# Population Architecture using Genomics and Epidemiology (PAGE)

Ver. 02/25/21

## PAGE Manuscript Proposal Template

Submit proposals by email to the PAGE Coordinating Center to Natalie Nudelman (nmakow@hginj.rutgers.edu)

Before submitting this form to Natalie, please fill out the yellow portion of the **PAGE II & III Ongoing Papers Google Sheet**, see, https://docs.google.com/spreadsheets/d/17E7E5G4u_nYWZEkzqqeRigwRbGxYzVNsuSUiVjXCytY/edit#gid=1451131466

*Do not exceed 3 pages in length (not including references).*

**PAGE Ms. Number: 4212** **Submission Date: _3/14/2023__** **Approval Date: _____**

**Title of Proposed MS:**
Replication of genetic risk scores for loci that uncouple excess adiposity from its comorbidities

**I. INVESTIGATOR INFORMATION:**

**Name of Lead Author:** Zhe Wang, Nathalie Chami | **Junior Investigator? Y**
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Authorship model*:

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| Others TBD | | |

Partner studies collaborating with PAGE in this ms. proposal:

| Name | Study | Email |
|---|---|---|
| | | |
| | | |
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**II. SCIENTIFIC RATIONALE** (Please be specific and concise)

Obesity is a major risk factor for a range of cardiometabolic abnormalities, including insulin resistance, dyslipidemia, prediabetes, and hypertension, which can lead to cardiometabolic outcomes, such as type-2 diabetes (T2D) and cardiovascular disease (CVD)[1-4]. Despite

the strong link between body weight and cardiometabolic health, the prevalence of cardiometabolic complications varies widely among individuals with obesity. Furthermore, a subset of individuals with obesity do not suffer from metabolic complications, rather they display a favorable lipid profile with no hypertension and high insulin sensitivity [5-9]. The physiological mechanisms that determine why some obese individuals are protected from metabolic complications, and why some normal weight individuals are at risk, are poorly understood. It has been speculated that pathways implicated in adipogenesis, adipose tissue expandability, fat distribution, ectopic fat accumulation, and responsiveness to endocrine secretions may, at least in part, explain why some obese individuals are protected and why some of normal weight are at risk [10-15]. Most of these insights have been obtained through experimental studies in animal models, while studies in humans are limited by sample size and lack of (non-invasive) methods to accurately assess activity in pathways presumed to be involved.

Identifying genetic loci that are associated with increased risk of obesity and have beneficial effects on cardiometabolic health, and vice versa, provides an alternative strategy to elucidate the biology that underlies individuals with obesity do not suffer from metabolic complications.

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

a. **Study Questions/Hypotheses**.
We aim to identify loci that increase obesity risk and, at the same time, have protective effects on cardiometabolic traits and vice versa, and build genetic risk scores (GRS) for those loci. With this proposal, we are requesting replication of associations between GRS and adiposity and cardiometabolic traits discovered in UK Biobank in the PAGE ARIC study. Because the GRS were built using European ancestry population, we will only use the baseline ARIC European ancestry participants.

b. **Outcomes, Covariates, OMICs Data Considered.**

Outcome: BMI, waist circumference, hip circumference, waist-to-hip ratio, body fat percentage, HDL-C, triglyceride, total cholesterol, systolic blood pressure, diastolic blood pressure, anti-hypertensive medication, lipids lowering medication, glucose.

Covariates: age, sex, and top 10 principal components

Genomic data will be utilized in the construction of the GRS.

c. **Analytical Approach**
Additive genetic risk scores will be constructed for body fat percentage loci (647 lead SNPs) and clusters of loci that uncouple excess adiposity from its comorbidities (266 lead SNPs). List of variants are based on discovery analyses in the UK Biobank. Linear regression analyses will be performed to test the GRSs' associations with anthropometric and cardiometabolic traits. In addition, we will compare the difference between individuals in the top decile of BFP GRS and those in the top decile of GRS that that uncouple excess adiposity from its comorbidities.

d. **Anticipated date of draft manuscript to P&P: ___05/2023____**

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

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

**IV. SOURCE OF DATA TO BE USED** (**Check all that apply)**

| Study Name | Included |
|---|---|
| ARIC | Y |
| HCHS/SOL | N- no European ancestry data available |
| CCHC | N- no European ancestry data available |
| MEC | N- no blood pressure data available |
| BioME | Y |
| WHI | Possibly |
| CARDIA | Possibly |
| MESA | N |

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

**V. REFERENCES**


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* We suggest inclusion of PAGE coauthors from all participating studies.