**DIABETES COG**

**Statistical Analysis for Specific Aim 1:**

Phase 1. Summary Statistics: We will summarize the characteristics of participants in each cohort study and the pooled cohort in Phase 1, including cognitive outcomes and independent variables (race and cumulative mean glucose levels). We will also examine the interpersonal correlation of cognitive tests across items and years.

Phase 2. Statistical Models: We will test **Hypothesis 1**, whether there is a significant effect of race on the slope of cognition after adjusting for cumulative mean glucose levels and other covariates, by fitting linear mixed-effects models to assess change in cognitive function over time using the pooled cohort data. Biostatistician/Co-I Galecki has extensive expertise in linear mixed-effects modeling with longitudinal data. The basic model is:

Subscripts and represent individual and observation at time , respectively. Time is expressed as years from initial cognitive measurement. The basic model includes race and age, along with their two-way interactions with time, and cumulative mean glucose. Random intercepts and slopes are included to accommodate the correlation of cognitive measures within participants over time and to allow participant-specific rates of cognitive change. The matrix defines variance-covariance for subject-specific random effects, which are assumed to be normally distributed. Random errors are independent from each other. The main effect of interest when testing **Hypothesis 1** is associated with the race by time interaction (i.e., ) and whether this effect is attenuated by introducing a cumulative glucose by time interaction into the basic model. The basic model includes select covariates for simplicity. Other covariates listed in **Section C2c** will be considered when developing the final model.

We will fit a series of models for each continuous cognitive outcome. GCP will be treated as the primary outcome and EF and Memory as secondary outcomes. Each outcome will be censored at the time of first expert-adjudicated incident stroke, death, loss to follow-up or the end of follow-up. We will inspect residual plots to check model assumptions. All analytic code will be made publicly available to optimize rigor and reproducibility.

**Assessing heterogeneity in associations:** We will determine whether the effect of cumulative mean glucose on cognitive slope differs by sex, age, diabetes treatment status or cohort by introducing interaction terms into the basic model.

**AD/ADRD as a secondary outcome:** Incident AD/ADRD will be examined as a secondary outcome using competing risk regression models. (Gerds et al., 2012) Incident all-cause mortality will be treated as a competing event. The basic model will include the same independent variables that were included in the primary analysis.

**Missing Data:** The cohorts use multiple tracking methods to minimize participant loss, although some covariate and outcome data is still missing due to non-response (i.e., missing items) and selective attrition (i.e., dropout due to poor health or death). We will impute missing covariate data under the assumption that it is Missing at Random (MAR). Assuming that the MAR assumption is not valid, an attempt will be made to incorporate the Missing Not at Random (MNAR) mechanism into the model using pattern-mixture, selection or shared parameter approaches as discussed in Little and Rubin (2019). We will also identify covariates associated with time-to-death to include in our models and perform sensitivity analyses to model the effects of non-response bias, missing covariates and death. Some cohorts minimize missing cognitive data using telephone-administered cognitive measures for those unable to attend in-person examinations. We will perform sensitivity analyses that include telephone-administered cognitive measures, which have been shown to reliably and precisely estimate GCP, EF and memory. [Refs needed]

**Statistical Power Considerations:** We estimated variance components using pooled data from the six cohort and the harmonized cognitive outcome of GCP (n=28,000). Preliminary data for GCP provided us with an estimate of standard deviation of the random slope =0.31, intercept=5.2 and residual =4.6. Assuming that these estimates are the same for the final data and a sample size of more than 28,000 adults with an average of 4 observations per adult, the sample size provides more than 90% power (alpha=0.05) to detect a difference of 0.035 points per year between the GCP slopes of Blacks and Whites. A difference in slope between the two groups can also be expressed as a ratio relative to the corresponding standard deviation of the slope variation (0.11=0.035/0.31). Considering a decline of ≥0.5 standard deviations in GCP to be clinically meaningful [refs needed], we are well positioned to detect even a small effect.

**C2c. Potential Problems and Alternative Strategies to Achieve Aim 1**

We may be unable to account for all cultural, economic, educational and biologic factors that contribute to racial differences in cognitive trajectories. However, we will account for proxies of educational quality, socioeconomic status and vascular risk factors to the best of our abilities. The pooled cohort does not contain data on adherence to diabetes treatment, although it does contain repeated measures of self-reported treatment status and actual glucose levels over time. Apolipoprotein (ApoE) genotype is a strong predictor of incident AD/ADRD [ref needed] and is known for a subset of participants in the pooled cohort. ApoE genotype will be examined as a covariate in sensitivity analyses. We recognize that participants from the FOS are predominantly White. Hispanic participants from NOMAS and MESA will be excluded from the pooled cohort due to previous research indicating that they have slower cognitive decline than Whites and Blacks. Black participants in the pooled cohort are more likely to be excluded than Whites due to stroke or AD/ADRD before the first cognitive assessment, which could reduce racial differences in cognitive decline. [Ref the B vs W paper] Smaller sample size and fewer cognitive assessments may also reduce the precision of estimates in Blacks.