Association of Physical Activity or Fitness With Incident Heart Failure:

A Systematic Review and Meta-Analysis

Echouffo-Tcheugui et al: Physical Activity or Fitness and Heart Failure

Justin B. Echouffo-Tcheugui, MD, PhD1; Javed Butler, MD, MPH2;
Clyde W. Yancy, MD, MSc3; Gregg C. Fonarow, MD4

From Rollins School of Public Health, Emory University, Atlanta, GA1; Cardiology Division, Stony Brook University, Stony Brook, NY2; Cardiology Division, Northwestern Feinberg School of Medicine, Chicago, IL3, Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan-UCLA Medical Center, Los Angeles, CA4

Correspondence to
Justin B. Echouffo-Tcheugui, MD, PhD
Rollins School of Public Health
Emory University
1518 Clifton Road NE, Atlanta, GA 30322
Tel: 404-404-5416
Fax: 404-427-4590
Email: jechouf@emory.edu

DOI: 10.1161/CIRCHEARTFAILURE.115.002070

Journal Subject Codes: [110] Congestive Heart Failure, [8] Epidemiology; [121] Primary prevention, [26] Exercise/exercise testing/rehabilitation
Abstract

Background—Previous studies have shown that high levels of physical activity are associated with lower risk of risk factors for heart failure (HF) such as coronary heart disease, hypertension and diabetes. However, the effects of physical activity or fitness on the incidence of HF remain unclear.

Methods and Results—MEDLINE and EMBASE were systematically searched until November 30, 2014. Prospective cohort studies reporting measures of the association of physical activity (n=10) or fitness (n=2) with incident HF were included. Extracted effect estimates from the eligible studies were pooled using a random-effects model meta-analysis, with heterogeneity assessed with the I² statistic. Ten cohort studies on physical activity eligible for meta-analysis included a total of 282,889 participants followed for 7 to 30 years. For the physical activity studies, maximum versus minimal amount of physical activity groups were used for analyses; with a total number of participants (n= 165,695). The pooled relative risk (95% confidence interval) for HF among those with a regular exercise pattern was 0.72 (95% CI: 0.67–0.79). Findings were similar for men (0.71 [95% CI: 0.61- 0.83]) and women (0.72 [95% CI: 0.67–0.77]) and by type of exercise. There was no evidence of publication bias (P value for Egger test: = 0.34). The pooled associated effect of physical fitness on incident HF was 0.79 (95% CI: 0.75–0.83) for each unit increase in metabolic equivalent of oxygen consumption.

Conclusions—Published literature support a significant association between increased physical activity or fitness and decreased incidence of HF.

Key Words: heart failure, epidemiology, physical exercise, physical fitness, physical activity
Heart failure (HF) affects over 6 million Americans aged 20 years and above and over 23 million people worldwide. If current trends continue in the US, there will be an estimated increase in HF prevalence by 25% by 2030.\(^1\) HF is associated with a substantial burden of morbidity, mortality, and healthcare expenditures.\(^1\) Given this rising burden and a high lifetime risk of HF in young adults,\(^2\) it is important to focus on preventing HF. There is accumulating evidence on the possibility of reducing HF risk among people at high risk through lifestyle modifications.\(^3\)\(^-\)\(^5\) Indeed, major risk factors including hypertension, diabetes mellitus and coronary artery disease that all account for a large proportion of HF cases may be favorably impacted by exercise.\(^6\)\(^-\)\(^9\) It is reasonable to hypothesize that higher levels of physical activity or fitness may have a protective effect against incident HF, given the effect of physical activity on the aforementioned HF risk factors.\(^10\) It is however also possible that physical activity has more direct protective effects in addition to impacting these risk factors. Whether increased physical activity can reduce the incidence of HF has not been tested in randomized clinical trials. Accruing population-based studies have documented the relation of physical activity to incident HF, but studies have shown various degrees of association. In addition, differences in this regards by gender, race/ethnicity, and type of physical activity, have not been well established. Exercise as a therapeutic adjunct in HF treatment has been incorporated in guidelines, but to date there are no guideline-driven recommendations regarding exercise as a means of preventing HF. Although an American Heart Association (AHA) consensus document suggests this a potential mean for HF prevention,\(^11\) this has not been integrated in daily practice. Furthermore, in exploring the relation of exercise to HF, it is important to examine both physical activity and fitness, which although closely related represent distinct characteristics.\(^12\) Physical activity is any bodily movement produced by skeletal muscle that results in energy expenditure. Fitness is a set of attributes that one possesses
(based on genetic profile) or achieves from regular physical activity, including muscular endurance (or cardiorespiratory fitness), muscular strength, body composition, and flexibility. In many individuals and particularly in those who have low levels of physical activity, increases in fitness can be achieved by increasing one’s physical activity.

We conducted a systematic review to examine the association of physical activity and incident HF, as well as the effect of fitness on HF occurrence.

**Methods**

**Data Sources and Searches**

We searched PubMed and EMBASE from 1990 until November 30, 2014 using a combination of terms related to physical activity or fitness and heart failure (Appendix A), restriction to English language papers. Two evaluators (JBE, JB) independently identified articles and sequentially screened them for inclusion (Figure 1). Reference lists of identified studies were manually scanned, and citing references screened through the ISI Web of Knowledge database, for possible additional eligible studies.

**Study selection/eligibility**

Both prospective cohort studies and nested case–control studies examining the relation of regular physical activity and/or fitness and incident HF were eligible for inclusion. Studies not reporting HF in controls, and traditional case–control studies, where it is difficult to establish temporality between exposure and outcome, were excluded. Studies that included HF-related mortality as the only outcome were also excluded, as well as those involving study populations overlapping with other studies. To avoid double counting of a cohort, study selection was limited to a single set of
results when multiple publications were available for the same cohort. The first priority for
selection was the study with the longest follow-up and the second was the study with full cohort
analysis covering the largest number of participants among articles from a single cohort.

Data extraction and quality assessment
Two investigators (JBE and JB) independently abstracted data from eligible studies and
conducted quality assessment. Discrepancies were resolved by discussion with a third
investigator (GCF) and by referencing the original report. We extracted data on study
characteristics including setting, period, design, participants (sample size, age, ethnicity), length
of follow-up, assessment of physical activity or fitness, ascertainment of HF, number of
participants developing HF, multivariate-adjusted relative risks (RRs) or hazard ratios (HRs) of
HF (and corresponding 95% confidence interval [CI]), and adjustments for potential
confounders. For physical activity, all studies used a categorical variable, we therefore abstracted
and used the maximally adjusted RRs of comparison of the HF risk between the highest physical
activity levels group with that in the lowest physical activity group. Therefore, when the highest
physical activity group was the referent, we converted the reported RR into its reciprocal. Fitness
was assessed both as a continuous and categorical variable, and we used RRs for both situations.
We assessed the quality of studies on the basis of the criteria developed by the United States
Preventive Services Task Force as good, fair, or poor.13

Exposure Assessment
All of the included physical activity studies divided subjects into 2 or 5 groups on the basis of
leisure-time,14–16 occupational and leisure-time physical activity,17,18 vigorous physical activity,19
cumulative/total physical activity. For all of the studies included, the extreme groups (i.e., maximum versus minimal amount of physical activity) were used for the current analyses. When a study assessed domains/types of physical activity in addition to total physical activity, we only used the estimate for total physical activity in the meta-analysis. For physical fitness, we used the continuous measure for the meta-analysis.

Exclusion criteria for the studies used in the meta-analysis were not uniform, with two studies excluding people with ischemic heart disease at baseline. Each study, however, excluded subjects with HF at baseline and incomplete information about physical activity, fitness or HF.

**Data synthesis and statistical analysis**

We conducted separate meta-analyses for risk of HF in relation to physical activity and fitness. We used the maximally adjusted relative risk (RR) estimate as a measure of effect size from each study, and estimated the pooled RRs and 95% CIs using a random-effects meta-analysis model. The random-effects model is the most conservative approach in this setting because it incorporates within and between-study heterogeneity in the CI. To assess heterogeneity, subgroup analyses were also performed. Statistical heterogeneity was calculated by the $I^2$ statistic, as recommended by the Cochrane collaboration (www.cochrane-handbook.org). $I^2$ values of 25% or less, 50%, and 75% or more represent low, moderate, and high inconsistency, respectively. For physical activity, we conducted stratified analyses by country, gender and ethnicity. To assess the potential for publication bias, we visually inspected funnel plots. However, because this method has limitations, we also added the Egger regression test $P$ value for funnel symmetry. All tests were 2-sided and statistical significance was defined as $P<0.05,$
with the exception of the heterogeneity assessment, which was considered statistically significant at P<0.10. Analyses were conducted with R with the use of the R statistical software version 2.13.0 [13-04-2011] (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Search Results

Figure 1 illustrates the study selection process. The search identified 24 full articles of which 12 studies were excluded. We included a total of 12 cohort studies, among which 10 examined the association of physical activity and HF and two the relation of fitness to incident HF.

Characteristics of Studies

Table 1 summarizes the characteristics of 10 cohort studies on the association of physical activity and incident HF. The sample size of included cohorts ranged from 1142 to 82695 (total: 282889), with the number of participants with HF ranging from 250 to 3614. Six cohort studies included U.S. populations,14,15,17–19,23 four studies included European populations from Finland,24 Denmark,16 and Sweden.20,21 The US-based studies included multiethnic populations; but overall the proportion of white individuals in these studies was greater than 50%. Two studies enrolled men only19,23 and one only women,21 while the rest enrolled both sexes. The age range of participants was 25 to 97 years. The duration of follow-up varied between 7.8 and 30 years.

Table 2 describes the characteristics of two cohort studies on the association of fitness and incident HF. The sample size of these studies ranged from 1873 to 20642 (total: 22515), with a number of participants with HF of 152 and 1051. One of the studies was US-based (including a multiethnic population)25 and the other was from Finland.26 These studies included participants
from both sexes aged 45 years and above, with a majority of white race and a follow-up period of 6.5 to 20.4 years.

Physical activity assessment was conducted through a questionnaire in all studies, but categorization of physical activity was defined differently at each study. Fitness was assessed through maximal oxygen uptake - V02 max (Table 2). The ascertainment of HF was mostly based on hospital or death records, with only one study distinguishing type of HF into HF with reduced ejection fraction (HFREF) versus HF with preserved ejection fraction (HFPEF).

The degree of covariate adjustment varied across studies, with eight studies accounting for intermediate states such as CHD either through adjustment or restriction of analyses to those with non-ischemic HF or exclusion of those with CHD at baseline (either as part of the original study design or a subgroup analysis).

Study quality varied among the included studies. The included studies were generally at low risk for bias of participation, study attrition. However, the included studies had different quality profiles for other domains such definition of physical activity and confounding adjustment. All of the selected studies were graded as fair to good by the criteria developed by the United States Preventive Services Task Force.

**Physical Activity and Incident Heart Failure**

Of the ten studies selected for the meta-analysis, we used 165695 subjects belonging to highest and lowest categories of physical activity for the current analysis. Using a random-effects model, the pooled RR of HF comparing the most physically active versus the least physically active groups was 0.72 (95% confidence interval, 0.67–0.79; P<0.001; Figure 2). We found there was significant heterogeneity across studies (I²= 56.3%, P<0.001) but no major asymmetrical
appearance in the funnel plot (Supplementary Figure 1) with a non-significant Egger test for publication bias (P= 0.34).

Among the included studies, three studies reported RR s in men and women, one in women only, and two in men only. Using these studies, we conducted a sex-stratified analysis; the pooled RR in women was 0.72 (95% CI: 0.67–0.77; P<0.001) and 0.71 (95% CI: 0.61–0.83; P<0.001) for men (Supplementary Figure 2). In another sensitivity analysis, restricted to US-based studies (n=6) vs. non-US based (n=4) showed a pooled RR for HF comparing the most versus the least physically active groups of 0.69 (95% CI: 0.64–0.75; P<0.0001) for the US-populations, and 0.78 (95% CI: 0.67–0.92; P<0.0001) for the non-US populations (Supplementary Figure 3).

Only one study reported race-based estimates among black individuals (0.59 [95% CI: 0.47, 0.74] for highest levels of physical activity) and among white individuals (0.64 [95% CI: 0.54, 0.75] for highest levels of physical activity). 18

Type of Physical Activity

Across studies, the influence of physical activity did not seem to be dependent upon the type of activity, though more vigorous or intense activity seemed to have a stronger effect on the reduction of HF occurrence. Indeed, studies that concomitantly assess various domains/types of physical activity found a consistent effect on incident HF. Rahman et al found the following risk estimates for various type of physical activity, 21 0.71 (0.64–0.80) for walking/bicycling ≥20 vs <20 minutes/day, 0.83 (0.75–0.92) for exercise ≥1 vs <1 hour a week, 0.93 (0.83–1.03) for work occupation active vs mostly sitting, and 0.82 (0.70–0.97) for home/household work ≥1 vs <1 hour/day. Two studies specifically looked at the effect of sedentarity, Rahman et al found no
association with a hazard ratio of 0.99 (0.83–1.18) for inactivity (watching TV/reading) <3 vs ≥3 hour/day. However, in the study by Young et al., controlling for physical activity and other covariates the hazard ratio (95% CI) of HF in the highest sedentary time category compared with the lowest was 1.34 (95% CI, 1.21–1.48); medium sedentary time also conveyed risk (hazard ratio, 1.13 [95% CI, 1.04–1.24]).

Accounting for prior ischemic disease did not substantially modify the direction and significance of effect estimates of relation of physical activity to incident HF in extant studies

Also, the assessment of the effect of physical activity by type of physical activity in one study showed a similar association for both HFPEF (hazard ratio of 0.60 [95% CI: 0.37–0.99] for highest levels of physical activity) and HFREF (0.69 [95% CI: 0.41–1.19] for highest levels of physical activity). One study assessed the relation of physical activity to lifetime risk of HF, finding that high frequency of exercise was associated with lower lifetime risk of HF - 11.44 (95% CI: 9.42–13.45) for ≥5 times/week and 14.28 (95% CI: 13.21–15.35) for < 5 times/week.3

Physical Fitness and Heart Failure

In the Cooper Center Longitudinal Study, a 1 unit greater fitness level in metabolic equivalents was associated with a lower risk of HF (HR [95% confidence interval], 0.79 [0.75–0.83] in men; and women: 0.81 [0.68–0.96]) Similarly, in a Finnish study, the adjusted HR for HF per unit increase in metabolic equivalents was associated with a 21% lower risk of HF. The combination of the effect estimates from these two studies in a random-effect model meta-analysis gave an estimate of 21% (HR: 0.79, 95% CI:0.75-0.83, P<0.001) lower risk of HF for each 1 unit increase in metabolic equivalents of oxygen (Figure 3).
Discussion

In this meta-analysis, we found that regular physical activity is associated with significantly lower risk of HF compared with sedentary lifestyle. Physical fitness also demonstrates a similar beneficial association with the incidence of HF. The inverse association of physical activity to HF risk was observed in both men and women, both U.S. and Northern European cohorts, and across race/ethnicities though studies were conducted in predominantly white populations; with the most persuasive effect of physical activity on HF observed in the elderly. To the best of our knowledge, this is the first meta-analysis to evaluate the relation between regular physical activity/fitness and HF. The results are relevant because they demonstrate that regular physical activity, which has been established to have beneficial associations with other cardiovascular diseases (CVD) outcomes may represent an important approach for HF prevention. Indeed, based on these findings, the current guidelines for CVD prevention which recommend 150 minutes of moderate physical activity per week or 75 minutes of vigorous exercise per week, should extend to HF prevention. Our findings would suggest the need for a change in the approach to HF prevention; perhaps not only at the guidelines level but as a part of an overall strategy for the prevention of CVD. More importantly, to the extent that exercise would prevent HFPEF, an otherwise untreatable condition, as suggested by Kraigher-Krainer et al in the Framingham Heart Study,\(^{17}\) this potentially represents a tremendous opportunity for HF prevention.

Mechanisms

Many physiological mechanisms by which physical activity may influence HF risk can be suggested, albeit speculative for the most of them. The protective effect of physical activity from HF may be direct or indirect, mediated in part by its effect on precursors including CHD and risk factors.
factors. Indeed physical activity has a favorable effect on blood pressure, lipid profile, insulin sensitivity, body weight, blood coagulation, and fibrinolysis,\textsuperscript{10} and contributes to a decreased risk of type 2 diabetes, and CHD.\textsuperscript{10} Physical activity may reduce CHD by augmenting myocardial oxygen supply, reducing myocardial work and oxygen demand, improving myocardial function, and increasing the electrical stability of the myocardium. The possibility of a direct protective effect of physical activity for HF is suggested by the fact that the association persists even after adjustment for the aforementioned intermediate factors or restriction of analyses to those without prior CHD, as well as by the similar influence of physical activity on types of HF (HFPEF or HFREF),\textsuperscript{17} which suggest a similar associations of physical activity with non-ischemic HF and all-cause HF. Potential direct beneficial effect of physical activity on the heart and thus on incident HF, include those on the cardiac function (increase in cardiac output and peak V\textsubscript{02}, increase or no change in contractility), regional blood flow (increased vasodilatory capacity, improved endothelial function and redistribution of flow), metabolism of skeletal muscle (increased aerobic enzymes, mitochondrial volume and density, and capillary density as well as decreased muscle receptor sensitivity) and autonomic nervous system (decrease in plasma norepinephrine, increased heart rate variability, reduced chemoreceptor and ergoreceptor sensitivity, reduced ventilatory response).\textsuperscript{27}

The studies included in the meta-analysis examined different types/domains of physical activity and categorized the amount of physical activity differently. The effect of the different types of physical activity was not explored in the meta-analysis, given the lack of a sizeable number of studies consistently reporting on the same type/domain of physical activity. However, it is unlikely that the observed association of physical activity and HF varies by type of activity, as indicated in some of the included studies, as well as in the study by Wang et al (not included
in the meta-analysis, who found a significantly reduced HF risk by 13% for occupational physical activity; 7% for commuting physical activity; and 21% for leisure time physical activity. A misclassification bias may have occurred because the classification of physical activity (into low, intermediate, and high physical activity) was study-specific and not based on standard cut-offs. Furthermore, the use of self-reporting may have led to some misclassification of physical activity. Nonetheless, it seems unlikely that this misclassification would have differed by future HF outcome, and it can thus be expected to have biased estimates of associations toward the null.

There is an inherent difficulty in combining data across studies in trying to define a dose-response relation between physical activity and HF, as data on the dose-response effect originates from different self-reported questionnaires assessing physical activity in one or more of domains of activity (leisure-time, household, occupation, and commuting activity). Although self-reported physical activity data are useful and can be valid, self-reports can be imprecise and of limited ability to identify light-intensity physical activity and to assess sedentary behavior comprehensively. Devices that allow for greater accuracy and precision of the assessment of physical activity and sedentary behavior in free-living populations, such as motion sensors (e.g., accelerometers, “fitness trackers”) and physiological monitors (e.g., heart rate monitors) are increasingly been used in large-scale cohort studies, and will likely lead to a better understanding of effect of physical activity on HF and dose-response relationships. The ascertainment of HF was mainly based on hospital discharge records, hence incidence of the outcome may have been under-reported in all of the studies because of asymptomatic or undiagnosed HF. The extent of adjustment for confounders varied across studies; it is therefore possible that the magnitude of HF risk attributable to physical activity was affected by residual confounding by unmeasured or imprecisely measured HF risk factors. However, the direction of
the association was similar across studies. Some of the included studies did not account for previous CHD/MI. Study-level data do not allow to tease out the role of intermediate factors such as CHD in the association of physical activity and HF. This would need clarification in more elaborated studies, including possibly individual-level patient meta-analyses that can allow consistent adjustment for confounders.

With respect to racial/ethnic groups, there are few data on non-Caucasian populations. A homogenous population does not allow probing into the whole scope of the variability in HF risk, especially as some ethnic/minority groups are particularly prone HF and exhibit low levels of physical activity compared to other groups (e.g., African-Americans). However, the available data indicate that the inverse association is most likely consistent across different racial/ethnic groups, but the magnitude may vary. Further investigations incorporating more subjects of different ethnic background are warranted.

Our meta-analysis has limitations. Firstly, we included observational studies; it is possible that the summary estimates were influenced by confounding and other biases. Secondly, heterogeneity was observed in the results of the various studies, suggesting that factors other than those examined in stratified analyses might be at play. Part of the heterogeneity is likely clinical related to the demographic diversity of the examined populations (variable age range, gender and race), as well as the variability in intrinsic levels of physical activity and a differential background incidence of HF across populations. Thirdly, the number and design of the studies included in the meta-analysis limited our ability to conduct sub-analyses to further assess heterogeneity and pathways, such as stratification by race/ethnicity or type of exercise. Moreover, we had no access to individual patient-level data, to address these issues as well as conduct consistent adjustment across studies. Such data would allow a more precise and robust
assessment of the reason for heterogeneity, i.e. conducting a meta-regression analysis accounting for covariates in a consistent manner across studies. Hence, further exploration, through an individual participant-level meta-analysis, is needed to determine whether our findings can be replicated or confirmed. Our systematic review has several strengths, including the novelty of examination of both physical activity and fitness (a marker of recent physical activity), inclusion of both men and women across age groups and from different geographic regions and a large overall sample size, which improved the statistical power to detect small effects.

Conclusion

These data support an association between regular physical activity and lower incidence of HF. These findings points to the importance of accounting for lifestyle factors in the preventive efforts to curb the toll of HF. This research should spur additional efforts to further clarify the relationship between physical activity and HF, especially in racial/ethnic minorities as well as provide more details on the dose-response relation and what combinations and duration and pace may be optimal for reducing HF risk. These results may also be used to further emphasize the importance and benefits of physical activity in CVD as well as HF prevention, especially given that only 46% of adults in the U.S. currently meet the general physical activity recommendations. 29

Disclosures

Dr. Fonarow reports significant consulting for Novartis, and modest consulting for Amgen, Bayer, Gambro, Medtronic, and Janssen; Dr. Fonarow holds the Eliot Corday Chair of
Cardiovascular Medicine at UCLA and is also supported by the Ahmanson Foundation (Los Angeles, California).

References


27. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, Fletcher BJ, Fleg JL, Myers JN, Sullivan MJ. Exercise and heart failure: A statement from the


<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample Size / Effective sample</th>
<th>Ethnicity</th>
<th>Age (years)</th>
<th>Type of physical activity assessed</th>
<th>Assessment of HF</th>
<th>Duration of follow-up (years)</th>
<th>Number of events</th>
<th>Effect estimate- Odds ratio or relative risk (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>He et al, 2001</td>
<td>USA / NHANES I epidemiologic follow-up study.</td>
<td>13 643 / 13 643</td>
<td>Multiethnic (38% of Blacks)</td>
<td>25 - 74</td>
<td>Recreational</td>
<td>Hospital/nursing home discharge ICD-9 codes 428.0 to 428.9 or death certificate with ICD-9 codes 428.0 to 428.9</td>
<td>19</td>
<td>1382</td>
<td>0.77 (0.62 -0.91)</td>
</tr>
<tr>
<td>Kenchaiah et al, 2009</td>
<td>USA / Physicians' Health Study</td>
<td>21 094 / 6290</td>
<td>Mainly Caucasian</td>
<td>40 - 84</td>
<td>Vigorous</td>
<td>HF self-reported by physician.</td>
<td>20.5</td>
<td>1109</td>
<td>0.73 (0.59 -0.90)</td>
</tr>
<tr>
<td>Hu et al, 2010</td>
<td>Finland /</td>
<td>59 178 / 41207 (20097 men, 21110 women)</td>
<td>Mainly Caucasian</td>
<td>25 - 74</td>
<td>Occupational, commuting and leisure-time</td>
<td>ICD codes 427.00 and 427.10 (ICD-8); 428, 4029B, and 4148A-X (ICD-9); and I 50, I11.0, I13.0, and I13.2 (ICD-10)</td>
<td>18.4</td>
<td>1921</td>
<td>0.69 (0.60 -0.80) in men and 0.68 (0.59 -0.78) in women</td>
</tr>
<tr>
<td>Kraigher-Krainer et al, 2013</td>
<td>USA/ Framingham Cohort Study</td>
<td>1142 / 766</td>
<td>Mainly Caucasian</td>
<td>67-97 (65% women)</td>
<td>Work place and leisure time</td>
<td>HF defined by Framingham criteria (presence of two major, or of one major plus two minor criteria). Identification through hospitalization or outpatient visits records, and data gathered at routine biennial follow-up visits or annual telephonic health history updates.</td>
<td>11.5</td>
<td>250 (108 with HFPEF and 106 with HFrEF)</td>
<td>0.65 (0.46 -0.91)</td>
</tr>
<tr>
<td>Patel, et al, 2013</td>
<td>USA / Cardiovascular Health Study (CHS)</td>
<td>5503 / 2959</td>
<td>Multiethnic (15.3% African-Americans)</td>
<td>≥65</td>
<td>Leisure time</td>
<td>Event adjudicated by a two-step process - self-reports of physician-diagnosis then records review</td>
<td>13</td>
<td>1137</td>
<td>0.79 (0.64 -0.97)</td>
</tr>
<tr>
<td>Bell et al, 2013</td>
<td>USA / Atherosclerosis Risk in Communities (ARIC) Cohort</td>
<td>13725 (3,707 Blacks and 626 African Americans) / 8703 (2439 Blacks and 10,018 Whites)</td>
<td>Multiethnic (73% Caucasian and 27% African Americans)</td>
<td>45 to 64</td>
<td>Leisure time</td>
<td>ICD-9 hospital discharge code of 428 (428.0 to 428.9) or 2) or death certificate with an ICD-9 code of 428 or an ICD-10 code of I50</td>
<td>17</td>
<td>1748</td>
<td>0.59 (0.47, 0.74) among AAs and 0.64 (0.54, 0.75) among Caucasians</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of cohort studies of the association between physical activity and risk of heart failure.
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sample Size</th>
<th>Study Population</th>
<th>Outcome Measure</th>
<th>Effect Size</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saeveired et al, 2014&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Denmark / Copenhagen City Heart Study (CCHS)</td>
<td>18,209 (8,422 men and 9,931 women)</td>
<td>Mainly Caucasian 20–80</td>
<td>Leisure time</td>
<td>Hospital discharge ICD8 codes 425.99, 427.09–427.11, 427.19, and 428.99 until 1st January 1994 and ICD10 codes 111.0, 125.5, 142.0, 142.6, 142.9, 150.0-9 from 1994 and onwards</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Andersen et al, 2014&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Sweden / National March Cohort</td>
<td>39,805 (25,301 women and 12,959 men)</td>
<td>Mainly Caucasian 20-95</td>
<td>Total and leisure time</td>
<td>Hospital discharge ICD codes 150.0-9 (or similar ICD-7 [434.1, 434.2], ICD-8 [427.0; 427.1], or ICD-9 [428.A; 428.B; 428.X] codes)</td>
<td>13.3</td>
</tr>
<tr>
<td>Rahman et al, 2014&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Sweden / The Swedish Mammography Cohort</td>
<td>27,895 (13,937 women)</td>
<td>Mainly Caucasian</td>
<td>47.7–83.7 (Total)</td>
<td>Hospital discharge ICD-10 codes I50 (HF) and I11.0 (hypertensive heart disease with HF).</td>
<td>13</td>
</tr>
<tr>
<td>Young et al, 2014&lt;sup&gt;23&lt;/sup&gt;</td>
<td>USA / California Men’s Health Study</td>
<td>82,695 (54,939 men)</td>
<td>Multiethnic (63% non-Hispanic white, 14% Hispanic, 11% Asian, 7% black, and 5% other)</td>
<td>≥45 Cumulative PA per week</td>
<td>ICD-9 diagnosis code of HF (402.X1, 404.X1, 404.X3, and 428.XX) or ≥2 outpatient diagnoses of HF.</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of cohort studies of the association between physical fitness and risk of heart failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Country / Study</th>
<th>Sample Size</th>
<th>Ethnicity</th>
<th>Age (years)</th>
<th>Exposure definition - physical fitness</th>
<th>Outcome definition</th>
<th>Duration of follow-up (years)</th>
<th>Number of events</th>
<th>Effect estimate - hazard ratio or relative risk (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berry et al, 2013&lt;sup&gt;25&lt;/sup&gt;</td>
<td>USA / Cooper Center Longitudinal Study</td>
<td>20 642 (4249 women and 16393)</td>
<td>Mainly Caucasian</td>
<td>≥65</td>
<td>Maximal oxygen uptake (VO2 max) – in METs</td>
<td>HF -hospitalization - ICD-9 codes 428, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, and 404.93.</td>
<td>6.5</td>
<td>1051</td>
<td>0.79 (0.75–0.83) per one unit increase in MET in men and 0.81 (0.68–0.96) in women</td>
</tr>
<tr>
<td>Khan et al, 2014&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Finland / Kuopio Ischemic Heart Disease Risk Factor Study</td>
<td>1873 men</td>
<td>Mainly Caucasian</td>
<td>42-61</td>
<td>Maximal oxygen uptake (VO2 max) in METs</td>
<td>HF -hospitalization - ICD-10 codes (I00–I99, and I50.0–I50.9, I11, I42.0–I42.9)</td>
<td>20.4</td>
<td>152</td>
<td>0.79 (0.67–0.93) for each 1 MET increment</td>
</tr>
</tbody>
</table>

CI: confidence interval, HF: heart failure, ICD: International Classification of Disease, MET: Metabolic equivalent of oxygen consumption.
Figure Legends

Figure 1. Study selection process
Flowchart showing literature search strategy and selection process for inclusion of studies in the systematic review.

Figure 2. Meta-analysis of effect estimates from studies of the association of physical activity with incident heart failure
Forest plot showing the overall estimate of the association of physical activity and heart failure.

Figure 3. Meta-analysis of effect estimates from studies of the association of physical fitness with incident heart failure
Forest plot showing the overall estimate of the association of physical fitness and heart failure.
Figure 1: Study selection process
**Figure 2: Meta-analysis of effect estimates from studies of the association of physical activity with incident heart failure**
<table>
<thead>
<tr>
<th>First author (Year of publication)</th>
<th>Country</th>
<th>Sample size</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berry et al, 2013</td>
<td>USA-Men</td>
<td>16303</td>
<td>0.79</td>
<td>(0.75 - 0.83)</td>
<td>84.2%</td>
</tr>
<tr>
<td>Berry et al, 2013</td>
<td>USA-Women</td>
<td>4339</td>
<td>0.81</td>
<td>(0.68 - 0.96)</td>
<td>7.4%</td>
</tr>
<tr>
<td>Khan et al, 2014</td>
<td>Finland</td>
<td>1873</td>
<td>0.79</td>
<td>(0.67 - 0.93)</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

**Random effects model**

Relative risk & 95% confidence interval

**Heterogeneity:** $I^2$-squared=0%, tau-squared=0, $p=0.9643$

**Figure 3:** Meta-analysis of effect estimates from studies of the association of physical fitness with incident heart failure
Supplementary Material - Figures and Appendix A

Figure Legends
Supplementary Figure 1: Funnel plot
Funnel plot exploring the risk of publication bias of studies of the association of physical fitness and heart failure

Supplementary Figure 2: Sex-stratified meta-analysis of effect estimates from studies of the association of physical activity with incident heart failure
Forest plot showing the overall sex-stratified estimate of the association of physical activity and heart failure

Supplementary Figure 3: Region-stratified meta-analysis of effect estimates from studies of the association of physical activity with incident heart failure
Forest plot showing the overall region-stratified estimate of the association of physical activity and heart failure
Supplementary Figure 1: Funnel plot
Supplementary Figure 2: Sex-stratified meta-analysis of effect estimates from studies of the association of physical activity with incident heart failure

<table>
<thead>
<tr>
<th>First author (Year of publication)</th>
<th>Country</th>
<th>Sample size</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex = Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>He et al, 2001</td>
<td>USA</td>
<td>8098</td>
<td>0.69</td>
<td>(0.62 - 0.77)</td>
<td>21.6%</td>
</tr>
<tr>
<td>Hu et al, 2010</td>
<td>Finland</td>
<td>30336</td>
<td>0.68</td>
<td>(0.46 - 1.01)</td>
<td>3.4%</td>
</tr>
<tr>
<td>Saevereid et al, 2014</td>
<td>Denmark</td>
<td>9931</td>
<td>0.81</td>
<td>(0.64 - 1.03)</td>
<td>8.2%</td>
</tr>
<tr>
<td>Rahman et al, 2014</td>
<td>USA</td>
<td>27895</td>
<td>0.73</td>
<td>(0.65 - 0.82)</td>
<td>20.1%</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
<td></td>
<td>0.72</td>
<td>(0.67 - 0.77)</td>
<td>53.3%</td>
</tr>
<tr>
<td>Heterogeneity: I-squared=0%, tau-squared=0, p=0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Sex = Men                         |         |             |               |        |        |
| He et al, 2001                    | USA     | 5545        | 0.67          | (0.51 - 0.88) | 6.4%  |
| Kenchaich et al, 2009             | USA     | 21094       | 0.73          | (0.59 - 0.90) | 9.5%  |
| Hu et al, 2010                    | Finland | 28842       | 0.69          | (0.60 - 0.79) | 16.6% |
| Saevereid et al, 2014             | Denmark | 8422        | 0.91          | (0.75 - 1.10) | 11.0% |
| Young et al, 2014                 | USA     | 82695       | 0.48          | (0.32 - 0.72) | 3.2%  |
| Random effects                    |         |             | 0.71          | (0.61 - 0.83) | 46.7% |
| Heterogeneity: I-squared=60.3%, tau-squared=0.0185, |         |             |               |        |        |

Random effects
Heterogeneity: I-squared=32.3%, tau-squared=0.004, 0.72 (0.67 - 0.78) 100%
<table>
<thead>
<tr>
<th>First author (Year of publication)</th>
<th>Country</th>
<th>Sample size</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country grouping = non-USA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu et al, 2010</td>
<td>Finland -Women</td>
<td>30336</td>
<td>0.68</td>
<td>(0.59 - 0.78)</td>
<td>10.8</td>
</tr>
<tr>
<td>Hu et al, 2010</td>
<td>Finland - Men</td>
<td>28842</td>
<td>0.69</td>
<td>(0.60 - 0.79)</td>
<td>10.9%</td>
</tr>
<tr>
<td>Saevereid et al, 2014</td>
<td>Denmark</td>
<td>18209</td>
<td>0.91</td>
<td>(0.77 - 1.08)</td>
<td>9.6%</td>
</tr>
<tr>
<td>Andersen et al, 2014</td>
<td>Sweden</td>
<td>39805</td>
<td>0.90</td>
<td>(0.76 - 1.07)</td>
<td>9.5%</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td></td>
<td></td>
<td>0.78</td>
<td>(0.67 - 0.92)</td>
<td>40.8</td>
</tr>
</tbody>
</table>

*Heterogeneity: I-squared=75.8%, tau-squared=0.0192, p=0.0061*

| **Country grouping = USA**        |                        |             |               |              |        |
| He et al, 2001                    | USA                    | 13643       | 0.77          | (0.62 - 0.96)| 7.5%   |
| Kenchaich et al, 2009             | USA                    | 21094       | 0.73          | (0.59 - 0.90)| 7.7%   |
| Kraigher-Krainer et al, 2013      | USA                    | 1142        | 0.65          | (0.46 - 0.92)| 4.2%   |
| Patel et al, 2013                 | USA                    | 5503        | 0.79          | (0.64 - 0.98)| 7.8%   |
| Bell et al.                       | USA - African-Americans| 3707        | 0.59          | (0.47 - 0.74)| 7.2%   |
| Bell et al.                       | USA - Caucasians       | 10018       | 0.64          | (0.54 - 0.76)| 9.5%   |
| Rahman et al, 2014                | USA                    | 27895       | 0.73          | (0.65 - 0.82)| 12.1%  |
| Young et al, 2014                 | USA                    | 82695       | 0.48          | (0.32 - 0.72)| 3.3%   |
| **Random effects model**          |                        |             | 0.69          | (0.64 - 0.75)| 59.2%  |

*Heterogeneity: I-squared=25.5%, tau-squared=0.0037, p=0.2252*

Random effects model

*Heterogeneity: I-squared=56.3%, tau-squared=0.0109, p=0.0087*

Supplementary Figure 3: Region-stratified meta-analysis of effect estimates from studies of the association of physical activity with incident heart failure
## Appendix A: Search terms

<table>
<thead>
<tr>
<th>Database: PubMed (January 1990 until November 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 &quot;physical activity&quot; OR &quot;physical fitness&quot; OR exercise OR walking OR cycling OR “oxygen consumption”</td>
</tr>
<tr>
<td>#2 &quot;heart failure&quot; OR &quot;cardiac insufficiency&quot; OR &quot;cardiac failure&quot;</td>
</tr>
<tr>
<td>#3 “cohort” OR “observational” OR “prospective” OR “trial” OR “epidemiology”</td>
</tr>
<tr>
<td>#4 #1 AND #2 AND #3</td>
</tr>
<tr>
<td>#5 (Animals[MeSH] NOT Humans[MeSH])</td>
</tr>
<tr>
<td>#6 #4 NOT #5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Database: EMBASE (January 1990 until November 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 &quot;physical activity&quot; OR &quot;physical fitness&quot; OR exercise OR walking OR cycling OR “oxygen consumption”</td>
</tr>
<tr>
<td>#2 &quot;heart failure&quot; OR &quot;cardiac insufficiency&quot; OR &quot;cardiac failure&quot;</td>
</tr>
<tr>
<td>#3 “cohort analysis” OR “observational study” OR “prospective study” OR “clinical trial” OR “randomized controlled trial” OR “epidemiology”</td>
</tr>
<tr>
<td>#4 #1 AND #2 AND #3</td>
</tr>
<tr>
<td>#5 #1 AND #2 AND #3 AND ([english]/lim OR [french]/lim) AND [humans]/lim AND [1-1-1990]/sd NOT [30-11-2014]/sd AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)</td>
</tr>
</tbody>
</table>
References


