21.0)				CES-D (0–60)	[a]6 (0–44)	
McHugh *et al.*, 2013 [112]	WOMAC	57.0 (18.5)	HADS (0–21)	7.6 (3.6		HADS (0–21)	7.4 (3.9)	
Goodin *et al.*, 2013 [108]	WOMAC	36.5 (22.5)				CES-D (0–60)	9.2 (6.9)	$r = 0.42$
Gignac *et al.*, 2013 [104]	VAS	60.5 (23.5)				CES-D (0–60)	14.5 (13.5)	$r = 0.447$
Hirschmann *et al.*, 2013 [109]	WOMAC	55 (24)	STAI (20–80)	34.5 (9.5	$r = 0.19$	BDI	7.0 (5.0)	$r = 0.26$
			SCL-90 (0–5)	2.9 (4.2	$r = 0.15$	SCL-90 (0–5)	4.9 (7.0)	$r = 0.17$
Steigerwald *et al.*, 2012 [115]	WOMAC	55.0 (15.6)	HADS (0–21)	6.7 (4.1		HADS (0–21)	7.0 (3.7)	
Perruccio *et al.*, 2012 [113]	WOMAC	52.5 (18.0)	HADS (0–21)	6.5 (4.0	$r = 0.291$	HADS (0–21)	5.3 (3.5)	$r = 0.404$
White *et al.*, 2012 [116]	VAS	23.7 (22.4)				CES-D (0–60)	6.6 (6.8)	
Wylde *et al.*, 2012 [118]	WOMAC	57 (18)	HADS (0–21)	6 (4		HADS (0–21)	5 (3)	
Ulus *et al.*, 2012 [114]	WOMAC	75.9 (16.1)	HADS (0–21)	8.8 (4.5		HADS (0–21)	7.4 (5.4)	
	VAS	48.0 (21.1)						
Hawker *et al.*, 2011 [126]	WOMAC	40.2 (21.1)				CES-D (0–60)	9.1 (6.9)	$r = 0.482$
Kim *et al.*, 2011 [123]	WOMAC	57.0 (21.0)				GDS (0–15)	10.4 (6.9)	
Bearne *et al.*, 2011 [122]	WOMAC	79.0 (53.7)	HADS (0–21)	4.6 (2.6		HADS (0–21)	3.0 (2.6)	
Perruccio *et al.*, 2011 [121]	HOOS/KOOS	58.9 (17.09)	HADS (0–100)	30.3 (18.5	$r = 0.257$	HADS (0–100)	25.5 (16.7)	$r = 0.377$
Hochman *et al.*, 2011 [125]	WOMAC	50.5 (18.5)				CES-D (0–60)	[a]9.0 (0–41)	
Riddle *et al.*, 2011 [120]	WOMAC	21.4 (18.8)				CES-D (0–60)	7.1 (7.3)	
Lopez-Olivo *et al.*, 2011 [124]	WOMAC	55.1 (18.1)	DASS21 (0–21)	3.9 (5.8		DASS21 (0–21)	3.9 (5.8)	
Tonelli *et al.*, 2011 [119]	BPI	50.7 (18.0)	STAI (20–80)	34.2 (10.0				
	KOOS	49.8 (19.8)						
	SF-36	38.5 (20.0)						
Stebbings *et al.*, 2010 [133]	VAS	63.8 (22.0)	HADS (0–21)	5.7 (3.7		HADS (0–21)	5.5 (3.3)	
White *et al.*, 2010 [132]	VAS	30.0 (22.0)				CES-D (0–60)	8.0 (7.7)	
Akyol *et al.*, 2010 [130]	WOMAC	57.9 (17.3)				BDI (0–63)	9.0 (5.0)	
	VAS	73.8 (20.4)						
Riddle *et al.*, 2010 [127]	WOMAC	51.6 (19.7)				PHQ-8	6.3 (5.0)	
Gandhi *et al.*, 2010 [131]	WOMAC	48.2 (20.5)	HADS (0–21)	6.4 (4.0	$r = 0.29$	HADS (0–21)	5.2 (3.4)	$r = 0.35$
Hawker *et al.*, 2010 [129]	WOMAC	45.1 (19.7)				CES-D (0–60)	11.4 (8.6)	
Chiou *et al.*, 2009 [134]	VAS	39.5 (28.8)				GDS (0–15)	6.7 (4.4)	$r = 0.218$
Corsinovi *et al.*, 2009 [137]	NRS	76.1 (13.7				BDI (0–63)	19.3 (4.5)	

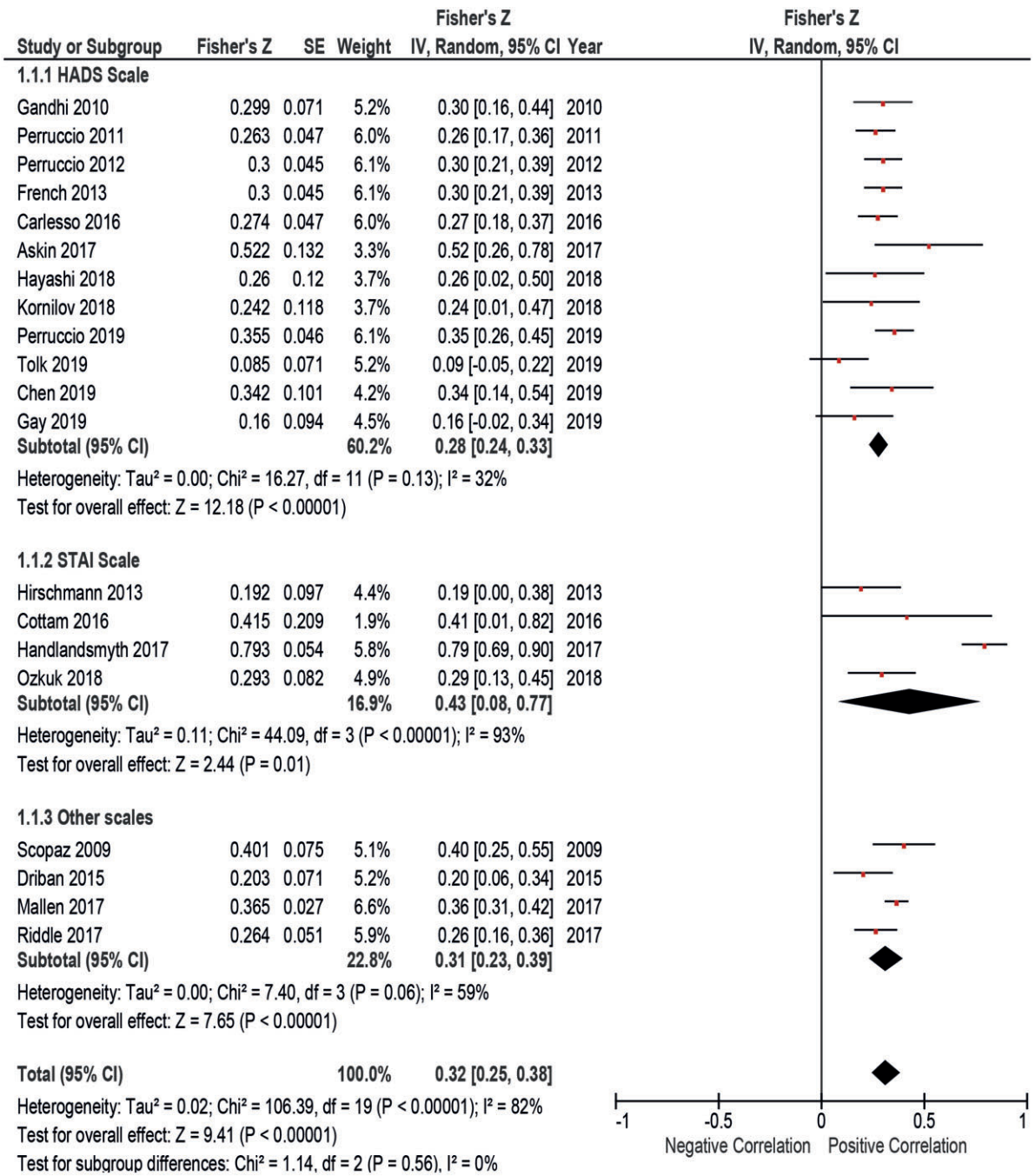
(continued)

Table 2 Continued

Article	Pain scale	Results (0-100)	Anxiety scale	Results	MA	Depression scale	Results	MA
Morone *et al*., 2009 [136]	VAS	24.4 (22.2)				GDS (0–15)	3.26 (3.8)	
	MPQ	27.3 (18.5)						
Allen *et al*., 2009 [138]	WOMAC	25.8 (24.3)				CES-D (0–60)	3.8 (7.6)	
Possley *et al*., 2009 [135]	WOMAC	61.5 (17.5)				CES-D (0–60)	15.4 (9.5)	$r = 0.43$
Scopaz *et al*., 2009 [21]	NRS	45.3 (25.1)	BAI (0–63)	4.73 (5.46	$r = 0.0.381$	CES-D (0–60)	7.30 (7.38)	$r = 0.187$
Wang *et al*., 2009 [22]	WOMAC	43.0 (16.3)				CES-D (0-60)	11.5 (10.6)	
	VAS	45.0 (20.0)						
de Groot *et al*., 2008 [24]	WOMAC	[a]38 (4–72)	HADS (0–21)	[a]5 (0–17)		HADS (0-21)	[a]5 (0–19)	
Chen *et al*., 2008 [27]	WOMAC	48.5 (20.8)	STAI (20–80)	44.1 (8.1		CES-D (0–60)	34.7 (6.7)	
	MPQ	24.6 (19.3)						
Power *et al*., 2008 [25]	WOMAC	43.5 (19.5)				CES-D (0–60)	15.4 (8.9)	
Sale *et al*., 2008 [26]	WOMAC	38.5 (16.0)				CES-D (0–60)	9.4 (8.0)	$r = 0.89$
Parrish *et al*., 2008 [23]	NRS	43.6 (17.8)				HAM-D (0–20)	5.9 (4.4)	
Appelt *et al*., 2007 [32]	WOMAC	45.5 (17.3)				GDS (0–15)	4.8 (3.7)	
Lange *et al*., 2007 [29]	WOMAC	30 (15)				GDS (0–15)	[a]2 (0–22)	
Tsai *et al*., 2007 [30]	BPI	35.1 (16.4)				GDS (0–15)	3.5 (3.2)	$r = 0.385$
Marks, 2007 [33]	VAS	49.2 (29.6)				CES-D (0-60)	12.3 (10.2)	$r = 0.24$
	AIMS	50.4 (22.0)						$r = 0.24$
Kalichman *et al*., 2007 [28]	WOMAC	35.4				CES-D (0–60)	7.0	
Maly *et al*., 2006 [34]	WOMAC	30.3 (18.6)	STAI (20–80)	31 (8		CES-D (0-60)	10 (9)	
Buszewicz *et al*., 2006 [35]	WOMAC	43.8 (18.3)	HADS (0–21)	7.3 (4.3		HADS (0–21)	5.5 (3.3)	
Sherman, 2003 [36]	MPQ	16.8 (17.3)				CES-D (0-60)	1.2 (1.8)	$r = 0.27$
Ibrahim *et al*., 2002 [37]	WOMAC	45.4 (17.0)				GDS (0–15)	4.8 (3.6)	
Creamer *et al*., 2000 [39]	WOMAC	38.0 (22.2)	STAI (20–80)	37.9 (10.1		CES-D (0-60)	9.9 (8.7)	
	MPQ	27.9 (15.4)						
Wilcox *et al*., 2000 [40]	WOMAC	24.5 (6.5)				CES-D (0–60)	9.59 (7.39)	$r = 0.256$
Keefe *et al*., 2000 [38]	AIMS	50.9 (19.3)				SCL-90R (0–4)	0.53 (0.48)	
Orbell *et al*., 1998b [41]	MPQ	49.7 (20.8)	HADS (0–21)	9.3 (4.9		CES-D (0–60)	9.4 (6.7)	
Creamer *et al*., 1998 [43]	WOMAC	39.9 (22.2)	STAI (20–80)	38.0 (10.0		CES-D (0–60)	9.8 (8.9)	
	VAS	56.2 (21.5)						
	MPQ	22.6 (12.1)						

Results presented as mean (S.D.) or [a]median [IQR] (range). **AKSS**: American Knee Society Score; **AOS**: Ankle Osteoarthritis Scale; **BAI**: Brief Anxiety Inventory; **BDI**: Beck Depression Inventory; **BPI**: Brief Pain Inventory; **CES-D**: 20-Item Center for Epidemiologic Studies Depression Scale; **DASS21**: Depression, Anxiety and Stress Scale; **GAD-7**: Generalized Anxiety Disorder 7-item Scale; **GCPS**: Graded Chronic Pain Grade Scale; **GDS**: Geriatric Depression Scale; **HADS**: Hospital Anxiety and Depression Scale; **HAM-D**: Hamilton Depression Scale; **HOOS/KOOS**: Hip/Knee and Osteoarthritis Outcome Score; **ICOAP**: Intermittent and Constant Osteoarthritis Pain scale; **JKOM**: Japanese Knee Osteoarthritis Measure; **MA**: Meta-analysis; **MPQ**: McGill Pain Questionnaire; **NRS**: Numeric Rating Scale; **OKS**: Oxford Knee Score; **PDI**: Pain Disability Index; **PEG**: Pain intensity (P), interference with enjoyment of life (E), and general (G) activity instrument; **PHQ-8** or **PHQ-9**: Patient Health Questionnaire 8/9; **PPT**: Pain Pressure Threshold; **PROMIS**: Patient-Reported Outcomes Measurement Information System; **QIDS**: Quick Inventory of Depressive Symptomology; **RCT**: Randomized Controlled Trial; **SCL-90** - Symptom Checklist-90; **SF-36**: SF-36 Health Survey; **STAI**: State-Trait Anxiety Inventory; **SDS**: Self-rating Depression Scale; **VAS**: Visual Analogue Scale.

FIG. 2 Correlation between pain severity and anxious symptomatology



to a range of 0–100, the weighted mean pain severity was 29.9 out of 100.

Some scales were used in less than three studies, namely: (i) measure of Intermittent and Constant OsteoArthritis Pain scale (ICOAP, one study, normalized mean of 63.5/100); (ii) Arthritis Impact Measurement Scales (AIMS, two studies, normalized mean of 50.7/100); (iii) Graded Chronic Pain Scale (GCPS, three studies, normalized mean of 58.2/100); (iv) Oxford Knee Score (OKS, two studies, normalized mean of 56.8/100); (v) Pain intensity, interference with the Enjoyment of life, and General activity instrument (PEG, one study, normalized mean of 58.0/100); (vi) Pain Disability Index (PDI, one study, normalized mean of 45.1/100); (vii) Pressure Pain Threshold (PPT, one study , normalized mean of 90.0/100); (viii) Ankle Osteoarthritis Scale (AOS,

one study, normalized mean of 60.5/100); and (iv) one study using the American Knee Society Score (AKSS) reported only a median value of pain severity of 40/100.

Assessment of anxiety

Of the total articles included, 52% did not evaluate anxiety and were, therefore, not included in this analysis (see Table 2).

The HADS (HADS-A) was the most frequently utilized scale (63.7%) for evaluating anxiety. The HADS-A scale range is 0–21, and the weighted mean anxiety level reported was 5.9. Six articles only provided the median value and were thus not included in this calculation. About 22.4% of the studies used the State-Trait Anxiety Inventory (STAI-T), whose total score range is 20–80, and the weighted average of anxiety level reported was 36.6. One article provided a median value of 33.0 and was not included in this estimate. Three studies used the Generalized Anxiety Disorder 7-item scale (GAD-7), which has a range of 0–21, and reported a weighted mean anxiety level of 5.19. The Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety form was also used in three studies, using two different scales. One study, using a scale range of 7–35, reported a mean anxiety level of 13.5, while another two studies, using a scale range of 36–82, reported a weighted average anxiety score of 50.1. The Depression, Anxiety and Stress Scale (DASS21) was used in two studies in which the subscale range was 0–21 and the weighted mean anxiety level was 3.2. The Beck Anxiety Inventory (BAI) was also used in two studies; the scale range was 0– 63 and the reported weighted mean anxiety level was 6.01.

Assessment of depression

Regarding depression in OA patients, a variety of scales were also used; a total of 10 studies did not evaluate this outcome and were not incorporated in the present analysis (see Table 2).

One of the most common scales used was the Hospital Anxiety and Depression Scale (HADS-D), which was reported by 24.8% of the studies. The HADS-D total scores range was 0–21, with a weighted average depression level of 5.1. Seven articles were not included in this analysis, because they only provided the median value. The Center for Epidemiologic Studies Depression Scale (CES-D) was used in 30.1% of the studies. It is a patient-reported measure with a maximal score of 60, and the weighted average depression level reported was 8.1. Four articles provided the median value and were not included in this calculation. The Beck Depression Inventory (BDI) was used in ∼13.3% of the studies; the BDI scale range was 0– 63, and the weighted average depression level calculated was 9.6. The Patient Health Questionnaire (PHQ) was used in 11 studies (9.7%). Six studies used the PHQ9, which has a range of 0–27, and a weighted mean depression level of 5.1 was reported; five articles used the PHQ8, which has a range of 0–24, and a weighted mean depression level of 5.9 was reported. The Geriatric Depression Scale (GDS), a scale specifically designed for the assessment of depression in the elderly, was used in a total of nine articles (7.9%) and it has a range of 0–15; the weighted average depression level reported was 5.8, and one study was not included as it only provided a median value. Some studies used questionnaires applied less frequently, such as the Depression, Anxiety and Stress Scale (DASS), which was used in two studies, and has a total score range of 0–21, reporting a weighted average depression level of 3.9. The Self-rating Depression scale (SDS), which has a range of 20–80, was used in one study, and the mean depression level reported was 39. Two studies used the Hamilton Depression Scale (HAM-D), which has a range of 0–20, reporting a weighted average depression level of 4.5. The SCL-90-R was used in two other studies with different scales, one reporting a mean depression level of 4.9 (range 0–5) and the other of 0.53 (range 0–4). Finally, one study used the Quick Inventory of Depressive Symptomology (QIDS), which has a range of 0– 27, and reported a mean depression level of 1.86.

Meta-analysis

Correlation between pain and anxiety severity in patients with OA

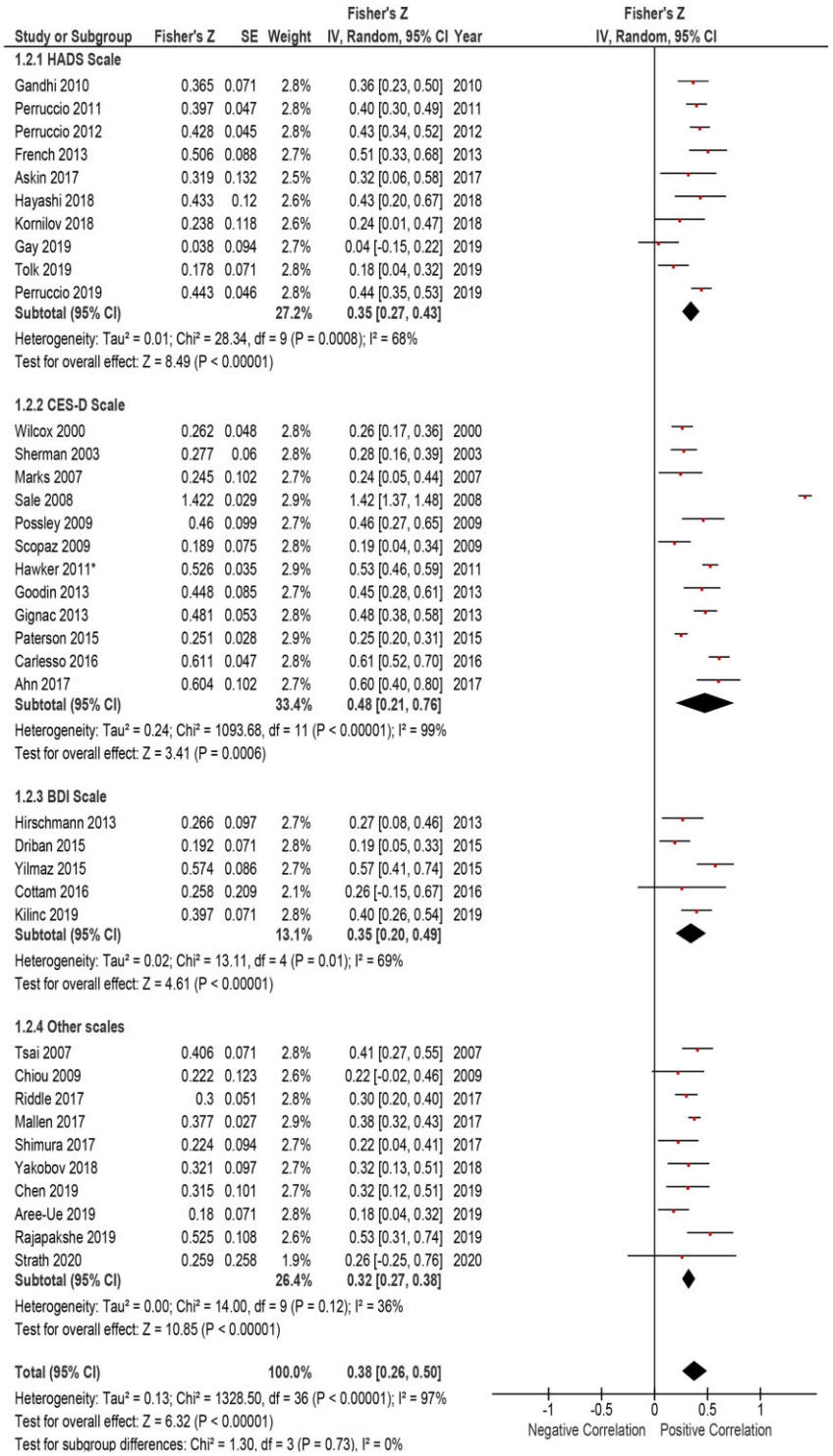
Regarding anxious symptomatology, 20 studies reported the correlation between pain severity and anxiety levels using the WOMAC, KOOS, VAS and NRS scales of pain severity and the HADS, GAD-7, STAI, PROMIS and BAI scales of anxiety symptomatology. These parameters were always positively correlated, but the calculated Fischer's Z ranged between 0.085 [51] and 0.79 [58]. Detailed correlation data can be found in Fig. 2. The random-effects meta-analysis demonstrated a pooled correlation of $r = 0.31$ ($Z = 9.41$, 95% CI = 0.25, 0.38) with high heterogeneity ($I^2 = 82\%$). Subgroup assessment showed no significant differences between the scales used to assess anxiety levels.

The leave-one-out sensitivity analysis showed the results of our meta-analysis were robust, and the direction of the outcomes did not vary markedly with the removal of each study (Supplementary Table S3, available at *Rheumatology* online). However, when removing the study by Handlandsmyth *et al.* 2017 [64], the overall effect significantly increased to $Z = 15.49$, with lower heterogeneity ($I^2 = 37\%$).

Correlation between pain and depression severity in patients with OA

Regarding depression, 37 studies reported its correlation with pain severity, using the WOMAC, NRS, VAS, PEG and MPQ scales of pain severity and the HADS, GDS, PHQ-8/PHQ-9, CES-D, SDS and BDI scales of depressive symptomatology. These parameters were always positively correlated, but Fischer's Z ranged between 0.038 [95] and 1.42 [26]. Detailed correlation by data can be found in Fig. 3. The random-effects meta-

FIG. 3 Correlation between pain severity and depressive symptomatology



#The same cohort of patients was used as in Hawker *et al.* 2010, using different subsets of patients; however, the author provided us with the data from all 829 patients.

analysis including the 16 studies demonstrated a pooled correlation of $r = 0.36$ (95% CI = 0.26, 0.50), with high heterogeneity between studies ($I^2 = 97\%$). Subgroup assessment showed no significant differences between the scales used to assess depression levels.

The leave-one-out sensitivity analysis showed the results of our meta-analysis were robust, and the direction of the outcomes did not vary markedly with the removal of each study (Supplementary Table S4, available at *Rheumatology* online). However, when removing the study by Sale *et al.* 2008 [26], the overall effect significantly increased to $Z = 15.49$ (95% CI = 0.31, 0.40), with lower heterogeneity ($I^2 = 76\%$).

Discussion

To the best of our knowledge, our results show for the first time a positive correlation between the severity of pain in OA patients and the severity of both anxiety and depression, despite there being a great disparity in the assessment tools used to assess pain and anxiety/depression severity. In general, the OA population is predominantly female, overweight, and aged over 60 years.

Correlation between pain intensity and anxiety/depression levels

Overall, in the studies herein included, OA patients reported moderate to severe levels of pain. These results are not surprising, as pain is the most common feature of OA and the event that leads patients to seek medical assistance [143]. Importantly, increased levels of pain are frequently associated with lower levels of treatment satisfaction [144]. Thus, effective pain management therapies are crucial for well-being, as pain is highly debilitating, both physically and emotionally.

Our systematic review showed that OA patients reported low to moderate levels of both anxiety and depression, and our meta-analysis confirmed a moderate positive correlation between pain severity and depression/anxiety levels. These data support a possible relationship between these disorders, highlighting that the management of OA patients' needs to be a coordinated approach, targeting both pain and psychological conditions. However, many physicians often overlook psychological comorbidities while treating OA and, by focusing on the physical components of the condition [145], neglect an essential aspect of the disease. To achieve a positive clinical outcome, it is becoming increasingly clear that the training of physicians, especially those in primary care, includes the use of tools for detecting and managing OA-associated anxiety and depression early on.

Currently, the available treatment options for OA include behavioural changes such as weight loss, exercise, and physical therapy in addition to analgesics, ambulatory assistive devices and surgery [6, 146]. However, since analgesics alone are insufficient for pain relief in most patients, physicians ought to address pain comorbidities, as suggested previously [11], through the inclusion of mood-modifying treatments. It is also important to encourage patients to communicate better about their symptoms with their caregivers, so care providers can have a full understanding of the patient's well-being and treatment efficacy.

Technical considerations

In this work, evidence was drawn from 24 RCTs, 36 cross-sectional studies and 61 cohort studies, of which 75% of the RCTs and 63% of the observational studies were considered of good quality. Regarding quality assessment, the parameters in which most of the RCTs failed were the description of the blinding process and the analysis of the possible benefits of the intervention *vs* the harms and costs. The absence of blinding in these studies was mostly due to the nature of the intervention; this may have influenced our results by increasing the probability of bias in outcome assessment of both pain and emotional symptomatology. On the other hand, observational studies mostly failed at justifying the sample size, thus not guaranteeing an adequate sample for the evaluation of pain and anxiety/depression severity in the respective population, resulting in an increase in the variability between individuals within each study. Additionally, it raises the possibility of purposive sampling, e.g. the selection of information-rich cases.

The mean number of individuals per type of paper was 211.2 for RCTs and 344.2 for observational studies. The number of studies for which the number of participants did not reach the overall mean was, however, much higher than those exceeding it. This translated into decreased effect sizes and undermined the internal/external validity of the studies and thus did not present a good representation of the osteoarthritic population.

Importantly, studies of higher quality included a higher number of participants. As OA is a multifactorial disease, a higher number of subjects is more representative of the total population and allows for the association of components at several levels.

The study population comprised almost twice as many women (63%) as men (38%). These results were expected since, in a meta-analysis by Srikanth and colleagues [147], OA was shown to be more prevalent as well as more severe in women than in men. Additionally, women were also at a higher risk of developing knee and hand OA, especially in the postmenopausal period, which is in agreement with our results. Unfortunately, although the authors reported the number of male/female participants in their studies, the outcome data mostly included both genders, so did not allow further gender-specific analyses.

The average age of our population (64.3) was also in accordance with previous data on osteoarthritic patients [148]. The development of OA has been extensively associated with ageing, as changes in joint structure and function, associated with additional factors such as obesity and injuries, increase susceptibility to developing OA [149].

The mean BMI value in our sample was high (28.2), indicating an overweight population. Being overweight and obese are well-known risk factors for developing OA, especially on the knee [150]. While it was previously thought that the impact of obesity in the joint was related to an increase in the mechanical load and gait changes [151, 152], recent studies suggest obesity's influence on OA involves a complex interaction between biomechanical and systemic inflammatory factors [153, 154]. Importantly, obesity and OA both reduce mobility, leading to a feed-forward vicious cycle of events in which reduced activity promotes further weight gain and decreases muscle strength, which worsen joint damage, fostering disease progression.

Finally, most studies in this work focus on the knee joint (64%), which was expected since this is the most affected joint in OA patients. As this joint is subjected to high use, stress, and detrimental loading as a weight-bearing joint, it is a frequent site for painful conditions such as OA.

Strengths and limitations

Strengths of this systematic review and meta-analysis include its extensive, unbiased search of a large number of databases, conducted and reported following the PRISMA guidelines. We aimed to provide a clear description of the study selection and data extraction. In addition, we performed a quality assessment of the included studies and reviewed the population included, their results and respective reporting—providing a systematic review of the studies and a meta-analysis of correlation data. Finally, by contacting all the authors of the works in which anxiety and depression were reported in OA patients, we were able to double the number of papers included in the meta-analysis.

Some limitations arose during the review process. First, it is important to note that a substantial number of included studies were cohorts of OA patients scheduled for total joint arthroplasty ($N = 36$, 28.8%). Current OA treatment options are limited and, as there are no disease-modifying drugs to prevent or halt joint destruction, joint replacement is the ultimate therapeutic when other treatments fail [6]. However, this emerges as a limitation of this review, because these cohorts, commonly end-stage OA patients, only comprise ~20% of patients [155] and therefore are not representative of the total osteoarthritic population. Second, the discrepancy of the scales used to evaluate the main outcomes was the greatest limitation, as it hindered the process of comparing results and studies, impeding a global view of the problem. For example, regarding pain severity, most studies used a disease-specific scale, WOMAC, which was developed to be used in the context of OA. Nonetheless, some authors used a site-specific scale, such as KOOS or HOOS (which focused on a specific joint), or generic scales, such as VAS. Specific scales provide better validity, with their main disadvantage being that they do not allow comparison between different groups of osteoarthritic patients. However, while generic scales provide a more general evaluation of the symptom and allow the comparing of different groups, the drawbacks include lower sensitivity and the inability to focus on outcomes such as joint function, which might be particularly important in patients with OA [156, 157].

Conclusion

Overall, our results confirm the existence of comorbidity between pain and depression/anxiety in OA patients and, more importantly, that the severity of pain is correlated with the severity of emotional impairments in these patients. Hence, there is a need for the introduction of guidelines for the screening of anxiety and depression to increase the efficacy of OA pain management therapies and to increase clinical awareness of the correlation between chronic pain and its psychological aspects.

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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