1.a. Full Title: Environmental and Occupational Risk Factors for ALS: A Case Cohort Study

b. Abbreviated Title (Length 26 characters): Environmental Risk Factors for ALS

2. Writing Group:
   Writing group members:

Evelyn O. Talbott, DrPH, Yue Fang Chang, PhD, Vincent Arena, PhD, Angela M. Malek, PhD, Judith Rager, MPH, Ravi Sharma, PhD, James Stewart, GISP, Eric A. Whitsel, MD, MPH, and others who may be interested

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

First author: Evelyn O. Talbott, DrPH
Address: A-526 Crabtree Hall, University of Pittsburgh, Pittsburgh, PA 15261

Phone: (412) 624-3074 Fax: 412-624-7397
E-mail: eot1@pitt.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Eric A. Whitsel, MD, MPH
Associate Professor of Epidemiology and Cardiovascular Program Lead
Gillings School of Global Public Health
Adjunct Associate Professor of Medicine
School of Medicine
University of North Carolina
123 West Franklin Street, Suite 410, Room 4226
Chapel Hill, NC 27516-8050
(T) 919-966-3168 or 1967
(F) 919-966-9800
eric_whitsel@unc.edu

3. Timeline: 08/01/19 – 07/31/20
4. Rationale:

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease (MND) in adults, characterized by degeneration of motor neurons in the brain and spinal cord. Currently less than 10-15% of ALS cases have been linked to a genetic mutation leaving 85% of unknown origin. This highlights the importance of an increased focus on environmental risk factors for ALS. The relationship of air pollution and the risk of other neurodegenerative diseases such as Parkinson’s disease and dementia has been reported in the literature. Thus far there have been very few investigations involving ambient air pollution and ALS (Seelen 2017 and Malek et al. 2015).

5. Main Hypothesis/Study Questions:

Specific Aim 1: Evaluate exposure to air toxics based on all residences for each set of ALS cases and non ALS controls (subcohort) at the census tract level as risk factors for ALS within the Atherosclerosis Risk in Communities Study of 15,792 individuals aged 45-64 recruited from 4 field centers and followed since 1987, as well as the Women's Health Initiative National study of 161,809 women aged 50-79 followed since 1993. We will make use of the National-Scale Air Toxics Assessment (NATA) database, compiled by U.S. Environmental Protection Agency (EPA) at the census tract level, for 35 suspected neurotoxicants (e.g., metals, pesticides, solvents) of the ~187 total hazardous air pollutants (HAPs) available for the following years: 1996, 1999, 2002, 2005, 2011 and 2014. In addition to the aforementioned matching criteria, we will also consider potential confounders such as smoking and occupation.

https://www.epa.gov/national-air-toxics-assessment

Specific Aim 2: Evaluate the association of long term environmental exposure to levels of the criteria air pollutant, lead, in ALS cases and non ALS controls (subcohort) within the cohorts from the Atherosclerosis Risk in Communities Study and the Women's Health Initiative national study. Lead exposure and ALS risk has been widely studied in the occupational literature, but never modeled using daily ambient air lead levels. We will estimate a cumulative time weighted exposure using U.S. Environmental Protection Agency (EPA) air quality monitor data accumulated over up to 25 years. The proposed study will link monitored lead levels to ALS cases and the subcohort’s location (residence) over a twenty-five year or longer period (1987-2018) depending on the cohort. In addition to the monitors, we can also make use of the USEPA TRI (Toxic Release Inventory) which provides a yearly amount of lead emissions for each facility in the US (N=2229) since 1987 as well as its location. (https://www.epa.gov/outdoor-air-quality-data/download-daily-data) and (https://www.epa.gov/toxics-release-inventory-tri-program)

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).
A case-cohort study will be conducted to examine the potential association between environmental risk factors and ALS using individuals who are enrolled in two cohort studies. The Atherosclerosis Risk in Communities (ARIC) Study is a cohort study initiated in 1987 to investigate causes of atherosclerosis and associated outcomes as well as variations in demographic characteristics and cardiovascular risk factors. The ARIC study recruited a total of 15,792 men and women aged 45-64 from 4 field centers. After 25 years of follow up, there have been 6,283 deaths within the ARIC cohort. Assuming an average current age of the cohort of approximately 80 years, there may be an estimated 30-40 deaths from ALS. The Women's Health Initiative (WHI) is a cohort study initiated in 1994 that followed 161,809 women for cardiovascular and other endpoints. Follow up is complete through March 2018 and thus far has yielded 256 adjudicated deaths from ALS. We will evaluate environmental exposure to ambient levels of air pollution and air toxics for all residences within the WHI cohort as risk factors for ALS with adjustment for potential confounders (smoking, education, occupation, etc.).

This investigation will study the association between exposure to air pollution (lead) and other air toxics and ALS. We will make use of the air toxics database (National-Scale Air Toxics Assessment [NATA], compiled by USEPA at the census tract level) for 35 of 187 neurotoxicants available for the following years: 1996, 1999, 2002, 2005, 2011, and 2014 (USEPA NATA). Ambient lead levels have been modeled nationally by the USEPA at the census tract level and will be included for the period 1987 until the present. The proposed study is novel because it will be one of the first to examine ambient air toxics and the criteria air pollutant, lead, in relation to the risk of ALS. Further, findings from this study will contribute to the knowledge of the relationships of pollutants and lead exposure in ALS and provide reproducible estimates.

Moreover, although ambient lead levels been monitored and reported throughout the US for many decades; lead levels have never been linked by residence over time. Lead has been studied extensively with inconsistent results; these were largely occupational investigations with small samples sizes. These were based largely on self-reported exposures and were all retrospective in nature. This would be one of the first investigations to make use of two large cohorts of men and women followed for over 25 years. Unique to both cohorts will be the availability of environmental measures over the majority of the time period, as well as baseline and yearly follow up and over time of personal risk factors, occupational as well as medical history.

**Exclusions**
In order to be eligible, cases will consist of individuals with an underlying cause of death of ALS (ICD-9: 335.2; ICD-10: G12.2). Cases and non ALS controls (subcohort) will be excluded with baseline history of any of the following neurodegenerative conditions: Parkinson’s disease, Alzheimer’s disease, poliomyelitis/post-polio syndrome, Parkinsonism, or Huntington’s disease, conditional on their availability. The subcohort will also be required to be free from ALS, conditional on availability.

**Exposures**
Daily mean concentrations of ambient lead levels will be linked to the ALS case and the subcohort locations from the Atherosclerosis Risk in Communities study and the Women's Health Initiative study between 1987-2018 and 1993-2018, respectively. A cumulative time weighted exposure will be estimated using USEPA air quality monitor data accumulated over up
to 25 years. In addition to the monitors, we can also make use of the USEPA TRI (Toxic Release Inventory) which provides a yearly amount of lead emissions for each facility in the US (N=2229) since 1987 and its location. Ambient concentrations of air toxics (35 neurotoxicants of 187) available from the USEPA NATA data will be linked by census tract to the ALS case and subcohort locations from the Atherosclerosis Risk in Communities study and the Women's Health Initiative study for the following years: 1996, 1999, 2002, 2005, 2011, and 2014.

**Statistical Analysis**

Descriptive statistics including chi-square tests and t-tests will be used to compare demographic characteristics and other characteristics of cases and the subcohort. Residential and environmental exposures of the study population as well as and pollution / meteorological variables will also be described. Crude and weighted Cox proportional hazards regression models will be used to estimate hazards ratios (95% confidence intervals). Analyses of the 35 neurotoxicants will include Bonferroni correction for multiple comparisons. Multivariate models with adjustment for additional confounders such as smoking and education, potential effect modifiers like physical activity, and when appropriate, interaction between covariates will be fit. The results for the two cohort studies will be shown both individually and as pooled multivariate hazard ratios. Analyses will be conducted using SAS version 9.4 (SAS Institute, Cary, NC) and IBM SPSS version 25. Effects will be represented as increases in the hazards of ALS death per unit or interquartile range (IQR) increase in pollution concentrations.

Anticipated methodologic challenges or limitations include: As ALS was not a condition that was routinely monitored through baseline exams or medical history; death certificates will be used to identify those individuals who have an underlying cause of death on the death certificate of ALS. The cases will be identified through death certificates reported through ARIC followup. As the first USEPA NATA assessment took place in 1996, exposure to neurotoxicants will be limited to the same time period. We realize the use of two separate cohorts will require pooling of the data, similar to past studies (Sugawara. J Cancer. 2018; 9(23):4422-4429; Wakai. Cancer Sci. 2015;106(8):1057-1065; Hunter. NEJM. 1996;334(6):356-361).

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 ICTDER 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.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

___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)?

To our knowledge, there are no other manuscripts focusing on ALS; however, Dr. Whitsel is an author on a manuscript related to traffic density and lung function within the ARIC cohort (Thorax, 2007) and is a collaborator on this manuscript proposal.

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* __________)

___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.