Personalized Nutrition by Prediction of Glycemic Responses

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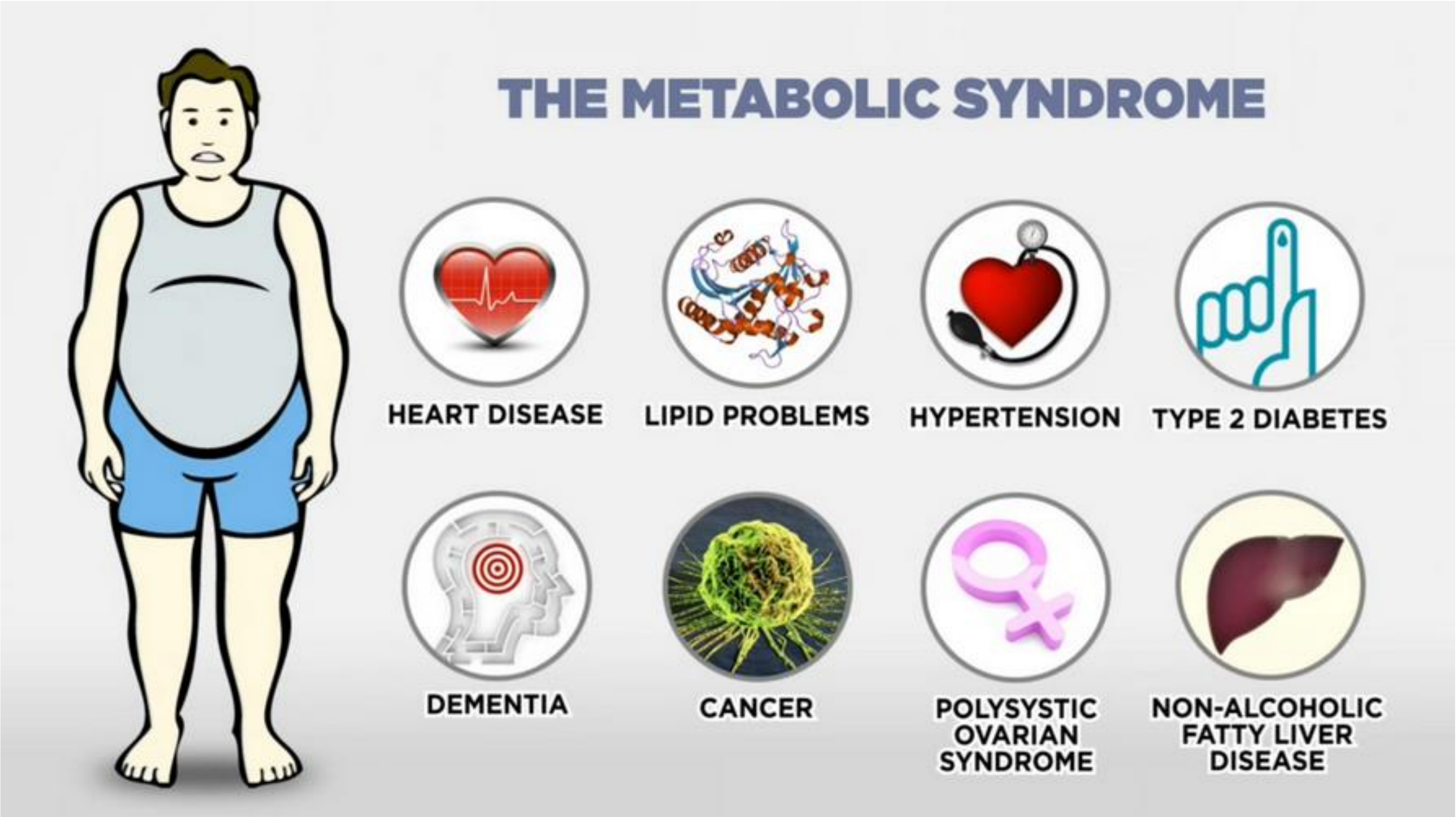
Lab of Prof. Eran Segal
Weizmann Institute of Science

Changes in our nutrition greatly contributed to the recent metabolic syndrome epidemic



General recommendations in nutrition

1943 — 1992 — 2015

Source: USDA

Consumption of artificial sweeteners

Increase in artificial sweetener consumption is a major recent change in our nutrition

- 86% of Americans use ‘diet’ products
- Consumers spend $21B per year on diet drinks

Artificial sweeteners are recommended for weight loss and for assisting in blood glucose control

American Heart Association
Learn and Live

American Diabetes Association

AHA & ADA joint statement

From Gardner *et al.*, published July 2012 in Circulation and in Diabetes care:

"REPLACING SUGARY FOODS AND DRINKS WITH SUGAR-FREE OPTIONS CONTAINING NON-NUTRITIVE SWEETENERS IS ONE WAY TO LIMIT CALORIES AND **ACHIEVE OR MAINTAIN A HEALTHY WEIGHT**."

"WHEN USED TO REPLACE FOODS AND DRINKS WITH ADDED SUGARS, IT CAN **HELP PEOPLE WITH DIABETES MANAGE BLOOD GLUCOSE LEVELS**"

ARTICLE

doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez[1], Tal Korem[2*], David Zeevi[2*], Gili Zilberman-Schapira[1*], Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]

Jotham Suez

Eran Elinav

Suez *et al.*, Nature 2014

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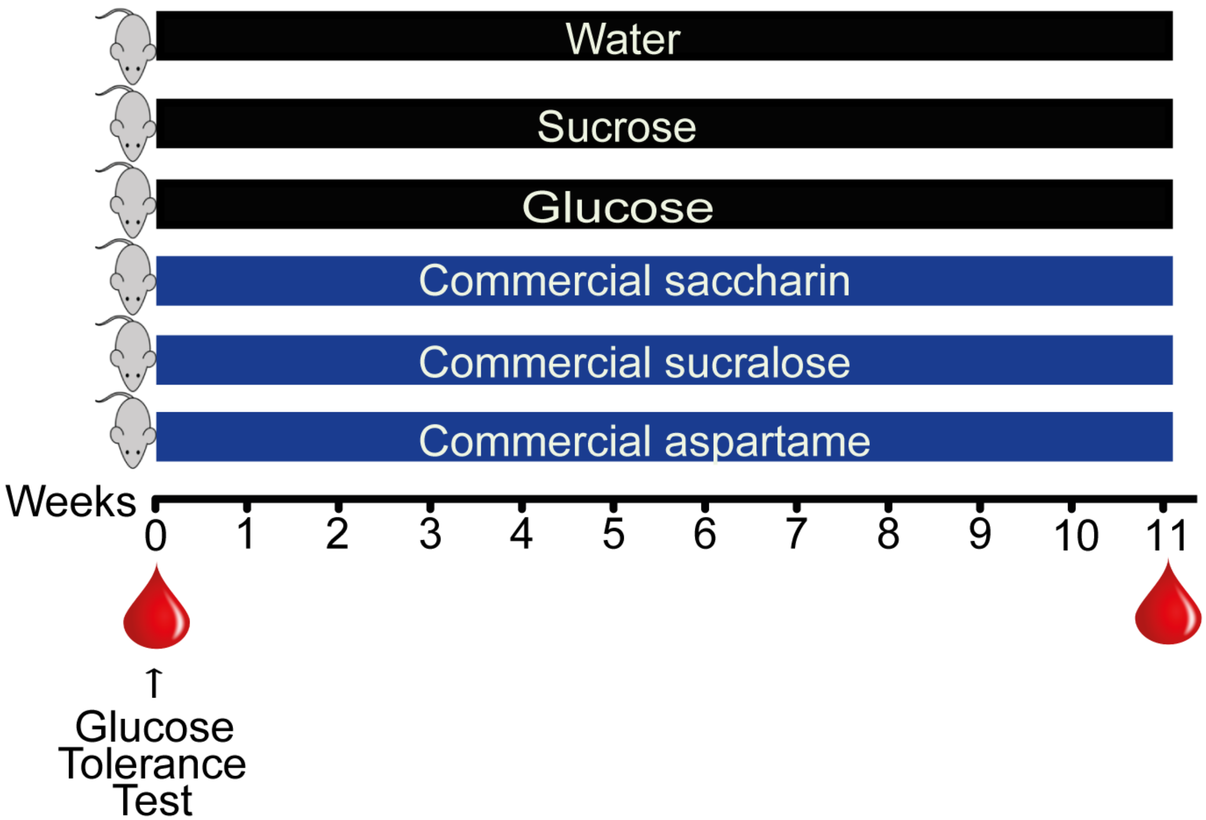
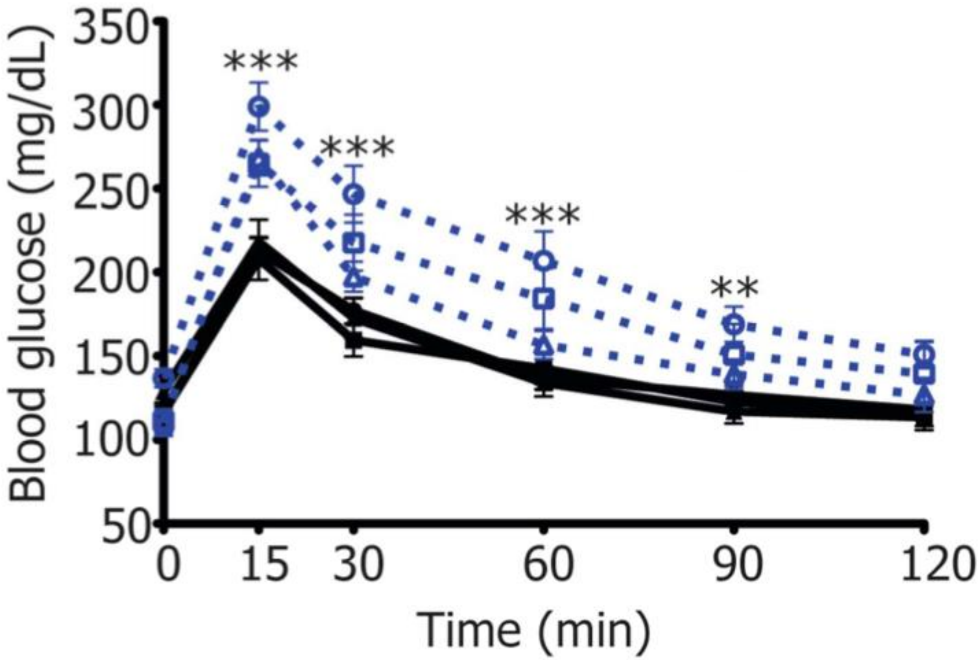
What is the effect of artificial sweeteners on mice?

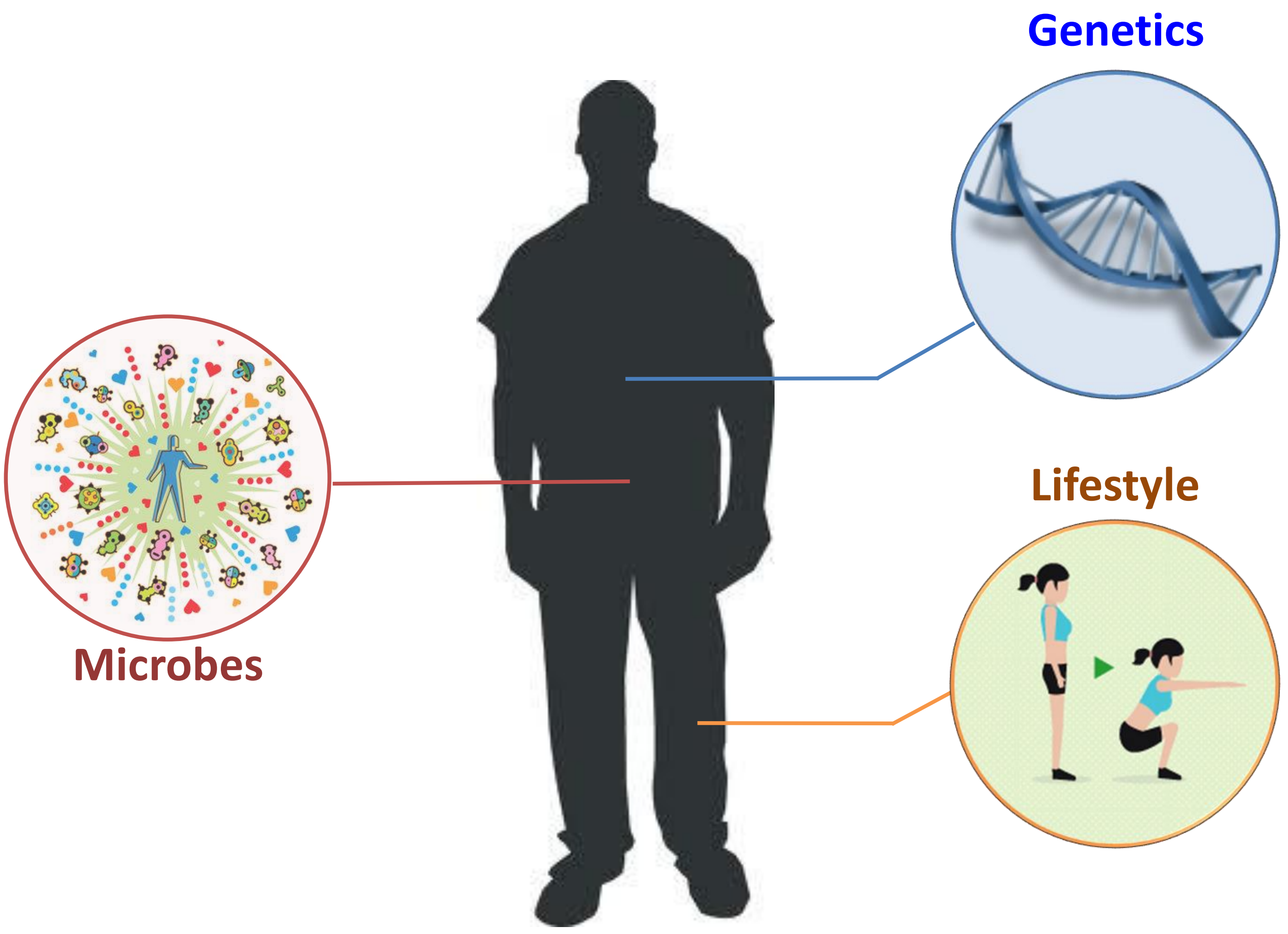


Artificial sweeteners induce glucose intolerance in mice



- ✓ Lean mice
- ✓ Obese mice
- ✓ Different formulations
- ✓ Different doses
- ✓ Different mouse strains

Do artificial sweeteners interact with the microbiome?



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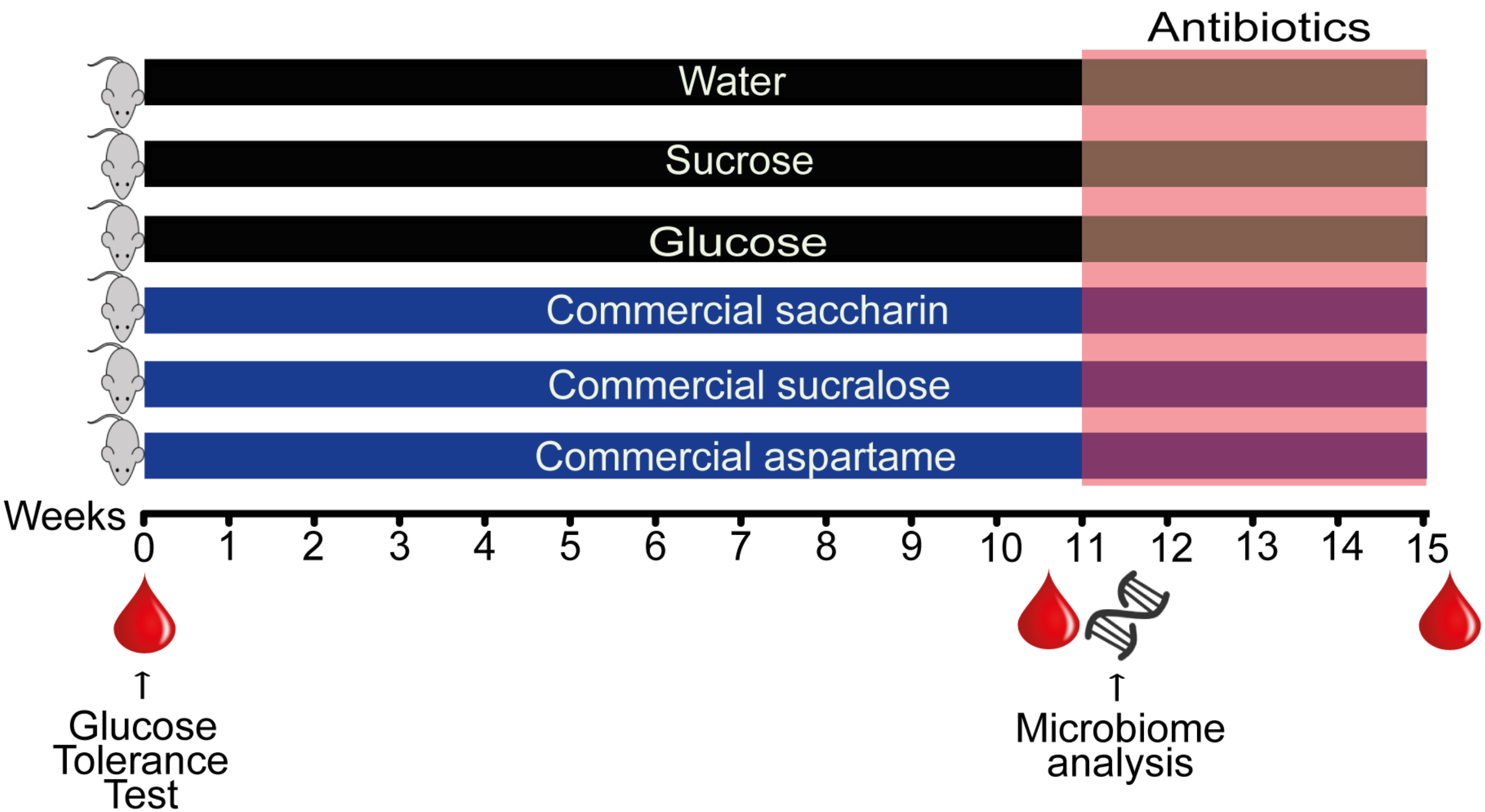
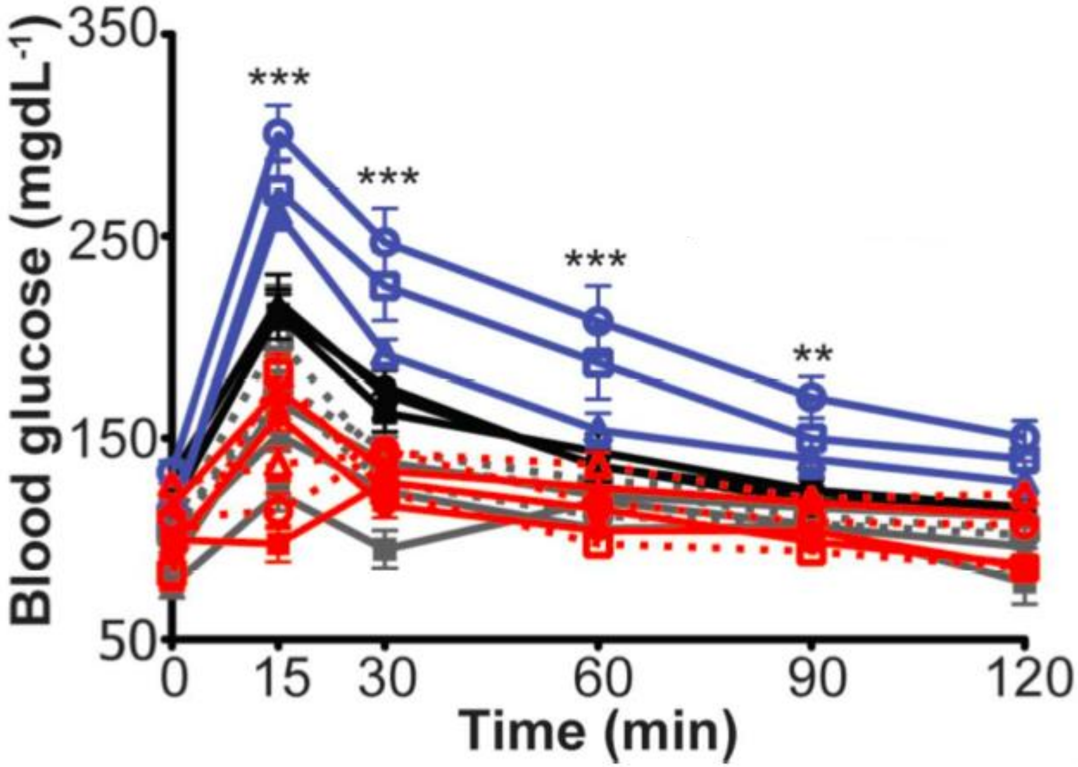
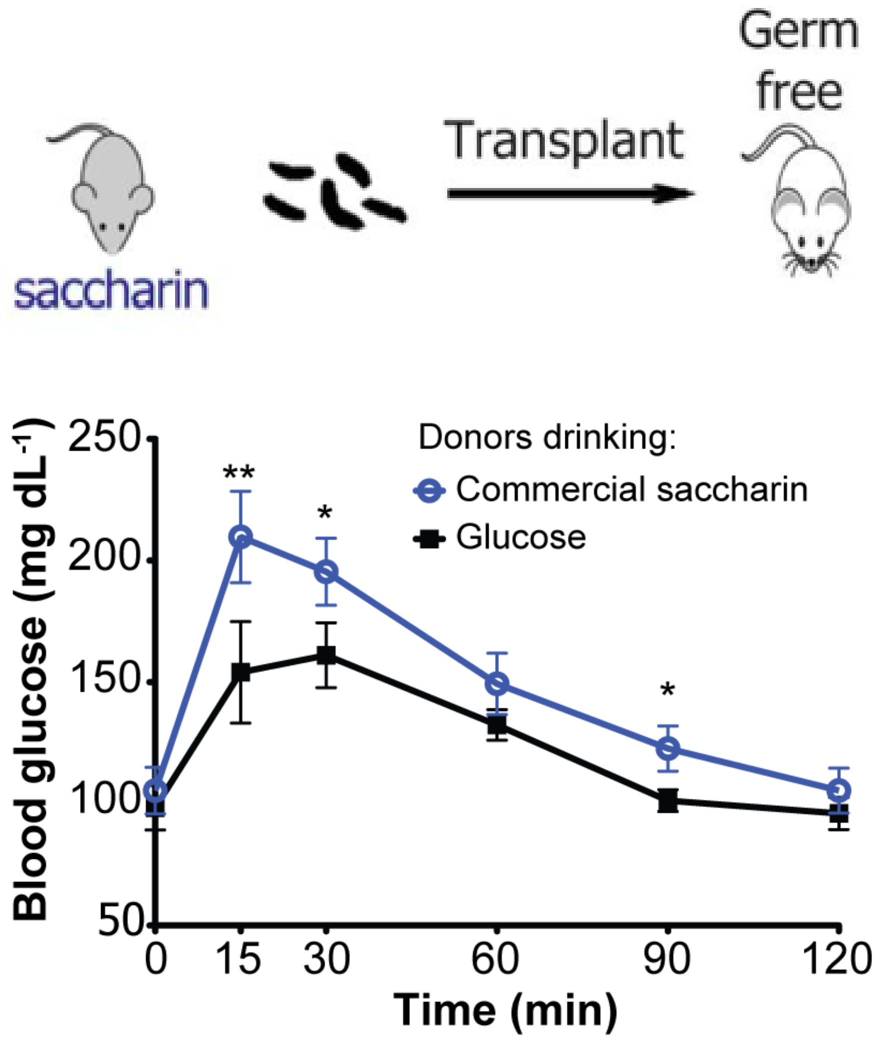


Antibiotics reverse the effect of artificial sweeteners

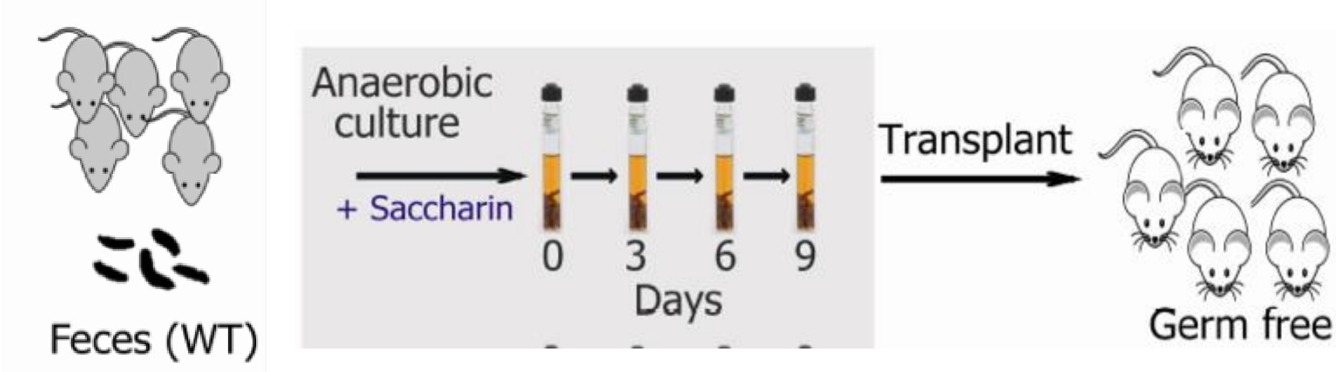


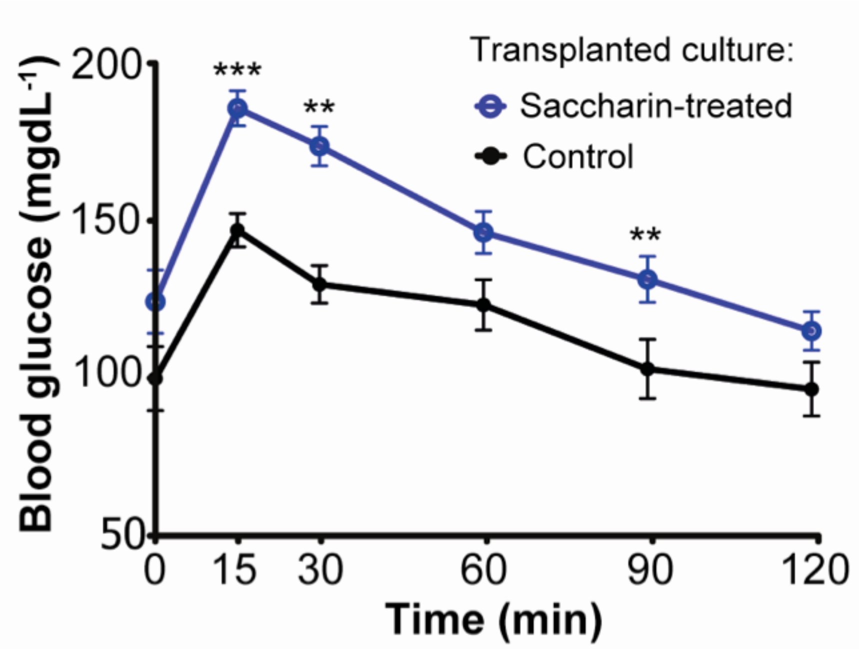
A, Ciprofloxacin & Metronidazole (targets Gram-)
B, Vancomycin (targets Gram+)

Transferring the microbiota of mice that consume artificial sweeteners transfers the glucose intolerance



Transferring the microbiota grown in the presence of artificial sweeteners transfers the glucose intolerance



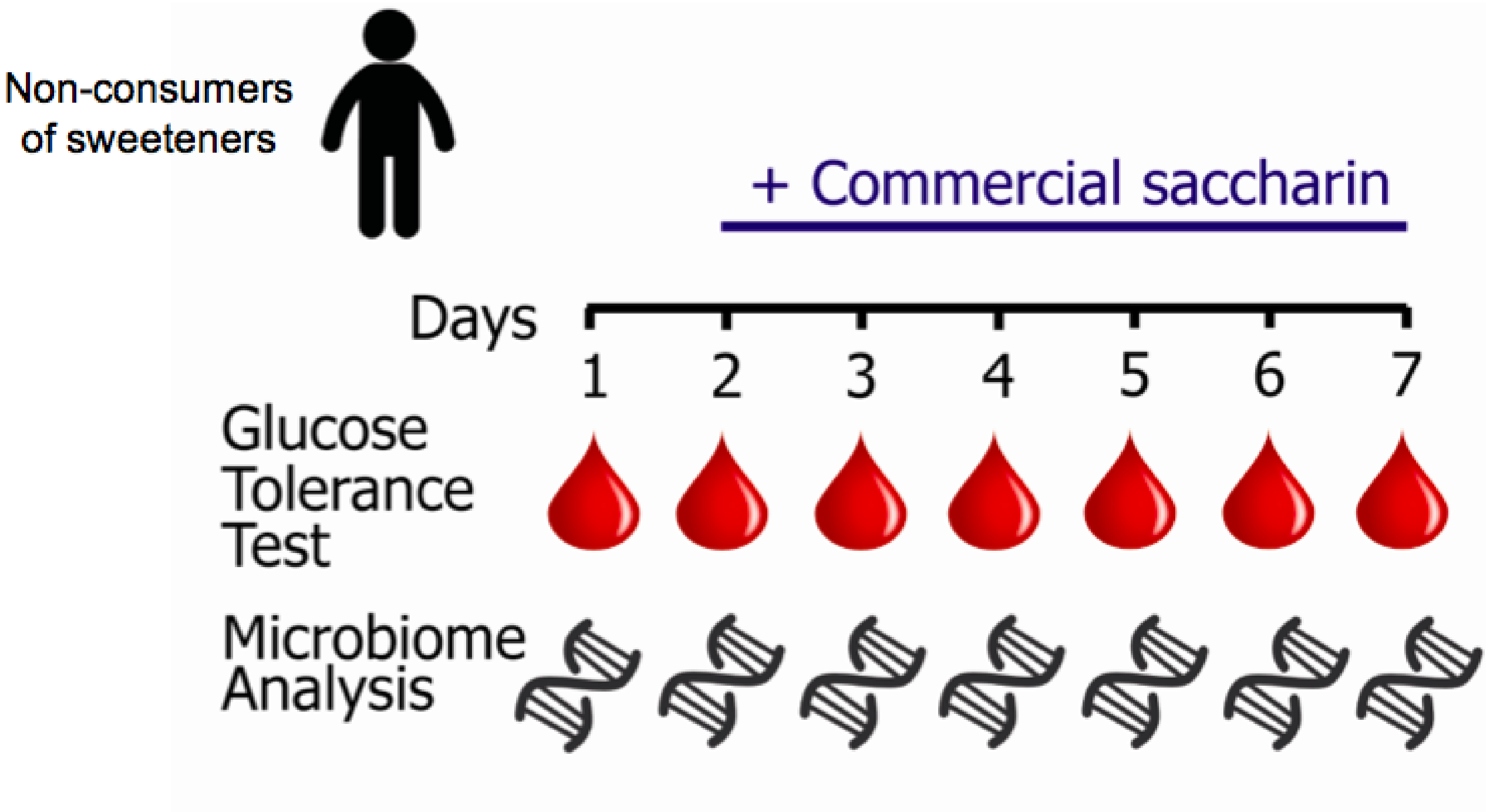


Suez et al., *Nature* 2014

Artificial sweeteners drive glucose intolerance in mice by altering the gut microbiota

… but what about people?

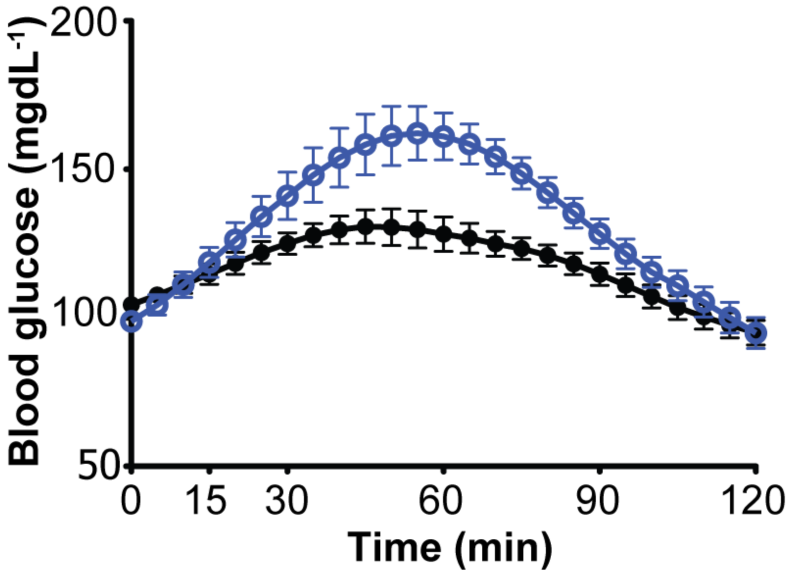
What happens to humans after just five days of consuming artificial sweeteners?



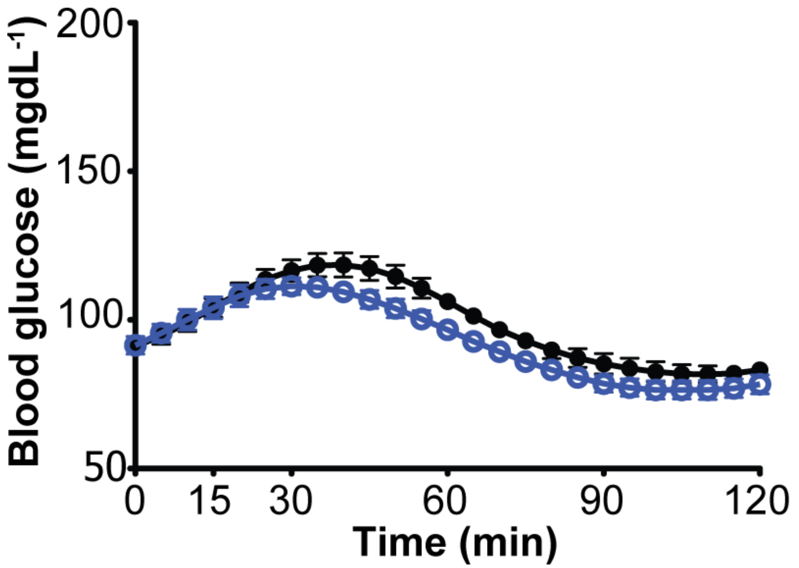
Suez et al., *Nature* 2014

Artificial sweeteners induce glucose intolerance in most but not all individuals

Responders

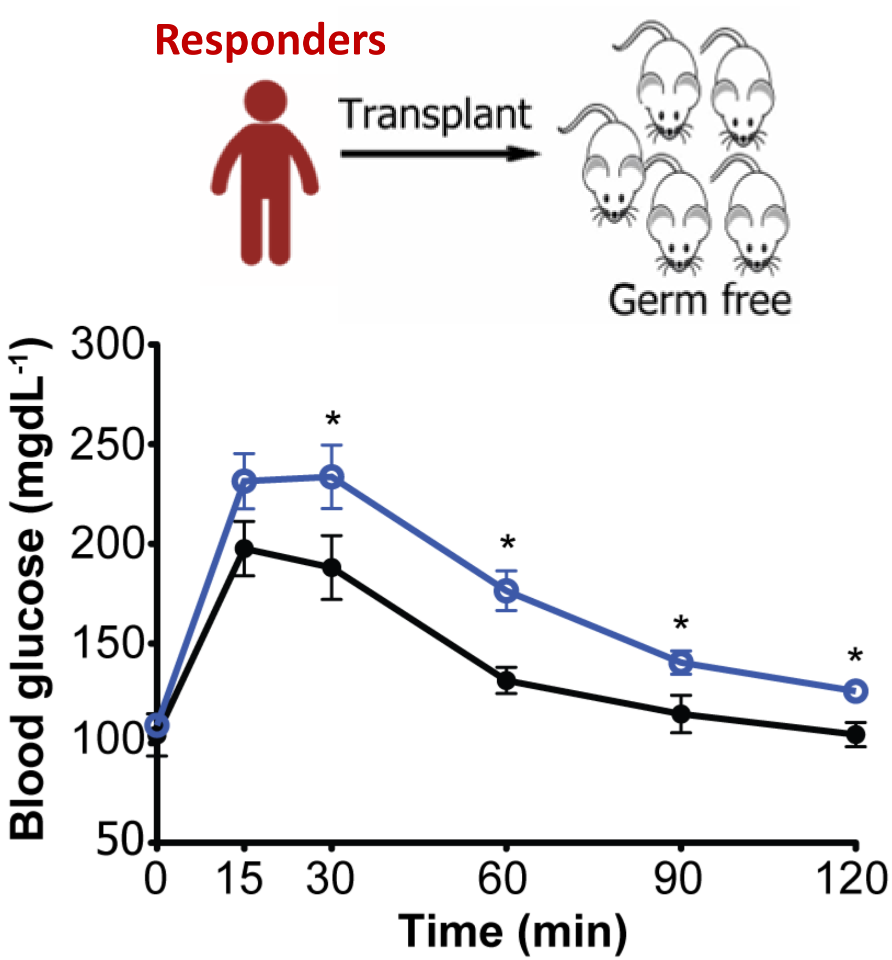


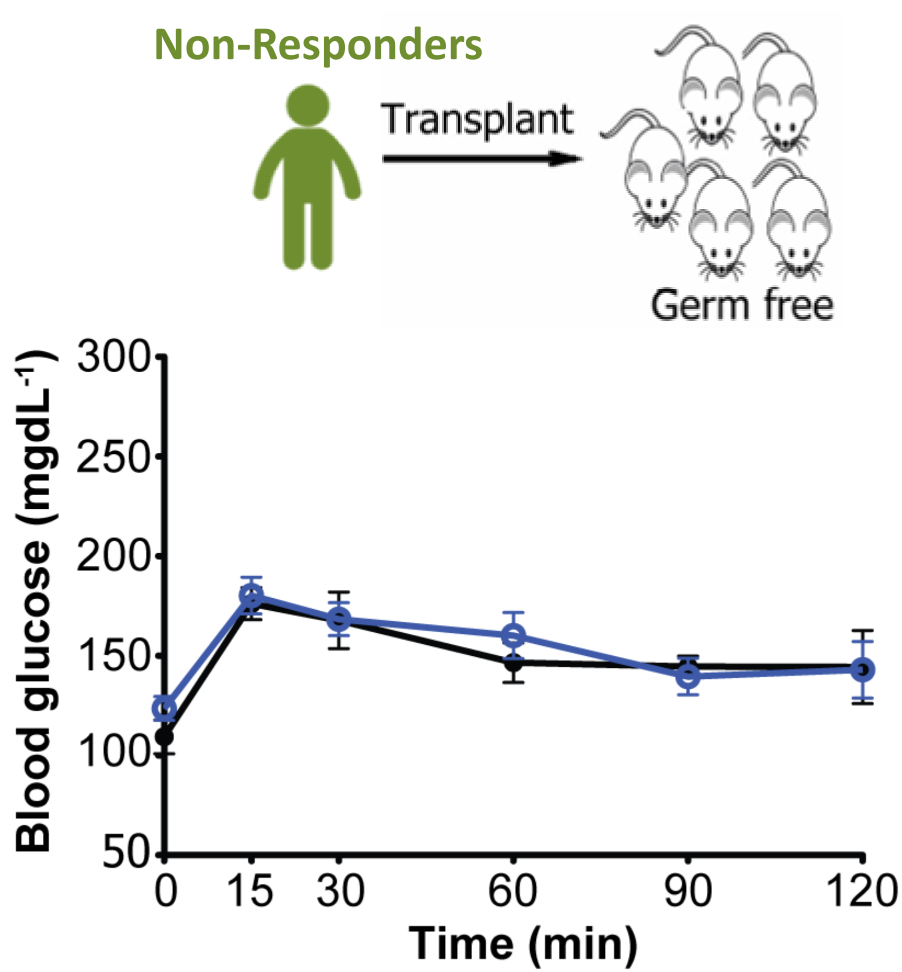
Non-responders



● Before massive consumption
● After massive consumption

Transferring the microbiota of responders to artificial sweeteners transfers the glucose intolerance phenotype





Suez et al., *Nature* 2014

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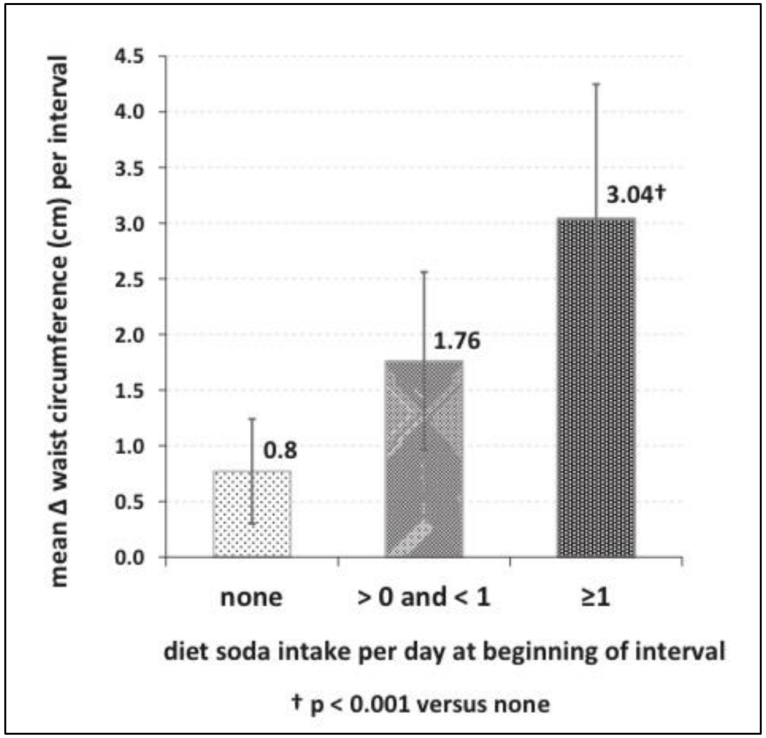
Validation studies (2015)



CLINICAL INVESTIGATIONS

Diet Soda Intake Is Associated with Long-Term Increases in Waist Circumference in a Biethnic Cohort of Older Adults: The San Antonio Longitudinal Study of Aging

Sharon P.G. Fowler, MPH, Ken Williams, MS,*† and Helen P. Hazuda, PhD**

Positive association between artificially sweetened beverage consumption and incidence of diabetes

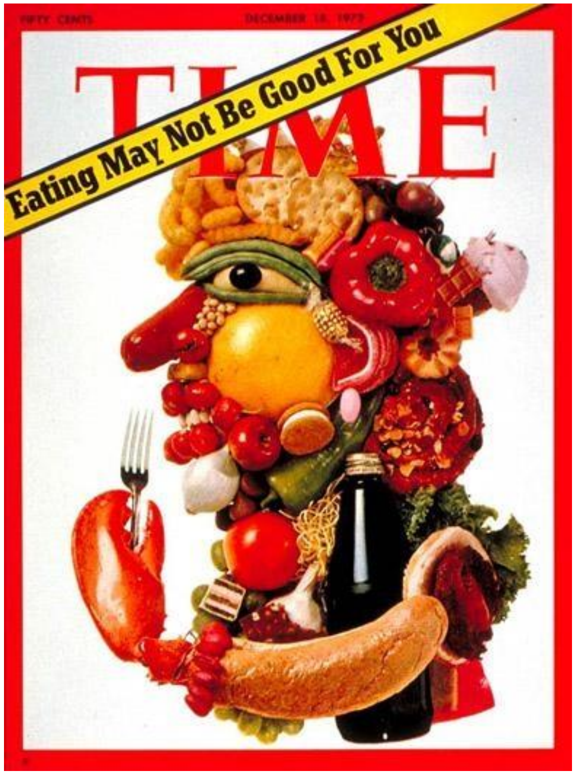
Allison C. Sylvetsky Meni[1,2] & Susan E. Swithers[3] & Kristina I. Rother[1]

Diet Drink Consumption and the Risk of Cardiovascular Events: A Report from the Women's Health Initiative

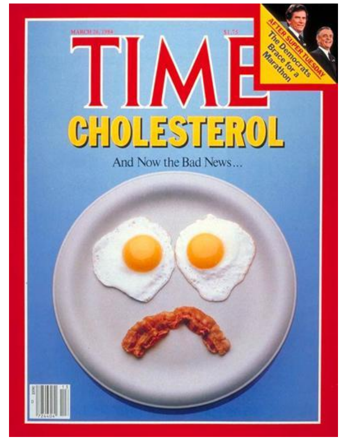
Ankur Vyas, MD[1], Linda Rubenstein, PhD[2], Jennifer Robinson, MD, MPH[1,2], Rebecca A. Seguin, PhD, CSCS[3], Mara Z. Vitolins, DrPH, MPH, RD[4], Rasa Kazlauskaite, MD, MSc, FACE[5,6], James M. Shikany, DrPH[7], Karen C. Johnson, MD, MPH[8], Linda Snetselaar, RD, PhD[2], and Robert Wallace, MD, MSc[2,9]

If nutritional changes drove the metabolic syndrome epidemic, can it be treated by restoring healthy nutrition?

What is healthy nutrition?

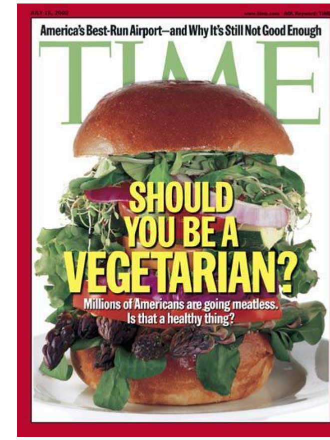


1972



1984

1999



2002

2003

2011

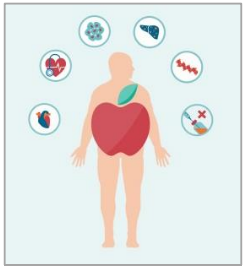
2014

How can we take a science-based approach to nutrition?

David Zeevi

What should a marker of healthy nutrition satisfy?

Relevant for weight management

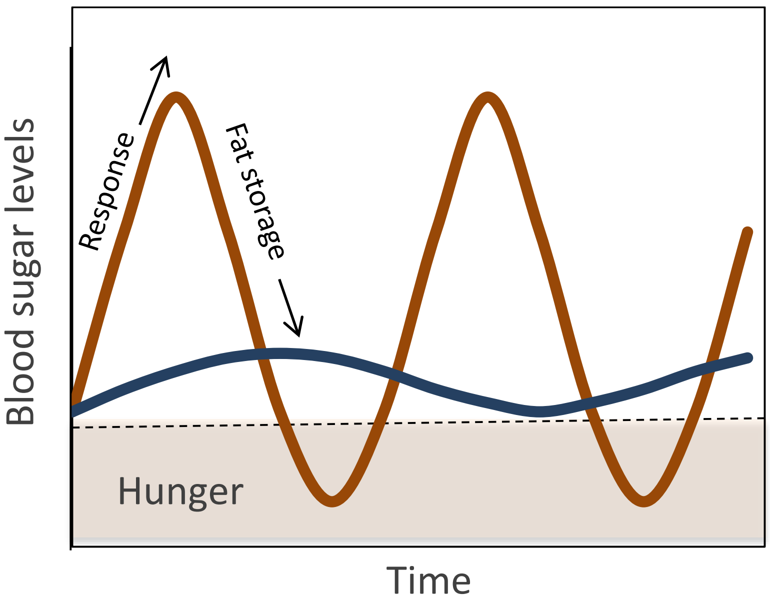


Relevant for metabolic disease

Easily measurable quantitatively

Postprandial (post-meal) glucose response as a measure of healthy nutrition

Directly affects fat storage, weight gain and hunger



Strongly associated with disease

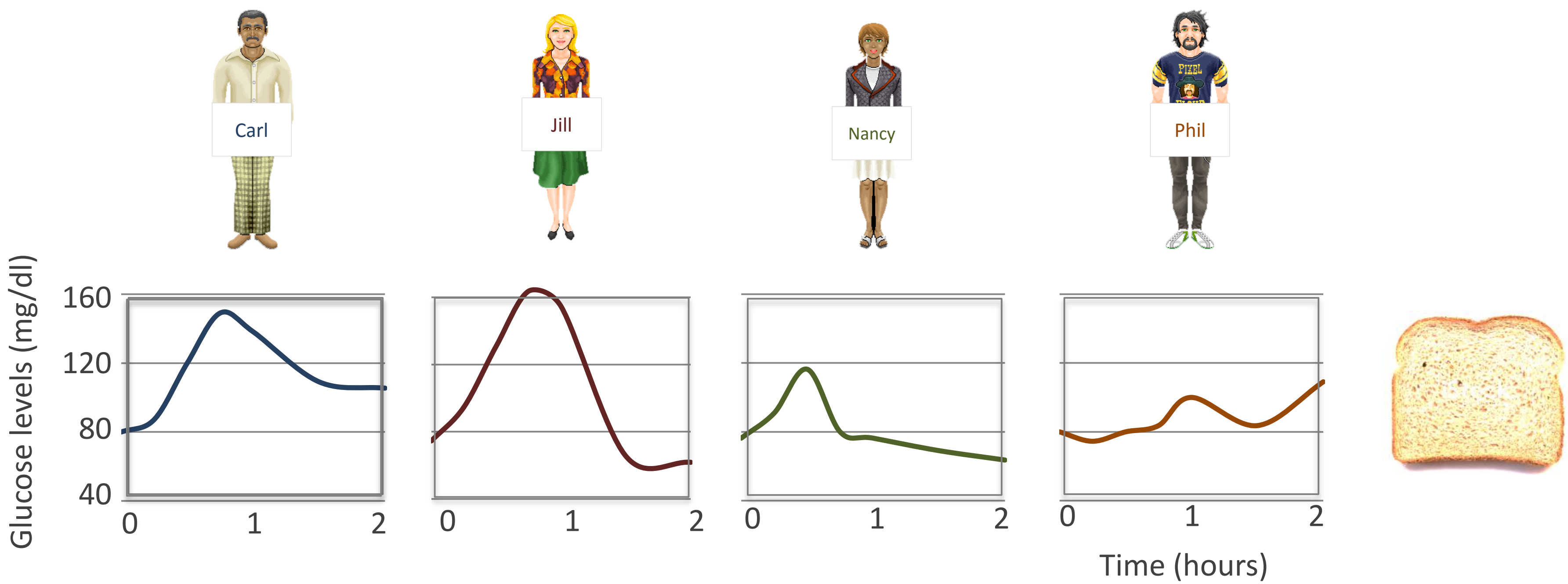
- Diabetes
- Obesity
- Cardiovascular disease
- Chronic metabolic disorders

Easily measurable

Bonora et al., *Diabetologia* 2001; Cavalot et al., *Diabetes Care* 2011; Wang et al., *Diabetes Care* 2004; Temelkova-Kurktschiev et al., *Diabetes Care* 2000; O'Keefe et al., Am J Cardiol 2007

Maintaining normal blood glucose levels is key to fighting the rise in disease

People have widely different glucose responses to the same food



Adapted from Vega-López *et al.*, Diabetes Care 2007

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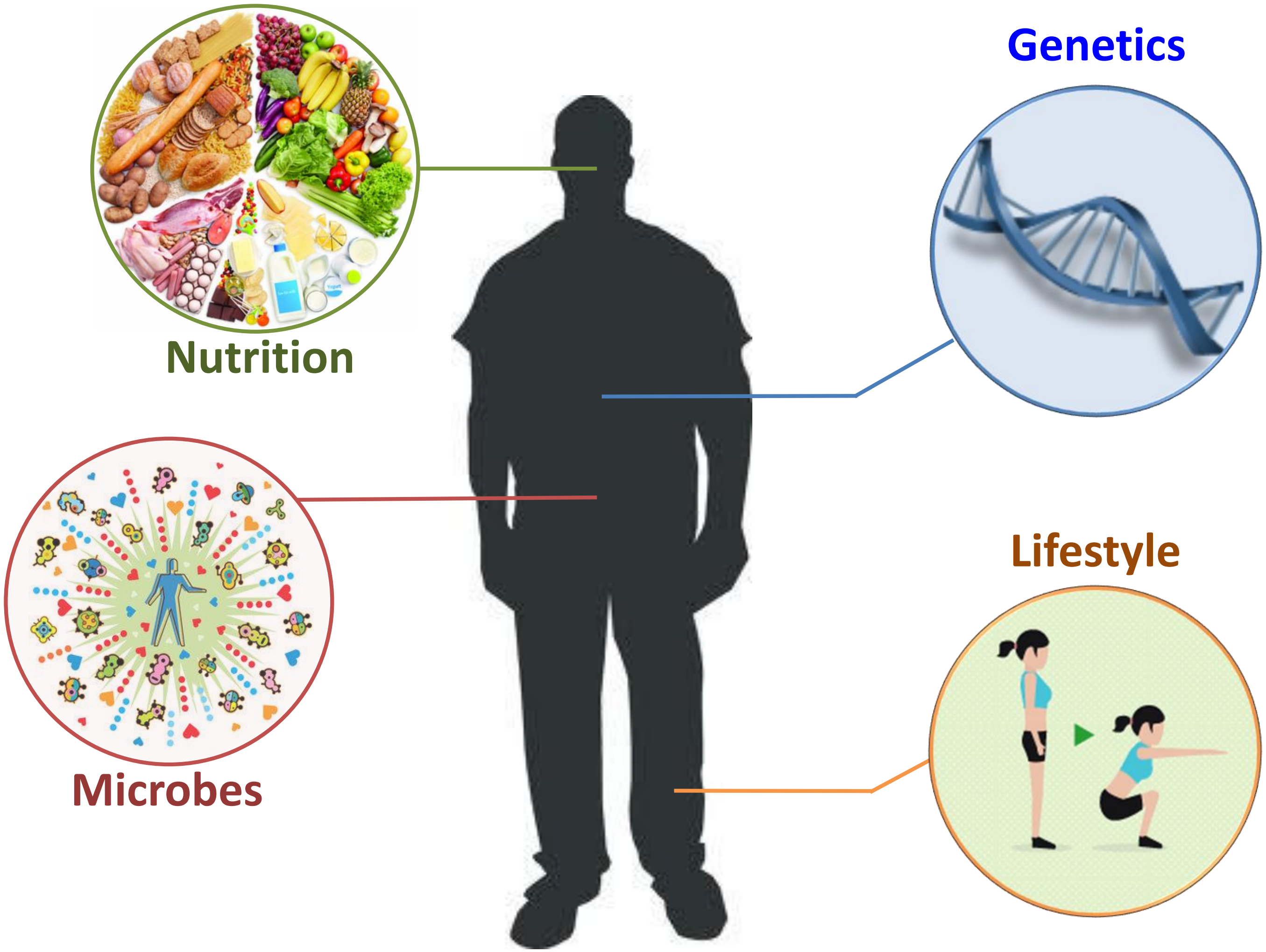
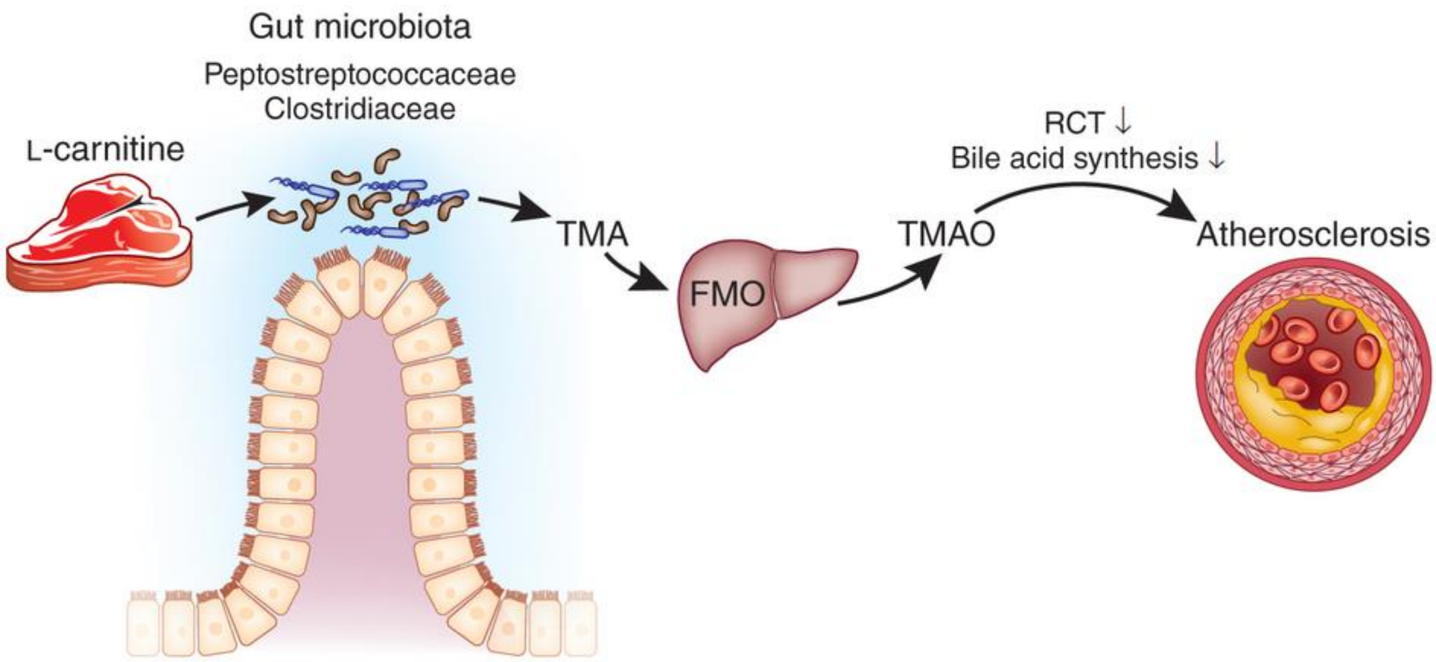
Diets that maintain normal blood glucose levels must be personally tailored

What could affect our response to food?

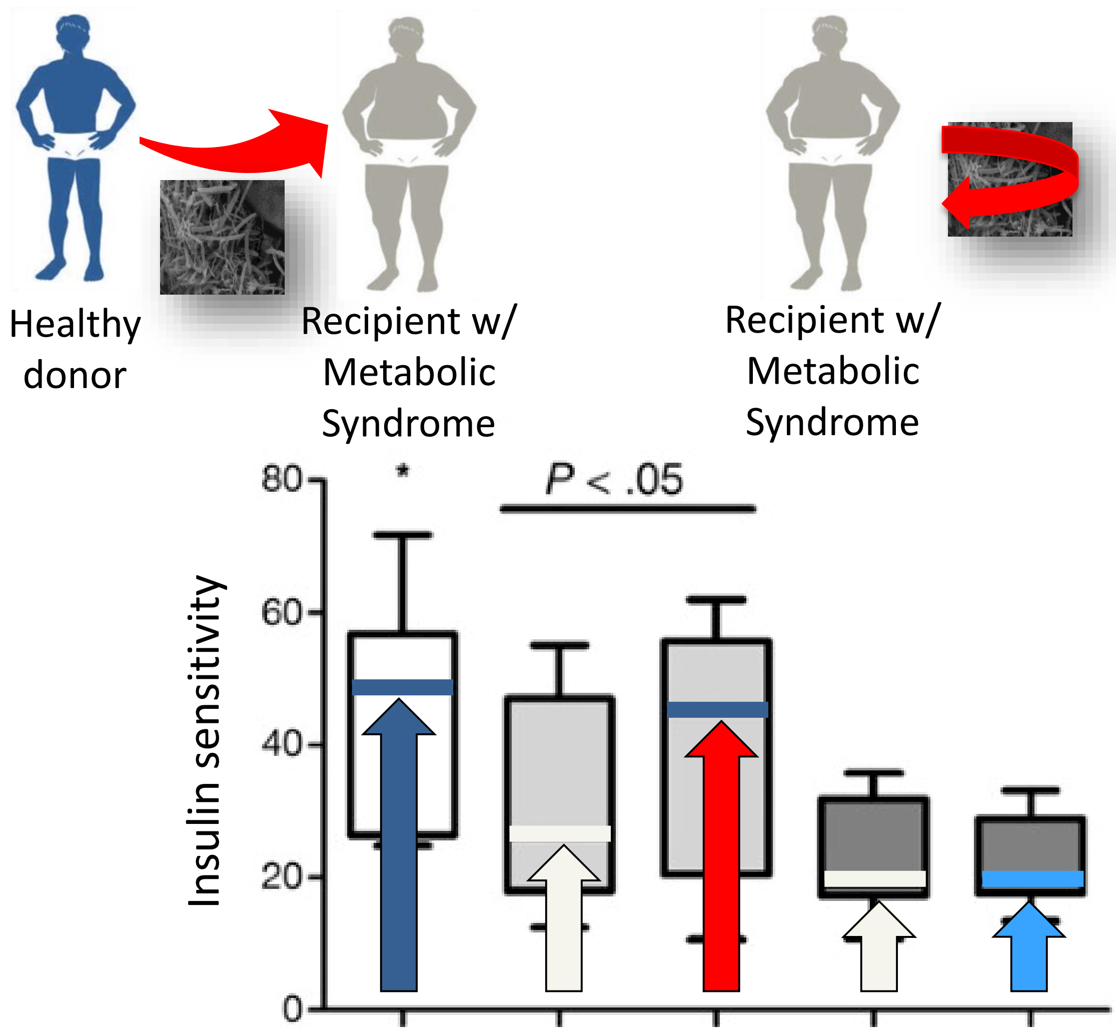


The microbiome affects our response to food



Koeth *et al.*, Nature Medicine 2013

Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome



Vrieze et al, *Gastroenterology* 2012

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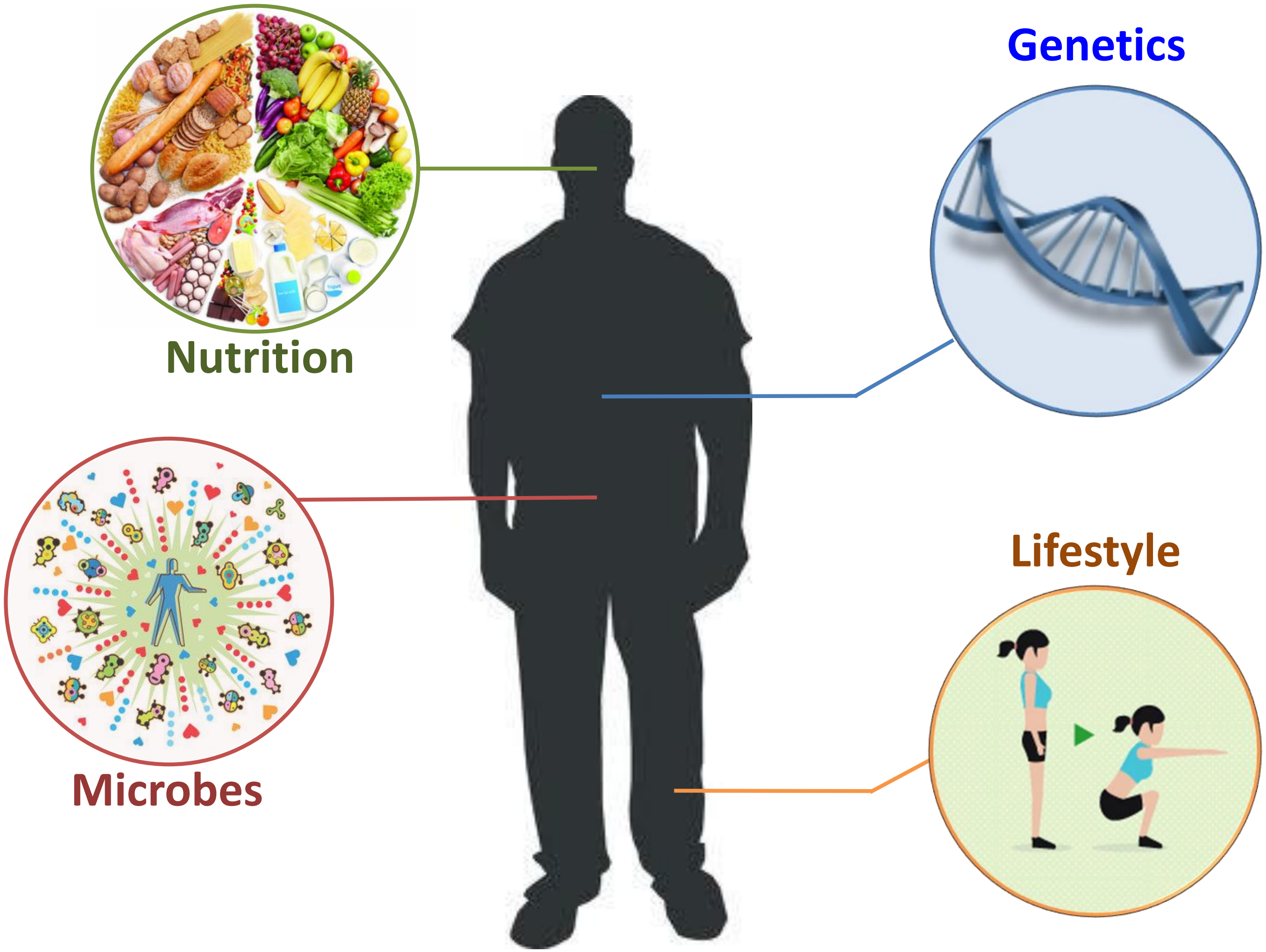
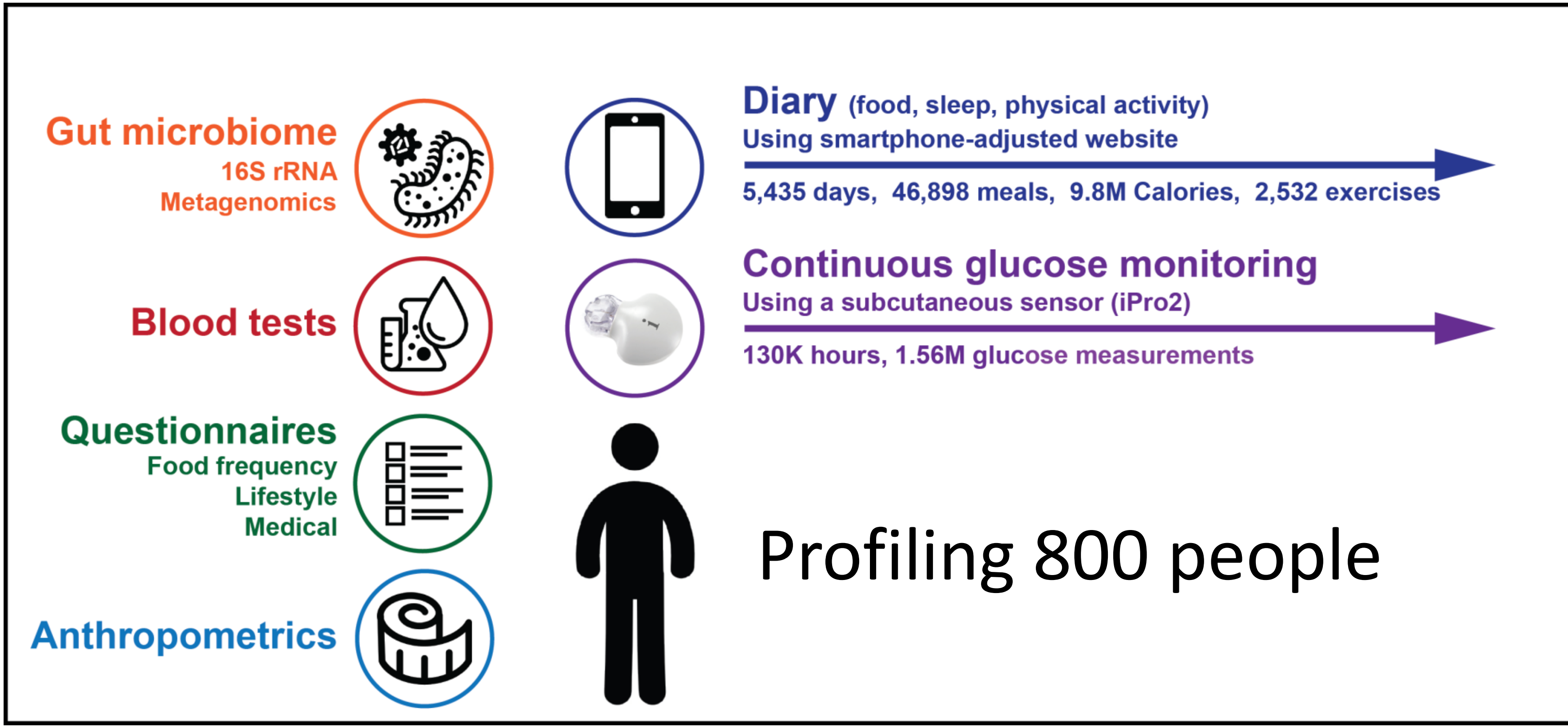
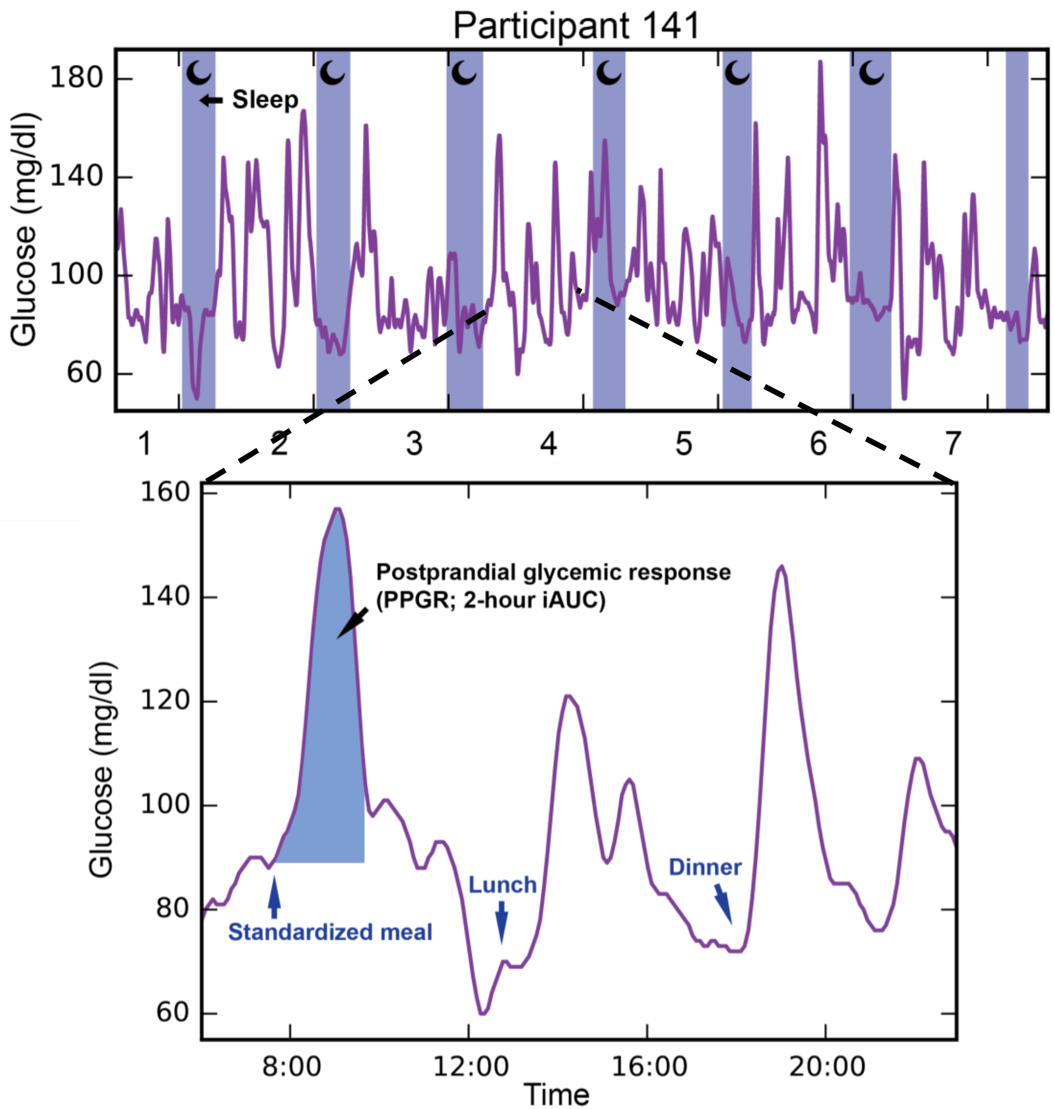
What could affect our response to food?



The Personalized Nutrition Project: Clinical and microbiome data collected



Continuous glucose monitoring



Zeevi *et al.*, Cell 2015

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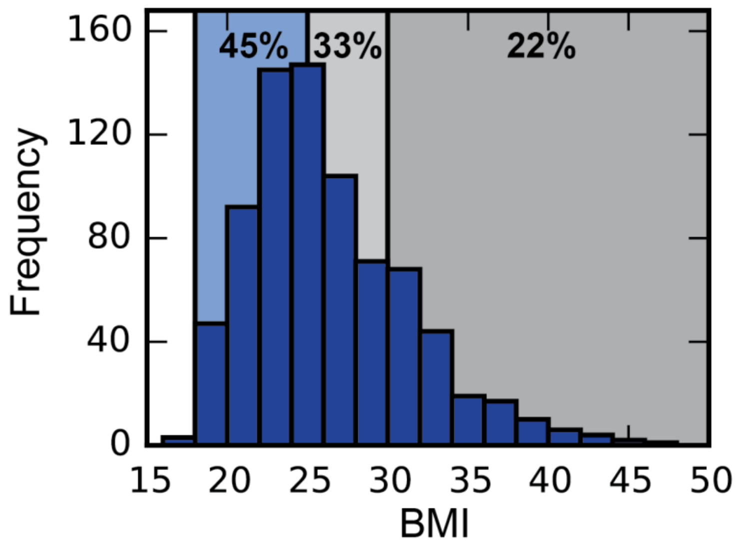
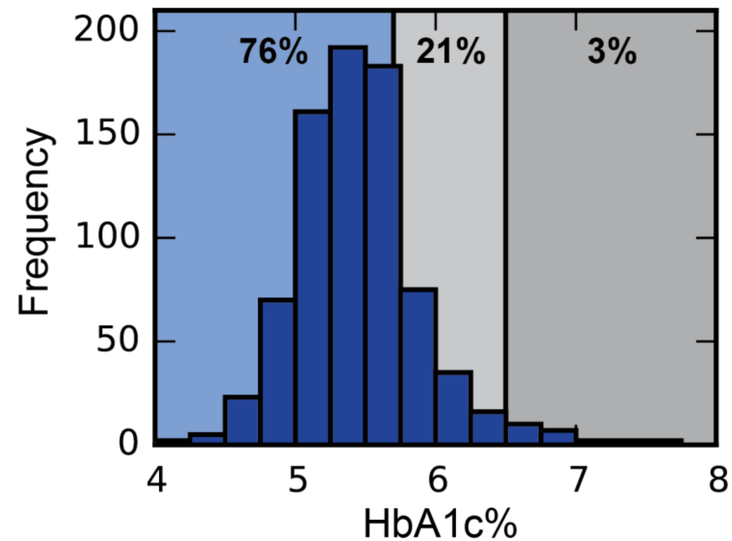
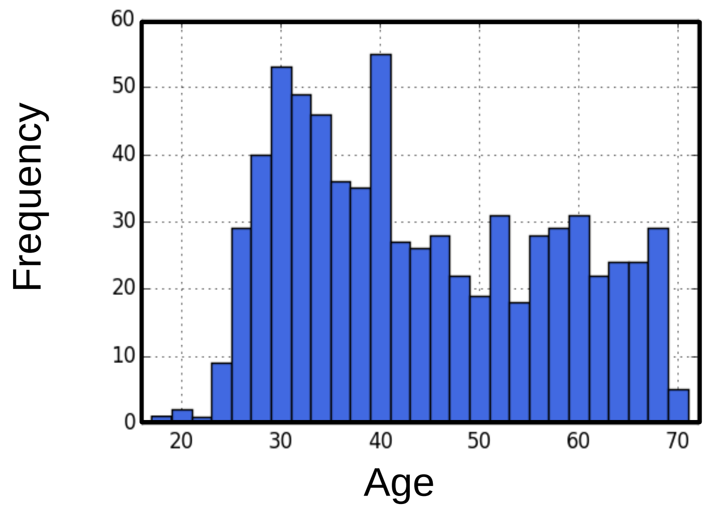
The Personalized Nutrition Project: Cohort statistics







- 25-70 years of age
- 55% overweight
- 22% obese
- 21% pre-diabetic

Zeevi *et al.*, Cell 2015

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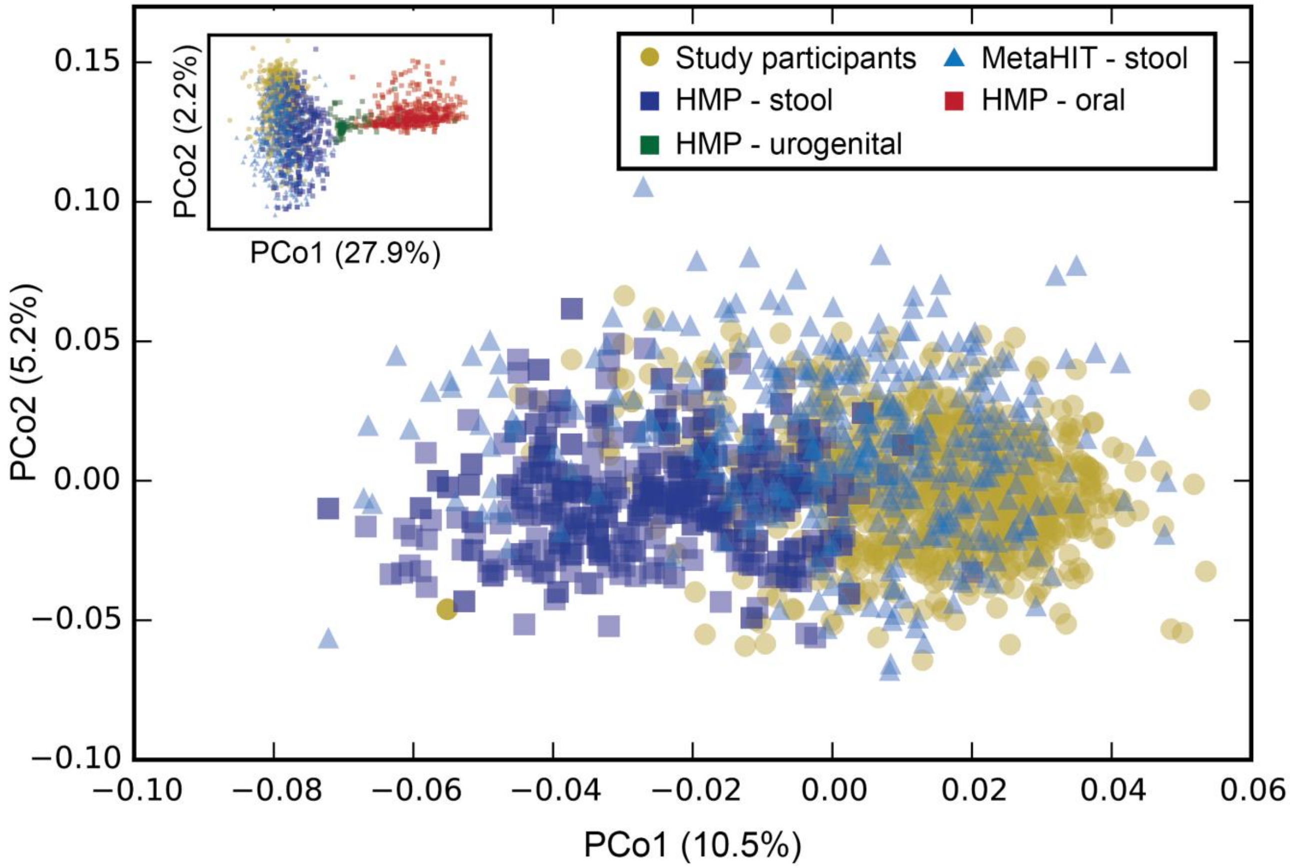
Cohort bacterial composition comparable to other international cohorts



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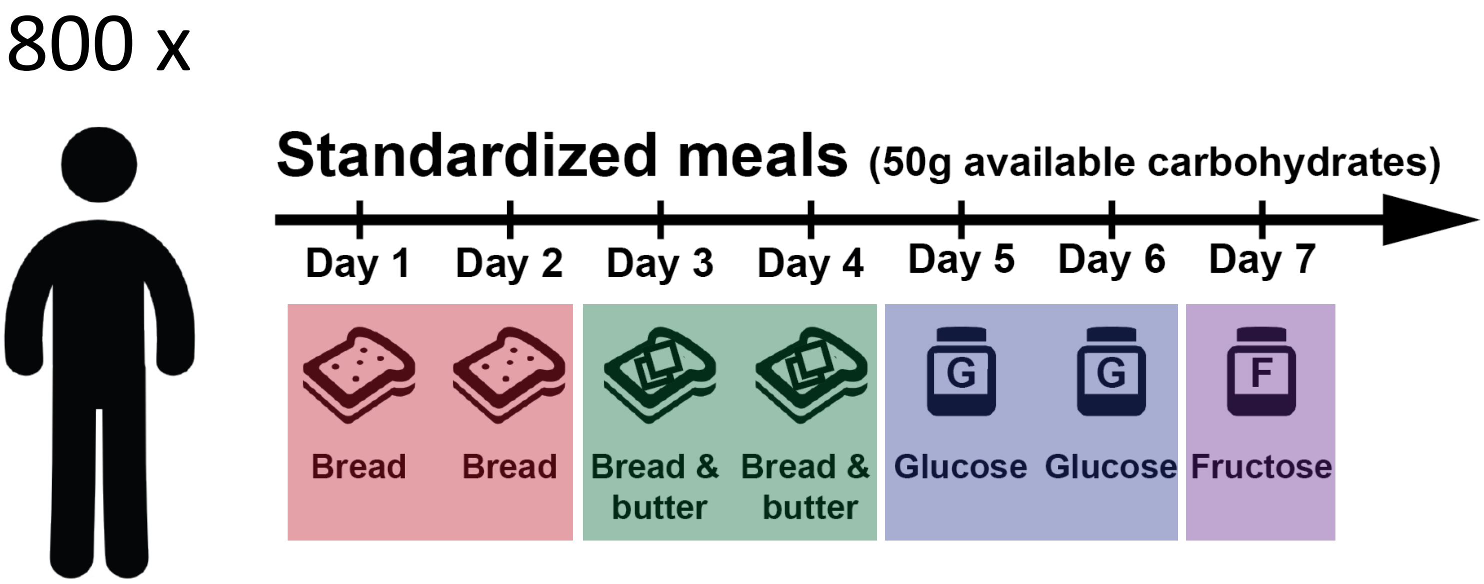
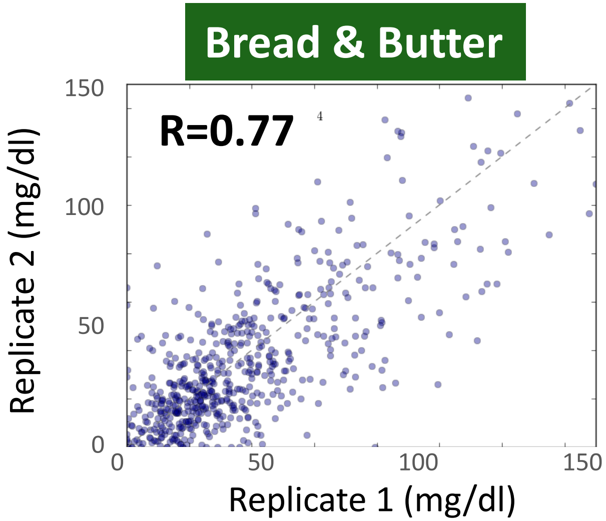
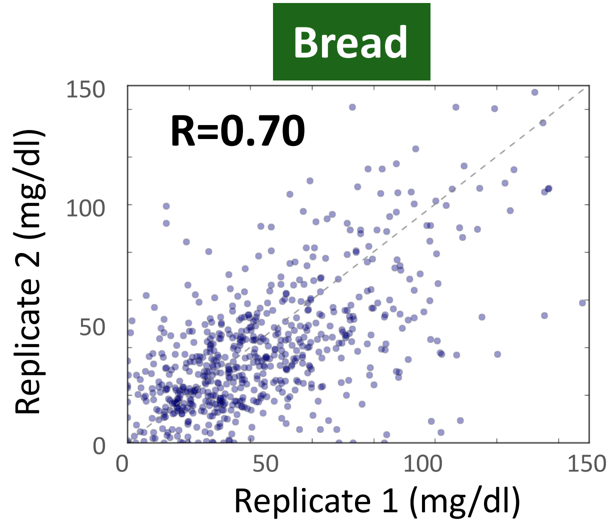
What is the variability across people in the response to the same food?

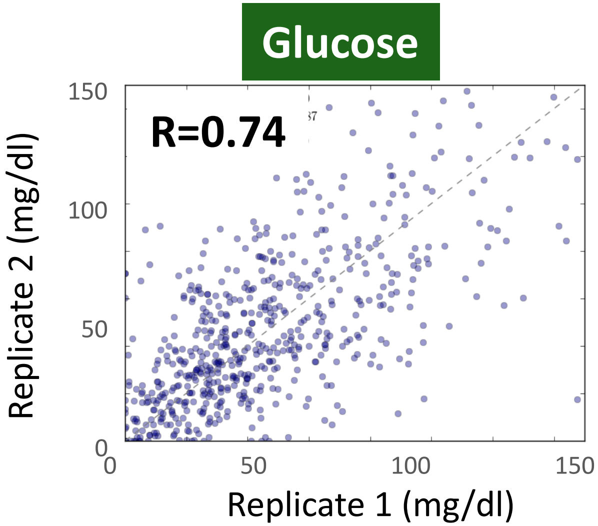
Testing the cohort response to standardized meals



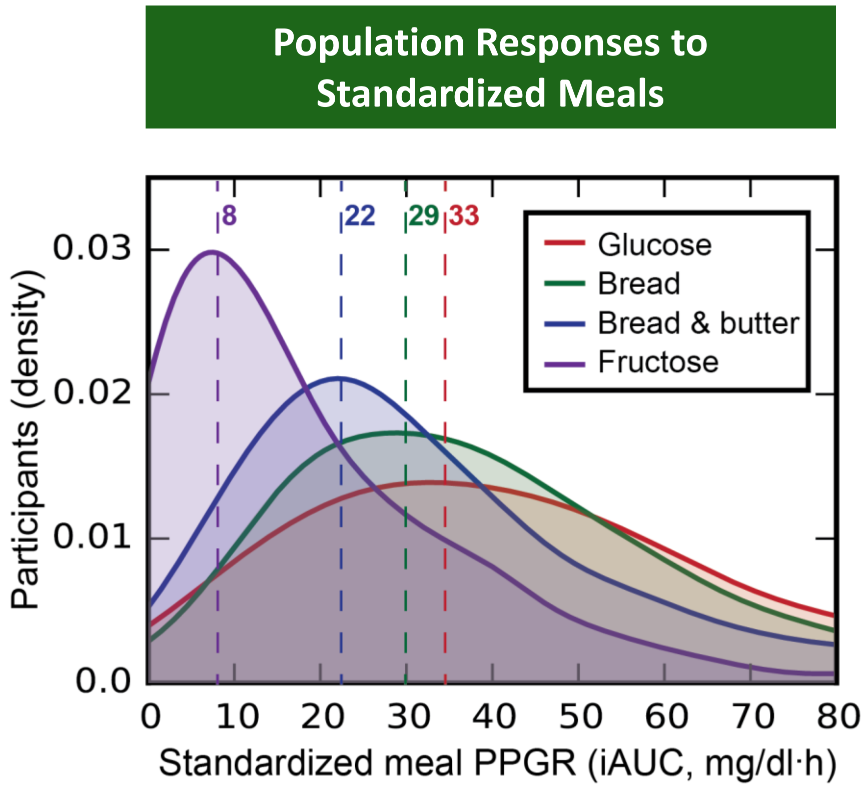
The same person has a highly similar post-meal response to the same standardized meal across different days

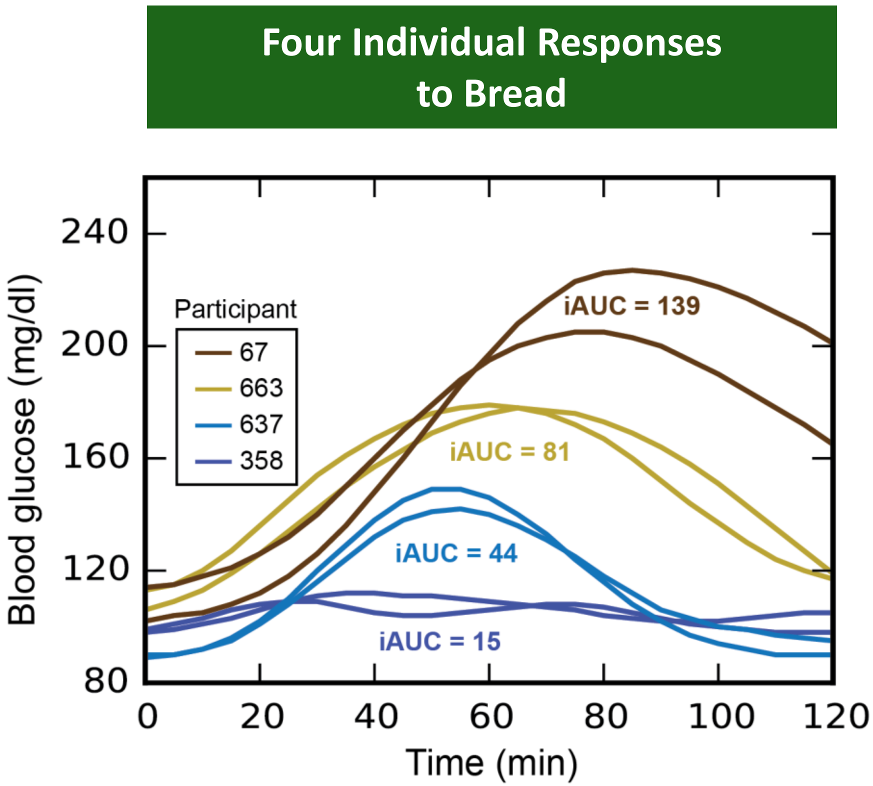






Different people have widely different post-meal responses to the same standardized meal





Zeevi *et al.*, Cell 2015

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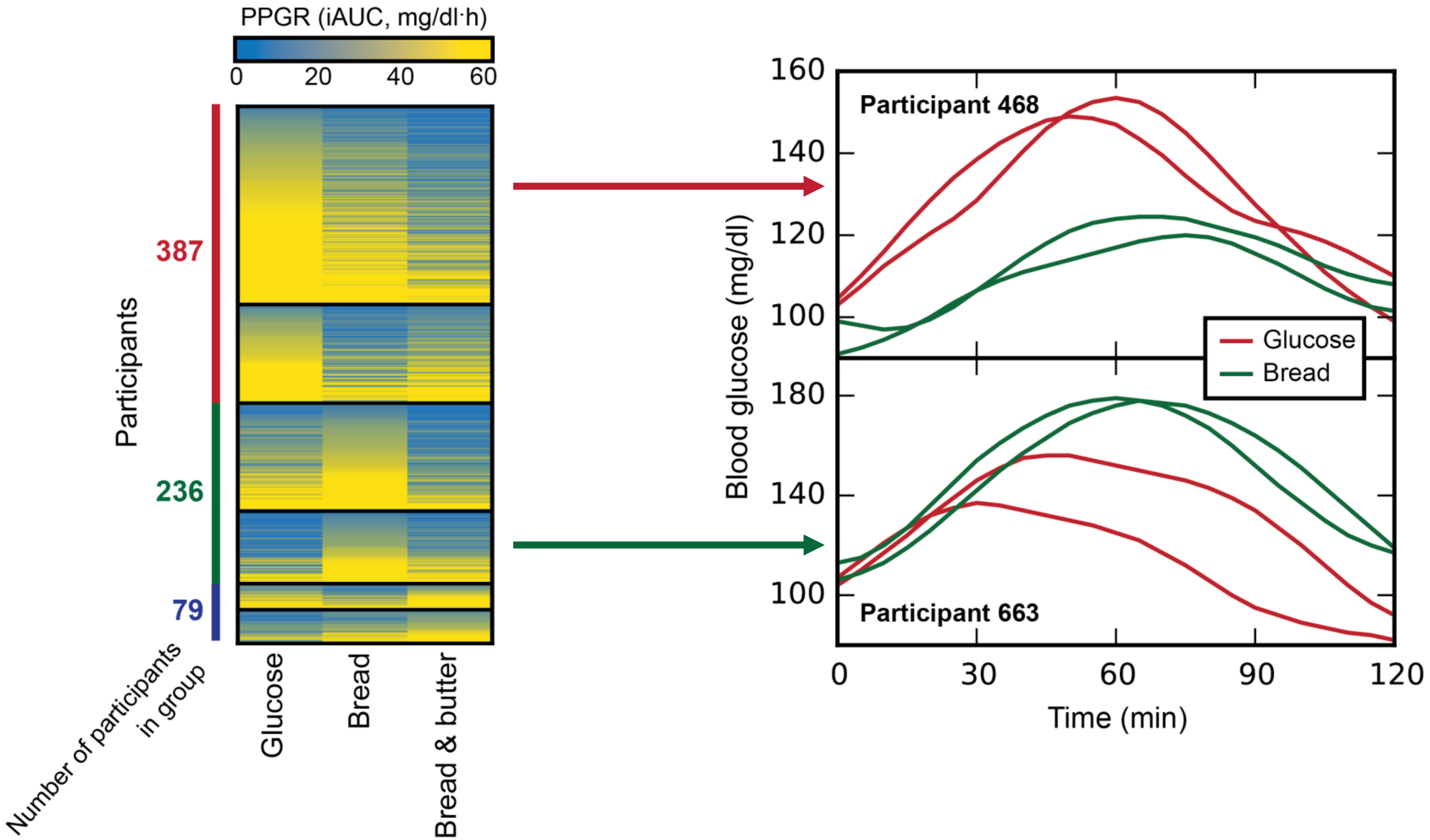
Different people have opposite responses to different standardized meals



Zeevi *et al.*, Cell 2015

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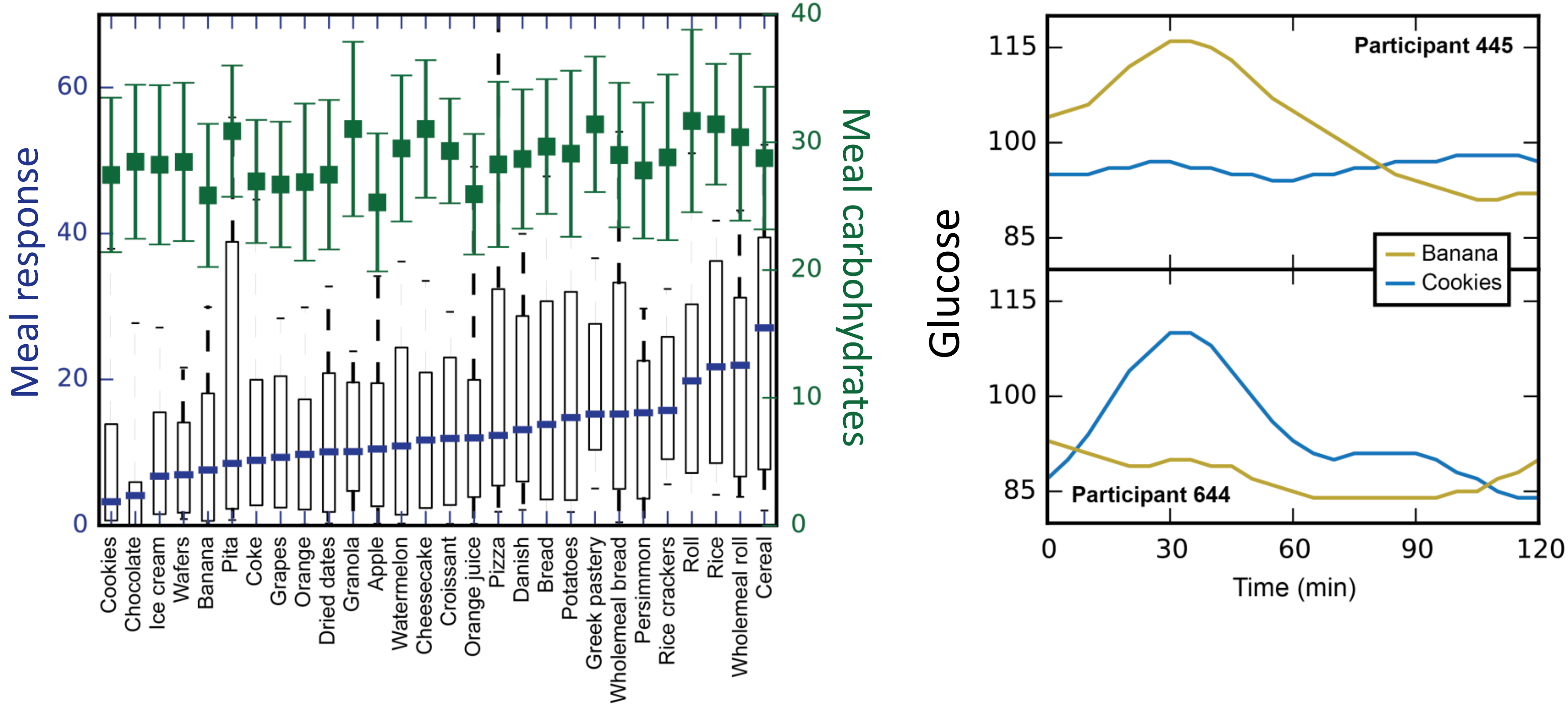
Different people have widely different post-meal responses to the same real-life meals



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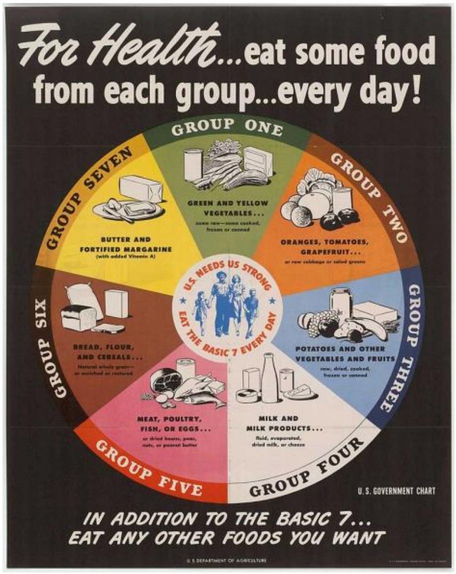
General recommendations in nutrition



1943

1992

2015

Source: USDA

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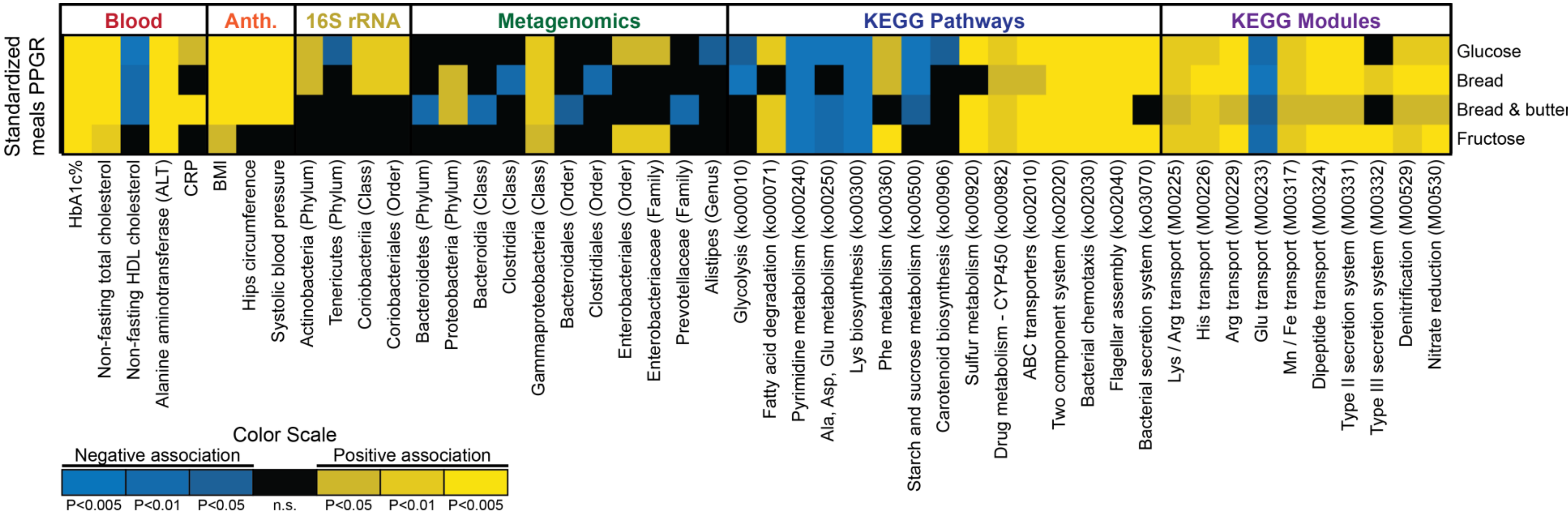
What explains the variability in people's response to the same food?

Variability in post-meal glucose response across people associates with microbiota composition and function



Zeevi *et al.*, Cell 2015

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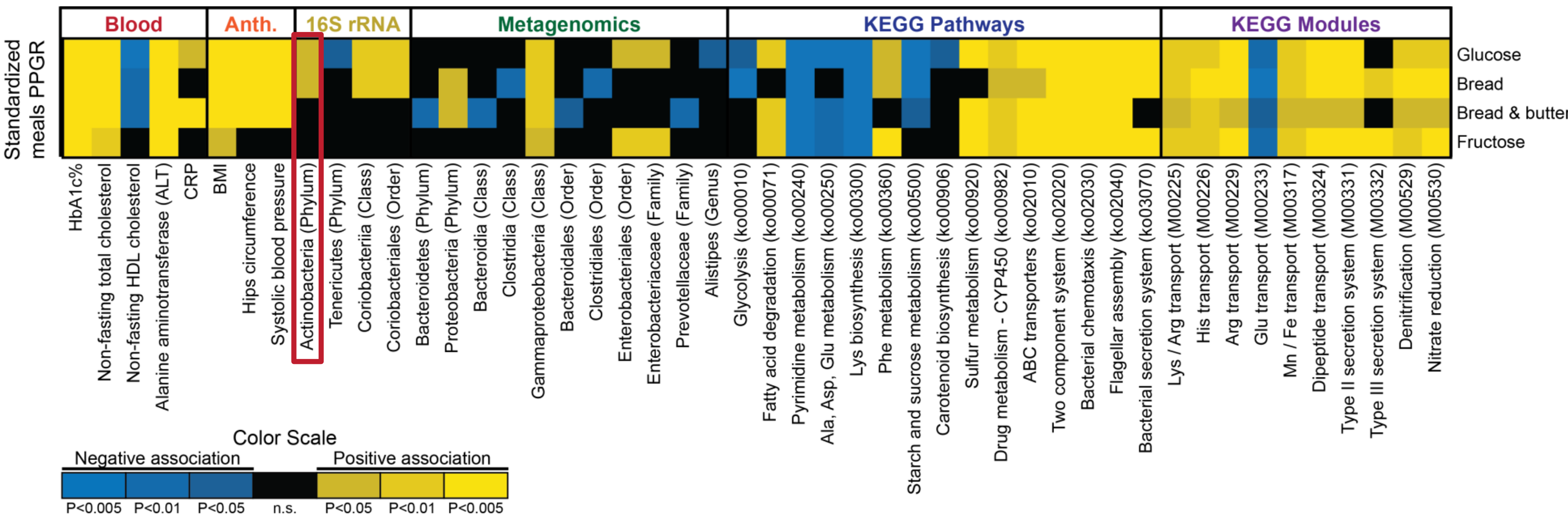
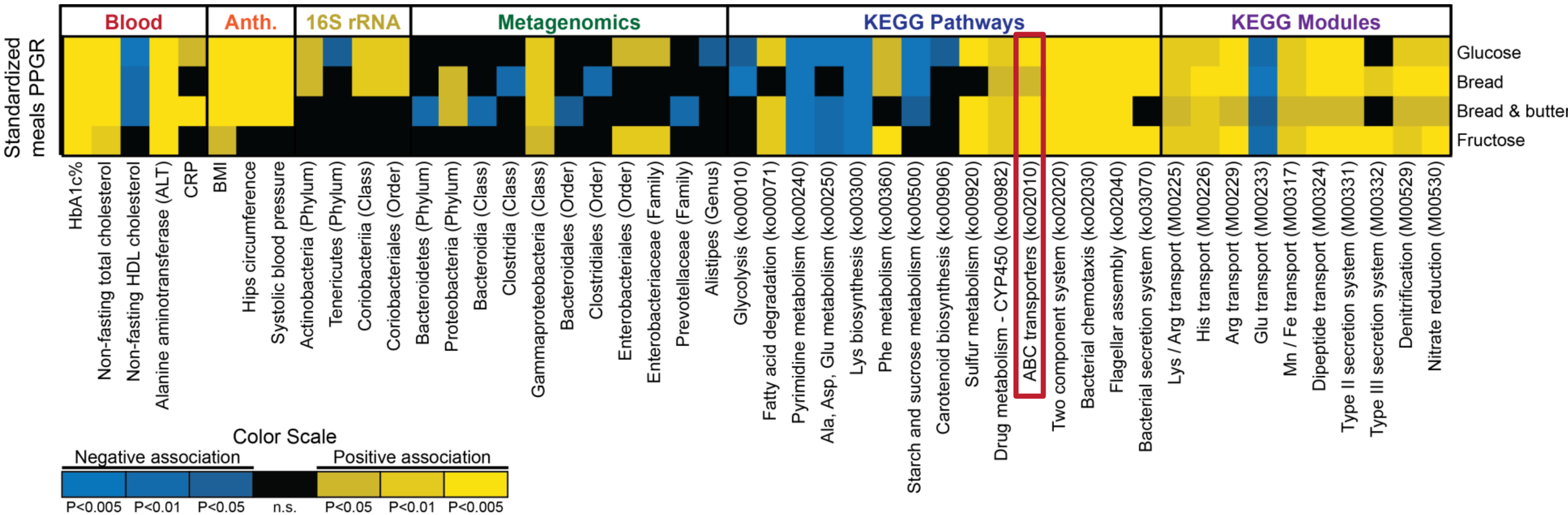
Variability in post-meal glucose response across people associates with microbiota composition and function



- **Positive association** with PPGR to **glucose + bread**
- High levels associate with a **high-fat low-fiber diet**

(Wu et al., 2011)

Positive association between ABC transporters and post-meal glucose response to all standardized meals

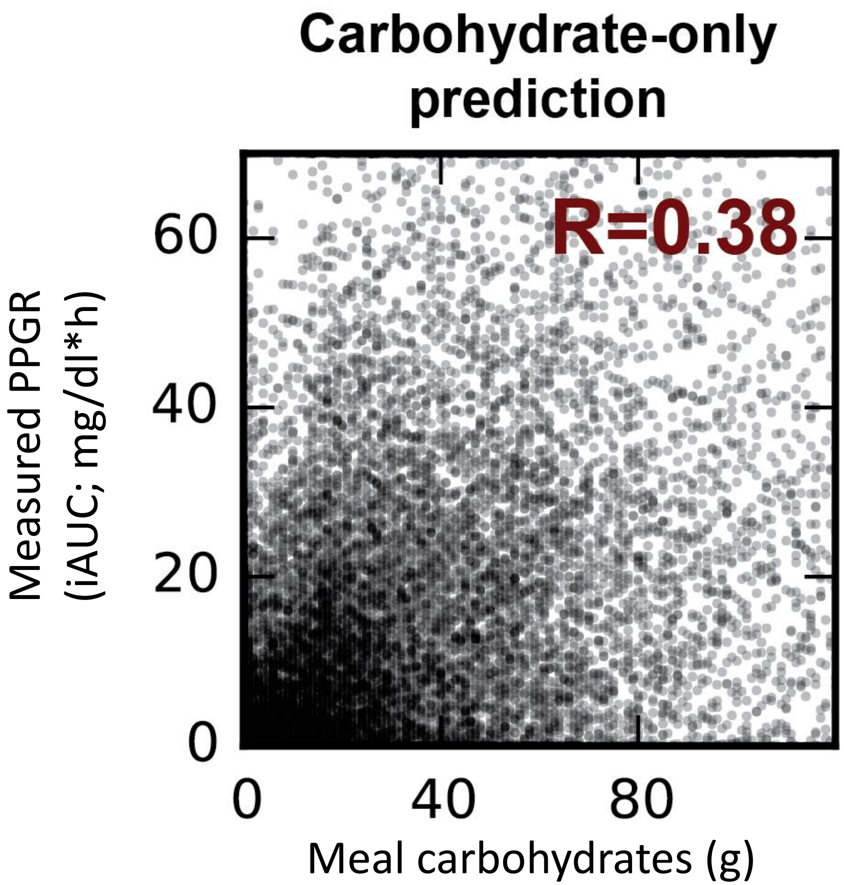


- Positive association with **TIIDM** (Karlsson et al., 2013)
- Positive association with **western high-fat/high-sugar diet** (Turnbaugh et al., 2009)

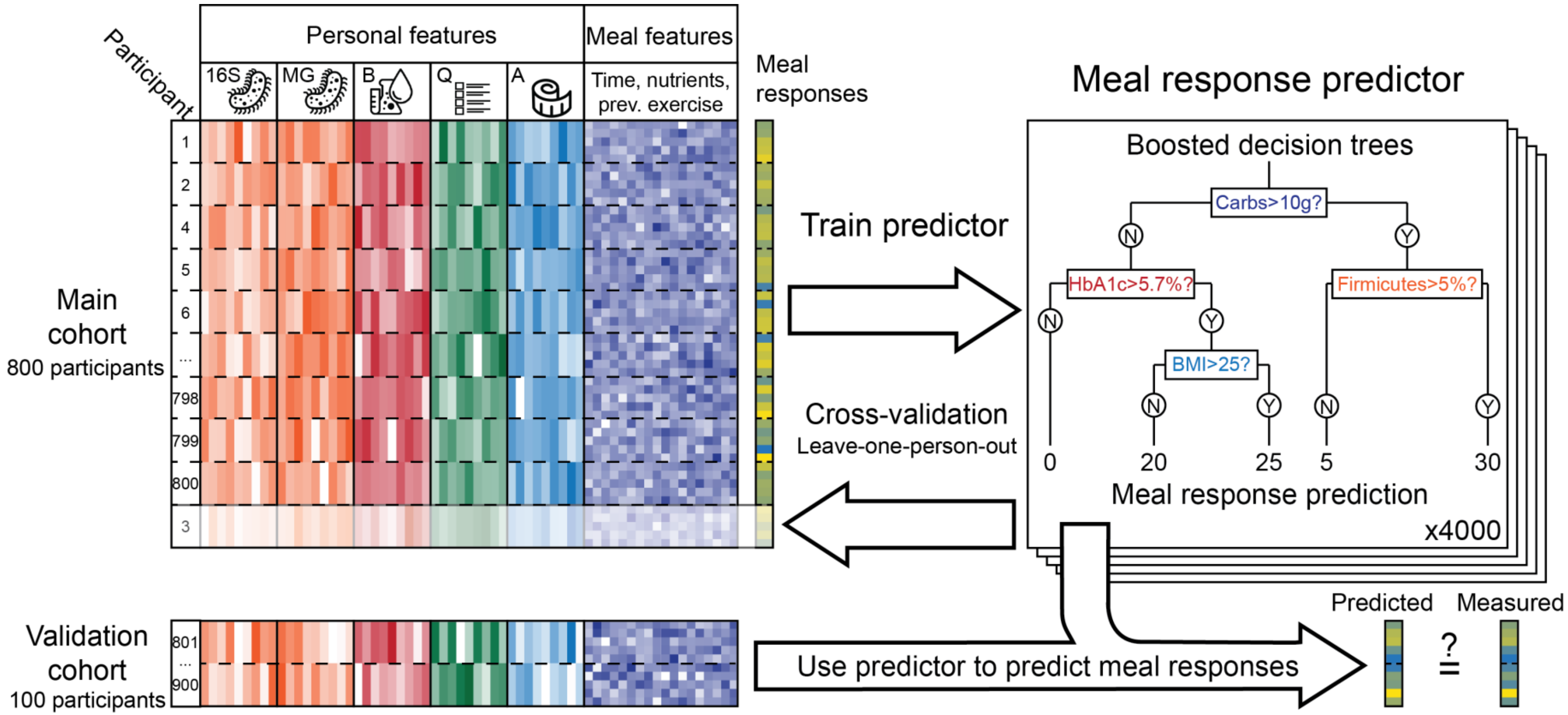
Can we predict the personal post-prandial glucose response to any complex meal?

Meal Carbohydrates: State of the art in predicting post-meal glucose responses

State of the art



Prediction scheme



Model features

800 People X MetaPhlAn abundances | KEGG abundances | 16S OTUs | Growth dynamics

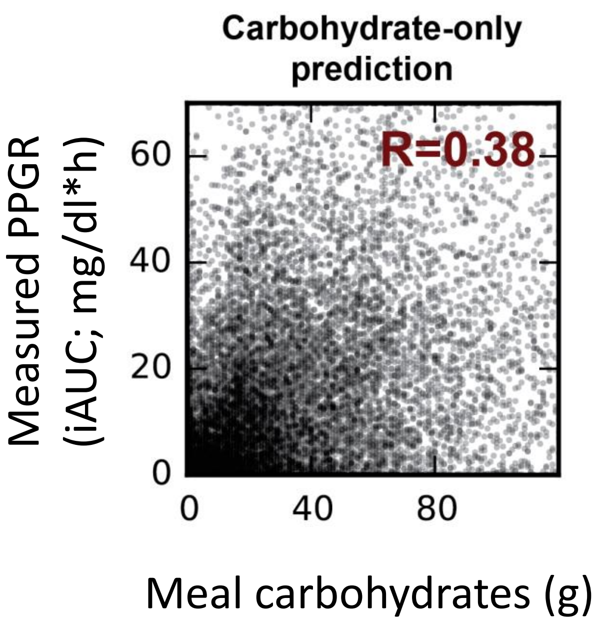
46,898 Meals X 200 Nutrients
Including fatty acids, vitamins and minerals

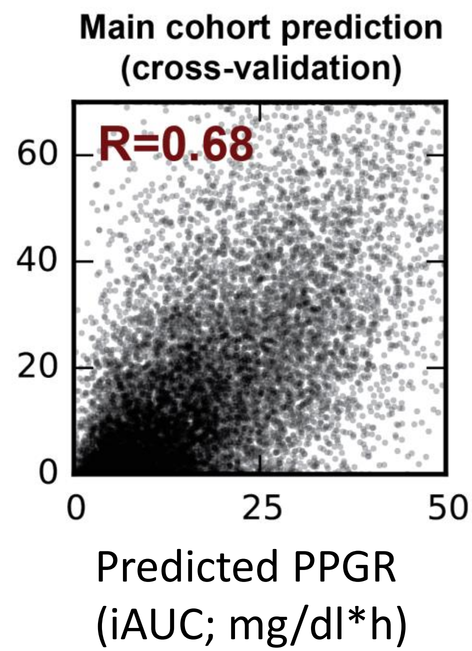
5,417 Days X Multiple recorded features
Meal times, sleep, exercise, stress, hunger, medication

800 People X 30 Blood parameters | 100 Questions | 100 FFQ features

Accurate predictions of personalized glucose responses

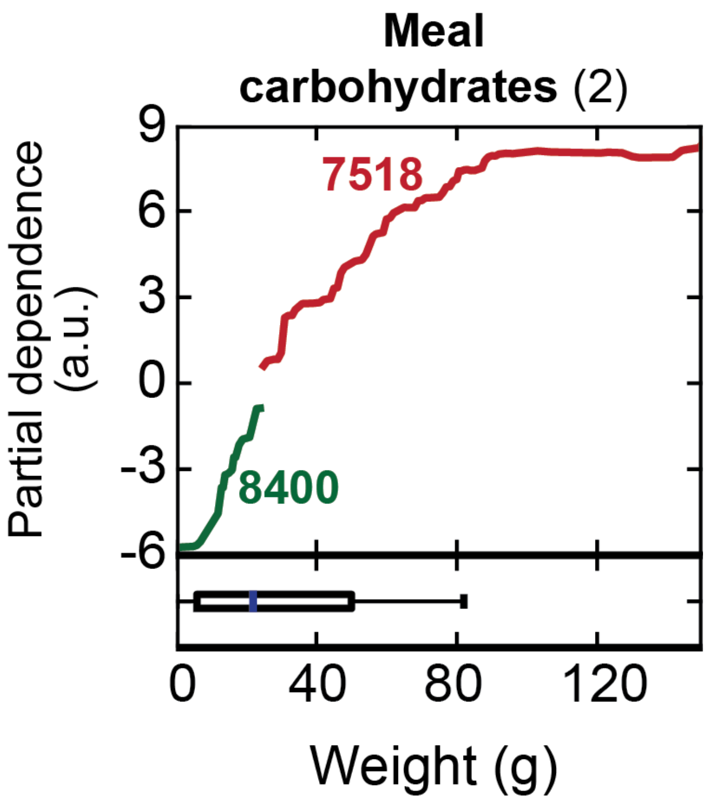
State of the art	**Our prediction** 800 participants	**Prediction validation** 100 participants

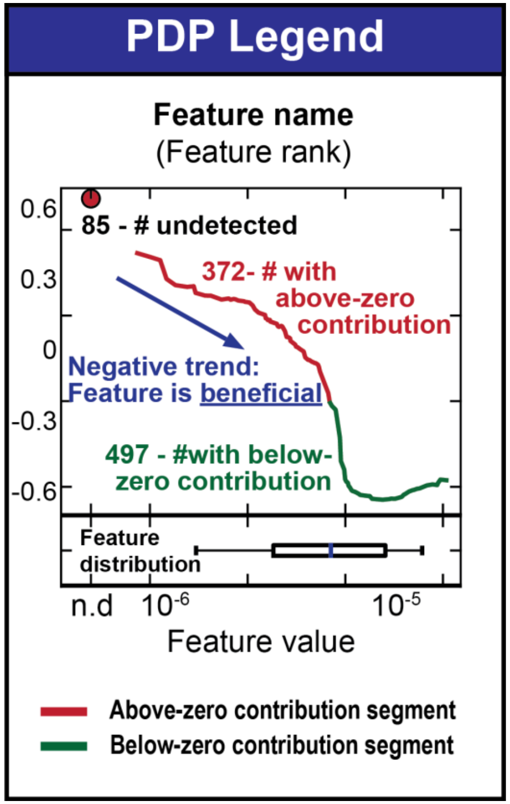




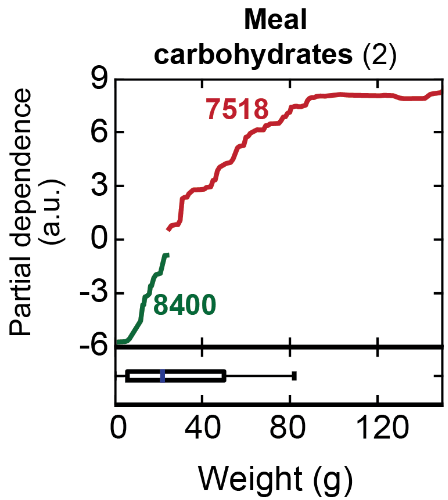
Predicted PPGR
(iAUC; mg/dl*h)

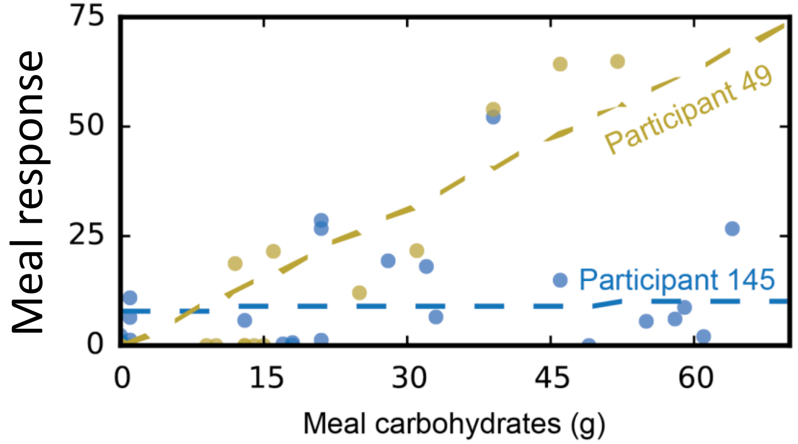
Features contributing to prediction



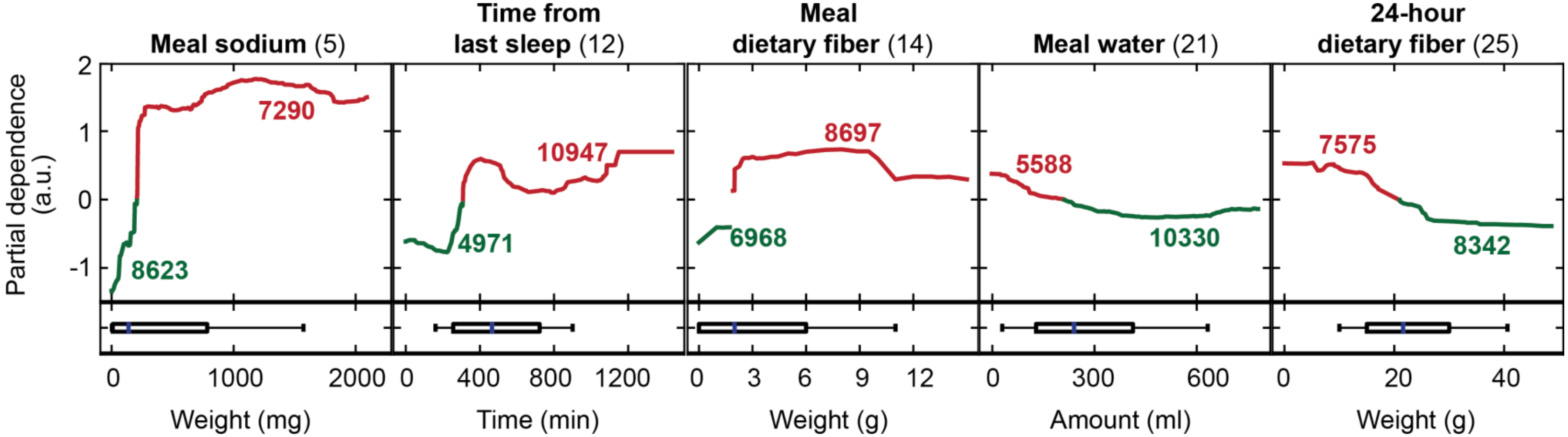


Features contributing to prediction



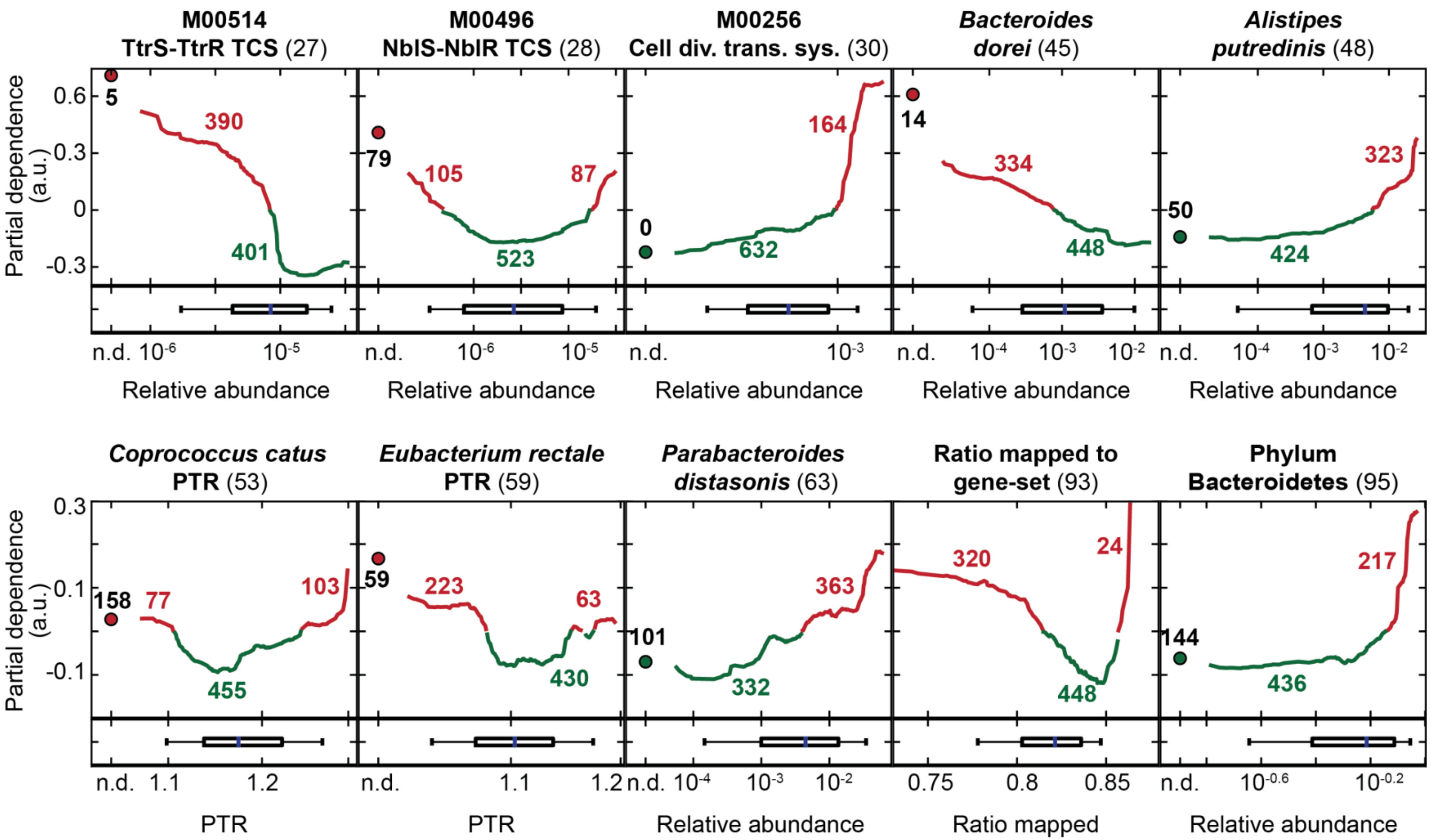


Features contributing to prediction



Zeevi *et al.*, Cell 2015

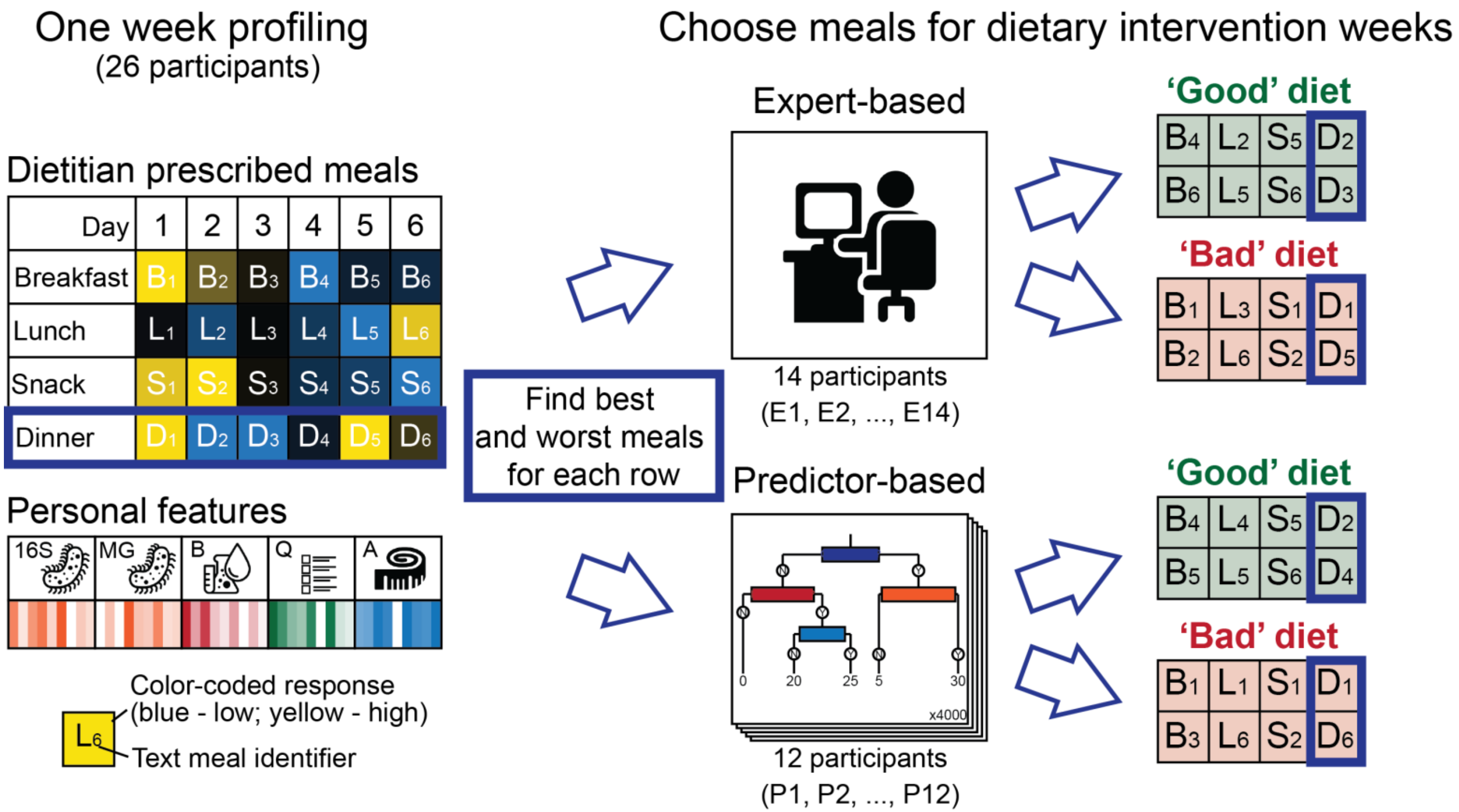
Features contributing to prediction



Zeevi *et al.*, Cell 2015

Can personally tailored dietary interventions improve post-prandial glucose responses?

Constructing personally tailored diets that achieve normal post-prandial glucose responses



Can you distinguish between the good and bad menus?

	“Bad” Diet / “Good “ Diet ?		“Bad” Diet / “Good “ Diet ?	
Breakfast		Muesli		Egg with bread and coffee
Lunch		Sushi		Hummus and pita
Snack		Marzipan		Edamame
Dinner		Corn and nuts		Vegetable noodles with tofu
Night snack		Toblerone and coffee		Ice cream

Can you distinguish between the good and bad menus?

	Bad Diet	Good Diet
Breakfast	 Muesli	 Egg with bread and coffee
Lunch	 Sushi	 Hummus and pita
Snack	 Marzipan	 Edamame
Dinner	 Corn and nuts	 Vegetable noodles with tofu
Night snack	 Toblerone and coffee	 Ice cream

Zeevi *et al.*, Cell 2015

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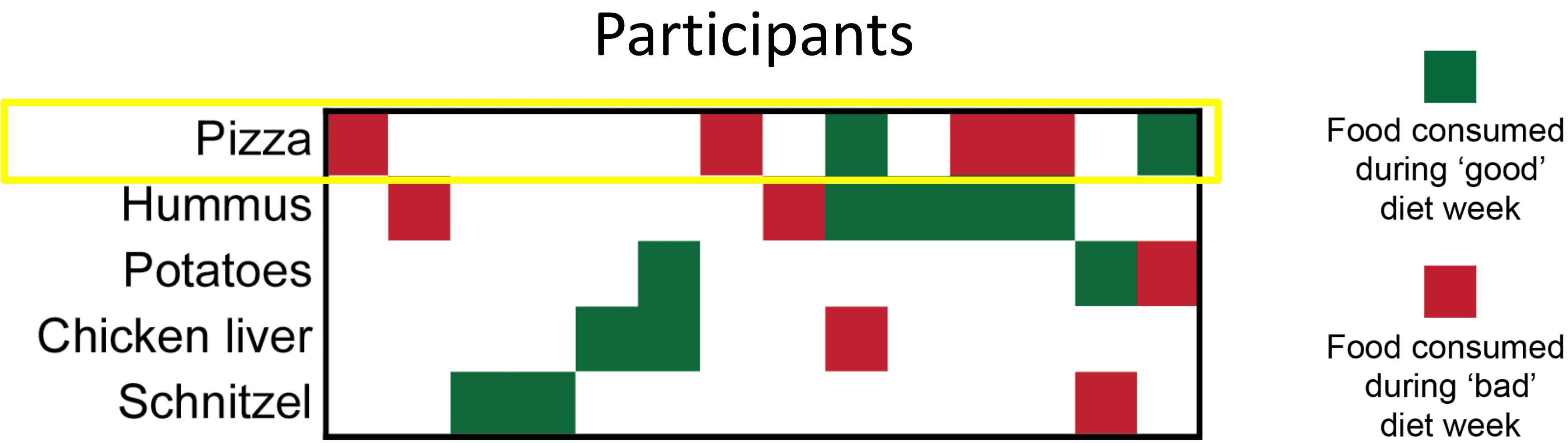
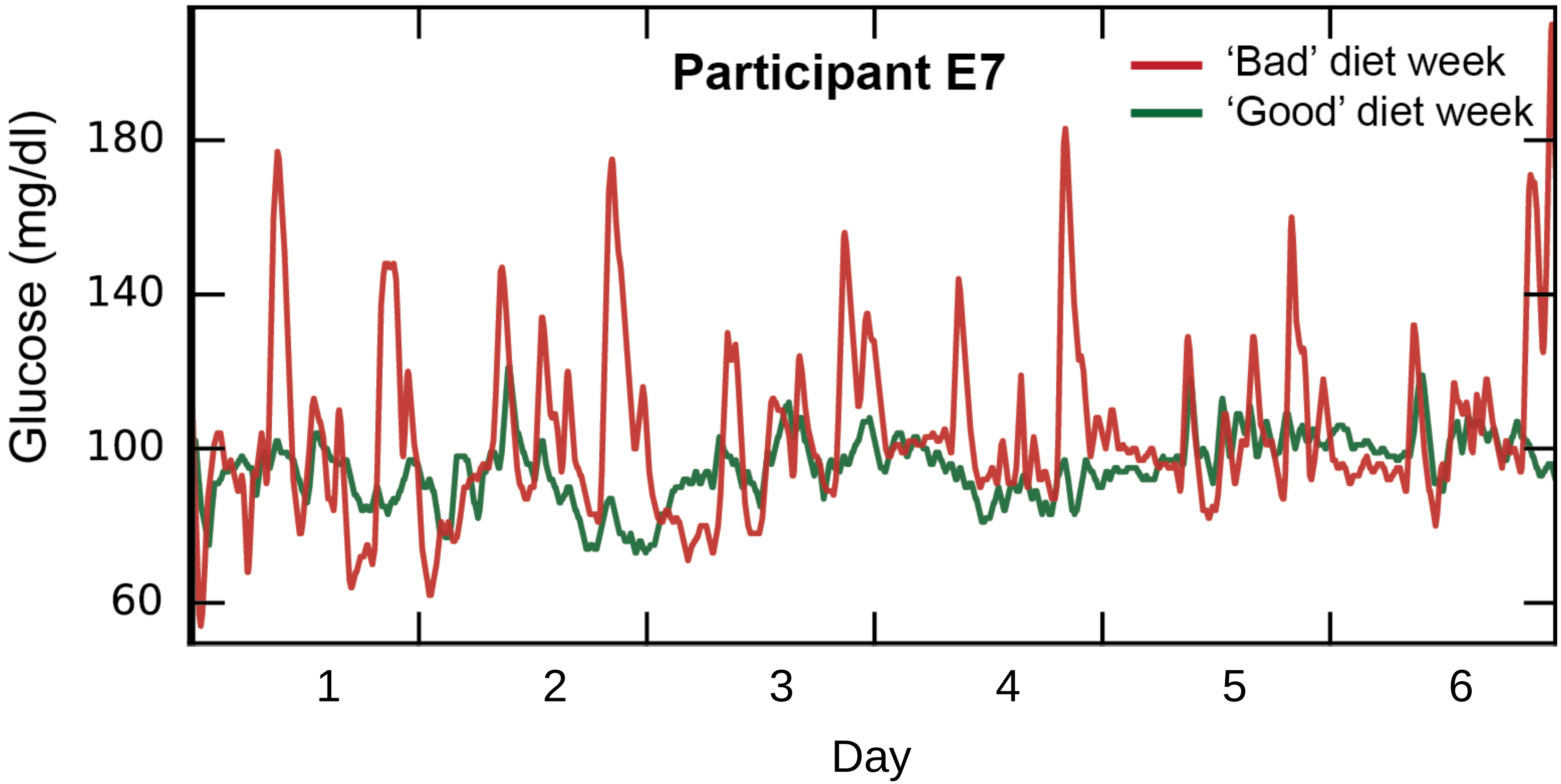
A 'good' meal for one person can be a 'bad' meal for another

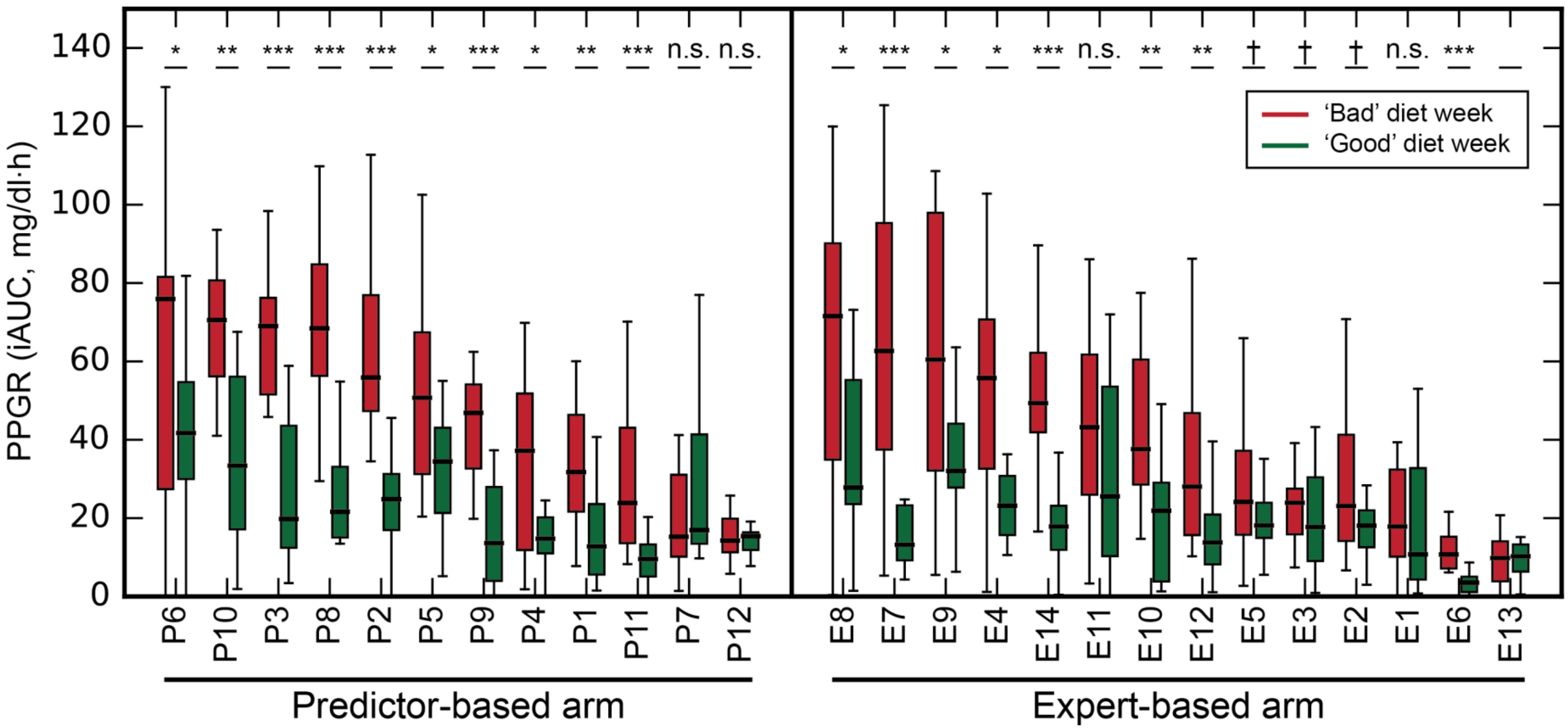


Personally tailored diets reduce the post-prandial glucose response

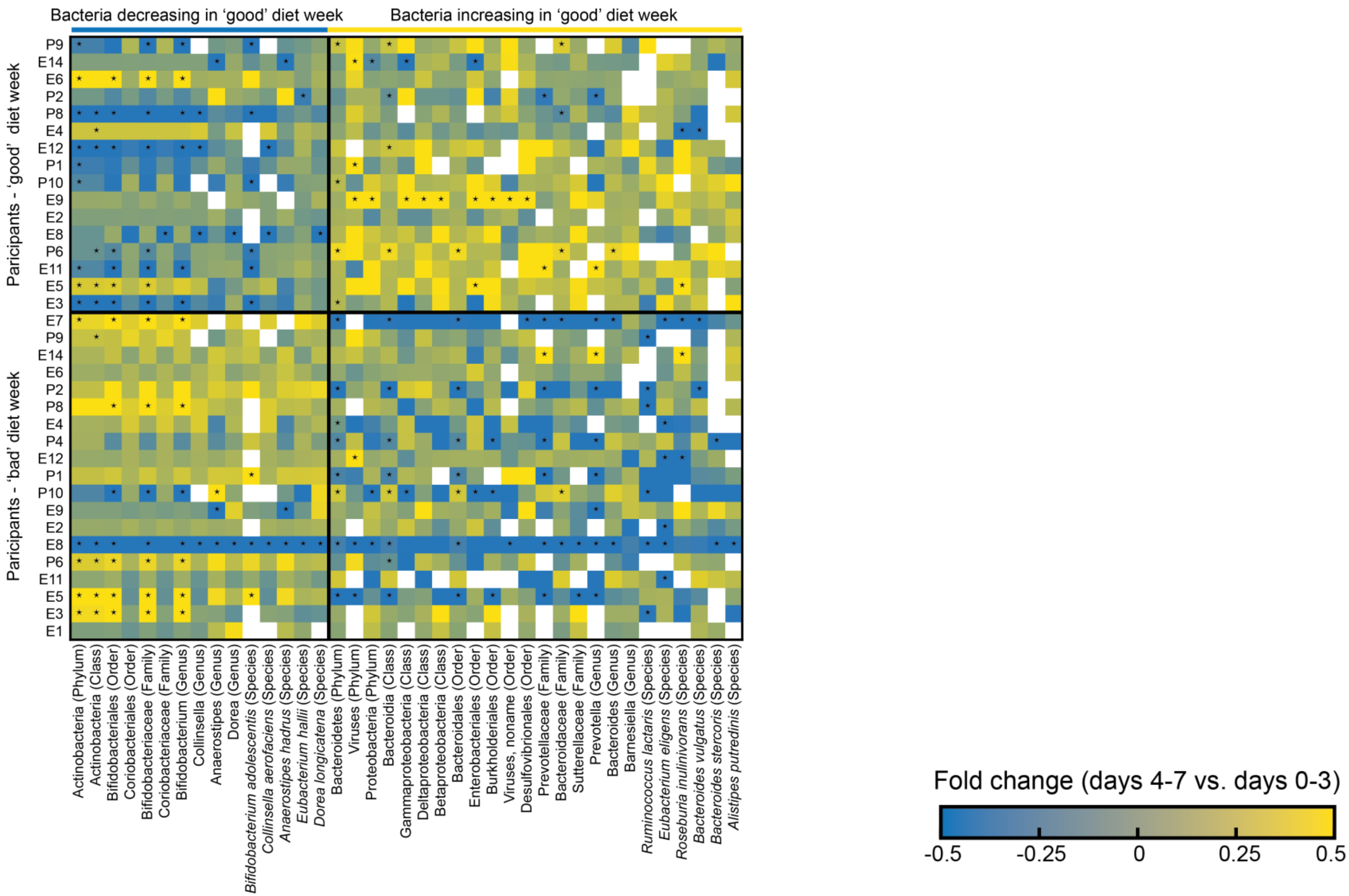


Zeevi *et al.*, Cell 2015

Personally tailored diets improve post-meal responses



Dietary interventions targeting post-meal glucose responses induce consistent changes in microbiota



Zeevi *et al.*, Cell 2015

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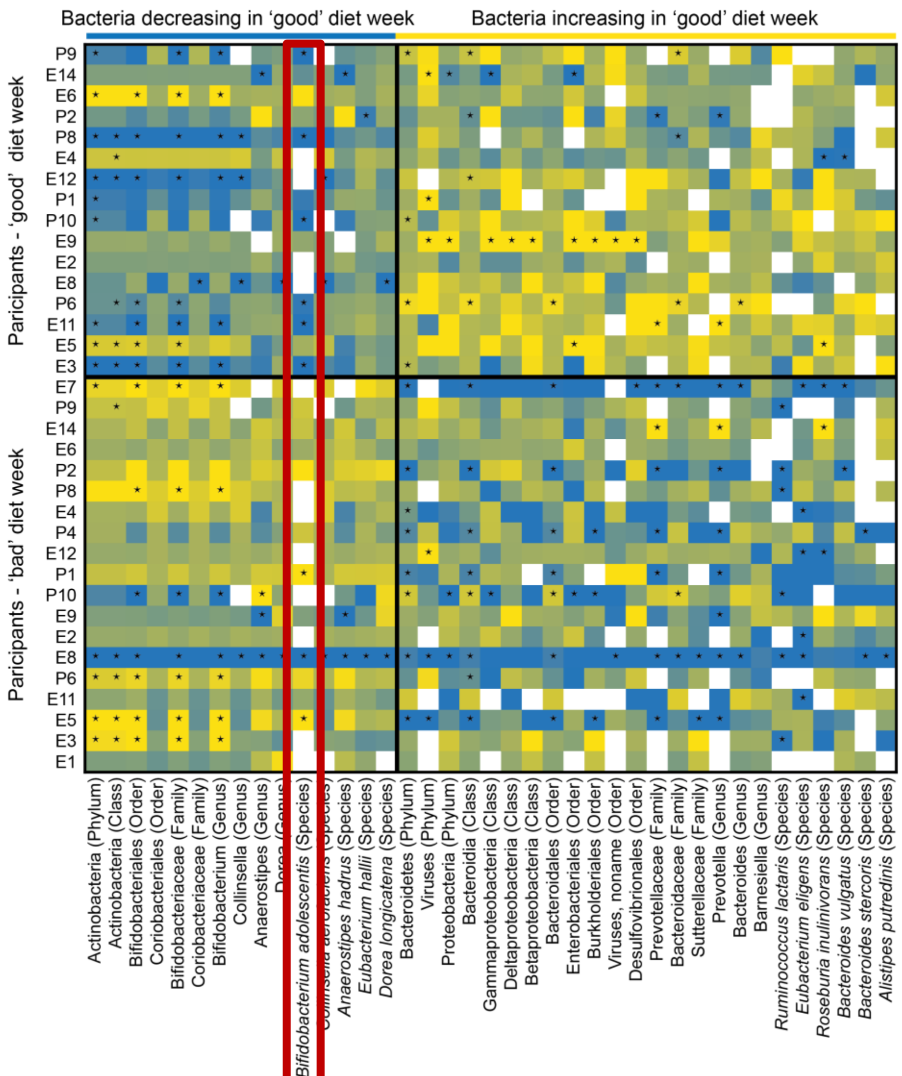
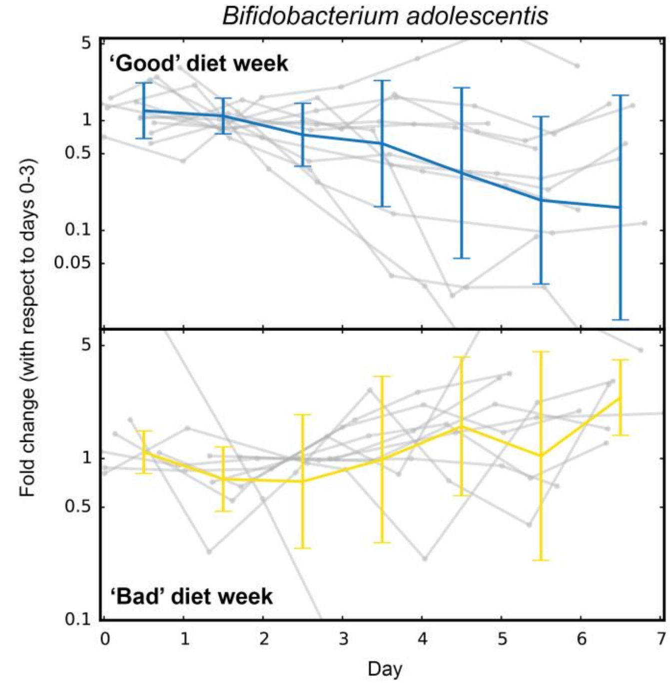
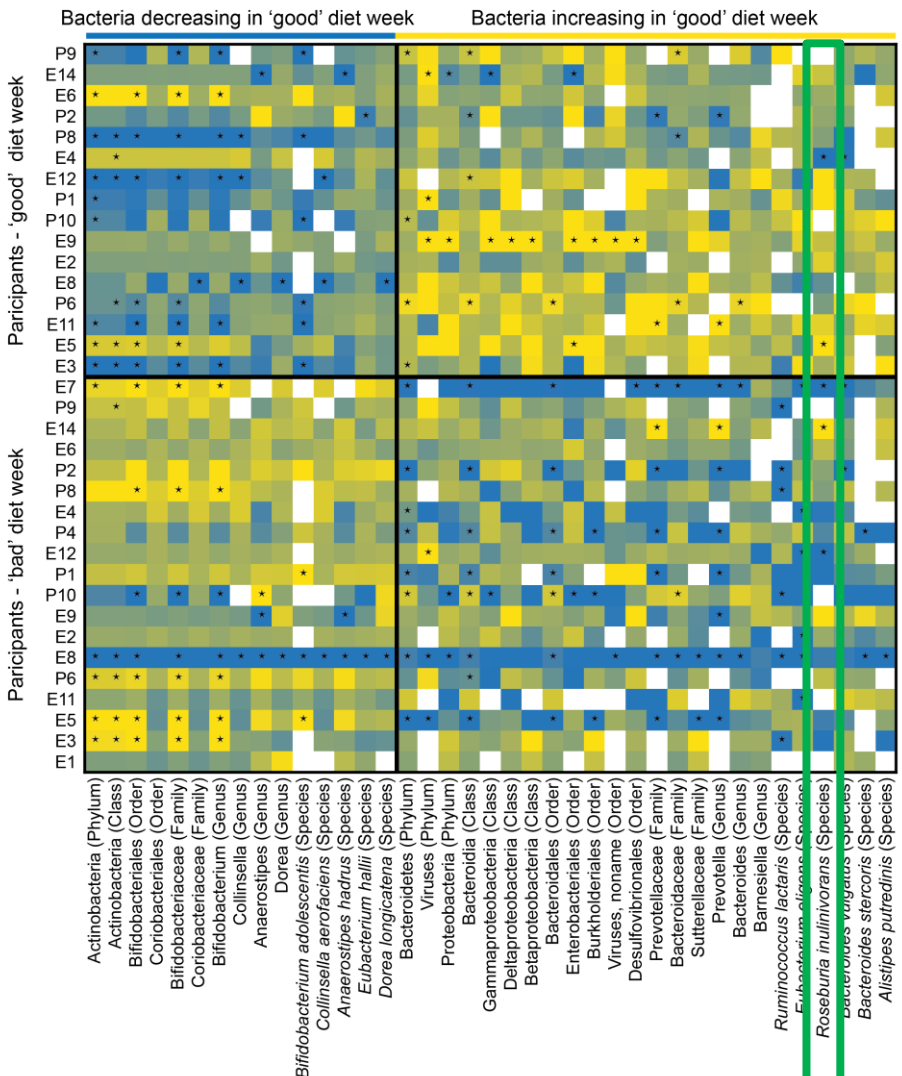
Dietary interventions targeting post-prandial glucose responses induce consistent changes in microbiota

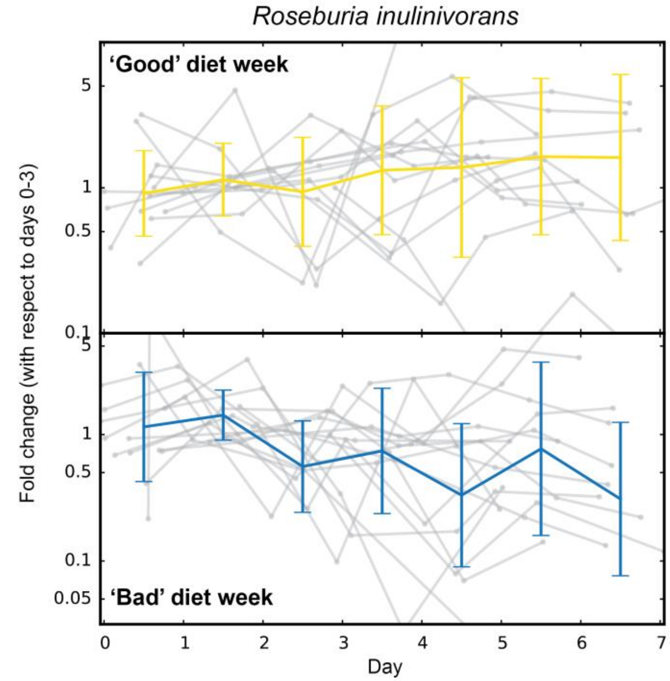




- *Bifidobacterium adolescentis* decreases during 'good' week.
- Low levels associated with greater weight loss (Santacruz et al., 2009)

Dietary interventions targeting post-meal glucose responses induce consistent changes in microbiota





- *Roseburia inulinivorans* increases following the 'good' diet week
- Low levels associate with TIIDM (Qin et al., 2012)

Zeevi *et al.*, Cell 2015

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Summary

- **Artificial sweeteners induce glucose intolerance** driven by gut microbial changes
- **High interpersonal variability** in post-meal glucose observed in an 800-person cohort
- Using personal and microbiome features enables **accurate glucose response prediction**
- Short-term personalized dietary interventions **successfully lower post-meal glucose**

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