ORIGINAL ARTICLE

Physical activity for secondary prevention of disease

Systematic reviews of randomised clinical trials

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ABSTRACT

Background: Physical activity is recommended for secondary prevention of several diseases but it is not always clear how reliable the evidence is.

Methods: We searched MEDLINE and The Cochrane Library for systematic reviews of randomised clinical trials published 1998-2004.

Results: We identified 30 eligible systematic reviews and excluded 13 that contained trials covered in larger reviews or were older than other reviews on the same subject. Physical activity decreased all-cause mortality in patients with coronary heart disease, odds ratio 0.73 (95% confidence interval 0.54 to 0.98), increased maximum walking time in patients with intermittent claudication by 6.5 min (4.4 to 8.7), and decreased pain in patients with osteoarthritis of the knee, standardised mean difference 0.34 (0.24 to 0.44). There were positive effects also in heart failure, chronic obstructive lung disease, type 2 diabetes and fibromyalgia, but they need confirmation in high-quality trials. Exercise improved quality of life in several conditions and generally led to improved physical performance. An effect was not shown in stroke, asthma, rheumatoid arthritis, acute or chronic low back pain, chronic fatigue syndrome, depression, cystic fibrosis or HIV/AIDS. The occurrence of harms was generally not reported.

Conclusion: Physical activity can have important, and even life-saving, effects as secondary prevention of disease, but more and better trials are needed to fully assess its benefits and harms, in particular trials that compare exercise with drugs.

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Health care focuses increasingly on elements in our daily life that can reduce our risk of catching life-style diseases (primary prevention) or slow down the progression of diseases (secondary prevention) (1). Accordingly, reduction of risk factors has become a common medical undertaking, especially as regards smoking and unhealthy eating (2).

Physical inactivity is also an important risk factor (3, 4), but it has been less branded. One of the reasons could be that health care workers are unaware what the benefits of physical activity are and therefore have not recommended this form of prevention. We present here an overview of the existing systematic reviews of physical activity for secondary prevention of disease.

METHODS

We conducted a MEDLINE search after consultation with a librarian (5). The MeSH terms *"physical activity" OR "physical inactivity" OR exertion OR exercise OR sports OR "physical education and training" OR "exercise therapy" OR "physical fitness" OR "physical endurance" OR "motor activity"* were combined with *meta-analysis OR "systematic review" OR "cochrane database syst rev".*

We also searched The Cochrane Database of Systematic Reviews in The Cochrane Library with the terms *"exercise", "training" or "physical"* restricted to the title. We limited this search to studies published from 1998 to 2004, since Cochrane Reviews are electronic publications that are regularly updated, ideally every two years.

We included systematic reviews that as a minimum contained a methods section and a search strategy for identification of relevant randomised trials and were published 1998-2004. We excluded systematic reviews if they contained observational studies and did not provide results separately for randomised trials, or if the research design was unclear. To judge the reliability of the reviews, we noted whether the authors had considered the quality of the randomisation process, blinding (if appropriate), and exclusions of participants after randomisation.

We included reviews in European languages of trials in healthy people or patients of any age where the intervention groups had performed various types of physical exercise or training that involved the whole body, such as running, walking, aerobics and bicycling, and where the controls had no such prescription or a prescription of less intensity. We selected the same primary outcome as the review authors had done; in a few cases in which it was not clear what was the primary outcome, we selected the one we felt was most relevant for the condition in question. Selection of reviews and outcomes were made by one author (KK); ambiguities were discussed with another (PCG), and the reviews finally selected were read by both authors.

The MEDLINE search resulted in 591 hits (5). We found 61 systematic reviews on secondary prevention of disease, and an additional five from the Cochrane Library alone. We read the full version of the 66 articles and excluded 36 (**Figure 1**). There were considerable overlaps among the 30 remaining reviews, and we therefore selected 17 that were more comprehensive, i.e. contained more trials or had more information on the trials, or were newer than the others.

RESULTS

Of the 17 systematic reviews we included (6-22), 12 were Cochrane Reviews and five reviews from printed medical journals. The conditions reviewed were coronary heart disease, chronic heart failure, stroke, intermittent claudication, chronic obstructive lung disease, asthma, cardiorespiratory fitness in diabetes, rheumatoid arthritis, osteoarthritis, acute and chronic low back pain, physical performance in elderly patients, fibromyalgia syndrome, chronic fatigue syndrome, depression, cystic fibrosis, and HIV/AIDS.

The methodological quality of the reviews was generally good, but many of the included trials were of poor quality, as they did not describe the randomisation method, or adherence to the regimens, or had few participants. There was also considerable heterogeneity in the design of the trials, outcome measures, interventions, and exercise intensity and duration.

Coronary heart disease (12 trials, 2582 patients) (6). The patients had previous myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris or coronary heart disease defined by angiography. The intervention groups carried out cardiac rehabilitation as inpatient, outpatient or community-based exercise training. The duration of the intervention was at least six months. Exercise training, in addition to usual care alone, reduced all-cause mortality, odds ratio 0.73 (95% confidence interval (CI) 0.54 to 0.98) and cardiac mortality, odds ratio 0.69 (0.51 to 0.94). These results were robust to trial quality, e.g. they were confirmed in the subgroup of trials where an adequate randomisation method was described.

Chronic heart failure (nine trials, 801 patients) (7). All the intervention groups performed exercise in the form of supervised cycling; other exercises were walking and swimming, at least twice a week. Duration lasted from eight weeks to over a year. Individual patient data were collected, but the review was not a meta-analysis, despite being so labelled by the authors, but a simple pooling of data as if they had originated from only one trial. This was corrected in response to criticism (23), and the results still showed a large effect on mortality, odds ratio 0.67 (95% CI 0.47 to 0.95) (24). However, the authors used Cox regression that weighs heavily one trial with much longer follow-up than the other trials (24) and which had an unusually large effect, nine versus 20 deaths (25). We replicated the analysis, using relative risk in a fixed effect model as there was no heterogeneity between the nine trials ($P=0.31$, $I^2=15\%$). We found a

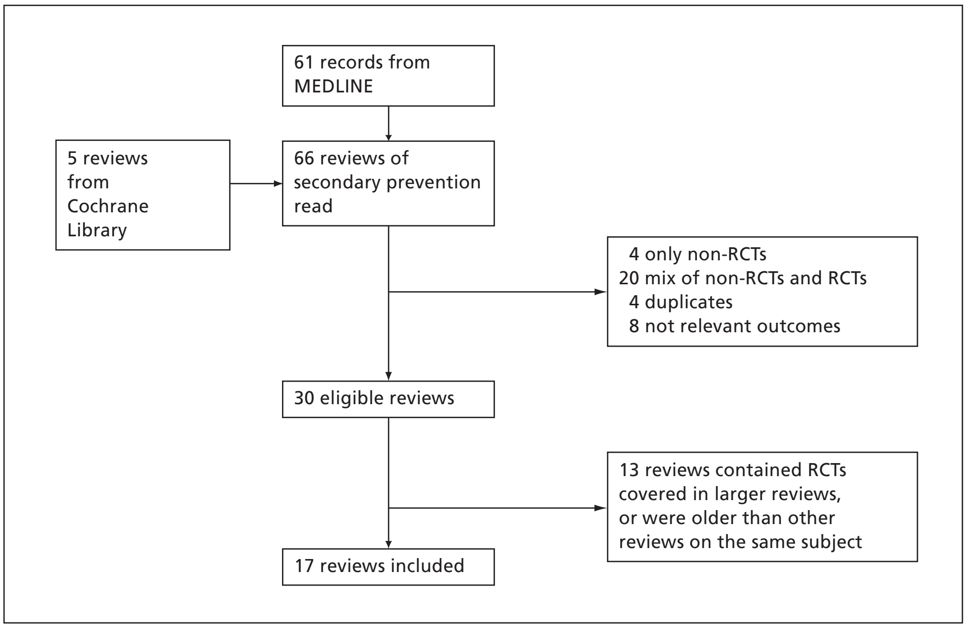

Figure 1. Flow chart for identification of systematic reviews (RCT: randomised clinical trial).

relative risk of 0.88 that was not statistically significant (95% CI 0.70 to 1.10). Another problem with the meta-analysis is that the authors did not assess the quality of the trials. This was done in a Cochrane review that reported that the method of allocation concealment was unclear in most of the trials (26); this review found that exercise increased maximum oxygen uptake, weighted mean difference 2.2 ml/kg/min (1.5 to 2.8) and 6-minute walking distance, 41 m (17 to 65). The possible effect of exercise on mortality needs confirmation in the ongoing large trials (26).

Stroke (12 trials, 289 patients) (8). Trials were mostly of poor quality, with many losses to follow-up. Aerobic exercise and strength training were carried out by intervention groups, three or more days per week for two to 12 weeks after they had had a stroke. Case fatality, death or dependence and disability were the main outcomes, but none was reported to have died and no measures of dependence were reported. Disability was only reported in two trials and showed no significant effect of training. No data were available on incidence of falls, fractures or training induced injury.

Intermittent claudication (three trials, 53 patients) (9). The disease was diagnosed either by questionnaire or clinically. The intervention groups performed various exercises like walking, running and skipping for 12 weeks to 15 months, twice a week. Exercise increased maximal walking time, weighted mean difference 6.5 min (95% CI 4.4 to 8.7) and walking ability overall, but in none of the trial reports was it stated that a blinded assessor had been used.

Chronic obstructive pulmonary disease (10). The disease was diagnosed clinically, or the best recorded FEV1/FVC ratio was below 70%, or the best recorded FEV1 was below 70% of predicted. The intervention was exercise training for at least four weeks. In half of the trials, the outcome assessors were blinded; all trials but one were described as appropriately randomised but no details were given of the methods. Exercise improved maximal exercise capacity, weighted mean difference 5.5 W (95% CI 0.5 to 10.2) (14 trials, 488 patients), 6-minute walk test, weighted mean difference 49 m (26 to 72) (10 trials, 454 patients), and health-related quality of life related to dyspnoea, weighted mean difference 1.0 units (0.8 to 1.2) on a 7-point scale (nine trials, 519 patients).

Asthma (11). The participants were eight years and older with asthma diagnosed by a physician or by objective criteria such as bronchodilator reversibility. The intervention was aerobic exercise for 20-30 min 2-3 times a week for at least four weeks. The trials were small and generally of poor quality. Exercise had no significant effect on lung function or episodes of wheeze, but improved maximum oxygen uptake by 5.6 ml/kg/min (95% CI 3.9 to 7.2) (five trials, 114 patients) and work capacity by 28 W (23 to 33) (one trial, 20 patients).

Cardiorespiratory fitness in type 2 diabetes mellitus (seven trials, 266 patients) (12). The trials were of low quality, none was blind or had adequate allocation concealment. Regular aerobic exercise, cycling or walking, three times a week for 20 weeks, on average, had a beneficial significant effect on $VO_{2\,max}$, standardised mean difference (SMD) 0.53 (95% CI 0.18 to 0.88), and on HbA_{1C}, SMD –0.71 (–1.10 to –0.32).

Rheumatoid arthritis (six trials, about 13 patients per group, on average) (13). Participants had classical or definitive rheumatoid arthritis according to the American Rheumatism Association criteria, interventions were exercise for 20 min twice a week for at least six weeks. Data were not pooled. None of the trials described the treatment allocation, and only two had blinded assessors; no significant effects were reported for those two trials.

Osteoarthritis of the knee (17 trials, 2562 patients) (14). Muscle strengthening and aerobic exercise were performed for a range of four to 12 weeks. As expected, the effect was smaller in trials of good quality, but there was a clear effect even in these trials; for pain, SMD was 0.34 (0.24 to 0.44) in trials with blinded outcome assessment and 0.35 (0.25 to 0.45) in trials with intention-to-treat analysis. There was also an effect on self-reported physical function, SMD 0.26 (0.17 to 0.35) and SMD 0.28 (0.19 to 0.37), respectively.

Acute low back pain (four trials, 888 patients) (15). Patients with or without pain radiation to the legs were included whereas patients with specific pathology were excluded. Physical activity was various types of aerobic and non-aerobic exercise. The trials were not pooled. There was no convincing evidence that exercise was effective for the treatment of acute low back pain.

Chronic low back pain (16 trials, 1730 patients) (16). Participants performed strengthening training or aerobic exercise. The authors' predefined outcomes were pain, work disability, back specific function, generic health status and satisfaction with care. The authors scored 51 trials for methodological quality, and excluded 34, 14 of which were of medium or high quality. The reasons for all these exclusions were not explained and no numerical data were presented, only P-values were given. The authors call for more high-quality trials and more appropriate outcomes. We were unable to draw conclusions based on this review.

Physical performance in institutionalised elderly patients (16 trials, 1269 patients) (17). Patient suffered from multiple diagnoses that were not described. Progressive exercise of various types were attended by intervention groups for ten weeks up to two years, one to seven times a week. The authors conclude that there is strong evidence for a positive effect of physical training on muscle strength and mobility. However, this means that there is concordant results in more than half of the trials of high quality. No data on outcomes are presented, and the review basically relies on vote counting (number of significant results compared to non-significant results). We were unable to draw conclusions based on this review.

Fibromyalgia syndrome (18). Patients were diagnosed according to standard criteria. Interventions were aerobics and other types of exercise. In a subgroup of four high-quality aerobics studies (149 patients, intensity 40-85% of maximal heart rate for 20 min at a time for at least six weeks), there was no significant effect on pain whereas there were substantial short-term improvements in pain threshold of tender points, SMD 1.19 (95% CI 0.64 to 1.75), and in cardiovascular fitness, SMD 0.79 (0.37 to 1.21). The outcome assessors were blinded, but the trials were small and none of them appeared to have had concealed allocation of the patients.

Chronic fatigue syndrome (five trials, 286 patients) (19). The intervention groups performed aerobic exercise three to five times a week for 12 weeks. The five trials were small but of good quality; all were considered to have adequate allocation concealment, four used intention-to-treat analysis and four measured compliance. Exercise reduced fatigue, SMD –0.77 (95% CI –1.26 to –0.28) and improved physical functioning, SMD –0.64 (–0.33 to –0.96). There were 23 versus 13 drop-outs.

Depression (14 trials) (20). The disease was confirmed by any method of diagnosis and any severity was included. The interventions were various types of exercise for four to 12 weeks. It was not possible to draw conclusions because of the poor quality of the trials, brief follow-up and inclusion of non-clinical volunteers.

Cystic fibrosis (six trials, 184 participants) (21). Participants were of any age and any disease severity, diagnosed on clinical criteria and sweat testing or genotype analysis. Different kinds of exercise were used. Data were not pooled. None of the trials described the treatment allocation or had blinded assessors, and conclusions were furthermore limited by the small size, short duration and incomplete reporting of the trials. A three-year trial (65 patients) reported less decline in annual forced vital capacity in the exercise group, weighted mean difference 2.2% of predicted (95% CI 0.5 to 3.9).

HIV/AIDS (eight trials, about ten patients per group, on average) (22). The intervention was aerobic exercise three times a week for at least four weeks. These small trials had large drop-out rates, the treatment allocation was not described, and only two of them were blinded. No reliable conclusions can be drawn.

DISCUSSION

Our assessment of the value of regular exercise for secondary prevention of disease is limited by the quality of the trials. Most trials were small and therefore of doubtful validity because of possible publication bias and other biases. Furthermore, their results may not be generalisable since an effect seen in a team of highly motivated researchers and patients may not be reproducible in routine clinical practice. The randomisation method was rarely described, and trials with unknown methods have been shown to exaggerate the estimated effect by about 30%, on average, measured as odds ratio (27).

Participants in trials of exercise cannot be blinded, unless there is also some level of regular exercise in the control group, but the outcome assessors can. Lack of blinding of the assessors was frequent. It is less of a problem when the outcome is the direct effect of the exercise, e.g. maximum oxygen uptake, but can be important for disease-specific outcomes. For example, encouragement during a 6-minute walking test was found to bias the results by 30 m in patients with chronic obstructive lung disease (28).

There were also problems with drop-outs. Patients who do not adhere to the training programmes will be expected to have a worse prognosis than those who do, but they were rarely accounted for in an intention-to-treat analysis.

A major problem was that the occurrence of harms, e.g. strains and sprains, fractures, infections, and traffic injuries, was generally not reported.

Taking the various shortcomings of the trials into account, we believe there is good evidence from systematic reviews that regular exercise has important disease-specific benefits in heart disease, intermittent claudication, chronic obstructive lung disease, and type 2 diabetes. As expected, exercise led to improved physical performance in several additional conditions.

HEART DISEASE

The effect of exercise for secondary prevention of coronary heart disease is a robust result as it was also found in subsamples of high-quality trials (6). Since the disease is common, the documented effect on mortality of training patients for at least six months is very important. The effect corresponds to one patient saved for every 50 patients which is about the same effect as that which is obtained by treating patients with myocardial infarction with either aspirin or streptokinase (29).

There was also a possible effect of exercise on mortality from heart failure, but this result should be confirmed by the ongoing large trials before any definite conclusions can be drawn. It would be interesting also from an academic standpoint if this effect were true as medical textbooks until recently adviced that such patients should avoid exercise to prevent further deterioration of functional capacity (30, 31).

INTERMITTENT CLAUDICATION

The effect of training could not be established reliably in the systematic review as the trials were small and unblinded. A subsequent large trial of 882 patients was handicapped by the fact that the training group was also advised to stop smoking (32). After one year, 23% in the intervention group and 15% in the control group had improved their maximum walking distance (P=0.008). Whether this effect is too large to be explained by smoking cessation alone is difficult to say; differential encouragement in a walking test in an unblinded trial could also influence the result.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Progressive aerobic training of patients with chronic obstructive lung disease has no effect on lung function, but markedly enhances aerobic capacity (33). Thereby, the main disease symptom, dyspnoea, is reduced. Patients reported beneficial effects on walking distance and frequency and severity of symptoms after just four weeks of training (33) which suggests that training may exert at least part of its effect by reducing anxiety symptoms.

TYPE 2 DIABETES

The mechanisms whereby exercise exerts its beneficial effects on chronic diseases are multifactorial, but a major mechanism is muscle contraction-induced enhanced insulin sensitivity (34). The effect of exercise (12, 35) is comparable to the effect of metformin (36) and it was obtained without weight loss. This effect is very important, but as the trials of exercise were of low quality, it needs confirmation in a high-quality trial.

DEPRESSION

An effect of exercise on depression has not been shown. Exercise has been compared with the antidepressant sertraline in a trial of 156 patients that found a similar effect of the two interventions after four months (37), but since the effect of selective serotonin reuptake inhibitors is small (38) and there was no untreated control group, this result cannot prove an effect of exercise. A follow-up of this trial after ten months that focused on the subgroup of patients in remission reported better effect of exercise (39), but as the follow-up was unplanned and as the diagnostic criteria were changed, this result is also doubtful.

MUSCULOSKELETAL DISORDERS

The most promising result was the effect shown for osteoarthritis (14). The effect on pain was not large, however (standardised mean difference of 0.34). For comparison, the effect of nonsteroidal, anti-inflammatory drugs on pain in rheumatoid arthitis is 0.84 (40).

The possible effect on fibromyalgia is also interesting. Patients with fibromyalgia have low aerobic capacity (41-43) and physical inactivity may contribute to the pathogenesis. However, the result should be confirmed in a large trial of adequate quality before it can be concluded whether exercise is a worthwhile treatment in this difficult-to-treat disease where medical treatment has been disappointing (44).

There was little evidence for an effect in other musculoskelatal disorders (rheumatoid arthritis, and acute and chronic low back pain) or in the chronic fatigue syndrome.

CONCLUSIONS

An important effect of exercise has been unequivocally demonstrated for secondary prevention of coronary heart disease and for osteoarthritis. It may also exist for heart failure, intermittent claudication, chronic obstructive lung disease, type 2 diabetes and fibromyalgia, but the positive results need confirmation in additional trials. There is an urgent need for large high-quality trials that also assess harms reliably, and for trials that compare exercise with drugs.

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