1.a. Full Title: The association between smoking, hormone replacement therapy, and the risk of cardiovascular disease in postmenopausal women

b. Abbreviated Title (Length 26 characters): Smoking, HRT & risk of CVD

2. Writing Group (list individual with lead responsibility first):

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4. Rationale:
   Among postmenopausal women, it has been suggested that hormone replacement therapy (HRT) may be associated with a decreased risk of myocardial infarction (1) and cerebrovascular disease (2), while correlated with an increased risk of endometrial, breast, and gallbladder cancers (3). A study of hemostatic factors in relation to HRT found lower plasma concentrations of fibrinogen and higher levels of plasminogen and factor VIIc (4). The results were adjusted for age and obesity, but adjusting for cigarette smoking did not change the findings. Lower levels of tissue-type plasminogen activator and plasminogen activator inhibitor – 1 antigen have also been reported with HRT, although these differences were not present in adjusted analyses (5). Relative weight and total serum cholesterol were found in the Framingham Heart Study to be lower in postmenopausal estrogen users than among nonusers (6). These results were adjusted for age but not for smoking status.

   There is an apparent interaction between smoking and HRT whereby the protective effect of HRT against CVD is attenuated by cigarette smoking. This interaction has been reported for myocardial infarction, where the conclusion was that HRT was only protective among non-smokers (1), for cerebrovascular disease, where greater risk reduction was reported for smokers (7), and
specifically for spontaneous subarachnoidal hemorrhage, where risk reduction was greater among women who had smoked (8). Wilson et al. however found that not only was there no beneficial effect on either all-cause mortality or on total cardiovascular morbidity, but that HRT produced an increased risk in smokers for myocardial infarction and angina pectoris (6).

The mechanism of these interactions has been investigated but is not yet explained. Smoking was found to depress high-density lipoprotein cholesterol in both HRT users and nonusers, but also increased total cholesterol, triglycerides and low-density lipoprotein cholesterol in women not treated with HRT (9). In a randomized, placebo controlled study, sequentially combined HRT produced cyclic variations in high-density lipoprotein cholesterol and apolipoprotein A1 for the two years of follow-up (10). Cigarette smoking was associated with an exaggeration of the cyclic effect.

A questionnaire survey of Norwegian general practitioners indicated restrained attitudes towards prescription of HRT (11). Smoking was regarded as one of the contraindications. If the interaction between HRT and smoking in affecting the risk for CVD is such that HRT may benefit smokers more than it does nonsmokers, it is important to demonstrate this phenomenon.

Studies reporting the risk interaction between HRT and smoking have been subject to various limitations. The study reporting risk of myocardial infarction was based on a database of care provided within the British National Health Service (1). Smoking status was unknown for about half the subjects in the study, and these subjects were assumed to be non-smokers. In the analysis of the Copenhagen City Heart Study, current cigarette smoking was recorded from self-reports at two cardiovascular examinations spaced five years apart (7). The effect of HRT was estimated among 4716 postmenopausal women, in whom 238 events of stroke or transient ischemic attack had occurred. In this apparently powerful analysis, the interaction effect between HRT and smoking was demonstrated at .04 significance, not a very strong result for such a large study. Also, much of the HRT research has used self-selected subjects, in terms of HRT usage and smoking status, but has failed to establish participants’ pre-HRT morbidity risk (6). For example, in the Framingham Heart Study, Wilson et al. found that their estrogen users has favorable profiles well in advance of taking estrogen.

The purpose of this proposed analysis will be to estimate the risk of cardiovascular diseases among women reporting HRT in the ARIC sample, and among the residual sample of age matched women not reporting HRT. The risks associated with smoking and the interaction between HRT and smoking will be reported.

5. Main Hypothesis/Study Questions:
The primary hypothesis is that there will be an interaction between smoking and the use of HRT among post-menopausal women in their risk of CHD and CVD.
6. Data (variables, time window, source, inclusions/exclusions):
Data to be used will include baseline and Visit 2 data for female participants.
Variables will include reported use of HRT (estrogen, progestin), menopausal
status, smoking status, smoking amount, use of alcohol, age, gender, BMI,
income, and education. Outcome measures will include follow-up of evidence of
coronary heart disease and cardiovascular disease, and evidence of deaths
attributed to these diseases.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___x__ Yes
_____ No

   b. If Yes, is the author aware that the file ICTDER01 must be used to exclude
persons with a value RES_OTH = “CVD Research” for non-DNA analysis,
and for DNA analysis RES_DNA = “CVD Research” would be used?
(This file ICTDER01 has been distributed to ARIC PIs, and contains the
responses to consent updates related to stored samples use for research.) ___x__
Yes _____ No

8.a. Will the DNA data be used in this manuscript? _____ Yes ___x__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating
Center must be used, or the file ICTDER01 must be used to exclude those with value
RES_DNA = “No use/storage DNA”? _____ Yes ___x__ No, NA