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

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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 with random-effects models. Generalized least-squares regression models were used to assess the quantitative relationship between PA (metabolic equivalent [MET]–min/wk) 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 for highest versus lowest PA, 0.70; 95% confidence interval, 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/wk; 2008 US federal guidelines) had modest reductions in HF risk (pooled hazard ratio, 0.90; 95% confidence interval, 0.87–0.92). In contrast, a substantial risk reduction was observed among individuals who engaged in PA at twice (hazard ratio for 1000 MET-min/wk, 0.81; 95% confidence interval, 0.77–0.86) and 4 times (hazard ratio for 2000 MET-min/wk, 0.65; 95% confidence interval, 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. **(*Circulation*. 2015;132:1786-1794. DOI: 10.1161/CIRCULATIONAHA.115.015853.)**

Key Words: exercise ■ heart failure ■ meta-analysis ■ prevention and control

Heart failure (HF) affects >5.1 million adults in the United States, accounts for a significant proportion of hospitalizations and deaths among older Americans, and consumes >$30 billion per year in healthcare costs.[1,2] The prevalence of HF is expected to increase by 25% from 2010 to 2030.[3] As a result, novel preventive approaches focused on modifying risk factors for HF are urgently needed to combat this growing epidemic.

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Physical inactivity and low fitness have been identified as significant contributing factors for cardiovascular diseases.[4–10] Over the past 3 decades, the inverse dose–response relationship between physical activity (PA) and risk coronary heart disease (CHD) has been well established.[8,9,11–13] Thus, physical inactivity is considered a major modifiable risk factor for CHD,[14] and current American Heart Association guidelines recommend at least 150 min/wk of moderate-intensity aerobic PA to reduce the burden of CHD risk factors and the risk of CHD.[15–17]

In contrast, the role of PA in reducing risk of HF has not been emphasized in existing guidelines and public health recommendations.[15] Although observational cohort studies have reported an inverse association between higher levels of PA and HF risk,[18–32] a comprehensive assessment of the quantitative dose–response association between PA and HF risk has not been previously reported. Understanding this relationship is important because recent studies suggest that there may be important differences in the mechanisms

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through which PA modifies HF risk and CHD risk,[20] and the dose of PA needed to significantly lower HF risk may differ from that currently recommended to reduce CHD risk.[25] Previous studies have used a 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.[33–35] In the present study, we have used a similar approach and performed a dose–response meta-analysis 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 an inverse dose-dependent 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 the Cochrane database) and performed additional manual searches through the reference lists 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, and cardiac failure risk (full search terms available on request). The search was restricted to articles that focused on human participants and were published between January 1, 1995, and September 24, 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 or the larger sample size. Two independent investigators (A.P., M.K.) conducted the initial screening of all titles or abstracts and then evaluated all potentially relevant articles on the basis of full-text reviews. Studies were excluded if they failed to meet all the criteria detailed above. All discrepancies in study inclusions were adjudicated by the senior author (J.D.B.). The study quality was assessed with the Newcastle-Ottawa quality assessment scale, which allowed a total score of up to 9 points (9 representing the highest quality) summarizing 8 aspects of each study.[38]

Data Collection

Two authors (A.P., M.K.) 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 mellitus, smoking, and 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 (HR)/relative risk of HF and confidence intervals (CIs); and variables entered into the multivariable model as potential confounders. Information on quantitative dose of PA 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 HR or relative risk (as available) and 95% CIs as a measure of the effect size associated with each category of PA for all studies. In articles that studied >1 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 independently of other cardiovascular and noncardiovascular 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 the presence of risk factors such as hypertension, diabetes mellitus, and body mass index for primary analysis. One study[19] reported separate HRs for HF risk associated with different PA levels for blacks and whites. As a result, we included data from both the black and white cohorts 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 4 categories of PA: lowest, light, moderate, and highest. For each study that was included, the lowest and highest PA categories corresponded to the lowest and highest groups, respectively. For studies with at least 3 exposure categories, the second- and third-highest PA categories corresponded to the moderate and light groups, respectively. The pooled HRs and 95% CIs 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 by use of 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 and lowest PA levels included all available studies (n=12), whereas comparisons of moderate (second-highest PA category) and light (third-highest PA category) PA with the lowest PA category included studies that stratified participants into at least 3 (n=10) and 4 (n=4) PA categories, respectively. We assessed for heterogeneity using the I^2 test (I^2> 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 the robustness of the observed associations. Publication bias was assessed with contour-enhanced funnel plots, the Egger linear regression test, and the Begg rank correlation test at the P<0.10 level of significance. All P values were 2 tailed. For all tests, a value of P<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 were not included in the quantitative analysis.[24,32] Three studies reported the range of leisure-time PA dose for each category in metabolic equivalent (MET)–minutes per week or metabolic equivalent–hours per week. The other 5 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-minutes per week (Methods in the online-only Data Supplement). We assigned the median dose of PA for each category to the corresponding HR 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 PA level category, we assumed that the difference from the lowest range of this category to its median was equivalent to the difference from the lowest range of the closest adjacent category to its median (Table I in the online-only Data Supplement). Continuous dose–response relationships between PA (MET-min/wk) and HF risk were assessed with a generalized least-squares regression model using SAS version 9.2 (SAS Institute, Inc, Cary, NC). 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.[33–35] 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. Nonlinear relationship between PA and HF risk was assessed by modeling PA dose with the use of restricted cubic splines with 3 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 HRs. We then combined the study specific estimates using the restricted maximum likelihood method in a multivariate random-effects meta-analysis. We used the PA–versus–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/wk) and 2 times (1000 MET-min/wk) and 4 times (2000 MET-min/wk) 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 12 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 2 included participants of randomized, controlled trials (Cholesterol and Recurrent Events [CARE] Study and Physician Health Study). Two studies included only men; 2 studies included only women; and 8 studies included both men and women. Eight studies were conducted in United States, and 4 studies were conducted in Europe. European study cohorts had a lower burden of comorbidities such as diabetes mellitus and hypertension compared with the 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 PA levels (n=8), pooled prevalence of cardiovascular risk factors such as hypertension, diabetes mellitus, and smoking was greater in the lowest PA category compared with the 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 (*International Classification of Diseases* 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 with 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, 0.70; 95% CI, 0.67–0.73; I^2=36.4%; Figure I in the online-only Data Supplement). Moderate (131 014 participants across 10 studies) and light (20 564 participants across 4 studies) PA category participants also had a 22% and 15% lower risk of HF compared with the lowest PA group (moderate PA: pooled HR, 0.78; 95% CI, 0.75–0.82; I^2=20.3%; Figure II in the online-only Data Supplement; light PA: pooled HR, 0.85; 95% CI, 0.79–0.92; I^2=3.4%; Figure III in the online-only Data Supplement). In subgroup analyses, the association between the highest levels of PA (versus lowest PA levels) and HF risk was similar across different age (<55

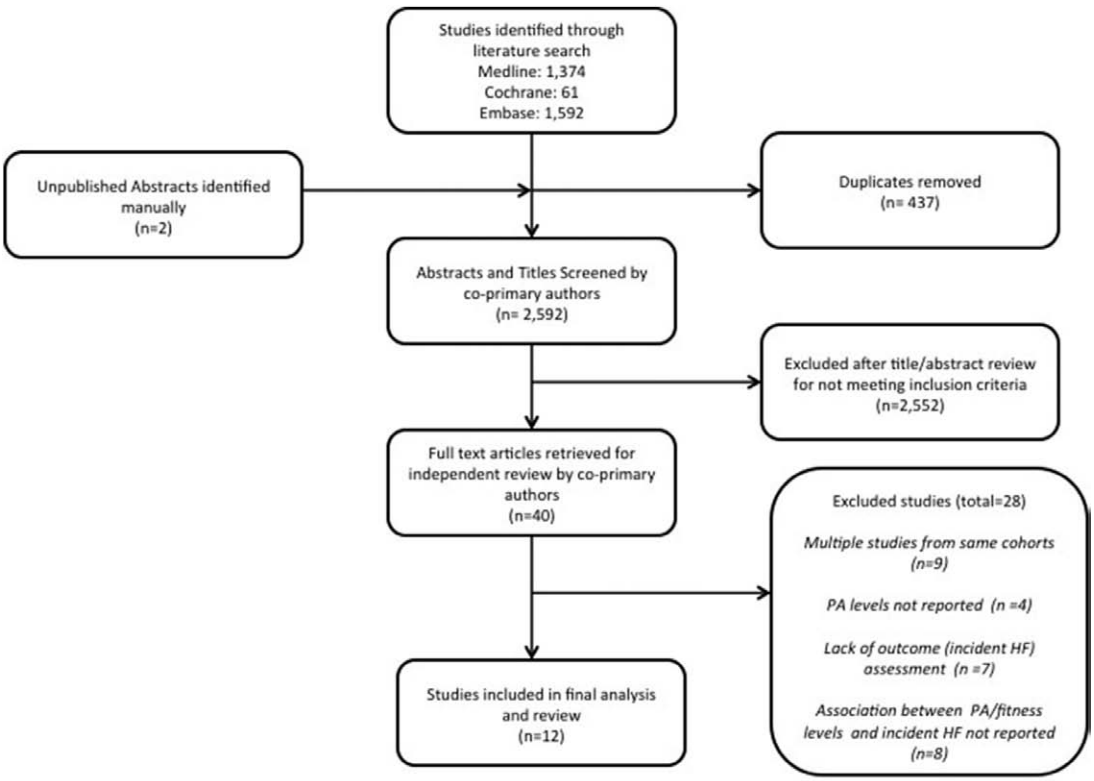

Figure 1. Flowchart of study selection for the meta-analysis. HF indicates heart failure; and PA, physical activity.

Table 1. Baseline Characteristics of the Studies Included in the Meta-Analysis

Study	Country	Study Name	Participants, n	Mean Age, y	Women, %	With HTN/DM/CHD, %	Follow-Up, y	HF Events Observed, n
He et al,[22] 2001	US	NHANES	13 643	50	59	28/4/5	19	1382
Lewis et al,[30] 2003	US	CARE study	3860	58	14	42/13/100	5	243
Kenchaiah et al,[23] 2009	US	Physician Health Study	21 094	53	0	24/3/0	20	1109
Wang et al,[27] 2010	Finland	Finnish database	58 208	44	51	11/2/2	18	3508
Bell et al,[19] 2013	US	ARIC Study	13 725	54	56	32/10/0	17	1748
Kraigher-Krainer et al,[24] 2013	US	Framingham Heart Study	1142	76	65	76/11/0	11.5	250
Patel et al,[25] 2013	US	Cardiovascular Health Study	5503	73	58	58/16/17	13	1137
Young et al,[28] 2014	US	CMHS	82 695	58	0	43/2/13	8	3473
Saevereid et al,[26] 2014	Sweden	Copenhagen City Heart Study	18 353	50	54	6/2/0	30	1580
Agha et al,[31] 2014	US	Women's Health Initiative Study	84 537	64	100	33/4/5	11	1826
Andersen et al,[18] 2014	Sweden	National March Cohort	39 805	53	65	13/3/1.5	13	1545
Rahman et al,[32] 2014	Sweden	Swedish Mammography Cohort	27 895	61	100	20/3/0	13	2402

ARIC indicates Atherosclerosis Risk in Communities Study; CHD, coronary heart disease; CMHS, California Men's Health Study; DM, diabetes mellitus; HF, heart failure; HTN, Hypertension; and NHANES, National Health and Nutrition Examination Survey.

versus ≥55 years, $P_{interaction}$=0.64), sex (men versus women, $P_{interaction}$=0.51), and geographical (Europe versus United States, $P_{interaction}$=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- min/wk) and HF risk. The pooled results showed a consistent, inverse dose–response association between PA and risk of HF. Participants who met the minimum guideline-recommended PA levels (≈500 MET-min/wk) had a 10% lower risk of HF compared with those with no PA (HR, 0.90; 95% CI, 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-min/wk) and 4 times (≈2000 MET-min/wk) the basic guideline-recommended levels had 19% (HR, 0.81; 95% CI, 0.77–0.86) and 35% (HR, 0.65; 95% CI, 0.58–0.73) 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 (Table II in the online-only Data Supplement). We did not observe a significant publication bias in the present meta-analysis (for the Egger linear regression test, P=0.75; for the Begg rank correlation test, P=0.54; Figure IV in the online-only Data Supplement).

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 a history of myocardial infarction or prevalent coronary artery disease among participants at baseline (n=5), and studies with low (<10%; n=8) and high (>10%; n=4) incidence of HF on follow-up. We also conducted additional sensitivity analyses excluding studies with significantly different study populations (Lewis et al[30] with post–myocardial infarction population) or effect sizes compared with other studies (the black cohort in the Bell et al[19] study). 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 (Table III in the online-only Data Supplement). To determine the impact of multivariable adjustment, we also conducted a sensitivity analysis pooling HRs from multivariable-adjusted models without adjustment for cardiovascular risk factors such as hypertension, diabetes mellitus, CHD, and body mass index (n=11 studies) and observed that the magnitude of the pooled estimate (pooled HR, 0.66; 95% CI, 0.61–0.71; Table III in the online-only Data Supplement) did not change significantly compared with primary pooled analysis including the most adjusted models (pooled HR, 0.70; 95% CI, 0.67–0.73). Similar findings were also observed in sensitivity analyses excluding studies that did not adjust for socioeconomic factors such as income and education (pooled HR, 0.73; 95% CI, 0.68–0.79; Table III in the online-only Data Supplement).

Discussion

To the best of 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 2 important findings in this study. First, there is a linear, dose-dependent, inverse association between PA and HF risk. This relationship, observed with both

Table 2. Exposure and Outcomes Assessments in the Included Studies

Study	Categories of PA	Outcome Assessment	Results HR (95% CI) (Reference Group, Lowest PA)	Adjusted Covariates
Kenchaiah et al,[23] 2009	>30 min moderate to vigorous PA Cat 1: 5–7 times/wk Cat 2: 1–4 times/wk Cat 3: 1–3 times/mo Cat 4: Inactive	Self-reported HF	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	Age; smoking; alcohol; family Hx of MI; treatment group; cardiovascular comorbidities; BMI
Wang et al,[27] 2010	Cat 1: >3 h/wk VIPA Cat 2: >4 h/wk MIPA Cat 3: Inactive	*ICD-9* codes for HF admission	Cat 1: 0.69 (0.60–0.79) Cat 2: 0.83 (0.77–0.89) Cat 3: Ref	Age; sex; year; education; smoking; alcohol use; CVD risk factors; CAD; lung disease; anti-HTN medication use; BP; total cholesterol; BMI
Bell et al,[19] 2013	Cat 1: >150 min/wk MIPA Cat 2: 1–149 min/wk of MIPA or 1-44 min/wk of VIPA Cat 3: Inactive	*ICD-9* codes for HF admission	Cat 1: Black: 0.59 (0.47–0.74) White: 0.64 (0.54 – 0.75) Cat 2: Black: 0.62 (0.51–0.75) White: 0.76 (0.65 – 0.88) Cat 3: Ref	Age; sex; smoking; alcohol; diet; education; hormone therapy
Patel et al,[25] 2013	Cat 1: High PA (>1000 MET-min/wk) Cat 2: medium PA (500–999 MET-min/wk) Cat 3: low PA (1–499 MET-min/wk) Cat 4: Inactive	Adjudication based on chart review	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	Age; sex; race; SE factors; alcohol; smoking; BMI; CV risk factors; BP; Cr, CRP, cholesterol, albumin; MMSE score; depression
Young et al,[28] 2014	Cat 1: high (>1585 MET-min/wk) Cat 2:medium (471–1584 MET-min/wk) Cat 3: Low (<470 MET-min/wk)	*ICD-9* codes for HF admission	Cat 1: Ref Cat 2: 1.15 (1.04–1.26) Cat 3: 1.52 (1.38–1.67)	Age; race; SE factors; BMI; smoking; Hx of HTN, DM, CAD, anti-HTN medication use; levels of HDL, glucose; diet; alcohol
Saevereid et al,[26] 2014	Cat 1: moderate to high Cat 2: light Cat 3: sedentary	*ICD-8* and *ICD-10* codes for HF admission	Cat 1: 0.88 (0.75–1.03) Cat 2: 0.80 (0.69–0.92) Cat 3: Ref	Age; sex; alcohol; education; income; family history of CVD
Andersen et al,[18] 2014	Quintiles of PA Cat 1: highest quintile Cat 2: fourth quintile Cat 3: third quintile Cat 4: second quintile Cat 5: lowest quintile	*ICD-9* and *ICD-10* codes for HF admission	Cat 1: 0.65 (0.53–0.81) Cat 2: 0.73 (0.60–0.89) Cat 3: 0.79 (0.67–0.94) Cat 4: 0.93 (0.79–1.09) Cat 5: Ref	Age; sex; BMI; alcohol and tobacco use; cardiovascular comorbidities
Agha et al,[31] 2014	Cat 1: >150 min/wk MIPA Cat 2: 1–149 min/wk MIPA Cat 3: Inactive	Self-reported HF with clinical adjudication from medical records	Cat 1: 0.69 (0.61–0.79) Cat 2: 0.77 (0.67 -0.87) Cat 3: Ref	Age; race; education; Hx of HTN, DM, CAD; US region
He et al,[22] 2001	Recreational PA Cat 1: High PA Cat 2: Medium or low PA	*ICD-9* codes for HF admission	Cat 1: Ref Cat 2: 1.23 (1.09–1.38)	Age; sex; race; education; income; BMI; smoking; Hx of HTN, DM, CAD, valvular heart disease; alcohol use
Lewis et al,[30] 2003	Recreational PA Cat 1: >3 times/wk MIPA Cat 2: <3 times/wk MIPA	Event adjudication based on patient chart review	Cat 1: 0.67 (0.52–0.86) Cat 2: Ref	Multivariable adjusted, otherwise unspecified in the primary analysis
Kraigher-Krainer et al,[24] 2013	Recreational PA index tertiles Cat 1: high (tertile 3) Cat 2: medium (tertile 2) Cat 3: low (tertile 1)	Patient chart review or telephone-based health history update	Cat 1: 0.65 (0.46–0.91) Cat 2: 0.84 (0.60–1.17) Cat 3: Ref	Age; sex; systolic BP; HTN: DM; valve disease; alcohol use; LVH; BMI
Rahman et al,[32] 2014	Total PA Cat 1: highest quartile Cat 2: third quartile Cat 3: second quartile Cat 4: lowest quartile	*ICD-9* codes for HF admission	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	Age; education; alcohol; smoking; family Hx of MI, HTN, DM, stroke; BMI; waist circumference

BMI indicates body mass index; CAD, coronary artery disease; Cat, category; Cr, creatinine; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoproteins; HF, heart failure; HTN, hypertension; Hx, history; *ICD-8*, *International Classification of Diseases, Eighth Revision*; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, 10th Revision*; LVH, left ventricular hypertrophy; MI, myocardial infarction; MIPA, moderate-intensity physical activity; MMSE, Mini Mental Status Examination; PA, physical activity; Ref, referent; SBP, systolic blood pressure; and VIPA, vigorous-intensity physical activity.

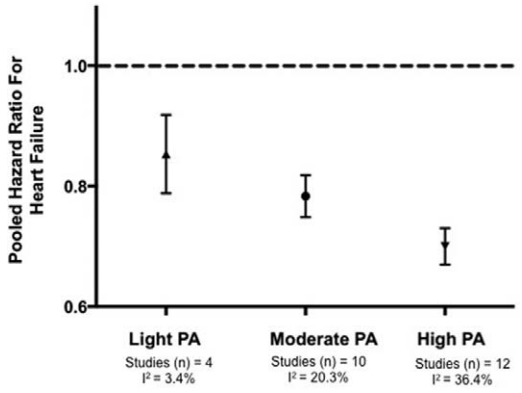

Figure 2. Pooled estimates of the relative risk of incident heart failure associated with different categories of physical activity (PA). The high PA group represents participants in each study with the highest dose of PA; the moderate and light PA groups represent participants with progressively lower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

categorical and continuous quantitative estimates of PA levels, 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 the risk of HF significantly.

The dose–response association between PA and atherosclerotic cardiovascular disease has previously been reported.[16,40] Sattelmair et al[16] observed an inverse dose–response association between PA and CHD risk with a significant reductions in CHD risk with levels of PA at par with or even lower than the current guideline-recommended minimum dose of PA (500 MET-min/wk). 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 Sattelmair et al. The reduction in HF risk observed at lower levels of PA were modest compared with that reported for CHD. For example, Sattelmair et al reported up to a 15% reduction in CAD risk at PA levels of 250 and 500 MET-min/wk. In contrast, we observed only a 5% and 10% reduction in HF risk at PA levels of 250 and 500 MET-min/wk, 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/wk). However, although Sattelmair et al observed a plateau in the risk reduction for CAD at doses >1000 MET-min/wk, we observed a linear dose response for HF risk with a marked reduction in risk at very high doses of PA (≈35% risk reduction at 2000 MET-min/wk). These findings suggest that although 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 versus 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 compared with myocardial infarction risk among healthy individuals.[20] PA lowers risk of CHD predominantly through favorable changes in the risk factor profile such as lowering of blood pressure, low-density lipoprotein, and non–high-density lipoprotein 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.[44–48] Noncardiac mechanisms may also contribute to the observed inverse dose-dependent association between PA and HF risk. HF is a systemic syndrome, and previous studies have identified subclinical dysfunction in multiple noncardiac organ systems, including lungs, skeletal muscle, the neuroendocrine system, and the peripheral vasculature, as a significant risk factor for HF.[48] Higher levels of PA are associated with a lower antecedent burden of these noncardiac risk factors, which may reduce future HF risk.[47,49–51]

Age-related decline in left ventricular compliance and diastolic function has been implicated in the development of HF, particularly HF with preserved ejection fraction.[52–55] In a recent study, Bhella et al[56] observed that high levels of lifetime exercise (ie, 4–5 times per week) were associated with more favorable left ventricular compliance. In contrast, there

Table 3. Association Between PA and HF Risk Among Different Subgroups

Study Groups	Studies, n	Pooled HR (95% CI), Highest Versus Lowest PA	I^2, %	*P* for Heterogeneity
Combined	12	0.70 (0.67–0.73)	36	0.10
Men	4	0.75 (0.63–0.87)	74	0.01
Women	5	0.73 (0.68–0.78)	0	0.80
Mean age <55 y	6	0.71 (0.64–0.79)	60	0.02
Mean age ≥55 y	6	0.69 (0.65–0.73)	0	0.68
US cohort	8	0.69 (0.65–0.73)	28	0.19
European cohort	4	0.73 (0.65–0.81)	53	0.10

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; and PA, physical activity.

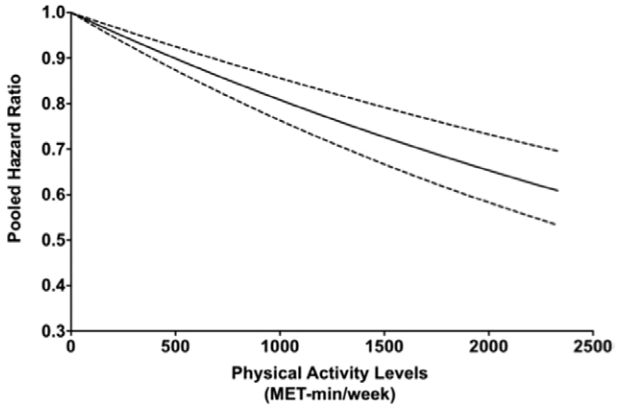

Figure 3. Dose–response association between physical activity and heart failure risk. The graph here shows spline (smoothed fit) and 95% confidence interval of pooled relative risk of heart failure by metabolic equivalent (MET)–min/wk.

were no differences in left ventricular compliance between sedentary individuals and casual exercisers (ie, 1–2 times per week).[56] Thus, doses of PA in excess of current guideline recommendations may be required to achieve favorable changes in cardiac structure and function and to lower HF risk.

We observed a 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 cardiovascular disease risk factors such as blood pressure, fitness, and metabolic syndrome.[57] In contrast, Sattelmair et al[16] 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 2 studies remain unclear but could also reflect differences in the physiological mechanisms through which PA modifies the risk of HF versus 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.[58] 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 level and the population level.

There are several strengths of 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 to 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 because it was assessed in most studies by the use of questionnaires or self-reported frequency of light/moderate/vigorous PA. However, measurement error tends to bias toward the null; 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 (eg, leisure-time PA versus occupational PA) with HF risk, given the amount of detail on the subtypes of PA reported from prior studies.[26,27] Fourth, differential adjustment for confounders across different studies could potentially influence our study findings. However, this was not observed in pooled analyses using HR associated with models with versus 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 studies) represent >80% of the overall pooled study population.

Conclusions

We observe an inverse dose-dependent association between PA and risk of HF. Furthermore, our study findings suggest that doses of PA in excess of current guideline-recommended minimum levels (500 MET-min/wk) 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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Disclosures

None.

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CLINICAL PERSPECTIVE

Physical inactivity is considered a major, modifiable risk factor for coronary heart disease, and guideline-recommend doses of physical activity (500 metabolic equivalent [MET]–min/wk) have been shown to significantly reduce the risk for coronary heart disease. However, the role of physical activity in reducing the risk for heart failure has not been emphasized in the existing guidelines, and the dose of physical activity needed to significantly lower heart failure risk is not known. The present study highlights the dose of physical activity required for heart failure prevention, providing quantitative measures of the magnitude of the risk reduction associated with different levels of physical activity. We observed that guideline-recommended minimum physical activity levels (500 MET-min/wk) were associated with only a modest reduction in heart failure risk (≈10%). Significant reductions in heart failure risk were observed at higher levels of physical activity; for example, individuals who engaged in physical activity at twice (1000 MET-min/wk) and 4 times (2000 MET-min/wk) the minimum guideline-recommended levels had a 19% and 35% reduction in heart failure risk. These findings suggest that doses of physical activity in excess of guideline-recommended minimum levels may be required to significantly reduce the risk of heart failure.