# Jackson Heart Study Manuscript Proposal

**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:** *Hormone Replacement Therapy and Cardiovascular Risk in Postmenopausal African-American Women: Jackson Heart Study*

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**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**):

**4. Background/Rationale**

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity[6-7,10], specifically consistent ovulation. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological etiology[6-7,10]. The age of onset for menopause is generally between 45-55 years of age[7]. Menopause is associated with a number of physical (e.g. hot flashes, night sweats, insomnia, fatigue) and psychological (e.g. anxiety, mood swings, irritability, depression) symptoms[7,9], in addition to an increased risk for atherosclerosis, CVD, osteoporosis, cancer (e.g. Ovarian and Breast)[3]. Hormone Replacement Therapy (HRT) was developed in an effort to reduce many of the symptoms associated with menopause[8-9]. Although considered to be self-limiting and non-life threatening, menopausal symptoms can be associated with poor quality of life for women. HRT has also been used for the management and prevention of chronic diseases such as cardiovascular disease, osteoporosis and dementia in older women[7].

HRT includes either estrogen alone (estrogen-only HT) or estrogen combined with a progestogen (combined HT). HRT has been used in the treatment of postmenopausal symptoms such as hot flashes, mood disorders, vaginal atrophy, and sleep disturbances for more than 50 years[8-9]. Cochrane reviews reported a 75% reduction in the frequency of hot flashes for perimenopausal and postmenopausal women using HRT, relative to placebo as well as a reduction in severity of symptoms[3]. In the past 25 years, HRT has also been used as a preventative measure for heart disease, osteoporosis, dementia and some cancer[7]. It was widely accepted throughout the

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1990s that HRT was beneficial for most postmenopausal women[2-3,7-8,10]. Observational studies indicated HRT reduced risk of coronary heart disease (CHD) by 30% compared to non-users[6]. The "Postmenopausal Estrogen/Progestin Interventions Trial" (PEPI) showed a reduction of "bad" LDL cholesterol and an increase of "good" HDL cholesterol by both types of HT[6]. However, randomized control trials not only failed to reproduce the CHD benefits from HRT characterized in observational studies, but actually raised concerns that HRT increased risk of disease[6]. In July 2002, clinical trials findings showed long-term use of HRT poses serious risks (e.g. what serious risks) and may increase the risk of heart attack and stroke[6].

Recent research indicates the risk may vary according to race/ethnicity and other factors (e.g. BMI[4]). One study found that HRT use was associated with greater than 20% increased risk of breast cancer in white, Asian, and Hispanic but not black women[4]. In review of the literature, there appears to be a paucity of research that examines the effects of HRT in minority women, specifically African American women populations. Of the 30 studies examining CHD and HRT, which consisted of 148,437 participants, African American (AA) women were known to comprise only 0.1% (173)[2]. Less than 7% of the dual HRT trial in Women's Health Initiative were AA[2].

The Jackson Heart Study provides a unique opportunity to further explore the relationship between CVD and HRT in African-American women. The JHS cohort is comprised of 3202 African-American women between the ages of 35 and 84. 73.7% of these women indicated they were postmenopausal (2360) and 22.6% of the women who defined themselves as postmenopausal indicated they were using HRT (724).

This study seeks to explore the relationship between Hormone Replacement Therapy and Cardiovascular risk in postmenopausal African American women using Jackson Heart Study data. By filling in the gap in the literature, this study aspires to endow health care providers with information that will enhance the decision making process for treatment.

**Commented [BWC1]:** Women's Health Initiative

**Commented [BWC2]:** How about changing this to read: ...will enhance the decision making process for treatment.

## 5. Research Hypothesis

1. Identify the prevalence of African-American women prescribed Hormone replacement therapy.

2. Identify the prevalence/incidence of African-American women diagnosed with CVD.

3. Hormone replacement therapy is not associated with increased cardiovascular risk in postmenopausal African-American women.

## 6. Inclusions/Exclusions

*Exposure definition:*

- Menopausal status: Women who answered no to having had menstrual periods or bleeding during the past two years at the baseline examination will be defined as postmenopausal.
    - Variable: Reproductive History (Exam 1 RHXACODES)- [*Categorical*]

**Commented [JYR3]:**
**I feel like we should know how long a person has been menopausal. Does the literature suggest a person has greater risk the longer they are menopausal? If so, we need to know the onset of menopause.** Does the dataset have that information? If not, we will need to approximate the "time of onset".

First step: is onset of menopause available in the JHS database?
Second step: search the literature for a relationship between menopause time of onset or duration of menopause and CVD.
If there is a relationship, we need to include the variable here.

Please provide your response to the above questions here.

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- HRT use: Women will be classified as currently taking HRT, if they responded "yes" to either of the following questions: are you currently taking: (a) first identified hormone, (b) second identified hormone or (c) third identified hormone in the reproductive history questionnaire, and provided proof of hormone use based on medications that were brought to clinic visit. Medications were transcribed and coded as HRT by a pharmacist using the Medispan dictionary and classified according to the Therapeutic Classification System.
    - Variables: Reproductive History (Exam 1 RHXACODES)- [*Categorical*]
      Medications (Exam 1,2,3 RHXA/MEDCODES/MSRA)- [*Categorical*]

- Type of HRT use: Women will be classified by type of HRT- estrogen only or combined estrogen-progestin.
    - Variables: Reproductive History (Exam 1 RHXACODES)- [*Categorical*]
      Medications (Exam 1,2,3 RHXA/MEDCODES/MSRA)- [*Categorical*]

- Length of HRT use: Duration of HRT treatment will be calculated using the answer provided on the reproductive history questionnaire. Women will be stratified according to age at initiation of treatment (<60 vs. 60+) and time between onset of menopause and initiation of HRT therapy (early initiation- less than 10 years from onset of menopause vs. late initiation-greater than 10 years from menopause onset).
    - Variable: Reproductive History (Exam 1 RHXACODES)- [*Categorical*]

*Outcome Indications:*

- Cardiovascular risk: CVD events incidence (CVD operational definition- coronary heart disease, nonfatal MI, or acute coronary heart disease death or stroke defined as noncarotid embolic or thrombotic brain infarction, brain hemorrhage, or subarachnoid hemorrhage)
    - Annual telephone follow-ups, hospitalizations surveillance, review of medical records/death certificates [*Categorical*]

**7. Statistical Analysis Plan and Methods**

*Methods:*

7.1 Data source: Jackson Heart Study

7.2 Study population

- Individuals enrolled in Jackson Heart Study
- Inclusion/exclusion criteria: Post-menopausal African-American women enrolled in the Jackson Heart Study (n=2360), excluding those with history of cardiovascular disease diagnosed at baseline

7.3 Study measures

- Exposure variables: Menopausal status, HRT use

**Commented [TE4R3]:** I agree, duration of menopause is important for this study
The literature indicates that initiating HT 10+ years after menopausal onset or at age 60+ has greater risk for CVD . Based on this we may need to stratify data by age at HT initiation and/or how soon after menopause did they initiate HT.

This information is available in the data set. The **Reproductive History Form** asks "At what age did you stop bleeding" if the patient indicates they are postmenopausal. The form also asks if they're menopause was natural, surgical, and if they have hot flashes. The form further goes on to ask about hormone therapy including name, dose, duration of use, etc.

**Commented [JYR5]: I feel like I have asked this question in the past as well.**

**I believe we should know how long a person has been taking HRT. Does the literature suggest a person has greater risk of CVD with extended use of HRT? If so, we need to know when they started using HRT?** Does the dataset have that information? If not, we will need to approximate the "medication start date (if between exams)".

First step: is HRT start date available in the JHS database?
Second step: search the literature for a relationship start date or duration of HRT use and CVD.
If there is a relationship, we need to include the variable here.

Please provide your response to the above questions here.

**Commented [TE6]:** Stratifying groups based on data from the literature which suggests that women who start HT within 10 years of menopause onset and at the age of 60 or younger have better outcomes

**Commented [JYR7]: 8.2:**
-I was thinking that we exclude those with a history of CVD at baseline so that only those who have never been diagnosed with CVD will be included. That way we can measure incidence.

Do you have a suggestion- is it better to do it another way? I will defer to you

USUALLY WHEN WE HAVE A QUESTION AS TO HOW TO MOVE FORWARD, IT IS IMPORTANT TO REVIEW THE LITERATURE. WHAT DOES THE LITERATURE (PEER REVIEW JOURNALS) SAY ABOUT MEASURING INCIDENCE? THIS MEANS: You should complete a literature review to determine how our colleagues in the field are measuring ...

**Commented [TE8R7]:** In all of the literature women with a history of CVD were not included.
Cumulative incidence most often reported –( # of increased cases per 10,000 women per year)
Most of the literature reports in RR and AR.
**Hazard ratios (cox regression) were also calculated in most studies; however, I am not super familiar with these.

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- Outcome variables: Cardiovascular risk (e.g. occurrence of cardiovascular event, diagnosed with cardiovascular disease)
- Covariates/potential confounding factors: many including treatment time, family history of CVD, educational attainment, household income, physical activity, smoking status, alcohol use, BMI, diabetes, hypertension, dyslipidemia, statin use, and diet
- How missing data will be dealt with: The plan is to exclude cases with missing data.
- Comparison groups:
    - Intervention: Post-menopausal AA women who are taking HRT.
        - HT initiation: fewer than 10 years since menopause onset; 10+ years
        - HT initiation: age 60 and younger; over age 60
    - Control: Post-menopausal AA women who are not taking HRT.

7.4 Sequence of planned analyses, including

- Cross-tabulation of relationship of CVD risk to potential confounding factors
- Cross-tabulation of relationship of primary exposures to CVD risk
- Adjusted OR of CVD risk (generalized linear models) according to HRT usage
    - Length of treatment
    - Type of HRT used (Estrogen only vs. Combined Estrogen/Progesterone/Progestin)
    - Dosage of HRT (e.g. mg and times per day)
- Adjusted OR of CVD risk controlling for the following variables.
    - Family history of CVD, physical activity, BMI, and diet

7.5 Analysis software: SPSS

**8. References (maximum 15)**


1. Campbell Jenkins, Brenda W. et al. “Association of the Joint Effect of Menopause and Hormone Replacement Therapy and Cancer in African American Women: The Jackson Heart Study.” *International Journal of Environmental Research and Public Health* 8.6 (2011): 2491–2504. *PMC*. Web. 19 May 2016.
2. Carroll, L. Natalie. “Implications of Menopausal Hormonal Therapy for African-American and Hispanic Women.” *Journal of the National Medical Association* 95.4 (2003): 253–256. Print.
3. Marjoribanks, Jane, Cindy Farquhar, Helen Roberts, and Anne Lethaby. "Long Term Hormone Therapy for Perimenopausal and Postmenopausal Women." *Cochrane Database of Systematic Reviews Reviews* (2012): 1-231. Web. 22 September 2016.
4. Hou, N., S. Hong, W. Wang, O. I. Olopade, J. J. Dignam, and D. Huo. "Hormone Replacement Therapy and Breast Cancer: Heterogeneous Risks by Race, Weight, and Breast Density." *JNCI Journal of the National Cancer Institute* 105.18 (2013): 1365-372. Web. 19 May 2016.
5. Nicholson, Wanda K., et al. "Hormone Replacement Therapy for African American Women." *Menopause* 6.2 (1999): 147-55. Web. 19 May 2016.
6. "Postmenopausal Hormone Therapy: Cardiovascular Risks." *Prescrire International* 12.64 (2003): 65. Web. 19 May 2016.
7. "Research on the menopause in the 1990s. Report of a WHO Scientific Group." *World Health Organization Technical Report Series* (1996):1-79. Web.


**Commented [JYR9]:** CHECK THE LITERATURE (FIND ARTICLES ON HRT AND CVD) TO MAKE SURE THERE ARE NO OTHER VARIABLES WE NEED TO ADD AS COVARIATES?

**Commented [TE10]:** Stratified groups

**Commented [JYR11]: 8.3:**
-Exposure variables: When I say "usage" I want this to be the use of HRT (categorical yes or no). I have changed it to HRT treatment- does this make it more clear? YES, CLEAR. ALWAYS REVIEW THE LITERATURE FOR WORDING AND TERMINOLOGY USED FOR THE TOPIC SO OTHERS IN THE FIELD ARE QUICK TO DETERMINE WHAT YOU ARE REFERRING TO.

-Deleted "subgroups to be considered: many"
-Deleted " level of physical activity. Work status etc" from the comparison groups.

**Commented [TE12R11]:** The literature most often uses the term HRT use

8. Rozenberg , Serge S. "Postmenopausal Hormone Therapy: Risks and Benefits.". *Nature reviews. Endocrinology 9.4* (2013): 216.Web. 22 September 2016.

9. "Treatment of Menopause-Associated Vasomotor Symptoms: Position Statement of the North American Menopause Society.". 11.1 (2004): 11-33. Web. 22 September 2016.
10. U. S. Department of Health and Human Services, National Institutes of Health, National Center for Complementary and Integrative Health. (2016). *Menopausal Symptoms: In Depth* (NIH Publication No. 05-5200). Bethesda, MD: U.S. Government Printing Office.