1. Full Title: Traffic exposure and age at menopause

2. Abbreviated Title (Length 26 characters): Traffic and menopause

2. Writing Group:
Anne Steiner, MD, MPH
Assistant Professor
Department of Obstetrics and Gynecology
University of North Carolina
CB #7570, Old Clinic Building
Chapel Hill, NC 27599
Tele: (919) 966-5283
Fax: (919) 966-5214
asteiner@med.unc.edu

Stephanie London, MD, PhD
NIEHS/NIH
PO Box 12233, Mail Drop A3-05
Research Triangle Park, North Carolina 27709
Tele: (919) 541-5772
Fax: (919) 541-2511
London2@niehs.nih.gov

Donna Baird, PhD
NIEHS/NIH
PO Box 12233, Mail Drop A3-05
Research Triangle Park, North Carolina 27709
Tele: (919) 541-2786
Fax: (919) 541-2511
baird@niehs.nih.gov

Kathryn Rose, PhD
University of North Carolina, School of Public Health
Department of Epidemiology

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AZS____ [please confirm with your initials electronically or in writing]
3. Timeline:
October 2009: manuscript proposal submission
November 2009: creation of variable for age at menopause and cause of menopause
December 2009: Univariate analyses
Jan 2010: Bivariate analyses
Feb 2010: Modeling
March 2010: Presentation of preliminary analyses and results (to writing group)
April 2010: Rerun analysis
May 2010: Sensitivity analyses
June 2010: Manuscript preparation
July 2010: Internal review (NIEHS)
August 2010: ARIC review
September 2010: Submission

4. Rationale:
Menopause is a transition not only from the reproductive years to reproductive senescence but also a health transition. Following menopause, hormonal and metabolic changes occur, leading to an increase in cardiovascular disease risk (1) and risk of fractures (2). Age at menopause appears to be directly correlated with preceding events such as age at onset of the perimenopausal transition (3). Therefore, factors that influence age at menopause may not only affect timing of cessation of menses, but also reproductive and cardiovascular health.

Reproductive aging, the natural progression through the stages of fertility, subfertility, the menopause transition and finally menopause, progresses with the decline in the number of oocytes (4). Thus, age at menopause is thought to reflect the size of the initial cohort of follicles and the rate of loss of oocytes (5). Presumably factors that may impact on the
rate of loss or the initial size of the cohort, may change the age at menopause. Previous studies have shown that environmental exposures in adulthood such as smoking (6) and exposure to toxicants such as chemotherapeutic agents (7), and alcohol (8) appear to affect age at menopause.

It is not known if air pollutants increase the rate of oocyte loss and advance age at menopause. Studies of the effect of second hand smoke on age at menopause have been mixed (9, 10). Female mice exposed to ambient particulate matter had 36% fewer antral follicles compared to mice that were unexposed (11). Decreased fertility was also observed among exposed mice (11, 12).

Road traffic, producing fine particulate matter, carbon monoxide, and oxides of nitrogen is a common contributor to air pollution in industrialized countries. While road traffic has been found to be a reproductive toxicant in pregnancy, resulting in lower birth weights (13), preterm birth (14), and miscarriage, its impact on timing of reproductive senescence is not known.

5. Main Hypothesis/Study Questions:
The objective of this paper is to examine the relation between traffic exposure and age at menopause. We hypothesize that greater exposure to road traffic will be associated with an earlier age at menopause.

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).
ARIC data including traffic and background air pollution data will be used for this secondary analysis. Our cohort will include women between the ages of 45 and 55 at the time of the first study visit. We will exclude women who never have menses, do not provide information on menopausal status, or underwent natural menopause prior to age 30, as these cases are likely due to sex chromosome aneuploidy (15). In addition participants for whom traffic density can not be estimated or who did not consent to non-CVD research will be excluded from the analysis. The primary outcome will be self-reported age at natural menopause. Traffic density will be the main exposure. Covariates, thought to be potential confounders, will include research center, ethnicity, age at first visit, smoking status between 40 and 49 years of age (or current smoking status if under 40), body mass index, alcohol consumption, occupation, educational level, family income, census tract socioeconomic factors, and background air pollution levels.

The primary outcome will be age at natural menopause. Data from the reproductive questionnaire at the first, third, and fourth visit will be used to ascertain age at natural menopause. Women will be considered menopausal if they answer yes to the question “Have you reached menopause?” Age at menopause will be defined by the answer to the question “At what age did menopause begin?” However if a woman had a hysterectomy, bilateral oophorectomy, or radiation therapy resulting in amenorrhea, she will be censored at her age of surgically or medically induced amenorrhea. Those women premenopausal at the first visit will have age at menopause determined by the same questions at visits 3 or 4.
Cox proportional hazard models will be created to estimate hazard ratios for the risk of menopause over time by tertile of traffic exposure. Kaplan Meier curves and log log plots will be used initially to assess whether there is a violation of proportional hazards assumption (constancy of the effect of covariate over time). Survival time will be the number of years from age 30 to age at menopause or censoring. Subjects will be censored at the time of surgical menopause or radiation induced menopause or if they have not entered menopause by visit four. Covariates will be included in the model as potential effect modifiers (first) and/or confounders.

This study is limited by the cross-sectional nature of the data. Traffic exposure was determined at the date of the first visit. Some women were already menopausal at this time point. To address this issue, we restricted the analysis to women who were between the ages of 45 and 55 at the first visit and living at their residence for at least 5 years. In addition we will determine if age is an effect modifier (implying that the effect of exposure is dependent on timing (or age) of exposure).

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 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?

     _x___ 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?  ____ 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 ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?

     ____ 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.cseec.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* 2003.03_)

_____  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.cscn.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.

Literature References

5. Gougeon A, Chainy GB. Morphometric studies of small follicles in ovaries of women at different ages. JReprodFertil 1987;81:433-42.