INTERACCIÓN DE LOS PROBIÓTICOS CON LA MICROBIOTA INTESTINAL Y LA OBESIDAD

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Divulgación de conflicto de intereses

Barbara Peters, PhD

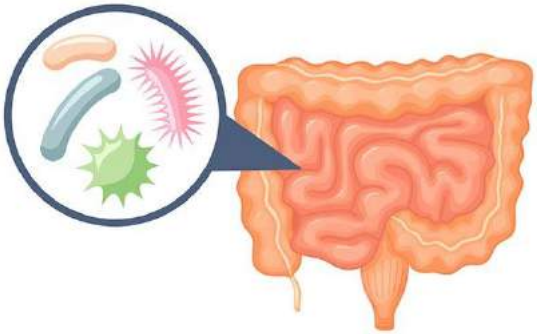
Nutricionista

Esta presentación NO es respaldada por ninguna subvención

Probióticos

"Microorganismos vivos que, cuando se administran en cantidades apropiadas, confieren al huésped un beneficio para la salud"

FAO/OMS 2001



Composición de la Microbiota Intestinal

Cinco filos

Bacteroidetes

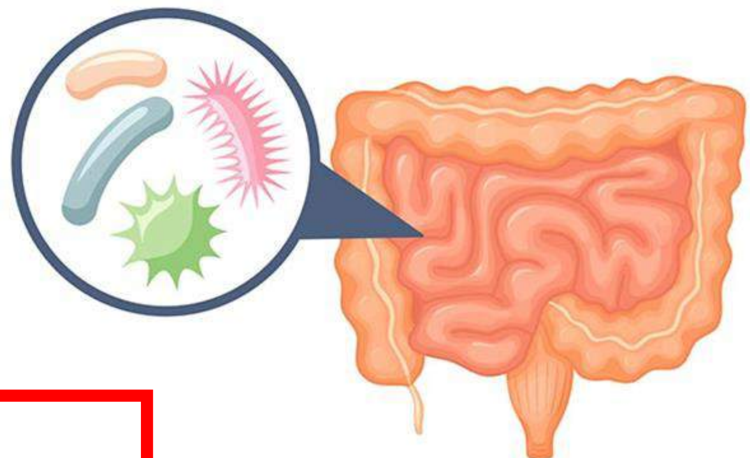
Firmicutes

Actinobacteria

Proteobacteria

Fusobacteria

Verrucomicrobia



baja concentración de oxígeno

más de 800 especies bacterianas

hasta 1012 células / gramo de heces

90% de las bacterias totales

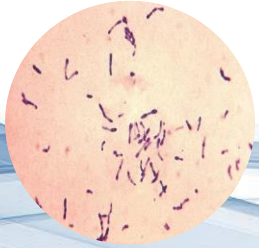
DERRIEN, VAN HYLCKAMA VLIEG, 2015; LAPARRA, SANZ, 2010; SHEN et al., 2013

Firmicutes

Los géneros notables incluyen *Bacillus, Enterococcus, Streptococcus, Staphylococcus, Listeria,* ***Lactobacillus*** (en la clase Bacilli), *Clostridium* (en la clase Clostridia) y *Mycoplasma* (en la clase Mollicutes).

Bacteroidetes

Una de las especies del género clínicamente más importantes es el *Bacteroides fragilis.*



Actinobacteria

Las especies del género ***Bifidobacterium*** desempeñan un papel fundamental en la regulación de la actividad intestinal normal, principalmente en bebés lactantes.

Especies bacterianas aceptadas como probióticos

Lactobacillus:

Acidophilus

Casei

Fermentum

Gasseri

Johnsonii

Paracasei

Plantarum

Rhamnosus

salivarius

***Bifidobacterium*:**

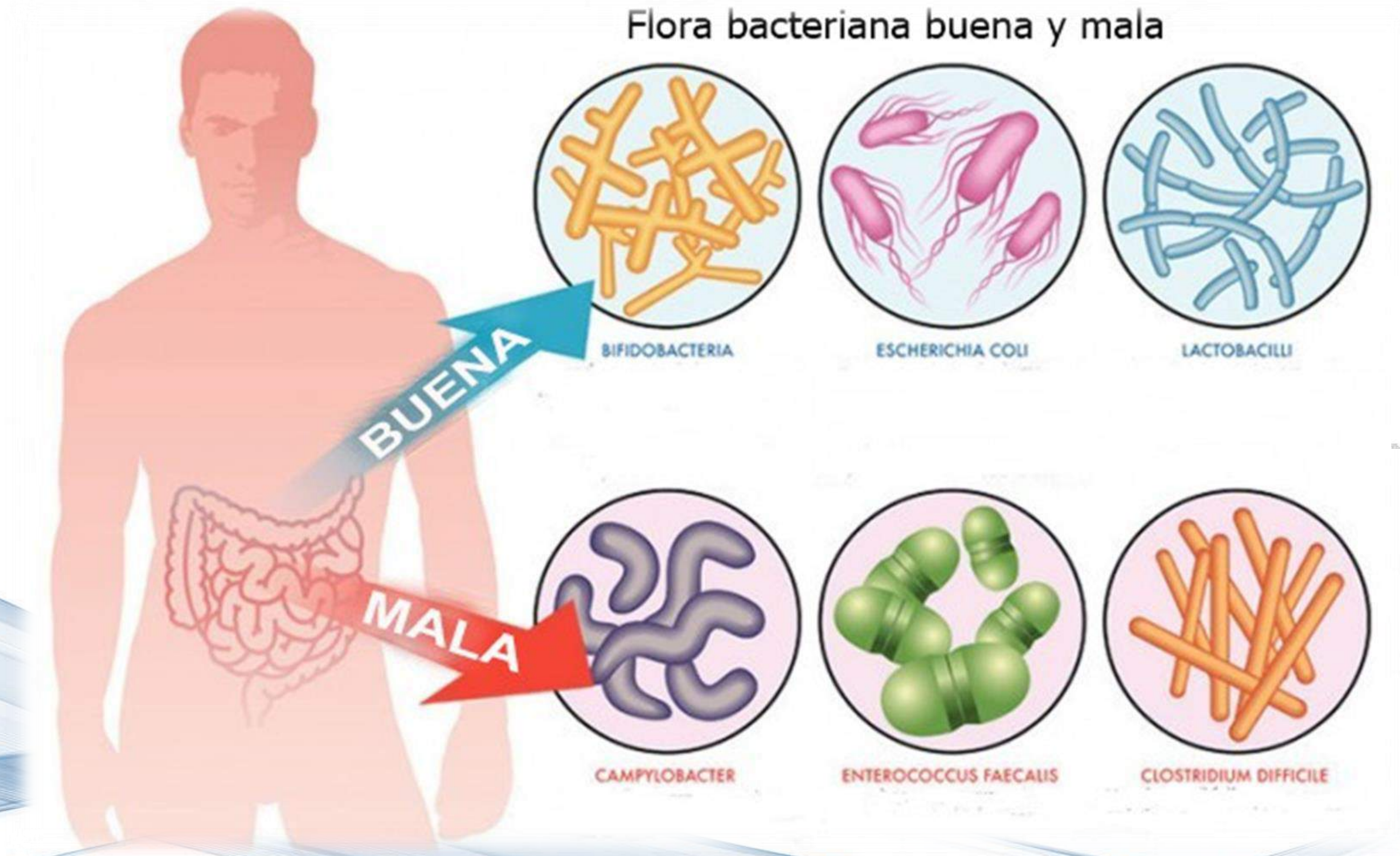
Adolescentes

Animalis

Bifidum

Breve

longum


Flora bacteriana buena y mala
BUENA
MALA
BIFIDOBACTERIA
ESCHERICHIA COLI
LACTOBACILLI
CAMPYLOBACTER
ENTEROCOCCUS FAECALIS
CLOSTRIDIUM DIFFICILE

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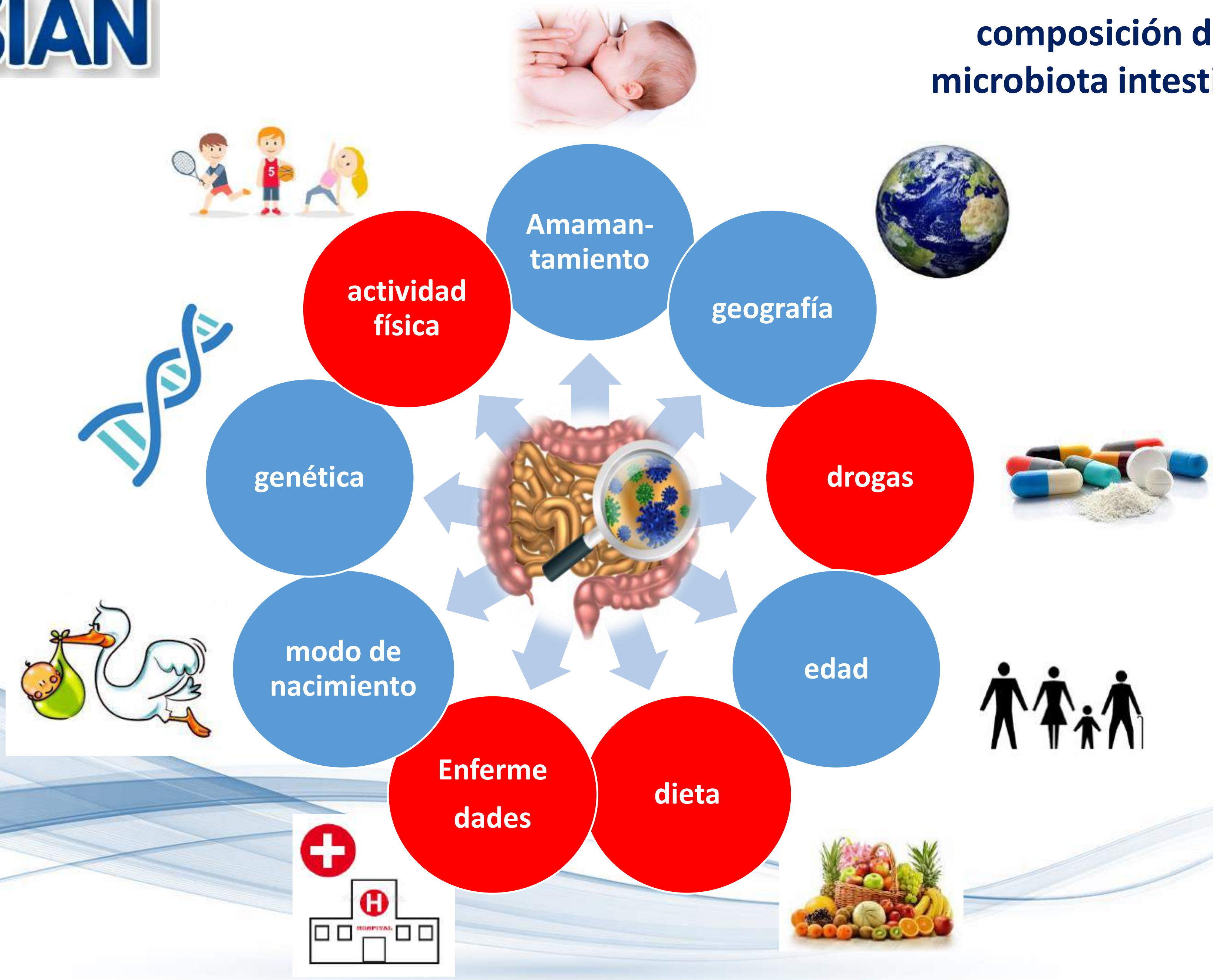
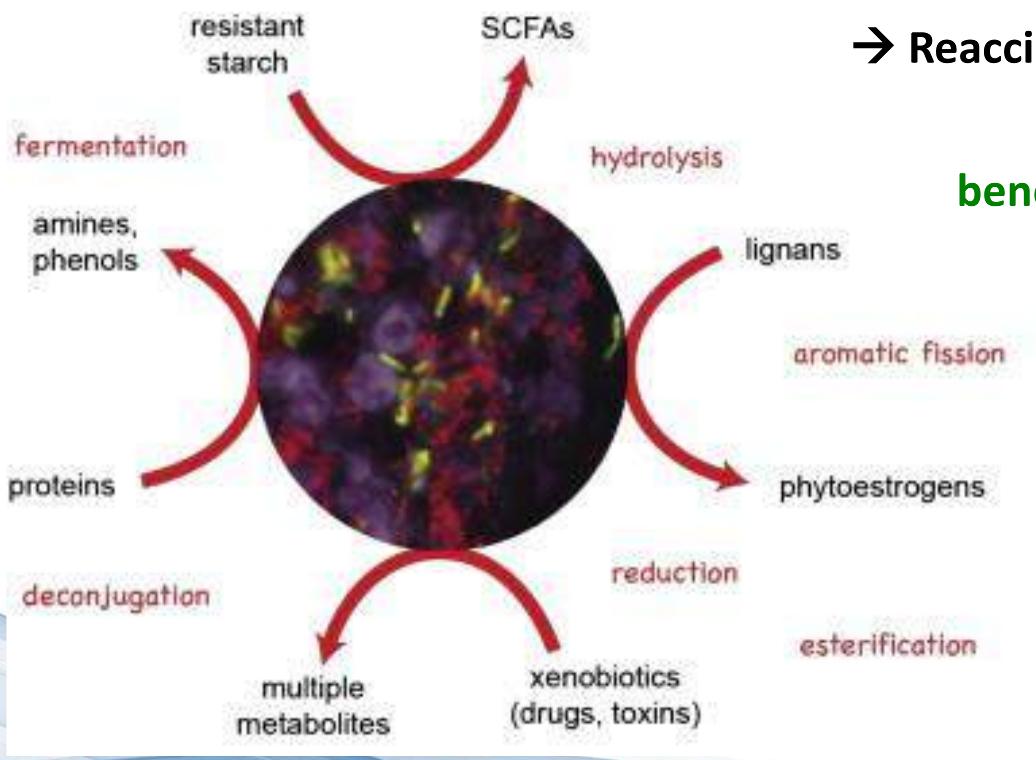
Determinantes de la composición de la microbiota intestinal



Papel de la microbiota en la salud



→ **Reacciones de conversión química**

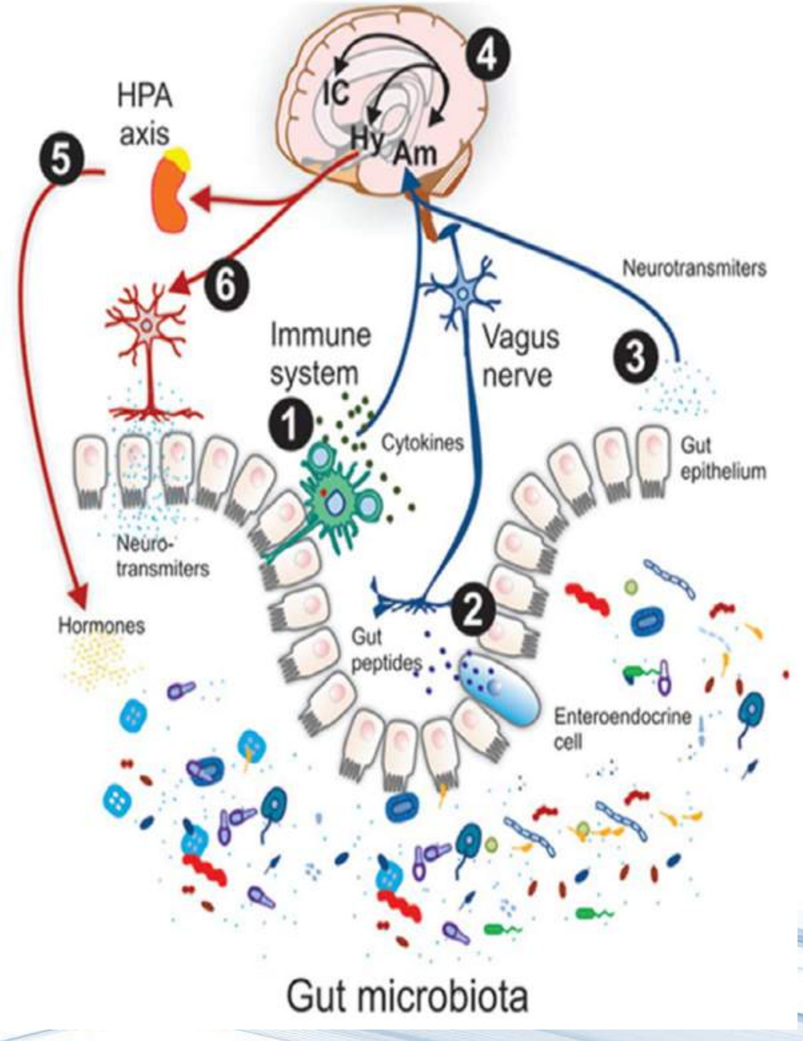
beneficiosas

perjudiciales

Simbiosis
X
Disbiosis

Backhed et al. Cell Host & Microbe 15, 2012

Eje microbiota-intestino-cerebro



1 - Linfocitos: acciones endocrinas o paracrinas
2 - Terminales sensoriales neuronales: activación por péptidos intestinales
3 - Neurotransmisores o sus precursores: efectos endocrinos o paracrinos
4 - Activación del hipotálamo, amígdala y cortex insular
5 – Corticosteroides: liberados como resultado de la activación del eje hipotalámico-pituitario-adrenal (HPA)
6 - Activación eferente neuronal: reflejo colinérgico antiinflamatorio" y/o la activación simpática

Montiel-Castro et al. Front. Integr. Neurosci., 07, 2013

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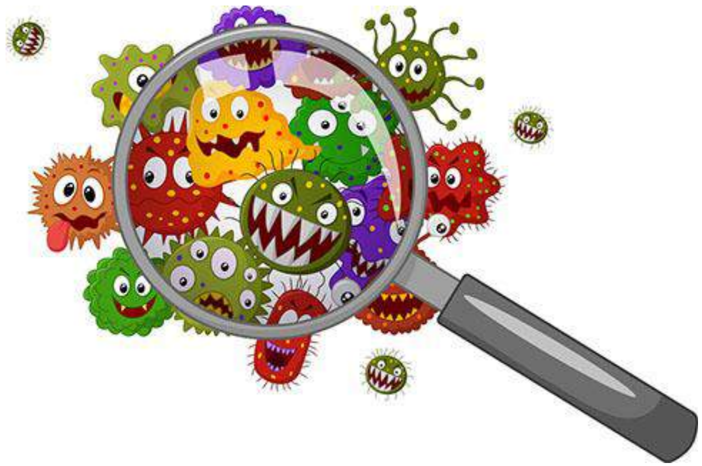
GLORIA

Disbiosis y enfermedades

→ Enfermedades del intestino

- Síndrome de malabsorción
- Enfermedades malignas: cáncer colorrectal
- Enfermedad inflamatoria intestinal
- Síndrome del intestino irritable
- Enfermedades diarreicas
- Infección por Clostridium Difficile



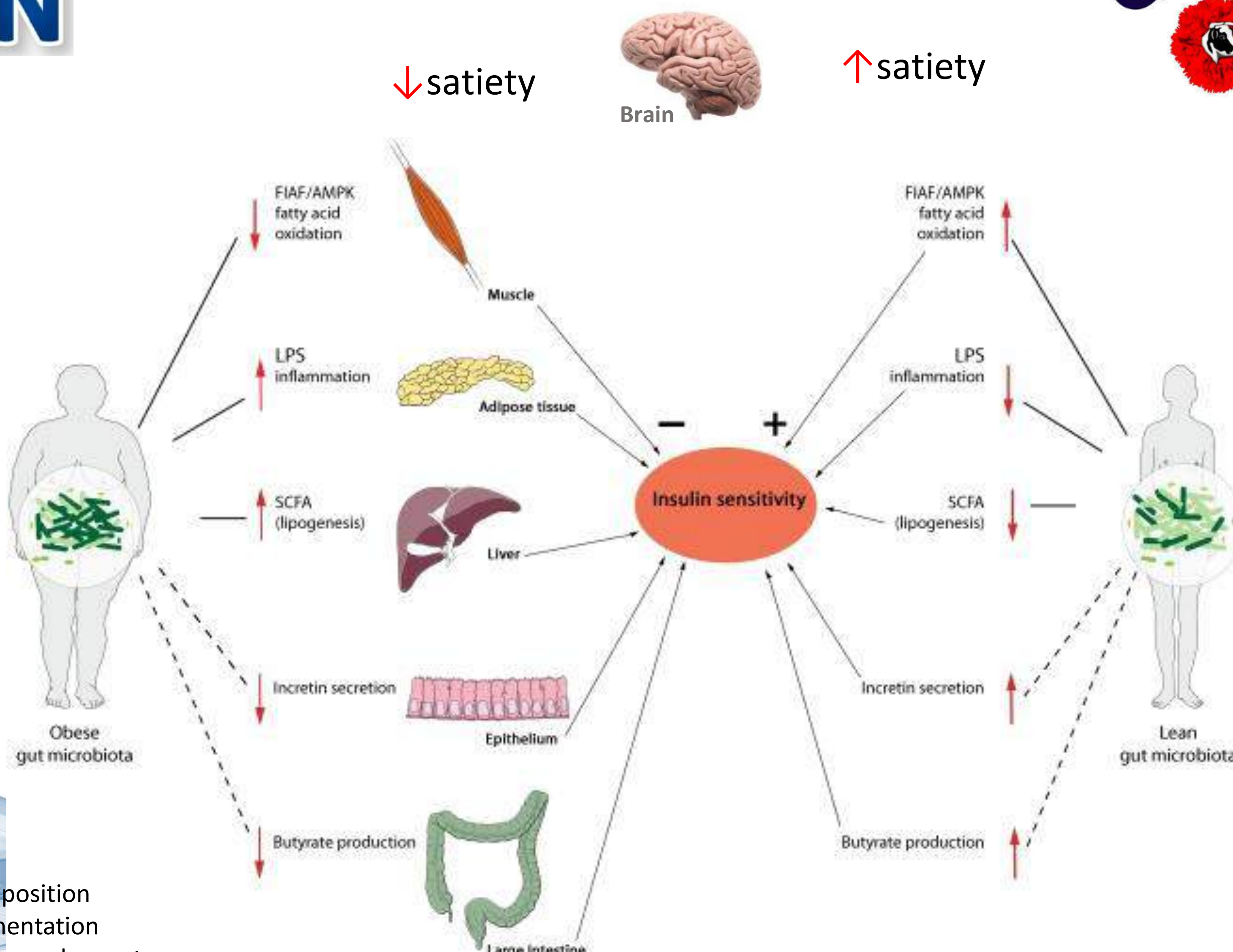
→ Otras enfermedades

- Malignas: cáncer de hígado, cáncer de mama
- Complicaciones del hígado: cirrosis
- Afecciones alérgicas
- Trastornos autoinmunes (DM1, artritis, etc.)
- Anomalías del eje intestino-cerebro
- Autismo y otros trastornos neurológicos
- **Obesidad y otros transtornos metabólicos**
- Síndrome de fatiga crónica
- Enfermedades periodontales

(NEISH, 2009; SOMMER; BACKHED, 2013)

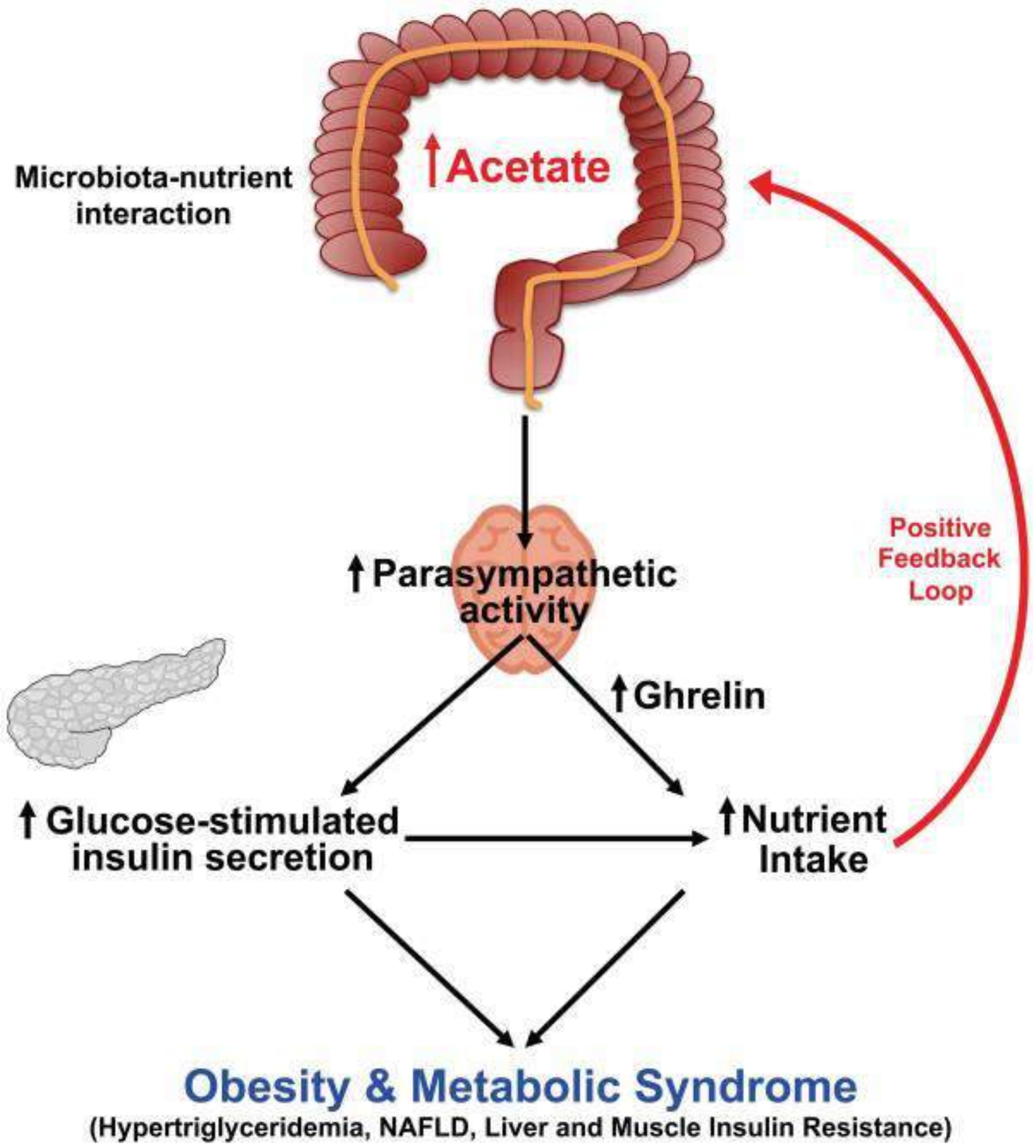
Microbiota intestinal y obesidad

Mayor cantidad relativa de Firmicutes
en relación a los Bacteroidetes



- Altered composition
- Altered fermentation
- Increased energy harvest

Vrieze et al. Diabetologia. 2010 Apr; 53(4): 606–613

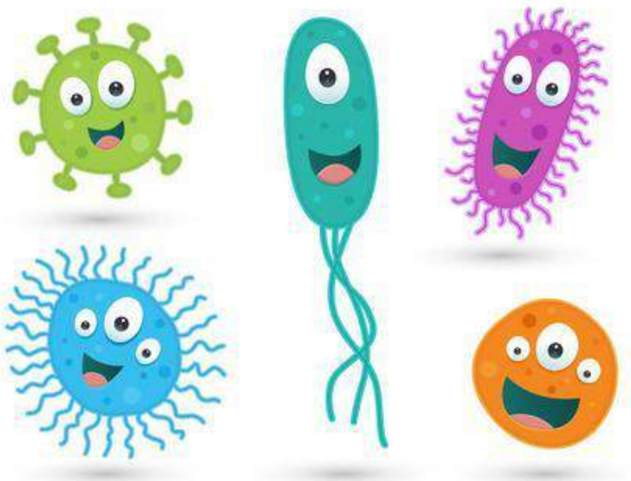


El **aumento de acetato** conduce a un **aumento de la ingesta de alimentos**, desencadenando un ciclo de **retroalimentación positiva** que impulsa la obesidad y la resistencia a la insulina

Síndrome Metabólico

Perry et al. Nature. 2016 Jun 9; 534(7606): 213–217

Tratamiento o prevención de la obesidad



Probióticos

TABLE 1 | Effects of probiotics on gut microbiota of animals and their physiological outcomes.

Probiotics	Animal model	Influence on gut microbiota	Metabolic outcome	Reference
VSL#3	C57J/B67 HFD and *ob/ob* mice	↓ *Firmicutes*, ↑*Bacteroidetes*, and *bifidobacteria*. * NC on *lactobacilli*	↓ Body weight (BW), food intake and adiposity, ↑ insulin sensitivity, glucose tolerance, production of GLP-1 and SCFA butyrate	Yadav et al., 2013
L. curvatus HY7601 and *L. Plantarum* KY1034	C57BL/6J HFD mice	NC in *Firmicutes* and *Bacteroidetes*. Phylum *Verrucomicrobia* was absent and ↓ *Proteobacteria*. ↑ Four Species belonging to the *Ruminococcaceae* and *Lachnospiraceae* families of the order *Clostridiales* and phylum *Firmicutes*. ↑ endogenous *B. pseudolongum* was found higher	↓ BW and fat accumulation, plasma insulin, leptin, total cholesterol (TC) and liver toxicity biomarkers and adipose tissue, ↓ pro-inflammatory genes in adipose tissue while ↑ fatty acid oxidation genes in liver	Park et al., 2013
L. salivarius UCC118	C57BL/J6 HFD mice	NC in *Firmicutes*, ↑ *Bacteroidetes* and *Proteobacteria* and ↓ *Actinobacteria*	No alteration in metabolic profiles	Murphy et al., 2013
L. salivarius UCC118	C57BL/J6 HFD mice	↑ In proportions of *Bacteroidetes* and *Peptococcaceae* and significantly ↓ in population of *Rikenellaceae* and *Porphyromonadaceae*	↓ BW at appropriate time	Clarke et al., 2013
L. coryniformis CECT5711	C57BL/6J HFD mice	↑ *Lactobacillus* spp. cluster	↓ Plasma glycaemia, insulin resistance and LPS levels and improves gut permeability.	Toral et al., 2014
L. casei NCDC 19	C57BL/6J HFD mice	NC in total bacterial counts, *Eubacterium rectale–Clostridium coccoides* and *lactobacilli–Enterococcus* (LAB) groups. Significant ↑ in population of *bifidobacteria* was observed	↓ BW, epididymal fat, blood glucose, plasma lipids and leptin; ↑ adiponectin	Rather et al., 2014
L. brevis OK56	C57BL/6J HFD mice	↑ *Bifidobacteria* population	↓ Body and epididymal fat, ↓ NF-κB activation and LPS production. ↓ Pro-inflammatory cytokines	Kim et al., 2015
L. rhamnosus NCDC17	High fat diet fed and streptozotocin treated Wistar rats	↑ *Bifidobacteria* and *lactobacilli* proportions	↑ Glucose tolerance, blood glucose, plasma insulin, glycosylated hemoglobin, FFA, TGs, serum lipids and cholesterol, oxidative stress. ↑ GLP1 and adiponectin, ↓ pro-inflammatory cytokines and propionate in caecum	Singh et al., 2016
Probiotic mixture (*L. salivarius* 33, *L. rhamnosus* LMG S-28148, *B. animalis* subsp. *lactis* LMG P-28149)	C57BL/6J HFD mice	↑ *Bacteroidetes*, Restores the adundance of *Rikenellaceae* ↓ *Lactobacillaceae*. Probiotic treatment induced a modification in the *bifidobacterial* population: *B. pseudolongum* was no longer detected that was present in HFD group. ↓ *Lactobacillus–Leuconostoc–Pediococcus* group. Restoration of *A. muciniphila* after treatment	↓ BW and adiposity with improvement in insulin resistance, ↓ adipose tissue inflammation, ↑ dyslipidemia through adipose tissue immune cell-remodeling	Alard et al., 2016
L. plantarum HAC01	C57BL/6J HFD mice	↑ *Lachnospiraceae*, ↓ *Deferribacteraceae*, *Mucispirillum* and *Lactobacillaceae* with NC in proportion of *Firmicutes* and *Bacteroidetes*	↓ BW gain and mesenteric fat weight, blood glucose, TC and triacylglycerol, ↑ lipid oxidative genes	Park et al., 2017

TABLE 2 | Effect of probiotics supplementation on human gut microbiota and their metabolic outcomes.

Probiotic and subject	Study Design	Influence on gut microbiota	outcome	Reference
L. rhamnosus GG, ATCC 53103 pregnant women and children	Double-blind placebo controlled Mothers: 4 weeks before deliver Children: 6 months after birth	No clear cut study on gut/fecal microbiota	The authors proposed that the reduction in BW was due to positive modulation of gut microbiota by probiotic during the critical development period.	Luoto et al., 2010
L. salivarius Ls-33 obese adolescents	Double-blind placebo controlled 12 weeks	↑ *Bacteroides–Prevotella–Porphyromonas* group to *Firmicutes* belonging bacteria, including *Clostridium* cluster XIV, *Blautia coccoides_Eubacteria rectale* and *Roseburia intestinalis* group. NC of ingestion on *Clostridium* cluster I/IV, *F. prausnitzii*, *Enterobacteriaceae*, *Enterococcus*, *Lactobacillus*, and *Bifidobacterium* group	Feeding strain might have modified the fecal microbiota in obese adolescents by a mechanism that is not associated to metabolic syndrome.	Larsen et al., 2013
Probiotic (*S. thermophiles*, *L. plantarum*, *L. acidophilus*, *L. rhamnosus*, *B. lactis*, *B. longum* and *B. breve*) and *Bofutsushosan* herb, subjects having BMI > 25 kg/m^2 and waist circumference > 85 cm were only included in the study	Double-blind, placebo controlled 8 weeks	↑ *B. breve*, *B. lactis*, *L. rhamnosus*, and *L. plantarum*. ↓ *Firmicutes/Bacteroidetes* ratio was also observed upon treatment.	↓ Weight, waist circumference and ↑ in HDL-cholesterol. Change in body composition is positively related to levels of LPS and *L. plantarum*	Lee et al., 2014
L. salivarius UBL S22 and Prebiotic Fructoligosaccharide healthy human volunteers	Double-blind, placebo controlled 6 weeks	↑ *lactobacilli* and ↓ *E. coli* after intervention period.	Improvement in serum TGs and lipid profile with ↓ in inflammatory cytokines	Rajkumar et al., 2015

Dahiya et al. Frontiers in Microbiology 2017, 8 . Article 563

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European Journal of Clinical Nutrition (2010) 64, 636–643

0954-3007/10
www.nature.com/ejcn

ORIGINAL ARTICLE

Regulation of abdominal adiposity by probiotics (*Lactobacillus gasseri* SBT2055) in adults with obese tendencies in a randomized controlled trial

Y Kadooka[1], M Sato[2], K Imaizumi[2], A Ogawa[1], K Ikuyama[3], Y Akai[3], M Okano[3], M Kagoshima[4] and T Tsuchida[5]

- **ensayo de intervención doble ciego, aleatorizado, controlado con placebo**
- **sobrepeso y obesos**
- **33 a 63 años de edad**
- **grupo control (n=44) y grupo placebo (n=44)**
- **Lactobacillus gasseri SBT2055 en leche fermentada**
- **12 semanas**

2018 SIAN

European Journal of Clinical Nutrition (2010) 64, 636–643

0954-3007/10
www.nature.com/ejcn

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Table 2 Abdominal fat areas

Parameters	*Values*	*Groups*	*W0*	*W12*			*Group-by-time* *Group*
Visceral fat (cm^2)	Measured	Active	127.3 (119.7, 134.9)	121.5 (130.2, 112.8)	**		##
		Control	119.3 (112.8, 125.8)	120.7 (114.0, 127.4)			
	Change from W0	Active	—	−5.8 (−10.0, −1.7)		##	
		Control	—	1.4 (−2.2, 5.1)			
Subcutaneous fat (cm^2)	Measured	Active	222.2 (196.9, 247.5)	214.8 (189.4, 240.3)	**		#
		Control	227.8 (204.4, 251.2)	226.5 (204.0, 249.1)			
	Change from W0	Active	—	−7.4 (−11.6, −3.1)		#	
		Control	—	−1.3 (−4.9, 2.4)			
Total fat (cm^2)	Measured	Active	349.5 (322.5, 376.6)	336.3 (309.5, 363.2)	**		##
		Control	347.1 (321.3, 372.9)	347.2 (321.9, 372.6)			
	Change from W0	Active	—	−13.2 (−20.5, −6.0)		##	
		Control	—	0.1 (−5.7, 6.1)			

Values are means (95% confidence interval (CI)). Within-group comparisons between week 0 (W0) and W12: $^{**}P<0.01$. Between-group comparisons: $^{\#}P<0.05$, $^{\#\#}P<0.01$. Group-by-time interaction ('Group-by-time'): $^{\#}P<0.05$, $^{\#\#}P<0.01$. Group-effect ('Group'): not significant.

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Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

The Additional Effects of a Probiotic Mix on Abdominal Adiposity and Antioxidant Status: A Double-Blind, Randomized Trial

Aline Corado Gomes[1], Rávila Graziany Machado de Sousa[1], Patrícia Borges Botelho[1], Tatyanne Letícia Nogueira Gomes[1], Patrícia Oliveira Prada[2], and João Felipe Mota[1]

- **Ensayo aleatorizado, doble ciego**

- **sobrepeso y obesas**
- **20 a 59 años de edad**
- **grupo control (n=21) y grupo placebo (n=22)**
- **8 semanas**
- **mix de probióticos: Lactobacillus acidophilus LA-14, Lactobacillus casei LC-11, Lactococcus lactis LL-23, Bifidobacterium bifidum BB-06, y Bifidobacterium lactis**

TABLE 1 Body composition before and after treatment with dietary intervention or a dietary intervention plus probiotic mix in women with overweight and obesity

	Dietary intervention (n = 22)				Dietary intervention + probiotic mix (n = 21)					Intervention effect	
	Baseline	Week 8	Mean change	P^a	Baseline	Week 8	Mean change	P^a	P^b	Effect (95% CI)	P^c
BMI (kg/m^2)	33.34 ± 4.69	32.61 ± 4.53	−0.72	0.00	31.70 ± 3.90	31.24 ± 3.96	−0.45	0.01	0.41	−0.49 (−3.24 to 2.25)	0.71
Weight (kg)	83.55 ± 13.44	82.59 ± 13.00	−0.95	0.02	76.58 ± 9.94	75.60 ± 10.24	−0.98	0.02	0.18	−3.64 (−11.24 to 3.95)	0.33
WC (cm)	97.50 ± 10.40	94.18 ± 10.24	−3.32	0.00	93.95 ± 8.37	88.80 ± 7.26	−5.14	0.00	0.33	1.81 (0.13 to 3.50)	0.03
Body fat (%)	48.82 ± 4.39	48.03 ± 4.18	−0.79	0.02	48.56 ± 4.28	47.37 ± 5.00	−1.19	0.00	0.91	−1.09 (−3.91 to 1.72)	0.43
FM (kg)	39.73 ± 8.23	39.05 ± 7.35	−0.68	0.29	36.30 ± 7.32	34.96 ± 7.52	−1.33	0.00	0.60	−1.93 (−7.02 to 3.15)	0.44
FFM (%)	49.68 ± 4.33	50.36 ± 4.09	0.68	0.04	49.79 ± 4.09	50.92 ± 4.76	1.13	0.00	0.79	−0.94 (−1.79 to 3.69)	0.48
FFM (kg)	41.37 ± 6.74	41.46 ± 6.53	0.09	0.77	37.86 ± 3.65	38.20 ± 4.20	0.33	0.26	0.00	−1.13 (−4.68 to 2.41)	0.52
Android (%)	54.36 ± 3.35	53.05 ± 3.23	−1.31	0.00	54.80 ± 3.36	53.50 ± 4.14	−1.30	0.02	0.98	0.03 (−2.32 to 2.39)	0.97
Gynoid (%)	53.98 ± 5.31	52.75 ± 5.42	−1.22	0.00	53.95 ± 4.66	53.13 ± 4.70	−0.81	0.00	0.56	−1.92 (5.12 to 1.26)	0.23
WHR	0.61 ± 0.06	0.59 ± 0.06	−0.02	0.00	0.60 ± 0.06	0.57 ± 0.05	−0.03	0.00	0.87	0.01 (0.00 to 0.02)	0.02
Conicity index	1.23 ± 0.07	1.19 ± 0.07	−0.03	0.00	1.22 ± 0.07	1.16 ± 0.06	−0.05	0.92	0.91	0.02 (0.00,0.04)	0.03

Values are presented as mean ± standard deviation.
[a]Difference between baseline and end point. P value obtained from paired t-test/Wilcoxon matched-pairs signed-rank test for the within-group comparisons.
[b]Homoscedasticity test between groups on baseline.
[c]Obtained from unpaired Student's t-test or Mann–Whitney test, as statistical difference between changes (DI vs. DI + P). The effect of the probiotic mix associated with dietary intervention on the variables measured was examined using ANCOVA with adjustment for the screening/baseline observation.
FFM, free-fat mass; FM, fat mass; WC, waist circumference; WHR, waist-to-height ratio.

↓ de la adiposidad abdominal

TABLE 5 Oxidative and inflammatory parameters before and after treatment with dietary intervention or a dietary intervention plus probiotic mix in women with overweight and obesity

	Dietary intervention (n = 22)				Dietary intervention + probiotic mix (n = 21)					Intervention effect	
	Baseline	Week 8	Mean change	P^a	Baseline	Week 8	Mean change	P^a	P^b	Effect (95% CI)	P^c
CAT (U/mg)	8.10 ± 2.01	7.17 ± 2.05	−0.92	0.15	8.20 ± 1.26	7.71 ± 1.15	−0.49	0.65	0.06	0.30 (−0.50 to 0.11)	0.44
SOD (U/mg)	5.88 ± 1.94	6.28 ± 1.90	0.40	0.55	5.35 ± 2.50	7.31 ± 6.29	1.95	0.00	0.10	−0.62 (−2.79 to 1.54)	0.56
GPx (U/mg)	0.42 ± 0.12	0.34 ± 0.10	−0.07	0.00	0.32 ± 0.13	0.37 ± 0.11	0.05	0.04	0.31	−0.12 (−0.22 to 0.02)	0.01
MDA (nmol/mL)	0.16 ± 0.04	0.16 ± 0.04	0.00	0.83	0.18 ± 0.25	0.21 ± 0.28	0.02	0.39	0.00	−0.01 (−0.13 to 0.10)	0.81
LPS (EU/mL)	0.85 ± 0.44	0.95 ± 0.60	0.09	0.49	0.67 ± 0.11	0.65 ± 0.11	0.02	0.34	0.00	0.08 (−0.26 to 0.44)	0.62
IL-10 (pg/mL)	4.65 ± 4.34	4.53 ± 3.14	−0.12	0.88	3.57 ± 1.66	3.96 ± 1.84	0.39	0.15	0.00	−1.29 (−3.34 to 0.74)	0.20
IL-6 (pg/mL)	1.35 ± 1.81	0.80 ± 1.81	−0.54	0.07	0.58 ± 0.27	0.58 ± 0.31	0.00	0.94	0.00	−1.98 (−4.15 to 0.18)	0.07
TNF-α (pg/mL)	2.49 ± 0.89	2.07 ± 0.78	−0.42	0.07	1.72 ± 0.44	1.88 ± 0.37	0.16	0.24	0.00	−0.84 (−1.47 to −0.20)	0.01
ADIPO (ug/mL)	35.59 ± 20.76	38.44 ± 29.93	2.84	0.65	33.72 ± 29.78	36.33 ± 27.46	2.61	0.63	0.11	3.92 (−15.27 to 23.11)	0.68

Values are presented as mean ± standard deviation.
[a]Difference between baseline and end point. P value obtained from paired t-test/Wilcoxon matched-pairs signed-rank test for the within-group comparisons.
[b]Homoscedasticity test between groups on baseline.
[c]Obtained from unpaired Student's t-test or Mann–Whitney test, as statistical difference between changes (DI vs. DI + P). The effect of the probiotic mix associated with dietary intervention on the variables measured was examined using ANCOVA with adjustment for the screening/baseline observation.
ADIPO, adiponectin; CAT, catalase; SOD, superoxide dismutase; GPx, glutathione peroxidase; IL, interleukin; LPS, lipopolysaccharide; MDA, malondialdehyde, TNF-α, tumor necrosis factor-α.

↑ de la actividad enzimática antioxidante

Scientific Documentation

Bifidobacterium animalis ssp. _lactis_ 420 (B420™) for metabolic health – a decade of research

2008 & 2016	2011–2015	2015	2013–2016
Cell culture studies: B420™ improves epithelial barrier function	**Mouse studies:** B420™ improves metabolic health and gut barrier function	**Mouse studies:** B420™ + Litesse® Ultra improves metabolic health	**Clinical study:** B420™ with or without Litesse® Ultra controls body fat mass
Putaala et al. Res Microbiol 2008	Amar et al. EMBO Mol Med 2011	Garidou et al. Cell Metab 2015	Stenman et al. EBioMedicine 2016
Mokkala et al. Nutr Res 2016	Stenman et al. Benef Microbes 2014		
	Stenman et al. Diabetol Metab Syndr 2015		

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EBioMedicine 13 (2016) 190–200

Contents lists available at ScienceDirect

EBioMedicine

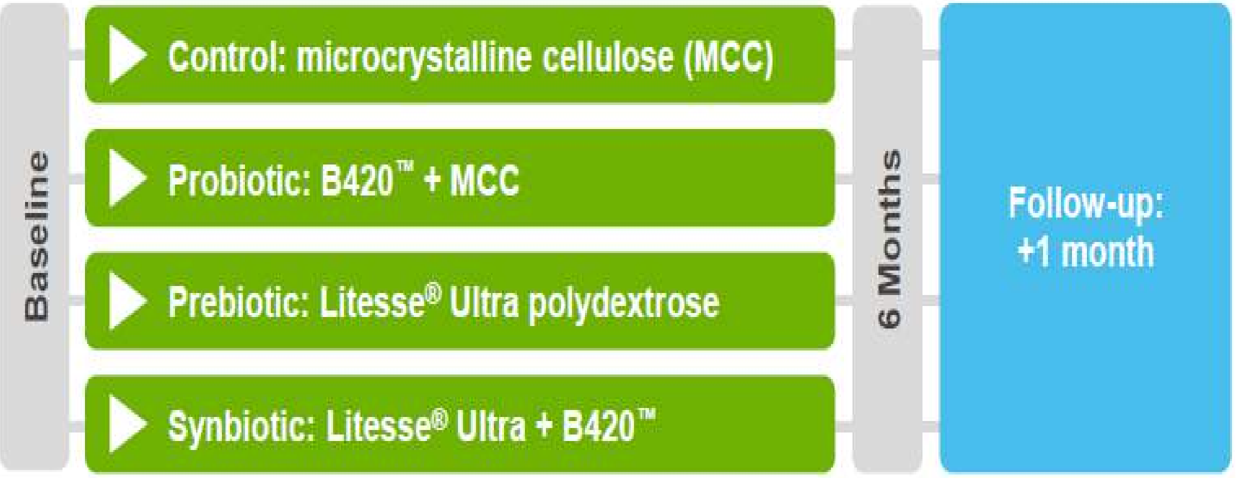
journal homepage: www.ebiomedicine.com

Research Paper

Probiotic With or Without Fiber Controls Body Fat Mass, Associated With Serum Zonulin, in Overweight and Obese Adults—Randomized Controlled Trial☆,☆☆

Lotta K. Stenman [a,*], Markus J. Lehtinen [a], Nils Meland [b], Jeffrey E. Christensen [c], Nicolas Yeung [a], Markku T. Saarinen [a], Michael Courtney [c], Rémy Burcelin [c], Marja-Leena Lähdeaho [d], Jüri Linros [e], Dan Apter [f], Mika Scheinin [g], Hilde Kloster Smerud [b], Aila Rissanen [h], Sampo Lahtinen [a]

- **ensayo de intervención doble ciego, aleatorizado, controlado con placebo**
- **255 participantes**
- **sobrepeso y obesos**
- **18 a 65 años de edad**



B420™

- 12 g microcrystalline cellulose
- 10^{10} CFU/day *B. lactis* 420

Litesse® Ultra

- 12 g Litesse® Ultra polydextrose

Litesse® Ultra + B420™

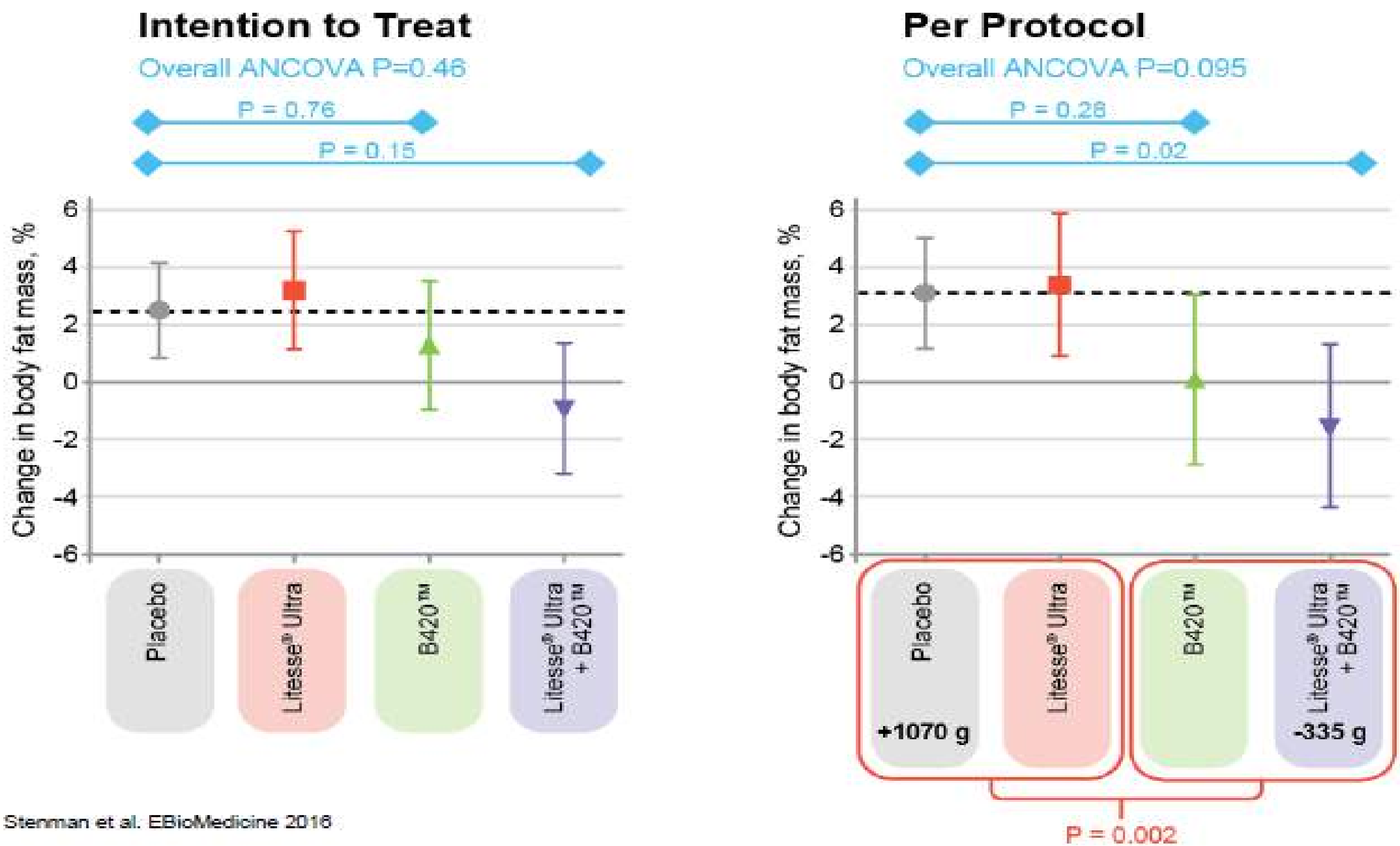
- 12 g Litesse® Ultra polydextrose
- 10^{10} CFU/day *B. lactis* 420

Placebo

- 12 g microcrystalline cellulose (no energy; less fermented)

Smoothie contains 130 kcal/day

Stenman et al. EBioMedicine 2016

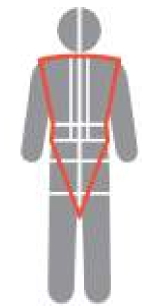


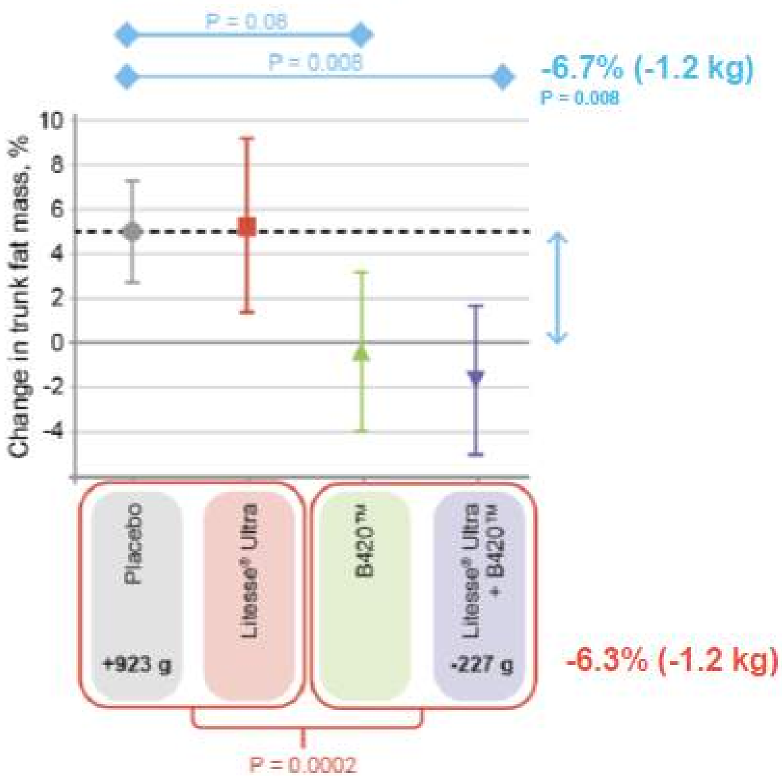
Stenman et al. EBioMedicine 2016

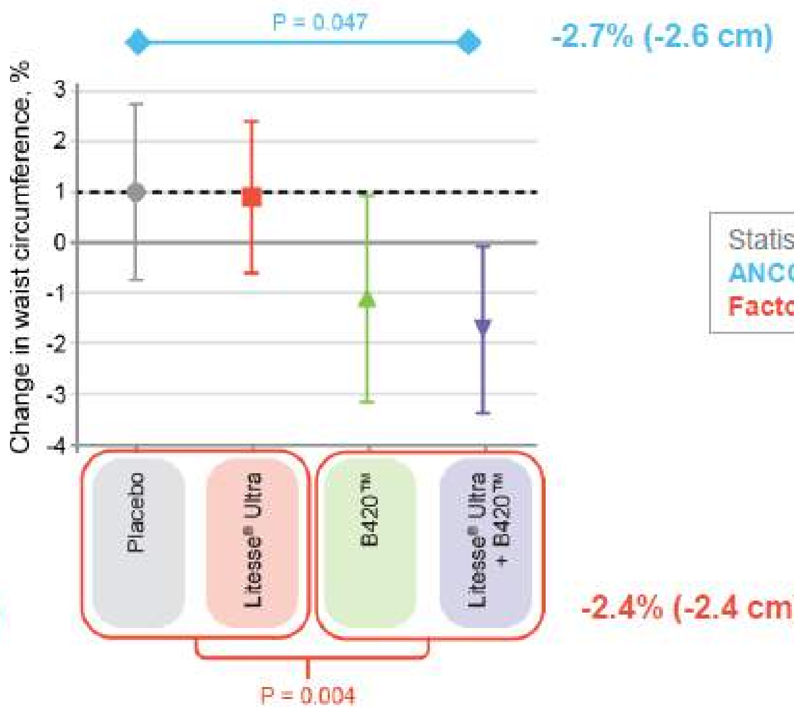
→**Redución en 4,5% (-1,4 Kg) de grasa corporal comparado con placebo**

→ Efecto concentrado en el área abdominal

Effect concentrated to abdominal area

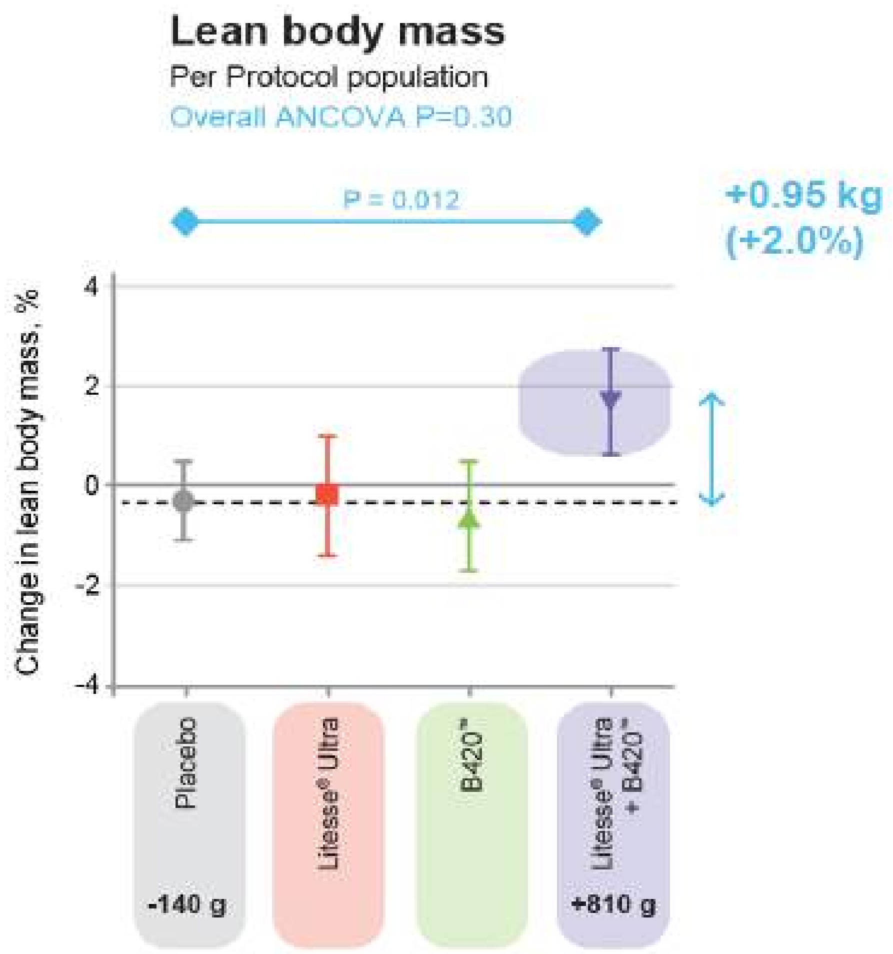


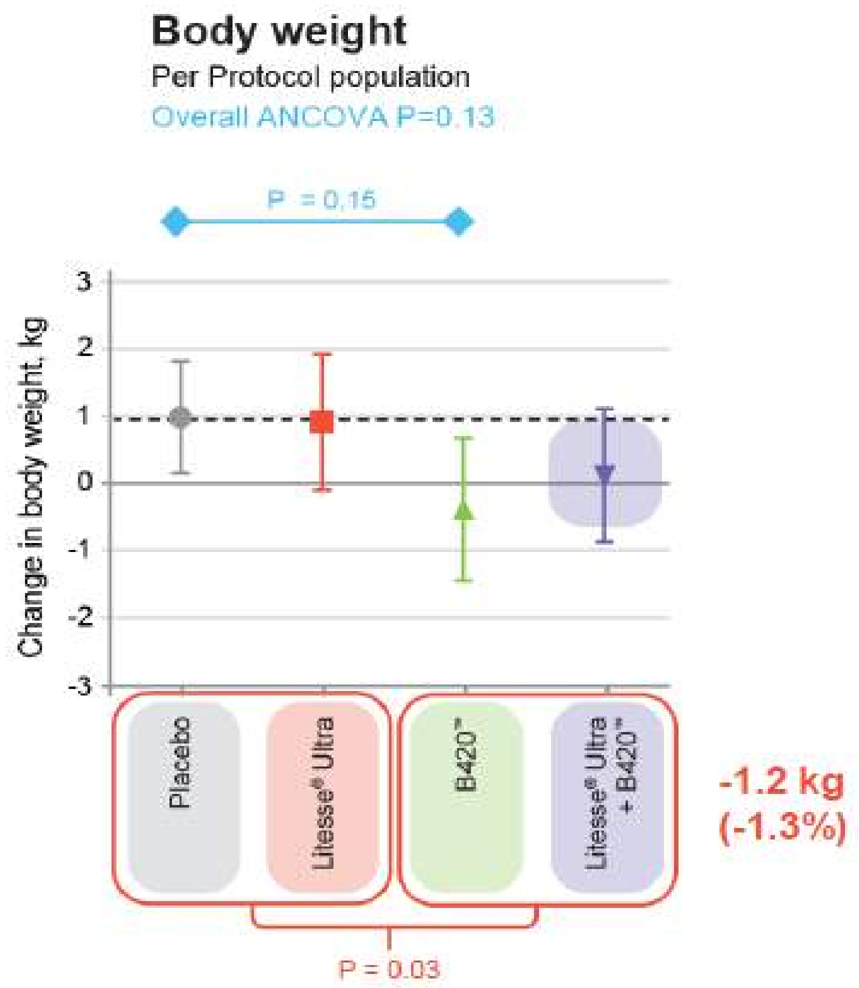




Statistical analyses:
ANCOVA values
Factorial analysis

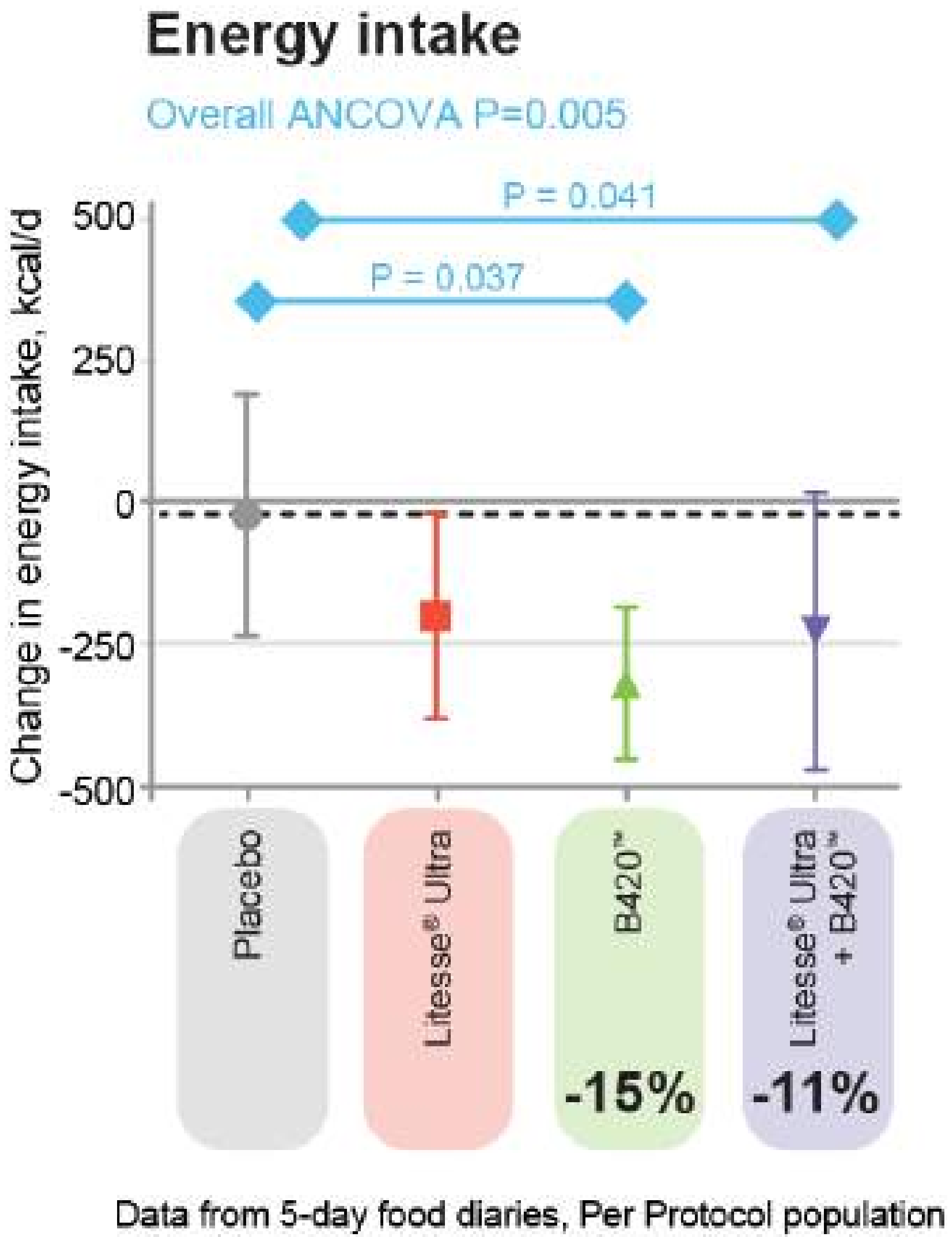
Stenman et al. EBioMedicine 2016





Stenman et al. EBioMedicine 2016

→ Redución en 1,2 Kg de peso corporal comparado con placebo



→ **B420™ solo o con polidextrosis reduce la ingesta de energia**

Stenman et al. EBioMedicine 2016

2018 SIAN

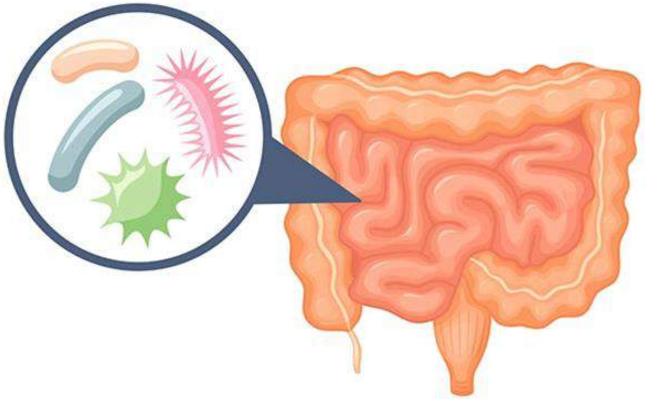
GLORIA

Probióticos

Tratamiento o prevención de la obesidad

Gracias por su atención!

bpeters@usp.br



INTERACCIÓN DE LOS PROBIÓTICOS CON LA MICROBIOTA INTESTINAL Y OBESIDAD

Dra. Bárbara Emo Peters