Jackson Heart Study Manuscript Proposal

1. **Proposal Title:** Regional Adiposity and Risk of Heart Failure and Mortality: The Jackson Heart Study

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3. **Overview**: Regional adiposity describes fat accumulation in the pericardial, visceral, and subcutaneous compartments. Longitudinal studies demonstrate that regional fat depots exhibit unequal risk of incident heart failure (HF) and mortality. However, it is unclear whether regional fat deposition plays a role on incident HF and mortality independent of total body fat accumulation, especially within subgroups that exhibit increased cardiovascular risk. Additionally, whether regional fat depots present a differential risk in incident HF and mortality among high risk populations, such as those with diabetes and hypertension, remains to be studied. In this proposal, we examine the effect of regional adiposity on incident HF and mortality across obesity subgroups and among individuals with cardiovascular risk factors.

4. **Background/Rationale:**

Heart failure (HF) is a major problem in the US affecting approximately 6.5 million (1). Risk factors for HF include older age, hypertension, diabetes, kidney disease, and obesity (2). Obesity represents excess total body adiposity and has increased in prevalence worldwide over recent decades (3). Obesity is most commonly defined by anthropometrics, including body mass index (BMI), waist circumference (WC), and waist-hip-ratio (WHR). While total body accumulation of adiposity tissue is thought to contribute to cardiovascular risk, the deleterious cardiovascular effects of obesity may actually result from the specific distribution of excess adipose tissue (4). Higher BMI predicts HF and its effect may vary by sex (5).

Different depots of regional fat accumulation include the pericardium, visceral, and subcutaneous compartments. Visceral adipose tissue (VAT) refers to the intra-abdominal adipose accumulation of omental and mesenteric adipose tissue, excluding subcutaneous and intramuscular fat (6). VAT is pro-inflammatory and increases cardiovascular risk by promoting diseases such as diabetes, dyslipidemia, and hypertension (7). VAT can be quantified by computed tomography (CT) scans at the level of the umbilicus, L2-L3, or L4-L5 (8). While anthropometrics such as WC and WHR are intended to indirectly represent the burden of visceral adiposity, they in fact do not accurately quantify visceral fat (6). VAT and not BMI is directly associated with mortality, especially among obese people with coronary artery disease (9). Even among those who are normal weight or overweight (i.e. BMI < 30 kg/m^2), elevated VAT appears to be associated with metabolic derangements and prevalence of cardiometabolic diseases (10). Pericardial adipose tissue (PEAT) is also deleterious and refers to regional fat surrounding the heart. PEAT can be measured by quantifying fat thickness using 2-dimensional transthoracic echocardiography (TTE) (11). Pericardial fat is associated with accelerated coronary atherosclerosis, insulin resistance and hypertension both in obese and non-obese individuals (12) . Further, PEAT thickness in itself, which trends with higher BMI, correlates with the prevalence of hypertension (11). Subcutaneous adipose tissue (SAT) refers to the accumulation of adipose tissue outside of the abdominal cavity. SAT appears to have different effects on cardiometabolic risk than VAT and does not appear to be independently associated with subclinical and clinical cardiovascular disease (13).

Regarding heart failure risk, VAT predicts incident HF among Blacks (14), and particularly predicts incident HF with preserved ejection fraction (HFpEF) (5). While not statistically significant, VAT also provided a trend towards increased risk of HFpEF among people with normal BMI (i.e. BMI < 25),

increased VAT predicted a trend towards increased incidence of hospitalized HFpEF but not incident HF with reduced ejection fraction (HFrEF) (5), leading to a "silent obesity phenotype." No studies have investigated the role PEAT plays in incidence of HF. SAT, on the other hand, has not shown to have an independent effect on cardiovascular risk (15) and incident heart failure and its subtypes HFpEF and HFrEF (5).

At present, it is not well understood how regional adiposity plays a role in the development of HF across populations with higher risk. In this proposal, we will compare VAT, PEAT, and SAT measures independently and together to conventional anthropometric measures of obesity (BMI, WC, WHR) on incidence of heart failure and all-cause mortality to determine their incremental prognostic value as a cardiovascular risk factor. We will also compare discordant categories of obesity (i.e. normal or overweight BMI and high VAT/PEAT) to identify groups of people who may benefit from more targeted screening. Additionally, we will compare the incremental risk of heart failure and mortality across high risk subgroups, including those with diabetes and hypertension. These results will be helpful in understanding the effectiveness of different measures of excess adiposity in relation to risk of heart failure and aid in identifying subgroups of people who would benefit from preventive strategies to improve body fat compositions and prevent heart failure events.

5. Research Hypotheses:

Primary Hypotheses:

(1) We hypothesize that directly measured visceral adipose tissue (VAT) and pericardial adipose tissue (PEAT), but not subcutaneous adipose tissue (SAT), are associated with incident HF and all-cause mortality, and this risk increases across groups who have normal BMI (BMI < 25 kg/m^2), overweight (BMI ≥ 25 but <30 kg/m^2), and obesity (BMI ≥ 30 kg/m^2).

Secondary Hypotheses:

(2) In the combined cohort with both available abdominal CT and TTE imaging, we plan to characterize concordant and discordant trends in VAT and PEAT measures across BMI subgroups. We hypothesize that increased VAT and increased PEAT are predictive of incident HF and all-cause mortality than compared to those without increased PEAT + VAT across the BMI subgroups of normal BMI (BMI < 25 kg/m^2) and overweight and obesity (BMI ≥ 25 kg/m^2)).

(3) In the combined cohort with both available abdominal CT and TTE imaging, we hypothesize that increased PEAT and VAT are more predictive of incident HF and all-cause mortality across groups who have cardiovascular risk factors, including diabetes and hypertension, than compared to those who do not have these cardiovascular risk factors.

6. Inclusions / Exclusions:

Participants (inclusions/exclusions):

For Aim 1 (cohorts with adiposity measures), we will include all participants from the baseline exam of JHS with measured BMI, WC, and WHR who have available outcomes determined for incident HF and all-cause mortality.

PEAT imaging was taken at Exam 2 between 2007-2008:

PEAT cohort included a total N of 1235 with complete PEAT, BMI, WC, and WHR measurements at Exam 2

Outcomes:

- 61 HF events
- 138 deaths

VAT and SAT measurements were also taken at Exam 2 between 2005-2008:

VAT and SAT cohort included a total N of 2525 with complete VAT, BMI, WC, and WHR measurements at Exam 2

Outcomes:

- 134 HF events
- 278 deaths

For subjects with both PEAT and VAT measurements, from the latest scan or visit date

PEAT and VAT cohort included a total N of 1232 with complete PEAT, VAT, BMI, WC, and WHR measurements at Exam 2

Outcomes:

- 61 HF events
- 138 deaths

Participants with missing data on exposures or outcomes will be excluded.

Exposures: BMI, WC, WHR from Exam 2 (baseline with TTE measuring PEAT and CT for VAT and SAT); PEAT from Exam 2; VAT/SAT from Exam 2.

VAT is defined as the total adipose tissue enclosed within the abdominal cavity, and SAT is defined as the total adipose tissue outside of the abdominal cavity but not within muscle tissue. PEAT is defined as pericardial fat thickness around the heart.

We will define ectopic fat exposures as continuous measures, and also as by quartiles to assess non-linear relationships. For Aim 2, for comparing discordant/concordant groups, we will use dichotomized BMI subgroups as normal BMI (18.5-<25 kg/m^2) and overweight / obesity BMIs (≥25 kg/m^2).

Outcomes: Incident adjudicated HF, including its subtypes HFpEF and HFrEF if available, and all-cause mortality in the most current frozen JHS dataset.

Covariates**:** Age, sex, education, smoking, systolic blood pressure (BP), use of anti-hypertensive medications, diabetes (defined fasting blood glucose ≥126 mg/dL and/or the self-reported history of a physician-diagnosis of diabetes, or the use of diabetes medications), total cholesterol, use of lipid lowering medications, estimated glomerular filtration rates (eGFR) using the CKD-EPI equation.

7. Statistical Analysis and Plans:

Baseline continuous variables will be presented as means ± standard deviation or median and interquartile range (IQR) as appropriate. Categorical variables will be presented as count and relative frequency (%).

Specific Aim 1: We will calculate Kaplan-Meier estimates of incident HF and all-cause mortality by quartiles of the adiposity measure and will use log-rank tests to test for differences between groups. Both unadjusted and adjusted cox proportional hazard regression models will be used to assess the relationship of each adiposity measure (from the JHS Exam 2) with incident HF and all-cause mortality as separate outcomes.

We will test for collinearity between covariates and remove those where the variance inflation factor is >3. Models will be progressively adjusted as follows:
Model 1: adiposity measure only
Model 2: adiposity measure + demographic factors of age, sex
Model 3: model 2 + lifestyle factors of education, smoking
Model 4: model 3 + CVD risk factors of systolic BP, use of antihypertensive medications, total cholesterol, HDL-C, use of lipid lowering medications, diabetes, and eGFR

We will include BMI as an interaction term between adiposity measure and outcome, and if significant, we will then investigate whether these associations are stronger at higher levels of BMI in the example table.

BMI Category	Hazard Ratios and 95% CI by incremental VAT on Outcomes		Hazard Ratios and 95% CI by incremental PEAT on Outcomes	
	Incident HF	Mortality	Incident HF	Mortality
Normal BMI (< 25 kg/m^2)	-	-	-	-
Overweight (BMI ≥ 25 -<30 kg/m^2)	-	-	-	-
Obese (BMI ≥ 30 kg/m^2)	-	-	-	-

Interaction analyses will be explored in pre-specified subgroups defined by age and sex.

Specific Aim 2:

We will categorize subjects into below and above median VAT measures and stratify them by normal, overweight, and obese BMI categories as above. Comparison of incident heart failure and mortality events will be performed among discordant groups and concordant groups using analysis of variance statistical model. A sample table is shown below of Hazard Ratios and 95% CI on incident HF and all-cause mortality outcomes. *This analysis will be exploratory due to the limited number of outcomes in this combined VAT and PEAT cohort.*

Concordant adiposity measures	Below median VAT and below median PEAT measures		Above median VAT and above median PEAT measures	
	Normal BMI	Overweight / Obese	Normal BMI	Overweight / Obese
Incident Heart Failure (#)	-	-	-	-
Mortality (#)	-	-	-	-

Discordant adiposity measures	Below median VAT and above median PEAT measures		Above median VAT and below median PEAT measures	
	Normal BMI	Overweight / Obese	Normal BMI	Overweight / Obese
Incident Heart Failure (#)	-	-	-	-
Mortality (#)	-	-	-	-

Two sided P values <0.05 will be considered to be statistically significant. All analyses will be performed using SAS 9.4.

Specific Aim 3:

We will categorize subjects by cardiovascular risk factors including diabetes and hypertension and perform cox proportional hazard regression to determine incremental risk of VAT and PEAT among groups with and without these risk factors on incident heart failure and mortality. A sample table is shown below. *This analysis will be exploratory due to the limited number of outcomes in this combined VAT and PEAT cohort.*

Cardiovascular Risk Factor	Hazard Ratios and 95% CI by incremental VAT on Outcomes		Hazard Ratios and 95% CI by incremental PEAT on Outcomes	
	Incident HF	Mortality	Incident HF	Mortality
Diabetes	-	-	-	-
Hypertension	-	-	-	-
Diabetes + Hypertension	-	-	-	-
No Diabetes / Hypertension	-	-	-	-

Limitations: We may have limited power to explore differences in subgroups of age and sex by HF subtype; so all subgroup analyses will be considered exploratory.

Potential Overlap: After review of the JHS publications, and after discussion with Dr. Mentz, we have identified no significant overlap with prior work. The most closely related publications are as follows:

(1) Pandey et al. "Association Between Regional Adipose Tissue Distribution and Risk of Heart Failure Among Blacks." Circ Heart Fail. 2018 Nov;11(11). Dr. Pandey and colleagues described visceral and subcutaneous fat on incident heart failure and mortality, and sub analyses of MRI-measured left ventricular function and morphology. Our proposal differs as we intend to determine the incremental increased risk VAT and PEAT serve on incident HF and mortality across various groups, including normal BMI, overweight, and obese subgroups, as well as subgroups with various cardiovascular risk factors. We hope to characterize the incremental cardiovascular risk of regional adiposity beyond known traditional risk factors.

Dr. Mentz is coauthor previous proposals involving regional adiposity and heart failure and can ensure there is no overlap.

8. References:

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14. Pandey A, Kondamudi N, Patel KV et al. Association Between Regional Adipose Tissue Distribution and Risk of Heart Failure Among Blacks. Circ Heart Fail 2018;11:e005629.
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