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Darmmicrobiota: Een centrale rol in gezondheid en ziekte?

Working on a healthy society

Dr. Olaf Larsen

Conflicts of interest

- Asst. Professor @ Athena Institute, Vrije Universiteit Amsterdam (0.2 FTE)
- Senior Manager Science @ Yakult Nederland B.V.

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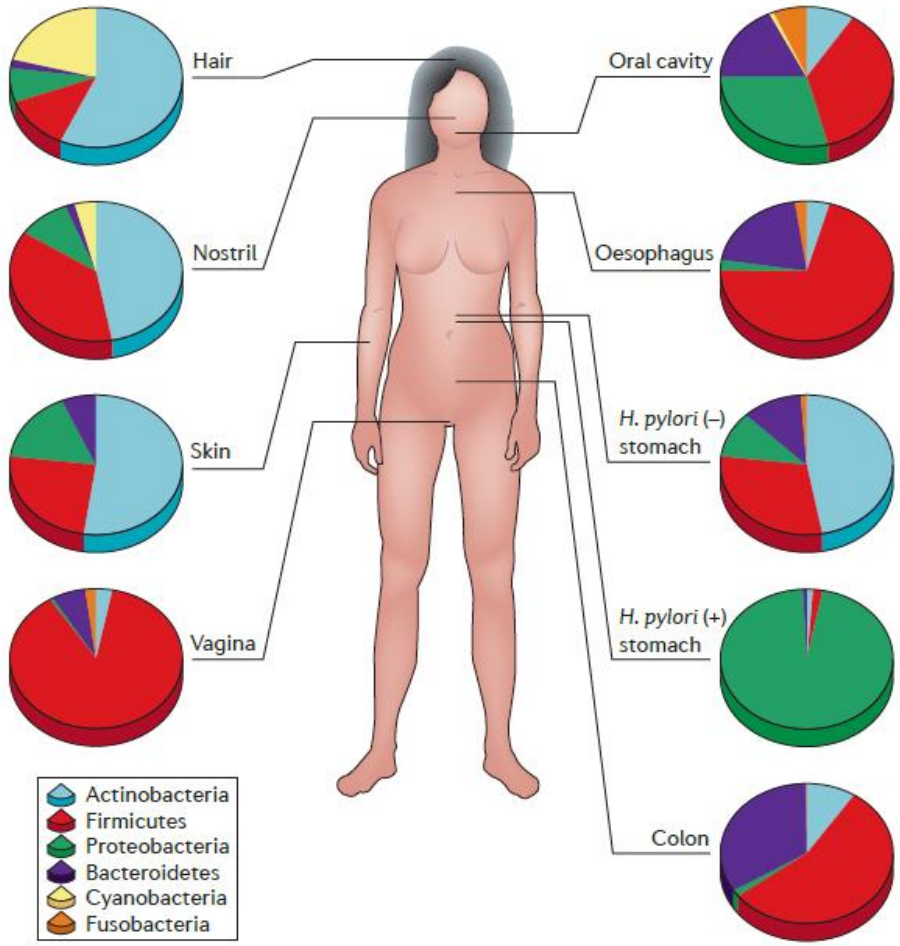
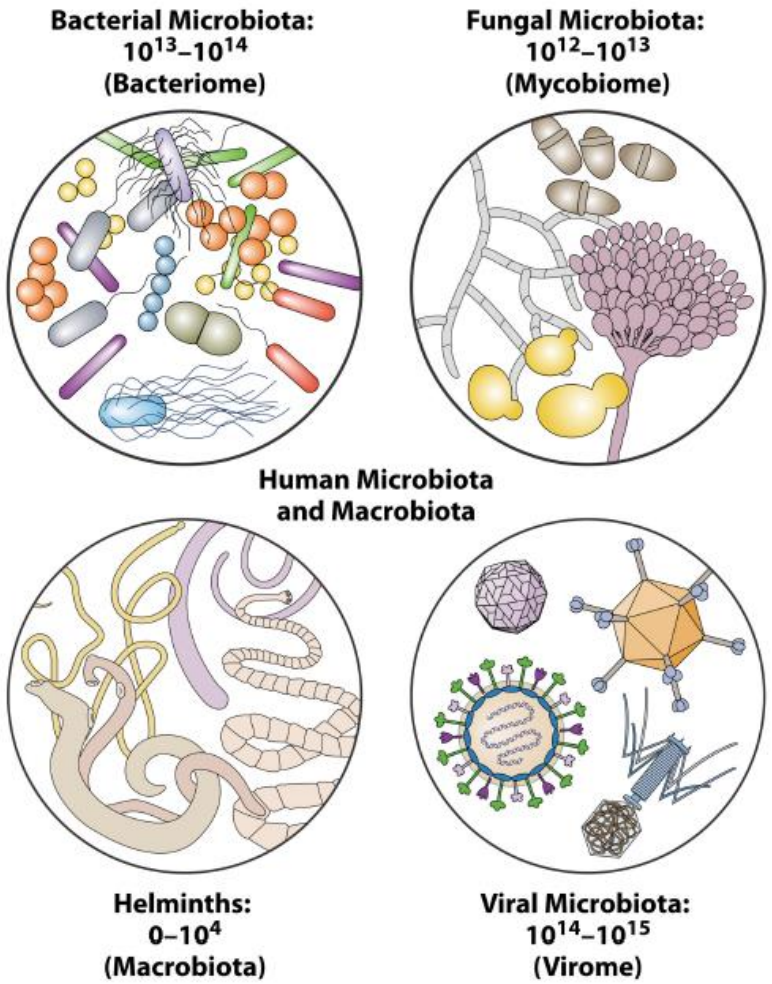
De humane microbiota





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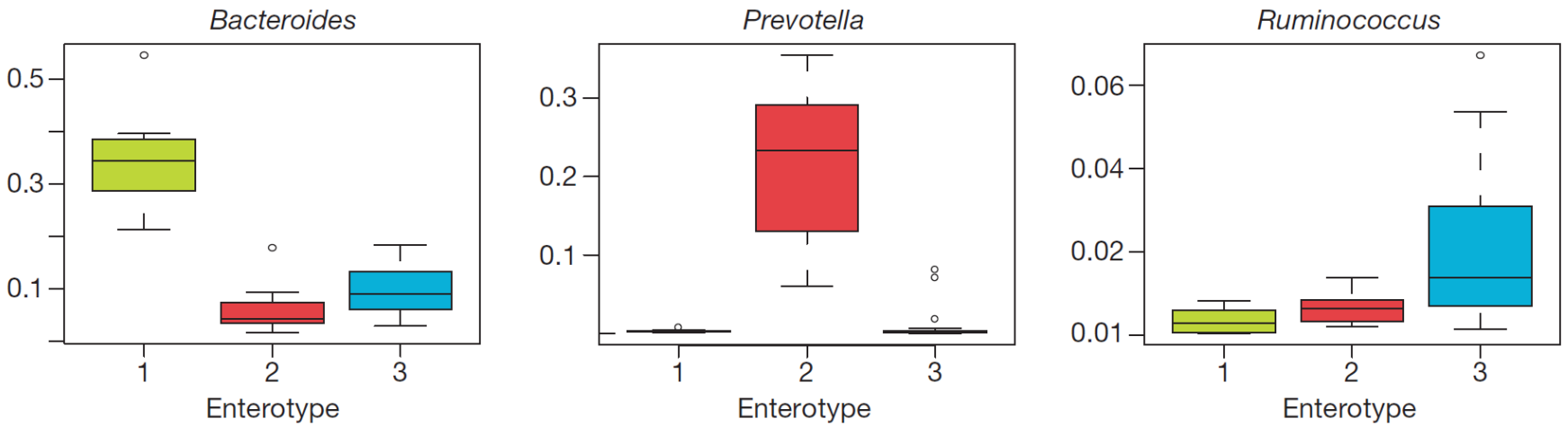
De humane darm-microbiota



Arumugam, et al. (2011). Nature, 473(7346), 174-180.

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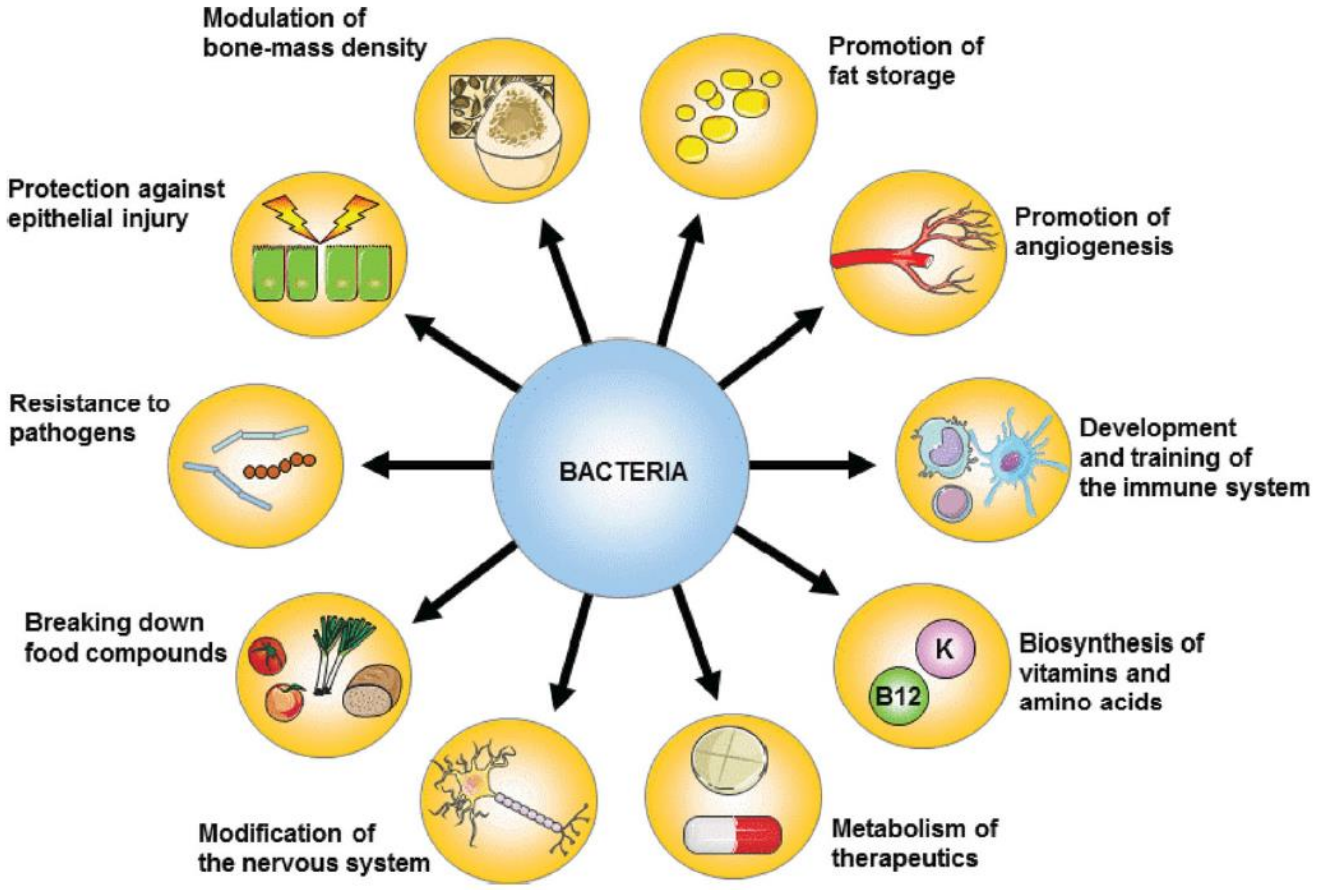
Functionaliteiten darm-microbiota



Laukens et al, FEMS Microbiology Reviews, 2016, Vol. 40, No. 1

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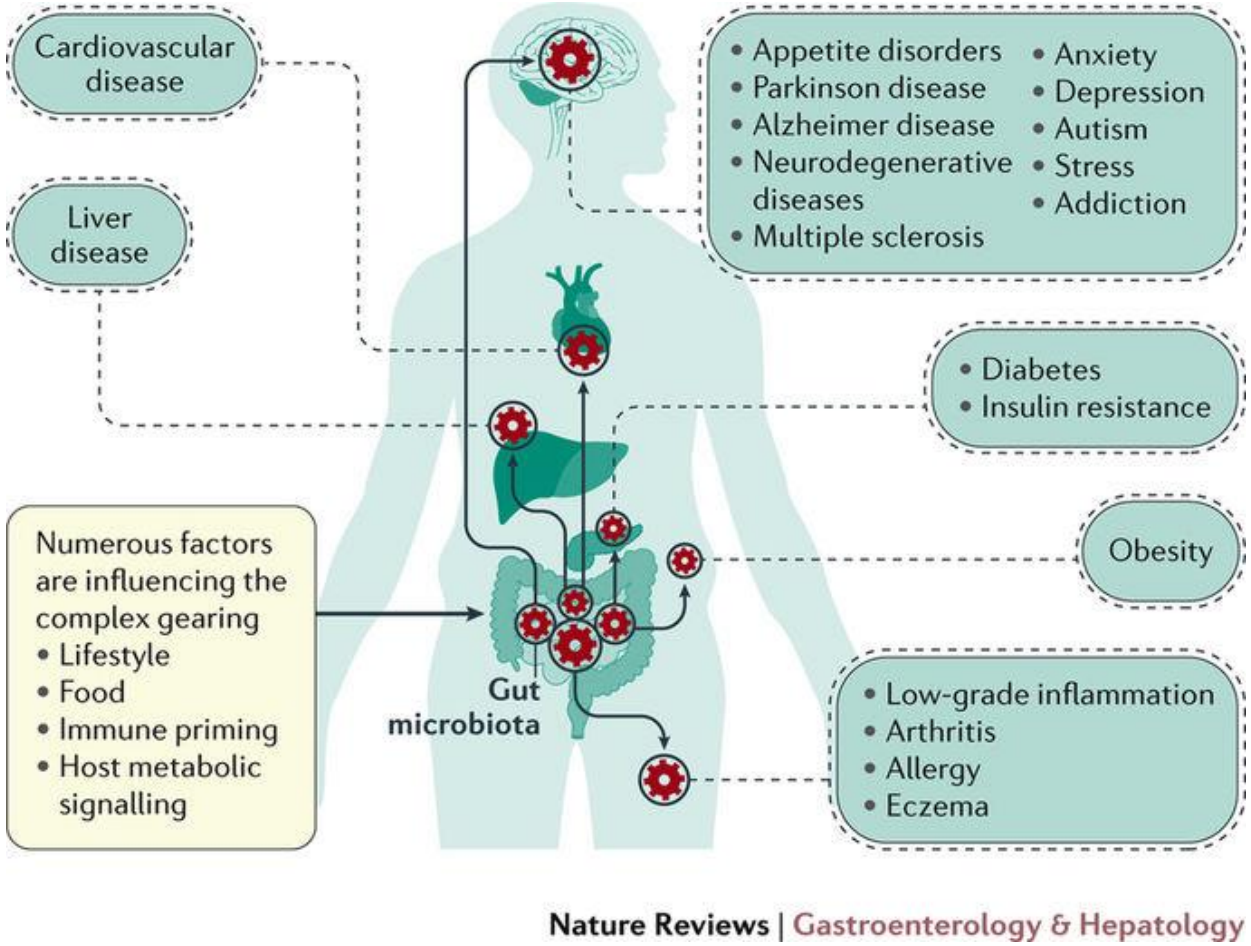
Op het snijvlak van alles?



Cani, Nature Reviews Gastroenterology & Hepatology, 14, 321-322,2017

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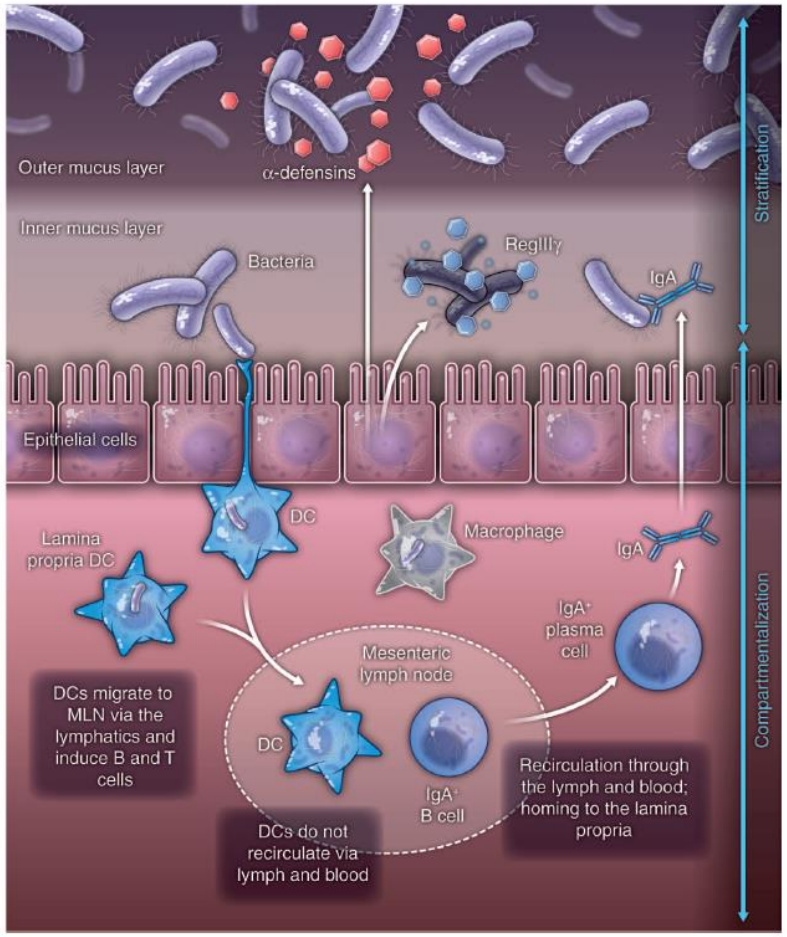
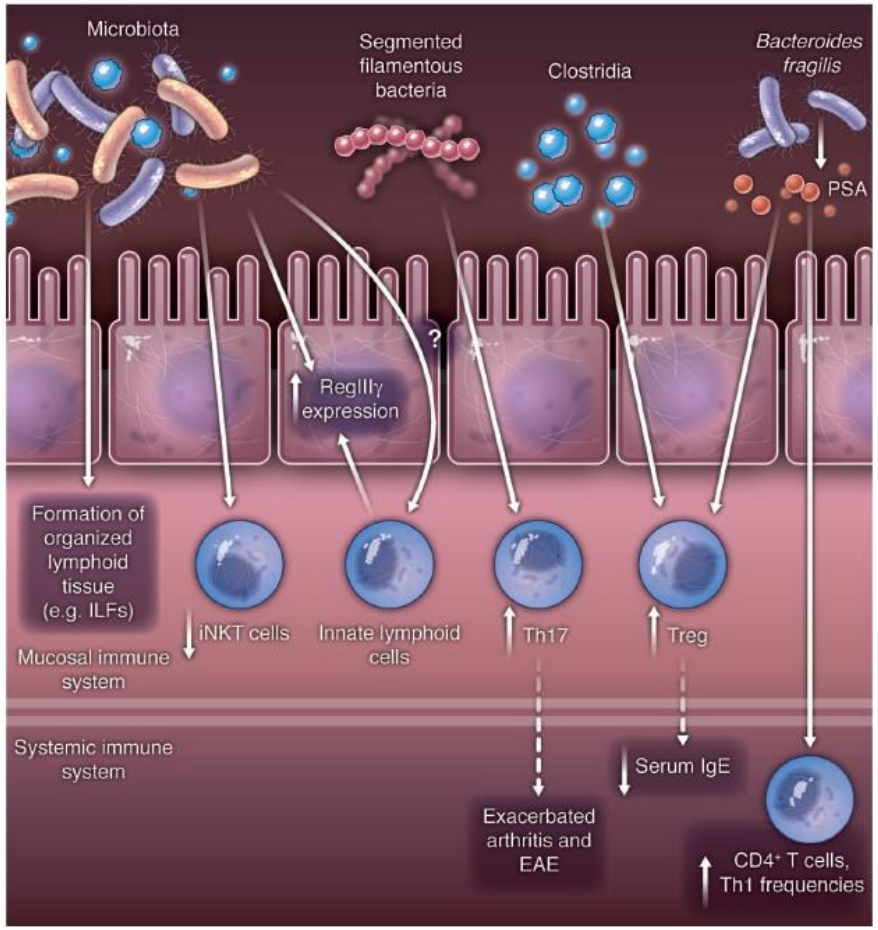
In mijn praktijk denk ik bij de diagnose van patiënten ook aan de darmmicrobiota

De darmmicrobiota: immunologische functies (1)





Hooper et al. (2012). Science, 336(6086), 1268-1273.

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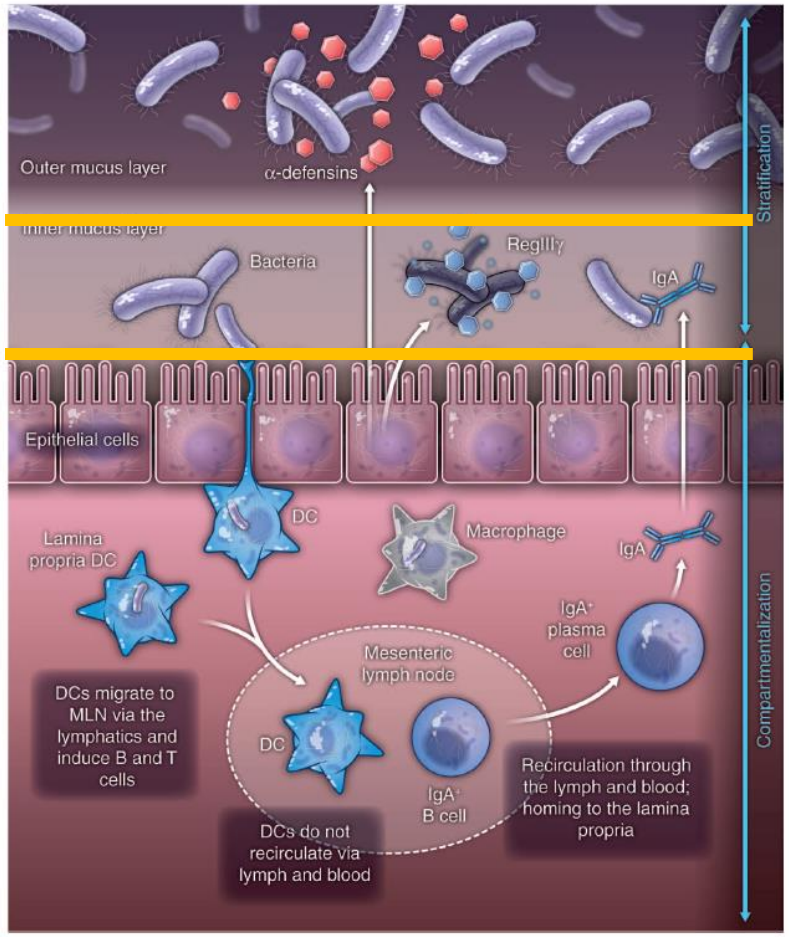
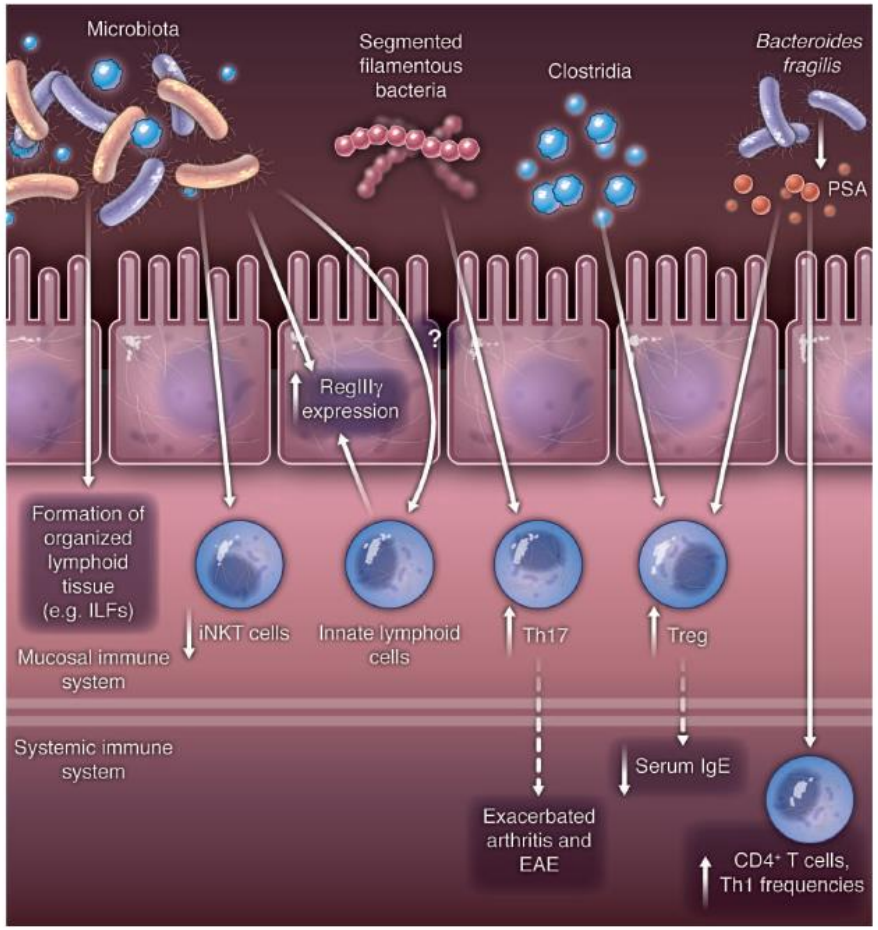
De darmmicrobiota: immunologische functies (2)





Hooper et al. (2012). Science, 336(6086), 1268-1273.

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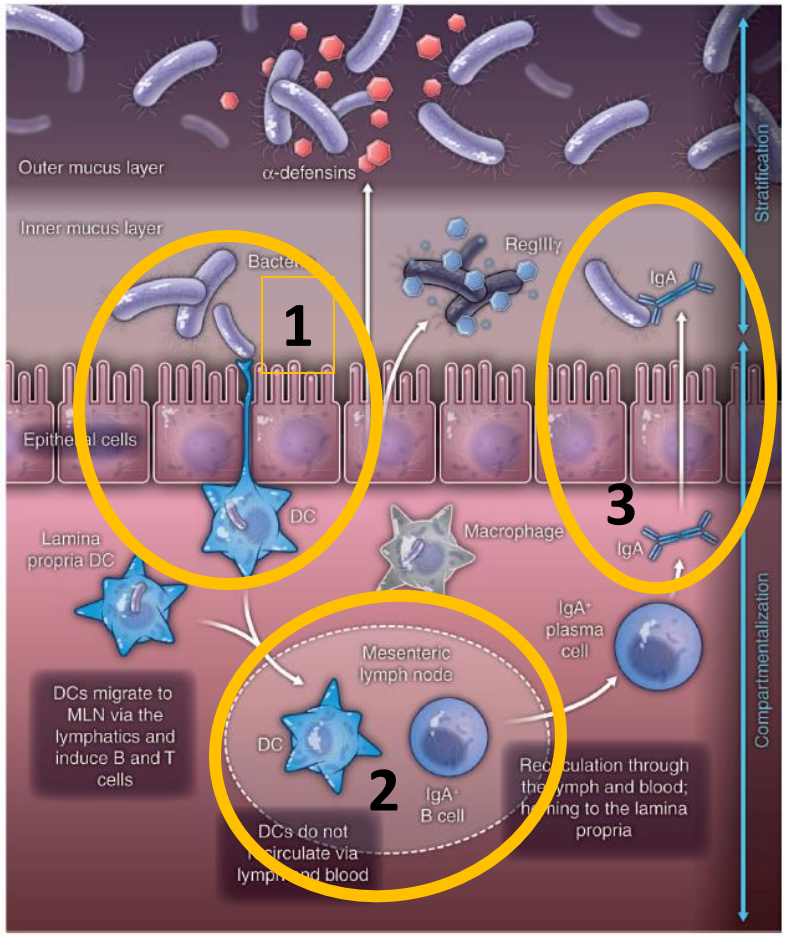
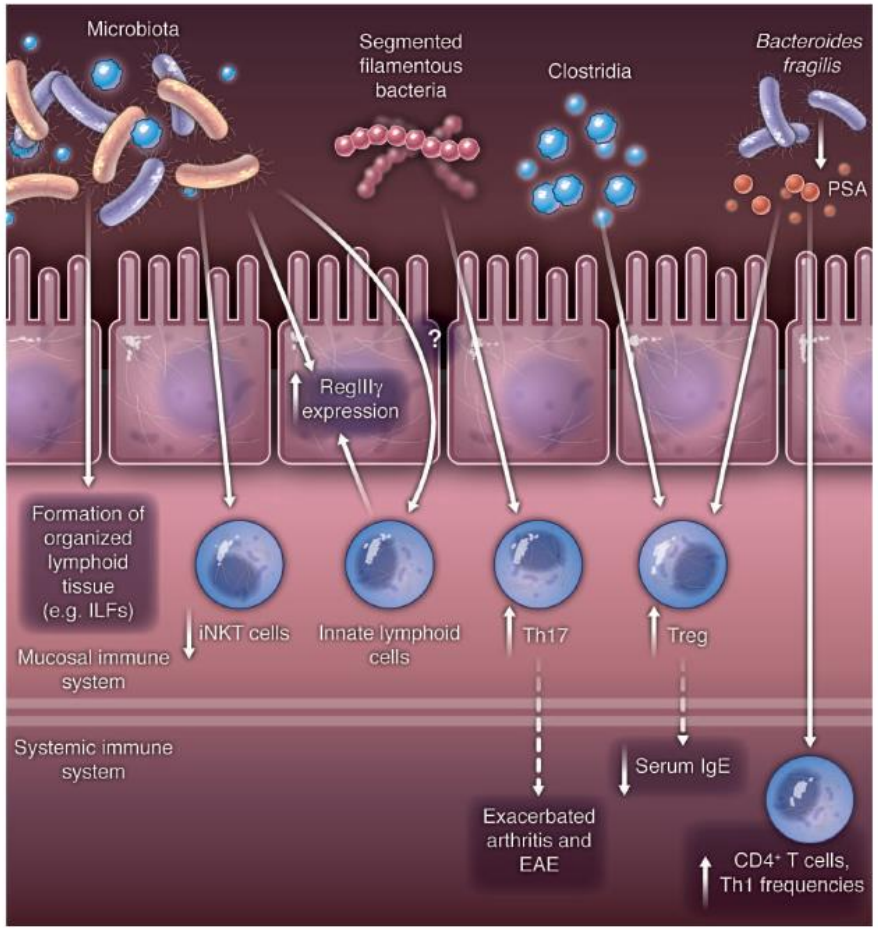
De darmmicrobiota: immunologische functies (3)





Hooper et al. (2012). Science, 336(6086), 1268-1273.

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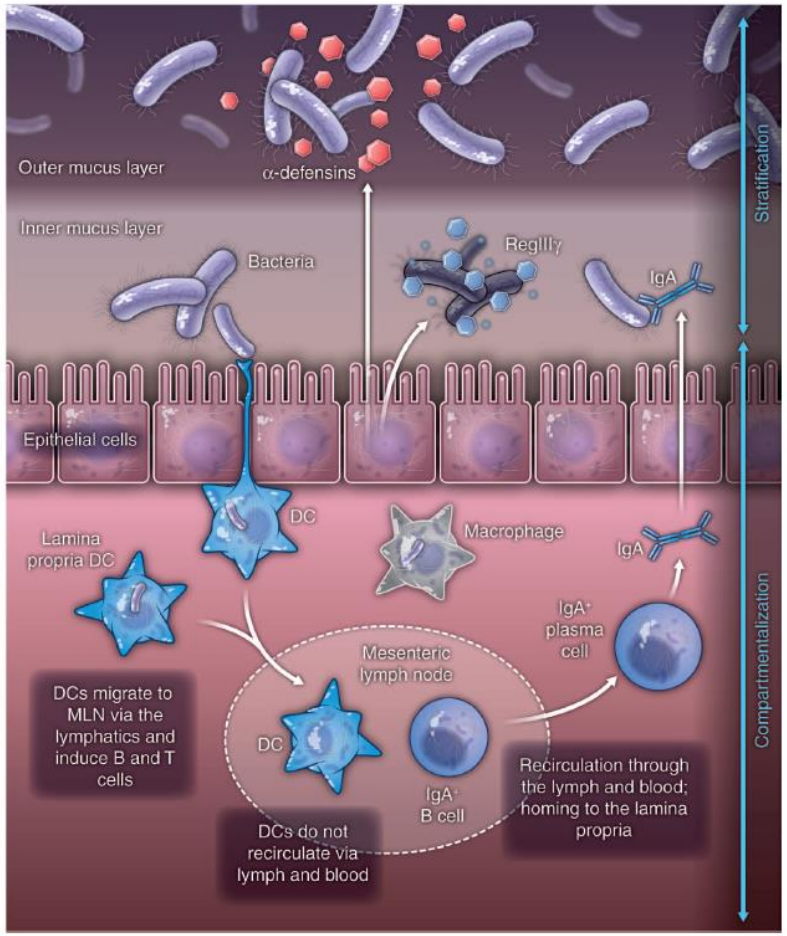
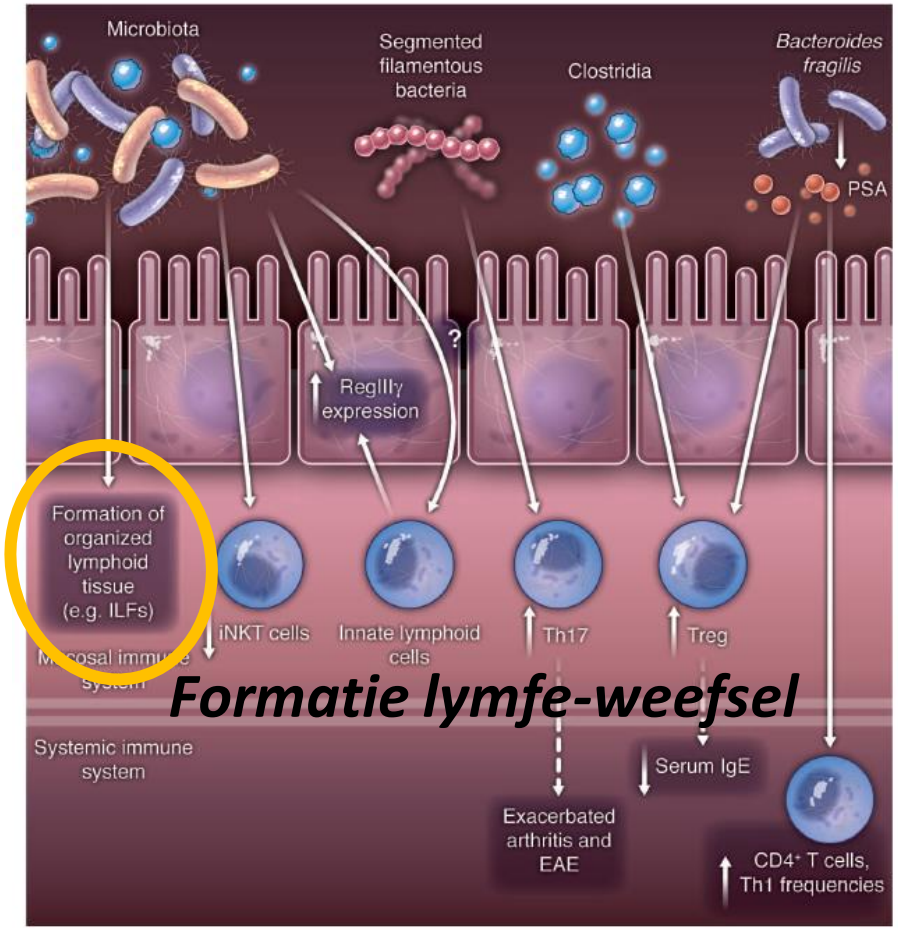
De darmmicrobiota: immunologische functies (4)





Formatie lymfe-weefsel

Hooper et al. (2012). Science, 336(6086), 1268-1273.

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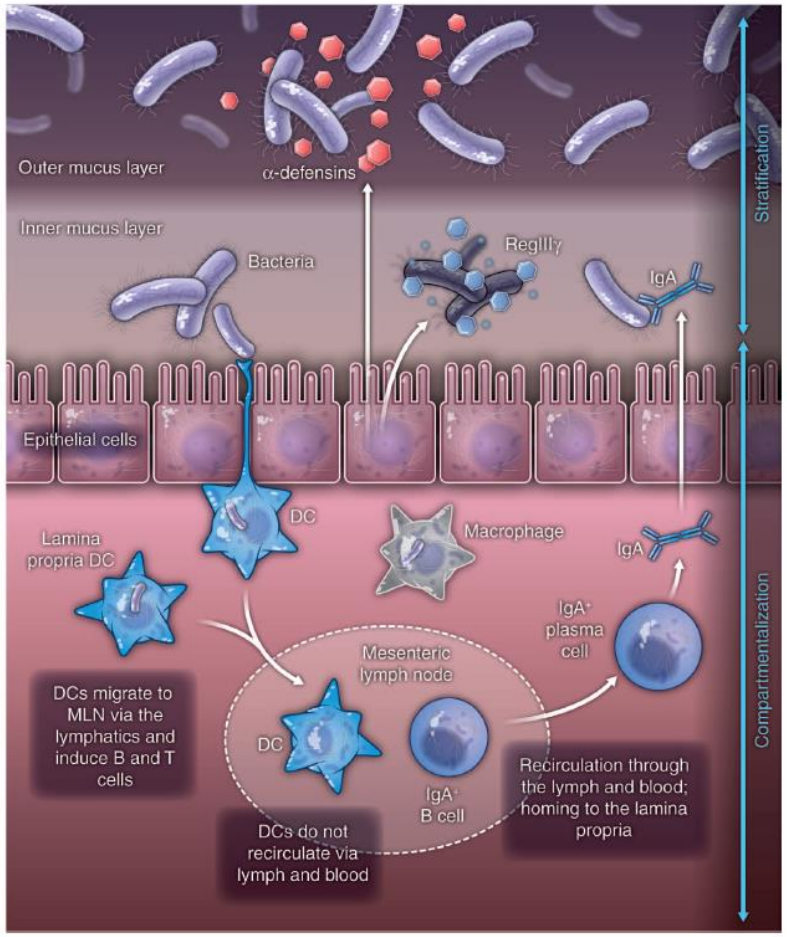
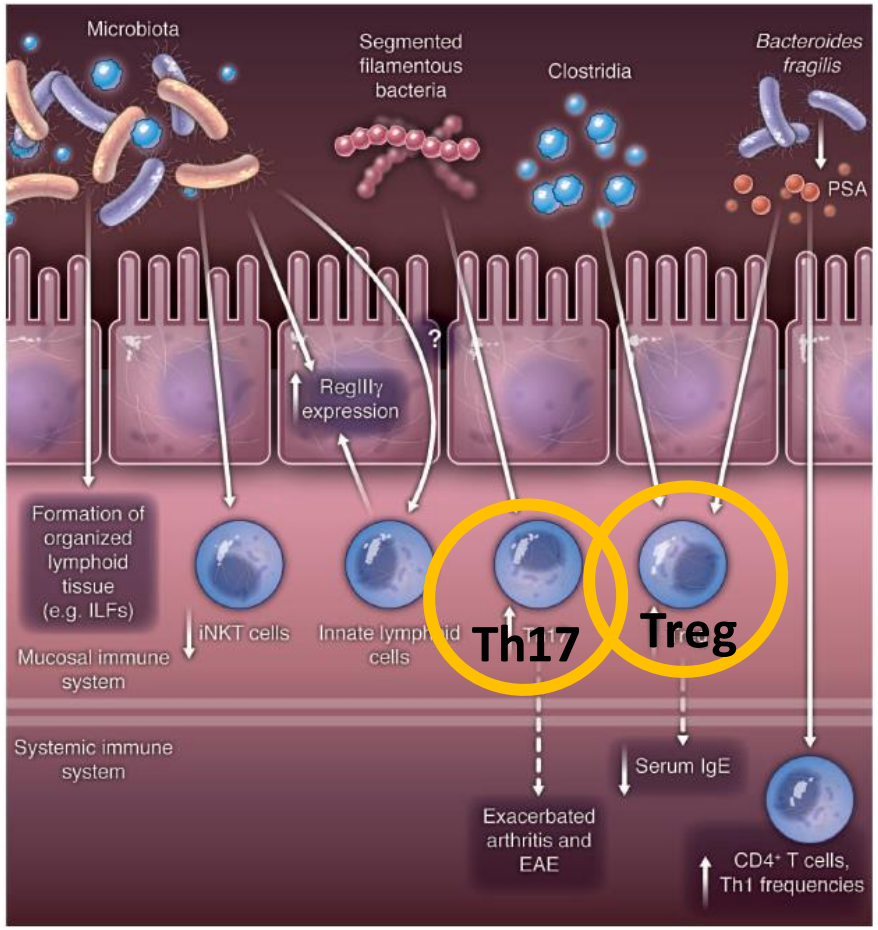
De darmmicrobiota: immunologische functies (5)





Hooper et al. (2012). Science, 336(6086), 1268-1273.

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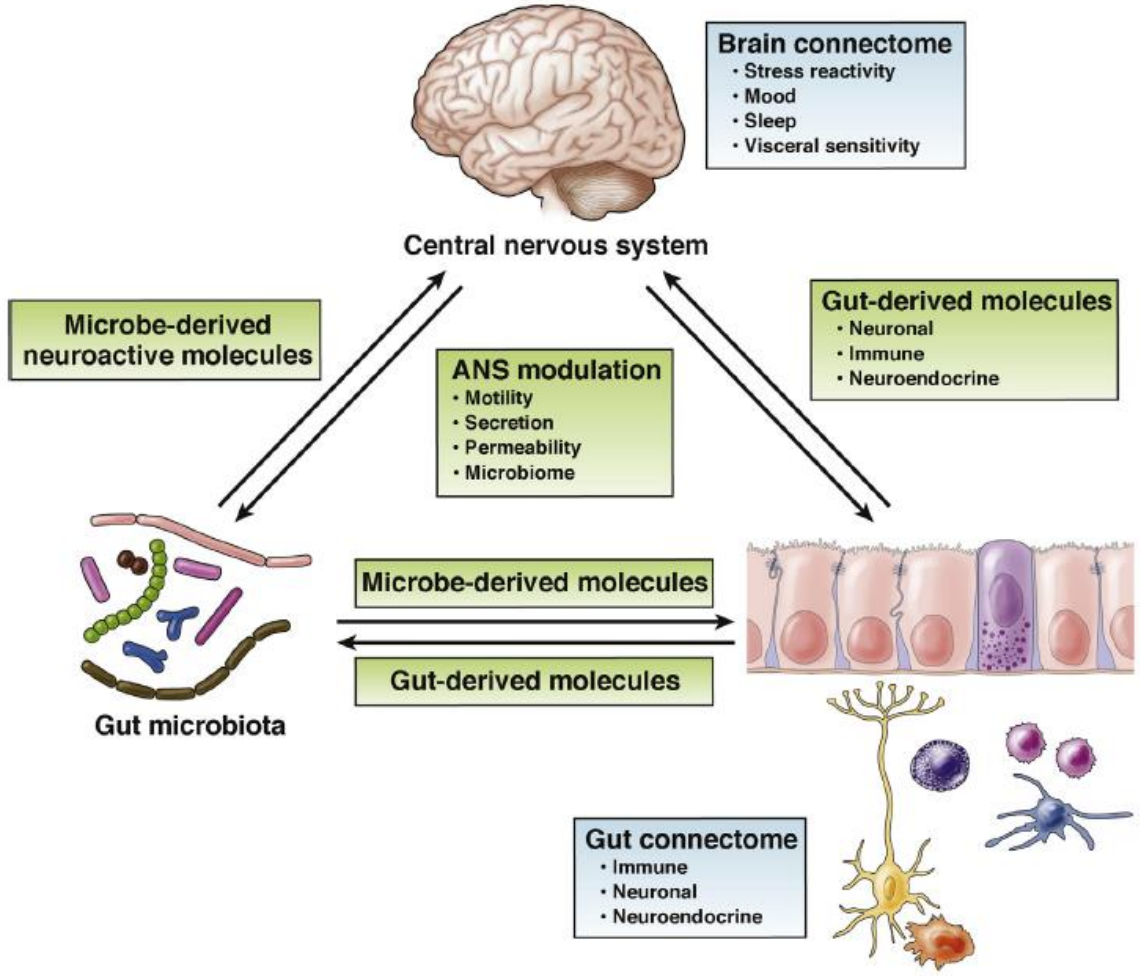
De darmmicrobiota-brein-as



Martin at al. (2018). Cellular and molecular gastroenterology and hepatology, 6(2), 133-148.

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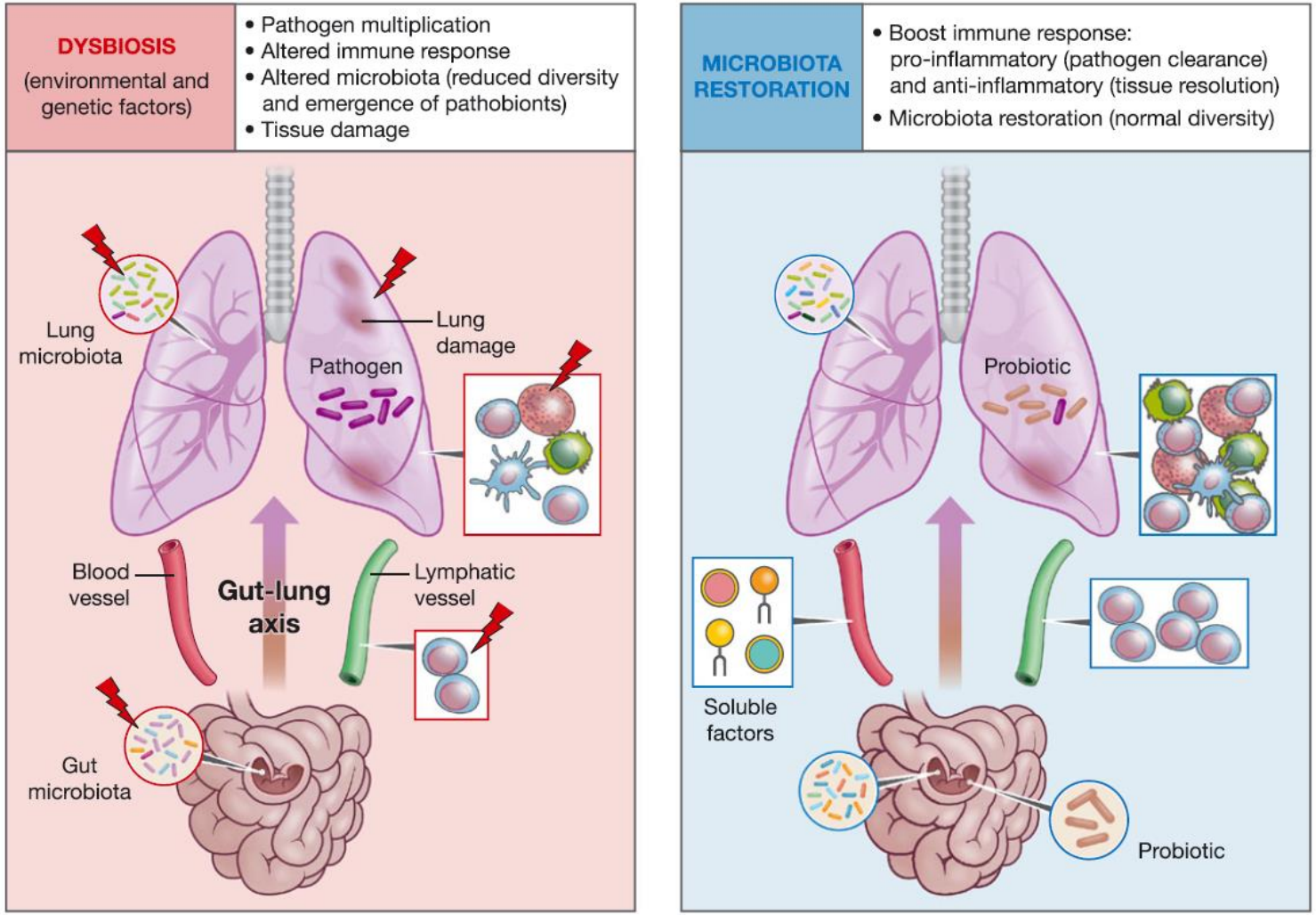
De darmmicrobiota-long-as



Dumas et al. (2018). Cellular microbiology, 20(12), e12966.

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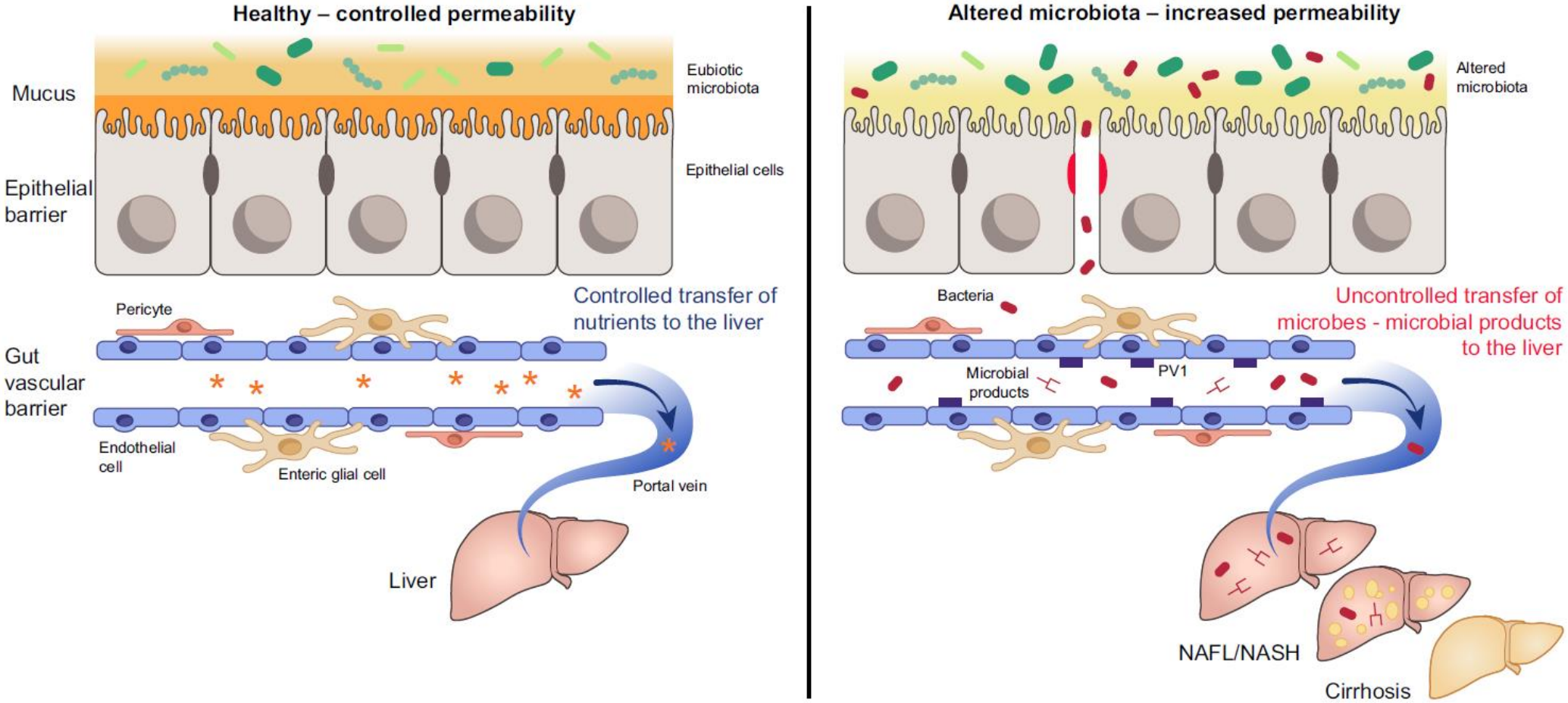
De darmmicrobiota-lever-as



Albillos, A., De Gottardi, A., & Rescigno, M. (2020). Journal of hepatology, 72(3), 558-577.

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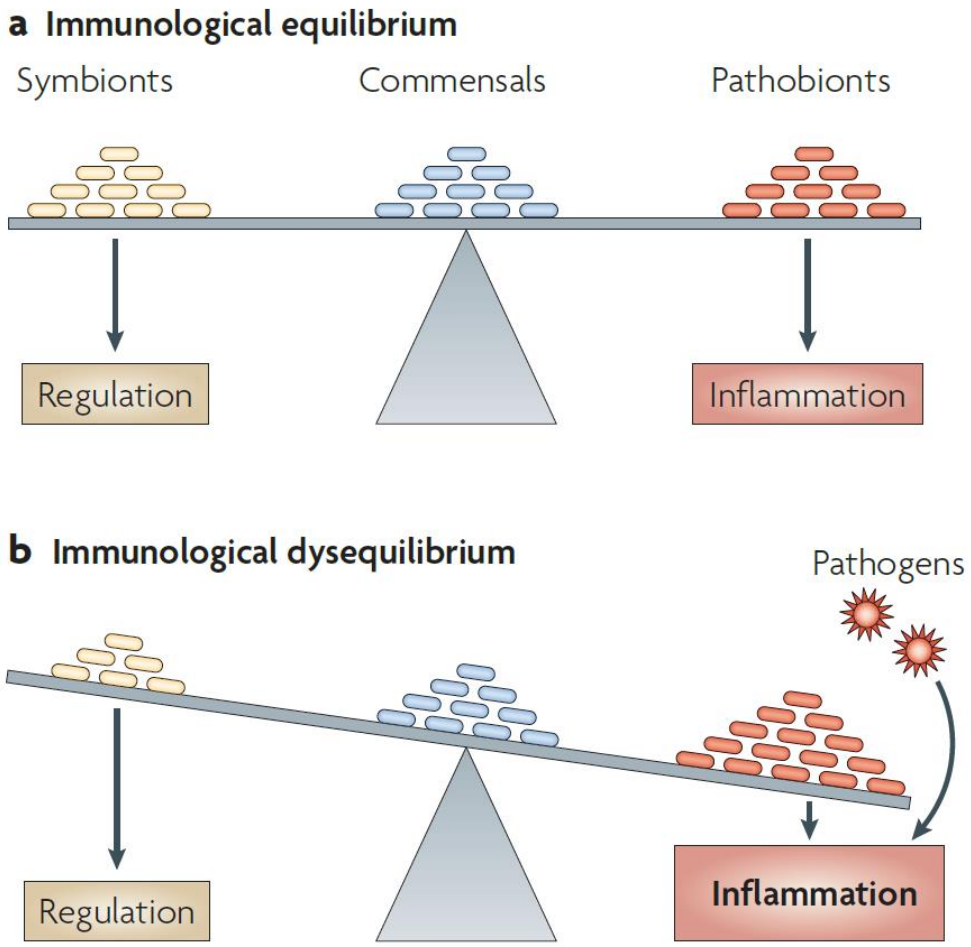
De darmmicrobiota: dysbiose door externe stressoren



Round & Mazmanian, Nature Rev. Immunology, 2009

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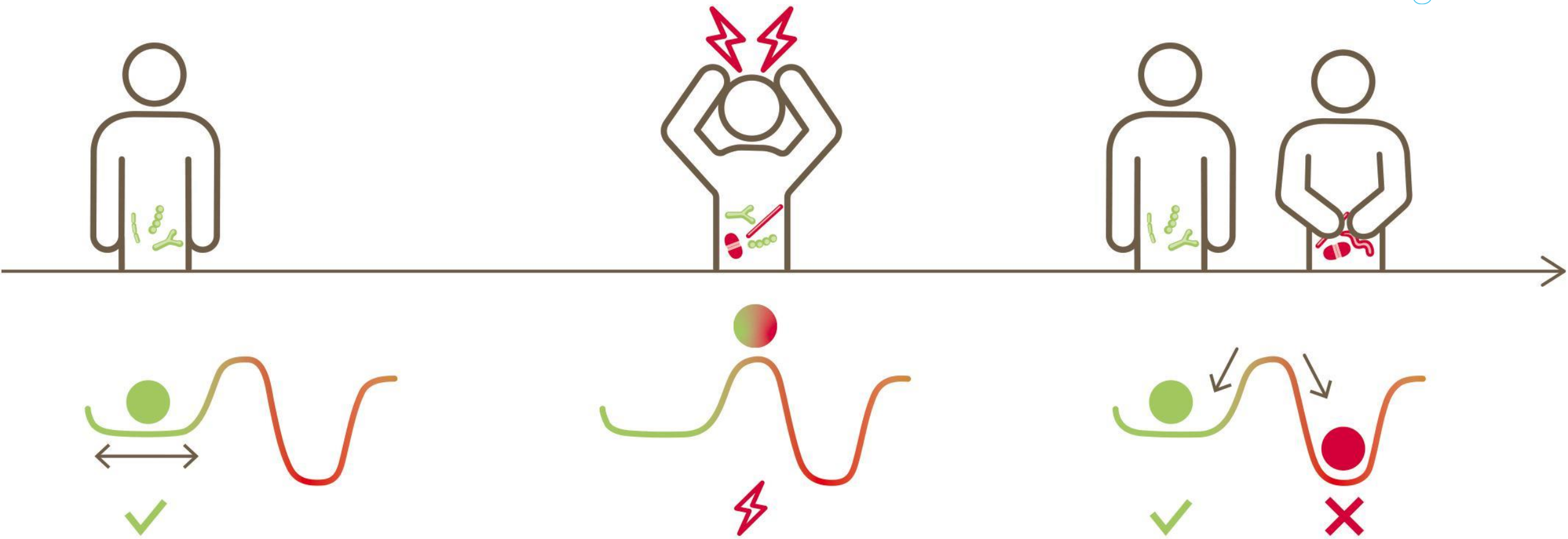
De darmmicrobiota: diversiteit & veerkracht



Dogra, S. K., Doré, J., & Damak, S. (2020). *Frontiers in Microbiology*, *11*, 2245.

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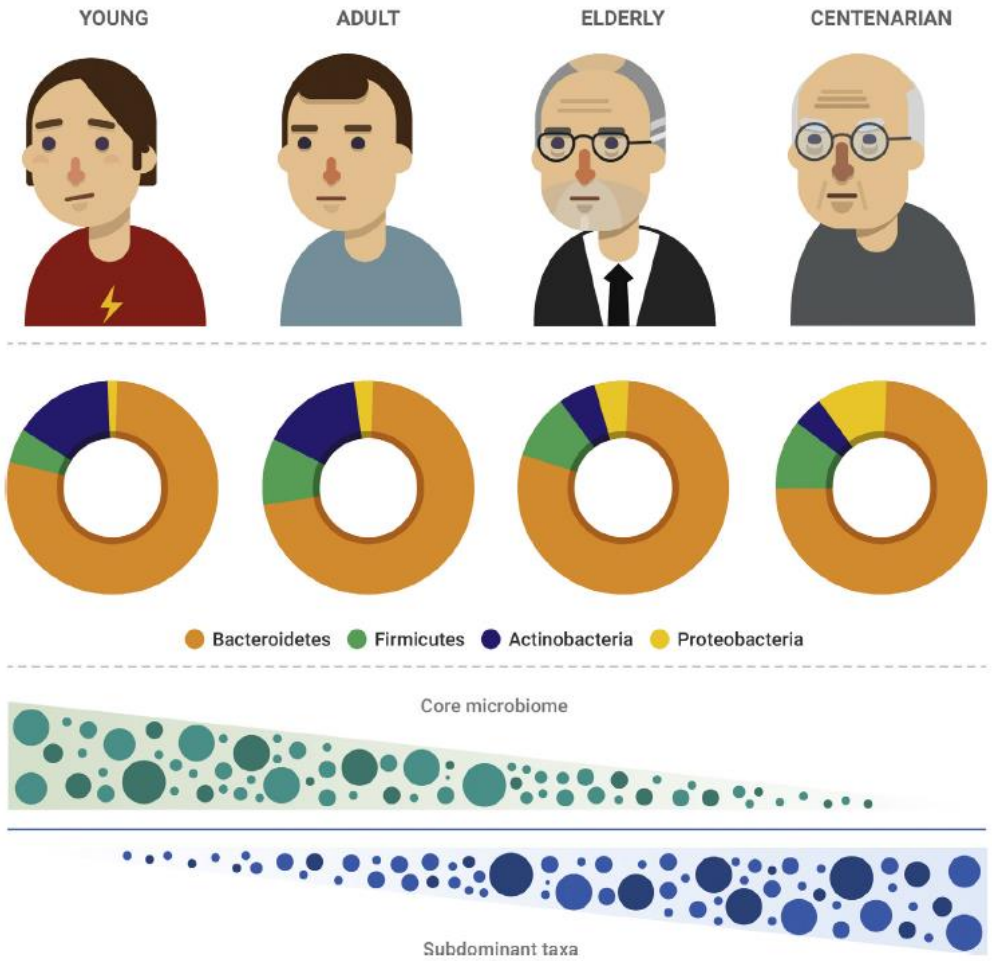
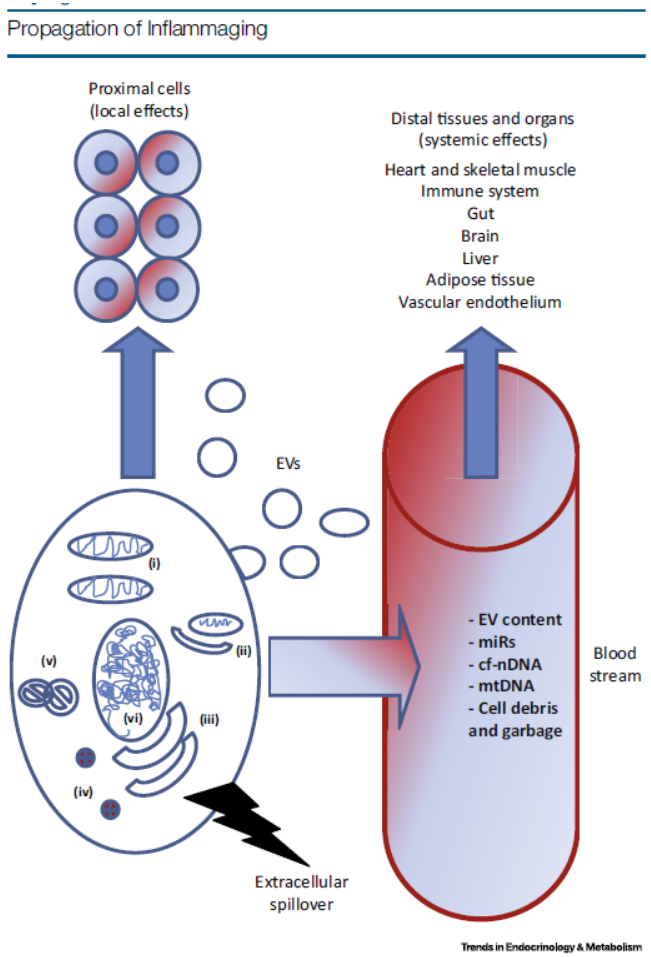
De darmmicrobiota: veroudering





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Franceschi et al. Trends in Endocrinology & Metabolism 28.3 (2017): 199-212.

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Vragen?

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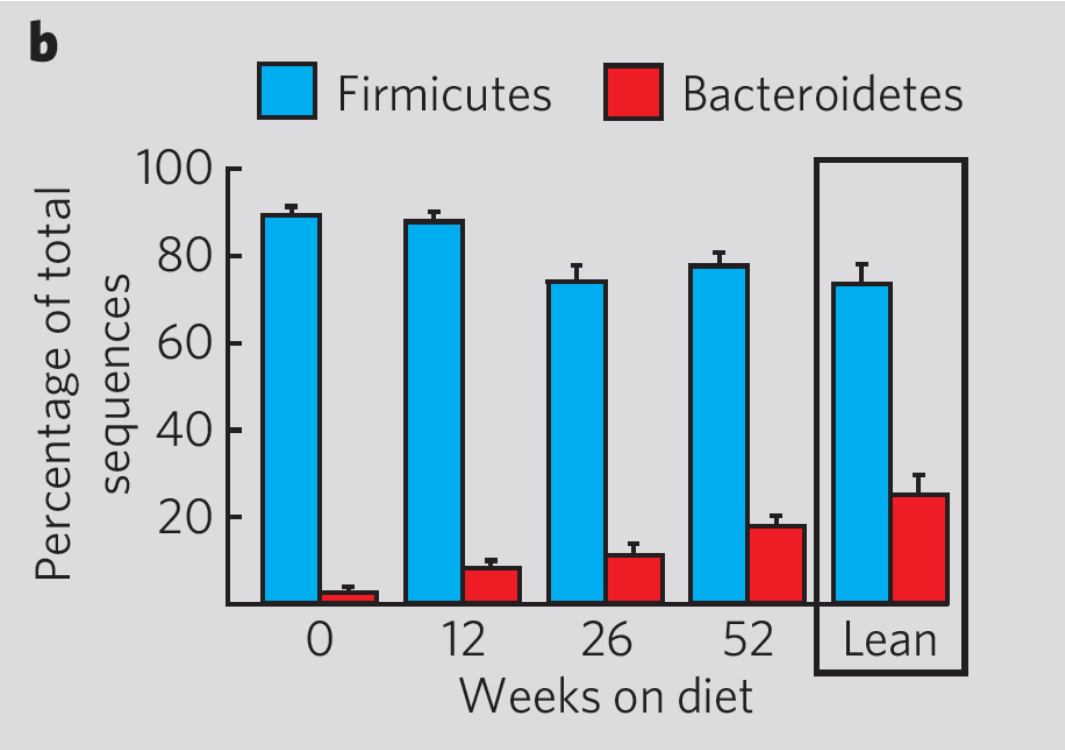
Een gezonde microbiota wordt gekarakteriseerd door:

De darmmicrobiota: metabole functies



Turnbaugh, et al. (2006). Nature, 444(7122), 1027.

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De darmmicrobiota: metabole functies (2)

$$\frac{Firmicutes}{Bacteroidetes}$$

Schwiertz, A., Taras, D., Schäfer, K., Beijer, S., Bos, N. A., Donus, C., & Hardt, P. D. (2010). Obesity, 18(1), 190-195.

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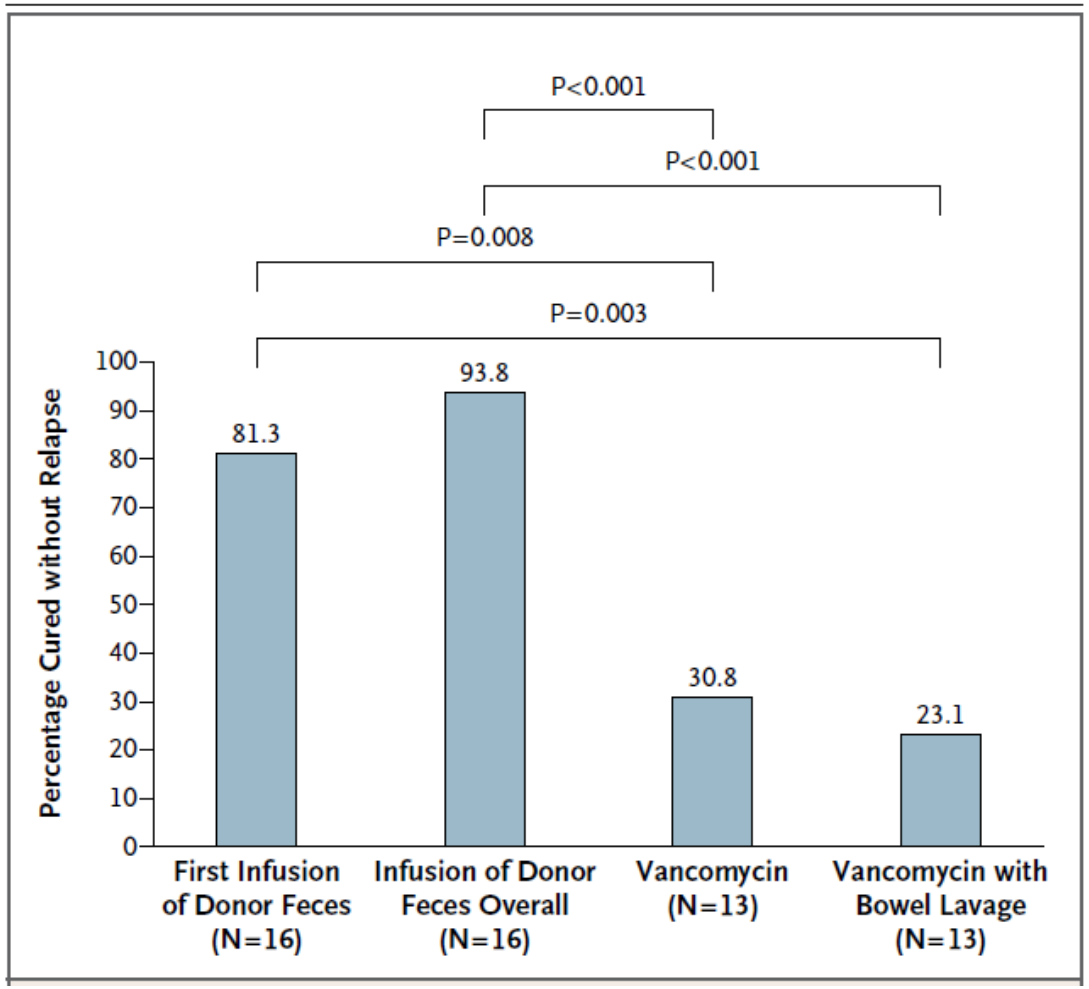
Interventie met FMT: terugkerende *C. difficile* infectie



Van Nood, E., Vrieze, A., Nieuwdorp, M., Fuentes, S., Zoetendal, E. G., de Vos, W. M., ... & Keller, J. J. (2013). New England Journal of Medicine, 368(5), 407-415.

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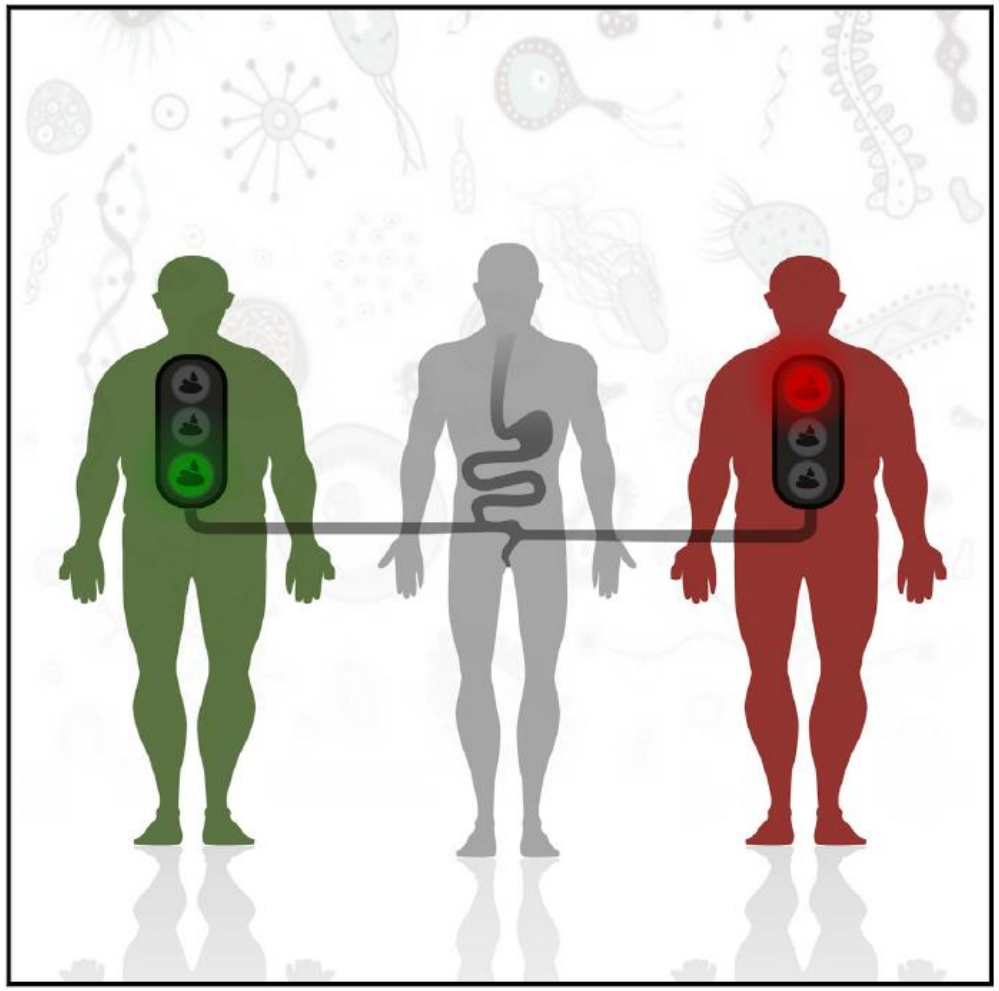
Interventie met FMT: insuline gevoeligheid



Kootte, R. S., Levin, E., Salojärvi, J., Smits, L. P., Hartstra, A. V., Udayappan, S. D., ... & Nieuwdorp, M. (2017). Cell metabolism, 26(4), 611-619.

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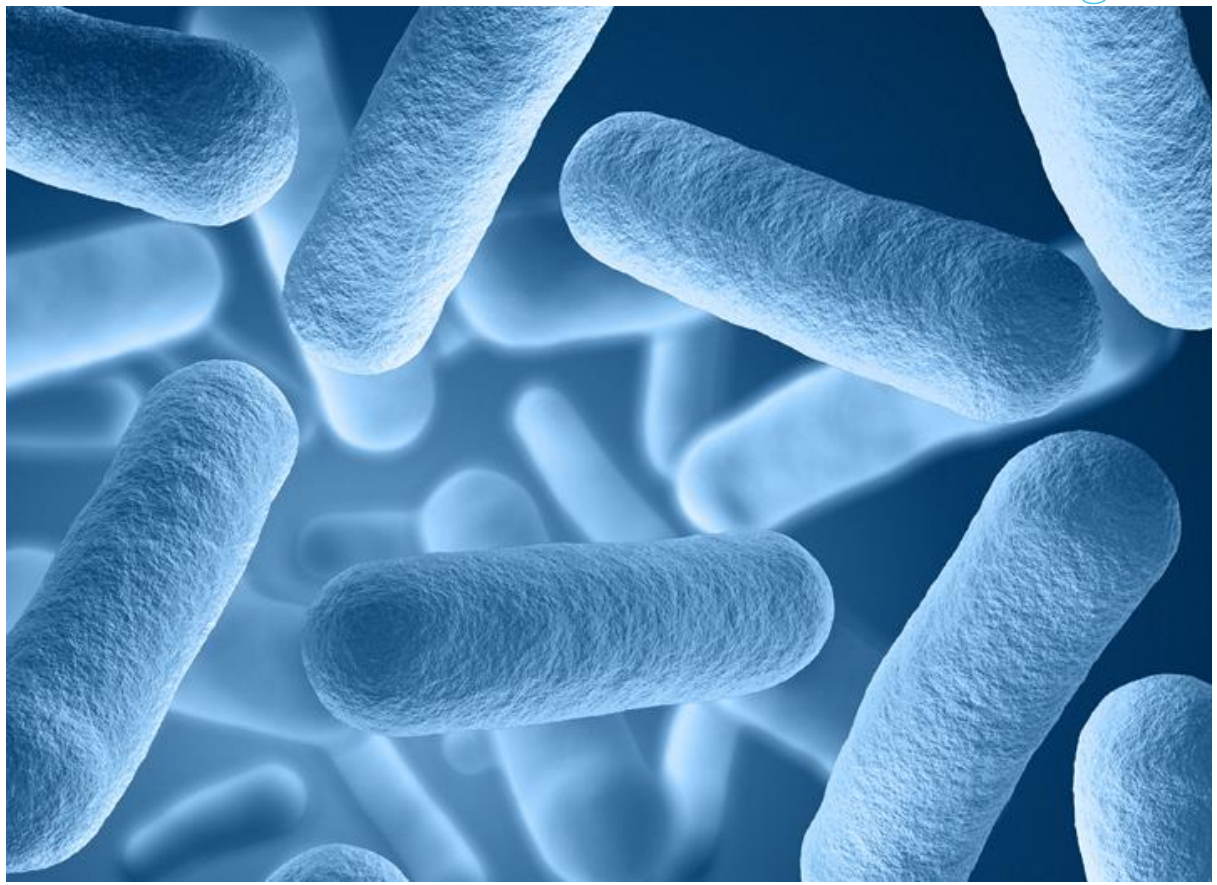
Interventie met probiotica

“Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”

WHO/FAO



- Survive the stomach
- > 1EXP9 microorganisms
- Characterized up to strain-level
- Scientific literature

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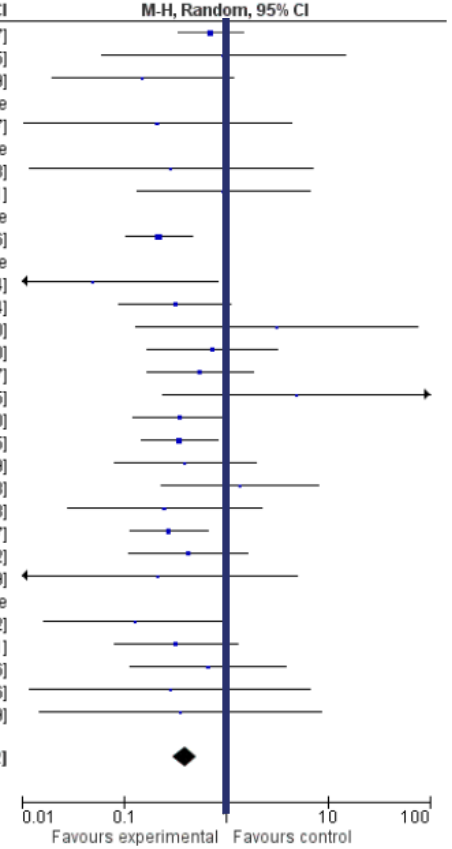
Meta analyse: *Clostricium difficile* – geassocieerde diarree

Figure 3. Forest plot of comparison: 1 C. difficile associated diarrhea, outcome: 1.1 Incidence CDAD: complete case.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Allen 2013	12	1404	17	1406	14.3%	0.71 [0.34, 1.47]
Arvola 1999	1	61	1	58	1.0%	0.95 [0.06, 14.85]
Beausoleil 2007	1	39	7	42	1.8%	0.15 [0.02, 1.19]
Bravo 2008	0	41	0	41		Not estimable
Can 2006	0	73	2	78	0.8%	0.21 [0.01, 4.37]
Cindoruk 2007	0	59	0	51		Not estimable
Duman 2005	0	185	1	161	0.8%	0.29 [0.01, 7.08]
Ehrhardt 2016	2	246	2	231	2.0%	0.94 [0.13, 6.61]
Fominykh 2013	0	80	0	40		Not estimable
Gao 2010	9	171	20	84	14.0%	0.22 [0.11, 0.46]
Georgieva 2015	0	49	0	48		Not estimable
Hickson 2007	0	56	9	53	1.0%	0.05 [0.00, 0.84]
Kotowska 2005	3	119	10	127	4.8%	0.32 [0.09, 1.14]
Lonnermark 2010	1	76	0	80	0.8%	3.16 [0.13, 76.30]
McFarland 1995	3	80	4	79	3.6%	0.74 [0.17, 3.20]
Miller 2008a	4	95	7	94	5.4%	0.57 [0.17, 1.87]
Miller 2008b	2	156	0	155	0.8%	4.97 [0.24, 102.65]
Ouwehand 2014	6	304	8	143	7.1%	0.35 [0.12, 1.00]
Pancheva 2009	6	78	17	78	10.0%	0.35 [0.15, 0.85]
Plummer 2004	2	69	5	69	3.0%	0.40 [0.08, 1.99]
Pozzoni 2012	3	106	2	98	2.5%	1.39 [0.24, 8.13]
Psaradellis 2010	1	185	4	186	1.6%	0.25 [0.03, 2.23]
Rafiq 2007	5	45	22	55	9.8%	0.28 [0.11, 0.67]
Ruszczynski 2008	3	120	7	120	4.4%	0.43 [0.11, 1.62]
Safdar 2008	0	22	1	14	0.8%	0.22 [0.01, 4.99]
Selinger 2013	0	111	0	106		Not estimable
Shan 2013	1	139	8	144	1.8%	0.13 [0.02, 1.02]
Surawicz 1989	3	113	5	61	3.9%	0.32 [0.08, 1.31]
Thomas 2001	2	133	3	134	2.5%	0.67 [0.11, 3.96]
Wenus 2008	0	34	1	29	0.8%	0.29 [0.01, 6.76]
Wong 2014	0	76	1	82	0.8%	0.36 [0.01, 8.69]
Total (95% CI)		**4525**		**4147**	**100.0%**	**0.40 [0.30, 0.52]**
Total events	70		164			

Heterogeneity: Tau² = 0.00; Chi² = 19.06, df = 25 (P = 0.79); I² = 0%
Test for overall effect: Z = 6.54 (P < 0.00001)



Favors probiotic *Favors control*

Goldenberg, Joshua Z., et al. "Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children." Cochrane Database of Systematic Reviews 12 (2017).

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Meta analyse: *Clostricium difficile* – geassocieerde diarree

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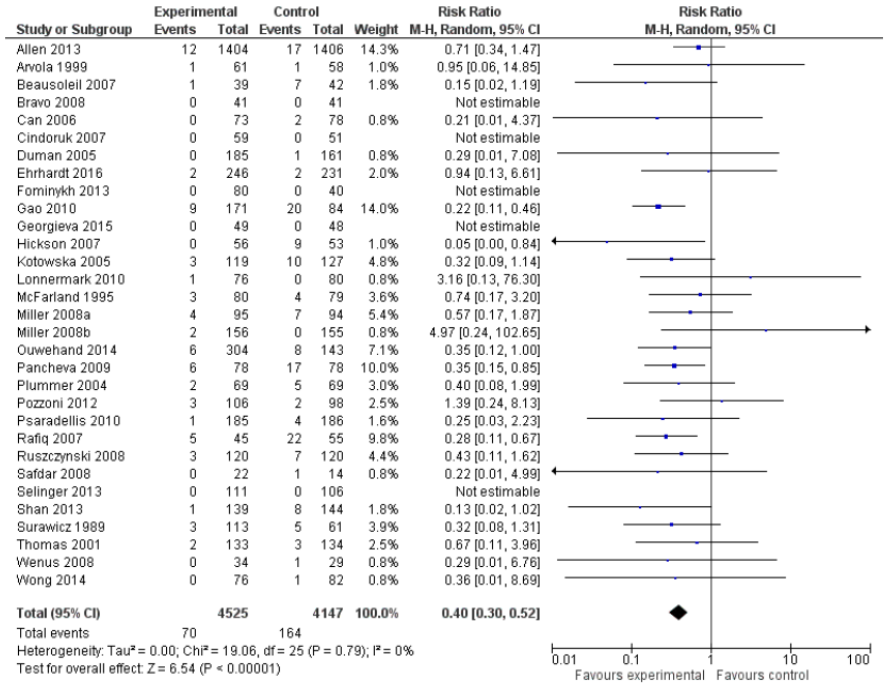

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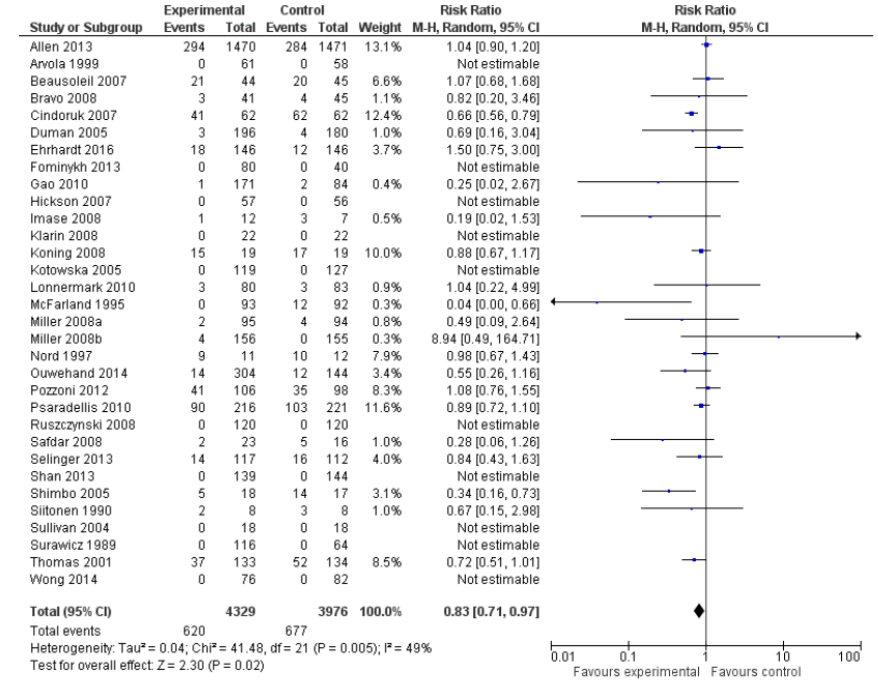
Test for overall effect: Z = 6.54 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours experimental Favours control

Figure 4. Forest plot of comparison: 1 Probiotics versus control, outcome: 1.24 Adverse Events: complete case.



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Allen 2013	294	1470	284	1471	13.1%	1.04 [0.90, 1.20]
Arvola 1999	0	61	0	58		Not estimable
Beausoleil 2007	21	44	20	45	6.6%	1.07 [0.68, 1.68]
Bravo 2008	3	41	4	45	1.1%	0.82 [0.20, 3.46]
Cindoruk 2007	41	62	62	62	12.4%	0.66 [0.56, 0.79]
Duman 2005	3	196	4	180	1.0%	0.69 [0.16, 3.04]
Ehrhardt 2016	18	146	12	146	3.7%	1.50 [0.75, 3.00]
Fominykh 2013	0	80	0	40		Not estimable
Gao 2010	1	171	2	84	0.4%	0.25 [0.02, 2.67]
Hickson 2007	0	57	0	56		Not estimable
Imase 2008	1	12	3	7	0.5%	0.19 [0.02, 1.53]
Klarin 2008	0	22	0	22		Not estimable
Koning 2008	15	19	17	19	10.0%	0.88 [0.67, 1.17]
Kotowska 2005	0	119	0	127		Not estimable
Lonnermark 2010	3	80	3	83	0.9%	1.04 [0.22, 4.99]
McFarland 1995	0	93	12	92	0.3%	0.04 [0.00, 0.66]
Miller 2008a	2	95	4	94	0.8%	0.49 [0.09, 2.64]
Miller 2008b	4	156	0	155	0.3%	8.94 [0.49, 164.71]
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Ouwehand 2014	14	304	12	144	3.4%	0.55 [0.26, 1.16]
Pozzoni 2012	41	106	35	98	8.3%	1.08 [0.76, 1.55]
Psaradellis 2010	90	216	103	221	11.6%	0.89 [0.72, 1.10]
Ruszczynski 2008	0	120	0	120		Not estimable
Safdar 2008	2	23	5	16	1.0%	0.28 [0.06, 1.26]
Selinger 2013	14	117	16	112	4.0%	0.84 [0.43, 1.63]
Shan 2013	0	139	0	144		Not estimable
Shimbo 2005	5	18	14	17	3.1%	0.34 [0.16, 0.73]
Siitonen 1990	2	8	3	8	1.0%	0.67 [0.15, 2.98]
Sullivan 2004	0	18	0	18		Not estimable
Surawicz 1989	0	116	0	64		Not estimable
Thomas 2001	37	133	52	134	8.5%	0.72 [0.51, 1.01]
Wong 2014	0	76	0	82		Not estimable
Total (95% CI)		**4329**		**3976**	**100.0%**	**0.83 [0.71, 0.97]**
Total events	620		677			

Heterogeneity: Tau² = 0.04; Chi² = 41.48, df = 21 (P = 0.005); I² = 49%
Test for overall effect: Z = 2.30 (P = 0.02)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours experimental Favours control

"Thirty-one studies (8672 participants) assessed the effectiveness of probiotics for preventing CDAD among participants taking antibiotics. Our results suggest that when probiotics are given with antibiotics the risk of developing CDAD is reduced by 60% on average."

Goldenberg, Joshua Z., et al. "Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children." Cochrane Database of Systematic Reviews 12 (2017).

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Meta analyse: AAD bij kinderen

The overall evidence suggests a moderate protective effect of probiotics for preventing AAD (NNTB 9, 95% CI 7 to 13). Using five criteria to evaluate the credibility of the subgroup analysis on probiotic dose, the results indicate the subgroup effect based on high dose probiotics (≥ 5 billion CFUs per day) was credible. Based on high dose probiotics, the NNTB to prevent one case of diarrhea is 6 (95% CI 5 to 9). The overall certainty of the evidence for the primary endpoint, incidence of AAD, based on high dose probiotics was moderate due to the minor issues with risk of bias and inconsistency related to a diversity of probiotic agents used. Evidence also suggests that probiotics may moderately reduce the duration of diarrhea, a reduction by almost one day . The benefit of high dose probiotics (e.g. Lactobacillus rhamnosus or Saccharomyces boulardii) needs to be confirmed by a large well designed multi centered randomized trial. It is premature to draw firm conclusions about the efficacy and safety of 'other' probiotic agents as an adjunct to antibiotics in children. Adverse event rates were low and no serious adverse events were attributable to probiotics.

Guo et al., Cochrane Database of Systematic Reviews 2019

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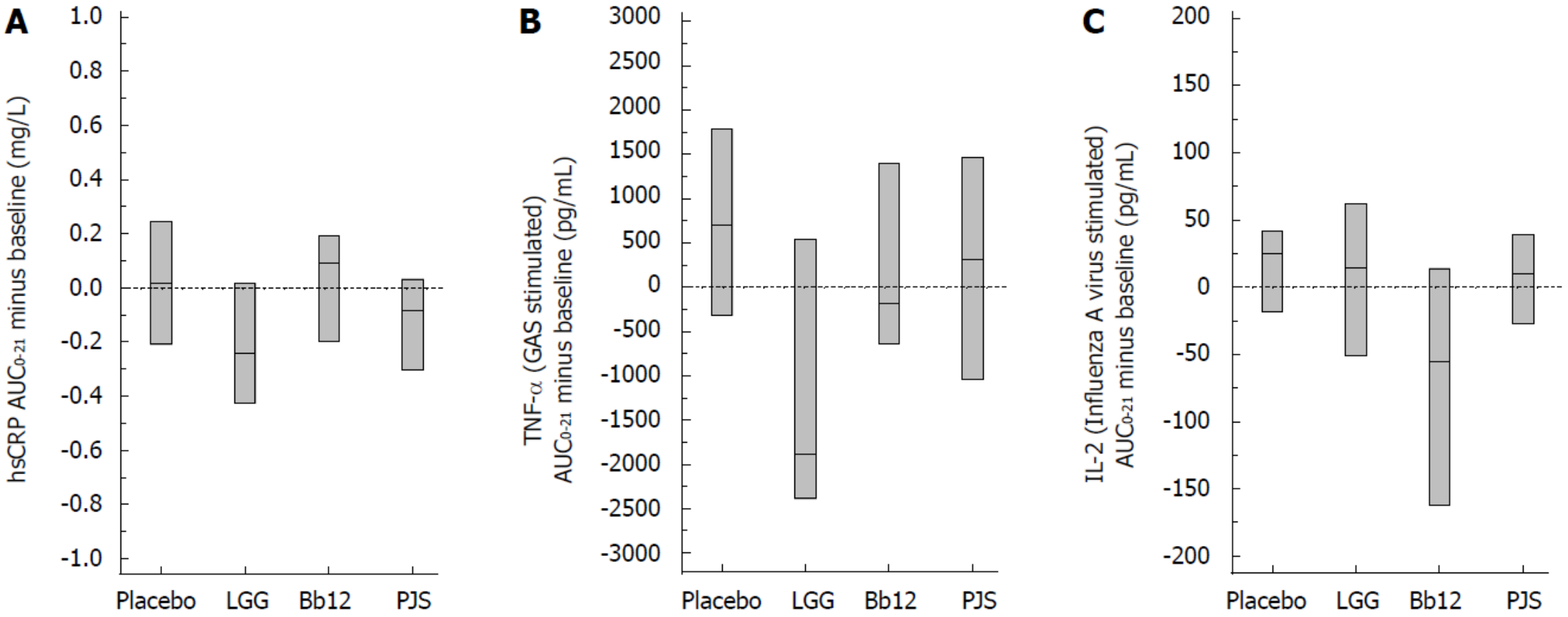
Genus / Stam specificiteit



Kekkonen, R. A., Lummela, N., Karjalainen, H., Latvala, S., Tynkkynen, S., Järvenpää, S., ... & Korpela, R. (2008). World journal of gastroenterology: WJG, 14(13), 2029.

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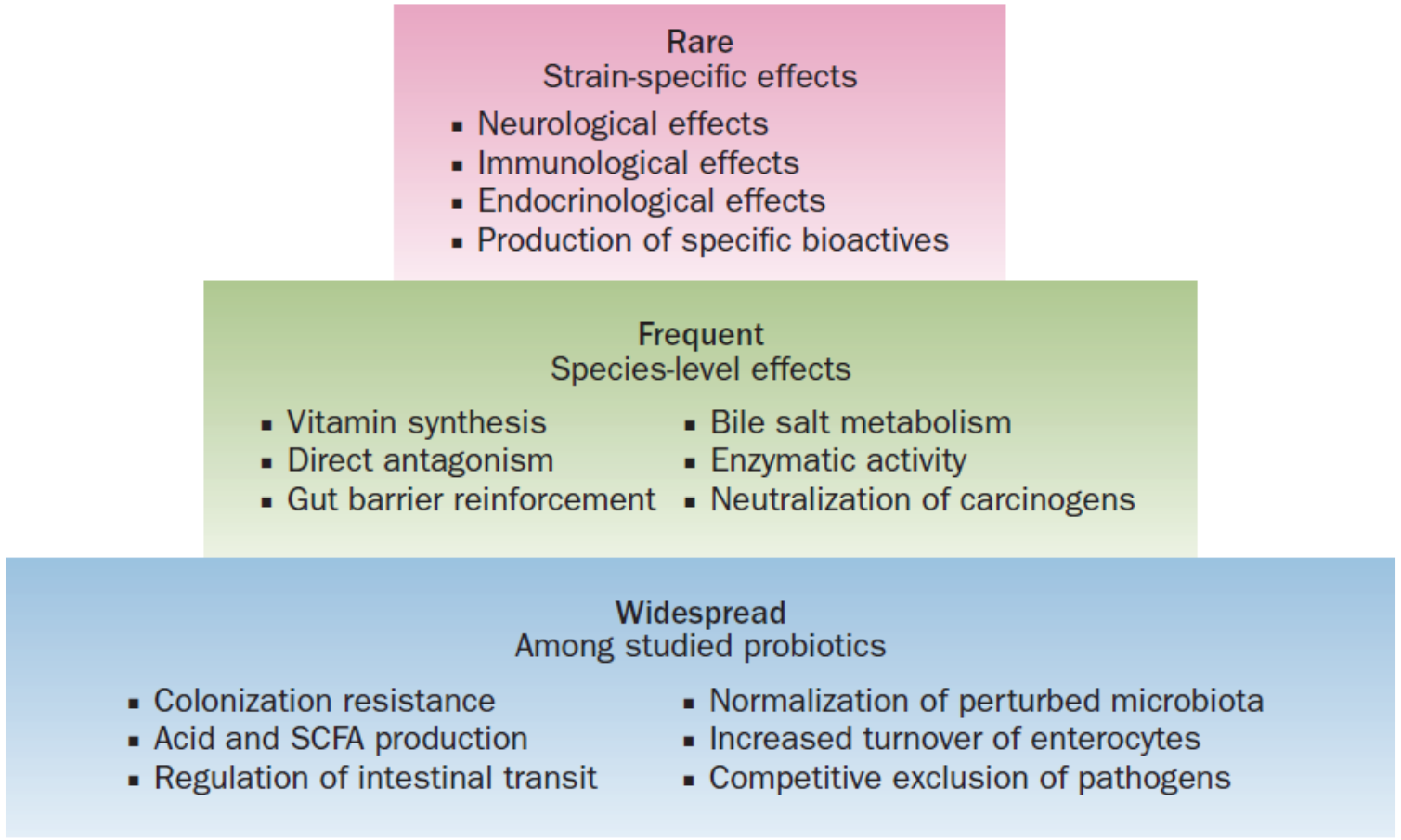
Probiotica: van generiek naar stam-specifiek



Colin Hill et al. Nat Rev Gastroenterol Hepatol 11.8 (2014): 506-514.

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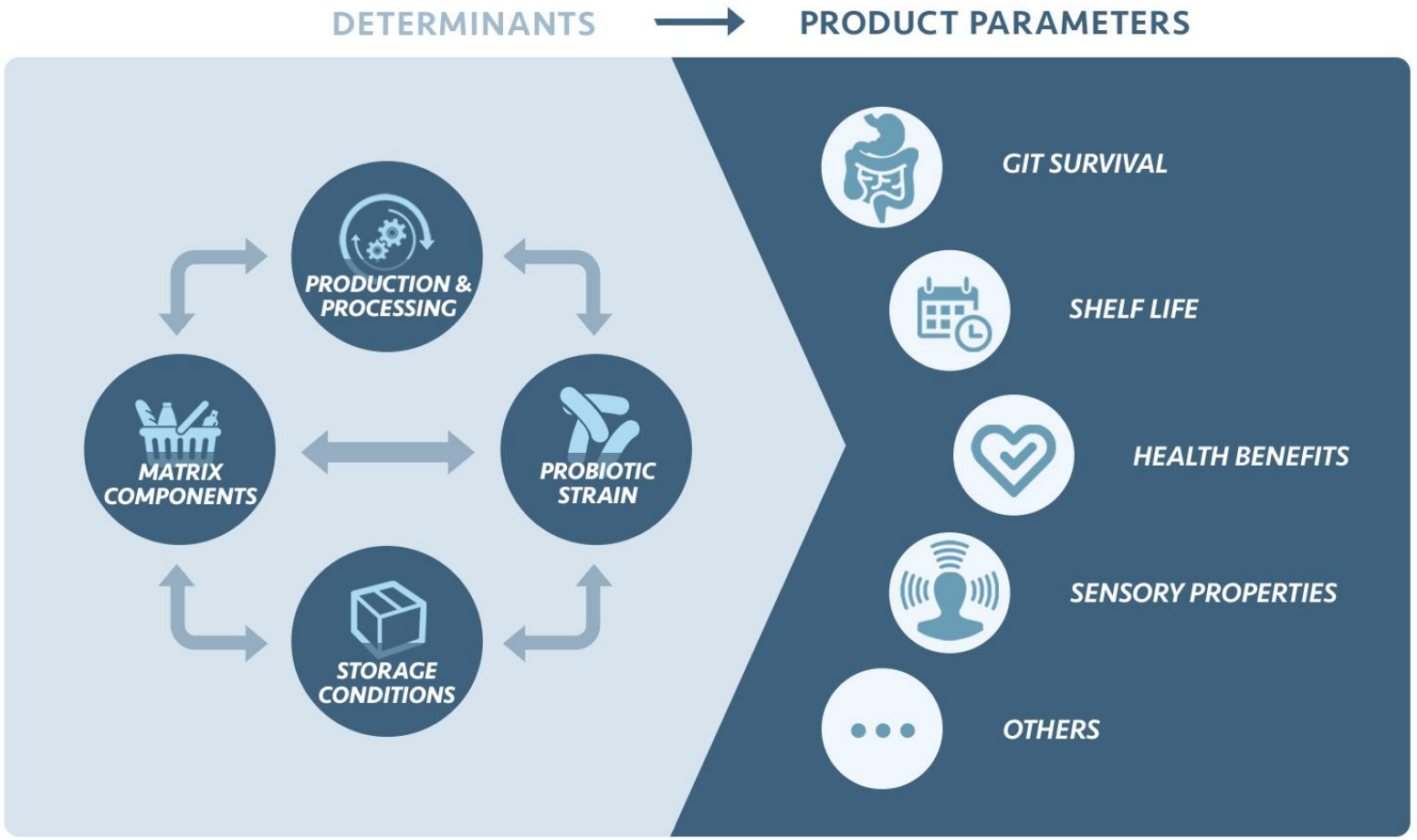
Probiotica: van stam- naar product-specifiek



Flach, Koks, v.d. Waal, v.d. Nieuwboer, Claassen & Larsen, Critical reviews in food science and nutrition (2017): 1-15

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In mijn praktijk adviseer ik patiënten probiotica

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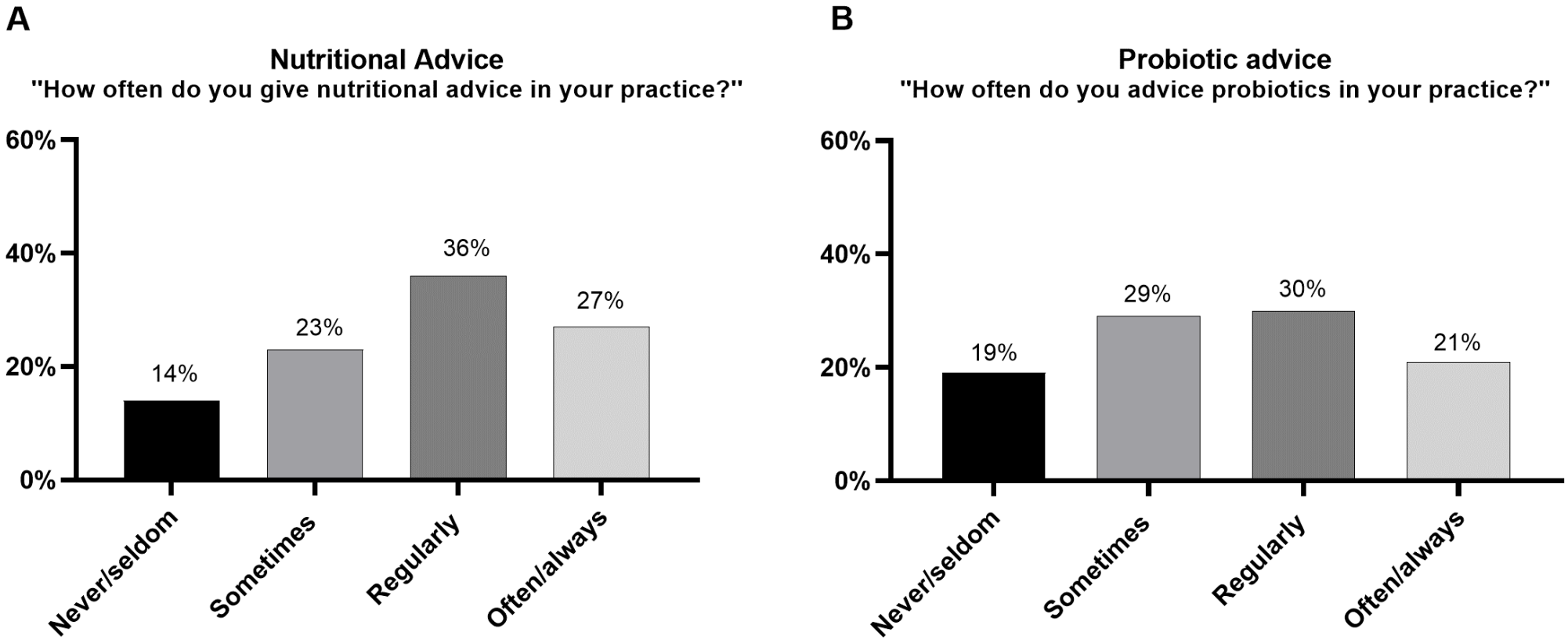
Vragen?

Recente resultaten: >1.300 huisartsen in West Europa



Van der Geest, A. M., Flach, J., Claassen, E., Sijlmans, A. W., Van de Burgwal, L. H. M., & Larsen, O. F. A. (2020). *PharmaNutrition*, *11*, 100178.

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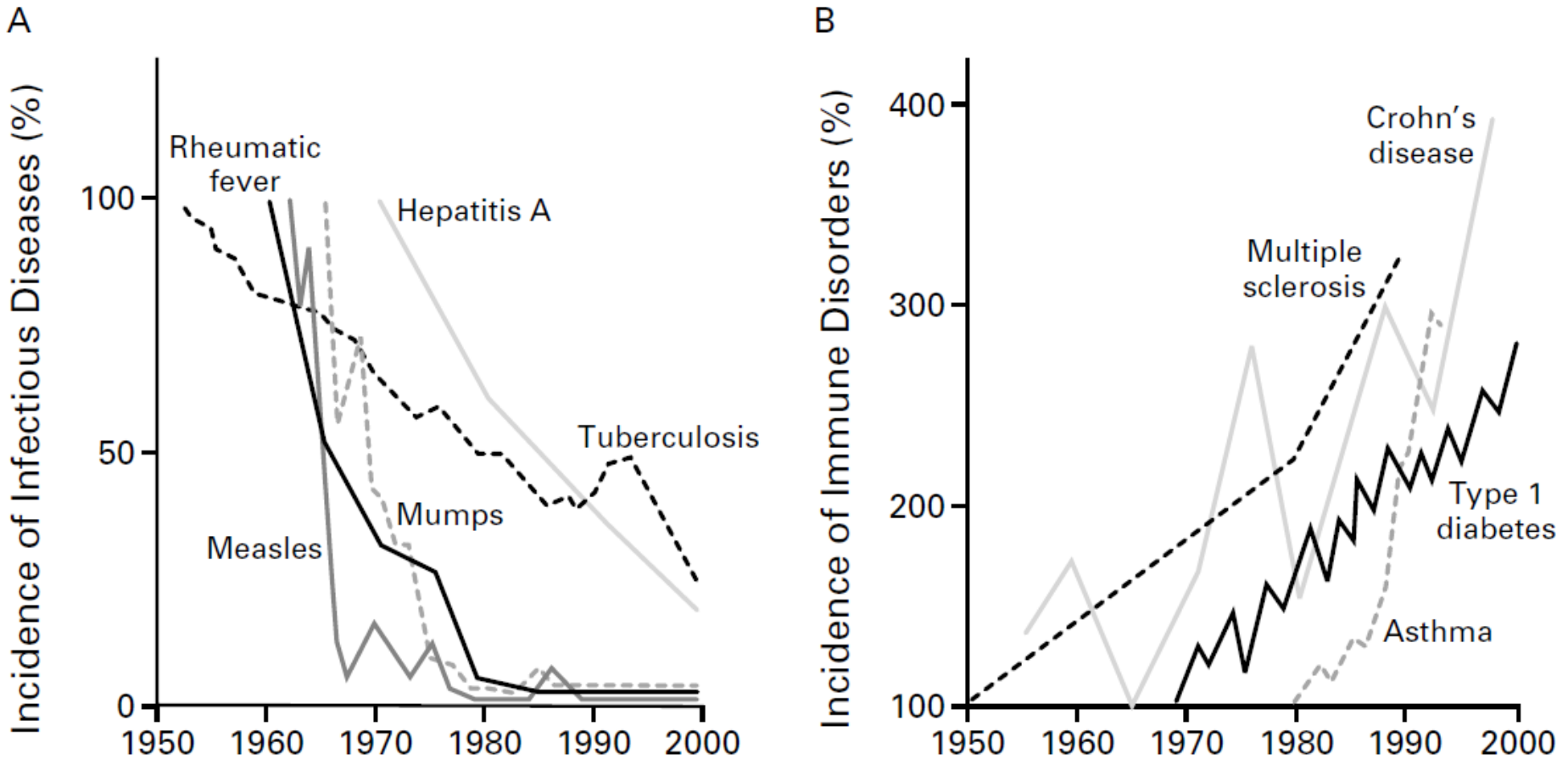
Initiele “interventie”: *old friends*



Bach, J. F. (2002). New England journal of medicine, 347(12), 911-920..

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Diversiteit & robuustheid: *old friends*

Received: 31 July 2019 | Revised: 31 August 2019 | Accepted: 6 September 2019

DOI: 10.1002/mbo3.939

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MicrobiologyOpen Open Access WILEY

ORIGINAL ARTICLE

An examination of data from the American Gut Project reveals that the dominance of the genus *Bifidobacterium* is associated with the diversity and robustness of the gut microbiota

Yuqing Feng[1,2] | Yunfeng Duan[1] | Zhenjiang Xu[3] | Na Lyu[1] | Fei Liu[1] | Shihao Liang[1] | Baoli Zhu[1,2,4,5]

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Veerkracht kantoormedewerkers: probiotica interventie

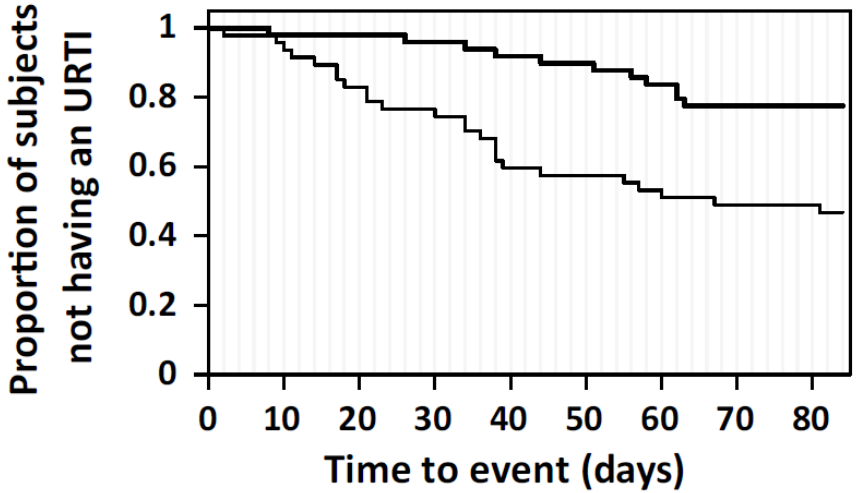

Fig. 2 Kaplan–Meier time-to-event curves for the first URTI. The URTI-free rates were 0.78 (95 % CI 0.66–0.89) and 0.47 (95 % CI 0.33–0.61) in the LcS-FM (*thick line*) and the CM (*thin line*) groups, respectively

Shida et al., Eur J Nutr, DOI 10.1007/s00394-015-1056-1 (2015)

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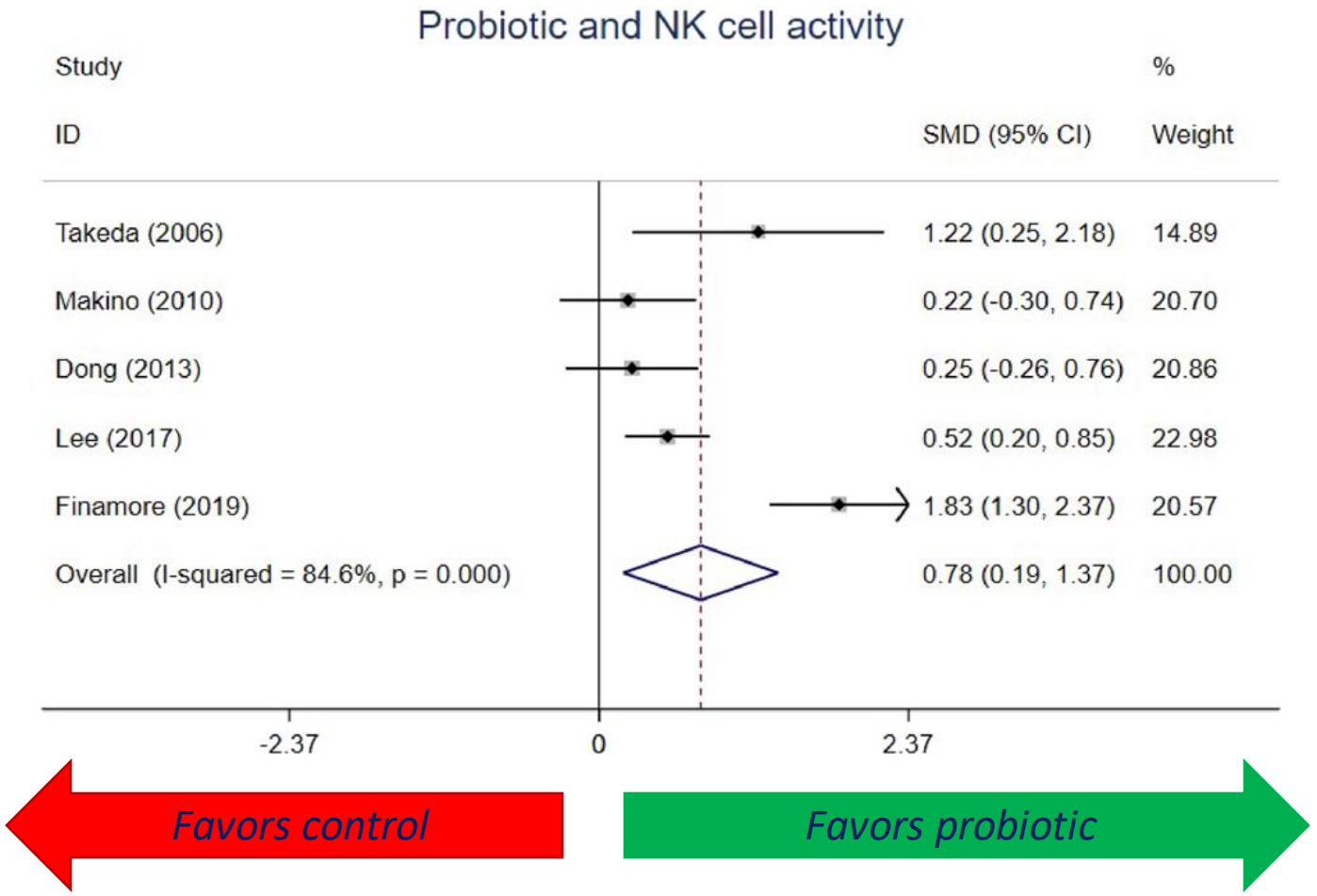
NK cel verhoging bij ouderen



Gui et al. (2020). Effects of probiotic supplementation on natural killer cell function in healthy elderly individuals: a meta-analysis of randomized controlled trials. European Journal of Clinical Nutrition, 1-8.

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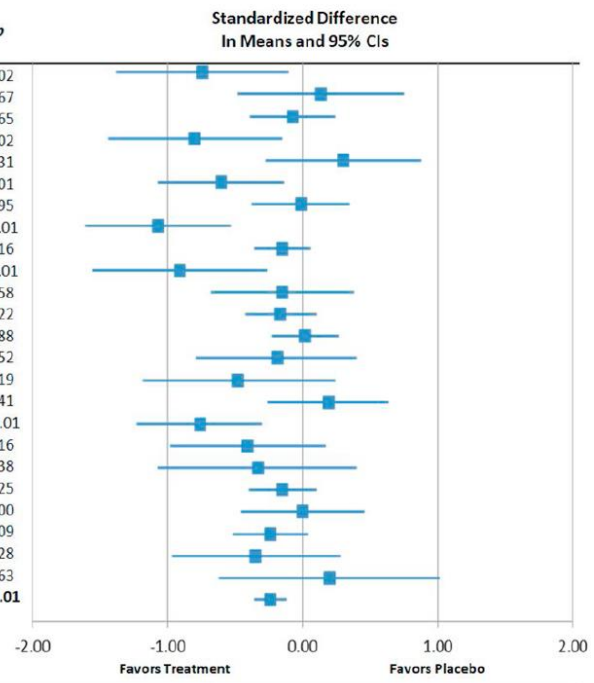
Microbiota restoratie: depressie & angststoornissen

2c. Probiotics and depression

Statistics for Each Study

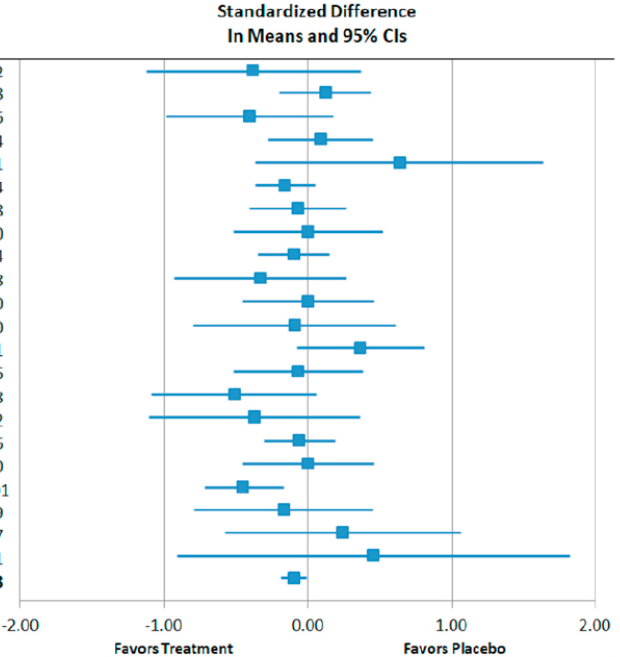
First Author, Year	Standardized Difference in Means	Lower Limit	Upper Limit	p
Akkasheh et al. (2016)	-0.74	-1.38	-0.10	0.02
Chung et al. (2014)	0.13	-0.48	0.75	0.67
Cremon et al. (2018)	-0.07	-0.39	0.24	0.65
Ghorbani et al. (2018)	-0.80	-1.44	-0.15	0.02
Kato-Kataoka et al. (2016)	0.30	-0.28	0.88	0.31
Kazemi et al. (in press)	-0.60	-1.07	-0.14	0.01
Kelly et al. (2017)	-0.01	-0.38	0.35	0.95
Kouchaki et al. (2017)	-1.07	-1.61	-0.53	<0.01
Lyra et al. (2016)	-0.15	-0.36	0.06	0.16
Majeed et al. (2018)	-0.91	-1.56	-0.26	<0.01
Messaoudi et al. (2011)	-0.15	-0.68	0.38	0.58
Nishihira et al. (2014)	-0.17	-0.43	0.10	0.22
Östlund-Lagerström et al. (2016)	0.02	-0.23	0.27	0.88
Pinto-Sanchez et al. (2017)	-0.19	-0.79	0.40	0.52
Roman et al. (2018)	-0.48	-1.19	0.24	0.19
Romjin et al. (2017)	0.19	-0.26	0.63	0.41
Sanchez et al. (2017) Female subsample	-0.76	-1.23	-0.30	< 0.01
Sanchez et al. (2017) Male subsample	-0.41	-0.98	0.17	0.16
Sashihara et al. (2013)	-0.33	-1.07	0.40	0.38
Shinkai et al. (2012)	-0.15	-0.40	0.10	0.25
Simrén et al. (2010)	0.00	-0.46	0.46	1.00
Slykerman et al. (2018)	-0.24	-0.52	0.04	0.09
Steenbergen et al. (2015)	-0.35	-0.97	0.28	0.28
Tillisch et al. (2013)	0.20	-0.62	1.02	0.63
Total	**-0.24**	**-0.36**	**-0.12**	**< 0.01**



2d. Probiotics and anxiety

Statistics for Each Study

First Author, Year	Standardized Difference in Means	Lower Limit	Upper Limit	p
Colica et al. (2017)	-0.38	-1.13	0.37	0.32
Cremon et al. (2018)	0.12	-0.20	0.44	0.48
Kato-Kataoka et al. (2016)	-0.41	-0.99	0.17	0.16
Kelly et al. (2017)	0.09	-0.28	0.45	0.64
Kitaoka et al. (2009)	0.64	-0.37	1.64	0.21
Lyra et al. (2016)	-0.16	-0.37	0.05	0.14
Marcos et al. (2004)	-0.07	-0.41	0.27	0.68
Messaoudi et al. (2011)	<0.01	-0.52	0.52	1.00
Östlund-Lagerström et al. (2016)	-0.10	-0.35	0.15	0.44
Pinto-Sanchez et al. (2017)	-0.33	-0.93	0.27	0.28
Reale et al. (2012)	< 0.01	-0.46	0.46	1.00
Roman et al. (2018)	-0.09	-0.80	0.61	0.80
Romjin et al. (2017)	0.36	-0.08	0.81	0.11
Sanchez et al. (2017) Female subsample	-0.07	-0.52	0.38	0.76
Sanchez et al. (2017) Male subsample	-0.51	-1.09	0.06	0.08
Sashihara et al. (2013)	-0.37	-1.11	0.36	0.32
Shinkai et al. (2012)	-0.06	-0.31	0.19	0.66
Simrén et al. (2010)	0.00	-0.46	0.46	1.00
Slykerman et al. (2018)	-0.45	-0.72	-0.17	< 0.01
Steenbergen et al. (2015)	-0.17	-0.79	0.45	0.59
Tillisch et al. (2013)	0.24	-0.58	1.06	0.57
Vaghef-Mehrabany et al. (2014)	0.46	-0.91	1.82	0.51
Total	**-0.10**	**-0.19**	**-0.01**	**0.03**



Favors probiotic | *Favors control*

Liu, et al. (2019). Neuroscience & Biobehavioral Reviews, 102, 13-23.

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6-
De Eenige Oprechte Haarlemmerolie
in FLESCHJES en CAPSULES
ANTWERP 1906
LONDON 1907
PARIS 1906
LONDON 1907
LONDON 1907
EERERUIS
LONDON 1907
N.V. Oprechte Haarlemmerolie Fabriek
ACHTERSTRAAT 8 - 8a - 8b
HAARLEM

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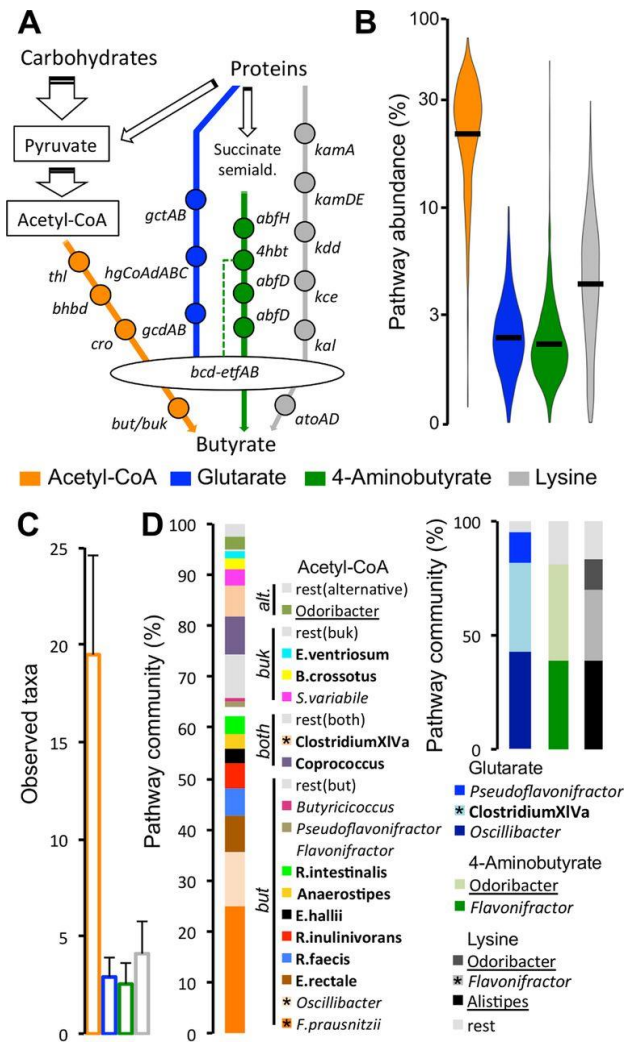
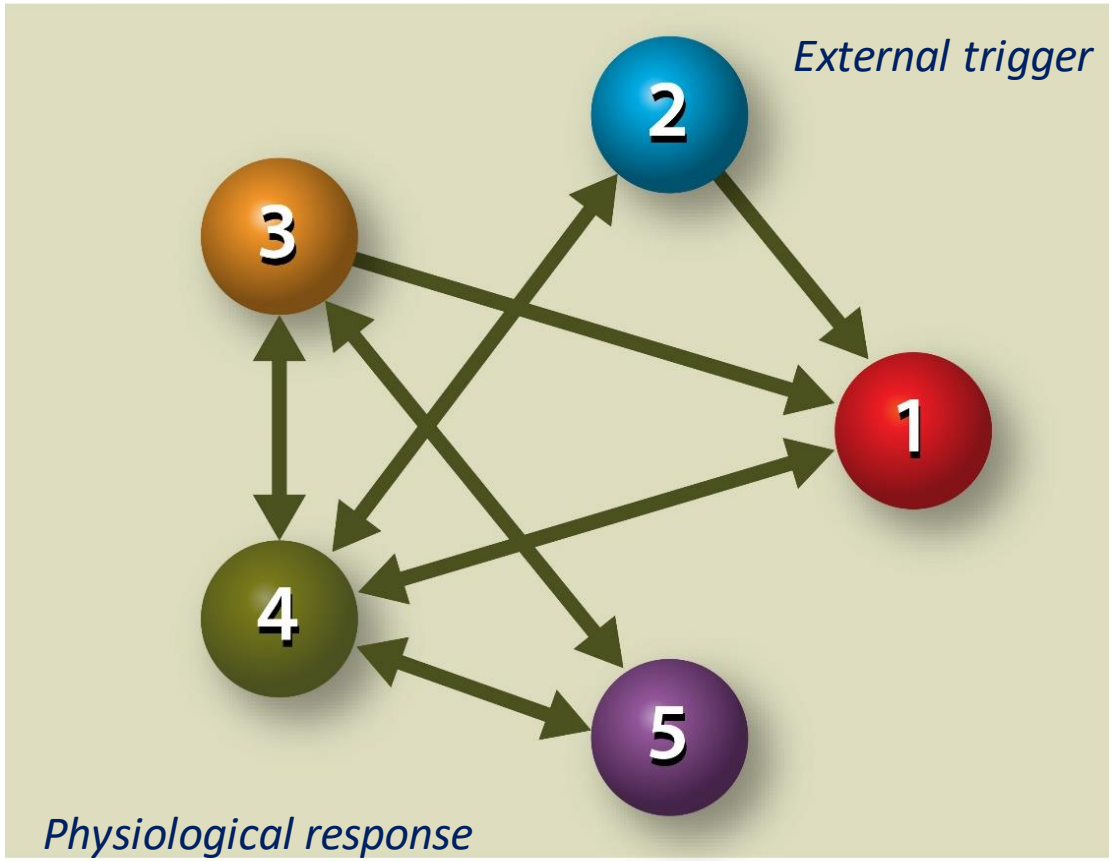
In mijn praktijk komen patiënten met de uitslag van een zelf meegebrachte fecale analyse

Van microben naar functionele eenheden: butyraat





Vital, M., Karch, A., & Pieper, D. H. (2017). Colonic butyrate-producing communities in humans: an overview using omics data. *Msystems*, *2*(6).

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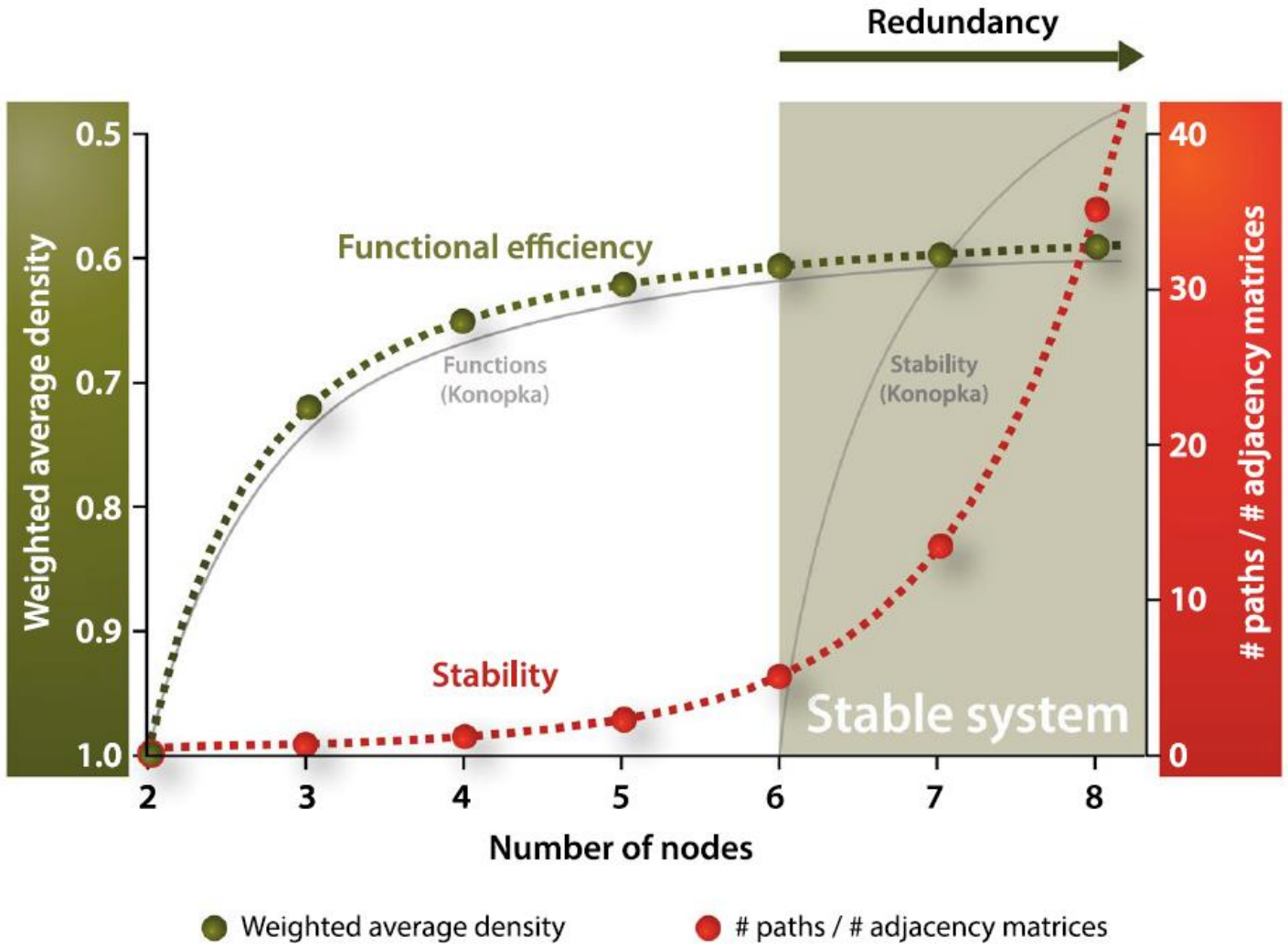
Stappen richting mechanistisch inzicht



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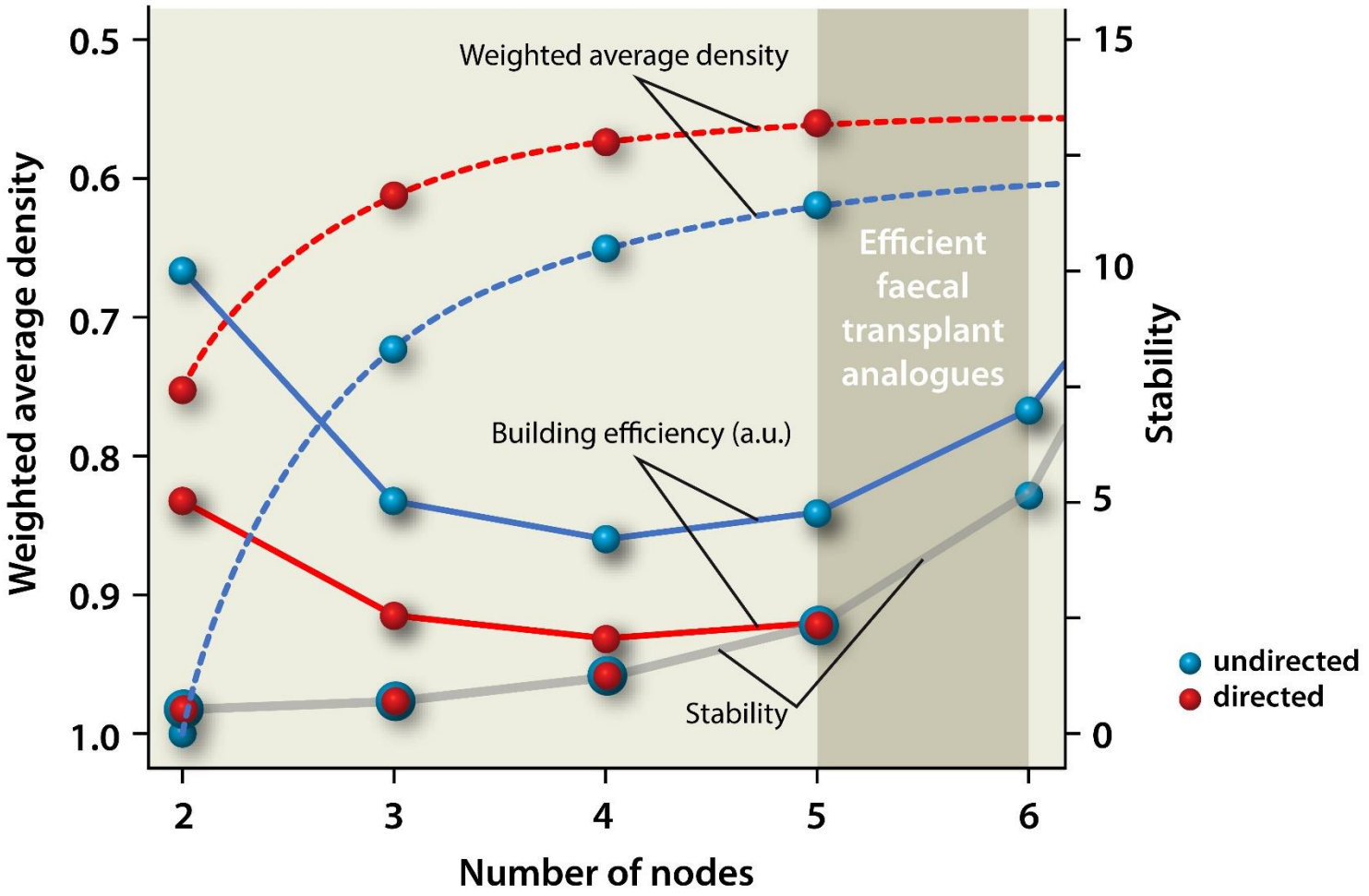
Stappen richting gepersonaliseerde interventie



Larsen, O. F.A., Koning, A. H., van der Spek, P. J., & Claassen, E. (2019). Scientific reports, 9(1), 1-6.

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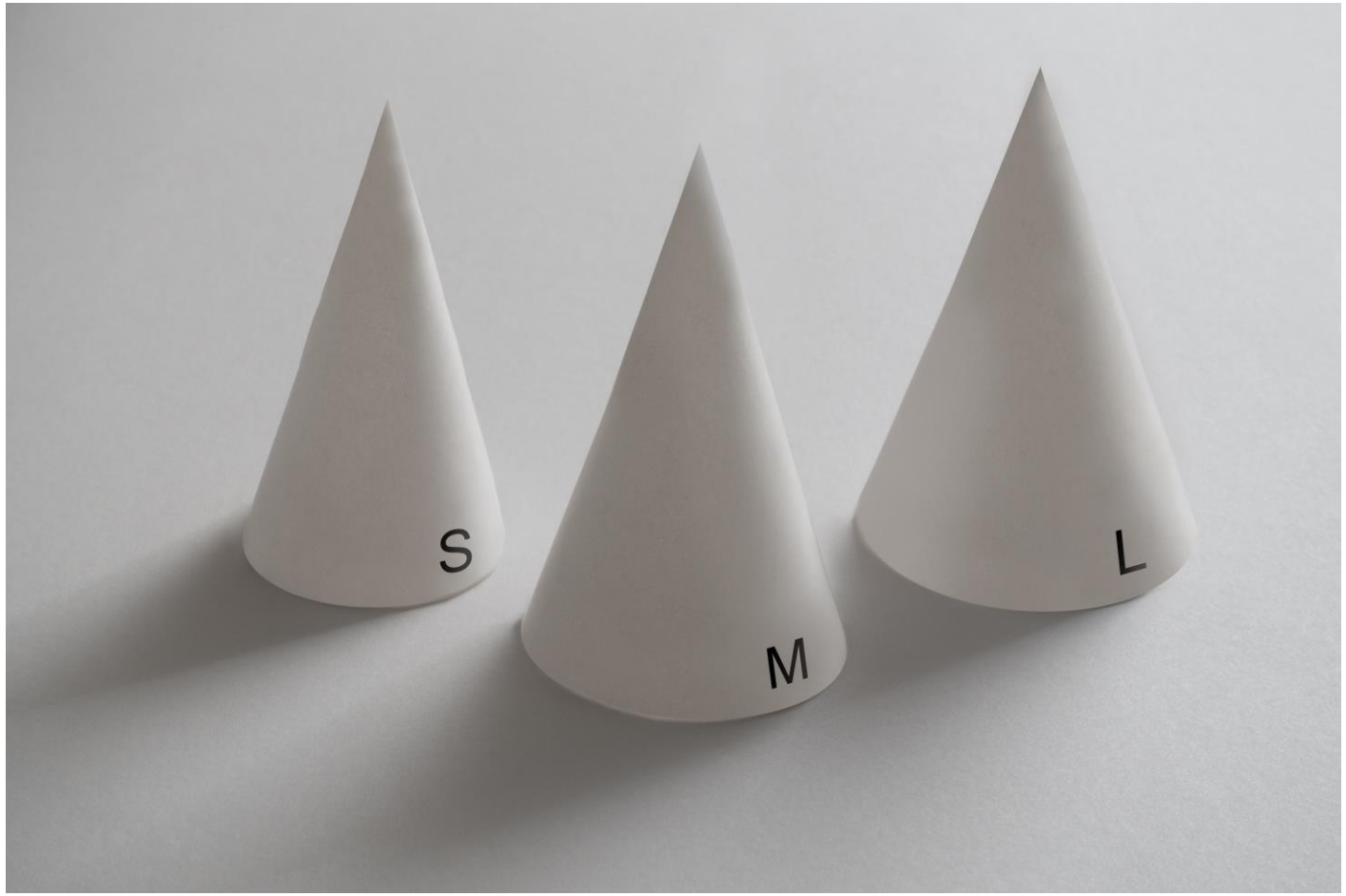
Wrap up



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Dank voor uw aandacht!

Vragen?

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