Disclosure belangen spreker Arts & Leefstijl webinar

Spreker: Dr. Karen Koning

(potentiële) belangenverstrengeling	Geen / Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	
• Sponsoring of onderzoeksgeld	• Nee
• Honorarium of andere (financiële) vergoeding	• Nee
• Aandeelhouder	• Nee
• Anders namelijk, …..	• Werknemer Winclove Probiotics

Medicatie en het microbioom

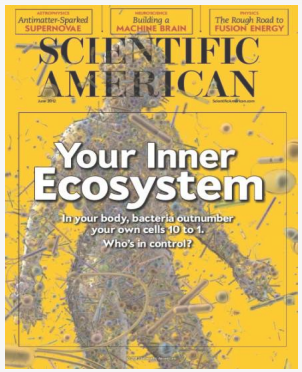
Dr. Karen Koning

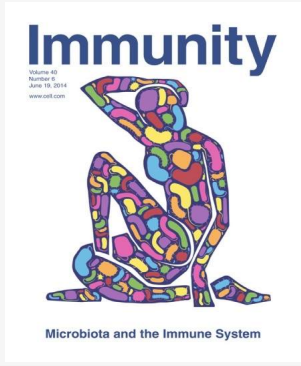
September, 2021

Bacteriën zijn overall

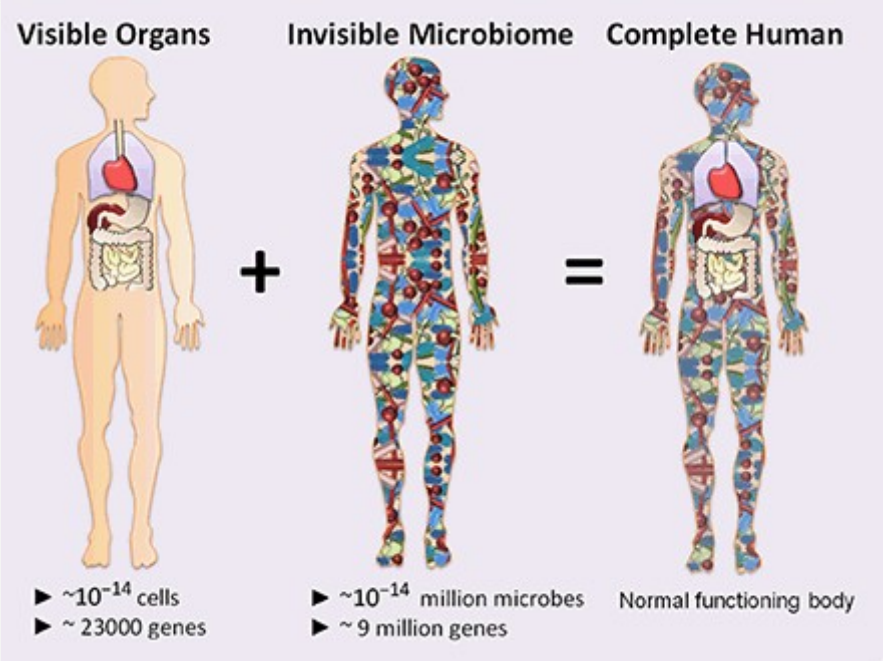
Met tongzoenen wissel je 80 miljoen bacteriën uit!

‘Hot topic’ in de wetenschap



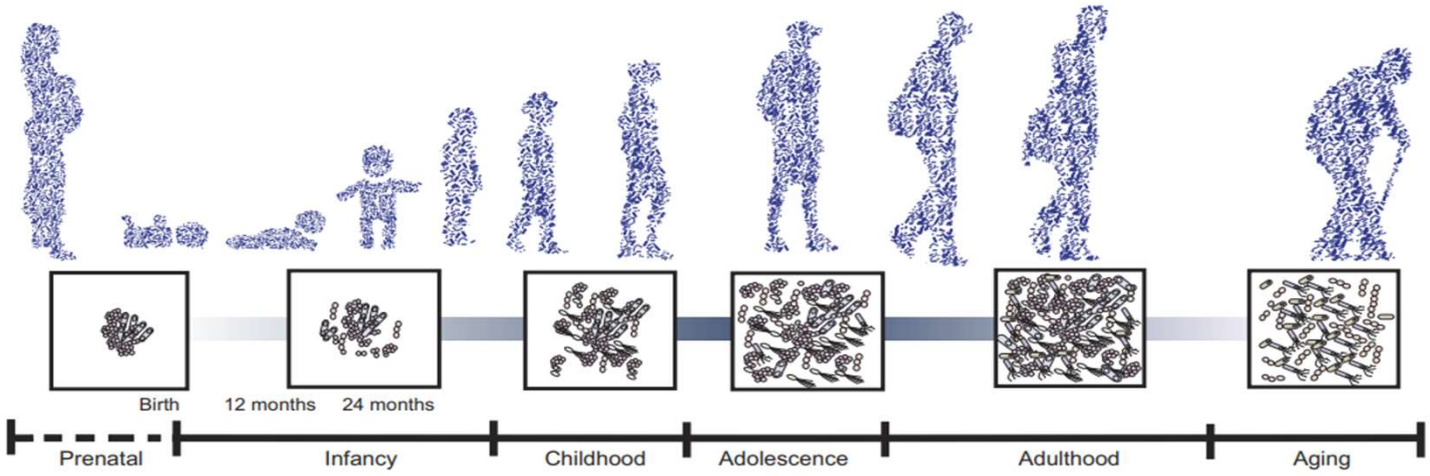


Wat is het microbioom?



A treasure trove waiting to be unlocked

Microbiota ontwikkeling



Adapted from Stiemsma 2015 and Cryan 2019

Microbiota ontwikkeling

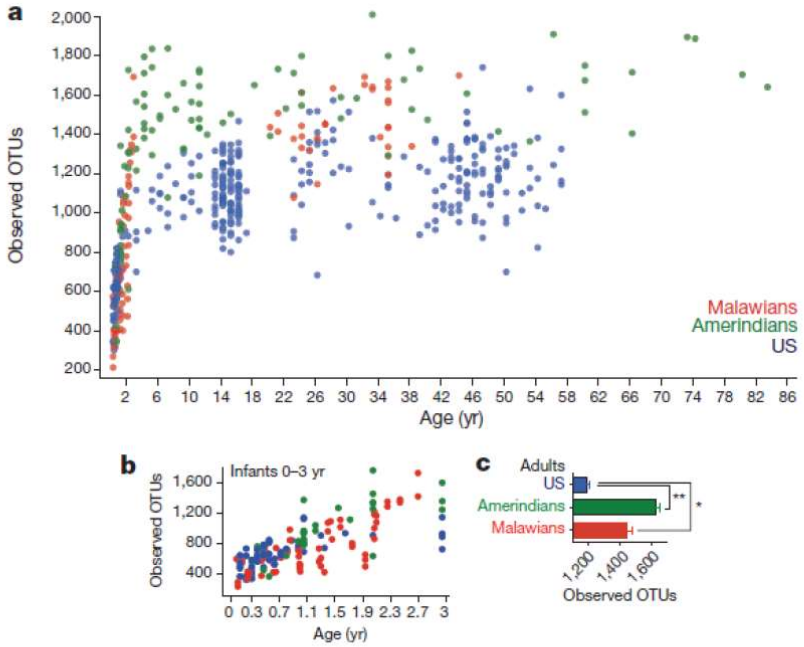
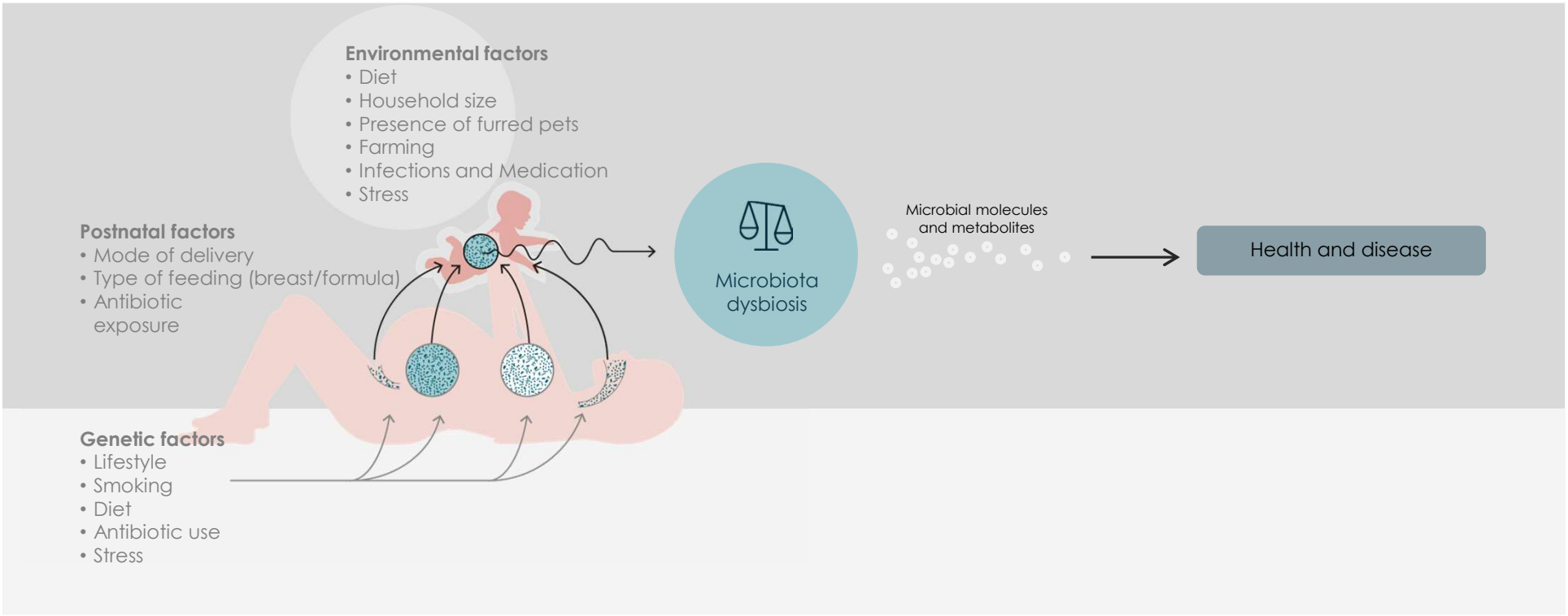


Figure 2 | Bacterial diversity increases with age in each population. a–c, The

Ontwikkeling microbioom



Onze microbiota

We zijn
MEER BACTERIE DAN MENS

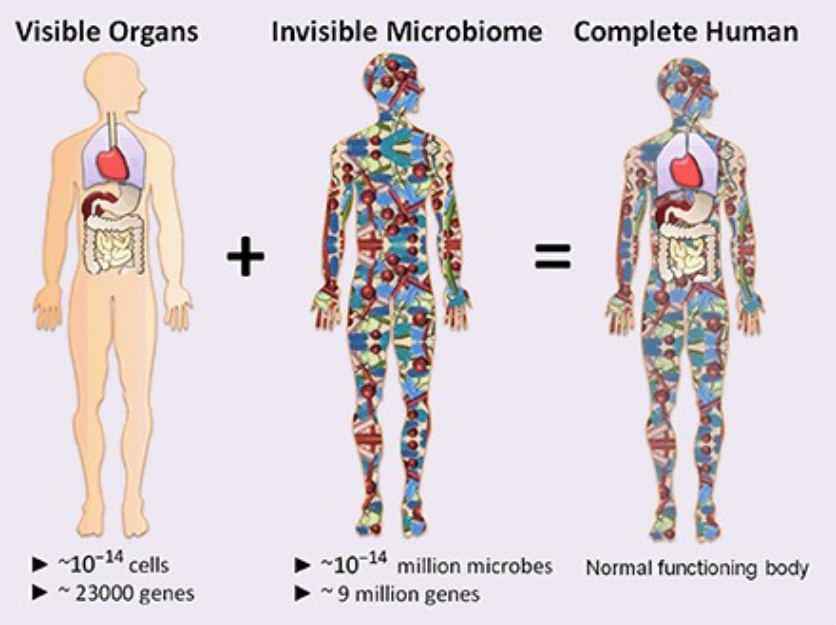
De microbiota bevat **360X** meer DNA dan de mens

Het menselijk microbioom bevat
4930
soorten
MICRO-ORGANISMEN

De microbiota weegt
1-2 KG

60-80 % van het **IMMUUNSYSTEEM** zit rond de darm

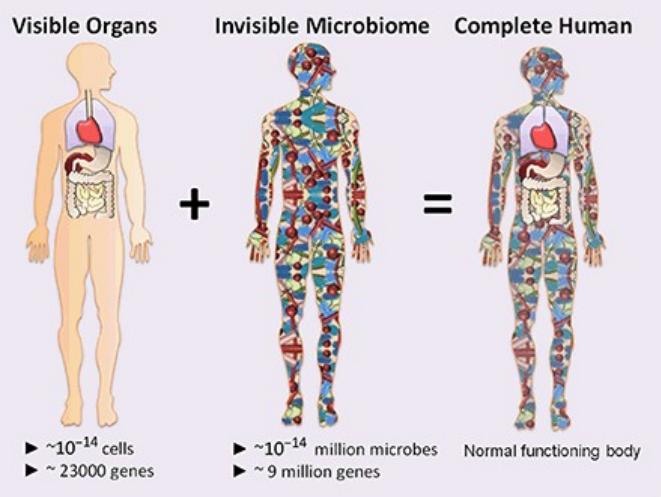
Naast elkaar kunnen onze microben **2,5x** de wereld rond



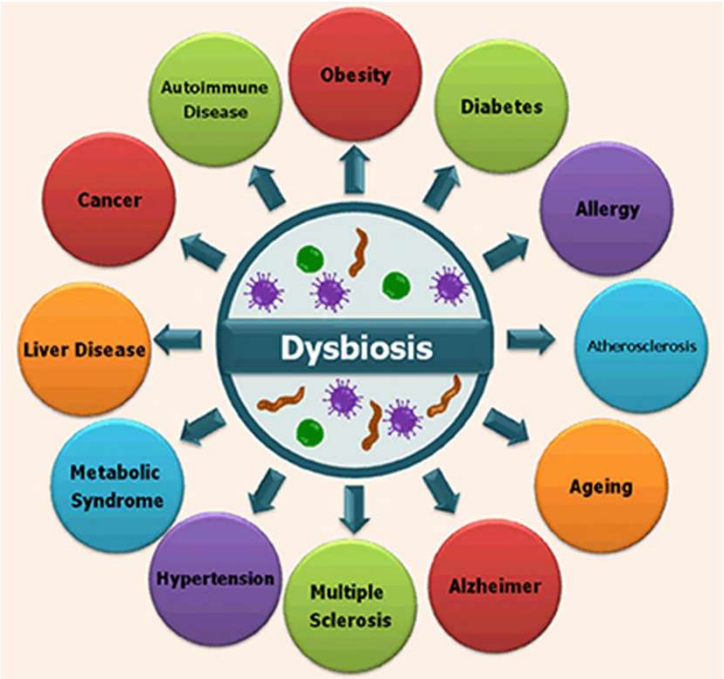
Onze microbiota

- Unieke persoonlijke microbiota, relatief stabiel

- Verlies van diversiteit is geassocieerd met afname/verslechtering van gezondheid

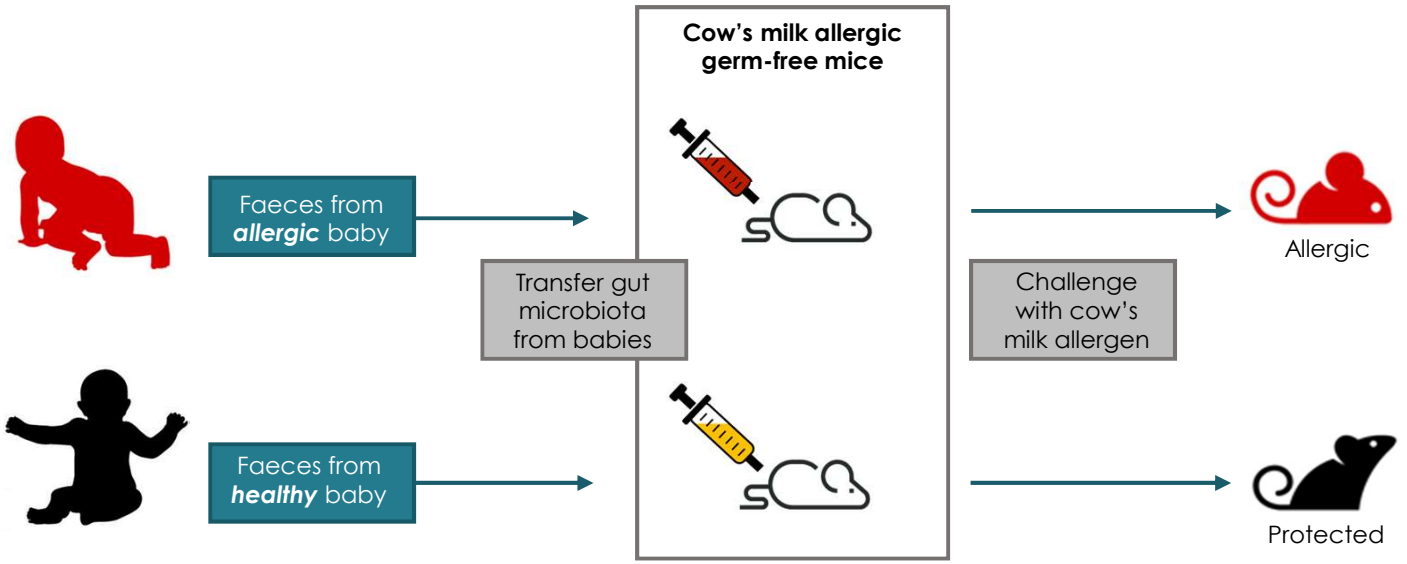


Microbiotaverstoring en ziekte



Human microbes – The power within, 2018

Microbiota en allergie



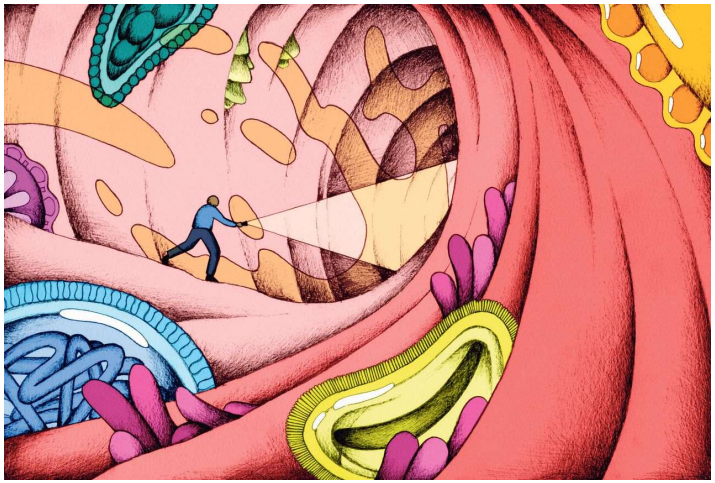
Adapted from Feehley 2019

Microbiota en IVF

Een saaie vagina is juist heel gezond

Medische microbiologie

Het beste kun je één of twee bacteriesoorten in je vagina hebben, aldus promovendi Martin Singer en Charlotte van der Veer. 'Met een ongunstig microbioom is de slagingskans van ivf maar 5 procent'.



NRC, 2019

Verstoring van de microbiota

Gezonde microbiota

Oorzaken verstoring

- Voeding/dieët
- Medicatie
- Stress

Verstoorde microbiota

Verstoring van de microbiota

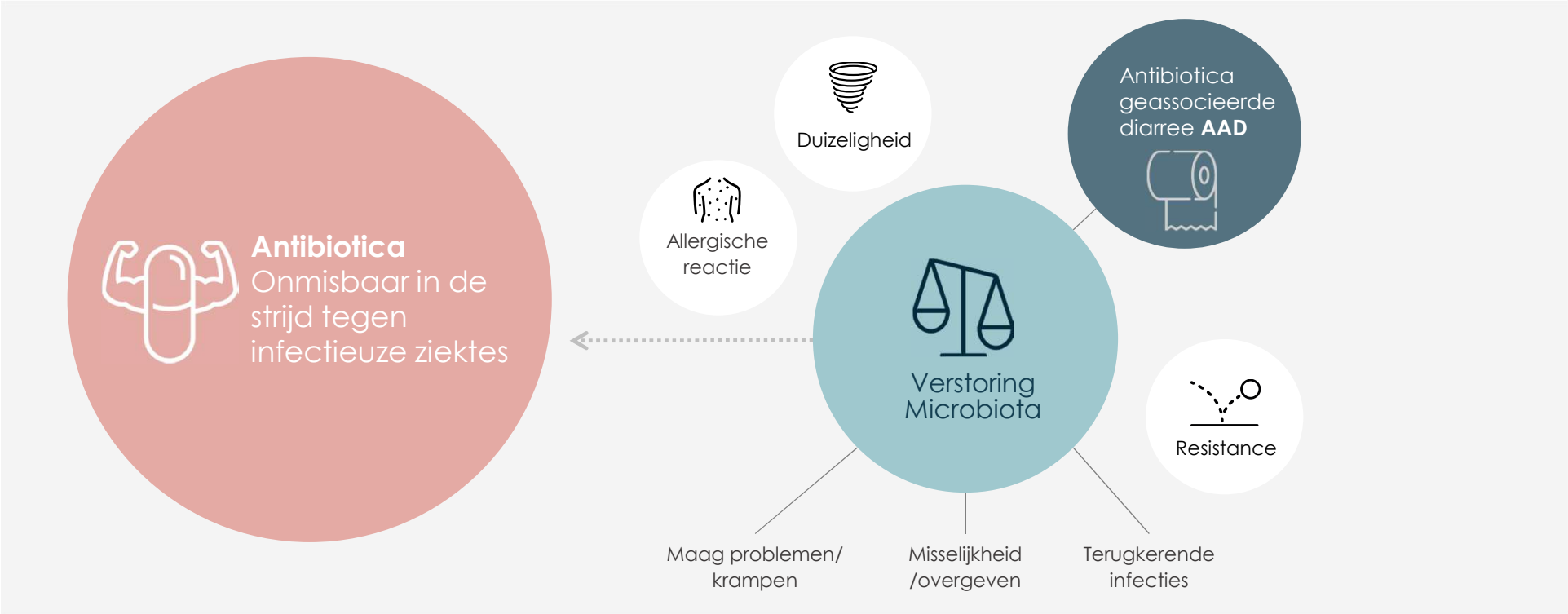
Gezonde microbiota

Oorzaken verstoring

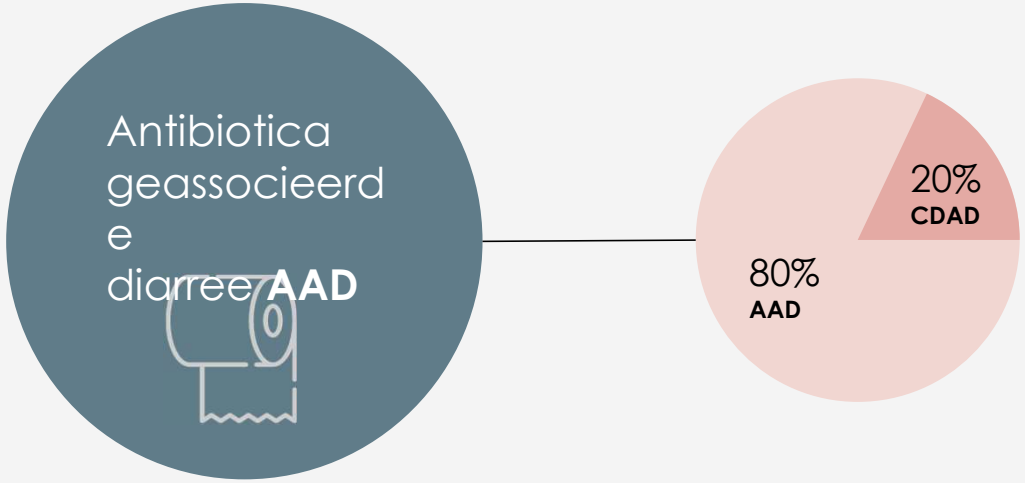
- Voeding/dieët
- Medicatie
- Stress

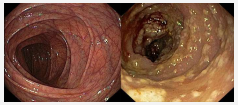
Verstoorde microbiota

Bijwerkingen antibioticagebruik



Antibiotica geassocieerde diarree (AAD)





***Clostridium difficile* geassocieerde diarree (CDAD)**

- Herhalingspercentage(5-56%)
- Ernstige pseudomembraneuze colitis
- Hoge mortaliteit (2-4%)

Niet specifieke AAD

- vaak mild en gaat vanzelf over

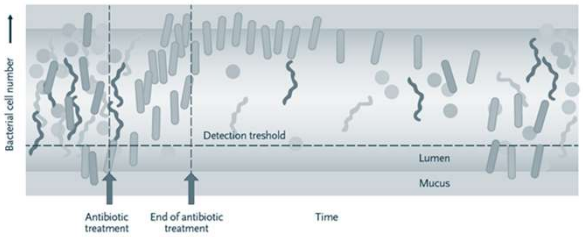
Verstoring microbiota

! Ook als diarree niet optreedt is er toch een verstoring van de microbiota

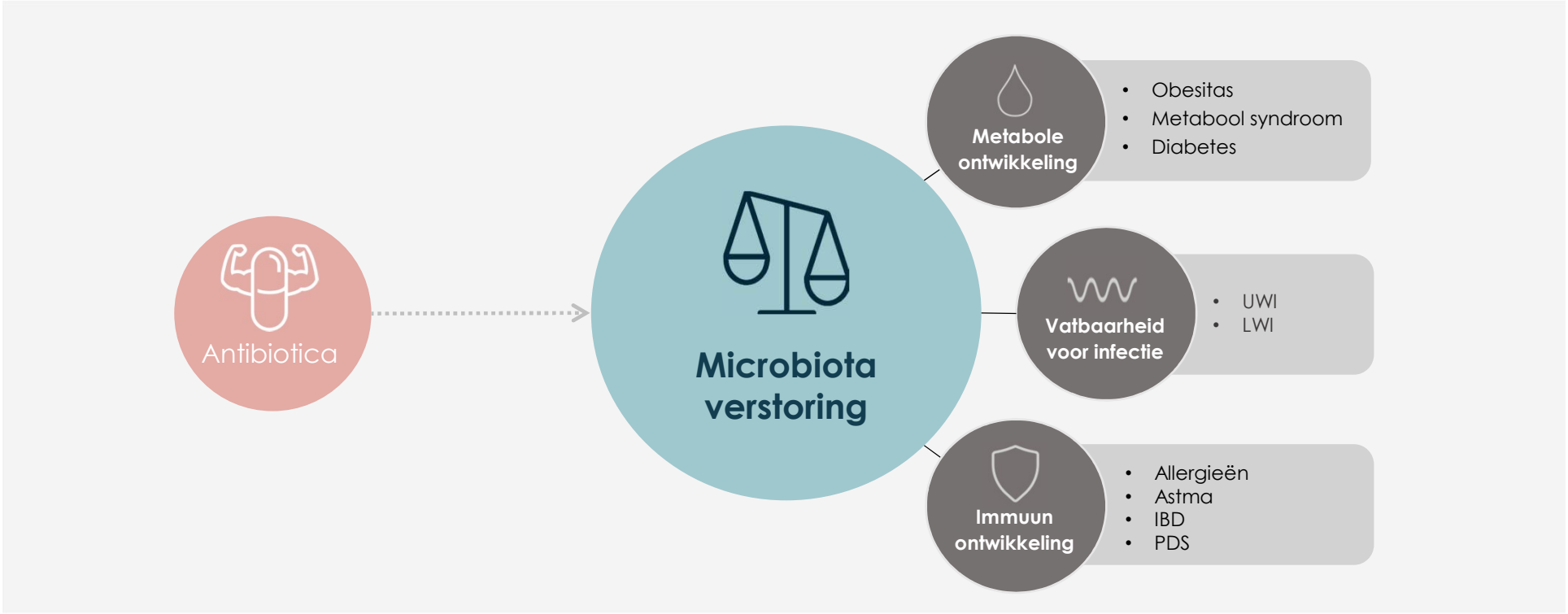
Korte termijn AB gebruik leidt tot lange termijn verstoringen in specifieke bacteriële populaties.

→ AB gebruik ↓ diversiteit

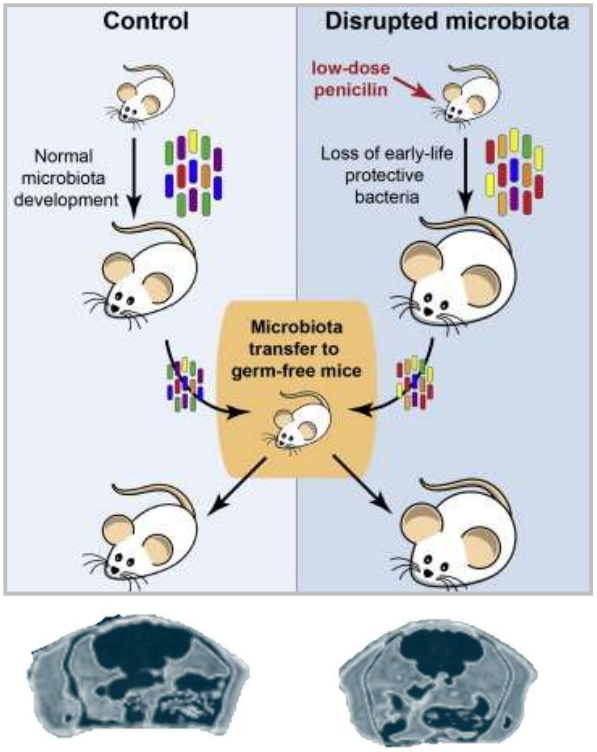
(Jernberg *et al.* 2007,, O'Sullivan *et al.* 2012 Fouhy *et al.* 2012, Schokker *et al*. 2015)



Gezondheidsrisico's antibiotica

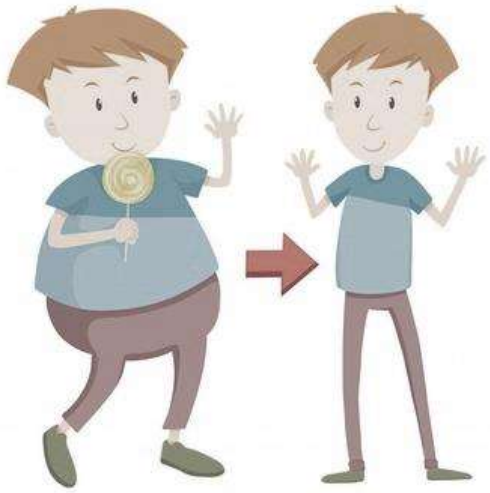


Antibiotica maakt dik!



Cox LM *et al.* 2014

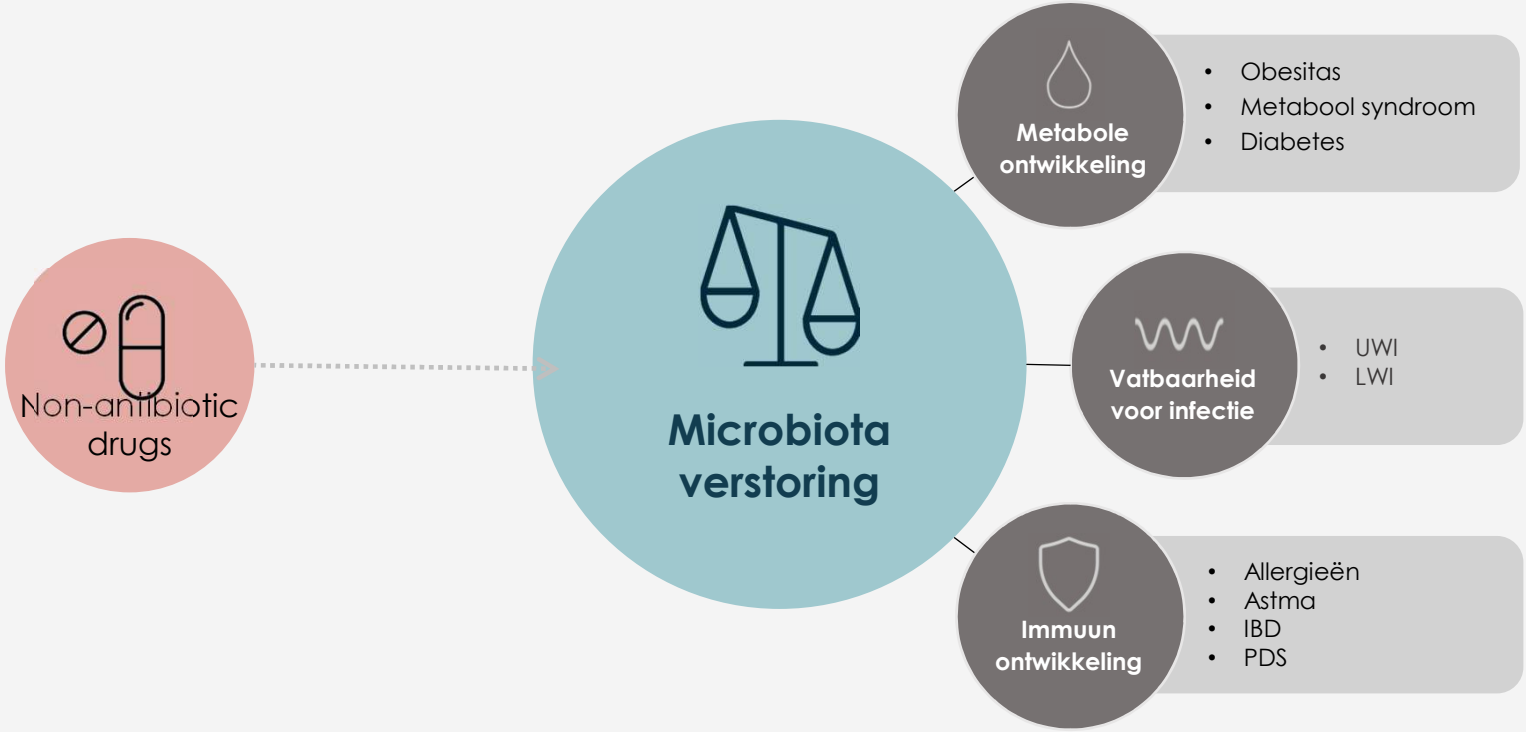
Antibiotica en overgewicht?



Recent onderzoek uit Nieuw-Zeeland heeft laten zien dat kinderen die in de eerste één tot twee jaar van hun leven antibiotica krijgen, een groter risico lopen op een hogere body-mass index (BMI) of op de leeftijd van vier of vijf jaar zwaarlijvig te worden.

Chelimo C et al. 2020
Leong KSW et al. 2020

Medicatie en de microbiota



Effects of common drugs on microbiota

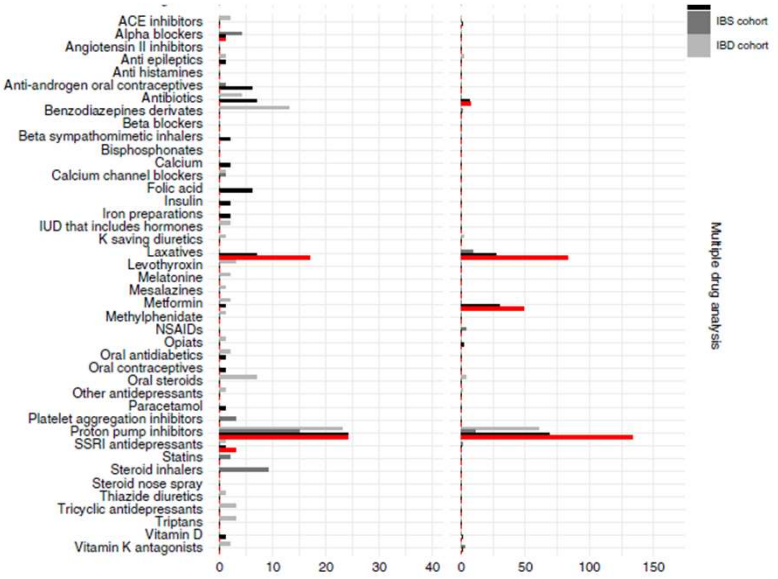
Table 1 Effect of common drugs on the microbiome in population studies

Name (analogue UK)	NL% n=1124	UK% n=2757	Effect on alpha div	Effect on beta-div prop. of core genera	Decreased taxa	Increased taxa
ACE inhibitors	3.91	11.7			s_Dorea_longicatena (1)	g_Rothia (1); g_Blautia (1)
Alpha blockers	0.89	2.73				f_Lactobacillaceae (1); g_Lactobacillus (1); f_Veillonellaceae (1); g_Dialister (1)
Angiotensin-II-receptor antagonists (Sartan)	2.94	6.84		Yes (2)		
Antibiotics (previous month antibiotics)	1.16	6.45	0.45*	Yes (1, 2, 3, 4)	f_Bifidobacteriaceae (1); g_Bifidobacterium (1); s_Bifidobacterium_longum (1); s_Bifidobacterium_adolescentis (1); f_Prevotellaceae (3); f_Peptococcaceae (3); f_Odoribacteraceae (3); f_Clostridiaceae (3); f_Alcaligenaceae (3); f_Anaeroplasmataceae (3); g_unclassified_Lachnospiraceae (4)	f_Enterococcaceae (3); g_Bacteroides (4); g_Oscillibacter (4); g_unclassified_Ruminococcaceae (4)
Antihistamines (H1 inhibitor)	6.14	4.93		Yes (4)	f_Dehalobacteriaceae (3); f_Christensenellaceae (3)	s_Clostridium_bolteae (1)
Beta blockers	5.43	7.42		Yes (1 to 2)	0	f_Streptococcaceae (1); g_Streptococcus (1); s_Streptococcus_mutans (1); g_Rothia (1)
Calcium	1.25	15.7		Yes (1, 2)		f_Gemellaceae (3)
Laxatives	1.87	3.19		Yes (3, 2, 4)	g_Collinsella (1); s_Collinsella_aerofaciens (1); f_Lachnospiraceae (1); s_Ruminococcus_obeum (1); g_Coprococcus (1); s_Coprococcus_catus (1); s_Coprococcus_comes (1); g_Dorea (1); g_Faecalibacterium (4)	s_Bifidobacterium_pseudocatenulatum (1); g_Bacteroides (1); s_Bacteroides_stercoris (1); s_Bacteroidales_bacterium_ph8 (1); f_Enterobacteriaceae (1); g_Escherichia (1); g_unclassified_Rhodospirillaceae (4); g_Bacteroides (4); g_Oscillibacter (4); g_Barnesiella (4)
Metformin	1.33	2.9	0.9*	Yes (3, 2, 3)	s_Bacteroides_dorei (1); g_Coprococcus (1); s_Coprococcus_comes (1); g_Dorea (1); s_Dorea_longicatena (1); f_Clostridiaceae (3); f_Ruminococcaceae (3); f_Barnesiellaceae (3); f_Christensenellaceae (3)	f_Streptococcaceae (1); g_Streptococcus (1); f_Enterobacteriaceae (1,3); g_Escherichia (1); s_Escherichia_coli (1)
Opiates (opioid)	1.16	8.58		Yes (3)	f_Dehalobacteriaceae (3);	f_Streptococcaceae (3); f_Micrococcaceae (3); f_Lactobacillaceae (3); f_Eubacteriaceae (3)
Oral contraceptives	10.1	2.61		Yes (2 to 4)		g_Rothia (1)
Paracetamol	0.98	10.6	0.6*	Yes (3)	f_Lachnospiraceae (1); g_Dorea (1); f_Christensenellaceae (3); f_Dehalobacteriaceae (3); f_Oxalobacteraceae (3)	s_Bifidobacterium_dentium (1); s_Streptococcus_salivarius (1); f_Streptococcaceae (3); f_Peptostreptococcaceae (3); f_Eubacteriaceae (3); f_Micrococcaceae (3);
Platelet aggregation inhibitors (aspirin)	2.85	7.83		Yes (1 to 2)	f_Bifidobacteriaceae (1); g_Bifidobacterium (1); s_Bifidobacterium_adolescentis (1)	g_Rothia (1); s_Bifidobacterium_dentium (1); s_Bacteroides_ovatus (1); f_Streptococcaceae (1); g_Streptococcus (1); s_Streptococcus_mutans (1); s_Streptococcus_parasanguinis (1); s_Streptococcus_sanguinis (1); s_Clostridium_bolteae (1); g_Blautia (1); s_Lachnospiraceae_bacterium_3_1_57FAA_CT1 (1); s_Lachnospiraceae_bacterium_7_1_58FAA (1); f_Eubacteriaceae (3)
Proton pump inhibitors	8.27	18.7	8.7*	Yes (1, 2, 3, 4)	s_Eubacterium_hallii (1); s_Eubacterium_ventriosum (1); s_Coprococcus_catus (1); g_Dorea (1); s_Dorea_longicatena (1); f_Ruminococcaceae (1, 3); f_Alcaligenaceae (3); f_Peptococcaceae (3); f_Dehalobacteriaceae (3); f_Coriobacteriaceae (3)	f_Actinomycetaceae (1, 3); g_Actinomyces (1); s_Bifidobacterium_dentium (1); f_Lactobacillaceae (1, 3); g_Lactobacillus (1); f_Streptococcaceae (1, 3); g_Streptococcus (1); s_Streptococcus_anginosus (1); s_Streptococcus_mutans (1); s_Streptococcus_parasanguinis (1); s_Streptococcus_sanguinis (1); s_Streptococcus_salivarius (1); s_Clostridium_bolteae (1); g_Erysipelotrichaceae_noname (1); g_Veillonella (1); s_Veillonella_parvula (1); s_Veillonella_unclassified (1); f_Pasteurellaceae (1, 3); g_Haemophilus (1); s_Haemophilus_parainfluenzae (1); f_Micrococcaceae (3); f_Gemellaceae (3); f_Enterococcaceae (3); f_Fusobacteriaceae (3); f_Enterobacteriaceae (3)
SSRI antidepressants	2.49	6.55		Yes (1, 2, 3)	f_Turicibacteraceae (3); f_Clostridiaceae (3); f_Bifidobacteriaceae (3); f_Peptostreptococcaceae (3); f_Paraprevotellaceae (3); f_Coriobacteriaceae (3)	
Statins	4.89	25.7		Yes (1, 2, 3)	s_Methanobrevibacter_unclassified (1); g_Coprococcus (1); s_Coprococcus_comes (1); g_Dorea (1); s_Dorea_longicatena (1); f_Peptostreptococcaceae (1); g_Peptostreptococcaceae_noname (1); s_Peptostreptococcaceae_noname_unclassified (1); s_Faecalibacterium_prausnitzii (1)	g_Rothia (1); f_Streptococcaceae (1); g_Streptococcus (1); s_Clostridium_bolteae (1); g_Blautia (1); s_Lachnospiraceae_bacterium_2_1_58FAA (1); s_Lachnospiraceae_bacterium_3_1_57FAA_CT1 (1); s_Coprobacillus_unclassified (1)
Tricyclic antidepressants	0.89	3.77		Yes (1 to 2)	f_Bifidobacteriaceae (1); g_Bifidobacterium (1); f_Streptococcaceae (3); f_Enterobacteriaceae (3); f_Lactobacillaceae (3)	
Vitamin D (cholecalciferol)	1.25	16.5		Yes (1 to 2)		s_Streptococcus_salivarius (1)

- Microbial associations to 19 out of 42 commonly used drugs → antibiotics but alos many non-antibiotic drugs
- The top microbiome-associated drugs included PPIs, lipid-lowering statins, laxatives, metformin, beta-blockers, ACE inhibitors and SSRIs
- Similar associations also observed in a Belgium Flemish cohort15 and in the TwinsUK cohort

Weersema R *et al.* 2020

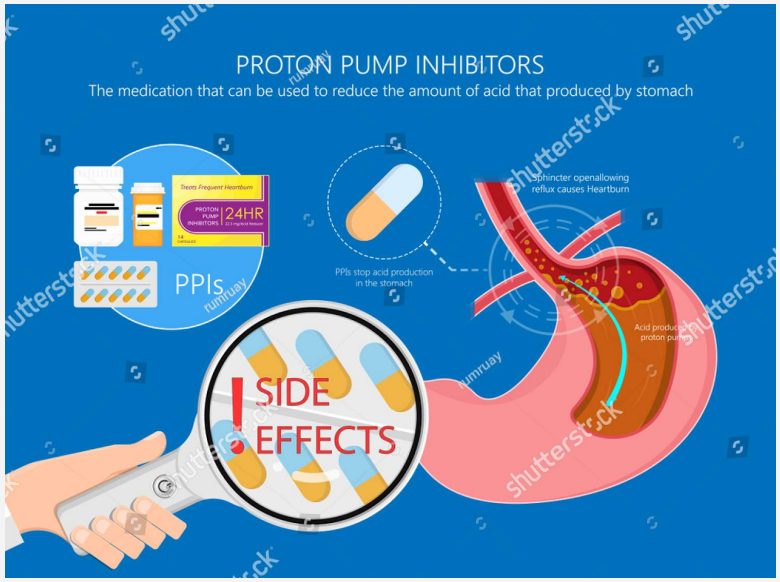
Effects of common drugs on microbiota



- Drug-microbe associations were mostly assessed for individual drugs → patients often take multiple drugs
- Meta-analysis with three independent cohorts found19 of the 41 medication categories studied associated with microbiota.
- After statistically correcting for polypharmacy, PPIs, metformin, antibiotics and laxatives still showed the strongest associations with the microbiota

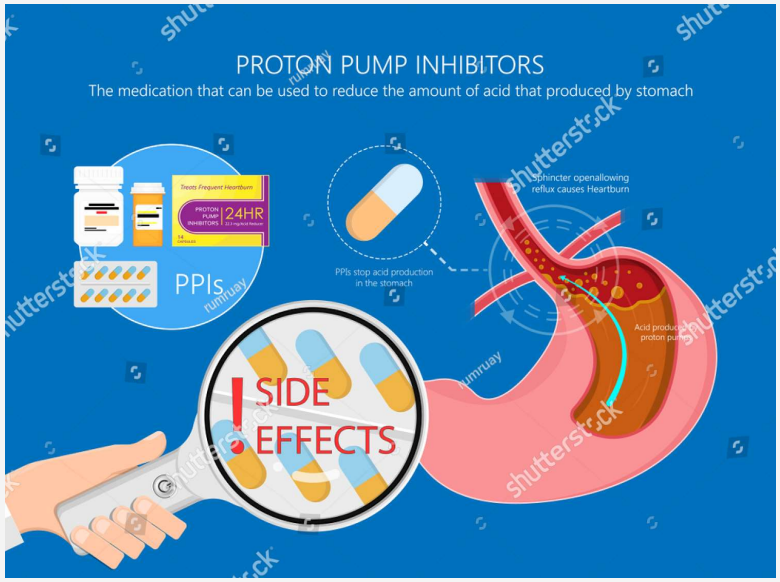
(Vila A, et al 2020)

PPIs – microbiota



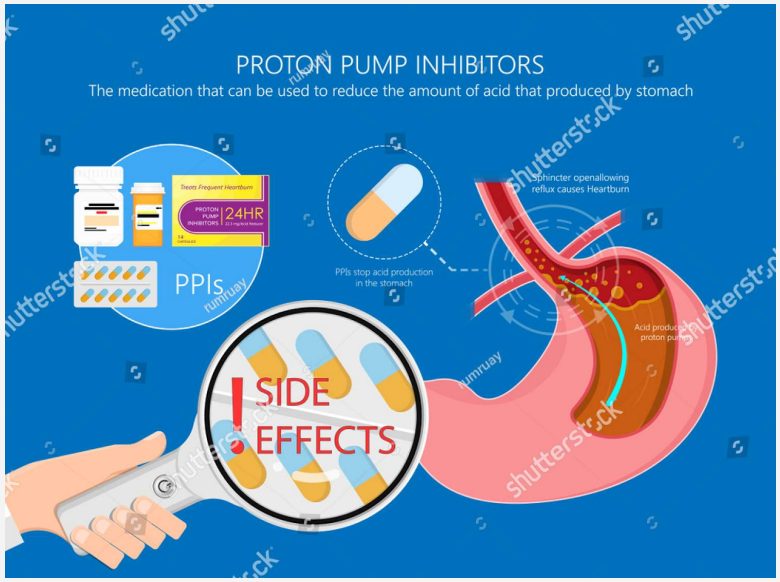
- 2 million people in NL (~12%) use PPIs b prescription → up to 70% may be unnecessary
- PPIs were the drugs most associated to a decreased diversity and taxonomical changes in the gut microbiome → ↓commensal bacteria of the intestine and ↑ bacteria from the oral cavity
- PPIs were significantly associated with 24 taxa and 133 pathways (Vila A, et al 2020)

PPIs – microbiota



- Reduction of gastric acidity thought to be responsible for observed microbial changes
- Possible direct effect – in vitro study showed marked changes in bacterial growth rates by PPIs → effect potentially mediated through binding of PPIs to bacterial H+/K+ATP ases (Maier L, et al. 2018)

PPIs – microbiota



PPI-induced changes in the microbiota might be contributing to clinically important diseases.

- Change microbiota lead to reduced colonisation resistance → ↑ enteric infections *(Leonard J, et al. 2007)*
- PPI initiation and withdrawal influences clinical course in decompensated liver cirrhosis, potentially through changes in the gut microbiota (Bajaj JS, et al. 2018)
- PPIs use in early childhood may induce long-term changes in developing microbiota (health consequences) (Stark CM, et al. 2019)

Metformin – microbiota

- Observed changes in the gut microbiome thought to be driven by the underlying T2D were actually caused by the use of metformin (Forslund K, et al. 2015)
- HV study: use of metformin resulted in a change in >80 species compared a control group receiving placebo

→ ↑ *Escherichia coli* and ↓ *Intestinibacter* abundance → in line with findings from untreated compared to metformin-treated patients with T2D

Metformin – microbiota

- Faecal samples from metformin-treated or placebo-treated donors into germ-free mice and observed lower blood glucose levels in the mice that received faecal samples from metformin-treated volunteers→ a direct effect of the gut microbiome on blood glucose levels (Wu H, et al. 2016)
- Effect is thought to be mediated by metformin's effect on short-chain fatty acid (butyrate)-producing bacteria and the abundance of *Akkermansia muciniphila*

Metformin – microbiota

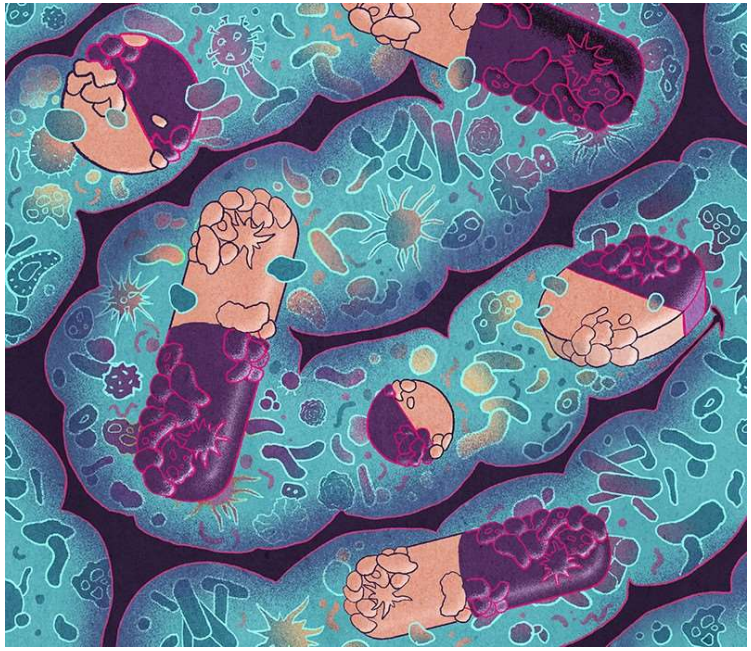
- Clinically well known that up to one-third of metformin patients report GI side effects like diarrhoea, bloating and nausea→ the identified metformin-induced changes, including the increase of virulence factors and gas metabolism genes (mainly derived from an increase of *E. coli* species), can contribute to these side effects

- Microbiota changes explain part of the drug's therapeutic function as well as some of its side effects

Psychofarmaca

- Veel subklassen van antipsychotica en antidepressiva hebben een antibacterieel effect
- Het effect op de microbiota is echter heel specifiek
- Effect op microbiota kan worden beschouwd als een bijwerking, maar mogelijk ook als een werkingsmechnisme (effect deel juist door effect op microbioom)

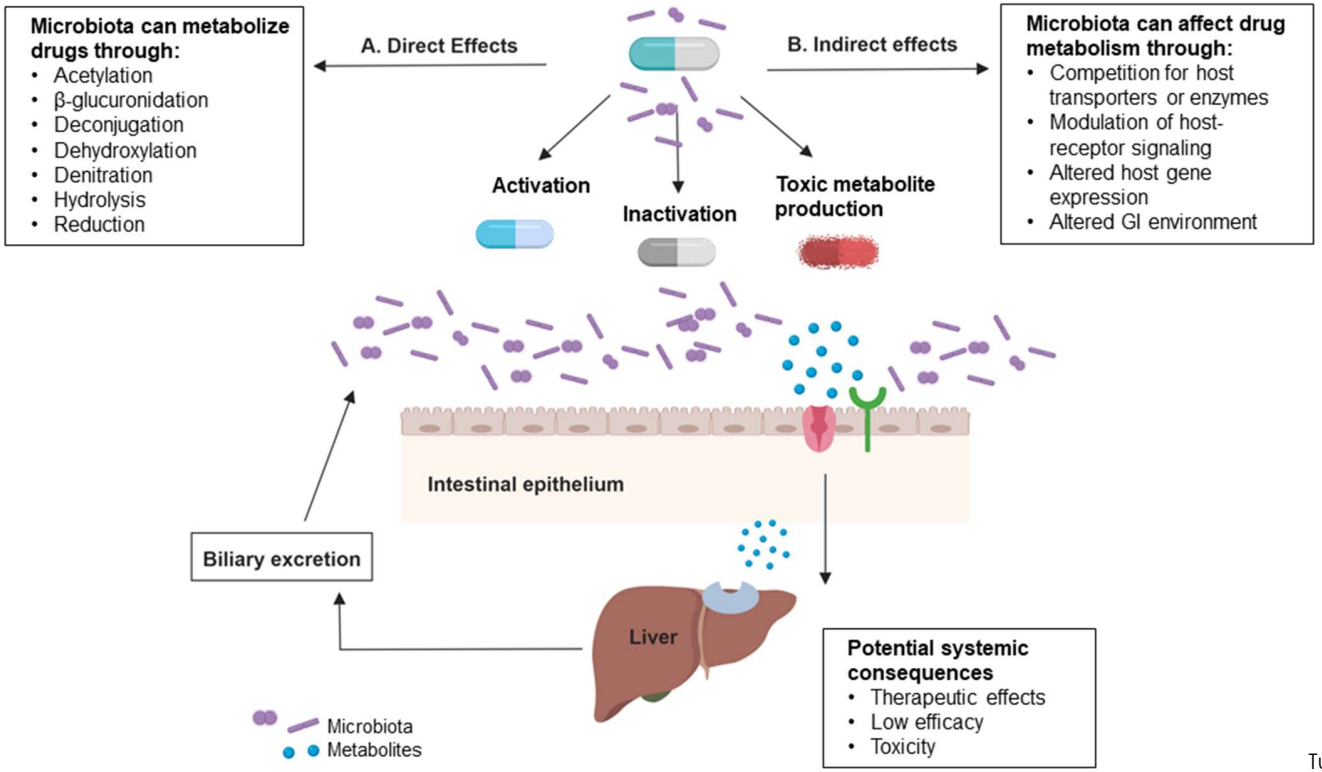
Drug-microbiota interaction bi-directional



Interactie is complex en tweerichtings-verkeer

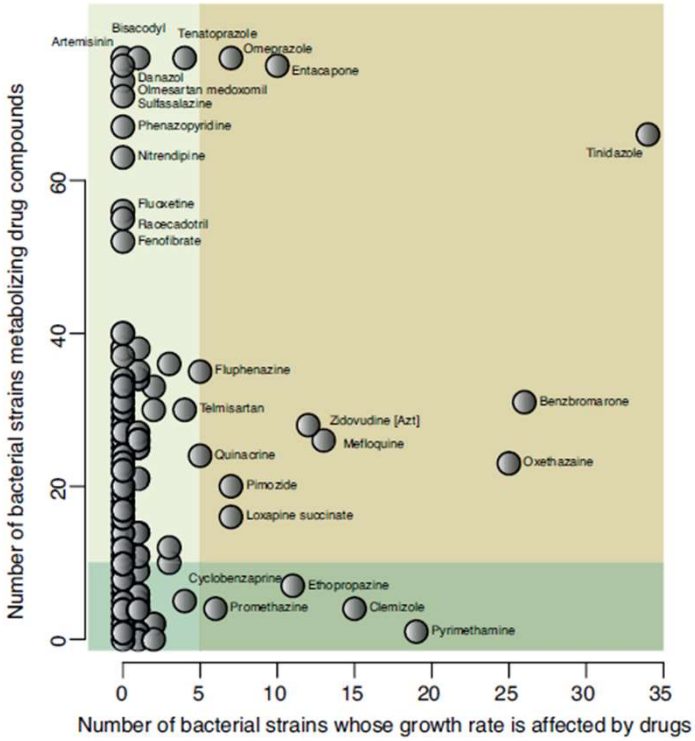
- De samenstelling van het darmmicrobioom kan worden beïnvloed door medicijnen
- Het darmmicrobioom beinvloedt de reactie van een individu op een medicijn (farmacomicrobiomics).

Microbiota and drug response



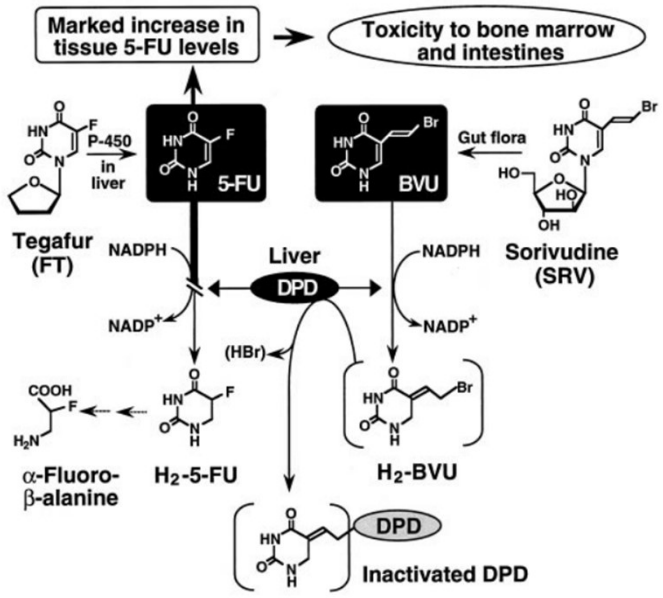
Tuteja S *et al.* 2019

Bi-directtional effects of commonly used drugs



Weersema R *et al.* 2020

Microbiota – drug/drug interaction

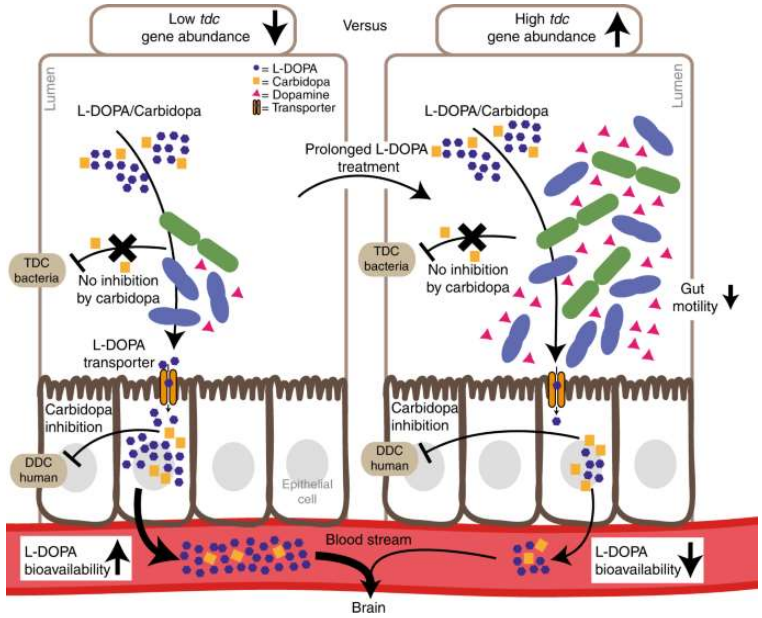


- Sorivudine (antiviral drug) turned deadly in 18 cancer patients (mid '90) due to interactions between sorivudine and oral 5-fluorouracil (5-FU)
- Sorivudine's metabolite (BVU) inactivated the liver enzyme (DPD) needed to metabolize 5-FU → ↑in 5-FU tissue levels led to toxcicity (Okuda et al.1998)

- BVU is generated from sorivudine by gut microbiota, especially *Bacteroides* species, which are abundantly present in GI tract

(Nakayama et al. 1997)

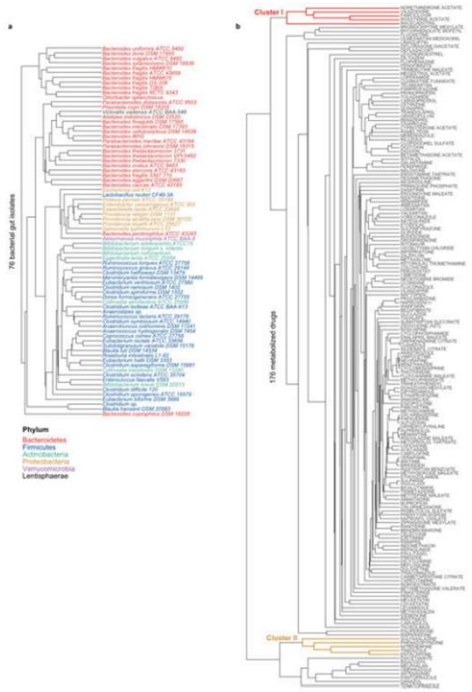
Levodopa – microbiota



- Particular bacteria from the gut microbiota (*E. faecalis*) metabolize Levodopa (L-dopa), reducing bioavailability of the drug for treating Parkinson's disease

van Kessel S, et al. 2019

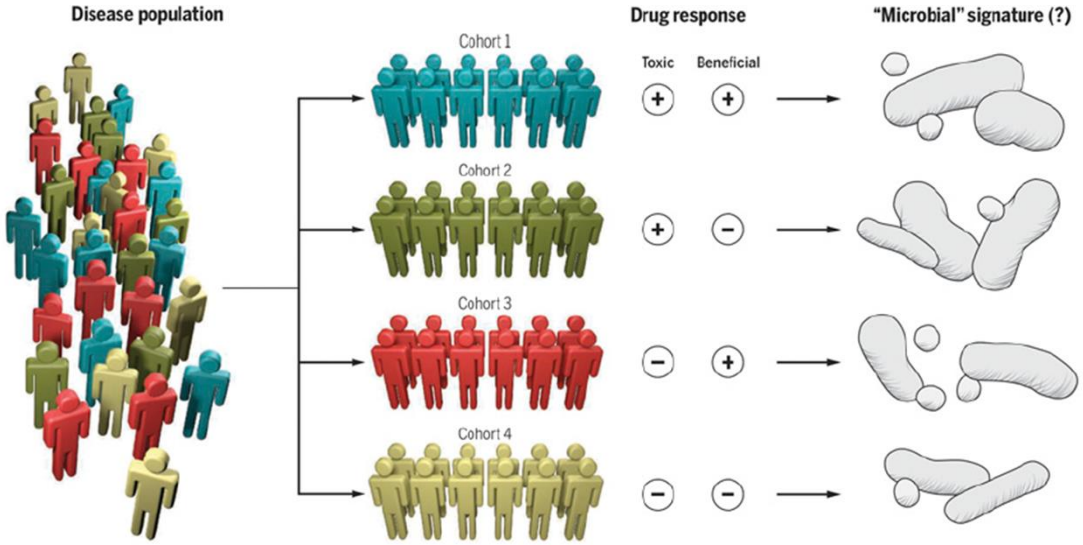
Microbiota – drug interaction

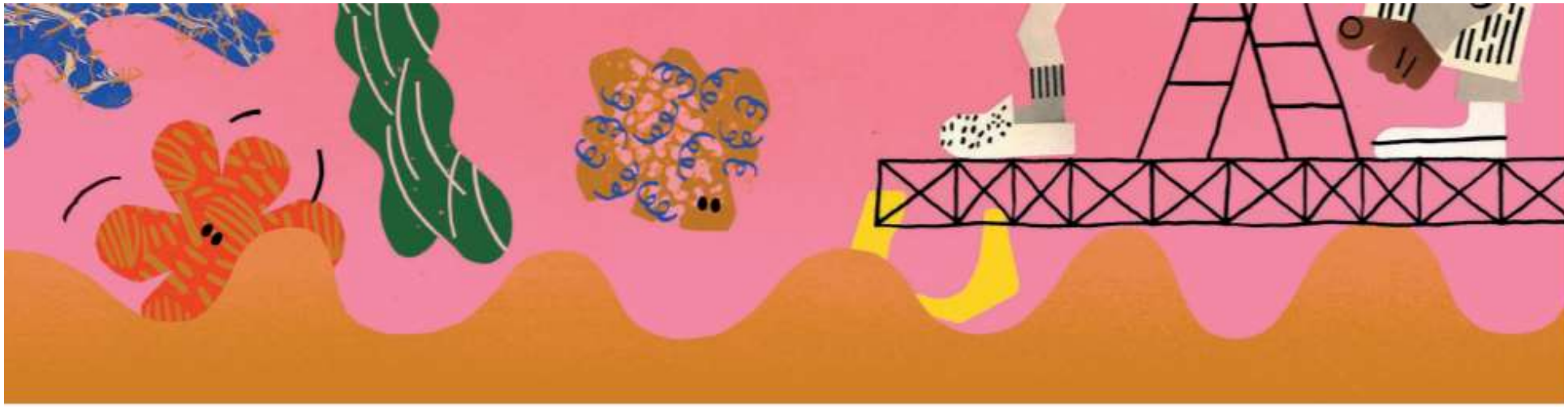


- The ability of 76 diverse human gut bacteria to metabolize 271oral drugs was measured
- Two thirds (176) of drugs are significantly reduced (>20) by at least one bacterial strain
- each strain can metabolizes 11–95 different drugs
- The capacity of microbes to metabolize drugs was much broader than expected → difficult to predict precisely which medications would be metabolized

Zimmerman M *et al.* 2019

Farmacomicrobiomics





GUT MICROBES JOIN THE FIGHT AGAINST CANCER

The intestinal microbiome seems to influence how well some cancer drugs work. But is the science ripe for clinical trials?

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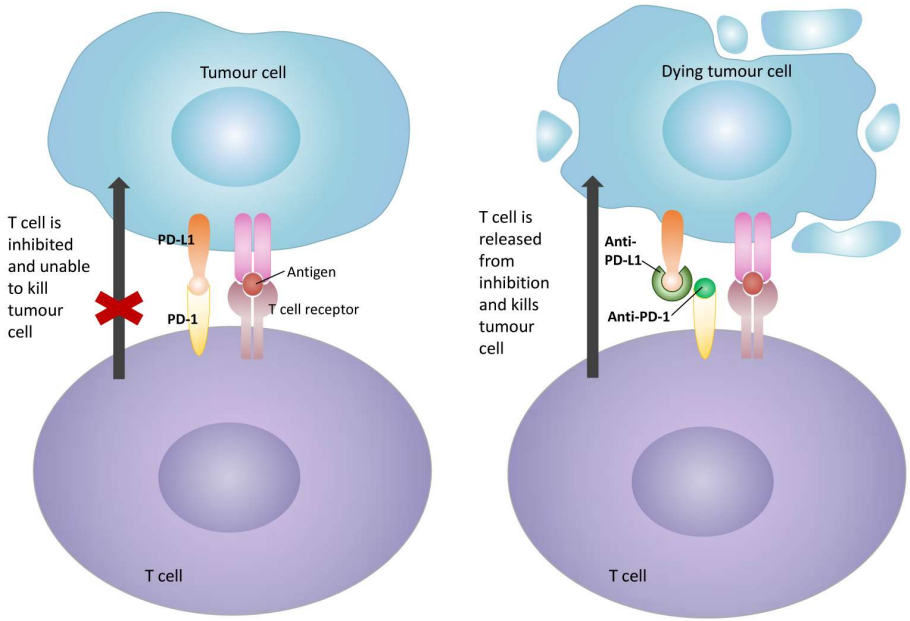
Immuuntherapie



Credit: Dr Koh Shimin Grace, Department of Paediatrics, NUS

Het microbioom en immuuntherapie bij kanker

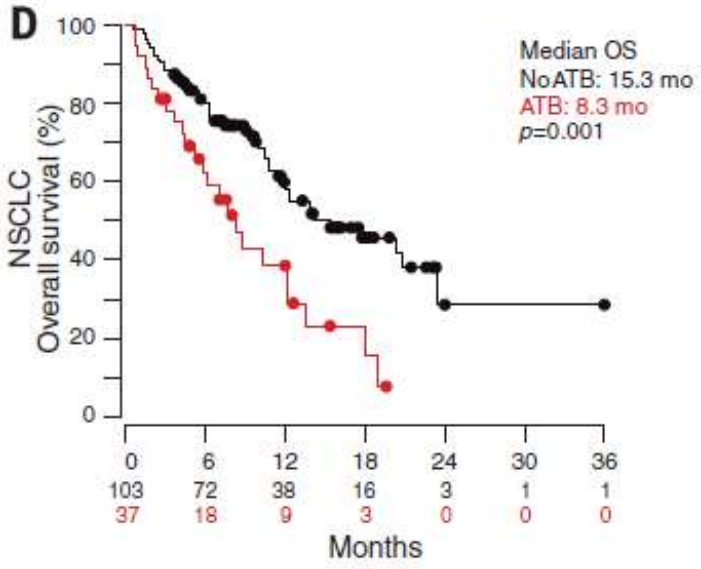
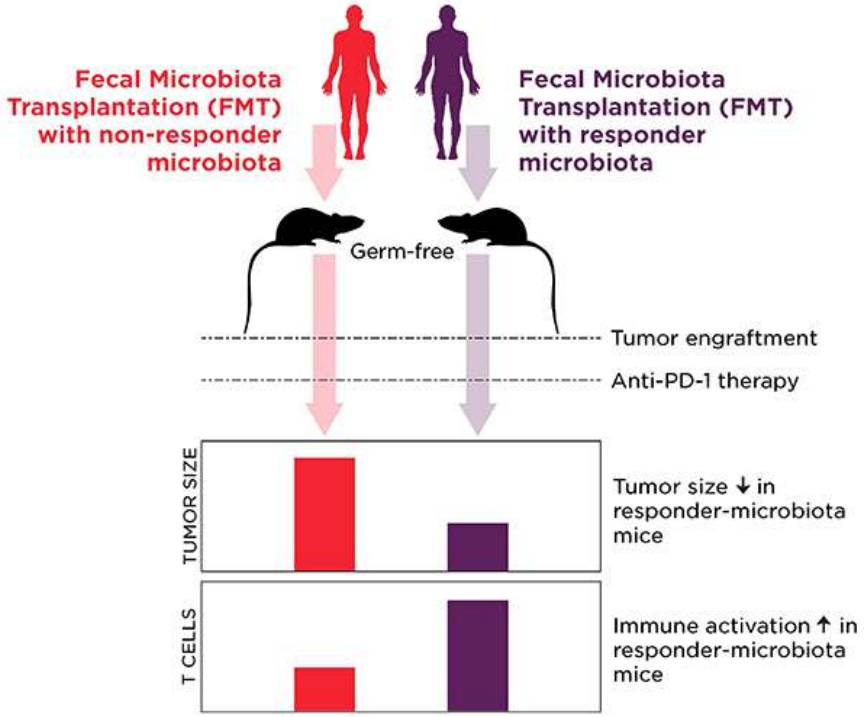


Fig. 1. Antibiotics compromise the efficacy of PD-1 blockade in mouse tumor models and cancer patients. (**A**) Tumor growth kinetics of RET melanoma (left) and MCA-205 sarcoma in m

Routy *et al.*, *Science* **359**, 91–97 (2018) 5 January 2018

Het microbioom en immuuntherapie bij kanker



Routy et al, 2017

GUT MICROBIOME IN CANCER IMMUNOTHERAPY

The gut microbial composition of cancer patients is linked to a lack of response for a certain type of immunotherapy. Antibiotics are key players in this resistance.

ABUNDANCE OF *AKKERMANSIA MUCINIPHILA* IS INDICATIVE OF TREATMENT SUCCESS.

69% of responders

58% of stable patients

34% of non-responders

Specific types of bacteria are linked to the beneficial effects of tumor therapies. For instance, responders to immunotherapy reported higher levels of *Akkermansia muciniphila*.

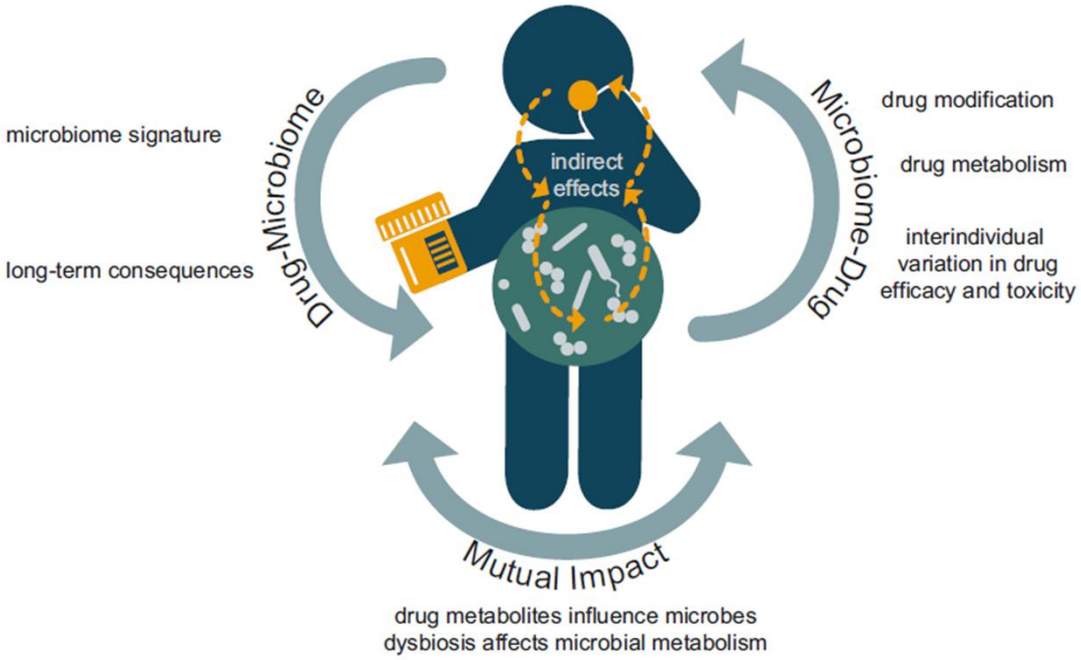
Transferring **"good"** bacteria from immunotherapy responders to mice with tumors, transfers treatment success too.

Antibiotics

No Antibiotics

Antibiotic treatment before or after immunotherapy leads to resistance to treatment

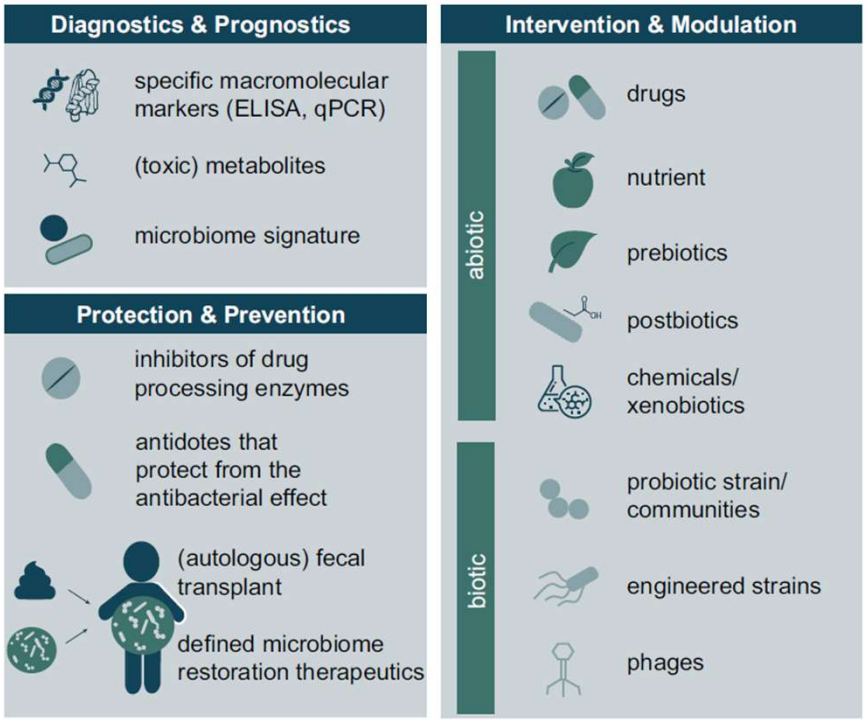
Drug-microbiome-host interaction: a complex interplay



Zimmerman M *et al.* 2021

Beperk medicatiegebruik

Possible applications



Zimmerman M *et al.* 2021

Voeding

Yoghurt en koffie blijken goed voor de spijsvertering

AREND VAN WIJNGAARDEN

GRONINGEN Onze voeding heeft een nog grotere invloed op onze darmbacteriën en dus onze gezondheid dan al bekend was.

Zo hebben mensen die veel yoghurt, karnemelk, koffie of wijn gebruiken een gezondere spijsvertering dan mensen die calorierijk eten en volle melk drinken. Dit blijkt uit een grootschalig onderzoek dat is uitgevoerd onder leiding van professor Cisca Wijmenga, geneticus aan het UMCG. De resultaten zijn vandaag gepubliceerd in het wetenschappelijke tijdschrift *Science*.

Voor het onderzoek is ontlasting verzameld bij meer dan 1100 personen uit het LifeLines programma, waarin de gezondheid van 165.000 inwoners van Noord-Nederland wordt gevolgd. Het DNA van de bacteriën en andere micro-organismen in de darm is vervolgens geanalyseerd. Naast ontlasting is ook informatie verzameld over dieet, medicijngebruik en gezondheid.

Bijzonder aan deze studie is dat een groep gewone mensen is onderzocht. Eerder onderzoek richtte zich vaak op patiënten met een specifieke ziekte. Daarnaast is de omvang van de groep uitzonderlijk groot, en is het DNA in detail bestudeerd:

Cisca Wijmenga

„Normaal gesproken kijken onderzoekers maar naar één bepaald stukje DNA waarmee verschillende groepen bacteriën min of meer te onderscheiden zijn", legt Wijmenga uit. „Wij hebben het complete DNA in kaart gebracht, wat meer gedetailleerde informatie over bacterietypen oplevert."

Hierdoor was het mogelijk te zoeken naar factoren die de samenstelling van de darmflora veranderen. Dat bleken er zeer veel te zijn. Wijmenga: „Je ziet bijvoorbeeld het effect van voeding terug in de darm." Naast voeding hebben ook minstens 19 verschillende soorten medicijnen invloed op die diversiteit.

Eerder publiceerden Groningse onderzoekers al dat maagzuurremmers de diversiteit doen afnemen. Maar bijvoorbeeld ook antibiotica en het middel metformine, dat suikerpatiënten gebruiken, hebben effect.

Dit zijn belangrijke constateringen, benadrukt Wijmenga: „Ziekten ontstaan vaak door een veelheid aan factoren. De meeste factoren, zoals je genen of je leeftijd, kun je niet beïnvloeden. Maar het is dus wel mogelijk de samenstelling van je darmbacteriën te wijzigen via voeding of geneesmiddelen. Wanneer we goed begrijpen hoe dat kan, biedt dat grote mogelijkheden."

Microbiota management

Gezonde microbiota

Stress (maagdarm) infectie Antibiotica

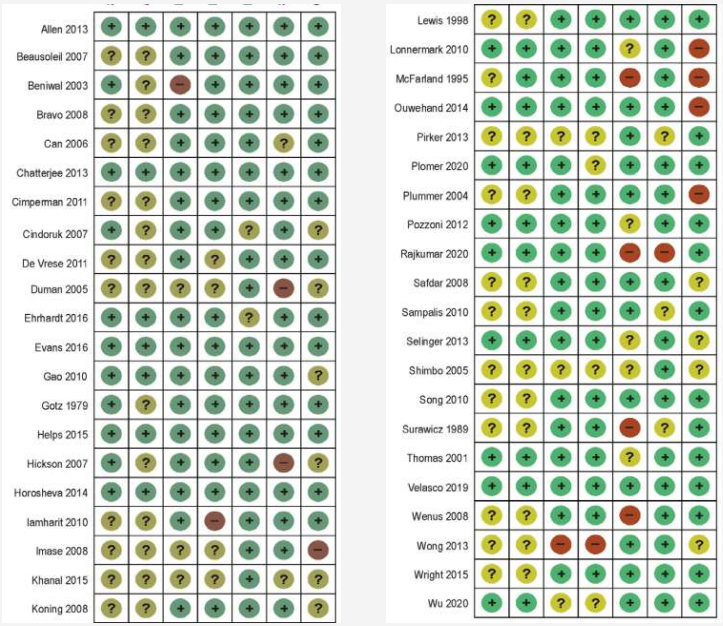
Dysbiose

Prebiotica

Probiotica

Feces transplantatie

Probiotics and AAD – evidence from literature



42 studies, N= 11305

37% reduction in the risk of AAD in children (RR 0.63, 95% CI 0.54 to 0.73)

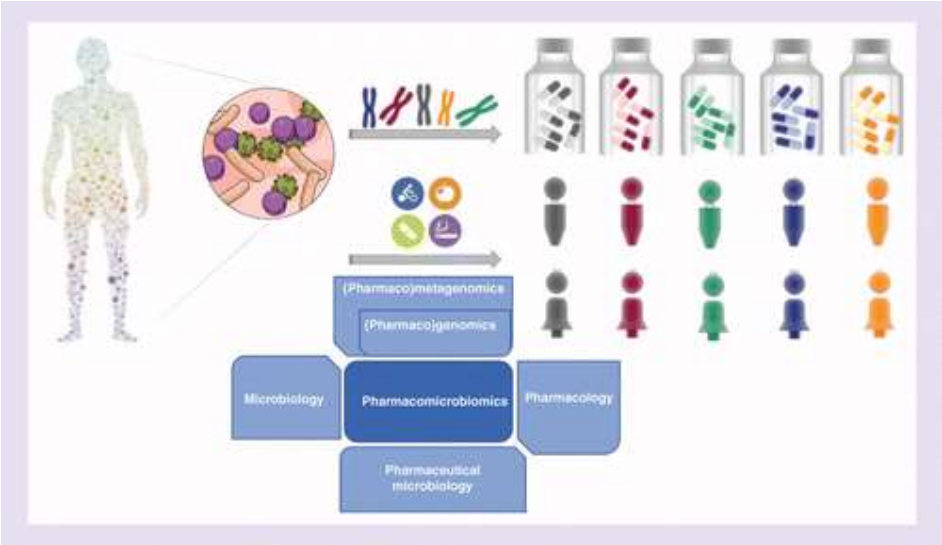
Goodman C, *et al.* 2021

Targeting microbiota

- The dose-limiting side effect of the common colon cancer chemotherapeutic CPT-11 is severe diarrhea caused by symbiotic bacterial β-glucuronidases that reactivate the drug in the gut
- A molecule they named SBX-1 was able to inhibit these microbial enzymes in living aerobic and anaerobic bacteria
- Oral administration of SBX-1 protected mice from CPT-11–induced toxicity.

The microbiota contains druggable targets which could be targeted to improve clinical outcome

Zimmerman B *et al.* 2010



To improve an individuals drug response

- Pharmacogenomics
- Pharmacomicrobiomics

Difficult to alter a persons genome → opportunity to alter a person's microbiome

Bedankt voor jullie aandacht!