ARIC Manuscript Proposal Form

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Publication Committee Review Date: **_12/10/24_**
ARIC Manuscript Proposal Number: **# 4538**

1.a. Full Title: The Influence of Vision Impairments on Dementia in Stroke Survivors

b. Abbreviated Title (Length 26 characters): Vision Impairment and Dementia

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members (alphabetical): Kimberly Hreha (first), Marissa Ashner, Jennifer Deal (invited), Rebecca Gottesman, Sarah Peskoe, Priya Palta, Heather Whitson, Beverly Gwen Windham, Lisa Wruck

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline:June 2024- June 2026
Aim 1: Manuscript Submission by December 2024
Aim 2: Manuscript Submission by April 2025

Aim 3: Manuscript Submission by December 2025

4. Rationale:

Scientific rationale: Each year, almost 800,000 Americans have a stroke and survive, resulting in long term disability. One symptom of long-term disability in stroke survivors includes vision impairment; many strokes affect the visual pathways within the brain and also the retina and optic nerve. Stroke-related vision impairments have been shown to contribute to long-term disability due to the impact on functional performance (Rowe et al., 2017) and psychological health (Heesterbeek et al 2017). Another key symptom of stroke disability is dementia, although the mechanisms related to post-stroke dementia are incompletely understood. We and others have shown associations between self-reported vision impairment and cognitive impairment in stroke survivors (Hreha, et al 2021; Patel et al, 2002). We also found that stroke survivors with worse vision had lower cognitive functioning but not greater cognitive decline than stroke survivors with excellent-to-very good vision but this was a cross-sectional (Hreha et al., 2021). One type of vision impairment, retinopathy, is more likely to present in people with a history of stroke, and individuals with retinopathy were found to have an increased risk of cerebrovascular related dementia (Deal et al 2019). This current body of work on vision impairment and dementia in stroke survivors is limited and still has gaps, therefore it is a crucial to investigate this topic further, for example if the presence of specific types of vision impairment (i.e., age-related vision impairment and stroke-related vision impairment) influence the stroke-dementia relationship and determine the downstream consequences (including possible depression, impairments in physical performance, etc.) of stroke-related vision impairment in a cohort of stroke survivors overtime. Using extant data to explore our questions is both time- and cost- effective. The ARIC study has collected relevant variables to test our hypotheses and address our aims.

5. Main Hypothesis/Study Aims: There are two primary aims of this study examining vision impairment (stroke-related vision impairment, meaning there was evidence of hemianopia, diplopia, and/or cranial nerve palsy symptoms at the time of stroke hospitalization, or self-reported pre-stroke vision impairment, identified from retinal exams prior to the index stroke) and dementia among stroke survivors:

Aim 1: (1) characterize the prevalence of vision impairment among stroke survivors and (2) quantify the associations between vision impairment (a) and a risk of MCI or prevalent dementia in late life, (b) presence of depressive symptoms, and (c) physical performance. *Hypothesis*: We hypothesize that stroke survivors with stroke-related vision impairments will have a greater risk of MCI and prevalent dementia, greater presence of depressive symptoms, and lower physical performance compared to those with normal vision.

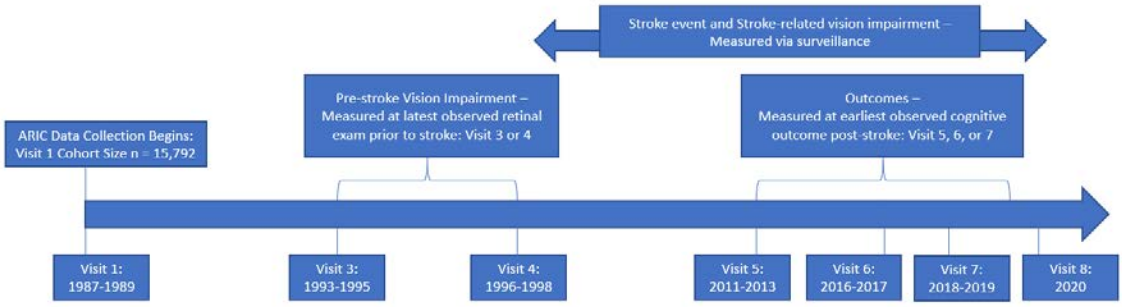
Aim 2: Determine the association between stroke-related vision impairment and time to incident dementia onset, from time of stroke. *Hypothesis*: The hazard of developing incident dementia will be higher for stroke survivors with stroke-related vision impairment, compared to stroke survivors with normal vision.

6. Design and analysis - please address the following aspects:

Aim 1:

a. **Study Design:** This is an observational cohort study using ARIC data. For each participant, outcome data from either visit 5 (2011-2013), visit 6 (2016-2017), visit 7 (2018-2019), visit 8 (2020) will be used. The time of outcome determination will be chosen for each participant from the first complete cognitive assessment following their most recent stroke event. We will also use ARIC stroke surveillance data for stroke event ascertainment and retinal exam data from Visits 3 and 4.

b. **Inclusion/Exclusion:** ARIC participants with a probable or definite all types of stroke captured from the hospital surveillance data (adjudicated events) will be included. Participants will be excluded if they did not have a retinal exam prior to their most recent stroke event or if they had a fatal stroke event before their first complete NCS cognitive status diagnosis (COGDIAG variable, described further below). **See below Figure schematic of Aim 1's design:**



c. **Primary Exposures** (see Table 1 for more information including definitions)**:**
   i. Stroke-related vision impairment (binary --yes/no)-- taken from the year of most recent non-fatal stroke event (measured at time of stroke, from cohort stroke abstraction form).
   ii. Pre-stroke vision impairment (binary—yes/no)-- taken from retinal exams,
   iii. Either/both types of vision impairment (at least one of stroke-related and pre-stroke vision impairments)

d. **Primary Outcomes** (see Table 1 for more information):
   i. Presence of any cognitive impairment measured at earliest observed timepoint post-stroke (MCI or prevalent dementia, as defined by the COGDIAG variable)
      1. Presence of adjudicated, prevalent level 1 dementia measured at earliest observed timepoint post-stroke (yes/no)
   ii. Depression, integer variable with range 0-22, representing CES depression score (11 items from 0-2), higher score means more depressed --(measured at earliest observed timepoint post-stroke). We are using the continuous measure to represent the variation in the data.
   iii. Short Physical Performance Battery (SPPB)**,** integer variable with range 0-12, representing the sum of the 4-meter walk score (0-4), the balance score (0-4), and the chair stand (0-4), higher scores mean better function --(measured at earliest observed timepoint post-stroke)

e. **Other variables of interest (see Table 1 for more information):**
   i. age at time of stroke

ii. education and sex (taken at ARIC baseline)

iii. we will also summarize variables that may be related to the outcome such as: hypertension, diabetes, BMI, etc.

f. Table 1. Variables to be used in Aim 1

Outcome	Description	Variables and Source
Stroke-related vision impairment	At least one condition (i.e., hemianopia, diplopia, and cranial nerve palsy), condition abstracted from the medical records.	Cohort incident stroke abstraction form questions 38, 39, and 46 STRC38A, STRC39A, STRC46A
Pre-stroke vision impairment	At least one self-reported condition (i.e., , glaucoma, age-related macular degeneration, diabetes-related eye problems, cataracts, surgery, blindness—unrelated to the stroke and occurring prior to the stroke)	Retinal exams from visits 3 and 4 REXA3A, REXB3A REXA4A, REXB4A,…
Cognitive impairment	The Neuro Cognitive Study (NCS) defined cognitive via an expanded 10-test battery and informant interviews, and then used a computer algorithm generated preliminary diagnoses that were verified by expert review. We use the cognitive diagnosis defined by the classification committee's cognitive diagnosis for the participants that were selected to stage 2 in the NCS, or the computer-determined syndromic diagnosis for the rest. The possible diagnoses include normal, mild cognitive impairment (MCI), and dementia. We consider participants with mild cognitive impairment or dementia as having any cognitive impairment.	COGDIAG51, COGDIAG61, COGDIAG71 From the STATUS71 dataset COGDIAG = M or D defines any cognitive impairment
Dementia		COGDIAG = D defines prevalent dementia
The Center for Epidemiological Studies-Depression (CES-D)	self-report tool that measures depressive symptoms experienced, integer with a range of 0-22 (higher score is more depressed)	CESD51, CESD61, CESD71 from derived datasets
Short physical performance battery	Objective assessment for functional mobility or physical function that incorporates three tasks to get a composite score ranging from 0-12.	SPPB51, SPPB61, SPPB71 from derived datasets
age	Integer age at time of outcome determination	V5AGE51, V6AGE61, V7AGE71 from derived datasets
sex	Categorical variable with levels male, female	GENDER from visit 1 derived dataset
education	Integer variable representing the number of years of education	HOM54 from home interview

g. Data Analysis: We will conduct multivariable linear and logistic regressions, controlling for age, sex and education. We will run the relevant model for each combination of exposures (pre-stroke vision impairment, stroke-related vision impairment, OR either/both types of vision impairment) and outcomes (see above). The models with stroke-related vision impairment will also be adjusted for number of years since stroke.

h. Limitations/Challenges:

i. The retinal exams were only conducted at Visits 3 (all participants) and 4 (some participants), meaning some participants pre-stroke age-related vision impairment variables may be missing, because it was a long time from retinal exam to the stroke date. We understand that this may limit our ability to assess pre-

stroke vision impairment variable. Namely, we hypothesize this would lead to an underestimation of the exposure. Further, we recognize that the stroke survivors' data who had the longest time between the retinal exam and their stroke will likely produce the greatest under-estimated exposure.

ii. Even though the stroke-related vision impairment was only captured at the time of stroke, based on clinical experience we expect this to be persistent. However, we realize that we only have one time point of data and therefore this is a limitation.

Aim 2:

a. **Study Design:** This is a longitudinal, observational study using ARIC data from the stroke surveillance, as well as the incident dementia surveillance (level 3) diagnoses.
b. **Inclusion/Exclusion:** ARIC participants with a non-fatal probable or definite stroke captured from the hospital surveillance data will be included. Participants will be excluded if they if they were diagnosed with incident dementia prior to their incident stroke, or if they had a stroke prior to their baseline visit.
c. **Primary Outcome:** Time to incident dementia onset (time origin (time zero): time of non-fatal incident stroke event)
d. **Other variables of interest:**
    a. incident stroke events will be taken anytime from the start of the surveillance data),
    b. presence of stroke-related vision impairment (taken from surveillance, as defined in Aim 1)
    c. age at time of stroke event, (calculated using the age at baseline and year of stroke event)
    d. education level and sex (as defined in Aim 1)
e. **Data Analysis:** We will conduct survival analysis, using Cox proportional hazard models with time origin being the year of the stroke, and the outcome being the number of years from stroke to dementia onset. We will adjust for age, sex, and education. The outcome will be right censored at death, dropout, or last follow-up. However, follow-up sensitivity analyses will assess the impact of defining death as a competing risk. The viability of the proportionality assumption for the model will be tested using the Schoenfeld residual method.
f. **Limitations/Challenges:** None anticipated

Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC

investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ **Yes** ☒ **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 is distributed to ARIC PIs annually, 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 current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ **Yes** ☐ **No**

9. The lead author or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
MS#s 2120A, 4174, 4044, 3156, 1894, 3672

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☐ **Yes** ☒ **No → Skip to question 12**

11.b. If yes to 11.a., is the proposal

☐ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* __

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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