UNIVERSITÀ DEGLI STUDI DI PAVIA
Dipartimento di Scienze Clinico-Chirurgiche,
Diagnostiche e Pediatriche

FONDAZIONE IRCCS POLICLINICO
SAN MATTEO
U.O. Malattie Infettive

Care of liver after HCV cure: from NAFLD to microbiome

Raffaele Bruno,MD

Outline

- The epidemiology of non-alcoholic fatty liver disease
- Risk factors:
  - Diabetes
  - CV Risk
  - Sedentary Lifestyle
  - Genetic Factors
- Microbiome & NAFLD

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The epidemiology of non-alcoholic fatty liver disease

Prevalence of NAFLD in different population in Europe

	Case Identification	Prevalence NAFLD
14 EU Countries	FLI	33% (adults)
Germany	US and LE	2% (36% in obese children)
Germany	US	30% (adults)
Greece	Histology	31% (adults)
Italy	US	26% (adults)
Italy	US	12.5% (adolescents)
Italy	US	44% (obese children)
Italy	US	69.5% (diabetic pts)
Romania	US	20% (adults)
Spain	US	25.8% (adults)
UK	US	46.2% (diabetic pts)

FLI, fatty liver index; US, ultrasound; LE, liver enzymes.

Stefano Bellentani. Liver International 2017; 37 (Suppl. 1): 81–84

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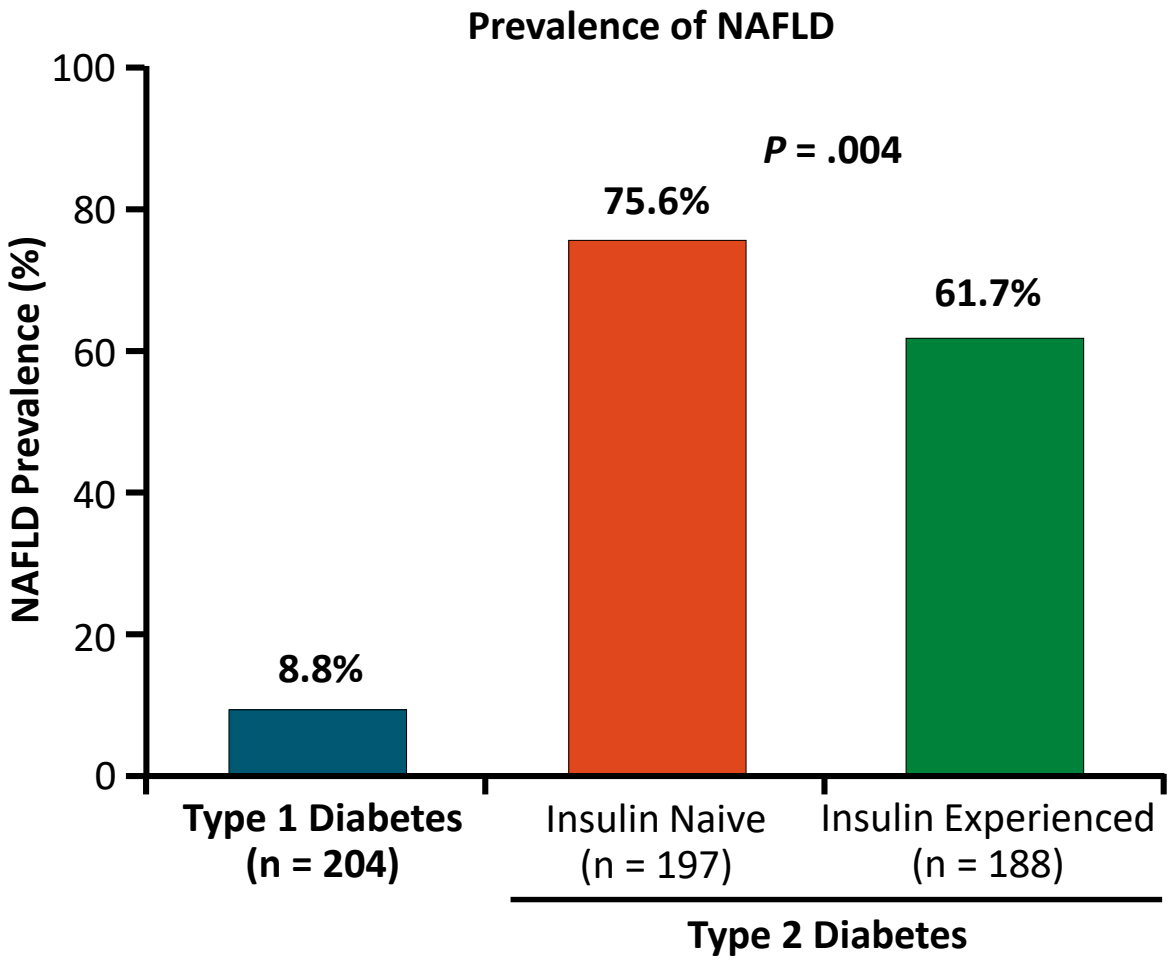
Prevalence of NAFLD in Patients With Type 1 and 2 Diabetes

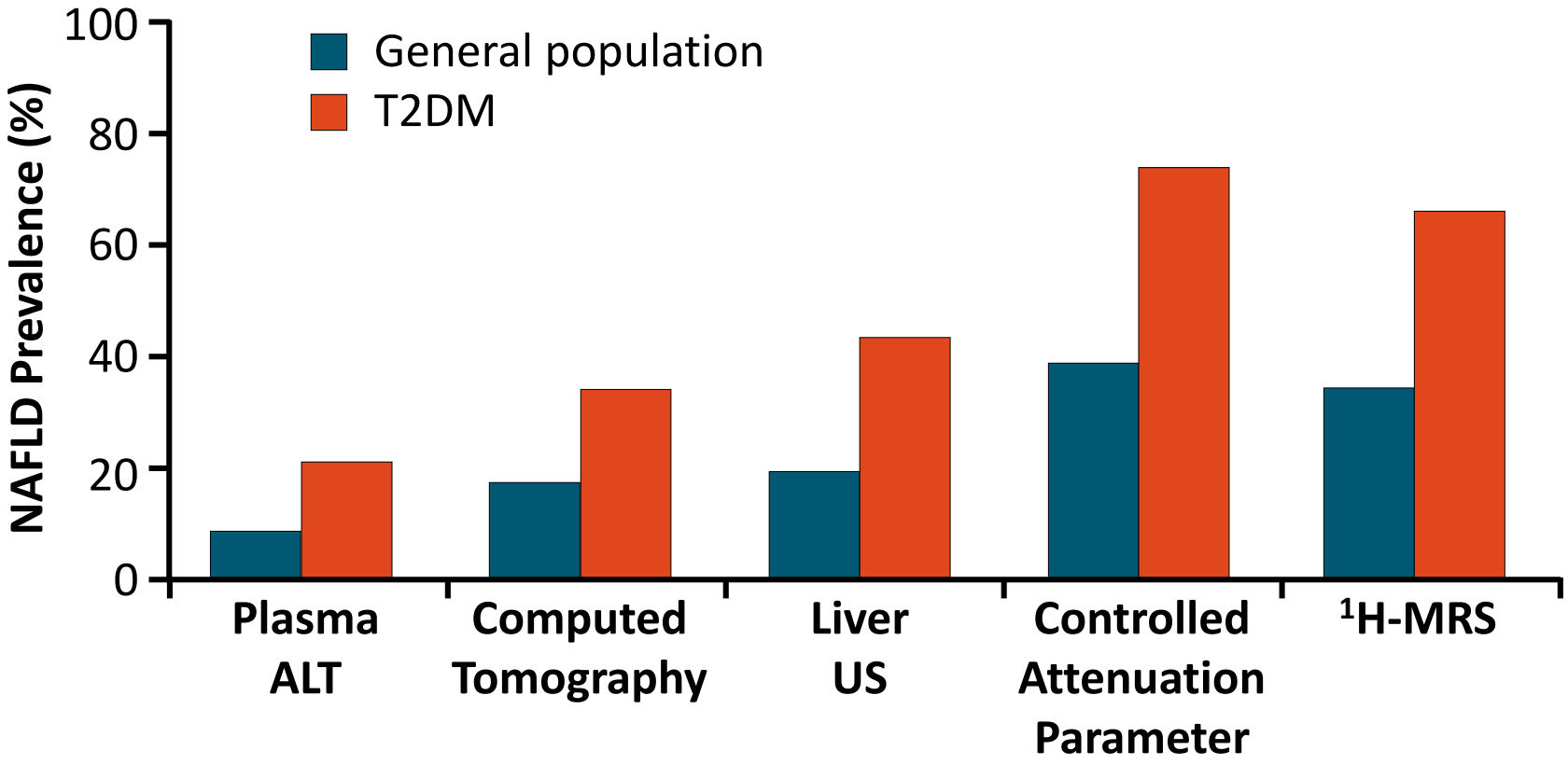
- Post hoc analysis of baseline data from 4 phase III trials (N = 589)
- The prevalence of NAFLD is low in T1D patients but high in T2D patients
- NAFLD is more frequent in insulin-naïve T2D patients compared to those previously treated with insulin



Cusi. Diabetes Obes Metab. 2017;19:1630.

Prevalence of NAFLD in the general population and in patients with T2DM according to different diagnostic tools

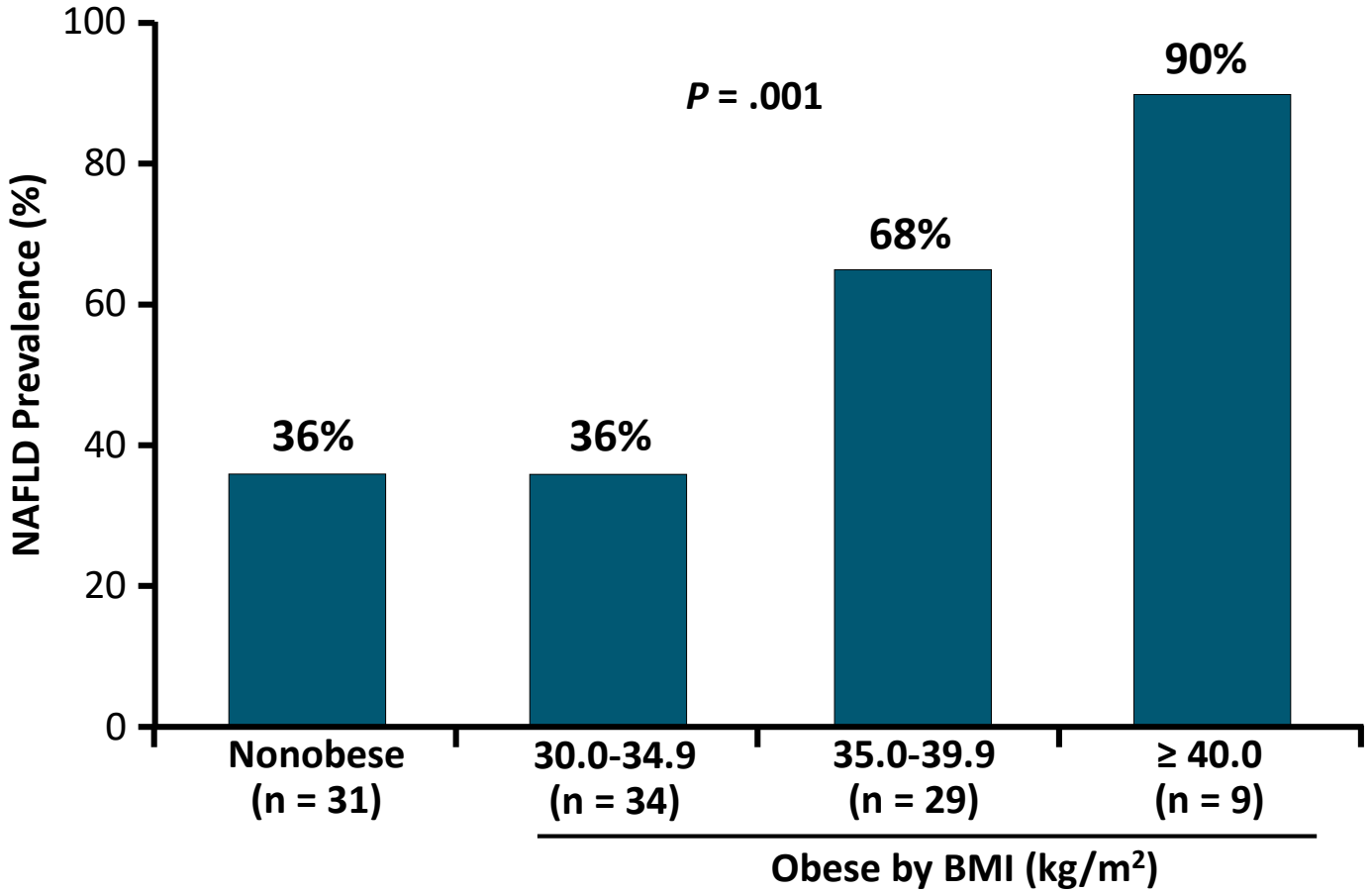
- The presence of T2DM significantly increases the prevalence of NAFLD in comparison of general population



Bril. Diabetes Care. 2017;40:419.

Prevalence of NAFLD in Patients With *Type 2 diabetes* and Normal Plasma AST or ALT

- The prevalence of NAFLD is higher also in overweight/obese patients with T2DM and normal aminotransferases. (N = 103)



Portillo-Sanchez. J Clin Endocrinol Metab. 2015;100:2231. Stål. World J Gastroenterol. 2015;21:11077.

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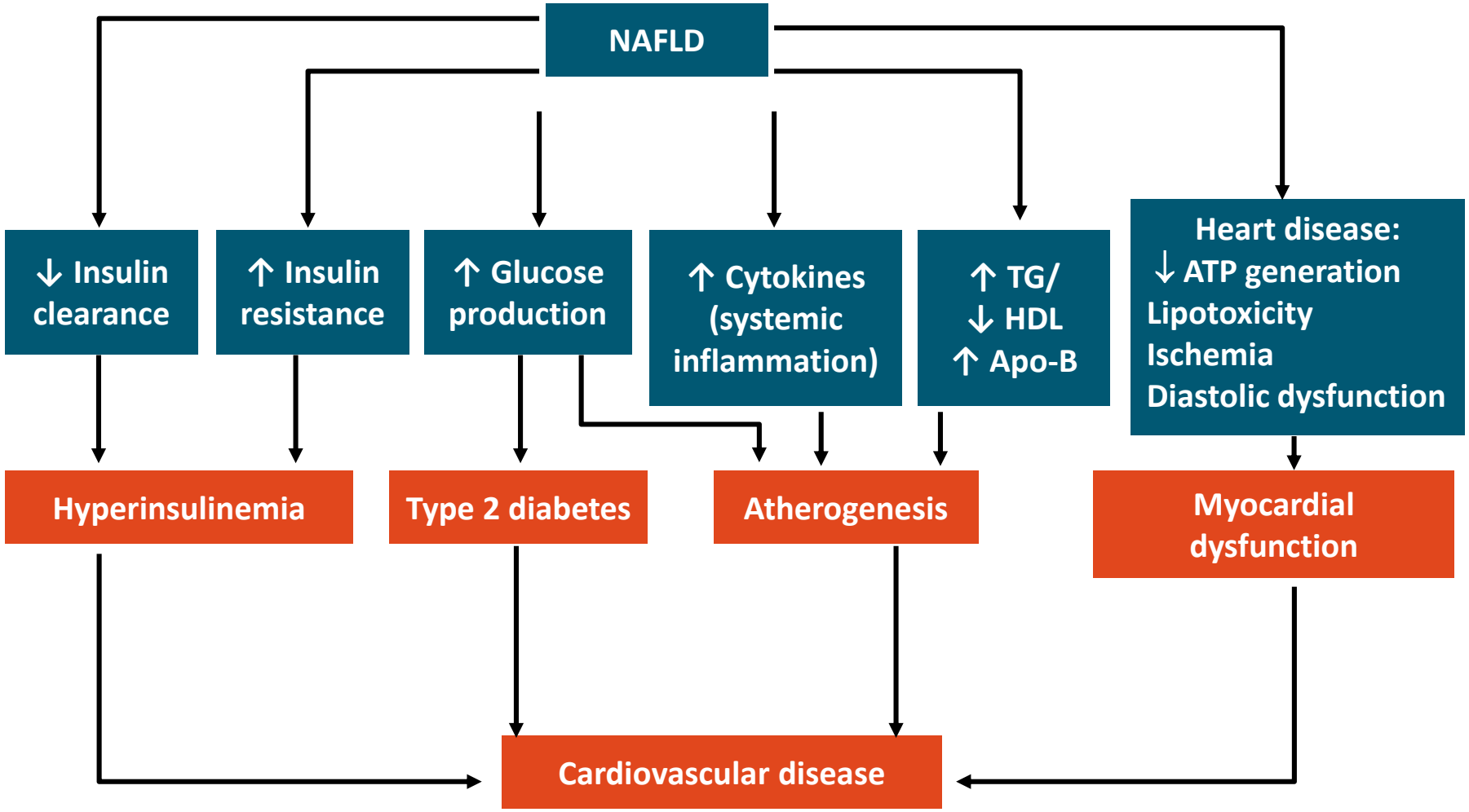
Metabolic Consequences of NAFLD

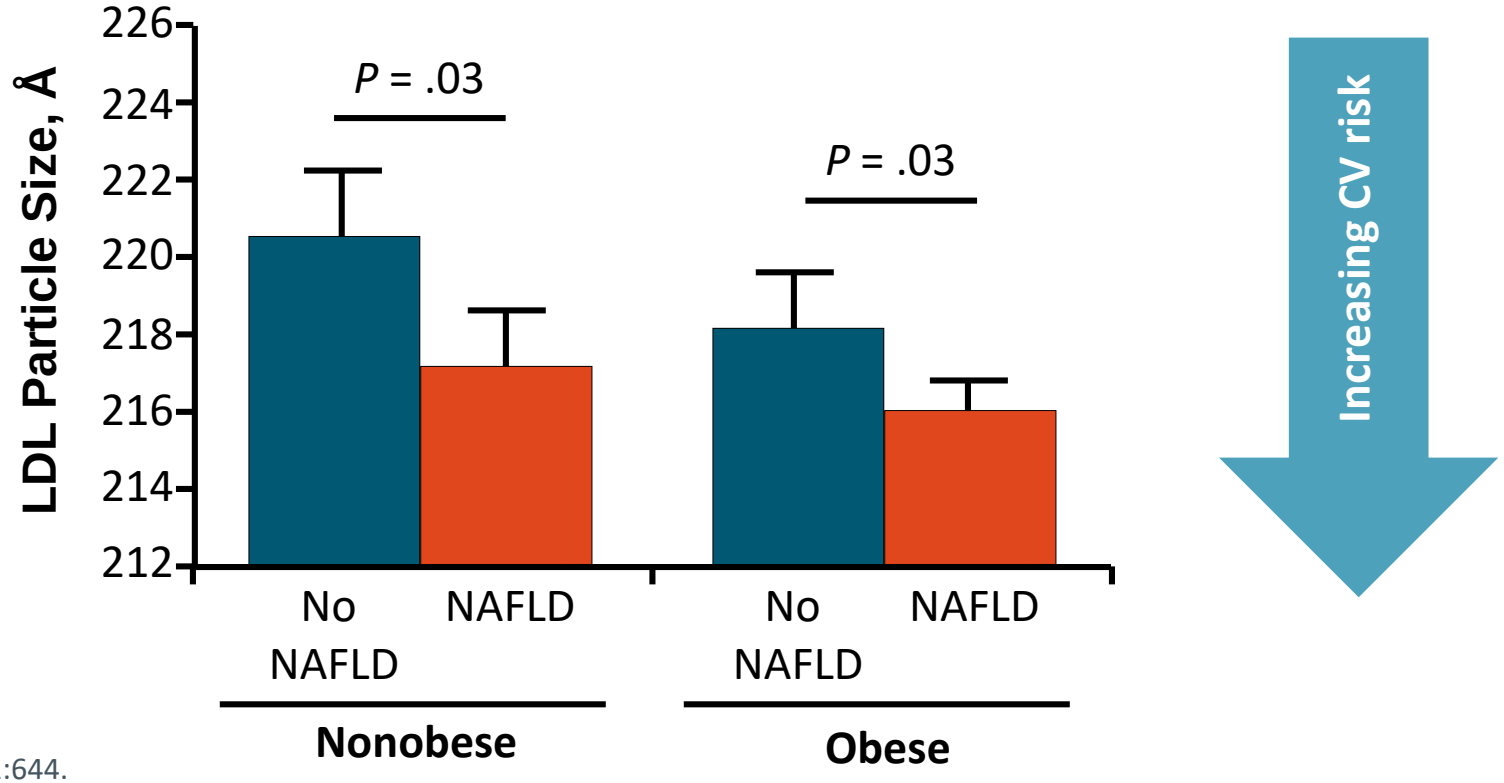


Cusi. Gastroenterology. 2012;142:711.

NAFLD, nonalcoholic fatty liver disease; TG, triglycerides; HDL, high-density lipoprotein; Apo-B, apolipoprotein B

Hepatic Steatosis and Insulin Resistance, But Not Steatohepatitis, Promote Atherogenic Dyslipidemia in NAFLD.

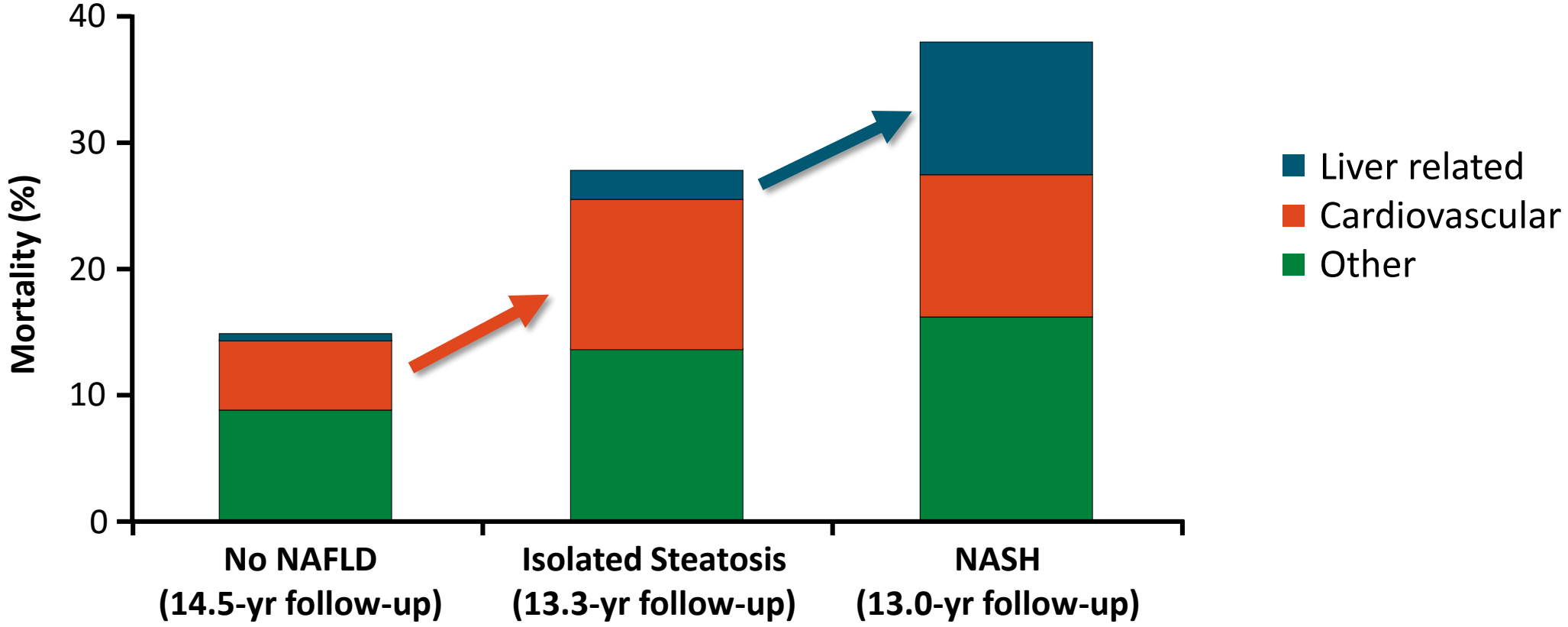
- NAFLD was associated with a worse atherogenic lipoprotein profile (LDL Particle Size Is Reduced in NAFLD), regardless of similar body mass index and other clinical parameters



Bril. J Clin Endocrinol Metab. 2016;101:644.

Mortality Risk Associated With Isolated Steatosis and NASH

- Analysis of all-cause mortality in 6 separate studies among patients without NAFLD vs with and without NASH
  - NAFLD determined by ultrasound; NASH determined by liver biopsy



Bril. Endocrinol Metab Clin N Am. 2016;45:765.

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Sedentary Lifestyle in NAFLD

- Physical inactivity linked to
  - Increased body weight
  - Central adiposity
  - Insulin resistance
  - Increased risk of metabolic syndrome
  - NAFLD
  - Severity of NASH

Hannah. Dig Dis Sci. 2016;61:1365.

Genetic Risks for NAFLD

- Known: PNPLA3, others
- Unknown:
  - Family history of diabetes, even among people without diabetes, is associated with NASH and NAFLD fibrosis[2]
  - Increased odds of advanced cirrhosis in first-degree relatives of patients with NAFLD cirrhosis[1]

1. Caussy. J Clin Invest. 2017;127:2697. 2. Loomba. Hepatology. 2012;56:943.

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How to define an EUBIOTIC enterotype?

EU= good ***BIOS= life***

- **Composition:** ***Diversity***
  Richness
  Relative Abundance

- ***Our gut is a sophisticated ecosystem that is regulated by the logic of RELATIONAL HARMONY***
- ***Microbiota and Host live in a COOPERATIVE SYSTEMIC AGGREGATION MODEL***

EUBIOSIS

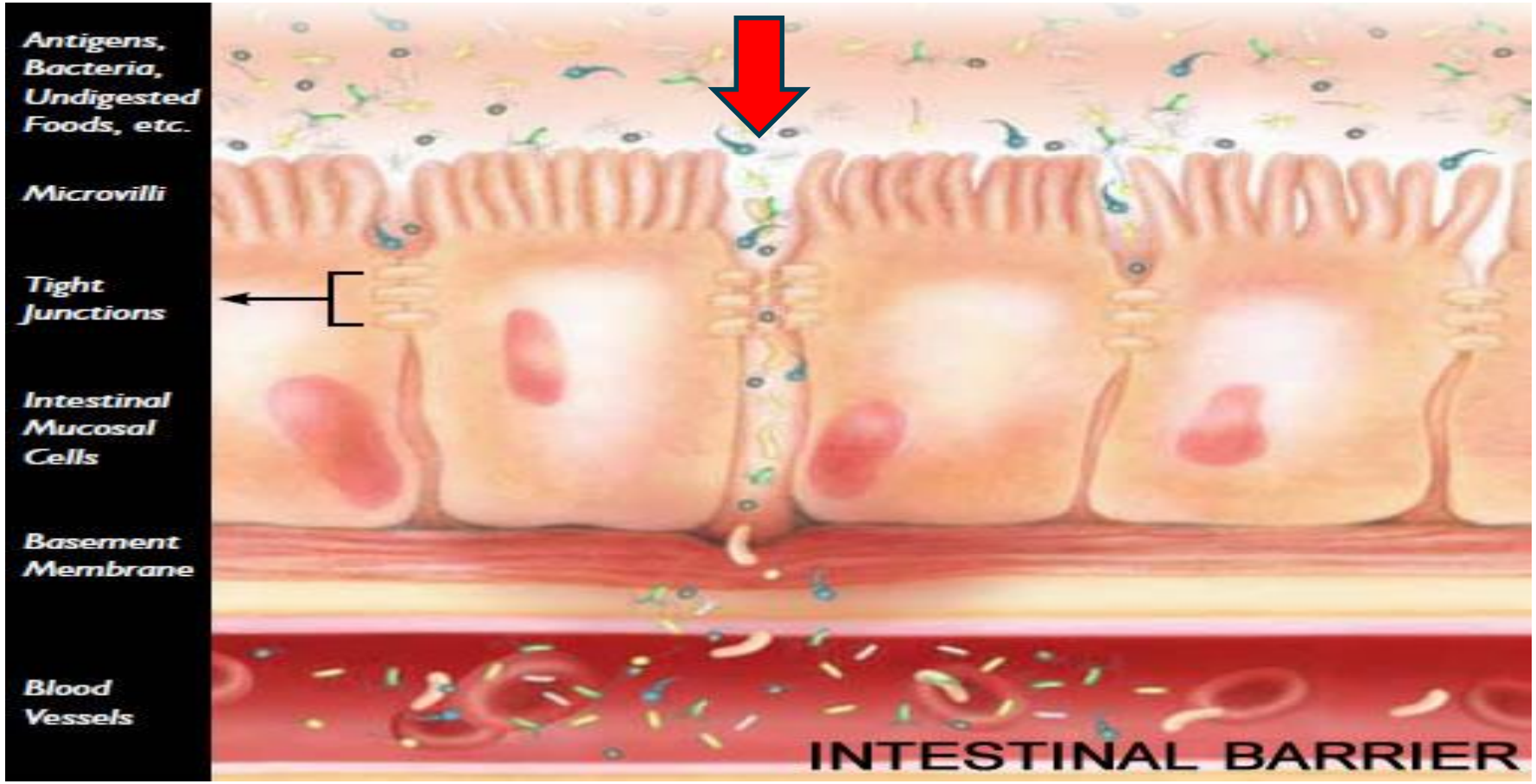
Failure of HOST-MICROBIOTA equilibrium

Quali-quantitative alterations of oral, esophageal, gastric, small bowel and/or colonic microbiota

DYSBIOSIS

Gut Barrier disfunction

Intestinal permeability: Leaky gut



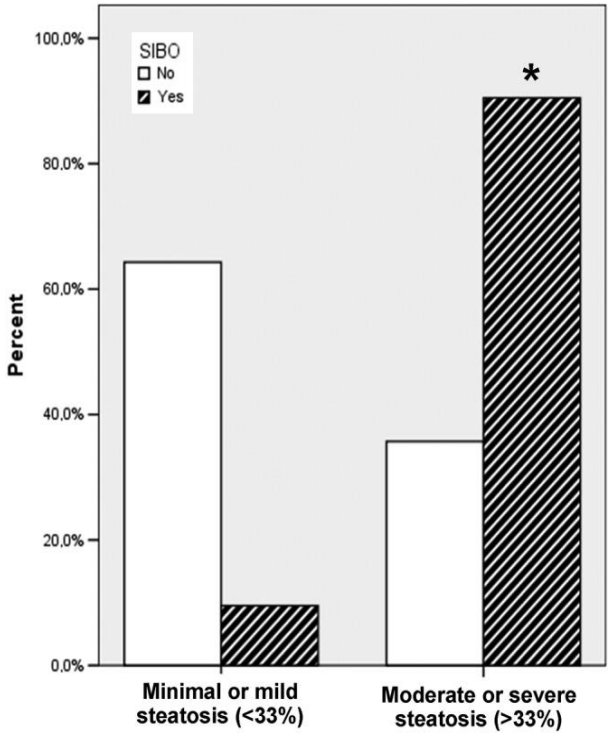
Increased Intestinal Permeability and Tight Junction Alterations in Nonalcoholic Fatty Liver Disease

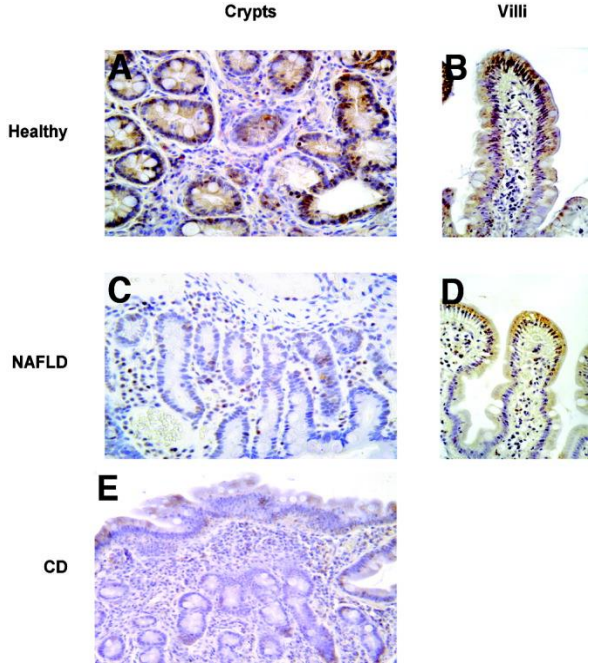
Luca Miele,[1] Venanzio Valenza,[2*] Giuseppe La Torre,[3*] Massimo Montalto,[1*] Giovanni Cammarota,[1] Riccardo Ricci,[4] Roberta Mascianà,[1] Alessandra Forgione,[1] Maria L. Gabrieli,[1] Germano Perotti,[2] Fabio M. Vecchio,[4] Gianlodovico Rapaccini,[1] Giovanni Gasbarrini,[1] Chris P. Day,[5**] and Antonio Grieco[1**]

Intestinal permeability is increased in children with non-alcoholic fatty liver disease, and correlates with liver disease severity

Valentina Giorgio[a,1], Luca Miele[b,c,1], Luigi Principessa[d], Francesca Ferretti[a], Maria Pia Villa[d], Valentina Negro[d], Antonio Grieco[b], Anna Alisi[a], Valerio Nobili[a,*]

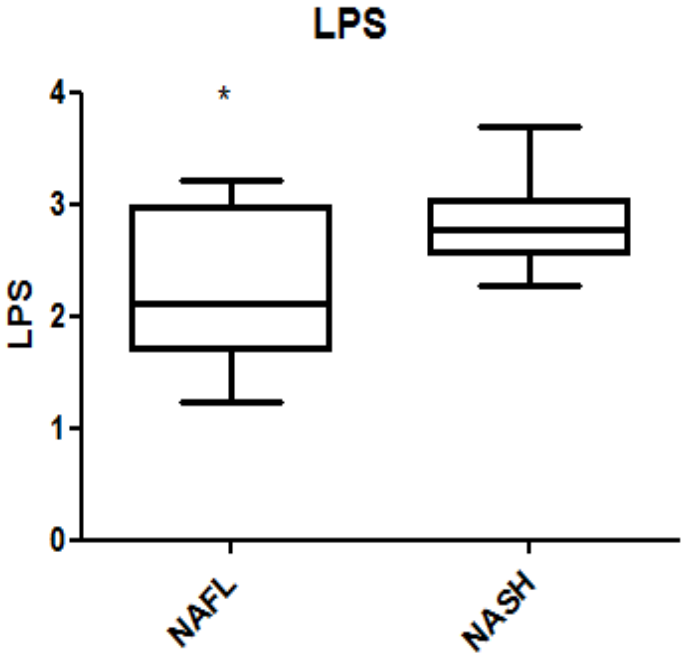
- NAFLD in humans is associated with increased gut permeability and that his abnormality is related to the increased prevalence of SIBO in these patients.
- The increased permeability appears to be caused by disruption of intercellular tight junctions in the intestine, and it may play an important role in the pathogenesis of hepatic fat deposition





(Hepatology 2009;49:1877-1887.)

↑ Severity of NASH and LPS in children

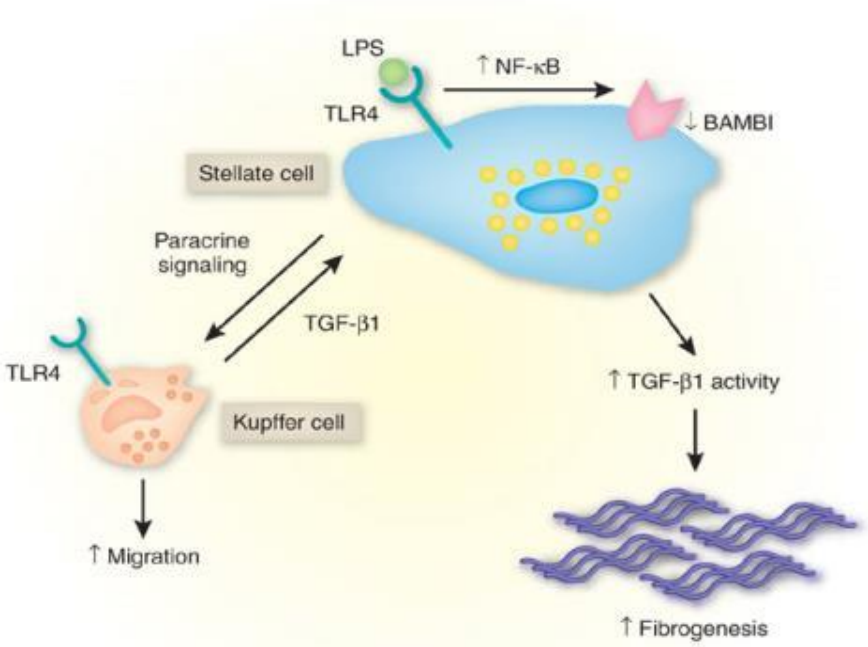


Digestive and Liver Disease xxx (2014) xxx–xxx

Translocation & NAFLD

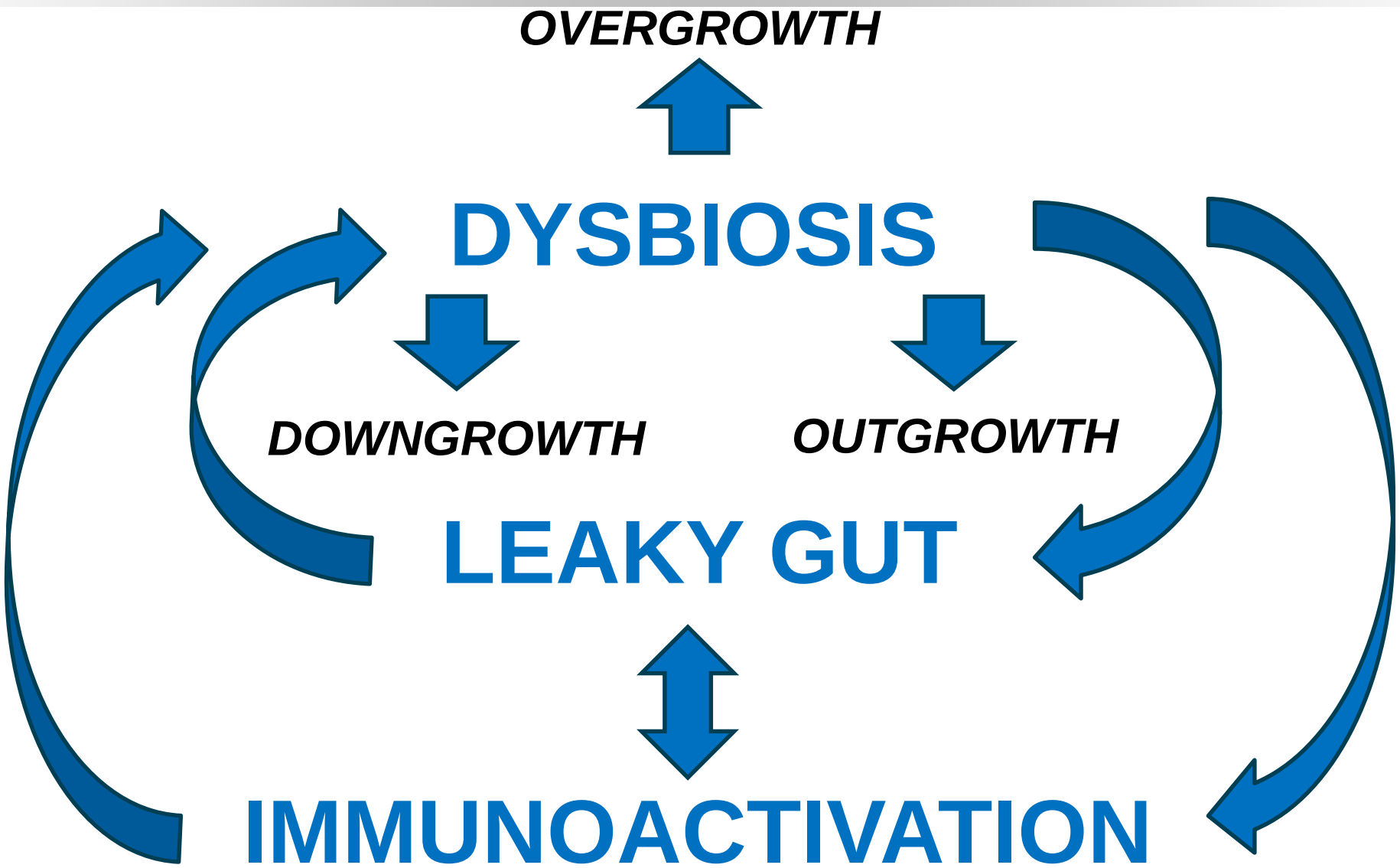
- Translocated microbial products might contribute to the pathogenesis of fatty liver disease by several mechanisms.

- Activation of Toll-like receptors (TLRs) on hepatic Kupffer cells and stellate cells to stimulate pro-inflammatory and profibrotic pathways via a range of cytokines.



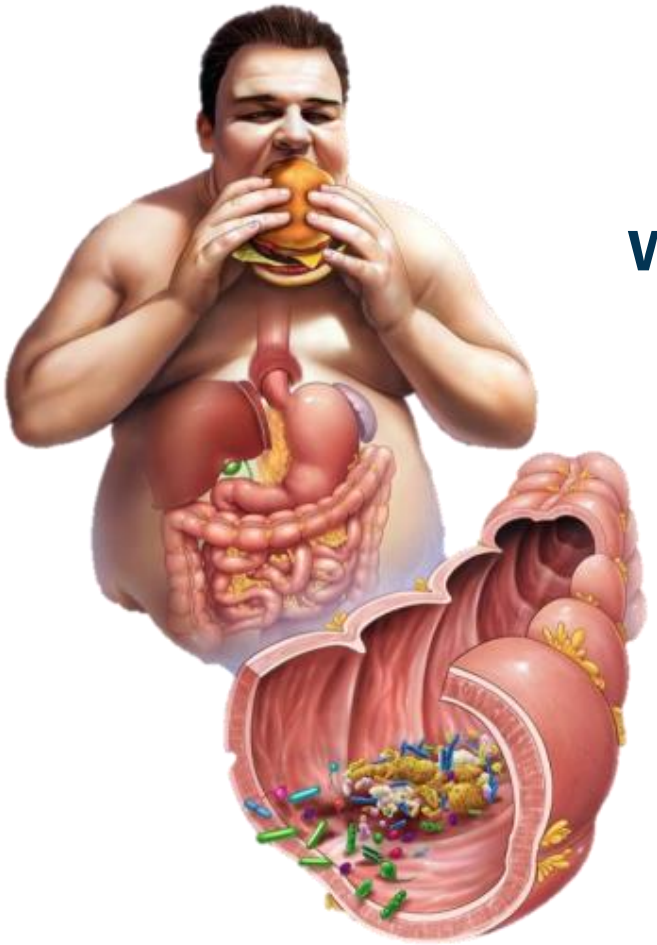
Lipopolysaccharide signaling through the Toll-like receptors downregulates an inhibitory pseudoreceptor of TGF-β, enhancing hepatic fibrosis and liver injury

Friedman SL. Nat Med 2007 - Saki et al. Nat Med 2007



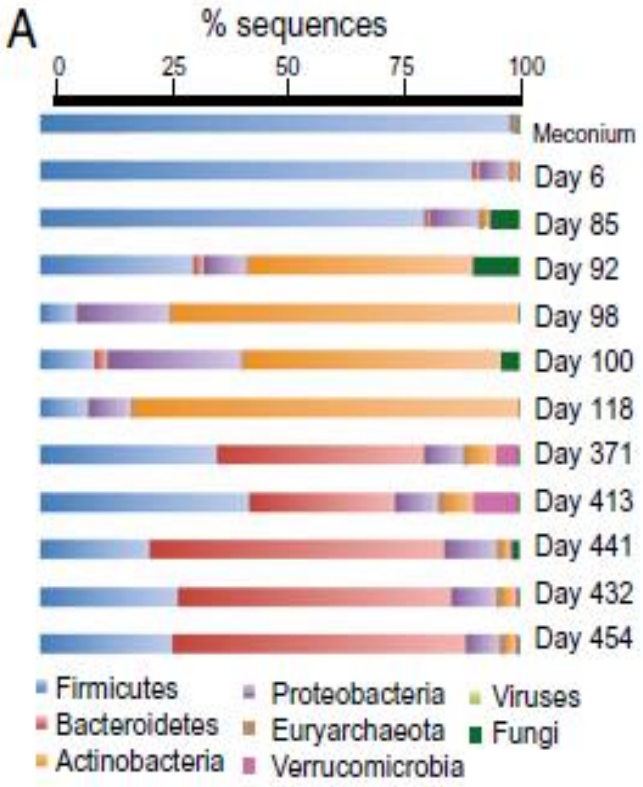
ENTEROPATHOGENIC SYNDROMES

Microbiota in NAFLD



which bacteria are involved?

At birth the human body is sterile



Vaginal microbiota (mother)

Fecal microbiota (mother)

Skin microbiota (mother/father/parents/babysitter)

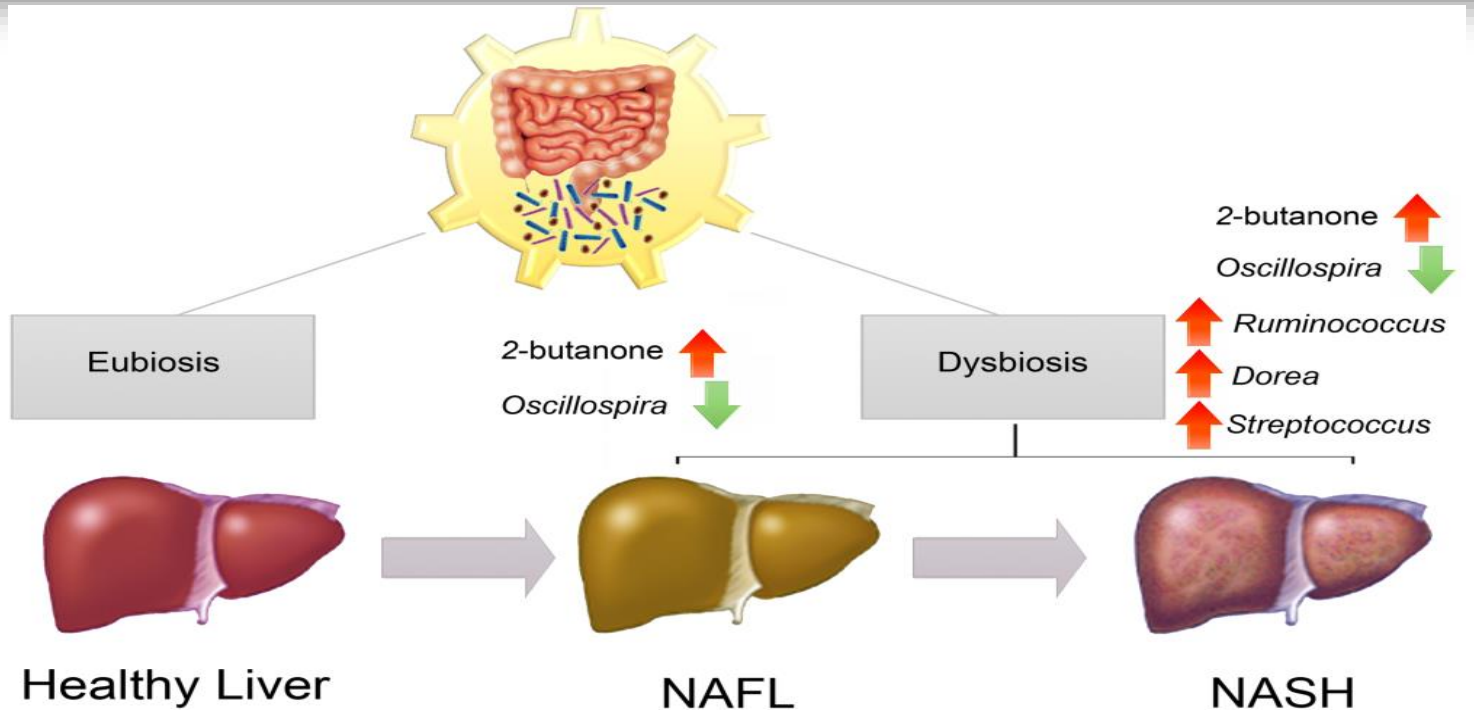
Diet

Ambient

Native CORE microbiota (8-36 months of life)

Gut Microbiota Profiling of Pediatric Nonalcoholic Fatty Liver Disease and Obese Patients Unveiled by an Integrated Meta-omics-Based Approach

Federica Del Chierico,[1*] Valerio Nobili,[2,3*] Pamela Vernocchi,[1] Alessandra Russo,[1] Cristiano De Stefanis,[3] Daniela Gnani,[3] Cesare Furlanello,[4] Alessandro Zandonà,[4] Paola Paci,[5,6] Giorgio Capuani,[7] Bruno Dallapiccola,[8] Alfredo Miccheli,[7] Anna Alisi,[3] and Lorenza Putignani[1,9]



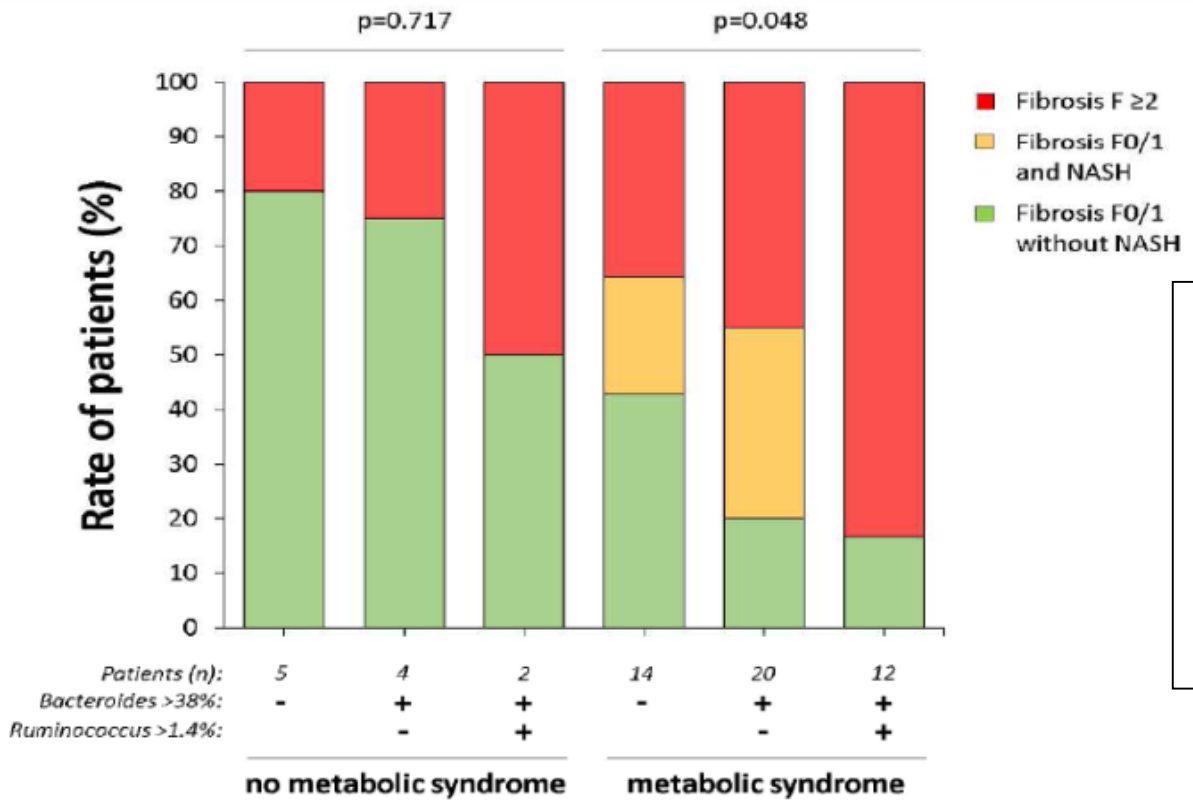
- The combination of a low abundance of *Oscillospira* with high levels of 2-butanone may be a specific intestinal profile for liver steatosis in children.
- The high relative abundance of Lachnospiraceae, *Ruminococcus*, and *Dorea* observed in pediatric patients with NASH suggests that changes in the gut microbiota are associated with disease severity.

HEPATOLOGY, VOL. 00, NO. 00, 2016

The Severity of Nonalcoholic Fatty Liver Disease Is Associated With Gut Dysbiosis and Shift in the Metabolic Function of the Gut Microbiota

Jérôme Boursier,[1,2] Olaf Mueller,[3] Matthieu Barret,[4] Mariana Machado,[5] Lionel Fizanne,[2] Felix Araujo-Perez,[6] Cynthia D. Guy,[7] Patrick C. Seed,[3,6] John F. Rawls,[3] Lawrence A. David,[3] Gilles Hunault,[2] Frédéric Oberti,[1,2] Paul Calès,[1,2] and Anna Mae Diehl[5]

HEPATOLOGY, VOL. 63, NO. 3, 2016

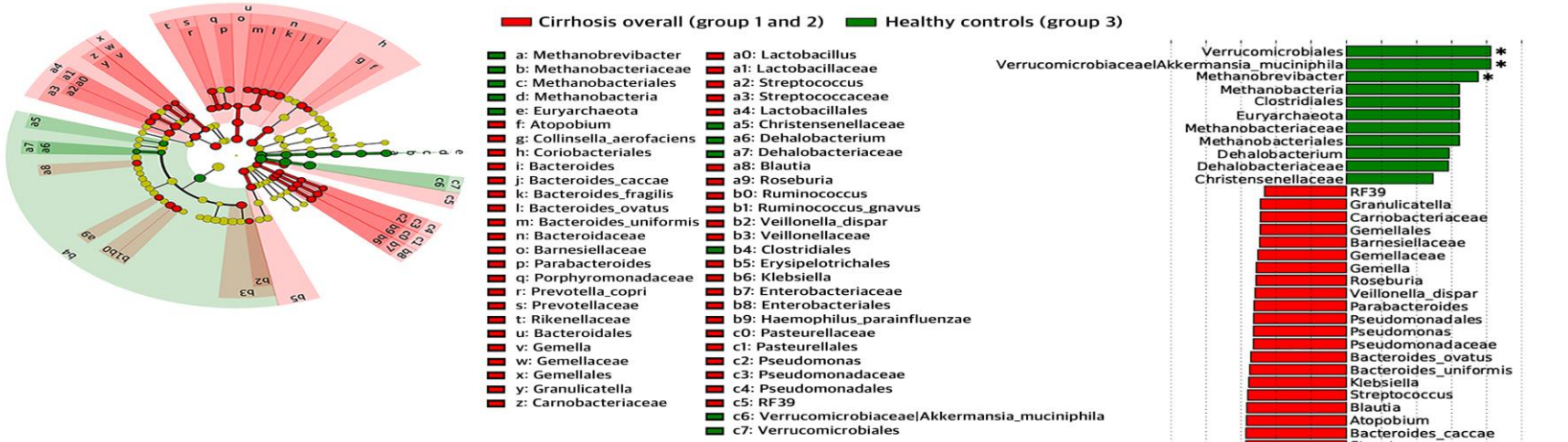


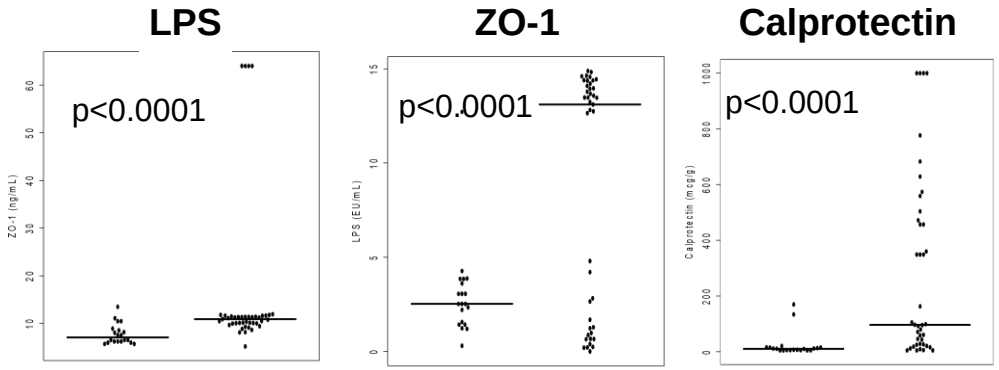
Bacteroides abundance was independently associated with NASH and Ruminococcus with F≥2 fibrosis

Stratification according to the abundance of these 2 bacteria generated 3 patient subgroups with increasing severity of NAFLD lesions

Hepatocellular Carcinoma Is Associated With Gut Microbiota Profile and Inflammation in Nonalcoholic Fatty Liver Disease

Francesca Romana Ponziani ,[1,*] Sherrie Bhoori,[2] Chiara Castelli,[3] Lorenza Putignani,[4,5] Licia Rivoltini,[3] Federica Del Chierico,[4] Maurizio Sanguinetti,[6] Daniele Morelli,[7] Francesco Paroni Sterbini,[6] Valentina Petito,[1] Sofia Reddel,[4] Riccardo Calvani,[8] Chiara Camisaschi,[3] Anna Picca,[8] Alessandra Tuccitto,[3] Antonio Gasbarrini,[1] Maurizio Pompili,[1*] and Vincenzo Mazzaferro[2*]





NAFLD cirrhotic patients have increased LPS, intestinal permeability (ZO-1), and calprotectin

↑ *Bacteroides*, Enterobacteriaceae, *Ruminococcus,* and

↓ decreased abundance of *Akkermansia*, *Methanobrevibacter* and *Dehalobacterium* compared to healthy controls.

Ponziani FR et al. Hepatology 2018

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

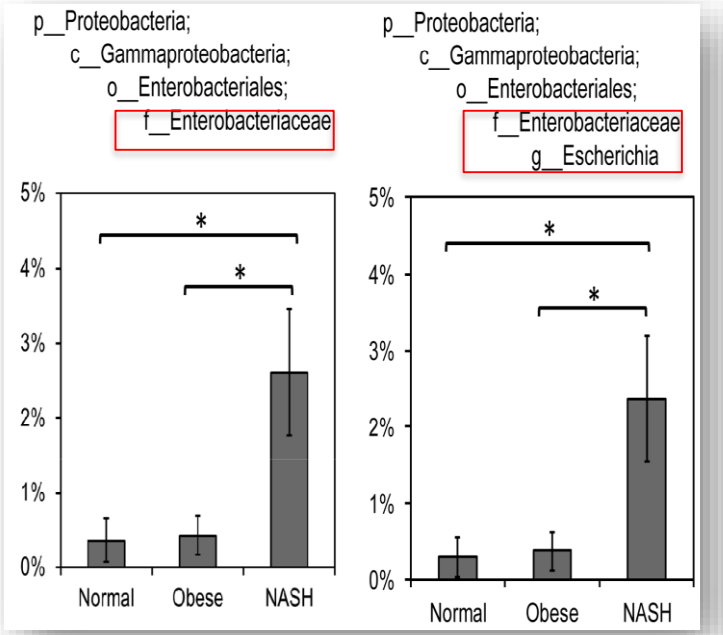
(HEPATOLOGY 2013;57:601-609)

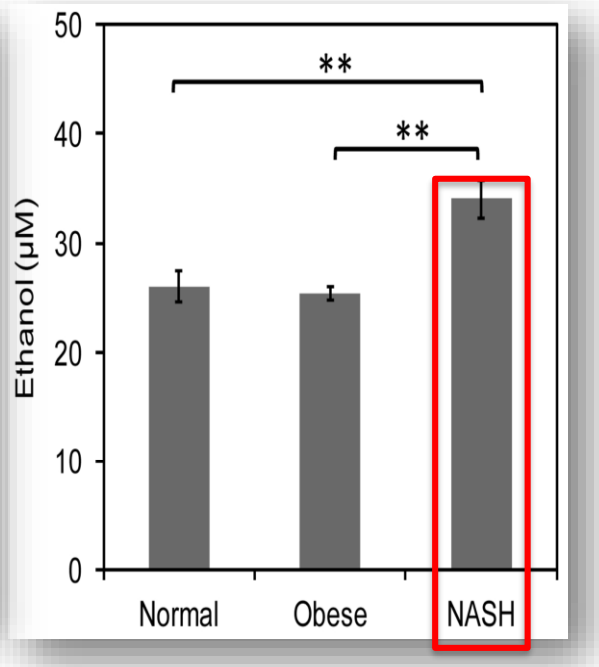
Lixin Zhu,[1] Susan S. Baker,[1] Chelsea Gill,[2] Wensheng Liu,[1] Razan Alkhouri,[1] Robert D. Baker,[1] and Steven R. Gill[2]

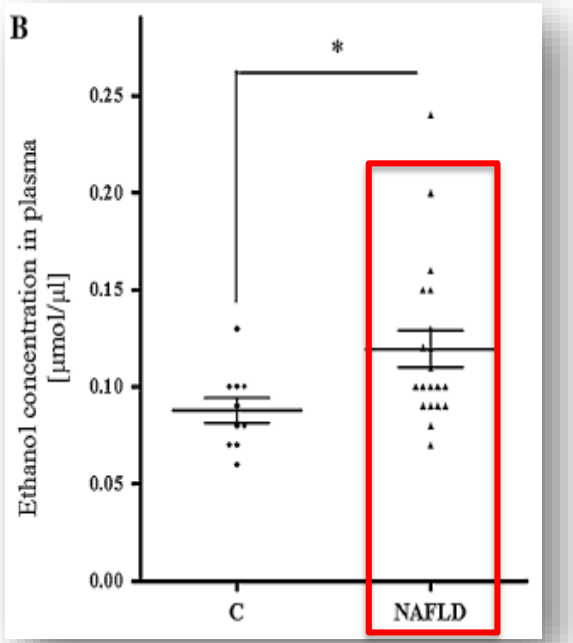
Nutrition, Intestinal Permeability, and Blood Ethanol Levels Are Altered in Patients with Nonalcoholic Fatty Liver Disease (NAFLD)

Dig Dis Sci (2012) 57:1932–1941

Valentina Volynets · Markus A. Küper · Stefan Strahl · Ina B. Maier · Astrid Spruss · Sabine Wagnerberger · Alfred Königsrainer · Stephan C. Bischoff · Ina Bergheim

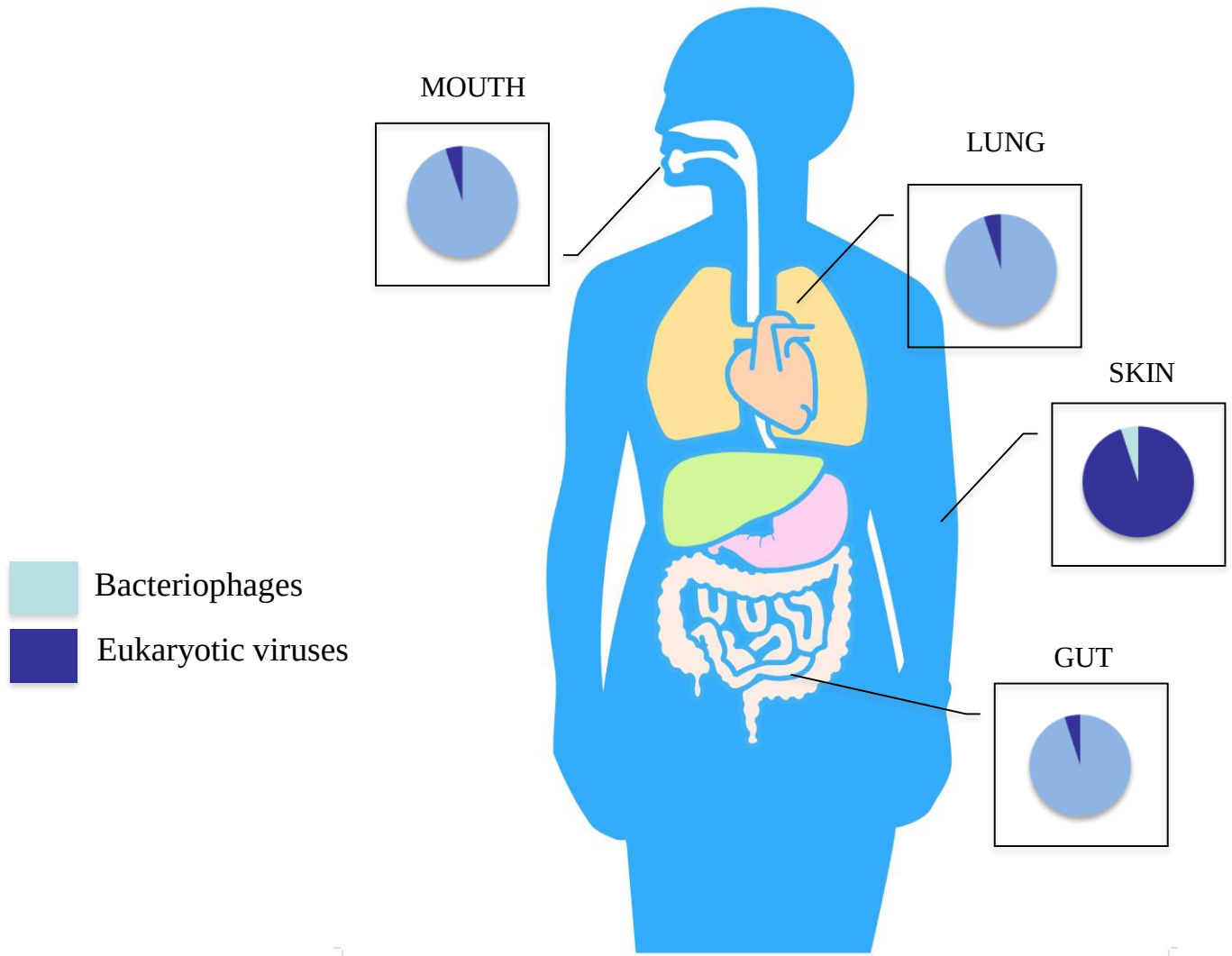






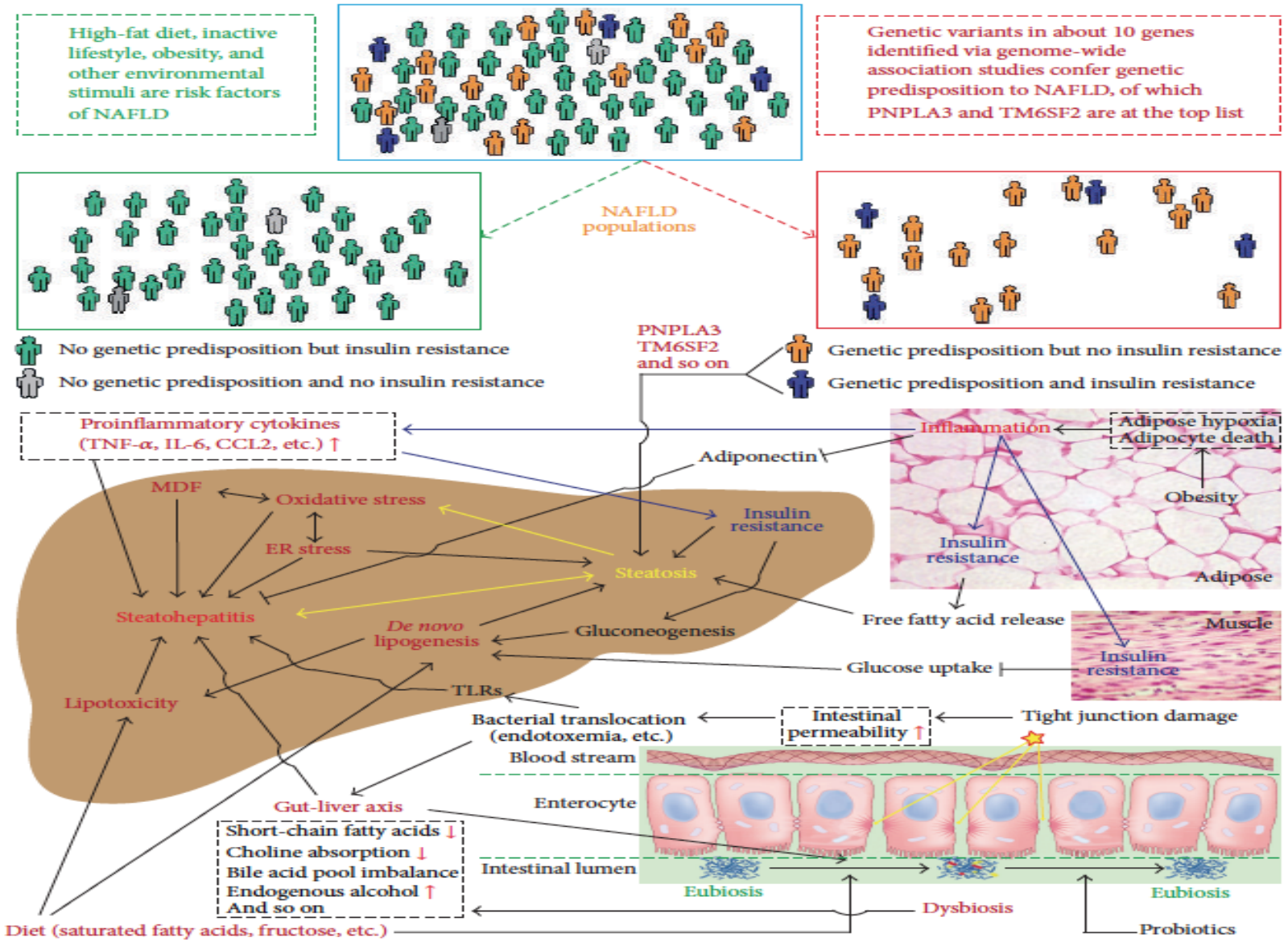
The increased abundance of alcohol-producing bacteria in NASH microbiomes, elevated blood-ethanol concentration in NASH patients, and the well-established role of alcohol metabolism in oxidative stress and, consequently, liver inflammation suggest a role for alcohol-producing microbiota in the pathogenesis of NASH

GUT - VIROME



Bruno R. et al. Beyond the gut bacterial microbiota: The gut virome - Journal of Medical Virology 88:1467–1472 (2016)

Overview at the pathogenesis of nonalcoholic fatty liver disease (NAFLD)



(+ gut microbiota)...

Is NAFLD also an "infectious" disease?