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| **eMERGE Network: Proposal for Analysis**  Project/Manuscript Concept Sheet | |
| **Reference Number** |  |
| **Submission Date** | 7/28/2017 |
| **Project Title** | Mendelian Randomization to Identify Phenotypes and Procedures Associated with BMI and Obesity |
| **Tentative Lead Investigator** *(first author)* | Jamie Robinson |
| **Tentative Senior Author**  *(last author)* | Josh Denny |
| **All Other Authors** | Dan Roden, Lisa Bastarache, Robert Carroll, Wei-Qi Wei |
| **Sites Involved** | All adult sites |
| **Background / Significance** | Over two-thirds of the adult population in the United States is overweight or obese. The prevalence of obesity has doubled in over 70 countries in the last 3 decades, with the burden of obesity now spanning the globe. Obesity, defined as having a body-mass index (BMI) of 30.0 mg/kg2 or greater, continues to increase in prevalence worldwide. Analyses of prospective large-scale studies have shown that BMI both below (underweight BMI <18.5 mg/kg2) and above (overweight BMI > 25.0 mg/kg2) the World Health Organization-defined normal range are associated with comorbidities and increased overall mortality, spanning continents. Some of the diseases with the strongest association to obesity include cardiovascular disease, diabetes mellitus, several cancers, and musculoskeletal disease. A limitation of previous studies is that they were performed to analyze for specific outcomes, potentially missing the overall disease burden associated with obesity. This has resulted in a lack of knowledge on the full extent to which extremes of BMI are associated with comorbidities. The wide deployment and use of electronic health records (EHRs) provides a method to use comprehensive, structured data containing rich phenotypic information in longitudinal records. Prior studies have demonstrated not only the feasibility, but also the success, of using phenome-wide association studies (PheWAS) with hypothesis-free methods to gain insights into associations and patterns of disease. However, despite the success of PheWAS, to date these studies have focused primarily on diagnoses and limited laboratory data. |
| **Outline of Project** | Our goal is to use the eMERGE cohort to validate a ProcedureWAS approach (procedure-wide association study) with the use of aggregated Current Procedural Terminology (CPT) codes to find patterns of association with extremes of BMI. We aimed to demonstrate the utility of ProcedureWAS to complement current PheWAS methods in evaluating phenotypic and genetic associations with underweight and obesity. We also aim to use Mendelian Randomization (MR) to validate the associations discovered with PheWAS and ProcedureWAS. The MR will be built using a weighted genetic risk score for obesity derived from Locke et al. with 97 SNPs associated with obesity.1  1Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518(7538):197-206. |
| **Desired Variables**  *(essential for analysis*  *indicated by* ***\*****)* | \*Current age, race/ethnicity, gender  \*All recorded inpatient and outpatient BMIs for each patient  \*All inpatient and outpatient ICD9 and ICD10 codes  \*All inpatient and outpatient CPT codes  \*Genetic results |
| **Desired Data** | E1-3 imputed GWAS cohorts |
| **Planned Statistical Analyses** | Phenome-wide association study of BMI against PheWAS codes  Phenome-wide association study of MR for obesity against PheWAS codes  Procedure-wide association study of BMI against ProcedureWAS groupings  Procedure-wide association study of MR for obesity against ProcedureWAS groupings |
| **Ethical Considerations** | None |
| **Target Journal** | TBD - JAMA |
| **Milestones\*\*** | 9/1/17: study approval  10/1/17: delivery of data  12/1/17: first draft of paper  1/1/18: submission of manuscript |

***\*\**** *This section should include the timeline for completion of project, including: approval, project duration, first and second draft of the paper and submission.*