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ABSTRACT

Objectives We systemically reviewed published studies that evaluated aerobic exercise interventions in patients with knee osteoarthritis (OA) to: (1) report the frequency, intensity, type and time (FITT) of exercise prescriptions and (2) quantify the changes in markers of cardiovascular health and systemic inflammation.

Data sources PubMed, CINAHL, Scopus; inception to January 2019.

Eligibility criteria Randomised clinical trials (RCT), cohort studies, case series.

Design We summarised exercise prescriptions for all studies and calculated effect sizes with 95% CIs for between-group (RCTs that compared exercise and control groups) and within-group (pre-post exercise) differences in aerobic capacity (VO_2), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and inflammatory markers (interleukin-6 (IL-6), tumour necrosis factor-alpha). We pooled results where possible using random effects models.

Results Interventions from 49 studies were summarised; 8% (4/49) met all FITT guidelines; 16% (8/49) met all or most FITT guidelines. Fourteen studies (10 RCTs) reported at least one marker of cardiovascular health or systemic inflammation. Mean differences (95% CI) indicated a small to moderate increase in VO_2 (0.84 mL/min/kg; 95% CI 0.37 to 1.31), decrease in HR (−3.56 beats per minute; 95% CI −5.60 to −1.52) and DBP (−4.10 mm Hg; 95% CI −4.82 to −3.38) and no change in SBP (−0.36 mm Hg; 95% CI −3.88 to 3.16) and IL-6 (0.37 pg/mL; 95% CI −0.11 to 0.85). Within-group differences were also small to moderate.

Conclusions In studies of aerobic exercise in patients with knee OA, very few interventions met guideline-recommended dose; there were small to moderate changes in markers of cardiovascular health and no decrease in markers of systemic inflammation. These findings question whether aerobic exercise is being used to its full potential in patients with knee OA.

PROSPERO registration number CRD42018087859.

INTRODUCTION

The burden of knee osteoarthritis (OA) is substantial and growing.[1] Patients with knee OA have multiple comorbidities including obesity, cardiovascular disease, diabetes and metabolic syndrome.[1–4] Knee OA is associated with cardiovascular events and all-cause mortality.[5 6] Mechanisms of OA progression include chronic low-grade inflammation, vascular endothelial dysfunction and metabolic disturbances.[2 7–9] Markers of systemic inflammation are associated with increased knee OA structural progression and increased pain.[10–12]

Given the well-established effects of aerobic exercise on cardiovascular health and systemic inflammation,[13 14] there is strong rationale for its therapeutic use in patients with knee OA. Aerobic exercise is recommended for chronic diseases because of its ability to improve multiple physiological impairments,[13 15 16] and does so in a dose-related manner; higher frequency and intensity of exercise improves cardiovascular health,[17 18] expends calories[19] and reduces chronic inflammation.[20 21] The American College of Sports Medicine (ACSM) provides guidelines for aerobic exercise prescription expressed as the frequency, intensity, type and time (FITT) principle (online supplementary table 1).[22]

Exercise programmes of various types (ie, aerobic, strength, neuromuscular) reduce pain and increase function immediately after treatment in patients with knee OA,[23 24] but the effects of aerobic exercise beyond musculoskeletal outcomes are unclear.[23 25] Despite strong physiological rationale for aerobic interventions, the exercise prescriptions and changes in markers of cardiovascular health and systemic inflammation have not been systematically reviewed in patients with knee OA.

Therefore, we systemically reviewed published studies in patients with knee OA that evaluated the effect of aerobic exercise interventions to: (1) report the exercise prescriptions according to the FITT principle and (2) quantify the changes in markers of cardiovascular health and systemic inflammation.

METHODS

Protocol and registration

This study conformed to Preferred Reporting Items for Systematic Reviews and Meta-Analyses

methodological guidelines[26] and the Cochrane Handbook[27] and has been registered in PROSPERO.

Eligibility criteria

We included randomised clinical trials (RCT), cohort studies and case series that evaluated an aerobic exercise intervention (strictly aerobic or mixed interventions that included an aerobic portion) in patients diagnosed with knee OA (tibiofemoral and/or patellofemoral; unilateral and/or bilateral). The interventions were considered aerobic as defined by ACSM; a mode of physical activity that results in improvement and maintenance of cardiorespiratory function, including walking, running, swimming, cycling and dancing.[22] Studies must have compared outcome measures to a control group (between-group) or pre-post aerobic exercise (within-group).

Search

We searched PubMed, CINAHL and Scopus from database inception to January 2019. The search terms included [Osteoarthritis AND (knee OR knees OR knee joint OR knee joints) AND (exercise OR aerobic OR walk OR walking OR run OR running OR cycle OR cycling OR jog OR jogging OR swim OR swimming OR dance OR dancing)]. Additionally, we manually searched reference lists from previous systematic reviews. Studies were restricted to those written in either English or French. Eight reviewers (four pairs) independently examined one-quarter of the titles and abstracts and classified each to exclude or retrieve for full-text review, using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, www.covidence.org). The same eight reviewers independently assessed full-text articles for eligibility. One reviewer (JMS) instructed all other reviewers on study eligibility (titles, abstracts and full-text review) and data extraction procedures. If the decision regarding eligibility differed among any pair, the same reviewer (JMS) consulted with the pair to reach consensus.

Data extraction

Each reviewer individually extracted data for: study design, age, sex, body mass index (BMI), OA diagnosis (ie, radiographic and Kellgren and Lawrence grade if provided and/or symptomatic OA) and characteristics of the exercise programme including type of exercise, frequency (sessions/week), intensity (heart rate (%HR_{max})/aerobic capacity (%VO_{2max})/heart rate reserve (%HRR)/rating of perceived exertion), time (minutes/session, including warm-up and cool down), duration of intervention (number of weeks), presence of a supervisor and the extent to which ACSM criteria were met.

For studies that reported a marker of cardiovascular health or systemic inflammation, we extracted the method used to assess the outcome and associated statistics for preintervention and postintervention scores in all groups (and subgroups) involved. For all studies, unadjusted mean differences (MD) were extracted, unless reported otherwise (two RCTs[28 29] reported adjusted means). Reported markers of cardiovascular health included VO_2 (mL/min/mm Hg), HR (beats per minute; bpm), systolic blood pressure (SBP; mm Hg) and diastolic blood pressure (DBP; mm Hg). Reported markers of systemic inflammation included interleukin-6 (IL-6; pg/mL) and tumour necrosis factor-alpha (TNF-α; pg/mL). Additionally, as the 6 min walk test (6MWT (metres)) is a measure of cardiorespiratory fitness and musculoskeletal health, we evaluated it separately and included it in online supplementary appendix 1. Study authors were contacted if additional data were required, and manual estimates from figures were obtained if insufficient data were provided.

Risk of bias

We used the Cochrane Risk of Bias tool and the Risk of Bias in Non-randomized Studies of Interventions to rate the quality of RCTs and non-RCTs, respectively.[30 31] The reviewers independently assessed each study using the same procedures described above, so that risk of bias for each study was rated by two reviewers and the same third reviewer (JMS) consulted to reach consensus for any discrepancies. Quality of the studies was ranked as 'low', 'some' and 'high' bias based on the following study design factors: randomisation, deviations from intended interventions, missing outcome data, measurement of outcome and selection of the reported result. Additionally, bias due to confounding, in the selection of participants and in the classification of the intervention, was rated for non-RCTs. An overall risk rating for the study was estimated from the individual risks of each domain. A weighted kappa (κ_w) for inter-rater agreement was calculated for each pair of reviewers before discrepancies were resolved (SPSS V.23, IBM). We also used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to rate the overall quality of evidence in the systematic reviews,[32] and the Template for Intervention Description and Replication to aid in the description of the exercise interventions.[33]

Synthesis of results

We calculated the raw MD and 95% CIs for each study and pooled data using random effects meta-analyses. We first analysed between-group differences (ie, aerobic exercise intervention vs control) from RCTs. We then analysed within-group (ie, pre-post aerobic exercise) paired differences for all study designs. All but one study[28] provided preintervention and postintervention or change data.

When not reported, the SD was estimated from the SE of the mean, 95% CI, p value or other methods suggested in the Cochrane Handbook.[27] Means and SDs were estimated from median and range for two studies.[34] Following Cochrane guidelines, for any study that included two different intervention groups (ie, cycling vs walking) and one control group, the sample size in the control group was evenly divided so a comparison could be made to each intervention.[27] We imputed r=0.5 when the correlation of prescores and postscores was required and we performed sensitivity analyses using r values ranging from 0.1 to 0.9.[35 36] Heterogeneity was examined using the I^2 statistic and p values, where an absence of inconsistency was represented as 0%, less than 40% was considered low, 30%–60% was moderate, 50%–90% was substantial, 75%–100% was considerable and 100% indicated maximal inconsistency (ie, high heterogeneity).[37] Additional subgroup and sensitivity analyses were planned based on *a priori* hypotheses described in online supplementary appendix 1. Meta-analyses were performed using Comprehensive Meta-Analysis software program (V.3, Biostat).

RESULTS

Study selection

Our electronic search yielded 5857 studies with 244 eligible for full-text review. Forty-nine studies met our eligibility criteria for objective 1, review of exercise prescriptions (figure 1).[28 29 38–83] Twenty-three RCTs compared an aerobic exercise group to a non-exercising control group, 15 RCTs compared groups completing different types of exercise and 11 studies compared outcomes

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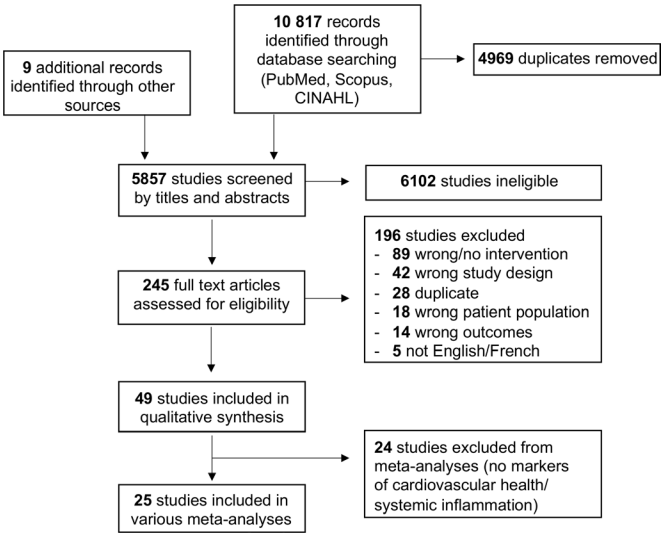

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of included and excluded studies.

before and after aerobic exercise in one group. Fourteen studies reported a marker of cardiovascular health and/or systemic inflammation and were included in various meta-analyses. For between-group analyses, 10 RCTs that included a control group were included (online supplementary table 2). Four studies compared VO_2, three compared HR, two compared SBP and DBP and three compared IL-6. For within-group analyses, all study types were included. In total, five studies reported VO_2, four reported HR, three reported SBP and DBP, five reported IL-6 and four reported TNF-α (online supplementary table 3).

Participant and intervention characteristics

A total of 3448 patients were included for objective 1 (76% female, age=63±7 years; BMI=29.3±4.9 kg/m^2; mean±SD). Three studies[39 40 44] where patients had OA at multiple joints were included because over 60% of the participants had knee OA (online supplementary table 2).

Comparison to ACSM guidelines for aerobic exercise

Interventions in 2 of the 49 studies (4%) met all domains of the ACSM FITT criteria, and another two[46 64] met the criteria progressively over time, whereby the duration (ie, minutes/session) and/or intensity (ie, %HR_{max}/VO_{2max}) increased as the intervention advanced forward. Therefore, all domains were met by the end of the intervention (4/49, 8%). Interventions in another four studies (8%)[29 69 70 72] met three of the FITT criteria recommended by ACSM, with the exception of 150 min of aerobic exercise/week. Therefore, 8/49 (16%) met all or most of the criteria. All exercise interventions were classified as moderate intensity (or less) according to ACSM criteria (online supplementary table 1). The overall average patient adherence to the intervention was 86%, measured by attendance or dropout (online supplementary table 3).

Risk of bias

There was substantial agreement on items with the exception of bias in the selection of participants and bias in the reporting of results for non-RCTs, requiring the third reviewer to reach consensus ($p<0.05$, κ_w ranging from 0.13 to 0.75). For RCTs, 45% (17/38) of studies had 'high' risk for measurement bias. Most studies had 'low' or 'some' risk for selection, performance and detection bias. All non-RCTs had a high risk of bias for confounding, and most (8/11, 72%) had a high risk for intervention classification. Patient and personnel blinding was not possible in all studies; however, most had inappropriate methods to control for confounding variables or did not blind outcome assessors. All studies had a 'low' risk for participant selection bias, because selection was not based on characteristics observed after the start of the study. Overall, most studies (36/49, 74%) had a 'high' risk of bias, 9 (18%) had a 'low' risk of bias and 4 (8%) had 'some' risk of bias (online supplementary table 3, online supplementary figure 1). Additionally, all studies rated low in the quality of evidence according to GRADE.

Markers of cardiovascular health and systemic inflammation

Synthesis of results comparing aerobic exercise to control

Between-group (RCT) analyses (MD, 95% CI) indicated a statistically significant increase in VO_2 (0.84 mL/min/kg; 95% CI 0.37 to 1.3), decrease in HR (−3.56 bpm; 95% CI −5.60 to −1.52) and decrease in DBP (−4.10 mm Hg; 95% CI −4.82 to −3.38), $p<0.05$ (figure 2A,B,D). There were no statistically significant differences in SBP (−0.36 mm Hg; 95% CI −3.88 to 3.16) and IL-6 (0.37 pg/mL; 95% CI −0.11 to 0.85); $p>0.05$ (figure 2C,E).

Synthesis of results comparing pre-aerobic to post-aerobic exercise

The within-group (pre-post exercise) analyses indicated a statistically significant increase in VO_2 (1.69 mL/min/kg; 95% CI 0.51 to 2.87), decrease in HR (−4.54 bpm; 95% CI −6.82 to −2.25) and decrease in SBP (−7.19 mm Hg; 95% CI −11.40 to −2.25) and DBP (−4.66 mm Hg; 95% CI −6.03 to −3.28) (online supplementary appendix 1; figure 2A–D). There was no statistically significant change in IL-6 (−0.09 pg/mL; 95% CI −0.63 to 0.44, $p>0.05$) (online supplementary appendix 1; figure 2E) and a statistically significant *increase* in TNF-α (0.99 pg/mL; 95% CI 0.21 to 1.77, $p<0.05$) (online supplementary appendix 1; figure 2F).

Results for additional analyses including 6MWT are reported in online supplementary appendix 1 (figure 3). Results of subgroup and sensitivity analyses were generally consistent with the primary analysis(online supplementary appendix 1; table 4).

DISCUSSION

What are the aerobic exercise prescriptions studied in patients with knee OA?

Only 16% (8/49) of published studies in patients with knee OA evaluated interventions that met all or most of the ACSM guidelines for aerobic exercise prescription. Most interventions reviewed (45/49, 92%) did not meet the target of 150 min/week of moderate to vigorous activity. Additionally, most studies (40/49, 82%) did not measure HR or VO_2 to ensure patients were exercising at the target intensity. Several exercise programmes (22/49, 45%) were less than 12 weeks; durations ranged from 4 to 78 weeks (online supplementary table 2). Most studies had a 'high' risk of bias (online supplementary table 3, online supplementary figure 1); and all studies rated low in the quality of evidence according to GRADE.

Why are the interventions not meeting recommended dose?

We suggest the likely reasons the studied interventions did not strictly follow aerobic exercise guidelines include the perceived lack of ability for patients with knee OA to adhere to the guidelines, the fear of exacerbating symptoms and increasing adverse events and/or the desire to limit patients from dropping out. While well accepted as providing the physiological dose required to evoke

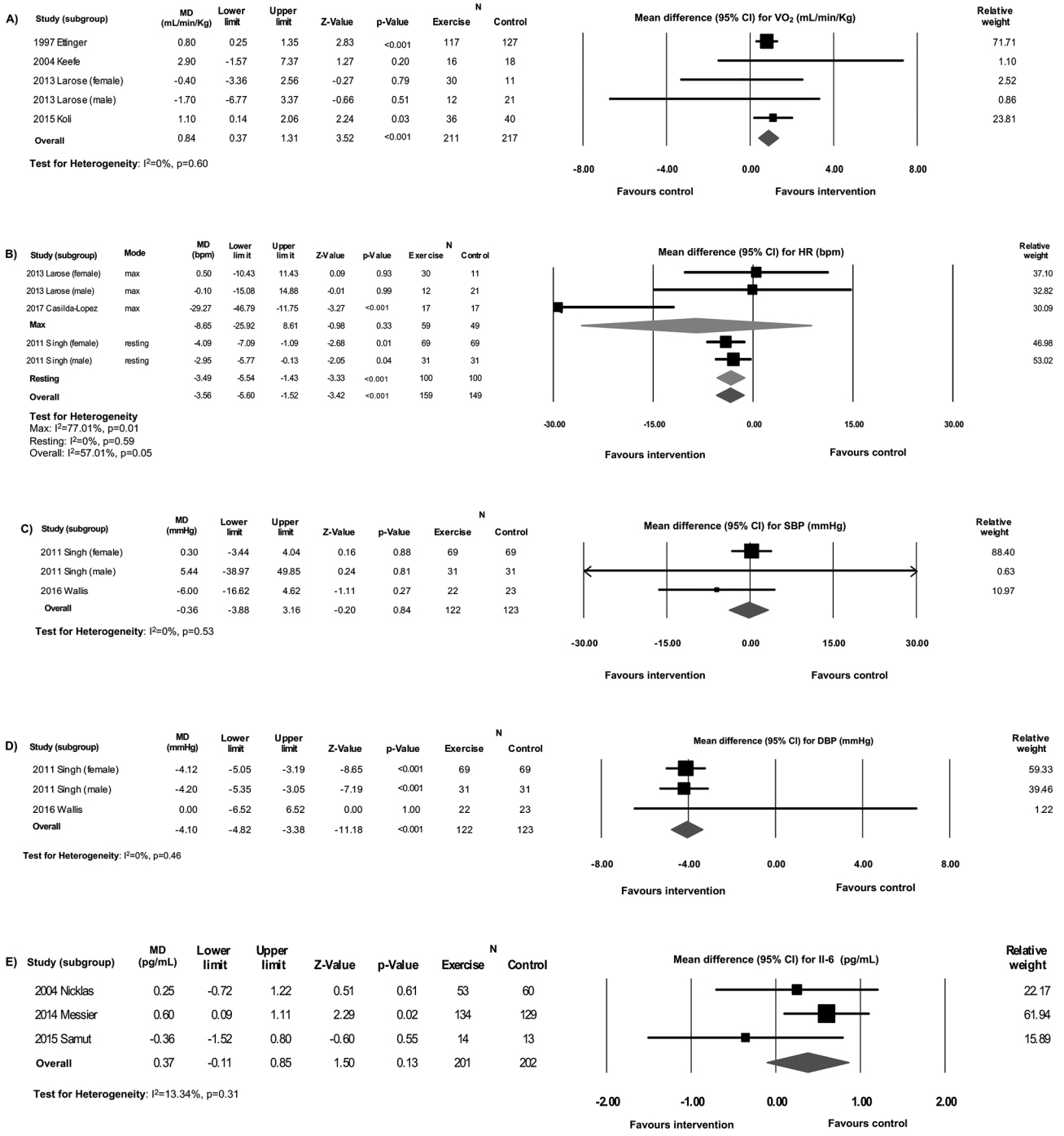

Figure 2 Forest plot of between-group analyses (ie, randomised clinical trials (RCT); exercise vs control) for the following outcomes: aerobic capacity (VO_2, A); heart rate (HR, B); systolic blood pressure (SBP, C); diastolic blood pressure (DBP, D); and interleukin-6 (IL-6, E). Weights are from a random effects analysis. Overall effects are shown as mean difference (MD) with 95% CI. N, number of patients.

improvements in cardiovascular health and chronic inflammation, the FITT guidelines are not disease specific. Therefore, patients and their health providers must adjust guideline parameters to meet individual patient needs.[84] Other recently published meta-analyses suggest that patients with knee OA do not experience increased pain with exercise,[24] and that knee loading with exercise is not harmful to the articular cartilage.[85] Therefore, published exercise prescription guidelines are recommended to guide exercise interventions for people with OA.[86]

Aerobic exercise in patients for other chronic diseases has been able to meet ACSM guidelines. In patients with type 2 diabetes, higher intensities of aerobic exercise resulted in greater improvements in cardiorespiratory fitness.[87] A recent systematic review of the effects of aerobic exercise for patients with metabolic syndrome only included studies with interventions that met the FITT criteria. It reported substantial improvements in HR, SBP and VO_2, with vigorous intensity interventions providing greater effects.[88]

What are the effects on markers of cardiovascular health and systemic inflammation?

Only 14 of the studies (29%) evaluated the effects of aerobic exercise using a marker of cardiovascular health or systemic

inflammation. Meta-analyses of those results indicated only small to moderate improvements in VO_2, HR and DBP (online supplementary appendix 1; figure 2). Although some of these improvements may arguably be clinically important, they are less than typically observed following aerobic exercise interventions and are likely to fall short in evoking optimal effects for patients with knee OA. As administered in the studies reviewed, the aerobic exercise interventions did not decrease circulating inflammatory factors IL-6 and TNF-α (online supplementary appendix 1; figure 2).

When ACSM guideline-recommended dose is met, aerobic exercise can markedly improve cardiovascular health,[89 90] decrease systemic inflammation[91 92] and increase caloric expenditure.[19] Such physiological outcomes have potential to affect multiple disease processes linked to OA[93–95] and may be reasonably hypothesised to decrease the risk of progression of knee OA and associated comorbidities. The caveat lies in the proper administration and adherence to aerobic exercise guidelines. Importantly, as suggested by the present data, when patients with OA are not meeting recommended guidelines, optimal improvements in cardiovascular health and systemic inflammation do not occur. Without such physiological changes, there may be no concomitant improvement in OA progression or comorbidities, and improvements in pain and function may be less than possible. Therefore, the true potential of aerobic exercise as a treatment for knee OA may be unrealised.

It is important to acknowledge that despite not meeting ACSM guidelines, the interventions were generally well attended by patients and did provide small to moderate improvements in some markers of cardiovascular health (online supplementary appendix 1; figure 2). As studied, the interventions also provided moderate improvements in the 6MWT (online supplementary appendix 1; figure 3).The results of the present review do not negate the importance of encouraging patients with knee OA to exercise, even at lower levels than those suggested to evoke optimal changes in cardiovascular health and systemic inflammation, given the other health benefits of physical activity.[24 96–99]

Limitations

The present estimates of the within-group pre-post exercise changes (online supplementary appendix 1; figure 2) should be interpreted carefully. For these analyses, the true intervention effects may not be discernible from effects caused by the simple passage of time, measurement error and/or characteristics of the patients and setting.[100] Similarly, including non-randomised studies may contribute to uncontrolled confounding. Regardless, our between-group and within-group comparisons reveal *lower* changes in cardiovascular health and systemic inflammation than previously observed in randomised trials of aerobic exercise in patients with other chronic diseases.[87 88]

The present methods used to determine effect sizes assume normally distributed outcomes within each study and this may not always be the case, especially for the several relatively small studies included in this review. Moreover, although studies reported the same markers, pooled data across all studies were sometimes assessed using slightly different methods (ie, calculated max vs peak VO_2, using a treadmill protocol vs cycling protocol, and so on). While we reported individual and pooled study effect sizes, and performed sensitivity analyses where possible, results may differ based on study methods. Lastly, few studies reported sex-specific analyses. These should be performed in future, adequately powered studies.

CONCLUSIONS

Despite the strong rationale to improve cardiovascular health and reduce systemic inflammation in patients with knee OA, published studies include aerobic exercise interventions that rarely meet recommended dose guidelines. The pooled results from studies reporting a marker of cardiovascular health or systemic inflammation suggest only small to moderate effects on VO_2, HR and blood pressure and no decrease in inflammatory markers. Therefore, clinicians may not be extracting the full potential benefit of aerobic exercise in patients with knee OA. Whether this is the case or not needs to be studied.

What is already known

- Knee osteoarthritis (OA) is associated with systemic inflammation, cardiovascular events and all-cause mortality.
- Aerobic exercise improves cardiovascular health and reduces systemic inflammation—this is a strong rationale for its use in patients with knee OA.

What are the new findings

- In studies of aerobic exercise in patients with knee OA, the interventions did not meet recommended exercise dose; postexercise anticipated increase in VO_2 and decreases in heart rate and blood pressure were small to moderate; there was no decrease in systemic inflammatory markers interleukin-6 and tumour necrosis factor-alpha.
- The therapeutic effects of aerobic exercise in patients with knee OA remain unclear. We encourage studies of interventions that evoke more substantial changes in cardiovascular health and systemic inflammation.

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Contributors JMS conceptualised the project, analysed the data, and drafted and edited the manuscript. TBB, RJP, FB and DMB contributed to conception and design and critical revision of the article. DMB provided statistical expertise. HFA, EW, CAP, MJL, BKA, MCMK and BOZ contributed to data collection and synthesis. CTA and JKS provided critical analysis of the data and critical revision of the article. All authors edited and approved the final version of the manuscript.

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