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Quantifying the time-varying association between objectively measured physical activity and mortality in US older adults over a 12-year follow-up period: The NHANES 2003-2006 study

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Abstract

Objectively measuring physical activity (PA) has consistently shown an association with reduced all-cause mortality risk in cross-sectional studies. However, the strength of this association may change over time. We quantify the time-varying, covariate-adjusted association between the total volume of PA and all-cause mortality over a 12-year follow-up period using Cox regression with a time varying effect of population-referenced quantile TAC adjusted for traditional risk factors. Analyses focus on participants 50 to 84 years old with adequate accelerometer wear time and without missing covariates. The findings suggest that: 1) the use of baseline PA in Cox models with long follow-up periods may be inappropriate without time-varying effects; and 2) the use of accelerometry derived volume of PA in risk score calculations may be most appropriate for short-to-medium term risk scores.

What is already known on this topic –

Previous research has established a strong association between objectively measured physical activity (PA) levels and a reduced risk of all-cause mortality. It is well-documented that PA tends to decline with age and the accumulation of multisystem functional deficits. This age-related decline could potentially influence the strength of the association between PA measured at the beginning of a study (baseline) and the risk of mortality in the future.

What this study adds –

This study adds to the existing knowledge by quantifying the time-varying relationship between PA and all-cause mortality over a 12-year follow-up period.

How this study might affect research, practice or policy -

The findings suggest that using baseline PA measurements in statistical models with long follow-up periods may not be appropriate without considering time-varying effects. Additionally, the study suggests that incorporating the volume of PA into risk score calculations may be most suitable for short-to-medium-term risk assessments.

INTRODUCTION

Physical activity (PA) assessment is a fundamental component of public health research and clinical practice. Both objective and self-reported measures of PA have garnered substantial attention in recent years due to their distinct characteristics and implications. While objective measures involve using instruments to quantify activity levels, self-reported measures rely on individuals' recollections and reports of PA through surveys, questionnaires, or interviews.

The association between objectively measured PA using accelerometers and mortality has been extensively documented in the literature(1-4). The reasons for the increased focus on quantifying this association are that accelerometry-derived PA measurements: (1) are among the strongest predictors of all-cause mortality(5-7); (2) are not subject to the well-documented inherent biases and measurement errors of self-report(8-10); and (3) allow for resolution and details that cannot be achieved by self-report(11-13).

Most approaches for analyzing this association have either focused on single time horizon models (e.g., five-year all-cause mortality)(7, 14, 15) or time-to-event models with time-invariant effects(16-18). These models are not designed to quantify the time-variant effect i.e., the

association between objectively measured PA and mortality depending on follow-up time from PA measurement. Recently, using UK Biobank data Strain et al. (2019)(17) reported a potential attenuation of the association of PA and all-cause mortality with an increase in follow-up time cut-off from one to seven years.

The objectives of the current study are to: (1) quantify the time-varying association between objectively measured PA and mortality in US older adults accounting for traditional risk factors; (2) evaluate the shape of the log-hazard of mortality as a function of follow-up time; and (3) characterize short, medium and long-term all-cause mortality prediction performance of objective measures of PA.

METHODS

Study population

The NHANES is a major initiative by the Centers for Disease Control and Prevention (CDC) to assess health and nutritional status of the US population. NHANES is a cross-sectional study with a complex survey structure and is conducted continuously in two-year waves. The 2003-2004 and 2005-2006 NHANES waves collected minute level accelerometry data using a hip-worn physical activity monitor for up to seven days. NHANES also collected demographic, socioeconomic, dietary, and health-related information as part of the interview component and medical, dental, physiological measurements, and laboratory tests information during the examination component. We linked NHANES to mortality follow-up data by the National Death Index (NDI) from the date of survey participation through December 31, 2015 to create a prospective cohort study (19).

To ensure that the NHANES data is representative of the civilian non-institutionalized U.S. population, a sample weight is assigned to each participant to account for oversampling, reduce non-response bias, and adjust for post-stratification(20, 21). The sample weight corresponds to the number of people in the US population who are represented by that individual. NHANES has a survey sample structure, which is accounted for by the nested design of primary sampling units (PSU) within strata. Data are downloaded directly from the CDC website and are processed using the R package rnhanesdata(22).

The study included participants who have both accelerometry and mortality data in the age group 50-84 years from the combined NHANES 2003-2004 and 2005-2006 waves. The final data analysis included participants with at least 3 days of data with 10 or more hours of estimated wear time and non-missing demographics, comorbidity, lifestyle variables or mortality data.

Features

Traditional risk factors

In addition to objective physical activity all models contained traditional risk factors for mortality including demographic, lifestyle, health status, and self-reported medically diagnosed variables. Demographic variables included: age (years), body mass index (kg/m^2), race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other), gender (male and female) and education level (less than high school, high school and more than high school). Lifestyle variables included: self-reported cigarette smoking status (never, former, and current) and current alcohol consumption status (non-drinker, moderate drinker, heavy drinker). Self-

reported medically diagnosed conditions included congestive heart failure (CHF), coronary heart disease (CHD), cancer, stroke (all categorized into yes, no, refused, do not know), diabetes (yes, no, borderline, refused, do not know), and presence of a mobility issue defined as using any special equipment to walk or any difficulty either climbing 10 stairs or walking a quarter mile.

Accelerometry derived variables

The hip worn ActiGraph accelerometer in NHANES 2003-2006 recorded uniaxial magnitude of acceleration summarized into minute-level "activity counts" up to 7 days. Participants were instructed to take the device off during bedtime and water activities. We focus on one summary measure of objective PA obtained from accelerometry: average total activity count (TAC)(23-25). This is obtained for each study participant by taking the sum of all activity counts for each valid day and then averaging these total activity counts over valid days. Average TAC quantifies the total volume of PA, is highly correlated with measures of moderate to vigorous PA (MVPA) but has an advantage over MVPA of never being truncated to zero, which is common for low-function elderly NHANES participants. TAC is also intuitive and simple to compute. For increased interpretability of results and to reduce the influence of outliers, TAC was transformed to population quantiles and multiplied by 100 prior to statistical analyses. For example, the median (50th percentile) of TAC in our sample was 190326. For statistical analyses, an individual with TAC of 190326 would be transformed to 50. As a result, regression coefficients associated with TAC are interpretable as the change in the log hazard associated with a one percent shift in the population distribution of TAC. Hereafter we refer to the quantile transformed TAC as TAC_q. Distribution summaries for the traditional risk factors and accelerometry derived variables are provided in Table 1.

Statistical Analysis

The main goal of the paper was to analyze whether PA as measured by TAC has a time-varying effect on mortality and quantify how the effect changes as a function of the follow-up period. We started with a graphical display of TAC distribution over the follow-up time among individuals who are alive versus who experienced death in the preceding year to look for potential time-varying effect of TAC. We then tested two models. The first model fit was a Cox proportional hazard model (26) with fixed time effects of TAC_q and all traditional risk factors described in the *Features* section. We tested the hazard proportionality assumption for the effect of TAC_q using an individual Wald test and a global chi-square test based on the Schoenfeld residuals (27). Having a significantly small p-value indicates that the effect of TAC_q on the hazard of mortality is time-invariant.

The second model fit was a Cox model with time-varying coefficient for TAC_q (28, 29). The hazard of mortality is modeled as a function of covariates as

$$\lambda(t \mid X, \mathrm{TAC}_q) = \lambda_0(t)\, e^{X\gamma + \mathrm{TAC}_q\, \beta(t)},$$

where $\lambda_0(t)$ is an unspecified baseline hazard function, X is the vector of all traditional risk factors described in the *Features* section, γ is the vector of parameters associated with X, and $\beta(\cdot)$ denotes the time dependent effect for TAC_q. The first approach was to estimate $\beta(\cdot)$ non-parametrically using penalized cubic spline smother implemented in mgcv (30-33) package in R (34). As this approach provided an estimator indistinguishable from a linear effect, we fit a simpler linear parametric form $\beta(t) = \beta_0 + \beta_1 t$. This is equivalent to adding an interaction term between

TAC_q and time to the model. To account for missing data, sampling weights were reweighted using the function reweight_accel() in the rnhanesdata (22) R package. The re-weighting is performed using age, sex, and ethnicity strata applied to each wave separately. To account for the survey structure of the data we used the survey-weighted Cox proportional hazard model implemented in the R package survey.

The accompanying vignette is designed to make our approach fully reproducible and is available in Github https://github.com/agneha2010/time_varying_effect. The vignette includes two parts – a data section which explains data creation and a method section which explains the analyses and results to support the three objectives.

RESULTS

Our study included 3,772 participants aged 50-84 years who had both accelerometry and mortality data available. The final cohort of 3,218 individuals excluded participants with less than 3 days of valid accelerometer data, each containing 10 or more hours of estimated wear time (n=507) and individuals with missing demographic information, comorbidity data, lifestyle variables, or mortality data (n=47). During a cumulative follow-up period of 30,927 person-years, we recorded a total of 867 mortality events, with an average event time of 6.05 years.

To investigate the impact of physical activity on mortality, Figure 1 displays the distributions of TAC_q for individuals who survived (shown in gray) versus those who died (shown in white) stratified by one-year time intervals from baseline. The numbers shown at the top of boxes provide the number of individuals who survived and died, respectively, in that time interval. For example,

for year three, 3024 study participants survived at least three years and 68 participants died between year two and three from baseline visit. We observed marked disparities in TACq distributions between participants who experienced mortality and those who survived across all time intervals. Notably, these differences were most pronounced for shorter timeframes and gradually attenuated for longer durations. This visual representation suggests that the effect of TAC_q on mortality may vary with time.

The first model fit was a fully adjusted linear model with non-varying (fixed) time effect of TAC_q on risk of mortality. In this model the estimated hazard ratio (HR) of TAC_q is 0.98 (95% CI: 0.98-0.99, $p < 0.001$) indicating a 2% decrease in the risk of death for one percentile increase in TAC. However, the global chi-square test for the null hypothesis of hazard proportionality for this model had a p-value 0.002. In addition, the individual Wald test corresponding to TAC_q had a p-value 0.008, indicating strong evidence that this model may not be appropriate. One potential reason could be that the model does not account for a strong time-varying effect of TAC_q on mortality.

The second model, a fully adjusted Cox regression model with linear time-varying effect of TAC_q, was used to quantify and evaluate on the shape of time-varying effect of PA on mortality. Figure 2 displays the estimated linear effect of time-varying TAC_q on mortality with a statistically significantly negative intercept ($\hat{\beta}_0 = -0.026$, CI: (-0.036, -0.016); $p < 0.001$) and positive slope ($\hat{\beta}_1 = 0.001$, CI: (0.00, 0.003); $p = 0.021$). On the HR scale the covariate adjusted effect of one percentile increase in TAC corresponds to an HR = 0.974, (CI: (0.965, 0.984); $p < 0.001$) for mortality immediately after PA measurement and HR = 0.991 (CI: (0.985, 0.997); $p = 0.002$) 12 years later. The HR increases at a rate of 0.139 percent per year (CI: (0.02, 0.257); $p = 0.021$).

Table 2 indicates that an increase of one year of age (after age 50) is associated with a higher mortality risk (HR = 1.07; CI: (1.06, 1.09); p < 0.001). Being female is associated with a lower risk of mortality compared to males (HR = 0.57, CI: (0.47, 0.68); p < 0.001). Having a high school (HR = 0.92; CI: (0.69, 1.22); p = 0.544) and more than a high school education (HR = 0.79; CI: (0.612, 1.02); p = 0.067) are not significantly associated with a lower mortality risk compared to having less than a high school education. Being a current smoker (HR = 2.06; CI: (1.71, 2.47); p < 0.001) or former smoker (HR = 1.32; CI: (1.05, 1.66); p = 0.016) is associated with a higher mortality risk compared to non-smokers. Compared to moderate alcohol consumption, individuals who report no alcohol consumption (HR = 1.40; CI: (1.15,1.70); p<0.001), heavy alcohol consumption (HR = 1.71; CI: (1.11, 2.64); p = 0.015), or are missing alcohol consumption data (HR = 2.00; CI: (1.39,2.88); p<0.001) have increased risk of mortality. Finally, history of diabetes (HR = 1.31, CI: (1.11, 1.54); p = 0.001), congestive heart failure (HR = 1.76, CI: (1.36, 2.28); p < 0.001), cancer (HR = 1.36, CI: (1.12, 1.67); p = 0.001) and Mobility Problem: Any difficulty (HR = 1.48, CI: (1.30, 1.67); p < 0.001) are associated with increased risk of mortality. We note that the Wald tests for alcohol consumption (p=0.043) and mobility problem (p=0.04) was also below the nominal threshold of p<0.05. However, exploration of potential time-varying effects of these variables is beyond the scope of current work.

To characterize short, medium and long-term all-cause mortality prediction performance of objective measures of PA, Figure 3 displays the covariate-adjusted estimated survival functions for two individuals, one in his 50s (left panel) and the other in his 70s (right panel), both identified as white males who attended more than high school, with a normal BMI, and no history of diabetes,

CHF, CHD, cancer, stroke, mobility problem, alcohol consumption, and cigarette smoking. Survival functions are shown by quartiles of TAC_q: first quartile of TAC_q (solid line), second quartile (dashed) and third quartile (dotted). The quantiles values are adjusted for age using a quantile regression of TAC_q on age. Blue curves correspond to the survival function estimates at baseline and the yellow curves correspond to survival functions conditional on being alive 10 years after baseline measurement.

The Figure 3 indicates that for a male in his 50s the survival curves are substantially different immediately after baseline visit as a function of the TAC_q quartile. By five years after baseline the estimated survival probabilities are substantially different (0.975 for first quartile, 0.985 for median, and 0.99 for third quartile). By 10 years after baseline the difference between estimated survival probabilities increases further (0.925 for first quartile, 0.95 for median, and 0.962 for third quartile). Conditional on surviving for 10 years from baseline measurements, survival curves are notably different by the quartiles of TAC_q at baseline. Indeed, the estimated survival probability at 12 years conditional on survival for 10 years after baseline are 0.97 for first quartile, 0.976 for median, and 0.98 for third quartile of baseline TAC_q. Similar, but more pronounced differences can be viewed for the estimated curves corresponding to a male in his 70s. Indeed, the survival probabilities decrease much faster with time from baseline while the absolute differences between the estimated survival probabilities are larger as a function of TAC_q quartiles.

DISCUSSION

The association between objective PA and all-cause mortality in NHANES was analyzed as a function of time from the baseline measurement. Total volume of PA was summarized by average total activity count (TAC), transformed into population reference quantiles. Results show that objectively measured PA is a strong predictor of all-cause mortality for US individuals over the age of 50 even after adjusting for traditional risk factors. Its prediction performance is strongest immediately after the PA measurement and then slowly decreases but remains statistically significant 12 years after the PA measurement was obtained. The analysis provides insights on subject-specific prediction of predicted probability of death at any age and provide alternative predictions for changes in PA. For example, for someone who is not as physically active would have higher probability of survival if they moved to be moderately active for their age.

Given that multiple studies (5-7) have shown that PA is the strongest modifiable predictor of mortality, it is ideal for interventions. Results suggests that any sustained increased in PA is associated with increased odds of survival.

The reduced association of PA with mortality farther from the PA baseline measurement can have multiple explanations: (1) PA is itself time-varying and a PA measurement taken farther away in the past may not be as representative of the current health status; (2) life- and health-events are more likely to occur during a longer follow-up period, which can substantially change the frailty and health status of the individual; and (3) biological age has a stronger relative effect on mortality for longer times from baseline measurements.

One potential limitation of the analysis is that we considered only linear effects of TAC_q. In future studies one could investigate the potential non-linear associations between TAC and mortality and expand the number and type of PA summaries. Other potential weaknesses include: (1) not considering more complex interaction models among PA summaries; (2) not considering the entire trajectory of PA during the day; (3) not accounting for potential nonlinear time-varying effects of age; and (4) not including potential confounding variables related to dietary habits and other important health conditions such as hypertension or chronic respiratory disease in the model.

In conclusion, objective measures of PA obtained from hip-worn accelerometers are strong predictors of mortality even after adjusting for traditional risk factors. The strength of the association decreases with time from PA measurement but remains statistically significant twelve years later.

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COMPETING INTERESTS

Dr. Crainiceanu is consulting with Bayer and Johnson and Johnson on methods development for wearable devices in clinical trials. The details of the contracts are disclosed through the Johns Hopkins University eDisclose system and have no direct or apparent relationship with this manuscript.

ETHICS APPROVAL STATEMENT

This study involving human participants has received ethical approval from the National Center for Health Statistics (NCHS) Ethics Review Board (ERB) under Protocol Numbers 98-12 and 2005-06. All participants provided informed consent prior to their involvement in the study.

CONTRIBUTORSHIP STATEMENT

Author's role: Study concept and design: VZ, AL, CC; Acquisition of the data: AL and NA; Analysis and interpretation of the data: AL and NA; Preparation of manuscript: AL, NA, CC and VZ. The funding agencies that supported the research had no role in the development of these analyses or the preparation of the manuscript.

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Table 1. Distribution summaries for the traditional risk factors and accelerometry derived variables by mortality status (alive/deceased).

	Mean(SD)/N(%)a	
Features	Alive	Deceased
n	2351	867
Age	63.53 (8.77)	72.54 (8.93)
Gender: Female	1251 (53.2)	344 (39.7)
Race		
White	1320 (56.1)	552 (63.7)
Mexican American	446 (19.0)	132 (15.2)
Other Hispanic	48 (2.0)	13 (1.5)
Black	455 (19.4)	149 (17.2)
Other	82 (3.5)	20 (2.3)

Education Adult		
Less than high school	663 (28.2)	366 (42.3)
High school	584 (24.8)	215 (24.8)
More than high school	1104 (47.0)	285 (32.9)
Smoke Cigarettes		
Never	1142 (48.6)	294 (33.9)
Former	836 (35.6)	401 (46.3)
Current	373 (15.9)	171 (19.7)
Drinking Status		
Moderate drinker	1204 (51.2)	317 (36.6)
Non-Drinker	929 (39.5)	440 (50.8)
Heavy drinker	124 (5.3)	64 (7.4)
Missing alcohol	94 (4.0)	45 (5.2)
BMI		
Normal	588 (25.0)	243 (28.1)
Underweight	14 (0.6)	16 (1.8)
Overweight	903 (38.4)	323 (37.3)
Obese	846 (36.0)	284 (32.8)
Diabetes: Yes	353 (15.0)	222 (25.6)
CHF: Yes	77 (3.3)	114 (13.2)
CHD: Yes	136 (5.8)	131 (15.1)
Stroke: Yes	86 (3.7)	107 (12.4)
Cancer: Yes	293 (12.5)	212 (24.5)

Mobility Problem: Any Difficulty	587 (25.0)	452 (52.2)
TAC_q	56.55 (26.79)	32.29 (26.81)

Notes: Combined data from the NHANES 2003-2004 and 2005-2006 waves.

Table 2. Estimated hazard ratio (HR), 95% confidence interval and P-values in the fully adjusted varying coefficient model for TAC_q.

	Estimate	CI (95%)	p-value
Age	1.069	(1.057, 1.082)	<0.001
Gender: Female	0.565	(0.467, 0.684)	<0.001
Race			
Mexican American	1.000	(0.788, 1.269)	0.999
Other Hispanic	1.284	(0.745, 2.215)	0.368
Black	1.028	(0.827, 1.278)	0.803
Other	0.916	(0.487, 1.724)	0.787
Education Adult			
High school	0.916	(0.690, 1.216)	0.544
More than high school	0.792	(0.617, 1.016)	0.067
Smoke Cigarettes			
Former	1.322	(1.054, 1.658)	0.016
Current	2.057	(1.712, 2.471)	<0.001
Drinking Status			
Moderate drinker	0.713	(0.587, 0.866)	0.001
Heavy drinker	1.222	(0.803, 1.861)	0.350
Missing alcohol	1.426	(0.981, 2.073)	0.063
BMI			
Underweight	2.572	(1.329, 4.979)	0.005

Overweight	0.766	(0.664, 0.884)	<0.001
Obese	0.837	(0.669, 1.048)	0.121
Diabetes: Yes	1.308	(1.109, 1.543)	0.001
CHF: Yes	1.761	(1.362, 2.278)	<0.001
CHD: Yes	1.133	(0.893, 1.437)	0.303
Stroke: Yes	1.270	(0.982, 1.643)	0.068
Cancer: Yes	1.355	(1.124, 1.634)	0.001
Mobility Problem: Any Difficulty	1.476	(1.301, 1.675)	<0.001
TAC_q	0.974	(0.965, 0.984)	<0.001
Time*TAC_q	1.001	(1.000, 1.003)	0.021

Notes: For each regression model, coefficient estimates are presented with 95% confidence intervals in parentheses.

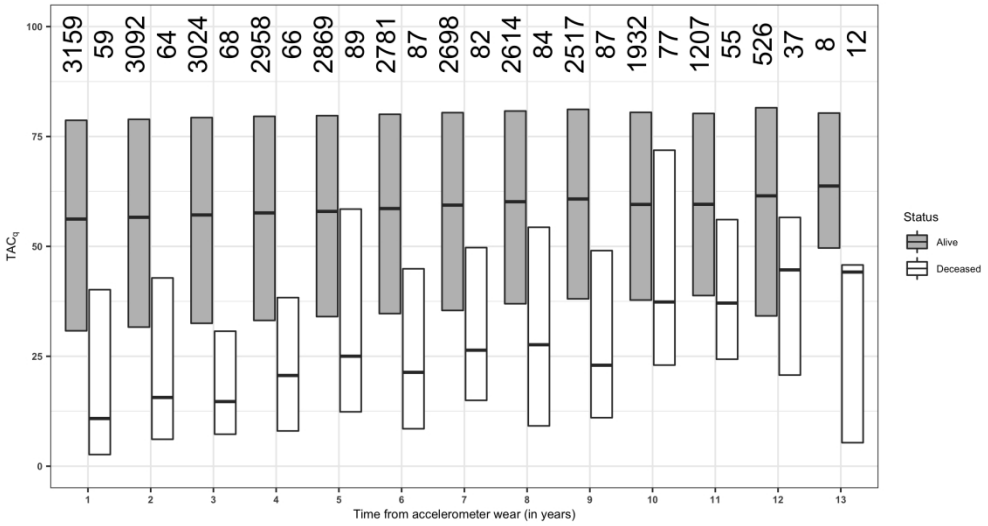

Figure 1. Distributions of population quantile TAC for individuals who survived (shown in gray) versus those who experienced mortality (shown in white) in the time interval [t-1,t] for t=1, …, 12. The boxes correspond to the median, first and third quartile of the distributions, respectively.

952x529mm (72 x 72 DPI)

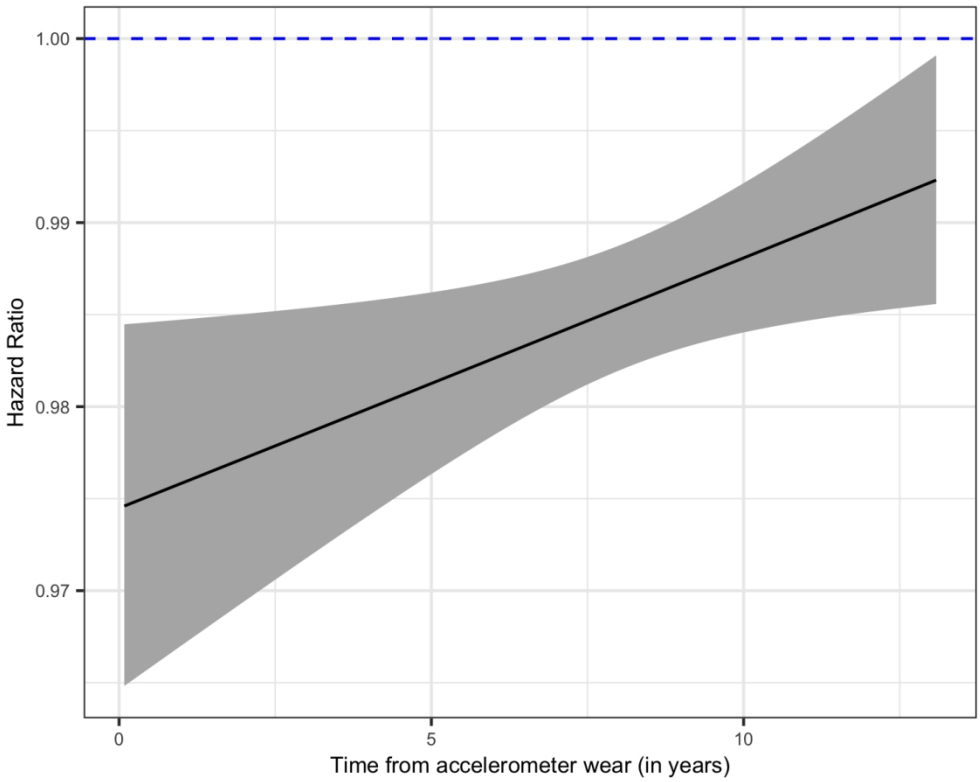

Figure 2. Adjusted estimated hazard ratio (black solid) with 95% pointwise confidence bands (shaded areas) for the effect of one standard deviation increase of population quantile TAC on mortality risk as a function of time.

529x423mm (72 x 72 DPI)

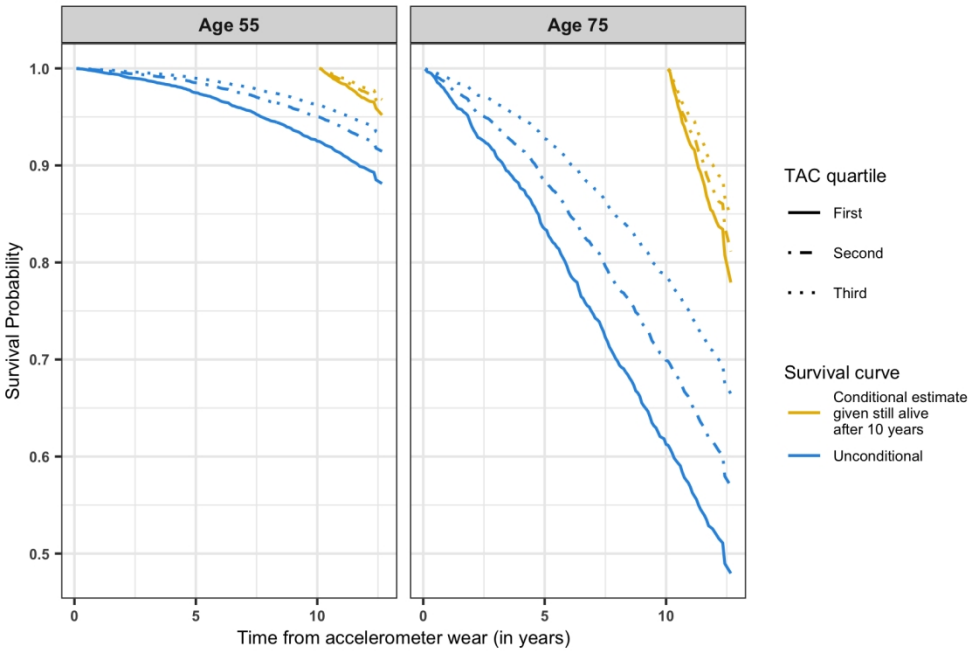

Figure 3. Covariate-adjusted estimated survival functions for a healthy white male age 55 (left panel) and 75 (right panel) at the baseline visit, respectively by quartiles of TACq: first quartile of TACq (solid line), second quartile (dashed) and third quartile (dotted). Black curves correspond to the survival function estimates at baseline and the blue curves correspond to survival functions conditional on being alive 10 years after the baseline measurement.

635x423mm (72 x 72 DPI)

Quantifying the time-varying association between objectively measured physical activity and mortality in US older adults: The NHANES study

The outline of the vignette includes a data section followed by the methods section. The data section elaborates each step of the data creation. We partition the methods section into the following three objectives- a. quantify the time-varying association between objectively measured PA and mortality in US older adults accounting for traditional risk factors; b. evaluate the shape of the log-hazard of mortality as a function of follow-up time; and c. characterize short, medium and long-term all-cause mortality prediction performance of objective measures of PA.

Load the following packages.

```
library(rnhanesdata)
library(reshape2)
library(ggplot2)
library(gridExtra)
library(dplyr)
library(tableone)
library(survey)
library(survival)
library(survminer)
library(quantreg)
library(reshape2)
library(mgcv)
library(stringr)
library(formatR)
```

1. Data

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States[1]. The NHANES accelerometry data is a cross-sectional study of the US population performed in 2-year waves, namely 2003-04 wave and 2005-06 wave. The device placed on the right hip, records uniaxial "intensity" of movement upto 7 days for each participant except during swimming, sleeping, etc. Acceleration summarized into minute-level "activity counts". The NDI mortality data provides mortality follow-up data through December 31, 2015. It is already known that physical activity is linked with mortality. We link the accelerometer data with the mortality data to answer "How far into the future does physical activity (PA) predict mortality?"

We include individuals with

- at least 3 days of data and at least 10 hours of estimated wear time
- non-missing demographic and lifestyle variables and mortality data
- ages 50-84 Individuals who died due to accidents were censored at their time of death. The following chunk of code explains data creation in details.

```
## load the data from rnhanesdata package
data("PAXINTEN_C");data("PAXINTEN_D")
data("Flags_C");data("Flags_D")
data("Covariate_C");data("Covariate_D")
data("Mortality_2015_C");data("Mortality_2015_D")

## re-code activity counts which are considered "non-wear" to be 0
## this doesn't impact much data, most estimated non-wear times correspond to 0 counts anyway
PAXINTEN_C[,paste0("MIN",1:1440)] <- PAXINTEN_C[,paste0("MIN",1:1440)]*
  Flags_C[,paste0("MIN",1:1440)]
PAXINTEN_D[,paste0("MIN",1:1440)] <- PAXINTEN_D[,paste0("MIN",1:1440)]*
  Flags_D[,paste0("MIN",1:1440)]

## Merge covariate, mortality, and accelerometry data
## note that both PAXINTEN_* and Covariate_* have a column
## called "SDDSRVYR" indicating which NHANES wave the data is associated with.
## To avoid duplicating this column in the merged data, we add this variable to the "by"
## argument in left_join()
AllAct_C <- left_join(PAXINTEN_C, Mortality_2015_C, by = "SEQN") %>%
        left_join(Covariate_C, by=c("SEQN", "SDDSRVYR"))
AllAct_D <- left_join(PAXINTEN_D, Mortality_2015_D, by = "SEQN") %>%
        left_join(Covariate_D, by=c("SEQN", "SDDSRVYR"))

AllFlags_C <- left_join(Flags_C, Mortality_2015_C, by = "SEQN") %>%
        left_join(Covariate_C, by=c("SEQN", "SDDSRVYR"))
AllFlags_D <- left_join(Flags_D, Mortality_2015_D, by = "SEQN") %>%
        left_join(Covariate_D, by=c("SEQN", "SDDSRVYR"))

## clean up the workspace for memory purposes
rm(list=c(paste0(c("PAXINTEN_", "Covariate_","Mortality_2015_","Flags_"),rep(LETTERS[3:4],each=4))))

## combine data for the two waves
AllAct   <- rbind.data.frame(AllAct_C,AllAct_D)
AllFlags <- rbind.data.frame(AllFlags_C,AllFlags_D)


## clean up the workspace again
rm(list=c("AllAct_C","AllAct_D","AllFlags_C","AllFlags_D"))
#############################################################################
##                                                                         ##
##  Section 1b: create new variables/relevel factor variables for analyses  ##
##                                                                         ##
#############################################################################

## Code year 5 mortality, NAs for individuals with follow up less than 5 years and alive
AllAct$yr5_mort <- AllFlags$yr5_mort <- as.integer(ifelse(AllAct$permth_exm/12 <= 5 & AllAct$mortstat ==
                                                    ifelse(AllAct$permth_exm/12 < 5 & AllAct$mortstat
## Create Age in years using the age at examination (i.e. when participants wore the device)
AllAct$Age <- AllFlags$Age <- AllAct$RIDAGEEX/12

## Re-level comorbidities to assign refused/don't know as not having the condition
## Note that in practice this does not affect many individuals, but it is an
## assumption we're making.
```

```
levels(AllAct$CHD) <- levels(AllFlags$CHD) <- list("No" = c("No","Refused","Don't know"),"Yes" = c("Yes
levels(AllAct$CHF) <- levels(AllFlags$CHF) <- list("No" = c("No","Refused","Don't know"),"Yes" = c("Yes
levels(AllAct$Stroke) <- levels(AllFlags$Stroke) <- list("No" = c("No","Refused","Don't know"),"Yes" =
levels(AllAct$Cancer) <- levels(AllFlags$Cancer) <- list("No" = c("No","Refused","Don't know"),"Yes" =
levels(AllAct$Diabetes) <- levels(AllFlags$Diabetes) <- list("No" = c("No","Borderline","Refused","Don't

## Re-level education to have 3 levels and categorize don't know/refused to be missing
levels(AllAct$EducationAdult) <- levels(AllFlags$EducationAdult) <- list("Less than high school"= c("Les

## Re-level alcohol consumption to include a level for "missing"
levels(AllAct$DrinkStatus) <- levels(AllFlags$DrinkStatus) <- c(levels(AllAct$DrinkStatus),"Missing alco
AllAct$DrinkStatus[is.na(AllAct$DrinkStatus)] <- AllFlags$DrinkStatus[is.na(AllAct$DrinkStatus)] <- "Mis

## Re-order columns so that activity and wear/non-wear flags are the last 1440 columns of our two
## data matrices. This is a personal preference and is absolutely not necessary.
act_cols <- which(colnames(AllAct) %in% paste0("MIN",1:1440))
oth_cols <- which(!colnames(AllAct) %in% paste0("MIN",1:1440))
AllAct   <- AllAct[,c(oth_cols,act_cols)]
AllFlags <- AllFlags[,c(oth_cols,act_cols)]
rm(list=c("act_cols","oth_cols"))

##############################################################
##                                                          ##
##  Section 2: Calcualte common accelerometery features     ##
##                                                          ##
##############################################################

## Assign just the activity and wear/non-wear flag data to matrices.
## This makes computing the features faster but is technically required.
act_mat  <- as.matrix(AllAct[,paste0("MIN",1:1440)])
flag_mat <- as.matrix(AllFlags[,paste0("MIN",1:1440)])

## replace NAs with 0s
## As described in the manuscript, this only affects 501 minutes for 1 day, for one subject
act_mat[is.na(act_mat)]   <- 0
flag_mat[is.na(flag_mat)] <- 0

AllAct$TAC   <- AllFlags$TAC   <- rowSums(act_mat)
AllAct$TLAC  <- AllFlags$TLAC  <- rowSums(log(1+act_mat))
AllAct$WT    <- AllFlags$WT    <- rowSums(flag_mat)
AllAct$ST    <- AllFlags$ST    <- rowSums(act_mat < 100)
AllAct$MVPA  <- AllFlags$MVPA  <- rowSums(act_mat >= 2020)

## calculate fragmentation measures
bout_mat <- apply(act_mat >= 100, 1, function(x){
    mat <- rle(x)
    sed <- mat$lengths[which(mat$values == FALSE)]
    act <- mat$length[mat$values == TRUE]

    sed <- ifelse(length(sed) == 0, NA, mean(sed))
    act <- ifelse(length(act) == 0, NA, mean(act))
    c(sed,act)
})
```

```
AllAct$SBout <- AllFlags$SBout <- bout_mat[1,]
AllAct$ABout <- AllFlags$ABout <- bout_mat[2,]
AllAct$SATP  <- AllFlags$SATP  <- 1/AllAct$SBout
AllAct$ASTP  <- AllFlags$ASTP  <- 1/AllAct$ABout
rm(list=c("act_mat","flag_mat","bout_mat"))

##########################################
##                                      ##
##  Section 3: Apply exclusion criteria  ##
##                                      ##
##########################################

## make dataframe with one row per individual to create table 1.
## Remove columns associated with activity to avoid any confusion.
table_dat <- AllAct[!duplicated(AllAct$SEQN),-which(colnames(AllAct) %in% c(paste0("MIN",1:1440),
                                                                            "TAC","TLAC","WT","ST","MVPA

## subset based on our age inclusion/exclusion criteria
## note that individuals age 85 and over are coded as NA
table_dat <- subset(table_dat, !(Age < 50 | is.na(Age)))

## get the SEQN (id variable) associated with individuals with fewer than 3 days accelerometer
## wear time with at least 10 hours OR had their data quality/device calibration flagged by NHANES
keep_inx       <- exclude_accel(AllAct, AllFlags)
Act_Analysis   <- AllAct[keep_inx,]
Flags_Analysis <- AllFlags[keep_inx,]
nms_rm         <- unique(c(Act_Analysis$SEQN[-which(Act_Analysis$SEQN %in% names(table(Act_Analysis$SEQN
rm(list=c("keep_inx"))

## Additional inclusion/exclusion criteria.
## Aside from mortality or accelerometer weartime, the only missingness is in
## Education (6) and BMI (35).
criteria_vec <- c("(is.na(table_dat$BMI_cat))",          # missing BMI
                  "(is.na(table_dat$EducationAdult))",  # missing education
                  "(table_dat$SEQN %in% nms_rm)",       # too few "good" days of accel data
                  "((!table_dat$eligstat %in% 1) | is.na(table_dat$mortstat) |
                  is.na(table_dat$permth_exm))") # missing mortality data, or accidental death

## create matrix of pairwise missing data based on our exclusion criterial
tab_miss <- matrix(NA, ncol=length(criteria_vec), nrow=length(criteria_vec))
for(i in seq_along(criteria_vec)){
    for(j in seq_along(criteria_vec)){
        eval(parse(text=paste0("miss_cur <- which(", criteria_vec[i], "&", criteria_vec[j],")")))
        tab_miss[i,j] <- length(miss_cur)
        rm(list=c("miss_cur"))
    }
}
rownames(tab_miss) <- colnames(tab_miss) <- c("BMI","Education","Bad Accel Data","Mortality")
rm(list=c("i","j"))
## view missing data pattern
tab_miss
```

```
##                 BMI Education Bad Accel Data Mortality
```

```
## BMI              35         0              8         0
## Education         0         6              2         0
## Bad Accel Data    8         2            517         0
## Mortality         0         0              0         6
```

```
## add in column indicating exclusion:
##   Exclude = 1 indicates an individual does not meet our inclusion criteria
##   Exclude = 0 indicates an individual does meet our inclusion criteria
eval(parse(text=paste0("table_dat$Exclude <- as.integer(", paste0(criteria_vec,collapse="|"), ")")))

## Create our dataset for analysis with one row per subject
## containing only those subjects who meet our inclusion criteria.
data_analysis  <- subset(table_dat, Exclude == 0)
data_analysis$mortstat <- ifelse((data_analysis$ucod_leading %in% "004" & data_analysis$mortstat ==1),0
## get adjusted survey weights using the reweight_accel function
data_analysis  <- reweight_accel(data_analysis)

## Get activity/flag data for only those included participants AND who have 3 good days of data.
## Since we've already removed the "bad" days from Act_Analysis and Act_Flags,
## we need only subset based on subject ID now.
Act_Analysis   <- subset(Act_Analysis, SEQN %in% data_analysis$SEQN)
Flags_Analysis <- subset(Flags_Analysis, SEQN %in% data_analysis$SEQN)

## calculate subject specific averages of the accelerometry features
## using only the "good" days of data
act_var_nms <- c("TAC","TLAC","WT","ST","MVPA","SATP","ASTP")
for(i in act_var_nms){
    data_analysis[[i]] <- vapply(data_analysis$SEQN, function(x) mean(Act_Analysis[[i]][Act_Analysis$SE
}

## verify there's no missingness in the rest of our predictors of interest
vars_interest <- c("Age", "Gender", "Race", "EducationAdult", "SmokeCigs", "DrinkStatus", "BMI_cat",
                   "Diabetes","CHF",  "CHD", "Stroke","Cancer", "MobilityProblem","permth_exm")

## clean up the workspace
rm(list=c("AllAct","AllFlags","i","criteria_vec","nms_rm","tab_miss"))
#gc()

###### data for EDA
data_analysis$time <- data_analysis$permth_exm/12
data_eda = data_analysis

# number of participants
#nrow(data_analysis)
# number of deaths
#sum(data_analysis$mortstat==1)
# person years of follow up time.
#sum(data_analysis$time)

### summary table for missing individuals
data_analysis_excluded  <- subset(table_dat, Exclude == 1)
data_analysis_excluded$mortstat <- ifelse((data_analysis_excluded$ucod_leading %in% "004" & data_analysi
data_analysis_excluded  <- reweight_accel(data_analysis_excluded)
```

```
## Get activity/flag data for only those included participants AND who have 3 good days of data.
## Since we've already removed the "bad" days from Act_Analysis and Act_Flags,
## we need only subset based on subject ID now.
Act_Analysis   <- subset(Act_Analysis, SEQN %in% data_analysis_excluded$SEQN)
Flags_Analysis <- subset(Flags_Analysis, SEQN %in% data_analysis_excluded$SEQN)

## calculate subject specific averages of the accelerometry features
## using only the "good" days of data
act_var_nms <- c("TAC","TLAC","WT","ST","MVPA","SATP","ASTP")
for(i in act_var_nms){
    data_analysis_excluded[[i]] <- vapply(data_analysis_excluded$SEQN, function(x) mean(data_analysis_e
}

vars <- c("Age", "Gender", "Race", "EducationAdult", "SmokeCigs", "DrinkStatus",
          "DrinksPerWeek","BMI_cat","Diabetes","CHF",  "CHD", "Stroke", "Cancer",
          "MobilityProblem","TAC")

data_analysis_excluded$mortstat = as.factor(data_analysis_excluded$mortstat)
levels(data_analysis_excluded$mortstat) = c("Alive","Deceased")
data_eda$TAC <- 100*ecdf(data_eda$TAC)(data_eda$TAC)
colnames(data_eda)[53] = c("TAC~q~")
table2 <- CreateTableOne(vars = vars,data = data_eda, strata = "mortstat",test=F)
table <- kableone(table2, align="c",caption= "Distribution summaries for the traditional risk factors a
#table
```

2. Methods

As part of exploratory data analysis, we investigate the presence of time-varying effect of physical activity on mortality using the following plot. We denote the quantile transformed total activity counts, TAC as TACq. We plot the distribution of TACq for survivors (individuals at risk) at the end of a year vs those who died in the preceding 1 year interval for mortality data 2015.

```
### creating 13 columns for 13 years of follow-up marking indivuals who are
### alive at the end of each year as 'alive' and 'dead' for individuals who
### experience death in between previous year to this year
data_eda$TAC <- 100 * ecdf(data_eda$TAC)(data_eda$TAC)
data_eda$yr_1 <- ifelse(data_eda$time <= 1 & data_eda$mortstat == 1, "Deceased",
    "Alive")
for (i in 2:14) {
    varname = paste0("yr_", i)
    data_eda = data_eda %>%
        mutate(!!varname := NA)
    ind = which(colnames(data_eda) == varname)
    data_eda[, ind] <- ifelse(data_eda$time <= (i - 1) | (data_eda$time < i & data_eda$mortstat ==
        0), NA, ifelse(data_eda$time > (i - 1) & data_eda$time <= i & data_eda$mortstat ==
        1, "Deceased", "Alive"))
}

yr_name <- paste0("yr_", seq(1, 13, 1))

### Preparing the data for boxplot
colnames(data_eda)[52] = "weight"
inx_adj = which(grepl("adj", colnames(data_eda)))
```

```
data_eda = data_eda[, -inx_adj]  ## removing unnecessary columns
inx_sp <- which(grepl("yr_", colnames(data_eda)))
inx_sp1 <- colnames(data_eda)[-inx_sp]

data_eda_1 <- melt(data_eda, id.vars = inx_sp1)
data_eda_1 <- subset(data_eda_1, !value %in% NA)
data_eda_1$Status <- data_eda_1$value
ind <- which(grepl("TAC", colnames(data_eda_1)))
```

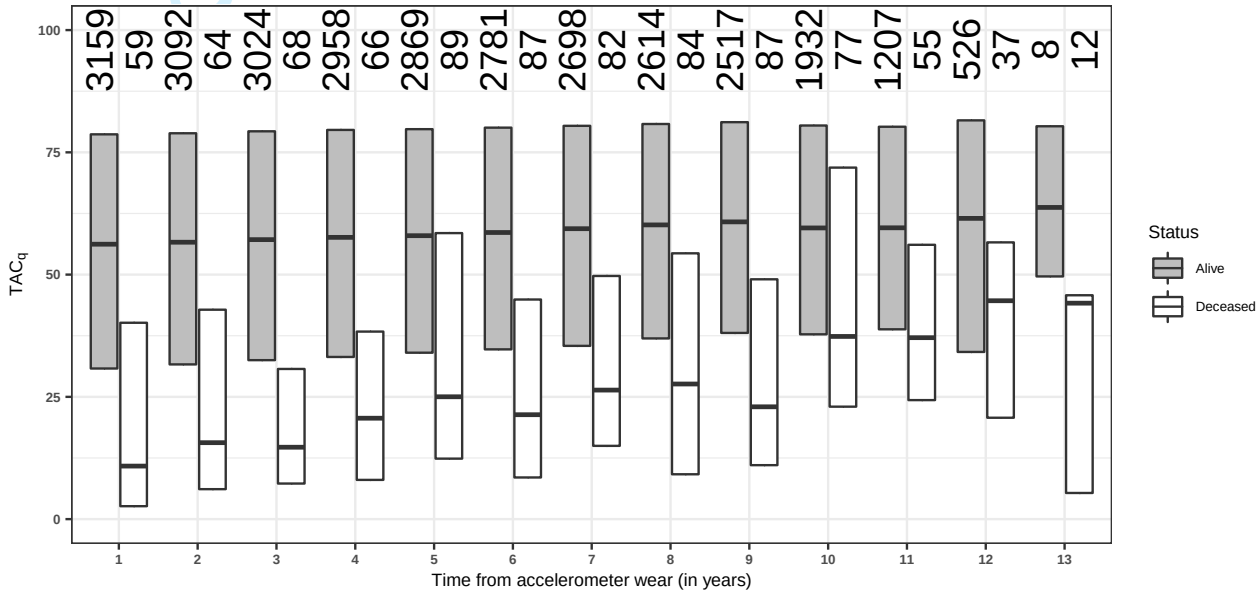

Figure S1: Distributions of TACq for individuals who survived at the end of each year (shown in gray) versus those who died in the preceding 1 year interval (shown in white).

From the boxplot, we can visualise that the median TACq for the alive population is more than that of the dead population. In addition, an increasing trend in the median TACq is observed for the dead population. We present the summary staistics for the risk factors among these two populations in the following table.

```
# plot2 = ggplot(data_eda_1, aes(x=variable,y=TAC,fill=Status)) + theme_bw() +
# geom_boxplot(outlier.shape = NA, coef = 0) + theme(axis.text.x =
# element_text(angle = 0)) + labs(title='', Position='center', y = TAC_expr, x
# = 'Time from accelerometer wear (in years)') + theme(plot.title =
# element_text(hjust = 0.5)) + scale_fill_manual(values=c('grey', 'white'))+
# stat_summary(fun.data = stat_box_data, geom = 'text', group='Status', angle =
# 90, size=2.5, hjust = 0.5, position = position_dodge2(1))+
# scale_x_discrete(limits=yr_name,labels=break_points) plot2
# ggsave('boxplot_plot_weighted_colourful.png', plot2, width = 10,height=5, dpi
# = 300)
```

Table S1: Distribution summaries for the traditional risk factors and accelerometry derived variables by mortality status (alive/deceased).

	Alive	Deceased
n	2351	867
Age (mean (SD))	63.53 (8.77)	72.53 (8.94)
Gender = Female (%)	1251 (53.2)	345 (39.8)
Race (%)		
White	1320 (56.1)	552 (63.7)
Mexican American	446 (19.0)	132 (15.2)
Other Hispanic	48 (2.0)	13 (1.5)
Black	455 (19.4)	150 (17.3)
Other	82 (3.5)	20 (2.3)
EducationAdult (%)		
Less than high school	663 (28.2)	367 (42.3)
High school	584 (24.8)	215 (24.8)
More than high school	1104 (47.0)	285 (32.9)
SmokeCigs (%)		
Never	1142 (48.6)	295 (34.0)
Former	836 (35.6)	401 (46.3)
Current	373 (15.9)	171 (19.7)
DrinkStatus (%)		
Moderate Drinker	1204 (51.2)	317 (36.6)
Non-Drinker	929 (39.5)	440 (50.7)
Heavy Drinker	124 (5.3)	65 (7.5)
Missing alcohol	94 (4.0)	45 (5.2)
DrinksPerWeek (mean (SD))	2.44 (5.73)	3.03 (8.46)
BMI_cat (%)		
Normal	588 (25.0)	243 (28.0)
Underweight	14 (0.6)	16 (1.8)
Overweight	903 (38.4)	323 (37.3)
Obese	846 (36.0)	285 (32.9)
Diabetes = Yes (%)	353 (15.0)	222 (25.6)
CHF = Yes (%)	77 (3.3)	114 (13.1)
CHD = Yes (%)	136 (5.8)	131 (15.1)
Stroke = Yes (%)	86 (3.7)	107 (12.3)
Cancer = Yes (%)	293 (12.5)	212 (24.5)
MobilityProblem = Any Difficulty (%)	587 (25.0)	453 (52.2)
TAC (mean (SD))	56.55 (26.79)	32.29 (26.81)

As part of modeling, we first want to investigate TACq is significantly associated with mortality. For this, we fit a Cox proportional hazard model where all the risk factors including the physical activity count, TACq is considered fixed.

```
####---------------- fixed model with weights ----------------####
data_analysis$TAC <- 100 * ecdf(data_analysis$TAC)(data_analysis$TAC)

test <- data_analysis[, c(1, 7, 13:14, 21:31, 33, 35, 52:53, 60)]

demo_vars <- c("Age", "Gender", "Race", "EducationAdult", "SmokeCigs", "DrinkStatus",
    "BMI_cat", "Diabetes", "CHF", "CHD", "Stroke", "Cancer", "MobilityProblem")
```

```
cut.points <- unique(test$time[test$mortstat == 1])
test2 <- survSplit(data = test, cut = cut.points, end = "time", start = "time0",
    event = "mortstat")

form1 <- paste0(paste0(demo_vars, collapse = "+"), "+TAC")
data_analysis_svy <- svydesign(id = ~SDMVPSU, strata = ~SDMVSTRA, weights = ~wtmec4yr_adj_norm,
    data = test2, nest = TRUE)

fit1 <- svycoxph(as.formula(paste("Surv(time0,time,mortstat) ~", form1)), design = data_analysis_svy)
```

Table S2: Estimated hazard ratio (HR), 95% confidence interval and P-values in the fully adjusted Cox Proportional Hazard model with fixed TACq

	Estimate	Lower CI	Upper CI	Pr(>|t|)
Age	1.069	1.057	1.082	0.000
GenderFemale	0.561	0.462	0.680	0.000
RaceMexican American	0.999	0.785	1.270	0.991
RaceOther Hispanic	1.288	0.748	2.217	0.361
RaceBlack	1.029	0.826	1.281	0.799
RaceOther	0.901	0.476	1.705	0.748
EducationAdultHigh school	0.916	0.688	1.220	0.549
EducationAdultMore than high school	0.792	0.616	1.017	0.067
SmokeCigsFormer	1.324	1.053	1.665	0.016
SmokeCigsCurrent	2.052	1.705	2.470	0.000
DrinkStatusNon-Drinker	1.404	1.154	1.707	0.001
DrinkStatusHeavy Drinker	1.709	1.107	2.637	0.015
DrinkStatusMissing alcohol	2.025	1.406	2.917	0.000
BMI_catUnderweight	2.598	1.345	5.018	0.004
BMI_catOverweight	0.760	0.658	0.878	0.000
BMI_catObese	0.833	0.662	1.049	0.120
DiabetesYes	1.302	1.100	1.541	0.002
CHFYes	1.779	1.378	2.296	0.000
CHDYes	1.132	0.891	1.439	0.309
StrokeYes	1.284	0.992	1.662	0.058
CancerYes	1.357	1.124	1.637	0.001
MobilityProblemAny Difficulty	1.489	1.314	1.688	0.000
TAC_q	0.983	0.979	0.987	0.000

We test for the proportionality assumption of all the risk factors for the Cox regression model fit. The model shows that a 2% decrease in the risk of death for one percentile increase in TAC. However, the global test of proportionality is rejected with p-value 0.002 and the individual test for TACq is rejected with p-value 0.008. Having a significantly small p-value indicates that the effect of TACq on the hazard of mortality is time-invariant.

Objective 1: Quantify the time-varying association between objectively measured PA and mortality in US older adults accounting for traditional risk factors

We used a time-varying Cox model where the parameter for TACq, $\beta_{TACq}(t)$ is fit non-parametrically using penalized cubic spline. This is implemented using *mgcv* package in R. We were not able to account for the survey weights for this model.

```r
#### fitting \beta(t) non-parametrically
ut <- sort(unique(data_analysis$time[data_analysis$mortstat == 1]))
nt <- length(ut)
di_tv <- ti_tv <- inx_tv <- c()
for (i in 1:nt) {
    inx_tv_i <- which(data_analysis$time >= ut[i])
    di_tv_i <- as.numeric(data_analysis$mortstat[inx_tv_i] * (data_analysis$time[inx_tv_i] ==
        ut[i]))
    ti_tv <- c(ti_tv, rep(ut[i], length(inx_tv_i)))
    di_tv <- c(di_tv, di_tv_i)
    inx_tv <- c(inx_tv, inx_tv_i)
}

data_tv <- data.frame(data_analysis[inx_tv, ], di_tv = di_tv, ti_tv = ti_tv, t_fac = factor(ti_tv))


fit_tv_gam_tac <- bam(di_tv ~ t_fac - 1 + Age + Gender + Race + EducationAdult +
    SmokeCigs + DrinkStatus + BMI_cat + Diabetes + CHF + CHD + Stroke + Cancer +
    MobilityProblem + s(ti_tv, by = TAC), data = data_tv, family = quasipoisson,
    method = "fREML", discrete = TRUE)

tind <- seq(0, 13, len = 100)
df_pred <- data_tv
df_pred$ti_tv = df_pred$TAC <- NULL
coef_fit <- predict(fit_tv_gam_tac, newdata = data.frame(df_pred[1, ], ti_tv = tind,
    TAC = 1), se.fit = TRUE, type = "terms")
```

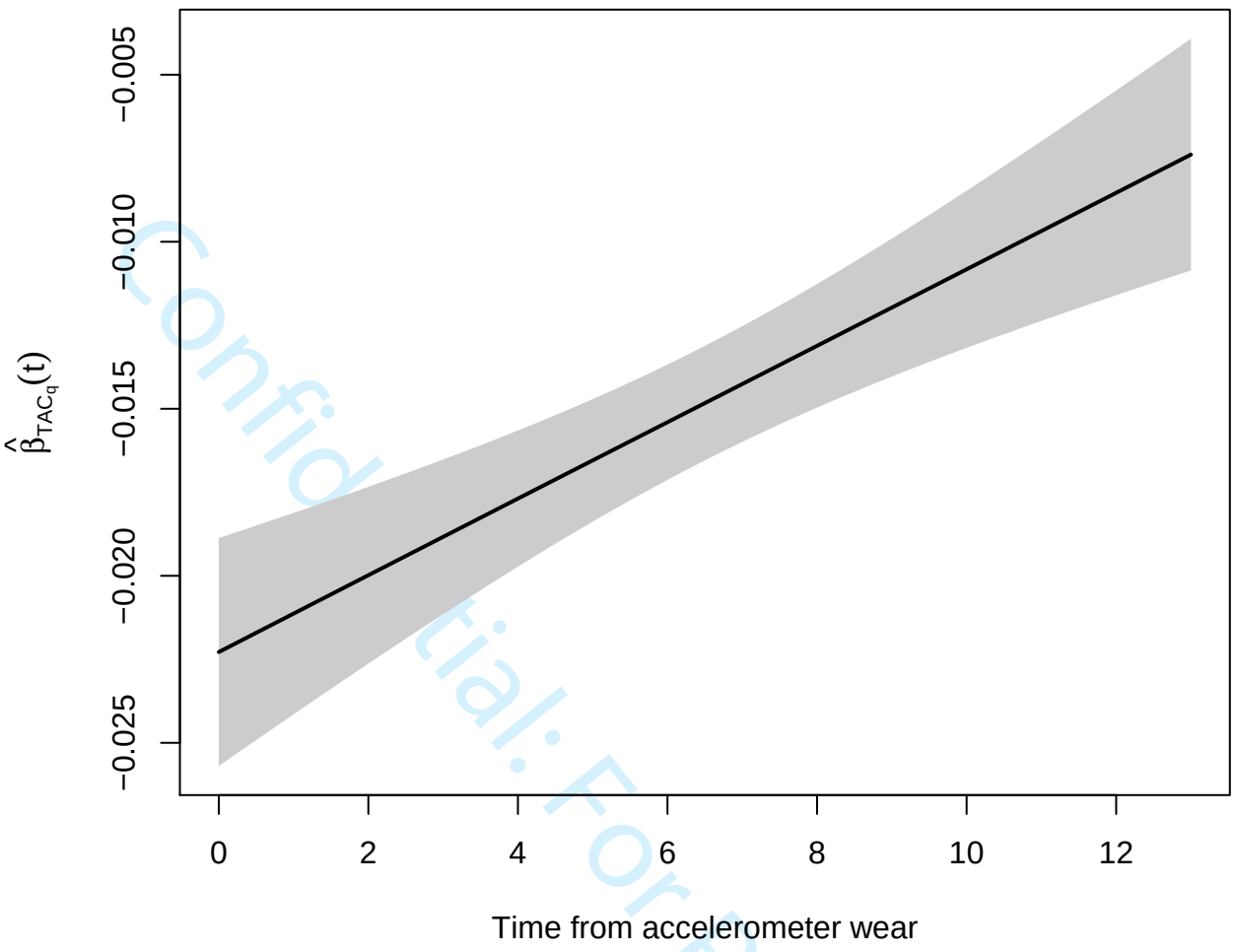

Figure S2: Adjusted estimated $\beta(t)$ (black solid) with 95% pointwise confidence bands (shaded areas) non-parametric fit for the effect of one percentile increase of TAC on mortality risk as a function of time.

Since, we cannot adjust for the weights in the non-parametric setting of a time-varying coefficient model and the $\beta_{TACq}(t)$ can be approximated by a linear effect as seen from the figure, we fit a model where $\beta_{TACq}(t) = \beta_0 + \beta_1\ TACq$.

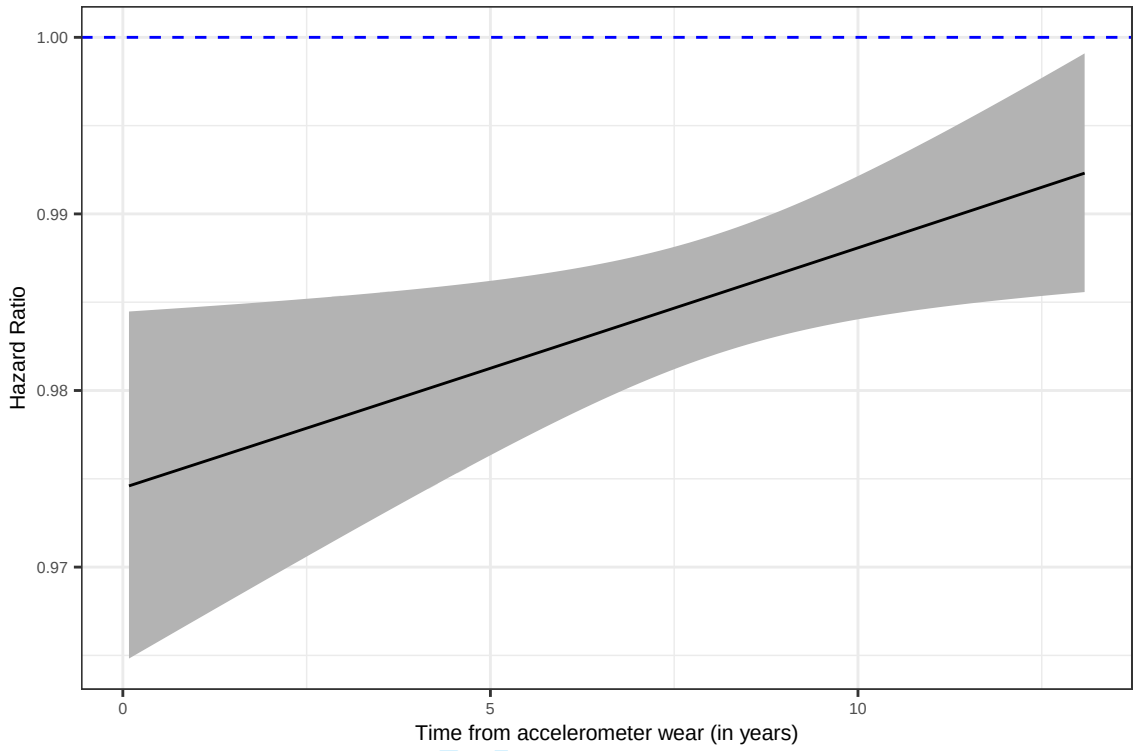

Figure S3: Adjusted estimated Hazard Ratio (black solid) linear fit with 95% pointwise confidence bands (shaded areas) for the effect of one percentile increase of TAC on mortality risk as a function of time.

Table S3: Estimated hazard ratio (HR), 95% confidence interval and P-values in the fully adjusted Cox model with time varying coefficient for TACq.

	Estimate	Lower CI	Upper CI	Pr(>|t|)
Age	1.069	1.057	1.082	0.000
GenderFemale	0.565	0.467	0.684	0.000
RaceMexican American	1.000	0.788	1.269	0.999
RaceOther Hispanic	1.284	0.745	2.215	0.368
RaceBlack	1.028	0.827	1.278	0.803
RaceOther	0.916	0.487	1.724	0.787
EducationAdultHigh school	0.916	0.690	1.216	0.544
EducationAdultMore than high school	0.792	0.617	1.016	0.067
SmokeCigsFormer	1.322	1.054	1.658	0.016
SmokeCigsCurrent	2.057	1.712	2.471	0.000
DrinkStatusModerate Drinker	0.713	0.587	0.866	0.001
DrinkStatusHeavy Drinker	1.222	0.803	1.861	0.350
DrinkStatusMissing alcohol	1.426	0.981	2.073	0.063
BMI_catUnderweight	2.572	1.329	4.979	0.005
BMI_catOverweight	0.766	0.664	0.884	0.000
BMI_catObese	0.837	0.669	1.048	0.121
DiabetesYes	1.308	1.109	1.543	0.001
CHFYes	1.761	1.362	2.278	0.000
CHDYes	1.133	0.893	1.437	0.303
StrokeYes	1.270	0.982	1.643	0.068

	Estimate	Lower CI	Upper CI	Pr(>|t|)
CancerYes	1.355	1.124	1.634	0.001
MobilityProblemAny Difficulty	1.476	1.301	1.675	0.000
TAC_q	0.974	0.965	0.984	0.000
Time*TAC_q	1.001	1.000	1.003	0.021

Objective 2. Evaluate the shape of the log-hazard of mortality as a function of follow-up time

The covariate adjusted effect of one percentile increase in TACq corresponds to an HR = 0.974 (CI: (0.965,0.984); $p < 0.001$) for mortality immediately after the PA measurement and HR = 0.991 (CI: (0.985, 0.997); p = 0.0016475) 12 years later. The HR increases at a rate of 0.139 percent per year (CI: (0.02, 0.257) percent increase in HR per year; p = 0.021).

Objective 3. Characterize short, medium and long-term all-cause mortality prediction performance of objective measures of PA

We illustrate the characterization of the short, medium and long-term all-cause mortality prediction performance of objective measures of PA using the survival probabilities for two profile instances. We consider a healthy white male who attended more than high school, with a normal BMI, and no history of diabetes, CHF, CHD, cancer, stroke, mobility problem, alcohol consumption, and cigarette smoking. For two different age, 55 years and 75 years, we plot the survival functions are shown by quartiles of TACq. The quantiles values are adjusted for age using a quantile regression of TACq on age.

```
#####----- survival plot
rqfit1 <- rq(TAC ~ Age, data = test, tau = c(0.25))
rqfit2 <- rq(TAC ~ Age, data = test, tau = c(0.5))
rqfit3 <- rq(TAC ~ Age, data = test, tau = c(0.75))

newdata <- data.frame(Age = rbind(55, 75))
pred1 <- predict(rqfit1, newdata = newdata)
pred2 <- predict(rqfit2, newdata = newdata)
pred3 <- predict(rqfit3, newdata = newdata)

## prediction at newdata
last <- test2$SEQN[which.max(test2$time)]
intervals <- test2[test2$SEQN == last, c("time0", "time", "mortstat")]
# intervals[nrow(intervals),] = c(12.66667,13,0) intervals[nrow(intervals)+1,]
# = c(13,13.08333,0)

covs1 <- data.frame(Age = 55, Gender = "Male", BMI_cat = "Normal", Race = "White",
    Diabetes = "No", CHF = "No", CHD = "No", Stroke = "No", Cancer = "No", MobilityProblem = "No Difficu
    EducationAdult = "More than high school", SmokeCigs = "Never", DrinkStatus = "Non-Drinker",
    TAC = pred1[1])

covs2 <- data.frame(Age = 55, Gender = "Male", BMI_cat = "Normal", Race = "White",
    Diabetes = "No", CHF = "No", CHD = "No", Stroke = "No", Cancer = "No", MobilityProblem = "No Difficu
    EducationAdult = "More than high school", SmokeCigs = "Never", DrinkStatus = "Non-Drinker",
    TAC = pred2[1])

covs3 <- data.frame(Age = 55, Gender = "Male", BMI_cat = "Normal", Race = "White",
    Diabetes = "No", CHF = "No", CHD = "No", Stroke = "No", Cancer = "No", MobilityProblem = "No Difficu
```

```
    EducationAdult = "More than high school", SmokeCigs = "Never", DrinkStatus = "Non-Drinker",
    TAC = pred3[1])
# vardefn <- function(data) { data$TAC_time <- data$TAC * data$time
# return(data) } Min.  1st Qu.  Median Mean 3rd Qu.  Max.
#-1.763005 -0.734484 -0.144802  0.000443  0.536557  6.292688
newdata1 <- data.frame(covs1, intervals, row.names = NULL)
newdata2 <- data.frame(covs2, intervals, row.names = NULL)
newdata3 <- data.frame(covs3, intervals, row.names = NULL)
newdata1 <- vardefn(newdata1)
newdata2 <- vardefn(newdata2)
newdata3 <- vardefn(newdata3)

shat1 = summary(survfit(fit2, newdata = newdata1, individual = TRUE))
shat2 = summary(survfit(fit2, newdata = newdata2, individual = TRUE))
shat3 = summary(survfit(fit2, newdata = newdata3, individual = TRUE))

store <- data.frame(time = shat1$time, TAC1 = shat1$surv, TAC2 = shat2$surv, TAC3 = shat3$surv)

## given survival of 10 years
shat11 = summary(survfit(fit2, newdata = newdata1, individual = TRUE, start.time = 10))
shat21 = summary(survfit(fit2, newdata = newdata2, individual = TRUE, start.time = 10))
shat31 = summary(survfit(fit2, newdata = newdata3, individual = TRUE, start.time = 10))

store1 <- data.frame(time = shat11$time, TAC11 = shat11$surv, TAC21 = shat21$surv,
    TAC31 = shat31$surv)

# plotting 0 years survival and at least 10 years survival individuals

inx_sp <- which(grepl("TAC", colnames(store)))
inx_sp1 <- colnames(store)[-inx_sp]
temp <- melt(store, id.vars = inx_sp1)
temp1 <- melt(store1, id.vars = inx_sp1)
temp2 <- rbind(temp, temp1)
```

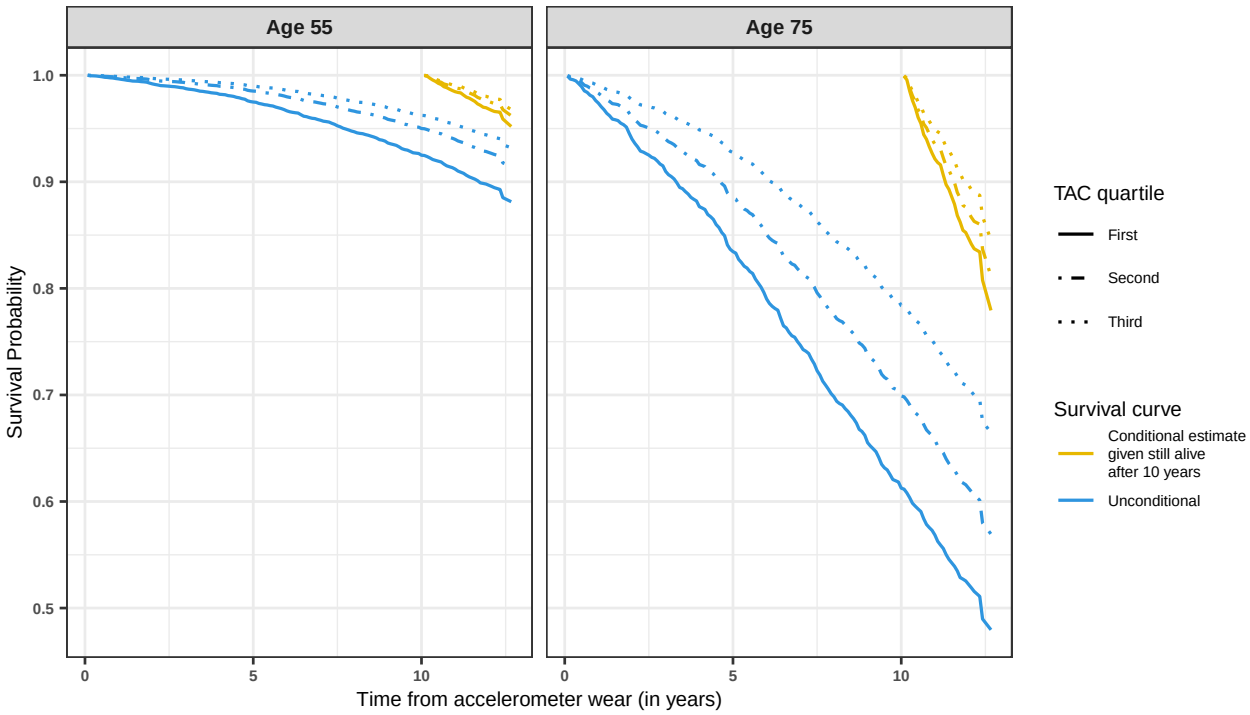

Figure S4: Covariate-adjusted estimated survival functions for two individuals, one in his 50s (left panel) and the other in his 70s (right panel), both identified as healthy white males, by quartiles of TACq: first quartile (solid line), second quartile (dashed) and third quartile (dotted).

In the above figure, the blue curves correspond to the survival function estimates at baseline and the yellow curves correspond to survival functions conditional on being alive 10 years after the baseline measurement.

The difference between the conditional survival curves for the three quartiles of TACq, though visible, has decreased relative to the survival curves at baseline for both the age-groups. For example, by five years after baseline the estimated survival probabilities are substantially different (0.975 for the first quartile, 0.985 for the median, and 0.99 for the third quartile) whereas the estimated survival probability at 12 years conditional on survival for 10 years after the baseline measurements are 0.97 for the first quartile, 0.976 for the median, and 0.98 for the third quartile of baseline TACq

Response to Reviewers and Editor-in-chief

We would like to thank the reviewers and the editor-in-chief for the very important and thoughtful comments. Below are the major revisions we have made to address the comments.

EiC comments:

1) You have not provided a point-by-point response of the first round. We would expect now a point-by-point response for both rounds.

> *Response: We clarified this point with the editorial production assistant and the editor has found our responses from the previous round.*

2) The structure of the article is still inadequate. Research Methods and Reporting should be a guide on the methods applied and how could others do the same thing, and you have not provided clear guidance that the reader can follow your three objectives outlined in the manuscript:

(1) quantify the time-varying association between objectively measured PA and mortality in US older adults accounting for traditional risk factors;
(2) evaluate the shape of the log-hazard of mortality as a function of follow-up time; and
(3) characterize short, medium and long-term all-cause mortality prediction performance of objective measures of PA.
This was also commented in the previous round and you have not addressed this comment.

> *Response: We have added details in the vignette on how to conduct the analysis. The vignette shows the analyses and result including the figures partitioned by these three objectives. In the body of the paper, we have summarized the vignette and provided direct references to the vignette.*

3) The same goes with the figures, the purpose of the article is to understand how you applied your methods in the NHANES study, not only to provide the results, so you need to choose better the figures that represent your objectives and explain them thoroughly.

> *Response: This is an excellent point. The vignette now shows the figures partitioned by these three objectives. We have also added some texts in the main document to connect the figures to the objectives.*

Reviewer: 1

Comments to the Author

Most of the comments were addressed and corrected in the manuscript. Only the most relevant one about the discussion was not correctly managed.
What was suggested to the authors was that the discussion could add some analysis or

reflection on whether the results are clinically relevant and how these results contribute to decision-making in primary prevention, even secondary prevention, in the light of so many other already studied and validated predictors of mortality.
Instead of adding some reflections to the discussion, the authors corrected the conclusion that was originally very well stated (and now is not)

Response: We thank the reviewer for the helpful and positive comments. We have now added back the conclusion from the original submission that the reviewer pointed out as very well stated. In addition, we have added some reflection in discussion on how "this analysis can provide subject-specific prediction of the predicted probability of death at any age and provide alternative predictions for changes to a different quantile". We have also added some discussion on the clinical relevance of the results.

Reviewer: 2

Comments to the Author

The manuscript is very statistical. I do think the paper lacks of a more detailed clinical analysis based on the relevance of the reduced HR found on relevant risk factors and mainly on different levels of PA. As an example, how relevant is a reduced risk of 2%?
What kind of recommendation would you suggest about PA based on these results?

Response: We thank the reviewer for the helpful and positive comments. In addition, we have added some in the discussion "this analysis can provide subject-specific prediction of the predicted probability of death at any age and provide alternative predictions for changes to a different quantile". We have also added some discussion on the clinical relevance of the results.

We would like to explain the author's point on the relevance of reduced risk of 2%. The objective of this analyses is to point out that this the 2% reduction in the risk of death for one percentile increase in TAC which is an averaged effect over the time of follow-up, doesn't hold since the effect of TAC is not fixed. Indeed, we show that since the time-varying effect of TAC exists, the reduction in risk ranges from 2.6% to 1% depending on if we are looking at immediately after baseline or 12 years after baseline. Also, in terms of the survival probabilities, we see from Figure 3 that hazard ratios in these range can lead to steep decrease in survival probabilities depending on the other covariates. So although the effect size in hazard scale is not huge, the survival probabilities are.