

**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:**
2. **Lead Author:**
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**):

The 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline recommends initiation of antihypertensive medication for adults with stage 1 hypertension, systolic BP of 130 to 139 mmHg or diastolic BP of 80 to 89 mmHg, and high cardiovascular disease (CVD) risk. In this guideline, the definition of high CVD risk included 10-year predicted atherosclerotic CVD (ASCVD) risk ≥10% using the Pooled Cohort Equations. In 2023, the American Heart Association published the PREVENT equations. Many adults with 10-year predicted ASCVD risk ≥10% by the Pooled Cohort Equations have 10-year predicted ASCVD or total CVD risk <10% by the PREVENT equations. There are PREVENT equations to estimate 30-year ASCVD and total CVD risk. It may be reasonable to recommend initiation of antihypertensive medication for adults with stage 1 hypertension and high 10-year or 30-year predicted risk if these individuals have a high incidence of stage 2 hypertension, systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or initiation of antihypertensive medication, and they have sub-clinical CVD when they develop stage 2 hypertension. We propose to study the association between 30-year predicted total CVD risk using the PREVENT equations with the incidence of stage 2 hypertension among Jackson Heart Study participants. We hypothesize the incidence of stage 2 hypertension will increase progressively with higher 30-year predicted total CVD risk. In addition, we hypothesize that a high proportion of participants that develop stage 2 hypertension will have evidence of sub-clinical CVD, estimated by higher left ventricular mass index at Visit 3.

1. **Background/Rationale**

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

1. **Research Hypothesis**

Our primary hypothesis is that 30-year predicted total CVD risk using the PREVENT equations is associated with incident stage 2 hypertension. Our secondary hypotheses are as follows:

1. Incident CVD events are associated with higher 30-year predicted total CVD risk using the PREVENT equations at visit 1.
2. Among participants who did not experience a CVD event between visit 1 and visit 3 and with 10-year predicted total CVD risk using the PREVENT equations < 10% at visit 1, 30-year predicted total CVD risk using the PREVENT equations at visit 1 is associated with higher left ventricular mass index at visit 3.
3. Among participants who did not experience a CVD event between visit 1 and visit 3, with 10-year predicted total CVD risk using the PREVENT equations < 10% at visit 1, and with stage 2 hypertension at visit 3, 30-year predicted total CVD risk using the PREVENT equations is associated with sub-clinical CVD at visit 3, defined by left ventricular mass ≥ XYZ.

In exploratory analyses, we will test the four hypotheses above in subgroups based on BP levels at visit 1: *normotensive* (systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg), *elevated* (systolic BP 120 to < 130 mm Hg and diastolic BP < 80 mm Hg), and *stage 1 hypertension* (systolic BP 130 to < 140 mm Hg with diastolic BP < 90 mm Hg or diastolic BP 80 to < 89 with systolic BP < 140 mm Hg).

1. **Inclusions/Exclusions**

We will include participants who were aged 30 to < 60 years at visit 1. We will restrict our sample to participants who consented to CVD follow-up and had no history of CVD at visit 1. We will exclude participants without information on self-reported antihypertensive medication use and BP at visit 1 and will also exclude participants who did not have information on variables in the 10-year and 30-year CVD PREVENT equations at visit 1. Furthermore, we will exclude participants with inputs for the PREVENT equations at visit 1 that are outside the range of recommended values. Last, we will restrict the sample to include participants without hypertension at visit 1 and with known hypertension status at either visit 2 or visit 3. We anticipate over 1,000 JHS participants will meet these criteria.

1. **Statistical Analysis Plan and Methods**

*Descriptive statistics.* Participant characteristics will be summarized using the mean for continuous and percentage for categorical variables, overall and in subgroups based on BP (normotensive, elevated, and stage 1 hypertension). Medians with 25th and 75th percentiles will be presented instead of means for continuous variables that exhibit skew (e.g., predicted CVD risk is often skewed towards lower values). We will summarize the distribution of JHS participants included in the current analysis according to 10-year and 30-year total CVD risk using the PREVENT equations. Specifically, we will compute the proportion of participants with 10-year total CVD risk < 10%. Among the participants with 10-year total CVD risk < 10%, we will compute the proportion with 30-year total CVD risk <10%, 10% to <15%, 15% to <20%, 20% to <25%, 25% to <30%, and ≥30%.

*Hypothesis testing.* Interval censored Cox regression models will be used to test whether 30-year predicted CVD risk using the PREVENT equations at visit 1 is associated with incident hypertension at visits 2 or 3. Cox regression models will be applied to test whether 30-year predicted CVD risk using the PREVENT equations at visit 1 is associated with incident CVD. Linear regression will be used to test whether 30-year predicted CVD risk using the PREVENT equations at visit 1 is associated with left ventricular mass at visit 3. Poisson regression with robust standard errors will be used to test whether 30-year predicted risk using the PREVENT equations at visit 1 is associated with left ventricular hypertrophy at visit 3.

*Multivariable adjustment.* Because predicted risk using the PREVENT equations is a primary independent variable in our models, we do not include multivariable adjustment for traditional variables (e.g., age) that contribute to predicted risk from these equations.

*Secondary analyses using splines.* Our primary analyses will assume that 30-year predicted risk using the PREVENT equations at visit 1 has a linear relationship with the designated outcome. In secondary analyses, we will relax this assumption by leveraging a natural cubic spline to model a non-linear relationship instead of a linear one. These secondary analyses will perform the same hypothesis tests as our primary analyses and will be summarized with visualization in supplemental material.

*Sensitivity analysis.* A number of participants may have missing data for left ventricular mass at visit 3. Our primary analysis will assume these data are missing completely at random and perform a complete case analysis. In a sensitivity analysis, we will assess how robust our complete case analysis is by performing multiple imputation and testing the same hypotheses. If multiple imputation leads to conflicting inferences compared to complete case analysis, we will note that data may not have been missing completely at random as a limitation and present the multiply imputed results in our primary analysis.

1. **References (maximum 15)**