Exercise and Inflammation in Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomised Trials.

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Abstract

Current evidence suggests that chronic inflammation contributes to the development and progression of coronary artery disease (CAD). Interestingly, exercise may constitute a method of reducing inflammation in this patient population. As such, this systematic review and meta-analysis examined the evidence generated by randomised studies that investigated the effect of exercise on inflammatory biomarkers in CAD. Literature was sought from various sources. Outcomes were pooled in a random-effects model to calculate standardised mean differences (SMD) with 95% confidence intervals (CI). Twenty-five studies were reviewed; post-intervention C-reactive protein (SMD: -0.55 (95% CI: -0.93, -0.16), P= 0.005), fibrinogen (SMD: -0.52 (95% CI: -0.74, -0.29, P= <0.00001), and von Willebrand factor (SMD: -1.57 (95% CI: -2.23, -0.92), P= <0.00001) values were significantly lower in exercise groups compared to controls. In addition, qualitative analyses identified evidence that supports a beneficial effect of exercise on these acute-phase reactants. However, the impact of exercise on anti-inflammatory cytokines, adhesion molecules, and chemokines is equivocal, which may be attributed to a paucity of research. Nevertheless, the findings of this review suggest that exercise induces an anti-inflammatory effect in CAD patients. Although, the quality of evidence needs to be improved by further randomised studies with high methodological qualities and large sample sizes.

KEYWORDS: Exercise, inflammation, coronary artery disease, systematic review, meta-analysis

Introduction

Coronary artery disease (CAD) involves an attenuation of myocardial perfusion due to progressive intraluminal accumulation of fibrous atherosclerotic plaque within an epicardial coronary artery (1). The ramifications of this may include: acute coronary syndrome comprising myocardial infarction and angina pectoris, impaired ventricular function, or heart failure (2,3). Despite improvements in cardiovascular disease (CVD) science and medical care over the past few decades, CAD remains a leading cause of mortality throughout the world (4).

The global prevalence of CAD has provoked scientific investigations to elucidate the underlying pathophysiological mechanisms responsible for atherogenesis. As a consequence, it is becoming increasingly clear that low-grade chronic inflammation is implicated in each pathological stage of atherosclerotic development (5,6). Notably, Ridker et al. (7) recently documented that the administration of canakinumab, a monoclonal antibody that targets the interleukin-1 beta innate immunity pathway, contributed to a significant reduction in high sensitivity C-reactive protein (hs-CRP) and recurrent cardiovascular complications in CAD patients with previous myocardial infarction and a residual inflammatory response (hs-CRP > 2 milligrams per litre) compared to placebo. Therefore, this investigation provided evidence of the benefits of targeting inflammatory pathways to improve clinical outcomes in high-risk CAD patients.

Exercise is an established therapeutic strategy for primary and secondary prevention of CAD (8-11). Interestingly, a meta-analysis performed by Swardfager et al. (12) concluded that exercise may reduce inflammatory activity in CAD patients, as indicated by lower post-intervention values of C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), and vascular cell adhesion molecule-1 (VCAM-1). As such, this conclusion suggests that exercise may induce an anti-inflammatory effect in CAD patients, which may partially represent a mechanism by which secondary prevention is conferred. However, the evidence produced by Swardfager et al. (12) was generated by pooling randomised and non-randomised studies; the latter study design potentially decreasing the validity of the results due to selection bias (13). As such, this systematic review and meta-analysis will analyse randomised studies that investigated the effect of exercise on inflammatory biomarkers in CAD patients. Utilising this approach will provide a timely update to the evidence base by synthesising a rigorous examination of the capability of exercise to serve as an anti-inflammatory strategy in CAD.

Methods

The methodology implemented in this systematic review and meta-analysis adhered to guidelines presented in the Cochrane Handbook for Systematic Reviews of Interventions (14), and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) recommendations (15) (PROSPERO registration number: CRD42018105245).

Search Strategy

A computerised search of the following databases from inception to August 2019 was performed: MEDLINE, EMBASE, AMED, CINAHL, Cochrane Central Register of Controlled Trials, and SPORT Discus. To ensure a comprehensive search strategy was implemented, various search terms comprising Medical Subject Headings

(MeSH), database specific subject headings, and key words were derived from four primary concepts: "coronary artery disease", "exercise", "inflammatory biomarker", and "randomised trial". The search strategy was limited to human trials and English publications. An example of the implemented search strategy for Cochrane Central Register of Controlled Trials is presented in Electronic Supplementary Material (ESM) 1, Appendix S1. To minimise the risk of introducing bias to this review, grey literature was sought from the following resources: Google Scholar, specialised databases (National Rehabilitation Information Centre, Physiotherapy Evidence Database, and the National Institute for Health Research Journals Library), and the International Clinical Trials Registry Platform. Hand searching of reference lists of articles and previous reviews was also performed to identify additional trials that were potentially eligible. All identified publications were read as either abstracts or full texts.

Inclusion and Exclusion Criteria

A protocol comprising inclusion and exclusion criteria was established to ascertain suitable studies for inclusion (see Table 1).

Data Extraction

Data not reported in main text or tables were extracted from figures when possible. If available, data analysed using the intention-to-treat principles were preferentially extracted to mitigate bias and permit clinical relevance (16). When insufficient information was reported by a study, a member of the review team (Mr Gareth Thompson (GT)) contacted the authors to request any missing data. Two members of the review team (GT and Dr Ciara M. Hughes (CMH)) independently extracted the necessary data from each included study into a preformatted data collection form designed by the Cochrane Collaboration. Discrepancies were identified and discussed until disagreements were resolved by consensus (a third member of the review team (Mrs Jacqui Crawford (JC) was consulted when necessary). The lead review author (GT) entered the data into tables and inserted a unified data set into Review Manager Version 5.3 for the completion of meta-analyses.

Quality Assessment

The reliability of the results provided by each trial was determined by conducting a risk of bias (ROB) assessment in accordance with guidelines presented in the Cochrane Handbook for Systematic Reviews of Interventions (16). In accordance with Sveaas et al. (17), the "blinding of participants and personnel" ROB item was excluded as such an approach is very difficult, if not impossible to utilise in studies that implemented an exercise intervention. When available, published *a priori* study protocols were used to supplement the assessment of ROB.

The quality of evidence for each outcome that was included in the post-intervention inflammatory biomarker value comparisons between exercise and control groups was rated in accordance with the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system (18) (see Table 2). Three members (GT, CMH, and JC) of the review team independently performed a ROB and GRADE assessment on the included studies to mitigate the influence of individual subjectivity during quality assessment; disagreements were discussed at a meeting until the final decisions were agreed by consensus.

Statistical Analysis

A random-effects inverse variance model was used to calculate standardised mean differences (SMD) with 95% confidence intervals (CIs). In accordance with Swardfager et al. (12), meta-analyses were conducted to facilitate post-intervention value comparisons between exercise and control groups (a negative SMD represents a lower value in the exercise group compared to control group). A random-effects inverse variance model was chosen due to anticipated clinical heterogeneity between studies, and SMD was calculated due to expected variance in outcome measurement methodology (19). An SMD ≤ 0.4 was interpreted as a small effect size, between 0.5 and 0.7 was considered to be a medium effect size, and ≥ 0.8 was deemed a large effect size (20). Data were pooled for meta-analyses when $\geq$ two studies measured the same outcome and data was available in a suitable format (mean ± standard deviation (SD)). If studies reported data as median and range or interquartile range (IQR), the sample means ± SDs were estimated by utilising the formula proposed by Wan et al. (21). Further, if mean ± standard error of the mean (SEM) was reported, the Review Manager Version 5.3 calculator resource was used to estimate SD. When a study implemented multiple exercise groups, the data for each group was entered separately as an independent data point. Additionally, the sample size of the control group was divided by the number of intervention groups to prevent a unit of analysis error (19). A P value of ≤ 0.05 was considered statistically significant. Heterogeneity was investigated through inspection of I^2 and χ^2 test values; a P value of ≤ 0.1 for the χ^2 test or an I^2 value of $\geq 50\%$ was considered to be indicative of substantial heterogeneity (22). Sub-group analyses were performed using χ^2 heterogeneity statistics to investigate if the following variables influenced the magnitude of effect (SMD) or contributed to heterogeneity in the overall pooled results:

- Duration of exercise programme: < 12-weeks versus ≥ 12-weeks.
- Sessions per week: ≤ 3 compared to > 3.
- Exercise modality: aerobic interval exercise (AIE) versus continuous aerobic exercise (CAE) versus resistance training (RT) verses a combination of RT and cardiorespiratory exercise (AIE or CAE).
- Exercise alongside cardiac rehabilitation (CR) versus exercise only.

A statistically significant test for sub-group differences was considered as $P \leq 0.1$ (χ^2) (19). Sensitivity analyses were performed to assess the robustness of the pooled results by removing the studies that reported data that required the estimation of mean ± SD from median and range or IQR, or SD from the SEM. Additionally, the influence of "outlying" data generated by one study (23) on the results of the post-intervention CRP value comparison was investigated. All meta-analyses were performed using Review Manager Version 5.3. Descriptive analyses were performed for studies and outcomes that could not be meta-analysed.

Results

Study Selection

A total of 8,290 articles were identified by various literature searches. The lead author (GT) performed the initial screening process, which entailed reading the titles and abstracts of articles to exclude irrelevant studies that did

not meet the inclusion criteria. Following the initial screening process, a full text evaluation of thirty-three articles was independently performed by three members (GT, CMH, and JC) of the review team to ascertain correlation with the inclusion criteria. Authors were contacted if any uncertainty existed surrounding the suitability of a particular study for inclusion. If no reply was provided, the study was excluded. A meeting was held between the three members (GT, CMH, and JC) of the review team to discuss findings, until disagreements were agreed by consensus. Consequently, twenty-five randomised studies (23-47) were deemed appropriate for inclusion in this systematic review; ten (24,26,28,29,33,35,36,41,44,46) of which were unsuitable for meta-analyses (see Figure 1 for PRISMA flow diagram depicting the study selection process).

Study Characteristics

The main study characteristics are presented in ESM 1, Tables S1, S2, S3, and S4. Studies were published between 2006 and 2017. Of the twenty-five randomised studies that were included, eighteen trials (23,25,27,30-32,34,36-40,42-47) randomised participants to an exercise intervention or control group, three studies (26,28,33) randomised participants to different forms of exercise, one study (35) randomised participants to an exercise intervention or low-energy diet, two studies (24,29) randomised participants to different forms of CR, and one study (41) randomised participants to a combination of exercise and a standard dose of rosuvastatin or atorvastatin treatment.

Participant Characteristics

Sample populations in the twenty-five included studies varied from 28 to 275 participants. Overall, the included studies provided results for 2105 (1426 exercising and 679 control) participants, of which, 73% were male (1527). The mean age of the participants was 59.9 ± 4.2 years (range: 51-68 years). The condition of CAD in the included participants encompassed: post- revascularisation (coronary artery bypass graft/ percutaneous coronary intervention), post-myocardial infarction, stable angina pectoris, and ≥ 3 months after cardiovascular complication or revascularisation. Finally, participant baseline inflammatory biomarker concentrations varied from low to high across the included studies (see ESM 1, Tables S5.1 and S5.2 for participant baseline inflammatory biomarker concentrations).

Exercise Intervention Characteristics

A detailed description of the exercise intervention characteristics can be found in ESM 1, Tables S1, S2, S3, and S4. Each of the included studies implemented a cardiorespiratory (CAE and/ or AIE) intervention. Moreover, six of the included studies (24,28,29,40,42,44) implemented a group that received a RT intervention alone or in combination with cardiorespiratory exercise. Across which, the utilised RT exercises (weights, resistance bands, resistance machines, and wall-pulleys) activated major muscle groups (upper and/ or lower body).

According to exercise intensity classifications published by the American College of Sports Medicine (48), eighteen of the included studies (23,25-30,32-35,38,40,42-46) prescribed a vigorous intensity for the cardiorespiratory exercise intervention, and the remaining seven studies (24,31,36,37,39,41,47) prescribed a

moderate intensity. The prescribed RT intensity across two studies (28,40) ranged from 60-65% of one-repetition maximum. Furthermore, one study (42) prescribed a RT intensity of 60% of maximum voluntary contraction, one study (44) described the RT intensity as being similar to that of the accompanying vigorous intensity cardiorespiratory exercise, and two studies (24,29) did not report the prescribed RT intensity. Overall, mean exercise session duration was 38 ± 12 minutes (range: 15-75 minutes); mean exercise session frequency was 4 ± 1 sessions per week (range: 2-7 sessions per week); and mean exercise intervention period was 14 ± 10 weeks (range: 3-48 weeks).

Synthesis of Results

Ten studies were not included in any of the meta-analyses performed; seven of which did not implement a control group (24,26,28,29,33,35,41), El Missiri and Taher (46) reported a baseline imbalance in CRP values, Luk et al. (44) presented data in an inappropriate format (mean change ± SD), and Raygan et al. (36) was the only study to report data for interleukin-33 (IL-33) and interleukin-35 (IL-35). Moreover, Oliveira et al. (34) was excluded from the post-intervention CRP value comparison due to a baseline imbalance in CRP concentrations. Summaries of the various meta-analyses that were performed are provided in ESM 2, Table S1.

Post-Intervention Inflammatory Biomarker Comparisons

The results of the post-intervention inflammatory biomarker comparisons between exercise and control groups are depicted in Figures 2.1, 2.2, 2.3, and 3. Very low qualities of evidence for significant medium and large beneficial effect sizes for exercise on CRP (SMD: -0.55 (95% CI: -0.93, -0.16), P= 0.005), fibrinogen (SMD: -0.52 (95% CI: -0.74, -0.29, P= <0.00001), and von Willebrand factor (vWF) (SMD: -1.57 (95% CI: -2.23, -0.92), P= <0.00001) were documented. However, between-study heterogeneity was substantial for CRP (I^2= 85%, χ^2 P= <0.00001) and vWF (I^2= 76%, χ^2 P= 0.007). Significant effect sizes were not documented for IL-6, interleukin-10 (IL-10), tumour necrosis factor-alpha (TNF-α), VCAM-1, intercellular adhesion molecule-1 (ICAM-1), E-selectin, P-selectin, interleukin-8 (IL-8), and regulated on activation, normal T-cell expressed and secreted (RANTES).

Descriptive Analyses

A summary of the results for each of the included studies is presented in ESM 1, Tables S1, S2, S3, and S4. Across the outcomes that could not be meta-analysed, beneficial within-exercise group changes were demonstrated for soluble tumour necrosis factor- alpha receptor 1 (TNF-α SR1) (P< 0.001) (47), chemokine (C-C motif) ligand 21 (CCL21) (P< 0.05) (43), and IL-35 (P= 0.001) (36). Also, positive differences between exercise and control groups were observed for TNF-α SR1 (P= 0.004) (47), IL-35 (P= 0.002) (36) and interferon gamma-induced protein 10 (IP-10) (P= 0.03) (27). No significant changes were reported within or between-groups for IL-33 (36), monokine induced by gamma interferon (Mig) (27), monocyte chemoattractant protein 1 (MCP-1) (43), chemokine (C-C motif) ligand 19 (CCL19) (43), chemokine (C-X-C motif) ligand 16 (CXCL16) (43), CD40 ligand (CD40L) (43), and pentraxin 3 (PTX-3) (43).

In terms of the studies that were not included in the meta-analyses, eight trials (26,28,29,33,35,41,44,46) investigated the impact of exercise on CRP. Across which, beneficial within-exercise group changes were observed by four studies (26,29,41,46), whilst no significant changes were reported by the other four studies (28,33,35,44). Three trials (28,29,35) examined the effect of exercise on IL-6; one study (29) documented beneficial within-exercise group changes, whilst the remaining two studies (28,35) observed no significant changes. Two studies (29,35) reported data regarding the influence of exercise on TNF-α. Beneficial within-exercise group changes were observed by one study (29), whereas the other trial documented no significant changes (35). Finally, beneficial within-exercise group changes were reported for ICAM-1 (29), fibrinogen (24), and vWF (24), whilst no significant changes were observed for IL-8 (28) or P-selectin (24).

Quality Assessment

A summary of the ROB assessment for the twenty-five included studies is presented in Figure 4. Three studies (24,33,35) were rated as a low risk of bias for each domain. However, inadequate reporting of random sequence generation and allocation concealment decreased the reliability of the results across most of the included studies. The results for the quality of evidence assessment using the GRADE system are presented in ESM 2, Table S2. Issues pertaining to the before mentioned ROB study limitations, along with inconsistency of results, indirectness of evidence, and imprecision resulted in the overall quality of evidence ranging from very low to moderate for the inflammatory biomarkers included in the post-intervention value comparisons.

Sub-group Analyses

The results of the sub-group analyses are presented in ESM 3, Tables S1, S2, S3, and S4. Various statistically significant (χ^2 $P \leq 0.1$) sub-group differences were detected (see ESM 4, Table S1 for summaries of the statistically significant sub-group differences). However, an uneven covariate (a limited or unbalanced number of studies and / or participants contributing to each sub-group) distribution rendered the results meaningless (49). As such, the results of the statistically significant sub-group differences were not discussed in order to circumvent misleading conclusions.

Sensitivity Analyses

The results of the sensitivity analyses are presented in ESM 4, Tables S2 and S3. Removal of the six studies (27,34,37,38,40,47) that presented data that necessitated the estimation of mean ± SD or SD from the corresponding meta-analyses precluded post-intervention value comparisons for IL-8, IL-10, TNF-α, P-selectin, and RANTES as < 2 studies were available for pooling. As such, the results of these meta-analyses should be interpreted with caution. Nevertheless, of the sensitivity analyses that could be performed, the results indicated that the inclusion of data that required the estimation of mean ± SD or SD did not substantially influence the directions and significance levels of the effect sizes, or substantially increase the between-study heterogeneity across the CRP, IL-6, and VCAM-1 meta-analyses (see ESM 4, Table S2). However, the removal of data that required the estimation of mean ± SD or SD resulted in significant medium beneficial effect sizes for exercise on

ICAM-1 (before; SMD: -0.35 (95% CI: -0.72, 0.01), P= 0.06, after; SMD: -0.77 (95% CI: -1.23, -0.31), P= 0.001) and E-selectin (before; SMD: -0.31 (95% CI: -0.66, 0.05), P= 0.09, after; SMD: -0.57 (95% CI: -1.03, -0.11), P= 0.01). Moreover, the between-study heterogeneity was reduced for ICAM-1 (before: I^2= 58%, χ^2 P= 0.07, after: I^2= 0%, χ^2 P= 0.61) and E-selectin (before: I^2= 35%, χ^2 P= 0.22, after: I^2= 0%, χ^2 P= 0.85). Nonetheless, these results should be interpreted with caution due to the small sample sizes of the meta-analyses (ICAM: 40 exercise participants and 38 controls, E-selectin: 38 exercise participants and 38 controls).

The study performed by Giallauria et al. (23) generated a noticeably larger beneficial effect size in comparison to the other pooled studies in the post-intervention CRP value comparison. Therefore, a sensitivity analysis was performed to ascertain the influence of this "outlying" data on the overall pooled results by removing Giallauria et al. (23). Consequently, no major impact on the direction and significance level of the pooled effect size, or substantial change in between-study heterogeneity was documented (see ESM 4, Table S3).

Adverse Events, Withdrawals, and Exercise Session Compliance

A detailed report of adverse events, withdrawals, and exercise session compliance can be found in ESM 4, Table S4). Fourteen of the included studies (23,25,26,28,32-35,37,38,40,42,43,47) reported on adverse events. Exercise was safe; no adverse events during or as a result of exercise were reported. Across the included studies, the mean withdrawal rate was 5% (range: 0-22%). Information regarding participant compliance with the prescribed exercise sessions was reported by thirteen studies (23,26,28,29,31-35,37,42-44). On average, the participants across these studies completed 88% (range: 60-100%) of the prescribed exercise sessions.

Discussion

The contribution of chronic inflammation to the development and progression of CAD is now well established (5,6). Interestingly, there is evidence to suggest that exercise may constitute a method of reducing inflammatory activity in this patient population (12), which potentially partially explains the secondary prevention induced by this intervention. As such, the purpose of this systematic review and meta-analysis was to provide a timely update to the literature by rigorously examining the influence of exercise on various inflammatory biomarkers in CAD patients.

Twenty-five randomised studies comprising 2105 (1426 exercising and 679 controls) participants were reviewed. Saliently, an anti-inflammatory effect of exercise was documented, as indicated by significant beneficial effects on CRP, fibrinogen, and vWF. Moreover, the meta-analyses of inflammatory biomarkers that documented non-significant results generated SMDs that represented lower post-intervention values in the exercise groups compared to controls. Failure to reach significance for these inflammatory biomarker outcomes could be a result of wide confidence intervals due to small sample sizes.

The anti-inflammatory effects of exercise in CAD patients, as documented in this review, may lack generalisability in healthy populations. In particular, there is inconsistent evidence for an anti-inflammatory effect

of exercise in healthy populations (50-54). Therefore, the discrepancy between the results of this review and the evidence for an anti-inflammatory effect in healthy populations may be attributed to a more pronounced effect in CAD patients due to higher baseline levels of inflammatory activity (55), or an amelioration of principal CVD risk factors that promote inflammation, such as: dyslipidaemia, hypertension, diabetes, and obesity (56,57). Whilst it was beyond the scope of this review to investigate these relationships, Swardfager et al. (12) reported that elevated baseline CRP values and adverse lipid profiles were associated with greater reductions in CRP values in CAD patients. Moreover, a recent meta-analysis performed by Fedewa et al. (54) demonstrated that exercise induced greater reductions in CRP when accompanied by a decrease in body mass index in healthy and clinical populations. Besides improving CVD risk factors, exercise may also incite anti-inflammatory protection by directly modulating various overlapping signalling pathways associated with oxidative stress and inflammation (58). However, the influence of exercise on these underlying mechanisms is poorly understood (58), and is an area for future research.

Pro-inflammatory Cytokines

In accordance with the results of the meta-analysis performed by Swardfager et al. (12), the post-intervention IL-6 and TNF-α value comparisons between exercise and control groups were not significantly different. Although, the paucity of data from studies that implemented a control group may account for these non-significant findings. Regarding the studies that were not included in the meta-analyses, the evidence for a beneficial effect of exercise on pro-inflammatory cytokines was inconsistent. To elaborate, one study (29) documented beneficial within-exercise group changes in IL-6 and TNF-α, whilst two studies reported no significant changes (28,35). However, the trials performed by Hansen et al. (28) and Pedersen et al. (35) may have been underpowered to detect changes in IL-6 or TNF-α as sample size calculations based on pro-inflammatory cytokines were not performed. When considering the individual results of the included studies, Schumacher et al. (38) recorded a significant inverse correlation between physical performance and levels of IL-6. Moreover, Munk et al. (43) observed positive differences between exercise and control groups in IL-6, and Balen et al. (47) documented beneficial differences between exercise and control groups in TNF-α SR1. As such, these findings potentially represent a positive effect of exercise on pro-inflammatory cytokines. Nevertheless, the results of this review failed to generate conclusive evidence that exercise significantly reduces pro-inflammatory cytokines. Therefore, further research regarding the effect of exercise on these inflammatory mediators is required.

Anti-inflammatory Cytokines

The meta-analyses performed in this review failed to demonstrate a beneficial effect of exercise on IL-10 concentrations, which may be attributed to the small number of pooled studies. Overall, the individual results of four (36,37,43,47) out of the five studies (34,36,37,43,47) that examined the effect of exercise on anti-inflammatory cytokines documented positive influences. Nevertheless, the paucity of evidence in this area precluded a robust evaluation. As such, further research into the effect of exercise on anti-inflammatory cytokines in CAD patients is required.

Acute-phase Reactants

The results of this review documented a positive influence of exercise on acute-phase reactants; post-intervention CRP, fibrinogen, and vWF value comparisons documented very low qualities of evidence for significantly lower values in exercise groups compared to controls. However, the results of the CRP and vWF meta-analyses should be interpreted with caution as substantial between-study heterogeneity was identified. Moreover, the post-intervention vWF value comparison comprised two studies, which limits the validity of the result. Qualitatively, the findings of the trials that were not included in the meta-analyses support the quantitative results of this review; five (24,26,29,41,46) out of the nine studies (24,26,28,29,33,35,41,44,46) that investigated the impact of exercise on acute-phase reactants reported beneficial within-exercise group changes. Altogether, the results of this review support the ability of exercise to reduce CRP, fibrinogen, and vWF in CAD patients. The correlation between these acute-phase reactants and adverse outcomes accentuates the potential importance of this finding (59-63).

Adhesion Molecules

The meta-analyses failed to find significant post-intervention differences between exercise and control groups for VCAM-1, ICAM-1, P-selectin and E-selectin. Although, a positive effect of exercise on ICAM-1 approached statistical significance (P= 0.06). When considering the results of the studies individually, only three (29,38,45) of the eight studies (24,27,29,34,37,38,43,45) that investigated the effect of exercise on adhesion molecules demonstrated a significant effect. However, two of these studies (29,38) provided an exercise intervention alongside a comprehensive CR programme, which limits attributing these results to an independent effect of exercise. With regard to Ribeiro et al. (37), no significant within-exercise group changes in the post-intervention levels of ICAM-1 and VCAM-1 were documented. Yet, the post-intervention values of these adhesion molecules significantly increased in the control group, which resulted in significant between-group differences for changes in ICAM-1 and VCAM-1 levels. Interestingly, these results imply that exercise may supress deterioration in endothelial function. Collectively, the results of this review failed to demonstrate conclusive evidence for a beneficial effect of exercise on adhesion molecules. Nevertheless, the majority of studies possessed small sample sizes, which may account for the non-significant results. Also, the limited data for each adhesion molecule precluded a robust evaluation. Despite the equivocal effect of exercise on adhesion molecules, six studies (24,26,33,39,42,44) in this review demonstrated an improvement in endothelial function as measured via brachial flow mediated dilatation (FMD). The ability of exercise to stimulate an improvement in brachial FMD was also supported by a recent meta-analysis (64). As such, studies should continue to explore the effect of exercise on adhesion molecules to further illuminate the exercise induced improvements in endothelial function.

Chemokines

The meta-analyses failed to find significant post-intervention differences between exercise and control groups for IL-8 and RANTES, which may be attributed to the small number of pooled studies. In terms of the qualitative analysis, the effect of exercise on chemokines was equivocal. To elaborate, across the included studies, no significant effects on post-intervention values of Mig, RANTES, CXCL16, CCL19, MCP-1, and CD40L were

documented. However, two (43,47) out of the three studies (28,43,47) that evaluated the impact of exercise on IL-8 observed significantly lower post-intervention values in exercise groups compared to controls. Moreover, Fernandes et al. (27) demonstrated beneficial between-group differences in post-intervention IP-10 values, and Munk et al. (43) recorded significant within-exercise group reductions in CCL21 levels. In particular, the results generated by Fernandes et al. (27) are of interest as there is evidence to suggest that increased levels of IP-10 correlate with restenosis following PCI in CAD patients (65). Overall, the limited amount of evidence for the effect of exercise on chemokines prevented a valid evaluation. Moreover, the reviewed studies consisted of small sample sizes, which as mentioned before, may have precluded the identification of significant results. Given the vital role of chemokines in orchestrating atherogenesis (66), and in acknowledgment of the qualitative findings, further research into the effect of exercise on chemokines is required.

Sub-group Analyses

An uneven covariate distribution precluded valid sub-group analyses of the influence of exercise intervention characteristics on inflammatory biomarker changes. However, six of the included studies (24,26,28,33,40,42) compared the effects of different exercise modalities on inflammatory biomarkers. Across which, no statistically significant between-exercise group differences in post-intervention inflammatory biomarker values were seen.

The acute response to exercise involves the release of IL-6 from skeletal muscle cells, which serves as a stimulus for anti-inflammatory adaptation (57). Importantly, the intensity (67) and duration of exercise (57), along with the involved muscle mass (57,68) determine the acute rise in IL-6. However, evidence regarding optimal exercise characteristics for inducing anti-inflammatory protection is equivocal. To elaborate, Hayashino et al. (69) stated that longer exercise programmes and greater exercise session frequencies were associated with greater reductions in IL-6, albeit results from type 2 diabetes patients. In contrast, Swardfager et al. (12) demonstrated that the duration of exercise programmes was not associated with a decrease in CRP in CAD patients. Moreover, Fedewa et al. (54) concluded that duration, frequency, and mode of exercise were not associated with reductions in CRP in healthy and clinical populations. As such, further research to identify optimal exercise characteristics for reducing inflammation in CAD patients is necessary.

Strengths and Limitations

To our combined knowledge, this is the first systematic review and meta-analysis to exclusively evaluate randomised studies that investigated the effect of exercise on inflammatory biomarkers in CAD patients. The exclusion of studies that possessed confounding variables, such as: the recruitment of CAD patients with severe heart failure (New York Heart Association (NYHA) Class III or IV or left ventricular ejection fraction (LVEF) ≤ 30%), or the provision of co-interventions (e.g. a hypocaloric diet or antioxidant/ vitamin supplement) to exercise increased the validity of the findings. Further strengths of this review include: a comprehensive literature search, evaluation of overall quality of evidence using the GRADE system, and the pooling of data for meta-analyses. Moreover, qualitative analyses of studies and outcomes that could not be meta-analysed were performed to circumvent the exclusion of valuable findings.

The exclusion of studies that recruited patients with severe heart failure (NYHA Class III or IV or LVEF ≤ 30%) limits extrapolating the results of this review to CAD patients with these deteriorated conditions. Whilst a comprehensive literature search was performed, the exclusion of studies that were not reported in English may have introduced publication bias. Nevertheless, this issue was not strongly suspected for any outcome as both negative and positive findings were reported by studies with varying sample sizes.

A further limitation involves the sub-group analyses of exercise intervention characteristics failing to provide a valid evaluation of potential sources of between-study heterogeneity. However, the level of between-study heterogeneity may also have been influenced by the following factors: population characteristics (i.e. comorbidities) (56), diet (70), medication (71), natural recovery following cardiovascular complication/ surgical intervention (72,73), measurement medium (plasma or serum) (74), and methods employed for blood sample preparation and handling (74-76).

With regard to study quality, inadequate reporting of random sequence generation and allocation concealment, along with imprecision as a result of small sample sizes decreased the reliability of the results across most of the included studies and limited the overall quality of evidence. As such, the results of this review should be interpreted with caution until further randomised studies with high methodological qualities and large sample sizes are conducted.

Conclusion

This systematic review and meta-analysis demonstrates that exercise reduces CRP, fibrinogen, and vWF concentrations in CAD patients. In addition, qualitative analyses identified evidence that supports a positive effect on these acute-phase reactants. However, current evidence surrounding the effect of exercise on anti-inflammatory cytokines, adhesion molecules, and chemokines is equivocal, which may be attributed to a paucity of research. Nevertheless, whilst the findings of this review support the ability of exercise to reduce inflammatory activity in CAD patients, various requirements for future research have been identified. Firstly, the quality of evidence for this area needs to be improved by further randomised studies with high methodological qualities and large sample sizes. Moreover, additional research into the effect of exercise on proximal mediators of inflammation and anti-inflammatory cytokines is required. In order for exercise to be utilised as an anti-inflammatory strategy in CAD, future studies should seek to identify optimal exercise characteristics for mitigating inflammation. Finally, to generate a comprehensive understanding of the anti-inflammatory effect of exercise, future research should explore the underlying molecular mechanisms that may be responsible for orchestrating an exercise induced reduction in inflammation.

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Disclosure of interest

The authors report no conflict of interest.

Data availability statement

The authors confirm that the data supporting the findings of this systematic review and meta-analysis are available within the article and its supplementary materials.

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Table 1. Inclusion and exclusion protocol.

Inclusion criteria	***Exclusion criteria***
• Report published in English • Randomised trial • In consideration of standard treatment, studies involving control groups that routinely received usual care (i.e. pharmacological treatment and lifestyle recommendations) were included • Recruited only formally diagnosed coronary artery disease patients with history of a myocardial infarction, acute coronary syndrome, coronary revascularisation by percutaneous coronary intervention or coronary artery bypass graft, or ≥ 50% occlusion of at least one major coronary artery as confirmed by an angiogram • At least one inflammatory biomarker measured in blood (plasma or serum) before and after an exercise intervention (any form of aerobic, resistance training, or aerobic and resistance training combined) with a duration > 2-weeks, which may allow potential changes in inflammatory biomarkers to be representative of exercise induced physiological adaptation • Studies comprising exercise training in combination with a comprehensive cardiac rehabilitation programme (i.e. lifestyle/ risk factor advice and psychosocial management) were included if the additional components of the programme were solely educational	• Studies were excluded if a co-intervention was reported (i.e. provision of a hypocaloric diet or antioxidant/ vitamin supplement), to allow the results to potentially reflect an independent effect of exercise • Studies that recruited CAD patients with severe heart failure (New York Heart Association Class III or IV or left ventricular ejection fraction ≤ 30%) were excluded to standardise the severity of CAD in the included participants, along with the reduced exercise tolerance and increased inflammatory state associated with severe heart failure being potential confounding variables (77,78)

Table 2. GRADE system guidelines for rating overall quality of evidence (18).

GRADE Domain	***Description***
Study Limitations	The quality of evidence is downgraded by the existence of internal limitations such as: lack of allocation concealment, lack of blinding, incomplete accounting of patients and outcome measures, selective outcome reporting, or terminating early for benefit.
Inconsistency of Results	The quality of evidence is downgraded by the following criteria: wide variance of point estimates across studies, minimal or no overlap of confidence intervals, statistical tests for heterogeneity (χ^2) generate low P-values (≤ 0.1), or large I^2 values are documented.
Indirectness of Evidence	The quality of evidence is downgraded if interventions were not compared directly to one another, or if a restricted version of the main review question in terms of population, intervention, or outcomes was investigated.
Imprecision	The quality of the evidence is downgraded when studies included relatively few participants and thus had wide confidence intervals around the estimate of effect.
Publication Bias	The quality of the evidence is downgraded if a systematic under-estimation or an over-estimation of significant or non-significant intervention effects due to the selective publication of studies is suspected.

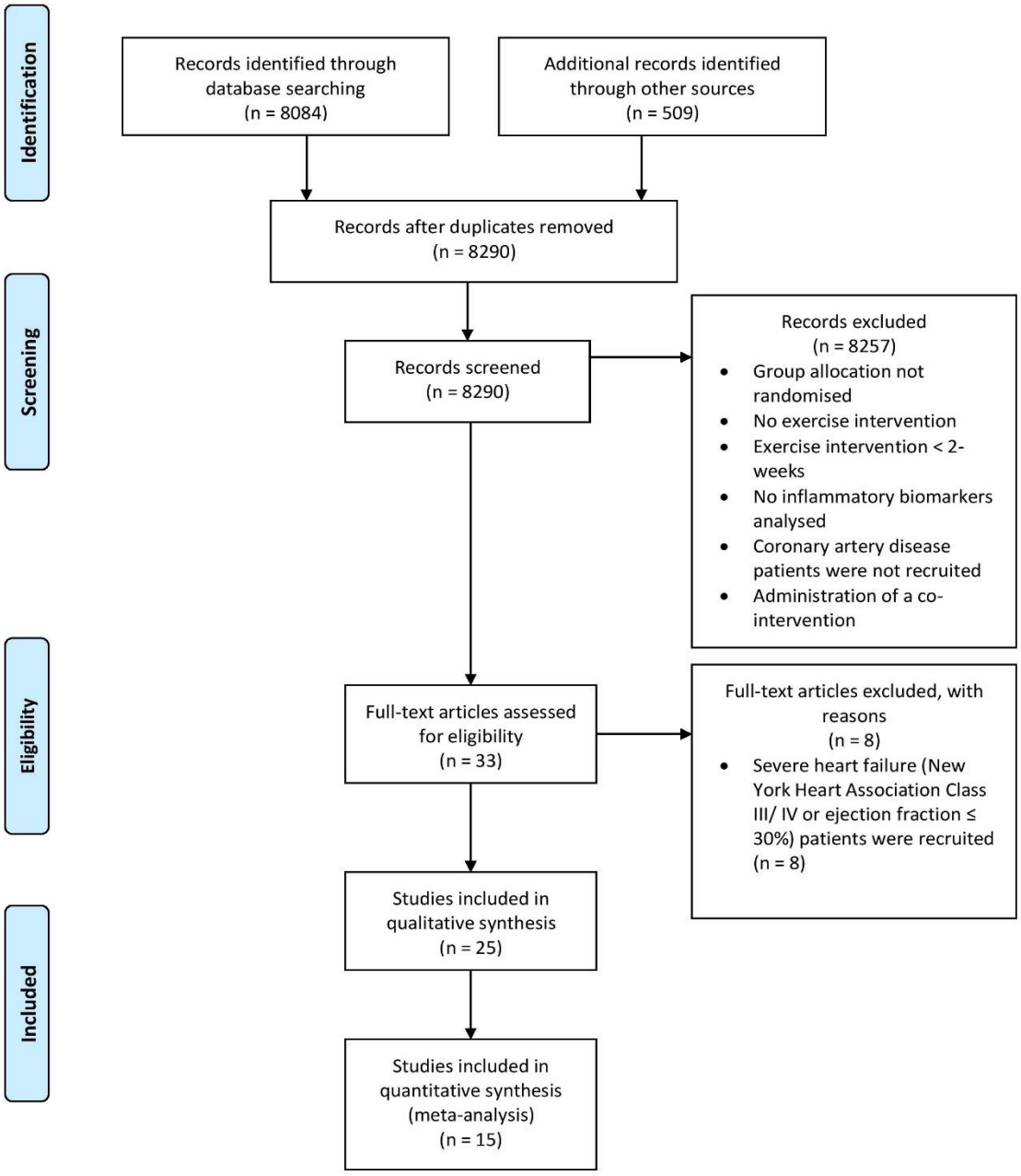

Figure 1. PRISMA flow diagram depicting the study selection process.

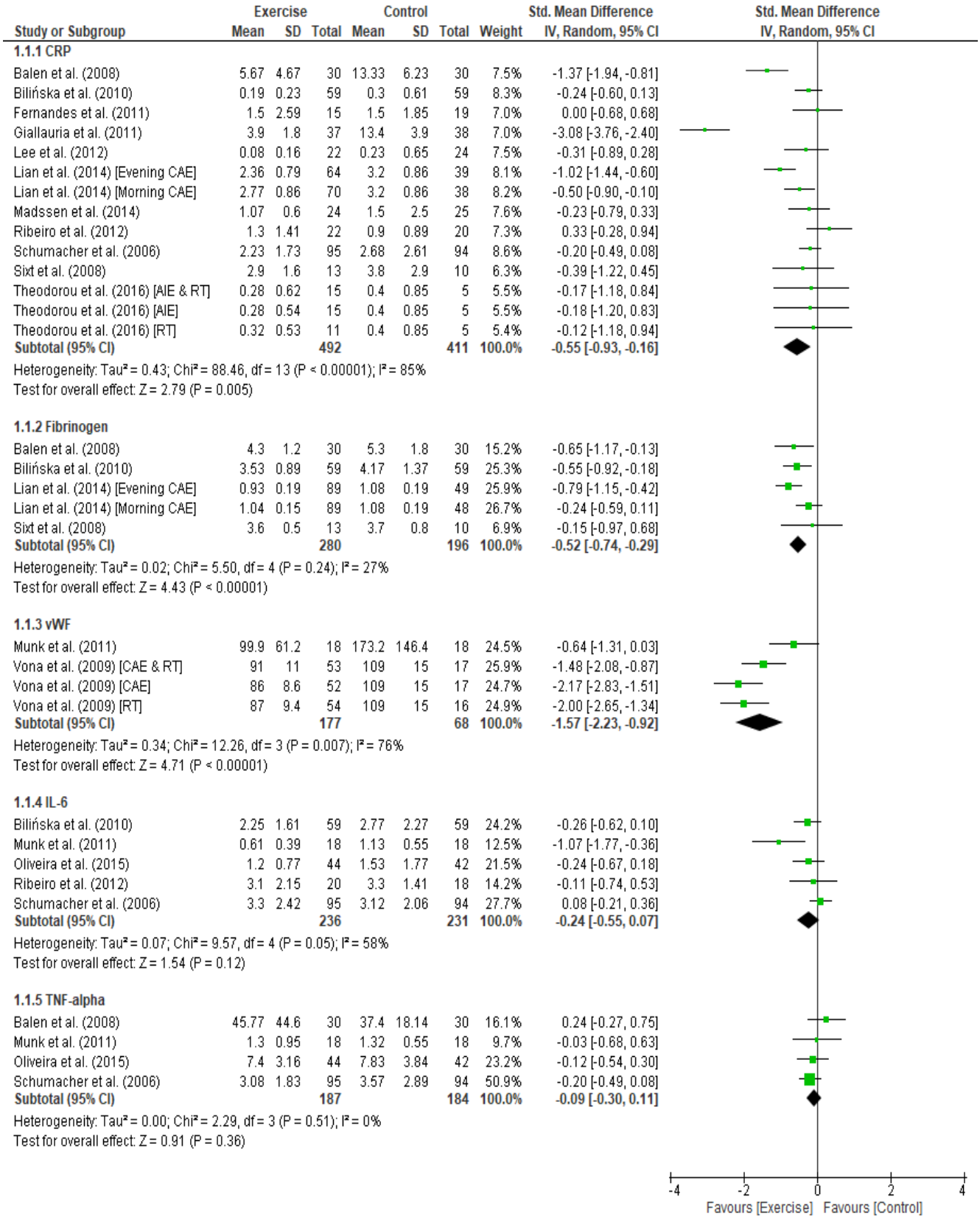

Figure 2.1. Forest plots of post-intervention inflammatory biomarker value comparisons between exercise and control groups.

Key: *SD* standard deviation, *Std* standardised, *IV* inverse variance, *CI* confidence interval, *CRP* C-reactive protein, *vWF* von Willebrand factor, *IL-6* interleukin-6, *TNF-alpha* tumour necrosis factor-alpha, *CAE* continuous aerobic exercise, *AIE* aerobic interval exercise, *RT* resistance training

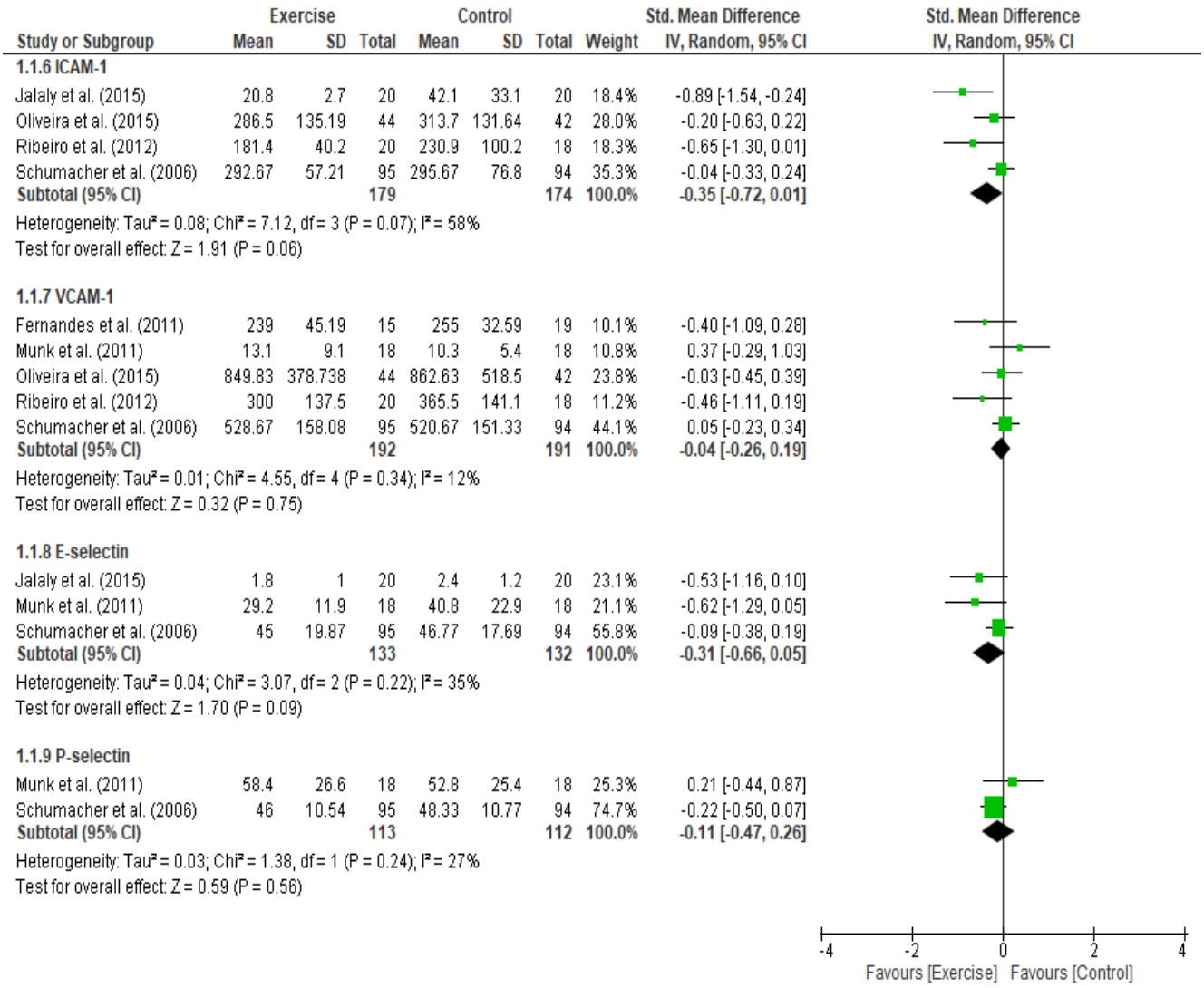

Figure 2.2. Forest plots of post-intervention inflammatory biomarker value comparisons between exercise and control groups.

Key: *SD* standard deviation, *Std* standardised, *IV* inverse variance, *CI* confidence interval, *ICAM-1* intercellular adhesion molecule-1, *VCAM-1* vascular cell adhesion molecule-1

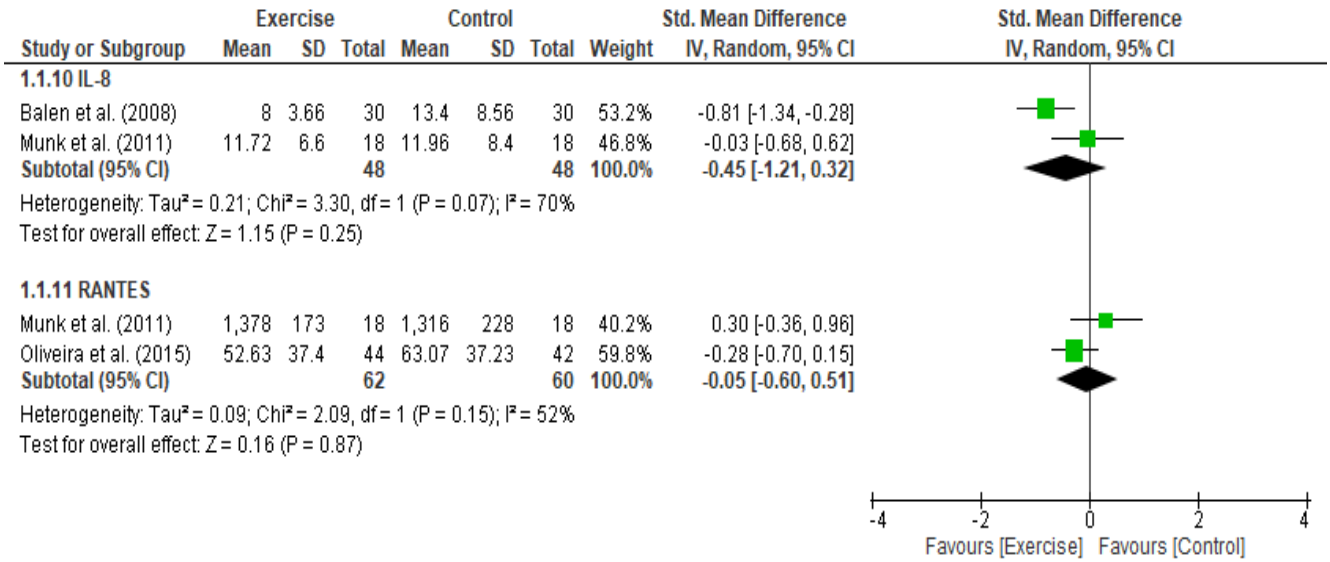

Figure 2.3. Forest plots of post-intervention inflammatory biomarker value comparisons between exercise and control groups.

Key: *SD* standard deviation, *Std* standardised, *IV* inverse variance, *CI* confidence interval, *IL-8* interleukin-8, *RANTES* regulated on activation, normal T-cell expressed and secreted

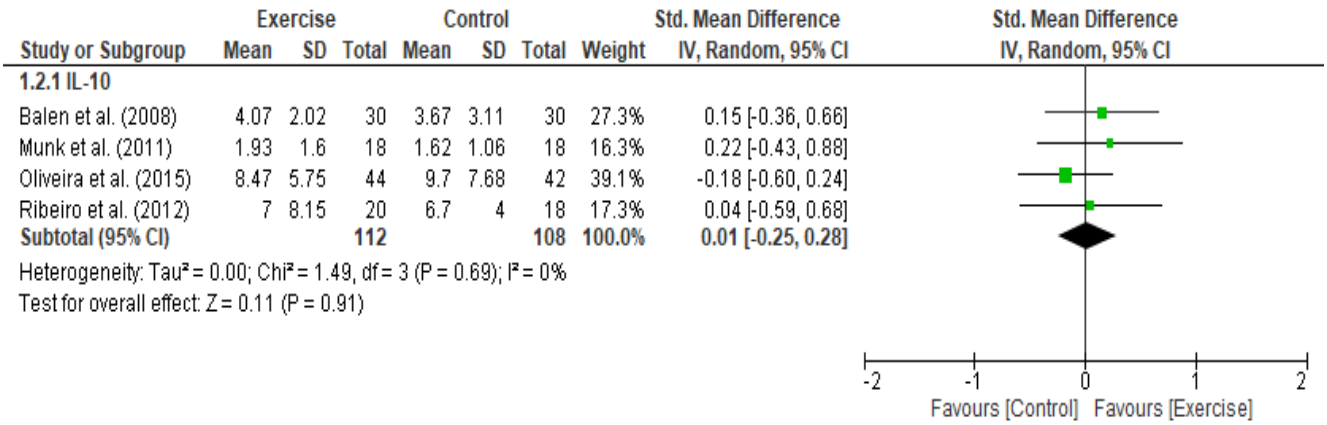

Figure 3. Forest plot of post-intervention IL-10 value comparison between exercise and control groups.

Key: *SD* standard deviation, *Std* standardised, *IV* inverse variance, *CI* confidence interval, *IL-10* interleukin-10

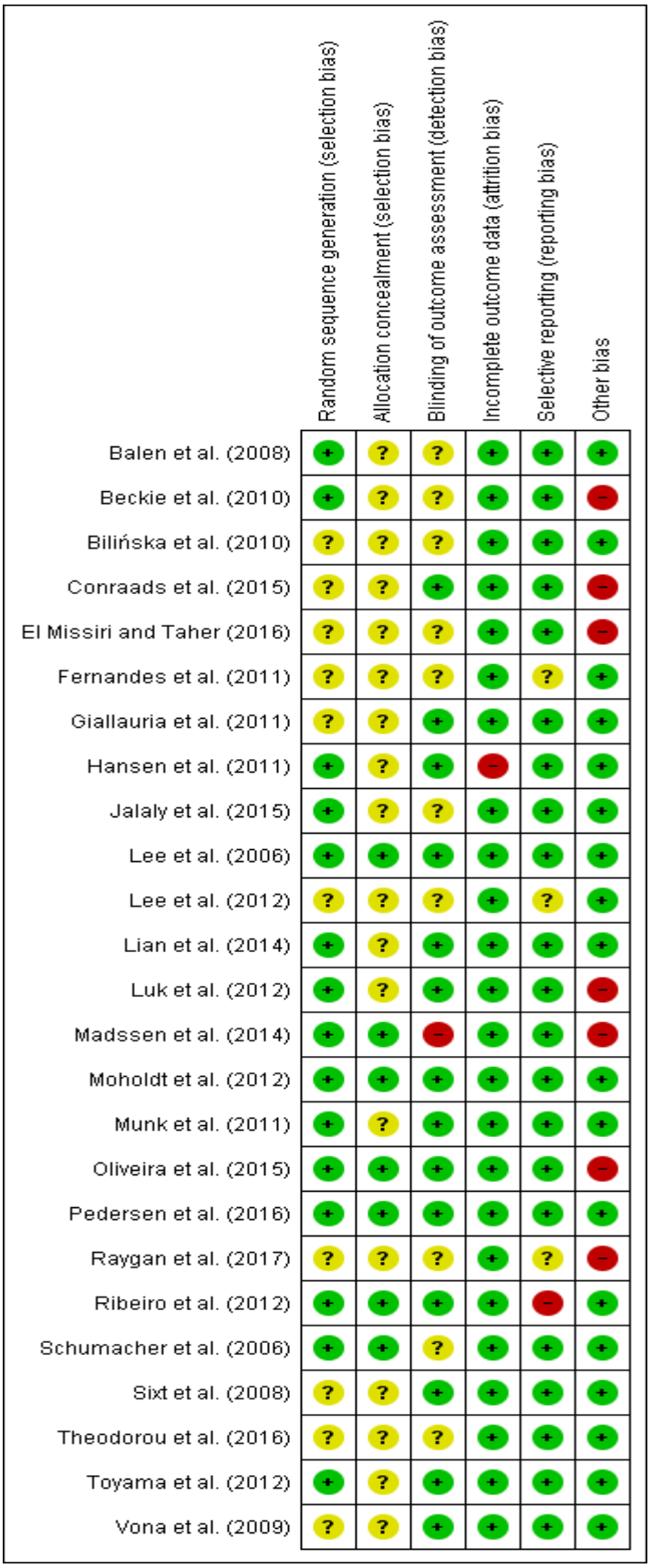

Figure 4. Review authors' judgements about each risk of bias item for each included study.

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Figure 3. Forest plot of post-intervention IL-10 value comparison between exercise and control groups.

Figure 4. Review authors' judgements about each risk of bias item for each included study.