ARIC Manuscript Proposal # 1385

PC Reviewed: 07/08/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Prospective analysis of traffic exposure in relation to deep vein thrombosis: the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Traffic and DVT in ARIC

2. Writing Group:

Writing group members: Haidong Kan, Aaron Folsom, Mary Cushman, Kathryn Rose, Wayne Rosamond, Duanping Liao, Stephanie J. London

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

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3. Timeline: A first manuscript should be available for circulation to the ARIC investigators before Dec. 30, 2008.

4. Rationale:

Outdoor air pollution has been associated with increased risk of coronary heart disease and stroke [1]. A recent case-control study in Italy shows that long-term exposure to particulate air pollution is associated with increased risk of deep vein thrombosis (DVT) [2]. To our knowledge, no prospective evidence exists about outdoor air pollution and incident DVT.

Road traffic is a major contributor to outdoor air pollution in industrialized countries, contributing fine particulate matter, carbon monoxide, oxides of nitrogen, and other pollutants. Assessment of traffic exposure can enhance studies of health effects of outdoor air pollution because local sources are important, and because few people live close to the monitoring stations which are often purposefully located away from local sources like busy roads. For example, in the ARIC participants, it was exposure to traffic-related air pollution, but not background air pollution, that was associated with reduced lung function [3] and increase risk of coronary heart disease [4]. We are unaware of any population-based study on the relation between traffic-related air pollution and DVT.

The ARIC study (visits 1-4 and the annual follow-up) provides a good opportunity to study the relation between DVT and long-term traffic exposure.

5. Main Hypothesis/Study Questions:

Subjects with higher exposure to traffic-related air pollution have higher risk of incident DVT.

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).

In the proposed study, we will prospectively examine the association of residential exposure to traffic with deep vein thrombosis (DVT) or pulmonary embolus (PE) among the ARIC participants. The endpoints of interest are incident DVT (including PE); therefore, participants will be excluded if they had a history of DVT at the baseline or were taking warafin. We will also exclude persons who meet the following criteria: ethnicity other than African-American or white, African-Americans from Minnesota and Maryland field centers, missing geocoding information.

DVT and PE have been identified since baseline in the ARIC cohort by the LITE study and validated by physician review. We are just finishing an update of incident cases through 2005 and expect to have approximately 500 events.

Small-scale spatial variations of traffic exposure will be quantified by two measurements: geographical information system (GIS)-mapped traffic density assignments at residences, and the distance of residences to nearest roadways of various types. Generally, traffic density values give a relative indication of which residence locations are likely to be most exposed to traffic activity. These two measurements have been successfully applied in assessing the association of traffic exposure and lung function in the ARIC participants [3, 4]. Data on the background ambient air pollution will be acquired from the Environmental Protection Agency (EPA) air quality data retrieval system. The traffic and background air pollution data cover the period between visit 1 and visit 4. Consistent with previous air pollution prospective analyses in which

exposure was assessed at the beginning of follow-up [5-7], we will use traffic exposure at the baseline residences (visit 1, 1987-1989) for this analysis.

Cox proportional hazards regression analyses will be used to assess the relations of traffic exposure with the risk of incident DVT. Our basic models will adjust for age, sex, center and ethnicity. In the adjusted models, we will include factors that we hypothesized *a priori* could be potential confounders, including age, sex, study center, ethnicity, BMI, income, education, census tract level median household income, physical activity, hormone replacement therapy (HRT) (treated as a time dependent covariate), diabetes status, and background air pollution level (PM_{10}, NO_2 and O_3). We will conduct stratified analyses by sex, age, ethnicity and HRT, to examine potential modifiers of traffic exposure. Our previous analysis suggested potential geocoding error in Washington County which may reflect a renaming of streets that occurred there [3, 4]; therefore, we will also conduct sensitivity analysis excluding Washington County from our analysis. In addition, we will examine the association of traffic exposure with intermediate phenotypes such as Factor VIII and activated partial thromboplastin time (aPTT).

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 ICTDER02 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 ICTDER02 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 ICTDER02 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.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)?

 # 450, 760, 782, 860, 861, 907

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* AS#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.cscc.unc.edu/aric/forms/

Note that Haidong Kan was involved in this manuscript proposal while a postdoctoral fellow at NIEHS with Dr. London and maintains a special investigator position with her at NIEHS.

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.

Reference:

1. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC, Jr., Tager I: **Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association.** *Circulation* 2004, **109:**2655-2671.
2. Baccarelli A, Martinelli I, Zanobetti A, Grillo P, Hou LF, Bertazzi PA, Mannucci PM, Schwartz J: **Exposure to particulate air pollution and risk of deep vein thrombosis.** *Arch Intern Med* 2008, **168:**920-927.
3. Kan H, Heiss G, Rose KM, Whitsel E, Lurmann F, London SJ: **Traffic exposure and lung function in adults: the Atherosclerosis Risk in Communities study.** *Thorax* 2007, **62:**873-879.
4. Kan H, Heiss G, Rose KM, Whitsel E, Lurmann F, London SJ: **Prospective analysis of traffic exposure as a risk factor for incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study.** *Environ Health Perspect* 2008, **in revision**.
5. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA: **Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study.** *Lancet* 2002, **360:**1203-1209.
6. Pope CA, 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD: **Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution.** *Jama* 2002, **287:**1132-1141.
7. Pope CA, 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ: **Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease.** *Circulation* 2004, **109:**71-77.