Gut-Brain-Microbiota axis: probiotic potential

Working on a healthy society

Dr. Olaf Larsen
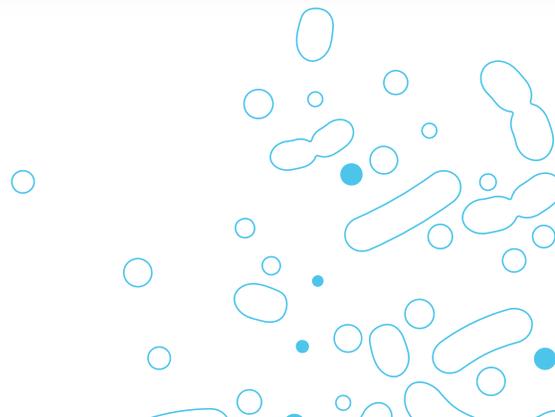
Disclosure belangen spreker Olaf Larsen

Geen (potentiële) belangenverstrengeling

Voor bijeenkomst mogelijk relevante relaties: Senior Manager Science @ Yakult Nederland B.V.
Asst. Professor @ Athena Institute, Vrije Universiteit
Amsterdam (0.2 FTE)

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

The gut-microbiota-brain axis
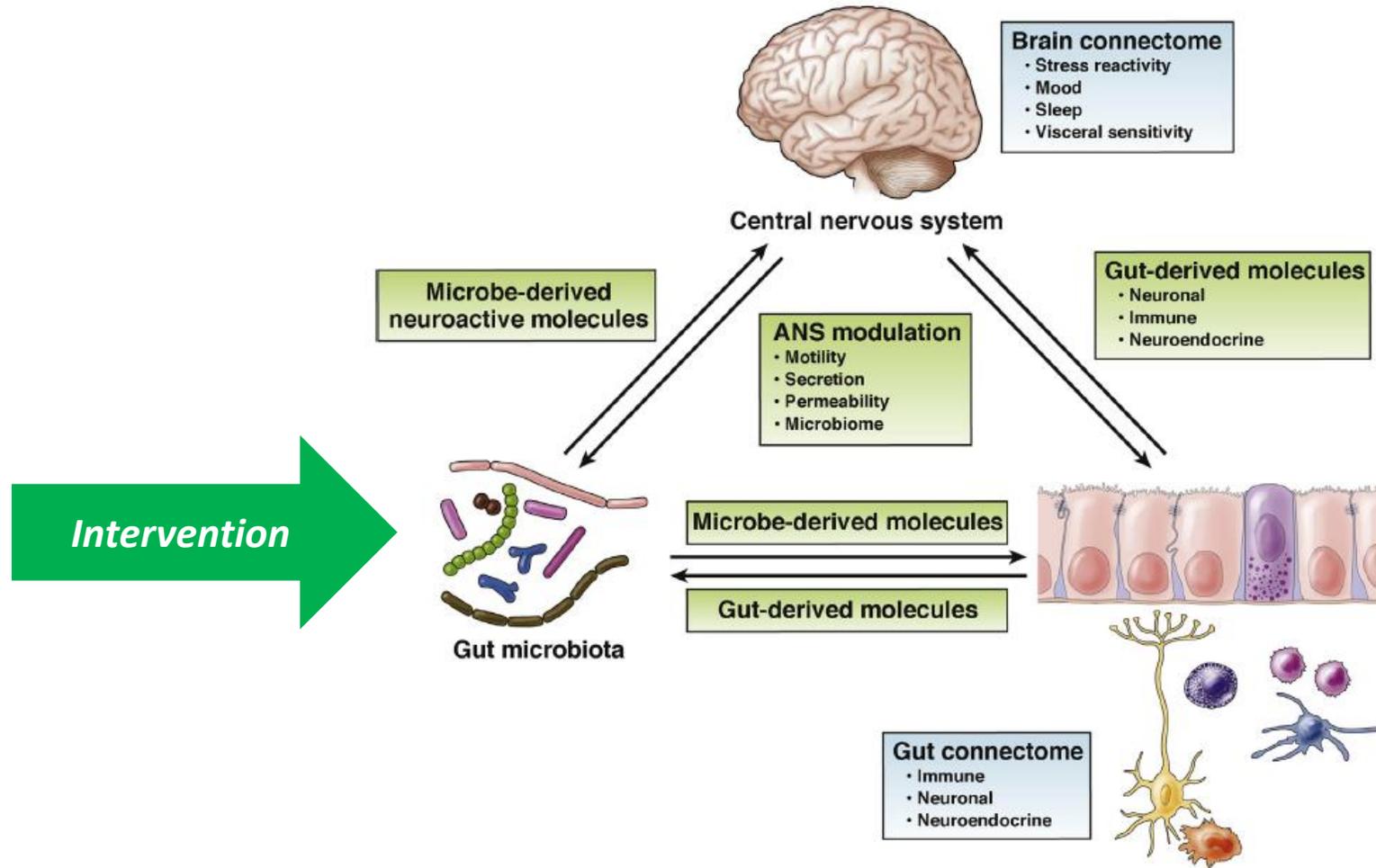
Martin at al. (2018). Cellular and molecular gastroenterology and hepatology, 6(2), 133-148.

Poll
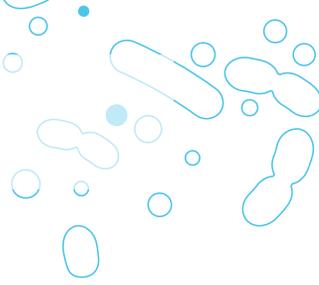
"In mijn praktijk adviseer ik patiënten probiotica"

- Nooit
- Zelden
- Regelmatig
- Vaak / Altijd

Recent results among >1.300 GP's in Western Europe

A

Nutritional Advice
"How often do you give nutritional advice in your practice?"

- Never/seldom: 14%
- Sometimes: 23%
- Regularly: 36%
- Often/always: 27%

B

Probiotic advice
"How often do you advice probiotics in your practice?"

- Never/seldom: 19%
- Sometimes: 29%
- Regularly: 30%
- Often/always: 21%
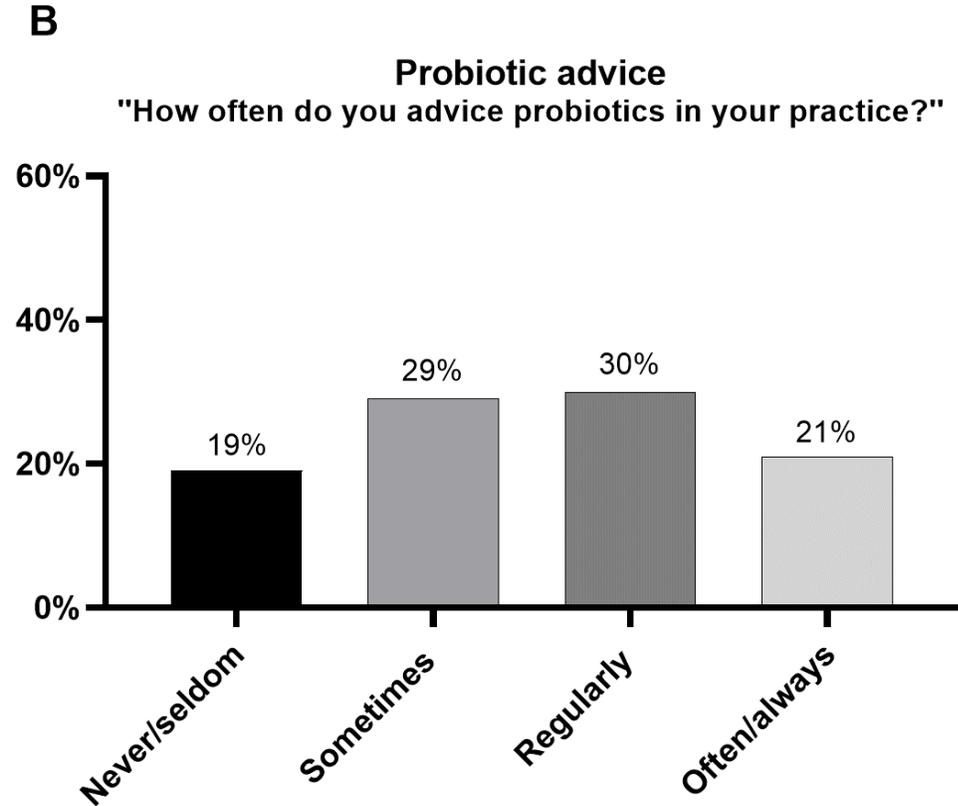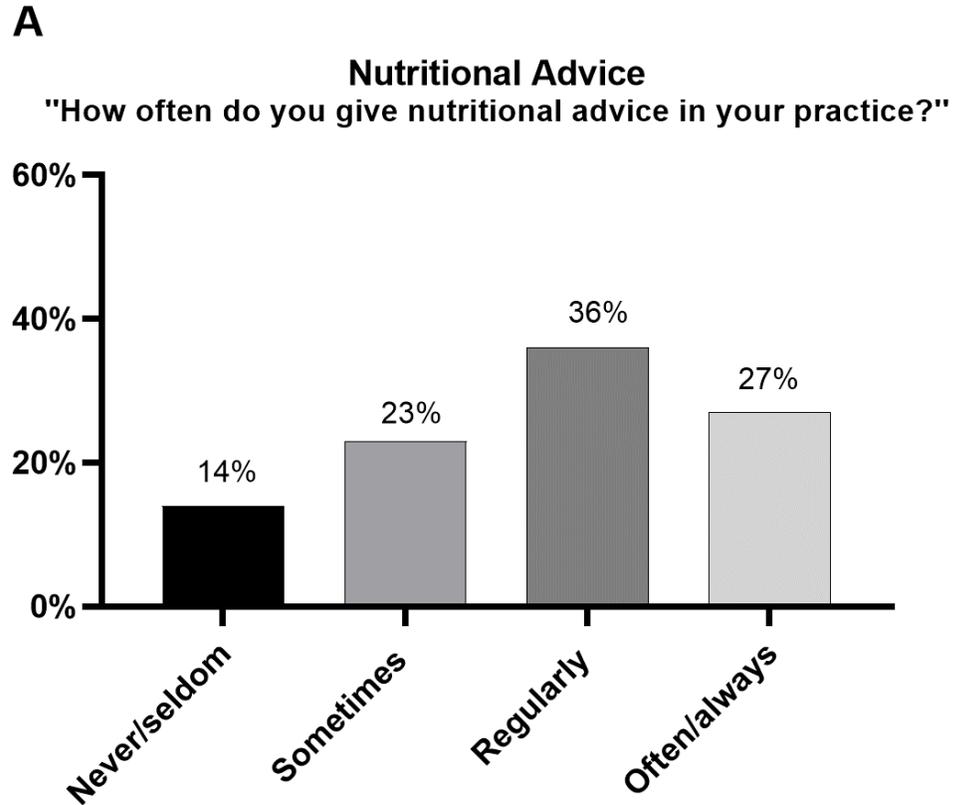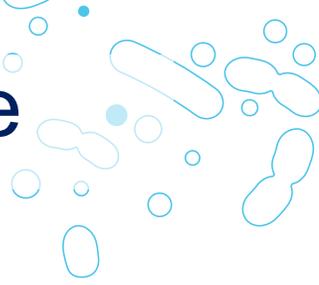
Van der Geest, A. M., Flach, J., Claassen, E., Sijlmans, A. W., Van de Burgwal, L. H. M., & Larsen, O. F. A. (2020). *PharmaNutrition*, *11*, 100178.

Intervention through probiotics

"Life microorganisms which 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
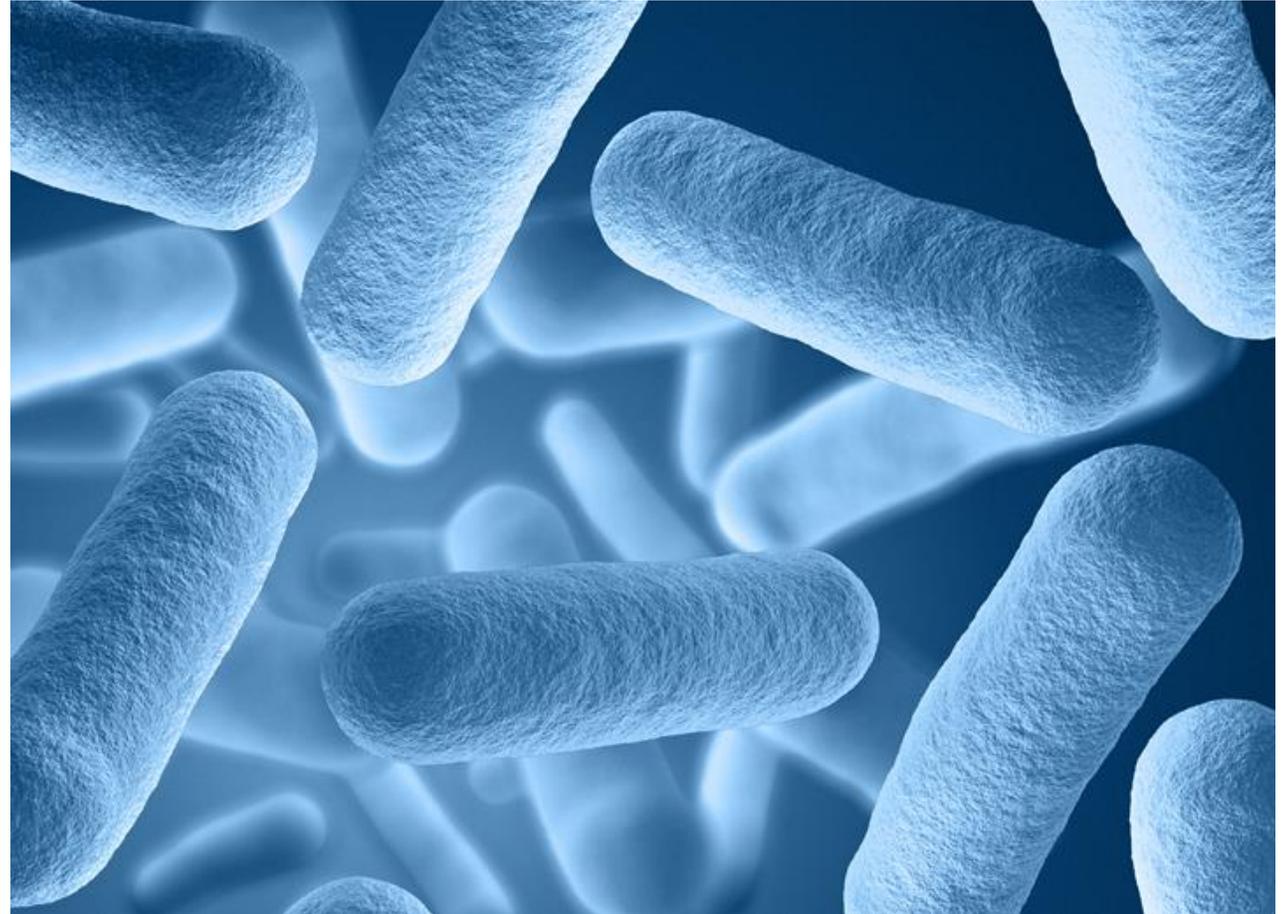
Probiotics: from generic to strain specificity

Rare
Strain-specific effects
- Neurological effects
- Immunological effects
- Endocrinological effects
- Production of specific bioactives

Frequent
Species-level effects
- Vitamin synthesis
- Direct antagonism
- Gut barrier reinforcement
- Bile salt metabolism
- Enzymatic activity
- Neutralization of carcinogens

Widespread
Among studied probiotics
- Colonization resistance
- Acid and SCFA production
- Regulation of intestinal transit
- Normalization of perturbed microbiota
- Increased turnover of enterocytes
- Competitive exclusion of pathogens

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

Probiotics: from strain to product specificity

DETERMINANTS → PRODUCT PARAMETERS

PRODUCTION & PROCESSING

MATRIX COMPONENTS

PROBIOTIC STRAIN

STORAGE CONDITIONS

GIT SURVIVAL

SHELF LIFE

HEALTH BENEFITS

SENSORY PROPERTIES

OTHERS

Flach, Koks, v.d. Waal, v.d. Nieuwboer, Claassen & Larsen, Critical reviews in food science and nutrition (2017): 1-15
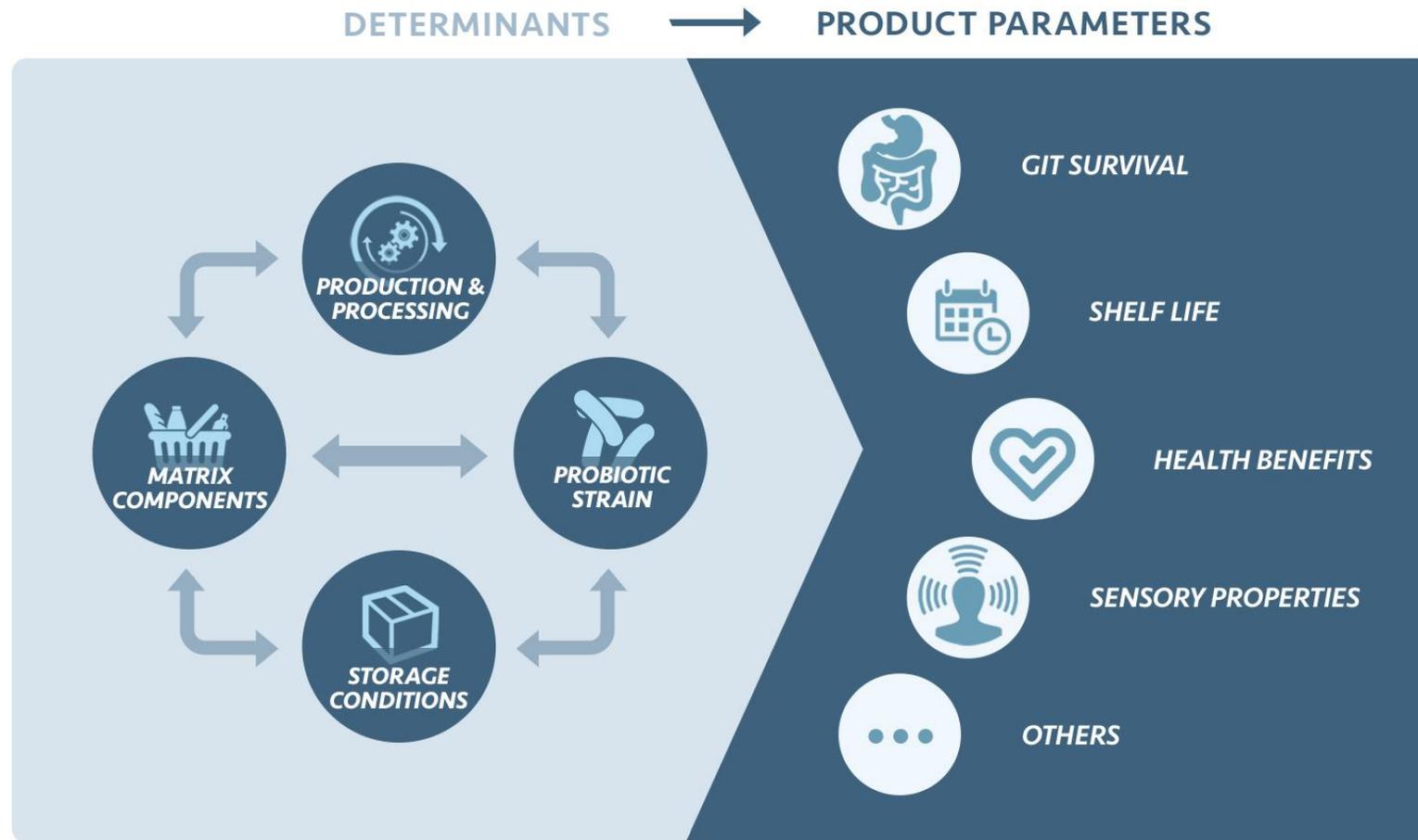
The human gut microbiota
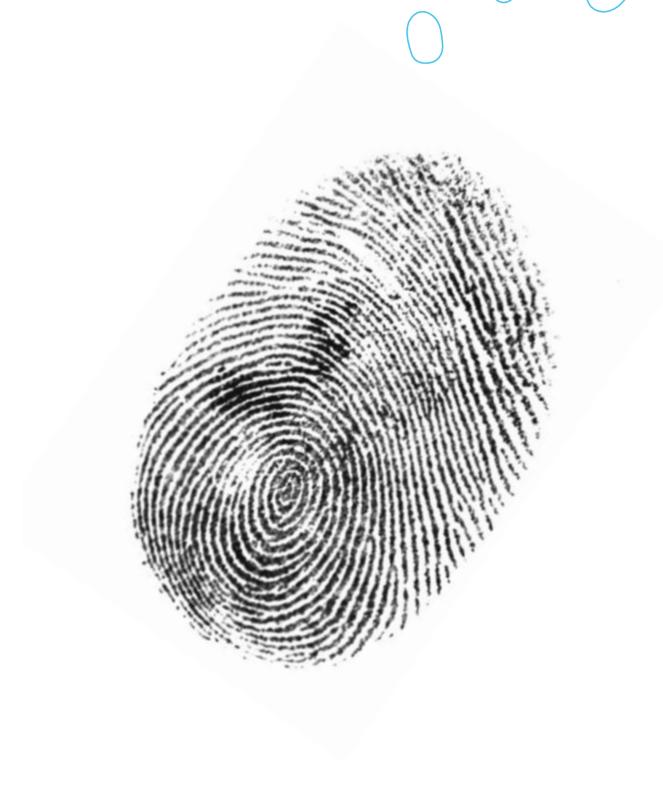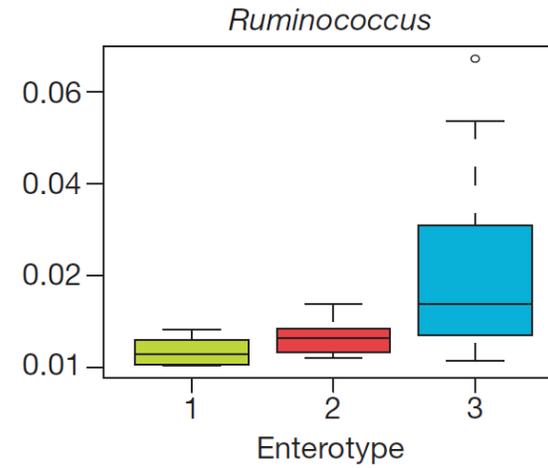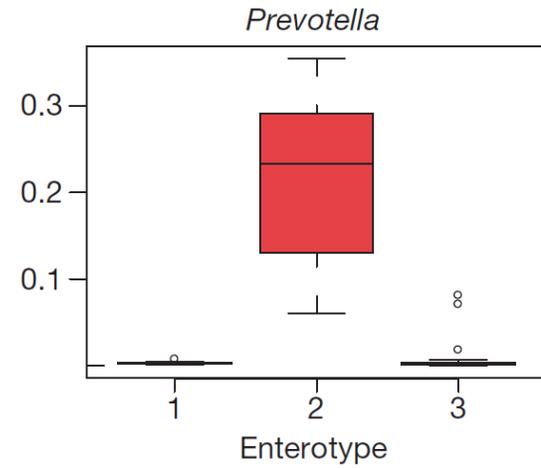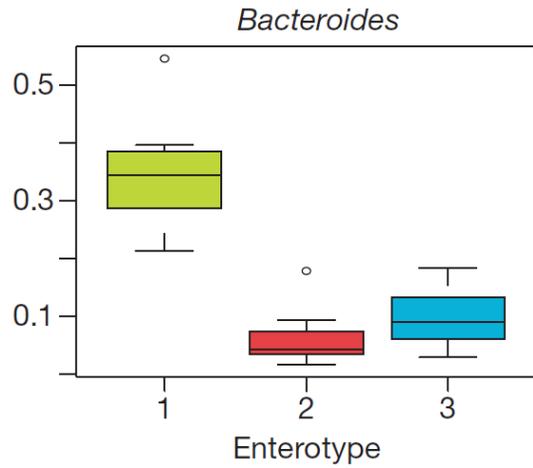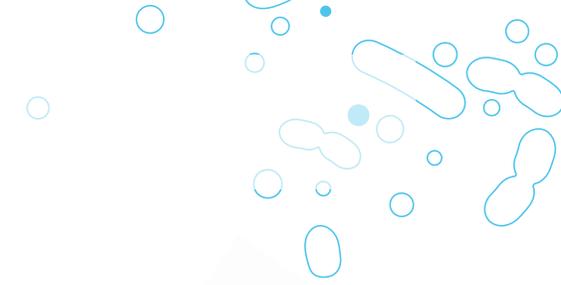
Arumugam, et al. (2011). Nature, 473(7346), 174-180.

Meta analysis: *Clostricium difficile* - associated diarrhea

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

| Study or Subgroup	Experimental Events	Total	Control Events	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).

Meta analysis: *Clostricium difficile* - associated diarrhea

Figure 3. Forest plot of comparison: 1 C. difficile associated diarrhea, outcome: 1.1 Incidence CDAD: complete case.
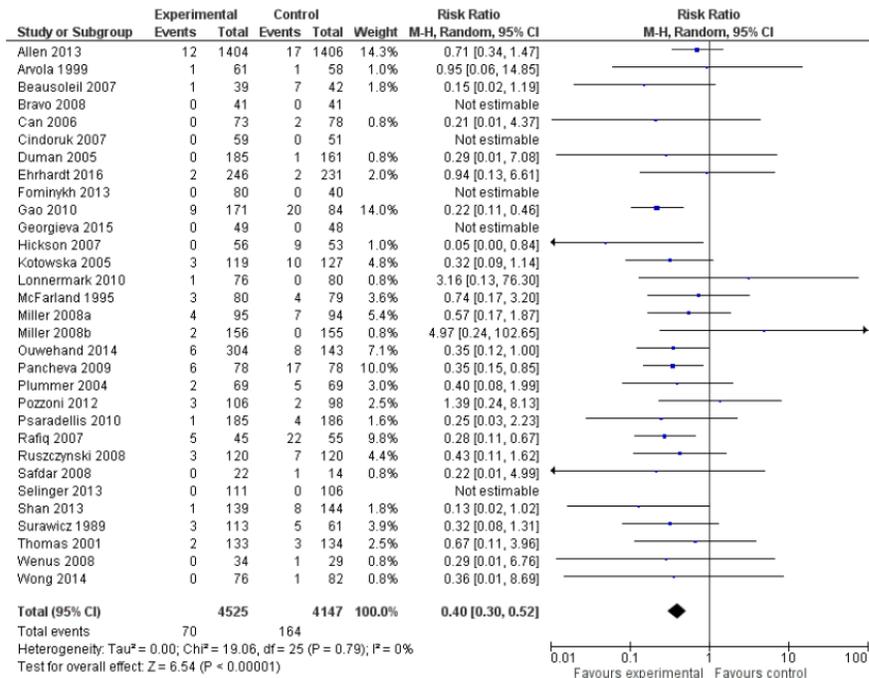
Figure 4. Forest plot of comparison: 1 Probiotics versus control, outcome: 1.24 Adverse Events: complete case.
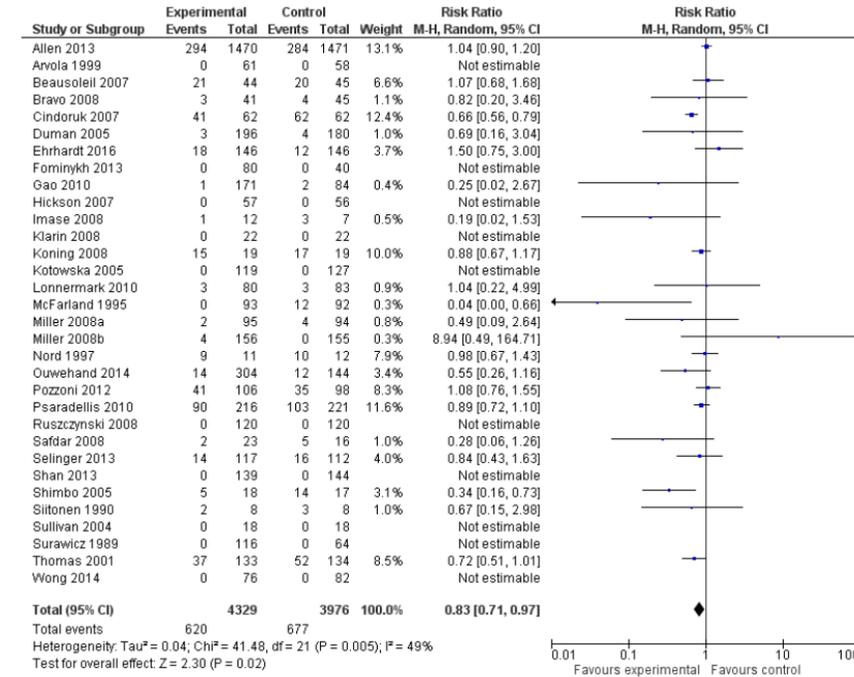
> *"Thirty-one studies (8672 participants) assessed the effectiveness of probiotics for preventing CDAD among participants taking antibiotics. Our results suggest that when probiotics are given with antibiotics the risk of developing CDAD is reduced by 60% on average."*

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).

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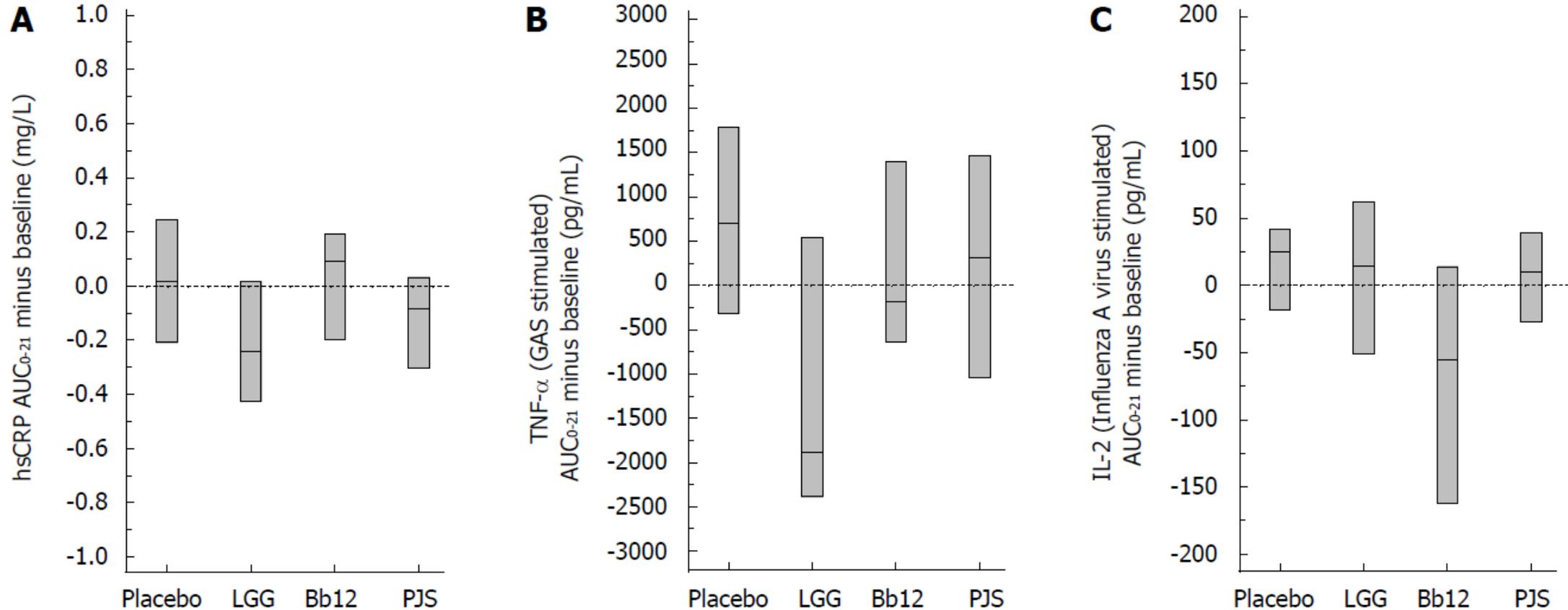
Kekkonen, R. A., Lummela, N., Karjalainen, H., Latvala, S., Tynkkynen, S., Järvenpää, S., ... & Korpela, R. (2008). World journal of gastroenterology: WJG, 14(13), 2029.

# Microbiota restoration: depression & anxiety
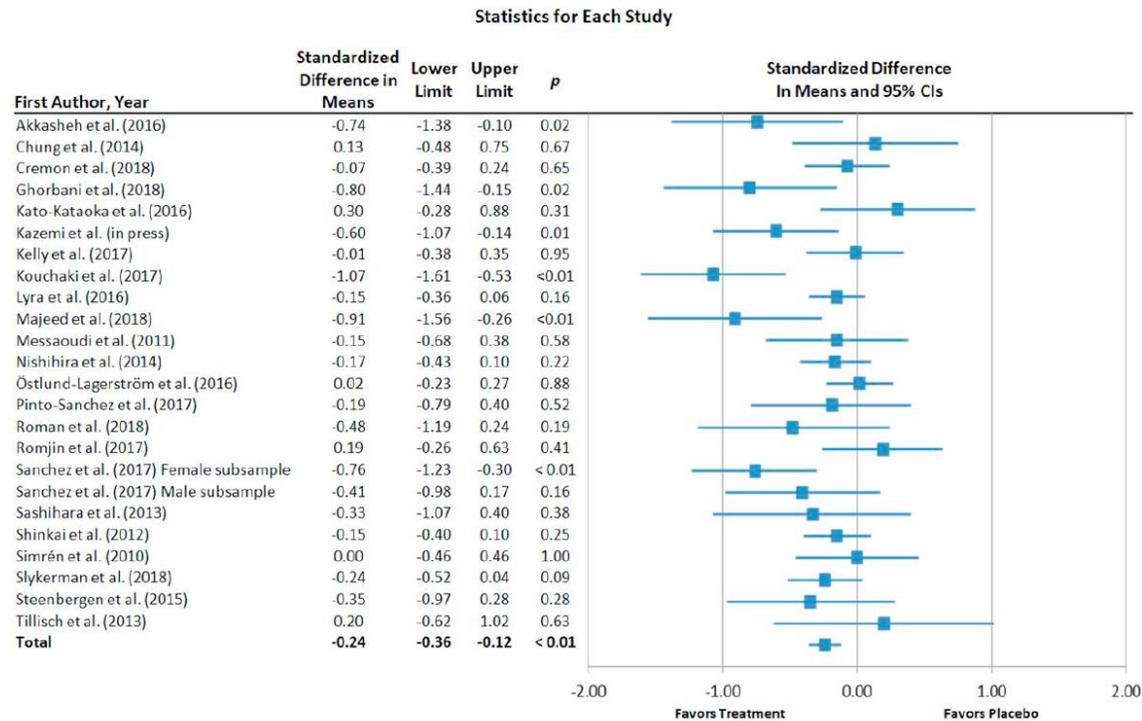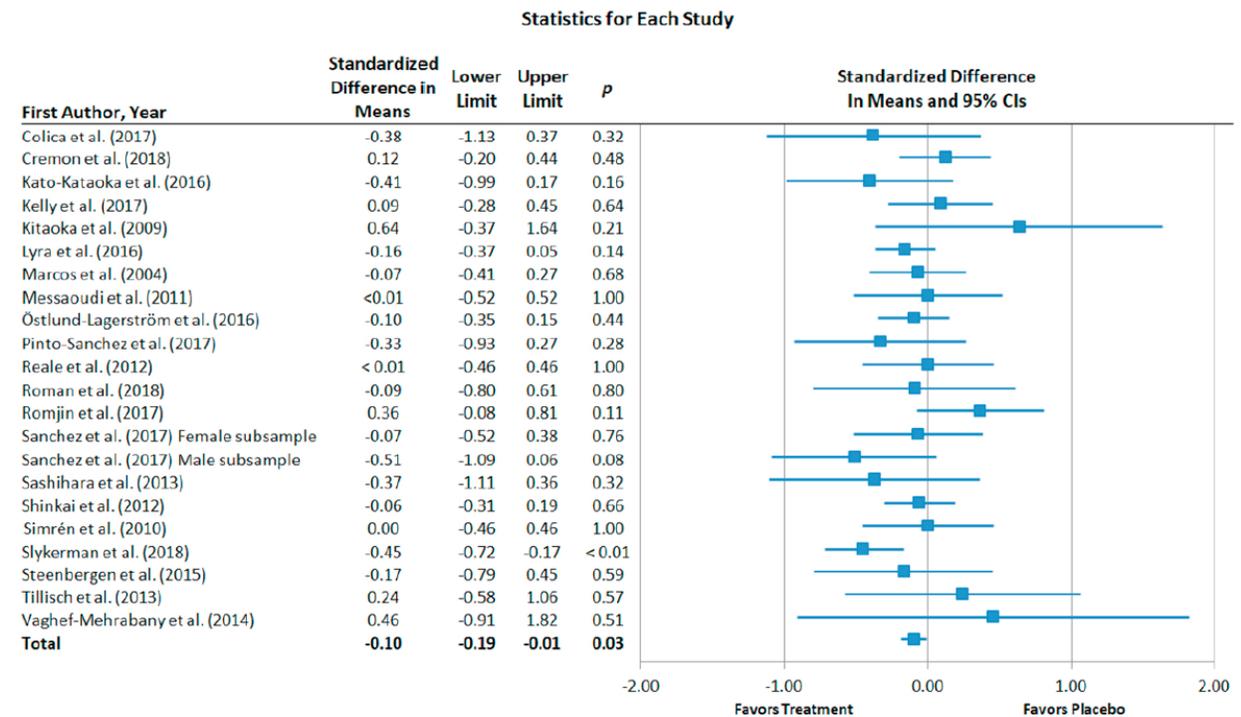

Liu, et al. (2019). Neuroscience & Biobehavioral Reviews, 102, 13-23.

Academic stress reduction (1)

Takada, M., at al. (2016). Neurogastroenterology & Motility, 28(7), 1027-1036.

Academic stress reduction (2)

Kato-Kataoka, et al. (2016). Beneficial microbes, 7(2), 153-156.
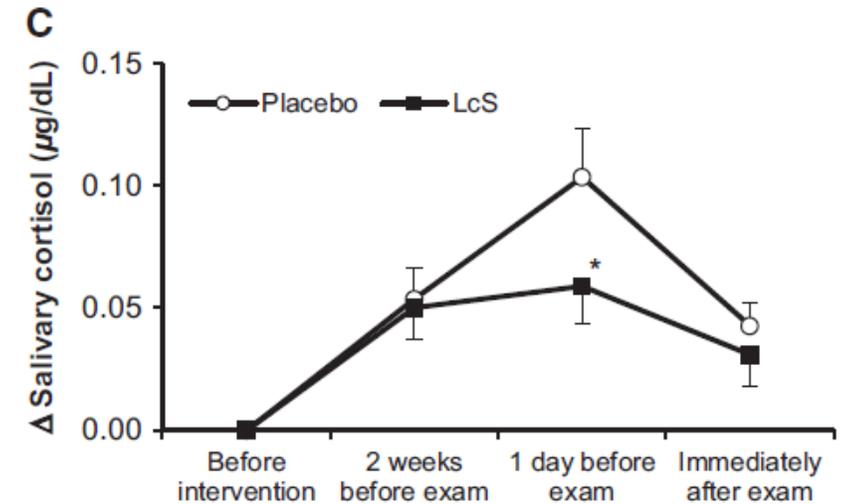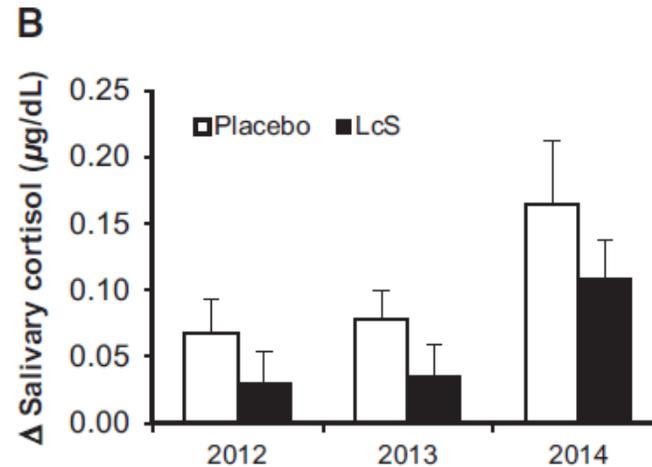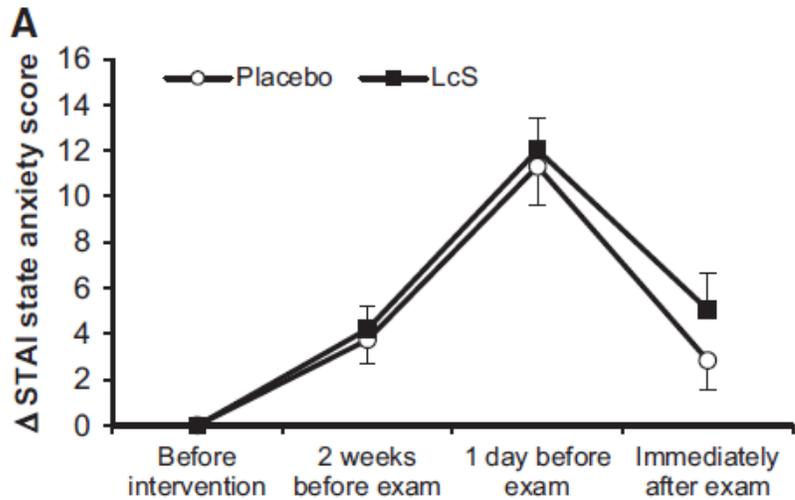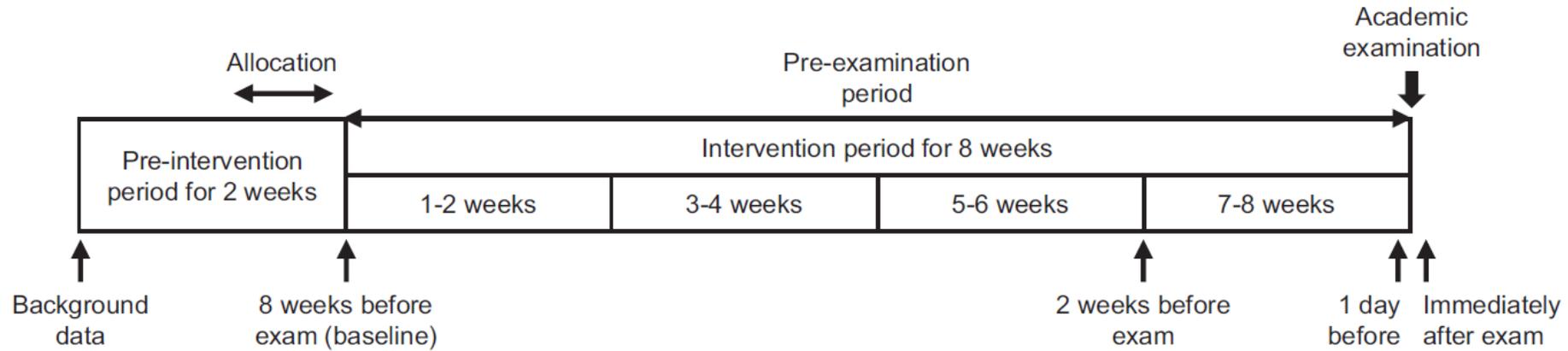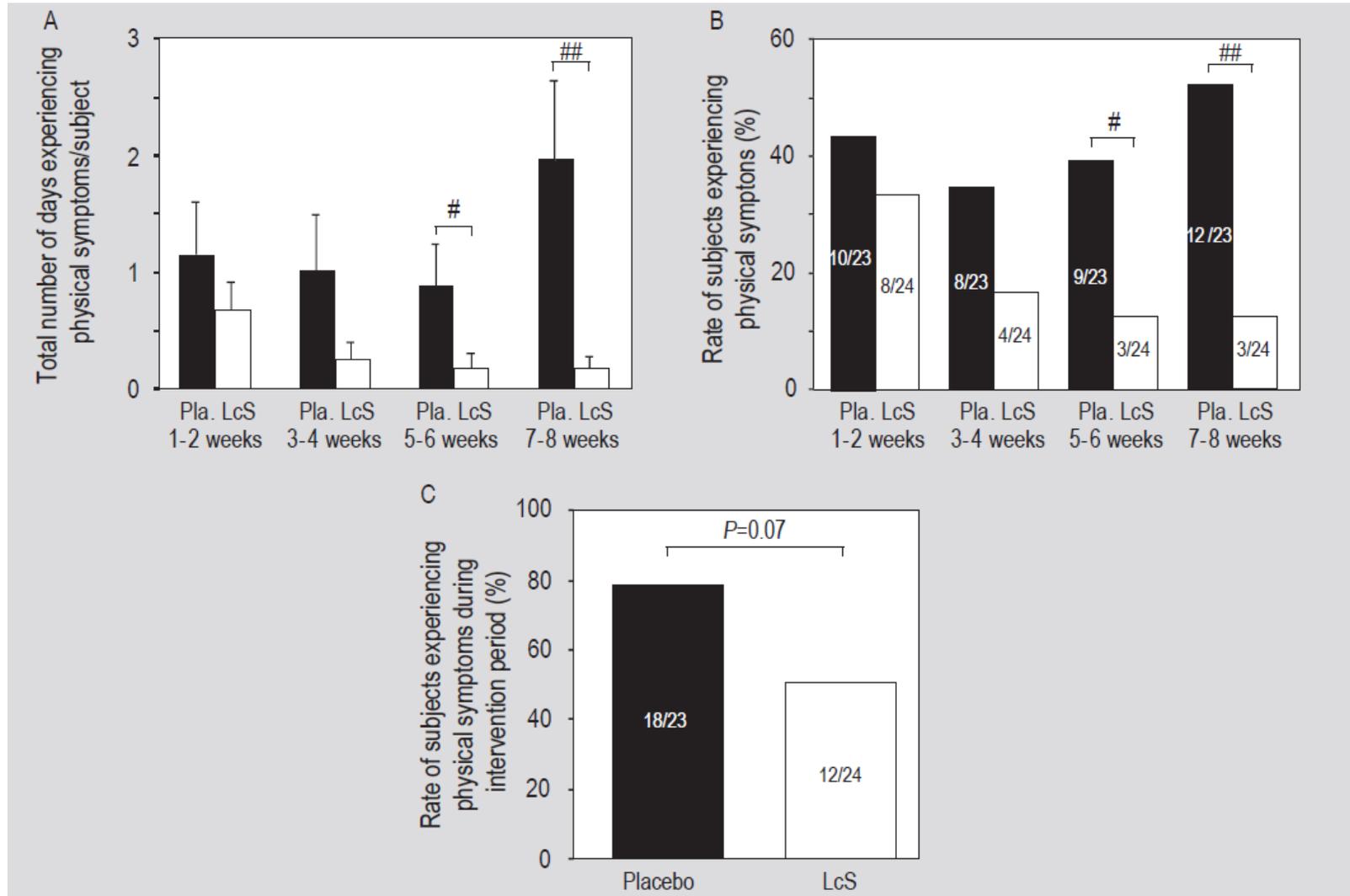
Sleep metrics and the gut microbiota

Table 1
Gut microbial phyla descriptives ($N = 37$).

Microbial phylum	Proportion of total bacteria				PSQI r_s	Stroop Word r_s	Stroop Color r_s	Stroop Color-Word r_s
	Minimum	Mean	Median	Maximum				
Euryarchaeota	0	2.41×10^{-4}	0	3.53×10^{-3}	0.04	−0.23	−0.13	−0.02
Actinobacteria	9.95×10^{-2}	9.06×10^{-3}	4.55×10^{-3}	5.43×10^{-2}	−0.18	0.27	0.37*	−0.02
Bacteroidetes	4.76	3.16×10^{-1}	3.02×10^{-1}	6.36×10^{-1}	0.08	−0.20	−0.31	−0.33*
Chloroflexi	0	1.47×10^{-6}	0	5.45×10^{-5}	−0.09	0.27	0.15	0.07
Cyanobacteria	0	1.84×10^{-3}	0	2.13×10^{-2}	−0.20	0.32	−0.10	0.14
Elusimicrobia	0	1.66×10^{-4}	0	6.13×10^{-3}	0.08	−0.21	−0.20	0.02
Firmicutes	1.53×10^{-1}	5.99×10^{-1}	6.11×10^{-1}	9.18×10^{-1}	0.10	0.05	0.19	0.21
Fusobacteria	0	1.36×10^{-4}	0	4.26×10^{-3}	0.20	−0.16	−0.24	−0.08
Lentisphaerae	0	6.21×10^{-5}	0	7.44×10^{-4}	−0.37*	0.11	0.02	0.35*
Proteobacteria	8.41×10^{-4}	4.19×10^{-2}	1.78×10^{-2}	4.03×10^{-1}	0.11	−0.14	−0.11	−0.13
Spirochetes	0	7.35×10^{-7}	0	2.72×10^{-5}	−0.09	0.27	0.15	0.07
Synergistetes	0	6.25×10^{-5}	0	1.83×10^{-3}	−0.17	0.08	0.08	0.15
TM7	0	1.23×10^{-5}	0	1.01×10^{-4}	−0.14	0.02	−0.002	−0.02
Tenericutes	0	9.26×10^{-4}	0	1.03×10^{-2}	−0.21	0.002	−0.03	0.20
Verrucomicrobia	0	3.10×10^{-2}	6.81×10^{-3}	4.03×10^{-1}	−0.52**	0.37	0.34*	0.29
Thermi	0	2.20×10^{-6}	0	3.38×10^{-5}	0.06	0.007	0.26	−0.16

Note: *: $p < 0.05$, **: $p < 0.01$. PSQI = Pittsburgh Sleep Quality Index.

Demonstratie Stroop-effect
Noem zo snel mogelijk de kleuren van de woorden.

| Congruent	Incongruent
Groen	Blauw
Blauw	Rood
Paars	Groen
Blauw	Rood
Rood	Paars

Het Stroop-effect houdt in dat het meer tijd kost om de kleuren te benoemen in de incongruente dan in de congruente conditie.

Anderson, Jason R., et al. "A preliminary examination of gut microbiota, sleep, and cognitive flexibility in healthy older adults." Sleep medicine 38 (2017): 104-107.

Sleep metrics and probiotic intervention

Fig. 2 Forest plot displaying the effect of consuming probiotics/paraprobiotics treatment vs. placebo on Δ PSQI score. Size of the squares is proportional to the weight of the study. A positive mean difference indicates a beneficial effect of consuming probiotics/paraprobiotics.

PSQI: Pittsburgh Sleep Quality Index

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value
Nishida, Sawada, Kuwano et al (2017)a	-0.060	0.521	-1.082	0.962	0.908
Marotta et al (2019)a	0.140	0.679	-1.190	1.470	0.837
Wong et al (2015)	0.440	0.772	-1.074	1.954	0.569
Kelly et al 2017	0.540	0.505	-0.449	1.529	0.285
Kato-Kataoka et al (2016)a	0.590	0.607	-0.599	1.779	0.331
Nishida, Sawada, Kuwano et al (2017)b	1.070	0.544	0.003	2.137	0.049
Kato-Kataoka et al (2016)b	1.200	0.714	-0.200	2.600	0.093
Marotta et al (2019)b	1.270	0.646	0.004	2.536	0.049
Dhiman et al (2014)	1.320	1.471	-1.563	4.203	0.369
Sawada et al (2017)	1.690	0.798	0.126	3.254	0.034
Nishida, Sawada, Kawai et al (2017)	1.760	0.726	0.337	3.183	0.015
	0.780	0.197	0.395	1.166	0.000

Difference in means and 95% CI

-4.50   -2.25   0.00   2.25   4.50

Favours Control   Favours Treatment

Irwin, C., McCartney, D., Desbrow, B., & Khalesi, S. (2020). European Journal of Clinical Nutrition, 74(11), 1536-1549.

Poll

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

- Nooit
- Zelden
- Regelmatig
- Vaak / Altijd
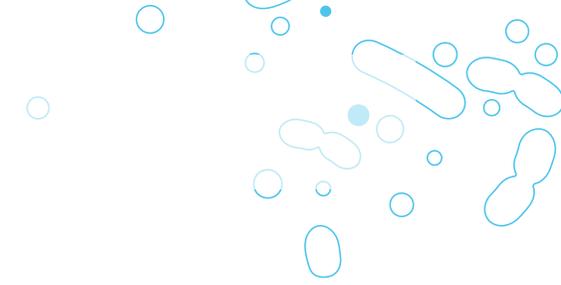
# From microbes to functional entities: butyrate example
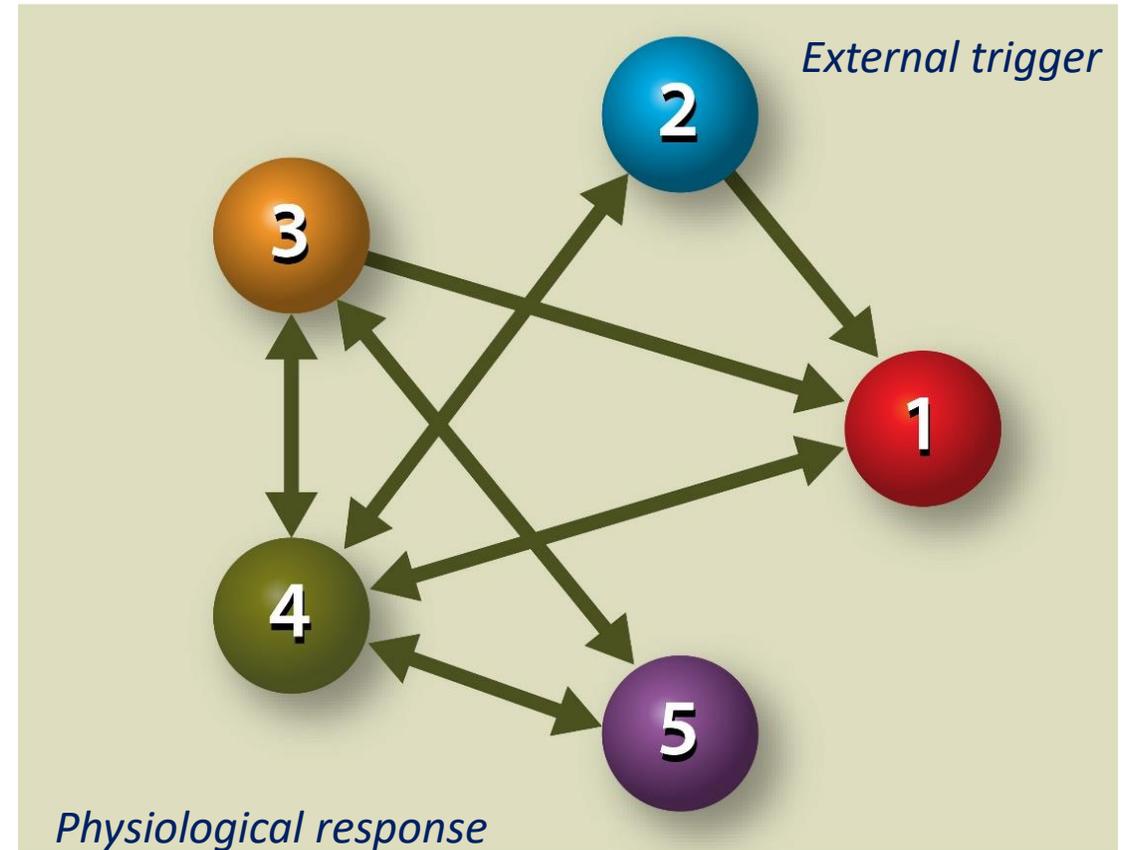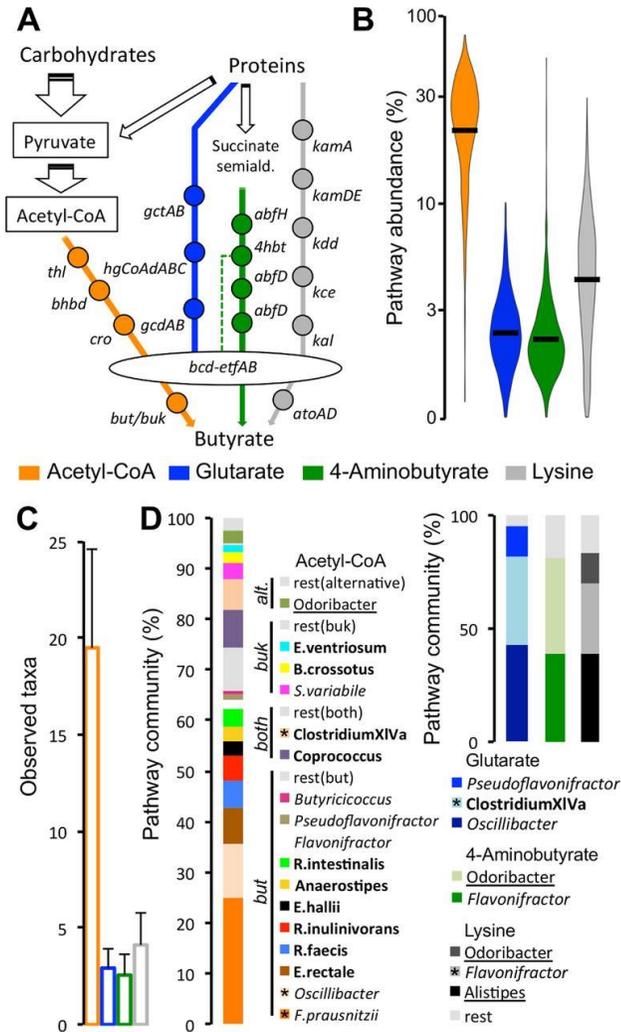
Vital, M., Karch, A., & Pieper, D. H. (2017). Colonic butyrate-producing communities in humans: an overview using omics data. *Msystems*, *2*(6).

Towards a personalized intervention

Larsen, O. F.A., Koning, A. H., van der Spek, P. J., & Claassen, E. (2019). Scientific reports, 9(1), 1-6.
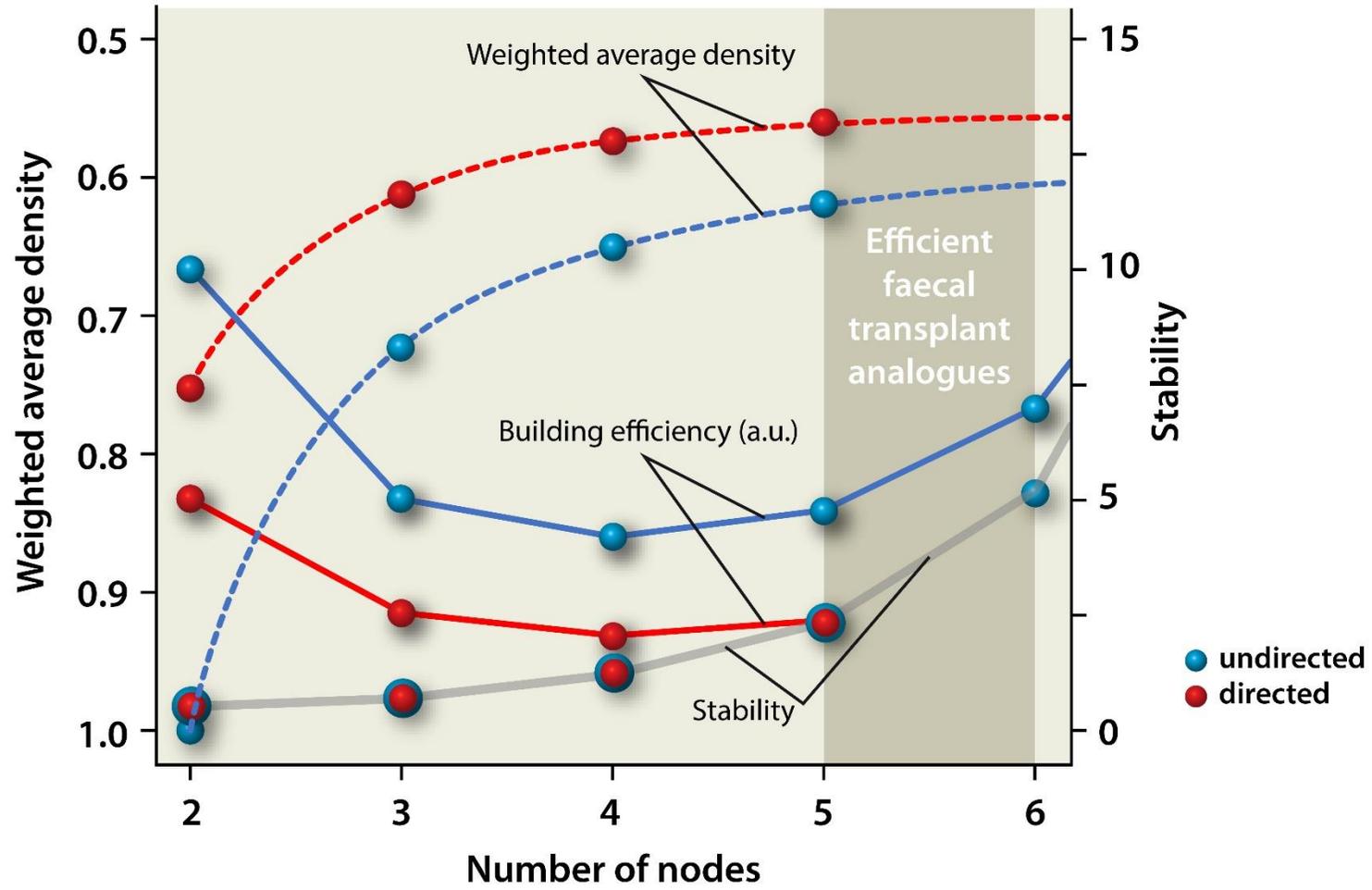
Wrap up
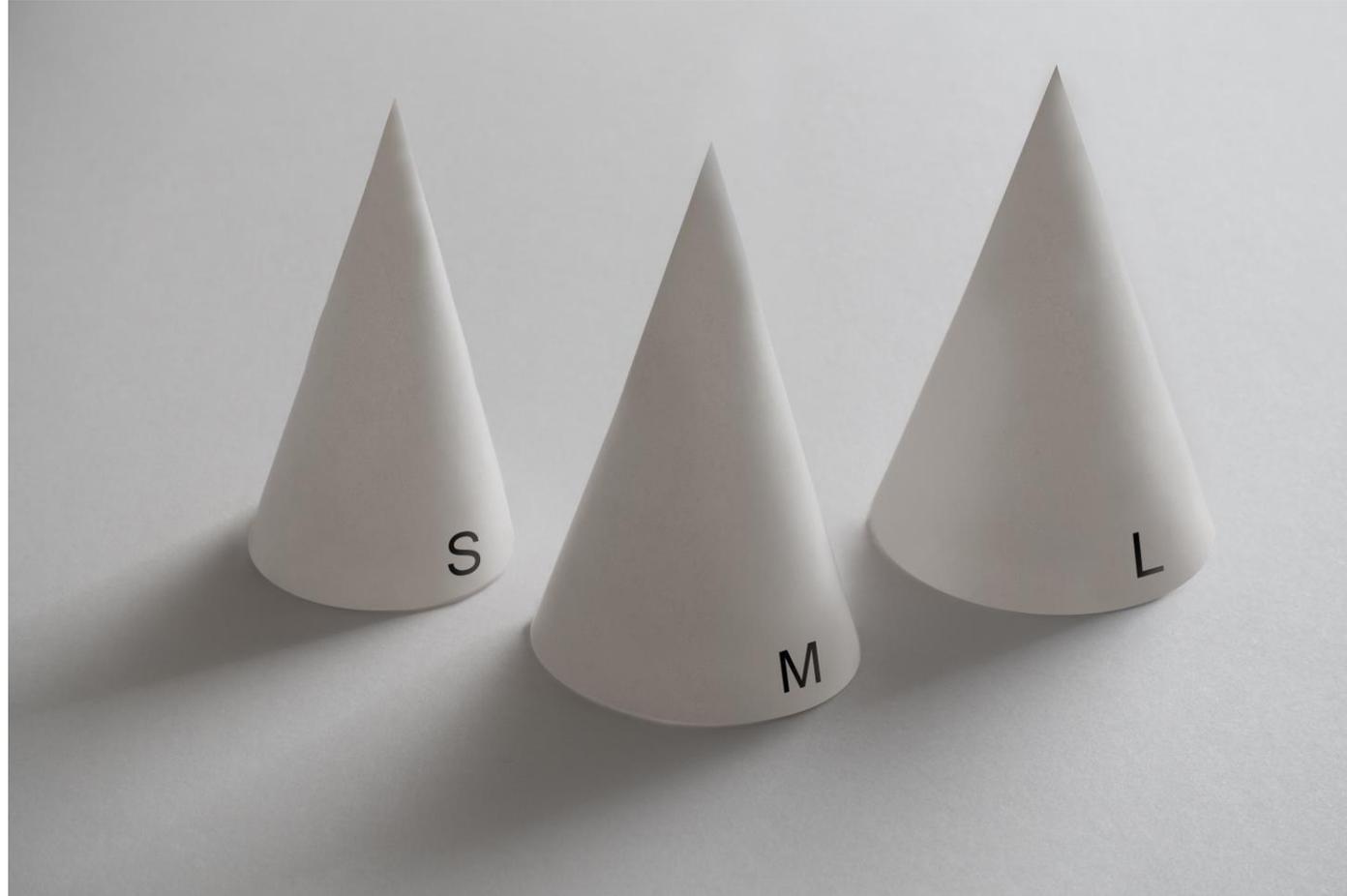
Hartelijk dank voor je deelname!

- Na afloop direct doorgelinkt naar evaluatie (niet wegklikken)

- Voor artsen verplichte toets voor accreditatiepunten

- Hand-outs

- Replay

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