DRPP Manuscript Proposal

Publication Committee Review Date: **04/09/24**

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I. Title:

Midlife and late-life population attributable fractions of risk factors for dementia in the United States: The Dementia Risk Pooling Project

II. Abbreviated Title:

Midlife and late-life population attributable fractions of risk factors for dementia in the United States

III. Select cohorts to be used in proposal:

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

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

IV. Writing Group:

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DRPP Manuscript Proposal

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V. Background

The number of individuals with dementia in the US is estimated to nearly double from 5.3 million in 2019 to 10.5 million in 2050[1]. With a rapidly aging population, addressing modifiable risk factors is essential to preventing the onset of dementia. Previous research has found that 40% of global dementia cases may be prevented by eliminating 12 modifiable risk factors: low education, hearing loss, hypertension, excessive alcohol consumption, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and traumatic brain injury (TBI)[2]. In response to the significant burden of dementia, US Department of Health and Health Services has set a goal of reducing dementia risk factors by 15% before 2030[3].

The relationships between modifiable risk factors and dementia risk vary with age. Although positive associations with dementia onset have been found in middle-aged study populations, non-significant or even inverse associations have been found in late-life cohorts for risk factors including diabetes, hypertension, alcohol use, and obesity[4-8]. Additionally, the strength of positive association between low education, depression, smoking, and physical inactivity with incident dementia varies with population age[9]. Although the associations between modifiable risk factors and dementia risk have been characterized, few studies have calculated the associations between these risk factors and dementia across the lifespan[10]. Previous analyses have also been limited by the sample size of existing cohorts and the lack of racial and ethnic diversity.

Therefore, this study aims to apply a life-course approach to dementia risk by estimating the population attributable fractions (PAFs) for eight midlife and late-life modifiable risk factors in the United States. We also calculate potential impact fractions (PIFs) to estimate the cases of dementia that could be prevented by reducing the prevalence of these risk factors[3]. These estimates may help inform clinical and public health interventions to reduce the prevalence of dementia.

VI. Main Study Questions and Hypotheses

- What are the population attributable fractions (PAFs) for eight midlife and late-life modifiable dementia risk factors in the US?
- What are the potential impact fractions (PIFs) for eight midlife and late-life modifiable dementia risk factors?

We hypothesize that the combined PAF and PIF for all risk factors will be greater during exposure in midlife compared to late-life.

VII. DRPP data to be used

We will use data from six US cohorts of the Dementia Risk Pooling Project (DRPP):
1) Atherosclerosis Risk in Communities Study (ARIC)
2) Cardiovascular Health Study (CHS)
3) Framingham Heart Study (FHS)
4) Kuakini Honolulu-Asia Aging Study (HAAS)
5) Multi-Ethnic Study of Atherosclerosis (MESA)
6) The Sacramento Area Latino Study on Aging (SALSA)

All data has been rigorously harmonized by the DRPP research team at Northwestern University for analysis.

Exclusion criteria: participants younger than 45 years of age.

Variables:
Exposure in midlife (45-64 years of age) and late-life (65+ years) to eight risk factors: education, obesity, hypertension, diabetes, smoking, physical inactivity, excessive alcohol, and depression.

VIII. Analytic Plan

We will calculate the midlife and late-life population prevalence (P_e) of each risk factor *e* using data from 2013-2020 (pre-COVID) of the National Health and Nutrition Examination Survey (NHANES). We will use the Taylor series linearization method to estimate the standard errors of all prevalences.

To account for missing data, we will use the R package jomo to impute missing variables and covariates 25-fold[11]. Non-probable imputed values will be set to the variable mean. We will use cause-specific Cox proportional hazard models to estimate hazard ratios (HR) for each risk factor. The follow-up period will be calculated beginning at first visit within the midlife or late-life group until incident dementia, death, or censoring. Models will be adjusted for all risk factors as well as age, sex, race (White, Black, or other), ethnicity (Hispanic or Non-Hispanic), and APOE4 allele (22/23, 24, 33, or 34/44). Validity of the proportional hazards assumption will be evaluated through visual inspection of the log-log Kaplan-Meier curves. Effect estimates will be pooled across the 25 imputed datasets using Rubin's rules.

PAFs will be calculated using Levin's formula: $PAF_e = \frac{[Pe\ (HRe-1)]}{Pe\ [HRe-1]+1}$[12]. We will use 1000 Monte Carlo simulations to combine the uncertainty across prevalence and PAF estimates to calculate 95% confidence intervals (CIs) for PAFs[13]. PAF estimates for each risk factor will be summed to produce a combined midlife PAF estimate and a combined late-life PAF estimate[14]. PIFs will be calculated using $PIF_e = \frac{[Pe - P'e]*[HRe-1]}{Pe\ [HRe-1]+1}$ where $P'_e = P_e - 0.15$, for the counterfactual prevalence

assuming a 15% proportional reduction in prevalence[12]. Statistical significance will be set *a priori* at α=0.05. All analyses will be conducted in R version 4.3.0 using dplyr and survivalpackages[15-17].

IX. Timeline

March 2023: Undergraduate summer research grant submission
June–July 2023: Literature review, development of initial statistical analysis plan
July–Sept 2023: Preliminary results analysis, preparation of conference abstract & manuscript draft
Oct 2023: AHA Epi abstract submission
Dec 2023–Jan 2024: Methods fine-tuning
Jan–June 2024: Manuscript finalization & submission

X. References

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