**Sedentary behavior and Cardiovascular Disease: Using “Big Data” to Determine if Sedentary Behavior Adds to the Predictive Capacity of the American Heart Association’s “Simple 7”?**

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**A. Significance of the proposed work (250 Words)**

Globally [1] and nationally one in three deaths are attributable to CVD [2]. Up to 95% of adults do not meet the optimal risk profile for ideal heart health (see Table 1) as defined by the American Heart Association (AHA)[2, 3]. Achieving national guidelines of a 20% improvement in CVD by 2020 will require novel, efficacious, achievable and sustainable CVD prevention approaches [4, 5]. Sedentary behavior is a separate construct to physical activity [6], that predicts higher triglyceride level, a higher triglycerides-high-density lipoprotein cholesterol ratio, a higher body mass index, waist circumference, body fat percentage [7-10] and death [11]. Yet, sedentary time has yet to be recognized as an independent risk factor for CVD as demonstrated by its omission from composite CVD risk scores such as the American Heart Association’s, “Simple 7,”[3] the Framingham Heart Score[12] and the European Heart Score [13]. Interventions to address other, “established” behavioral cardiovascular risk factors such as tobacco use, physical inactivity and poor dietary behaviors lack long-term efficacy [14, 15]. As a causal factor for CVD, sedentary behavior may be more amenable to long-term individual change than physical activity (for example). Limiting this approach is the absence of empirically supported guidelines for adult sedentary behavior other than a general, “reduce sedentary time.” Defining a threshold of sedentary time per day, for example, that would significantly increase risk for key cardiovascular disease outcomes (e.g., angina, myocardial infarction and stroke) could help guide assessment, monitoring and intervention efforts to reduce sedentary time [16].

**Description of proposed research or scholarly actiVITY (1250 Words)**

1. **Study Overview:** This study will determine the predictive capacity of sedentary behavior (e.g., sitting, screen time and driving) for key cardiovascular disease outcomes including angina, myocardial infarction and stroke, independent of the American Heart Association’s 7 heart health metrics[3] including dietary intake, physical activity, tobacco use, body mass index, glycemic control, cholesterol and blood pressure. A threshold of hours of sedentary time per day beyond which the risk of cardiovascular disease increases significantly will also be identified. Using data from ~150,000 adults aged 40-69 years [17, 18] Cox regression models with the original “Simple 7” covariates will be generated and then sedentary behavior added to determine the added predictive capacity of 5-year CVD incidence for sedentary behavior (Figure 1). Hours of sedentary time per week that confers greatest CVD risk will be identified. These data will quantify the role of sedentary behavior in the lifestyle etiology of CVD and lay the basis for a line of investigation into the effects of sedentary behavior intervention on subsequent CVD risk and outcomes.
2. **The UK Biobank.** The UK Biobank is a 20-year cohort study comprised of National Health Service members that began in 2005 [18]. Baseline data were collected between 2006-2010 (N=503,325) and 5-year data collection is on-going [19, 20]. For the current study, participants having a history of myocardial infarction, stroke or angina and those who have not completed the follow-up assessment will not be included in the baseline sample (N~150,000).

**3. Study Measures**

*Outcome Variables*: The 5-year medical-chart verified incidence of myocardial infarction, stroke, and angina (yes/no) and the date of each CVD event is the outcome.

*Independent Variable: Sedentary Behavior:* Accelerometry data will measure sedentary behavior with a cutpoint of fewer than 100 counts/minute used as the threshold.[21, 22] A continuous variable of total minutes of verified sedentary behavior per week are computed by UK Biobank at baseline.[23]

American Heart Association, “Simple 7” Heart Score Variables:

*Physical activity:* Accelerometry data will measure baseline physical activity as counts per minute with light activity < 1,951 counts per minute (cpm), moderate activity = 1,952–5,724 cpm, and vigorous activity = 5,724 cpm. Total minutes of light, moderate, and vigorous activity per week are computed by UK Biobank.[23] Ideal, intermediate and poor physical activity categories will also be generated [3](Table 1).

*Diet:* Average daily intake of fruits/vegetables and whole grains, average weekly intake of fish and sugar-sweetened beverages and use of sodium (rarely/sometimes/usually/always) over the past year will be used to generate a composite healthy diet variable.[24] Ideal thresholds met for each of the 5 food items determines the overall ideal, intermediate and poor heart health classification (Table 1).[3]

*Tobacco use:* Participants self-reported smoking status is recorded categorically as current smoker (smoked >1 cigarettes in the last month), former smoker (quit >1 year) and never smoker (never smoked a cigarette). Ideal, intermediate and poor tobacco use will be generated (Table 1).[3]

*Body mass index (BMI):* BMI will be computed from measured weights and standing or seated heights (Seca 202).[25] Ideal, intermediate and poor BMI categories will be generated (See Table 1).[3]

*Blood pressure*: Blood pressure was measured with an automated blood pressure cuff reading (Omron HEM-7015IT).[26] A categorical variable of ideal, intermediate and poor blood pressure will also be generated (See Table 1).[3]

*Total cholesterol*: Total cholesterol levels will be measured from non-fasting venous samples aliquotted at 40C, and stored at -800C in SST vacutainers by the UK Biobank. A categorical variable of ideal, intermediate and poor total cholesterol will also be generated (See Table 1).[3]

*Hemoglobin A1C*: will measure glycemic control from non-fasting blood samples [27] clotted for 25-30 minutes, centrifuged at 2,500 for 10 minutes aliquotted at 40C, and stored in EDTA vacutainers by the UK Biobank. A categorical variable of ideal, intermediate and poor total Hemoglobin A1C will also be generated (See Table 1).

**Moderating Variables:** Moderating variables to be included in the analysis are age (continuous), sex (male/female), ethnicity (coded as White, Asian/Asian British/Chinese, Black/Black British, mixed/other), attended college (coded as yes/no), shift work (yes/no), and employment (coded as employed, not-employed, or retired).

**Covariates:** The covariates of medication use,[28]depression status, family history of cardiovascular disease, sleep duration[29] are self-report variables that were verified using patient medical records.

**4. Data Analysis**

4a.Descriptive Statistics: Means and standard deviations for continuous data and frequencies and percentages for categorical data, will be reported. The assumptions for all models will be evaluated, and the nominal significance level will be used, a =.05. Maximum likelihood methods will be used to aid in estimation in the presence of missing data.

4b. Aim 1 will quantify the predictive capacity of the baseline AHA “simple 7” heart score versus the “simple 7” heart score + sedentary behavior for key cardiovascular events (angina, myocardial infarction, stroke), independent of medication use, family history of cardiovascular disease, sleep and depression. This aim will be assessed in three steps. First, three Cox Regression models will be used to test if baseline sedentary behavior is related to the 5-year incidence of each of the 3 outcomes (angina, myocardial infarction, and stroke) separately after adjusting for the covariates of medication use, family history of CVD, depression, and sleep duration. Second: the Simple 7 variables (dietary intake, physical activity, tobacco use, body mass index, glycemic control, cholesterol and blood pressure) will be added to each of the Cox Regression models and the pseudo-R2, as well as log-likelihood fit statistics will be compared to see how much predictive power is added over and above the covariates and the simple 7. Third: the analysis will be repeated using a single Poisson regression model of a cumulative 5-year incidence of angina, myocardial infarction and stroke combined to determine the predictive capacity of the simple 7 for any of the cardiovascular outcomes when sedentary behavior is included.

4c. Aim 2 will identify the threshold of cumulative sedentary time beyond which risk for key cardiovascular disease events increases exponentially. To do this, a Receiver Operator Characteristic (ROC) will be used to establish the area under the curve (AUC). An AUC less than .50 for an outcome measure would indicate that it has no ability beyond chance to discriminate those who had the event and who did not; whereas, an AUC of 1.0 indicates a perfect ability to discriminate. By using the ROC curve to identify the point nearest the upper left-hand corner, we will be able to determine the best cut-off score for discrimination.

4d. Aim 3 will examine whether the relationships examined in Aims 1 and 2 vary (are moderated by) demographic factors such as age, sex, race, college attendance, residence and employment status. To do this, the moderation of relationship between sedentary behavior and outcomes (angina, myocardial infarction, stroke) by age, sex, race, college attendance, residence and employment status will be tested. This will be done by adding the interaction terms to each of the models run in aim 1 and 2 to determine if the model fit is improved by the consideration of these variables.

4e. Potential Analyses Issues: If there is an issue with getting the models to run or there is an overabundance of missing data on the date of the cardiovascular events, logistic regression models will be used to test the relationship between baseline sedentary behavior with each of the 3 outcomes, angina, myocardial infarction, and stroke (adjusting for other simple 7 metrics).

Additional Information

1. **Significance and Innovation of Proposed Project:** The proposed study is both conceptually and methodologically innovative. Conceptually this study is innovative because it: (1) evaluates the predictive capacity of sedentary behavior for cardiovascular disease outcomes, independent of other known risk factors for CVD; (2) connects cross-sectional to longitudinal data; (3) evaluates sedentary behavior as a risk factor in concert with other behavioral and physiological risk factors for cardiovascular disease, and, (4) conceptualizes sociodemographics as key moderators in the relationships between sedentary behavior and cardiovascular disease outcomes. Methodologically, this study is innovative because it: (1) uses a complex Cox Proportional Regression approach to study sedentary behavior and cardiovascular disease, and, (2) examines a large prospective cohort that assesses sedentary behavior as well as other behavioral health risk factors objectively. As such, this study represents an important vertical step in the elucidation of the role of sedentary behavior in the behavioral etiology of cardiovascular disease and will propel a line of investigation into strategies to reduce sedentary time and the longitudinal effects on CVD risk and incidence.

**plans for submission of this project to other funding sources.**

A positive signal from this study will lay the basis for several other grant proposals. Samples of three funding mechanisms, and plausible research concepts that will be pursued are described below.

**1. PA-14-114 Behavioral Interventions to Address Multiple Chronic Health Conditions in Primary Care (R01), National Heart, Lung and Blood Institute. January 2017.**

* A plausible follow-up study would be to determine the efficacy of a clinical intervention to decrease sedentary time, and consistent with the multiple health behavior change framework, whether decreased sedentary time improved other behavioral risk factors for cardiovascular disease including physical activity and dietary intake.

**2. Pfizer GRAND, June 2017**

* The purpose of the Pfizer GRAND mechanism is to identify new methodologies for smoking cessation and nicotine dependence treatment. Assuming that the predictive capacity of CVD outcomes is improved by the consideration of sedentary behavior, one novel study might be to examine: (1) if reductions in sedentary behavior optimized response to standard nicotine dependence treatment; (2) if reduced sedentary time + cessation improved cardiovascular outcomes more than cessation alone (i.e., test for synergistic effects).

**3. PA-15-037. Diabetes and Cardiovascular Disease in Older Adults (R01) October, 2017**

* Whereas achieving the recommended levels of physical activity is not always achievable for older adults, decreasing sedentary behavior levels may be more attainable. Having ascertained the predictive capacity of sedentary behavior for cardiovascular disease and guidelines for recommended sedentary time, systems approaches targeted to older adults could be developed and prospectively tested under this mechanism.

**Executive Summary (250 Words)**

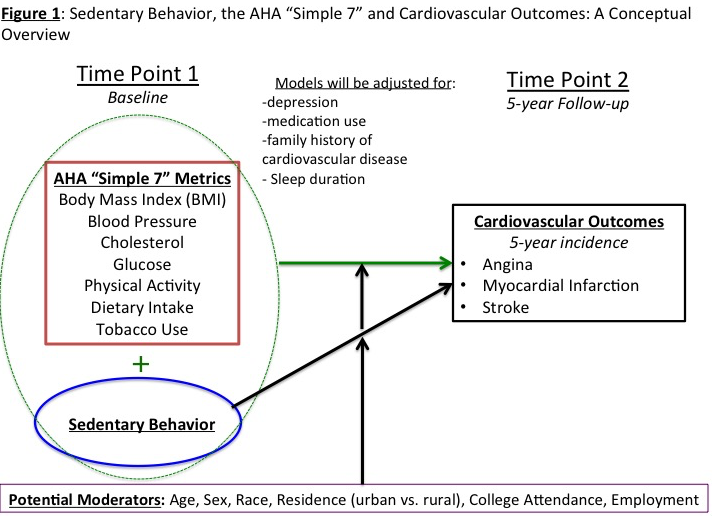
Up to 95% of American adults do not achieve ideal heart health as defined by the American Heart Association (AHA). Although sedentary behavior is a predictor of cardiovascular diseases (CVD), it is not recognized as an independent risk factor for CVD as demonstrated by its omission from cardiovascular risk scores such as the AHA “Simple 7.” Limiting this recognition is: (1) lack of empirical evidence to quantify the added predictive capacity that sedentary behavior brings to existing risk scores for CVD; (2) lack of public health recommendations on the amount of sedentary time that will elevate risk for CVD. The current study will address these limitations by using Cox regression models to determine the added predictive capacity that sedentary behavior brings to the AHA “simple 7” model and the threshold of hours of sedentary time per day beyond which risk of cardiovascular disease (angina, myocardial infarction and stroke) increases exponentially. Participants are 150,000 adults with five year CVD incidence data collected as part of the UK Biobank cohort study. This study will: (1) quantify the added predictive capacity of the AHA “simple 7” for 5-year CVD incidence that sedentary behavior brings, (2) identify the threshold of sedentary time that confers greatest CVD risk overall and for different demographic subgroups, (3) propel a line of investigation into strategies to reduce sedentary time and the longitudinal effects on CVD risk and incidence. Sources of funding from this work include the American Heart Association, the National Institutes of Health and Pfizer.

**Additional information in support of proposal**

**Table 1: Definition of Ideal, Intermediate and Poor for the Seven Heart Health Metrics** [3, 30]

|  |  |  |  |
| --- | --- | --- | --- |
| **Heart Health Metric** | **Ideal** | **Intermediate** | **Poor** |
| **Physical activity** | > 150 min/week moderate, or > 75 minutes per week vigorous, or > 150 min/week moderate plus vigorous | 1 – 149 min/week moderate, or 1 – 74 min/week vigorous, or 1 – 149 min/week moderate plus vigorous | 0 min/week |
| **Diet** | 4-5 of the healthy diet components | 2-3 of the healthy diet components | 0 -1 of the healthy diet components |
| **Tobacco use** | Never smoked | Previously smoked (>1 year ago) | Currently smokes or quit <1 year |
| **BMI** | < 22.9 | 23 to 26.9 | > 27.0 |
| **Blood pressure** | < 120.80 mm/Hg, | 120 – 139 / 80 mm/Hg | > 140 / 80 mm/Hg |
| **Cholesterol** | <200 mg/dL, untreated | 200 to 239 mg/dL or treated to goal | > 240 mg/dL |
| **Hemoglobin A1C** | < 6.0% untreated | 6.0% - 6.9% | > 7.0% |

**Figure 1. Study Conceptual Model**

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**Table 2. Study Timeline**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **6/1/2016- 5/31/2017** | **J** | **J** | **A** | **S** | **O** | **N** | **D** | **J** | **F** | **M** | **A** | **M** |
| Obtain UK Biobank Data; Institution sign material transfer agreements; IRB Approval | X | X |  |  |  |  |  |  |  |  |  |  |
| Data cleaning, codebook generation |  | X | X |  |  |  |  |  |  |  |  |  |
| Aim 1 and 3 Analysis and Manuscript |  |  |  | X | X | X | X | X |  |  |  |  |
| Aim 2 and 3 Analysis and Manuscript |  |  |  |  |  |  |  | X | X | X | X | X |
| SBM Conference Presentation |  |  |  |  |  |  |  |  |  |  | X |  |
| Grant Proposal Preparation and Submission |  |  |  |  |  |  |  | X |  |  |  | X |

**References**

1. Callow, A.D., *Cardiovascular disease 2005--the global picture.* Vascul Pharmacol, 2006. **45**(5): p. 302-7.

2. Mozaffarian, D., et al., *Heart disease and stroke statistics--2015 update: a report from the American Heart Association.* Circulation, 2015. **131**(4): p. e29-322.

3. Lloyd-Jones, D.M., et al., *Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond.* Circulation, 2010. **121**(4): p. 586-613.

4. Franklin, B.A. and M. Cushman, *Recent advances in preventive cardiology and lifestyle medicine: a themed series.* Circulation, 2011. **123**(20): p. 2274-83.

5. Spring, B., et al., *Better population health through behavior change in adults: a call to action.* Circulation, 2013. **128**(19): p. 2169-76.

6. Owen, N., et al., *Environmental determinants of physical activity and sedentary behavior.* Exerc Sport Sci Rev, 2000. **28**(4): p. 153-8.

7. Shuval, K., et al., *Sedentary behavior, cardiorespiratory fitness, physical activity, and cardiometabolic risk in men: the cooper center longitudinal study.* Mayo Clin Proc, 2014. **89**(8): p. 1052-62.

8. Qi, Q., et al., *Objectively Measured Sedentary Time and Cardiometabolic Biomarkers in US Hispanic/Latino Adults: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL).* Circulation, 2015. **132**(16): p. 1560-9.

9. Chastin, S.F., et al., *Combined Effects of Time Spent in Physical Activity, Sedentary Behaviors and Sleep on Obesity and Cardio-Metabolic Health Markers: A Novel Compositional Data Analysis Approach.* PLoS One, 2015. **10**(10): p. e0139984.

10. Chomistek, A.K., et al., *Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative.* J Am Coll Cardiol, 2013. **61**(23): p. 2346-54.

11. Katzmarzyk, P.T., et al., *Sitting time and mortality from all causes, cardiovascular disease, and cancer.* Med Sci Sports Exerc, 2009. **41**(5): p. 998-1005.

12. Simmons, R.K., et al., *Evaluation of the Framingham risk score in the European Prospective Investigation of Cancer-Norfolk cohort: does adding glycated hemoglobin improve the prediction of coronary heart disease events?* Arch Intern Med, 2008. **168**(11): p. 1209-16.

13. Stovring, H., et al., *A competing risk approach for the European Heart SCORE model based on cause-specific and all-cause mortality.* Eur J Prev Cardiol, 2013. **20**(5): p. 827-36.

14. Rothman, A.J., *Toward a theory-based analysis of behavioral maintenance.* Health Psychol, 2000. **19**(1 Suppl): p. 64-9.

15. Artinian, N.T., et al., *Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association.* Circulation, 2010. **122**(4): p. 406-41.

16. Hamilton, M.T., et al., *Too Little Exercise and Too Much Sitting: Inactivity Physiology and the Need for New Recommendations on Sedentary Behavior.* Curr Cardiovasc Risk Rep, 2008. **2**(4): p. 292-298.

17. Ollier, W., T. Sprosen, and T. Peakman, *UK Biobank: from concept to reality.* Pharmacogenomics, 2005. **6**(6): p. 639-46.

18. Sudlow, C., et al., *UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age.* PLoS Med, 2015. **12**(3): p. e1001779.

19. Allen, N., et al., *UK Biobank: Current status and what it means for epidemiology.* Health Policy and Technology, 2012. **1**(3): p. 123-126.

20. UK Biobank. 2015 [cited 2015 August 15]; Available from: <http://www.ukbiobank.ac.uk/>.

21. Hagstromer, M., P. Oja, and M. Sjostrom, *Physical activity and inactivity in an adult population assessed by accelerometry.* Med Sci Sports Exerc, 2007. **39**(9): p. 1502-8.

22. Hagstromer, M., et al., *Comparison of a subjective and an objective measure of physical activity in a population sample.* J Phys Act Health, 2010. **7**(4): p. 541-50.

23. Freedson, P.S., E.L. Melanson, and J.R. Sirard, *Calibration of the Computer Science and Applications, Inc. accelerometer.* Medicine and science in sports and exercise, 1998. **30**(5): p. 777-781.

24. Kim, D.J. and E.J. Holowaty, *Brief, validated survey instruments for the measurement of fruit and vegetable intakes in adults: a review.* Preventive Medicine, 2003. **36**(4): p. 440-447.

25. Romero-Corral, A., et al., *Accuracy of body mass index in diagnosing obesity in the adult general population.* Int J Obes (Lond), 2008. **32**(6): p. 959-66.

26. White, W. and Y. Anwar, *Evaluation of the overall efficacy of the Omron office digital blood pressure HEM-907 monitor in adults.* Blood pressure monitoring, 2001. **6**(2): p. 107-110.

27. Ford, E.S., *Habitual sleep duration and predicted 10-year cardiovascular risk using the pooled cohort risk equations among US adults.* J Am Heart Assoc, 2014. **3**(6): p. e001454.

28. UK Biobank, *UK Biobank: Protocol for a large-scale prospective epidemiological resource*. 2007.

29. Grandner, M.A., et al., *Habitual sleep duration associated with self-reported and objectively determined cardiometabolic risk factors.* Sleep Med, 2014. **15**(1): p. 42-50.

30. Saudek, C.D., et al., *A new look at screening and diagnosing diabetes mellitus.* J Clin Endocrinol Metab, 2008. **93**(7): p. 2447-53.