Look, you've got it all wrong.

Monty Python's LIFE OF BRIAN

WE ARE ALL INDIVIDUALS
WE ARE ALL INDIVIDUALS
MICROBIOME

HUMAN GENOME

EXPOSOME

Hannelore Daniel
Hannelore Daniel

DNA

GWAS

3 x 10^{12} bases

age
gender
body weight (BMI)
blood pressure
disease history
fasting blood sample

Phenotype
The phenotype is a function of genome x environment and is highly dynamic.

The metabolic phenotype is highly dynamic.

Phenotypic flexibility as key factor in the human nutrition and health relationship.
van Ommen B, van der Greef J, Ordovas JM, Daniel H.
The metabolic phenotype is highly dynamic

The HuMet study
The HuMet study

Antropometric data

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>15</td>
<td>22</td>
<td>33</td>
<td>27.8</td>
<td>2.98</td>
<td>0.77</td>
<td>10.72%</td>
</tr>
<tr>
<td>Height (m)</td>
<td>15</td>
<td>1.71</td>
<td>1.92</td>
<td>1.83</td>
<td>0.06</td>
<td>0.02</td>
<td>3.47%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>15</td>
<td>63.5</td>
<td>90.4</td>
<td>77.5</td>
<td>7.09</td>
<td>1.83</td>
<td>9.14%</td>
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<tr>
<td>BMI</td>
<td>15</td>
<td>20.4</td>
<td>25.5</td>
<td>23.1</td>
<td>1.76</td>
<td>0.45</td>
<td>7.61%</td>
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<tr>
<td>WHR</td>
<td>15</td>
<td>0.8</td>
<td>1</td>
<td>0.89</td>
<td>0.05</td>
<td>0.01</td>
<td>5.12%</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>15</td>
<td>70.5</td>
<td>87.5</td>
<td>80.5</td>
<td>4.59</td>
<td>1.19</td>
<td>5.72%</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>15</td>
<td>84</td>
<td>98</td>
<td>90.1</td>
<td>4.72</td>
<td>1.22</td>
<td>5.24%</td>
</tr>
<tr>
<td>Heart rate (1/min)</td>
<td>15</td>
<td>44</td>
<td>84</td>
<td>62</td>
<td>11.37</td>
<td>2.94</td>
<td>18.39%</td>
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<tr>
<td>Blood pressure (syst.)</td>
<td>15</td>
<td>106</td>
<td>160</td>
<td>121.5</td>
<td>12.07</td>
<td>3.12</td>
<td>9.93%</td>
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<tr>
<td>Blood pressure (diast.)</td>
<td>15</td>
<td>70</td>
<td>93</td>
<td>81.9</td>
<td>5.95</td>
<td>1.54</td>
<td>7.26%</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>15</td>
<td>8.84</td>
<td>19</td>
<td>14.4</td>
<td>3.32</td>
<td>0.86</td>
<td>23.05%</td>
</tr>
<tr>
<td>Fat (%) whole body</td>
<td>15</td>
<td>13.6</td>
<td>23.9</td>
<td>18.7</td>
<td>2.92</td>
<td>0.76</td>
<td>15.67%</td>
</tr>
<tr>
<td>Fat (%) trunk</td>
<td>15</td>
<td>12.9</td>
<td>22.3</td>
<td>17.2</td>
<td>3.07</td>
<td>0.79</td>
<td>17.84%</td>
</tr>
<tr>
<td>Muscle (kg)</td>
<td>15</td>
<td>47.7</td>
<td>70.4</td>
<td>59.5</td>
<td>5.91</td>
<td>1.53</td>
<td>9.94%</td>
</tr>
<tr>
<td>24h-BMR (kcal)</td>
<td>15</td>
<td>1300</td>
<td>2160</td>
<td>1721</td>
<td>223.60</td>
<td>57.73</td>
<td>12.99%</td>
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<tr>
<td>RQ</td>
<td>15</td>
<td>0.78</td>
<td>0.99</td>
<td>0.85</td>
<td>0.06</td>
<td>0.01</td>
<td>6.47%</td>
</tr>
<tr>
<td>Body surface area(m²)</td>
<td>15</td>
<td>1.77</td>
<td>2.19</td>
<td>1.99</td>
<td>0.12</td>
<td>0.03</td>
<td>5.80%</td>
</tr>
</tbody>
</table>
4 days in house in the study center at TUM (2 times 2 days) a total of 56 blood samples from each volunteer a total of 56 breath samples from each volunteer a total of 25 urine samples from each volunteer

The challenges
Fasting 36h

8:00
Day 1

20:00
last meal

Day 1

8:00

Day 2

24:00

10
12
14
16
18
20
22

plasma

breath condensate

urine

Hannelore Daniel
Kendall Correlation amongst metabolites quantified over all challenges
Principal component analysis
Principal component analysis
How „robust“ is a metabolic phenotype?
Quantifying phenotypic flexibility from time-profiles of metabolite levels in plasma during challenge test

The **NutriTech** study
The NUTRITECH study

38 women and 34 men, on average 59 years old with mean BMI of 29

12 weeks (control) → 32 participants

12 weeks (intervention) → 40 participants

72 participants

Reduction of energy intake by 20% → weight loss: around 5.5 kg

Dietary challenges

+ challenge experiments
The NUTRITECH study

38 women and 34 men, on average 59 years old with mean BMI of 29

- Exome sequencing
- Muscle & adipose tissue biopsy’s
- PBMC-transcriptome analysis
- Microbiome analysis

Around 3,000 samples
More than 400 metabolites identified and/or quantified by using LC-MS/MS, GC-MS, NMR and clinical chemistry.
The NUTRITECH study

38 women and 34 men, on average 59 years old with mean BMI of 29

correlation of 664 variables in fasting state
How „robust“ is a metabolic phenotype?

3 month

72 participants

Dietary challenges

ORAL GLUCOSE TOLERANCE TEST (OGTT)
75 g glucose in 250 mL water

<table>
<thead>
<tr>
<th>Overnight</th>
<th>fast</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>

MIXED MEAL TOLERANCE TEST (MMT)
Liquid diet (884 Kcal - 56% lipids, 34% carbohydrates, 10% proteins)

<table>
<thead>
<tr>
<th>Overnight</th>
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<tbody>
<tr>
<td>0</td>
<td>1 h</td>
</tr>
</tbody>
</table>

MIXED MEAL TOLERANCE TEST and PHYSICAL ACTIVITY (MMT + PA)
Liquid diet (884 Kcal - 56% lipids, 34% carbohydrates, 10% proteins) + 30 min physical activity after t=0

<table>
<thead>
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<tr>
<td>0</td>
<td>1 h</td>
</tr>
</tbody>
</table>

Around 3,000 samples with more than 300 metabolites identified using LC-MS/MS, GC-MS, NMR and clinical chemistry.
Responses in the OGTT at t=0 and t=3 month

Glucose (mM) versus time (min)

- t1: Response at t=1 month
- t2: Response at t=2 months

Euclidian distance

= Identity Index
The IDENTITY INDEX of all measured blood parameters in the NutriTech OGTT samples

**METABOLITES**

**Identity Index (%)**

Ranking of metabolites w.r.t. reproducibility of measurements (t=0 and 12 weeks) within the OGTT
cluster A = 38 volunteers
cluster B = 34 volunteers
data are mean ± SEM, n=38 and n=34
data are mean ± SEM, n=38 and n=34
... taking it into concepts of INDIVIDUALIZED NUTRITION
**INPUT**
- anthropometrics
- food intake
- physical activity
- metabotype
- genotype

**OUTPUT**
- advice systems
- data centre
- personalized menus

ALGORITHMS

food frequency questionnaire
physical activity monitoring
anthropometric measurements
DNA from buccal swaps
dry blood spots for LC/GC-MS analysis

1,607 participants

food4me.org

Hannelore Daniel

personalized menus

advice systems

data centre

ALGORITHMS
INPUT
- anthropometrics
- food intake
- metabotype
- genotype

ADVISE LEVEL
- generic
- food intake based
- food intake + metabotype
- food intake + metabotype + genotype

EFFECT-SIZE
- energy intake (kJ·day⁻¹)
  - N=312
  - p = 0.022
- Healthy eating index
  - N=377
  - p = 0.010
WHAT IS HABIT?

Habit is a science-based, personalized nutrition solution to help you eat with confidence and feel your best.
Take home message

- The genome x diet interaction is in essence unexplored.
- Findings from GWAS studies explain only a small fraction of human metabolic diversity and measure only against a very small set of phenotypic parameters.
- Human metabolism is highly dynamic and most phenotyping studies lack the time-dimension of response.
- There are „robust metabotypes“ in healthy populations
- These „metabotypes „ can be targeted for improving health via individualized advise systems and treatments
THANK YOU ALL