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Accelerometer-Measured Sedentary Behavior and Risk of Future Cardiovascular Disease

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ABSTRACT

BACKGROUND Beyond serving as a marker for insufficient physical activity, sedentary behavior may directly affect future cardiovascular (CV) disease risk.

OBJECTIVES This study sought to examine associations between accelerometer-measured sedentary behavior with risk of specific CV outcomes, including potential relations with moderate to vigorous physical activity (MVPA).

METHODS Among participants of the UK Biobank prospective cohort study, we fit Cox models adjusted for demographic and lifestyle factors to assess associations between accelerometer-measured daily sedentary time with incident atrial fibrillation (AF), myocardial infarction (MI), heart failure (HF), and CV mortality. We assessed the potential effect of MVPA on associations between sedentary time and CV disease by including MVPA as an adjustment variable, as well as performing subgroup analyses stratified at the guideline-recommended MVPA threshold (ie, ≥150 min/wk). We then performed compositional analyses to estimate the effects of reallocating sedentary time to other activities.

RESULTS Among 89,530 individuals (age 62 ± 8 years, 56.4% women) undergoing 1 week of accelerometry, median sedentary time was 9.4 h/d (Q1-Q3: 8.2-10.6). In multivariable models, using the second quartile (8.2-9.4 h/d) as a referent, sedentary time in the top quartile (>10.6 h/d) was associated with greater risks of HF (HR: 1.45; 95% CI: 1.28-1.65) and CV mortality (HR: 1.62; 95% CI: 1.34-1.96), with an inflection of risk at 10.6 h/d. Higher sedentary time was also associated with greater risks of incident AF (HR: 1.11; 95% CI: 1.01-1.21) and MI (HR: 1.15; 95% CI: 1.00-1.32), with an approximately linear relation. Associations with HF and CV mortality persisted among individuals meeting guideline-recommended MVPA levels. Among individuals with >10.6 h/d of sedentary time, reallocating sedentary behavior to other activities substantially reduced the excess CV risk conferred by sedentary behavior (eg, 30-minute decrease in sedentary time for HF: HR: 0.93; 95% CI: 0.90-0.96), even among individuals meeting guideline-recommended MVPA (HR: 0.93; 95% CI: 0.87-0.99).

CONCLUSIONS Sedentary behavior is broadly associated with future adverse CV outcomes, with particularly prominent effects on HF and CV mortality, where risk inflected at approximately 10.6 h/d. Although guideline-adherent MVPA partially mitigates excess risk, optimizing sedentary behavior appears to be important even among physically active individuals. (JACC. 2025;85:473-486) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CV = cardiovascular

HF = heart failure

MI = myocardial infarction

MVPA = moderate to vigorous physical activity

Insufficient physical activity is a risk factor for incident cardiovascular (CV) disease.[1,2] Current guidelines emphasize the importance of achieving ≥150 minutes of moderate to vigorous physical activity (MVPA) per week to promote cardiovascular health.[3] However, MVPA generally represents a small fraction (<2%) of overall physical activity.[4,5]

By contrast, adults in the United States spend an average of 9.5 hours/day engaging in sedentary behavior.[6] Sedentary behavior refers to waking activity with low energy expenditure (≤1.5 metabolic equivalents) while sitting, reclining, or lying down. Sedentary behavior differs from inactivity, which denotes insufficient MVPA.[6] Despite accumulating evidence that excess sedentary behavior may be associated with CV disease risk directly rather than simply serving as a marker of insufficient MVPA, current physical activity guidelines fail to provide specific guidance on sedentary behavior.[7-13] In particular, the specific levels of sedentary time at which CV disease risk may inflect, and potential relations between sedentary behavior and physical activity with regard to CV disease risk, remain poorly understood.[14]

Most analyses of sedentary behavior have relied on self-reported data, which are prone to recall bias and can underestimate sedentary time by 40% to 60%.[7,10] More recently, wearable accelerometers have facilitated more precise and reproducible quantification of free-living activity. Furthermore, recent machine learning methods validated against manually labeled activities provide substantially more accurate classification of movement behaviors[15-17] than do approaches relying solely on intensity thresholds.[18-20] A recent study leveraging machine learning-based behavior classification demonstrated that every 1 hour/day increase in sedentary behavior was associated with a 5% higher risk of overall CV disease.[15] Although important, such a broad focus limits insight into relations between sedentary behavior and specific CV outcomes, which may differ on the basis of individual diseases.[7,9,11,21]

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Here, we leverage a unique resource of nearly 90,000 middle-aged and older adults who underwent prospective accelerometer-based physical activity measurement and behavior classification using a validated machine learning-based method, to examine associations of sedentary behavior with future risks of atrial fibrillation (AF), heart failure (HF), myocardial infarction (MI), and CV mortality, including the potential interplay between sedentary behavior and MVPA.

METHODS

STUDY POPULATION. The UK Biobank is a prospective cohort of 502,629 participants enrolled from 2006 to 2010.[17] Briefly, 9.2 million individuals aged 40 to 69 years living within 25 miles of 22 assessment centers in the UK were invited, and 5.4% participated in the baseline assessment. Questionnaires and physical measurements were collected at recruitment, and all participants were followed up for outcomes through linkage to national health-related data sets. Participants provided written informed consent. The UK Biobank was approved by the UK Biobank Research Ethics Committee (reference 11/NW/0382). Use of UK Biobank data (application 17488) was approved by the local Massachusetts General Brigham Institutional Review Board.

ACCELEROMETER-MEASURED PHYSICAL ACTIVITY. Between February 2013 and December 2015, 236,519 UK Biobank participants were invited to participate in the accelerometer substudy, and 103,691 submitted data from an Axivity AX3 (Newcastle upon Tyne, United Kingdom) wrist-worn triaxial accelerometer.[22] The sensor captured acceleration during 7 days at 100 Hz with dynamic range ±8 *g*. Signals were calibrated to gravity.[22] Sample data were combined into 5-s epochs representing the average vector magnitude. Nonwear time was identified as consecutive stationary episodes ≥60 minutes in which all 3 axes had SD <13.0 mg.[23] Epochs representing nonwear time were imputed on the basis of the mean of similar time-of-day vector magnitude and intensity distribution data points on different dates. We excluded individuals with insufficient wear time to support imputation (<72 h of wear time or no wear data in each 1-h period of the 24-h cycle), whose signals were insufficient for calibration or movement classification, whose mean acceleration values were nonphysiological, and who did not contribute a full week (Supplemental Figure 1).[15]

Raw accelerometer signals were categorized into 1 of 4 activity classes (sleep, sedentary, light physical activity, MVPA) using a machine learning method designed to classify a broad range of sedentary activities (eg, sitting at a computer, watching television, eating indoors or outdoors) based on manually labeled behaviors and previously validated in a UK-based sample.[15] The algorithm was also validated against a traditional activity-intensity cutpoint method using data from 152 free-living individuals where it showed high agreement (overall accuracy

88% with a κ statistic of 0.80).[15] The primary exposure in the present analysis was overall sedentary time accumulated during the week and averaged as a daily rate (h/d). Individuals with extreme values of sedentary time (>18 h/d) were excluded from the primary analyses.[24]

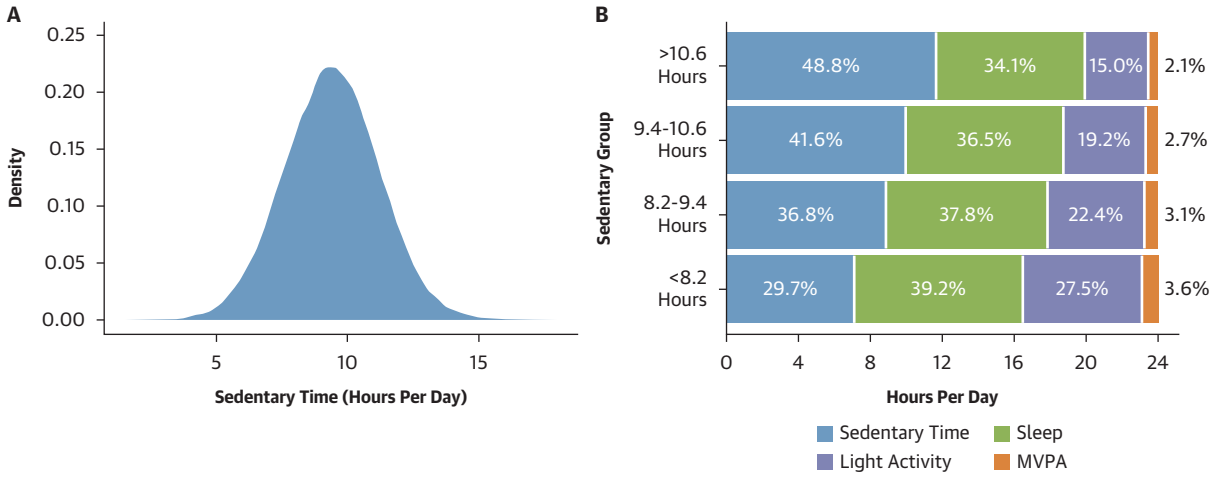
COVARIATE ASCERTAINMENT. Age, sex, body mass index, blood pressure, and use of antihypertensive agents were obtained from the study visit that most closely preceded the start of accelerometer wear. Race was based on self-report using fixed categories. Tobacco and alcohol use were ascertained using a standardized questionnaire. Alcohol use was quantified as total grams of alcohol consumed per week. The Townsend Deprivation Index was obtained as a surrogate for socioeconomic deprivation.[25] Self-reported educational history and degree/qualification status were converted to years of educational attainment.[26] Diet quality was classified as healthy, intermediate, or unhealthy on the basis of responses to dietary questionnaires.[27] Full covariate definitions are provided in Supplemental Table 1.

OUTCOMES. We assessed associations between sedentary time (h/d) and 4 incident diseases: AF, HF, MI, and CV mortality. Outcomes were defined using published definitions comprising self-reported diagnoses, diagnostic/procedural codes linked to hospital encounters, and death records (Supplemental Table 2).[28,29] Definitions for MI (positive predictive value 75%-100%) and AF (positive predictive value 92%) have been previously validated, and the definition for HF has been applied in several published studies and consistently demonstrates expected exposure-outcome associations.[30-33] To maximize statistical power for association testing, only individuals with the target disease prevalent at the time of accelerometer wear were excluded from incident analyses for that disease (whereas secondary models were fit with exclusion of all prevalent CV disease; see Supplemental Methods). Follow-up observations began at the conclusion of accelerometry and ended at the earliest of an outcome event, death, or the last follow-up visit. The duration of follow-up observation was contingent on the availability of linked health data, with a defined end date of October 31, 2022, for participants enrolled in England (n = 80,328, 90%), August 31, 2022 for participants enrolled in Scotland (5,826, 6.5%), and May 31, 2022, for participants enrolled in Wales (3,376, 3.8%). Duration of follow-up was similar across all regions: England (median 8.0 years [Q1-Q3: 7.5-8.5 years]), Scotland (8.2 years [Q1-Q3: 7.5-8.7 years]), Wales (8.2 years [Q1-Q3: 7.5-8.7 years]).

STATISTICAL ANALYSIS. We examined the distribution of each activity type (sedentary, sleep, light activity, MVPA) across quartiles of sedentary time. In our primary model, we examined the associations between accelerometer-measured sedentary time and incident disease using Cox proportional hazards regression. Given a low death rate (5.4 events per 1,000 person-years; 95% CI: 5.2-5.6), death was modeled as a censoring event. To facilitate comparisons between diseases, we adjusted each model for a uniform set of covariates. Covariates were selected a priori on the basis of known or suspected associations with physical activity and CV disease reported in prior literature as well as previous analyses of activity patterns in the UK Biobank.[15,28] Specifically, we adjusted for age, sex, racial and ethnic background, tobacco use, Townsend Deprivation Index, alcohol intake, educational attainment, employment status, self-reported health, and diet quality. Information on race and ethnicity was included, given prior associations with physical activity and CV events. Several cardiometabolic factors (body mass index, blood pressure, antihypertensive use, and diabetes) were considered potential mediators of associations between sedentary behavior and CV events, and therefore were not included as covariates in the primary models but were included in secondary models (Supplemental Methods). E-values were calculated to assess the potential robustness of observed associations to unadjusted confounding.[34]

We then sought to assess the functional form of the relationship between sedentary time and each CV outcome by fitting multivariable-adjusted B-spline basis functions with 3 degrees of freedom. The Akaike Information Criterion was used to determine whether incorporation of nonlinear terms improved model fit. Given the evidence of substantive nonlinearity in associations between sedentary time and incident CV outcomes, in our primary analyses we categorized sedentary time as quartiles. The second quartile (sedentary time 8.2-9.4 h/d) was used as the reference group to ensure that the results were less sensitive to extreme values in the sedentary time distribution. On the basis of the functional form of the relationship between sedentary time and some CV outcomes, which suggested an inflection point at approximately 10.6 h/d, we assessed the associations with sedentary time stratified at a binary threshold of 10.6 h/d and quantified the associations with continuous sedentary time (h/d) above and below this threshold while testing for interaction. We tabulated crude incidence rates within strata of sedentary time and plotted corresponding Kaplan-Meier cumulative incidence curves. To examine potential modification

FIGURE 1 Distribution of Activities During a 24-Hour Period



Depicted is the distribution of daily sedentary time in the overall cohort (A) and the distribution of daily sedentary time and other activities by sedentary quartile (B). MVPA = moderate to vigorous physical activity.

of the effect of sedentary time on incident CV outcomes on the basis of physical activity, we stratified the cohort based on the guideline-based threshold of ≥150 min/wk of MVPA, re-examined the associations between sedentary time and each CV outcome, and tested for interaction. Disease incidence rates and cumulative incidence curves were generated across strata of both MVPA and sedentary time (at the 10.6 h/d threshold).

Given the strong associations between sedentary behavior and HF and CV mortality, which persisted among individuals meeting guideline-adherent MVPA levels, we performed compositional data analysis to estimate the impact of reallocating sedentary time to other behaviors.[15] Briefly, the approach uses log-transformed ratios of behavior (sedentary, sleep, light activity, MVPA) to model relative time spent in each behavior. The ratios are then incorporated into multivariable Cox proportional hazards models (adjusted analogously to our primary models) to facilitate estimation of the relative hazard associated with reallocating sedentary time to other behaviors. We focused this analysis on HF and CV mortality, and performed it within: 1) all individuals with excess sedentary time (ie, >10.6 h/d); and 2) individuals with excess sedentary time who also met guideline-adherent MVPA levels. In each group, we assessed the relative hazard of reallocating sedentary time to: 1) all other activities proportionally; 2) MVPA only; and 3) light activity only.

We performed multiple secondary and sensitivity analyses (Supplemental Methods). The proportional hazards assumption was assessed by inspecting Schoenfeld residuals. Analyses were performed using R version 4.1.1 (R Foundation), and compositional analyses were performed using the epicoda and zCompositions packages (R Foundation). A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

SAMPLE CHARACTERISTICS. Of 103,691 UK Biobank participants who underwent activity measurement between June 8, 2013, and December 30, 2015, we excluded 12,176 for insufficient accelerometer data, including <1 full week. After the exclusion of an additional 44 for withdrawn consent, 1,907 for missing information on covariates, 20 for loss to follow-up, and 14 for sedentary behavior >18 h/d, 89,530 individuals were included in the analysis (Supplemental Figure 1). The participants were 56% women, and the mean age was 62 ± 8 years. The median sedentary time was 9.4 h/d (Q1-Q3: 8.2-10.6 h/d) (**Figure 1A**). Across increasing quartiles of sedentary time, time spent in light activity and MVPA were correspondingly shorter (**Figure 1B**). Sample characteristics and event rates across quartiles of sedentary time are presented in **Table 1** and Supplemental Table 3.

ASSOCIATIONS BETWEEN SEDENTARY TIME AND INCIDENT CV DISEASE AND MORTALITY. During a median follow-up time of 8.0 years (Q1-Q3: 7.5-8.5 years), a total of 3,638 individuals experienced incident AF (cumulative risk of AF 4.9% [95% CI:

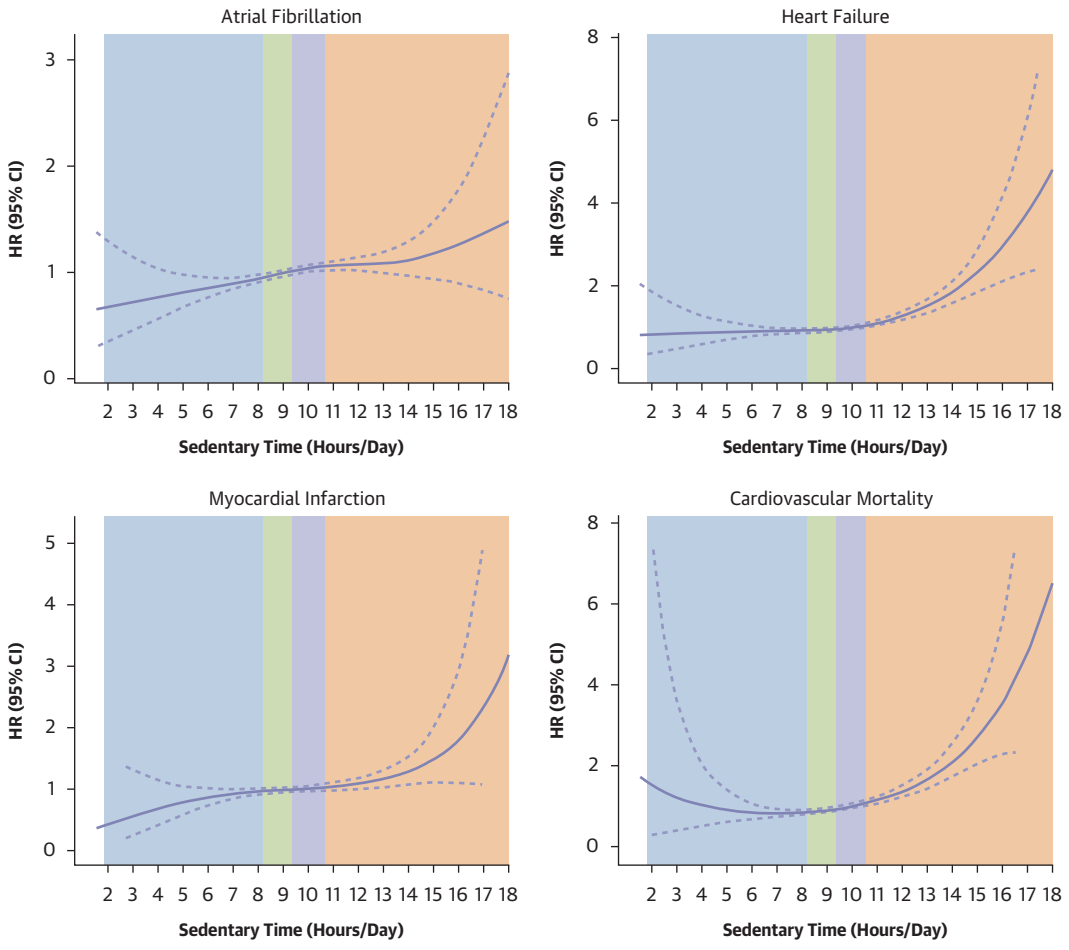
TABLE 1 Baseline Characteristics of the Analysis Sample

	Overall (N = 89,530)	Quartile 1 (<8.2 h/d) (n = 22,827)	Quartile 2 (8.2-9.4 h/d) (n = 22,045)	Quartile 3 (9.4-10.6 h/d) (n = 22,303)	Quartile 4 (>10.6 h/d) (n = 22,355)
Age, y	62 ± 8	62 ± 8	63 ± 8	62 ± 8	62 ± 8
Sex					
Female	50,452 (56)	15,119 (66)	13,566 (62)	12,192 (55)	9,575 (43)
Male	39,078 (44)	7,708 (34)	8,479 (38)	10,111 (45)	12,780 (57)
Race[a]					
Asian	1,024 (1.1)	284 (1.2)	213 (1.0)	239 (1.1)	288 (1.3)
Black	728 (0.8)	179 (0.8)	162 (0.7)	177 (0.8)	210 (0.9)
Other	949 (1.1)	259 (1.1)	219 (1.0)	237 (1.1)	234 (1.0)
White	86,829 (97)	22,105 (97)	21,451 (97)	21,650 (97)	21,623 (97)
Body mass index, kg/m^2[b]	26.7 ± 4.5	25.6 ± 4.0	26.2 ± 4.2	26.9 ± 4.4	28.1 ± 5.1
Systolic blood pressure, mm Hg[b]	137 ± 18	136 ± 18	136 ± 18	137 ± 18	138 ± 18
Diastolic blood pressure, mm Hg[b]	82 ± 10	81 ± 10	81 ± 10	82 ± 10	83 ± 10
Antihypertensive medication[b]	15,575 (17)	3,234 (14)	3,611 (16)	3,948 (18)	4,782 (21)
Lipid-lowering therapy[b]	13,125 (15)	2,578 (11)	3,065 (14)	3,320 (15)	4,162 (19)
Hormone replacement therapy[b]	3,875 (4.3)	1,179 (5.2)	1,022 (4.6)	948 (4.3)	726 (3.2)
Obese[c]	17,343 (19)	2,929 (13)	3,509 (16)	4,449 (20)	6,456 (29)
Diabetes[b]	4,081 (4.6)	639 (2.8)	833 (3.8)	1,028 (4.6)	1,581 (7.1)
Depression[b]	6,489 (7.2)	1,694 (7.4)	1,536 (7.0)	1,584 (7.1)	1,675 (7.5)
Hyperlipidemia[b]	15,029 (17)	3,206 (14)	3,526 (16)	3,798 (17)	4,499 (20)
Tobacco use					
Current	5,952 (6.6)	1,374 (6.0)	1,351 (6.1)	1,409 (6.3)	1,818 (8.1)
Former	32,186 (36)	7,997 (35)	7,988 (36)	8,178 (37)	8,023 (36)
Never	51,392 (57)	13,456 (59)	12,706 (58)	12,716 (57)	12,514 (56)
Alcohol intake, g/wk[d]	122 ± 132	115 ± 125	120 ± 128	124 ± 129	130 ± 143
Townsend Deprivation Index	−1.74 ± 2.81	−1.85 ± 2.73	−1.86 ± 2.74	−1.75 ± 2.78	−1.50 ± 2.96
Self-rated health					
Excellent	19,331 (22)	5,238 (23)	4,956 (22)	4,899 (22)	4,238 (19)
Good	53,717 (60)	13,977 (61)	13,532 (61)	13,450 (60)	12,758 (57)
Fair	14,155 (16)	3,163 (14)	3,122 (14)	3,468 (16)	4,402 (20)
Poor	2,327 (2.6)	449 (2.0)	435 (2.0)	486 (2.2)	957 (4.3)
Educational attainment, y	15 ± 5	15 ± 5	15 ± 5	16 ± 5	16 ± 5
Employment status					
Employed	54,276 (61)	13,402 (59)	12,768 (58)	13,649 (61)	14,457 (65)
Unemployed/retired	35,254 (39)	9,425 (41)	9,277 (42)	8,654 (39)	7,898 (35)
Diet					
Healthy	15,880 (18)	4,567 (20)	4,049 (18)	3,891 (17)	3,373 (15)
Intermediate	44,871 (50)	11,681 (51)	11,214 (51)	11,112 (50)	10,864 (49)
Unhealthy	28,779 (32)	6,579 (29)	6,782 (31)	7,300 (33)	8,118 (36)

Values are mean ± SD or n (%). [a]Represents self-reported racial and ethnic background. Race classification of "other" defined as self-report of a race other than Asian, Black, multiracial, multiethnic, or white. [b]Indicates covariates that likely lie in the causal pathway between sedentary behavior and cardiovascular events and are included in secondary adjusted models (see Supplemental Tables 10 and 11). [c]Defined as body mass index ≥30 kg/m^2. [d]Can be converted to standard U.S. drinks per week by dividing by 14 g.

4.06%-4.32%]), 1,854 experienced incident HF (2.09% [95% CI: 1.99%-2.18%]), 1,610 experienced incident MI (1.84% [95% CI: 1.75%-1.93%]), and 846 died of CV causes (0.94% [95% CI: 0.88%-1.01%]) (Supplemental Table 3). In multivariable-adjusted models, greater sedentary time was associated with higher risks of incident AF, HF, MI, and CV mortality. However, the nature of the associations differed by outcome (**Figure 2**). Specifically, associations between sedentary time and AF and MI failed to show substantial deviation from linearity ($P = 1$ for improved fit when including nonlinear spline term). However, associations between sedentary time and HF and CV mortality appeared substantially nonlinear, with evidence of a threshold effect within the top quartile (>10.6 h/d) ($P < 0.01$ and $P = 0.01$ for improved fit when including nonlinear term, respectively). When examined by quartiles of sedentary time and using the second quartile (8.2-9.6 h/d) as a referent, sedentary time in the top

FIGURE 2 Multivariable-Adjusted Hazard for Cardiovascular Disease Across Increasing Sedentary Time



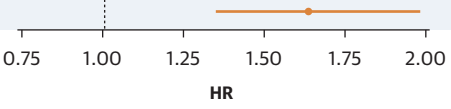
Depicted are plots of fitted curves using a B-spline basis fit to model hazards as a function of increased hours of sedentary time per week. The x-axis depicts increasing sedentary time. The y-axis depicts the relative hazard compared with an x-axis value of 9.4 (median sedentary time). The colored areas represent the sedentary quartiles.

quartile (>10.6 h/d) was associated with modestly higher risks of incident AF (HR: 1.11; 95% CI: 1.01-1.21) and MI (HR: 1.15; 95% CI: 1.00-1.32) and substantially higher risks of HF (HR: 1.45; 95% CI: 1.28-1.65) and CV mortality (HR: 1.62; 95% CI: 1.34-1.96) (**Figure 3**). Our analyses suggest that considerable residual confounding would be needed to nullify observed associations (**Figure 3**). For example, an E-value of 2.26 (corresponding to the effect of sedentary behavior in the top quartile on risk of HF) suggests that an unadjusted confounder would need to be associated with an at least 2.26-fold hazard of the exposure and outcome to nullify the observed association.

INFLECTION OF RISK FOR HF AND CV MORTALITY AT 10.6 HOURS/DAY. Given evidence of an apparent inflection in risk for HF and CV mortality at the top quartile of sedentary time, we examined relations between sedentary time and CV outcomes at the corresponding 10.6 hours/day threshold. This threshold was exceeded a median of 2 out of 7 days (quartile 1: 0 days; quartile 3: 4 days) (Supplemental Figure 2). Compared with individuals with sedentary time ≤10.6 hours/day, those with sedentary time exceeding 10.6 hours/day had substantially higher risks of HF and CV mortality (HR: 1.40; 95% CI: 1.27-1.54, and HR: 1.54; 95% CI: 1.33-1.77, respectively) (Supplemental Figure 3). A dose-response

FIGURE 3 Associations Between Sedentary Time and Incident Cardiovascular Disease

Outcome	Sedentary Group	Events, N (%)	HR (95% CI)	E_{point} (E_{null})
Atrial Fibrillation	Q1	766 (3.43%)	0.93 (0.84-1.03)	1.36 (1.00)
	Q2	867 (4.04%)	*Ref*	*Ref*
	Q3	959 (4.43%)	1.07 (0.98-1.18)	1.36 (1.00)
	Q4	1,046 (4.87%)	1.11 (1.01-1.21)	1.46 (1.12)
Heart Failure	Q1	382 (1.69%)	1.06 (0.92-1.22)	1.30 (1.00)
	Q2	387 (1.76%)	*Ref*	*Ref*
	Q3	429 (1.94%)	1.06 (0.92-1.21)	1.31 (1.00)
	Q4	656 (2.97%)	1.45 (1.28-1.65)	2.26 (1.87)
Myocardial Infarction	Q1	352 (1.57%)	0.99 (0.86-1.15)	1.09 (1.00)
	Q2	369 (1.63%	*Ref*	*Ref*
	Q3	392 (1.80%)	1.01 (0.87-1.16)	1.08 (1.00)
	Q4	497 (2.30%)	1.15 (1.00-1.32)	1.56 (1.03)
CV Mortality	Q1	145 (0.64%)	0.99 (0.79-1.24)	1.10 (1.00)
	Q2	161 (0.73%)	*Ref*	*Ref*
	Q3	200 (0.90%)	1.14 (0.93-1.41)	1.55 (1.00)
	Q4	340 (1.52%)	1.62 (1.34-1.96)	2.61 (2.01)



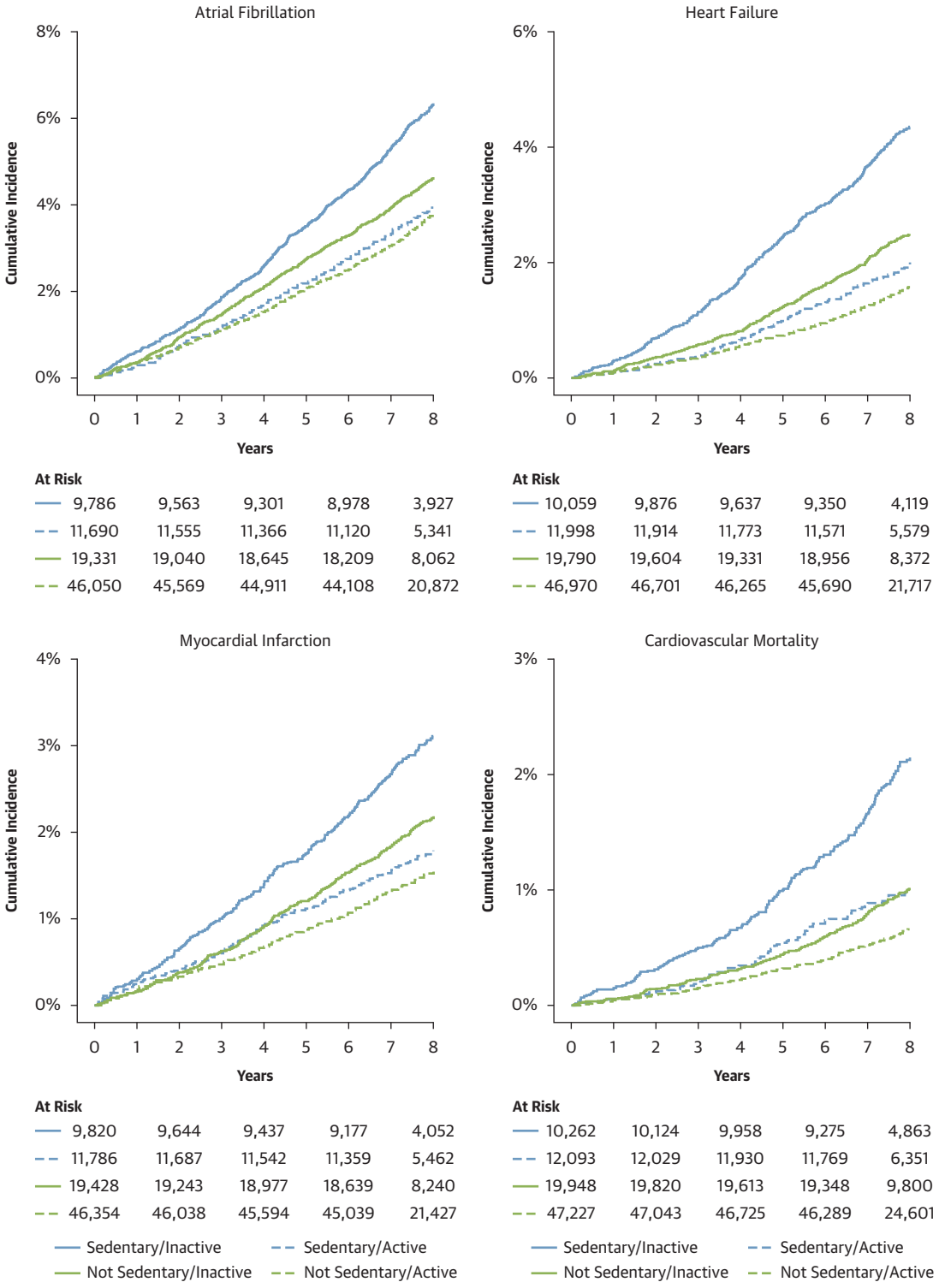
Depicted is a plot of multivariable adjusted associations between sedentary time and incident atrial fibrillation, myocardial infarction, heart failure, and CV mortality. Quartiles 1 (<8.2 h/d), 3 (9.4-10.6 h/d) and 4 (>10.6 h/d) are compared to quartile 2 (8.2-9.4 h/d). The models were adjusted for age, sex, racial and ethnic background, tobacco use, Townsend Deprivation Index, alcohol intake, educational attainment, employment status, self-reported health, and diet quality. E-values estimate the minimum strength of association on the risk ratio scale that a potential confounder would need to have with the exposure and outcome to nullify the observed association. Epoint denotes E-values for the point estimate, and Enull denotes the E-value for the confidence interval bound closest to the null. CV = cardiovascular.

relationship was observed between the number of days the 10.6-hour sedentary threshold was exceeded and risk of HF (HR: 1.07 per 1-day increase; 95% CI: 1.05-1.09) and CV mortality (HR: 1.10 per 1-day increase; 95% CI: 1.06-1.13), with the majority of excess risk observed after ≥4 days meeting >10.6 hours/day (Supplemental Figure 4). Each additional hour of daily sedentary time was associated with increasing risk of HF (HR: 1.18; 95% CI: 1.10-1.26) and CV mortality (HR: 1.23; 95% CI: 1.12-1.34) above the 10.6 hours/day threshold, but not below (interaction $P < 0.01$ for both) (Supplemental Figure 5). Consistent with the absence of an inflection of risk for AF and MI, no interactions were observed at the 10.6-hours/day threshold, but individuals above 10.6 hours/day did have greater risk of AF (HR: 1.10; 95% CI: 1.02-1.19) and MI (HR: 1.15; 95% CI: 1.03-1.28) (Supplemental Figure 3).

INTERACTIONS BETWEEN SEDENTARY TIME AND PHYSICAL ACTIVITY. Achievement of guideline-recommended MVPA levels modified associations between sedentary time and increased risk of CV events to varying degrees (Supplemental Figures 6 to 9). For each CV outcome, associations between sedentary time >10.6 hours/day and greater risk of events were most prominent among individuals failing to achieve ≥150 minutes/week of MVPA (AF, HR: 1.14; 95% CI: 1.02-1.26; MI, HR: 1.15; 95% CI: 0.99-1.34; HF, 1.44; 95% CI: 1.25-1.64; CV mortality, HR: 1.53; 95% CI: 1.26-1.87). Effect sizes were uniformly smaller among individuals meeting ≥150 minutes/week of MVPA, including fully attenuated associations with AF (HR: 0.99; 95% CI: 0.89-1.10) and MI (HR: 1.00; 95% CI: 0.86-1.17) and a weaker association with HF (HR: 1.15; 95% CI: 0.99-1.34). Although the effect size was smaller, the association with CV mortality remained robust (HR: 1.33; 95% CI: 1.07-1.64). A statistical interaction between sedentary time and MVPA was observed only for HF ($P = 0.04$) and AF ($P = 0.05$). Observations were consistent when crude event rates were compared among individuals with excess sedentary time above vs below guideline-based MVPA recommendations (**Figure 4**, Supplemental Tables 4 and 5).

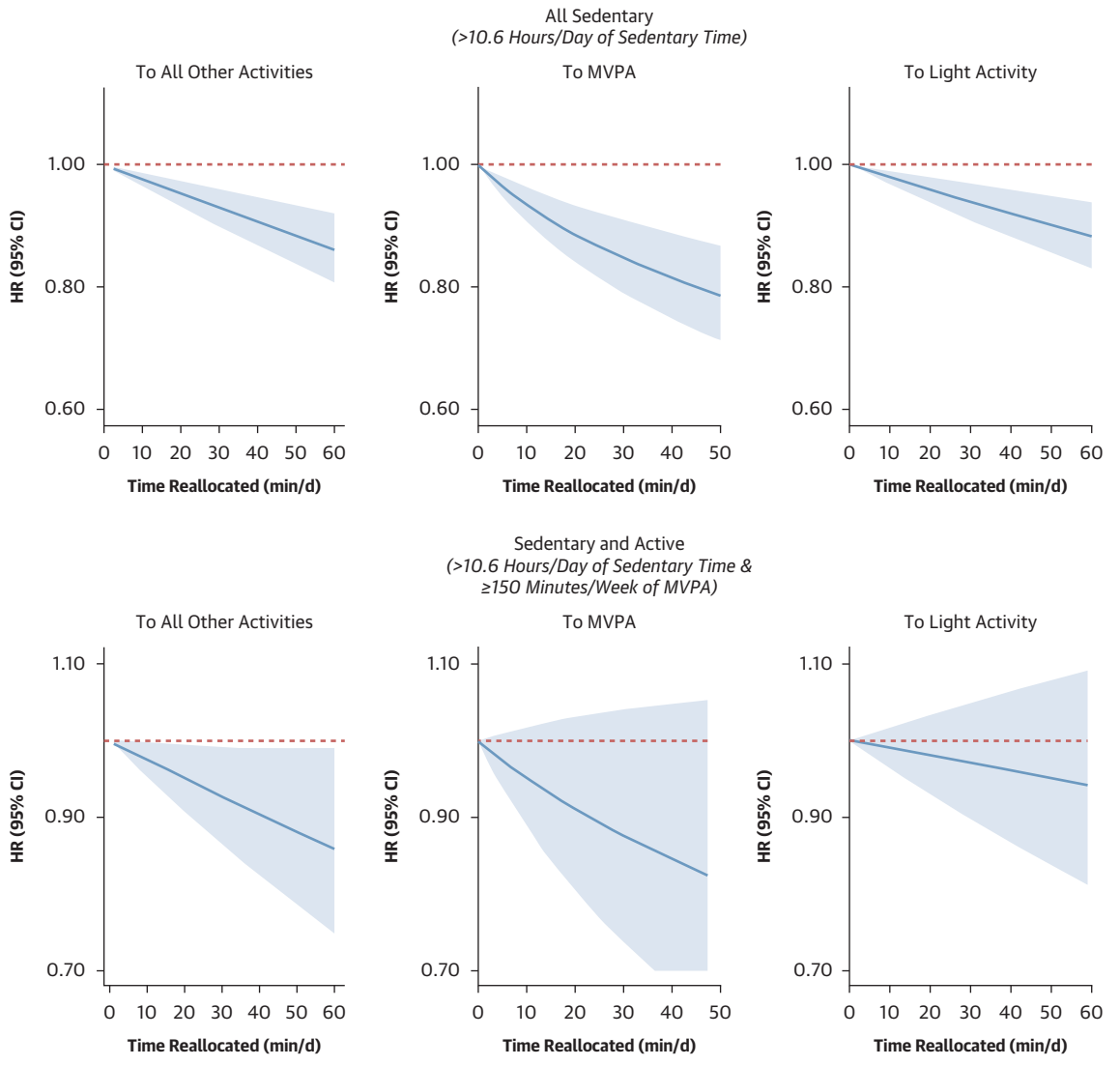
EFFECTS OF REALLOCATING SEDENTARY TIME ON HF AND CV MORTALITY RISK. Among individuals with sedentary time >10.6 hours/day, we estimated the effects of reallocating sedentary time on HF and CV mortality risk (**Figure 5**, Supplemental Figure 10). Within this subset, reducing sedentary time was associated with lower risks of HF and CV mortality, whether reallocation was to all activities proportionally (eg, 30-min decrease in sedentary time: HR: 0.93;

FIGURE 4 Cumulative Risk of Cardiovascular Disease Stratified by Sedentary Behavior and Guideline-Based Moderate to Vigorous Physical Activity



Depicted are plots of crude cumulative risk of cardiovascular events, stratified by MVPA guideline recommendations (active, ≥150 min/wk MVPA; inactive, <150 min/wk MVPA) and daily sedentary time (sedentary, >10.6 h/d; not sedentary, 10.6 h/d). Abbreviation as in Figure 1.

FIGURE 5 Relative Hazard of Incident Heart Failure With Reallocation of Sedentary Time to Other Behaviors Among Sedentary Individuals



The plots in the first row are based on individuals with mean sedentary time >10.6 h/d; plots in the second row are based on the subset from this group with MVPA ≥150 min/wk. Estimates are relative to the mean behavior composition among individuals in each group. Mean behavior composition among individuals with mean sedentary time 10.6 h/d was >3.5 h/d light activity, 0.4 h/d MVPA, 11.9 h/d sedentary time, and 8.3 h/d sleep. For the subset of individuals with MVPA ≥150 min/wk, mean behavior composition was 3.5 h/d light activity, 0.7 h/d moderate to vigorous physical activity, 11.7 h/d sedentary time, 8.1 h/d sleep. Models were adjusted for age, sex, racial and ethnic background, tobacco use, Townsend Deprivation Index, alcohol intake, educational attainment, employment status, self-reported health, and diet quality. Reallocation to MVPA is truncated at 50 minutes because precision of estimates beyond this point is limited. Abbreviation as in Figure 1.

95% CI: 0.90-0.96 for HF; HR: 0.92; 95% CI: 0.88-0.97 for CV mortality), MVPA only (HR: 0.85; 95% CI: 0.79-0.91; HR: 0.90; 95% CI: 0.82-0.99), or light activity only (HR: 0.94; 95% CI: 0.91-0.97; HR: 0.91; 95% CI: 0.88-0.95). Although precision of estimates was more limited, patterns were broadly consistent among individuals meeting guideline-adherent MVPA levels, where risks appeared lower with reallocation to all other activities proportionally (eg, 30-min decrease in sedentary time: HR: 0.93; 95% CI: 0.87-0.99 for HF; HR: 0.96; 95% CI: 0.87-1.07 for CV mortality), MVPA only (HR: 0.88; 95% CI: 0.74-1.04; HR: 0.89; 95% CI: 0.70-1.13), or light activity only (HR: 0.97; 95% CI: 0.90-1.05; HR: 0.98; 95% CI: 0.88-1.09). Proportional

reallocations solely to increased MVPA were also associated with lower risks of HF and CV mortality, and proportional reallocations solely to light activity had modest effects (Supplemental Figures 11 and 12).

SECONDARY ANALYSES. Effect modification observed with MVPA at the sample median threshold (>230 minutes/week) (Supplemental Figures 7 and 9) and with vigorous physical activity (Supplemental Figure 13) were similar to that observed with MVPA at the guideline-based threshold. Associations observed in the primary analyses were similar with additional adjustment for sleep duration (Supplemental Table 6) and light activity (Supplemental Table 7). With additional adjustment for MVPA (Supplemental Table 8) or MVPA and light activity (Supplemental Table 9), associations between sedentary time and incident HF and CV mortality were modestly attenuated but remained significant, whereas associations with AF and MI were no longer observed. Similarly, adjustment for potential mediators (body mass index, prevalent hyperlipidemia, diabetes) and additional potential confounders (depression, blood pressure, use of antihypertensive agents, use of lipid-lowering therapy and hormone therapy) attenuated associations with AF and MI, but associations with HF and CV mortality remained significant (Supplemental Tables 10 and 11). Results were similar when the cohort was stratified by obesity (Supplemental Table 12) and diabetes (Supplemental Table 13), with larger effect sizes for HF in the presence of diabetes or obesity. Associations were similar regardless of the presence of a prevalent musculoskeletal condition (Supplemental Table 14) and across self-rated health status (Supplemental Table 15). Results were also similar with simultaneous exclusion of all individuals with prevalent AF, MI, and HF (Supplemental Figure 14). Associations with HF and CV mortality remained robust with exclusion of individuals with prevalent AF and MI and censoring person-time at incident AF and MI occurring before an outcome event (Supplemental Figure 15). Findings were also consistent when individuals with extreme sedentary time values were included (Supplemental Table 16), and when a 2-year blanking period was used (Supplemental Table 17).

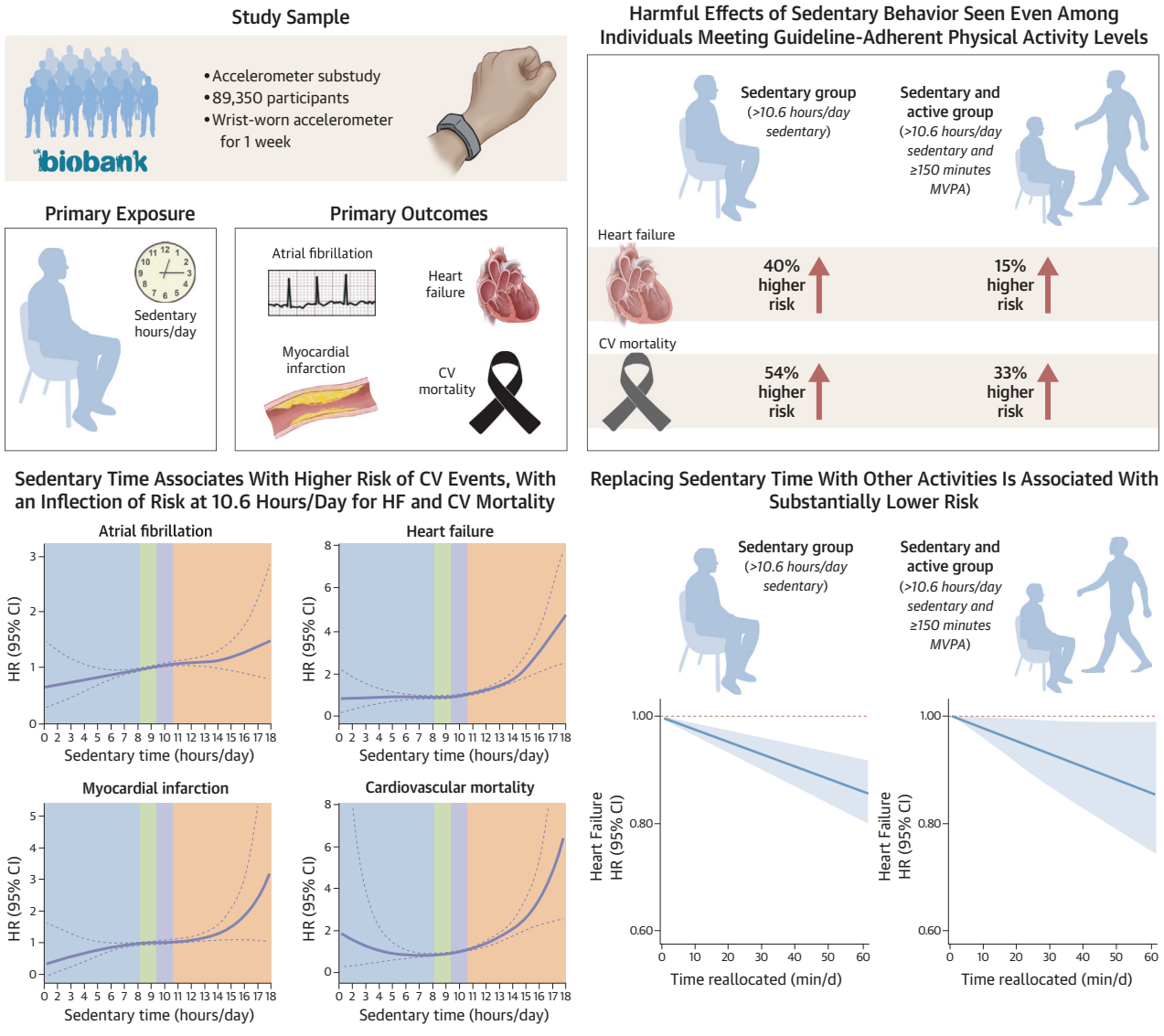
DISCUSSION

Among nearly 90,000 community-dwelling middle-aged and older adults wearing a wrist-based activity sensor for 1 week and followed up prospectively for almost a decade, we observed associations between greater sedentary time and higher risk of AF, HF, MI, and CV mortality (**Central Illustration**). Importantly, effects of sedentary time varied by outcome. Associations with HF and CV mortality were comparably large, exhibited an inflection of risk at approximately 10.6 hours, and remained robust to adjustment for additional activity types (eg, MVPA). By contrast, associations with AF and MI were smaller, were approximately linear, and were attenuated by adjustment for MVPA. Although achievement of guideline-adherent MVPA levels (≥150 min/wk) partially mitigated the excess risk conferred by sedentary behavior, associations with higher risk of HF and CV mortality persisted even among active individuals, in whom reallocating sedentary time to other activities appeared beneficial.

Our findings support and extend prior analyses linking sedentary behavior with greater risk of CV disease.[21,35-37] Several studies focused on self-reported sedentary behavior have observed greater risks of all-cause and CV mortality.[35] One accelerometer study including 7,058 individuals found that participants in the top (≥10.2 hours) vs the bottom quartile (<8.3 hours) of daily sedentary time had a 53% higher risk of a composite CV endpoint after adjustment for MVPA.[38] Comparably few studies have examined measured sedentary behavior with respect to specific CV outcomes such as MI and HF.[39,40] In an analysis of 16,031 women from the Women's Health Study, compared with women who spent <7.4 hours/day sedentary, those who spent ≥9.5 hours/day did not have higher risk of incident MI.[39] In a study of 5,951 women from the Objective Activity and Cardiovascular Health Study, each 1-SD increase in daily sedentary time was associated with a 17% higher risk of overall HF.[40] The applicability of these measured activity studies is limited by analysis of specific demographic groups (eg, 1 sex), focus on individual CV outcomes, and comparably smaller sample sizes. Furthermore, classification of activity solely on the basis of acceleration intensity thresholds is prone to misclassification.[16] Our findings therefore substantially extend prior studies by leveraging a validated machine learning approach to enable accurate activity classification with sufficient statistical power to characterize both the magnitude and the form of associations between measured sedentary time and specific CV outcomes in a community sample, as well as quantify relations between sedentary time and MVPA. Our results permit the following key implications.

First, efforts to reduce sedentary time may have varying effects on CV disease and mortality. Although greater sedentary time was associated with higher risks of incident AF, MI, HF, and CV mortality after adjustment for demographic and lifestyle factors,

CENTRAL ILLUSTRATION **Accelerometer-Measured Sedentary Behavior and Future Cardiovascular Disease**



Conclusion: Avoiding excess sedentary behavior appears important to reduce cardiovascular disease risk even if you are physically active.

Ajufo E, et al. JACC. 2025;85(5):473–486.

CV = cardiovascular; HF = heart failure; MVPA = moderate to vigorous physical activity.

effects were most pronounced for HF and CV mortality. For example, compared with the second quartile (8.2-9.6 h/d), sedentary time in the top quartile (>10.6 h/d) was associated with a roughly 50% higher relative hazard of HF and CV mortality, as opposed to roughly 10% to 15% higher relative hazards of AF and MI. Our findings support prior data from questionnaire-based studies suggesting greater effects of sedentary behavior[41] and physical activity[9] on HF compared with other CV outcomes. Future work is warranted to elucidate whether observed associations between sedentary behavior and future HF may be causal, and whether specific mechanisms can be identified, including potential effects on inflammation, glucose homeostasis, and autonomic balance.[9,42] Taken together, our findings demonstrate that excess sedentary behavior is broadly associated with future CV disease risk, but optimization of

sedentary behavior may have particular importance for prevention of HF and CV mortality.

Second, our results support current recommendations to minimize sedentary time for CV disease risk while also identifying 10.6 hours/day as a candidate inflection point with particular relevance for HF and CV mortality. Our findings are consistent with prior studies suggesting a threshold effect of sedentary behavior on CV mortality or composite CV disease at ~10 hours.[21,43] Here, we further observed a dose-response relationship in which risk of HF and CV mortality were increasingly higher as the number of days meeting the 10.6 hours/day threshold increased (particularly at ≥4 d/wk). Although associations between sedentary time and AF and MI were more linear, risk was still substantially higher above the 10.6 hours/day threshold. Thus, our findings suggest that ensuring avoidance of sedentary time in excess of 10.6 hours/day may represent a reasonable minimum target for public health interventions focused on sedentary behavior. Among individuals already meeting this threshold, further avoidance of sedentary behavior may provide some additional benefits (eg, for MI and AF), but prioritizing other lifestyle modifications (eg, ensuring achievement of guideline-adherent MVPA) may be reasonable. Although potential mechanisms underlying the inflection of risk for HF and CV mortality observed above certain volumes of sedentary time remain unknown, critical periods of sedentary behavior may be necessary to induce changes in skeletal muscle gene expression,[44] as well as lipid and glucose homeostasis.[45]

Third, our analysis highlights a complex interplay between sedentary behavior and physical activity, ultimately suggesting that sedentary behavior remains relevant for CV disease risk even among individuals meeting sufficient MVPA levels. Current guidelines emphasize the importance of achieving a minimal volume of MVPA (generally ≥150 min/wk).[28] Our findings support the notion that physical activity modifies the effect of sedentary behavior,[7,41,46,47] such that effect sizes for sedentary time on each CV outcome were consistently smaller among individuals achieving ≥150 minutes/week of MVPA. Again, however, relations between MVPA, sedentary behavior, and CV disease risk were not entirely uniform across conditions. In models adjusted for total MVPA, associations between sedentary behavior and AF and MI were no longer observed, whereas robust associations with HF and CV mortality persisted. Our findings therefore suggest that associations between sedentary behavior and AF and MI may be driven primarily by insufficient MVPA, whereas considerable effects on HF and CV mortality appear independent of MVPA volume. To this end, our compositional analysis suggests that among individuals with >10.6 hours/day of sedentary time, reallocating sedentary time to other physical activity types (eg, MVPA, light activity) should result in lower risks of HF and CV mortality even among individuals already meeting guideline-adherent MVPA levels. Taken together, our findings underscore the importance of optimizing sedentary behavior for CV benefit in all individuals, including those who are active.

STUDY LIMITATIONS. First, accelerometer-based data cannot assess the specific context for sedentary behavior (eg, workplace), which may affect potential risks conferred by excess sedentary time. Second, wrist-based accelerometers do not fully resolve posture and may therefore misclassify standing time as sedentary time. This limitation is common to most accelerometer devices that lack cameras or inclinometers. Third, physical activity was measured for only 1 week. Longer monitoring might have provided a more accurate representation of habitual activity patterns. Similarly, individuals may have modified their behavior on account of being observed. Reassuringly, the distribution of sedentary time we have in our study is highly consistent with estimates obtained from the general population.[6] Fourth, despite attempts to control for known confounders and mitigate reverse causality (eg, 2-year blanking analysis), both may persist in our results, which cannot be used to infer causal relations. Fifth, the generalizability of our results may have been affected by selection bias introduced by the response rates of the UK Biobank (5.5%) and the subsequent accelerometer substudy (45%). Given that the accelerometer substudy was performed several years after enrollment, the accelerometer cohort is also likely healthier than the UK Biobank at large on account of survivorship. Selection effects are relevant to the inflection of risk we observed at 10.6 hours/day of sedentary time because thresholds may vary in different populations. We also recognize that the UK Biobank sample is predominantly White and is enriched generally for health and socioeconomic status; however, prior analyses have supported the validity of exposure-outcome associations in the UK Biobank.[48] We anticipate that the increasing availability of measured activity data in diverse populations will enable validation of our findings in future studies. Sixth, we did not analyze sedentary time as a function of specific bout frequency or duration, given evidence supporting the role of total activity volume rather than

bouts of arbitrary duration.[49] Seventh, our compositional data analysis models the estimated effects of reallocating sedentary time to other activities, but actual effects of reallocation cannot be measured without longitudinal study and repeated measurements. Eighth, there is imperfect correlation between the data obtained from wrist- and thigh-worn accelerometers (r ~0.6-0.7).[50] Although wrist-worn accelerometers are more commonly used, potentially promote better adherence, and may provide favorable accuracy for certain activities compared with thigh-worn devices,[50] we acknowledge that findings may differ when other forms of activity tracking are used.

CONCLUSIONS

Among nearly 90,000 individuals during roughly a decade of follow-up, accelerometer-derived sedentary behavior was associated with higher risks of incident AF, MI, HF, and CV mortality. Associations were particularly robust for HF and CV mortality, where risk appeared to inflect at approximately 10.6 h/d and persisted even among individuals meeting guideline-recommended levels of MVPA. Future guidelines and public health efforts should emphasize the importance of reducing time spent engaging in sedentary behavior, regardless of whether individuals already meet guideline-adherent MVPA levels, and avoidance of sedentary behavior in excess of 10.6 hours/day may represent a reasonable minimal target.

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