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Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis

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ABSTRACT

Objective: (i) To determine the association between the presence of comorbidities and severity of pain and physical dysfunction in people with knee and/or hip osteoarthritis; (ii) To explore associations between specific comorbidities (cardiac disease and/or hypertension, diabetes, depression, back pain) and symptom severity.

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Methods: Studies were identified through systematic searches in four electronic databases and grey literature, and, subsequently, methodologically appraised. Eligible citations entailed cross-sectional or longitudinal studies as well as randomised controlled trials providing data of a direct association between comorbidity presence and the severity of self-reported and/or performance-based symptoms of pain and/or physical functioning, in people with knee and/or hip osteoarthritis. We performed random-effects meta-analysis if at least two citations of low-to-moderate risk of bias were available. The quality of the body of evidence was determined using Cochrane-recommended methods.

Results: Of all eligible citations (n=26), 17 studies were entered in meta-analysis. Moderate quality evidence revealed an association between having ≥1 general comorbidity and worsening of pain (regression coefficient (95% confidence interval (CI)): 0.18 (95% CI: 0.14,0.22)) and/or performance-based physical functioning (0.20 (95%CI: 0.10,0.29)). The presence of cardiac disease and/or hypertension (self-reported: 0.08 (95% CI: 0.01,0.16); performance-based: 0.11 (95%CI: 0.02,0.20)), or back pain (self-reported: 0.12 (95%CI: 0.04,0.20)) predicted deteriorated physical functioning. Co-existing diabetes was associated with worse pain (0.10 (95%CI: 0.02,0.17)). Other findings were non-significant and/or the evidence of poor quality.

Conclusions: Greater comorbidity burden contributes to worse pain and performance-based physical function in people with knee and/or hip osteoarthritis. Suffering comorbid cardiac disease including hypertension, back pain or diabetes may have differential effects on symptom severity.

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KEY WORDS

pain, physical function, comorbidity, prognosis

1. INTRODUCTION

Knee and/or hip osteoarthritis is a common and leading cause of disability worldwide.[1, 2] Pain and physical dysfunction are the most important symptoms, and, thus, are typically monitored to evaluate disease burden or treatment success over time. The clinical presentation of osteoarthritis

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patients, however, is diverse and a plethora of factors have been implicated in the onset and/or progression of the disease.[3]

A considerable proportion of osteoarthritis patients presents with co-existing medical conditions. In a recent meta-analysis, Hall et al.[4] reported that approximately 40% of patients suffered cardiovascular disease. Obesity and metabolic syndrome are also prevalent which likely contributes to on average 10-14% of this patient population having diabetes.[5, 6] Whilst one in two people with knee and/or hip osteoarthritis complain of musculoskeletal comorbidities such as back pain[7], osteoarthritis may also impose a significant mental health burden on afflicted individuals.[8, 9]

Traditionally, clinicians query the presence of comorbidities to gauge the patient's disease state and to inform the course of treatment. Furthermore, epidemiological research has suggested that comorbidities exacerbate the impact of osteoarthritis, and, thus, may negatively affect the prognosis of symptoms deteriorating over time.[10] This has led to numerous prognostic studies of clinical symptoms in osteoarthritis to account for the underlying role of comorbidity burden in study designs and/or analysis (eg, [11, 12]). However, to date, no conclusive evidence exists to underpin the role of comorbid conditions, and specific types of comorbidities, in symptomatic decline amongst people with knee and/or hip osteoarthritis.

The primary goal of this study was to quantitatively synthesise the literature on the association between the presence of comorbidities and prognosis of symptomatic disease in terms of severity of pain and physical dysfunction, in people with knee and/or hip osteoarthritis. Secondly, we aimed to explore the association between the presence of specific and common comorbid conditions (ie, cardiac disease and/or hypertension, diabetes, back pain and depression) and the severity of clinical symptoms.

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2. METHODS

This meta-analysis was designed and conducted following the PRISMA statement and was registered in PROSPERO (ID 42017056246).[13]

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2.1.Literature sourcing

Relevant studies were sourced up to May 17th, 2017 through Boolean searches in four electronic databases (ie, Pubmed, Excerpta Medica Database, the Cumulative Index to Nursing and Allied Health Literature and Web of Science). Using search strategies in accordance with the semantics of each database (Appendix A), key – if applicable MeSH terms – and synonyms were entered separately in 3 filters that were ultimately combined. Filters included search terms around (i) osteoarthritis, knee and/or hip, (ii) comorbidity, and (iii) clinical symptoms of pain and/or physical dysfunction. Grey published literature was also sourced manually from the reference lists of eligible studies and relevant systematic reviews.

2.2.Study selection

After removal of duplicates, titles and abstracts, and subsequently full-texts, were screened by three independent assessors (EVA, FM, NO) and verified for consensus by a review author (AVG). Between-rater agreement was excellent (absolute agreement: 93%, κ-coefficient: 0.85). Eligible citations included full reports of cohort, cross-sectional or case-control studies and randomised controlled trials with the latter allowing associations to be examined irrespective of treatment. Study participants were at least 45 years of age on average[14] and had a primary diagnosis of knee and/or hip osteoarthritis as defined by the original study investigators. This could entail self-reported, symptomatic and/or radiographic diagnoses of osteoarthritis. Finally, studies were required to investigate, and provide data of, a direct association between the presence of comorbidities and severity, or changes in severity, of clinical symptoms of pain and/or physical dysfunction. As per Feinstein et al.[15], a comorbidity was defined as any distinct additional disease entity that has existed or may occur during the clinical course of a patient who has the index disease (ie, osteoarthritis). Any medical and/or psychosocial diseases were considered on condition that they were listed in the ICD-10 Version of the International Statistical Classification of Diseases and Related Health Problems.[16] Studies that did not categorise participants under distinct comorbid conditions were excluded. In case mixed patient samples were described and data for the population of interest could not be extracted separately, at least 75% of the sample had to have hip and/or knee osteoarthritis. Studies were also excluded if (i) participants had undergone arthroplasty surgery or suffered inflammatory arthropathies; (ii) no full report of original research was published (ie, reviews, editorials and commentaries,

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letters, protocols, guidelines, conference proceedings or case studies), (iii) no abstract or full text could be retrieved, and/or (iii) studies were published in languages other than English, French, German or Dutch. Multiple reports utilising data from a similar cohort were accepted if the eligibility criteria were not violated and novel relationships were investigated. Of the reports generating duplicate data, the citation published first was retained for further analysis.

2.3.Data extraction

Data were independently extracted by three data collectors (EVA, FM, NO) and subsequently verified by a senior author (AVG). Electronic sheets were used which were piloted by multiple investigators (EVA, FM, NO, AVG). Items of data extraction are listed in Table 1. If studies presented data of participants with hip or knee osteoarthritis separately, multiple entries were used in meta-analysis (eg, Van Dijk 2010a and Van Dijk 2010b).

<<Table 1 inserted here>>

2.4. Within-study risk of bias

The methodological quality was rated at the study level for all eligible reports by three independent assessors (NO, FM, EVA; absolute agreement: 81%, kappa coefficient=0.71), which was again verified for consensus by the same author (AVG). Given the prognostic nature of the research question, the QUality In Prognostic Studies (QUIPS) tool was used to assess the risk of bias for six domains (ie, "study participation", "study attrition", "prognostic factor measurement", "outcome measurement", "study confounding", "statistical analysis and reporting") as "low", "moderate" or "high".[17] The QUIPS tool assumes longitudinal study designs, and, thus, does not specifically downgrade the methodological quality of cross-sectional studies in this field. Cross-sectional studies are less suited to evaluate the actual impact of candidate prognostic factors on disease progression, and, were therefore assigned a moderate risk of bias in the least for the domain "study confounding". Subsequently, for each study, the overall risk of bias was determined based on the highest risk ratings that were obtained for the domains deemed most critical to methodological quality.[17] That is, the highest risk rating

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assigned to either domains of "study attrition", "study confounding" or "statistical analysis and reporting" was set as the overall risk of bias of a particular study, which was up-graded by one level if a high risk of bias was recorded for any of the other QUIPS domains.

2.5. Data synthesis and quality of the body of evidence

Data synthesis was performed by one review author (AVG) for outcomes of decline in pain and physical function. Summary data of relevant citations were statistically pooled if the following criteria were met: (i) at least two citations of low-to-moderate risk of bias were available; (ii) summary data were reported as regression coefficients and standard errors, or recalculation was possible from the original study data using methods described in the Cochrane Handbook.[18] Regression coefficients were standardised into scale-free effect estimates, whenever possible, to facilitate comparison across studies.[19]

In a primary analysis, we investigated whether the presence of at least one comorbidity (ie, total count/presence) was associated with worse (changes in) symptoms of pain and/or physical functioning. Secondly, from the data available in the eligible reports, exploratory analyses examined whether the presence of a specific comorbid condition (ie, type) was associated with symptom deterioration. Specific comorbidities of interest involved cardiac disease and/or hypertension, diabetes, depression and back pain.

We performed DerSimonian-Laird random-effects meta-analysis using the METAAN command in STATA (v.15.0, Statacorp, Texas, USA).(18) The Q test assessed the likelihood of heterogeneity of the results (I^2) (with "0% = no heterogeneity" and "100% =maximum heterogeneity").[18] Sub-analyses were not planned. Results are reported as regression coefficients (95% confidence intervals (CI)) and the level of statistical significance was set at $\alpha<0.05$.

Following meta-analysis, the strength of the body of evidence was evaluated and rated as "high" to "very low" following the recommendations of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[18] Briefly, the quality of the evidence was downgraded from "high" by one level for each of the applicable GRADE criteria. These criteria entailed limitations such as a high likelihood of within-study risk of bias, indirectness of the evidence, unexplained heterogeneity or inconsistency of the findings, and imprecise findings.

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Assessment of publication bias was found appropriate in only one analysis[18], and thus, this criterion was omitted from the GRADE assessment.

3. RESULTS

A total of 794 citations were screened. Twenty-six studies [20-45] were deemed eligible for an assessment of methodological quality, and, of those, 17 citations [21, 28-34, 36-44] were ultimately included in meta-analysis. The flowchart, including reasons for exclusion, is depicted in Figure 1.

<<Figure 1 inserted here>>

3.1. Characteristics of eligible studies

As outlined in Table 2, studies were published between 1997 and 2016 with the majority conducted in the Netherlands (n=11, 42%), United States of America (n=11, 23%) or the United Kingdom (n=4, 15%). With a follow-up duration of one to six years, less than half of the studies had a longitudinal observational design (n=11, 42% of studies) and most participants were recruited from outpatient clinics (n=21, 81% of studies) as opposed to the community (n=10, 38% studies). All but six studies provided data separately for people with knee and/or hip osteoarthritis. Study participants were overweight to obese, on average 68 years of age and the majority was female. The diagnosis of osteoarthritis was generally ascertained implementing symptom-based criteria and commonly confirmed by radiography.

<<Table 2 inserted here>>

Briefly, the presence of comorbidities was queried using a variety of self-report tools such as open-ended questioning[21, 23], researcher-designed lists[22, 24, 25, 28, 30, 31, 33, 35, 37, 38, 40, 42, 45], dedicated comorbidity assessment scales[29, 34, 39, 41, 43, 44], disease-specific questionnaires[36, 41], population health resources[32] or other methods[20, 26, 27, 40].

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Irrespective of the tool, the majority of studies assessed the presence of medical comorbidities involving musculoskeletal problems (in 18 studies), cardiovascular & respiratory diseases (17 studies), metabolic & endocrine conditions (15 studies), neurological (8 studies) and/or other comorbid conditions (16 studies). In approximately one third of studies (n=10, 38%) psychosocial comorbidities such as depression, were also incorporated in the comorbidity assessment tools. The Western Ontario McMasters Osteoarthritis index (WOMAC) was most often utilized to assess the severity of self-reported symptoms (in 72% of relevant studies), whilst five studies objectified physical functioning as time spent during a walking activity. Appendix B lists the methods of comorbidity and symptom measurements and provides a narrative summary of each study's relevant findings.

3.2. Risk of bias of eligible studies

Notably, only one fifth of eligible papers (n=5, 19%) had an overall low risk of bias, whilst the majority exhibited a moderate (n=13, 50%) or high risk of bias (n=8, 31%). A high risk of bias was most often assigned to the domain “study participation” (in 6 studies) mainly due to poor description of study participants. The domains "study confounding" and "prognostic factor measurement" received a greater proportion of moderate bias ratings compared to the other domains. That is, in 14 studies, cross-sectional study designs were used and/or relevant confounders were insufficiently addressed, whilst, in 15 studies, valid comorbidity assessment tools were lacking and/or tools were poorly described. (Table 3)

<<Table 3 inserted here>>

3.3. Association between presence of comorbidity and severity of symptoms

Figure 2 depicts the forest plots of the primary analysis. One in four participants reported at least one comorbidity in general (1129 of 4580 participants, 25%).[21, 28, 29, 31, 34, 38-42, 44] In people with knee and/or hip osteoarthritis, evidence of moderate quality was found to indicate a significant association between the presence of at least one comorbidity and worse, or greater changes in, symptoms of pain (regression coefficient (95% CI): 0.18 (0.14,0.22), $p<0.001$; $I^2=0\%$) and performance-based physical functioning (regression coefficient (95% CI): 0.20 (0.10,0.29), $p<0.001$; $I^2=0\%$). Whilst the association with worsened self-reported physical

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function was also significant, this evidence was of low quality as substantial heterogeneity was evident (I^2=75%).(Table 4)

Four studies[30, 33, 37, 40] specifically examined the relationship between the presence of musculoskeletal comorbidity including joint pain comorbidities, and severity of clinical symptoms. Musculoskeletal comorbidity was common (in 944 of 2340 participants, 40%). The presence of at least one musculoskeletal comorbid condition predicted worse, or greater changes in, symptoms of pain (regression coefficient (95% CI): 0.85 (0.06,1.63), p=0.034, I^2=90%) whilst no significant relationships could be established for outcomes of self-reported functioning (regression coefficient (95% CI): 0.51 (-0.30,1.31), p=0.22, I^2=88). The quality of the latter evidence was rated as "very low".(Table 4) Table 5 lists the specific comorbidities that were studied classified according to the *a priori* defined disease categories.

<<Figure 2 inserted here>>

<< Table 4 inserted here>>

<< Table 5 inserted here>>

Forty-five percent (n=396) of 873 participants reported cardiac disease and/or hypertension.[29, 32, 34, 44] Evidence of moderate quality showed that the participants with cardiac comorbidity suffered significantly worse, or greater changes in, self-reported (regression coefficient (95% CI): 0.08 (0.01,0.16), p=0.036, I^2=0%) and/or performance-based physical dysfunction (regression coefficient (95% CI): 0.11 (0.02,0.20), p=0.016, I^2=0%) than those without this comorbidity. No significant associations could be established for outcomes of self-reported pain (regression coefficient (95% CI): 0.04 (-0.03,0.12), p=0.30, I^2=0%).(Table 4)

Of 588 participants, 24% (n=142) reported diabetes.[32, 44] Evidence of moderate quality indicated a significant association between suffering diabetes and worse pain (regression coefficient (95% CI): 0.10 (0.02,0.17), p=0.009, I^2=0%), but not with physical functioning (regression coefficient (95% CI): 0.07 (-0.02,0.16), p=0.13, I^2=25%). (Table 4)

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Fourteen percent of 2894 participants (n=406) were classified as suffering depression.[36, 41, 44] Reporting depressive symptoms was not significantly associated with worse (changes in) self-reported pain (regression coefficient (95% CI): 1.11 (-0.13,2.35), p=0.08, I^2=91%) nor with physical dysfunction (regression coefficient (95% CI): 0.81 (-0.80, 2.41), p=0.12, I^2=90%). Due to substantial heterogeneity, the overall quality of this evidence was rated as "very low".(Table 4)

Fifty-six percent of 1978 participants (n=1109) reported back pain.[32, 33, 44] Evidence of moderate quality was found to underpin a significant association between the presence of back pain and deteriorated physical functioning (regression coefficient (95% CI): 0.12 (0.04,0.20), p=0.003, I^2=0%). For outcomes of pain severity, no significant association could be found (regression coefficient (95% CI): 0.17 (-0.01,0.35), p=0.06, I^2=74%). The quality of the latter evidence was rated as "low" due to substantial heterogeneity. (Table 4)

4. DISCUSSION

This meta-analysis aimed to quantitatively review the published literature on the relationship between the presence of comorbidities and the prognosis of clinical symptoms in people with knee and/or hip osteoarthritis.

A greater comorbidity count was associated with worse, or greater deterioration of, outcomes of pain severity and performance-based physical functioning. Thus, our findings support the use of comorbidity burden as a relevant confounder in prognostic studies of symptom progression in this population. Alternatively, in clinical practice, comorbidity assessments may facilitate the appraisal of the patient's disease burden. Interestingly, meta-analysis findings did not show consistent results for the outcomes of self-reported, as opposed to performance-based, physical functioning, as the analysis was prone to substantial heterogeneity. As we did not plan any sub-group analyses *a priori*, we can only speculate about potential explanations for this observation. It is likely that the consistent findings of performance-based functioning may have been the result of fewer studies pooling comparable outcomes of time spent during a walking activity. As self-reported physical functioning scales were utilised by the majority of studies, these scales generally query the level of difficulty for a variety of activities of daily living and of varying

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relevance with respect to the comorbidities under study.[46, 47] As such, this may have introduced inconsistent relationships. Secondly, inspection of forest plots suggests that, compared to the cross-sectional studies, longitudinal studies may have generated stronger relationships between comorbidity presence and symptom deterioration. Similarly, participants suffering at least one musculoskeletal comorbidity were more likely to experience worse symptoms of joint pain. Whilst the association with the severity of self-reported physical function did not attain statistical significance, both analyses, however, yielded inconsistent findings. The inclusion of a diverse range of musculoskeletal conditions and the relatively wide scope of physical functioning scales may constitute plausible sources of heterogeneity. Yet, unlike the findings of general comorbidities, forest plots suggested greater effects of musculoskeletal comorbidities on symptom severity across the cross-sectional rather than prospective cohort studies. This calls for the need to conduct more longitudinal observational studies as to better understand whether comorbidities, and which types of conditions, affect the progression of symptomatic disease over time in people with knee and/or hip osteoarthritis.

Our data yielded evidence of moderate quality to show a significant relationship between the presence of cardiac disease and/or hypertension and greater severity of both performance-based and self-reported physical functioning. Although the pooled findings were derived from relatively few studies, this observation concurs with large-scaled epidemiological studies confirming that cardiovascular pathology is amongst the most important medical conditions to further physical disability in the elderly.[46, 48-50] Given the direct influence on activities requiring aerobic work capacity, cardiovascular comorbidity likely has a greater impact on physical dysfunction than on the severity of joint pain,[46] as was also corroborated by the current data.

In contrast, consistent findings were obtained supporting a significant association between having diabetes and increased joint pain severity. A recent study by Eitner et al.[51] suggested that, when compared to non-diabetic patients, synovitis may be an important mechanism to underlie enhanced pain sensations in diabetic knee osteoarthritis patients. Additionally, 10-20% of diabetic patients may develop painful neuropathy in the distal extremities, potentially contributing to worse pain symptoms.[51, 52] Although the causal pathway between diabetes and physical disability remains not fully understood, diabetes-related complications (eg, neuropathy, myopathy, cardiovascular disease, retinopathy, nephropathy)

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were suggested to not fully explain the patients' level of physical deterioration.[52] Rather, frailty was acknowledged as a potential mediator in the pathway from diabetes to disability.[52] This may clarify why the current results failed to endorse a significant and direct association with outcomes of physical dysfunction.

This meta-analysis did not show a significant association between depression and deterioration in symptoms. This was unexpected given depression and persistent pain generally occur together and their reciprocal association contributes to worse pain as well as a higher risk of physical decline, or patient-underestimated assessments of functional ability, particularly in elderly populations.[53-56] Whilst in the current analysis all but one studies utilised a valid method to ascertain the presence of clinically-relevant depressive symptoms, the prevalence of depression (14%) tended to be lower than previously reported for osteoarthritis populations (20%).[9] We excluded reports that did not classify participants under distinct comorbid conditions. One may argue that other studies have established relationships between higher scores of depressive symptoms and severity of osteoarthritis symptoms (eg, [57-59]). Yet, these analyses were conducted in cohorts with participants primarily at risk of knee osteoarthritis rather than with established disease and/or irrespective of whether depressive symptoms were clinically-relevant. Considering depressive symptoms are dynamic[56] and we obtained a relatively small sample of studies, these differences altogether may explain our observation.

In a final exploratory analysis, we found that suffering co-existing back pain was significantly associated with worse physical functioning. Back pain is an important cause of absence from work as well as physical disability and has been identified as a predictor of worse functional outcomes following knee arthroplasty surgery, all of which support the present data.[7, 60, 61] Nevertheless, we were unable to underpin a significant association with more severe knee and/or hip pain, as findings were heterogeneous and only a limited sample of papers was identified. Inconsistency of results may be due to the use of mixed populations consisting of people with knee and/or hip osteoarthritis. That is, considering the hip-spine syndrome, concomitant back pain may likely aggravate hip pain, or vice versa.[62] The underlying mechanisms by which back pain may exacerbate knee pain are complex and potentially also involve referred pain stemming from the spine, central sensitisation of pain and/or generalised joint pain conditions[33], all of which likely contribute to patients' inconsistent clinical presentation.

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This meta-analysis has two main limitations. Firstly, analyses did not consider whether the development of comorbidities (eg diabetes or cardiovascular pathology) may have been driven by other underlying pathologies (eg, the metabolic syndrome and obesity).(63) For this reason, we did not investigate obesity as a comorbidity as such. Secondly, the search strategy was developed to accommodate the primary research question, and thus, comorbid-specific meta-analyses are required to confirm, or refute, our exploratory findings.

5. CONCLUSION

This meta-analysis showed that, in people with knee and/or hip osteoarthritis, having at least one comorbidity in general was significantly associated with worse, or greater deterioration, of symptoms of pain and performance-based physical functioning. Exploratory analyses suggested that co-existing cardiac disease and/or hypertension, or back pain, may aggravate physical dysfunction whilst suffering diabetes resulted in worse joint pain. Multi-morbidity should be considered in the prognosis of osteoarthritis symptoms.

6. FUNDING

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7. ACKNOWLEDGEMENTS

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8. CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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FIGURES

Figure 1. Flowchart of the study selection process.

Figure 2. Forest plots of the primary analysis. Pooled results (regression coefficients (effects sizes) and 95% confidence intervals (CI)). A (top panel): the association between the presence of at least one general comorbidity and self-reported pain as well as self-reported/ performance-based physical function. B (bottom panel): the association between the presence of musculoskeletal comorbidity and severity of self-reported pain and physical dysfunction. Positive effect sizes indicate worsening of symptoms. *Longitudinal observational study design

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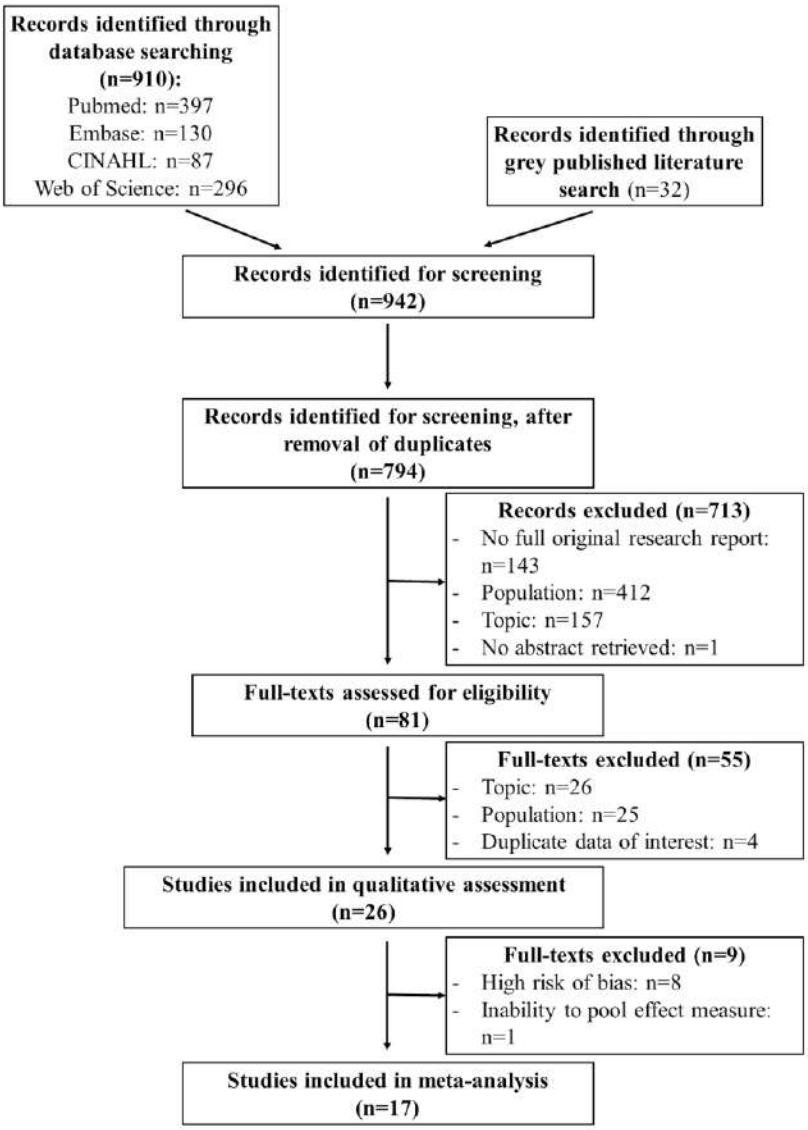

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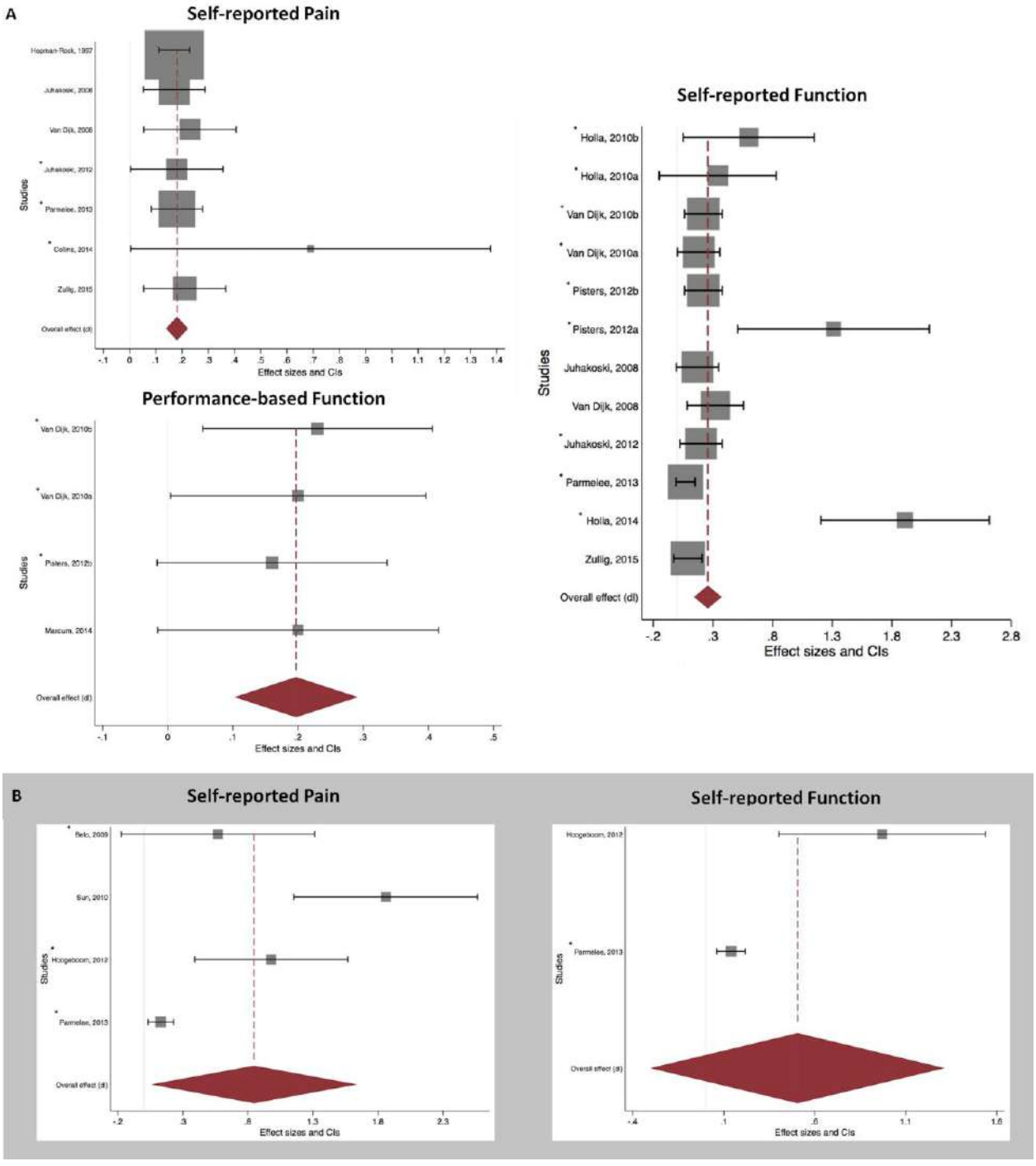

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TABLES

Table 1. Items for data extraction

Category	Data items	Comments
Study ID	• Author, year, title • Country	
Osteoarthritis diagnosis	• Index joint (knee, hip, mixed) • Diagnosis method (self-reported, symptomatic and/or radiographic criteria)	
Participant characteristics	• Average age (years) • Average body mass index (kg/m^2) • % females • % Kellgren-Lawrence ≥grade 2	
Methodology	• Sample size • Study design • Setting • Duration of follow-up (years) • Study attrition (or complete data sets in cross-sectional studies) (%) • Drop-outs (number and description) • Clinical trial identifiers (if relevant)	
Comorbidity	• Variable name • Category (total count/presence or type) • Measurement method • Prevalence (n, %)	Specific types of comorbidities were categorised as "medical (ie, musculoskeletal, cardiovascular & respiratory, metabolic & endocrine, neurological, other)" or "psychosocial" for descriptive purposes.
Clinical symptoms	• Variable name • Measurement method	For studies reporting multiple variables for symptoms of pain and/or physical dysfunction, a previously published hierarchy[64] was implemented as to ensure single data points for synthesis.
Results	• Effect measure (eg, regression coefficient) and variance (eg, standard error) and summary data • Narrative summary of relevant study findings	If the sample was stratified according to severity for the prognostic (comorbidity) and/or dependent (clinical symptoms) variables, the summary data pertaining to associations with the

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		most severe categories were extracted.[65] For studies reporting both cross-sectional and longitudinal observations, only the longitudinal data were extracted. If possible, effect measures were extracted adjusted for confounders.[65]
Comments	• Any other comments relevant to assessment of methodological quality or interpretation of the findings	

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Table 2. Characteristics of eligible studies (n=26)

Study ID		**Methodology**				**Participant Characteristics**					
Author, yr	**Country**	**Design**	**FU**	**Setting**	***n***	**OA Diagnosis**	**Index joint**	**Age**	**BMI**	**%female**	**%KL grade ≥2**
Hopman-Rock, 1997	Netherlands	CS	NA	Community	306	Sx	Knee, Hip	64.9	26.5	70	Knee: 67 Hip: 40
Wolfe, 1999	USA	CS	NA	Clinic-outpatient	655	Sx & Rx	Knee, Hip	67.8	NR	NR	NR
Cimmino, 2005	Italy	CS	NA	Clinic-outpatient	25589	Sx	Knee, Hip	70	NR	69	NA
Peters, 2005	United Kingdom	LO	1 yr	Clinic-outpatient & Community	287	Sx	Knee, Hip	NR	NR	61	NA
Salaffi, 2005	Italy	CS	NA	Clinic-outpatient	302	Sx & Rx	Knee, Hip	68.2	27.8	59	Knee: 91 Hip: 90
Croft,	United	CS	N	Clinic-	2210	Sx	Kne	NR	NR	58	NA

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2005	Kingdom		A	outpatient			e				
Peat, 2006	United Kingdom	CS	NA	Clinic-outpatient	2429	Sx	Knee, Hip	65.6	NR	59	NA
Jinks, 2008	United Kingdom	LO	3yr	Clinic-outpatient	923	Sx	Knee	NR	NR	56	NA
Juhakoski, 2008	Finland	CS	NA	Clinic-outpatient & Community	118	Sx & Rx	Hip	67	NR	70	59
van Dijk, 2008	Netherlands	CS	NA	Clinic-outpatient	288	Sx &/or Rx	Knee, Hip	66	NR	71	NR*
Belo, 2009	Netherlands	LO	1 yr	Clinic-outpatient	549	Sx	Knee	53.8	27	49	NA
Holla, 2010	Netherlands	LO	2 yr	Clinic-outpatient & Community	1002	Sx	Knee, Hip	55.9	25.5	80	Knee: 7 Hip: 8
Reeuwijk, 2010	Netherlands	CS	NA	Clinic-outpatient	288	Sx &/or Rx	Knee, Hip	66	27.8	71	Knee: 95 Hip:98
Suri, 2010	USA	CS	NA	Community	1309	Sx & Rx	Knee	61.4	30.2	57	92
van Dijk 2010	Netherlands	LO	3 yr	Clinic-outpatient	288	Sx &/or Rx	Knee, Hip	66	27.6	71	Knee: 95 Hip: 91
Leite, 2011	Brazil	CS	NA	Clinic-outpatient	91	Sx (Rx unclear)	Knee	59.3	NR	91	Unclear
Knoop, 2011	Netherlands	CS	NA	Community	842	Sx & Rx	Knee	63.2	29.9	55	84
Hoogeboom, 2012	Netherlands	CS	NA	Clinic-outpatient	489	Sx	Knee, Hip	58	27	58	76
Juhakoski, 2012	Finland	LO (RCT)	2 yr	Clinic-outpatient & Community	118	Sx & Rx	Hip	66.6	NR	70	59
Pisters, 2012	Netherlands	LO	5 yr	Clinic-outpatient	288	Sx &/or Rx	Knee, Hip	66.4	27.7	50	NR
Parmelee, 2013	USA	LO	1 yr	Clinic-outpatien	367	Unclear	Knee	67.9	NR	64	Unclear

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				t & Community							
Collins, 2014	USA	LO	6 yr	Community	1753	Rx	Knee	62	30.1	59	100
Holla, 2014	Netherlands	LO	5 yr	Clinic-outpatient	701	Sx	Knee	56	26.6	81	0
Marcum, 2014	USA	CS	NA	Community	190	Sx & Rx	Knee	66	32.4	15	NR
Zullig, 2015	USA	CS	NA	Clinic-outpatient	300	Sx &/or Rx	Knee, Hip	61.1	33.8	9	NR
Bastick, 2016	Netherlands	LO	5 yr	Clinic-outpatient	734	Sx	Knee	56	26.5	81	0

yr: year. FU: duration of follow-up. *n*: number of participants. OA: osteoarthritis. KL: Kellgren-Lawrence. Sx: Symptomatic. Rx: Radiographic. NA: Not Applicable. NR: Not Reported. *not reported using Kellgren-Lawrence grading system. CS: cross-sectional study. LO: longitudinal, observational study. RCT: randomized controlled trial

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Table 3. Within-study risk of bias of all eligible studies (n=26)

Study ID	QUIPS Domains						Overall Risk of Bias[1]
Author, yr	Participation	Attrition	Prognostic Factor	Outcome	Confounding	Statistical Analysis & Reporting	
Hopman-Rock, 1997	L	L	M	M	M	L	M
Wolfe, 1999	H	L	M	L	M	L	H
Cimmino, 2005	L	L	L	L	H	M	H
Peters, 2005	H	L	M	M	M	M	H
Salaffi, 2005	L	L	M	M	H	H	H
Croft, 2005	H	L	L	L	M	L	H
Peat, 2006	H	L	M	L	M	H	H
Jinks, 2008	H	M	M	M	L	L	H
Juhakoski, 2008	L	L	M	L	L	L	L
van Dijk, 2008	L	L	L	L	M	M	M
Belo, 2009	L	L	H	M	L	L	M
Holla, 2010	L	L	M	L	L	L	L
Reeuwijk, 2010	L	L	L	L	M	L	M
Suri, 2010	L	L	M	L	M	L	M
van Dijk 2010	L	L	L	L	L	M	M
Leite, 2011	H	L	M	L	H	M	H
Knoop, 2011	L	L	L	L	M	L	M
Hoogeboom, 2012	L	L	M	L	M	M	M
Juhakoski, 2012	L	L	M	L	M	L	M
Pisters, 2012	L	M	L	L	L	L	M
Parmelee, 2013	M	M	M	M	M	M	M
Collins, 2014	L	L	L	L	L	L	L
Holla, 2014	L	L	M	L	L	L	L
Marcum, 2014	L	L	L	M	M	L	M
Zullig, 2015	M	L	L	L	M	L	M
Bastick, 2016	L	L	M	L	L	L	L

QUIPS: QUality In Prognostic Studies tool. Yr: year. H: high risk of bias. M: moderate risk of bias. L: low risk of bias.

[1]Determined based on the highest risk ratings from the domains "attrition", "confounding" and "statistical analysis & reporting", augmented by one level (ie, to a greater risk of bias) if a high risk was assigned to any of the other QUIPS domains.

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Table 4. Meta-analysis and GRADE assessment findings (n=17)

			Meta-analysis Findings		GRADE Assessment					
Comorbidity	**Symptoms**	***n***	**Regression coefficient (95% CI)[1]**	***P*[2]**	**Bias**	**Indirectness**	**Heterogeneity (I^2)**	**Imprecision**	**Publication bias[3]**	**Quality evidence**
Total count/Presence										
General	SR pain	7	0.18 (0.14,0.22)	<0.001*	M	L	0%	L	NA	M
	SR function	12	0.26 (0.14,0.37)	<0.001*	M	L	75%	L	H	L
	PB function	4	0.20 (0.10,0.29)	<0.001*	M	L	0%	L	NA	M
Musculoskeletal	SF pain	4	0.85 (0.06,1.63)	0.034*	M	M	90%	L	NA	VL
	SF function	2	0.51 (-0.30,1.31)	0.22	M	M	88%	L	NA	VL
Type										
Depression	SF pain	3	1.11 (-0.13,2.35)	0.08	M	L	91%	M	NA	VL
	SF function	2	0.81 (-0.79, 2.41)	0.33	M	L	90%	H	NA	VL
Cardiac Disease & hypertension	SF pain	3	0.04 (-0.03,0.12)	0.30	M	L	0%	L	NA	M
	SF function	4	0.08 (0.01,0.16)	0.036*	M	L	0%	L	NA	M
	PB function	2	0.11 (0.02, 0.20)	0.016*	M	L	0%	L	NA	M
Back pain	SR pain	3	0.17 (-0.01,0.35)	0.06	M	L	74%	L	NA	L

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	SR function	2	0.12 (0.04,0.20)	0.003*	M	L	0%	L	NA	M
Diabetes	SR pain	2	0.10 (0.02,0.17)	0.009*	M	L	0%	L	NA	M
	SR function	2	0.07 (-0.02, 0.16)	0.13	M	L	25%	L	NA	M

n: number of studies included in the analysis. GRADE: Grades of Recommendation, Assessment, Development and Evaluation. NA: not applicable. SR: self-reported. PB: performance-based. H: high. M: moderate. L: low. VL: very low.

[1]pooled regression coefficient (95% confidence interval: lower limit, upper limit); a positive estimate indicates worse symptoms in the presence of comorbidity.

[2]Test for overall effect from a random-effects model.

[3]Only assessed for analyses containing >10 studies using funnel plots, and thus, not included in the GRADE assessment.

*Significant overall effect at $\alpha<0.05$

Table 5. List of general disease groupings and/or specific diseases as included in the comorbidity assessment tools of studies in the primary analysis and classified according to disease categories (ie, musculoskeletal, cardiovascular & respiratory, metabolic & endocrine, neurological, psychosocial, or other).

Musculoskeletal [29-31,33-34,39-42,44]	Cardiovascular & Respiratory [20,28-29,31,34,38-39,41-42,44]	Metabolic & Endocrine [20,28-29, 31, 34, 38-39, 41-42, 44]	Neurological [20,29,31,34,39, 41-42]	Psychosocial [29,34,39,44]	Other [20,29,31,34,39,41-42,44]
General - Muscle, bone and skin diseases **Specific** - Joint pain comorbidities - Back pain - Connective tissue disease - Rheumatoid arthritis	**General** - Cardiac, cardiovascular and/or respiratory diseases - Vascular diseases **Specific** - Hypertension - Coronary disease - Myocardial infarction - Cardiac/congestive heart failure - Chronic	**General** - Endocrine and metabolic diseases - Thyroid gland diseases **Specific** - Diabetes Mellitus - Osteoporosis	**General** - Neurological diseases **Specific** - Headache - Dementia - Parkinson's disease - Cerebrovascular disease & stroke - Epileptic insults - Hemiplegia	**General** - Psychiatric diseases **Specific** - Depression - Sleep disorders - Conditions needing psychological counselling	**General** - Eye, ear, nose, throat, larynx diseases - Diseases of the upper/lower gastro-intestinal tract - Genitourinary diseases - Hepatic diseases - Renal diseases - Cancer - Severe skin

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	respiratory disease/chronic obstructive pulmonary disease - Lung disease - Wheezing and/or asthmatic attacks - Peripheral vascular disease - Lower extremity arterial disease - Deep venous thrombosis	diseases - Anemia or blood diseases **Specific** - Chronic sinusitis - Visual impairment - Gastric/peptic ulcer - Gallstones - AIDS

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