IX REUNIÓN DE
DIABETES Y OBESIDAD

MICROBIOTA INTESTINAL

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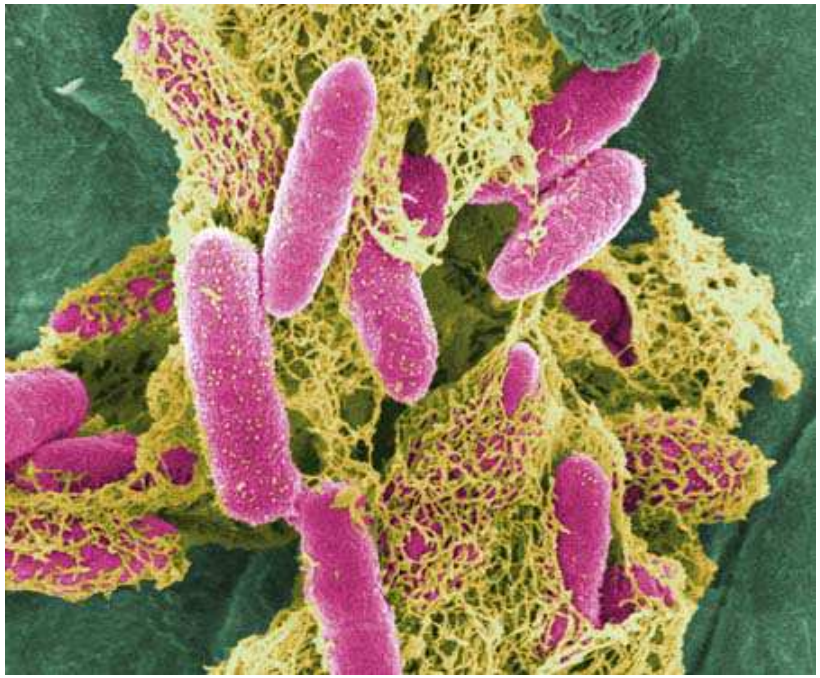
Hospitales Regional y Virgen de la Victoria de Málaga

GUION

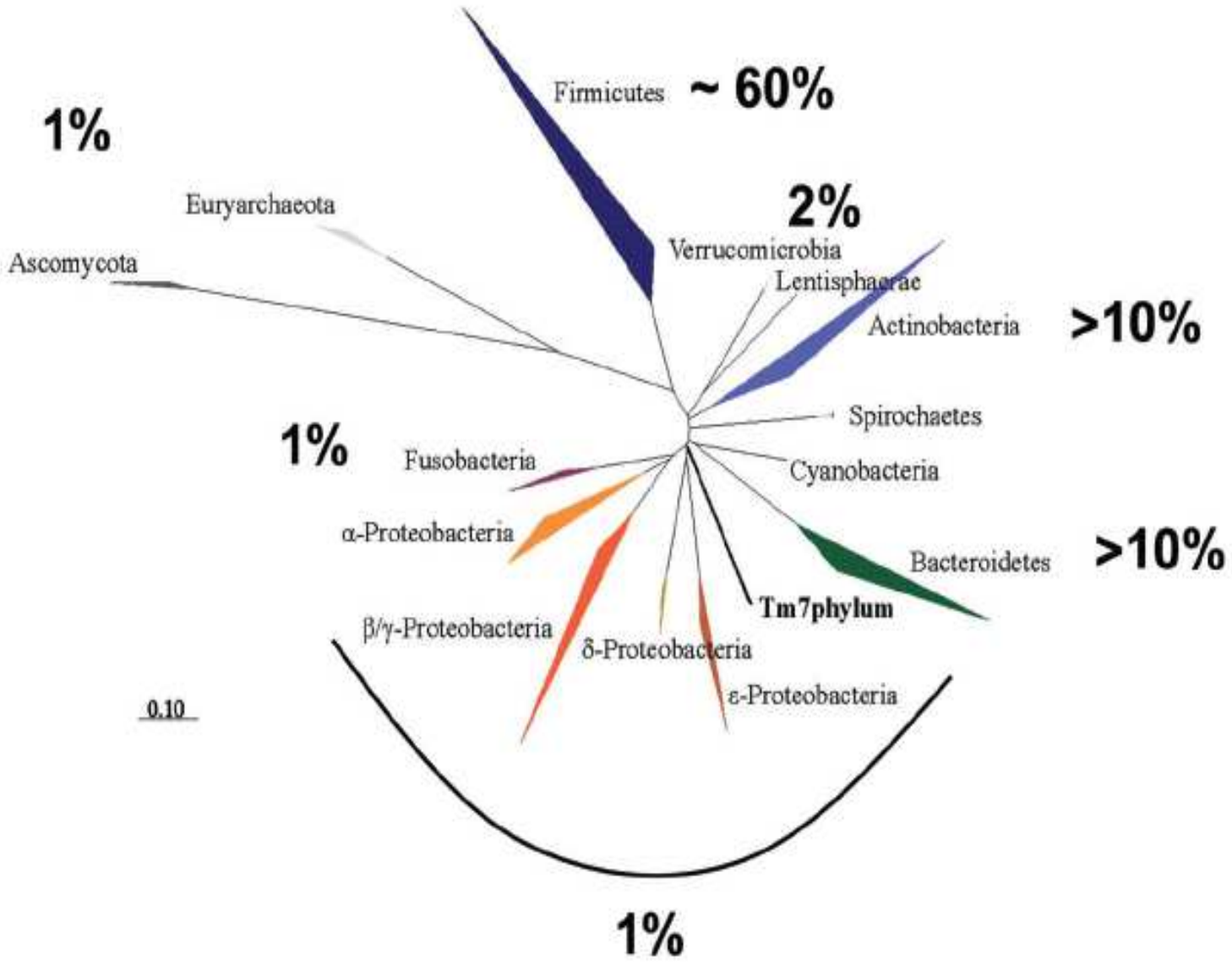
- EPIDEMIOLOGIA
- MICROBIOTA OBESIDAD Y DIABETES
- MECANISMOS
- ¿COMO SE MODIFICA LA MICROBIOTA?

Qué es la microbiota?

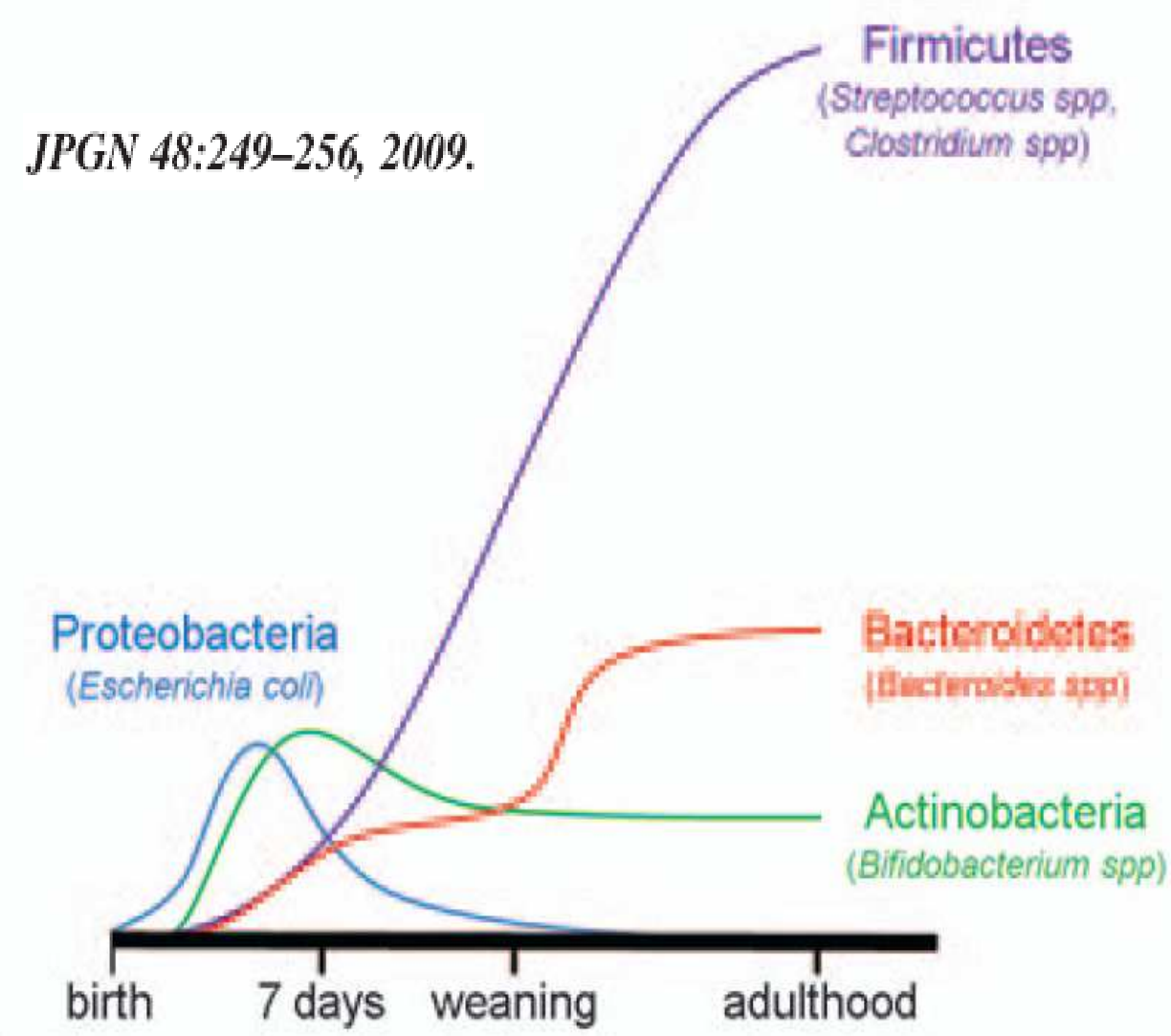


MICROBIOTA

- Tienen un peso de 1.5 Kg
- Superan al genoma humano en 100-veces
- Tres trillones de gérmenes
- 1000 especies


Firmicutes
~ 60%
1%
2%
Euryarchaeota
Ascomycota
Verrucomicrobia
Lentisphaerae
Actinobacteria
>10%
Spirochaetes
1%
Fusobacteria
Cyanobacteria
α-Proteobacteria
Bacteroidetes
>10%
Tm7phylum
β/γ-Proteobacteria
δ-Proteobacteria
ε-Proteobacteria
0.10
1%

MICROBIOTA-EDAD



FUNCIONES DE LA MICROBIOTA

FUNCIÓN INMUNE

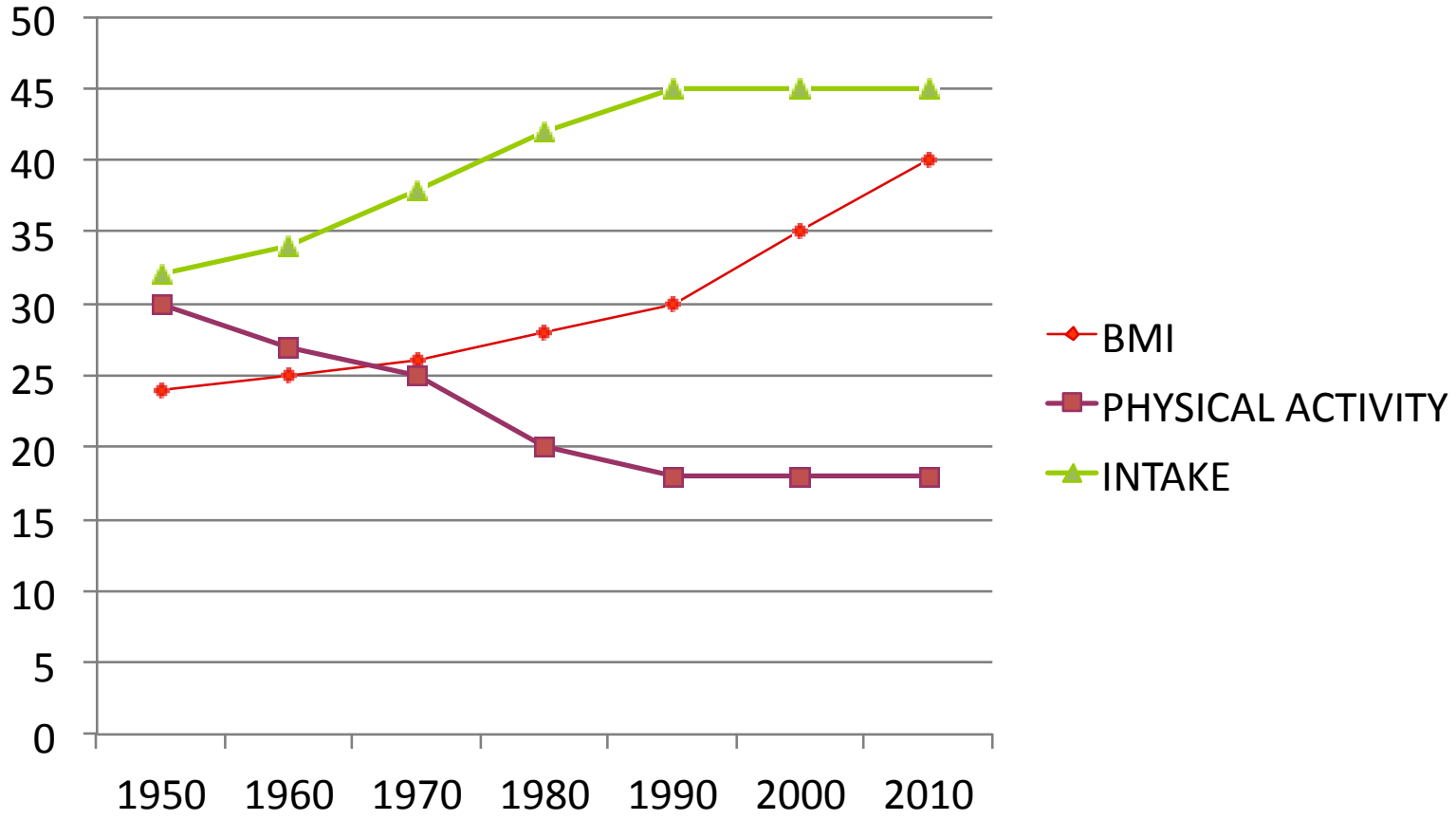
- Destrucción toxinas /carcinógenos
- Colonización por bacterias patógenas
- Desarrollo del SI
- Modulación del estado inflamatorio

FUNCIÓN DIGESTIVA

- Motilidad digestiva
- Síntesis micronutrientes
- Absorción electrolitos/ minerales
- Fermentación sustancias indigeribles

Gill, SR *et al*. Metagenomic analysis of the human distal gut microbiome. Science. 2006; 312 (5778): 1355-59.

BMI-ESTILOS DE VIDA



¿ Se han producido cambios de la microbiota en las últimas décadas?

PERDIDA DE BIODIVERSIDAD EN EL INTESTINO

Nature Reviews Microbiology | AOP, published online 9 November 2009; doi:10.1038/nrmicro2245

PERSPECTIVES

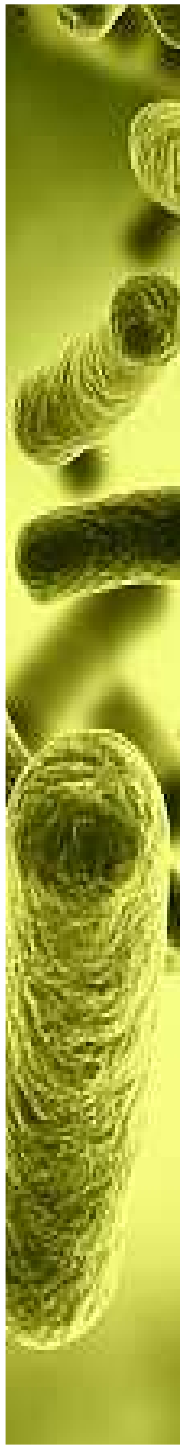
ESSAY

What are the consequences of the disappearing human microbiota?

Martin J. Blaser and Stanley Falkow

(symbiotic or mutualistic relationships). Co-evolution, co-adaptation and codependency are all features of our relationships with our indigenous microbiota[4,5].

The vertebrate microbiota can be characterized as: ancient, with deep ancestries; conserved in their host species; often present for defined life cycle events or persisting for life; and host niche specific. These properties



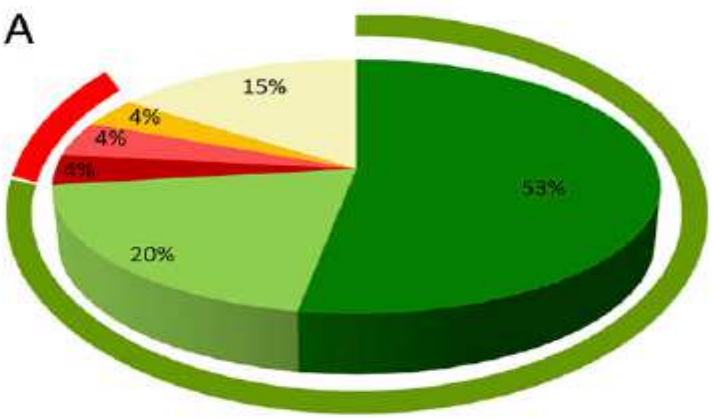
CAMBIOS EN ECOLOGIA HUMANA AFECTAN A LA COMPOSICIÓN DE LA MICROBIOTA

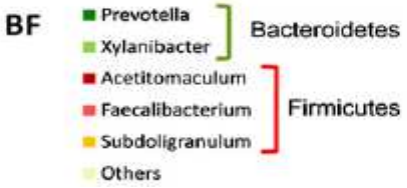
CHANGE	CONSEQUENCES
Water sanitation	Fecal transmission decrease
Cesarean surgery increase	Vaginal transmission decrease
Increase of the antibiotic use in preterm	Vaginal transmission decrease
Lactation reduction	Cutaneous transmission decrease
Small families	Early contamination decrease
Antibiotic use increase	Microbiota changes
Antibacterial soaps and toiletries increase	Microbiota changes
Mercury-amalgam dental filling increase	Microbiota changes

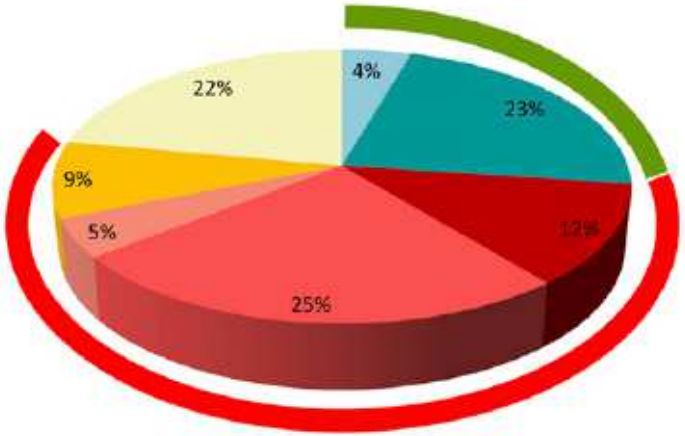
Nature Reviews Microbiology | AOP, published online 9 November 2009;

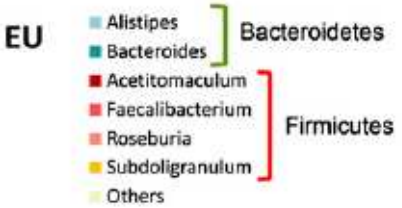
B. FASO CHILDREN

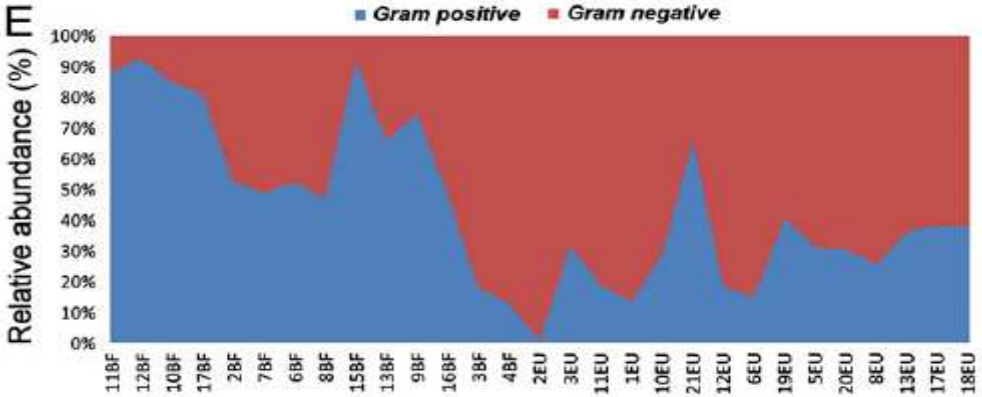
EUROPEAN CHILDREN



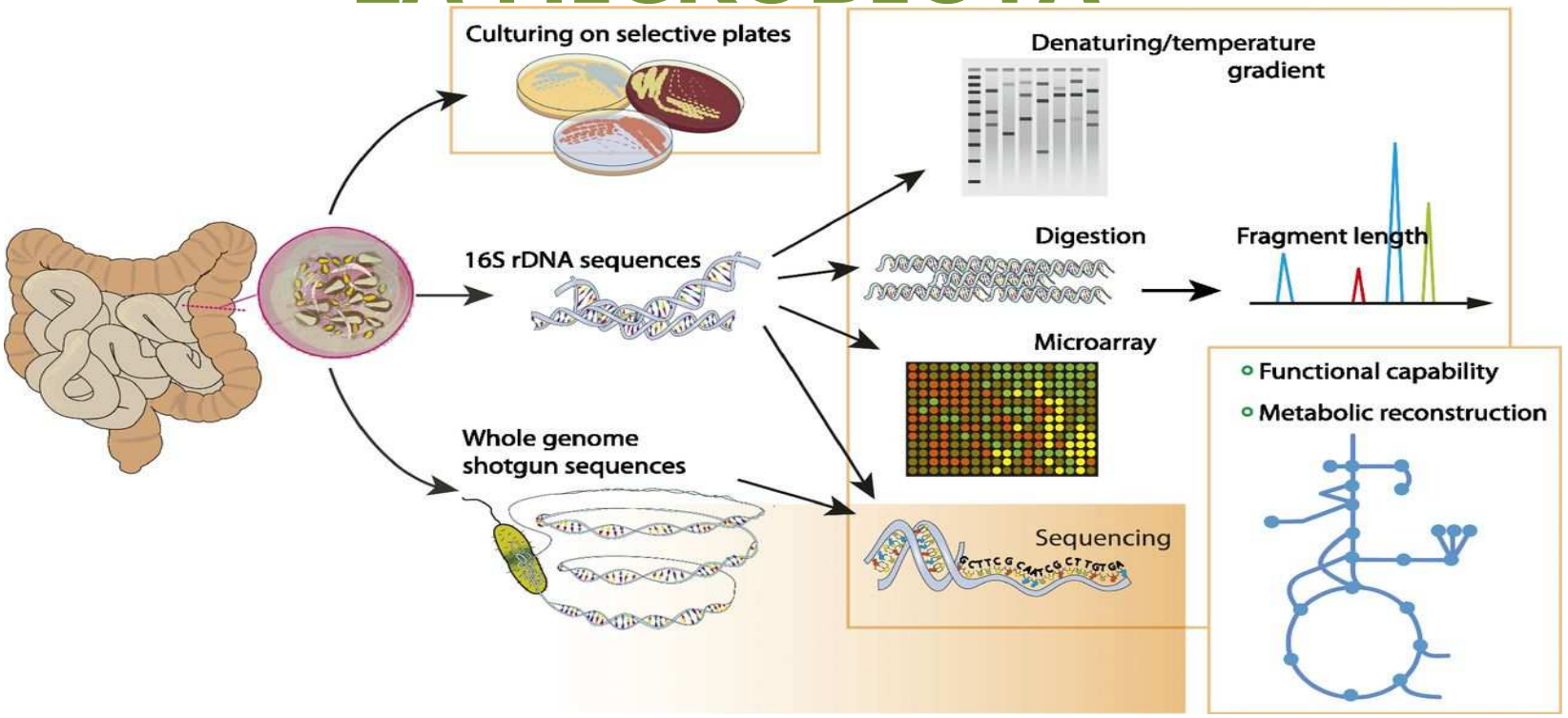


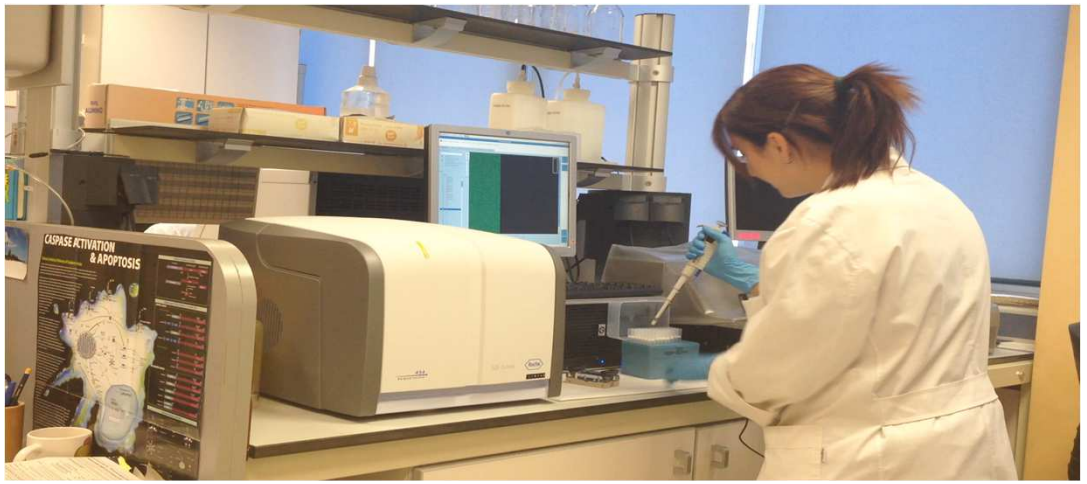




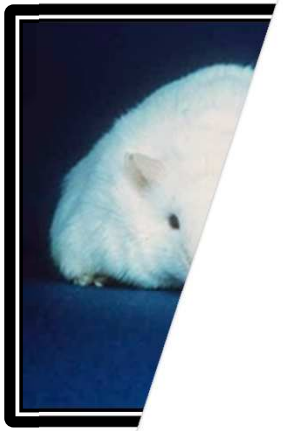


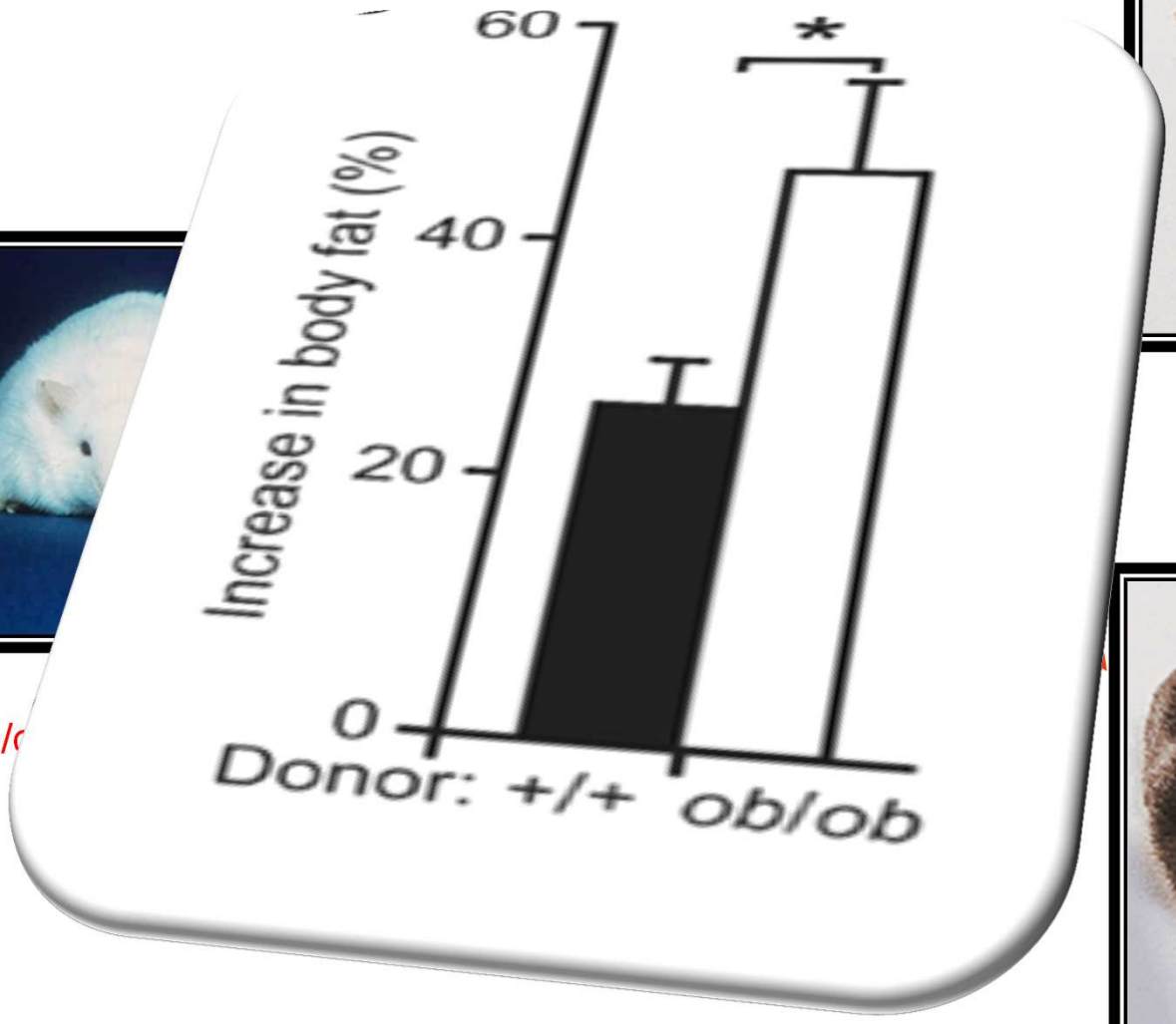
METODOS DE DETERMINACION DE LA MICROBIOTA





MICROBIOTA OBESIDAD





+/+

ob/ob

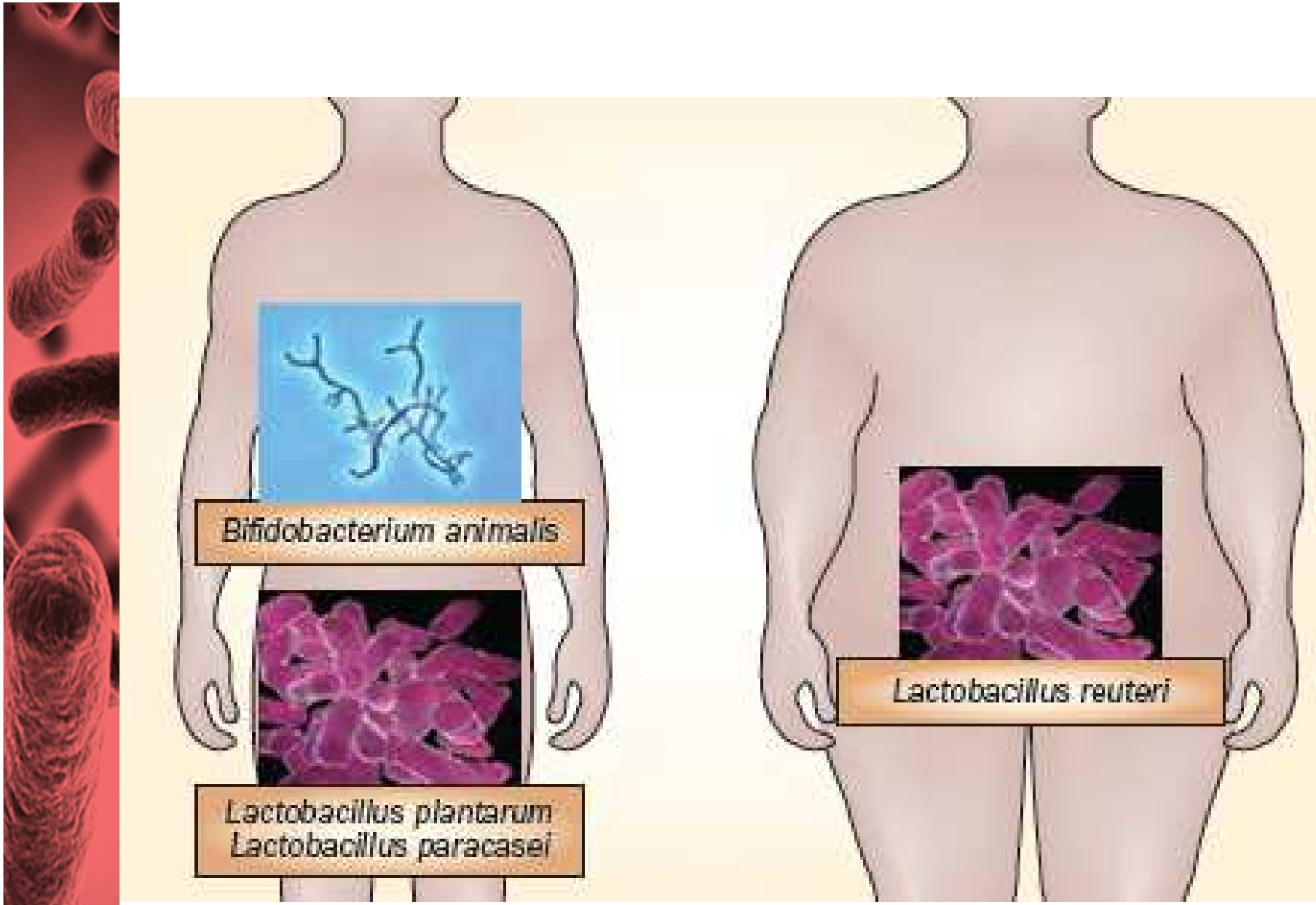
Turnbaugh, PJ et al. Nature. 2006; 444 (7122): 1027-31.

COMPOSICIÓN DE LA FLORA EN OBESOS/DELGADOS

- En obesos < Bacteroidetes
  > Firmicutes

► Tras pérdida de peso aumento de proporción de bacteroidetes

Ley R et al.Nature. 2006; 444 (7122): 1022-23.



Million M et al. Int J Obes 2011 Aug

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

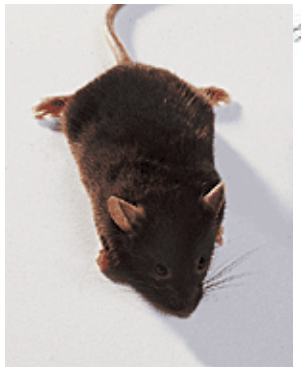
Vanessa K. Ridaura *et al.*

Science **341**, (2013);

DOI: 10.1126/science.1241214

delgado ← → **obeso**

Ln



Ob

Dieta LF-HPP: baja en grasa-alta en polisacáridos de vegetales.

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

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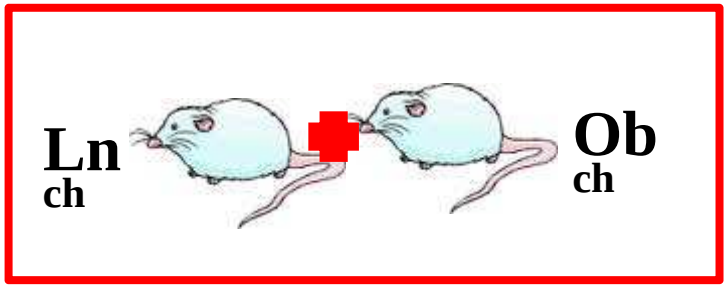
Dieta: LF-HPP



Ob ^{ch} : Menor aumento de la adiposidad que el Ob (similar a Ln o Ln ^{ch})

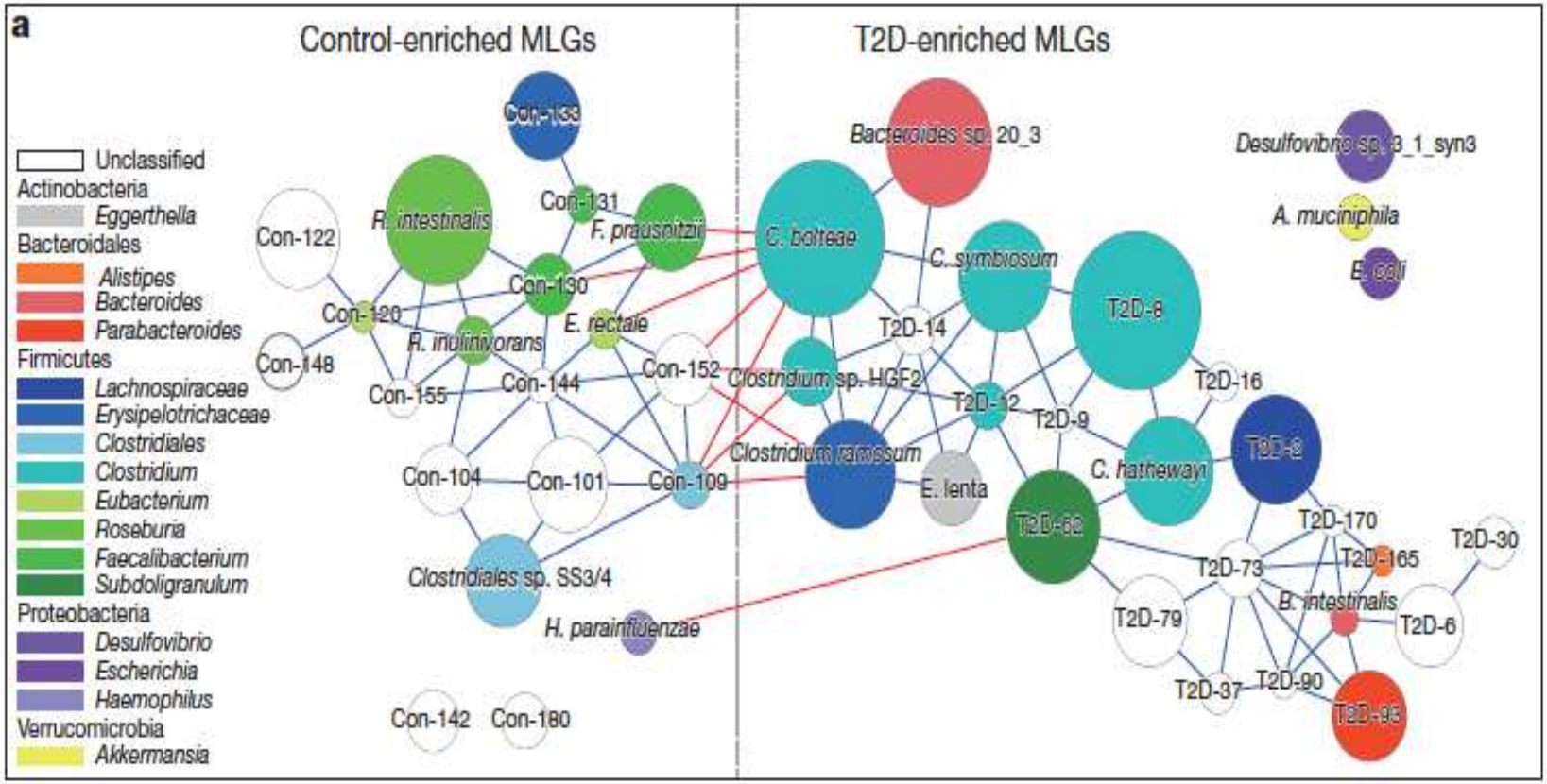
Conclusión: Las interacciones modificables y transmisibles entre la dieta y la microbiota influyen en la biología del hospedador.

Dieta LF-HPP: baja en grasa-alta en polisacáridos vegetales.

Dieta HiSF-LoFV: alta en grasas saturadas, baja en frutas y verduras

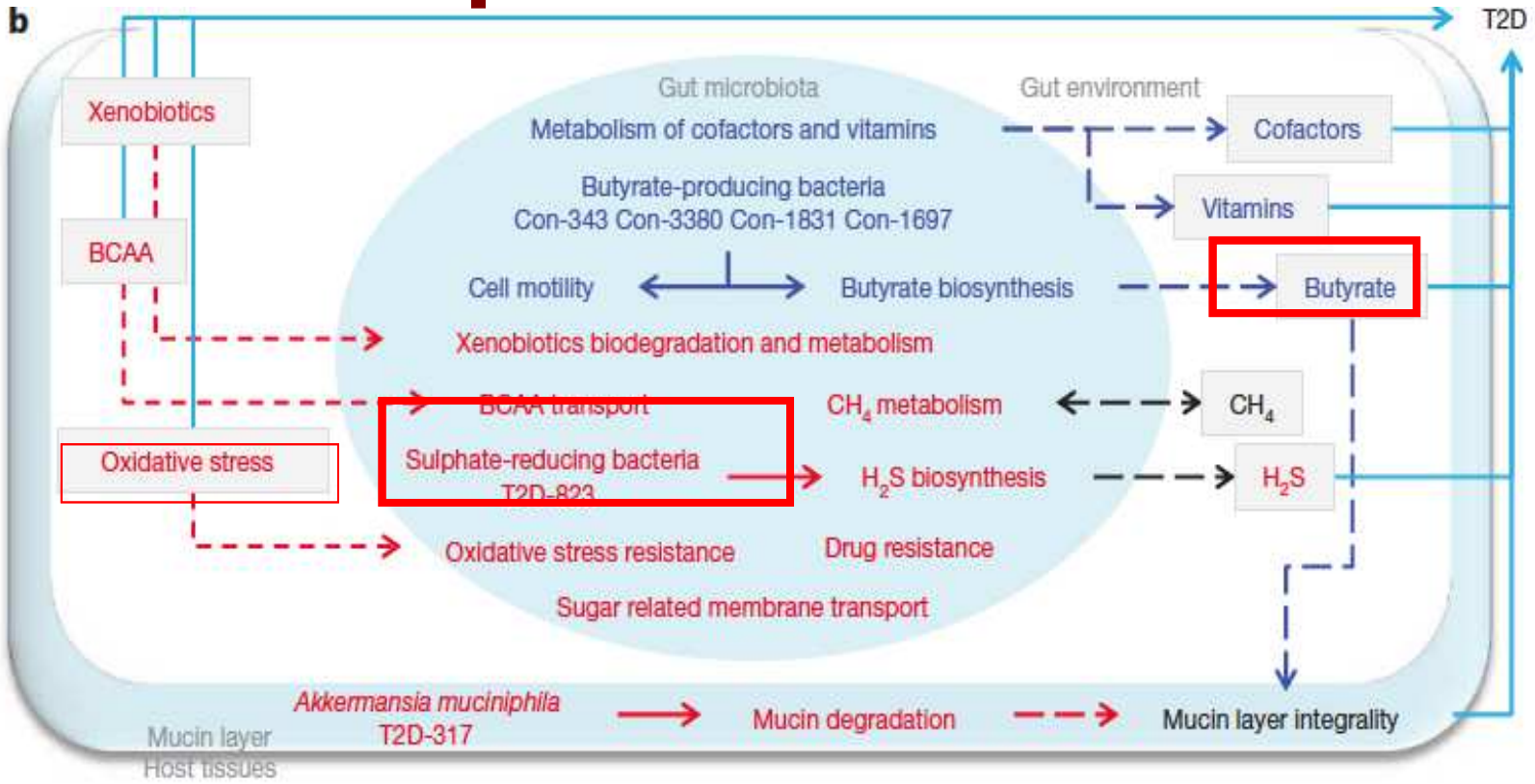
DIABETES MICROBIOTA

Microbiota intestinal en diabetes tipo 2. Cohorte China



Junjie Qin et al. Nature 2012;490:55–60

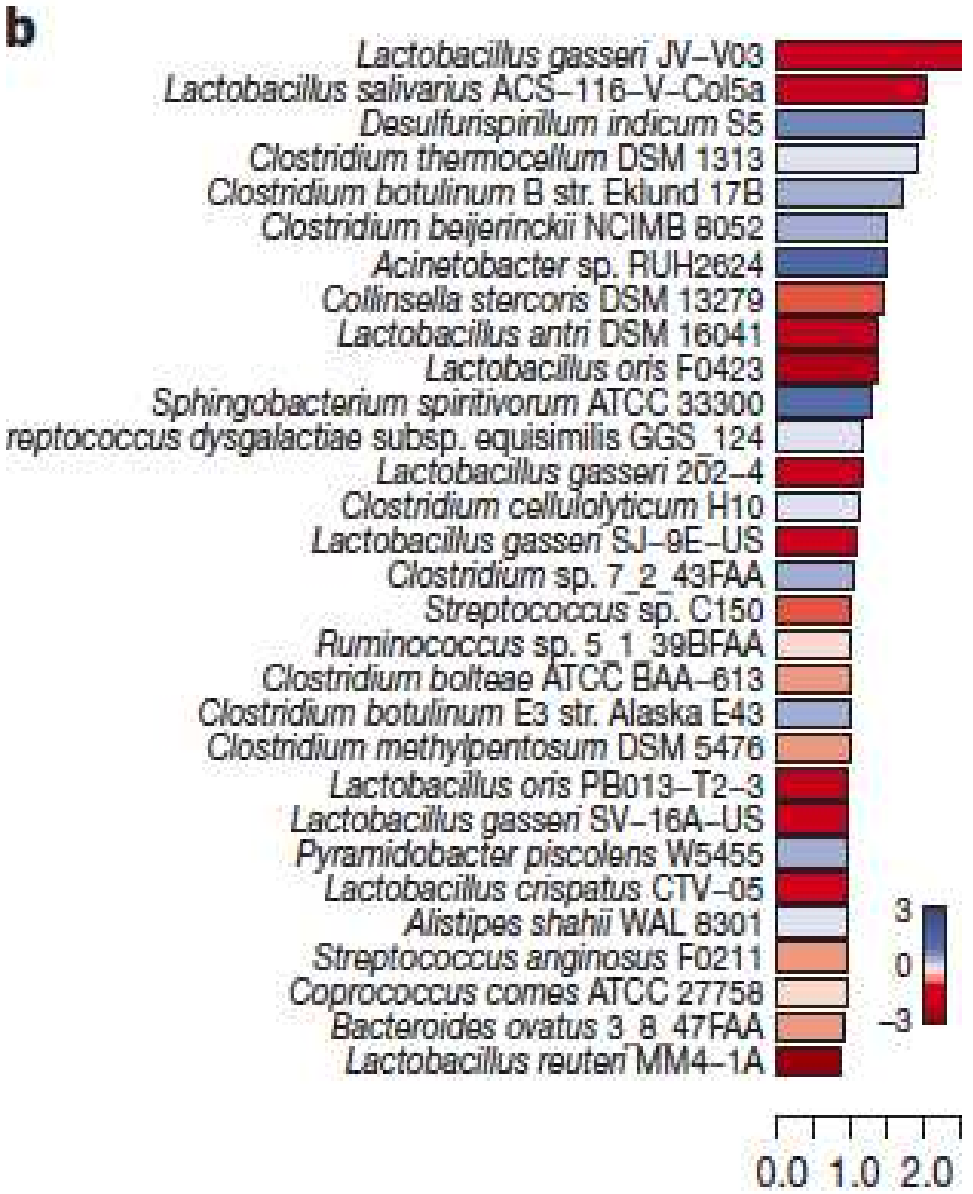
Microbiota intestinal en diabetes tipo 2. Cohorte China



- Los pacientes con T2D tenían un descenso en especies productoras de butirato. **Roseburia intestinals y F prausnitzii.**

Junjie Qin et al. Nature 2012;490:55–60

Microbiota intestinal en diabetes tipo 2. Cohorte EU



Nature. 2013 Jun 6;498(7452):99-103

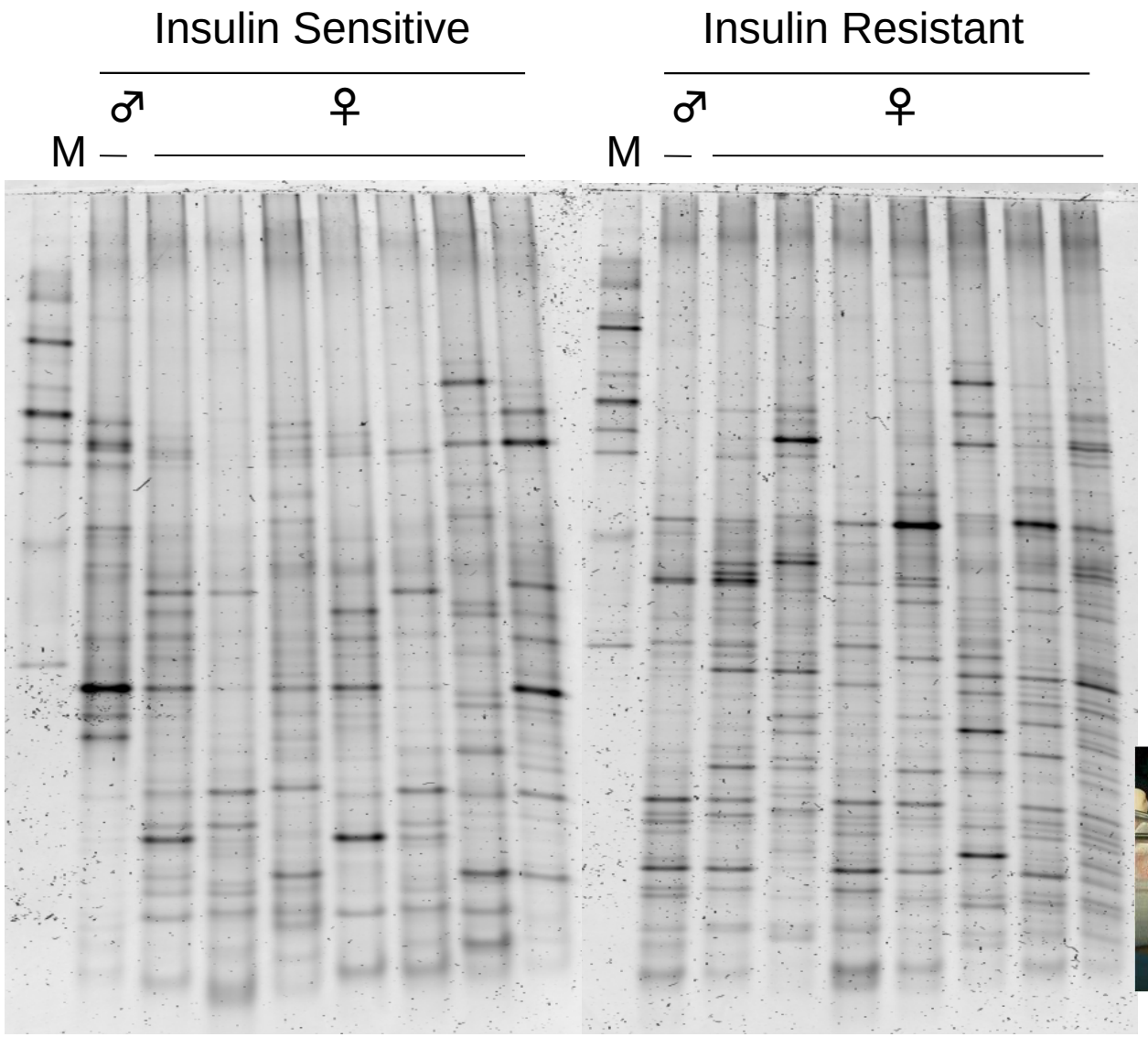
Hallazgos mayores en el análisis del metagenoma en diabetes tipo 2

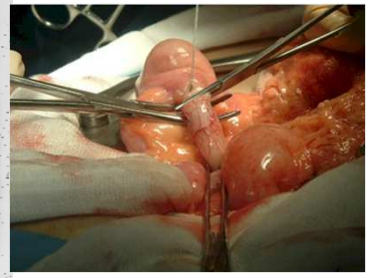
- Descenso de bacterias productoras de butirato como Roseburia intestinalis and Faecalibacterium prausnitzii
- Lactobacillus gasseri and Streptococcus mutans y ciertos Clostridiales mas elevados en T2D
- Proteobacteria más alta en T2D
- Incremento de expresión de genes de la microbiota envueltos en estrés oxidativo e inflamación

Tilg H et al. Gut. 2014 Sep;63(9):1513-21

OBESOS MORBIDOS SIN IR

Parameters	Control	No-IR morbid obese subjects	IR morbid obese subjects
N (men/women)	8 (5/3)	13 (8/5)	13 (8/6)
Age (years)	54.0 ± 17.8	45.2+10.9	38.8+8.6
Weight (kg)	71.3 ± 7.3 [b]	156.3+32.4 [a]	155.2+25.5 [a]
BMI (Kg/m^2)	28.6 ± 4.1 [b]	56.4+7.4 [a]	55.8+6.1 [a]
Waist (cm)	83.4±7.5 [b]	145.8+24.3 [a]	142.5+17.6 [a]
HOMA-IR	2.57+2.23 [b]	2.73+0.99 [b]	12.92+4.57 [a]

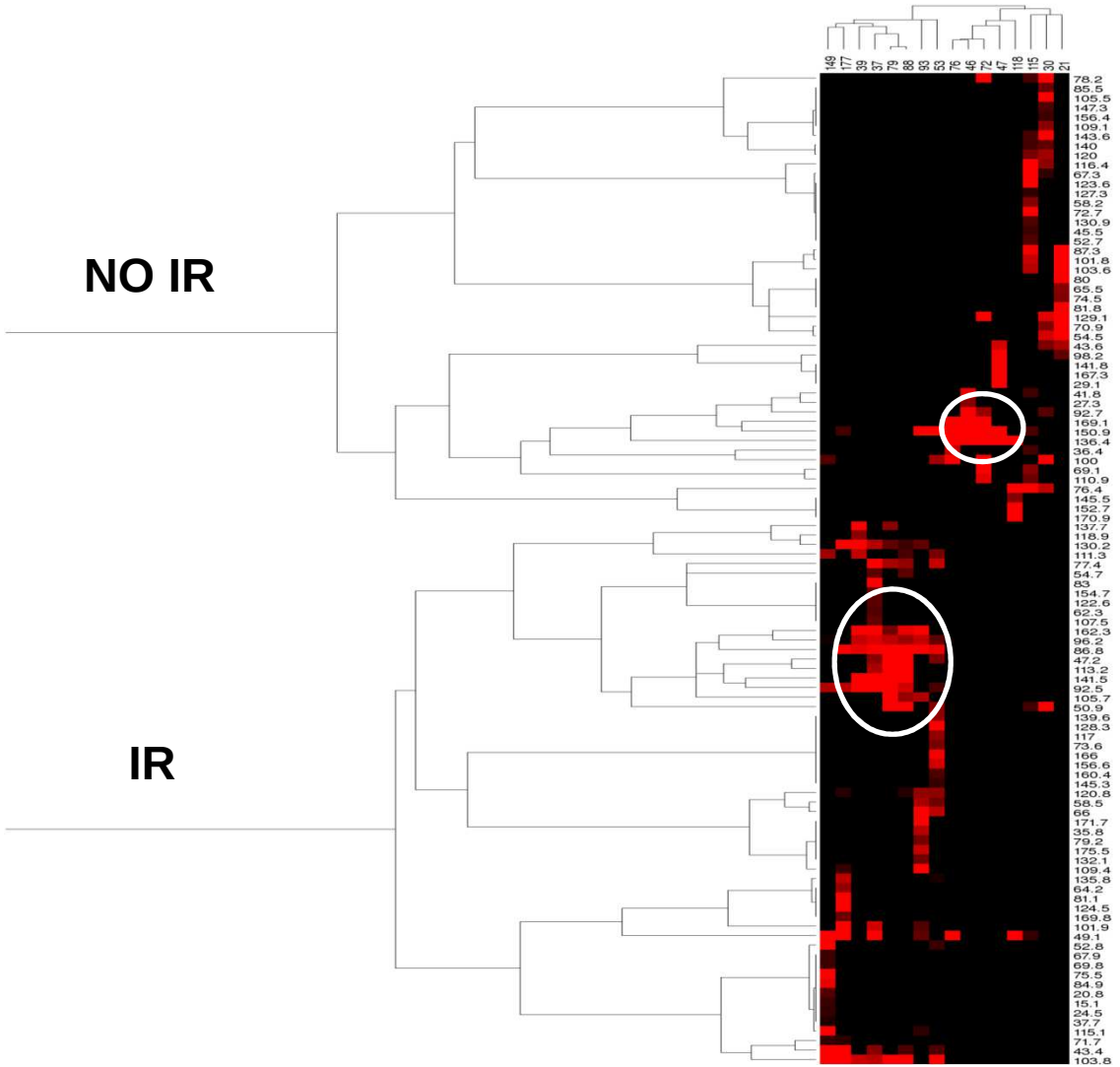




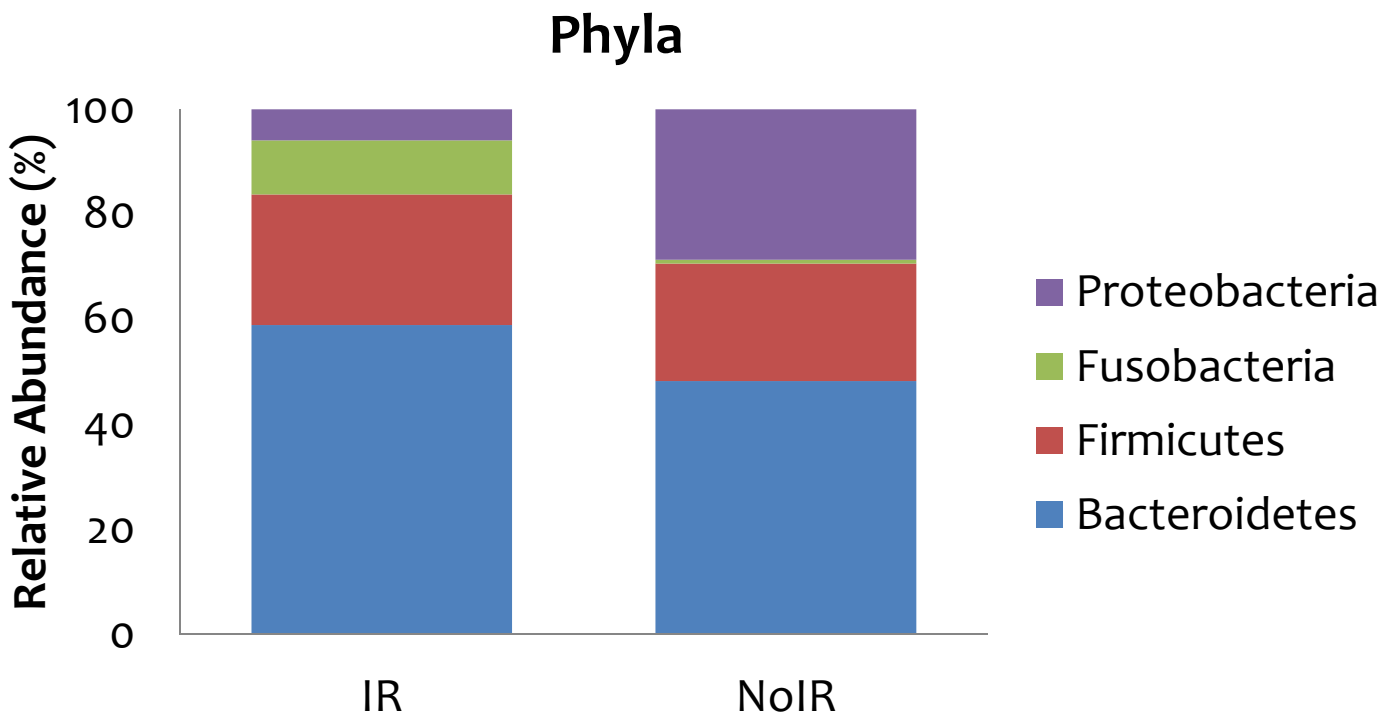
TAXONOMIC DIFFERENCES BETWEEN APPENDICES FROM MORBIDLY OBESE INSULIN SENSITIVE AND RESISTANT

Serino M et al. Act Diabetol 2012

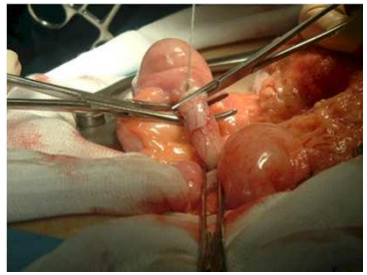
- MICROBIOTA DIFFERENCES BETWEEN THE APPENDIX FROM MORBIDLY OBESE SUBJECTS WITH OR WITHOUT INSULIN RESISTANCE



Serino M et al. Act Diabetol 2012



Taxon	IR	NoIR	*P*
Bacteroidetes	58,87	48,22	7,8E-03
Firmicutes	24,88	22,34	3,84E-09
Fusobacteria	10,34	0,78	4,90E-04
Proteobacteria	5,89	28,64	1,1E-03



MECANISMOS :RELACION MICROBIOTA OBESIDAD

Fermentación sustancias indigeribles

Polisacáridos indigeribles

Firmicutes intestinales

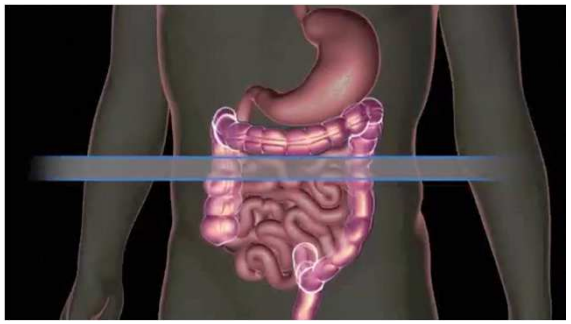
H_2

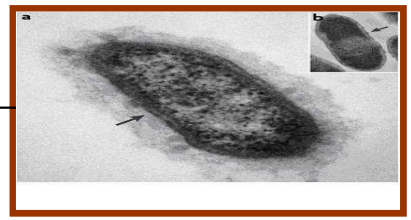
Monosacáridos

SCFA

Energía

(-)





M Smithii (Archaea)

Metano

Raoult, D. Obesity pandemics and the modification of digestive bacterial flora. Eur J Clin Microbiol Infect Dis. 2008; 27: 631-634.

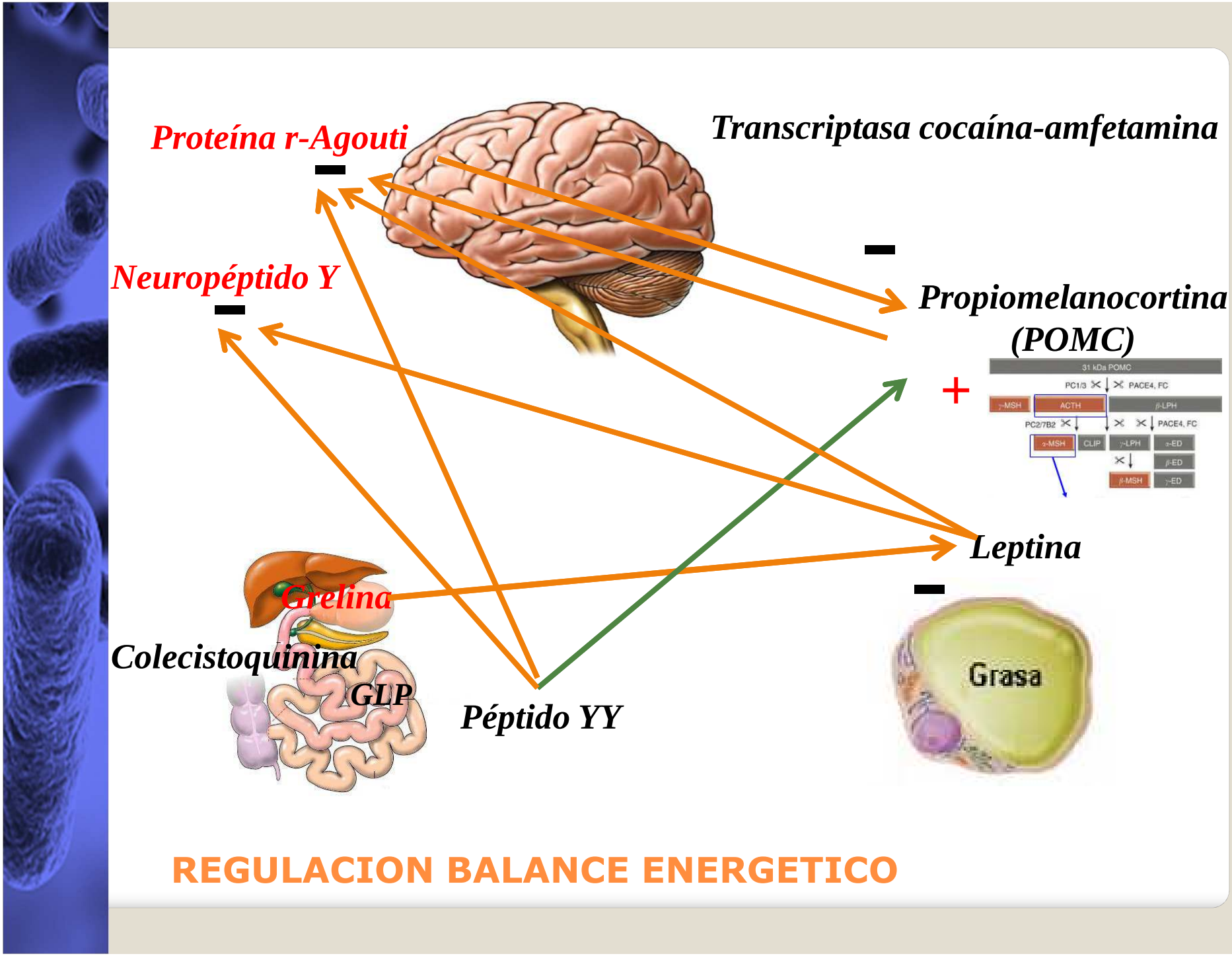
REGULACION BALANCE ENERGETICO

20 KILOCALORIAS MAS AL DIA

20 AÑOS

20 KILOS MAS

Modificación de la secreción de incretinas



REGULACION BALANCE ENERGETICO

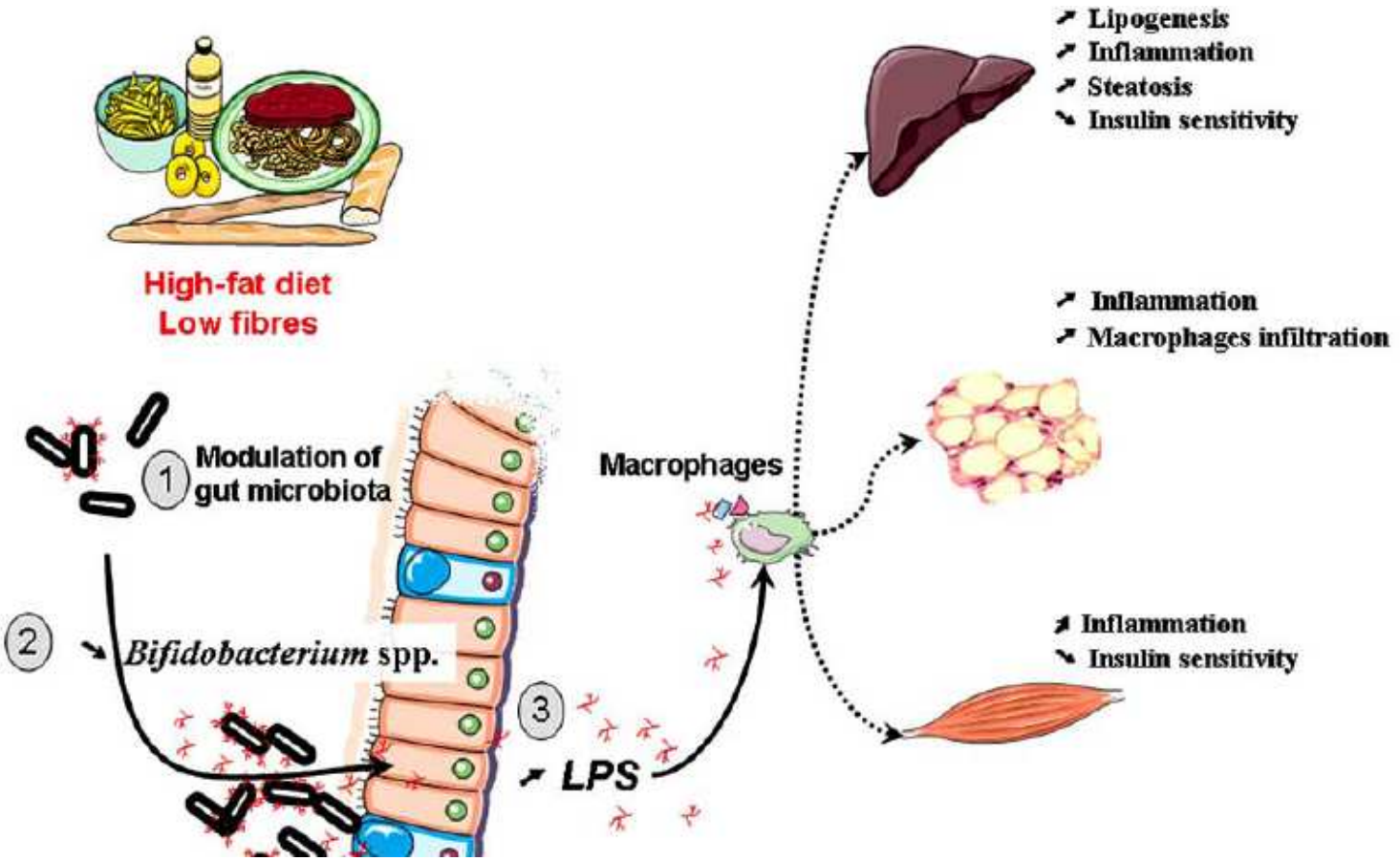
MECANISMOS :RELACION MICROBIOTA DIABETES

Microbiota/Diabetes causalidad

ENDOTOXEMIA

PRODUCCION DE BUTIRATO

ENDOTOXEMIA



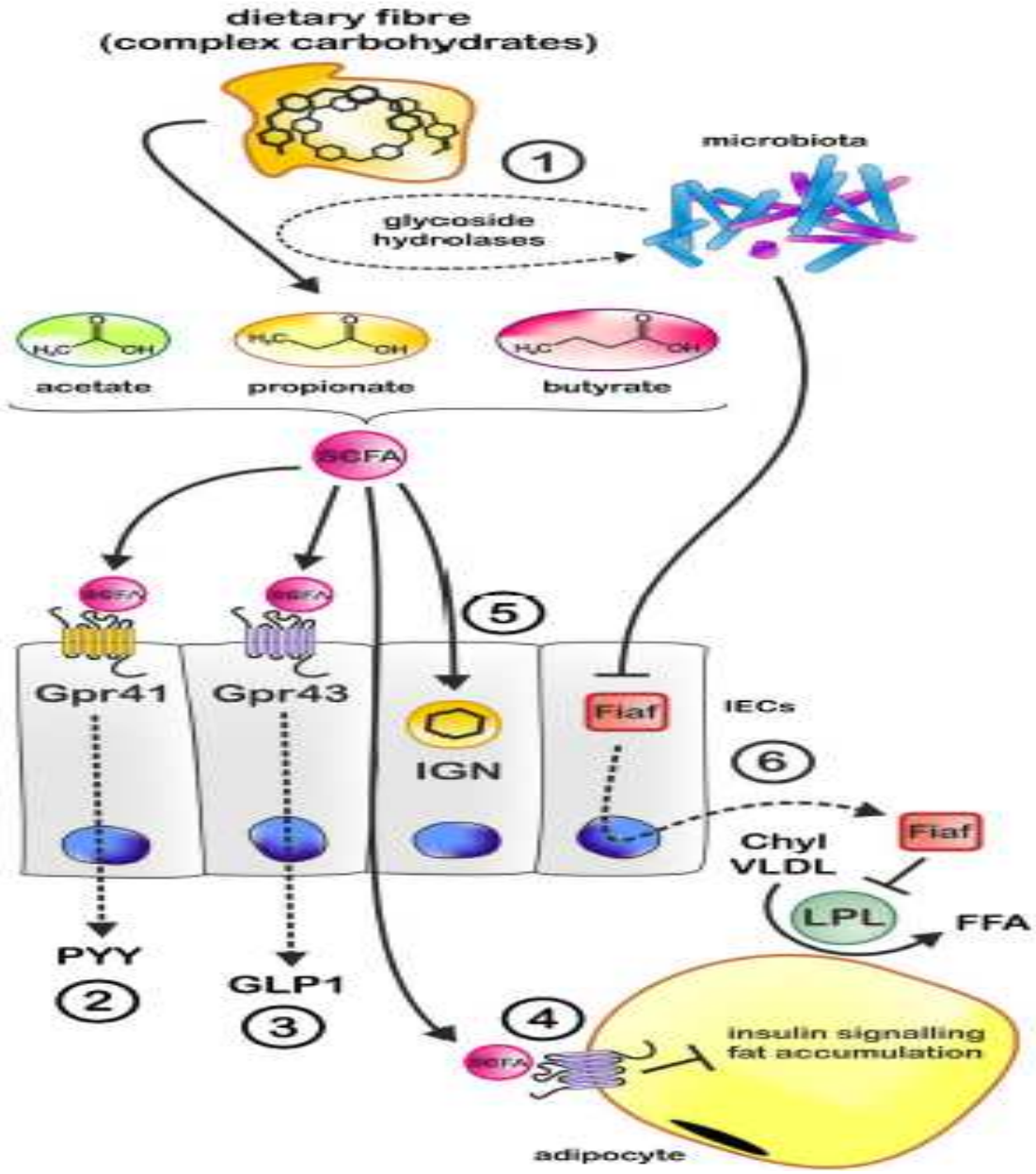
Current Pharmaceutical Design, 2009, *15*, 1546-1558

NIVELES BASALES DE LPS E INCIDENCIA DE DIABETES

		95% CI		
	HR	Lower bound	Upper bound	Significance
Model 1				
Age (years)	1.046	1.036	1.056	<0.001
Male	1.382	1.139	1.678	0.001
Endotoxin quartiles*	1.000			<0.001†
Q1				
Q2	1.073	0.768	1.498	0.681
Q3	1.703	1.255	2.309	0.001
Q4	2.751	2.071	3.654	<0.001
BMI (kg/m^2)	1.149	1.128	1.171	<0.001

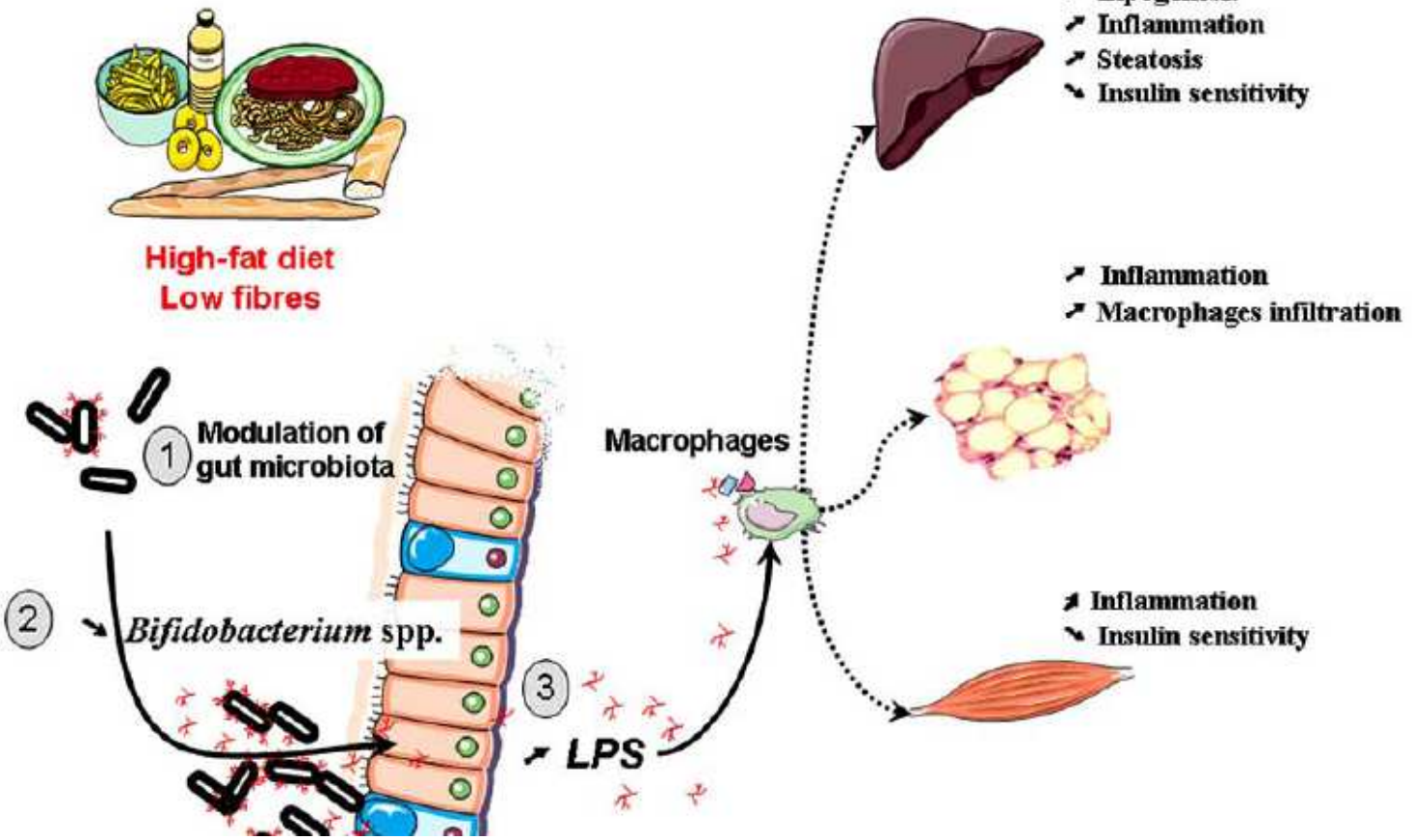
Diabetes Care 34:392–397, 2011

PRODUCCION DE BUTIRATO



¿COMO SE MODIFICA LA MICROBIOTA?

DIETA



Current Pharmaceutical Design, 2009, *15*, 1546-1558

WINE MICROBIOTA

STUDY DESIGN

UNIVERSITAT DE BARCELONA

FUNDACIÓN IMABIS

Dr F. J. Tinahones
Servicio de Endocrinología
Nutrición. Hospital Universitario Virgen de la Victoria de Málaga. CIBEROBN (CB06/03/010), Instituto de Salud Carlos III, Málaga, Spain .

10 volunteers with cardiovascular risk factors

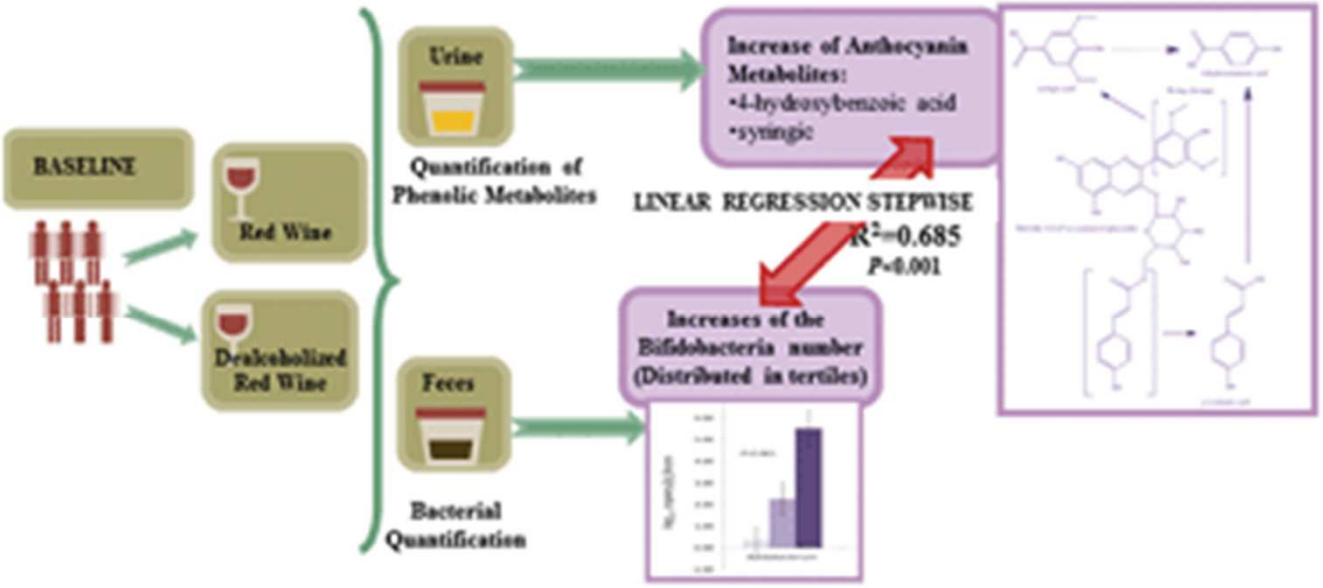
Crossover, randomized, controlled

Washout

1st Intervention 20 days **272 ml RED WINE**	**2nd Intervention** 20 days **272 ml RED WINE**	**3rd Intervention** 20 days **272 ml RED WINE**	
1st Intervention 20 days **272 ml DEALCOHOLIZED RED WINE (Polyphenol Control)**	**2nd Intervention** 20 days **272 ml DEALCOHOLIZED RED WINE (Polyphenol Control)**	**3rd Intervention** 20 days **272 ml DEALCOHOLIZED RED WINE (Polyphenol Control)**	
1st Intervention 20 days **100 ml GIN (Alcohol Control)**	**2nd Intervention** 20 days **100 ml GIN (Alcohol Control)**	**3rd Intervention** 20 days **100 ml GIN (Alcohol Control)**	
FECES	**FECES**	**FECES**	**FECES**

EFFECTS OF MODERATE WINE CONSUMPTION IN SUBJECTS WITH CARDIOVASCULAR RISK ON THE MICROBIAL COMPOSITION IN FECES

RESULTS



Firmicutes (

Bacteroidete

Fusobacteri

Enterococcu

Bacteroides

Prevotella s

Clostridium

Bifidobacterium spp ↑

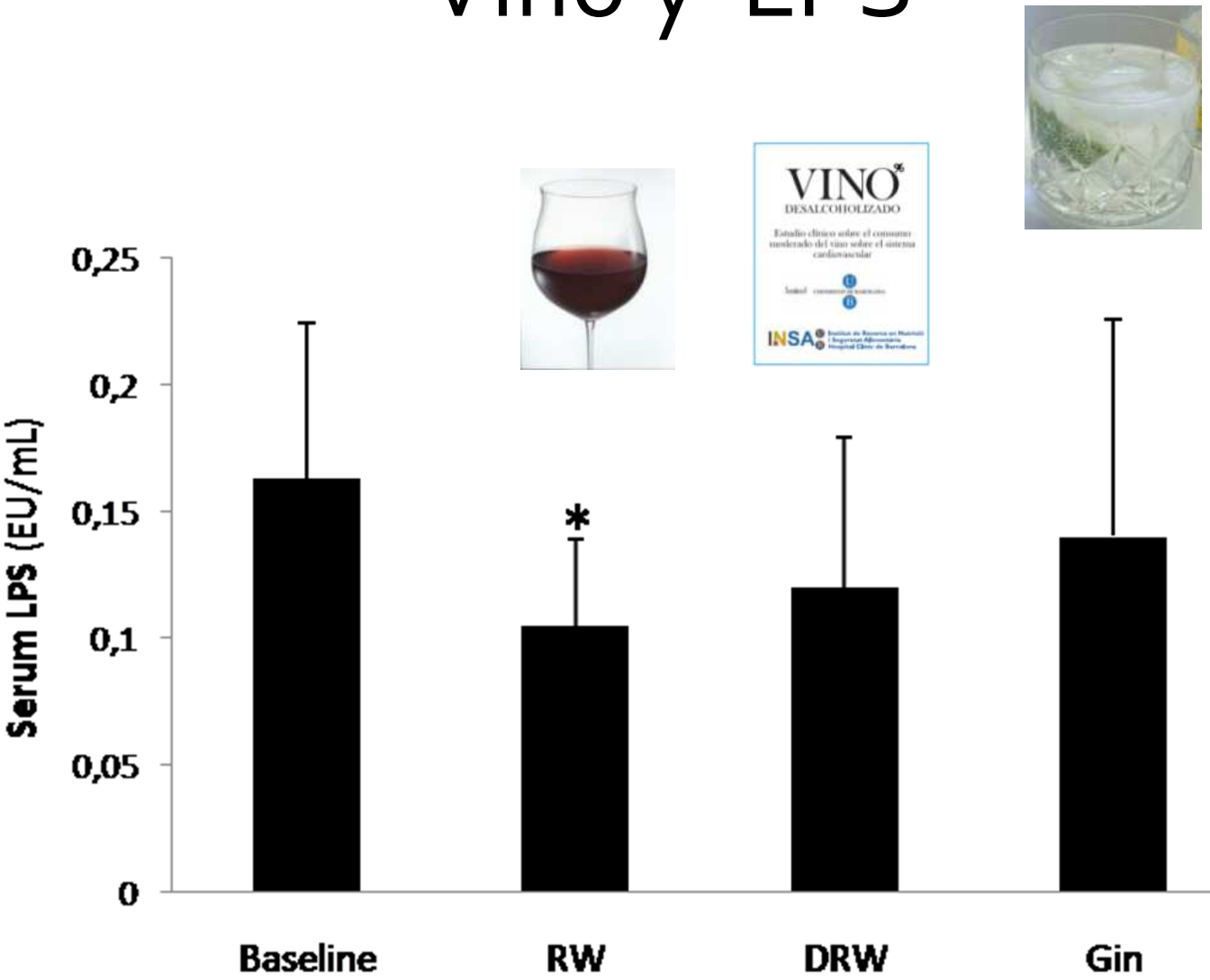
Lactobacillus spp ↑

—

Boto M et al Food Funct. 2014 Aug;5(8):1932-8.

Queipo-Ortuño MI. Am J Clin Nutr 2012

Vino y LPS



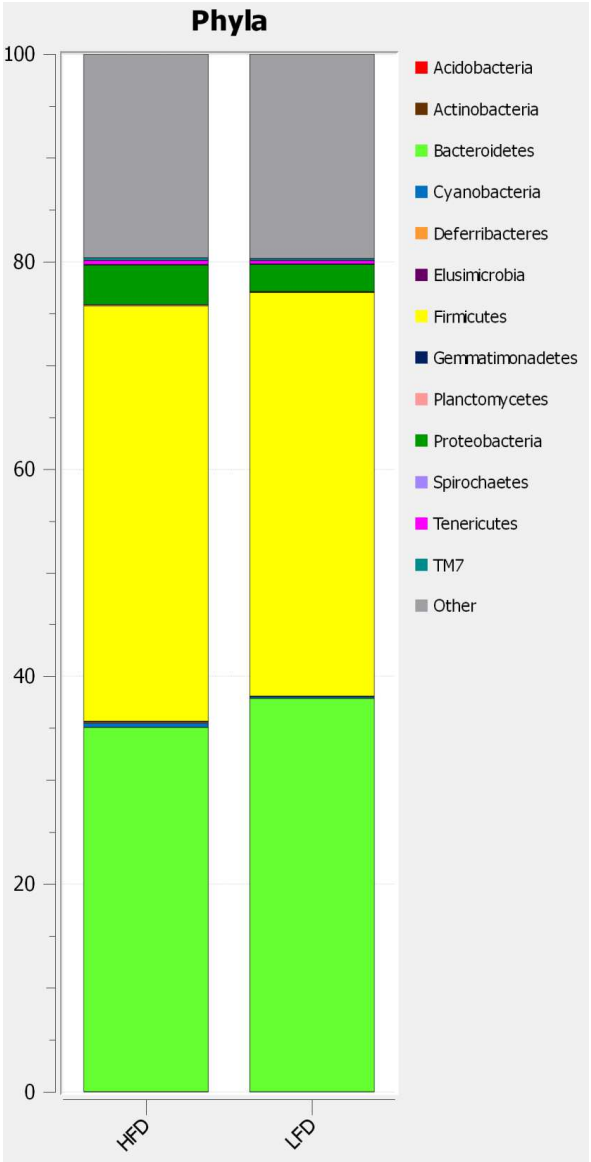
Clemente M et al. Am J Clin Nutr 2013

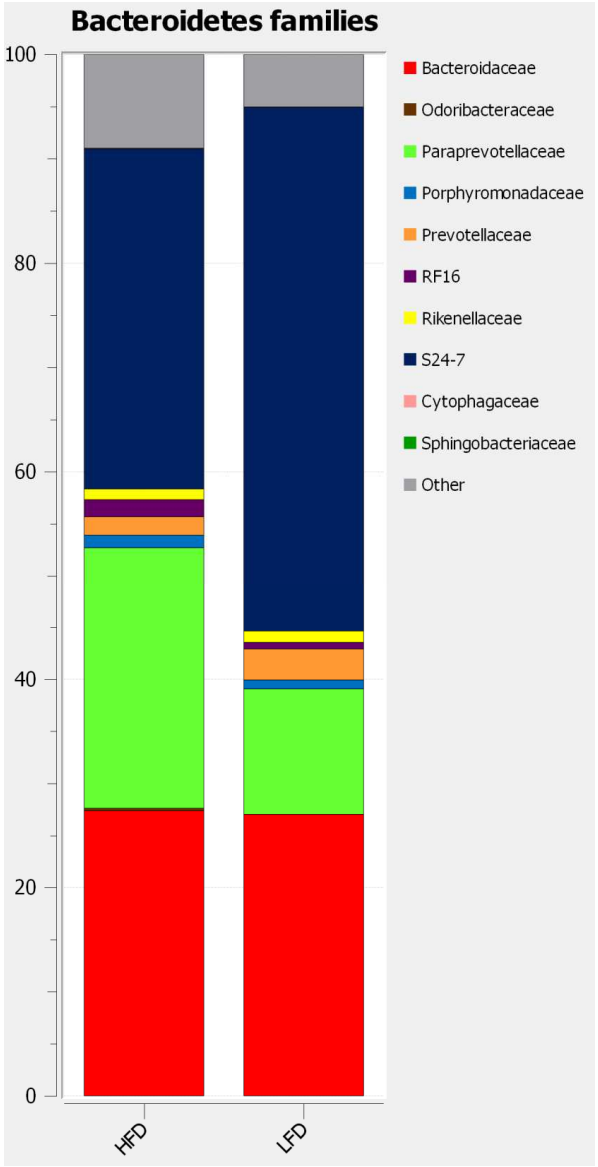
DIETA vs HORMONAS SEXUALES

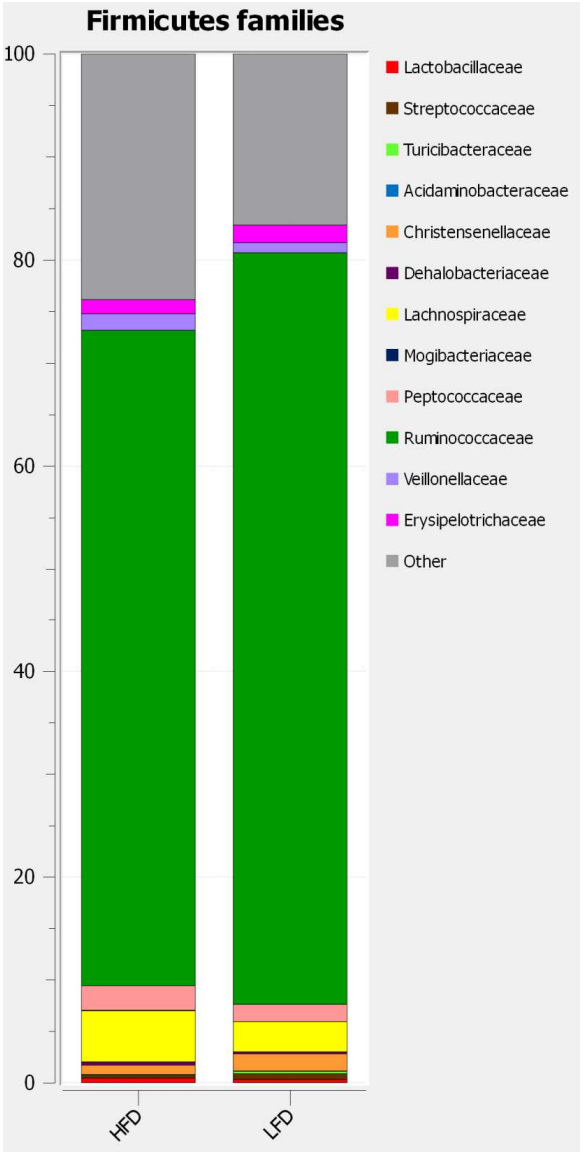
- DIETA BAJA EN GRASA Y ALTA
- CRIAS SIN OVARIOS VS CRIAS DE MADRES ANDROGENIZADAS

HFD

LFD


Phyla
100
80
60
40
20
0
HFD
LFD
Acidobacteria
Actinobacteria
Bacteroidetes
Cyanobacteria
Deferribacteres
Elusimicrobia
Firmicutes
Gemmatimonadetes
Planctomycetes
Proteobacteria
Spirochaetes
Tenericutes
TM7
Other

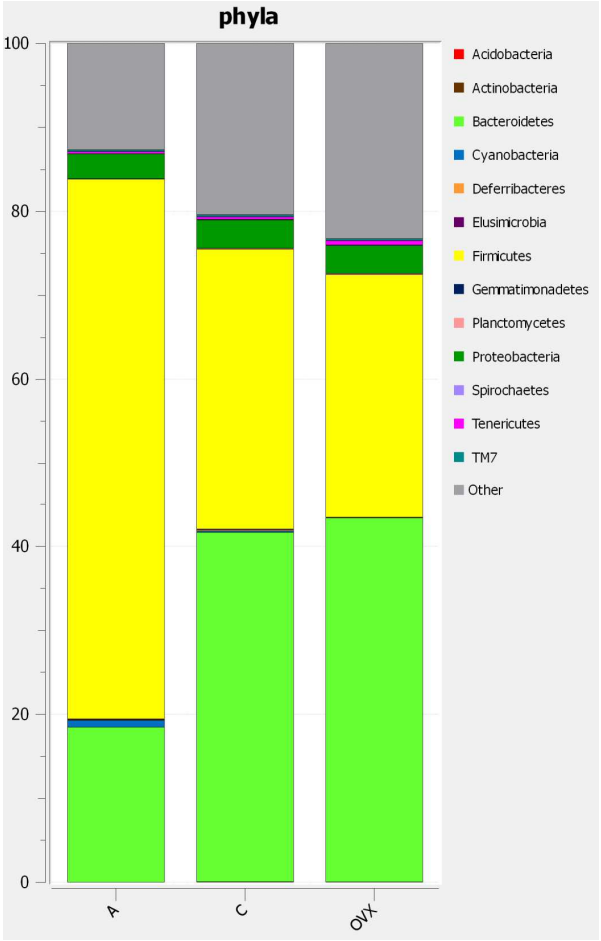

Bacteroidetes families
100
80
60
40
20
0
HFD
LFD
Bacteroidaceae
Odoribacteraceae
Paraprevotellaceae
Porphyromonadaceae
Prevotellaceae
RF16
Rikenellaceae
S24-7
Cytophagaceae
Sphingobacteriaceae
Other

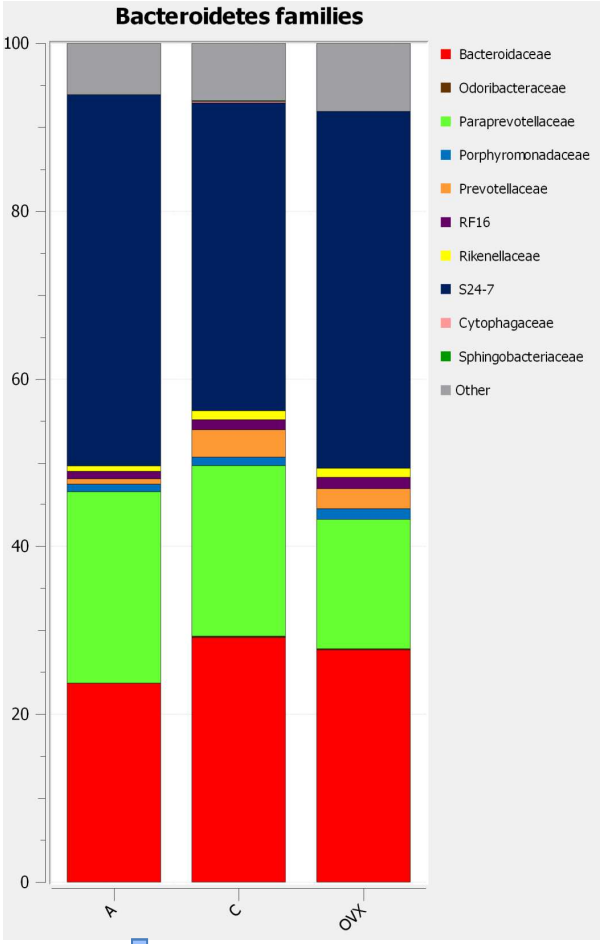

Firmicutes families
100
80
60
40
20
0
HFD
LFD
Lactobacillaceae
Streptococcaceae
Turicibacteraceae
Acidaminobacteraceae
Christensenellaceae
Dehalobacteriaceae
Lachnospiraceae
Mogibacteriaceae
Peptococcaceae
Ruminococcaceae
Veillonellaceae
Erysipelotrichaceae
Other

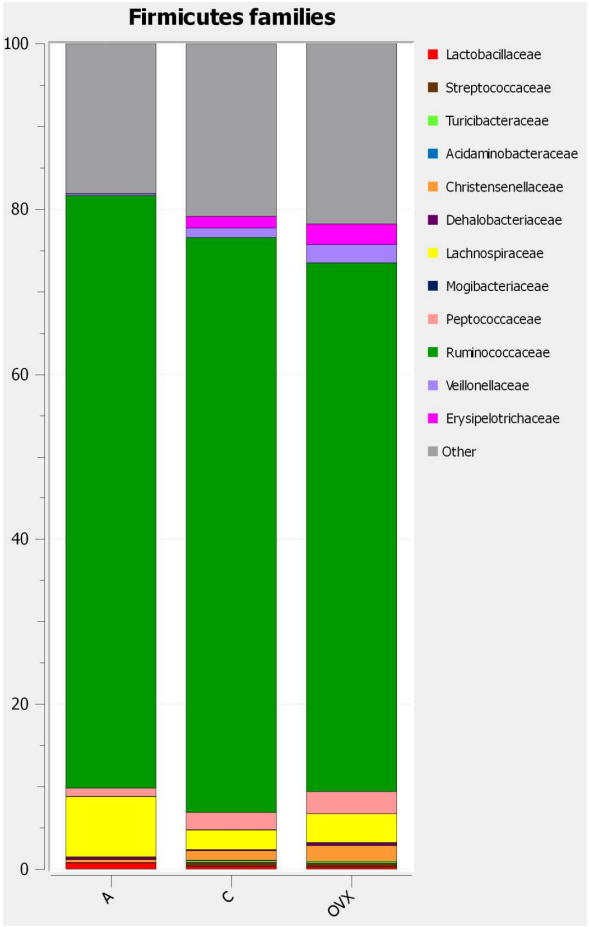
A  

C  control

OVX  ooforectomía







A: ↑ Firmicutes

↓ Bacterioidetes

A: ↓ Prevotellaceae

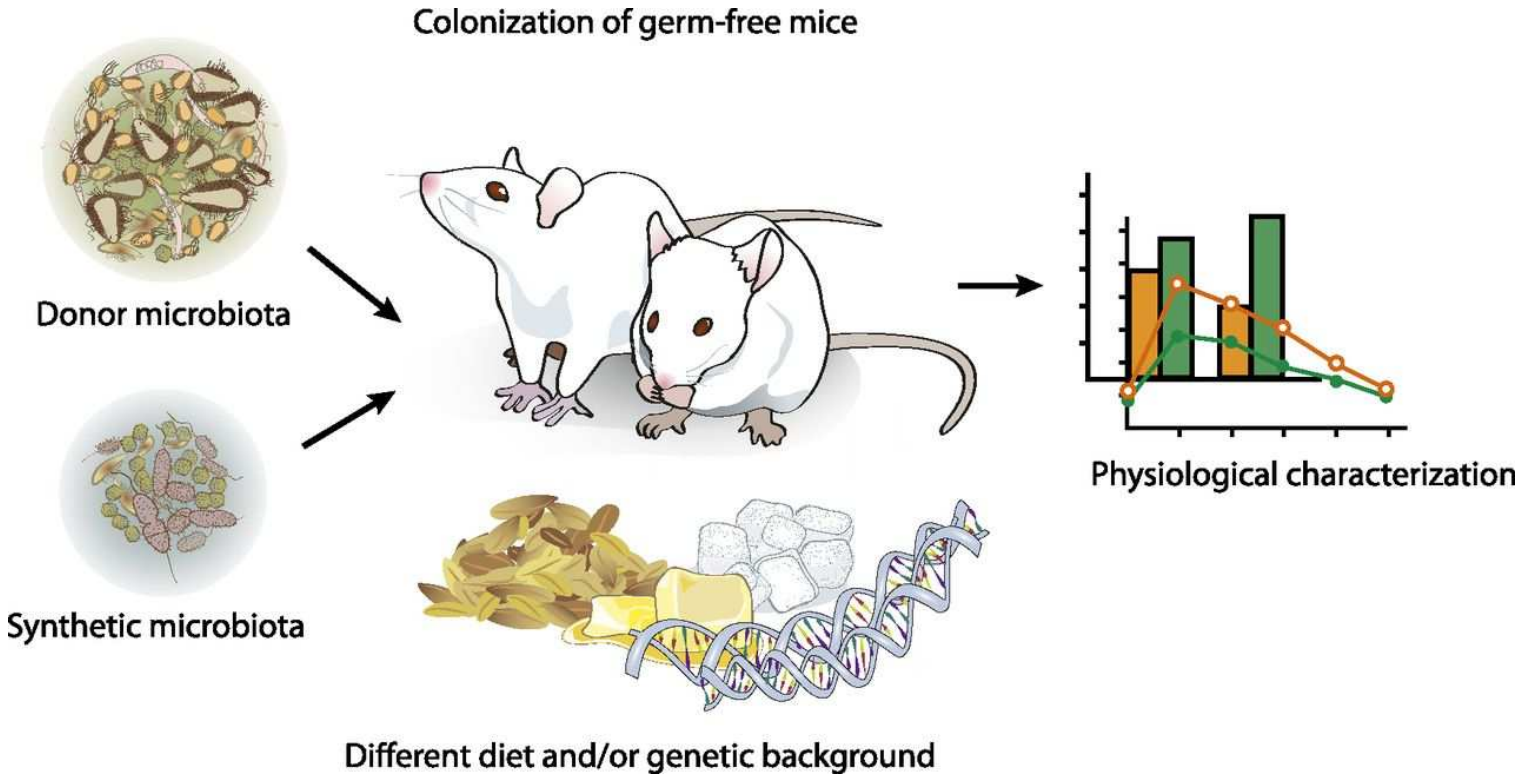
↓ Bacterioidaceae

A: ↑ Lachnospiraceae

↓ Vellonaceae

TRANSPLANTE DE MICROBIOTA

MODELOS EXPERIMENTALES



BRIEF REPORT

Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome

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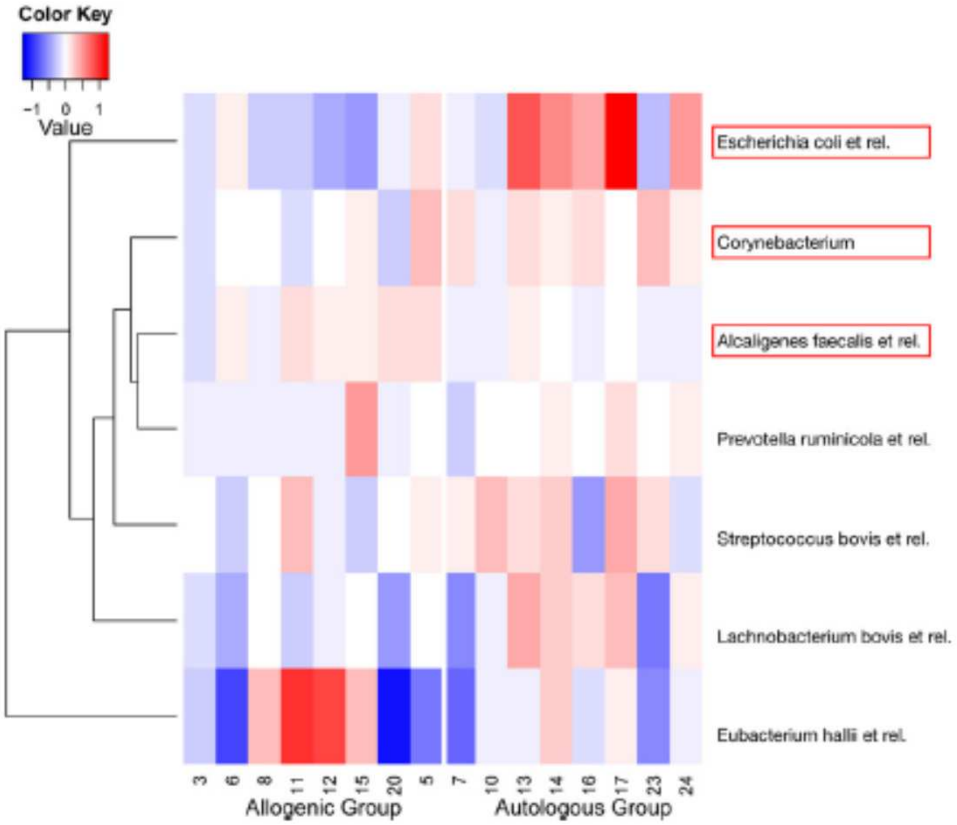

GASTROENTEROLOGY 2012;143:913–916

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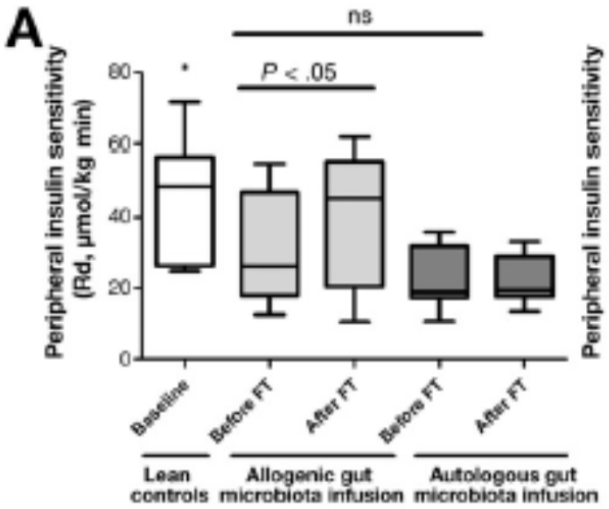

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