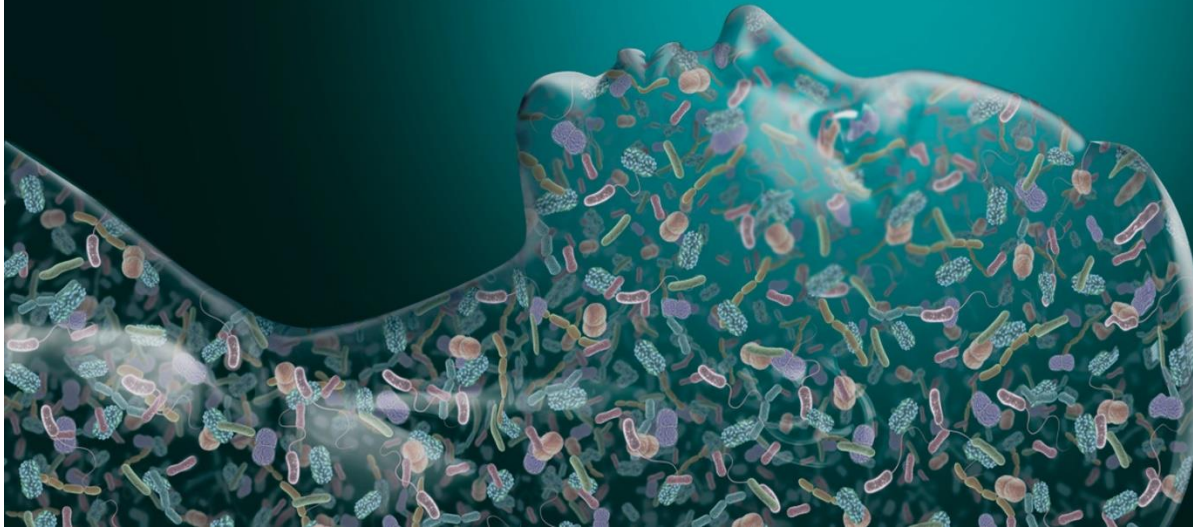


Our microbiome and us

We are inhabited by as many as ten thousand bacterial species; these cells outnumber those which we consider our own by ten to one, and weigh, all told, about three pounds—the same as our brain. Together, they are referred to as our microbiome—and they play such a crucial role in our lives that scientists have begun to reconsider what it means to be human.

-Michael Specter



National
SCIENCE
Challenges

A BETTER
START

E Tipu e Rea

Prof Wayne S Cutfield

Director A Better Start

National Science Challenge

Liggins Institute, University of Auckland

Auckland 2019



LIGGINS
INSTITUTE

Contents

- The obesity epidemic
- Mouse intervention (GMT) studies
- Gut microbiome physiology
- Human association studies
- Human intervention (GMT) studies
- Vaginal seeding and C section
- Conclusions

Early childhood overweight/obesity prevalence NZ Before School Check (4-5 yrs old)

51,507 children 2015-6, 95% capture

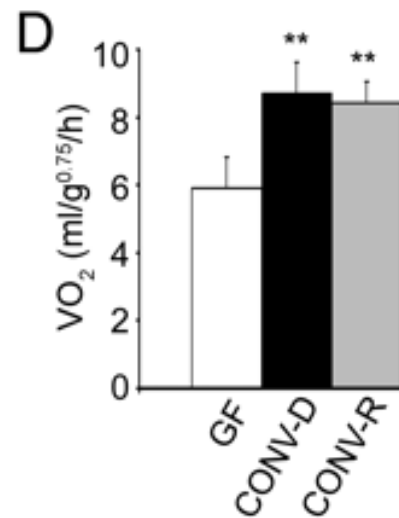
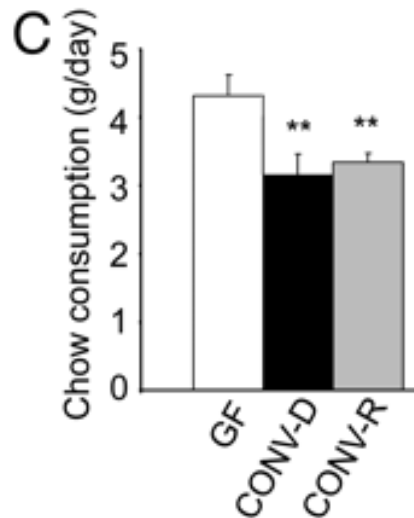
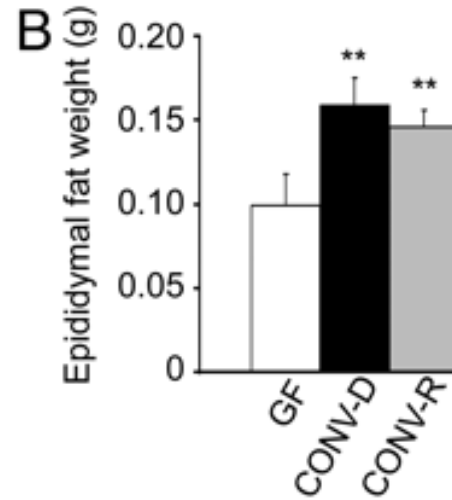
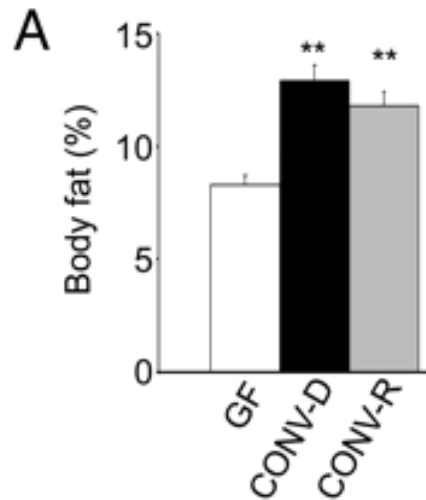
Overweight and obesity prevalence:

Overall	33.4%
Males	36.8% (females 29.9%)
European	31.2%
Maori	41.1%
Pasifika	53.1%
Asian	20.7%
Lowest affluence quintile	42.5%

Germ free mice and the gut microbiome

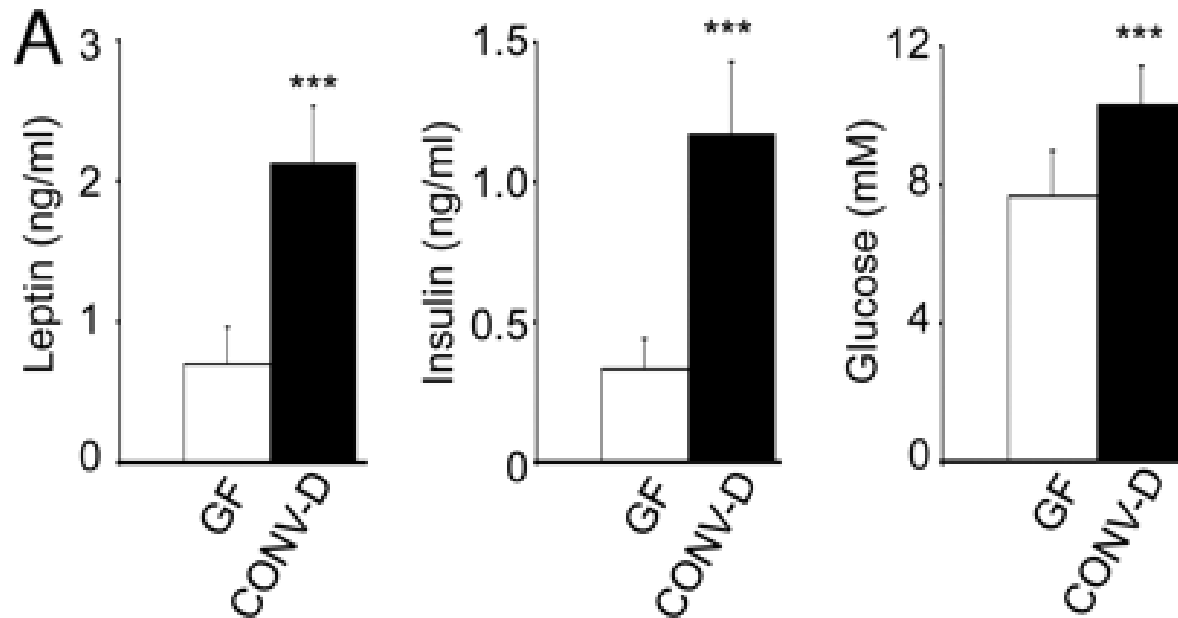


GF mice colonised with gut microbiome



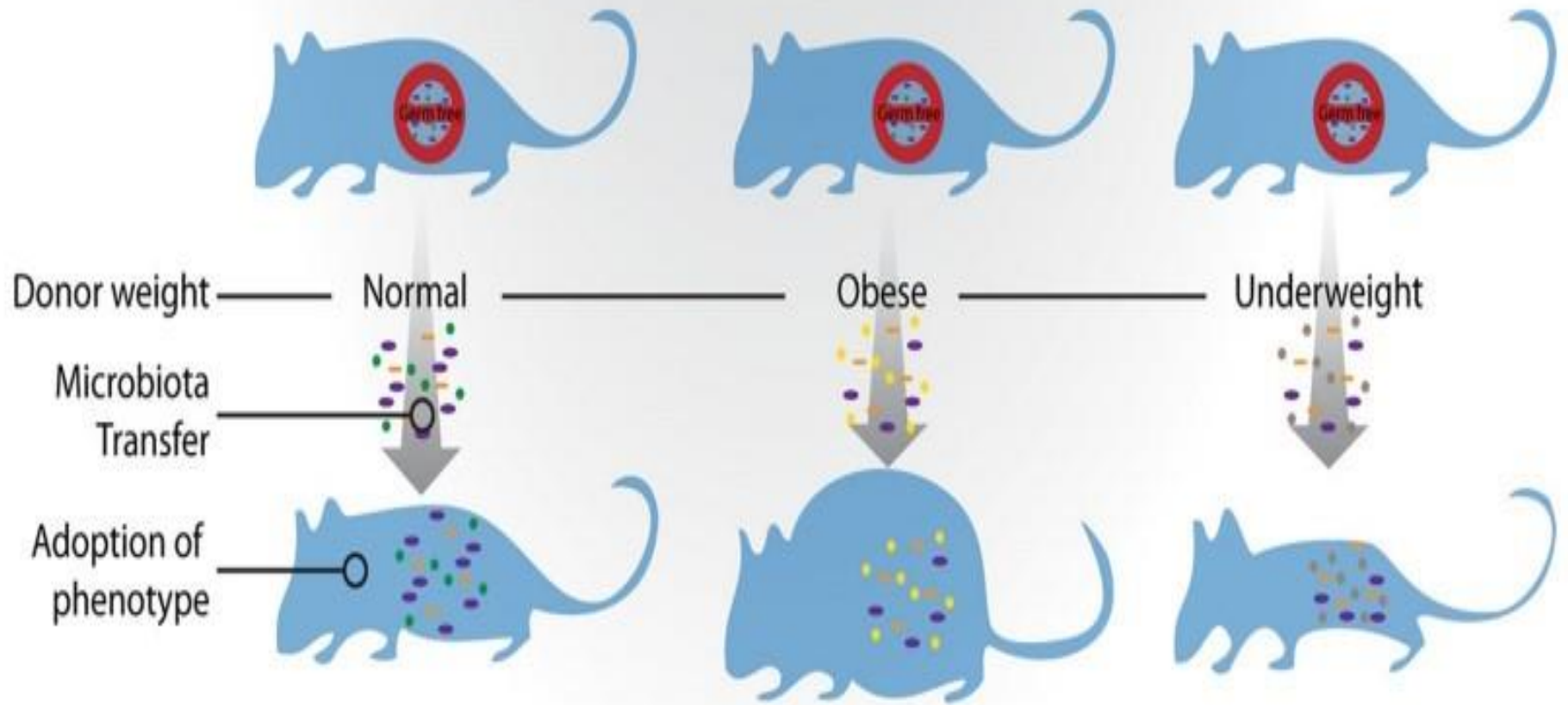
Colonised at birth
Followed to adulthood
CONV-R GF until adulthood and
then colonised for last 2 weeks
Donor: cecal contents of normal
mice

GF mice colonised with gut microbiome



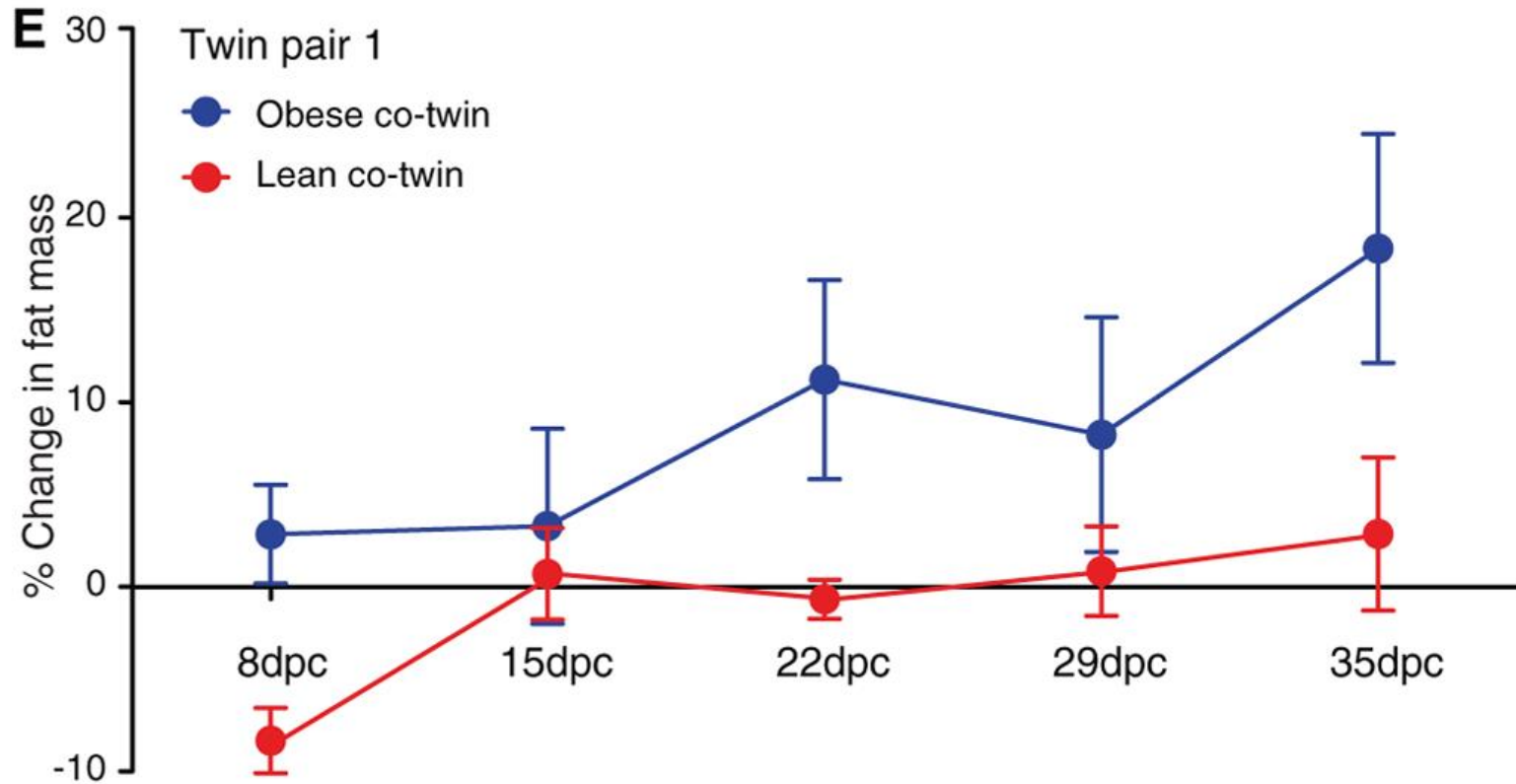
*Backhed F et al
PNAS 2004; 101:
15718-23*

Germ-free animals adopt phenotype of microbiota donor

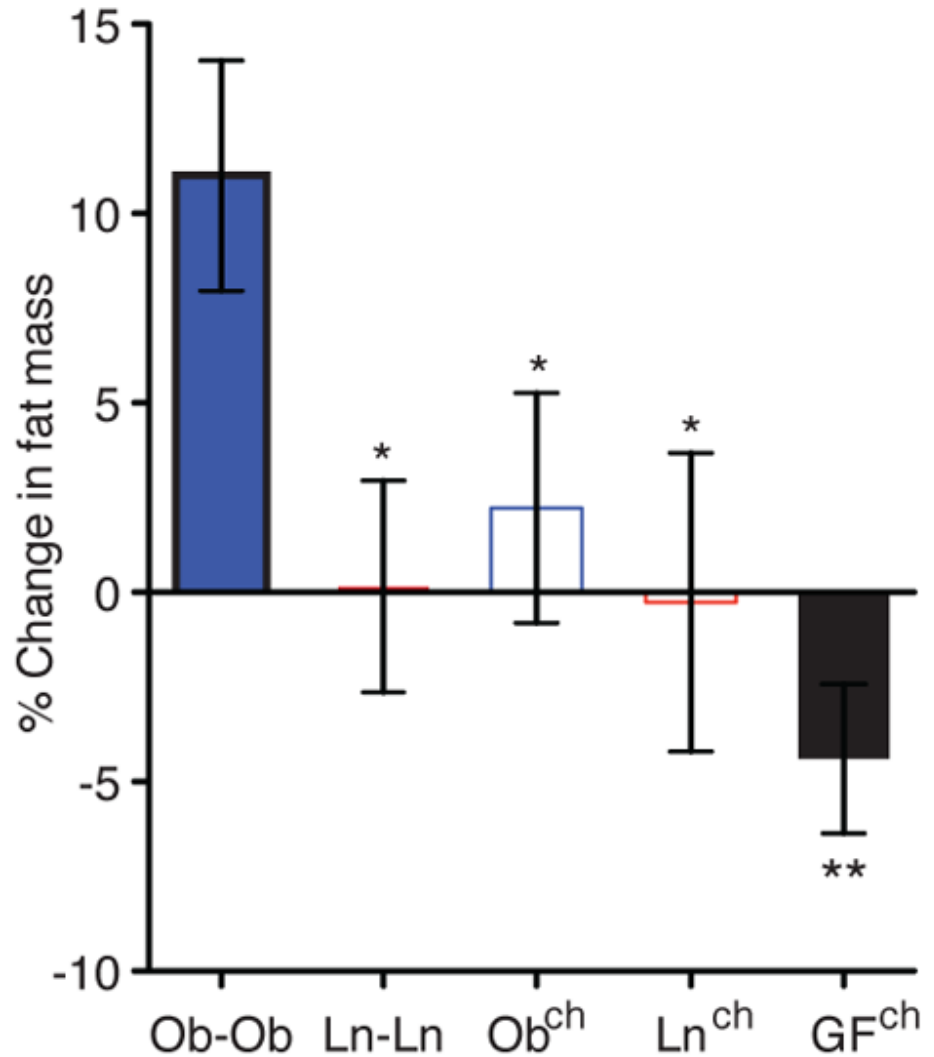
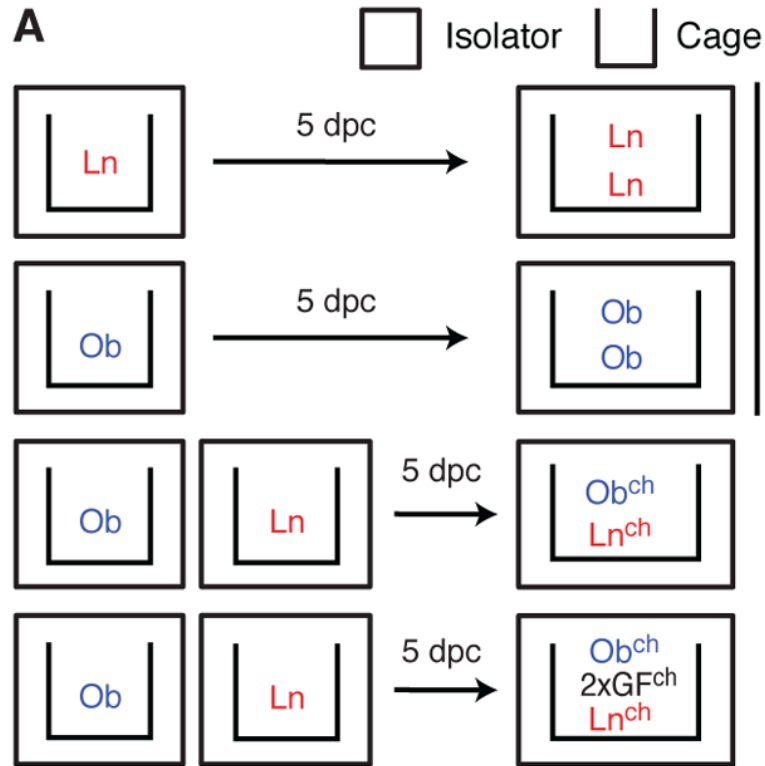


Human to GF mouse gut microbiome transfer

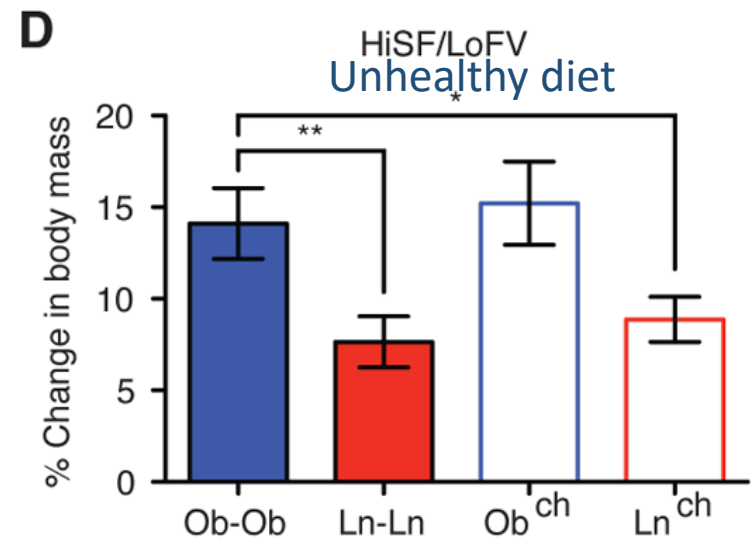
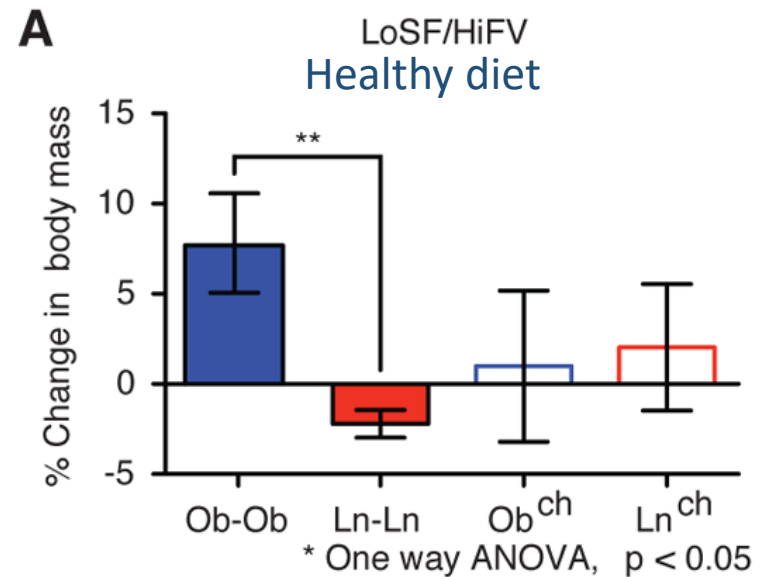
Twin Pair	1 (DZ)		2 (DZ)		3 (DZ)		4 (MZ)	
BMI (kg/m ²)	23	32	25.5	31	19.5	30.7	24	33



Mixing Obese and lean GF mice: Lean wins!

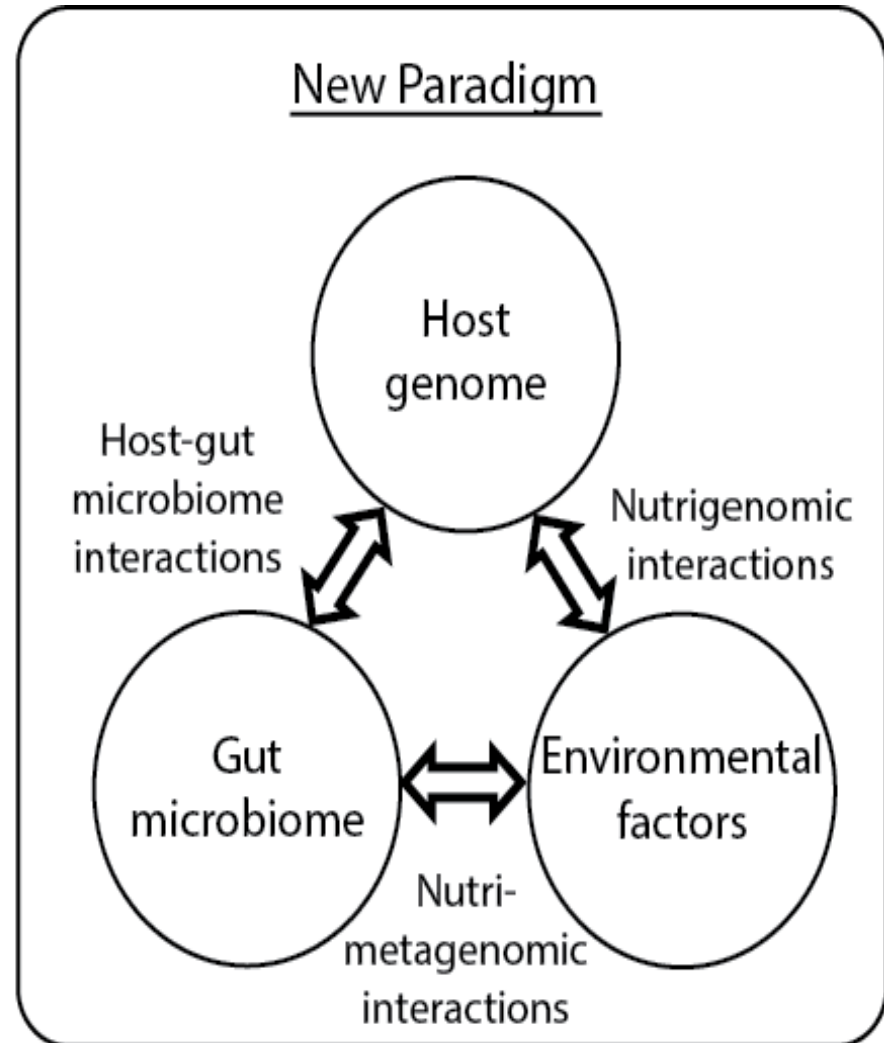
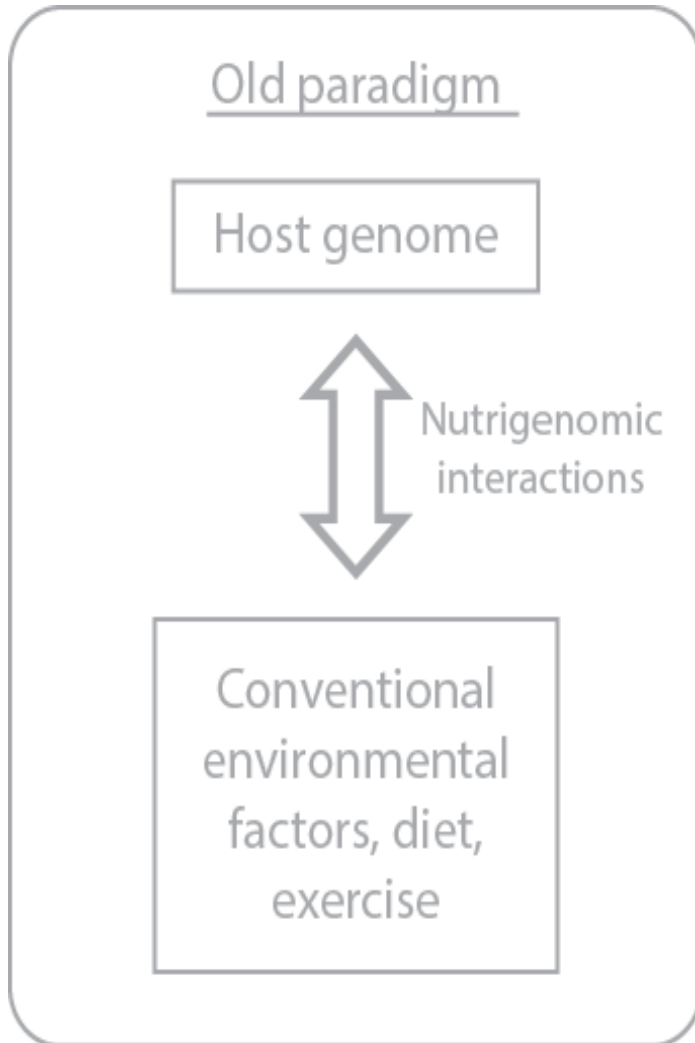


Mixing obese and lean GF mice: Poor diet wins!

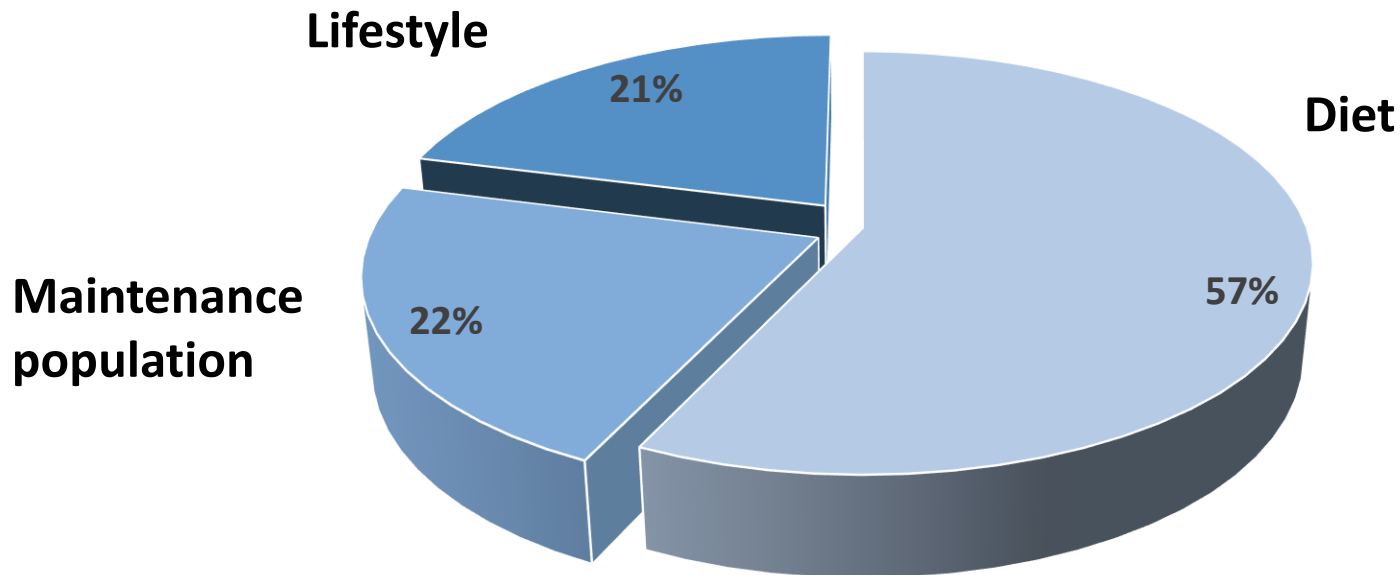


*Ridaura VK et al Science 2013; 341: DOI 10.1126/Science.
1241214*

Microbiome role in health and disease



Influences on gut microbiome



Lifestyle includes:

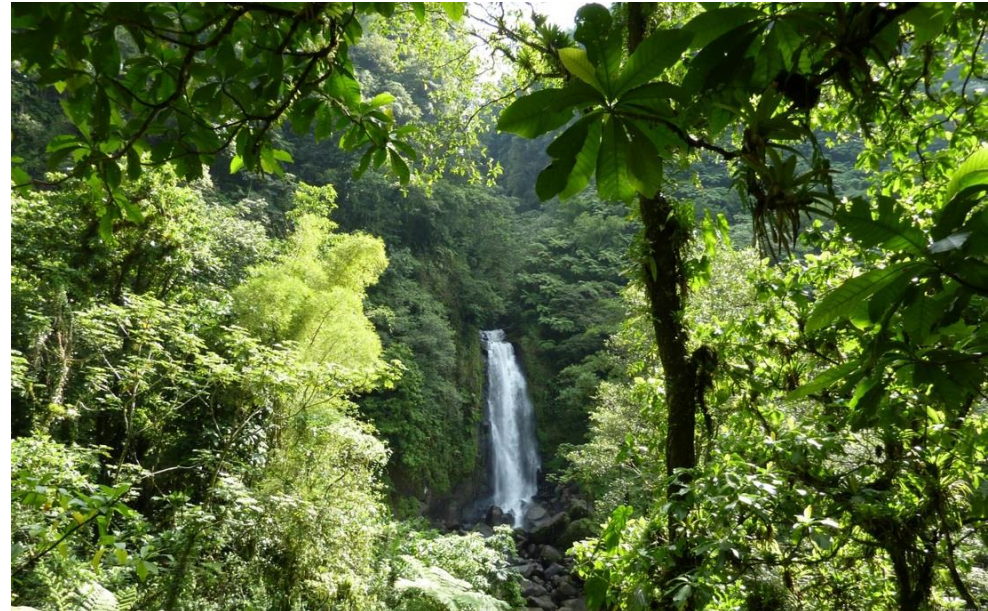
- Antibiotics
- Other drugs
- Probiotics
- Illness (particularly gut infections/disease)
- Stress



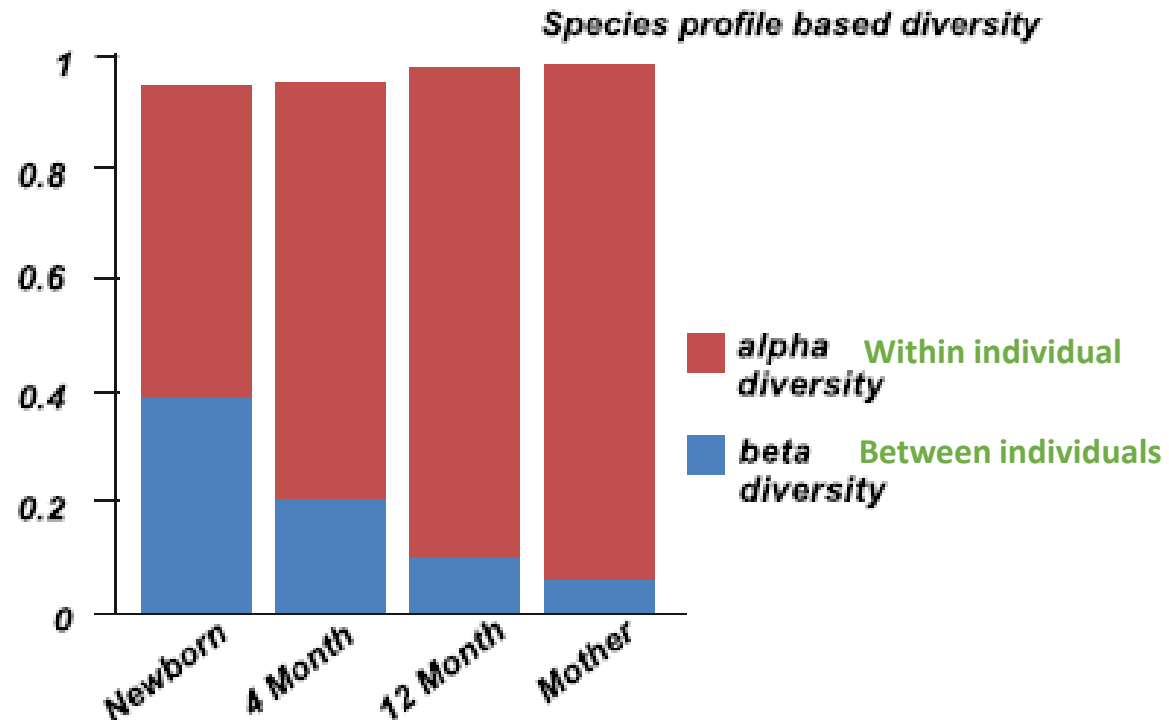
Gut bacteria influence:

- Calories provided (up to 200 kcal per day)
- Fat storage
- Inflammation and immunity
- Appetite

Diversity of gut bacteria is important for good health



Gut microbiome evolves during infancy



Backhed F et al Cell Host Microbiome 2015; 17: 690-703

What happens over one individual's lifetime? n=Billy Apple®

Excretory Wipings (1971, Apple, 161 West 23rd St, New York), censored in *From Barrie Bates to Billy Apple 1960-1974* (1974, Serpentine Gallery, London)



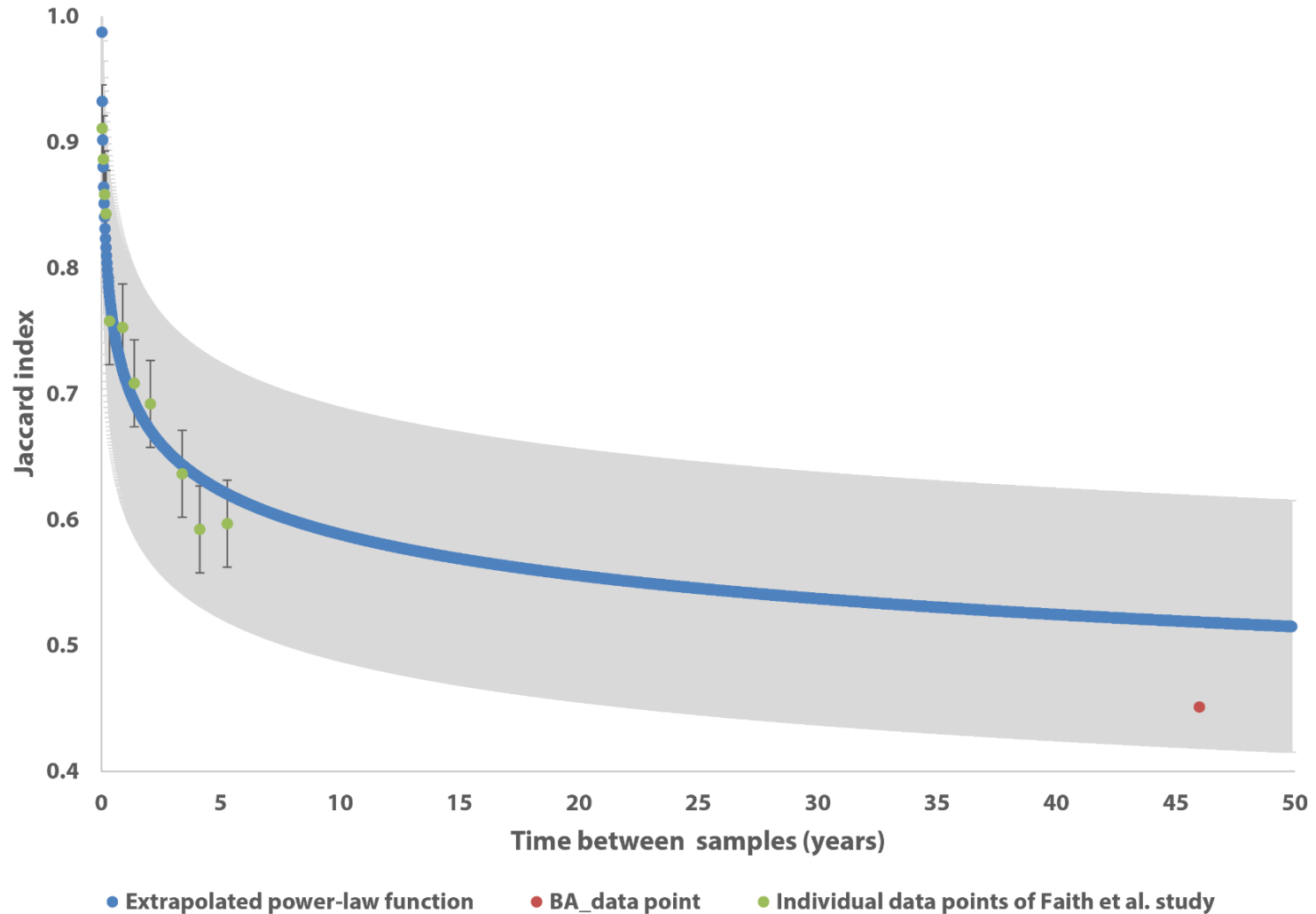
1970



2016

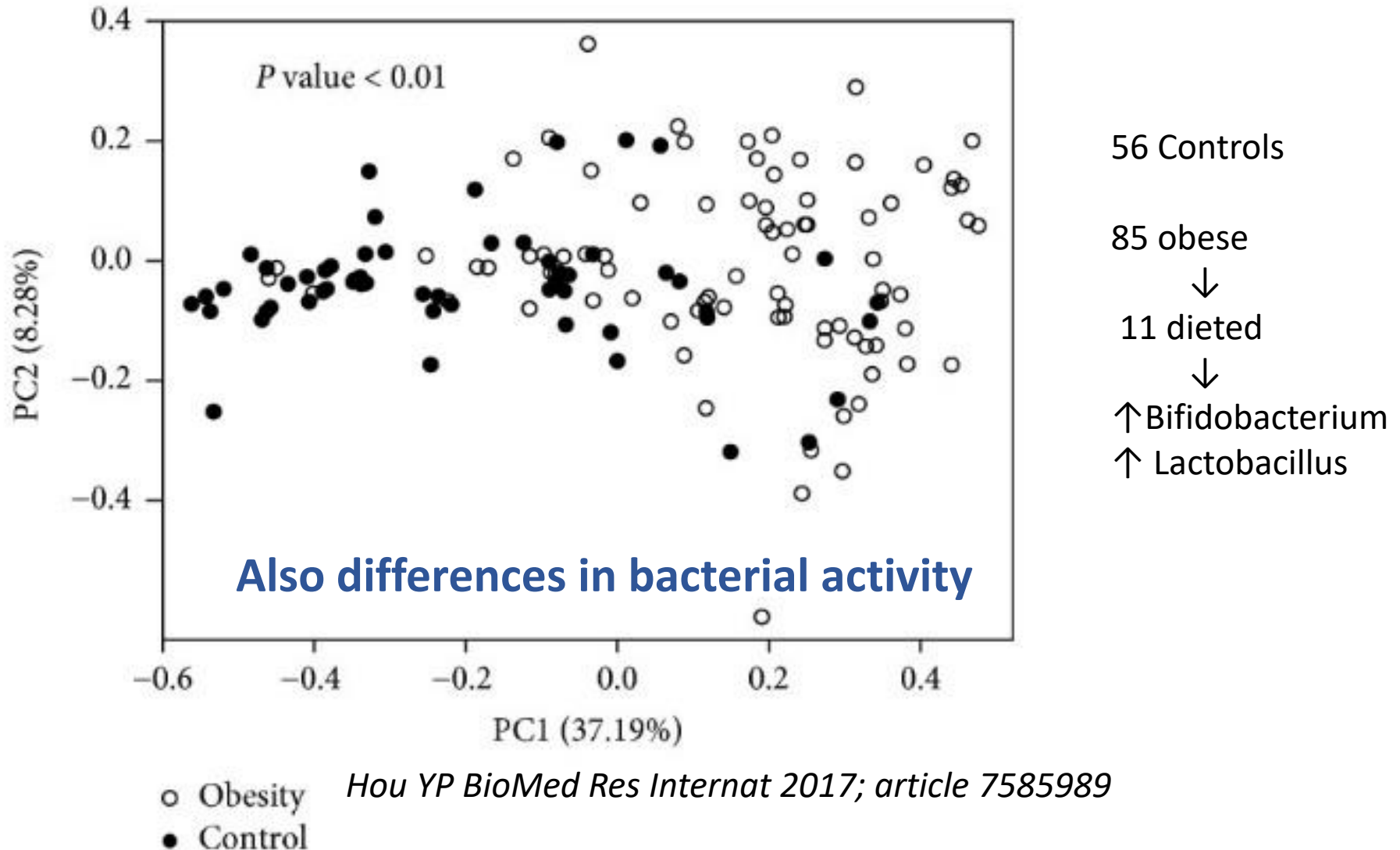
Jayasinghe T et al in press

~50% of the microbial population structure is predicted to be stable over 46 years.

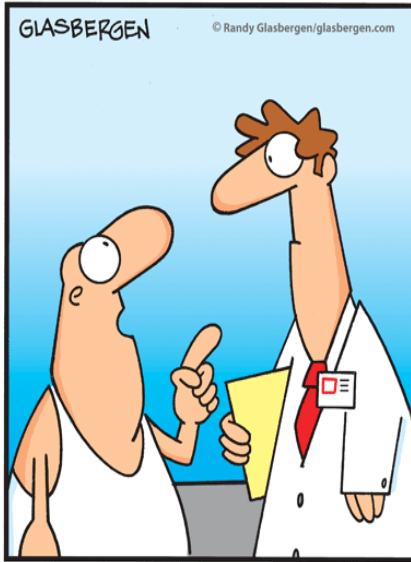


Faith, J. et al. (2013) Science, 341(6141)

The gut microbiome is different in obese children



Hou YP BioMed Res Internat 2017; article 7585989



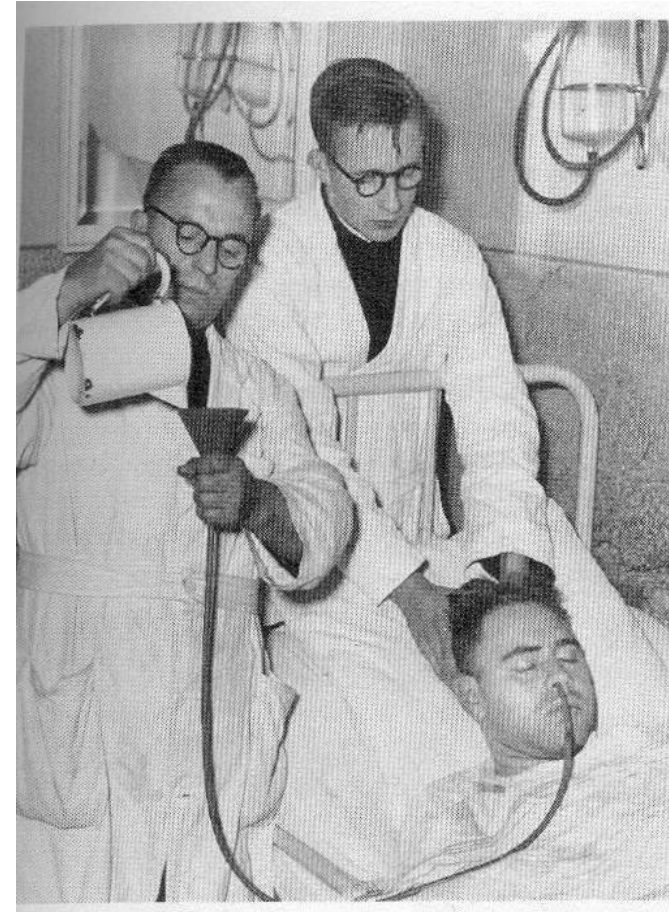
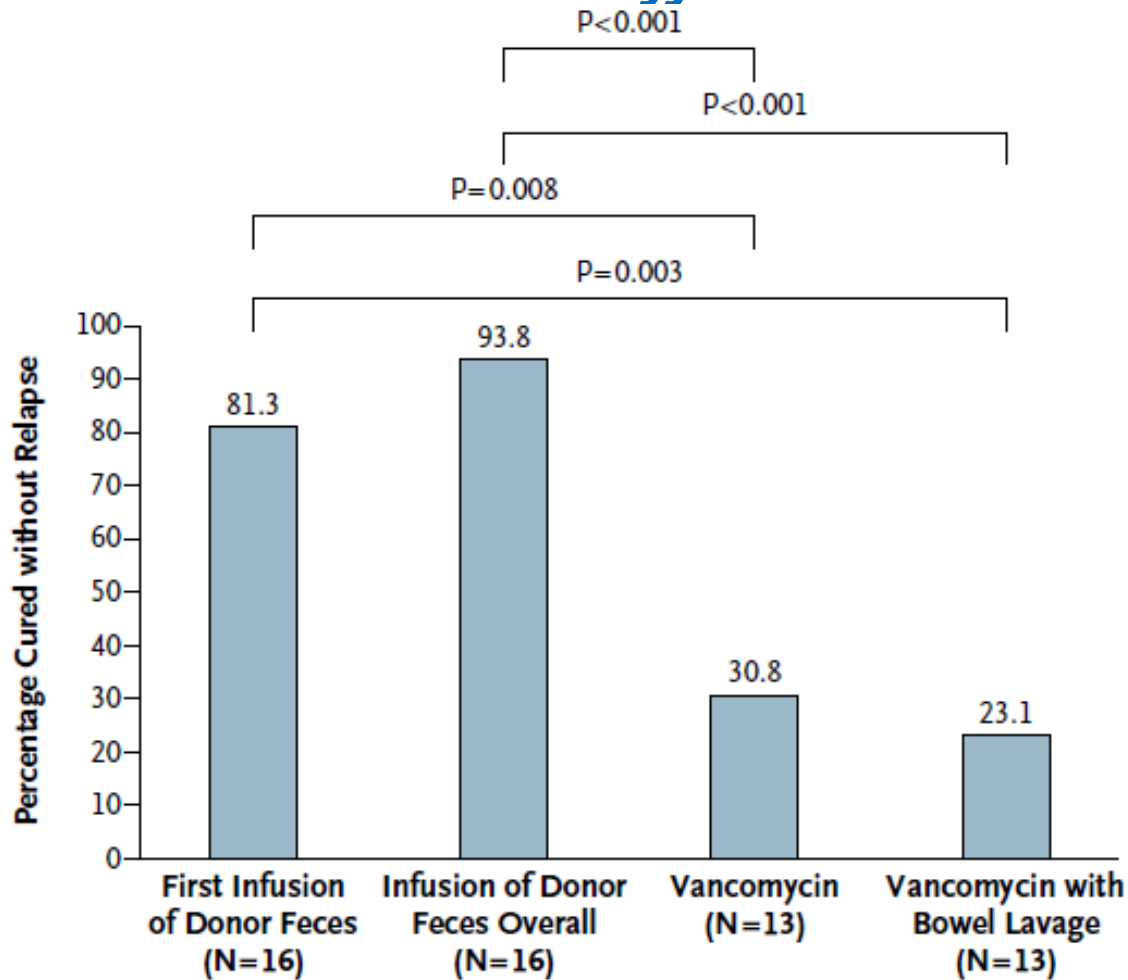
“Diabetes has increased dramatically over the past 20 years. That proves that diabetes is caused by global warming!”

Association studies in humans



- Obesity associated with reduced diversity of gut microbiome
- Gut microbiome dysbiosis in type 2 diabetes
- Gut microbiome dysbiosis in allergic diseases
- Gut microbiome associated with inflammatory bowel disease
- Gut microbiome dysbiosis in depression, autism, Parkinson’s disease, Alzheimer’s disease, mania

Gut microbiome transfer curative in chronic *C. difficile* infection



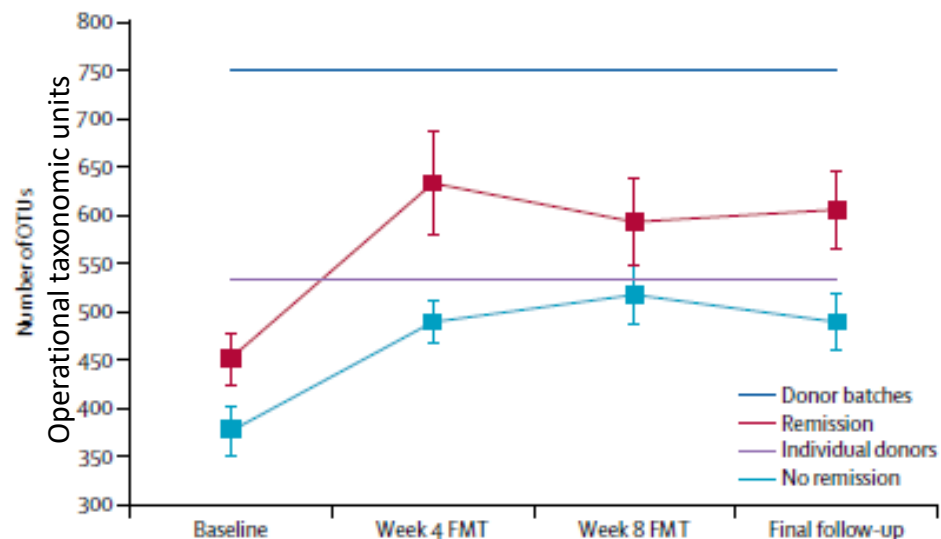
Van Nood E et al *N Engl J Med* 2013; 368: 407-15

FMT successful in Ulcerative colitis

	Faecal microbiota transplantation (n=41)	Placebo (n=40)	Risk ratio (95% CI)	p value
Primary outcome				
Steroid-free clinical remission and endoscopic remission or response*	11 (27%)	3 (8%)	3.6 (1.1-11.9)	0.021
Secondary outcomes				
Steroid-free clinical remission†	18 (44%)	8 (20%)	2.2 (1.1-4.5)	0.021
Steroid-free clinical response‡	22 (54%)	9 (23%)	2.4 (1.3-4.5)	0.004
Steroid-free endoscopic remission§	5 (12%)	3 (8%)	1.6 (0.4-6.4)	0.48
Steroid-free endoscopic response¶	13 (32%)	4 (10%)	3.2 (1.1-8.9)	0.016

*Total Mayo score ≤ 2 , with all subscores ≤ 1 , and ≥ 1 point reduction from baseline in endoscopy subscore.
 †Combined Mayo subscores of ≤ 1 for rectal bleeding plus stool frequency. ‡Decrease of ≥ 3 points or $\geq 50\%$ reduction from baseline (or both) in combined Mayo subscores for rectal bleeding plus stool frequency. §Mayo endoscopy subscore 0. ¶Mayo endoscopy subscore ≤ 1 , with ≥ 1 point reduction from baseline.

Table 2: Primary and secondary outcomes at week 8

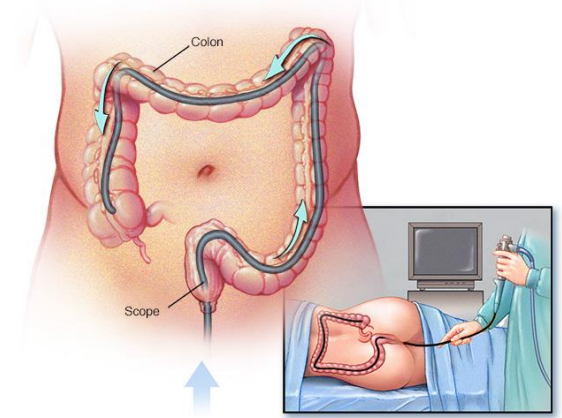


Treatment:

Initial colonoscopy infusion

FMT enemas 5 days/wk x 8 wks

Gut microbiome for irritable bowel syndrome in adults



© MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH. ALL RIGHTS RESERVED.

18-75 yrs with moderate to severe IBS, Norway

Double blind RCT

55 treated and 28 placebo

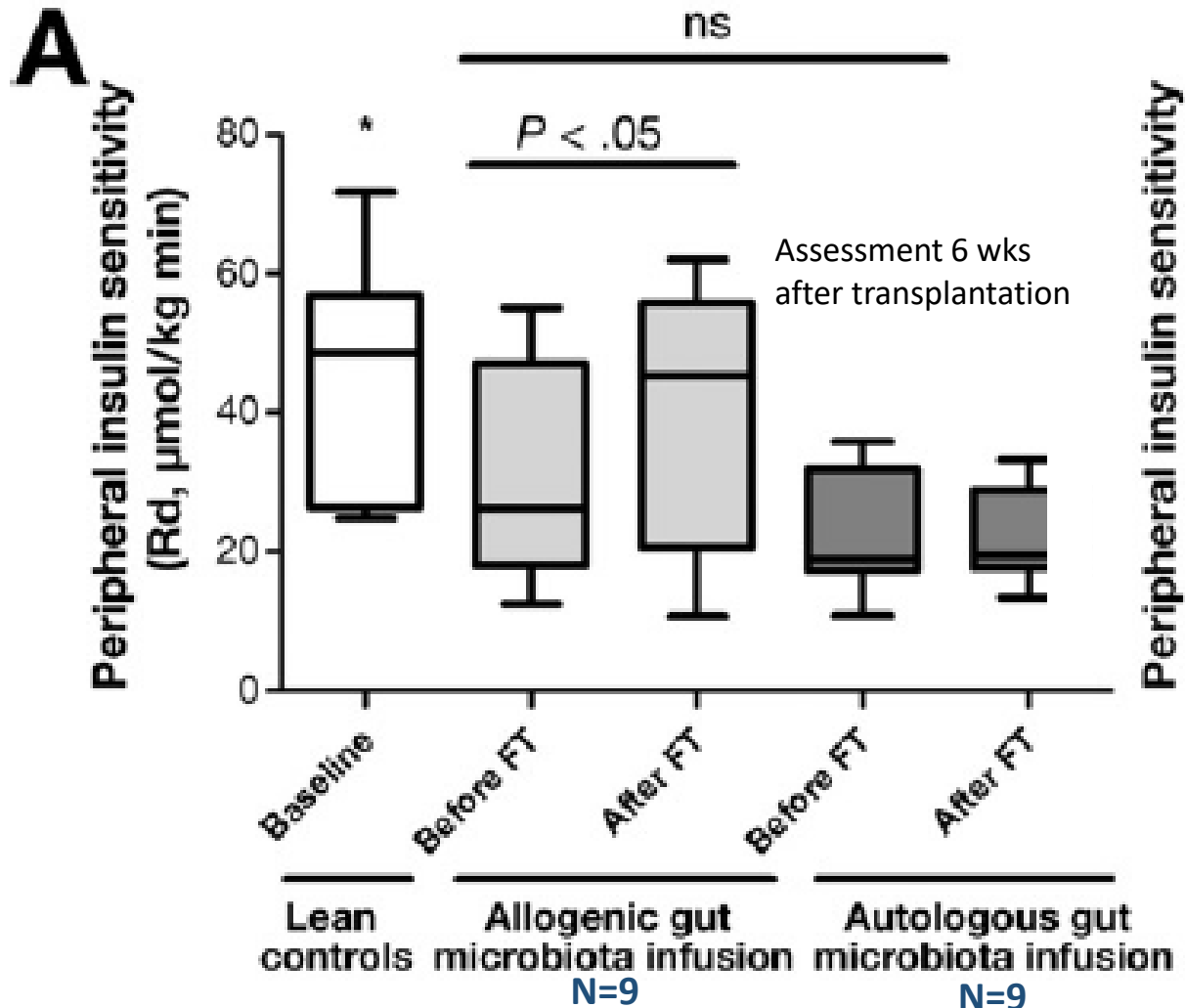
“healthy donors” stool (treated), own stool (placebo)

Colonoscopy administration to caecum

65% treated vs 43% placebo showed improvement at 3 months ($p=0.049$)

7% treated had adverse effects (soiling, nausea, abdo pain)

Gut microbiome transfer in type 2 diabetes



Vreize A et al Gastro 2012; 143: 913-16

FMT causing obesity human to human transfer

BRIEF REPORT

Weight Gain After Fecal Microbiota Transplantation

Neha Alang¹ and Colleen R. Kelly²

Fecal microbiota transplantation (FMT) is a promising treatment for recurrent *Clostridium difficile* infection. We report a case of a woman successfully treated with FMT who developed new-onset obesity after receiving stool from a healthy but overweight donor.

Open Forum Infect Dis 2015 Feb 4;2(1):1-2



“Potential has a shelf life.”
— Margaret Atwood

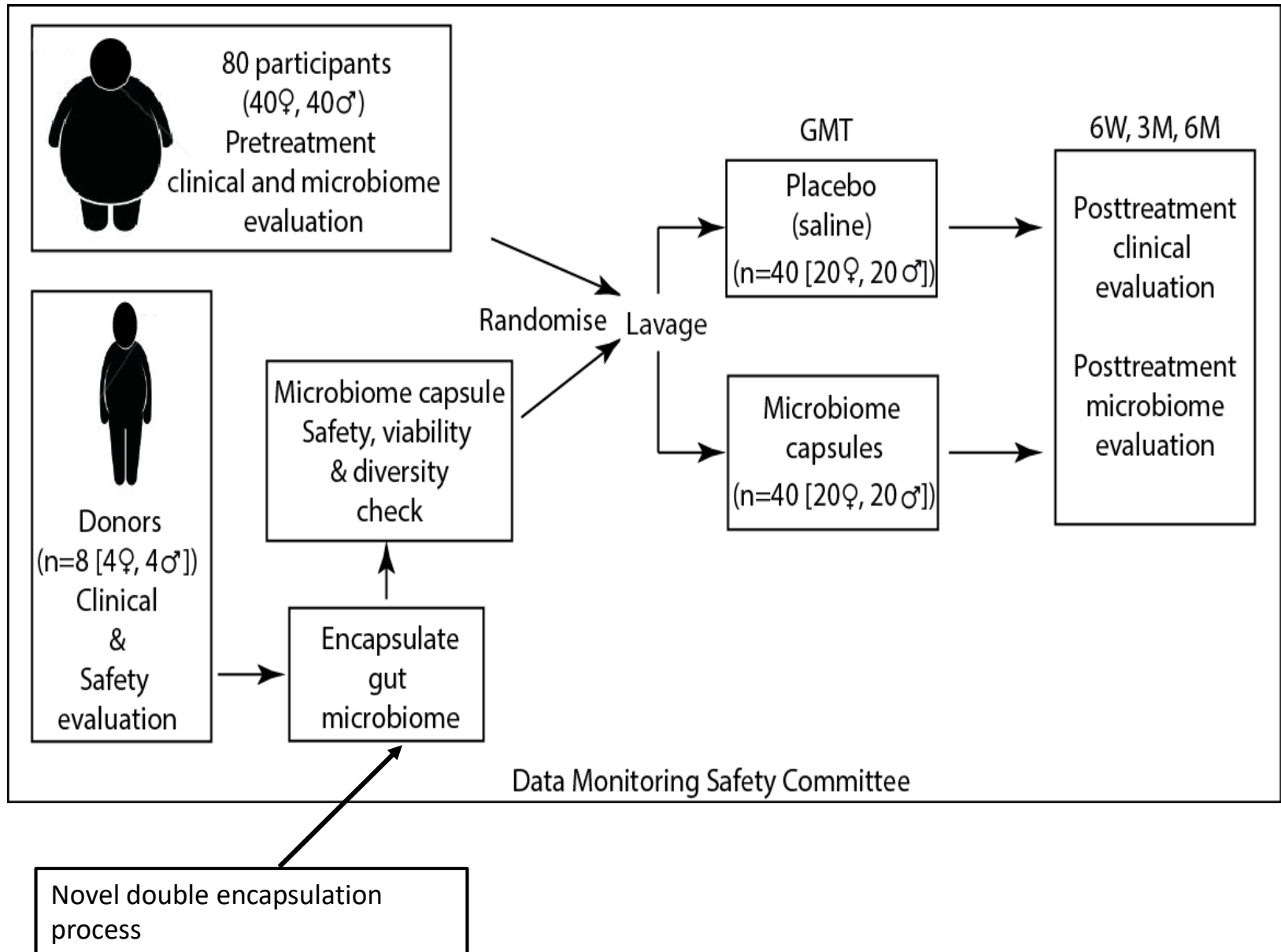


Feature story on TV3 The Project twice, weeknight current affairs

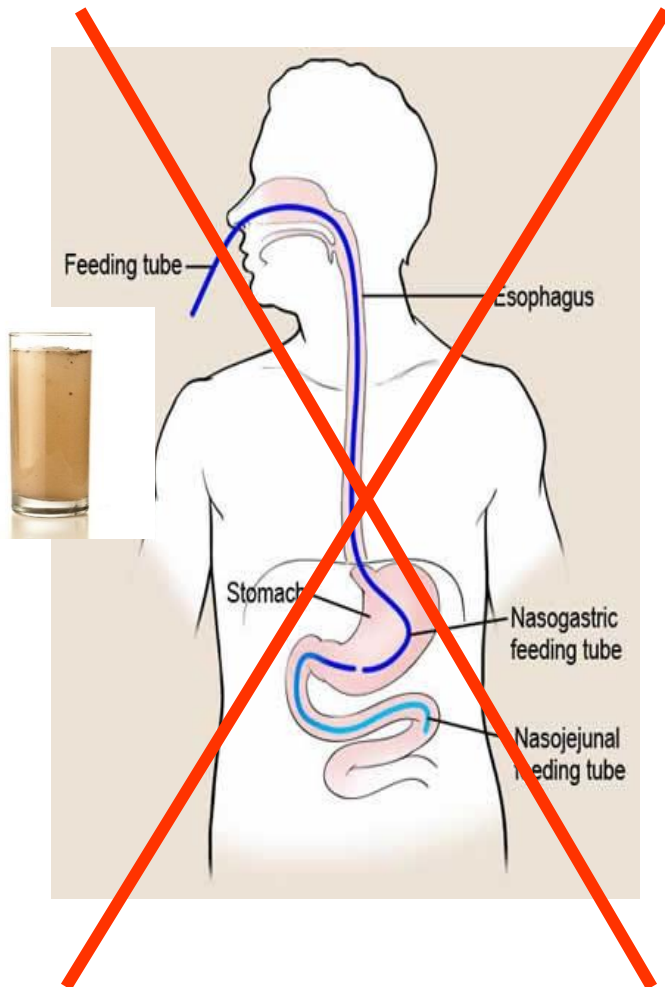
The Gut Bugs Study documentary series



The Gut Bugs trial



Bacteria double encapsulated (smaller capsule inside a bigger capsule)



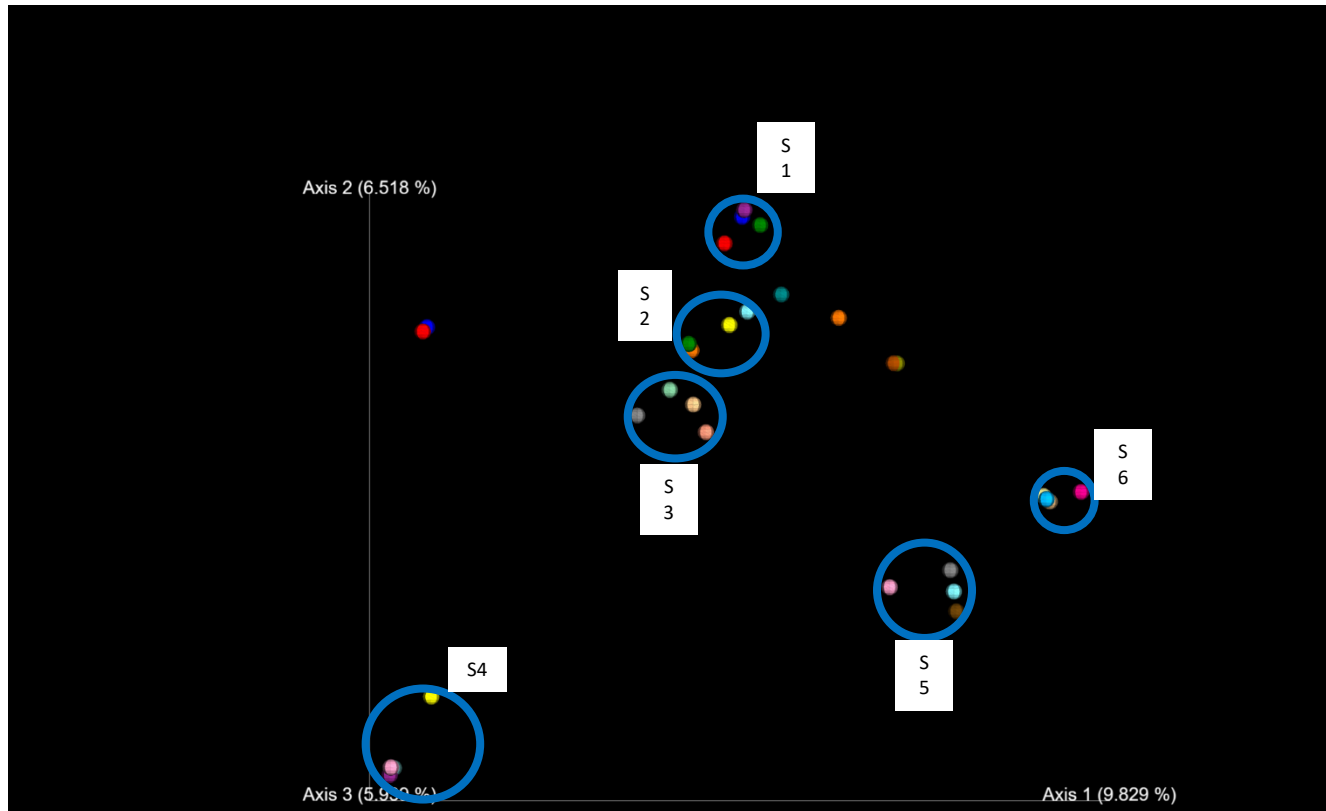
Capsules
release
bacteria
in the bowel
where they
are effective

70% of
bacteria
recovered
following 3
mos at -80°C

What will we measure on recipients?

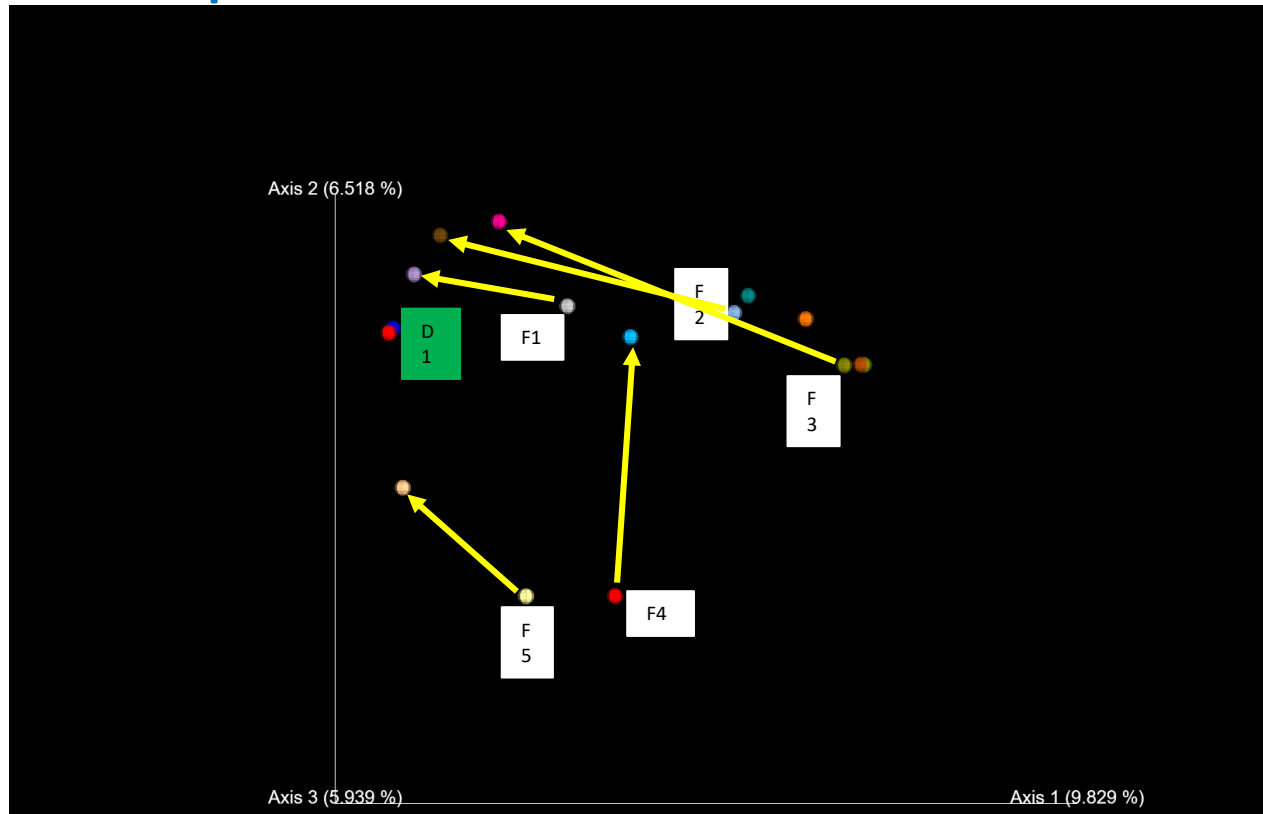
- BMI
- Body fat (DEXA)
- Insulin sensitivity
- 24 hr ambulatory blood pressure
- Inflammation
- Liver function and lipids
- Gut microbiome
- Gut microbiome products in stools and blood
- Well-being and behaviour
- General health (including gut health)

Placebo pilot subjects show no changes in gut microbiome over 6 months



3- dimensional principal component analysis plot

Treated pilot subjects show engraftment and sustained change in gut microbiome towards super donor over 6 months



3- dimensional principal component analysis plot

GMT

Conclusions

Donor microbiome needs to be better characterised

“One stool does not fit all”

Our current treatment paradigm is unsophisticated



“Vaginal seeding” for C section babies

Rise in elective caesarean sections triggers ADHB to review the practice

MANDY TE 14:02, Nov 10 2017



Last year 36 per cent of babies born in Auckland hospital were delivered via caesarean section. This was higher than the national rate of 25.5 per cent.

LUSCS and childhood obesity



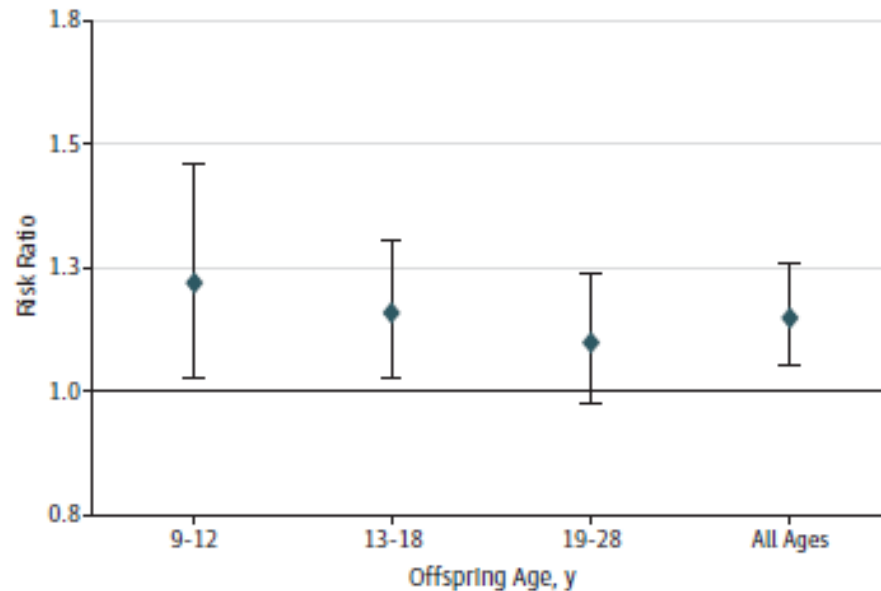
National
SCIENCE
Challenges



LIGGINS
INSTITUTE

LUSCS associated with obesity

Figure. Adjusted Risk Ratios for Cesarean Birth and Obesity in Offspring



GUTS (USA)
22,068 offspring
Prospectively followed from 1984
Model adjusted for:
Maternal age
Ethnicity
Region
Year of birth
Pre-pregnancy BMI
Maternal height
Gestational diabetes
Pre-eclampsia
PIH
Birth wt
Smoking
Previous LUSCS
Offspring sex
Birth order

National
SCIENCE
Challenges



Yuan et al JAMA Pediatr 2016; 170(11): 1=8



LIGGINS
INSTITUTE

Caesarean delivery and offspring allergic disease

- Meta-analyses of 26 studies
- C section associated with offspring:
 - Food allergy (OR 1.3)
 - Allergic rhinitis (OR 1.2)
 - Asthma (OR 1.2)
 - Hospitalisation with asthma (OR 1.2)
 - NOT eczema

42

Apr;38(4)-33.



National
SCIENCE
Challenges

A BETTER
START

1 Year in Review

Bager P Clin Exp Allergy 2008 Apr;38(4):634-

Thavagnanam S Clin Exp Allergy 2008

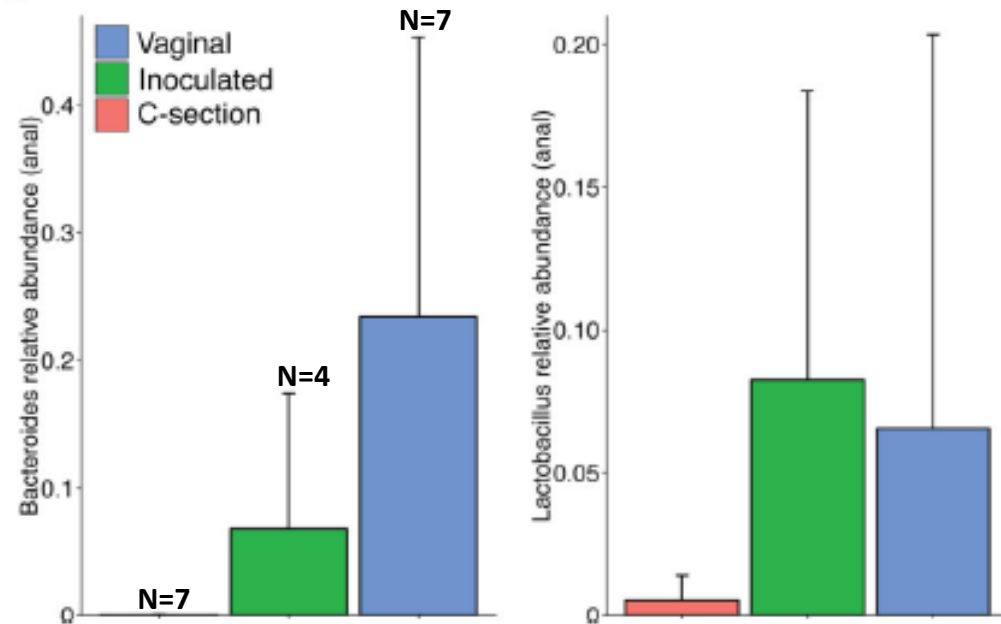


LIGGINS
INSTITUTE

C-section: partial restoration of gut microbiota

Maternal vaginal swab to baby mouth, face, skin

30 days follow-up



Dominguez MG Nat Med 2016; 22: 250-3

ECOBABe (Early Colonisation with Bacteria After Birth) Study

40 pregnant mothers with twins

Elective LUSCS

Vaginal swab inserted 30 mins prior to C section

Half the swab mixed with 5 ml sterile water in syringe for treatment

Half the swab mixed with 5 ml sterile water in syringe for sequencing

One twin treated with maternal vaginal secretions

One twin untreated

16s amplicon sequencing of mat secretions, infant stools at <48 hrs, 1 mos, 3 mos)

Later follow-up infant anthropometry and allergic diseases

ECOBABe Study (Treating CS offspring)

Second control group

40 singleton infants born by vaginal delivery

Untreated

16s amplicon sequencing of infant stools at <48 hrs, 1 mos, 3 mos

Vaginal seeding for C section babies

Still experimental

Clear benefits not yet been shown

Dangerous if not performed appropriately

Has great potential to get C section babies off to the best start



Thanks!

