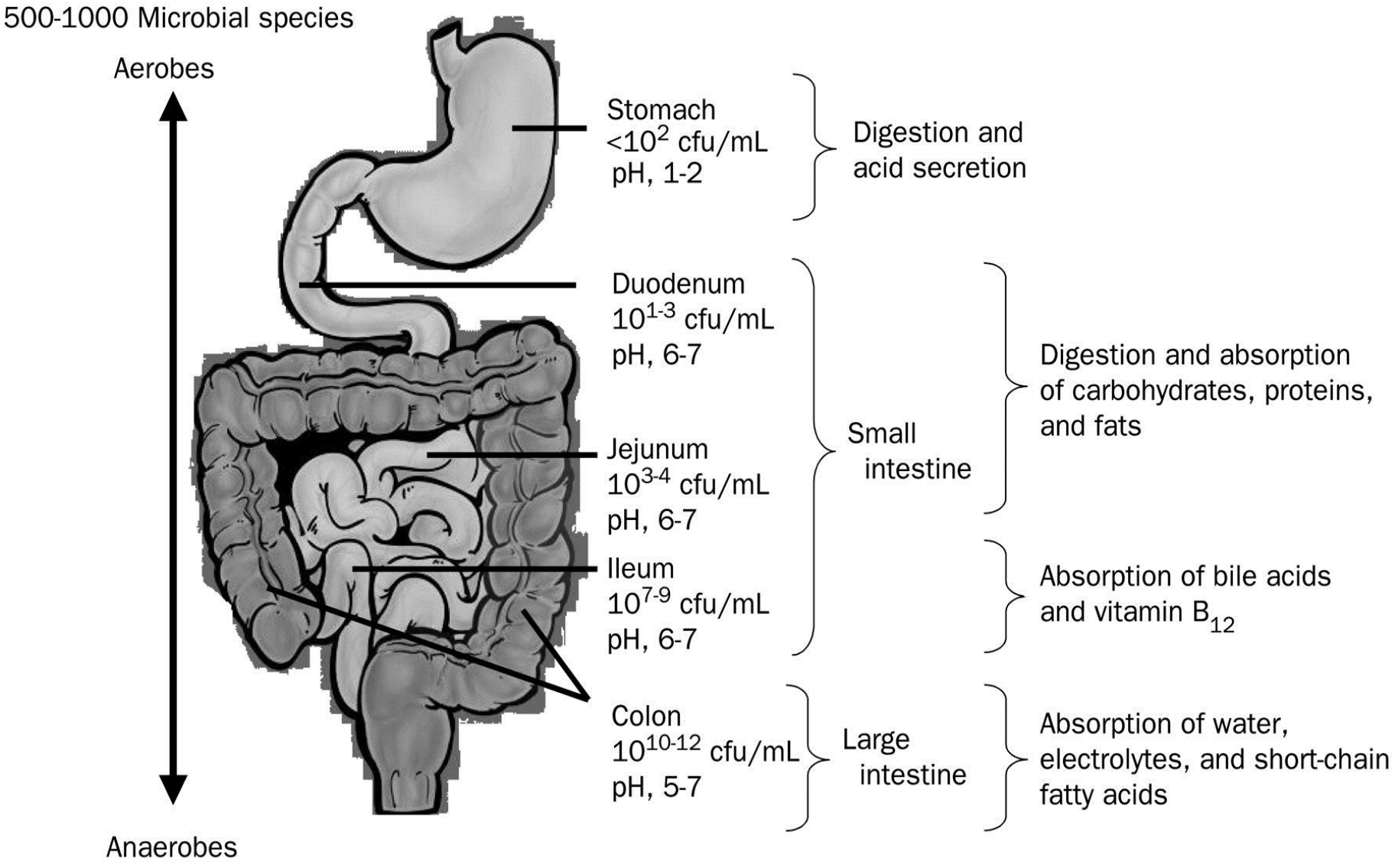
Erişkinde Mikrobiyota

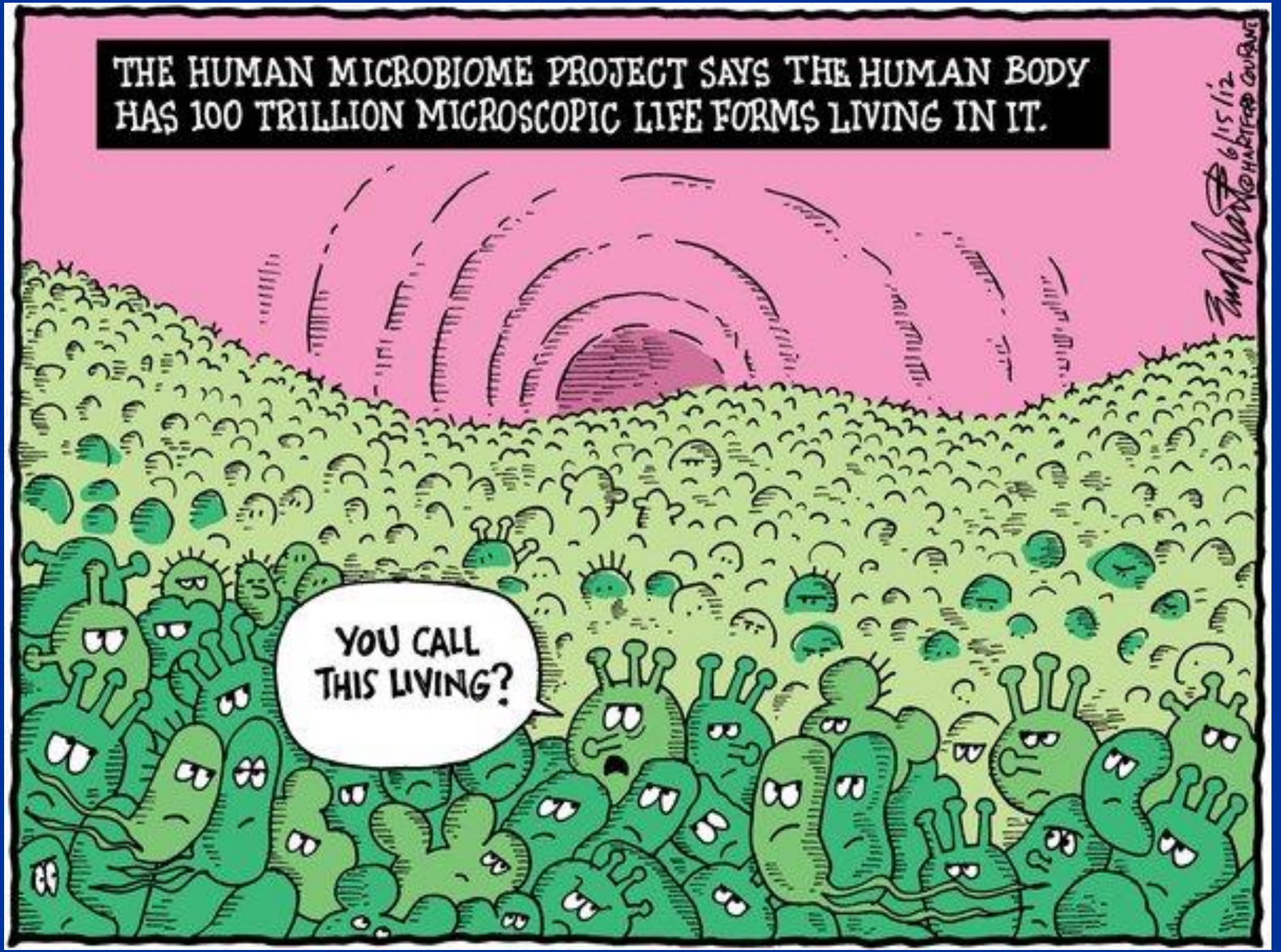
Dr Tarkan Karakan
Gazi Üniversitesi
Gastroenteroloji Bilim Dalı

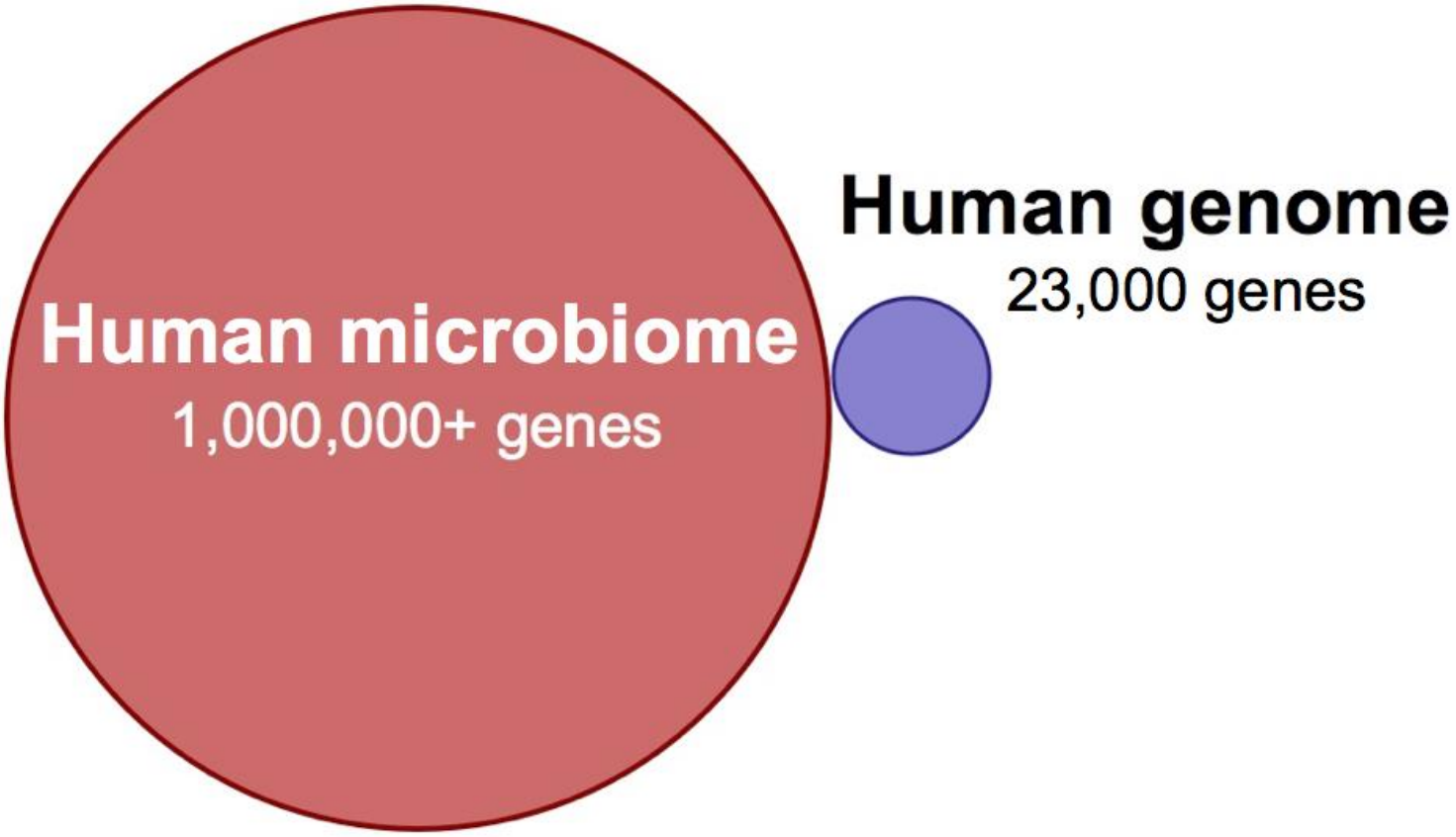
İnsan ve bakteri ilişkisi

- İnsan vücudundaki bakterilerin yüzey alanı = 400 m^2 (Tenis kortu kadar)
- İnsandaki gen sayısı: 35,000
- Bakteriyel genom: > 2 milyon gen
  - Barsakta 100 trilyon canlı bakteri
  - Kolonda 500 üzerinde tür
- Toplam hücre sayısı: İnsan = 10^{14} Bakteri = 10^{15}
- Bakteri ve konakçı arasında etkileşim (çapraz-konuşma)
  - Bir bakteri türü diğerlerinin 100 genini aktive edebilir
  - Dendritik hücre/makrofajların üzerindeki Toll-like reseptörler
  - Barsakta kompleks nöroendokrin sistemle etkileşim

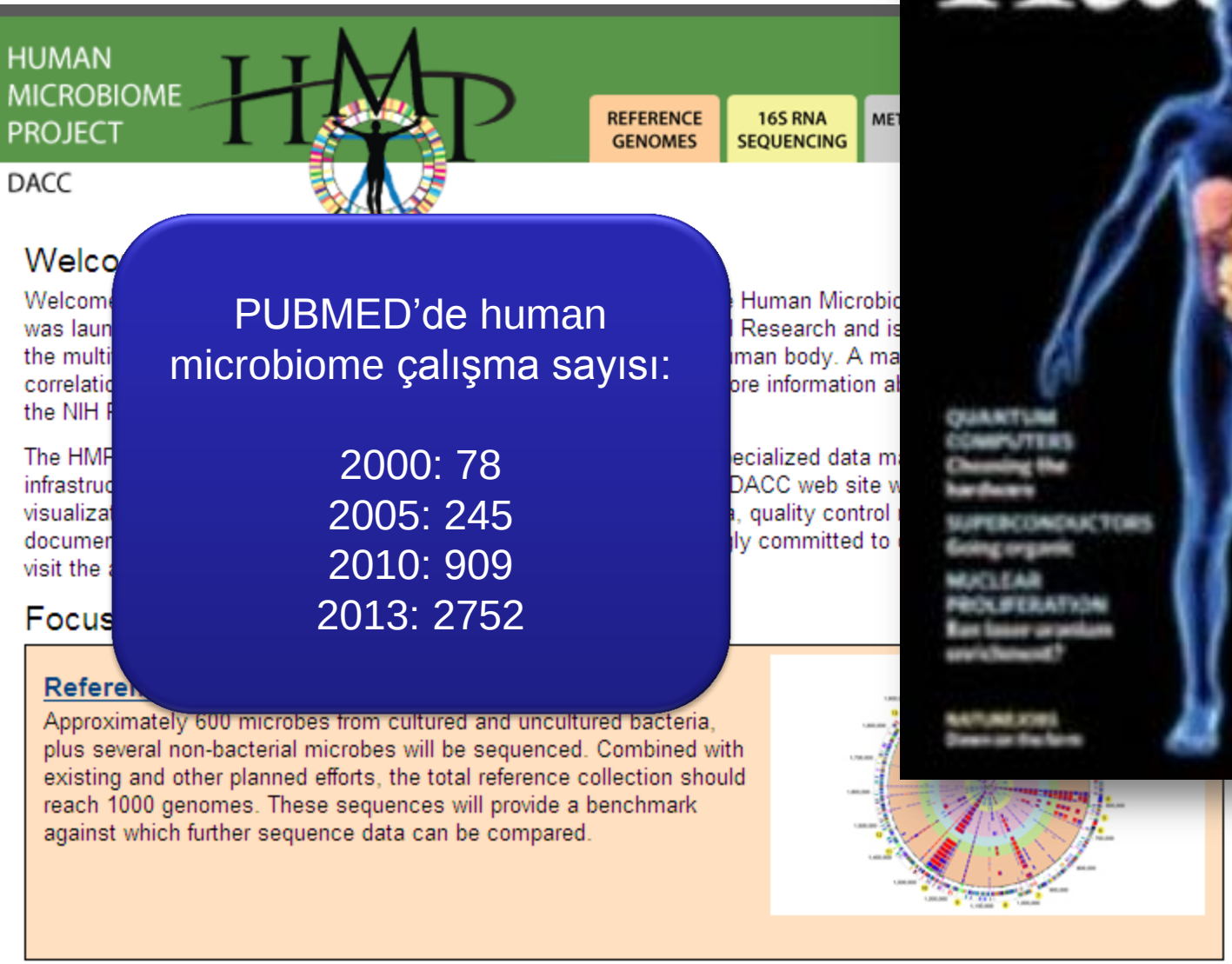

500-1000 Microbial species
Aerobes
Anaerobes
Stomach
<10^2 cfu/mL
pH, 1-2
Digestion and
acid secretion
Duodenum
10^{1-3} cfu/mL
pH, 6-7
Jejunum
10^{3-4} cfu/mL
pH, 6-7
Small
intestine
Digestion and absorption
of carbohydrates, proteins,
and fats
Ileum
10^{7-9} cfu/mL
pH, 6-7
Absorption of bile acids
and vitamin B_{12}
Colon
10^{10-12} cfu/mL
pH, 5-7
Large
intestine
Absorption of water,
electrolytes, and short-chain
fatty acids

İnsan vücudundaki toplam hücrelerin sadece ONDA BİRİ insan hücresi


THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.
YOU CALL THIS LIVING?
6/15/12
©HABITFOOD COMICS


Human microbiome
1,000,000+ genes
Human genome
23,000 genes

2009 ‘da NIH Human Microb



PUBMED’de human microbiome çalışma sayısı:

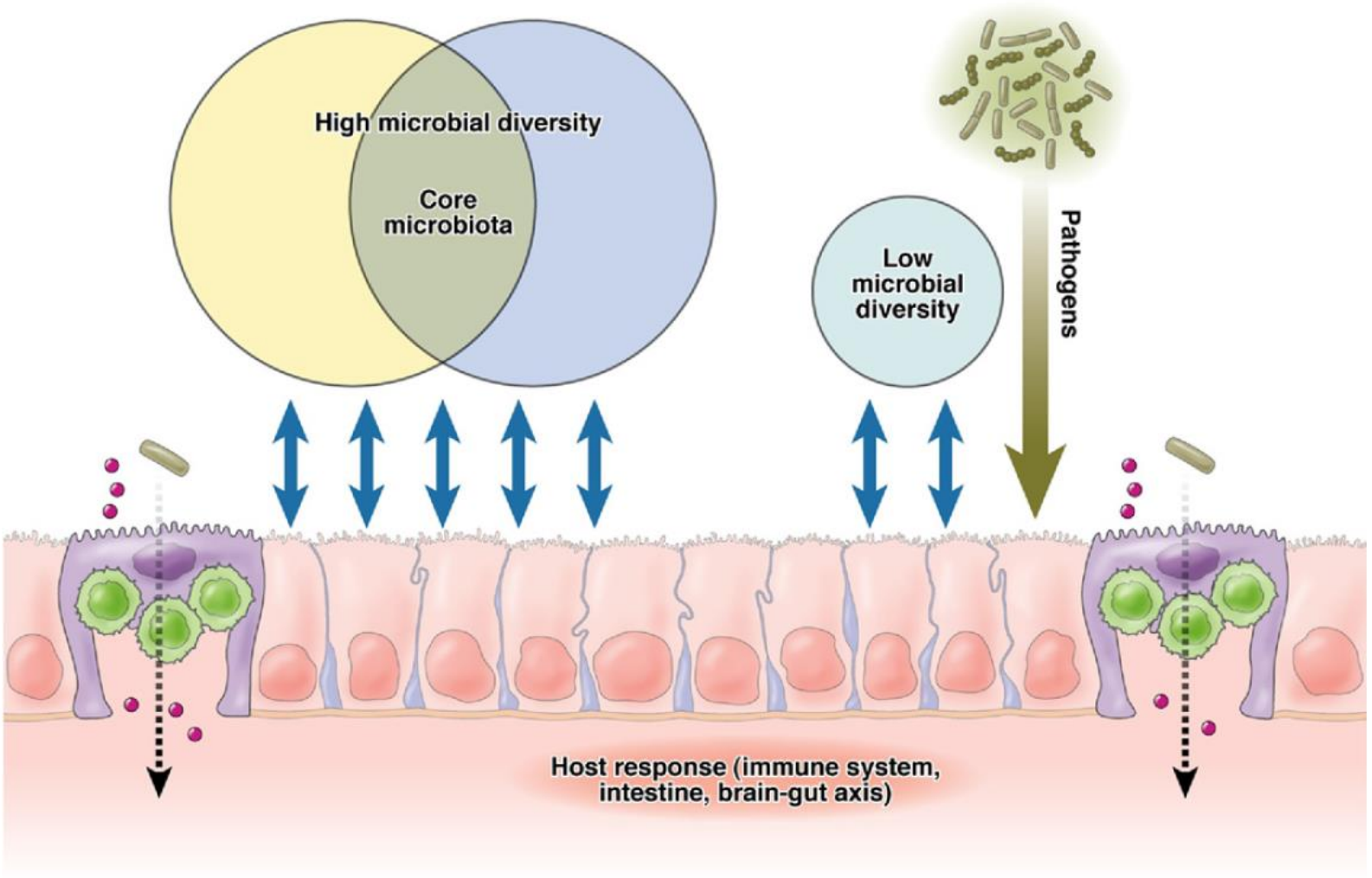
2000: 78
2005: 245
2010: 909
2013: 2752

Bakteriler doğumdan itibaren olmasaydı, immün sistem gelişemezdi

TABLE 2. Main Intestinal Features in the Germ-free Animal Model

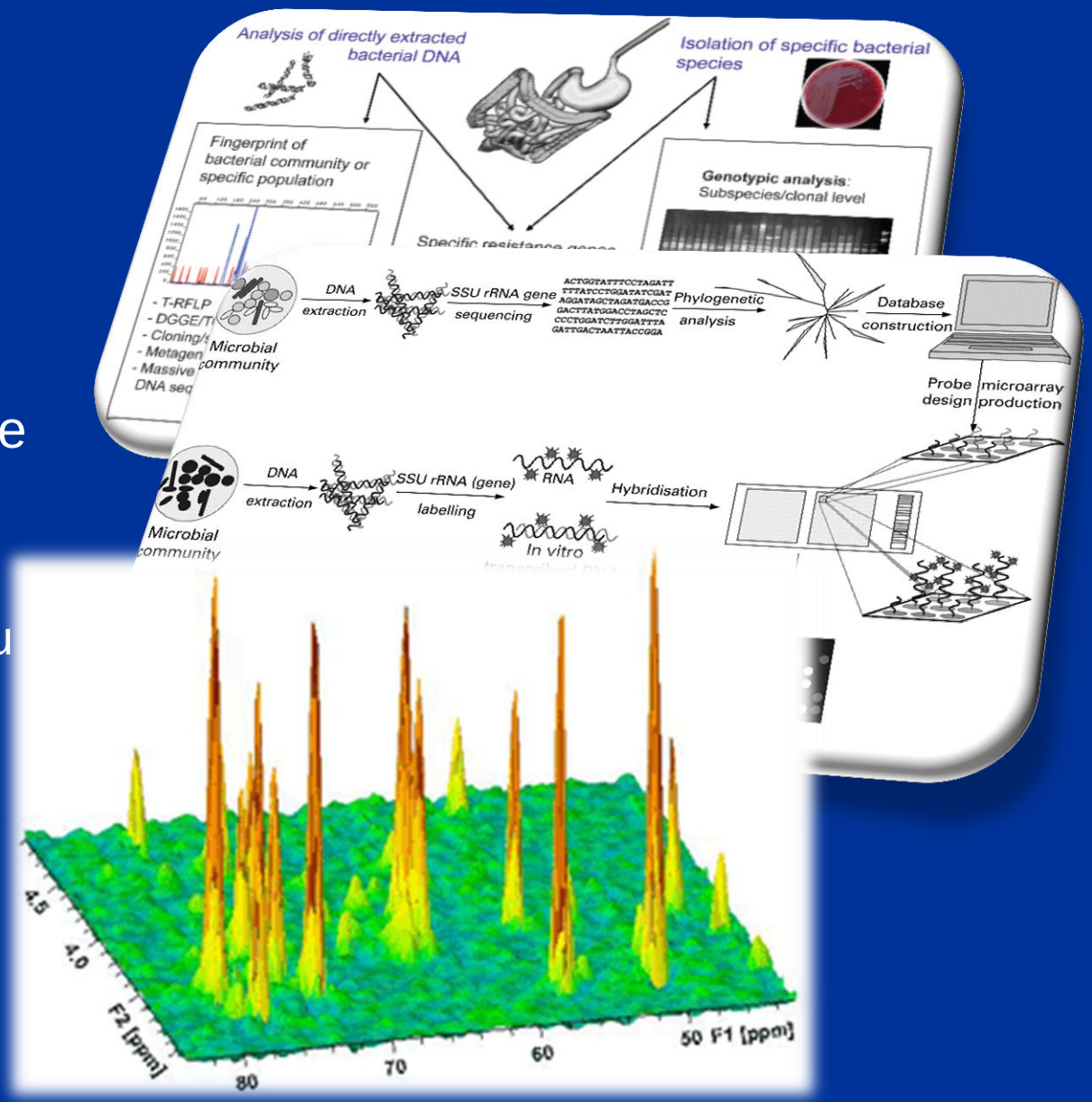
Function	Features
Mucosal growth	↓↓
Brush border enzymatic activities	↓
Blood flow	↓↓
Motility	↓↓↓
Cytokine production	↓
GALT and MALT	↓↓
Immunity	↓↓
Susceptibility to infections	↑↑↑
Oral tolerance	↓↓

GALT indicates gastrointestinal-associated lymphoid tissue; MALT, mucosal-associated lymphoid tissue.

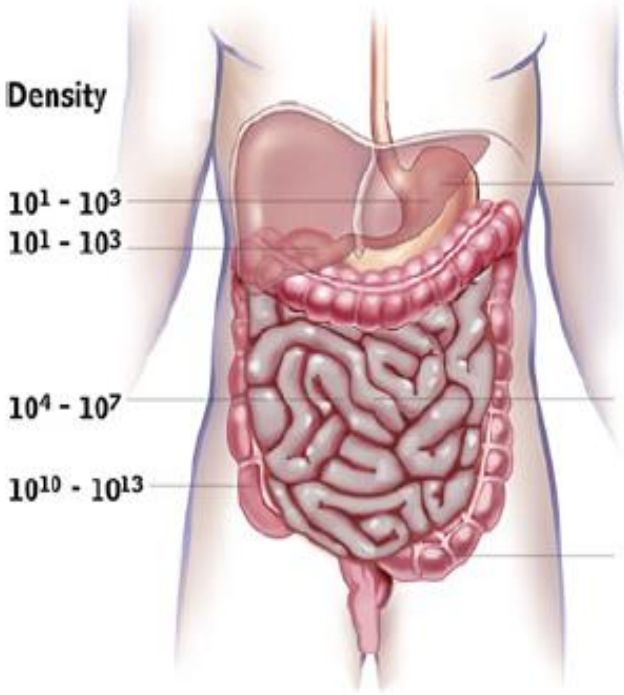

High microbial diversity
Core microbiota
Low microbial diversity
Pathogens
Host response (immune system, intestine, brain-gut axis)

İntestinal flora araştırma teknikleri

- Kültür ve 16SrRNA ve benzeri testler:
  - Belirli bir kişiyi aramak için
- Microarray analiz ve benzeri moleküler genetik testler:
  - Orada kaç farklı insan var (ama bu kişileri tanımıyor)
- Metabolomics:
  - Oradakiler neler yapıyor?

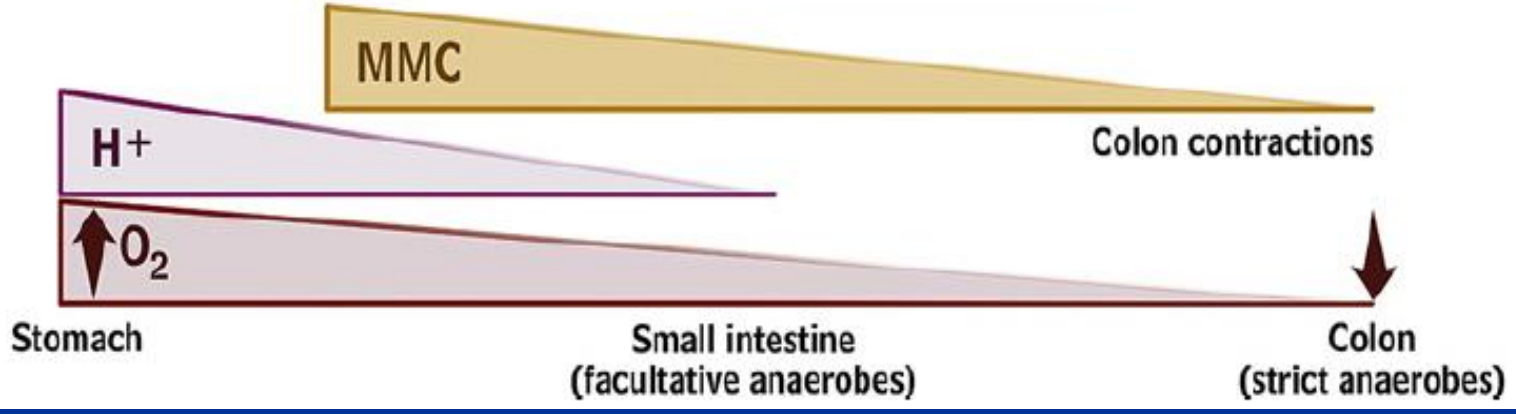


Barsak Mikrobiyotasını Etkileyen Faktörler

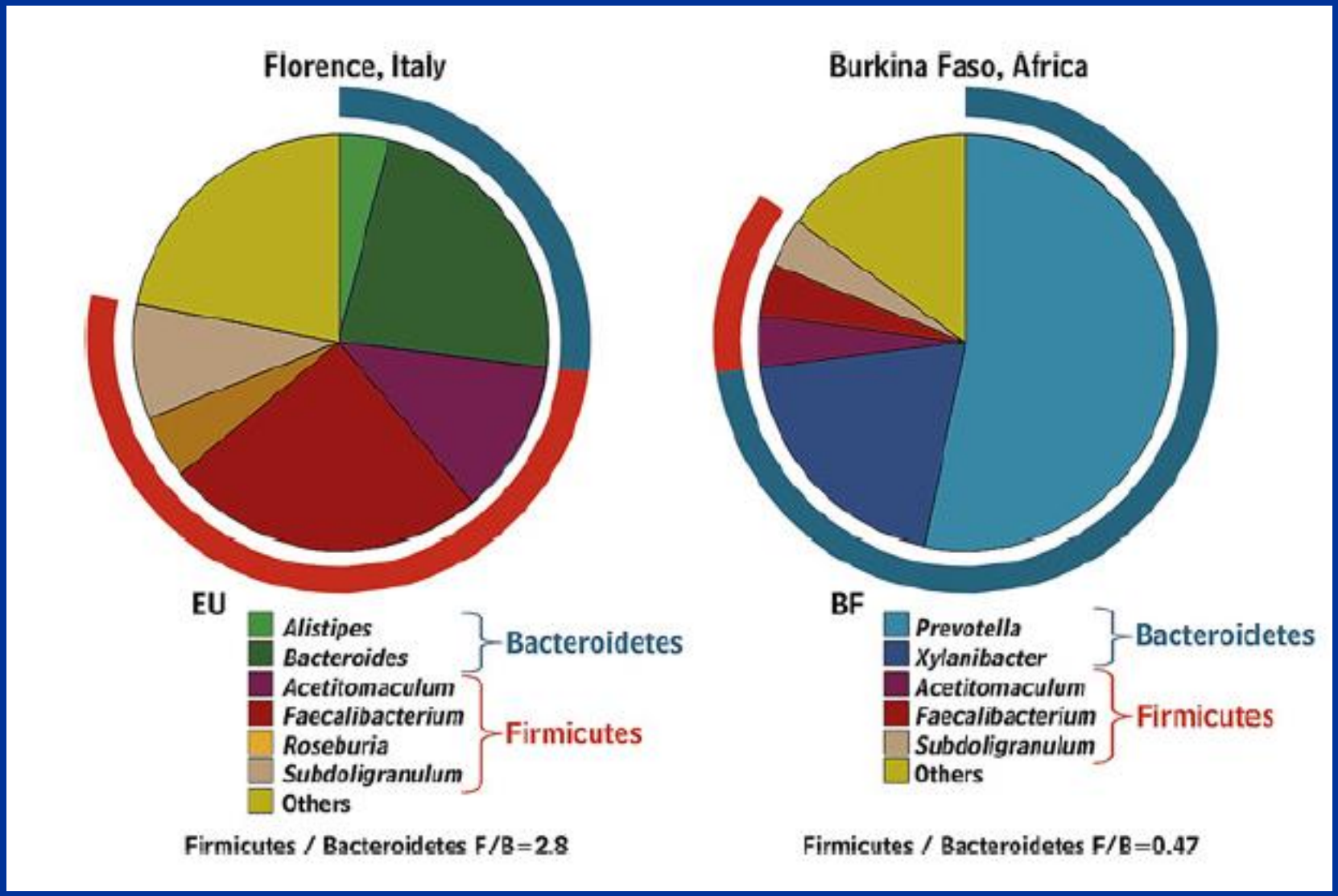


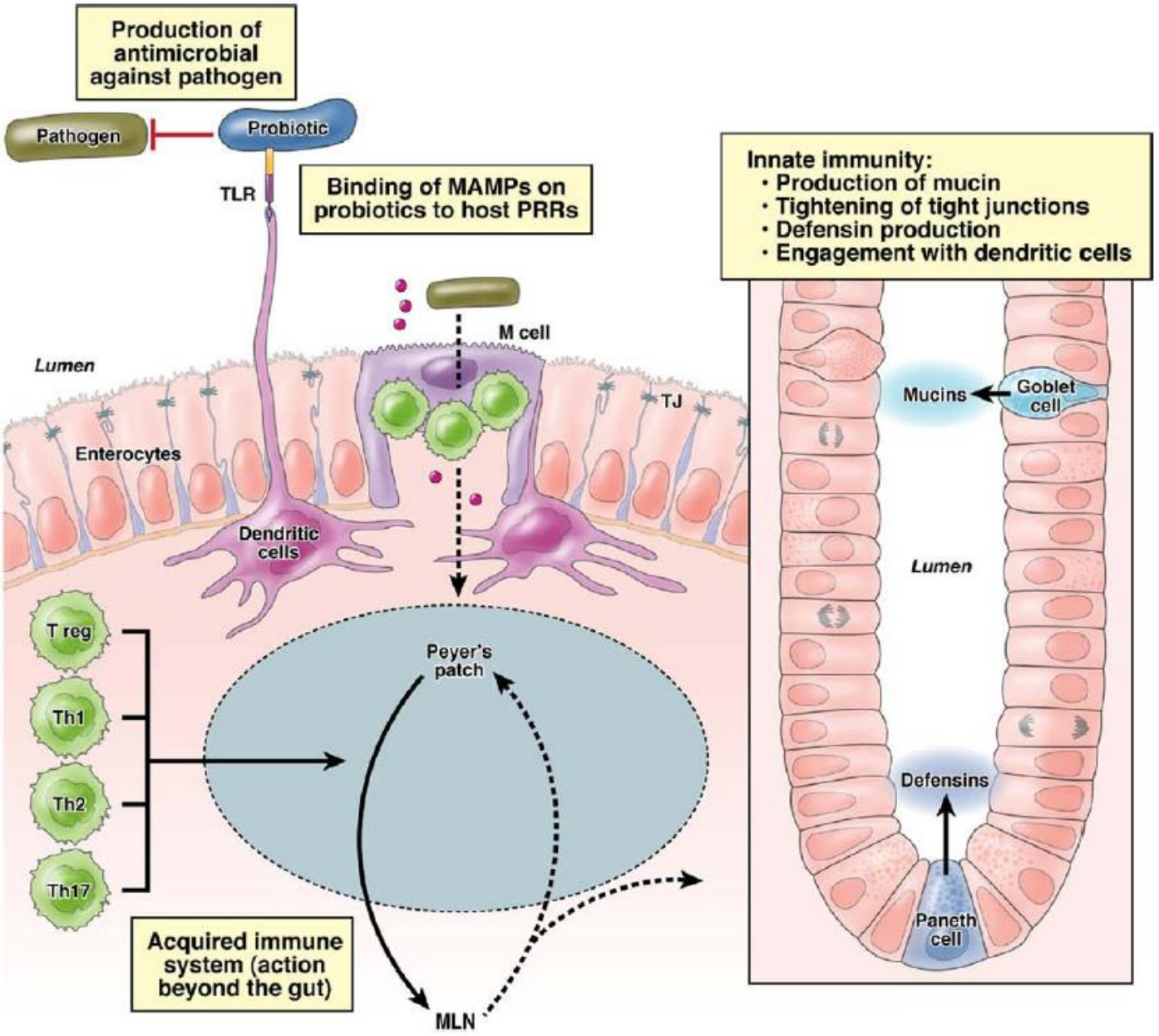
Density	Composition
$10^1 - 10^3$	Streptococcus
$10^1 - 10^3$	Lactobacillus
$10^4 - 10^7$	Streptococcus
	Lactobacillus
	Enterobacteriaceae
$10^{10} - 10^{13}$	Bacteroides
	Eubacterium
	Clostridium
	Ruminococcus
	Bifidobacterium

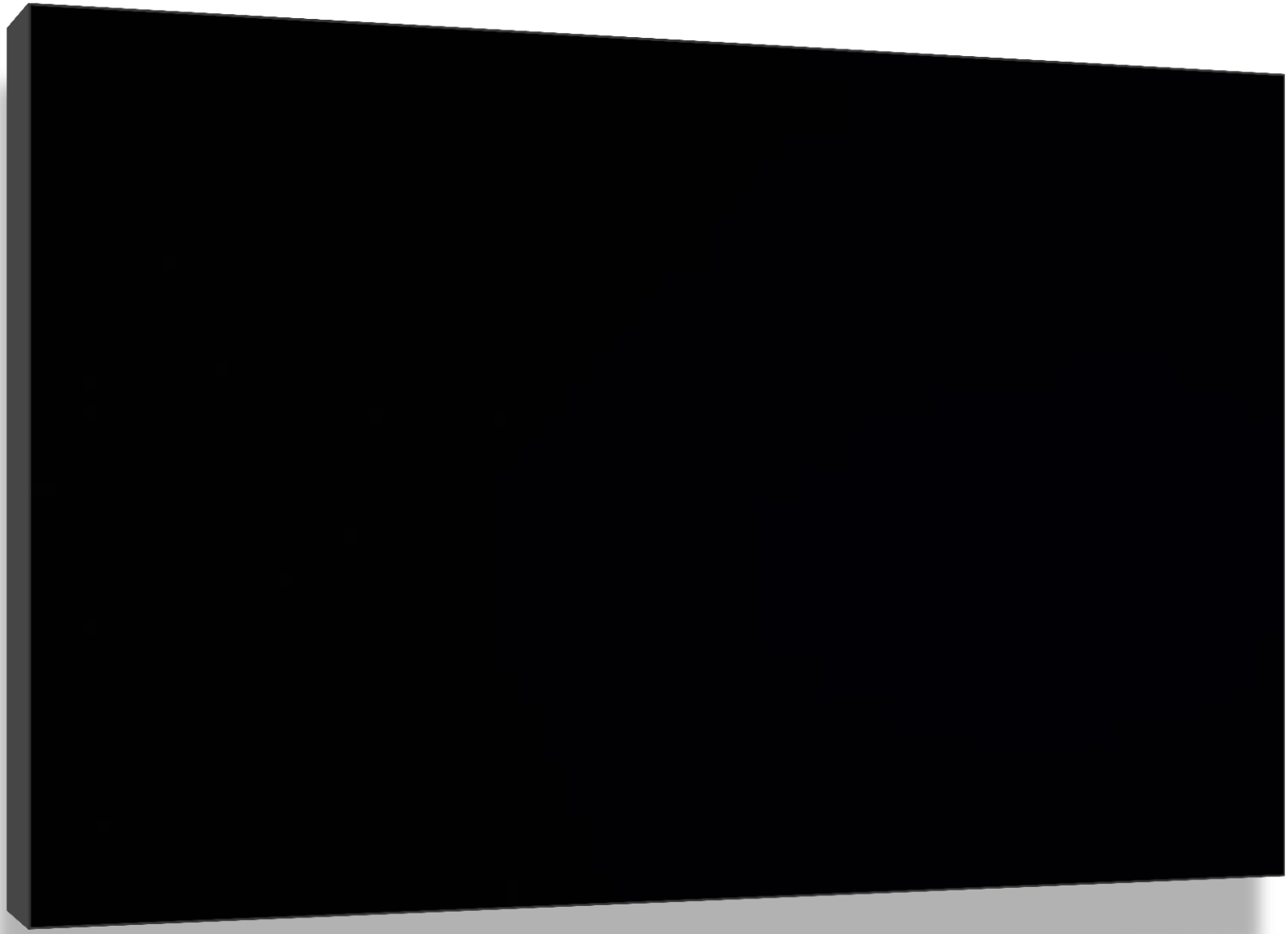
Intrinsic factors	Extrinsic factors
Gastric acid	Diet, Pre and probiotics
O_2	PPIs, H2 blockers
Motility	Antibiotics
Mucus	Prokinetics
GI secretions	Laxatives
Antimicrobial peptides	Opioids
Immunity (sIgA)	NSAIDs



Afrika köyünde yaşayan çocukla İtalya'da şehirde yaşayan arasındaki fark




Production of antimicrobial against pathogen
Pathogen
Probiotic
TLR
Binding of MAMPs on probiotics to host PRRs
Innate immunity:
· Production of mucin
· Tightening of tight junctions
· Defensin production
· Engagement with dendritic cells
M cell
Lumen
TJ
Enterocytes
Dendritic cells
Mucins
Goblet cell
Lumen
T reg
Th1
Th2
Th17
Peyer's patch
Defensins
Paneth cell
Acquired immune system (action beyond the gut)
MLN



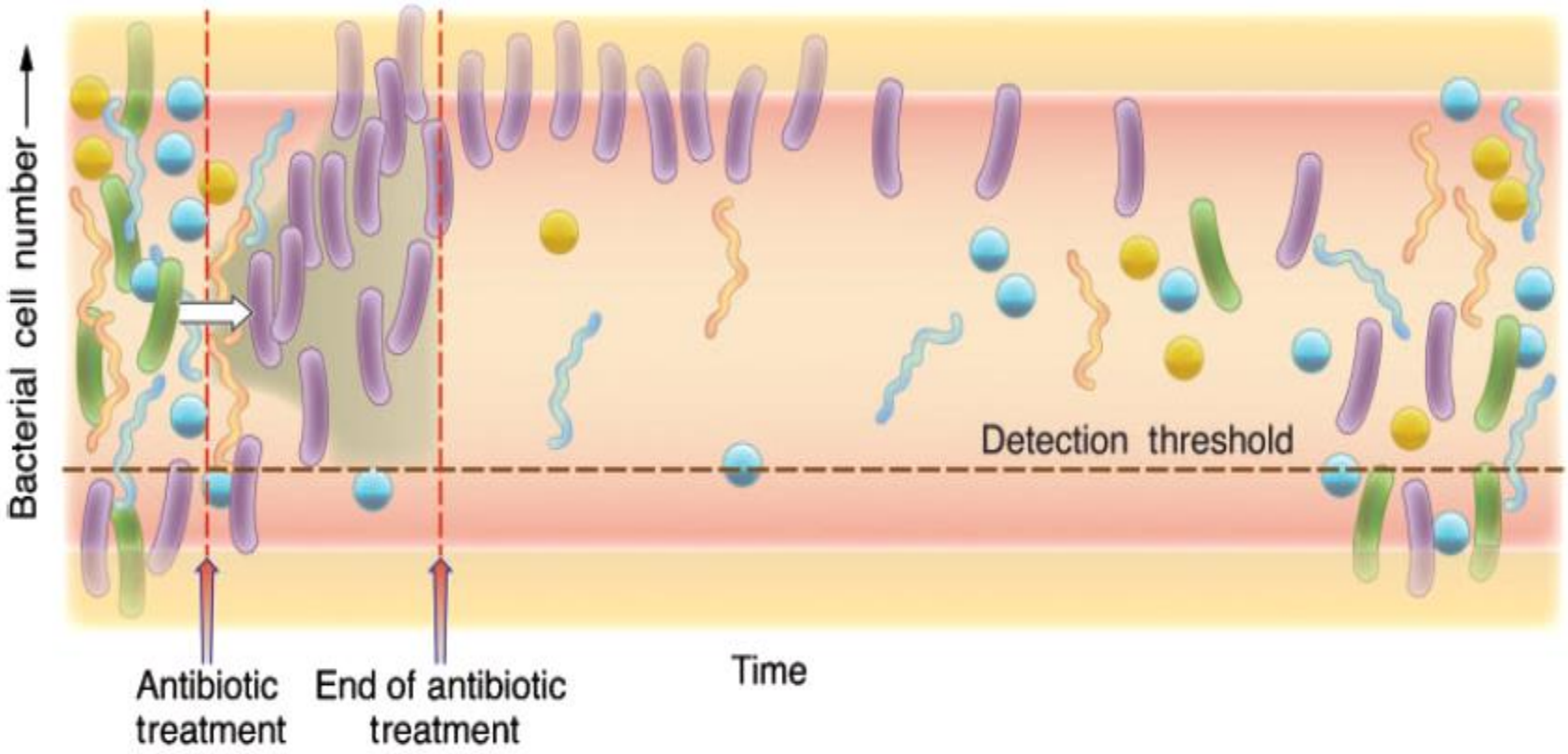
Mikrobiyal Flora Bozukluğu (Disbiyozis) eşlik eden hastalıklar

TABLE 1. Diseases and Disorders Associated with Human Gut Microbiome Aberrations (Adapted from[26])

Disease	Reference
Atopy and asthma	27
Celiac disease	28
Colon cancer	29
Type I diabetes	30
Type II diabetes	31
HIV infection	32
Inflammatory bowel disease	33–35
Irritable bowel syndrome	36–37
Gastroenteritis	38,39
Necrotizing enterocolitis	40
Obesity	41
Rheumatoid arthritis	42

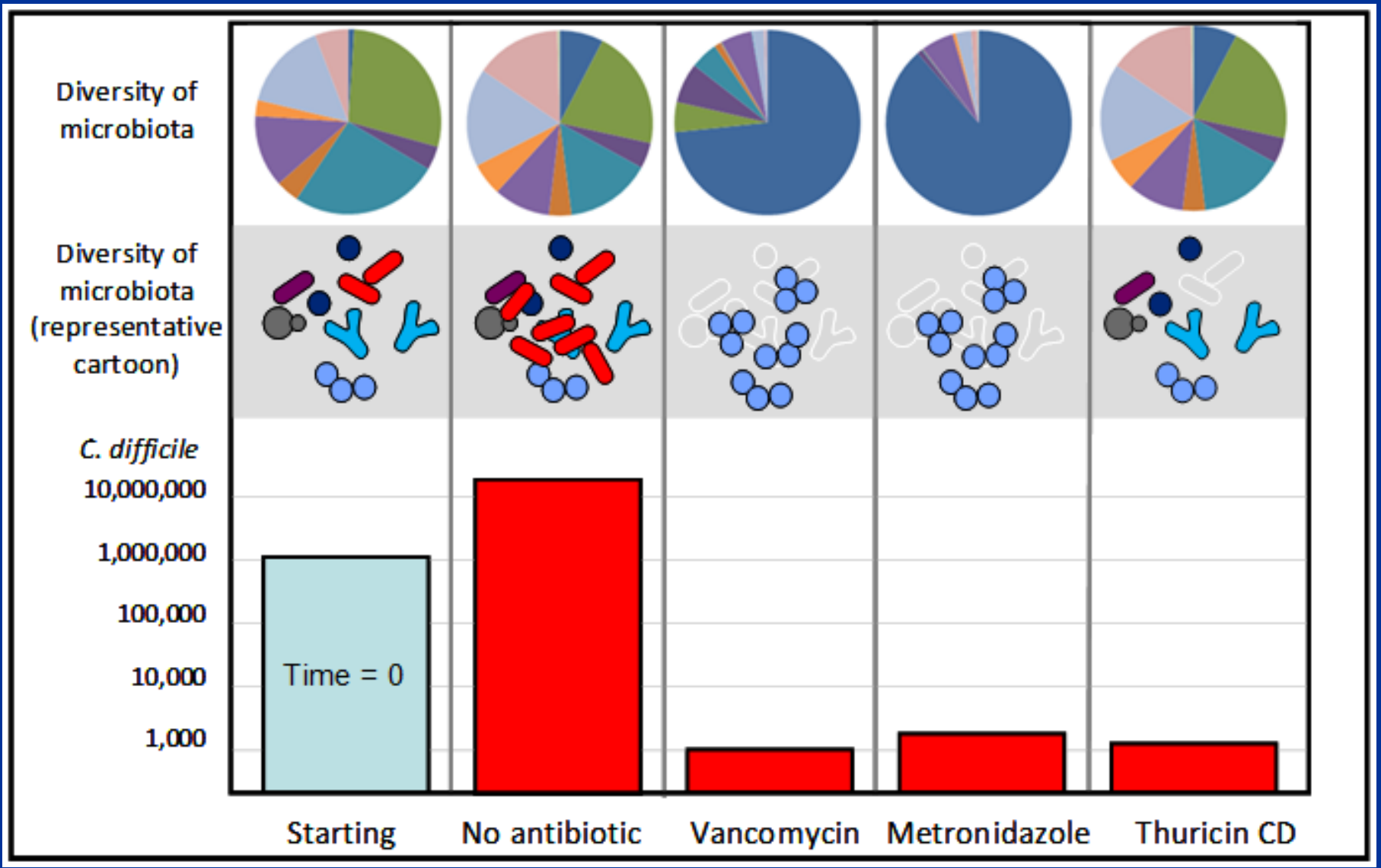
J Clin Gastroenterol • Volume 45, Supp. 3, November/December 2011

Antibiyotik kullanımının mikroflora üzerine etkisi



Microbiology (2010), **156**, 3216–3223

Antibiyotikler ve mikrobiyota



Antibiyotiklerin barsak florasına etkisi

Table 1. Impact of selected groups of antibiotics on the normal intestinal microbiota assessed by cultivation and MIC values

↓↓, Strong suppression; ↓, moderate suppression; ↑, increase in number; ↑↓, positive and negative effects seen in different studies. NC, No change detected; +, resistant strains detected. The table is adapted from the paper by Sullivan *et al.* (2001).

Antibiotic	Impact on:			Emergence of resistant strains in:	
	Anaerobes	Aerobic Gram positive cocci	Enterobacteria	Enterococci	Enterobacteria
Amoxicillin/clavulanic acid	NC	↑	↑	NC	NC
Ciprofloxacin (high conc. in faeces)	NC	NC	↓↓	NC	+
Clarithromycin/metronidazole	↓	↑	↓	+	+
Cephalosporins (high conc. in faeces)	NC	↑	↓↓	NC	+
Clindamycin	↓↓	↑	↑	+	+
Vancomycin	↓	↑↓	NC	+	+

Microbiology (2010), **156**, 3216–3223

Probiyotiklerin bozulmuş florayı düzeltmesi

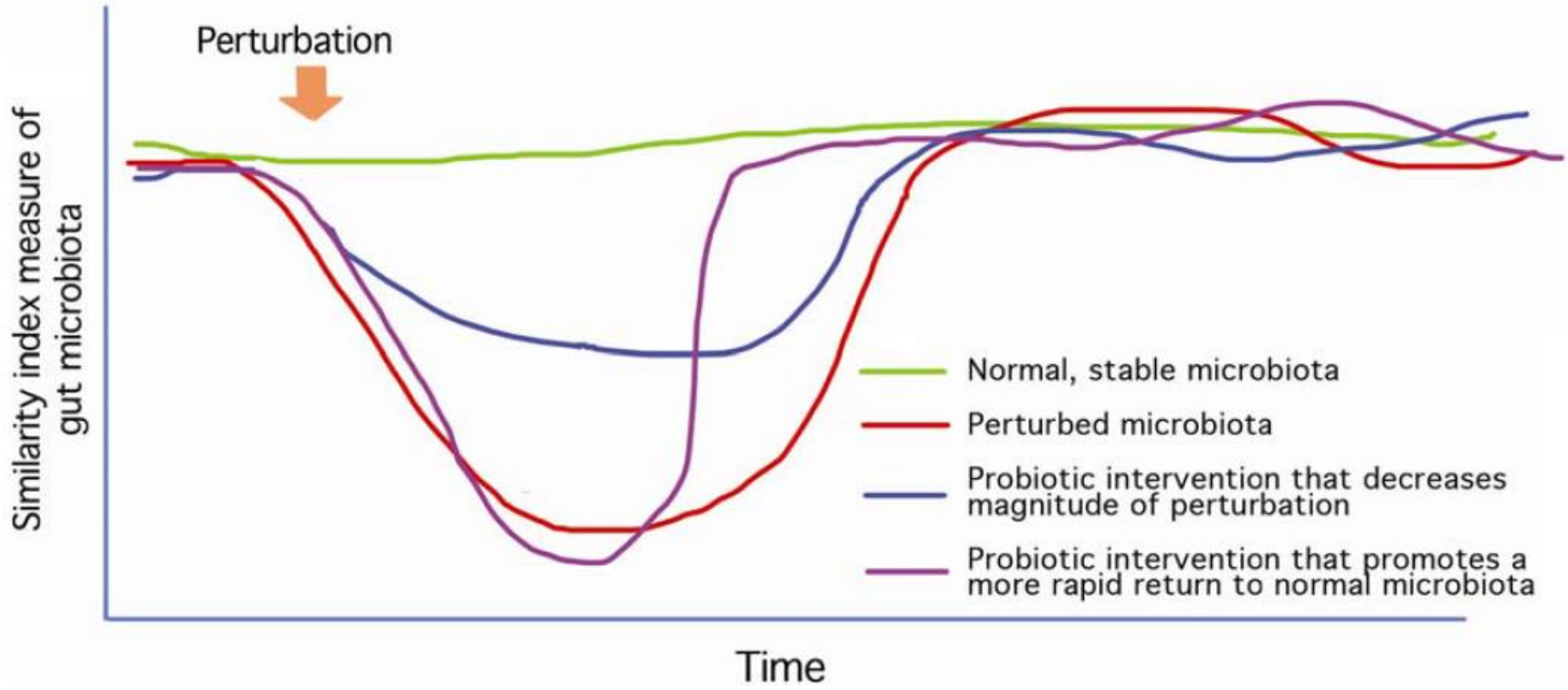


FIGURE 1. Probiotic intervention that decreases the magnitude of change or promotes a more rapid return to normal in a perturbed gut bacterial community. (Sanders et al. In Press). Reprinted with permission from Gut Microbes.

İrritabl Barsak Sendromu

İntestinal ekolojik disbiyozis hipotezi

IBS

Artmış veya azalmış bakteriyel değişkenlik

IBS-D

Lactobacilli azalmış

Streptococ artmış

R. Torques artmış

Clostridium thermosuccinogenes artmış

Sağlıklı kontrol

IBS-C

Lactobacilli ve Veillonella artmış

C.Coccoides ve Eubacterium rectale azalmış

Ruminococcus bromii artmış

IBS-A

Clostridium histolyticum artmış

C.Symbiosum azalmış

Prevotella oralis azalmış

C. Thermosuccinogenes artmış

Veillonella artmış

Microbiology (2010), 156, 3205–3215

Neurogastroenterology & Motility

Neurogastroenterol Motil (2012) **24**, 31–39 doi: 10.1111/j.1365-2982.2011.01803.x

Distinct microbial populations exist in the sub-groups

, * M. C. LOMER, *,† J. BROSTOFF, *

College London, London, UK
Trust, London, UK

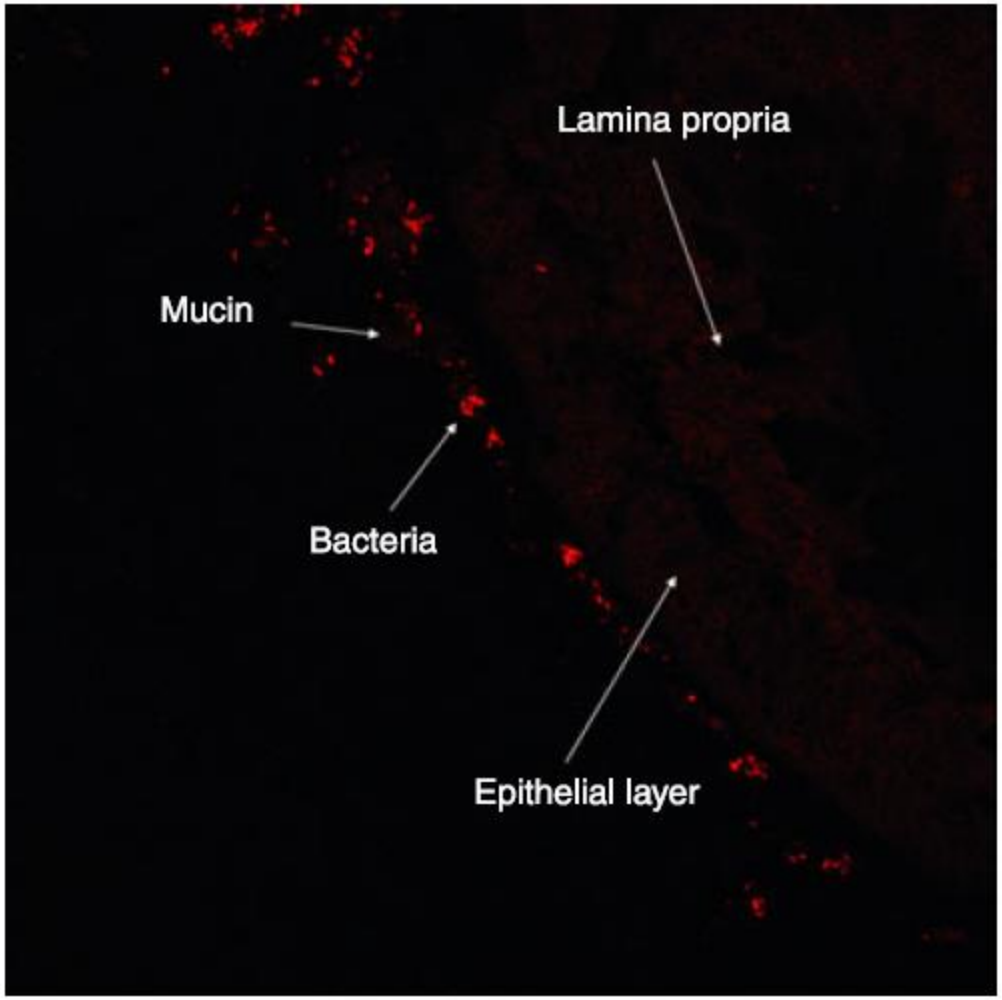
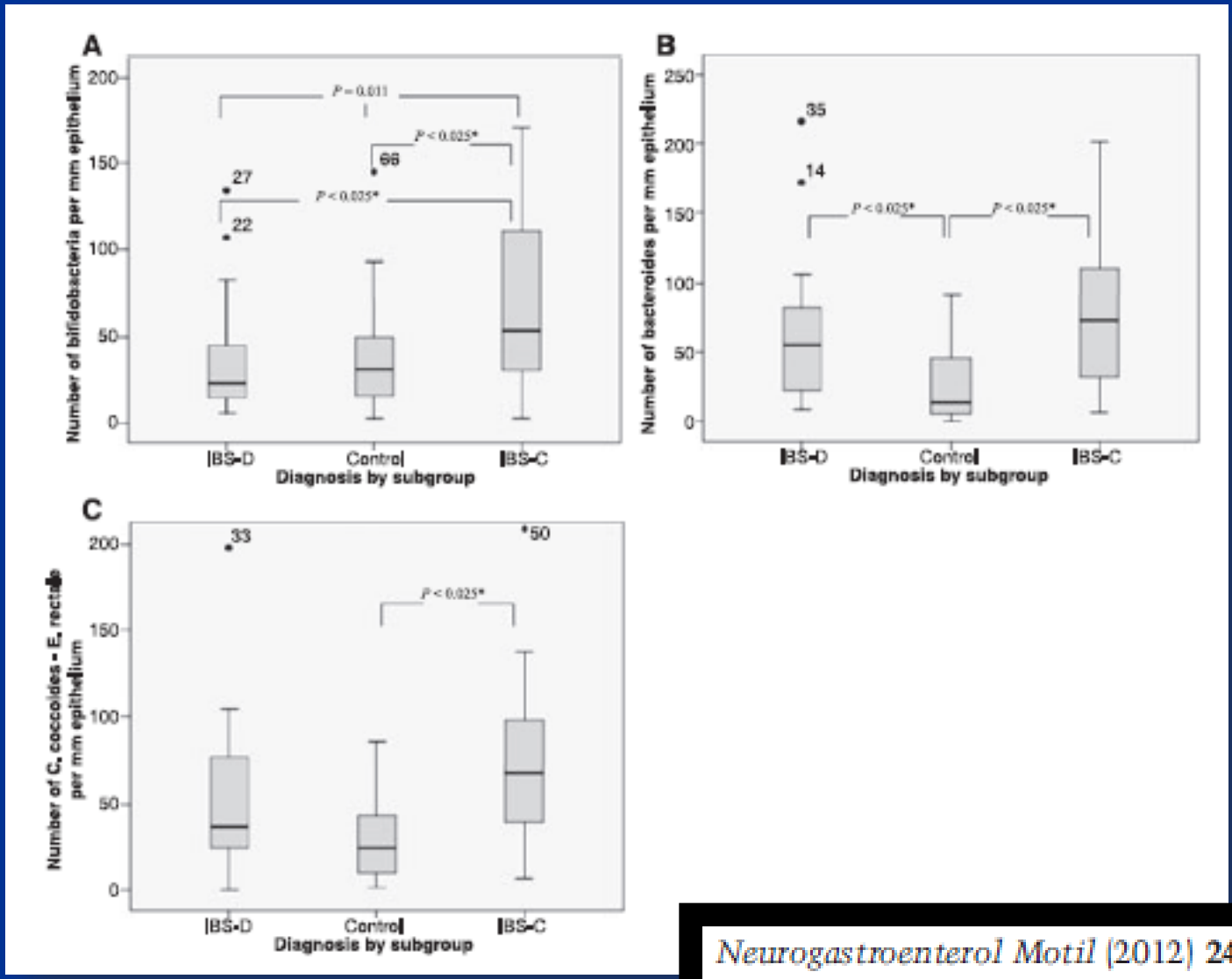


Figure 1 Fluorescent *in situ* hybridization with the eubacteria probe showing the spatial organization of the mucosa-associated microbiota.

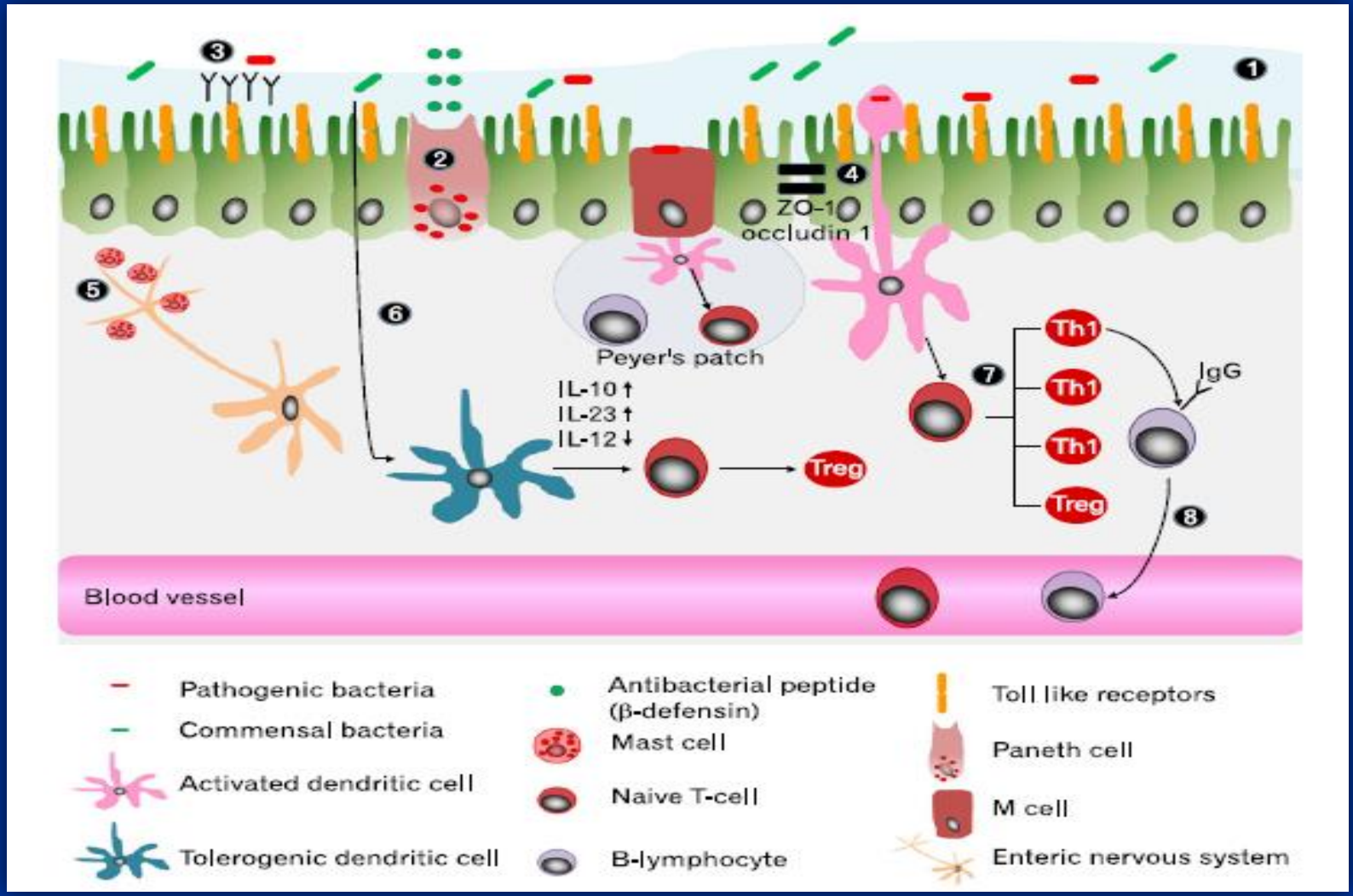
Neurogastroenterol Motil (2012) **24**, 31–39

İBS sub-gruplarında mikrobiyal dağılım



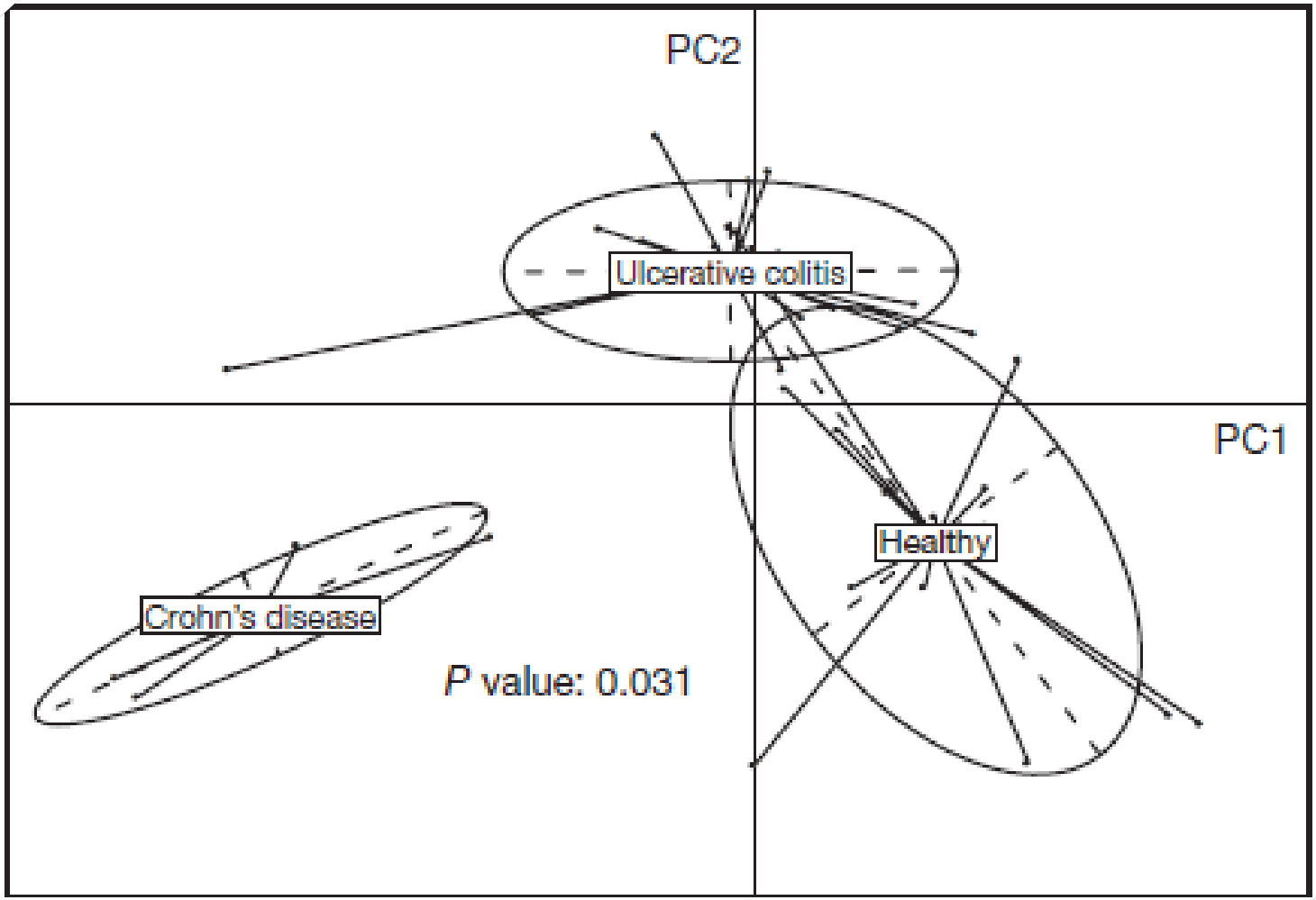
Neurogastroenterol Motil (2012) **24**, 31–39

IBS mukozal bariyer ve inflamasyon



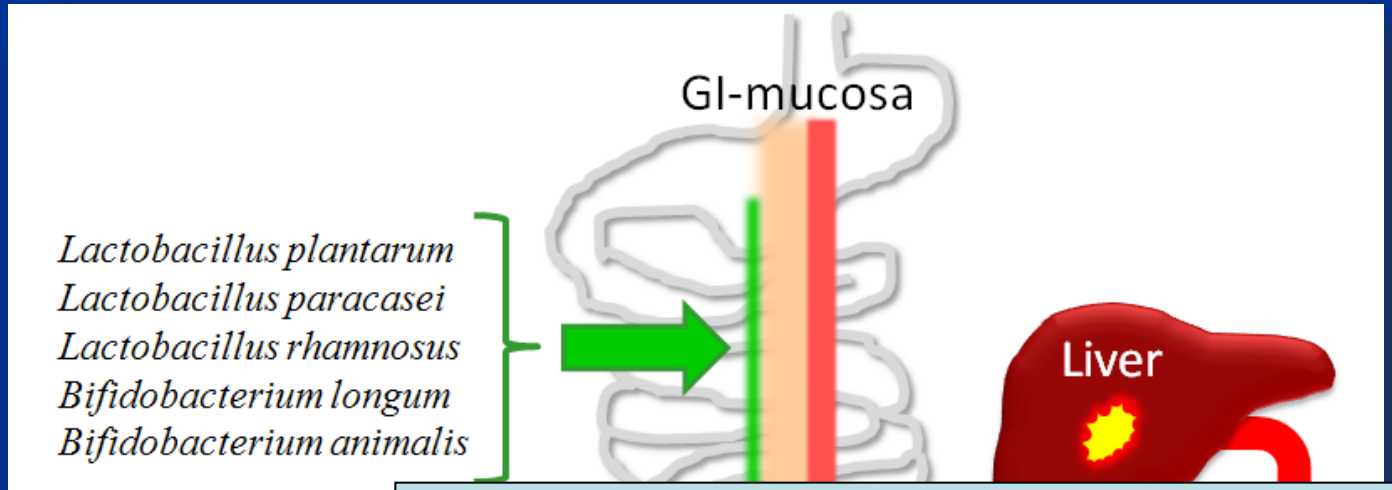
İnflamatuvar Barsak Hastalığı

MetaHIT projesinde İBH hastalarının mikrobiyomları farklılık gösteriyor



Vol 464|4 March 2010|doi:10.1038/nature08821

KARACİĞER HASTALIKLARI VE MİKROBİYOTA



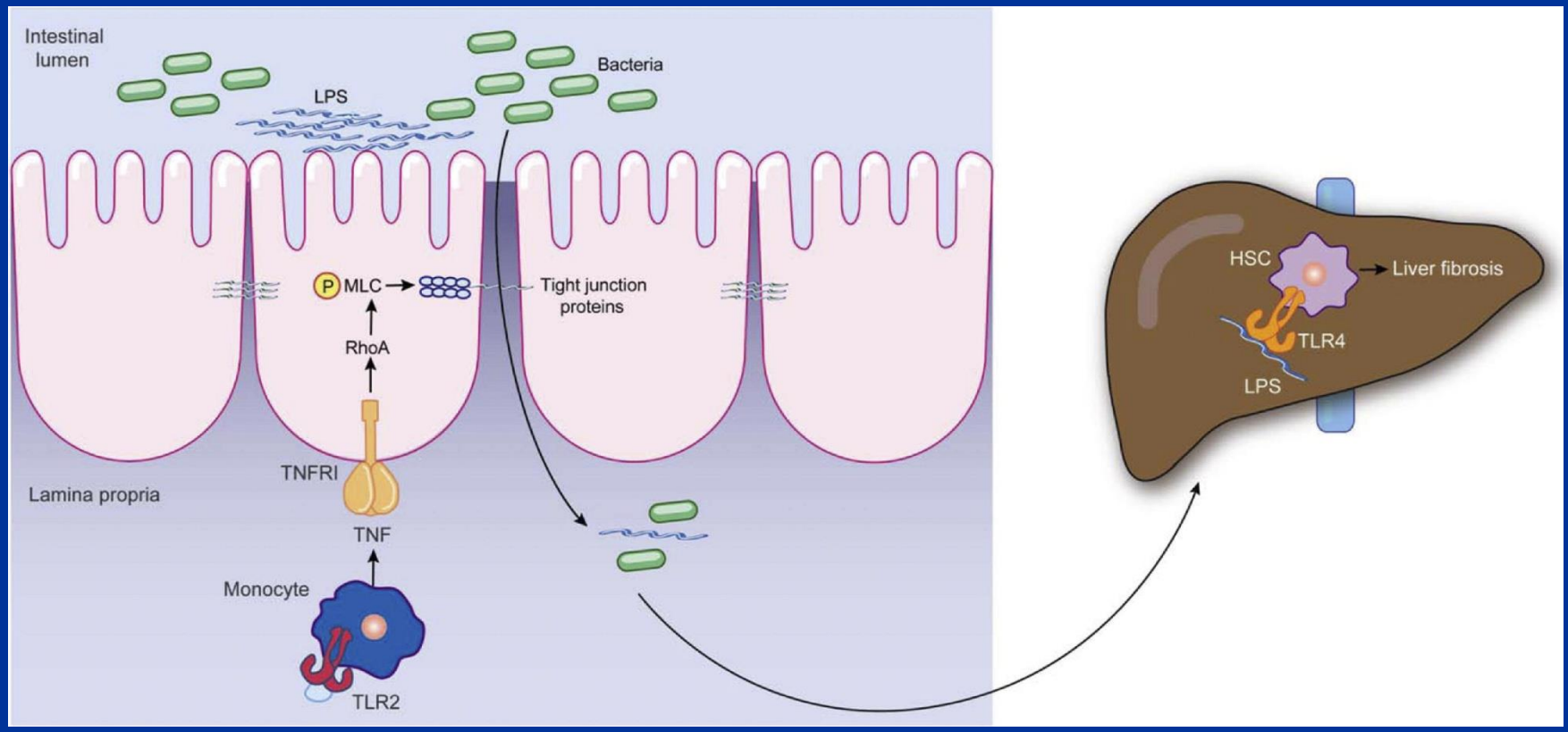
Lactobacillus plantarum
Lactobacillus paracasei
Lactobacillus rhamnosus
Bifidobacterium longum
Bifidobacterium animalis

Escherichia coli
Klebsiella pneumoniae
Sutterella wadsworthe
Bilophila wadsworthia
Acinetobacter lwoffii
Bacteroides fragilis
Prevotella melaninoge
Fusobacterium varium
Brachyspira aalborgi
Streptococcus anginos
Streptococcus pneumo
Peptostreptococcus an

Hepatolojide Barsak Florası ile ilgili alanlar

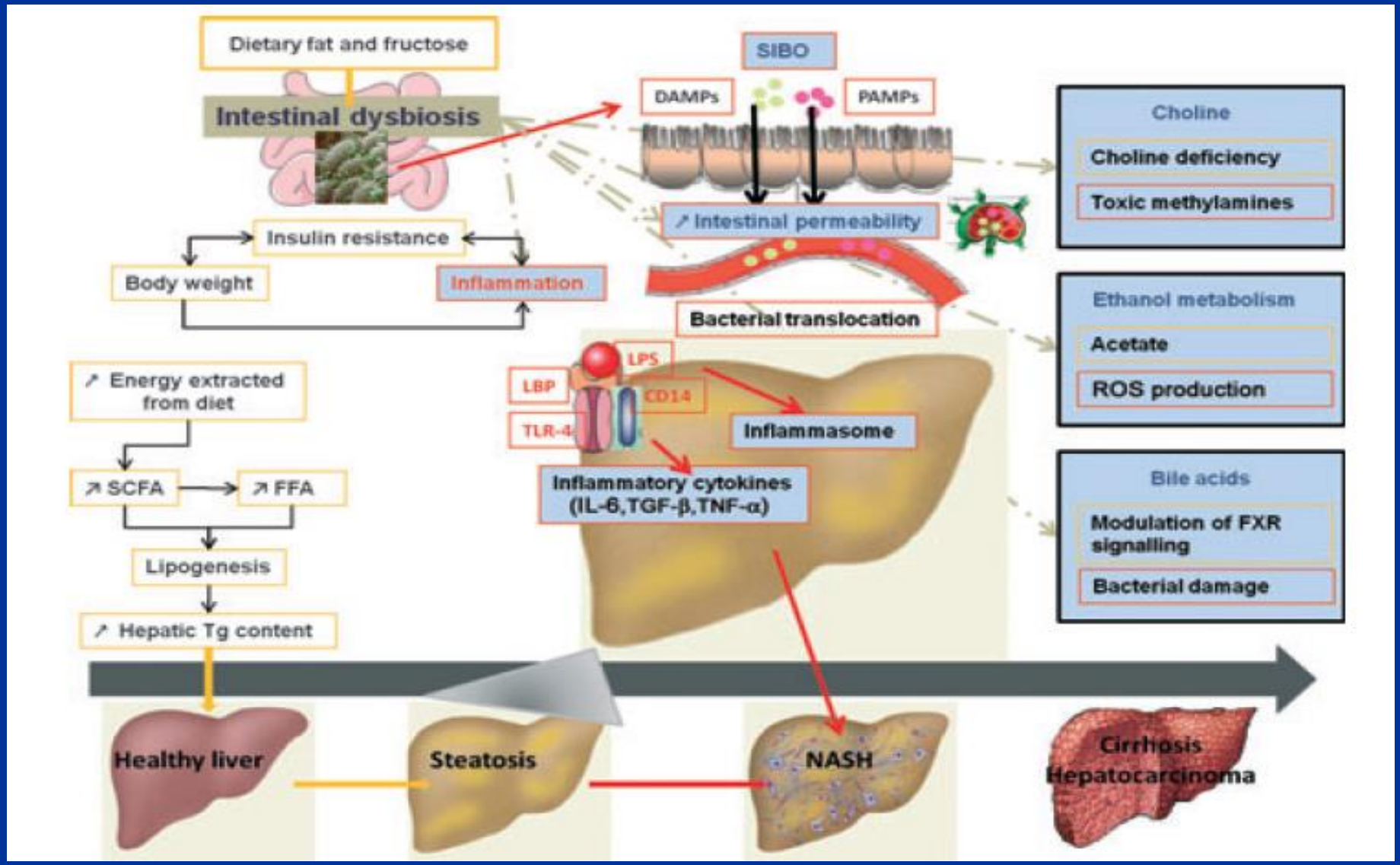
1. Hepatik Ensefalopati
2. NASH
3. Alkolik Hepatit
4. KC transplantasyonu
5. Kronik KC ve Siroz
6. Otoimmün KC hastalıkları ?

TLR4 ve Hepatik Fibrozis

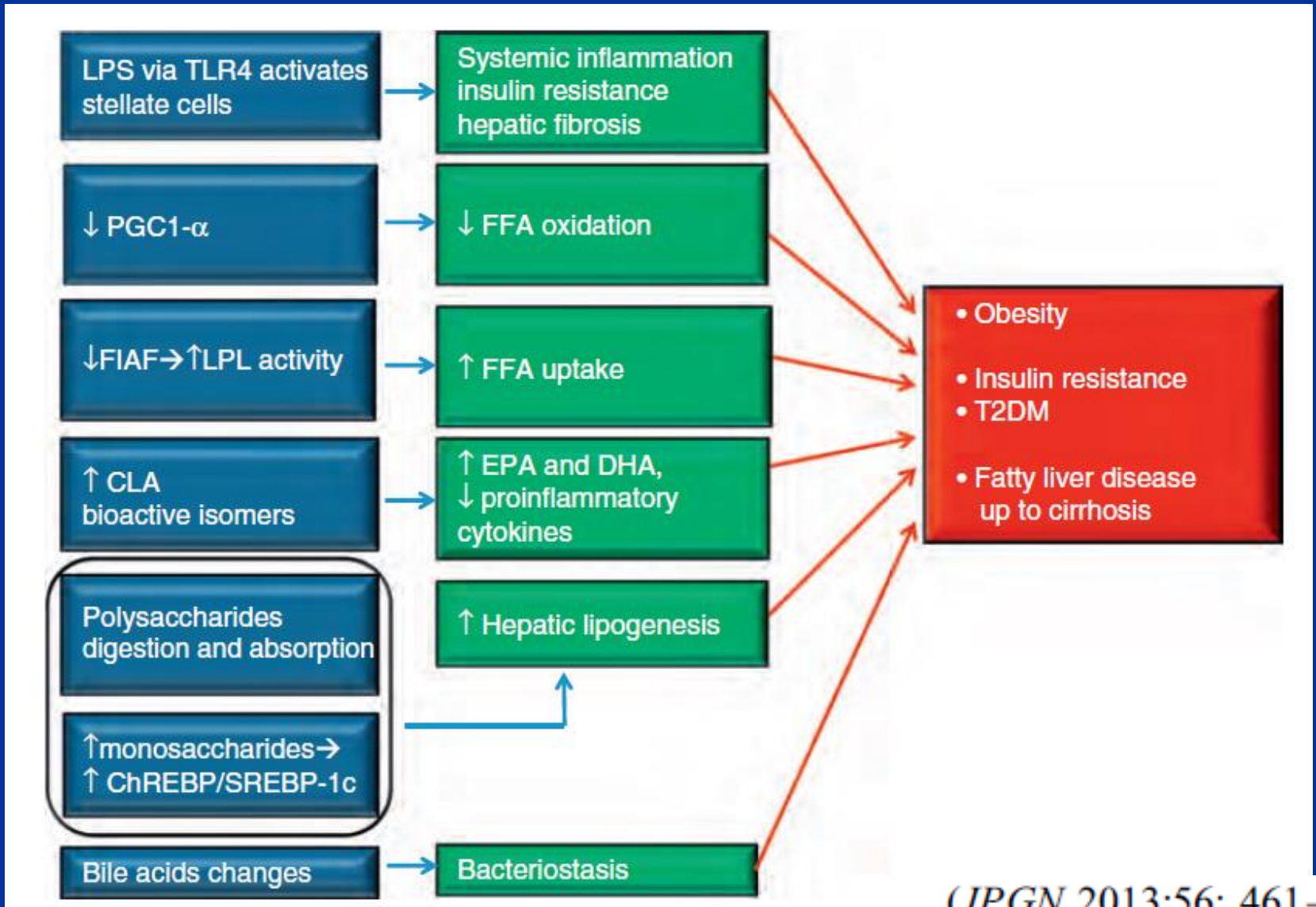


GASTROENTEROLOGY 2012;143:1330–1340

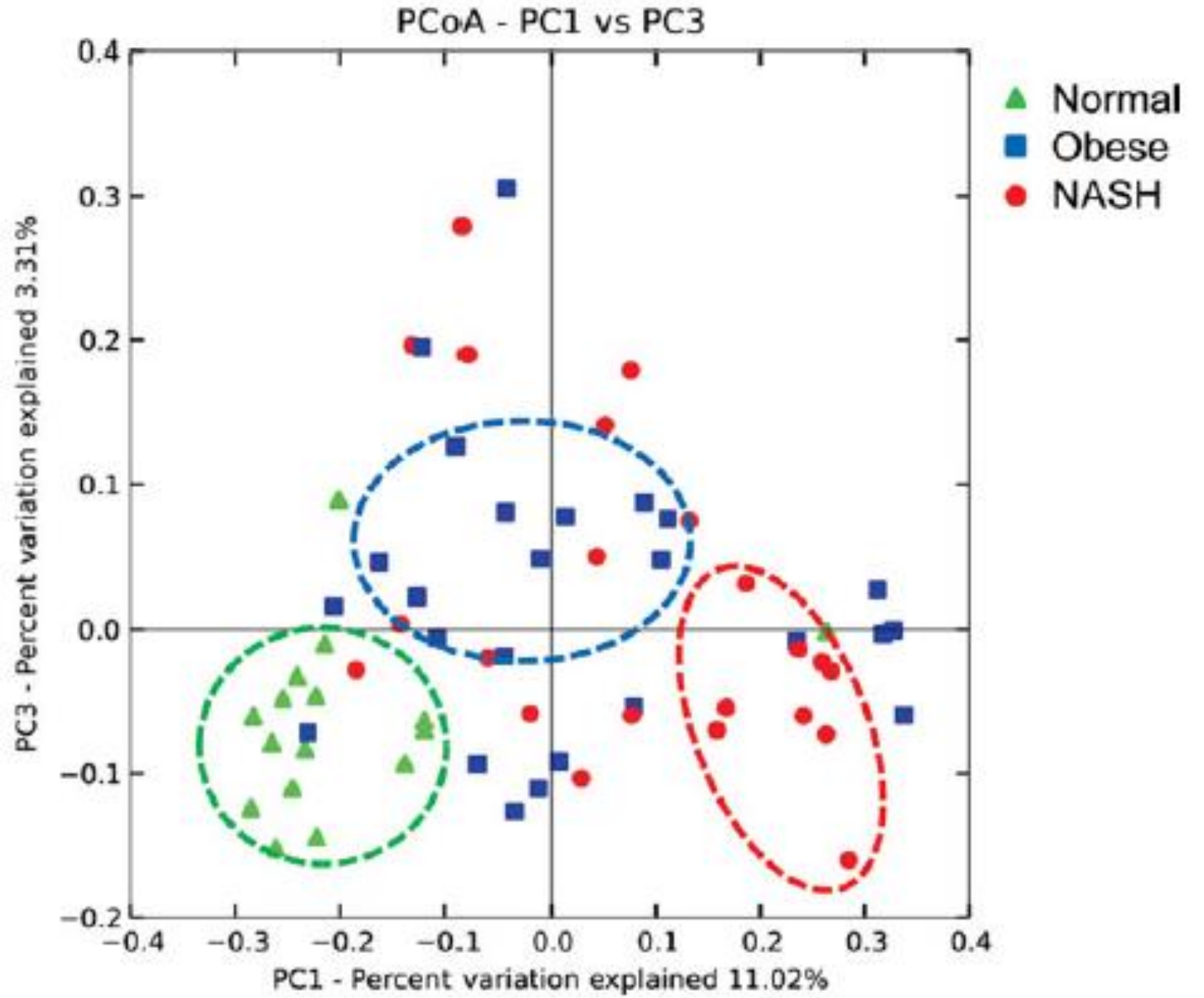
NAFLD ve mikrobiyota



Barsak mikrobiyotasının metabolik hastalıklar üzerine etkileri



(*JPGN* 2013;56: 461–468)


PCoA - PC1 vs PC3
Normal
Obese
NASH
PC3 - Percent variation explained 3.31%
PC1 - Percent variation explained 11.02%
0.4
0.3
0.2
0.1
0.0
−0.1
−0.2
−0.4
−0.3
−0.2
−0.1
0.0
0.1
0.2
0.3
0.4

Non-alkolik ? Mikro-alkolik? Steatohepatitis

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Characterization of Gut Microbiomes in Nonalcoholic Steatohepatitis (NASH) Patients: A Connection Between Endogenous Alcohol and NASH

Lixin Zhu,[1] Susan S. Baker,[1] Chelsea Gill,[2] Wensheng Liu,[1] Razan Alkhouri,[1] Robert D. Baker,[1] and Steven R. Gill[2]

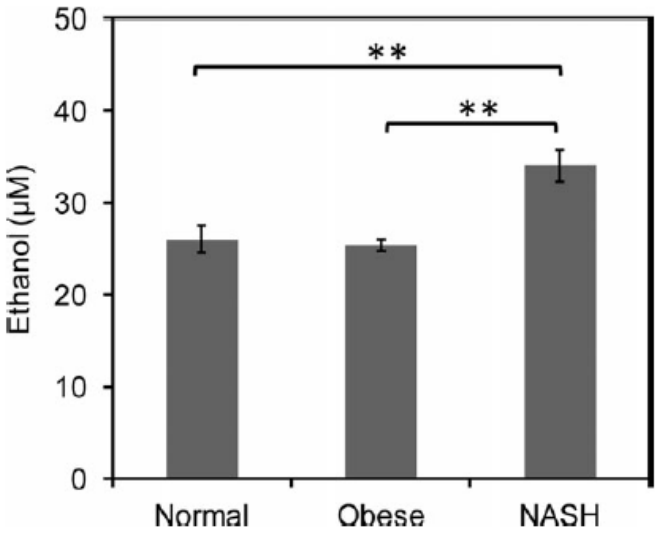


Fig. 4. Elevated serum ethanol concentration in NASH patients. Serum ethanol of healthy subjects (healthy; n = 10), obese patients (n = 7), and NASH patients (n = 13) were measured using an ethanol assay kit from BioVision (Milpitas, CA). Data represent mean ± standard error of the mean. Significant difference was detected among three groups ($P < 0.001$; ANOVA). $^{**}P < 0.01$ in Tukey's honest significance test.

Hepatology. 2013 Feb;57(2):601-9.

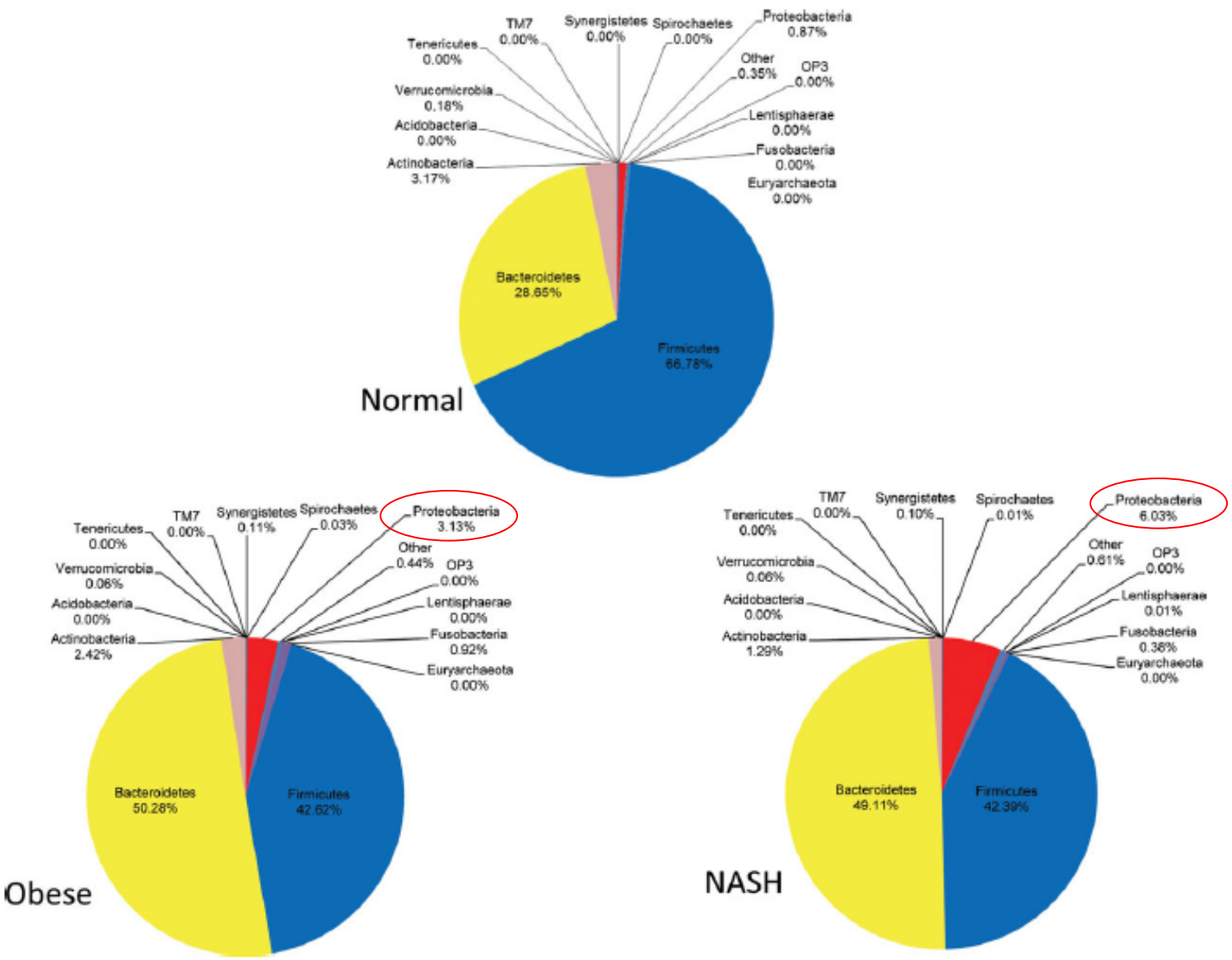


Fig. 2. Average phylum distribution of gut microbiomes of healthy subjects, obese patients, and NASH patients.

Hepatology. 2013 Feb;57(2):601-9.

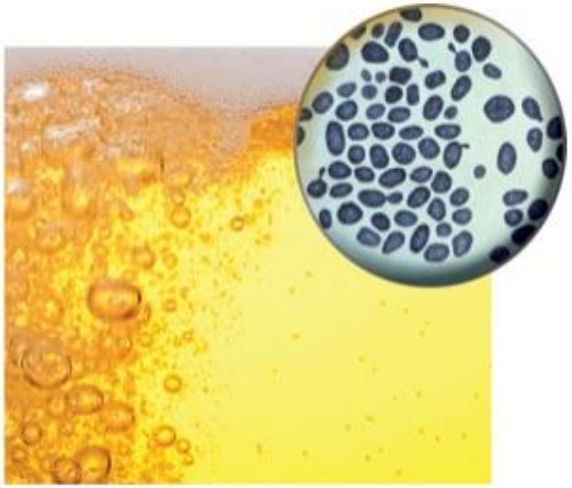
Gastroenterology & Endoscopy News
THE INDEPENDENT MONTHLY NEWSPAPER FOR GASTROENTEROLOGISTS
Last Update: May 27, 2014

From the Literature

ISSUE: MAY 2014 | VOLUME: 65:5

The Case of the Drunken Teetotaler

by Christina Frangou



Did you hear the one about the Texas man who became drunk without touching a drop of alcohol?

That's no joke. It's a case study published last year that should be required reading for every gastroenterologist, say authors and experts in gastroenterology.

In a paper published in the *International Journal of Clinical Medicine* (2013;4:309-312), authors Barbara Cordell, RN, PhD, dean of nursing at Panola College in Carthage, Texas, and Justin McCarthy, MD, a gastroenterologist in Lubbock, Texas, detail how a man spent five years becoming inexplicably drunk before doctors realized the cause was an overgrowth of *Saccharomyces cerevisiae*, also known as brewer's yeast.

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- Spotting Spin and Bias in Clinical Trials
- G&E Digest: April 7, 2014
- Physicians, Patients Becoming More Aware of Effects of Diet in IBS
- Blood Test for Pancreatic Cancer
- Trials, Data Needed To Guide Biosimilar Adoption

International Journal of Clinical Medicine, 2013, 4, 309-312
http://dx.doi.org/10.4236/ijcm.2013.47054 Published Online July 2013 (http://www.scirp.org/journal/ijcm)

Scientific Research

A Case Study of Gut Fermentation Syndrome (Auto-Brewery) with *Saccharomyces cerevisiae* as the Causative Organism

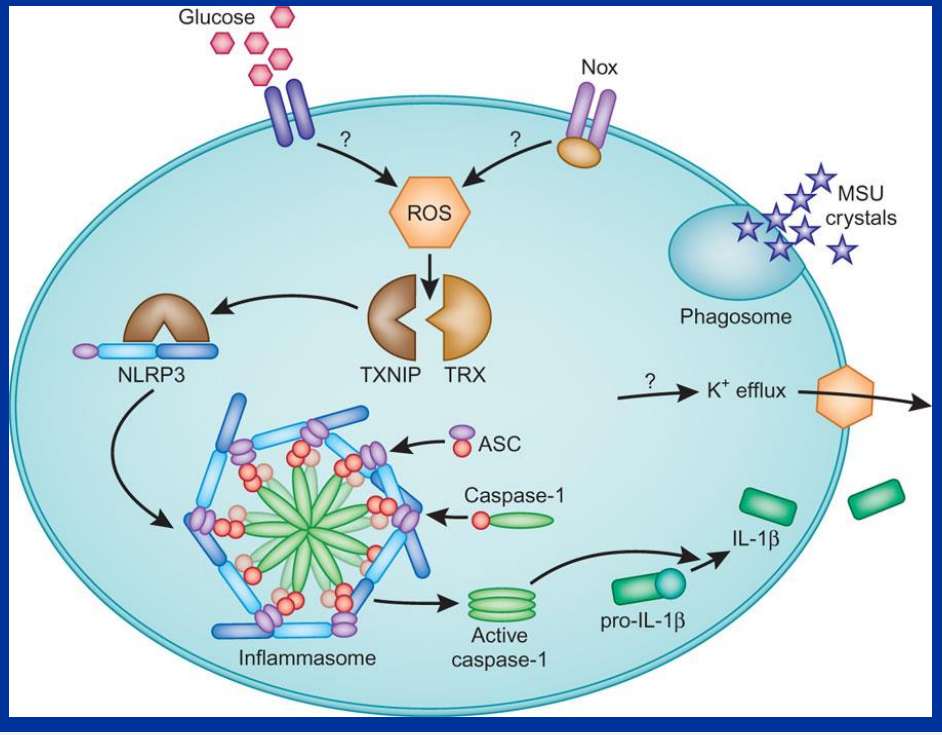
Barbara Cordell, Justin McCarthy

Panola College, Carthage, TX, USA.
Email: bcordell@panola.edu

Received April 25th, 2013; revised May 30th, 2013; accepted June 12th, 2013

İnflammazom aracılı disbiyozis NAFLD ve Obezite

- İnflammazomlar sitoplazmik multi-protein kompleks yapılardır. Görevleri endojen ve egzojen patojenleri tanımak ve inflamatuvar yanıtı kontrol etmektir.
- Disbiyozis inflammazom eksikliğine neden olur.
- TLR4 ve TLR9 agonistlerinin portal dolaşıma geçmesi ile steatohepatit oluşur.

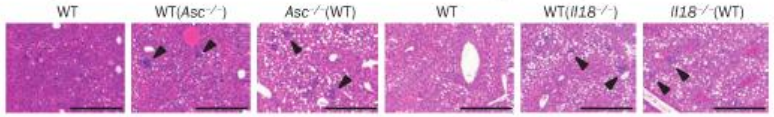


MICROBIOTA

Dysbiosis driven by inflammasome deficiency exacerbates hepatic steatosis and governs rate of NAFLD progression

The findings of a study by Richard Flavell and colleagues provide evidence of a link between inflammasomes, the gut microbiota and NAFLD (the hepatic manifestation of metabolic syndrome).

Inflammasomes—proinflammatory multiprotein complexes consisting of



NASH severity is increased in mice deficient in Asc (ASC is an inflammasome adaptor protein) or *IL18* and can be transmitted to co-housed wild-type mice. Hematoxylin and eosin-stained liver sections from wild-type mice (WT), wild-type mice co-housed with *Asc*−/− mice (WT(Asc−/−)) or with *Il18*−/− mice (WT(*Il18*−/−)), and *Asc*−/− mice or *Il18*−/− mice co-housed with WT mice (*Asc*−/−(WT) and *Il18*−/−(WT)). Arrowheads indicate inflammatory foci. Scale bar = 200 μm. © Henao-Mejia, J. et al. *Nature* doi:10.1038/nature10809

Nature.2012 ; 482(7384): 179–185.

Journal of Gastroenterology and Hepatology

JGHF

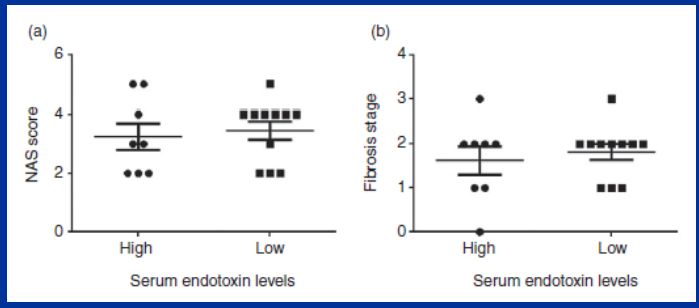
doi:10.1111/jgh.12510

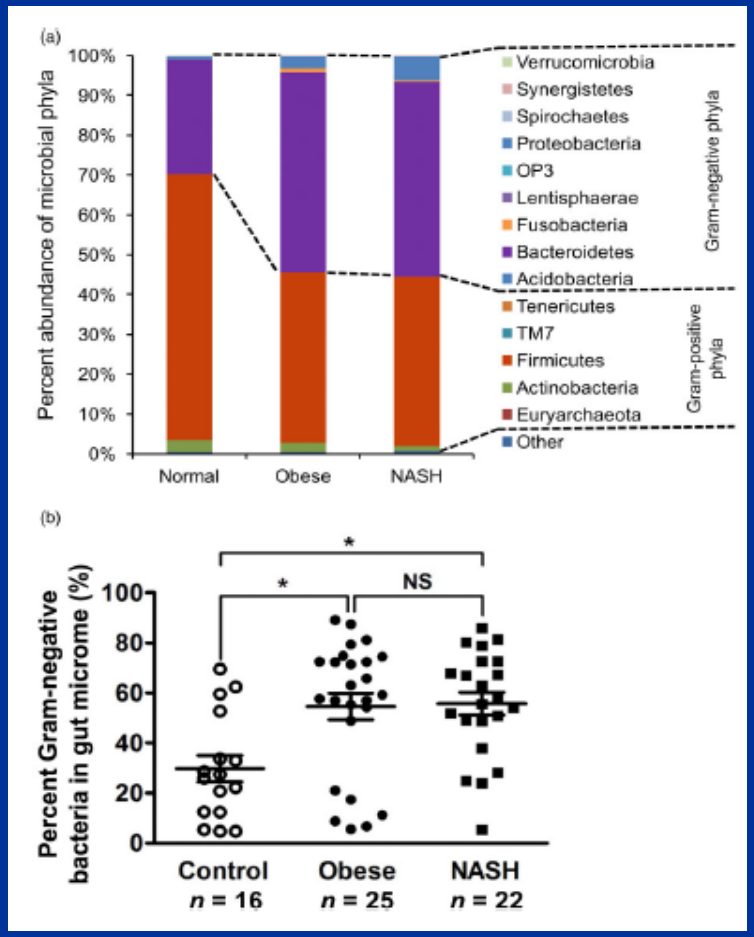
HEPATOLOGY

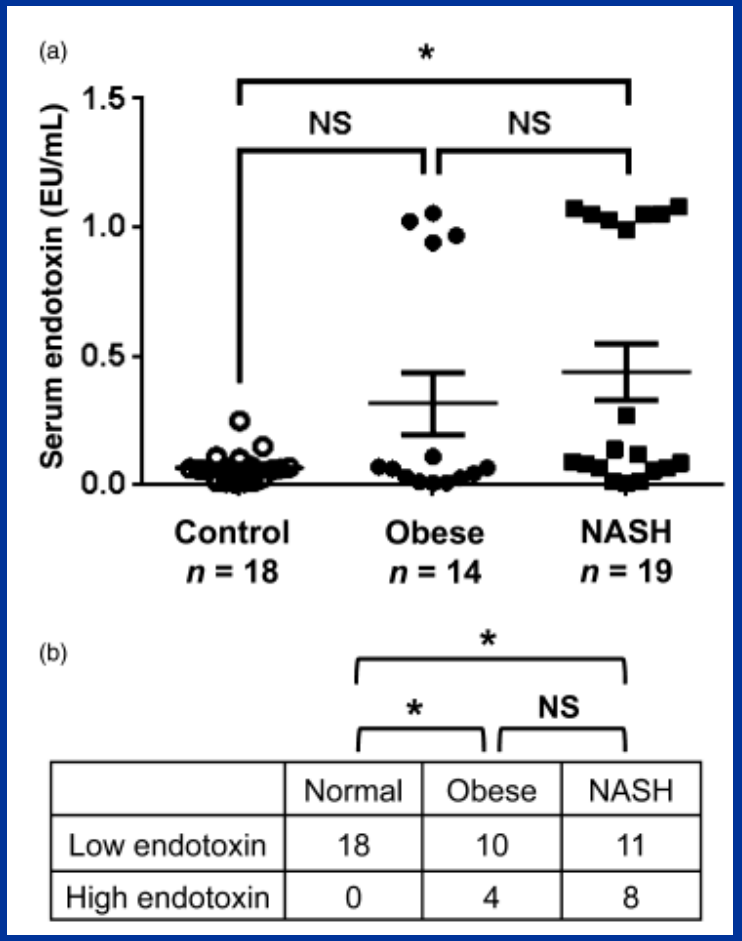
Endotoxemia unrequired in the pathogenesis of pediatric nonalcoholic steatohepatitis

Jianye Yuan,*,† Susan S Baker,* Wensheng Liu,* Razan Alkhouri,* Robert D Baker,* Jianqun Xie,† Guang Ji† and Lixin Zhu*

*Digestive Diseases and Nutrition Center, Department of Pediatrics, The State University of New York at Buffalo, Buffalo, New York, USA; and †Institute of Digestive Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

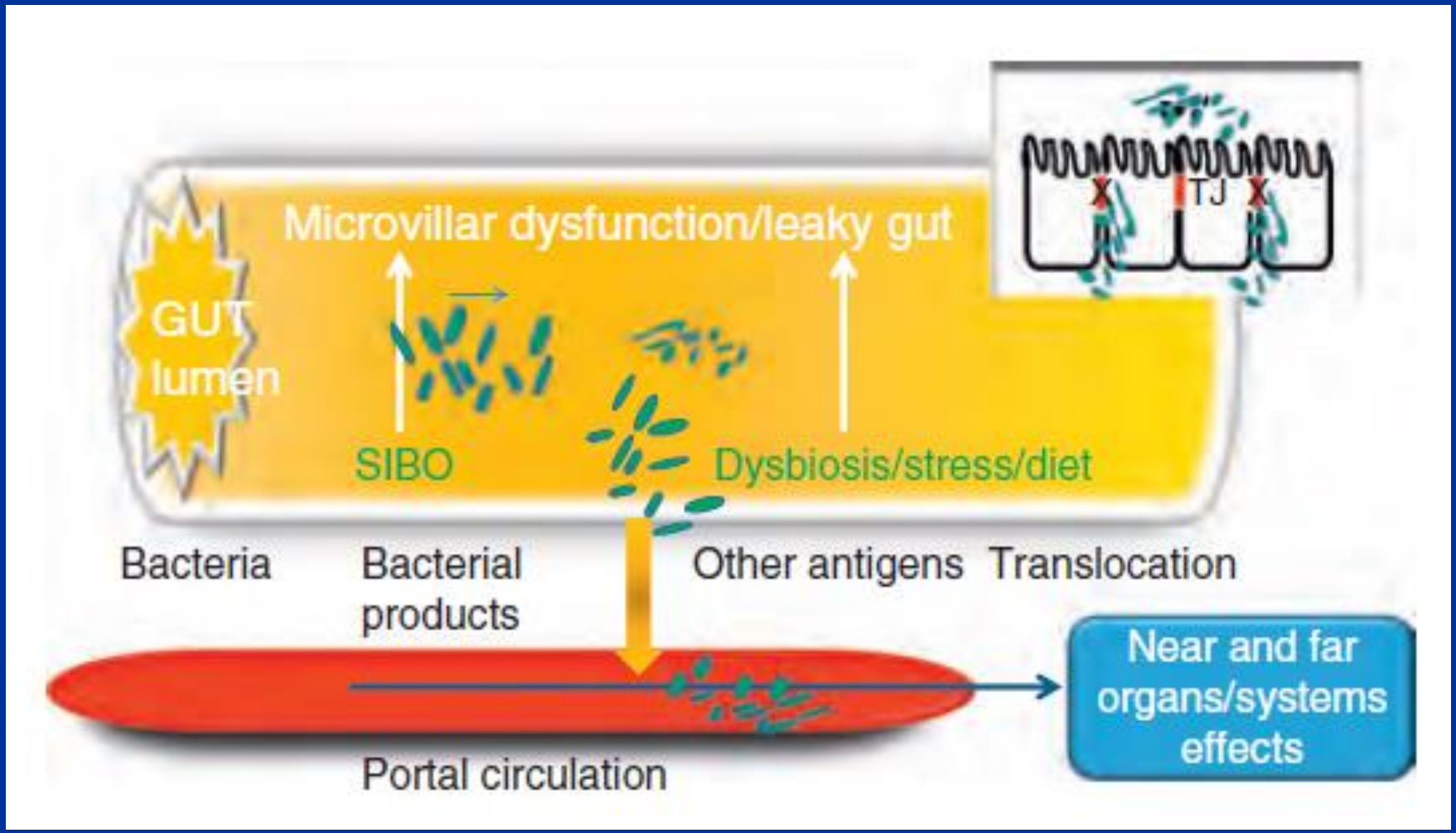






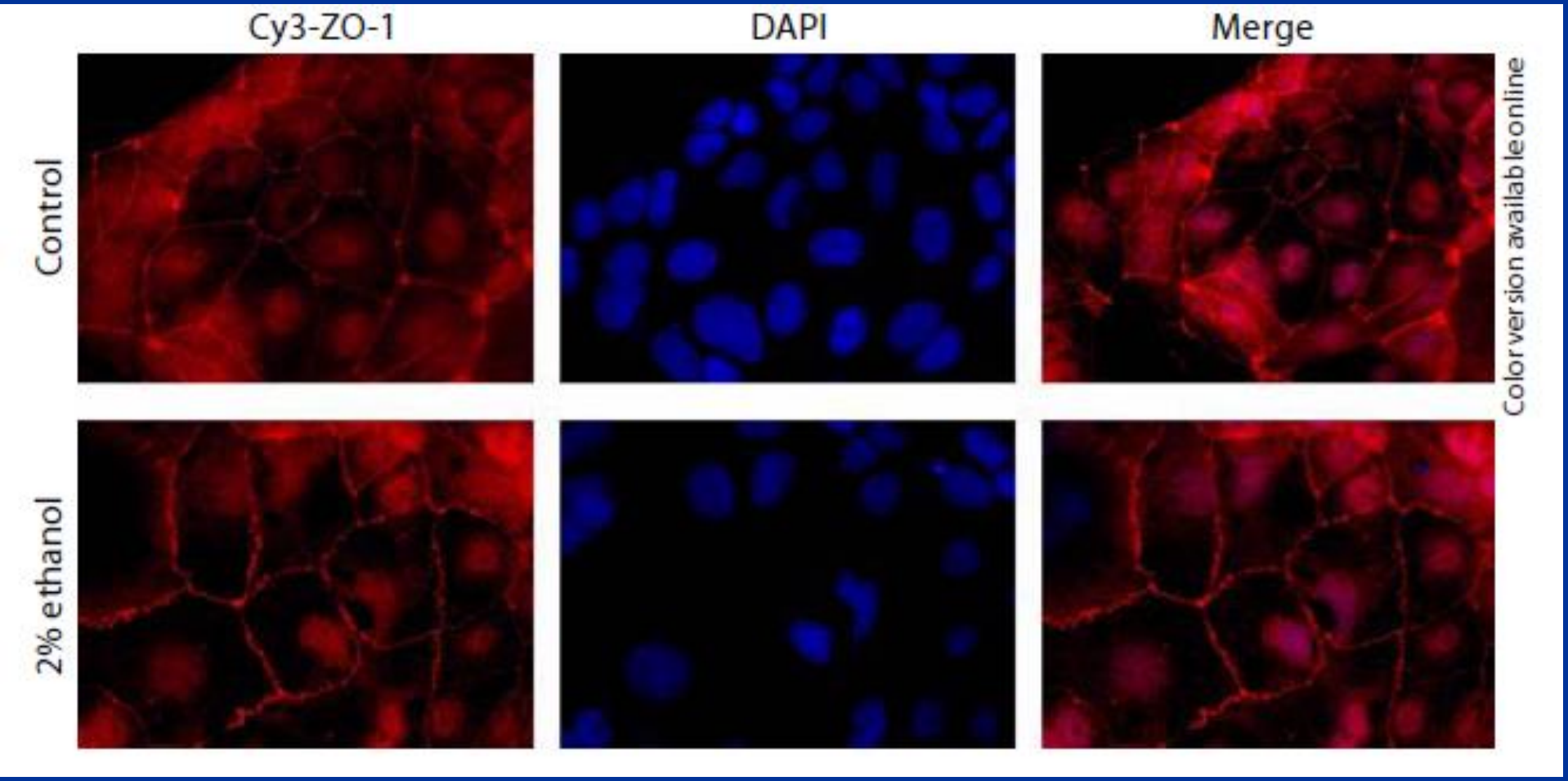
	Normal	Obese	NASH
Low endotoxin	18	10	11
High endotoxin	0	4	8

İntestinal permeabilite ve inflamasyon



(*JPGN* 2013;56: 461–468)

NASH'de barsaktaki sıkı bağlantı proteinlerini azalır (ZO-1)



Dig Dis 2010;28:737–744

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World J Gastroenterol 2012 June 7; 18(21): 2609-2618
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Leaky gut and the liver: A role for bacterial translocation in nonalcoholic steatohepatitis

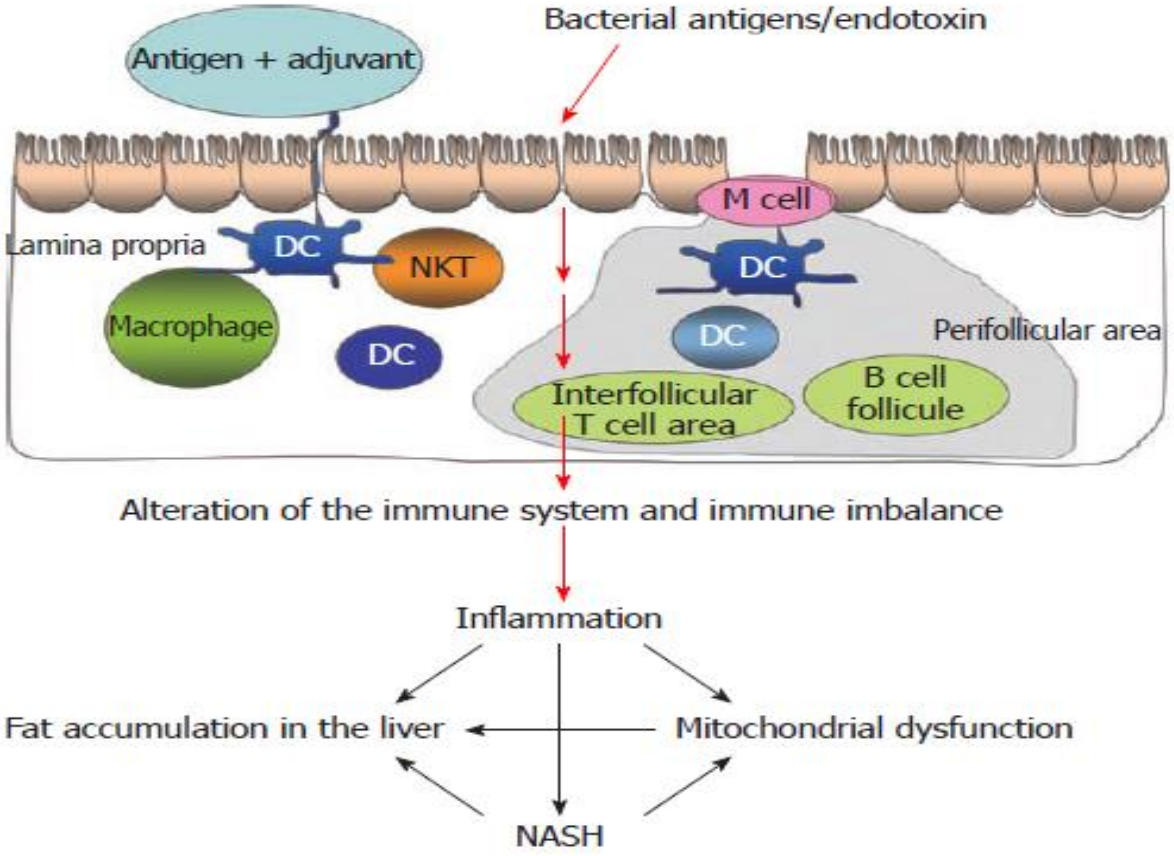
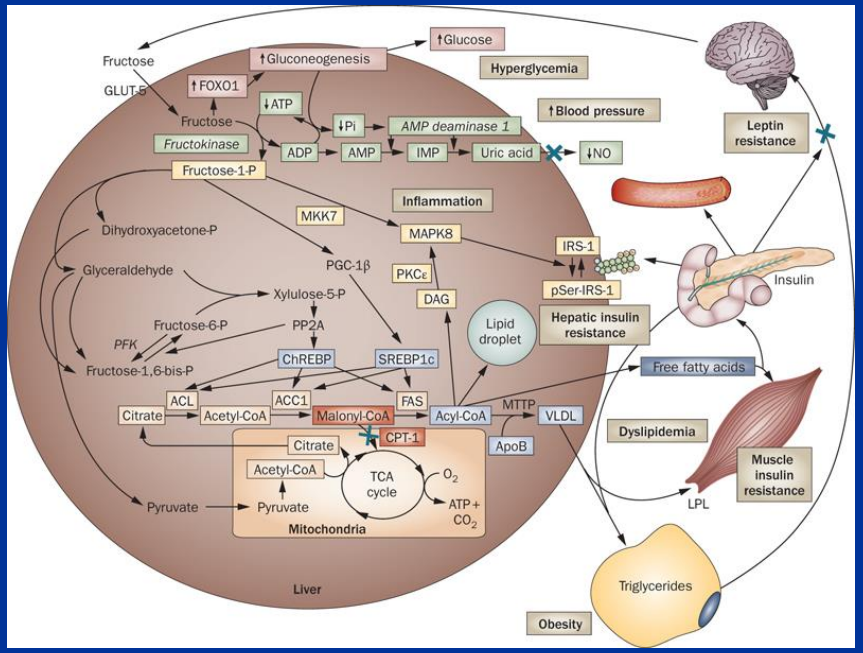


Figure 1 Bacterial translocation is associated with the development of nonalcoholic steatohepatitis. NASH: Nonalcoholic steatohepatitis.

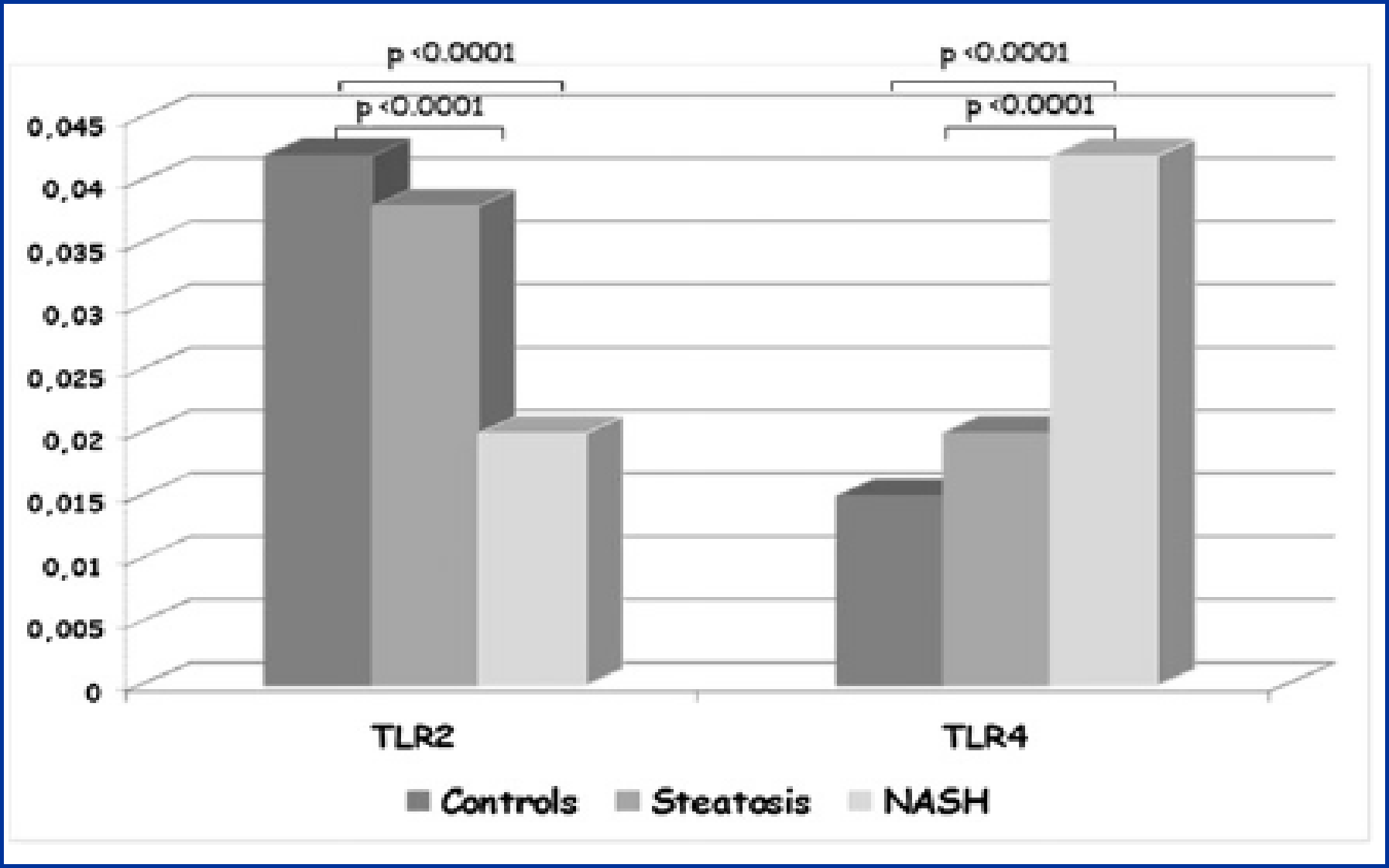
Fruktoz-NAFLD-Mikrobiyota

- Fruktozla indüklenmiş steatozda KC'de
  - TLR 1-4, 6-8 indüklenmekte,
  - TNF-alfa, iNOS, MyD88 artmaktadır.
- Bu etkiler antibiyotik almakta olan farelerde azalmaktadır.
- Duodenumda barsak geçirgenliği artmaktadır.
- Fruktoz barsak mikrobiyotasını etkileyerek, patojen bakteri sayısını artırır ve KC içinde steatoz ve inflamasyonu tetikler.



British Journal of Nutrition (2012), 107, 1727–1738

TLR ve NASH



Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 471—476

NASH Probiyotik Hayvan Çalışmaları

Table 1 Animal interventional studies on probiotics and metabolic liver diseases.

Author	Year	Animal model	Treatment	Results
Li Z [44]	2003	*Ob/Ob* mice	VSL#3	↓ Total hepatic fat ↓ ALT ↓ TNFα RNA
Ewaschuk J [45]	2007	129Sv/Ev WT + LPS 129Sv/Ev IL-10- + LPS		↓ Liver damage ↓ Intestinal damage
Ma X [46]	2008	C57BL6 mice	VSL#3	↓ Liver NK cells ↓ TNFα IL-4
Velayudham A [47]	2009	C57BL6 mice C57BL6 mice + MCD diet	VSL#3	↓ TGFβ receptor ↓ Liver fibrosis
Nardone G [48]	2010	Winstar rats	*Lactobacillus paracasei* F19	↓ TNFα, IL-1β, IL-6 RNA ↓ Serum LPS ↓ Liver inflammation, steatosis and fibrosis

Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 471–476

İnsan Çalışmaları

Table 1 RCT studies with probiotics in adult and pediatric NAFLD.

Authors (reference)	Aller et al. [3]	Vajro et al. [4]
Year of publication	2011	2011
Type of study	Double blind RCT	Double blind RCT
Number of pts/disease	30 NAFLD	20 NAFLD
Mean age (years)	49.4 ± 10.9 treated group 44.3 ± 15.1 placebo group	10.7 ± 2.1
Treatment	*Lactobacillus bulgaricus* and *Streptococcus thermophiles* 500 millions CFU	Lactobacillus GG
Primary end-point	Aminotransferase and GGT variation, cytokines (TNF α, IL6)	ALT and GGT variation, liver echogenicity, TNFα values, H2BT, PG-PS IgA, Hepatorenal-US ratio
Results	Decrease of AST, ALT, GGT in probiotic treated group ALT: 67.7 ± 25.1 to 60.4 ± 30.4 ($p < 0.05$); AST 41.3 ± 15.5 to 35.6 ± 10.4 ($p < 0.05$); GGT: 118.2 ± .63.1 to 107.7 ± 60.8 ($p < 0.05$). Unchanged in placebo group. Cytokines unchanged. Dietary intake unchanged (hypocaloric)	Δ ALT and PG-PS IgA treated vs control $p < 0.03$ for both. ALT normalization 8/10 cases in treated vs 3/7 in placebo. Dietary intake unchanged
Treatment duration (months)	3	2
Anthropometric parameters	Weight, BMI, waist to hip circumference, fat mass: all unchanged	BMI z score, US visceral fat, weight, height, waist: all unchanged

Abbreviations: ALT: alanine aminotransferase U/l; AST: aspartate aminotransferase U/l; BMI: body mass index; GGT gamma glutamil-transpeptidase U/l; H2BT: hydrogen breath test; NAFLD: non alcoholic fatty liver disease; PG-PS: peptidoglycan-polysaccharide; RCT: randomized clinical trial; TNF: tumor necrosis factor; US: ultrasonography.

AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic stea

A. Alisi*[,1], G. Bedogni[†,1], G. Baviera[‡,1], V. Giorgio*, E. Porro[‡], C. Paris[‡], P

	Placebo (n = 22; males = 14)			VSL#3 (n = 22; males = 10)		
	Median	IQR		Median	IQR	
Age (years)	11	10	12	10	9	12
Weight (kg)	53.9	47.8	65.0	60.5	55.7	70.5
Height (cm)	1.47	1.39	1.52	1.49	1.43	1.55
BMI (kg/m^2)	25.6	23.2	27.9	27.3	24.7	28.6
BMI (SDS)	1.69	1.23	2.12	2.01	1.63	2.37
Glucose (mg/dL)	85	78	89	84	79	91
Insulin (μU/mL)	16	12	21	18	14	27
HOMA	3.1	2.3	4.7	3.9	2.7	5.4
Cholesterol (mg/dL)	156	135	179	156	137	175
Triglycerides (mg/dL)	94	64	118	86	63	121
HDL cholesterol (mg/dL)	48	42	54	45	38	53
LDL cholesterol (mg/dL)	92	80	111	83	71	101
ALT (U/L)	32	23	42	27	20	50
AST (U/L)	63	53	74	56	51	70
GLP-1 (pmol/L)	2.1	1.8	2.6	2.9	1.9	2.3
aGLP-1 (pmol/L)	1.3	1.1	1.8	1.3	1.0	2.1

BMI, body mass index; SDS, standard deviation scores; HOMA, homoeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine transaminase; AST, aspartate transaminase; GLP-1, glucagon-like peptide-1; aGLP-1, activated glucagon-like peptide-1.

Table 2 | Liver histopathology of the children randomised to VSL#3 and placebo

	Placebo		VSL#3	
	n	%	n	%
Fatty liver at US				
Moderate	14	63.6	12	54.5
Severe	8	36.4	10	45.5
Steatosis				
5–33%	3	13.6	2	9.1
33–66%	9	40.9	10	45.5
>66%	10	45.5	10	45.5
Inflammation				
<2 foci	7	31.8	7	31.8
2–4 foci	12	54.5	9	40.9
>4 foci	3	13.6	6	27.3
Ballooning				
Few balloon cells	13	59.1	15	68.2
Prominent balloon cells	9	40.9	7	31.8
Fibrosis				
Periportal or perisinusoidal	12	54.5	10	45.5
Perisinusoidal and portal/periportal	8	36.4	9	40.9
Bridging fibrosis	2	9.1	3	13.6
Non-alcoholic steatohepatitis score (NAS)				
3	1	4.5	2	9.1
4	3	13.6	4	18.2
5	5	22.7	3	13.6
6	9	40.9	6	27.3
7	4	18.2	5	22.7
8	0	0.0	2	9.1

FEBS Letters xxx (2014) xxx–xxx

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FEBS Letters

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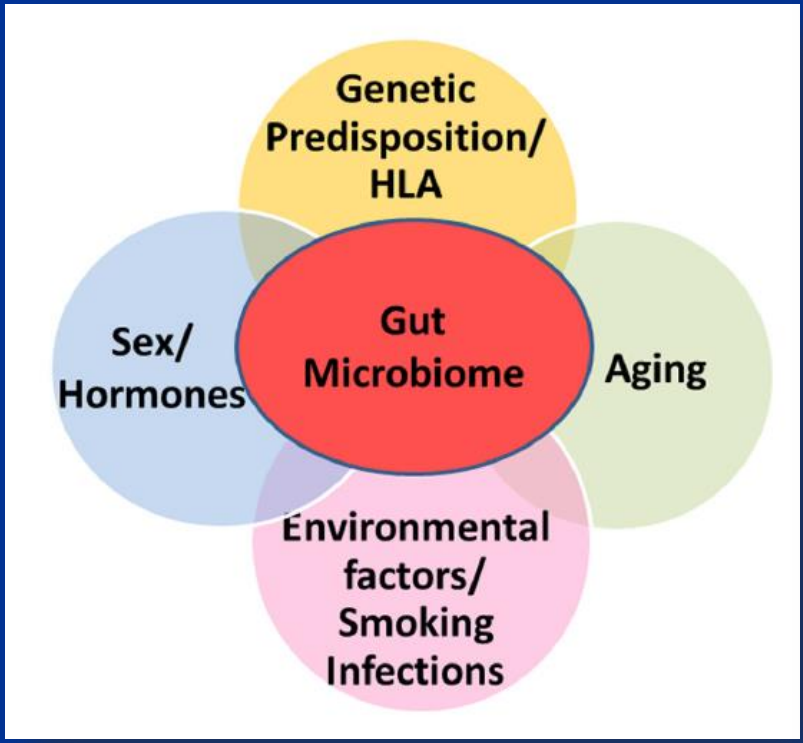
1964–2014

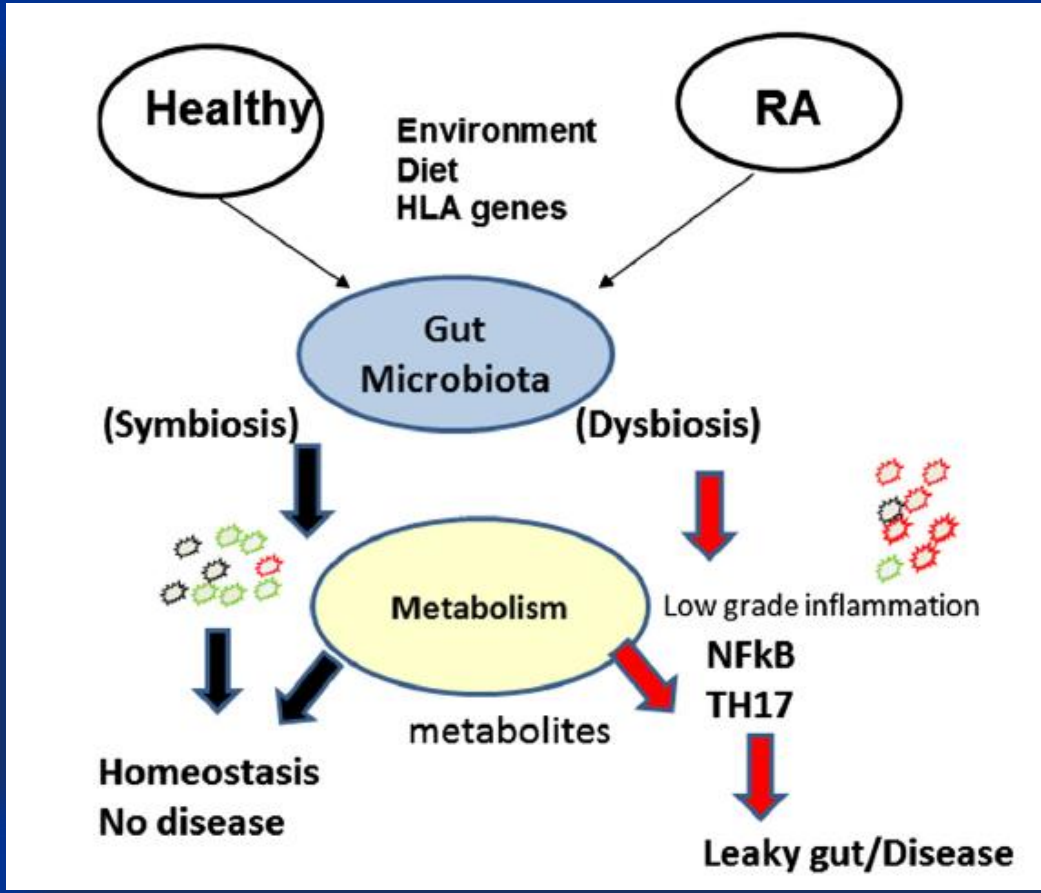
Review

Arthritis susceptibility and the gut microbiome

Veena Taneja *

Department of Immunology and Division of Rheumatology, Mayo Clinic, Rochester, MN 55905, United States

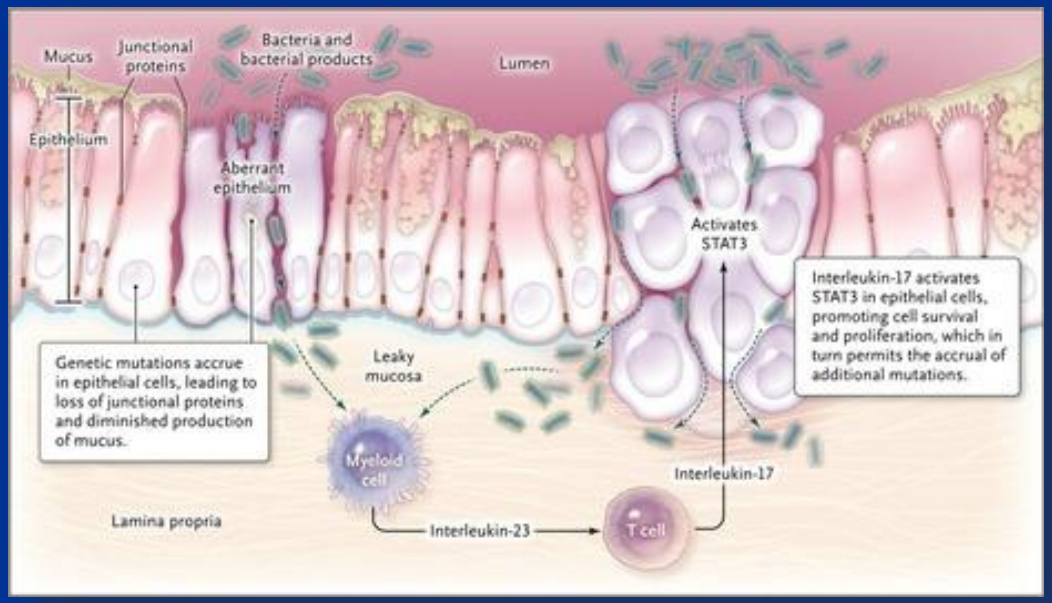


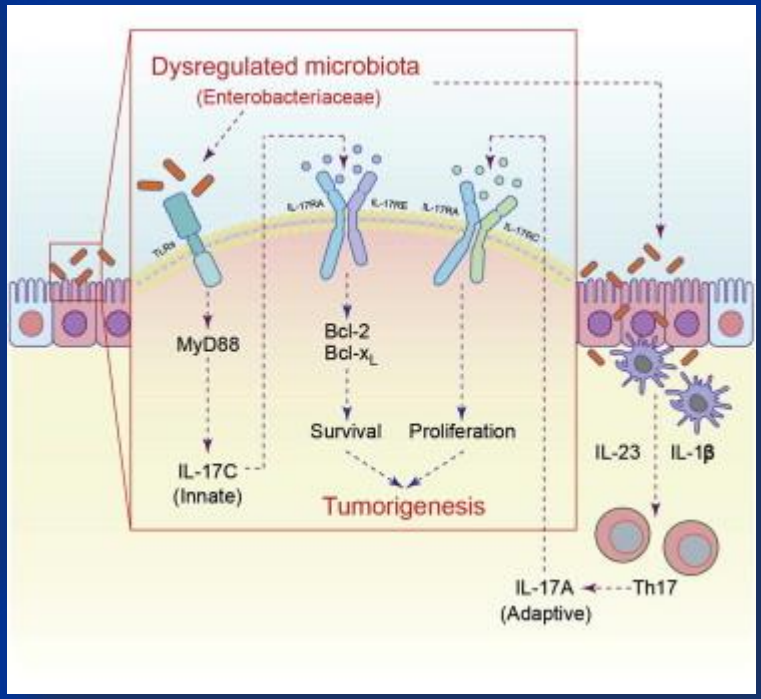


REVIEW ARTICLE

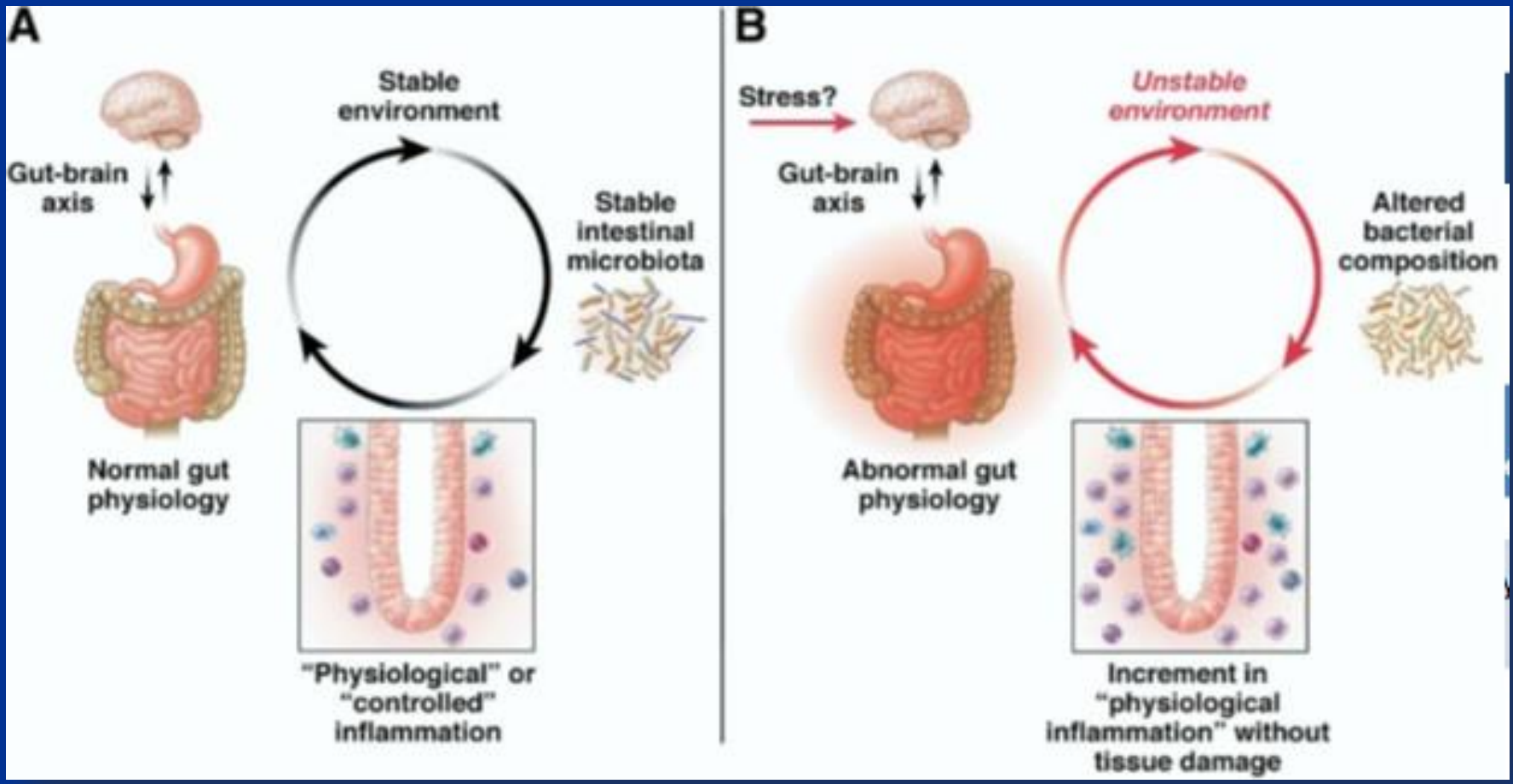
Microbiota and Immune Responses in Colon Cancer
More to Learn

Florencia McAllister, MD, Franck Housseau, MD,* and Cynthia L. Sears, MPH*†*

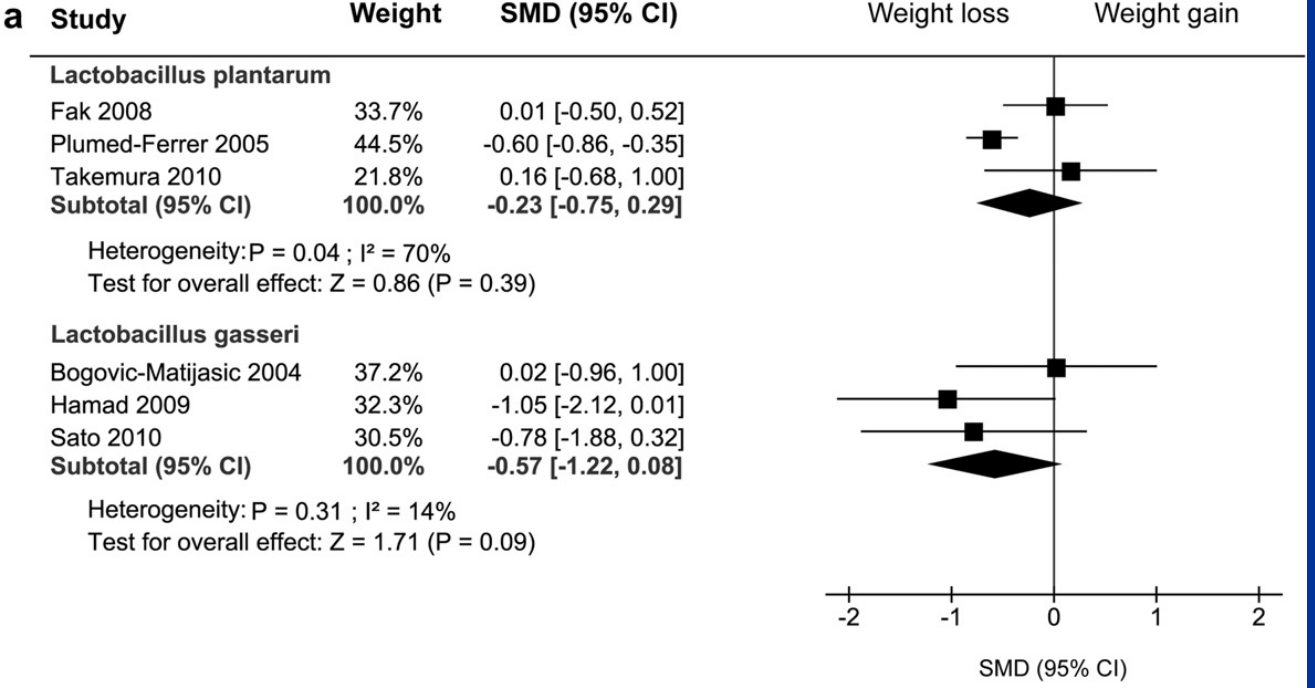


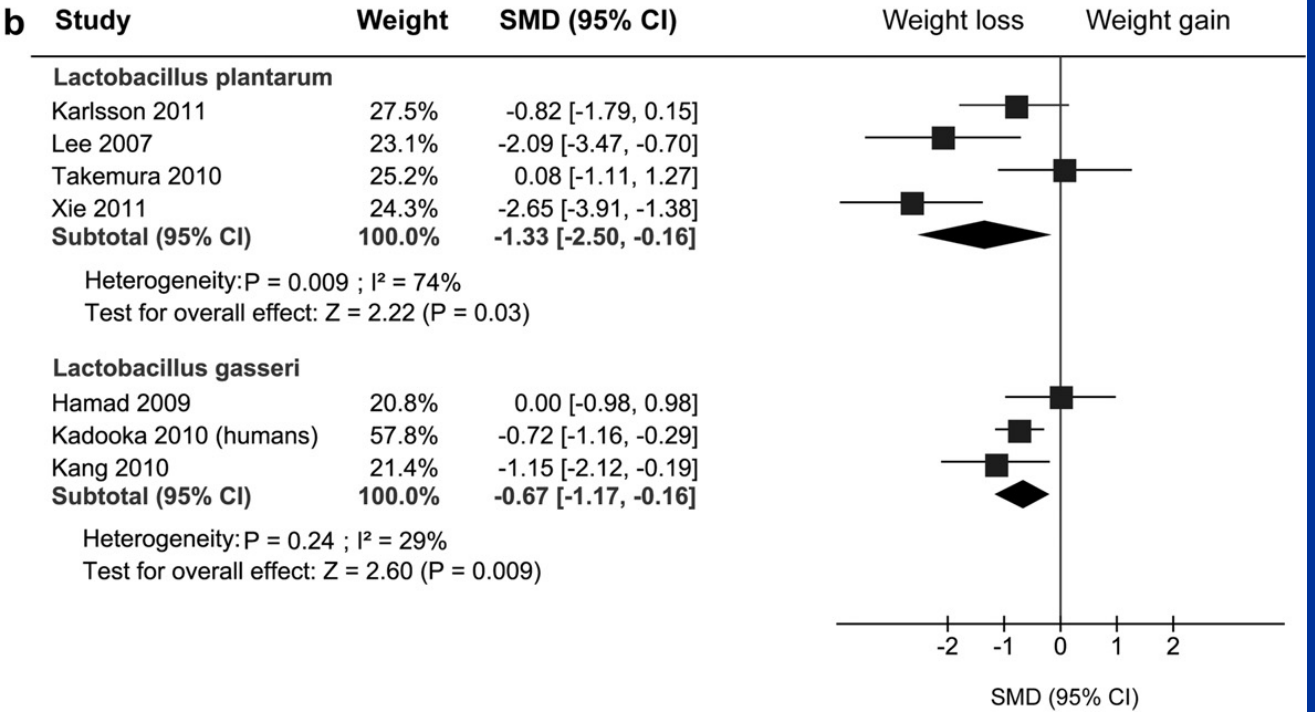


Stress ve Mikrobiyota Barsak-Beyin Ekseni



Obezite





M. Million et al. /
Microbial Pathogenesis xxx (2012) 1e9

Obezite, metabolik sendrom ve barsak florası

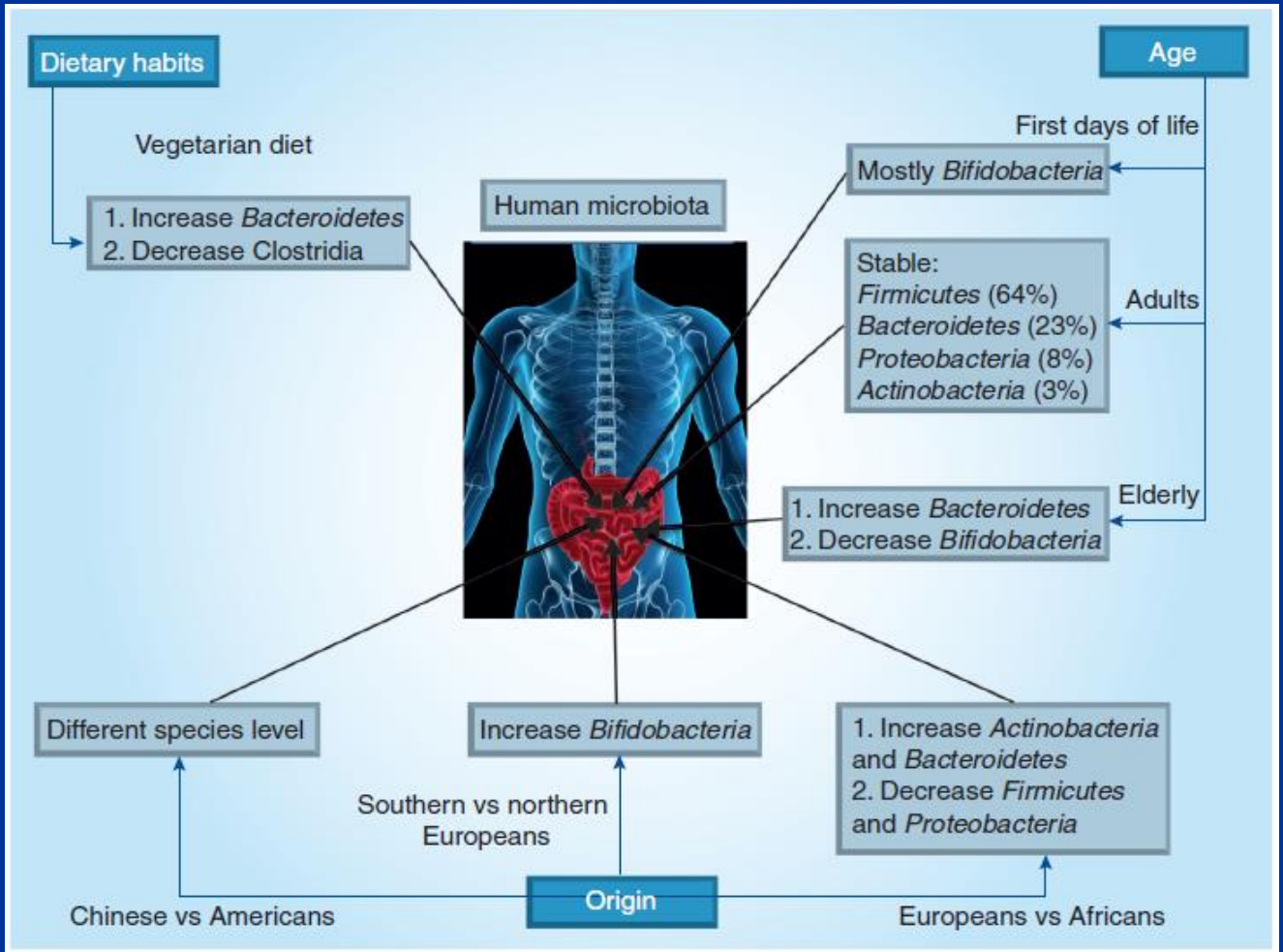
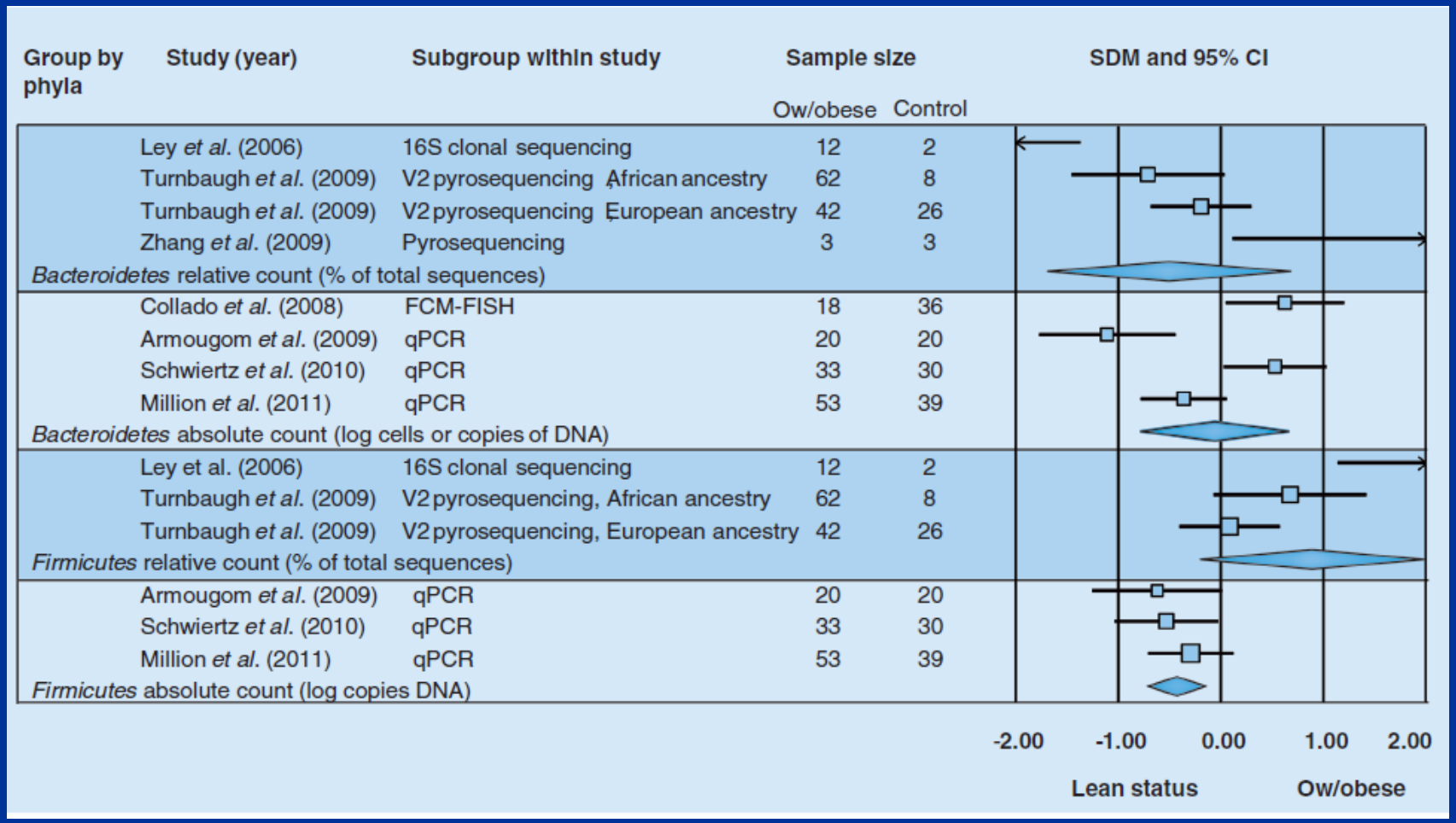
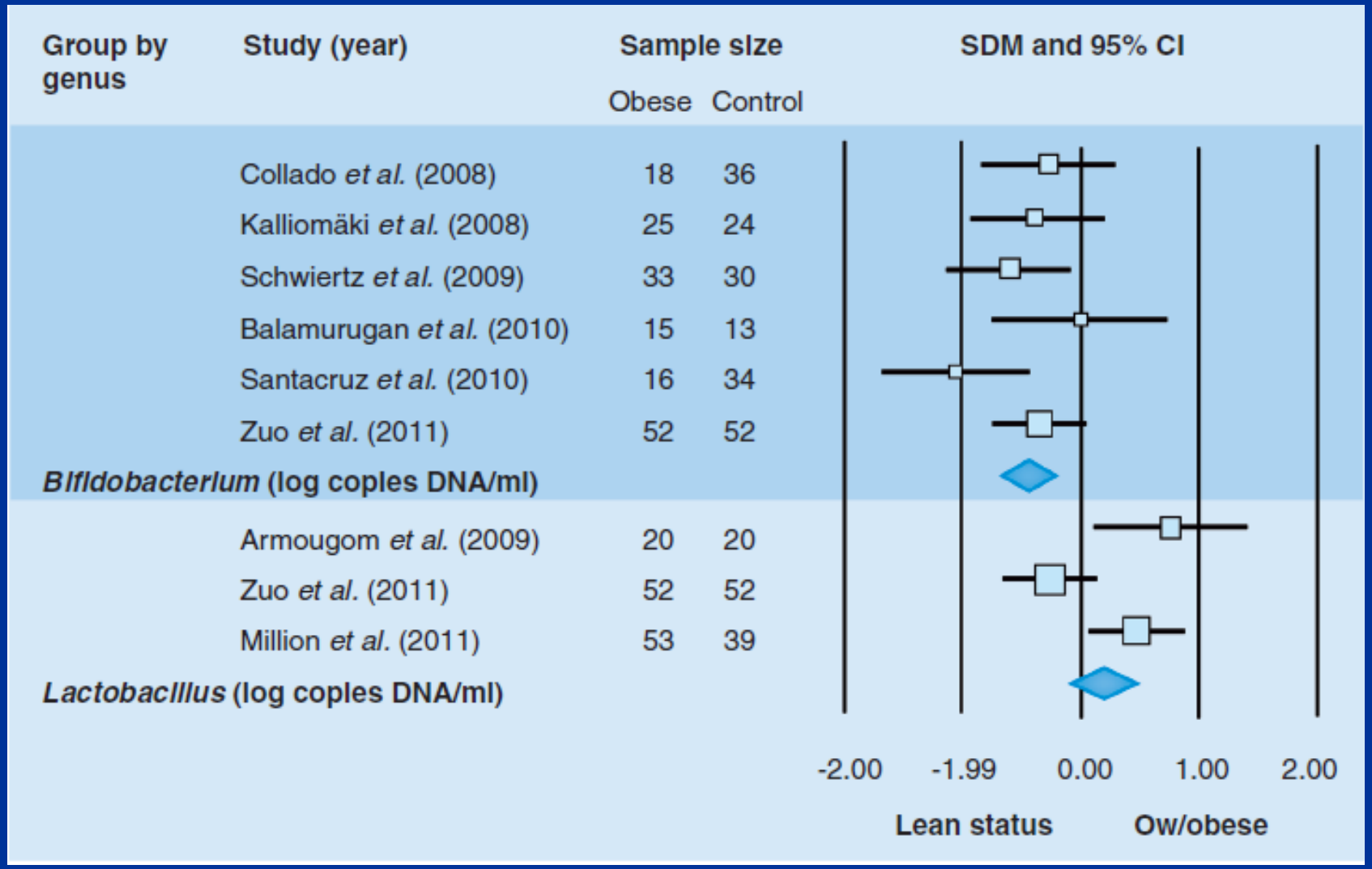


Figure 1. Impact factors for the composition of the human gut microbiota.

Obez ve zayıf insanlardaki barsak florası farklı (Obezlerde firmicutes artışı, bacteroidetes azalması)



Genus seviyesinde obezlerde Bifidobacterium azalması var



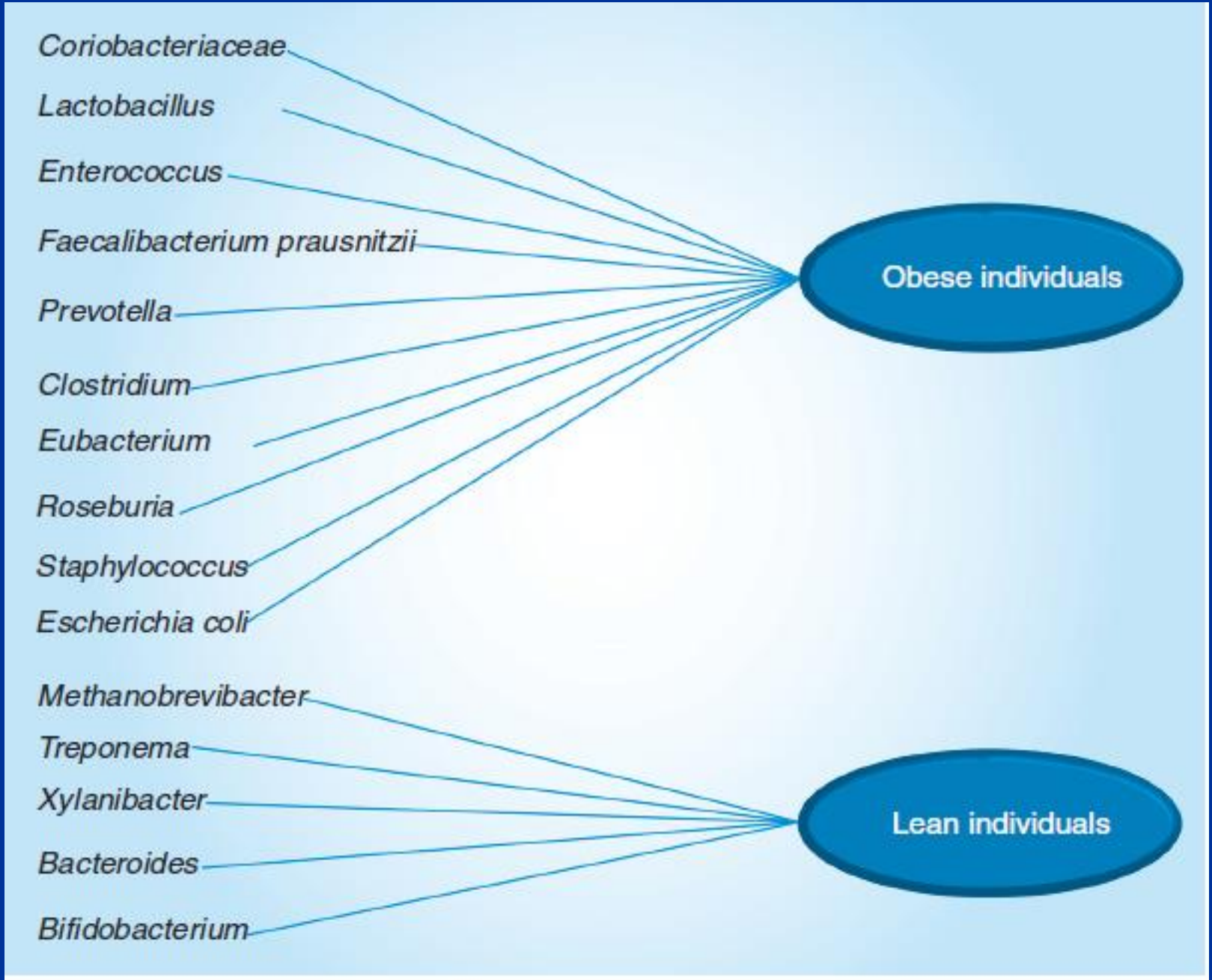


Figure 6. Population of bacteria found to increase in obese and lean individuals.

Tek yumurta ikizi çalışmaları

- Farklı kilosu olan ikizlerde bakılan barsak florası çalışmalarındaki sonuçlar:
  - Obezlerde barsak florası değişkenliği azalmış
  - Bacteroidetes türünde azalma
  - Bakterilerin karbonhidrat parçalayan enzimlerini kodlayan genlerde bile farklılıklar var

Koroner Arter Hastalığı Mikrobiyota

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 25, 2013 VOL. 368 NO. 17

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

W.H. Wilson Tang, M.D., Zeneng Wang, Ph.D., Bruce S. Levison, Ph.D., Robert A. Koeth, B.S., Earl B. Britt, M.D., Xiaoming Fu, M.S., Yuping Wu, Ph.D., and Stanley L. Hazen, M.D., Ph.D.

4007 koroner anjiografi yapılan hasta 3 yıl prospektif izleniyor

Bazal TMAO artışı ile majör KVH riski 2.54 kat artıyor

Geniş spektrumlu antibiyotik ile barsak mikrobiyotası baskılandığında, yediklerinden bağımsız olarak TMAO yükselmiyor

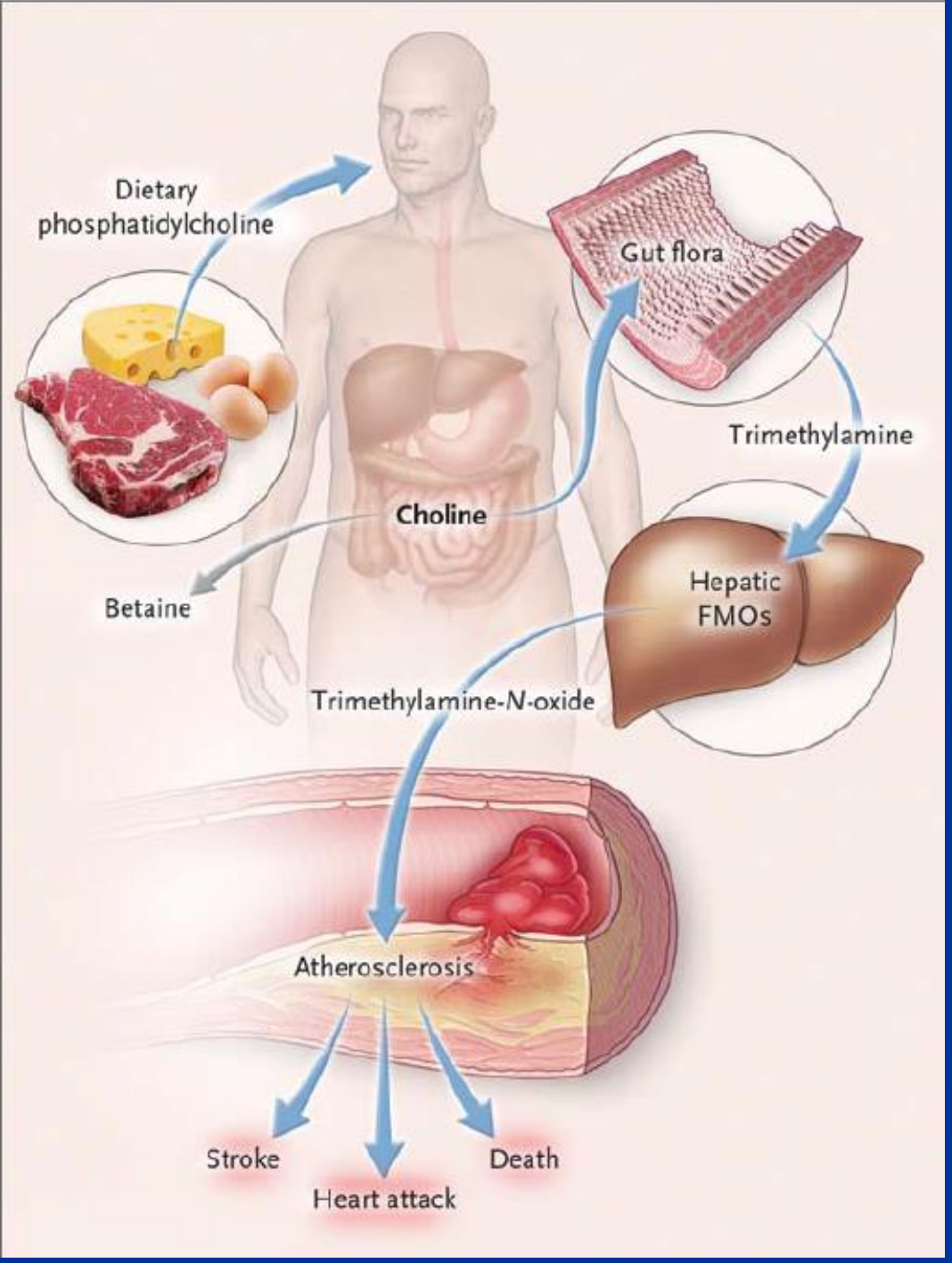


Figure 3. Pathways Linking Dietary Phosphatidylcholine, Intestinal Microbiota, and Incident Adverse Cardiovascular Events.

Ingested phosphatidylcholine (lecithin), the major dietary source of total choline, is acted on by intestinal lipases to form a variety of metabolic products, including the choline-containing nutrients glycerophosphocholine, phosphocholine, and choline. Choline-containing nutrients that reach the cecum and large bowel may serve as fuel for intestinal microbiota (gut flora), producing trimethylamine (TMA). TMA is rapidly further oxidized to trimethylamine-*N*-oxide (TMAO) by hepatic flavin-containing monooxygenases (FMOs). TMAO enhances the accumulation of cholesterol in macrophages, the accumulation of foam cells in artery walls, and atherosclerosis,[7] all factors that are associated with an increased risk of heart attack, stroke, and death. Choline can also be oxidized to betaine in both the liver and kidneys.[20] Dietary betaine can serve as a substrate for bacteria to form TMA[21] and presumably TMAO.

European Heart Journal (2014) **35**, 904–910
doi:10.1093/eurheartj/ehu002

Prognostic value of choline and betaine depends on intestinal microbiota-generated metabolite trimethylamine-*N*-oxide

Zeneng Wang[1], W. H. Wilson Tang[1,2], Jennifer A. Buffa[1], Xiaoming Fu[1], Earl B. Britt[1], Robert A. Koeth[1], Bruce S. Levison[1], Yiying Fan[3], Yuping Wu[3], and Stanley L. Hazen[1,2]*

[1]Department of Cellular and Molecular Medicine, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA; [2]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH, USA; and [3]Department of Mathematics, Cleveland State University, Cleveland, OH, USA

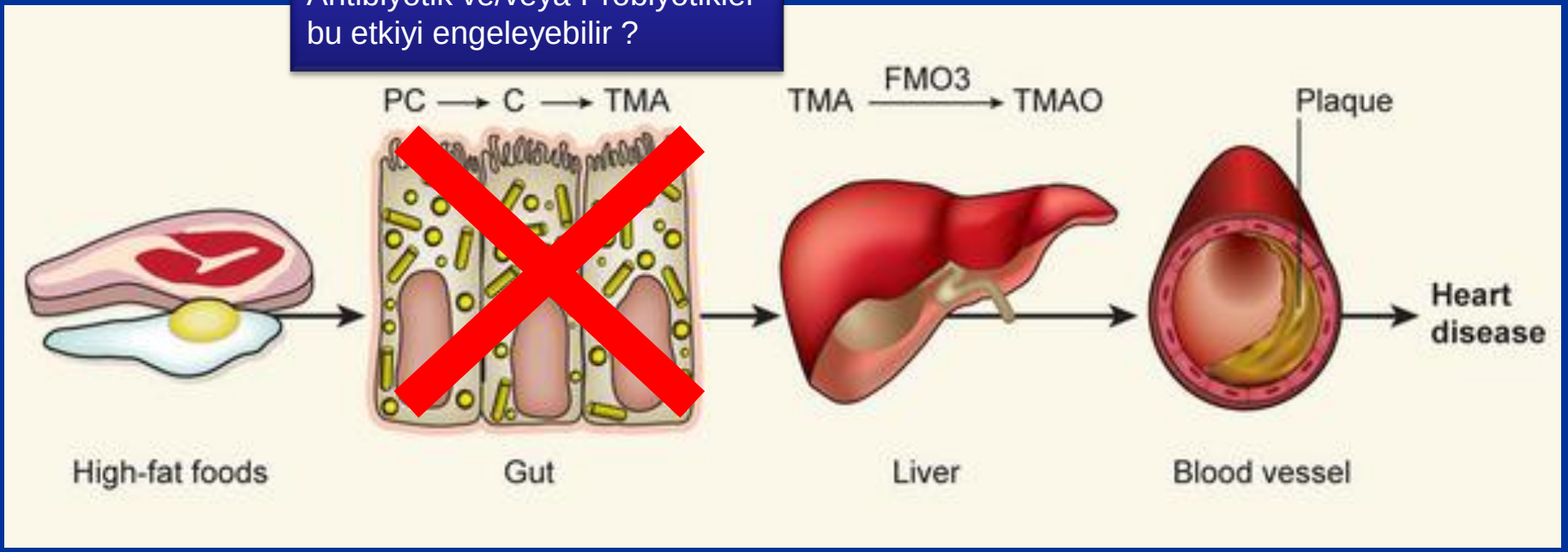
Received 28 July

plasma levels of choline and betaine, which individually are associated with poorer prognosis, only confer this added risk when associated with concomitant TMAO elevation. In other words, subjects in whom one observes the absence of high TMAO levels despite high choline and betaine levels (i.e. low TMAO producers) are significantly less likely to have an adverse cardiovascular event than those with intestinal microbiota that readily produces TMA and TMAO (i.e. high TMAO producers).

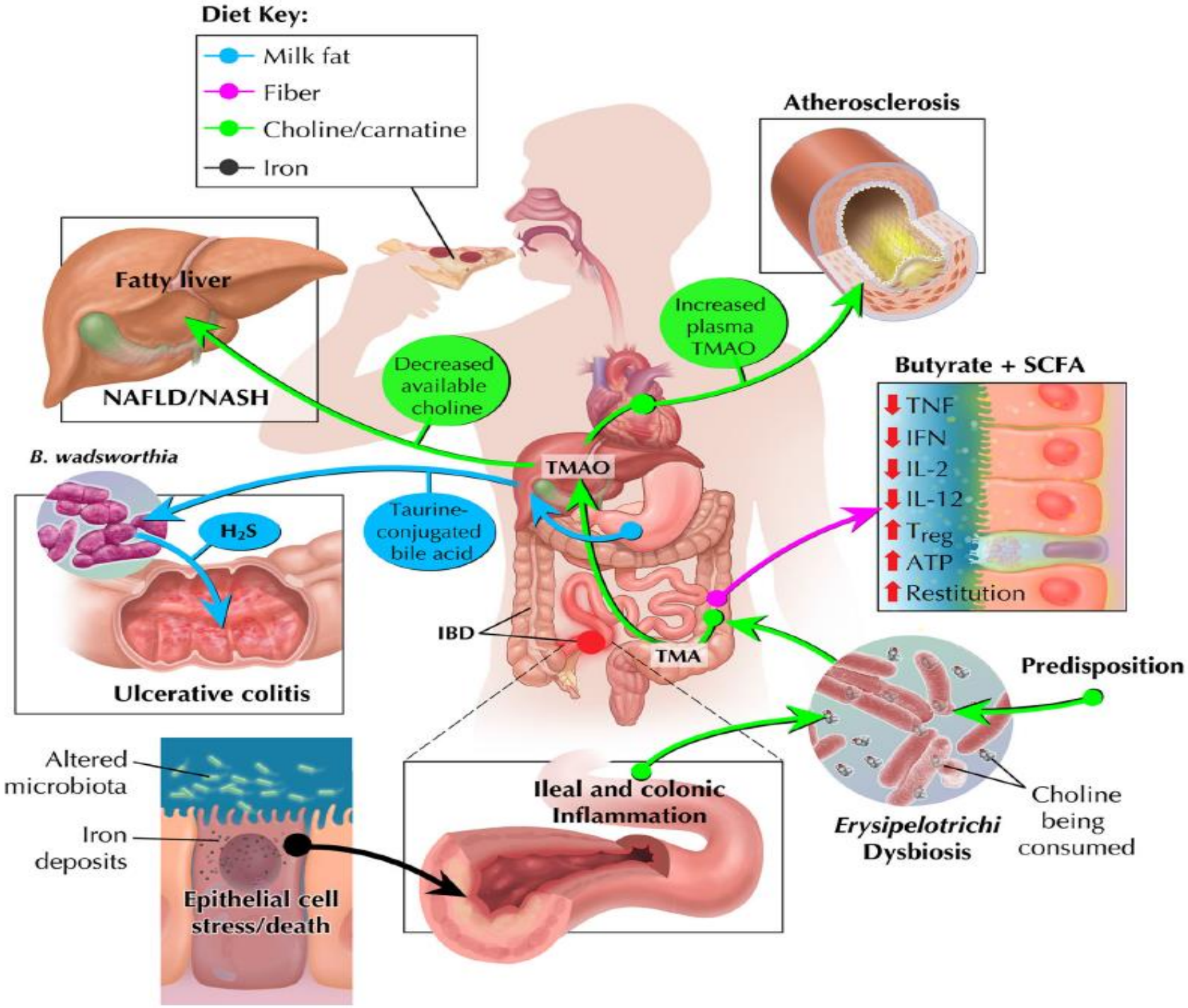
Figure 5 Relationship between plasma choline concentration and risk for major adverse cardiac events in the context of plasma trimethylamine-*N*-oxide levels. Kaplan–Meier plot and hazard ratio with 95% confidence intervals for unadjusted model, or following adjustments for traditional risk factors and hs C-reactive protein as in *Figure 4A*. Median plasma concentration of choline (9.8 μM) and trimethylamine-*N*-oxide (3.7 μM) within the cohorts were used to stratify subjects as 'high' (≥median) or 'low' (<median) values.

Kolin eksikliği ve NAFLD- ASKH

Antibiyotik ve/veya Probiyotikler bu etkiyi engeleyebilir ?



Yağlı diyet mikrobiyotayı değiştirir
Diyetteki kolini metilaminlere çevirir, fosfotidilkolin azalır
Fosfotidil kolin, VLDL oluşumu ve sekresyonu için gerekli
Mikrobiyota-ilişkili kolin eksikliği hepatositlerde yağ birikimine neden olur.
TMA ve KC metaboliti TMAO ise ateroskleroza neden olur.


Diet Key:
Milk fat
Fiber
Choline/carnatine
Iron
Atherosclerosis
Fatty liver
NAFLD/NASH
Increased plasma TMAO
Decreased available choline
Butyrate + SCFA
TNF
IFN
IL-2
IL-12
Treg
ATP
Restitution
B. wadsworthia
TMAO
H2S
Taurine-conjugated bile acid
IBD
TMA
Ulcerative colitis
Predisposition
Altered microbiota
Iron deposits
Epithelial cell stress/death
Ileal and colonic Inflammation
Erysipelotrichi Dysbiosis
Choline being consumed

Sonuç

- Barsak mikrobiyotası
  - Unutulmuş organ
  - Sanal organ
  - İkinci genom gibi isimlerle anılmaktadır

- Barsak mikrobiyotası gelecek 20 yılın tıp alanında en çok araştırma yapılacak alanı olması muhtemel
- Araştırılması gereken konular
  - Bakteri çeşit ve sayısı dışında fonksiyonları
  - Konakçı ile etkileşimi
  - Bakteri-bakteri etkileşimi
  - Mikobiyom
  - Virom

TEŞEKKÜRLER