

Metabolomic Scores Mediate Associations between Dietary Patterns and Insulin Homeostasis in The Microbiome and Insulin Longitudinal Evaluation Study (MILES)

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Objectives: To examine whether the metabolomic correlates of three diet patterns mediate the observed associations between diet and insulin homeostasis.

Methods: Data were included from 295 adults without diabetes (mean age 59.3 y ± 9.00; 63.46% non-Hispanic White and 36.54% African American) participating in MILES. An oral glucose tolerance test was used to measure fasting glucose, insulin, and C-peptide, as well as insulin secretion, insulin sensitivity, and disposition index. Self-reported dietary intake was used to create three diet scores: a Mediterranean-style diet, the Dietary Approaches to Stop Hypertension, and the USDA's Healthy Eating Index-2015. A global metabolomics panel of 1525 metabolites was measured using LC/MS global metabolomic profiling using validated reference standards in

fasting plasma. Main effects models that controlled for age, sex, ethnicity, socioeconomic status, smoking status, physical activity, and daily energy intake examined associations between the three diet scores, metabolite information and insulin homeostasis. 115 individual diet-metabolite associations across 76 metabolites reached significance after correcting for the effective number of independent tests ($P < 3.4 * 10^{-05}$), informing the creation of diet-specific unweighted metabolite sum scores (MSS). Where warranted, mediation was assessed using the 'mediate' package in R.

Results: Insulin secretion did not show a significant association with any diet nor any MSS (all $P > 0.01$). All other insulin homeostasis traits were strongly associated with all diet-specific MSSs ($P < 0.001$ - $P < 2.5 * 10^{-09}$). MSSs significantly mediated any associations between insulin homeostasis and diet scores ($P < 0.04$ - $P < 2.0 * 10^{-16}$) with no evidence of direct effects of diet on insulin homeostasis in mediation models (all $P > 0.05$).

Conclusions: These data suggest that the metabolomic correlates of three diet patterns, when aggregated, mark insulin homeostasis and mediate the associations of diet with insulin traits. Such metabolomic diet scores may hold promise for revealing the underlying pathways between a healthy diet and glycemic control.

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