Original Article

Association of Physical Activity or Fitness With Incident Heart Failure
A Systematic Review and Meta-Analysis

Justin B. Echouffo-Tcheugui, MD, PhD; Javed Butler, MD, MPH; Clyde W. Yancy, MD, MSc; Gregg C. Fonarow, MD

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 mellitus. 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 [CI]) 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. (Circ Heart Fail. 2015;8:853–861. DOI: 10.1161/CIRCHEARTFAILURE.115.002070.)

Key Words: epidemiology ■ exercise ■ heart failure ■ motor activity ■ physical fitness

Heart failure (HF) affects >6 million Americans aged ≥20 years and >23 million people worldwide. If current trends continue in the United States, 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 regard by sex, 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 about exercise as a means of preventing HF. Although an American Heart Association 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. Physical activity is any bodily movement produced by skeletal muscle that results in energy expenditure. Fitness is a set of attributes that I 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 HF (Appendix I in the Data Supplement), restriction to English language papers. Two evaluators (J.B.E. and J.B.) 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 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 (J.B.E. and J.B.) independently abstracted data from eligible studies and conducted quality assessment. Discrepancies were resolved by discussion with a third investigator (G.C.F.) and by referencing the original report. We extracted data on

![Figure 1. Study selection process. Flowchart showing literature search strategy and selection process for inclusion of studies in the systematic review.](http://circheartfailure.ahajournals.org/)
study characteristics, including setting, period, design, participants (sample size, age, and 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 US Preventive Services Task Force as good, fair, or poor.\textsuperscript{13}

Exposure Assessment
All the included physical activity studies divided subjects into 2 or 5 groups on the basis of leisure time,\textsuperscript{14,16} occupational and leisure-time physical activity,\textsuperscript{17,18} vigorous physical activity,\textsuperscript{19} cumulative/total physical activity.\textsuperscript{20,21} For all studies included, the extreme groups (ie, 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 2 studies excluding people with ischemic heart disease at baseline.\textsuperscript{16,19} 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 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).\textsuperscript{22} $P$ values $\leq 25\%$, 50%, and $>25\%$ represent low, moderate, and high inconsistency, respectively.\textsuperscript{22} For physical activity, we conducted stratified analyses by country, sex, 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 (April 13, 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 2 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 82 695 (total: 282 889), with the number of participants with HF ranging from 250 to 3614. Six cohort studies included US populations,\textsuperscript{14,15,17–19,21} 4 studies included European populations from Finland,\textsuperscript{24} Denmark,\textsuperscript{16} and Sweden.\textsuperscript{20,21} The US-based studies included multiethnic populations; but overall the proportion of white individuals in these studies was >50%. Two studies enrolled men only\textsuperscript{19,21} and one only women,\textsuperscript{21} whereas the rest enrolled both the 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 2 cohort studies on the association of fitness and incident HF. The sample size of these studies ranged from 1873 to 20642 (total: 22 515), with many participants with HF of 152 and 1051. One of the studies was US based (including a multiethnic population)\textsuperscript{20} and the other was from Finland.\textsuperscript{26} These studies included participants from both the sexes aged $\geq$45 years, 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, VO$_2$ max (Table 2).\textsuperscript{23,25} The ascertainment of HF was mostly based on hospital or death records, with only 1 study distinguishing type of HF into HF with reduced ejection fraction versus HF with preserved ejection fraction.\textsuperscript{17}

The degree of covariate adjustment varied across studies, with 8 studies accounting for intermediate states such as coronary heart disease (CHD) either through adjustment\textsuperscript{14,18,21,24} or restriction of analyses to those with nonischemic HF\textsuperscript{19,20,21} or exclusion of those with CHD at baseline (either as part of the original study design or a subgroup analysis).\textsuperscript{19,24} 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 the selected studies were graded as fair to good by the criteria developed by the US Preventive Services Task Force.\textsuperscript{13}

Physical Activity and Incident HF
Of the 10 studies selected for the meta-analysis, we used 165 695 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% CI, 0.67–0.79; $P<0.001$; Figure 2). We found there was significant heterogeneity across studies ($P=56.3\%$; $P<0.001$) but no major asymmetrical appearance in the funnel plot (Figure I in the Data Supplement) with a nonsignificant Egger test for publication bias ($P=0.34$).

Among the included studies, 3 studies reported RRs in men and women, 1 in women only, and 2 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 (Figure II in the Data Supplement). In another sensitivity analysis, restricted to US-based studies (n=6) versus non-US based (n=4) showed a pooled RR for HF comparing the most versus...
Type of Physical Activity

Across studies, the influence of physical activity did not seem to be dependent on the type of activity, although 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\textsuperscript{21} found the following risk estimates for various type of physical activity. 0.71 (0.64–0.80) for walking/bicycling ≥20 versus <20 min/d, 0.83 (0.75–0.92) for exercise ≥1 versus <1 hour a week, 0.93 (0.83–1.03) for work occupation active versus mostly sitting, and 0.82 (0.70–0.97) for home/household work ≥1 versus <1 h/d. Two studies specifically looked at the effect of sedentarity, Rahman et al\textsuperscript{21} found no association with a HR of 0.99 (0.83–1.18) for inactivity (watching TV/reading) <3 versus ≥3 h/d. However, in the study by Young et al\textsuperscript{23} controlling for physical activity and other covariates the HR (95% CI) of HF in the highest sedentary time category compared with the lowest was 1.34 (95% CI, 1.13–1.54); medium sedentary time also conveyed risk (HR, 1.13 [95% CI, 1.04–1.24]).

Accounting for previous ischemic disease did not substantially modify the direction and significance of effect estimates of relation of physical activity to incident HF in extant studies\textsuperscript{14,16,18–21,23,24}. Also, the assessment of the effect of physical activity by type of physical activity in 1 study showed a similar association for both HF with preserved ejection fraction (HR, 0.60 [95% CI, 0.37–0.99] for highest levels of physical activity) and HF with reduced ejection fraction (0.69

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 (Figure III in the Data Supplement).

Only 1 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).\textsuperscript{18}
[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×/wk and 14.28 (95% CI, 13.21–15.35) for <5×/wk.3

### Physical Fitness and HF

In the Cooper Center Longitudinal Study, a 1 U greater fitness level in metabolic equivalents was associated with a lower risk of HF (HR, 0.79 [95% CI, 0.75–0.83] in men; and women: HR, 0.81 [95% CI, 0.68–0.96]).23 Similarly, in a Finnish study, the adjusted HR for HF per unit increase in metabolic equivalents was associated with a 21% (HR, 0.79 [95% CI, 0.67 to 0.93]) lower risk of HF.26 The combination of the effect estimates from these 2 studies in a random-effects 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 U 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 US and Northern European cohorts, and across race/ethnicities although 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 disease outcomes may represent an important approach for HF prevention. Indeed, based on these findings, the current guidelines for cardiovascular disease 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 cardiovascular disease. More importantly, to the extent that exercise would prevent HF with preserved ejection fraction, an otherwise untreatable condition, as suggested by Kraigher-Krainer et al.17 in the Framingham Heart Study, 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. Indeed, physical activity has a favorable effect on blood pressure, lipid profile, insulin sensitivity, body weight, blood coagulation, and fibrinolysis,10 and contributes to a decreased risk of type 2 diabetes mellitus, and CHD.10 Physical activity may reduce CHD by augmenting myocardial oxygen supply, reducing myocardial work and oxygen demand, improving myocardial function, and increasing the electric 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 previous CHD, as well as by the similar influence of physical activity on types of HF (HF with preserved ejection fraction or HF with reduced ejection fraction),17 which suggest a similar associations of physical activity with nonischemic 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 VO₂, 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, and reduced ventilatory response).27

Table 2. Characteristics of Cohort Studies of the Association Between Physical Fitness and Risk of HF

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample Size</th>
<th>Ethnicity</th>
<th>Age, y</th>
<th>Exposure Definition—Physical Fitness</th>
<th>Outcome Definition</th>
<th>Duration of Follow-Up, y</th>
<th>No. of events</th>
<th>Effect Estimate—Hazard Ratio or Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berry et al.25</td>
<td>USA/Cooper Center</td>
<td>20,642 (4249 women and 16,393)</td>
<td>Mainly white ≥65</td>
<td></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 1 unit increase in MET in men and 0.81 (0.68–0.96) in women</td>
</tr>
<tr>
<td>Khan et al.26</td>
<td>Finland/Kuopio</td>
<td>1873 men</td>
<td>Mainly white 42–61</td>
<td></td>
<td>Maximal oxygen uptake (VO₂ max) in METs</td>
<td>HF hospitalization—ICD-10 codes (I00–I99, and I50.0–I50.9, I11, 420.0–424.9)</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 indicates confidence interval; HF, heart failure; ICD, International Classification of Disease; and MET, metabolic equivalent of oxygen consumption.

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. CI indicates confidence interval.
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 al28 (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 ≥1 of domains of activity (leisure time, household, occupation, and commuting activity).15,16,20,21 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 (eg, accelerometers and fitness trackers) and physiological monitors (eg, heart rate monitors) are increasingly 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 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/myocardial infarction. 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-white 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 with other groups (eg, blacks). 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. First, we included observational studies; it is possible that the summary estimates were influenced by confounding and other biases. Second, 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 probably clinical related to the demographic diversity of the examined populations (variable age range, sex, and race), as well as the variability in intrinsic levels of physical activity and a differential background incidence of HF across populations. Finally, the number and design of the studies included in the meta-analysis limited our ability to conduct subanalyses 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, that is, 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.

Conclusions

These data support an association between regular physical activity and lower incidence of HF. These findings point 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 cardiovascular disease as well as HF prevention, especially given that only 46% of adults in the United States currently meet the general physical activity recommendations.29

Disclosures

Dr Fonarow reports significant consulting for Novartis, and moderates for the American Heart Association. The University of California, Los Angeles and is also supported by the Ahmanson Foundation (Los Angeles, CA).

References


Accruing evidence has been suggesting that increasing levels of physical activity is inversely associated with incident heart failure; however, available data on this association may be limited and potentially inconsistent. To investigate whether regular physical activity is associated with a lower risk of heart failure, we systematically analyzed published data until November 2014 identifying 10 cohort studies, including 282,889 participants followed for 7 to 30 years. The analysis demonstrated that regular physical activity was associated with at least a 25% reduction in heart failure incidence, irrespective of a history of previous coronary heart disease. The associated benefit was observed in both women and men. These findings suggest that exercise recommendations of 30 minutes or more of daily moderate-intensity activity as indicated in multiple US guidelines can be extended to the primary and secondary prevention of heart failure, over and beyond the prevention of coronary heart disease.
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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>
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<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>
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<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>
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<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>
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<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>
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<td><strong>Sex = Men</strong></td>
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<td>He et al, 2001</td>
<td>USA</td>
<td>5545</td>
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<td>(0.51 - 0.88)</td>
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<td>21094</td>
<td>0.73</td>
<td>(0.59 - 0.90)</td>
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<td>Hu et al, 2010</td>
<td>Finland</td>
<td>28842</td>
<td>0.69</td>
<td>(0.60 - 0.79)</td>
<td>16.6%</td>
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<tr>
<td>Saevereid et al, 2014</td>
<td>Denmark</td>
<td>8422</td>
<td>0.91</td>
<td>(0.75 - 1.10)</td>
<td>11.0%</td>
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<td>Young et al, 2014</td>
<td>USA</td>
<td>82695</td>
<td>0.48</td>
<td>(0.32 - 0.72)</td>
<td>3.2%</td>
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<tr>
<td><strong>Random effects</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
<td>(0.67 - 0.78)</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Heterogeneity: I-squared=0%, tau-squared=0, p=0.64**

**Heterogeneity: I-squared=60.3%, tau-squared=0.0185,**

**Random effects**

**Heterogeneity: I-squared=32.3%, tau-squared=0.004,**

Relative risk & 95% confidence interval
**Supplementary Figure 3: Region-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>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></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Heterogeneity: I-squared=75.8%, tau-squared=0.0192, p=0.0061</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 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   |
| **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**

Relative risk & 95% confidence interval

Relative risk 0.72 (0.67 - 0.79) 100%

---

**First author (Year of publication)**

**Country**

**Sample size**

**Relative risk**

**95% CI**

**Weight**
## Appendix A: Search terms

### Database: PubMed (January 1990 until November 2014)

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

### Database: EMBASE (January 1990 until November 2014)

<table>
<thead>
<tr>
<th>#1</th>
<th>&quot;physical activity&quot; OR &quot;physical fitness&quot; OR exercise OR walking OR cycling OR “oxygen consumption”</th>
</tr>
</thead>
<tbody>
<tr>
<td>#2</td>
<td>&quot;heart failure&quot; OR &quot;cardiac insufficiency&quot; OR &quot;cardiac failure&quot;</td>
</tr>
<tr>
<td>#3</td>
<td>&quot;cohort analysis&quot; OR &quot;observational study&quot; OR “prospective study” OR “clinical trial” OR “randomized controlled trial” OR “epidemiology”</td>
</tr>
<tr>
<td>#4</td>
<td>#1 AND #2 AND #3</td>
</tr>
<tr>
<td>#5</td>
<td>#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


