



MRC Integrative
Epidemiology
Unit



University of
BRISTOL

Discovery science using high-throughput metabolomics in clinical settings

Dr Laura Corbin, Research Fellow

Integrative Epidemiology of Obesity Group, <https://teamtimpson.github.io/>

MRC Integrative Epidemiology Unit (IEU) at University of Bristol

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Overview

1. Research context
2. Research overview
3. Dietary intervention
4. Surgical intervention
5. Next steps

Integrative Epidemiology of Obesity

BMI -> Health Research Group



BMI -> Health Research Group

The screenshot shows a Zoom meeting grid with 15 participants in a 3x5 layout. The participants are: Lucy Goudswaard, David Hughes, Ahmed Elhakeem, Sam Neaves, Emma Hazelwood, Vanessa Tan, Andrei Constantinescu, Nicholas Timpson, Emma Vincent, Matthew Lee, Fergus Hamilton, Ana Goncalves Soares, Kaitlin Wade, Maddy Smith, and Caroline Bull. To the right of the grid is a sidebar containing: a title 'BMI -> HEALTH Research Group', two diagrams labeled WP1a and WP2 showing human figures with arrows, a graph labeled WP1b showing 'Meal (hrs)' on the x-axis and a green area under a curve, a diagram labeled WP2 showing a staircase and a wavy line, and logos for Wellcome, MRC Medical Research Council, University of BRISTOL, and NIHR Cancer Research UK.



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University of
BRISTOL

Redefining obesity

The Lancet Diabetes & Endocrinology Commission

Definition and diagnostic criteria of clinical obesity



Francesco Rubino, David E Cummings, Robert H Eckel, Ricardo V Cohen, John P H Wilding, Wendy A Brown, Fatima Cody Stanford, Rachel L Batterham, I Sadaf Farooqi, Nathalie J Farpour-Lambert, Carel W le Roux, Naveed Sattar, Louise A Baur, Katherine M Morrison, Anoop Misra, Takashi Kadowaki, Kwang Wei Tham, Priya Sumithran, W Timothy Garvey, John P Kirwan, José-Manuel Fernández-Real, Barbara E Corkey, Hermann Toplak, Alexander Kokkinos, Robert F Kushner, Francesco Branca, Jonathan Valabhji, Matthias Blüher, Stefan R Bornstein, Harvey J Grill, Eric Ravussin, Edward Gregg, Noor B Al Busaidi, Nasreen F Alfaris, Ebaa Al Ozairi, Lena M S Carlsson, Karine Clément, Jean-Pierre Després, John B Dixon, Gauden Galea, Lee M Kaplan, Blandine Laferrère, Martine Laville, Soo Lim, Jesús R Luna Fuentes, Vicki M Mooney, Joseph Nadglowski Jr, Agbo Urudinachi, Magdalena Olszanecka-Glinianowicz, An Pan, Francois Pattou, Philip R Schauer, Matthias H Tschöp, Maria T van der Merwe, Roberto Vettor, Geltrude Mingrone

“The Commission **defines obesity** as a condition characterised by **excess adiposity**, with or without abnormal distribution or function of adipose tissue ... We define **clinical obesity** as a **chronic, systemic illness** characterised by **alterations in the function of tissues, organs, the entire individual**, or a combination thereof, due to excess adiposity ... We define **preclinical obesity** as a state of excess adiposity with **preserved function** of other tissues and organs ...”

“**Weight-based bias and stigma are major obstacles** in efforts to effectively prevent and treat obesity; health-care professionals and policy makers should receive proper training to address this important issue of obesity.”

Overweight and obesity management

NICE guideline | NG246 | Published: 14 January 2025

“Ensure that all ... **communications** with people living with overweight and obesity use **non-stigmatising language and images** ...

Use **BMI as a practical measure** of overweight and obesity ... **Interpret it with caution** because it is not a direct measure of central adiposity ...

Classify the degree of central adiposity based on waist-to-height ratio ...

OPEN ACCESS

SPECIALIST REVIEW

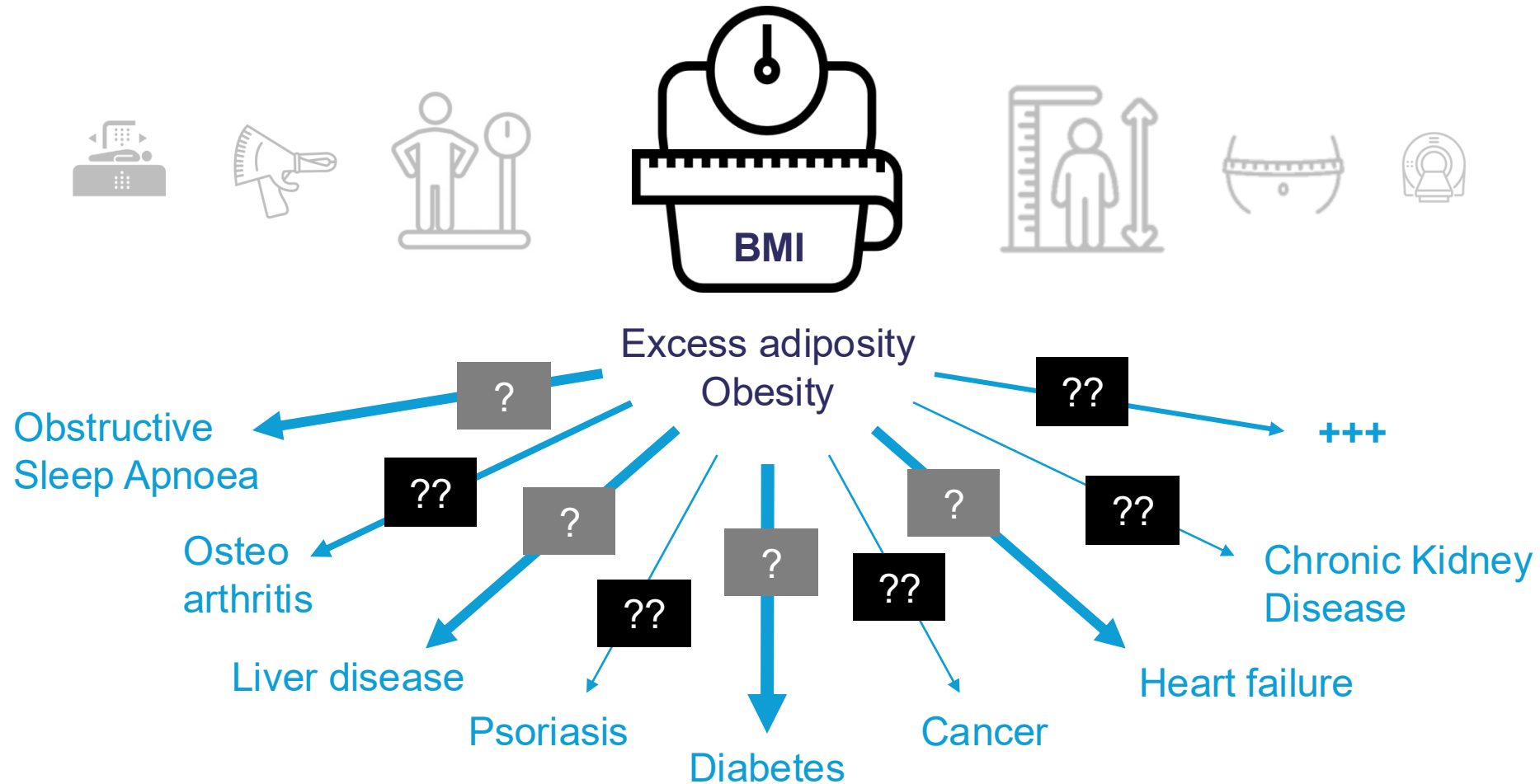
bmjmedicine



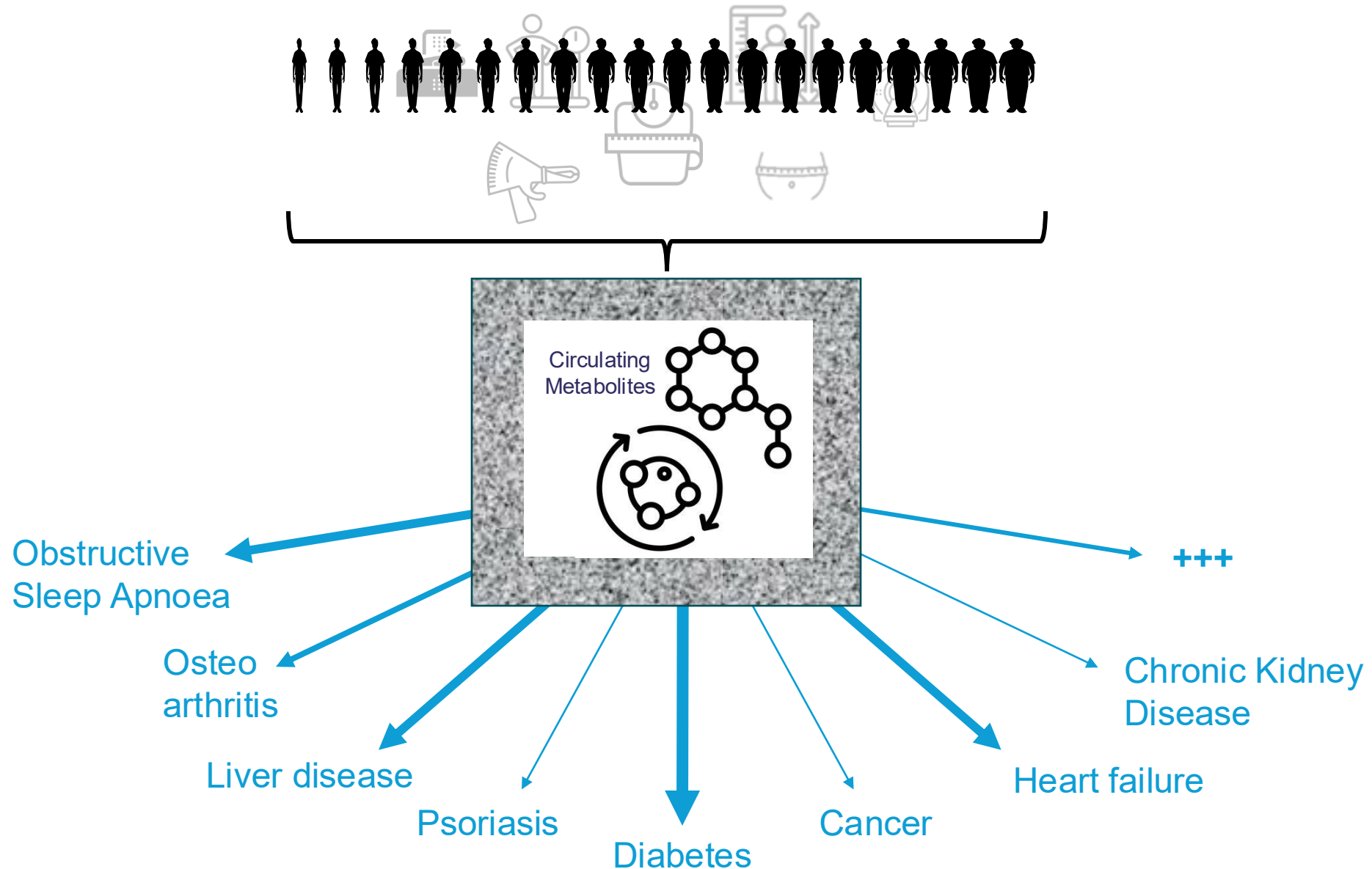
New insights into understanding obesity: from measures to mechanisms

Nicholas J Timpson,^{1,2} Kaitlin H Wade,^{1,2} Madeleine L Smith,^{1,2} Lucy J Goudswaard,^{1,2} Naveed Sattar,³ Dimitri J Pournaras,⁴ Laura J Corbin ^{1,2}

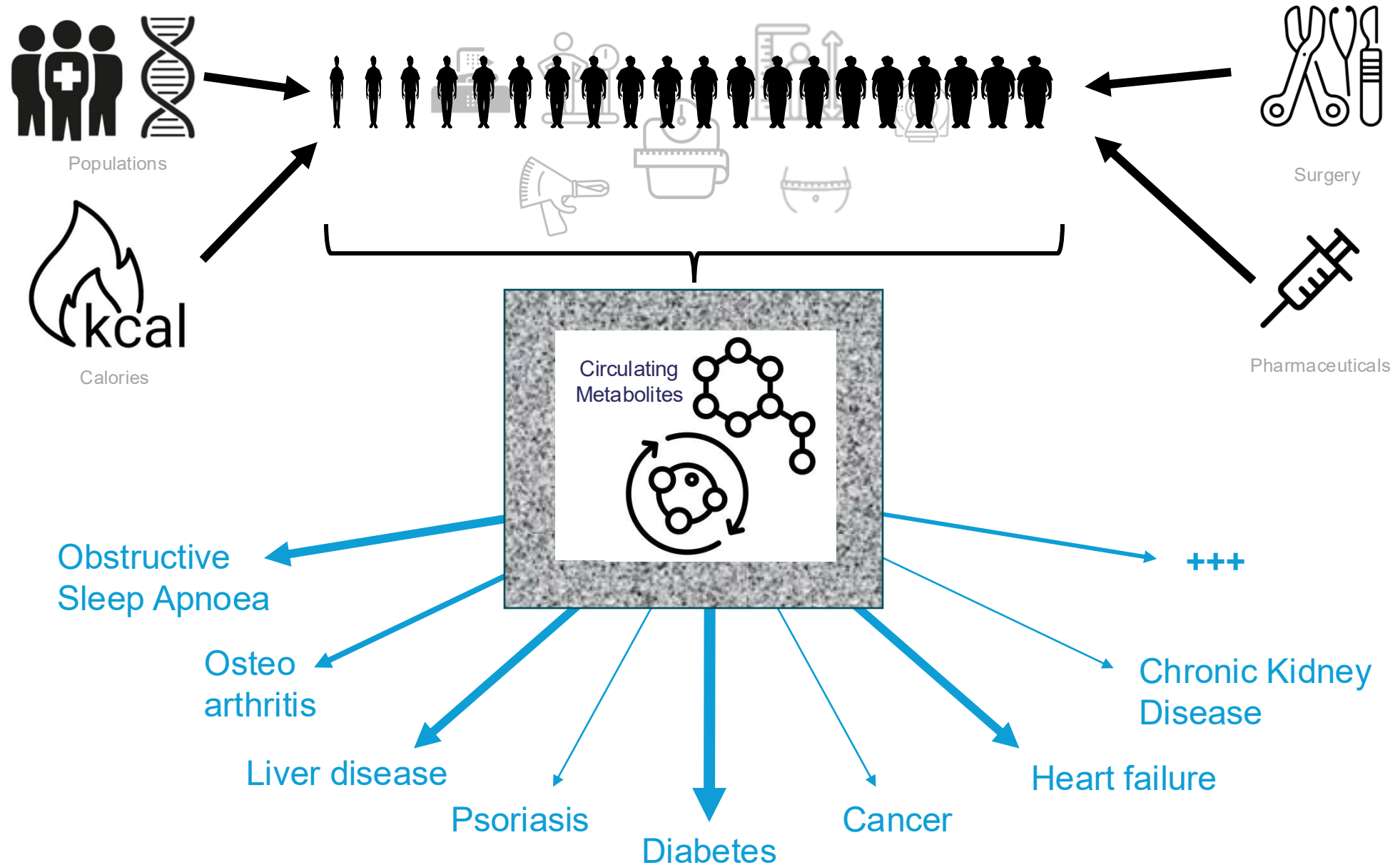
Why and how is body mass index (BMI) associated with increased morbidity and mortality?



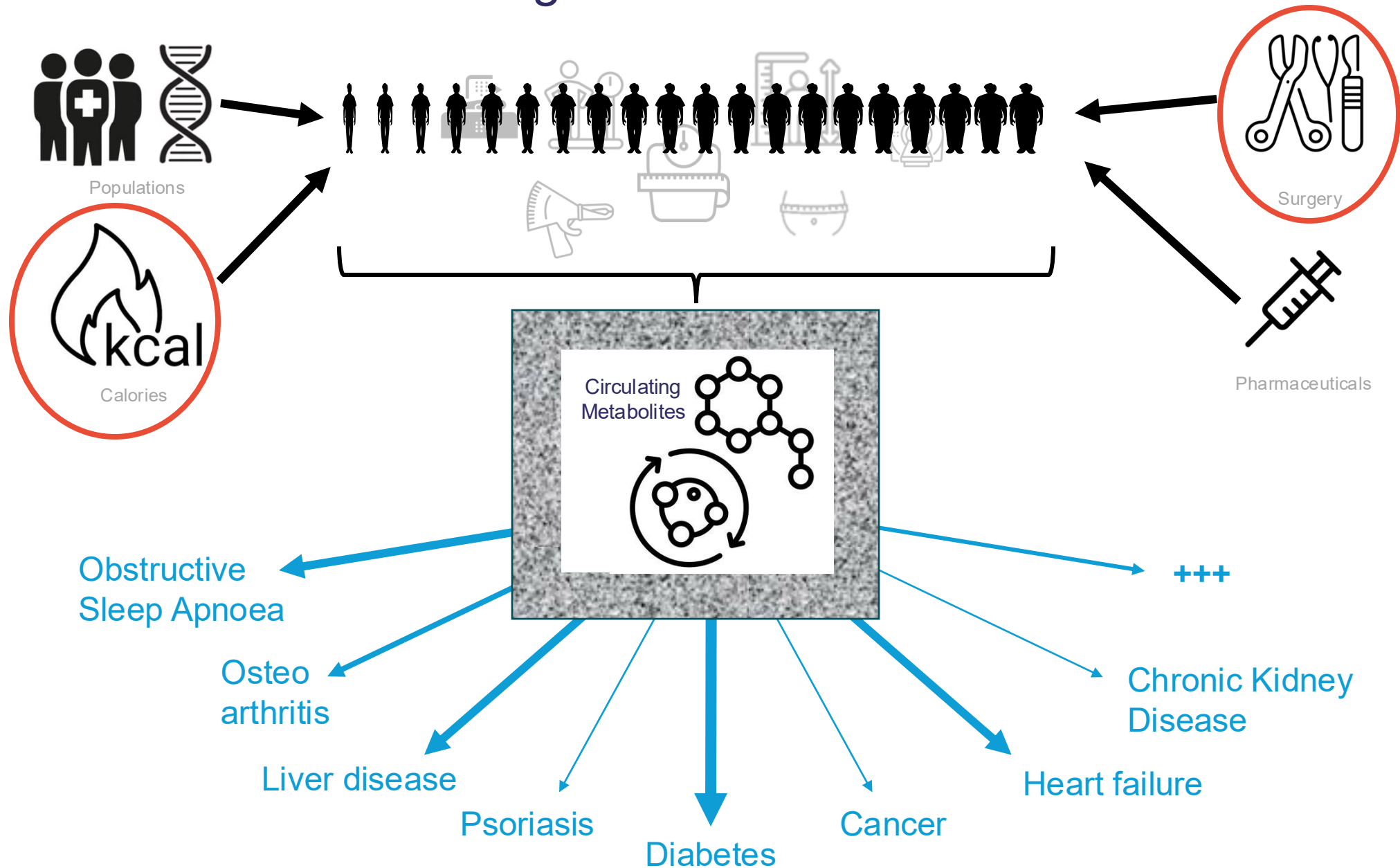
High-throughput metabolomics - a molecular read out of adiposity



Contrasting sources of BMI variation



Contrasting sources of BMI variation



The Diabetes Remission Clinical Trial (DiRECT)



Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Michael EJ Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor**

Research

Michael Lean, Naomi Brosnahan, Philip McLoone, Louise McCombie, Anna Bell Higgs, Hazel Ross, Mhairi Mackenzie, Eleanor Grieve, Nick Finer, John Reckless, David Haslam, Billy Sloan and David Morrison

Feasibility and indicative results from a 12-month low-energy liquid diet treatment and maintenance programme for severe obesity

- 49 primary care practices in Scotland and Tyneside
- Randomized to deliver either **Counterweight Plus** (intervention) or **standard care** (control)
- **298 patients** with type 2 diabetes (149 per arm)
- Intervention:
 1. Total diet replacement phase – 12 weeks (up to 20 weeks)
 2. Structured food re-introduction phase – 2-8 weeks
 3. Long-term weight loss maintenance (monthly visits) – until 2 years

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BASELINE SAMPLING – metabolomics (NMR & MS)

1. Total diet replacement phase – 12 weeks (up to 20 weeks)
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12-MONTH SAMPLING – metabolomics (NMR & MS)

Weight loss:
adjusted
difference of
-8.8 kg

3. Dietary intervention

A pre-analytical pipeline: *metaboprep*



Nightingale

- 574 samples from 306 individuals
- 227 NMR-derived molecules
- 1276 MS-derived metabolites

Bioinformatics, 38(7), 2022, 1980–1987
<https://doi.org/10.1093/bioinformatics/btac059>
Advance Access Publication Date: 4 February 2022
Original Paper

OXFORD

Systems biology

metaboprep: an R package for preanalysis data description and processing

David A. Hughes^{1,2,*}, Kurt Taylor^{1,2}, Nancy McBride^{1,2,3}, Matthew A. Lee^{1,2},
Dan Mason⁴, Deborah A. Lawlor^{1,2,3}, Nicholas J. Timpson^{1,2} and Laura J. Corbin^{1,2,*}

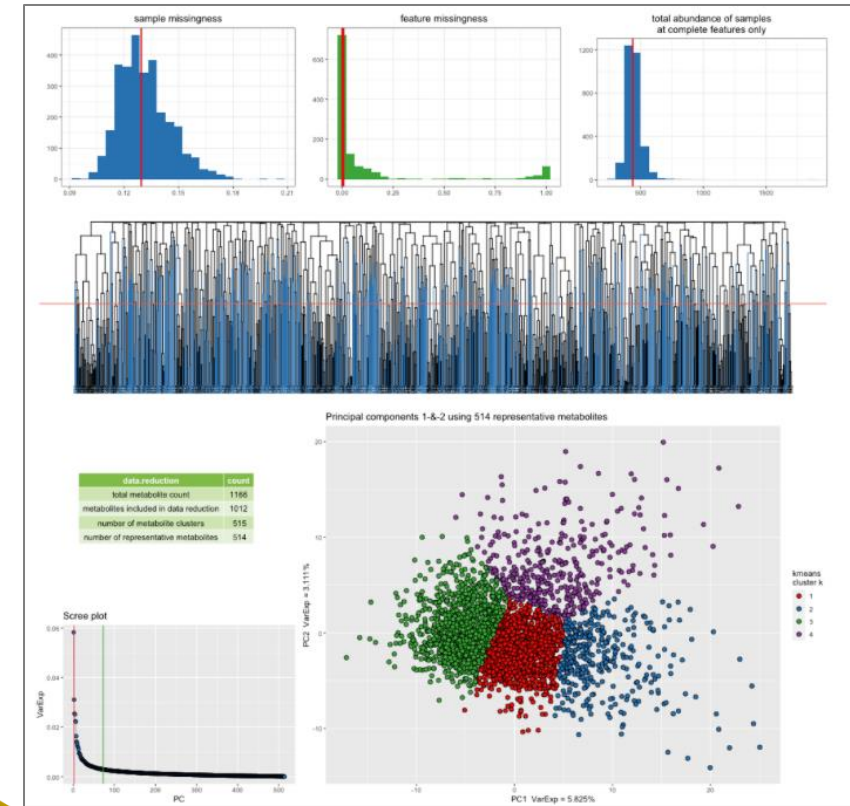
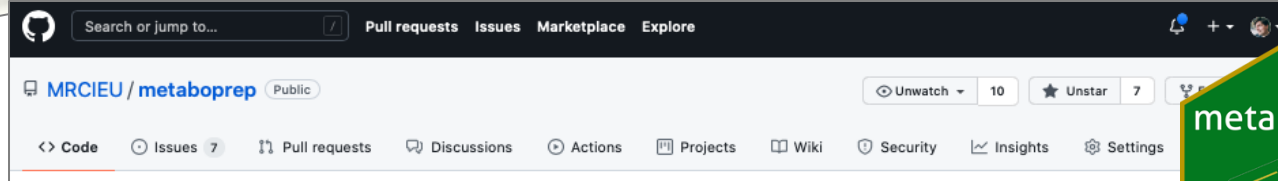


A pre-analytical pipeline: *metaboprep*

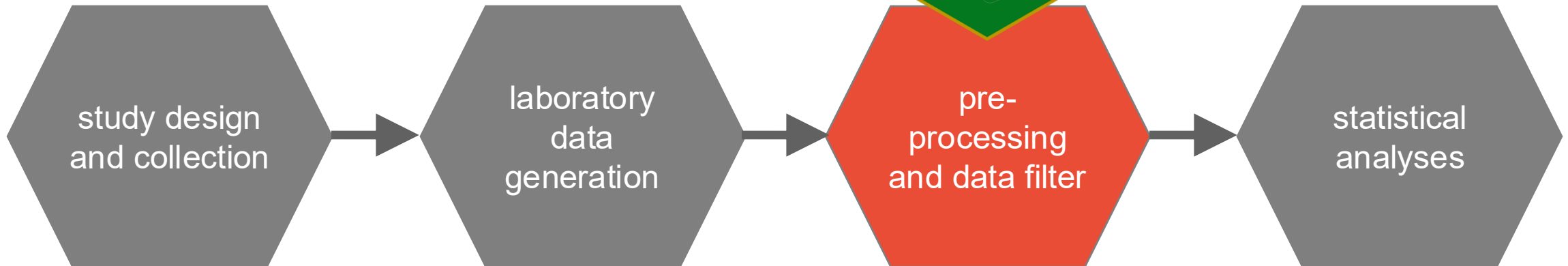
Metabolon

Nightingale

- ❖ Single pipeline
- ❖ Flexible
- ❖ Reproducible
- ❖ Citable

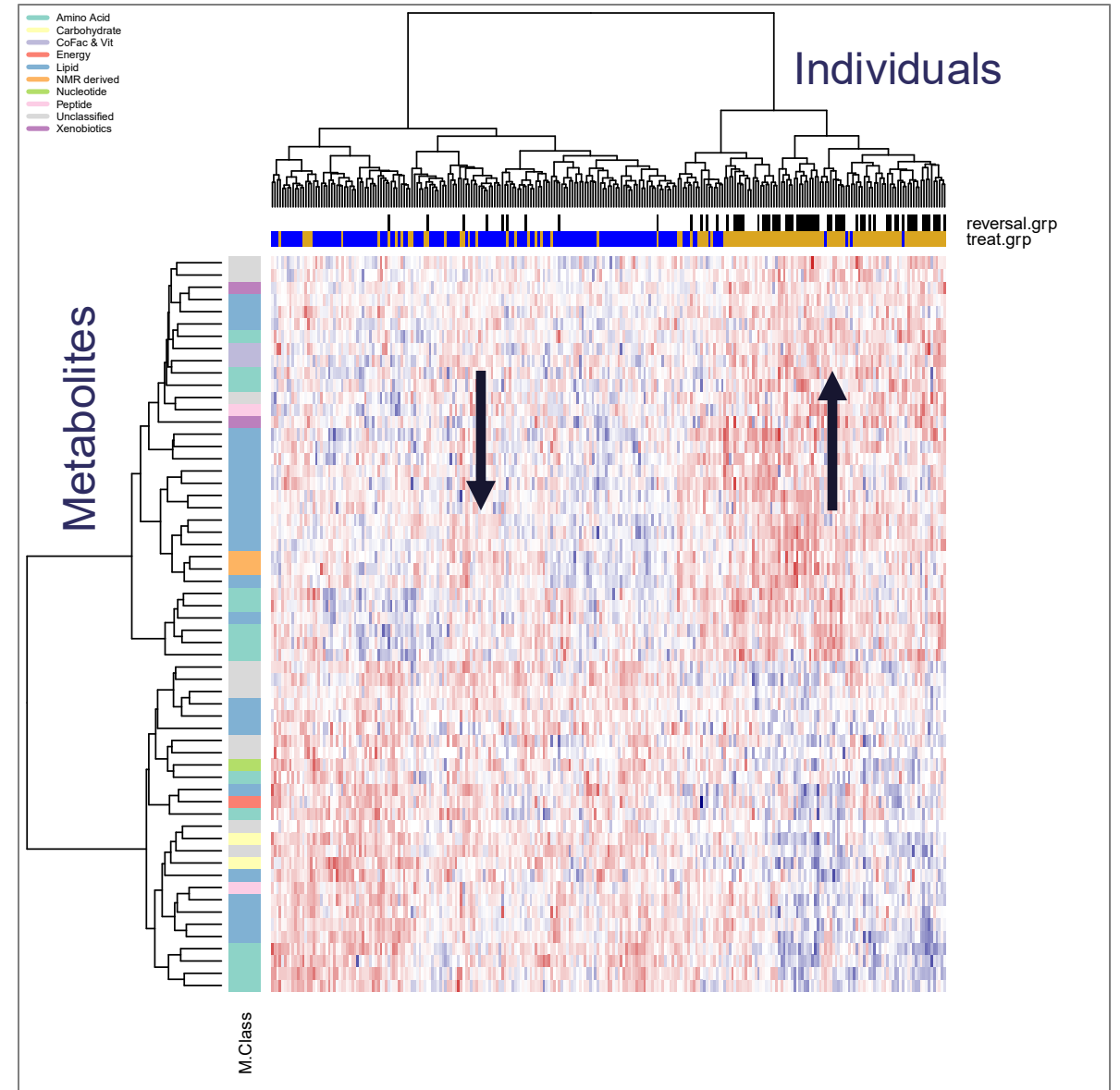


metaboprep



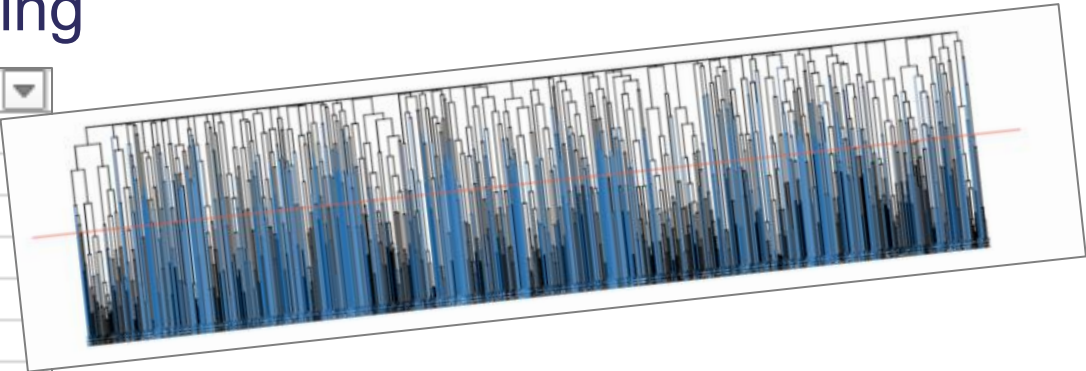
The metabolomic signature of the intervention

- **Linear regression** used to estimate the effect of the intervention on each metabolite in turn
- **Logistic regression** used to look for differential missingness in metabolites reported in only a fraction of samples, e.g., drugs
- Control arm provides reference
- **NMR: 59 (26%) associated**
- **MS: 127 (12%) associated**
- **19 MS metabolites enriched/depleted** in the trial arm (e.g., metformin, dietary biomarkers)
- Evidence not only of weight change but of sustained changes to diet and lifestyle



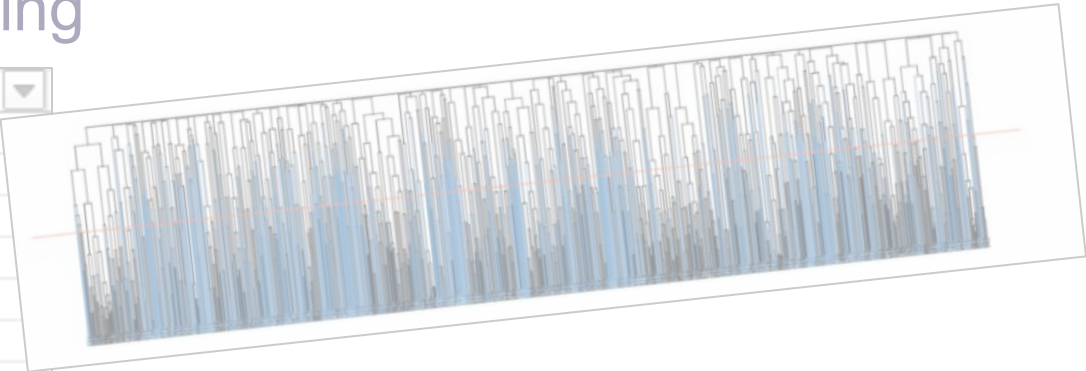
Metabolite ‘families’ based on hierarchical clustering

biochemical	super.pathway	sub.pathway
erythronate*	Carbohydrate	Aminosugar Metabolism
ribitol	Carbohydrate	Pentose Metabolism
orotidine	Nucleotide	Pyrimidine Metabolism, Orotate containing
erythritol	Xenobiotics	Food Component/Plant
2-isopropylmalate	Xenobiotics	Food Component/Plant
N-acetylglutamate	Amino Acid	Glutamate Metabolism
arabitol/xylitol	Carbohydrate	Pentose Metabolism



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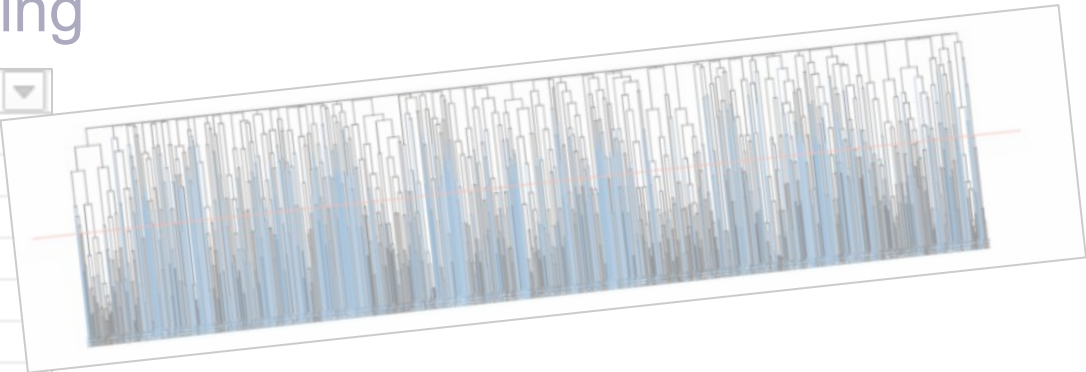


Adjustment for ‘weight change’ –
most but not all effects related to
weight loss

- Omega-3 fatty acids
- Total cholesterol in IDL
- Total cholesterol in large LDL
- Total cholesterol in LDL
- Phospholipids in IDL
- Cholesterol esters to total lipids ratio in large LDL
- Cholesterol esters in small LDL
- Sphingomyelin (d17:1/14:0, d16:1/15:0)*

Metabolite ‘families’ based on hierarchical clustering

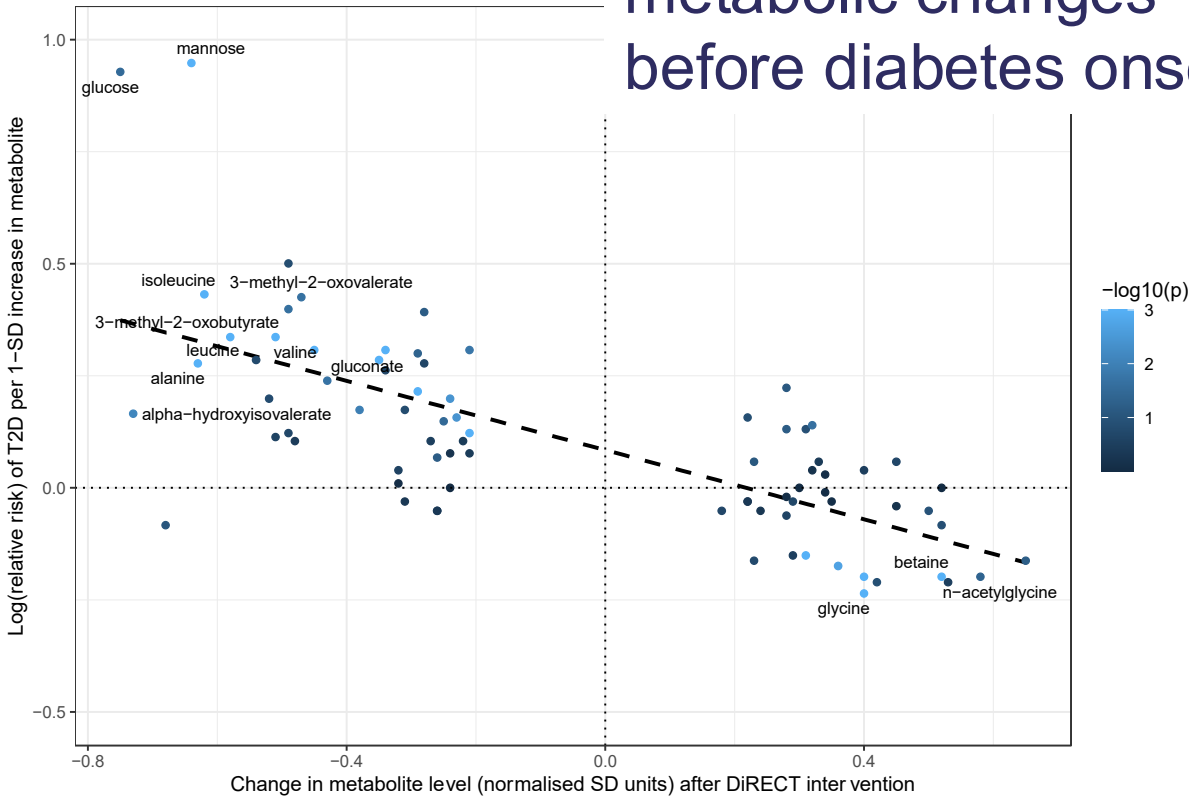
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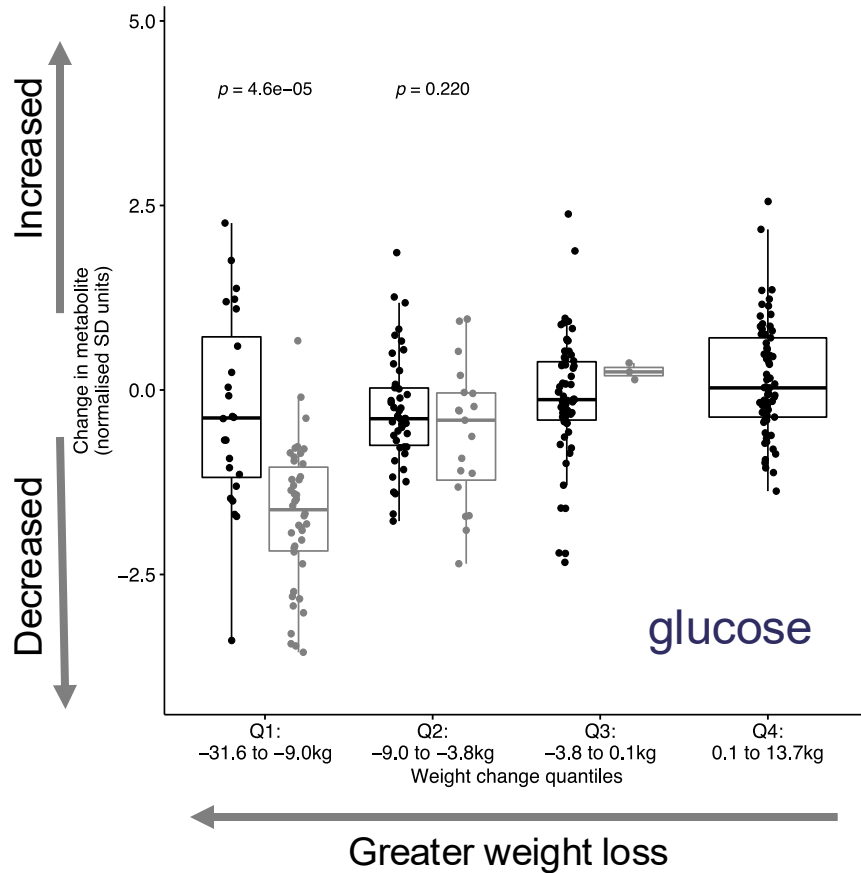
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Comparison to metabolic changes before diabetes onset



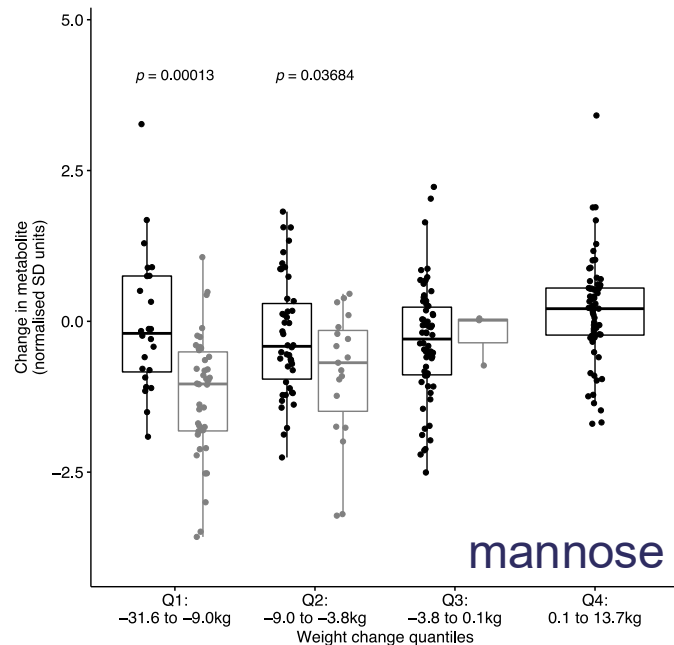
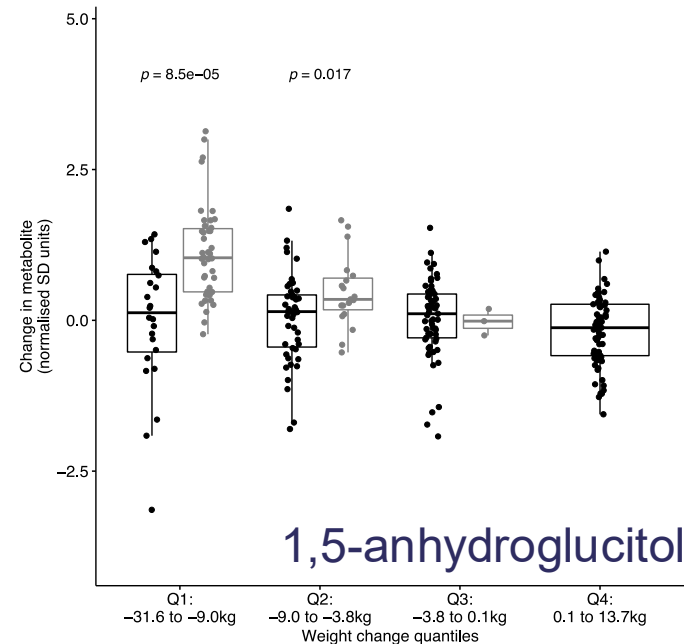
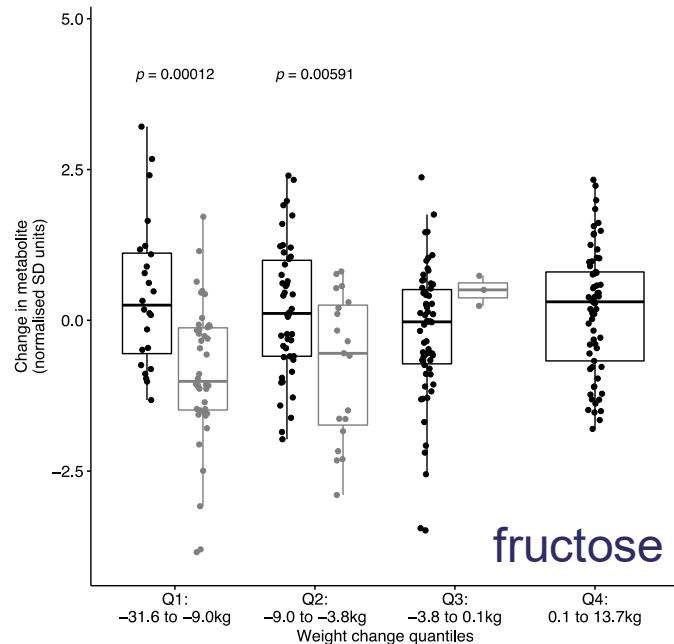
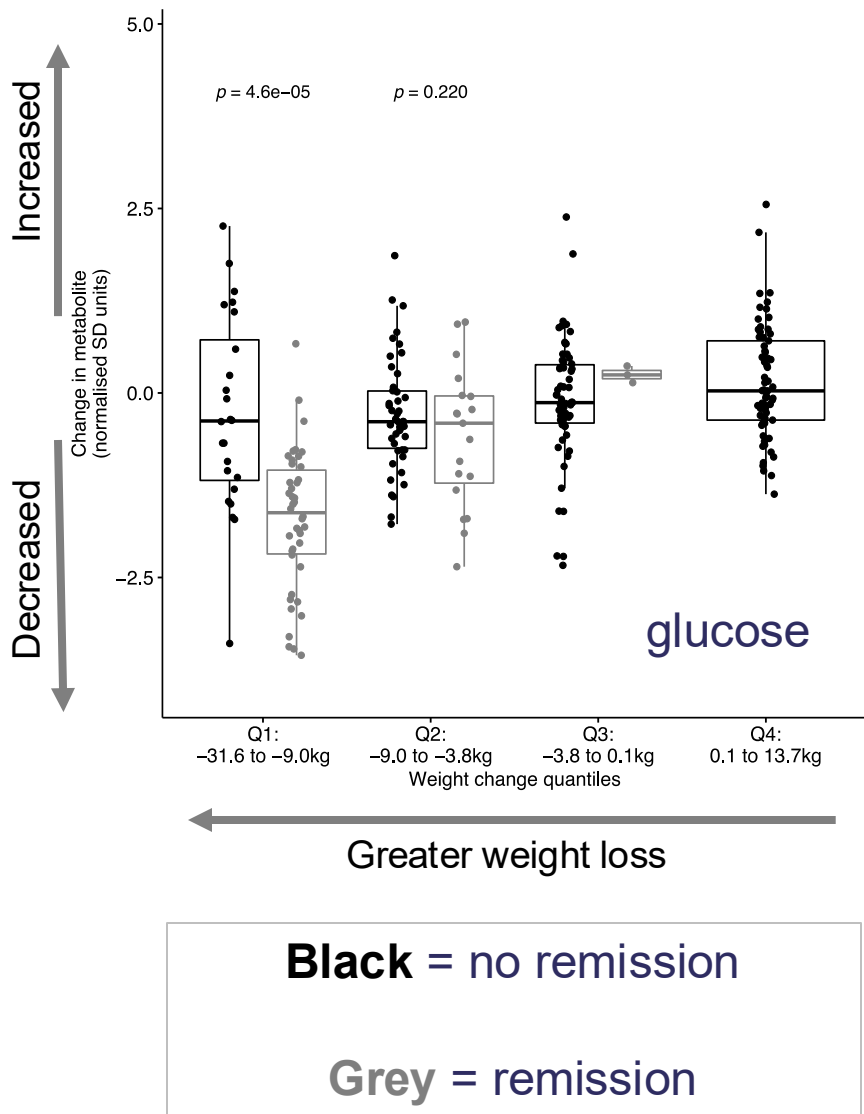
Weight loss does not guarantee regain of glycaemic control



Black = no remission

Grey = remission

Weight loss does not guarantee regain of glycaemic control



The By-Band-Sleeve Trial



STUDY PROTOCOL

Open Access

The By-Band study: gastric bypass or adjustable gastric band surgery to treat morbid obesity: study protocol for a multi-centre randomised controlled trial with an internal pilot phase

Roux-en-Y gastric bypass, adjustable gastric banding, or sleeve gastrectomy for severe obesity (By-Band-Sleeve): a multicentre, open label, three-group, randomised controlled trial

*The By-Band-Sleeve Collaborative Group**

- A multi-centre RCT to evaluate the effectiveness of three surgical procedures
- 12 hospitals from across England (10 with samples)
- 1351 patients randomised (1:1:1) (2012 - 2019)
- Intervention:
 1. Randomised to surgery
 2. Surgery performed (5-6mths post-randomization)
 3. Follow-up (4wks, 6mths, 12mths, 24mths, 36mths)

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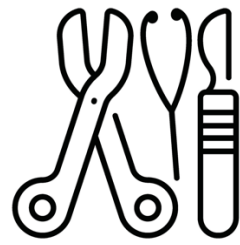
BASELINE SAMPLING – metabolomics (NMR & MS)

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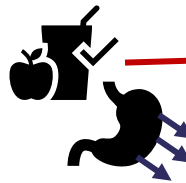
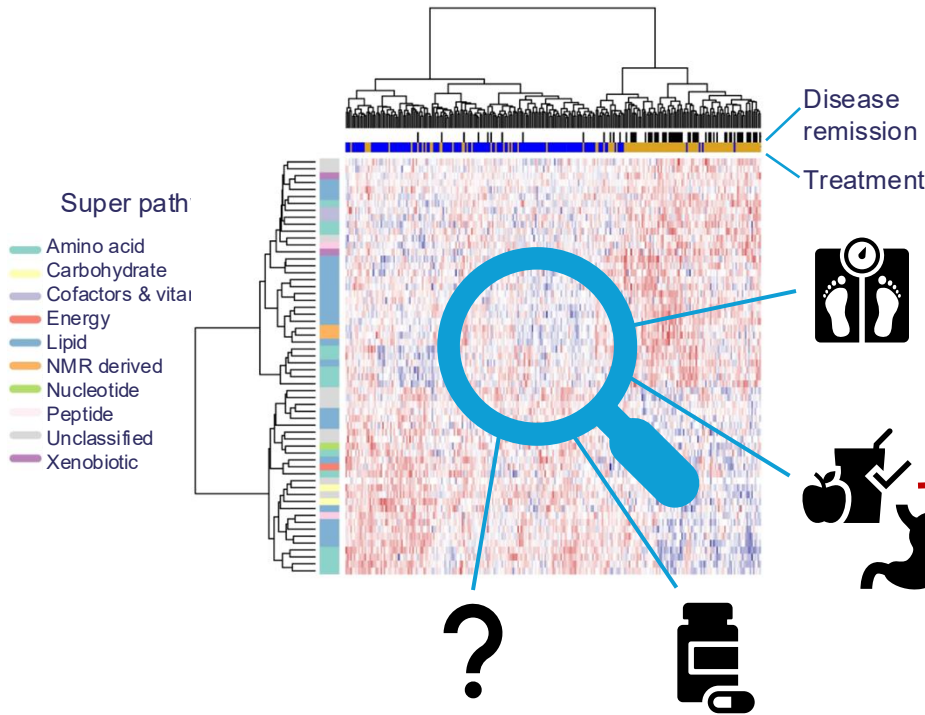
36-MONTH SAMPLING – metabolomics (NMR & MS)

14% to 27%
total weight
loss

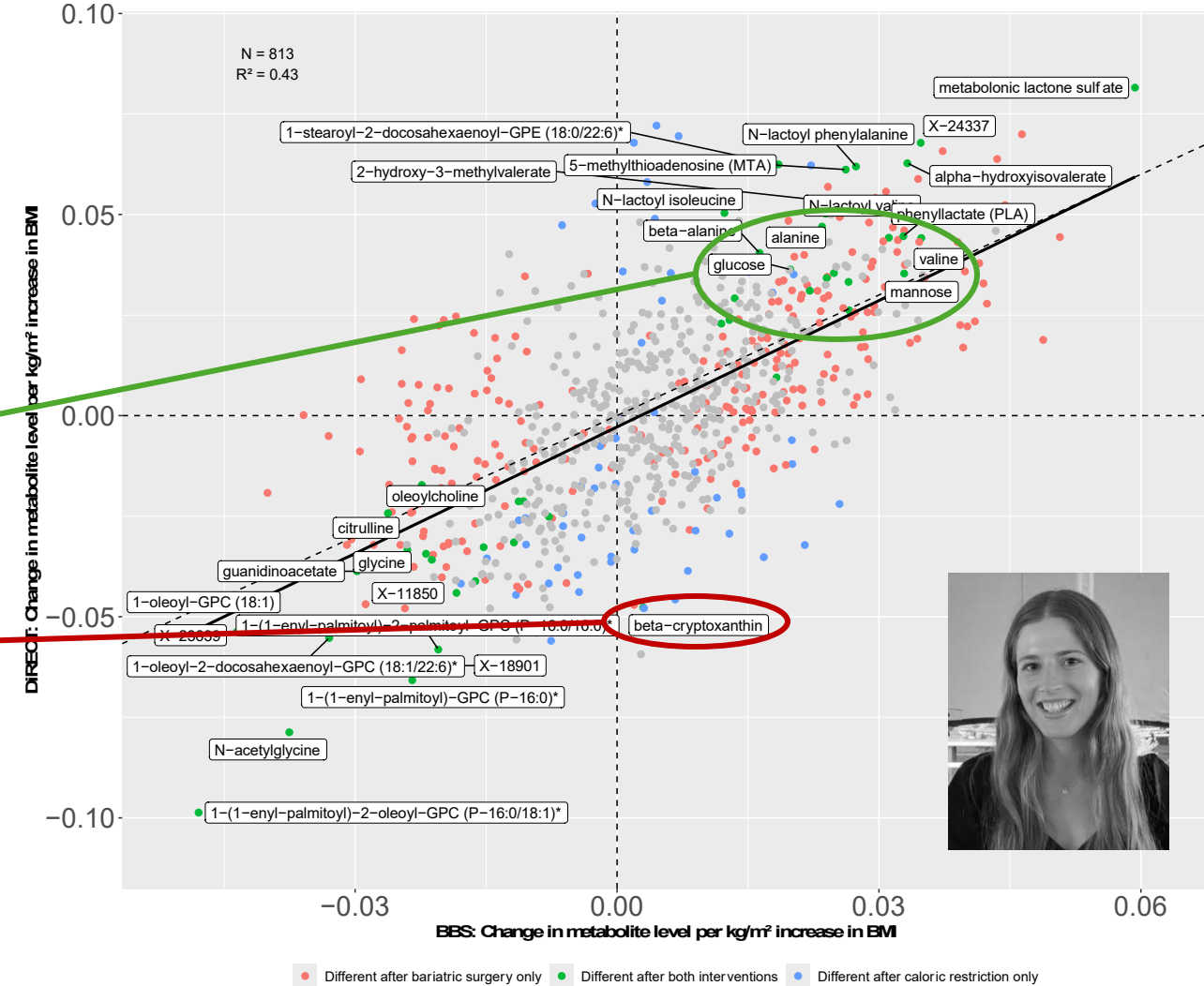
4. Surgical intervention



Surgery



Shared effect: Amino acids & simple sugars – reduced after both interventions

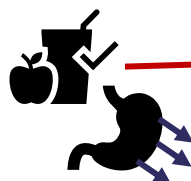
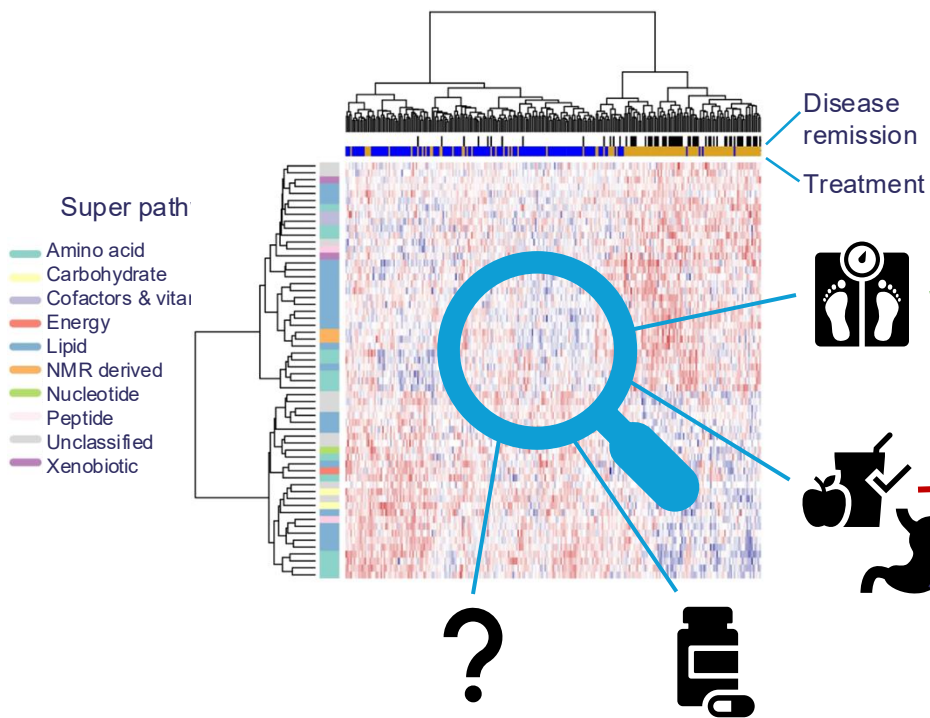


Non-shared effect: Vitamin A pre-cursor – raised after dietary intervention only

4. Surgical intervention

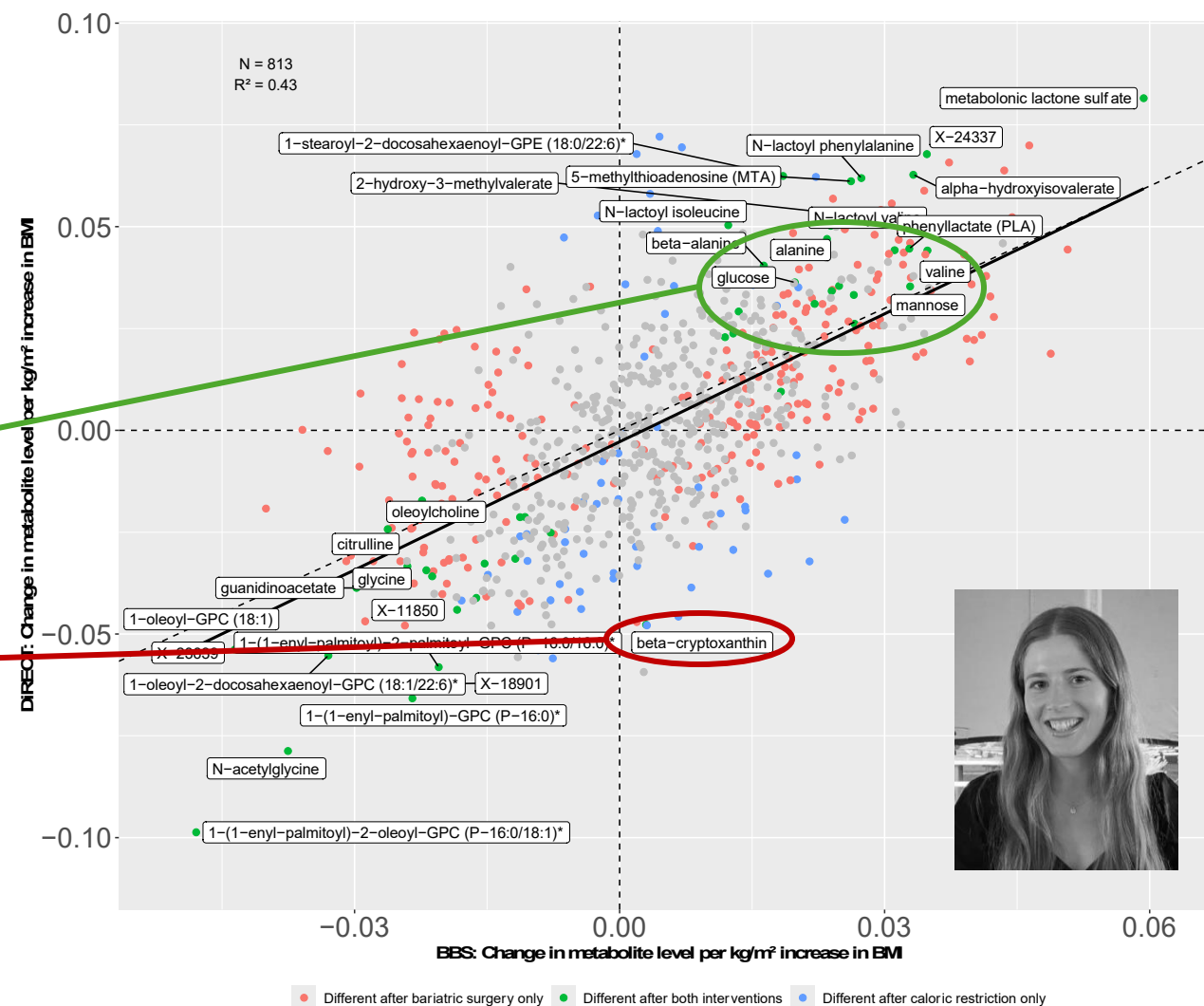


Surgery



Pharmaceutical intervention

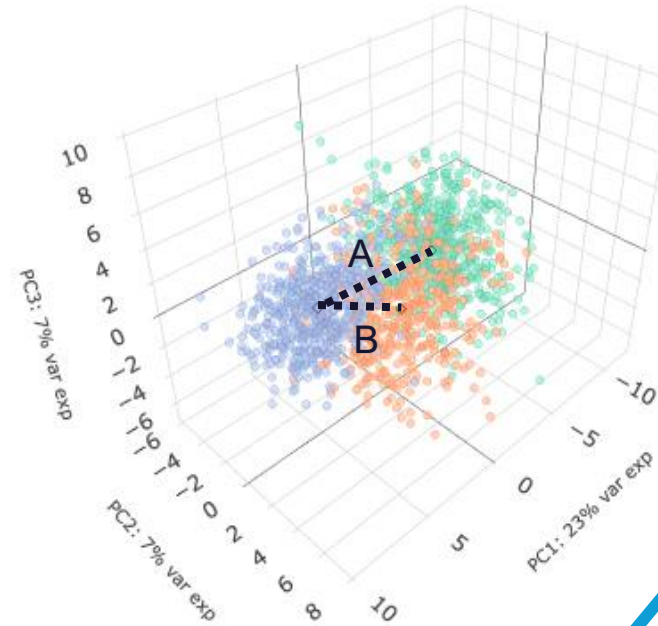
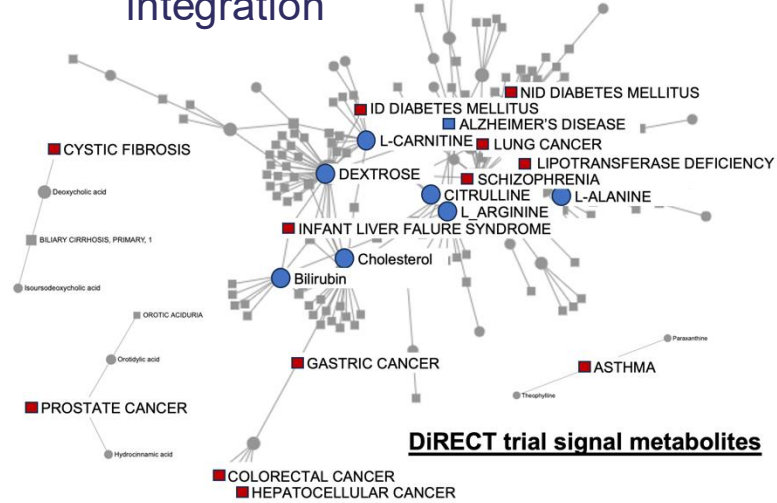
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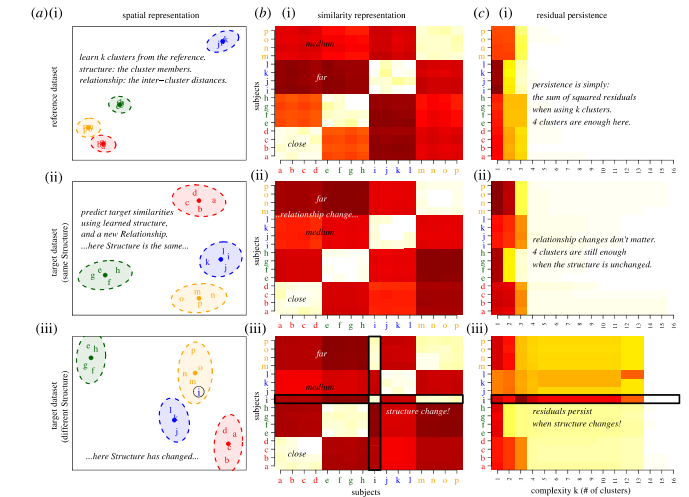
Next steps...

Knowledge-based data integration

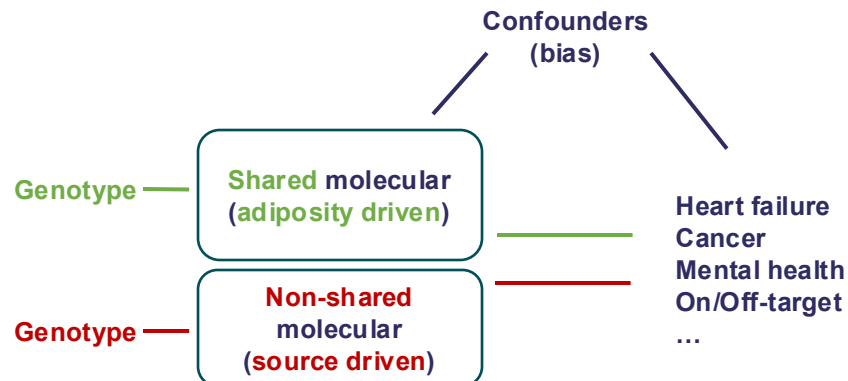


Cross-study experiments

Multivariate analysis of signals



Genetic & prospective epidemiology



<https://github.com/danjlawson/CLARITY>

Acknowledgements

Many thanks to everyone in the 'Integrative epidemiology of obesity' group <https://teamtimpson.github.io/>, to all our collaborators and to participants.



DiABETES UK
KNOW DIABETES. FIGHT DIABETES.

Roy Taylor (PI)
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Naveed Sattar (co-PI)
Alex McConnachie
Claudia-Martina Messow
Paul Welsh

We are enormously grateful to trial sites, GP practices, health-care professionals and volunteers for their participation.



NIHR | National Institute for Health and Care Research

NIHR By-Band-Sleeve Management Group
Jane Blazeby (CI)
Chris Rogers
Graziella Mazza
Eleanor Gidman

We thank all the By-Band-Sleeve contributors including the investigators, research dieticians and nurses, the independent trial steering committee and data monitoring and safety committee. We are grateful to all the patients who participated in this trial.

NHS
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NHS Portsmouth Hospitals NHS Trust

NHS
University Hospital Southampton NHS Foundation Trust

NHS
Derby Teaching Hospitals NHS Foundation Trust

NHS
The Leeds Teaching Hospitals NHS Trust

HEART of ENGLAND
NHS Foundation Trust

NHS
The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust

NHS
North Bristol NHS Trust

NHS
Homerton University Hospital NHS Foundation Trust

NHS
Royal Cornwall Hospitals NHS Trust

NHS
City Hospitals Sunderland NHS Foundation Trust

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Dataset for analysis

NMR data: 258 individuals (115 intervention group)

MS data: 261 individuals (117 intervention group)

Primary analysis of intervention effect (metabolites with <40% missing data)

Linear model applied to RNT data to estimate the effect of group (intervention/ control) on metabolite level at T_1

Calculate variance in metabolite level at T_1 explained by model components

List of associated metabolites extracted based on unadjusted $p < 0.05$

List of associated metabolites extracted based on Holm-corrected $p < 0.05$

Comparison of intervention effect to metabolic footprint of incident type 2 diabetes

Exploratory analysis of associated metabolites

Linear model applied to RNT data without group fitted and residuals extracted

Hierarchical clustering performed on residuals and metabolite clusters defined based on a tree cut height of 0.8

List of associated metabolites reduced such that only one metabolite per cluster remains

Enrichment analysis performed on associated subset based on super-pathway designations

Primary analysis of intervention effect (metabolites with $\geq 40\%$ missing data)

Logistic regression applied to PA data to estimate enrichment/depletion of metabolites at T_1 by group (intervention/control)

List of associated metabolites extracted based on $p < 0.05$

Sample PCA performed based on the subset of representative associated metabolites

Spearman's correlation analysis performed between principal components and quantitative clinical phenotypes

**Roux-en-Y gastric
bypass**



Gastric band



Sleeve gastrectomy

