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## Personal metabolic responses to food predicted using multi-omics machine learning in 1,100 twins and singletons: The PREDICT I Study.

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### Abstract

Glycemic, insulinemic and lipemic postprandial responses are multi-factorial and contribute to diabetes, obesity and CVD. The aim of the PREDICT I study is to assess the genetic, metabolic, metagenomic, and meal-context contribution to postprandial responses, integrating the metabolic burden and gut microbiome to predict individual responses to food using a machine learning algorithm.

A multi-center postprandial study of 1,000 individuals from the UK (unrelated, identical and non-identical twins) and 100 unrelated individuals from the US, assessed postprandial (0–6h) metabolic responses to sequential mixed-nutrient dietary challenges (50 g fat and 85 g carbohydrate at 0 h; 22 g fat and 71 g carbohydrate at 4h) in a clinic setting. Glycemic responses to 5 duplicate isocaloric meals of different macronutrient content and self-selected meals (> 100,000), were tested at home using a continuous glucose monitor (CGM). Baseline factors included metabolomics, genomics, gut metagenomics and body composition. Genetic contributions to postprandial responses were determined by classical twin methods.

Inter-individual variability in postprandial responses (glucose, insulin and triacylglycerol (TG)) was high in the clinic setting: iAUC IQR (median) was (n = 644); glucose (0–2h) 1.97 (1.89) mmol/L.h, insulin (0–2h) 45.6 (67.7) mIU/L.h and TG (0–6h) 2.37 (2.42) mmol/L.h. The unadjusted genetic contribution for glucose, insulin and TG responses were 54%, 29% and 27% respectively. Within-individual concordance (ICC) in glucose responses (iAUC 0–2h) for at home duplicate isocaloric meals was moderate-to-high, depending on the test meal: ICC (95%CI) was; high carbohydrate 0.62 (0.58,0.66), (carbohydrate = 95g/76% energy; n = 764), average lunch 0.57 (0.53, 0.62) (carbohydrate = 68g/54% energy; n = 763), OGTT 0.65 (0.61,0.70) (carbohydrate = 75 g; n = 754), high fat 0.35 (0.28, 0.41) (fat = 40g/71% energy; n = 576) and high protein 0.56, (0.48,0.62) (protein = 41g/32% energy; n = 364). An interim machine learning algorithm predicted 46% of the variation in glycemic responses based on meal content, meal context and participant's baseline characteristics, excluding genetic and microbiome features. Only 29% of variation could be explained by the macronutrient content of the meal.

This is the most comprehensive postprandial study performed to date. The large and modifiable variation in metabolic responses to identical meals in healthy people explains why 'one size fits all' nutritional guidelines are problematic. The genetic component to these responses is moderate, leaving the majority of the variation potentially modifiable. By collecting information on glucose responses to > 100,000 meals, alongside environmental, genetic and microbiome variables, we will have excellent power to use machine learning to optimise and predict individual responses to foods.

### Conflict of Interest

The study is part funded by Zoe Ltd.