

# Gut Microbiota – Academic Overview

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# Disclosures

Research Support: NGM Biopharmaceuticals

Journal Scientific Advisor: HOST Therabiomics  
Ferring Pharmaceuticals  
Intercept Pharmaceuticals

# Intestinal homeostasis

Lumen

Outer mucus layer

Inner mucus layer

Bacteria

Antimicrobial proteins

Tight junction

$\gamma\delta$  intraepithelial lymphocyte

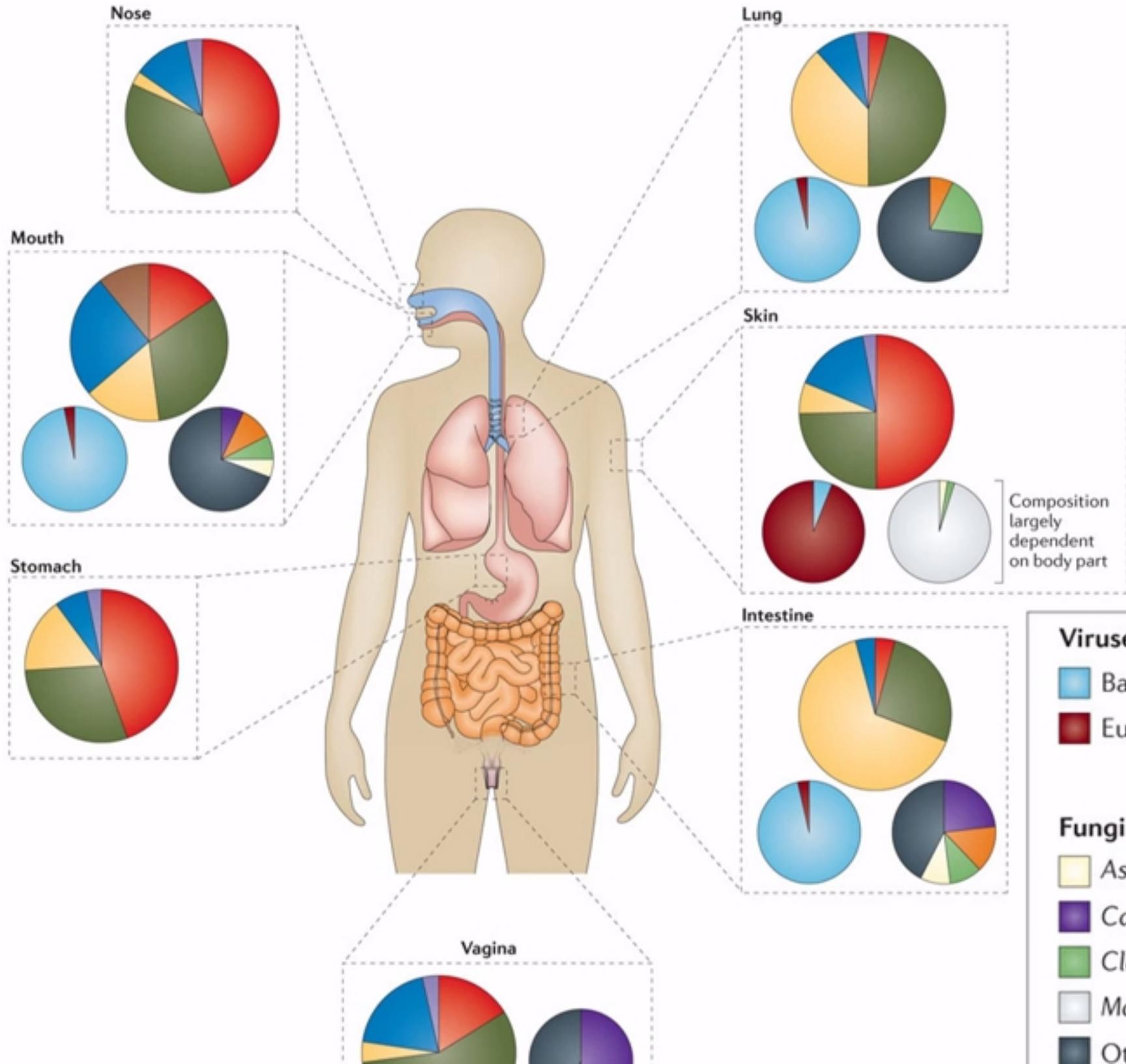
Transcytosis

IgA

Phagocytosis of invasive bacteria

Epithelial cell

IgA-secreting



# Human microbiome

## Benefits

## Risk factor

Development of the immune system

Chronic inflammatory diseases

Nutrient metabolism

Cancer

Bile acids

Sepsis

Complex carbohydrates

Metabolic diseases

Vitamins

Neurologic diseases

Liver diseases

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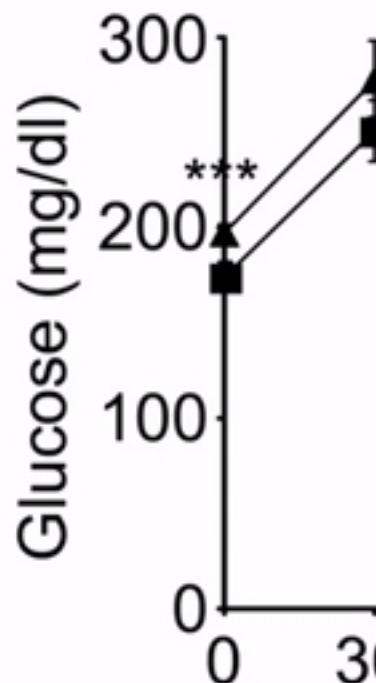
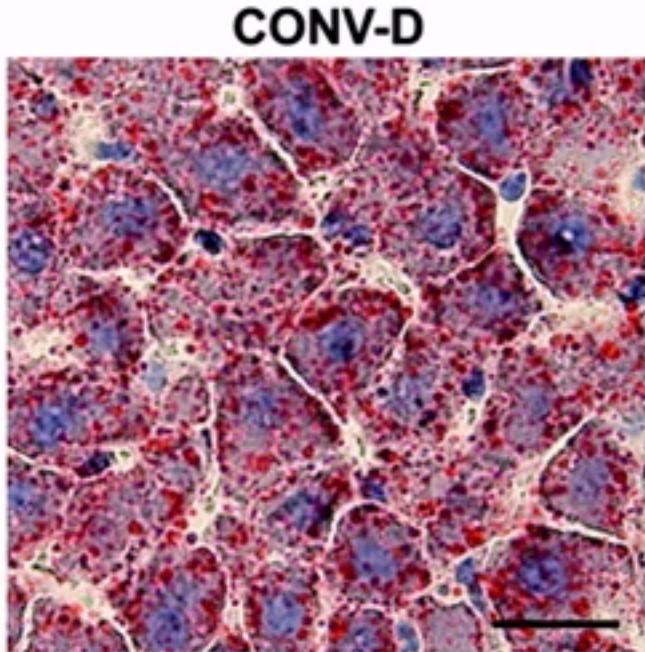
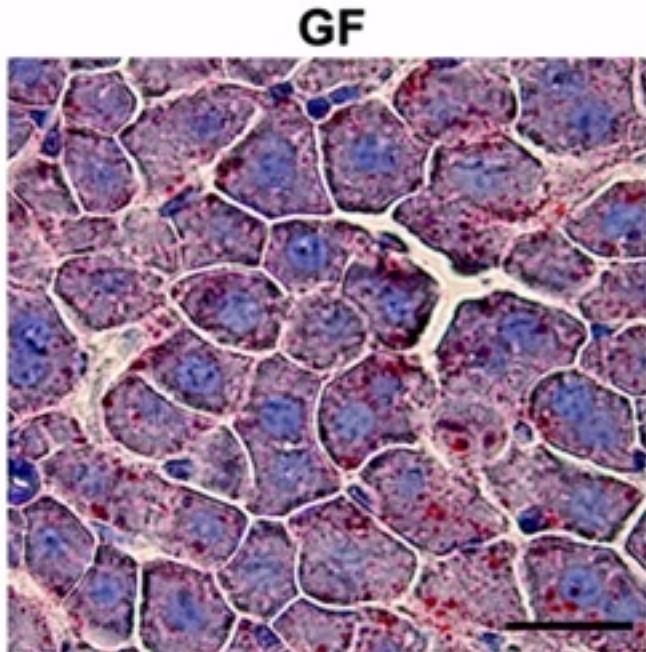
Colonization resistance against pathogens

Regulation of xenobiotic metabolism

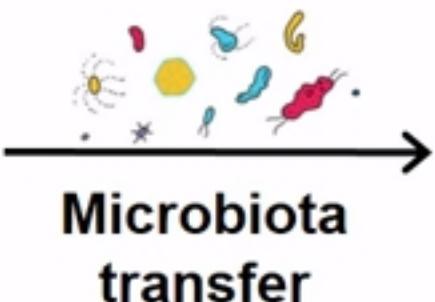
# **Does the gut microbiota contribute to NAFLD?**

# The microbiota contribute to body fat composition and hepatic steatosis in m

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ΔV-R

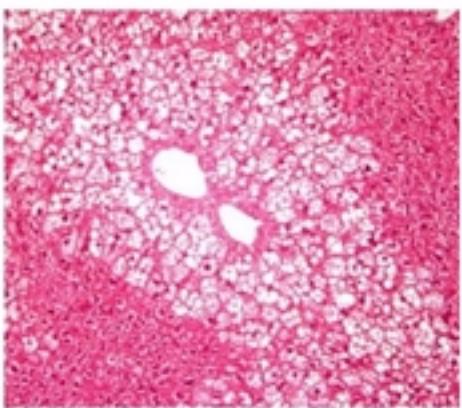


# NAFL and NASH are transmissible in mice

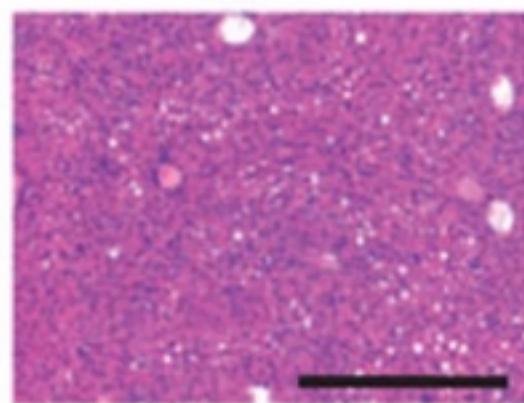


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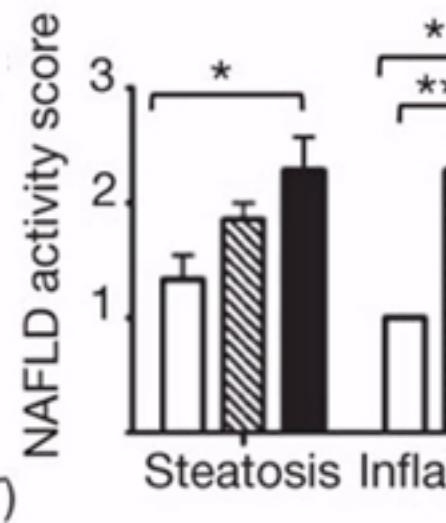
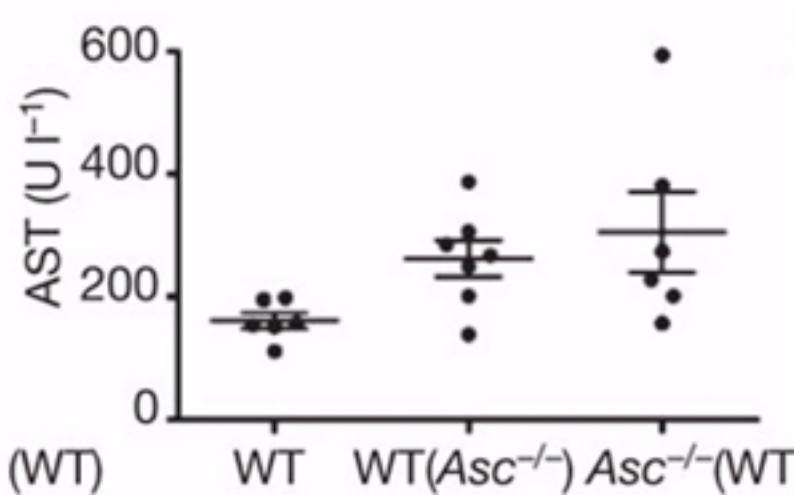
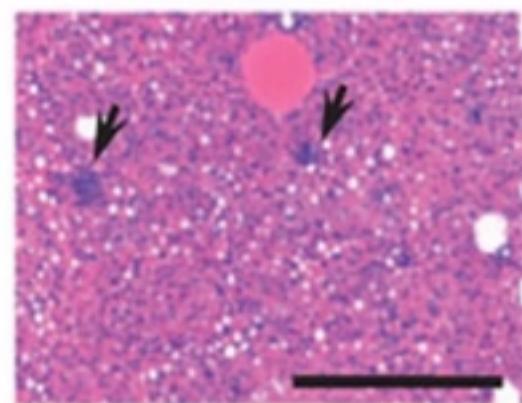
Obesity susceptible mouse



WT

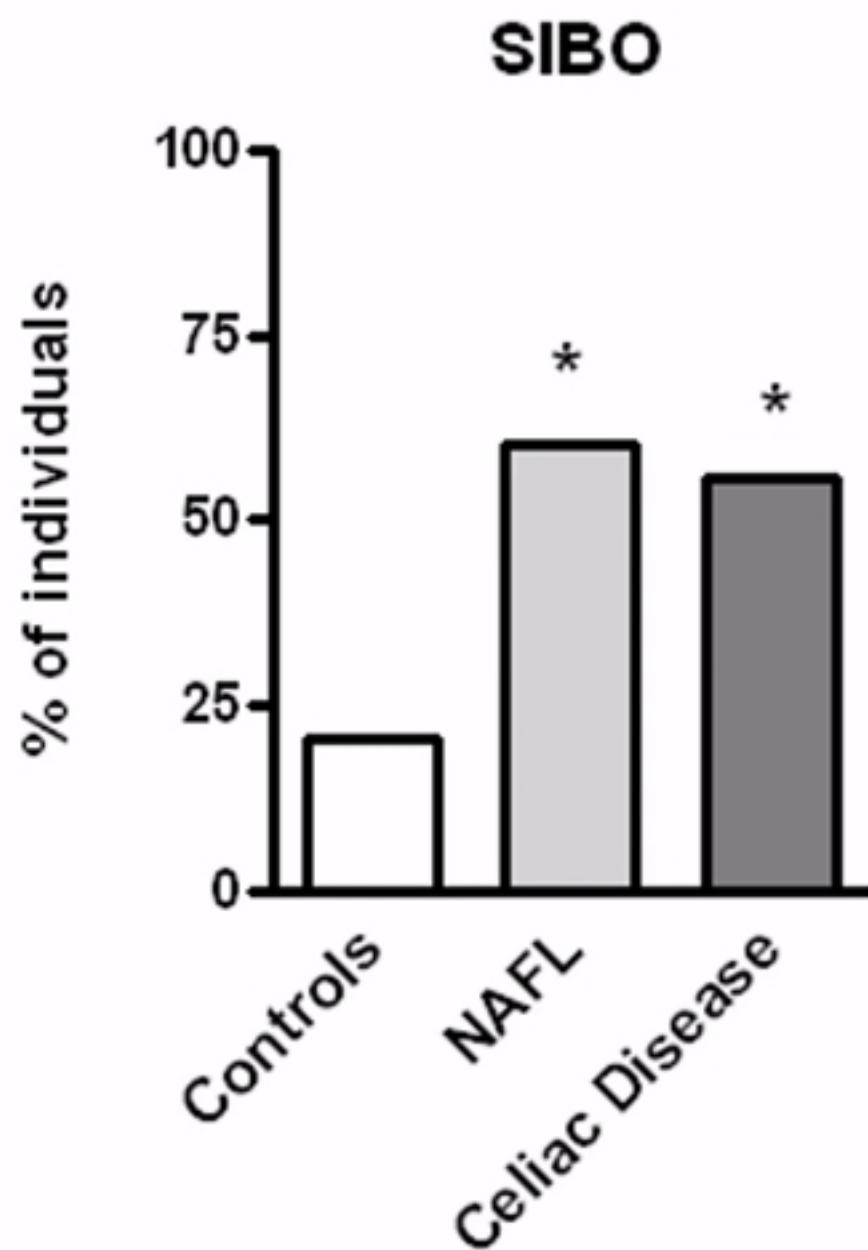


WT( $Asc^{-/-}$ )

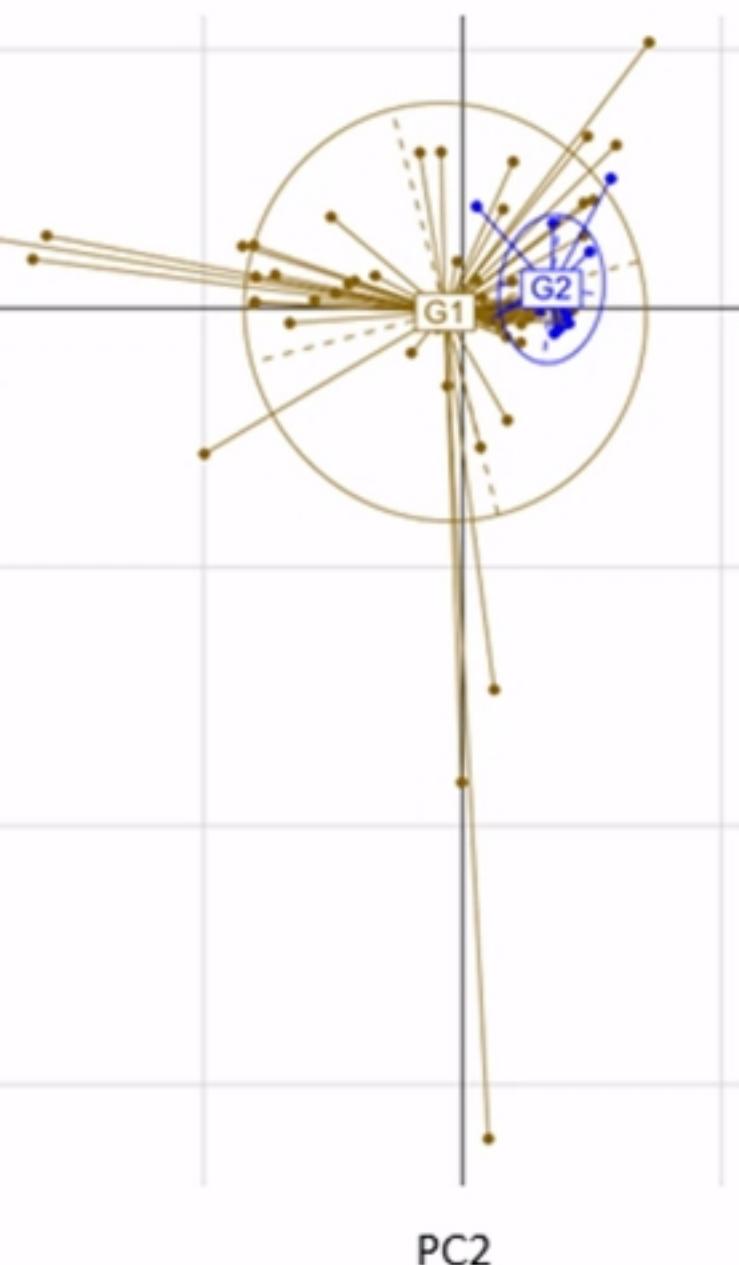


# **How does the gut microbiome change in patients with NAFLD?**

# Intestinal bacterial overgrowth in patients with



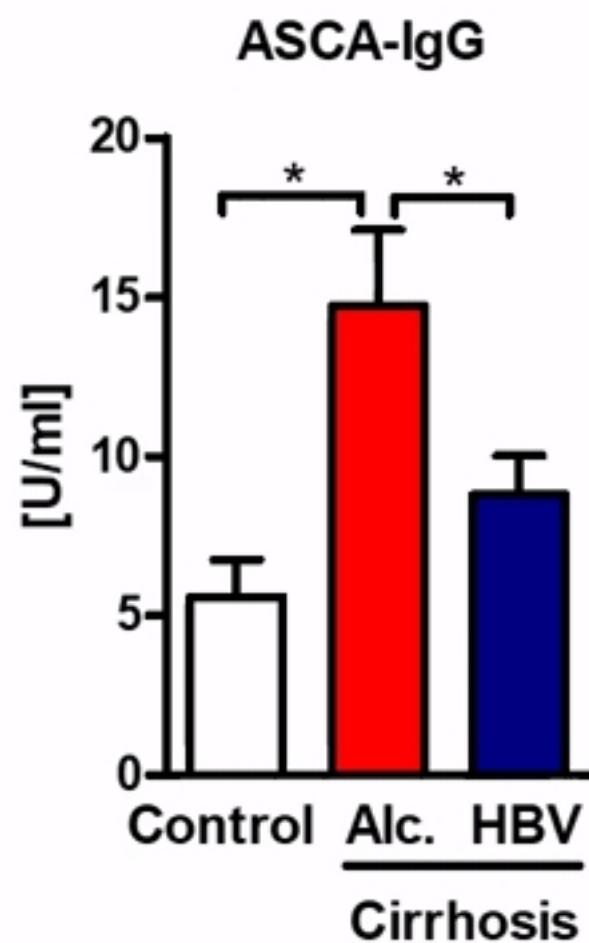
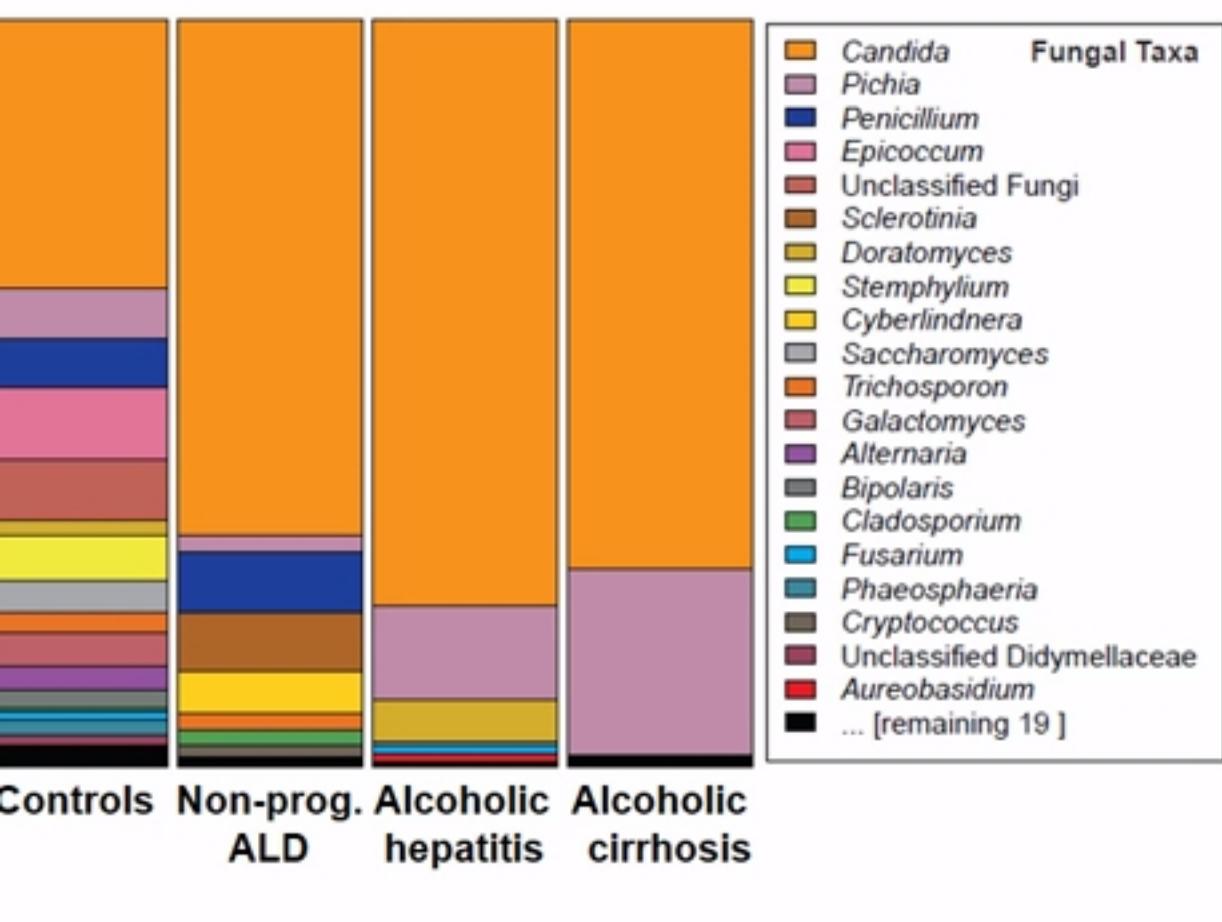
# Economic composition of metagenomes between mild/moderate NAFLD versus advanced fibrosis



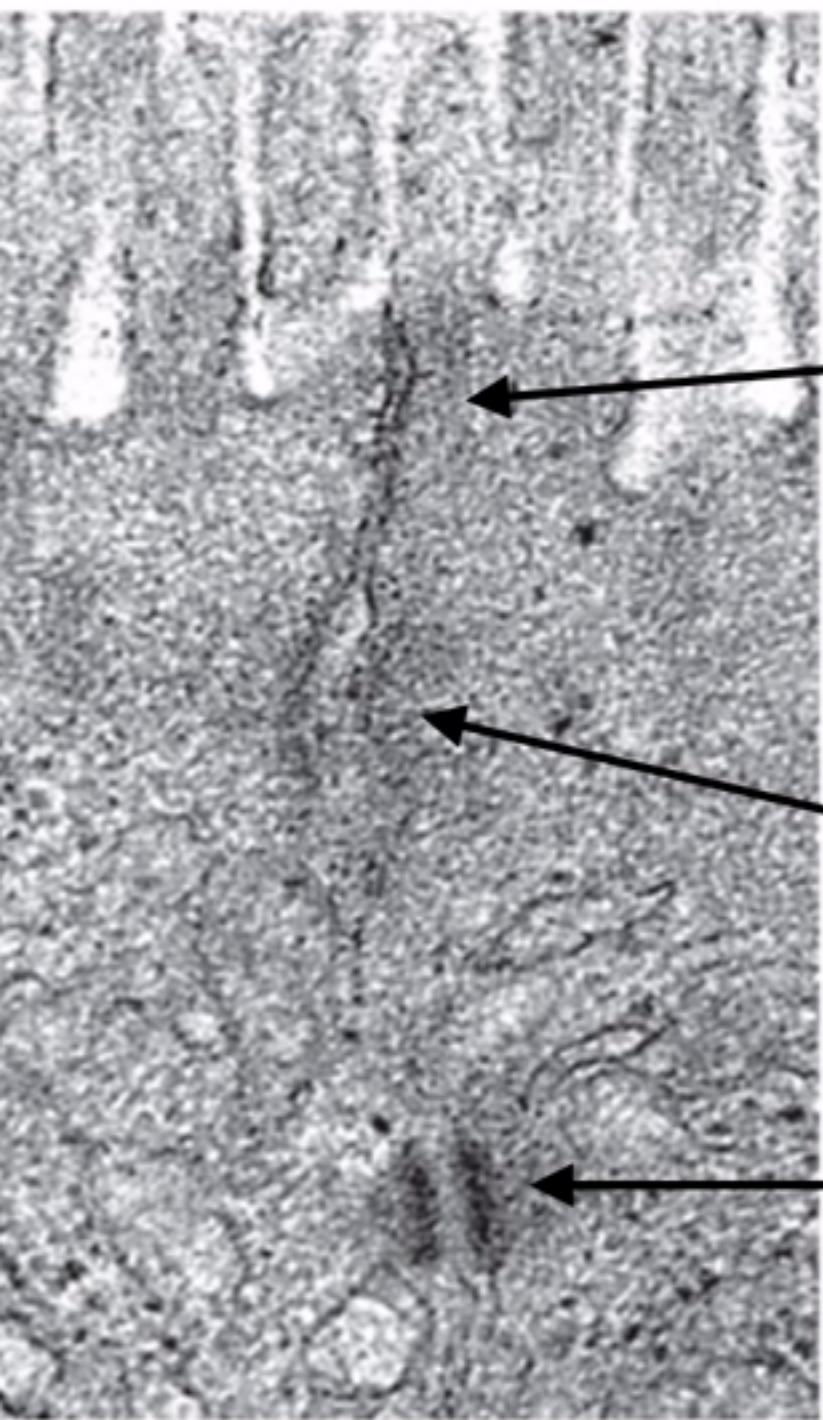
## Species

Species	G1 Median	M
<i>Eubacterium rectale</i>	2.56%	0
<i>Faecalibacterium prausnitzii</i>	1.63%	0
<i>Escherichia coli</i>	0.29%	0
<i>Ruminococcus obeum</i>		0
CAG:39	0.06%	0
<i>Ruminococcus obeum</i>	0.29%	0

# Fungal dysbiosis in patients with alcohol abuse



# Intestinal epithelial cells as barrier



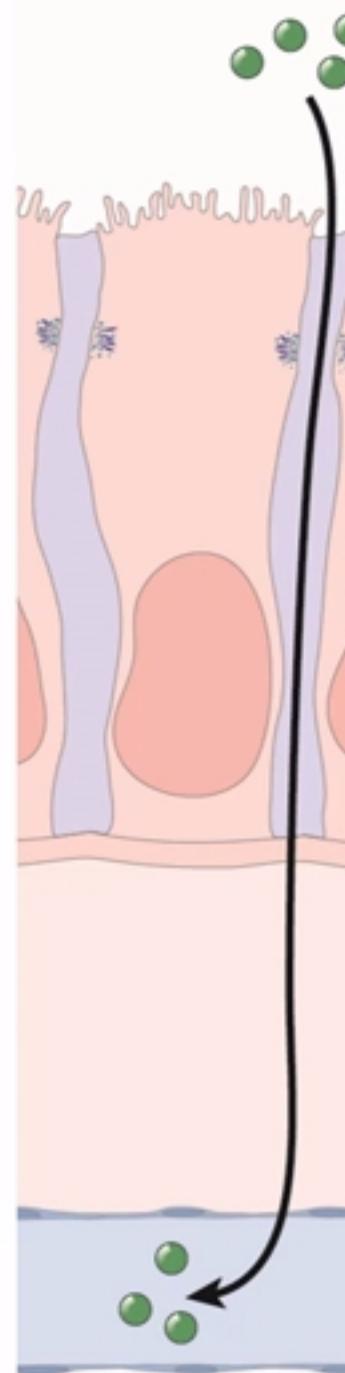
**Tight junction**

Claudin  
Occludin  
Zonula occludens  
Junctional adhesion  
molecule (JAM)

**Adherens junction**

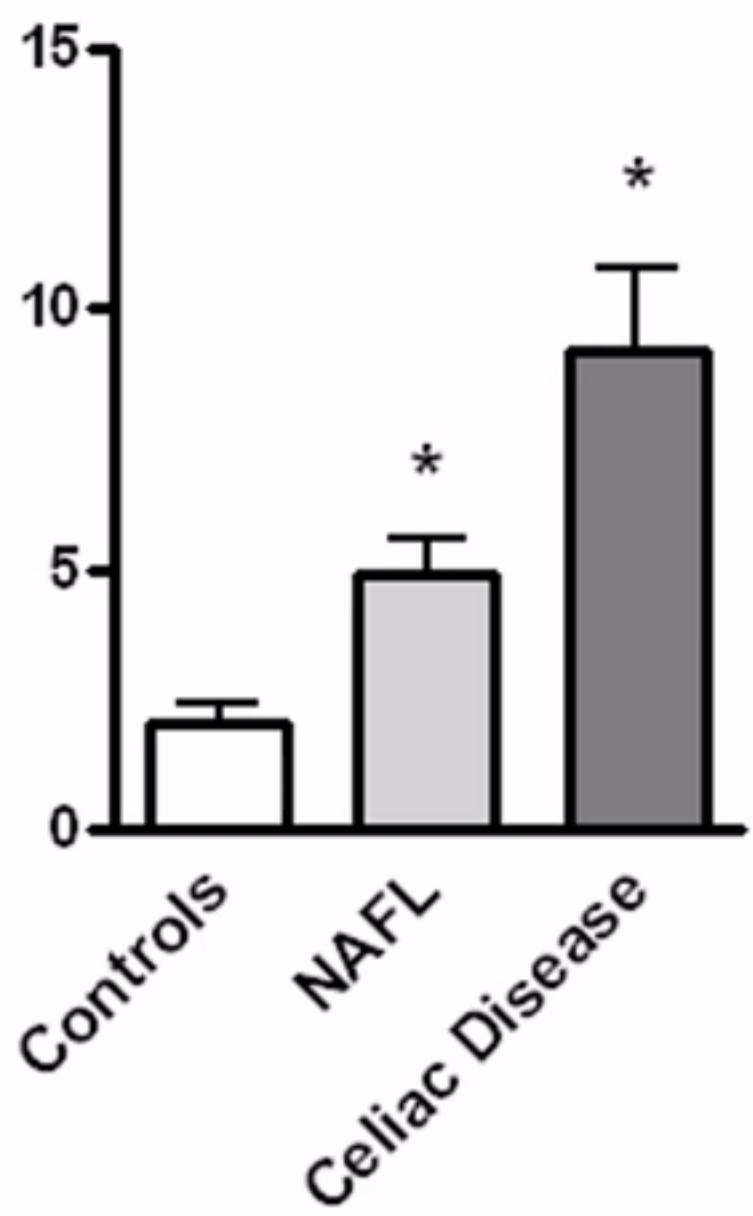
E-cadherin

**Desmosome**

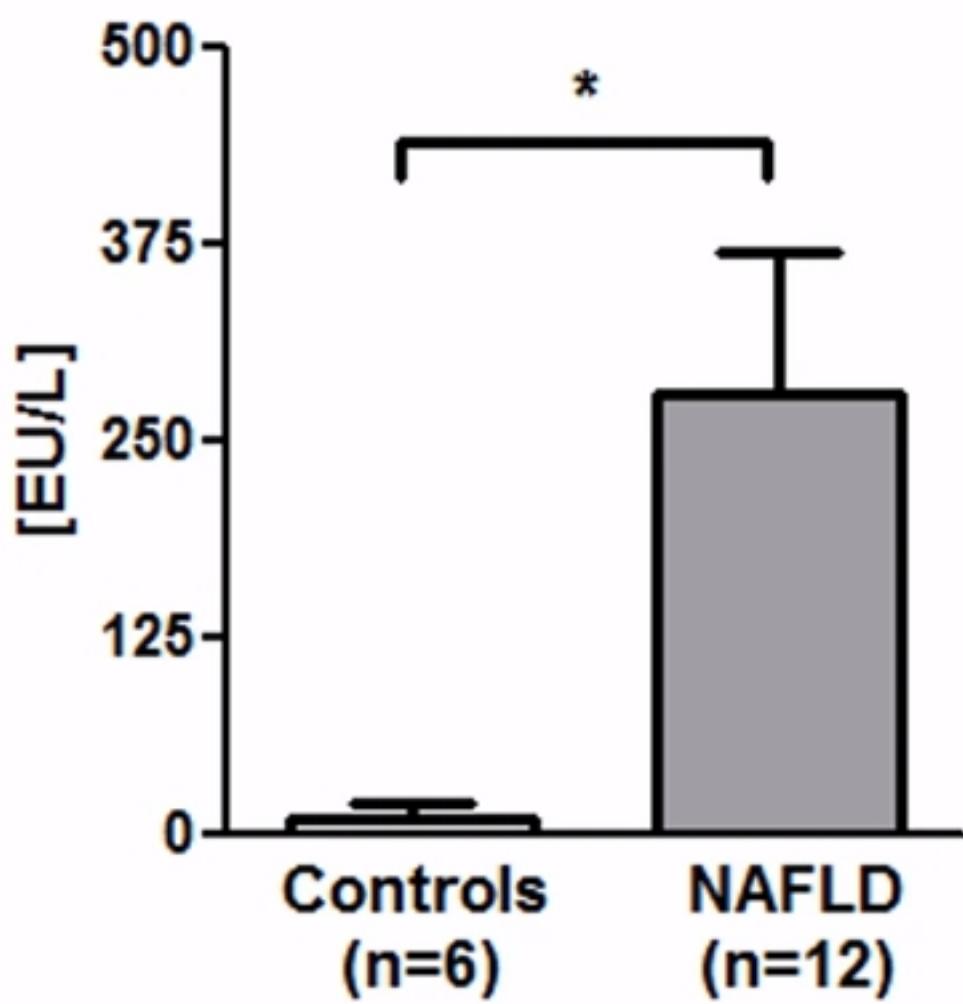


# Intestinal barrier dysfunction in patients with NAFLD

## Intestinal Permeability

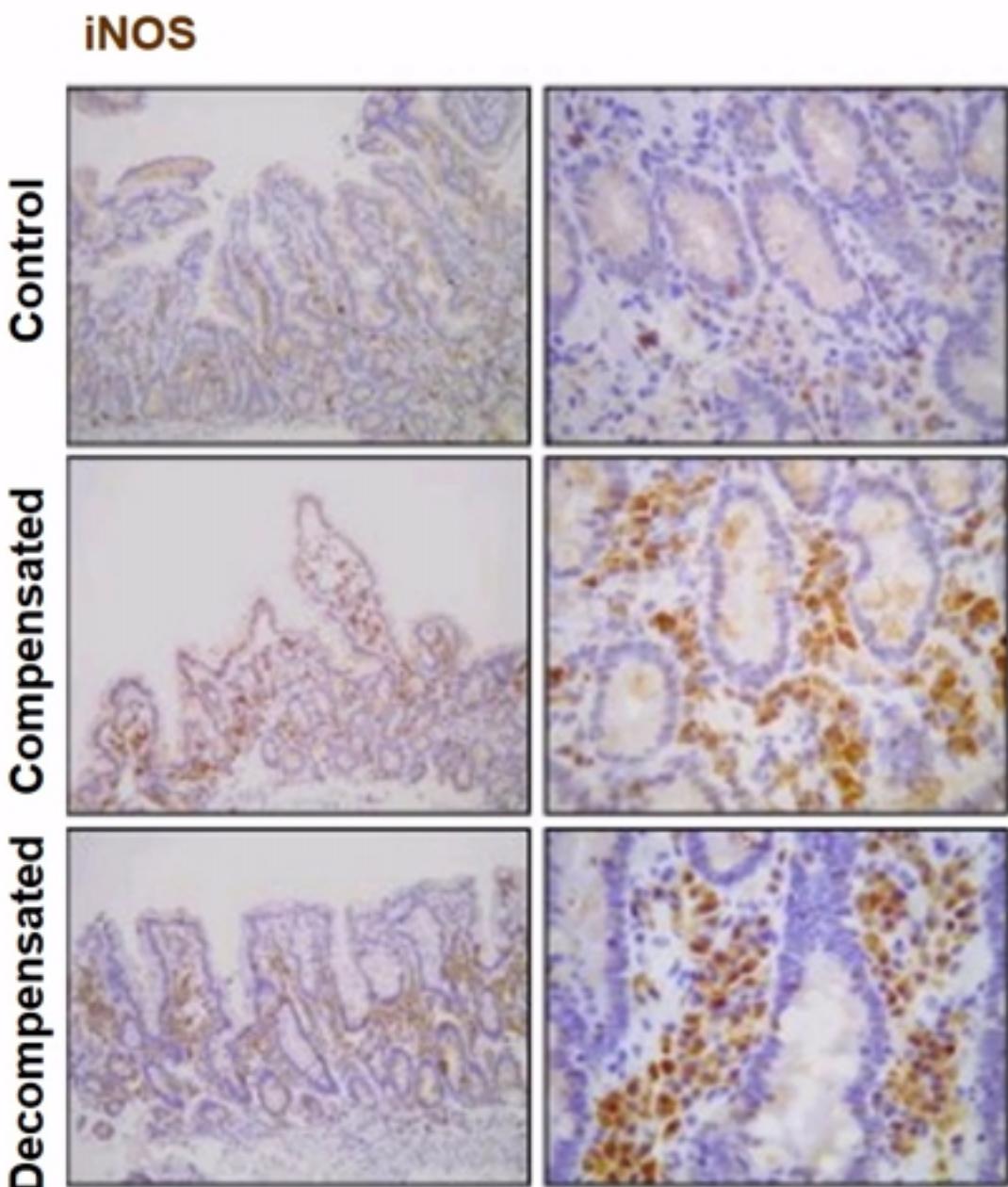
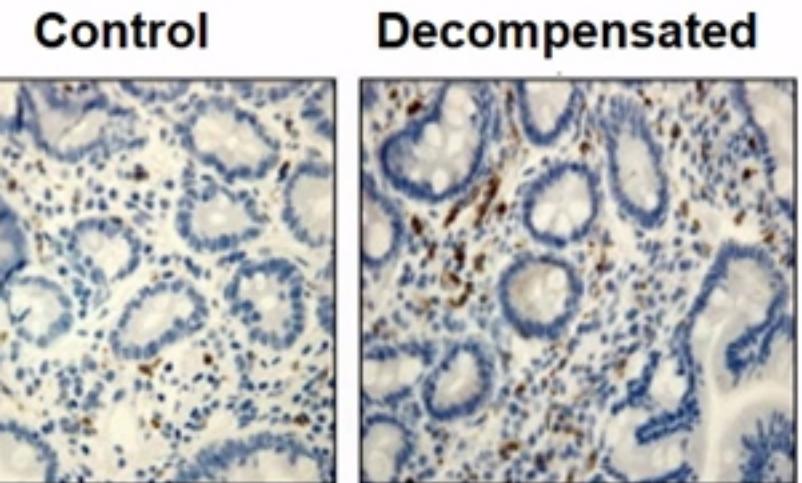


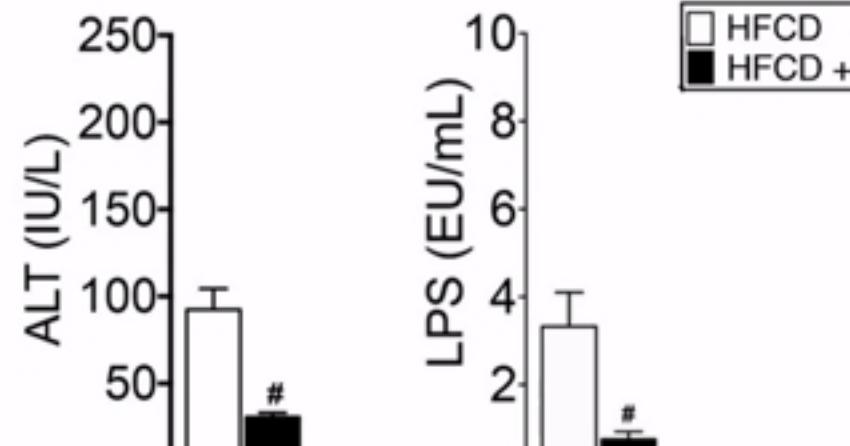
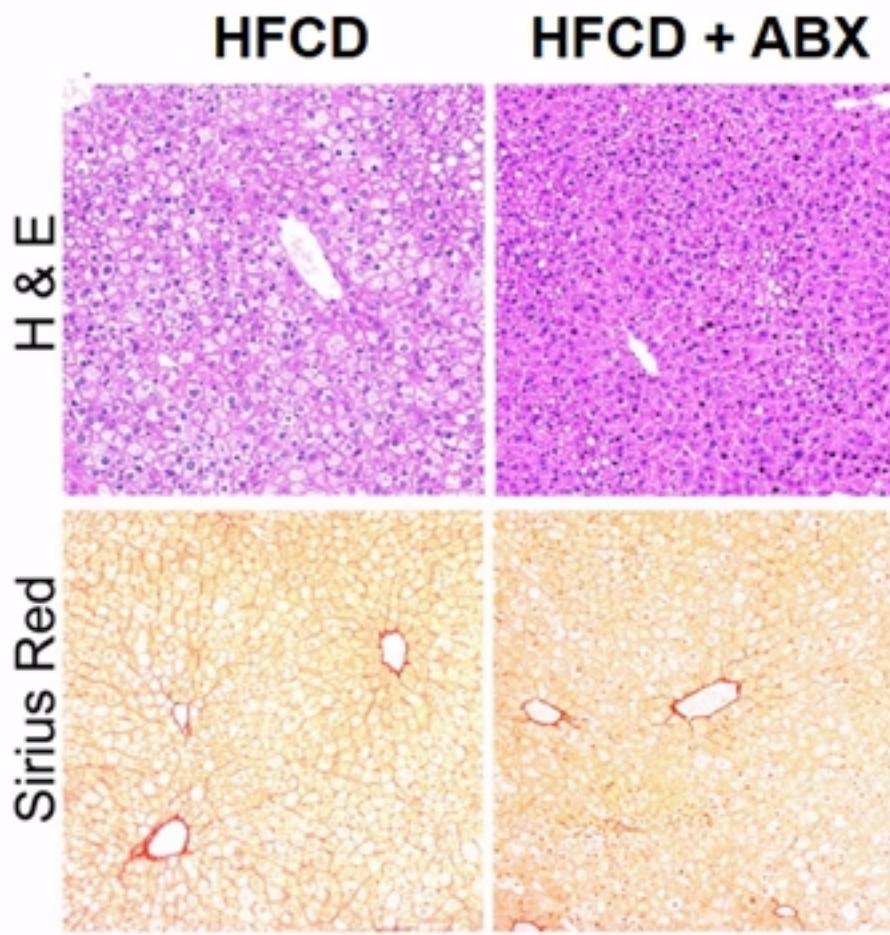
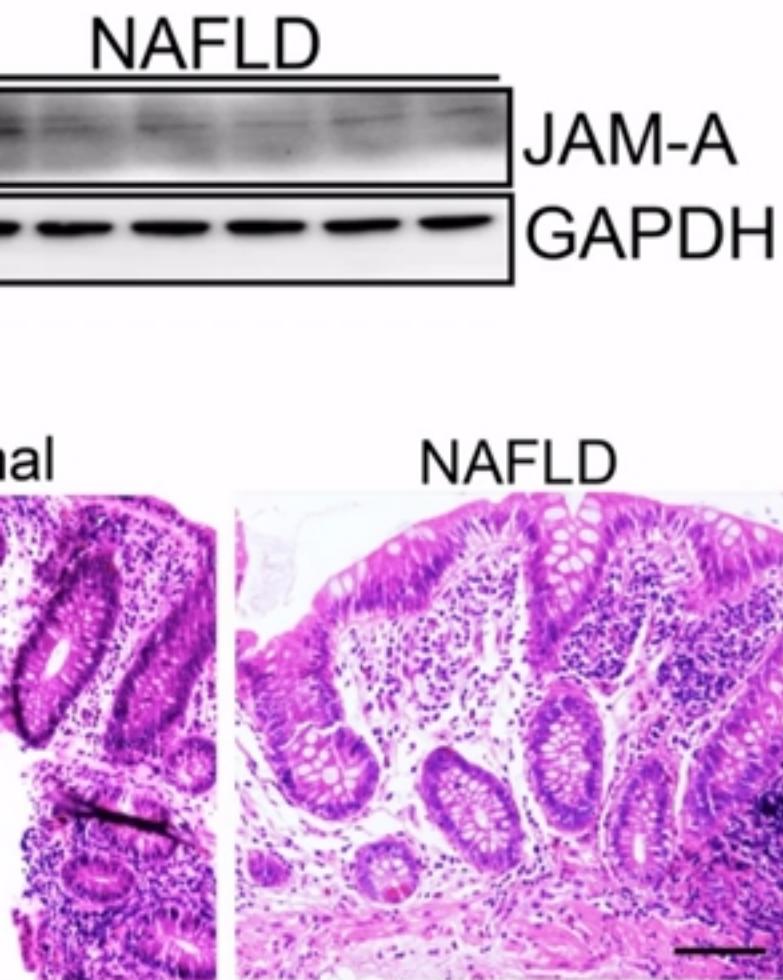
## Plasma endotoxin



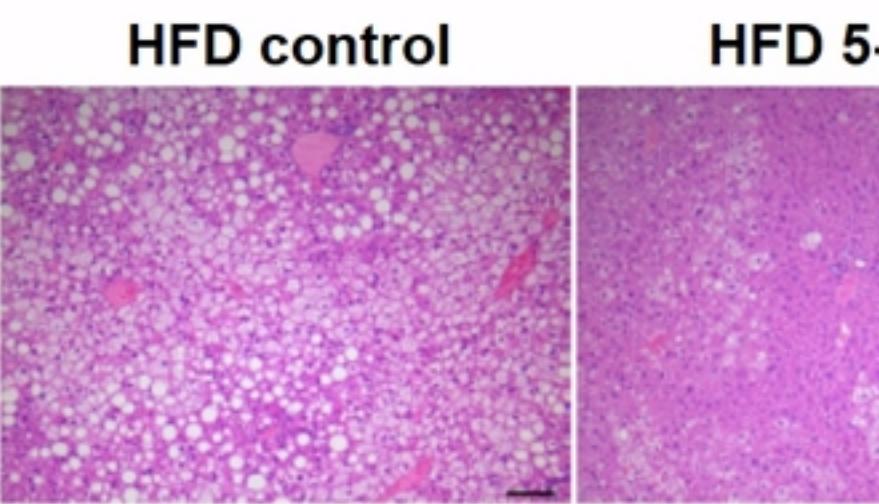
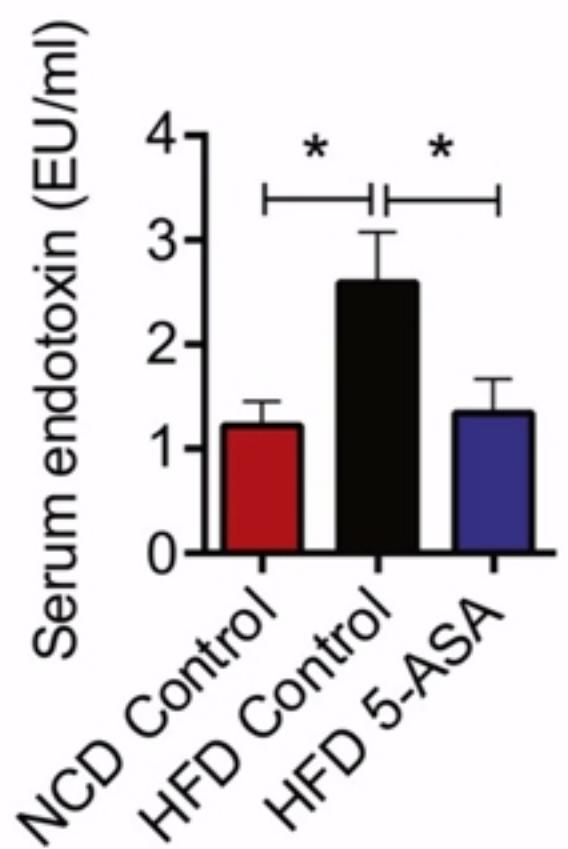
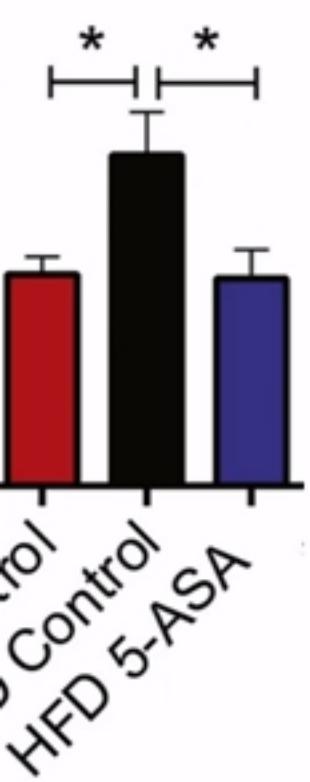
**Is there a link between intestinal dysbiosis and gut barrier dysfunction?**

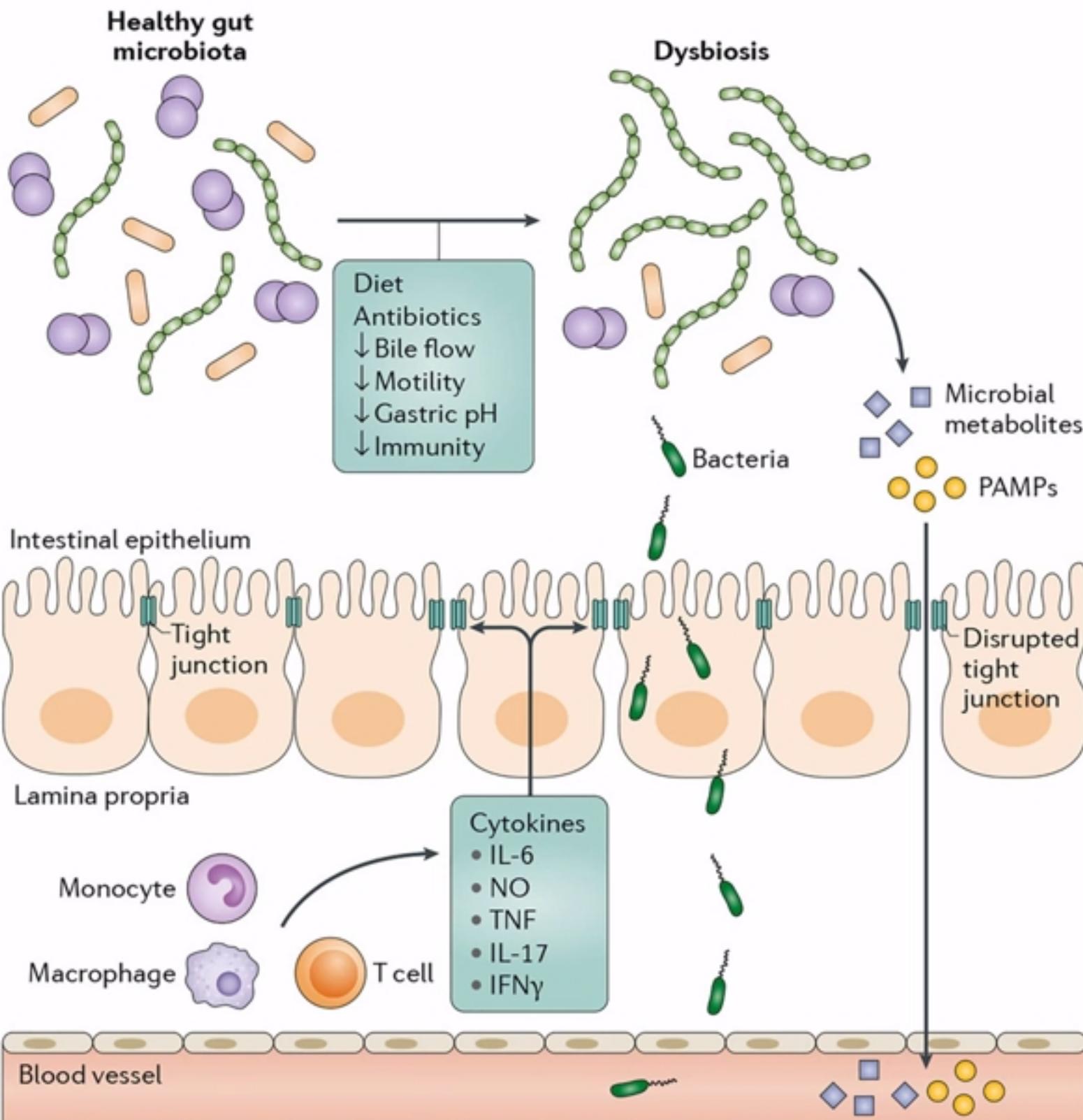
# Activated intestinal macrophages in patients w/ cirrhosis release nitric oxide





# Reducing intestinal inflammation improves NAFL

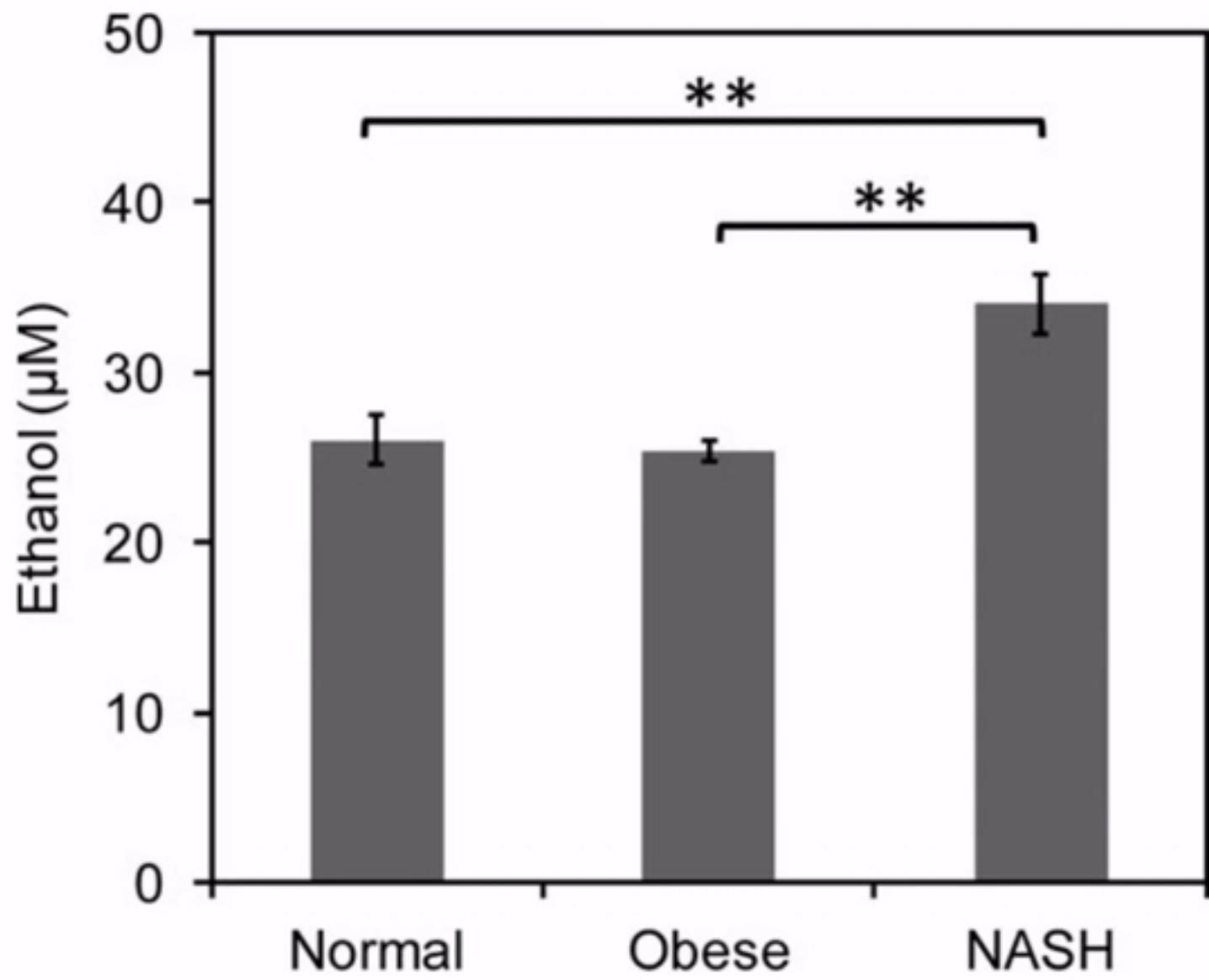




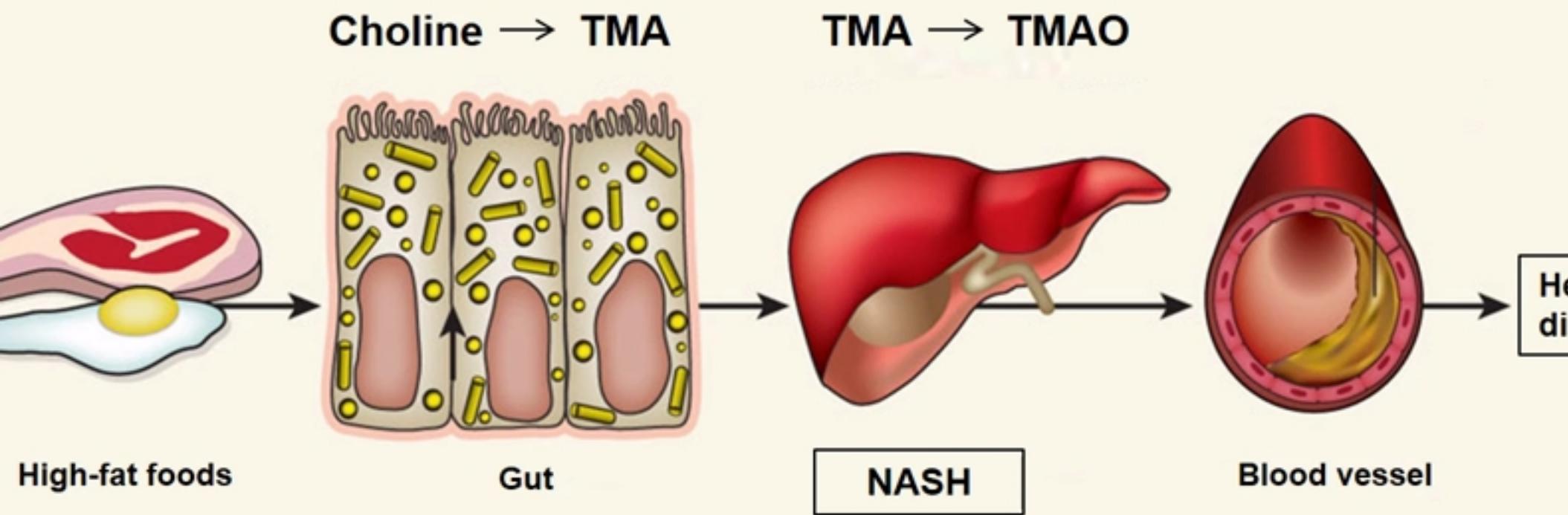
**TJ disrupt**  
**Cyp2E1**  
**HNF4a**  
**Circadian genes**  
**Nitric oxide**  
**miRNAs**  
**Systemic inflammation**

## **How does the gut microbiota contribute to NAFLD?**

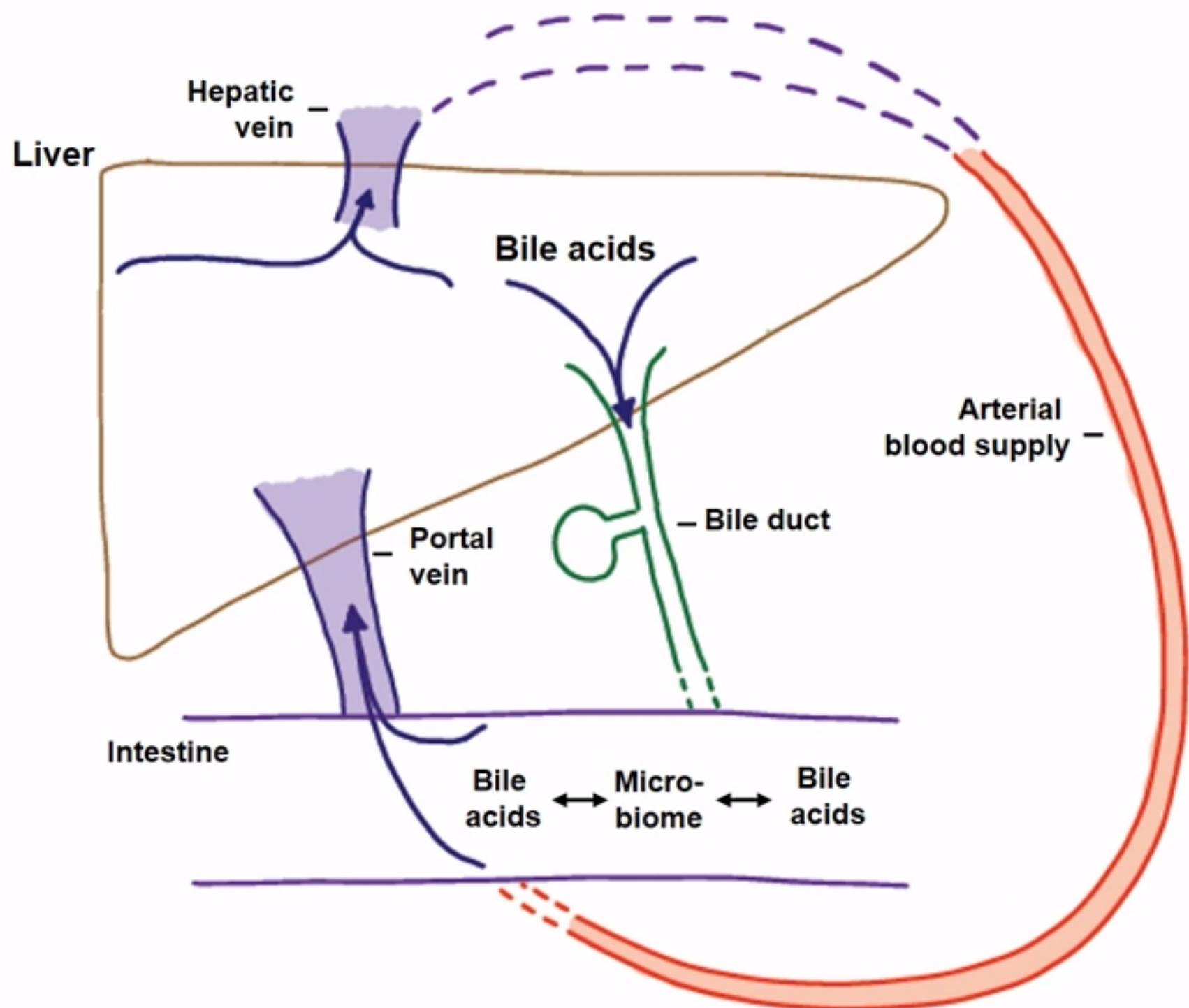
# Ethanol production in pediatric obese and NASH pa



# Dysbiosis Reduces Choline availability



# Intestinal communication between gut and liver via

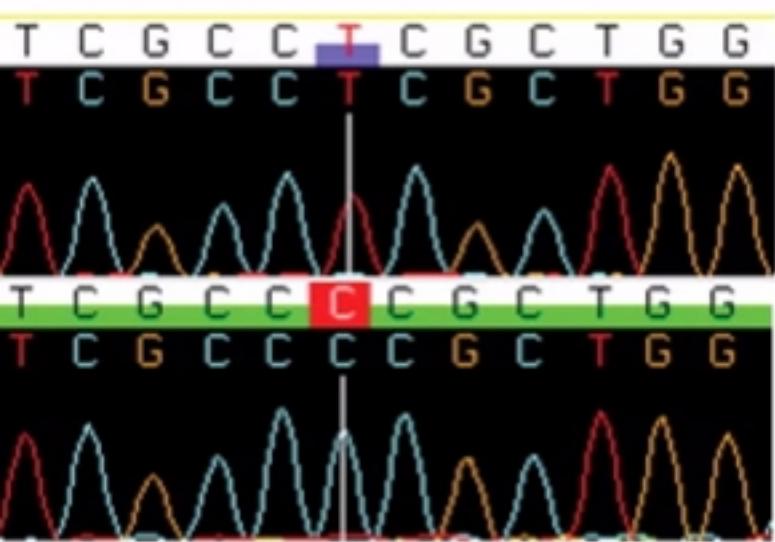


# **Does gastric acid suppression affect the progression of NAFLD?**

# Gastric acid secretion

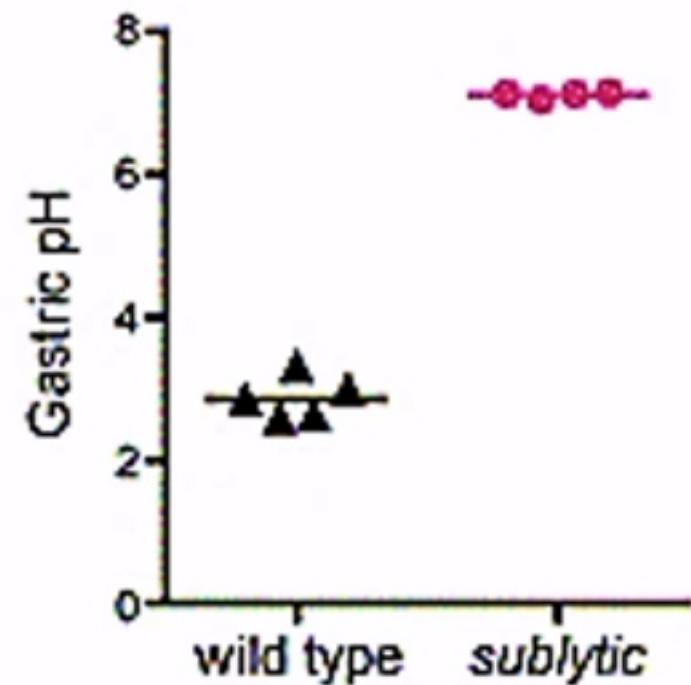
- Gastric acid kills ingested microbes
- Proton pump inhibitors (PPIs) decrease daily gastric acid production by 90%
- 6-15% of the general population is on acid suppression therapy
  - Hvid-Jensen F, Clin Epidemiol 2013
  - Johansen ME, JAMA Intern Med 2011
- 40% of obese patients and 67-72% of patients with cirrhosis are using acid reducing medication
  - Mello M, Dig Dis Sci 2012; Merli M, Liver Int 2015; Ness-Jensen E, Am J Gastro 2013

# *ATP4a<sup>SI/SI</sup>* mice lacking gastric acid

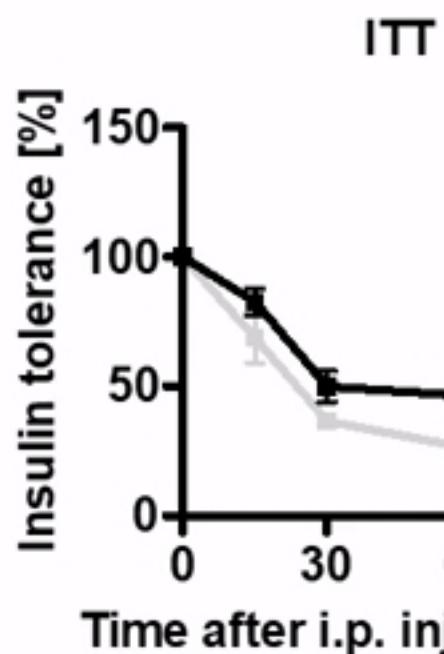
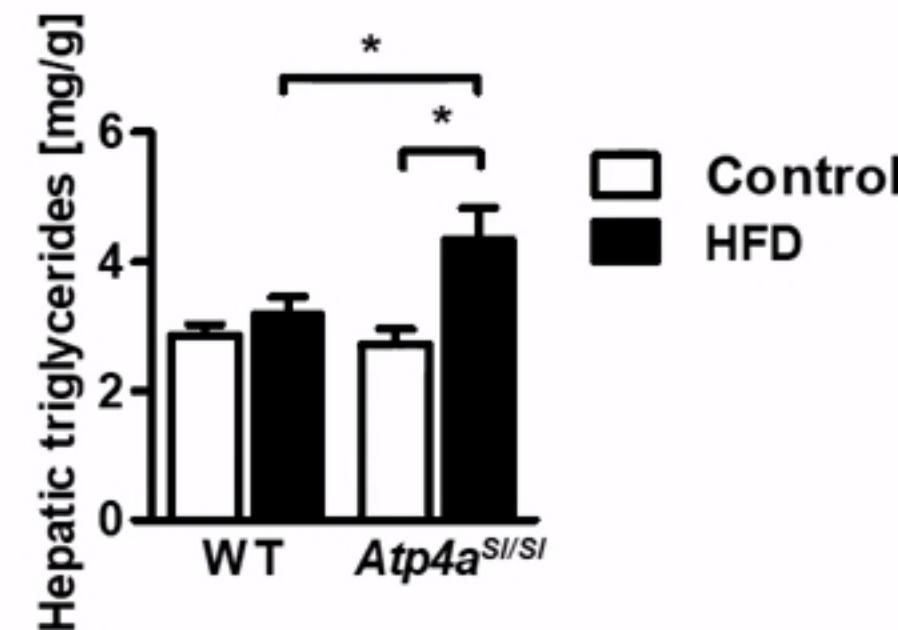
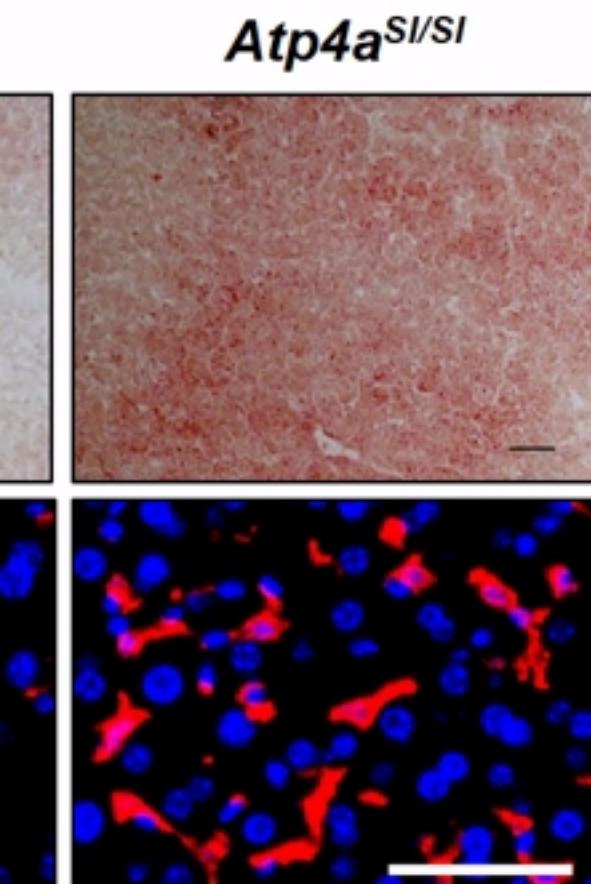


C57BL/6J

*sublytic*

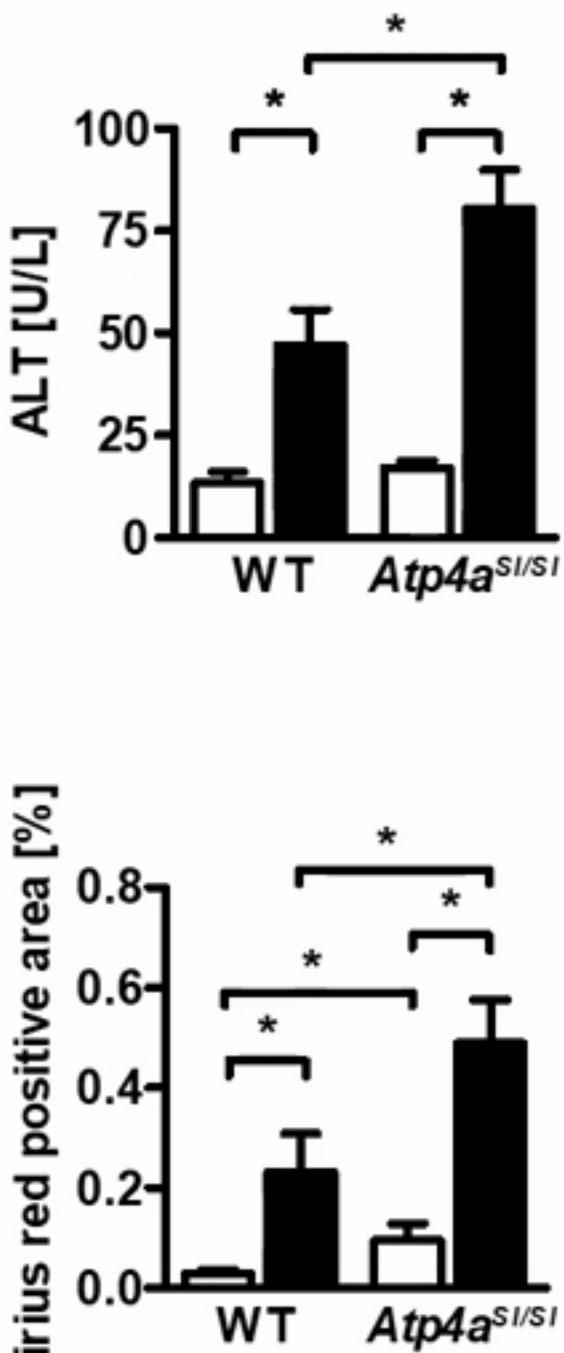
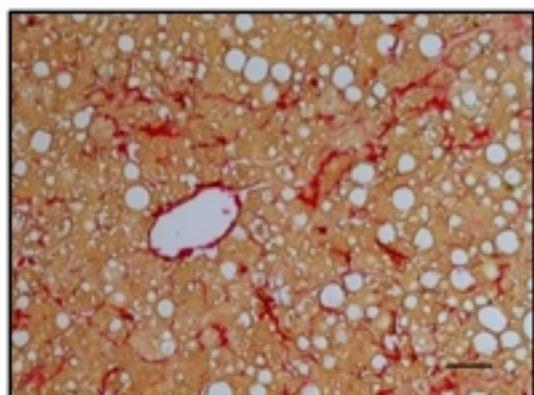
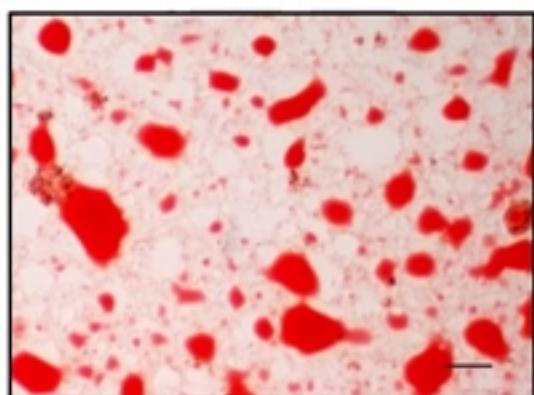
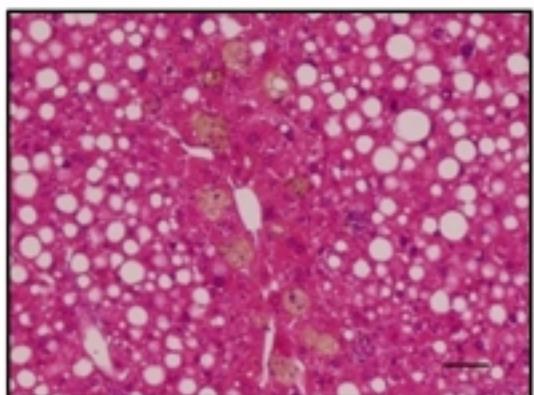


# NAFLD and insulin resistance is increased in the absence of gastric acid

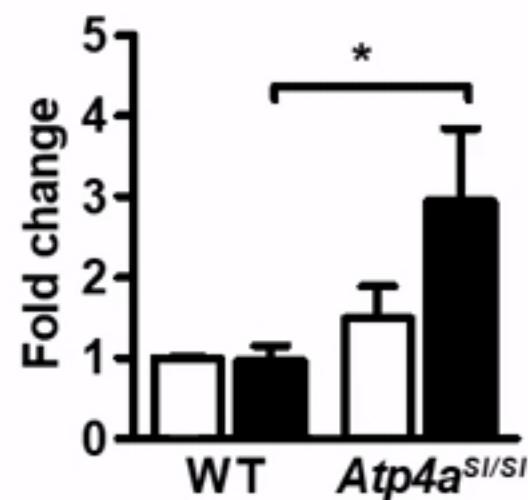


# Absence of gastric acid secretion increases the severity of non-alcoholic steatohepatitis

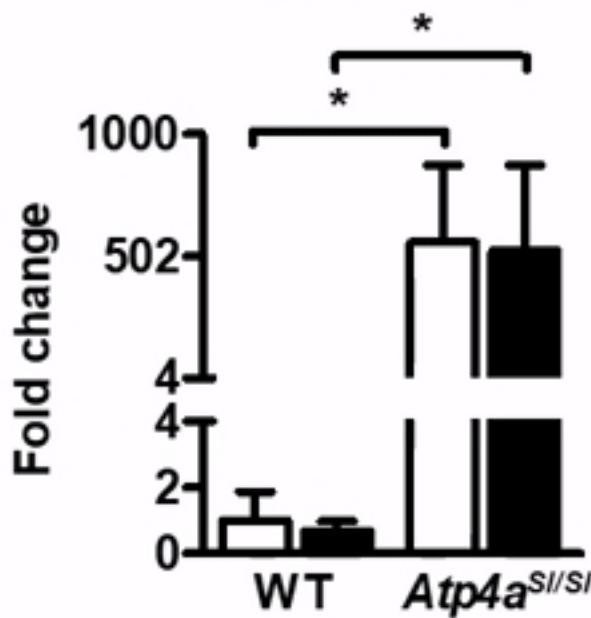
*Atp4a<sup>SI/SI</sup>*



Hepatic cleaved IL1B



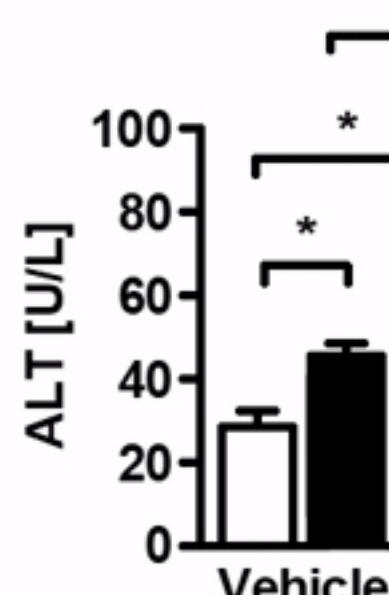
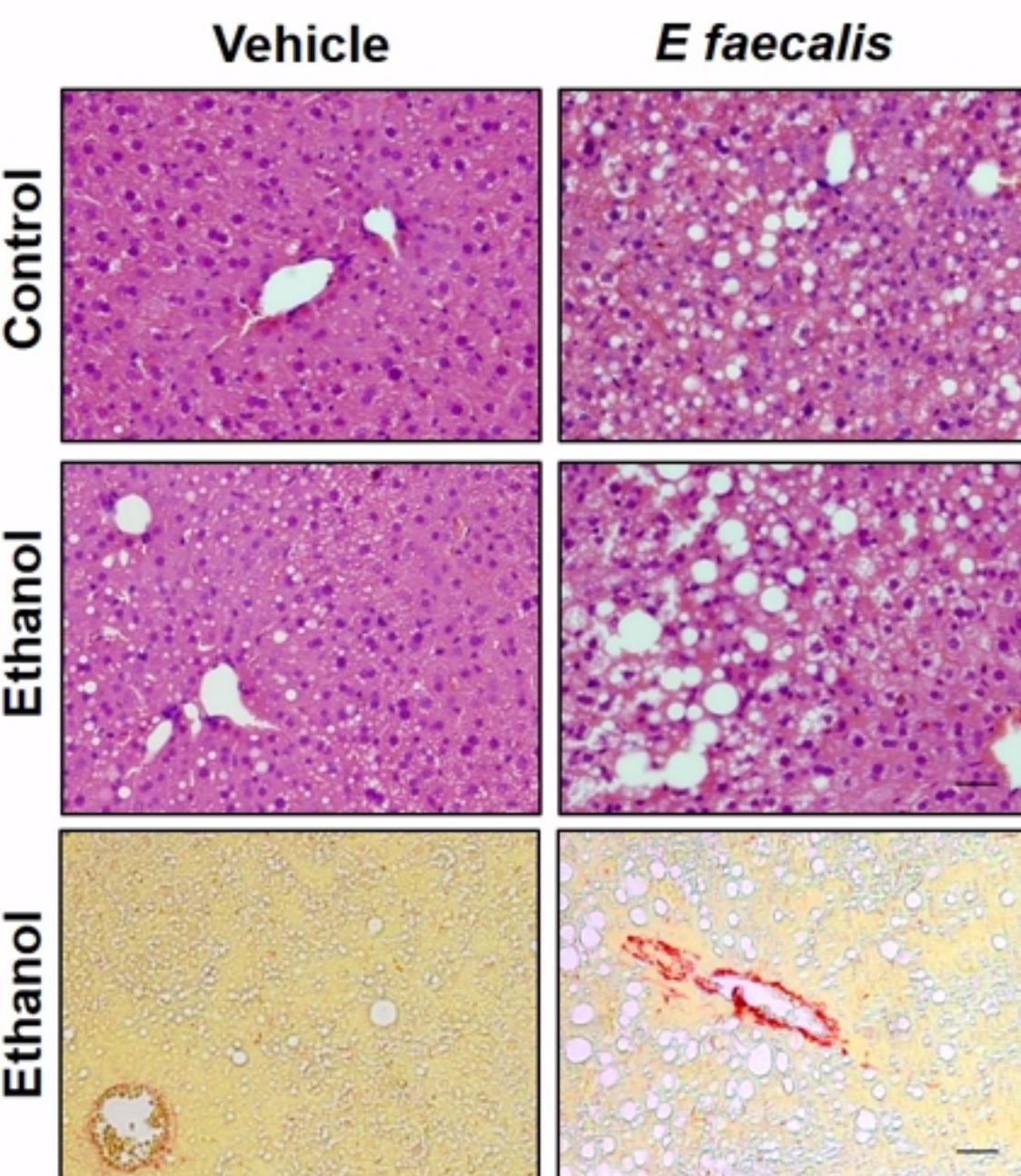
*Enterococcus*



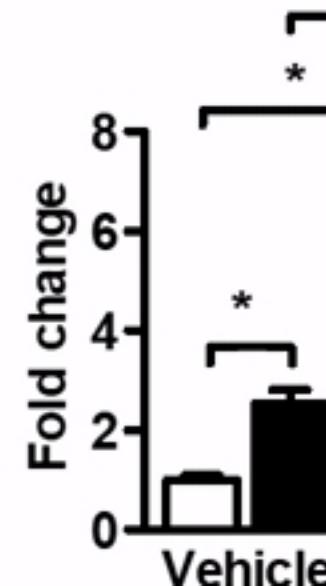
# *Enterococcus faecalis* alone is sufficient to cause mild steatotic liver disease in mice



*Enterococcus faecalis*

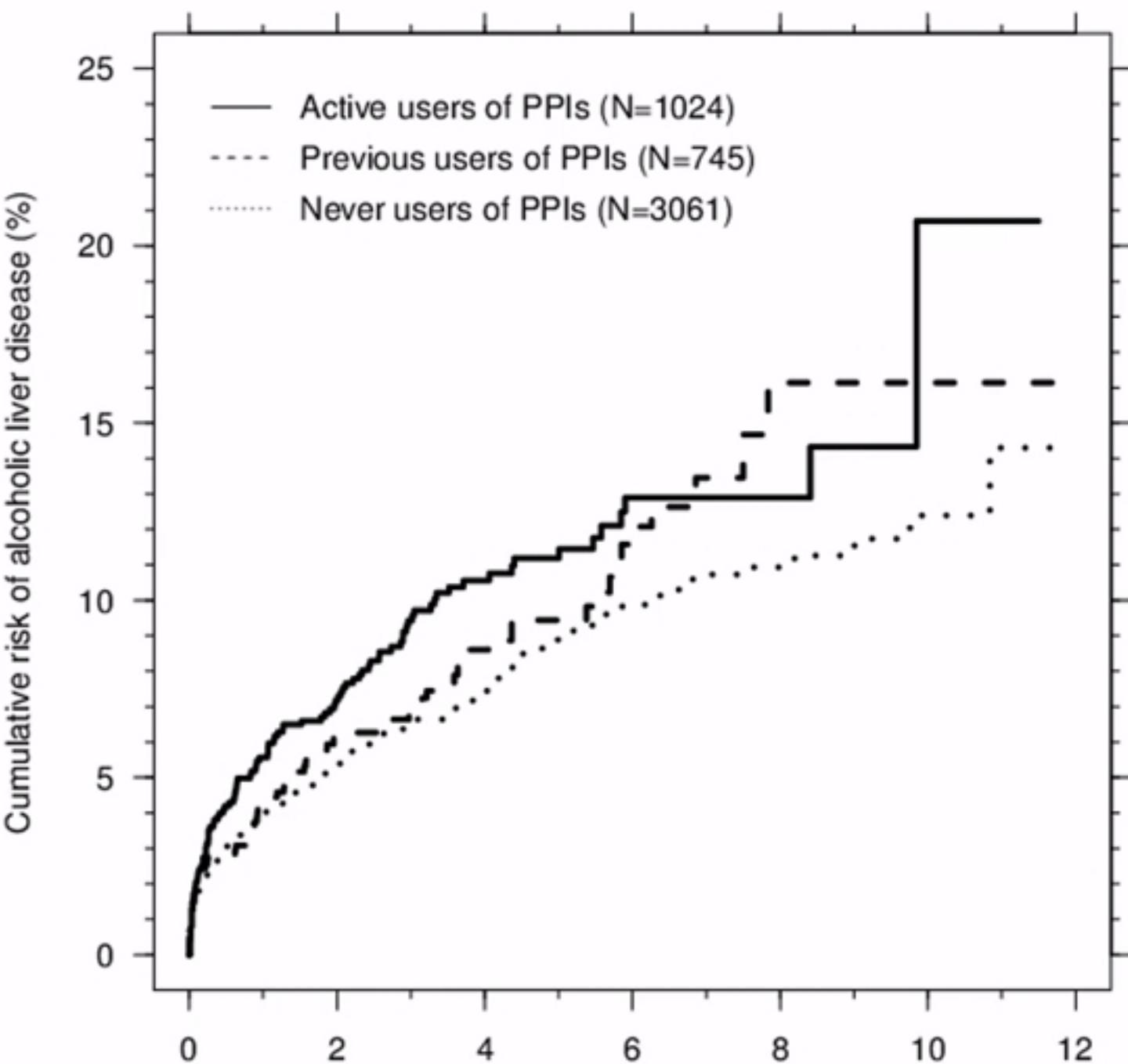


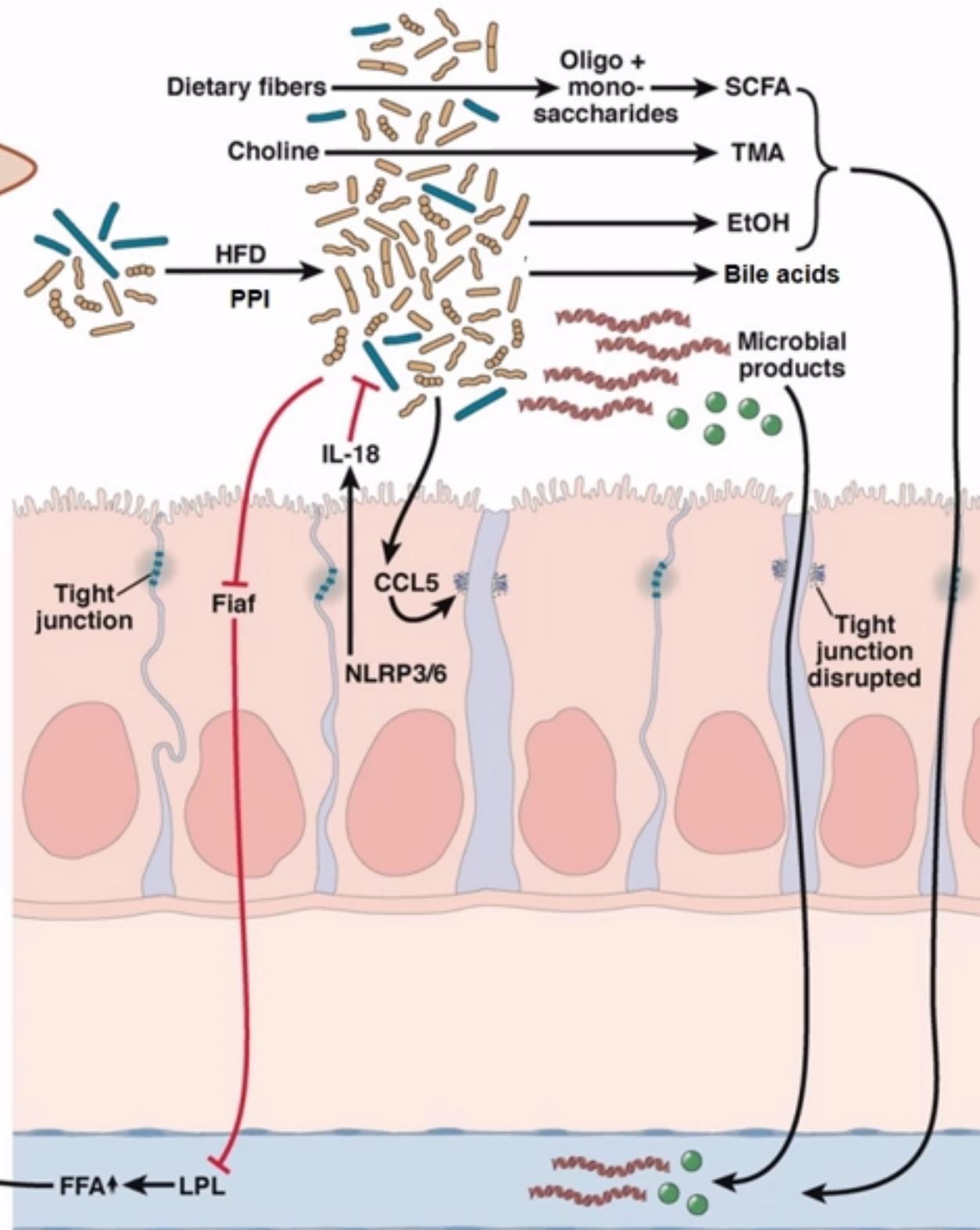
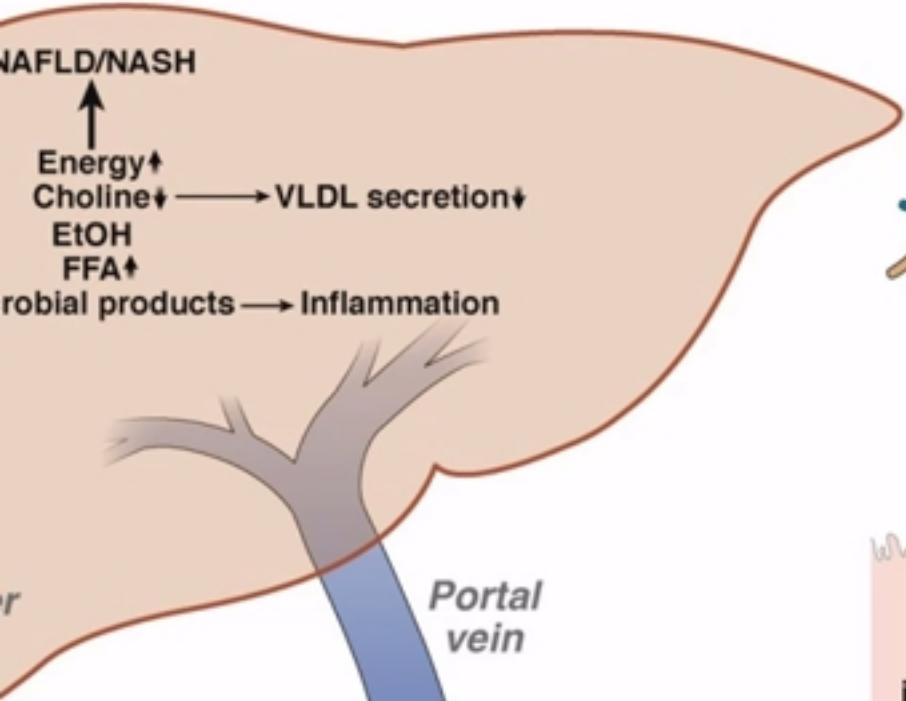
Hepatic cl



# PPI treatment increases the risk of liver disease development in chronic alcoholics

Alcoholics







An aerial photograph of a coastal city, likely Stanford University in California. The foreground shows a dense cluster of modern buildings, including several large research facilities with blue roofs. A network of roads and parking lots is visible. Behind the buildings, a large green area with many trees and a few smaller buildings, possibly a stadium or sports complex, stretches across the middle ground. In the background, the city extends towards a coastline where a beach meets a clear blue ocean. The sky is bright and clear.

Than