1.a. Full Title: Sex-specific differences in risk factors for cardiovascular disease: A meta-analysis of prospective cohort studies

b. Abbreviated Title (Length 26 characters): Sex differences and CVD risk

2. Writing Group:
Rachel R. Huxley, Sanne Peters, Crystal Lee, Morgana L. Mongraw-Chaffin, Mark Woodward, others.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _RH_ [please confirm with your initials electronically or in writing]

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3. Timeline:
Data analysis – 3 months
First draft of the manuscript – 3 months

4. Rationale:
Previous studies have indicated that there are significant sex differences – to the detriment of women - in the impact of several cardiovascular risk factors on cardiovascular outcomes that remain even after adjusting for differences in other important risk factors. For example, we have previously shown in two previous meta-
analyses that smoking and diabetes pose a greater cardiovascular hazard to women than to men:


To determine whether this sex difference exists for other major risk factors we intend on conducting a series of meta-analyses of prospective cohort studies of the effects of hypertension, dislipidemia, and obesity/overweight between women and men in coronary disease and stroke. We are seeking permission to include the ARIC cohort in these meta-analyses.

5. Main Hypothesis/Study Questions:

We hypothesize that there are sex differences in the magnitude of the association between important cardiovascular risk factors (i.e. hypertension, dyslipidemia and obesity) with cardiovascular disease.

Specifically, we will conduct a series of meta-analyses of prospective cohort studies (and where possible include individual participant data as with ARIC) of the association between each of these risk factors with coronary heart disease and stroke.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

We will perform a systematic review of available literature according to the MOOSE guidelines. Relevant studies published between 1966 and the current date will be identified from CINAHL, EMBASE, PubMed, and the Cochrane Library using a combined text and the following MeSH heading search strategies.

Study selection and data extraction

Studies will be included in these reviews if they have published quantitative estimates (including variability) of the association between cardiovascular risk factors and CHD and/or stroke in both men and women, which had been adjusted at least for age. Studies will be excluded if they do not report a means of estimating the variance around the point estimate or if they were conducted only in single-sex populations.

Data synthesis and analysis
The primary analysis will be a comparison of the sex-specific relative risk of CHD and stroke among individuals with and without particular cardiovascular risk factors. For each study, sex-specific RRs and their 95% confidence intervals (95% CI) will be used to estimate the female to male ratio of relative risks (RRR) and its 95% CI. Pooled estimates across studies will be obtained by means of random-effects models, after log transformation. Studies will be weighted according to an estimate of statistical size, defined as the inverse of the variance of the log RRR.

The percentage of variability across studies attributable to between-study heterogeneity will be estimated using the I² statistic. Random effects meta-regression will be used to assess the contribution to heterogeneity of mean duration of study follow-up, the prevalence of female smoking, and the ratio of female to male prevalence of smoking. Funnel plots of the natural log of the RRR against its standard error will be used to assess publication bias and trim and fill analyses will be used to adjust the RRRs for the presence of publication bias. All analyses will be carried out using Stata Version 11.

**Limitations**
The main limitation is that it will be necessary to tailor our analyses to the way they are reported in the majority of published papers.

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

b. If Yes, is the author aware that the file ICTDER03 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?  ____ Yes  ____ No

(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  _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 ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  ____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X__ Yes _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _______X__ Yes _______ No

11.b. If yes, is the proposal

__X___ A. primarily the result of an ancillary study (list number* 2006.15 and 2008.12)

_____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________  __________

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

6. References
