A Multi-Omics Study of Individual Responses to Long-Term Mediterranean Diet Interventions in the DIRECT-PLUS Trial

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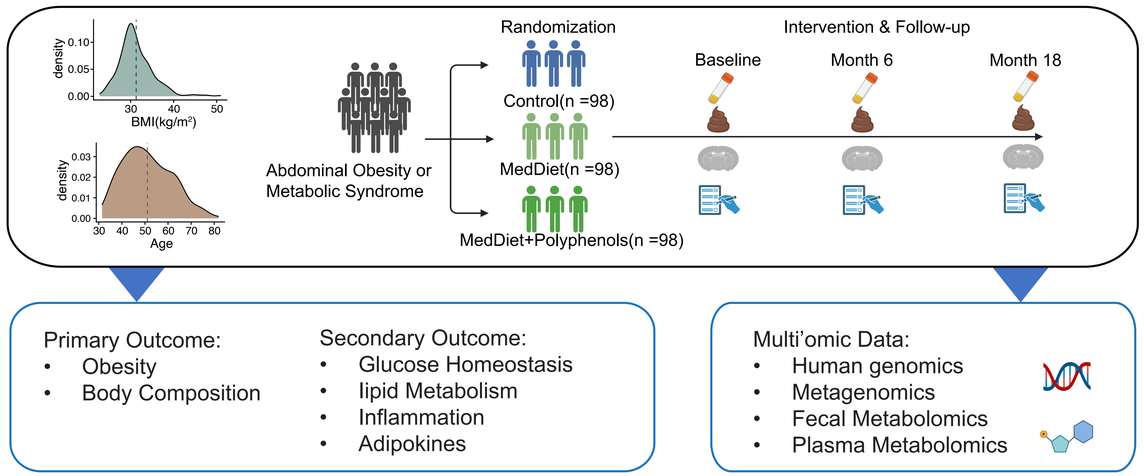
ABSTRACT

The benefits of the Mediterranean diet (MedDiet) for reducing metabolic risk vary significantly by individuals' gut microbial profiles. However, few studies have applied multi-omics to elucidate the personalized response and MedDiet's impact on the gut microbiome within a long-term randomized controlled trial. Here, we conducted a multi-omics study, combining host genetics, metagenomics, and fecal and plasma metabolomics, in the DIRECT-PLUS trial of MedDiet Interventions. We revealed that baseline 'omic profiles explain substantial proportions of variation in individuals' response, quantified as changes in body adiposity and plasma biomarkers of metabolic risk and inflammation, following dietary interventions. A random forest model that integrates multi-omics exhibits exceptional performance in distinguishing those who respond to MedDiet from non-responders. Our study lays the groundwork for precision nutrition and discovered novel biological mechanisms for more effective prevention of metabolic disease.

Establishment of a Multi-Omics Study in a Successful Randomized Controlled MedDiet Trial



Primary Outcome:
- Obesity
- Body Composition

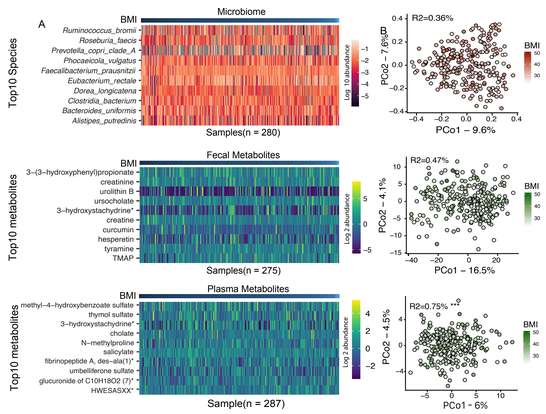
Secondary Outcome:
- Glucose Homeostasis
- Iipid Metabolism
- Inflammation
- Adipokines

Multi'omic Data:
- Human genomics
- Metagenomics
- Fecal Metabolomics
- Plasma Metabolomics

- **Study Design:** 18-month randomized controlled trial of 294 men and women (women: 11.9%), aged 31-82 years (mean:51 years) in Israel
- **Interventions:** Group 1: Healthy dietary guidelines
  Group 2: MedDiet + Walnuts
  Group 3: MedDiet + Walnuts + polyphenol-rich foods
- **Host Genetics:** Genotyping using Infinium Global Screening Array
- **Microbiome:** Shotgun metagenomic sequencing; Longitudinal sampling at baseline, 6 months, 18 months
- **Fecal and Plasma Metabolomics:** UPLC-MS/MS; Longitudinal sampling at baseline, 6 months, 18 months

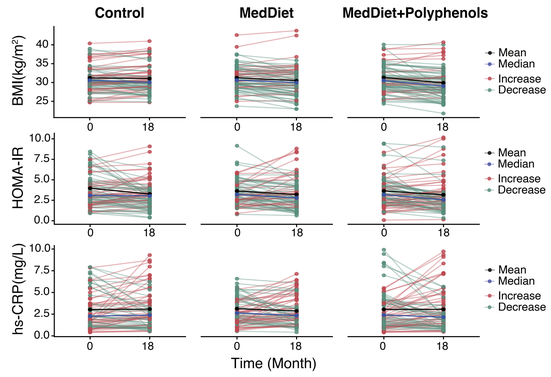
RESULTS

Overview of metagenomic, fecal and plasma metabolomic data

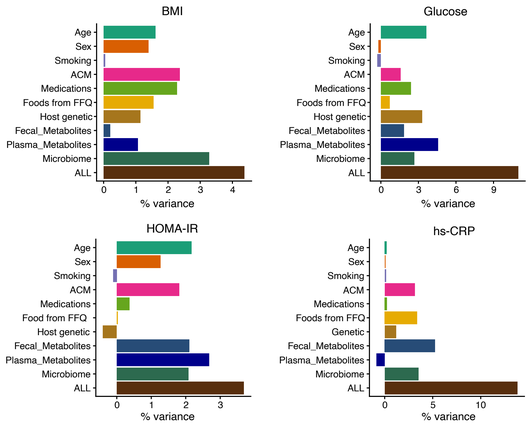


- Plant polysaccharide degraders and butyrate producers are among the highly abundant gut microbes
- Most highly abundant fecal (5/10) or plasma (7/10) metabolites are xenobiotics
- Body mass index is significantly associated with overall plasma metabolome but not associated with gut microbiome and fecal metabolome

Substantial variability in individuals' responses to dietary interventions across multiple metabolic markers



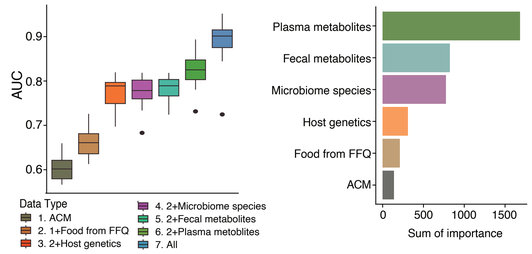
Host genetics and baseline profiles of the gut microbiome, fecal and plasma metabolomes explained a substantial proportion of the personalized response to diet.



ACM: Anthropometric & Clinical Measures (Weight, BMI, WC, Pulse, DBP, SBP)

- Baseline fecal metabolites demonstrate the best performance in explaining individual responses to diet in glucose homeostasis, while the gut microbiome exhibits the best performance in explaining primary outcomes (adiposity)

Integration of multi-omics significantly improves the prediction of personalized responsiveness to diet



- The boxplot shows the ability of different types of baseline data to predict responders vs. non-responders to dietary intervention
- Responsiveness is jointly defined by post-intervention changes in BMI, HOMA-IR, LDL/HDL, and hs-CRP
- The bar plot shows the importance of different data types in the final integrated model (7), with plasma metabolites contributing the most to the prediction

CONCLUSIONS

- Our study highlights substantial inter-individual variations in response to long-term diet interventions, with multi-omics, particularly metagenomics and metabolomics, offering insights on explaining personalized responsiveness.
- Our study lays the groundwork for precision nutrition for more effective prevention of metabolic disease.

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