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CLINICAL RESEARCH

Physical Activity and Incidence of Heart Failure in Postmenopausal Women



Michael J. LaMonte, PhD, MPH,^a JoAnn E. Manson, MD, DrPH,^b Andrea K. Chomistek, ScD,^c Joseph C. Larson, MS,^d Cora E. Lewis, MD, MSPH,^e Jennifer W. Bea, PhD,^f Karen C. Johnson, MD, MPH,^g Wenjun Li, PhD,^h Liviu Klein, MD,ⁱ Andrea Z. LaCroix, PhD,^j Marcia L. Stefanick, PhD,^{k,l} Jean Wactawski-Wende, PhD,^a Charles B. Eaton, MD, MS^{m,n}

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CME/MOC/ECME Objectives for This Article: Upon completion of this activity, the learner should be able to: 1) discuss the amount and intensity of physical activity associated with reduced risk of heart failure in postmenopausal women; 2) identify potential biologic mechanisms for the association of physical activity with reduced risk of heart failure; and 3) discuss the phenomenon of reverse causation bias in observational epidemiologic studies and identify potential strategies for mitigating such bias.

CME/MOC/ECME Editor Disclosure: Editor-in-Chief Christopher M. O'Connor, MD, has received consultant fees/honoraria from AbbVie, Inc., Actelion Pharmaceuticals Ltd., Bayer, Bristol-Myers Squibb, Cardiorientis, Merck & Co., Inc., ResMed, and Roche Diagnostics; and has ownership interest in Biscardia, LLC. Executive Editor Mona Fiazat, PharmD, has received research support from ResMed, Gilead, Critical Diagnostics, Otsuka, and Roche Diagnostics. Tariq Ahmad, MD, MPH, has received a travel scholarship from Thoratec. Abhinav Sharma, MD, has received support from Bayer-Canadian Cardiovascular Society, Alberta Innovates Health Solution, Roche Diagnostics, and Takeda. Mitchell Psotka, MD, PhD, and Kishan Parikh, MD, have no relationships relevant to the contents of this paper to disclose.

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Physical Activity and Incidence of Heart Failure in Postmenopausal Women

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ABSTRACT

OBJECTIVES This study prospectively examined physical activity levels and the incidence of heart failure (HF) in 137,303 women, ages 50 to 79 years, and examined a subset of 35,272 women who, it was determined, had HF with preserved ejection fraction (HFpEF) and HF with reduced EF (HFrEF).

BACKGROUND The role of physical activity in HF risk among older women is unclear, particularly for incidence of HFpEF or HFrEF.

METHODS Women were free of HF and reported ability to walk at least 1 block without assistance at baseline. Recreational physical activity was self-reported. The study documented 2,523 cases of total HF, and 451 and 734 cases of HFrEF and HFpEF, respectively, during a mean 14-year follow-up.

RESULTS After controlling for age, race, education, income, smoking, alcohol, hormone therapy, and hysterectomy status, compared with women who reported no physical activity (reference group), inverse associations were observed across incremental tertiles of total physical activity for overall HF (hazard ratio [HR]: Tertile 1 = 0.89, Tertile 2 = 0.74, Tertile 3 = 0.65; trend $p < 0.001$), HFpEF (HR: 0.93, 0.70, 0.68; $p < 0.001$), and HFrEF (HR: 0.81, 0.59, 0.68; $p = 0.01$). Additional controlling for potential mediating factors included attenuated time-varying coronary heart disease (CHD) (nonfatal myocardial infarction, coronary revascularization) diagnosis but did not eliminate the inverse associations. Walking, the most common form of physical activity in older women, was also inversely associated with HF risks (overall: 1.00, 0.98, 0.93, 0.72; $p < 0.001$; HFpEF: 1.00, 0.98, 0.87, 0.67; $p < 0.001$; HFrEF: 1.00, 0.75, 0.78, 0.67; $p = 0.01$). Associations between total physical activity and HF were consistent across subgroups, defined by age, body mass index, diabetes, hypertension, physical function, and CHD diagnosis. Analysis of physical activity as a time-varying exposure yielded findings comparable to those of baseline physical activity.

CONCLUSIONS Higher levels of recreational physical activity, including walking, are associated with significantly reduced HF risk in community-dwelling older women. (J Am Coll Cardiol HF 2018;6:983-95)
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Two expert reviews of published scientific data indicated that the evidence on physical activity and primary prevention of cardiovascular disease is clearest and strongest for coronary heart disease (CHD) and ischemic stroke outcomes (1,2). Limited available data at the time of each review (1996 and 2008) precluded a consensus statement pertaining to heart failure (HF). Findings from recent

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prospective cohort studies suggested that physical activity might be inversely associated with HF incidence (3-12). Few studies have focused on older women (3,6,8,9), racial/ethnic subgroups (3,5,6), or associations with HF with preserved ejection fraction (HFpEF) and HF with reduced EF (HFrEF) (8). HF disproportionately affects older adults, with approximately 80% of cases occurring in individuals age 65 years and older, in whom HF is the leading cause of hospitalization (13). The U.S. adult population aged 65 years and older will double by 2050, with women outnumbering men (14). In epidemiological cohorts, 40% to 70% of incident HF occurs as HFpEF, which is also more common in women (13,15). Although sizable proportions of HF risk are attributed to history of hypertension and ischemic coronary disease (15-17), understanding how modifiable factors such as physical activity contribute to HF incidence could improve prevention strategies, especially in older women, who are understudied.

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We comprehensively evaluated the prospective association between recreational physical activity and incidence of overall HF, HFpEF, and HFrEF in a cohort of older women enrolled in the Women's Health Initiative (WHI) study, and evaluated models with physical activity and CHD as time-varying parameters. We evaluated the unique contribution of walking, the most common type of physical activity in older women, as well as differentiating the contribution of physical activity volume and intensity. The omnibus hypothesis was that greater total recreational physical activity and walking would be associated with lower risks of each HF endpoint.

METHODS

Details of the WHI design have been published (18,19). Briefly, postmenopausal women, ages 50 to 79 years at baseline who had no terminal illness, enrolled in either the clinical trials or the observational study component. All 161,808 women in the original cohort were followed for incidence of acute hospitalized HF from enrollment (1993 to 1998) to December 2015 (16). The incidence of HFpEF or HFrEF was determined in a subcohort of 44,174 women (20). The subcohort was formed within the larger WHI, beginning in the 2010 to 2015 extension period as part of an expanded HF adjudication process that involved obtaining records on echocardiographic and other imaging information to allow for HF subtype determination, which was not feasible in the entire cohort. Thus, although not available for the entire cohort,

missing HFpEF and HFrEF status was not a function of individual participation or health status; rather, it was because of when and how this adjudication process was implemented. To enhance the subsample diversity and the variation in HF rates and related characteristics, the expanded HF adjudication was completed among all women who participated in the WHI Hormone Trials, as well as all African American and Hispanic women from the beginning of WHI (1993 to 1998) through 2010 (20). Women with self-reported HF at baseline (2,048 overall; 684 in the subcohort) and women who reported inability to walk 1 block without assistance (13,784 overall; 5,183 in the subcohort) were excluded. Following further exclusion for missing information on physical activity or covariates (8,673 overall; 3,035 in the subcohort), the final analytic sample was 137,303 women overall and 35,272 in the subcohort. Institutional review board approval and participant informed consent were obtained at all 40 clinical centers.

PHYSICAL ACTIVITY ASSESSMENT. At baseline and periodically during follow-up, participants completed a self-administered questionnaire on the frequency (days per week) and duration (min) of usual mild, moderate, and strenuous recreational physical activity (Online Appendix) (19,21,22). Physical activity was summarized as energy expenditure calculated as the product of metabolic equivalents (METs) of task intensity values for each physical activity (23) multiplied by the hours per week of reported participation (MET-h/week). Intensity-specific physical activity, walking, and total physical activity assessed by this questionnaire demonstrated reproducibility (intraclass correlations = 0.51 to 0.77) (22) and validity ($r = 0.45$ to 0.52) with accelerometer criterion measures (24).

ASCERTAINMENT OF INCIDENT HF. WHI clinical trial participants had self-report outcomes collected every 6 months; the outcomes of the observational study participants were collected every year. Self-reported hospitalized HF was adjudicated by trained physicians. For overall HF, a diagnosis of new-onset congestive HF at hospital admission and at least 1 of 4 clinical observations, described elsewhere (16), were required. This method had strong agreement ($\kappa = 0.79$) comparing central and local adjudicated HF (25). The comprehensive adjudication criteria for HFpEF and HFrEF (Online Appendix) were previously published (20). Acute HF with an EF $<45\%$ or $\geq 45\%$ was classified as HFrEF and HFpEF, respectively. If no EF was

ABBREVIATIONS AND ACRONYMS

BMI = body mass index
CHD = coronary heart disease
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
MET = metabolic equivalent

TABLE 1 Baseline Characteristics for the Overall Cohort and According to Categories of Total Physical Activity Level

	Overall (N = 137,303)	Total Physical Activity (MET-h/week)				p Value*
		0 (n = 18,992)	>0-7.2 (n = 39,736)	7.3-17.0 (n = 39,577)	>17.0 (n = 38,998)	
Physical activity level (MET-h/week)						
Total	9.0 (2.8-18.8)	0.0 (0.0-0.0)	3.8 (1.9-5.0)	11.4 (9.0-14.0)	26.0 (21.0-35.0)	<0.001†
Mild	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-2.5)	0.0 (0.0-3.5)	<0.001†
Moderate	0.0 (0.0-4.5)	0.0 (0.0-0.0)	0.0 (0.0-1.5)	1.5 (0.0-5.3)	5.3 (0.0-11.3)	<0.001†
Strenuous	0.0 (0.0-1.2)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	8.2 (0.0-17.5)	<0.001†
Walking	3.5 (0.0-7.5)	0.0 (0.0-0.0)	1.5 (0.0-3.8)	5.0 (1.9-8.3)	8.3 (3.8-16.7)	<0.001†
Age (yrs)	63.1 ± 7.2	62.2 ± 7.1	63.1 ± 7.2	63.4 ± 7.2	63.3 ± 7.2	<0.001
50-59	33.6	38.5	34.0	32.1	32.3	
60-69	45.3	43.8	45.0	45.5	46.0	
70-79	21.2	17.7	21.0	22.5	21.7	
Race-ethnicity						<0.001‡
White	83.7	78.0	81.8	85.5	86.5	
African American	8.2	12.1	9.6	7.0	6.1	
Hispanic	3.7	5.3	4.2	3.1	2.8	
Native American	0.4	0.4	0.4	0.4	0.4	
Asian/Pacific Islander	2.8	2.8	2.7	2.7	2.9	
Education						<0.001
High school or less	20.9	29.1	24.1	19.0	15.5	
Some college	37.4	39.1	39.2	37.0	35.2	
College graduate	41.0	31.1	35.9	43.3	48.5	
Income, \$						<0.001
<\$20,000	13.7	17.4	16.3	12.4	10.7	
\$20,000-\$49,999	41.7	44.0	44.2	41.9	38.0	
\$50,000-\$74,999	19.4	18.1	18.4	20.1	20.3	
≥\$75,000	18.6	13.6	14.9	19.2	24.2	
Smoking						<0.001
Never	50.8	51.1	52.6	51.2	48.3	
Former	41.6	37.5	38.3	42.3	46.3	
Current	6.6	10.4	8.1	5.5	4.4	
Alcohol use						<0.001§
Never	10.3	13.2	11.7	10.0	7.6	
Former	17.3	21.8	19.4	15.7	14.7	
Current	71.9	64.3	68.4	73.8	77.2	
Hormone therapy use						<0.001§
Never	42.8	46.0	45.2	41.9	39.9	
Former	15.7	16.0	16.0	15.6	15.5	
Current	41.4	38.0	38.8	42.5	44.6	

Continued on the next page

available, it was not included in the analysis. This classification system showed good percentage agreement with other HF epidemiological algorithms, including Framingham (69.5%), modified Boston (63.7%), the National Health and Nutrition Examination Survey (60.9%), Gothenburg (59.5%), and the International Classification of Disease-9th Revision-Clinical Modification (62.9%), and demonstrated modest kappa coefficients (0.10 to 0.32), high sensitivity (0.80 to 0.95), and moderate positive predictive values (0.62 to 0.68) compared with these HF algorithms (26).

COVARIABLE ASSESSMENT. Information on demographics, personal health history, medication use, and lifestyle habits were obtained by self-administered

questionnaires (18,19). Body mass index (BMI; kilograms divided square meters) was calculated from measured weight and height. Seated resting blood pressure was measured using auscultatory methods with cuff size determined by measured arm circumference (18,19). Physical functioning was assessed using the Short Form Survey-36 instrument (18).

STATISTICAL ANALYSIS. To compare participant characteristics according to categories of total physical activity at baseline, p values were calculated from a linear (continuous covariates) or logistic (dichotomous covariates) model, with the covariate of interest as a function of linear trend across physical activity quartiles, using the median value

TABLE 1 Continued

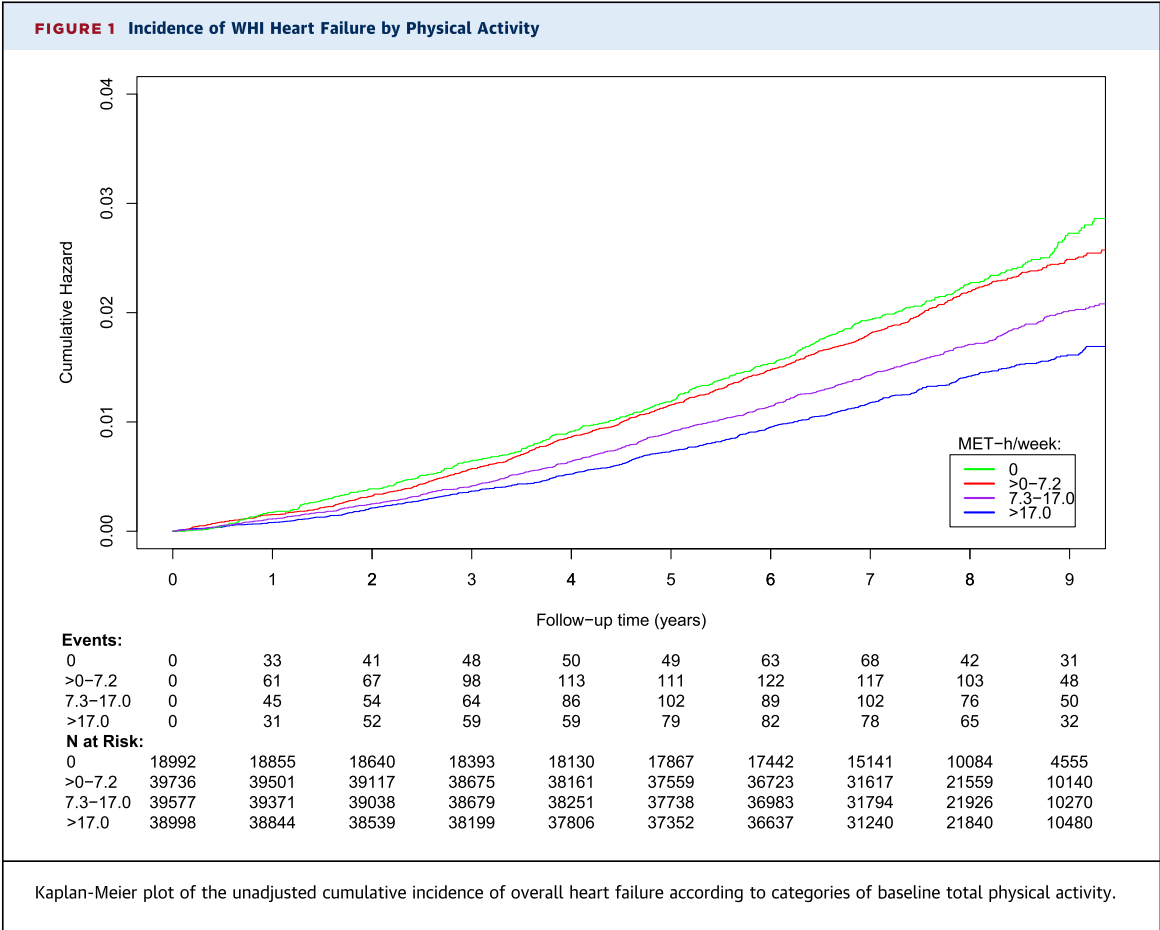
	Overall (N = 137,303)	Total Physical Activity (MET-h/week)				p Value*
		0 (n = 18,992)	>0-7.2 (n = 39,736)	7.3-17.0 (n = 39,577)	>17.0 (n = 38,998)	
History of hysterectomy	40.8	44.4	42.9	40.2	37.6	<0.001
Hypertension	39.9	43.6	43.5	39.3	34.8	<0.001
Treated diabetes	3.6	4.5	4.6	3.2	2.4	<0.001
Atrial fibrillation diagnosis	3.7	3.7	3.9	3.9	3.4	<0.001
CHD diagnosis	2.4	2.0	2.6	2.5	2.3	0.41
ADL score¶	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.2	4.0 ± 0.3	0.01
Physical function score#	85.2 ± 16.6	80.3 ± 16.3	82.1 ± 15.6	86.0 ± 13.5	89.9 ± 11.8	<0.001
Systolic BP (mm Hg)	126.8 ± 17.6	127.9 ± 17.2	127.9 ± 17.5	126.6 ± 17.7	125.4 ± 17.7	<0.001
Diastolic BP (mm Hg)	75.1 ± 9.2	75.8 ± 9.3	75.6 ± 9.3	74.9 ± 9.2	74.6 ± 9.2	<0.001
BMI (kg/m ²)	27.5 ± 2.6	29.5 ± 6.2	28.5 ± 5.8	27.1 ± 5.2	26.0 ± 4.9	<0.001
Clinical trial randomization						
Active hormone therapy	8.1	10.4	9.2	7.4	6.7	<0.001**
Active dietary modification	11.5	15.0	13.2	10.8	8.8	<0.001**

Values are median (interquartile range), mean ± SD, or %. *Trend p value computed from a linear (continuous) or logistic (dichotomous) model with the demographic variable as a function of linear trend over median values of each category of physical activity. †Trend p values for physical activity variables are evaluated using log-transformed values. ‡Trend p value compares percentage of white vs. non-white participants. §p Value compares current vs. past and/or never users. ||Hypertension defined as history of physician-diagnosed and treated hypertension, or measured systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg. ¶Activities of daily living (ADL) score (range 4 to 12) higher values reflect greater functional limitations in daily activities. #Physical function score (range 0 to 100) assessed using the Short Form Survey-36 instrument; higher values reflect greater physical functioning. **p value compares active vs. placebo and/or not randomized. Mean ± SD physical activity levels for the Overall Cohort, 0, >0-7.2, 7.3-17.0, and >17.0 MET-hr/wk categories are 13.0 (13.9), 0.0 (0.0), 3.6 (1.9), 11.6 (2.9) and 30.4 (13.7) for total; 1.4 (3.1), 0.0 (0.0), 0.6 (1.3), 1.4 (2.6), and 2.7 (4.7) for mild; 3.1 (5.2) 0.0 (0.0), 0.9 (1.6), 3.1 (3.9), and 7.0 (7.3) for moderate; 3.6 (8.1), 0.0 (0.0), 0.2 (0.8), 1.5 (3.3), and 11.0 (12.0) for strenuous; and 5.0 (6.1), 0.0 (0.0), 2.0 (1.9), 5.6 (4.3), and 9.8 (8.0) for walking.

BMI = body mass index; CHD = coronary heart disease; MET = metabolic equivalent.

within each quartile. The primary analysis used time-to-event methods based on the Cox proportional hazards regression model with ties handled using the approximate likelihood of Efron. Time-to-event was accrued from date of randomization in the clinical trials or date of enrollment in the observational study to the date of first hospitalization for acute HF (earliest date for HFpEF or HFrEF), death, loss to follow-up, or December 31, 2015, whichever came first. When evaluating incidence of HFpEF and HFrEF, only the first occurrence of either HF subtype was included in the analysis. All models were stratified by the WHI clinical trial or observational study component. Hazard ratios and 95% confidence intervals for incident HF according to physical activity categories were computed with increasing control for potential confounding, beginning with a model that included sociodemographic factors, smoking, alcohol use, hormone therapy use, and hysterectomy status, then adding factors that potentially mediated the association between physical activity and HF. The primary exposure variable was total physical activity assessed at baseline. Categories were defined as none (0 MET-h/week; referent group) and tertiles of physical activity exposure. Tests for linear trend were conducted across median values of categorical physical activity. Continuous physical activity was log-transformed for modeling. In addition to total physical activity, all

outcomes were separately modeled by physical activity intensities (mild, moderate, strenuous) and walking. Tests for interaction were based on the interaction term from a proportional hazards model, with HF as a function of continuous physical activity, the subgroup of interest, and their interaction. For the primary analysis, all baseline predictors, including physical activity, remained fixed during follow-up, except CHD diagnosis, which was a time-varying parameter. Because post-baseline changes in physical activity levels could influence HF occurrence separately from the effect of baseline physical activity, we conducted a secondary analysis using time-varying physical activity levels, and controlled for baseline covariates and time-varying CHD. The proportional hazards assumption was examined by graphically plotting survival by physical activity categories and by modeling each HF outcome as a function of the interaction between physical activity and follow-up time. In both cases, no appreciable violations were noted. The potential impact of sub-clinical morbidity at baseline was examined by discarding the first 2 years of follow-up, by excluding women with any difficulty in daily living activities, and by stratifying the primary results on baseline physical functioning. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina), and p values were for 2-sided hypothesis tests at alpha = 0.05.



RESULTS

The cohort at baseline (Table 1) was an average of 63 years of age, with most being white, educated beyond high school, and former or never smokers. The prevalence of diagnosed diabetes and CHD was low, whereas more than one-third of women had hypertension. Of the mean 13 MET-h/week of total physical activity, the largest proportion was accounted for by walking (38%). All baseline characteristics, except history of CHD, were significantly associated with total physical activity (Table 1). Baseline characteristics, presented separately for the overall group and the subcohort, are reported for descriptive purposes in Online Table 1. The 2 groups were comparable on key factors that were most relevant to evaluating the association of interest (e.g., age, BMI, CHD, hypertension, smoking pack-years, physical functioning, total physical activity).

We documented 2,523 (1.8%) incident cases of overall HF during 1.2 million person-years follow-up, and 734 (2.1%) and 451 (1.3%) incident cases of HFpEF and HFrEF during 480,313 person-years in the subcohort. The cumulative incidence of overall HF was

lower with increasing physical activity, particularly for women in the upper 2 tertiles compared with those who reported no activity at baseline (Figure 1). HF incidence (per 1,000 person-years), which compared no activity with the upper tertile of activity, was 2.9 versus 1.8 for overall HF, 1.7 versus 1.3 for HFpEF, and 1.2 versus 0.8 for HFrEF (Table 2). After controlling for sociodemographic factors, smoking, alcohol, hormone therapy, and hysterectomy, statistically significant inverse associations with total physical activity were observed for each HF endpoint (trend $p \leq 0.01$). Further control for factors that potentially mediated these associations (model 2), as well as time-varying CHD (model 3), attenuated but did not eliminate the inverse associations. When analyzed as a continuous exposure (model 3 covariates), each 1-log MET-h/week of baseline total physical activity (≈ 60 min/week in brisk walking) was associated, on average, with a risk reduction of 9%, 8%, and 10% in overall HF, HFpEF, and HFrEF, respectively.

Results of secondary analysis for time-dependent total physical activity are shown in Online Table 2. Although the overall pattern of results were similar

TABLE 2 Rates and Relative Risks of HF According to Category of Total Physical Activity Level at Baseline

	Total Physical Activity (MET-h/wk)				Linear Trend p Value
	0	>0-7.2	7.3-17.0	>17.0	
Overall HF (N =137,303; 2,523 cases)					
Physical activity	0.0	3.8	11.4	26.0	
No. of cases (rate/1,000 person-yrs)	434 (2.9)	855 (2.7)	682 (2.2)	552 (1.8)	
Unadjusted	1.00 (ref)	0.94 (0.84-1.05)	0.75 (0.66-0.85)	0.61 (0.54-0.70)	<0.001
Model 1	1.00 (ref)	0.89 (0.79-1.00)	0.74 (0.66-0.84)	0.65 (0.57-0.74)	<0.001
Model 2	1.00 (ref)	0.89 (0.80-1.00)	0.81 (0.71-0.91)	0.75 (0.66-0.86)	<0.001
Model 3	1.00 (ref)	0.88 (0.79-0.99)	0.79 (0.70-0.90)	0.75 (0.65-0.85)	<0.001
HFpEF (n = 35,272; 734 cases)					
Physical activity	0.0	3.5	11.0	25.8	
No. of cases (rate/1,000 person-yrs)	145 (1.7)	272 (1.8)	170 (1.4)	147 (1.3)	
Unadjusted	1.00 (ref)	1.01 (0.82-1.23)	0.76 (0.61-0.95)	0.71 (0.57-0.90)	<0.001
Model 1	1.00 (ref)	0.93 (0.76-1.14)	0.70 (0.56-0.88)	0.68 (0.54-0.86)	<0.001
Model 2	1.00 (ref)	0.95 (0.77-1.16)	0.78 (0.62-0.98)	0.82 (0.65-1.03)	0.06
Model 3	1.00 (ref)	0.93 (0.76-1.14)	0.77 (0.61-0.96)	0.81 (0.64-1.03)	0.07
HFrEF (n = 35,272; 451 cases)					
Physical activity	0.0	3.5	11.0	25.8	
No. of cases (rate/1,000 person-yrs)	103 (1.2)	160 (1.0)	94 (0.8)	94 (0.8)	
Unadjusted	1.00 (ref)	0.85 (0.66-1.08)	0.60 (0.45-0.79)	0.65 (0.49-0.87)	0.003
Model 1	1.00 (ref)	0.81 (0.63-1.04)	0.59 (0.45-0.79)	0.68 (0.51-0.91)	0.01
Model 2	1.00 (ref)	0.79 (0.61-1.01)	0.60 (0.45-0.79)	0.71 (0.54-0.95)	0.05
Model 3	1.00 (ref)	0.77 (0.60-0.99)	0.58 (0.44-0.77)	0.71 (0.54-0.95)	0.06
Values are mean or hazards ratio (95% confidence intervals), unless otherwise indicated. All models stratified by hormone trials and dietary modification trial arms. Model 1 included age (yrs), race/ethnicity (5 categories), education (less than high school, some college, college graduate), income (4 categories), smoking (never, former, current), alcohol use (never, former, current), hormone therapy use (never, former, current), and history of hysterectomy. Model 2 included the variables in model 1, plus treated diabetes, treated hypertension, systolic BP (mm Hg), diastolic BP (mm Hg), BMI (kg/m ²), and atrial fibrillation diagnosis. Model 3 included the variables in model 2, plus time-varying CHD (myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty) diagnosis.					
HF = heart failure; HFpEF = HF with preserved ejection fraction; HFrEF = HF with reduced ejection fraction; other abbreviations as in Table 1 .					

to those for baseline physical activity, point estimates were somewhat stronger in the time-varying analysis. When fully adjusted (model 3), statistically significant inverse trends across incremental categories of time-varying total physical activity was observed for each HF endpoint. Each 1-log MET-h/week of time-varying total physical activity was associated, on average, with significant risk reductions of 16%, 12%, and 10% in overall HF, HFpEF, and HFrEF, respectively.

Table 3 shows results for HF endpoints associated with a 1-log MET-h/week increment in baseline total physical activity according to cohort subgroups. Associations between total physical activity and HF endpoints generally were consistent across subgroup categories, and interaction tests were nonsignificant, with few exceptions. For overall HF, the association was somewhat stronger in younger women (interaction $p = 0.001$), women without a history of CHD (interaction $p = 0.06$), and in women with the highest physical function score (interaction $p = 0.08$). For HFrEF, a stronger association existed in women without hypertension (interaction $p = 0.03$).

In the multivariable-adjusted models, moderate and strenuous intensity baseline physical activity

were inversely associated with overall HF risk, but after further mutually controlling for each intensity, these associations no longer were evident ([Online Tables 3 to 5](#), model 2). When analyses were repeated using time-varying physical activity, statistically significant inverse associations ($p < 0.01$, each) with overall HF were evident for mild, moderate, and strenuous activity ([Online Tables 3 to 5](#)). For HFpEF and HFrEF, relative risks tended to be stronger when based on time-varying activity types; however, a statistically significant inverse trend was observed only between strenuous activity and HFpEF. Results for walking were more robust. Even when mutually controlling for other physical activity intensities ([Online Table 3](#), model 2), greater walking was inversely and significantly associated with each HF endpoint for both baseline and time-varying walking exposures.

Sensitivity analyses that excluded HF cases in the first 2 years of follow-up and that excluded women with any difficulties in daily living activities resulted in patterns of association between baseline ([Online Table 6](#)) as well as time-varying ([Online Table 7](#)) total physical activity, and each HF endpoint was consistent with the results of the primary analysis.

TABLE 3 Rates and Relative Risks of HF Associated With Total Physical Activity Stratified on Cohort Subgroups at Baseline

	No. of Cases (Rate/1,000 Person-Years)	HR* (95% CI)	Interaction p Value
Overall HF (N = 137,303; 2,523 cases)			
Age, yrs			0.001
50-64 (n = 78,084)	678 (1.1)	0.83 (0.78-0.89)	
65-79 (n = 59,219)	1,845 (4.0)	0.94 (0.91-0.98)	
BMI, kg/m ²			0.66
<30 (n = 99,845)	1,530 (1.9)	0.90 (0.86-0.94)	
≥30 (n = 37,458)	993 (3.4)	0.91 (0.87-0.97)	
Treated diabetes			0.80
No (n = 132,256)	2,130 (2.0)	0.91 (0.87-0.97)	
Yes (n = 4,939)	386 (10.6)	0.92 (0.84-1.00)	
Treated hypertension			0.74
No (n = 97,663)	1,162 (1.5)	0.91 (0.87-0.96)	
Yes (n = 38,540)	1,327 (4.4)	0.90 (0.86-0.95)	
CHD diagnosis†			0.06
No (n = 132,254)	2,179 (2.1)	0.90 (0.86-0.93)	
Yes (n = 3,283)	300 (12.5)	0.99 (0.90-1.10)	
Physical function score			0.08
<70 (n = 17,641)	760 (5.7)	0.97 (0.91-1.04)	
70-90 (n = 42,545)	979 (2.9)	0.97 (0.91-1.02)	
≥90 (n = 75,761)	751 (1.2)	0.90 (0.85-0.96)	
HFpEF (N = 35,272; 734 cases)			
Age, yrs			0.12
50-64 (n = 21,350)	224 (0.7)	0.86 (0.77-0.96)	
65-79 (n = 13,922)	510 (2.9)	0.95 (0.88-1.03)	
BMI, kg/m ²			0.14
<30 (n = 21,870)	378 (1.3)	0.95 (0.87-1.04)	
≥30 (n = 13,402)	356 (2.0)	0.86 (0.79-0.95)	
Treated diabetes			0.97
No (n = 33,029)	611 (1.4)	0.92 (0.86-0.99)	
Yes (n = 2,207)	122 (5.0)	0.92 (0.79-1.08)	
Treated hypertension			0.68
No (n = 23,301)	367 (1.1)	0.91 (0.83-0.99)	
Yes (n = 11,600)	358 (2.4)	0.93 (0.85-1.02)	
CHD diagnosis†			0.46
No (n = 33,861)	661 (1.4)	0.92 (0.86-0.98)	
Yes (n = 878)	58 (5.9)	1.00 (0.80-1.26)	
Physical function score			0.89
<70 (n = 5,384)	193 (3.0)	0.92 (0.81-1.05)	
70-90 (n = 11,106)	306 (2.1)	0.96 (0.87-1.06)	
≥90 (n = 18,225)	226 (0.9)	0.95 (0.84-1.06)	

Continued on the next page

DISCUSSION

These prospective data supported the hypothesis that higher levels of self-reported total recreational physical activity and higher levels of walking are associated with a lower risk of developing overall HF, HFpEF, and HFrEF. To our knowledge, this was one of the most comprehensive evaluations of physical activity and HF risk, and was the first study to demonstrate that greater amounts of physical activity are associated with a lower risk of both

HFpEF and HFrEF in older women. Evaluation of time-varying physical activity levels yielded results similar to those for baseline physical activity. The inverse association with total physical activity was evident, even when controlling for potential mediating factors measured at baseline and time-varying CHD diagnosis antecedent to HF occurrence. Intensity-specific baseline physical activity showed no association with HF risks when simultaneously controlling for each intensity; however, time-varying, intensity-specific activity was significantly associated with lower risk of overall HF. More walking, baseline and time-varying, was associated with significantly lower risks of each HF endpoint after controlling for other activity intensities. This was important because walking accounted for the largest proportion of total physical activity among these older women. That total and walking physical activity was inversely associated with HF development, whereas intensity-specific physical activity was not, suggested that physical activity volume (e.g., movement), rather than intensity, might be the driver that underlies HF benefit in later life. These findings extended those of previous studies on predominantly men and middle-aged adults (4,7,9-12) to a cohort of older women in the U.S. community. Because HFpEF prevalence is high in older women, and there are limited effective therapies for its management, the present results, if confirmed, suggested that prevention strategies focused on physical activity could have important implications on controlling the increasing HFpEF burden.

Table 4 provides a summary of published epidemiological studies that evaluated prospective associations between physical activity and HF incidence. There were 18 primary studies, 1 pooled cohort study, and 2 meta-analyses. Among primary studies, cohort size ranged from 1,142 to 84,537 participants, follow-up intervals from 7 to 22 years, incident counts of overall HF from 88 to 3,614 cases, and there were 108 HFpEF cases and 106 HFrEF cases. Seven studies reported results for women, 3 of which reported HF risks across ≥3 physical activity groups (3,27,28). Statistically significant inverse associations for overall HF were observed with physical activity exposures defined by combined occupational and/or leisure activities (27) and recreational activity and/or walking (3), whereas no association was observed with transportation and/or commuting activity (11). Adjusted relative risks for overall HF comparing the highest and lowest activity categories were 0.68 and 0.69 in the 2 studies in which results achieved statistical significance (3,27), similar to the HRs observed herein. None of the

studies in [Table 4](#) evaluated time-varying physical activity, and only 1 included time-varying CHD as a covariate. Compared with the previous 2 studies on women ([3,27](#)), our study was larger, included HF subtypes (HFpEF, HFrEF), controlled for time-varying CHD, evaluated time-varying activity levels, and used a no activity referent group. Failure to control for the influence of CHD before HF, potential changes in physical activity during follow-up, and mixing of inactive and somewhat active individuals in the referent group could obscure measures of association with HF risk.

The only published primary study on physical activity and incidence of HFpEF and HFrEF was in the 1,142 Framingham Study participants who were followed for a mean of 10 years ([8](#)). In models that included adjustments similar to those in our study, physical activity was not significantly associated with HFpEF or HFrEF. Results specifically for women were not reported. In the pooled cohort analysis by Pandey et al. ([29](#)), physical activity was associated with lower incidence of HFpEF but not HFrEF ([Table 4](#)). We observed a clear inverse association for total physical activity and walking with both HFpEF and HFrEF. Our analysis excluded nonambulatory women, utilized a no activity reference group, and controlled for HF determinants, including time-varying CHD; lower risks persisted when analyzing time-varying physical activity and discarding events during early follow-up. These attributes enhanced confidence in an apparent role for physical activity in HF prevention, a hypothesis-requiring confirmation by a randomized HF prevention trial.

Physical activity improves risk factors that are causal in HF pathogenesis. These pathways include obesity, blood pressure, glucose regulation, inflammation and oxidative stress ([2](#)), left ventricular compliance, systolic and diastolic heart function ([30,31](#)), arterial function and aerobic capacity ([32](#)), renal insufficiency ([33](#)), and CHD risk ([21,34](#)). Several cardiometabolic mechanisms can be improved in women through walking ([35,36](#)), which was strongly associated with lower HF risk in the present study. The favorable impact of physical activity on skeletal muscle fiber distribution, metabolism, and micro-RNA ([37-39](#)) could potentially mitigate characteristics of the skeletal myopathy seen in early HF ([40](#)). Physical activity reduced development of onerous conditions antecedent to HF diagnosis, such as CHD ([21,34](#)), diabetes ([41](#)), and atrial fibrillation ([42](#)), in women in WHI. We did not evaluate interim atrial fibrillation, diabetes, or hypertension as potential mediating factors. It was possible that any effect

TABLE 3 Continued

	No. of Cases (Rate/1,000 Person-Years)	HR* (95% CI)	Interaction p Value
HFrEF (N = 35,272; 451 cases)			
Age, yrs			0.24
50-64 (n = 21,350)	171 (0.6)	0.85 (0.75-0.97)	
65-79 (n = 13,922)	280 (1.6)	0.94 (0.85-1.04)	
BMI, kg/m ²			0.10
<30 (n = 21,870)	259 (0.9)	0.86 (0.77-0.95)	
≥30 (n = 13,402)	192 (1.1)	0.98 (0.87-1.11)	
Treated diabetes			0.10
No (n = 33,029)	377 (0.8)	0.88 (0.81-0.96)	
Yes (n = 2,207)	73 (3.0)	1.06 (0.86-1.30)	
Treated hypertension			0.03
No (n = 23,301)	222 (0.7)	0.83 (0.74-0.93)	
Yes (n = 11,600)	225 (1.5)	0.99 (0.89-1.11)	
CHD diagnosis†			0.67
No (n = 33,861)	391 (0.9)	0.88 (0.81-0.96)	
Yes (n = 878)	51 (5.2)	0.93 (0.73-1.19)	
Physical function score‡			0.76
<70 (n = 5,384)	116 (1.8)	0.89 (0.75-1.05)	
70-90 (n = 11,106)	157 (1.1)	1.02 (0.89-1.17)	
≥90 (n = 18,225)	171 (0.7)	0.87 (0.76-0.99)	

Models are stratified by hormone therapy trials and dietary modification trial arms, and included age, race/ethnicity, education, income, smoking, alcohol use, hormone therapy use, history of hysterectomy, treated diabetes (except diabetes strata), treated hypertension (except hypertension strata), systolic BP, diastolic BP, BMI, atrial fibrillation diagnosis, and time-varying CHD diagnosis, as defined in the footnote of [Table 2](#). *HRs and 95% CIs are for a 1 log MET-h/week increment in total physical activity. †CHD diagnosis subgroup model does not include adjustment for time-varying CHD. ‡Physical function score was assessed using the Short Form Survey-36 instrument and ranges from 0 to 100; higher scores indicate better physical function.
CI = confidence interval; HR = hazard ratio; other abbreviations as in [Tables 1 and 2](#).

physical activity had on post-baseline development of these conditions could explain some of the inverse association with HF.

STUDY STRENGTHS AND LIMITATIONS. Study strengths included the large cohort of older women with sufficient incident HF endpoint events, which allowed for comprehensive analysis of their associations with physical activity. Reverse causation bias was a reasonable concern, but its likelihood was reduced by excluding nonambulatory women, controlling for time-varying CHD diagnosis, and by the consistency in findings after stratifying for baseline physical function score, discarding events that occurred early in follow-up, excluding women with any difficulty in activities of daily living, and analysis of time-varying physical activity. Evaluating intensity-specific activity and walking exposures provided unique information beyond previous studies ([Table 4](#)).

Limitations include self-reported physical activity information, which inevitably resulted in some amount of exposure misclassification. Because of the prospective design, resulting bias most likely would be non-differential—directing associations toward the null. Ascertainment of EF information to classify

TABLE 4 Prospective Observational Associations Between Physical Activity and Heart Failure Incidence

Study Population (Online Ref. #)	HF Outcome, Follow-Up (No. of HF Cases)	HFpEF, HFrEF	Physical Activity Exposure	Time Varying Physical Activity	Time Varying CHD	Main Finding
Primary cohort studies						
5,545 men; 8,098 women U.S. NHANES Follow-up Study (Online Ref. 7)	HF hospitalization or HF death Mean 19 yrs (741 men, 641 women)	No	Inactive vs. active	No	Yes	Significant inverse association in women but not men.
20,900 men Physician's Health Study (Online Ref. 5)	HF diagnosis or HF death Mean 22.4 yrs (1,200)	No	Vigorous PA (times/week)	No	No	Significant inverse association with lifetime HF risk.
21,094 men Physicians Health Study (Online Ref. 9)	HF diagnosis or HF death Mean 20.5 yrs (1,109)	No	Vigorous PA (times/week)	No	No	Significant inverse trend in HF risk across incremental categories of PA. Association seen men without, but not with, diabetes.
28,842 men; 30,366 women FINN-MONICA study (Online Ref. 8)	HF diagnosis Mean 18.4 yrs (1,921 men, 1,693 women)	No	Combined occupational, commuting, leisure PA	No	No	Significant inverse trend in HF risk across incremental categories of PA in men and in women.
28,334 men; 29,874 women, FINN-MONICA study (Online Ref. 20)	HF diagnosis Mean 18.4 yrs (3,508)	No	Commuting PA	No	No	No association between weekly duration of cycling or walking to work and HF risk in men or in women.
3,707 blacks; 10,018 whites ARIC study (Online Ref. 3)	HF hospitalization or HF death Mean ≈17 yrs (1,748)	No	Combined occupational, sport, leisure PA	No	No	Significant inverse trend in HF risk across incremental categories of PA in blacks and in whites.
1,142 men and women Framingham Heart Study (Online Ref. 11)	HF hospitalization HFrEF (LVEF ≤45%), HFpEF (LVEF >45%) Mean 10 yrs (250 overall HF; 108 HFpEF; 106 HFrEF)	Yes	Combined occupation and leisure PA	No	No	Significant inverse trend in overall HF risk across incremental categories of PA (sex-adjusted). Significant inverse association with HFpEF eliminated when adjusted for BMI. No association with HFrEF.
5,503 men and women Cardiovascular Health Study (Online Ref. 17)	HF diagnosis 13 yrs (88)	No	Leisure PA	No	No	Significant inverse trend in HF risk across incremental categories of PA (sex-adjusted).
84,537 women Women's Health Initiative (Online Ref. 1)	HF hospitalization Mean 11 yrs (1,826)	No	Recreational PA, walking	No	No	Nonsignificant inverse trend in HF risk across incremental categories of PA.
39,805 men and women Swedish March Cohort (Online Ref. 2)	HF hospitalization Median 13 yrs (1,545)	No	Combined occupational, household, exercise, leisure PA	No	No	Significant inverse trend in HF risk across incremental categories of leisure but not total PA.
27,895 women, Swedish Mammography Cohort (Online Ref. 18)	HF hospitalization or HF death Mean 13 yrs (2,402)	No	Combined occupational, household, commuting, exercise PA	No	No	Significantly higher HF risk in women below the median value for total PA and in those engaged in <20 min/day commuting PA and <1 h/day in household chores.
82,695 men California Men's Health Study (Online Ref. 21)	HF hospitalization Mean 7.8 yrs (3,473)	No	Leisure PA	No	No	Significant inverse trend in HF risk across incremental categories of PA. Significant inverse association seen in those with and without CHD or hypertension, and in whites, Hispanics and Asians, but not blacks.
4,490 adults Cardiovascular Health Study (Online Ref. 4)	HF diagnosis Max 21.5 yrs (1,380)	No	Leisure PA, walking	No	No	Significant inverse association between HF risk and levels of both leisure PA and walking.

Continued on the next page

HFpEF and HFrEF was not systematically begun in WHI until the 2010 study extension period; therefore, this information was not available for HF cases that occurred earlier in the follow-up interval. Although all hypothesis tests reported herein were pre-specified, caution is required in the interpretation of *p* values due to multiple comparisons. Subgroup analyses (Table 3) might have been limited by the sample size or case counts, and results should be

interpreted accordingly. Emerging evidence has suggested that low cardiorespiratory fitness might contribute to a unique and stronger risk for HF than self-reported physical activity (43). Because a direct measure of fitness was not available in our study, this could not be evaluated. However, we observed significant inverse associations between physical activity and HF risks in women with higher and lower physical functioning scores, which is correlated strongly

TABLE 4 Continued

Study Population (Online Ref. #)	HF Outcome, Follow-Up (No. of HF Cases)	HFpEF, HFrEF	Physical Activity Exposure	Time Varying Physical Activity	Time Varying CHD	Main Finding
33,012 men Cohort of Swedish Men Study (Online Ref. 19)	HF hospitalization or HF death Mean 13 yrs (3,609)	No	Combined occupational, household, commuting, exercise PA	No	No	Significant inverse association between total PA and HF risk; significantly lower risk in men with higher commuting and exercise, but not household PA.
33,966 men; 30,713 women Swedish Cohort Studies (Online Ref. 13)	HF hospitalization or HF death Mean 13 yrs (1,488 men, 1,096 women)	No	Combined commuting, exercise PA	No	No	Significant inverse association between PA and HF risk in men and in women.
4,066 black men and women Jackson Heart Study (Online Ref. 10)	HF hospitalization Mean 7 yrs (168)	No	Combined occupational, leisure, sport PA	No	No*	Significant inverse trend in HF risk across incremental categories of PA (sex-adjusted). *Association remained significant after excluding those with CHD interim to HF hospitalization.
5,807 men; 7,252 women ARIC Study (Online Ref. 12)	HF hospitalization or HF death Mean 18.9 yrs (not reported)	No	Combined occupational, sport, leisure PA	No	No	Significant inverse trend in lifetime HF risks across incremental categories of PA in men and in women.
6,506 men and women MESA Study (Online Ref. 14)	HF diagnosis Median 12 yrs (262)	No	Combined occupational, sport/exercise, household, leisure PA	No	No	Significant inverse trends in HF risk across incremental categories of PA in the overall cohort, and in whites, blacks, and Hispanics.
Pooled cohorts analysis						
51,451 adults, pooled from 3 large U.S. cohorts: Cardiovascular Health Study, Women's Health Initiative, MESA Study (Online Ref. 16)	HF hospitalization HFpEF (LVEF $\geq$ 45%), HFrEF (LVEF <45%) Mean 11 yrs (3,180 overall; 1,252 HFpEF; 941 HFrEF)	Yes	Recreational, leisure PA	No	No	Significant inverse trend in HF risk across incremental categories of PA for overall HF and for HFpEF, but not for HFrEF.
Meta-analysis						
12 prospective cohorts; 370,460 adults (Online Ref. 15)	HF hospitalization, diagnosis, or death 13 years (20,203)	No	Recreational, leisure, exercise, walking PA	No	No	Significant inverse associations between HF risk and PA overall; in men and in women; in those <55 and $\geq$ 55 years of age.
10 prospective cohorts; 282,889 adults (Online Ref. 6)	HF hospitalization, diagnosis, or death 7-30 yrs (14,626)	Yes	Recreational, leisure, exercise, walking PA	No	No	Significant inverse association between HF risk and PA for overall HF and HFpEF, but not HFrEF.
Present study						
137,303 postmenopausal women Women's Health Initiative	HF hospitalization HFpEF (LVEF $\geq$ 45%) HFrEF (LVEF <45%) Mean 14 yrs (2,523 overall; 734 HFpEF; 451 HFrEF)	Yes	Recreational, walking PA	Yes	Yes	Significant inverse associations for total PA and for walking with overall HF, HFpEF and HFrEF, when based on baseline or time-varying PA; and when controlling for time-varying CHD, as well as other HF predictors.
Some of the references for the studies included in this table are provided in the Online Appendix . *Summarized study results are for the most fully adjusted multivariable analysis reported in the source study. ARIC = Atherosclerosis Risk in Communities; FINN-MONICA = Finnish (FINN) component of the World Health Organizations Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) Study; LVEF = left ventricular ejection fraction; NHANES = National Health and Nutrition Examination Survey; PA = physical activity; other abbreviations as in Tables 1 and 2 .						

with measured fitness levels. The role of fitness in HF risk at older ages requires clarification. The study population of volunteers in WHI was not a representative cross section of women in the United States. Results of this study, although not extended directly to men, are consistent with previously published studies ([Table 4](#)).

CONCLUSIONS

These prospective data from a cohort of older women indicated that higher levels of total physical activity

and walking were associated with reduced risks of developing HF and its subtypes HFpEF and HFrEF in later life. With continued growth in the number of older women and the challenges in treating HFpEF, the present results, if confirmed, strongly support promotion of physical activity in HF prevention guidelines for older adults.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Higher amounts of recreational physical activity, particularly walking, which is common in older adults, is associated with numerous cardiovascular benefits, including lower incidence of HF with HFpEF or HFrEF as determined in the present study. Higher levels of walking also were specifically inversely associated with overall HF (trend $p < 0.001$), HFpEF (trend, $p = 0.001$), and HFrEF (trend $p = 0.02$). These findings suggest that physical activity volume (e.g., movement), rather than intensity, may be responsible for the protective association. Vigilance in promoting greater physical activity, for example, brisk walking (3.3 mph on level ground) with the target of achieving 30 min/day on 5 or more days of the week, might be especially prudent in older adults with increased risk for HF because of existing diabetes, hypertension, or CHD.

TRANSLATIONAL OUTLOOK: Clinical trials are needed to determine the specific type and dose of physical activity required to reduce incidence of acute HF (and its subtypes) at older ages, as well as to identify any risks associated with increasing physical activity in those with elevated susceptibility for HF. If these findings are confirmed, translation to clinical practice and public health action will require understanding how best to approach physical activity promotion and change among women in later life, because they spend a high proportion of daily awake time in sedentary behaviors.

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KEY WORDS aging, cardiovascular disease, congestive heart failure, exercise, women's health

APPENDIX For supplemental tables and figures, please see the online version of this paper.



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