1.a. Full Title: Omega-3, traffic exposure and cardiorespiratory outcomes in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
   Writing group members: Haidong Kan, Ronald Klein, Kathryn M. Rose, Eric Whitsel, Fred Lurmann, Stephanie 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]

First author: Haidong Kan
Address: Epidemiology Branch, National Institute of Environmental Health Sciences, P.O Box 12233, Mail Drop A3-05, Research Triangle Park, NC 27709
   Phone: 919-316-4506      Fax: 919-541-2511
   E-mail: kanh@niehs.nih.gov

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Stephanie J. London
Address: Epidemiology Branch, National Institute of Environmental Health Sciences, P.O Box 12233, Mail Drop A3-05, Research Triangle Park, NC 27709
   Phone: 919-541-5772      Fax: 919-541-2511
   E-mail: london2@niehs.nih.gov

3. Timeline: A first manuscript should be available for circulation to the ARIC investigators before Dec. 1, 2006,

4. Rationale:
   Traffic is a major contributor to air pollution in urban areas. An expanding body of epidemiologic research suggests that traffic-related exposures may be associated with cardiorespiratory outcomes. This analysis builds on the traffic density and distance to road information for subjects in the ARIC study at each study visit collected by ancillary study AS 2003.03. Its purpose was to examine traffic related air pollution in relation to cardiac and respiratory outcomes in ARIC. An extension to cardiac outcomes was approved as an amendment to this ancillary study.
To date, our preliminary data analysis has found that traffic-related air pollution adversely affected lung function (FEV\(_1\) and FVC) in female ARIC participants. Relative to the lowest quartile of traffic density, the adjusted differences across increasing quartiles were 1.8, -17.8 and -23.4 ml for FEV\(_1\) (p trend =0.04), and -0.2, -25.2 and -35.9 ml for FVC (p trend=0.01). Retinal abnormalities (arteriovenous nicking and arteriolar narrowing) were also significantly associated with higher traffic exposure in the ARIC cohort. Relative to the lowest quartile of traffic density, the adjusted odds ratios (ORs) across increasing quartiles were 1.06, 1.08 and 1.24 for arteriovenous nicking (p trend <0.01), and 1.01, 1.00 and 1.17 for arteriolar narrowing (p trend =0.01). We also examined several other cardiorespiratory outcomes (respiratory symptoms, heart rate variability, myocardial infarction, plaque, carotid thickness, blood pressure, fibrinogen and lipids) but found no appreciable association with traffic-related air pollution.

Intake of omega-3 polyunsaturated fatty acids has been related with decreased risk of cardiovascular diseases\(^4\)\(^-\)\(^5\) and subclinical pathology such as retinal microvascular disorders\(^6\). Omega-3 fatty acids can block many inflammation pathways through which traffic-related pollutants may adversely affect cardiorespiratory systems\(^7\)\(^-\)\(^8\) and high levels of omega-3 fatty acid intake could plausibly modify the traffic-related cardiorespiratory hazards. A recent study has found that supplementation of omega-3 prevented decline of heart rate variability (HRV) related to exposure to ambient fine particulate matter (PM\(_{2.5}\)), a component of traffic-related pollution\(^9\). Dietary assessment at the 1\(^{st}\) and 3\(^{rd}\) visit of the ARIC study provides us an opportunity to examine the interaction of omega-3 and traffic exposure in inducing the cardiorespiratory outcomes. Previously, intake of omega-3 fatty acid intake, as assessed by questionnaire, was found to be inversely associated with chronic obstructive pulmonary disease in the ARIC study\(^10\). High levels of omega-3 intake from fish were found to modify the blood levels of several coagulation factors in the ARIC participants\(^11\). To our knowledge, there have been no large-scale observational data investigating the protective effect of omega-3 on health hazards due to traffic exposure.

5. Main Hypothesis/Study Questions:
Intake of omega-3 may modify the adverse effects of exposure to traffic-related air pollution on a variety of cardiorespiratory endpoints. Given the positive main effect observed in our previous analysis, we will focus on two categories of outcomes: lung function measurements (FEV\(_1\) and FVC) at visit 1 and retinal abnormalities at visit 3. Because it is possible that effect modification by omega-3 intake could exist for outcomes for which there is no main effect of traffic, we will also examine respiratory symptoms and cardiovascular outcomes (including heart rate variability, incident myocardial infarction, plaque, carotid thickness, blood pressure, fibrinogen, and lipids) for completeness.

As stated before, we will quantify small-scale spatial variations of traffic exposure by GIS-mapped traffic density assignments at residences which generally give a relative indication of which residence locations are likely to be most exposed to traffic activity.

The interaction of omega-3 intake and traffic exposure in relation with those cardiorespiratory outcomes will be examined in multiple-variable regression models that consider sets of covariates relevant to the dependent variable, from among gender, research center, race group, age, smoking (status including never, former and current smokers, and pack years), ETS exposure, BMI, occupations, educational level, height, square of height, and background air pollution level et al.

6. Data (variables, time window, source, inclusions/exclusions):
Dietary data were collected at visits 1 and 3.

Visits 1: pulmonary function measures (FEV\(_1\) and FVC), respiratory symptoms (cough, phlegm, wheeze, breathlessness), cardiovascular outcomes (heart rate variability, plaque, carotid thickness, blood pressure, fibrinogen, lipids etc), dietary assessment (omega-3, total energy
intake), research center, race group, age, smoking (status including never, former and current smokers, and pack years), exposure to environmental tobacco smoke, BMI, occupations, educational level, census tract SES variables, height, and background air pollution level.

Visit 3: retinal abnormalities (arteriovenous nicking, generalized arteriolar narrowing, venular dilation, and retinopathy), cardiovascular outcomes (heart rate variability, plaque, carotid thickness, blood pressure, fibrinogen, lipids etc), dietary assessment (omega-3, total energy intake), anthropometric measures, blood pressure at the time of the retinal exam, demographic characteristic, smoking, exposure to environmental tobacco smoke, diabetes, other cardiovascular risk factors, traffic exposure, census tract SES variables, and background air pollution concentration at visit 3.

Visit 4: heart rate variability parameters, visit 3 dietary assessment (omega-3, total energy intake), anthropometric measures, blood pressure at the time of the retinal exam, demographic characteristic, smoking, exposure to environmental tobacco smoke, diabetes, other cardiovascular risk factors, traffic exposure, census tract SES variables, and background air pollution concentration at visit 4.

7.a. Will the data be used for non-CVD analysis in this manuscript?  
   ___ Yes  ___ 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  ___ 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
   ___ 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)*

Note – original ancillary study proposal expansion to include cardiovascular endpoints was approved by the Steering Committee at the meeting on April 14, 2004.

*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.

Reference: