Longitudinal Proteomics of Body Mass Index and Waist Hip Ratio

Katherine Xing, Jayna Nicholas, Daeeun Kim, Madeline Gillman, Laura Raffield

Cardiometabolic diseases, such as obesity and type 2 diabetes, are a leading cause of death world-wide, yet few treatment options exist. Longitudinal profiling of plasma proteins using high-throughput proteomic platforms, such as Olink 3k, may help identify metabolic alterations associated with these conditions. Here, we used body mass index (BMI) and waist hip ratio (WHR) as quantitative predictors of cardiometabolic disease risk. Our analysis included 2,946 proteins from 2,311 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) from visits 1, 5, and 6. We used linear regression with adjustment for age, sex, and time to follow-up to identify 850 and 112 proteins (p-value<0.05/2941 proteins tested) significantly associated with cross-sectional BMI and WHR adjusted for BMI (WHRadjBMI), as well as 103 and 165 proteins nominally significantly associated with longitudinal BMI and WHRadjBMI trajectories across the three visits. We further identified 112 and 0 protein trajectories associated with visit 1 measures of BMI and WHR. Pathway analysis highlighted several pathways significantly altered across multiple phenotypes, with, for instance, alterations in neutrophil degranulation and regulation of insulin-like growth factor pathways significantly enriched across both cross-sectional and longitudinal BMI models. We further identified phenotype-specific pathway alterations, with 29 pathways altered in longitudinal BMI and/or WHR models but not cross-sectional including cardiac hypertrophy signaling, as well as several other immune- and inflammatory-regulatory pathways. Our findings validate existing protein associations with obesity and cardiometabolic diseases, and reveal novel longitudinal protein associations with BMI and WHR.