Machine learning predicts novel lipid markers of the metabolic syndrome in black and white women in the USA

Raghav Jain1, Chris Coe2, Carol Ryff2, and Judith Simcox2
1Department of Biochemistry, University of Wisconsin-Madison, Madison, WI
2Department of Psychology, University of Wisconsin-Madison, Madison, WI

Abstract
The metabolic syndrome (MetS) leads to increased risk of diseases including type 2 diabetes and cardiovascular disease (CVD). When comparing men and women with MetS, women are at an over 2-fold higher risk for developing CVD than men. In white and black women, MetS rates are similar (~20%) yet black women have higher rates of type 2 diabetes and CVD mortality. Hence, women, especially black women, are disproportionately affected by MetS and related diseases. Current MetS risk factors are a poor predictor for CVD in women than men. To improve detection of MetS in women, we analyzed data from the Midlife in the United States (MIDUS), a national study of middle-aged Americans, to identify novel lipid biomarkers of MetS. All clinical data was collected according to MIDUS guidelines, over 800 lipids were quantified via differential mobility spectrometry refinement of liquid chromatography mass spectrometry by Metabolon Inc., and data was analyzed in R. MetS prevalence was 40% in black and 20% in white women. Black women without diagnosed MetS had a significantly higher waist circumference and blood pressure than white women without MetS. There was a broad increase in circulating lipids during MetS regardless of race. Using machine learning-based regressions, we identified 3 lipids in black and 32 in white women predictive of MetS. Future studies will verify these findings with independent data from the Survey of the Health of Wisconsin (SHOW) cohort.

Background
• The risk of metabolic diseases is increased several fold in women suffering from MetS.
• Unlike men, women - particularly black women - are at a higher risk of MetS and related diseases as they age.
• Clinical screens rely on a set of five criteria to diagnose MetS. Expansion of this definition is critical to capturing the true prevalence of MetS, which is likely underestimated in women and especially in black women.
• Lipids play diverse roles in physiology including signaling, and changes in circulating lipids during MetS are not well understood in women or with respect to ethnicity.
• The MIDUS (Midlife in the United States) study has a diverse subject pool with clinical and lipidomic data available to identify novel biomarkers of MetS in black and white women.

Objective
To identify novel lipid biomarkers indicative of the metabolic syndrome in black and white women.

Methods
MIDUS
Clinical measurements (n=872)
• Age
• Waist circumference
• Cholesterol
• Triglycerides
• Blood pressure
• Glucose
• Cytokines
Lipidomics by Metabolon Inc.
• LC/MS-MS
• 800 lipid species identified

Results
Figure 1. Age distribution of participants (A) and comparison of the prevalence of MetS risk factors (B) in each race.

Figure 2. Comparison of waist circumference (A), systolic blood pressure (B) and IL-6 (C) between participants with or without MetS. P-value is from Welch unpaired t-test of inter-race difference, and asterisk (*) denotes significant (p<0.05) difference for inter-race comparison of MetS group.

Figure 3. Volcano plot of individual lipid species for black (A) and white women (B) showing mean fold change = met/s no met of lipids and a Venn diagram (C) of lipids significantly upregulated in the metabolic syndrome. P-values adjusted using Benjamini-Hochberg (BH) false discovery method.

Conclusions
• The most prevalent MetS risk factor is obesity, defined as a waist circumference greater than 88 cm, regardless of race.
• Black women not diagnosed with MetS have a significantly higher waist circumference, blood pressure, and circulating IL-6 than white women without MetS. These differences disappear when comparing black and white women with MetS.
• Broad lipid changes occur during MetS with almost 500 individual lipids increased in circulation, regardless of race.
• There is a greater diversity of lipid types significantly higher during MetS in black than white women, though unique lipid signatures exist in both populations.
• Using a lasso regression with a ten-fold cross validation loss, we identified 9 lipids in black women and 33 lipids in white women predictive of, and therefore candidate novel biomarkers for MetS.

Future Directions
• Improve regression model through inclusion of alternate markers of inflammation such as cytokines.
• Test model stability on independent Survey of the Health of Wisconsin (SHOW) population study cohort.
• Propose novel biomarkers of the metabolic syndrome for black and white women.

References

Funding
The MIDUS investigation is funded by the NIH National Center for Advancing Translational Sciences (UL1 TR000445). The investigators are funded by grants from the NIH National Institute on Aging (U01 AG064418), the National Cancer Institute (R01 CA188448), the National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK113638), and the National Institute of Mental Health (R01 MH111305).