Arthritis Care & Research
Vol. 72, No. 7, July 2020, pp 991–1000
DOI 10.1002/acr.24008

American College of Rheumatology
Empowering Rheumatology Professionals

Comorbidities in Osteoarthritis: A Systematic Review and Meta-Analysis of Observational Studies

Subhashisa Swain,[1] Aliya Sarmanova,[1] Carol Coupland,[2] Michael Doherty,[1] and Weiya Zhang[1]

Objective. Osteoarthritis (OA) is a common chronic condition in older individuals, but its association with other chronic conditions is largely unknown. This study aimed to systematically review the literature on comorbidities in individuals with OA compared to those without.

Methods. We searched 4 databases for observational studies on comorbidities in individuals with OA. Studies of OA only or in comparison with non-OA controls were included. The risk of bias and study quality were assessed using the Newcastle-Ottawa Scale. The prevalence of comorbidities in the OA group and the prevalence ratio (PR) and 95% confidence interval (95% CI) between OA and non-OA groups were calculated.

Results. In all, 42 studies from 16 countries (27 case-only and 15 comparative studies) met the inclusion criteria. The mean age of participants varied from 51 to 76 years. The pooled prevalence of any comorbidity was 67% (95% CI 57–74) in individuals with OA versus 56% (95% CI 44–68) in individuals without OA. The pooled PR for any comorbidity was 1.21 (95% CI 1.02–1.45). The PR increased from 0.73 (95% CI 0.43–1.25) for 1 comorbidity to 1.58 (95% CI 1.03–2.42) for 2, and to 1.94 (95% CI 1.45–2.59) for ≥3 comorbidities. The key comorbidities associated with OA were stroke (PR 2.61 [95% CI 2.13–3.21]), peptic ulcer (PR 2.36 [95% CI 1.71–3.27]), and metabolic syndrome (PR 1.94 [95% CI 1.21–3.12]).

Conclusion. Individuals with OA are more likely to have other chronic conditions. The association is dose-dependent in terms of the number of comorbidities, suggesting multimorbidities. Further studies on the causality of this association and clinical implications are needed.

INTRODUCTION

Osteoarthritis (OA) is by far the most common form of arthritis and is a major cause of pain and disability in older individuals (1). It is a common, complex disorder with multiple genetic, constitutional, and environmental risk factors (2). The presence of multiple chronic conditions in a single individual causes higher mortality, increased hospitalization, impaired physical and mental health, worse disease outcome, and poorer quality of life (3,4). The coexistence of chronic conditions with OA is also very common, especially in the later decades of life (5,6). For example, according to the Centers for Disease Control and Prevention, >30% of individuals with diabetes mellitus and heart disease have OA (7).

Most literature on OA comorbidity was published in the last 3 years. The review articles focused on the distribution and impact of individual chronic conditions such as cardiovascular diseases, diabetes mellitus, and depression in OA (8–11). Even though comorbidity was discussed as a concept in the 1960s, only in 1996 was a distinct definition first suggested to differentiate comorbidity (implying an index disease with mechanistically linked additional conditions) and multimorbidity (implying any co-occurrence of medical conditions) within an individual (12). Comorbidity research in OA is still at a preliminary stage, and the evidence is yet to be accumulated.

A systematic review on OA reported worsening of pain and a decline in functional activities among individuals due to the presence of other chronic conditions (13). Clinically, comorbidities in OA create greater challenges for management. The number and pattern of different comorbid conditions determine the severity and burden in patients with multimorbidities (14,15). However, except for shared risk factors such as aging and obesity, little is known about biologic plausibility to explain the concurrence of OA and associated comorbidities (16,17). According to the European League Against Rheumatism (EULAR) and the National Institute

PROSPERO: CRD42016038484.
Supported by Versus Arthritis (grants 20777 and 21595), formerly Arthritis Research UK, the University of Nottingham Vice-Chancellor's Scholarship, and a Beijing Joint Care Foundation Scholarship.
[1]Subhashisa Swain, MPH, Aliya Sarmanova, PhD, Michael Doherty, MD, Weiya Zhang, PhD: University of Nottingham, Nottingham, UK; [2]Carol Coupland, PhD: School of Medicine, University of Nottingham, Nottingham, UK.

No potential conflicts of interest relevant to this article were reported.
Address correspondence to Weiya Zhang, PhD, Academic Rheumatology, Division of Rheumatology, Orthopaedics and Dermatology, The University of Nottingham, Nottingham, UK. E-mail: Weiya.Zhang@nottingham.ac.uk.
Submitted for publication October 11, 2018; accepted in revised form June 11, 2019.

SIGNIFICANCE & INNOVATIONS

- This is the first systematic review of the current literature on comorbidities in osteoarthritis (OA), with an extensive list of the conditions.
- In total, 67% of individuals with OA have at least 1 other chronic condition, which is 20% higher than for those without OA.
- There was a graded effect in terms of the risk of having 1, 2, and ≥3 comorbidities in individuals with OA compared to those without.
- In individuals with OA, the systems most likely to be affected by comorbidities are upper gastrointestinal, psychological, cardiovascular, and endocrine.
- Stroke, peptic ulcer, and metabolic syndrome are the most common comorbidities.

for Health and Care Excellence, the diagnosis and management of specific comorbidities and understanding their pattern in OA are important and are recommended for best practice (18,19). An Arthritis Research UK report on multimorbidity in OA also highlighted the importance of understanding the presence of multiple comorbidities with OA for formulating a patient-centered management plan (20). This study aimed to systematically review the current literature on the comorbidities in OA, specifically, the risk (prevalence or incidence) of comorbidities in individuals with OA compared to those without OA.

MATERIALS AND METHODS

Search methods and sources. A protocol adhering to the Preferred Reporting Items for Systematic Review and Meta-Analysis 2015 statement was designed and registered online with PROSPERO. Medline, PubMed, Embase, and Scopus databases were used to identify studies conducted in any country between January 1, 1995 and December 31, 2017. Additionally, "comorbidity in OA" was searched in the Google Scholar search engine, and the first 1,000 articles were screened for inclusion. The complete search consisted of searches for OA (any joint), searches for comorbidities, and searches for observational studies. The 3 search strategies were then combined using AND to generate citations. The details of the search strategies can be seen in Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract. In addition, websites of international societies dealing with arthritis such as EULAR, the American College of Rheumatology, and Osteoarthritis Research Society International were searched (18,21,22). References within systematic reviews and review articles were also read for additional relevant original articles.

Selection criteria. All types of observational studies (with or without a non-OA control) documenting prevalence or incidence and the risk ratio of OA comorbidity were included in the study. We defined comorbidity as the presence of any concurrent chronic condition in individuals with OA (as an index disease).

Studies included individuals with OA diagnosed by a physician through physical examination or radiographic findings. OA was the primary exposure, and outcomes were the presence of any comorbidities. Other comparisons included studies comparing the prevalence/incidence of comorbidities in OA with non-OA controls (comparative) and studies of comorbidities in individuals with OA (case-only).

According to the above criteria, all studies identified by title and abstract were gathered, and duplicates were removed. Potentially relevant articles were selected through initial title and abstract screening by 2 authors (SS and AS) independently. Any disagreement was discussed with a third author (WZ). The full text copies of these relevant articles were then retrieved. We retained articles that studied the prevalence of other chronic conditions in individuals with OA. Full texts of potentially suitable articles were further screened for inclusion (SS). Disagreement in the screening of full texts was resolved by a third reviewer (WZ). There was no language limitation. We used Endnote for screening of articles, and data extraction was done without using any software.

Quality assessment. One reviewer (SS) independently assessed study quality based on items in the Newcastle-Ottawa Scale (NOS) checklist (23). Any concern on quality scoring was decided in consultation with another reviewer (AS or WZ). The NOS tool has a scoring scale under 3 sections: participant selection and representativeness, comparability of study groups, and assessment of outcome or exposure. The quality score is based on a star system (range 0–9 stars for case–control and cohort studies and 0–10 for cross-sectional studies), with a higher score representing better methodologic quality.

Data extraction. A customized data extraction form was used to extract data from each study. For each included study, we collected the following information: authors and publication year, title and journal, study country and location (urban or rural), study design, sampling method (random or nonrandom), sample size, sample characteristics such as age and sex, the number of conditions included, methods of comorbidity measurement, and prevalence (overall and group specific for each comorbidity).

Outcome. The primary outcome was the risk (prevalence) of comorbidities in individuals with OA (cases) versus those without OA (controls), and secondary outcomes included the types of comorbidities associated with OA. The risk of having the comorbidity between OA and non-OA controls was estimated through the prevalence ratio (PR), separately for all comparative studies and for age- and sex-matched/adjusted comparative studies. For cohort studies, the prevalence of comorbidities reported at baseline was included for the estimation because in these studies comorbidity was not reported as the outcome.

Statistical analysis. Descriptive characteristics of the studies are expressed as means/medians and/or frequencies, as appropriate, depending on the variables. For comorbidity count, we used the median because of wider variation in the list of the diseases across the studies. Heterogeneity between studies was measured using the I^2 (%) and Q test (*P* value) (24,25). Publication bias was assessed using funnel plots and Egger's test, with statistical significance being conferred to a *P* value less than 0.05 (26). For heterogeneity, I^2 above 75% was considered as wider heterogeneity, demanding careful interpretation of the findings (25). Prevalence and PR and 95% confidence intervals (95% CIs) were calculated wherever possible for each comorbidity. The PR was chosen over odds ratio (OR) because we had prevalence data for both OA cases (exposure) and non-OA controls (non-exposure). In this scenario, PR is recommended over OR to minimize the overestimation of the relative risk (27). For prevalence estimation, subgroup analysis was done according to the study design (cross-sectional, case–control, and cohort). For PR, however, only 1 article had a different study design from the others, thus not allowing us to perform the subgroup analysis as per the study design. Therefore, for the PR estimation, subgroup analysis was done as per the NOS. We used the median NOS score of 6 as a cutoff for grouping the studies. To remove the impact of age and sex, the association of disease-specific and system-specific comorbidities analysis was done for all the comparative studies and for age-/sex-matched control comparative studies. The results across different studies were pooled using the random effects meta-analysis Metaprop module (28), an additional function of Stata software, version 15 (29), and Revman software, version 5.3 (30).

RESULTS

Search results and study qualities. The initial search yielded 70,014 articles from 4 databases. After removal of duplicates, 48,661 remained, of which 1,091 appeared relevant after title screening. Abstract reading confirmed 56 relevant articles and full-text articles that were fully assessed. In all, 42 articles met the inclusion criteria (Figure 1). On the quality assessment scale (maximum of 10) for cross-sectional studies (n = 33), the aver-

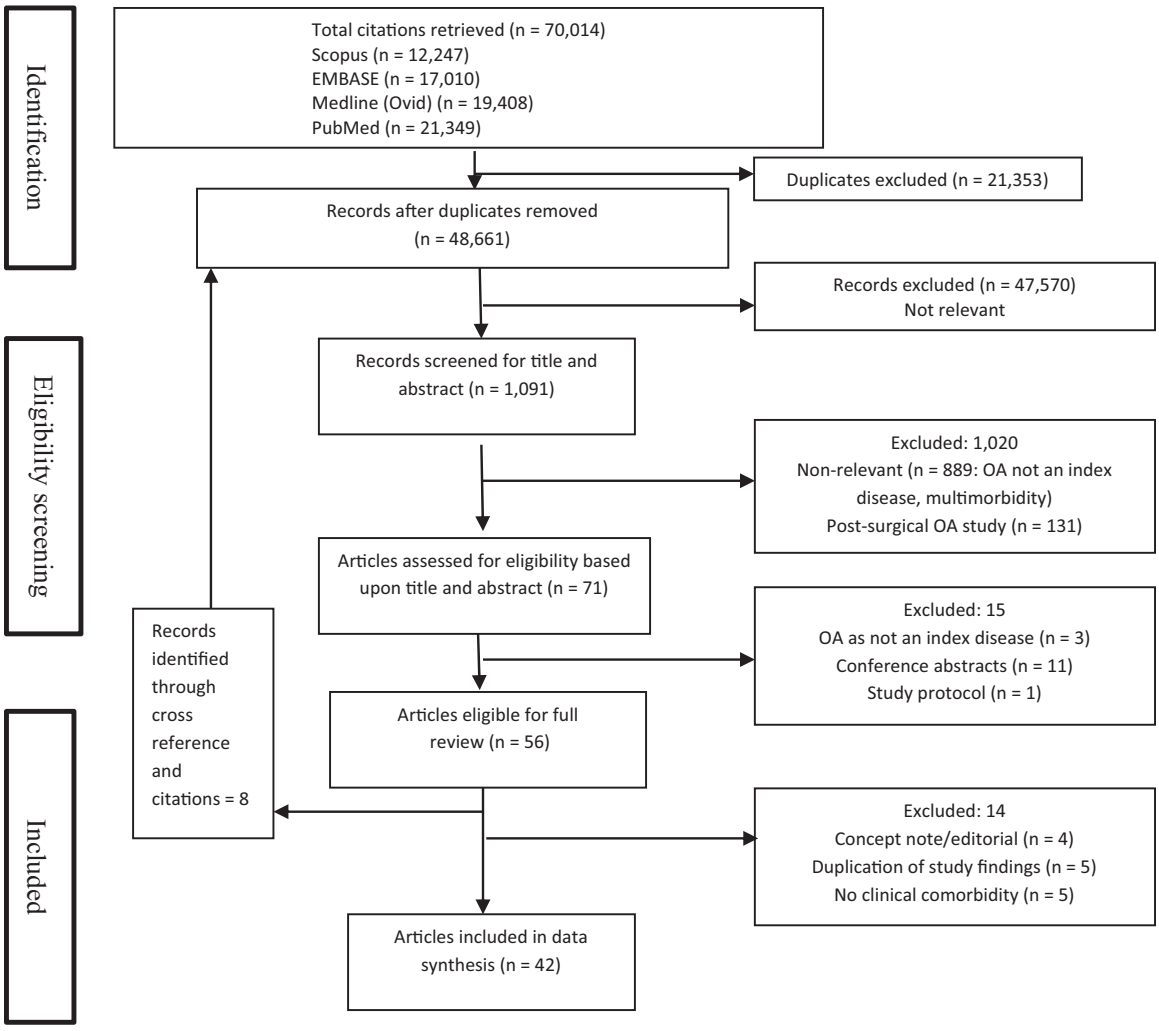

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study selection. OA = osteoarthritis.

age score was 5.44 (median 6), and of those, 22 studies had ≥5 stars (31–52). Five case–control and 4 cohort studies had an average score of 5.22 (range 0–9), with 6 studies (6,33,53–56) having ≥5 stars (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract). References 51–92 are in Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract.

Study characteristics. Of the 42 included studies, 15 compared comorbidities between individuals with OA and those without (comparative studies), whereas 27 examined comorbidities in individuals with OA only (case-only studies). These included 3 case–control studies (6,57,58), 6 cohort studies (53–56,59,60), and 33 cross-sectional studies that explored comorbidity in individuals with OA (1,5,31–52,61–70) (Table 1). We used the baseline comorbidity information from the cohort studies. Thus, we could calculate prevalence only for the comorbidities. Twelve studies were from the US (32,34–40,53,57,63,65), 9 from the Netherlands (1,33,41–44,54,55,59,60), 4 from the UK (6,45,46,66), 2 each from Finland (47,48), Japan (49,56), and Italy (61,67), and 1 each from Canada (50), Hong Kong (5), Spain (68), Australia (51), South Korea (52), Germany (31), Turkey (62), India (69), Brazil (70), Iraq (58), and Latin America (64). Twelve studies were community-based (6,40,45,47,49,51–53,55,56,65,66), 2 were based on national insurance data (32,57), and 28 were hospital-based studies. Eleven studies collected information on knee OA (5,37,49,52,53,56–58,62,68,69), 2 were on hip OA (47,63), 14 were on both knee and hip OA (1,6,33,39,41,42,45,54,55,60,66,67,71), and there was 1 each on ankle (35), hand (43), and hip/knee/hand OA (61). Of 15 comparative studies, 12

Table 1. Characteristics of included studies*

Characteristic	Comparative studies (OA versus non-OA)	Case-only studies (OA only)
Studies	15	27
Study participants	773,592	832,423
Age, mean (range) years	60.1 (50.8–76.1)	63.9 (54.1–74.0)
Women, % (95% CI)	53.0 (35.0–70.0)	63.0 (57.0–69.0)
Body mass index, mean (range)†	27.3 (24.0–29.8) (3 studies)	27.0 (22.0–31.3) (17 studies)
Obesity prevalence, % (95% CI)†	53.4 (42.7–64.1) (7 studies)	31.9 (21.6–42.3) (18 studies)
Comorbidities assessed, median (IQR)‡	6 (4–24) (15 studies)	13 (8–15) (27 studies)
OA site		
Knee	5	6
Hip	0	2
Ankle	1	0
Both knee and hip	3	11
Hand	0	1
Any joint	5	6
Hand, hip, and knee	0	1
Not given	1	0
Methods of comorbidity measurement		
Charlson Comorbidity Index	0	2
Chronic Illness Rating Scale	1	3
Simple count	10	16
Functional comorbidity assessment	1	0
Self-assessed comorbidity questionnaire	0	1
Three methods	0	1
Not mentioned	3	4
Study settings		
Community-based	7	5
Hospital-based	6	22
Insurance data	2	0
Methods of OA diagnosis		
Physician diagnosed	6	18
Self-reported	3	1
Radiographic	1	0
Physician diagnosed and radiographic	5	8

* Values are the number unless indicated otherwise. OA = osteoarthritis; 95% CI = 95% confidence interval; IQR = interquartile range.
† Information on the variable was available on the number of studies.
‡ Number of comorbidities assessed in the studies. Information on the variable was available on the number of studies.

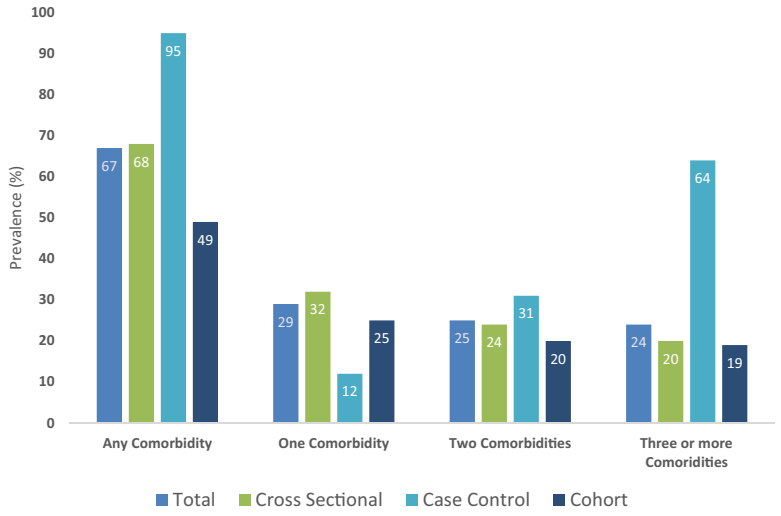

Figure 2. Prevalence of the number of any comorbidities in individuals with osteoarthritis across the study design. Number of studies in each group: Any Comorbidity: total (21), cross-sectional (16), case–control (1), cohort (4); One Comorbidity: total (18), cross-sectional (13), case–control (2), cohort (3); Two Comorbidities: total (16), cross-sectional (12), case–control (2), cohort (2); Three or more Comorbidities: total (14), cross-sectional (10), case–control (2), cohort (2).

had controls minimally matched for age and sex of OA cases. In the included studies, OA was diagnosed in the following ways: clinician assessment without radiographic findings (n = 24), clinical assessment with radiographic diagnosis (n = 13), self-reported physician-given diagnosis (n = 4) (40,45,51,65), and radiographic findings alone (n = 1) (62). Details of the study characteristics are provided in Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract.

The mean age of the study participants varied from 50.8 years to 76.1 years across studies. The sample size of the included studies ranged from 91 to 237,172 (40,49) and included both men and women, except 1 study that had only women (56). The detailed demographic information (age, sex, body mass index, and obesity) is shown in Table 1.

Prevalence of comorbidities. Of 42 included studies, 15 case-only studies and 8 comparative studies had data on the comorbidity count for analysis. The pooled prevalence of any chronic condition in all studies among individuals with OA was 66% (95% CI 58–74). In OA cases, 29% of participants had a single comorbidity, 25% had 2, and 24% had ≥3. Further subgroup prevalence across the study design is shown in Figure 2. High heterogeneity was observed across studies. Technical details of the data extraction are provided in Supplementary Tables 3 and 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract.

The leading systems in terms of pooled prevalence in individuals with OA were cardiovascular (35%), musculoskeletal (34%), neurologic (30%), and upper gastrointestinal (19%). The leading chronic conditions reported among individuals with OA were hypertension (50% [95% CI 36–57]), dyslipidemia (48% [95% CI 14–66]), and back pain (33% [95% CI 11–37]), followed by thyroid disorder (26% [95% CI 6–68]) and depression (17% [95% CI 12–22]). The proportion of chronic conditions was reported to be higher in case–control and cross-sectional studies compared to cohort studies (Figure 3). Details of the prevalence across the study designs are given in Supplementary Tables 5 and 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract. All the included studies were cross-sectional in nature except for 2 studies.

Comparison between individuals with and without OA. Forest plots for PR and 95% CI between OA and the number of chronic conditions in comparative studies are shown in Figure 4. Eight studies reported the prevalence of comorbidities in individuals with OA and in age- and sex-matched controls, which were used to estimate PR for matched studies (6,34,44,45,49,56,64,65).

The pooled PR for any comorbidity in studies matched for age and sex was 1.21 (95% CI 1.02–1.45; I^2 = 100%; $P < 0.001$) (Figure 4). The PR increased from 0.73 (95% CI 0.43–1.25) for 1 comorbidity to 1.58 (95% CI 1.03–2.42) for 2, and to 1.94 (95% CI 1.45–2.59) for ≥3 comorbidities in OA compared with individuals without OA (Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract). Subgroup analysis was done for the studies according to the NOS score (Figure 4). Funnel plots for the studies are given in Supplementary Figure 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract, and Egger's test reported nonsignificant publication bias (P = 0.72).

The risks for having system-specific comorbidities in age- and sex-matched/adjusted studies among individuals with OA

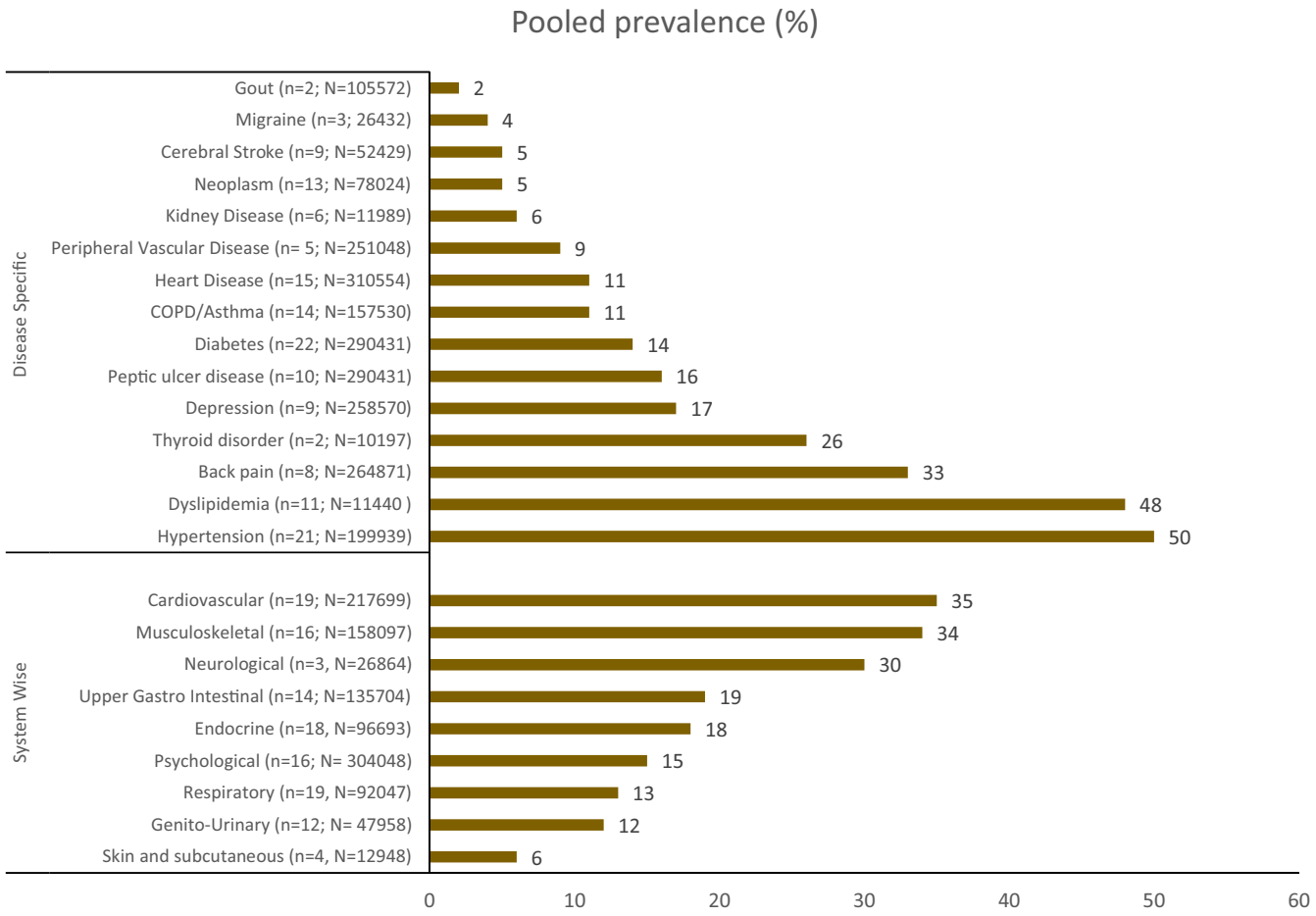

Figure 3. Prevalence (%) of comorbidities in individuals with osteoarthritis (disease and system specific). n = number of studies; N = number of participants; COPD = chronic obstructive pulmonary disease. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract.

were significantly high for upper gastrointestinal disorder (PR 2.36 [95% CI 2.31–2.41]), psychological conditions (PR 1.75 [95% CI 1.20–2.54]), and cardiovascular disease (PR 1.56 [95% CI 1.34–1.86]) compared to individuals without OA. For specific diseases, the risk of stroke was 2.61 (95% CI 2.13–3.21) times higher among individuals with OA compared to those without OA, followed by peptic ulcer (PR 2.36 [95% CI 1.71–3.27]) and metabolic syndrome (PR 1.94 [95% CI 1.21–3.12]) (Table 2).

DISCUSSION

To our knowledge, this is the first systematic review of the literature to examine the evidence of an extensive list of comorbidities in OA. A total of 42 studies from 16 countries were included. The key findings are: 1) 67% of individuals with OA had at least 1 other chronic condition, a level 20% higher than for those without OA, 2) there was a graded effect in terms of the risk of having 1, 2, and ≥3 comorbidities in individuals with OA compared to those without, 3) the systems most likely to be affected by comorbidities in individuals with OA were upper gastrointestinal, psychological, cardiovascular, and endocrine, and 4) stroke, peptic ulcer, and metabolic syndrome were the most common comorbidities in OA.

Studies on multimorbidity from both the developed and developing countries reported OA as a leading chronic condition (14,15,72,73). The risk of having any comorbidities in OA was reported to be 2.35 times higher in the UK general practices population (46), and the risk for multimorbidity was 3 times higher in the Australian population compared to a non-OA group (51). The stronger association of the number of comorbidities in OA indicates the existence of the problem of multimorbidity among these individuals. Besides the number, a pattern of chronic conditions in OA influences management decisions. Comorbidities increase the complexity of care through increased exposure to medication and other chronic conditions. However, the relationship of these factors with the comorbidities is yet to be discovered. The association with multiple chronic conditions requires further research to explore the pattern and causality of comorbidities in OA.

However, the risk for patients with OA of developing comorbidities and the biologic plausibility of such comorbidities is not well investigated. Of the 42 studies included, only 12 primarily

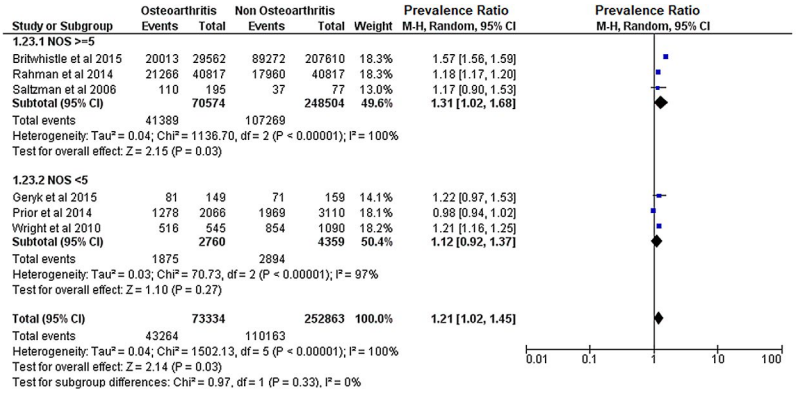

Figure 4. Risk of having comorbidities among individuals with osteoarthritis compared to individuals without osteoarthritis. Only information on systemic comorbidities has been used from the study by Saltzman et al (35) in all estimates. M-H = Mantel-Haenszel; 95% CI = 95% confidence interval; NOS = Newcastle-Ottawa Scale. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24008/abstract.

examined the comorbidity in OA, 15 had a comparative group, and 27 were published in the years 2010–2017. This summary indicates the quality of the evidence and growing interest in OA comorbidity. Evidence on the risk of having disease-specific comorbidities is not well documented, except for hypertension, diabetes mellitus, and heart diseases, and these comorbidities are further less reported according to the system (61). Few studies are available to explain the association. For example, a meta-analysis done by Wang et al (9) on the association of OA with cardiovascular diseases reported an association with a risk ratio of 1.24, which is less than in our study. Strong associations with other generalized and localized musculoskeletal conditions appeared evident (74,75), but whether coexistence with respiratory diseases was independent or related was considered inconclusive (76), in contrast to our result. According to Parkinson et al (77), individuals with OA are at a 1.41 times higher risk of getting diabetes mellitus. Nearly one-fifth of OA patients have depression (11,78), but previous systematic reviews have been inconclusive about the extent of an association (11). We report risks of 11 comorbidities among patients with OA, which is more comprehensive than any previous study to date.

Exploring factors for comorbidities can be difficult because OA might share different common risk factors with different diseases. The presence of multiple comorbidities could be explained by aging, an important risk factor for OA and other chronic conditions, but we found positive associations in age-matched comparative studies. Associations of OA with gastrointestinal diseases are well documented and usually attributed to long-term use of analgesics, particularly nonsteroidal antiinflammatory drugs (NSAIDs) (79,80). We found nonuniform recording of symptomatic gastrointestinal disorders by the studies, which necessitates correct diagnosis and reporting among patients with OA. The coexistence of cardiovascular comorbidities could be due to shared risk factors such as obesity and metabolic syndrome (81,82). Besides these, NSAIDs and impaired physical activities in OA have been reported to increase risks of developing cardiovascular disease (82–85). Nevertheless, the causal association between OA and cardiovascular disease is not well understood and could in part be attributable to a genetic linkage (86-88). For the association of OA with depression, we hypothesized that the chronicity of the disease, pain, repeated health care utilization, health expenditure, and functional limitation could be the drivers of depression among individuals having OA, and depression can also influence pain experience (78). Endocrine disorders such as hypothyroidism and diabetes mellitus could have an association with OA at specific joint sites (89), but a lack of joint-specific information and endocrine conditions in many studies limits our findings. We did not find fair evidence for musculoskeletal comorbidities in OA, even though we found reports of similar age-related changes in other joints (90) or muscle weakness or injury causing biomechanical derangement leading to pain (91). The increased reporting of back pain and migraine among patients with both symptomatic OA and asymptomatic OA might reflect multiple regional pain resulting from altered pain physiology and central pain mechanisms (92).

Although we estimated the pooled prevalence, it needs careful interpretation owing to the large heterogeneity. However, this is only a systematic review of the current literature, and the purpose of the review is to identify a signal for future research, not to confirm the prevalence and the risk ratio. Prevalence reported in epidemiologic studies is determined by the study design, sample size, case definition, and diagnostic method. The reported prevalence as per the system and disease indicates the existing burden of other chronic conditions in OA, which might affect care. Most of the chronic conditions are age related, and thus understanding their coexistence across the age groups could have been helpful. However, because of the limited articles available, we could not perform such subgroup analysis, and we limited our discussion to the association only. The heterogeneity of the studies

Table 2. Prevalence ratio of comorbidities associated with osteoarthritis (comparative studies)*

	All studies					Age-/sex-matched studies				
	Studies	Participants (OA)	Participants (non-OA)	PR (95% CI)	I^2, % (P_{heter})	Studies	Participants (OA)	Participants (non-OA)	PR (95% CI)	I^2, % (P_{heter})
Systems involved										
Upper gastrointestinal	3	127,943	130,021	2.35 (2.31–2.40)†	100 (<0.00001)	2	124,326	124,731	2.36 (2.31–2.41)†	100 (<0.00001)
Psychological condition	4	129,817	139,895	1.67 (1.23–2.29)†	98 (<0.00001)	2	124,326	124,731	1.45 (1.01–2.34)†	99 (<0.00001)
Cardiovascular	9	177,056	342,858	1.57 (1.35–1.82)†	99 (<0.00001)	5	167,274	168,723	1.42 (1.41–1.43)†	100 (<0.00001)
Endocrine	5	56,125	58,496	1.26 (1.14–1.39)†	76 (0.002)	3	52,257	52,662	1.18 (1.13–1.23)†	16 (0.30)
Genitourinary	2	14,992	17,070	1.43 (0.91–2.25)	96 (<0.00001)	1	11,375	11,780	1.14 (1.07–1.22)†	NA
Musculoskeletal	3	124,521	124,826	2.20 (0.83–5.80)	100 (<0.00001)	3	124,521	124,826	2.20 (0.83–5.80)	100 (<0.00001)
Respiratory diseases	3	55,809	57,887	1.11 (1.00–1.24)	85 (0.001)	2	52,192	52,597	1.05 (0.96–1.15)	76 (0.04)
Disease specific										
Stroke	2	5,491	15,164	1.52 (1.30–1.79)†	98 (<0.00001)	1	1,874	9,874	2.61 (2.13–3.21)	NA
Peptic ulcer disease	2	124,326	124,371	2.36 (1.71–3.27)†	88 (0.004)	2	124,326	124,371	2.36 (1.71–3.27)†	88 (0.004)
Metabolic syndrome	2	316	597	1.60 (1.20–2.13)†	1 (0.31)	1	65	65	1.94 (1.21–3.12)†	NA
Peripheral vascular disease	2	124,326	124,731	1.76 (1.04–2.97)†	96 (<0.0001)	2	124,326	124,731	1.76 (1.04–2.97)†	96 (<0.0001)
Depression	4	129,817	139,895	1.94 (1.62–2.32)†	84 (0.0003)	2	124,326	124,731	1.70 (1.29–2.24)†	90 (0.001)
Dyslipidemia	5	120,924	277,277	1.45 (1.15–1.84)†	97 (<0.0001)	2	113,016	113,016	1.57 (1.55–1.58)†	0 (0.93)
Hypertension	8	165,681	331,078	1.76 (1.44–2.17)†	100 (<0.0001)	4	155,899	156,943	1.55 (1.26–2.07)†	100 (<0.0001)
COPD/asthma	3	55,809	57,887	1.45 (1.21–1.74)†	85 (0.001)	2	52,192	52,597	1.35 (1.10–1.66)†	89 (0.003)
Back pain	2	124,326	124,731	1.92 (1.00–3.66)	99 (<0.0001)	2	124,326	124,731	1.92 (1.00–3.66)	99 (<0.0001)
Coronary heart disease	5	131,883	143,005	1.27 (0.69–2.33)	99 (<0.0001)	3	123,692	127,841	0.98 (0.39–2.44)	100 (<0.0001)
Diabetes mellitus	4	44,750	46,716	1.17 (1.13–1.21)†	0 (0.55)	2	40,882	40,882	1.25 (0.87–1.78)	26 (0.25)
Neoplasm	2	14,992	17,070	2.08 (0.47–9.18)	99 (<0.0001)	1	11,375	11,780	0.98 (0.87–1.10)	NA

* Values are the number unless indicated otherwise. OA = osteoarthritis; PR = prevalence ratio; 95% CI = 95% confidence interval; NA = not applicable; COPD = chronic obstructive pulmonary disease.
† $P < 0.05$; $P_{heter} = P$ for heterogeneity test.

and the limited research highlight the need for better-quality comorbidity research in OA.

There are several limitations to this study. First, since multimorbidity/comorbidity in OA is not well indexed in literature databases, we may have omitted some studies. Second, heterogeneity in the prevalence estimates observed in our review, stemming from diversity of methodologies, may have caused uncertainty of the results. Third, there was ambiguity in disease definitions, which creates uncertainty, for example over whether peptic ulcer, gastritis, and acidity should be considered separate entities. Fourth, suboptimal information about OA reported in studies made it difficult to differentiate between structural OA and symptomatic OA and to determine whether associations were linked primarily with structural OA or with pain experience. Similarly, the count of chronic conditions and the definition used varied considerably between studies and may have influenced the estimates (93). Our comparative groups included any non-OA cases, so the comorbidity pattern might have been different because of the selection of comparative/control groups, which needs to be interpreted with caution. Furthermore, the unavailability of joint-specific OA within comparative studies limited the estimation of joint-specific comorbidities. The study also compiles data from different study designs and thus has limitations for understanding the time sequences of OA with comorbidities. Unfortunately, there were not enough studies in each subgroup (only 1 in the cohort design) in comparative studies to perform subgroup analysis as per the study design.

In conclusion, individuals with OA are 1.2 times more likely to have any comorbidity than non-OA controls and 2.5 times more likely to have ≥3 comorbidities. The comorbidities with the highest increase in risk are stroke, peptic ulcer, hypertension, and depression. Further research is needed to determine the causality between OA and these common comorbidities to optimize treatment and develop preventive strategies.

ACKNOWLEDGMENT

The authors thank Soumya Suravita Nanda, who was involved in the initial stage of the protocol preparation.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Mr. Swain had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Swain, Doherty, Zhang.
Acquisition of data. Swain, Sarmanova.
Analysis and interpretation of data. Swain, Coupland, Zhang.

REFERENCES

1. Van Dijk GM, Veenhof C, Lankhorst GJ, Dekker J. Limitations in activities in patients with osteoarthritis of the hip or knee: the relationship with body functions, comorbidity and cognitive functioning. Disabil Rehabil 2009;31:1685–91.
2. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull 2013;105:185–99.
3. Ryan A, Wallace E, O'Hara P, Smith SM. Multimorbidity and functional decline in community-dwelling adults: a systematic review. Health Qual Life Outcomes 2015;13:168.
4. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes 2004;2:51.
5. Chan KW, Ngai HY, Ip KK, Lam KH, Lai WW. Co-morbidities of patients with knee osteoarthritis. Hong Kong Med J 2009;15:168–72.
6. Kadam U, Jordan K, Croft P. Clinical comorbidity in patients with osteoarthritis: a case-control study of general practice consulters in England and Wales. Ann Rheum Dis 2004;63:408–14.
7. Centers for Disease Control and Prevention. Comorbidities: what does "comorbidity" mean? 2018. URL: https://www.cdc.gov/arthritis/data_statistics/comorbidities.htm.
8. Hall AJ, Stubbs B, Mamas MA, Myint PK, Smith TO. Association between osteoarthritis and cardiovascular disease: systematic review and meta-analysis. Eur J Prev Cardiol 2016;23:938–46.
9. Wang H, Bai J, He B, Hu X, Liu D. Osteoarthritis and the risk of cardiovascular disease: a meta-analysis of observational studies. Sci Rep 2016;6:39672.
10. Louati K, Vidal C, Berenbaum F, Sellam J. Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. RMD Open 2015;1:e000077.
11. Stubbs B, Aluko Y, Myint PK, Smith TO. Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. Age Ageing 2016;45:228–35.
12. Van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity. Eur J Gen Pract 1996;2:65–70.
13. Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;47:805–13.
14. Freund T, Kunz CU, Ose D, Szecsenyi J, Peters-Klimm F. Patterns of multimorbidity in primary care patients at high risk of future hospitalization. Popul Health Manag 2012;15:119–24.
15. Garin N, Koyanagi A, Chatterji S, Tyrovolas S, Olaya B, Leonardi M, et al. Global multimorbidity patterns: a cross-sectional, population-based, multi-country study. J Gerontol A Biol Sci Med Sci 2016;71:205–14.
16. Prados-Torres A, Calderón-Larrañaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. J Clin Epidemiol 2014;67:254–66.
17. Ricci-Cabello I, Stevens S, Kontopantelis E, Dalton AR, Griffiths RI, Campbell JL, et al. Impact of the prevalence of concordant and discordant conditions on the quality of diabetes care in family practices in England. Ann Fam Med 2015;13:514–22.
18. European League Against Rheumatism. EULAR. URL: https://www.eular.org/index.cfm.
19. National Institute for Health and Care Excellence. Osteoarthritis: care and management. URL: https://www.nice.org.uk/guidance/cg177/chapter/1-recommendations.
20. Arthritis Research UK. Musculoskeletal conditions and multimorbidities report. 2018. URL: https://www.arthritisresearchuk.org/policy-and-public-affairs/policy-reports/multimorbidity.aspx.
21. Goldberg VM, Buckwalter J, Halpin M, Jiranek W, Mihalko W, Pinzur M, et al. Recommendations of the OARSI FDA Osteoarthritis Devices Working Group. Osteoarthritis Cartilage 2011;19:509–14.

22. American College of Rheumatology. Osteoarthritis. URL: https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Osteoarthritis.
23. Wells G, Shea B, O'Connell D. Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in metaanalysis. Ottawa (ON): The Ottawa Hospital. URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. 2007.
24. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004;23:1663–82.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
26. Van Enst WA, Ochodo E, Scholten RJ, Hooft L, Leeflang MM. Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study. BMC Med Res Methodol 2014;14:70.
27. Tamhane AR, Westfall AO, Burkholder GA, Cutter GR. Prevalence odds ratio versus prevalence ratio: choice comes with consequences. Stat Med 2016;35:5730–5.
28. Hunter JE, Schmidt FL. Methods of meta-analysis. Thousand Oaks (CA): SAGE Publications; 2004.
29. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health 2014;72:39.
30. Review Manager (RevMan). Copenhagen: The Cochrane Collaboration; 2014.
31. Rosemann T, Laux G, Szecsenyi J, Wensing M, Grol R. Pain and osteoarthritis in primary care: factors associated with pain perception in a sample of 1,021 patients. Pain Med 2008;9:903–10.
32. Gore M, Tai KS, Sadosky A, Leslie D, Stacey BR. Clinical comorbidities, treatment patterns, and direct medical costs of patients with osteoarthritis in usual care: a retrospective claims database analysis. J Med Econ 2011;14:497–507.
33. Van Dijk GM, Veenhof C, Schellevis F, Hulsmans H, Bakker JP, Arwert H, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord 2008;9:95.
34. Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the third National Health and Nutrition Examination Survey. Am J Manag Care 2002;8:S383–91.
35. Saltzman CL, Zimmerman MB, O'Rourke M, Brown TD, Buckwalter JA, Johnston R. Impact of comorbidities on the measurement of health in patients with ankle osteoarthritis. J Bone Joint Surg Am 2006;88:2366–72.
36. Dominick KL, Dudley TK, Coffman CJ, Bosworth HB. Comparison of three comorbidity measures for predicting health service use in patients with osteoarthritis. Arthritis Rheum 2005;53:666–72.
37. Inneh IA. The combined influence of sociodemographic, preoperative comorbid and intraoperative factors on longer length of stay after elective primary total knee arthroplasty. J Arthroplasty 2015; 30:1883–6.
38. Zullig LL, Bosworth HB, Jeffreys AS, Corsino L, Coffman CJ, Oddone EZ, et al. The association of comorbid conditions with patient-reported outcomes in veterans with hip and knee osteoarthritis. Clin Rheumatol 2015;34:1435–41.
39. Gad BV, Higuera CA, Klika AK, Elsharkawy KA, Barsoum WK. Validity of patient-reported comorbidities before total knee and hip arthroplasty in patients older than 65 years. J Arthroplasty 2012;27:1750–6.
40. Ong KL, Wu BJ, Cheung BM, Barter PJ, Rye KA. Arthritis: its prevalence, risk factors, and association with cardiovascular diseases in the United States, 1999 to 2008. Ann Epidemiol 2013;23:80–6.
41. Hoogeboom TJ, den Broeder AA, Swierstra BA, de Bie RA, van den Ende CH. Joint-pain comorbidity, health status, and medication use in hip and knee osteoarthritis: a cross-sectional study. Arthritis Care Res (Hoboken) 2012;64:54–8.
42. Reeuwijk KG, de Rooij M, van Dijk GM, Veenhof C, Steultjens MP, Dekker J. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? Clin Rheumatol 2010;29:739–47.
43. Damman W, Liu R, Kroon FP, Reijnierse M, Huizinga TW, Rosendaal FR, et al. Do Comorbidities play a role in hand osteoarthritis disease burden? Data from the Hand Osteoarthritis in Secondary Care cohort. J Rheumatol 2017;44:1659–66.
44. Nielen MM, van Sijl AM, Peters MJ, Verheij RA, Schellevis FG, Nurmohamed MT. Cardiovascular disease prevalence in patients with inflammatory arthritis, diabetes mellitus and osteoarthritis: a cross-sectional study in primary care. BMC Musculoskelet Disord 2012;13:150.
45. Rahman MM, Kopec JA, Cibere J, Goldsmith CH, Anis AH. The relationship between osteoarthritis and cardiovascular disease in a population health survey: a cross-sectional study. BMJ Open 2013;3:e002624.
46. Kadam UT, Croft PR. Clinical comorbidity in osteoarthritis: associations with physical function in older patients in family practice. J Rheumatol 2007;34:1899–904.
47. Juhakoski R, Tenhonen S, Anttonen T, Kauppinen T, Arokoski JP. Factors affecting self-reported pain and physical function in patients with hip osteoarthritis. Arch Phys Med Rehabil 2008;89:1066–73.
48. Tuominen U, Blom M, Hirvonen J, Seitsalo S, Lehto M, Paavolainen P, et al. The effect of co-morbidities on health-related quality of life in patients placed on the waiting list for total joint replacement. Health Qual Life Outcomes 2007;5:16.
49. Inoue R, Ishibashi Y, Tsuda E, Yamamoto Y, Toh S, Matsuzaka M, et al. Medical problems and risk factors of metabolic syndrome among radiographic knee osteoarthritis patients in the Japanese general population. J Orthop Sci 2011;16:704–9.
50. Birtwhistle R, Morkem R, Peat G, Williamson T, Green ME, Khan S, et al. Prevalence and management of osteoarthritis in primary care: an epidemiologic cohort study from the Canadian Primary Care Sentinel Surveillance Network. CMAJ Open 2015;3:E270–5.