Clinical Investigation

Sedentary Time and Cumulative Risk of Preserved and Reduced Ejection Fraction Heart Failure: From the Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Background: This study examined the relationship between self-reported sedentary time (ST) and the cumulative risk of heart failure with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) in a diverse cohort of U.S. adults 45−84 years of age.

Methods and Results: Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), we identified 6,814 subjects, all free of baseline cardiovascular disease. Cox regression was used to calculate the hazard ratios (HR) associated with risk of HFpEF and HFrEF. Weekly ST was dichotomized based on the 75th percentile (1890 min/wk). During ∼11.2 years of follow-up there were 178 first incident HF diagnoses: 74 HFpEF and 69 HFrEF. Baseline ST >1890 min/wk was significantly associated with an increased risk of HFpEF (HR 1.87, 95% confidence interval [CI] 1.13−3.09, $P = .01$), but not of HFrEF. The relationship with HFpEF remained significant in fully adjusted models including physical activity and waist circumference (HR 2.16, 95% CI 1.23−3.78, $P < .01$). In addition, every 60-minute increase in weekly ST was associated with a 3% increased risk of HFpEF (HR 1.03, 95% CI 1.01−1.05, $P < .01$).

Conclusions: Sedentary time >1890 min/wk (∼4.5 h/d) is a significant predictor of HFpEF, independently from physical activity and adiposity. (*J Cardiac Fail 2019;25:418−424*)

Key Words: Sitting time, sedentary lifestyle, cardiovascular disease.

Heart failure (HF) is a complex clinical syndrome that can result from any cardiac disorder that impairs the ability of the ventricle to function properly.[1] According to 2017 estimates,[2] the number of U.S. adults with HF is 6.5 million. By 2030, this number is projected to reach 8.5 million, an increase of 46% from 2012 estimates.[3] At 45 years of age, the lifetime risk of developing HF ranges from 20% to 45%.[4] Presently, the prognosis after being diagnosed with HF is grim: ∼50% of those diagnosed die within 5 years.[5−7] HF primarily affects the left ventricle. Indeed, the most common cause of right-side HF is left-side HF. Two subtypes of left-side HF are currently recognized: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[1,8]

The American Heart Association and the American College of Cardiology[8] recommend that HFrEF is defined as an ejection fraction (EF) ≤40%, HFpEF as an EF ≥50%, with an EF of 41%−49% considered to be borderline HFpEF. This differential diagnosis based on EF is clinically relevant. Research has demonstrated that the risk factors, pathophysiology, prognosis, and response to pharmaceutical and rehabilitative therapy are different among these subtypes.[9−15] Specifically, for HFrEF, myocardial remodeling is driven by cardiomyocyte death due to oxidative stress originating in the cardiomyocytes as a result of ischemia, infection, or toxicity. In many cases, HFrEF is precipitated by myocardial ischemia, and important risk factors are the same as those for coronary artery disease. The etiology of HFpEF is not fully understood but is thought to be related to systemic inflammation. Inflammation appears to underlie the vascular and cardiac changes associated with HFpEF,

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such as endothelium dysfunction and myocardial fibrosis, as well as abnormalities in skeletal muscle metabolic function.[14,16] In addition, therapeutic strategies that are successful in patients with HFrEF have proven to be ineffective in patients with HFpEF.[9,10] This renders efforts to prevent the onset of HFpEF even more important. The identification of modifiable risk factors that may play a role in the development of HFpEF is urgently needed.

Sedentary behavior has been defined as any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents (METs) while in a sitting, reclining, or lying posture.[17] Therefore, sedentary time (ST) is the total amount of time spent engaging in sedentary behaviors. Activities associated with ST are time spent watching television or working on a computer, for example. This is distinctly different from physical inactivity, defined as an insufficient amount of physical activity (PA) to meet present PA recommendations.[18] It is possible that one could meet the PA recommendations and spend large portions of their day engaged in sedentary behavior. The recognition of ST as an independent risk factor for the development of deleterious health outcomes, including cardiovascular disease (CVD), cancer, and diabetes, has been increasing in recent years.[19]

A meta-analysis of 47 studies concluded that self-reported prolonged ST was significantly associated with CVD incidence and CVD mortality, independently from PA.[19] Young et al[20] found a significant association between increased ST and HF risk. In addition, a study by Wijndaele at al[21] observed that television viewing time, a common form of ST, was positively associated with incident HF, independently from PA. Finally, a science advisory from the American Heart Association published in 2016 highlighted the importance of this research and gave guidance for future research endeavors.[22]

To date, little is known about the relationship between ST and the risk of HFpEF and HFrEF. Bennett et al[23] reported on the presence of diastolic dysfunction with preserved systolic function (DD-PSF), identified with the use of echocardiography, in a cohort of Swedish men and women. ST was defined as low levels of leisure-time physical activity (LTPA), which included both inactivity and less strenuous and moderate PA. Diastolic dysfunction with preserved systolic function was associated with sedentary LTPA and smoking in women only. Moreover, the positive predictive value of diagnosing DD-SPF in women was 80% when considering sedentary LTPA, hypertension, and obesity. Doukky et al[24] sought to determine the impact of sedentary behavior on patients with established HF regardless of subtype. The results confirmed that physical inactivity was associated with a higher risk of all-cause and cardiac mortality in all patients with established HF. The results of an exploratory analysis demonstrated no significant difference in the risk of mortality between the 2 subtypes of HF, HFpEF and HFrEF. However, none of these studies directly addressed how higher amounts of ST increase the risk of developing HFpEF or HFrEF.

The purpose of the present study was to examine the relationship between self-reported baseline ST and the cumulative risk of HFpEF and HFrEF in a diverse population-based sample of U.S. adults. Based on the inflammation-driven pathophysiology and common cardiometabolic risk factors associated with HFpEF, along with previous research demonstrating a stronger relationship with lower PA and higher body mass index (BMI) and HFpEF,[12] we hypothesized that a higher volume of ST would be associated with increased risk of HFpEF but not of HFrEF.

Methods

This study analyzed data from the Multi-Ethnic Study of Atherosclerosis (MESA),[25] a continuous survey sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health. MESA is a diverse population-based sample that examines the characteristics of subclinical cardiovascular disease and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. Details on this study have been published elsewhere.[25] In brief, the sample (n = 6814) consisted of men and women (45−84 years of age) who were asymptomatic and free of baseline CVD at enrollment. The MESA used both physical examinations and questionnaires. The first examinations took place from July 2000 to July 2002, and a total of 4 additional follow-up examinations were completed by 2012. Participants are continuously contacted every 9−12 months to assess clinical morbidity and mortality data. Data from the MESA were requested and obtained from the National Institutes of Health/National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center.[26] The use of MESA data was approved by the Institutional Review Board of the University of North Florida.

Dependent Variable

Heart failure, classified as either definite or probable, was an adjudicated event in MESA determined by a panel of physicians following review of patient medical records. Probable HF was defined as HF diagnosed by a physician and the patient receiving medical treatment for HF. Definite HF determination required additional evidence from the medical record of pulmonary edema or congestion, dilated ventricle, poor left ventricular function, or left ventricular diastolic dysfunction. Data on EF, determined via echocardiography at the time of diagnosis, were also recorded by MESA from the review of medical records. In the present study, those with an EF ≤40% at the time of diagnosis were classified as HFrEF, and those with a borderline EF (41%−49%) or an EF ≥50% were classified as HFpEF.

Independent Variable

Self-reported baseline ST was based on the typical week physical activity survey (TWPAS) that was completed by all MESA participants. The following 2 questions from the survey were used to estimate total weekly sedentary

minutes: "In a typical week in the past month, did you sit or recline and watch TV?" and "In a typical week in the past month, did you read, knit, sew, visit, do nothing, nonwork recreational computer?" Responses included yes or no, days per week,[1−7] hours per day (1−5 or >5), and minutes per day (5, 15, 30, or 45). Total hours per day (converted to minutes) and minutes per day were summed and multiplied by days per week to accumulate an estimated minutes per week of total ST. Total weekly ST was then used to create 2 ST variables, one dichotomized at the 75th percentile (≤1890 or >1890 min/wk) and one that represented every 60-minute interval of ST.

Other Independent Measures

Age, sex, race, and smoking status were self-reported at baseline on the personal history form. Hypertension and diabetes were also self-reported at baseline on the medical history form. Metabolic syndrome was a calculated variable provided in MESA based on participants' measured waist circumference, triglycerides, high-density lipoprotein cholesterol, blood pressure, and fasting blood glucose. The National Cholesterol Education Program Guidelines[27] was used by MESA researchers to define metabolic syndrome.

Intentional exercise was measured according to a formula defined by MESA. The formula used the sum of 7 questions from the TWPAS including those regarding walking for exercise, participation in sports or dance activities, and moderate to heavy effort conditioning reported in MET-minutes per day. This was used to determine risk independently from PA. BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2) with the use of measurements obtained at examination 1. Waist circumference (WC) in centimeters (cm) was also measured at examination 1.

Statistical Analysis

Data was managed with the use of SAS 9.4 software,[28] where complex variable recodes, coding verification, and statistical analyses were performed. To construct the descriptive characteristics tables, the means and *t* test procedures (PROC MEANS and PROC TTEST) were used for the continuous variables, and the frequency and chi-square procedures (PROC FREQ and CHISQ) were used for the categoric variables. The univariate procedure (PROC UNIVARIATE) was used to determine the 75th percentile of self-reported ST. Separate proportional hazards regression procedures (PROC PHREG) were used to calculate multivariable adjusted hazard ratios (HRs) to determine risk of overall HF, HFpEF, and HFrEF according to baseline ST. Incident HF without data on EF were excluded from the primary HF subtype analysis, but separate post hoc sensitivity analyses were conducted including these cases in both HFpEF and HFrEF subgroups.

Six separate models were constructed for each of the HF outcome categories. Model 1 was unadjusted. Model 2 controlled for the demographic variables age, sex, and race. Model 3 additionally controlled for the other common HF risk factors: smoking, hypertension, diabetes, and metabolic syndrome. Model 4 controlled for all variables in model 3 plus PA. Finally, 2 separate adiposity models were created because of the high collinearity of WC and BMI: model 5 controlled for all variables in model 4 plus WC, and model 6 controlled for all variables in model 4 plus BMI. The variables included in the models were based on those used in previous literature.

Results

Among the 178 subjects that developed HF, 143 subjects had a known EF at the time of HF diagnosis. Of those, 74 were categorized as HFpEF and 69 as HFrEF. The overall total person-years for the sample was 52,177.52. The incidence of any HF among the MESA participants was 341.1 per 100,000 person-years. The incidences of HFpEF and HFrEF were, respectively, 141.2 and 132.2 per 100,000 person-years. Table 1 presents the baseline characteristics, including demographics, race, clinical characteristics, and ST according to HFpEF, HFrEF, overall HF, and no HF. Table 2 presents the baseline characteristics of the sample according to baseline ST category. Figure 1 illustrates the distribution of baseline self-reported ST among the sample in min/wk.

The multivariable adjusted HRs derived from the proportional hazards regression procedure for overall HF, HFpEF, and HFrEF are presented in Table 3. For risk of HF, regardless of subtype, baseline ST >1890 min/wk was borderline significant, with a 38% increased risk in the unadjusted model (HR 1.38, 95% CI 1.00−1.89; $P = .05$). However, this relationship was attenuated with further adjustments for demographics, common risk factors, PA, and adiposity measures and did not reach significance. Similarly, the risk of HFrEF was not significantly associated with baseline ST in any model tested.

In the unadjusted model, baseline ST >1890 min/wk was significantly associated with an 87% increased risk of HFpEF (HR 1.87, 95% CI 1.13−3.09) compared with those with ST ≤1890 min/wk. The relationship remained significant after adjustments for demographic factors (HR 1.84, 95% CI 1.07−3.14), smoking, hypertension, diabetes, and metabolic syndrome (HR 1.90, 95% CI 1.09−3.30). The addition of PA (HR 1.92, 95% CI 0.10−3.36) and adiposity measures WC (HR 2.16, 95% CI 1.23−3.78) and BMI (HR 2.17, 95% CI 1.24−3.80) did not attenuate the significance. A pairwise analysis for interaction terms was conducted using all independent variables in the model, revealing no significant interactions in any of the models.

In addition, when ST was evaluated for every 60-minute increase, a significant relationship was observed only with HFpEF. Every 60-minute increase in weekly ST was associated with a 3% increased risk of HFpEF (HR 1.03, 95% CI 1.01−1.05), independently from all variables in model 5. A 1% increased risk was observed for overall HF that was borderline significant ($P = .06$) in the crude model, but significance was lost after further adjustment. No such relationship was observed with HFrEF. A sensitivity analysis conducted to account for the 35 cases of unknown EF by adding them

Table 1. Baseline Characteristics by Heart Failure Outcome

Total (n = 6814)	HFrEF (n = 69)	HFpEF (n = 74)	Overall HF (n = 178)	No HF (n = 6636)	Within-Variable *P* Value
Demographics					
Age (y)	68 ± 9.0	69 ± 8.6	69 ± 8.7	62 ± 10.2	<.01
Male	49 (71.0%)	38 (51.4%)	106 (59.6%)	3107 (46.8%)	<.01
Income ≥ $40,000	29 (42.0%)	29 (39.2%)	68 (38.2%)	3164 (47.7%)	.01
Education ≥ bachelor's	19 (27.5%)	24 (32.4%)	56 (31.5%)	2337 (35.2%)	.30
Race/ethnicity					
White	28 (40.6%)	32 (43.2%)	69 (38.8%)	2553 (38.5%)	.03
Black	28 (40.6%)	18 (24.3%)	61 (34.3%)	1831 (27.6%)	
Hispanic	13 (18.8%)	15 (20.3%)	38 (21.4%)	1458 (22.0%)	
Chinese	0 (0.0%)	9 (12.2%)	10 (5.6%)	794 (12.0%)	
Clinical characteristics					
Heart rate (beats/min)	64 ± 11.5	64 ± 9.8	65 ± 11.1	63 ± 9.6	.01
BMI (kg/m^2)	29.2 ± 5.1	30.3 ± 6.0	30.2 ± 6.2	28.3 ± 5.4	<.01
WC (cm)	104.1 ± 18	105.6 ± 15.1	105.7 ± 17.3	98.0 ± 14.3	<.01
Hypertension	51 (73.9%)	58 (78.4%)	135 (75.8%)	2,923 (44.1%)	<.01
Metabolic syndrome	33 (47.8%)	44 (59.5%)	96 (53.9%)	2,353 (35.6%)	<.01
Diabetes	19 (27.9%)	25 (33.8%)	56 (31.6%)	717 (10.8%)	<.01
Current smoking	15 (21.7%)	8 (10.8%)	28 (15.7%)	860 (13.0%)	.28
Sedentary time					
Average (min/wk)	1687.3	1595.3	1648.0	1427.4	<.01
≤1890 min/wk	45 (66.2%)	50 (67.6%)	119 (67.2%)	5001 (75.6%)	.01
>1890 min/wk	23 (33.8%)	24 (32.4%)	58 (32.8%)	1617 (24.4%)	

Values are expressed as mean ± SD for continuous variables and n (%) for categoric variables. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index; WC, waist circumference.

Table 2. Baseline Characteristics by Baseline Sedentary Time Category.

Total (n = 6795)	ST ≤1890 min/wk (n = 5120)	ST >1890 min/wk (n = 1675)	Within-Variable *P* Value
Demographics			
Age (y)	61.31 ± 10.10	64.71 ± 10.21	<.01
Male	2624 (51.25%)	965 (57.61%)	<.01
Income ≥ $40,000	2568 (50.16%)	662 (39.52%)	<.01
Education ≥ bachelor's	1879 (36.70%)	513 (30.63%)	<.01
Race/ethnicity			
White	1991 (38.89%)	624 (37.25%)	<.01
Black	1230 (24.02%)	651 (38.87%)	
Hispanic	1209 (23.61%)	286 (17.07%)	
Chinese	690 (13.48%)	114 (6.81%)	
Clinical characteristics			
Heart rate (beats/min)	62.65 ± 9.53	64.60 ± 9.86	<.01
BMI (kg/m^2)	28.06 ± 5.28	29.15 ± 5.77	<.01
WC (cm)	97.27 ± 15.00	100.87 ± 14.98	<.01
Hypertension	2,138 (41.76%)	907 (54.15%)	<.01
Metabolic syndrome	1,731 (33.90%)	712 (42.63%)	<.01
Diabetes	539 (10.54%)	232 (13.86%)	<.01
Current smoking	605 (11.82%)	282 (16.84%)	<.01
Heart failure outcome			
Overall heart failure	119 (2.32%)	58 (3.46%)	.01
HFpEF	50 (0.99%)	24 (1.46%)	.11
HFrEF	45 (0.89%)	23 (1.40%)	.07
Unknown EF	24 (0.47%)	11 (0.66%)	.35

Values are expressed as mean ± SD for continuous variables and n (%) for categoric variables. Abbreviations as in Table 1.

to the HFpEF and HFrEF groups separately revealed no significant relationships for either group in any model.

Discussion

In this study, a statistically significant relationship between a higher amount of baseline ST and risk of HFpEF was observed. In addition, this relationship remained significant when demographics, several traditional risk factors, intentional exercise, and adiposity measures were added to the model. Furthermore, for every hour of increased weekly ST, a significant 3% increased risk of HFpEF was observed. Borderline significance was observed for overall HF, but this was attenuated after further adjustment, and no association between ST and risk of HFrEF was detected in any of the models.

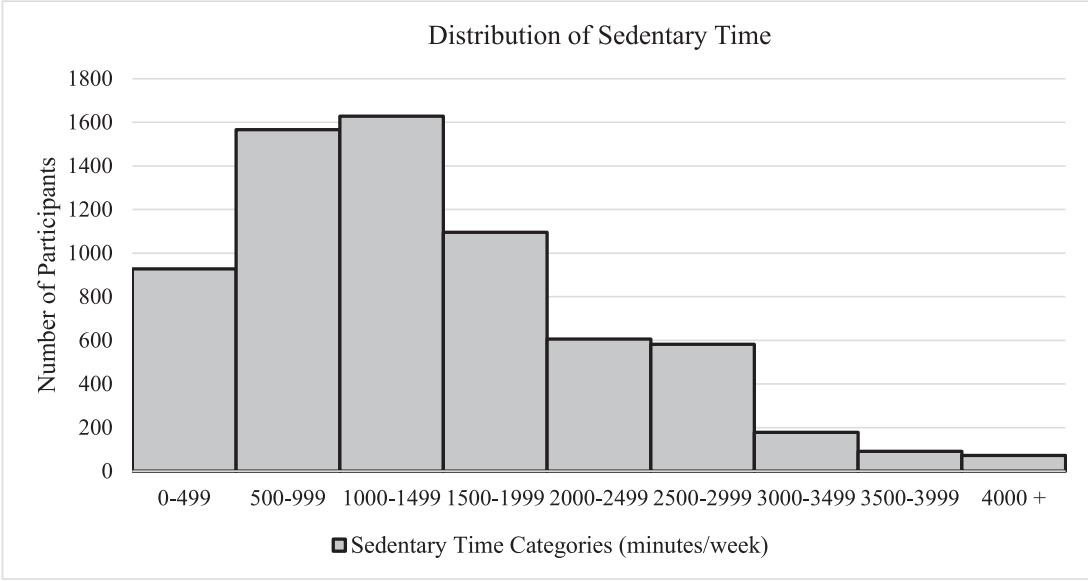

Fig. 1. Distribution of self-reported weekly sedentary time in minutes per week for the study sample at baseline.

Table 3. Hazard Ratios Associated With Sedentary Time (ST) >1890 min/wk and Risk of Incident HF

	Overall HF (n = 178)		HFpEF (n = 74)		HFrEF (n = 69)	
Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
1	1.38 (1.00−1.89)	.05	1.87 (1.13−3.09)	.01	1.30 (0.78−2.15)	.32
2	1.28 (0.92−1.79)	.14	1.84 (1.07−3.14)	.03	1.24 (0.73−2.12)	.42
3	1.25 (0.89−1.74)	.20	1.90 (1.09−3.30)	.02	1.15 (0.66−2.00)	.62
4	1.25 (0.90−1.75)	.19	1.92 (1.10−3.36)	.02	1.15 (0.66−2.00)	.63
5	1.25 (0.89−1.75)	.20	2.16 (1.23−3.78)	<.01	1.20 (0.64−2.23)	.57
6	1.23 (0.88−1.72)	.24	2.17 (1.24−3.80)	<.01	1.18 (0.65−2.15)	.58
Per 60 min ST	1.01 (1.00−1.02)	.28	1.03 (1.01−1.05)	<.01	1.01 (0.99−1.02)	.57

Model 1: unadjusted; model 2: adjusted for age, sex, and race; model 3: model 2 additionally adjusted for smoking, hypertension, diabetes, and metabolic syndrome; model 4: model 3 additionally adjusted for physical activity (metabolic equivalents); model 5: model 4 additionally adjusted for waist circumference; model 6: model 4 additionally adjusted for body mass index; per 60 min ST: adjusted for all variables in model 5. HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 1.

Several studies have found an association between higher volumes of ST and increased risk of overall HF,[20,21] but the relationship between ST and the HF subtypes was previously unexplored. Recently, a study by Pandey et al[12] demonstrated an inverse dose-response relationship between leisure-time PA and risk of overall HF and HFpEF, but not HFrEF. The authors suggested that this association is likely due in part to difference in the pathophysiology of HFpEF and HFrEF. Because lower amounts of ST, independently from PA, are also associated with lower cardiovascular risk,[19] this rationale could also potentially explain the relationship between HFpEF and ST.

The etiology of HFpEF is likely inflammatory. The risk factors and comorbidities associated with HFpEF are all highly associated with proinflammatory and high oxidative stress states, specifically, obesity, diabetes, chronic obstructive pulmonary disease, hypertension, and chronic kidney disease. ST has been shown to be associated with chronic systemic inflammation. Henson et al[29] reported that in 558 men and women at high risk of developing diabetes type 2, markers of inflammation, such as C-reactive protein (CRP), interleukin-6 (IL-6), and leptin, were significantly increased. CRP, IL-6, leptin, and others were associated with self-reported ST in women but not in men in a sample of 505 adults, mostly of white European and South-Asian ethnicity, being screened for diabetes.[30] Falconer et al[31] found in 285 adults with newly diagnosed type 2 diabetes that levels of IL-6 were associated with ST and that levels of CRP, though not associated with ST at baseline, were improved with reductions in ST in women. DuBrock et al[32] found CRP to be significantly elevated in patients with HFpEF and increasingly so for each additional comorbidity.

Systemic inflammation is associated with many clinically meaningful outcomes. In a prospective registry study, mortality was predicted by CRP. Furthermore, CRP added prognostic value to N-terminal pro−B-type natriuretic peptide, which is widely viewed as among the most important biomarkers in HF. Inflammation is also associated with acute decompensation in patients with HFpEF.[33] Importantly, Paulus et al[14] proposed that the mechanism of HFpEF results from systemic inflammation causing local cardiac dysfunction mediated by endothelial injury.

Therefore, the role of inflammation in both HFpEF and ST may also explain why, in the present study, ST was associated only with HFpEF and not with HFrEF.

This study adds to the literature by characterizing, for the first time, the positive relationship between ST and risk of HFpEF, independently from intentional exercise and adiposity. This study suggests that spending >4.5 h/d sedentary, regardless of intentional exercise or adiposity, significantly increases risk of HFpEF but not of HFrEF. Reducing ST, along with increasing PA, should be emphasized to prevent the development of HFpEF and should be a therapeutic target to potentially prevent the pathologic progression of HFpEF. Future studies should investigate ST objectively and seek to establish a target goal for ST recommendations for this population.

This study was not without limitations. The use of self-reported baseline ST is subject to recall and self-report bias. However, in a cohort of older adults, total ST by self-report had good reliability and modest validity and was responsive to change.[34] The time to the first HF event was used to establish incident HF, and EF was established at the time of initial diagnosis, so subsequent HF events by the same participant or changes in EF measurement over time were not included in the analysis. Similarly, only baseline ST and PA were examined for all participants, so changes in behavior over the time of the study could not be taken into consideration for risk determination. In addition, individuals with unknown EF data were excluded from the main analysis and a sensitivity analysis conducted adding the 35 unknown EF cases to each of the HFpEF and HFrEF groups resulted in insignificant results for both groups. It should also be noted that models 3−6 should be considered as exploratory owing to the number of variables in the models in relation to the size of the groups, and the results should therefore be interpreted as such. However, some data suggests this rule of thumb may be overly conservative.[35]

In conclusion, this study suggests that ST is positively associated with the cumulative risk of HFpEF. This relationship is independent from demographics, common risk factors, intentional exercise, and adiposity measures. This identifies a potential area of intervention for preventing HFpEF and adds to the evidence of HFpEF and HFrEF having separate causal pathways and risk factors.

Disclosures: None.

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