Physical Activity and All-cause Mortality: An Updated Meta-analysis with Different Intensity Categories

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Key words
- primary prevention
- physical training
- fitness
- aging
- gender

Abstract

In a meta-analysis we investigated the effect of physical activity with different intensity categories on all-cause mortality. Many studies have reported positive effects of regular physical activity on primary prevention. This recent meta-analysis analyzed all-cause mortality with special reference to intensity categories. A computerized systematic literature search was performed in EMBASE, PUBMED, and MEDLINE data bases (1990–2006) for prospective cohort studies on physical leisure activity. Thirty-eight studies were identified and evaluated. The presentation refers to studies with 3 or 4 different intensities of regular physical activity according to a standard questionnaire. There was a significant association of lower all-cause mortality for active individuals compared with sedentary persons. For studies with three activity categories (mildly, moderately, and highly active) and multivariate-adjusted models, highly active men had a 22% lower risk of all-cause mortality (RR = 0.78; 95% CI: 0.72 to 0.84) compared to mildly active men. For women, the relative risk was 0.69 (95% CI: 0.53 to 0.90). We observed similar results in moderately active persons compared to mildly active individuals (RR = 0.81 for men and RR = 0.76 for women). This association of activity to all-cause mortality was similar and significant in older subjects. Regular physical activity over longer time is strongly associated with a reduction in all-cause mortality in active subjects compared to sedentary persons. There is a dose-response curve especially from sedentary subjects to those with mild and moderate exercise with only a minor additional reduction with further increase in activity level.

accepted after revision
December 9, 2008

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DOI 10.1055/s-0028-1128150
Published online:
February 6, 2009
Int J Sports Med 2009; 30: 213–224 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0172-4622

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Introduction

It is generally accepted today that regular physical activity has a beneficial effect in preventing cardiovascular and other diseases [5, 60]. Many studies also demonstrate reduction of mortality and morbidity by regular physical activity. In addition, physical fitness is a complementary factor to determine longevity in healthy and even in ill subjects.

Powell et al. [47] and, later, Berlin and Colditz [3] published the first meta-analyses focusing on the associations of physical activity on coronary heart disease incidence. These analyses dealt with leisure time and occupational activity. Since then, a large number of prospective cohort studies on physical activity versus inactivity has been performed and published. As physical activity can nowadays be equated with physical leisure time activity in industrialized countries, we use the term physical activity to reflect physical leisure time activity. Two recent systematic reviews [5, 60] indicated a positive impact of physical activity on all-cause mortality. But, since no numerical meta-analysis on the effect of physical activity on all-cause mortality has been published recently, we conducted a systematic data search and performed a meta-analysis.

Background

Several cohort studies described a beneficial association of physical activity with all-cause mortality as compared to inactivity. Our working hypothesis now is that physical activity, even light besides moderate and intense activity, has an overall beneficial impact on all-cause mortality. We do not assume that there is a linear activity-response relationship, but each type of activity should be associated with a significant risk reduction.

The definition of the cohorts based on the intensity of activity as well as the number of cohorts or activity groups may differ from study to study. The outcomes of each study were estimates of risk reduction for each activity group compared to the inactive group. To estimate risk reduction, proportional hazard models or logistic regression models can be used. A justification for using estimates from these two different models in combining results can be found in D'Agostino et al. [9]. Estimates may be age- or multivariate-adjusted, where we assume that multivariate-adjusted estimators have been adjusted for all relevant confounders in each single study. Since multivariate-adjusted estimates are generally more conservative and reliable compared to age-adjusted estimates, the main conclusions are based on combining multivariate-adjusted estimates.

Search

A computerized systematic literature search was performed according to the consensus statement (QUORUM statement) [38, 54] in EMBASE, PUBMED, and MEDLINE data bases (1990–2006) using subject headings as primary prevention, physical activity, mortality, morbidity, all-cause mortality, cardiovascular mortality, cohort study, inactivity, sedentary persons, sports, exercise training, and aerobic exercise. In addition, current reviews were analyzed and checked for additional cohort studies missed in the computerized search. Abstracts and unpublished studies were not considered. Only papers published in English were evaluated. Studies with incomplete data set were discarded. Reasons for exclusion were missing data, mostly confidence intervals or undefined cohorts, lack of accurate definitions of duration and intensity of physical activity, or incomplete communication of confounding variables. There was no contact with the authors of the studies. Three experienced investigators, two experts in statistics and one cardiologist and exercise physiologist analyzed all the relevant studies. In case of differing opinions, data were discussed in detail and a consensus was accepted.

Only prospective cohort studies on physical leisure activity were included with a study duration of at least four years. Studies were selected only when the following data were reported: number of subjects, sex, age, duration of study, kind of exercise, intensity (MET) with two or more activity categories.

As a result 38 studies were identified and evaluated [1, 2, 4, 8, 11–14, 17, 19, 22, 23, 25–30, 32–35, 37, 40, 41, 45, 46, 48, 49, 51–53, 55–59, 62]. Studies included a wide range of countries in North and Central Europe as well as North America. Two investigators once more reviewed the papers and selected those with complete data set. The third investigator checked all the data. Parameters identified were unadjusted, age-, and/or multivariate-adjusted relative risks with respect to all-cause mortality.

The following variables were checked and registered: first author, journal and year of publication, country of study, follow-up in years, sex ratio, number of participants, cohort definition, total mortality, cardiovascular mortality, unadjusted or age-adjusted relative risk (RR) plus 95% confidence interval, multivariate-adjusted relative risk plus 95% confidence interval, adjustment for confounding variables, number of activity levels, and type of statistical model used in the analysis. Adjustment was done mostly for age, smoking status, blood pressure, cholesterol level, body weight or BMI, lung disease (in some studies). In addition, general health status was checked by the questionnaire.

Material and Methods

The statistical analysis models used in the publications were either proportional hazard models or logistic regression models. In all the studies eligible for meta-analysis either age-adjusted, multivariate-adjusted or both types of relative risk estimates with corresponding confidence intervals were reported. D'Agostino et al. [9] investigated the relation of estimating relative risks from proportional hazard models and logistic regression models and we conclude from this paper that pooling estimating relative risks from these two different models is acceptable and leads to meaningful results.

We further assume that multivariate-adjusted estimates are derived from models after adjusting for all relevant confounders in the corresponding studies. Beside age, confounding variables were, for instance, overweight (body mass index), smoking, alcohol, and elevated blood pressure.

All results presented are relative risks of all-cause mortality associated with physical activity compared to inactivity. After presenting the results compared to the most active group in the single studies, we conducted a transformation for the meta-analysis.

Since multivariate-adjusted estimates exclude the effect of confounding variables, the main conclusions of the meta-analysis are drawn from pooling multivariate-adjusted relative risk estimates. As sensitivity analyses, we also present the results for pooling age-adjusted estimates.

In some studies [19, 22, 25, 26, 28, 30, 35, 49], additional analyses were conducted omitting the first years (range: 1–12 years) after physical activity assessment to minimize potential bias from ill health in the starting population. But the results from these subgroup analyses did not or only little affect the associations or results found in the total cohorts in all the studies. Consequently, we could base the meta-analysis on the estimates for the total cohorts.

For pooling estimates, we used the random effects meta-analysis model that accounts for between-study variability. For estimating this heterogeneity parameter, we calculated the DerSimonian-Laird estimator; see DerSimonian and Laird [10]. In cases where this estimate was negative, we set the estimate equal to zero and then applied the fixed effects model. To describe the amount of possible heterogeneity, we report the p-value from Cochran's homogeneity test; see DerSimonian and Laird [10]. We used the refined meta-analysis method proposed by Hartung and Knapp [20] for combining results from four or more studies. For combining results from two or three studies, the Hartung and Knapp approach [20] can yield an unreasonably wide confidence interval for practical purposes because of the t-distribution involved with one or two degrees of freedom. In this case, we combined the results using the method described in DerSimonian and Laird [10]. All meta-analysis procedures were done on the logarithmic relative risk scale and the results were then retransformed to the relative risk scale.

Separate analyses (subgroup analyses) were calculated according to age or multivariate adjustment, for gender (male, female), age (<65 years or ≥ 65 years), and levels of activity. The focus was put on studies with three or four intensities of physical activity (e.g., none, light, moderate, or vigorous activity) according to a questionnaire in most studies [44, 50]. The physical activity classification in the papers analyzed mostly refer to Kcal or METs with describing inactive (or sedentary) with less than 200 Kcal/week (or less than 1 MET), lightly active with

200–599 Kcal/week (<3 METs), moderate activity with 600–1 499 Kcal/week (or 3–6 METs) or vigorous activities with more than 1 500 Kcal/week (or >6 METS) [21, 39]. Correctly, kcals/week corresponds to MET-hrs/week.

General Results

We identified 38 studies involving more than 271 000 participants. Subjects included in this analysis were females and males aged from 20 to 80 years with activity categories ranging from two to six. Observation period ranged from 4 to 40 years with a median of 12 years. All studies were prospective cohort studies reflecting good evidence. Basic data are given in Appendix A, ▸ **Tables A1–A8**. In 33 studies, three or more intensities of activity were available. There was a non-linear relationship of risk reduction with activity, with light and moderate activities showing a marked reduction in mortality, with only a small additional risk reduction with vigorous exercise intensity. This observation was shown in many studies in this meta-analysis review.

Analysis in detail yielded a multivariate-adjusted risk lowering in males of 19% (relative risk of 0.81 (95% CI: [0.75, 0.87])) for moderate activity and a relative risk of 0.78 (95% CI: [0.72, 0.84]) for the most active (vigorous) group in studies with three levels of activity. Similar results were obtained for women with a relative risk of 0.76 (95% CI: [0.66, 0.89]) or a risk reduction of 24% for moderate activity and a relative risk of 0.69 (95% CI: [0.54, 0.89]) or a risk reduction of 31% for the most active group. The age-adjusted results were followed by multivariate results which were attenuated but remained significant. The risk reduction in males therefore is 24% (relative risk of 0.76 (95% CI: [0.71, 0.82])) for moderate activity and 35% (relative risk of 0.65 (95% CI: [0.55, 0.76])) for the vigorous group. For women, the risk reduction is 31% (relative risk of 0.69 (95% CI: [0.56, 0.84])) for moderate activity and 44% (relative risk of 0.56 (95% CI: [0.37, 0.95])) for the most active group.

The associations seem to be stronger for older men, 65 years and older with relative risk of 0.67 (95% CI: [0.60, 0.81]) compared to those below 65 years with relative risk of 0.81 (95% CI: [0.72–0.92], moderate activity) and 0.70 (95% CI [0.53–0.94], vigorous activity) thus resulting in relative risk reduction of 33% for moderate activity and of 45% (relative risk 0.55 (95% CI: [0.31, 0.98])) for the vigorous activity group using age-adjusted estimates.

Fewer studies are available with four groups with different levels of activities however. The meta-analytical results of studies with four levels of activity groups confirm the findings of the meta-analysis with three levels of activities. The results for all meta-analyses with three and four groups are summarized in ▸ **Table 1**.

Results in Detail

Studies with three levels of activities

Eleven studies provided multivariate-adjusted estimates for men. The outcome results in all studies favoured the activity groups compared to sedentary subjects. In five studies, the effect was significant for the moderately active group, and in eight studies, a significant effect was observed for the most active group. The combined estimator for the moderately active group is 0.81 (95% CI: [0.75, 0.87]) indicating a significant risk reduction of approximately 20% for moderately active subjects compared to sedentary subjects. For the most active group, the combined estimator is 0.78 (95% CI: [0.72, 0.84]) showing a significant risk reduction of around 22%. The results are graphically displayed in confidence interval plots, see ▸ **Figs. 1,2**. Using age-adjusted estimates for men, available from ten studies, the effects are more pronounced with a relative risk estimate of 0.77 (95% CI: [0.71, 0.82]) for subjects in the moderate active group

Table 1 Results of meta-analysis for studies with three and four levels of activity. Reported are the combined relative risk estimates with corresponding 95% confidence interval as well as the p value of the test of homogeneity.

Sex	Activity	Number of studies	Age-adjusted	Number of studies	Multivariate-adjusted
Three levels of activity					
both sexes					
	moderate	3	0.69 (0.55–0.86) ($p_{hom}=0.455$)	3	0.78 (0.61–1.00) ($p_{hom}=0.426$)
	vigorous	3	0.65 (0.45–0.93) ($p_{hom}=0.392$)	3	0.80 (0.66–0.97) ($p_{hom}=0.786$)
men					
	moderate	10	0.76 (0.71–0.82) ($p_{hom}=0.040$)	11	0.81 (0.75–0.87) ($p_{hom}=0.001$)
	vigorous	10	0.65 (0.55–0.76) ($p_{hom}<0.001$)	11	0.78 (0.72–0.84) ($p_{hom}=0.067$)
women					
	moderate	5	0.69 (0.56–0.84) ($p_{hom}<0.001$)	7	0.76 (0.66–0.89) ($p_{hom}<0.001$)
	vigorous	5	0.56 (0.37–0.84) ($p_{hom}<0.001$)	7	0.69 (0.54–0.89) ($p_{hom}<0.001$)
Four cohorts					
both sexes					
	light	2	0.68 (0.65–0.72) ($p_{hom}=1$)	1	1.14 (0.74–1.78)
	moderate	2	0.52 (0.34–0.77) ($p_{hom}=0.034$)	1	0.53 (0.35–0.82)
	vigorous	2	0.48 (0.36–0.62) ($p_{hom}=0.206$)	1	0.52 (0.35–0.78)
men					
	light	4	0.79 (0.63–0.99) ($p_{hom}=0.163$)	9	0.78 (0.68–0.90) ($p_{hom}=0.289$)
	moderate	4	0.72 (0.47–1.11) ($p_{hom}=0.024$)	9	0.74 (0.60–0.92) ($p_{hom}=0.043$)
	vigorous	4	0.64 (0.36–1.13) ($p_{hom}=0.003$)	9	0.61 (0.49–0.76) ($p_{hom}=0.008$)
women					
	light	1	0.91 (0.66–1.25)	3	0.75 (0.49–1.12) ($p_{hom}=0.100$)
	moderate	1	0.94 (0.72–1.23)	3	0.82 (0.53–1.27) ($p_{hom}=0.120$)
	vigorous	1	0.89 (0.67–1.17)	3	0.47 (0.26–0.87) ($p_{hom}=0.014$)

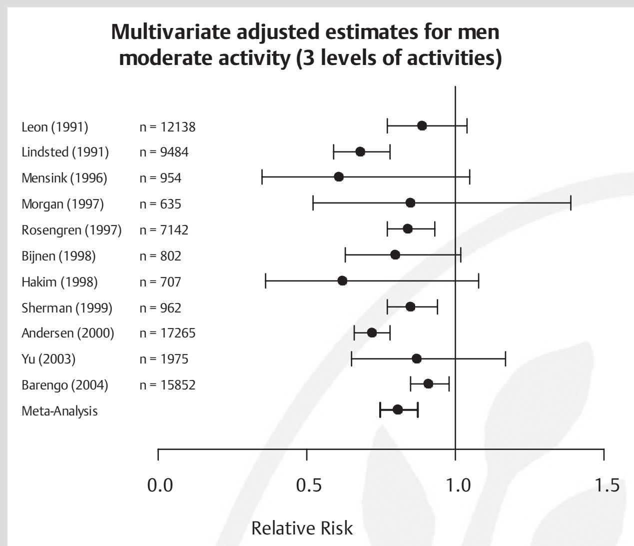

Fig. 1 Study-specific confidence intervals and meta-analytical confidence interval for the male moderate activity group in studies with three levels of activities ("n = " is the total sample size of the study).

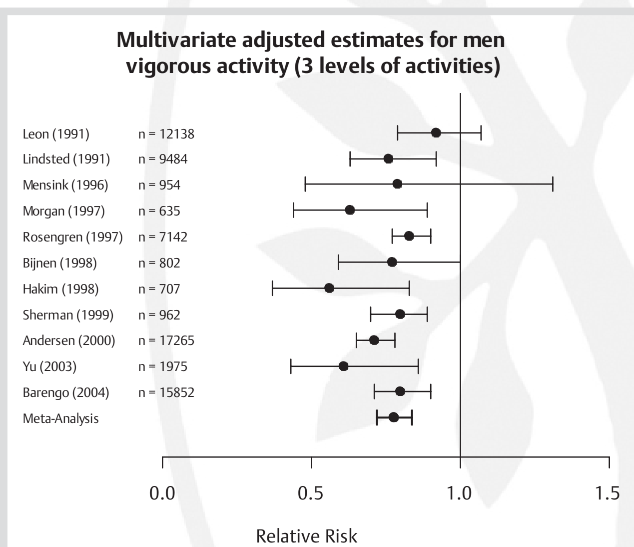

Fig. 2 Study-specific confidence intervals and meta-analytical confidence interval for the male vigorous activity group in studies with three levels of activities ("n = " is the total sample size of the study).

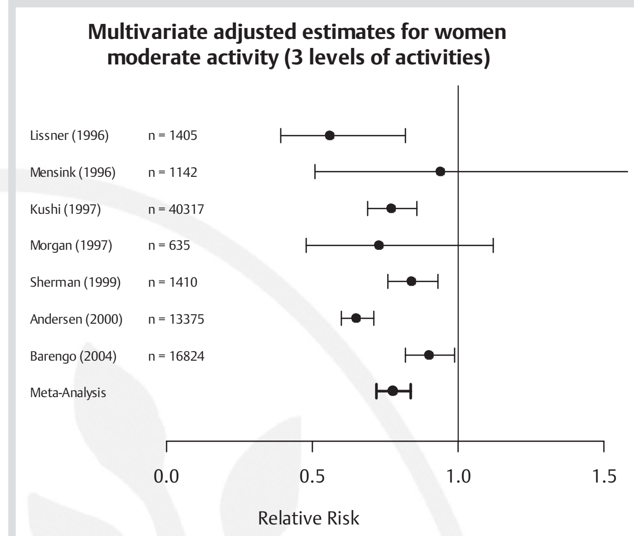

Fig. 3 Study-specific confidence intervals and meta-analytical confidence interval for the female moderate activity group in studies with three levels of activities ("n = " is the total sample size of the study).

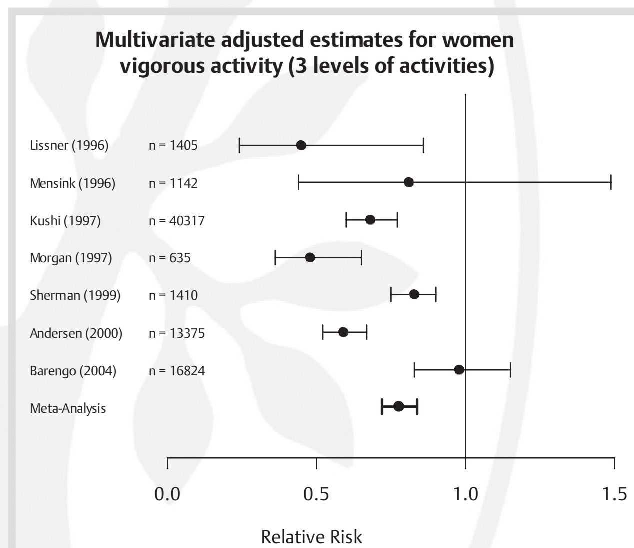

Fig. 4 Study-specific confidence intervals and meta-analytical confidence interval for the female vigorous activity group in studies with three levels of activities ("n = " is the total sample size of the study).

and relative risk estimate of 0.65 (95% CI: [0.55, 0.76]) for subjects in the most active group.

Seven studies provided multivariate-adjusted estimates for women. All estimates favoured activity groups. A significant association was observed in each of five studies for both activity groups.

The combined estimator for the moderately actively group is 0.76 (95% CI: [0.66, 0.89]) indicating a significant risk reduction of nearly 24%. For the most active group, the combined relative risk is 0.69 (95% CI: [0.54, 0.89]) showing a significant risk reduction of approximately 31%. The results are graphically displayed in confidence interval plots, see ◉ **Figs. 3,4**. Using age-adjusted estimates, available in five studies, the associations are somewhat more pronounced in women than in men. The relative risk estimate is 0.69 (95% CI: [0.56, 0.84]) for the moderately active group and 0.56 (95% CI: [0.37, 0.84]) for the most active group.

In three studies, age- as well as multivariate-adjusted estimates were reported but not separately for men and women. Combining the multivariate-adjusted estimates, the relative risk estimate is 0.78 (95% CI: [0.61, 1.00]) for the moderate active group and 0.80 (95% CI: [0.66, 0.97]) for the most active group. Using age-adjusted estimates, the relative risk estimate is 0.69 (95% CI: [0.55, 0.86]) for the moderate active group and 0.65 (95% CI: [0.45, 0.93]) for the most active group.

A possible explanation for the heterogeneity observed in combining the results for men and women, respectively, may be the influence of age. Since a sufficient number of studies was available for men, a subgroup analysis was done. Six studies were identified with participants younger than 65 years providing multivariate-adjusted estimates. For the moderately active group the homogeneity test is still significant ($p_{hom}=0.01$) and the combined estimate is 0.83 (95% CI: [0.72, 0.95]). For the most

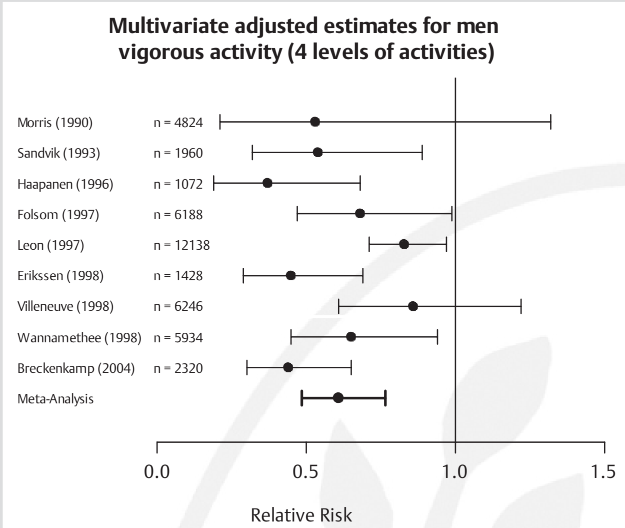

Fig. 5 Study-specific confidence intervals and meta-analytical confidence interval for the male vigorous activity group in studies with four levels of activities ("n = " is the total sample size of the study).

active group, the test of homogeneity does not reject the homogeneity assumption ($p_{hom}=0.312$) and the combined estimate is 0.82 (95 % CI: [0.75, 0.90]). In both activity groups, the combined estimates indicate a lower risk reduction than the overall results.

Three studies were identified with participants aged 65 years and older providing multivariate-adjusted estimates. The results for both the activity groups are rather homogeneous ($p_{hom}=0.660$ and $p_{hom}=0.383$). The combined relative risk estimate is 0.78 (95 % CI: [0.59, 0.96]) for the moderately active group and 0.68 (95 % CI: [0.56, 0.82]) for the most active group. These results indicate that the elderly men may benefit a little more than younger subjects. The same conclusion holds true when using age-adjusted estimates (results not shown).

Studies with four levels of activities

Nine studies provided multivariate-adjusted estimates for men. Each study had an estimate in favour of all three activity groups compared to the inactive group. Four studies yielded a significant result for the mildly active group, only two studies for the moderately active group, but seven studies for the most active group. The combined relative risk estimate is 0.78 (95 % CI: [0.68, 0.90]) for the mildly active group, 0.74 (95 % CI: [0.60, 0.92]) for the moderately active group, and 0.61 (95 % CI: [0.49, 0.76]) for the highly active group. The results for the most active group are graphically displayed in a confidence interval plot (▶ **Fig. 5**).

Eight of the nine studies included only men younger than 65 years and the combined estimates are a little closer to 1 but still significant. Only four studies provided age-adjusted estimates and the combined estimates are of the same magnitude as the combined multivariate-adjusted estimates, but the confidence intervals are wider due to the smaller number of studies.

Only three studies were available which provided multivariate-adjusted estimates for women. All relative risk estimates are in favour of the three activity groups compared to the inactive group except one estimate for the moderately active group which is slightly larger than 1. In one study, the estimates of the activity groups were strongly significant. In another study, all observed associations, though all smaller than 1, were found to be not significant. In the third study, a significant association was found for the most active group. The combined relative risk estimates are 0.75 (95 % CI: [0.49, 1.12]) for the mildly active group, 0.82 (95 % CI: [0.53, 1.27]) for the moderately active group, and 0.47 (95 % CI: [0.26, 0.87]) for the most active group. One study provided age-adjusted estimates for women with estimates in favour of the activity groups, but the associations were not found to be significant.

One study provided multivariate-adjusted estimates for both men and women. For the moderately and the most active group, the observed relative risks were significant, whereas a relative risk larger than one was observed for the mildly active group. Two studies provided age-adjusted estimates for both men and women. All observed relative risks were found to be significant in favour of the activity groups except one estimate for the mildly active group.

Further results

Six studies considered only groups with two levels of activity. All the observed eight associations, either age- or multivariate-adjusted for men, women, or both sexes, were in favour of the active group and three associations were marginally not significant at the 5 % level. Four studies reported multivariate-adjusted estimates for men. The combined relative risk estimate of these four studies is 0.75 (95 % CI: [0.52, 1.09]).

Four studies considered groups with five levels of activities. All the observed risk reductions, either age- or multivariate-adjusted for men, women, or both sexes, were in favour of the activity groups and, except two relative risk estimates for the moderately active group, all associations were found to be significant. One study with six intensity groups reported age- as well as multivariate-adjusted relative risk estimates. All the estimates were found to be significant in favour of the activity groups, even in the very mildly active group. The study included men younger than 65 years.

Discussion

Regular physical activity over longer periods of observation, ranging from 4 to 40 years, is strongly associated with lowering all-cause mortality in active subjects compared to sedentary subjects. There is a dose-response curve especially from sedentary subjects to those with low and moderate exercise intensity with an only minor additional risk reduction with further increase of activity level (▶ **Figs. 6,7**). Results are more pronounced in age-adjusted data. However, the associations using multivariate-adjusted data are also highly significant, but the lowered mortality is somewhat attenuated compared to age-adjusted results. These conclusions also hold true for the elderly and also for women. Data of this analysis indicates that moderate levels of regular activity are associated with health benefits. Expending more calories or increasing activity intensity may improve physical fitness but has moderate to low effect only in reducing all-cause mortality.

There are some limitations inherent to meta-analysis in general and to interpretation of physical activity. There may be a tendency for publication bias as positive studies may be preferred for publication. However, there are some studies with negative results in this analysis. Therefore, the publication bias may be small or can be neglected. The total amount of physical activity has been analyzed in different ways though most authors used a

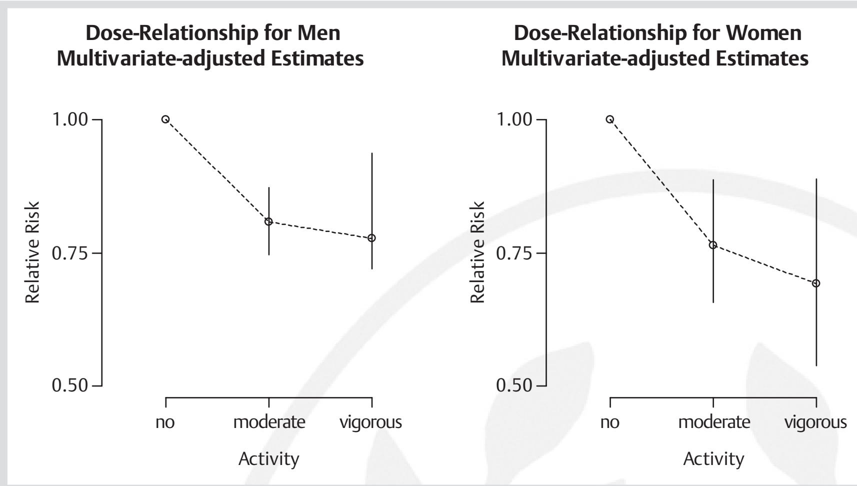

Fig. 6 Dose-response relationship based on meta-analytical results of multivariate-adjusted estimates for men (left) and women (right) in studies with three levels of activities (estimates plus 95 % confidence intervals).

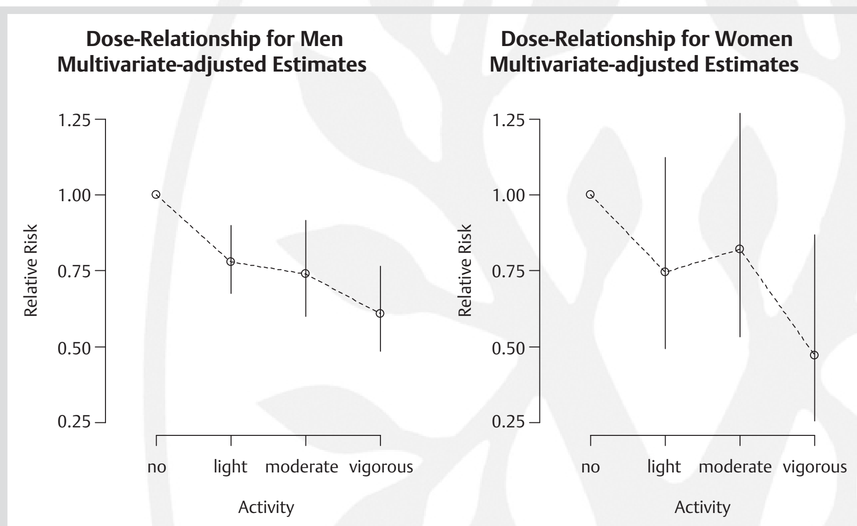

Fig. 7 Dose-relationship based on meta-analytical results of multivariate-adjusted estimates for men (left) and women (right) in studies with four levels of activities (estimates plus 95 % confidence intervals).

standardized and reliable questionnaire. Different interpretation may weaken the results. Classification of activity and varying levels of intensity are sometimes difficult to compare and may be prone to different interpretation. Intensity and amount of activity may differ according to duration, and frequency of physical activity and may lead to increased variability of results. The relationship of intensity categories in reducing mortalitiy may point to the role of intensity in decreasing all-cause mortality. Intensity thus may be more important than amount of the activity lowering all-cause mortality in the most active group. Further, the increase of variability of data usually lowers statistical significance. The significant results observed in this meta-analysis then reflect more statistical power and provide important information for the general practitioner and clinician as well.

Gender effect

The indicated stronger risk reduction in women than in men can be explained by a multifactorial approach. Women are protected against cardiovascular diseases up to menopausal period. Thereafter, the risk of cardiovascular events such as myocardial infarction or cerebral ischemia increases. The more pronounced associations in women may also depend on a recent observation that women were in general less active in sports in earlier years. However, there has been a general increase of awareness of risk factors among women, promoting more physical activity [42]. On the other hand these data can be explained by the observation that the least active group in women is less active than the least active group of men in most studies. This then also may explain the apparently stronger association in older men, who in general tend to be less active and less fit than younger men.

Women tend to be more conscious about following a healthy lifestyle with increasing age. This greater awareness of being active as an important goal for preventing cardiovascular diseases as well as cancer or osteoporosis is now becoming more widespread. Nonetheless, this should not influence the magnitude of relative risk reduction as most of this activity should have been started a decade ago. Such a conclusion however is not supported by the literature. In addition, it should be admitted that there are fewer cohort studies with women than with men, with fewer participants, and with categories definitions that may be somewhat weaker between genders. Consequently, the combined effect from these studies has a larger standard error. Therefore, a moderate selection bias cannot be excluded. To conclude, there is a pronounced risk reduction in women indicating that a healthy lifestyle should be a goal for every woman [42]. The effects are quite similar to those observed in men.

Effect of age

Subgroup analysis with regard to age resulted in a significant decrease of relative risk of all-cause mortality even in subjects older than 65 years. Also, more intensive physical activity resulted in more pronounced lower risk, even in subjects over 65 years of age compared to those younger than 65 years. This may be explained by a stronger relative risk reduction in elderly when continuing or starting with regular physical exercise compared to sedentary subjects. This is confirmed by recent studies showing that elderly people have lower exercise efficiency and capacity. However, regular physical activity in the aged, improves efficiency more compared to young subjects [61]. It is now well established that in older subjects there is a continuing age dependent decrease of physical fitness paralleled by an increase in morbidity and mortality. Thus elderly subjects without exercise training may be more prone to cardiovascular events than active people. Also, the least active group of older subjects is less active than the least active group in younger subjects. This means that for this analysis, there is stronger association when the reference group is less active.

The present results then confirm that physical training indeed is effective in reducing mortality especially in older subjects. This is underlined by the well-known attenuated age-dependent decrease of physical fitness in physically active subjects. These data show that older subjects who are more active experience a more protective effect from cardiovascular disease than those with moderate activity level only [22]. The age related decrease of mortality is in a similar range as reported by others, e.g., Greg et al. [18].

Role of levels of activities

Subgroup analysis consistently shows a decrease of risk reduction with more intense physical activity or with increasing activity categories. In all subgroups there is a consistent intensity-dependent decrease of the risk reduction values. Similar reports point to a non-linear risk reduction curve with increasing amount of activity [5, 60].

However, the present study shows only a weaker exponential or non-linear relationship of intensity groups in the subgroup analysis. Although our data point to a somewhat lower all-cause mortality with intense physical activity, in keeping with other studies, it appears some kind of saturation curve may exist. To achieve a healthly lifestyle, it may be sufficient to exercise moderately. This then reduces all-cause mortality effectively without increasing risks due to cardiovascular side-effects. This recommendation holds true especially for the elderly as has been shown in some single studies such as Hakim et al. [18, 19] and Lee et al. [30, 31].

Comparison with previous studies

Risk reduction in this analysis is comparable to those results in previous studies and reviews. The lower rates of all-cause mortality are more pronounced in some subgroups in our study than described previously. This especially holds true for women and older subjects. The general results of this analysis are in keeping with previous studies and meta-analyses. Some older studies contained a lower number of single studies [60] or rather addressed the question of fitness versus training [5, 60]. Further, our study was calculated more strictly with multivariate-adjusted estimates in a random effects meta-analysis compared to other studies which used only age-adjusted risk reduction. However, even using such a strict calculation approach resulted in significant decreases of risk reduction in all subgroups and all groups for men and women. In the Blair study [5], for example, this level of significance was not reached for such a strict approach. This multivariate approach with smaller differences of relative risk could also be due to the adjustments including risk factors causally related to all-cause mortality.

Physical activity and lowered mortality

Two reviews addressed the question whether reduced mortality in physically active subjects may be secondary to training (physical activity) or to fitness [5–7, 43, 60]. From studies of Williams [60], one may assume that fitness is superior to physical activity. However, Blair et al. [5] point out that there is a quite different methodological approach: Fitness can be measured very exactly by exercise testing and spiroergometry [15]. Physical training however, especially when registered or observed over many years by questionnaires, may be less precise giving larger variation of estimated caloric consumption. The present paper does not contribute to the role of fitness but gives some additional arguments for prescribing regular physical activity for primary prevention. There is now conclusive evidence from numerous prospective cohort studies that physical activity not only reduces all-cause mortality but also decreases mortality stepwise with varied levels of exercise intensity. The kind of relationship between exercise intensity and mortality reduction may be non-linear. However, this point deserves further investigation.

Studies on reliability of questionnaires show that they are valid but less valid than a quantitative assessment of physical capacity or fitness by exercise testing or a doubly labelled water method [24, 36]. This may weaken the apparent difference between risk reduction given by fitness or physical training analysis [5]. On the other hand, direct measurement of daily energy expenditure and mortality in older adults with the doubly labeled water method results in an underestimation of physical activity using the questionnaire approach [36]. As a further limitation of this meta-analysis it cannot be excluded that people performing higher intensity exercise may also be performing a greater amount of exercise. On the other hand, the most important risk reduction does occur from sedentary to light activity level. This is more likely in keeping with exercise intensity as the key variable. This meta-analysis with different intensity categories supports the assumption that intensity of physical activity is superior to the role of amount of exercise.

To summarize, physical activity is effective for everyone for preventive purposes. The magnitude of absolute effects with identical levels of training intensity and frequency may differ in individual subjects and in homogeneous groups due to genetic factors. The unresolved question of fitness versus physical activity can only be answered by a double approach involving long-term observation of a cohort which initially has been studied using fitness testing. In addition, closer comparisons of questionnaires with fitness tests over time may better validate these questionnaires.

Conclusion

▼

The present analysis confirms the widespread recommendations of the report on Physical Activity and Health from the General Surgeon and the guidelines of medical societies for sports medicine and cardiology. It is recommended that everyone be physically active, implementing activities in daily life including sports such as walking, nordic walking or jogging. Gardening and housework are also moderate activity measures effective in reducing mortality. In addition, activities such as dancing, swimming, or cycling can also be recommended as an active approach. The somewhat more pronounced effects in women and in older subjects mainly depend on methodological findings. However, these findings in general underline that training effects are similar in women and in men. Training with higher intensities may be effective for competitive purposes, but is not required for primary prevention. It is noteworthy that lower rates of all-cause mortality are also significantly observed in the elderly thus demonstrating that even in the aged protective and preventive effects can be obtained by regular physical activity at a moderate intensity. Irrespective of these statements, the prospective cohort studies analyzed here provide compelling evidence of positive associations between physical activity and lower rates of mortality independent of age and sex.

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Appendix A

Tables A1–A8

Table A1 Studies with **two** intensity groups of physical activity.

First author (year)	Country	Follow-up (yrs)	Sex	Adjustment	Age group	Number of participants	RR in the active group + (95 % CI)
Kaplan (1996)	USA	28	all	multivariate	3	6 131	0.84 (0.77–0.92)
Knoops (2004)	Europe	10	all	multivariate	2	2 339	0.63 (0.55–0.72)
Hedblad (1997)	S	25	men	age	1	642	0.68 (0.49–0.94)
Hedblad (1997)	S	25	men	multivariate	1	642	0.70 (0.50–0.98)
Villeneuve (1998)	CDN	7	men	multivariate	1	6 246	0.82 (0.65–1.04)
Schnoor (2000)	DK	22	men	multivariate	3	4 658	0.39 (0.19–0.73)
Panagiotakos (2004)	GR	40	men	multivariate	1	529	0.83 (0.66–1.02)
Villeneuve (1998)	CDN	7	women	multivariate	1	8 196	0.88 (0.68–1.04)

Definition of age group: 1 = " <65 years", 2 = " ≥65 years", 3 = "all ages"

Table A2 Studies with **three** intensity groups of physical activity: **Sex = all**.

First author (year)	Country	Follow-up (yrs)	Adjustment	Age group	Number of participants	RR in the moderate active group + (95 % CI)	RR in the most active group + (95 % CI)
LaCroix (1996)	USA	5	age	2	1 645	0.69 (0.46–1.06)	0.73 (0.48–1.10)
Kujala (1998)	FIN	19	age	1	15 902	0.71 (0.62–0.81)	0.57 (0.45–0.74)
Hillsdon (2003)	GB	12	age	1	10 522	0.57 (0.42–0.79)	0.72 (0.54–0.95)
LaCroix (1996)	USA	5	multivariate	2	1 645	0.83 (0.53–1.29)	0.91 (0.58–1.42)
Kujala (1998)	FIN	19	multivariate	1	15 902	0.80 (0.69–0.91)	0.76 (0.59–0.98)
Hillsdon (2003)	GB	12	multivariate	1	10 522	0.63 (0.45–0.89)	0.81 (0.60–1.09)

Table A3 Studies with **three** intensity groups of physical activity: **Sex = men**.

First author (year)	Country	Follow-up (yrs)	Adjustment	Age group	Number of participants	RR in the moderate active group + (95 % CI)	RR in the most active group + (95 % CI)
Leon (1991)	USA	10.5	age	1	12 138	0.85 (0.73–0.99)	0.87 (0.74–1.01)
Paffenbarger (1993)	USA	9	age	3	10 269	0.70 (0.54–0.88)	0.68 (0.54–0.95)
LaCroix (1996)	USA	5	age	2	615	0.78 (0.43–1.45)	0.89 (0.49–1.62)
Morgan (1997)	GB	10	age	2	635	0.62 (0.38–1.00)	0.36 (0.26–0.51)
Rosengren (1997)	S	20	age	1	7 142	0.74 (0.68–0.82)	0.73 (0.68–0.79)
Bijnen (1998)	NL	10	age	2	802	0.67 (0.52–0.85)	0.64 (0.50–0.83)
Hakim (1998)	USA	12	age	2	707	0.64 (0.38–1.12)	0.53 (0.34–0.77)
Andersen (2000)	DK	14.5	age	3	17 265	0.71 (0.66–0.76)	0.65 (0.59–0.70)
Yu (2003)	GB	11	age	1	1 975	0.88 (0.66–1.18)	0.58 (0.41–0.82)
Barengo (2004)	FIN	20	age	1	15 853	0.85 (0.79–0.92)	0.60 (0.53–0.68)
Leon (1991)	USA	10.5	multivariate	1	12 138	0.89 (0.77–1.04)	0.92 (0.79–1.07)
Lindsted (1991)	USA	26	multivariate	1	9 484	0.68 (0.59–0.78)	0.76 (0.63–0.92)
Mensink (1996)	D	8	multivariate	1	954	0.61 (0.35–1.05)	0.79 (0.48–1.31)
Morgan (1997)	GB	10	multivariate	2	635	0.85 (0.52–1.39)	0.63 (0.44–0.89)
Rosengren (1997)	S	20	multivariate	1	7 142	0.84 (0.77–0.93)	0.83 (0.77–0.90)
Bijnen (1998)	NL	10	multivariate	2	802	0.80 (0.63–1.02)	0.77 (0.59–1.00)
Hakim (1998)	USA	12	multivariate	2	707	0.62 (0.36–1.08)	0.56 (0.37–0.83)
Sherman (1999)	USA	16	multivariate	3	962	0.85 (0.77–0.94)	0.80 (0.70–0.89)
Andersen (2000)	DK	14.5	multivariate	3	17 265	0.72 (0.66–0.78)	0.71 (0.65–0.78)
Yu (2003)	GB	11	multivariate	1	1 975	0.87 (0.65–1.17)	0.61 (0.43–0.86)
Barengo (2004)	FIN	20	multivariate	1	15 853	0.91 (0.85–0.98)	0.80 (0.71–0.90)

Table A4 Studies with **three** intensity groups of physical activity: **Sex = women**.

First author (year)	Country	Follow-up (yrs)	Adjustment	Age group	Number of participants	RR in the moderate active group + (95 % CI)	RR in the most active group + (95 % CI)
LaCroix (1996)	USA	5	age	2	1 030	0.50 (0.28–0.90)	0.45 (0.25–0.83)
Kushi (1997)	USA	7	age	1	40 417	0.66 (0.60–0.73)	0.58 (0.52–0.65)
Morgan (1997)	GB	10	age	2	635	0.61 (0.40–0.92)	0.36 (0.27–0.48)
Andersen (2000)	DK	14.5	age	3	13 375	0.64 (0.59–0.69)	0.55 (0.49–0.62)
Barengo (2004)	FIN	20	age	1	16 824	0.85 (0.77–0.94)	0.87 (0.74–1.02)
Lissner (1996)	S	20	multivariate	1	1 405	0.56 (0.39–0.82)	0.45 (0.24–0.86)
Mensink (1996)	D	8	multivariate	1	1 142	0.94 (0.51–1.75)	0.81 (0.44–1.49)
Kushi (1997)	USA	7	multivariate	1	40 417	0.77 (0.69–0.86)	0.68 (0.60–0.77)
Morgan (1997)	GB	10	multivariate	2	635	0.73 (0.48–1.12)	0.48 (0.36–0.65)
Sherman (1999)	USA	16	multivariate	3	1 410	0.84 (0.76–0.93)	0.83 (0.75–0.90)
Andersen (2000)	DK	14.5	multivariate	3	13 375	0.65 (0.60–0.71)	0.59 (0.52–0.67)
Barengo (2004)	FIN	20	multivariate	1	16 824	0.90 (0.82–0.99)	0.98 (0.83–1.15)

Table A5 Studies with **four** intensity groups of physical activity: **Sex = all**.

First author (year)	Country	Follow-up (yrs)	Adjustment	Age group	Number of participants	RR in the light active group + (95 % CI)	RR in the moderate active group + (95 % CI)	RR in the most active group + (95 % CI)
Andersen (2000)	DK	14.5	age	3	30 640	0.68 (0.64–0.71)	0.61 (0.57–0.66)	0.53 (0.41–0.68)
Hillsdon (2003)	GB	12	age	1	7 704	0.68 (0.45–1.05)	0.40 (0.27–0.58)	0.40 (0.28–0.57)
Hillsdon (2003)	GB	12	multivariate	1	7 704	1.14 (0.74–1.78)	0.53 (0.35–0.82)	0.52 (0.35–0.78)

Table A6 Studies with **four** intensity groups of physical activity: **Sex = men**.

First author (year)	Country	Follow-up (yrs)	Adjustment	Age group	Number of participants	RR in the light active group + (95 % CI)	RR in the moderate active group + (95 % CI)	RR in the most active group + (95 % CI)
Morris (1990)	GB	9.5	age	1	9 376	0.88 (0.66–1.17)	0.78 (0.54–1.12)	0.34 (0.18–0.66)
Eaton (1995)	ISR	21	age	3	8 463	0.84 (0.74–0.94)	0.81 (0.73–0.90)	0.84 (0.72–0.98)
Leon (1997)	USA	16	age	1	12 138	0.78 (0.67–0.91)	0.77 (0.66–0.90)	0.74 (0.63–0.86)
Wannamethee (1998)	GB	4	age	3	5 934	0.57 (0.40–0.78)	0.39 (0.25–0.62)	0.48 (0.34–0.68)
Morris (1990)	GB	9.5	multivariate	1	4 824	0.90 (0.57–1.44)	0.59 (0.34–1.05)	0.53 (0.21–1.32)
Sandvik (1993)	N	16	multivariate	1	1 960	0.92 (0.66–1.28)	1.00 (0.71–1.41)	0.54 (0.32–0.89)
Haapanen (1996)	FIN	11	multivariate	1	1 072	0.40 (0.21–0.75)	0.64 (0.34–1.20)	0.37 (0.19–0.68)
Folsom (1997)	USA	7	multivariate	1	6 188	0.83 (0.60–1.14)	0.97 (0.65–1.45)	0.68 (0.47–0.99)
Leon (1997)	USA	16	multivariate	1	12 138	0.85 (0.73–0.99)	0.87 (0.75–1.02)	0.83 (0.71–0.97
Erikssen (1998)	N	13	multivariate	1	1 428	0.72 (0.52–0.99)	0.48 (0.33–0.71)	0.45 (0.29–0.69)
Villeneuve (1998)	CDN	7	multivariate	1	6 246	0.81 (0.59–1.11)	0.79 (0.54–1.13)	0.86 (0.61–1.22)
Wannamethee (1998)	GB	4	multivariate	3	5 934	0.61 (0.43–0.86)	0.50 (0.31–0.79)	0.65 (0.45–0.94)
Breckenkamp (2004)	D	14	multivariate	1	2 320	0.62 (0.35–1.08)	0.76 (0.45–1.29)	0.44 (0.30–0.65)

Table A7 Studies with **four** intensity groups of physical activity: **Sex = women**.

First author (year)	Country	Follow-up (yrs)	Adjustment	Age group	Number of participants	RR in the light active group + (95 % CI)	RR in the moderate active group + (95 % CI)	RR in the most active group + (95 % CI)
Weller (1998)	CDN	7	age	3	6 620	0.91 (0.66–1.25)	0.94 (0.72–1.23)	0.89 (0.67–1.17)
Folsom (1997)	USA	7	multivariate	1	7 852	0.79 (0.53–1.18)	1.05 (0.66–1.66)	0.58 (0.36–0.92)
Villeneuve (1998)	CDN	7	multivariate	1	8 196	0.94 (0.69–1.30)	0.92 (0.64–1.34)	0.71 (0.45–1.11)
Breckenkamp (2004)	D	14	multivariate	1	2 320	0.34 (0.14–0.81)	0.39 (0.17–0.91)	0.23 (0.12–0.42)

Table A8 Studies with **five** intensity groups of physical activity.

First author (year)	Country	Follow-up (year)	Sex	Adjustment	Age group
Fried (1998)	USA	5	all	age	2
Fried (1998)	USA	5	all	multivariate	2
Sundquist (2004)	S	12	all	multivariate	2
Sundquist (2004)	S	12	men	age	2
Lee (1995)	USA	26	men	multivariate	1
Sundquist (2004)	S	12	women	age	2
Rockhill (2001)	USA	20	women	age	1
Rockhill (2001)	USA	20	women	multivariate	1
First author (year)	**Number of participants**	**RR in the light active group + (95 % CI)**	**RR in the moderate active group + (95 % CI)**	**RR in the active group + (95 % CI)**	**RR in the most active group + (95 % CI)**
Fried (1998)	5201	0.62	0.55	0.43	0.29
		(0.49–0.80)	(0.43–0.70)	(0.34–0.55)	(0.23–0.38)
Fried (1998)	5201	0.78	0.81	0.72	0.56
		(0.60–1.00)	(0.63–1.05)	(0.55–0.93)	(0.43–0.74)
Sundquist (2004)	3206	0.72	0.60	0.50	0.60
		0.64–0.81)	(0.50–0.71)	(0.42–0.59)	(0.46–0.79)
Sundquist (2004)	1414	0.74	0.57	0.51	0.60
		(0.62–0.87)	(0.44–0.73)	(0.41–0.64)	(0.44–0.82)
Lee (1995)	17321	0.88	0.92	0.87	0.87
		(0.82–0.96)	(0.82–1.02)	(0.77–0.99)	(0.78–0.97)
Sundquist (2004)	1792	0.70	0.59	0.47	0.54
		(0.59–0.82)	(0.46–0.77)	(0.35–0.62)	(0.31–0.94)
Rockhill (2001)	4746	0.76	0.66	0.64	0.62
		(0.70–0.82)	(0.61–0.71)	(0.58–0.70)	(0.54–0.72)
Rockhill (2001)	4746	0.82	0.75	0.74	0.71
		(0.76–0.89)	(0.69–0.81)	(0.68–0.81)	(0.61–0.82)

(Above: Authors,Country,Follow-up,Sex,Adjustment, Age; Below:No of participants,RR according to the groups compared to sedentary group)