**Manuscript Proposal Outline (Upload)**

**Instructions:** Use a font size of 11 points or larger with at least one-half inch margins (top, bottom, left, and right) for all pages. Note: Supplemental materials such as table shells must be uploaded separately.

1. **Proposal Title:** Does socioeconomic or psychosocial adversity contribute to cardiovascular risk prediction?: The Jackson Heart Study
2. **Lead Author:** Margaret Hicken; Institute for Social Research; University of Michigan
3. **Overview**

Provide a brief overview of the proposal including the nature of the problem to be addressed, scientific relevance, objectives/aims, research question/hypotheses, and methods/analytical plan (**<250 words**):

Cardiovascular disease (CVD) is the leading cause of death among US men and women (1) and prevention has been a major concern. Risk scores have been developed to predict the risk of CVD based on a set of risk factors and are used to guide clinical practice (2-4). The currently recommended score is the American College of Cardiology/American Heart Association pooled cohort risk estimator (ACC/AHA)(4) which estimates the 10-year risk of atherosclerotic cardiovascular disease (ASCVD) based on age, sex, smoking, blood pressure, total cholesterol, and HDL cholesterol (4).

Notable has been the omission of social and psychological risk factors, which are associated with CVD (5, 6). Similarly, psychological adversity (e.g., high depressive symptoms, anger, and hostility) and psychosocial stress have also been shown to be positively associated with cardiovascular morbidity and mortality (5, 7). While some of these socioeconomic and psychosocial factors may increase risk through the clinical and behavioral risk factors included in the risk scores, research suggests that they may also operate through other mechanisms. Omission of these factors from risks prediction equations could result in underestimation of risk in low socioeconomic status (SES) groups and inadequate treatment recommendations, which may further result in missed opportunities to reduce social inequalities in CVD.

The objective of this study is to examine the added predictive value of including socioeconomic and psychosocial adversity measures in the ACC/AHA risk score in the Jackson Heart Study (JHS). We are conducting a parallel set of analyses in the Multi-Ethnic Study of Atherosclerosis (MESA) and would like to publish these parallel analyses in the same manuscript. (Note that we do not propose to pool the data, but to present the analyses together). We hypothesize that the addition of these measures will improve ASCVD prediction, particularly in those with low SES and high psychosocial adversity. This improved prediction can help guide prevention efforts to reduce inequalities.

1. **Background/Rationale**

Please include discussion on relevance of African Americans to the proposed topic (**<1000 words**).

Racial inequalities in CVD. A large literature has documented the racial/ethnic inequalities in CVD, particularly those between Black and White Americans. Despite the resources that have been invested toward the research and intervention of these inequalities, evidence indicates that these inequalities have remained steady and may even be widening (8). In general, efforts to understand CVD inequalities focus on conventional risk factors such as health behaviors and lipid profiles (9). However, researchers have shown that CVD inequalities persist after adjusting for inequalities in these conventional risk factors (10).

Health disparities researchers theorize that socioeconomic and psychosocial factors may be an important determinant of CVD inequalities (11). These factors are gaining recognition as important risk factors for CVD overall (5) and because researchers have shown that non-White racial/ethnic groups experience higher levels of socioeconomic and psychosocial adversity (e.g., higher levels of depressive symptoms) compared to Whites, these higher levels may explain CVD inequalities. The empirical literature on the contribution of psychosocial factors to cardiovascular inequalities – or even health inequalities more broadly – is sparse, although the few existing reports suggest that psychosocial stress makes some contribution (12, 13).

Risk scores and CVD. Risk scores have been developed to predict the risk of coronary heart disease (CHD) or CVD based on a set of (generally conventional) risk factors. In the primary care setting, these scores are used to guide treatment options. Until 2013, most widely used in the US is the Framingham Risk Score-Adult Treatment Panel III (FRS2002) which estimates the 10-year risk of CHD based on an individual’s age, sex, smoking, blood pressure, total cholesterol, and HDL cholesterol. Recently, this score has been modified to include markers of inflammation and family history of premature myocardial infarction (MI) (Reynolds risk score, RSS) or to predict CVD more broadly (3). Developed in 2013, the currently recommended score is ACC/AHA which estimates the 10-year risk of ASCVD based on age, sex, smoking, blood pressure, total cholesterol, and HDL cholesterol (4).

Risk scores and socioeconomic and psychosocial factors. A large literature has documented the socioeconomic gradient in health outcomes, including cardiovascular morbidity and mortality (14). Similarly, psychosocial adversity (e.g., high psychosocial stress, depressive symptoms, anger, and hostility) has also been shown to be positively associated with cardiovascular morbidity and mortality. Despite these associations with cardiovascular health, these factors are rarely included in the prediction of cardiovascular risk.

Researchers have examined FRS2002 score performance after inclusion of individual-level (15) and area-level (16) SES measures. They reported that, without measures of SES, the FRS2002 underestimated CHD risk in low SES groups, a bias that was mitigated with the addition of SES measures to the risk score. However, a study conducted in Scotland found no evidence of differential prediction accuracy by social class for the FRS2002 and no improvement in prediction when individual-level lifetime social class or psychosocial factors were added (17). More recently, researchers reported that the ACC/AHA risk score overestimated CVD in more socially advantaged groups in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) (18). No work on the inclusion of psychosocial factors has been done in US samples. The potential contribution of SES and psychosocial factors to the ACC/AHA risk score may be particularly important for Black Americans, as researchers have documented that, compared to White Americans, they experience greater exposure to socioeconomic stressors and report higher levels of psychosocial stress and distress (12, 19).

Examining the risk score performance after integrating socioeconomic or psychosocial adversity to current risk scores has important implications. Omission of SES or psychosocial factors could underestimate the risk of CVD for persons with high levels of these adversities. Because clinicians often use these scores to guide treatment for cardiovascular health, underestimating risk in certain persons could result in missed opportunities for intervention.

1. **Research Hypothesis**
* The ACC/AHA risk score will systematically underestimate ASCVD in the JHS (and MESA) for those persons of: (a) low SES or (b) high psychosocial adversity.
* The addition of SES or psychosocial factors, respectively, will improve the prediction of ASCVD in JHS (and MESA).
1. **Inclusions/Exclusions**

We will include all participants who were free of ASCVD at the baseline exam: CHD (includes myocardial infarction, coronary insufficiency, and angina pectoris), stroke (ischemic or hemorrhagic), transient ischemic attack, congestive heart failure, intermittent claudication. We will exclude those who have missing information on the variables, underlined in this Data Section, or the outcome variable. We will require all ASCVD events available up to the 2014 adjudication and all remaining variables from the baseline exam. Because there may be considerable variation in the time between exams, we will require the date of the baseline exam, the date of the first ASCVD event or the date of the last follow up conducted (which will facilitate proper censoring in the hazard models described in the Analysis Section).

*Outcome variable: ASCVD events*

First occurrence of any fatal or non-fatal ASCVD event: CHD (definite and probable MI, CHD death), cardiac procedure, stroke, or stroke death.

*Key independent variables*:

The ACC/AHA which estimates the 10-year risk of ASCVD based on age, sex, smoking status, blood pressure, total cholesterol, and HDL cholesterol (4).

Based on previous work (15, 16, 18, 20), we will examine individual-level SES as education and household income. We would also like to include family income status (unique to JHS) and wealth, as an index marked by ownership of home, car, land, or investments. We will examine area-level SES as an index developed by co-author Diez-Roux using principal components analysis of census tract information on: median housing value log, % HS education, % Bachelor’s degree, % managerial occupation, median HH income log, and % interest/dividend income. A higher value indicates a better SES. This will be missing if any variables are missing.

The literature on stress and CVD suggests that a composite measure of stress may better capture the multi-dimensional nature of psychosocial stress (12, 21, 22). In a recent paper on this topic (12), researchers created a composite measure of psychosocial stress from multiple measures, representing multiple domains. Researchers argue that the composite stress measure “reflect the key arenas in which people operate (e.g., home, job, neighborhood) and the major roles and statuses they assume” (12, p. 97, 23, 24). In the JHS, there is a “Hassles and Moods” and “Global Stress instruments, each with numerous items on the extent to which various situations across multiple domains that may have occurred over the past week are stressful. Domains include, for example, job, finances, family, and social networks. We will examine multiple measures of psychological adversity that have been shown to be related to CVD or CVD risk factors, including: depressive symptoms, outwardly expressed anger, and inwardly expressed anger (7).

1. **Statistical Analysis Plan and Methods**

Include power calculations, if necessary.

Cox proportional hazards regression analysis will be used to estimate the risk (i.e., hazard ratios, HR, with 95% confidence intervals, CI) of events, with survival considered to be time to the event (first nonfatal event or fatal event) or censoring, with follow up to 2014.

*Descriptive characteristics*: We will examine the characteristics of the JHS baseline sample, including only those who have not experienced an ASCVD event at baseline. Characteristics will be examined in the entire baseline sample, and by quartiles of the distributions of SES, psychosocial stress, and psychological adversity composite scores.

*Performance of ACC/AHA in JHS*: After checking proportionality assumptions, we will examine the ACC/AHA performance in JHS, following methods used by others (18). To assess calibration, events are divided into tertiles of risk. Observed and predicted events will be compared within tertiles using χ2 goodness-of-fit statistic, for which larger probability values reflect better fit. To assess discrimination, we will calculate Harrell’s c statistic from the hazard models and the net reclassification index (NRI) by event status, following the literature (18).

*Performance of ACC/AHA accounting for SES, psychosocial adversity*: We will examine the impact of SES, psychosocial stress, and psychological adversity on risk prediction using the ACC/AHA in three ways. We will first assess whether these measures predict events independently of the ACC/AHA by examining the statistical significance of the SES and psychosocial adversity coefficients in hazard models. Second, we will assess the performance of the ACC/AHA in groups across tertiles of SES and psychosocial adversity. Within each of these tertiles, we will examine model discrimination and calibration. Third, to examine whether model calibration is the same across tertiles of SES/adversity, we will first attempt traditional approaches to calibration assessment (i.e., graphical plots and goodness-of-fit statistics). However, because events may be too low within these groups, we will use two other methods, following the literature (15), to examine the extent to which the predicted and observed events match. In the first method, we will calculate Martingale residuals for each individual as: M = O – CS, where M is the Martingale residual, O is the variable for the observed event (1=event; 0=no event), and CS is the Cox-Snell residual from the hazard model. We will then estimate the mean Martingale residual within each adversity group. A Martingale residual closer to zero indicates a better calibration (i.e. better match between predicted and observed events). All analyses will be run in STATA MP 14.0 (StataCorp, College Station, TX).

1. **References (maximum 15)**

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