Wednesday July 24, 2013

MICROBIOME COLONIZATION AND ASSEMBLY

Human Microbiome Science:
Vision for the future

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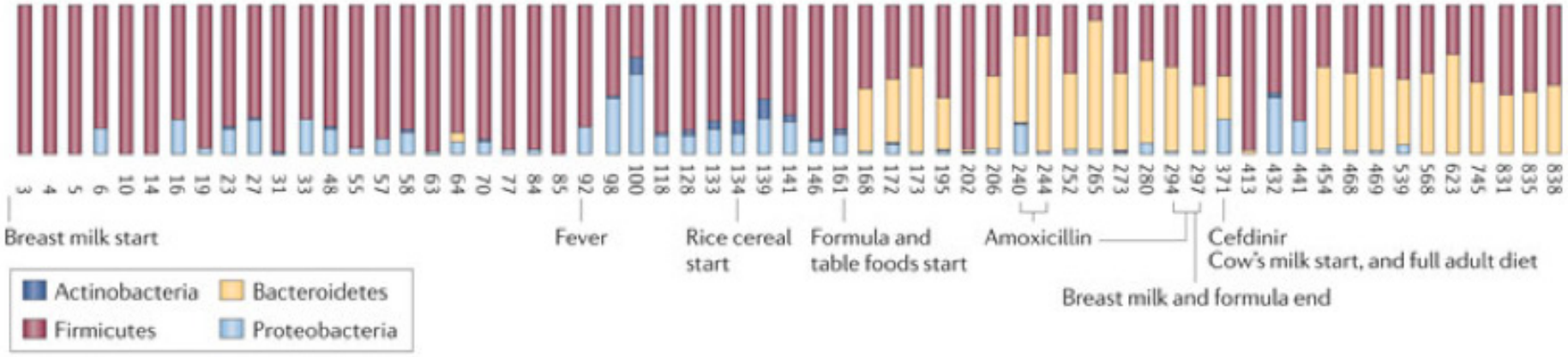
Cornell University

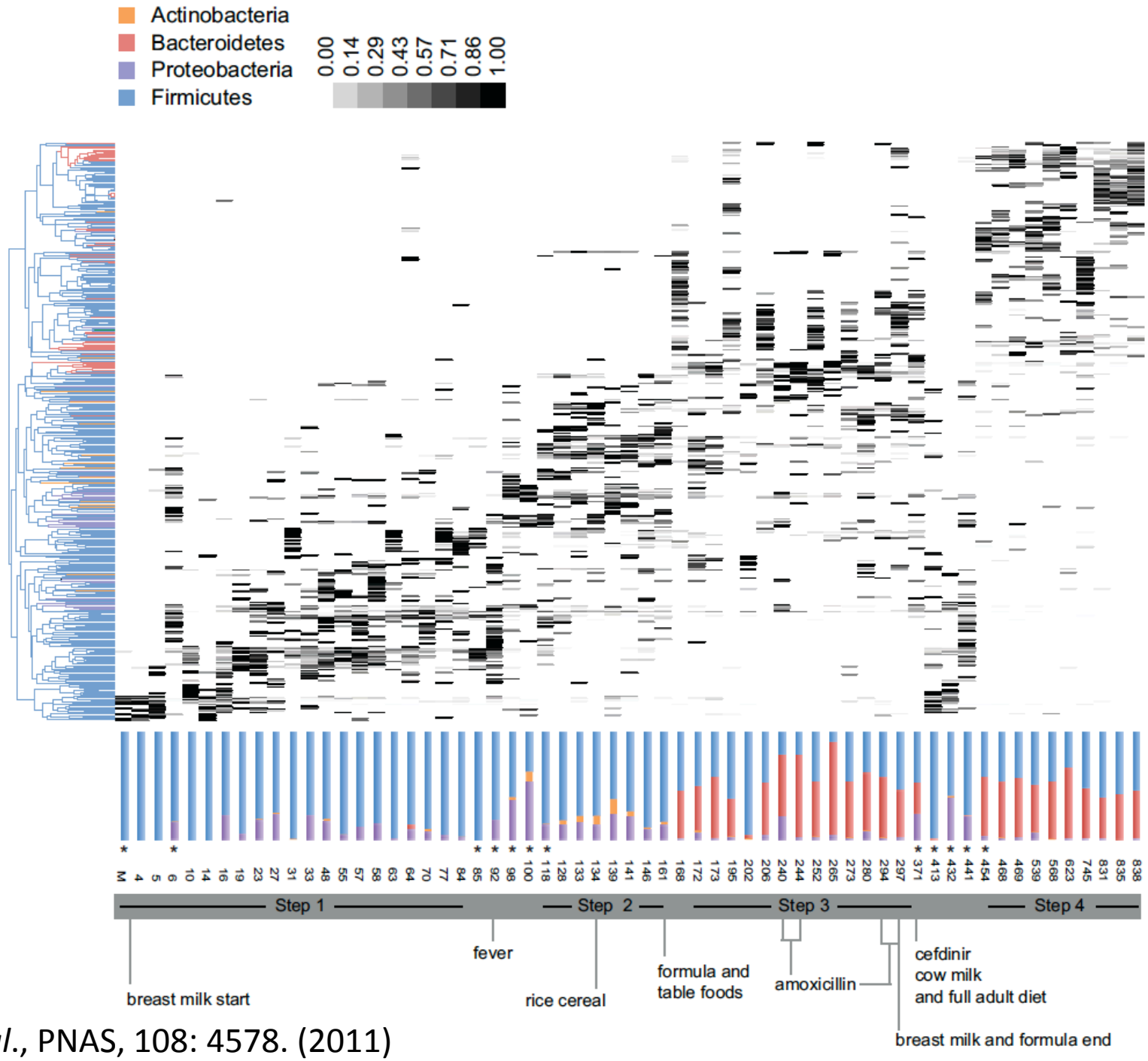
I need microbes!!!!!

Life events such as diet changes, antibiotics and fever influence microbiome **structure**



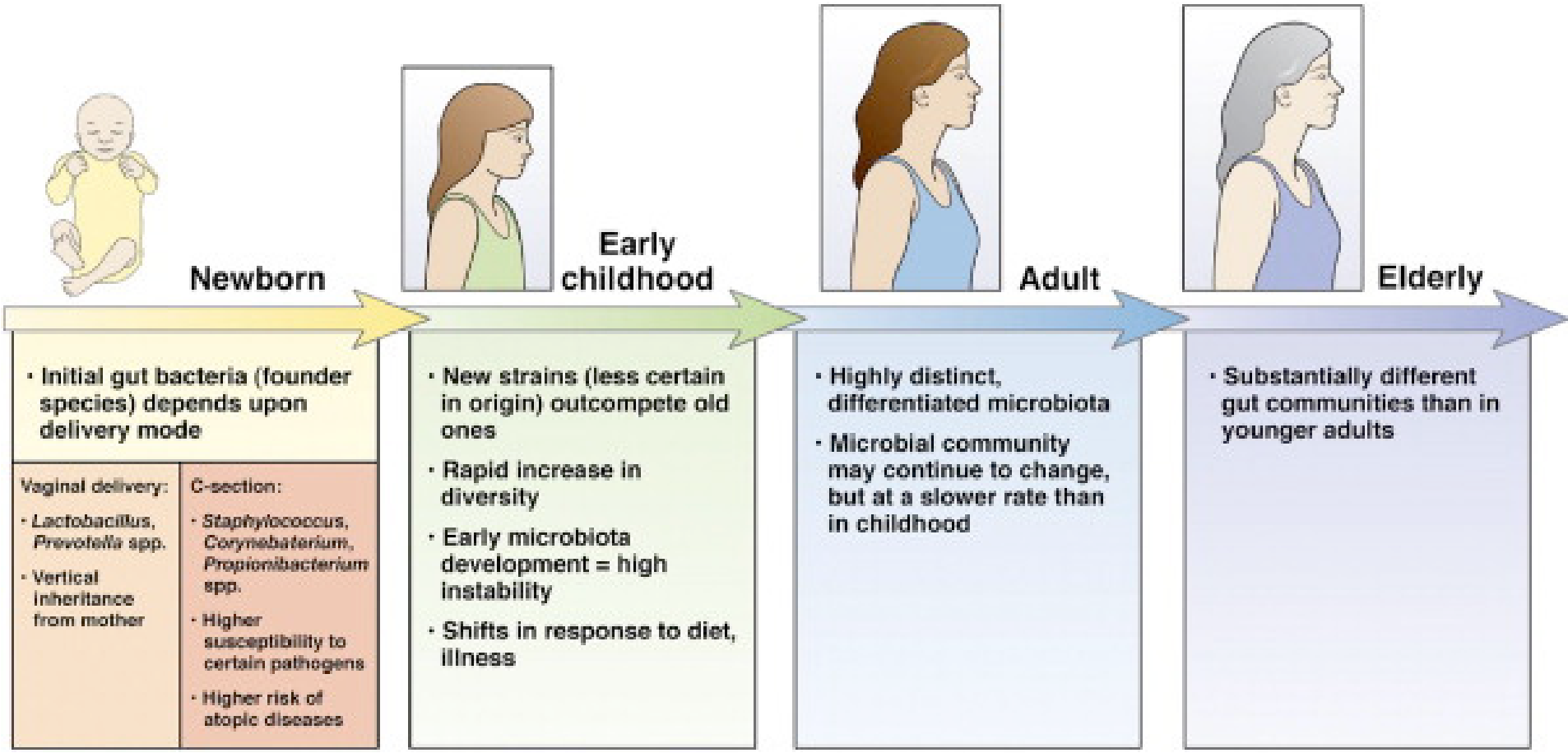
Case study of 1 individual followed for 2.5 years

Spor, Koren and Ley. Nature Reviews Microbiology 9: 279. (2011)
Koenig *et al*., PNAS, 108: 4578. (2011)



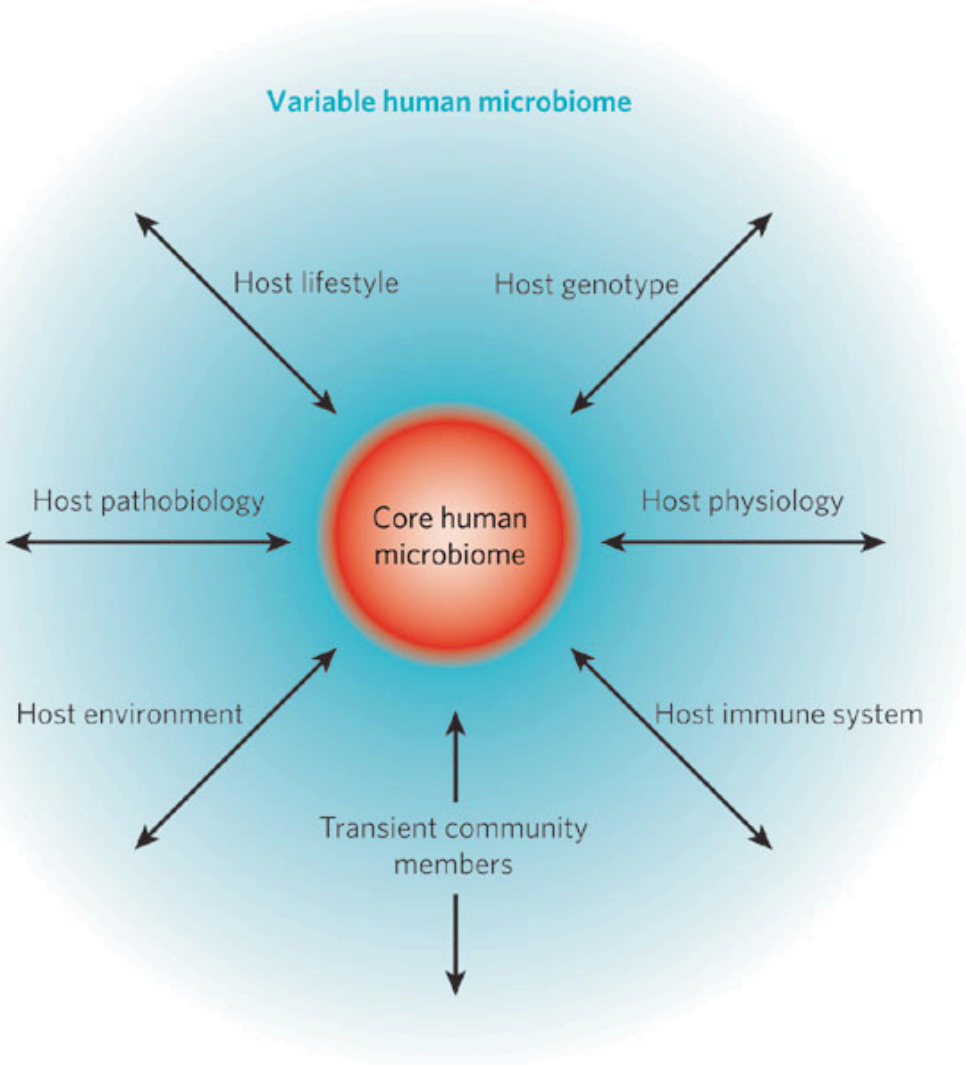
Koenig *et al.*, PNAS, 108: 4578. (2011)

Do early colonizers impact microbiome later in life?



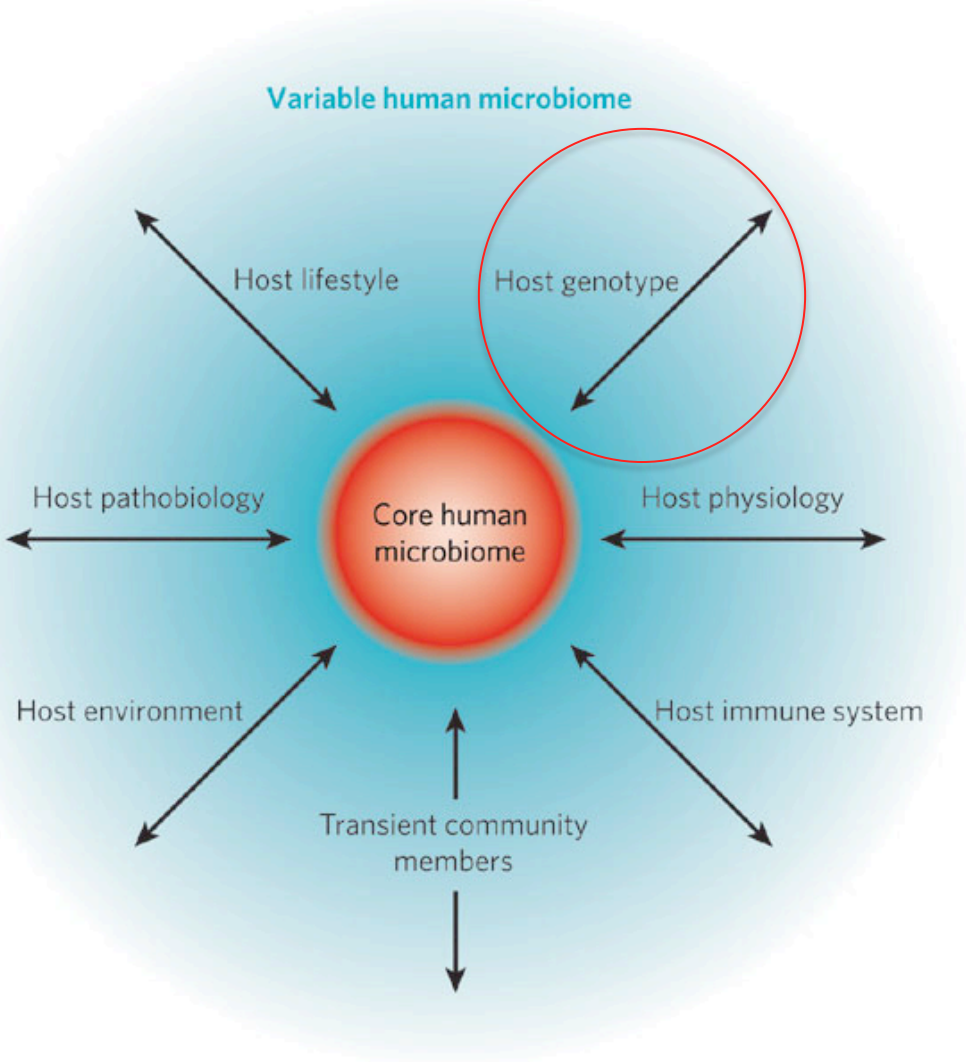
Dominguez-Bello, M. G., M. J. Blaser, R. E. Ley and R. Knight. Development of the infant gut microbiota: insights from high-throughput sequencing. Gastroenterology 140: 1713-1719. (2011)

What does impact microbiome later in life?



P. J. Turnbaugh, R. E. Ley, M. Hamady, C. M. Fraser-Liggett, R. Knight & J. I. Gordon. Nature **449**, 804-810 (2007)

What does impact microbiome later in life?



P. J. Turnbaugh, R. E. Ley, M. Hamady, C. M. Fraser-Liggett, R. Knight & J. I. Gordon. Nature **449**, 804-810 (2007)

A need for genetic studies in humans:

- QTL mapping studies in mice have revealed associations with loci
  - Loci can be quite big
- Studies with candidate genes in humans
  - e.g., NOD2 (Li *et al*., PloS One, 2012)
  - You know what you are looking for
- No published genome-wide association studies in humans

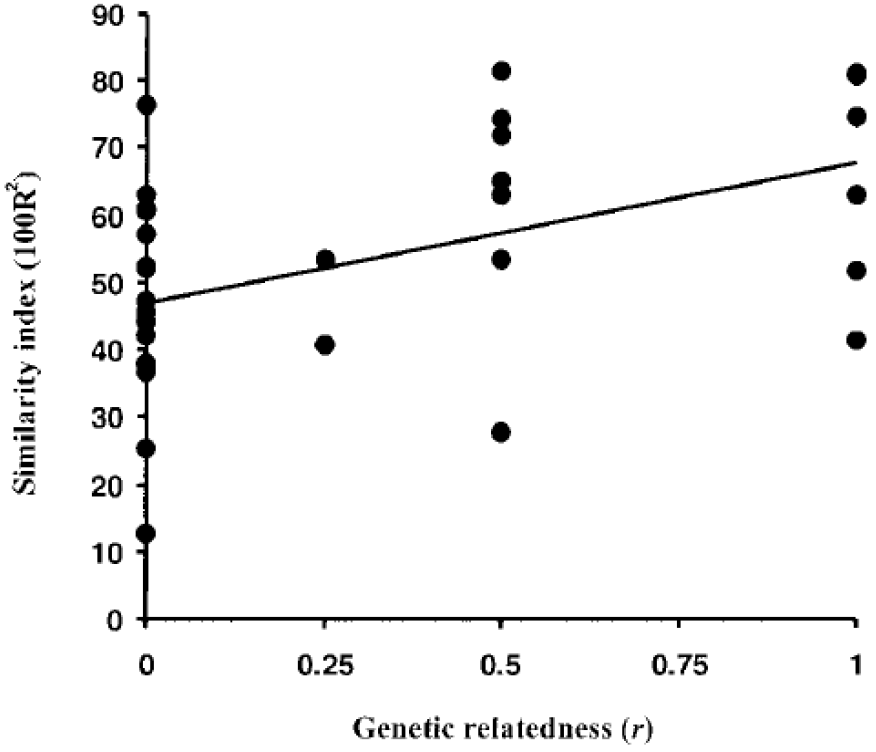
Monozygotic versus dizygotic twins

Human Mirror, NYC Subway

The Host Genotype Affects the Bacterial Community in the Human Gastrointestinal Tract

Erwin G. Zoetendal[1,2], Antoon D. L. Akkermans[1], Wilma M. Akkermans-van Vliet[1], J. Arjan G. M. de Visser[1] and Willem M. de Vos[1,2]

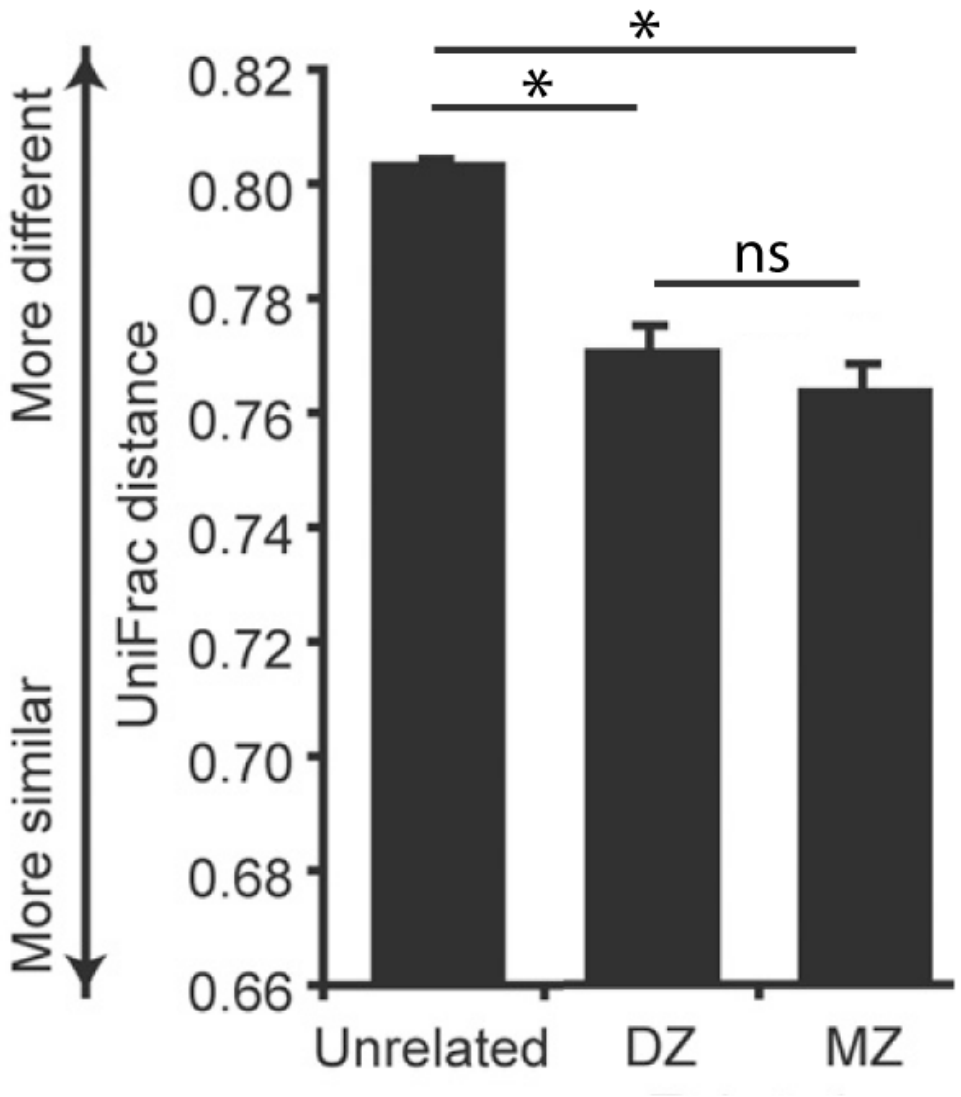
From the [1]Laboratory of Microbiology, Wageningen University, Hesselink van Suchtelenweg 4, 6703 CT, Wageningen, [2]Wageningen Center for Food Sciences, PO Box 557, 6700 AL, Wageningen, The Netherlands



DGGE patterns

Microbial Ecology in Health and Disease 13: 129 (2001)

Within MZ = within DZ bacterial diversity



31 monozygotic (MZ)
23 dizygotic (DZ)

16S rRNA pyrosequencing

Turnbaugh et al., Nature 457, 480 (2009)

Genotyped MZ and DZ twins

KING'S College LONDON

University of London

Twin Registry (TwinsUK)

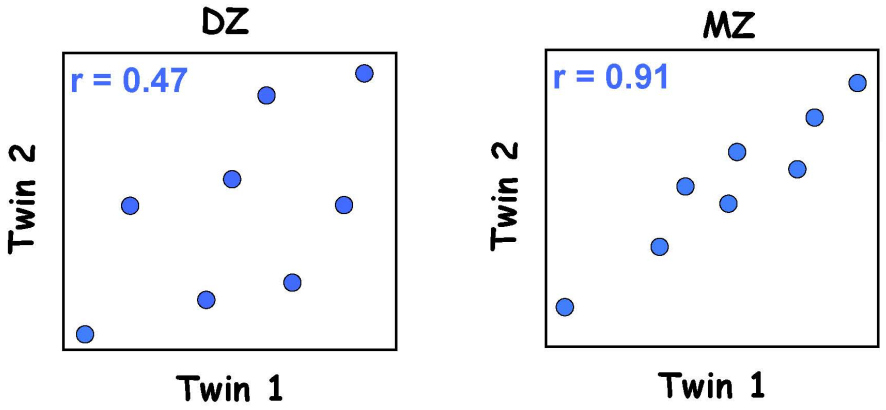
- 2,300 twins genotyped with Illumina 300 HapChip
  3,500 twins genotyped with the Illumina 600 HapChip

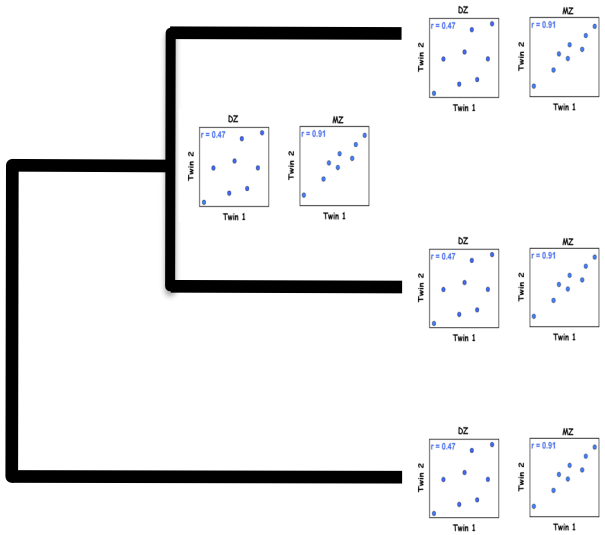
- ~1,000 Fecal samples collected to date
  - 249 DZ pairs
  - 157 MZ pairs
  - 163 unrelated
  - 36 repeat samples
  - 32 to 87 (average 64) years old
  - Mostly Female

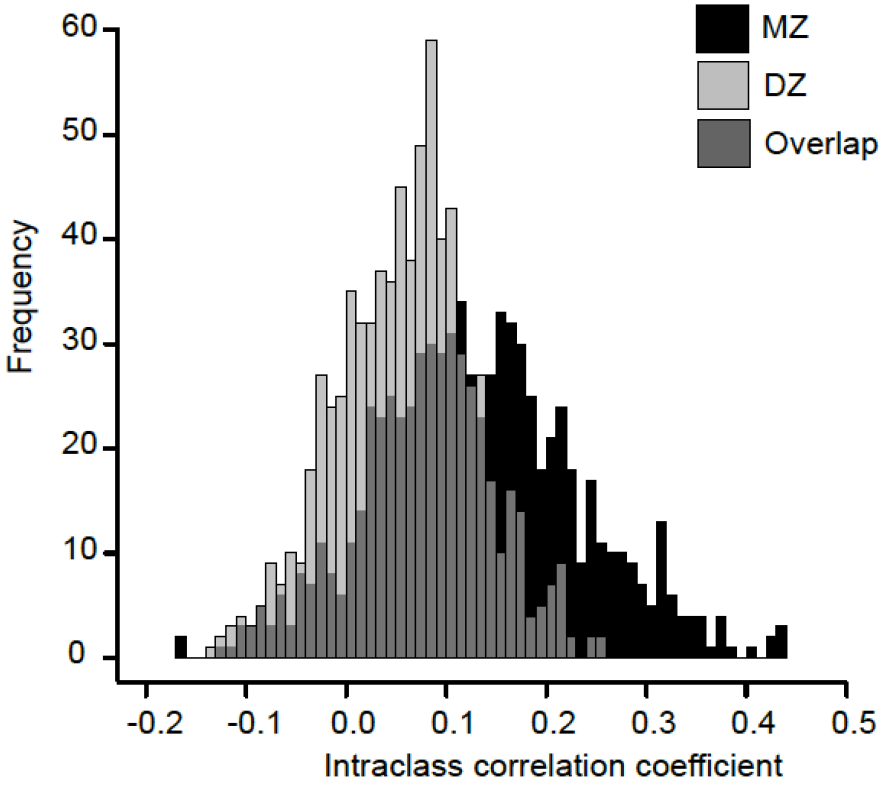
Collaborators:
Andy Clark (Cornell)
Tim Spector, Jordana Bell (KCL)

16S rRNA diversity with MiSeq

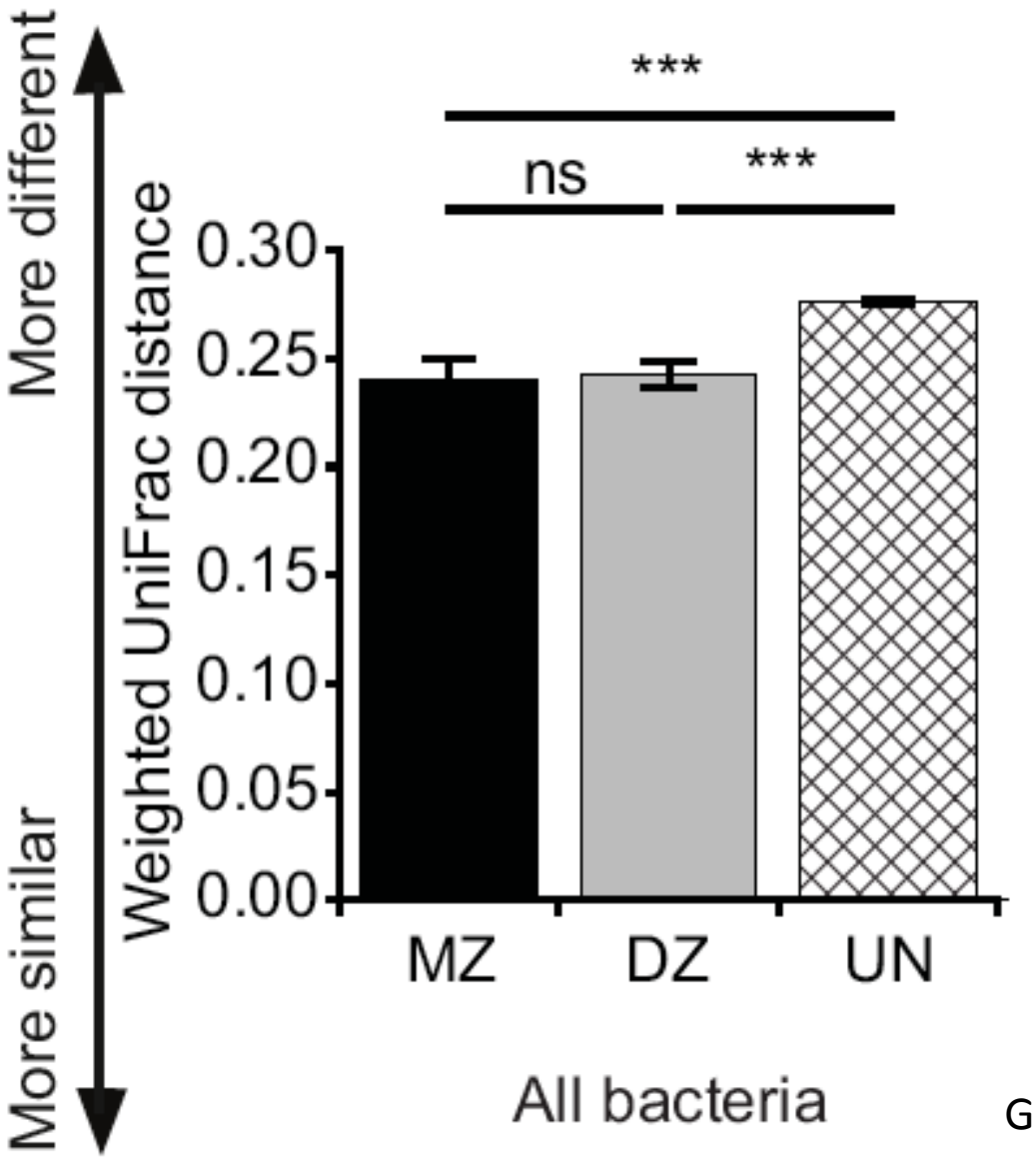
MZ twins have stronger correlations than DZ twins





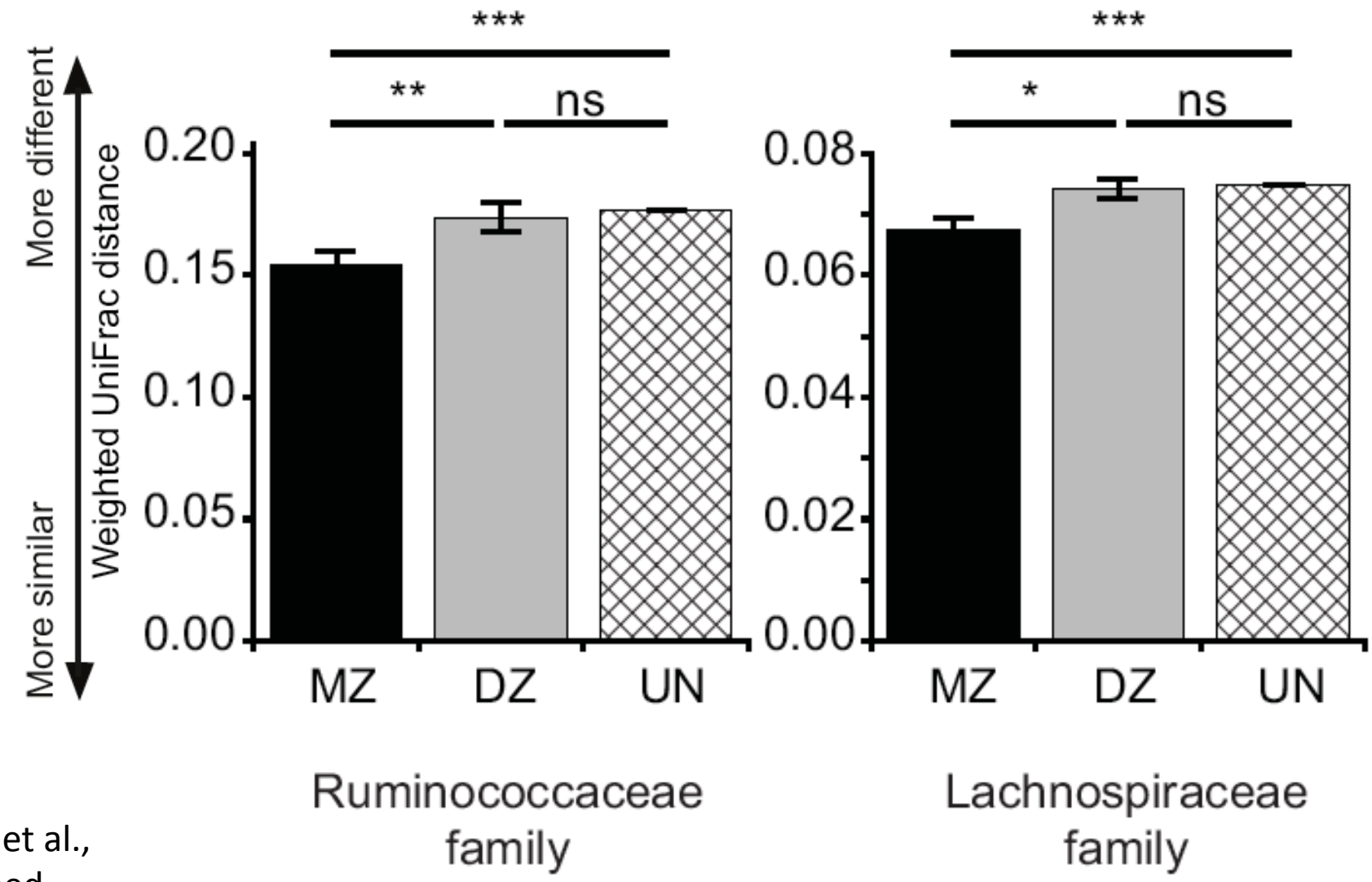


MZ = DZ for total diversity



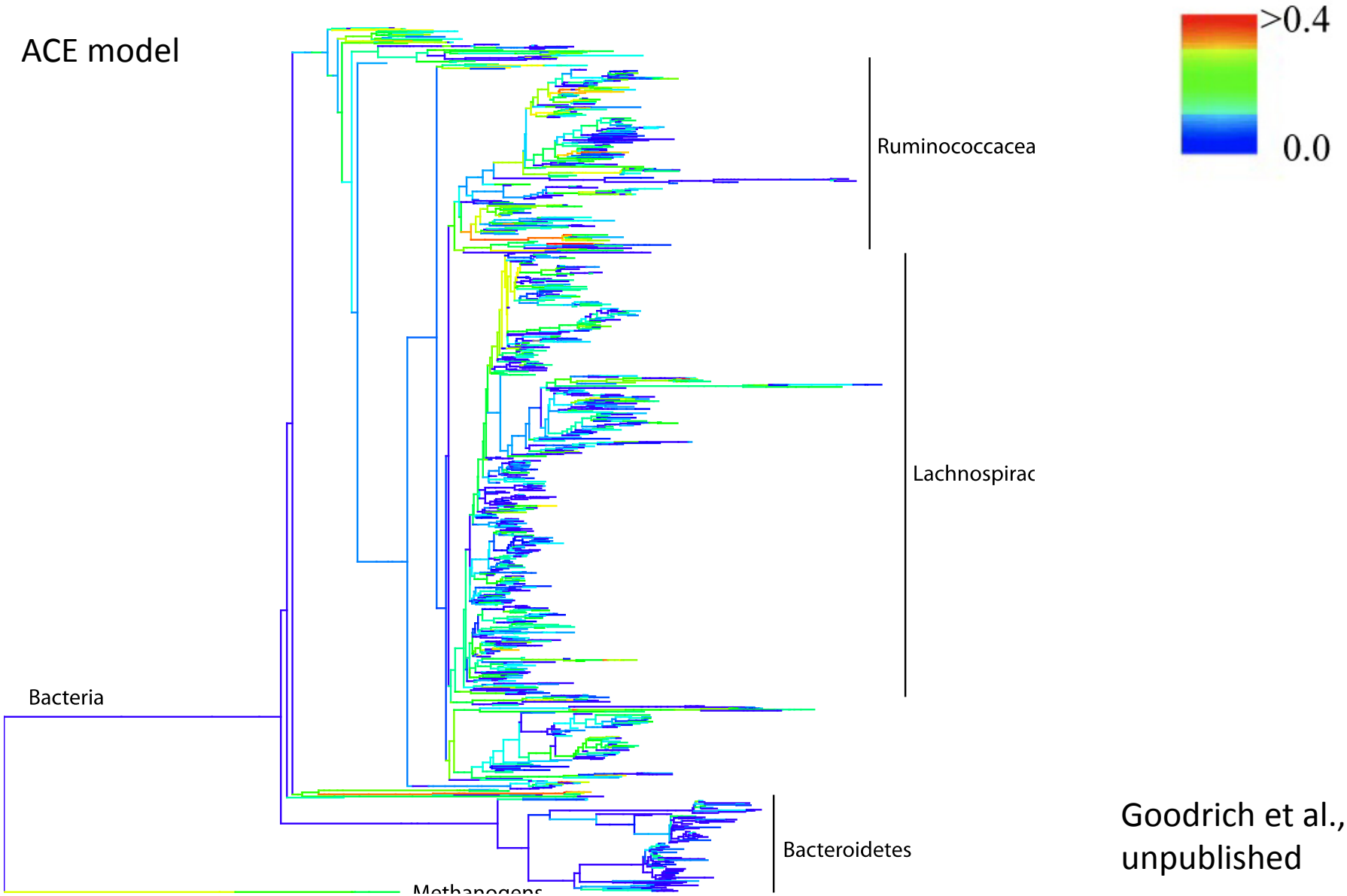
Goodrich et al., unpublished

MZ < DZ for specific families of Firmicutes



Goodrich et al., unpublished

Heritable branches within the bacterial tree



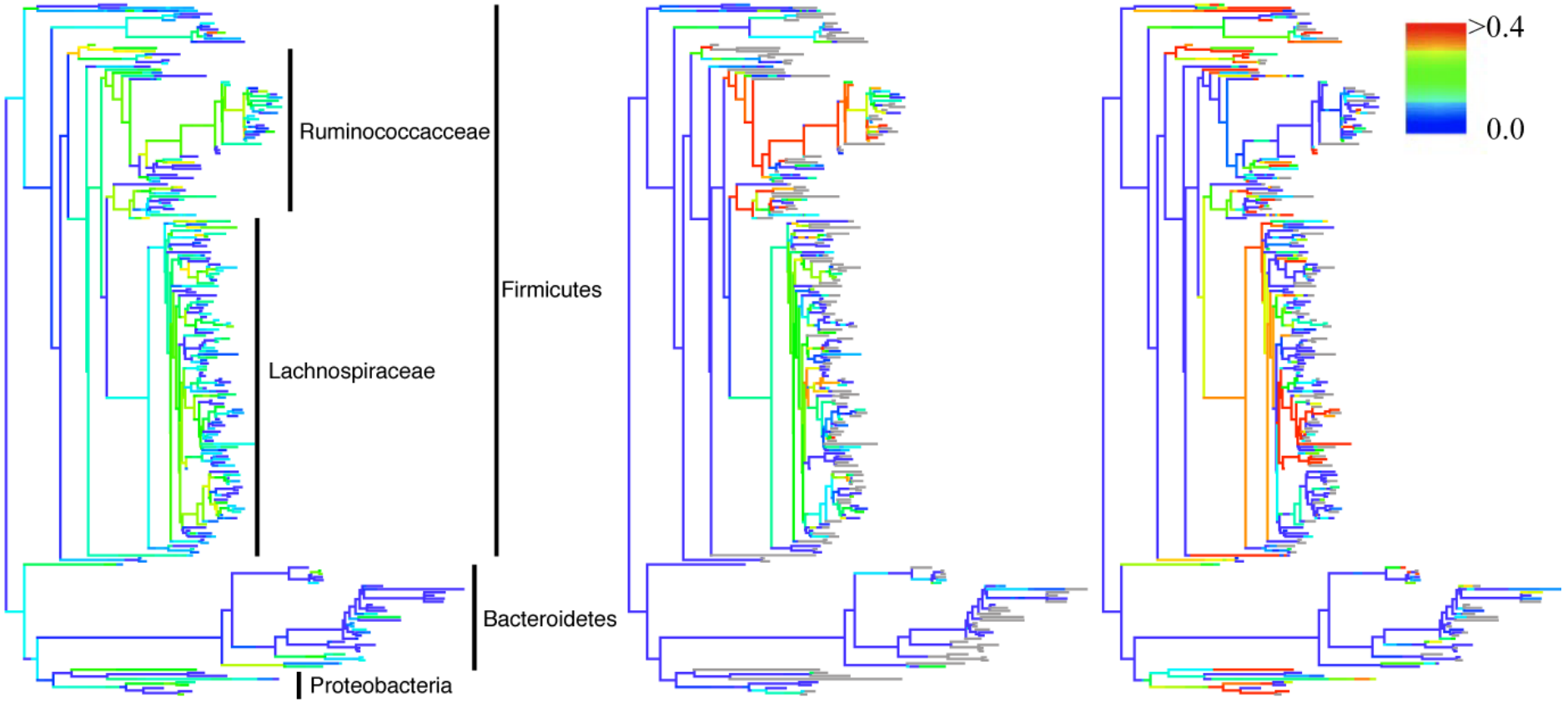
Goodrich et al., unpublished

Similar pattern of heritability across studies

This study
UK Twins 32-87 yrs

Turnbaugh 2009
US Twins 21-32 yrs

Yatsunenko 2012
US Twins 13-17 yrs

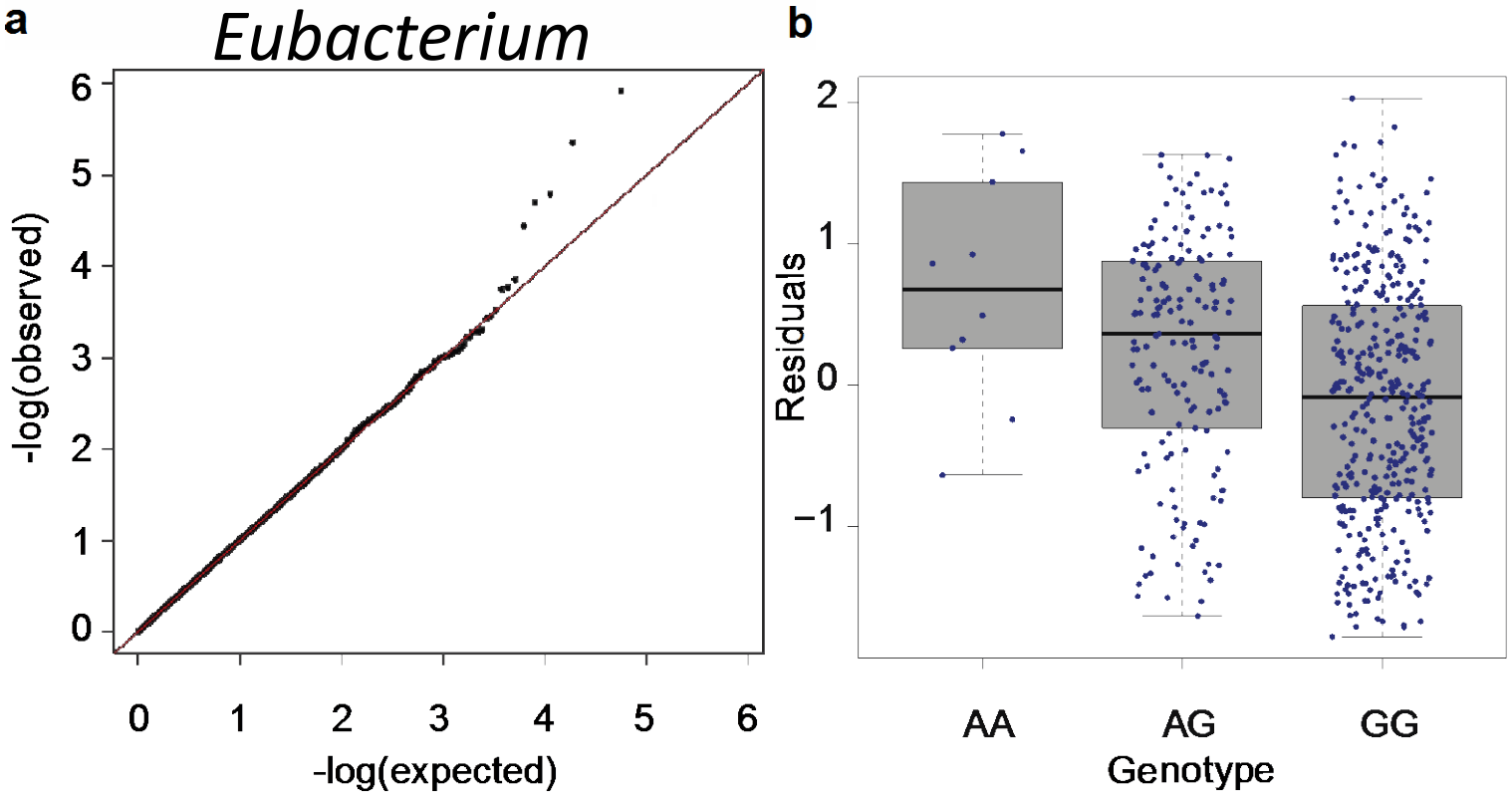


Example of early result

GWAS

SNP rs1016883 on chromosome 2

In gene for phospholipase C-like 1 (*PLCL1*)



G = Risk allele for Crohn's

PLCL1 had a role in insulin-induced GABA (A) receptor expression

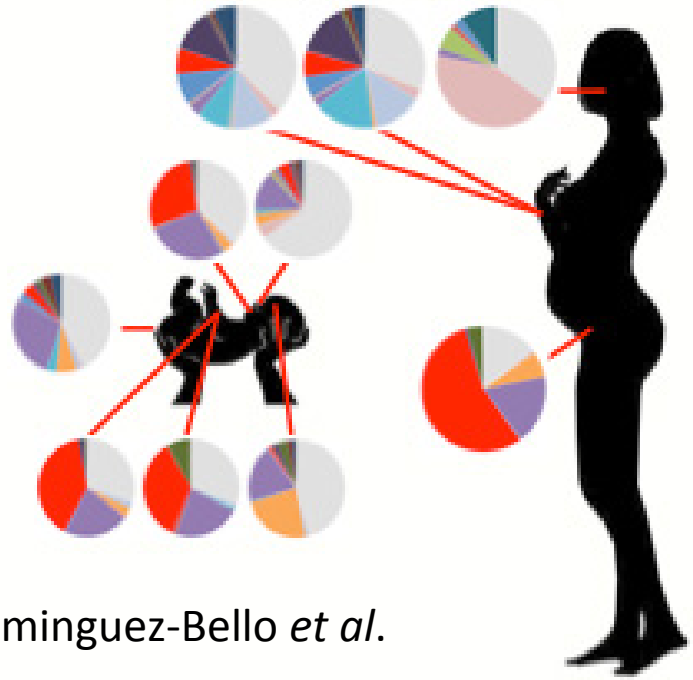
Goodrich et al., unpublished

Gaps

- How does the host genotype determine the microbiome?
- How does the microbiome interact with the host genotype to determine risk susceptibilities to diseases?
- How much more variation (in any host trait) can be explained with a microbiota component in addition to, or in combination with genotype?

I want my own personalized microbes!!!!!

I got Mummy's microbes???

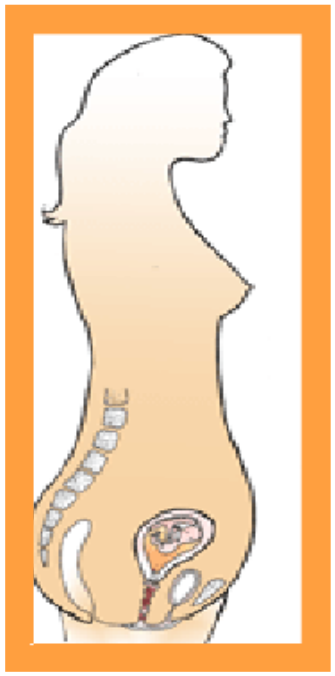


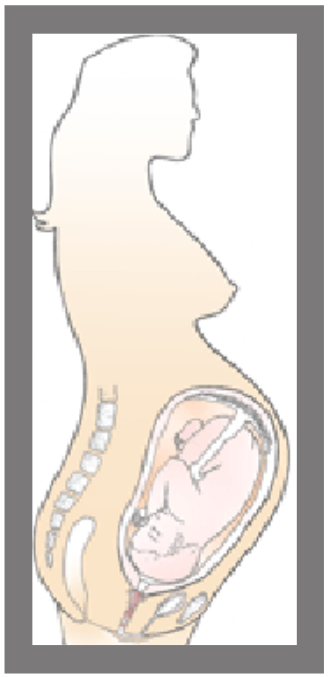
Dominguez-Bello *et al*.

Microbiome in pregnancy

First trimester

Third trimester





Fat Mass

Blood glucose

Insulin sensitivity

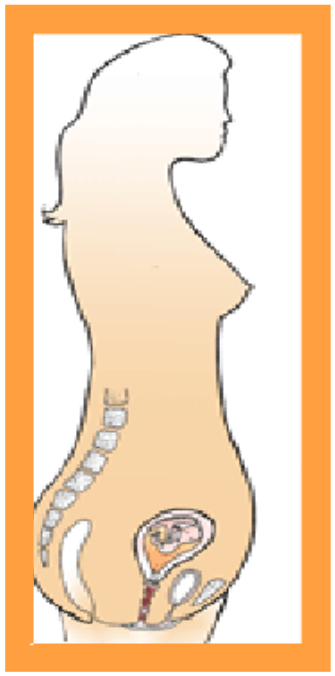
T1

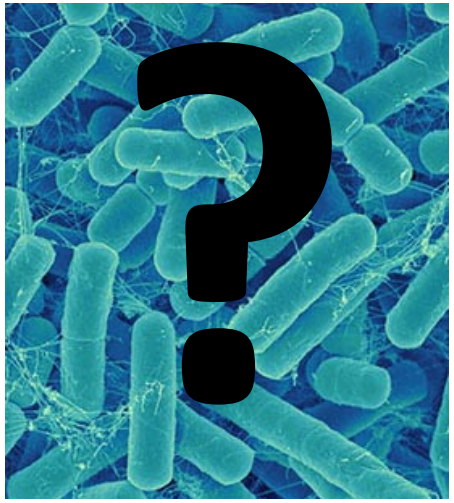
T3

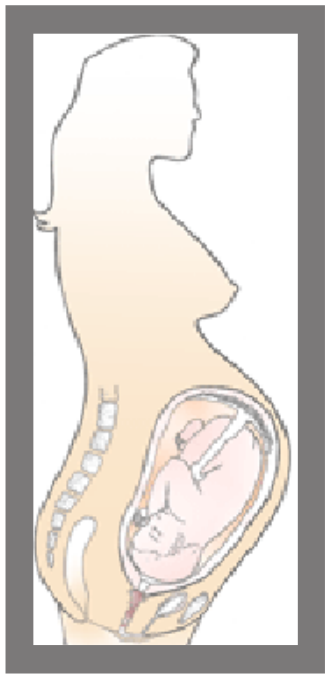
Normal pregnancy

First trimester

Third trimester





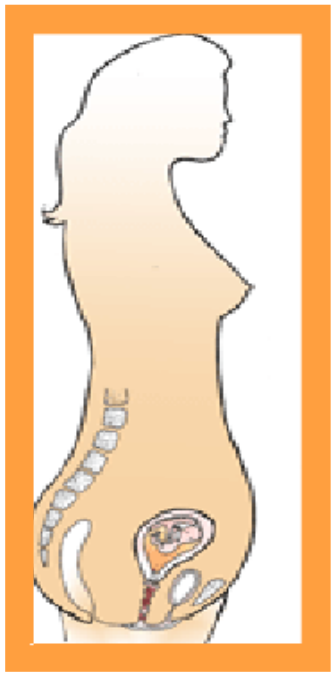


T1

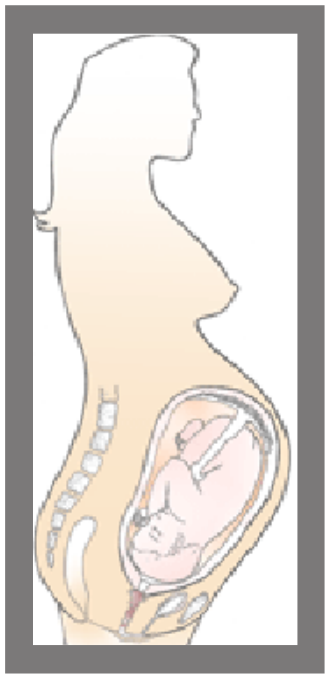
T3

91 women from Finland

First trimester Third trimester



T1

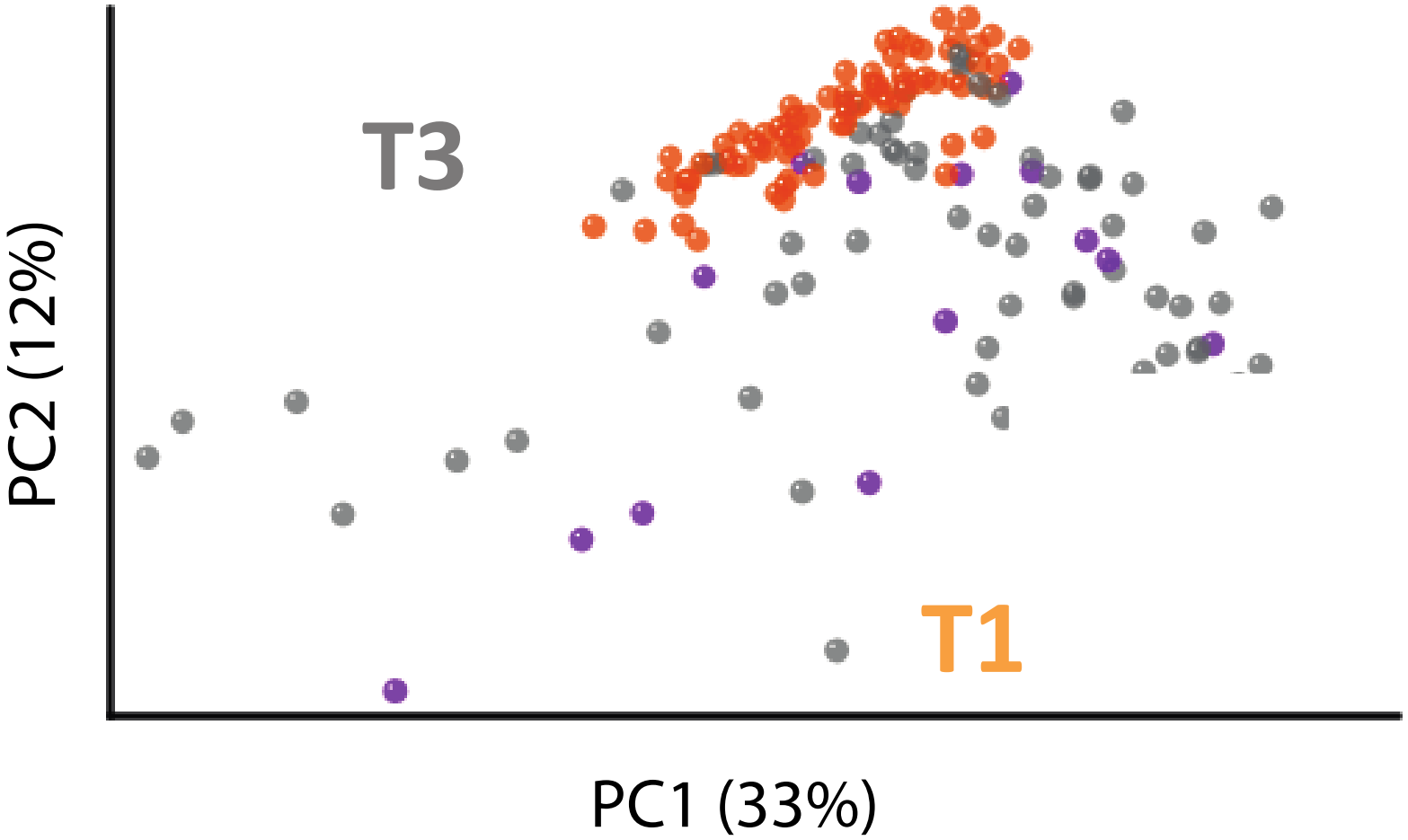


T3

Stool samples
Diet data
Clinical Data
Stool from babies

Erika Isolauri
Seppo Salminen

Between-individual diversity expands

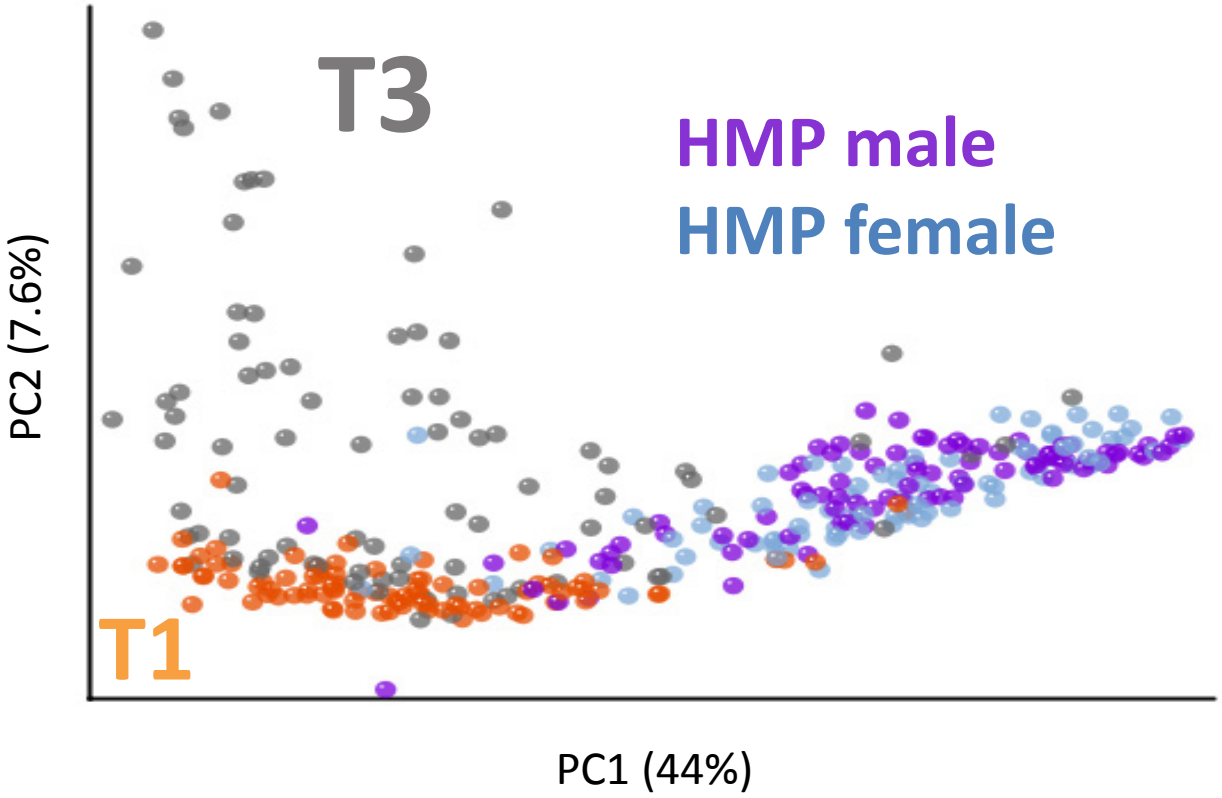


16S rRNA diversity

Koren *et al.* Cell 150: 1 (2012)

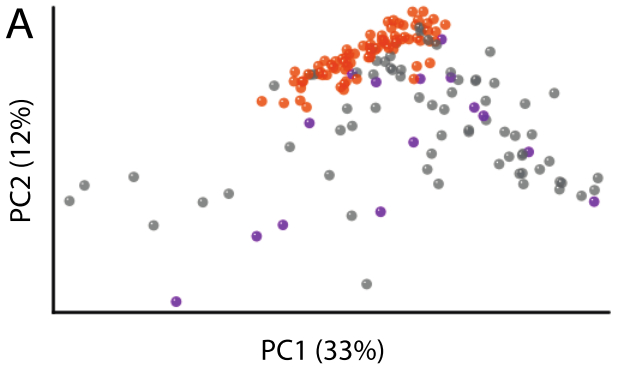
Which is normal? T1 or T3?

T1 diversity similar to “Normal” from Human Microbiome Project

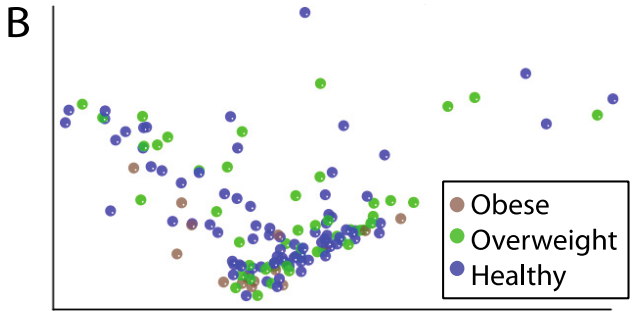


Koren *et al.* Cell 150: 1 (2012)

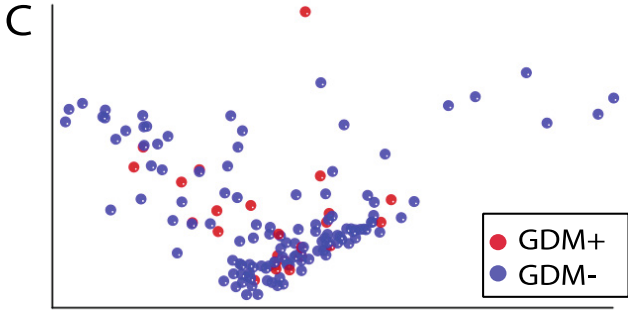
What does the pattern associate with?



No association with:

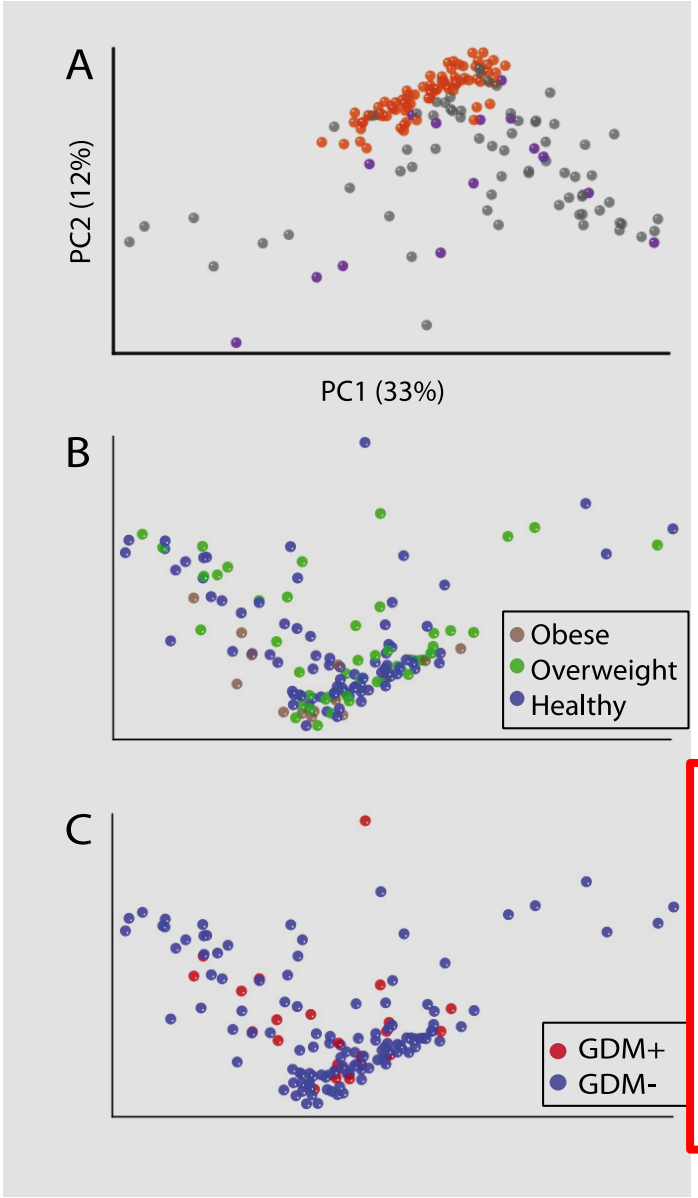


Pre-pregnancy obesity and overweight

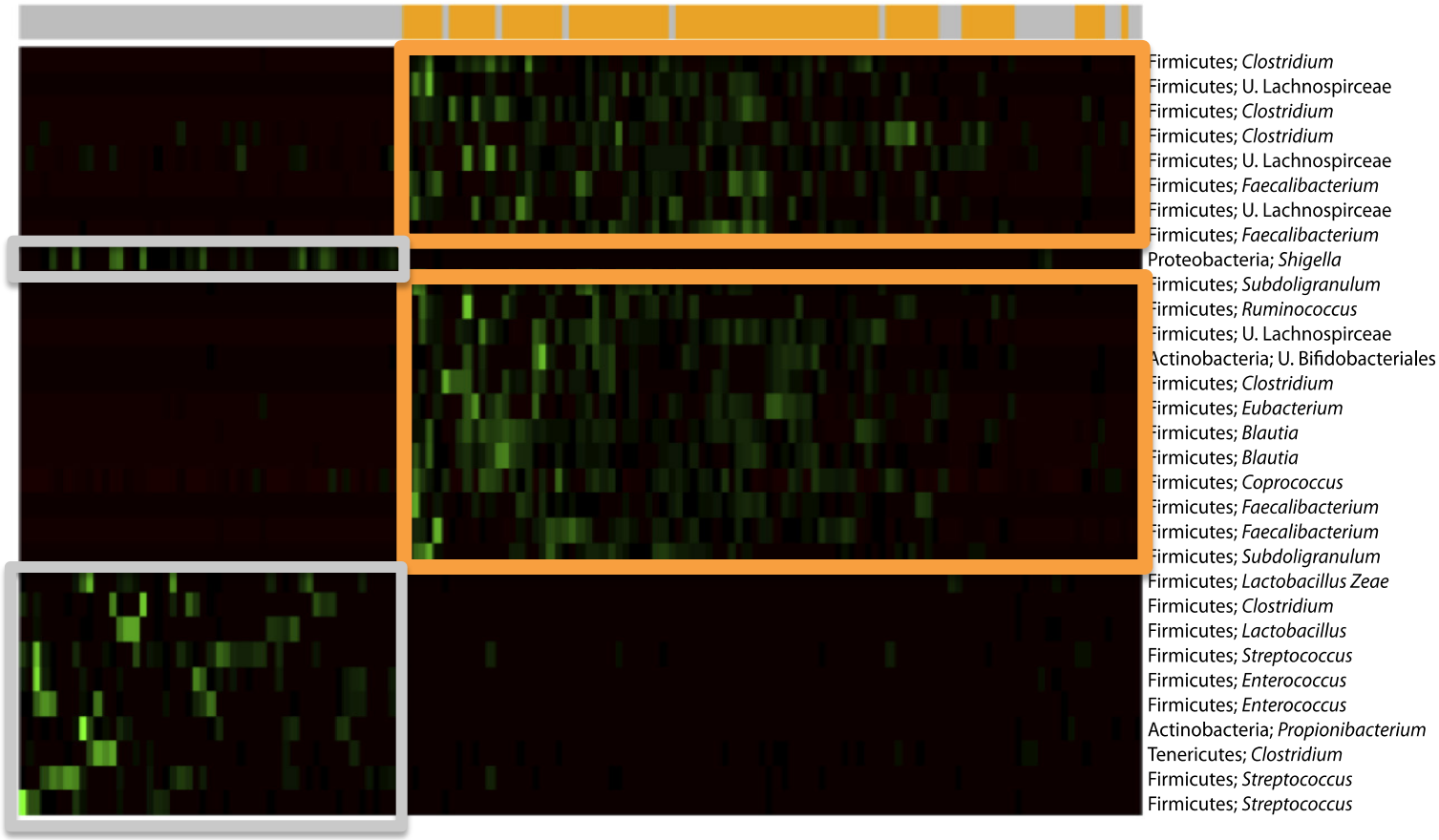


Gestational diabetes status

Gradients of abundances of taxa



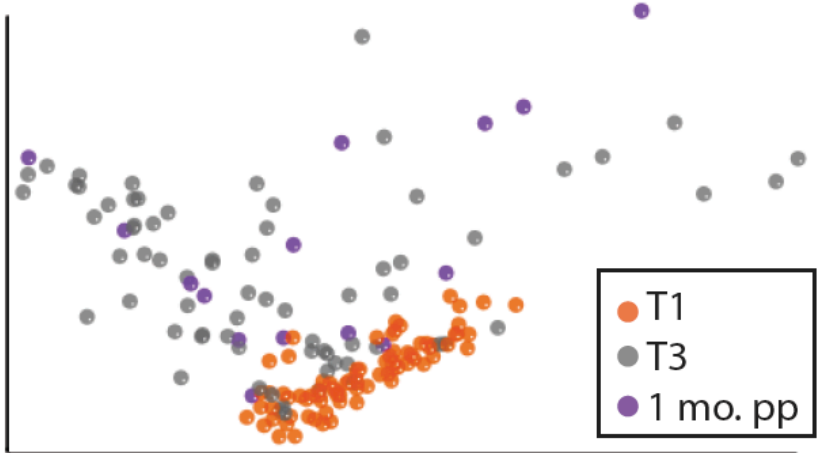
Shift in abundant bacterial genera

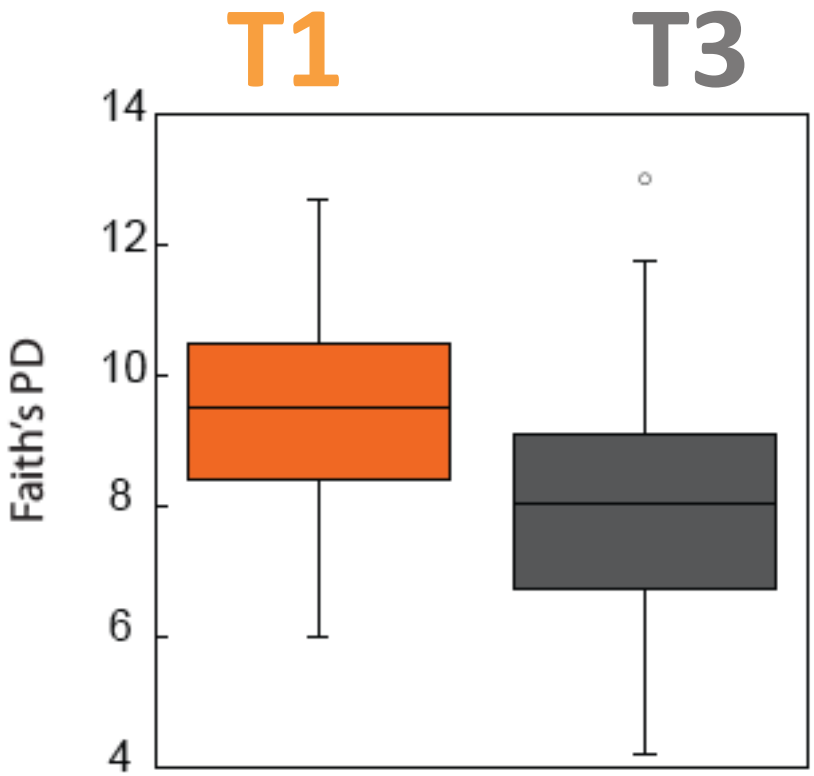


T1: More SCFA producers

T3: More opportunistic pathogens

Each microbiota is depleted in its own way





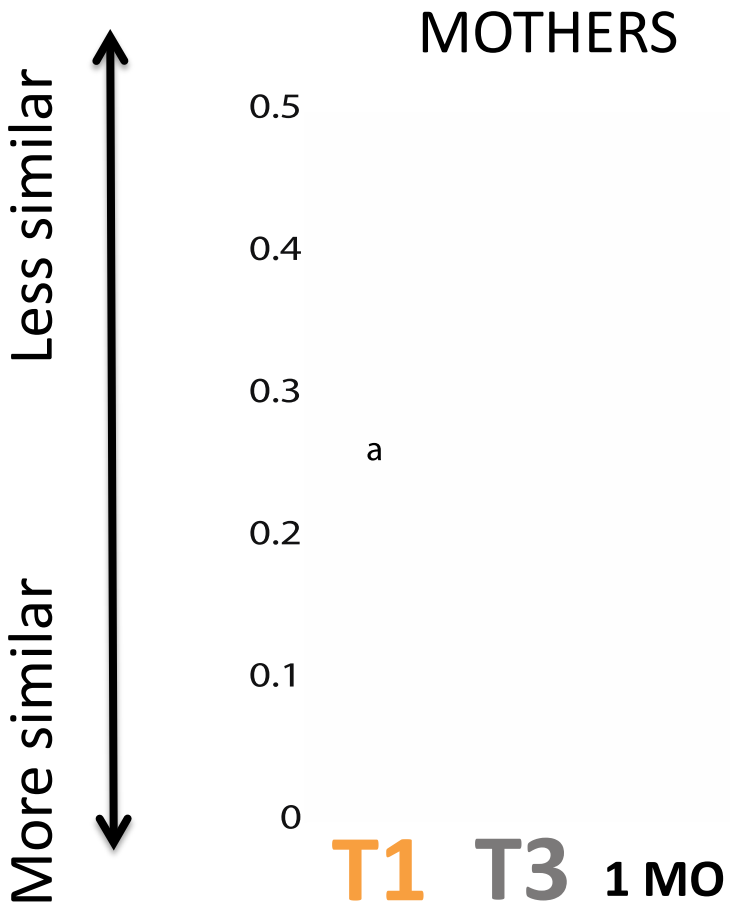
Between individuals

T3: High

Within individuals

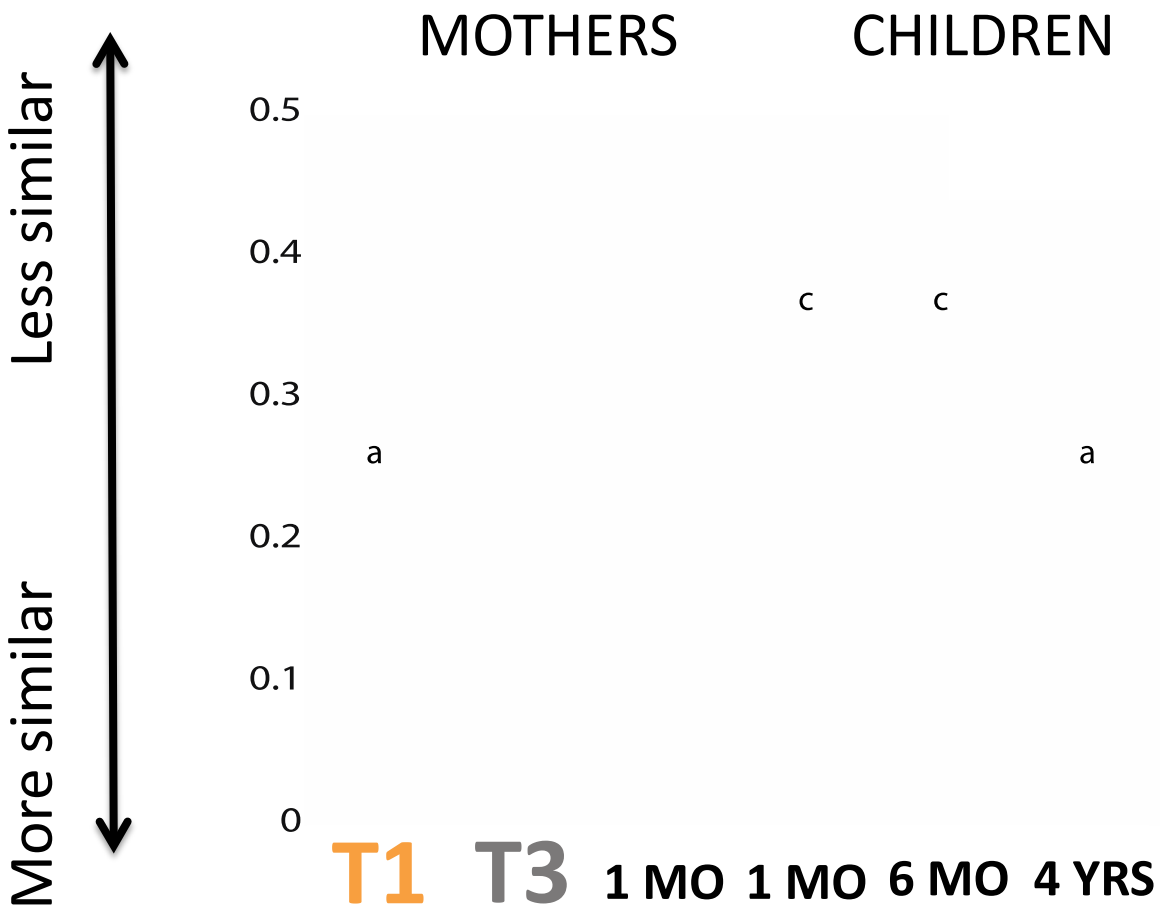
T3: Low

High between-individual diversity persists 1 month post-partum…



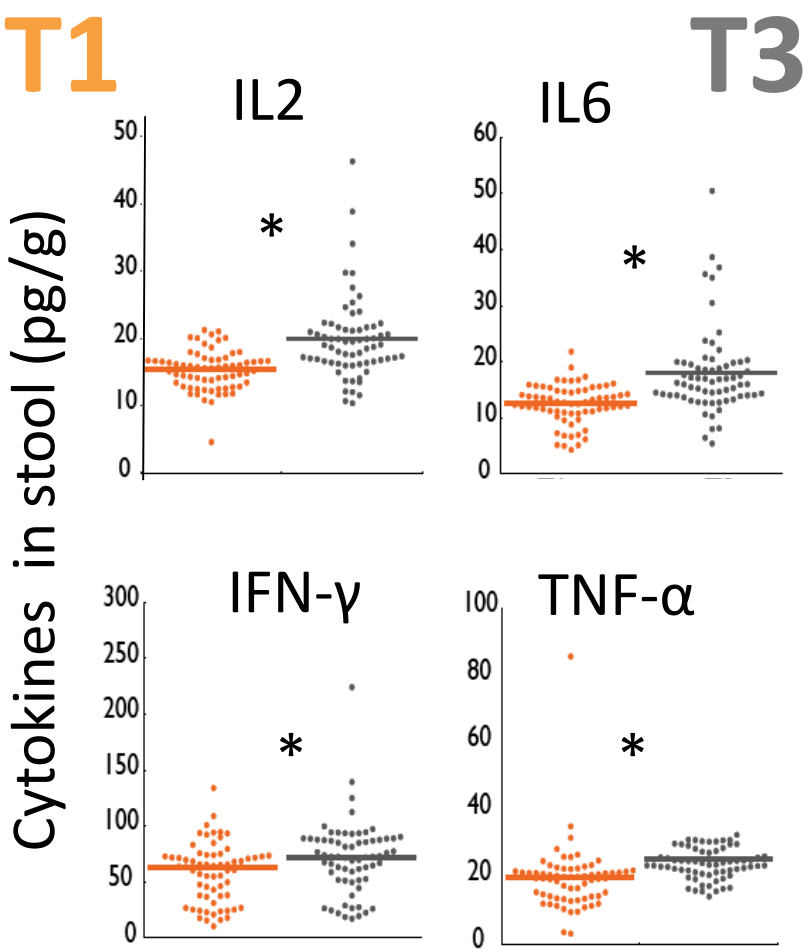
Koren *et al.* Cell 150: 1 (2012)

….and in the babies



Baby gut microbiotas not more similar to own mother than unrelated mothers
BUT similarities greatest for 4yrs- own mother T1 (p=0.003)

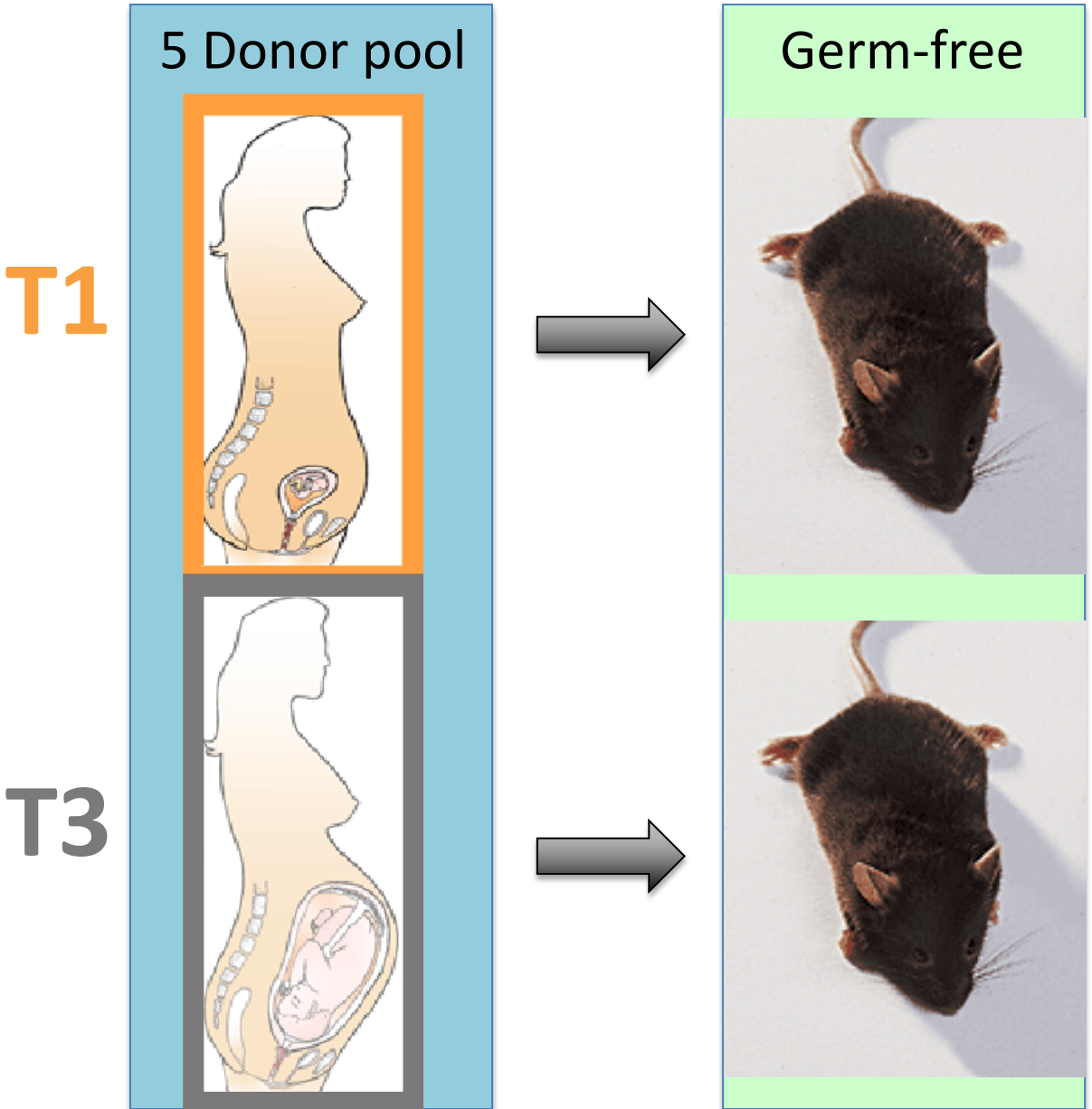
Greater inflammation in T3 stool



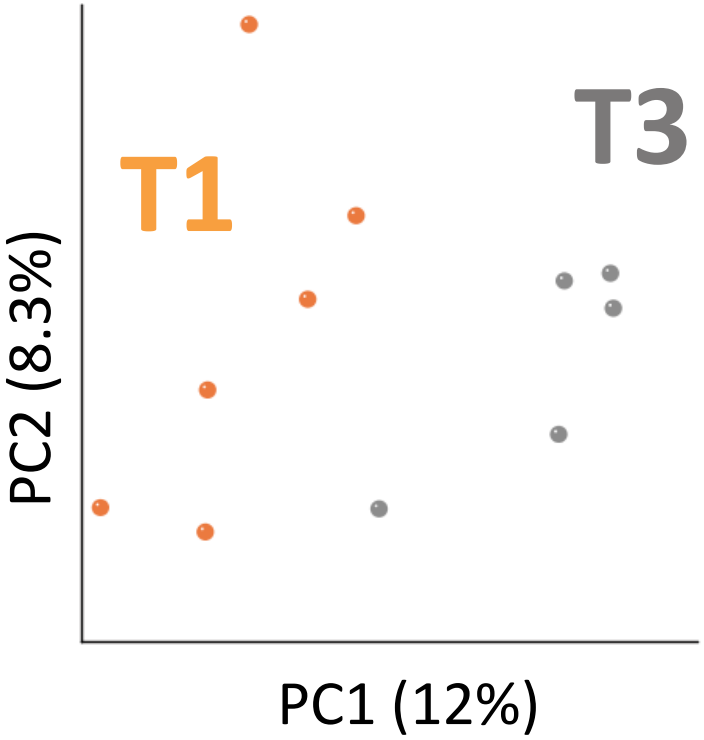
Elevated levels of inflammatory cytokines in T3 stool

Koren *et al.* Cell 150: 1 (2012)

Pregnant microbiome transfer to GF mice



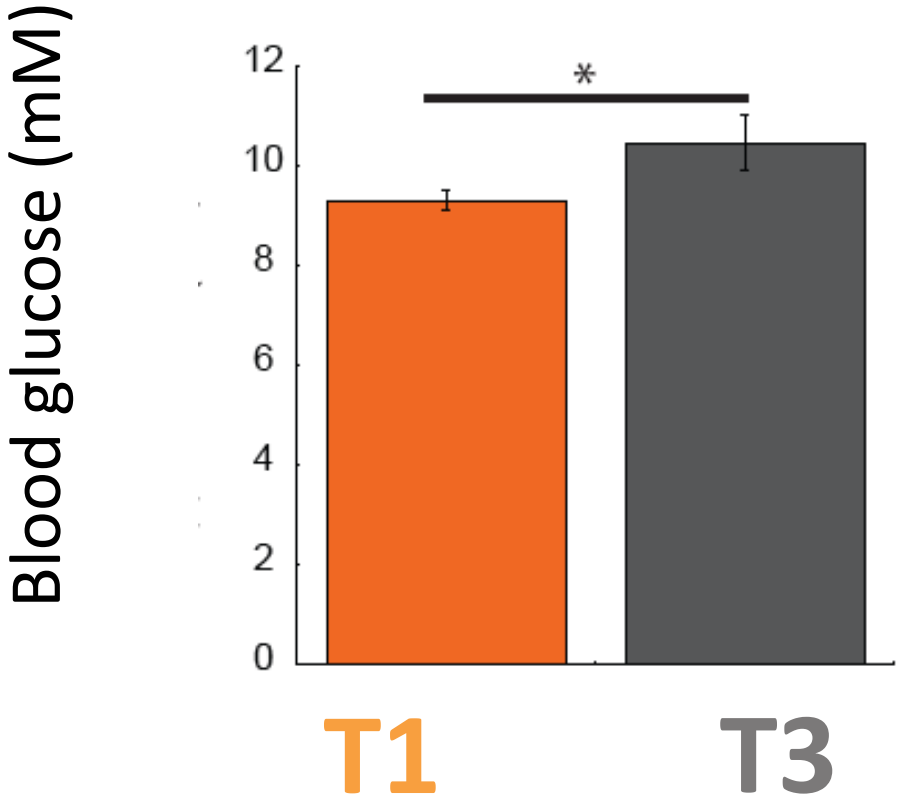
Recipient mice of T3: greater inflammation



Differences in microbiota between T1 and T3 are maintained for 2 weeks

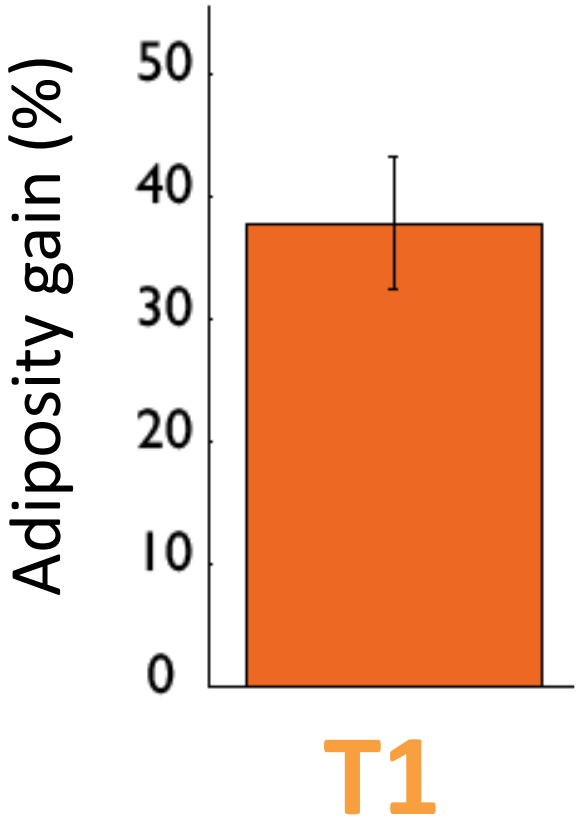
Koren *et al.* Cell 150: 1 (2012)

T3 microbiota induce higher blood glucose levels



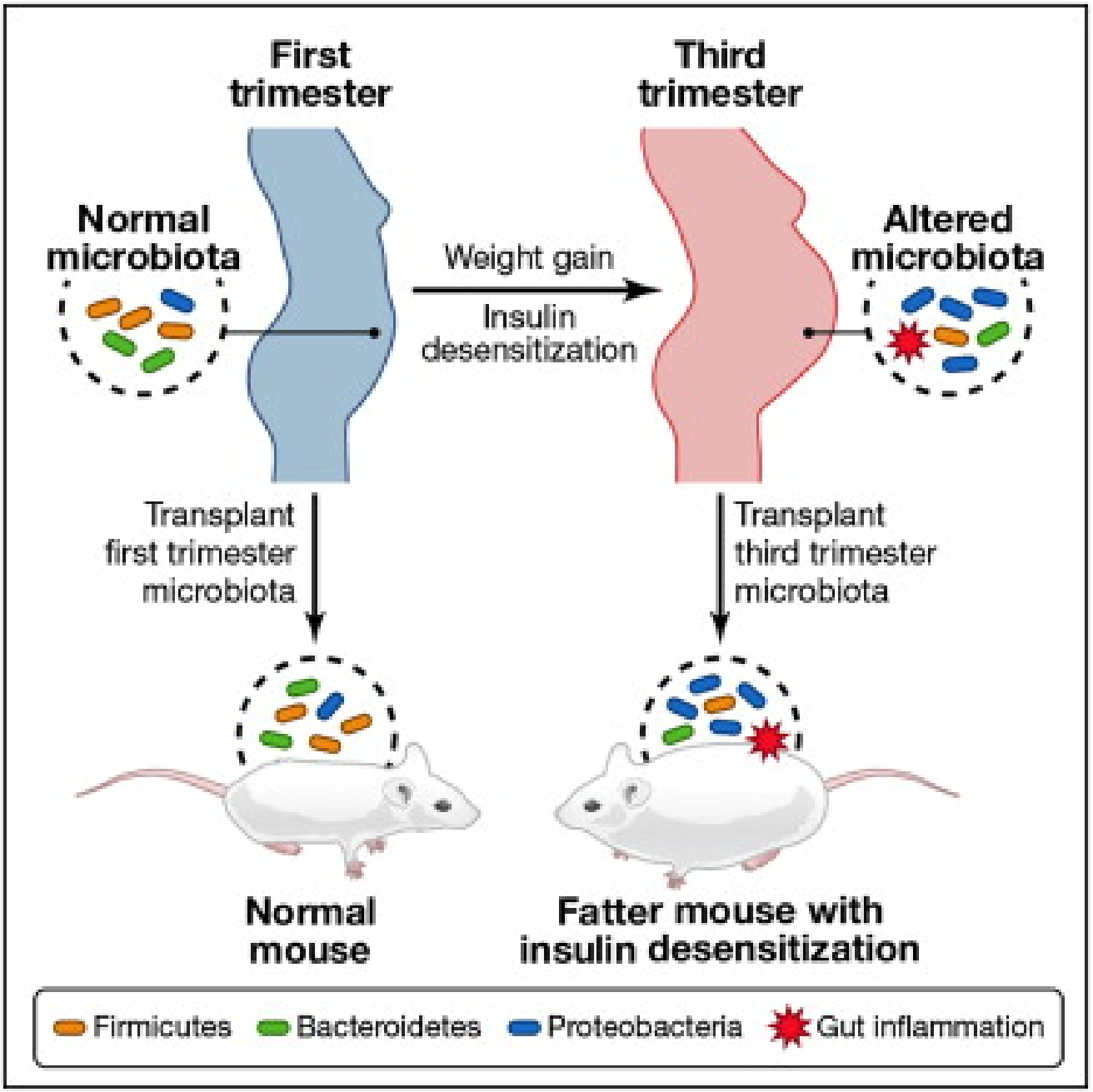
Fasting plasma glucose after 2 week period

T3 microbiota make a fatter mouse



Greater adiposity gain in T3 recipients after 2 weeks

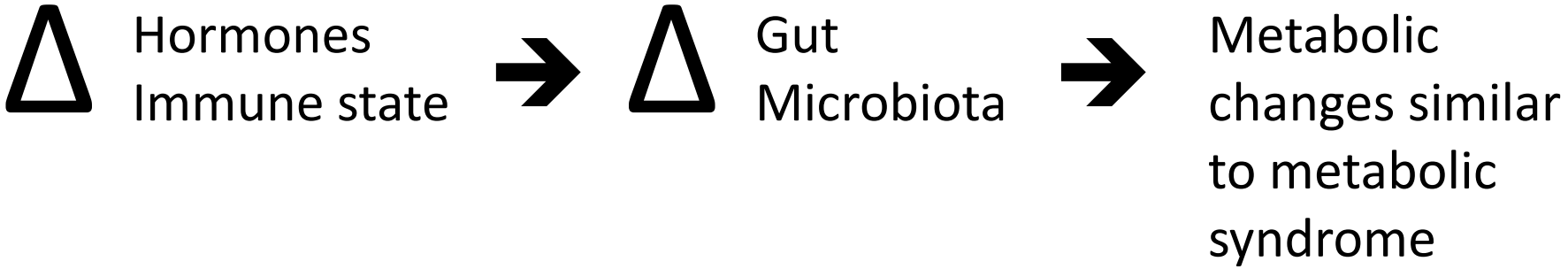
Koren *et al.* Cell 150: 1 (2012)


First trimester
Third trimester
Normal microbiota
Weight gain
Insulin desensitization
Altered microbiota
Transplant first trimester microbiota
Transplant third trimester microbiota
Normal mouse
Fatter mouse with insulin desensitization
Firmicutes
Bacteroidetes
Proteobacteria
Gut inflammation

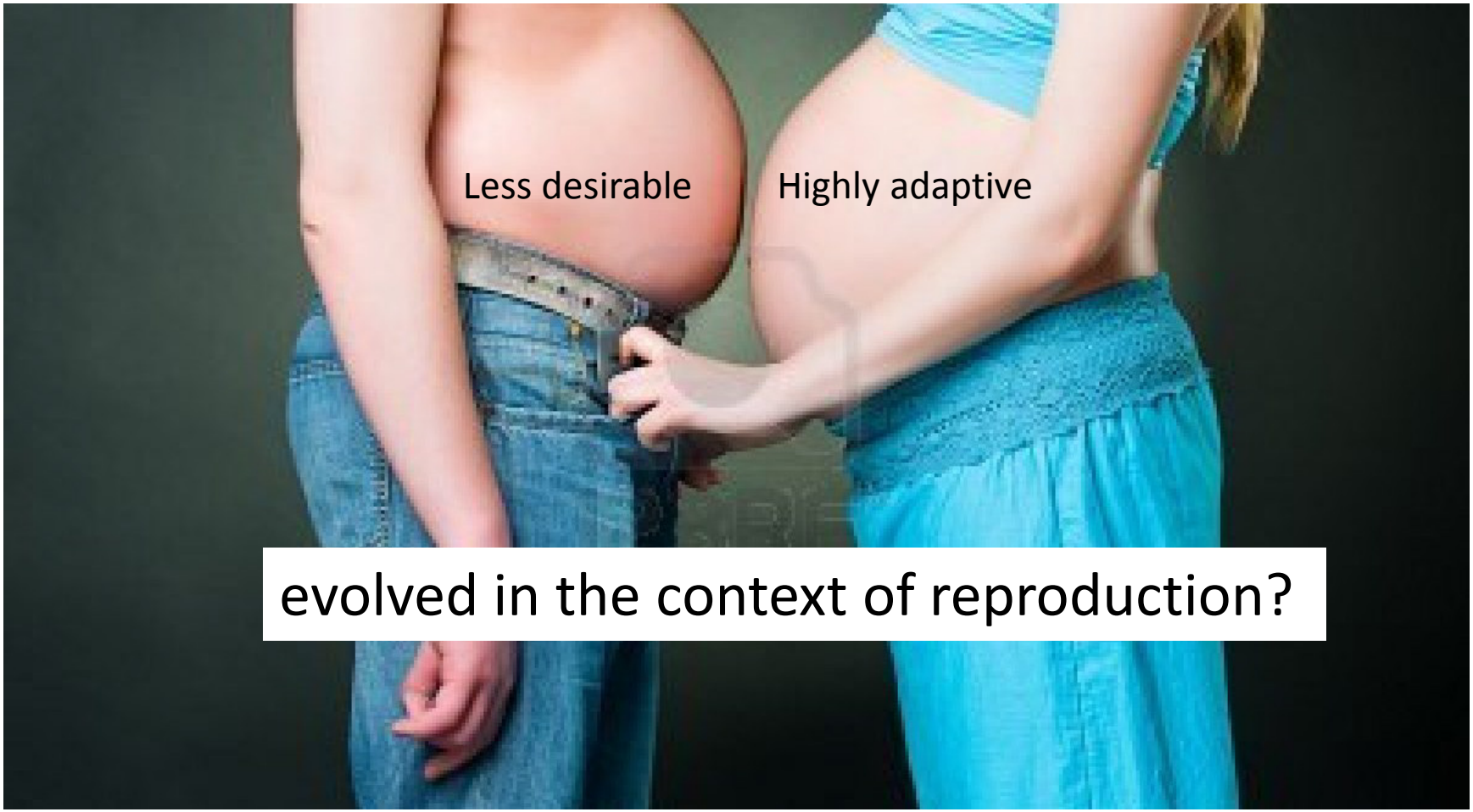
Healthy pregnancy

Metabolic changes include reduced insulin sensitivity, low-grade inflammation

- Highly adaptive in the context of pregnancy
- Are the gut microbes a link in the chain?



Gut microbes impact host metabolism



www.123rf.com

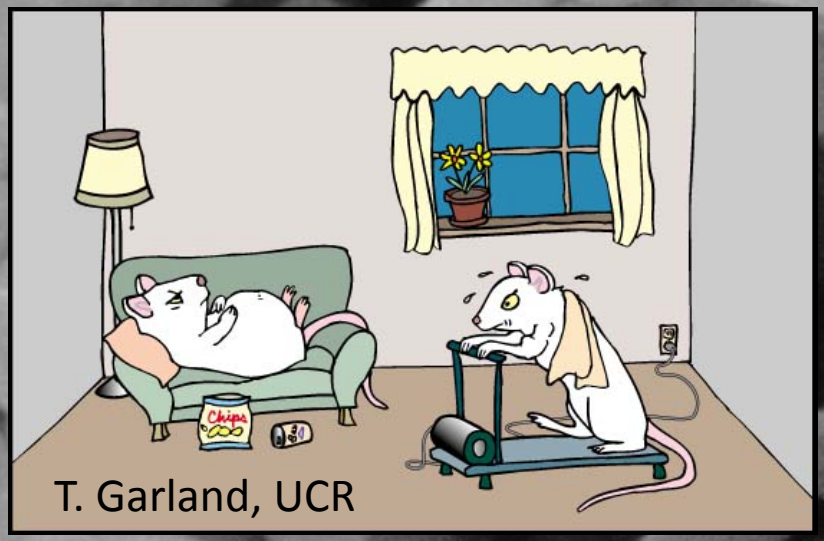
What is the extent of microbial effect on host phenotype?

What is known:

Some aspects of metabolism, immunity, behavior

What is not known:

Fertility, longevity, activity, physiology, etc…



T. Garland, UCR

Selected Collaborators:

USA: Dirk Gevers (Broad Institute) **Andrew Gewirtz, Matam Vijay-Kumar** (Georgia State University), **Rob Knight** (CU Boulder, HHMI)**, Curtis Huttenhower** (Harvard), **Lora Hooper** (UT Southwestern, HHMI)

Europe: Tim Spector, Jordana Bell, Michelle Beaumont (King's College London), **Fredrik Backhed** (Gothenburg University) **Erika Isolauri, Seppo Salminen** (Turku University)

Cornell: Andy Clark, Ran Blekhman, Alon Keinan, Qi Sun, Robert Bukowski, Ed Buckler, Jeff Werner, Lars Angenent

THANK YOU:

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FOUNDATION

General
Mills

THE HARTWELL FOUNDATION
BENEFITTING CHILDREN BY
INSPIRING INNOVATION
AND ACHIEVEMENT

NSF