Population Architecture using Genomics and Epidemiology (PAGE)
Ver. 09/30/16

PAGE Manuscript Proposal Template
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All sections must be completed; incomplete applications will be returned.
Do not exceed 3 pages in length (not including references).

PAGE Ms. Number: 4088 **Submission Date: 8/9/22** **[Approval Date:]**

Title of Proposed MS: Interactions with type 2 diabetes genetic risk factors among African Americans

Abbreviated Title of Proposed MS: T2D genetic interactions in AAs

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II. SCIENTIFIC RATIONALE (Please be specific and concise)

Background

Type 2 diabetes (T2D) is believed to originate from an interplay between genetic and lifestyle factors,[1] and lifestyle interventions can significantly reduce the risk of progression to diabetes in high-risk populations.[2] Prior work in populations of predominantly European ancestry suggests that the risk associated with some demographic, lifestyle, and health factors differs with the underlying genetic susceptibility to T2D, including obesity, age, dietary factors, physical activity, and smoking.[3–5]However, the interactions between genetic risk for T2D and other risk factors have not been systematically investigated among African Americans. Therefore, we aim to quantify the combined effects of genetic, demographic, lifestyle, and health factors on risk of T2D in African Americans in PAGE cohorts in order to inform strategies for prevention in this population that carries a high burden of disease.

Genetic risk scores (GRS) are an important tool that summarize the cumulative effects of multiple genetic variants that individually may have small effects on disease risk. We will examine interactions between T2D GRS and the following: sex, age, obesity, waist circumference, smoking, dietary quality, physical activity, stress, and depression. Our preliminary work on this proposed project in REGARDS and JHS shows nominally significant interactions between T2D GRS and obesity status, waist circumference, physical activity and age. This study will add insight about genetic interactions with various factors in relation to T2D among African Americans.

III. OBJECTIVES AND PLAN (Please be specific and concise)

To investigate interactions between genetic risk for type 2 diabetes and other risk factors in relation to prevalent/incident T2D in African Americans of PAGE cohorts.

g. **Ancestry information used? No __ Yes_X_ How is it used in the analyses?**
Control for population stratification.

h. **Anticipated date of draft manuscript to P&P: _**2023**_____**

What manuscript proposals listed on *www.pagestudy.org/index.php/manuscripts/* **are most related to the work proposed here? Approved PAGE ms. numbers:** A63: T2D PRS and T2D Complications

- **If any: Have the lead authors of these proposals been contacted for comments and/or collaboration? Yes_X_ No__**

IV. METHODS

a. Data. We will restrict analyses to cohorts with substantial populations of African Americans. We have already begun the work in REGARDs and JHS, and we propose to extend this work to MESA, WHI, ARIC, MEC, and CARDIA. We will meta-analyze the results. We propose to include all African Americans with the following data:

- Genetics
- Prevalent T2D (incident T2D if available)
- Age, sex, BMI, waist circumference, visceral adiposity (if available), smoking status, AHA Life Simply 7 diet score, AHA Life Simply 7 physical activity score, perceived stress (as available), and depression (CESD), alternative diet quality and physical activity scores if available.

b. Hypotheses to be tested

We hypothesize that the T2D GRS will show interactions with age, sex, BMI, waist circumference, smoking, dietary quality, physical activity, perceived stress, and depression in relation to incident and prevalent T2D. We hypothesize that the direction of these effects will be as follows: younger age, lower BMI / waist circumference, non-sedentary behavior, smoking, lower dietary quality, depression, and higher stress will be associated with pronounced effects of the genetic risk scores on prevalence/incidence of T2D.

c. Statistical analyses.

We will examine two genetic risk scores developed in African American or transethnic populations: a GRS based on the most up-to-date and largest trans-ethnic T2D GWAS including almost 40k African Americans[7]; and a recently developed transethnic polygenic risk score (PRS) for T2D through eMERGE that was specifically evaluated in multiple African American populations.[8] We will exclude any variants with poor imputation quality (R^2<0.3). For the GRS, we will calculate a weighted genetic risk score as the weighted sum of the number of risk alleles at each of the risk loci.[7] We will standardize the GRS to have mean of zero and standard deviation of one, so that each unit change in GRS corresponds to one standard deviation. The T2D PRS involves about a million SNPs, and the calculation of the PRS is a straight-forward application of provided weights.

We will center and scale quantitative risk traits. We will use logistic regression to model incident/prevalent T2D as a function of the GRS/PRS, controlling for age, sex, BMI, and the first 10 genetic principal components. We will then examine interaction models, evaluating the significance of interaction terms with the risk scores for the following: sex, age, obesity, visceral adipose tissue, waist circumference, smoking, dietary quality, physical activity, stress level, and depression. (We will not control for BMI when examining obesity interactions). We will perform 2 secondary analyses: 1) we will use linear regression models to assess interactions in relation to fasting glucose and HOMA-IR (we will examine cases and controls separately, as our prior work suggests differences in the association between GRS and glycemic traits); and 2) we will examine interactions with the top T2D risk variants (e.g. the SNPs from the GRS) using the GxEScanR package. We will complete the modeling in the PAGE cohorts, and then we will meta-analyze the results using METAL. We will adjust the results for multiple comparisons using a Bonferroni correction.

V. SOURCE OF DATA TO BE USED (Provide rationale for any data whose relevance to this manuscript is not obvious): **Check all that apply:**

Aggregate/summary data to be generated by investigators of the study(ies) mentioned:

[ ] ISMMS; **[X]** CALiCO; **[X]** MEC; **[X]** WHI; **[ ]** CC; **[X]** Other:__MESA

If CALiCo please specify: Included on MEGA Array: **[ ]** SOL

Studies not on MEGA: **[X]** ARIC; **[X]** CARDIA; **[ ]** SHS-Fam; **[ ]** SHS-Cohort

I, MS, affirm that this proposal has been reviewed and approved by all listed investigators.

V1. REFERENCES

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