JACC: HEART FAILURE
VOL. 5, NO. 5, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2017.02.002

Physical Activity, Obesity, and Subclinical Myocardial Damage

Roberta Florido, MD,[a] Chiadi E. Ndumele, MD, MHS,[a,b] Lucia Kwak, MS,[b] Yuanjie Pang, ScM,[b] Kunihiro Matsushita, MD, PhD,[b] Jennifer A. Schrack, PhD,[b] Mariana Lazo, MD, PhD,[b,c] Vijay Nambi, MD, PhD,[d,e] Roger S. Blumenthal, MD,[a] Aaron R. Folsom, MD, MPH,[f] Josef Coresh, MD, PhD,[b] Christie M. Ballantyne, MD,[e] Elizabeth Selvin, PhD, MPH[b]

ABSTRACT

OBJECTIVES This study sought to evaluate the association of physical activity with chronic myocardial damage, assessed by elevated high-sensitivity cardiac troponin T (hs-cTnT), in individuals with and without obesity.

BACKGROUND Physical activity is associated with reduced risk of heart failure (HF), particularly among obese people. The role of chronic myocardial damage in this association is uncertain.

METHODS We studied 9,427 participants in the Atherosclerosis Risk in Communities Study without cardiovascular disease, with body mass index >18.5 kg/m^2. Physical activity was categorized per American Heart Association guidelines as recommended, intermediate, or poor. We evaluated cross-sectional associations of physical activity and obesity with elevated hs-cTnT (≥14 ng/l). In prospective analyses, we quantified the association of elevated hs-cTnT with HF risk within cross-categories of baseline physical activity and obesity.

RESULTS People with poor physical activity were more likely to have elevated hs-cTnT than those with recommended levels (odds ratio [OR]: 1.39; 95% confidence interval [CI]: 1.15 to 1.68). In cross-categories of physical activity and obesity, using the non-obese/recommended activity group as the reference, individuals with obesity and poor activity were most likely to have elevated hs-cTnT (OR: 2.46; 95% CI: 1.91 to 3.19), whereas the obese/recommended activity group had a weaker association (OR: 1.68; 95% CI: 1.28 to 2.21; $p < 0.001$ for interaction between physical activity and obesity). In prospective analyses, elevated hs-cTnT was strongly associated ($p < 0.001$) with incident HF in all obesity/physical activity cross-categories ($p > 0.20$ for interaction).

CONCLUSIONS Physical activity is inversely associated with chronic subclinical myocardial damage. Physical activity might lessen the association between obesity and subclinical myocardial damage, which could represent a mechanism by which physical activity reduces HF risk. (J Am Coll Cardiol HF 2017;5:377–84) © 2017 by the American College of Cardiology Foundation.

From the [a]Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland; [b]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [c]Department of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [d]Michael E. DeBakey Veterans Affairs Hospital, Houston, Texas; [e]Division of Atherosclerosis and Vascular Medicine, Baylor College of Medicine, and Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart and Vascular Center, Houston, Texas; and the [f]Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs. ARIC is conducted as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). This work was supported by a Robert Wood Johnson Amos Medical Faculty Development Award and a National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute grant (K23HL12247) awarded to Dr. Ndumele and by an NIH/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant (R01DK089174) awarded to Dr. Selvin. Dr. Selvin was also supported by NIH/NIDDK grant K24DK106414. Dr. Schrack is a consultant for EMD Serono Research & Development Institute, Inc. Dr. Nambi has served as an event adjudicator for a study sponsored by Siemens to evaluate a new high-sensitivity troponin assay. Drs. Selvin and Ballantyne have served on an advisory board for Roche Diagnostics. Drs. Ballantyne and Nambi, along with Roche and Baylor College of Medicine, have filed a provisional patent (patent #61721475) entitled "Biomarkers to Improve Prediction of Heart Failure Risk." All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 21, 2016; revised manuscript received February 1, 2017, accepted February 1, 2017.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CI = confidence interval

CVD = cardiovascular disease

eGFR = estimated glomerular filtration rate

HDL = high-density lipoprotein

HF = heart failure

HR = hazard ratio

hs-CRP = high-sensitivity C-reactive protein

hs-cTnT = high-sensitivity cardiac troponin T

METs = metabolic equivalents of task

NT-proBNP = N-terminal pro-B-type natriuretic peptide

OR = odds ratio

SBP = systolic blood pressure

Physical activity is widely appreciated as a key component of strategies to reduce risk of heart failure (HF) (1). Physical activity has been linked to a lower likelihood of HF among people with obesity, a group at particularly elevated risk of HF (2,3). Notably, the reduced HF risk associated with physical activity among people with obesity is not fully explained by traditional risk factors for cardiovascular disease (CVD), which suggests the protective association of physical activity against HF might be mediated in part through nontraditional mechanisms.

Obesity has potent associations with abnormalities of myocardial structure and function and subsequent HF (4) via unclear pathways (5). An increasingly appreciated risk factor for the development of HF is subclinical myocardial damage, as reflected by levels of cardiac troponin T measured with novel high-sensitivity assays (hs-cTnT) (6,7). Indeed, among individuals without prior CVD, obesity has been independently linked to elevated hs-cTnT levels, and the combination of obesity and elevated hs-cTnT is associated with markedly increased HF risk (8). It is presently unknown whether higher physical activity is associated with lower levels of subclinical myocardial damage in the presence or absence of obesity. Decreased myocardial damage could represent a pathway by which physical activity is related to lower HF risk.

SEE PAGE 385

We therefore tested the hypothesis that physical activity has an inverse association with elevated hs-cTnT in a community-based population of men and women without clinical CVD and that higher physical activity lessens the association between obesity and subclinical myocardial damage. To evaluate the clinical importance of these associations, we also assessed the link between elevated hs-cTnT and subsequent HF risk within groups defined by physical activity and obesity status.

METHODS

STUDY POPULATION. The ARIC (Atherosclerosis Risk In Community) study is a multicenter, prospective, observational cohort investigation of CVD and related conditions in middle-aged men and women. The study design has been described previously (9). Briefly, a total of 15,792 people age 45 to 64 years were enrolled between 1987 and 1989 from 4 US communities. Participants were examined at baseline, at 3 subsequent visits that occurred approximately every 3 years, and at a fifth visit conducted from 2011 to 2013. Physical activity was assessed in all participants at visit 3 (1993 to 1995), whereas measurements of hs-cTnT were obtained for all participants at visit 4 (1996 to 1998). We therefore performed nonconcurrent cross-sectional analyses evaluating the associations of physical activity and obesity status at visit 3 with prevalent hs-cTnT levels at visit 4. In prospective analyses, we additionally assessed the risk of incident HF associated with elevated hs-cTnT within cross-categories of physical activity and obesity.

Of 12,887 individuals who attended visit 3, a total of 9,427 were eligible for this study. We excluded individuals for whom data were missing on physical activity or body mass index (BMI) at visit 3 (n = 40) or on hs-cTnT at visit 4 (n = 1,796); those with self-reported CVD, a CVD clinical event (HF or coronary heart disease, including coronary revascularization procedures), or silent myocardial infarction at or before visit 4 (n = 1,492); those not of black or white race (n = 38); and those with a BMI <18.5 kg/m^2 (n = 94). All participants provided informed consent, and the study protocol was approved by the institutional review boards at each study site.

MEASUREMENT OF STUDY VARIABLES. The primary exposure was physical activity, measured through a modified Baecke questionnaire (10) at visit 3 (1993 to 1995). The questionnaire asked questions on participation in up to 4 sports or exercise physical activity within the previous year and the number of hours per week and months per year spent on each sport. As has been done in prior ARIC analyses (11,12), we converted the Baecke sports indices into minutes per week of moderate or vigorous exercise. Each activity was converted into metabolic equivalents of task (METs) based on the Compendium of Physical Activities. Moderate activities were defined as those involving a workload of 3 to 6 METs, and vigorous activities were those involving a workload of >6 METs. We subsequently categorized physical activity according to the American Heart Association guidelines as recommended (≥75 min/week of vigorous intensity or ≥150 min/week of any combination of moderate and vigorous intensity), intermediate (1 to 74 min/week of vigorous intensity or 1 to 149 min/week of any combination of moderate and vigorous intensity), or poor (0 min/week of moderate or vigorous exercise) (13). We also modeled physical activity as a continuous variable in MET × min/week and used this continuous variable to generate quartiles of physical activity.

BMI was calculated from measured height and weight at visit 3 and categorized as non-obese

(BMI 18.5 to <30 kg/m^2) or obese (BMI ≥30 kg/m^2). Information on additional covariates of interest was obtained through history, physical examination, and laboratory data at visit 3. Smoking status was categorized as current or noncurrent smoker, and alcohol consumption was quantified in grams per week. Diabetes mellitus was defined as fasting glucose ≥126 mg/dl, nonfasting glucose ≥200 mg/dl, self-reported history of diabetes mellitus, or use of hypoglycemic agents. Systolic blood pressure (SBP) was measured 3 times, and the mean of the second and third measurements was used for analyses.

Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured with standardized enzymatic assays. Renal function was assessed by use of the estimated glomerular filtration rate (eGFR) calculated based on serum creatinine at visit 4 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (14). N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hs-CRP) were measured from plasma collected at visit 4 and frozen at −80°C.

The primary outcome in cross-sectional analyses was elevated hs-cTnT, defined as a level ≥14 ng/l, a cutpoint that has been used in several prior analyses (6,7). Hs-cTnT levels were measured in 2011 from visit 4 plasma samples that had been stored at −80°C, using a high-sensitivity assay (Elecsys troponin T, Roche Diagnostics, Indianapolis, Indiana). As reported previously, the reliability coefficient for hs-cTnT measurements among the ARIC study participants was 0.94 (15). The between-assay coefficient of variation for control materials was 6.9% for mean hs-cTnT concentrations of 29 ng/l.

INCIDENT HF. In prospective analyses, the outcome of interest was incident HF, defined as the first hospitalization or death related to HF. HF deaths were identified by hospital discharge codes and death certificates, with International Classification of Diseases-9th Revision code 428 used to identify hospitalizations and deaths early in follow-up and International Classification of Diseases-10th Revision code I-50 used for HF deaths in later follow-up. Information on hospitalizations was obtained from participants via yearly telephone calls, and vital records were examined for all deaths. HF events occurring from 2005 onward were additionally adjudicated by an expert panel (16).

STATISTICAL ANALYSIS. We used multivariable logistic regression models to evaluate the adjusted associations of physical activity categories with myocardial damage, as assessed by elevated hs-cTnT. We used the highest ("recommended") physical activity category (individuals performing ≥75 min/week of vigorous-intensity activity or ≥150 min/week of any combination of moderate- and vigorous-intensity exercise physical activity) as the reference group. We constructed 2 models, one with confounders and a second that also included potential mediators of the effects of physical activity on subclinical myocardial damage. Model 1 included age, sex, race, smoking status, and alcohol intake. Model 2 included all variables from model 1 plus SBP, antihypertensive medication use, diabetes mellitus, total cholesterol, HDL cholesterol, and triglycerides. We constructed a third adjustment model that included the variables in model 2 and additional predictors of future HF, such as heart rate, eGFR, NT-proBNP, and hs-CRP. Covariates were selected a priori based on previously published data and known risk factors for HF. We conducted sensitivity analyses with physical activity modeled as quartiles. We additionally evaluated the continuous association of physical activity (in MET × min/week) with elevated hs-cTnT by scaling per 1 SD and constructing restricted cubic spline models. We tested for multiplicative interactions with age (≥ or <65 years), race, and sex on the association between physical activity and hs-cTnT.

To evaluate the association between physical activity and hs-cTnT in the presence and absence of obesity, we conducted analyses stratified by obesity status (non-obese and obese) using regression models that included the same covariates outlined above. We also created cross-categories of physical activity (recommended, intermediate, poor) and obesity status (non-obese, obese) to assess the combined association of these 2 exposure variables with elevated hs-cTnT, using a common reference group of non-obese individuals with recommended physical activity. We performed additional analyses using abdominal obesity, defined by World Health Organization criteria as a waist circumference ≥88 cm for women and ≥102 cm for men, as an alternative measure of adiposity.

In prospective analyses, the baseline was ARIC visit 4 (the time point of hs-cTnT measurement), with follow-up for incident HF through December 31, 2012. We constructed Poisson and Cox proportional hazards regression models, with adjustment for covariates at visit 3, to estimate the adjusted incidence rates and hazard ratios (HRs) with associated 95% confidence intervals (CIs) for incident HF within each cross-category of physical activity and obesity. To evaluate the clinical implications of the associations of physical activity and obesity with elevated hs-cTnT, we then constructed regression models to estimate the incidence rates and HRs for HF associated with

TABLE 1 Characteristics of Study Population According to Physical Activity Categories at Baseline: The ARIC Study (1993 to 1995)

	Physical Activity Category			
	Recommended (n = 4,043) (43%)	Intermediate (n = 2,178) (23%)	Poor (n = 3,206) (34%)	p Value
Age, yrs	60.6 ± 5.8	60.0 ± 5.6	59.6 ± 5.5	<0.0001
Female, %	51.8	65.0	60.5	<0.0001
African American, %	15.2	20.8	28.6	<0.0001
Current smoker, %	12.5	14.6	21.0	<0.0001
Alcohol intake, g/week	42.0 (90.7)	37.4 (94.8)	37.9 (116.0)	0.13
Antihypertensive medications, %	29.1	31.4	34.9	<0.0001
SBP, mm Hg	122.3 ± 17.5	123.2 ± 18.4	125.1 ± 19.0	<0.0001
Diabetes, %	10.2	13.0	15.1	<0.0001
HDL cholesterol, mg/dl	53.7 ± 18.4	54.2 ± 18.7	51.7 ± 17.0	<0.0001
Total cholesterol, mg/dl	207.2 ± 37.0	209.4 ± 37.1	207.5 ± 37.4	0.06
Triglycerides, mg/dl	137.4 ± 93.9	139.5 ± 78.9	141.3 ± 83.5	0.16
BMI, kg/m^2	27.5 ± 4.6	28.5 ± 5.1	29.4 ± 6.0	<0.0001
Heart rate, beats per min	64.2 ± 9.5	66.0 ± 9.6	66.4 ± 9.8	<0.0001
eGFR, ml/min/1.73 m^2	85.7 ± 14.5	86.6 ± 15.8	87.9 ± 16.5	<0.0001
NT-proBNP, pg/ml	155.5 ± 3019.2	128.3 ± 532.0	113.9 ± 368.0	0.67
hs-CRP, mg/l	3.7 ± 6.0	4.2 ± 5.7	5.2 ± 7.5	<0.0001

Values are mean ± SD, or n (%). Physical activity categories defined as follows: poor (0 min/week moderate or vigorous), intermediate (1 to 74 min/week of vigorous or 1 to 149 min/week of moderate and vigorous), and recommended (≥75 min/week of vigorous or ≥150 min/week of moderate and vigorous).

BMI = body mass index; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure.

elevated hs-cTnT within each of the cross-categories of physical activity and obesity status. We created an interaction term and performed likelihood ratio tests to test for heterogeneity in the associations between elevated hs-cTnT and incident HF across the cross-categories.

Statistical analyses were performed with Stata version 13.1. All p values presented are 2-sided.

RESULTS

Characteristics of the study population according to physical activity categories are presented in Table 1.

TABLE 2 ORs (95% CIs) for Elevated hs-cTnT Associated With Lower Physical Activity Categories

	Physical Activity Category			
	Recommended (n = 4,043)	Intermediate (n = 2,178)	Poor (n = 3,206)	p Value for Trend*
Model 1	Ref. (1)	1.34† (1.08–1.66)	1.39† (1.15–1.68)	<0.001
Model 2	Ref. (1)	1.25 (1.00–1.57)	1.31† (1.08–1.59)	0.001
Model 3	Ref. (1)	1.15 (0.91–1.45)	1.21 (0.99–1.49)	0.02

Model 1: adjusted for age, race, sex, smoking status, and alcohol use. Model 2: adjusted for model 1 plus SBP, antihypertensive medication use, diabetes, total cholesterol, HDL cholesterol, and triglycerides. Model 3: adjusted for model 2 plus heart rate, eGFR, NT-proBNP, and hs-CRP. *Calculated using continuous physical activity, in METs (metabolic equivalents of task) × min per week. †Statistically significant.

CI = confidence interval; hs-cTnT = high-sensitivity cardiac troponin T; OR = odds ratio.

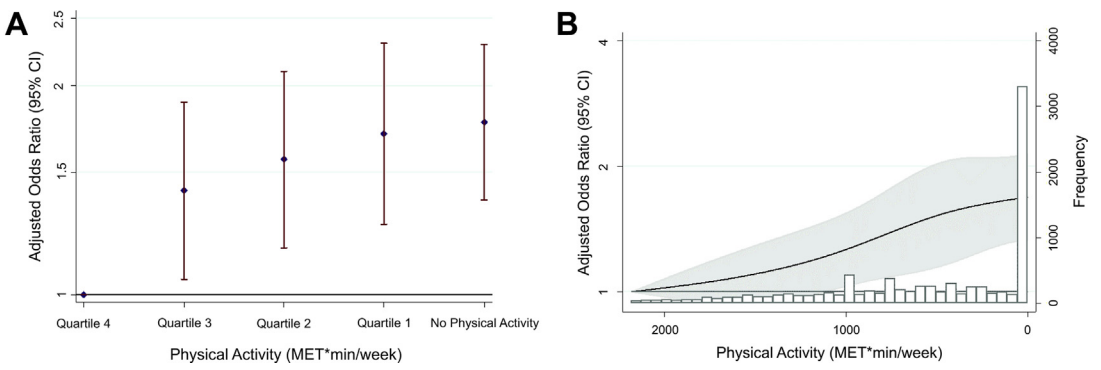
Physical activity categories were fairly evenly distributed across the study population, with 43% of individuals reporting recommended, 23% intermediate, and 34% poor levels of physical activity. Among those with and without obesity, 33% and 47%, respectively, performed recommended levels of physical activity. Compared with those with recommended physical activity, participants with lower levels of physical activity were more likely to be women, African-Americans, and current smokers and had higher SBP, prevalence of diabetes, and BMI. Lower physical activity was also associated with lower HDL cholesterol levels and higher heart rate, eGFR, and hs-CRP. There were no significant differences in NT-proBNP levels across categories of physical activity.

Within the study population, 7.2% of individuals had elevated hs-cTnT levels. The prevalence of elevated hs-cTnT increased with lower physical activity levels, being found among 6.8%, 7.0%, and 7.7% of individuals with recommended, intermediate, and poor activity levels, respectively.

In logistic regression analyses, lower categories of physical activity were associated with significantly higher odds of subclinical myocardial damage. Relative to those with recommended physical activity levels, people with poor physical activity were more likely to have elevated hs-cTnT (odds ratio [OR]: 1.39; 95% CI: 1.15 to 1.68) after adjustment for confounders (Table 2). Notably, a significant inverse association between physical activity and elevated hs-cTnT remained after additional adjustment for several potential CVD mediators (OR: 1.31; 95% CI: 1.08 to 1.59) (Table 2). We noted similar trends, although of only borderline statistical significance, after additional adjustment for heart rate, eGFR, NT-proBNP, and hs-CRP (OR: 1.21; 95% CI: 0.99 to 1.49) (Table 2). When physical activity was modeled continuously, its association with elevated hs-cTnT remained significant (p = 0.02). In analyses that modeled physical activity as quartiles, we observed a significant association between lower physical activity quartiles and a higher likelihood of myocardial damage (Figure 1A). A graded association between lower levels of physical activity and higher odds of subclinical myocardial damage was also demonstrated in restricted cubic spline models (Figure 1B). Results were similar across age, race, and sex subgroups, with no significant interaction between physical activity and these demographic variables on the outcome of elevated hs-cTnT.

We found similar results in analyses stratified by obesity status. A significant inverse relationship was observed between physical activity modeled continuously and elevated hs-cTnT among both obese (p = 0.01) and non-obese (p = 0.02) participants.

FIGURE 1 Association of Physical Activity With Elevated High-Sensitivity Cardiac Troponin T



(A) Association of quartiles of physical activity with odds ratios and 95% confidence intervals (CI) for elevated high-sensitivity cardiac troponin T. Reference: Quartile 4: ≥1,365.9 MET × min/week. Adjusted for age, race, sex, smoking status, and alcohol use. Cutpoints for quartiles of physical activity: Quartile 1: 0 to 453.6 MET × min/week; quartile 2: 453.6 to 846.3 MET × min/week; quartile 3: 846.3 to 1364.9 MET × min/week; and quartile 4: ≥1,365.9 MET × min/week. **(B)** Continuous association between physical activity and elevated high-sensitivity cardiac troponin T among participants without clinical cardiovascular disease in restricted cubic spline models. Reference: 95th percentile, 2,182 MET × min/week. *Adjusted for age, race, sex, smoking status, and alcohol use. MET = metabolic equivalents of task.

Each 1-SD lower physical activity level (781 MET × min/week) was significantly associated with a higher likelihood of elevated hs-cTnT both in people who were obese (OR: 1.22; 95% CI: 1.05 to 1.42) and those who were non-obese (OR: 1.14; 95% CI: 1.02 to 1.27).

In analyses evaluating the association of cross-categories of physical activity and obesity status with elevated hs-cTnT after adjustment for confounders (Table 3), using the non-obese and recommended activity group as the reference, we found that individuals in the obese and poor physical activity group were most likely to have elevated hs-cTnT (OR: 2.46; 95% CI: 1.91 to 3.19). However, the combination of obesity and recommended physical activity levels had a weaker association with elevated hs-cTnT (OR: 1.68; 95% CI: 1.28 to 2.21). After further adjustment for CVD mediators (Table 3), the combination of obesity and recommended physical activity levels was no longer significantly associated with elevated hs-cTnT (OR: 1.20; 95% CI: 0.90 to 1.61). Similar trends were noted after additional adjustment for heart rate, eGFR, NT-proBNP, and hs-CRP (Table 3). Notably, a statistically significant interaction between physical activity and obesity on the outcomes of hs-cTnT was seen in all models. Analogous patterns were seen when waist circumference, categorized with World Health Organization criteria for abdominal obesity, was used as an alternative metric for adiposity (Online Table 1).

In prospective analyses, we evaluated the association between elevated hs-cTnT and subsequent HF risk within each cross-category of physical activity and obesity status. Over a median 15 years of follow-up, there were 1,178 HF events in the study population. As shown in Online Table 2, the adjusted incidence rate for HF (per thousand person-years) was lowest in the subgroup who were not obese and who had recommended activity levels (5.75), whereas the highest rates were seen in the obese and poor activity subgroup (14.09). A similar pattern was seen in Cox regression

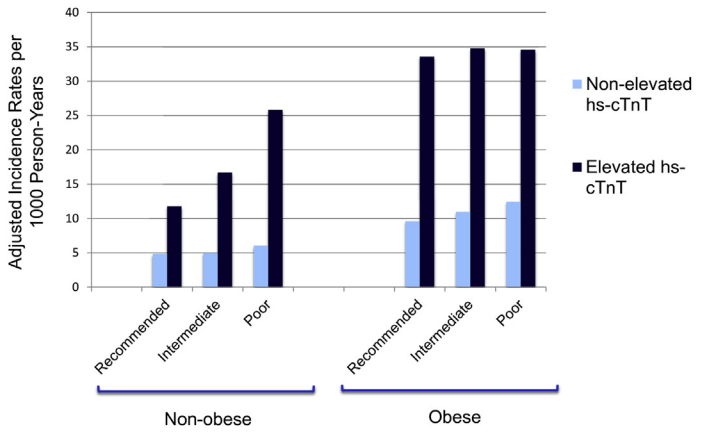
TABLE 3 Adjusted ORs* (95% CIs) for Elevated hs-cTnT According to Cross-Categories of Physical Activity and Obesity Status at Baseline

	Recommended	Intermediate	Poor	p Value for Trend*	p Value for Interaction†
Model 1					
Non-obese	1.00 (Ref. (1)) n = 3,043	1.22 (0.92–1.62) n = 1,459	1.20 (0.93–1.54) n = 1,935	0.02	<0.001
Obese	1.68‡ (1.28–2.21) n = 1,000	2.37‡ (1.74–3.23) n = 719	2.46‡ (1.91–3.19) n = 1,271	0.01	
Model 2					
Non-obese	1.00 (Ref. (1)) n = 3,043	1.17 (0.88–1.55) n = 1,459	1.18 (0.91–1.52) n = 1,935	0.03	0.011
Obese	1.20 (0.90–1.61) n = 1,000	1.66‡ (1.20–2.29) n = 719	1.73‡ (1.32–2.27) n = 1,271	0.01	
Model 3					
Non-obese	1.00 (Ref. (1)) n = 3,043	0.99 (0.73–1.34) n = 1,459	1.03 (0.79–1.35) n = 1,935	0.32	0.003
Obese	1.11 (0.81–1.49) n = 1,000	1.56‡ (1.11–2.18) n = 719	1.63‡ (1.23–2.15) n = 1,271	0.01	

Using a common reference group of non-obese with poor physical activity. Non-obese: BMI 18.5 to <30 kg/m^2; obese: ≥30 kg/m^2. Model 1: adjusted for age, race, sex, smoking status, and alcohol use. Model 2: adjusted for model 1 variables plus SBP, antihypertensive medication use, diabetes, total cholesterol, HDL cholesterol, and triglycerides. Model 3: adjusted for model 2 plus heart rate, eGFR, NT-proBNP, and hs-CRP. *Calculated with continuous physical activity, in MET × min/week. †Interaction term across cross-categories calculated with likelihood ratio tests. ‡Statistically significant.

Abbreviations as in Tables 1 and 2.

FIGURE 2 Adjusted Incidence Rates for Incident HF Associated With Elevated and Nonelevated hs-cTnT Within Each Cross-Category of Physical Activity and Obesity Status



The p values for the incidence rate difference between elevated and nonelevated high-sensitivity cardiac troponin T (hs-cTnT) within each obesity-physical activity cross-category were <0.001 for all groups. HF = heart failure.

analyses (Online Figure 1), with the highest HF risk among the cross-categories seen for those with obesity and poor activity (HR: 2.55; 95% CI: 2.14 to 3.04).

Within each cross-category of physical activity and obesity status, the presence of elevated hs-cTnT was strongly associated with higher incidence rates for HF relative to nonelevated hs-cTnT (**Figure 2**). Analogously, in multivariable Cox regression analyses, elevated hs-cTnT was strongly associated with significantly increased HF risk compared with nonelevated hs-cTnT within each obesity-physical activity cross-category (Online Table 3). A test for an interaction in the association between elevated hs-cTnT and incident HF across the cross-categories was not significant (p for interaction = 0.21). Among those with obesity and poor physical activity (the subgroup with the highest likelihood of myocardial damage), elevated hs-cTnT was associated with a 3-fold higher risk of HF compared with nonelevated hs-cTnT (HR: 3.19; 95% CI: 2.28 to 4.47).

DISCUSSION

In this analysis of a biracial community-based sample of men and women without a history of CVD at baseline, we found that physical activity was inversely associated with chronic subclinical myocardial damage, as assessed by elevated hs-cTnT levels. This association was seen among individuals with and without obesity. Findings were consistent across demographic subgroups. When we examined cross-categories of physical activity and obesity status, those with recommended physical activity levels and without obesity had the lowest likelihood of subclinical myocardial damage, whereas those with poor activity levels and obesity were most likely to have myocardial damage. Importantly, our results also suggest that recommended physical activity levels might lessen the association between obesity and myocardial damage. Furthermore, the presence of subclinical myocardial damage was significantly and similarly associated with incident HF within each cross-category of physical activity and obesity. The protective association of physical activity against subclinical myocardial damage could have implications for HF risk reduction, particularly among the high-risk group of individuals with excess weight.

Subclinical myocardial damage, as reflected by hs-cTnT, is increasingly appreciated as a potent risk factor for the development of HF (6,7). In prior work, obesity has been linked to elevated hs-cTnT, and those individuals with both obesity and elevated hs-cTnT had a 9-fold higher risk of future HF than individuals with normal weight and undetectable hs-cTnT (8). Although a prior study in an elderly population demonstrated an association between greater physical activity and lower hs-cTnT levels (17), there are limited data regarding how combinations of physical activity and obesity influence the likelihood of subclinical myocardial damage. The present study extends prior work by showing a graded inverse association between physical activity and hs-cTnT in a population that includes both middle-aged and elderly adults in the general community. Furthermore, we found a statistically significant interaction between physical activity and obesity on myocardial damage, which indicates that this protective association might be stronger among individuals with obesity, a group at particularly high risk for future HF.

In the current study, the association between higher physical activity and a lower likelihood of elevated hs-cTnT was seen even after accounting for traditional CVD mediators but was attenuated after adjustment for additional predictors of HF, including hs-CRP. This suggests the associations of physical inactivity with myocardial damage might be related to pathways beyond the effects of physical activity on risk factor levels, which might include decreased inflammation (18). The mechanisms by which physical activity might lead to less myocardial damage are incompletely understood. Laboratory studies have shown modulatory effects of physical activity on several myocellular defense mechanisms, with improved cardiac antioxidant capacity and mitochondrial respiratory function, ultimately leading to

improved myocardial tolerance to noxious stimuli (19,20). Physical activity also has favorable effects on cardiac structure and function (21). Further investigation will be needed to understand whether these and other pathways mediate the association between physical inactivity and myocardial damage.

CLINICAL IMPLICATIONS. Our study has several important clinical implications. Given the high morbidity and mortality associated with HF, as well as its growing prevalence, there is an emerging focus on the early detection of high-risk individuals, such as those with obesity, who would benefit the most from targeted prevention strategies (13). Given prior data demonstrating a potent association between obesity and incident HF that is unlikely to be addressed solely by controlling adiposity-associated cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia (22), promoting increased physical activity could be a particularly important strategy for HF risk reduction among individuals with obesity.

Additionally, a dose-response relationship between physical activity and myocardial damage was observed, with those individuals with American Heart Association–recommended levels of physical activity having a lower likelihood of elevated hs-cTnT than those with poor physical activity. However, only 43% of the study population performed guideline-recommended levels of physical activity, and this number was even lower among those with obesity (33%). Given the strong association of subclinical myocardial damage with incident HF, further studies should explore whether hs-cTnT might be used as a marker of cardiovascular health in association with changes in physical activity. This could be particularly relevant among people with obesity, a group known to have higher levels of subclinical myocardial damage and increased HF risk.

The present study does have certain limitations. Usual physical activity levels were assessed by a questionnaire at a single point in time. Self-reported activity levels are likely associated with some misclassification and might not fully capture the cumulative effect of regular physical activity on myocardial damage. Furthermore, we did not have information on fitness in the ARIC study. hs-cTnT was measured from stored blood samples, and degradation over time could have modestly affected the absolute values of hs-cTnT; however, given the high correlations observed in prior validity studies (15), relative measures of association should remain unbiased. The nonconcurrence of physical activity and hs-cTnT measurements is also a limitation, and we cannot establish temporality of the observed associations of physical activity with myocardial damage in this study. As with all observational studies, we cannot exclude the presence of residual confounding. Additionally, we cannot exclude possible false positive findings resulting from multiple testing in our multivariable analyses. Nonetheless, our findings within a large, well-characterized, community-based biracial cohort offer new insights regarding the interrelationship of physical activity and obesity with myocardial damage that are likely broadly generalizable.

CONCLUSIONS

In summary, among middle-aged and older adults without a history of clinical CVD, physical activity was inversely associated with subclinical myocardial damage. Additionally, higher physical activity might lessen the association between obesity and subclinical myocardial damage. These results could have important implications for HF prevention, particularly in people with obesity.

ACKNOWLEDGMENTS The authors thank the staff and participants of the ARIC study for their important contributions.

ADDRESS FOR CORRESPONDENCE: Dr. Elizabeth Selvin, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2024 East Monument Street, Suite 2-600, Baltimore, Maryland 21287. E-mail: eselvin@jhu.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Obesity and subclinical myocardial damage are important risk factors for heart failure. Physical activity is associated with lower risk of heart failure among both non-obese and obese individuals, through unknown mechanisms. In this analysis of ARIC, we found that physical activity was inversely associated with subclinical myocardial damage. Additionally, higher physical activity might lessen the association between obesity and subclinical myocardial damage. Given the strong association of hs-cTnT and heart failure, the current study supports promotion of physical activity as a key strategy for heart failure prevention, particularly among high-risk subgroups such as people with obesity.

TRANSLATIONAL OUTLOOK: Physical activity was inversely associated with subclinical myocardial damage among both non-obese and obese individuals, which could represent a mechanism by which physical activity reduces heart failure risk. Further research is needed to elucidate the mechanisms underlying the association of physical activity and heart failure.

REFERENCES

1. Pandey A, Garg S, Khunger M, et al. Dose-response relationship between physical activity and risk of heart failure: a meta-analysis. Circulation 2015;132:1786–94.

2. Hu G, Jousilahti P, Antikainen R, Katzmarzyk PT, Tuomilehto J. Joint effects of physical activity, body mass index, waist circumference, and waist-to-hip ratio on the risk of heart failure. Circulation 2010;121:237–44.

3. Kenchaiah S, Sesso HD, Gaziano JM. Body mass index and vigorous physical activity and the risk of heart failure among men. Circulation 2009;119:44–52.

4. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305–13.

5. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev 2008;88:389–419.

6. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494–502.

7. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367–76.

8. Ndumele CE, Coresh J, Lazo M, et al. Obesity, subclinical myocardial injury, and incident heart failure. J Am Coll Cardiol HF 2014;2:600–7.

9. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol 1989;129:687–702.

10. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36:936–42.

11. Autenrieth CS, Evenson KR, Yatsuya H, Shahar E, Baggett C, Rosamond WD. Association between physical activity and risk of stroke subtypes: the Atherosclerosis Risk in Communities study. Neuroepidemiology 2013;40:109–16.

12. Bell EJ, Lutsey PL, Windham BG, Folsom AR. Physical activity and cardiovascular disease in African Americans in Atherosclerosis Risk in Communities. Med Sci Sports Exerc 2013;45:901–7.

13. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in J Am Coll Cardiol 2014;63(Pt B):3027–8. J Am Coll Cardiol 2014;63:2960–84.

14. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate [published correction appears in Ann Intern Med 2011;155:408]. Ann Intern Med 2009;150:604–12.

15. Agarwal SK, Avery CL, Ballantyne CM, et al. Sources of variability in measurements of cardiac troponin T in a community-based sample: the Atherosclerosis Risk in Communities study. Clin Chem 2011;57:891–7.

16. Rosamond WD, Chang PP, Baggett C, et al. Classification of heart failure in the Atherosclerosis Risk in Communities (ARIC) study: a comparison of diagnostic criteria. Circ Heart Fail 2012;5:152–9.

17. deFilippi CR, de Lemos JA, Tkaczuk AT, et al. Physical activity, change in biomarkers of myocardial stress and injury, and subsequent heart failure risk in older adults. J Am Coll Cardiol 2012;60:2539–47.

18. Ertek S, Cicero A. Impact of physical activity on inflammation: effects on cardiovascular disease risk and other inflammatory conditions. Arch Med Sci 2012;8:794–804.

19. Ascensao A, Ferreira R, Magalhaes J. Exercise-induced cardioprotection: biochemical, morphological and functional evidence in whole tissue and isolated mitochondria. Int J Cardiol 2007;117:16–30.

20. Werner C, Hanhoun M, Widmann T, et al. Effects of physical exercise on myocardial telomere-regulating proteins, survival pathways, and apoptosis. J Am Coll Cardiol 2008;52:470–82.

21. Hegde SM, Goncalves A, Claggett B, et al. Cardiac structure and function and leisure-time physical activity in the elderly: The Atherosclerosis Risk in Communities Study. Eur Heart J 2016;37:2544–51.

22. Ndumele CE, Matsushita K, Lazo M, et al. Obesity and subtypes of incident cardiovascular disease. J Am Heart Assoc 2016;5:e003921.

KEY WORDS epidemiology, heart failure, obesity, physical activity, troponin T

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