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EUROPEAN SOCIETY OF CARDIOLOGY®

Review

Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis

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Received 29 August 2007 **Accepted** 7 December 2007

Background Over the past several decades, numerous large cohort studies have attempted to quantify the protective effect of physical activity on cardiovascular and all-cause mortality. The aim of the authors' review was to provide an up-to-date overview of the study results.

Methods In a systematic MEDLINE search conducted in May 2007, the authors included cohort studies that assessed the primary preventive impact of physical activity on all-cause and cardiovascular mortality. The authors reported risk reductions on the basis of comparison between the least active and the most active population subgroups, with the least active population subgroup as the reference group. Random-effect models were used for meta-analysis.

Results A total of 33 studies with 883 372 participants were included. Follow-up ranged from 4 years to over 20 years. The majority of studies reported significant risk reductions for physically active participants. Concerning cardiovascular mortality, physical activity was associated with a risk reduction of 35% (95% confidence interval, 30–40%). All-cause mortality was reduced by 33% (95% confidence interval, 28–37%). Studies that used patient questionnaires to assess physical activity reported lower risk reductions than studies that used more objective measures of fitness.

Conclusions Physical activity is associated with a marked decrease in cardiovascular and all-cause mortality in both men and women, even after adjusting for other relevant risk factors. *Eur J Cardiovasc Prev Rehabil* 15:239–246 © 2008 The European Society of Cardiology

European Journal of Cardiovascular Prevention and Rehabilitation 2008, **15**:239–246

Keywords: exercise, mortality, physical activity, physical fitness

Introduction

Physical inactivity increases the risk of developing a variety of diseases, including overweight, diabetes, hypertension, osteoporosis, and depression. Moreover, inactivity has been associated with higher all-cause and cardiovascular mortality [1,2]. Numerous large cohort studies assessed self-reported physical activity, objective measures of physical fitness, activities of daily living, and systematic exercise training to determine the risks associated with a sedentary lifestyle in men and women [1]. According to a study by Mokdad *et al.* [3], physical inactivity, along with smoking and malnutrition, is one of the most important lifestyle-related risk factors.

Although most studies have reported a significant relative reduction in mortality for physically active participants, the range of benefit has varied considerably. For example, Myers *et al.* [4] reported a reduction in all-cause mortality of 72% between their most and least fit male participants during 6 years of follow-up, whereas Lee *et al.* [5] found a risk reduction of only 13%. Risk reduction may also vary depending on adjustment for important covariables such as blood pressure or diabetes. However the extent to which the risk reduction achieved through physical activity is attenuated by adjusting for other important risk factors remains unclear [6,7].

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Table 1 Study characteristics

Study	Population	Sex	Age	Physical activity assessed by	Follow-up in years (mean)	Results adjusted for
Arraiz *et al.* [8]	9792	Men and women	30–69	Fitness test	7	Age, sex, BMI, smoking
Barengo *et al.* [9]	32 677	15 853 men; 16 824 women	30–59	Self-report	20	Age, study year, BMI, systolic blood pressure, cholesterol, education, smoking, other physical activity
Blair *et al.* [10][a]	9777	Men	20–82	Fitness test	5	Age
Blair *et al.* [11]	32 421	25 341 men; 7080 women	20–88	Fitness test	8	Age, smoking, cholesterol, blood pressure, health status
Bucksch [12]	7187	3742 men; 3445 women	30–69	Self-report	16	Age, smoking, BMI, cardiovascular risk factors, alcohol use, diet, chronic disease index, social status
Carlsson *et al.* [13]	27 734	Women	51–83	Self-report	5	Age, smoking, education, number of children, hormone replacement, fruit/vegetable intake, BMI, blood pressure, comorbidity
Church *et al.* [14]	22 167	Men	Mean 43	Fitness test	14	Age, examination year, alcohol use, smoking, family history of CVD, cholesterol, BMI, fasting glucose
Davey *et al.* [15]	6702	Men	40–64	Self-report	25	Age, employment, smoking, BMI, forced expiratory volume
Evenson *et al.* 2004 [16]	5712	3000 men, 2712 women	≥ 30	Fitness test	24, 26	Age, smoking, education, alcohol use, BMI, race, cholesterol
Fang *et al.* [17]	9790	3730 men, 6060 women	25–74	Self-report	17	Age, sex, race, family income, education, diabetes, smoking, systolic blood pressure, cholesterol, illnesses affecting eating
Gregg *et al.* [18]	7553	Women	≥ 65	Self-report	7	Age, smoking, BMI, stroke, diabetes, hypertension, self-rated health status
Hillsdon *et al.* [19]	10 522	Men and women	35–64	Self-report	10	Age, sex, smoking, alcohol use, health status, social class
Hu *et al.* [20]	80 921	Women	30–55	Self-report	24	Age, smoking, family history of CVD, menopausal status, hormone use
Hu *et al.* [7]	47 212	22 528 men; 24 684 women	25–64	Self-report	18	Age, study year, smoking, systolic blood pressure, cholesterol, BMI, diabetes, education
Kaplan *et al.* [21]	6131	Men and women	16–94, mean 43	Self-report	28	Age, sex, race, education, health status, social isolation
Katzmarzyk *et al.* [22]	19 223	Men	20–83, mean 43	Fitness test	10	Age, year of examination, alcohol use, smoking, family history of CVD, BMI
Katzmarzyk *et al.* [23]	5421	Women	20–69	Self-report	12	Age, smoking, alcohol use, waist circumference
Khaw *et al.* [24]	22 191	9984 men; 12 207 women	45–79	Self-report	8	Age, BMI, systolic blood pressure, cholesterol, smoking, alcohol use, diabetes, social status
Kohl *et al.* [25]	8108	Men	20–84, mean 42	Fitness test	8	Age, glycemic status, systolic blood pressure, cholesterol, BMI, family history of CVD, smoking
Kushi *et al.* [26]	33 154	Women	55–69	Self-report	7	Age, age at menarche/menopause/first live birth, parity, smoking, alcohol use, BMI, waist-to-hip ratio, energy intake, oestrogen use, hypertension, diabetes, education, marital status
Lee *et al.* [5]	17 231	Men	Mean 46	Self-report	22, 26	Age, smoking, hypertension, diabetes, early parental death
Leon *et al.* [27]	12 138	Men	35–57, mean 46	Self-report	16	Age, education, smoking, cholesterol, diastolic blood pressure, BMI
Matthews *et al.* [28]	67 143	Women	40–70, mean 52	Self-report	6	Age, marital status, education, income, smoking, alcohol use, number of pregnancies, oral contraceptive use, menopausal status, diabetes, hypertension, respiratory disease, chronic hepatitis
Richardson *et al.* [29]	9611	Men and women	51–61	Self-report	8	Age, sex, race, self-rated health, history of cancer, obesity, CVD risk
Rockhill *et al.* [30]	80 348	Women	30–55	Self-report	14	Age, smoking, alcohol use, height, BMI, hormone use
Schooling *et al.* [31]	56 167	18 759 men; 37 417 women	> 65	Self-report	4	Age, sex, education, alcohol use, smoking, income, BMI
Stevens *et al.* [32]	5366	2860 men; 2506 women	Mean 46	Fitness test	22, 26	Age, education, smoking, alcohol use, diet
Trolle-Lagerros *et al.* [33]	99 099	Women	30–49	Self-report	11	Age, education, BMI, alcohol use, smoking
Vatten *et al.* [34]	54 248	26 515 men; 27 769 women	≥ 20	Self-report	16	Age, BMI, marital status, education, alcohol use, smoking, blood pressure, blood pressure medication
Wannamethee *et al.* [35][b]	4311	Men	40–59	Self-report	4	Age, smoking, BMI, social class, self-rated health, other physical activity
Wei *et al.* [36]	25 714 normal weight	Men	Mean 44	Fitness test	10	Age, examination year, BMI, family history of CVD, CVD, diabetes, cholesterol, hypertension, smoking
Weller and Corey [37]	6620	Women	> 30	Self-report	7	Age
Wisloff *et al.* [38]	56 072	27 143 men; 28 929 women	Mean 47	Self-report	16	Age, BMI, marital status, education, alcohol use, smoking, blood pressure

[a]Outcome cardiovascular mortality; all-cause mortality was extracted from the larger 1996 study by Blair. [b]$N = 4311$ men with no history of coronary heart disease. BMI, body mass index; CVD, cardiovascular disease.

The aim of this systematic review was therefore to summarise the results of the largest cohort studies that examine the effects of physical activity on cardiovascular and all-cause mortality.

Methods

In a systematic MEDLINE search conducted in May 2007, the authors identified prospective cohort studies that assessed the impact of physical activity on all-cause and cardiovascular mortality. Studies analysing populations with a history of cardiovascular or other serious diseases were excluded. To be included in the authors' review, studies needed to be published in English or German and have a minimum population size of 5000 and a minimum follow-up of 3 years. The authors reported risk reductions on the basis of comparison between the least active and the most active population subgroups, with the least active population subgroup as the reference group. In cases where results were adjusted for relevant variables in addition to age, the authors selected the results of the most extensively adjusted models.

Meta-analyses were performed using a generic inverse variance approach with RevMan version 4.2 (The Cochrane Collaboration, Copenhagen, Denmark). Funnel plots were used to assess publication bias. The results of the meta-analysis were presented using forest plots stratified according to the mean by which physical activity had been assessed (i.e. self-reported or objectively measured). Random-effect models were used to pool study results. Heterogeneity was assessed using χ^2 and I^2 methods. The authors performed sensitivity and subgroup analyses to determine the impact of sex, the number of variables in the final model, and the number of physical activity categories.

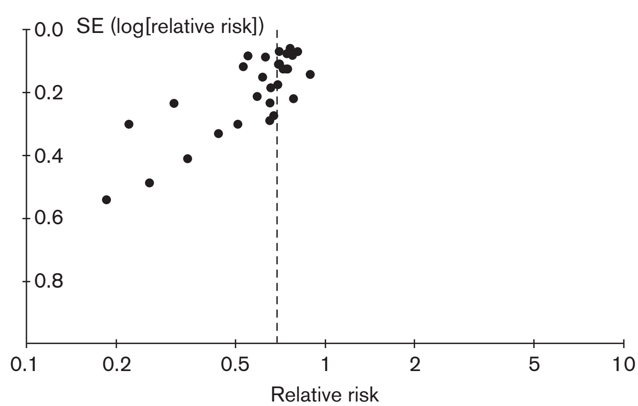
Results

The authors' MEDLINE search yielded 1768 articles, 1469 of which were excluded on the basis of a review of the title and the abstract. The remaining 299 studies were analysed in greater detail, and 33 studies fulfilled all inclusion criteria. The main study characteristics are presented in Table 1. The studies ultimately included in the authors' analysis published between 1992 and 2007, had a total of 883 372 participants, and included a roughly equal number of men and women (not all studies provided information on the number of men and women in their samples). The follow-up period in the included studies ranged from 4 years to more than 20 years. A total of nine studies used a fitness test (usually a treadmill test) to assess physical activity, and 24 studies used patient questionnaires. Most studies reported results adjusted for other known risk factors such as hypertension, high cholesterol, and obesity, and 15 studies also reported results for parsimonious models (usually adjusted only for age).

Funnel plots for cardiovascular and all-cause mortality are presented in Figs 1 and 2. For cardiovascular mortality, the distribution of studies is not symmetrical. Although the majority of studies is grouped around the pooled effect, some studies reported larger risk reductions, which is an indicator of publication bias. All studies reporting larger risk reductions were, however, based on objective fitness tests and had less precise effect estimates. The funnel plot for all-cause mortality shows similar nonsymmetrical distributions, though outliers are closer to the pooled estimate than in Fig. 1. Here, too, studies based on objective fitness tests tended to report larger risk reductions.

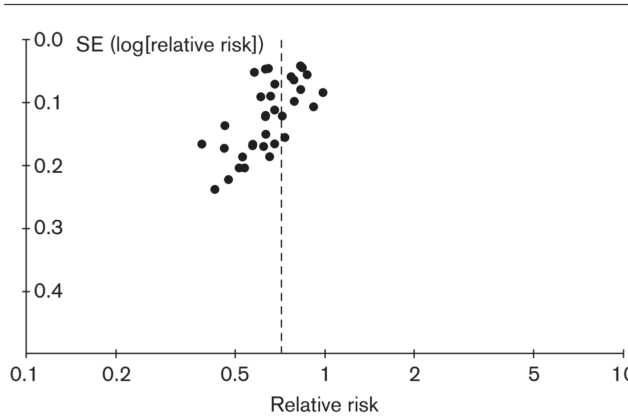
Associations between physical activity and cardiovascular mortality are presented in Fig. 3. Of all the studies

Fig. 1



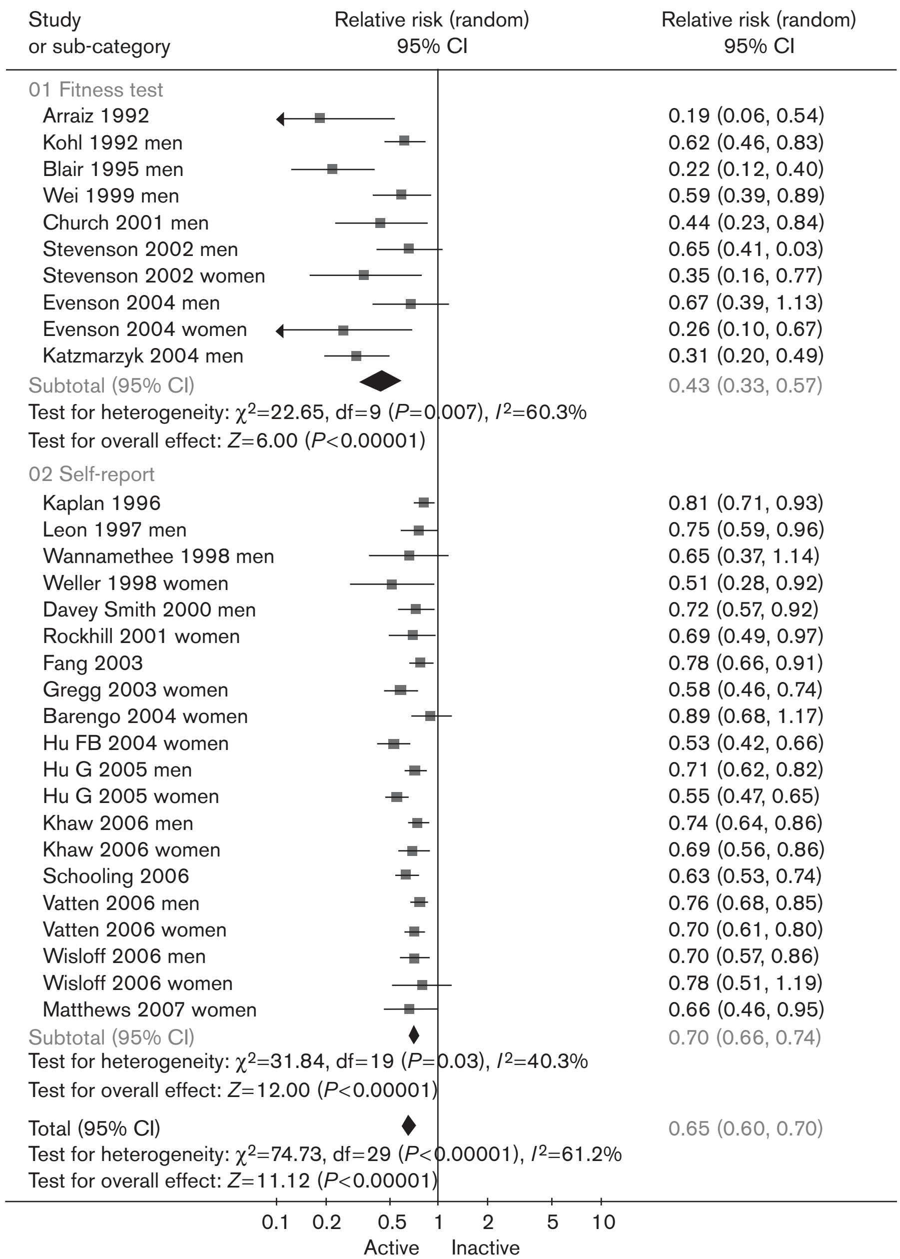
Funnel plot for physical activity and cardiovascular mortality.

Fig. 2



Funnel plot for physical activity and all-cause mortality.

Fig. 3



Relative risk of cardiovascular mortality in physically active versus physically inactive participants (fully adjusted models).

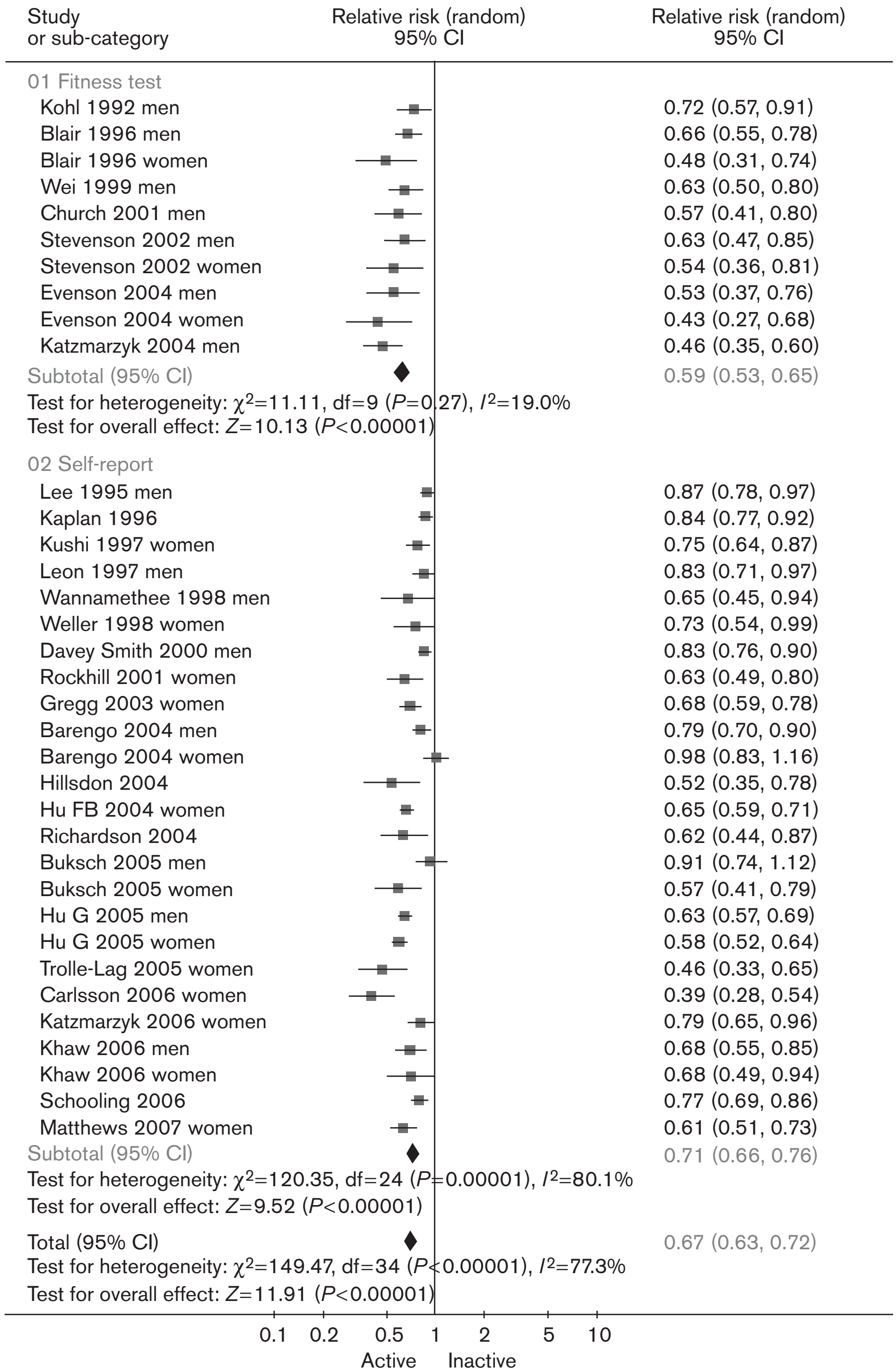
included in the authors' analysis, five reported nonsignificant results and 26 reported statistically significant risk reductions. Reductions in risk ranged from 11 to 81%. Most studies reported a risk reduction of 30–50%. Risk reductions were found for both men and women.

The overall pooled risk reduction was 35%. Studies that used a fitness test to assess physical activity reported larger risk reductions than studies based on self-reported activity (57 vs. 30%).

The results were similar for the association between physical activity and all-cause mortality (Fig. 4). Here, the reductions in risk ranged from 2 to 61%, with 33 of the 35 results being significant. The overall pooled risk reduction was 33%. Again, the largest reductions were found in studies that used a fitness test to assess physical activity (41 vs. 29%).

Sensitivity and subgroup analyses are presented in Table 2. Overall, 15 studies reported age-adjusted

Fig. 4



Relative risk of all-cause mortality in physically active versus physically inactive participants (fully adjusted models).

results in addition to fully adjusted models. The age-adjusted risk reductions were always larger than the fully adjusted reductions. Stratifying the fitness status of the study populations into more categories (e.g., five instead of three fitness categories) increased the risk reductions moderately. The overall results were similar in men and women. After stratifying the data according to the method that had been used to assess physical activity (i.e. by self-reported or objectively measured data), the risk reductions associated with physical activity were larger for women than for men (Table 2).

Table 2 Sensitivity/subgroup analyses for physical activity and cardiovascular/all-cause mortality

	Fitness test	Self-report	Total
Cardiovascular mortality			
Only age adjusted			
Relative risk (95% CI)	0.27 (0.20–0.36)	0.59 (0.53–0.66)	0.53 (0.46–0.61)
Number of studies	*N*=3	*N*=10	*N*=13
Fitness categories compared <=3			
Relative risk (95% CI)	0.49 (0.36–0.68)	0.69 (0.61–0.78)	0.66 (0.59–0.74)
Number of studies	*N*=4	*N*=9	*N*=13
Fitness categories compared >3			
Relative risk (95% CI)	0.37 (0.23–0.60)	0.70 (0.63–0.79)	0.65 (0.59–0.72)
Number of studies	*N*=6	*N*=12	*N*=18
Men			
Relative risk (95% CI)	0.48 (0.36–0.64)	0.74 (0.70–0.79)	0.65 (0.57–0.72)
Number of studies	*N*=7	*N*=8	*N*=15
Women			
Relative risk (95% CI)	0.31 (0.17–0.56)	0.65 (0.58–0.72)	0.63 (0.56–0.71)
Number of studies	*N*=2	*N*=10	*N*=12
All-cause mortality			
Only age-adjusted			
Relative risk (95% CI)	0.46 (0.38–0.55)	0.60 (0.54–0.67)	0.59 (0.53–0.65)
Number of studies	*N*=3	*N*=16	*N*=19
Fitness categories compared <=3			
Relative risk (95% CI)	0.60 (0.52–0.69)	0.73 (0.67–0.80)	0.69 (0.64–0.75)
Number of studies	*N*=6	*N*=12	*N*=18
Fitness categories compared >3			
Relative risk (95% CI)	0.55 (0.46–0.66)	0.67 (0.60–0.76)	0.65 (0.58–0.72)
Number of studies	*N*=4	*N*=13	*N*=17
Men			
Relative risk (95% CI)	0.61 (0.55–0.68)	0.78 (0.70–0.68)	0.70 (0.64–0.77)
Number of studies	*N*=7	*N*=8	*N*=15
Women			
Relative risk (95% CI)	0.49 (0.38–0.62)	0.65 (0.59–0.73)	0.63 (0.57–0.70)
Number of studies	*N*=3	*N*=13	*N*=16

Discussion

Physical activity is associated with a marked decrease in cardiovascular and all-cause mortality. Most studies included in the authors' meta-analysis reported risk reductions of 30–50% for cardiovascular mortality and of 20–50% for all-cause mortality, with pooled risk reductions of 35% for the former and 33% for the latter. These results are based on studies including a total of nearly 900 000 participants.

Most of these findings were based on regression models adjusted for important risk factors such as hypertension, hypercholesterolemia, and diabetes, which themselves are associated with physical inactivity. As a result, the risk reductions reported were rather conservative. Adjusting only for age, increased the already large risk reductions for cardiovascular mortality from 35 to 47% and for all-cause mortality from 33 to 41%. Accordingly, the largest reductions in the risk of cardiovascular mortality were reported by the two studies that did not adjust for important confounding variables [8,10]. In one study [7], including these variables attenuated the risk reduction for all-cause mortality compared to a model adjusted only for age by 6% for women and 10% for men, and for cardiovascular mortality by 8% for women and 13% for men.

Both men and women benefited from physical activity. According to the authors' subgroup analyses, risk reductions were larger for women than for men after stratifying the populations according to the method that had been used to assess physical activity. With regard to age, most studies in this review focused on middle-aged populations. Three studies [18,26,31] included older participants and reported similar decreases in mortality.

Although the large majority of studies reported that physical activity had protective effects on both cardiovascular and all-cause mortality, the risk reductions varied considerably. The most important reason for heterogeneity was the differing methods used to assess physical activity. The authors included studies that assessed physical fitness (i.e. a physiological state measured by treadmill tests) as well as studies that relied on patient self-reports of the duration and intensity of physical activities. Studies with a more objective means of assessment tended to report larger risk reductions. Accordingly, a study by Myers *et al.* [4], which directly compared both methods found that exercise testing outperformed self-reported physical activity in predicting mortality. It seems likely that participants overestimated their levels of physical activity in self-reports, thus minimising the true protective effect. However, even studies based on the less reliable self-reported measures of activity have shown marked protective effects on mortality.

The authors' study has several important limitations. Based on the authors' inclusion and exclusion criteria, a bias in the selection of studies is possible. The authors included only large studies with more than 5000 participants. Though this was an arbitrary cut-off, the large number of studies that fulfilled this criterion (i.e. with a total of nearly 900 000 participants) and the overall homogeneity in the direction of effects support the validity of the authors' findings. Another limitation is that the participants were not classified into distinct activity groups in a homogenous manner across the studies, especially when classification was based on patient questionnaires. Moreover, the number of activity categories differed across studies. Whereas most studies compared three physical activity groups (e.g. low, moderate, and high), some studies categorized the populations into four or five subgroups, thus increasing the range between the least and most active groups. Including only studies that compared three distinct activity groups, however, had only small effects on overall risk reductions.

These results once again confirm the impressive protective effect of physical activity. Despite this knowledge, a large majority of individuals still lead a primarily sedentary life. Numerous studies have addressed the question of how to promote physical activity [39]. Positive results have been shown for information campaigns, behavioural and social interventions, and environmental interventions, such as providing easy access to sports or exercise facilities. The key is to translate these findings into permanent public health efforts.

Acknowledgement

Competing interests: none.

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