Dose Response Relationship Between Physical Activity and Risk of Heart Failure:
A Meta-Analysis

Running title: Pandey et al.; Physical activity and heart failure risk

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Journal Subject Terms: Congestive; Epidemiology
Abstract

**Background**—Prior studies have reported an inverse association between physical activity (PA) and risk of heart failure (HF). However, a comprehensive assessment of the quantitative dose-response association between PA and HF risk has not been reported previously.

**Methods and Results**—Prospective cohort studies with participants >18 years of age that reported association of baseline PA levels and incident HF were included. Categorical dose response relationships between PA and HF risk were assessed using random effects models. Generalized least squares regression models were used to assess the quantitative relationship between PA (MET-min/week) and HF risk across studies reporting quantitative PA estimates. Twelve prospective cohort studies with 20,203 HF events among 370,460 participants (53.5% women; median follow-up: 13 years) were included. The highest levels of PA were associated with significantly reduced risk of HF [Pooled Hazard Ratio (HR) Highest vs. lowest PA: 0.70 (0.67-0.73)]. Compared with participants reporting no leisure time PA, those who engaged in guideline recommended minimum levels of PA (500 MET-min/week, 2008 US Federal Guidelines) had modest reductions in HF risk [RR: 0.90 (0.87 – 0.92)]. In contrast, a substantial risk reduction was observed among individuals who engaged in PA at twice [HR for 1000 MET-min/week: 0.81(0.77 – 0.86)] and four times [HR for 2000 MET-min/week: 0.65 (0.58 – 0.73)] the minimum guideline recommended levels.

**Conclusions**—There is an inverse, dose-response relationship between PA and HF risk. Doses of PA in excess of the guideline recommended minimum PA levels may be required for more substantial reductions in HF risk.

**Key words:** heart failure; physical exercise; prevention; meta-analysis
Introduction

Heart failure (HF) affects over 5.1 million adults in United States, accounts for a significant proportion of hospitalizations and deaths among older Americans, and consumes over $30 billion per year in healthcare cost. The prevalence of HF is expected to increase by 25% from 2010 to 2030. As a result, novel preventive approaches focused on modifying risk factors for HF are urgently needed to combat this growing epidemic.

Physical inactivity and low fitness have been identified as significant contributing factors for cardiovascular diseases (CVD). Over the past three decades, the inverse, dose-response relationship between physical activity (PA) and risk coronary heart disease (CHD) has been well established. Thus, physical inactivity is considered a major, modifiable risk factor for CHD, and current American Heart Association (AHA) guidelines recommend at least 150 minutes/week of moderate intensity aerobic PA to reduce the burden of CHD risk factors and the risk of CHD.

In contrast, the role of PA in reducing risk of HF has not been emphasized in existing guidelines and public health recommendations. Although observational cohort studies have reported an inverse association between higher levels of PA and HF risk, a comprehensive assessment of the quantitative dose response association between PA and HF risk has not been previously reported. Understanding this relationship is important since recent studies suggest that there may be important differences in the mechanisms through which PA modifies HF risk and CHD risk, and the dose of PA needed to significantly lower HF risk may differ from that currently recommended to reduce CHD risk. Previous studies have used dose response meta-analysis of epidemiological studies to better understand the quantitative association between lifestyle risk factors such as coffee intake, dietary patterns and cardiovascular outcomes.
the present study we have utilized a similar approach and performed a dose-response meta-
alysis of prospective cohort studies to determine the categorical and quantitative dose response
association between PA and risk of HF. We hypothesized that there would be a dose-dependent,
inverse association between PA and risk of HF.

Methods:

Literature search strategy

We followed the meta-analysis of observational studies in epidemiology protocol for performing
and reporting the present meta-analysis. 36 We searched for all prospective cohort studies that
examined the associations between PA and incident HF among adult participants (> 18 years of
age at baseline). We systematically searched electronic databases (Medline, EMBASE and
Cochrane database) and performed additional manual searches through the reference list of
original publications and review articles. We used the following key words, among others, to
perform the search “physical activity,” “walking”, “exercise”, “exercise training”,
“cardiorespiratory fitness”, “fitness”, “heart failure risk”, “cardiac failure risk” (full search term
available on request). The search was restricted to articles that focused on human participants
and were published between January 1st, 1995 and September 24th 2014. The time restriction was
applied to reflect likely changes in PA categorization for analyses by investigators after
publication of the 1995 US Centers for Disease Control and Prevention/American College of
Sports Medicine guideline. 37

Study Selection

Prospective cohort studies that reported the association between baseline PA levels and incident
HF were included. Studies with all types of PA (leisure time PA, walking time, occupational PA,
total PA) were included in the initial study selection process. If multiple articles were published from the same cohort, we included data from the study with the most detailed report of PA levels and/or the larger sample size. Two independent investigators (AP, MK) conducted the initial screening of all titles or abstracts and then evaluated all potentially relevant articles based on full text reviews. Studies were excluded if they failed to meet all the criteria detailed above. All discrepancies regarding study inclusions were adjudicated by the senior author (JB). The study quality was assessed using the Newcastle-Ottawa quality assessment scale that allowed a total score of up to 9 points (9 representing the highest quality) summarizing eight aspects of each study.  

Data Collection

Two authors (AP, MK) independently performed the data collection using a standardized form. The following information was recorded for each study: author, year of publication, cohort/study name, geographic location, proportion of women, prevalence of HF risk factors such as hypertension, diabetes, smoking, coronary artery disease at baseline, types of PA, PA levels, method used to estimate PA, total number of participants, total number of HF events, method of ascertainment of outcomes, follow up duration, hazard ratio/relative risk of HF and confidence intervals, and variables that were entered into the multivariable model as potential confounders. Information on quantitative dose of PA and/or duration and intensity of PA performed per week was also recorded, as reported in the study.

Statistical Analysis

For the present meta-analysis we used hazard ratio (HR) or relative risk (as available) and 95% confidence intervals as a measure of the effect size associated with each category of PA for all studies. In articles that studied more than one type of PA, only leisure time PA was preferentially
included for analysis. The primary aim of our analysis is to quantify the risk of HF that is associated with different PA levels independent of other cardiovascular and non-cardiovascular risk factor burden. Therefore, we used the results of the original studies from multivariable adjusted models with the most complete adjustment for potential baseline confounders including presence of risk factors such as hypertension (HTN), diabetes (DM), and body mass index (BMI) for primary analysis. One study (Bell, et al.) reported separate hazard ratios for HF risk associated with different PA levels for African Americans and whites. As a result, we included data from both the African American and the white cohort separately in the pooled analysis.

The categorical dose response analysis was performed with STATA 10.0 (STATA Corp, College Station, TX). For this, we generated four categories of physical activity: lowest, light, moderate, and highest. For each study that was included, the lowest and the highest PA categories corresponded to the lowest and highest groups, respectively. For studies with at least 3 or more exposure categories, the second and third highest PA categories corresponded to the moderate and light groups, respectively. The pooled hazard ratios and 95% CI for HF associated with different categories of PA were calculated by comparing each PA category (highest, moderate and light PA) with the lowest PA category using the random effects modeling technique as described by Dersimonian and Laird. 39 Maximally adjusted HRs, when reported, were used for the primary analysis to account for confounding variables. Pooled analysis comparing highest vs. lowest PA levels included all available studies (n=12) while comparisons of moderate (2nd highest PA category) and light PA (3rd highest PA category) vs. the lowest PA category included studies that stratified participants into at least 3 (n=10) and 4 PA (n=4) categories, respectively. We assessed for heterogeneity using the I² test (I² > 50% was assumed to be a result of significant heterogeneity). We performed several sensitivity and subgroup analyses.
based on sex, age, geographical region, study population characteristics, CHD prevalence at baseline, HF incidence rates on follow-up, and multivariable adjustment strategy used in analyses (using HR associated with models without adjustment for cardiovascular risk factors) to test for the robustness of the observed associations. Publication bias was assessed using contour-enhanced funnel plots, Egger’s linear regression test, and Begg’s rank correlation test at the P <0.10 level of significance. All p values were two tailed. For all tests, a probability level <0.05 was considered statistically significant.

Eight studies allowed quantitative estimation of leisure time PA levels associated with each category and were used to perform the continuous, dose-response meta-analysis. Two studies reported the dose of total PA with no separate information about the dose of leisure time PA and was not included in the quantitative analysis.\textsuperscript{24,32} Three studies reported the range of leisure time PA dose for each category in MET-min/week or Met-Hour/week. The other five studies reported total duration and intensity of PA (light or moderate or vigorous) associated with each category, which was used to estimate the mean dose of PA in met-min/week. (Supplemental Methods). We assigned the median dose of PA for each category to the corresponding hazard ratio for each study. If medians for that category were not reported, we estimated the approximate medians by using the midpoints of the lower and upper bounds. For studies with an open-ended highest physical activity level category, 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 closest adjacent category and its median (Supplemental Table 1). Continuous dose response relationships between PA (MET-mins/week) and HF risk were assessed using a generalized least squares regression model using SAS version 9.2 (SAS Corporation, Cary, North Carolina). This method is well described in the literature for meta-
analyses of epidemiological studies having multiple risk estimates per study and accounts for appropriate variance-covariance relationships between and within studies. This model uses the multiple data points available in all studies simultaneously to provide the best overall pooled estimate of the dose-response in a single estimation. Non-linear relationship between PA and HF risk was assessed by modeling PA dose with use of restricted cubic splines with three knots at fixed centiles (5%, 50% and 95%) of the distribution. We first estimated a restricted cubic spline model with a generalized least squares regression, considering the correlation within each set of reported hazard ratios. We then combined the study specific estimates, using the restricted maximum likelihood method in a multivariate random effects meta-analysis. We used the PA vs. HF risk dose-response curve to determine the reduction in HF risk among individuals engaging in PA at minimum guideline recommended levels (500 MET-min/week) as well as two times (1000 MET-min/week) and four times (2000 MET-min/week) the minimum guideline recommended levels.

Results

Characteristics of Included Studies

The study selection process and results from the literature search are shown in Figure 1. We included twelve cohort studies with 370,460 participants and 20,203 HF events over a median follow up of 13 years. Baseline characteristics of the included studies are shown in Table 1. Ten studies included cohort study participants and two included participants of randomized controlled trials (CARE Study and Physician Health Study). Two studies included only men; two included only women and eight included both men and women. Eight studies were conducted in United States and four were conducted in Europe. European study cohorts had a lower burden of co-morbidities such as diabetes and hypertension as compared to US study cohorts. Seven
studies included participants with prevalent coronary artery disease or previous myocardial infarction history at baseline. Among studies that reported baseline characteristics stratified by physical activity levels (n = 8), pooled prevalence of cardiovascular risk factors such as HTN, DM and smoking was greater in lowest PA category as compared with highest PA category. Table 2 describes the methodology used for the assessment of exposure and outcome variables in the included studies. Eight studies allowed quantitative estimation of leisure time PA. Objective criteria (ICD codes or clinical adjudication based on patient charts) were used for diagnosing HF in most of the studies. Most studies adjusted for covariates such as age, sex, body mass index, smoking, alcohol intake, and cardiovascular comorbidities.

Categorical Association between PA and HF risk

Figure 2 shows the pooled estimates of HR for HF associated with different categories of PA. Compared to the lowest PA category, the risk of HF was 30% lower among the highest PA category participants [117,733 participants across 12 studies; Pooled HR (95% CI) = 0.70 (0.67 to 0.73), I² = 36.4%, Supplemental Figure 1]. Moderate (131,014 participants across 10 studies) and light PA category (20,564 participants across 4 studies) participants also had 22% and 15% lower risk of HF as compared to the lowest PA group [Moderate PA: Pooled HR (95% CI) = 0.78 (0.75 to 0.82), I² = 20.3% Supplemental Figure 2]; Light PA: [Pooled HR (95% CI) = 0.85 (0.79 to 0.92), I² = 3.4% Supplemental Figure 3]. In subgroup analyses, the association between the highest levels of PA (vs. lowest PA levels) and HF risk was similar across different age (< 55 years vs. ≥ 55 years; Pinteraction = 0.64), sex (men vs. women; Pinteraction = 0.51) and geographical (Europe vs. US; Pinteraction = 0.38) subgroups. (Table 3)

Continuous Dose-response Association between PA and HF risk

Figure 3 shows the continuous, dose-response association between quantitative estimates of PA
(MET-mins/week) and HF risk. The pooled results showed a consistent, dose-response, inverse association between PA and risk of HF. Participants who met the minimum guideline recommended PA levels (~500 MET-mins/week) had 10% lower risk of HF compared to those with no PA [HR (95%CI) = 0.90 (0.87 – 0.92)]. The magnitude of the risk reduction was substantially greater among participants with significantly higher levels of PA. For example, participants who engaged in PA at twice (~1000 MET-mins/week) and four times (~2000 MET-mins/week) the basic guideline recommended levels had 19% [HR (95% CI): 0.81 (0.77 to 0.86)] and 35% [HR (95%CI): 0.65 (0.58 to 0.73)] lower risk of HF respectively.

**Study Quality, Publication Bias and Subgroup analysis**

Assessment of study quality yielded an average score of 8.4 (9 representing the highest quality), and 11 studies had a score of 6.5 or above (Supplemental Table 2). We did not observe a significant publication bias in the present meta-analysis (P-value for Egger’s line regression test: 0.75; P-value Begg’s rank correlation test: 0.54 Supplemental Figure 4).

To confirm the robustness of our study findings, we conducted sensitivity analyses evaluating the association between the highest levels of PA and HF risk among the following subgroups: studies with quantitative assessment of PA only (n=8); studies without history of myocardial infarction or prevalent coronary artery disease among participants at baseline (n=5); studies with low (<10%, n = 8) and high incidence (≥10%, n = 4) of HF on follow-up. We also conducted additional sensitivity analysis excluding studies with significantly different study populations (Lewis, et al. with post MI population) or effect sizes as compared to other studies (Bell, et al. African-American cohort). We did not observe any significant change in the magnitude or direction of the effect size for association between highest levels of PA and HF risk with these sensitivity analyses (Supplemental Table 3). To determine the impact of
multivariable adjustment, we also conducted a sensitivity analysis pooling hazard ratios from multivariable adjusted models without adjustment for cardiovascular risk factors such as HTN, DM, CHD, and BMI (n = 11 studies) and observed that the magnitude of the pooled estimate [Pooled HR (95% CI): 0.66 (0.61 to 0.71), Supplemental Table 3] did not change significantly as compared with primary pooled analysis including the most adjusted models [Pooled HR (95% CI): 0.70 (0.67 to 0.73)]. Similar findings were also observed in sensitivity analyses excluding studies that did not adjust for socioeconomic factors such as income and/or education [Pooled HR (95% CI): 0.73 (0.68 to 0.79)] (Supplemental Table 3).

Discussion

To our knowledge, the present meta-analysis is the largest and most comprehensive evaluation of the dose-response relationship between PA and HF risk in the general population. We observed two important findings in this study. First, there is a linear, dose dependent, inverse association between PA and HF risk. This relationship was observed with both categorical as well as continuous quantitative estimates of PA levels, and is consistent across age, sex and geographical region based subgroups. Second, guideline recommended minimum PA levels are associated with only modest reductions in HF risk, and higher doses of PA may be required to reduce significantly the risk of HF.

The dose response association between PA and atherosclerotic CVD has been previously reported. Sattelmair, et al. observed an inverse dose-response association between PA and CHD risk with significant reductions in CHD risk with levels of PA at par or even lower than the current guideline-recommended minimum dose of PA (500 MET-min/week). In the present study, we observed a similar inverse dose-response association between PA and HF risk.
However, the observed dose response relationship between PA and HF risk differs significantly from that reported between PA and CHD risk by Sattelmaier, et al. The reduction in HF risk observed at lower levels of PA were modest as compared to that reported for CHD. For example, Sattelmaier, et al. reported up to a 15% reduction in CAD risk at PA levels of 250 and 500 MET-min/week. In contrast, we observed only 5% and 10% reduction in HF risk at PA levels of 250 and 500 MET-min/week, respectively. At higher doses of PA, the magnitude of reduction in HF risk was similar to that reported for CHD (~20% risk reduction for HF and CAD at 1000 MET-min/week). However, while Sattelmaier et, al. observed a plateau in the risk reduction for CAD at doses higher than 1000 MET-min/week, we observed a linear dose response for HF risk with marked reduction in risk at very high doses of PA (~35% risk reduction at 2000 MET-min/week). These findings suggest that while current guideline recommended minimum levels of PA might be sufficient to mitigate CHD risk, considerably higher levels of PA may be required to achieve more robust reductions in risk for incident HF.

This difference in the magnitude of risk reduction for HF vs. CHD could be related to differences in the mechanism through which PA modifies the risk of these diseases. This is supported by previous studies from our group that have shown a stronger association between fitness and HF risk as compared with MI risk among healthy individuals. 20 PA predominantly lowers risk of CHD through favorable changes in the risk factor profile such as lowering of BP, LDL and non-HDL cholesterol. 41 Findings observed in recent studies suggest that the association between low PA/fitness levels and CHD risk is attenuated after adjustment for prevalent traditional cardiovascular risk factors. 42, 43 In contrast, the relationship of low PA/fitness levels is independent of interval development of these risk factors and is more likely related to direct effects of PA/fitness on cardiac structure and function. 44-47, 48 Non-cardiac
mechanisms may also contribute to the observed dose-dependent inverse association between PA and HF risk. HF is a systemic syndrome and previous studies have identified subclinical dysfunction in multiple non-cardiac organ systems including lungs, skeletal muscle, neuroendocrine system, and peripheral vasculature as significant risk factors for HF. Higher levels of PA are associated with a lower antecedent burden of these non-cardiac risk factors, which may reduce future HF risk.

Age related decline in left ventricular compliance and diastolic function have been implicated in development of heart failure, particularly heart failure with preserved ejection fraction. In a recent study Bhella, et al. observed that high levels of lifetime exercise (i.e. 4-5 times per week) were associated with more favorable left ventricular compliance. In contrast, there were no differences in left ventricular compliance between sedentary and casual exercisers (i.e. 1-2 times per week). Thus, doses of PA in excess of current guideline recommendations may be required to achieve favorable changes in cardiac structure and function and lower HF risk.

We observed similar reduction in risk of HF with higher levels of PA among men and women. This is in agreement with prior studies that have shown no sex-based differences in the association between PA and CVD risk factors such as blood pressure, fitness and metabolic syndrome. In contrast, Sattelmair et al. observed that the association between PA and CHD risk was stronger in women than in men. The mechanisms underlying this difference in interaction by sex between the two studies remain unclear but could also reflect differences in the physiological mechanisms through which PA modifies the risk of HF vs. CHD.

Our study findings may have important public health implications. HF is a growing public health problem, and there is an urgent need for novel preventive strategies that can be
implemented at a population level. The present study highlights the dose of PA required for HF prevention, providing quantitative measures of the magnitude of the risk reduction associated with different levels of PA. These findings may help guide physicians and health policy-makers in making recommendations about the dose of PA for optimal HF prevention at both the individual and the population level.

There are several strengths to our study. First, the pooled sample size of our meta-analysis was large with a long duration of follow-up. Second, we were able to quantify the amount of PA and assess the risk of HF associated with specific, quantitative levels of PA. Third, we used risk estimates from fully adjusted models for the pooled analysis to reduce the potential for confounding. Fourth, we did not observe any significant statistical heterogeneity across the studies included in the present meta-analysis. Fifth, to confirm the robustness of our study findings we performed several sensitivity and subgroup analyses, and we observed no significant change in the magnitude or the direction of the effect for the association between PA levels and HF risk.

This study also has several important limitations. First, because this is a meta-analysis of observational studies, the results could be subject to unmeasured or residual confounding. However, because of the large number of included studies with different study characteristics, we were able to conduct numerous sensitivity analyses across different subgroups of interest suggesting the robustness of our findings. Second, there could be errors in the measurement of PA since it was assessed in most studies by using questionnaires or self reported frequency of light/moderate/vigorous PA. However, measurement error tends to bias toward the null, and therefore it is unlikely that measurement error contributed to the dose-response relationship observed in the present study. Third, we could not compare the association of different types of
PA (For example, leisure time PA vs. occupational PA) with HF risk given the amount of detail on subtypes of PA reported from prior studies. Fourth, differential adjustment for confounders across different studies could potentially influence our study findings. However, this was not observed on pooled analyses using HR associated with models with vs. without adjustment for cardiovascular risk factors. Finally, quantitative estimates of PA were not available in all studies. However, the studies included in the quantitative dose response analysis (8 of 12) represent more than 80% of the overall pooled study population.

In conclusion, we observe an inverse dose-dependent association between physical activity and risk of HF. Furthermore, our study findings suggest that doses of physical activity in excess of current guideline recommended minimum levels (500 MET-min/week) might be required to provide more robust reductions in the risk of HF. Future studies comparing different doses PA/exercise-training interventions are needed to determine the optimum dose of PA required for HF prevention.

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**Conflict of Interest Disclosures:** None.

**References:**


11. Morris JN, Everitt MG, Pollard R, Chave SP, Semmence AM. Vigorous exercise in leisure-


21. deFilippi CR, de Lemos JA, Tkaczuk AT, Christenson RH, Carnethon MR, Siscovick DS, Gottdiener JS, Seliger SL. Physical activity, change in biomarkers of myocardial stress and


33. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption


Table 1. Baseline Characteristics of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study name</th>
<th>No. of participants</th>
<th>Mean Age</th>
<th>Women (%)</th>
<th>%Percent with HTN/DM/CHD</th>
<th>Years of follow up</th>
<th>HF events Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>He 2001&lt;sup&gt;22&lt;/sup&gt;</td>
<td>USA</td>
<td>NHANES</td>
<td>13,643</td>
<td>50</td>
<td>59</td>
<td>28/4/5</td>
<td>19</td>
<td>1,382</td>
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<tr>
<td>Lewis 2003&lt;sup&gt;30&lt;/sup&gt;</td>
<td>USA</td>
<td>CARE study</td>
<td>3,860</td>
<td>58</td>
<td>14</td>
<td>42/13/100</td>
<td>5</td>
<td>243</td>
</tr>
<tr>
<td>Kenchaiah 2009&lt;sup&gt;23&lt;/sup&gt;</td>
<td>USA</td>
<td>Physician health study</td>
<td>21,094</td>
<td>53</td>
<td>0</td>
<td>24/3/0</td>
<td>20</td>
<td>1,109</td>
</tr>
<tr>
<td>Wang 2010&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Finland</td>
<td>Finnish database</td>
<td>58,208</td>
<td>44</td>
<td>51</td>
<td>11/2/2</td>
<td>18</td>
<td>3,508</td>
</tr>
<tr>
<td>Bell 2013&lt;sup&gt;19&lt;/sup&gt;</td>
<td>USA</td>
<td>ARIC Study</td>
<td>13,725</td>
<td>54</td>
<td>56</td>
<td>32/10/0</td>
<td>17</td>
<td>1,748</td>
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<tr>
<td>K-kramer 2013&lt;sup&gt;24&lt;/sup&gt;</td>
<td>USA</td>
<td>Framingham Heart Study</td>
<td>1,142</td>
<td>76</td>
<td>65</td>
<td>76/11/0</td>
<td>11.5</td>
<td>250</td>
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<tr>
<td>Patel 2013&lt;sup&gt;25&lt;/sup&gt;</td>
<td>USA</td>
<td>Cardiovascular health Study</td>
<td>5,503</td>
<td>73</td>
<td>58</td>
<td>58/16/17</td>
<td>13</td>
<td>1,137</td>
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<td>Young 2014&lt;sup&gt;28&lt;/sup&gt;</td>
<td>USA</td>
<td>CMHS</td>
<td>82,695</td>
<td>58</td>
<td>0</td>
<td>43/2/13</td>
<td>8</td>
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<td>Saevereid 2014&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Sweden</td>
<td>Copenhagen City Heart Study</td>
<td>18,353</td>
<td>50</td>
<td>54</td>
<td>6/2/0</td>
<td>30</td>
<td>1,580</td>
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<tr>
<td>Agha 2014&lt;sup&gt;31&lt;/sup&gt;</td>
<td>USA</td>
<td>Women’s Health Initiative Study</td>
<td>84,537</td>
<td>64</td>
<td>100</td>
<td>33/4/5</td>
<td>11</td>
<td>1,826</td>
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<tr>
<td>Andersen 2014&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Sweden</td>
<td>National March Cohort</td>
<td>39,805</td>
<td>53</td>
<td>65</td>
<td>13/3/1.5</td>
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<td>Rahman 2014&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Sweden</td>
<td>Swedish Mammography Cohort</td>
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<td>61</td>
<td>100</td>
<td>20/3/0</td>
<td>13</td>
<td>2,402</td>
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</table>

ARIC: Atherosclerosis risk in communities study; CMHS: California Men’s Health Study; NHANES: National Health and Nutrition Examination Survey; HTN: Hypertension; CHD: Coronary heart disease; DM: Diabetes Mellitus; HF: Heart Failure
### Table 2. Exposure and outcomes assessments in the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Categories of Physical activity</th>
<th>Outcome assessment</th>
<th>Results HR (95% CI) (Ref group: lowest PA)</th>
<th>Adjusted Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenchaiah 2009 21</td>
<td>30min Moderate to vigorous PA Cat 1: 5-7 times/week Cat 2: 1-4 times/week Cat 3: 1-3 times/month Cat 4: Inactive</td>
<td>Self-reported HF</td>
<td>Cat 1: 0.73 (0.59-0.90) Cat 2: 0.86 (0.73-1.01) Cat 3: 0.78 (0.63-0.97) Cat 4: Ref</td>
<td>Age; smoking; alcohol; family Hx of MI; treatment group; cardiovascular comorbidities; BMI</td>
</tr>
<tr>
<td>Wang 2010 27</td>
<td>Cat 1: &gt; 3 Hr./week VIPA Cat 2: &gt; 4 Hr./week MIPA Cat 3: Inactive</td>
<td>ICD-9 codes for HF admission</td>
<td>Cat 1: 0.69 (0.60-0.79) Cat 2: 0.83 (0.77-0.89) Cat 3: Ref</td>
<td>Age; sex; year; education, smoking, alcohol use; CVD risk factors, CAD, lung disease, anti-HTN use; BP, total chol; BMI</td>
</tr>
<tr>
<td>Bell 2013 19</td>
<td>Cat 1: &gt; 150 min/week MIPA Cat 2: 1-149 min/week of MIPA or 1-44 min/week of VIPA Cat 3: Inactive</td>
<td>ICD-9 codes for HF admission</td>
<td>Cat 1: A: 0.59 (0.47-0.74) W: 0.64 (0.54-0.75) Cat 2: A: 0.62 (0.51-0.75) W: 0.76 (0.65-0.88) Cat 3: Ref</td>
<td>Age; sex; smoking; alcohol; diet; education; hormone therapy</td>
</tr>
<tr>
<td>Patel 2013 25</td>
<td>Cat 1: High PA (&gt;1,000 MET-min/week) Cat 2: medium PA (500 - 999 MET-min/week) Cat 3: low PA (1-499 MET-min/week) Cat 4: Inactive</td>
<td>Adjudication based on chart review</td>
<td>Cat 1: 0.79 (0.64-0.97) Cat 2: 0.86 (0.69-1.08) Cat 3: 0.97 (0.79-1.20) Cat 4: Ref</td>
<td>Age; sex; race; SE factors; smoking; BMI; CV risk factors; BP, Cr, CRP, Cholesterol, Albumin; MMSE score, depression</td>
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<tr>
<td>Young 2014 28</td>
<td>Cat 1: high (&gt;1585 MET-min/week) Cat 2:medium (471-1584 MET-min/week) Cat 3: Low (&lt;470 MET-min/week)</td>
<td>ICD-9 codes for HF admission</td>
<td>Cat 1: Ref Cat 2: 1.15 (1.04-1.26) Cat 3: 1.52 (1.38-1.67)</td>
<td>Age; race; SE factors; BMI; smoking; Hx of HTN, DM, CAD, anti HTN use; levels of HDL, Glucose; diet; alcohol</td>
</tr>
<tr>
<td>Saevereid 2014 26</td>
<td>Cat 1: moderate to high Cat 2: Light Cat 3: Sedentary</td>
<td>ICD-8 &amp; 10 codes for HF admission</td>
<td>Cat 1: 0.88 (0.73-1.03) Cat 2: 0.89 (0.69-0.92) Cat 3: Ref</td>
<td>Age, sex, alcohol, education, income, family history of CVD</td>
</tr>
<tr>
<td>Andersen 2014 38</td>
<td>Quintiles of PA Cat 1: highest Quintile Cat 2: second quintile Cat 3: Third Quintile Cat 4:Second Quintile</td>
<td>ICD-9 &amp; 10 codes for HF admission</td>
<td>Cat 1: 0.65 (0.53-0.81) Cat 2: 0.75 (0.60-0.90) Cat 3: 0.79 (0.66-0.94) Cat 4: 0.93 (0.79-1.09)</td>
<td>Age; sex; BMI; Alcohol and tobacco use; cardiovascular comorbidities</td>
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<tr>
<td>Agha 2014 31</td>
<td>Cat 1: &gt; 150 min/week MIPA Cat 2: 1-149 min/week MIPA Cat 3: Inactive</td>
<td>Self-reported HF with clinical adjudication from medical records</td>
<td>Cat 1: 0.69 (0.61-0.79) Cat 2: 0.77 (0.67-0.87) Cat 3: Ref</td>
<td>Age; race; education; Hx of HTN, DM CAD, US region</td>
</tr>
<tr>
<td>He 2001 22</td>
<td>Recreational PA Cat 1: High PA Cat 2: Medium or low PA</td>
<td>ICD-9 codes for HF admission</td>
<td>Cat 1: Ref Cat 2: 1.23 (1.09-1.38)</td>
<td>Age; sex; race; education; income; BMI; smoking; Hx. of HTN, DM, CAD, valvular heart disease; alcohol use</td>
</tr>
<tr>
<td>Lewis 2003 30</td>
<td>Recreational PA Cat 1: ≥ 3 times/week MIPA Cat 2:3-5 times/week MIPA</td>
<td>Event adjudication based on patient chart review</td>
<td>Cat 1: 0.67 (0.52-0.86) Cat 2: Ref</td>
<td>Multivariable adjusted, otherwise unspecified in the primary analysis</td>
</tr>
<tr>
<td>K-krainer 2013 24</td>
<td>Recreational PA index tertiles Cat 1: High (Tertile 3) Cat 2: medium (Tertile 2) Cat 3: Low (Tertile 1)</td>
<td>Patient chart review or telephone based health history update</td>
<td>Cat 1: 0.65 (0.46-0.91) Cat 2: 0.84 (0.60-1.17) Cat 3: Ref</td>
<td>Age; sex; Systolic BP; HTN: DM; valve disease; alcohol use; LVH; BMI</td>
</tr>
<tr>
<td>Rahman 2014 32</td>
<td>Total PA Cat 1: highest quartile Cat 2: third quartile Cat 3: second quartile Cat 4: lowest quartile</td>
<td>ICD-9 codes for HF admission</td>
<td>Cat 1: 0.73 (0.65-0.82) Cat 2: 0.76 (0.68-0.85) Cat 3: 0.88 (0.79-0.98) Cat 4: Ref</td>
<td>Age, Education; Alcohol; smoking; family hx of MI; HTN; DM; Stroke; BMI; waist circumference</td>
</tr>
</tbody>
</table>

Cat: Category; PA: physical activity; MIPA: moderate intensity physical activity; VIPA: vigorous intensity physical activity; CAD: coronary artery disease; HF: heart failure; f/u: follow up; CVD: cardiovascular disease; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index; MI: myocardial infarction; SBP: systolic blood pressure; hx: history; MMSE: mini mental status examination; Cr: creatinine; CRP: C-reactive protein; HDL: high density lipoproteins; LVH: left ventricular hypertrophy
Table 3. Association between physical activity and heart failure risk among different subgroups.

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>No. of studies</th>
<th>Pooled Hazard Ratio (95% Confidence Interval)</th>
<th>I² %</th>
<th>P-value for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>12</td>
<td>0.70 (0.67 to 0.73)</td>
<td>36</td>
<td>0.10</td>
</tr>
<tr>
<td>Men</td>
<td>4</td>
<td>0.75 (0.63 to 0.87)</td>
<td>74</td>
<td>0.01</td>
</tr>
<tr>
<td>Women</td>
<td>5</td>
<td>0.73 (0.68 to 0.78)</td>
<td>0</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean age &lt; 55 years</td>
<td>6</td>
<td>0.71 (0.64 to 0.79)</td>
<td>60</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean age ≥ 55 years</td>
<td>6</td>
<td>0.69 (0.65 to 0.73)</td>
<td>0</td>
<td>0.68</td>
</tr>
<tr>
<td>US cohort</td>
<td>8</td>
<td>0.69 (0.65 to 0.73)</td>
<td>28</td>
<td>0.019</td>
</tr>
<tr>
<td>European Cohort</td>
<td>4</td>
<td>0.73 (0.65 to 0.81)</td>
<td>53</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Flowchart of Study Selection for the Meta-analysis.

Figure 2. Pooled estimates of the relative risk of incident HF associated with different categories of physical activity. The high physical activity group represents participants in each study with highest dose of physical activity while the moderate and light physical activity groups represent participants with progressively lower levels of physical activity in each study. Pooled analysis for high physical activity included all available studies while that for moderate and light physical activity included only those studies that stratified participants into at least 3 and 4 physical activity categories, respectively. Participants with the lowest dose of physical activity in each study have been used as the referent group. I² represents the degree of heterogeneity.

Figure 3. Dose response association between physical activity and heart failure risk. The graph here shows spline (smoothed fit) and 95% confidence interval of pooled relative risk of heart failure by MET-min/week.
Figure 1

Studies identified through literature search
- Medline: 1,374
- Cochrane: 61
- Embase: 1,592

Unpublished Abstracts identified manually (n=2)

Abstracts and Titles Screened by co-primary authors (n=2,592)

Duplicates removed (n=437)

Excluded after title/abstract review for not meeting inclusion criteria (n=2,552)

Full text articles retrieved for independent review by co-primary authors (n=40)

Excluded studies (total=28)
- Multiple studies from same cohorts (n=9)
- PA levels not reported (n=4)
- Lack of outcome (incident HF) assessment (n=7)
- Association between PA/fitness levels and incident HF not reported (n=8)

Studies included in final analysis and review (n=12)
Figure 2

Pooled Hazard Ratio For Heart Failure

Light PA
Studies (n) = 4
I² = 3.4%

Moderate PA
Studies (n) = 10
I² = 20.3%

High PA
Studies (n) = 12
I² = 36.4%
Dose Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis
Ambarish Pandey, Sushil Garg, Monica Khunger, Douglas Darden, Colby Ayers, Dharam J. Kumbhani, Helen G. Mayo, James A. de Lemos and Jarett D. Berry

Circulation, published online October 5, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2015/09/18/CIRCULATIONAHA.115.015853

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2015/09/18/CIRCULATIONAHA.115.015853.DC1

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Supplementary Methods:

Dose calculation for different physical activity categories: Based on available literature\textsuperscript{1}, we used following mean energy expenditure rates for different intensities of physical activity (PA): 3 METs for Light, 5 METs for moderate and 9 METs for vigorous intensity PA. PA dose for each category was calculated as the product of duration of light/moderate/vigorous intensity PA per week and respective mean energy expenditure rate. In one study by Kenchaiah et al.\textsuperscript{2}, PA levels were ascertained among study participants using the question “How often do you exercise vigorously enough to work up a sweat?” Previous studies have shown that “exercise vigorous enough to work up a sweat” is equivalent to 30 mins or more of moderate to vigorous intensity PA.\textsuperscript{3} We used a dose based on an energy expenditure rate that is an average of MIPA and VIPA (~7 METS) and duration of at least 30 min per episode reported for each PA group.
Supplemental Figure legends

**Supplemental Figure 1**: Forest plot showing pooled estimate of the relative risk for incident HF comparing high dose physical activity to the lowest category of physical activity (references: 2, 4-14).

**Supplemental Figure 2**: Forest plot showing pooled estimate of the relative risk for incident HF associated with moderate dose physical activity compared to the lowest category of physical activity (references: 2, 4-11, 14).

**Supplemental Figure 3**: Forest plot showing pooled estimate of the relative risk for incident HF associated with light dose physical activity compared to the lowest category of physical activity (references: 2, 6, 9, 14).

**Supplemental Figure 4**: Inverted funnel plot for assessment of publication bias.
**Supplemental Table 1**: Estimated mean leisure time physical activity doses (in MET-min/week) associated with different physical activity categories among studies that allowed a quantitative estimation of physical activity levels

<table>
<thead>
<tr>
<th>Study</th>
<th>Categories of Physical activity/Fitness</th>
<th>Estimated Leisure Time PA dose (MET-min/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenchaiah 2009 ²</td>
<td>&gt;30 min Moderate to vigorous PA&lt;br&gt;Cat 1: 5-7 times/week&lt;br&gt;Cat 2: 1-4 times/week&lt;br&gt;Cat 3: 1-3 times/month&lt;br&gt;Cat 4: Inactive</td>
<td>Cat 1: 1,260&lt;br&gt;Cat 2: 525&lt;br&gt;Cat 3: 105&lt;br&gt;Cat 4: 0</td>
</tr>
<tr>
<td>Wang 2010 ⁴</td>
<td>Cat 1 &gt; 3 Hr./week VIPA&lt;br&gt;Cat 2 &gt; 4 Hr./week MIPA&lt;br&gt;Cat 3: Inactive</td>
<td>Cat 1: 1,830&lt;br&gt;Cat 2: 1,410&lt;br&gt;Cat 3: 210</td>
</tr>
<tr>
<td>Bell 2013 ⁵</td>
<td>Cat 1 &gt; 150 min/week MIPA&lt;br&gt;Cat 2: 1,149 min/week of MIPA or 1,44 min/week of VIPA&lt;br&gt;Cat 3: Inactive</td>
<td>Cat 1: 1,125&lt;br&gt;Cat 2: 375&lt;br&gt;Cat 3: 0</td>
</tr>
<tr>
<td>Patel 2013 ⁶</td>
<td>Cat 1: High PA&lt;br&gt;(&gt;1,000 MET-min/week)&lt;br&gt;Cat 2: medium PA&lt;br&gt;(500 - 999 MET-min/week)&lt;br&gt;Cat 3: low PA&lt;br&gt;(1 – 499 MET-min/week)&lt;br&gt;Cat 4: Inactive</td>
<td>Cat 1: 1,250&lt;br&gt;Cat 2: 750&lt;br&gt;Cat 3: 250&lt;br&gt;Cat 4: 0</td>
</tr>
<tr>
<td>Young 2014 ⁷</td>
<td>Cat 1: high&lt;br&gt;(&gt;1,585 MET-min/week)&lt;br&gt;Cat 2: medium&lt;br&gt;(471-1,584 MET-min/week)&lt;br&gt;Cat 3: Low&lt;br&gt;(&lt; 474 MET-min/week)</td>
<td>Cat 1: 2,142&lt;br&gt;Cat 2: 1,027&lt;br&gt;Cat 3: 235</td>
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<tr>
<td>Saevereid 2014 ⁸</td>
<td>Cat 1: moderate to high&lt;br&gt;Cat 2: Light&lt;br&gt;Cat 3: Sedentary</td>
<td>Cat 1: 1,200&lt;br&gt;Cat 2: 540&lt;br&gt;Cat 3: 180</td>
</tr>
<tr>
<td>Andersen 2014</td>
<td>Cat 1: &gt;1,638 MET-min/week</td>
<td>Cat 2: 1,092 -1,638 MET-min/week</td>
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<tr>
<td>Cat 1: 2,331</td>
<td>Cat 2: 1,617</td>
<td>Cat 3: 1,029</td>
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</table>

<table>
<thead>
<tr>
<th>Agha 2014</th>
<th>Cat 1: &gt; 150 min/week MIPA</th>
<th>Cat 2: 1-149 min/week MIPA</th>
<th>Cat 3: Inactive</th>
</tr>
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<tbody>
<tr>
<td>Cat 1: 1,125</td>
<td>Cat 2: 375</td>
<td>Cat 3: 0</td>
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Cat: Category; MIPA: moderate intensity physical activity; VIPA: vigorous intensity physical activity
### Supplemental Table 2: Quality assessment of included studies

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**Supplemental Table 3**: Sensitivity analyses among different study subgroups

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Hazard Ratio (95% CI)</th>
<th>²</th>
<th>P-value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Studies</td>
<td>12</td>
<td>0.70 (0.67 to 0.73)</td>
<td>36%</td>
</tr>
<tr>
<td>Studies with quantitative estimates of LTPA levels</td>
<td>8</td>
<td>0.68 (0.65 to 0.72)</td>
<td>37%</td>
</tr>
<tr>
<td>Studies without CAD among participants at baseline</td>
<td>5</td>
<td>0.70 (0.63 to 0.78)</td>
<td>54%</td>
</tr>
<tr>
<td>Studies with low incidence of HF on f/u (&lt; 10%)</td>
<td>8</td>
<td>0.70 (0.66 to 0.73)</td>
<td>23%</td>
</tr>
<tr>
<td>Studies with high incidence of HF on f/u (≥10%)</td>
<td>4</td>
<td>0.70 (0.60 to 0.79)</td>
<td>59%</td>
</tr>
<tr>
<td>Excluding Bell, et al’s African American Cohort</td>
<td>12</td>
<td>0.71 (0.68 to 0.74)</td>
<td>32%</td>
</tr>
<tr>
<td>Excluding CARE study (Lewis, et al13)</td>
<td>11</td>
<td>0.70 (0.67 to 0.73)</td>
<td>41%</td>
</tr>
<tr>
<td>Pooled analysis of HR from models without adjustment for CVD risk factors such as DM, HTN, and BMI</td>
<td>11</td>
<td>0.66 (0.61 to 0.71)</td>
<td>62%</td>
</tr>
<tr>
<td>Studies with adjustment for Socioeconomic Factors</td>
<td>7</td>
<td>0.73 (0.68 to 0.79)</td>
<td>55%</td>
</tr>
</tbody>
</table>

LTPA: leisure time physical activity; CAD: coronary artery disease; HF: heart failure; f/u: follow up; CVD: cardiovascular disease; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index
Supplemental Fig 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio (95% CI)</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>KENCHAIH, ET AL. 2009</td>
<td>0.86 (0.73, 1.01)</td>
<td>5.57</td>
</tr>
<tr>
<td>WANG, ET AL. 2010</td>
<td>0.83 (0.77, 0.89)</td>
<td>30.34</td>
</tr>
<tr>
<td>KRAIGHER-KRAINER, ET AL. 2013</td>
<td>0.84 (0.60, 1.17)</td>
<td>1.34</td>
</tr>
<tr>
<td>PATEL, ET AL. 2013</td>
<td>0.86 (0.60, 1.08)</td>
<td>2.87</td>
</tr>
<tr>
<td>BELL, ET AL. 2013 AFRICAN AMERICANS</td>
<td>0.62 (0.51, 0.75)</td>
<td>7.58</td>
</tr>
<tr>
<td>BELL, ET AL. 2013 CAUCASIANS</td>
<td>0.76 (0.65, 0.88)</td>
<td>8.26</td>
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<tr>
<td>YOUNG, ET AL. 2014</td>
<td>0.76 (0.62, 0.93)</td>
<td>4.55</td>
</tr>
<tr>
<td>SAEVREID, ET AL. 2014</td>
<td>0.80 (0.69, 0.92)</td>
<td>8.26</td>
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<tr>
<td>AGHA, ET AL. 2014</td>
<td>0.77 (0.67, 0.87)</td>
<td>10.92</td>
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<td>ANDERSEN, ET AL. 2014</td>
<td>0.73 (0.60, 0.89)</td>
<td>5.19</td>
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<tr>
<td>RAHMAN, ET AL. 2014</td>
<td>0.76 (0.66, 0.85)</td>
<td>15.12</td>
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<tr>
<td>Overall (I-squared = 20.3%, p = 0.250)</td>
<td>0.78 (0.75, 0.82)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
References:


