

Patient Activity and Survival Following Implantable Cardioverter-Defibrillator Implantation: The ALTITUDE Activity Study

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Background—Physical activity data are collected automatically by implantable cardioverter-defibrillators (ICDs). Though these data potentially provide a quantifiable and easily accessible measure of functional status, its relationship with survival has not been well studied.

Methods and Results—Patients enrolled in the Boston Scientific LATITUDE remote monitoring system from 2008 to 2012 with ICDs were eligible. Remote monitoring data were used to calculate mean daily activity at baseline (30 to 60 days after implantation), and longitudinally. Cox regression was used to examine the association between survival and increments of 30 minutes/day in both (1) mean baseline activity and (2) time-varying activity, with both adjusted for demographic and device characteristics. A total of 98 437 patients were followed for a median of 2.2 years (mean age of 67.7 ± 13.1 years; 71.7% male). Mean baseline daily activity was 107.5 ± 66.2 minutes/day. The proportion of patients surviving after 4 years was significantly higher among those in the most versus least active quintile of mean baseline activity (90.5% vs. 50.0%; log-rank *P* value, <0.001). Lower mean baseline activity (i.e., incremental difference of 30-minutes/day) was independently associated with a higher risk of death (adjusted hazard ratio [AHR], 1.44; 95% confidence interval [CI], 1.427 to 1.462). Time-varying activity was similarly associated with a higher risk of death (AHR, 1.48; 95% CI, 1.451 to 1.508), indicating that a patient having 30 minutes per day less activity in a given month has a 48% increased hazard for death when compared to a similar patient in the same month.

Conclusions—Patient activity measured by ICDs strongly correlates with survival following ICD implantation. (*J Am Heart Assoc.* 2015;4:e001775 doi: 10.1161/JAHA.115.001775)

Key Words: death • implantable cardioverter-defibrillators • sudden

Implantable cardioverter-defibrillator (ICD) therapy provides life-saving treatment for patients at high risk for sudden cardiac arrest.¹ However, despite advancements in medical therapy and device programming, many patients remain at high risk for short-term death despite ICD implantation.^{2,3} Predicting which patients are at highest risk for adverse

clinical outcomes has important implications for clinical management and the design of interventions aimed at reducing morbidity and mortality following ICD implantation. Several existing risk models leverage patient clinical characteristics to predict short-term survival in ICD patients.^{2–4} Though this work has demonstrated an increasing risk for death with accumulated comorbidity, calculating risk scores at the bedside may be laborious, and no model has an established role in either clinical practice or research.⁵

Patient physical activity information is collected automatically by many ICDs. These activity data provide a quantitative, easily accessible measure that may reflect individual functional status.^{6,7} Previous studies evaluating patient activity alone⁶ or integrated with other diagnostics⁸ in heart failure (HF) patients with ICDs suggest an inverse relationship with survival, adjusted for other clinical factors. However, these studies were relatively small, did not evaluate patients without HF, and provided only limited descriptions of activity patterns over time.

Thus, the aims of this study were to investigate the distribution of patient activity following ICD implantation and the relationship between patient activity and survival. Specifically, we analyzed a large, nation-wide database of ICD

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recipients to evaluate survival according to patient activity at baseline, measured shortly after implantation, and longitudinally using a time-varying analytic approach.

Methods

Data Source

The ALTITUDE registry was established in 2008 to prospectively analyze data from ICD and cardiac resynchronization therapy (CRT-D) devices followed through the LATITUDE clinical remote monitoring system (Boston Scientific Corp, Natick, MA). LATITUDE earned U.S. Food and Drug Administration approval in 2005, and since 2006, all new Boston Scientific ICD and CRT-D implants have been eligible for enrollment in this remote follow-up network. The remote system consists of a base station capable of device interrogation and transmission that is placed in the patient's home. These interrogations may be patient initiated or (for some models) performed automatically by wireless telemetry. Data are then transferred by telephone line and are accessible for routine clinical care through a secure website administered by Boston Scientific. The decision to enroll a patient in the remote follow-up system is made by the implanting physician at the time of device implantation or at routine postimplantation follow-up clinic visits.

Deidentified data from the LATITUDE network forms the data set for ALTITUDE studies. Investigator-initiated proposals to ALTITUDE are reviewed by an independent physician leadership panel and projects with sufficient scientific merit are supported. Several previous studies have successfully queried the ALTITUDE database to assess arrhythmic events and survival.^{9–11}

This project was additionally reviewed by the Hebrew SeniorLife Institute for Aging Research Institutional Review Board (Boston, MA).

Study Population

Patients receiving new or replacement ICD or CRT-D devices from January 1, 2008 to December 31, 2012 who were entered into the LATITUDE network were eligible for inclusion. This entry date was chosen to coincide with introduction of an ICD software platform that supported daily recording and upload of patient activity. Study follow-up ended on March 1, 2013 to allow collection of baseline activity information for all included subjects, while also providing sufficient lag time for reporting of deaths into the national death index (NDI). Patients without a compatible ICD platform, missing demographic information (including Social Security numbers), or without usable patient activity data were excluded from analysis (see Figure 1). The majority of exclusions owing to

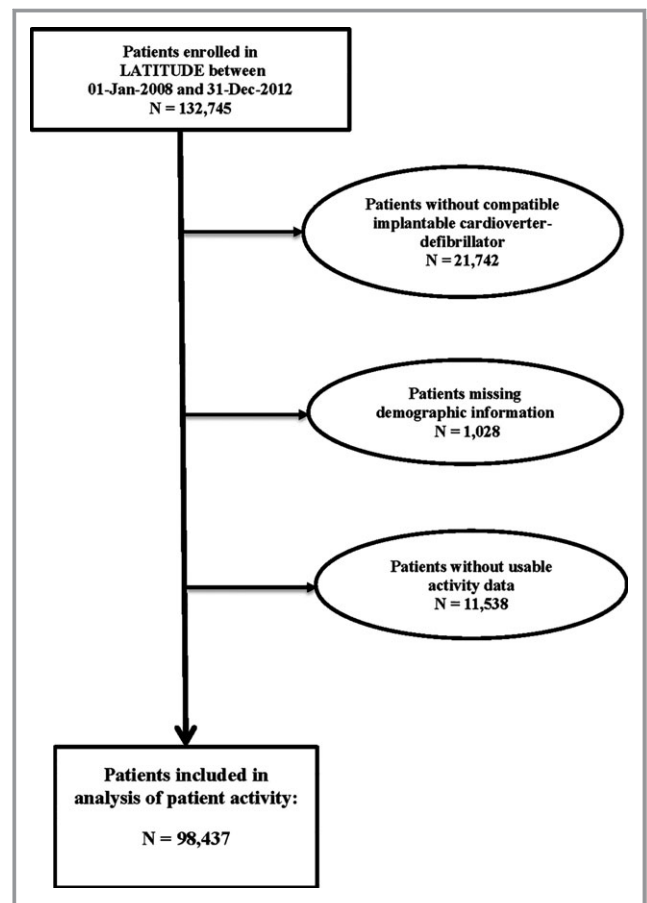


Figure 1. Study flow with derivation of the study population.

unusable activity data arose from patients in whom a truncated transmission to LATITUDE resulted in loss of historical activity information.

Patient Activity

Patient activity in Boston Scientific devices is measured through an integrated circuit accelerometer embedded in the pulse generator itself, which, in applicable patients, can also be used for rate-responsive pacing. The accelerometer detects both the frequency and amplitude of patient motion and translates this into a proportional electrical signal. A proprietary algorithm interprets this signal and specifies whether the sensor exceeds a threshold of 25 milligravities, corresponding to an approximate walking speed of 2 miles/h, in order to determine a state of “active” or “not active” for a given minute. The sensor maintains a log of the percent of time a patient is considered active or not active for each daily 24-hour period. The device models marketed during the study period are capable of storing up to 1 year of daily patient activity data. At each LATITUDE upload, all available activity data are uploaded. Thus, for our analysis, complete patient

activity data were available for each patient with at least 1 upload per 12-month rolling period.

We defined “baseline” patient activity as the mean minutes/day considered active for the period 30 to 60 days after device implant. This time period was selected *a priori* to account for clinical procedural recovery and the expected short delay between implant and successful enrollment in LATITUDE. In addition, longitudinal daily patient activity was recorded from day 60 through the date of the patient’s last upload to LATITUDE.

Survival

Vital status and, when applicable, date of death were drawn from the Boston Scientific Data Tracking database, which monitors patient clinical status through 2 complementary means. First, linkage to the NDI allows for rolling updates of patient vital status. For our study, we selected March 1, 2013 as our last follow-up date to allow for a potential lag in reporting. In addition, deaths reported to Boston Scientific as part of routine patient care are included on the Boston Scientific Tracking database records. Patient follow-up was censored at the date of death, the last LATITUDE transmission, or end of study.

Other Variables

The ALTITUDE registry provides selected demographic variables, including age at implant and sex. Procedural and device-specific variables collected included the date of implant; single-chamber, dual-chamber, or CRT-D device; and previous ICD implant.

Statistical Analysis

All baseline demographic data, clinical information, and procedural variables were described using frequencies for categorical variables and means/medians with SDs/interquartile ranges for continuous variables. For baseline patient activity, we first identified the mean±SD minutes/day active during the 30- to 60-day period for the entire population. Next, we divided the cohort into quintiles of baseline activity and summarized activity levels as well as baseline characteristics for each quintile. Patient characteristics across quintiles were compared using ANOVA for continuous variables or chi-square test for categorical variables.

Unadjusted survival for the overall cohort and each quintile was evaluated with the Kaplan-Meier method, with calculation of hazard ratios (HRs) and 95% confidence intervals (CIs) using the log-rank test for association between quintile and survival with 4 *df*. To further evaluate the relationship between patient activity and survival, we used Cox regression and considered

baseline patient activity as a continuous variable, with an incremental change of 30 minutes/day considered the unit of analysis. This model included age, gender, device type, previous ICD implant, and minutes/day of activity, yielding an adjusted hazard ratio (AHR) with 95% CI.

For our longitudinal analysis, we considered activity as a time-varying variable, which allows for each subject to have separate evaluable activity measurements for each time point of follow-up. This approach is commonly used for variables expected to vary over time, such as blood pressure. We first evaluated the calculated mean ± SD of monthly patient activity, which describes *interpersonal* variability over time. We also calculated the mean±SD of the SD of activity over time, which provides a measure of *intrapersonal* variability over time. Last, we repeated the Cox regression model using mean patient activity in each 30-day period (30 minutes/day incremental change) as a time-varying variable, adjusting for age, sex, device type (CRT vs. non-CRT), and previous ICD, yielding HRs and 95% CIs for each covariate.

Results

Baseline Characteristics

From 132 745 patients implanted with Boston Scientific ICDs and enrolled in LATITUDE during the study period, 98 437 were eligible for analysis (Figure 1). Median follow-up time for the final cohort was 2.2 years. Demographic and device-based characteristics of the overall cohort and stratified by quintile of activity level are shown in Table 1. Overall, patients had a mean age of 67.7±13.1 years and 71.7% were male, with 43.4% and 56.6% receiving CRT or ICD (single- or dual-chamber) devices, respectively, and 30.5% having had an ICD previously.

Baseline physical activity for the entire cohort in the 30- to 60-day window post-ICD implantation averaged 107.5±66.2 minutes/day, ranging from a mean of 32.5±13.5 minutes/day in the lowest quintile to 207.7±58.5 minutes/day in the most active quintile (Table 1; $P<0.0001$, by ANOVA for trend across quintiles). Compared with the most active quintile, patients in the least active quintile tended to be older (mean age 74.6±10.3 vs. 59.3±14.0 years), female (35.6% vs. 21.1%), and more commonly received a CRT device (53.2% vs. 30.4%), compared to patients in the most active quintile (Table 1; $P<0.0001$, for trend across quintile groups for all characteristics).

Association Between Baseline Activity and Survival

Estimated survival by the Kaplan-Meier method for the entire cohort at 1 and 4 years were 95.0% and 76.1%, respectively (Table 2, Figure 2). In unadjusted analyses, baseline activity

Table 1. Demographic and Clinical Characteristics of the Entire Study Population and Stratified By Quintile of Baseline Physical Activity

Characteristic	Entire Study (N=98 437)	Quintile 1 (N=19 693)	Quintile 2 (N=19 691)	Quintile 3 (N=19 674)	Quintile 4 (N=19 692)	Quintile 5 (N=19 687)	P Value**
Mean baseline activity, minutes/day*	107.5±66.2	32.5±13.5	67.6±8.6	97.3±8.9	132.5±12.0	207.7±58.5	<0.0001
Age, mean±SD	67.7±13.1	74.6±10.3	71.6±10.9	68.4±11.7	64.6±12.5	59.3±14.0	<0.0001
Male (%)	70 533 (71.7)	12 675 (64.4)	13 649 (69.3)	14 038 (71.4)	14 629 (74.3)	15 542 (78.9)	<0.0001
CRT device (%)	42 675 (43.4)	10 480 (53.2)	9786 (49.7)	8793 (44.7)	7630 (38.7)	5986 (30.4)	<0.0001
Previous ICD implant (%)	30 005 (32.5)	6926 (35.2)	6129 (31.1)	5961 (30.3)	5618 (28.5)	5371 (27.3)	<0.0001

CRT indicates cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

*Mean minutes/day active in the first 30 to 60 days post-ICD implantation).

**P value for comparison across quintiles by ANOVA.

by quintile was strongly associated with survival. At 1 year post-ICD implant, the most active quintile demonstrated survival of 98.7% versus 86.5% for the least active ($P<0.001$). The proportion of patients surviving after 4 years was strikingly higher among those in the highest (most active) versus lowest (least active) quintile of mean baseline activity (90.5% vs. 50.0%; P value, <0.001). After adjustment for age, gender, CRT versus non-CRT device, and de novo versus replacement ICD, lower mean baseline activity (i.e., incremental difference of 30 minutes/day) was independently associated with a higher risk of death (AHR, 1.44; 95% CI, 1.427 to 1.462).

Time-Varying Analysis

During the study follow-up period, an average of 720.3 ± 436.3 daily measurements were collected from each patient at a median of 2.2 years of follow-up. As expected, the number of patients with observed daily activity measurements and total number of activity measurements/patient declined proportionally with time. However, for each month of follow-up, patients contributed, on average, nearly 30 days of measurements. Over time, mean patient activity was 111.0 ± 66.1 minutes/day, similar to the 107.5 ± 66.2 for the baseline period. In terms of within-patient variability, mean SD of activity was 37.2 ± 21.0 minutes/day, indicating that, 95% of the time, any given patient's daily activity ranged ± 79.2 minutes from his or her mean daily activity.

Time-varying patient activity predicted survival in a multivariate Cox regression model including age, sex, device type, and previous ICD alongside each patient's activity in any given 30-day period. The AHR of 1.479 (95% CI, 1.451 to 1.508; Table 3) indicates that a patient having 30 minutes per day less activity in a given month had a 48% increased hazard for death, when compared to a similar patient in the same month.

Discussion

This study presents, to our knowledge, the largest evaluation of patient activity in ICD patients. The principal finding is that device-detected activity is strongly correlated with survival after adjustment for age, sex, and device type. Patient physical activity considered in just the first 30 to 60 days after implantation yielded a 40% *absolute* difference in survival at 4 years between the most and least active quintiles (90.8% vs. 50.0%). This marked inverse relationship between activity and mortality was similar regardless of whether baseline activity or longitudinal activity is considered, with a similarly increased hazard for death for incremental difference of activity of only 30 minutes after adjustment for demographic and clinical covariates.

This study builds upon previous work evaluating patient activity in patients with ICDs, particularly those with HF. For example, Conraads et al.⁶ evaluated 781 HF patients blended from the SENSE-HF and DOT-HF studies, both of which enrolled patients with chronic systolic HF despite optimal medical therapy. "Early patient activity," defined as average activity in the earliest available 30-day window, predicted survival at a mean follow-up of 15 ± 7 months, with an HR of 0.93 for each 10 minutes/day of activity after adjustment for several clinical variables. In this study, adding activity to the CHARM risk model for HF significantly improved risk stratification. These data complement work from Whellan et al.⁸ from the PARTNERS-HF study, in which 694 patients with CRT-D implants were evaluated using a diagnostic algorithm combining low patient activity (<1 hour/day) with atrial fibrillation duration and ventricular response, ICD shocks, nighttime heart rate, heart rate variability, transthoracic impedance, and percent of CRT pacing. At 11.7 ± 2 months of follow-up, patients whose algorithms met prespecified thresholds were 5.5 times as likely to experience an HF hospitalization, though the

Table 2. Survival for Entire Study Cohort and Stratified by Quintile of Mean Minutes/Day Active in the First 30 to 60 Days After Implantable Cardioverter-Defibrillator Implantation

Survival Outcomes	Mean Baseline Activity (Minutes/Day)						P Value*
	Entire Study (N=98 437) 107.5±66.2	Quintile 1 (N=19 693) 32.5±13.5	Quintile 2 (N=19 691) 67.6±8.6	Quintile 3 (N=19 674) 97.3±8.9	Quintile 4 (N=19 692) 132.5±12.0	Quintile 5 (N=19 687) 207.7±58.5	
Survival at 1 year (95% CI)	0.950 (0.948 to 0.951)	0.865 (0.860 to 0.870)	0.945 (0.942 to 0.948)	0.968 (0.965 to 0.970)	0.982 (0.980 to 0.984)	0.987 (0.986 to 0.989)	<0.0001
Survival at 2 years (95% CI)	0.882 (0.879 to 0.884)	0.713 (0.705 to 0.720)	0.858 (0.852 to 0.863)	0.916 (0.911 to 0.920)	0.947 (0.943 to 0.950)	0.965 (0.962 to 0.968)	<0.0001
Survival at 3 years (95% CI)	0.818 (0.815 to 0.821)	0.593 (0.584 to 0.602)	0.774 (0.767 to 0.782)	0.855 (0.848 to 0.861)	0.906 (0.901 to 0.911)	0.939 (0.935 to 0.943)	<0.0001
Survival at 4 years (95% CI)	0.761 (0.757 to 0.765)	0.500 (0.488 to 0.512)	0.704 (0.694 to 0.715)	0.794 (0.785 to 0.804)	0.865 (0.857 to 0.873)	0.908 (0.901 to 0.914)	<0.0001

CI indicates confidence interval.

*P value for trend across quintiles according to log-rank test.

performance of patient activity alone was not reported. A follow-up study from Cowie et al.¹² validating a “heart failure score” using a similar suite of variables in 1310 patients (including those from the PARTNERS-HF study) identified 2.5-fold increase in the risk for an HF hospitalization in the next 30 days for patients with low activity alone. Our study thus supports and solidifies a growing body of literature on the use of activity alone or alongside other diagnostic parameters to identify ICD patients at high risk for adverse clinical events.

Our results raise questions about the underlying mechanisms and associations of patient activity. Presumably,

patients with better overall health would be expected both to live longer and be more active, and we cannot evaluate causality in our study design. However, relatively few data describe specific correlates of activity in ICD populations. Conraads et al.⁶ identified age, HF severity, peripheral and ischemic arterial disease, and atrial fibrillation to be predictors of patient activity, though the strong relationship with survival persisted after adjustment for these factors.⁶ Notably, however, this study excluded patients with chronic obstructive lung disease, pulmonary hypertension, and those undergoing hemodialysis, comorbidities potentially relevant for a significant proportion of ICD recipients.^{3,13}

Similarly, Vegh et al. evaluated physical activity and 6-minute walk tests in a single-center study of 164 CRT patients, finding both to predict HF hospitalizations with similar HRs after adjustment for clinical factors and medication use.¹⁴ Interestingly, though, the correlation between activity and the 6-minute walk was only modest. Kadhiresan et al.⁷ evaluated patient activity as well as 6-minute walk tests in 30 patients receiving CRT devices and found activity to be 84% sensitive and 73% specific for changes in distance walked. Thus, a more complete understanding of the components of activity in ICD patients will require further investigation. In particular, the activity measurements from the ICDs used in our study have not, to our knowledge, been validated against other accepted measures of activity, such as omnidirectional accelerometry.

In addition to a need for external validation of our activity measure, the principal limitation of our analysis is the lack of clinical covariates for inclusion in our modeling of survival. Though other work in this area has found that

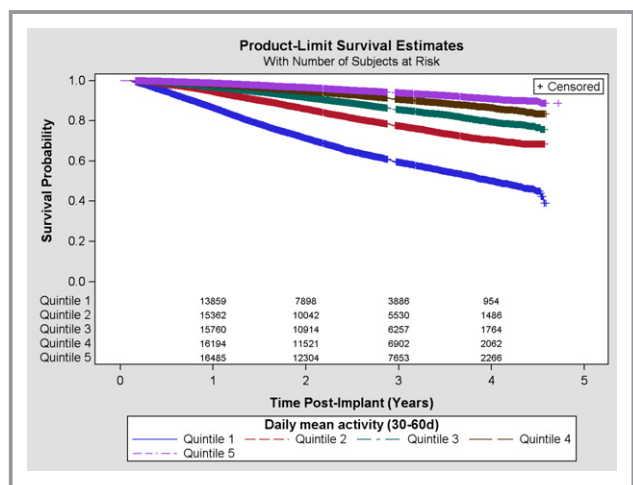


Figure 2. Survival and number of patients at risk for entire study population and stratified by quintile of patient baseline daily activity.

Table 3. Multivariate Analysis of Patient Characteristics and Survival After Implantable Cardioverter-Defibrillator Using Time-Varying Analysis of Activity

Variable	AHR (95% CI)*
Age (per 5-year increment)	1.118 (1.103 to 1.134)
ICD type (CRT vs. non-CRT device)	1.356 (1.285 to 1.429)
Male	1.666 (1.564 to 1.776)
Previous ICD implant	1.201 (1.137 to 1.269)
30-day mean daily activity (minutes/day) (per 30 minutes/day increment)**	1.479 (1.451 to 1.508)

AHR indicates adjusted odds ratio; CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

*Hazard ratios reported from model adjusted for age, device type, gender, previous ICD, and mean daily activity (minutes/day) treated as a time-varying covariate.

**That is, for every 30 minutes less of mean daily activity in any previous 30-day period, a 47.9% increased hazard for death was observed, adjusted for other covariates.

activity remains important after adjustment for HF severity and other comorbidities, our study design did not allow for a comparable statistical model. In addition, our data source only included patients from a single manufacturer's ICDs, as well as those who elected to participate in remote monitoring. Whether these results extend to other brands of ICDs, whose algorithms for measuring activity may differ, remains unknown. Again, measurement of patient activity by pectoral accelerometer may be insensitive to specific types of exercise, such as stationary bicycling or swimming, and of uncertain validity compared with other measurements of activity.¹⁵ However, the relatively low threshold for identifying a time period as active would argue that subjects regularly engaged in biking or swimming would likely be identified as comparatively active in daily life otherwise. Our survival analysis depended on identification of vital status using the Social Security Death Index, which may result in under-reporting of deaths, though we selected the endpoint for our follow-up period to account for a lag in reporting. Our analysis could not identify cause of death, which further emphasizes the need to more clearly explore the mechanisms through which patient activity predicts survival. In particular, whether activity in a broadly selected ICD population distinguishes sudden and nonsudden deaths remains uncertain, and, in either case, we again note that the association we have identified does not imply a causal relationship. Indeed, though we were able to clearly risk stratify patients for death according to activity, without a non-ICD control group we cannot comment on whether protection from arrhythmic death specifically benefited different quintiles of activity differentially.

Despite these limitations, there may be clinical and research opportunities for utilizing activity information gleaned from ICDs, which, unlike more-complex risk models,

is readily available. If further validated, our findings suggest that evaluating activity in an ICD patient before undergoing an ICD replacement procedure may provide additional prognostic information. Decisions around ICD replacement remain controversial and plagued by relatively scarce data regarding outcomes, compared with new ICD implantation.^{13,16,17} For patients and clinicians uncertain about expected survival with an ICD, patient activity provides a simple risk discriminator that—in our study of >225 000 patient-years of follow-up—starkly separated outcomes for high- and low-activity individuals. Again, though survival without an ICD in these subpopulations is unknown, patient and physician expectations about survival with a device may support shared decision making.^{18,19} Use of device-adjudicated activity levels to measure patient response to, for example, CRT implantation or optimization, may also provide a simple, quantitative assessment of functional response more rigorous and granular than New York Heart Association class and simpler than typical patient-reported outcome scales.

In sum, we observe, in a nation-wide sample of ICD patients, a striking relationship between both early and time-varying activity and survival. Future work, including external validation of the activity measurement, may expand our understanding of the components of activity itself while clarifying the causal relationship and mechanisms underlying this association.

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