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Cochrane Database of Systematic Reviews 2014, Issue 8. Art. No.: CD009387.

DOI: 10.1002/14651858.CD009387.pub2.

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Exercise for people with high cardiovascular risk

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Editorial group: Cochrane Heart Group.

Publication status and date: New, published in Issue 8, 2014.

Citation: Seron P, Lanas F, Pardo Hernandez H, Bonfill Cosp X. Exercise for people with high cardiovascular risk. *Cochrane Database of Systematic Reviews* 2014, Issue 8. Art. No.: CD009387. DOI: 10.1002/14651858.CD009387.pub2.

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ABSTRACT

Background

When two or more cardiovascular risk factors occur in one individual, they may interact in a multiplicative way promoting cardiovascular disease. Exercise has proven to be effective in controlling individual risk factors but its effect on overall cardiovascular risk remains uncertain.

Objectives

To assess the effects of exercise training in people with increased cardiovascular risk but without a concurrent cardiovascular disease on general cardiovascular mortality, incidence of cardiovascular events, and total cardiovascular risk.

Search methods

A search was conducted in CENTRAL (*The Cochrane Library* 2013, Issue 10 of 12), Ovid MEDLINE (1946 to week 2 November 2013), EMBASE Classic + EMBASE via Ovid (1947 to Week 47 2013), CINAHL Plus with Full Text via EBSCO (to November 2013), Science Citation Index Expanded (SCI-EXPANDED) (1970 to 22 November 2013), and Conference Proceedings Citation Index - Science (CPCI-S) (1990 to 22 November 2013) on Web of Science (Thomson Reuters). We did not apply any date or language restrictions.

Selection criteria

Randomized clinical trials comparing aerobic or resistance exercise training versus no exercise or any standard approach that does not include exercise. Participants had to be 18 years of age or older with an average 10-year Framingham risk score of 10% for cardiovascular disease over 10 years, or with two or more cardiovascular risk factors, and no history of cardiovascular disease.

Data collection and analysis

The selection of studies and subsequent data collection process were conducted by two independent authors. Disagreements were solved by consensus. The results were reported descriptively. It was not possible to conduct a meta-analysis because of the high heterogeneity and high risk of bias in the included studies.

Main results

A total of four studies were included that involved 823 participants, 412 in the exercise group and 411 in the control group. Follow-up of participants ranged from 16 weeks to 6 months. Overall, the included studies had a high risk of selection, detection, and attrition bias. Meta-analysis was not possible because the interventions (setting, type and intensity of exercise) and outcome measurements were not comparable, and the risk of bias in the identified studies was high. No study assessed cardiovascular or all-cause mortality or cardiovascular events as individual outcomes. One or more of the studies reported on total cardiovascular risk, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, blood pressure, body mass index, exercise capacity, and health-related quality of life but the available evidence was not sufficient to determine the effectiveness of exercise. Adverse events and smoking cessation were not assessed in the included studies.

Authors' conclusions

Evidence to date is entirely limited to small studies with regard to sample size, short-term follow-up, and high risk of methodological bias, which makes it difficult to derive any conclusions on the efficacy or safety of aerobic or resistance exercise on groups with increased cardiovascular risk or in individuals with two or more coexisting risk factors. Further randomized clinical trials assessing controlled exercise programmes on total cardiovascular risk in individuals are warranted.

PLAIN LANGUAGE SUMMARY

Exercise for people with increased cardiovascular risk

Individuals with more than one cardiovascular risk factor, such as hypertension, high cholesterol, or smoking, are more likely to present with cardiovascular disease. While exercise has been proven to be effective in controlling individual risk factors, the evidence for its effect on multiple risks remains uncertain. We included four studies, with 823 participants in total, comparing exercise for increased-risk individuals against control or no treatment. Follow-up of patients ranged from 16 weeks to six months. No study assessed cardiovascular or all-cause mortality, or cardiovascular events as individual outcomes. One or more of the studies reported on total cardiovascular risk, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, blood pressure, body mass index, exercise capacity, and health-related quality of life, but the results did not provide conclusive evidence of the effects of exercise in this population. The included studies did not assess smoking cessation or any adverse effects of the exercise intervention. We conclude that the evidence to date is entirely limited to small studies in terms of sample size, short-term follow-up, and high-risk of methodological bias, which makes it difficult to derive any conclusions on the efficacy or safety of the exercise carried out in the included trials on total cardiovascular risk, mortality, or cardiovascular events. It is necessary to conduct high-quality clinical trials that evaluate the effect of exercise on people with increased cardiovascular risk.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is the major cause of morbidity and premature death worldwide. While in the past it was a major problem only in wealthy, industrialized countries, it is currently a global problem (Murray 2012). It is expected that in the year 2020 more than 80% of CVD will occur in low- and middle-income countries (Teo 2009). There are nine modifiable factors that can explain 90% of the acute myocardial infarcts that occur. These

risk factors include dyslipidemia, smoking, diabetes, hypertension, abdominal obesity, and psychosocial factors. On the other hand, protective factors are a diet rich in fruits and vegetables, physical activity, and moderate consumption of alcohol (Yusuf 2004).

When the risk factors concur, they interact in a multiplicative manner to promote disease (Jackson 2005; Yusuf 2004). Thus, for instance, a combination of smoking, elevated blood pressure, and high cholesterol is responsible for 80% of the cases of premature arterial coronary disease (Emberson 2003). One way of predicting the impact of this combination of risk factors has been the development of formulas or risk tables that provide an estimate of the

probability of developing CVD or of dying from it within a certain time span. One such formula is the SCORE system (Systematic COronary Risk Evaluation), which estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or another major cardiac events. According to the SCORE criteria, everyone with a 10-year cardiovascular mortality risk of 5% or more is at increased risk (Graham 2007). Another formula is the 10-year Framingham Risk Score, which estimates the 10-year risk of CVD (Wilson 1998), including coronary heart disease, cerebrovascular events, peripheral arterial disease, and heart failure (D'Agostino 2008). Based on this system, a probability of CVD between 5% and 9% is considered high risk; between 10% and 19%, increased risk; and 20% or more, very high risk.

As seen in the estimation and diagnosis of CVD risk, management of CVD should also have a multifactorial approach in order to produce greater benefits because the effect of modifying several risk factors is also multiplicative (Graham 2007; NICE 2008). A moderate reduction in various risk factors can be more effective than a major reduction in only one of them (Jackson 2005). Consequently, the main objective of CVD prevention is the control of risk factors through changes such as a healthier diet and increased physical activity. Therapeutic efforts are directed towards lowering blood pressure, triglycerides, and low-density lipoprotein (LDL) cholesterol, as well as smoking cessation, increasing high-density lipoprotein (HDL) cholesterol, and controlling glycemia, thereby reducing the probability of cardiovascular events or death (D'Agostino 2008).

Description of the intervention

Physical exercise is a planned, structured, and repetitive activity performed with the objective of maintaining or improving one or more components of the physical structure (Boraita 2008).

There are two main types of physical exercise, aerobic and resistance training. Aerobic exercise has been recognised for a long time as the more beneficial of the two, but recent studies on resistance training show that skeletal muscle is the primary metabolic sink for glucose and triglyceride disposal and is an important determinant of the resting metabolic rate. Accordingly, it has been hypothesized that resistance training and subsequent increases in muscle mass may reduce multiple CVD risk factors (Braith 2006).

It has been demonstrated that regular physical activity is a protective factor regarding myocardial infarction (odds ratio (OR) 0.86, 95% confidence interval (CI) 0.76 to 0.97) and that it reduces the population attributable risk by 12% (Yusuf 2004). This effect has been observed in males and females of all ages, and in different parts of the world (Yusuf 2004). Physical inactivity also has an influence on other risk factors; it has potential effects on body weight, blood pressure, obesity and blood lipids, vascular structure and function, myocardial function, and development of CVD (Metkus 2010). It also accounts for 3.3% of deaths and 19 mil-

lion disability-adjusted life years (DALYs) worldwide (Bull 2004). Physical activity during adult life can increase total life expectancy and life expectancy free of CVD by 1.3 to 3.5 years (Franco 2005). Physical training, with its beneficial effects on atherosclerosis, reduces total mortality and cardiovascular mortality (Heran 2011). The effects of exercise on individual risk factors have been extensively studied. In appropriate doses, regular exercise produces a decrease in blood pressure that remains 8 to 12 hours after each exercise session (Pescatello 1991). It has also been estimated that nearly 30% of patients who exercise regularly achieve a reduction in systolic blood pressure of 10 mmHg or higher in the short term and for up to one year (NICE 2006). Furthermore, the effects of exercise can be associated with an increase in lipoprotein lipase (Grandjean 2000) as well as a decrease in total cholesterol levels, LDL, and triglycerides in obese individuals and with increased aerobic resistance and weight loss (Kelley 2005). Aerobic exercise does not have to take place at a very intense level in order to produce an effect on lipid levels (between approximately 1000 and 1200 kilocalories/week). HDL cholesterol appears to increase at different levels of exercise intensity (King 1995).

How the intervention might work

Exercising raises HDL cholesterol; lowers LDL cholesterol, triglycerides, and blood pressure; improves fasting and postprandial glucose-insulin homeostasis; induces and maintains weight loss; improves psychological well-being. It is also likely to reduce inflammation; improve endothelial function; and facilitate smoking cessation (Mozaffarian 2008).

The underlying mechanisms related to the benefits of exercise include multiple alterations in the myocardium, skeletal muscle, and vascular system (Schuler 2013) associated with changes in inflammation and endothelial function. It is known that chronic low-grade systemic inflammation may be involved in atherosclerosis, diabetes, and pathogenesis of several chronic pathological conditions (Pinto 2012). Muscle tissue may act as an 'endocrine organ', with myokines that facilitate cross-talk between adipose tissue, the immune system, the hypothalamus, and muscle cells. The principal consideration is that the absence of classical proinflammatory cytokines with exercise induces a cytokine cascade that creates an anti-inflammatory environment that prevents CVD (Ertek 2012). In the vascular system, exercising promotes shear stress, which can be explained by a better endothelial function and nitric oxide bioavailability; endothelial repair by stem cells; and decreased arterial stiffness. These phenomena are mediated by increased activity of endothelial nitric oxide synthase with a concomitant increase in vascular nitric oxide production, mobilization of endothelial progenitor cells, and of mesenchymal stem cells from the bone marrow. In addition, an improvement in the functional capacity of the cells as well as structural changes associated with collagen and elastin are observed. Other effects can be explained by microRNA

regulation and an increase in collateral growth or arteriogenesis in the myocardium (Schuler 2013).

Why it is important to do this review

Among all strategies for preventing CVD there are some interventions aimed at asymptomatic individuals in different categories of total risk (Graham 2007), from changes in lifestyle to pharmacologic treatment, which are supported by different levels of evidence.

There are previous systematic reviews that have evaluated the effects of exercise on each CVD risk factor. A review of studies on people with type 2 diabetes showed that exercise significantly improves glycaemic control and reduces visceral adipose tissue and plasma triglycerides, but not plasma cholesterol, even without weight loss (Thomas 2006). Two reviews that assessed the effects of exercise on blood pressure concluded that progressive resistance exercise training reduces resting systolic and diastolic blood pressure in adults (Kelley 2000), and that aerobic exercise reduces blood pressure in both hypertensive and normotensive people (Whelton 2002). A review that included trials with overweight or obese participants concluded that increases in maximum oxygen consumption are associated with higher levels of HDL, as well as that exercise reduces triglycerides and that lower body weight is associated with lower levels of LDL (Kelley 2005). Another review that was focused on this population supports the use of exercise as a weight loss intervention, particularly when combined with dietary changes (Shaw 2006). Lastly, a review indicates that aerobic exercise training produced small but favorable modifications to blood lipids in previously sedentary adults (Halbert 1999).

There is no conclusive evidence on the relationship of exercise and smoking cessation; a review of 13 clinical trials found that only one trial offered evidence that exercise was correlated with smoking cessation at 12-month follow-up (Ussher 2008).

While the effect of exercise on individual risk factors seems to be well defined and understood, evidence of its effect on total cardiovascular risk is conflicting. Current available data are variable and insufficient to make a definitive statement about the role of exercise on total cardiovascular risk. To achieve this goal, it is necessary to gather evidence that assesses the effects of exercise not only on the control of risk factors but also on total risk profiles and on the incidence of cardiovascular events.

This review set out to clarify the existing evidence on the relationship of exercise and CVD by taking a comprehensive approach to participants, considering that they are affected by a constellation of risk factors, thus attempting to make results more applicable to clinical practice.

OBJECTIVES

To assess the effects of exercise training in people with increased cardiovascular risk but without a concurrent cardiovascular disease on general cardiovascular mortality, incidence of cardiovascular events, and total cardiovascular risk.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized clinical trials (RCTs) comparing aerobic or resistance exercise training versus no exercise or any standard approach that did not include exercise.

Trials with different times of exercise exposure were included in order to compare, in a subgroup analysis, the results of brief programs (eight weeks or less) against longer programs (more than eight weeks). We defined the threshold as eight weeks because programs of at least this duration could have positive and chronic effects on the cardiovascular system. Shorter programs may have acute but not durable effects (Kelley 2005; Thomas 2006).

Types of participants

People who:

- were 18 years of age or older;
- had a 10-year Framingham risk score equal to or greater than 10% over 10 years, or for whom it was possible to calculate the average 10-year Framingham risk score with data from the aggregated published data. In trials where such data were insufficient, alternative inclusion criteria were having two or more cardiovascular risk factors;
- did not have a history of cardiovascular events (acute myocardial infarction or stroke).

Types of interventions

Exercise interventions were defined as predetermined programs of planned, structured, and repetitive physical activity performed regularly. Exercise could be aerobic or resistance training.

Aerobic exercise is defined as any activity that uses large muscle groups, can be maintained continuously, and is rhythmic in nature. Resistance training is defined as any exercise that causes the muscles to contract against an external resistance with the expectation of increases in strength, tone, mass, or endurance.

The exercise prescriptions included specific recommendations for the type, intensity, frequency, and duration of physical activity with specific fitness or health objectives. Studies involving dietary or medication changes were eligible for inclusion only if the

same treatments were applied to both the intervention and control groups.

The review included studies involving the following comparisons:

- exercise intervention versus no exercise (control);
- exercise and diet versus diet alone;
- exercise and medication versus medication alone;
- exercise and any other intervention versus that intervention alone.

Types of outcome measures

Primary outcomes

1. All-cause mortality and CVD-related mortality
2. Incidence of acute myocardial infarction
3. Incidence of stroke

Secondary outcomes

1. Total CVD risk (difference of changes in the 10-year Framingham score or any other validated score)
2. Total cholesterol
3. HDL and LDL cholesterol
4. Blood pressure
5. Body mass index (BMI)
6. Smoking cessation
7. Exercise capacity (VO₂max, calories, or meters in six minutes walking test)
8. Quality of life (Short Form-36 (SF-36) questionnaire or others)
9. Adverse events

Search methods for identification of studies

Electronic searches

We conducted a systematic search for RCTs in electronic databases (from their inception to the latest available entry date) on 26 November 2013:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 10 of 12) in *The Cochrane Library*;
- MEDLINE (Ovid) (1946 to week 2 November 2013);
- EMBASE Classic + EMBASE (Ovid) (1947 to Week 47 2013);
- CINAHL Plus (EBSCOhost);
- Science Citation Index Expanded (SCI-EXPANDED) (1970 to 22 November 2013), and Conference Proceedings Citation Index - Science (CPCI-S) (1990 to 22 November 2013) in Web of Science (Thomson Reuters).

The search strategies used are included in [Appendix 1](#). The MEDLINE strategy includes the Cochrane RCT filter (sensitivity-maximizing version) ([Lefebvre 2011](#)) and this has been adapted for use in the other databases except CENTRAL.

We did not apply any language restrictions.

Searching other resources

We conducted searches in clinical trial registers using the terms “exercise” AND “cardiovascular risk”. This search was conducted in November 2013 in the following clinical trial registers:

- Meta Register of Controlled Trials (www.controlled-trials.com/mrct/);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

Additionally, we reviewed references of relevant articles. It was not necessary to contact any trial authors to obtain unpublished data.

Data collection and analysis

Selection of studies

References of trials found through the aforementioned search were evaluated for inclusion by reading their respective titles and abstracts. Of those that remained, two authors (PS, FL) independently analyzed their full texts to determine their eligibility. Disagreements were solved by consensus or by consulting a third author (XB).

Data extraction and management

Two authors (PS, FL) independently extracted data of interest from each of the included trials. Disagreements were resolved by consensus or by consulting a third author (XB).

Calculation of 10-year Framingham risk score in primary studies

In studies that did not include 10-year Framingham risk scores, we proceeded to calculate the scores from the data reported for each of the individual risk factors at the beginning and end of the monitoring period.

We started with baseline measurements. For continuous variables, we used mean values and standard deviations (SD). For categorical variables (smoking status and presence of left ventricular hypertrophy) the most conservative (or less risky) scenario was assumed. The total average cardiovascular risk of the sample was estimated (using averages) as well as the minimum and maximum values

(using SD). We made these estimates separately for men and women.

Regarding cardiovascular risk at the end of the follow-up period, we implemented the same parameters except that we used the 95% confidence intervals reported in each study instead of SD.

Assessment of risk of bias in included studies

We assessed the risk of bias in all trials under the following domains (Higgins 2011).

1. Sequence generation: the methods used to generate the allocation sequence allow groups to be comparable.
 2. Measures to conceal allocation: the intervention allocation could have been foreseen, before or during recruitment, or changed after assignment.
 3. Blinding: provides information on whether the intended blinding was effective. If blinding was not possible, determination of whether the lack of blinding was likely to have introduced bias. Blinding was assessed separately for different outcomes or classes of outcomes.
 4. Completeness of outcome data: determine if attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomized participants), reasons for attrition or exclusion, and whether missing data were balanced across groups or were related to outcomes.
 5. Selective reporting: determine how the possibility of selective outcome reporting bias was examined for each included study and report any findings.
- Two authors independently assessed these categories in the selected studies. We solved disagreements by discussion and consensus.

Measures of treatment effect

We had planned to conduct a meta-analysis of the collected data. However, since the identified interventions (setting, type and intensity of exercise) and outcome measurements were not comparable, and the risk of bias in the identified studies was high, this meta-analysis could not be completed. In future updates, relative risks (RR) will be calculated for dichotomous data and pooled weighted mean differences (with 95% confidence intervals (CIs)) for continuous variables.

Assessment of heterogeneity

The statistical heterogeneity was to be examined using the I^2 statistic. However, this was not completed due to the reasons given in the 'Measures of treatment effect' section.

Assessment of reporting biases

The presence of publication bias, based on data for the primary outcomes, will be assessed in future updates of this review.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be conducted, where possible or necessary, in future updates. The potential subgroups are the following.

- Sex: (1) male; (2) female.
- Age: (1) 18 to 45 years; (2) 46 to 60 years; (3) 61 or more years.
- Intensity of exercise: (1) moderate; (2) vigorous.
- Duration of the program: (1) 8 weeks or less; (2) greater than 8 weeks.
- Duration of the follow-up: (1) short-term follow-up, or six months or less after completing the exercise program; (2) long-term follow-up, or greater than six months after completing the exercise program.
- BMI: (1) normal; (2) overweight; (3) obese.

Sensitivity analysis

We had planned to conduct a sensitivity analysis in the following situations.

- Type of exercise program (individual or group), because the nature of the intervention may produce a cluster effect.
- Quality of primary studies.
- Type of analysis (random-effects model or fixed-effect model).

However, sensitivity analysis was not conducted because the collected data were not meta-analysed.

RESULTS

Description of studies

See: [Characteristics of included studies](#). [Characteristics of excluded studies](#).

Results of the search

Figure 1 shows the study selection process (until November 2013). Initially 9845 citations were identified in the electronic databases, of which 6017 remained after de-duplication. At the same time 941 records were identified in clinical trial registers, making a total of 6958 citations. We excluded 6933 studies after screening the titles and abstracts. Of the 25 remaining, we excluded 21 after comprehensively reading the full-texts. We included the four remaining studies in this review.

Figure 1. Study flow diagram.

Included studies

The four included studies (Fukahori 1999; Hellenius 1993; Mendivil 2006; Nishijima 2007) comprised 823 participants with a mean age of 52.6 years. Of these, 412 participants were assigned to exercise groups and 411 to control groups. Two studies were conducted in Japan (Fukahori 1999; Nishijima 2007), one in Sweden (Hellenius 1993), and one in Colombia (Mendivil 2006). One of the studies used a factorial design (Hellenius 1993) where one group received a dietary intervention, another undertook exercise, another received diet plus exercise, and another acted as a control. The three other studies consisted of two parallel groups, one undergoing one of several exercise programmes, such as aerobic training on a treadmill (Fukahori 1999), walking or jogging (Hellenius 1993), dance or sports such as football and basketball (Mendivil 2006), or cycling in a fitness club (Nishijima 2007).

Follow-up periods ranged from 16 weeks (Mendivil 2006) to six months (Fukahori 1999; Hellenius 1993; Nishijima 2007).

Only one of the included studies considered total cardiovascular risk as an inclusion criterion (Mendivil 2006). In this study, participants had to have a 10-year Framingham risk score > 1, which implies that participants were classified as having low, increased, or high risk of CVD. The score of the study sample, estimated with the measurement of the participants at baseline, was 10.4%

(95% CI 8.2 to 12.8). Two of the three other studies reported baseline information that allowed estimating the 10-year Framingham risk score (Hellenius 1993; Nishijima 2007). The average 10-year Framingham risk score was found to be 13.2% (range 2.5% to 54.9%) in Hellenius 1993 and 15.7% (range 6% to 68.3%) in Nishijima 2007. For one study (Fukahori 1999) it was not possible to determine the 10-year Framingham risk score.

The table 'Characteristics of included studies' shows further details on participants, interventions, and outcomes in each study.

Characteristics of included interventions

Exercise routines were diverse. Participants in the experimental group of one of the studies underwent interval training consisting of 2.5-minute walking on a 5% slope at 70% to 75% of the maximum heart rate (HR) alternated with 3-minute flat walking for a total of 20 minutes exercise, three times a week (Fukahori 1999). The three other studies used aerobic fitness exercise as the main component of the intervention. The different types of aerobic exercise were: walking or jogging for 30 to 45 minutes, at an intensity adjusted to 60% to 80% of the maximum HR, two to three times a week (Hellenius 1993); dance or playing a sport such as football or basketball in 45-minute sessions at 50% to 55% of the maximum HR three times a week at the beginning of the programme, 60 minutes at 60% to 70% of the maximum HR five

times a week during the second part of the programme (Mendivil 2006); and attending a fitness club where 60-minute cycling was performed at 40% of the VO_2 peak during the first phase of the programme, increasing 5 to 10 watts for the two subsequent phases, ending with 90-minute sessions two to four times a week (Nishijima 2007). Two studies added a resistance exercise component to the aerobic exercise (Mendivil 2006; Nishijima 2007). The modalities of supervision and the personnel were different across studies. In one study the exercise programme was prescribed by an industrial physician in a work setting as part of a health promotion plan (Fukahori 1999). In another study a physician provided verbal and written information about physical training to each participant (Hellenius 1993). In the third, all exercise sessions were directed and supervised by three trained physical therapists (Mendivil 2006). And in the last study a certified fitness instructor directly supervised the exercise routine (Nishijima 2007).

Excluded studies

The 21 studies that were excluded were either not randomized, participants had already suffered a cardiovascular event (coronary heart disease), exercise routines were combined with other interventions, there was no assessment of exercise training but rather an indication or advice to engage in physical activity, or they did not include the outcomes of interest. See the [Characteristics of excluded studies](#) for details of the respective reasons for excluding each study.

Risk of bias in included studies

Besides the reporting limitations of each study, the included studies had a high risk of selection, detection, and attrition biases overall. The graphic representation of the risk of bias of the included studies can be found in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Fukahori 1999	?	-	-	?	-	+
Hellenius 1993	?	-	-	?	+	-
Mendivil 2006	+	?	-	?	-	+
Nishijima 2007	+	-	-	?	+	+

Allocation

Two studies mentioned that allocation to the interventions was randomized although without describing a specific method to ensure, for example, balance between the groups, which was an important aspect considering the small size of the studies (Fukahori 1999; Hellenius 1993). The two other studies described a method of computational random number generator (Mendivil 2006) and a block randomization lottery-like technique (Nishijima 2007). None of the four studies reported if allocation concealment was maintained. In only one of them the intervention allocation was presumably concealed, due to the randomization method used (Mendivil 2006).

Blinding

In an exercise-based intervention, neither participants nor investigators can be blinded. However, it is possible to assess outcomes in a blinded manner. None of the studies reported if outcome assessment was conducted in a blinded manner (Fukahori 1999; Hellenius 1993; Mendivil 2006; Nishijima 2007).

Incomplete outcome data

Patients lost to follow-up varied across studies. Two studies showed a low risk of bias in this domain: one of them reported one loss in the control group, which constituted 2.5% of the sample (Hellenius 1993); whereas the other study reported 11% and 10% losses to follow-up in the experimental and control groups, respectively, for similar reasons in both groups (Nishijima 2007). The two other studies showed a high risk of bias in this regard as one of them had different loss rates between the groups (9.2% in the experimental group and 3.7% in the control group) (Fukahori 1999), while the other reported high rates of losses in both groups (43% in the experimental group and 26% in the control group) (Mendivil 2006). None of the four studies reported an intention-to-treat analysis.

Selective reporting

Three of the included studies showed a low risk of bias in this respect as they all described the results obtained for each of the outcomes included in the objectives or the methods section (Fukahori 1999; Mendivil 2006; Nishijima 2007). The other study had a high risk of bias because it presented the results as differences between the initial and final values (Hellenius 1993).

Effects of interventions

We could not conduct a meta-analysis due to the clinical heterogeneity, with different interventions (setting, type and intensity of

exercise) and outcome measurements reported in the trials. Moreover, the risk of bias was high for all the identified studies.

Mortality

None of the four included studies considered all-cause or cardiovascular mortality as outcomes.

Cardiovascular events

None of the four included studies considered any cardiovascular event, such as acute myocardial infarction or stroke, as an outcome.

Total cardiovascular risk

Two studies considered total cardiovascular risk as an outcome. There appeared to be no significant differences between the study groups (Mendivil 2006, Hellenius 1993). One of the studies reported an 8.38% (standard error (SE) 1.1) and 10.71% (SE 1.5) average probability of suffering a cardiovascular event at 10 years after the 16-week follow-up in the experimental and the control groups, respectively ($P = 0.054$) (Mendivil 2006).

The other study, which did not describe the baseline values for the total cardiovascular risk, only reported the differences observed in each group: -0.87% (95% CI -1.57 to -0.17) in the exercise group versus 0.21% (95% CI -0.52 to 0.94) in the control group. Additionally, the average 10-year Framingham risk score by the end of the six months of intervention was estimated to be 8.8% (95% CI 5.5 to 12.5) in the exercise group and 9.1% (95% CI 6 to 13.5) in the control group. The differences between groups were not significant (Hellenius 1993).

The two remaining studies did not report this outcome. However, in one study it was possible to estimate the averages of each group using the reported data on individual risk factors. The average 10-year Framingham risk score for women by the end of the six months of intervention in the exercise group was 13.4% (95% CI 10 to 17.2), which was similar to the 14.4% (95% CI 10.07 to 18.3) average seen in the control group. For men, the average 10-year Framingham risk score was 21.9% (95% CI 16.1 to 28) in the exercise group, which did not differ from the control group average of 23.1% (95% CI 17.1 to 29.4) (Nishijima 2007).

Total cholesterol

All four studies assessed this outcome, but none of them reported statistically significant differences between the exercise and control groups.

One of the studies showed figures of the results, which did not allow us to obtain an accurate value for each group. These figures

showed a tendency for total cholesterol to increase in both groups at months three and six of follow-up, which was reported to be significant in the control group at month six ($P < 0.01$) (Fukahori 1999).

Two studies showed the results as differences from baseline after the follow-up period (Hellenius 1993; Nishijima 2007). One of them reported a change of -0.12 mmol/l (95% CI -0.35 to 0.11) in the exercise group and -0.13 mmol/l (95% CI -0.3 to 0.07) in the control group. These differences were not significant (Hellenius 1993). The other study reported a difference of -0.08 mmol/l (95% CI -0.16 to 0.01) in the exercise group versus -0.03 mmol/l (95% CI -0.12 to 0.05) in the control group, and a -0.04 mmol/l (95% CI -0.14 to 0.06) baseline-adjusted difference between groups by the end of the six months of follow-up (Nishijima 2007). The last study showed the values obtained in each group by the end of the follow-up period. The total cholesterol was 5.63 ± 0.20 mmol/l in the exercise group versus 5.14 ± 0.20 mmol/l in the control group ($P = 0.219$) (Mendivil 2006).

LDL and HDL cholesterol

Three studies reported LDL cholesterol results, with no differences between the exercise and the control groups.

As with total cholesterol two studies showed the results as differences with respect to each group's baseline measurement (Hellenius 1993; Nishijima 2007). One of them showed a difference from baseline of -0.09 mmol/l (95% CI -0.24 to 0.07) in the exercise group versus -0.15 mmol/l (95% CI -0.33 to 0.02) in the control group after six months (Hellenius 1993). The other study showed a -3.99 mg/dl (95% CI -6.66 to -1.31) difference in the exercise group versus -1.65 mg/dl (95% CI -4.47 to 1.17) in the control group, and a -1.9 mg/dl (95% CI -5.3 to 1.6) baseline-adjusted difference between the groups by the end of the follow-up period of six months ($P = 0.29$) (Nishijima 2007). The third study reported a 3.69 ± 0.21 mmol/l LDL cholesterol level in the exercise group versus 3.20 ± 0.17 mmol/l in the control group ($P = 0.185$) at the end of 16 weeks of intervention (Mendivil 2006).

Regarding HDL cholesterol, all of the four included studies assessed this outcome. Two studies showed significant differences but these were not clinically important; one study reported an increase of HDL cholesterol at both three and six months of follow-up in the exercise group ($P < 0.05$) and at six months in the control group ($P < 0.01$), but did not report whether there were differences between groups (Fukahori 1999). The other reported a 1.04 ± 0.05 mmol/l HDL cholesterol level by the end of the follow-up period in the exercise group compared to 0.89 ± 0.04 mmol/l in the control group ($P = 0.026$) (Mendivil 2006). The two other studies (Hellenius 1993; Nishijima 2007) showed no differences between groups regarding this outcome.

Blood pressure

Three studies assessed the systolic and diastolic blood pressure levels (Hellenius 1993; Mendivil 2006; Nishijima 2007); two of them found significant differences between the study arms that were not clinically important (Hellenius 1993; Nishijima 2007). Regarding systolic blood pressure, one study reported a difference from baseline of -5 mmHg (95% CI -9 to -0.3) by the end of six months in the exercise group, which was higher than the -1 mmHg (95% CI -3 to 1) difference in the control group ($P < 0.05$) (Hellenius 1993). The other study found a difference of -8.30 mmHg (95% CI -9.97 to -6.63) in the exercise group, which was higher than the -6.17 mmHg (95% CI -7.60 to -4.74) difference in the control group. The difference between groups at the end of the follow-up period, adjusted by the baseline measurement, was -2.46 mmHg (95% CI -4.50 to -0.42) ($P = 0.018$) (Nishijima 2007).

Regarding diastolic blood pressure, the first study reported a difference between the baseline measurement and that performed by the end of the intervention of -4 mmHg (95% CI -7 to -2) in the exercise group, which was greater than the -1 mmHg (95% CI -3 to 1) difference in the control group ($P < 0.05$) (Hellenius 1993). The second study showed a -4.77 mmHg (95% CI -5.72 to -3.83) and a -3.60 mmHg (95% CI -4.44 to -2.76) difference in the exercise and the control groups, respectively. The difference between groups at the end of six months of follow-up, adjusted by the baseline measurement, was -1.4 (95% CI -2.6 to -0.2) ($P = 0.019$) (Nishijima 2007).

The third study assessing blood pressure found no differences between the study groups for systolic and diastolic blood pressure (Mendivil 2006).

Body mass index (BMI)

Three studies assessed this outcome (Fukahori 1999; Hellenius 1993; Mendivil 2006), two of which found significant differences between groups. One of these studies reported a BMI reduction of -0.3 kg/m² (95% CI -0.5 to -0.01) from baseline by the end of the

follow-up period in the exercise group, and a 0.3 kg/m² (95% CI 0.1 to 0.5) increase in BMI in the control group ($P < 0.01$) (Hellenius 1993). The other study reported a BMI of 25.45 ± 0.8 kg/m² by the end of the follow-up period in the exercise group, which was less than the BMI of the control group, 27.15 ± 0.6 kg/m² ($P = 0.012$) (Mendivil 2006). The third study measuring this outcome showed no differences in the BMIs between the groups at the end of the follow-up period (Fukahori 1999).

Smoking cessation

None of the four studies considered smoking cessation as an outcome.

Exercise capacity

Two studies reported results related to exercise capacity. One of them applied an incremental exercise tolerance test that failed to reveal differences between the groups after six months of intervention as determined by the HR at a workload of 150 watts (Hellenius 1993). The other study measured the peak oxygen uptake (VO₂ peak) through a symptom-limited maximal incremental exercise test. After six months of intervention a significant difference of 2.0 ml/kg/min (IC 95% 1.53 to 2.48) favored the intervention group (Nishijima 2007).

Quality of life

Only one study reported this outcome. Using the SF-36 questionnaire the study found significant improvements ($P > 0.05$) in three of the eight subscales. In the general health subscale, there was an increase from 64.3 to 69.5 points in the exercise group versus a change from 65.8 to 65.2 points in the control group. In the vitality subscale, there appeared to be an increase from 70.7 to 74.8 points in the exercise group and a decrease from 73.0 to 70.1 points in the control group. In the mental health subscale, the study reported an increase from 79.9 to 82.1 points in the exercise group versus a decrease from 79.6 to 77.6 points in the control group (Nishijima 2007).

Adverse events

None of the four included studies considered adverse events as an outcome.

DISCUSSION

Summary of main results

This review found three individual studies that showed no significant differences between exercise and no exercise on total cardiovascular risk. The results could not be meta-analysed and the studies were at high risk of bias. Two of the studies reported this outcome directly (Hellenius 1993; Mendivil 2006) and one study included data allowing the outcome to be calculated (Nishijima 2007). Likewise, individual studies showed no significant differences between groups for total or LDL cholesterol. Some studies found significant differences between groups with respect to HDL cholesterol (Fukahori 1999; Mendivil 2006), blood pressure (Hellenius 1993; Nishijima 2007), BMI (Hellenius 1993; Mendivil 2006), exercise capacity (Nishijima 2007), and health-related quality of life (Nishijima 2007) but the differences were not clinically significant. Additionally, other studies found no significant differences for HDL cholesterol (Hellenius 1993; Nishijima

2007); blood pressure (Mendivil 2006); and BMI (Fukahori 1999). None of the studies included all-cause or cardiovascular mortality, cardiovascular events, or smoking cessation as outcomes. The results of this review are limited by the small number of studies and the low methodological quality and lack of comparability between studies.

Overall completeness and applicability of evidence

Participants in the included studies were mostly men with dyslipidemia (total cholesterol, altered LDL or HDL) and high blood pressure. Obesity and hyperglycemia were considered as inclusion criteria by some authors (Fukahori 1999; Nishijima 2007). In only one of the studies (Mendivil 2006) total cardiovascular risk was considered as an inclusion criterion. The outcomes assessed were total cholesterol, LDL and HDL levels, and systolic and diastolic blood pressure. Two studies included outcome variables related to exercise capacity such as the heart rate (HR) at 150 watts of workload (Hellenius 1993) and VO₂ peak (Nishijima 2007). One study further considered hemoglobin A1c (HbA1c) and quality of life (Nishijima 2007). Two studies assessed total cardiovascular risk (Hellenius 1993; Mendivil 2006).

Although including participants with two or more cardiovascular risk factors, or performing measurements of several risk factors at baseline and at the end of the study, may imply a concern for the coexistence of these factors in individuals, the few available studies show little or no consideration of the overall risk approach when assessing exercise impact. To date, efforts have focused on studying the effects of exercise on individual risk factors (Kelley 2005; Shaw 2006; Thomas 2006; Ussher 2008; Whelton 2002). This evidence contributes to decision-making in these patients but does not emphasize the fact that there is a coexistence of risk factors in many patients that act in a multiplicative manner to promote cardiovascular disease, hindering the applicability of the results.

As when the effect of exercise was studied on individual risk factors, most of the studies in this review considered aerobic exercise, together with some interventions involving resistance exercise. Only one study assessed the effect of high-intensity interval exercises, which are increasingly being implemented both in healthy and at-risk individuals. This establishes the need to assess this type of training in individuals with different cardiovascular risk levels. As in other studies, the duration of the exercise programmes and the corresponding follow-up was six months, which is understandable as it is difficult from both a logistic and an economic point of view to have longer follow-up periods. However, this limits the scope of the findings with respect to the maintenance of a potential benefit and the impact on the variables of high interest such as mortality and cardiovascular events.

Quality of the evidence

The most critical aspect of this review is the high risk of bias in the primary studies. Although all studies stated they were randomized, half of them failed to describe the method used and none established the existence of allocation concealment, which may introduce significant selection bias. Given the characteristics of the assessed intervention, it is important to note that it was not feasible to blind the participants or the clinicians administering the exercise. The investigators measuring the outcomes could have been blinded, but this was not reported in any of the included studies.

The number of dropouts and participants lost to follow-up that were reported in two of the included studies is a matter of concern. Although losses and dropouts are plausible with an outpatient and repeated-dose intervention, it is important to take steps to monitor and report losses, their causes, and to achieve the highest level of compliance, as well as to conduct an intention-to-treat analysis. Other important aspects to consider are those related to the differences in the interventions applied in the studies, the low number of included studies, and the small sample sizes considered in some of the studies, considerations that do not allow direct comparison of the results to provide a more precise estimate of the effect of exercise in people at increased cardiovascular risk. The fact of having to calculate the Framingham risk score of the sample in each study, using the data provided by the articles, potentially introduces a difference in the intended population, more heterogeneity between studies, and affects the precision and the directness of the conclusions.

Potential biases in the review process

The study search was thorough, with no language or time limitations. There was also a search conducted in clinical trial registers for ongoing studies as well as an inspection of the reference sections of articles with similar scopes. A potential risk of publication bias may arise since unpublished data were not obtained, and additionally the fact that the search strategy was adjusted in order to increase specificity could have led to some studies not being detected.

An important potential bias is related to the changes to the inclusion criteria because of the absence of studies in people with high cardiovascular risk (defined as risk of death from CVD equal to 5% or more within 10 years). This protocol change broadened the studies that were included and was potentially influenced by the knowledge of existing studies. Nevertheless, only a few studies that were of low methodological quality were included establishing the necessity for clinical trials to determine the effects of exercise in people with high or increased cardiovascular risk.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence to date is entirely limited to small studies with small sample sizes, short-term follow-up, and at high risk of methodological bias, which makes it difficult to derive any conclusions on the efficacy or safety of aerobic or resistance exercise among individuals with increased risk of cardiovascular disease or with two or more coexisting risk factors. We cannot, therefore, reach any conclusion, neither in favor nor against this intervention. The available evidence evaluating the effect of exercise on cardiovascular risk factors individually, such as diabetes, high blood pressure, or obesity, suggest the existence of a potential benefit associated with this intervention.

Implications for research

There appears to be a need to conduct randomized clinical trials (RCTs) to determine whether a controlled exercise programme, including aerobic and resistance training, is effective in individuals with increased total cardiovascular risk regarding outcomes of interest such as mortality, development of cardiovascular events, occurrence of adverse events, and compliance to physical activity. The intervention should include strategies for permanent change of behaviour and be applied for at least three to six months with a long follow-up post-intervention. These RCTs should be designed and conducted with the highest possible bias control, including randomized allocation of the participants to the study groups, an appropriate allocation concealment method, and blinded assessment of outcomes. Furthermore, a sample size which grants a sufficiently high statistical power should be considered.

ACKNOWLEDGEMENTS

Pamela Serón is a PhD candidate at the Paediatrics, Obstetrics and Gynaecology and Preventive Medicine Department, Universitat Autònoma de Barcelona, Spain.

We acknowledge the help of Farhad Shokraneh with the reading of a Persian article.

The authors would like to thank the editorial staff at the Cochrane Heart Group for revising and running the search strategy, for advising on the inclusion criteria of the primary studies and for their support in the review process.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Fukahori 1999

Methods	RCT conducted in 1996 in Japan involving 108 workers. Six-month follow-up with measurements at months 3 and 6
Participants	Workers from a petroleum complex were recruited, 19-61 years of age, able to follow an exercise programme prescribed by an industrial physician, with two or more of the following risk factors: - Hyperlipidemia (CholTotal $\geq$ 220 mg/dl or HDL $\leq$ 40 mg/dl) - High blood pressure (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg, no medication) - Obesity (BMI $\geq$ 24 kg/m ²) - Hyperglycaemia (fasting blood sugar $\geq$ 110 mg/dl)
Interventions	The experimental group underwent interval training on a treadmill, consisting of 2.5-minute walking with a 5% slope at 70-75% of the HRmax alternated with 3-minute flat walking, for a total of 20 minutes exercise The exercise program was prescribed by an industrial physician in a work setting as part a health promotion plan Sessions were conducted 3 times a week for 6 months during normal business hours The control group received no exercise or alternative intervention
Outcomes	Total cholesterol, HDL cholesterol, and walking speed
Notes	Data to calculate total cardiovascular risk was not available. This study was included because it considers participants with two or more risk factors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A total of 108 participants are randomized, 54 to each group, but a specific method to balance participants in each group is not defined
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. In an exercise-based intervention, neither patients nor personnel can be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Fukahori 1999 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Five losses in the exercise group (9.2%) and two in the control group (3.7%). Reasons were change of job or injury
Selective reporting (reporting bias)	Low risk	In the objectives section, authors state that effects on lipids and walking speed would be assessed. Both of these outcomes are reported

Hellenius 1993

Methods	RCT conducted in Japan involving 158 participants. Six-month follow-up	
Participants	Eligible participants included men with no cardiovascular disease, diabetes, or other severe disease history, taking no medication regularly and with: - Cholesterol between 5.2 and 7.8 mmol/l - Fasting triglycerides $\leq$ 5.6 mmol/l - DBP >100 mmHg	
Interventions	Subjects were randomized to one of the following groups: (1) Diet: Participants received counselling from a nutritionist based on the National Cholesterol Education Program Step 1 diet and considering a total fat consumption <30%; saturated fat <10%; polyunsaturated fat <10%; monounsaturated fat 10-15%; carbohydrates (complex) 50-60%; proteins 10-20% and cholesterol <300 mg/day (2) Exercise: Participants were prescribed aerobic exercise (walking, jogging, etc) for 30-45 minutes at an intensity of 60-80% HRmax, 2-3 times a week. They were asked to keep an activity log with date, type of activity, time and intensity of exercise (using the Borg Scale). They were also given the opportunity to practice monitored exercise (3) Group with diet plus exercise according to the previous description (4) Control group: no diet or exercise intervention/advice A physician provided verbal and written information about physical training in groups 2 and 3	
Outcomes	Cardiovascular risk factors: weight, blood pressure, lipoproteins, and estimated risk of cardiovascular disease	
Notes	Data to calculate probability of a cardiovascular event in 10 years (10-year Framingham risk) is available. In average, this probability was 13.2% (from 2.5% to 54.9%)	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study describes randomization of participants to one of the four groups, but it does not mention methods to assure balance of participants in the final distribution of the groups

Hellenius 1993 (Continued)

Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. In an exercise based intervention, neither patients nor personnel can be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one subject lost in the control group
Selective reporting (reporting bias)	High risk	The results are presented as differences between initial and final values

Mendivil 2006

Methods	Parallel-group RCT conducted in Colombia involving 75 participants. 16-week follow-up
Participants	The study included adults between 40 and 70 years of age with 10-year Framingham cardiovascular risk $\geq 1\%$. The study excluded individuals with diabetes mellitus, BMI under 18.5 kg/m ² , chronic kidney failure, physical disability preventing exercise development, serious gastrointestinal disorders, malignant or secondary hypertension, recent acute myocardial infarction, unstable angina, or severe dental loss
Interventions	<p>The control group received a dietetic intervention which considered a caloric consumption computed according to ideal weight and exercise-related caloric expenditure. If BMI was >25, intake was reduced by 400 calories. Nutrients distribution was done following the NCEP-ATPIII</p> <p>The intervention group received the same dietetic intervention plus aerobic exercise (dance, football, basketball, kick boxing) and resistance exercise with incremental time and intensity throughout the 16 weeks that lasted the intervention:</p> <ul style="list-style-type: none"> - Duration 45 minutes from week 1 to 12 and 60 minutes from week 13 to 16 - Intensity 50%-55% maximum HR from week 1 to 8, and 60%-70% maximum HR from week 9 to 16 - Dosage 3 times a week from week 1 to 8 and 5 times a week from week 9 to 16 <p>All exercise sessions were directed and supervised by three trained physical therapists</p>
Outcomes	The outcomes considered were: overall cardiovascular risk (10-year Framingham), total LDL and HDL cholesterol, and systolic and diastolic blood pressure
Notes	This study measured 10-year Framingham total cardiovascular risk. The mean value at baseline was 10.4% (95% CI 8.2 to 12.8)
<i>Risk of bias</i>	

Mendivil 2006 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to control group or experimental group by a computer random number generator
Allocation concealment (selection bias)	Unclear risk	Not described, but the randomization method allows allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. In an exercise-based intervention, neither patients nor personnel can be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 43% and 26% losses in the exercise and control groups, respectively. The authors state that losses to follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified variable outcomes are reported

Nishijima 2007

Methods	Parallel-group RTC conducted between 2003 and 2004 in Japan, involving 561 participants
Participants	<p>The study included participants 40-89 years of age with a BMI between 24.2-34.9 and two or more of the following cardiovascular risk factors:</p> <ul style="list-style-type: none"> - Systolic blood pressure at rest between 130 and 179 mmHg - Fasting glycemia between 110 and 139 mg/dl, or HbA1c $\geq$ 5.8, when casual blood sugar was 140-199 mg/dl - LDL cholesterol between 120 and 219 mg/dl <p>The study excluded individuals with diastolic blood pressure $\geq$ 110 mmHg, history of heart disease or stroke, orthopedic problems interfering with exercise, abnormal ECG during exercise stress test, and those described by their private physician as unsuitable for exercising</p>
Interventions	<p>The experimental group received advice on lifestyle and attended a fitness club where they performed aerobic exercise (cycling), 'light' resistance exercise, and stretching at the end of each session. Sessions were progressive regarding duration and intensity, starting at 60 minutes and reaching 90 at the end of the follow-up. Exercise load started at 40% VO² peak, increasing from 5 to 10 watts in the following two phases. Resistance exercises were mild to moderate</p> <p>The intervention period lasted 6 months. Participants performed 8 sessions with a coach and conducted the exercises on their own the rest of the time, 2-4 times a week</p>

	A certified fitness instructor directly supervised the exercise routine The control group received advice on lifestyle
Outcomes	Systolic blood pressure, LDL cholesterol and HbA1c were considered as primary outcomes. Secondary outcomes included hsCRP, waist circumference, VO ² peak, and health-related quality of life
Notes	The information needed to estimate the probability of a cardiovascular event in 10 years (10-year Framingham risk) is available. On average, this probability was 15.7% (from 6% to 68.3%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A 'lottery-like' (4 or 6) block randomization was implemented. Stratification according to fitness club, age, and sex was carried out
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. In an exercise-based intervention, neither patients nor personnel can be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study describes that staff administering the exercise and the exercise stress tests were blinded. However, it does not specify whether the remaining assessments were conducted in a blinded manner
Incomplete outcome data (attrition bias) All outcomes	Low risk	11.4% of participants were lost to follow-up in the exercise group and 10% in the control group. Reasons for leaving the study were similar in both groups
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes described in the methods section are reported in the results

RCT: Randomized clinical trial

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

BMI: Body mass index

CholTotal: Total cholesterol

HR: Heart rate

HRmax: Maximal heart rate

HDL: High density lipoprotein

LDL: Low density lipoprotein

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderssen 1995	Participants with multiple risk factors, but not necessarily with increased cardiovascular risk. The results were markers of homeostasis, which are not relevant to this review
Avram 2011	Compared intensive lifestyle counselling (diet and exercise indication) versus usual care. Exercise was not an isolated intervention
Cupples 1999	Subsequent follow-up of participants from an RCT. The intervention was health promotion activities and combined several actions
Englert 2007	The intervention is combined (education on diet, exercise, and smoking) and there is no control group
Eriksson 2009	Compared exercise plus diet counselling (intensive modification of lifestyle) versus indication of diet plus exercise. Evaluates diet, not exercise
From 2010	The intervention evaluated is exercise promoted by a nurse. Participants included men with at least two risk factors, which is not necessarily increased cardiovascular risk. No statistical results reported
Goodpaster 2010	Severely obese participants, but not necessarily at increased cardiovascular risk (with other risk factors). 10-year Framingham risk score calculated at baseline: average of 9%
Hazar 2010	Observational study. Outcomes are muscle damage and inflammation markers
Hussein 2010	Patients with a coronary event, which is an exclusion criterion
Jennings 1986	Subjects were not at increased cardiovascular risk. Twelve normal participants were included
Kokkinos 1991	It is a clinical trial, but not randomized
Madden 2010	The outcome, baroreflex sensitivity, is not part of this review's inclusion criteria. Furthermore, it is unclear whether participants had all the cardiovascular risk factors listed or just one or some of them
Naito 2008	Observational study comparing factories with and without workplace-based intervention program
Price 2008	The intervention is not exercise. The study implements a factorial design to compare exposure to individualized cardiovascular risk estimation versus advice on lifestyle versus both versus none
Rahimian 2010	Participating women were obese or overweight and hypertensive but in state 1, which cannot be defined as increased cardiovascular risk or 10-year Framingham risk score over 10%

(Continued)

Singh 1992	Patients with cardiovascular risk factors, however, authors do not specify the total risk or if they had more than one risk factor. Available data are not sufficient to estimate the total cardiovascular risk, but the tables show small proportions of participants with risk factors (no more than 50 per group for each risk factor)
Torjesen 1997	Participants have several cardiovascular risk factors, but in range not high enough to be considered increased cardiovascular risk. Basal data allowed estimating 10-year Framingham risk score, which was 8.3% in non-smokers and 16% in smokers
Tuthill 2007	The intervention is combined. Participants included obese patients suffering from diabetes mellitus, who are high-risk patients but who had already been included in previous Cochrane reviews
Vadheim 2010	The intervention was the motivation of achieving goals. There were no specific exercise routines
Watkins 2003	Compares exercise versus exercise and diet in patients with syndrome X
Wu 2007	It is a clinical trial, but not randomized. Women with at least one risk factor, which is not necessarily increased cardiovascular risk

APPENDICES

Appendix I. Search strategies

CENTRAL

- #1 heart score
- #2 ETHRISK
- #3 Framingham near/3 score
- #4 PROCAM
- #5 ASSIGN score
- #6 risk near/5 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*):ti,ab,kw
- #7 score near/5 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*):ti,ab,kw
- #8 calcul* near/5 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*):ti,ab,kw
- #9 (new zealand near/2 risk calculator)
- #10 HeartScore
- #11 (sheffield near/2 table)
- #12 ASSIGN tool
- #13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
- #14 MeSH descriptor: [Diabetes Mellitus] this term only
- #15 MeSH descriptor: [Diabetes Mellitus, Type 2] this term only
- #16 (diabetes near/3 mellitus)
- #17 MeSH descriptor: [Hyperglycemia] explode all trees

#18 hyperglycemia*
 #19 glycemia*
 #20 MeSH descriptor: [Smoking] this term only
 #21 MeSH descriptor: [Tobacco Use Cessation] explode all trees
 #22 MeSH descriptor: [Tobacco Use Disorder] explode all trees
 #23 (smoke or smoking or smoker or smokers or smoked)
 #24 ((cigar* or tobacco or nicotin*) near/2 consum*)
 #25 MeSH descriptor: [Hypertension] explode all trees
 #26 hypertensi*
 #27 ((high or increased or elevated) near/2 blood pressure)
 #28 MeSH descriptor: [Blood Pressure] this term only
 #29 (systolic blood pressure) OR (diastolic blood pressure)
 #30 MeSH descriptor: [Dyslipidemias] explode all trees
 #31 dyslipidemia*
 #32 dyslipoproteinemia*
 #33 hypercholesterolemia*
 #34 hypercholesteremia*
 #35 hyperlipidemia*
 #36 hyperlipemia*
 #37 lipidemia*
 #38 lipemia*
 #39 hyperlipoproteinemia*
 #40 hyperchylomicronemia*
 #41 lipoproteinemia*
 #42 hypertriglyceridaemia*
 #43 MeSH descriptor: [Cholesterol] this term only
 #44 Cholesterol*
 #45 MeSH descriptor: [Cholesterol, HDL] this term only
 #46 MeSH descriptor: [Cholesterol, LDL] this term only
 #47 MeSH descriptor: [Triglycerides] this term only
 #48 Triglyceride*
 #49 triacylglycerol*
 #50 ((low or high) near/3 lipoprotein*)
 #51 bmi
 #52 overweight
 #53 MeSH descriptor: [Body Mass Index] this term only
 #54 MeSH descriptor: [Abdominal Fat] explode all trees
 #55 MeSH descriptor: [Overweight] explode all trees
 #56 obes*
 #57 (weight adj2 (gain* or chang*))
 #58 body mass index OR body mass indexes OR body mass indices
 #59 abdominal fat
 #60 (quetelet* index)
 #61 high near/2 (body weight) OR increased near/2 (body weight)
 #62 (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61)
 #63 MeSH descriptor: [Exercise] explode all trees
 #64 MeSH descriptor: [Exercise Therapy] explode all trees
 #65 MeSH descriptor: [Exercise Tolerance] this term only
 #66 exercis*
 #67 (physical near/3 activ*)
 #68 (fitness or fitter or fit)

#69 physical near/3 train*
 #70 aerobic near/3 (train* or activ*) OR resistance near/3 (train* or activ*)
 #71 muscle near/3 (train* or activ*)
 #72 sport*
 #73 MeSH descriptor: [Sports] this term only
 #74 physical near/3 (fit* or train* or therap* or activ*)
 #75 train* near/3 (strength* or aerobic or exercise*)
 #76 exercise* near/3 (treatment or intervent* or program*) OR fitness near/3 (treatment or intervent* or program*):ti
 #77 MeSH descriptor: [Physical Fitness] this term only
 #78 #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77
 #79 #13 and #62 and #78

MEDLINE

1. Heart Score.tw.
2. ETHRISK.tw.
3. (Framingham adj3 score).tw.
4. PROCAM.tw.
5. ASSIGN score.tw.
6. ((risk or score or calcul*) adj5 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*)).tw.
7. (new zealand adj2 risk calculator).tw.
8. HeartScore.tw.
9. (sheffield adj2 table).tw.
10. ASSIGN tool.tw.
11. or/1-10
12. Diabetes Mellitus/
13. Diabetes Mellitus, Type 2/
14. (diabetes adj3 mellitus).tw.
15. exp Hyperglycemia/
16. hyperglycemia*.tw.
17. glycemia*.tw.
18. Smoking/
19. exp "Tobacco Use Cessation"/
20. "Tobacco Use Disorder"/
21. (smoke or smoking or smoker or smokers or smoked).tw.
22. ((cigar* or tobacco or nicotin*) adj2 consum*).tw.
23. exp Hypertension/
24. hypertensi*.tw.
25. ((high or increased or elevated) adj2 blood pressure).tw.
26. Blood Pressure/
27. ((systolic or diastolic) adj blood pressure).tw.
28. exp Dyslipidemias/
29. dyslipidemia*.tw.
30. dyslipoproteinemia*.tw.
31. hypercholesterolemia*.tw.
32. hypercholesteremia*.tw.
33. hyperlipidemia*.tw.
34. hyperlipemia*.tw.
35. lipidemia*.tw.
36. lipemia*.tw.
37. hyperlipoproteinemia*.tw.
38. hyperchylomicronemia*.tw.

39. lipoproteinemia*.tw.
 40. hypertriglyceridaemia*.tw.
 41. Cholesterol/
 42. cholesterol*.tw.
 43. Cholesterol, HDL/
 44. Cholesterol, LDL/
 45. Triglycerides/
 46. triglyceride*.tw.
 47. triacylglycerol*.tw.
 48. ((low or high) adj3 lipoprotein*).tw.
 49. bmi.tw.
 50. overweight.tw.
 51. body mass index/
 52. exp Abdominal Fat/
 53. exp Overweight/
 54. obes*.tw.
 55. (weight adj2 (gain* or chang*)).tw.
 56. (body mass adj (index or indexes or indices)).tw.
 57. abdominal fat.tw.
 58. quetelet* index.tw.
 59. ((high or increased) adj2 body weight).tw.
 60. or/12-59
 61. exp Exercise/
 62. exp Exercise Therapy/
 63. Exercise Tolerance/
 64. exercis*.tw.
 65. (physical adj3 activ*).tw.
 66. (fitness or fitter or fit).tw.
 67. (physical adj3 train*).tw.
 68. ((aerobic or resistance) adj3 (train* or activ*)).tw.
 69. (muscle* adj3 (train* or activ*)).tw.
 70. sport*.tw.
 71. Sports/
 72. (physical* adj3 (fit* or train* or therap* or activ*)).tw.
 73. (train* adj3 (strength* or aerobic or exercise*)).tw.
 74. ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw.
 75. Physical Fitness/
 76. or/61-75
 77. 11 and 60 and 76
 78. randomized controlled trial.pt.
 79. controlled clinical trial.pt.
 80. randomized.ab.
 81. placebo.ab.
 82. clinical trials as topic.sh.
 83. randomly.ab.
 84. trial.ti.
 85. 78 or 79 or 80 or 81 or 82 or 83 or 84
 86. exp animals/ not humans.sh.
 87. 85 not 86
 88. 77 and 87

EMBASE

1. Heart Score.tw.
2. ETHRISK.tw.
3. (Framingham adj3 score).tw.
4. PROCAM.tw.
5. ASSIGN score.tw.
6. ((risk or score or calcul*) adj5 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*)).tw.
7. (new zealand adj2 risk calculator).tw.
8. HeartScore.tw.
9. (sheffield adj2 table).tw.
10. ASSIGN tool.tw.
11. or/1-10
12. diabetes mellitus/
13. (diabetes adj3 mellitus).tw.
14. hyperglycemia/
15. glucose intolerance/
16. glycaemia*.tw.
17. hyperglyc?emia*.tw.
18. exp smoking/
19. smoking cessation/
20. (smoke or smoking or smoker or smokers or smoked).tw.
21. ((cigar* or tobacco or nicotin*) adj2 consum*).tw.
22. exp hypertension/
23. hypertensi*.tw.
24. ((high or increased or elevated) adj2 blood pressure).tw.
25. exp blood pressure/
26. ((systolic or diastolic) adj blood pressure).tw.
27. dyslipidemia/
28. exp hyperlipidemia/
29. dyslipidemia*.tw.
30. dyslipoproteinemia*.tw.
31. hypercholesterolemia*.tw.
32. hypercholesteremia*.tw.
33. hyperlipidemia*.tw.
34. hyperlipemia*.tw.
35. lipidemia*.tw.
36. lipemia*.tw.
37. hyperlipoproteinemia*.tw.
38. exp hyperlipoproteinemia/
39. hyperchylomicronemia*.tw.
40. lipoproteinemia*.tw.
41. hypertriglyceridemia*.tw.
42. cholesterol/
43. cholesterol*.tw.
44. high density lipoprotein cholesterol/
45. low density lipoprotein cholesterol/
46. exp triacylglycerol/
47. triglyceride*.tw.
48. triacylglycerol*.tw.
49. ((low or high) adj3 lipoprotein*).tw.
50. body mass/
51. bmi.tw.
52. overweight.tw.

53. exp abdominal fat/
54. exp obesity/
55. obes*.tw.
56. (weight adj2 (gain* or chang*)).tw.
57. (body mass adj (index or indexes or indices)).tw.
58. abdominal fat.tw.
59. quetelet* index.tw.
60. ((high or increased) adj2 body weight).tw.
61. or/12-60
62. exp exercise/
63. exp kinesiotherapy/
64. exercise tolerance/
65. exercis*.tw.
66. (physical adj3 activ*).tw.
67. (fitness or fitter or fit).tw.
68. (physical adj3 train*).tw.
69. ((aerobic or resistance) adj3 (train* or activ*)).tw.
70. (muscle* adj3 (train* or activ*)).tw.
71. sport*.tw.
72. sport/
73. (physical* adj3 (fit* or train* or therap* or activ*)).tw.
74. (train* adj3 (strength* or aerobic or exercise*)).tw.
75. ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw.
76. fitness/
77. or/62-76
78. 11 and 61 and 77
79. random\$.tw.
80. factorial\$.tw.
81. crossover\$.tw.
82. cross over\$.tw.
83. cross-over\$.tw.
84. placebo\$.tw.
85. (doubl\$ adj blind\$).tw.
86. (singl\$ adj blind\$).tw.
87. assign\$.tw.
88. allocat\$.tw.
89. volunteer\$.tw.
90. crossover procedure/
91. double blind procedure/
92. randomized controlled trial/
93. single blind procedure/
94. 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93
95. (animal/ or nonhuman/) not human/
96. 94 not 95
97. 78 and 96
98. limit 97 to embase

CINAHL

- S91 S87 and S88 and S89 and S90
 S90 S75 or S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86
 S89 S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74

S88 S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or
 S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58
 S87 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12
 S86 (allocat* random*)
 S85 (MH "Quantitative Studies")
 S84 (MH "Placebos")
 S83 placebo*
 S82 (random* allocat*)
 S81 (MH "Random Assignment")
 S80 (randomi?ed control* trial*)
 S79 (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)
 S78 (trebl* blind*)
 S77 (tripl* blind*)
 S76 (doubl* blind*)
 S75 (singl* blind*)
 S74 (MH "Physical Fitness")
 S73 (fitness N3 (treatment or intervent* or program*))
 S72 (exercise* N3 (treatment or intervent* or program*))
 S71 (train* N3 (strength* or aerobic* or exercise*))
 S70 (physical* N3 (fit* or train* or therap* or activ*))
 S69 (MH "Sports")
 S68 sport*
 S67 muscle* N3 (train* or activ*)
 S66 aerobic N3 (train* or activ*) or resistance N3 (train* or activ*)
 S65 physical N3 train*
 S64 fitness or fitter or fit
 S63 physical N3 activ*
 S62 exercis*
 S61 (MH "Exercise Tolerance")
 S60 (MH "Exercise+")
 S59 (MH "Therapeutic Exercise+")
 S58 (High N2 body weight) or (increased N2 body weight)
 S57 quetelet* index
 S56 abdominal fat
 S55 (body mass index) or (body mass indexes) or (body mass indices)
 S54 weight N2 (gain* or chang*)
 S53 obes*
 S52 (MH "Abdominal Fat")
 S51 body mass index
 S50 overweight
 S49 bmi
 S48 (low or high) N3 lipoprotein*
 S47 triacylglycerol*
 S46 triglyceride*
 S45 (MH "Triglycerides")
 S44 (MH "Lipoproteins, LDL Cholesterol")
 S43 (MH "Lipoproteins, HDL Cholesterol")
 S42 cholesterol*
 S41 (MH "Cholesterol")
 S40 hypertriglyceridemia*
 S39 lipoproteinemia*
 S38 hyperchylomicronemia*

S37 hyperlipoproteinemia*
 S36 lipemia*
 S35 lipidemia*
 S34 hyperlipemia*
 S33 hyperlipidemia*
 S32 hypercholesteremia*
 S31 hypercholesterolemia*
 S30 dyslipoproteinemia*
 S29 dyslipidemia*
 S28 (MH "Hyperlipidemia+")
 S27 diastolic blood pressure
 S26 systolic blood pressure
 S25 (MH "Blood Pressure")
 S24 (high or increased or elevated) N2 (blood pressure)
 S23 hypertensi*
 S22 (MH "Hypertension")
 S21 (cigar* or tobacco or nicotin*) N2 consum*
 S20 smoke or smoking or smoker or smokers or smoked
 S19 (MH "Smoking")
 S18 glycemia*
 S17 hyperglycemia*
 S16 (MH "Hyperglycemia+")
 S15 diabetes N3 mellitus
 S14 (MH "Diabetes Mellitus, Non-Insulin-Dependent")
 S13 (MH "Diabetes Mellitus")
 S12 ASSIGN tool
 S11 sheffield N2 table
 S10 HeartScore
 S9 new zealand N2 risk calculator
 S8 calcul* N5 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*)
 S7 score N5 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*)
 S6 risk N5 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*)
 S5 ASSIGN score
 S4 PROCAM
 S3 Framingham N3 score
 S2 ETHRISK
 S1 heart score

Web of Science

#15 #14 AND #13 AND #4 AND #1
 #14 #12 OR #11 OR #10 OR #9 OR #8
 #13 #7 OR #6 OR #5
 #12 TS=(bmi or overweight* or obes* or "weight gain*" or "weight chang*" or "body mass index" or "body mass indexes" or "body mass indices" or "abdominal fat" or "quetelet* index" or "high body weight" or "increased body weight")
 #11 TS=(dyslipidemia* or dyslipoproteinemia* or hypercholesterolemia* or hypercholesteremia* or hyperlipidemia* or hyperlipemia* or lipidemia* or lipemia* or hyperlipoproteinemia* or hyperchylomicronemia* or lipoproteinemia* or hypertriglyceridemia* or cholesterol* or triglyceride* or triacylglycerol* or ((low or high) Near/3 (Lipoprotein*)))
 #10 TS=(hypertensi* or ((high or elevated or increased) Near/2 ("blood pressure")) or "systolic blood pressure" or "diatolic blood pressure")

#9 TS=(smoke or smoking or smoker or smokers or smoked or ((cigar* or tobacco or nicotin*) Near/2 consum*))
 #8 TS=((diabetes Near/3 mellitus) or hyperglycemia* or glycemia*)
 #7 TS=((“new zealand ” Near/2 “risk calculator”) or heartscore or “sheffield table” or “assign tool”)
 #6 TS=((risk or score or calcul*) Near/3 (heart* or cardio* or cardia* or isch?em* or angina or coronary or infarct* or cvd or stroke or strokes or myocard* or cerebrovasc*))
 #5 TS=(“heart score” or ETHRISK or “Framingham score” or PROCAM or “assign score”)
 #4 #3 OR #2
 #3 TS=(exercis* or fitness or fitter or fit or sport* or (physical Near/3 (train* or activ*)) or ((aerobic or resistance or muscle*) near/3 (train* or activ*)))
 #2 TS=((physical* Near/3 (fit* or train* or therap* or activ*)) or (train* Near/3 (strength* or aerobic or exercise*)) or ((exercise* or fitness) Near/3 (treatment or intervent* or program*)))
 #1 TS=((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))

CONTRIBUTIONS OF AUTHORS

PS conceived and wrote the protocol, coordinated the review process, screened search results, extracted data, and wrote the review.

FL provided general advice on the protocol and the review, screened search results, and extracted data.

HP provided general advice and contributed to writing the protocol and the review.

XB contributed to the conception of the protocol, interpretation of results, and writing of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- CIGES, Universidad de La Frontera, Temuco, Chile.
- Centro Cochrane Iberoamericano, Barcelona, Spain.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol required participants “to have high cardiovascular risk defined as risk of death from CVD equal to 5% or more within 10 years” using the SCORE definition as an inclusion criterion. However, this approach yielded no studies for inclusion in this review.

After discussing this issue with the editorial team, we decided to include trials in which an estimate of the average 10-year Framingham risk score could be calculated from the aggregate published data, as well as studies in which this score was 10% CVD risk over 10 years. In trials where insufficient data to estimate a 10-year Framingham risk score were available, alternative criteria were used to determine inclusion, including participants 18 years of age or older, having two or more cardiovascular risk factors, and not having a history of cardiovascular events (acute myocardial infarction or stroke). We add an outcome related to adverse events.

The search strategy for primary studies had to be adjusted to increase specificity. The initial search generated 38,458 citations, which was narrowed down to 6958 titles in this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise; Blood Pressure; Body Mass Index; Cardiovascular Diseases [blood; *prevention & control]; Cholesterol, HDL [blood]; Cholesterol, LDL [blood]; Exercise Tolerance; Quality of Life; Randomized Controlled Trials as Topic; Risk Factors; Smoking

MeSH check words

Humans; Middle Aged