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LIFESTYLE-RELATED RISK FACTORS

Domains of physical activity and all-cause mortality: systematic review and dose–response meta-analysis of cohort studies

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Background The dose–response relation between physical activity and all-cause mortality is not well defined at present. We conducted a systematic review and meta-analysis to determine the association with all-cause mortality of different domains of physical activity and of defined increases in physical activity and energy expenditure.

Methods MEDLINE, Embase and the Cochrane Library were searched up to September 2010 for cohort studies examining all-cause mortality across different domains and levels of physical activity in adult general populations. We estimated combined risk ratios (RRs) associated with defined increments and recommended levels, using random-effects meta-analysis and dose–response meta-regression models.

Results Data from 80 studies with 1 338 143 participants (118 121 deaths) were included. Combined RRs comparing highest with lowest activity levels were 0.65 [95% confidence interval (95% CI) 0.60–0.71] for total activity, 0.74 (95% CI 0.70–0.77) for leisure activity, 0.64 (95% CI 0.55–0.75) for activities of daily living and 0.83 (95% CI 0.71–0.97) for occupational activity. RRs per 1-h increment per week were 0.91 (95% CI 0.87–0.94) for vigorous exercise and 0.96 (95% CI 0.93–0.98) for moderate-intensity activities of daily living. RRs corresponding to 150 and 300 min/week of moderate to vigorous activity were 0.86 (95% CI 0.80–0.92) and 0.74 (95% CI 0.65–0.85), respectively. Mortality reductions were more pronounced in women.

Conclusion Higher levels of total and domain-specific physical activity were associated with reduced all-cause mortality. Risk reduction per unit of time increase was largest for vigorous exercise. Moderate-intensity activities of daily living were to a lesser extent beneficial in reducing mortality.

Keywords Physical activity, energy expenditure, all-cause mortality, meta-analysis

Introduction

Physical activity, defined as movements produced by skeletal muscles that result in energy expenditure,[1] has repeatedly been shown to be associated with reductions in the risk of all-cause mortality[2,3] and reductions in major causes of death, such as cardiovascular disease[4–6] and cancer.[7] However, the likely reductions in mortality associated with different domains and different levels of physical activity and energy expenditure are not well defined at present.[8–10]

Physical activity is undertaken in different contexts or domains, which are related to occupation, the routines of daily living (e.g. domestic activities, active commuting) and leisure (e.g. recreational activities, exercise and sports).[11,12] The intensity, duration and frequency within each of these domains are used to estimate the total amount of physical activity.[11,12] Table 1 summarizes physical activity guidelines from leading public health agencies.[13–16] The most recent guidelines recommend a minimum of 150 min/week of moderate-intensity physical activity or 75 min/week of vigorous-intensity physical activity or an equivalent combination of moderate and vigorous activities.[16] Activities of 3–6 metabolic units (METs) are generally defined as moderate and activities >6 METs are considered as vigorous.[15,17] Resting energy expenditure is assumed to be 1 MET (~3.5 ml oxygen uptake/kg/min).

We conducted a systematic review and meta-analysis of prospective epidemiological studies in general population samples to quantify relationships between all-cause mortality and different domains of physical activity, with standardized increments and recommended levels of physical activity and energy expenditure.

Methods

Search strategy and eligibility criteria

We searched MEDLINE (from 1966 to 1 September 2010) and Embase (from 1980 to 1 September 2010) and the Cochrane Database of Systematic Reviews (up to issue 8, 2010), with no language restrictions, for studies in humans of the association between physical activity and all-cause mortality. Our search consisted of terms related to physical activity (for example, 'motor activity', 'leisure activities', 'exercise', 'activities of daily living', 'active transport') combined with terms for mortality and prospective studies. The detailed MEDLINE search is given in Supplementary

Table 1 Public health statements on the recommended minimal levels of physical activity in adults

Year, Organization	Recommendation (text)	Recommended minimal levels
1996, Surgeon General's Report Guidelines[13]	'The report recommends a moderate amount of physical activity equivalent to physical activity that uses ~150 kcal of energy per day, or 1000 kcal per week.'	150 kcal/day, or 1000 kcal/week
2004, United Kingdom Chief Medical Officer's Report Guidelines[14]	'For general health benefit, adults should achieve a total of at least 30 minutes a day of at least moderate-intensity physical activity on 5 or more days of the week. The activity can be lifestyle activity or structured exercise or sport, or a combination of these.'	150 min of moderate-intensity physical activity per week
2007, ACSM-AHA updated Guidelines for Adults[15]	'30 min of moderate-intensity aerobic physical activity 5 days per week or 20 min of vigorous-intensity physical activity on 3 days per week, or a combination of moderate- and vigorous activity. Moderate-intensive activity can be accumulated towards the 30 minimum from bouts lasting 10 or more minutes. This activity is in addition to the light intensity activities performed during daily life.'	150 min of moderate-intensity aerobic physical activity per week or 60 min of vigorous-intensity aerobic physical activity per week
2008, Physical Activity Guidelines for Americans[16]	'Adults should do at least 150 minutes a week of moderate-intensity aerobic physical activity or 75 minutes of vigorous-intensity aerobic physical activity. For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 minutes a week of moderate-intensity or 150 minutes a week of vigorous-intensity aerobic physical activity.'	150 min of moderate-intensity aerobic physical activity per week or 75 min of vigorous-intensity aerobic physical activity per week

ACSM: American College of Sports Medicine; AHA: American Heart Association.

Table S1, available as Supplementary Data at *IJE* online. We also searched the reference lists of relevant articles, and of previous reviews and meta-analyses.

We included cohort studies in adult general populations with a follow-up duration of at least 2 years if they assessed levels of physical activity at baseline and recorded mortality during follow-up. Studies of total physical activity (related to work, leisure and activities of daily living) and studies of domain-specific physical activity (leisure-time physical activity, exercise and sports, routine activities of daily living, physical activity for transportation, occupational physical activity if not assessed exclusively) were eligible.

We excluded cohorts of patients with chronic disease (for example, cardiovascular disease) and studies using measures of fitness. Studies had to report risk ratios (RRs) with confidence intervals (CIs) or standard errors, comparing groups defined by different levels of physical activity or energy expenditure. Two investigators (G.S. and M.Z.) independently screened titles and abstracts. A citation was evaluated further if one of the two reviewers selected it. Eligibility was determined by consensus based on the full-text articles.

Data extraction and quality assessment

The same two reviewers independently extracted data on the cohort and the domains of physical activity assessed, the type of physical activity questionnaire used, the measurement of exposure (e.g. frequency per week, minutes per day or per week, MET-hours per day or per week, kilocalories per day or per week,) the number of assessments and, within each domain, the amount of physical activity or energy expenditure, the number of deaths and total number of person-years of follow-up. We extracted results from crude or minimally adjusted models (adjusted for few variables, e.g. age and sex) and from maximally adjusted models, which were additionally adjusted for other variables, including cardiovascular risk factors, behavioural and socio-economic variables.

Assessment of quality was based on whether or not the study was population-based (a representative sample of the population under study), whether participants had been selected randomly, whether characteristics of study populations were clearly described (with respect to age, sex, racial or ethnic affiliation, health status, physical activity, cardiovascular risk factors and education), whether a clinical examination had taken place prior to study onset and whether follow-up was near-complete ($\geqslant$90%). We also assessed whether analyses had been adjusted for the following potential confounding factors: family history for coronary heart disease, cigarette smoking, hypertension or systolic or diastolic blood pressure, lipid factors, diabetes mellitus or blood glucose level, body mass index (BMI), alcohol consumption, diet, education, income or social status and marital status. Finally, we recorded the type of physical activity questionnaire used (complex questionnaire including quantitative history or simpler questionnaire), how it was administered (interviewer or self-administered) and how often the exposure variable was assessed during the course of follow-up (only once at baseline or at baseline and during follow-up). First authors of eligible studies were contacted if further information or clarifications were needed.

Statistical analysis and definitions

We combined minimally and maximally adjusted RRs comparing the highest with the lowest activity level for total physical activity (related to occupation, daily living and leisure) and for specific domains of physical activity using the DerSimonian and Laird random-effects model[18] that accounts for both within- and between-study variation. We considered the following domains: leisure time, leisure time combined with activities of daily living, activities of daily living only, exercise and sports only, transportation and occupational activities. Results for subgroups (e.g. by gender, by age, by county) were included as separate data sets. We assessed heterogeneity between studies using the I^2 statistic,[19] which estimates the proportion of total variation that is due to heterogeneity, rather than chance. Values of 25, 50 and 75% correspond to low, moderate and high degrees of heterogeneity, respectively.

We analysed the association between increments in physical activity and mortality in two steps. In the first step, we used the method of Greenland and Longnecker[20,21] to estimate the increase in log RR per 1 unit increase of physical activity. Only studies with three or more quantitative exposure levels were included in these analyses. For each study, the median or mean level of physical activity was assigned to the corresponding RR estimate. We assigned the mid-point of the upper and lower boundaries in each category if median or mean were not reported. Some studies reported open upper boundaries for the highest category (for example >200 min/week); we multiplied the reported upper boundary by 1.25 and used this value (250 min in the example).

In the second step, the study-specific risk increments were combined in random-effects meta-analysis. We grouped studies into three groups: (i) studies that reported activity levels in units of time; (ii) studies that reported activity dose in terms of kilocalories; and (iii) studies that used MET-hours to describe physical activity dose. We expressed results in relevant increments in physical activity, e.g. 1 additional h/week, 1000 additional kcal/week or 2 additional MET-h/day. Since most recent activity guidelines use time per week, we also estimated reductions in mortality associated with minimal amounts (150 min/week of moderate-intensity physical activity or 75 min/week of vigorous-intensity physical activity) and optimal amounts (300 min/week of moderate-intensity physical activity or 150 min/week of vigorous-intensity physical activity) as recommended by guidelines.[16]

Subgroup and sensitivity analysis

We used univariable and multivariable random-effects meta-regression models[22] to examine the influence of study-level variables on the association between physical activity and all-cause mortality, including gender distribution (all male, all female, mixed), mean age (<50, 50–69, ⩾70 years), region (Europe, North America, Asia), type of questionnaire used (complex questionnaire vs simple instrument) and duration (⩾11 vs <11 years) and completeness (⩾90 vs <90%) of follow-up. We also examined the importance of adjusting for smoking, BMI or several metabolic factors. We repeated analyses with minimally adjusted RRs. We excluded smaller studies with standard errors of log (RR) > 0.2. Publication bias was examined in funnel plots and a regression test of funnel plot asymmetry.[23] We used STATA version 11 (College Station, TX, USA) for all analyses.

Results

Identification and characteristics of studies

Our search identified 6933 potentially relevant reports, of which 180 were retrieved for detailed evaluation (Figure 1). Totally, 79 reports were excluded for the reasons given in Supplementary Table S2, available as Supplementary Data at *IJE* online. A total of 101 study reports met the inclusion criteria, including 21 reports from the same study. A total of 80 studies (1 338 143 study participants) were included in analyses, comparing highest with lowest levels of physical activity.[24–103] A total of 47 studies had to be excluded from the dose–response analyses for the reasons given in Supplementary Table S3, available as Supplementary Data at *IJE* online; 33 studies (844 026 participants) were included in these analyses.[32,35,40,43,46,48,49,52–55,57,62,69,71,72,76,78,81,83,84,86,88–92,95–97,100,102,103]

Of the 80 studies, 23 (28.8%) included men only, 9 studies (11.3%) included women only and 24 studies (30.0%) reported results combining men and women (Table 2). The studies covered a broad range of populations of middle and older age. Younger adults were under-represented. The mean age of cohort participants at baseline ranged from 28.8 to 85.9 years with a median of 56.4 years. Most studies were from Europe and North America and published in 2000–10. A total of 35 studies (43.8%) used detailed physical activity questionnaires, 43 (53.8%) used one to four questions or a brief global physical activity questionnaire and in 2 studies (2.5%),[27,63] it was unclear what questionnaire had been used. About 41 studies (51.3%) assessed leisure-time physical activity only and 35 studies (43.8%) assessed either total physical activity or leisure-time activity combined with routine activities of daily living. Only six studies (7.5%) assessed physical activities of daily living separately. A total of 70 studies (87.5%) assessed physical activity at baseline only and 10 (12.5%) performed repeat assessments. About half of the studies used ordinal categories (e.g. low, moderate, high), 24 (30.0%) used time units per day or week, 11 (13.8%) estimated MET-hours and 10 (12.5%) reported calorie expenditure. The 33 studies included in the dose–response analyses were published more recently, larger and of higher quality, with greater completeness of follow-up and frequent use of detailed questionnaires. Further details are given in Supplementary Table S4, available as Supplementary Data at *IJE* online.

Most studies adjusted for age, three-quarters of the studies adjusted for cigarette smoking and half of the studies adjusted for BMI and blood pressure (Supplementary Table S5, available as Supplementary Data at *IJE* online). Other confounders such as diabetes mellitus, lipid factors and alcohol consumption were considered in less than half of the studies, and measures of socio-economic status and marital status were included in less than one-third of studies. Adjustment in maximally adjusted analyses ranged from 2 to 23 variables, with a median of 7 variables.

Lowest vs highest level of physical activity

Table 3 shows combined RRs from maximally adjusted analyses of all-cause mortality comparing highest with lowest levels of total and domain-specific physical activity. Figures 2 and 3 show the forest plots for total and leisure activity. The forest plots for all other domains are shown in Supplementary Figures S1–S5, available as Supplementary Data at *IJE* online. The strongest associations between physical activity and mortality were observed for total activity (RR 0.65; 95% CI 0.60–0.71), exercise and sports (RR 0.66; 95% CI 0.61–0.71) and physical activities of daily living (RR 0.64; 95% CI 0.55–0.75). Weaker associations were found for occupational physical activity (RR 0.83; 95% CI 0.71–0.97) and transport-related physical activity (RR 0.88; 95% CI 0.79–0.98). Physical activity of daily living and occupational activity were associated with reduced mortality in women but not in men (Supplementary Figures S3 and S5, available as Supplementary Data at *IJE* online), and physical activity for transportation was associated with reduced mortality in the overall analysis but not in the sex-specific analysis (Supplementary Figure S4, available as Supplementary Data at *IJE* online).

For all domains, there was heterogeneity between studies, which was highest for occupational physical activity ($I^2 = 87.6\%$, $P < 0.001$) and lowest for exercise and sports ($I^2 = 39.9\%$, $P = 0.046$). Across all domains of physical activity, there was a consistently greater

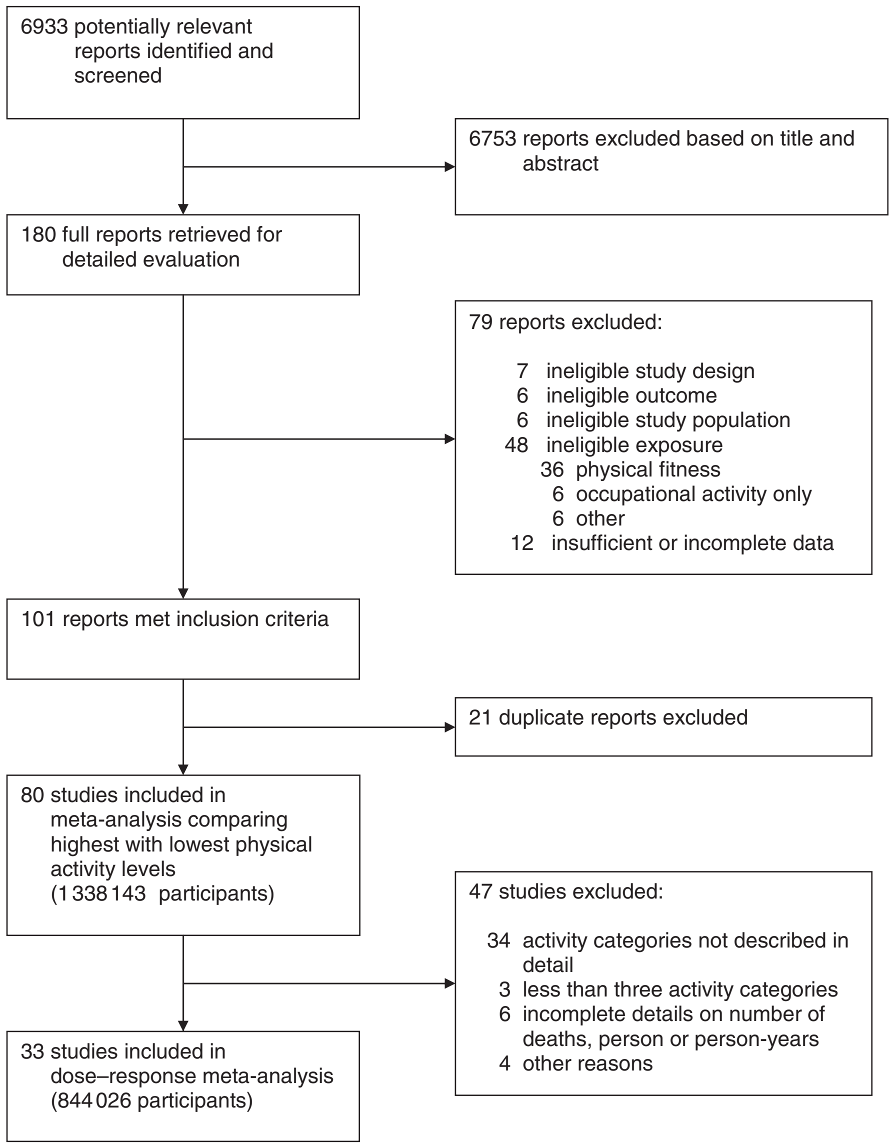

Figure 1 Selection of studies for meta-analysis

reduction of mortality in women compared with men: combined RR for total activity (0.58; 95% CI 0.52–0.66 vs 0.72; 95% CI 0.65–0.81) ($P = 0.018$ from meta-regression, Supplementary Table S6, available as Supplementary Data at *IJE* online). For leisure-time physical activity ($P = 0.028$ from meta-regression), activities of daily living ($P = 0.118$) and physical activity for transportation ($P = 0.038$), we observed a larger reduction in mortality for cohorts with a mean age of ⩾70 years compared with cohorts of younger age groups. The reduction in mortality was smaller in studies that used a complex physical activity questionnaire. The administration of the questionnaire (interview or self-administered) and the number of measurements (at baseline or at baseline and during follow-up) did not affect risk estimates. For studies of leisure-time activity, reductions in mortality were smaller with a longer (⩾11 vs <11 years; $P = 0.014$) and near complete (⩾90 vs <90%; $P = 0.064$) follow-up (Supplementary Table S6, available as Supplementary Data at *IJE* online). Finally, when we repeated analyses with RRs from minimally adjusted models, the association of physical activity and all-cause mortality was stronger: RR for total physical activity (0.54; 95% CI 0.49–0.60) (Supplementary Table S7, available as Supplementary Data at *IJE* online).

In multivariable meta-regression analyses, I^2 was reduced by 20–25% when we included sex, cohort age, type of physical activity questionnaire, duration and completeness of follow-up and study region. When we additionally considered whether studies had adjusted for smoking, BMI and other cardio-metabolic and socio-economic variables, I^2

Table 2 Characteristics of studies of physical activity and all-cause mortality included in meta-analyses

Characteristic	Comparisons of highest vs lowest level of physical activity ($n = 80$)	Analyses of increments in physical activity ($n = 33$)
Study population		
Median study size (range)	7136 (248–252 925)	10385 (248–252 925)
Median of mean age[a], years (range)	56.4 (28.8–85.9)	56.5 (33.8–85.9)
Men only	23 (28.8)	7 (21.2)
Women only	9 (11.3)	5 (15.2)
Men and women	48 (60.0)	21 (63.6)
Study region		
Europe	42 (52.5)	16 (48.5)
North America	26 (32.5)	10 (30.3)
Asia/Australia	12 (15.0)	7 (21.2)
Duration of follow-up		
Median of means, years (range)	10.7 (2.0–55.3)	9.7 (2.0–24.0)
Completeness of follow-up		
⩾90%	24 (30.0)	24 (72.7)
<90% or not reported	56 (70.0)	9 (27.3)
Year of publication		
<2000	30 (37.5)	8 (24.2)
2000–10	50 (62.5)	25 (75.8)
Physical activity questionnaire		
Detailed questionnaire	35 (43.8)	28 (84.8)
Brief questionnaire	43 (53.8)	5 (15.2)
Type of questionnaire not described	2 (2.5)	0 (0.0)
Interviewer administered	39 (48.8)	12 (36.4)
Self-administered	38 (47.5)	21 (63.6)
Administration of questionnaire not described	3 (3.8)	0 (0.0)
Dimensions/types of physical activity assessed		
Total physical activity	21 (26.3)	6 (18.2)
Leisure time with activities of daily living	14 (17.5)	4 (12.1)
Leisure-time physical activity	41 (51.3)	4 (12.1)
Exercise and sports	13 (16.3)	8 (24.2)
Walking	11 (13.8)	10 (30.3)
Activities of daily living	6 (7.5)	4 (12.1)
Physical activity for transportation	6 (7.5)	5 (15.2)
Occupational physical activity	8 (10.0)	1 (3.0)
Measures of activity dose or energy expenditure		
Ordinal categories,[b] *n* (%)	41 (51.3)	0 (0.0)
Minutes/hours per day/week	24 (30.0)	22 (66.7)
Kilocalories per day/week	10 (12.5)	8 (24.2)
Metabolic equivalent hours per day/week	11 (13.8)	6 (18.2)
Frequency of physical activity per week	4 (5.0)	2 (6.1)
Miles/kilometres walked per day/week	2 (3.0)	0 (0.0)

Number of studies (%) unless otherwise indicated.
[a]Mean age was estimated for studies which reported age range only.
[b]For example, 'inactive' or 'low' for the lowest and 'active' or 'high' for the highest activity group.

Table 3 Maximally adjusted combined RRs comparing groups with highest and lowest levels of physical activity

Domain of physical activity	No. of studies	No. of participants/ deaths	RR (95% CI)	I^2 (%)	*P*-value[a]
Total physical activity[b]	21	395 655/31 169	0.65 (0.60–0.71)	79.4	<0.001
Leisure time with routine activities of daily living[c]	14	480 057/23 007	0.66 (0.61–0.71)	48.8	0.010
Leisure-time physical activity[d]	41	544 056/61 465	0.74 (0.70–0.77)	68.1	0.018
Exercise and sports[e]	13	460 924/20 209	0.66 (0.61–0.71)	39.9	0.046
Physical activities of daily living[f]	6	116 712/9065	0.64 (0.55–0.75)	77.0	0.039
Physical activity for transportation[g]	6	145 011/16 471	0.88 (0.79–0.98)	76.8	0.016
Occupational physical activity[h]	6	82 412/17 069	0.83 (0.71–0.97)	87.6	<0.001

Results from random-effects meta-analyses, adjusted for a median of 7 variables (interquartile range 5–10 variables)
[a]Represents *P*-value for heterogeneity,
[b]Includes studies assessing leisure-time physical activity, routine activities of daily living and occupational physical activity.
[c]Includes studies assessing leisure-time physical activity and one or more components of physical activities of daily living.
[d]Includes studies assessing recreational activities including callisthenics, dancing, walking, hiking, golf, bicycling, swimming, games, exercise and sports.
[e]Includes studies assessing structured aerobic and muscle-strengthening exercise and sports.
[f]Includes non-exercise activities including housework, gardening, stair climbing, walking and cycling as part of daily life.
[g]Includes studies assessing walking and/or cycling to and from work.
[h]Includes physical activities as part of occupation. Two studies[30,42] did not report relative risks for occupational physical activity because there was no association with all-cause mortality.

was not reduced further. Supplementary Figures S6 and S7, available as Supplementary Data at *IJE* online show the funnel plots for total and leisure activity. There was some evidence of funnel plot asymmetry for total and leisure activity ($P=0.20$ and 0.052 from regression test) but not for other domains. Results were similar when excluding smaller studies with standard errors of $\log(RR) > 0.2$.

Combined RRs comparing highest with lowest categories of physical activity from the 33 studies included in the analyses of incremental increases in physical activity were identical with the results from all 80 studies: 0.71 (95% CI 0.67–0.75) and 0.71 (95% CI 0.68–0.73), respectively.

Results by increments of physical activity

Among the 33 studies estimating RRs associated with incremental levels of physical activity (Table 2), a total of 22 studies[32,35,40,43,49,52,53,55,57,59,62,76,78,81,88–90,92,95,96,102,103] were included in the analysis of time units. Six of these studies assessed leisure-time activities of moderate and vigorous intensity[43,49,53,90,92,102] and eight assessed vigorous exercise and sports separately.[35,40,49,55,89,90,96,103] Ten studies examined walking,[32,52,57,62,78,88,89,95,96,102] four activities of daily living[81 89,96,102] and five assessed physical activities for transportation.[59,76,89,96,102]

Figure 4 shows the forest plots of maximally adjusted RRs per increment of physical activity of 1 h/week. The largest reduction in mortality was observed for vigorous-intensity exercise and sports (combined RR 0.91; 95% CI 0.87–0.94). The reduction was smaller for moderate to vigorous leisure-time activities (combined RR 0.94; 95% CI 0.92–0.97) and smallest for moderate-intensity activities of daily living, walking and physical activity for transportation, with combined RRs of 0.96–0.97. RRs comparing minimum or optimum levels of physical activity (75, 150, 300 min/week), as recommended by recent guidelines,[16] with the lowest level of activity ranged from 0.97 to 0.61, depending on level, domain and intensity of activity (Table 4).

There was substantial heterogeneity between studies ($I^2 = 73.1–96.4\%$). For activities of daily living ($P=0.031$ from meta-regression) and walking ($P=0.19$), we observed a larger reduction in mortality for cohorts with a mean age of $\geqslant 70$ years compared with those of younger age groups. RRs were again closer to 1, if a complex questionnaire had been used to assess physical activity.

Eight studies (56 773 study participants; 7742 deaths) examined the amount of energy spent on leisure-time activities,[48,72,86] leisure time combined with activities of daily living[46,54,55,71] or activities of daily living alone.[81] An increment of 1000 kcal/week was associated with an 11% lower mortality (RR 0.89; 95% CI 0.85–0.93) (Figure 5). RRs comparing minimum recommended or higher levels of energy expenditure (500, 1000, 2000, 3000 kcal/week) with the lowest level of activity ranged from 0.92 to 0.61 in women and from 0.97 to 0.81 in men (Table 5).

There was moderate heterogeneity across studies ($I^2 = 49.7\%$, $P=0.030$). The reduction in mortality per 1000 kcal increment per week was considerably

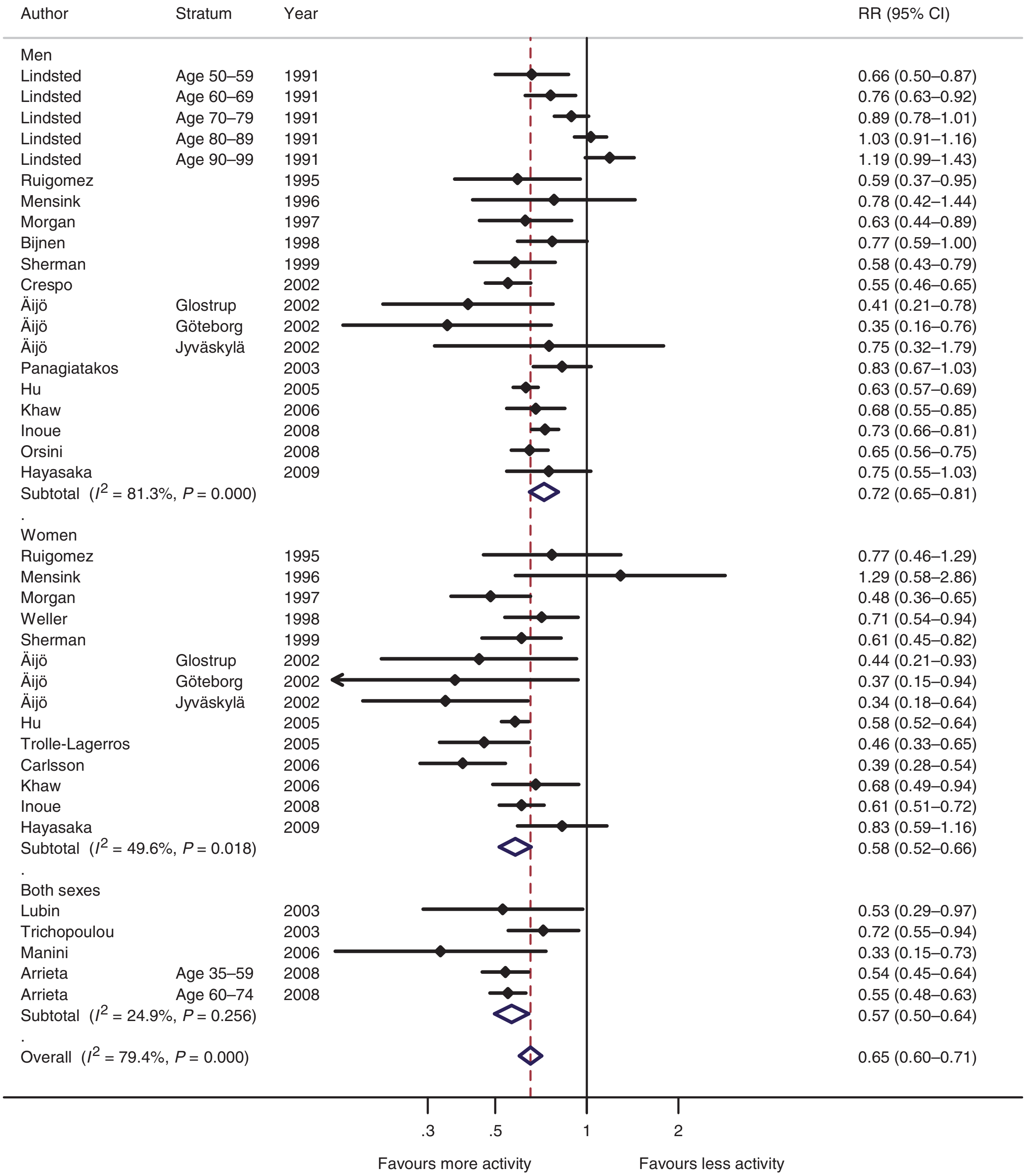

Figure 2 Mortality from all causes in individuals with highest compared with lowest levels of total physical activity. Results from random-effects meta-analysis of maximally adjusted RRs from 21 cohort studies (395 655 participants; 31 169 deaths). Arrows indicate that the plotted 95% CI is not showing the full width of the calculated 95% CI which is given in the RR column. The open diamonds show the summary estimate from the meta-analysis, and the dashed line the value of the summary estimate for all studies combined

stronger for women (RR 0.85; 95% CI 0.81–0.89) when compared with men (RR 0.93; 95% CI 0.91–0.96) ($P = 0.009$ from meta-regression), and for studies of cohorts with a median age ⩾70 years (RR 0.84; 95% CI 0.80–0.88) compared with studies of younger cohorts with RRs in the range of 0.91–0.92 ($P = 0.074$ from meta-regression). Reduction in mortality was smaller in studies with a longer duration of

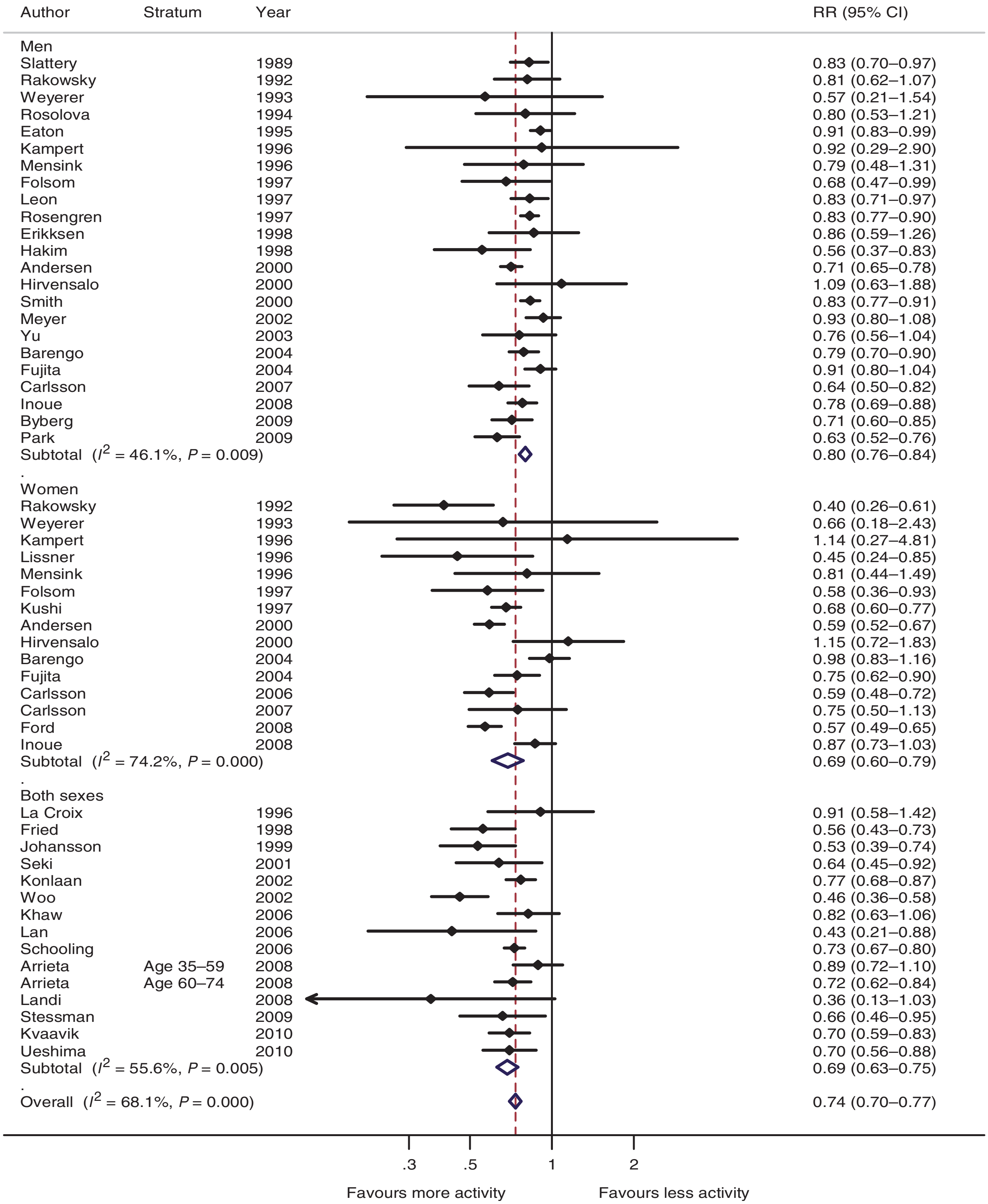

Figure 3 Mortality from all causes in individuals with highest compared with lowest levels of leisure-time physical activity. Results from random-effects meta-analysis of maximally adjusted RRs from 41 cohort studies (544 056 participants; 61 465 deaths). Arrows indicate that the plotted 95% CI is not showing the full width of the calculated 95% CI which is given in the RR column. The open diamonds show the summary estimate from the meta-analysis, and the dashed line the value of the summary estimate for all studies combined

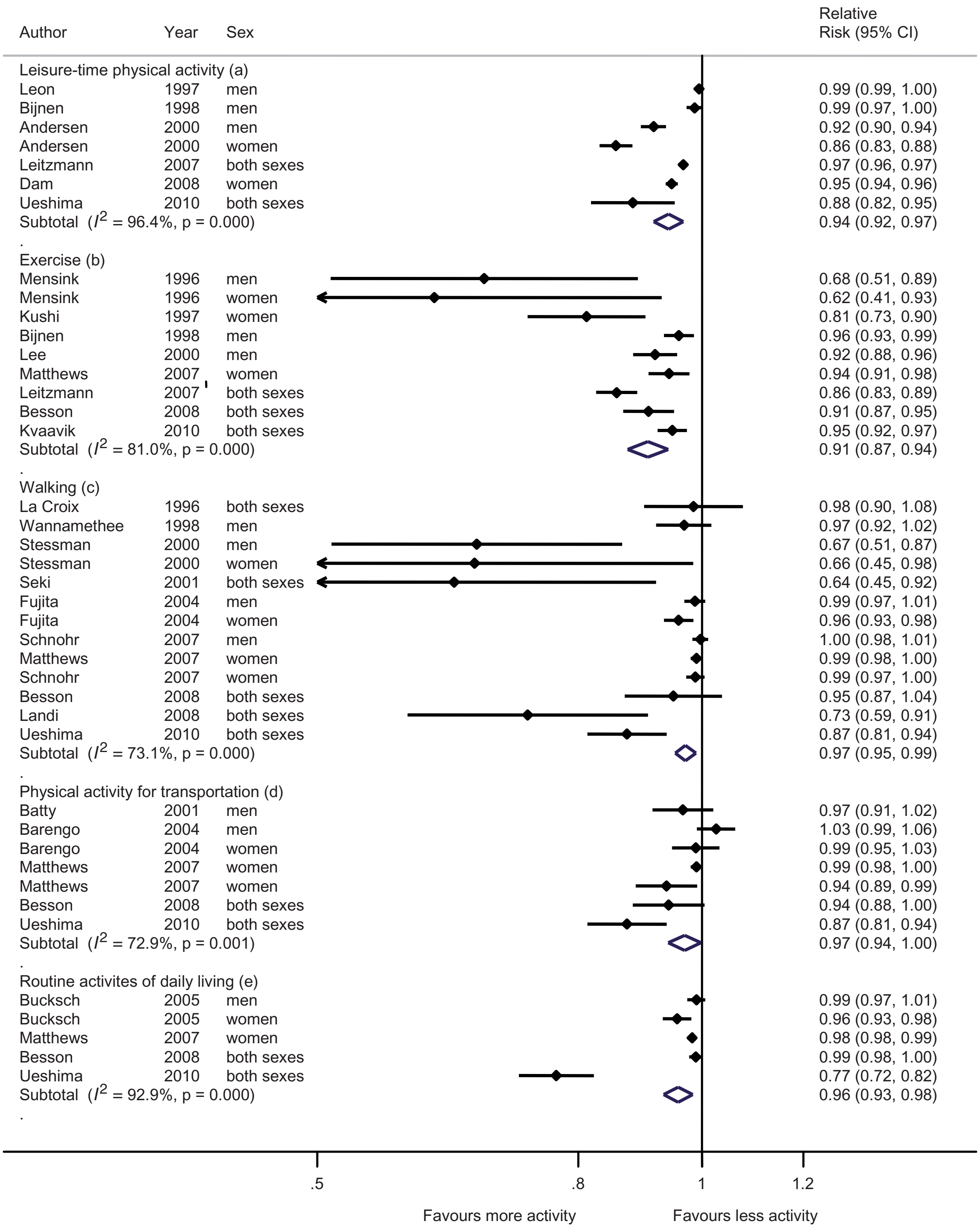

Figure 4 Meta-analysis of maximally adjusted RRs for all-cause mortality per increment of 1 h of physical activity per week for different domains and subdomains of physical activity. Results from random-effects meta-analysis of maximally adjusted RRs from 22 cohort studies (638 871 participants; 50 563 deaths). The median dose of physical activity for the lowest (reference) and highest activity category was 11 and 420 min/week, respectively. [a]Included studies that assessed mixed leisure-time physical activities of moderate and vigorous intensity. [b]Included studies that assessed vigorous-intensity exercise and sports. [c]Included studies that assessed walking as part of daily life, for transportation and for exercise. [d]Included studies that assessed walking and/or cycling to and from work. [e]Included studies that assessed moderate-intensity activities including housework, gardening, stair climbing, walking and cycling as part of daily life. Arrows indicate that the plotted 95% CI is not showing the full width of the calculated 95% CI which is given in the RR column. The open diamonds show the summary estimate from the meta-analysis, and the dashed line the value of the summary estimate for all studies combined

Table 4 Maximally adjusted RRs of all-cause mortality for 60, 150 and 300 min/week of physical activity compared with lowest level of activity for different domains and types of moderate- and vigorous-intensity physical activity

Domain or type of physical activity	No. of studies	Combined RR (95% CI)		
		60 min (75 min)[a]	150 min[a]	300 min[b]
Vigorous exercise and sports[c]	8	0.91 (0.87–0.94) [0.89 (0.85–0.93)]	0.78 (0.72–0.88)	0.61 (0.51–0.74)
Moderate and vigorous leisure-time activities[d]	6	0.94 (0.92–0.97)	0.86 (0.80–0.92)	0.74 (0.65–0.85)
Moderate activities of daily living[e]	4	0.96 (0.93–0.98)	0.90 (0.84–0.96)	0.81 (0.71–0.92)
Walking[f]	10	0.97 (0.95–0.99)	0.93 (0.87–0.97)	0.86 (0.79–0.95)
Physical activity for transportation[g]	5	0.97 (0.94–1.00)	0.92 (0.86–0.99)	0.85 (0.74–0.99)

The median amount of physical activity for the lowest activity category (reference) was 11 min/week.

[a]The US Department of Health and Human Services (HHS) Guidelines 2008[16] recommend at least 150 min/week of moderate-intensity aerobic physical activity or 75 min of vigorous-intensity aerobic physical activity.

[b]For additional and more extensive health benefits, the HHS recommends that adults should increase their aerobic physical activity to 300 min/week of moderate-intensity or 150 min/week of vigorous-intensity aerobic physical activity.

[c]Included studies assessed vigorous-intensity exercise and sports.

[d]Included studies assessed mixed leisure-time physical activity of moderate and vigorous intensity.

[e]Included studies assessed moderate-intensity activities including housework, gardening, stair climbing, walking and cycling as part of daily life.

[f]Included studies assessed walking as part of daily life, for transportation and for exercise.

[g]Included studies assessed walking and/or cycling to and from work.

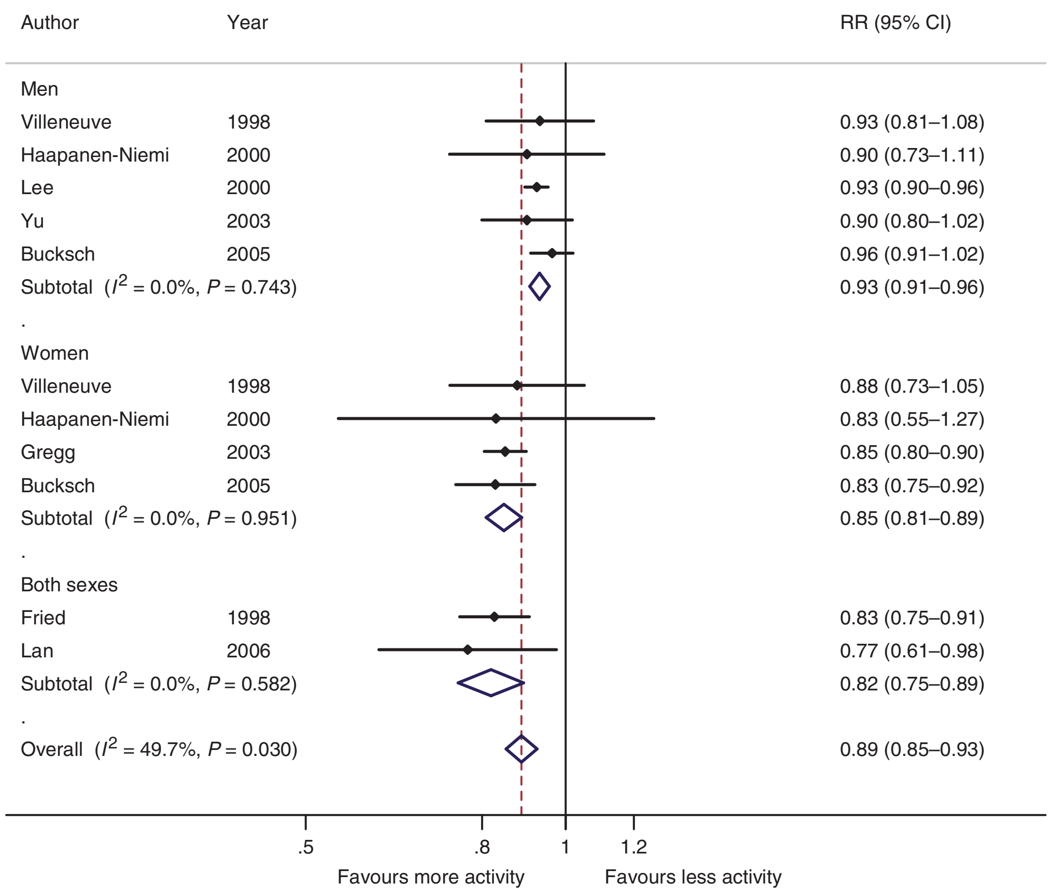

Figure 5 Meta-analysis of maximally adjusted RRs of all-cause mortality for 1000 kcal in energy expenditure per week compared with lowest level of activity. Results from random-effects meta-analysis from eight cohort studies (56 773 study participants; 7742 deaths) of moderate- and vigorous-intensity leisure-time activities and moderate-intensity activities of daily living. The median level of energy expenditure for the lowest (reference) and highest activity category was 114 and 2490 kcal/week, respectively. Arrows indicate that the plotted 95% CI is not showing the full width of the calculated 95% CI which is given in the RR column. The open diamonds show the summary estimate from the meta-analysis, and the dashed line the value of the summary estimate for all studies combined

Table 5 Maximally adjusted RRs of all-cause mortality for 500, 1000, 2000 and 3000 kcal/week of physical activity compared with lowest level of activity

Sex	No. of studies	Combined RR (95% CI)			
		500 kcal[a]	1000 kcal[b]	2000 kcal	3000 kcal
Men	5	0.97 (0.95–0.98)	0.93 (0.91–0.96)	0.87 (0.83–0.92)	0.81 (0.75–0.88)
Women	4	0.92 (0.90–0.94)	0.85 (0.81–0.89)	0.72 (0.65–0.79)	0.61 (0.53–0.70)
Overall	8	0.94 (0.92–0.96)	0.89 (0.85–0.93)	0.78 (0.72–0.86)	0.69 (0.61–0.79)

The median level of energy expenditure for the lowest activity category (reference) was 114 kcal/week

[a]A consensus statement on dose–response issues concerning physical activity and health suggested that volumes of physical activity as low as 500 kcal/week might demonstrate a slight favourable effect on all-cause mortality[10].

[b]The Surgeon General's Report Guidelines[13] recommend a moderate amount of physical activity that uses ~1000 kcal/week as minimum level for achieving substantial health benefits. This amount is roughly equivalent to 150–200 min of moderate-intensity physical activity per week.

follow-up (>11 vs <11 years) ($P = 0.043$ from meta-regression).

Finally, in six studies (183 271 participants; 13 289 deaths),[69,84,91,96,97,100] total physical activity was expressed in MET-hours per day. All studies investigated cohorts with a median age of 50–59 years and used a similar, complex questionnaire to assess total activity. All studies except one[96] measured total activity over 24 h. An increment of 2 MET-h/day (~1 h of light-intensity activity or 30 min of moderate-intensity activity) was associated with a 5% lower risk in all-cause mortality (RR 0.95; 95% CI 0.93–0.96), with moderate heterogeneity across studies ($I^2 = 68.7\%$, $P = 0.002$) (Figure 6). RRs for increments of 2, 4 and 7 MET-h/day ranged from 0.79 to 0.94 in women and from 0.83 to 0.95 in men (Table 6); $P = 0.51$ for difference between genders from meta-regression.

Discussion

This systematic review and meta-analysis of cohort studies in general populations supports an inverse relationship between increasing levels of total and domain-specific physical activity and all-cause mortality, with stronger associations for women than for men, and for exercise and sports, leisure-time activities and activities of daily living than for occupational and transport-related activity. Reductions in mortality per increment of time of physical activity were larger for vigorous exercise and moderate to vigorous leisure activities than for moderate activities of daily living, physical activity for transportation and walking. Reductions in all-cause mortality rates corresponding to recommended minimum levels of physical activity or energy expenditure ranged from 7 to 14%.

Findings in relation to previous studies and recommendations

This study extends the results from previous reviews and meta-analyses[2,3,104–107] but is, to our knowledge, the first to quantify the reduction in all-cause mortality risk associated with well-defined increments in total and domain-specific physical activity and energy expenditure. A recent systematic review and meta-analysis combined cohort studies of different domains of physical activity and found a 29% reduction in all-cause mortality, when comparing the least and most active groups of 21 cohorts; a result identical to the combined RR of all 80 studies included in our systematic review (0.71; 95% CI 0.68–0.73).[105] Similar to our results, the risk reduction was larger for women than for men. Löllgen *et al*.[106] combined data from cohort studies of leisure-time physical activity and found also larger reductions in women. Hamer and Chida[104] examined the association between walking and mortality and suggested a 20% risk reduction for an estimated exposure of ~3 h/week, a considerably larger reduction compared with this study (RR 0.91; 95% CI 0.86–0.97), but their estimate was not based on a formal dose–response analysis. In our analysis of studies of walking, the mortality reduction per increment in time per week was comparable with that observed for other moderate-intensity activities of daily living. A recent meta-analysis[107] also found a smaller reduction in mortality risk for studies that assessed walking. This meta-analysis[107] quantified the dose–response relationship of non-vigorous physical activity and all-cause mortality in 22 cohort studies and found, compared with no activity, a 19% reduction in mortality risk associated with 11 MET-h/week (~2.5 h of moderate physical activity). This study suggested a curvilinear relationship between physical activity and all-cause mortality with larger benefits from moving from little activity to low levels of activity and smaller additional benefits when the same increment is added to higher levels of activity. The results implied that 1 h/week of physical activity (compared with 0 h) offers nearly two-thirds of the mortality reduction associated with 10 h/week, which may not be plausible and could reflect reverse causality, where in the lowest activity group many individuals are sedentary because of ill health. One large cohort study found evidence for such a phenomenon.[108]

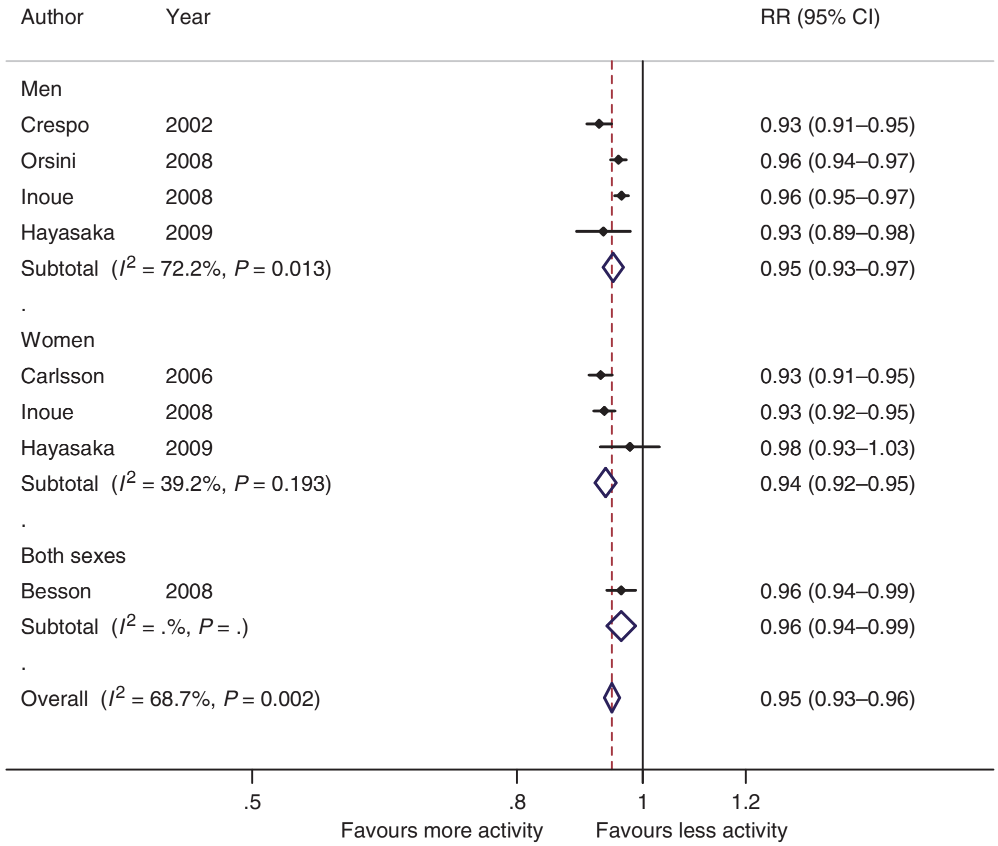

Figure 6 Meta-analysis of maximally adjusted RRs for all-cause mortality per increment of 2 MET-h/day. Results from random-effects meta-analysis from six cohort studies (183 271 participants; 13 289 deaths) of total physical activity. The median level for the lowest (reference) and highest activity category was 27.3 and 44.4 MET-h/day, respectively. 1 MET represents an individual's energy expenditure while sitting quietly, which is ~3.5 ml O_2/kg/min.[17] Activities <3 METs are generally defined as light, activities 3–6 METs are considered as moderate and activities >6 METs are defined as vigorous.[15,17] MET-hours per day are estimated by multiplying the time score spent at each activity per day by its MET value. About 24 MET-h correspond to sitting quietly for 24 h. For example, an office worker with no outside exercise could have a score of 27 MET-h. A labourer who is involved in heavy activity in his job could have a score of >40 MET-h. An increment of 2 MET-h/day is ~1 h of light-intensity activity based on a MET value of 2.0 or 30 min of moderate-intensity activity based on a MET value of 4.5

Table 6 Maximally adjusted RRs of all-cause mortality associated with an increment of 2, 4 and 7 MET-h in total physical activity per day compared with lowest level of activity

		Combined RR (95% CI)		
Sex	**No. of studies**	2 MET-h/day (~850 MET-min/week)[a]	4 MET-h/day (~1800 MET-min/week)[a,b]	7 MET-h/day (~3000 MET-min/week)[b]
Men	4	0.95 (0.93–0.97)	0.90 (0.87–0.93)	0.83 (0.78–0.89)
Women	3	0.94 (0.92–0.95)	0.88 (0.87–0.93)	0.79 (0.74–0.85)
Overall	6	0.95 (0.93–0.96)	0.90 (0.87–0.92)	0.83 (0.79–0.87)

The median level for the lowest activity category (reference) was 27.3 MET-h/day. Twenty-four MET-hours correspond to sitting quietly for 24 h.

[a]The International Physical Activity questionnaire[131] uses 600–2999 MET-min/week as the range for classifying total activity as 'moderate' and 3000 MET-min/week as the cut point for classifying total activity as 'high'.

[b]In The Eurobarometer study,[110] <600 MET-min/week of total activity were classified as 'sedentary', 600–2999 MET-min/week were classified as 'low total activity' (some activity but not sufficient for health) and >3000 MET-min/week were classified as 'sufficient total activity', this is in addition to 24 MET-h/day.

Our study found a larger reduction in mortality per increment of time of physical activity per week for vigorous-intensity exercise and sports but a smaller reduction for moderate-intensity activities of daily living, including domestic activities, gardening and walking. It is unclear whether this difference in risk reduction between vigorous- and lower-intensity activities for the same total duration can be attributed to the intensity of the activity or merely to the difference in energy expenditure. Vigorous-intensity physical activities expend more total energy per unit of time than do lower intensity physical activities.[17] Only few studies accounted for this correlation.

Two earlier reviews, without meta-analysis,[2,3] suggested an energy expenditure of ~1000 kcal/week as recommended by the Surgeon General[13] would reduce all-cause mortality by 20–30% and risk reduction would be comparable for men and women. In our study, 1000 kcal/week were associated with a 7% (95% CI 4–9) reduction in men and 15% (95% CI 11–19) reduction in women. The level of kilocalories per week associated with a certain amount of physical activity differs by body mass.[109] Calorie goals corrected for body mass or based on sex are required when making physical activity recommendations in terms of kilocalories per week. In our study, a 10% reduction in all-cause mortality corresponded to an energy expenditure of 1500 kcal/week in men and 650 kcal/week in women.

Finally, our study was the first to combine data of studies that assessed total activity (daily living, active commuting, occupation, leisure time). The Eurobarometer study[110] proposed 3000 MET-min/week accumulated over 7 days (~7 MET-h/day) as the cut-point for 'sufficient total activity'. In our study, this level was associated with a reduction in mortality risk of 17% in men and 21% in women.

Strengths and limitations

Our study has several strengths. We assessed the association with all-cause mortality for total activity but also for each domain of physical activity. This is important because activities within domains are likely to differ between men and women and between different age groups.[96] We calculated RRs associated with standardized differences in physical activity using accepted methods.[8,20,21] We excluded studies of patients with chronic conditions to reduce the possibility that low levels of physical activity are a consequence of disease. We excluded studies of physical fitness: although physical activity and fitness are interrelated, other factors determine levels of fitness, including genetic factors.[111] We did not use scales to measure study quality or risk of bias, which may produce misleading results[112] but assessed the importance of key methodological characteristics and other sources of hetereogeneity in meta-regression analyses.[19,22] We did not convert different measures or units, such as hours per week, kilocalories per week or MET-hours per week to one common measure (e.g. MET-hours per week), because we think that such calculations are problematic and prone to error. For example, the widely used definition of 1 MET as 3.5 ml O_2/kg/min may be a substantial overestimation of resting energy expenditure,[113] which would seriously affect calculations of energy expenditure from physical activity questionnaires.

Our analysis was based on observational studies and is therefore susceptible to the biases inherent in the original studies.[114,115] Most studies considered several potential confounders. Interestingly, associations were attenuated only slightly when adjusting for these, but we cannot rule out residual confounding. The methods used to measure physical activity varied among studies and relied on self-reported data, which may be susceptible to recall and other information bias.[116,117] The assessment of physical activity at baseline only may also have introduced bias, particularly in studies of longer duration. Overall, it seems likely that inaccuracies in the measurement of physical activity led to non-differential misclassification and attenuation of associations. Of note, a study that measured energy expenditure in elderly individuals objectively, using doubly labelled water, found larger reductions in mortality than typically seen in studies relying on self-reported data.[82]

We assumed a linear relation between the natural logarithm of the RR and increasing levels of physical activity, but did not test the appropriateness of this assumption. Several studies of physical activity and mortality[2] that tested for a linear trend of declining all-cause mortality rates with increasing levels of physical activity found such a trend, which have led to consensus statements that incorporated a linearity between volume of physical activity and mortality rates.[10]

Another limitation relates to the substantial heterogeneity between the results from the different studies. While many studies used ordinal categories (e.g. 'inactive', 'moderately active', 'highly active'), others used more objective criteria (e.g. MET-hours, kilocalories). Heterogeneity was smaller in the latter. Length and loss of follow-up, and to what extent studies adjusted for confounding factors were other sources of heterogeneity.[118] When comparing highest with lowest activity categories, heterogeneity was lower for vigorous exercise and sports and higher for moderate-intensity activities. Vigorous-intensity activities are recalled more reliable than moderate- and light-intensity activities.

Biological mechanisms and future research directions

Several biological mechanisms may contribute to the reduction in the risk of premature death associated with physical activity. Physical activity leads to favourable changes in cardiovascular risk factor profiles and improvements in endothelial function.[119,120]

Reductions in cancer mortality may be related to reduced fat stores, increased energy expenditure, changes in sex hormone levels, improved immune function, reductions in insulin levels and insulin-like growth factors and reduced generation of free radicals.[121–123] In elderly people, regular physical activity reduces the risk of falls, of osteoporotic fractures and disability, which in turn may reduce mortality.[124] Reductions in mortality were consistently higher in women when compared with men, independently of the domain of physical activity assessed. It therefore seems unlikely that this gender difference is simply due to differential reporting of physical activity and misclassification.[125,126] In women, increases in physical activity have been associated with changes in hormone levels, in oestrogen metabolism and body fat distribution.[127,128]

Our study may underestimate the true magnitude of associations due to imprecise measurements of physical activity but reductions in all-cause mortality of even a few percent are important at the population level. Questions remain not only about the true magnitude of the effect on mortality and the exact shape of the dose–response relation, but also on the importance of intensity, duration and frequency of physical activity, independent of total activity and about the role of gender and age on the association between physical activity and mortality. Future studies should use instruments that capture all subdomains of total activity, and provide accurate estimates of absolute amounts of activity or energy expenditure. Objective methods such as heart rate recorders and movement sensors, or doubly labelled water,[82,116,129,130] are promising in this context, but difficult to apply in large population-based studies.

Supplementary Data

Supplementary Data are available at *IJE* online.

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All authors contributed to the design of the study. G.S. conducted the literature search. G.S. and M.Z. decided on inclusion of studies and study reports, consulting with M.E. in case of disagreements. G.S. and M.Z. extracted the data and did the data management. M.Z. did the statistical analyses in consultation with M.E. G.S. wrote the first draft of the report, which was subsequently revised by M.E. and M.Z. All authors contributed to the final version of the manuscript. All authors had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: None declared.

KEY MESSAGES

- This meta-analysis is the first to quantify the reduction in all-cause mortality associated with increments in total and domain-specific physical activity and energy expenditure.
- Reduction in mortality risk was greatest for increments of vigorous exercise and sports and smaller for moderate-intensity activities of daily living.
- The relative reduction in mortality risk was consistently greater in women than in men.
- Relative mortality reductions corresponding to 150 and 300 min of moderate to vigorous physical activity per week were 14 and 26%, respectively, supporting the 'some is good; more is better' message

References

1 Casperson CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985;**100:**126–31.

2 Lee I-M, Skerrett PJ. Physical activity and all-cause mortality: what is the dose-response relation? *Med Sci Sports Exerc* 2001;**33:**S459–71.

3 Oguma Y, Sesso HD, Paffenbarger RS, Lee I-M. Physical activity and all cause mortality in women: a review of the evidence. *Br J Sports Med* 2002;**36:**162–72.

4 Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 1990;**132:**612–28.

5 Sofi F, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil* 2008;**15:** 247–57.

6 Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk. A meta-analysis. *Stroke* 2003;**34:**2475–82.

7 Thune I, Fuhrberg AF. Physical activity and cancer risk: dose-response and cancer, all sites and site-specific. *Med Sci Sports Exerc* 2001;**33:**S530–50.

8 Lamonte MJ, Ainsworth BE. Quantifying energy expenditure and physical activity in the context of dose response. *Med Sci Sports Exerc* 2001;**33:**S370–78.

9 Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: the evidence. *CMAJ* 2006;**174:** 801–9.

10 Kesianemie YA, Danforth E, Jensen MD, Kopelman PG, Levebre P, Reeder BA. Consensus statement on dose-response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exerc* 2001; **33:**S351–58.

11 Howley ET. Type of activity: resistance, aerobic and leisure versus occupational physical activity. *Med Sci Sports Exerc* 2001;**33:**S364–69.

12 Montoye HJ, Kemper HCG, Saris WHM, Washburn RA. Measuring Physical Activity and Energy Expenditure. Champaign, IL: Human Kinetics, 1996.

13 US Department of Health and Human Services. *Physical Activity and Health: a Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services; Centers for Disease Control and Prevention, and National Center for Chronic Disease Prevention and Health Promotion, 1996.

14 Department of Health. At least five a week: evidence on the impact of physical activity and its relationship to health. *A Report from the Chief Medical Officer*. London, 2004.

15 Haskell WL, Lee I-M, Pate RR *et al*. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 2007;**116:**1081–93.

16 U.S. Department of Health and Human Services. *Physical Activity Guidelines for Americans. Be Active, Healthy, and Happy*. Washington, D.C., USA, 2008.

17 Ainsworth BE, Haskell WL, Whitt MC *et al*. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;**32:** S498–504.

18 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7:**177–88.

19 Higgings JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21:**1539–58.

20 Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;**135:** 1301–9.

21 Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J* 2006;**6:**40–57.

22 Sterne JAC, Jüni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in ''meta-epidemiological'' research. *Statist Med* 2002;**21:** 1513–24.

23 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;**315:**629–34.

24 Slattery ML, Jacobs DR, Nichaman MZ. Leisure time physical activity and coronary heart disease death. The US Railroad Study. *Circulation* 1989;**79:**304–11.

25 Lindsted KD, Tonstad S, Kuzma JW. Self-report of physical activity and patterns of mortality in seventh-day adventist men. *J Clin Epidemiol* 1991;**44:**355–64.

26 Rakowski W, Mor V. The association of physical activity with mortality among older adults in the Longitudinal Study of Aging (1984-1988). *J Gerontol A Biol Sci Med Sci* 1992;**47:**122–29.

27 Chang-Claude J, Frentzel-Beyme R. Dietary and lifestyle determinants of mortality among german vegetarians. *Int J Epidemiol* 1993;**22:**228–36.

28 Simonsick EM, Lafferty ME, Phillips CL *et al*. Risk due to inactivity in physically capable older adults. *Am J Public Health* 1993;**83:**1443–50.

29 Weyerer S. Effects of physical inactivity on all-cause mortality risk in upper Bavaria. *Percept Mot Skills* 1993;**77:** 499–505.

30 Rosolova H, Simon J, Sefrna F. Impact of cardiovascular risk factors on morbidity and mortality in Czeck middle-aged men: Pilsen Longitudinal Study. *Cardiology* 1994;**85:**61–68.

31 Eaton CB, Medalie JH, Flocke SA, Zyzanski SJ, Yaari S, Goldbourt U. Self-reported physical activity predicts long-term coronary heart disease and all-cause mortalities. Twenty-one-year follow-up of the Isreali Ischemic Heart Disease Study. *Arch Fam Med* 1995;**4:** 323–29.

32 LaCroix AZ, Leveille SG, Hecht JA, Grothaus LC, Wagner EH. Does walking decrease the risk of cardiovascular disease hospitalizations and death in older adults? *J Am Geriatr Soc* 1996;**44:**113–20.

33 Kampert JB, Blair SN, Barlow CE, Kohl HW, 3rd. Physical activity, physical fitness, and all-cause and cancer mortality: a prospective study in men and women. *Ann Epidemiol* 1996;**6:**452–57.

34 Ruigomez A, Alonso J, Anto JM. Relationship of health behaviours to five-year mortality in an elderly cohort. *Age Ageing* 1995;**24:**113–19.

35 Mensink GBM, Deketh M, Mul MDM, Schuit AJ, Hoffmeister H. Physical activity and its association with cardiovascular risk factors and mortality. *Epidemiology* 1996;**7:**391–97.

36 Lissner L, Bengtsson C, Bjorkelund C, Wedel H. Physical activity levels and changes in relation to longevity. A prospective study of Swedish women. *Am J Epidemiol* 1996; **143:**54–62.

37 Kaplan GA, Strawbridge WJ, Cohen RD, Hungerford LR. Natural history of leisure-time physical activity and its correlates: associations with mortality from all-causes and cardiovascular disease over 28 years. *Am J Epidemiol* 1996;**144:**793–97.

38 Hedblad B, Ogren M, Isacsson S-O, Janzon L. Reduced cardiovascular mortality risk in male smokers who are physically active. *Arch Intern Med* 1997;**157:** 893–99.

39 Rosengren A, Wilhelmsen L. Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year follow-up of the Primary Prevention Study in Göteborg. *Ann Epidemiol* 1997;**7:**69–75.

40 Kushi LH, Fee RM, Folsom AR, Mink PJ, Anderson KE, Sellers TA. Physical activity and mortality in postmenopausal women. *JAMA* 1997;**277:**1287–92.

[41] Morgan K, Clarke D. Customary physical activity and survival in later life: a study in Nottingham, UK. *J Epidemiol Community Health* 1997;**51:**490–93.

[42] Folsom AR, Arnett DK, Hutchinson RG, Liao F, Clegg LX, Cooper LS. Physical activity and incidence of coronary heart disease in middle-aged women and men. *Med Sci Sports Exerc* 1997;**29:**901–09.

[43] Leon AS, Myers MJ, Connett J. Leisure time physical activity and the 16-year risks of mortality from coronary heart disease and all-causes in the Multiple Risk Factor Intervention Trial (MRFIT). *Int J Sports Med* 1997; **18(Suppl 3):**208–15.

[44] Hakim AA, Petrovitch H, Burchfiel CM *et al*. Effects of walking on mortality among nonsmoking retired men. *N Engl J Med* 1998;**338:**94–99.

[45] Erikssen G, Liestol K, Bjornholt J, Thaulow E, Sandvik L, Erikssen J. Changes in physical fitness and changes in mortality. *Lancet* 1998;**352:**795–62.

[46] Villeneuve PJ, Morrison HI, Craig CL, Schaubel DE. Physical activity, physical fitness, and risk of dying. *Epidemiology* 1998;**9:**626–31.

[47] Weller I, Corey P. The impact of excluding non-leisure energy expenditure on the relation between physical activity and mortality in women. *Epidemiology* 1998;**9:** 632–35.

[48] Fried LP, Kronmal RA, Newman AB *et al*. Risk factors for 5-year mortality in older adults. The Cardiovascular Health Study. *JAMA* 1998;**279:**585–92.

[49] Bijnen FCH, Caspersen CJ, Feskens EJM, Saris WHM, Mosterd WL, Kromhout D. Physical activity and 10-year mortality from cardiovascular diseases and all causes. The Zutphen Elderly Study. *Arch Intern Med* 1998;**158:** 1499–505.

[50] Johansson S-E, Sundquist J. Change in lifestyle factors and their influence on health status and all-cause mortality. *Int J Epidemiol* 1999;**28:**1073–80.

[51] Sherman SE, D'Agostino RB, Silbershatz H, Kannel WB. Comparison of past versus recent physical activity in the prevention or premature death and coronary artery disease. *Am Heart J* 1999;**138:**900–7.

[52] Stessman J, Maaravi Y, Hammerman-Rozenberg R, Cohen A. The effects of physical activity on mortality in the Jerusalem 70-Year-Olds Longitudinal Study. *J Am Geriatr Soc* 2000;**48:**499–504.

[53] Andersen LB, Schnohr P, Schroll M, Hein HO. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. *Arch Intern Med* 2000;**160:**1621–28.

[54] Haapanen-Niemi N, Miilunpalo S, Pasanen M, Vuori I, Oja P, Malmberg J. Body mass index, physical inactivity and low level of physical fitness as determinants of all-cause and cardiovascular disease mortality – 16 y follow-up of middle-aged and elderly men and women. *Int J Obes* 2000;**24:**1465–74.

[55] Lee I-M, Paffenbarger RS. Associations of light, moderate, and vigorous intensity physical activity with longevity. The Harvard Alumni Health Study. *Am J Epidemiol* 2000; **151:**293–99.

[56] Hirvensalo M, Rantanen T, Heikkinen E. Mobility difficulties and physical activity as predictors of mortality and loss of independence in the community-living older population. *J Am Geriatr Soc* 2000;**48:**493–98.

[57] Wannamethee SG, Shaper AG, Walker M. Changes in physical activity, mortality, and incidence of coronary heart disease in older men. *Lancet* 1998;**351:**1603–8.

[58] Smith GD, Shipley MJ, Batty GD, Morris JN, Marmot M. Physical activity and cause-specific mortality in the Whitehall study. *Public Health* 2000;**114:**308–15.

[59] Batty GD, Shipley MJ, Marmot M, Smith GD. Physical activity and cause-specific mortality in men: further evidence from the Whitehall study. *Eur J Epidemiol* 2001;**17:** 863–69.

[60] Kilander L, Berglund L, Boberg M, Vessby B, Lithell H. Education, lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year follow-up of Swedish 50-year-old men. *Int J Epidemiol* 2001;**30:**1119–26.

[61] Osler M, Heitmann BL, Gerdes LU, Jorgensen LM, Schroll M. Dietary patterns and mortality in Danish men and women: a prospective observational study. *Br J Nutr* 2001;**85:**219–25.

[62] Seki N. Relationships between walking hours, sleeping hours, meaningfulness of life (Ikigai) and mortality in the elderly: prospective cohort study. *Jpn J Hyg* 2001;**56:** 535–40.

[63] Woo J, Ho SC, Yu ALM. Lifestyle factors and health outcomes in elderly Hong Kong Chinese aged 70 years and over. *Gerontology* 2002;**48:**234–40.

[64] Ostbye T, Taylor DH, Jung S-H. A longitudinal study of effects of tobacco smoking and other modifiable risk factors on ill health in middle-aged and old Americans: Results from the Health and Retirement Study and Asset and Health Dynamics among the Oldest Old Survey. *Prev Med* 2002;**34:**334–45.

[65] Äijö M, Heikkinen E, Schroll M, Steen B. Physical activity and mortality of 75-year-old people in three nordic localities: a five-year follow-up. *Aging Clin Exp Res* 2002;**14:** 83–89.

[66] Konlaan BB, Theobald H, Bygren L-O. Leisure time activity as a determinant of survival: a 26-year follow-up of a Swedish cohort. *Public Health* 2002;**116:**227–30.

[67] Haveman-Nies A, de Groot PGM, Burema J *et al*. Dietary quality and lifestyle factors in relation to 10-year mortality in older Europeans. The SENECA Study. *Am J Epidemiol* 2002;**156:**962–68.

[68] Kujala UM, Kaprio J, Koskenvuo M. Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. *Am J Epidemiol* 2002; **156:**985–93.

[69] Crespo CJ, Palmieri MR, Perdomo RP *et al*. The relationship of physical activity and body weight with all-cause mortality: results from the Puerto Rico Heart Health Program. *Ann Epidemiol* 2002;**12:**543–52.

[70] Meyer HE, Sogaard AJ, Tverdal A, Selmer RM. Body mass index and mortality: the influence of physical activity and smoking. *Med Sci Sports Exerc* 2002;**34:**1065–70.

[71] Gregg EW, Cauley JA, Stone K *et al*. Relationship of changes in physical activity and mortality among older women. *JAMA* 2003;**289:**2379–68.

[72] Yu S, Yarnell JWG, Sweetnam PM, Murray L. What level of physical activity protects against premature cardiovascular death? The Caerphilly study. *Heart* 2003;**89:**502–6.

[73] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;**348:**2599–608.

[74] Lubin F, Lusky A, Chetrit A, Dankner R. Lifestyle and ethnicity play a role in all-cause mortality. *J Nutr* 2003; **133:**1180–85.

[75] Panagiotakos DB, Chrysohoou C, Pitsavos C *et al*. Forty-years (1961-2001) of all-cause and coronary heart disease mortality and its determinants: the Corfu cohort from the Seven Countries Study. *Int J Cardiol* 2003;**90:** 73–79.

[76] Barengo NC, Hu G, Lakka TA, Pekkarinen H, Nissinen A, Tuomilehto J. Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. *Eur Heart J* 2004;**25:** 2204–11.

[77] Myers J, Kaykha A, George S *et al*. Fitness versus physical activity patterns in predicting mortality in men. *Am J Med* 2004;**117:**912–18.

[78] Fujita K, Takahashi H, Miura C *et al*. Walking and mortality in Japan: The Miyagi Cohort Study. *J Epidemiol* 2004;**14:**26–32.

[79] Trolle-Lagerros Y, Mucci LA, Kumle M *et al*. Physical activity as a determinant of mortality in women. *Epidemiology* 2005;**16:**780–85.

[80] Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P. The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47212 middle-aged Finnish men and women. *Int J Obes* 2005;**29:**894–902.

[81] Bucksch J. Physical activity of moderate intensity in leisure time and the risk of all cause mortality. *Br J Sports Med* 2005;**39:**632–38.

[82] Manini TM, Everhart JE, Patel KV *et al*. Daily activity energy expenditure and mortality among older adults. *JAMA* 2006;**296:**171–79.

[83] Khaw K-T, Jakes R, Bingham S *et al*. Work and leisure time physical activity assessed using a simple, pragmatic, validated questionnaire and incident cardiovascular disease and all-cause mortality in men and women: The European Prospective Investigation into Cancer in Norfolk prospective population study. *Int J Epidemiol* 2006;**35:**1034–43.

[84] Carlsson S, Andersson T, Wolk A, Ahlbom A. Low physical activity and mortality in women: Baseline lifestyle and health as alternative explanations. *Scand J Public Health* 2006;**34:**480–87.

[85] Schooling CM, Lam TH, Li ZB *et al*. Obesity, physical activity, and mortality in a prospective chinese elderly cohort. *Arch Intern Med* 2006;**166:**1498–504.

[86] Lan T-Y, Chang H-Y, Tai T-Y. Relationship between components of leisure physical activity and mortality in Taiwanese older adults. *Prev Med* 2006;**43:**36–41.

[87] Carlsson S, Andersson T, Lichtenstein P, Michaelsson K, Ahlbom A. Physical activity and mortality: is the association explained by genetic selection? *Am J Epidemiol* 2007; **166:**255–59.

[88] Schnohr P, Scharling H, Jensen JS. Intensity versus duration of walking, impact on mortality: the Copenhagen City Heart Study. *Eur J Cardiovasc Prev Rehabil* 2007;**14:** 72–78.

[89] Matthews CE, Jurj AL, Shu X *et al*. Influence of exercise, walking, cycling, and overall nonexercise physical activity on mortality in chinese women. *Am J Epidemiol* 2007;**165:** 1343–50.

[90] Leitzmann MF, Park Y, Blair A *et al*. Physical activity recommendations and decreased risk of mortality. *Arch Intern Med* 2007;**167:**2453–60.

[91] Inoue M, Iso H, Yamamoto S *et al*. Daily total physical activity level and premature death in men and women: results from a large-scale population-based cohort study in Japan (JPHC study). *Ann Epidemiol* 2008;**18:**522–30.

[92] van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *BMJ* 2008;**337:** a1440.

[93] Ford J, Spallek M, Dobson A. Self-rated health and a healthy lifestyle are the most important predictors of survival in elderly women. *Age Ageing* 2008;**37:**194–200.

[94] Arrieta A, Russell LB. Effects of leisure and non-leisure physical activity on mortality in U.S. adults over two decades. *Ann Epidemiol* 2008;**18:**889–95.

[95] Landi F, Russo A, Cesari M *et al*. Walking one hour or more per day prevented mortality among older persons: results from ilSIRENTE study. *Prev Med* 2008;**47:**422–26.

[96] Besson H, Ekelund U, Brage S *et al*. Relationship between subdomains of total physical activity and mortality. *Med Sci Sports Exerc* 2008;**40:**1909–15.

[97] Orsini N, Bellocco R, Bottai M, Pagano M, Michaelsson K, Wolk A. Combined effects of obesity and physical activity in predicting mortality among men. *J Intern Med* 2008;**264:**442–51.

[98] Stessman J, Hammerman-Rozenberg R, Cohen A, Ein-Mor E, Jacobs JM. Physical activity, function, and longevity among the very old. *Arch Intern Med* 2009;**169:** 1476–83.

[99] Byberg L, Melhus H, Gedeborg R *et al*. Total mortality after changes in leisure time physical activity in 50 year old men: 35 year follow-up of population based cohort. *BMJ* 2009;**338:**b688.

[100] Hayasaka S, Shibata Y, Ishikawa S *et al*. Physical activity and all-cause mortality in Japan: the Jichi Medical School (JMS) Cohort Study. *J Epidemiol* 2009;**19:**24–27.

[101] Park MS, Chung SY, Chang Y, Kim K. Physical activity and physical fitness as predictors of all-cause mortality in Korean men. *J Korean Med Sci* 2009;**24:**13–19.

[102] Ueshima K, Ishikawa-Takata K, Yorifuji T *et al*. Physical activity and mortality risk in the Japanese elderly: a cohort study. *Am J Prev Med* 2010;**38:**410–18.

[103] Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. *Arch Intern Med* 2010;**170:**711–18.

[104] Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. *Br J Sports Med* 2008;**42:**238–43.

[105] Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil* 2008;**15:**239–46.

[106] Löllgen H, Böckenhoff A, Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. *Int J Sports Med* 2009;**30:** 213–24.

107 Woodcock J, Franco OH, Orsini N, Roberts I. Non-vigorous physical activity and all-cause mortality: systematic review and meta-analysis of cohort studies. *Int J Epidemiol* 2011;**40:**121–38.

108 Rockhill B, Willett WC, Manson J-AE *et al*. Physical activity and mortality: a prospective study among women. *Am J Public Health* 2001;**91:**578–83.

109 Lagerros YT, Lagiou P. Assessment of physical activity and energy expenditure in epidemiological research of chronic diseases. *Eur J Epidemiol* 2007;**22:**353–62.

110 Sjöström M, Oja P, Hagströmer M, Smith BJ, Bauman A. Health-enhancing physical activity across European Union countries: the Eurobarometer study. *J Public Health* 2006;**14:**291–300.

111 Pols MA, Peeters PHM, Kemper HCG, Grobbee DE. Methodological aspects of physical activity assessment in epidemiological studies. *Eur J Epidemiol* 1998;**14:** 63–70.

112 Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;**282:**1054–60.

113 Byrne NM, Hills AP, Hunter GR, Weinsier RL, Schutz Y. Metabolic equivalent: one size does not fit all. *J Appl Physiol* 2005;**99:**1112–19.

114 Egger M, Schneider M, Smith GD. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998;**316:** 140–44.

115 Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;**359:**248–52.

116 Trolle-Lagerros Y, Lagiou P. Assessment of physical activity and energy expenditure in epidemiological research of chronic disease. *Eur J Epidemiol* 2007;**22:**353–62.

117 Sallis JF, Saelens BE. Assessment of physical activity by self-report: status, limitations, and future directions. *Res Q Exerc Sport* 2000;**71:**S1–14.

118 Colditz GA, Burdick E, Mosteller F. Heterogeneity in meta-analysis of data from epidemiologic studies: a commentary. *Am J Epidemiol* 1995;**142:**371–82.

119 Hambrecht R, Wolf A, Gielen S *et al*. Effects of exercise on coronary endothelial function in patients with chronic artery disease. *N Engl J Med* 2000;**342:**454–60.

120 Majorana A, O'Driscoll G, Taylor R. Exercise and the nitric oxide vasodilator system. *Sports Med* 2003;**33:** 1013–35.

121 Shephard RJ, Futcher R. Physical activity and cancer: How may protection be maximized? *Crit Rev Oncog* 1997;**8:**219–72.

122 Westerlind KC. Physical activity and cancer prevention – mechanisms. *Med Sci Sports Exerc* 2003;**35:**1834–40.

123 Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;**371:**569–78.

124 Gregg EW, Cauley JA, Seeley DA, Ensrud KE, Bauer DG. Physical activity and osteoporotic fracture risk in older women: the Study of Osteoporotic Fractures. *Ann Intern Med* 1998;**129:**81–88.

125 Masse LC, Ainsworth BE, Tortolero S *et al*. Measuring physical activity in midlife, older, and minority women: issues from an expert panel. *J Womens Health* 1998;**7:**57–67.

126 Weller I, Corey P. The impact of excluding non-leisure energy expenditure on the relation between physical activity and mortality in women. *Epidemiol* 1998;**9:**632–35.

127 Friedenreich CM, Woolcott CG, McTiernan A *et al*. Alberta physical activity and breast cancer prevention trial: sex hormone changes in a year-long exercise intervention among postmenopausal women. *J Clin Oncol* 2010;**28:**1458–66.

128 Lara S, Casanova G, Spritzer PM. Influence of habitual physical activity on body composition, fat distribution and metabolic variables in early postmenopausal women receiving hormonal therapy. *Eur J Obstet Gynecol Reprod Biol* 2010;**150:**52–56.

129 Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ. Reliability and validity of the combined heart rate and movement sensor Actiheart. *Eur J Clin Nutr* 2005;**59:** 561–70.

130 Sesso HD. Invited commentary: a challenge for physical activity epidemiology. *Am J Epidemiol* 2007;**165:**1351–53.

131 IPAQ Research Committee. *Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ) – short and long forms*. 2009. http://www.ipaq.ki.se/scoring.pdf (12 October 2010 date last accessed)