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Effects of exercise on c-reactive protein in healthy patients and in patients with heart disease: A meta-analysis

Tracy L. Hammonds, PhD[a,b], **Emily C. Gathright, MA**[a], **Carly M. Goldstein, PhD**[a,b,c], **Marc S. Penn, MD, PhD**[b,d], and **Joel W. Hughes, PhD**[a,b,*]

[a]Kent State University, P.O. Box 5190, Kent, OH, USA

[b]Cardiovascular Institute, Summa Health System, 95 Arch St, Akron, OH, USA

[c]Warren Alpert Medical School of Brown University, Providence, RI, USA

[d]Department of Integrated Medical Sciences, Northeast Ohio Medical University, Rootstown, OH, USA

Abstract

Decreases in circulating hsCRP have been associated with increased physical activity and exercise training, although the ability of exercise interventions to reduce hsCRP and which individuals benefit the most remains unclear. This meta-analysis evaluates the ability of exercise to reduce hsCRP levels in healthy individuals and in individuals with heart disease. A systematic review and meta-analysis was conducted that included exercise interventions trials from 1995 to 2012. Forty-three studies were included in the final analysis for a total of 3575 participants. Exercise interventions significantly reduced hsCRP (standardized mean difference −0.53 mg/L; 95% CI, −0.74 to −0.33). Results of sub-analysis revealed no significant difference in reductions in hsCRP between healthy adults and those with heart disease ($p = .20$). Heterogeneity between studies could not be attributed to age, gender, intervention length, intervention type, or inclusion of diet modification. Exercise interventions reduced hsCRP levels in adults irrespective of the presence of heart disease.

Keywords

Coronary disease; Exercise; Heart disease; Inflammation; Biological marker c-reactive protein

Introduction

Circulating levels of high-sensitivity c-reactive protein (hsCRP) is a modifiable risk factor for cardiovascular disease (CVD).[1,2] hsCRP was found to be an independent predictor of CVD in a cohort study of 15,792 adults, ages 45–64 years, designed to identify whether hsCRP levels in middle-aged adults was associated with future risk of CVD.[3] The authors went on to state that hsCRP may be a good early predictor of CVD even when other

*Corresponding author: Department of Psychology, P.O. Box 5190, Kent, OH 44242, USA. Tel.: +1 330 672 7721; fax: +1 330 672 3786., jhughes1@kent.edu (J.W. Hughes).

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traditional risk factors, such as high levels of low-density lipoprotein C (LDL-C), are not present. In another cohort of 3345 German men, the authors found that hsCRP levels were associated with risk of CVD independent of the Framington Risk Score (FRS), and enhanced the prognostic value of the FRS in persons with intermediate risk for CVD.[4]

Decreases in circulating hsCRP have been associated with lifestyle changes including changes in diet[5–8] as well as increased physical activity[9–14] and exercise training.[15–20] Although accumulating evidence supports the clinical use of hsCRP measurements in healthy individuals to direct preventative treatment regimens, questions remain as to whether exercise interventions reliably reduce hsCRP and which individuals are most likely benefit from programs aimed at reducing circulating levels of hsCRP. Epidemiological studies in patients diagnosed with heart disease as well as in healthy individuals have shown that increased physical activity is associated with decreased levels of hsCRP as well as lower risk of heart disease[14,21–28]; but, these studies are retrospective in nature and depend on self-report measures of physical activity. Controlled studies in patients with diagnosed heart disease have shown that exercise training is associated with reduced circulating hsCRP[29]; yet, results in healthy people have been inconclusive.[20,30–34] The most recent meta-analysis suggested that hsCRP is not lowered in healthy adults enrolled in an aerobic exercise program ($M \pm$ SEM = −0.11 ± 0.14 mg/L, 95% CI: −0.39 to 0.17 mg/L), but at that time only 5 clinical trials met the inclusion criteria.[30] A recent meta-analysis in persons diagnosed with heart disease revealed that an exercise intervention is associated with lower hsCRP levels (Standardized Mean Difference (SDM) = −0.345, 95% CI: −0.444 to −0.246); but the meta-analysis included studies that were pre/post-design with no control group.[29]

There are several explanations for the inconsistent results observed in studies examining the potential of exercise to lower hsCRP. Gender differences in hsCRP levels have been observed, with higher hsCRP levels being associated with intima-media-thickness, a measure of early artherosclerosis, in women but not in men.[35] Additionally, decreases in hsCRP level due to an exercise intervention have been observed in obese individuals with glucose intolerance in the absence of cardiovascular disease.[36] There is research suggesting that increasing fitness is not associated with lowered hsCRP, but lowered hsCRP following exercise intervention can be explained by resultant reductions in weight.[37] Finally, baseline hsCRP may be elevated in patients who have recently experienced a cardiac event,[38] and post exercise levels of hsCRP may be elevated in the period directly following intense exercise.[39]

The primary goals of this meta-analysis were to determine if exercise reduces hsCRP in healthy adults and in individuals with heart disease, and to determine if the reduction is significantly different between groups. A secondary goal of this study was to determine factors that may lead to variance in the intervention effect not explained by chance (i.e., study heterogeneity). The following factors were reviewed: age, gender, intervention duration, intervention type, inclusion of diet in the intervention, timing of blood draws, and presence of risks associated with metabolic syndrome.

Methods

Data sources

Studies for this systematic review and meta-analysis were retrieved through computerized literature searches of PubMED and The Cochrane Central Register of Controlled Trials as well as cross-referencing of review articles and retrieved studies. Keywords used in the search included exercise, physical activity, c-reactive protein, coronary heart disease, cardiovascular disease, inflammation, clinical trials, and adults. The study results were reported using the PRISMA framework, with the exception of the abstract.

Inclusion criteria

Studies performed between the years of 1995 and 2012 were included in the systematic review and meta-analysis if they met the following criteria: 1) randomized and non-randomized trials; 2) exercise intervention ≥4 weeks but ≤3 years; 3) assessment of hsCRP at baseline and following the last exercise session; 4) human subjects >18 years of age; 5) inclusion of control group that did not receive an exercise intervention; 6) studies of healthy adults and/or adults with ischemic heart disease and heart failure without other significant disease processes; and 7) English language studies published in scientific journals. The earliest search date was set at 1995 due to the availability of reliable assays to assess hsCRP levels in blood serum.[40] The time frame for the exercise interventions was chosen based on similar inclusion criteria used in a prior meta-analysis of randomized trials in healthy adults.[30] Study selection did not include articles in foreign-languages due to concerns regarding translation of results, and it was decided to only include scientific journal articles to ensure inclusion of quality studies.

Data abstraction

An electronic spreadsheet was created to record data from the studies reviewed. Categories that were coded included study characteristics (e.g., source and date), subject characteristics (e.g., age, gender, and health status), exercise training program characteristics (e.g., duration and frequency), change in hsCRP (mg/L), and hsCRP assessment procedure (e.g., time before and after exercise). Subject health status data included abstraction of indicators of metabolic syndrome in accordance with International Diabetes Foundation's (IDF) consensus statement on metabolic syndrome,[41] which defines metabolic syndrome as having central obesity (BMI ≥ 30 kg/m^2) and at least two of the following: 1) raised tri-glycerides (≥150 mg/dL or treatment for such), 2) reduced high-density lipoprotein (HDL) cholesterol (<40 mg/dL in males, <50 mg/dL in females, or treatment for such), 3) high blood pressure (systolic ≥130, diastolic ≥85, or treatment for such), and 4) raised fasting glucose (≥100 mg/dL or diagnosis of type II diabetes). A literature review was conducted by the research assistant. Data were abstracted and eligibility was determined by two reviewers. Discrepancies in the data were resolved by consensus.

Statistical analysis

For each study included in the meta-analysis, the mean difference in hsCRP was calculated by subtracting the change difference in the control group from the change difference in the

intervention group. A random effects model was used to estimate the standard mean difference in change from baseline for hsCRP. The random effects model was chosen because of its ability to statistically control for heterogeneity as well as to provide for wider 95% confidence intervals (CI) than the fixed-effects model when significant heterogeneity is expected. Ninety-five percent CI were used to establish statistical significance of the results. If the results did not cross zero, they were considered to be significant. Heterogeneity was also examined using the I^2-statistic, which is a measure of intervention effect due to known differences in study design.[42]

Analyses of interaction effects (moderators) for several a priori explanatory variables were conducted. The interaction effects examined included age, gender, duration of exercise intervention, and type of exercise intervention. A subgroup analysis to determine difference in effect for healthy adults versus adults with cardiac disease was also conducted. A one-way, random effects ANOVA model was used to estimate the standard error and variance for each group and to test whether these means were different between groups. It was assumed that the variance among each group was different. Prior to performing the analysis, the moderators were categorized. Interaction effects due to presence of factors related to metabolic syndrome and timing of blood draws was not conducted due to insufficient information within the individual studies.

The quality of the studies was assessed using a previously developed 5-point scale that has been shown to be both reliable and valid.[43] The scale ranges from 0 to 5 with higher scores representing greater study quality.

In cases where the standard deviation for the change in hsCRP was not reported, it was imputed using the following formula[44]:

$$SD_{\Delta} = \sqrt{SD^2_{Baseline} + SD^2_{Final} - (2 * Corr * SD_{Baseline} * SD_{Final})},$$

where “Corr” is the correlation coefficient between the standard deviations for the baseline and the standard deviations for the final measures of hsCRP in both the experimental and control groups derived from studies with known standard deviation for change. Corr for both the experimental and control groups were calculated as follows:

$$Corr = \frac{SD^2_{baseline} + SD^2_{final} - SD^2_{change}}{2 \times SD_{baseline} \times SD_{final}}$$

The correlation coefficients were averaged to obtain a Corr equal to 0.80. The averaged Corr was included in the equation to impute the standard deviation for hsCRP.

Descriptive statistics were presented as mean ± SD. Primary and secondary outcomes were presented as standardized mean difference (SMD) with 95% CI as well as mean difference (MD) with 95% CI. Hedge’s g statistic was used as the standardized mean difference effect size since it accounts for variance in size of the studies by pooling weighted standard deviations.[45]

The Egger regression approach was used to examine the sensitivity of changed to hsCRP due to publication bias.[46] An α level of <0.05 was used to determine if significant publication bias existed.

All analyses were conducted using Review Manager 5.1 (The Cochrane Corporation, Copenhagen, Denmark).

Results

Study characteristics

Healthy adults—Characteristics of the included studies can be found in Table 1. Of the 150 studies reviewed, 33 studies were included in the final analysis. A description of the review process, including reasons for exclusion, is located in Fig. 1. Nineteen of the studies were performed in the United States, 3 each in Korea and the United Kingdom, 2 each in Canada and Iran, and 1 each in Australia, Brazil, New Zealand, and Portugal. The results for a total of 3575 participants (1918 exercisers and 1657 controls) were pooled and analyzed. Total study size ranged from a low of 14 participants to a high of 349 participants. Mean study quality was 3 out of a possible 5 points (Range = 0–5). Results of the Egger regression test indicated absence of publication bias ($p = 0.26$).

Adults with CHD—A description of the studies included for review is contained in Table 2. Out of the 56 studies found, 10 studies were included in the final analysis. A description of the review process, including reasons for exclusion, is located in Fig. 2. One trial was performed in each of the following countries: United States, Sweden, Italy, Serbia, Portugal, and China. Two studies came from each of the following countries: Norway and Germany. The results for a total of 827 participants (510 exercisers and 317 controls) were pooled and analyzed. Total study size ranged from 22 participants to 277 participants. Mean study quality was 2 out of a possible 5 points (Range = 0–5). Results of the Egger regression test indicated absence of publication bias ($p = 0.86$).

Subjects

Healthy adults—Twelve studies were limited to women only, whereas results for men only were reported in 4 studies. The remaining 17 studies evaluated results for both males and females, although two of these studies did a breakdown of the results by gender. Thirteen studies reported that the women were postmenopausal, and two studies specified that the women were premenopausal. Women using hormone replacement therapy were excluded in 8 studies.

One study reported the use of physically active individuals as the control group, whereas the remaining studies indicated that all participants were sedentary. Being overweight (body mass index [BMI] ≥ 25 kg/m^2) was an inclusion criterion in seven studies, with two studies including only obese participants (BMI ≥ 30 kg/m^2). Participants with hypertension were studied exclusively in 4 studies, whereas another 4 studies excluded hypertensive participants. Two of the studies examined participants with dyslipidemia and one study each examined participants with diabetes mellitus (Type 2) and metabolic syndrome. One study limited participation to subjects with baseline hsCRP levels between 2 mg/L and 10 mg/L.

Participants with a history of metabolic disorders were excluded from 13 studies, and a history of smoking in the prior 12-months were excluded from 9 studies.

Adults with CHD—One study reported results for men only, whereas the remaining 9 studies included results for both men and women. Inclusion for 8 of the studies required a diagnosis of stable coronary artery disease (CAD), with 4 of the 8 studies requiring participants to be post-acute myocardial infarction (AMI), percutaneous intervention (PCI), and/or coronary artery bypass graft (CABG) surgery. One of the six studies enrolled participants who were scheduled for PCI, and another of the studies examined patients who would be eligible for PCI due to the presence of 75% blockage, and studied the difference between a group of participants who underwent PCI versus a group of participants who voluntarily participated in a 24-month regimen of aerobic exercise rather than undergoing PCI. In the exercise group, seven patients were removed from the final analysis due to undergoing emergent PCI and/or revascularization for AMI and/or unstable angina. Two of the studies reviewed included patients with heart failure rated as New York Heart Association (NYHA) class II or III.

Assessment of hsCRP

Healthy adults—The average concentration of hsCRP in healthy adults at baseline was 4.6 mg/L ± 4.7 mg/L. Blood samples for hsCRP analysis in 7 studies were drawn 24-h after completion of the last exercise session. One study specified that blood samples were drawn 48-h after the last exercise session, and another specified that blood samples were drawn 2–3 days after the last exercise session. The remaining 24 studies documented blood draws after conclusion of the last exercise session. Fasting blood sampling was conducted in 24 studies, and 14 studies specified that blood sampling was conducted in the AM.

Adults with CHD—The average hsCRP at baseline in adults diagnosed with CHD was 4.3 mg/L ± 4.7 mg/L. All hsCRP measurements were taken after an 8- to 24-h fast. Two of the studies enrolling participants after a coronary event reported that baseline hsCRP levels were assessed after waiting for a period of 16-days in one study and 3–5 weeks in the other study following the event. None of the other studies that enrolled participants after a coronary event reported how long they waited prior to assessing baseline hsCRP levels. All final hsCRP measurements were performed within 24-h after the completion of the exercise intervention.

Intervention programs

Healthy adults—An aerobic exercise intervention was examined in 23 of the studies analyzed, whereas 7 of the studies examined an intervention that included a mix of aerobic, strength, flexibility, and balance exercises. Two studies examined the effect of resistance exercise only on circulating hsCRP. There was one study that did not report the type of exercise intervention.[55] The length of the exercise intervention ranged from 6-weeks to 18-months. The length of the individual exercise sessions lasted from 20-min to 90-min with the majority lasting between 45-min and 60-min. The frequency of exercise sessions was 3–6 times per week with the majority specifying 3 sessions per week. Seven studies specified

total energy expenditure per week (kilocalorie/kilogram/week [KKW]) rather than times per week with total energy expenditure ranging from 4 KKW to 26 KKW.

The average intensity of the aerobic exercise sessions was approximately 70%–75% of VO_2 maximum with a range of 50%–90% of VO_2 maximum. For the studies examining resistance training, interventions were established to produce 75%–80% of 1 maximum rep (RM). One study reported results for 55% of 1 RM.

Two studies incorporated a diet program as well as an exercise program into the intervention, whereas another study provided the participants with written diet education at the beginning of the trial. Four studies included a treatment group receiving a diet and exercise intervention as well as an exercise intervention only treatment group. Three studies provided all participants with information regarding healthy living at the beginning of the study, and one study enrolled all participants in a healthy living class that met 1 time per month throughout the duration of the study.

Adults with CHD—Each of the studies reviewed contained an aerobic exercise component, whereas one study added resistance training using bands as well. The shortest intervention length was 4-weeks and the longest was 24-months. The average duration of the exercise intervention for all studies was 148.8 ± 210.8 days. Nine studies reported individual session lengths ranging from 30-min to 55-min, and frequency of exercise was reported for 9 studies with a frequency range of 2–6 times per week. The intensity of aerobic exercise sessions ranged from 65% to 80% maximum heart rate.

Exercise and hsCRP change

Pooled data from the 43 studies analyzed revealed a significant reduction in hsCRP favoring the exercise intervention group (SMD = −0.53; 95% CI, −0.74 to −0.33; MD = −0.67 mg/L; 95% CI, −0.93 to −0.42; Fig. 3). However, significant heterogeneity was observed between studies ($\chi^2(42, N = 43) = 380.7$, $p < 0.001$, $I^2 = 89\%$). Subgroup analysis revealed significant reductions in hsCRP for both healthy adults (SMD = −0.59; 95% CI, −0.83 to −0.35; MD = −0.74 mg/L; 95% CI, −1.05 to −0.44) as well as in adults with cardiovascular disease (SMD = −0.34; 95% CI, −0.64 to −0.05; MD = −0.42 mg/L; 95% CI, −0.81 to −0.06). No significant differences were found in effect size for healthy adults versus those with cardiovascular disease ($p = 0.20$). A large degree of heterogeneity was observed between studies in healthy adults ($I^2 = 91\%$), thus the following variables were examined as possible sources of the observed heterogeneity: gender, age, intervention duration, and intervention type (Table 3). There were no significant interaction effects observed due to the possible sources of heterogeneity analyzed.

Discussion

Exercise is associated with a significant reduction in hsCRP for both healthy adults and those with CVD. The pooled effect sizes for each sub group did not differ based on the presence of cardiovascular disease. In a past meta-analysis, it appeared that exercise did not lower hsCRP in adults without CVD.[30] This meta-analysis did not support that conclusion. When individual studies were considered, 17 out of the 33 did not report a significant

reduction in change in hsCRP in participants enrolled in an exercise intervention compared to controls. Yet, a reduction in hsCRP from baseline due to an exercise intervention was observed in all but one of the studies analyzed. A narrative review could easily reach the conclusion that exercise interventions do not reduce hsCRP levels in healthy adults due to lack of statistical significance between groups, whereas this quantitative review suggests that it does. However, there was substantial heterogeneity between studies in the magnitude of the effect, including when studies enrolling healthy adults or adults with CHD were considered separately; thus the results should be evaluated with caution. Results of the moderator analysis showed that the heterogeneity in effect size for studies enrolling healthy adults was not attributable to age, gender, intervention length, intervention type, or the inclusion of diet modification.

One hypothesis for varying results in randomized trials of patients with heart disease is that the timing of baseline hsCRP measurements influences the effect size. Schumacher et al[38] reported significant drops in hsCRP in both the exercise intervention group and controls, but no between-group differences in change in hsCRP were observed. Baseline measurements of hsCRP were taken approximately 16-days after a first episode of AMI and were found to be extremely elevated in both the exercise intervention participants and controls (5.91 mg/L and 5.22 mg/L respectively). In this case, the extreme elevation may be due to heart tissue trauma and the reduction in hsCRP may be due to stabilization of the acute phase response rather than an exercise intervention.[38] Sixt et al[85] also observed reductions hsCRP in both the control and intervention group after 4-weeks, but further examination revealed that the baseline hsCRP level for the participants in the control group was abnormally high. Since the control group consisted of only 10 subjects, an individual with an abnormally high hsCRP value possibly influenced the mean. In the other studies with non-significant results, the baseline levels of hsCRP were normal or mildly increased (range 0.9–1.52 mg/L) in both groups and failed to demonstrate a reduction in hsCRP.[78,79,84] Finally, a majority of the studies included in the healthy adults did not report an exact time for conducting the blood draws post intervention. Evidence exists showing exercise increases hsCRP up to 24-h post exercise, but this is in individuals who have performed very strenuous physical activities such as running marathons.[87] In a cohort of patients with coronary artery disease, Mouridsen et al[39] found that hsCRP increased in the first 5 min following a moderate exercise test, but that this increase was attenuated at 20-h.[39] These results indicate that exercise could cause unwanted variation in post intervention hsCRP levels.

An additional hypothesis generated from this meta-analysis is that overweight individuals may be most likely to benefit from an exercise intervention to reduce hsCRP. With respect to obesity, Phillips et al[72] found that hsCRP levels were significantly reduced in obese, post-menopausal women who underwent 12-weeks of resistance training. Consistent with this hypothesis, a 34% reduction in hsCRP from baseline was realized in a cohort of obese, older (≥65 years) men and women who underwent an exercise and diet intervention designed to reduce their daily caloric energy by approximately 750 kcal/day.[77] Several of the studies stratified the results on various anthropometric measures with change in hsCRP. Arikawa, Thomas, Schmitz, & Kurzer[47] found that the observed significant decrease in hsCRP levels due to 16-weeks of aerobic exercise were largely driven by the effects of exercise in obese participants, who had an overall decrease in hsCRP of −4.38 ± 1.4 mg/L versus obese

controls who had an increase in hsCRP of 1.44 ± 1.2 mg/L. No significant differences in change in hsCRP were found due to loss of body fat.[24] In women, Campbell et al[52] found significant reductions in hsCRP due to an aerobic exercise intervention at both 3-months and 12-months that were not realized in non-obese females. Results were similar when stratified by abdominal obesity (waist circumference > 88 cm).[52] Church et al[53] reported that sedentary men and women who were in the top tertile for weight loss and DEXA-measured body fat experienced the largest decrease in hsCRP due to exercise.[62] Similarly, Jae et al[62] found that participants in the top two highest quartiles of weight loss had the greatest reduction in hsCRP due to an exercise intervention and Stewart, Earnest, Blair, & Church[37] found that participants in the highest quartile for weight loss had the greatest reduction in hsCRP. Women who lost 5% of their body weight due to an exercise and/or exercise plus diet intervention were found to have a significant decrease in hsCRP versus controls.[61] In contrast, Marcell, McAuley, Traustodottir, & Reaven[65] found no significant change in hsCRP due to exercise before and after stratification by reduction in body fat. Similarly, Campbell et al[52] found no difference in change in hsCRP due to exercise when stratified by obesity (BMI > 30 kg/m^2) and non-obesity regardless of gender.

Finally, it is interesting to note that inclusion of a modified diet in addition to exercise trended toward an enhanced the decrease in hsCRP from baseline when compared to exercise alone. One reason for this may be a greater propensity to lose weight, as discussed above. Another theory is that what we eat may contribute to a rise in inflammatory response. There is some evidence that low-glycemic load diets are more effective at lowering hsCRP than low-fat diets and high-glycemic load diets.[88,89] In a recently funded, randomized trial of 811 overweight and obese adults, hsCRP levels did not change due to changes in diet composition (e.g., fats, carbohydrates, proteins).[90] The authors concluded the hsCRP levels were more likely to be associated with amount of adipose tissue.

Potential limitations

The studies analyzed in this meta-analysis utilized many different study designs that may have contributed to the significant amount of heterogeneity observed. For example, differences were noted in the intervention procedures, the length of intervention, and inclusion and exclusion criteria. We were unable to assess heterogeneity due to factors associated with metabolic syndrome or timing of blood draws, thus leaving a question as to the effect of these variables on the overall result of the meta-analysis.

This meta-analysis included studies that were both randomized and non-randomized controlled trials. In addition, the majority of the studies reviewed did not report blinding of study personnel and investigators. Finally, a limited search strategy may have led to incomplete retrieval of studies as well as publication bias. These limitations may have impacted the results observed in this meta-analysis in addition to potentially decreasing overall generalizability.

Conclusions

In conclusion, exercise interventions decreased hsCRP in both healthy adults and those with CVD. The difference in effect size was not significantly different, indicating that exercise in

healthy adults may lower future risk of CVD. Exercise interventions may be most beneficial to overweight individuals. Inclusion of a diet modification plan to reduce body fat in addition to physical activity lead to even greater reductions in hsCRP, a hypothesis which requires further study. Additional clinical trials, with enhanced control of potential confounders, are necessary in order to identify best practice for implementing an exercise intervention in both healthy adults as well as in adults with heart disease.

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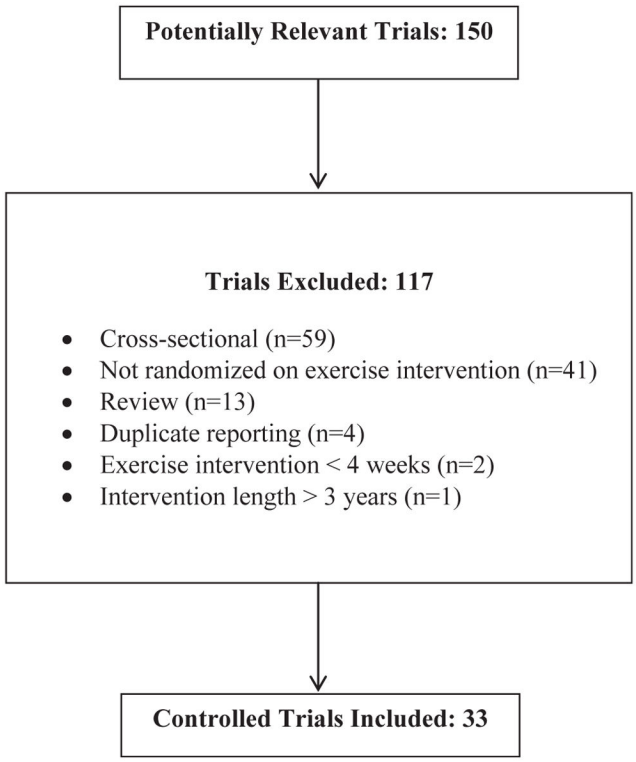

Fig. 1.

Flow diagram. Flow diagram for the selection for the selection of studies performed in healthy adults.

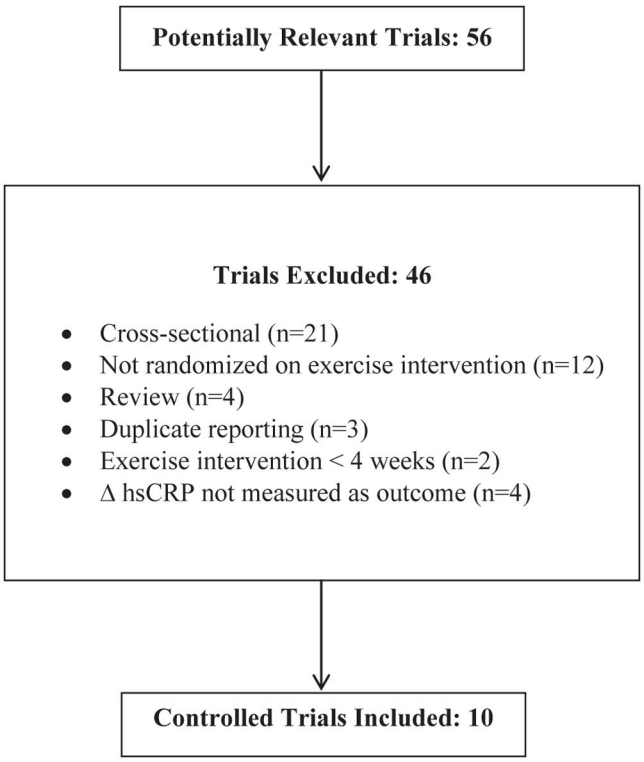

Fig. 2.

Flow diagram. Flow diagram for the selection of studies performed in persons with heart disease.

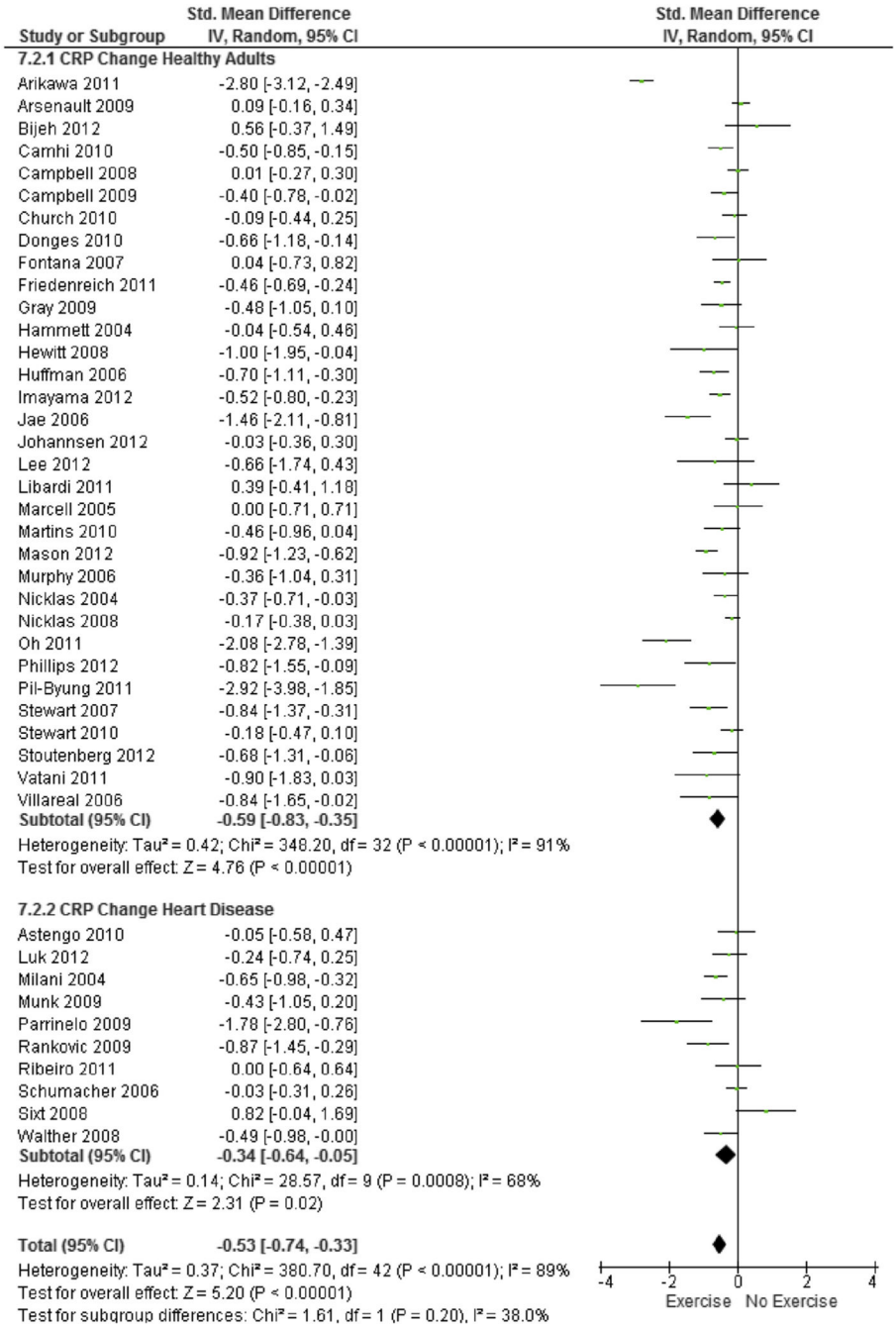

Fig. 3.

Forest plot of change in hsCRP due to exercise. Forest plot of change in hsCRP due to exercise in healthy adults as well as individuals with cardiovascular disease. Pooled analysis shows that there is a significant effect of exercise on hsCRP (standardized mean difference −0.53; 95% CI, −0.74 to −0.33). No significant difference in effect sized due to presence of cardiovascular disease was observed ($\chi^2(1,2) = 1.61$, $p = 0.20$).

Table 1

Characteristics for studies including healthy individuals.

Reference	Total *N* Males/females	Age Mean (SD)	Participant characteristics	Intervention type	Intervention length	Significance Control vs. exercise
Arikawa et al. 2011[47]	319 0/319	25.2 (3.5)	Pre-menopausal, sedentary females	Aerobic	16-weeks	$p = 0.04$
Arsenault et al. 2009[48]	267 0/267	57.3 (6.6)	Post-menopausal, overweight, sedentary females	Aerobic	6-months	NS
Bijeh et al. 2012[49]	19 0/19	42.3 (3.3)	Sedentary females	Aerobic	6-months	NS
Camhi et al. 2010[50]	278 149/125	52.9 (6.6)	Dyslipidemic, sedentary males and post-menopausal females	Aerobic	12-months	$p = 0.02$ in women with metabolic syndrome; NS for men and women w/out metabolic syndrome
Campbell et al. (a) 2008[51]	202 102/100	55.2 (6.7)	Sedentary males and females	Aerobic	12-months	NS
Campbell et al. (b) 2009[52]	115 0/115	60.7 (6.9)	Post-menopausal, sedentary females	Aerobic	3- and 12-months	$p = 0.01$
Church et al. 2010[53]	137 19/118	49.7 (10.9)	Sedentary males and females with hsCRP >2 mg/dL and <10 mg/dL	Aerobic	4-months	NS
Donges et al. 2010[54]	102 45/57	NR	Sedentary males and females	Aerobic or resistance	10-weeks	$p \leq 0.05$
Fontana et al. 2007[55]	46 17/29	56.7 (2.9)	Sedentary males and females who received healthy living literature	NR	12-months	$p = 0.02$ for diet + exercise intervention; NS for exercise only intervention
Friedenreich et al. 2011[56]	320 0/320	60.9 (5.6)	Post-menopausal, sedentary females	Aerobic	6- and 12-months	$p = 0.005$
Gray et al. 2009[57]	48 11/37	49.7 (8.8)	Sedentary males and females	Aerobic	12-weeks	NS
Hammett et al. 2004[58]	61 27/34	67.0 (5.0)	Sedentary males and post-menopausal females	Aerobic	6-months	NS
Hewitt et al. 2008[59]	20 NR	41.4 (8.0)	Sedentary males and females	Aerobic	12-weeks	NS
Huffman et al. 2006[60]	193 104/89	52.8 (6.4)	Overweight, sedentary males and post-menopausal females	Aerobic	6-months	NS

Reference	Total *N* Males/females	Age Mean (SD)	Participant characteristics	Intervention type	Intervention length	Significance Control vs. exercise
Imayama et al. 2012[61]	320 0/320	57.9 (4.6)	Sedentary females	Aerobic	12-months	$p \leq 0.001$
Jae et al. 2006[62]	47 35/12	49.7 (6.9)	Sedentary males and females who received diet literature at first visit	Aerobic	3-months	$p < 0.05$
Johanssen et al. 2012[63]	339 0/339	57.3 (6.4)	Hypertensive, post-menopausal, overweight, sedentary females	Aerobic	6-months	NS
Lee et al. 2012[64]	22 NR	40.5 (4.6)	Pre-menopausal, overweight, sedentary females	Aerobic	14-weeks	NS
Libardi et al. 2011[42]	36 36/0	48.7 (5.3)	Sedentary males	Aerobic and resistance or resistance only	16-weeks	NS
Marcell et al. 2005[65]	51 20/31	45.3 (8.3)	Sedentary males and females	Aerobic	16-weeks	NS
Martins et al. 2010[66]	63 25/38	76.0 (8.0)	Sedentary males and females	Aerobic or resistance	16-weeks	$p < 0.05$
Mason et al. 2012[67]	294 0/294	58.0 (5.2)	Sedentary, post-menopausal females	Aerobic	12-months	NS
Murphy et al. 2006[68]	20 NR	41.5 (9.3)	Sedentary males and females	Aerobic	8-weeks	NS
Nicklas et al. (a) 2004[69]	201 NR	69.0 (6.0)	Elderly, overweight, sedentary males and females	Aerobic and resistance	18-months	$p = 0.01$
Nicklas et al. (b) 2008[70]	369 118/251	76.6 (4.3)	Elderly, sedentary males and females enrolled in a healthy living class 1× per month	Aerobic, strength, balance, and flexibility	12-months	NS
Oh et al. 2011[71]	52 0/52	63.4 (8.5)	Sedentary females with metabolic syndrome	Aerobic and strength	6-months	$p = 0.029$
Phillips et al. 2012[72]	23 0/23	65.6 (2.6)	Obese, sedentary females attending a health and stretching class 1× per week	Resistance	12-weeks	$p < 0.05$
Pil-Byung et al. 2011[73]	30 30/0	23.5 (0.4)	Sedentary males and females who watched a healthy video	Aerobic	8-weeks	$p < 0.05$
Stewart et al. (a) 2007[74]	60 30/30	N/a[a]	Physically active males and females stratified by age	Aerobic and resistance	12-weeks	$p < 0.01$
Stewart et al. (b) 2010[37]	421 0/421	57.3 (6.4)	Hypertensive, post-menopausal, overweight, sedentary females	Aerobic	6-months	NS
Stoutenberg et al. 2012[75]	43 43/0	NR	Sedentary males	Aerobic	12- and16-weeks	NS
Vatani et al. 2011[76]	30 30/0	20.5 (1.1)	Sedentary males	Resistance	6-weeks	$p \leq 0.05$
Villareal et al. 2006[77]	27 9/18	69.7 (4.6)	Elderly, obese, sedentary males and females	Aerobic, strength, balance and flexibility	6-months	$p < 0.01$

NS – not significant; NR – not reported.

[a] Age of young participants 25.0 ± 4.9 years and age of older participants 71.0 ± 4.0 years.

Table 2

Characteristics for studies in individuals with heart disease.

Reference	Total *N* Males/females	Age Mean (SD)	Participant characteristics	Intervention type	Intervention length	Significance Control vs. exercise
Astengo et al. 2009[78]	56 45/11	63.0 (7.8)	Males and females w/stable angina and scheduled for PCI due to advanced CAD	Aerobic and resistance	8-months	NS
Luk et al. 2012[79]	64 48/16	67.2 (8.5)	Males and females with stable CAD	Aerobic	8-weeks	NS
Milani et al. 2004[80]	277 202/75	66.3 (11.0)	Males and females post AMI, CABG, or PCI	Aerobic	12-weeks	$p = 0.002$
Munk et al. 2009[81]	40 33/7	59.0 (12.0)	Males and females post PCI w/out prior MI or CABG	Aerobic	6-months	$p = 0.03$
Parrinello et al. 2008[82]	22 15/7	62.7 (4.8)	Sedentary males and females with NYHA class II or III congestive heart failure	Aerobic	10-weeks	$p < 0.05$
Rankovic et al. 2009[83]	52 29/23	60.2 (7.4)	Males and females w/stable CAD	Aerobic	6-weeks	$p < 0.01$
Ribeiro et al. 2011[84]	38 31/7	55.6 (9.3)	Males and females w/CAD following a 1st AMI	Aerobic	8-weeks	NS
Schumacher et al. 2006[38]	197 162/35	55.0 (8.0)	Males and females w/CAD following an AMI treated w/PCI and/or CABG	Aerobic	6-months	NS
Sixt et al. 2008[85]	23 17/6	64.0 (6.0)	Males and females w/CAD and impaired glucose tolerance	Aerobic	4-weeks	
Walther et al. 2008[86]	66 0/66	NR	Males w/stable CAD and eligible for PCI due to a 75% blockage	Aerobic	24-months	$p = 0.03$

NS – no significance; NR – not reported; CAD – coronary artery disease; PCI – percutaneous intervention; AMI – acute myocardial infarction; CABG – coronary artery bypass graft; NYHA – New York Heart Association.

Table 3

Subgroup analysis evaluating covariates of interest on the effect size of standardized mean difference in hsCRP.

Covariate for Δ hsCRP	Effect size (95% CI)	Interaction significance
Gender		
Males (n = 6)	−0.60 (−1.31, 0.12)	} p = 0.91
Females (n = 14)	−0.64 (−1.09, −0.19)	
Age		
<60 years (n = 5)	−1.01 (−2.28, 0.27)	} p = 0.69
≥60 years (n = 7)	−0.73 (−1.22, −0.24)	
Intervention length		
≤3-months (n = 11)	−0.83 (−1.20, −0.47)	
3–6 months (n = 7)	−0.59 (−1.63, 0.46)	} p = 0.17
6-months (n = 9)	−0.36 (−0.67, −0.04)	
≥12-months (n = 9)	−0.39 (−0.58, −0.20)	
Intervention type		
Aerobic (n = 23)	−0.59 (−0.91, −0.27)	
Resistance (n = 4)	−0.32 (−0.87, 0.22)	} p = 0.67
Mixed intervention (n = 6)	−0.63 (−1.13, −0.12)	
Inclusion of diet		
Yes (n = 6)	−2.17 (−3.69, −0.65)	} p = 0.09
No (n = 30)	−0.81 (−1.19, −0.43)	