Physical activity for primary prevention of disease

Systematic reviews of randomised clinical trials

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ABSTRACT
Background: Drugs are heavily promoted for primary prevention of disease whereas possible benefits of physical activity have received less attention. We have studied whether there is reliable evidence that exercise is effective.

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

Results: We identified 31 eligible reviews and excluded 20 that contained trials covered in larger reviews or were older than other reviews on the same subject. The 11 included reviews comprised altogether 252 trials and 16,179 participants. Generally, the included trials were of poor quality. The most reliable result was that exercise in the elderly can reduce falls resulting in injury, relative risk 0.7 (95% confidence interval 0.5 to 0.9), although this effect could be due to modification of risk factors. Other results were a reduction in systolic blood pressure by 3.8 mmHg (2.7 to 5.0) and diastolic blood pressure by 2.6 mmHg (1.8 to 3.4), beneficial changes in blood lipids, a positive effect on bone mineral density in the spine of 1.8% (0.6% to 3.0%), and a lack of effect on smoking cessation. The reporting of harms of exercise was virtually non-existent.

Conclusions: Exercise can have important benefits. There is a need for large trials that live up to accepted standards and include measurement of harms, in particular for trials that compare exercise with drugs.

Dan Med Bull 2005;52:86-89.

The level of the necessary physical activity in the population has been steadily decreasing throughout many years in developed countries because of increased mechanisation. At the same time, the pharmaceutical industry has become more powerful in setting the agenda for healthcare research and practice. The proportion of industry funded clinical research increased from 32% in 1980 to 60% in 2000 in USA (1) and there is systematic bias that favours new drugs (1, 2).

Drugs are heavily promoted for use in healthy people with risk factors, such as increased blood pressure and low bone mineral content, although increased physical activity could also be effective. Physical activity has the advantage of addressing several risk factors simultaneously; no single drug has such a broad spectrum of possible benefits. Furthermore, it has immediate benefits in terms of increased well-being, and by prescribing physical activity, adverse effects of drugs can be avoided.

Primary prevention of disease should be the main target of health care, especially for lifestyle diseases. If effective, increased physical activity could therefore become one of the most important improvements in health care within the next decade. Since it is not entirely clear what the benefits and harms are, we did an overview of existing systematic reviews of randomised clinical trials that had studied the effects of physical activity for primary prevention of disease.

METHODS

We conducted a MEDLINE search after consultation with a librarian. 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 during 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. In order to judge the reliability of the reviews, we noted whether or not 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 in which 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 when 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 was made by one author (KK); ambiguities were discussed with another (PCG), and the reviews finally selected were read by all authors.

Our MEDLINE search resulted in 591 records (**Figure 1**). We excluded 277 that were not reviews of exercise and ten that were not systematic reviews according to the title. The remaining 304 abstracts were read and a further 225 articles were excluded for various reasons (Figure 1). The search in the Cochrane Database yielded 46 articles, of which 45 were excluded (20 were already found in the MEDLINE search, 22 were not reviews of exercise, and three were systematic reviews of secondary prevention of disease).

This left 80 potentially eligible reviews, of which 49 were excluded after careful reading (Figure 1). Twelve of these only contained observational studies, 23 were a mix of randomised trials and observational studies, and four had not described the design of the studies. Three of the remaining reviews had no relevant outcome, two had too narrow focus (i.e. measured only abdominal fat when addressing obesity), and five were non-systematic in their search strategy.

There was considerable overlapping in the remaining 31 systematic reviews and we therefore selected 11 that were more comprehensive, i.e. contained more trials, had more information on the trials, or were more recent than the others.

RESULTS

Of the 11 systematic reviews we included (3-13), six were Cochrane Reviews and five reviews from printed medical journals. The conditions reviewed were hypertension, hyperlipidaemia, osteoporosis, prevention of falls, smoking cessation, obesity, physical disability in older people, self-esteem in children and young people, and sleeping problems in adults. The reviews comprised altogether 252 trials and 16,179 participants.

Methodological quality. The methodological quality of most of the included trials in the reviews was poor. The quality of the reviews was better. Six reviews (4, 6, 7, 11-13) reported on allocation concealment for the reviewed trials. Two reviews included trials in any language (6, 11), three included only trials in English (3-5), and six gave no information on language. Two reviews on obesity (9, 10) did not present 95% confidence intervals for their results; one had violated the principle of randomisation by calculating separate weighted means for the exercise arms and the control arms in the

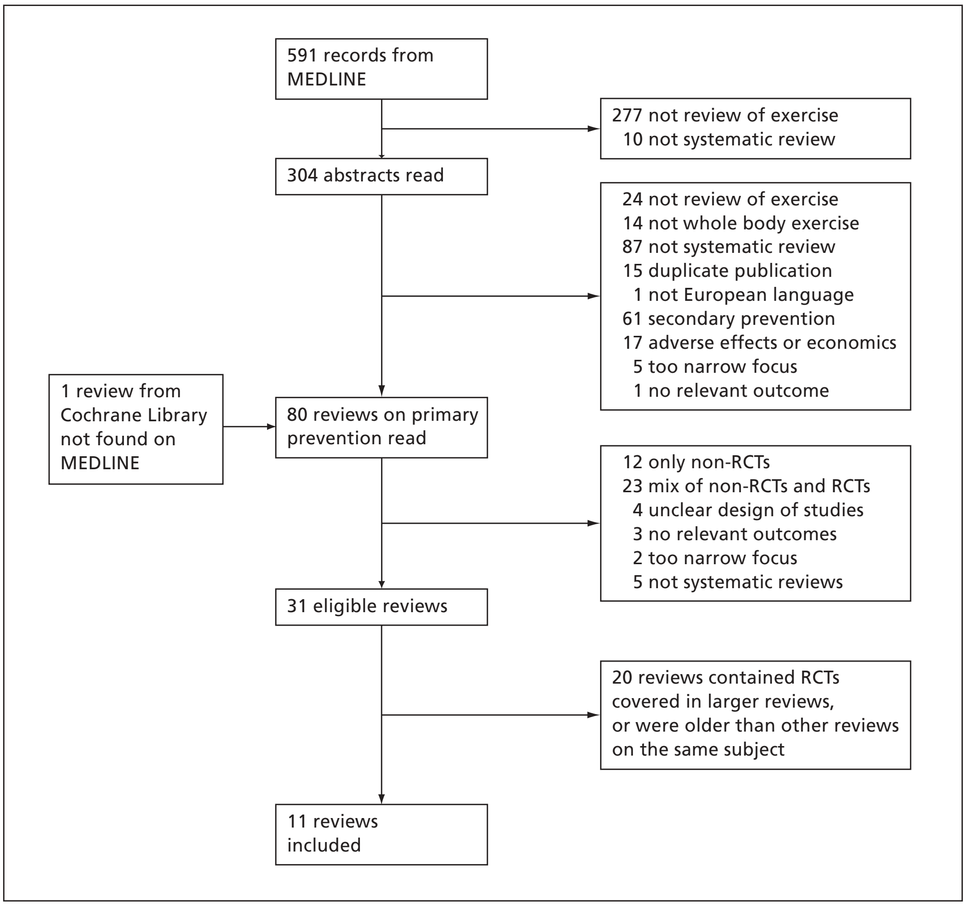

Figure 1. Flow chart for identification of systematic reviews (RCT: randomised clinical trial).

trials (10), and the other presented means but it was unclear whether these were weighted (9).

The adherence to the exercise programs was rarely reported, but one review (8) commented that the compliance was high and that there were methods, like supervision during exercise sessions and telephone follow-up of non-attenders, to ensure adherence to the program.

Hypertension (53 trials, 2419 persons) (3). The participants were a mix of hypertensive and normotensive. The intervention group carried out aerobic exercise, with a median duration of three months, and in most of the trials the controls were instructed not to modify their lifestyle, including physical activity. The mean systolic blood pressure dropped by 3.8 mmHg (95% confidence interval 2.7 to 5.0), and the diastolic blood pressure by 2.6 mmHg (1.8 to 3.4). The effect was lower in trials with long follow-up. Subgroup analysis of hypertensive patients demonstrated a decrease in systolic blood pressure by 4.9 mmHg (2.7 to 7.2) and diastolic blood pressure by 3.7 mmHg (1.8 to 5.7).

Blood lipids, aerobic exercise (31 trials, 1833 persons) (4). The participants were hyperlipidaemic or normolipidaemic; none of the trials had adequate allocation concealment. The intervention groups performed aerobic exercise or resistance training. Aerobic exercise programs with a mean duration of six months resulted in favourable but marginal changes in blood lipids (decreases of 0.1 mmol/l in total cholesterol, triglycerides and low density lipoprotein, with 95% CI from 0.0 to 0.1 or 0.2), and an increase in high density lipoprotein of 0.1 mmol/l (0.0 to 0.2). Comparisons of exercise intensities showed that programs at intensities greater than 70% $VO_{2\ max}$ produced larger changes in cholesterol and low density lipoprotein. Resistance training gave inconclusive results.

Blood lipids, walking (25 trials, 1176 persons) (5). Many participants had blood lipids in the normal range. Most were randomised to brisk walking for at least 30 min. five days a weak or to a control group, for at least eight weeks. The review did not report on allocation concealment. Compliance was only reported in half of the trials, and only one trial used intention-to-treat analysis. Total cholesterol declined by 3.4 mg/dL (95% CI 0.7 to 7.5) and low-density lipoprotein by 5.5 mg/dL (1.2 to 9.9). There were no significant changes in high-density lipoprotein or triglycerides.

Osteoporosis (18 trials, 1423 persons) (6). The authors criticised many of the trials for having low methodological quality, especially for allocation concealment and blinding. The interventions were aerobics, weight bearing program, walking and resistance exercises, with widely varying durations. There was a positive effect on bone mineral density in the spine of 1.8% (0.6% to 3.0%), but only one small, negative trial had adequate allocation concealment. Vertebral fractures were only reported in one trial, there were six in 49 persons in the intervention group and five in 48 in the control group.

Prevention of falls in elderly people (14 trials, 2046 persons) (7). Eleven trials of group exercise found a nonsignificant effect on number of fallers, relative risk 0.89 (0.78 to 1.01). Three trials of an individually tailored exercise program with progressive muscle strengthening, balance retraining and a walking plan found fewer falls, relative risk 0.80 (0.66 to 0.98), and fewer falls resulting in injury, relative risk 0.67 (0.51 to 0.89). These three trials all had adequate concealment of allocation.

Smoking cessation (eight trials, 744 persons) (8). There was no description of the allocation concealment and a meta-analysis was not done. The authors claimed that the biggest trial, of 281 patients, showed a significant benefit from the exercise program at long term follow-up, but they reported a nonsignificant odds ratio of 2.36 (0.97 to 5.70).

Obesity, weight reduction (nine trials, 520 persons) (9). Five short term trials of 8-16 weeks duration were characterised by relatively high energy expenditures and an average weight loss of 0.26 kg/week (method unclear, and no confidence interval; the result is therefore of doubtful validity). Four long term trials of at least six months duration resulted in a reduction of 0.06 kg/week, i.e. 3 kg/yr (no confidence interval).

Obesity, weight regain (eight trials, 475 persons) (10). Review of trials of overweight or obese persons who had obtained a weight reduction of more than 5% of their initial weight after randomisation to exercise training or control (with or without diet). After the weight reduction phase there was a passive follow-up period of a mean duration of 20 months. The difference in mean weight regain was 1.8 kg (90 g/month, no confidence interval) favouring a better weight maintenance in the exercise groups. The analysis is unreliable, however, as the exercise and control arms were pooled separately.

Reduction of physical disability in older adults (62 trials, 3674 persons) (11). Cochrane Review, also published in a paper-based journal, with the same results. Intervention groups carried out progressive resistance strength training for 2-104 weeks. The review did not find an effect of training on physical disability, defined as impairments and limitations in simple activities (ten trials, 722 persons, standardised mean difference (SMD) 0.01 (95% CI –0.14 to 0.16)). There was a positive effect on lower limb strength (41 trials, 1955 persons, SMD 0.68 (0.52 to 0.84), but most of the trials were considered of poor quality, and the effect was much smaller in trials with blinded assessors, SMD 0.29 (0.12 to 0.47).

Self-esteem in children and young people (23 trials, 1821 persons) (12). It is not possible to draw firm conclusions as many trials had allowed co-interventions in addition to exercise in the experimental group, many trials were of low quality and were small, and some were of healthy people and not of people with reduced self-esteem. There was a surprisingly large effect in a high-quality trial of 24 healthy 3-5 year-old boys and girls, SMD 1.33 (0.43 to 2.23) whereas three trials (136 persons) with a moderate risk of bias showed a nonsignificant SMD of 0.21 (-0.17 to 0.59).

Sleep problems (one trial, 48 persons) (13). Intervention group performed low-impact aerobics or brisk walking 30-40 minutes four times a week for 16 weeks. Mean age of the participants was 62 years. The persons fell asleep 12 minutes quicker (P=0.007), slept 42 minutes longer (P=0.05) and improved by 3.4 points (1.9 to 5.4) on a sleep quality index scale from 0 to 21.

DISCUSSION

We found important effects of exercise. The literature was generally of low quality, however, and there is a need for large randomised trials and for systematic reviews that live up to accepted standards (14-17). Although we restricted our literature searches to systematic reviews published fairly recently, between 1998 and 2004, we had to exclude 102 reviews (Figure 1) that did not fulfil even the most basic requirements for systematic reviews, the existence of a methods section and a search strategy. We excluded an additional 27 reviews because the authors had paid no attention to study design but had mixed randomised trials with observational studies, or had not described the research design. Even in the 11 reviews we included, there were substantial methodological problems, primarily related to lack of quality assessment of the included trials.

The most reliable result seems to be that exercise in the elderly can reduce falls resulting in injury. Poorly designed and reported studies tend to exaggerate the estimated effect (18), and many of the outcomes were intermediate ones. It is therefore difficult to know, based on the systematic reviews, whether exercise has other beneficial effects for primary prevention.

However, if exercise reduces blood pressure, as suggested in the reviews, even a minor effect could be important from a public health perspective since lowering of blood pressure is a good predictor of reduced cardiovascular morbidity and mortality. Another interesting finding was the reduction in low-density lipoprotein of 5.5 mg/dL (5), since a reduction of 7.7 mg/dL obtained with statins has been reported to reduce the risk of ischaemic heart disease by 21% after six or more years (5).

Recent, large randomised trials not covered in the reviews have demonstrated major benefits of exercise for prevention of type 2 diabetes. A Chinese trial found a cumulative incidence of diabetes at six years of 41% in an exercise group and 68% in the control group (19); a Finnish trial found that the risk of diabetes was reduced by 58% in an exercise/diet group although the difference in weight loss after two years was only 2.7 kg (20); and a US study found that a lifestyle modification program with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week reduced the incidence of diabetes by 58% compared with placebo, and that the lifestyle intervention was significantly more effective than metformin (21).

None of the three trial reports described the randomisation method in detail, but the groups were comparable at baseline.

Exercise has obvious effects that do not require testing in randomised trials. It it is easier to climb stairs and raise oneself after a fall if the muscles are regularly trained, and exercise can be pleasant in itself and may lead to helpful social contacts in sports clubs. Unfortunately, harms were poorly monitored and reported in the trials, and one of the reviews noted that several trials reported drop-outs due to pain or injury, but failed to report any adverse events (11).

Public health initiatives have often been introduced based on less evidence than provided for the effects of exercise. But there have also been serious set-backs, recently most notably provided by hormone replacement therapy where observational studies suggested a 50% reduction in heart disease (22), but the subsequent randomised trials showed that the treatment is harmful (23, 24). Many observational studies suggest that there could be major health benefits of exercise, but because of the "healthy jogger effect", it is important to have these confirmed or refuted in randomised trials that are sufficiently large to allow estimation not only of clinically beneficial outcomes, but also of the occurrence of harms, e.g. strains and sprains, fractures, infections, and traffic injuries.

Physiologically, excercise has many benefits (25) and it could be that some important clinical effects do not become apparent in short-term trials but require a lifestyle change that persists over many years. It is also a problem with exercise studies that the controls have some level of physical activity which is difficult to measure and incorporate into the results, and that this activity may increase when the persons are told that they have been randomised to a control group without exercise.

We conclude that important effects of exercise have been demonstrated for primary prevention of disease. Many questions remain, however, and although it can be hard to demonstrate the effects of exercise in randomised trials, it should be tried. In particular, there is an urgent need for trials that compare exercise with drugs. Since pharmaceutical companies are unlikely to fund such trials, funding should be provided from public sources.

Conflicts of interest: none.

Financial support: none.

Contributions of authors: Peter C. Gøtzsche conceived the project and wrote the protocol for the study, Katrine Karmisholt did the literature search, organised the data and wrote the first draft of the manuscript. All authors contributed to the protocol and the manuscript and read the included reviews. Peter C. Gøtzsche is guarantor.

Acknowledgement: We thank Bente Klarlund Pedersen for helpful advice.

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