Longitudinal Proteomics of Body Mass Index and Waist Hip Ratio

Katherine Xing[1], Jayna Nicholas[2], Daeeun Kim[2], Madeline Gillman[2], Laura Raffield[2]

[1]Department of Biostatistics, University of North Carolina at Chapel Hill, [2]Department of Genetics, University of North Carolina at Chapel Hill School of Medicine

SCHOOL OF MEDICINE DEPARTMENT OF GENETICS

Introduction

- Body Mass Index (BMI) and Waist Hip Ratio adjusted for BMI (WHRadjBMI) are useful, inexpensive, and easily obtained anthropometric measures for predicting cardiometabolic disease risk.
- Characterizing the relationship between BMI/WHR and change in circulating protein levels over time can yield insight on mechanisms of metabolic change and cardiometabolic disease risk.

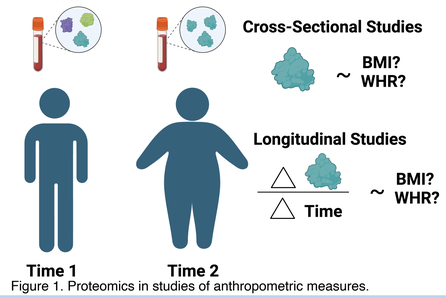

Figure 1. Proteomics in studies of anthropometric measures.

Objective:
Use longitudinal data from the MESA study to assess the relationship between the changing protein levels and anthropometric measures.

Methods

Study population: The Multi-Ethnic Study of Atherosclerosis (MESA) cohort consists of 6000+ men and women from 6 diverse communities in the USA. In the current study, we measured 2,946 proteins using Olink 3k proteomics in plasma samples from 2,311 MESA participants.

- Proteomics data was cleaned and inverse normalized. All data analysis was done in RStudio.
- We built linear regression models for cross-sectional and longitudinal analysis across visits 1, 5, and 6 adjusted for age, sex, and time to follow up (mean = 15.8 years, sd = 0.78). Bonferroni correction was applied to p-values.
- Further analysis of significant proteins included pathway overexpression analysis in Ingenuity Pathway Analysis (IPA).

Table 1. Demographic summary of MESA participants at Initial Visit 1

Variable[1]		MESA (n=2311)
Age (years)		58.7 (8.94)
Sex, n (%)	Male	1112 (62.2)
	Female	1199 (37.8)
Race/Ethnicity, n (%)	White	972 (42.1)
	Chinese	328 (10.2)
	Black	561(24.3)
	Hispanic/Latino	450 (19.5)
WHR		0.92 (0.09)
BMI (kg/m^2)		28.0 (5.36)

[1]Data are mean (SD) unless otherwise stated

Association Results

Cross-Sectional model:
Phenotype$_{visit\ 1}$ ~ protein level$_{visit\ 1}$, χ + age + sex + follow-up time

Longitudinal protein model:
Phenotype$_{visit\ 6}$ ~ Δprotein level, χ + age + sex + follow-up time

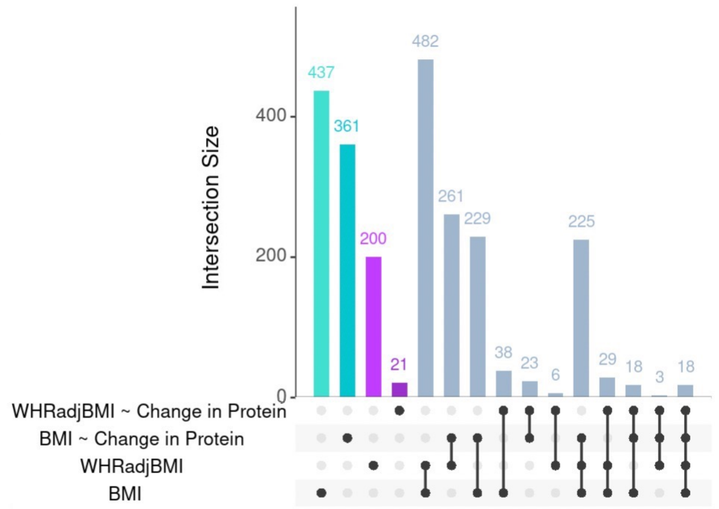

Figure 2. Upset plot showing proteins significantly associated at nominal p < 0.05 with longitudinal proteomics measures and cross-sectional BMI and WHR adj BMI, as well as intersections between sets.

Table 2. Number of Significant Associations

	Cross-Sectional Protein Measure	Longitudinal Protein Measure
BMI	1476 (850)	1138 (112)
WHR adj. BMI	1224 (252)	156 (0)

**Data are nominal p < 0.05 (Bonferroni-adj p < 0.05) unless otherwise stated. 2,946 proteins tested.*

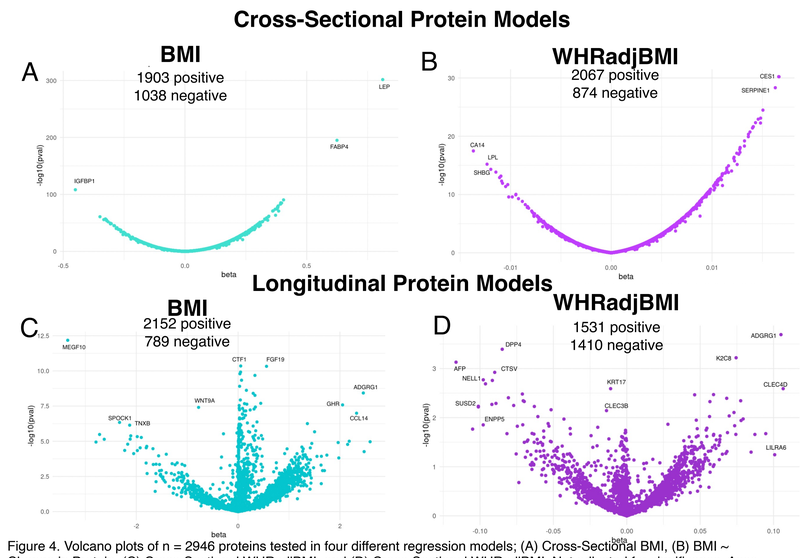

Figure 4. Volcano plots of n = 2946 proteins tested in four different regression models; (A) Cross-Sectional BMI, (B) BMI ~ Change in Protein, (C) Cross-Sectional WHRadjBMI, and (D) Cross-Sectional WHRadjBMI. Not adjusted for significance. Axes are not on the same scale.

Pathway Analysis

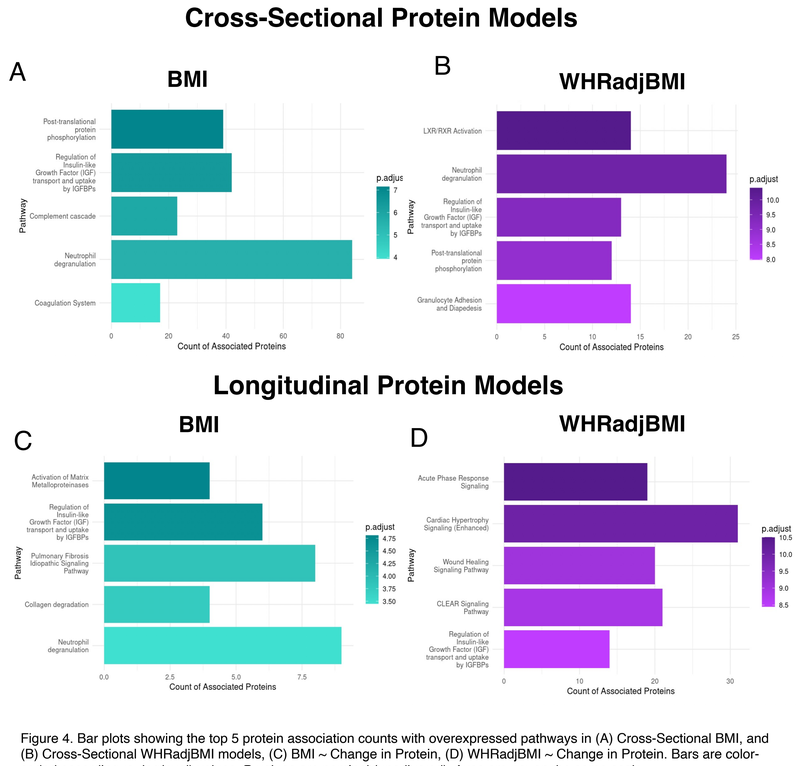

Figure 4. Bar plots showing the top 5 protein association counts with overexpressed pathways in (A) Cross-Sectional BMI, and (B) Cross-Sectional WHRadjBMI models, (C) BMI ~ Change in Protein, (D) WHRadjBMI ~ Change in Protein. Bars are color-coded according to -log(pval) values. P-values are nominal (unadjusted). Axes are not on the same scale.

Conclusions

- We identified cross-sectional and longitudinal protein associations for BMI and WHRadjBMI, with shared and distinct proteins significant across models.
- Pathway analysis generally reveals alterations in inflammation and immune-related processes across models, although the most significantly enriched pathways differed between models.

Future Directions

- Adjust for baseline protein measure in protein trajectory model.
- Determine which significant proteins have previously been associated with adverse outcomes in literature.
- Replicate and validate results in Jackson Heart Study (JHS) cohort.

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