Predicting personal metabolic responses to food using multi-omics machine learning in over 1000 twins and singletons from the UK and US: The PREDICT 1 Study

Tim Spector
Professor of Genetic Epidemiology
Dept of Twins Research and Genetic Epidemiology, King’s College London
# Faculty Disclosure

<table>
<thead>
<tr>
<th>Financial Relationship (prior 12 months)</th>
<th>Commercial Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
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</tr>
<tr>
<td>Scientific Advisory Board/Consultant/Board of Directors</td>
<td>SAB Zoe Global</td>
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<tr>
<td>Speakers Bureau</td>
<td>N/A</td>
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<tr>
<td>Stock Shareholder</td>
<td>Zoe Global</td>
</tr>
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<td>Employee</td>
<td>Kings College London</td>
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<td>Other</td>
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Food guidelines: Does one size fit all?

Why do some people respond to low fat and others low carb? Maybe our individual responses to food are more variable than we believed?

Understanding these factors is key to predicting individual food responses.
Why do we need to look at postprandial responses?

Single Meal

Typical Day
Why do prolonged post-prandial peaks matter?

- Raised Insulin Secretion
- Lipoprotein Re-modelling
- Oxidative Stress
- Inflammation
- Endothelial Dysfunction

**Weight Gain**
- Increased risk for
  - Cardiovascular Disease
  - Metabolic Disease (Type 2 Diabetes, Fatty Liver, Insulin Resistance)

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**PREDICT STUDY**

**Aim:**
Use genetic, metabolomic, metagenomic and meal-context information to predict individuals’ metabolic response to food

1. How much variability between people?

2. What explains these differences?

3. Can we PREDICT individual responses using machine learning?
Multiple Test Meal Challenge study: Clinic day + 2 weeks at home

Clinic (1 day)

- Questionnaires
- Blood pressure and heart rate
- Anthropometry
- Training

Controlled Time (Mins)

- Fasted

<table>
<thead>
<tr>
<th>Time (Mins)</th>
<th>00</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>270</th>
<th>300</th>
<th>360</th>
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</thead>
<tbody>
<tr>
<td>52g Fat</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85g Carb</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>22g Fat</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>71g Carb</td>
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</table>

Serum

- Genetics Clinical assays
- Metabolomics

Saliva

- Metabolomics

Urine

- Metabolomics/Clinical assays

Capillary Blood

- Metabolomics/Clinical assays

Faeces

- Metagenomics 16s rRNA

Inclusion criteria:
- Aged 18-65 years
- Healthy volunteers
# Predict Study Design

## Multiple Test Meal Challenge study: Clinic day + 2 weeks at home

<table>
<thead>
<tr>
<th>Home (2 Weeks)</th>
<th>Standardized set meals + Free-living meals</th>
</tr>
</thead>
</table>

### Test Meal Challenges
- 12 days of standardized meals in duplicate
- 75g OGTT isocaloric muffins with varying macronutrient composition
- Self-selected Free-living meals

### Sleep and Exercise

<table>
<thead>
<tr>
<th>Time of day</th>
<th>Activity</th>
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<tbody>
<tr>
<td>0700</td>
<td></td>
</tr>
<tr>
<td>0900</td>
<td></td>
</tr>
<tr>
<td>1100</td>
<td></td>
</tr>
<tr>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>1500</td>
<td></td>
</tr>
<tr>
<td>1700</td>
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</table>

### Metabolites
- Continuous glucose monitoring
- Capillary Blood
- Metabolomics / Clinical assays

### Microbiome
- Metagenomics
- 16s rRNA

### Dietary Assessment:
- Real-time App by Zoe
- Real-time Dashboard by Zoe
**P R E D I C T  S T U D Y  R E S U L T S**

Sample n=1,100

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
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<tbody>
<tr>
<td>MZ Twins</td>
<td>479</td>
</tr>
<tr>
<td>DZ Twins</td>
<td>172</td>
</tr>
<tr>
<td>Non-Twins</td>
<td>351</td>
</tr>
<tr>
<td>Drop-out</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

**Mean (SD)***

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45.7 (12.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 (5.0)</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>72 F/ 28 M</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>1.1 (0.5)</td>
</tr>
<tr>
<td>Insulin (IU/mL)</td>
<td>6.1 (4.3)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.0 (0.5)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.0 (1.0)</td>
</tr>
</tbody>
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32,000 muffins consumed
132,000 meals logged

2,022,000 CGM glucose readings
28,000 TAG readings

* \( n = 1,001 \)
PREDICT STUDY RESULTS

Significant variability between healthy individuals

**Triacylglycerol**

- Baseline: CV 50%
- 6h rise: CV 103%

**Glucose**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2h IAUC</th>
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</thead>
<tbody>
<tr>
<td>CV</td>
<td>10%</td>
<td>68%</td>
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</table>

**Insulin**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2h IAUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV</td>
<td>69%</td>
<td>59%</td>
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n = 1,001

INTERIM UNPUBLISHED DATA
Intra-individual variability is lower than inter-individual variability

**Triacylglycerol** (6h rise, n=1018 meals at home and in clinic)

- **Inter-individual CV = 68%**
- **Intra-individual CV = 36%**

**Glucose (IAUC 0-2h, n=7898 meals at home)**

- **Inter-individual CV = 40%**
- **Intra-individual CV = 24%**

Interindividual CV is calculated for identical meals, between random pairs of individuals. Intraindividual CV is calculated between pairs of nutritionally identical meals for the same individual.

INTERIM UNPUBLISHED DATA
Identical twins have very different responses

**Height**

- Pearson R: 0.969 p-value: 3.847e-111

**Glucose (iAUC 0-2h)**

- Pearson R: 0.531 p-value: 2.475e-13

**Triacylglycerol (6h iAUC)**

- Pearson R: 0.434 p-value: 6.048e-08

**Key:**
- Genetics: 30%
- Upbringing: 21%
- Environment: 48%

- Genetics: 5%
- Upbringing: 38%
- Environment: 57%

**INTERIM UNPUBLISHED DATA**

Genetics do not explain most nutritional differences
Case Study
Example of a twin pair with different responses

Twin’s responses to High Carb muffin

Twin’s responses to set meals
Glucose and TAG responses are not well correlated

TAG iAUC 0-6h vs. Glucose iAUC 0-2h

Knowing glucose responses won’t tell you a person’s fat responses
Machine Learning can predict individual responses

Initial machine learning model correlates 73% to measured glucose responses
Macronutrients explain 16-32% of responses to at home meals

- Macronutrients 16-32%
- Complex Meal Properties TBD%
- Individual Factors TBD%

Factors explaining glucose responses to at home meals:

- Microbiome, genetics, health, medication, etc
- Timing: meal timing, meal order, circadian rhythm
- Sleep
- Exercise

n=9376 free living meals. Impact of macronutrients varies depending on meal dataset used
Conclusion

• Everyone is unique in food response – even identical twins
• Genetics explains less than half of metabolic response: most is potentially modifiable
• The macronutrient composition of foods only explains 16-32% of our responses
• Initial machine learning model already correlates 73% to measured glucose responses

What next?

• Build more sophisticated machine learning models, using all the data collected
• Launch PREDICT 2 home study today with MGH and Stanford: https://predict.study

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