Dose Response Between Physical Activity and Risk of Coronary Heart Disease
A Meta-Analysis

Jacob Sattelmair, MSc, ScD; Jeremy Pertman, MS; Eric L. Ding, ScD; Harold W. Kohl III, PhD; William Haskell, PhD; I-Min Lee, MBBS, ScD

Background—No reviews have quantified the specific amounts of physical activity required for lower risks of coronary heart disease when assessing the dose-response relation. Instead, previous reviews have used qualitative estimates such as low, moderate, and high physical activity.

Methods and Results—We performed an aggregate data meta-analysis of epidemiological studies investigating physical activity and primary prevention of CHD. We included prospective cohort studies published in English since 1995. After reviewing 3194 abstracts, we included 33 studies. We used random-effects generalized least squares spline models for trend estimation to derive pooled dose-response estimates. Among the 33 studies, 9 allowed quantitative estimates of leisure-time physical activity. Individuals who engaged in the equivalent of 150 min/wk of moderate-intensity leisure-time physical activity (minimum amount, 2008 US federal guidelines) had a 14% lower coronary heart disease risk (relative risk, 0.86; 95% confidence interval, 0.77 to 0.96) compared with those reporting no leisure-time physical activity. Those engaging in the equivalent of 300 min/wk of moderate-intensity leisure-time physical activity (2008 US federal guidelines for additional benefits) had a 20% (relative risk, 0.80; 95% confidence interval, 0.74 to 0.88) lower risk. At higher levels of physical activity, relative risks were modestly lower. People who were physically active at levels lower than the minimum recommended amount also had significantly lower risk of coronary heart disease. There was a significant interaction by sex (P=0.03); the association was stronger among women than men.

Conclusions—These findings provide quantitative data supporting US physical activity guidelines that stipulate that “some physical activity is better than none” and “additional benefits occur with more physical activity.” (Circulation. 2011;124:789-795.)

Key Words: coronary heart disease ■ exercise ■ meta-analysis ■ physical activity ■ women

Although prevalence and incidence rates of coronary heart disease (CHD) mortality have declined since the 1960s, it is estimated that ≈17 million people in the United States are living with CHD in 2010.1 Coronary heart disease causes ≈425 000 annual deaths in the United States, making it the leading cause of mortality nationwide.1 Identifying and characterizing modifiable risk factors for CHD remain important for public health and clinical medicine.

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The independent role of physical activity in the primary prevention of CHD is well established and has been assessed in numerous reviews or meta-analyses.2–8 Although all reviews agree that physical activity is associated with a 20% to 30% lower risk of CHD,7,8 no work to date has designated quantitative assessments of the amount of physical activity required for these lower risks, referring instead to qualitative levels of physical activity (eg, high versus low).8 Public health guidelines on the amount of physical activity required for health benefits have relied on individual studies rather than a systematic assessment of the overall evidence.9

Many early studies that assessed the relation between physical activity and CHD dichotomized participants according to their activity levels (eg, active versus inactive); however, more recent
studies have grouped participants into multiple quantitatively designated categories of specific types of physical activity (eg, quartiles of leisure-time physical activity [LTPA]), making it possible to assess and describe in detail the dose-response relation. The purpose of this meta-analysis is to pool results from prospective cohort studies to quantify the dose-response relationship between physical activity and risk of CHD, including both the amount of physical activity required and the magnitude of benefit to CHD risk.

Methods

We followed the Meta-Analysis of Observational Studies in Epidemiology protocols throughout the design, implementation, analysis, and reporting for this study.

Literature Search Strategy

We searched for all prospective cohort studies that assessed potential associations among various types of physical activity and incidence of CHD in adults (≥18 years of age at baseline). Searches were performed with electronic databases (MEDLINE and EMBASE) and were supplemented by manual searches through the reference lists of original publications and review articles. Key words included, among others, "physical activity," "motor activity," "energy expenditure," "walking," "exercise," "coronary disease," "heart disease," "ischemic heart disease," "myocardial infarction," and "sudden death" (full search terms available on request). Searches were restricted to articles that focused on adults that were published in English between January 1, 1995, and July 31, 2009. The 1995 cutoff was chosen to reflect likely changes in physical activity categorization for analyses by investigators after publication of the 1995 US Centers for Disease Control and Prevention/American College of Sports Medicine guideline, which allowed for moderate-intensity activities, such as walking, in contrast to recommendations before 1995, which primarily recognized only vigorous-intensity activities as counting toward meeting guidelines.

Inclusion Criteria

The final collection of selected articles was chosen on the basis of the following a priori inclusion criteria: The article, published in English between January 1, 1995, and July 31, 2009, reported a prospective cohort study among human adults that measured effect sizes (relative risks [RRs]) of CHD (primary prevention) by level of physical activity (providing either confidence intervals [CIs] or SEs). All types of physical activity, including LTPA, time spent walking, walking pace, occupational physical activity, transport physical activity, nonleisure physical activity, and total physical activity, were included. If multiple articles were published from the same cohort, we included the article with the most detailed report for each type of physical activity.

Selection of Articles

Initially, titles were reviewed to ascertain the potential fit to the inclusion criteria. If relevancy was doubted during the title review, a subsequent assessment was conducted. The list of potential articles was further shortened by reviewing abstracts and performing detailed evaluations of the methods and results of each remaining article. Please refer to Figure I in the online-only Data Supplement for more detailed information on inclusion and exclusion criteria. Disagreements were adjudicated by a third reader (I.-M.L.).

Data Extraction

The following details were recorded for each study: author, year of publication, cohort/study name, geographic location of study (North America, Europe, other), participants’ sex (male, female, combined), mean age at baseline, health at baseline (healthy, diabetic), and race. We also recorded CHD outcome (fatal, nonfatal, both), type of physical activity (eg, leisure, walking, occupational), categorical physical activity level (eg, 1, 2, 3), and when possible (and at each activity level) mean dose of physical activity (eg, kilocalories per week, metabolic equivalent [MET] hours per week, minutes per week, kilometers per hour), RR of CHD and CI (or SE), and number of cases and total subjects (or person-time). We further noted variable assessment of confounding (crude, age-adjusted, multivariate, multivariate including plausible biological intermediates; the multivariate model that included the most plausible confounders while excluding biological intermediates was chosen for the primary analyses). Mean quantitative physical activity information was directly recorded or inferred through the use of the available cohort-specific or population norms (eg, for height and weight). Data abstraction was conducted independently by 2 investigators (J.S., J.P.), with disagreements adjudicated by a third reader (I.-M.L.). For articles in which quantitative data regarding LTPA were unclear, we contacted authors for additional data. Please refer to Table I in the online-only Data Supplement for further details.

Meta-Analysis Statistical Techniques

The RRs of CHD were reported for each category of physical activity. For studies that allowed quantitative estimates of physical activity, the mean (7 studies) or median (2 studies) of each category was used to define the median physical activity level for that category. For studies with a open-ended highest physical activity category or unspecified maximum dose, we assumed that the difference from the lowest range of this category to its median was equivalent to the difference between the lowest range of the closest adjacent category and its median. We excluded from the main analysis studies wherein all participants were diabetic at baseline, instead selecting from those wherein adults were at usual risk of CHD. We did not assess or adjust for quality score because there has not been uniform agreement for correction for study quality affects results. Additionally, we believe that the detailed level of data required to be included in the present analysis was such that study quality would be generally high and uniform among the studies included.

In an initial qualitative analysis intended for comparison with results of previous reviews, we assessed the random effects summary RR of CHD by comparing the highest and lowest categories of physical activity across studies for each type of activity reported. Random effects models allowed for heterogeneity between studies. Study-specific plots (trend lines) were then constructed to graphically depict the dose-response relation across levels of physical activity (assessed categorically, normalized to 5 levels of physical activity) and RR of CHD.

We used generalized least squares (GLST) regression models to assess the pooled dose-response relation between physical activity and risk of CHD across prospective cohort studies that had heterogeneous categorizations of physical activity. This modeling technique allows the estimation of a weighted average of the log RRs across all studies, with the weight depending in part on the inverse of the variance of the log of the RR (ie, larger studies carry more weight). Random effects methods were used to take into account heterogeneity among study results.

All quantitative studies (those that allowed quantitative estimates of physical activity levels) were eligible for inclusion in GLST analyses. However, we were able to apply only GLST methods to assess LTPA because there were too few (≤2) studies that allowed quantitative estimates of other physical activity types or too much heterogeneity among studies (such as for walking time, for which CIs were too wide for reasonable estimates). We used spline models to conduct GLST analyses for LTPA, which allowed the relation between physical activity and CHD to vary across the range of physical activity dose in kilocalories per week but assumed linear relations between designated doses.

Guidelines from the 2008 US physical activity guidelines were used to assign the first 2 doses of physical activity at which to compute RR. These guidelines recommend 150 minutes of moderate-intensity (3 to <6 METs) physical activity per week as a minimum amount for health enhancement (referred to hereafter as basic) and 300 min/wk for additional health benefits (advanced). Alternatively, guidelines recommend equivalent expenditure from vigorous-intensity (≥6 METs) physical activity (75 and 150 min/wk, respectively) or any combination of moderate- and vigorous-intensity activity that results in energy expenditure equivalent to either regimen. The cutoffs associated with the basic and advanced guidelines, converted into approximate units of kilocalories per week, were 550 and 1100 kcal/wk, respectively, for both sexes combined, 600 and 1200 kcal/wk for men, and 500 and 1000 kcal/wk for women.
for women (based on population norms for weight). These intervals were used as a guide to extend analyses to higher levels of LTPA to fit the available data; higher doses were assigned to balance model parsimony and goodness of fit. In a sensitivity analysis, we examined lower doses of physical activity (eg, 275 kcal/wk for both sexes combined) to test the statement in the 2008 US guidelines that, in addition to recommending levels of physical activity, says, “All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of activity gain some health benefits.”

We also assessed prespecified potential interaction by geographic region (North America, Europe, Middle East), adjustment for confounding (multivariate, multivariate inclusive of intermediates), and CHD outcome (fatal, nonfatal, combined) using GLST spline models, evaluating $P$ values for interaction terms with indicator variables. We were unable to assess potential interaction by age ($<65$ or $\geq65$ years of age at baseline) or race (white, black, other) because there was insufficient variation among included studies. Because assessment of interaction with spline models had less power (owing to multiple degrees of freedom), as a secondary analysis, we assessed potential interaction using quadratic models. When appropriate, we performed GLST analyses restricted to strata of potential effect modifiers. Potential publication bias was assessed with the Begg test and a funnel plot.

All analysis were performed with STATA 10.0 (STATA Corp, College Station, TX), with 2-tailed $\alpha$ set at $P<0.05$ for statistical significance.

Results

Search Results

The initial search produced 1545 articles using PubMed and 1649 articles using EMBASE; 87 and 129 studies were selected for further evaluation from PubMed and EMBASE, respectively. On the basis of information from abstracts, 68 studies warranted further assessment. Inclusion or exclusion was determined after a detailed evaluation of the study design, population, physical activity assessment, and CHD assessment. An additional 7 studies were identified by a manual search through references of recent reviews. Finally, 33 prospective cohort studies were selected for analysis (see Figure 1 for selection flow and Tables I and II in the online-only Data Supplement for characteristics of all studies selected for analysis) from which 30

<table>
<thead>
<tr>
<th>Type of Activity</th>
<th>Sex</th>
<th>Studies</th>
<th>Relative Risk (95% CI)</th>
<th>$I^2$, %</th>
<th>Studies, n$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTPA Combined All studies</td>
<td>0.74 (0.69–0.78)</td>
<td>28.3</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational PA Combined All studies</td>
<td>0.84 (0.79–0.90)</td>
<td>0</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transport PA Combined All studies</td>
<td>0.87 (0.74–1.02)</td>
<td>81.0</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PA Combined All studies</td>
<td>0.74 (0.62–0.90)</td>
<td>0</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-specific PA Combined All studies</td>
<td>0.79 (0.59–1.07)</td>
<td>18.9</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies Combined All studies</td>
<td>0.75 (0.71–0.79)</td>
<td>47.6</td>
<td>33†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LTPA indicates leisure-time physical activity; $I^2$, percentage of variation across studies that is due to heterogeneity rather than chance; All studies, studies that characterized physical activity quantitatively or qualitatively; Quant, only those studies that categorized physical activity quantitatively; and PA, physical activity.

*Actual number of comparisons included was greater than the number of studies for several types of physical activity because some studies provided comparisons for both sexes. In particular, the 26 studies of LTPA provided 30 comparisons, and the 9 quantitative studies of LTPA provided 10 comparisons.†These 33 studies included 56 physical activity-type-specific assessments; many studies included comparisons from multiple physical activity types (eg, LTPA, walking time, and walking pace assessed in the same study) and/or comparisons from both sexes.

assessments of LTPA were analyzed, 10 of which provided quantitative estimates of LTPA categories.

Binary Analysis

To relate our findings to past reviews, we first compared the highest and lowest (or referent) categories of physical activity for each type of physical activity using random effects pooled RRs (the Table). The majority of physical activity types were associated with significantly lower risks of CHD, which varied between 6% and 51%. The summary risk among all studies that assessed LTPA indicated a 26% risk reduction (RR, 0.74; 95% CI, 0.69 to 0.78).
Within each type of physical activity, pooled RRs were also provided for each sex (when there were ≥2 studies for each sex). For the majority of physical activity types, the RR among the most active women was lower than the corresponding value among men by 0.10. Among all studies that assessed LTPA, those conducted in men showed a 22% lower risk (RR, 0.78; 95% CI, 0.73 to 0.82) comparing most with least active and those conducted in women showed a 33% lower risk (RR, 0.67; 95% CI, 0.61 to 0.74).

Within each type of physical activity, RRs were also provided for the subset of studies that included quantitative assessments of physical activity (when there were ≥2 studies). These quantitative studies tended to demonstrate RRs of magnitudes similar to those observed when all studies were included (the Table).

**Dose-Response Analysis**

Plots of the dose-response relation between LTPA, assessed categorically, and CHD risk (30 comparisons [26 studies] of 56 comparisons [33 studies] included data on LTPA) are shown in Figure 1. Studies that allowed quantitative estimates of LTPA demonstrated trends similar to those of studies that assessed LTPA only qualitatively.

Plots of the dose-response relation between quantitative estimates of LTPA in kilocalories per week and CHD risk (10 comparisons; 9 studies), including a trend line derived from random effects, 1-stage GLST spline analysis for both sexes combined, is shown in Figure 2. Pooled results indicated the expected inverse relation between LTPA and CHD risk. Individuals who met the basic guideline had a 14% lower risk of CHD than those who engaged in no LTPA (RR, 0.86; 95% CI, 0.77 to 0.96), whereas those who met the advanced guideline had a 20% lower risk (RR, 0.80; 95% CI, 0.74 to 0.88). Additionally lower risks of moderate magnitude were observed among those with higher physical activity levels; eg, there was a 25% lower risk for those active at 5 times the basic guideline. Among persons who were physically active at half the basic guideline level (275 kcal/wk), we found a 14% lower risk of CHD (RR, 0.86; 95% CI, 0.76 to 0.97).

Using GLST spline models, we observed significant interaction by sex \( P = 0.03 \). Figure 3 shows trend lines from gender-specific GLST spline analysis. Men who met the basic and advanced guidelines were at 9% (RR, 0.91; 95% CI, 0.79 to 1.04) and 18% (RR, 0.82; 95% CI, 0.74 to 0.91) lower risk of CHD, respectively, than men with no LTPA. Minimally lower risk was observed among men who participated in higher levels of LTPA; eg, there was a 21% lower risk among men who were physically active at 5 times the basic guideline. Women who met the basic guideline were at 20% lower risk (RR, 0.80; 95% CI, 0.69 to 0.92) of CHD than women who engaged in no LTPA; women who met the advanced guideline were at 28% lower risk (RR, 0.72; 95% CI, 0.63 to 0.83). Among women, no added lower risks were observed at higher levels of LTPA until 5 times the basic guideline, which was associated with a 48% lower risk (RR, 0.52; 95% CI, 0.40 to 0.67).

We observed no interaction by geographic region, adjustment strategy for confounding variables, or CHD outcome (data not shown). Because the interaction assessment with spline models had low power, as a secondary analysis, we assessed potential interaction using quadratic models. We found significant interaction by sex, adjustment for confounding, and CHD outcome (all \( P < 0.05 \)). Despite the low power, we found that among studies that controlled for plausible...
biological intermediates (eg, body mass index, hypertension, and diabetes mellitus), CHD RRs were higher by ∼0.1 than those from studies that did not, indicating that additional adjustment for plausible intermediates attenuated the observed associations. We observed no effect modification by geography. We found no evidence for publication bias using the Begg test (with funnel plot) (P = 0.21).

Discussion
This meta-analysis is the first to quantify the dose-response relation between physical activity and CHD risk with regard to both physical activity amount and magnitude of lower CHD risk. We found that individuals who met the basic US physical activity guideline for health had a 14% lower risk of CHD compared with those with no LTPA. Those meeting the advanced guideline had a 20% lower risk of CHD. At higher levels of physical activity, modest increments of risk reduction were observed. We also noted lower RRs among persons who were physically active below the basic guideline, supporting the guideline’s assertion that some physical activity is better than none.

Interestingly, we observed a significant interaction by sex such that the association of physical activity and CHD risk was stronger in women than in men. We were unable to assess whether the association differed by race or age because of insufficient variation among studies. Geographic region of origin did not influence the association.

It is unclear why we observed a significant interaction by sex. Possible explanations include biological differences, methodological considerations, or some combination of both. Previous evidence does not support more favorable effects of habitual physical activity on CHD risk factors (including blood pressure, lipid levels, vascular indicators, cardiorespiratory fitness, and metabolic syndrome) among women compared with men. The type or intensity of physical activity contributing to total LTPA energy expenditure may differ between men and women (eg, men favor vigorous activities and women are more likely to engage in moderate activities). However, this does not explain the stronger effects in women because there are limited data suggesting that vigorous-intensity physical activity may be associated with additional cardiovascular benefits beyond its contribution to energy expenditure.

Methodological issues may explain a portion of the difference. For instance, women have lower CHD rates; thus, the presence of imprecisely measured or unmeasured plausible confounders (such as smoking habit and diet) may have a smaller effect in women than men.

There may be sex differences in the reporting of physical activities. However, it is unlikely that such misclassification would be greater among men than women because vigorous-intensity activities (in which men are more likely to engage) tend to be better reported than activities of lesser intensity. Of the studies included, longer duration of follow-up was more likely in studies of men, leading to greater potential for misclassification of energy expenditure. However, analyzing a subset of studies with comparable follow-up in men and women did not change our main results.

The primary strength of this study was the quantification of physical activity amount in analyses, enabling assessments of the risk associated with specific quantitative levels of LTPA. We chose to quantify physical activity in units of kilocalories per week (and accounting for the different average weights of men and women) because they were more frequently reported in studies and are more easily understood than other units. We also assessed potential effect modification by numerous variables and reported sex-specific results.

Although the selection of studies that included quantitative estimates of physical activity allowed this more quantitative approach, it also limited the number of studies that could be included. In a secondary analysis, we included several additional studies for which we were able to crudely estimate quantitative levels of LTPA; findings were similar to those of the main analyses. We also examined the potential influence of single studies and found that no single study changed results.

This study was limited by inclusion of only English language studies, possibly resulting in bias because statistically significant results may be more likely to be published in English. However, it is unclear whether inclusion of only English language articles causes bias. By designating meta-analytic methods a priori, we aimed to minimize any potential investigator bias caused by preconceptions. However, it is possible that the a priori designations and subsequent interpretations were subject to personal biases. Because this is a meta-analysis of observational studies, the potential for residual confounding and bias cannot be addressed through pooling. A primary source of potential residual confounding is likely to stem from confounding variables that were either unmeasured or insufficiently measured in the individual studies themselves. For instance, dietary intake was rarely assessed in the studies reviewed. In all studies included, physical activity was assessed by self-report; some misclassification of activity levels is probable, and quantitative characterizations should therefore be considered approximate in nature.

We were able to conduct our primary analysis on LTPA on only 9 of 26 of potential studies. As result, there were insufficient data to assess potential interaction by several important factors (eg, baseline age and race). Among women alone, it appeared that there was a marked and sudden decline in risk at 5 times the minimally recommended level of physical activity (Figure 3). However, this data point was based on only 2 studies.

We contacted the authors of the remaining 17 studies to request unpublished quantitative physical activity data; however, little additional usable information was obtained because many of these studies used qualitative categories to assess physical activity. The inclusion of only the 9 studies for quantitative analyses was unlikely to have biased results because these 9 studies appeared representative of the broader group of 26 eligible studies. In initial analyses comparing high and low physical activity, which included all 26 studies, findings were similar to those including only the 9 studies. Furthermore, in a comparison of our findings with previous reviews, which quantified only the magnitude of lower RRs but not the amount of physical activity required, the results are comparable. Our comparison of high and low physical activity yielded an RR of 0.75 for CHD, similar in magnitude to several past reviews.

Conclusions
The present study provides quantitative data supporting the 2008 Physical Activity Guidelines for Americans, which recommend...
the equivalent of 150 min/wk of moderate-intensity physical activity for health and 300 min/wk for additional health benefits and encourage any amount of activity for those unable to meet the minimum. Future studies that quantitatively assess the dose-response relation between LTPA and other types and features of physical activity and CHD risk will help clarify the upper end of the dose-response curve and enable additional quantitative evaluations in future reviews such as exploring potential differences by age and race. Additionally, individual participant meta-analyses conducted via collaboration among research groups, although resource intensive, can use existing studies to further clarify dose-response relationships.51

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Physical activity has clearly been shown to decrease the risk of developing coronary heart disease. However, the dose-response relation (How much activity is needed? What level of risk reduction is associated with specified levels of activity? Does the risk continue to decrease at higher levels of activity?) is less clear. This is the first meta-analysis of epidemiological studies to quantify the dose-response relation, examining both the specific amounts of physical activity and associated risk reductions for coronary heart disease (Previous meta-analyses have quantified only risk reductions, not the specific doses of activity required). We found that individuals who engaged in the equivalent of 150 min/wk of moderate-intensity leisure-time physical activity (corresponding to the minimum amount recommended by the 2008 US federal guidelines) had a 14% lower coronary heart disease risk compared with those reporting no leisure-time physical activity. Those engaging in the equivalent of 300 min/wk of moderate-intensity leisure-time activity had a 20% lower risk. At higher levels of physical activity, relative risks were modestly lower; eg, at 5 times the minimum recommended, there was a 25% lower risk. Persons who were physically active at levels lower than the minimum recommended amount also had a significantly lower risk of coronary heart disease. These findings provide quantitative data that support the 2008 US physical activity guidelines. They indicate that the biggest bang for the buck for coronary heart disease risk reduction occurs at the lower end of the activity spectrum: very modest, achievable levels of physical activity.
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Supplemental Material

Supplemental Table 1: Studies Selected for Analysis

Supplemental Table 2. Selected Studies by Type of Physical Activity

Supplemental Figure 1: Flow Chart of Study Selection
### Supplemental Table 1: Studies Selected for Analysis

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Name &amp; Country</th>
<th>Gender (M, W, C)</th>
<th>N</th>
<th>Mean Baseline Age (SE) or Age Range</th>
<th>Baseline Health Status</th>
<th>Mean Years of Follow-up Time</th>
<th>Physical Activity Type</th>
<th>CHD Outcome</th>
<th>Results RR (95% CI) P for Linear Trend</th>
<th>Adjusted For:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eaton (1995)</td>
<td>The Israeli Ischemic Heart Disease study, Israel</td>
<td>M</td>
<td>8,463</td>
<td>40+</td>
<td>Healthy</td>
<td>21</td>
<td>LTPA</td>
<td>Mortality</td>
<td>LTPA: 1.00 Light: 0.79 (0.63,0.99) Light Daily: 0.73 (0.59,0.89) Heavy: 0.71 (0.52,0.98) Occ. PA: Sitting: 1.00 Standing: 0.99 (0.75,1.18) Walking: 0.94 (0.78,1.12) Physical labor: 0.87 (0.67,1.10)</td>
<td>Age</td>
</tr>
<tr>
<td>Qvist (1996)</td>
<td>Swedish level of Living Survey, Sweden</td>
<td>C</td>
<td>5,306</td>
<td>45-74</td>
<td>Healthy</td>
<td>10</td>
<td>LTPA</td>
<td>Mortality</td>
<td>LTPA - M Inactive: 1.26 (0.9,1.8) Active: 1.00 LTPA - F Inactive: 1.35 (0.8,2.2) Active: 1.00</td>
<td>Age, BP, weight index, smoking</td>
</tr>
<tr>
<td>Folsom (1997)</td>
<td>Atherosclerosis Risk in Communities (ARIC), USA &amp; Italy</td>
<td>C</td>
<td>14,040</td>
<td>45-64</td>
<td>Healthy</td>
<td>4-7</td>
<td>LTPA</td>
<td>Incidence</td>
<td>LTPA - M Q1: 1.00 Q2: 0.96 (0.67,1.37) Q3: 0.70 (0.44,1.13) Q4: 0.76 (0.51,1.13) P: 0.08 LTPA - F Q1: 1.00 Q2: 0.74 (0.43,1.27) Q3: 0.85 (0.44,1.64) Q4: 0.56 90.30,1.06) P: 0.12</td>
<td>Age, education, smoking, alcohol, HRT, race, and field-center</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Sample Size</td>
<td>Age Range</td>
<td>Healthy Status</td>
<td>LTPA Activity</td>
<td>MET-hours/week</td>
<td>Analysis</td>
<td>Covariates</td>
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</tr>
<tr>
<td>Rosengren (1997)</td>
<td>Multifactor Primary Prevention Study</td>
<td>Sweden</td>
<td>7,142</td>
<td>47-55</td>
<td>Healthy</td>
<td>20 LTPA</td>
<td>Occ. PA</td>
<td>Mortality</td>
<td>LTPA: 1.00 Sedentary: 1.00 Moderate: 0.84 (0.71,1.00) Regular Exercise / Athletic Sports: 0.84 (0.73,0.96) Occ. PA Sedentary: 1.00 Very stren. work: 0.83 (0.62,1.12)</td>
<td>Age, smoking, BP, cholesterol, BMI, diabetes, alcohol abuse, occupational class</td>
</tr>
<tr>
<td>Leon (1997)</td>
<td>MRFIT</td>
<td>USA</td>
<td>12,138</td>
<td>35-57</td>
<td>Healthy</td>
<td>16 LTPA</td>
<td>Mortality</td>
<td>LTPA: D1: 1.00 D2-4: 0.75 (0.54,0.96) 5-7: 0.81 (0.64,1.04) DB-10: 0.75 (0.59,0.96)</td>
<td>Age, intervention group, education, smoking, cholesterol, BP, BMI</td>
<td></td>
</tr>
<tr>
<td>Weller (1998)</td>
<td>Canada Fitness Survey Cohort</td>
<td>Canada</td>
<td>6,620</td>
<td>50 (15) 30+</td>
<td>Healthy</td>
<td>7 LTPA</td>
<td>Walking Non-LTPA</td>
<td>Q1: 1.00 Q2: 0.61 (0.07,1.19) Q3: 0.84 (0.52,1.37) Q4: 0.63 (0.36,1.09) Walking &lt;½ the time: 1.00 ½ the time: 0.67 (0.40,1.11) &gt;½ the time: 0.76 (0.43,1.39) Non-LTPA Q1: 1.00 Q2: 0.71 (0.44,1.16) Q3: 0.57 (0.33,0.97) Q4: 0.49 (0.26,0.92)</td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Bijnen (1998)</td>
<td>Zutphen Study</td>
<td>Dutch</td>
<td>802</td>
<td>71.4 (5.2) 64-84</td>
<td>Healthy</td>
<td>10 Total PA</td>
<td>Mortality</td>
<td>Total PA T1: 1.00 T2: 0.87 (0.52,1.45) T3: 1.01 (0.60,1.71) P: 0.99</td>
<td>Age, major chronic diseases, smoking, alcohol</td>
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<tr>
<td>Chen (1999)</td>
<td>National Population Health Survey</td>
<td>Canada</td>
<td>7,158</td>
<td>20+</td>
<td>Healthy</td>
<td>2 LTPA</td>
<td>Incidence</td>
<td>LTPA Sedentary: 5.0 (1.84,13.59) Light: 3.7 (1.26,10.87) Moderate: 1.0 Active: 1.3 (0.41,3.89)</td>
<td>“A number of possible confounding factors”</td>
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<tr>
<td>Manson (1999)</td>
<td>Nurse’s Health Study</td>
<td>USA</td>
<td>72, 488</td>
<td>40-65</td>
<td>Healthy</td>
<td>8 LTPA</td>
<td>Walking</td>
<td>LTPA (MET-hrs/wk) Q1 (0-2.0): 1.00 Q2 (2.1-4.6): 0.85 (0.69,1.06) Q3 (4.7-10.4): 0.78 (0.62,0.99)</td>
<td>Age, smoking, menopausal status, parental history of MI, vitamin</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Gender</td>
<td>Age Range</td>
<td>Healthy</td>
<td>LTPA Type</td>
<td>Incidence</td>
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<td>Hakim (1999)</td>
<td>Honolulu Heart</td>
<td>M</td>
<td>2,678</td>
<td>71-93</td>
<td>Walking</td>
<td>Incidence</td>
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<td>USA</td>
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<td>Study</td>
<td>Cohort Finland</td>
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<td>Wannamethee (2000)</td>
<td>British Regional</td>
<td>M</td>
<td>5,159</td>
<td>40-59</td>
<td>LTPA</td>
<td>Incidence</td>
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<tr>
<td>Sesso (2000)</td>
<td>Harvard Alumni</td>
<td>M</td>
<td>12,156</td>
<td>57.7</td>
<td>LTPA</td>
<td>Incidence</td>
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<tr>
<td>Study</td>
<td>Health Study</td>
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<tr>
<td>Haapanen-Northeast</td>
<td>C</td>
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<td>6,787</td>
<td>35-63</td>
<td>LTPA</td>
<td>Mortality</td>
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<td>Study</td>
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</table>

**Walk Pace**

Q4 (10.5-21.7): 0.69 (0.54,0.88)  
Q5 (>21.7): 0.60 (0.46,0.77)  
P <0.001  
Walking (hrs/wk)  
Q1 (<0.5): 1.00  
Q2 (0.6-2.0): 0.78 (0.57,1.06)  
Q3 (2.1-3.8): 0.88 (0.65,1.21)  
Q4 (3.9-9.9): 0.70 (0.51,0.95)  
Q5 (≥10): 0.65 (0.47,0.91)  
P: 0.02  
Walk Pace (mph)  
Easy (<2): 1.00  
Average (2-2.9): 0.75 (0.6,0.95)  
(Very) Brisk (3+): 0.64 (0.45,0.9)  

**supplement use, alcohol, aspirin**

Finnish Twin Cohort  
Finland  
M 8,205 25-69 Healthy 18 LTPA Incidence LTPA (MET-hrs/day)  
Sedentary (0.54): 1.00  
Occasional Exercisers (2.32): 0.84 (0.70,1.01)  
Conditioning Exercisers (7.57): 0.68 (0.50,0.92)  
P: 0.01  
Age, BMI, smoking, hypertension, and diabetes

British Regional Heart Study  
Great Britain  
M 5,159 40-59 Healthy 16.8 LTPA Incidence LTPA  
Inactive: 1.00  
Occasional: 0.68 (0.52,0.89)  
Light: 0.76 (0.58,0.99)  
Moderate: 0.46 (0.33,0.64)  
Mod. Vig./Vig.: 0.82 (0.61,1.09)  
P: 0.01  
Age, smoking, alcohol, social class, BMI, preexisting CHD

**Sesso (2000)**  
Harvard Alumni Health Study  
USA  
M 12,156 57.7 39-88 Healthy 17 LTPA Incidence LTPA (kJ/wk)  
<2,100: 1.00  
2,100-4,199: 0.90 (.79,1.03)  
4,200-8,399: 0.81 (.71,.92)  
8,400-12,599: 0.80 (.69,.93)  
≥12,600: 0.81 (.71,.94)  
P: 0.003  
Age, BMI, alcohol, hypertension, diabetes, smoking, early parental death before age of 65

**Haapanen-Northeast**  
C 6,787 35-63 Healthy 16 LTPA Mortality LTPA - M (kcal/wk)  
Age, employment
<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Country</th>
<th>Gender</th>
<th>Sample Size</th>
<th>Age Range</th>
<th>Health Status</th>
<th>Outcome</th>
<th>Walk Pace</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Niemi</td>
<td>Finland</td>
<td>M, F</td>
<td>1090 M, 1122 F</td>
<td>40-64</td>
<td>Healthy</td>
<td>LTPA</td>
<td>- F: kcal/wk</td>
<td>0-1,000: 1.70 (0.90,3.21) 1,001-1,900: .88 (0.44,1.76) &gt;1,900: 1.00 P: 0.056</td>
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<tr>
<td>2001</td>
<td>Lee</td>
<td>USA</td>
<td>W</td>
<td>39,372</td>
<td>45+</td>
<td>Healthy</td>
<td>Incidence</td>
<td>Walk pace (km/hr)</td>
<td>DNW: 1.00 &lt;3.2: 0.56 (0.32,0.97) 3.2-4.7: 0.71 (0.47,1.05) ≥4.8: 0.52 (0.30,0.90) P: 0.02</td>
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<tr>
<td>2001</td>
<td>Batty</td>
<td>UK</td>
<td>M</td>
<td>11,633</td>
<td>40-64</td>
<td>Healthy</td>
<td>Mortality</td>
<td>Trans. PA (min/day)</td>
<td>0: 1.10 (1.0, 1.3) 10-19: 1.06 (1.0, 1.2) 20+: 1.00</td>
</tr>
<tr>
<td>2002</td>
<td>Batty</td>
<td>UK</td>
<td>M</td>
<td>6,408</td>
<td>Healthy</td>
<td>6056</td>
<td>LTPA</td>
<td>Walk Pace</td>
<td>Inactive: 1.05 (0.9,1.3) Moderately Active: 0.92 (0.8,1.1) Active: 1.00</td>
</tr>
<tr>
<td>2002</td>
<td>Tanasescu</td>
<td>USA</td>
<td>M</td>
<td>44,452</td>
<td>40-75</td>
<td>Healthy</td>
<td>Incidence</td>
<td>Walking (MET-hr/wk)</td>
<td>Q1 (0-1.19): 1.00 Q2 (1.20-3.49): 1.00 (0.83,1.21) Q3 (3.50-6.00): 0.90 (0.74,1.10) Q4 (7.00-14.74): 1.02 (0.84,1.23) Q5 (≥14.75): 0.82 (0.67,1.00) P: 0.04</td>
</tr>
</tbody>
</table>

**Risk Factors:**
- Status, marital status, perceived health status, smoking and alcohol
- Age, smoking, alcohol, saturated fat, fiber, fruits and vegetables, menopausal status, HRT, MI history
- Age, employment, SBP, smoking, BMI, glucose intolerance, diabetes, FEV1
- Age, grade, SBP, cholesterol, smoking, BMI, FEV1, disease at study entry
- Age, alcohol, smoking, family history of MI, nutrient intake
- *Plus diabetes, cholesterol, hypertension
<table>
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<tr>
<th>Study (Year)</th>
<th>Design/Location</th>
<th>N</th>
<th>Age Range</th>
<th>Health Status</th>
<th>LTPA Measure</th>
<th>Type</th>
<th>Incidence/Odds Ratio (95% CI)</th>
<th>Other Factors/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manson (2002)</td>
<td>Women Health’s Initiative Observational Study, USA</td>
<td>73,743</td>
<td>50-79</td>
<td>Healthy</td>
<td>LTPA Walking</td>
<td>Incidence</td>
<td>Walking (MET-hr/wk) Q1 (0-2.4): 1.00</td>
<td>Incidence: Q2 (2.6-7.2): 0.73 (0.53,0.99), Q3 (7.3-13.4): 0.69 (0.51,0.95), Q4 (13.5-23.3): 0.68 (0.50,0.93), Q5 (≥23.3): 0.47 (0.33,0.67)</td>
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<td></td>
<td></td>
<td>P &lt;0.001</td>
<td>Age</td>
</tr>
<tr>
<td>Wagner (2002)</td>
<td>PRIME Study, Ireland/France</td>
<td>9,758</td>
<td>50-59</td>
<td>Healthy</td>
<td>LTPA Trans. PA</td>
<td>Incidence</td>
<td>Walking (MET-hr/wk) Q1 (0): 1.00</td>
<td>Walking (MET-hr/wk): Q2 (0.1-2.5): 0.71 (0.53,0.96), Q3 (2.6-5.0): 0.60 (0.44,0.83), Q4 (5.1-10.0): 0.54 (0.39,0.76), Q5 (&gt;10): 0.61 (0.44,0.84)</td>
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<td></td>
<td>P: 0.004</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Yu (2003)</td>
<td>Caerphilly Collaborative Heart Disease Study, United Kingdom</td>
<td>1,975</td>
<td>49-64</td>
<td>Healthy</td>
<td>LTPA</td>
<td>Mortality</td>
<td>LTPA (kcal/wk) 0-1,133: 1.00</td>
<td>Mortality: LTPA 1,134-2,769: 0.74 (0.44,1.25), 2,770-19,230: 0.55 (0.31,0.98) P: 0.039</td>
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<td>Age, BP, BMI, smoking, class, family history of CHD, diabetes, job PA</td>
</tr>
<tr>
<td>Hillsdon (2004)</td>
<td>OXCHECK trial, UK</td>
<td>10,522</td>
<td>35-64</td>
<td>Healthy</td>
<td>LTPA</td>
<td>Mortality</td>
<td>LTPA Never/&lt;1/month: 1.00</td>
<td>Mortality: LTPA &lt;2 times/week: 0.46 (0.19,1.12), ≥2 times/week: 0.96 (0.53,1.75)</td>
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<td>Age, sex, smoking, alcohol, pre-existing disease, social class</td>
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<tr>
<td>Knoops (2004)</td>
<td>HALE Project, 11 European Countries</td>
<td>1,507</td>
<td>70-90</td>
<td>Healthy</td>
<td>LTPA</td>
<td>Mortality</td>
<td>LTPA Low: 1.00</td>
<td>Mortality: LTPA High: 0.72 (0.48,1.07)</td>
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<td>Age, gender, education, BMI, study, dietary and lifestyle factors</td>
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<tr>
<td>Sundquist (2005)</td>
<td>Swedish Annual Level-of-Living Survey, Germany</td>
<td>5,196</td>
<td>35-74</td>
<td>Healthy</td>
<td>LTPA</td>
<td>Incidence</td>
<td>LTPA 1 (none): 1.00</td>
<td>Incidence: LTPA 2 (occasionally): 0.74 (0.53,1.03)</td>
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<td></td>
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<td>2,645 M</td>
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<td>Age, sex, income, smoking</td>
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<tr>
<td>Study</td>
<td>Population</td>
<td>Gender</td>
<td>Age Range</td>
<td>Healthy Age</td>
<td>LTPA Incidence</td>
<td>LTPA (hr/wk)</td>
<td>Incidence Factors</td>
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<td>Chiuve (2006)</td>
<td>HPFS</td>
<td>M</td>
<td>40-75</td>
<td>16</td>
<td>LTPA</td>
<td>3 (1-2/wk): 0.70 (0.50,0.97)</td>
<td>Age, family history of MI, aspirin use, antihypertensive meds, hypercholesterolem ia, hypertension, lifestyle factors</td>
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<td>4 (2+/wk vig.): 0.52 (0.33,0.83)</td>
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<tr>
<td>Meisinger (2007)</td>
<td>MONICA Augsburg Studies</td>
<td>C</td>
<td>45-74</td>
<td>8.6</td>
<td>LTPA</td>
<td>LTPA – M: (per/wk) 0: 1.00 &lt;1: 1.02 (0.74,1.41) 1-2: 0.76 (0.54,1.07) &gt;2: 0.80 (0.57,1.13)</td>
<td>Age, survey, diabetes, smoking, alcohol, family history of MI, education</td>
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<td>LTPA – F: (per/wk) 0: 1.00 &lt;1: 0.96 (0.54,1.71) 1-2: 0.45 (0.22,0.91) &gt;2: 0.18 (0.04,0.75)</td>
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<tr>
<td>Hu (2007)</td>
<td>Finnish Population Surveys</td>
<td>C</td>
<td>25-64</td>
<td>18.9</td>
<td>LTPA</td>
<td>LTPA – M Low: 1.00 Moderate: 0.93 (0.86, 1.00) High: 0.73 (0.65,0.83)</td>
<td>Age, study year, education, alcohol, smoking</td>
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<td></td>
<td>LTPA – F Low: 1.00 Moderate: 0.80 (0.72,0.89) High: 0.64 (0.51,0.80)</td>
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<td></td>
<td>Occ. PA - M Low: 1.00 Moderate: 0.82 (0.74,0.91) High: 0.87 (0.81,0.95)</td>
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<td></td>
<td>Occ. PA - F Low: 1.00 Moderate: 0.67 (0.59,0.77) High: 0.77 (0.68,0.87)</td>
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<td></td>
<td>Trans. PA – M (min/day) 0: 1.00 1:29: 0.92 (0.85,1.00) 30+: 0.91 (0.83,1.00)</td>
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<tr>
<td>Study (Year)</td>
<td>Study Description</td>
<td>Gender</td>
<td>Total</td>
<td>Age Range</td>
<td>Healthy</td>
<td>Incidence Estimate</td>
<td>LTPA (hr/wk)</td>
<td>Mortality Estimate</td>
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<tr>
<td>Akesson (2007)</td>
<td>Swedish Mammography Cohort Sweden</td>
<td>W</td>
<td>24,444</td>
<td>49-83</td>
<td>Healthy</td>
<td>6.2 LTPA Trans. PA</td>
<td>Incidence</td>
<td>LTPA (hr/wk)</td>
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<td>1-29: 0.83 (0.73,0.94)</td>
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<tr>
<td>Smith (2007)</td>
<td>Rancho Bernardo Study USA</td>
<td>C</td>
<td>1,3217</td>
<td>50-90</td>
<td>Healthy</td>
<td>10 Walking</td>
<td>Mortality</td>
<td>Walking (miles/day)</td>
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<tr>
<td>Virkkunen (2007)</td>
<td>Helsinki Heart Study Finland</td>
<td>M</td>
<td>1288</td>
<td>40-55</td>
<td>Healthy</td>
<td>8 Occ. PA</td>
<td>Incidence</td>
<td>Occ. PA</td>
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<tr>
<td>Weinstein (2008)</td>
<td>Women’s Health Study USA</td>
<td>W</td>
<td>38,987</td>
<td>45+</td>
<td>Healthy</td>
<td>10.9 LTPA Walking</td>
<td>Incidence</td>
<td>LTPA (kcal/wk)</td>
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<td>Walking (hours/wk)</td>
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<td>Inoue (2008)</td>
<td>JPHC Study Japan</td>
<td>C</td>
<td>83,034</td>
<td>45-74</td>
<td>Healthy</td>
<td>8.7 LTPA</td>
<td>Mortality</td>
<td>LTPA – M</td>
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</table>

Notes:
- Trans. PA = F (min/day) 0: 1.00 1-29: 0.83 (0.73,0.94) 30+: 0.66 (0.58,0.76)
- Age, education, family history of MI, cholesterol, hypertension, hormone therapy, aspirin, energy intake, alcohol, smoking, WHR, other PA
- Age, sex, smoking, BMI, alcohol, exercise, history of CHD, hypertension, triglycerides, HDL
- Age, smoking, day-shift work
- Age, treatment, parental history of MI, alcohol, smoking, hormone therapy, dietary factors
- Age, area, occupation, history of diabetes, smoking, alcohol, BMI, energy intake, leisure sports/exercise
<table>
<thead>
<tr>
<th>Pedersen (2008)</th>
<th>Copenhagen City Heart Study</th>
<th>C</th>
<th>11,914</th>
<th>20+</th>
<th>Healthy</th>
<th>20</th>
<th>LTPA</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Denmark</td>
<td></td>
<td>5272 M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6642 F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table Key**

- **M; W; C**: Men; Women; Combined or both genders
- **LTPA**: Leisure-time physical activity
- **Vig. PA**: Vigorous intensity physical activity
- **Walking**: Time spent walking per week
- **Walk Pace**: Usual pace of walking
- **Occ. PA**: Occupational physical activity
- **Trans. PA**: Transport physical activity
- **Total PA**: Total physical activity; includes two or more physical activity types
- **Non-LTPA**: Physical activities outside of the ‘leisure’ type
- **Healthy**: Participants free of coronary heart disease at baseline
- **Mortality**: Restricted to fatal cases of CHD only
- **Incidence**: Inclusive of both fatal and non-fatal cases of CHD
- **Q; T; D**: Quartile/Quintile; Tertile; Decile
- **BP**: Blood pressure
- **HRT**: Hormone therapy
- **BMI**: Body Mass Index
- **FEV1**: Forced expiratory volume in 1 minute
- **HDL; LDL**: High density lipoprotein; Low density lipoprotein
- **Age, smoking, BMI, education, marital status, diabetes, alcohol**
## Supplemental Table 2. Selected Studies by Type of Physical Activity

<table>
<thead>
<tr>
<th>Physical Activity Type</th>
<th>Total No. of Studies (M, W, C)</th>
<th>No. of Quantitative Studies (M, W, C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT PA</td>
<td>26 (15, 11, 5)</td>
<td>9 (5, 5, 0)</td>
</tr>
<tr>
<td>Walk time</td>
<td>7 (2, 4, 1)</td>
<td>5 (2, 3, 0)</td>
</tr>
<tr>
<td>Walk pace</td>
<td>3 (2, 1, 0)</td>
<td>2 (1, 1, 0)</td>
</tr>
<tr>
<td>Occupational PA</td>
<td>4 (3, 1, 1)</td>
<td>0</td>
</tr>
<tr>
<td>Transport PA</td>
<td>4 (3, 2, 0)</td>
<td>0</td>
</tr>
<tr>
<td>Total PA</td>
<td>3 (2, 2, 0)</td>
<td>0</td>
</tr>
<tr>
<td>Non-Leisure PA</td>
<td>1 (0, 1, 0)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>33 (21, 13, 6)</strong></td>
<td><strong>12 (7, 6, 0)</strong></td>
</tr>
</tbody>
</table>

* Total studies and Quantitative Studies refer to studies with both qualitative and quantitative categorization of physical activity. Only studies with quantitative categorization of physical activity include Men (M), Women (W), and Combined genders (C).

* These 33 total studies included 56 total physical activity-type-specific comparisons; many studies included comparisons from multiple physical activity types (e.g., LTPA, walking time, and vigorous PA assessed in the same study), and/or both genders.
Supplemental Figure 1: Flow Chart of Study Selection

PubMed (n = 1545) → Embase (n = 1649) → From References (n = 7) → Search results combined (n = 3201) → Duplicates (n = 31) → Titles & abstracts evaluated → Excluded (n = 3126) → Full text evaluation (n = 75) → Excluded (n = 42):
- Duplicated data (n=18)
- CHD not an outcome (n=11)
- FA not exposure variable (n=7)
- N or RR or CI provided (n=3)
- Case control study design (n=3)
- No # of subjects or cases/group (n=1)
- All subjects diabetic at baseline (n=1) → Included in final analysis (n = 33)
Supplemental References


26. Meisinger C, Lowel H, Heier M, Kandler U, Doring A. Association of sports activities in leisure time and incident myocardial infarction in middle-aged men and women from the general


