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Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals

The Future of the Microbiome Summit  
March, 23 2021

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### the Human Microbiome



Bacteria, archaea, fungi, viruses, and microeukaryotes, living in a specific human body site



- Degrades indigestible food components
- Modulates the immune system
- Prevents pathogen colonization

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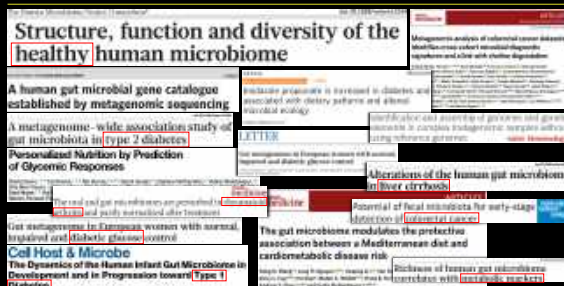
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### Microbiome & Health and Disease



Structure, function and diversity of the healthy human microbiome

A human gut microbial gene catalogue established by metagenomic sequencing

A metagenome-wide association study of gut microbiota in type 2 diabetes

Personalized Nutrition by Prediction of Glycemic Responses

Aberrations of the human gut microbiome in liver cirrhosis

The gut microbiome modulates the protective association between a Mediterranean diet and cardiovascular disease risk

Cell Host & Microbe

The Dysbiosis of the Human Infant Gut Microbiome in Development and in Progression toward Type 1 Diabetes

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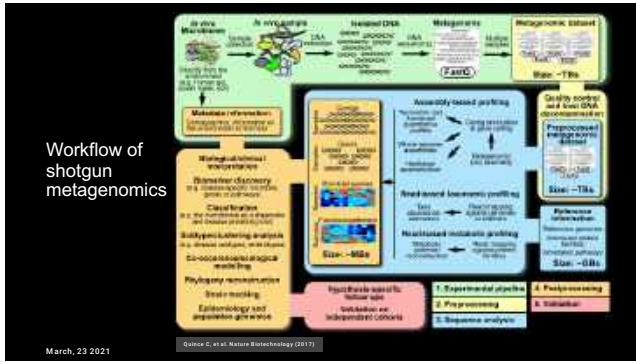
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### The PREDICT 1 cohort

The PREDICT 1 study aimed to quantify and predict individual variations in metabolic responses to standardized meals

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### The PREDICT 1 cohort

The PREDICT 1 cohort includes 1,002 health adults from the UK (both twins and unrelated) and 100 healthy unrelated adults from the US

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### The PREDICT 1 cohort

At baseline, participants were given a standardized metabolic challenge meal for breakfast and lunch

Fasting and postprandial blood, a stool sample, anthropometry, and a FFQ questionnaire on habitual diet were collected

A second stool sample collected at home at the end of the study

**PREDICT 1 UK cohort**  
1000 participants  
500 (stool)

**PREDICT 1 US cohort**  
1000 participants  
500 (stool)

Stool metagenomics

Food Frequency Questionnaire  
Diary, DVA  
Serum metabolomics  
Continuous Glucose Monitor

**Microbiome data**      **Metadata**

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Stool metagenomics

Food Frequency Questionnaire  
Diary, DVA  
Serum metabolomics  
Continuous Glucose Monitor

| Microbiome data   |            |            | Metadata  |  |
|---|------------|------------|---|--|
| 0.3 exp 2.2 seq. Glonaxipie<br>68.7 exp 14.8 of. Breadstancle |            |            | <b>1 Personal</b><br>Age, Sex, Height, Weight, BMI, Physical Activity, Diet, Sleep, Blood Pressure          | <b>3 Habitual diet</b><br>Dietary Fiber intake, Reducing Red Meat, Increasing Plant-based proteins |
| Taxonomic   | Functional | Assembly   | <b>2 Fasting</b><br>Glucose, Insulin, HbA1c, Cholesterol, Triglycerides, FFA, TSH, Thyroid, Glucose, Lipids | <b>4 Post-prandial</b><br>40 blood measures (at 0, 1, 2, 4, 8, 12, 16, 20, 24h)                    |
| 140 species   | 21,407     | 40,192,828 | 34, 17  | 34, 223  |
| 13 spp. 100% preserved  | 13,322     | 26,235,340 |   |  |
| 11 spp. 100% preserved  | 6,143      | 18,140,840 | 34, 109   | 34, 1248   |
| 1 spp. 100% preserved   | 1,817      | 4,110,140  |   |  |

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### Alpha diversity highlights novel association with health biomarkers

We looked at alpha diversity and found positive and negative associations with HDL, a novel marker of systemic inflammation and of cardiovascular disease risk, and hepatic steatosis markers

| Biomarker  | Correlation |
|------------|-------------|
| Weight     | 0.15        |
| Weight_BMI | 0.18        |
| EM         | 0.12        |
| LDL_C      | 0.08        |
| VLDL_C     | 0.10        |
| ATL_C      | 0.14        |
| APOC2      | 0.16        |
| APOC3      | 0.14        |
| APOC4      | 0.12        |
| APOC6      | 0.10        |
| APOC8      | 0.12        |
| APOC9      | 0.14        |
| LDL_B      | 0.16        |
| VLDL_B     | 0.18        |
| ATL_B      | 0.14        |
| APOB       | 0.16        |
| APOE       | 0.12        |
| LDL_C_1    | 0.14        |
| VLDL_C_1   | 0.16        |
| ATL_C_1    | 0.14        |
| APOC2_1    | 0.16        |
| APOC3_1    | 0.14        |
| APOC4_1    | 0.12        |
| APOC6_1    | 0.10        |
| APOC8_1    | 0.12        |
| APOC9_1    | 0.14        |
| LDL_B_1    | 0.16        |
| VLDL_B_1   | 0.18        |
| ATL_B_1    | 0.14        |
| APOB_1     | 0.16        |
| APOE_1     | 0.12        |

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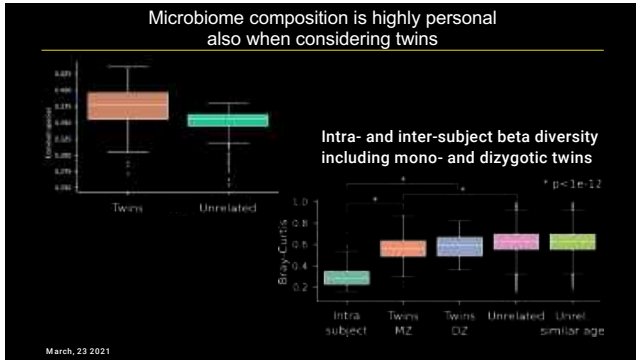
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### Machine Learning framework

- Based on scikit-learn Python package
- Using Random Forest classification and regression algorithms
- 100 bootstrap iterations with 80/20 random split of training and testing folds
- Remove any twin from the training fold if the twin-pair present in the testing fold
- PREDICT 1 US used as independent validation to test the models trained on PREDICT 1 UK
- Microbiome data based on the MetaPhlan 3 species relative abundances

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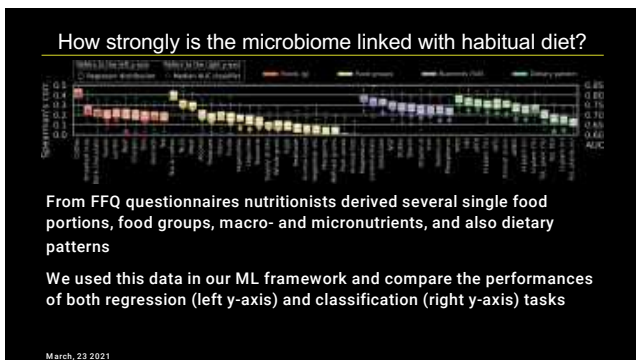
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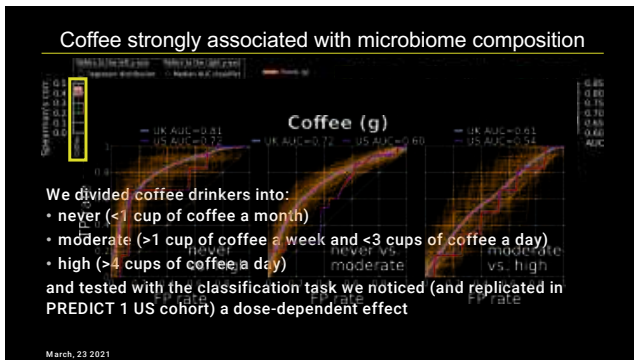
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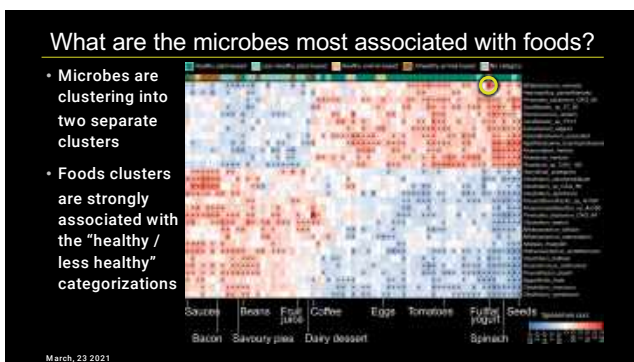
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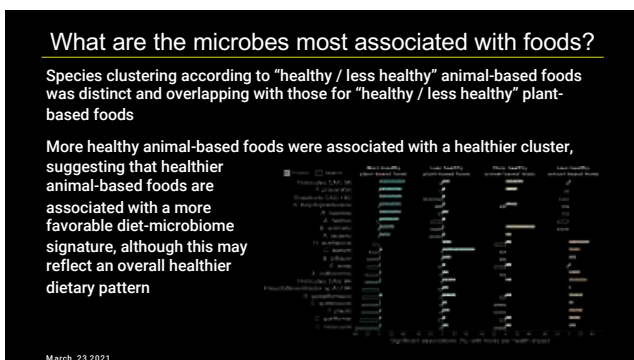
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### Microbiome strongly linked with visceral fat (more than weight and BMI)

- We found visceral fat to be more strongly linked with the microbiome composition than BMI
- We replicate the ML results for BMI in publicly available cohorts collected in the curatedMetagenomicData R package

Passali E, Schiffer L, Manghi P, et al. Nature Methods (2021)  
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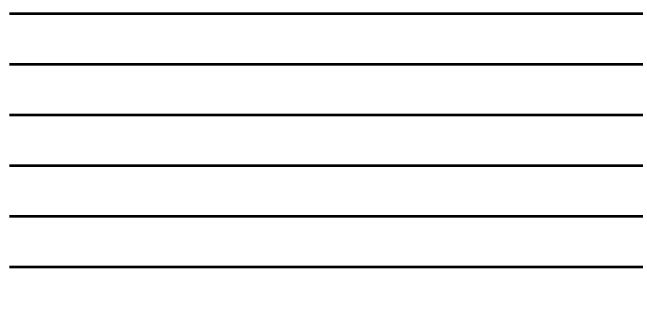
### Single microbial species associated with indicators of obesity

Relative abundances of single microbiome species correlated with age, BMI, and visceral fat, show a greater effect for visceral fat than BMI

Most of these species were also indicators of a more/less healthy dietary patterns (after adjusting for BMI), suggesting that diet and obesity microbiome signatures are linked but not identical

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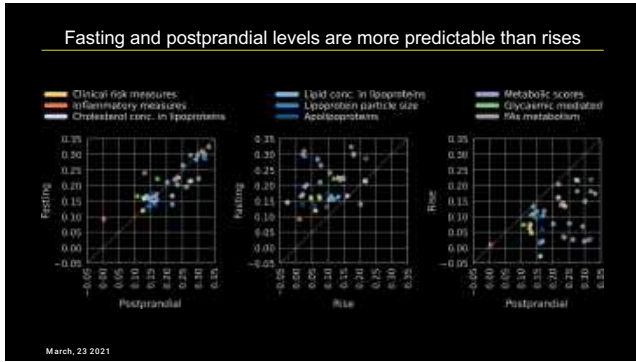
### Gut microbiome links with fasting cardio-metabolic markers

- Associations between traditional clinical measures for cardio-metabolic health at fasting state
- We also explored the relationship with the inflammatory markers IL-6 and GlycA and serum lipoprotein particles measured from NMR

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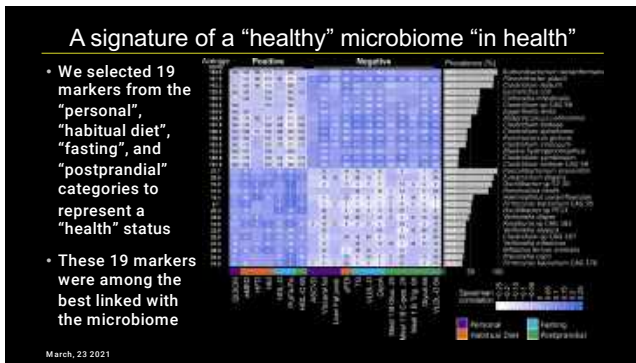
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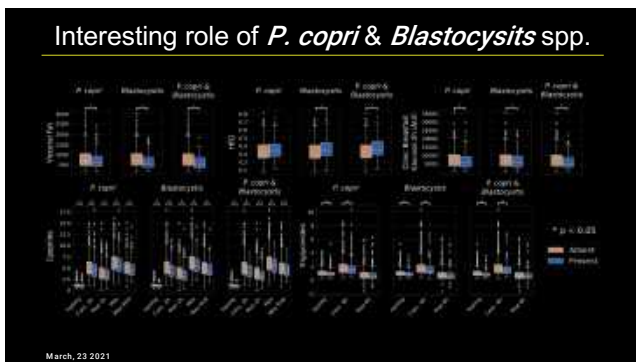
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Gut transit time measured via blue poo is strongly linked with microbiome composition in PREDICT 1

- PREDICT 1 participants were given 2 blue muffins and then self-reported the first appearance of blue poo
- We found that gut transit time is more linked with the microbiome than traditional measures (like Bristol Stool Form scale and number of bowel movements)
- This can be used to measure gut transit time in very large-scale cohorts

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Amici F, Leeming D, Smith E, et al. Gut (2021)

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# Thank you!



- Nicola Segata
- The Segata Lab
- Sarah E. Berry
- Tim Spector
- ZOE




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