The relationships between body mass index and metabolite response to a standardized meal challenge.

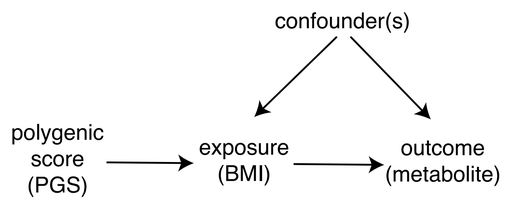
David A. Hughes[1], Ruifang Li-Gao[2], Caroline J. Bull[1], Laura J. Corbin[1], Renée de Mutsert[2], Frits R. Rosendaal[2], Dennis O. Mook-Kanamori[2], Ko Willems van Dijk[2], Nicholas J. Timpson[1].

[1]MRC Integrative Epidemiology Unit, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.
[2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands.

Introduction

The response, or change, of metabolite abundance to a meal is an emergent trait in studies of disease. Body mass index (BMI) is a recognized risk factor for numerous health outcomes and may influence metabolite response to feeding. Here we use the **Netherlands Epidemiology of Obesity (NEO)** study to examine associations between BMI and metabolic response to standardized liquid meals and extend this by using Mendelian randomization to estimate causal effects.

Figure 1
The directed acyclic graph (DAG) of Mendelian randomization (MR) illustrate the assumptions of the methodology. Namely, the instrument or PGS here, is associated with the exposure, but independent of the outcome and of variables that are confounded with the exposure and outcome.



PGS constructed with the 656 SNP associations reported by Yengo et al HMG 2018.

Methods

The NEO study conducted a standardized liquid meal challenge in 5700 participants and measured metabolome profiles using the Nightingale Health metabolomics platform. Observational and one-sample Mendelian randomization (MR) analysis (Fig1) were conducted, by linear modelling, to estimate the effect of BMI on metabolites in the fasting, postprandial, and response (or change in abundance) states.

Population Description

Population characteristics	complete NEO study population	high BMI oversampling sub-population	randomly sampled Leiderdrop sub-population
sample size (n)	5518	4112	1406
% female	51.58%	50.17%	55.69%
age (years)	55.9	55.95	56.13
BMI (kg/m^2)	**29.98** (95% CI: 21.4-41.35)	**31.26** (95% CI: 26.02-42.18)	**26.24** (95% CI: 19.94-37.20)
BMI-PGS	10.2 (95% CI: 9.64-10.78)	10.22 (95% CI: 9.67-10.8)	10.14 (95% CI: 9.56-10.71)
Variance in BMI explained by the BMI-PGS (%)	**4.34%**	**2.46%**	**4.27%**

Results

We observed 95 metabolites (53 fasting, 35 postprandial, 7 response) that are associated with BMI in MR analyses at a nominal P value threshold of 0.05, with all 95 directionally consistent with observational analyses. After correcting for multiple testing four metabolites have evidence of a BMI effect, …

Results Continued

… two of which are the branch chain amino acids (BCAA) ***isoleucine*** (beta=-0.00069, SE=0.00018 mmol/L change per unit increase in BMI (kg/m^2)) and ***leucine*** (beta=-0.00086, SE=0.00023) in the response state. These point estimates represent ~0.05 SD units of the fasting state BCAAs.

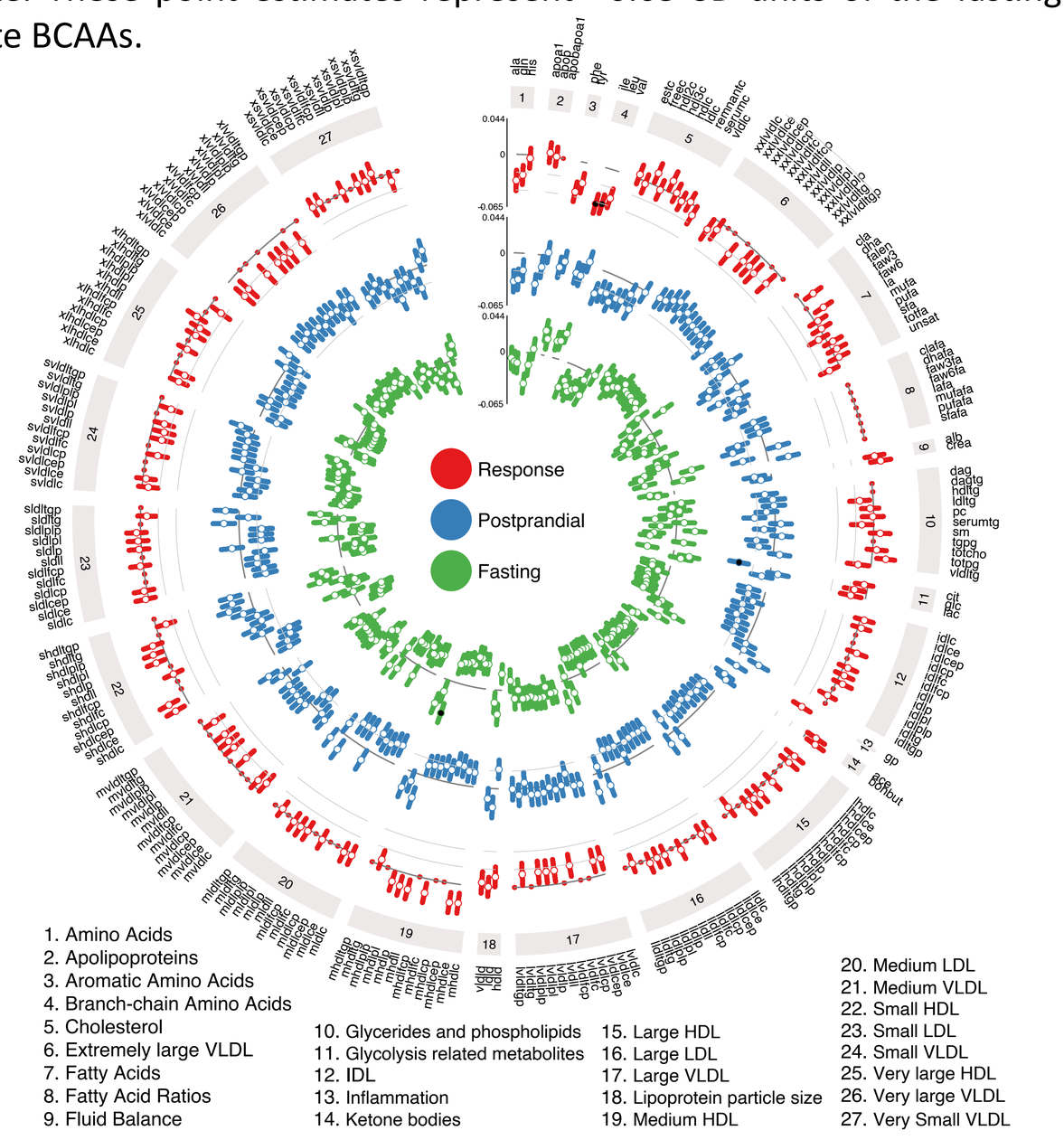
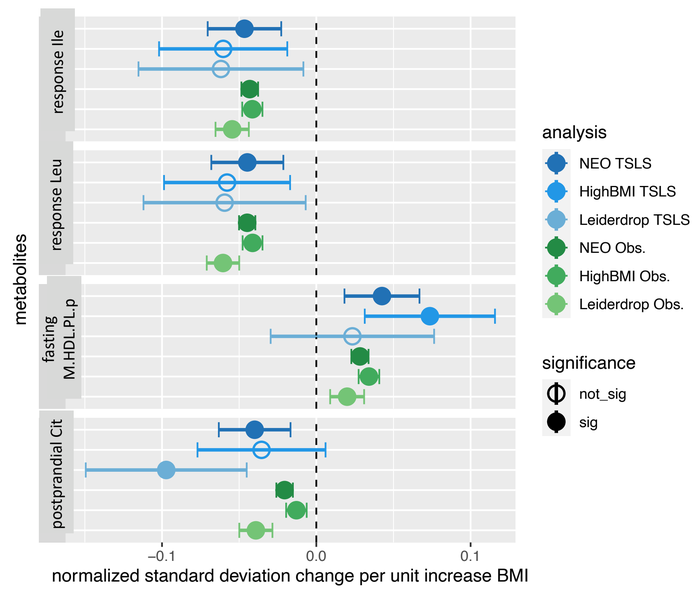


Figure 2
Circos plot of one-sample MR point estimates and standard errors (normalized standard deviation change per unit increase BMI). Estimates are presented for each metabolite in the response (red), postprandial (blue), and fasting (green) dietary state. Response traits are the product of orthogonal nonlinear least squares regression as many metabolites illustrated a plateauing effect that could not be accounted for in linear models. In addition, metabolite traits that are ratios were not evaluated as response traits and are indicated as small red dots under the zero line for reference purposes. Metabolites sub-classifications as provided by Nightingale Health are used to annotate metabolite groups. *Figure generated with EpiViz (https://github.com/mattlee821/EpiViz).*

Figure 3
Forest plot of observations that withstand multiple test correction (n = 40; p = 0.00125). All linear models included sample data, sex and age as covariates, and all metabolites were rank normal transformed prior to regression analyses. Observational (Obs.) results are presented in green while one-sample MR (TSLS) results are presented in blue. Results that surpass multiple test correction have a solid circle. Results for the entire NEO study and each of the two sub-populations are presented.



Conclusion

Our results suggest that BMI is broadly associated with metabolites totalling 415 or 69% of all tested metabolites, in the observational analyses, including 51 response metabolites. Further, our work suggests that the branch chain amino acids isoleucine and leucine are particularly likely to have feeding response abundance differences influenced by BMI that might mark life course risk exposures derived from regular feeding.

Ethics & consent:
All 6,671 NEO participants gave written informed consent and the Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the study design.

Acknowledgments:
We are grateful to all the participants of the Netherlands Epidemiology of Obesity (NEO) study. This work would be impossible without their participation.

Contact: (1) website https://teamtimpson.github.io; (2) email d.a.hughes@bristol.ac.uk

Funding:
1. Wellcome Trust Investigator (202802/Z/16/Z)
2. Avon Longitudinal Study of Parents and Children (MRC & WT 102215/2/13/2)
3. University of Bristol NIHR Biomedical Research Centre (BRC-1215-20011)
4. MRC Integrative Epidemiology Unit (MC_UU_12013/3)
5. CRUK Integrative Cancer Epidemiology Programme (C18281/A19169)
6. Netherlands Cardiovascular Research Initiative
7. Dutch Heart Foundation (CVON2014-02 ENERGISE)