

Research Use Statement for Application for Genomic Data from NIAGADS

Please limit to 2,200 characters max.

Objectives of the Proposed Research:

In the U.S. among older adults (aged ≥ 65), ~8% live with dementia.¹ A healthy lifestyle has been shown to offset the genetic risk of dementia among white participants aged ≥ 60 in the large cohort of UK Biobank.² Among those in the top quintile of genetic risk, a favorable lifestyle reduced the risk of dementia by 32%.² Overall African Americans have 30% higher risk of dementia compared with whites in the U.S.³ The extent that a healthy lifestyle could offset genetic risk of dementia in African Americans has not been assessed.

The proposed research will use the GWAS summary statistics from Rietz et al.⁴ to derive a genetic risk score (GRS) for dementia in the African American cohort of the Atherosclerosis Risk in Communities (ARIC) study. These GRS will be used to evaluate the interplay between genetic risk and lifestyle factors for dementia in African Americans.

Although the study of Rietz et al. is a GWAS of Alzheimer's disease (AD), its summary statistics is acceptable for deriving a GRS for the study of dementia given the lack of large-scale published GWAS of all-cause dementia (one is ongoing in CHARGE) and AD is the most common form of dementia.⁵ In addition, patients of AD often present with other dementia pathologies,^{6,7} GWAS summary statistics of AD could have captured genetic risk for other forms of dementia.

The ARIC study is a longitudinal cohort study of 15,892 U.S. adults (African Americans $n=4,266$) aged 45 to 65 at visit 1 (1987-89).⁸ Dementia diagnosis for all participants have been carefully assessed by a panel of experts using predefined criteria based on information from cognitive tests, neuropsychological battery, informant interview, and ICD-9 code for dementia at hospital discharge or on death certificate.⁹ We will analyze dementia outcome up to September 1, 2013.

Study Design:

Longitudinal cohort study with ARIC visit 1 as baseline

Analysis Plan:

Given the long follow-up time, we will use competing risk survival analysis based on the Fine & Gray method to account for mortality, which can preclude the development of dementia.¹⁰ Significance level will be set at $p\text{-value} < 0.05$.

Given genetic risk for dementia may differ by race, we will conduct competing risk analysis stratified by self-reported race. The methods for meta-analysis to combine the results from the race groups, e.g. fixed or random effects, will depend on the results from the assessment of heterogeneity.¹¹

Explanation of how the proposed research is consistent with the data use limitations for the requested dataset(s):

The data use limitation of the requested dataset is: Disease-Specific (Alzheimer's Disease and Related Dementias, IRB, NPU) (DS-ADRD-IRB-NPU)

This proposed research is consistent with the data use limitations, which include dementia. In addition, consistent with the limitation of the IRB and NPU codes, our research is not-for-profit and have also obtained IRB approved.

Brief description of any planned collaboration with researchers at other institutions, including the name of the collaborator(s) and their institution(s).

The initial analysis will be conducted at UMMC, which is a study site of the ARIC study. Investigators from the other three sites (Forsyth, NC; Mineapolis suburb, MN; and Washington country, MD) will contribute to reviewing and interpretation of the results and do not need direct access to the summary statistics from Reitz et al.

In the event that any investigators outside of UMMC need to access the summary statistics from Reitz et al., we will submit an amendment to this request.

List the NIAGADS datasets you are requesting for analysis (ex. NG00017):

ng00039 ADGC African American Summary Statistics- Reitz et al. (2013)

Non-Technical Summary for Application for Genomic Data from NIAGADS

Investigators will provide a non-technical summary of their proposed research. If the project is approved, this statement will be publicly available for lay audiences to read the purpose and objectives of the research. Please limit to 1,100 characters.

Almost 10% of the older adults in the U.S live with dementia. Treatment options are limited and have small benefits. A healthy lifestyle has been shown to offset the genetic risk of dementia among whites in a large study in the UK. Among those in the top 20 percentile of dementia genetic risk, a favorable lifestyle reduced the risk by 32%. Similar studies have not been conducted among African Americans in the US. More research on the interplay between genetic risk and lifestyle improve the use of lifestyle factors for the prevention and treatment of dementia. The proposed research will use the genome-wide summary statistics from Reitz et al. to compute a genetic risk score for dementia to study the interplay between lifestyle factors and genetic risk for dementia.

References

- 1 Langa, K. M. *et al.* A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. *JAMA Intern Med* **177**, 51-58, doi:2587084 [pii] 10.1001/jamainternmed.2016.6807 [doi] (2017).
- 2 Lourida, I. *et al.* Association of Lifestyle and Genetic Risk With Incidence of Dementia. *JAMA*, doi:2738355 [pii] 10.1001/jama.2019.9879 [doi] (2019).
- 3 Mayeda, E. R., Glymour, M. M., Quesenberry, C. P. & Whitmer, R. A. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimer's & dementia : the journal of the Alzheimer's Association* **12**, 216-224, doi:S1552-5260(15)03031-9 [pii] 10.1016/j.jalz.2015.12.007 [doi] (2016).
- 4 Reitz, C. *et al.* Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4, and the risk of late-onset Alzheimer disease in African Americans. *JAMA* **309**, 1483-1492, doi:1677372 [pii]

- 10.1001/jama.2013.2973 [doi] (2013).
- 5 Fiest, K. M. *et al.* The Prevalence and Incidence of Dementia Due to Alzheimer's Disease: a Systematic Review and Meta-Analysis. *Can J Neurol Sci* **43 Suppl 1**, S51-82, doi:S0317167116000366 [pii]
- 10.1017/cjn.2016.36 [doi] (2016).
- 6 Schneider, J. A., Arvanitakis, Z., Bang, W. & Bennett, D. A. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* **69**, 2197-2204, doi:01.wnl.0000271090.28148.24 [pii]
- 10.1212/01.wnl.0000271090.28148.24 [doi] (2007).
- 7 Barnes, L. L. *et al.* Mixed pathology is more likely in black than white decedents with Alzheimer dementia. *Neurology* **85**, 528-534, doi:WNL.0000000000001834 [pii]
- 10.1212/WNL.0000000000001834 [doi] (2015).
- 8 ARIC. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol* **129**, 687-702 (1989).
- 9 Knopman, D. S. *et al.* Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimers Dement (Amst)* **2**, 1-11, doi:10.1016/j.dadm.2015.12.002 [doi] (2016).
- 10 Fine, J. P. & Gray, R. J. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association* **94**, 496-509 (1999).
- 11 Hardy, R. J. & Thompson, S. G. Detecting and describing heterogeneity in meta-analysis. *Statistics in Medicine* **17**, 841-856, doi:10.1002/(SICI)1097-0258(19980430)17:8<841::AID-SIM781>3.0.CO;2-D (1998).