Exploring Sedentary Behavior as a Secondary Prevention Target for Heart Disease

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ABSTRACT

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The purpose of this dissertation series was to describe sedentary behavior and its associations with cardiovascular disease (CVD) biomarkers and outcomes, and to explore the potential that reducing sedentary behavior may be a secondary prevention target for Acute Coronary Syndrome (ACS) survivors. As such, the following series of research studies evaluate the mechanisms, patterns, and correlates of sedentary behavior in relation to CVD risk and examine whether sedentary behavior might be a risk factor for CVD outcomes among ACS survivors. In Chapter II, a cross-sectional study of young, healthy adults examined a set of biomarkers representing several aspects of endothelial cell health to elucidate the relationship between free-living, habitual sedentary time and endothelial dysfunction. Results showed that there were no differences in measures of endothelial cell injury, endothelial cell reparative capacity, or upper extremity endothelium-dependent vasodilatation in participants with high compared with low volumes of device-measured sedentary behavior in a sample of young, healthy adults. These findings suggest that physiological mechanisms other than endothelial dysfunction may need to be explored as a potential link between habitual prolonged sedentary time and CVD in young adults. Chapter III employed group-based trajectory modeling to identify distinct patterns of sedentary behavior, as measured by accelerometry, in ACS survivors over the 28 consecutive days following hospital discharge, and, secondly, to explore potential correlates of these patterns. Results demonstrated that ACS patients as a group engaged in high volumes of accelerometer-measured sedentary time. Three patterns of sedentary behavior over the first month post-discharge

were identified; these involved either gradual or rapid reductions in sedentary behavior. Several measures of disease severity and physical health (e.g., GRACE CVD risk score, physical health-related quality of life), and partner status (i.e., married or partnered or without partner), were associated with the worst patterns of sedentary behavior (i.e., high volume of sedentary time with only a slight decline over time). These findings provide insight on the different patterns of sedentary behavior that emerge as patients resume their daily life over the first month post hospital discharge. Chapter IV, building upon the study presented in Chapter III, examined whether accelerometer-measured sedentary behavior of ACS survivors over the first month post hospital discharge was associated with 1-year health outcomes. The purpose of this study was to understand whether sedentary behavior in the early post hospital discharge period may be an important risk factor in ACS survivors, that might be targeted in secondary prevention strategies. Results demonstrated that the average sedentary behavior over the first month post hospital discharge was not significantly associated with increased risk of 1-year recurrent major adverse cardiovascular events or hospitalizations. These findings do not support sedentary behavior in the early post hospital discharge period as a prognostic risk factor that should be modified in ACS survivors as part of secondary heart disease prevention strategy. However, studies with larger sample sizes, and that evaluate sedentary behavior patterns beyond the first month are needed. Collectively, these studies show that high volumes of sedentary behavior are prevalent in ACS survivors over the first month immediately following hospital discharge. Future work is needed to further study the underlying mechanisms through which sedentary behavior may confer CVD risk and to determine whether sedentary behavior is an important modifiable risk factor in ACS survivors.

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DEDICATION

I would like to dedicate this dissertation to my loving Bompa and Grandmama

CHAPTER I

Introduction

Acute coronary syndrome (ACS), characterized by unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), is among the top causes of death in the modern, industrialized world (Fuster & Kovacic, 2014). In the United States, more than 1.1 million people are hospitalized annually for an ACS event (Mozaffarian et al., 2015). Despite improvements in acute care, 21% of ACS survivors will be re-hospitalized and approximately 1 in 5 patients will die within 1 year following hospitalization (Menzin, Wygant, Hauch, Jackel, & Friedman, 2008). Much of the increased morbidity and mortality risk among ACS survivors remains unexplained (Berton, Cordiano, Palmieri, Cavuto, & Pellegrinet, 2014; Fox et al., 2010). Thus, there is a need to identify modifiable risk factors for intervention to increase survival and reduce recurrent events among ACS patients.

Sedentary behavior, defined as any sitting or reclining behavior with energy expenditure $\leq$ 1.5 metabolic equivalents (METs; i.e. watching TV, computer use, etc.), has emerged as a distinct cardiovascular disease (CVD) risk factor that may carry clinical relevance beyond how much one exercises (Roger et al., 2011; World Health Organization, 2009). Accumulating evidence from population-based studies indicate that sedentary behavior is associated with elevated CVD morbidity and mortality, and worsened CVD risk factors, such as impaired glucose regulation and dyslipidemia (Wilmot et al., 2012). Notably, the deleterious effects of sedentary behavior are attenuated only by high levels of moderate-to-vigorous physical activity (MVPA) (~60 to 75 min/d), which exceed physical activity recommendations (Ekelund et al., 2016; Garber et al., 2011). This raises the question as to whether reducing sedentary behavior may represent another

therapeutic target for secondary prevention and rehabilitation of ACS survivors, in addition to existing MVPA recommendations (Amsterdam et al., 2014).

To understand the clinical utility of sedentary behavior reduction as a secondary prevention target in ACS survivors, the biological mechanisms that underlie the deleterious relationship between sedentary behavior and CVD must be established. Endothelial dysfunction, an early pathogenic process underlying atherosclerosis, is a promising mechanism purported to be a contributing factor to the sedentary behavior-CVD link (Ross, 1999; Versari, Daghini, Virdis, Ghiadoni, & Taddei, 2009). The sitting posture (the primary sedentary posture) promotes muscle inactivity of the lower extremities and changes in the angles at which the femoral and popliteal arteries run (Restaino, Holwerda, Credeur, Fadel, & Padilla, 2015); eliciting adverse hemodynamic changes within the arterial tree (Delp & Laughlin, 1998; Padilla, Johnson, et al., 2009; Padilla, Sheldon, Sitar, & Newcomer, 2009; Restaino et al., 2015). As such, it is hypothesized that prolonged sitting may confer CVD risk by exposing the endothelium to a pro-atherogenic milieu, facilitating endothelial dysfunction over time (Hamilton, Hamilton, & Zderic, 2007; Thosar, Johnson, Johnston, & Wallace, 2012). If this sitting-induced endothelial dysfunction hypothesis is confirmed, sedentary behavior reduction may be a meaningful secondary prevention target for ACS survivors.

In addition to understanding the mechanisms, it's important to describe the patterns and pervasiveness of sedentary behavior in ACS survivors during the period immediately following hospitalization, as well as determine whether these patterns are linked to survival and recurrent cardiac events. Currently, no studies have examined the amount of time ACS survivors engage in sedentary behaviors immediately after hospitalization, a critical time period when lifestyle interventions ideally begin (e.g., cardiac rehabilitation). Therefore, the purpose of this dissertation

series is to provide a foundation of empirical evidence to recognize the implications of sedentary behavior as a potential secondary prevention target for ACS survivors. As such, the following research studies attempt to understand the mechanisms, patterns, and correlates of sedentary behavior in relation to CVD, as well as whether sedentary behavior is linked to CVD health outcomes in ACS survivors.

Significance

Technological advancements in transportation, communication, the workplace and domestic-entertainment have cultivated occupational, home and social environments that oblige or promote sedentary behavior (Brownson, Boehmer, & Luke, 2005; Owen, 2012). As a result, time spent in sedentary behavior has continued to increase and physical activity levels have continued to decline over the past 50 years in the United States (Ng & Popkin, 2012). U.S. adults now spend an alarming 9 to 10 hours per day in sedentary behavior, including occupational sitting, TV viewing, and computer use (Dunstan, Howard, Healy, & Owen, 2012). Given the ubiquitous nature and high volumes of sedentary behavior detected among U.S. adults, as well as the adverse health consequences of too much sitting (previously described), there is an urgent need to identify populations that spend excessive time engrossed in sedentary behaviors (Rosenberg et al., 2015). ACS survivors, a vulnerable population at high risk for recurrent cardiac events and mortality, experience psychosocial and physical barriers to movement as they regain functional independence, (re)form lifestyle habits and integrate back into their daily activities (Conraads et al., 2012; Yates, Price-Fowlkes, & Agrawal, 2003). Consequently, ACS survivors may engage in high volumes of sedentariness after hospitalization. Thus, efforts are needed to understand whether sedentary-reduction strategies are needed for the vulnerable population of ACS survivors.

By employing a multi-faceted, comprehensive approach to characterizing sedentary behavior and its underlying physiological mechanisms, this dissertation series will provide a foundation for understanding the implications of sedentary-reduction strategies in ACS survivors. Collectively, the findings from the studies included in this dissertation series will:

1) impart crucial insight as to whether endothelial dysfunction is a contributing factor to the sedentary behavior-CVD link.

2) characterize ACS survivors according to their sedentary behavior as they recuperate from their ACS event, which may reveal unique patterns and subsets of patients in whom sedentary reduction strategies may be most beneficial.

3) provide fundamental information about whether sedentary behavior is an important risk factor of CVD outcomes and hospitalizations in ACS survivors, which can inform secondary prevention guidelines.

Overview

This dissertation series on sedentary behavior and CVD includes three discrete, yet related, cross-sectional studies that focus on 1) endothelial dysfunction as a potential underlying mechanism that links sedentary behavior to CVD, 2) the characterization of sedentary behavior in ACS survivors during the first month post hospital discharge, and 3) the exploration of the association between sedentary behavior during the first month post hospital discharge and increased risk of health outcomes in ACS survivors. Study one examines the association of habitual sedentary behavior with comprehensive markers of endothelial dysfunction among young, healthy adults. The second study employs group-based trajectory modeling to identify distinct patterns of sedentary behavior, measured by accelerometry for 28 consecutive days post-hospital discharge, in ACS survivors, as well as potential correlates of these patterns. The third study, which builds

off the methods of study two, utilizes cox proportional hazard regression modeling to calculate the hazard ratio for health outcomes associated with sedentary time, with the goal to understand whether sedentary behavior during the first month post hospital discharge is an important risk factor of recurrent cardiac events and hospitalizations in ACS survivors.

The specific aims of this dissertation are to:

1) comprehensively examine whether habitual accelerometer-measured sedentary time is associated with markers of endothelial function in a cohort of healthy adults

2) identify and evaluate patterns of change in sedentary behavior over the 28-day convalescent period following ACS, as well as identify correlates of the observed patterns

3) determine whether accelerometer-measured sedentary behavior is associated with risk of 1-year recurrent major adverse cardiac events and recurrent hospitalizations in ACS survivors.

The hypotheses for each specific aim of this dissertation are:

1) greater sedentary time will be associated with poorer endothelial cell health in healthy adults (i.e., lower endothelial-dependent vasodilation, higher circulating endothelial microparticles, lower circulating endothelial progenitor cells)

2) ACS survivors will exhibit at least two unique patterns of change in sedentary behavior over the 28-day period post-hospital discharge and markers of disease severity will be correlates of these unique patterns

3) greater sedentary time during the first month post-hospital discharge will be predictive of increased 1-year risk of recurrent major adverse cardiac events and recurrent hospitalizations in ACS survivors.

Dissertation Structure

      Chapters II, III, and IV are three separate studies that have utilized accelerometry to measure sedentary behavior in adults with and without ACS, with the overarching goal to provide empirical evidence to support further exploration of sedentary behavior as a potential secondary prevention target in ACS survivors. Accordingly, Chapters II-IV aim to understand the mechanisms, characterization, and correlates of accelerometer-measured sedentary behavior in relation to CVD, and whether this behavior is linked to CVD health outcomes. For each chapter, an abstract, introduction, methods, results, discussion, conclusion, references, related tables and figures, and supplemental material are presented. Appendix A includes the literature review for the dissertation series. Appendix B includes details about the EndoPAT™ protocol used to measure endothelial-dependent vasodilation in study one. Appendix C contains information on the endothelial cell transformations used for each outcome variable in study one. Appendix D includes the calculations used to derive the estimate statement for obtaining mean sedentary time in the multilevel growth curve models in study three. Appendices E and F comprises all relevant study instruments used within study one and study two/three, respectively. Related Institutional Review Board documents from Teachers College, Columbia University, and where applicable, Columbia University Medical Center, are included for all primary dissertation studies and are provided in Appendix G.

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CHAPTER II

Exploring the Associations Between Habitual Sedentary Behavior and Endothelial Cell Health

Abstract

Endothelial dysfunction, an early pathogenic process underlying atherosclerosis, is a mechanism that may explain the link between prolonged sedentary time and cardiovascular disease (CVD). However, the relationship between habitual sedentary behavior and markers of endothelial function have yet to be explored. **Purpose:** Examine the association of accelerometer-measured sedentary time with markers of endothelial function. **Methods:** Participants (n=83; 43.4% male; 25.5±5.8 y) with valid accelerometer and endothelial function data from the **P**utative Mechanisms **U**nderlying **M**yocardial Infarction Onset and **E**motions (PUME) study were examined. Sedentary behavior and moderate-to-vigorous physical activity (MVPA) were measured for 7-days by accelerometer. Endothelial function measures included endothelium-dependent vasodilation [reactive hyperemia index (RHI)]; circulating endothelial microparticles (EMPs) [CD62E+ and CD31+/CD42- surface markers]; and circulating endothelial progenitor cells (EPCs) [CD34+/CD133+/KDR+ and CD34+/KDR+ surface markers]. Participants were classified as having high or low sedentary time based on a median split of total sedentary time. Multivariable regressions were used to examine differences of endothelial cell variables between low and high sedentary behavior groups. Models were adjusted for age, sex, race, ethnicity, and education (Model 1), MVPA (Model 2), and body mass index (Model 3). **Results:** Mean (±SD) sedentary time and MVPA for the overall sample was respectively 9.9 ± 1.7 h/day and 64.5 ± 28.0 min/day over a 16-hour waking day. Participants in the low and high sedentary behavior groups spent a mean (SD) of 8.6 ± 1.1 and 11.1 ± 1.0 h/day in sedentary time, respectively, over a 16-hour waking

day. No significant differences between the low and high sedentary behavior groups were detected in RHI, EMPs (CD62E+, CD31+/CD42-), or EPCs (CD34+/KDR+, CD34+/CD133+/KDR+), even after adjusting for selected covariates ($p>0.05$ for all). **Conclusion:** Among young, healthy, active adults, sedentary behavior was not associated with markers of endothelial cell health. This suggests that, in this population, mechanisms other than endothelial dysfunction should be explored as a potential link between prolonged sedentary time and CVD.

Introduction

  Accumulating evidence indicates that prolonged sedentary time is associated with incident cardiovascular disease (CVD), incidence of CVD-related risk factors, and mortality, potentially independent of moderate-to-vigorous physical activity (MVPA) (Biswas et al., 2015; Wilmot et al., 2012). However, the mechanisms underlying the associations between sedentary behavior and CVD have not been elucidated. Endothelial dysfunction, an early pathogenic process underlying atherosclerosis, is a putative contributory mechanism (R. Ross, 1999; Versari, Daghini, Virdis, Ghiadoni, & Taddei, 2009). The sitting posture (the primary sedentary posture) promotes muscle inactivity of the lower extremities and changes in the angles at which the femoral and popliteal arteries run, causing bends within the arterial tree (Restaino, Holwerda, Credeur, Fadel, & Padilla, 2015). These physiological conditions elicit hemodynamic changes that include blood pooling in the legs, decreased thigh and calf blood flow, and augmented turbulent blood flow in the deformed arterial segments (Delp & Laughlin, 1998; Padilla, Johnson, et al., 2009; Padilla, Sheldon, Sitar, & Newcomer, 2009; Restaino et al., 2015). For these reasons, it is thought that prolonged sitting promotes atherosclerosis and increased CVD risk by exposing the endothelium to a pro-atherogenic milieu, facilitating endothelial dysfunction over time (Hamilton, Hamilton, & Zderic, 2007; Thosar, Johnson, Johnston, & Wallace, 2012).

  Experimental evidence from laboratory studies has shown that prolonged exposure to the sitting posture blights endothelial function in the leg vasculature, as indicated by impaired endothelial-dependent vasodilation (EDV) in the popliteal and femoral arteries following uninterrupted sitting bouts of 1-6 hours (Morishima et al., 2016; Morishima, Restaino, Walsh, Kanaley, & Padilla, 2017; Padilla & Fadel, 2017; Thosar, Bielko, Mather, Johnston, & Wallace, 2015). This sitting induced, leg-specific endothelial dysfunction, however, has shown to be restored with light muscular activity (e.g., light-intensity walking, leg fidgeting, etc.), questioning

the long-term effects of prolonged sitting on the vasculature outside the context of an acute laboratory setting (Morishima et al., 2016; Thosar et al., 2015). Moreover, the laboratory based models employed in existing studies are limited because 1) acute periods of sitting in the lab over a single day (or in most cases a few hours) is not indicative of chronic exposure to sitting (e.g., 24 hours, 7 days/week), and 2) the control condition (non-movement of the legs and feet in the sitting position for hours at a time) does not have real world generalizability since few adults engage in such prolonged, uninterrupted sedentary periods during a typical day (e.g., workday). Thus, it is unclear if chronic exposure to such conditions with prolonged sitting contributes to endothelial dysfunction. Observational studies, therefore, are needed to determine whether free-living, habitual patterns of sedentary behavior (indicative of more chronic exposure) are linked to impairments in the function of the vasculature.

Studies conventionally define endothelial dysfunction solely as an impairment in EDV. This narrow focus provides insight concerning only one aspect of endothelial function. Lab-based investigations have elucidated the upstream processes underlying endothelial dysfunction, which include endothelial cell injury and diminished endothelial cell reparative capacity. A comprehensive evaluation of endothelial function not only includes the assessment of EDV, but also cellular measures such as circulating endothelial microparticles (EMPs) and circulating endothelial progenitor cells (EPCs) (Deanfield, Halcox, & Rabelink, 2007). Therefore, the purpose of the current study was to comprehensively examine whether habitual accelerometer-measured sedentary time is associated with markers of endothelial function, including EDV, circulating levels of EMPs (a measure of endothelial cell injury), and circulating levels of EPCs (a measure of endothelial cell reparative capacity), in a cohort of healthy adults. It was hypothesized that

participants with greater sedentary time would exhibit poorer endothelial cell health (i.e., lower EDV, higher circulating EMPs, lower circulating EPCs).

Methods

Participants: Healthy adult participants were enrolled into the **P**utative Mechanisms **U**nderlying **M**yocardial Infarction Onset and **E**motions (PUME) study, a laboratory-based, single-blind, randomized controlled experimental study conducted from September 2013 to December 2018 (N=280). As described elsewhere, PUME was designed to examine the impact of induced negative emotions (i.e., anger, anxiety and sadness) on endothelial function (Ensari et al., 2018). Inclusion criteria included adults ≥18 years of age with English proficiency. Exclusion criteria included individuals with any: (a) chronic medical condition including prevalent CVD and traditional CVD risk factors including history of hypertension, diabetes, dyslipidemia; (b) active smoking; (c) medication use including over-the-counter drugs and herbal medications; or (d) self-reported history of psychosis, mood disorders, or personality disorder diagnoses.

Instrumented measures of sedentary behavior were collected in a subsample of PUME participants over the period from October 2014 to December 2018. All active PUME participants were invited to complete a 7-day accelerometer protocol: 160 were eligible and consented to participate, 66 declined or were unable to be scheduled, and 94 participated. Excluding those with missing data and non-adherent wear time (n=11), useable data were available from 83 participants. Thus, the analysis was restricted to participants who were adherent to an accelerometry protocol requiring at least 3 days with 10 or more hours of wear over a consecutive 7-day period. Characteristics of PUME participants included and those excluded in the present analyses are presented in Supplemental Table 1.

Procedures: Participants came into the Center for Behavioral Cardiovascular Health's research laboratory on two occasions. The first visit entailed collection/measurement of endothelial markers, for which the participants were instructed to arrive at 08:30 am following a fast from the previous midnight, and to refrain from any strenuous exercise in the 12 hours prior to their visit. To maintain adequate hydration levels, participants were asked to drink 64 ounces of water in the 24 hours prior to their visit. Upon arrival, they were escorted to a temperature-controlled room and seated in a comfortable chair for the entire visit, which lasted approximately 3.5 hours. A 20-gauge intravenous catheter was inserted into an antecubital vein of the dominant arm. Afterwards, the participant was instrumented with the EndoPAT2000 device and instructed to relax for 30 min. Following this rest, EDV assessment was completed (described below). Blood was then drawn into serum tubes, EDTA tubes and citrate tubes. The first tube of the withdrawn blood was discarded (i.e., 'discard tube') to avoid spurious hemolysis in subsequent sample tubes and improve sample quality (Heiligers-Duckers, Peters, van Dijck, Hoeijmakers, & Janssen, 2013; Munnix, Schellart, Gorissen, & Kleinveld, 2011). One citrated tube was used to measure circulating EMPs. One EDTA tube was used to measure EPCs.

Accelerometer Protocol: A second visit was scheduled 7–14 days after the initial laboratory visit. At the second visit, participants were fitted with the activPAL™ (V.3, PAL Technologies, Glasgow, UK), a thigh-worn triaxial accelerometer and inclinometer that has been validated for determining step counts, physical activity, activity intensities, posture (sitting/lying, standing or stepping), and sedentary time in healthy adults (Godfrey, Culhane, & Lyons, 2007; Grant, Ryan, Tigbe, & Granat, 2006; Hart, McClain, & Tudor-Locke, 2011; Kozey-Keadle, Libertine, Lyden, Staudenmayer, & Freedson, 2011; Lyden, Keadle, Staudenmayer, & Freedson, 2017; Lyden, Kozey Keadle, Staudenmayer, & Freedson, 2012; Ryan, Grant, Tigbe, & Granat, 2006). The

activPAL™ was waterproofed via a nitrile sleeve and worn by participants on the midline of their right thigh, held in place with a hypoallergenic adhesive dressing (Hypafix® or Tegaderm™). Participants were instructed to wear the device continuously for 7 days and to not remove the monitor unless it was to be fully submerged in water (e.g., swimming, bath). Participants were also asked to complete a sleep and wear-time log sheet to record daily sleep ('lights out') and wake times, and times when the device was removed (if any).

Accelerometer Processing: Time-stamped 15-second epoch data files were exported using the activPAL™ software for subsequent processing and analysis in SAS 9.4. Non-wear and sleep time recorded in the logs were excluded from analyses. For each participant, minutes of sedentary time, light-intensity physical activity (LIPA, defined as 1.5-2.99 metabolic equivalents [METs] which are derived from stepping cadence), and MVPA (defined as ≥3 METs which are derived from stepping cadence) were summed for each day and averaged across the number of valid days (≥10 h of wear) to derive 'per day' values (Lyden et al., 2017). Sedentary and MVPA bouts were also quantified. A sedentary bout was defined as consecutive epochs in which the activPAL™ registered no standing or stepping events of any length. An MVPA bout was defined as any stepping period of ≥10 minutes for which each consecutive epoch had a stepping cadence assigned an activity intensity of ≥3 METs. We corrected for the influence of variation in wear time by standardizing sedentary time using the residuals obtained when regressing sedentary time on wear time (Healy, Matthews, Dunstan, Winkler, & Owen, 2011; Qi et al., 2015; Willett & Stampfer, 1986). As a result, sedentary time is expressed as the mean predicted sedentary time given a wear time of 16 h/day.

Endothelium-dependent Vasodilation: Endothelial-dependent vasodilation was determined using the reactive hyperemia index (RHI), which is measured as the transient increase in blood

flow following a brief period of arterial occlusion. RHI moderately correlates with endothelial vasodilator function in the coronary arteries (Piero O. Bonetti et al., 2004), and with brachial flow-mediated dilation (Kuvin et al., 2003). RHI was assessed using EndoPAT™2000, a validated peripheral arterial tonometry (PAT) device (Barac, Campia, & Panza, 2007; Piero O. Bonetti et al., 2004; Goor et al., 2004; Hansen, Butt, Holm-Yildiz, Karlsson, & Kruuse, 2017). A finger probe for the EndoPAT™2000 device was placed on the first digit of each hand. A blood pressure (BP) cuff was placed on the non-dominant forearm for inducing reactive hyperemia. After instrumentation, the participant relaxed for 30 min. Following this rest, EDV assessment was completed.

To induce reactive hyperemia, the BP cuff was inflated to 200 mmHg or 60 mmHg plus systolic BP (i.e., whichever occlusion pressure was higher); the pressure was maintained for 5 min, and then the cuff was deflated (P. O. Bonetti et al., 2003; Piero O. Bonetti et al., 2004; Goor et al., 2004). RHI was calculated as the ratio of the average amplitude of the PAT signal through the range of a 90–120 s period post deflation, divided by the average amplitude of the PAT signal of a 2 min period before cuff inflation (i.e., resting period) (Hamburg et al., 2008). RHI values were then normalized to the concurrent signal from the contralateral, control arm (P. O. Bonetti et al., 2003; Piero O. Bonetti et al., 2004; Kuvin et al., 2003) to control for fluctuations in sympathetic nerve outflow that may induce changes in peripheral arterial tone, superimposed on the hyperemic response (Axtell, Gomari, & Cooke, 2010).

Endothelial-cell Derived Microparticles: Endothelial-cell (EC) injury was assessed by measuring circulating EMPs (Boulanger, Amabile, & Tedgui, 2006). Previous studies indicate that peripheral EMPs expressing CD62E+ are phenotypic for EC activation, and EMPs expressing

CD31+ are indicative of EC apoptosis (Bernal-Mizrachi et al., 2003; Garcia et al., 2005; Joaquin J Jimenez et al., 2003).

EMPs were measured using flow cytometry as previously described (Bernal-Mizrachi et al., 2003; Garcia et al., 2005; Joaquin J Jimenez et al., 2003). Citrated blood was centrifuged at $160 \times g$ for 10 min to prepare platelet-rich plasma (PRP), and the PRP was further centrifuged for 6 min at $1500 \times g$ to obtain platelet-poor plasma (PPP). Fifty microliters of PPP were incubated with two sets: (a) 4 µL of phycoerythrin (PE)-conjugated monoclonal antibody to CD31 (BD) and 4 µL of fluorescein isothiocyanate (FITC)-conjugated monoclonal antibody to CD42b (BD); and (b) 5 µL of PE-conjugated monoclonal antibody to CD62E (BD). EMPs were defined as the number of particles with a size <1.5 µm and that were positively labelled by CD62E+ (EMPs expressing CD62E), and positively labelled by CD31 and negatively labelled by CD42 (CD31+/CD42 EMPs). Appropriate FITC-labelled and PE-labelled isotype-matched IgG were used as negative controls. Using standard beads (Bang Laboratories), total flow cytometry counts for each experiment were converted to the number of EMPs per microliter.

Endothelial Progenitor Cells: The EC reparative capacity was assessed by measuring circulating EPCs, which are bone-marrow-derived hematopoietic progenitor cells that differentiate into mature ECs and contribute to EC repair after ischemic injury. A reduced number of EPCs expressing CD34+/CD133+/KDR+ and CD34+/KDR+ have been associated with increased risk of subclinical atherosclerosis, ischemic stroke, and future vascular events (Fadini et al., 2006; Jevon, Dorling, & Hornick, 2008; Martí-Fàbregas et al., 2015; Schmidt-Lucke et al., 2005; Carmen Urbich & Stefanie Dimmeler, 2004; Werner et al., 2005). Blood samples were prepared and processed using flow cytometry (BD FACS Calibur) and analyzed using previously published protocols (Jelic et al., 2008; Peichev et al., 2000; Shimbo et al., 2013; Carmen Urbich & Stefanie

Dimmeler, 2004; Werner et al., 2005). Mononuclear cells in EDTA-anticoagulated blood were isolated by density-gradient centrifugation with Ficoll (Sigma) and counted using a Coulter Counter (Abx Pentra 60, Horiba). One million mononuclear cells were first aliquoted and incubated with 15 µL mouse serum (Sigma) to block non-specific binding of antibodies, followed by an incubation with monoclonal antibodies against human KDR (PE-labelled) (10 µL; R&D Systems), CD34 (FITC-labelled) (20 µL; BD) and CD133 (APC-labelled) (20 µL; Miltenyi Biotec). Isotype-identical antibodies IgG1-PE (BD), IgG-FITC (BD) and IgG2b-APC (eBioscience) served as negative controls. Data were gated on the mononuclear lymphocytic population, and 500,000 events were collected in the gated region for each sample. Data for the two EPCs measures were expressed as the proportion of the mononuclear lymphocytic populations that consist of CD34+/CD133+/KDR+ cells, the primary EPC outcome and CD34+/KDR+ cells, a secondary EPC outcome.

Statistical Analyses: Participants were classified into high and low total sedentary time groups by a median split of 589 min/day of sedentary time. Descriptive statistics, including means ± standard deviation and frequencies, were computed to characterize the high and low sedentary groups. For each endothelial cell variable, outliers were winsorized and thereafter transformed when appropriate. EMP data were multiplied by a correction factor of 0.91141 and natural log transformed. EPC data were divided by a correction factor of 20,000 to convert raw data into a proportion of anti-body per 20,000 cells and square root transformed because zero was a possible value. EMP and EPC data were transformed back to its original scale for ease of interpretation.

Multivariable linear regression models were used to compare the levels of each endothelial cell variable (RHI, EMPs and EPCs) between high and low sedentary groups. Prior to evaluating the association between sedentary time and each endothelial cell variable, we considered three

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different possibilities for education to be included in adjusted models. We then conducted a forward selection regression analysis and found that education represented as a binary variable that dichotomized participants by education less than a college degree or at least a college degree added the most predictive value above age, sex, ethnicity and race. Unadjusted models were first conducted. Subsequent models adjusted for age, sex, race, ethnicity and education (Model 1), and further adjusted for MVPA (Model 2) and body mass index (BMI) (Model 3). As a sensitivity analysis, all analyses were repeated with total sedentary behavior expressed as a continuous variable in hours/day.

As some evidence suggests that prolonged, uninterrupted sedentary bouts (e.g. sitting for hours at a time) may potentially be the most hazardous form of sedentary behavior (Diaz, Goldsmith, et al., 2017; Diaz, Howard, et al., 2017; Healy et al., 2008; Healy et al., 2011), the above analyses were repeated examining mean sedentary bout duration (a measure of overall prolonged, uninterrupted sedentary behavior that has been linked to mortality) as the exposure variable. Participants were classified into high and low sedentary bout groups by a median split 17.2 min/bout of mean sedentary bout duration, respectively. All analyses were conducted using SAS, version 9.4 (SAS Institute).

A priori power analyses were conducted using Power Analysis and Sample Size Analysis Software Version:15.0.1. The sample provided 80% power to detect the least meaningful detectable difference of 0.5, 492.1, 209.2, 83.9, and 2.5 between groups for RHI, CD62+ EMPs, CD631+/CD42- EMPs, CD34+/KDR+ EPCs, and CD34+/CD133+/KDR+ EPCs, respectively.

Results

Participants: The mean (± SD) of age and BMI of the overall sample (n=83) was 25.5±5.8 yr and 24.1±4.0 kg/m^2, respectively. Participants were predominantly female (56.6%), 25.3% were Hispanic, and the majority had at least a college degree (75.9%). Sedentary behavior accounted

for 61.7 ± 10.2 % of wear time, equivalent to 9.9 ± 1.7 hours/day over a 16-hour waking day. The mean (±SD) mean sedentary bout duration was 18.7 ± 7.4 min/bout. LIPA and MVPA accounted for 31.6 ± 9.3 % and 6.7 ± 2.9 % of wear time, respectively, equivalent to 306.6 ± 95.8 min/day, and 64.5 ± 28.0 min/day. Table 1 presents the characteristics of the 83 participants classified into the high and low sedentary groups according to total sedentary time. Participants in the high sedentary group were significantly younger in age, more likely to be male, and engaged in lower levels of MVPA.

Sedentary Behavior and Endothelial Cell Health: Differences in the markers of endothelial cell health between the high and low total sedentary time groups are shown in Table 2. In unadjusted and adjusted models, there were no significant differences between high and low total sedentary time groups in endothelial-dependent vasodilation as indicated by the RHI. There was also no significant difference in circulating levels of EMPs (CD62E+ and CD31+/CD42-) or EPCs (CD34+/KDR+ and CD34+/CD133+/KDR+) in both unadjusted and adjusted models. In an unadjusted model and after adjustment for age, sex, race, ethnicity, and education, circulating levels of CD62E+ EMPs trended towards being significantly lower among those in the high sedentary group; however, this difference was no longer close to statistical significance after additional adjustment for MVPA (Model 2) and BMI (Model 3). Similarly, when high and low sedentary groups were defined according to accumulation of sedentary time in prolonged, uninterrupted sedentary bouts (e.g. mean sedentary bout duration), there were no significant differences between the high and low groups for any of the endothelial measures (Table 3). In sensitivity analyses expressing total sedentary time and prolonged, uninterrupted sedentary bouts as continuous variables, there was no significant associations observed for any of the endothelial cell variables (Supplemental Table 2 & 3).

Discussion

In this cross-sectional study of young, healthy adults, we evaluated a comprehensive set of biomarkers that represent several aspects of endothelial cell health to examine the relationship between free-living, habitual sedentary time and endothelial dysfunction. It was hypothesized that participants with greater sedentary time would exhibit poorer endothelial cell health (i.e., lower EDV, higher circulating EMPs, lower circulating EPCs). Contrary to this hypothesis, it was found that there were no differences in measures of EC injury, EC reparative capacity, or upper extremity EDV in participants with high compared with low volumes of accelerometer-measured sedentary time among a sample of young, healthy adults. These findings provide preliminary evidence that habitual sedentary behavior does not incur CVD risk, in part, through endothelial dysfunction.

EDV of the peripheral upper extremities has been shown to be highly correlated with EDV of the coronary arteries, and it has demonstrated prognostic utility beyond traditional CVD risk factors (Matsuzawa, Kwon, Lennon, Lerman, & Lerman, 2015; Poredos & Jezovnik, 2013; Takase et al., 1998). Previous experimental findings from Thosar et al. (2014) and Padilla et al. (2009) collectively demonstrated that an acute bout of prolonged sitting causes impairment in brachial artery shear rate patterns (e.g. decrease in antegrade shear rate, increase in oscillatory shear index) in young, healthy adults; however, paradoxically brachial artery FMD was preserved. The preservation of brachial artery FMD, despite alterations in brachial artery hemodynamics, was postulated to be due to the acute exposure and relatively short duration of sitting (i.e., 3 hours), necessitating a need to elucidate the relationship of upper extremity endothelial function with chronic exposure to sedentary behavior. Utilizing a 7-day accelerometer protocol to ascertain habitual levels of sedentary behavior levels (which we infer to be reflective of chronic exposure to sedentary time), no differences were observed in RHI among those with higher and lower levels of free-living, habitual sedentary behavior, suggesting that sedentary behavior does not attenuate

EDV of the upper extremities. This may be because the arteries of the upper extremities are more resilient to reductions in shear compared to arteries of the lower extremities, as atherosclerotic lesions are distributed nonuniformly throughout the vasculature and develop primarily in the lower extremities (Padilla & Fadel, 2017). However, the lack of differences in the systemic measures of endothelial cell injury and repair among those with higher and lower levels of sedentary behavior support these EDV results, suggesting that endothelial dysfunction does not manifest as a result of chronic exposure to sedentary behavior.

Jenkins and colleagues (2013) were the first to provide *in vivo* experimental evidence that disturbed blood flow in the distal forearm acutely induces endothelial activation and apoptosis in humans, as reflected by release of microparticles from activated ($CD62E^+$) and apoptotic ($CD31^+/CD42b^-$) endothelial cells. As the sitting posture promotes blood pooling in the legs, decreased thigh and calf blood flow, and augmented turbulent blood flow in the deformed arterial segments (Delp & Laughlin, 1998; Padilla, Johnson, et al., 2009; Padilla, Sheldon, et al., 2009; Restaino et al., 2015), it is hypothesized that sustained reductions of shear stress as a result of chronic exposure to high volumes of sitting would result in elevated circulating EMPs. In support of this hypothesis, Navasiolava et al. (2010) and Boyle et al. (2013) used experimental models of physical inactivity (dry water immersion for 7 days; <5,000 steps for 5 days) and found that circulating EMPs indicative of endothelial apoptosis (i.e., $CD31^+/CD42b^-$ EMPs) were significantly elevated following induction of inactivity. However, no changes were observed in circulating EMPs indicative of endothelial activation (i.e., $CD62E^+$) in either study (Boyle et al., 2013; Navasiolava et al., 2010). Because this marker is only expressed and released from endothelial cells when they are in an inflamed state, it was hypothesized that the lack of increase in $CD62E^+$ EMPs was due to the relatively short nature of the study design (5-7 days) wherein

substantive inflammation was not incurred to facilitate EMP release (Boyle et al., 2013; J. J. Jimenez et al., 2003; Krogh-Madsen et al., 2010). The finding that circulating CD62E$^+$ EMPs levels were similar among young, healthy adults with high and low amounts of habitual sedentary behavior in the current study, however, does not support this hypothesis, suggesting that the inflammatory milieu necessary for the CD62E$^+$ EMP phenotype to be expressed may not have been present in the current study's population of young, healthy adults whom exhibit higher levels of habitual sedentary behavior. Furthermore, no differences were observed in circulating CD31+/CD42b- EMPs between participants with higher and lower levels of habitual sedentary behavior, which is also contrary to previous experimental findings from Navasiolava et al. and Boyle et al. Reasons for the discrepant findings are unclear but could be attributed to differences in study design (cross-sectional vs. acute induction of inactivity wherein it is difficult to ascertain whether the observed effects are the result of increases in sedentary behavior or reductions in MVPA), inclusion of women (only men were studied in the previous experimental studies), and differences in the processing and analyzing of EMPs (which widely vary from investigator to investigator).

Bone marrow-derived EPCs are circulating precursors of EC that have the ability to promote endothelial repair, regeneration, and neovascularization (Adams et al., 2004; Mobius-Winkler, Hollriegel, Schuler, & Adams, 2009; Umemura & Higashi, 2008; C. Urbich & S. Dimmeler, 2004). Physical exercise can promote EPC mobilization from the bone marrow into circulation, while detraining and experimental induction of physical inactivity for 10 days have been shown to reduce circulating EPCs, suggestive that regular physical activity is necessary to maintain EPC levels (Guhanarayan, Jablonski, & Witkowski, 2014). As such, chronic exposure to a sedentary life style may be associated with lower percentage of EPCs among adults (M. D. Ross,

Malone, & Florida-James, 2016; S. Witkowski et al., 2010). Contrary to this hypothesis, the current study observed no differences in circulating EPC levels between high and low sedentary individuals. Similarly, D'ascenzi and colleagues (2016) found that no differences in resting levels of circulating EPCs were detected between elite athletes and age- and sex-matched sedentary healthy subjects. Studies evaluating the effect of physical activity interventions on circulating EPCs have yielded inconsistent results wherein physical activity interventions have been reported to yield improvements in circulating EPCs among patients with coronary artery disease, coronary artery disease risk factors, or heart failure, while no improvements were observed among healthy young and older men (Sarah Witkowski et al., 2010). As such, it is plausible that basal levels of circulating EPCs are static in disease-free populations, which may be a contributing factor to the lack of differences in circulating EPCs observed in the present study. Future studies in older populations and those with chronic diseases may be warranted.

There are several strengths to our study. First, the current study utilized both EDV and molecular measures of endothelial function. Measuring EMPs and EPCs, in addition to EDV, enabled us to complete a comprehensive evaluation of EC health at the systemic level, which is essential to unveil the complex processes that underlie endothelial dysfunction (e.g., EC injury, repair and regeneration). Second, the activPAL™ was used for measuring habitual sedentary behavior. This device is widely considered the gold-standard measure of sedentary behavior because it is extremely accurate (≥96%) and is one of the only devices capable of distinguishing motionless standing from sedentary time, thus allowing us to adhere to the consensus sedentary behavior definition, which includes both intensity of activity (≤1.5 METS) and position (sitting or reclining) (Gibbs, Hergenroeder, Katzmarzyk, Lee, & Jakicic, 2015). Third, young healthy adults are an ideal population to study the effects of sitting on endothelial function as this population is

generally free of overt chronic disease which could confound associations (e.g. those with multi-morbidities have poor physical function and are thus more sedentary) (Deanfield et al., 2007). Finally, our study utilized a 7-day accelerometer protocol to assess habitual, as opposed to acute or extreme, sedentary behavior. Evidence shows that 3 to 5 days of monitoring yields reliable estimates of one's usual or habitual activity/inactivity (Trost, McIver, & Pate, 2005). Previous experimental physical inactivity models examining the influence of sedentary behavior on endothelial function included bed rest, dry water immersion, and acute, uninterrupted sitting (Thosar et al., 2012), which fails to reflect chronic conditions and has limited real world generalizability since few adults engage in such prolonged, uninterrupted sedentary periods and/or bed rest during a typical day (e.g., workday).

Several limitations must be acknowledged when interpreting our study findings. First, this was a cross-sectional study, which limits our ability to evaluate the effect of sedentary time on endothelial function, as causation cannot be implied. Second, EDV of the upper extremity microvasculature was measured. Laboratory evidence suggests the pathophysiological consequences of prolonged sitting are primarily manifested in the vasculature of the lower extremities. Thus, studies evaluating the association of habitual sedentary behavior with lower extremity EDV are still needed (Padilla & Fadel, 2017). Finally, this is a relatively small, single-center study in an urban academic medical center, which may limit the generalizability of our findings and statistical power to detect significant differences between high and low sedentary groups. Thus, caution is warranted when interpreting our study findings given the possibility of a type II error. Nonetheless, our study was powered to detect relatively small differences in the endothelial measures (i.e., 80% power to detect a 0.5 difference in RHI). Further, some of the observed non-significant differences were in the opposite direction of our hypotheses (e.g.

circulating EMPs were non-significantly lower in the high sedentary group compared to the low sedentary group); thus, even with greater statistical power we would still have not yielded evidence to support endothelial dysfunction as a link between sedentary behavior and CVD risk.

Conclusion

In conclusion, this study demonstrated that there were no differences in a comprehensive battery of endothelial function measures, including measures of EDV, EC injury, ad EC reparative capacity, when comparing young, healthy adults that accumulated higher and lower levels of habitual sedentary behavior (both the total volume and accumulation in prolonged, uninterrupted bouts). These findings suggest that physiological mechanisms other than endothelial dysfunction (e.g., glucose and lipid metabolism) may need to be explored as a potential link between habitual prolonged sedentary time and CVD. However, future research is needed to explore the link between habitual sedentary behavior and lower extremity endothelial function.

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Table 1. Characteristics of participants in the high and low total sedentary time groups (n=83).

	Sedentary Behavior Group		
Variables	**Low** *(n=41)*	**High** *(n=42)*	**P-Value**
Participant Characteristics			
Age (yr)	26.7 (7.3)	24.4 (3.4)	0.08
Men (%)	31.7	54.7	0.03
Black Race (%)	7.3	2.4	0.29
Hispanic Ethnicity (%)	29.3	21.4	0.40
Education			0.16
$\leq$ High School Graduate (%)	9.8	2.4	
Some College (%)	17.1	19.1	
College Graduate (%)	29.3	50.0	
Graduate/Professional School (%)	43.9	28.6	
Body Mass Index (kg/m^2)	24.7 (4.1)	23.5 (3.8)	0.16
Accelerometer Characteristics			
Total Sedentary Time (mins/day)	515.5 (68.6)	668.4 (57.2)	<0.001
Mean Sedentary Bout Duration (mins/bout)	15.1 (3.7)	22.3 (8.3)	<0.001
Standing Time (mins/day)	312.8 (78.5)	206.1 (55.6)	<0.001
LIPA (mins/day)	370.1 (82.7)	244.6 (60.8)	<0.001
MVPA (mins/day)	75.7 (27.3)	53.5 (24.3)	<0.001
MVPA Bouts (mins/day)	13.8 (12.4)	8.4 (9.8)	0.03
Wear Time (mins/day)	961.8 (63.0)	971.9 (56.0)	0.44
Valid Wear Days			0.15
3-5 days (%)	5.0	0.0	
6-7 days (%)	95.0	100.00	

Data are presented as mean (standard deviation) or frequency

LIPA= light intensity physical activity; MVPA= moderate-vigorous physical activity.

MVPA Bouts= total minutes of MVPA accrued in bouts $\geq$10 min; defined as any period of $\geq$10 minutes for which each consecutive 15-sec epoch had an activity intensity was $\geq$3 METs.

Median split cut-point for high and low total sedentary time groups was 589 min/day

Table 2. Reactive hyperemia index, endothelial microparticles, and endothelial progenitor cells by median split of accelerometer-measured sedentary time (n=83).

	Sedentary Behavior Group		
Endothelial Cell Variable	**Low** *(n=41)*	**High** *(n=42)*	**P-value**
Reactive Hyperemia Index			
Unadjusted	2.53 (2.24 – 2.83)	2.32 (2.08 – 2.55)	0.25
Model 1	2.48 (2.22 – 2.75)	2.36 (2.10 – 2.62)	0.53
Model 2	2.46 (2.18 – 2.75)	2.38 (2.10 – 2.66)	0.72
Model 3	2.51 (2.21 – 2.81)	2.36 (2.07 – 2.64)	0.50
Endothelial Microparticles			
CD62E+ (counts/μl)			
Unadjusted	830.71 (720.94 – 957.20)	696.14 (617.90 – 784.28)	0.06
Model 1	832.05 (732.10 – 945.65)	695.04 (612.54 – 788.65)	0.06
Model 2	816.86 (711.81 – 937.41)	707.66 (617.86 – 810.51)	0.19
Model 3	810.62 (701.81 – 936.30)	703.26 (613.98 – 805.54)	0.20
CD31+/CD42- (counts/μl)			
Unadjusted	508.08 (428.53 – 602.40)	510.64 (450.01 – 579.43)	0.96
Model 1	513.93 (444.21 – 594.61)	504.96 (437.26 – 583.14)	0.87
Model 2	533.07 (456.21 – 622.88)	487.25 (417.92 – 568.09)	0.46
Model 3	523.93 (446.30 – 615.05)	482.26 (414.65 – 560.89)	0.50
Endothelial Progenitor Cells			
CD34+/KDR+ (%)			
Unadjusted	81.21 (53.55 – 114.61)	99.12 (71.38 – 131.40)	0.40
Model 1	86.69 (59.93 - 118.39)	93.39 (65.84 –125.75)	0.76
Model 2	76.74 (50.43 – 108.56)	104.07 (73.38 – 140.10)	0.27
Model 3	72.61 (45.81 – 105.55)	107.97 (76.39 – 145.01)	0.17
CD34+/CD133+/KDR+ (%)			
Unadjusted	1.89 (1.00 – 3.05)	2.31 (1.53 – 3.24)	0.53
Model 1	1.86 (1.06 – 2.88)	2.33 (1.42 – 3.45)	0.51
Model 2	1.86 (1.01 – 2.98)	2.33 (1.37 – 2.98)	0.57
Model 3	1.71 (0.86 – 2.83)	2.42 (1.44 – 3.65)	0.39

Data are presented as mean (95% confidence interval) for unadjusted analyses or estimated marginal mean (95% confidence interval) for adjusted analyses. Data were back transformed.
Model 1: Adjusted for age, sex, race, ethnicity and education
Model 2: Adjusted for covariates in model 1 plus moderate-vigorous physical activity.
Model 3: Adjusted for covariates in model 2 plus body mass index
Median split cut-point was 589 min/day for total sedentary time

Table 3. Reactive hyperemia index, endothelial microparticles, and endothelial progenitor cells by median split of mean sedentary bout duration (n=83).

Endothelial Cell Variable	Sedentary Bout Group		
	Low *(n=41)*	**High** *(n=42)*	**P-value**
Reactive Hyperemia Index			
Unadjusted	2.45 (2.16 – 2.74)	2.40 (2.15 – 2.65)	0.81
Model 1	2.37 (2.11 – 2.63)	2.48 (2.22 – 2.73)	0.58
Model 2	2.36 (2.09 – 2.62)	2.49 (2.23 – 2.75)	0.49
Model 3	2.39 (2.12 – 2.67)	2.46 (2.20 – 2.73)	0.74
Endothelial Microparticles			
CD62E+ (counts/μl)			
Unadjusted	812.40 (699.52 – 943.49)	711.45 (635.62 – 796.33)	0.15
Model 1	815.23 (717.49 – 926.28)	709.04 (625.03 – 804.35)	0.14
Model 2	806.23 (709.13 – 916.63)	716.76 (631.46 – 813.59)	0.22
Model 3	800.83 (702.11 – 913.43)	708.98 (623.74 – 805.88)	0.21
CD31+/CD42- (counts/μl)			
Unadjusted	515.82 (442.45 – 601.36)	503.15 (435.08 – 581.87)	0.81
Model 1	520.64 (450.77 - 601.34)	498.61 (432.47 – 574.85)	0.68
Model 2	526.54 (455.42 – 608.76)	493.15 (427.34 – 569.11)	0.54
Model 3	509.92 (440.36 – 590.48)	493.85 (428.13 – 569.66)	0.77
Endothelial Progenitor Cells			
CD34+/KDR+ (%)			
Unadjusted	80.53 (54.58 – 111.50)	99.86 (70.23 – 134.71)	0.37
Model 1	87.36 (60.74 – 118.81)	92.71 (65.53 – 124.60)	0.80
Model 2	84.41 (58.27 – 115.38)	95.74 (68.07 – 128.11)	0.60
Model 3	83.46 (56.53 – 115.60)	97.06 (68.52 – 130.56)	0.55
CD34+/CD133+/KDR+ (%)			
Unadjusted	2.19 (1.25 – 3.38)	2.00 (1.25 – 2.94)	0.78
Model 1	2.20 (1.33 – 3.30)	1.99 (1.17 – 3.02)	0.71
Model 2	2.23 (1.34 – 3.35)	1.96 (1.14 – 3.01)	0.68
Model 3	2.32 (1.39 – 3.49)	1.83 (1.04 – 2.85)	0.51

Data are presented as mean (95% confidence interval) for unadjusted analyses or estimated marginal mean (95% confidence interval) for adjusted analyses. Data presented were back transformed.
Model 1: Adjusted for age, sex, race, ethnicity and education
Model 2: Adjusted for covariates in model 1 plus moderate-vigorous physical activity.
Model 3: Adjusted for covariates in model 2 plus body mass index
Median split cut-point was 17.2 min/bout for mean sedentary bout duration.

Supplemental Material

Supplemental Table 1. Characteristics of PUME study participants who were included or excluded from the present analyses.

Variables	Included (n=83)	Excluded (n=197)	P-Value
Participant Characteristics			
Age (yrs)	25.5 (24.3 – 26.8)	26.5 (25.4 – 27.6)	0.29
Men (%)	43.4	50.25	0.29
Black Race (%)	4.82	17.26	<0.01
Hispanic Ethnicity (%)	25.3	29.95	0.19
Education			0.46
≤ High School Graduate (%)	6.0	8.1	0.01
Some College (%)	18.1	23.4	
College Graduate (%)	39.8	49.8	
Graduate/Professional School (%)	36.1	18.3	
Body Mass Index (kg/m^2)	24.1 (23.2 – 25.0)	24.9 (24.3 – 25.5)	0.15
Endothelial Cell Variables			
Reactive Hyperemia Index	2.42 (2.23 – 2.61)	2.31 (2.20 – 2.42)	0.29
Endothelial Microparticles			
CD62E+ (counts/μl)	759.64 (692.53 – 833.26)	808.21 (755.43 – 864.68)	0.31
CD31+/CD42- (counts/μl)	509.37 (459.34 – 564.86)	515.54 (481.83 – 551.59)	0.85
Endothelial Progenitor Cells			
CD34+/KDR+ (%)	90.05 (70.17 – 112.41)	94.92 (83.57 – 107.00)	0.67
CD34+/CD133+/KDR+ (%)	2.09 (1.48 – 2.81)	4.12 (3.36 – 4.95)	<0.01

Data are presented as mean (95% confidence interval) or frequency

Supplemental Table 2. Association of total sedentary time (expressed continuously) with endothelial measures (n=83).

Endothelial Cell Variable	β	95% CI	P-value
Reactive Hyperemia Index			
Unadjusted	-0.019	(-0.133 - 0.094)	0.736
Model 1	0.043	(-0.083 – 0.168)	0.502
Model 2	0.091	(-0.058 - 0.239)	0.227
Model 3	0.062	(-0.090 – 0.215)	0.417
Endothelial Microparticles			
CD62E+ (counts/μl)			
Unadjusted	-0.035	(-0.091 – 0.021)	0.220
Model 1	-0.048	(-0.110 – 0.013)	0.121
Model 2	-0.033	(-0.105 – 0.040)	0.375
Model 3	-0.033	(-0.107 – 0.042)	0.386
CD31+/CD42- (counts/μl)			
Unadjusted	0.009	(-0.054 - 0.072)	0.774
Model 1	0.012	(-0.057 - 0.082)	0.725
Model 2	-0.010	(-0.092 - 0.072)	0.805
Model 3	-0.002	(-0.085 - 0.081)	0.965
Endothelial Progenitor Cells			
CD34+/KDR+ (%)			
Unadjusted	0.030×10^{-3}	$(-4.786 – 4.846) \times 10^{-3}$	0.990
Model 1	-1.600×10^{-3}	$(-6.871 – 3.671) \times 10^{-3}$	0.547
Model 2	0.607×10^{-3}	$(-5.609 – 6.823) \times 10^{-3}$	0.846
Model 3	1.426×10^{-3}	$(-5.030 – 7.881) \times 10^{-3}$	0.661
CD34+/CD133+/KDR+ (%)			
Unadjusted	-0.232×10^{-3}	$(-1.218 – 0.755) \times 10^{-3}$	0.642
Model 1	-0.098×10^{-3}	$(-1.226 – 1.030) \times 10^{-3}$	0.863
Model 2	-0.277×10^{-3}	$(-1.621 - 1.066) \times 10^{-3}$	0.682
Model 3	-0.258×10^{-3}	$(-1.635 – 1.118) \times 10^{-3}$	0.709

Data are presented as unadjusted/adjusted parameter estimate and 95% confidence interval; sedentary time was converted to hours per day for analyses.

Model 1: Adjusted for age, sex, race, ethnicity and education

Model 2: Adjusted for covariates in model 1 plus moderate-vigorous physical activity.

Model 3: Adjusted for covariates in model 2 plus body mass index

Supplemental Table 3. Association of mean sedentary bout duration (expressed continuously) with endothelial measures (n=83).

Endothelial Cell Variable	β	95% CI	P-value
Reactive Hyperemia Index			
Unadjusted	0.346	(-1.186 – 1.877)	0.655
Model 1	0.637	(-0.896 - 2.170)	0.411
Model 2	0.897	(-0.725 - 2.520)	0.274
Model 3	0.677	(-0.970 - 2.323)	0.415
Endothelial Microparticles			
CD62E+ (counts/μl)			
Unadjusted	-0.671	(-1.421 - 0.079)	0.079
Model 1	-0.718	(-1.462 – 0.026)	0.058
Model 2	-0.594	(-1.382 - 0.194)	0.137
Model 3	-0.536	(-1.337 - 0.265)	0.186
CD31+/CD42- (counts/μl)			
Unadjusted	-0.326	(-1.177 - 0.525)	0.448
Model 1	-0.234	(-1.081 – 0.613)	0.584
Model 2	-0.425	(-1.317 - 0.467)	0.346
Model 3	-0.336	(-0.034 - 0.027)	0.455
Endothelial Progenitor Cells			
CD34+/KDR+ (%)			
Unadjusted	-1.647×10^{-2}	$(-8.140 - 4.845) \times 10^{-2}$	0.615
Model 1	-1.848×10^{-2}	$(-8.295 - 4.599) \times 10^{-2}$	0.570
Model 2	-0.376×10^{-2}	$(-7.164 - 6.413) \times 10^{-2}$	0.913
Model 3	-0.050×10^{-2}	$(-7.034 - 6.934) \times 10^{-2}$	0.989
CD34+/CD133+/KDR+ (%)			
Unadjusted	-0.489×10^{-2}	$(-1.818 - 0.841) \times 10^{-2}$	0.467
Model 1	-0.282×10^{-2}	$(-1.660 - 1.096) \times 10^{-2}$	0.685
Model 2	-0.398×10^{-2}	$(-1.864 - 1.067) \times 10^{-2}$	0.590
Model 3	-0.487×10^{-2}	$(-1.971 - 0.998) \times 10^{-2}$	0.516

Data are presented as unadjusted/adjusted parameter estimate and 95% confidence interval;
WBC=white blood cells; sedentary bout duration was converted to hours per bout for analyses.
Model 1: Adjusted for age, sex, race, ethnicity and education
Model 2: Adjusted for covariates in model 1 plus moderate-vigorous physical activity.
Model 3: Adjusted for covariates in model 2 plus body mass index

CHAPTER III

Patterns of Sedentary Behavior in the First Month after Acute Coronary Syndrome

Abstract

Sedentary behavior is a key contributor to cardiovascular disease. Few data exist on the sedentary behavior patterns of acute coronary syndrome (ACS) patients. **Purpose:** To characterize patterns of sedentary time and their correlates in 149 ACS patients over the first month post hospital discharge, a critical period when patients recuperate from their ACS event. **Methods:** Sedentary time was measured by accelerometry for 28-days post hospital discharge. Group-based modeling at the day level was used to characterize sedentary patterns. Logistic regression models were conducted to examine correlates of membership in the most sedentary trajectory group. **Results:** Participants spent a mean of 9.7±2.0 h/day in sedentary behavior during the 28-days post hospital discharge, with significant decreases in sedentary time observed in each consecutive week (p<0.01 for all). Three distinct sedentary patterns were identified: high (20.6% of participants), moderate (47.9%), and low (31.5%). The high and moderate sedentary groups spent a mean of 12.6±0.8 and 10.0±0.7 h/day sedentary, respectively, and had only minimal decreases in their sedentary time (< 3 min/day) over the 28-days. The low sedentary group spent a mean of 7.3±0.8 h/day sedentary, with a rapid decrease in sedentary time (14 min/day) observed during the first week post hospital discharge followed by a relatively smaller decrease (~5 min/day) that persisted until day 21 post-discharge. Non-Hispanic ethnicity, left ventricular ejection fraction <40%, lower perceived physical health, and not having a partner were associated with a higher odds of being in the high sedentary group. **Conclusion:** ACS survivors accrued high volumes of sedentary time during the first month post hospital discharge, with most showing little change over time. Interventions targeting reductions in sedentary time among ACS survivors may be warranted particularly for those with poor physical health and greater disease severity.

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Introduction

In the United States, more than 1.1 million patients are hospitalized annually for an acute coronary syndrome (ACS) (Mozaffarian et al., 2015). Even with improvements in acute care, 21% of ACS survivors will be re-hospitalized and approximately 1 in 5 patients will die within 1 year following hospitalization (Menzin, Wygant, Hauch, Jackel, & Friedman, 2008). Much of the increased morbidity and mortality risk among ACS survivors remains unexplained (Berton, Cordiano, Palmieri, Cavuto, & Pellegrinet, 2014; Fox et al., 2010). Thus, there is a need to identify novel modifiable risk factors for intervention to increase survival and reduce recurrent events among ACS patients.

Sedentary behavior (i.e. watching TV, computer use, etc.) has emerged as a distinct cardiovascular disease (CVD) risk factor that may carry clinical relevance beyond how much one exercises (Biswas et al., 2015; Roger et al., 2011; World Health Organization, 2009). Accumulating evidence from population-based studies indicate that sedentary behavior is associated with CVD morbidity and mortality, and CVD risk factors, such as insulin resistance (Wilmot et al., 2012). Notably, the deleterious effects of sedentary behavior are eliminated only by high levels of moderate-to-vigorous physical activity (MVPA) (~60 to 75 min/d), which exceed physical activity recommendations (Ekelund et al., 2016). Accordingly, the American Heart Association has released a scientific statement on sedentary behavior that endorsed the public health message "sit less, move more" (Young et al., 2016). This raises the question as to whether reducing sedentary behavior may represent another therapeutic target for secondary prevention and rehabilitation of ACS survivors, in addition to existing MVPA recommendations.

Despite strong links between sedentary behavior and cardiovascular health, few data exist on the sedentary behavior patterns of ACS survivors. Furthermore, no studies have examined the change in sedentary behavior over time in ACS survivors during the period immediately following

hospitalization. Characterizing ACS survivors according to their sedentary behavior as they recuperate from their ACS event may reveal unique patterns and subsets of patients in whom sedentary reduction strategies may be most beneficial. Therefore, the primary aim of the current study was to characterize the amount of sedentary behavior in ACS survivors and its trajectory of change over the first month post-discharge, a critical time period when health behaviors may be influenced and when lifestyle interventions ideally begin (e.g. cardiac rehabilitation). Group-based trajectory modeling was utilized to identify and evaluate unique patterns of change in sedentary behavior over the 28-day convalescent period following ACS. A secondary aim was to identify correlates of sedentary behavior patterns in ACS survivors over the first month post-discharge.

Methods

Study Population: ACS patients from a tertiary care academic medical center were enrolled into the Prescription Use, Lifestyle, and Stress Evaluation (PULSE) study, an observational cohort study conducted from February 2009 to September 2012 (N=1087). PULSE was designed to examine behavioral and biological pathways that may confer increased risk for recurrent cardiac events (Whang et al., 2013). A diagnosis of and hospitalization for ACS was the inclusion criterion, where ACS events were defined according to American Heart Association/American College of Cardiology (AHA/ACC) criteria as either acute myocardial infarction (MI, with or without ST-elevation) or unstable angina (Amsterdam et al., 2014). Exclusion criteria included individuals less than 18 years of age, without English or Spanish proficiency, inability to complete the baseline assessment or to comply with the study protocol, and those who were medically unstable.

This paper reports on a sub-study whose purpose was to examine physical activity and sedentary behavior as behavioral pathways that may confer increased risk for recurrent cardiac

events. Accordingly, physical activity and sedentary behavior were accelerometer-measured for up to 45 days post-discharge via accelerometry, conducted among the PULSE study cohort from August 2009 – September 2012 (Green et al., 2013). A total of 149 participants returned the accelerometer with usable data, adhered to accelerometer wear requirements (≥3 days with accelerometer wear > 10 h/day each week over the first 28 days post-discharge [weeks 1-4] (Kocherginsky, Huisingh-Scheetz, Dale, Lauderdale, & Waite, 2017; Trost, McIver, & Pate, 2005), did not receive coronary artery bypass grafting and/or were not re-hospitalized before the 28th day post-discharge, and were available for the current analysis (Supplemental Figure 1). The PULSE protocols were approved by the Columbia University Medical Center Institutional Review Board and written informed consent was obtained from all participants before they were enrolled into the study. Characteristics of ancillary study participants and those who were excluded from the current analyses are shown in Supplemental Table 1.

Accelerometer Protocol: Participants were fitted at or soon after hospital discharge with an Actical™ accelerometer (Philips Respironics, Bend, OR) on their non-dominant wrist, and were asked to wear the device continuously for 45 days post-discharge, and then to return the device via mail at the end of the monitoring period. Participants were instructed to remove the device when bathing and during sleep. The Actical™, an omni-directional accelerometer that can detect acceleration in all planes, has been validated for the measurement of physical activity when worn on the wrist (Diaz et al., 2018; Heil, 2006). Activity counts were collected in 1-minute epochs.

Accelerometer Processing: Non-wear time was determined using the Choi algorithm, defined as at least 90 consecutive minutes of zero counts, with allowance of 1 or 2 minutes of nonzero counts as long as no counts were detected in the 30-minute windows at the start or end of the 90-minute (or longer) period (Choi, Liu, Matthews, & Buchowski, 2011). Epochs with less than 100 counts

per minute (cpm) and ≥1065 cpm were classified as sedentary behavior and MVPA, respectively (Hooker et al., 2011; Kulinski, Kozlitina, Berry, de Lemos, & Khera, 2016). Time spent in sedentary behavior was determined by summing the number of minutes in a day when the activity counts met these criteria. Physical activity recommendations endorse bouts of 10 minutes or more of MVPA as a health enhancing bout of physical activity. Accordingly, we defined a MVPA bout as any period of ≥10 minutes for which each consecutive 10-min window contained ≤2 minutes for which the activity count was below threshold (1065 cpm) (Garber et al., 2011; Troiano et al., 2008). For each compliant day (≥10 hours of wear), the total number of sedentary minutes and the total time spent in MVPA bouts were calculated.

Presently, there are no validated cut-points to classify sedentary behavior using the Actical™ when worn on the wrist. A sedentary cut-point of 100 counts per minute (cpm) was selected for the present study based on findings and methods defined in the Dallas Heart Study, a longitudinal, multiethnic population-based probability sample of Dallas County residents (Kulinski et al., 2016). The Dallas Heart Study assessed sedentary time with a wrist-worn Actical™ accelerometer and classified sedentary time as <100cpm. Findings from the Dallas Heart Study demonstrated that accelerometer-measured sedentary time was associated with subclinical atherosclerosis (Kulinski et al., 2016) and myocardial injury (Harrington et al., 2017). Given that sedentary time classified as <100cpm was associated with meaningful cardiovascular health indices in a large, representative sample, the present study incorporated the same cut-point for its analyses as that utilized in the Dallas Heart Study.

Because of a high correlation between sedentary time and wear time (r=0.78), the current study corrected for the influence of variation in wear time by standardizing sedentary time using the residuals obtained when regressing sedentary time on wear time at the group level (Healy,

Winkler, Brakenridge, Reeves, & Eakin, 2015; Qi et al., 2015; Willett & Stampfer, 1986). As a result, sedentary time is expressed as the predicted sedentary time for that day, had the participant worn the device for 16 h.

Potential Correlates of Sedentary Behavior: Sociodemographic factors (age, sex, race, ethnicity, education, partner status, Medicaid), hospitalization characteristics/procedures (ACS type, length of hospital stay, percutaneous coronary intervention [PCI]), measures of health status/disease severity (body mass index [BMI], left ventricular ejection fraction [LVEF], CVD history, Charlson Comorbidity Index (de Groot, Beckerman, Lankhorst, & Bouter, 2003; Núñez et al., 2004), Global Registry of Acute Coronary Events (GRACE) risk score (Granger et al., 2003) , depression, physical- and mental health-related quality of life), prior exercise history, cardiac rehabilitation participation, and sleep quality were examined as potential correlates of accelerometer-measured sedentary behavior characteristics. Details on all potential correlates are available in the Supplemental Methods of the Supplemental Material section.

Statistical Analysis: Descriptive statistics, including frequencies and means ± standard deviations, were computed to characterize the sociodemographic and health characteristics as well as the patterns of sedentary behavior during weeks 1, 2, 3, and 4 and the whole month. Multilevel growth curve models were then used to examine and compare the pattern of time spent in sedentary behavior each week (Schwartz, Stone, Shiffman, Atienza, & Nebeling, 2007).

Classes or natural groupings of participants who tended to exhibit similar patterns of sedentary behavior over the 28 days post-discharge were identified and characterized using group-based trajectory modeling (GBTM) (Nagin & Odgers, 2010). Using this approach, each individual is presumed to belong to only one group, and each group is assumed to have its own distinct trajectory (Nagin, 2005; Nagin & Odgers, 2010). Quadratic trajectories and a normal probability

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distribution for the estimated sedentary time, given a wear time of 16 h/day, were used to compare 1-, 2-, 3-, 4-, 5-, and 6-group solutions to identify the model that best characterized sedentary patterns among ACS survivors over the first 28 days post-discharge without overfitting the data. The best fit model was selected using the Bayesian information criterion (BIC), subject to the condition that each group contained at least 10% of participants (Nagin & Odgers, 2010). All analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina) and the PROC TRAJ macro (Jones, 2005). Based on the BIC and group proportion, a 3-group model was selected as the final model.

Multilevel growth curve models were then used to examine time effects within each trajectory group. Logistic regression models were conducted to examine correlates of membership in the most sedentary trajectory group. All correlates were initially examined, one at a time, in separate models that included age, gender, race and ethnicity as covariates (Model 1). In order to identify the strongest correlates of the most sedentary trajectory group, a backwards elimination regression analysis that included all correlates was then conducted to arrive at a parsimonious model that retained only those potential predictors that were statistically significant at the $\alpha = 0.05$ level; age, sex, race, and ethnicity were again included as covariates in the model (Model 2). Because a validated wrist-based Actical™ cut-point has not been established, a sensitivity analysis was conducted with all analyses repeated defining sedentary behavior as epochs with less than 200 cpm. Additionally, to exclude possible accelerometer wear during sleep, a sensitivity analysis was conducted restricting the accelerometer analysis period to 8:00 AM to 8:00 PM.

Results

Table 1 presents the sociodemographic and health characteristics of the 149 participants who comprised the analytic sample. Participants were predominantly male, and racially and

ethnically diverse. The mean (± SD) of age and BMI was 62.8 ± 11.2 and 28.6 ± 5.0, respectively. The majority presented with unstable angina (n=78; 52.3%), received PCI during hospitalization (n=128; 85.9%), and did not attend cardiac rehabilitation post hospitalization (n=132; 88.6%). Additionally, the majority of participants had a partner/spouse (n=90; 60.4%) and almost half reported regular participation in exercise prior to their ACS event (n=68; 45.6%).

Over the first month post-discharge, on average, sedentary behavior accounted for 60.6% of wear time over a 16-hour waking day, equivalent to a mean (SD) of $9.7 ± 2.0$ h/day. The mean (SD) sedentary time was $10.3 ± 2.0$, $9.8 ± 2.1$, $9.4 ± 2.2$, and $9.3 ± 2.2$ h/day over a 16-hour waking day in weeks 1, 2, 3, and 4 post-discharge, respectively. Sedentary time declined over the first month post-discharge ($F_{3, 592}=25.53$, $p<0.001$ for overall time effect), with decreases in sedentary time observed in each consecutive week ($p<0.01$ for weeks 1 vs. 2, 2 vs. 3, and 3 vs. 4).

Figure 1 shows the 3-group sedentary trajectories determined by the GBTM. Low, moderate, and high sedentary time trajectory groups were identified, which comprised 31.5%, 47.9%, and 20.6% of the analytic sample, respectively. Characteristics of the 3 sedentary trajectory groups are shown in Supplemental Table 2. The mean ± SD of total sedentary time for the low, moderate and high trajectory groups was $7.3 ± 0.8$, $10.0 ± 0.7$, $12.6 ± 0.8$ h/day, respectively. Each sedentary trajectory group had a significant change in day-level sedentary time over the 28-day post-hospitalization period ($p<0.05$ for all). The high and moderate groups decreased their sedentary time at a rate of 1.9 ($p=0.003$) and 2.9 ($p<0.001$) min/day, respectively. The low sedentary trajectory group decreased their sedentary time at a rate of 14.0 min/day immediately post-discharge ($p<0.001$). After two weeks post-hospitalization, the rate in which sedentary time decreased reduced to 4.8 min/day and bottomed out at day 21 and thereafter increased to a rate of 4.8 min/day at day 28. The low trajectory group had a significantly greater rate of change in

sedentary time compared to the high and moderate groups over the 28-day post-discharge period ($<p=0.01$ for both). The difference in the rate of change in sedentary time between the high and moderate trajectory groups was not statistically significant (1.9 versus 2.9 min/day; $p=0.22$). In sensitivity analyses, similar 3-group trajectories were observed when using a sedentary cut-point of 200 cpm (Supplemental Figure 1) and when restricting the accelerometer analysis period to 8:00 AM to 8:00 PM (Supplemental Figure 2).

Multivariable models examining the correlates of the high sedentary trajectory group are shown in Table 2. The final parsimonious model identified Hispanic ethnicity, having a partner, left ventricular ejection fraction (LVEF) $< 40\%$, history of CVD, BMI, GRACE risk score, and physical health-related quality of life as significant bivariate correlates of the high sedentary trajectory group, controlling for age, sex, black race and ethnicity. ACS survivors with Hispanic ethnicity, a partner/spouse, history of CVD and higher BMI were less likely to be in the high total sedentary trajectory group. On the other hand, those with a LVEF $< 40\%$, higher GRACE risk score or lower physical health-related quality of life were more likely to be in the high total sedentary time group.

Discussion

The current study found that ACS survivors spent, on average, more than 9 hours of a 16-hour waking day engaged in sedentary behavior over the first month immediately following hospitalization. Sedentary time was greatest during the first week and decreased in subsequent weeks as ACS survivors assimilated back into everyday life after discharge. Our analysis suggests the presence of three distinct patterns of change. Two of these patterns, comprising approximately 70% of study participants, exhibited small, but statistically significant rates of decline in sedentary time over the first month after discharge. Over the same time period, those in the third pattern

exhibited less sedentary behavior initially and a more rapid decline in sedentary time during the first 2-3 weeks, before leveling off at about 6¾ h/day of sedentary time. Several factors, including greater disease severity, lower physical health-related quality of life, and not having a partner were positively associated with the most hazardous post-hospital trajectory of sedentary time (e.g., high volume of sedentary time with only a modest improvement over time).

It was previously reported in this cohort of ACS survivors that only ~16% met MVPA guidelines, and strikingly, ~40% of patients did not engage in a single day of health-enhancing physical activity akin to exercise (e.g. ≥30 MVPA bout min) (Kronish, Diaz, Goldsmith, Moise, & Schwartz, 2017). Collectively, the present and previous study provide a comprehensive description of the physical activity and sedentary behavior profile of ACS survivors in the first month after hospitalization. These results suggest that few ACS survivors engage in sufficient levels of MVPA, and many adopt a sedentary lifestyle immediately upon returning home; with most participants exhibiting relatively little change thereafter. These findings highlight a need to develop strategies for promoting movement in this vulnerable population. While cardiac rehabilitation is a cornerstone of secondary prevention, only 11.4% of our participants attended a cardiac rehabilitation program. This is not surprising, as low cardiac rehabilitation rates and poor adherence to exercise-based programs are well established among cardiac patients (Lawler, Filion, & Eisenberg, 2011; Leon et al., 2005). Furthermore, recent evidence has demonstrated that exercise-based cardiac rehabilitation programs do not yield reductions in sedentary time (since one can exercise for 30 min and be sedentary the rest of the day) (Biswas, Oh, Faulkner, & Alter, 2017; Martin et al., 2015; Prince, Blanchard, Grace, & Reid, 2016). Thus, a specific focus on sedentary behavior reduction strategies, in addition to exercise-based strategies, may be needed to promote greater activity in ACS survivors.

The total volume of sedentary behavior detected among ACS survivors in the current study is lower than that observed in other clinical populations (e.g., stroke, chronic obstructive pulmonary disease, etc.) (English et al., 2016; L. K. Lewis, Hunt, Williams, English, & Olds, 2016). However, between-study differences in accelerometer protocols and processing (e.g., device, wear location, sedentary count threshold, and non-wear threshold duration) make it difficult (and potentially problematic) to compare results in the present study to those reported in other clinical conditions (Kozey-Keadle, Libertine, Lyden, Staudenmayer, & Freedson, 2011; Oliver, Badland, Schofield, & Shepherd, 2011; Paul, Kramer, Moshfegh, Baer, & Rumpler, 2007). A similar study suitable for comparing results from the current study is the Dallas Heart Study, a longitudinal, multiethnic population-based probability sample of 2,031 Dallas County adults without CVD. Utilizing a wrist-worn Actical™ accelerometer and a 100 cpm threshold to define sedentary behavior (identical to the present study), sedentary time accounted for a mean of 5.1 h/day over a 12-hour time period from 8AM to 8PM in the Dallas Heart Study. Similarly, when the present study restricted the analytic period to 8AM to 8PM, it was observed that ACS survivors spent a mean of 5.4 h/day sedentary. The similar total volume of sedentary time observed between the current study sample and that of the Dallas Heart Study may be attributed to the high percentage of UA patients in the existing study sample (~52%), as these patients are reported to typically have persevered cardiac function and return to work soon after hospitalization relative to those with MI (Eggers, Jernberg, & Lindahl, 2017; Slebus et al., 2012). Future research may be needed to elucidate whether ACS survivors are prone to more hazardous volumes of sedentary behavior relative to their healthier peers.

A unique contribution of the present study is the application of group-based trajectory modeling techniques to identify distinct patterns of change in sedentary behavior in a post-

hospitalization patient group. The first month after hospital discharge was studied under the premise that this is a critical period when ACS survivors recuperate from their event and wherein different trajectories might be observed. Although significant decreases in sedentary time from one week to the next were observed for the full sample, different patterns of change emerged which were in some cases gradual and in others, more rapid. Regardless of the change observed over time, most patients still exhibited high volumes of sedentary behavior throughout the first month, which may indicate that intervening at any point during this critical time period could yield beneficial reductions in sedentary time and help mitigate future health risk.

Understanding the factors that influence the amount of time ACS survivors spend sedentary may help to inform the development of effective interventions in this population. When examining factors associated with sedentary behavior among ACS survivors in the present study, it was unsurprisingly observed that sicker, more ill patients with poorer physical function were more likely to accrue higher volumes of sedentary time. Specifically, indices of disease severity (i.e. LVEF<40% and GRACE risk score) and physical health-related quality of life were among the factors associated with being classified in the most hazardous sedentary trajectory group (i.e., high volume and minimal improvement over time). In light of the fact the such patients are likely to have difficulty attaining MVPA recommendations (Forechi et al., 2018; Jefferis et al., 2014; Lohne-Seiler, Hansen, Kolle, & Anderssen, 2014), the replacement of sedentary time with even light-intensity activities of daily living may be beneficial. For example, in a general population-based study, theoretical statistical simulations via isotemporal substitution have suggested that replacing 30 min of sedentary time with light physical activity could reduce all-cause mortality risk by 18% among low active adults (Keith M. Diaz et al., 2018).

Partner status was also a significant correlate, such that those without a partner or spouse were more likely to engage in hazardous amounts of sedentary time. Broadly, partner support is linked to a wide range of positive health behaviors and health outcomes (Lindsay Smith, Banting, Eime, O'Sullivan, & van Uffelen, 2017; Robles, Slatcher, Trombello, & McGinn, 2014). Partners often attempt to directly influence each other's health behaviors (Franks et al., 2006), and partners may even engage in activities with patients as an effective strategy for illness management (Tucker & Mueller, 2000). Theorists have highlighted the importance of communal coping (i.e., appraising an illness as relevant for the couple and engaging collaboratively to manage patient illness) in promoting positive behavioral and health outcomes (Helgeson, Jakubiak, Van Vleet, & Zajdel, 2018; M. A. Lewis et al., 2006; Lyons, Mickelson, Sullivan, & Coyne, 1998). In sum, the findings of the current study suggest that greater disease severity, lower physical health-related quality of life, and not having a partner may be important factors to consider when approaching the development and implementation of sedentary behavior reduction strategies for patients that recently experienced an ACS event. However, caution is warranted when interpreting these findings as causality cannot be inferred based on the cross-sectional nature of the current study.

A strength of the present study is the accelerometer-measurement of sedentary behavior via accelerometry over 28 consecutive days immediately post-hospital discharge, which is a critical period when patients recover from their event and secondary prevention interventions ideally begin. Conventional accelerometer protocols often entail 7-day monitoring periods; thus, the present study represents one of the longest accelerometer protocols conducted in ACS patients. These findings, however, should be interpreted in the context of several limitations. First, the Actical™ accelerometer cannot distinguish between different postures (e.g. sitting, standing); thus, an intensity-only definition of sedentary was utilized (Gibbs, Hergenroeder, Katzmarzyk, Lee, &

Jakicic, 2015). Second, wrist-worn accelerometers lack validated wrist-based cut-points and have been shown to be less accurate than hip/thigh accelerometers for estimating sedentary time, as they tend to underestimate daily sedentary time due to greater movement of the upper extremities during everyday activities (Koster et al., 2016). Despite existing limitations, wrist-worn accelerometers have been adopted by many population-based studies to increase wear compliance by alleviating the discomfort or inconvenience of hip-based accelerometer wear (Troiano, McClain, Brychta, & Chen, 2014). Use of a wrist-worn accelerometer in the present study permitted the evaluation of sedentary behavior over a far-longer period of time (28 days) relative to conventional hip-based accelerometer protocols (~7 days); thus, allowing the exploration of important post-hospital trajectories. Third, information about participants' return to work post hospitalization was not collected. Return to work represents a critical indicator of recovery from illness (Perk, 2007; Warraich, Kaltenbach, Fonarow, Peterson, & Wang, 2018). Furthermore, prior studies have demonstrated that occupation can largely influence daily physical activity levels (Steeves et al., 2018). Thus, return to work (or lack thereof) could have influenced the observed findings. Lastly, this is a small, single-center study in an urban academic medical center, which may limit the generalizability of the current findings. Most participants presented with unstable angina (~52%), which may limit applicability of the results for patients with MI. Further, compliance to the accelerometer protocol was relatively low (~45%). Participants excluded from the current analyses were more likely to have a length of hospital stay >4 days, lower physical health-related quality of life, and less likely to receive PCI. Thus, the findings from the current study may not be generalizable to the full PULSE study cohort.

Conclusion

In conclusion, this study demonstrated that ACS patients as a group engaged in high volumes of accelerometer-measured sedentary time, with patients exhibiting different patterns over the first month post-discharge, which involved either gradual or rapid reductions in sedentary behavior. Several measures of disease severity and physical health (LVEF<40%, GRACE risk score, physical health-related quality of life), as well as partner status, were associated with the most hazardous pattern of sedentary behavior. These findings provide a foundation for characterizing different patterns of sedentary behavior as patients assimilate back into their daily life and routine over the first month post-discharge. Future research is needed to determine whether these patterns of sedentary behavior are linked to the risk of adverse events after an ACS and to inform whether, amongst the multitude of secondary prevention strategies recommended for ACS survivors, sedentary behavior should also be targeted.

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Table 1. Characteristics of Acute Coronary Syndrome survivors.

Participant Characteristics	Overall (n=149)
Sociodemographic	
Age (years)	62.8 (11.2)
Male (%)	69.8 (n=104)
Black Race (%)	17.4 (n=26)
Hispanic Ethnicity (%)	38.3 (n=57)
Education ≤ High School Graduation (%)	43.0 (n=64)
Partner/Spouse (%)	60.4 (n=90)
Medicaid (%)	34.0 (n=50)
Hospitalization	
Acute Coronary Syndrome Type	
Unstable Angina (%)	52.3 (n=78)
NSTEMI (%)	31.5 (n=47)
STEMI (%)	16.1 (n=24)
Length of Hospital Stay > 4 days (%)	23.5 (n=35)
Percutaneous Coronary Intervention (%)	85.9 (n=128)
Physical & Psychosocial	
Exercise Participation Pre-ACS event (%)	45.6 (n=68)
Cardiac Rehabilitation Post-ACS event (%)	11.4 (n=17)
Body Mass Index (kg/m^2)	28.6 (5.0)
Left Ventricular Ejection Fraction < 40% (%)	14.1 (n=21)
CVD History (%)	33.6 (n=50)
Charlson Comorbidity Index	1.5 (1.6)
GRACE Risk Score	87.8 (28.3)
Depression[*] (%)	30.9 (n=46)
Physical Health-Related Quality of Life	40.0 (10.9)
Mental Health-Related Quality of Life	53.0 (10.7)
Sleep Quality	5.2 (4)
Accelerometer Characteristics	
Wear Time (mins/day)	1219.0 (224.1)
Valid Wear Days	25.7 (2.8)
Total Sedentary Time (mins/day)	581.4 (121.6)
MVPA Bout Minutes (mins/day)	22.7 (37.6)

Values presented as mean (SD) or %. CVD (cardiovascular disease), GRACE (Global Registry of Acute Coronary Events), MVPA (moderate-to-vigorous physical activity), NSTEMI (non-ST segment elevation myocardial infarction), STEMI (ST segment elevation myocardial infarction).
[*]Depression= Beck Depression Inventory score > 10.

Table 2. Correlates of being in the high sedentary behavior trajectory (versus either of the other two sedentary behavior trajectories).

Variables	Model 1*		Model 2†	
	OR (95% CI)‡	*P-Value*	OR (95% CI)‡	*P-Value*
Sociodemographic				
Age	1.06 (1.02 - 1.11)	0.01	0.97 (0.89 – 1.06)	0.46
Male	1.48 (0.56 - 3.90)	0.43	2.32 (0.52 – 10.31)	0.27
Black Race	1.63 (0.50 - 5.30)	0.42	0.70 (0.16 – 3.11)	0.64
Hispanic Ethnicity	1.33 (0.53 - 3.32)	0.54	0.20 (0.06 - 0.74)	0.02
≤ High School Education	0.71 (0.27 - 1.84)	0.48	-	-
Partner/Spouse	0.40 (0.15 - 1.08)	0.07	0.28 (0.08 – 0.97)	0.04
Medicaid	5.56 (1.45 - 21.36)	0.01	-	-
Hospitalization				
STEMI (reference =UA/NSTEMI)	2.11 (0.75 - 5.96)	0.16	-	-
Length of Hospital Stay > 4 days	4.51 (1.75 - 11.62)	<0.01	-	-
PCI	0.50 (0.16 - 1.53)	0.22	-	-
Physical & Psychosocial				
Exercise Participation Pre-event	0.87 (0.37, 2.05)	0.76	-	-
Cardiac Rehabilitation Post-event	2.29 (0.67 – 7.87)	0.19	-	
Body Mass Index	0.93 (0.84 - 1.02)	0.13	0.87 (0.77 – 0.99)	0.04
LVEF < 40%	11.22 (3.67 - 34.3)	<0.01	9.24 (2.03 – 42.00)	<0.01
CVD History	0.98 (0.40 - 2.37)	0.96	0.17 (0.05 – 0.68)	0.01
Charlson Comorbidity Index	1.08 (0.83 - 1.41)	0.55	-	-
GRACE Risk Score	1.04 (1.02 - 1.07)	<0.01	1.05 (1.01 – 1.09)	<0.01
Depression§	1.30 (0.51 - 3.28)	0.58	-	-
Physical Health-Related QoL	0.96 (0.92 - 1.00)	0.06	0.94 (0.89 – 0.99)	0.02
Mental Health-Related QoL	0.95 (0.92 - 0.99)	0.03	-	-
Sleep Quality	1.00 (0.9 - 1.12)	0.98	-	-

CVD (cardiovascular disease), CI (confidence interval), GRACE (Global Registry of Acute Coronary Events), LVEF (left ventricular ejection fraction), OR (odds ratio), PCI (Percutaneous Coronary Intervention), NSTEMI (non-ST segment elevation myocardial infarction), QoL (Quality of Life), STEMI (ST-segment elevation myocardial infarction), UA (unstable angina).
*Separate logistic regression models for each correlate adjusted for Age, Sex, Black Race, and Hispanic Ethnicity.
*Separate logistic regression models for each correlate adjusted for Age, Sex, Black Race, and Hispanic Ethnicity.
†Parsimonious backward elimination regression model after including all correlates and adjusting for Age, Sex, Black Race, and Hispanic Ethnicity.
‡Odds ratio for high sedentary group membership. Low and moderate groups were combined and set as the reference group.
§Depression= Beck Depression Inventory score > 10.

Figure 1. Sedentary time over the 28 days post-discharge period among low, moderate and high trajectory groups of Acute Coronary Syndrome survivors. Data are presented as mean ± 1 standard error for each day, by sedentary trajectory group.
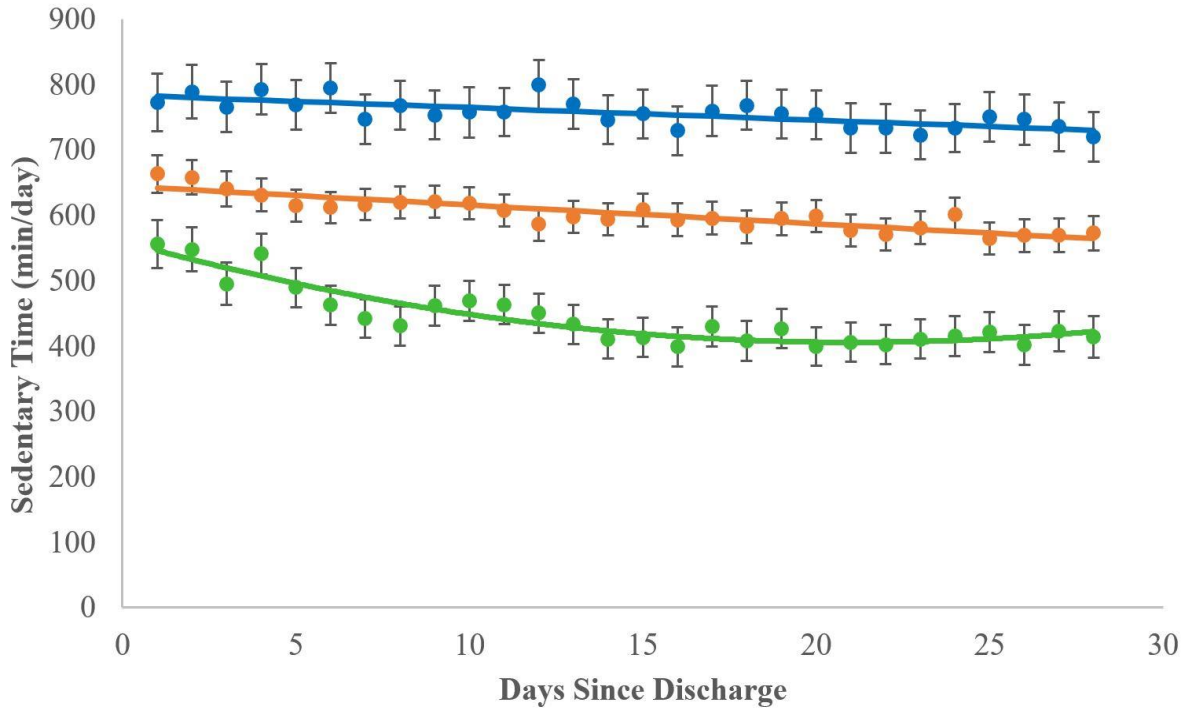
Supplemental Material

Supplemental Methods

Socio-demographic factors (age, sex, race, ethnicity, education, partner status, Medicaid), hospitalization characteristics/procedures (ACS type, length of hospital stay, percutaneous coronary intervention [PCI]), measures of health status/disease severity (body mass index [BMI], left ventricular ejection fraction [LVEF], CVD history, Charlson Comorbidity Index, GRACE risk score, physical- and mental health-related quality of life), prior exercise history, cardiac rehabilitation participation, depression, and sleep quality were all examined as potential correlates of accelerometer-measured sedentary behavior characteristics.

Socio-demographic factors and prior exercise participation were determined by patient interview at baseline using standard questionnaires. Medicaid is a state-administered assistance program designed to provide health coverage for low-income people under the age of 65 years who cannot finance their own medical expenses or have qualifying comorbid conditions (Calvin et al., 2006). As such, Medicaid is considered a proxy for low socioeconomic status. Prior exercise participation was assessed by the single item "In the three months prior to this hospitalization, were you exercising regularly?" with "yes" and "no" response options. Cardiac rehabilitation participation was ascertained at 1-month post-hospitalization with a one item question "Since the last study visit, have you participated in cardiac rehabilitation" that had "yes" and "no" response options. Cardiac rehabilitation participation was determined by patient interview at one-month post hospitalization. LVEF, prior CVD, length of hospital stay, in-hospital cardiovascular procedures (PCI), and ACS type (unstable angina, non-ST-segment elevation MI, ST-segment elevation MI) were ascertained by medical record chart review. LVEF and length of hospital stay were expressed categorically (LVEF: <40% vs. ≥40%; length of stay: <4 days vs. ≥4 days) (Lopez-Jimenez et al., 2004; Vavalle et al., 2012). The 6-month post-ACS mortality risk was assessed

using the Global Registry of Acute Coronary Events (GRACE) index. The GRACE index tabulates scores related to clinical health measures (age, heart rate, systolic blood pressure, serum creatinine, congestive heart failure Killip class, presence of cardiac arrest at admission, ST segment deviation, and elevated cardiac enzymes or biomarkers) that range from 1 to 263 points, with higher scores indicating greater mortality risk (Granger et al., 2003). To assess the severity of comorbidities the Charlson comorbidity (CCI) index was used. The CCI takes into account 17 categories of comorbidity (such as diabetes, dyslipidemia and hypertension), weighting each category by its mortality risk, sums the weighted scores and subgroups these into four categories (Núñez et al., 2004). Numerous studies have supported the consistency and predictive validity of the CCI (de Groot, Beckerman, Lankhorst, & Bouter, 2003).

Physical and mental health-related quality of life was assessed in-hospital by the Short Form 12 Health Survey (SF-12), a 12-item multi-purpose measure of health-related quality of life, which is based on eight health-related concepts, adapted from the longer SF-36 (Ware et al., 2002). The SF-12 subscales include physical functioning, role-physical (e.g., how physical problems affect daily life), and social functioning, mental health, role-emotional (e.g., how emotional problems affect daily life), bodily pain, vitality, and general health. Composite scores of physical and mental health-related quality of life are derived from a combination of the eight sub-scales, and these are reported in this study.

Depressive symptoms were measured in-hospital by the 21-item Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Participants rated on a 4-point scale the extent to which various depression symptoms (21-items describing cognitive, affective, and somatic symptoms) had been present or absent for the previous week. Ratings were summed, and higher levels indicated greater symptom severity. Sleep quality was measured at 1-month

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follow-up by the Pittsburgh Sleep Quality Index, a 19-item self-rated questionnaire that assesses sleep quality and disturbances (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Because sleep disturbance has been well documented among hospitalized patients (Redeker & Hedges, 2002), we elected to assess sleep quality at 1-month follow-up instead of in-hospital.

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Supplemental Figure 1. Consort of Accelerometer Device Return.
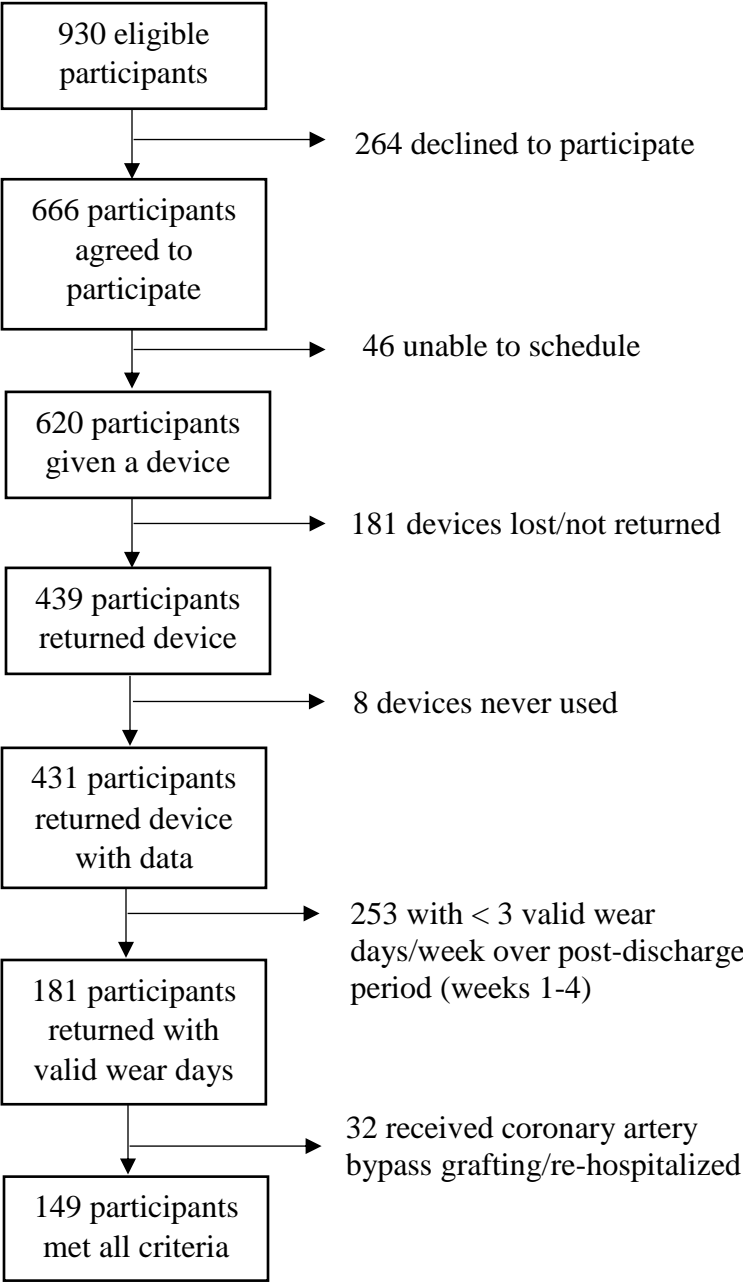
Supplemental Table 1. Characteristics of participants included vs. excluded from the present analyses who consented to participate in the ancillary physical activity study.

Participant Characteristics	Included (n=149)	Excluded (n=471)	*P-Value*
Sociodemographic			
Age (yrs)	62.8 (11.2)	63.4 (11.7)	0.58
Male (%)	69.8	64.5	0.24
Black Race (%)	17.5	23.7	0.11
Hispanic Ethnicity (%)	38.3	36.7	0.74
Education ≤ High School (%)	43.0	50.7	0.10
Partner/Spouse (%)	60.4	55.1	0.26
Medicaid (%)	34.0	32.0	0.65
Hospitalization			
Acute Coronary Syndrome Type			0.44
Unstable Angina (%)	52.4	54.4	
NSTEMI (%)	31.5	32.1	
STEMI (%)	16.1	13.6	
Length of Hospital Stay > 4 days (%)	23.5	40.8	<0.01
Percutaneous Coronary Intervention (%)	85.9	76.0	0.01
Physical & Psychosocial			
Exercise Participation Pre-ACS event (%)	45.6	44.0	0.69
Cardiac Rehabilitation Post-ACS event (%)	11.4	12.5	0.72
Body Mass Index (kg/m^2)	28.6 (5.0)	29.2 (5.9)	0.22
Left Ventricular Ejection Fraction < 40% (%)	14.1	13.6	0.88
CVD History (%)	33.6	32.2	0.78
Charlson Comorbidity Index	1.5 (1.6)	1.7 (1.7)	0.29
GRACE Risk Score	87.8 (28.3)	91.7 (30.5)	0.16
Depression[*] (%)	30.9	33.6	0.55
Physical Health-Related QoL	40.0 (10.9)	37.8 (11.0)	0.03
Mental Health-Related QoL	53.0 (10.7)	54.0 (10.7)	0.35
Sleep Quality	5.2 (4)	5.6 (4.2)	0.38

Values presented as mean (SD) or %. CVD (cardiovascular disease), GRACE (Global Registry of Acute Coronary Events), NSTEMI (non-ST segment elevation myocardial infarction), QoL (quality of life), STEMI (ST segment elevation myocardial infarction).

[*]Depression= Beck Depression Inventory score > 10.

Supplemental Table 2. Characteristics of Acute Coronary Syndrome survivors stratified by total sedentary time trajectory groups.

Participant Characteristics	Low (n=47)	Moderate (n=72)	High (n=30)
Sociodemographic			
Age (yrs)	58.5 (10.7)	63.7 (10.8)	67.6 (11.0)
Male (%)	70.2	68.1	73.3
Black Race (%)	21.3	15.3	16.7
Hispanic Ethnicity (%)	42.6	38.9	30.0
Education ≤ High School (%)	48.9	41.7	36.7
Partner/Spouse (%)	55.3	68.1	50.0
Medicaid (%)	29.8	32.9	43.3
Hospitalization			
Acute Coronary Syndrome Type			
Unstable Angina (%)	57.4	54.2	40.0
NSTEMI (%)	36.2	26.4	36.7
STEMI (%)	6.4	19.4	23.3
Length of Hospital Stay > 4 days (%)	17.0	18.1	46.7
Percutaneous Coronary Intervention (%)	93.6	83.3	80.0
Physical & Psychosocial			
Exercise Participation Pre-ACS event (%)	48.9	44.4	43.3
Cardiac Rehabilitation Post-ACS event (%)	10.6	9.7	16.7
Body Mass Index (kg/m^2)	28.8 (5.4)	29.2 (4.9)	27 (4.5)
Left Ventricular Ejection Fraction < 40% (%)	4.3	9.7	40.0
CVD History (%)	31.9	33.3	36.7
Charlson Comorbidity Index	1.3 (1.4)	1.4 (1.7)	1.9 (1.6)
GRACE Risk Score	77.2 (23.5)	86.4 (23.9)	107.4 (35)
Depression[*] (%)	29.8	29.2	36.7
Physical Health-Related QoL	41.3 (10.6)	40.6 (11.1)	36.6 (10.5)
Mental Health-Related QoL	55.1 (8.5)	53 (11.3)	49.9 (11.7)
Sleep Quality	5.6 (4.4)	5 (3.9)	5.2 (3.5)
Accelerometer Characteristics			
Wear Time (mins/day)	1251.1 (219.8)	1173.4 (240.3)	1278.1 (166.9)
Valid Wear Days	26 (2.6)	25.1 (3.1)	26.4 (2.6)
Total Sedentary Time (mins/day)	440.3 (50.2)	601.1 (44.1)	755.4 (46.5)
MVPA Bout Minutes (mins/day)	42.3 (56.8)	16.6 (20.7)	6.6 (8.6)

Values presented as mean (SD) or %. CVD (cardiovascular disease), GRACE (Global Registry of Acute Coronary Events), MVPA (moderate-to-vigorous physical activity), NSTEMI (non-ST segment elevation myocardial infarction), QoL (quality of life), STEMI (ST segment elevation myocardial infarction).
[*]Depression= Beck Depression Inventory score > 10.

Supplemental Figure 1. Sedentary time over the 28 days post-discharge period among low, moderate and high trajectory groups of Acute Coronary Syndrome survivors using a 200 count per minute threshold. Data are presented as mean ± 1 standard error for each day, by sedentary trajectory group.
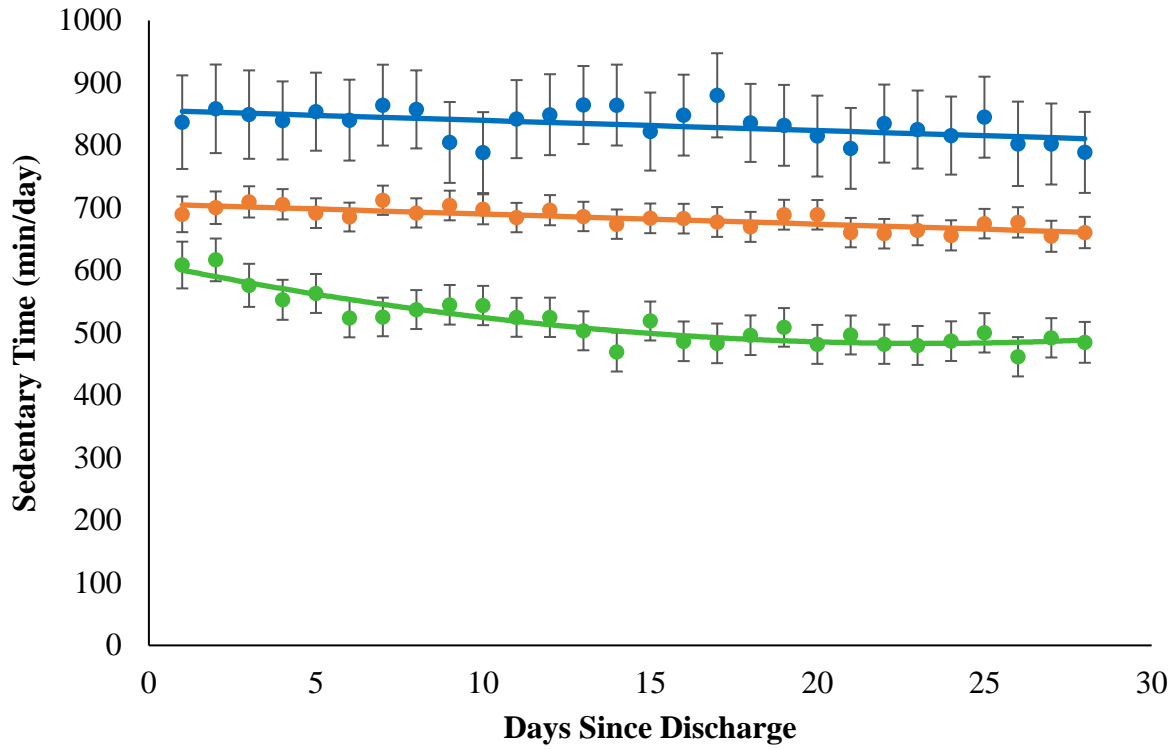
Supplemental Figure 2. Sedentary time over the 28 days post-discharge period among low, moderate and high trajectory groups of Acute Coronary Syndrome survivors when restricting wear time from 8am-8pm. Data are presented as mean ± 1 standard error for each day, by sedentary trajectory group.
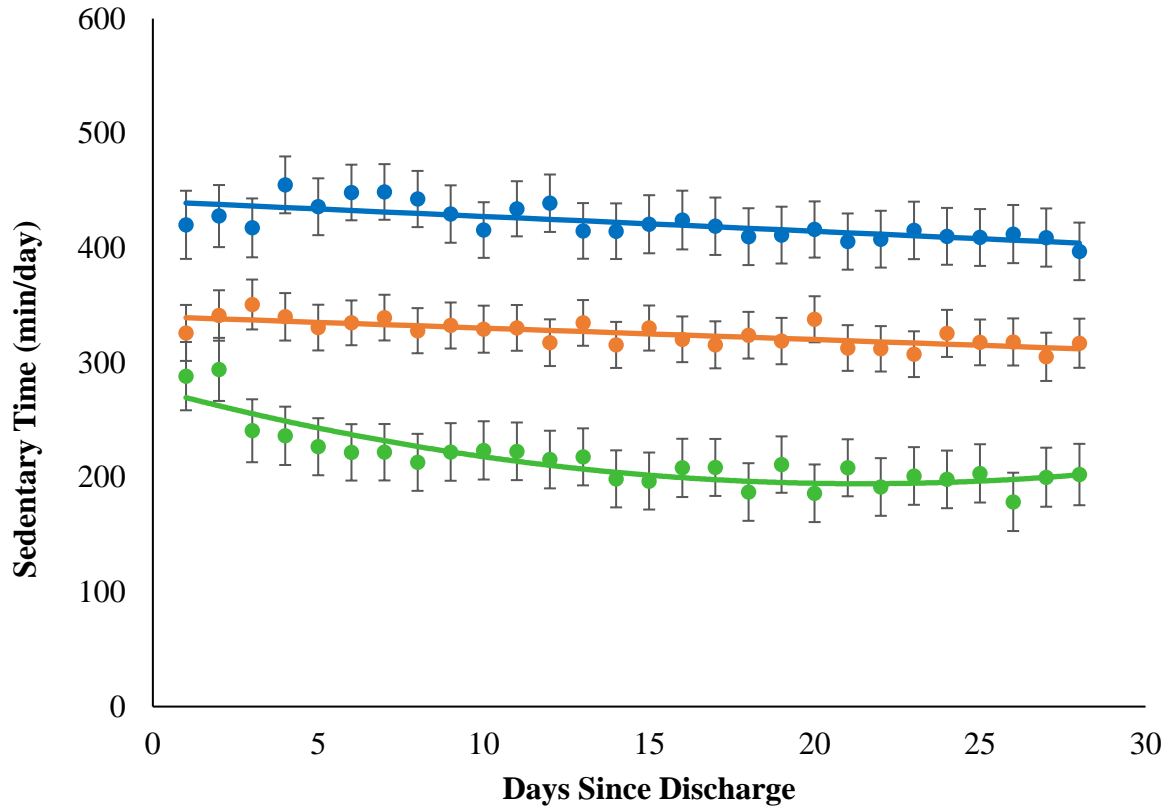
CHAPTER IV

Accelerometer-Measured Sedentary Behavior and Health Outcomes in Acute Coronary Syndrome Survivors

Abstract

Acute coronary syndrome (ACS) survivors engage in high volumes of sedentary behavior over the first month after hospitalization. However, the relationships between sedentary behavior during this time period and health outcomes in ACS patients are unknown. **Purpose:** To determine whether accelerometer-measured sedentary behavior during the first month post hospital discharge is associated with the risk of 1-year recurrent major adverse cardiovascular events (MACE) or hospitalizations in ACS patients. **Methods:** Participants (n=323; 68.7% male; 62.9±10.9 y) with confirmed ACS and valid accelerometer data from the Prescription Use, Lifestyle, and Stress Evaluation (PULSE) study were examined. Sedentary time was measured by accelerometry for 28-days post-hospital discharge. MACE included a composite of recurrent non-fatal MI, urgent cardiac revascularization, and unstable angina hospitalization. Hospitalizations included the first occurrence of a hospitalization during or after completion of the accelerometer protocol, regardless of cause. Unadjusted and adjusted Cox proportional hazards regression modeling was used to calculate the hazard ratio (HR) for MACE and hospitalizations associated with mean sedentary time estimates. **Results:** Participants spent a mean (SD) of 9.9 ± 2.1 h/day in sedentary behavior during the 28-days post-hospital discharge, which accounted for 61.9% of wear time over a 16-hour waking day. At 1-year follow up, there were 40 recurrent MACE events and 142 hospitalizations. Mean sedentary time was not associated with risk of recurrent MACE or hospitalizations in unadjusted (HR [95% Confidence Interval (CI)]: 1.07 [0.93 – 1.24]; HR [95% CI]: 1.07 [0.99 – 1.16]; respectively) and multivariable adjusted models (HR [95% CI]: 0.98 [0.83 – 1.15]; HR [95% CI]: 1.03 [0.95 – 1.14]; respectively). **Conclusion:** Sedentary behavior

during the immediate month after hospitalization was not associated with increased risk of 1-year recurrent major adverse cardiac events or hospitalizations in ACS survivors, suggesting that sedentary behavior during this post-hospital time window may not be a prognostic risk factor in ACS survivors.

Introduction

More than one million patients are hospitalized each year for Acute Coronary Syndrome (ACS) in the United States alone (Mozaffarian et al., 2015). Accordingly, new technologies, interventions, medications, and treatment guidelines have been implemented over recent decades to improve survival after ACS, resulting in a growing population of ACS survivors. Existing treatments after ACS includes long-term medical and interventional therapy and secondary prevention strategies (Amsterdam et al., 2014). Current American Heart Association/American College of Cardiology (ACC/AHA) guidelines recognize physical activity and cardiac rehabilitation as Class I secondary prevention strategies (Amsterdam et al., 2014); however, few patients attain these lifestyle targets (e.g., ≥150 mins/week of moderate- to vigorous intensity physical activity [MVPA] or attend cardiac rehabilitation) as a result of different barriers (e.g., physical, social, provider referral, etc.) (Chow et al., 2019; Kronish, Diaz, Goldsmith, Moise, & Schwartz, 2017). Consequently, ACS survivors remain at substantial risk for recurrent cardiac events and mortality (Menzin, Wygant, Hauch, Jackel, & Friedman, 2008), underscoring a critical need to identify additional prognostic risk factors that can be targeted for intervention to prolong survival and reduce recurrent events in this vulnerable population. One such risk factor may be sedentary behavior.

Evidence from population-based studies has linked prolonged sedentary behavior to increased risk for cardiovascular morbidity and mortality (Biswas et al., 2015; Wilmot et al., 2012), wherein only high levels of MVPA (~60 to 75 min/d) may mitigate the risk conferred by prolonged sedentariness (Ekelund et al., 2016). Previous findings characterizing the physical activity and sedentary habits of ACS survivors over the first month after hospitalization show that few patients engage in sufficient levels of MVPA. Moreover, many rapidly adopt a sedentary lifestyle immediately upon returning home, with most patients exhibiting relatively little change thereafter

(Duran, Garber, Schwartz, & Diaz, 2018; Kronish et al., 2017). However, no existing U.S. guidelines for secondary prevention in ACS patients mention sedentary behavior as a risk factor to be treated. This omission may be due to existing controversies about the adverse effects of sedentary behavior in the general population (e.g., uncertainty whether health effects are independent of MVPA; physiological mechanisms underlying adverse effects; feasibility of sedentary behavior reduction in adults) and/or a lack of empirical evidence (Young et al., 2016), as there is currently no published data to quantify how accelerometer-measured sedentary behavior relates to health outcomes in ACS patients.

To inform secondary prevention guidelines on reducing sedentary behavior, evidence from prospective studies is needed to confirm the association between sedentary time and health outcomes in ACS survivors. Therefore, the primary aim of the current study was to determine whether sedentary behavior was associated with risk of 1-year recurrent major adverse cardiovascular event (MACE) and all-cause mortality (ACM) among ACS survivors. A secondary aim was to determine whether sedentary behavior was associated with risk of 1-year recurrent cardiovascular disease related hospitalizations in this same population. It was hypothesized that greater sedentary time during the first month post-discharge will predict increased 1-year risk of MACE, ACM, and hospitalizations in ACS survivors.

Methods

Study Population: ACS patients hospitalized in tertiary care academic medical center were enrolled into the Prescription Use, Lifestyle, and Stress Evaluation (PULSE) study, an observational cohort study conducted from February 2009 to September 2012 (N=1087). PULSE was designed to examine behavioral and biological pathways that may confer increased risk for recurrent cardiac events (Whang et al., 2013). Hospitalization with an adjudicated diagnosis of

ACS was the inclusion criterion. ACS events were defined according to American Heart Association/American College of Cardiology (AHA/ACC) criteria as either acute myocardial infarction (MI, with or without ST-elevation) or unstable angina (Amsterdam et al., 2014). Exclusion criteria included individuals less than 18 years of age, without English or Spanish proficiency, inability to complete the baseline assessment or to adhere with the study protocol, and those who were medically unstable.

This paper reports on a sub-study whose purpose was to measure physical activity and sedentary behavior for up to 45 days following hospital discharge via accelerometry, conducted among the PULSE study cohort from August 2009 – September 2012 (Green et al., 2013). To stay consistent with methods from Chapter III, an accelerometer wear period of 28 days was selected for the current study. A total of 620 participants were given an accelerometer. Of these individuals, 323 participants returned the accelerometer with usable data and adhered to accelerometer wear requirements (≥3 days with accelerometer wear ≥ 10 h/day for at least one week over the first 28 days post-discharge) (Kocherginsky, Huisingh-Scheetz, Dale, Lauderdale, & Waite, 2017; Trost, McIver, & Pate, 2005) (Supplemental Figure 1A). The PULSE protocols were approved by the Columbia University Medical Center Institutional Review Board and verbal and written informed consent was obtained from all participants before they were enrolled into the study. Characteristics of ancillary study participants, and those who were excluded from the current analyses are shown in Supplemental Table 1.

Accelerometer Protocol: Participants were fitted at or soon after hospital discharge with an accelerometer (Actical™; Philips Respironics, Bend, OR) on their non-dominant wrist, and were instructed to wear the device continuously for 45 days, except when bathing or sleeping, and to return the device via mail at the end of the monitoring period. The accelerometer is an omni-

directional accelerometer that has been validated for the measurement of physical activity when worn on the wrist (Diaz et al., 2018; Heil, 2006). Activity counts were collected in 1-minute epochs.

Accelerometer Processing: Non-wear time was determined using the Choi algorithm, defined as at least 90 consecutive minutes of zero counts, with allowance of 1 or 2 minutes of nonzero counts as long as no counts were detected in the 30-minute windows at the start or end of the 90-minute (or longer) period (Choi, Liu, Matthews, & Buchowski, 2011). Epochs with less than 100 counts per minute (cpm) and ≥1065 cpm were classified as sedentary behavior and MVPA, respectively (Hooker et al., 2011; Kulinski, Kozlitina, Berry, de Lemos, & Khera, 2016). Time spent in sedentary behavior was determined by summing the number of minutes in a day when the activity counts met these criteria. Presently, there are no validated cut-points to classify sedentary behavior using this device when worn on the wrist. A sedentary cut-point of 100 counts per minute (cpm) was selected based on findings and methods defined in the Dallas Heart Study, a longitudinal, multiethnic population-based probability sample of Dallas County residents (Kulinski et al., 2016). The Dallas Heart Study assessed sedentary time with the same model wrist-worn accelerometer and classified sedentary time as <100cpm. Findings from the Dallas Heart Study demonstrated that accelerometer-measured sedentary time was associated with subclinical atherosclerosis (Kulinski et al., 2016), and chronic subclinical myocardial injury (Harrington et al., 2017). Given that sedentary time classified as <100cpm was associated with meaningful cardiovascular health indices in a large, representative sample, it was decided to incorporate the same cut-point for the current analyses as that utilized in the Dallas Heart Study.

For each compliant day (≥10 hours of wear) during the immediate 28-day post-discharge period, the total number sedentary minutes and the total time spent in MVPA were calculated.

Compliant days that occurred on or after a re-occurring event (i.e., MACE/ACM or hospitalization) were removed from analyses. Because of a high correlation between sedentary time and wear time for both analytic samples (r=0.80 for both), we corrected for the influence of variation in wear time by standardizing sedentary time using the residuals obtained when regressing sedentary time on wear time at the group level (Healy, Winkler, Brakenridge, Reeves, & Eakin, 2015; Qi et al., 2015; Willett & Stampfer, 1986). As a result, sedentary time is expressed as the predicted sedentary time for that day, had the participant worn the device for 16 h.

Outcome Ascertainment: The primary outcome was the first occurrence of either a major adverse cardiovascular event or all-cause mortality. Hospitalizations and vital status were assessed at participant follow-up phone calls completed at 1-, 6-, and 12-months after enrollment. Medical record extraction was done uniformly for any reports of hospitalizations during the course of the study for adjudication of MACE and ACM. An Endpoint Classification Committee, which consisted of two board certified cardiologists, independently reviewed the medical record and classified cause of each hospitalization. Full agreement by both reviewers was required to classify an event. In the case of a disagreement, a third independent reviewer was consulted to adjudicate the end points determination. The reviewers were blinded to the medical record discharge codes. MACE was defined as the composite of a recurrent non-fatal MI, urgent cardiac revascularization (defined as ischemic symptoms that resulted in either urgent percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), and unstable angina hospitalization. The criteria for each MACE category were abstracted from the ACC/AHA consensus of data elements for measuring outcomes and were used by the Endpoint Classification Committee to determine if, and on what date, one of these events occurred. ACM was defined as any death regardless of cause. Dates of death were confirmed through review of death certificates, medical records, and

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administrative databases. The secondary outcome was recurrent hospitalization, defined as the first occurrence of a hospitalization during or after completion of the accelerometer protocol regardless of cause. All outcomes were operationalized as a binary variable based on event status (i.e., event occurred or no event) for analyses.

Covariates: Potential covariates associated with risk of MACE/ACM and hospitalizations were measured. These included sociodemographic factors (age, sex, race, ethnicity, education, partner status); hospitalization characteristics/procedures (length of hospital stay, PCI, CABG); measures of health status/disease severity (body mass index [BMI; left ventricular ejection fraction [LVEF], estimated glomerular filtration rate less than 60 mL/ min/1.73 m^2; hypertension; dyslipidemia; CVD history; Charlson Comorbidity Index (de Groot, Beckerman, Lankhorst, & Bouter, 2003; Núñez et al., 2004); Global Registry for Acute Coronary Events [GRACE] risk score (Granger et al., 2003)); current smoking; prior exercise history; and cardiac rehabilitation participation. Details of the measurement and scoring of all potential correlates are available in the Supplemental Material section of Chapter III (pages 66-68).

Statistical Analysis: Descriptive statistics, including frequencies and means ± standard deviations, were computed to characterize participant sociodemographic, health, accelerometer and outcome characteristics. Multilevel growth curve models were then used to create mean sedentary time estimates for each participant based on model parameters specified from previous analyses conducted in Chapter III. The mean sedentary time estimates are adjusted for the temporal trend in the data and the number of days with valid wear time. Cox proportional hazards regression modeling was used to calculate the hazard ratio (HR) for MACE/ACM (primary aim) and hospitalizations (secondary aim) associated with mean sedentary time estimates. Crude HRs and 95% confidence intervals (CI) were initially calculated. Subsequent HRs and 95% CI were

calculated after adjustment for covariates identified in separate preliminary backwards elimination regression analyses that included 20 potential correlates of MACE/ACM and hospitalizations. The parsimonious model for MACE/ACM included Charlson Comorbidity Index and GRACE Risk Score as potential covariates that were statistically significant at the $\alpha = 0.05$ level. The parsimonious model for hospitalizations included sex, education, exercise participation prior to ACS event, estimated glomerular filtration rate less than 60 mL/ min/1.73 m^2, and Charlson Comorbidity Index as potential predictors that were statistically significant at the $\alpha = 0.05$ level.

Because a validated cut-point for sedentary behavior using this wrist-based device has not been established, a sensitivity analysis was conducted, with all analyses repeated with sedentary behavior defined as epochs with less than 200 cpm. Additionally, to exclude possible accelerometer wear during sleep, a sensitivity analysis was conducted restricting the accelerometer analysis period to 8:00 AM to 8:00 PM. Lastly, a sensitivity analysis was conducted restricting the accelerometer analysis to participants that had ≥ 3 day of valid wear each week over the 28 days post-discharge (weeks 1-4). All analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Participant Characteristics

Table 1 presents the sociodemographic, health and accelerometer characteristics of the analytic sample (n=323). Participants were predominantly male, and racially and ethnically diverse. The majority presented with unstable angina, received PCI during hospitalization, had hypertension and dyslipidemia, and did not attend cardiac rehabilitation. Additionally, the majority of participants had an education greater than a high school graduation, and almost half reported regular participation in exercise prior to their ACS event. Over the first month after

discharge, sedentary behavior accounted for a mean of 61.9% of wear time over a 16-hour waking day, equivalent to a mean (SD) of 9.9 ± 2.1 hours of sedentary time per day.

Sedentary Time and Risk of MACE/ACM

At 1-year follow up, there were 40 recurrent MACE and there were no ACM events. Table 2 (Upper Panel) presents the unadjusted and adjusted hazard ratios and 95% CI for MACE associated with mean sedentary time over the 28 days post-discharge period. Mean sedentary time was not associated with risk of recurrent MACE in either the unadjusted or multivariable adjusted models. In sensitivity analyses, similar results were observed when using a sedentary cut-point of 200 cpm (Supplemental Table 2: Upper Panel), when restricting the accelerometer analysis period to 8:00 AM to 8:00 PM (Supplemental Table 2: Middle Panel), and when restricting for valid wear time on $\geq$ 3 days each week over the 28 days post-hospital discharge period (Supplemental Table 2: Lower Panel).

Sedentary Time and Risk of Hospitalizations

At 1-year follow up, there were 142 recurrent hospitalizations for any cause. Table 2 (Lower Panel) presents the unadjusted and adjusted hazard ratios and 95% CI for hospitalizations associated with mean sedentary time over the 28 days post-discharge period. Mean sedentary time was not significantly associated with risk of recurrent hospitalizations in the unadjusted and multivariable adjusted models. Similar results were observed when using a sedentary cut-point of 200 cpm (Supplemental Table 3: Upper Panel), when restricting the accelerometer analysis period to 8:00 AM to 8:00 PM (Supplemental Table 3: Middle Panel), and when restricting for valid wear time on $\geq$ 3 days each week over the 28 days post-discharge period (Supplemental Table 3: Lower Panel).

Discussion

In this prospective study of ACS survivors, the average sedentary time over the first month after hospitalization was not associated with an increased 1-year risk of recurrent MACE or hospitalizations. Contrary to our hypothesis, these preliminary findings suggest that sedentary behavior during the immediate month after hospitalization is not a prognostic risk factor of recurrent events and hospitalizations in ACS survivors.

Secondary prevention is a vital feature of the management of care for ACS survivors, wherein subsequent cardiovascular morbidity and mortality can be reduced by a comprehensive approach (e.g., lifestyle changes, risk factor education, medical therapy) to constructively modify patients' risk profiles (Amsterdam et al., 2014; Smith et al., 2011). Strong evidence exists on the cardiovascular protective effects induced by physical activity in secondary prevention, such as reducing the impact of disease, slowing its progress, and preventing recurrence of an acute event (Alves et al., 2016). However, little is known about the adverse effects elicited by sedentary behavior during secondary prevention efforts among ACS survivors. In an observational cohort study of more than 1,000 patients with coronary heart disease, Mons and colleagues (2014) found that patients who self-reported the least amount of activity at 12 months had a two-fold elevated risk for major cardiovascular events over the course of a 10-year follow-up period (Mons, Hahmann, & Brenner, 2014). However, the aforementioned study focused on physical activity levels as opposed to sedentary behavior, as well as measured activity levels at a timepoint when most lifestyle secondary prevention strategies may have already been completed.

The present study fills a gap in the available evidence by examining the association between accelerometer-measured sedentary behavior (vs. physical activity) during the first month immediately after hospitalization (vs. 1-year post hospitalization) and 1-year recurrent cardiovascular events. The first month of recovery following ACS may present a critical period

when secondary prevention strategies begin to be adopted, and so this high degree of sedentariness is of concern. While the findings from this study suggest that sedentary behavior during the first month post-hospitalization is not associated with 1-year recurrent cardiac events among ACS survivors, it's possible that a different post-hospitalization time period (e.g., 6 month) and/or longer post-hospitalization time period is needed (i.e., duration longer than one-year) to detect the adverse effects of sedentary behavior in ACS survivors.

Previous studies have examined the association between accelerometer-measured physical activity and 30-day all-cause hospital readmissions in other clinical conditions such as heart failure and COPD. Waring and colleagues (2017) measured physical activity via a wrist-worn accelerometer in a group of heart failure patients and found that lower levels of physical activity over the first week post-discharge was related to higher 30-day all-cause readmissions (Waring, Gross, Soucier, & ZuWallack, 2017). Similarly, Chawla and colleagues (2014) found that lower physical activity over the first week post-discharge for a clinical exacerbation of Chronic Obstructive Pulmonary Disease was associated with more 30-day all-cause readmissions (Chawla, Bulathsinghala, Tejada, Wakefield, & ZuWallack, 2014). Although both studies found an association between lower physical activity levels and hospitalizations, comparison between findings of the current study and those reported in other clinical conditions is difficult due to differences in accelerometer protocols and processing (e.g., device, intensity threshold, vector magnitude units vs. count per minute, and non-wear threshold duration) and duration of the follow-up (30 days vs. 1 year).

A strength of the current study is the measurement of sedentary behavior via accelerometry over 28 consecutive days immediately post-hospital discharge in a racially/ethnically diverse sample of ACS survivors, which allowed for more precise measurement of habitual sedentary time

over several weeks. Conventional accelerometer protocols often entail 5 to 7-day monitoring periods, making the present study one of the longest accelerometer protocols conducted in ACS patients. Nonetheless, several limitations should be acknowledged when interpreting the findings of the current study. First, the Actical™ accelerometer cannot distinguish between different postures (e.g. sitting, standing). This limits the current study's ability to adhere to the consensus sedentary behavior definition, which includes both intensity of activity (≤ 1.5 METS) and position (sitting or reclining) (Gibbs, Hergenroeder, Katzmarzyk, Lee, & Jakicic, 2015; Sedentary Behaviour Research, 2012). Therefore, an intensity-only definition of sedentary behavior was employed, which may have overestimated sedentary time as some standing may also be included (Gibbs et al., 2015). Secondly, wrist-worn accelerometers lack validated wrist-based cut-points, and have been shown to tend to underestimate daily sedentary time (Koster et al., 2016). Despite existing limitations, wrist-worn accelerometer placement have shown to increase wear adherence by alleviating the discomfort or inconvenience of hip-based accelerometer wear (Troiano, McClain, Brychta, & Chen, 2014), which was the rationale for using a wrist-based device for the current study protocol. To account for this limitation, however, a sensitivity analysis with an alternative cut-point (200 cpm) was conducted, which yielded similar results for both recurrent MACE and hospitalizations. Lastly, this is a small, single-center study in an urban academic tertiary care medical center, which may limit this study's power to detect associations, as well as the generalizability of the current findings. For instance, the majority of our sample presented with unstable angina (~54%), which may limit applicability of the results for patients with MI, as these are lower-risk patients.

Conclusion

In conclusion, this study was unable to detect significant associations between sedentary behavior during the immediate month after hospitalization and the risk of 1-year recurrent major adverse cardiac events or hospitalizations in ACS survivors. While the findings of this study might suggest that targeting sedentary behavior is not an essential secondary prevention target in the periods, by far, these results are not definitive as to the potential benefit of a strategy of reducing sedentary behavior early in the post ACS recovery period. Future research with a larger sample and longer follow-up is needed to confirm the prognostic utility (or lack thereof) of sedentary behavior in the early and later post ACS recovery period.

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Table 1. Characteristics of Acute Coronary Syndrome survivors in the primary analytic sample (n=323).

Participant Characteristics	Mean (SD) or %
Sociodemographics	
Age (yrs)	62.9 (10.9)
Male (%)	68.7
Black Race (%)	20.0
Hispanic Ethnicity (%)	39.3
Education ≤ High School Graduation (%)	45.2
Partner/Spouse (%)	57.9
Medicaid (%)	32.6
Hospitalization	
Acute Coronary Syndrome Type	
Unstable Angina (%)	53.6
NSTEMI (%)	31.3
STEMI (%)	15.2
Length of Hospital Stay > 4 days (%)	31.3
Percutaneous Coronary Intervention (%)	79.3
Coronary Artery Bypass Graft Surgery (%)	8.4
Physical & Psychosocial	
Exercise Participation Pre-ACS event (%)	46.7
Cardiac Rehabilitation Post-ACS event (%)	12.7
Current Smoker (%)	13.3
Body Mass Index (kg/m^2)	29.0 (5.5)
Left Ventricular Ejection Fraction < 40% (%)	14.9
Hypertension (%)	77.4
Dyslipidemia (%)	63.2
eGFR < 60 mL/min/1.73 m^2 (%)	22.5
CVD History (%)	33.7
Charlson Comorbidity Index	1.6 (1.6)
GRACE Risk Score	89.2 (28.7)
Depression[*] (%)	34.4
Physical Health-Related Quality of Life	39.0 (10.7)
Mental Health-Related Quality of Life	53.4 (10.8)
Accelerometer Characteristics	
Wear Time (mins/day)	1171.5 (230.7)
Valid Wear Days	20.0 (7.6)
Total Sedentary Time (mins/day)	594.0 (126.0)
Total MVPA Minutes (mins/day)	49.4 (44.8)
MVPA Bout Minutes (mins/day)	14.9 (21.1)

Values presented as mean (SD) or %. CVD (cardiovascular disease), eGFR (estimated glomerular filtration rate), GRACE (Global Registry for Acute Coronary Events), MVPA (moderate-to-vigorous physical activity), NSTEMI (non-ST segment elevation myocardial infarction), STEMI (ST segment elevation myocardial infarction). [*]Depression= Beck Depression Inventory score > 10.

Table 2. Unadjusted and adjusted hazard ratios and 95% CI for major adverse cardiac events and hospitalizations associated with mean sedentary time.

Variables	Unadjusted Model			Adjusted Model		
	HR	(95% CI)	*P-Value*	HR	(95% CI)	*P-Value*
MACE (number of events=40)						
Sedentary Time (mins/day)	1.07	(0.93 – 1.24)	0.34	0.98	(0.83 – 1.15)	0.79
Hospitalizations (number of events=142)						
Sedentary Time (mins/day)	1.07	(0.99 – 1.16)	0.08	1.03	(0.95 – 1.14)	0.49

Notes: CI (confidence interval), HR (hazard ratio), MACE (major adverse cardiac event). MACE model adjusted for Charlson Comorbidity Index and GRACE (Global Registry for Acute Coronary Events) risk score. Hospitalization model adjusted for sex, education, exercise participation pre-event, estimated glomerular filtration rate less than 60 mL/ min/1.73 m^2, and Charlson Comorbidity Index.

Supplemental Material

Supplemental Figure 1. Consort of Accelerometer Device Return.

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                    ┌─────────────────────┐
                    │    930 eligible     │
                    │    participants     │
                    └──────────┬──────────┘
                               │           ──────►  264 declined to participate
                    ┌──────────▼──────────┐
                    │   666 participants  │
                    │      agreed to      │
                    │     participate     │
                    └──────────┬──────────┘
                               │           ──────►  46 unable to schedule
                    ┌──────────▼──────────┐
                    │   620 participants  │
                    │    given a device   │
                    └──────────┬──────────┘
                               │           ──────►  181 devices lost/not returned
                    ┌──────────▼──────────┐
                    │   439 participants  │
                    │    returned device  │
                    └──────────┬──────────┘
                               │           ──────►  8 devices never used
                    ┌──────────▼──────────┐
                    │   431 participants  │
                    │    returned device  │
                    │      with data      │
                    └──────────┬──────────┘
                               │           ──────►  108 with < 3 valid wear
                    ┌──────────▼──────────┐          days/week over post-discharge
                    │   323 participants  │          period
                    │     returned with   │
                    │    valid wear days  │
                    └─────────────────────┘
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Supplemental Table 1. Characteristics of participants included vs. excluded from the primary analytic sample who consented to participate in the ancillary physical activity study.

Participant Characteristics	Included (n=323)	Excluded (n=297)	*P-Value*
Sociodemographics			
Age (yrs)	62.9 (10.9)	63.7 (12.2)	0.40
Male (%)	68.7	62.6	0.11
Black Race (%)	20.0	24.6	0.17
Hispanic Ethnicity (%)	39.3	34.7	0.23
Education ≤ High School Graduation (%)	45.2	52.86	0.06
Partner/Spouse (%)	57.9	54.7	0.43
Medicaid (%)	32.6	32.4	0.96
Hospitalization			
Acute Coronary Syndrome Type			0.76
Unstable Angina (%)	53.6	54.2	
NSTEMI (%)	31.3	32.7	
STEMI (%)	15.2	13.1	
Length of Hospital Stay > 4 days (%)	31.3	42.4	<0.01
Percutaneous Coronary Intervention (%)	79.3	77.4	0.58
Coronary Artery Bypass Graft Surgery (%)	8.4	11.8	0.16
Physical & Psychosocial			
Exercise Participation Pre-ACS event (%)	46.7	41.8	0.17
Cardiac Rehabilitation Post-ACS event (%)	12.7	11.8	0.73
Current Smoker (%)	13.3	16.5	0.27
Body Mass Index (kg/m^2)	29.0 (5.5)	29.2 (5.8)	0.68
Left Ventricular Ejection Fraction < 40% (%)	14.9	12.5	0.38
Hypertension (%)	77.4	81.1	0.25
Dyslipidemia (%)	63.2	61.6	0.69
eGFR < 60 mL/min/1.73 m^2 (%)	22.5	23.5	0.78
CVD History (%)	33.7	33.8	0.50
Charlson Comorbidity Index	1.6 (1.6)	1.6 (1.7)	0.76
GRACE Risk Score	89.2 (28.7)	92.5 (31.3)	0.16
Depression[*] (%)	34.4	31.3	0.42
Physical Health-Related Quality of Life	39.0 (10.7)	37.6 (11.3)	0.11
Mental Health-Related Quality of Life	53.4 (10.8)	54.1 (10.5)	0.39

Values presented as mean (SD) or %. CVD (cardiovascular disease), eGFR (estimated glomerular filtration rate), GRACE (Global Registry for Acute Coronary Events), NSTEMI (non-ST segment elevation myocardial infarction), STEMI (ST segment elevation myocardial infarction). [*]Depression= Beck Depression Inventory score > 10.
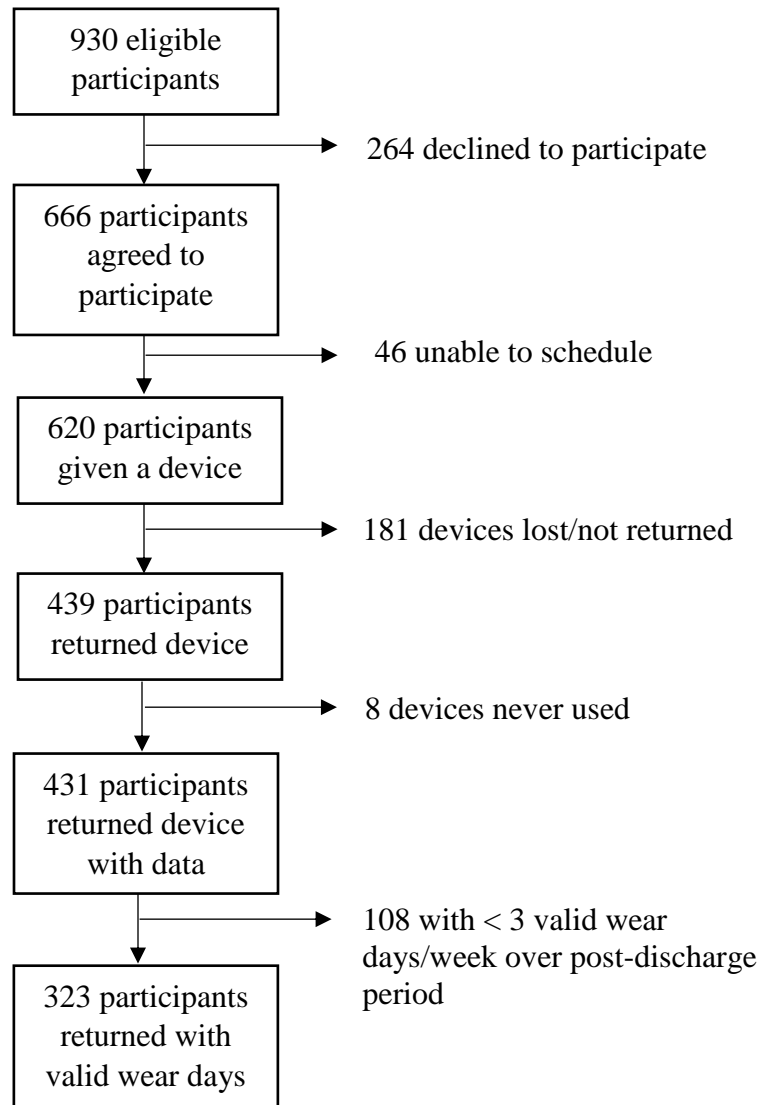
Supplemental Table 2. Unadjusted and adjusted hazard ratios and 95% CI for MACE associated with mean sedentary time in three separate sensitivity analyses classifying sedentary time: 1) using a 200 count per minute threshold (Upper Panel); 2) when restricting wear time from 8am to 8pm (Middle Panel); and 3) when restricting for valid wear time on ≥3 days/week over the 28 day post-disccharge period (Lower Panel).

Variables	Unadjusted Model			Adjusted Model		
	HR	(95% CI)	*P-Value*	HR	(95% CI)	*P-Value*
Sensitivity Analysis #1[*]						
Sedentary Time (mins/day)	1.09	(0.93 – 1.28)	0.31	0.96	(0.80 – 1.16)	0.70
Sensitivity Analysis #2[*]						
Sedentary Time (mins/day)	1.09	(0.88 – 1.34)	0.45	0.98	(0.77 – 1.24)	0.87
Sensitivity Analysis #3[†]						
Sedentary Time (mins/day)	1.19	(0.95 – 1.49)	0.13	1.08	(0.83 – 1.39)	0.58

Notes: CI (confidence interval), HR (hazard ratio), MACE (major adverse cardiac event). Models adjusted for Charlson Comorbidity Index and GRACE (Global Registry for Acute Coronary Events) risk score.
[*]Number of events=40; n=323
[†]Number of events=17; n=172

Supplemental Table 3. Unadjusted and adjusted hazard ratios and 95% CI for hospitalizations associated with mean sedentary time in three separate sensitivity analyses classifying sedentary time: 1) using a 200 count per minute threshold (Upper Panel); 2) when restricting wear time from 8am to 8pm (Middle Panel); and 3) when restricting for valid wear time on ≥3 days/week over the 28 day post-discharge period (Lower Panel).

Variables	**Unadjusted Model**			**Adjusted Model**		
	HR	(95% CI)	*P-Value*	HR	(95% CI)	*P-Value*
Sensitivity Analysis #1[*]						
Sedentary Time (mins/day)	1.11	(1.02 – 1.21)	0.02	1.05	(0.96 – 1.15)	0.27
Sensitivity Analysis #2[*]						
Sedentary Time (mins/day)	1.05	(0.94 – 1.18)	0.36	1.00	(0.89 – 1.13)	0.95
Sensitivity Analysis #3[†]						
Sedentary Time (mins/day)	1.07	(0.94 – 1.21)	0.31	1.02	(0.91 – 1.16)	0.72

Notes: CI (confidence interval), HR (hazard ratio). Models adjusted for sex, education, exercise participation pre-event, estimated glomerular filtration rate less than 60 mL/ min/1.73 m^2, and Charlson Comorbidity Index.
[*]Number of events=142; n=316
[†]Number of events=60; n=166

CHAPTER V

Conclusion

The goal of this dissertation series was to provide a foundation of empirical evidence to describe sedentary behavior and its associations with cardiovascular disease (CVD) biomarkers and outcomes, and to explore the potential that reducing sedentary behavior may be a secondary prevention target for Acute Coronary Syndrome (ACS) survivors. Accordingly, three separate cross-sectional studies were conducted that focused on 1) endothelial dysfunction as a potential underlying mechanism that links sedentary behavior to CVD mechanisms; 2) the characterization of sedentary behavior in ACS survivors during the first month post-hospital discharge; and 3) sedentary behavior as a prognostic risk factor for increased risk of 1-year health outcomes in ACS survivors. Study one found that free-living, habitual sedentary behavior was not associated with markers of endothelial function, including endothelial-dependent vasodilation, circulating levels of endothelial microparticles, and circulating levels of endothelial progenitor cells, in a cohort of healthy adults. Study two revealed that ACS patients, as a group, engaged in high volumes of accelerometer-measured sedentary time, with patients exhibiting either gradual or rapid reductions in sedentary behavior over the first month post-discharge. Study three demonstrated that sedentary time over the first month post-hospital discharge, on average, was not significantly associated with increased risk of 1-year recurrent major adverse cardiovascular events or recurrent hospitalizations. Collectively, this dissertation series on sedentary behavior and CVD provides empirical evidence that 1) habitual sedentary behavior is not associated with endothelial dysfunction in young adults; 2) ACS survivors engage in high volumes of sedentary behavior, with three identified patterns of either gradual or rapid reductions in sedentary behavior during the first month post-hospital discharge; and 3) sedentary time during the first month post-hospital discharge may not be associated with 1-year health outcomes in ACS survivors. Overall, these findings

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suggest that sedentary behavior is prevalent in ACS survivors, albeit future work is needed to unveil whether sedentary behavior may be a viable secondary prevention target for ACS survivors.

Several limitations should be taken into consideration when interpreting the results of the current dissertation series. First, study one included a sample of young, healthy, and active adults, wherein detectable endothelial dysfunction or subclinical atherosclerosis may not have been present. Second, study one participants accumulated, on average, high levels of MVPA (i.e., 64.5 ± 28.0 min/day of MVPA), which may have moderated the adverse effects of sedentary behavior (Ekelund et al., 2016). For instance, a meta-analysis demonstrated that the association between daily sedentary behavior and all-cause mortality was considerably reduced at higher levels of physical activity, while eliminated in adults who were most active (e.g., 60-75 min/day of MVPA). Moreover, high levels of physical activity may elicit protective effects against sitting-induced endothelial dysfunction, as regular exercise training is antiatherogenic (Szostak & Laurant, 2011) and reduces oxidative stress through upregulation of antioxidants, such as superoxide dismutase (Fukai et al., 2000; Miyazaki et al., 2001; Ross, Malone, & Florida-James, 2016). Third, study two and three included a sample of ACS survivors that received care from a major tertiary care academic medical center, wherein standards of care may be more comprehensive and follow current clinical recommendations relative to other hospital profiles in the United States (e.g., minor teaching, community, federal government, etc.). Therefore, results from study two and three may not be generalizable to the overall ACS population receiving care in the United States. Considering existing limitations, future work is warranted to expand the applicability and breadth of the preliminary evidence presented in the current dissertation series.

Significance

Secondary prevention is essential to the management of care for ACS survivors, wherein successive cardiovascular morbidity and mortality can be reduced by a comprehensive approach to positively modify patients' risk profiles (Amsterdam et al., 2014; Smith et al., 2011). Strong evidence exists on the cardiovascular protective effects stimulated by physical activity in secondary prevention, such as reducing the impact of disease, slowing its progress, reducing CVD risk factors, and preventing recurrence (Alves et al., 2016). However, little is known about the adverse effects elicited by sedentary behavior among ACS survivors. Other studies in general populations and in other clinical populations suggest that targeting sedentary behavior may be another modifiable risk factor that may attenuate risks in ACS survivors. This may be particularly important to target, because few patients meet recommended physical activity targets or attend cardiac rehabilitation. The studies included in this dissertation series fill this important gap in the literature by exploring the mechanisms, patterns, and correlates of sedentary behavior in relation to CVD risks, as well as uncovering whether sedentary behavior is linked to health outcomes in ACS survivors. As such, the findings from this dissertation series impart meaningful insight because they:

1) suggest that physiological mechanisms other than endothelial dysfunction (e.g., glucose and lipid metabolism) may need to be explored as a potential link between habitual prolonged sedentary time and CVD in younger adults,

2) established that high volumes of sedentary behavior were prevalent in ACS survivors as they recover and resume daily activities over the first month following hospital discharge,

3) suggest that greater disease severity, lower physical health quality of life, and not having a partner may be important factors affecting sedentary behavior,

4) provided empirical evidence that sedentary behavior during the first month after hospitalization might not be a prognostic risk factor of 1-year CVD outcomes and hospitalizations in ACS survivors.

Overall, the findings unveiled from this dissertation provide a preliminary foundation for understanding the implications of sedentary behavior as a potential secondary prevention target in ACS survivors. Although our findings suggest that sedentary behavior may not be a secondary prevention target for reducing CVD risks in ACS survivors, future research in larger prospective cohorts is needed to confirm and extend the findings of this dissertation series.

Future Directions

- Future work is needed to elicit the underlying biological mechanisms through which habitual sedentary behavior confers CVD risk.

  Rationale: Understanding the biological mechanisms that underlie the associations between sedentary behavior and adverse health outcomes in the general population and in people with CVD is necessary to determine the causal nature of these relationships. Identifying the pathways that link sedentary behavior to CVD can inform primary and secondary prevention strategies on how to mitigate CVD risk. Based on existing evidence in the general adult population, future studies should explore impaired glucose regulation and dyslipidemia as potential pathways wherein habitual sedentary behavior.

- Future studies are needed to elucidate why ACS patients exhibit high levels of sedentary time post-hospital discharge, especially among those that show minimal reductions over time.

Rationale: Most ACS survivors in this dissertation exhibited high volumes of sedentary behavior throughout the first month post-discharge, but the reasons for this are unknown. Therefore, it's essential to understand why patients are sedentary during this post-discharge period, and to allow for identification of ways that prolonged sedentary time may be reduced.

- Future studies using prospective cohorts with larger sample sizes are needed to determine whether sedentary behavior during the early recovery period and longer periods of time is an independent risk factor that may be modified for secondary prevention in ACS survivors.

  Rationale: Evidence on the prospective associations between sedentary behavior and health outcomes in ACS survivors is limited, as this dissertation is the first to report on these associations. However, the current study included a small sample size and low event rate. More research on the prognostic utility of sedentary behavior at various time points post-discharge period can help confirm whether sedentary behavior is an important secondary prevention target for ACS survivors.

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APPENDIX A

Literature Review

Acute Coronary Syndrome

Epidemiology

Acute coronary syndrome (ACS), characterized by unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI), is among the top causes of death in the modern, industrialized world (Fuster & Kovacic, 2014). More than 1.1 million patients are hospitalized annually for ACS in the United States alone (Mozaffarian et al., 2015). Most patients hospitalized with an ACS survive, however they remain at high risk for recurrent cardiac events and mortality (Menzin, Wygant, Hauch, Jackel, & Friedman, 2008); highlighting the need to optimize secondary prevention strategies to increase survival and reduce recurrent events among ACS survivors.

ACS presentation usually occurs in the sixth decade of life, with a median ACS presentation age of 68 years (interquartile range: 56 – 79) and a 3:2 male-to-female ratio in the United States (Amsterdam et al., 2014; Bob-Manuel, Ifedili, Reed, Ibebuogu, & Khouzam, 2017; Mozaffarian et al., 2015). It is estimated that more than 780,000 persons will experience an ACS each year in the United States, with approximately three-fourths of these patients presenting with NSTEMI (Amsterdam et al., 2014; Mozaffarian et al., 2015). Despite improvements in acute care, 21% of ACS survivors will be re-hospitalized and ~1 in 5 will die within 1 year post-hospitalization (Menzin et al., 2008). Approximately $8 billion is spent annually on the care and management of ACS in the United States, with approximately $22,500 to $32,400 spent on one ACS patient over the course of a year (Hedayati, Yadav, & Khanagavi, 2018; Xiao, 2017). The high economic burden is primarily due to the cost of re-hospitalizations and prolonged length of hospital stays.

Given its high prevalence, morbidity, mortality, and economic burden, ACS is considered the most serious among the coronary artery diseases to address from a public health perspective.

Etiology and Pathophysiology

Among the ACS categories, UA and NSTEMI are similar conditions that occur when there is subtotal occlusion of the vessel, while STEMI occurs when there is complete occlusion of the vessel leading to myocardial injury and necrosis (Hedayati et al., 2018; Wright et al., 2011). UA and NSTEMI are strongly connected conditions with similar pathogenesis and clinical presentations, but the conditions differ in gravity (Amsterdam et al., 2014; Hedayati et al., 2018); such that UA does not result in detectable quantities of myocardial injury biomarkers (i.e., troponin), while NSTEMI does present such biomarkers (Mozaffarian et al., 2015; Wright et al., 2011). As such, the recent American College of Cardiology/American Heart Association guidelines constitute UA and NSTEMI as NSTE-ACS (Amsterdam et al., 2014), which accounts for approximately two-thirds of all hospital admissions for ACS in the United States each year.

The development of ACS can be attributed to numerous factors, such as genetics, environment, psychosocial stressors, obesity, cardiometabolic diseases, smoking and physical inactivity (Bob-Manuel et al., 2017; Crea & Liuzzo, 2013). The underlying pathology of ACS is the sudden mismatch between myocardial oxygen consumption and demand, which is commonly caused by coronary artery obstruction due to the rupture and thrombosis of an atherosclerotic plaque in the coronary arteries (Amsterdam et al., 2014; Hedayati et al., 2018; Wright et al., 2011). In 1985, M.J. Davies was the first to propose that plaque rupture (also referred to as fissure) was the link between atherosclerosis and thrombosis. In 1994, Liuzzo and colleagues found that patients with ACS and high levels of C-Reactive Protein had a worse outcome than patients with normal levels of CRP, suggesting that plaque inflammation was responsible for plaque fissure.

More recently, a handful of review articles have been published to elucidate different pathological pathways to ACS. After reviewing postmortem and *in vivo* studies using intravascular imaging, Crea & Libby published a review in 2017 suggesting 4 pathological pathways to ACS: plaque rupture with systemic inflammation (macrophage rich lesions, "red" thrombus, systemic inflammation), plaque rupture without systemic inflammation (low systemic inflammation), plaque erosion (no fissure/rupture, "white" thrombus, neutrophils), and plaque without thrombosis (epicardial or microvascular spasm). Other causes of ACS exist, such as coronary embolism and coronary arteritis; noncoronary causes of myocardial oxygen supply-demand mismatch (i.e. hypotension, severe anemia, etc.); and non-ischemic myocardial injury (Amsterdam et al., 2014). Superficial erosion of the intima can also precipitate ACS, but this mechanism has a less clear relationship with inflammation (Libby et al., 2014, Wright et al., 2011). The most common pathophysiology leading to ACS (i.e., 60-80% of cases) is coronary artery obstruction via plaque rupture, which will be the primary pathophysiological pathway discussed in this response.

Endothelial dysfunction and arterial inflammation are the primary components in the pathogenesis of ACS, as they each contribute to the atherogenic process (i.e., atherosclerotic lesions, plaque formation and rupture) (Amsterdam et al., 2014; Hedayati et al., 2018; Wright et al., 2011). Atherosclerosis is a maladaptive, non-resolving chronic inflammatory disease in which plaque forms and accumulates within the arterial walls from as early as childhood. Atherosclerotic plaques primarily form at sites of low endothelial shear stress, such as the coronary arteries (Bob-Manuel et al., 2017; R. Ross, 1993), whereas regions of high endothelial shear stress are generally protected. Atherosclerotic lesions and plaque formation, also known as 'fatty streaks,' results from a buildup of oxidized low-density lipoprotein (LDL) cholesterol in the tunic intima, which causes injury to the endothelium and underlying smooth muscle (R. Ross, 1993). The accrual of oxidized

LDL elicits the expression of adhesion molecules and growth factors from smooth and endothelial cells, which eventually triggers an inflammatory cascade towards plaque instability and rupture.

Impairments in endothelial function precede the development of atherosclerosis and contributes to the configuration, progression and adverse complications of atherosclerotic plaque (Barac, Campia, & Panza, 2007; R. Ross, 1993). Endothelial cells form a single-cell lining covering the internal walls of blood vessels throughout the entire vascular system, also known as the endothelium (Alberts et al., 2002; Della Corte et al., 2016). The endothelium is recognized as the key regulator of vascular wall homeostasis due to its critical role in preserving vascular tone, vascular permeability to plasma elements, platelet and leukocyte adhesion and aggregation, and thrombosis (Alberts et al., 2002; Barac et al., 2007; Poredos & Jezovnik, 2013). Endothelial dysfunction is a pathophysiological condition characterized by a dysregulation of homeostatic mechanisms necessary to maintain healthy endothelium. Endothelial dysfunction is associated with abnormal modulation of vascular tone, platelet activation, leukocyte adherence, increased oxidative stress, and vascular inflammation; each of which can lead to the migration and proliferation of smooth cells and lipid-containing macrophages called foam cells (Barac et al. 2007, Della Corte et al., 2016). Eventually, the lesions of atherosclerosis will enlarge, and trigger continued activation of arterial inflammation. Thus, endothelial dysfunction seems to be a systemic vascular process that not only facilitates the development of the atherosclerotic plaque, but may modulate its clinical course as well.

Arterial inflammation is the most common underlying molecular and cellular pathophysiology of disturbed atherosclerotic plaque (Wright et al., 2011). Distinct features of atherosclerotic plaques that predispose to ACS include a thin fibrous cap, a large assortment of macrophages, a big lipid (necrotic) core, spotty calcification and expansive remodeling (Falk &

Virmani). Both innate and adaptive immunity play a key role in the formation and rupture of these vulnerable plaques (Crea & Liuzzo, 2013; Libby, 2001; Libby, Tabas, Fredman, & Fisher, 2014). Regarding innate immunity, macrophages likely pave the way for the rupture of the fibrous cap of the plaque, as well as contributes to the necrotic core of the plaque. For instance, when macrophages are activated, they release enzymes (i.e., matrix metalloproteinases and cathepins) that degrade all components of the arterial extracellular matrix (Crea & Libby, 2017). When macrophages undergo apoptosis, they can lead to plaque necrosis by defective phagocytic clearance of the apoptotic cells or primary necrosis (Hansson, Libby, & Tabas, 2015). Moreover, mast cells infiltrate the advanced atherosclerotic plaque and, when activated, release a host of mediators and enzymes (i.e., histamine, serotonin, etc.), cytokines and a set or serine proteases, all of which exacerbates the inflammation in the atherosclerotic lesion. Adaptive immunity also plays a role in coronary plaque instability, such that subsets of T lymphocytes (major participants in adaptive immunity) can either promote local plaque formation (effector T cells) or suppress inflammation (regulatory T cells). Ultimately, the effector: regulatory T-cell balance promotes progressive inflammation (Hansson et al., 2015). This inflammatory milieu can lead to the loss of mechanical stability, primarily due to the diminished tensile strength of the collagen cap surrounding the plaque, and ultimately lead to plaque rupture (Crea & Liuzzo, 2013; Hansson et al., 2015; Libby, 2001; Libby et al., 2014). However, it should be noted that inflammation may not drive all transition from stable atherosclerosis to acute thrombotic events, such that coronary artery thrombosis caused by plaque rupture can occur with or without concomitant inflammation (Crea & Libby, 2017). Plaque rupture that occurs in the absence of systemic inflammation may be a result of psychological stress or extreme emotional disturbance. Another possibility is that cholesterol crystals (created when macrophage foam cells die) may activate local innate immune

pathways within the atherosclerotic plaque. More research is needed to clarify the molecular mechanisms leading to coronary instability in ACS patients without systemic inflammation.

When the fibrous cap of the plaque cannot withstand the mechanical force of blood pressure, superficial fissures are formed in the cap. Upon rupture, components of the thrombogenic necrotic core (i.e., phospholipids, tissue factor and matrix molecules) are exposed to the blood, activating platelet receptors and coagulation factors that ultimately lead to the formation of a thrombus (Badimon & Vilahur, 2014; Santos-Gallego, Picatoste, & Badimon, 2014). The thrombus expands rapidly and can fill the lumen within minutes, resulting in an abrupt coronary artery obstruction and sudden mismatch between myocardial oxygen consumption and demand. The thrombus may occlude the artery at the site of plaque rupture or detach from the site of plaque rupture as an embolus and occlude the arterial lumen downstream. However, it's important to differentiate the degree of occlusion in STEMI vs. NSTE-ACS, such that occlusion is complete and prolonged in STEMI and transient and partial in NSTE-ACS.

The precipitation of the thrombotic event is likely due to the imbalance between prothrombotic and fibrinolytic activity on the plaque surface, as well as the fluid phase of blood. Rudolf Virchow was the first to recognize that thrombi precipitate on damaged vascular surfaces. Innate immunity plays a vital role in thrombosis, such that proinflammatory cytokines are stored in the alpha-granules of platelets and favor formation of thrombus on the atheroma plaque, as well as induce endothelial cell apoptosis. In response to inflammation, both the solid state of plaque and fluid phase of blood unite to promote thrombus accumulation by increased thrombogenicity, decreased anti-coagulant properties, and impaired fibrinolytic activity, However, the detailed series of events that operate in vivo has yet to be elucidated (Hansson et al., 2015).

Signs & Symptoms

Early detection of symptoms of ACS and risk stratification is important, such that expedited and accurate diagnosis is essential to reduce the high mortality and morbidity associated with ACS. Symptoms of ACS can be categorized as "typical" or "atypical," with atypical symptoms more prevalent in women, older adults ($\geq$ 75 years of age), patients with diabetes mellitus, impaired renal function, and dementia (Amsterdam et al., 2014; Hedayati et al., 2018; Wright et al., 2011). Typical symptoms include pressure-type chest pain that usually occurs at rest or with minimal exertion persisting for at least ten minutes (Amsterdam et al., 2014; Wright et al., 2011). Pain or discomfort typically starts in the substernal location and can radiate to the neck, jaw epigastrium or arms, often described as "squeezing," 'griplike," "pressurelike," "suffocating," or "heavy" (Hedayati et al., 2018). Atypical symptoms include pleuritic pain, abdominal discomfort, pain that radiates into the lower extremities, among others. Other atypical signs and symptoms with or without chest pain include dyspnea, indigestion, syncope, diaphoresis, and unexplained fatigue (Amsterdam et al., 2014; Hedayati et al., 2018). Once a patient's symptoms are suspected to be representative of ACS, a clincal history, physical examination, electrocardiogram (ECG) and biomarkers of myocardial necrosis must be evaluated for proper risk stratification and diagnosis (Amsterdam et al., 2014; Wright et al., 2011).

Treatment & Management Recommendations

Standard of care for patients that present with ACS include supplemental oxygen, antianginal, antiplatelet, and anticoagulation therapy; which are further managed with either an early-invasive strategy or ischemia-guided strategy (Amsterdam et al., 2014; Bob-Manuel et al., 2017). If therapy is ineffective, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) may be performed, with the latter resulting in a longer hospital stay (Amsterdam et al., 2014). After patients have been sufficiently treated in an inpatient setting, they

are discharged and provided with secondary prevention strategies to reduce symptoms, re-hospitalization and mortality (Amsterdam et al., 2014).

Current post-ACS treatment includes long-term medical therapy and secondary prevention strategies (Wright et al., 2011). Long-term medical therapy is beyond the scope of the current review but can be found in the ACC/AHA Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes (Amsterdam et al., 2014). Current ACC/AHA Class I secondary prevention strategies include cardiac rehabilitation (CR) and physical activity (PA) for patients with a recent ACS event (Kronish, Diaz, Goldsmith, Moise, & Schwartz, 2017; Wright et al., 2011). Outpatient CR services are delivered to patients within the first 3 to 6 months after a cardiovascular event (Thomas et al., 2007). A primary goal of outpatient CR programs is to develop and assist ACS survivors implement a safe and effective formal exercise and lifestyle PA program (American College of Sports, Riebe, Ehrman, Liguori, & Magal, 2018).

Benefits of Habitual Physical Activity & Exercise for ACS Survivors

Increasing levels of habitual PA is an important goal for CR programs, such that regular PA has been linked with a decreased severity of ACS, reduced in-hospital mortality rates, and improved short-term prognosis (Pitsavos et al., 2008). Regular PA can improve exercise capacity, reduce physical and depressive symptoms of ACS, enhance functional capacity, aid in weight loss and maintenance, and help improve risk factors such as hypertension, hyperlipidemia and glucose metabolism (Thompson et al., 2003). Underlying mechanisms in which PA confers its benefits are through favorable adaptations in the vasculature, systemic oxidative stress and inflammation, and morphological adaptations of the Left and Right ventricle which can improve cardiac output and exercise capacity (Lavie et al., 2015; Xiao, 2017); each of which target the pathophysiology of ACS.

When addressing the benefits of PA, it's important to note that PA and exercise are different. PA is considered any bodily movement generated by skeletal muscle contraction that leads to a rise in caloric requirements greater than resting energy expenditure (Caspersen, Powell, & Christenson, 1985). Exercise, on the other hand, is a type of PA involving planned, structured and repetitive bodily movement performed with the goal to maintain or improve one's physical fitness (Caspersen et al., 1985). ACS survivors can benefit from both PA and exercise, but most health benefits are elicited through chronic exercise training; hence the benefits seen with exercise-based CR programs (Anderson et al., 2016). For instance, increases of 10% to 60% in functional capacity and decreases of 10% to 25% in myocardial oxygen requirements have been observed after 12 weeks of exercise-based CR post-hospitalization (Williams, 2001; Williams et al., 2002). Additionally, chronic aerobic exercise training can improve endothelial function, ventricular function and attenuate ventricular remodeling (Xiao, 2017). Despite the well-established and overwhelming benefits of exercise-based CR, patient compliance within the programs is challenging due to logistical and monitoring abilities such as age, gender, socioeconomic status, travel distance and other comorbidities (Corra et al., 2010). Thus, there is a need to identify novel modifiable risk factors for intervention to increase survival and reduce recurrent events among ACS patients, one of which may be sedentary behavior.

Sedentary Behavior

Technological advancements in transportation, communication, the workplace and domestic-entertainment have cultivated occupational, home and social environments that oblige or promote sedentary behavior (Brownson, Boehmer, & Luke, 2005; Owen, 2012). As a result, time spent in sedentary behavior has continued to increase and physical activity levels have continued to decline over the past 50 years in the United States (Ng & Popkin, 2012). U.S. adults

now spend an alarming 9 to 10 hours per day in sedentary behavior, including sitting, TV viewing, screen time, and computer use (Dunstan, Howard, Healy, & Owen, 2012). Moreover, population-based studies demonstrate that that average U.S. adult spends more than half of his or her day in sedentary behaviors (i.e., 51-68% of adults' total waking hours are spent sedentary) (Dunstan, Howard, et al., 2012; Owen, Sparling, Healy, Dunstan, & Matthews, 2010). Accordingly, the expression "sitting is the new smoking" has been coined to describe the current epidemic of sedentary behavior within industrialized nations (Yeager S., 2016, Sturt & Nordstrom, 2016, Gerstacker D., 2016).

Sedentary behavior (e.g., watching TV, computer use, etc.) has emerged as a distinct cardiovascular disease (CVD) risk factor that may carry clinical relevance beyond how much one exercises (Roger et al., 2011; World Health Organization, 2009). Accumulating evidence from population-based studies indicate that sedentary behavior is associated with CVD morbidity and mortality, and CVD risk factors, such as insulin resistance (Wilmot et al., 2012). Notably, the deleterious effects of sedentary behavior are eliminated only by high levels of moderate-to-vigorous physical activity (MVPA) (~60 to 75 min/d), which exceed physical activity recommendations. This raises the question as to whether reducing sedentary behavior may represent another therapeutic target for secondary prevention and rehabilitation of ACS survivors, in addition to existing MVPA recommendations. The following sections will review critical aspects necessary to understand the public health significance of sedentary behavior, as well as the physiological responses of sedentary behavior that confer cardiovascular disease risk.

Sedentary Behavior Characterization

When deciding how to address the problem of too much sitting, it's important to establish a standardized definition of sedentary behavior, which can improve between-study comparisons

and distinction between sedentary behavior and physical inactivity. The word 'sedentary' originates from the Latin origin 'sedere' – to sit, highlighting the importance of position or posture when defining sedentary behaviors. As such, sedentary behaviors are defined by both their posture and their low energy expenditure (Dunstan, Howard, et al., 2012). According to the Sedentary Behavior Research Network, sedentary behavior is defined as any waking behavior with an energy expenditure less than or equal to 1.5 times the resting metabolic rate while in a sitting or reclining posture (Chastin et al., 2016; Gibbs, Hergenroeder, Katzmarzyk, Lee, & Jakicic, 2015). Sedentary behavior includes activities such as sitting, watching TV, computer use, reading, driving, among other activities (Endorsed by The Obesity et al., 2016). In contrast, physical inactivity represents the lack of meeting the physical activity guidelines (i.e. $\geq$ 150 minutes/week of moderate- to vigorous-intensity physical activity)(Garber et al., 2011). This differentiation is important because current strategies exist to reduce physical inactivity via physical activity promotion, while a dearth of sedentary reduction strategies in health and wellness programs exist. Although the appropriate definition of sedentary behavior should be applied when developing methods for accelerometry processing, it's important to note that definition of sedentary behavior was not standardized until 2012. Thus, there is a wide range of assessment and analysis of sedentary behavior in the existing sedentary behavior literature.

In order to measure the exposure to sedentary behaviors in epidemiological studies, one must decide which aspect of sedentary behavior is needed, such as total sedentary time, episodes of sedentary time, or a specific domain of sedentary behavior (e.g., work, transport, leisure, etc.). Accurate measurement is necessary to characterize patterns of, as well as changes in, sedentary behavior within and between individuals overtime. Accordingly, assessment methods that can reliably and accurately measure the frequency, duration, and volume of the sedentary behavior

exposure while abating bias should be selected. Additionally, researchers should make efforts to minimize the potential for bias due to measurement errors, whether systematic (differential) or random (non-differential) in nature.

Sedentary Behavior Measurement

Numerous studies have measured sedentary behavior utilizing different assessment tools and methodology. Among these assessment tools are questionnaire and surveys, self-recorded diaries, pedometers, actometers, accelerometers, and inclinometers (Atkin et al., 2012). Prior to the development of microelectronic technologies (i.e., accelerometers), most epidemiological studies in the United States relied on subjective methods (i.e., questionnaires and surveys) to measure estimates of time spent in sedentary behaviors. However, subjective methods used to measure sedentary behavior provides a narrow scope of overall levels of sedentary behavior accumulated in a typical waking day (Matthews et al., 2008). Moreover, self-report methods are prone to systematic errors through an incorrect classification of sedentary behaviors from a scoring perspective or inability of participants to accurately recall and estimate their sedentary time.

Given the errors accompanied with self-report methods, the ideal measure of sedentary time would encompass the following: 1) accurate and reliable measurements across different population groups; 2) classify among sleep, reclining, sitting and standing; 3) differentiate among distinct domains and specific behaviors; 4) entail minimal cost and low participant burden; 5) ability to be worn continuously for extended periods of time; 6) produce data that can be provided in real-time that are easily analyzed and interpreted (Healy, Clark, et al., 2011). As such, a mix of subjective and objects measurements of sedentary behavior are essential to understand sedentary behavior epidemiology (Atkin et al., 2012). Thus, below is a brief overview of subjective and objective methods of sedentary behavior measurement.

Subjective Methods of Sedentary Behavior Measurement

Subjective measurements of sedentary behavior conventionally include questionnaires to provide a self-reported description of sedentary behaviors and to quantify the total time spent in sedentary behaviors as categorized by posture and energy expenditure (Ainsworth, Rivière, & Florez-Pregonero, 2018). Subjective methods include self-report questionnaires, proxy-report questionnaires, diaries, and ecological momentary assessment (EMA). Among the available subjective methods, the most commonly reported method used is questionnaires, the majority of which are self-administered and contain items that primarily focus on TV viewing and other screen-based behaviors (e.g., computer use) (Clark et al., 2009). A narrative review by Atkin and colleagues (2012) demonstrated that subjective methods demonstrate moderate reliability and slight to moderate validity, with questionnaires being the most popular method because of their low cost and ease of use. Global questionnaires (i.e., short [1-3 items] population health surveys) and quantitative recall questionnaires (e.g., Sedentary Behavior Questionnaire [SBQ]; Last 7-day Sedentary Time Questionnaire [SIT-Q-7d]) are the two types of questionnaires employed in sedentary behavior research and are often tailored for use by settings (e.g., population and intervention studies) and by the types of information obtained (e.g., impressions of sedentary behavior or time spent in specific sedentary behaviors) (Ainsworth et al., 2018). Generally, global questionnaires aim to categorize an individual's sedentary behavior level, while quantitative recall questionnaires intend to capture the frequency, duration, mode and types of sedentary behaviors. Regardless of type, questionnaires vary in their mode of administration (e.g., self-administered vs. interviewer-administered), content (e.g., domain, recall frame, frequency, duration, and interruption), and psychometric properties (e.g., validity, reliability and responsiveness), each of

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which should be taken into consideration when deciding which questionnaire should be employed for a specific study design and objectives (Atkin et al., 2012; Healy, Clark, et al., 2011).

Objective Methods of Sedentary Behavior Measurement

The insights into how most adults spend their day in sedentary time, as well as the proportion of their overall waking hours spent in sedentary time, can be attributed to the advancements in microelectronic technologies. Microelectronic technologies include the pedometer, accelerometers, and inclinometers, which have enabled objective (i.e., device-based) methods of sedentary behavior measurement (Ainsworth et al., 2018). Among the evolved microelectronic technologies, the accelerometer has become widely used in population-based studies due to its ability to objectively derive time spent in sedentary, light-, moderate-, and vigorous-intensity physical activity behaviors (Healy, Clark, et al., 2011). Accelerometers are small, lightweight, battery-operated devices that are commonly worn on the hip or wrist with an elastic belt and are either uniaxial (i.e., detect movement in the vertical plane) or tri-axial (i.e., detect movement in the vertical and horizontal planes). These electronic motion sensor devices measure the frequency and amplitude of the acceleration of the body segment to which the accelerometer is attached and combine this information into movement 'counts' (Chen & Bassett, 2005). Accordingly, accelerometer cutpoints have been proposed for defining sedentary time in adults, with <100 cpm being the most common cutpoint employed when using the ActiGraph™ (ActiGraph LLC, Pensacola, FL, USA) and Actical™ activity monitor (Mini-Mitter, Bend, OR, USA) (Atkin et al., 2012) worn on the hip. However, the ActiGraph™ and Actical™ accelerometer cannot distinguish between different postures (e.g. sitting, standing), which limits researchers' ability to adhere to the consensus sedentary behavior definition, which includes both intensity of activity (≤1.5 METS) and position (sitting or reclining) [48, 49]. Newer models of the ActiGraph™

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(GT3X and GT3X+) include an inclinometer function, which can improve the device's ability to distinguish between postures, albeit validity of this function is limited (Atkin et al., 2012).

The activPAL™ (V.3, PAL Technologies , Glasgow, UK) is a thigh-worn triaxial accelerometer and inclinometer that has been validated for determining step counts, physical activity, activity intensities, posture (sitting/lying, standing or stepping), and sedentary time in healthy adults (Godfrey, Culhane, & Lyons, 2007; Grant, Ryan, Tigbe, & Granat, 2006; Hart, McClain, & Tudor-Locke, 2011; Kozey-Keadle, Libertine, Lyden, Staudenmayer, & Freedson, 2011; Lyden, Keadle, Staudenmayer, & Freedson, 2017; Lyden, Kozey Keadle, Staudenmayer, & Freedson, 2012; Ryan, Grant, Tigbe, & Granat, 2006). This device is widely considered the gold-standard measure of sedentary behavior because it is extremely accurate ($\geq 96\%$) and is one of the only devices capable of distinguishing motionless standing from sedentary time, thus allowing us to adhere to the consensus sedentary behavior definition, which includes both intensity of activity (≤ 1.5 METS) and position (sitting or reclining) (Gibbs et al., 2015). However, it's important to note that the activPAL™ has not been used in population-based studies.

The GENEActiv™ is a small (36 mm x 30 mm x 12 mm), lightweight (16 g), waterproof, wrist-worn device that contains a near-body temperature sensor to determine wear and non-wear time. It has a storage capacity of 45 days at a sampling frequency of 10 Hz that permits capture of frequent changes in activity. The GENEActiv™ device has shown to be valid and reliable for objectively measuring sedentary time and physical activity, as well as distinguishing between sedentary (sitting/reclining) and non-sedentary posture (standing) (Esliger et al., 2011; Pavey, Gomersall, Clark, & Brown, 2016; Rowlands et al., 2014; Rowlands et al., 2016; H. Zhang, Chin, Ang, Guan, & Wang, 2011). The GENEActiv™ estimates a person's posture using the gravitational component of the acceleration signal from the wrist orientation of the monitor based

on the Euclidian norm minus one (ENMO) method (van Hees et al., 2013). Similar to the activPAL™, the GENEActiv™ has yet to be used as an objective method to measure sedentary time in population-based studies.

Among the available device-based measures of sedentary time available for use in epidemiological research, the ActiGraph™ is the most widely used accelerometer for adults and older adults to date (Healy, Clark, et al., 2011; Heesch, Hill, Aguilar-Farias, van Uffelen, & Pavey, 2018). In a small validation study by Matthews and colleagues (2008), the ActiGraph™ (<100 counts/minute) and the Intelligent Device for Energy Expenditure and Activity (IDEEA) detected similar amounts of time spent in sedentary behaviors (8.63 ± 1.90 hours/day vs. 8.53 ± 1.86 hours/day, respectively [p = 0.82]), and correlations between the measures were moderately high (ρ = 0.59, p < 0.01; unpublished observations) (K. Zhang, Werner, Sun, Pi-Sunyer, & Boozer, 2003). When compared to the activPAL™, recorded sedentary time was lower for the ActiGraph™ activity monitor (mean [SD]=8.7[1.6] hour/day vs. 9.0 [1.8] hours/day), but the correlation between the measures was relatively high (ρ=0.76, p < 0.01). However, Bland-Altman analysis revealed a small mean difference and wide 95% limits of agreement, suggesting that ActiGraph™ can substantially over- and under-estimate sedentary time compared with the activPAL™. Overall, when interpreting between-study differences in sedentary behavior, it's important to take into consideration the device, location of device (e.g., hip vs. wrist), sedentary count threshold, and non-wear threshold duration used in each study, as these factors have been reported to influence classification of sedentary time (Kozey-Keadle et al., 2011; Oliver, Badland, Schofield, & Shepherd, 2011; Paul, Kramer, Moshfegh, Baer, & Rumpler, 2007).

Sedentary Behavior Epidemiology

Sedentary behavior epidemiology is the population-level study of the distribution, determinants, and adverse health effects of sedentary behaviors, which can help guide future research efforts and intervention development. The current review of literature will focus on the sedentary behavior epidemiology in the United States, as the participants for each dissertation study resided in the United States. Prior to the development of microelectronic technologies (i.e., accelerometers), most epidemiological studies in the United States relied on subjective methods (i.e., questionnaires and surveys) to measure estimates of time spent in sedentary behaviors. However, subjective methods used to measure sedentary behavior provides a narrow scope of overall levels of sedentary behavior accumulated in a typical waking day (Matthews et al., 2008). Moreover, self-report methods are prone to systematic errors through an incorrect classification of sedentary behaviors from a scoring perspective or inability of participants to accurately recall and estimate their sedentary time. Thus, the current review will focus on epidemiological studies that employed accelerometer-derived measurements of sedentary behavior. However, it should not be ignored that self-reported measures of sedentary behavior are important to capture important domain- and behavior-specific sedentary time information in population-based studies, which have gravely contributed to our understating of sedentary behavior epidemiology (see previous section). The descriptive epidemiology of sedentary time in the U.S. as measured by self-report can be found in a review by Healy and colleagues (2011) titled "Measurements of Adults' Sedentary Time in Population-Based Studies" (Healy, Clark, et al., 2011).

Matthews and colleagues (2008) were the first to describe the objective measure of the amount of time spent in overall sedentary behaviors in the United States, by gender, age, and racial/ethnic group. These authors evaluated participants (n=6,392) from the 2003-2004 National Health and Nutrition Examination Survey (NHANES) aged ≥ 6 years who wore an ActiGraph™

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accelerometer for at least 10 hours/day on their right hip for 7 consecutive days (Matthews et al., 2008). Sedentary behavior was classified as the amount of time accumulated below 100 counts/minute during periods when the monitor was worn and expressed as a proportion of monitor-wearing time (percent) and as total duration (hours/day). Time spent in overall sedentary behaviors reflects the accumulation of time spent sitting, reclining or lying down across different sedentary behavior domains, such as at home, school, in transit and during leisure time. Findings demonstrated that participants spent 54.9% of their monitored time (i.e., 7.7 hours/day) in sedentary behaviors, with the most sedentary groups being older adolescents and adults aged ≥ 60 years. In regard to gender, females were found to be more sedentary than males before the age of 30 years, with the reverse of this pattern observed after the age of 60 years. Regarding racial/ethnic group, Mexican-American adults exhibited sedentary levels that were significantly less than other U.S. adults, while White and Black females demonstrated similar levels of sedentary behaviors after the age of 12 years.

Building off the initial findings from Matthews et al., Owens and colleagues wrote a commentary on sedentary behavior as a new health risk due to its omnipresence and high volume in developed nations (Owen et al., 2010). In this commentary, the authors reported on the 2003 to 2004 and 2005 to 2006 NHANES accelerometry data and showed the differences in time spent in light activity and exercise across quartiles of sedentary time (Centers for Disease Control and Prevention, 2009-2010). These data demonstrated that the lowest and highest quartile of sedentary time was 6.3 and 10.2 hours/day, respectively, with most of the variance in sedentary time attributed to the change in light-intensity activity. They also reported that 1 in 4 white U.S. adults spend approximately 70% of their waking hours sitting, 30% in light activities, and little or no

time in exercise. However, these analyses only focused on the total time spent sedentary (i.e., volume), while overlooking how sedentary time is accumulated throughout a waking day.

In 2008, Healy and colleagues pioneered, as well as provided evidence, for the concept that breaks (interruptions) in sedentary is important for metabolic health, highlighting the need to evaluate both the total volume and the pattern in which sedentary time is accumulated. This 'breaks' hypothesis was first explored among adults from the 2004 to 2005 Australian Diabetes, Obesity and Lifestyle Study (AusDiab) study, which demonstrated that adults whose sedentary time was accumulated in prolonged, uninterrupted periods had a poorer cardiometabolic health profile compared to those who frequently interrupted their sedentary time. Similarly, findings from the 2003 to 2004 and 2005 to 2006 population-representative U.S. National Health and Nutrition Examination Survey (NHANES) study found that total sedentary time was detrimentally associated with insulin, beta-cell function (HOMA-%B), and insulin sensitivity (HOMA-%S), while breaks in sedentary time were beneficially associated with fasting plasma glucose levels (Healy, Matthews, Dunstan, Winkler, & Owen, 2011). As such, studies in the past 10 years have begun to assess both total volume and patterns of sedentary behavior to elucidate how sedentary time is accumulated in the real world and whether sedentary patterns are relevant for health.

Shiroma and colleagues (2013) were the first to report on the sedentary behavior patterns among a large cohort of women from the Women's Health Study. The Women's Health Study included an observational ancillary study (2011-2013) to assess physical activity using accelerometers (i.e., ActiGraph™ GT3X+, ActiGraph Corp) among a cohort of healthy women throughout the United States (n=7,247; age (mean±SD)=71.4±5.8 yr). Sedentary behavior was defined using a <100 count per minute (cpm) cut point. This study reported that women spent 65.5±9.0% of their wear time in sedentary behavior, equivalent to mean ± SD of 9.7 ± 1.5

hours/day, in which most sedentary time (~71%) was accumulated in shorter bouts lasting less than 30 minutes. This study provided important information about the sedentary behavior patterns among a large sample of older women, suggesting that women spend a large proportion of their (~2/3) waking time in sedentary behavior, most of which was accumulated in shorter bout durations (i.e., < 30 mins). Findings from this study are limited, however, because the data are restricted to middle- or older-aged women who are primarily white and of higher socioeconomic status.

Recently, Diaz and colleagues (2016) characterized patterns of sedentary behavior in a U.S. national cohort of middle- and older-aged adults (n=8,096; age (%)=45-54 yr (4.7), 55-64 yr (25.1), 65-74 yr (41.8), ≥75 yr (28.4); Male (%)= 45.8) enrolled in the Reasons for Geographical and Racial Differences in Stroke (REGARDS) study, a population-based study of black and white adults ≥ 45 years. Seven-day accelerometry was conducted via a hip-worn Actical™ (Mini Mitter Respironincs, Inc., Bend, OR) accelerometer to collect objective measurements of sedentary behavior and physical activity from May 2009 to January 2013. Sedentary behavior was defined using a <50 cpm cut point. This study found that adults from the REGARDS sample spent on average over 11 hours of the waking day in sedentary behavior, almost half of which was accumulated in prolonged, uninterrupted sedentary bouts ≥ 30 minutes. Additionally, several factors were identified as significant correlates of the observed patterns of prolonged sedentary behavior, including older age, male sex, residence in non-stroke belt/buckle region, overweightness/obesity, winter season, and lower amounts MVPA. The proportion of total sedentary time accumulated in prolonged, uninterrupted bouts in the REGARDS sample are considerably higher than that reported among women in the Women's Health Study. For instance, sedentary bouts ≥20, ≥30, and ≥60 minutes accounted for 60%, 48%, and 26% of total sedentary

time in the REGARDS sample, but only accounted for 44%, 31%, and 11% of total sedentary time in the Women's Health Study, even when restricting the REGARDS sample to females only (black females: 59%, 47%, and 27%; white females: 58%, 46%, and 24%). Discrepancies in findings from the REGARDS and Women's Health Study may be attributed to differences in sample characteristics (e.g., age, occupation, race/ethnicity, socioeconomic status, etc.) and differences in accelerometer protocol/processing (e.g., device, sedentary count threshold, and non-wear threshold duration). More research is needed to understand the proportion of sedentary behavior accumulated in prolonged, uninterrupted bouts among U.S. adults.

Given that ACS presentation usually occurs in the sixth decade of life, it's important to understand prevalence of sedentary behavior in older adults. Harvey and colleagues (2013) conducted a systematic review on the prevalence of sedentary behavior objectively measured in, or subjectively reported by, older adults aged $\geq$ 60 years (Harvey, Chastin, & Skelton, 2013). This review assessed 23 reports of prevalence of sedentary behavior in older adults sourced from 7 countries by self-reported sitting (number of surveys=9), TV viewing (n=10), computer use and screen time (n=3), as well as by accelerometry (n=1). This study found that approximately 60% of older adults self-reported sitting for more than 4 hours per day and over 54% reported watching more than 3 hours of TV and 65% sit in front of a screen for over 3 hours. Accelerometer-derived sedentary behavior revealed that 67% of the older population were sedentary for more than 8.5 hours per day. Findings from this study demonstrated that, whether measurements are subjective or objective, most older adults are sedentary. However, only one study (n=649) evaluated sedentary time via accelerometry, highlighting the need to employ more studies evaluating objectively measured sedentary behavior in older adults before generalizing findings to the general population.

Harvey and colleagues (2015) conducted another systematic literature review to synthesize the existing evidence on amount of sedentary behavior reported by and measured in older adults. The review included large-scale population studies/surveys reporting the amount of sedentary behavior (objective/subjective) in older adults aged ≥ 60 years of age (n=349,698 adults within 22 studies) published between 1981 and 2014. Results indicated that older adults spent an average of 9.4 hours per day in accelerometer-derived sedentary behavior, accounting for 65-80% of their waking day. Similar to their previous review, self-reported sedentary behavior was lower, with average weighted self-reports being 5.3 hours per day. The findings from this review are similar to that of Harvey et al. (2013) in the fact that estimated sedentary behavior time from self-report was substantially lower than that derived from objective methods (i.e., accelerometry), suggesting that most self-report surveys vastly underestimate the actual time older adults spend in sedentary behavior. Given the discrepancies between subjective and objective methodologies of measurement, future studies should employ objective methods to accurately capture sedentary behavior in older adults.

In an effort to understand the prevalence of sedentary behavior among adults with established cardiovascular disease, Evenson and colleagues (2014) described the prevalence of self-reported and accelerometer-measured sedentary behavior among U.S. adults with CVD (n=680; Male (%) = range 53.3%-66.4%; non-Hispanic Whites (%)= 80.9%-86.1%), including angina (mean age = 69.6 yr), coronary heart disease (CHD, mean age=70.2 yr), congestive heart failure (CHF, mean age=69.3 yr), and myocardial infarction (MI, mean age=69.9 yr), from the 2003-2006 NHANES study. A group without CVD (n=1,000) with similar age, gender, and race/ethnic distributions as those with CVD was chosen as the referent to compare sedentary behavior estimates. Self-reported past-month daily duration of screen-time exposure to television,

video and computer use that were unrelated to work was used to assess sedentary behavior via the NHANES physical activity questionnaire. Objective measurements of sedentary behavior were measured by 7-day accelerometry via a hip-worn ActiGraph device (ActiGraph model 7164; ActiGraph LLC; Fort Walton Beach, FL). Sedentary behavior was defined using a ≤100 cpm cutpoint. This study found that among those with CVD, the proportion of individuals engaged in self-reported television watching ≥4 hours/day ranged from 36.2% (MI) to 44.8% (CHF) and accelerometer-derived sedentary behavior ranged from 9.6 hours/day (angina) to 10.1 hours/day (CHF). Additionally, all four CVD groups had higher television watching and sedentary behavior values when compared to the referent group, with CHF patients exhibiting lower PA and higher sedentary behavior compared to other CVD groups. Importantly, sedentary behavior was higher for MI participants 2-5 years (p=0.003), 6-10 years (p=0.08), and ≥ 10 years (p=0.03) from diagnosis compared to those within 1 year of diagnosis. This study highlighted the high prevalence of sedentary behaviors in vulnerable populations at risk for a recurrent CVD event, which provided a foundation for the notion that increased and targeted efforts are needed to reduce sedentary behavior for secondary prevention of CVD. Given the limited descriptive epidemiology of sedentary behavior among CVD populations, the current dissertation series will further explore the patterns of sedentary behavior among ACS survivors post hospitalization.

Sedentary Behavior and Cardiovascular Morbidity and Mortality

Overview

Sedentary behavior has been estimated to cause 30% of the global cardiovascular disease burden and is the fourth leading cause for mortality worldwide (Roger et al., 2011; World Health Organization, 2009). The dangers of high volumes of sitting were first emphasized when Morris et al. (1953) identified a twofold increase in the risk of myocardial infarction in London bus drivers

compared with active bus conductors. Since then, evidence from population-based studies has linked prolonged sedentary behavior to increased risk for cardiovascular disease, type 2 diabetes, osteoporosis, breast and colon cancer and all-cause mortality, highlighting the negative impact of too much sedentary time on the nation's health and well-being (Biswas et al., 2015; Chastin et al., 2016; Endorsed by The Obesity et al., 2016; Wilmot et al., 2012). Moreover, recent evidence suggests that both total daily sedentary time and how often sedentary time is interrupted are important aspects to consider when looking at cardiovascular health outcomes among U.S. adults of different ages and racial/ethnic backgrounds (Diaz, Goldsmith, et al., 2017; Diaz et al., 2016; Diaz, Howard, et al., 2017).

Data from over 240,000 adults in a national level study showed that spending more than 7 hours/day in sedentary behavior was associated with a 2-fold greater risk of cardiovascular mortality, even among persons who engaged in more than 7 hours/week of moderate- to vigorous-intensity physical activity (Matthews et al., 2012). Shockingly, approximately 60 to 75 mins per day of moderate- to vigorous-intensity physical activity is needed to mitigate the deleterious effects of prolonged sedentary behavior, which exceeds the current physical activity guidelines (Ekelund et al., 2016; Services, 2008). As a result, prolonged sedentary behavior is now thought to represent a unique aspect of an individual's overall physical activity profile and is no longer considered simply to be the extreme low end of the physical activity continuum (Diaz et al., 2016; Diaz, Howard, et al., 2017; Dunstan, Howard, et al., 2012). Accordingly, physical activity recommendations from the American College of Sports Medicine and World Health Organization have expanded beyond promoting exercise and now also advocate for reductions in sedentary time (Garber et al., 2011; Organization, 2010). Thus, targeting a reduction in sedentary time, in addition to physical activity promotion, is needed to improve the nation's health and wellness.

Meta-Analyses

Over the past decade, a total of 9 meta-analyses have been conducted to estimate the potential impact of sedentary behavior on specific health outcomes, such as diabetes, CVD and mortality. Of these meta-analyses, 7 have determined the association of sedentary time with risk of Type 2 Diabetes (T2D), CVD, and/or CVD mortality (Grontved et al., 2011, Wilmot et al., 2012, Ford et al., 2012, Biswas et al., 2015, Pandey et al., 2016, Patterson et al., 2018, Ekelund et al., 2018), while the remainder only evaluated the association between sedentary time and all-cause mortality (Chau et al., 2013, Sun et al., 2015, Ekelund et al., 2016). Moreover, few meta-analyses have examined the dose-response associations to reveal whether there is an evident increase in risk of incident disease or mortality at a specific level on the sedentary time continuum. Given the interest of understanding sedentary behavior as a potential secondary-prevention strategy in ACS patients, the current review will focus primarily on findings from meta-analyses that explored the associations between sedentary time and outcomes relevant for CVD morbidity and mortality.

Grontved and Hu (2011) conducted a meta-analysis of all prospective cohort studies from 1970 to March 2011 to determine the association between TV viewing time and risk of T2D and fatal or nonfatal CVD. Eight relevant studies were identified by researchers that met the following criteria: published in the English language, had a prospective design (cohort, case-cohort, and nested case-control), a study population that was healthy at baseline, and had estimates of relative risk (RR) or odds ration with 95% confidence intervals (CIs) or reported data to calculates these outcomes. Of these studies, 4 reported results on T2D (N=175,938; incident cases= 6,248 during 1.1. million person-years to follow-up) and 4 reported on fatal or nonfatal CVD (N=34,253, incident cases=1052 with no indication of person-years at risk). Results indicated that greater TV

viewing time was associated with a higher risk of T2D (pooled RR, 1.20 [95%CI, 1.14-1.27] per 2 hours of TV viewing time; $p<0.001$) and an increased risk of fatal or nonfatal CVD (RR, 1.15 [95% CI, 1.06-1.23] per 2 hours of TV viewing per day; $p<0.001$), with a linear dose-response relationship observed for both. Based on incidence rates in the U.S., it was estimated that the absolute difference (cases per 100,000 individuals per year) per 2 hours of TV viewing per day was 176 and 38 for T2D and fatal CVD, respectively. However, this meta-analysis is limited in the small number of studies included, as well as the evidence to suggest that TV viewing is not a good representation of total sedentary time, especially in men (Sugiyama, Healy, Dunstan, Salmon, & Owen, 2008).

Wilmot and colleagues (2012) conducted a systematic review and meta-analysis to examine the association of sedentary time with T2D, CVD, and CVD mortality. Eighteen studies (2 cross-sectional, 16 prospective) were included, with 794,577 participants, that met the following criteria: cross-sectional and prospective design, report data on adults ≥18 years of age, include self-reported or objective measurement of sedentary time, report data on a relevant health outcome (diabetes, CVD, CVD mortality). RR or hazard ratio (HR), and 95% Cis comparing the highest level of sedentary behavior with the lowest were extracted for each study. Results demonstrated that the greatest sedentary time compared with the lowest was associated with a 112% increase in the RR of diabetes (RR 2.12; 95% credible interval [CrI] 1.61, 2.78), a 147% increase in the RR of CVD (RR 2.47; 95% CI 1.44, 2.24), and a 90% increase in the risk of CVD mortality (HR 1.90; 95% CrI 1.36, 2.66). The Bayesian predictive effect and interval were only significant for diabetes, demonstrating that the association between sedentary time and diabetes is stronger and more consistent than for CVD outcomes. This was the first meta-analysis to systematically quantify the strength of the association between sedentary behavior (as opposed to TV viewing only) and health

outcomes, demonstrating a strong association between sedentary time and adverse health outcomes. However, this meta-analysis, as well as that of Grontved and Hu (2011), relied solely on self-reported measures of sedentary behavior, which is likely to have poor validity (Clark et al., 2009); highlighting the need to utilize objective measures of sedentary behavior (e.g., accelerometers, inclinometers, etc.) in future large population-based studies.

Ford and colleagues (2012) examined the associations between self-reported screen time and sitting time and fatal and non-fatal CVD. Twelve relevant studies were included that met the following criteria: prospective design, report incidence or mortality from CVD as an outcome, report data on adults ≥18 years of age, and specifically assess sedentary behavior (screen time and sitting). Meta-analyses of the dose-response relationships for screen time or sitting time were conducted. This study found that compared with the lowest levels of sedentary time, risk estimated ranged up to 2.25 for the highest level of screen time and 1.68 for the highest level of sitting time, even after adjusting for physical activity. For six studies that measured screen time and CVD, the summary HR per 2 hour increase was 1.17 (95% CI: 1.13-1.20), while the summary HR per 2 hour increase of sitting time was 1.05 (95% CI: 1.01-1.09), albeit this summary HR was based on two studies of sitting time. Limitations of the current study include the limited number of prospective studies examining the link between various forms of sedentary behavior and risks of fatal or nonfatal CVD, as well as the self-reported assessment of sedentary time.

Biswas and colleagues (2015) quantified the association between sedentary time and hospitalizations, CVD incidence and mortality, and T2D incidence in adults independent of physical activity. Forty-four studies (prospective, cross-sectional and case-control study designs) were included that provided statistical effects relevant to the meta-analyses on CVD incidence and mortalities (551,366 participants) and T2D incidence (26,700 participants), while only one study

examined the association between sedentary time and hospitalizations. All included studies were primary research studies that assessed sedentary behavior in adult participants as a clear predictor variable, independent of physical activity and correlated to at least 1 health outcome. Studies that assessed the effects of varying physical activity intensities were included, as long as they also correlated a measure of sedentary behavior with an outcome. The study's primary exposure was overall sedentary or sitting time (hours per week or hours per day) and odds ratios, RR ratios, and HRs with associated 95% CIs were collected from studies for each outcome, if available. Significant HR associations were found with CVD mortality (HR, 1.150 [CI, 1.090 to 1.410]), CVD incidence (HR, 1.143 [CI 1.002 to 1.729]), and T2D (HR, 1.910 [CI, 1.642 to 2.222]). These findings demonstrated that sedentary time (assessed as either daily overall sedentary time, sitting time, TV or screen time, or leisure time spent sitting) was independently associated with a greater risk for CVD incidence or mortality and T2D in adults, even after statistical adjustment for physical activity. Moreover, this study found that HRs associated with sedentary time and outcomes were generally more prominent at lower levels of physical activity than at higher levels. A strength of this study is the exclusive focus on studies that adjusted for physical activity, which enhanced that precision in the estimated independent effect sizes of associations between sedentary time and outcomes. However, limitations existed in the noticeable heterogeneity in research design and the assessment of sedentary time and physical activity, with all but 1 study used self-reported methods to measure patterns of sedentary behavior and physical activity.

Ekelund and colleagues (2016) examined the associations of sedentary behavior and physical activity with CVD mortality as a secondary analysis. Sixteen studies were included in the meta-analysis, with nine studies including data on the associations between sedentary time (daily sitting or TV viewing time) and physical activity with CVD mortality (n=849.108, number of

deaths=24,481). Data on exposure variables were harmonized based on predefined criteria and categorized into four groups for sedentary behaviors (0 to < 4 hour/day, 4 to <6 hours/day, 6-8 hour/day, and > 8 hour/day) and quartiles for physical activity (Quartile 1: 2.5 Met-hour/week; 5 min/day of MVPA; Quartile 2: 16 MET-hour/week; 25-35 min/day of MVPA; Quartile 3: 30 MET-hour/week; 50-65 min/day of MVPA; Quartile 4: 35.3 MET-hour/week; 60-75 min/day of MVPA). Compared to those in the lowest sedentary/most active group (i.e., < 4 hour/day and highest quartile of physical activity), CVD mortality rates were 23-74% higher in the two lowest quartiles of physical activity. However, daily sitting was not associated with increased CVD mortality in the most active quartile of physical activity (HR [95% CI]= 1.07 [0.96, 1.20]). The findings from this study demonstrated that across sitting time categories, all-cause mortality was considerably reduced at higher levels of physical activity, while eliminated in those who were most active. These findings are in conflict with the findings of those from Biswas and colleagues (2015), however Biswas and colleagues did not directly compare the joint effects of different, specified levels of physical activity and sitting time, to investigate the different amounts of sitting time and physical activity in relation to CVD mortality.

Pandey and colleagues (2016) determined the categorical and quantitative dose-response association between sedentary time and CVD risk. Nine relevant prospective cohort studies with 720, 425 unique participants (Male (%) = 24.9; mean age=54.5 yrs) and 25,769 unique cardiovascular events and a median follow up of 11 years were included that met the following criteria: had a prospective cohort design that reported the association between baseline sedentary time and the risk for CVD incidence (i.e., coronary artery disease, nonfatal myocardial infarction, stroke, and CV-related mortality) after adjusting for physical activity among adults participants (i.e., ≥18 years of age at baseline). Median sedentary time duration for each sedentary time

category was estimated and assigned a corresponding HR for each study. Categorical and continuous dose-response analysis was performed in the current study, with total sedentary time as the exposure variable and incident atherosclerotic CVD as the primary outcome of interest. The median durations of the pooled highest, intermediate, and lowest sedentary time categories were 2.5 (interquartile range[IR]: 1.5-2.9), 7.5 (IR; 6.6-7.6), and 12.5 (IR:9.5-13.8) hours, respectively. Categorical analyses revealed that, compared with the lowest sedentary time category, participants in the highest sedentary time category had an increased risk for CVD (HR, 1.14, 95% CI, 1.09-1.19), albeit no apparent risk associated with intermediate levels of sedentary time were detected. Continuous analyses demonstrated a nonlinear association between sedentary time levels and CVD risk (p for nonlinearity < 0.001), with increased risk observed only at a sedentary duration greater than 10 hours per day (pooled HR, 1.08; 95% CI, 1.00-1.14). The nonlinear association between total sedentary time and CVD risk detected by Pandey and colleagues differs from the linear association between TV time and CVD risk observed by Grontved and Hu (2012), which may be attributed to differences in the measures of sedentary behavior and pooled HRs for CVD events used in each study. Similar to other meta-analyses, the current study is limited by the measurement errors in self-reported sedentary time and variability in the scale of sitting time across studies.

Patterson et al. (2018) estimated the strength and shape of the dose-response relationship between sedentary behavior and CVD mortality and incident type 2 diabetes, adjusted for physical activity. Thirty-four prospective studies with 1,331,468 unique participants that reported associations between total daily sedentary time or TV viewing time and ≥ one outcome of interest were included, yielding a total of 8 exposure-outcome combinations. Findings revealed a nonlinear relationship between total sedentary behavior and CVD mortality (RR per 1 hour/day: 1.01 (0.99-1.02) ≤ 6 hour/day; 1.04 (1.03-1.04) > 6 hour/day), after adjusting for physical activity. Stronger

nonlinear physical activity-adjusted associations were detected for TV viewing (hour/day) and CVD mortality (1.02 (0.99-1.04) ≤ 4 hour/day; 1.08 (1.05-1.12) > 4 hour/day). Significant linear associations were detected between total sedentary behavior and T2D (1.01 (1.00-1.01)) and TV viewing and T2D (1.09 (1.07-1.12)). These results indicate that total sitting and TV viewing time are associated with greater risk for CVD mortality and T2D, independent of PA. For CVD mortality, is appears that a threshold of 6 hour/day of total sitting and 4 hour/day of TV viewing exists, suggesting that exceeding these thresholds can increase risk.

Ekelund and colleagues (2018) conducted the most recent meta-analysis, which examined whether the associations between sedentary behaviors and mortality from CVD differ by different levels of physical activity. Nine prospective cohort studies (n=850,060 participants, median follow-up=10.2 years; deaths=25,730) and five studies with data on TV-viewing time (n=458,127; median follow-up=8.5 years; deaths=12,230) were included, as they provided individual level data on both sedentary behaviors and effect estimated for CVD. Data on exposure variables were harmonized based on predefined criteria and categorized into four groups for sedentary behaviors (0 to < 4 hour/day, 4 to <6 hours/day, 6-8 hour/day, and > 8 hour/day) and quartiles for physical activity (Quartile 1: 2.5 Met-hour/week; 5 min/day of MVPA; Quartile 2: 16 MET-hour/week; 25-35 min/day of MVPA; Quartile 3: 30 MET-hour/week; 50-65 min/day of MVPA; Quartile 4: 35.3 MET-hour/week; 60-75 min/day of MVPA). The association between sitting time and mortality were separately examined for each of the quartiles of physical activity. Results indicated that a dose-response association between sitting time (9%-32% higher risk; p for trend <0.001) and TV time (3%-59% higher risk; p for trend < 0.001) with CVD mortality was detected in the lowest quartile of physical activity, while associations were less consistent in the second and third quartiles of physical activity. Furthermore, there was no increased risk for CVD mortality with

increasing sedentary behaviors in the highest (i.e., most active) quartile. The authors of this study concluded that physical activity modifies the associations between sedentary behaviors and CVD mortality. However, it cannot be ignored that the top quartile, wherein no association between sedentary behavior and CVD mortality was detected, vastly exceeds the current physical activity recommendations (i.e., 60-75 min/day of MVPA vs. 21.4 min/day). Given the dearth of U.S. adults that meet the current physical activity recommendations of 150 min/week of MVPA, it's unlikely that individuals will obtain the volume of MVPA detected in this meta-analysis necessary to offset the deleterious consequences of sedentary behavior.

The existing meta-analyses have greatly increased the awareness of the adverse effects of sedentary behavior on CVD morbidity and mortality. Biswas and colleagues (2015) were the first to take into account physical activity when examining the associations between total sedentary time and CVD outcomes, which became standard in the methods of subsequent meta-analyses (i.e., Pandey et al., Patterson et al., and Ekelund et al.). However, it should be noted that a majority of the studies included in these meta-analyses assessed sedentary behavior by questionnaire, with few studies (i.e., ≤ 3) using accelerometry to objectively measure sedentary behavior. A repeated limitation noted by the meta-analyses is the limited data on objectively measured sedentary time levels. Thus, the next section will review existing literature on the associations between objectively measured sedentary behavior and CVD specific mortality and morbidity.

Original Research: Accelerometer-Measured Sedentary Behavior and CVD Morbidity and Mortality

To date, only 2 population-based studies have reported on the association between accelerometer-measured sedentary time and mortality, including U.S. adults from NHANES and REGARDS. Findings from accelerometer-derived sedentary time and all-cause mortality from

NHANES have been reported in several separate analyses (Evenson, Wen, & Herring, 2016; Koster et al., 2012; Loprinzi & Sng, 2016; Matthews et al., 2016; Schmid, Ricci, & Leitzmann, 2015), with only one study reporting on the associations of accelerometry-assessed physical activity and sedentary behavior with CVD mortality among U.S. adults (Evenson et al., 2016). Furthermore, only one study from REGARDS evaluated the association between accelerometer-derived sedentary behavior (both its total volume and accrual in prolonged, uninterrupted bouts) and all-cause mortality, but did not look at CVD mortality (Diaz, Howard, et al., 2017).

Evenson et al. (2016) explored the associations between physical activity and sedentary behavior with CVD mortality among a cohort of U.S. adults (n=3,809; average follow-up=6.7 years, CVD deaths=107; mean age=55.3 years; Male (%)=45.4) from the 2003-2006 NHANES study. MVPA (≥760 cpm), LIPA (100-759 cpm), and sedentary behavior (<100 cpm) were measured with a hip-worn ActiGraph accelerometer for 7 consecutive days. Sedentary behavior was expressed as total volume (min/day), sedentary bouts (≥30 minutes with at least 80% of the minutes falling below <100 cpm), and percent of the day spent in sedentary behavior (%) and split into quartiles for analyses. Participants were included in the analysis if they wore the accelerometer for ≥8 hours on ≥3 days. CVD mortality was defined based on cardiovascular deaths coded as International Classification of Disease-10 100-199 and no adults had congenital heart defects as their primary cause of death from the National Death Index provided by the National Center for Health Statistics, which recorded deaths through December 31,2011. This study found that the associations of sedentary time or percent of day spent in sedentary time with CVD mortality was not sustained after adjusting for LIPA and MVPA, as well as potential mediators (e.g., age, gender, race/ethnicity, etc.) (Highest quartile vs. lowest quartile of sedentary time: HR (95% CI)= 1.46 (0.72, 2.93); p=0.55; Highest quartile vs. lowest quartile of percent of day in sedentary time: HR

(95% CI)=1.14 (0.42, 3.06); p=0.22). Interestingly, when compared with persons from the lowest quartile, those in the second quartile of sedentary bouts had lower risks of CVD mortality in the fully adjusted model (adjusted HR [95% CI]=0.46 [0.21-1.00]), albeit this association disappeared when those with CVD were included in the analyses. Authors of this study concluded that no consistent associations between accelerometer-assessed sedentary behavior (average time, bouts, or percent of day) and CVD mortality were observed, which may be attributed to inherent study limitations (e.g., short follow-up time, imperfect LIPA and MVPA cutpoints, and inability of accelerometer to detect postures, potentially misclassifying standing as sedentary behavior). Thus, future research is needed to understand the association between accelerometer-measured sedentary time and CVD mortality.

Moreover, limited data are available describing the effects of sedentary time on CVD morbidity, such as chronic myocardial injury. Harrington and colleagues (2017) evaluated the association between accelerometer-measured sedentary time and markers of chronic subclinical myocardial injury (i.e., high-sensitivity assays for cardiac troponin T and I) among individuals from the Dallas Heart Study, a longitudinal, multi-ethnic population-based probability sample of Dallas County residents. Sedentary time (<100 cpm) and MVPA (>1500 cpm) were assessed using a wrist-work Actical™ (Phillips Respironics, Bend OR) device for 7 days. Using thawed frozen samples, high-sensitivity assays for cardiac troponin T and I were measured with appropriate assays. This study found that sedentary time was strongly and inversely correlated with MVPA, and moderately correlated with cardiac troponin T and I . However, multivariable linear regression analyses revealed that associations between sedentary time and both cardiac troponin T and I remained significant after adjusting for select covariates and MVPA. These findings suggest that the association between increased sedentary time and chronic myocardial injury may be

independent of relevant confounders and MVPA (Harrington et al., 2017). Moreover, Kulinski and colleagues (2016) investigated with association between accelerometer measured sedentary behavior and coronary artery calcium (CAC), a measure of subclinical atherosclerosis, using data from the Dallas Heart Study (n=2,031 with valid accelerometer data [≥4 days wear] and CAC; mean age±SD= 50±10 years; Male (%)= 38). Sedentary time and MVPA were assessed and classified the same as previously described. After multivariable adjustment of traditional CVD risk factors, socioeconomic factors, and MVPA, each additional hour of sedentary time was significantly associated with a 12% higher odds of having subclinical atherosclerosis in participants without known CVD (OR [95% CI]=1.12 [1.02-1.23]; p=0.017). Additional studies evaluating the adverse effects of sedentary behavior on cardiometabolic health outcomes are described in sections below.

Proposed Physiological Pathways that Link Sedentary Behavior to Cardiovascular Disease

Although strong evidence exists to support the SED-CVD link, the underlying mechanisms of this deleterious relationship have yet to be fully elucidated. Understanding the biological mechanisms that underlie the associations between prolonged sitting and adverse health outcomes is necessary to identify the exact causal nature of these relationships. Based on the sedentary behavior research to date, the strongest evidence exists for impaired glucose regulation, hyperlipidemia and endothelial dysfunction as potential pathways that link sedentary behavior to CVD.

Impaired Glucose Regulation

Impaired glucose regulation is an important cardiovascular risk factor, such that chronic hyperglycemia can lead to type 2 diabetes and CVD. Regular ingestion of high-calorie meals rich in processed carbohydrates can lead to transient exacerbated postprandial spikes in glucose, which

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can promote an inflammatory milieu conducive for the development of atherosclerosis and CVD (Ceriello et al., 2008; O'Keefe & Bell, 2007). The main cellular mechanism responsible for reducing postprandial blood glucose levels and regulating whole body glucose homeostasis is insulin-stimulated transport of glucose from the blood into skeletal muscle (Huang & Czech, 2007). The principle glucose transporter protein that facilitates this uptake is GLUT4, which resides within the cytoplasm of adipose and skeletal muscle cells in the form of vesicles. When stimulated, GLUT4 will translocate to the cell surface and allows passive diffusion of glucose molecules into the cell. GLUT4 can be stimulated by both insulin via insulin receptor signaling and skeletal muscle contraction, which is independent of insulin. GLUT4 recruitment to the cell surface of muscle and adipose cells can be stimulated by both insulin and skeletal muscle contraction.

Regarding skeletal muscle contraction, studies have shown that increased skeletal muscle contraction via light- and moderate-intensity physical activity can reduce postprandial glucose and insulin levels (Bailey & Locke, 2015; Benatti & Ried-Larsen, 2015; Dunstan, Kingwell, et al., 2012). In contrast, decreased skeletal muscle contractile activity reduces the translocation of GLUT4 to the cell surface, which impairs clearance of postprandial glucose (Richter & Hargreaves, 2013). This link was initially proposed from a series of rodent studies conducted by Booth and colleagues (Booth, Chakravarthy, Gordon, & Spangenburg, 2002). These researchers used wheel lock models, which involved restricting habitual or voluntary activity to cage movement only for up to 7 days. These studies found that a rapid decrease in insulin-stimulated glucose transport was reported within 2 days of wheel lock and reduced activity (Kump & Booth, 2005). This reduction in insulin-stimulated glucose transport was linked to reduced activation of the insulin-signaling pathway and reduced GLUT4 protein content. Moreover, fewer skeletal

muscle contractions may result in lower insulin sensitivity and less glucose-stimulated insulin secretion due to impairments of pancreatic beta-cell function, both which negatively impact glucose regulation (Healy, Matthews, et al., 2011). Since prolonged sedentary behavior promotes muscle inactivity, these animal studies provide a foundation to reveal a molecular pathway that may link sedentary behavior to CVD. Therefore, it has been proposed that prolonged sedentary behavior confers CVD risk, in part, through impaired glucose regulation.

In addition to animal studies, population-based, observational studies provided a foundation to support impaired glucose regulation as a pathway that contributes to the sedentary behavior-CVD link. Initial findings from the 2004 to 2005 Australian Diabetes, Obesity and Lifestyle Study (AusDiab) reported that accelerometer derived sedentary time was adversely associated with blood glucose levels, even when accounting for MVPA (Healy, Dunstan, et al., 2008; Healy, Wijndaele, et al., 2008). Healy and colleagues (2008) showed that adults from the AusDiab study whose sedentary time was accumulated in prolonged, uninterrupted periods had a poorer cardiometabolic health profile compared to those who frequently interrupted their sedentary time. These findings pioneered the concept that both the total volume and the pattern in which sedentary time is accumulated is important for metabolic health. Findings from the 2003 to 2004 and 2005 to 2006 population-representative U.S. National Health and Nutrition Examination Survey (NHANES) study found that total sedentary time was detrimentally associated with insulin, beta-cell function (HOMA-%B), and insulin sensitivity (HOMA-%S), while breaks in sedentary time were beneficially associated with fasting plasma glucose levels (Healy, Matthews, et al., 2011). These findings complement and build upon those from the AusDiab study, albeit NHANES comprised a much larger (n=4,757 vs. n=169) and more racially/ethnic diverse population. Recent findings from the 2008 to 2011 Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

showed that accelerometer-measured sedentary time accumulated in prolonged, uninterrupted bouts was detrimentally associated with glycemic biomarker, independent of MVPA, albeit not independent of total sedentary time (Diaz, Goldsmith, et al., 2017). These findings suggest that total sedentary time and prolonged, uninterrupted sedentary bouts are jointly associated with poorer glucose regulation among US Hispanic/Latino adults. Together, these epidemiological studies, among others not mentioned here, provide a foundation for experimental studies to further explore the deleterious consequences of prolonged sedentary time, which can provide confirmation and insight of mechanisms underlying the SED-CVD link.

Over the past decade, numerous prospective experimental studies designed to evaluate the short-term effects of breaking up prolonged sitting with physical activity and/or standing on the cardiometabolic profile have been published (Benatti & Ried-Larsen, 2015). Dunstan and colleagues (2012) were the first to demonstrate that breaking up prolonged sitting reduces postprandial glucose and insulin responses when compared to prolonged, uninterrupted sitting. These researchers conducted a laboratory-based study among overweight/obese middle-aged adults and found that both insulinemic and glycemic responses to a liquid meal test were reduced after light- and moderate-intensity physical activity breaks (2 minutes in duration every 20 minutes for 5 hours post meal consumption) when compared to 7 hours of uninterrupted sitting (Dunstan, Kingwell, et al., 2012). Since then, multiple laboratory-based studies have been conducted and showed that glycemic benefits are detected when prolonged sitting is reduced or interrupted with intermittent bouts ranging from 1 min and 40 secs to 8 min of light- or moderate-intensity post-meal physical activity (i.e. walking, cycling, etc.) at frequencies ranging from every 20 min to every 60 mins among active-healthy, overweight/obese-sedentary, and dysglycemic populations

(Bailey & Locke, 2015; Duvivier et al., 2013; Latouche et al., 2013; Newsom, Everett, Hinko, & Horowitz, 2013; Peddie et al., 2013; van Dijk et al., 2013).

In regards to standing, there are mixed findings as to whether breaking up sitting time with bouts of standing is a sufficient stimulus to improve postprandial glucose and insulin responses (Bailey & Locke, 2015; Buckley, Mellor, Morris, & Joseph, 2014; Thorp et al., 2014). For instance, Thorp and colleagues (2014) found that alternating standing and sitting in 30 min bouts via a sit-stand workstation significantly attenuated the postprandial glucose responses when compared to seated work posture in overweight/obese office workers. In contrast, Bailey & Locke (2015) found that breaking up sitting time with 2-minute bouts of standing every 20 minutes in a laboratory setting did not significantly improve postprandial glucose responses when compared to uninterrupted sitting in non-obese adults. Taken together, the current acute laboratory- or office-based studies provide considerable evidence that prolonged, uninterrupted sitting has detrimental effects on glucose regulation, while breaking up prolonged sitting time has positive effects on metabolic health. However, the optimal type, intensity, and frequency or physical activity necessary to counteract the deleterious effects of prolonged sitting have yet to be established.

Dyslipidemia

Dyslipidemia, characterized by abnormal levels of cholesterol and/or triglycerides in the blood, is a strong risk factor for CVD (Nelson, 2013). Regular ingestion of high-calorie meals rich in saturated fat can lead to transient exacerbated postprandial spikes in lipids, which can eventually lead to chronic hyperlipidemia (O'Keefe & Bell, 2007). Hyperlipidemia promotes oxidative stress, arterial inflammation, endothelial dysfunction, which can facilitate the development of atherosclerosis (Ceriello et al., 2004). The main cellular mechanism responsible for reducing postprandial blood lipid levels is lipoprotein lipase (LPL). LPL is a rate-limiting enzyme involved

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in the hydrolysis of triglyceride-rich lipoproteins, such as very low density lipoproteins (VLDL) and chylomicrons, and production of substrates needed for the maturation of high density lipoprotein (HDL) cholesterol (Beisiegel & Heeren, 1997; Bey, Areiqat, Sano, & Hamilton, 2001). Defects in LPL activity has been associated with blunted plasma triglyceride uptake and reduced HDL levels (Hamilton, Hamilton, & Zderic, 2007). As such, research has shown that low LPL activity is atherogenic.

Dyslipidemia predominantly results from unhealthy lifestyle influences, such as poor composition of diet (e.g., high fat), smoking habits, and lack of exercise(Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel, 2014). In regards to exercise, previous studies in both rats and humans have shown that exercise increases LPL activity and expression in the skeletal muscle (Hamilton, Etienne, McClure, Pavey, & Holloway, 1998). In contrast, decreased skeletal muscle contractile activity due to physical inactivity or extreme bed rest has shown to suppress LPL activity, blunt clearance of triglycerides, and reduce HDL levels (Hamilton et al., 2007). For instance, rat studies demonstrated LPL activity associated with microvasculature of the most oxidative muscles was lost within 1 day of inactivity when compared to controls, with decreases detected after ~4 hours of inactivity. The suppression of LPL activity observed with inactivity may be due to the upregulation of a gene other than LPL that rapidly switches off the functional LPL activity found on the capillary endothelium. In 1998, a human study examining the effects of 20 days bed rest on LPL activity found that LPL activity was decreased, followed by increased very low density lipoprotein (VLDL) triglycerides and decreased HDL in healthy participants (Yanagibori et al., 1997). Moreover, it appears that the cellular responses to inactivity and exercise for LPL regulation are qualitatively different, such that the magnitude of LPL suppression during inactivity after reducing standing/low-intensity ambulation was much larger

than the increase after adding exercise. Taken together, the reduced LPL activity observed with physical inactivity has provided a molecular foundation to propose hyperlipidemia as a potential pathway that links sedentary behavior to cardiovascular disease

Although findings from animal models of physical inactivity are consistent, findings from human experimental studies examining the effects of breaking up prolonged sitting on fasting and postprandial plasma lipid responses are less consistent. Among healthy, young adults, normal-weight adults, and overweight/obese adults, studies demonstrated that interrupting prolonged sitting time with regular walking bouts of different durations (i.e., 1 min 40 secs, 2 mins, 3 mins, etc.) every 15-30 mins or with intermittent standing bouts of different durations (i.e., 30 minutes, 2 mins, etc.) every 30-45 minutes did not effectively lower postprandial triglyceride responses when compared to uninterrupted sitting (Bailey & Locke, 2015; Miyashita, Burns, & Stensel, 2013; Miyashita et al., 2016; Peddie et al., 2013; Thorp et al., 2014). In contrast, Kim et al. (2014) found that intermittent bouts of light intensity walking of various durations (e.g., 20-60 mins) significantly reduced postprandial triglycerides and improved whole body fat oxidation when compared with prolonged, uninterrupted sitting in young healthy individuals (Kim, Park, Trombold, & Coyle, 2014). Moreover, Dempsey and colleagues found that 3 minute bouts of simple resistance exercises activating large muscles of the lower extremities every 30 minutes led to significant reductions in postprandial triglyceride responses compared to prolonged, uninterrupted sitting (Dempsey et al., 2016). These findings suggest that brief bouts of light intensity walking (e.g., <3 mins) and standing may not be a sufficient stimulus to enhance LPL activity, suggesting that longer bouts of LPA or different modes of exercise may be needed to attenuate postprandial lipemia.

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Moreover, findings from Kim et al. (2014) and Phillips et al. (2017) found that continuous MVPA and VPA were more effective in lowering postprandial triglyceride levels than intermittent light-or moderate-intensity physical activity, respectively (Kim et al., 2014; Phillips, Dillon, & Perry, 2018). The inconsistencies between studies may be due to the different populations studied (i.e. healthy, young adults vs. type 2 diabetics), experimental designs (i.e., concurrent vs. next-day effects), meals (i.e., composition of macronutrients and content), highlighting the complex interplay these factors may have on lipid metabolism. Moreover, the discrepancies between animal/bed-rest studies and human studies where prolonged sitting was interrupted may be because the activity stimulus or the duration of studies was not sufficient to induce changes in lipid metabolism.

Endothelial Dysfunction

Endothelial dysfunction, an early pathogenic process underlying atherosclerosis, is a promising mechanism purported to be a contributing factor to the SED-CVD link (R. Ross, 1999; Versari, Daghini, Virdis, Ghiadoni, & Taddei, 2009). The sitting posture (the primary sedentary posture) promotes muscle inactivity of the lower extremities and changes in the angles at which the femoral and popliteal arteries run, causing bends within the arterial tree (Restaino, Holwerda, Credeur, Fadel, & Padilla, 2015). These physiological conditions elicit hemodynamic changes including blood pooling in the legs, decreased thigh and calf blood flow, and augmented turbulent blood flow in the deformed arterial segments (Delp & Laughlin, 1998; Padilla, Johnson, et al., 2009; Padilla, Sheldon, Sitar, & Newcomer, 2009; Restaino et al., 2015). For these reasons, it is thought that prolonged sitting confers CVD risk by exposing the endothelium to a pro-atherogenic milieu, facilitating endothelial dysfunction over time (Hamilton et al., 2007; Thosar, Johnson, Johnston, & Wallace, 2012).

Over the past decade, experimental evidence from laboratory-based studies has shown that prolonged exposure to the sitting posture (e.g. from 1 to 6 hours) and episodes of reduced shear stress blights endothelial function in the leg vasculature, including both the femoral and popliteal arteries (McManus et al., 2015; Morishima et al., 2016; Morishima, Restaino, Walsh, Kanaley, & Padilla, 2017; Padilla & Fadel, 2017; Padilla, Johnson, et al., 2009; Padilla, Sheldon, et al., 2009; Restaino et al., 2015; Restaino et al., 2016; Thosar, Bielko, Mather, Johnston, & Wallace, 2015). For instance, Thosar and colleagues (2014) found that 3 hours of uninterrupted sitting impaired FMD and decreased mean and antegrade shear rates in the superficial femoral artery (SFA). Similarly, Restaino et al. (2016) found that 6 hours of prolonged, uninterrupted sitting impaired both microvascular dilator function (i.e., blood flow and velocity) and macrovascular dilator function (i.e., FMD) of the popliteal artery. However, both of these studies found that sitting-induced vascular impairments were fully restored when sitting time was interrupted with intermittent light activity breaks (5 mins @ 2mph) or a 10-minute bout of walking. Moreover, Morishima and colleagues found that prolonged sitting-induced endothelial dysfunction in the lower extremities is preventable with small amounts of leg movement while sitting, such as fidgeting. Collectively, these studies demonstrated that prolonged, uninterrupted sitting reduce blood flow and shear stress, that ultimately leads to leg endothelial dysfunction, albeit the impaired vasculature can be can be attenuated with light muscular activity (e.g., light-intensity walking, leg fidgeting, etc.).

One of the most important findings to support the endothelial dysfunction as a proponent in the SED-CVD link is that sitting-induced endothelial dysfunction is specific to the lower extremities, such that impaired FMD does not manifest in the upper extremities (Thosar, Bielko, Wiggins, & Wallace, 2014). Thosar and colleagues (2014) were the first to report that prolonged,

uninterrupted sitting resulted in impaired FMD of the lower extremities (i.e., femoral artery), but not the upper extremities (i.e., brachial artery). Likewise, Restaino and colleagues (2015) found that prolonged sitting reduced popliteal, but not brachial, artery FMD. It has been speculated that the lack of a sitting-induced impairment in brachial artery FMD may be because the brachial artery is more resilient to reductions in shear compared to arteries of the lower extremities and/or brachial artery FMD may not be a sensitive measure of systemic endothelial dysfunction during prolonged sitting. However, future research is needed to understand that leg specific sitting vasculopathy.

Despite supportive experimental evidence for endothelial dysfunction being a potential contributing factor to the sedentary behavior-CVD link; such work is limited in that acute periods of sitting in the lab over a single day (or in most cases a few hours) is not indicative of chronic conditions. Furthermore, the control condition (uninterrupted sitting for hours at a time) does not have real world generalizability since few adults engage in such prolonged, uninterrupted sedentary periods during a typical day (e.g., workday). To date, the relationship between habitual sedentary behavior and markers of endothelial function have yet to be explored. Thus, observational studies are needed to determine whether inactive sitting (volumes and prolonged, uninterrupted bouts) throughout a typical sitting day are linked to impairments in the leg vasculature. Moreover, studies conventionally define endothelial dysfunction solely as an impairment in endothelial-dependent vasodilation. This narrow focus provides insight concerning only one aspect of endothelial function. Lab-based investigations have elucidated the upstream processes underlying endothelial dysfunction, which include endothelial cell injury and diminished endothelial cell reparative capacity, in addition to impaired endothelial-dependent vasodilation. A comprehensive evaluation of endothelial function thus not only includes the assessment of endothelium-dependent vasodilation (EDV), but also cellular measures such as

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circulating endothelial microparticles (EMPs) and circulating endothelial progenitor cells (EPCs) (Deanfield, Halcox, & Rabelink, 2007).

In order to understand physiological changes or responses to sedentary behavior, it's important to understand that physical inactivity and sedentary behavior-induced physiological changes have been studied under several different models and contexts. The approaches used to date include animal models, detraining, bed rest, imposed physical inactivity and prolonged sitting time. However, these experimental designs fail to address real world generalizability since few adults engage in such prolonged, uninterrupted sedentary periods and/or bed rest during a typical day (e.g., workday). Thus, Intervention studies conducted in real-world settings targeting the feasibility, acceptability and efficacy of reducing and breaking up occupational, transit and domestic sedentary time are needed. However, future research examining the skeletal muscle regulatory pathways at the epigenetic, gene expression and protein level are needed to better characterize the mechanisms underlying the impact of prolonged sitting on cardio-metabolic risk.

Measurement and Interpretation of Endothelial Dysfunction

Endothelial cells form a single-cell lining covering the internal walls of blood vessels throughout the entire vascular system, also known as the endothelium (Alberts et al., 2002; Della Corte et al., 2016). The endothelium is recognized as the key regulator of vascular wall homeostasis due to its critical role in preserving vascular tone, vascular permeability to plasma elements, platelet and leukocyte adhesion and aggregation, and thrombosis (Alberts et al., 2002; Barac et al., 2007; Poredos & Jezovnik, 2013). The endothelium is thought to have its largest effect on vascular tone (Poredos & Jezovnik, 2013), such that healthy endothelium releases a balance of endothelium-derived relaxing (i.e. nitric oxide, prostacyclin) and constricting (i.e. endothelin, vasoconstrictor prostanoids) factors, which preserves a relaxed vascular tone and low levels of

oxidative stress (Barac et al., 2007; Della Corte et al., 2016). The imbalance between endothelial-dependent relaxing and constricting vasoactive substances inhibits the vasodilatory response, indicating the presence of endothelial dysfunction. Endothelium-dependent vasodilatation (EDV) represents the dynamic biology and vasomotor properties of the endothelium to maintain vascular tone through the synthesis and release of endothelial-derived vasoactive substances. An imbalance between vasodilating and vasoconstricting mediators can impair EDV, indicating the presence of endothelial dysfunction.

Endothelial dysfunction is a pathophysiological condition characterized by a dysregulation of homeostatic mechanisms necessary to maintain healthy endothelium (Barac et al., 2007). Endothelial dysfunction is associated with abnormal modulation of vascular tone, platelet activation, thrombosis, leukocyte adherence, increased oxidative stress, vascular inflammation and atherosclerosis (Barac et al. 2007, Della Corte et al., 2016). Thus, impairments in endothelial function precede the development of atherosclerosis and contributes to the configuration, progression and adverse complications of atherosclerotic plaque (Barac et al., 2007; R. Ross, 1993). In addition to its role in the pathogenesis of atherosclerosis, endothelial dysfunction is an independent risk factor of future cardiovascular events in patients with stable ischemic heart disease (Halcox et al., 2002) and in patients with acute coronary syndromes (Fichtlscherer, Breuer, & Zeiher, 2004). The endothelium's role in the complex and highly regulated network of physiological mechanisms necessary to maintain vascular homeostasis, as well as the adverse health effects of endothelial dysfunction, highlights the importance of endothelial function assessment.

Invasive and Noninvasive Techniques

Over the past three decades, both invasive and noninvasive techniques have been developed to measure endothelial dysfunction via the assessment of EDV. Such testing requires pharmacological and/or physiological stimulation of the endothelium to activate the release of endothelial-derived vasoactive factors, which was first observed from the pioneering studies of Furchgott and Zwadzki. In the early 1980s, these researchers developed a method to assess endothelial function by means of local infusion of acetylcholine on the vessels of the coronary circulation of animals (i.e., rabbit, dog, etc.) (Furchgott & Zawadzki, 1980). The results from these experiments demonstrated that acetylcholine triggered the release of nitric oxide (NO) from vessels with intact endothelium, eliciting vasodilation. In 1986, Ludmer and colleagues applied the same intracoronary infusion technique, as well as measured vessel diameter change with quantitative coronary angiography, in human coronary arteries in situ. This study found that vasoconstriction occurred in subjects with atherosclerotic coronary arteries, while vasodilation occurred in healthy subjects, demonstrating that this technique can be used to detect endothelial dysfunction in humans (Ludmer et al., 1986). These studies laid the foundation for endothelial function testing, as well as offered insight to the molecule mechanisms underlying EDV.

Due to the relationship between human coronary and peripheral circulations, the invasive method of intracoronary infusion has been applied to the brachial artery. As such, intracoronary and intrabrachial infusion of vasoactive substances, which are both invasive techniques, are denoted the "gold standard" method for early detection of endothelial dysfunction (Tousoulis, Antoniades, & Stefanadis, 2005). Although optimal from a methodological standpoint, these invasive techniques are not entirely feasible due to their high costs, burden to the participant, and inability to be used in large-scale studies and asymptomatic subjects, such as children and young adults at risk for cardiovascular disease.

To offset the limitations of invasive techniques, noninvasive methods with comparable results and good reproducibility have been developed to measure endothelial function. In order to assess EDV, most noninvasive techniques measure vascular reactivity of the conduit arteries (i.e., radial, brachial, femoral) in response to reactive hyperemia, which is the transient increase in blood flow to an organ following ischemia (Dhindsa et al., 2008). Noninvasive techniques developed to evaluate vascular reactivity include flow-mediated dilatation, changes in pulse wave velocity between the brachial and radial arteries, reactive hyperemia index assessed by fingertip peripheral arterial tonometry (PAT) via the EndoPAT™, temperature rebound and skin reactive hyperemia index. Of these techniques, flow-mediated dilatation (FMD), which was developed in 1992 by Celermajer and colleagues, is considered the "gold standard" noninvasive method for clinical research on conduit artery endothelial dysfunction (Flammer et al., 2012). Thus, an understanding of the measurement and interpretation of FMD is essential to comprehend vascular pathophysiology and its clinical implications in relation to endothelial dysfunction.

Flow-Mediated Dilatation

Measurement and Analysis

FMD is a noninvasive, ultrasound-based technique designed to assess conduit artery vascular function in the systemic circulation (Celermajer et al., 1992). FMD is based on the principle that increased blood flow in an artery via reactive hyperemia causes an increase in shear stress parallel to the long axis of the vessel, which triggers generation of endothelial derived vasoactive mediators (i.e. nitric oxide), resulting in arterial vasodilation (Doshi et al., 2001; Raitakari & Celermajer, 2000). The ability of the endothelium to modify its biosynthetic activity in response to the shear stress is measured by the change in the diameter of the target conduit artery (i.e. brachial, radial, femoral, etc.) via ultrasound imaging (Barac et al., 2007, Raitakari &

Celermajer, 2000). Thus, accurate baseline and reactive hyperemia measurements of the target conduit artery must be obtained to assess and interpret FMD results.

To ensure an accurate baseline assessment of the arterial diameter and blood flow, subjects should rest in a temperature controlled (22-24ºC), quiet room and in the position (i.e. supine, prone, seated, etc.) in which the study will be performed for at least 20 minutes (Corretti et al., 2002, Harris et al., 2010). While resting, the transducer of the ultrasound machine is placed in the longitudinal plane above the anatomical location necessary to identify a clear image of the target conduit artery (e.g., above the antecubital fossa for brachial artery; proximal to the popliteal fossa for the popliteal artery). Once a segment with well-defined anterior and posterior intimal surfaces between the lumen and vessel wall of the target artery is identified, baseline measures of the artery diameter and blood flow velocity are taken for at least one minute (Eskurza, Seals, DeSouza, & Tanaka, 2001; Flammer et al., 2012). After baseline measurements are taken, vascular occlusion occurs, and reactive hyperemia measurements are obtained.

Briefly, a blood pressure cuff is placed distal to the ultrasound probe and inflated for 5 minutes to occlude blood flow, creating an area of ischemic tissue distal to the site of occlusion. After the 5-minute period of ischemia, the cuff is deflated, and measurements of the target artery diameter and blood flow velocity are taken with the ultrasound transducer for a total of 3 minutes (180 seconds). This 3-minute period is known as the post-ischemia and/or reactive hyperemia period. Blood flow measurements are taken during the first 45 seconds of the reactive hyperemia period (0:00-0:45) to obtain peak blood flow and shear stress. Conduit artery diameter measurements are obtained immediately after the 45 seconds post-ischemia until the end of the assessment (0:45-3:00; 135 seconds) to capture peak arterial diameter. These measurements are taken in this order because the peak blood flow velocity occurs within the first 15 seconds post-ischemia, while peak

vasodilation is expected to occur 45 to 80 seconds post-ischemia, with these times differing between populations (Black, Cable, Thijssen, & Green, 2008). The shear rate over time is calculated using the Area Under the Curve (AUC), quantifying the accumulated shear stress that contributed to the FMD response (Pyke & Tschakovsky, 2007). It should be noted that the reactive hyperemia shear stress induced by the temporary vascular occlusion is the primary stimulus for FMD (Celermajer et al., 1992). Thus, the temporal kinetics of arterial diameters and blood velocity measured via the duplex mode on the ultrasound system during reactive hyperemia are crucial for overall FMD analyses.

After baseline and reactive hyperemia measurements are obtained, FMD analyses are conducted using edge detection software and calculations. Traditionally, FMD is calculated as a percentage of change in the vessel caliber (Corretti et al., 2002), reflecting the arterial vasodilatory response to reactive hyperemia in relation to the baseline diameter (FMD%=[peak diameter-baseline diameter]/baseline diameter) (Harris, Nishiyama, Wray, & Richardson, 2010). More recently, due to potential mathematical bias and varying reactivity of smaller vs. larger vessels (Pyke & Tschakovsky, 2005), baseline diameters, absolute change in diameter and shear rate (AUC) are presented in addition to FMD percentage (Harris et al., 2010). Since FMD is triggered by shear stress, evidence suggests that FMD should be normalized by dividing the percentage of FMD by shear rate (AUC) (Harris et al., 2010). However, debate exists as to which method optimally normalizes FMD for shear stress (Atkinson et al., 2009). It is important to note that each diameter (i.e. baseline and reactive hyperemia) and blood flow measurement (i.e. blood flow velocity, reactive hyperemic flow, and hyperemic shear stress) via ultrasound contribute to overall FMD analyses, highlighting the significance of proper equipment and technique needed for this method.

Interpretation and Application

In regard to interpretation, the magnitude of dilatation (i.e., FMD%) reflects the endothelium-dependent vasodilator function, serving as a surrogate marker of endothelial dysfunction and vascular health. Results from previous studies examining the clinical utility of FMD consider endothelial function to be "normal" if FMD is greater than 10% and "impaired" if FMD is less than 10%. As such, a FMD<10% is thought to indicate the presence of endothelial dysfunction (Modena, Bonetti, Coppi, Bursi, & Rossi, 2002; Vogel, 1997). Moreover, a recent meta-analysis found that a 1% decrease in FMD was associated with a 13% change in cardiovascular risk, independent of the group studied. However, multiple review studies have established that FMD values vary widely between studies, ranging from -1.9-19.2%, and overlap between populations (i.e., healthy, coronary artery disease, diabetes mellitus, etc.), hindering the utility of FMD reference values and interpretation (Bots, Westerink, Rabelink, & de Koning, 2005). The variability in the FMD values may be due to technical measurement controversies, such as cuff placement, occlusion pressures, occlusion duration, and ultrasound techniques (Celermajer, 2008). As such, different iterations of the FMD protocol are employed across different laboratories (i.e., subject preparation, cuff placement, length of vascular occlusion, etc.). For instance, if the environmental conditions of the room are not regulated, the FMD results can be influenced and potentially reflect a false negative due to a transient state vs. true pathology. Moreover, small changes in cuff placement can modify the endothelial-derived vasoactive substances contributing to the FMD response (i.e., NO vs. prostaglandins vs. hyperpolarizing factor). Thus, there is a need to standardize FMD protocols across laboratories to ensure meaningful and comparable results. Moreover, intra- and inter-observer variability, as well as time-dependent reproducibility of FMD are important to report because the outcome of each measurement is highly operator dependent.

Regarding clinical application, numerous studies demonstrated that FMD% serves as a strong indicator of cardiovascular disease in both diseased and healthy populations (Thijssen et al., 2011). For instance, previous population-based studies demonstrated that FMD% is an independent predictor of future events and survival in patients with established CVD or CVD risk (Lieberman et al., 1996; Mitchell et al., 2004). FMD% has also shown to be an independent risk factor for future CVD in healthy men and women, potentially exceeding the predictive values of traditional risk factors. A recent study examining the correlations between endothelial function assessed by FMD and severity of coronary artery disease (CAD) demonstrated that FMD% > 10 reliably rules out obstructive CAD and FMD < 10% predicts the presence of CAD (Sancheti, Shah, & Phalgune, 2018). This study further stratified FMD% values and found that FMD < 6% predicts obstructive CAD, while FMD 6-10% predicts the presence of CAD but non-obstructive. These findings confirm the clinical utility of FMD in clinical populations. However, it's important to note that the prognostic role of FMD is based primarily on FMD derived from the brachial artery, as there are no existing data pertaining to the prognostic role of FMD derived from the popliteal and femoral arteries. Thus, future studies are needed to better interpret FMD results of the lower extremities.

Strengths & Limitations

Although FMD is considered the gold standard for noninvasive assessment of endothelial dysfunction in clinical research, this method has both strengths and limitation. The strengths of FMD include this technique's validity and reproducibility relative to other noninvasive methods, epidemiological and clinical applications, and the ability to evaluate conduit artery endothelial biology across different populations and age groups (i.e., children, young adults, older adults). This technique can also be used in large-scale studies, contributing to vascular epidemiology. FMD

is also a strong predictor of cardiovascular events in patients with established CVD and is an endothelial function assessment recommended by the Brachial Artery Reactivity Task Force.

Although FMD presents numerous strengths, limitations do exist. First, the ultrasound technique is difficult to perform and requires a highly trained sonographer. Second, due to the sophisticated equipment and trained technician needed to conduct each test, FMD can be expensive, hindering the feasibility of this technique to be used in the general public. Important to note is that other reviews consider FMD to be inexpensive and refer to its low cost as an advantage; highlighting inconsistencies in how researchers view the strengths and limitations of this method. Third, the normalization of FMD for shear rate is under debate. Last, FMD gives insight to only one aspect of endothelial dysfunction (i.e. EDV), which doesn't take into account the complex nature of endothelial dysfunction (e.g., regulation of thrombosis and fibrinolysis, endothelial cell injury and repair, etc.).

Controversies

In addition to the strengths and limitations of FMD as a tool to measure endothelial function, controversies exist on this methods validity, generalizability, and assessment. In regards to validity, previous studies demonstrated that FMD is endothelium-dependent and mediated by NO in the radial, brachial, and superficial femoral arteries of humans, but not in other deep or smaller arteries (i.e., posterior tibial, popliteal, deep femoral, etc.) (Joannides et al., 1995; Kooijman et al., 2008). These findings suggest that vessel type and size may influence the relative contribution of NO to vascular reactivity, such that endothelial NO synthase differs throughout the arterial tree (Laughlin, Turk, Schrage, Woodman, & Price, 2003; Shimokawa et al., 1996). Therefore, the mediation of vasodilation may differ between conduit arteries, making this technique only valid for large superficial arteries in humans. Additionally, different

methodological approaches have shown to limit FMD's validity as a clinical research tool for endothelial function.

Regarding generalizability, controversy exists with the doctrine that FMD responses obtained at the brachial artery can be generalized to other vascular beds throughout the circulation. The concept that brachial artery FMD represents a "barometer" of systemic endothelial function is due to previous research reporting associations between brachial artery FMD and coronary artery vasomotor function. As a result, most studies measure brachial artery FMD to evaluate endothelial dysfunction. However, atherosclerotic lesions are distributed nonuniformly throughout the vasculature, with the lower limbs demonstrating a higher incidence of clinical vascular disease and claudication. Moreover, a plethora of studies over the past decade have demonstrated that upper and lower limb vasculatures demonstrate different vasomotor responses to shear and pharmacological vasoactive substances in humans. For instance, Thijseen and colleagues (2011) were the first to demonstrate that there was no correlation between brachial and superficial femoral artery FMD or between brachial and popliteal artery FMD. These data suggest that conduit artery vasodilator of the upper extremities is not predictive of that in the lower extremities. However, this study was conducted among young, healthy subjects, which may limit their results, such that subjects with cardiovascular risk factor or with endothelial dysfunction may have revealed a relationship between vasomotor properties of the lower and upper extremities. These findings have since been confirmed, albeit most studies were conducted in laboratory settings, include young, healthy subjects, and have shown transient effects. Given the nonexistent relationship between FMD of the conduit arteries in the upper and lower limbs, future studies should avoid generalizing brachial artery FMD as a systemic index of endothelial function in other vascular beds among healthy adults.

In regard to FMD assessment, uncertainty exists as to whether FMD should be normalized for shear stress and whether the current normalization methods appropriately reflect endothelial biology. Support for normalizing FMD for shear stress is based on the physiological and mechanistic basis that increased shear stress is the physiological stimulus for FMD. However, numerous factors can influence the physiological and mechanical transduction of shear stress into conduit artery dilation, such as arterial stiffness, blood viscosity, blood flow patterns and/or methodological variations. The uncertainty on normalizing FMD stems from the inconsistencies reported in the literature about the relationship between FMD and shear stress. For instance, the Framingham Heart Study found that local brachial artery shear stress at baseline and during reactive hyperemia were strongly associated with brachial artery FMD, as well as CVD risk factors (i.e. pulse pressure, obesity, fasting glucose, etc.) in their Offspring Cohort (n=2,045). These findings suggest that the shear stress response should be considered when interpreting the brachial artery dilatory response detected by FMD. In contrast, Dhindsa and colleagues (2008), among other studies, found that FMD was not significantly associated with reactive hyperemia or hyperemic shear stress, possibly due to the microvascular function involved with reactive hyperemia vs. macrovascular function detected by FMD. These conflicting results suggest that methods other than FMD, such as PAT, may be needed to understand the underlying physiology of peripheral micro-and macrovascular reactivity and its implications for endothelial function in healthy, at risk and diseased populations.

Other Endothelial Function Measures

Reactive Hyperemia Index

Since the beginning of the 21st century, abnormalities in pulse wave amplitude (PWA) in the peripheral vessels have been considered an independent marker of endothelial dysfunction (Kuvin

et al., 2003). Given the ability to measure PWA with noninvasive techniques, peripheral arterial tonometry (PAT) was developed to assess PWA during reactive hyperemia with the goal to noninvasively study peripheral vascular endothelial function (Kuvin et al., 2003, Schnall et al., 1999). PAT utilizes finger plethysmograph to measure changes in pulse wave amplitude (PWA) in response to reactive hyperemia. A most common name used for this technique is reactive hyperemia peripheral arterial tonometry (RH-PAT) and the most common device is called the EndoPAT 2000 (Itamar Medical, Caesarea, Israel).

RH-PAT measures changes in pulse wave amplitude (PWA) in response to reactive hyperemia. Reactive hyperemia is induced using the same methods described for FMD. However, instead of using a Doppler ultrasound machine, the EndoPAT 2000 device is used to measure changes in peripheral arterial tone. In order to do so, the EndoPAT 2000 uses finger plethysmography, which measures peripheral arterial tone from changes is PWA detected by pneumatic cuff probes placed on one finger of each hand (Bonetti et al., 2004). The pneumatic cuff encapsulates the middle finger of both hands and evaluates digital volume changes with each pulse wave (Kuvin et al., 2003). PWA measurements are recorded continuously before, during and after cuff deflation. An algorithm built in the EndoPAT 2000 analyzes the data and computes the reactive hyperemia index (RHI). RHI is the ratio of average PWA during the one-minute period after cuff deflation to the average pulse wave amplitude during 210-seconds baseline period (Kuvin et al., 2003).

Numerous studies have been conducted to show that RH-PAT is correlated with endothelial function, as well as other measures of endothelial function. For instance, RHI moderately correlates with endothelial vasodilator function in the coronary arteries (Bonetti et al., 2004) , and with brachial flow-mediated dilation (Kuvin et al., 2003). In regard to physiological mechanisms of endothelial function, pulse wave amplitude changes to RH-PAT compared to baseline have been

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shown to be NO-dependent, suggesting that PAT is a true measure of endothelial function (Martin et al., 2012, 10). However, there is evidence to suggest that FMD and EndoPAT™ reflect different aspects of vascular function in selected vascular beds and vessel size, suggesting that FMD and PAT measure different aspects of the hyperemic response. For instance, FMD measures the dilation capability of the large conduit arteries (i.e. brachial, femoral, radial), whereas PAT measures flow response hyperemia, which is related to endothelial function of the small arteries and microcirculation (Poredos & Jezovnik, 2013). Regardless, a systematic review and meta-analysis revealed that both FMD and RH-PAT significantly predicted cardiovascular events (adjusted relative risk [95% CI]: 1% increase in FMD 0.88 [0.84–0.91], P<0.001, 0.1 increase in natural log transformed RHI 0.79 [0.71–0.87], P<0.001), with similar prognostic magnitude (Matsuzawa, Kwon, Lennon, Lerman, & Lerman, 2015). Based on these findings, RH-PAT may be an accurate operator independent tool to identify patients with coronary microvascular endothelial dysfunction (Barac et al., 2007). Further research is needed to determine if RH-PAT is feasible and effective in cardiovascular risk stratification.

Endothelial Microparticles

In recent years, endothelial microparticles (EMPs) have emerged as a novel biomarker that provides valuable information about the biological status of the endothelium because they represent a direct measure of EC injury. Previous studies indicate that peripheral EMPs expressing CD62E+ are phenotypic for EC activation, and EMPs expressing CD31+ are indicative of EC apoptosis (Bernal-Mizrachi et al., 2003; Garcia et al., 2005; Joaquin J Jimenez et al., 2003). Jenkins and colleagues (2013) were the first to provide *in vivo* experimental evidence that disturbed blood flow in the distal forearm acutely induced endothelial activation and apoptosis in humans, as reflected by release of microparticles from activated ($CD62E^+$) and apoptotic ($CD31^+$/$CD42b^-$)

endothelial cells. Thus, one would hypothesize that the sustained reduction of shear stress during sitting would result in elevated circulating EMPs. To further elucidate the influence of reduced shear stress on endothelial cell injury, Navasiolava et al. (2010) used a model of extreme physical inactivity and found that circulating EMPs indicative of endothelial apoptosis (i.e., $CD31^+/CD42b^-$ EMPs) were significantly elevated following 7 days of dry water immersion, with no changes in plasma concentrations of soluble CD62D protein (Navasiolava et al., 2010). Similarly, but with a more modest physical activity reduction approach, Boyle and colleagues (2013) found that reducing daily physical activity by taking <5,000 steps/day and refraining from planned exercise led to significant elevations in $CD31^+/CD42b^-$ EMPs, with no alterations detected in $CD62E^+$ EMPs (Boyle et al., 2013). These authors hypothesized that the lack of increase in $CD62E^+$ EMPs and soluble CD62D protein may be because this marker is only expressed and released from endothelial cells when they are in an inflamed state (Boyle et al., 2013; J. J. Jimenez et al., 2003; Krogh-Madsen et al., 2010).

Endothelial Progenitor Cells

Bone marrow-derived EPCs are important biomarkers to evaluate when examining endothelial dysfunction because they are capable of EC repair and regeneration,(Adams et al., 2004; Mobius-Winkler, Hollriegel, Schuler, & Adams, 2009; Umemura & Higashi, 2008; Urbich & Dimmeler, 2004) indicating that endothelial function represents a balance between EC injury and repair. Detraining and inactivity have shown to play a role in reducing the vascular regenerative capacity of EPCs, which might suggest that chronic exposure to a sedentary life style may be associated with lower percentage of EPCs among adults (M. D. Ross, Malone, & Florida-James, 2016; Witkowski et al., 2010). Moreover, a reduced number of circulating EPCs are associated with traditional risk factors and the presence of atherosclerosis(Jevon, Dorling, & Hornick, 2008;

Mobius-Winkler et al., 2009; Werner et al., 2005), as well as predicts an increased occurrence of CVD events and death from cardiovascular causes.(Werner et al., 2005)

According to Fadini et al. (2008), CD34 and KDR display an overlapping expression on stem cells and endothelial cells. CD34 and KDR are expressed on primary hemangioblast islets in the yolk sac mesoderm during early embryonic vasculogenesis, suggesting that $CD34^+KDR^+$ cells could be immature cells with endothelial priming (Pelosi et al., 2002). Although, $CD34^+KDR^+$ cells may represent putative EPCs or post-natal hemangioblast, the $CD34^+KDR^+$ phenotype may overlap in part with that of mature endothelial cells because CD34 is also expressed on some microvascular endothelia. Of the putative EPC phenotypes, $CD34^+KDR^+$ produces the highest cell counts and is the only phenotype to repeatedly and convincingly be demonstrated as an independent predictor of cardiovascular outcomes (Fadini et al., 2008).

Although $CD34^+KDR^+CD133^+$ and $CD133^+KDR^+$ phenotypes of EPCs may be more specific, reduced $CD34^+KDR^+$ EPCs have been associated with the earliest anatomic sign of atherosclerotic remodeling, increased intima-media thickness, in healthy subjects independently of CRP and Framingham risk score (Fadini et al., 2012, Fadini et al., 2006, Chironi et al., 2007). Moreover, Schmidt-Lucke et al. (2005) found that a $CD34^+KDR^+$ EPC level below the median value was associated with a higher incidence of composite CV end point suggestive of atherosclerotic disease progression (Fadini et al., 2012). Werner et al. (2005) found that $CD34^+KDR^+$ EPCs were predictive of a first major cardiovascular event, independent of potential confounders (Fadini et al., 2012). According to a review by Fadini and colleagues (2012), the $CD34^+KDR^+$ antigenic combination appears to be the best EPC phenotype in terms of sensitivity, specificity and reliability to quantify EPCs in the clinical setting.

Future Directions

Methods used to assess endothelial function should be safe, noninvasive, reproducible, repeatable, affordable, and standardized between laboratories. Based on the existing literature and evidence, it appears that the measurement of endothelial function with FMD via ultrasound meets most of these requirements, but improvements are needed with standardization. Future studies should confirm the validity and reproducibility of FMD in large clinical series, as well as isolate and examine within and between subjects' relationship between shear rate and FMD. The limited literature on FMD as a valid measure in small, deep arteries suggest that further work is needed to determine to role of NO in mediating FMD responses in these types of arteries. Most importantly, endothelial function assessment should reflect the complex biology of the endothelium throughout the natural history or atherosclerotic disease, suggesting that FMD assessment alone may not be sufficient to capture the dynamic endothelial biology. Thus, future studies should include simultaneous measurements of cellular (i.e., endothelial microparticles, endothelial progenitor cells, etc.), microvascular (i.e., PAT via EndoPAT), and macrovascular (FMD) assessments to fully capture the multifaceted nature of endothelial function.

Conclusion

Overall, multiple techniques, both invasive and noninvasive in nature, have been developed to measure and interpret endothelial dysfunction. Based on the existing literature and evidence to date, intracoronary infusion of vasoactive substances and FMD are considered the gold standard invasive and noninvasive methods to assess endothelial dysfunction, respectively. Given the limitations of invasive techniques, FMD is widely used in clinical research. FMD had proven to be a powerful predictor of future CVD is asymptomatic men and women, as well as an independent predictor of future CVD events and survival in patients with existing CVD. The validity and reliability of FMD are controversial when compared to invasive methods, but superior when

compared to other noninvasive techniques. Overall, FMD appears to be a valuable noninvasive technique to evaluate endothelial dysfunction via EDV, but future research is needed to improve the validity, standardization and interpretation of this technique.

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APPENDIX B

EndoPAT™ Protocol

Endothelium-dependent vasodilation

Background. Endothelium-dependent vasodilation will be assessed by a peripheral arterial tonometry (PAT) device (EndoPAT™2000). The EndoPAT™2000 is a small, portable device that is approved by the FDA for endothelial function testing. The EndoPAT™2000 non-invasively measures the endothelium-mediated alterations in vascular tone in peripheral arterial beds. The PAT probe is attached to a pressure transducer and through it to the central processing unit, which records the amplitude of each pulse wave as a continuous tracing, providing a measure of the micro-arterial smooth muscle tone in the fingertip. To induce reactive hyperemia, the BP cuff located on the non-dominant forearm is inflated for 5 minutes to whichever occlusion pressure is higher: 200 mmHg or 60 mmHg plus systolic BP. After the 5-minute occlusion period, the cuff is deflated, while PAT recording continues.

RHI will be quantified using the Framingham algorithm calculated as the ratio of the average amplitude of the PAT signal over a 90-120 second post deflation period after cuff deflation divided by the average amplitude of the PAT signal of a 2-minute period before cuff inflation (resting). RHI values from the study arm are normalized to the control arm. RHI is the primary measure of endothelial-dependent vasodilation in this study.

Protocol for EndoPAT™ set up:

1. Switch on:
    a. Laptop (password: [personal profile password entered])
    b. EndoPAT™2000 device (**at least 20 minutes prior to use**) using on/off switch found on the back panel of the device towards the bottom. The power indicator light will glow orange, indicating that the power is turned on.
    c. Ensure USB-to-COM adaptor cable is connected to the USB port closest to the track pad of the computer. (COM24 was established and is automatically selected when using this specific USB port)
    d. Connect two new probes to the EndoPAT™2000 system connectors.
    e. Launch EndoPAT™2000 software by double clicking on the Endo-PAT2000 icon found on the desktop.
2. When Endo-PAT™2000 software is launched, the main screen will appear and an automatic COM port search and communication test with the device will be performed. Communication with the device using COM24 is automatically established if the USB-to-COM adaptor cable is connected to the proper USB port described above.
    a. If the software is unable to establish communication with the device, a COM-port search dialog box will open. While the dialogue box is open the system continues trying to establish communication with the device, going through COM ports 1 to 10 in a cyclical manner. This continues until communication is established or "Work Disconnected" is selected.

EndoPAT™ Connection:

1. RC takes two BPTru readings on the subject's nondominant arm (one minute apart), calculates the average BP reading, and uses this average BP value to create the EndoPAT™ patient file as follows:

   1) Click on the 'patient information' icon on the tool bar or activate the Patient information dialog box from the Test Analysis menu.
   2) All mandatory fields must be completed in order to proceed to the next step. The field description is as follows: Enter Patient ID (Ex. PUME1234 [SID number]), Age, Gender, Systolic and Diastolic BP (use the average BP calculation from the initial BPTru readings), Height (ft/in) and Weight (lb). Although height and weight are required, these values are not used for data analysis. Standard height and weight values can be entered for all subjects.
   3) Once the required fields are completed, click OK. The Patient Information dialog box will close.

      Note: The data acquired during a study session is automatically stored to the computer's hard disk in the following location: Local Disk (C:) > Itamar-Medical > Data. This data will also be saved to the Columbia University Network P-drive and Pume USB drive in the locations specified in the 'EndoPAT Data Analysis' section below, once the session is completed.

      The file name of the stored data will correspond with the Patient ID initially entered and file type suffix: S32 (Ex. PUME1234.S32). This data can be subsequently retrieved for off-line review and analysis.

2. RC inserts intravenous catheter in the participant's dominant arm.
3. RC places EndoPAT™ arm-supports on tables along both sides of the participant and inserts the PAT probes inside the arm-support sockets.
   6. RC fully deflates the probes by pressing the deflate button on the device.
   7. RC places study fingers into the probes, making sure the fingers are inserted all the way to the end of the probe.
      a. RC instructs participant to fit wire against fingertip (underneath fingernail)
         i. The index finger is the recommended finger for the study; however if the index finger is too large to comfortably fit into the probe or is otherwise unsuitable, another finger (except the thumb) may be used, as long as it is the same finger in both hands
   8. RC inflates probes by pressing the Inflate button on the device or clicking on the icon.
   9. RC lifts the participant's probed index finger out of the arm socket, removes the arm-support, and places the participant's hand on the side table. Instructions provided to maintain the arm with the IV straight.
   10. A blue foam anchor ring is placed on the adjacent finger (middle finger) of the probed finger, as near as possible to the finger's root.
      a. The anchors should be placed as far back as possible on the finger so that they do not come in contact with the PAT probe (such contact may result in mechanical artifacts during recording).

11. RC pulls back the tubing stemming from the anchor and tapes it to the hand's dorsal surface, ensuring probes and foam anchor are free of contact with any object, including the supporting surface.
12. RC instructs the patient to refrain from moving the fingers to the extent possible.
13. RC tapes the participant's arm with the IV to the arm board.
14. The EndoPAT™ BP cuff is applied snuggly, without excess pressure, on the non-dominant forearm and left deflated.
15. RC selects Standby Mode on the EndoPAT™ system, confirms PAT signals, and adjusts amplitude and time settings for a clear visual display of signals.
Note: On standby mode, data is not being recorded.

EndoPAT Recording:

21. RC ensures correct placement of participant's hands, checks PAT signals, sets timer, and presses "**GO**" on the EndoPAT™ computer to begin the EndoPAT™ **Baseline Period** (5 minutes)

22. RC inflates blood pressure cuff to 250mmHg (or +60mmHg above systolic BP as determined by the BPTru rating at baseline) to begin the **Occlusion Period** (5 minutes)

23. RC deflates blood pressure cuff to begin the **Post-Occlusion** Period (5 minutes)

24. RC flags mood inductor in the control room and inductor confirms readiness by flagging RC back.

25. RC notates end time of **Post-Occlusion** Period

EndoPAT Data Analysis:

1. Prior to data analysis for each timepoint, refer to the 'EndoPAT Testing Data Collection' case report form for progress notes highlighting any deviations or issues encountered during all five EndoPAT™ sessions conducted for each laboratory visit. These forms can be found in the following location by subject ID #: P:\Study Folders\PUME\CRFs
2. To begin analysis, open the EndoPAT software and click on the 'Open file' icon found on the main screen tool bar to acquire data automatically stored for completed study sessions.
3. A dialog box titled 'Open S32 file' appears displaying the 'Data' folder
4. Select the desired study session file from the list (Note: file name will appear as PUME(SID#).S32, Ex: PUME7016.S32) and copy and paste into the:
   a) Columbia Network P Drive (P:) > Desktop > EndoPAT - Shortcut > COMPLETED LAB VISITS 2013-2014 > RAW DATA, and
   b) USB Drive (F:) > PUME > COMPLETED LAB VISITS 2013-2014 > RAW DATA
5. Once the study session file has been saved in both locations, double click on the file to open and view results

6. Adjust amplitude and time settings for a clear visual display of signals
7. <u>Identify and manually mark the Occlusion Period, Artifacts, and Segments</u> (Baseline and Test)
   a) <u>Occlusion Period</u> - Find the start occlusion point (the point at which baseline signals fluctuate), point the mouse and right click to select 'Set Automatic 5 min Occlusion' from the popup menu. A five minute occlusion period will be marked in BLUE. The end occlusion point selected can be adjusted by clicking and dragging to the point desired.
   b) <u>Artifacts</u> – Include PAT leaks and noise/mechanical artifacts, appearing as abnormal signal spikes, in the baseline and test periods. Artifacts must be marked prior to identifying baseline and test segments to ensure exclusion from data analysis.
      ▪ Select an artifact by selecting and dragging the mouse horizontally and highlighting the segment. Mark the artifact in YELLOW by clicking on the 'Mark Segment as Artifact' icon found on the toolbar.
   c) <u>Baseline Segment</u> - **Two minute period** directly before the occlusion period.
      ▪ Highlight the segment by selecting and dragging the mouse horizontally from the start occlusion point to the left for a two minute period. Mark the segment in GREEN by clicking on the 'Mark Segment as Baseline' icon found on the toolbar.
   d) <u>Test Segment</u> - **90-120 second post deflation period** (i.e. starting 90 seconds after cuff deflation point and continuing for 30 seconds until 120 seconds after cuff deflation).
      ▪ Identify the 90 second post deflation point by dragging the mouse horizontally, from the end occlusion point to the right, for 90 seconds. At this 90 second mark, begin selection by selecting and dragging the mouse horizontally to the right for a 30 second period. Mark the segment in RED by clicking on the 'Mark Segment as Test' icon found on the toolbar.

Note: Manual selection of segments and artifacts providing automated PAT ratios must be performed and notated for each individual occlusion period. The EndoPAT™ software will not save these automated calculations. There are a total of five occlusion periods conducted during every laboratory visit.

8. <u>Reactive Hyperemia Index (RHI) Analysis</u>
   a) After the baseline and test segments are manually marked, their PAT ratios are automatically calculated and results are displayed on the right side of the screen as T/B1 (Probe 1) and T/B2 (Probe 2).
      ▪ During recording, T/B1 (Probe 1) and T/B2 (Probe 2) must be identified as the test arm and control arm in order to calculate the RHI. Identification of arms is documented on the 'EndoPAT Testing Data Collection' case report form mentioned earlier.

- Formula used to calculate RHI is: **Test Arm/Control Arm**

b) PAT ratios must be entered into Filemaker upon completion of EndoPAT™ analysis for all five timepoints.

c) Standardized RHIs are automatically calculated when PAT ratios for test arm and control arm are entered into the Filemaker database for each laboratory visit.

d) PAT ratios are also notated and documented in 'EndoPAT Results and Analysis' spreadsheet located in Columbia Network P Drive (P:)
  - P:\Study Folders\PUME\EndoPAT\COMPLETED LAB VISITS 2013-2014\ RHI Data Analysis

Endothelial Cell Transformations

Report prepared on March 23, 2018 by William F. Chaplin and Ipek Ensari

Overview

   There are three measure of endothelial function that were the primary outcome variables, RHI, EMP CD62, and EPC CD34/KDR. Of these the most well-established measure is RHI. We began by assessing these variables distributional properties and transformed them as appropriate. Specifically, we began by assessing the data for outliers by the visual inspection of boxplots (see below). If outliers were detected we winsorizing the data by changing the outlying values of the cases to the most extreme, but non-outlying value in the data set. For all the cases on one tail of the distribution that were winsorizing we changed the values of an equivalent number of cases on the other tail using the same procedure even if those cases were not outliers. Once the outliers had been winsorizing we then assessed the distribution for non-normality and undertook a further transformation (e.g. natural log, square root) to reduce the skewness.

Transformations

<u>RHI</u>: The RHI data was not highly skewed, but did contain some outlying data points. Across the 5 time points the skewness values are 1.13, .844, .905, 1.17, and 1.04. To reduce the impact of the outliers on the analyses we winsorized these data. Specifically, at baseline, 3 minutes and 40 minutes we identified one case at each time that had an outlying value of 6 and these values were winsorized. For 70 and 100 minutes there were no clear outlying values so no winsorization performed.

 Here is the boxplot of the original RHI data at baseline (the only time point used for current analysis):
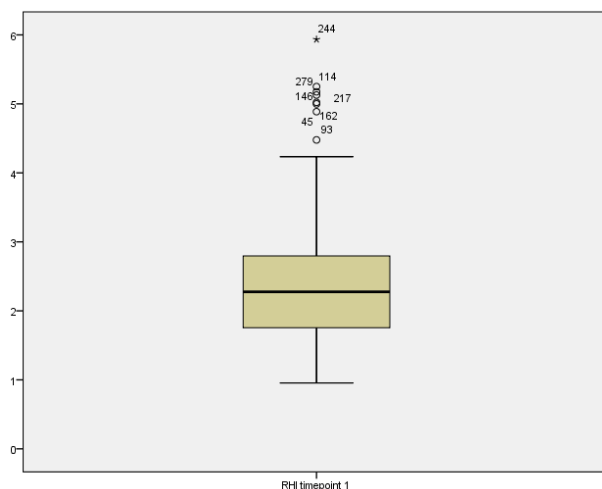
EMP62: We began by using a standard correction factor of the EMP data which was to multiply each value by .91441. We then assessed these corrected data for outliers and non normality. For the baseline values 19 high scores were winsorized, at 3 minutes 14 high scores were winsorized, at 40 minutes, 14 scores were winsorized, at 70 minutes 14 were winsorized and at 100 minutes 14 were winsorized. Although the winsorizing reduced the skew, the data was still substantially non-normal with skewness values across the 5 time points of 4.73, 6.38, 5.30, 6.86, and 5.87, respectively. Thus, we further used a natural log transformation on the data. This transformation greatly reduced the skew to .649, .464, .443, .523, and .613.

Here is the boxplot of the original EMP62 data at baseline:
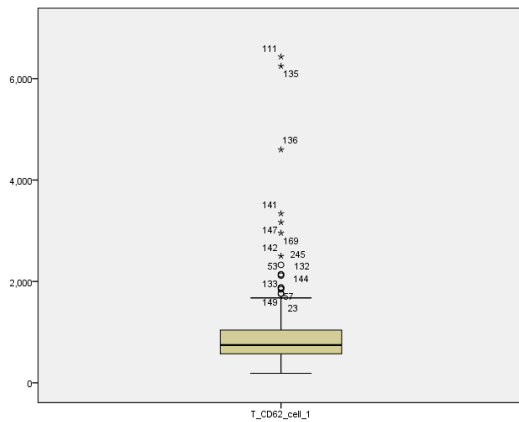
EPC CD34 KDR: We first applied a standard correction factor to the EPC data which was to divide each value by 20,000 which converts the raw data into a proportion of antibody/per 20,000 cells. We then assessed these data for outliers and winsorized 9 cases with high scores at baseline, and 19, 14, 8, and 29 at time points 2 through 5 respectively. Again, winsorizing the data reduced, but did not eliminate the skewness. The skewness values were 2.49, 1.96, 2.03, 2.51, 1.70 across the 5 time points, respectively. We performed a square root transformation on these data because 0 was a possible value. These reduced the skewness to 1.22, 1.07, .992, 1.34, and .941 across the time points, respectively.

Here is the boxplot for the raw EPC data at baseline:
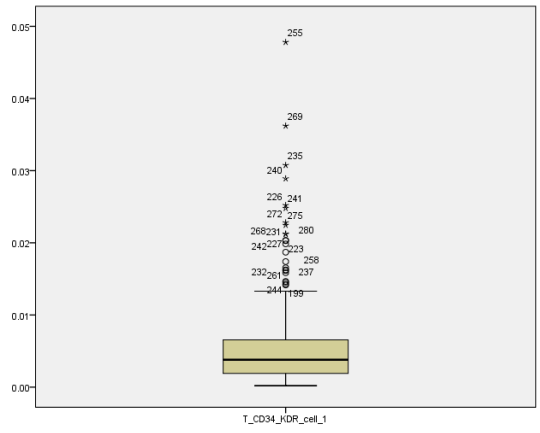
Mean Sedentary Time Estimate Equation

$$AUC = \int_{-\frac{13.5}{7}}^{\frac{13.5}{7}} (a + bX + cX^2)\, dx = \left|_{-\frac{13.5}{7}}^{\frac{13.5}{7}} \left(aX + \frac{bX^2}{2} + \frac{cX^3}{3} \right)\right.$$

$$= \left(\frac{27}{7}\right) a + 0b + \frac{2}{3}\left(\frac{13.5}{7}\right)^3 c = \left(\frac{27}{7}\right) a + \frac{2}{3}\left(\frac{13.5}{7}\right)^3 c$$

$$Mean = \frac{AUC}{width} = \frac{AUC}{\left(\frac{27}{7}\right)} = a + \left(\frac{1}{3}\right)\left(\frac{13.5}{7}\right)^2 c = a + 1.2398\, c$$

APPENDIX E

Study One Instruments

ActivPal Care and Instructions

Placement and Use

- The activePAL™ should be worn on the mid-line of the thigh, one third of the way between the hip and knee. The rounded top of the activePAL™ should be upright pointed toward your head. A nitrile flexible sleeve should be wrapped around the activePAL™ to ensure it is not damaged by the adhesives.
- The activPAL may be worn in the shower; however, must never be fully submerged in water (e.g. baths, swimming)

For Adhesion:

- **Tegaderm film may be used.**
    1. Peel off back of tegaderm film
    2. Place tegaderm film over the activePAL™ that is in a nitrile sleeve
    3. Peel off the edges of the tegaderm wrapper after placement
    4. Replace tegaderm when uncomfortable, when adhesion decreases, or after showering
    5. The tegaderm dressing is easiestly removed after showering or exercising (sweating).
    6. To remove the tegaderm, pull on the activPAL monitor. The tegarderm dressing should come off as you remove the monitor from your thigh
        - * If you are having extreme difficulties removing the tegaderm dressing, use scissors to cut the dressing around the activPAL monitor. Then peel off the tegaderm.
- **Hypafix tape may be used.**
    1. Peel off backing of hypafix tape
    2. Place hypafix tape over the activePAL™ that is in a nitrile sleeve
    3. Make sure that the entire activePAL™ is covered by the hypafix tape
    4. Remove in same fashion as tegaderm film

Start Date:_____   Drop-Off Date:_____

Sleep Diary

Instructions: In the table below, record the times when you got into bed and when you turned off the lights to go to sleep. Also record the times when you woke up and when got out of bed to start your day.

Night of Sleep	What time did you get into bed?	What time did you turn the lights off to go to sleep?	What time did you wake up?	What time did you get out of bed to start the day?
Night 1	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM
Night 2	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM
Night 3	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM
Night 4	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM
Night 5	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM
Night 6	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM
Night 7	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM
Night 8	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM	Time:_____ ☐AM ☐PM

Activity Monitor Removal Diary

Instructions: In the table below, record any time that you removed the activity monitor from your thigh. Also record the time when you re-attached the monitor.

What day and time did you remove the monitor?		What day and time did you re-attach the monitor?		Reason for removal:
Date (mm/dd)	Time HH:MM AM/PM	Date (mm/dd)	Time HH:MM AM/PM	Describe in a brief sentence.
__/__	Time:_____ ☐AM ☐PM	__/__	Time:_____ ☐AM ☐PM	
__/__	Time:_____ ☐AM ☐PM	__/__	Time:_____ ☐AM ☐PM	
__/__	Time:_____ ☐AM ☐PM	__/__	Time:_____ ☐AM ☐PM	
__/__	Time:_____ ☐AM ☐PM	__/__	Time:_____ ☐AM ☐PM	
__/__	Time:_____ ☐AM ☐PM	__/__	Time:_____ ☐AM ☐PM	
__/__	Time:_____ ☐AM ☐PM	__/__	Time:_____ ☐AM ☐PM	
__/__	Time:_____ ☐AM ☐PM	__/__	Time:_____ ☐AM ☐PM	
__/__	Time:_____ ☐AM ☐PM	__/__	Time:_____ ☐AM ☐PM	

For Research Personnel
ID:_____   RP Entering Data: _____   RP Reviewing Data: _____

PUMÉ
<u>P</u>utative Mechanism <u>U</u>nderlying <u>M</u>yocardial Infarction Onset and <u>E</u>motions
Endo-PAT Testing Data Collection

Date: MM/DD/YY   **Subject ID: XXXX**

Age: _____ Room Temp: _____   Blood Pressure: _____

Amplitude: _____ Time: _____ Test Arm Probe: _____

Forearm Cuff Inflation Pressures

Time Point 1: _____   Time Point 2: _____   Time Point 3: _____

Time Point 4: _____   Time Point 5: _____

Notes:

_____
_____
_____
_____
_____

RHI Analysis:

Time Point 1 = <u>Test Arm</u> = _____ = _____
                     Ctrl Arm

Time Point 2 = <u>Test Arm</u> = _____ = _____
                     Ctrl Arm

Time Point 3 = <u>Test Arm</u> = _____ = _____
                     Ctrl Arm

Time Point 4 = <u>Test Arm</u> = _____ = _____
                     Ctrl Arm

Time Point 5 = <u>Test Arm</u> = _____ = _____
                     Ctrl Arm

APPENDIX F

Study Two and Three Instruments

TO BE COMPLETED BY ENDPOINT COMMITTEE

Reviewer#:   ☐1   ☐2   ☐3 (as needed)

Reviewer Name: _____

A MACE OUTCOME will be defined by:

PRIMARY MACE EVENT
Mortality
Myocardial infarction hospitalization
Unstable angina hospitalization
Need for urgent PCI or CABG

ADDITIONAL MACE EVENTS
Hospitalization for heart failure
Hospitalization for stroke
Hospitalization for TIA
Hospitalization for major bleeding episode
Hospitalization for elective PCI
Hospitalization for elective CABG
Hospitalization for peripheral arterial revascularization (percutaneous or surgical)

Use the subject's hospitalization chart to answer the following (see next page for definitions):

	NO	YES
Was patient admitted/discharged with an ACS event diagnosis?	☐	☐
If YES, please classify the type of ACS:		
Unstable Angina	☐	☐
Myocardial Infarction (MI)	☐	☐

If YES to MI, please classify type:

☐ ST-segment Elevation
☐ Non-ST-segment Elevation
☐ Bundle Branch Block/Uncertain Type

DEFINITIONS

UNSTABLE ANGINA

Angina pectoris (or equivalent type of ischemic discomfort) with no biochemical evidence of myocardial infarction (see below) and <u>any</u> of the following within the past 6 weeks:

- Angina occurring at rest and prolonged, usually greater than 20 minutes.
- New onset angina of least CCS class II severity.
- Recent acceleration of angina reflected by an increase in severity of at least 1 CCS class to at least CCS class II.

Class I: Ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.

Class II: Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, or in cold, in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal condition.

Class III: Marked limitations of ordinary physical activity. Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.

Class IV: Inability to perform any physical activity without discomfort—anginal symptoms may be present at rest.

MYOCARDIAL INFARCTION (MI)

Defined as one of the following:

- ST elevation MI - Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of MI (see below) with new or presumed new ST segment elevation (greater than or equal to 0.1 mV) at the J point in 2 or more contiguous leads.
- Non ST elevation MI - Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of MI (see below) with one of the following (in the absence of ST elevations):
  - ST segment depression
  - T wave abnormalities
  - Ischemic symptoms without ST segment depression or T wave abnormalities, in the presence or absence of chest discomfort (unexplained nausea and vomiting or diaphoresis; persistent shortness of breath; unexplained weakness, dizziness, lightheadedness, or syncope).
  - Bundle Branch Block/Uncertain Type MI -Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of myocardial necrosis (see next section) with:
  - Left BBB (new or old) or paced rhythm.
  - The initial ECG findings are not available or the patient presents beyond the time of ST segment changes (e.g. greater than 24 hours).

Biochemical Evidence of Myocardial Infarction (at least one of the following):

- Maximal concentration of troponin I greater than the MI decision limit on at least 1 occasion during the first 24 hrs after the index clinical event:
- Maximal value of CKMB, preferably CKMB mass, greater than upper limit of normal on 2 successive samples, OR maximal value of CKMB greater than 2 times the upper limit of normal on 1 occasion during the first hours after the index clinical event.
- Total CK (in absence of troponin or CKMB assay) greater than 2X the upper limit of normal.

NOTE: Reference values must be determined in each laboratory by studies using specific assays with appropriate quality control, as reported in peer-reviewed journals. Acceptable imprecision (coefficient of variation) at the 99th percentile for each assay should be defined as less than or equal to 10%. Each individual laboratory should confirm the range of reference values in their specific settings.

Upper limits of Normal at CUMC:

Cardiac Troponin I	0.39 ng/mL
CK-MB	5.5 ng/mL
Creatine Kinase (CK)	Male: 294 U/L
	Female: 238 U/L

	NO	YES
Patient admitted/discharged with a diagnosis of heart failure............	☐	☐

Patient admitted/discharged with a diagnosis of stroke .... ☐   ☐
[Loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms at least 24 hours after the onset. Neuroimaging is not required for the diagnosis of infarct]

Patient admitted/discharged with a diagnosis of TIA .... ☐   ☐
[A focal neurological deficit (usually corresponding to the territory of a single vessel) that resolves spontaneously without evidence of residual symptoms at 24 hours. Neuroimaging can be positive or negative for the presence of infarct]

Patient admitted/discharged with a diagnosis of major bleeding....... ☐   ☐
[TIMI Major bleeding: overt clinical bleeding (or documented intracranial or retroperitoneal bleeding) associated with a drop in hemoglobin greater than 5 g/dL or in hematocrit of greater than 15% (absolute).

Cardiovascular Procedures During the Hospitalization

PCI Performed.. ☐   ☐

If YES, then note status of the PCI.

☐ **Elective**
[The procedure could be deferred without increased risk of comprised outcome]

☐ **Urgent**
[Not elective, not emergent, and procedure required during same hospitalization to minimize chance of further clinical deterioration]

☐ **Emergent**
[Either of the following:

    A. Ischemic dysfunction (ongoing ischemia, acute MI, and/or pulmonary edema requiring intubation)
    B. Mechanical dysfunction (shock with or without circulatory support)

NOTE: "emergent PCI" as an event will be captured under ACS events]

Coronary Artery Bypass Surgery Performed........................... ☐   ☐

If YES, then note status of the CABG.

☐ **Elective**
[The procedure could be deferred without increased risk of comprised outcome]

☐ **Urgent**
[Not elective, not emergent, and procedure required during same hospitalization to minimize chance of further clinical deterioration]

☐ **Emergent**

[Either of the following:

      A. Ischemic dysfunction (ongoing ischemia, acute MI, and/or pulmonary edema requiring intubation)
      B. Mechanical dysfunction (shock with or without circulatory support)

      NOTE: "emergent CABG" as an event will be captured under ACS events]

Peripheral Arterial Revascularization......................................☐   ☐
[includes percutaneous route or surgery; includes carotid revascularization]

Other Cardiovascular Procedures...☐   ☐

      If YES, please list procedures here:

      _____

      _____

      _____

      _____

      _____

      _____

      _____

      _____

Subject Initials: _____

Staff ID: _____   Staff Signature: _____

Date (this form completed): _____ / _____ / 20___   Time: ____:____ am/pm
           Month   Day   Year

Contains:
Eligibility Form
ACS Symptoms form
BDI
BDI-II (partial)
BDI #9
Mini Mental State Exam (MMSE)
Psychosis Screen
Risk Factors Assessment
AUDIT
Substance Abuse Screening

ELIGIBILITY FORM

Center: _____ Hosp: _____ Subject ID: _____ Subject Initials: _____

Staff ID: _____ Staff Signature: _____

Date (this form completed): _____ / _____ / 20____   Time: ____:____ am/pm
                            Month Day   Year

ELIGIBILITY

	No	Yes
1. Presence of Acute Coronary Syndrome (ACS) categorized by either unstable angina or myocardial infarction?...	□₀	□₁ (If YES: go on)

	No	Yes
2. Documentation of ACS is photocopied and available for review?	□₀	□₁ (If YES: go on)

*If the patient meets criteria for ACS, please check **one** of the following:*

3a. ☐ Unstable Angina

Angina pectoris (or equivalent type of ischemic discomfort) with no biochemical evidence of myocardial infarction (see below) and **any** of the following within the past 6 weeks:
    a. Angina occurring at rest and prolonged, usually greater than 20 minutes.
    b. New onset angina of least CCS class II severity.
    c. Recent acceleration of angina reflected by an increase in severity of at least 1 CCS class to at least CCS class II.

Class I: Ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
Class II: Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, or in cold, in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal condition.
Class III: Marked limitations of ordinary physical activity. Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.

3b. ☐ Non-ST-Elevation Myocardial Infarction

Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB or CK) of biochemical markers of myocardial infarction (see below) with one of the following (in the absence of ST elevations):
    a. ST segment depression
    b. T wave abnormalities
    c. Ischemic symptoms without ST segment depression or T wave abnormalities, in the presence or absence of chest discomfort (other ischemia symptoms include: unexplained nausea and vomiting or diaphoresis; persistent shortness of breath; unexplained weakness, dizziness, lightheadedness, or syncope).

3c. ☐ **ST-Elevation Myocardial Infarction**

Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB or CK) of biochemical markers of myocardial infarction (see below) with new or presumed new ST segment elevation (greater than or equal to 0.1 mV) at the J point in 2 or more contiguous leads.

3d. ☐ **Bundle Branch Block/Uncertain Type Myocardial Infarction**

Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB or CK) of biochemical markers of myocardial necrosis (see next section) with:
   a. Left BBB (new or old) or paced rhythm.
   b. The initial ECG findings are not available or the patient presents beyond the time of ST segment changes (e.g. greater than 24 hours).

Biochemical Evidence of Myocardial Infarction (at least one of the following):

   a. Maximal concentration of troponin I greater than the MI decision limit (**positive ≥0.40 ng/mL at CUMC**) on at least 1 occasion during the first 24 hrs after the index clinical event:
   b. Maximal value of CKMB, preferably CKMB mass, greater than upper limit of normal (**positive > 5.5 ng/mL**) on 2 successive samples, OR maximal value of CKMB greater than 2 times the upper limit of normal (**positive > 11 ng/mL at CUMC**) on 1 occasion during the first hours after the index clinical event.
   c. Total CK (in absence of troponin or CKMB assay) greater than 2X the upper limit of normal (**positive > 588 U/L for males; positive > 476 U/L for females**).

Upper limits of Normal at CUMC:

Cardiac Troponin I	0.39 ng/mL
CK-MB	5.5 ng/mL
Creatine Kinase (CK)	Male: 294 U/L
	Female: 238 U/L

	No	Yes
4. Physician gave patient participation	$\square_0$	$\square_1$ (If YES, go or
5. Patient does not have terminal illness...	$\square_0$	$\square_1$ (If YES, go on)
6. Patient speaks English or Spanish...	$\square_0$	$\square_1$ (If YES, go on)
7. Patient is over 18 years of age...	$\square_0$	$\square_1$ (If YES, go on)
8. Patient agrees to screening / consent	$\square_0$	$\square_1$ (If YES, go on)
9. Patient available for follow-up..	$\square_0$	$\square_1$ (If YES, go on)
10. Patient able to complete screening	$\square_0$	$\square_1$ (If YES, go on)

Score on AUDIT _____

	No	Yes
11. Patient does not have current alcohol/substance abuse disorders.....	$\square_0$	$\square_1$ (If YES, go on)
12. Patient does not have serious cognitive impairments...........................	$\square_0$	$\square_1$ (If YES, go on)

(*For grade level > 8th grade, MMSE < 24; for grade level $\leq$ 8th grade, MMSE < 17*)

	No	Yes
13. Patient does not have active suicidal or homicidal ideation?..............	$\square_0$	$\square_1$ (If YES, go on)

(*If ideation is present, institute appropriate protocol*)

	No	Yes
14. Patient does not have current DSM-IV psychotic	$\square_0$	$\square_1$ (If YES, go on)
14a. Any positive symptoms on psychosis screen (current or by history) .	$\square_0$	$\square_1$
14b. If yes, any mitigating factors that convincingly account for symptoms (medication/drug/alcohol intoximation or withdrawal effects, fever, or severe illness, etc.)	$\square_0$	$\square_1$
14c. Does the patient report any psychotic symptoms (current or by history) that suggest a psychiatric disorder that would rule him/her out of the study?..	$\square_0$	$\square_1$
15. Patient is not a prisoner...	$\square_0$	$\square_1$ (If YES, go on)
16. Patient is within screening window..	$\square_0$	$\square_1$ (If YES, go on)
17. Patient qualifies for study?	$\square_0$	$\square_1$
18. Patient consents to study?	$\square_0$	$\square_1$

If patient does NOT qualify or NOT consent for study, collect the following:

.. **Age** _____

2. Sex (check one) $\square_1$ Male $\square_2$ Female

3. Which of the following best describes ethnicity? (check one)

$\square_1$ Hispanic or Latino $\square_2$ Not Hispanic or Latino

4. Which of the following best describe(s) Race? Check one

$\square_1$ White (non-Hispanic)
$\square_2$ White (Hispanic)
$\square_3$ Black (non-Hispanic)
$\square_4$ Black (Hispanic)
$\square_5$ Asian/Indian
$\square_6$ Asian/Pacific Islander
$\square_7$ Native American
$\square_8$ Other_____
$\square_9$ Unknown
$\square_{10}$ Decline to State

ACS SYMPTOMS FORM

Type of Symptoms (check all that apply):

- ☐ Chest pressure/pain
- ☐ Arm or jaw pain
- ☐ Dyspnea/shortness of breath
- ☐ Nausea/vomiting
- ☐ Syncope
- ☐ Other _____

Symptom Onset that Prompted Medical Attention:

Date: (XX/XX/XXXX): _____/_____/_____
Time: (XX:XX; military time): _____:_____

[Date and time of the onset of symptoms that prompted the patient to seek medical attention. Symptom onset refers to the onset of cardiac ischemic symptoms related to this acute event, commonly appearing as chest pain or pressure, arm or jaw pain, dyspnea, nausea/vomiting, or syncope. In the event of stuttering symptoms, ACS symptom onset is the time at which symptoms became constant in quality or intensity]

First Onset of these Symptoms

Date: (XX/XX/XXXX): _____/_____/_____
Time: (XX:XX; military time): _____:_____

[When were above symptoms FIRST noticed by patient]

Symptoms came and went, or were continuous?
☐ Came and went   ☐ Were continuous

If Came and Went, answer the following:
Total Number of Distinct Episodes of Ischemic Symptoms Prior to Admission:
_____

Number of Distinct Episodes of Ischemic Symptoms in the Last 24 hours Prior to Admission: _____

When did patient call 911, go to the Emergency Room, or call or go to physician's office?

Date: (XX/XX/XXXX): _____/_____/_____
Time: (XX:XX; military time): _____:_____

Psychosis History Screening Questions

or Staff: For each psychotic symptom coded "3," describe the actual content and the period of time during
'ich the symptom was present.

For any psychotic and associated symptoms coded "3," determine whether the symptom is definitely "primary"
or whether there is a possible or definite etiologic substance (including medications) or general medical
condition.

> The following questions may be useful if the overview has not already provided the information:
> Just before (PSYCHOTIC SXS) began:
> -Were you using drugs?
> -Were you on any medications?
> -Did you drink more than usual or stop drinking after you had been drinking a lot for a while?
> -Were you physically ill?
>
> If yes to any of the above: Has there been a time when you had (PSYCHOTIC SXS) and were not (USING
> DRUGS / TAKING MEDICATION / CHANGING YOUR DRINKING HABITS / ILL)?

Now I am going to ask you some questions about unusual experiences that people sometimes have.

1. Has it ever seemed to you like people were talking about you or taking special
notice of you?.. □? □1 □2 □3

    If YES: Were you convinced they were talking about you or did you think
    it might have been your imagination? .... □? □1 □2 □3

    DESCRIBE: _____

2. What about receiving special messages from the TV, radio, or newspaper, or
from the way things were arranged around you?.. □? □1 □2 □3

3. What about anyone going out of their way to give you a hard time, or trying
to hurt you? .... □? □1 □2 □3

    DESCRIBE: _____

4. Have you ever felt that you were especially important in some way, or that you had
special powers to do things that other people couldn't do?............................. □? □1 □2 □3

    DESCRIBE: _____

5. Have you ever felt that something was very wrong with you physically even though your
doctor said nothing was wrong, like you had cancer or some other terrible disease? ..... □? □1 □2 □3

    DESCRIBE: _____

6. Have you ever been convinced that something was very wrong with the way a part
or parts of your body looked? .... ☐₁   ☐₃

7. Did you ever hear things that other people couldn't hear, such as noises, or like voices
of people whispering or talking? (Were you awake at the time?) .... ☐?   ☐₁   ☐₂   ☐₃

      7a. If YES: What did you hear? How often did you hear it?
      DESCRIBE: _____

      _____

      7b. If VOICES: Did they comment on what you were doing or thinking? .... ☐?   ☐₁   ☐₂   ☐₃

      7c. If VOICES: How many voices did you hear? Were they talking to each other? ☐?   ☐₁   ☐₂   ☐₃

8. Did you ever have visions or see things that other people couldn't?
(Were you awake at the time?) .... ☐?   ☐₁   ☐₂   ☐₃

NOTE: Distinguish from an illusion, i.e. a misperception of a real external stimulus.

      DESCRIBE: _____

      _____

9. What about strange sensations in your body or on your skin?...................... ☐?   ☐₁   ☐₂   ☐₃

      DESCRIBE: _____

      _____

Was any item coded "3" in "primary" section?... ☐?   ☐₁   ☐₃

10. IF A MAJOR DEPRESSIVE OR MANIC EPISODE HAS EVER BEEN PRESENT:
Has there ever been a time when you had (PSYCHOTIC SXS) and you were not

(DEPRESSED / MANIC)? .... ☐?   ☐₁   ☐₃

      ?=inadequate information **1**=absent or false   **2**=subthreshold   **3**=threshold or true

	No	Yes
Any positive symptoms on psychosis screen (current or by history)?	☐	☐
12. If YES, any mitigating factors that convincingly account for symptoms (medication/ drug/alcohol intoxication or withdrawal effects, fever or severe illness, etc.)?	☐	☐
13. Does the patient report any psychotic symptoms (current or by history) that suggest a psychiatric disorder that would rule him or her out of the study?	☐	☐

(THIS ITEM SHOULD GO TO THE ELIGIBILITY PAGE)

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AUDIT

The following statements describe how people sometimes feel or act. For each statement, please indicate how often you feel or act the way described. Remember, your answers should reflect how you generally feel or act.

Be sure to read all the statements in each group before making your choice.

1. How often do you have a drink containing alcohol?

   □₀ Never   □₂ 2 to 4 times a month   □₄ 4 or more times a week
   □₁ Monthly or less   □₃ 2 to 3 times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

   □₀ 1 or 2   □₂ 5 or 6   □₄ 10 or more
   □₁ 3 or 4   □₃ 7 to 9

3. How often do you have six or more drinks on one occasion?

   □₀ Never   □₂ Monthly   □₄ Daily or almost daily
   □₁ < Monthly   □₃ Weekly

SCORE on items 1, 2, and 3: _____
** SCORE on above items is > 6 AND score on item 3 is > 1, then CONTINUE.

4. How often during the last year have you found that you were not able to stop drinking once you had started?

   □₀ Never   □₂ Monthly   □₄ Daily or almost daily
   □₁ < Monthly   □₃ Weekly

5. How often during the last year have you failed to do what was normally expected of you because of drinking?

   □₀ Never   □₂ Monthly   □₄ Daily or almost daily
   □₁ < Monthly   □₃ Weekly

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

   □₀ Never   □₂ Monthly   □₄ Daily or almost daily
   □₁ < Monthly   □₃ Weekly

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

   □₀ Never   □₂ Monthly   □₄ Daily or almost daily
   □₁ < Monthly   □₃ Weekly

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

   $\square_0$ Never $\square_2$ Monthly $\square_4$ Daily or almost daily
   $\square_1$ < Monthly $\square_3$ Weekly

9. Have you or someone else been injured as a result of your drinking?

   $\square_0$ No $\square_4$ Yes, during the last year.
   $\square_2$ Yes, but not in the last year

10. Has a relative or a friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

   $\square_0$ No $\square_4$ Yes, during the last year.
   $\square_2$ Yes, but not in the last year

SCORE on items 1-10: _____
(A score of > 8 is a rule-out for the study)

Substance Abuse Screening

'1) PRESCRIPTION MEDICATIONS

/an
Halcyon
Valium
Codeine
Cortisone

Restoril
Librium
Other Sleeping Medication
Darvon
Other Steroid

Dalmane
Miltown
Inhalants
Percodan
Ritalin

(2) CANNABIS

Hashish

Marijuana

THC

(3) BARBITURATES

Quaalude

Seconal

Other Barbiturates

(4) STIMULANTS

Amphetamine
Ice

Crystal Meth
Speed

Dexadrine
Other

(5) OPIOIDS

Morphine
Dilaudid
Other

Opium
Heroin

Demerol
Methadone

(6) COCAINE

rack
IV

Freebase
Speedball

Intranasal
Other

(7) HALLUCINOGENS - PCP

Angel Dust
LSD
PCP
STP

DMA
Mescaline
Peyote
Other

Ecstasy
Mushrooms
Psilocybin

(8) OTHER

Amyl or butyl nitrate
Paint

Glue

Nitrous oxide/laughing gas

Rule out the following:

1. Patients who indicate using **more** than prescribed or becoming **dependent** for category **1** in last **3 months**

2. Patients who indicate **abuse** of category **2** in last **3 months** ($\geq$ **8** times/month)

3. Patients who indicate **chronic use** of category **5** in last **3 months**

4. Patients who indicate **use** of categories **3-4, 6-8** in last **3 months**

Reminder to RA: Do not record drug name(s) or drug class

Baseline Packet – BY SUBJECT REPORT ONLY

bject Initials: _____

Staff ID: _____   Staff Signature: _____

Date (this form completed): _____ / _____ / 20____   Time: _____:_____ am/pm
                              Month   Day   Year

Contains:
General Release
Subject Contact
Demographics
Charlson Index Questions
Cardiovascular Disease History Questions
ESSI
PHQ9
Medication Beliefs (BMQ)
Self-efficacy and Perceived Risk
ʼndSignals Form
ʋdSignals Instructions

General Release

COLUMBIA UNIVERSITY MEDICAL CENTER

CENTER FOR BEHAVIORAL CARDIOVASCULAR HEALTH

Center for Behavioral
Cardiovascular Health
Division of General Medicine
622 West 168th Street, PH9-941
New York, NY 10032
212.342.4493 Tel
212.305.3172 Fax

www.behavioralhearthealth.org

In the event of a future hospitalization, I, _____,
hereby authorize you to release to the Columbia University College of Physicians and Surgeons:

[ ] A discharge summary for my hospitalization on _____.

[ ] Medical records pertaining to my hospitalization on _____
    which include the following information:
        a) Discharge Report
        b) Procedure Reports including cath, Echo, stress test
        c) Copy of my admission EKG
        d) Copy of my discharge EKG
        e) Lab work, including cardiac enzymes
        f) Hospitalization summary list with ICD9 codes for diagnosis
        g) Medication lists (outpatient and discharge, if available)

[ ] Other _____
    _____.

Patient Name: _____ Date of Birth:_____

Patient Address: _____
    _____
    _____
    _____

Social Security Number: _____

Signature of Patient _____ Date _____

SEND RECORDS TO:
    Dorota Gruber MS, GC
    Director of Research
    Center for Behavioral Cardiovascular Health
    Division of General Medicine
    622 West 168th Street, PH9-941
    New York, NY 10032

SUBJECT CONTACT INFORMATION

Center: _____ Hosp: _____ Subject ID: _____ Subject Initials: _____

Staff ID: _____ Staff Signature: _____

Date (this form completed): ____ /____ / 20____
                                        Month Day   Year   Time: ____:____ am/pm

Hosp. Adm. Date: ____ /____ / 20____   Hosp. Discharge Date: ____ /____ / 20____
                Month Day   Year   Month Day   Year

1. Last Name: _____   2. First Name: _____

3. Social Security Number: _____ - _____ - _____

4. Date of Enrollment: ____ /____ / 20____
                     Month Day   Year

5. Hospital Record Number (MRN): _____

6. Date of Birth: ____ /____ / 19____
    Month   Day   Year

7. Phone numbers: (_____) _____ - _____   (_____) _____ - _____
                          Home Number   Work Number

      (_____) _____ - _____   (_____) _____ - _____
              Cell Number   Other Number

8. Mailing Address: _____
                                     Street Address Line 1

                        _____
                                     Street Address Line 2

                        _____   _____ _____
                             City/Town   State   Zip Code

DEMOGRAPHICS

1. **Date of Birth:** __ __ / __ __ / 19 __ __
   Month   Day   Year

2. **Sex** (check one)   □₁ Male   □₂ Female

3. **Which of the following best describes your ethnicity? (check one)**
   □₁ Hispanic or Latino   □₂ Not Hispanic or Latino

4. **Which of the following best describe(s) your Race? (check one or more)**
   □₁ White (non-Hispanic)   □₆ Asian/Pacific Islander
   □₂ White (Hispanic)   □₇ Native American
   □₃ Black (non-Hispanic)   □₈ Other_____
   □₄ Black (Hispanic)   □₉ Unknown
   □₅ Asian/Indian   □₁₀ Decline to State

   4a. Were you born outside of the United States? (check one)   □₀ No   □₁ Yes

   4b. If Yes, how long have you lived in the United States? _____   _____
                                                                Years   Months

   4c. Do you consider English your native language? (check one) □₀ No   □₁ Yes

   4d. How well do you speak English?
      □₁ Not at all
      □₂ Poorly
      □₃ Fairly well
      □₄ Well
      □₅ Very well

5. **What is your partner status? (check one)**
   □₁ Single
   □₂ Partner / Spouse
   □₃ Separated
   □₄ Widowed
   □₅ Divorced

   5b. For how long have you been living with your spouse or partner? _____   _____
                                                                          Years   Months

6. **What is the highest grade (or year) of regular school you have completed?** (check one)

Elementary School	High School	College	Graduate School
01 □	09 □	13 □	17 □
02 □	10 □	14 □	18 □
03 □	11 □	15 □	19 □
04 □	12 □	16 □	20+ □
05 □			
06 □			
07 □			
08 □			

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7. **What is the highest degree you earned?** *(check one)*

☐1 High school diploma or equivalency (GED)
☐2 Associate degree (junior college)
☐3 Bachelor's degree
☐4 Master's degree
☐5 Doctorate
☐6 Professional (MD, JD, DDS, etc.)
☐7 Other (specify) _____
☐8 None of the above (less than high school)

8. **Which of the following best describes your main daily activities and /or responsibilities?** (Note: Question is repeated at each follow-up.) *(check one)*

☐1 Working full time
☐2 Working part-time
☐3 Unemployed or laid off
☐4 Looking for work
☐5 Keeping house or children full-time
☐6 Retired

9. **With regard to your current or most recent job activity:**
   9a. In what kind of business or industry do (did) you work?

   _____

   (For example: hospital, newspaper publishing, mail order house, auto engine, manufacturing.)

   9b. What kind of work do (did) you do? (Job Title)

   ☐1 Executive / Administrator / Manager
   ☐2 Professional
   ☐3 Technician
   ☐4 Marketing / Sales
   ☐5 Administrative Support, Clerical
   ☐6 Service
   ☐7 Agriculture / Forestry
   ☐8 Craft and Repair
   ☐9 Operator / Laborer
   ☐10 Other _____

   9c. How much did you earn from all employers, before taxes and other deductions, during the past 12 months? *(check one)*

   ☐1 Less than $5,000
   ☐2 $5,000 through $11,999
   ☐3 $12,000 through $15,999
   ☐4 $16,000 through $24,999
   ☐5 $25,000 through $34,999
   ☐6 $35,000 through $49,000
   ☐7 $50,000 through $74,999
   ☐8 $75,000 through $99,999
   ☐9 $100,000 through 149,999
   ☐10 $150,000 through 249,999
   ☐11 $250,000 and greater
   ☐12 Don't know
   ☐13 No response

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13c. How long does it take you to get directly from home to your usual source of medical care? minutes _____

14. There are several government programs which provide medical care or help pay medical bills.

	NO	YES	Not Sure/Refused
14a. Are you covered by Medicare or Medicaid?..................	☐	☐	☐
14b. Are you covered by CHAMPUS, VA, or military			
health care?...	☐	☐	☐
15. In the past two years, have you always had health insurance			
or other coverage for medical care?..	☐	☐	☐

If NO:
15a. For how much time during the past two years did you not have coverage?
years _____   months _____

16. **Was there anytime during the past two years when you did not seek medical care because it was too expensive or health insurance did not cover it?**
Do not include dental care. ....☐ ☐ ☐

17. **Overall, how hard has it been for you to get the health services you have needed?** (READ CATEGORIES 1 – 4.)
☐₁ Very hard
☐₂ Fairly hard
☐₃ Not too hard
☐₄ Not hard at all
☐₅ No answer

For the next set of questions, health insurance coverage refers to health insurance (like Blue Cross/Blue Shield) or participation in an HMO. Other than government programs, health insurance can be obtained through an employer, union, or school.

18a. Are you covered by health insurance of this type?.................☐ ☐ ☐

18b. Are you self-insured? That is, do you or someone else pay totally for your health insurance? ....☐ ☐ ☐

CHARLSON INDEX QUESTIONS

	NO	YES	MAYBE
1. Chronic Lung Disease	☐	☐	☐

[e.g. asthma, chronic obstructive pulmonary disease, chronic bronchitis, emphysema]

2. Chronic Kidney Disease	☐	☐	☐
3. History of Liver Disease	☐	☐	☐

3a. If YES, then answer the following:
☐ Mild (e.g. chronic hepatitis, or cirrhosis <u>without</u> complications such as varices, portal hypertension, encephalopathy, GI bleeding)
☐ Moderate/Severe (e.g. cirrhosis <u>with</u> complications such as varices, portal hypertension, encephalopathy, GI bleeding)

4. Rheumatologic Disease	☐	☐	☐

[e.g. lupus (SLE), polymyagia rheumatica (PMR), polymyositis, moderate to severe rheumatoid arthritis (RA), mixed connective tissue disease, scleroderma] Please note: osteoarthritis does not count as a rheumatologic disease.

5. History of Peptic Ulcer Disease Requiring Treatment	☐	☐	☐

[requiring treatment for ulcer or history of GI bleed due to ulcer] Please note: gastritis without ulcer disease does not count as Peptic Ulcer Disease here.

6. History of Any Solid Tumor (Benign or Cancer)	☐	☐	☐

[e.g. breast, lung, colon, prostate, brain, etc]

6a. If YES, then check any that apply:
☐ Benign .... Type(s): _____
☐ Cancer .... Type(s): _____

6b. If Cancer, **History of Metastases**	☐	☐	
7. History of Leukemia (blood cancer)	☐	☐	☐

[i.e. AML, CML, ALL, CLL, polycythemia vera]

8. History of Lymphoma (lymph node cancer)	☐	☐	☐

[e.g. Hodgkins, lymphosarcoma, Waldenstrom's macroglobulinemia, myeloma, and other lymphomas]

9. History of Thyroid Disease	☐	☐	☐

If YES, then answer the following:
☐ Hyperthyroidism
☐ Hypothyroidism

CARDIOVASCULAR DISEASE HISTORY QUESTIONS

	NO	**YES**	**MAYBE**

1. Prior Angina.. ☐   ☐   ☐
["Angina" refers to evidence or knowledge of symptoms before this acute event described as chest pain or pressure, jaw pain, arm pain, or other equivalent discomfort suggestive of cardiac ischemia]

    1a. If **YES**, then choose one of the following:
    ☐ Existed > 2 weeks before admission
    ☐ Existed ≤ 2 weeks before admission

2. Previous Myocardial Infarction .... ☐   ☐   ☐
[Diagnosed by physician and hospitalized for myocardial infarction]

3. Prior Percutaneous Coronary Intervention .... ☐   ☐   ☐

    3a. If **YES**, most recent PCI date (XX/XX/XXXX): ____/____/_____

4. Prior Coronary Artery Bypass Surgery .... ☐   ☐   ☐

    4a. If **YES,** most recent CABG date (XX/XX/XXXX): ____/____/_____

5. History of Stroke .... ☐   ☐   ☐

    5a. If **YES**, then answer the following:
    Hemiplegia .... ☐   ☐

6. History of TIA... ☐   ☐   ☐
[A focal neurological deficit (usually corresponding to the territory of a single vessel) that resolves spontaneously without evidence of residual symptoms at 24 hours]

7. History of Peripheral Arterial Disease .... ☐   ☐   ☐
[Peripheral arterial disease can include the following: (1) Claudication, either with exertion or at rest (2) Amputation for arterial vascular insufficiency (3) Vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (4) Documented aortic aneurysm (5) Positive noninvasive test (e.g., ankle brachial index less than 0.8).

8. Prior Congestive Heart Failure.. ☐   ☐   ☐

    8a. If **YES**, then classify heart failure:
    ☐ NYHA Class I – No symptoms and no limitation in ordinary physical activity (e.g. shortness of breath when walking, climbing stairs etc).
    ☐ NYHA Class II – Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
    ☐ NYHA Class III – Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
    ☐ NYHA Class IV – Severe limitations. Experiences symptoms at rest. Inability to carry our physical activity or symptoms at rest.

In the **three** months prior to this hospitalization:

	No	Yes	Unknown
9. Were you exercising regularly?	☐	☐	☐
10. Were you following a low-cholesterol, low-fat diet?	☐	☐	☐
11. Were you participating in a cardiac rehabilitation program?........	☐	☐	☐
12. Many people do not take their medications perfectly. In the three months before this hospitalization, did you ever miss taking your medications?	☐	☐	☐
13. Did any medical professional discuss with you the importance of taking your medications?.................................	☐	☐	☐
14. Were you taking aspirin on a daily basis during the *7 days* before you came to the hospital?..	☐	☐	☐

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CARDIOLOGISTS' ACS CLASSIFICATION FORM

Date form completed: _____

MD completing form: _____

Does patient meet eligibility criteria for ACS?   ☐ NO   ☐ YES

    If YES, please classify the type of ACS:

Unstable Angina   ☐ NO   ☐ YES

Myocardial Infarction (MI)   ☐ NO   ☐ YES

    If YES to MI, please classify type:

☐ ST-segment Elevation
☐ Non-ST-segment Elevation
☐ Bundle Branch Block/Uncertain Type

Comments:

DEFINITIONS

UNSTABLE ANGINA

Angina pectoris (or equivalent type of ischemic discomfort) with no biochemical evidence of myocardial infarction (see below) and any of the following within the past 6 weeks:

- Angina occurring at rest and prolonged, usually greater than 20 minutes.
- New onset angina of least CCS class II severity.
- Recent acceleration of angina reflected by an increase in severity of at least 1 CCS class to at least CCS class II.

Class I: Ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
Class II: Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly, walking uphill, walking or climbing stairs after meals, or in cold, in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal condition.
Class III: Marked limitations of ordinary physical activity. Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.
Class IV: Inability to perform any physical activity without discomfort—anginal symptoms may be present at rest.

MYOCARDIAL INFARCTION (MI)

Defined as one of the following:

- **ST elevation MI** - Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of MI (see below) with new or presumed new ST segment elevation (greater than or equal to 0.1 mV) at the J point in 2 or more contiguous leads.
- **Non ST elevation MI** - Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of MI (see below) with one of the following (in the absence of ST elevations):
  - ST segment depression
  - T wave abnormalities
  - Ischemic symptoms without ST segment depression or T wave abnormalities, in the presence or absence of chest discomfort (unexplained nausea and vomiting or diaphoresis; persistent shortness of breath; unexplained weakness, dizziness, lightheadedness, or syncope).
- **Bundle Branch Block/Uncertain Type MI** -Typical rise and gradual fall (troponin) or more rapid rise and fall (CKMB) of biochemical markers of myocardial necrosis (see next section) with:
  - Left BBB (new or old) or paced rhythm.
  - The initial ECG findings are not available or the patient presents beyond the time of ST segment changes (e.g. greater than 24 hours).

Biochemical Evidence of Myocardial Infarction (at least one of the following):

- Maximal concentration of troponin I greater than the MI decision limit **(positive ≥0.40 ng/mL at CUMC)** on at least 1 occasion during the first 24 hrs after the index clinical event:
- Maximal value of CKMB, preferably CKMB mass, greater than upper limit of normal **(positive > 5.5 ng/mL)** on 2 successive samples, OR maximal value of CKMB greater than 2 times the upper limit of normal **(positive > 11 ng/mL at CUMC)** on 1 occasion during the first hours after the index clinical event.
- Total CK (in absence of troponin or CKMB assay) greater than 2X the upper limit **(positive > 588 U/L for males; positive > 476 U/L for females)** of normal.

Upper limits of Normal at CUMC:

Cardiac Troponin I	0.39 ng/mL
CK-MB	5.5 ng/mL
Creatine Kinase (CK)	Male: 294 U/L
	Female: 238 U/L

ALL ITEMS TO BE DETERMINED BY CHART EXTRACTION
MEDICAL HISTORY AND CO-MORBID ILLNESS

RISK FACTORS

1. Hypertension
☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[As documented by at least one of the following: (1) History of hypertension diagnosed by a health care provider, (2) Blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic on at least 2 occasions, (3) Current use of antihypertensive pharmacological therapy]

2. Diabetes
☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[History of diabetes, diagnosed and/or treated by a health care provider]

If **YES**, then answer the following:
2a. Type of diabetic control (check all that apply):
☐ None ☐ Diet ☐ Oral agent ☐ Insulin

2b. Evidence of chronic complications (check all that apply):
☐ None ☐ Eye ☐ Kidney ☐ Nerves

3. Dyslipidemia
☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[History of dyslipidemia diagnosed and/or treated by a health care provider]

4. History of Cigarette Smoking
☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

4a. If **YES**, then choose from one of the following:
☐ Current (within 1 month of this admission)

☐ Recent (stopped 1 month to 1 year before this admission)
☐ Former (stopped >1 year before this admission)

4b. If **YES**, also answer the following:
Years Smoked: _____
Cigarettes/Day: _____

5. Family History of Coronary Disease
☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[Any direct blood relatives (parents, siblings, children) who have had any of the following at age less than 55 years: (1) Angina (2) Myocardial Infarction, (3)Sudden cardiac death without obvious cause]

CARDIOVASCULAR DISEASE HISTORY

6. Prior Angina
☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

["Angina" refers to evidence or knowledge of symptoms before this acute event described as chest pain or pressure, jaw pain, arm pain, or other equivalent discomfort suggestive of cardiac ischemia]

6a. If **YES**, then choose one of the following:
☐ Existed > 2 weeks before admission
☐ Existed ≤ 2 weeks before admission

7. Previous Myocardial Infarction
☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[Diagnosed by physician and hospitalized for myocardial infarction]

8. Prior Percutaneous Coronary Intervention
☐ Documentation as Positive History (YES)

☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

8a. If **YES**, most recent PCI date (XX/XX/XXXX): ____/____/_____

9. Prior Coronary Artery Bypass Surgery

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

9a. If **YES**, most recent CABG date (XX/XX/XXXX): ____/____/_____

10. History of Stroke

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

10a. If **YES**, then answer the following:
Hemiplegia   ☐ No ☐ Yes

11. History of TIA

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[A focal neurological deficit (usually corresponding to the territory of a single vessel) that resolves

spontaneously without evidence of residual symptoms at 24 hours]

12. History of Peripheral Arterial Disease

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[Peripheral arterial disease can include the following: (1) Claudication, either with exertion or at rest (2) Amputation for arterial vascular insufficiency (3) Vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (4) Documented aortic aneurysm (5) Positive noninvasive test (e.g., ankle brachial index less than 0.8).

13. Prior Congestive Heart Failure

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

If **YES**, then classify heart failure:
☐ NYHA Class I – No symptoms and no limitation in ordinary physical activity (e.g. shortness of breath when walking, climbing stairs etc).
☐ NYHA Class II – Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
☐ NYHA Class III – Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
☐ NYHA Class IV – Severe limitations. Experiences symptoms at rest. Inability to carry our physical activity or symptoms at rest.

OTHER MEDICAL HISTORY

14. Chronic Lung Disease

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[e.g. asthma, chronic obstructive pulmonary disease, chronic bronchitis, emphysema]

15. Chronic Kidney Disease

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

15a. If YES, then answer the following:
☐ Mild (e.g. initial* hospital creatinine ≤ 3.0)
☐ Moderate/Severe (e.g. initial* hospital creatinine > 3.0, on dialysis, and/or received kidney transplant)
* Initial = First Value During Hospitalization

16. History of Liver Disease

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

16a. If YES, then answer the following:
☐ Mild (e.g. chronic hepatitis, or cirrhosis without complications such as varices, portal hypertension, encephalopathy, GI bleeding)
☐ Moderate/Severe (e.g. cirrhosis with complications such as varices, portal hypertension, encephalopathy, GI bleeding)

17. Rheumatologic Disease

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[e.g. lupus (SLE), polymyagia rheumatica (PMR), polymyositis, moderate to severe rheumatoid arthritis (RA), mixed connective tissue disease, scleroderma] Please note: osteoarthritis does not count as a rheumatologic disease.

18. History of Peptic Ulcer Disease Requiring Treatment

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[requiring treatment for ulcer or history of GI bleed due to ulcer] Please note: gastritis without ulcer disease does not count as Peptic Ulcer Disease here.

19. Acquired Immunodeficiency Syndrome
[REMINDER: OBTAIN BY CHART ONLY]

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[i.e. not including those with asymptomatic HIV+]

20. History of Any Solid Tumor (Benign or Cancer)

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[e.g. breast, lung, colon, prostate, brain, etc]

20a. If YES, then check any that apply:
☐ Benign   Type(s): _____
☐ Cancer   Type(s): _____

20b. If Cancer, **History of Metastases**   ☐ No ☐ Yes

21. History of Leukemia (blood cancer)

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[i.e. AML, CML, ALL, CLL, polycythemia vera]

22. History of Lymphoma (lymph node cancer)

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)

☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

[e.g. Hodgkins, lymphosarcoma, Waldenstrom's macroglobulinemia, myeloma, and other lymphomas]

23. History of Thyroid Disease

☐ Documentation as Positive History (YES)
☐ Documentation as Negative History (NO)
☐ No Documentation of Positive or Negative History (UNKNOWN)
☐ Unclear Documentation (Maybe)

23a. If YES, then answer the following:
☐ Hyperthyroidism
☐ Hypothyroidism

24. OTHER MISCELLANEOUS MEDICAL HISTORY   ☐ No ☐ Yes

If YES, then list diagnoses here:

_____
_____
_____
_____
_____
_____

B.   CLINICAL PRESENTATION

25. Height (inches): _____

26. Weight (lbs):   _____

27. First Presentation to Hospital:

      27a. **Date:** (XX/XX/XXXX): ____/____/_____

      27b. **Time:** (XX:XX; military time): _____:_____
[Date and time the patient first presented to the hospital]

28. **Transferred from Another Hospital**   ☐ YES   ☐ NO

      28a. If YES, date of transfer to this hospital. **Date:** (XX/XX/XXXX):
____/____/_____

29. **Date of First Confirmation of the Diagnosis of ACS**
      Date: (XX/XX/XXXX): ____/____/_____

30. **Date of Discharge**
      Date: (XX/XX/XXXX): ____/____/_____

31. **Blood Pressure and Heart Rate at Initial Hospital Presentation**
      31a. **Resting Heart Rate (bpm):** _____
         Heart rate (beats per minute) at initial hospital presentation
      31b. **Systolic/Diastolic blood pressure (mmHg):** _____/_____
         Supine blood pressure at initial hospital presentation

32. **Killip Class at the Time of Initial Hospital Presentation**
Choose one of the following based on the clinical status at the time of first presentation (blood pressure and heart rate are based on above values):
    ☐ **Class 1:** Absence of rales over the lung fields and absence of S3 (no heart failure)
    ☐ **Class 2:** Rales over 50% or less of the lung fields or the presence of an S3
    ☐ **Class 3:** Rales over more than 50% of the lung fields
    ☐ **Class 4:** Cardiogenic shock

[Clinical criteria for cardiogenic shock are hypotension (a systolic blood pressure of less than 90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of greater than or equal to 90 mmHg), end-organ hypoperfusion (cool

extremities or a urine output of less than 30 ml/h, and a heart rate of greater than or equal to 60 beats per minute)]

33. Cardiac Arrest at Initial Hospital Arrival   ☐ No ☐ Yes

Blood Pressure and Heart Rate at Hospital Discharge

33a. **Heart Rate (bpm):** _____

[Heart rate (beats per minute) should be the recording that was done last at hospital discharge]

33b. **Systolic/Diastolic blood pressure (mmHg):** _____/_____

[Supine blood pressure should be the recording that was done last at hospital discharge]

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C. **FINDINGS OF INITIAL EKG PERFORMED FOR ACUTE EPISODE**
    34. EKG Available ☐ No ☐ Yes

        If YES, date and time of EKG:

        34a. **Date:** (XX/XX/XXXX): ____/____/_____

        34b. **Time:** (XX:XX; military time): _____:_____

    35. EKG Changes ☐ No ☐ Yes

        35a. If YES, check type(s) of EKG changes (check all that apply):

        ☐ ST-segment elevation greater than or equal to 0.1 mV elevation in 2 or more contiguous leads
            ☐ Inferior leads (II, III, AVF)
            ☐ Anterior leads (V1 to V4)
            ☐ Lateral leads (I, aVL, V5 to V6)
            ☐ True posterior (V1, V2) with tall R waves in these leads

        ☐ Q waves greater than or equal to 0.04 seconds in width and greater than or equal to 0.1 mV in depth in at least 2 contiguous leads
            ☐ Inferior leads (II, III, AVF)
            ☐ Anterior leads (V1 to V4)
            ☐ Lateral leads (I, aVL, V5 to V6)
            ☐ True posterior (tall R waves in V1 V2)

        ☐ ST-segment depression of at least 0.05 mV in 2 more contiguous leads (includes reciprocal changes)

        ☐ T-wave inversion of at least 0.1 mV

    36. Paced Rhythm ☐ No ☐ Yes

    37. Atrial fibrillation or flutter ☐ No ☐ Yes

    38. Bundle-branch Block ☐ No ☐ Yes

        38a. If YES, then answer questions about type and timing:
        ☐ RBBB ☐ LBBB
        ☐ New ☐ Old ☐ Unknown timing

D. LABORATORY TESTS

39. **Troponin I Assessment Performed** ☐ No ☐ Yes

    If YES, fill out the following:
    39a. Initial Troponin I at First Presentation to Hospital: _____ ng/mL

    39b. Peak Troponin I During Hospitalization: _____ ng/mL
    (peak prior to PCI or CABG if done)

40. **CK Assessment Performed** ☐ No ☐ Yes

    If YES, fill out the following:
    40a. Initial CK at First Presentation to Hospital: _____ U/L

    40b. Peak CK During Hospitalization: _____ U/L
    (peak prior to PCI or CABG if done)

41. **CKMB Assessment Performed** ☐ No ☐ Yes

    If YES, fill out the following:
    41a. Initial CKMB at First Presentation to Hospital: _____ U/L

    41b. Peak CKMB During Hospitalization: _____ U/L
    (peak prior to PCI or CABG if done)

Initial = First Value During Hospitalization

42. **Initial Creatinine** _____ mg/dL ☐ Not Performed

43. **Initial Total Cholesterol** _____ mg/dL ☐ Not Performed

44. **Initial Triglyercides** _____ mg/dL ☐ Not Performed

45. **Initial LDL** _____ mg/dL ☐ Not Performed

46. **Initial HDL** _____ mg/dL ☐ Not Performed

47. **Initial Hemoglobin A1c** _____ (%) ☐ Not Performed

E.   CARDIAC PROCEDURES PERFORMED DURING HOSPITALIZATION

    48. Stress Test   ☐ No   ☐ Yes

           If YES, then answer the following:

           48a. **Date** (XX/XX/XXXX): ____/____/_____

           48b. **Stress Type**
           ☐ Exercise
           ☐ Pharmacological

           48c. **Imaging Type**
           ☐ EKG only
           ☐ Nuclear
           ☐ PET
           ☐ Echocardiogram

           48d. **Ischemia Result**
           ☐ Positive
           ☐ Negative
           ☐ Equivocal

           48e. **Fixed Defect Indicating an old MI**
           ☐ Present   ☐ Absent

Left Ventricular (LV) Function Assessment
´ index ACS event is Unstable Angina (go to next section if MI), then answer the following:
  49. LV Function Assessment Done <u>During Hospitalization</u> ☐ No ☐ Yes

If YES, answer all of the following:

49a. On the first LV function assessment done during hospital stay, was assessment
  Qualitative or Quantitative? ☐ Qualitative   ☐ Quantitative

  49b. If **Quantitative**, then answer the following:
    First EF Obtained During Hospital Stay: _____ %
    [If only a range is estimated for EF, the midpoint of the range should
      be the value noted]

  49c. If **Qualitative**, then circle first qualitative assessment done during hospital
  stay.
    Normal/Low Normal
    Mildly Reduced
    Mildly to Moderately Reduced
    Moderately Reduced
    Moderately to Severely Reduced
    Severely Reduced

49d. Date of First LV Function Assessment (XX/XX/XXXX): ____/____/_____

49e. Type of Test Used to Determine First LV Function
        ☐ Echocardiography (by Ultrasound)
        ☐ Contract ventriculography (by CATH/angiogram)
        ☐ Radionuclide ventriculography or SPECT on stress testing (Nuclear)

If NO, answer all of the following:
49f. Was LV function assessed during the 30 days prior to hospitalization? ☐ YES
☐ NO

    If **YES**, answer all of the following:
    49g. Was assessment Qualitative or Quantitative? ☐ Qualitative ☐
Quantitative

      49h. If **Quantitative**, EF: _____ %
      [If only a range is estimated for EF, the midpoint of the range should
        be the value noted]

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49i. If **Qualitative**, then circle qualitative assessment.
      Normal/Low Normal
      Mildly Reduced
      Mildly to Moderately Reduced
      Moderately Reduced
      Moderately to Severely Reduced
      Severely Reduced

49j. Date of LV Function Assessment (XX/XX/XXXX): _____/_____/_____

49k. Type of Test Used to Determine First LV Function
    ☐ Echocardiography (by Ultrasound)
    ☐ Contract ventriculography (by CATH/angiogram)
    ☐ Radionuclide ventriculography or SPECT on stress testing (Nuclear)

If index ACS event is MI, then answer the following:

    50. LV Function Assessment Done <u>During Hospitalization</u> ☐ No ☐ Yes

        If YES, answer all of the following:
        50a. On the first LV function assessment done during hospital stay, was assessment
            Qualitative or Quantitative? ☐ Qualitative   ☐ Quantitative

            50b. If **Quantitative**, then answer the following:
                First EF Obtained During Hospital Stay: _____ %
            •   [If only a range is estimated for EF, the midpoint of the range should
                  be the value noted]

            50c. If **Qualitative**, then circle first qualitative assessment done during hospital
            stay.
                Normal/Low Normal
                Mildly Reduced
                Mildly to Moderately Reduced
                Moderately Reduced
                Moderately to Severely Reduced
                Severely Reduced

        50d. Date of First LV Function Assessment (XX/XX/XXXX): ___/___/_____

        50e. Type of Test Used to Determine First LV Function
                ☐ Echocardiography (by Ultrasound)
                ☐ Contract ventriculography (by CATH/angiogram)
                ☐ Radionuclide ventriculography or SPECT on stress testing (Nuclear)

51. Diagnostic Cardiac Catheterization ☐ No ☐ Yes

    If **YES**, then answer ALL of the following:

        51a. **Date** (XX/XX/XXXX): _____/_____/_____

        51b. **Maximum Stenoses by Vessel (0-100%)**
            Greatest stenosis assessed in the LAD or any major branch vessel (%)

            Greatest stenosis assessed in the LCx or any major branch vessel (%)

            Greatest stenosis assessed in the RCx or any major branch vessel (%)

            Greatest stenosis assessed in the LM (%) _____
            If applicable, greatest stenosis assessed in bypass graft (%) _____

        51c. **PCI Performed**   ☐ No   ☐ Yes

            If **YES**, then answer ALL of the following:

                51d. Date (XX/XX/XXXX): _____/_____/_____

                51e. Number of Stents Placed: _____

                    51f. If stent(s) was placed, circle one of the following:
                          Bare Metal   **Drug-eluting**

                51g. Complications of PCI   ☐ No ☐ Yes

                    51h. If YES, check any of the following:
                    ☐ Bleeding
                    ☐ Vascular complication
                    ☐ Cardiac tamponade
                    ☐ Arrhythmia
                    ☐ Stroke
                    ☐ Contrast reaction
                    ☐ Acute renal failure

52. Coronary Artery Bypass Surgery Performed   ☐ No   ☐ Yes

    If **YES**, then answer the following:

52a. **Date** (XX/XX/XXXX): _____/_____/_____

53. **IABP Used During Hospitalization** ☐ No ☐ Yes

54. **Permanent Pacemaker Used During Hospitalization** ☐ No ☐ Yes

1 Month Packet

Subject Initials: _____

Staff ID: _____ Staff Signature: _____

Date (this form completed): _____ / _____ / 20___   Time: ____:____ am/pm
                                Month Day Year

Note to RA: Please ask participants to bring in their medications to the visit.

Contains:
Subject Contact update
General release form
BDI
BDI-II (partial)
BDI #9
PHQ2
Lifestyle Follow-up
Refilling Procedures
Insurance and Cost
Drug Holiday Forms (Aspirin, Plavix, Statin, Beta-Blocker)
MACE Query
Hospitalization form
AE/UP Eligibility form

COLUMBIA UNIVERSITY MEDICAL CENTER

Center for Behavioral
Cardiovascular Health
Division of General Medicine
622 West 168th Street, PH9-941
New York, NY 10032
212.342.4493 Tel
212.305.3172 Fax

CENTER FOR
BEHAVIORAL
CARDIOVASCULAR
HEALTH

www.behavioralhearthealth.org

In the event of a future hospitalization, I, _____,
hereby authorize you to release to the Columbia University College of Physicians and Surgeons:

[ ] A discharge summary for my hospitalization on _____ .

[ ] Medical records pertaining to my hospitalization on _____
       which include the following information:
             a) Discharge Report
             b) Procedure Reports including cath, Echo, stress test
             c) Copy of my admission EKG
             d) Copy of my discharge EKG
             e) Lab work, including cardiac enzymes
             f) Hospitalization summary list with ICD9 codes for diagnosis
             g) Medication lists (outpatient and discharge, if available)

[ ] Other _____
       _____ .

Patient Name: _____ Date of Birth: _____

Patient Address: _____

_____

_____

_____

Social Security Number: _____

Signature of Patient _____ Date _____

SEND RECORDS TO:
       Dorota Gruber
       Center for Behavioral Cardiovascular Health
       Division of General Medicine
       622 West 168th Street, PH9-941
       New York, NY 10032

LIFESTYLE FOLLOW-UP

Since the last study visit, has patient:	NO	YES
1. Visited a doctor in the clinic for you cardiac care?	☐	☐
2. Engaged in counseling, psychotherapy, or .... stress management training?	☐	☐
3. Modified your diet?	☐	☐
4. Participated in cardiac rehabilitation?	☐	☐

Physical Activity

5. During the past month, did you regularly engage in physical exercise
   during your leisure time? [Regularly = at least once a week during
   the past month] .... ☐ ☐

6. During the last week, how many flights of stairs did you climb each day?
   [1 flight = 10 stairs]
   _____ **flights/day**

7. During the last week, how many city blocks or equivalent distance did you walk each day?
   [12 blocks = 1 mile]
   _____ **blocks/day**

8. During the last week, how many hours did you actively participate in light sports?
   [e.g. bowling, baseball, biking, boating, dancing, yard-work, etc]
   _____ **hours/week**

9. During the last week, how many hours did you actively participate in strenuous sports?
   [e.g. basketball, running, mountaineering, skiing, swimming, tennis, etc]
   _____ **hours/week**

10. In the last 7 days, have you smoked cigarettes or other tobacco
    products? .... ☐ ☐

    10a. If YES, average number of cigarettes per day smoked (1 pack = 20 cigarettes)? _____

    10b. Other tobacco product (_____) average per day? _____
    Fill in tobacco product

11. In the last 7 days, have you had a drink of alcohol? .... ☐ ☐

    11a. If YES, average number drinks per week consumed? _____

12. Taking medications for anxiety or depression .... ☐ ☐
    (If YES, use chart below)

    12a. If Yes, are they still taking that medication (ongoing use)? ..... ☐ ☐

    No longer taking, date stopped taking medication: _____

MACE Query Screening

I'd like to ask you some questions about what has been happening since your last visit with us (1-month after your initial hospitalization OR 6-months after your initial hospitalization).

	NO	YES
1. Have you been to the Emergency Room <u>(not requiring hospitalization)</u> since the last study visit? .... ☐		☐
2. Have you been <u>admitted</u> to a hospital, since the last study visit? .... ☐		☐

(If YES, please complete *Hospitalization Form*)

HOSPITALIZATION FORM

Center: _____ Hosp: _____ Subject ID: _____ Subject Initials: _____

Date (this form completed): ____/____/20____   Time: ____:____ am pm
Month Day Year

Staff ID: _____ Staff Signature: _____

INSTRUCTIONS: Complete this form for *each* hospitalization admission.

Requested / Photocopied from Hospital Medical Record

	Requested & Pending	Requested & Photocopied	Requested but NA
1. Discharge Report	$\square_0$	$\square_1$	$\square_2$
Notes: _____			
2. All Procedure Reports including CATH, Echo, Stress Test, EPS	$\square_0$	$\square_1$	$\square_2$
Notes: _____			
3. Admission EKG	$\square_0$	$\square_1$	$\square_2$
Notes: _____			
4. Discharge EKG	$\square_0$	$\square_1$	$\square_2$
Notes: _____			
5. Cardiac Enzymes (All that were done in-hospital)	$\square_0$	$\square_1$	$\square_2$
Notes: _____			
6. Hemaglobin/Hematocrit (All that were done in-hospital)	$\square_0$	$\square_1$	$\square_2$
Notes: _____			
7. Hospitalization summary list w/ ICD-9 codes for diagnosis and Procedures	$\square_0$	$\square_1$	$\square_2$
Notes: _____			

SCHARGE DIAGNOSIS

1. List the number of HOSPITALS related to this HOSPITALIZATION: _____

(2) First Hospital

(a)Name: _____   (f)Study Affiliation?:   ☐₁Affiliated
                                                                        ☐₂Non-affiliated

(b)Phone # for Medical Records: (_____) _____ - _____

(c) _____   (g)Medical Record #: _____
            Street Address Line 1

_____   (h)Chart located?: ☐₀No ☐₁Yes
            Street Address Line 2

_____ _____ _____
      City/Town   State   Zip Code

(d)Admission date to **first** hospital: ____ / ____ / 20____   (i)Admission Time (24-hr format): _____ _____
                                        Month Day   Year   Hour   Minutes

(e)Discharge / transfer date (for non-fatal case) or death: ____ / ____ / 20____
                                                           Month Day   Year

---

☐ Check if not applicable and skip to question #5   **(3) Second Hospital**

(a)Name: _____   (f)Study Affiliation?:   ☐₁Affiliated
                                                                        ☐₂Non-affiliated

(b)Phone # for Medical Records: (_____) _____ - _____

(c) _____   (g)Medical Record #: _____
            Street Address Line 1

_____   (h)Chart located?: ☐₀No ☐₁Yes
            Street Address Line 2

_____ _____ _____
      City/Town   State   Zip Code

(d)Admission date to **second** hospital: ____ / ____ / 20____   (i)Admission Time (24-hr format): _____ _____
                                         Month Day   Year   Hour   Minutes

(e)Discharge / transfer date (for non-fatal case) or death: ____ / ____ / 20____
                                                           Month Day   Year

☐ Check if not applicable and skip to question #5   **(4) Third Hospital**

(a)Name: _____   (b)Study Affiliation?: ☐₁Affiliated
                                                                 ☐₂Non-affiliated

(c)Phone # for Medical Records: (_____) ___ ___-___ ___ ___ ___

(e) _____   (d)Medical Record #: _____
              Street Address Line 1

                           (f)Chart located?: ☐₀No ☐₁Yes
              Street Address Line 2

      City/Town   State   Zip Code

(g)Admission date to **third** hospital: ___/___/20___   (h)Admission Time (24-hr format): ___ ___
                              Month Day Year   Hour Minutes

(i)Discharge / transfer date (for non-fatal case) or death: ___/___/20___
                                                 Month Day Year

5. What was the disposition of the patient on discharge from the **last hospital**?
    ☐₁ Deceased (*If Deceased, complete Death Certificate Form.*)
    ☐₂ Nursing home
    ☐₃ Rehabilitation hospital
    ☐₄ Home or other private residence
    ☐₅ Discharged alive, disposition unknown

6. *(Leave blank, and skip to #7 for nonfatal events)* Are any causes of death given on the discharge summary? ....☐₀ No   ☐₁ Yes

    Record the cause(s) of death:

    a. _____   b. _____

    c. _____   d. _____

7. List the hospital discharge diagnoses and codes exactly as they appear on the front sheet of the final discharge summary.

                     ICD-9 Codes   Discharge Diagnoses

         a. _____   _____
         b. _____   _____
         c. _____   _____
         d. _____   _____
         e. _____   _____
         f. _____   _____
         g. _____   _____
         h. _____   _____

SF-12

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ⊠ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3

3. **During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
b Were limited in the <u>kind</u> of work or other activities	☐1	☐2	☐3	☐4	☐5

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4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
b. Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5

5. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

6. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
b. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
c. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5

7. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

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Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

USUAL BED TIME

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

NUMBER OF MINUTES

3. During the past month, when have you usually gotten up in the morning?

USUAL GETTING UP TIME

4. During the past month, how many hours of actual sleep did you get, at night? (This may be different than the number of hours you spend in bed.)

HOURS OF SLEEP PER NIGHT

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you…

    (a) Cannot get to sleep within 30 minutes

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

    (b) Wake up in the middle of the night or early morning

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

    (c) Have to get up to use the bathroom

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

    (d) Cannot breathe comfortably

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

    (e) Cough or snore loudly

Not during the	Less than	Once or	Three or more

| past month ☐ | once a week ☐ | twice a week ☐ | times a week ☐ |

(f) Feel too cold

| Not during the | Less than | Once or | Three or more |
| past month ☐ | once a week ☐ | twice a week ☐ | times a week ☐ |

(g) Feel too hot

| Not during the | Less than | Once or | Three or more |
| past month ☐ | once a week ☐ | twice a week ☐ | times a week ☐ |

(h) Had bad dreams

| Not during the | Less than | Once or | Three or more |
| past month ☐ | once a week ☐ | twice a week ☐ | times a week ☐ |

(i) Have pain

| Not during the | Less than | Once or | Three or more |
| past month ☐ | once a week ☐ | twice a week ☐ | times a week ☐ |

(i) Other reason(s), please describe:

How often during the past month have you had trouble sleeping because of this?

| Not during the | Less than | Once or | Three or more |
| past month ☐ | once a week ☐ | twice a week ☐ | times a week ☐ |

6. During the past month, how would you rate your sleep quality overall?
  ☐ Very good
  ☐ Fairly good
  ☐ Fairly bad
  ☐ Very bad

7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help
you sleep?

| Not during the | Less than | Once or | Three or more |
| past month ☐ | once a week ☐ | twice a week ☐ | times a week ☐ |

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or
engaging in social activity?

| Not during the | Less than | Once or | Three or more |
| past month ☐ | once a week ☐ | twice a week ☐ | times a week ☐ |

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to
get things done?
  ☐ No problem at all
  ☐ Only a very slight problem

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☐ Somewhat of a problem
☐ A very big problem

10. Do you have a bed partner or roommate?
☐ No bed partner or roommate
☐ Partner/roommate in other room
☐ Partner in same room, but not same bed
☐ Partner In same bed

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

(a) Loud snoring

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

(b) Long pauses between breaths while asleep

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

(c) Legs twitching or jerking while you sleep

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

(d) Episodes of disorientation or confusion during sleep

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

(e) Other restlessness while you sleep: please describe

Not during the past month ☐	Less than once a week ☐	Once or twice a week ☐	Three or more times a week ☐

Beck Depression Inventory (BDI)

This questionnaire consists of groups of statements. Please read each group carefully, then pick out the one statement in each group which best describes the way you have been feeling **during the Past Week, Including Today.** Indicate your choice by crossing (X) the appropriate number. If several statements in the group seem to apply equally well, cross each one that applies. <u>Be sure to read all the statements in each group before making your choice.</u>

---

1 .   ⓪   I do not feel sad.

      ①   I feel sad.

      ②   I am sad all the time and I can't snap out of it.

      ③   I am so sad or unhappy that I can't stand it.

---

2 .   ⓪   I am not particularly discouraged about the future.

      ①   I feel discouraged about the future.

      ②   I feel I have nothing to look forward to.

      ③   I feel that the future is hopeless and that things cannot improve.

---

3.   ⓪   I do not feel like a failure.

      ①   I feel I have failed more than the average person.

      ②   As I look back on my life, all I can see is a lot of failure.

      ③   I feel I am a complete failure as a person.

4.	⓪	I get as much satisfaction out of things as I used to.
	①	I don't enjoy things the way I used to.
	②	I don't get real satisfaction out of anything anymore.
	③	I am dissatisfied or bored with everything.

5.	⓪	I don't feel particularly guilty.
	①	I feel guilty a good part of the time.
	②	I feel quite guilty most of the time.
	③	I feel guilty all of the time.

6.	⓪	I don't feel I am being punished.
	①	I feel I may be punished.
	②	I expect to be punished.
	③	I feel I am being punished.

7.	⓪	I don't feel disappointed in myself.
	①	I am disappointed in myself.
	②	I am disgusted with myself.
	③	I hate myself.

8.   ⓪   I don't feel I am any worse than anybody else.

     ①   I am critical of myself for my weaknesses or mistakes.

     ②   I blame myself all the time for my faults.

     ③   I blame myself for everything bad that happens.

---

9.   ⓪   I don't have any thoughts of killing myself.

     ①   I have thoughts of killing myself, but I would not carry them out.

     ②   I would like to kill myself.

     ③   I would kill myself if I had the chance.

---

10.   ⓪   I don't cry any more than usual.

     ①   I cry more now than I used to.

     ②   I cry all the time now.

     ③   I used to be able to cry, but now I can't cry even though I want to.

---

11.   ⓪   I am no more irritated now than I ever am.

     ①   I get annoyed or irritated more easily than I used to.

     ②   I feel irritated all the time now.

     ③   I don't get irritated at all by the things that used to irritate me.

12.	⓪	I have not lost interest in other people.
	①	I am less interested in other people than I used to be.
	②	I have lost most of my interest in other people.
	③	I have lost all of my interest in other people.

13.	⓪	I make decisions about as well as I ever could.
	①	I put off making decisions more than I used to.
	②	I have greater difficulty making decisions than before.
	③	I can't make decisions at all anymore.

14.	⓪	I don't feel I look any worse than I used to.
	①	I am worried that I am looking old or unattractive.
	②	I feel that there are permanent changes in my appearance that make me look unattractive.
	③	I believe that I look ugly.

15.	⓪	I can work about as well as before.
	①	It takes extra effort to get started at doing something.
	②	I have to push myself very hard to do anything.
	③	I can't do any work at all.

16.
   ⓪   I can sleep as well as usual.

      ①   I don't sleep as well as I used to.

      ②   I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

      ③   I wake up several hours earlier than I used to and cannot get back to sleep.

17.
   ⓪   I don't get more tired than usual.

      ①   I get tired more easily than I used to.

      ②   I get tired from doing almost anything.

      ③   I am too tired to do anything.

18.
   ⓪   My appetite is no worse than usual.

      ①   My appetite is not as good as it used to be.

      ②   My appetite is much worse now.

      ③   I have no appetite at all anymore.

19.
   ⓪   I haven't lost much weight, if any lately.

      ①   I have lost more than 5 pounds.

      ②   I have lost more than 10 pounds.

      ③   I have lost more than 15 pounds.

20.   I am purposely trying to lose weight by eating less.

                 NO   ⓪   YES   ①

---

21.   ⓪   I am no more worried about my health than usual.

     ①   I am worried about physical problems such as aches and pains, or upset stomach or constipation.

     ②   I am very worried about physical problems and it's hard to think of much else.

     ③   I am so worried about my physical problems that I cannot think about anything else.

---

22.   ⓪   I have not noticed any recent change in my interest in sex.

     ①   I am less interested in sex now.

     ②   I am much less interested in sex now.

     ③   I have lost interest in sex completely.

---

a) Approximately when did the symptoms mentioned in questions 1 through 21 start?

_____ / _____ / _____
Month   Day   Year

b) If participant answered "0" to questions 1 through 22, then check here: ☐ N/A

c) Have you ever received treatment for depression? ....☐ Yes
....☐ No

d) Have you ever been diagnosed by a health care professional
   with depression? ....☐ Yes
   ☐ No

e) How many times in the past have you had a period of 2 or more weeks in
   which you had strong feelings of depression or sadness?
         ☐ 0-1   ☐ 1-3   ☐ 3-5   ☐ 5 or more

f) In the last month has there been a period of time when you were feeling so good, "high,"
   excited, or hyper that other people thought you were not your normal self or you were so
   hyper that you got into trouble?...☐ Yes
....☐ No

g) Have you ever been diagnosed with manic depression
   or bipolar disorder? ....☐ Yes
....☐ No

BDI Question #9 Form

Subject score on BDI item #9:   ⓪   ①   ②   ③

Suicidal ideation (> 1):   No ⓪   Yes ① (If **YES**, ask the following questions.)

     1) Has pt considered and/or had access to any specific methods of suicide? .... No ⓪ Yes ①

     2) Does pt want, intend, or plan to commit suicide in the near future?................................ No ⓪ Yes ①

     3) Has pt rehearsed or made preparations to carry out the plan? .... No ⓪ Yes ①

     4) Does pt have a history of past suicide attempt(s)?... No ⓪ Yes ①

     5) Are there additional circumstances that may add to the risk of attempting or completing suicide? (e.g. current alcohol abuse, social isolation, hopelessness, or crisis).. No ⓪ Yes ①

Psychologist/Psychiatrist Contacted: No ⓪   Yes ①

_____
(Psychologist's Name)

(_____) _____ - _____
 (Psychologist's Phone #)

Patient's Physician Contacted: No ⓪   Yes ①

_____
     (Physician's Name)

(_____) _____ - _____
(Physician's Phone #)

Diagnosis: _____

_____

_____

Action Taken / Outcome: _____

_____

_____

(**22 Item Version, Last Week**)			
Patient ID ☐☐☐☐☐☐☐	Staff ID ☐☐☐☐		How Administered:
Date (mo, da, yr): __ / __ / 20__	Time __ : __ am pm		patient ①
Suicidal Ideation (item 9 ≥ 1)	No ⓪ Yes ①		interviewer ②
Notified in case of suicidal ideation:	_____ _____		
Total Score	if item 20 = 1 (yes), score 1 – 22 without the scores of item 19 and 20.	if item 20 = 0 (no), score 1 – 22.	Item 20 = 0 ⓪ = 1 ①	**Total Score:** _____

Comments:

_____

Staff Signature: _____

APPENDIX G

Institutional Review Board Documents

TEACHERS COLLEGE
COLUMBIA UNIVERSITY

To: Andrea Duran
From: Myra Luna Lucero, Research Compliance Manager
Subject: IRB Approval: 19-157 Protocol
Date: 01/12/2019

Thank you for submitting your study entitled, "*Exploring the Associations Between Habitual Sedentary Behavior and Endothelial Cell Health*;" the IRB has determined that your study is **Exempt** from committee review (Category **4**) on 01/12/2019.

Please keep in mind that the IRB Committee must be contacted if there are any changes to your research protocol. The number assigned to your protocol is **19-157**. Feel free to contact the IRB Office by using the "Messages" option in the electronic Mentor IRB system if you have any questions about this protocol.

You can retrieve a PDF copy of this approval letter from the Mentor site.

Best wishes for your research work.

Sincerely,
Dr. Myra Luna Lucero
Research Compliance Manager
irb@tc.edu

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAK4250
Principal Investigator: Daichi Shimbo
(ds2231)
IRB Protocol Title: Translational Research of Negative Emotions and Acute Endothelial Dysfunction

Consent Number: CF-AAAT6731
Participation Duration: 2 visits
Anticipated Number of Subjects: 291

Contact

Contact	Title	Contact Type	Numbers
Daichi Shimbo	M.D.	Principal Investigator	Telephone: 212-342-4490
Maria Moran	R.N.	Study Coordinator	Telephone: 212-305-6173

Research Purpose

We are doing this research to study the effects of emotions (such as, anger, depression, and anxiety) on blood vessel health in a laboratory setting. Previous research has shown that negative emotions, such as anger, feeling depressed or sad, and anxiety, are risk factors for developing heart problems. Damage to blood vessels is thought to be an early process in causing heart attacks. We are interested in seeing whether feeling angry, depressed/sad, or anxious has effects on the health of blood vessels.

You are being asked to take part in this study, because you are otherwise healthy, are age 18 or older, fluent in English, have no history of cardiovascular disease, hypertension, diabetes, high cholesterol, do not smoke, do not have a history of psychiatric disease, do not have any known latex allergies, do not take any medications including over-the-counter drugs, and do not have prior difficulties with having blood drawn from a vein in your arm. We anticipate enrolling about 291 people in this study, which consists of two visits, including today's.

Information on Research

Invitation to participate

The purpose of this form is to give you information to help you decide if you want to take part in a research study. This consent form includes information about:

- Why the study is being done;
- Things that you will be asked to do if you are in the study;
- Any known risks involved;
- Any potential benefit; and
- Options, other than taking part in this study, that you have.

A research assistant will discuss the study with you. If at any time you have questions about the study, please ask a member of the study team. Take all the time you need to decide whether you want to take part in this research study.

The purpose of this research is described above in the 'Research purpose' section of this consent form.

Procedures
Taking part in this study will last for up to five hours during two separate study visits; one being today. The timing of study visits and the procedures that will be done at each visit are as follows:

Today's Laboratory Screening Visit
This initial visit will take up to 30 minutes to complete. During today's laboratory screening visit, a trained member of the research staff will evaluate the veins in your arm and determine the adequacy for drawing blood. If your veins are acceptable, we will explain the laboratory visit procedures (see below) to you in detail and answer all of your questions. We will then review this consent form with you, and answer any questions you may have. If you agree to participate and sign the consent form, your height and weight will be taken and you will be provided with a link to complete several questionnaires online asking about different aspects of your personality, relationships, activity levels, and health. These questionnaires must be completed within approximately ten business days and may take 45 to 60 minutes. If you do not have access to a computer, you will be asked to stay and complete the questionnaires during the laboratory screening visit on a computer at the Center for Behavioral Cardiovascular Health. Once the laboratory screening visit is completed, you will be contacted by a study coordinator to schedule your laboratory visit.

Laboratory Visit
Within approximately eight weeks of completing the questionnaires, you will return to the Center for Behavioral Cardiovascular Health (PH 9) at Columbia University Medical Center. Your appointment will be scheduled in the morning and you will be asked to come to the office for a laboratory session. You will be asked not to exercise or have anything to eat, except water, after midnight before your visit. This entire visit should take approximately 4 hours. You will not be given anything to eat until after the visit, at which time you will be given a small snack, such as a granola bar, and juice. You will be expected to go without food a total of 12 hours for this research study. Should you feel you will need additional food, we encourage you to pack something to eat the day of your study visit to eat afterwards.

After you arrive, you will be seated in a comfortable chair for the entire laboratory session. You will be fitted with a standard blood pressure cuff around your upper arm and two blood pressure (BP) with heart rate (HR) readings will be taken one minute apart. A small tube used to draw blood or provide fluids (an intravenous catheter) will be inserted into a vein in your dominant (the side that you write with) arm by a trained member of the research staff who has experience drawing blood. On your opposite arm, you will be fitted with another BP cuff around your forearm, a blood oxygen monitor sensor will be placed on one of your fingertips, and small finger cuffs will be placed on your index (pointing) fingers of both your hands. These cuffs will allow us to measure how well your blood

vessels expand in response to blood flow. Lastly, we will place a heart rate monitor strap around your chest. This strap will allow us to measure your heart rate throughout the entire laboratory session.

You will rest for 30 minutes at this time. Afterwards, two BP and HR readings will be taken one minute apart. You will then be asked to rate how you feel. A blood sample of up to three tablespoons, will then be drawn to measure the health of the cells that make up the inner lining of the blood vessels. From this sample, some of your blood will be stored in a freezer. The frozen blood will be used later to measure additional markers related to stress and blood vessel health.

Next, we will inflate the blood pressure cuff around your forearm tightly to partially block the flow of blood. This cuff will remain inflated for approximately five minutes. You will probably feel some discomfort during this part of the procedure similar to the tingling you might feel when your hand "goes to sleep," but your hand will not be in danger or harm from low blood flow. If the cuff causes too much discomfort, it will be deflated immediately. After five minutes, the blood pressure cuff will be deflated and we will measure how much your blood vessels dilate.

Next, you will then be randomly assigned (like a flip of a coin) to participate in a session in which you will be asked to remember an event or read statements out loud about one of the following emotions: (1) anger, (2) depression/sadness, (3) anxiety, or (4) a session in which you will undergo a non-emotional task.

If you are assigned to a session in which you will undergo a non-emotional task, the research assistant will ask you to count in a relaxing manner from 1 to 100 over and over again until the session has finished.

All procedures (rating your feelings, blood draw, and cuff inflation and deflation) will be repeated 3, 40, 70, and 100 minutes after finishing the randomly assigned task. For the entire study visit, the total amount of blood drawn will not exceed 14 tablespoons.

After testing has been completed, the cuffs and intravenous catheter will be removed. You may be given a card with the telephone number of a licensed Clinical Psychologist in the event you find that the issues you discussed with the research assistant have made you distressed and wish to speak to someone.

If an intravenous catheter (IV) cannot be successfully placed or if the IV is placed but blood is not successfully drawn during the first blood draw period, the laboratory visit will end and you will be compensated for your time and travel expenses.

Because you are allowing your blood to be frozen and stored, we also would like to know how we might use your blood sample in future approved research studies. Please read through the following sentences and initial below to show whether or not you give permission for your blood to be used in the following ways:

_____ (initials) I do give permission to have my blood samples stored for the Principal Investigator (Dr. Daichi Shimbo) to use in future studies related to this research.

_____ (initials) I do give permission to have my blood samples stored for the Principal Investigator (Dr. Daichi Shimbo) to use in future studies NOT related to this research.

_____ (initials) I do NOT give permission to have my blood samples stored for the Principal Investigator (Dr. Daichi Shimbo) to use in future studies related or not related to this research.

You will not be informed of the results of any tests. The results of these tests are for research purposes only and have no clinical significance.

Permission for future contact
The researchers may want to contact you in the future. Healthy participants, like you, are important to research. We respect your privacy, and will keep your contact information strictly confidential. However, if you're interested in participating in a possible future study with the Center for Behavioral Cardiovascular Health (CBCH), where healthy volunteer participants are needed, we'll keep this information with your contact record. You would not be contacted more than once for any one study.

Please initial below to show whether or not you give permission for future contact:

_____ (initials) I do give permission to be contacted in the future for research purposes.

_____ (initials) I do NOT give permission to be contacted in the future for research purposes.

Risks
General risks
There may be risks or discomforts if you take part in this study. These may include: some feelings of distress while answering questions during the study, but these are generally mild and go away quickly. If you feel upset, or continue to feel upset, a member of the research team will be available to talk to you and discuss appropriate care.

Risk of blood draw
Risks of having blood drawn are soreness and/or a black and blue mark at the site from where the blood is drawn. Sometimes, people feel uncomfortable at the time of the blood draw. Occasionally people feel lightheaded or even faint. There is also a small risk of infection whenever blood is drawn.

Medical Center IRB: 212-305-5883
CF#: AAAT6731 Copied From #: AAAT6731
Printed on: 01/07/2019 at 22:34   Page 4 of 7

Columbia University IRB
IRB Approval Date: 11/21/2017
for use until: 01/30/2018

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There may be minimal discomfort during the laboratory session due to the finger and arm blood pressure cuffs, which remain inflated or partially inflated during the session. The discomfort is temporary and goes away quickly.

Risk of breach of confidentiality
A risk of taking part in this study is the possibility of a loss of confidentiality. Loss of confidentiality includes having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your confidentiality. Their plans for keeping your information private are described in the 'confidentiality' section of this consent form.

Benefits
You may or may not receive personal (direct) benefit from taking part in this study. While not a direct benefit, the information collected from this research may help others in the future.

Alternative Procedures
You may choose not to take part in this research study.

Confidentiality
Protections
Any information collected during this study that can identify you by name will be kept confidential. We will do everything we can to keep your data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely.

Your questionnaire responses will be assigned a code number, and separated from your name or any other information that could identify you. The research file that links your name to the code number will be kept in a locked file cabinet and only the investigator and study staff will have access to the file.

The following individuals and/or agencies will be able to look at and/or may copy your research records:
- The investigator, study staff and other medical professionals who may be evaluating the study;
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board ('IRB');
- The Office of Human Research Protections ('OHRP');
- If this study is sponsored (money or supplies are being provided), the sponsor of this study, National Institutes of Health ('NIH'), including persons or organizations working with or owned by the sponsor; and
- Other government regulatory agencies (including agencies in other countries) if the sponsor is seeking marketing approval for new products resulting from this research.

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Compensation

You may receive up to $150 for participating in this study:

- After completing the questionnaires, you will be paid $10 in cash.
- After completing the laboratory visit, you will also be paid $140 in cash.

If an IV cannot be successfully placed in your arm or if the IV is placed but blood is not successfully drawn during the first blood draw period, the laboratory visit will end and you will be compensated $50 for your time and travel expenses.

If the investigator decides to remove you as a participant, you will only be compensated for visits you have completed.

Additional Costs

There are no costs to you for participating in this study.

Voluntary Participation

Taking part in this study is your choice. You can decide not to take part in or stop being in the study at any time. Your choice will not affect the treatment you receive from doctors and staff at Columbia University Medical Center and New York Presbyterian Hospital.

Termination of participation by investigator

You should know that we will not let you participate in the study any more if you do not complete what is detailed in the "procedures" section of this consent form. In addition, your participation will end if the investigator or study sponsor stops the study earlier than expected.

Additional Information

If you have any questions or concerns about the study, you may contact the Principal Investigator by phone at (212) 342-1273 or by email at cbch@columbia.edu.

If you have any questions about your rights as a subject, you may contact:

Institutional Review Board
Columbia University Medical Center
154 Haven Avenue, First Floor
New York, NY 10032
Telephone: (212) 305-5883
Email: irboffice@columbia.edu

An Institutional Review Board is a committee organized to protect the rights and welfare of human subjects involved in research.

More information about taking part in a research study can be found on the Columbia University Medical Center IRB website at: http://www.cumc.columbia.edu/dept/irb

More information about the Center for Behavioral Cardiovascular Health (CBCH) can be found on our website: http://www.cumc.columbia.edu/cbch

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U. S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Satisfaction survey
Our research center is committed to assessing and improving our work with study participants. We would like your permission to contact you after you have completed the study to answer a Research Subject Satisfaction Survey. This survey is confidential and your responses will help us to improve our services and enhance the research experience for study participants.

Please initial below to show whether or not you give permission to contact you after you complete this study to answer a Subject Satisfaction Survey:

_____ (initials) I do give permission to be contacted after I complete this study to answer a Subject Satisfaction Survey.

_____ (initials) I do NOT give permission to be contacted after I complete this study to answer a Subject Satisfaction Survey.

Statement of consent
I have read the consent form and talked about this research study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing to take part in this research study and that I can stop being in the study at any time. I am not waiving (giving up) any of my legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Signature

Study Subject
Print Name_____ Signature_____ Date_____

Person Obtaining Consent
Print Name_____ Signature_____ Date_____

TEACHERS COLLEGE
COLUMBIA UNIVERSITY

To: Andrea Duran
From: Myra Luna Lucero, Research Compliance Manager
Subject: IRB Approval: 19-156 Protocol
Date: 01/08/2019

Thank you for submitting your study entitled, "*Patterns of Sedentary Behavior in the First Month after Acute Coronary Syndrome*;" the IRB has determined that your study is **Exempt** from committee review (Category **4**) on 01/08/2019.

Please keep in mind that the IRB Committee must be contacted if there are any changes to your research protocol. The number assigned to your protocol is **19-156**. Feel free to contact the IRB Office by using the "Messages" option in the electronic Mentor IRB system if you have any questions about this protocol.

You can retrieve a PDF copy of this approval letter from the Mentor site.

Best wishes for your research work.

Sincerely,
Dr. Myra Luna Lucero
Research Compliance Manager
irb@tc.edu

Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAB9286
Principal Investigator: Karina Davidson
(kd2124)
IRB Protocol Title: Prescription Use, Lifestyle, & Stress Evaluation (PULSE)

Consent Number:		**CF-AAAK0946**	
Participation Duration:		1 year	
Anticipated Number of Subjects:		1925	

Contact

Contact	Title	Contact Type	Numbers
Karina Davidson	Associate Professor	Principal Investigator	Telephone: 212-342-4493
Joan Duer-Hefele	Research Nurse	Study Coordinator	Telephone: 212-342-4507

Research Purpose

The purpose of this study is to understand how your prescription medications, your lifestyle, and your feelings impact your risk of future heart disease.

Information on Research

This study looks at the psychological and behavioral factors that may influence the course of cardiovascular disease. You have been asked to participate in this study because you have acute coronary syndrome (ACS) and because of your responses to the screening questions.

If you agree to participate in the study, then you will be asked questions about your health, your mood, and your interest in things/people. You will be asked to complete these questions with a study interviewer today, while you are in the hospital. The visit today should take between 45 minutes to 1 hour to complete.

Physician Contact

If, during your participation in the study, any of the symptoms suggest that you are unsafe, a brief consultation with the appropriate professional will be scheduled. Additionally, if you would like, we can contact your primary physician to inform him/her of these symptoms.

Do you agree to have your physician contacted about these symptoms, if appropriate?
     Please initial your response: Yes ____   No ___

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Blood Sample

If you choose to participate in this study, a sample of four (4) tablespoons of blood will be drawn during your hospital stay. The blood testing will be done in a way that is similar to how your doctor usually checks blood tests. A needle will be used to draw blood from your vein which we will test certain molecules in your blood for genetics, for inflammation levels, and for information on how your blood clots. Part of the blood sample will be stored for future testing. At the one-month visit, we will draw another blood sample.

Do you agree to have a blood sample drawn for the purposes of this study?
    Please initial: Yes___ No___

We will also study some of your genes (DNA) in the blood sample. In particular, your blood sample will be examined for genes that affect depression and cardiovascular disease.

Do you agree to have your blood used for genetic research as described above?
    Please initial: Yes___ No___

Medication Adherence

If you choose to participate in this study and you are currently prescribed aspirin and/or Plavix, you will be asked to use special pill bottles that record how often you take these prescribed medications. You will be asked to use the pill bottles for one month and return them at your one-month follow-up.

The study will provide you with a one-month supply of your prescribed aspirin; you will be responsible for your aspirin after that time. To obtain Plavix, you will need to visit your local pharmacist with a prescription from your doctor. Your Plavix prescription bottle should fit inside the special pill bottle we provide you.

Do you agree to use the pill bottles for at least one month for the purposes of this study?
    Please initial: Yes___ No___
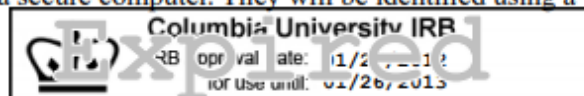
Activity Monitoring

We would like to fit you with a small activity monitor that is worn on the wrist. The device is approximately the size of a man's wrist watch and keeps a continuous record of your physical activity (i.e., how much you move your wrist). It can be worn in the shower and will not interfere with your daily activities.

Do you agree to wear the activity monitor for one month for the purposes of this study?
    Please initial: Yes___ No___

Phone Call Interviews

After you answer these questionnaires today, we will ask you to complete a phone interview with a member of the study staff; this interview will be completed within three (3) to seven (7) days of your discharge from this hospital. This interview will be audio-recorded (sound) for quality control and training. The recordings will be stored digitally on a secure computer. They will be identified using a

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unique subject ID, not your name. The recordings will be destroyed after study results are published.

You will also be contacted by phone in six (6) months and again after one (1) year to follow-up on your general health. These phone calls will take about 20 to 30 minutes to complete. These phone calls will not be recorded.

Office Visit

You will be asked to come into the study offices in one (1) month for a follow-up visit. If you are unable to travel to the study offices, arrangements may be made to conduct the visit at your home or by phone. During this visit/phone interview, you will be asked questions similar to those asked today. If you are able to come to the study offices, you will be asked to have an ECG done. An ECG records the electrical activity of your heart. This visit will take about 45 to 75 minutes to complete.

Benefits

You will not receive personal (direct) benefit from taking part in this research study. However, the information collected from this research may help others in the future.

Risks

Some stress is typical in answering questions about your stress, depression and anxiety levels.

The risks of having blood drawn include soreness and bruising at the puncture site, and sometimes there may be discomfort during the procedure. Occasionally, people feel lightheaded or faint. There is a small risk of infection whenever blood is drawn or when a plastic catheter (tube) is placed in the vein. The amount of blood to be taken is not considered to be a significant amount, and is therefore not expected to have any significant risk to you.

There may be slight discomfort from wearing the activity monitor, particularly during sleep. Additionally, there may be slight discomfort when applying or removing the ECG leads.

Informational Risk: Genetic (DNA) Testing

Your name and other identifying information will not be sent to the laboratory performing the analyses of your blood sample. The sample will be tested along with samples from other participants. The results of the tests will not be released to you or your family. No formal genetic counseling will be provided, because the clinical importance of the genes being tested is not known. At the end of the study, the results of the genetic testing may be published for all the subjects as a group, but it will not be possible to provide results for an individual patient.

However, in some situations, the research from your blood sample and/or additional testing may yield information that may immediately affect the health of you or your family. In this case, we will attempt to contact you/your physician. If you agree, your physician may perform testing in a clinical laboratory and may prescribe genetic counseling to determine how to best care for you.

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Please initial your response:

___Yes, I want you to contact me/my physician with results.

___No, I do not want you to contact me/my physician with results.

You should be aware that insurance companies sometimes use information on genetic testing to deny coverage to applicants. This study involves research that could be used to develop such genetic testing in the future. The information obtained in this research study cannot provide any meaningful information about a person. Since this is the case, if you are asked, you have not had a genetic test.

Compensation

You may receive up to $265 for your participation in this study. Payments will be made as follows:

Today (in hospital)
$25
plus $15 if you agree to have your medication monitored
plus $20 if you agree to have your blood drawn
plus $25 if you agree to wear the activity watch

Phone Call Interview (in 3 to 7 days)
$40
plus $5 if you agree to have your medication monitored

1-Month Follow-up Visit
$10
plus $10 if you agree to have your medication monitored
plus $40 if you agree to have your blood drawn
plus $20 if you have a study ECG done

6-Month Follow-up Phone Call
$20

12-Month Follow-up Phone Call
$35

Additional Compensation
In addition, you will be provided with breakfast during the 1-month office visit. Also, if you agree to have your medication adherence monitored, you will receive a one-month supply of your prescribed aspirin.

Additional Costs

There are no costs to you for participating in this study.

Alternative Procedures

The alternative is not to participate in this research study. Your decision whether or not to participate

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in this study will have no effect on your medical care at this hospital.

Confidentiality

Any information collected during this study that can identify you by name will be kept confidential. We will do everything we can to keep your data secure; however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems such as a stolen computer may occur, although it is highly unlikely.

Your specimens and questionnaire responses will be assigned a code number and separated from your name or any other information that could identify you.

The following individuals and/or agencies will be able to look at and copy your research records:
- The investigator, study staff and other medical professionals who may be evaluating the study
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board (IRB)
- The United States Office of Human Research Protections (OHRP)
- The sponsor of this study, the National Institutes of Health (NIH), including persons or organizations working with or owned by the sponsor

To further help us protect your privacy, the investigators have obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this certificate, the investigators cannot be forced (for example by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for the purpose of audit or evaluation.

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note, however, that if an insurer or employer learns about your participation, and obtains your consent to receive research information, the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

Any genetic information obtained during this study will remain strictly confidential. Once we take the blood sample, we will assign the specimen a unique identifier (a combination of letters and numbers) to be used for the duration of the study. Only the specimen will be sent on to the genetic laboratory for analysis. We will separate your name and any other information that points to your specimen. Genetic information will not be part of your medical record. Your identity will not be revealed when research findings are presented or published.

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The investigator is not required to report drug use as may be disclosed by you during the course of the study.

Additional Information
Additional Testing
While we do not have any further specific research plans at this time, we may want to use the blood sample you have provided for future studies. The unused sample will be given a unique sample identifier and the sample will be stored. You may choose not to have your sample stored for future research and still be part of the research study. Also, you may agree to have your specimen stored and later decide that you want to withdraw it from storage. If you make that decision, you should notify Dr. Davidson in writing requesting that your specimen be discarded.

The following check boxes allow you to choose whether or not you agree to the storage of your sample for future research. Please read the following statements and check and initial one or more of the following:

I agree to have my specimen of blood stored for Dr. Davidson to use in future research related to heart disease.
    Please initial: Yes____ No____

I agree to have my specimen of blood stored for Dr. Davidson to use in future research not related to heart disease.
    Please initial: Yes____ No____

If we distribute your sample to other individuals, it will be released with the unique sample identifier and without your name, medical record number, or other identifying information. This will make it very difficult for the doctor receiving the sample to find out the identity of the patient who provided the sample.

I agree that Dr. Davidson can share my specimen of blood for use in studies conducted by other investigators who are related to this research study.
    Please initial: Yes____ No____

I agree that Dr. Davidson can share my specimen of blood for use in studies conducted by other investigators who are not related to this research study.
    Please initial: Yes____ No____

Any new findings that may affect your willingness to allow samples to be used in this study for ongoing or future research will be communicated to you. However, all information obtained up to this point in time may be retained by the investigator.

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Future Contact
The investigators may want to call you in the future to inquire about your health and/or to invite you to participate in follow-up studies. If you agree to be called about future studies, you may receive phone calls asking if you would like to participate in other studies.

Do you agree to be contacted for future studies?
    Please initial: Yes___ No___

Questions/Concerns
If you have any questions or concerns about the study, you may contact Dr. Karina Davidson at (212) 342-4493.

If you have any questions about your rights as a subject, you may contact:

Institutional Review Board
Columbia University Health Sciences
722 West 168th Street, 4th Floor
New York, NY 10032
Telephone: (212) 305-5883

The Institutional Review Board is a committee organized to protect the rights and welfare of human subjects involved in research.

Voluntary Participation
Statement of Consent
I voluntarily consent to participate in the study. I have thoroughly read this consent form and understand the nature and the purpose of the study. I have fully discussed the study with the investigator or study staff, have had the opportunity to ask questions and have received satisfactory answers. The explanation I have been given has mentioned both the possible risks and benefits to participating in the study and the alternatives to participation.

I understand that I am free to not participate in the study or to withdraw at any time. My decision to not participate or to withdraw from the study will not affect my future care or status with this investigator.

I understand that I will receive and may keep a copy of this signed and dated consent form. By signing and dating this consent form, I have not waived any of the legal rights that I would have if I were not a participant in the study.

Signature

Study Subject
Print Name_____Signature_____Date_____

Person Obtaining Consent
Print Name_____Signature_____Date_____

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