DRPP Manuscript Proposal

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I. Title:

Risk factors for early- and late-onset dementia in a harmonized prospective cohort

II. Abbreviated Title:

Early-onset dementia risk factors

III. Select cohorts to be used in proposal:

AGES	ARIC	CHS	FHS	HAAS	MESA	REGARDS	SALSA	Whitehall II	Rotterdam*	3Cities*
	X		**X**		**X**			**X**		

**External cohorts; data must be run at cohort coordinating center.*

IV. Writing Group:

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V. Background

Approximately 3% of dementia cases occur in before the age of 65, thus classified as early-onset dementia (EOD).[1,2] This age threshold of 65 years defining early vs late onset dementia (LOD) was chosen because of the immense impact of experiencing the disease in middle age, as defined by the U.S. standard retirement age.[1] While the distinction between early and late onset comes from our understanding of its societal impacts, there can be important etiologic and clinical differences in early-onset cases compared to late-onset cases.[1,3-5] Whether the age cut-off of 65 is best for understanding these differences is not well established.

Much of our understanding of dementia risk factors comes from studies consisting of mostly late-onset cases. Up to 45% of dementia cases may be preventable by eliminating modifiable risk factors.[6] If not totally prevented, delaying the onset of dementia is still highly valuable, both to the patient and to their loved ones and communities. In fact, studies show that even a 1-year delay in symptom onset for the entire patient population could reduce total costs to the U.S. economy by $113 billion.[7] It is unclear whether the risk factors for LOD are also risk factors, and to what degree, for EOD. Some work has been done to estimate the association of modifiable risk factors with EOD, however some findings, such as with hypertension and diabetes, are inconsistent.[8-13] These studies also excluded or did not examine racial/ethnic minorities.[8,9,13] It is also of scientific interest to examine risk factors using different age cut-offs for the definition of EOD since the current definition is shaped primarily by societal rather than clinical implications.

VI. Main Study Questions and Hypotheses

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We will examine whether known risk factors for LOD have similar associations with EOD. Secondarily, we will examine these associations using multiple age cut-offs for the definition of EOD and by dementia subtype. We hypothesize that some risk factors will possess stronger associations with EOD because there is less confounding by other comorbid conditions in younger populations.

VII. DRPP data to be used

Demographic: Gender, race/ethnicity, education
Clinical: systolic blood pressure, hypertension, hba1c, diabetes, BMI, LDL cholesterol, hypercholesterolemia
Genetic: none
Lifestyle/Behavioral: depression, alcohol consumption, smoking, physical activity, physical inactivity
Outcomes:

- □ CHD
- □ CVD
- □ Death
- X Dementia (all types)
- □ Stroke

VIII. Analytic Plan

Data from 4 DRPP cohorts (ARIC, FHS, MESA, and Whitehall II) has already been pooled and harmonized by the DRPP team and will be used in this analysis along with data from UK Biobank (UKBB). UKBB data has been obtained and harmonized by the DRPP EOD Ancillary Study team. Missing data in UKBB has been imputed separately. Baseline will be the first exam for each individual in their respective cohorts. We will calculate crude incidence rates of dementia in 5-year age groups and use those results to estimate the number of new cases of EOD in the US each year.

The main analysis will consist of using cox proportional hazards regression models to estimate the association between various risk factors with early-onset dementia and late-onset dementia and test whether those associations are statistically different. We will achieve this by using a time-varying coefficient for the risk factor of interest, dividing follow-up time before and after age 65. We will first fit a crude model, then fit a model adjusting for cohort, sex, race/ethnicity, and education, then we will fit a fully adjusted model which adjusts for cohort, demographics, and all risk factors. Additional analyses will include changing the age cut-off for early-onset dementia to 70, 75, and 80 years of age and looking at associations by dementia subtype (UKBB data only for subtypes).

We will run several sensitivity analyses to account for to the use of pooled cohorts and the significantly larger sample size of UKBB (N > 500,000) compared to the other cohorts. We will do a sensitivity analysis excluding UKBB participants and will analyze each DRPP cohort separately where sample size allows. We will also conduct a sensitivity analysis in which any participant with dementia diagnosed within 3 years from baseline is excluded from the analysis to rule out the possibility of reverse causation. We will conduct a final sensitivity analysis in which each participant's follow-up

time is restricted to 10 and 15 years from baseline to limit the length of time between the exposure measurement and the outcome.

IX. Timeline

Analysis: August 2024 – February 2025
Writing: February 2025 – April 2025
Feedback and submit for publication: April 2025 – June 2025

X. References

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