

**Clinical relevance:  
gutmicrobiota in  
cardiometabolic disease**

Prof. dr. Max Nieuwdorp, internist,  
Amsterdam UMC

**1st Dutch Diabetes Academy –  
December 1st, 2020 1715-1745h**

# Disclosure belangen spreker: NAAM

**Dutch Diabetes Academy – 1 december 2020**

(potentiële) Belangenverstrengeling

Voor bijeenkomst mogelijk relevante relaties met bedrijven

geen

- Sponsoring of onderzoeksgeld
- Honorarium of andere (financiële) vergoeding
- Aandeelhouder
- Andere relatie, namelijk:

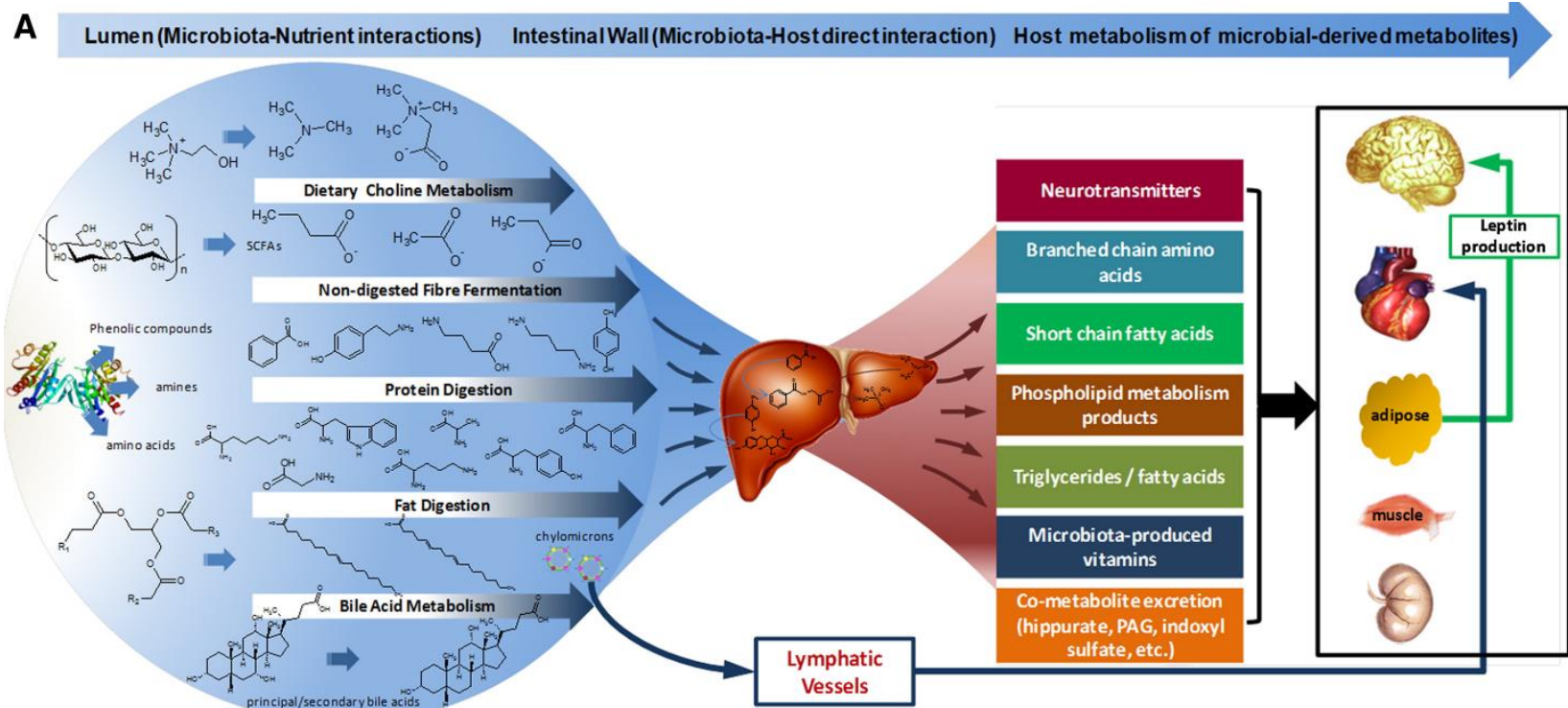
Geen

SAB Caelus health/Kaleido Biosciences

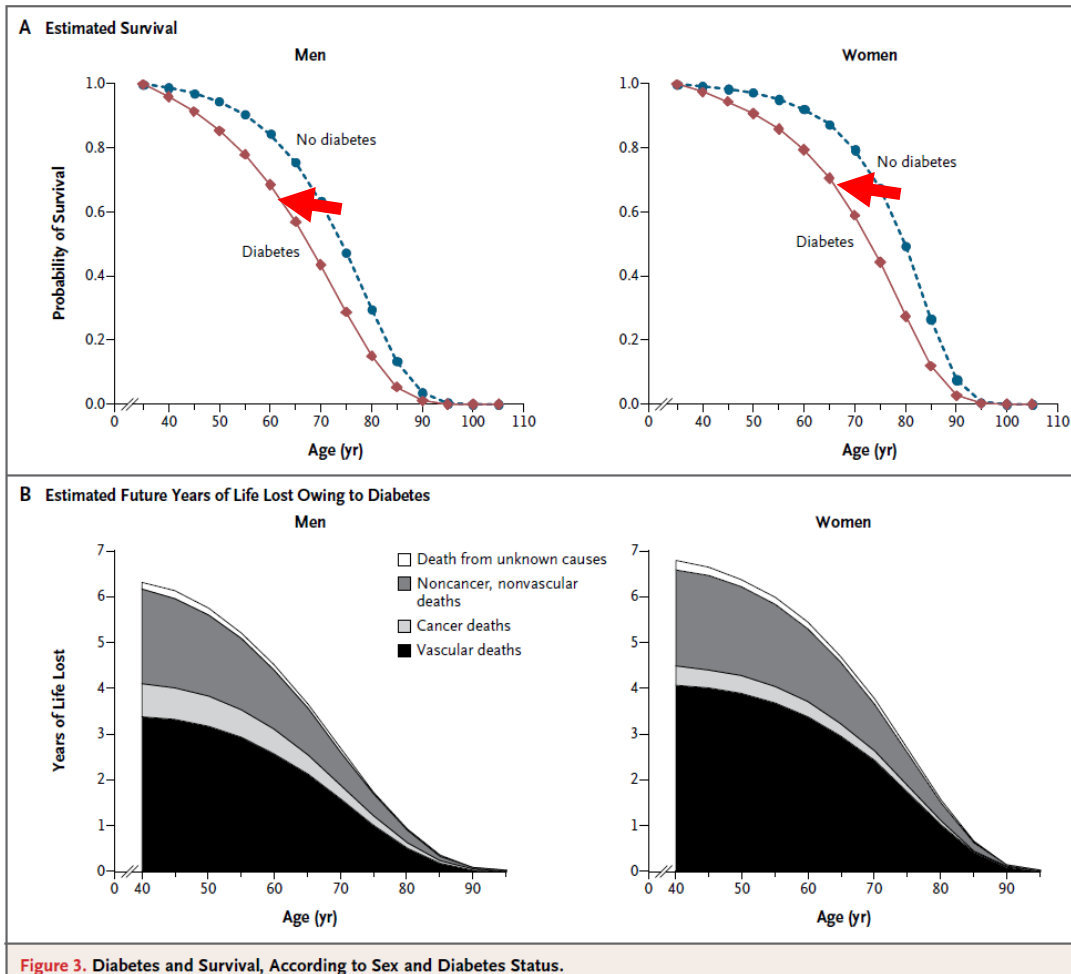
# Conclusions

- 1. (small) intestinal microbiota are associated with DM; is this causal factor or disease modifier (confounders)?
- 2. Ethnicity seems to be an important factor for gut microbiota composition
- 3. Using FMT in DM; from group to individual (responders-non responders)
- 4. other components of DM (NAFLD and altered gut-brain axis) also partly regulated by gut microbiota in humans
- 5. maybe treatment with (combination of) missing intestinal bacterial strains beneficial effects on DM1 and DM2 in certain subgroups?

# 1. Confounders in microbiota research



# Diabetes patients biologically 10 years older



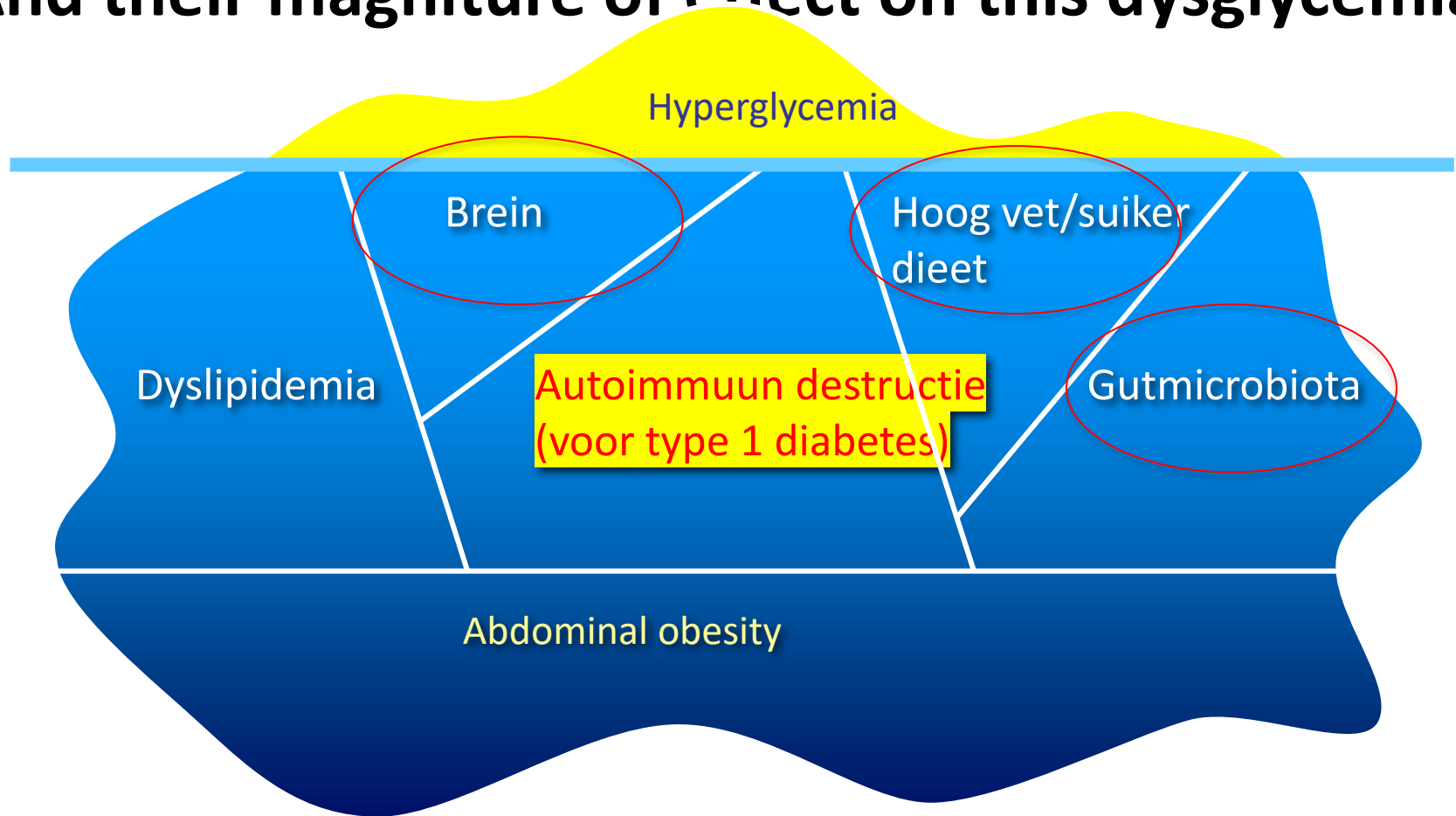
How?

We can only treat symptoms, not cure disease?



Why?

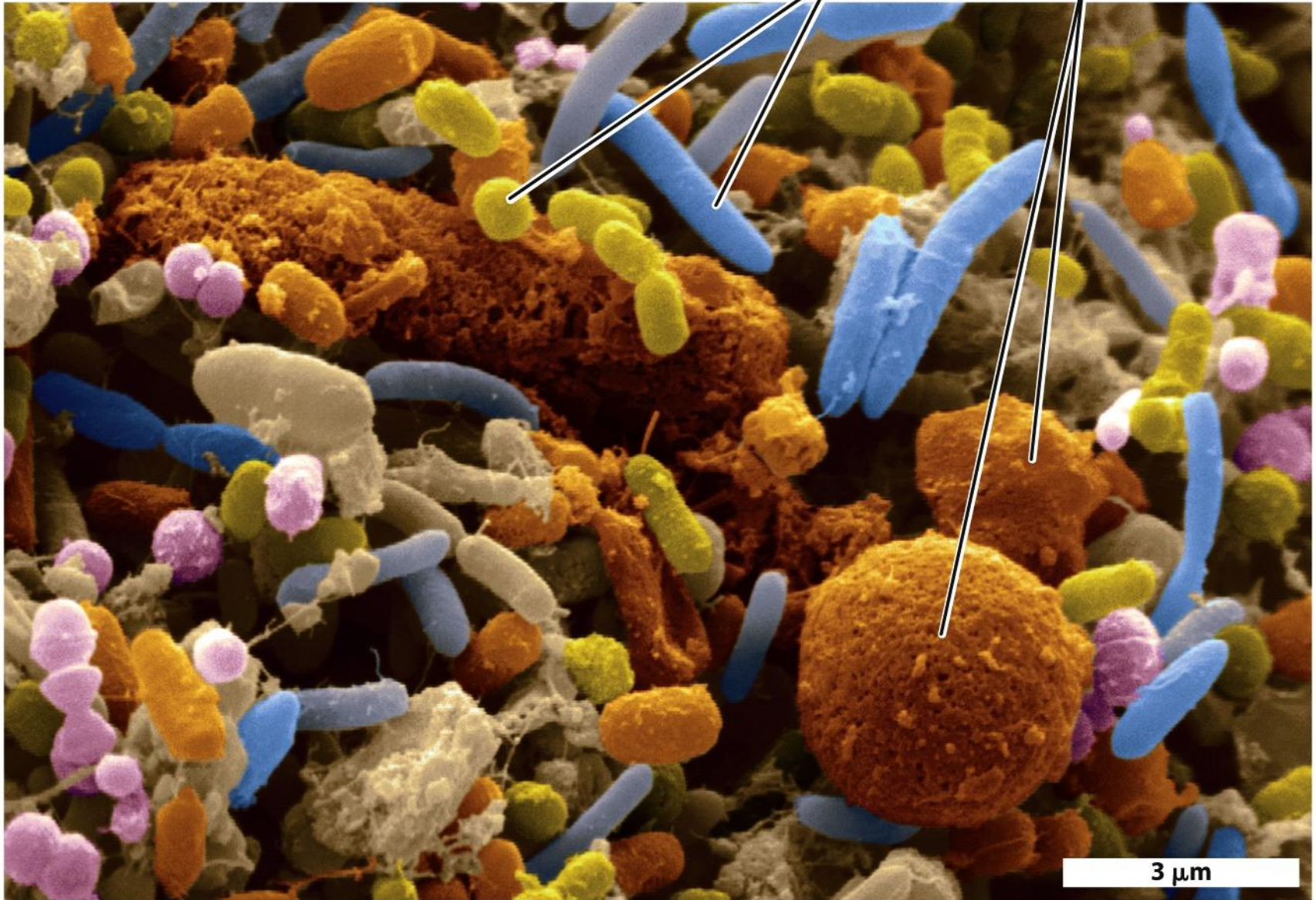
**Diabetes mellitus is diagnosed by hyperglycemia,  
Yet we don't understand the contributing factors  
And their magnitude of effect on this dysglycemia**



*Hyperglycemie is slechts het topje van de DM ijsberg,  
Als diagnosticum te laat om veel schade te voorkomen*

Human feces showing food particles and resident bacteria

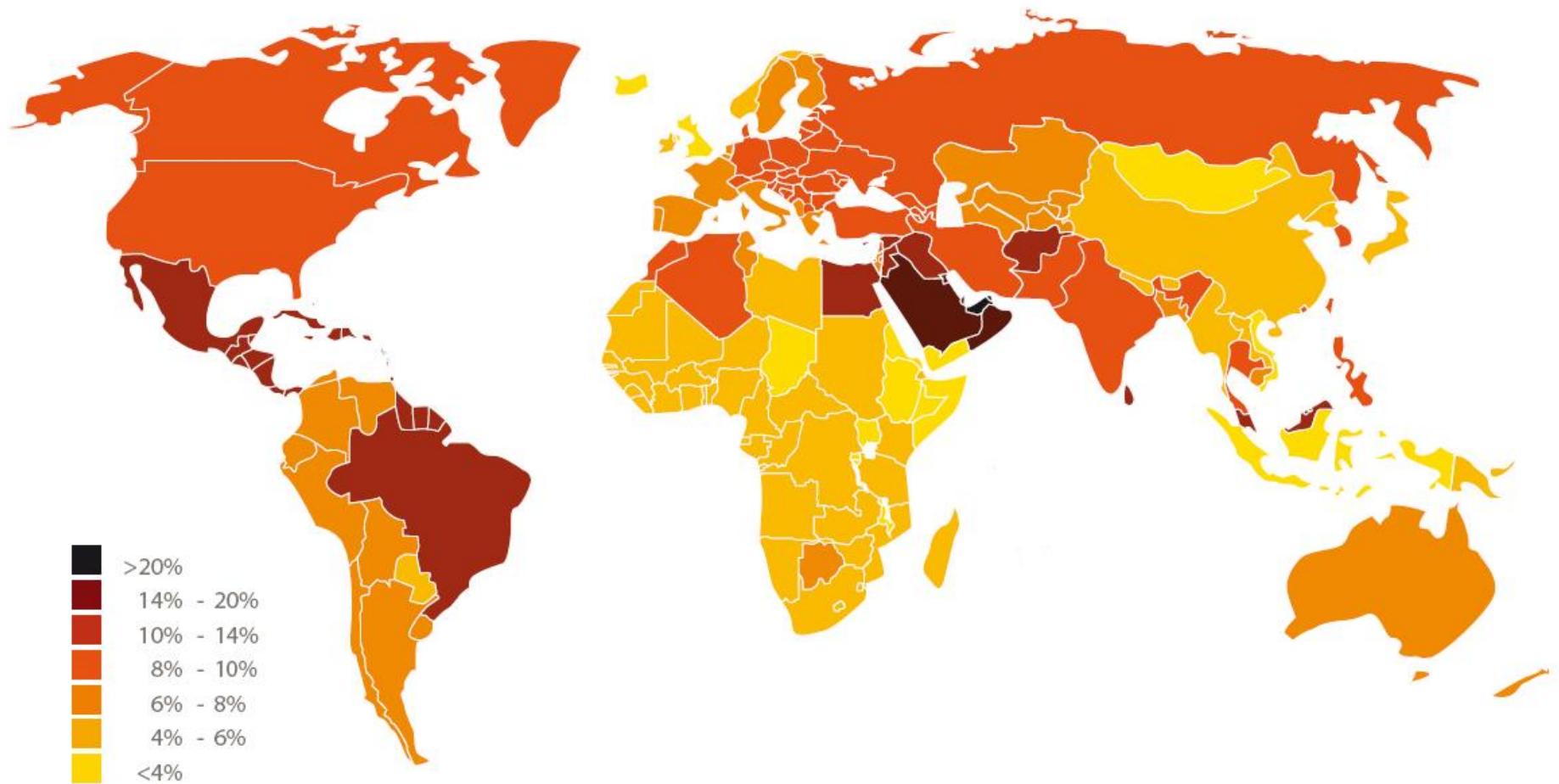
Microbes      Food particles



*Microbiology: An Evolving Science*, Third Edition Figure 23.7  
Copyright © 2014 W. W. Norton & Company, Inc.

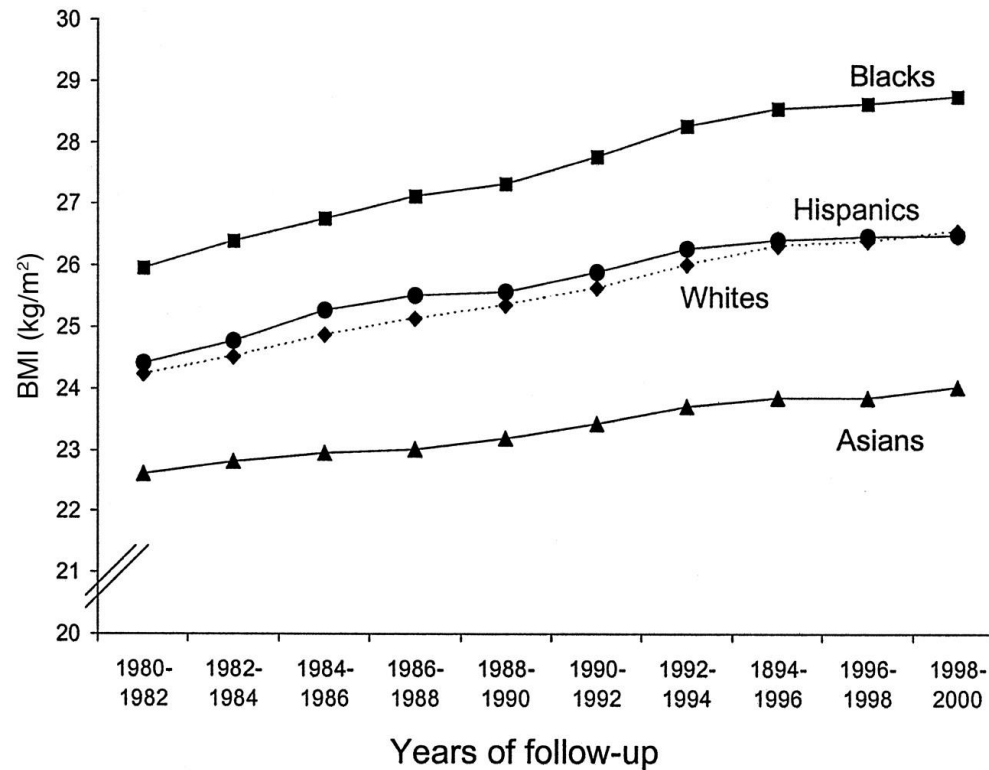


# Estimated Type 2 Diabetes prevalence in 2025



In 2050 15-20% adults worldwide will develop DM2 during their life

# Subjects from different ethnic background have differential BMI increase trajectories

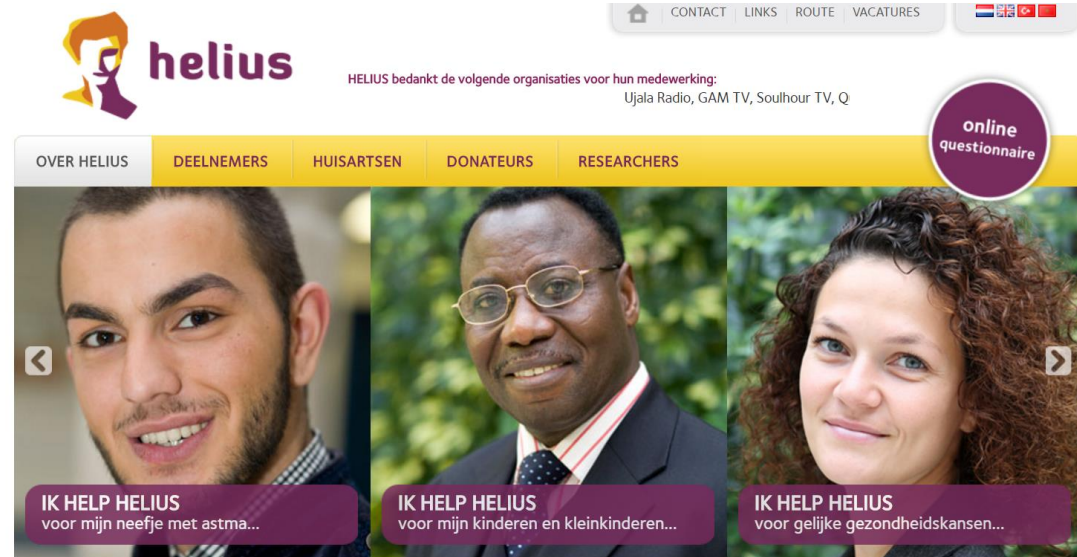


# Multiethnic HELIUS cohort (Healthy Life in an Urban Setting) in Amsterdam, the Netherlands

- **22,165 participants** (18-70 years) included between 2011 and 2016
  - ✓ **6 ethnic groups** in similar proportions: Dutch, Surinamese (African and South-Asian descent), Turkish, Moroccan and Ghanaian
  - ✓ Preferably 3 generations from one family (grandparents-children-grandchildren) included
  - ✓ Otherwise healthy (at baseline visit 30-50% obese with signs of metabolic syndrome)

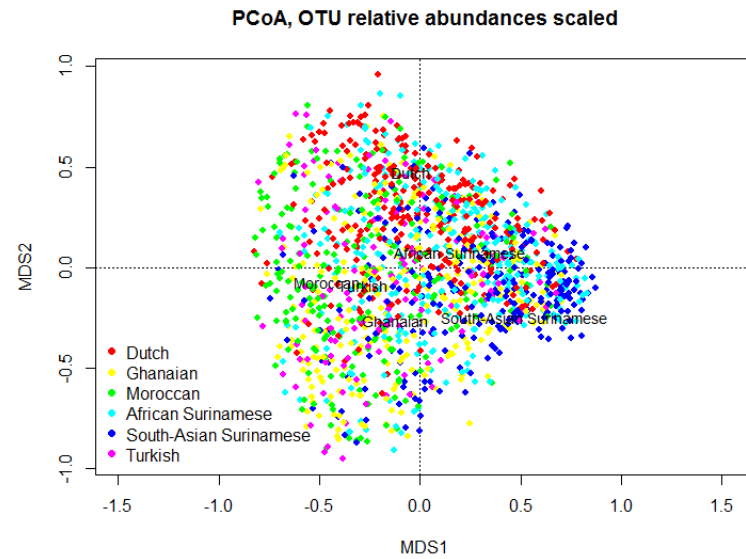
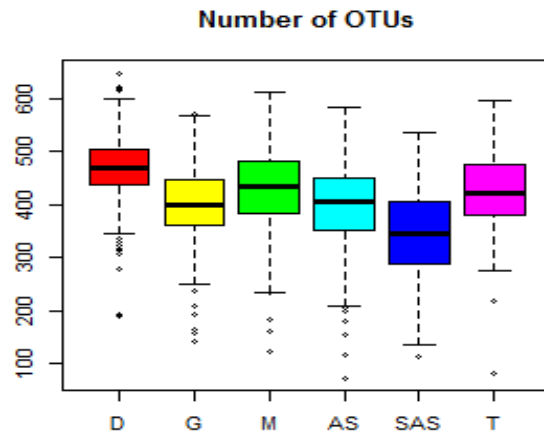
- Data collected:

- ✓ **Questionnaire:** sociodemographics, ethnicity, lifestyle, dietary habits, health, physical activity
- ✓ **Physical examination:** anthropometric measurements, clinical measurements, blood draw, medications, DNA, urine samples, vaginal and oral swabs for microbiome analyses
- ✓ **Morning feces samples** > 6000 subjects
- ✓ Detailed Food Frequency Questionnaires



**Currently sequenced (16S) 6048 fecal samples**  
(Dekker, BMC Public Health 2011; Stronks, BMC Public Health. 2013)

# Gutmicrobiota different between Caucasian dutch and Surinamese Dutch



# Loss of gutmicrobiota diversity due to antibiotics/medication and Western diet use

**SORE THROAT?**



**Antibiotic Candettes give immediate soothing relief!**

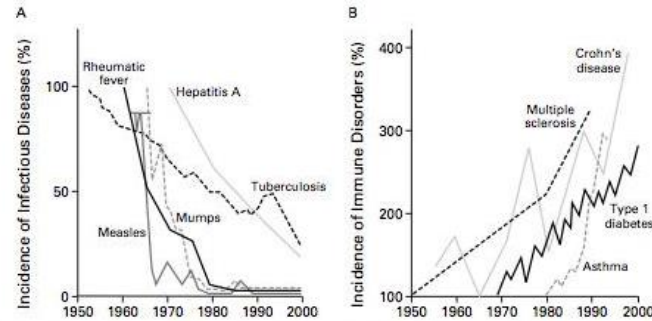
**CANDETTES work 2 ways:**

- 1 Double Antibiotic action...** fights germs! Not just one—but two safe, proven antibiotics kill many irritation-causing throat germs, on contact!
- 2 Anesthetic action...** relieves soreness! A safe and effective anesthetic acts instantly to relieve soreness of inflamed membranes.

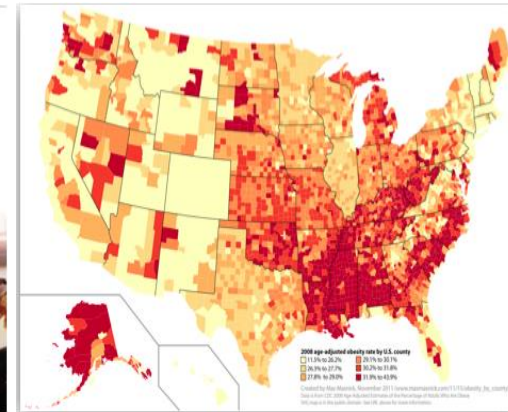
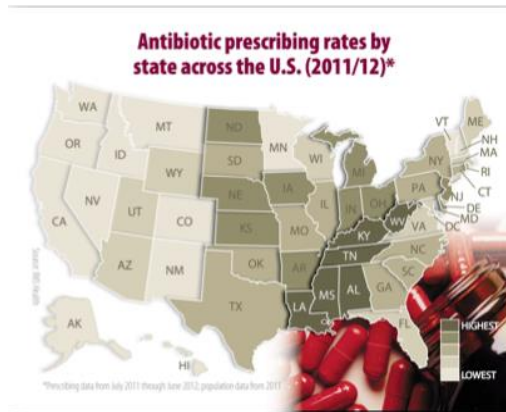
Not an ordinary cough drop—delicious, orange-flavored Candettes are a proven medication! Get them at your drug store.



**Candettes**  
By the World's Largest Producer of Antibiotics

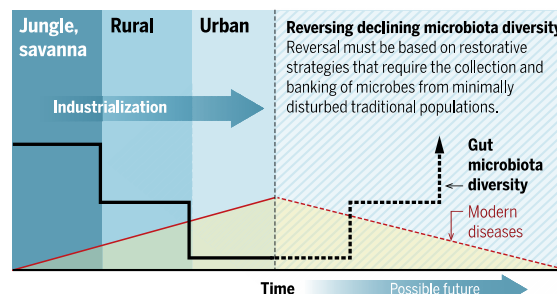
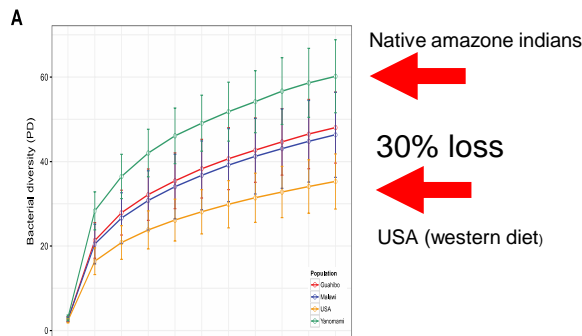


Bach NEJM 2002



# Urgent problem: loss of microbiota diversity due to lifestyle and medication

- **30% loss of fecal gutmicrobioa diversity in subjects from USA** (Westerndiet) vs Amazone inhabitants (traditional diet)
- Children probably inherit 50% of their gutmicrobiota composition from their children
- What is lost, doesn't get back automatically (but lost forever?)
- bacterial vault to protect and keep bacterial strains for later generations



Time Bomb

## Scientists Urge Doomsday Vault for 'Good' Germs

Antibiotics, filtered water and processed food are making us more vulnerable to disease.

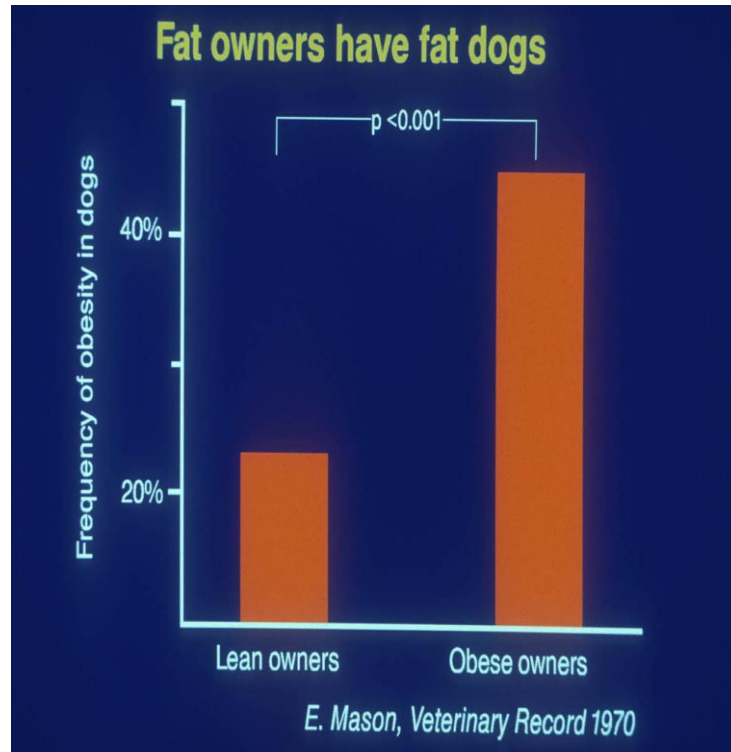
By Riley Griffin

4 oktober 2018 20:00 CEST Corrected 4 oktober 2018 22:51 CEST

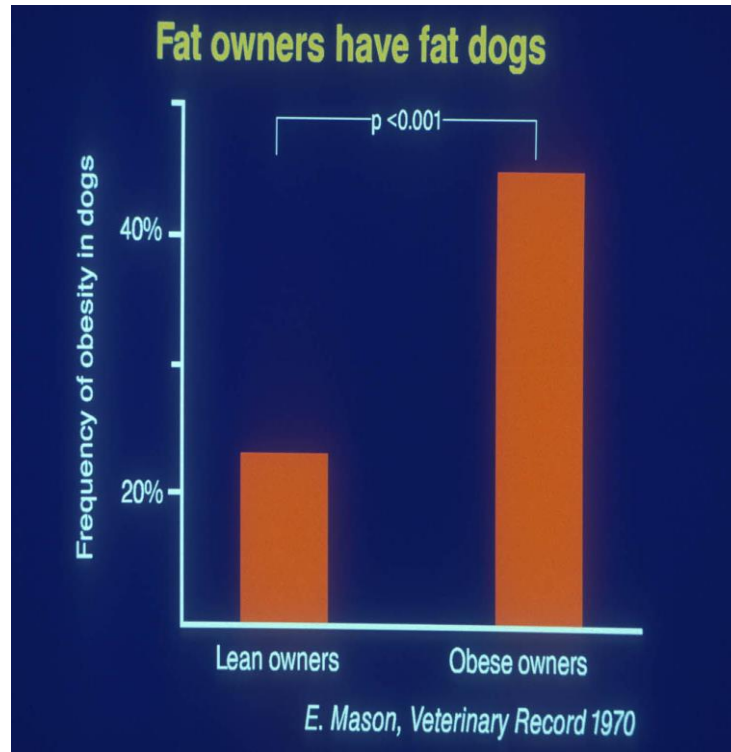


Entrance to the seed vault in Norway. Photographer: JUNGE, HEIKO/AFP

However the question is, are gutmicrobiota causally involved in obesity and DM?



## However the question is, are gutmicrobiota causally involved in obesity and DM?



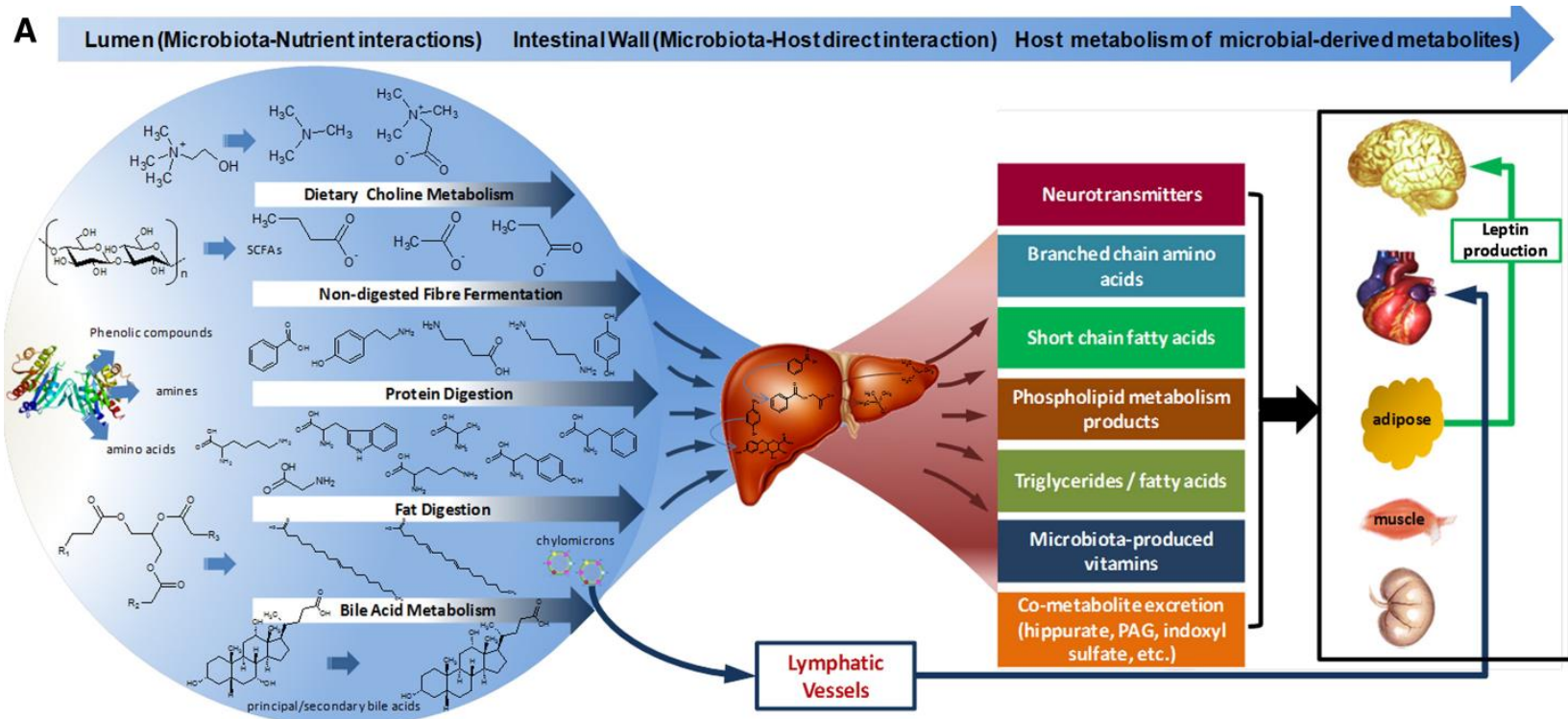
- Dogs have 50% identical gutmicrobiota as their owners
- In Feces, skin and mouth



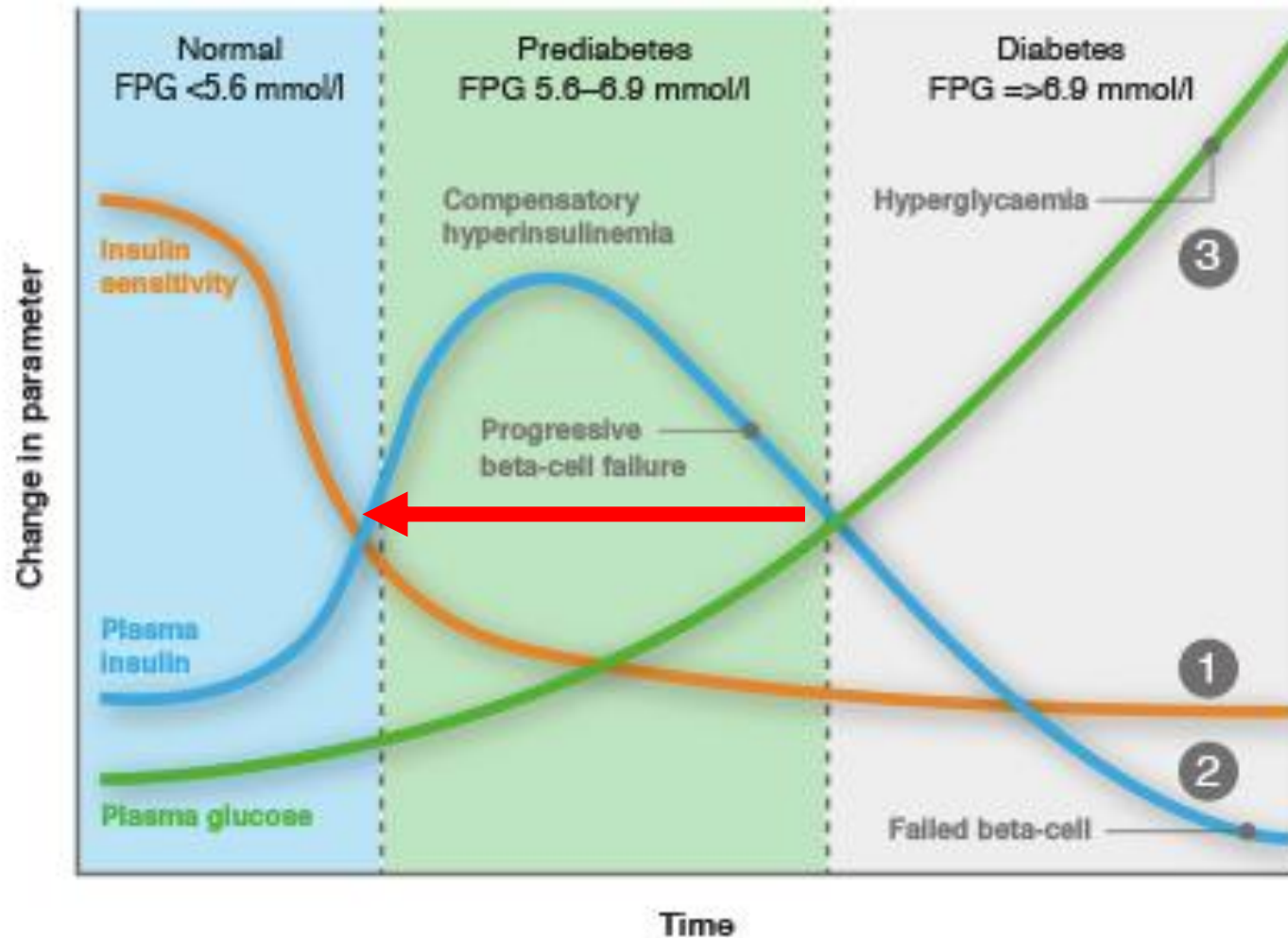
Song SJ, *Elife*. 2013 Apr 16;2:e00458.



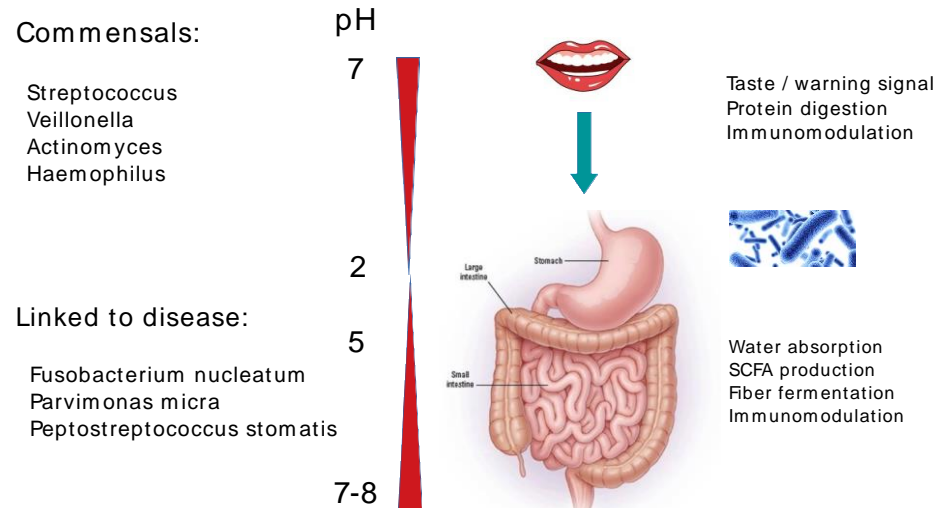
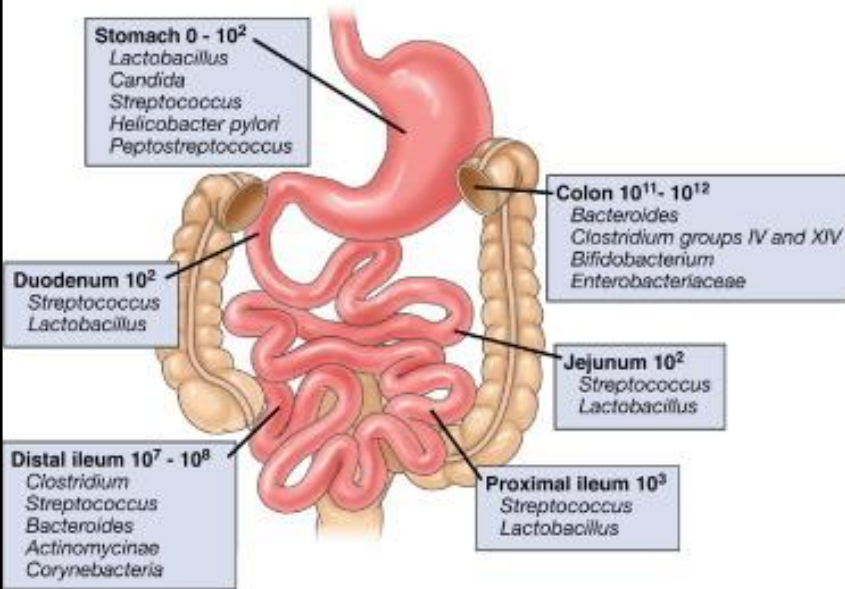
# 2. Causality of intestinal microbiota composition in human (glucose) metabolism and DM2?



# Hard to capture in which phase of insulin resistance an obese person is with fasting glucose/insulin...



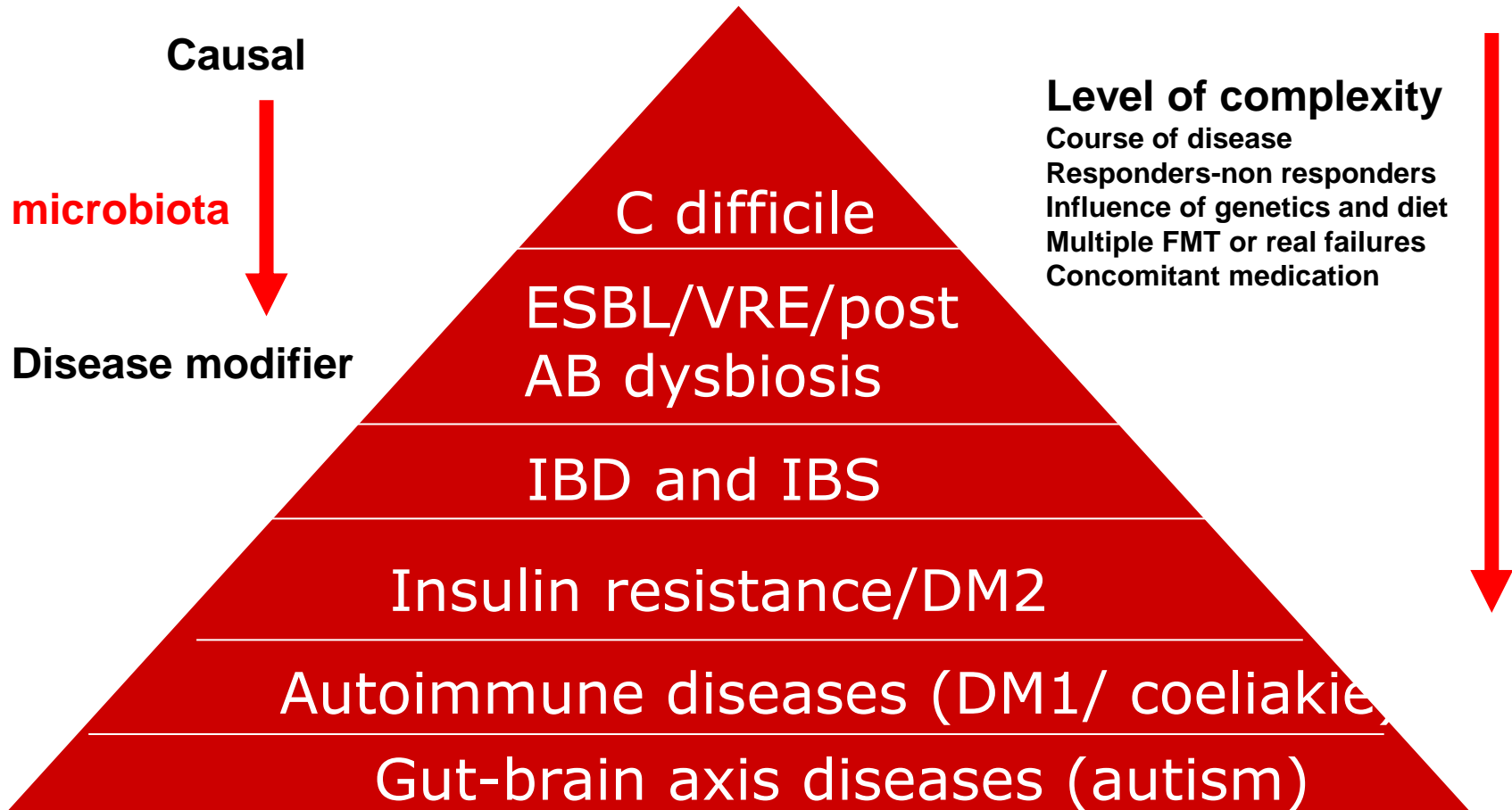
# Different microbiota composition and diversity across intestinal tract?



Mouth is an endogenous reservoir for intestinal strains

Oral-fecal transmission (and vice versa!) important  
 For guthomeostasis

# Relation microbiota and disease most likely not always causal



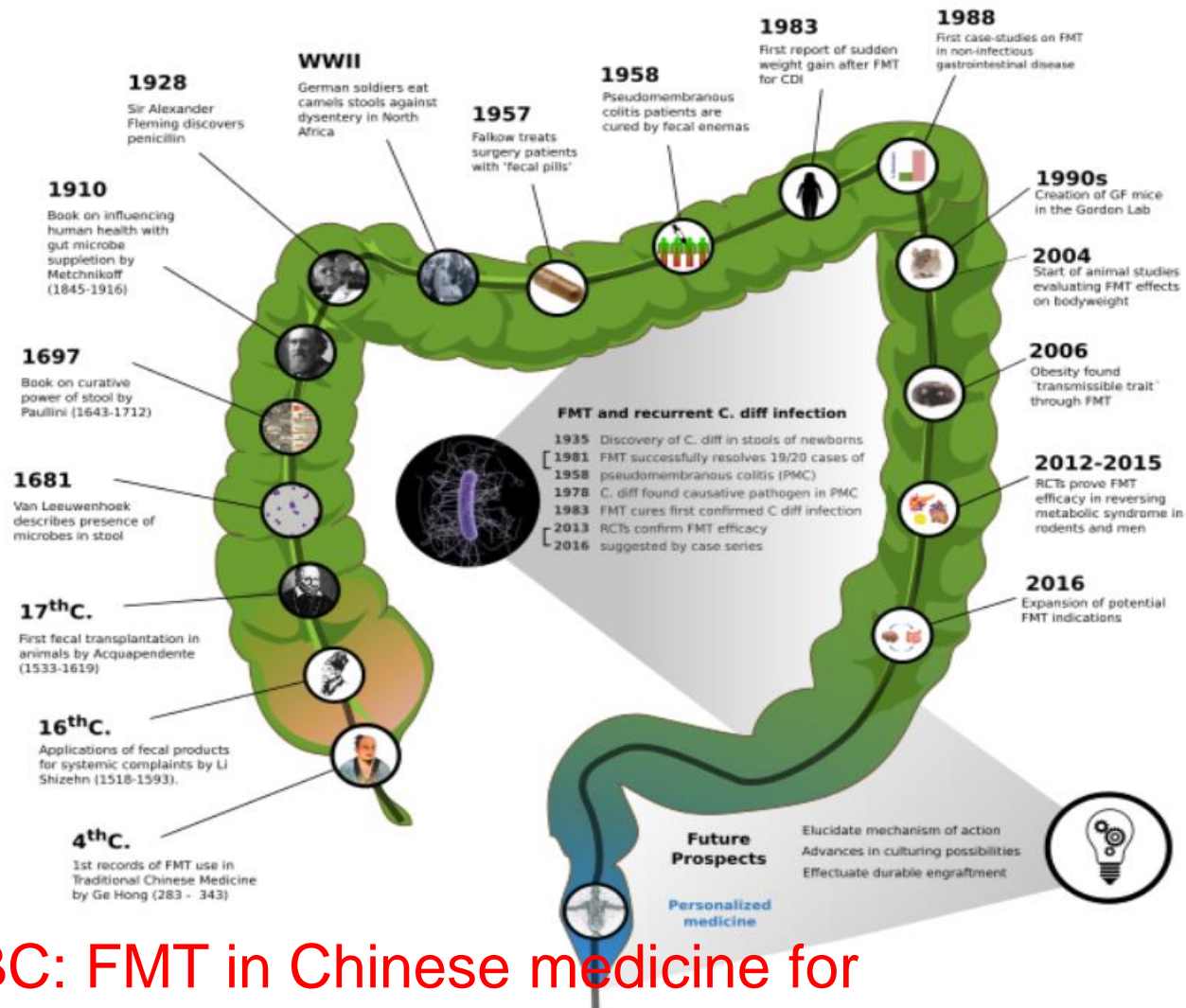
# Koch's postulates for causality of bacteria in human metabolic disease



- The microorganism must be identified/isolated from a diseased organ(ism). ✓
- The microorganism should be associated with disease (association/intervention) in people. ✓
- The introduced microorganism should reproduce fenotype (inoculation). ✗

# 1958: Eiseman, antibiotics-induced chronic diarrhea

## Timeline of Fecal Microbiota Transplantation



4<sup>th</sup> Century BC: FMT in Chinese medicine for food poisoning and diarrhea

Eric S. Rosenberg, M.D., Editor  
 Jo-Anne O. Shepard, M.D., Associate Editor  
 Sally H. Ebeling, Assistant Editor

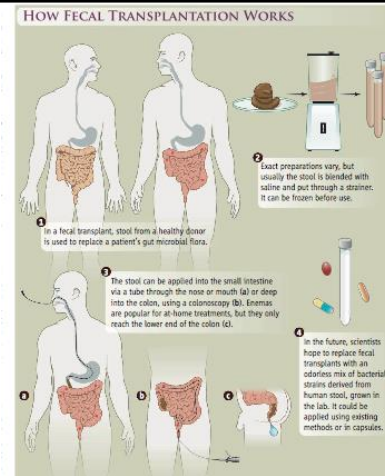
Founded by Richard C. Cabot

Nancy Lee Harris, M.D., Editor  
 Alice M. Cort, M.D., Associate Editor  
 Emily K. McDonald, Assistant Editor



## Case 25-2014: A 37-Year-Old Man with Ulcerative Colitis and Bloody Diarrhea

Elizabeth L. Hohmann, M.D., Ashwin N. Ananthakrishnan, M.D., M.P.H., and Vikram Deshpande, M.D.



DIY Fecal Transplants to cure yourself of digestive disease

**GLENN TAYLOR OF TAYMOUNT CLINIC**

Through Clinic, Scientists at Fecal Microbiota

The Taylor

Less Doing, More Living

LessDoing.Com

### ded Treatment Plan

before treatment programs can be arranged.

**FMT Fees for 10+2 Programme**  
 £4500

10 implant treatments over 2 weeks and 2 additional implants to take away with you and use at home.

Included in the price of the program above is a pre-treatment QOL questionnaire call and follow-up call(s) 3 months after FMT program is completed.

Dependent upon the presenting condition (as directed by our CMO), you may be asked to take



Urge to educate (with proper studies) public about therapeutic or non therapeutic effects of FMT

# Currently 295 trials with FMT ongoing

NIH U.S. National Library of Medicine

[ClinicalTrials.gov](https://clinicaltrials.gov)

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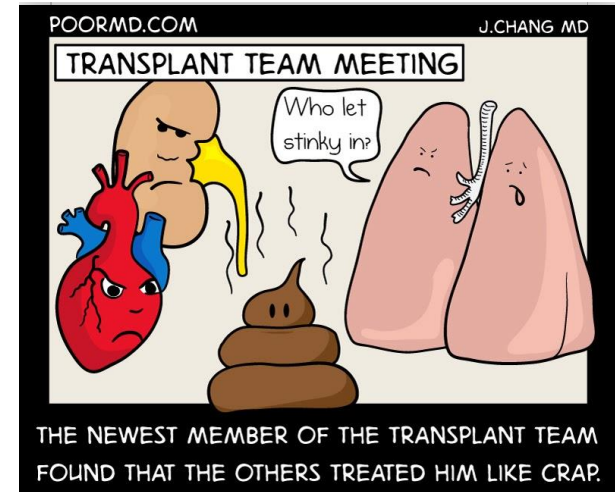


295 Studies found for: **fmt**

Also searched for **Fecal Microbiota Transplantation**, **Fecal transplant**, and **Fecal Transplantation**.

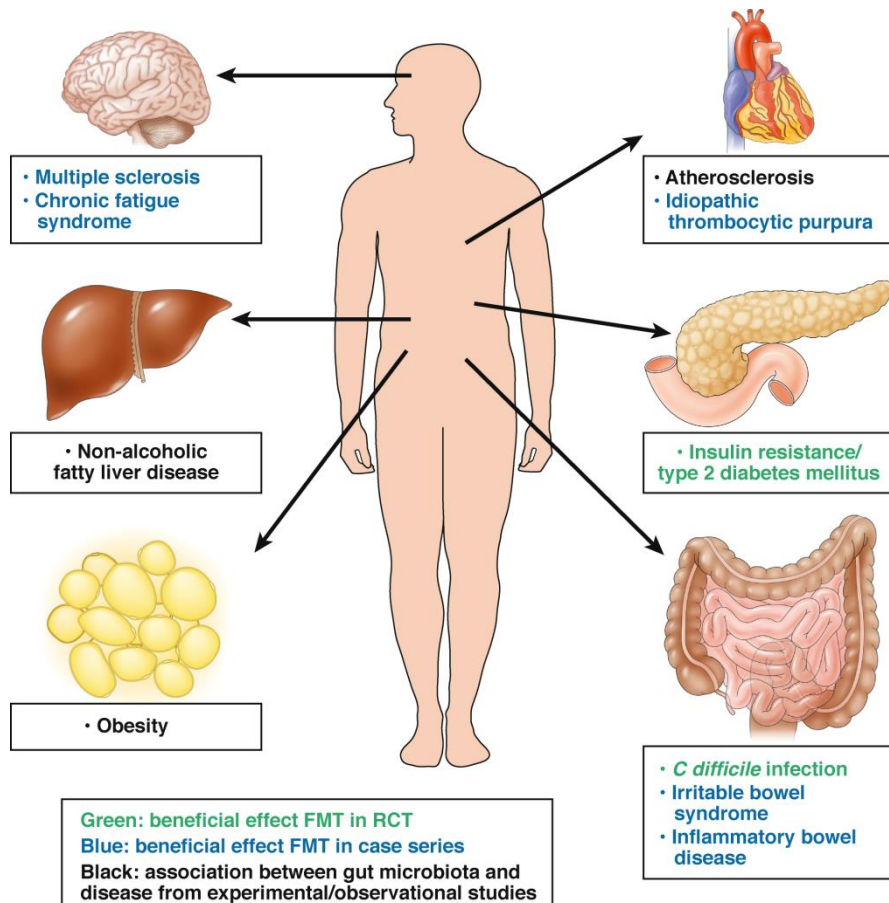
[See Search Details](#)

About 10 on FMT in obesity  
About 3 on FMT in NFLD/NASH





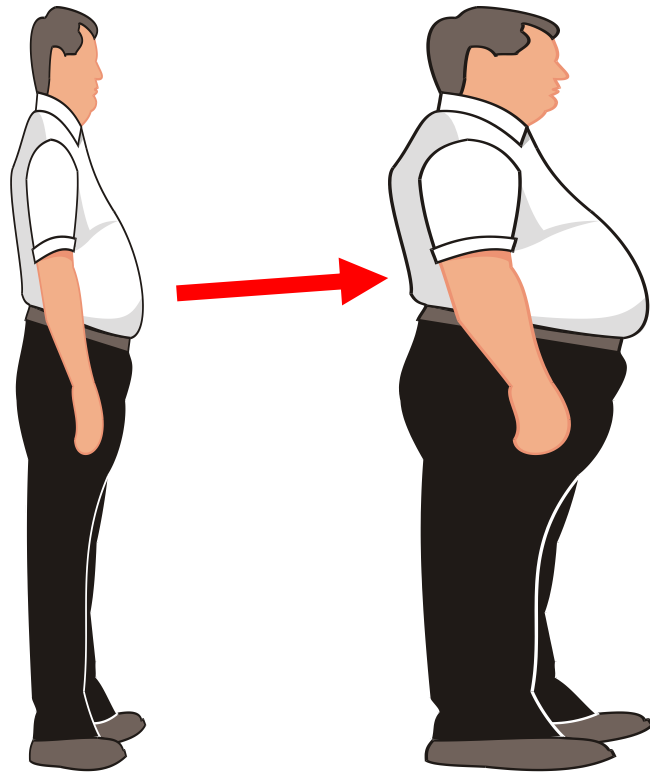
# Altering cardiometabolic phenotype in humans using fecal microbial transplant (FMT)



- at AMC >500 FMT's since 2006, predominantly in RCT due to large placebo effect
- Long term side effects not observed
- Large placebo effect
- At AMC ongoing/finished RCT's with single/multiple FMT using hard clinical endpoints for:
  - *C difficile* diarrhoea (van Nood, NEJM 2013)
  - ESBL(bacteria) (deGroot, BMC 2018)
  - inflammatory bowel disease (Rossen, Gastro 2015)
  - atherosclerosis (Smits, JAHA 2018)
  - metabolic syndrome (Vrieze, Gastro 2012/Kootte Cell metab 2017)
  - NAFLD/NASH (with liverbiopsies)
  - gutbrain axis (spect-MRI brain scans)
  - graft versus host after bonemarrow transplant
  - cancer cachexia
  - Type 1 diabetes

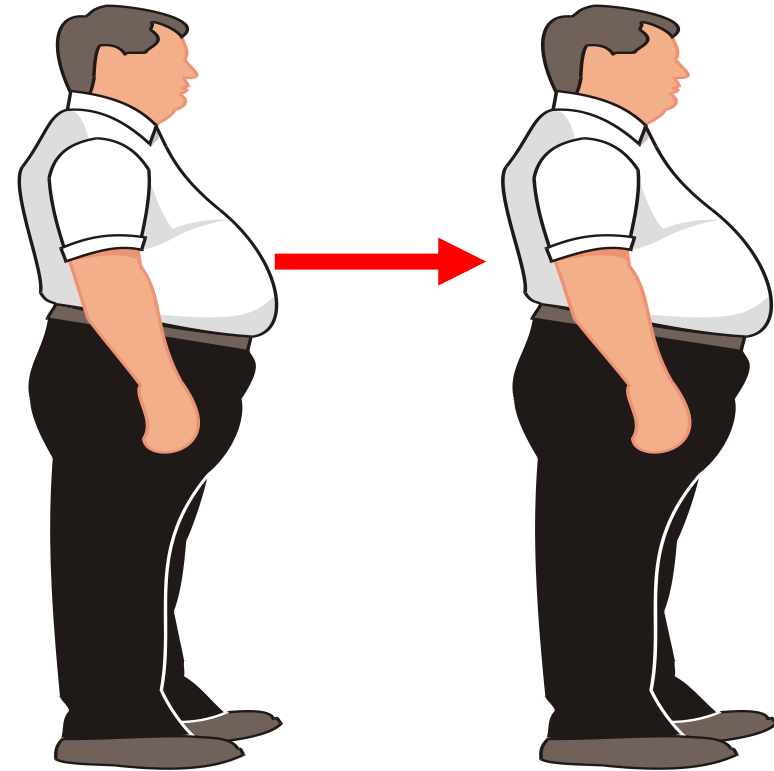
# Randomized controlled trial to study effect of allogenic lean donor versus own (autologous) FMT on insulin sensitivity

Lean to metsyn (Allogenic)



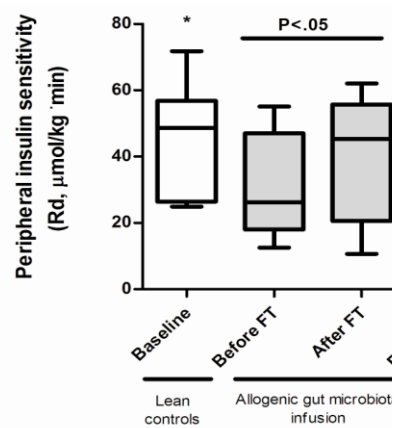
Versus

Own feces (Autologous)

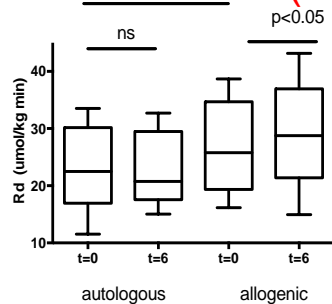


# Efficacy of FMT varies with studies, but similar effect of oral diabetes medication on insulin sensitivity

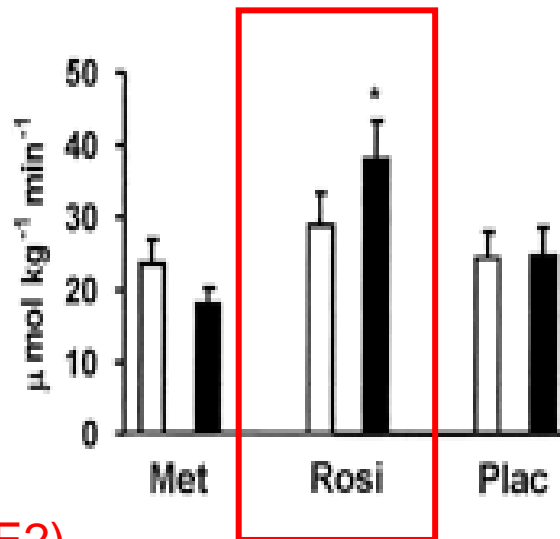
**Lean donor FMT:**  
insulin sensitivity (Rd)  
increase 23% (FATLOSE1)



**insulin sensitivity (Rd)**  
increase 15% (FATLOSE2)

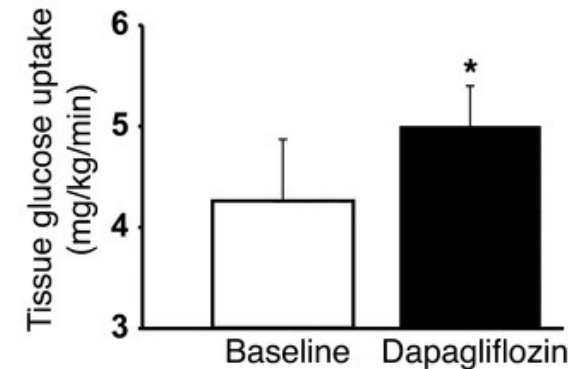


**PPARgamma agonist:**  
insulin sensitivity (Rd)  
increase 18%



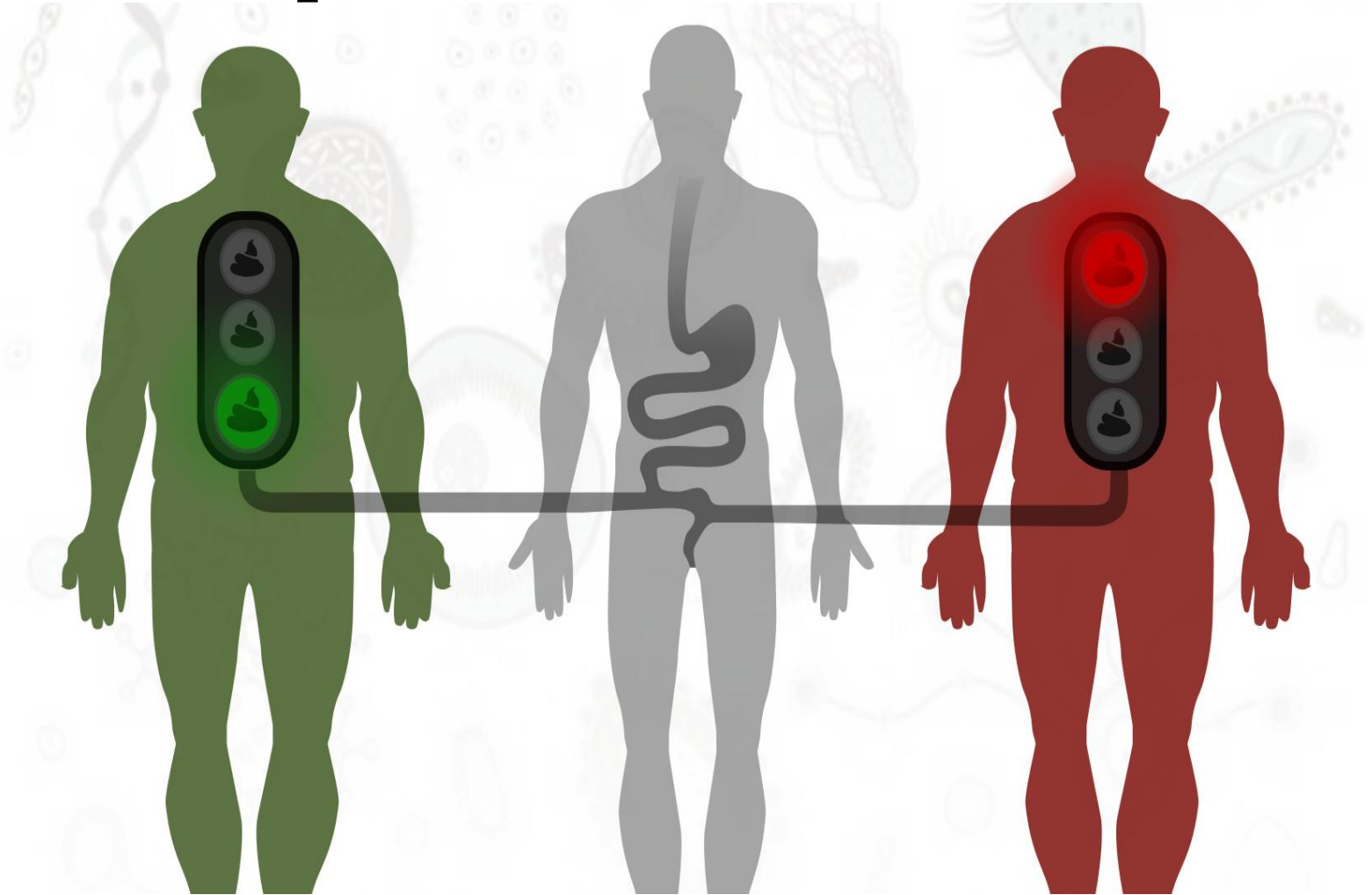
Karlsson, Diabetes. 2005;54(5):1459-67

**SGLT2 inhibition:**  
insulin sensitivity (Rd)  
increase 22%



Merovci A, J Clin Invest. 2014;124(2)

# Responders and non responders due to donor or recipient FMT characteristics?



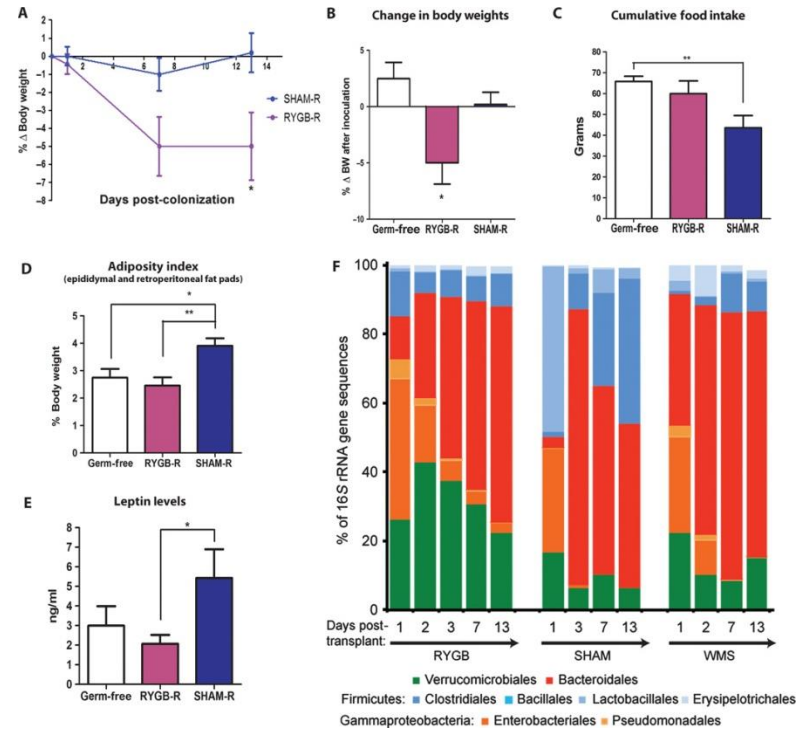
Kootte/Nieuwdorp, Cell Metabolism

# How about using donor feces from (previous) metabolically compromised subjects?

Roux-en-Y Gastric Bypass



40kg weightloss in 3 years

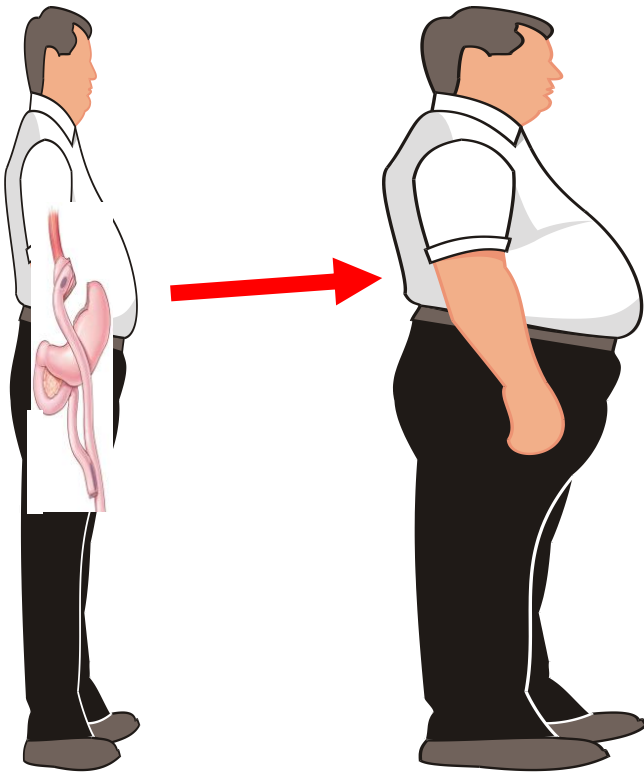


Liou, *Sci Transl Med.* 2013 Mar 27;5(178):17

Microbiota composition after bariatric surgery cause or consequence?

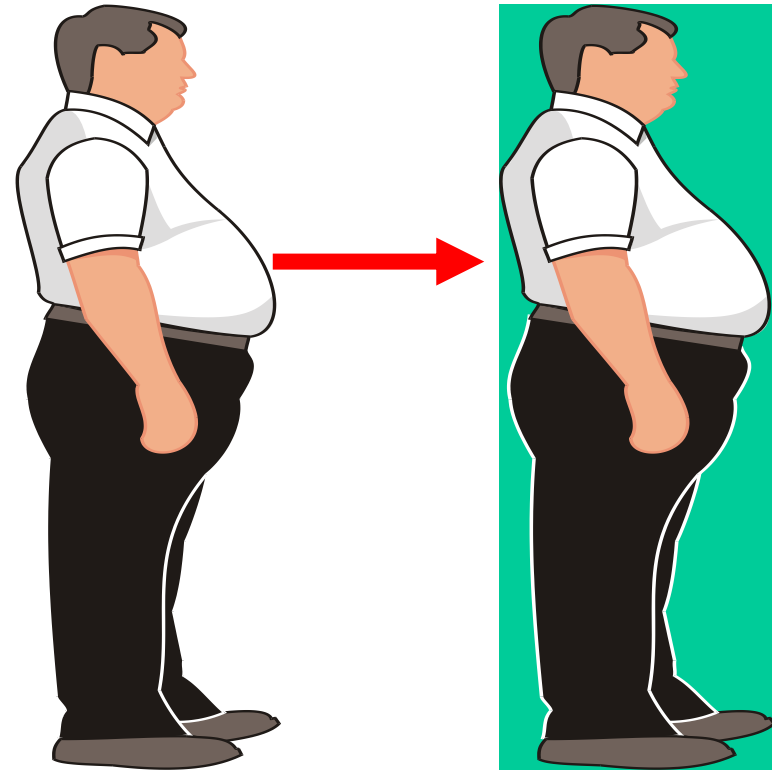
# Randomized controlled trial to study effect of postbariatric surgery FMT versus Metsyn FMT on insulin resistance

Postbariatric surgery to metsyn (RYGB-Recipient, n=12)



Versus

Metsyn to metsyn (Mets-Recipient, n =10)

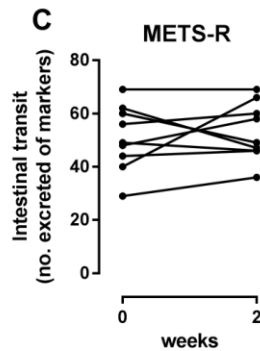
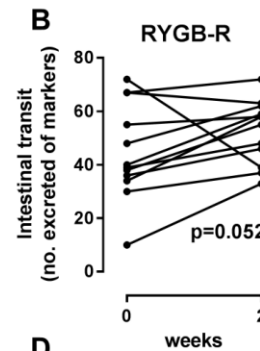
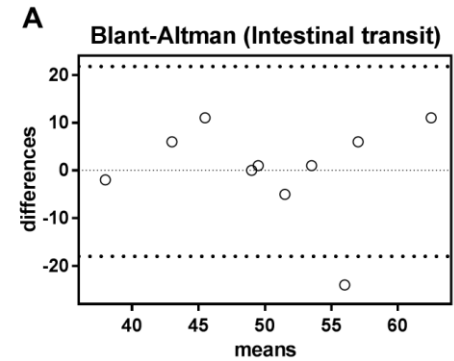
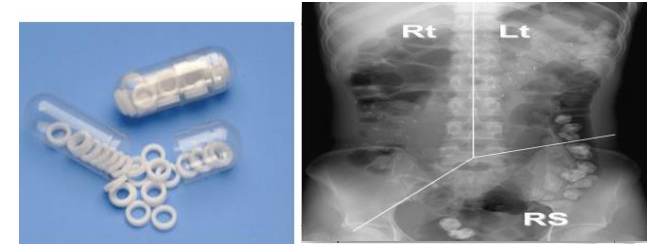
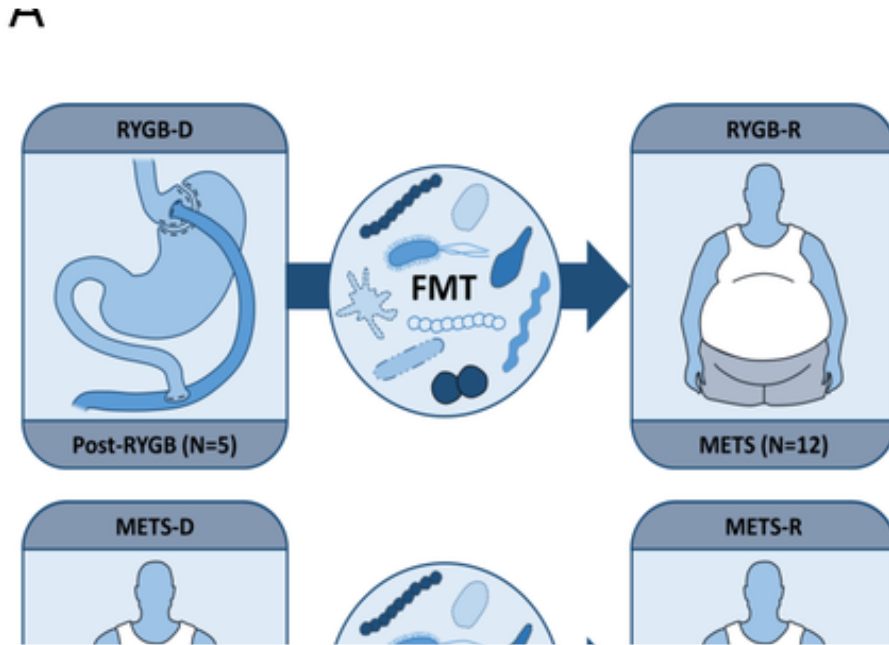


Metsyn 1

to.

Metsyn 2

# FMT from one metsyn to another metsyn subject (METS-R) worsens peripheral insulin sensitivity (Rd), but only post bariatric surgery donor improves intestinal transit time



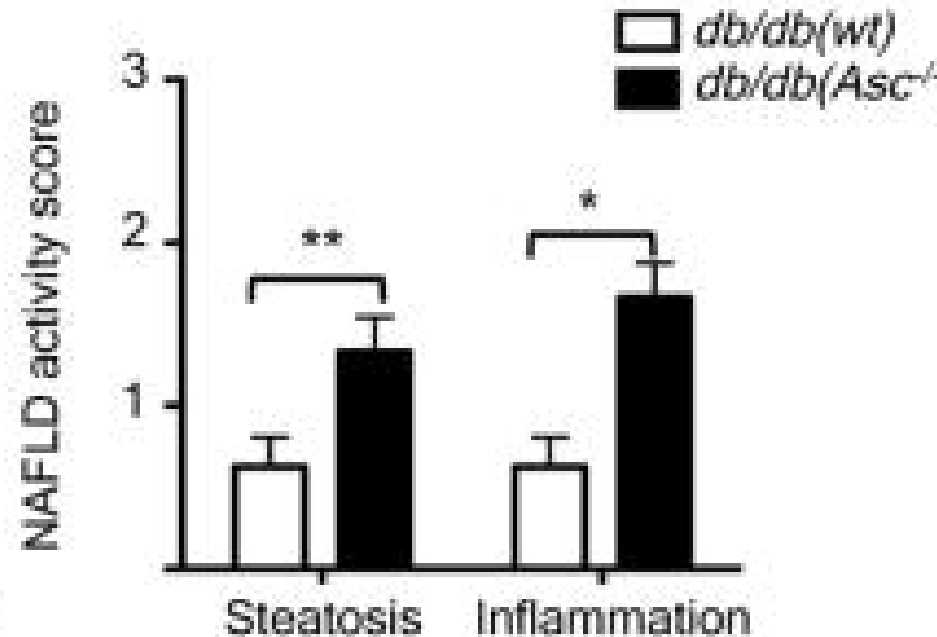
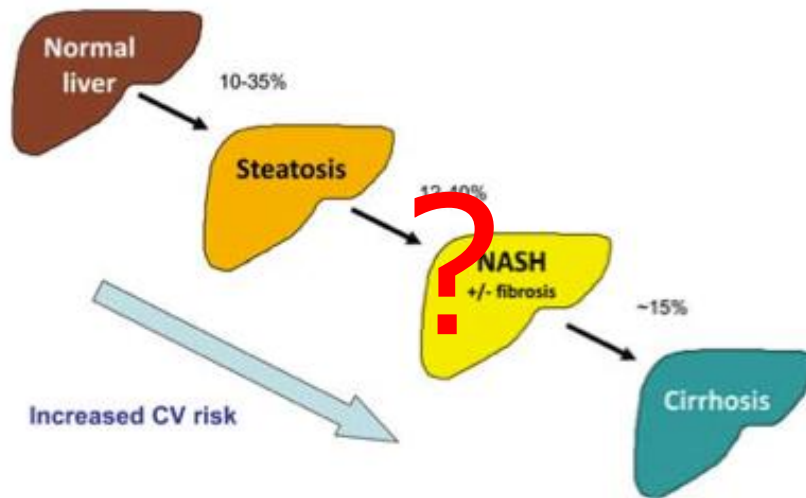
**D** weeks



Pieter de Groot

# Is there also causal role for donor FMT in NAFLD in NAFLD?

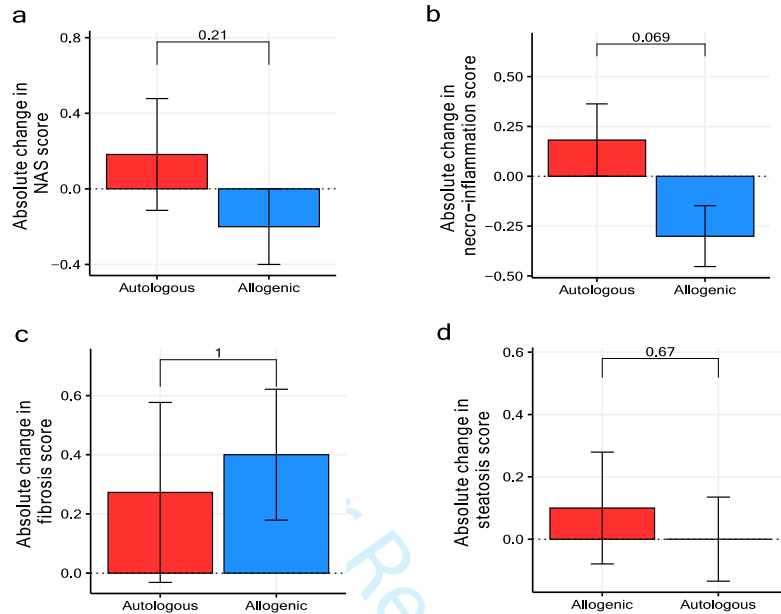
- 80% of DM2 subjects has NAFLD
- Modulation of gut microbiota drives NAFLD -NASH progression in animal models



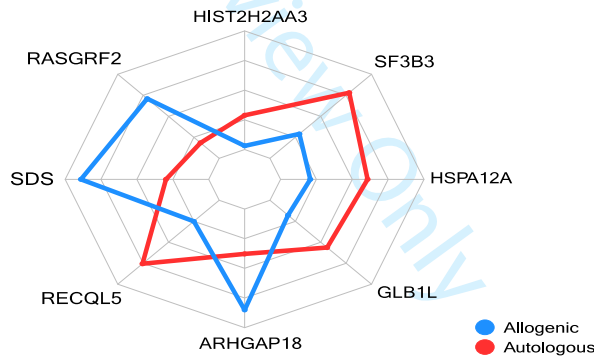
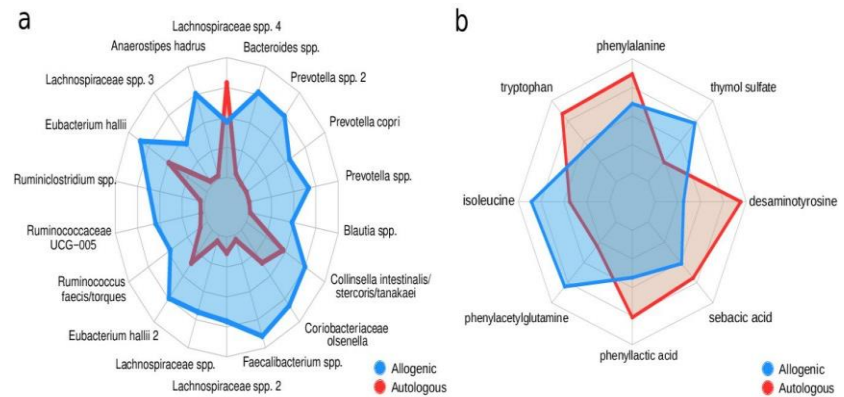


# Beneficial effects of 6 months donor FMT on liver histology and liver gene expression in obese NAFLD patients

## Liver histology

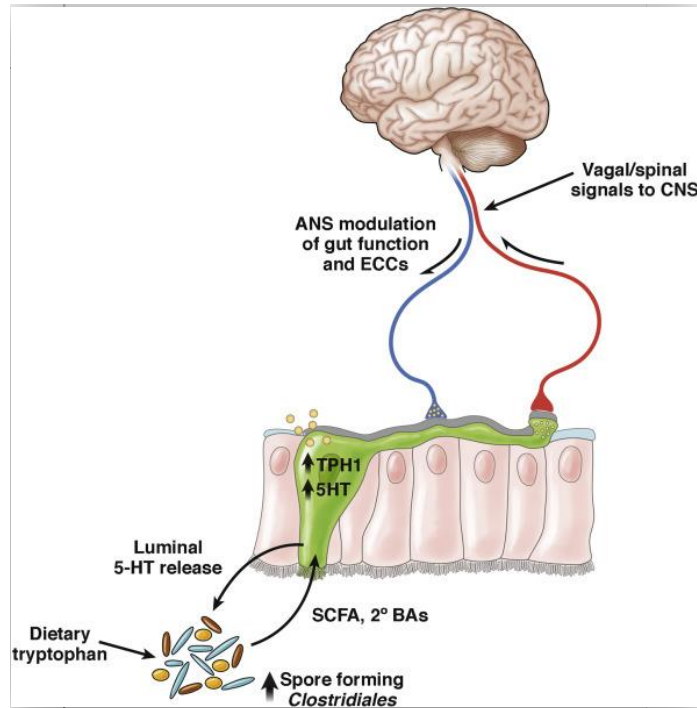


## Fecal microbiota



## Liver gene expression

## Gut brain axis: reciprocal connection



Martin, CMGH 2018: Volume 6, Issue 2, Pages 133–148

Your Gut Has a  
Mind of Its Own

# The Second Brain

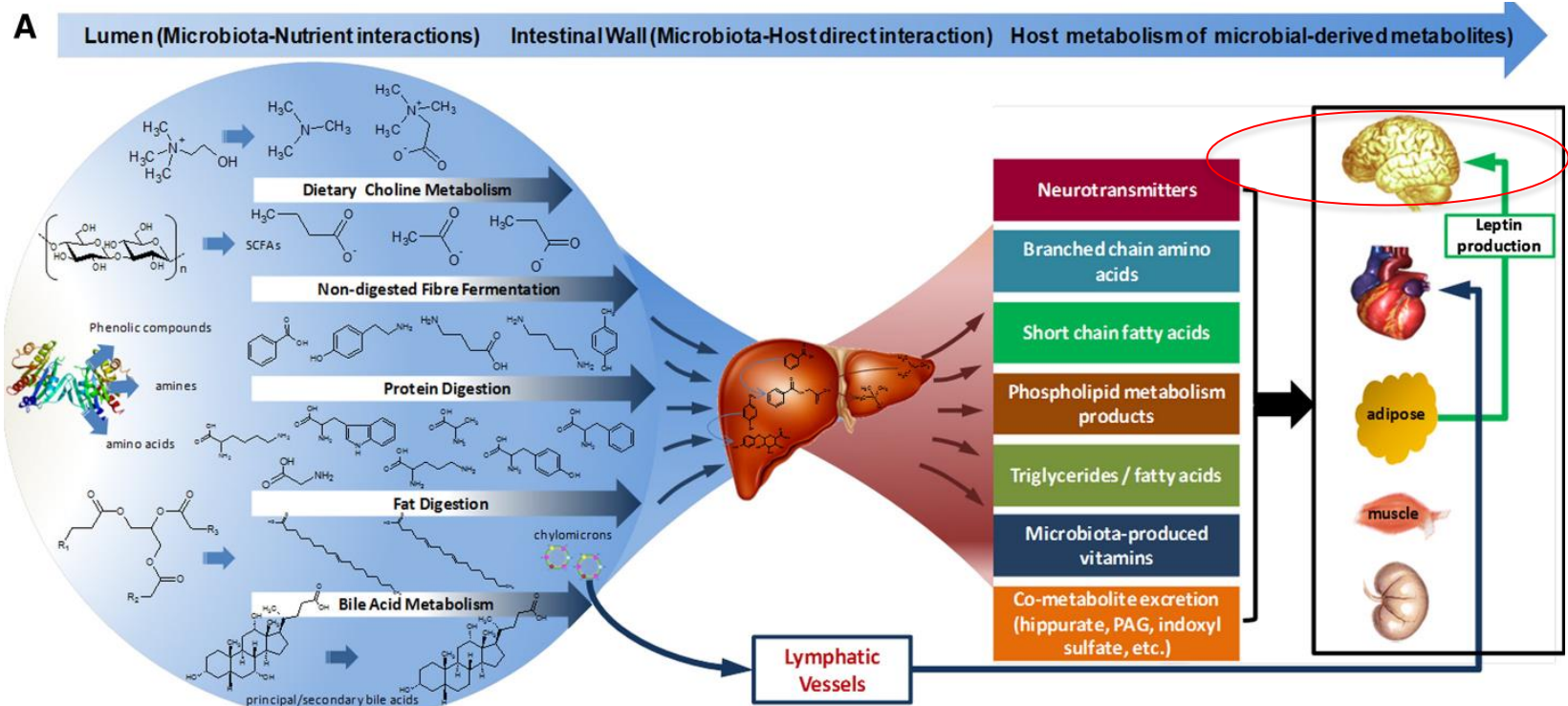
A Groundbreaking New Understanding  
of Nervous Disorders of the  
Stomach and Intestine

"Persuasive, impassioned . . . hopeful news [for those]  
suffering from functional bowel disease."

— *New York Times Book Review*

Michael D. Gershon, M.D.

# Does a gutbrain axis exist in humans?

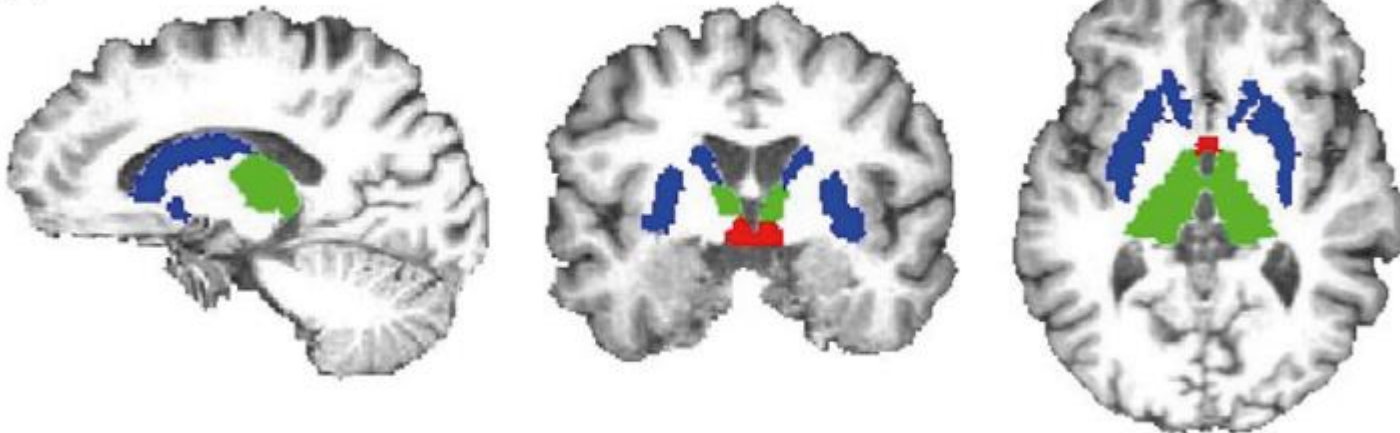


# Brain SPECT + MRI scan to study hypothalamic activation in insulin resistance/DM2

Intravenous Radiotracer labeled 100 MBq  $^{123}\text{I}$ -FP-CIT infusion

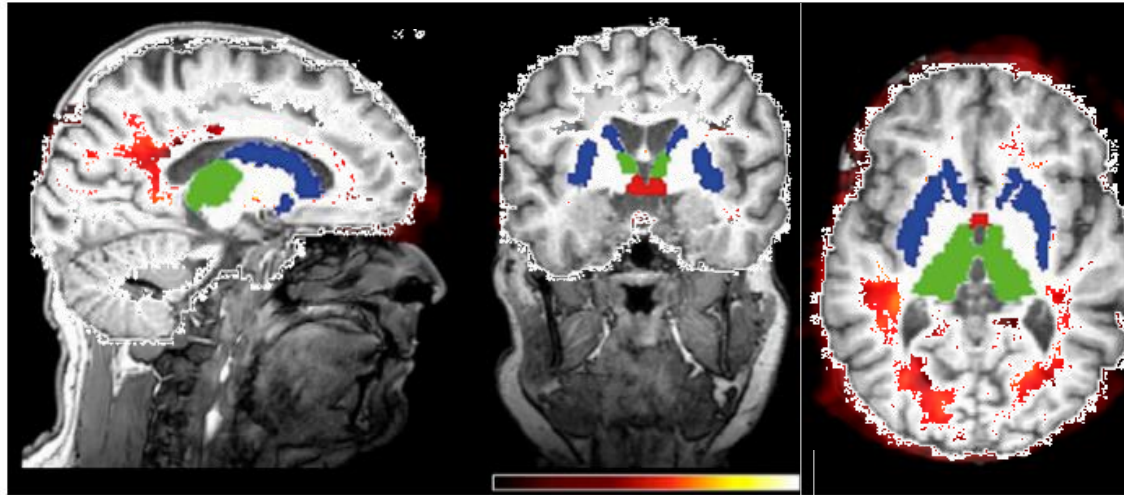
- Serotonin receptor expression in **thalamus** and **hypothalamus** (2h after infusion)
- Dopamine receptor expression in **striatum** (3h after infusion)

A



# ROI analyses

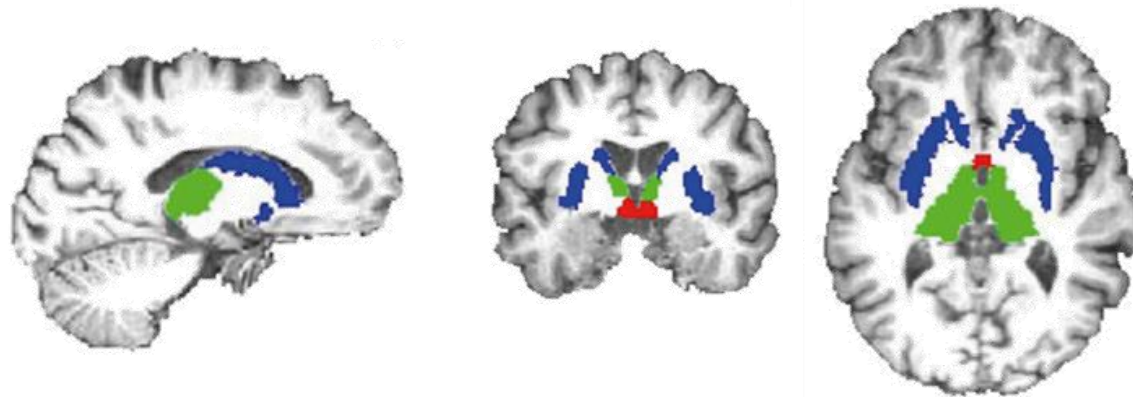
Bindingpotential (BP) per region of interest in the brain



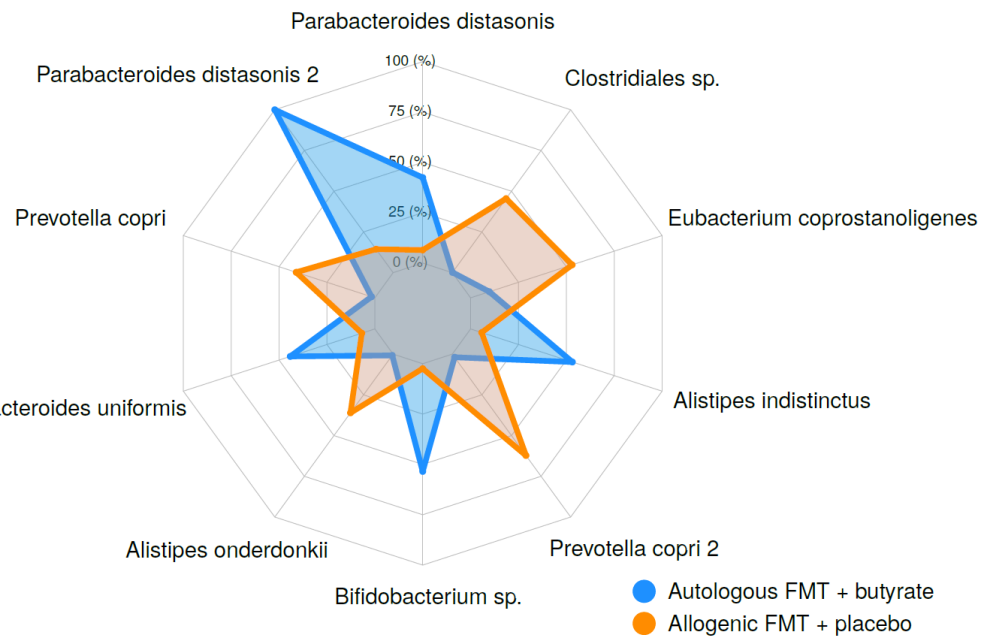
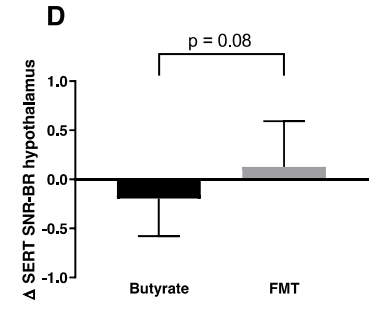
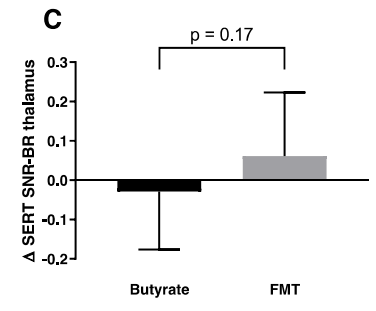
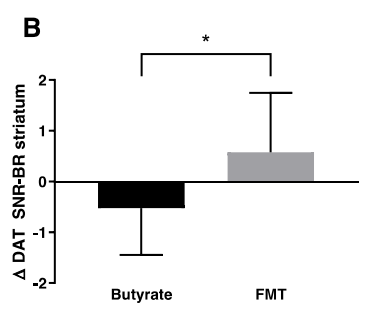
**striatum**

**thalamus**

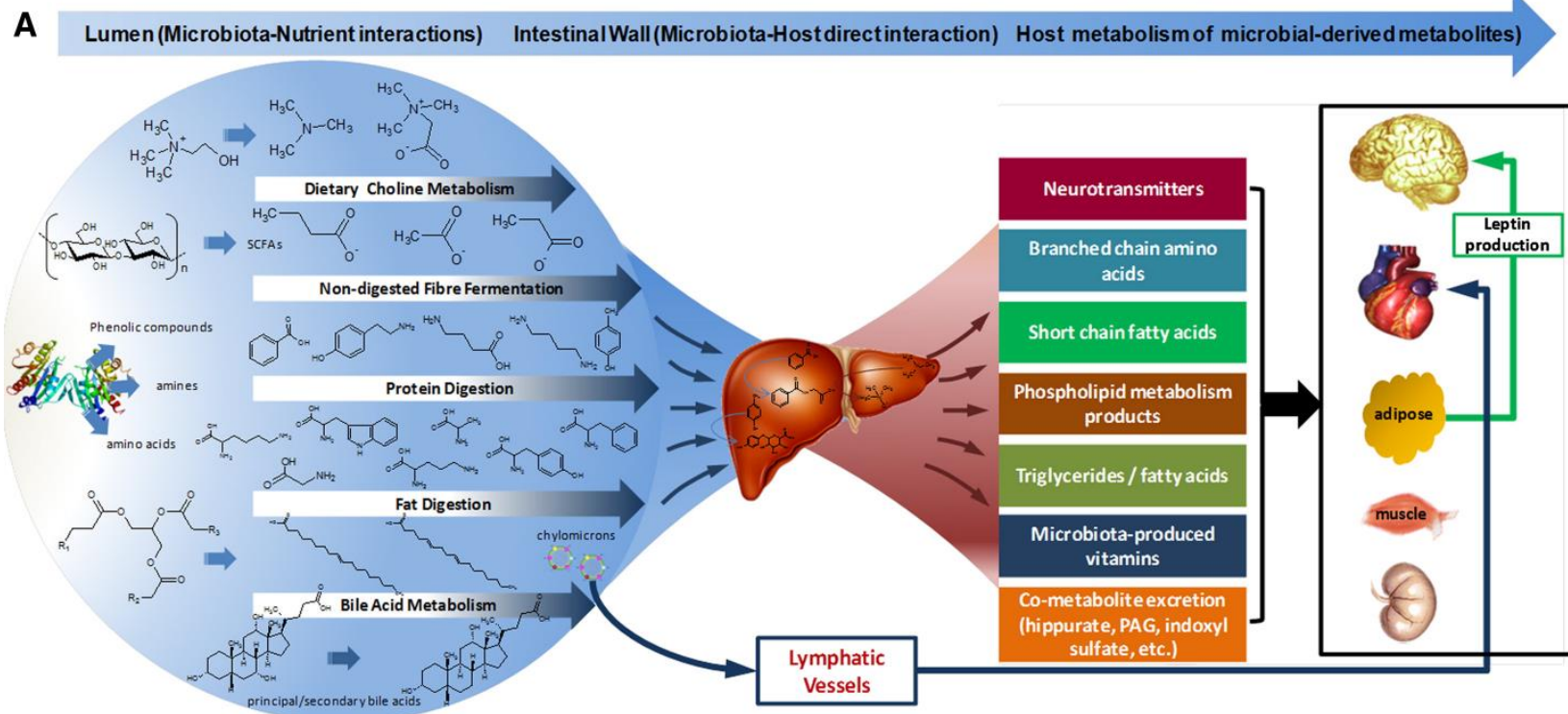
**hypothalamus**



# donor FMT improves gutbrain axis by increasing serotonin and dopamin receptor binding (in hypothalamus and striatum)



# Effect of replenishing missing (single) intestinal microbiota in human diabetes?



## LETTER

doi:10.1038/nature12198

### Gut metagenome in European women with normal, impaired and diabetic glucose control

Fredrik H. Karlsson<sup>1\*</sup>, Valentina Tremaroli<sup>1\*</sup>, Intawat Nookaew<sup>1</sup>, Göran Bergström<sup>1</sup>, Carl Johan Behre<sup>2</sup>, Björn Fagerberg<sup>2</sup>, Jens Nielsen<sup>3</sup> & Fredrik Bäckhed<sup>1,3</sup>

## LETTER

doi:10.1038/nature12566

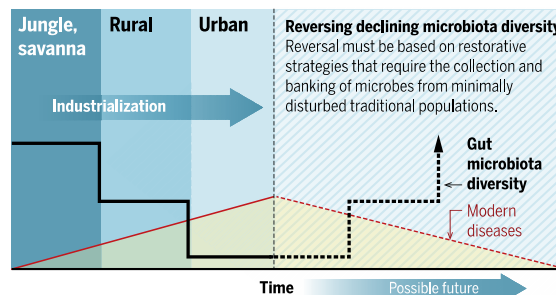
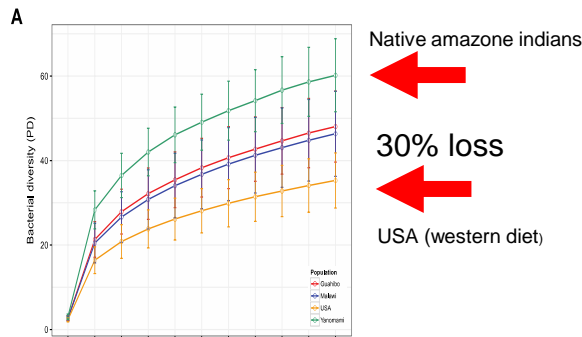
### Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota

Kristoffer Forslund<sup>1\*</sup>, Paul Hildebrand<sup>1,2\*</sup>, Trine Nielsen<sup>1,3\*</sup>, Gwen Falony<sup>1,4</sup>, Emmanuel Le Chatelier<sup>1,5</sup>, Shinsuke Sunagawa<sup>1</sup>, Jill Pflüger<sup>1,6</sup>, Sara Vieira-Silva<sup>1,7</sup>, Yuhong Guo<sup>1,8</sup>, Jelle Krögh Pedersen<sup>1,9</sup>, Manimozhyan Arumugam<sup>1</sup>, Karsten Kristiansen<sup>10</sup>, Anja Yvonne Voigt<sup>10,11</sup>, Henrik Vestergaard<sup>12</sup>, Rajna Herzig<sup>13</sup>, Paul Apré Corda<sup>14</sup>, Sora Ivan Kultima<sup>15</sup>, Justina L<sup>16</sup>, Torben Jørgensen<sup>17,18</sup>, Florence Leventis<sup>19</sup>, Jodi Heuer<sup>20</sup>, MetaHIT consortium<sup>1</sup>, J. Bjørn Nielsen<sup>1</sup>, Søren Brunak<sup>21</sup>, Jensen Rasmussen<sup>22</sup>, Torben Hansen<sup>23</sup>, Jun Wang<sup>24,25,26,27</sup>, S. Dusko Ehrlich<sup>28,29</sup>, Peer Bork<sup>30,31</sup> & Oluf Pedersen<sup>1</sup>

Holmes E, Cell Metabolism 2012 16, 559-564

# Urgent problem: loss of microbiota diversity due to lifestyle and medication

- **30% loss of fecal gutmicrobioa diversity in subjects from USA** (Westerndiet) vs Amazone inhabitants (traditional diet)
- Children probably inherit 50% of their gutmicrobiota composition from their children
- What is lost, doesn't get back automatically (but lost forever?)
- een “bacterie stam kluis” op te richten om aanwezige bacteriestammen te bewaren voor volgende generaties



Time Bomb

## Scientists Urge Doomsday Vault for 'Good' Germs

Antibiotics, filtered water and processed food are making us more vulnerable to disease.

By Riley Griffin

4 oktober 2018 20:00 CEST Corrected 4 oktober 2018 22:51 CEST



Entrance to the seed vault in Norway. Photographer: JUNGE, HEIKO/AFP



## **Diagnostics: Microbiome diagnostics in NL**

- <https://www.microbiome-center.nl>
  - 500 euro voor feces microbiom analyse + consult kosten, probiotica kosten afhankelijk van advies)
- <https://www.mymicrozoo.com/nl/Home>
  - Eenmalig microbiom analyse 135 euro, indien daarna voedingsadvies kunnen er meerdere samples bestudeerd worden voor 345 euro)

# And might supplementation of (immunomodulatory) Bacterial strains stabilize residual betacell function in human DM1 and insulin sensitivity in DM2

Dr. Ben Eiseman (1917 - 2012)



"In the early days of oral antibiotics we were plagued by frequent diarrhea in our patients due presumably to killing off intestinal bacteria. I was Chief of Surgery at the VA and simplistically considered merely reintroducing normal organisms to counter such absence. Those were days when if one had an idea, we simply tried it. It seemed to work and I wrote it up. It made a small splash... Best wishes. Ben Eiseman, Emeritus Professor of Surgery — Now age 93." (Sept. 20, 2011)

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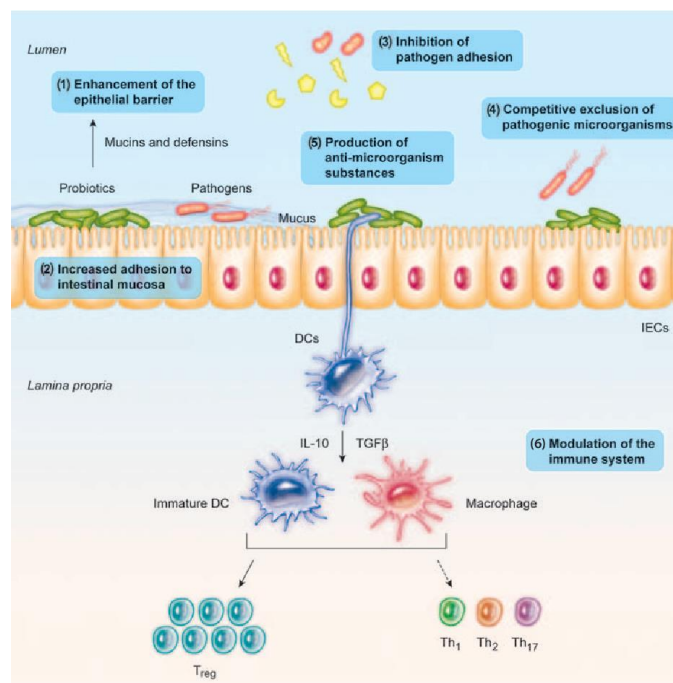
Should further clinical experience substantiate the beneficial effect of fecal enemas in the treatment of pseudomembranous enterocolitis,<sup>5</sup> more precise bacterial, viral, or bacteriophage substitution therapy might be employed. Since the disease occasionally involves parts of the intestinal tract proximal to the colon, the oral administration of pure cultures of these organisms in enteric-coated capsules might be both more aesthetic and more effective.

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## Probiotics beneficial in healthy subjects? -guideline by Micropia

### Publicatie Nationale Gids voor probiotica bij antibiotica een feit

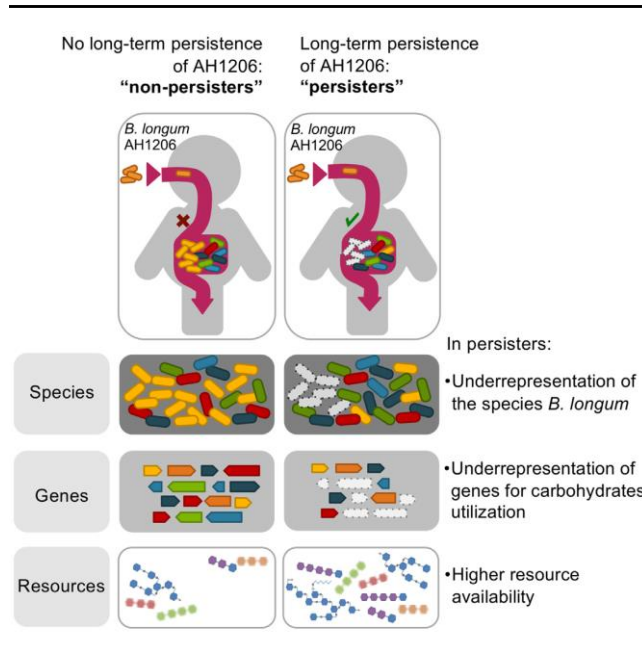
De Nationale Gids van klinisch bewezen probiotica bij antibioticagebruik werd gelanceerd door een wetenschappelijke publicatie in het tijdschrift *BMC Gastroenterology*.



**Mechanisms of action of probiotics**

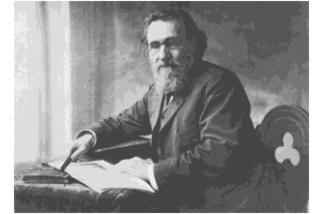
Agamennone, *BMC Gastroenterol.* 2018; Bermúdez-Brito, *Annals of Nutr&Met*, 2012

# Not everybody responds in the same way to a probiotic



- Responders (30% ) still have (2-6 months after bifidobacterium longum treatment) still presence in their stool
-

# Ilya Mechnikoff (1845-1916); ontdekker van de probiotica



- *“De belofte van de de intestinale microbiota ligt vnl in (nieuwe) probiotica. Het moet op den buur mogelijk zijn om een afwijkend darmmicrobioom te herstellen door inname van een capsule gevuld met miljarden bacterien, of door het eten van yoghurt”.*
- *ProbioticaWHO definitie: “levende micro-organismen, die wanneer toegediend in voldoende hoeveelheden een gunstig effect op gezondheid van de gastheer hebben”*
-

# Leveranciers van multiple stammen probiotica in Nederland

- Winclove (9 probiotica stammen 2dd 1 sachet, prijs 50 euro per maand )

- **Indicatie IBS, constipatie**  
<https://www.winbiotic.nl>

- Orthica orthiflor (9 stammen, 4 verschillend van Winclove, kosten 60 euro voor 120 capsules) **Indicatie darmgezondheid**

<https://www.orthica.nl/orthiflor-original>

- Ferring (VSL#3) (prijs 46 euro per maand voor

- 1dd 1 sachet) **indicatie: IBS.**

Negen specifiek geselecteerde bacterieculturen:

<i>Bifidobacterium bifidum</i>
<i>Bifidobacterium lactis</i>
<i>Enterococcus faecium</i>
<i>Lactobacillus acidophilus</i>
<i>Lactobacillus casei</i>
<i>Lactobacillus paracasei</i>
<i>Lactobacillus plantarum</i>
<i>Lactobacillus rhamnosus</i>
<i>Lactobacillus salivarius</i>

*Bifidobacterium bifidum*  
*Bifidobacterium lactis*  
*Enterococcus faecium*  
*Lactobacillus casei*  
*Lactobacillus gasseri*  
*Lactobacillus paracasei*  
*Lactobacillus plantarum*  
*Lactobacillus salivarius*  
*Lactococcus lactis*

PubMed

Format: Summary Sort by: Most Recent Per page: 20

Best matches for VSL#3 probiotic:

[The Probiotic Compound VSL#3 Modulates Mucosal, Peripheral, and Systemic Immunity Following Murine Broad-Spectrum Antibiotic Treatment.](#)  
Ekmeiciu I et al. Front Cell Infect Microbiol. (2017)

[Probiotic mixture VSL#3 reduces colonic inflammation and improves intestinal barrier function in Muc2 mucin-deficient mice.](#)  
Kumar M et al. Am J Physiol Gastrointest Liver Physiol. (2017)

[The effect of short term treatment with probiotic VSL#3 on various clinical and biochemical parameters in patients with liver cirrhosis.](#)  
Marlicz W et al. J Physiol Pharmacol. (2016)

[Switch to our new best match sort order](#)

Search results

Items: 1 to 20 of 282

# Leveranciers van enkel stam probiotica in Nederland

- Danone (yakult) (Lactobacillus casei, 40 euro per week) supermarkt:
- **Indicatie: darmgezondheid**



- E coli nissle stam 1dd capsule, na 1 week ophogen naar 2dd 1 capsule (52 euro)  
(<https://www.kalidashop.com/mutaflor-20-capsules.html>)
- **Indicatie: IBS, constipatie, Ulc Colitis, eczeem en diarrhee bij kinderen**



Kruis, [Int J Colorectal Dis](#). 2012 Apr; 27(4): 467–474.

- In 1917 had Duitse leger in Roemenie (Debrudie) last van dysenterie epidemie

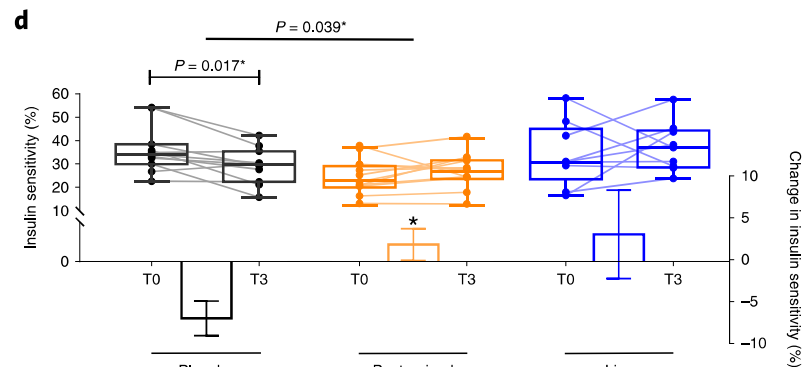


# First RCT with next generation probiotic in metabolic syndrome with *Akkermansia muciniphila* shows safety but no efficacy on glucose metabolism...

A Probiotic for Obesity? - The New York Times

12-09-20 14(45)

The New York Times | <https://nyti.ms/2Nqbv5Y>



Mean difference	$-6.79 \pm 2.07$	$2.13 \pm 1.89$	$3.24 \pm 5.28$
P value (Mann-Whitney U-test)		$0.002^*$	$0.095$
Mean difference from placebo	--	$8.92 \pm 1.89$	$10.03 \pm 5.28$
Mean difference from placebo (%)	--	$28.62 \pm 7.02\%$	$42.42 \pm 20.44\%$

## A Probiotic for Obesity?

People with metabolic disorders may benefit from supplements of a common gut bacterium, a small pilot study suggests.



By Nicholas Bakalar

July 1, 2019

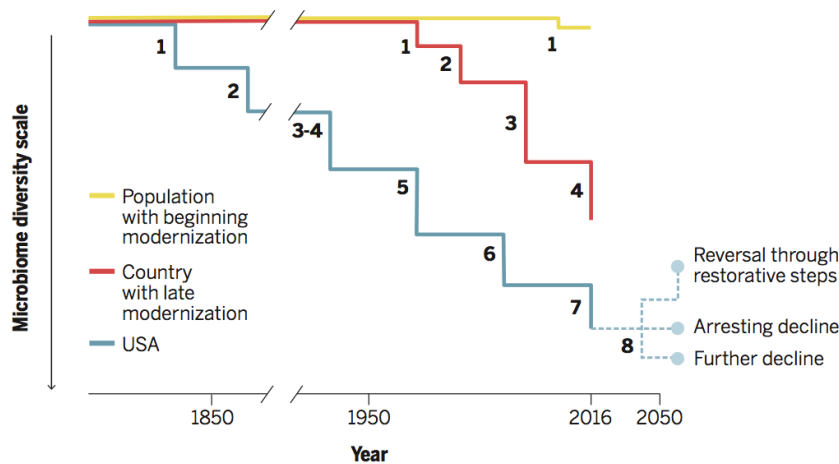
People with obesity-related disorders may benefit from supplements of a common gut bacterium, a small pilot study suggests.

Researchers tested the bacterium, *Akkermansia muciniphila*, in 32 men and women who met the criteria for metabolic syndrome by having at least three of five conditions: high fasting blood sugar, high blood pressure, high triglycerides, low HDL (the "good" cholesterol) or excessive waist circumference.



## Replenish bacterial strains missing in the gut microbiota to cure human disease

Should further clinical experience substantiate the beneficial effect of fecal enemas in the treatment of pseudomembranous enterocolitis,<sup>5</sup> more precise bacterial, viral, or bacteriophage substitution therapy might be employed. Since the disease occasionally involves parts of the intestinal tract proximal to the colon, the oral administration of pure cultures of these organisms in enteric-coated capsules might be both more aesthetic and more effective.



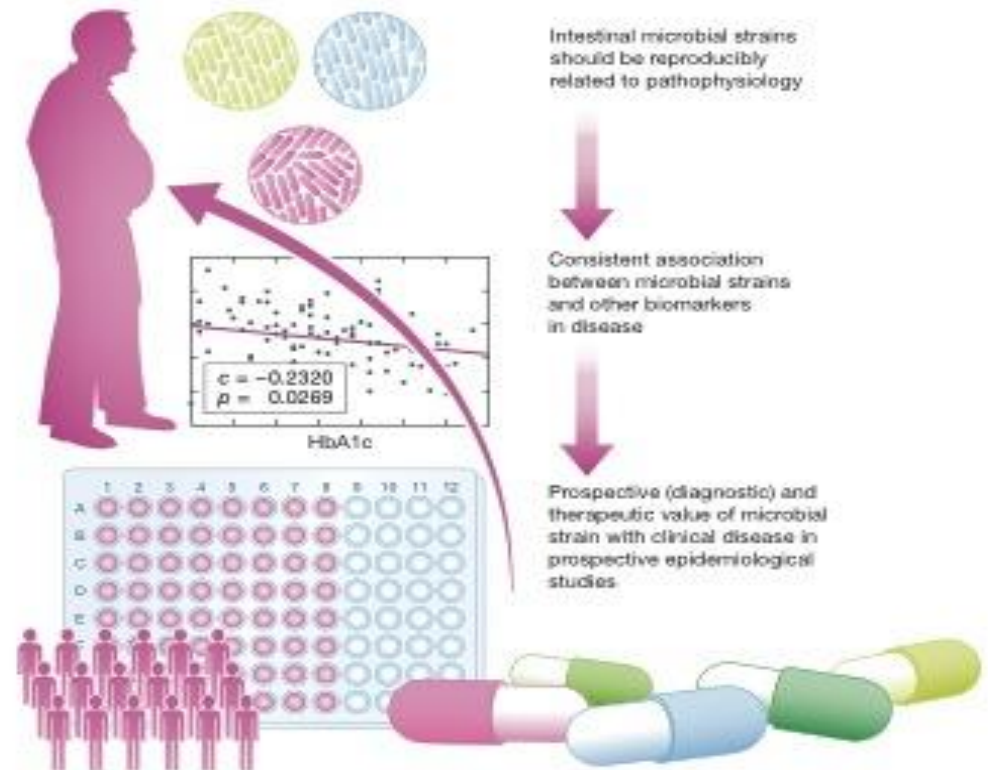
Eiseman (Surgery 1958)

Courtesy of Prof Blaser

# Replenishing (missing) intestinal microbiota or metabolites might improve diabetes mellitus:

## *Pitfalls and hurdles for future experiments*

- production bacterial strains as novel immunomodulatory probiotics (HACCP/GMP culture medium and > 80 liter of production)
- Shelf live and viability (freezedrying vs glycerol storage)
- Single vs multiple strains (GMP) and located delivery release (small-large intestine)
- Large and expensive phase I-IV clinical trials for validity (mouse  $\neq$  men)
- Different strains for DM1 and DM2
- No one size fits all ...no blockbusters (personalized medicine)



# Conclusions

- 1. (small) intestinal microbiota are associated with DM; is this causal factor or disease modifier (confounders)?
- 2. Ethnicity seems to be an important factor for gut microbiota composition
- 3. Using FMT in DM; from group to individual (responders-non responders)
- 4. other components of DM (NAFLD and altered gut-brain axis) also partly regulated by gut microbiota in humans
- 5. maybe treatment with (combination of) missing intestinal bacterial strains beneficial effects on DM1 and DM2 in certain subgroups?



Willem de Vos  
Wageningen



Fredrik backhed  
Gothenborg

Nieuwdorp diabetes groep

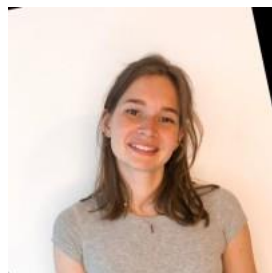
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Geesje Dallinga-Thie

