ARIC Manuscript Proposal #3823

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1.a. Full Title: Distance to Road, Cognitive Decline, and Incident Dementia

b. Abbreviated Title (Length 26 characters): Cognition and Distance to Road

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

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3. Timeline: 1 year after manuscript proposal approval

4. Rationale:

Alzheimer's disease and related dementias (ADRD) are a class of neurodegenerative diseases that occur most frequently in late life and are marked by decline in one or several domains of cognitive functioning [1, 2]. According to the World Health Organization, deaths from dementia doubled between 2000 to 2016, making dementia the fifth leading cause of death [3]. Currently, ADRD is responsible for significant global morbidity and mortality, and the burden of this class of disorders is expected to increase as early life mortality rates decreases

[3, 4]. This burden is exacerbated by the fact that no curative or disease-modifying treatment or approved prevention strategy exists to target ADRD [5]. Given this, finding ways to prevent or delay ADRD may serve as the best method of reducing economic and social burdens associated with ADRD [6-8].

Air pollution is responsible for a significant proportion of global mortality and morbidity. In 2016, it was estimated that air pollution was responsible for over 6.7 million deaths with the actual number of attributable deaths probably totaling millions more [5, 9]. Exposure to long term air pollution continues to be a serious public health concern as chronic air pollution exposure is a well-accepted risk factor for many cardiovascular and pulmonary diseases as well as a potential risk factor for neurodegenerative diseases [10-15]. Multiple reviews of the epidemiologic literature have focused on the relation of air pollution exposure and for late life cognitive health [6, 14, 16-21]. However, while the evidence continues to amass, the evidence linking pollutants other than particulate matter of 2.5 microns in aerodynamic diameter ($PM_{2.5}$) to cognitive health remains sparse.

Traffic-related air pollution (TRAP) is of particular interest to brain health [22]. Traffic sources produce air pollution in the form of oxides of nitrogen (NO_x/NO_2), particulate matter [23] – including ultrafine PM (particles ≤0.1 μm in diameter), carbon monoxide (CO), hydrocarbons, and other air toxics [24-26]. TRAP is of great concern because it usually comprises a significant proportion of ambient air pollution especially in population-dense urban centers [27, 28]. Currently, it is estimated that over 20% of the U.S. population lives in close residential proximity to a major roadway with rates disproportionately higher among people of color and low socioeconomic status (SES) [29-31]. These trends are especially harrowing considering the extensively reported association between TRAP exposure and a myriad of diseases including incident asthma, lung disease, cardiovascular disease, and adverse birth outcomes [32-36].

Animal and autopsy studies suggest that TRAP may be particularly determinantal to cognitive health [37]. Data from animal studies have shown that air pollution, including TRAP, may contribute to increases in oxidative stress and neuroinflammation both precursors to the neurodegenerative pathogenesis present in ADRD [22, 38-41]. Furthermore, TRAP components – especially ultrafine particulate matter - may enter the brain through the olfactory bulb, crossing the blood-brain barrier and acting as a neurotoxin [42]. Chronic exposure to TRAP has been shown to impact both amyloid-beta processing and antioxidant defense, and exposure to urban air pollution – which is high in TRAP - may impact brain inflammation or the fidelity of the blood brain barrier [43-45]. While the exact mechanisms remain unclear, chemical compounds most present in TRAP seem to be highly correlated with increased risk of ADRD [46].

Despite heterogeneity in outcome and exposure assessment, Increased exposures to TRAP appear negatively associated with cognitive test performance in a handful of epidemiologic studies. For example, Tonne et al. observed a negative correlation between exposure to traffic related particulate matter and scores on reasoning tests of cognition, with the strength of the association increasing as exposures were measured in the more distant past [47]. Wellenius et al. found that nearer residential proximity to major roadways was significantly associated with poorer performance on cognitive tests of immediate and delayed recall [48]. Similarly, a longitudinal study conducted on the Chinese Longitudinal Health Longevity Survey (CLHLS) found that nearer residential proximity to roadway was associated with elevated risk of

cognitive decline [49]. They reported significantly higher odds of cognitive impairment for participants who resided less than 50m, 50-100 m, 101-200 m, and 201-300 m from a major roadway compared to those whose residential proximity to roadway exceeded 300m [49].

To the contrary, the evidence linking TRAP to incident cognitive impairment or dementia is mixed. A Canadian study conducted by Chen et al. found that persons who lived closer to major roadways had increased risk of dementia [50]. However, Smargiassi et al. did not find an association between dementia pathogenesis and residential distance to major roadways in a cohort of 1,807,133 older adults in Quebec, Canada [51]. Finally, Carey et al., found reported higher risk of dementia for those within 50m of a major roadway; however, no dose-response relationship existed between distance and adjusted hazard ratio[52].

The Atherosclerosis Risk in Communities (ARIC) study is a large longitudinal cohort with decades of high-quality cognitive, medical, social, and demographic follow-up. Additionally, the ARIC cohort is unique relative to other cohorts that ascertain dementia in that it is possible to ascertain mid-life exposures, which may be most etiologically relevant to dementia pathogenesis. Therefore, we propose to use the ARIC cohort to examine the relationship between midlife exposure to TRAP, assessed as distance to a major roadway, and 25-year cognitive decline and incident dementia.

5. Main Hypothesis/Study Questions:

This study will explore whether residential proximity to major roadways in midlife is associated with accelerated cognitive decline or incident dementia. We hypothesize that residential proximity to major roadway in midlife is positively associated with accelerated cognitive decline and elevated incidence of dementia.

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).

Exclusions:

We will restrict our sample to those who participated at Visit 2 and provided complete cognitive data. Participants will be excluded if we are unable to generate residential distance to road data (e.g., due to a lack of geocoded address data). Additionally, participants who are non-white and non-Black in NC, as well as those who were non-white in MD or MN or non-Black in MS will be excluded due to small numbers in these groups. Lastly, those participants without necessary covariate data will be excluded as well; if this exclusion results in significant loss of sample size, we will consider using multiple imputation for missing covariates.

Exposure Assessment:

To estimate exposure, distance to road at the time of Visit 2 will be used as a proxy for TRAP concentrations in midlife. Estimates of residential proximity to nearest primary roadway were generated using major roads data from ESRI StreetMap and Data & Maps collections (www.esri.com) to calculate Euclidean distance and angle from participants' geocoded addresses to the nearest A1-A3 roadway within 10 miles. A1, A2, and A3 roadways were defined using the Census Feature Classification Code (CFCC) codes for road type designation

[53, 54]. We obtained distances to each road type separately, and residential road proximity was defined as the minimum distance to the nearest A1, A2, or A3 roadway. Distances to nearest A1-A3 roadways within 10 miles were categorized based on the following cut points of 0-50m, 50-200m, 200-300m, 300-400m and greater than 400m. Distances were categorized to account possible non-linear associations between exposure and outcome. Summed road lengths within Euclidian buffers of varying sizes will also be used to estimate road density for each geocoded location.

Dependent Variables:

For our primary analysis we will quantify the associations between distance to major roadway at Visit 2 and cognitive change. Cognitive status was assessed at visit 2 and visits 4-7. ARIC participants were administered the Delayed Word Recall Test (DWR), the Digit-Symbol Substitution Test (DSST), and the Word Fluency Test (WFT) at visits 2 and 4. At visits 5-7, the logical memory and incidental learning, trail making parts A and B, and the Boston naming test were also administered. We will evaluate whether distance to road is associated with an overall summary measure of cognitive change as well as domain-specific cognitive change [55]. In secondary analyses, we will also consider associations with change in the individual cognitive tests administered consistently across all study visits (DWRT, DSST, WFT) and a global summary z-score calculated from averaging the individual z-scores from these three tests. We may also consider alternate measures of TRAP such as summed road length as an estimate for road density in sensitivity analyses.

We will assess whether distance to road at Visit 2 is associated with incident dementia. All participants in the ARIC study were assessed for dementia in visits 5-7 with a variety of cognitive tests, neurologic examination, and informant interview. The final diagnosis was based on DSM-IV criteria [2]. For our primary analyses of incident dementia, we will utilize the Level 3 diagnosis of dementia. Level 3 diagnoses are based on all information available to the ARIC cohort, including algorithmic and reviewer diagnosis, telephone interviews, informant interviews, and hospital discharge records and ICD codes from death certificates.

In sensitivity analyses, Level 1 dementia ascertainment will be used to examine whether use of Level 3 ascertainment could lead to differential misclassification and bias of results. Level 1 diagnosis is made solely by algorithmic and reviewer diagnosis based on cognitive, behavioral, and functional assessments given at visits 5 and 6. If algorithmic and review diagnosis simultaneously, reviewer diagnosis is given priority.

Covariates:

Covariates of interest include: demographics (age, sex, race), personal SES (education, pre-retirement health insurance status), self-rated health, alcohol use, smoking status, leisure time physical activity)[56], and area level SES (% of residential census tract below the poverty line,

and a summary measure of neighborhood wealth/income, education level, and occupation based)[57].

Effect Modifiers:

We will examine whether our effects differ by site. If they do, all analyses will be conducted by site and summary estimates will be combined using meta-analyses as in our prior analysis of PM2.5 and visit 5 MRI outcomes (PMID: 29467108, ARIC MP: 2412). If no heterogeneity exists across sites, then analysis will feature an all-site combined analysis.

We will conduct exploratory analyses to determine whether there is effect measure modification by apolipoprotein E (APOE) e4 allele (genetic risk) status, gender, education, age at baseline, and area-level SES.

Statistical Analyses:

To begin, distance to nearest road at Visit 2 was assigned as the shortest distance between the Visit 2 geocoded address and nearest A1, A2, or A3 roadway within 10 miles. We will categorize proximity based on the following cut points: 0-50m, 50-200m, 200-300m, 300-400m and greater than 400m. As traffic emissions are of highest concentration at the point of release and steadily decrease as distance increases and steadily taper off as distance approaches 300m, it is essential to capture the variable gradients within that range [58].

For our primary analyses of incident cognitive impairment, Cox proportional models will be utilized to evaluate the association between residential proximity to major roadway and the incidence of dementia. We will utilize time in study as the timescale of survival with the Cox proportional models. For our primary analyses of cognitive change, we will use linear mixed effects models. All models will be adjusted for the covariates listed above.

We will conduct several sensitivity analyses to address the potential impact of confounding, missing data, and selection bias. We will consider analyses restricting to white participants or those who did not move during follow-up, censoring persons at time of stroke, and adjusting for vascular risk factors and cardiovascular disease. If distance to road is associated with attrition, we will use inverse probability weighting for attrition (analyses of incident dementia) and multiple imputation by chained equations (MICE) (analyses of cognitive decline) to address potential selection bias due to informative attrition. Lastly, additional analyses will be conducted utilizing interaction terms to examine effect measure modification by meteorological conditions, as the relationship between emission concentration and distance might be impacted by additional factors such as wind, altitude, and meteorology [59, 60].

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? _X___ 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _x___ 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)?

3348; "Ambient air pollution and late-life cognition and dementia" (Power)
3746; "The association between criteria air pollutant exposure and late-life amyloid burden" (Bennett)
3460; "Accounting for exposure measurement error in assessment of the effects of air pollution on dementia" (Park)
3417; "Novel Estimation of Inverse Probability Weights Accounting for Attrition" (Smith)
3502; "The associations of dietary copper with neurocognitive outcomes: The ARIC Study" (Wei)
3762; " Association of ambient particulate matter components with MRI outcomes" (Power)
3241; "Association between particulate matter and chronic kidney disease" (Blum)
2412; "Association of particulate matter air pollution with MRI outcomes" (Power)
2288; "Associations of Brain Imaging with Cognitive Change over 20 Years (Knopman)
2876; "Particulate Matter Air Pollution and DNA Methylation" (Gondalia)
2924; "Particulate Matter Air Pollution and Leukocyte Traits" (Gondalia)
2078; "Genome-wide Association Study of Particulate Matter and Ventricular Ectopy" (Napier)
1146; "Ambient air pollution is associated with the onset of acute events –The ARIC Study" (Liao)
760; "Association between air pollution and hemostatic/inflammation factors" (Liao)
2321; "Genome-wide Association Study of Particulate Matter and Supraventricular Ectopy" (Fransceschini)

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* _2016.20__)

___ 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.

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