Title:

The effect of exercise interventions on inflammatory biomarkers in healthy, physically inactive subjects: a systematic review.

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ABSTRACT

Background: Increases in physical activity ameliorate low-grade systemic inflammation in disease populations such as type 2 diabetes mellitus and coronary artery disease. The effects of aerobic and resistance training on inflammatory biomarker profiles in non-disease, physically inactive individuals are unknown.

Methods: A systematic review of randomised controlled trials measuring the effect of aerobic and resistance exercise on pro-inflammatory biomarkers in healthy, inactive adult populations was conducted. The available peer-reviewed literature was searched from January 1990 to June 2016 using the electronic databases PubMed and Scopus. A narrative synthesis of review findings was constructed with discussion of the impact of aerobic, resistance and combined training on C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8, interleukin-1β and tumour necrosis factor-α.

Results: The initial search revealed 1,596 potentially relevant studies. Application of the study eligibility criteria led to the full-text review of 54 articles with 11 studies deemed suitable for inclusion. Review of related articles and the reference lists of the 54 full-text articles led to the inclusion of 2 additional studies. The review revealed inconsistent findings relating to the effect of aerobic training and resistance training on CRP and IL-6. Studies of older-aged adults (>65 years old) demonstrated the greatest and most consistent reduction in inflammatory biomarkers post-training intervention.

Conclusions: A paucity of evidence exists relating to the effect of exercise training on inflammatory markers in non-disease, physically inactive adults. The available evidence suggests potential for the greatest benefit to be seen in older populations and with higher intensity aerobic exercise.

What is already known on this subject?

1. Physical inactivity predisposes to the development of chronic, non-communicable disorders such as coronary artery disease and diabetes mellitus.
2. Physical inactivity is characterized by increased adiposity, macrophage infiltration of visceral fat and elevated levels of circulating pro-inflammatory biomarkers.
3. In physically inactive, disease populations, exercise training ameliorates inflammatory marker profiles, reducing levels of low-grade systemic inflammation.

What this study adds?

1. The effect of aerobic and resistance training on inflammatory markers in healthy, physically inactive adults is inconsistent and unclear.
2. The greatest potential to improve inflammatory profiles is seen in healthy older subjects (aged greater than 65 years).

Introduction:

Physical inactivity is associated with undesired health consequences particularly the increased incidence of type 2 diabetes mellitus and cardiovascular disease.[1, 2] Insufficient physical activity predisposes to mal-adaptive physiological alterations characterized by increased central and peripheral adiposity, macrophage infiltration of visceral fat and low-grade systemic inflammation.[3] Chronically, these processes lead to pathological sequelae including neuro-degeneration, insulin resistance and atherosclerosis.[3] Mild increases in basal pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α)[4] and C-reactive protein (CRP),[5] indicate the presence

of low-grade systemic inflammation, and are associated with an increased risk of cardiovascular and cerebrovascular disease development.[5] Indeed, CRP measurement, in the absence of acute illness or metabolic disturbance, provides an independent predictor of cardiovascular disease risk.[5]

When adhered to, regular exercise or increases in daily physical activity represents one of the most consistently effective tools for overall health improvement.[6, 7] The anti-inflammatory effect of exercise occurs in a multi-organ fashion,[7, 8] and one such benefit of increasing physical activity through regular exercise is the reduction in circulating levels of classical inflammatory biomarkers. This phenomenon is evident in disease populations such as type 2 diabetic patients[9] and in populations with risk factors for, or with established, coronary artery disease.[10, 11] Although not conclusively proven, this effect is believed to contribute in some manner to the reduction in cardiovascular disease incidence evident in populations with greater levels of physical activity and fitness.[12]

However, the role of exercise training in ameliorating resting-state inflammatory tone in non-disease, physically inactive populations is currently unknown. To date, systematic reviews and meta-analyses have not investigated the effects of exercise on pro-inflammatory biomarker levels in “healthy”, physically inactive subjects and have predominantly focused on disease populations in which levels of these biomarkers are known to be elevated.[9, 11] Similarly, the impact of alternative modes of exercise training on inflammatory biomarker levels has received relatively little attention. For example, resistance training provides differential immunological and metabolic effects compared to traditional cardiorespiratory (aerobic) exercise.[13-15] The intent here is a systematic review of the impact of aerobic, resistance, and combined (aerobic plus resistance) exercise training on resting

inflammatory biomarkers in non-disease, physically inactive individuals. We applied a systematic approach to existing randomised controlled trials and constructed a narrative synthesis of the findings.

METHODOLOGY

Search strategy:

The literature was reviewed in conformity with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[16] A keyword search was performed to include English language articles (whole text English language availability required) published between the 1st of January 1990 and the 1st of June 2016. The online databases PubMed and Scopus were searched using combinations of relevant terms and keywords such as exercise, aerobic, resistance, cytokine, physically inactive and randomised controlled trial (For full details of the search terms used see online supplementary data).

Searches of the PubMed database were restricted to the publication types: clinical trial, comparative study, clinical study, controlled clinical trial, journal article or randomised controlled trial. Searches pertaining to Scopus were filtered to include articles, articles in press and short surveys, within the subject areas of medicine, neuroscience, multidisciplinary, nursing, immunology/microbiology, biochemistry/genetics/molecular biology, and health professions. The Scopus search was restricted by the keywords: Randomised controlled trial, controlled study, clinical trial, major clinical study, clinical article, or controlled clinical trial. A full list of reference articles was compiled and duplicate publications were removed manually where present.

Study selection

The complete article reference list was reviewed independently for study eligibility by 2 reviewers (OC, DK) according to an a priori systematic review protocol (PROSPERO Identification Number: CRD42016039503). In cases of divergence, a third reviewer (MGM) was consulted. Relevant data was extracted independently and crosschecked by the first two reviewers (OC, DK). Analysis was limited to include peer-reviewed publications, involving human participants, prospectively enrolled in a randomised controlled trial investigating the biological effects of an exercise intervention. Healthy, non-disease populations, aged over 16 years were included regardless of gender. All weight and body mass index (BMI) categories were eligible for inclusion, provided there was no formal inflammatory, metabolic or immunological diagnosis amongst the participants e.g. Diabetes Mellitus.

Studies were restricted based on the intervention prescribed and outcome variables measured, as well as the baseline physical activity of studied participants. Trials involving aerobic, resistance or combined aerobic-resistance training for a minimum of 2 weeks, at a frequency of at least twice per week were included, provided the duration and intensity of training performed achieved a threshold minimal level of exertion. In the case of aerobic training, the intensity of training had to achieve greater than or equal to 60% of maximum oxygen consumption (actual, predicted or estimated $VO_{2\ max}$) or maximum heart rate (actual, predicted or estimated). For assessment of the effects of resistance training, only studies with resistance training requiring greater than or equal to 50% of 1 repetition maximum (1RM) were included. The number of sets and repetitions performed did not determine inclusion.

Only trials examining the effects of exercise interventions alone on physically inactive populations were included. Physical inactivity was defined as an activity level insufficient to meet current recommendations and considered in this context to mean at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity throughout the week.[17] Studies whereby control groups received any form of intervention, such as educational material, dietary or lifestyle advice were excluded. Furthermore, all relevant studies were required to measure intervention effects on desired outcome variables before and after the intervention period. These comprised circulating plasma or serum levels of resting pro-inflammatory cytokines and biomarkers i.e. C-Reactive Protein, Tumour Necrosis Factor-α, Interleukin-6 (IL-6), Interleukin-1β (IL-1β) and Interleukin-8 (IL-8).

Quality assessment

A modified version of the original Downs and Black's index for the quality of randomised controlled trial methodology was performed on all included studies.[18] As previously performed, question 27 of the original tool was modified to award a single point if a sample size calculation was performed or a significant difference was detected.[19] Studies with a score greater than 20 were considered high quality in their methodology (maximum score of 28 points). Bias assessment, included as part of the Downs and Black's checklist was scored out of a maximum of 7 points, with a score of 7 indicating low risk of bias.

RESULTS

Search strategy

Application of the search strategy identified a total of 1,596 citations (Figure 1). Following removal of internal and external duplicates, 1,514 citations remained. The titles and abstracts of these records were screened for inclusion and exclusion criteria using the PICO format (population, intervention, comparison and outcome). The majority of references excluded at this juncture were due to the article not being a randomised controlled trial, or for use of an intervention and/or a study population outside the scope of the review. Following the initial screening 1,460 articles were excluded. The full-texts of the remaining 54 articles were assessed using the described inclusion/exclusion criteria, with 11 articles deemed suitable for inclusion (Table 1). To increase the number of eligible studies for inclusion, the "similar articles" function on PubMed was also searched for included articles. Furthermore, the reference lists of all 54 full-text reviewed articles were screened for suitable studies. These methods led to the inclusion of 2 further articles (Table 1).[20, 21] Omitted full-text articles were excluded for a number of reasons including absence of subject randomization, studies involving physically active subjects, studies of disease populations, exposure of the control group to an intervention, or failure to measure any of the outcome variables of interest (Figure 1).

Methodological quality

Assessment of all included studies using the modified Downs and Black's checklist revealed significant variation in the quality of the studies performed. The lowest recorded score was 12/28, with the greatest score of 23/28 (Table 2). Overall, methodological quality of the studies included was graded as adequate to high quality. Four of the thirteen studies included were deemed to be of high quality with a checklist score of greater than 20/28. Study quality was restricted by several

consistent factors. In the first instance, such is the nature of exercise intervention trials, the inability of investigators to conceal the intervention from the study subjects or to administer a suitable placebo restricts the potential score that can be acquired using the chosen methodological assessment tool (Questions 14 and 24). Furthermore, absence of a description of the sample population and comparison with the study population demographic was uniform across all studies (question 12) and questions the generalizability of the results to the intended review population i.e. male and female physically inactive adults aged over 16. Overall, methodological quality assessment indicated a moderate risk of bias across the studies (mean bias score 4.38 out of a maximum score of 7; lowest score of 3/7, highest score of 6/7).

Effects of aerobic, resistance and combined training on inflammatory biomarkers

Four out of the seven studies that investigated the effect of aerobic training on resting levels of CRP reported a significant reduction in CRP levels following a period of aerobic training (Table 4).[22-24] Sensitivity analysis examining differences in the effect of aerobic training on CRP in male (n=180 participants) and female participants (n=350 participants) suggested a more consistent reduction in CRP levels in older females performing regular aerobic training for 24 weeks or more. A greater inconsistency in CRP alteration was evident across male participants, however the duration, frequency and intensity of aerobic training employed were also more variable. Five studies examined the influence of aerobic training on levels of IL-6 with inconsistent results (Table 4).[24-27] Three studies examined the effect of aerobic exercise on TNF-α [24, 26] and a single study examined effects on IL-1β demonstrating no significant changes after either exercise intervention (small-sided games or

stationary cycling) (Table 4).[24] No included studies measured the impact of aerobic training on resting IL-8 levels (Table 3).

Three articles included in this review studied the effect of resistance training on CRP levels with inconsistent results (Table 4).[26, 28, 29] In all 3 of these studies the intervention comprised progressive weight lifting exercise. Levels of TNF-α did not differ following 8 or 12 weeks of progressive resistance training.[30, 31] Likewise, there was no effect on IL-1β levels following 12 weeks of progressive resistance training.[28] A single study examining the effects of combined aerobic and resistance training did not demonstrate any reduction in CRP, IL-6 or TNF-α after 16-weeks (Table 4).[26]

DISCUSSION

Exercise offers a therapeutic option for the treatment and prevention of many conditions including the metabolic, degenerative and inflammatory disorders type 2 diabetes mellitus,[13] non-alcoholic fatty liver disease,[32] and mild cognitive impairment.[33] Whether initiation of exercise in non-disease, inactive populations can ameliorate circulating inflammatory profiles, as it can in disease populations, remains unclear. This current review addressed this question, revealing a paucity of high-level evidence relating to exercise intervention studies in healthy but physically inactive populations. Following an initial screen of over 1,596 article references, only 13 randomised controlled trials were ultimately included in the review. Furthermore, this review also demonstrates a predominance of male volunteer participation in Exercise Medicine research with only 3 out of 13 studies enrolling female volunteers. This confirms findings highlighted previously.[34]

Findings relating to the effect of aerobic exercise on CRP in non-disease, physically inactive subjects were inconsistent. These inconsistencies are perhaps

explained by the heterogeneity of the exercise training prescribed across the included articles. The study by Moghadasi *et al.* reported the greatest reduction in resting CRP levels post-intervention (53% reduction).[23] However, the initial intensity of aerobic training assigned in this study was significantly higher (75-80% of VO_{2max} for 45 minutes)[23] than that commenced in the studies of Thompson *et al.* (50% VO_{2max}) and Alghadir *et al.* (60-70% VO_{2max}).[22, 25] Likewise, a large cohort of female volunteers experienced a persistent and significant reduction in CRP over a 6- and 12-month intervention period. This study by Friedenreich *et al.* also performed higher intensity aerobic exercise with participants exercising at 70 to 80% maximum heart rate. Although attempts were made in the systematic review protocol to ensure that all exercise interventions employed were of sufficient intensity and frequency to plausibly result in detectable alterations in pro-inflammatory cytokines, the variability of exercise intervention programs is such that complete uniformity is in several ways unachievable (e.g. variability in duration, frequency and intensity of exercise training). Furthermore, compliance with the randomised interventions is also variable, and in many instances was not described in the included studies.

Results outlining the effects of aerobic training on baseline resting-state IL-6 levels were also inconsistent with some but not all studies indicating a reduction in baseline IL-6 levels post-aerobic training.[24, 25] The investigation by Mendham *et al.* demonstrated a reduction in baseline IL-6 levels in the SSG intervention arm of this study (small sided games; variable intensity with periods of high and moderate intensity exercise) but not following 8-weeks of continuous stationary cycling (moderate intensity).[24] In contrast, the study by Thompson *et al.* indicates that progressive aerobic training of moderate intensity can reduce IL-6 levels, although it may require a longer duration of training (24 weeks).[25] In contrast, in a female cohort,

the large study by Friedenreich *et al.* did not demonstrate a significant reduction in IL-6 levels after 6 or 12 months of aerobic training. Another possible explanation for the inconsistency in IL-6 results relates to the timing of the blood collection and unintentional effects of recent exercise on circulating levels of IL-6. Circulating IL-6 levels are known to rise acutely post-exercise, and with sufficient intensity of exercise can reach levels 100-fold greater than the resting state, remaining elevated for as long as 24-hours post-completion in some instances.[35] In a number of the included studies the temporal relationship between last exercise session and phlebotomy for biomarker measurement is unclear. This is an important consideration for the design of future studies.

Similar to aerobic training interventions, the effects of resistance training on resting CRP levels in physically inactive non-disease populations are inconsistent in the studies reviewed. Only 5 out of 13 included studies analyzed the effect of resistance training on pro-inflammatory biomarkers, with only 3 studies measuring CRP and 3 studies including IL-6. Resistance training led to a reduction in resting CRP levels in only 1 of the 3 studies that measured the effect on CRP.[29] This study examined the effect of resistance training in older adults (65 to 78 year-olds) compared to the other trials that examined middle-aged and younger adults. No studies demonstrated a significant alteration in IL-6 levels following resistance training at 8, 12 or 16 weeks.[26, 30, 31] The generalizability of our findings in relation to resistance training is questionable in female populations as only a single, small trial examined the effect of RT in women.[29] Despite the relatively small number of studies measuring changes in resting levels of TNF-α (n = 6), the review findings were consistent suggesting circulating levels in healthy, physically inactive populations are not subject to alteration following initiation of resistance, aerobic or combined

training.

In the present systematic review the greatest changes in biomarkers following aerobic or resistance training exercises were evident in studies investigating effects in older, physically inactive adults [20, 22, 29] in contrast to those addressing younger or middle-aged volunteers.[27, 28, 31, 36] We propose that the reason for these findings relates to the comparatively high levels of inflammatory biomarkers associated with ageing and the potential for this to be reversed with physical activity.[37] Key findings from a recent meta-analysis suggest that a greater reduction in circulating pro-inflammatory biomarkers in disease populations is witnessed in those with significant weight and adipose tissue reduction post-exercise intervention.[38] This review of non-disease subjects did not reveal any significant patterns of change in studies of overweight and obese individuals.[23-26, 28-30]

A significant limitation of this review is the relatively small number of studies suitable for inclusion, each of which measured a selection of the inflammatory biomarkers of relevance. It is possible that the techniques used and electronic databases searched as part of the systematic review process lead to the omission of additional relevant studies. It is also important to acknowledge that in many of the included review articles, alterations in basal inflammatory biomarker levels were not the primary outcome measure, and the studies may not have been powered adequately to detect significant changes in secondary outcome measures, such as CRP. Furthermore, in the majority of included studies, adverse events that may affect inflammatory markers were not described in the article reports e.g. injury, illness occurring during the intervention period.

Conclusions

This is the first systematic review of randomised controlled trials to comprehensively assess the effect of aerobic, resistance and combined exercise training on inflammatory markers in non-disease, physically inactive adults. The available evidence suggests that the greatest benefit may be seen in older populations and with high-intensity aerobic exercise. There is a need to further understand the effects of various forms of exercise modalities on healthy, physically inactive adults to formulate lifestyle and physical activity recommendations to prevent chronic non-communicable inflammatory disorders.

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Conflicts of interest: None to declare.

Figure Legend:

Figure 1. Flow-chart of the literature review process using the PRISMA format.

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Table 1. Characteristics of the included studies.

Author	Year	Sample size	Age	Gender	BMI range	Control group described	Baseline physical activity described	Baseline cardiorespiratory fitness measurement
Alghadir	2016	100	65-95	Males & females (30% female)	Mean approx. 22	No	No	VO2max
Azizbeigi	2015	30	Young adults: Mean approx. 20 years	Males	Mean approx. 23	No	Yes	1RM values
Rodriguez-Miguelez	2014	26	65-78	Males & females (7:19)	Mean 27	No	No	1RM & Maximum Voluntary Isometric Contraction
Mendham	2014	33	Middle aged: Mean 48.6 years	Males	Mean approx. 28	Yes	Yes	VO2 (80%)
Nikseresht	2014	34	34-46	Males	BMI > 30	No	Yes	VO2max & 1RM
Reichkendler	2014	61	Young adults 20-40 years	Males	Mean approx. 28	Yes	Yes	VO2max
Croymans	2014	36	20-23 years	Males	29.7 - 34.7	Yes	Yes	1RM values
Jahromi	2014	28	18-24	Males	Mean 21.2	Yes	No	None
Weng	2013	30	Young adults: Approx. 20 years	Males	Mean approx. 22	Yes	Yes	VO2max
Libardi	2012	47	Middle aged: Mean approx. 49 years	Males	Mean approx. 26	No	No	VO2max & 1RM
Moghadasi	2012	16	Middle aged: Mean 41 years	Males	Mean 31.5	Yes	Yes	VO2max
Friedenreich	2012	320	50-74 (Mean approx. 60 years)	Female	22-40. Mean 29.1	Yes	Yes	VO2max
Thompson	2010	54	Middle aged: Mean approx. 53 years	Males	Mean 28, Over 35 excluded	Yes	Yes	VO2max

BMI = Body mass index; VO_{2max} = Maximal oxygen consumption; 1RM = One repetition maximum.

Table 2. Assessment of methodological quality of randomised controlled trials included in the systemic review using a modified version of the Downs and Black's index.[19] Maximum score equates to 28. A score of greater or equal to 20 indicates high methodological quality. Assessment using questions 1 to 27 listed.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Total
Alghadir	1	1	1	1	2	1	1	0	1	0	1	0	1	0	0	1	1	1	0	1	1	0	1	0	1	1	0	19
Azizbeigi	1	1	1	1	1	1	1	0	0	1	0	0	1	0	0	1	1	1	0	1	1	0	1	0	0	0	0	15
Rodriguez-Miguelez	1	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	1	1	0	1	0	0	1	0	0	0	0	13
Mendham	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	0	1	0	0	1	0	20
Nikseresht	1	1	1	1	1	1	1	0	0	1	0	0	1	0	0	1	1	1	0	1	0	0	1	0	0	0	1	15
Weng	1	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	0	1	1	1	0	0	1	0	0	0	1	14
Croymans	1	1	1	1	2	1	1	0	1	1	0	0	1	0	1	1	1	1	1	1	0	1	1	0	1	1	1	22
Thompson	1	1	1	1	2	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	0	1	0	0	1	1	22
Reichkendler	1	1	1	1	2	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	0	1	0	1	1	1	23
Moghadsai	1	1	1	1	1	1	1	0	0	0	0	0	1	0	0	0	1	1	0	1	0	0	1	0	1	0	0	13
Libardi	1	1	1	1	1	1	1	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	1	0	1	1	1	17
Jahromi	1	1	1	1	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1	0	1	1	0	0	0	1	12
Friedenreich	1	1	1	1	2	1	1	0	1	1	1	0	1	0	0	1	1	1	1	1	1	0	1	0	1	1	1	22

Table 3. Description of exercise interventions from included studies.

Author	Aerobic intervention(s)	Resistance intervention(s)	Combined training	Frequency of training	Intervention period
Aerobic training					
Alghadir	Moderate intensity	-	-	3 times per week	24 weeks
Weng	HIIT VS Moderate continuous AE	-	-	5 times per week	5 weeks
Thompson	Continuous AE commencing at 30mins of 50% VO2max, finishing at 70% VO2max for 60mins.	-	-	3-4 times per week	24 weeks
Mendham	Stationary cycling 40 to 50 mins VS small sided games (touch rugby)	-	-	3 times per week	8 weeks
Reichkendler	Moderate VS high volume AE	-	-	Daily	10 weeks
Moghadasi	Aerobic, high intensity continuous	-	-	4 times per week	12 weeks
Jahromi	Progressive low volume aerobic exercise (50% Max. heart rate to 70% Max. heart rate)	-	-	3 times per week	8 weeks
Friedenreich	Moderate intensity aerobic exercise (70-80% max. heart rate)	-	-	5 times per week	52 weeks
Resistance training					
Azizbeigi	-	Moderate and high intensity RT	-	3 times per week	8 weeks
Croymans	-	Linear periodization program with progressive numbers of sets and weight lifted	-	3 times per week	12 weeks
Rodriguez-Miguelez	-	Progressive RT	-	2 times per week	8 weeks
Combined and head-to-head interventions					
Nikseresht	HIIT	Non-linear RT protocol	-	3 times per week	12 weeks
Libardi	60mins of walking or running around athletics track of varying intensities, after 8 weeks change in intensity	3 lower body and 5 upper body exercises. Progressive weight, initially 3 sets of 10RM, then 3 sets of 8RM	Similar resistance protocol but half the duration of AE	3 times per week	16 weeks

HIIT = High intensity interval training; AE = Aerobic exercise; RT = Resistance training; VO_{2max} = maximal oxygen consumption; Mins = Minutes; 8RM and 10RM = 8 and 10 repetition maximum (i.e. The maximum achievable weight lifted against resistance for 8 or 10 consecutive repetitions).

Table 4. Effects of exercise interventions on inflammatory biomarkers.

Author	C-reactive protein	TNF - α	IL-6	IL-8	IL-1β
Aerobic training					
Alghadir	Significant reduction in CRP in the intervention group ($p<0.01$) compared to the control group which also saw a reduction ($p<0.05$)	-	-	-	-
Weng	-	-	No change in IL-6 level post-either intervention (HIIT or AE)	-	-
Thompson	No significant change after AT intervention	-	Statistically significant reduction after AT intervention ($p<0.03$)	-	-
Mendham	Significant reduction in CRP in both cycling ($p=0.02$) and small sided games groups ($p=0.008$)	No significant change after either intervention	Significant decrease in IL-6 levels post-small sided games but not in cycling or control groups ($p=0.002$)	-	No significant change after either intervention
Reichkendler	No significant reduction in CRP after either AT intervention	-	-	-	-
Moghadasi	Significant (53%) reduction in CRP level after high intensity continuous training ($p<0.05$)	-	-	-	-
Jahromi	-	No significant change in exercise group ($p>0.05$)	-	-	-
Friedenreich	Significant reduction in CRP level was detected at 6 & 12 months with intervention Effect ratio 0.87 (CI 0.79-0.96)	No significant change. Effect ratio 1 (CI 0.97-1.04)	No significant change. Effect ratio 0.99 (CI 0.92 –1.07)	-	-
Resistance training					
Azizbeigi	-	No significant change	No significant change	-	-
Croymans	Non-significant median change score between groups: −0.45 (CI −2.4–2.4)	-	-	Non-significant median change score between groups: 3.4 (CI −189.4–12.7)	-
Rodriguez-Miguelez	Progressive RT led to a significant reduction in CRP ($p<0.01$)	-	Progressive RT led to a significant reduction in IL-6 ($p<0.05$)	-	-
Combined training and head to head interventions					
Nikseresht	-	No significant change after HIIT or RT	-	-	-
Libardi	No significant change after any intervention	No significant change after any intervention	No significant change after any intervention	-	-

CRP = C-reactive protein; IL-6 = Interleukin 6; IL-8 = Interleukin 8; IL-1β = Interleukin-1β; TNF-α = Tumour Necrosis Factor α; RT = Resistance Training; HIIT = High Intensity Interval Training; AE = Aerobic exercise.

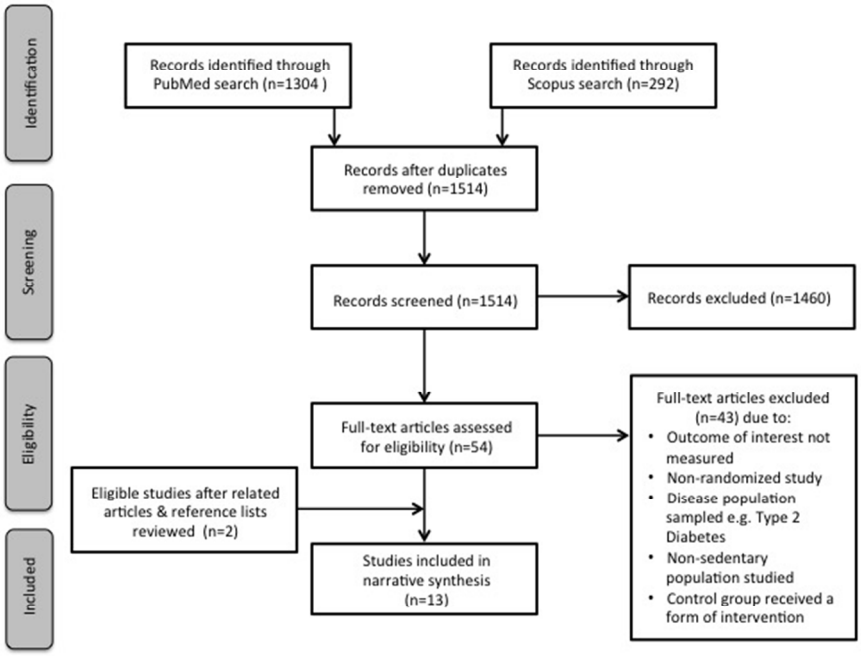

Figure 1. Flow-chart of the literature review process using the PRISMA format.

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