BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Are depression, anxiety and poor mental health risk factors for knee pain? A systematic review

Pyae P Phyomaung, Julia Dubowitz, Flavia M Cicuttini*, Sanduni Fernando, Anita E Wluka, Paul Raaijmaakers, Yuanyuan Wang and Donna M Urquhart

Abstract

Background: While it is recognized that psychosocial factors are important in the development and progression of musculoskeletal pain and disability, no systematic review has specifically focused on examining the relationship between psychosocial factors and knee pain. We aimed to systematically review the evidence to determine whether psychosocial factors, specifically depression, anxiety and poor mental health, are risk factors for knee pain.

Methods: Electronic searches of MEDLINE, EMBASE and PsycINFO were performed to identify relevant studies published up to August 2012 using MESH terms and keywords. We included studies that met a set of predefined criteria and two independent reviewers assessed the methodological quality of the selected studies. Due to the heterogeneity of the studies, a best evidence synthesis was performed.

Results: Sixteen studies were included in the review, of which 9 were considered high quality. The study populations were heterogeneous in terms of diagnosis of knee pain. We found a strong level of evidence for a relationship between depression and knee pain, limited evidence for no relationship between anxiety and knee pain, and minimal evidence for no relationship between poor mental health and knee pain.

Conclusions: Despite the heterogeneity of the included studies, these data show that depression plays a significant role in knee pain, and that a biopsychosocial approach to the management of this condition is integral to optimising outcomes for knee pain.

Keywords: Psychosocial factors, General mental health, Depression, Anxiety, Knee pain, Osteoarthritis

Background

Knee pain is a widespread clinical problem, with almost half of those aged 50 and over reporting pain at the knee and 25% of these experiencing symptoms of a chronic nature [1]. The main underlying cause of knee pain is osteoarthritis (OA), a chronic joint disorder imposing significant health care burden [2]. With the advent of new methods for assessing joint structure, in particular non-invasive techniques such as magnetic resonance imaging (MRI), there has been increasing interest in factors associated with pain in knee OA. We recently showed that improvements in knee pain were associated with increased vastus medialis cross sectional area and beneficial structural changes at the knee including a reduction in loss of knee cartilage and in the rate of knee replacements [3]. While a number of factors are involved in structural change at the knee, these findings suggests that managing pain may be one factor that is important in reducing OA progression and that reducing pain may have long term structural benefits at the knee.

It is becoming increasingly evident that structural changes alone do not account for all musculoskeletal pain. Psychosocial factors have been shown to be predictors of pain and disability in a number of musculoskeletal conditions including chronic low back pain [4] and neck pain [5]. While two systematic reviews of prognostic factors for knee pain have specifically examined one or two psychosocial factors within a number of demographic, physical and patient-related factors [6-8], no systematic review has specifically focused on examining the relationship between psychosocial factors and knee pain. Moreover, the evidence from studies of knee pain

* Correspondence: flavia.cicuttini@monash.edu
School of Public Health and Preventive Medicine, Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Commercial Rd, Melbourne 3004, Victoria, Australia

is conflicting. While several cross-sectional studies have reported no association between depression and knee pain [8,9], others have reported depressive symptoms to be related to pain at the knee (Salaffi et al [10]; Wright [11]), Understanding the relationship between psychosocial factors and pain at the knee is important if we are to optimally manage knee conditions. The aim of this review was to systematically review the literature to determine whether depression, anxiety and poor mental health are risk factors for knee pain.

Methods

A systematic review was conducted according to 2009 PRISMA statement [12].

Data sources and search strategy

An initial search of MEDLINE, EMBASE and PsycINFO was performed to identify studies that examined the relationship between psychosocial factors and knee pain using the MeSH terms; 'knee pain,' knee osteoarthritis,' and the keywords: 'knee', 'osteoarthritis', 'pain', 'psychosocial', 'psychosomatic', 'psychological', 'psychophysiologic'. The search was limited to human studies of adults published in the English language.

The results of this search showed that there were a large number of studies in this field investigating a broad range of psychosocial factors, with a considerable number focussing on the role of depression, anxiety and general mental health. Thus, a second search was undertaken to identify studies on these three psychosocial factors. All extracted studies were independently reviewed by two reviewers (SF, PP) to identify relevant articles. Where the reviewers disagreed and could not achieve consensus, a third reviewer (DU) gave a final judgement. The reference lists of all included studies were also examined to find any additional key studies.

Inclusion and exclusion criteria

Studies were included if they examined depression, anxiety and poor mental health as potential risk factors for knee pain, or trials which investigated the effect of interventions addressing these psychological factors on knee pain. Studies on knee pain were included whether or not knee OA was specified.

Exclusion criteria: (1) Studies that did not separate knee pain from pain in other regions such as the hip and back; (2) Studies investigating the reverse outcome (i.e. the effect of pain on psychosocial health); (3) Studies that did not focus on pain at the knee; (4) Study participants who had rheumatologic conditions or other associated medical conditions affecting joints; and (5) Study populations who had undergone knee surgery.

Data extraction

Data on the characteristics of the included studies were extracted, including: (1) Study design (including cross-sectional, case-control and cohort studies, and randomised control trials); study population; number of participants; mean age and percentage of female participants; definition of OA previous knee injury; (2) Method of assessment of psychosocial factors (depression, anxiety and poor mental health); (3) Outcome measures; assessment of knee pain and (4) Study results.

Methodological quality assessment

The methodological quality of each study was assessed independently by two reviewers (JD, SF) using standard criteria adapted from Lievense et al [13] (Table 1). These criteria allow the quality of cross-sectional, case-control and cohort studies to be assessed. Only relevant criteria for each study type were included in calculations of the total and percentage mean quality score. Scores were compared between raters and a consensus score was obtained by agreement for each study. Any study which obtained a score above the mean was considered to be of high quality.

As the Lievense et al [13] did not include criteria specific to the methodological assessment of randomised controlled trials (RCTs), the PEDro scale was used for the quality assessment of RCTs [14]. The PEDro scale rates 11 aspects of methodological quality of RCTs as being either absent or present (Table 2). As the first item (eligibility criteria) is not scored, the total score ranges from 0 to 10. Studies that obtain a score of <6 points are considered to have low quality, while those with a score ≥6 points are reported to be of high quality.

Data synthesis

Due to heterogeneity in the methodology between studies, the decision was made to use a best evidence synthesis to summarise the data (Table 3). Studies were ranked according to their design, with cohort studies considered to be a higher level of evidence than case control and cross-sectional studies. The level of evidence of studies was determined in conjunction with the quality score calculated for each study. Where we identified only a few high quality cross-sectional studies with consistent findings and these did not fit one of the best evidence synthesis levels of evidence (Table 3), we described the evidence as 'minimal'.

Results

Identification and selection of the literature

Of the 755 studies that were identified from our electronic database search, 34 were potentially eligible for inclusion (Figure 1). The full text of these studies was obtained and a further 18 were excluded as they examined self-management practices [15], the pain experience [16], ethnicity [17], musculoskeletal pain (not specifically knee pain) [18-21], walking speed [22], whole body pain intensity [23,24], OA in general (not specifically knee OA) [25-27],

Table 1 Criteria used to assess the methodological quality of selected cohort and cross-sectional studies

Item	Criterion	Study type
Study population		
1	Selection before disease was present or at uniform point	CH/CC/CS
2	Cases and controls were drawn from the same population	CC
3	Participation rate ≥80% for cases/cohort	CH/CC/CS
4	Participation rate ≥80% for controls	CC
5	Sufficient description of baseline characteristics	CH/CC/CS
Assessment of risk factor		
6	Psychosocial assessment was blinded	CH/CC/CS
7	Psychosocial factors were measured identical for cases and controls	CC
8	Psychosocial factors were assessed prior to the outcome	CH/CC/CS
Assessment of outcome		
9	Knee OA/pain was assessed identical in studied population	CH/CC/CS
10	Presence of knee OA/pain was assessed reproducibly	CH/CC/CS
11	Presence of knee OA/pain was assessed according to standard definitions	CH/CC/CS
Study design		
12	Prospective design was used	CH/CC/CS
13	Follow up time ≥2 years	CH
14	Withdrawals ≤20%	CH
Analysis and data presentation		
15	Appropriate analysis techniques were used	CH/CC/CS
16	Adjusted for at least age and sex	CH/CC/CS

CH, Applicable to cohort studies; *CC*, Applicable to case-control studies; *CS*, Applicable to cross-sectional studies; *OA*, Osteoarthritis.

prediction of somatisation disorder [28] and the effect of pain on psychological health [29]. Of the three remaining studies, one was a validation study [30], the second was a literature review [31] and the third was a RCT which assessed patients with hip and knee OA together [32].

Characteristics of included studies

Sixteen studies were included (Table 4). Of these, 10 were cross-sectional [8-11,33-38], 1 was nested case-control study [39], 2 were cohort studies [12,40] and 3 were randomised controlled trials [41-43]. Nine studies were

Table 2 The PEDro Scale Criteria used to assess the methodological quality of selected randomised control trials

	Yes	No	Where/ comments
1. Eligibility criteria were specified			
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)			
3. Allocation was concealed			
4. The groups were similar at baseline regarding the most important prognostic indicators			
5. There was blinding of all subjects			
6. There was blinding of all therapists who administered the therapy			
7. There was blinding of all assessors who measured at least one key outcome			
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups			
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"			
10. The results of between-group statistical comparisons are reported for at least one key outcome			
11. The study provides both point measures and measures of variability for at least one key outcome			
TOTAL (checked excluding eligibility criteria specified):			

Table 3 Criteria list for determining the level of evidence for best evidence synthesis, adapted from Lievense et al (2001) [13]

Level of evidence	Criteria for inclusion in best evidence synthesis
Strong evidence	generally consistent findings in:
	o multiple high quality cohort studies
Moderate evidence	generally consistent findings in:
	o 1 high quality cohort study & > 2 high quality case-control studies
	o > 3 high quality case-control studies
Limited evidence	generally consistent findings in:
	o single cohort study
	o 1 or 2 case-control studies or
	o multiple cross-sectional studies
Conflicting evidence	inconsistent findings in <75% of the trials
No evidence	No studies could be found

undertaken in the USA [8,11,34,35,38,40-42,44], 1 in the Netherlands [9], 2 in England [33,39], and 1 each in Italy [10], Egypt [43], New Zealand [36], and Japan [37].

Participants were recruited or participant data were obtained from: outpatient and rehabilitation clinics in 7 studies [8,10,34,40-43], GP clinics in 2 studies [9,33], previous studies, including the Baltimore Longitudinal Study of Aging (community-based), NHANES survey, KNEE study, and the Clinical Assessment Study of the Knee, in 4 studies [11,35,38,39], various occupational groups including nurses, postal and office workers, sales/marketing personnel and transportation operatives in 2 studies [36,37] and community and teaching hospitals in 1 study [44]. The mean age of the subjects ranged from 29.0 to 69.3 years with the percentage of females varying from 32 to 100 percent. One study excluded participants due to previous injury [40] and 6 studies as a result of previous surgery [11,34,39-42].

Diagnosis of OA in study participants

Various methods were used to identify OA in participants. Of the 10 studies that specified how the diagnosis of OA was confirmed; 8 studies used criteria specified by the American College of Rheumatology [8-11,34,41-43], 1 used x-rays graded according to the modified Kellgren/Lawrence score [44], and 1 used their own four point radiographic assessment score [38].

Assessment of pain

A number of scales were used to assess pain. The most common scales used were; the Western Ontario and McMaster Universities Arthritis Index (WOMAC) in 7 studies [11,34,39,41-44], the Visual Analogue Scale in 4

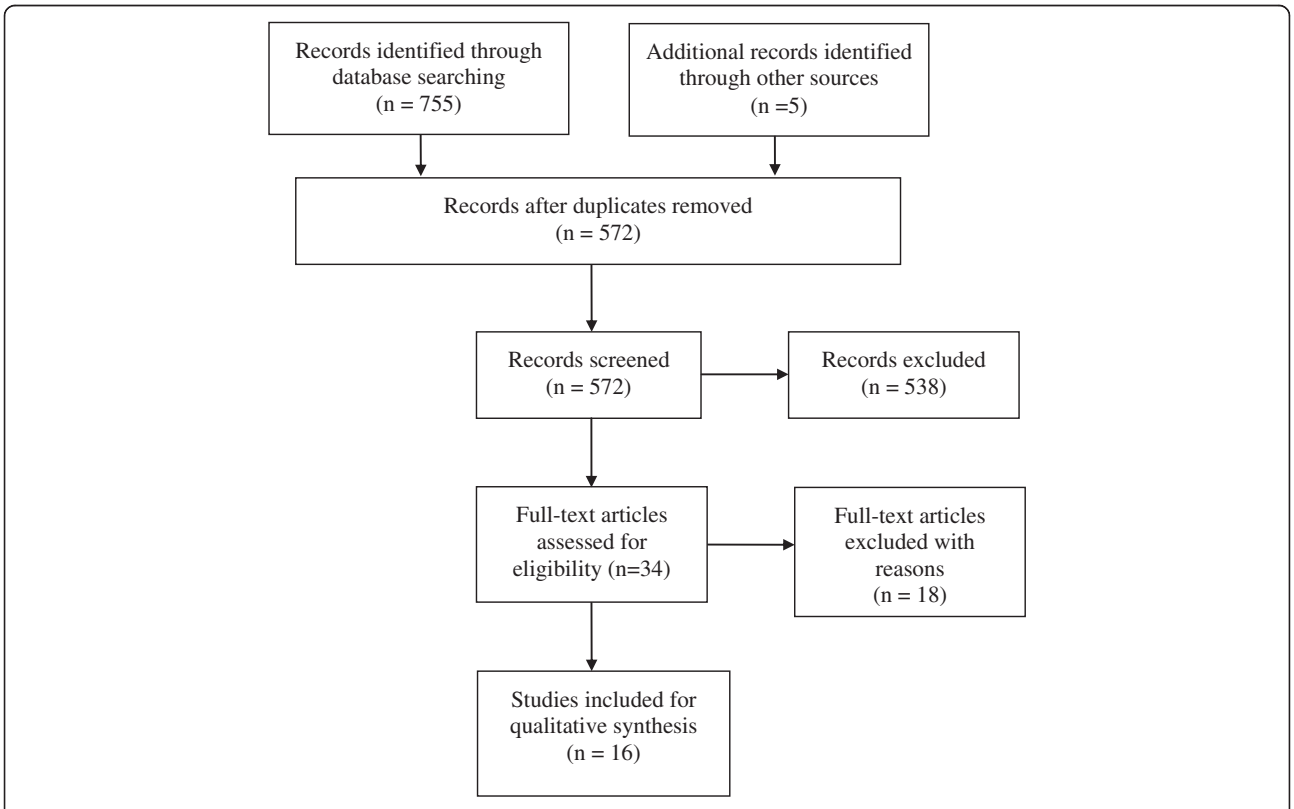

Figure 1 Flow diagram of included and excluded studies according to the PRISMA statement.

Table 4 Characteristics of included studies

Author (country, year)	Study population	No. of participants (% women)	Age (years) mean ± SD (range)	Definition of OA	Previous knee injury	Pain assessment	Psychosocial factor assessment	Quality score
Cross-sectional Studies								
O'Reilly (England, 1998)	Community participants registered at two general practices and aged 40–70 years	3323 (NA)	NA (range: 40–75)	NA	NA	Questions regarding knee pain on most days for at least a month (in the past year)	General mental health: Short Form 36 (SF36) subscale	45
Creamer (USA, 1999)	Recruited from the Baltimore Longitudinal Study of Aging; community-based individuals >40 years	374 (32)	Men: 63.8 ±0.80 Women: 62.8 ±1.08	NA	NA	Knee pain: National Health and Nutrition Examination Survey	Anxiety: Arthritis Impact Measurement Scales (AIMS) Depression: AIMS	55
Harcombe (New Zealand, 2010)	Randomly selected nurses, postal workers and office workers using computers	443 (NA)	NA (range: 20–59)	NA	NA	Self-reported knee pain lasting for more than a day in the month before the survey	General Mental health: Mental Health Inventory-5 (MHI-5)	73
Matsudaira (Japan, 2011)	Nurses, office workers, sales/marketing personnel and transportation operatives	2290 (32)	NA (range: 19–64)	NA	NA	Self-reported knee pain in the past month and past year	General Mental health: SF36 subscale	82
Creamer (USA, 1999)	Outpatients with prior physician diagnosis of knee OA and current knee pain	68 (69.1)	65.8 ± 10.4	American College of Rheumatology clinical criteria	Excluded if previous total knee replacement	Knee Pain and Severity: WOMAC, VAS, MPQ	Depression: Centre for Epidemiological Studies Depression Scale (CES-D) Anxiety: State-Trait Anxiety Inventory (STAI)	55
Davis (USA, 1992)	Study sample from NHANES I survey, aged 45–74 years, who had knee OA and knee pain	4056 (52)	(45–74)	OA based on radiographic criteria using the Atlas of Standard Radiographs of Arthritis.	NA	Knee pain on most days lasting one month in the past year or pain on active or passive motion during the examination	General Mental Health: NHANES General Wellbeing Index	45
Salaffi (Italy, 1991)	61 participants from outpatient clinic of a Rheumatic Disease Unit with symptomatic knee OA	61 (100)	63.5 ± 7.3	American College of Rheumatology clinical criteria	NA	Knee Pain: MPQ and Visual Analogue Scale	Depression: Zung Depression Inventory Anxiety: Zung Anxiety Inventory	45
van Baar (The Netherlands, 1998)	Participants presenting to their GPs with hip and knee OA	Hip OA: 73 (71.2) Knee OA: 112 (88.4)	Hip OA: 67.7 ± 8.7 Knee OA: 69.3 ± 8.1	American College of Rheumatology clinical criteria	Excluded if pathology explained the complaints	Severity of knee pain: Visual Analogue Scale	Anxiety and Depression: IRGL questionnaire	64

Table 4 Characteristics of included studies *(Continued)*

Author (country, year)	Study population	No. of participants (% women)	Age (years) mean ± SD (range)	Definition of OA	Previous knee injury	Pain assessment	Psychosocial factor assessment	Quality score
Pells (USA, 2008)	Subjects with knee OA recruited through Rheumatology, Orthopaedic Surgery, and Pain Management clinics	174 (82)	57.7 ± 9.8	American College of Rheumatology clinical criteria	NA	Knee pain: AIMS	Depression and Anxiety: Psychological Disability subscale of AIMS	64
Wright (USA, 2008)	Participants from the KNEE study, aged 35–64 years; pain on ≥4 days a week	275	NA (range 35–64)	American College of Rheumatology clinical criteria	Excluded if have inflammatory arthritis, previous knee surgery, Kellgren and Lawrence grade III-IV	Pain: WOMAC pain subscale Pain composite: pain assessments taken after physical function tests in pre-baseline assessment	Depressive symptoms: CES-D General mental health (Vitality): subscale of the SF-36	82
Nested case–control studies								
Peat (United Kingdom, 2009)	Both cases and control are recruited from the Clinical Assessment Study of the Knee	285 (55)	Cases: 66.3 ± 9.2 Controls: 64.6 ± 8.2	NA	Previous knee surgery n (%): 26 (9.1)	Characteristic pain intensity: Chronic Pain Grade Pain extent: areas of pain experienced in previous month shaded on whole-body manikin Night pain: single item on WOMAC	Anxiety and depression: Hospital Anxiety and Depression Scale	79
Longitudinal Studies								
Piva (USA, 2009)	Subjects diagnosed with patella-femoral pain syndrome (PFPS) recruited from rehabilitation clinics	74 (52)	29 ± 9	NA	Excluded if previous patellar dislocation, knee surgery past 2 years, ligamentous injury or laxity, internal derangement	Knee pain intensity measured using 11-point numerical pain rating scale (NPRS)	Anxiety: Beck Anxiety Index	85
Riddle (USA, 2011)	Community based recruitment through 4 teaching hospitals from different states (Osteoarthritis initiative study)	3405 (59.1%)	60.62 ±9.04	Modified Kellgren and Lawrence Knee OA	NA	Knee Pain: WOMAC pain scale Disability: WOMAC disability scale	General mental health: SF-12 Mental Component Summary (MCS) Depression: 20-item CES-D	92

Table 4 Characteristics of included studies *(Continued)*

Author (country, year)	Study population	No. of participants (% women)	Age (years) mean ± SD (range)	Definition of OA	Previous knee injury	Pain assessment	Psychosocial factor assessment	Quality score
Randomised controlled trials								
Chappell (USA, 2011)	Male and female outpatients ≥ 40 years of age. Recruitment by clinical sites in Canada, Greece, Russia, Sweden, and the USA by general practitioner and rheumatologists	Antidepressant (intervention)= 128 (69.5%) Placebo Control= 128(83.6%)	Antidepressant= 63.2 ± 8.8 Placebo= 61.9 ± 9.2	American College of Rheumatology clinical criteria	Excluded patients with invasive therapies to the index knee during the past 3 months or previous joint replacement anytime	Knee Pain: Brief Pain Inventory (BPI); WOMAC pain and stiffness subscales Perceived improvement: Clinical Global Impressions of Severity (CGI-S)	Depression: Beck Depression Inventory-II (BDI-II); Hospital Anxiety and Depression Scale anxiety subscale (HADS-A)	8*
Chappell (USA, 2009)	Outpatients of ≥40 years male and female with pain for 14 days of each month for 3 months before study entry, with a mean score on the 24-h average pain score (0–10) using the average of daily ratings from visit 1 to visit 2	Antidepressant (intervention)= 111 (63.1%) Placebo Control 120 (67.5%)	Antidepressant= 62.1 ± 9.6 Placebo= 62.5 ± 9.3	American College of Rheumatology clinical criteria	Excluded patients with previous invasive knee surgery, arthroscopy and joint replacement	Knee Pain: Weekly 24-h worst pain; WOMAC pain subscale Severity: BPI-S, Brief Pain Inventory-Severity; CGI-S, Clinical Global Impressions of Severity	Depression: Beck Depression Inventory-II Hospital Anxiety and Depression Scale (HADS)	9*
Abou-Raya (Egypt, 2012)	Aged 65 years and above attending the outpatient clinic	Antidepressant (intervention)= 144 (84%) Placebo Control 144 (84%)	Antidepressant= 68.9 ± 6.2 Placebo= 68.5 ± 5.8	American College of Rheumatology clinical criteria Radiographic criteria K/L grade I–III	NA	Knee Pain: Visual analogue pain scale WOMAC pain score	Depression: Geriatric depression scale	10*

NHANES, National Health and Nutritional Examination Survey; ***PFS***, Physical Functioning Score; ***WOMAC***, Western Ontario and McMaster University Osteoarthritis Index; ***PCI***, Pain Coping Inventory; ***4DSQ***, Four Dimensional Symptom Questionnaire; ***CES-D***, Centre for Epidemiological Studies Depression Scale; ***QOL***, Quality of Life; ***SF-36***, Short-Form-36 Health Survey; ***SSS***, Social Support Scale; ***VAS***, Visual Analogue Scale; ***OA***, osteoarthritis; ***K/L scale***, Kellgren and Lawrence Atlas of Standard Radiographs of Arthritis; ***WOMAC***, Western Ontario and McMaster University Arthritis Index; ***MPQ***, McGill Pain Questionnaire; ***AIMS***, Arthritis Impact Measurement Scales; ***ACR***, American College of Rheumatology; ***NA***, not available; ***PFS***, Physical Functioning Scale; ***IRGL***, Invloed van Reuma op Gezondheid en Leefwijze (Dutch version of the Arthritis Impact Measurement Scale). *Indicates quality scores for RCTs as per the PEDro scale.

studies [9,10,35,43] and question(s) regarding the prevalence of pain over the past month and/or year in 4 studies [33,36-38]. Other pain scales used were the Chronic Pain Grade Scale, McGill Pain Questionnaire and the National Health and Nutritional Examination Survey.

Assessment of psychosocial factors

The assessment of depression, anxiety and general mental health was performed using a variety of methods. Depression was assessed by 7 different methods, including the Centre for Epidemiological Studies Depression scales [11,34,44], Hospital Anxiety and Depression Scale [39,41,42] and Arthritis Impact Measurement Scales [8,35]. Anxiety was assessed using 5 different scales across 6 studies; Arthritis Impact Measurement Scales (both English and Dutch version) [9,35], Hospital Anxiety and Depression Scale [39], Beck Anxiety Index [40], Zung Anxiety Inventory [10], and the State-Trait Anxiety Inventory [34]. General mental health was assessed using 3 different questionnaires; the Short Form-36 [33] [37] the Mental Health Inventory [36] and the NHANES General Wellbeing Index [38].

Methodological quality assessment

The mean methodological quality score of the included observational studies was 67%, with scores ranging from 45% to 92% Additional file 1. Six of the 13 observational studies were considered to be of high quality (according to the Lievense criteria), as they were given a quality score above the mean. All three of the RCTs were considered high quality as they scored greater than 6 on the PEDro scale.

Analysis of the quality scores and criteria revealed that most studies achieved high scores on selection of participants with disease at uniform point (criteria 1), identical assessment of outcome (criteria 9), sufficient description of baseline characteristics (criteria 5), analysis technique (criteria 15), and adjustment for age and sex (criteria 16). However, a number of studies scored poorly on blinded assessment of the psychosocial risk factor (criteria 6), assessment of the risk factor prior to outcome (criteria 8) and reproducible assessment of outcome (criteria 10). Only 5 studies used prospective designs and of these, 2 were cohort studies and 3 were RCTs.

Relationship between depression and knee pain

Six cross-sectional studies [8-11,34,35], one nested case-control study [39], one longitudinal study [44], and three RCTs assessed the relationship between depression and knee pain [41-43] (Table 5).

Of the 6 cross-sectional studies, only one was considered high quality. The high quality study found a significant association between knee pain and depressive symptoms ($r= 0.21$, $p < 0.01$) [11]. Of the 5 low quality studies [8,10,34,35], only 1 study found a significant association between depression and knee pain ($r= 0.41$, $p < 0.01$) [38].

The nested case-control study, which was of high quality, found that substantial deterioration of knee pain was accompanied by higher frequency of depressive symptoms among cases (those participants experiencing progression of pain intensity from mild to severe) compared to controls (those not experiencing progression of pain) [39]. The single longitudinal cohort study was also of high quality and found the presence of baseline depressive symptoms was the most consistent psychological predictor of worsening pain over the follow up period (Coefficient (95% CI): 0.59 (0.18, 1.01), $p= 0.05$) [44].

The three RCTs, all rated as high quality, examined the effect of SNRI (Serotonin Noradrenalin Reuptake Inhibitor) antidepressant on change in pain intensity among knee OA patients [41-43]. All showed that treatment with antidepressant medication was associated with significant pain reduction and that SNRI antidepressants (duloxetine) reduced pain compared to placebo. One RCT [43] showed that older adults with knee OA treated for 16 weeks with duloxetine (SNRI) had significantly greater pain reduction than those treated with placebo. Subgroup analyses of two of the trials showed that the duration of pain and severity of OA did not affect the efficacy of treatment [41,42].

Relationship between anxiety and knee pain

Of the 6 studies that examined the relationship between anxiety and knee pain, 4 were cross-sectional studies [9,10,34,35], one was a nested case-control study [39] and one was a longitudinal cohort study [40] (Table 6). The cross-sectional studies were of low quality, while the nested case-control study [39] and the longitudinal cohort study [40] were of high quality. The low quality cross-sectional studies reported mixed results [9,10,34,35], while the high quality studies reported no significant association between anxiety and knee pain [39,40].

Relationship between poor mental health and knee pain

Of the 4 cross-sectional studies examining the relationship between poor mental health and knee pain [33,36-38], 2 were of high quality [36,37] (Table 7). In contrast to the low quality studies that found a significant association between poor mental health and knee pain, both high quality studies found no significant association.

Best evidence synthesis

Due to the heterogeneity of the study designs, a best evidence synthesis was performed using studies classified as being of high quality. A study was considered to be of high quality if the methodological quality score was greater than 67%.

Table 5 Studies examining the relationship between depression and knee pain

Author (year)	Study design	Assessment of depression	Assessment of pain pain/OA	Results	Conclusion	Quality score
Creamer (1999-Baltimore study)	Cross-sectional	Arthritis Impact Measurement Scales (AIMS) Questionnaire (Depression subscale)	Pain on most days for at least one month (National Health and Nutrition Examination Survey (NHANES-1))	Pain reporting was not related to depression (statistics not provided). Depression scores were higher in subjects reporting 'ever' pain in the presence of normal radiographs than in those without reported knee pain (1.70 ± 0.27 versus 1.16 ± 0.09), but this was not statistically significant ($P = 0.06$).	Depression was not associated with knee pain.	55
Creamer (1999)	Cross-sectional	Centre for Epidemiological Studies Depression Scale (CES-D)	Pain Severity (WOMAC, Visual Analogue Scale, McGill Pain Questionnaire (MPQ))	Unadjusted Correlations: MPQ: $r = 0.31$ ($p < 0.05$). VAS: $r = 0.19$ (NS) WOMAC: $r = 0.15$ (NS) In the stepwise regression models after adjustment, depression did not remain in the model.	There was no association between depression and pain severity after adjustment.	55
Salaffi (1991)	Cross-sectional	Zung Depression Inventory	Pain (McGill Pain Questionnaire (MPQ), Visual Analogue Scale (VAS))	Stepwise multiple regression: MPQ: $R = 0.41$; $t = 2.99$; $p < 0.01$ VAS $R = 0.39$; $t = 2.77$; $p < 0.01$	Depression was found to be associated with the pain experience.	45
van Baar (1998)	Cross-sectional	IRGL Questionnaire	Severity of pain: Visual Analogue Scale	Bivariate Correlation: Knee pain: $r = 0.28$ $p \leq 0.01$ Regression Analysis: NS (not remain in the model)	Depression was not associated with knee pain.	64
Wright (2008)	Cross-sectional	CES-D Psychological Disability subscale of AIMS	WOMAC pain scale	WOMAC: mean= 17.76 ± 14.47 Depressive Sx: mean= 1.80 ± 2.79 Neuroticism: mean= 2.26 ± 0.59 Negative affect: mean= 1.67 ± 0.51 Correlation between pain and depressive Sx: $r = 0.21$; $p < 0.01$ Correlation between pain and negative affect: $r = 0.15$; $p < 0.05$	There was an association between knee pain and depressive symptoms.	82

Table 5 Studies examining the relationship between depression and knee pain *(Continued)*

Author (year)	Study design	Assessment of depression	Assessment of pain pain/OA	Results	Conclusion	Quality score
Pells (2008)	Cross-sectional	Psychological Disability subscale of AIMS	AIMS	Correlation between psychosocial disability and AIMS pain scale: r= 0.24; p < 0.01. Multiple regression: NS	Pain did not demonstrate an association with psychological disability.	64
Peat (2009)	Nested case-controlled	Hospital Anxiety and Depression Scale	Characteristic pain intensity: Chronic Pain Grade Pain extent: areas of pain experienced in previous month shaded on whole-body manikin Night pain: single item on WOMAC	Mean difference (95% CI) of depression between cases and controls at 18 months: 2.2 (1.2 to 3.1) Cases were subjects who had mild knee pain at study entry and become severe at 18 months follow up. Controls were subjects who still had mild knee pain at 18 months follow up and were selected from similar cohort as cases).	Substantial deterioration of knee pain is accompanied by an increase in depressive symptoms.	79
Riddle (2011)	Longitudinal Cohort Study	20-item CES-D	Knee Pain: WOMAC pain scale Disability: WOMAC disability scale	dichotomised CES-D score (≥16) Univariate analysis: WOMAC Pain: Estimate (95% CI)= 0.36 (0.16 to 0.56); p < 0.001 Multivariate analysis: WOMAC Pain: Estimate (95% CI)= 0.59 (0.18 to 1.01); p= 0.005	Baseline depression is the most consistent psychological predictor of yearly worsening of pain. Association exists after adjusting for confounding variables.	92
Chappell (USA, 2011)	Randomised Controlled Trial(RCT) investigating the effect of antidepressant (Duloxetine) on knee OA	Beck Depression Inventory-II (BDI-II) Hospital Anxiety and Depression Scale anxiety subscale (HADS-A)	Knee Pain: Brief Pain Inventory (BPI); WOMAC pain and stiffness subscales Perceived improvement: Clinical Global Impressions of Severity (CGI-S)	Mean change in pain score from baseline (at 13 weeks) BPI average pain (% response) ≥30%= 65.3 (antidepressant group= I) & 44.1 (placebo= C); p ≤ 0.001 WOMAC: -13.74 (I) -17.51 (C); p ≤0.05 CGI-S: -0.40 (I) & -0.70(C); p ≤ 0.01	Treatment with duloxetine 60 to 120 mg was associated with significant pain reduction in patients with pain due to knee OA.	8*

Table 5 Studies examining the relationship between depression and knee pain *(Continued)*

Author (year)	Study design	Assessment of depression	Assessment of pain pain/OA	Results	Conclusion	Quality score
Chappell (USA, 2009)	RCT investigating the effect of antidepressant (Duloxetine) on knee OA	Beck Depression Inventory-II Hospital Anxiety and Depression Scale (HADS)	Knee Pain: Weekly 24-h worst pain; WOMAC pain subscale Severity: BPI-S, Brief Pain Inventory-Severity; CGI-S, Clinical Global Impressions of Severity	Mean change (SD) in pain score from baseline (at 13 weeks) BPI-S(Average pain): −2.82 ±0.21 (C) −1.85 ± 0.21(C); p < .001 WOMAC: −4.64 ± 0.35 (I) −3.24 ± 0.35(C); p= 0.003 CGI-S: -0.65 ±0.08(I) & −0.29 ± 0.08(C); p= 0.001	Duloxetine demonstrated statistically significant pain reduction compared with placebo.	9*
Abou-Raya (Egypt, 2012)	RCT investigating the effect of antidepressant (Duloxetine) on knee OA	Geriatric depression scale	Knee Pain Visual analogue pain scale; WOMAC pain score	WOMAC pain score (0–20): Mean (SD) At baseline: Intervention - 9.1 (4.6) Placebo - 8.9(5.1); p= 0.44 At 16 weeks : Intervention - 6.0 (4.1) Placebo - 8.4 (5.4); p= 0.05	Duloxetine has a dual beneficial effect of improving depression and pain symptoms in older adults with knee OA.	10*

NHANES, National Health and Nutritional Examination Survey; ***PFS***, Physical Functioning Score; ***WOMAC***, Western Ontario and McMaster University Osteoarthritis Index; ***PCI***, Pain Coping Inventory; ***4DSQ***, Four Dimensional Symptom Questionnaire; ***CES-D***, Centre for Epidemiological Studies Depression Scale; ***QOL***, Quality of Life; ***SF-36***, Short-Form-36 Health Survey; **SSS** - Social Support Scale; ***VAS***, Visual Analogue Scale; ***OA***, osteoarthritis; ***K/L scale***, Kellgren and Lawrence Atlas of Standard Radiographs of Arthritis; ***WOMAC***, Western Ontario and McMaster University Arthritis Index; ***MPQ***, McGill Pain Questionnaire; ***AIMS***, Arthritis Impact Measurement Scales; ***ACR***, American College of Rheumatology; ***NA***, not available; ***PFS***, Physical Functioning Scale; ***IRGL***, Invloed van Reuma op Gezondheid en Leefwijze (Dutch version of the Arthritis Impact Measurement Scale) *Indicates quality scores for RCTs as per the PEDro scale.

Table 6 Studies examining the relationship between anxiety and knee pain

Author (year)	Study design	Assessment of anxiety	Assessment of pain	Results	Conclusion	Quality score
Creamer (1999 – Baltimore study)	Cross-sectional	Arthritis Impact Measurement Scales (AIMS) Questionnaire: (Anxiety subscale)	Pain on most days for at least one month (NHANES-1)	Women reporting having knee pain had higher anxiety than those reporting never having knee pain (3.06 ± 0.26 vs 2.35 ± 0.17, p= 0.025).	Anxiety was associated with pain in women, but not men.	55
				Pain reporting was not related to anxiety in men (data not shown).	Women reporting knee pain, in the absence of radiographic osteoarthritis, had higher anxiety scores than those without pain.	
				Analysis stratified by radiographic severity. It showed that differences in anxiety were confined to subjects reporting knee pain in the absence of radiographic change (i.e., KL grade 0) (statistics not available).		
Creamer (1999)	Cross-sectional	State-Trait Anxiety Inventory (STAI)	Pain Severity	MPQ: r= 0.30 ($p < 0.05$).	Anxiety was not found to be associated with pain in patients with knee OA.	55
			(WOMAC, Visual Analogue Scale,	VAS: r= 0.19 (NS)		
				WOMAC: r= 0.23 (NS)		
			McGill Pain Questionnaire (MPQ))	In the stepwise regression models after adjustment, anxiety did not remain.		
Salaffi (1991)	Cross-sectional	Zung Anxiety Inventory	Pain	Stepwise multiple regression:	Anxiety was found to be related to pain.	45
			(McGill Pain Questionnaire (MPQ), Visual Analogue Scale (VAS))	MPQ: R= 0.19; t= 2.245 $p < 0.05$		
				VAS: R= 0.21; t= 2.88; $p < 0.01$		
Van Baar (1998)	Cross-sectional	IRGL Questionnaire	Severity of pain: Visual Analogue Scale	Bivariate Correlation:	Anxiety was not associated with knee pain although there was bivariate correlation between anxiety and pain.	64
				Knee pain: r= 0.30 $p \leq 0.01$		
				Regression Analysis: NS		
Peat (2009)	Nested case control	Hospital Anxiety and Depression Scale	Characteristic pain intensity: Chronic Pain Grade	Mean difference (95% CI) of anxiety between cases and controls at 18 months: 1.0	There was no significant association between knee pain and perceived anxiety.	79
			Pain extent: areas of pain experienced in previous month shaded on whole-body manikin	(−0.2 to 2.3)		
			Night pain: single item on WOMAC			
Piva (2009)	Longitudinal	Beck Anxiety Index	11 point Numerical Pain Rating Scale (NPRS)	Correlation with anxiety	There was no significant association between anxiety and pain.	85
				NPRS: r= 0.34; $P \leq 0.01$		
				Forward Multiple Regression- Not significant		

NHANES, National Health and Nutritional Examination Survey; ***PFS***, Physical Functioning Score; ***WOMAC***, Western Ontario and McMaster University Osteoarthritis Index; ***PCI***, Pain Coping Inventory; ***4DSQ***, Four Dimensional Symptom Questionnaire; ***CES-D***, Centre for Epidemiological Studies Depression Scale; ***QOL***, Quality of Life; ***SF-36***, Short-Form-36 Health Survey; ***SSS***, Social Support Scale; ***VAS***, Visual Analogue Scale; ***OA***, osteoarthritis; ***K/L scale***, Kellgren and Lawrence Atlas of Standard Radiographs of Arthritis; ***WOMAC***, Western Ontario and McMaster University Arthritis Index; ***MPQ***, McGill Pain Questionnaire; ***AIMS***, Arthritis Impact Measurement Scales; ***ACR***, American College of Rheumatology; ***NA***, not available; ***PFS***, Physical Functioning Scale; ***IRGL***, Invloed van Reuma op Gezondheid en Leefwijze (Dutch version of the Arthritis Impact Measurement Scale).

Table 7 Studies examining the relationship between poor mental health and knee pain

Author (year)	Study design	Assessment of general mental health	Assessment of pain	Results	Conclusion	Quality score
O'Reilly (1998)	Cross-sectional	SF-36 Questionnaire – Mental Health Component	Knee pain on most days for at least a month (in the past year)	Mental health score (<61): OR: 2.1 95% CI: 1.7-2.6 Knee pain: Median (IQR): 72(56–84) No knee pain: Median (IQR): 76(64–88). P < 0.001	Lower mental health scores were associated with increased odds of knee pain.	45
Matsudaira (2011)	Cross-sectional	SF36 subscale	Self reported knee pain in past month or in the past year	Knee pain and mental health: Not significant (Data not provided)	There was no association found between knee pain and general mental health.	82
Harcombe (2010)	Cross-sectional	Mental Health Inventory-5 (MHI-5)	Self-reported knee pain lasting for more than a day in the month Standardised Nordic Questionnaires for MSDs and Brief Symptom Inventory diagram showing the area of the body	Knee pain and mental health: OR (95% CI)= 0.96 (0.90 to 1.02); p value=0.194	There was no association between self-reported knee pain and mental health.	73
Davis (1992)	Cross-sectional	Psychological Wellbeing: NHANES General Wellbeing Index	Pain on most days lasting one month in the past year or knee pain on active or passive motion during the examination	Psychological wellbeing (score ≤70 & reference group >94) OA and No OA: OR (95% CI)= 1.4 (1.0 to 2.0) OA ± Pain: OR (95% CI)= 3.7 (1.8 to 7.6) Pain ± OA: OR (95% CI)= 3.2 (2.1 to 5.0)	Psychological wellbeing was associated with knee pain among participants with and without radiographic OA.	45

NHANES, National Health and Nutritional Examination Survey; ***PFS***, Physical Functioning Score; ***WOMAC***, Western Ontario and McMaster University Osteoarthritis Index; ***PCI***, Pain Coping Inventory; ***4DSQ***, Four Dimensional Symptom Questionnaire; ***CES-D***, Centre for Epidemiological Studies Depression Scale; ***QOL***, Quality of Life; ***SF-36***, Short-Form-36 Health Survey; ***SSS***, Social Support Scale; ***VAS***, Visual Analogue Scale; ***OA***, osteoarthritis; ***K/L scale***, Kellgren and Lawrence Atlas of Standard Radiographs of Arthritis; ***WOMAC***, Western Ontario and McMaster University Arthritis Index; ***MPQ***, McGill Pain Questionnaire; ***AIMS***, Arthritis Impact Measurement Scales; ***ACR***, American College of Rheumatology; ***NA***, not available; ***PFS***, Physical Functioning Scale; ***IRGL***, Invloed van Reuma op Gezondheid en Leefwijze (Dutch version of the Arthritis Impact Measurement Scale).

Depression and knee pain

One cross-sectional study, one nested case-control study, one longitudinal study and three RCTs were found to be of high quality. All of these high quality studies reported a significant association between depression and knee pain and thus there is strong evidence for this relationship. (level of evidence: strong).

Anxiety and knee pain

A nested case control study and longitudinal cohort study, both of high quality, found no association between anxiety and knee pain. Thus we conclude that there is evidence for no association between anxiety and knee pain (level of evidence: limited).

Poor mental health and knee pain

While there were four cross-sectional studies that examined the relationship between poor mental health and knee pain, only two were of high quality and both of these found no evidence of a relationship between poor mental health and knee pain. Thus there is evidence for no relationship between poor mental health and knee pain (level of evidence: minimal).

Discussion

In this systematic review we found strong evidence for a relationship between depression and knee pain, limited evidence that there is no association between anxiety and knee pain and minimal evidence suggesting there is no relationship between poor mental health and knee pain. These results highlight the important role of psychological functioning in knee pain and the need for a biopsychosocial approach to the management of this disabling condition.

We found strong evidence for a positive association between depression and knee pain in adults. This included evidence from 3 RCTs that showed treatment with antidepressant medication was associated with significant pain reduction. The emerging evidence on pathogenesis of depression suggests that it is associated with dysfunction in the inflammatory cytokine production as a response to stressors [45], dysregulation of autonomic nervous system [46,47] and destabilising effect on hypothalamic-pituitary-adrenal axis [48]. Each of these mechanisms also contributes to the provocation of chronic pain syndrome [46,49,50]. In addition, the noradrenaline and serotonin neurotransmitters, which are involved in the pathophysiology of depression [46], have been shown to have significant roles in endogenous pain inhibitory pathways [51,52]. These findings indicate that physiological similarities exist between depression and chronic pain [47]. Another explanation for the association between depression and knee pain may be via reduced physical activity which could be due to either fear of pain [53] or as a consequence of depression [54]. The resulting muscle wasting and reduced joint stability resulting from less activity may have a negative effect on function and disease outcomes of OA [55,56].

Although there was strong evidence for a relationship between depression and knee pain, we found limited evidence for no association between anxiety and knee pain. A major limitation in examining these studies is the lack of longitudinal data, with only one high quality longitudinal study and one nested case-control study examining the relationship between anxiety and knee pain. Further investigation to understand the relationship between anxiety and knee pain is needed as recent work suggests that higher anxiety is related to poorer function in patients with knee OA [53,57] and relationships between anxiety and pain exist in older community-based adults, which are both longitudinal and reciprocal in nature [58].

There was minimal evidence for no relationship between poor mental health and knee pain based on two high quality cross-sectional studies. These findings contrast to those of depression, where there was strong evidence for a relationship between depressive symptoms and knee pain, and may have resulted from the use of generic measures to measure mental health compared to the specific instruments used to assess depression. Our finding is consistent with a previous systematic review which also found minimal evidence that better mental health is protective of knee pain in those with knee OA [6]. Understanding the role of general mental health on knee pain continues to be limited by the absence of cohort studies and RCTs, as well as the paucity of high quality data. Further investigation is needed.

Knee pain results in significant disability and a substantial reduction in quality of life [59,60]. Although knee structural abnormalities are associated with knee pain, it is clear that structure alone does not account for knee pain. It has been suggested that psychosocial factors may play an important role in knee pain. However, previous systematic reviews have only found limited evidence for relationships between both depression and poor mental health and knee symptoms [6,7]. Our systematic review, which is the first to our knowledge to focus on the role of psychosocial factors in knee pain, found that depression has an important role in knee pain. Specifically, the three RCTs of depression found that the treatment with the antidepressant duloxetine resulted in a significant reduction in knee pain [41-43] and is 'proof of concept' that depression has an important role in knee pain. While pharmacological interventions, such as antidepressants may be important in the management of knee pain, non-pharmacological strategies, including cognitive behavioural therapy, may also play a significant role. Future research, particularly in the form of RCTs, is needed to examine the effectiveness of non-pharmacological treatment options for reducing depression in the treatment of knee pain.

There are several limitations in undertaking this review. Examining the role of psychosocial factors in knee pain is complex and preliminary searches identified a particularly large number of studies examining a variety of psychosocial factors. We were therefore required to narrow our review to depression, anxiety and general mental health, closely related psychological constructs, which means that there are psychosocial factors that are potentially important in the development of knee pain that we have not investigated. Moreover, while depression, anxiety and general mental health were considered separately and could not be combined due to measurement factors, it is important to note that there is potential overlap between these psychosocial factors.

Moreover, we were not able to perform a meta-analysis to summarize our results due to the heterogeneity of the studies included in this review, and therefore, a best-evidence synthesis was performed. Another limitation was the lack of high quality cohort and RCTs investigating poor mental health and anxiety as risk factors for knee pain. The majority of studies in this review were cross-sectional or case-control studies which limited the quality of the evidence. Another methodological issue identified was the lack of double-blinded assessment of participants which reduced the quality of the data. Furthermore, there was significant heterogeneity in terms of the instruments used to assess the psychological factors.

Conclusions

This systematic review found that psychological functioning plays an important role in knee pain, with strong evidence for depression being associated with knee pain. We also found limited evidence for anxiety having no relationship with knee pain and minimal evidence for no relationship between poor mental health and knee pain. This review highlights the need for a biopsychosocial approach, in particular addressing psychosocial factors such as depression, in optimising outcomes for knee pain. This is important given the increasing understanding of the complexity of knee pain and potential complications arising from many of the treatments in current use. A holistic approach to managing knee pain has the potential to improve patient outcomes.

Additional file

Additional file 1: Methodological Quality Assessment.

Abbreviations

OA: Osteoarthritis; MRI: Magnetic resonance imaging; RCT: Randomised controlled trial; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; WOMAC: Western Ontario and McMaster Universities Arthritis Index; SNRI: Serotonin noradrenalin reuptake inhibitor.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

PP was involved in data extraction and interpretation and manuscript preparation. JD was involved in acquisition of data, data extraction and manuscript preparation. FC contributed to conception/design, interpretation of data, and manuscript preparation. SF contributed to acquisition of data, data extraction and manuscript preparation. PR was involved in acquisition of data and manuscript preparation. AW and YW contributed to analysis and interpretation of data and manuscript preparation. DU contributed to conception/design, data interpretation and manuscript preparation. All authors read and approved the final manuscript.

Authors' information

Pyae Phyomaung and Julia Dubowitz: Joint first authors.

Acknowledgements

DU and AW were supported by NHMRC Fellowships (1011975 and 545876 respectively).

Received: 15 July 2013 Accepted: 25 November 2013
Published: 9 January 2014

References

1. Jinks C, Jordan K, Ong BN, Croft P: **A brief screening tool for knee pain in primary care (KNEST). 2. Results from a survey in the general population aged 50 and over.** *Rheumatology* 2004, **43**(1):55–61.
2. Bennell KL, Bowles KA, Payne C, Cicuttini F, Williamson E, Forbes A, *et al*: **Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial.** *BMJ* 2011, **342**:d2912.
3. Wang Y, Wluka A, Berry P, Siew T, Teichtahl A, Urquhart D, *et al*: **Increase in vastus medialis cross-sectional area is associated with reduced pain, cartilage loss, and joint replacement risk in knee osteoarthritis.** *Arthritis Rheum* 2012, **64**(12):3917–3925.
4. Pincus T, Burton AK, Vogel S, Field AP: **A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain.** *Spine (Phila Pa 1976)* 2002, **27**(5):E109–E120.
5. Christensen J, Knardahl S: **Work and neck pain: a prospective study of psychological, social, and mechanical risk factors.** *Pain* 2010, **151**(1):162–173.
6. van Dijk G, Dekker J, Veenhof C, van den Ende C, Group FtCS: **Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature.** *Arth Rheum* 2006, **55**(5):779–785.
7. Blagojevic M, Jinks C, Jeffery A, Jordan K: **Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis.** *Osteoarthritis Cartilage* 2010, **18**(1):24–33.
8. Pells JJ, Shelby RA, Keefe FJ, Dixon KE, Blumenthal JA, Lacaille L, *et al*: **Arthritis self-efficacy and self-efficacy for resisting eating: relationships to pain, disability, and eating behavior in overweight and obese individuals with osteoarthritic knee pain.** *Pain* 2008, **136**(3):340–347.
9. van Baar ME, Dekker J, Lemmens JA, Oostendorp RA, Bijlsma JW: **Pain and disability in patients with osteoarthritis of hip or knee: the relationship with articular, kinesiological, and psychological characteristics.** *J Rheumatol* 1998, **25**(1):125–133.
10. Salaffi F, Cavalieri F, Nolli M, Ferraccioli G: **Analysis of disability in knee osteoarthritis. Relationship with age and psychological variables but not with radiographic score.** *J Rheumatol* 1991, **18**(10):1581–1586.
11. Wright LJ, Zautra AJ, Going S: **Adaptation to early knee osteoarthritis: the role of risk, resilience, and disease severity on pain and physical functioning.** *Ann Behav Med* 2008, **36**(1):70–80.
12. Alessandro L, Douglas GA, Jennifer T, Cynthia M, Peter CG, John PAI, *et al*: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration.** *BMJ* 2009, **339**:b2700.
13. Lievense A, Bierma-Zeinstra S, Verhagen A, Verhaar J, Koes B: **Influence of work on the development of osteoarthritis of the hip: a systematic review.** *J Rheum* 2001, **28**(11):2520–2528.
14. de Morton NA: **The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study.** *Aust J Physiother* 2009, **55**(2):129–133.

15. Damush TM, Wu J, Bair MJ, Sutherland JM, Kroenke K: **Self-management practices among primary care patients with musculoskeletal pain and depression.** *J Behav Med* 2008, **31**(4):301–307.
16. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, *et al*: **Understanding the pain experience in hip and knee osteoarthritis–an OARSI/OMERACT initiative.** *Osteoarthritis Cartilage* 2008, **16**(4):415–422.
17. Ibrahim SA, Burant CJ, Mercer MB, Siminoff LA, Kwoh CK: **Older patients' perceptions of quality of chronic knee or hip pain: differences by ethnicity and relationship to clinical variables.** *J Gerontol A Biol Sci Med Sci* 2003, **58**(5):M472–M477.
18. Nahit ES, Pritchard CM, Cherry NM, Silman AJ, Macfarlane GJ: **The influence of work related psychosocial factors and psychological distress on regional musculoskeletal pain: a study of newly employed workers.** *J Rheumatol* 2001, **28**(6):1378–1384.
19. Kroenke K, Wu J, Bair MJ, Krebs EE, Damush TM, Tu W: **Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care.** *J Pain* 2011, **12**(9):964–973.
20. Ang D, Bair M, Damush T, Wu J, Tu W, Kroenke K: **Predictors of pain outcomes in patients with chronic musculoskeletal pain co-morbid with depression: results from a randomized controlled trial.** *Pain Med* 2010, **11**(4):482–491.
21. Bair M, Wu J, Damush T, Sutherland J, Kroenke K: **Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients.** *Psychosom Med* 2008, **70**(8):890–897.
22. Tiedemann A, Sherrington C, Lord SR: **Physiological and psychological predictors of walking speed in older community-dwelling people.** *Gerontology* 2005, **51**(6):390–395.
23. Chou K-L, Chi I: **Reciprocal relationship between pain and depression in elderly Chinese primary care patients.** *Int J Geriatr Psychiatry* 2005, **20**(10):945–952.
24. Chou KL: **Reciprocal relationship between pain and depression in older adults: evidence from the English Longitudinal study of ageing.** *J Affect Disord* 2007, **102**(1–3):115–123.
25. Vriezekolk J, Eijsbouts A, Evers A, Stenger A, van den Hoogen F, van Lankveld W: **Poor psychological health status among patients with inflammatory rheumatic diseases and osteoarthritis in multidisciplinary rehabilitation: need for a routine psychological assessment.** *Disabil Rehabil* 2010, **32**(10):836–844.
26. de Filippis LG, Gulli S, Caliri A, D'Avola G, Lo Gullo R, Morgante S, *et al*: **Factors influencing pain, physical function and social functioning in patients with osteoarthritis in southern Italy.** *Int J Clin Pharmacol Res* 2004, **24**(4):103–109.
27. Lin E, Katon W, von Korff M, Tang L, Williams JJ, Kroenke K: **Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial.** *JAMA* 2003, **290**(18):2428–2429.
28. Howard KJ, Ellis HB, Wang J, von der Gruen JK, Bucholz R: **Evaluating the effects of somatization disorder for patients with severe End-stage lower-extremity osteoarthritis.** *J Appl Biobehav Res* 2012, **17**(2):79–93.
29. Woo J, Leung J, Lau E: **Prevalence and correlates of musculoskeletal pain in Chinese elderly and the impact on 4-year physical function and quality of life.** *Public Health* 2009, **123**(8):549–556.
30. Perrot S, Poiraudeau S, Kabir M, Bertin P, Sichere P, Serrie A, *et al*: **Active or passive pain coping strategies in hip and knee osteoarthritis? Results of a national survey of 4,719 patients in a primary care setting.** *Arthritis Rheum* 2008, **59**(11):1555–1562.
31. Macfarlane GJ, Pallewatte N, Paudyal P, Blyth FM, Coggon D, Crombez G, *et al*: **Evaluation of work-related psychosocial factors and regional musculoskeletal pain: results from a EULAR Task Force.** *Ann Rheum Dis* 2009, **68**(6):885–891.
32. Sullivan MD, Bentley S, Fan M-Y, Gardner G: **A single-blind, placebo Run-in study of duloxetine for activity-limiting osteoarthritis pain.** *J Pain* 2009, **10**(2):208–213.
33. O'Reilly SC, Muir KR, Doherty M: **Knee pain and disability in the Nottingham community: association with poor health status and psychological distress.** *Br J Rheumatol* 1998, **37**(8):870–873.
34. Creamer P, Lethbridge-Cejku M, Hochberg MC: **Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures.** *J Rheumatol* 1999, **26**(8):1785–1792.
35. Creamer P, Lethbridge-Cejku M, Costa P, Tobin JD, Herbst JH, Hochberg MC: **The relationship of anxiety and depression with self-reported knee pain in the community: data from the Baltimore longitudinal study of aging.** *Arthritis Care Res* 1999, **12**(1):3–7.
36. Harcombe H, McBride D, Derrett S, Gray A: **Physical and psychosocial risk factors for musculoskeletal disorders in New Zealand nurses, postal workers and office workers.** *Inj Prev* 2010, **16**(2):96–100.
37. Matsudaira K, Palmer KT, Reading I, Hirai M, Yoshimura N, Coggon D: **Prevalence and correlates of regional pain and associated disability in Japanese workers.** *Occup Environ Med* 2011, **68**(3):191–196.
38. Davis MA, Ettinger WH, Neuhaus JM, Barclay JD, Segal MR: **Correlates of knee pain among US adults with and without radiographic knee osteoarthritis.** *J Rheumatol* 1992, **19**(12):1943–1949.
39. Peat G, Thomas E: **When knee pain becomes severe: a nested case-control analysis in community-dwelling older adults.** *J Pain* 2009, **10**(8):798–808.
40. Piva SR, Fitzgerald GK, Wisniewski S, Delitto A: **Predictors of pain and function outcome after rehabilitation in patients with patellofemoral pain syndrome.** *J Rehabil Med* 2009, **41**(8):604–612.
41. Chappell AS, Desaiah D, Liu-Seifert H, Zhang S, Skljarevski V, Belenkov Y, *et al*: **A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee.** *Pain Pract* 2011, **11**(1):33–41.
42. Chappell AS, Ossanna MJ, Liu-Seifert H, Iyengar S, Skljarevski V, Li LC, *et al*: **Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial.** *Pain* 2009, **146**(3):253–260.
43. Abou-Raya S, Abou-Raya A, Helmii M: **Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial.** *Age Ageing* 2012, **41**(5):646–652.
44. Riddle DL, Kong X, Fitzgerald GK: **Psychological health impact on 2-year changes in pain and function in persons with knee pain: data from the osteoarthritis initiative.** *Osteoarthritis Cartilage* 2011, **19**(9):1095–1101.
45. Hayley S, Poulter MO, Merali Z, Anisman H: **The pathogenesis of clinical depression: stressor- and cytokine-induced alterations of neuroplasticity.** *Neuroscience* 2005, **135**(3):659–678.
46. Maletic V, Raison CL: **Neurobiology of depression, fibromyalgia and neuropathic pain.** *Front Biosci* 2009, **14:**5291–5338.
47. Narasimhan M, Campbell N: **A tale of two comorbidities: understanding the neurobiology of depression and pain.** *Indian J. Psychiatry* 2010, **52**(2):127–130.
48. Pace TW, Hu F, Miller AH: **Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression.** *Brain Behav Immun* 2007, **21**(1):9–19.
49. Ross RL, Jones KD, Bennett RM, Ward RL, Druker BJ, Wood LJ: **Preliminary evidence of increased pain and elevated cytokines in fibromyalgia patients with defective growth hormone response to exercise.** *Open Immunol J* 2010, **3:**9–18.
50. D'Andrea G, Leon A: **Pathogenesis of migraine: from neurotransmitters to neuromodulators and beyond.** *Neurol Sci* 2010, **31**(Suppl 1):S1–S7.
51. Yoshimura M, Furue H: **Mechanisms for the anti-nociceptive actions of the descending noradrenergic and serotonergic systems in the spinal cord.** *J Pharmacol Sci* 2006, **101**(2):107–117.
52. Millan MJ: **Descending control of pain.** *Prog Neurobiol* 2002, **66**(6):355–474.
53. Leeuw M, Goossens ME, Linton SJ, Crombez G, Boersma K, Vlaeyen JW: **The fear-avoidance model of musculoskeletal pain: current state of scientific evidence.** *J Behav Med* 2007, **30**(1):77–94.
54. Vlaeyen JW, Linton SJ: **Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art.** *Pain* 2000, **85**(3):317–332.
55. Hurley M: **The role of muscle weakness in the pathogenesis of osteoarthritis.** *Rheum Dis Clin North Am* 1999, **25**(2):283–298.
56. Guilak F: **Biomechanical factors in osteoarthritis.** *Best Pract Res Clin Rheumatol* 2011, **25**(6):815–823.
57. Scopaz KA, Piva SR, Wisniewski S, Fitzgerald GK: **Relationships of fear, anxiety, and depression with physical function in patients with knee osteoarthritis.** *Arch Phys Med Rehabil* 2009, **90**(11):1866–1873 [Research Support, N.I.H., Extramural].
58. Arola H, Nicholls E, Mallen C, Thomas E: **Self-reported pain interference and symptoms of anxiety and depression in community-dwelling older adults: can a temporal relationship be determined?** *Eur J Pain* 2010, **14**(9):966–971.
59. Jinks C, Jordan K, Croft P: **Osteoarthritis as a public health problem: the impact of developing knee pain on physical function in adults living in the community: (KNEST 3).** *Rheumatology* 2007, **46**(877):81.
60. Donald I, Foy C: **A longitudinal study of joint pain in older people.** *Rheumatology* 2004, **43**(1256):60.

doi:10.1186/1471-2474-15-10
Cite this article as: Phyomaung *et al.*: Are depression, anxiety and poor mental health risk factors for knee pain? A systematic review. *BMC Musculoskeletal Disorders* 2014 **15**:10.