ASSOCIATIONS BETWEEN STEPS AND YEARS OF POTENTIAL LIFE LOST IN THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY: NHANES

BY

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LIST OF ABBREVIATIONS

ANOVA: Analysis of Variance

BMI: Body Mass Index

BP: Blood Pressure

CDC: Centers for Disease Control

CVD: Cardiovascular Disease

HTN: Hypertension

LPA: Light Intensity Physical Activity

METs: Metabolic Equivalents

MVPA: Moderate to Vigorous Physical Activity

NDI: National Death Index

NHANES: National Health and Nutrition Examination Survey

PA: Physical Activity

PAM: Physical Activity Monitor

STEPS/D: Steps Per Day

SUDAAN: Statistical Software for Weighting, Imputing, and Analyzing Data

US: United States

YPLL: Years of Potential Life Lost

ABSTRACT

Objective: We investigated the association between objectively measured steps and years of potential life lost (YPLL) using data from the National Health and Nutrition Examination Survey (NHANES).

Methods: Steps per day (steps/d) were obtained from the ActiGraph 7164 accelerometer, and worn by participants during the 2005-2006 NHANES survey. Step counts were divided into 2500 step categories, with <2,500 steps/d serving as the referent group. Mortality was ascertained from the National Death Index (NDI), and YPLL was calculated by subtracting the age of death from gender-specific life expectancy at baseline in 2005-2006. Differences across categories were determined using chi-square for proportions and analysis of variance (ANOVA) for means. Among individuals who died, we estimated the mean YPLL overall and by categories of average steps/d. Linear regression analysis was used to determine whether categories of average steps/d were associated with YPLL.

Results: Among the 4135 participants included in this study, the mean age was 46.3 years, 53.1% were female, and 71.6% were non-Hispanic white. Participants took an average of 9684 steps/d. Among the 534 participants who died, the mean YPLL was 8.1, with significantly more YPLL among individuals in higher compared to lower step categories. Compared to the referent group, those who walked between 2,500-4,999, 5,000-7,499, 7,500-9,999, and ≥10,000 steps/d had -1.32 YPLL [95%CI: -2.37, -0.27], -1.77 YPLL [95%CI: -2.68, -0.86], -2.59 YPLL [95%CI: -3.94, -1.25] and -1.01 YPLL [95%CI: -2.81, 0.79], respectively after full adjustment.

Conclusion: Higher compared to lower steps/d are associated with less YPLL in US adults. These findings underscore the importance of physical activity (PA) and steps in preventing premature death.

CHAPTER 1
LITERATURE REVIEW AND INTRODUCTION

Definitions

Physical activity (PA), exercise, and physical fitness are often used interchangeably, though clear definitions have been proposed in order to distinguish these terms from one another.[1] PA is as any bodily movement produced by skeletal muscle that results in energy expenditure. It encompasses all types, intensities, and domains of activity, and does not imply any quality or specific aspect of movement. Although the term "physical activity" is commonly used as a surrogate for moderate to vigorous PA (MVPA) in many studies, it does not confer any specific intensity. Rather, more specific descriptors including light, moderate, vigorous, or sedentary behavior are often used to convey the intensity of activity.

Exercise is a subset of PA that is planned, structured, and repetitive with the purpose of improving or maintaining one or more components of health, physical performance, or physical fitness, which represents a set of attributes that are health or skill related that people have or achieve. For the purposes of research, each of these definitions can be measured in different ways, though interactions exist between the terms.

PA can also be described by its predominant physiologic effect.[2] Aerobic PA includes any action that could be maintained using only oxygen supported metabolic energy pathways and can be continued for more than a few minutes. However, the term "aerobic" has come to mean any form of activity expected to maintain or improve an individual's cardiorespiratory fitness.[3]

Anaerobic PA refers to high intensity PA that exceeds the capacity of the cardiovascular system to provide oxygen to muscle cells for the usual oxygen consuming metabolic pathways.

While there are several other approaches to describing PA, these terms are the most commonly used in the literature. Other categories of PA recognized by the 2018 Physical Activity Guidelines for Americans (PA guidelines) include muscle and bone strengthening exercises, balance and flexibility training, and yoga, tai chi, or qigong.[2]

Intensity

PA intensity can be absolute or relative. Absolute intensity is the rate of energy expenditure required to perform any PA, and is frequently measured in metabolic equivalents (METs), kilocalories, joules, or oxygen consumption. METs are the most commonly used intensity metric, defined as the amount of oxygen consumed while sitting at rest, and is equal to 3.5 kg body weight/min.[4] METs are commonly divided into 4 categories: sedentary activity or behavior (1-1.5 METs), light intensity PA (LPA) (1.6-2.9 METs), moderate intensity PA (3-5.9 METs), and vigorous intensity PA (≥6 METs). Prior literature has established MET values for common activities in both the adult[5] and adolescent/youth population,[6] with a large portion of the literature expressing intensity in MET-hours per week. Adults generally spend <1% of energy expenditure in vigorous activity, and >50% of their waking time engaging in sedentary behavior.[7, 8]

Relative intensity refers to the ease or difficulty with which an individual performs any given PA, and can be described using physiologic parameters such as VO_2 max, a measure of maximal oxygen consumption, or percent of maximal heart rate achieved. For ease of use, several tools have been developed to help communicate intensity to the general population. For example, the sing-talk test has been described as follows: in LPA, one should be able to both talk and sing, in moderate intensity activity, one should be able to talk but not sing, and in vigorous PA one should not be able to talk or sing.[9]

While absolute intensity focuses on the activity itself, relative intensity focuses on the individual's level of effort during the activity of interest. Additionally, absolute intensity (METs in particular) is often measured objectively with tools such as accelerometers, whereas relative intensity is more subjective.

Measuring Physical Activity

Because of the complexity in type, volume, duration, and intensity of PA, accurately measuring its relationship with health outcomes can be challenging. The earliest published literature used job status to classify workers into higher or lower PA categories. Then, questionnaires became more prevalent, assessing primarily leisure-time PA. Today, technological advances have made device based assessment of body movements commonplace, with both commercial and research grade devices showing promise with increased accuracy compared to older methods of PA measurement. Device based, objectively measured PA using an accelerometer is now the preferred tool in many epidemiological studies,[2] and is considered the gold standard.[10]

This transition from questionnaire to device based PA measurement is significant because of the biases introduced with data obtained from questionnaires. For example, roughly half of the United States (US) adult population reports that they meet the aerobic guideline mandated ≥150 minutes of moderate or ≥75 minutes of vigorous PA per week.[11] However, when measured via accelerometry, <10% of US adults actually meet the guideline.[12] The reason for this large discrepancy is likely multifactorial. Self-reported PA is subject to recall bias and inflation of true amounts of activity. This inflation may occur due to the social desirability of being physically active,[13] or due to misinterpretation of the questionnaire. Likewise, evidence also suggests that individuals tend to overestimate the amount of higher intensity PA they achieve, while underestimating the amount of lower intensity PA.[14, 15]

Accelerometry

The ubiquity and lower cost of wearable monitors and devices have made these tools commonplace. In general, devices used to track PA can be divided into two categories, pedometers and accelerometers. Pedometers measure steps, whereas accelerometers measure limb or truncal accelerations.

While pedometers only measure steps, accelerometers can measure steps as well as many other types and forms of PA, making them the gold standard in activity related research. Modern accelerometry is based on continuous measurements of accelerations in three orthogonal directions [16] which can then be translated into other more meaningful metrics. Though the accuracy of these devices are improving, several challenges are apparent in using data obtained from an accelerometer, with consideration given to technical specification of the device itself, body site of attachment, wear time, metrics derived from the data, epoch length used in data analysis, and cut points used to classify PA intensity levels.[17]

Many different research grade accelerometers exist on the market, each with their own specifications. They differ in sampling rate, analog and digital filtering, sensor sensitivity, and resolution. Therefore, there is always some degree of data transformation necessary when processing the output. In order to avoid loss of potentially relevant information, unfiltered data are always preferred, with further transformation reserved for later analyses.[17]

There is also variability with respect to site of accelerometer attachment. While hip attachment has been the preferred site for many population based studies, wrist attachment has increased in popularity given its feasibility and better compliance rates.[18, 19] For example, the National Health and Nutrition Examination Survey (NHANES) changed its accelerometer attachment site from the hip to wrist in 2011.[7] However, measurements from the hip and wrist can vary considerably. Wrist accelerations can have potentially more "noise" than hip accelerations, as extraneous arm movements can create high accelerations without correspondingly high energy expenditure resulting in higher than true PA measurements.[20] Given these differences in attachment site, PA measurements may vary by as much as 20%.[21]

There is also considerable variability and little consensus on the definition of valid wear time, taking into account hours worn during the day and days worn per week (as well as weekends vs weekdays to better capture the "weekend warrior" phenomenon). Most consider ≥10 hours of wear time per day to be valid,[8] but there is debate as to how many days per week of wear time are necessary to accurately capture real life PA patterns, with some advocating for at least 4 days of wear per week,[22] while others believe only a single day is necessary.[8] It seems rational that more days of wear time would be more representative of true activity patterns, though Catrine Tudor-Locke, a leader in the realm of PA research, argues there is considerable bias with this logic. More active participants tend to wear their accelerometers for more days than less active participants, which can overestimate the data output significantly.[23] Additionally, participants may increase their PA simply because they are given an accelerometer, an inherent bias in this type of research. Thus, more days of wear can lead to compounding bias and further inflation of true PA.

Numerous metrics can be derived from accelerometers, including Euclidean Norm Minus One, activity index, mean amplitude deviation, and activity counts, the most commonly used raw output metric.[24-26] These metrics represent the mean movement induced acceleration over a period of time. Unfortunately, the device based algorithms used to determine activity counts is often proprietary and not transparent. Furthermore, activity counts, as well as the other raw output metrics mentioned, do not have any clinical meaning. Thus, in order to standardize PA studies, these raw metrics are often transformed into a more meaningful and universal metric, such as a MET, the most commonly used unit of PA intensity.

When processing accelerometry data, epoch length must also be taken into consideration, referring to the interval of time over which the units of accelerometer measures are summed.[27] For example, PA data obtained from NHANES uses 60-second epoch lengths.[7] The longer the epoch, the stronger the averaging effect, which effectively reduces the granularity or details that can be obtained from the data. Ideally, the chosen epoch length should match wear time and cut point definitions for a specific device and population, though this is rarely the case. Realistically, wear time algorithms and activity definitions are adjusted to match different epoch lengths, which have been shown to introduce error, leading to potential false interpretations and conclusions.[27]

Finally, cut points must be determined in order to translate the raw data into a form that is more clinically meaningful, with the majority of studies using activity count cut points that correspond to different MET levels of intensity, which then correspond to sedentary behavior, light, moderate, and vigorous intensity PA. With this logic, at least 2 data transformations take place (counts to METs, METs to PA intensity level) before achieving the final PA metric. Moreover, there is variability in choosing appropriate cut points, with consideration given towards the type of accelerometer and the individual, with different cut points proposed based on age, gender, and type of activity. These differences can be significant, with one study noting radically different cut points to define participation in moderate (cut point range 191-2743 counts/minute) and vigorous (cut point range 4945-7526 counts/minute) intensity PA,[28] which clearly can affect interpretation and bias conclusions.

The Burden of Physical Inactivity

Physical inactivity is a major risk factor for stroke and cardiovascular disease (CVD). Additionally, it is the fourth leading risk factor for global mortality, responsible for 1-2 million deaths annually.[29] In a study using data from the National Health Interview Survey, 8.7% of all-cause mortality was attributable to inadequate levels of PA.[30] For many individuals, this detrimental behavior begins in childhood and strengthens into adulthood. Survey data collected from high school students in 2015 reported that only 27.1% reported 60+ minutes of daily PA, the recommended amount of aerobic activity in youths aged 6-17 per the 2018 PA guidelines.[31] The authors also state this percentage is likely an overestimation due to recall bias.[32] Another survey from the National Center for Health Statistics demonstrated that only 22.5% of adults reported participating in adequate leisure time aerobic and muscle strengthening activities consistent with the 2008 PA guidelines.[33] When stratifying by gender, 26.3% of males and 18.8% of females met these guidelines. When stratifying by race, 25% of non-Hispanic Whites, 20.8% of non-Hispanic Blacks, 16.6% of Hispanic or Latino, 17% of Asians, and 14.7% of American Indians/Alaskans met the guideline, emphasizing the significant racial disparity. A similar, seminal study by Troiano et al. evaluated PA trends in the US measured by accelerometers using data from NHANES. When counting either minutes or bouts of activity, they found that the prevalence of meeting the PA guidelines in 6-11 year olds was 42%, then dropped drastically to 7.6% in 16-19 year olds, 3.5% in 20-59 year olds, and 2.4% in 60+ year olds.[7] The results from the two prior studies highlight the differences in self-reported versus objectively measured PA, as well as the significant decline in PA observed in US adults over time.

There is a substantial impact on cardiovascular health in those that are physically inactive. For example, youths with higher compared to lower amounts of accelerometry measured PA had lower systolic blood pressure (BP), glucose, and insulin levels.[34] Similarly, engagement in organized sports for roughly one year was associated with lower cardiovascular risk in a cohort of elementary school aged children.[35] Furthermore, evidence from researchers in Norway found that higher compared to lower levels of MVPA in 10 year olds was associated with lower triglyceride levels and lower insulin resistance at follow up.[36]

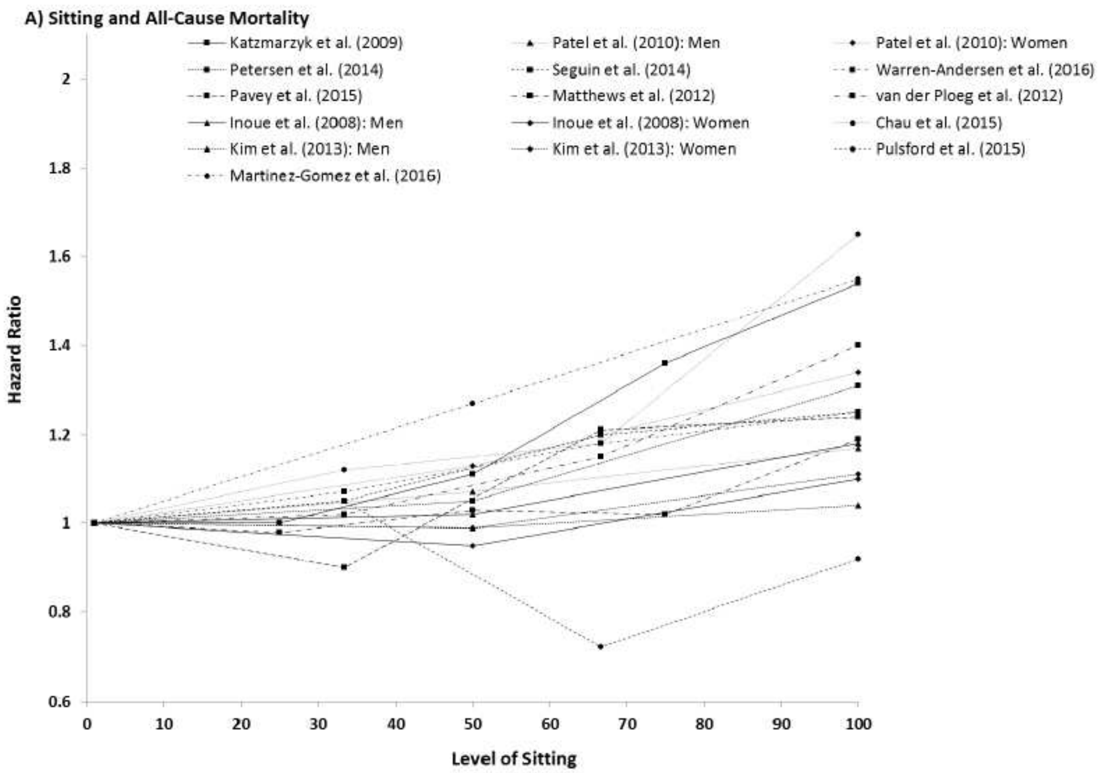
The risks of physical inactivity also continue into adulthood. For example, the prevalence of low HDL cholesterol was higher among adult individuals that did not meet guidelines (21%) versus those that did meet guidelines (17.7%).[37] Also, engaging in LPA, including yoga, was reported to improve body mass index (BMI), BP, triglycerides, LDL and HDL cholesterol.[38] Furthermore, a meta-analysis of 22 studies with a total of 330, 222 participants concluded that each 10 MET-hours per week higher level of leisure time PA was associated with a 6% lower risk of hypertension (HTN) [39]. Though these statistics can be disheartening, lifestyle modifications can make a significant impact. Data from the US Preventive Services Task Force demonstrated that 12 to 24 months of counseling interventions on healthy dietary patterns and regular PA in those at risk of CVD reduced cholesterol levels by 0.14 mmol/L, LDL cholesterol by 0.10 mmol/L, triglycerides by 0.09 mmol/L, systolic BP by 2.06 mmHg, diastolic BP by 1.30 mmHg, fasting glucose by 0.10 mmol/L, diabetes incidence by a relative risk of 0.54, and weight by a standardized difference of 0.24.[40] These results underscore the importance of lifestyle modifications in the prevention of CVD and its risk factors.

Sedentary Behavior

Though sometimes used interchangeably, physical inactivity and sedentary behavior represent fundamentally different concepts. Physically inactive individuals may do some PA, but not enough to gain meaningful health benefits. Many studies use this term to represent the inability of achieving the federal PA guidelines.[31] However, sedentary behavior generally refers to sitting or lying down for long periods of time, often characterized as 1.0-1.5 METs of energy expenditure.[41]

Data from NHANES suggests adults and children spend approximately 7.7 hours per day being sedentary (55% of total monitored time),[8] with a direct, curvilinear dose response relationship observed between sedentary behavior and all-cause mortality.[42-45] Biswas et al. conducted a meta-analysis composed of 14 cohort studies and reported a 1.22 HR (95%CI 1.09-1.41) on the relationship between sedentary behavior and all-cause mortality.[46] This relationship is illustrated in Figure F2-1 of the 2018 PA guidelines.[31]

Figure F2-1. Dose-Response Curves Showing Relationship Between Sedentary Behavior and All-Cause Mortality



Interestingly, the relationship between sedentary behavior and mortality is modified by levels of PA. Ekelund et al. conducted a harmonized meta-analysis of data from more than 1 million men and woman and found that individuals who accumulated >35 MET-hours per week of activity had little to no increased risk of all-cause mortality regardless of their amount of sedentary behavior. In contrast, those who accumulated ≤2.5 MET-hours per week of activity had a dose response relationship between hours per day of sitting and mortality.[47]

<u>The Importance of Physical Activity</u>

While physical inactivity and sedentary behavior place a substantial burden on public health in terms of morbidity and mortality, this burden can be mitigated and possibly reversed with increased levels of PA.

In addition to reducing all-cause, CVD, and cancer related mortality, PA also has been associated with improvements in BP and cholesterol, and reduced incidence of CAD, heart failure, stroke, type II diabetes mellitus, and sudden heart attacks.[2, 48, 49] Furthermore, these benefits have been observed across all age groups, in pregnant women, and in those with disabilities and chronic diseases. Importantly, there appears to be no lower threshold of benefit when considering all-cause mortality, with a leveling of risk reduction detected when >300 minutes per week of MVPA is achieved, which explants the upper limit of moderate intensity PA in the 2018 PA guidelines.[2, 50]

The 2018 PA guidelines Scientific Report represents the most complete and up-to-date compendium of PA related research highlighting several major important findings its last iteration in 2008. First, there is strong evidence that demonstrates that physically active individuals sleep better, feel better, and function better.[2] Also, benefits can be achieved in a variety of different ways and some happen immediately. For example, a single bout of MVPA can reduce BP, improve insulin sensitivity, improve sleep, reduce anxiety, and improve cognition on the day that it is performed, and these improvements strengthen with regular MVPA.[51, 52] While benefits regarding CVD and its associated risk factors are established, other less obvious associations have been proven. For example, there is now strong evidence to suggest PA reduces the risk of: falls and fall related injuries, dementia and cognitive decline, breast, colon, bladder, endometrial, esophageal, kidney, lung, and stomach cancer.[2]

Isotemporal Substitution

Much of the literature on PA to date has evaluated its relationship to outcomes without considering other factors that may play an important role. Given the confines of a 24-hour day, isotemporal substitution analysis seeks to understand the inter-relatedness among time spent in various aspects of daily living, often times using sleep, sedentary behavior, LPA, and MVPA as its variables. This type of analysis can be used to model the effects of replacing time in one variable into another variable to see how it effects an outcome. For example, an analysis by Schmid et al. used isotemporal substitution modeling to show that replacing sedentary time with an equivalent amount of LPA and MVPA was associated with a 14% and 50% reduction in mortality, respectively.[53] A similar analysis conducted by Matthews et al. using data from NHANES found that replacing one hour of sedentary time with either LPA or MVPA was associated with an 18% and 42% lower risk of mortality, respectively.[54]

The benefits of replacing sedentary behavior with activity hold true even with non-exercise activity. For example, a study of 154,614 older adults using data from the National Institutes of Health- American Association of Retired Persons Diet and Health Study found that replacing one hour or sitting time with an equal amount of activity in less active individuals was associated with lower all-cause mortality for both exercise (HR: 0.58; 95%CI: 0.54-0.63) and non-exercise activities (HR: 0.70; 95%CI: 0.66-0.74) which included household chores, lawn and garden work, and walking. Among more active individuals, replacing one hour of sitting time with purposeful exercise was associated with lower mortality (HR: 0.91; 95%CI: 0.88-0.94), but not with non-exercise activity. These results were similar when assessing for cardiovascular mortality.[55] These models are enticing given the alternative of conducting a large scale randomized controlled trial, which likely would be extremely challenging and costly. However, because these models are considered "isotemporal," the cause of the predicted benefit can be difficult to discern. Nevertheless, isotemporal substitution modeling is gaining in popularity among PA researchers, and soon may be considered the gold standard.[56]

Physical Activity and Mortality

Mortality is arguably the most important outcome in clinical research. Though mentioned previously, its worth reiterating the impact that PA has on longevity, with strong evidence demonstrating a clear inverse dose-response relationship between PA and mortality. Per the 2018 PA guidelines, the strength of the evidence is so strong that it is "very unlikely to be modified by more studies."[51] Additionally, the greatest benefit is seen early in the dose-response relationship, with no lower limit, and the benefit does not vary by age, sex, race, or weight status.

For example, a study using data obtained from NHANES found that meeting the aerobic component of the PA guideline reduced all-cause mortality by 36% after adjusting for confounding variables. Even in individuals that failed to meet the aerobic component, engaging in muscle-strengthening activity ≥2 times a week was associated with a 44% lower adjusted hazard ratio for all-cause mortality.[57] Additionally, a meta-analysis of 9 papers representing 122,417 participants found that as little as 15 minutes of MVPA reduced all-cause mortality in adults ≥60 years of age in a dose dependent manner. Consistent with the guideline, the most rapid reduction in mortality per minute of added PA was observed in those at the lowest level of activity, suggesting that adults can benefit from small as well as large amounts of PA, even at levels far below the federal guideline.[58]

Mortality benefits can be achieved with various types of PA. For example, a longitudinal study of 263, 540 participants from the UK Biobank reported that commuting by bicycle was associated with a lower risk of CVD mortality and all-cause mortality (HR(95%CI): 0.48(0.25-0.92) and 0.59(0.42-0.83), respectively), while commuting by walking was associated with a lower risk of CVD mortality (HR(95%CI): 0.64(0.45-0.91) but not all-cause mortality.[59] Another study involving 55,137 adult runners followed prospectively over an average of 15 years showed that compared to non-runners, runners had a 30% and 45% reduced risk of all-cause and CVD mortality respectively, with a 3 year life expectancy benefit. This benefit was similar across quintiles of run time, distance, frequency, amount, and speed. Additionally, running even 5 to 10 minutes per day was associated with a markedly reduced risk of CVD and of death attributable to all causes, even at slow speeds.[60] These studies demonstrate the impact of PA on public health, having the potential to motivate sedentary individuals to take control of their cardiovascular health and improve their mortality.

Step Counting

The recent surge of wearable technology has made step counting increasingly ubiquitous, allowing researchers to assess PA in various settings to inform the development of interventions to promote behavior change and improve health. Given the increased prevalence and projected continued growth of wearable health technology,[61] the Institute of Medicine has put out a call for an increase in the design and testing of these health technologies among researchers.[62] However, the 2018 PA guidelines make no recommendation on steps counting, citing insufficient evidence to support widespread endorsement.[31]

The current terminology (moderate or vigorous intensity PA, for example) used in the guideline can be difficult for both the clinician and patient to understand, but step counting is easily understood by individuals as well as the media, and blends well with public health messages of encouraging the use of stairs as opposed to elevators, walking in airports rather than taking the train or shuttle,[63] and parking further away from one's final destination. Step counts can also be tailored to meet individual needs and can be used to monitor progression towards personal goals.[64]

Locke et al. used data from the 2005-2006 NHANES survey to determine the population and sex specific epidemiology of objectively measured steps per day (steps/d) in the US population, with step data obtained from the ActiGraph 7164 accelerometer. On average, adults took 9676 ± 107 uncensored steps/d. Censoring (or removal) of individuals with <500 accelerometer activity counts per minute resulted in an average of 6540 ± 106 steps per day.[23] When stratifying by sex, men took 10,578 ± 134 uncensored or 7431 ± 129 censored steps/d, and women took 8882 ± 124 uncensored or 5756 ± 120 censored steps/d. The accelerometer used in NHANES is sensitive to low force movements which can lead to higher than true step estimates.[65, 66] Thus, censoring of the data was done to bring the accelerometer determined step values in alignment with current pedometer based scales.[67]

Subsequently, Dr. Tudor-Locke asked the question "are we ready" for a step based PA guideline, arguing that it is both necessary and timely for the scientific community to consider the development of step based guidelines.[68] While the data at present are limited, more studies are needed to take advantage of the plethora of existing information on steps in order to improve public health.

Cadence

While it is established that higher intensity PA translates to better outcomes, walking remains the most common form of exercise in US adults.[69] Steps are the basic unit of human locomotion, and the explosion of wearable activity monitors has made step counting widespread among the general population. However, the commonly used variable of steps/d provides the volume of activity, but does not encapsulate intensity. Cadence, or steps per minute, can be used to fill this gap so that step based measures can be translated into intensity values.

Cadence has been shown to correlate highly with objectively measured speed (r=0.97) and intensity (r=0.94).[70] Further research has also shown that ~100 steps/min corresponds to moderate intensity PA while ~130 steps/min corresponds to vigorous intensity PA.[71-73] Therefore, step based PA metrics can also be used to estimate not only volume but intensity as well.

Years of Potential Life Lost

In contrast to mortality, YPLL is a measure of premature mortality, comparing the age at death with life expectancy to estimate the average time an individual would have lived had he or she not died prematurely from a specific disease in proportion to the burden on society.[74] Whereas crude mortality rates describe death relative to a specific population, they do not quantify the loss resulting from this mortality. YPLL represents an index that focuses on the social and economic consequences of mortality, making the argument that this measure is superior to mortality in terms of representing the impact on public health. In fact, the Centers for Disease Control (CDC) introduced YPLL in 1982 to its comprehensive battery of health metrics because of its ability to "promote action to reduce unnecessary morbidity and premature mortality… [and] provide the greatest potential for health improvement."[75]

Given the majority of deaths occur in older persons, alternative measures were proposed to the CDC to better reflect mortality trends in younger individuals, and YPLL weigh deaths in younger ages more heavily than those occurring in older individuals. Thus, it encapsulates mortality in a variety of age ranges, as opposed to crude mortality statistics which focus on older populations only.[76]

Specific Aims and Hypotheses

PA is associated with a variety of health outcomes, including all-cause mortality. The majority of the literature, including the 2018 US PA guidelines, use intensity levels (light, moderate, and vigorous) when describing relationships between PA and outcomes. However, intensity levels vary from person to person, and can be difficult for both the health care provider and patient to understand. The advent of PA monitors has made steps counting ubiquitous, with steps representing a potentially easier metric than intensity levels for patients to understand and therefore implement as part of healthy lifestyle recommendations to improve outcomes such as all-cause mortality. Additionally, few studies have evaluated steps as a measure of activity and predictor variable when assessing its effects on important health outcomes. The relationship between steps and YPLL, a measure of premature death, has never been evaluated in a US based cohort of men and women, highlighting critical gaps in the literature. We propose the following aims to fill these crucial gaps using data obtained from the NHANES linked with the National Death Index (NDI).

Specific Aim 1: To describe the mean YPLL according to average objectively measured steps/d.

- Hypothesis 1: Those with higher steps/d will have a more YPLL compared to those with lower steps/d.
- Hypothesis 2: This relationship will be step-wise, so that higher compared to lower categories of steps/d will have a higher mean YPLL in a graded fashion.

Specific Aim 2: To understand the association between objectively measured steps/d and YPLL using regression analysis.

- Hypothesis: Higher steps/d will be associated with less YPLL compared to lower steps/d.

The knowledge generated from these aims will help fill important gaps in the literature regarding associations between steps and YPLL. We hope this information can help inform the population on the benefits of walking, PA, and maintaining a healthy lifestyle.

CHAPTER 2

STEPS AND YEARS OF POTENTIAL LIFE LOST IN US ADULTS

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Abstract

Objective: We investigated the association between objectively measured steps and years of potential life lost (YPLL) using data from the National Health and Nutrition Examination Survey (NHANES).

Methods: Steps per day (steps/d) were obtained from the ActiGraph 7164 accelerometer, and worn by participants during the 2005-2006 NHANES survey. Step counts were divided into 2500 step categories, with <2,500 steps/d serving as the referent group. Mortality was ascertained from the National Death Index (NDI), and YPLL was calculated by subtracting the age of death from gender-specific life expectancy at baseline in 2005-2006. Differences across categories were determined using chi-square for proportions and analysis of variance (ANOVA) for means. Among individuals who died, we estimated the mean YPLL overall and by categories of average steps/d. Linear regression analysis was used to determine whether categories of average steps/d were associated with YPLL.

Results: Among the 4135 participants included in this study, the mean age was 46.3 years, 53.1% were female, and 71.6% were non-Hispanic white. Participants took an average of 9684 steps/d. Among the 534 participants who died, the mean YPLL was 8.1, with significantly more YPLL among individuals in higher compared to lower step categories. Compared to the referent group, those who walked between 2,500-4,999, 5,000-7,499, 7,500-9,999, and ≥10,000 steps/d had -1.32 YPLL [95%CI: -2.37, -0.27], -1.77 YPLL [95%CI: -2.68, -0.86], -2.59 YPLL [95%CI: -3.94, -1.25] and -1.01 YPLL [95%CI: -2.81, 0.79], respectively after full adjustment.

Conclusion: Higher compared to lower steps/d are associated with less YPLL in US adults. These findings underscore the importance of physical activity (PA) and steps in preventing premature death.

Introduction

Physical inactivity is a public health epidemic, contributing significantly to the morbidity and mortality of our population, accounting for an estimated 5 million deaths per year.[29] In addition to the toll on human life, physical inactivity also places a significant burden on the health care system, costing an estimated $53 billion dollars worldwide, with $13.7 billion dollars of lost employment productivity, and 13.4 million disability adjusted life years.[77] PA guidelines have been established to combat this epidemic and improve health, with the most recent 2018 US Department of Health and Human Services guideline recommending at least 150 minutes of moderate or 75 minutes of vigorous PA per week in adults.[31]

Although there are robust data to suggest these recommendations can improve public health,[2] the guidelines can be difficult for both the healthcare provider and patient to understand and implement, with significant person to person variability. For example, an elite athlete may consider jogging as light PA, while an obese individual may consider jogging to be vigorous PA. Because of these limitations, some have proposed guideline recommended step counts to complement the moderate to vigorous PA (MVPA) recommendation.[70] Walking is a simple type of PA with known health benefits,[78] and the widespread use of wearable step-counting technology provides an unpresented opportunity to encourage individuals to move more and sit less. Because of its simplicity, step counts also represent a useful prescription tool for healthcare providers and trainers, as evidence suggests step count prescriptions can be useful for monitoring progress towards personal goals.[64] Furthermore, the metric of steps/d is already widely used in scientific literature; a simple PubMed search of "steps per day" or "steps/day" generates over 1,000 publications since 2000.[68]

The 2018 PA guideline highlights the strong positive relationship between higher doses of MVPA and improved longevity, reducing YPLL. These improvements in mortality are largely attributable to improvements in the prevention and treatment of cardiovascular disease (CVD), the leading cause of death in both men and women in the United States (US).[79] While steps are associated with several cardio-metabolic risk factors and CVD,[80] no study to our knowledge has assessed the relationship between steps and YPLL in a US based population. Thus, we sought to fill this gap in the literature by evaluating associations between accelerometry measured steps/d and YPLL using data from the National Health and Nutrition Examination Survey (NHANES) and the National Death Index (NDI).

Methods

Study Sample

NHANES is a cross-sectional nationally representative survey of US adults and children conducted over time. Data for this study were sourced from the 2005-2006 NHANES cycle, which included a PA monitoring examination in addition to the standardized NHANES protocol of questionnaires that assess socio-demographic and health information. This study included 4,135 adults aged 18 or older who completed the PA monitor (PAM) component of the survey and had at least one valid day of accelerometer data and confirmed vital status. All NHANES protocols were approved by the National Center for Health Statistics (NCHS) review board and informed consent for all participants was obtained prior to study initiation.

Steps Per Day

PA was measured using accelerometry. Participants (without walking impairments) were asked to wear a waist-worn PAM (ActiGraph accelerometer model 7164, Ft. Walton Beach, FL)[81] for up to 7 consecutive days and remove the device at bedtime and during water-based activities (i.e. showering or swimming). For each individual, the PAM collected minute to minute data on PA intensity and step counts. Step counts per minute deemed unreliable by NHANES were also excluded (e.g. >10 minutes with zero steps and >250 activity counts per minutes).[23] Finally, to facilitate analysis of PAM data, a SAS macro developed by the National Cancer Institute (https://epi.grants.cancer.gov/nhanes_pam/) was used to determine wear time per day for each individual.

Individual steps/d were calculated by summing steps per minute for each individual for each day. A valid day was defined as one in which wear time was ≥10 hours.[82] For our analysis, and following previously published methods, we included all individuals with at least one valid day.[23] Average steps/d was defined as the average daily step count for all valid days for each individual. We categorized average steps/d based partially on cut-points previously established in the NHANES cohort[23] as: <2,500 steps per day, 2,500 to 4,999 steps/d, 5,000 – 7,499 steps/d, 7,500 – 9,999 steps/d, and ≥10,000 steps/d.

Mortality and Years of Potential Life Lost

The NCHS has made NDI data publicly available for linkage to US based population surveys such as NHANES. NDI data are matched with survey participants through social security numbers, names, birthdates, and other personal identifiable information.[33] The 2005-2006 NHANES data were merged with de-identified NDI data ascertained through December 31, 2015 and available for public use. Our primary outcome is YPLL among individuals who died. YPLL was calculated by subtracting age of death from sex-specific life expectancy at baseline in 2005-2006 (75 years of age for men and 80 years of age for women).[83] If a given individual died past age 75 (among men) or 80 (among women), YPLL was set to zero.

Independent Variables

Full information on the physical examination (including the PAM) and survey instruments used to assess socio-demographic and health information can be found on the NHANES website: http://www.cdc.gov/nchs/nhanes.htm. Briefly, age, sex, and race (non-Hispanic White, Non-Hispanic Black, Hispanic, or Other) were assessed via questionnaire along with educational attainment (less than high school (HS), HS graduate, some college, or college graduate or more). Other socio-demographic factors such as household income, marital status, and insurance status were also self-reported using questionnaires. Health behavior information including: current smoking, alcoholic beverages per year, and self-rated diet quality (poor, fair, good, very good, or excellent) were reported via questionnaire.

Cardiovascular health risk factors were measured and self-reported. Body mass index (BMI) was measured during an examination and calculated as weight (in kg)/height (in m^2). BMI was further classified into the following categories (<18, 18-24.9, 25-29.9, 30+, or missing BMI). Systolic and diastolic blood pressure (BP) were also measured during the examination component of NHANES. After resting quietly in a chair for 5 minutes, BP was measured at the level of the heart with an appropriately sized cuff 3 times consecutively, waiting at least 30 seconds between readings. An average of valid BPs was used. (https://wwwn.cdc.gov/nchs/data/nhanes/2005-2006/manuals/PE.pdf). Hypertension (HTN) was defined according to guidelines at the time of data collection[84] as any of the following conditions: 1) self-report of HTN medication or 2) 'being told by a physician or a provider that you have high BP' or 3) average measured systolic BP ≥140 mmHg, or 4) average measured diastolic BP ≥90 mmHg. High cholesterol was defined as self-report of lipid lowering medication or 'being told by a physician or a provider that you have high cholesterol.' Diabetes was also defined as self-report of diabetes medication or 'being told by a physician or a provider that you have diabetes.' Prior CVD was based on self-reporting any of the following conditions: congestive heart failure, coronary heart disease, angina, heart attack, or stroke. Given slight variations in survey questions each year (i.e. 2005 and 2006) and that not all individuals participated in each physical examination, there was a high proportion of missing data for certain variables. To prevent observations with missing data from being removed from the analysis, we included a category for missing data for the specified variable. Covariates with a 'missing' category included: smoking, drinking in the past year, BMI category, HTN, and high cholesterol.

Statistical Analysis

We described socio-demographic, health characteristics, and mortality among the study sample overall and according to step count per day categories. Differences across step count categories were determined using chi-square tests for proportions and ANOVA for means.

Participants contributed observed time at risk (in months) beginning with their 2005-2006 NHANES mobile exam date and ending at the date of death ascertained through 2015. Participants still alive by 2015 were censored on December 31st 2015.

Among individuals who died, we estimated the mean unadjusted, and age adjusted YPLL overall and by categories of average steps/d. We then developed a series of 5 successive models using linear regression analyses to determine whether categories of average steps/d (with <2,500 steps/d as the reference) were associated with YPLL among those who died. Model 1adjusted for age as a continuous variable. Model 2 adjusted for model 1 plus sex and race/ethnicity. Model 3 adjusted for model 2 plus education, income, marital status, and insurance status. Model 4 adjusted for model 3 plus smoking, diet, and alcohol consumption. Model 5 adjusted for model 4 plus BMI, HTN, hypercholesterolemia, diabetes status, and prevalent CVD. All analyses utilized SUDAAN V 11.0.1 (Research Triangle Institute, Research Triangle Park, NC) to account for the complex survey design of the NHANES sample. A $P < 0.05$ or confidence interval that does not cross 1 was considered to be statistically significant.

Results

Descriptive characteristics are presented in **Table 1**. Among the 4,135 participants with valid accelerometer data, the mean age was 46.3 years, 53.1% were female, and 71.6% were Non-Hispanic white. Participants took an average of 9,684 steps/d, and significant differences in age, sex, race, education level, and household income were noted among those in different step categories.

Among individuals who died (n=534), the mean YPLL was 8.1 (**Figure 1**). When compared to the referent group (<2,500 steps/d), participants who took 7,500-9,999 and ≥10,000 steps/d had significantly more YPLL. However, when adjusting for age, there was no difference in YPLL among participants in different step categories (**Figure 2**).

Participants with 2,500-4,999 steps/d had -1.56 YPLL (95% CI: -2.62, -0.49) when adjusting for age only (**Table 2**). This trend continued in a progressive fashion, with less YPLL in those with 5,000-7,499 and 7,500-9,999 steps/d compared to the referent group [-2.19 YPLL (95% CI: -3.34, -1.04) and -2.77 YPLL (95% CI: -3.97, -1.57), respectively]. No significant difference was observed in those that took ≥10,000 steps/d [-1.13 YPLL (95%CI: -2.88, 0.62)].

Results from the fully adjusted model was slightly attenuated but similar. Compared to the referent group, those who took 2,500-4,999, 5,000-7,499, 7,500-9,999, and ≥10,000 steps/d had -1.32 YPLL (95% CI: -2.37, -0.27), -1.77 YPLL (95% CI: -2.68, -0.86), -2.59 YPLL (95% CI: -3.94, -1.25), and -1.01 YPLL (95% CI: -2.81, 0.79) respectively.

Discussion

This study examined the relationship between accelerometry measured steps and YPLL using data from the 2005-2006 NHANES cycle linked to the NDI. When compared to the referent group, higher average steps/d were associated with less YPLL, or more years of potential life gained, highlighting the importance of daily walking in achieving longevity.

YPLL is a measure of premature mortality, comparing the age at death with life expectancy to estimate the average time an individual would have lived had that individual not died prematurely from a specific disease in proportion to the burden on society.[74] Whereas crude mortality rates describe death relative to a specific population, they do not quantify the loss resulting from this mortality. In contrast, YPLL represents an index that focuses on the social and economic consequences of mortality, and better represents the impact on public health. In fact, the Centers for Disease Control (CDC) introduced YPLL in 1982 to its comprehensive battery of health metrics because of its ability to "promote action to reduce unnecessary morbidity and premature mortality… [and] provide the greatest potential for health improvement."[75] Given the majority of deaths occur in older persons, alternative measures were proposed to the CDC to better reflect mortality trends in younger individuals, and YPLL weigh deaths in younger ages more heavily than those occurring in older individuals. Thus, it encapsulates mortality in a variety of age ranges, as opposed to crude mortality statistics that focus on older populations only.[76]

To our knowledge, this is the first analysis to assess associations between accelerometry measured steps and YPLL, though similar studies have been conducted assessing the impact of steps on mortality. For example, Dwyer et al. demonstrated a strong linear, inverse relationship between steps/d and mortality among Australian adults.[85] However, they used pedometers to measure steps as opposed to accelerometers, the latter of which has shown superiority in accurately capturing steps at slower walking speeds.[86] Additionally, they included participants with 8 or more hours of wear time per day compared to 10 or more hours of wear time per day used in our analysis, which is more consistent with current accepted definitions and likely negatively influenced their estimate of PA.[7, 87] Additionally, they considered ≥2 valid days as opposed to one. While there is discrepancy in the literature regarding how many days of valid wear time is acceptable, we chose >1 valid day because others have demonstrated that individuals that wear PAMs for more days per week are more physically active than individuals that wear PAMs for fewer days per week, which may overestimate observations.[8, 23] Another study using a cohort of elderly Japanese participants demonstrated that those with higher steps/d had lower rates of all-cause mortality, though this relationship was not statistically significant.[88] Given both studies were completed using individuals from other countries with significantly different mean ages and risk factors, their results cannot be extrapolated to a U.S.-based population known to have a much higher burden of CVD, the main contributor to mortality, compared to Australians and Japanese based populations.[89] However, a recent study by Lee et al. evaluated associations between steps and all-cause mortality using data from the Woman's Health Initiative showing that higher steps/d are associated with improvements in mortality, however these results are only representative in older women.[90]

Our findings have significant public health implications and highlight the importance of steps to improve mortality and reduce YPLL. About one in four US adults were inactive in 2017,[11] accounting for 8.3% of deaths and $117 billion dollars in annual health care costs.[30, 91] Our results demonstrate that even relatively small increases in steps/d can have a large impact on mortality and YPLL. Walking is an easy form of PA that does not require any special skills, and represents the first step towards starting and maintaining a healthy lifestyle.[92] Additionally, wearable activity trackers are common and readily available to the general public. While knowledge of the PA guidelines is low among US adults, step counts from wearable devices provide a potentially useful and easily understood measure of PA which has been shown to effectively increase PA levels, especially when combined with other behavioral strategies.[31, 93]

Individual and population level interventions are needed in order to promote walking and change behavior to improve health. Health care providers play an important role in disseminating the benefits of PA and can help encourage activity in a variety of different ways. For example, PA prescriptions represent an efficient and cost effective strategy shown to improve levels of activity, [94, 95] which can be done easily during a clinic visit. Health care providers can also encourage PA by referring patients to community walking groups, which have the added social benefit of walking which likely aids in adherence, and can lead to improvements in not only cardiovascular health, but also BMI,[96] BP and cholesterol,[97] fasting blood sugar,[97] memory and cognitive function,[98] lower stress and improved mood,[99] and longer life.[100]

Limitations

This study has limitations which we acknowledge. First, given some of the NHANES data were collected via survey, it may be subject to residual confounding and recall bias. Second, several covariates were missing as not all individuals participated in each physical examination.

Thus we created a "missing data" category in order to preserve power. Third, though research grade accelerometers are becoming more accurate, there is variability among the wearable devices.[101] However, ActiGraph accelerometers have been shown to have the least amount of variability and the highest reliability compared to other devices.[102] Fourth, we used linear regression in computing differences in YPLL by step category. Though this outcome assumes linearity, the data was not completely linear. Fifth, we used uncensored steps/d based on two studies which demonstrated that the ActiGraph 7164 compares favorably to the StepWatch (Orthocare Innovations, Seattle, WA), which is considered the gold standard PAM when assessing steps in free living conditions.[103, 104] Furthermore, commercially based PAMs provide raw step counts, making uncensored steps/d more applicable when discussing its utility to the general public. Sixth, mean YPLL were higher than expected because participants that died in higher step categories were younger compared to those in lower step categories, meaning they have more potential life to lose because YPLL is a metric of premature death.

Conclusion

In summary, the mean YPLL was 8.1 among a US based representative cohort of adult men and women. Further, higher compared to lower average steps/d is associated with less YPLL. Steps are a simple metric of PA with known health benefits, which should be included in future guidelines, especially given the advent and increasing use of commercial PAMs in the general population. Our results are congruent with the US Department of Health and Human Services message: in order to improve the health of our population, we need to "move more and sit less."[31]

Table 1: Characteristics of the Study Sample Overall and by Average Steps Per Day, NHANES 2005-2006 (n=4,135)

		Steps per Day				
Characteristics	**Overall N=4,135**	**<2,500 n=121**	**2,500 – 4,999 n=476**	**5,000 – 7,499 n=857**	**7,500 – 9,999 n=1,059**	**≥10,000 N=1,622**
Age (y), mean (SE)*	46.3 (0.8)	67.8 (1.9)	58.5 (1.5)	48.8 (1.1)	44.7 (0.9)	42.3 (0.6)
18-44, % (SE)	48.1 (2.0)	14.0 (3.7)	24.5 (3.0)	43.8 (3.1)	49.8 (2.4)	55.9 (2.3)
45-64, % (SE)	35.2 (1.3)	16.1 (4.1)	28.7 (3.2)	31.1 (2.9)	38.2 (1.9)	37.4 (2.0)
65+, % (SE)	16.7 (1.3)	69.9 (4.5)	46.8 (3.1)	25.1 (1.9)	12.0 (1.8)	6.7 (0.9)
Female, % (SE)*	53.1 (0.8)	75.3 (9.4)	56.3 (3.3)	65.6 (2.4)	57.9 (1.4)	43.4 (1.2)
Race/Ethnicity, % (SE)*						
Non-Hispanic white	71.6 (2.6)	70.2 (4.6)	69.6 (4.4)	70.4 (3.0)	71.7 (2.8)	72.6 (2.7)
Non-Hispanic black	11.6 (2.0)	21.8 (4.4)	15.7 (3.5)	14.0 (2.6)	11.3 (2.1)	9.3 (1.8)
Hispanic	11.4 (1.3)	7.3 (3.4)	8.1 (1.8)	9.1 (1.4)	10.8 (1.5)	13.4 (1.7)
Other	5.4 (0.7)	0.8 (0.5)	6.6 (1.6)	6.6 (1.3)	6.1 (0.9)	4.7 (0.9)
Education, % (SE)*						
Less than HS	16.4 (1.3)	26.1 (6.9)	18.8 (3.3)	14.2 (1.9)	14.9 (1.6)	16.0 (1.7)
HS Graduate	24.3 (0.8)	25.4 (8.8)	21.9 (2.1)	23.4 (2.0)	22.0 (1.3)	25.9 (1.1)
Some college	30.9 (0.9)	21.6 (8.2)	30.8 (4.1)	34.1 (1.8)	31.2 (2.2)	29.4 (1.1)
College graduate	25.3 (2.1)	22.5 (9.6)	23.9 (4.1)	24.5 (2.2)	29.0 (3.6)	26.0 (2.0)
Household Income, % (SE)*						
<$25,000	20.0 (1.2)	31.0 (5.7)	30.0 (2.9)	20.7 (1.8)	18.6 (1.5)	16.8 (1.3)
$25,000 - <$55,000	31.3 (1.5)	31.1 (10.0)	31.6 (2.9)	32.6 (2.2)	29.7 (2.2)	32.9 (1.8)
$55,000 - <$75,000	15.1 (0.7)	5.0 (1.0)	13.9 (3.0)	13.3 (0.9)	16.9 (1.9)	14.9 (1.2)
$75,000 +	29.9 (2.2)	22.6 (9.8)	19.9 (3.4)	28.2 (2.5)	31.5 (2.6)	32.4 (2.4)
Married, % (SE)*	57.8 (1.5)	36.0 (7.2)	47.7 (3.3)	53.1 (2.4)	59.8 (2.3)	62.8 (2.1)
Insured, % (SE)*	81.7 (1.7)	74.2 (6.5)	79.7 (3.8)	79.7 (2.3)	83.9 (1.9)	81.5 (1.8)
ł Current Smoker, % (SE) *	11.3 (0.5)	16.1 (7.1)	9.0 (2.2)	12.9 (2.4)	11.0 (1.2)	11.1 (0.8)
ł12+ drinks/year, % (SE)*	27.8 (0.8)	38.8 (9.1)	26.9 (3.5)	29.2 (1.8)	27.6 (1.4)	26.7 (1.3)
Fair/poor diet quality, % (SE)*	27.1 (1.3)	35.4 (6.6)	32.0 (3.3)	29.5 (2.2)	23.6 (1.6)	26.9 (1.6)
BMI kg/m^2, mean (SE)	25.3 (0.2)	22.6 (0.9)	25.9 (0.4)	25.5 (0.4)	25.5 (0.2)	25.1 (0.3)
ł Hypertension,% (SE)	22.2 (0.6)	25.5 (6.4)	19.3 (4.7)	24.4 (1.5)	22.4 (1.0)	22.1 (1.2)
ł High cholesterol, % (SE)	12.0 (0.8)	11.6 (7.1)	8.0 (1.9)	13.9 (1.5)	12.2 (1.0)	11.4 (1.2)
Diabetes, % (SE)*	5.1 (0.4)	0.6 (0.3)	2.7 (1.3)	6.1 (1.3)	5.4 (0.8)	5.2 (0.7)
% Prevalent CVD	5.3 (0.7)	5.9 (4.2)	3.9 (1.6)	6.5 (1.5)	5.0 (1.2)	6.0 (1.0)
% Died*	9.7 (0.5)	32.0 (7.4)	20.7 (1.7)	9.2 (1.1)	6.9 (0.9)	4.3 (0.9)
Steps per day, mean (SE)*	9,684 (113)	1,504 (95)	3,996 (66)	6,335 (35)	8,797 (22)	13,309 (155)

*Estimate differs by steps per day (chi-square test for proportions or ANOVA for means P <0.05).
łProportion of the sample missing data are large and a missing category was created with proportions:

smoking: 24.2%; drinking: 58.2%; hypertension: 14.3%; high cholesterol: 68.5%; Diabetes: 5.5%. All estimates (except for age specific estimates) are age-standardized to the overall age distribution

Table 2: Association of Average Steps Per Day with Years of Potential Life Lost, NHANES 2005-2006 (n=534)

	Model 1 **β (95% CI)**	**Model 2** **β (95% CI)**	**Model 3** **β (95% CI)**	**Model 4** **β (95% CI)**	**Model 5** **β (95% CI)**
Steps per Day					
<2,500	ref	ref	ref	ref	ref
2,500 – 4,999	**-1.56 (-2.62, -0.49)**	**-1.40 (-2.37, -0.44)**	**-1.19 (-2.14, -0.25)**	**-1.22 (-2.15, -0.30)**	**-1.32 (-2.37, -0.27)**
5,000 – 7,499	**-2.19 (-3.34, -1.04)**	**-2.06 (-2.37, -0.44)**	**-1.89 (-2.73, -1.04)**	**-1.91 (-2.77, -1.05)**	**-1.77 (-2.68, -0.86)**
7,500 – 9,999	**-2.77 (-3.97, -1.57)**	**-2.73 (-3.97, -1.50)**	**-2.54 (-3.91, -1.16)**	**-2.49 (-3.83, -1.15)**	**-2.59 (-3.94, -1.25)**
≥10,000	-1.13 (-2.88, 0.62)	-1.19 (-2.93, 0.54)	-0.99 (-2.63, 0.65)	-0.95 (-27.2, 0.83)	-1.01 (-2.81, 0.79)

*β= Beta, CI= Confidence Interval

Model 1 is adjusted for continuous age; model 2 is additionally adjusted for: sex and race; model 3 is additionally adjusted for: education, income, marital status, and insurance status; model 4 is additionally adjusted for: smoking, diet, and alcohol consumption; model 5 is additionally adjusted for: body mass index, hypertension, hypercholesterolemia, diabetes, and prevalent cardiovascular disease

Figure 1: Unadjusted Mean Years of Potential Life Lost According to Average Steps Per Day, NHANES 2005-2006 (n=534)

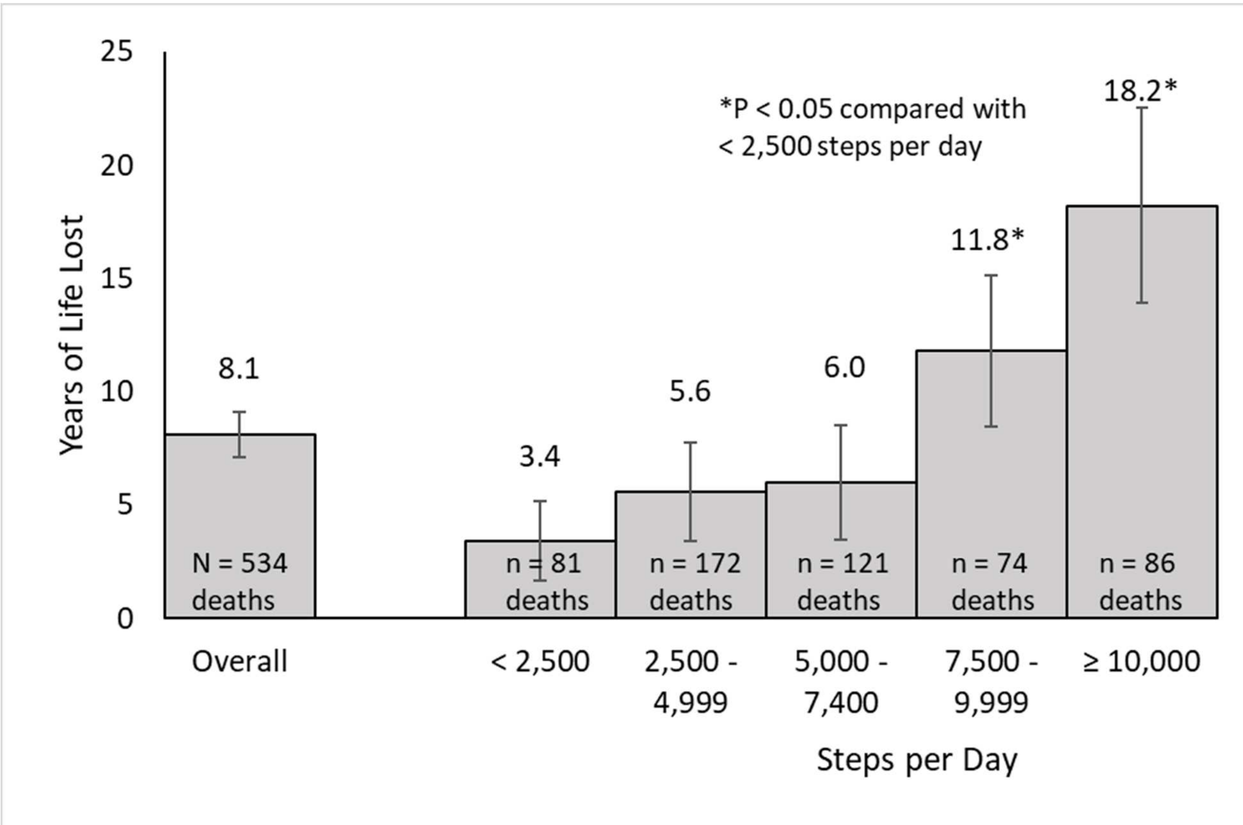
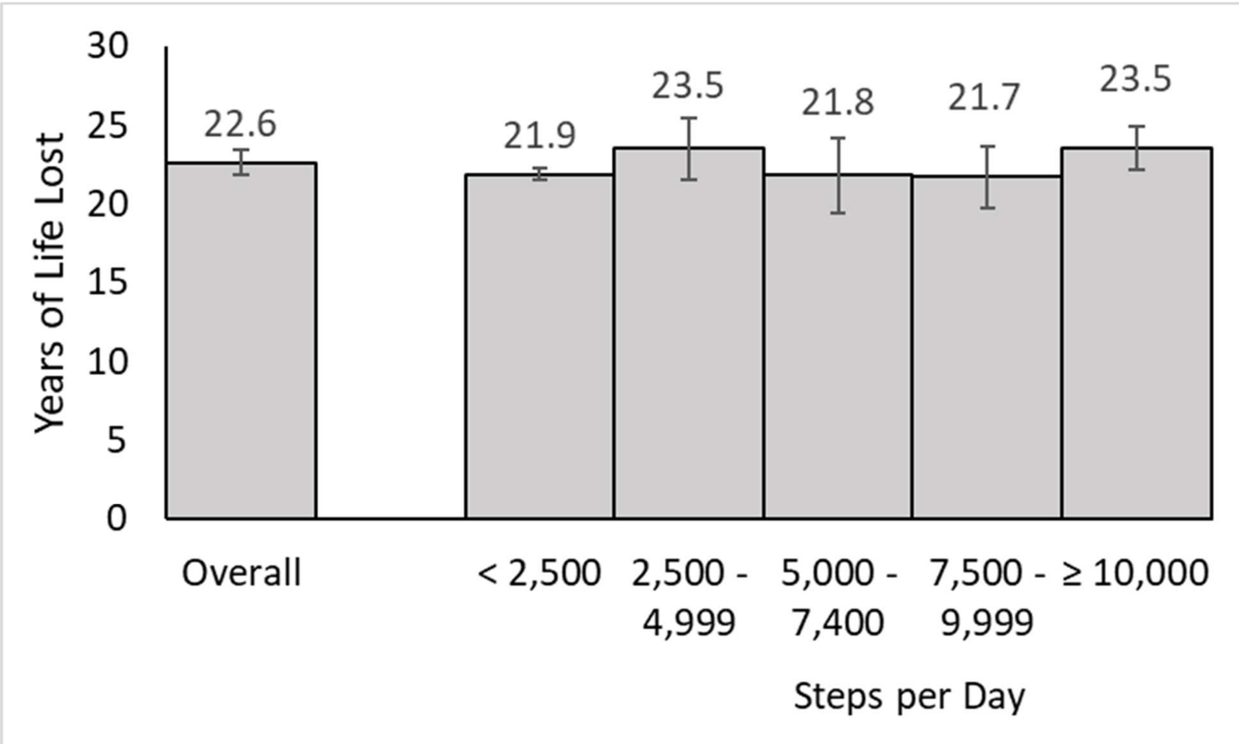


Figure 2: Age Adjusted Mean Years of Potential Life Lost According to Average Steps Per Day, NHANES 2005-2006 (n=534)



CHAPTER 3

ANCILLARY STUDIES

Steps and Years of Potential Life Lost: Censoring Steps <500 Counts Per Minute

Intensity counts represent the raw output from the Actigraph 7164 (Ft. Walton Beach, FL, USA), which can then be converted to other metrics of PA. Unfortunately, much of the PA literature differs regarding how best to analyze these data, with variability from study to study, making interpretation difficult.

We ultimately chose to use uncensored steps/d based on two studies which demonstrated that the ActiGraph 7164 compares favorably to the StepWatch (Orthocare Innovations, Seattle, WA), which is considered the gold standard physical activity monitor (PAM) when assessing steps in free living conditions.[103, 104] Furthermore, commercially based PAMs provide raw as opposed to censored step counts, making uncensored steps/d more applicable when discussing its utility to the general public, with the hope that this study may contribute to future physical activity (PA) guidelines.

In order to better understand how our study would change had we chosen to censor our data, a sensitivity analysis was performed to censor all steps taken with <500 activity counts per minute.[23] This threshold was adapted from several studies by Tudor-Locke et al., in which she argues PAMs may pick up sedentary behavior, as opposed to PA, given higher sensitivity to low force movements, which could lead to false, higher step counts.[65, 66, 86, 105] She also notes this threshold brings accelerometer determined steps/d more in line with current pedometer based scales.[67]

Descriptive statistics of our study sample with censored steps are presented in **Supplementary Table 1**. The overall sample averaged 6680 steps/d (as opposed to 9684 steps/d). When using censored step counts, participants were younger, with proportionately less females and non-Hispanic whites when compared to the data generated from censored step counts. Significant differences in age, sex, race, education level, and household income were noted among those in different step categories.

Notable changes were observed when using censored steps counts to assess associations of steps/d with YPLL (**Supplementary Table 2**). Results from the linear regression models show that compared to participants who walked <2,500 steps per day (steps/d) (referent group), those who walked 2,500-4,999 steps/d had -1.52 YPLL (95% CI: -2.69, -0.35) when adjusting for age only. Results from the fully adjusted models were slightly attenuated but still significant: compared to the referent group, those who walked between 2,500-4,999 and 7,500-9,999 steps/d had -1.33 (95% CI: -2.53, -0.13) and -1.65 (95% CI: -3.22, -0.09), YPLL respectively.

Compared to the uncensored step data, there were fewer differences between step categories and the magnitudes of YPLL were less as well. It is unclear why there is such discrepancy between the censored and uncensored data, though many of the step categories had <100 deaths. Lack of data linearity may have also contributed. Further studies with larger sample sizes and more death information are warranted to better understand relationships between accelerometry derived steps, mortality, and YPLL.

Supplementary Table 1: Characteristics of the Study Sample Overall and by Average Censored Steps Per Day, NHANES 2005-2006 (n=4,053)

Characteristics	Overall N=4,053	Categories of Average Steps per Day <2,500 n=558	2,500 - 4,999 n=1,063	5,000 – 7,499 n=1,118	7,500 - 9,999 n=689	≥ 10,000 n=625
Age (y), mean (SE)*	45.9 (0.7)	62.5 (1.4)	47.5 (0.8)	43.5 (1.0)	42.5 (0.8)	40.8 (0.9)
18-44, % (SE)	48.7 (2.0)	17.3 (2.5)	45.5 (2.2)	52.6 (3.3)	56.2 (2.7)	58.4 (3.9)
45-64, % (SE)	35.5 (1.4)	26.3 (2.6)	33.8 (1.9)	39.0 (3.1)	37.1 (2.2)	35.9 (3.0)
65+, % (SE)	15.8 (1.2)	56.4 (3.2)	20.7 (1.8)	8.4 (1.5)	6.7 (1.0)	5.7 (1.5)
Female, % (SE)*	52.8 (0.8)	59.7 (4.0)	64.8 (2.0)	56.2 (1.7)	45.9 (2.5)	32.5 (2.7)
Race/Ethnicity, % (SE)*						
Non-Hispanic white	71.5 (2.6)	69.3 (4.3)	68.3 (3.3)	71.7 (2.3)	75.3 (3.2)	72.5 (2.9)
Non-Hispanic black	11.6 (2.0)	18.3 (3.8)	14.1 (2.5)	11.2 (2.1)	9.0 (2.0)	8.1 (1.7)
Hispanic	11.5 (1.4)	8.1 (1.6)	10.2 (1.3)	11.0 (1.6)	12.0 (1.9)	14.8 (2.0)
Other	5.4 (0.7)	4.3 (1.4)	7.5 (1.6)	6.1 (0.7)	3.7 (1.2)	4.5 (1.6)
Educational attainment, % (SE)*						
Less than HS	16.2 (1.3)	23.6 (3.6)	14.9 (1.4)	14.7 (1.6)	12.8 (1.7)	19.0 (2.5)
HS Graduate	24.1 (0.8)	22.8 (3.3)	24.6 (1.7)	23.0 (1.2)	23.8 (2.8)	25.1 (2.0)
Some college	30.9 (0.9)	29.6 (4.0)	33.1 (1.7)	30.1 (1.7)	30.6 (3.0)	29.0 (1.9)
College graduate	25.6 (2.1)	20.9 (4.4)	23.5 (2.0)	29.2 (3.2)	30.3 (3.0)	23.9 (2.7)
Household Income, % (SE)*						
<$25,000	19.6 (1.1)	32.9 (3.7)	20.5 (1.2)	18.4 (2.0)	16.4 (1.4)	14.4 (2.2)
$25,000 - <$55,000	31.3 (1.5)	33.4 (3.4)	31.8 (2.0)	30.0 (2.0)	30.8 (2.8)	34.4 (3.6)
$55,000 - <$75,000	15.3 (0.7)	11.3 (3.1)	15.5 (0.8)	15.6 (1.5)	14.7 (1.6)	15.7 (1.9)
$75,000 +	30.2 (2.2)	15.8 (4.2)	27.3 (2.1)	32.9 (2.7)	35.4 (3.1)	32.3 (2.8)
Married, % (SE)*	58.2 (1.6)	46.9 (4.5)	55.4 (1.8)	60.1 (2.4)	63.5 (2.8)	61.6 (2.7)
Insured, % (SE)*	81.5 (1.7)	76.0 (3.9)	79.4 (2.2)	82.8 (1.8)	84.5 (2.2)	79.6 (2.4)
ł Current Smoker, % (SE)*	11.2 (0.5)	12.0 (3.9)	11.4 (1.7)	11.0 (1.0)	11.2 (1.6)	11.3 (1.1)
ł At least 12 drinks/year, % (SE)	27.7 (0.8)	27.9 (3.1)	28.5 (1.8)	28.8 (1.5)	24.5 (2.1)	28.0 (26)
Fair or poor diet quality, % (SE)*	27.2 (1.4)	32.3 (3.7)	29.3 (2.0)	25.1 (2.0)	26.8 (2.2)	25.2 (2.2)
BMI kg/m^2, mean (SE)	25.3 (0.2)	25.6 (0.3)	25.5 (0.4)	25.3 (0.5)	25.0 (0.4)	25.2 (0.4)
ł Hypertension,% (SE)*	22.2 (0.6)	22.6 (5.5)	22.3 (1.6)	25.1 (2.0)	21.9 (1.2)	23.6 (2.9)
ł High cholesterol, % (SE)*	11.8 (0.8)	8.8 (2.0)	13.6 (1.2)	11.0 (1.2)	13.3 (1.9)	10.7 (2.1)
Diabetes, % (SE)*	5.2 (0.4)	3.2 (1.6)	6.3 (0.8)	5.5 (0.9)	4.7 (0.9)	4.6 (1.5)
% Prevalent CVD	5.6 (0.7)	2.9 (1.2)	6.8 (1.2)	4.8 (1.2)	6.1 (1.0)	6.5 (1.7)
% Died*	8.7 (0.5)	20.9 (2.2)	9.0 (1.3)	5.1 (0.6)	3.2 (0.9)	5.2 (1.2)
Steps per day, mean (SE)*	6,680 (111)	1,624 (31)	3,872 (28)	6,214 (22)	8,640 (37)	12,567 (168)

*Estimate differs by steps per day (chi-square test for proportions or ANOVA for means P <0.05).
łProportion of the sample missing data are large and a missing category was created with proportions: smoking: 24.2%; drinking: 58.3%; hypertension: 14.3%; high cholesterol: 68.6%; Diabetes: 5.6%.
All estimates (except for age specific estimates) are age-standardized to the overall age distribution

Supplementary Table 2: Association of Average Steps Per Day with Years of Potential Life Lost, NHANES 2005-2006 (n=474)

	Model 1 **β (95% CI)**	**Model 2** **β (95% CI)**	**Model 3** **β (95% CI)**	**Model 4** **β (95% CI)**	**Model 5** **β (95% CI)**
Categorical SPD					
<2,500	ref	ref	ref	ref	ref
2,500-4,999	**-1.52 (-2.69, -0.35)**	**-1.46 (-2.61, -0.31)**	**-1.35 (-2.38, -0.32)**	**-1.31 (-2.43, -0.20)**	**-1.33 (-2.53, -0.13)**
5,000-7,500	-0.58 (-2.20, 1.05)	-0.28 (-1.87, 1.31)	-0.41 (-2.12, 1.30)	-0.38 (-2.10, 1.33)	-0.63 (-2.10, 0.84)
7,500-9,999	-1.11 (-3.30, 1.08)	-1.56 (-3.50, 0.38)	-1.52 (-3.05, 0.02)	-1.48 (-3.04, 0.08)	**-1.65 (-3.22, -0.09)**
≥10,000	1.30 (-0.26, 2.86)	1.22 (-0.36, 2.80)	1.31 (-0.19, 2.80)	1.30 (-0.12, 2.71)	1.35 (-0.30, 3.01)

*β= Beta, CI= Confidence Interval

Model 1 is adjusted for continuous age; model 2 is additionally adjusted for: sex and race; model 3 is additionally adjusted for: education, income, marital status, and insurance status; model 4 is additionally adjusted for: smoking, diet, and alcohol consumption; model 5 is additionally adjusted for: body mass index, hypertension, hypercholesterolemia, diabetes, and prevalent cardiovascular disease.

Steps and Mortality in NHANES

We chose to use YPLL as our outcome because it is a novel metric similar to mortality that takes premature death into consideration, arguably a better metric than crude mortality when considering implications for public health [74, 76].

However, mortality is arguably the most powerful outcome in all of clinical research and admittedly easier to understand compared to YPLL. When conceptualizing this manuscript and subsequent thesis, mortality was considered as our main outcome variable, though we learned of another group of researchers at the National Institutes of Health conducting a similar analysis in the National Health and Nutrition Examination Survey (NHANES). Therefore, we decided upon YPLL as our main outcome of interest in order to differentiate ourselves from this group.

We used a series of 5 successive cox proportional hazards regression models to determine whether average steps/d were associated with all-cause mortality using both continuous steps/d and categories of steps/d previously mentioned. We also obtained estimates stratified by sex and race, with interaction terms (i.e. steps*sex, steps*race/ethnicity) included in the model. Finally, another regression model was done to understand how continuous steps/d was associated with CVD mortality, defined as death from cerebrovascular disease or any disease of the heart.

An increase of 1000 average steps/d was associated with a 15% reduction in all-cause mortality in both the minimally adjusted and full adjusted models [HR(95% CI): 0.85(0.77,0.94), 0.85(0.76, 0.94), respectively] (**Supplementary Table 3**). When comparing step categories to the referent group (<2,500 steps/d), significant reductions in all-cause mortality were observed. However, this relationship was not linear but appears to be J-shaped. Successive, incremental reductions in all-cause mortality were observed when comparing the referent group to higher step categories, but there was a slight decrease in the magnitude or mortality reduction when comparing the 7,500-9,999 and ≥10,000 steps/d categories [HR(95% CI): 0.20(0.10, 0.38), 0.33(0.15, 0.06), respectively]. Data referenced in the 2018 Physical Activity Guidelines for Americans (PA guidelines) mentions no potential ceiling of benefit, and no evidence of increased risk at higher amounts of activity when using all-cause mortality as the outcome of interest, [2, 106] though other studies do show an apparent "uptick" in mortality risk at higher amounts of PA, [50, 107] which is congruent with our analysis. Furthermore, a study using data from the Woman's Health Study conducted a similar analysis to evaluate associations between objectively measured steps and all-cause mortality, and found that more steps/d were associated with successively lower mortality rates until approximately 7,500 steps/d.[90] Once participants (older women) reached 7,500 steps/d, there was no additional mortality benefit, suggesting our analysis is consistent with their study. However, this assertion would need to be verified in larger cohorts.

Sex and race stratified regression models are reported in **Supplementary Table 4** on the association between continuous steps/d and all-cause mortality. In the fully adjusted models, both men and woman had significant reductions in all-cause mortality [HR(95% CI): 0.83(0.68, 0.99), 0.86(0.78, 0.94), respectively], and there was no significant interaction (p= 0.07). When stratifying by race, significant reductions in all-cause mortality were observed in White and Black individuals, but not in Hispanics [HR(95% CI): 0.82(0.72, 0.94), 0.90(0.83, 0.98), 0.97(0.87, 1.09) for White, Black, and Hispanics respectively]. There was a significant interaction when stratifying by sex (p<0.01). These supplementary analyses are largely hypothesis generating given low power, but provide insight for additional studies that should be conducted in the future.

Finally, significant reductions in CVD mortality were observed **(Supplementary Table 5)**. An increase of 1,000 steps/d was associated with a 18% reduction in CVD mortality after full adjustment [HR(95% CI): 0.82(0.73, 0.92)]. However, interpretation of these data should be done with caution, as only 108 deaths from CVD were included. Similar to our sex and race stratified data, further studies are warranted to better understand this relationship.

Supplementary Table 3: Association of Average Steps Per Day with All-Cause Mortality, NHANES 2005-2006 (n=4,053)

	Model 1 **HR (95% CI)**	**Model 2** **HR (95% CI)**	**Model 3** **HR (95% CI)**	**Model 4** **HR (95% CI)**	**Model 5** **HR (95% CI)**
Per 1,000 Steps Per Day	**0.85 (0.77, 0.94)**	**0.83 (0.75, 0.92)**	**0.85 (0.77, 0.94)**	**0.85 (0.77, 0.94)**	**0.85 (0.76, 0.94)**
Categorical Steps Per Day					
2,500-4999 vs. <2,500	**0.50 (0.37, 0.68)**	**0.47 (0.35, 0.64)**	**0.50 (0.37, 0.68)**	**0.50 (0.37, 0.68)**	**0.50 (0.36, 0.68)**
5,000-7,500 vs. <2,500	**0.27 (0.19, 0.37)**	**0.24 (0.18, 0.33)**	**0.27 (0.20, 0.37)**	**0.27 (0.20, 0.37)**	**0.27 (0.19, 0.38)**
7,500-9,999 vs. <2,500	**0.20 (0.11, 0.39)**	**0.18 (0.09, 0.33)**	**0.20 (0.11, 0.39)**	**0.20 (0.10, 0.38)**	**0.20 (0.10, 0.38)**
≥10,000 vs. <2,500	**0.36 (0.19, 0.71)**	**0.29 (0.15, 0.57)**	**0.32 (0.16, 0.66)**	**0.32 (0.15, 0.65)**	**0.33 (0.15, 0.69)**

*HR= Hazard Ratio, CI= Confidence Interval

Model 1 is adjusted for continuous age; model 2 is additionally adjusted for: sex and race; model 3 is additionally adjusted for: education, income, marital status, and insurance status; model 4 is additionally adjusted for: smoking, diet, and alcohol consumption; model 5 is additionally adjusted for: body mass index, hypertension, hypercholesterolemia, diabetes, and prevalent cardiovascular disease.

Supplementary Table 4: Association of Average Steps Per Day with All-Cause Mortality Stratified by Sex and Race, NHANES 2005-2006 (n=474)

	Model 1 HR (95% CI)	**Model 2** HR (95% CI)	**Model 3** HR (95% CI)	**Model 4** HR (95% CI)	**Model 5** HR (95% CI)
Continuous Steps Per Day (Per 1,000 Step Increment)					
Sex Stratified (Interaction p = 0.07)					
Men	**0.83 (0.70, 0.97)**	**0.82 (0.69, 0.98)**	**0.83 (0.70, 0.99)**	**0.83 (0.69, 0.99)**	**0.83 (0.68, 0.99)**
Women	**0.83 (0.76, 0.92)**	**0.83 (0.76, 0.92)**	**0.85 (0.77, 0.93)**	**0.85 (0.78, 0.94)**	**0.86 (0.78, 0.94)**
Race Stratified (interaction p <0.01)					
White	**0.82 (0.72, 0.93)**	**0.80 (0.71, 0.91)**	**0.82 (0.73, 0.93)**	**0.82 (0.73, 0.93)**	**0.82 (0.72, 0.94)**
Black	**0.92 (0.86, 0.99)**	**0.90 (0.83, 0.97)**	**0.91 (0.85, 0.99)**	**0.91 (0.84, 0.99)**	**0.90 (0.83, 0.98)**
Hispanic	0.99 (0.90, 1.09)	0.98 (0.89, 1.08)	0.98 (0.89, 1.08)	0.97 (0.88, 1.08)	0.97 (0.87, 1.09)

*HR= Hazard Ratio, CI= Confidence Interval

Model 1 is adjusted for continuous age; model 2 is additionally adjusted for race; model 3 is additionally adjusted for: education, income, marital status, and insurance status; model 4 is additionally adjusted for: smoking, diet, and alcohol consumption; model 5 is additionally adjusted for: body mass index, hypertension, hypercholesterolemia, diabetes, and prevalent cardiovascular disease

Supplementary Table 5: Association of Average Steps Per Day with CVD Mortality, NHANES 2005-2006 (n=108)

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
Per 1,000 Steps Per Day	**0.83 (0.74, 0.94)**	**0.81 (0.71, 0.92)**	**0.82 (0.73, 0.93)**	**0.82 (0.73, 0.92)**	**0.82 (0.73, 0.92)**

*HR= Hazard Ratio, CI= Confidence Interval

Model 1 is adjusted for continuous age; model 2 is additionally adjusted for: sex and race; model 3 is additionally adjusted for: education, income, marital status, and insurance status; model 4 is additionally adjusted for: smoking, diet, and alcohol consumption; model 5 is additionally adjusted for: body mass index, hypertension, hypercholesterolemia, diabetes, and prevalent cardiovascular disease

Future Directions

As mentioned above, we hope to continue our analyses on the associations between steps and mortality/YPLL once more data are available. NHANES 2005-2006 was used in our main analysis because participants were given a PAM to measure PA. There are at least two other cycles, NHANES 2011-2012 and 2013-2014, in which participants were given PAMs, however these data are currently restricted.[16] Once these data becomes available to the public, we hope to have more power to better understand these relationships in more detail, particularly stratified by sex and race.

Moreover, we plan to use isotemporal substitution modeling in future PA analyses. As mentioned in Chapter 1, this model seeks to better explain the inter-relatedness among time spent in various aspects of daily living, often using sleep, sedentary behavior, light intensity PA (LPA), and moderate to vigorous PA (MVPA) as variables of interest in the context of a finite 24-hour day. This type of analysis, which would require 24-hour accelerometry data, can be used to model the effects of replacing time in one variable with the same amount of time in another variable to observe how it effects an outcome, and is considered by some to be the "gold standard" model for PA epidemiology research.[56]

The Multi-Ethnic Study of Atherosclerosis Sleep ancillary study represents an ideal observational cohort to investigate these relationships in a well characterized sample of multiethnic middle aged and older adults. Using isotemporal substitution modeling, we will investigate how reallocating time from sedentary behavior to sleep, LPA, or MVPA affect cardiovascular health. This cohort has all the necessary variables to conduct this type of analysis, and has the potential to inform public health guidelines to improve the health of our population. This analysis is already underway.

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Exercise Program Can Improve Cognitive Function and Neural Efficiency in Community-Dwelling Older Adults: A Randomized Controlled Trial. *Journal of the American Geriatrics Society*. 2015;63:1355-1363.

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CURRICULUM VITAE

NAME: Dr. Charles A. German

CURRENT TITLE: Cardiology Fellow
Wake Forest School of Medicine
Winston Salem, NC

ADDRESS: 2426 Queen St
Winston Salem, NC, 27103

EDUCATION:

BA Biology, University of Texas at Austin, 2009

MD, University of Texas Medical Branch School of Medicine, 2014

PROFESSIONAL LICENSURE:

Alabama, Internal Medicine, License #34736

North Carolina Medical License #2018-02008

CERTIFICATIONS:

ACLS Certified, 01/18/2018

BLS Certified, 01/18/2018

POSTDOCTORAL TRAINING

Internal Medicine Resident, 2014-2017

Tinsley Harrison Internal Medicine Residency Training Program

Department of Medicine, University of Alabama at Birmingham

School of Medicine, Birmingham, AL

Cardiology Fellow, 2017-present

Department of Medicine, Section on Cardiology

Wake Forest School of Medicine, Winston Salem, NC

NIH T32 Fellow, 2018-present

Cardiovascular Research Training Program

Department of Medicine, Section on Cardiology

Wake Forest School of Medicine, Winston Salem, NC

Graduate Student, 2018-present

MS in Clinical and Population Translational Sciences

Department of Public Health Sciences

Wake Forest Graduate School, Winston Salem, NC

RESEARCH EXPERIENCE

Fellow Research and Thesis Project, Steps and Years of Potential Life Lost in the US Population: NHANES, Wake Forest School of Medicine, 2018-Present, Thesis Committee: Dr. Peter Brubaker, Dr. Alain Bertoni, Dr. Michael Miller, Dr. Jason Fanning.

Resident Member, Vascular Biology and Hypertension Journal Club, University of Alabama at Birmingham, 2016-2017, Dr. Suzanne Oparil, Supervisor. This program emphasized cellular and molecular approaches to the study of cardiovascular control mechanisms.

Resident Research, Blood Pressure Dipping Patterns in Resistant HTN, University of Alabama at Birmingham, 2015-2017, Dr. David A Calhoun, Dr. Suzanne Oparil, Supervisors. Topic: Analysis of data collected from a cohort of 326 subjects with resistant hypertension, evaluating the effects of hyperaldosteronism and high sodium diet on blood pressure dipping patterns.

Summer Student, UT Southwestern-Bioinformatics, 2006, Dr. Harold “Skip” Garner, Supervisor. Topic: Novel uses for cardiovascular drugs currently on the market.

Summer Student, UT Southwestern-Psychiatry Department, 2005, Dr. Dwight German, Supervisor. Topic: Various projects regarding Alzheimer’s and Parkinson’s Diseases.

EMPLOYMENT

Research Technician, UT Southwestern-Psychiatry Department, Dallas, TX, 2009-2010, Dr. Colleen McClung, Supervisor.

MEMBERSHIPS:

American Heart Association

American College of Cardiology

National Lipid Association

American Society of Preventive Cardiology

Graduate Medical Education House Staff Council, University of Alabama, Birmingham

Diversity Enrichment, Committee, University of Alabama, Birmingham

Creative Effective Resident Teachers Scholar, University of Alabama, Birmingham

Health Disparities Track, University of Alabama, Birmingham

Pathways in Academic Medicine, University of Alabama, Birmingham

Gold Humanism Honor Society

Gold Humanism Honor Society Vice President (UTMB), Werner Forssman Osler Society

Treasurer (UTMB), Phi Beta Kappa (UT Austin), Graduated with Honors from UT Austin

GRAND ROUNDS PRESENTATIONS:

Clinical Cardiology Grand Rounds, “Physical Activity and Cardiovascular Health,”

10/9/2017

Clinical Cardiology Grand Rounds, “Update on the 2017 ACC/AHA Hypertension Guideline,” 12/11/2017

Clinical Cardiology Grand Rounds, “The Benefits of Cardiac Rehab,” 2/19/2018

Cardiology Research Grand Rounds, “2017 ACC/AHA Guidelines in MESA,” 5/11/2018

Clinical Cardiology Grand Rounds, “How Low is too Low? Cholesterol Management in the Era of PCSK9 Inhibitors,” 6/4/2018

Cardiology Research Grand Rounds, “Run Don’t Walk! Associations Between Steps and All Cause Mortality in NHANES,” 5/24/2019

Clinical Cardiology Grand Rounds, “CPET: Indications and Interpretation,” 7/15/2019

Clinical Cardiology Grand Rounds, “Advanced Lipid Testing,” 11/11/2019

JOURNAL CLUB PRESENTATIONS:

Heart Failure Journal Club, “Roadmap Study Year 2,” 9/17/2017

Heart Failure Journal Club, “Clinical Decision Support to Identify Patients Eligible for Advanced Heart Failure Therapies,” 11/27/2017

General Cardiology Journal Club, “Moderate to Vigorous Physical Activity and All Cause Mortality: Do Bouts Matter,” 4/12/2018

Heart Failure Journal Club, “Carvedilol Among Patients with Heart Failure with a Cocaine

Use Disorder," 11/12/2019

General Cardiology Journal Club, "Lipoprotein(a) Reduction in Persons with Cardiovascular In Persons with Cardiovascular Disease," 1/16/2020

GRANTS AND AWARDS:

Travel Award, National Lipid Association Clinical Lipid Update, 2018

Travel Award, American Society of Preventive Cardiology Congress on Prevention, 2019

Lifestyle and Cardiometabolic Health Early Career Investigator Award Finalist, American Heart Association Scientific Sessions, 2019

MANUSCRIPTS:

German C, Makarem N, Fanning J, Redline S, Elfassy T, McClain A, Abdalla M, Aggarwal B, Allen N, Carnethon M. Isotemporal Substitution Modeling to Evaluate Relationships Between Sleep, Sedentary Behavior, and Physical Activity on Cardiovascular Health in the Multi-Ethnic Study of Atherosclerosis: MESA. Manuscript in Preparation.

German C, Nelson B, Fanning J, Brubaker P, Kitzman DW. Associations Between Physical Activity, Exercise Capacity, and Quality of Life in Patients with HFpEF. Manuscript in Preparation.

German C, McClain A, Elfassy T, Omaru J, Saint-Maurice P, Matthews C, Carnethon M, Fulton J. Associations Between Steps and Years of Potential Life Gained in the United States: NHANES. Manuscript in Preparation.

Rongzi S, Yanek LR, Silverman-Lloyd LG, Kianoush S, Blaha MJ, German CA, Graham GN, Martin SS. Using Mobile Health Tools to Assess Physical Activity Guideline Adherence and Smoking Urges: A Secondary Analysis of mActive-Smoke. *Journal of Medical Internet Research Cardio*, 2019.

German C, Shapiro M. Assessing Atherosclerotic Cardiovascular Disease Risk with Advanced Lipid Testing: State of the Science. Submitted to European Cardiology Review.

Singleton MJ, German CA, Hari KJ, Saylor G, Herrington DM, Soliman EZ, Freedman BI, Bowden DW, Bhave PD, Yeboah J. QRS Duration is Associated with All-Cause Mortality in Type 2 Diabetics: The Diabetes Heart Study. *Journal of Electrocardiology*, 2019.

German C, Shapiro M. Small Interfering RNA Therapeutic Inclisiran: A New Approach to Targeting PCSK9. *BioDrugs*, 2019.

German C, Laughey B, Bertoni A, Yeboah J. Association Between BMI, Waist Circumference, Central Obesity and Outcomes in Type II Diabetes Mellitus: Analysis from the ACCORD Trial. *Journal of Diabetes and Its Complications*, 2019.

German CA, Ahmad MI, Li Y, Soliman EZ. Associations Between Physical Activity, Subclinical Myocardial Injury, and Cardiovascular Mortality in the General Population. *Am J Cardiol*. 2019.

German C, Yeboah J. Approach to Asymptomatic Intermediate Risk Individuals with High Coronary Artery Calcium Scores. *Expert Review of Cardiovascular Therapy*. 2019.

Branch M, German C, Bertoni A and Yeboah J. Incremental risk of cardiovascular disease and/or chronic kidney disease for future ASCVD and mortality in patients with type 2 diabetes mellitus: ACCORD trial. *Journal of Diabetes and its Complications*. 2019.

German CA, McEvoy JW, Blaha MJ, Bertoni A, Miedema MD, Burke GL and Yeboah J. Implications of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline in a Modern Primary Prevention Multi-Ethnic Prospective Cohort (Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol*. 2019.

Biswas M*, German C*, Patel R*, Kharod A, Nanda NC (*All three authors worked equally in writing this manuscript). Simulation Based Training in Echocardiography. Echocardiography. 2016 Oct; 33(10): 1581-1588.

* All three authors worked equally in writing this manuscript

German C, Nanda NC. Three-dimensional echocardiographic assessment of atrial septal defects. Annals of cardiac anaesthesia. 2015;18(1):69-73. Epub 2015/01/09. doi: 10.4103/0971-9784.148324. PubMed PMID: 25566714; PubMed Central PMCID: PMCPmc4900325.

German C, Nanda NC. Incremental Value of Three-Dimensional Echocardiography over Two-Dimensional Echocardiography in the Assessment of Atrial Septal Defects. Cardiovascular Journal. 2015, Jan; 7(2): 67-71.

German C, Nanda NC. Is Three-Dimensional Echocardiography Useful in the Evaluation of Atrial Septal Defects? International Cardiovascular Research Journal. 2015, Apr; 9(2): 67-70.

POSTER PRESENTATIONS/ABSTRACTS:

German C, Makarem N, Fanning J, Redline S, Eflassy T, McClain A, Abdalla M, Aggarwal B, Allen N, Carnethon M. Reallocating Sedentary Behavior with Sleep or Physical Activity is Associated with Favorable Cardiovascular Health in the Multi-Ethnic Study of Atherosclerosis: MESA. AHA Epi Lifestyle, March 2020.

Singleton MJ, German CA, Bertoni A, Ambrosius WT, Bhave PD, Soliman EZ, Yeboah J. Association of Silent Myocardial Infarction and Major Cardiovascular Events in Diabetes: The ACCORD Trial. ACC Scientific Sessions, March 2020.

German C, Ahmad MI, Li Y, Soliman EZ. Associations Between Physical Activity, Subclinical Myocardial Injury, and Cardiovascular Mortality in the General Population, Early Career Award Oral Presentation, AHA Scientific Sessions, November 2019.

German C, McClain A, Elfassy T. Associations Between Steps and Years of Potential Life Lost in the US Population. AHA Scientific Sessions, November 2019.

Singleton MJ, German CA, Hari K, Saylor G, Herrington DH, Soliman EZ, Freedman B, Bowden D, Bhave P, Yeboah J. QRS Duration is Associated with All-Cause Mortality in Type 2 Diabetics: The Diabetes Heart Study. AHA Scientific Sessions, November 2019.

German C, McClain A, Elfassy T. Steps and All-Cause Mortality in the US: NHANES. American Society of Preventive Cardiology 2019 Congress on CVD Prevention, July 2019.

German C, Nelson B, Fanning J, Brubaker P, Kitzman DW. Associations Between Physical Activity, Exercise Capacity, and Quality of Life in Patients with HFpEF. AHA Epi Lifestyle Scientific Sessions, March 2019.

German C, McEvoy JW, Blaha MJ, Bertoni A, Miedema MD, Burke GL, Yeboah J. Implications of the 2017 American College of Cardiology/American Heart Association Hypertension Guidelines in a Multi-Ethnic Cohort: MESA. AHA Scientific Sessions, November 2018.

Laughey B, German C, Bertoni A, Yeboah PN, Byington B, Yeboah J. Cardiovascular Risk Strata Among Persons with Diabetes Mellitus: A Post Hoc Analysis of the ACCORD Trial. AHA Scientific Sessions, November 2018.

German C, Dutta A, Patel N, Berdy A, Pisani B. Inhaled DDAVP Resulting in Hyponatremia in Acquired Von Willebrand's Disease. Wake Forest Internal Medicine Research Symposium, May 2018.

Berdy A, Patel N, German C, Dutta A, Pisani B (2018). Chylothorax as a Complication of Orthotopic Heart Transplant. Presented at Wake Forest Internal Medicine Research Symposium, May 2018 and HFSA 22nd Annual Meeting September 2018.

German C, Richardson K (2018) Constrictive Pericarditis: How Kussmaul's Sign Prevented Dialysis. ACC Scientific Sessions, March 2018.

German C., Ghazi L, Pimenta E, Gaddam K, Calhoun D, Dudenbostel T. Blood Pressure Control and Dipping Patterns in Patients with Resistant Hypertension L Combined Effects of Aldosterone and Sodium. AHA Scientific Sessions, November 2016.

German C., Ghazi L, Pimenta E, Gaddam K, Calhoun D, Dudenbostel T. Effects of Aldosterone Excess and Sodium on Dipping Patterns in Resistant Hypertensive Patients. AHA Council on Hypertension Scientific Sessions, September 2016.

German C., Ghazi L, Pimenta E, Gaddam K, Calhoun D, Dudenbostel T. Combined Effects of Aldosterone and Sodium on blood Pressure Control and Patterns in Patients with Resistant Hypertension. 32nd Annual UAB Trainee Research Symposium, March 2016.

STUDY ADJUDICATOR:

I3C Outcomes Study

Pooling data from 7 major childhood cohorts around the world to try and relate CV risk factors measured in childhood to CV events in adulthood. Opportunity to participate in manuscript writing as well.

EDITORIAL ACTIVITES:

Manuscript Reviewer for Echocardiography Journal, 2016-2017

Manuscript Reviewer for Circulation, 2018-present

Manuscript Reviewer for the Journal of the American College of Cardiology, 2018-present

Manuscript Reviewer for the Journal of Cardiovascular Development and Disease, 2018-present

Manuscript Reviewer for Journal of the American Medical Association Cardiology, 2019-present

Manuscript Reviewer for American Journal of Cardiology, 2019-present

Manuscript Reviewer for Journal of Science and Medicine in Sport, 2019-present

CLINICAL TRIALS CO-INVESTIGATOR:

1002-043 Esperion

A Randomized, Double-Blind, Placebo-Controlled Study To Assess The Effects Of Bempedoic Acid (Etc-1002) On The Occurrence Of Major Cardiovascular Events In Patients With, Or At High Risk For, Cardiovascular Disease Who Are Statin Intolerant
Evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of major adverse cardiovascular events (MACE) in patients with, or at high risk for, cardiovascular disease (CVD) who are statin intolerant.

20150230 Amgen
Getting to an improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management (GOULD) a Registry of High Cardiovascular Risk Subjects in the United States
A registry of lipid lowering treatment with goals of describing low-density lipoprotein treatment patterns over time in subjects with clinical atherosclerotic cardiovascular disease.

D5881C00004 AstraZeneca

A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova In High Cardiovascular Risk Patients With Hypertriglyceridemia (STRENGTH)
A phase III, randomized, double-blind, controlled, parallel group design that will enroll patients with high triglyceride levels to study the efficacy of EpaNova (O3FA) in reducing the occurrence of major cardiovascular events.

DAL-301 DalCor Pharma UK Ltd.
A phase III, double--blind, randomized placebo--controlled study to evaluate the effects of dalcetrapib on cardiovascular (CV) risk in a genetically defined population with a recent Acute Coronary Syndrome (ACS): The dal-GenE trial
Reduction of CV mortality and morbidity in subjects with documented recent Acute Coronary Syndrome and the AA genotype at variant rs1967309 in the adenylate cyclase type 9 (ACDY9) gene

CSL112_3001 CSL Behring LLC

A Phase III, multicenter, double-blind, randomized, placebo controlled, parallel group study to investigate the efficacy and safety of CSL112 (Apolipoprotein A-I) in subjects with Acute Coronary Syndrome: The Apo-I Event Reducing in Ischemic Syndromes II (AEGIS-II) Study

NCT03835429 Texas A&M Health Science Center

Oropharynx-Brainstem-Heart Connection: A Controlled Clinical Trial to Assess Atrial Fibrillation Attenuation in Patients Treated with Oral Appliance Therapy. A nonrandomized pilot study to assess the effect of oral appliance therapy to attenuate atrial fibrillation events in patients implanted with an AF monitoring device using sleep related biomarkers associated with cardio-respiratory dynamics

EXTRACURRICULAR CLINICAL ACTIVITES:

Cardiac Rehabilitation

I spend one morning a week with the program leaders and patients. I write exercise prescriptions for acute and post-acute rehabilitation following a variety of cardiac events and have been involved with quality improvement.

Weight Management Center

I am the cardiac risk consultant for the Wake Forest Weight Management Center, helping identify and treat patients with a high risk of cardiovascular disease

COMMUNITY ACTIVITES:

William G White Jr YMCA

I give lectures on cardiovascular health and wellness at the William G White Jr YMCA in Winston Salem, North Carolina.

Walk with a Doc Winston Salem

I lead the Winston Salem chapter of Walk with a Doc, an organization with the goal of encouraging health and physical activity in the community. We meet once a month to discuss topics in cardiac health and engage in a 1 mile walk.