ARIC Manuscript Proposal #4275

PC Reviewed: 6/13/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Midlife Vascular Risk Factors and Parkinson's Disease in the Atherosclerosis Risk in Communities (ARIC) Cohort

b. Abbreviated Title (Length 26 characters): **VRFs and Parkinson's Disease**

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:
Writing group members: Derrick N Okine (first author), Honglei Chen (last author), Srishti Shrestha, Kevin J Sullivan, Rebecca Gottesman

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

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3. Timeline: Manuscript to be prepared and submitted by Fall 2023.

4. Rationale:

The aim of this study is to investigate vascular risk factors that may be associated with risk of Parkinson's disease (PD) in the community-based ARIC cohort. Vascular risk factors such as hypertension, diabetes, and obesity, especially from midlife, have previously been associated with cognitive impairment and incident dementia.[1,7] In PD, some studies have suggested that the presence of vascular risk factors is associated with worse motor[2] and cognitive performance.[3,5] However, these studies often don't have access to these risk factors at midlife and often miss the relevance of multiple of these comorbidities.

Although studies suggest a stronger association between VRFs and cognition in PD, there are a few studies that have addressed whether vascular risk contributes to the motor phenotypes and clinical diagnosis of PD.[2] Since PD and other neurodegenerative disorders like dementia are not isolated pathogenically, it's possible that vascular risk factors may contribute to risk of PD beyond just its cognitive facets.

In addition to evaluating which risk factors may yield a higher risk of Parkinson's disease, this study also seeks to evaluate whether vascular risk may be more prevalent in Parkinson's patients with dementia when compared to those with PD but without dementia. There is extensive literature showing that vascular risk pathogenically contributes to dementia[1] and cognition[2,3,7]. With this in mind, we hypothesize that in this cohort, vascular risk factors will be associated not only with presence of PD (vs no PD) but also with PD-dementia (vs PD without dementia). We will also evaluate, in the entire cohort, the role of midlife vascular risk factors in PD-dementia compared to dementia (without PD), PD (without dementia), and in individuals with neither PD nor dementia.

5. Main Hypothesis/Study Questions:

1. Midlife vascular risk factors will be associated with a higher risk of Parkinson's Disease.
2. Midlife vascular risk will be elevated in individuals with PD-dementia, although we anticipate that associations will be similar to those between midlife vascular risk factors and dementia (but not PD), but both will be increased relative to associations between midlife vascular risk and PD (without dementia), and all will be elevated relative to no-PD/ no-dementia.
3. Within the population of ARIC participants with adjudicated PD diagnoses, those with dementia will be more likely to have a higher amount of vascular risk factors than those without 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).

Design: Prospective cohort

Participant inclusion: All ARIC participants will be eligible for inclusion. Any participants with a diagnosis of prevalent dementia or PD at visit 1 will be excluded.

Outcome: Our primary outcome for Hypothesis 1 will be adjudicated diagnosis of Parkinson's disease, with estimated dates of onset as derived in prior ancillary work. For Hypotheses 2 and 3, we will define Parkinson's Disease with Dementia as those individuals with both an adjudicated PD diagnosis (N=226) and a dementia diagnosis; we will not consider date of onset of this combined diagnosis because we anticipate that some individuals will get one diagnosis (such as PD) before the other (dementia), and others will be diagnosed in the opposite order, making it challenging to determine date of onset of the combined diagnosis.

Also for Hypothesis 2, we will use dementia / no-PD as level 3 dementia from prior ARIC work, and no-PD/ no-dementia as having no diagnosis of either condition at any point over follow-up.

Exposures of interest: The primary independent variables will be vascular risk factors collected primarily at baseline – smoking, diabetes, hypertension, hypercholesterolemia, and BMI. In addition to these, physical activity and presence of APOE e4 genotype will also be considered independent variables.

Data analysis: Cox proportional hazards models will be used if there are enough participants with information for date of diagnosis of PD; if there are not enough cases with an estimated date of diagnosis, we will focus on logistic regression as our primary analysis for Hypothesis #1. For hypothesis #2, the primary analysis will include a multinomial logistic regression, with no-PD/no-dementia as our reference group, and PD (no dementia), PD+dementia, and dementia (no PD) as separate outcomes.

Covariates: Presence of each vascular risk factor, number of VRFs, and ARIC stroke risk score will be used as independent variables in separate analyses for hypothesis 1. Hypotheses 2 and 3 will primarily use the summative tally of vascular risk factors as an independent variable. Individual vascular risk factors will be investigated as an independent variable for hypotheses 2/3 when the sample size is sufficient for such an analysis. We will use 3 sequentially nested models for adjustment in each analysis. Model 1 will include demographic factors- age, sex, race-center, and level of educational attainment. Model 2 – in addition to model 1, vascular risk factors (smoking, diabetes, hypertension, hypercholesterolemia, BMI, and presence of APOE e4 genotype) not including the independent variable where appropriate (not applicable for the model evaluating number of VRF's). Model 3 – in addition to model 2, preexisting conditions- coronary heart disease, prevalent stroke before visit 1, and incident stroke preceding PD/Dementia diagnosis.

For hypothesis #3, the analysis will be conducted among individuals with a diagnosis of PD, and Cox proportional hazards models will be used to evaluate time-to-dementia onset, with the same nested models as described above. If date of onset is not available, we will do logistic regression analyses to test these associations (dementia yes/ no among those with PD).

In addition to these models, a sensitivity analyses will be conducted to evaluate these relationships stratified by sex and race to determine if results differ in these subgroups. A separate sensitivity analysis will evaluate the impact of the competing risk of stroke and nondementia death using a competing risks proportional hazards model.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes ___X_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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)?

MP # 3691. Gottesman RF, Wu A, Coresh J, et al. "Associations of Vascular Risk and Amyloid Burden with Subsequent Dementia."
Huang X, Alonso A, Guo X, et al. "Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study."

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* _____)
___ 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 https://sites.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.

References

1. Gottesman, R. F., Albert, M. S., Alonso, A., Coker, L. H., Coresh, J., Davis, S. M., ... & Knopman, D. S. (2017). Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA neurology*, *74*(10), 1246-1254.
2. Malek, N., Lawton, M. A., Swallow, D. M., Grosset, K. A., Marrinan, S. L., Bajaj, N., ... & PRoBaND Clinical Consortium. (2016). Vascular disease and vascular risk factors in relation to motor features and cognition in early Parkinson's disease. *Movement Disorders*, *31*(10), 1518-1526.
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4. Schrag A, Bohlken J, Dammertz L, et al. Widening the Spectrum of Risk Factors, Comorbidities, and Prodromal Features of Parkinson Disease. *JAMA Neurol.*2023;80(2):161–171. doi:10.1001/jamaneurol.2022.3902
5. Vikdahl, M., Bäckman, L., Johansson, I., Forsgren, L., & Håglin, L. (2015). Cardiovascular risk factors and the risk of Parkinson's disease. *European Journal of Clinical Nutrition*, *69*(6), 729-733.
6. Kummer, B. R., Diaz, I., Wu, X., Aaroe, A. E., Chen, M. L., Iadecola, C., ... & Navi, B. B. (2019). Associations between cerebrovascular risk factors and parkinson disease. *Annals of neurology*, *86*(4), 572-581.
7. Pilotto A, Turrone R, Liepelt-Scarfone I, Bianchi M, Poli L, Borroni B, Alberici A, Premi E, Formenti A, Bigni B, Cosseddu M, Cottini E, Berg D, Padovani A. Vascular Risk Factors and Cognition in Parkinson's Disease. J Alzheimers Dis. 2016;51(2):563-70. doi: 10.3233/JAD-150610. PMID: 26890741.