Microbiota e steatosi epatica non alcolica: nuove evidenze

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UMG
Dubium sapientae initium

WE ARE HERE

1980:

Jürgen Ludwig coined the term:

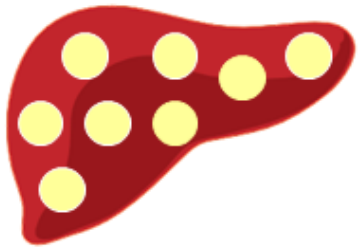
"non-alcoholic steatohepatitis"

PubMed

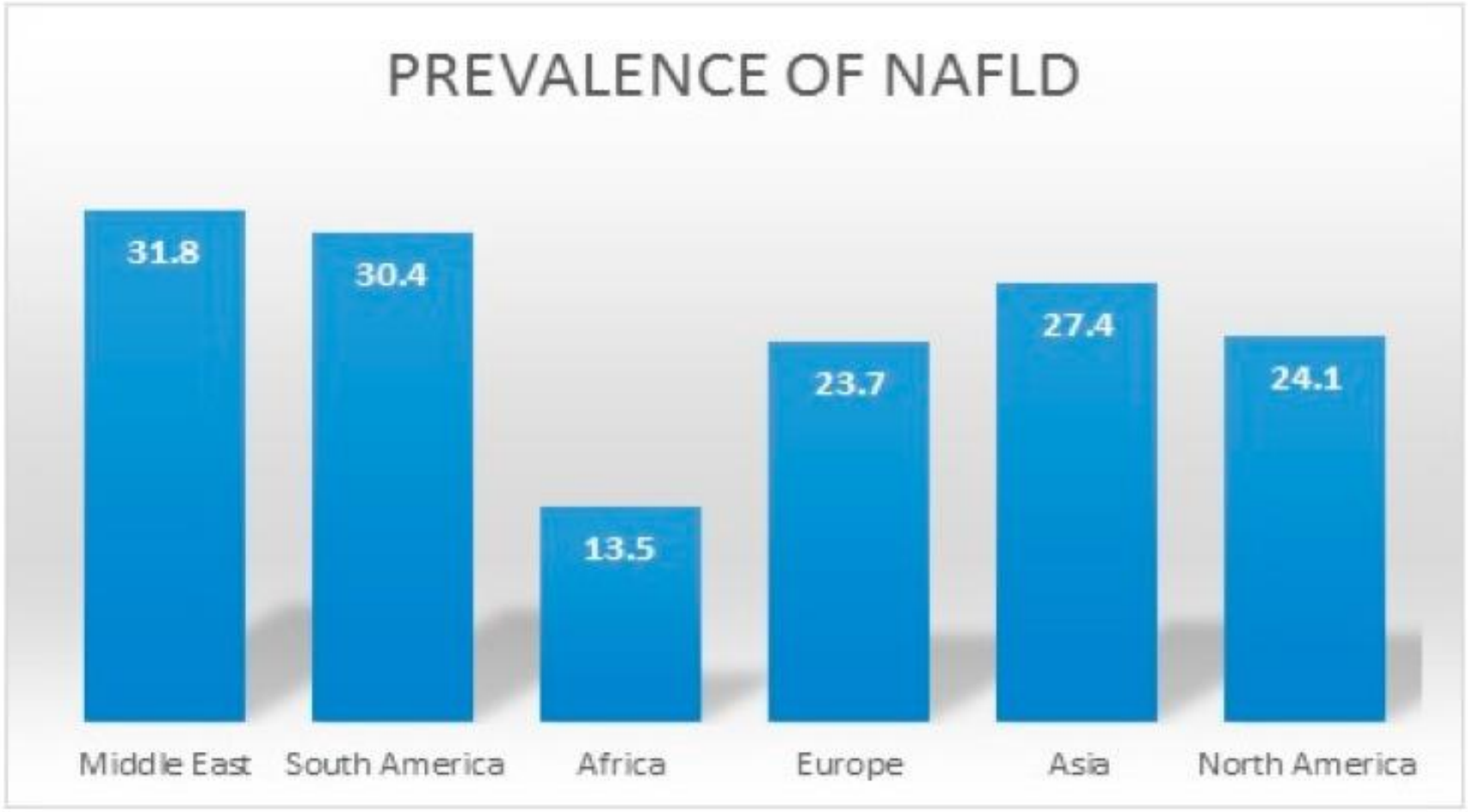
Items: 18767

PAST FUTURE

non-alcoholic fatty liver disease



EPIDEMIOLOGY



Iqbal *et al*. Medicines; 2019

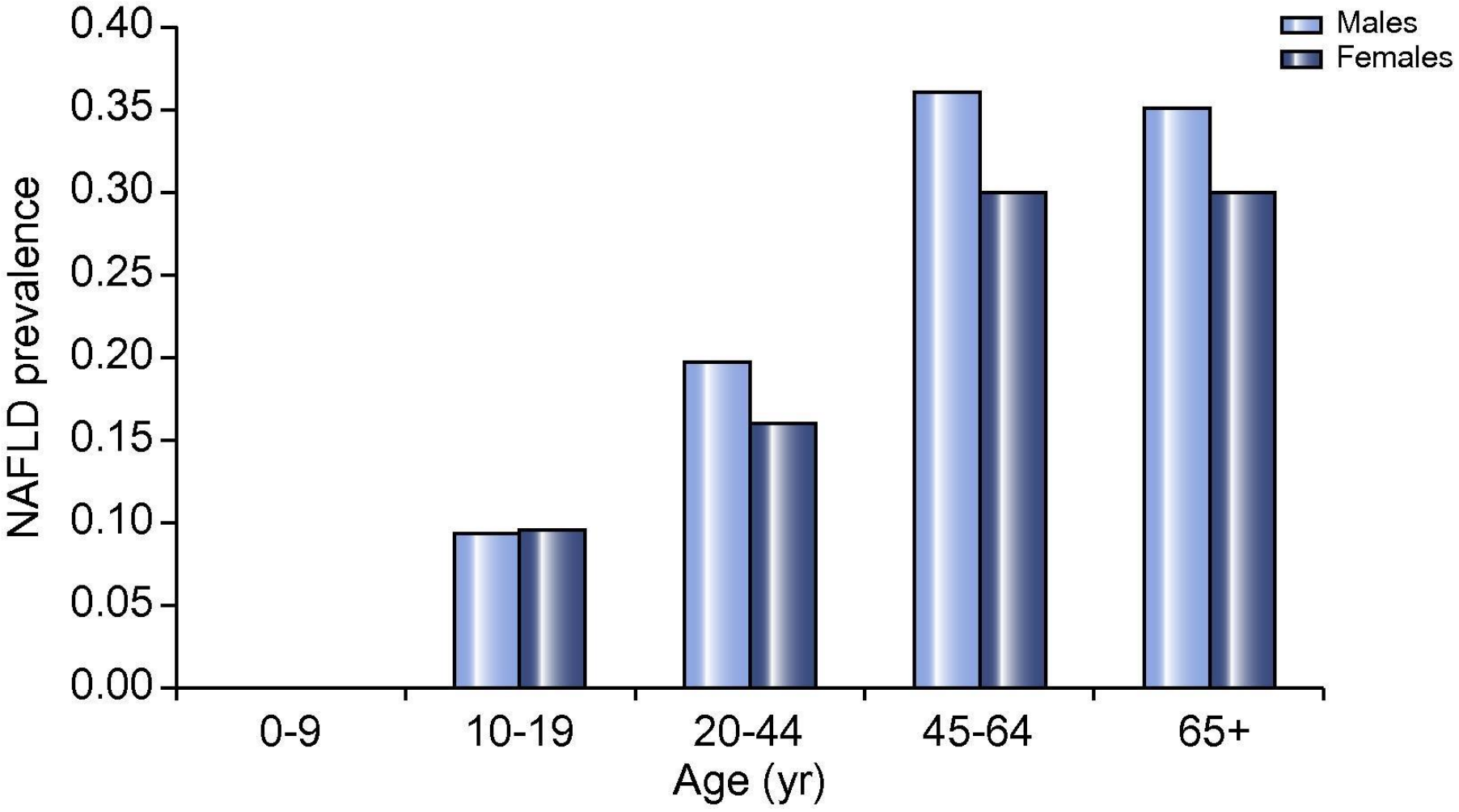
EPIDEMIOLOGY

European population: 741.400.000

- **prevalence: 33% (245 million)**
- **prevalence in obese adult: 50%**
- **prevalence in obese children: 40%**
- **prevalence in DM pts: 50%**
- **prevalence in MS pts: 80%**

Yanoussi et al. Hepatology; 2016
Bellentani et al. Liver Int; 2017

EPIDEMIOLOGY



Younossi. J Hepatol; 2019

NAFLD AND HCC

HCC is the 3° leading cause of cancer death worldwide, and fastest cause of cancer death in USA

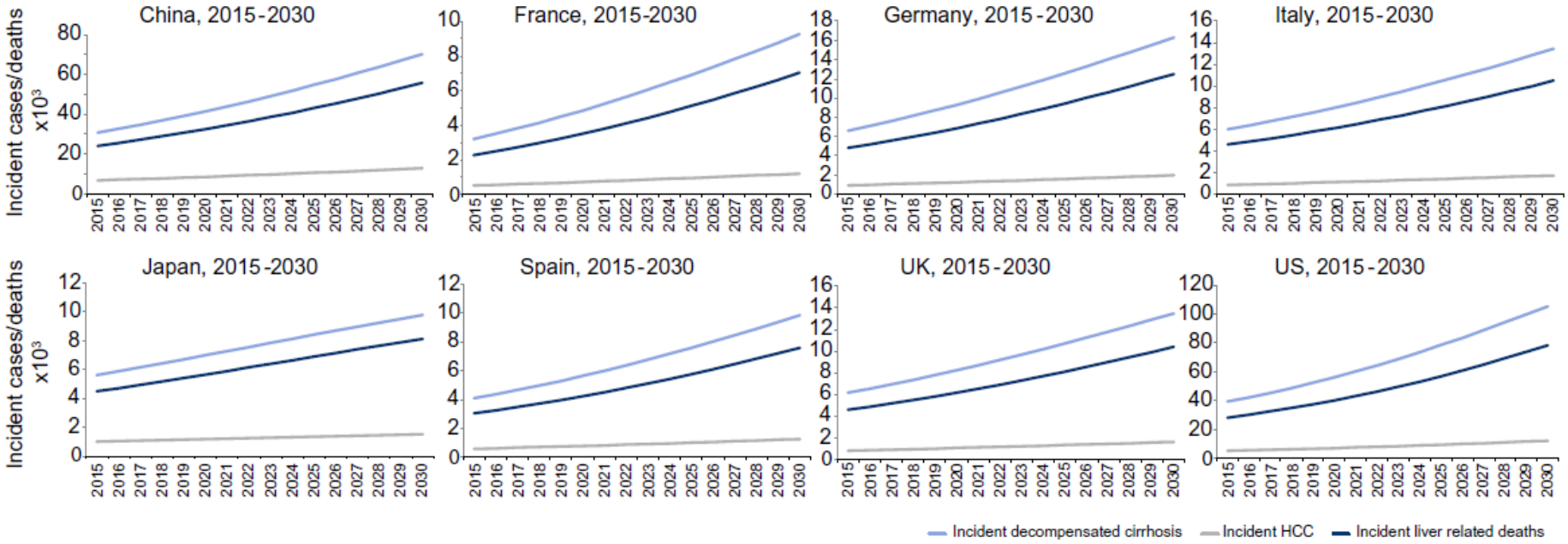
The high risk to HCC development, is related to global increase of diabetes and obesity

5-25% pts with NASH will get HCC (retrospective data)

Povsic *et al*. Adv Ther; 2019

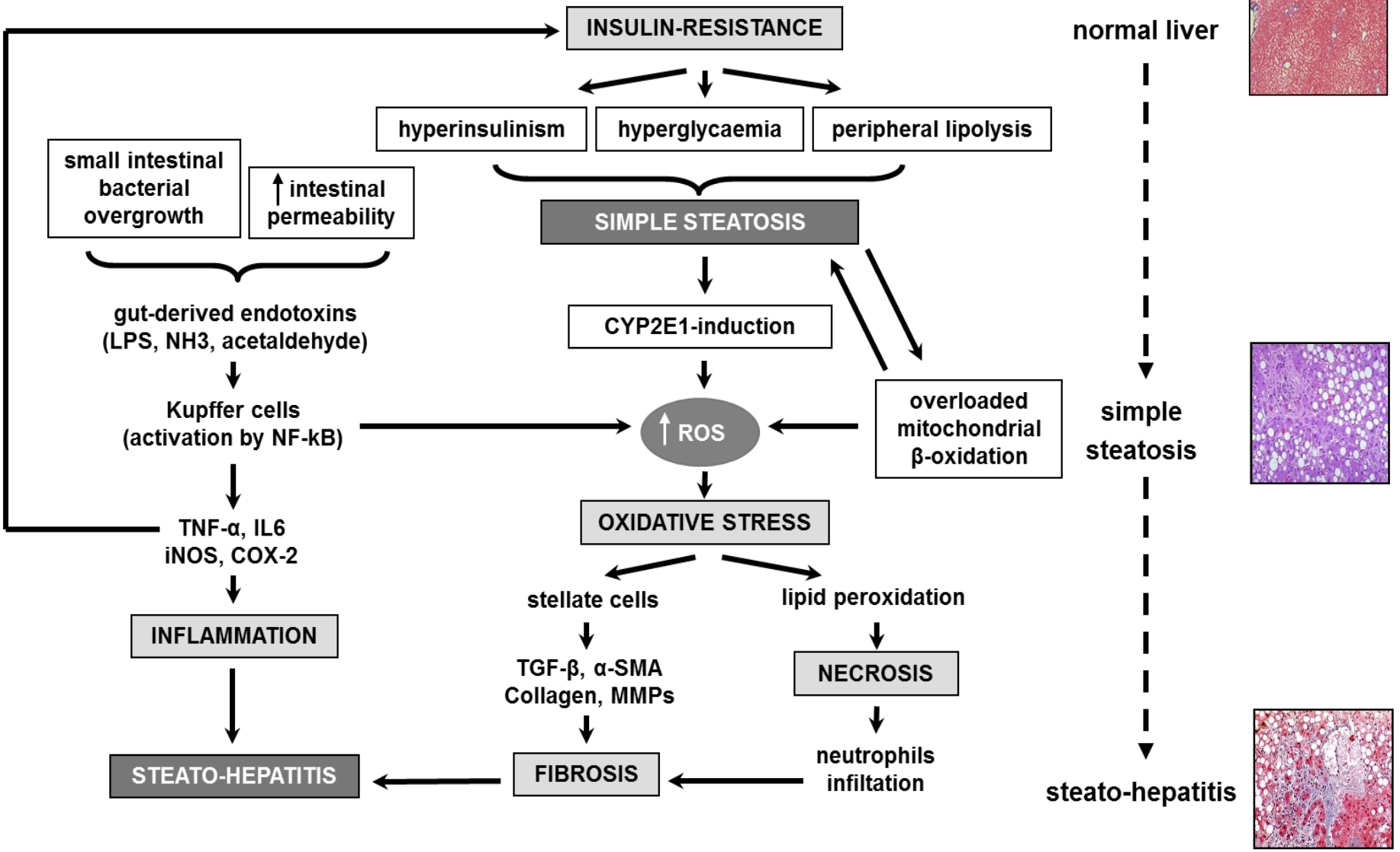
GLOBAL TREND

Incident decompensated cirrhosis, HCC and liver-related deaths in NAFLD population (2015–2030)

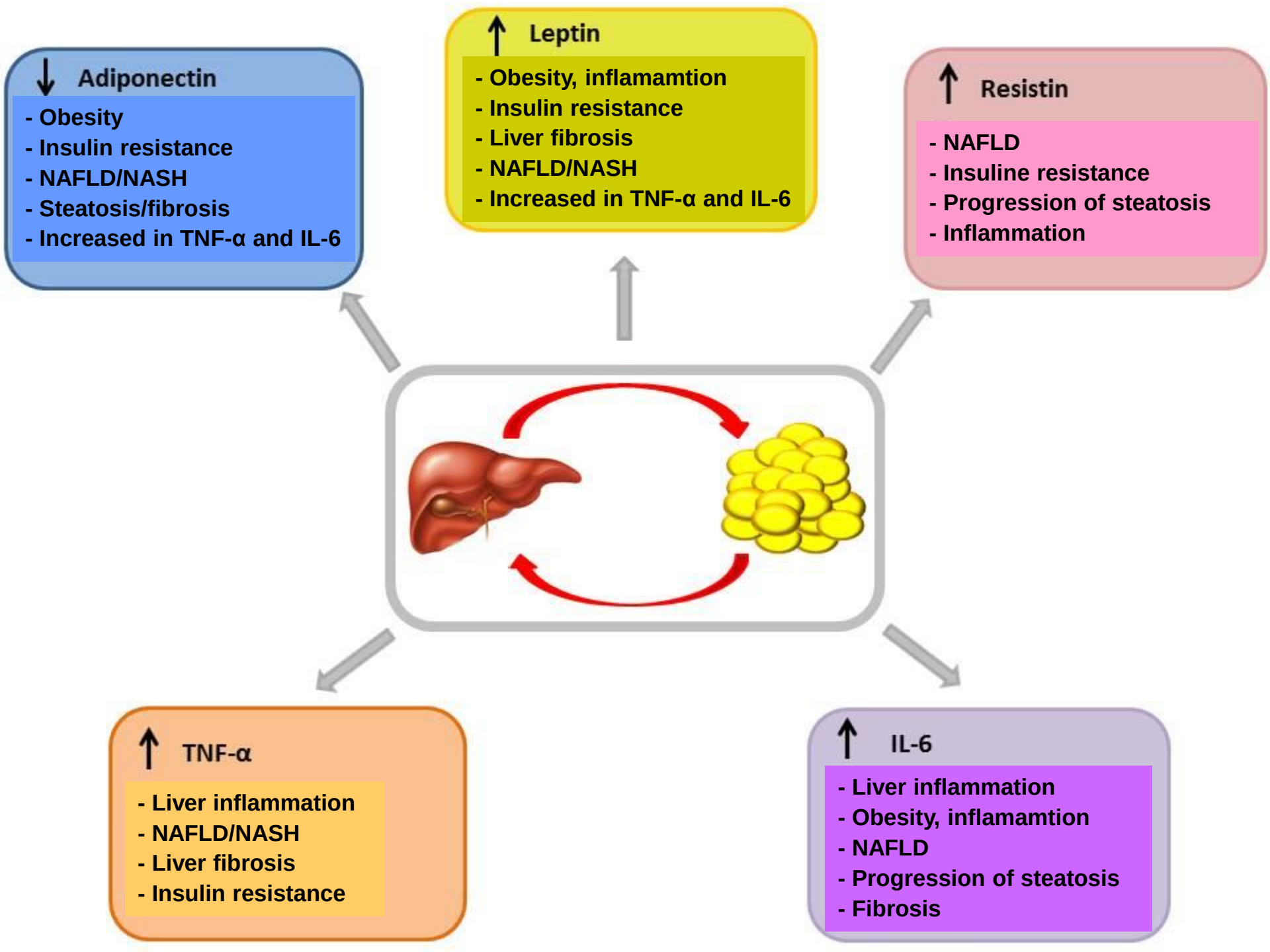


Estes *et al*. J Hepatol; 2018

PATHOGENESIS



Abenavoli *et al*. World J Gastroenterol; 2014

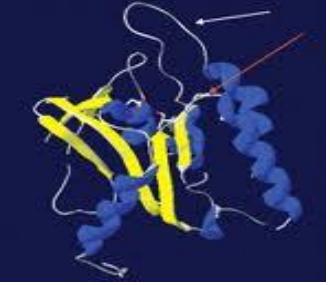

Adiponectin
- Obesity
- Insulin resistance
- NAFLD/NASH
- Steatosis/fibrosis
- Increased in TNF-α and IL-6
Leptin
- Obesity, inflamamtion
- Insulin resistance
- Liver fibrosis
- NAFLD/NASH
- Increased in TNF-α and IL-6
Resistin
- NAFLD
- Insuline resistance
- Progression of steatosis
- Inflammation
TNF-α
- Liver inflammation
- NAFLD/NASH
- Liver fibrosis
- Insulin resistance
IL-6
- Liver inflammation
- Obesity, inflamamtion
- NAFLD
- Progression of steatosis
- Fibrosis

RISK FACTORS FOR NASH PROGRESSION

- age ≥ 50 years
- diet (high fat, carbohydrate, fructose)
- BMI ≥ 28/Kg/m^2
- metabolic syndrome
- necro-inflammatory activity (biopsy)
- ALT ≥ 2N
- TG ≥ 150 mg/dl
- HOMA-IR ≥ 2.5
- genetic polymorphism

Yanoussi et al. Hepatology; 2016

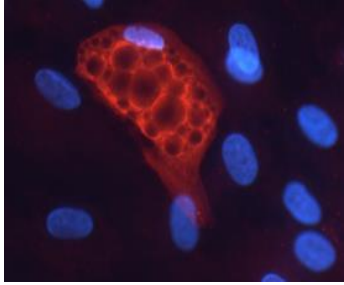
Bellentani et al. Liver Int; 2017

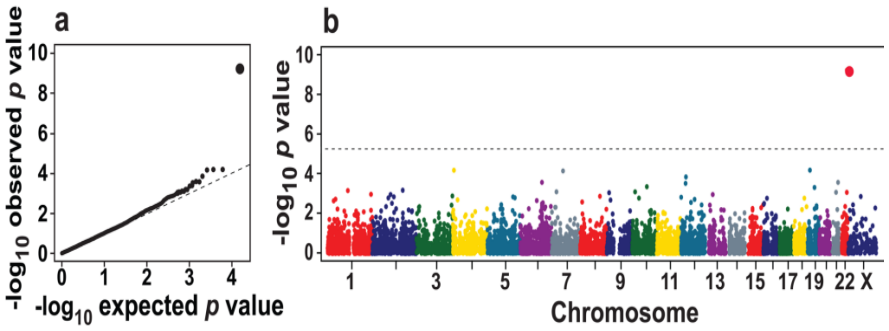


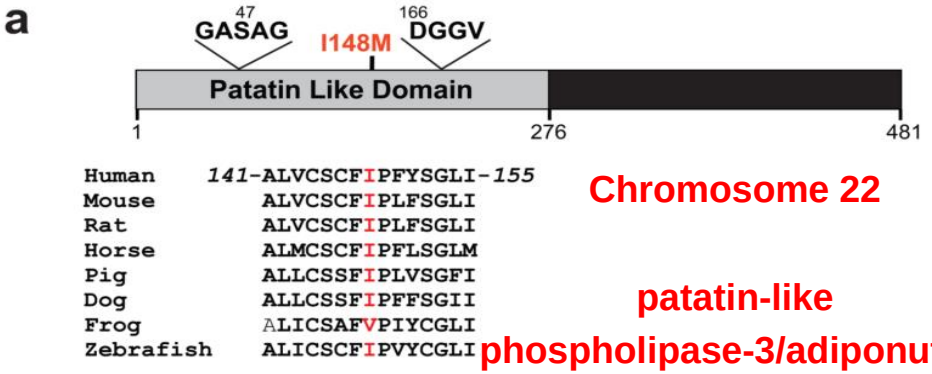
Genetic variation in *PNPLA3* confers susceptibility to nonalcoholic fatty liver disease

Nat Genet; 2008

Stefano Romeo[1,*], Julia Kozlitina[2,3,*], Chao Xing[1,2], Alexander Pertsemlidis[1], David Cox[4], Len A. Pennacchio[5], Eric Boerwinkle[6], Jonathan C. Cohen[1], and Helen H. Hobbs[1,7]

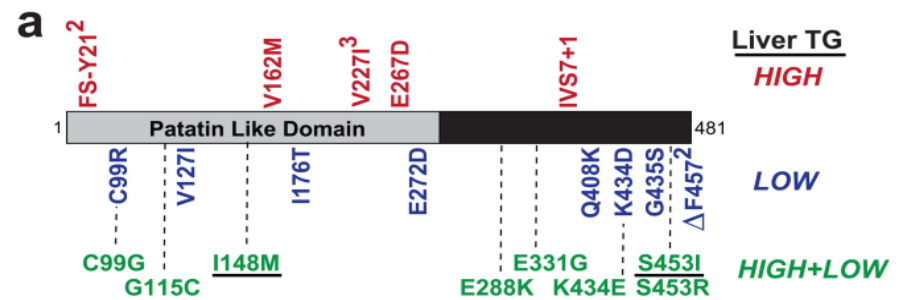


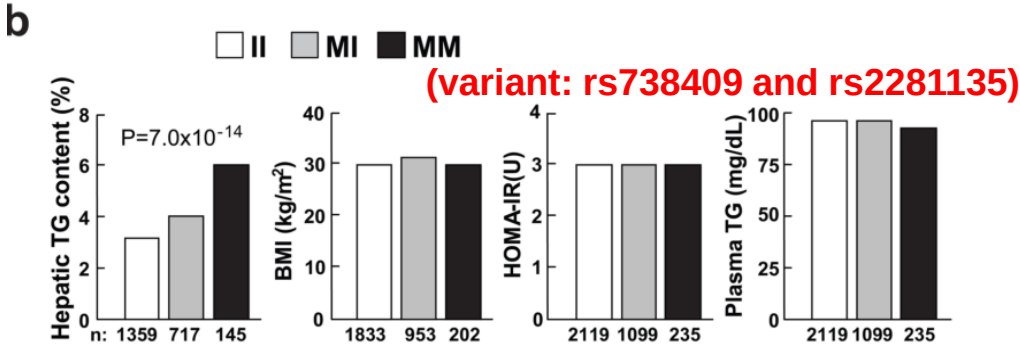




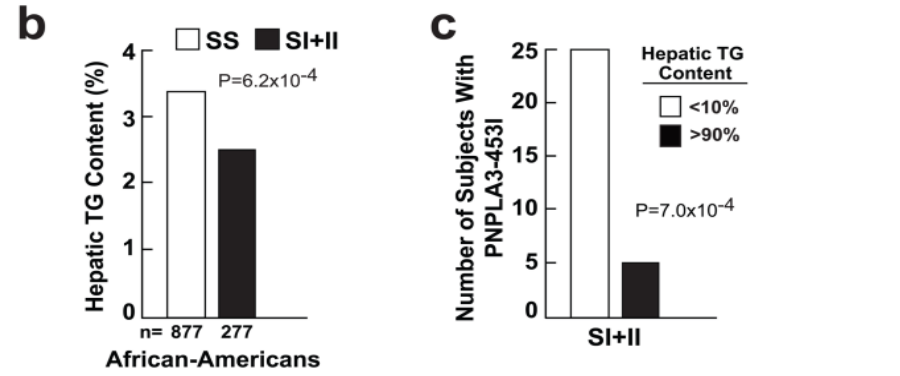
Chromosome 22

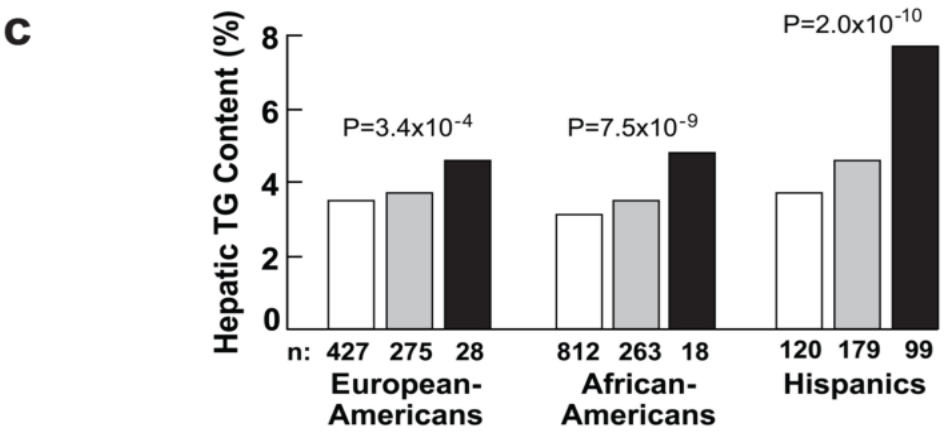
patatin-like phospholipase-3/adiponutrin



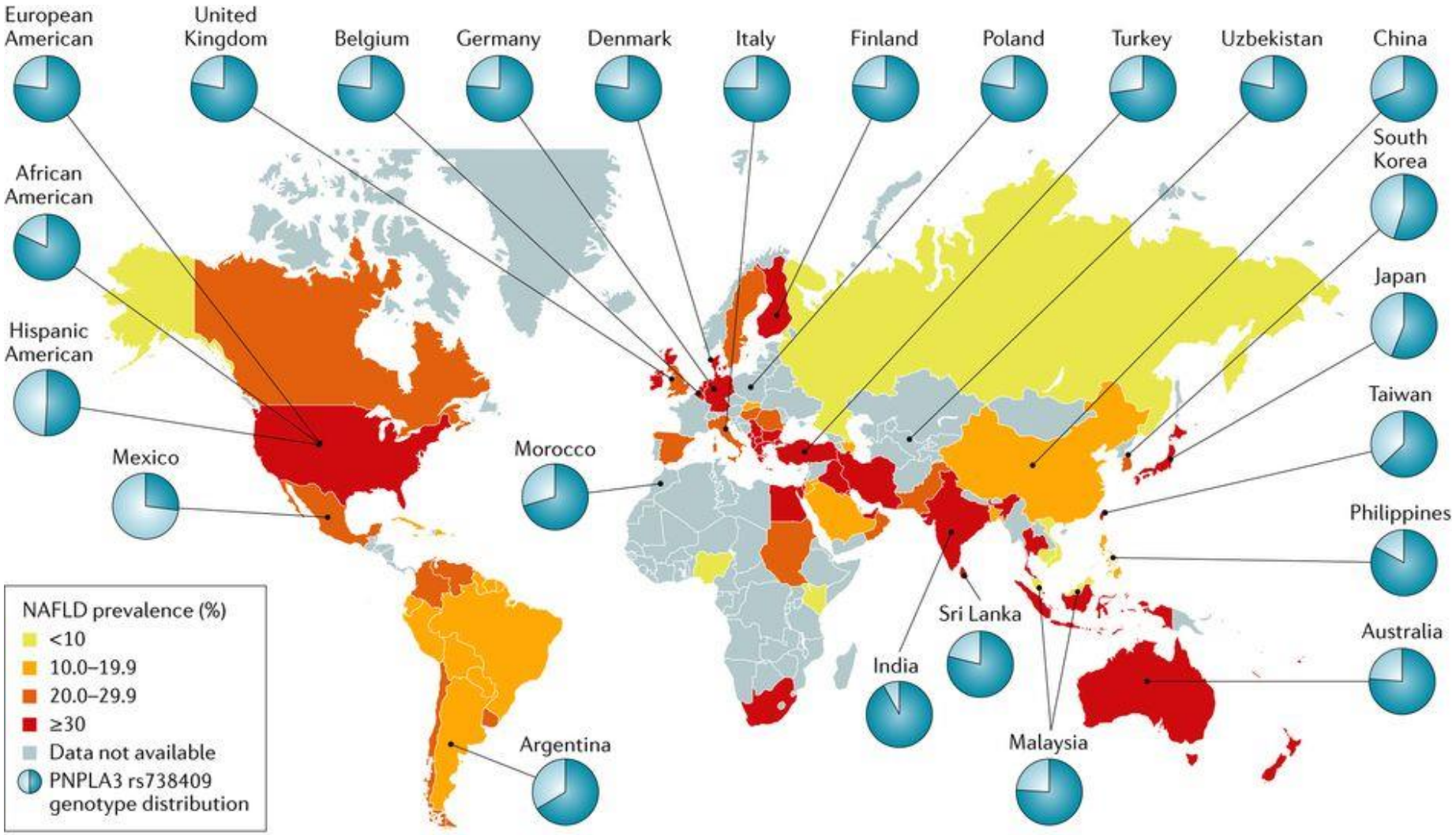


(variant: rs738409 and rs2281135)

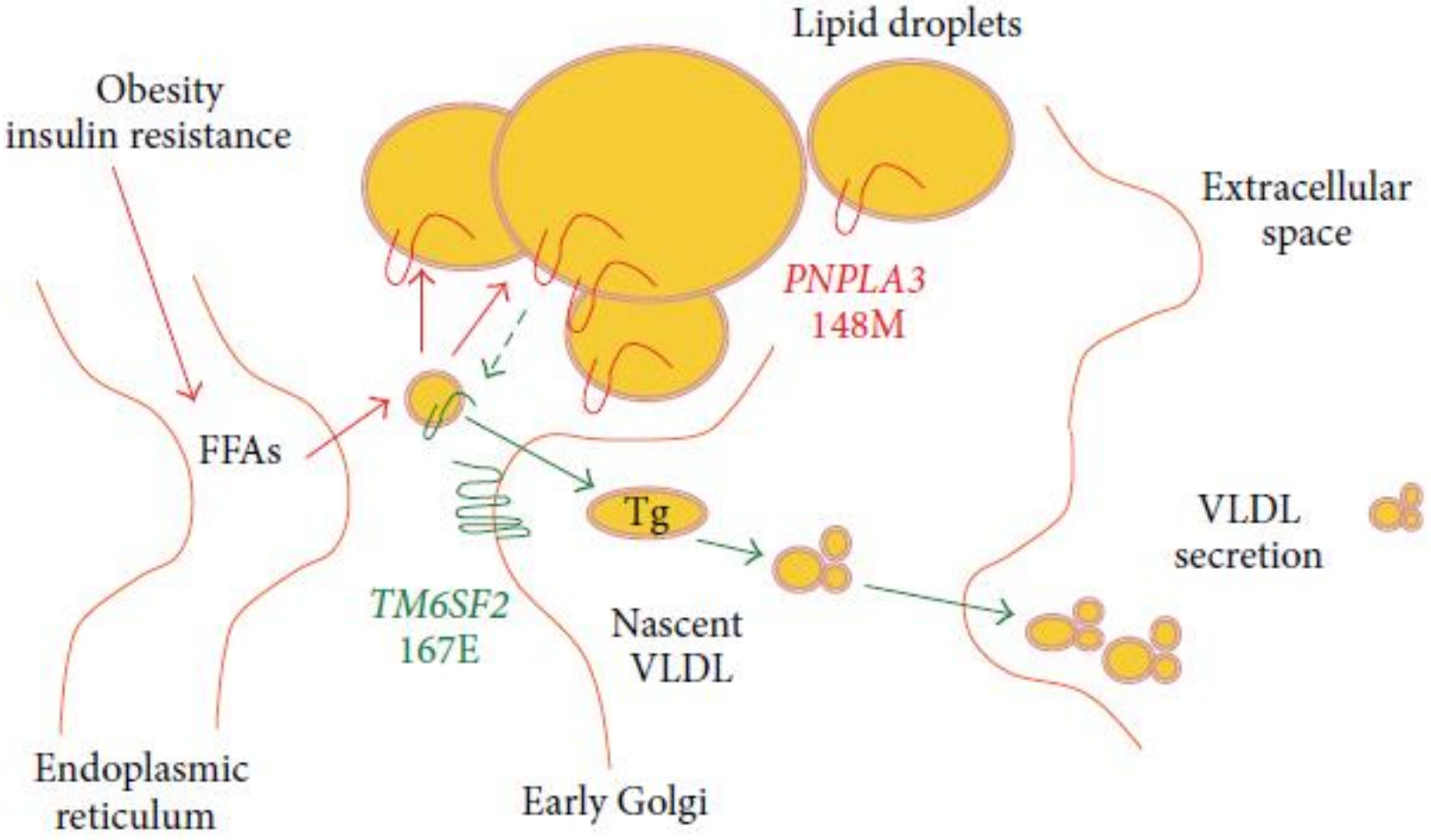




PNPLA3 DISTRIBUTION



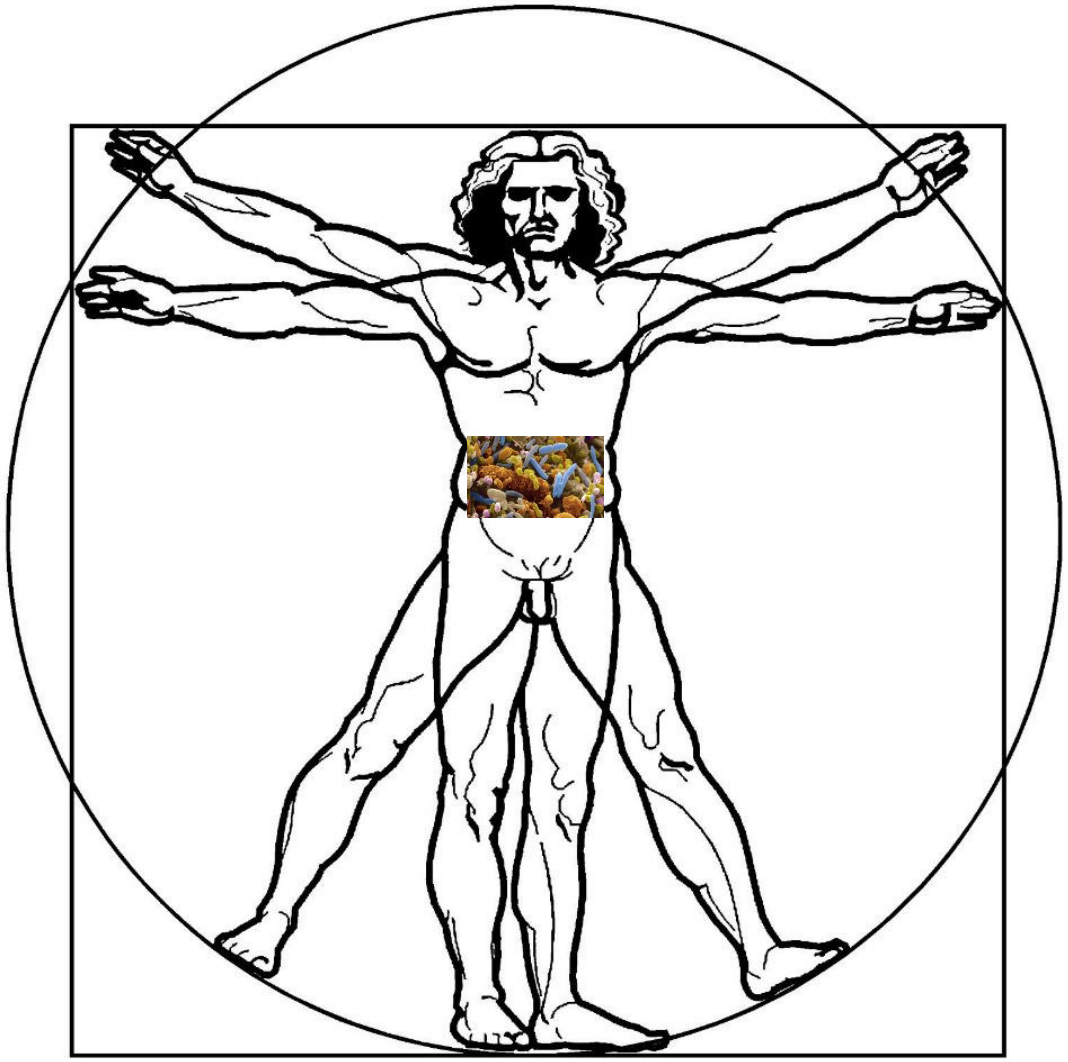
Nature Reviews | Gastroenterology & Hepatology



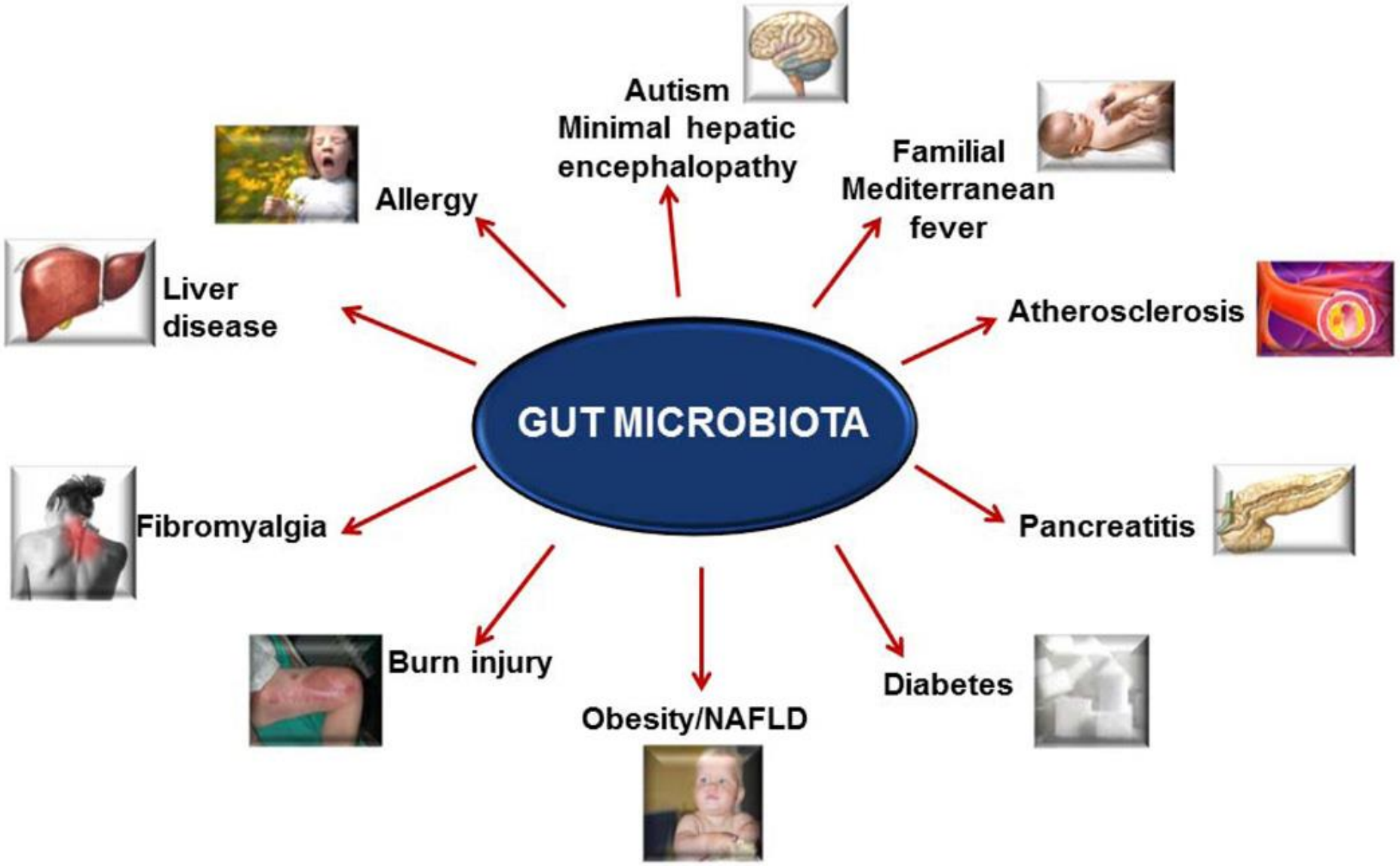
PNPLA3 **I148M variant C→G, is attached on the surface of lipid droplets reducing TG breakdown, with subsequent lipid retention in the hepatocyte and increased risk of liver steatosis, hepatic damage and fibrosis**

Homo bactericus

Brian Henderson (1996)

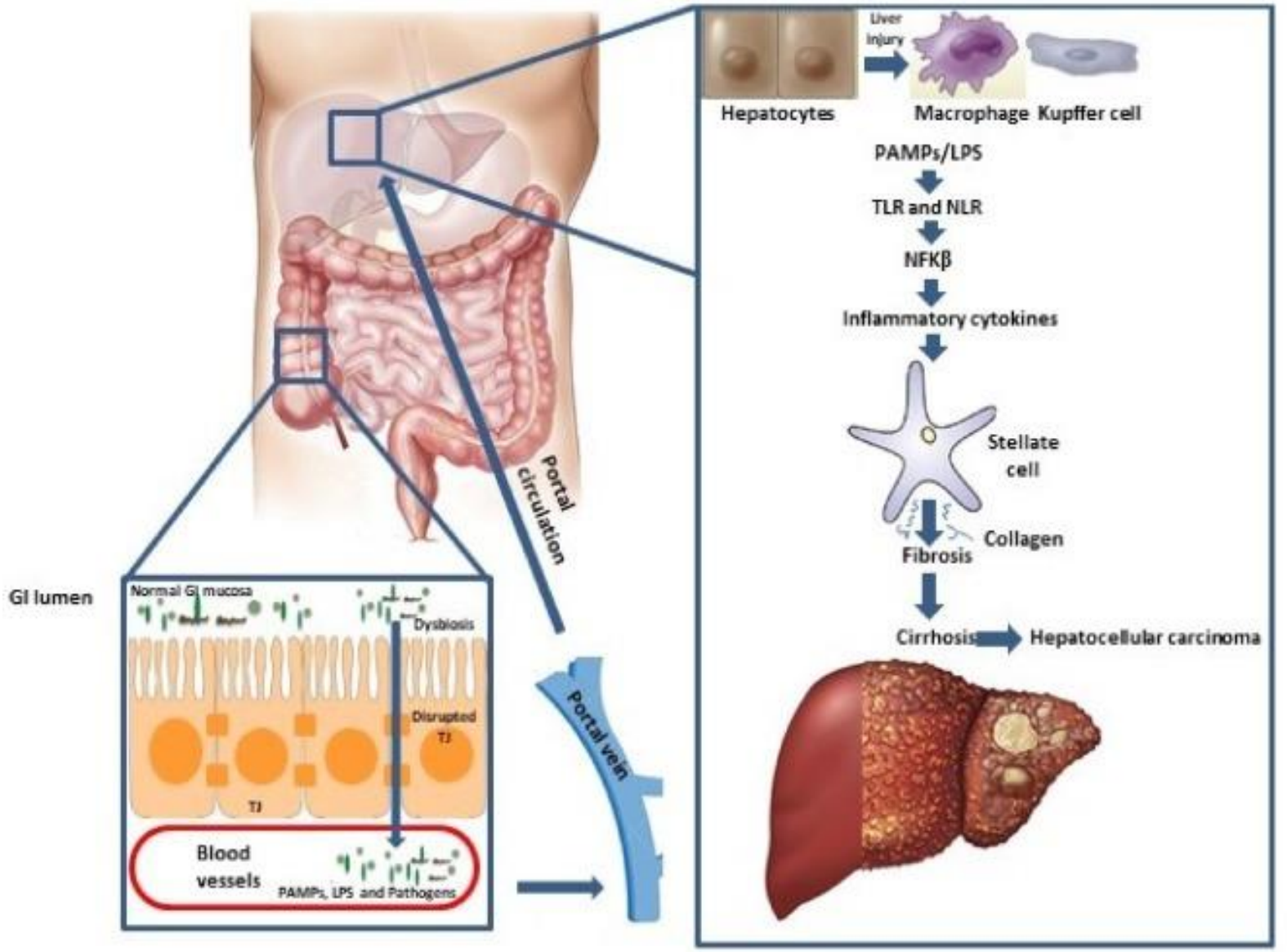


THE GUT MICROBIOTA



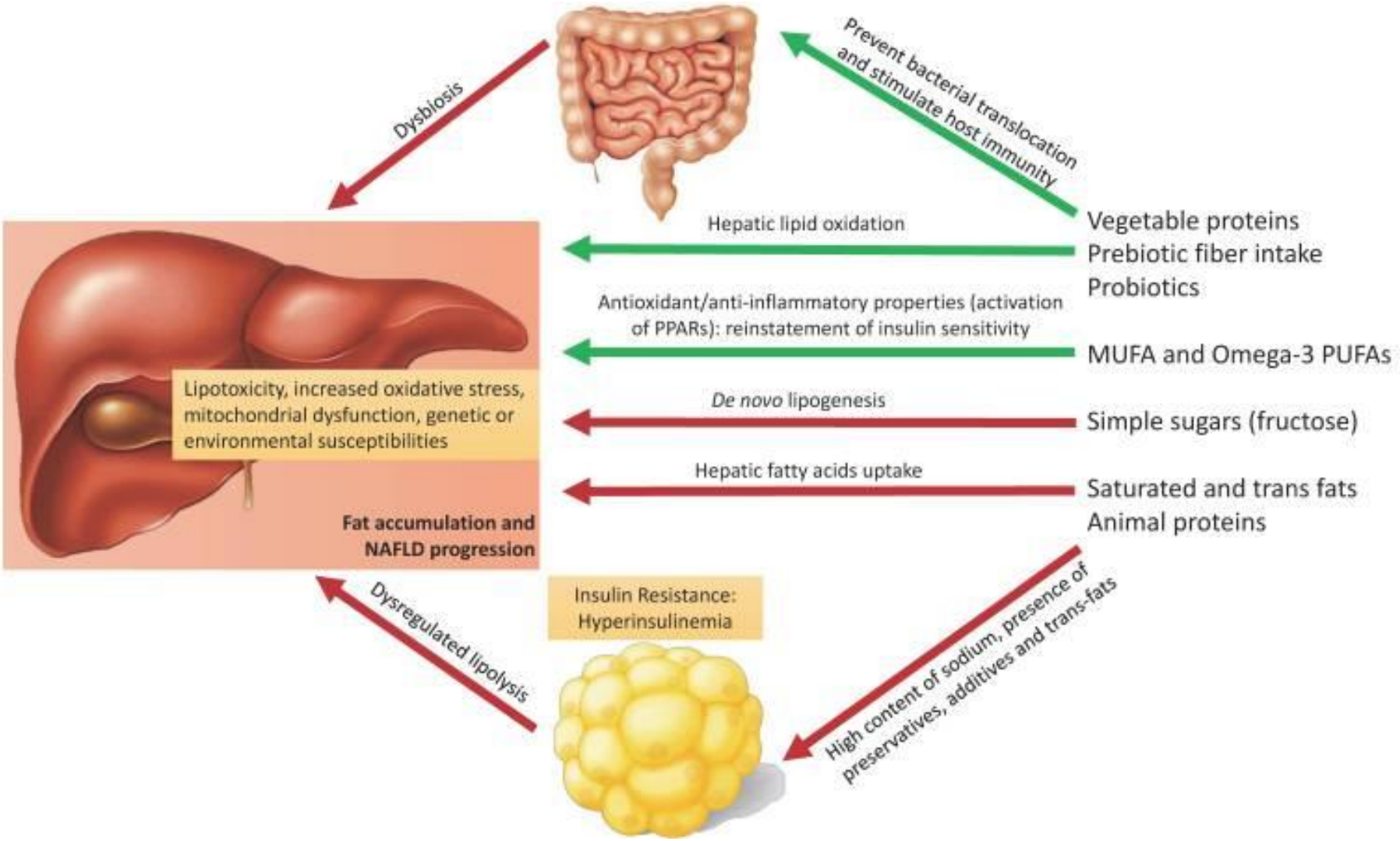
Vajro *et al*. J Pediatr Gastroenterol Nutr; 2013

THE GUT-LIVER AXIS

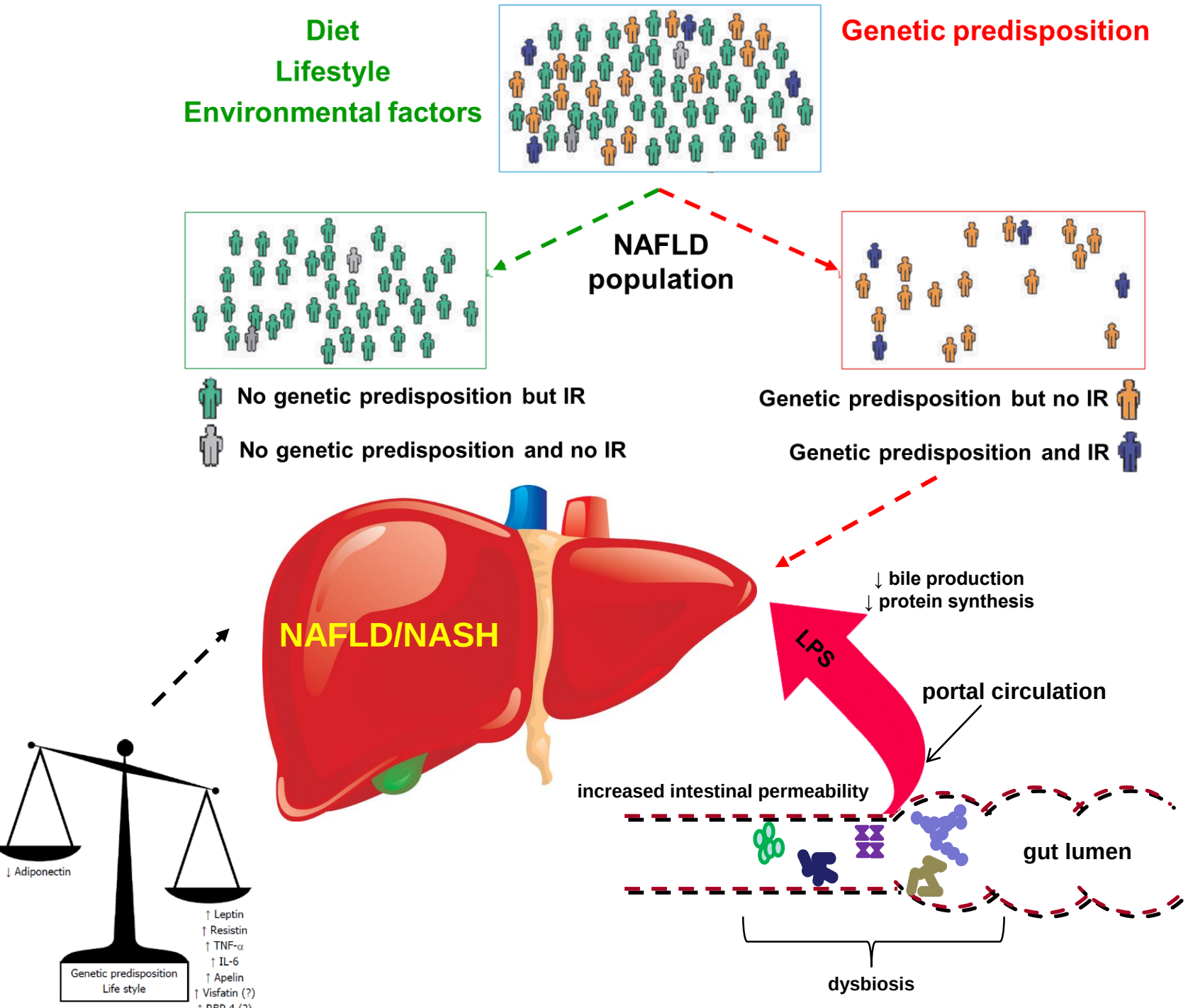


Liver immune response to dysbiosis

LIVER AND WESTERN DIET



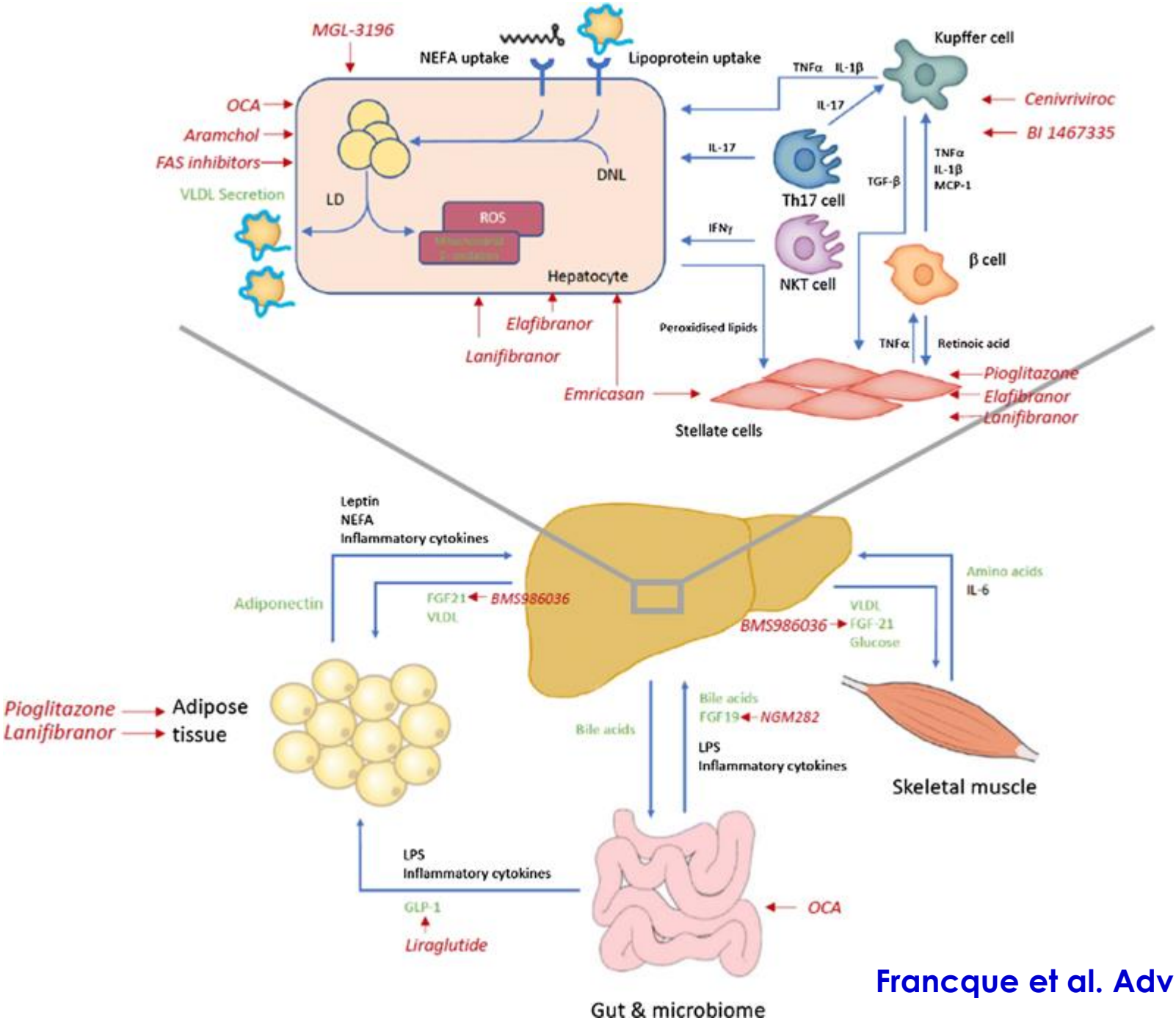
Perdomo et al. Nutrients; 2019


Diet
Lifestyle
Environmental factors
Genetic predisposition
NAFLD population
No genetic predisposition but IR
Genetic predisposition but no IR
No genetic predisposition and no IR
Genetic predisposition and IR
NAFLD/NASH
↓ bile production
↓ protein synthesis
LPS
portal circulation
increased intestinal permeability
gut lumen
dysbiosis
↓ Adiponectin
↑ Leptin
↑ Resistin
↑ TNF-α
↑ IL-6
↑ Apelin
↑ Visfatin (?)
Genetic predisposition
Life style


Time
Therapy
Natural history

THERAPEUTIC APPROACH

Area	Suggested intervetions
Total energy intake	Calorie restricted diet (600 calories fewer a day than you need)
Weight loss	To lose 0.5-1 kg per week Target weight of a BMI of 22 Lose higher than 10% body weight, lost over 6-12 month
Protein intake	Insufficient evidence to recommend about protein intake in NAFLD
Carbohydrate	Low glycemic index carbohydrate avoid high fructose corn syrup
Omega-3 PUFAs	>0.83 g/d (optimal dose not yet defined)
Physical activity	Increasing physical activity and decreased sedentary time are recommended Aerobic training and resistance exercise are all effective
Metformin	Not recommend as a specific treatment for NASH
Pioglitazone	Recommended for patients with biopsy-proven NASH at 45 mg/day (in patients with and without diabetes)
Vitamin E	800 IU/day in non-diabetic adults with biopsy proven NASH
UDCA	Not recommended
Probiotic	Insufficient evidence to recommend about type, dose, and treatment duration
Natural products	Bioactive food components and natural products have antifibrotic effects (i.e. curcumin, blueberry, silymarin, coffee, vitamins, resveratrol, choline)



Francque et al. Adv Ther; 2019

BEHAVIOUR THERAPY

Multidisciplinary approach and work-team:
- personalised diet (dietitian)
- personalised physical activity (supervisor)
- motivational support (psychologist)
- long term monitoring program

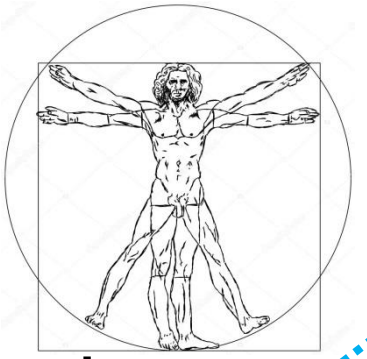
Dietary recommendations:
- 1.000/1.200 kcal/day for overweight women and 1.200/1.600 kcal/day for overweight men

Ideal diet: 50% carbohydrates, 30% lipids (7-10% saturated fatty acids), and 20% proteins

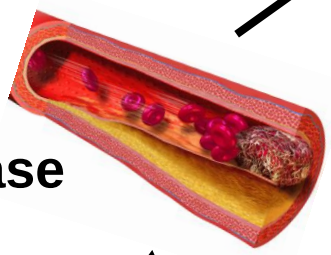
Diets are designed to create a calorie deficit of 500-1.000 kcal/day, producing a weight loss of 0.5-1.0 kg/week

EASL guidelines. J Hepatol; 2016

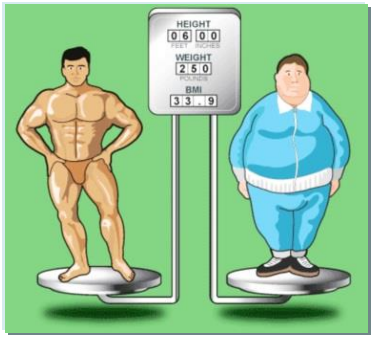
NUTRIGENOMIC



phenotype



disease



nutritional status

genotype

diet composition

ALIMENTARY APPROACH

- The influence of the diet in the pathogenesis of NAFLD has been reported

- The cornerstone in the management of NAFLD implies a dietary modification to decrease the body weight and to increase the physical exercise

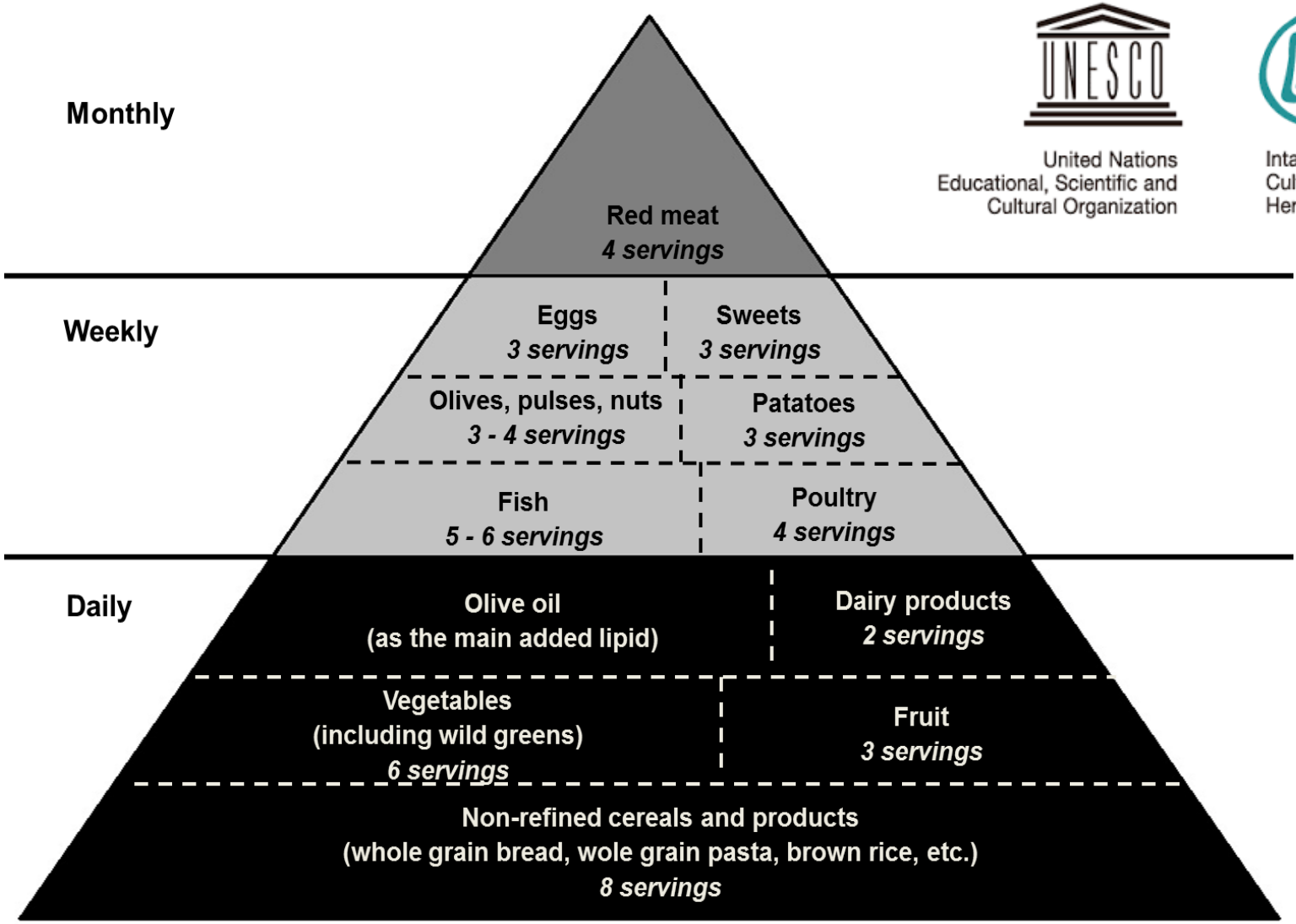
- A diet regimen rich in monounsaturated fatty acids and omega-3, fruit, vegetables, fiber and reduced intake of saturated fats, simple carbohydrates, sweetened drinks and moderate alcohol intake should be recommended to the NAFLD pts

Abenavoli *et al*. World J Gastroenterol; 2014

MEDITERRANEAN DIET

United Nations Educational, Scientific and Cultural Organization

Intangible Cultural Heritage



Also daily: physical activity; wine in moderation; 6 glasses of water

Abenavoli *et al*. World J Gastroenterol; 2014

MEDITERRANEAN DIET

PPAR-γ → Fatty acid synthase

PPAR-γ → CTP-1

Other polyphenols – ***Oleuropein, hydroxytyrosol, curcuminoids***

Anti-obesity effects

↑ β-oxidation
Inhibit fatty acids synthesis

Stilbens - ***Resveratrol*** → Synthesis of Malonyl-CoA

Resveratrol → AMPK

↑ β-oxidation
Inhibit gluconeogenesis
Improve insulin sensitivity

Anthocyanins → AMPK

Anthocyanins → PPAR-α, PPAR-δ → Fatty acid synthase

↑ β-oxidation
Inhibit fatty acids synthesis

Other polyphenols- ***Oleuropein*** → PPAR-γ → Adipocyte differentation

Other polyphenols- ***Oleuropein*** → UCP1

↑ Insulin sensitivity
Induce *Beige* adipose tissue

Other polyphenols- ***Hydroxytyrosol*** → AMPK

Other polyphenols- ***Hydroxytyrosol*** → PPAR-α, PPAR-γ

↑ β-oxidation
Inhibit adipocyte differentation

MEDITERRANEAN DIET AND NAFLD

Clinical Practice Guidelines

- Dietary recommendations should consider energy restriction and exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose. The macronutrient composition should be adjusted according to the Mediterranean diet (**B1**)

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

ELSEVIER

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Position Paper

AISF position paper on nonalcoholic fatty liver disease (NAFLD): Updates and future directions☆

The Italian Association for the Study of the Liver (AISF)

Indeed, among all the proposed diets, the Mediterranean diet appears as the most effective dietary option for inducing a weight loss together with beneficial effects on all cardio-metabolic risk factors associated with NAFLD.

MEDITERRANEAN DIET AND NAFLD

overweight

cytonecrosis

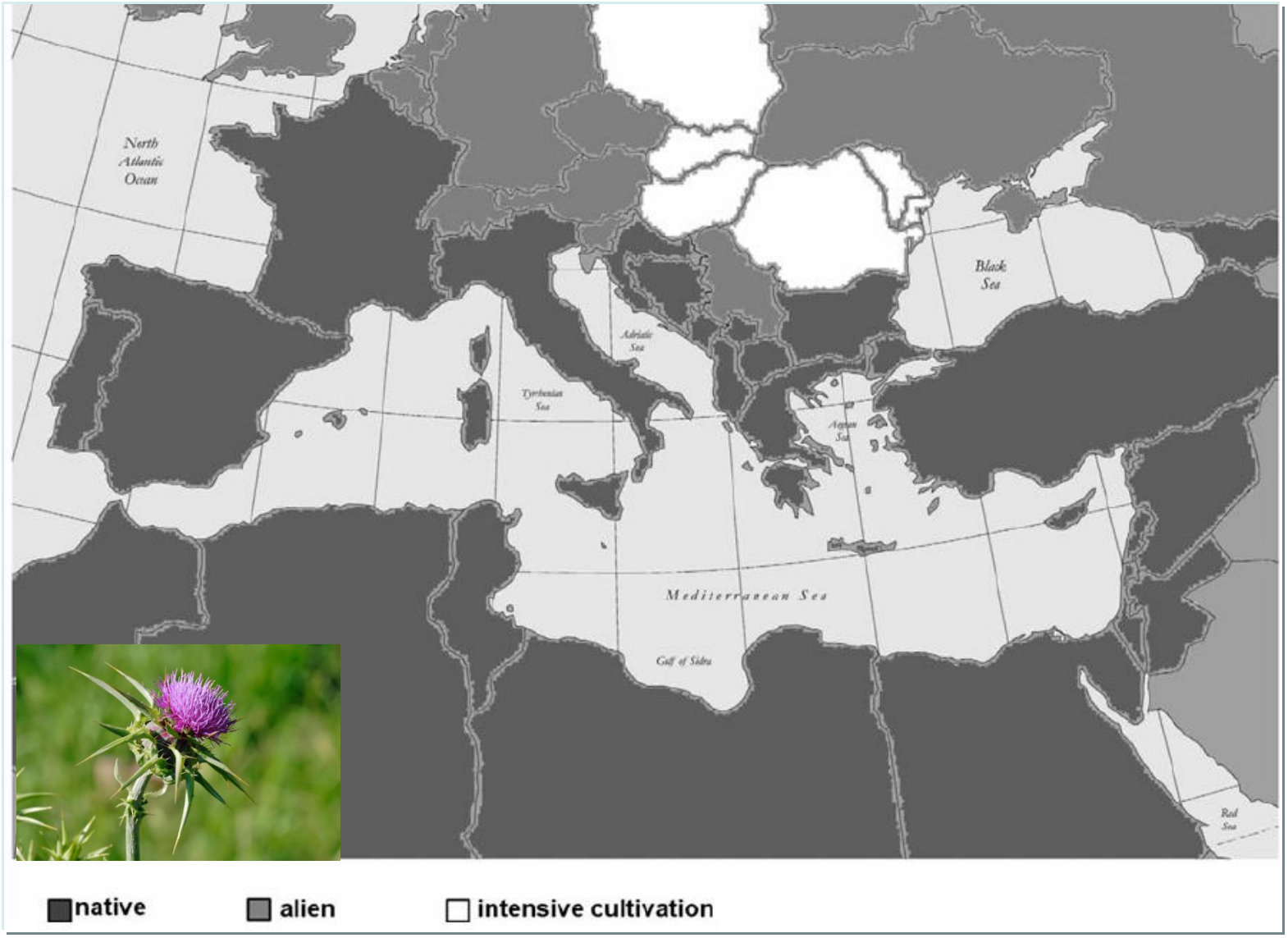
hepatic fat accumulation

insulin sensitivity

gut microbiota

inflammatory status

MILK THISTLE CULTIVATION



Abenavoli *et al*. Phytother Res; 2018

MILK THISTLE AND NAFLD

Free Radical Biology & Medicine 52 (2012) 1658–1665

Contents lists available at SciVerse ScienceDirect

Free Radical Biology & Medicine

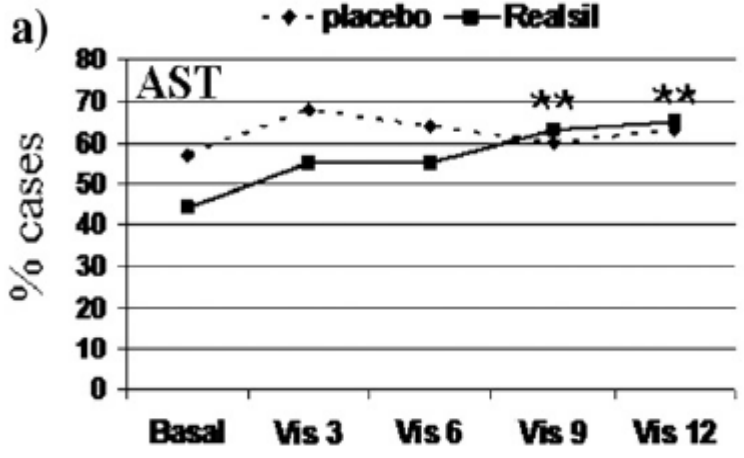
journal homepage: www.elsevier.com/locate/freeradbiomed

Original Contribution

Silybin combined with phosphatidylcholine and vitamin E in patients with nonalcoholic fatty liver disease: A randomized controlled trial

Carmela Loguercio [a,*], Pietro Andreone [b], Ciprian Brisc [c], Michaela Cristina Brisc [c], Elisabetta Bugianesi [d], Maria Chiaramonte [e], Carmela Cursaro [b], Mirela Danila [f], Ilario de Sio [a], Annarosa Floreani [g], Maria Antonietta Freni [h], Antonio Grieco [i], Marzia Groppo [j], Roberta Lazzari [g], Salvatore Lobello [g], Elisabetta Lorefice [k], Marzia Margotti [b], Luca Miele [i], Stefano Milani [k], Lajos Okolicsanyi [j], Giuseppe Palasciano [l], Piero Portincasa [l], Patrizia Saltarelli [m], Antonina Smedile [d], Francesco Somalvico [n], Aldo Spadaro [h], Ioan Sporea [f], Paolo Sorrentino [o], Raffaela Vecchione [o], Concetta Tuccillo [a], Camillo Del Vecchio Blanco [a], Alessandro Federico [a]

First phase III, multicenter, randomized, double-blind controlled clinical trial on MT complex *vs* placebo (for 12 months) in pts with NAFLD


a)
placebo
Realsil
AST
% cases
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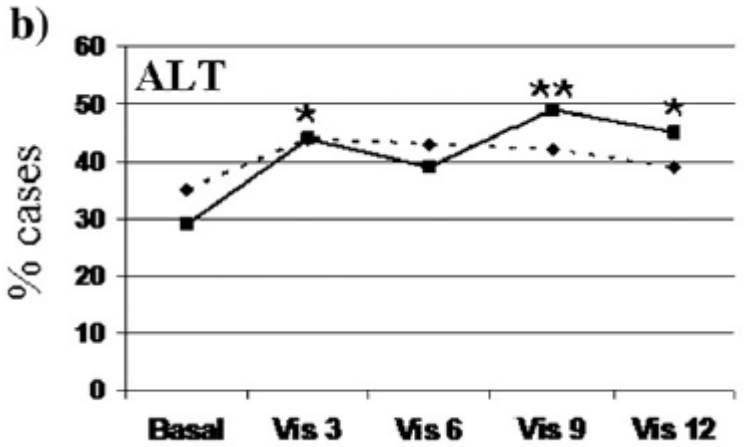
10
20
30
40
50
60
70
80
**
**
Basal
Vis 3
Vis 6
Vis 9
Vis 12


b)
ALT
% cases
0
10
20
30
40
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60
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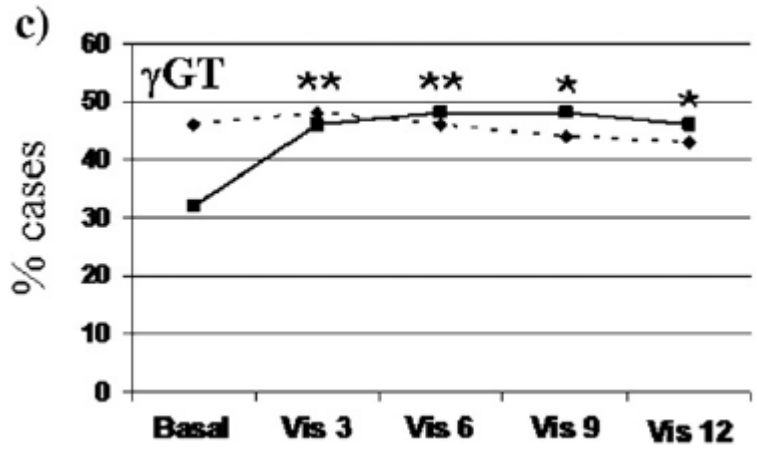
*
Basal
Vis 3
Vis 6
Vis 9
Vis 12

***p<0.05 **p<0.001**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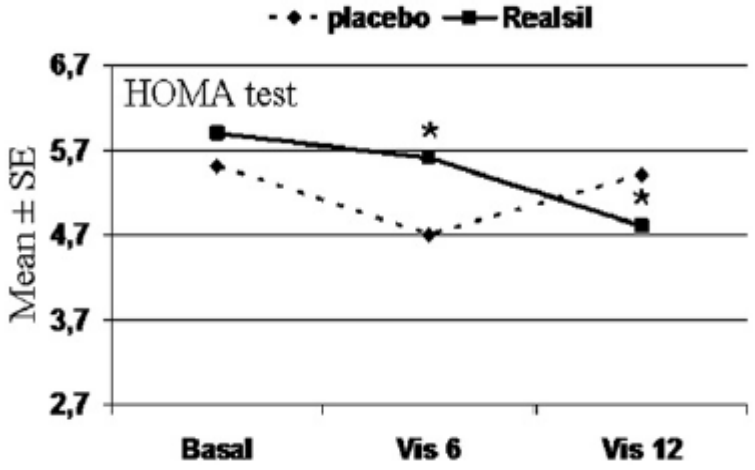
Vis 12


placebo
Realsil
HOMA test
Mean ± SE
2,7
3,7
4,7
5,7
6,7
*
*
Basal
Vis 6
Vis 12

Effect of RA or P treatment on liver histology at T_{12}.

	RA group			P group		
	T_0	T_{12}	p (T_0 vs T_{12})	T_0	T_{12}	p (T_0 vs T_{12})
Steatosis			0.004			0.32
Low/moderate	40	75		83	83	
Severe	60	25		17	17	
Lobular inflammation			0.013			0.11
Absent/low	63	89		100	100	
Moderate	37	11		0	0	
Ballooning			0.009			0.11
Absent/low	50	90		75	73	
Moderate	50	30		25	25	
Fibrosis			0.023			0.69
Absent/minimal	20	60		75	66	
Moderate	25	5		0	17	
Portal–periportal	15	25		17	9	
Perisinusoidal	35	5		0	0	
Bridging fibrosis	5	5		8	8	
NAS (mean ± SD)	5.05 ± 1.35	3.47 ± 1.95	0.003	3.90 ± 0.88	3.32 ± 1.93	0.13

RA, Realsil; P, placebo; T_0, baseline; T_{12}, 12 months of treatment; NAS, nonalcoholic fatty liver disease activity score.

MILK THISTLE AND NAFLD

"Effect of Mediterranean Diet and Antioxidant Formulation in Non-Alcoholic Fatty Liver Disease: A Randomized Study"

Abenavoli *et al*. Nutrients; 2017

	Group A	Group B	Group C	*p*
Weight (Kg)	6% (-)	7% (-)	0.5% (-)	A vs C **0.0001** B vs C **0.030** A vs B 0.665
BMI (Kg/m^2)	7.5% (-)	9% (-)	0.45% (-)	A vs C **0.0001** B vs C **0.0001** A vs B 0.935
Waist circumference (cm)	2.8% (-)	6% (-)	0.3% (-)	A vs C **0.0001** B vs C **0.0001** A vs B **0.030**
Hip circumference (cm)	3.3% (-)	4% (-)	0.7% (-)	A vs C **0.001** B vs C **0.001** A vs B 0.206
Fasting glucose (mg/dL)	3.5% (-)	11% (-)	0.5% (-)	A vs C 0.724 B vs C **0.006** A vs B **0.016**
Insulin (mU/L)	10% (+)	38% (-)	25% (+)	A vs C **0.045** B vs C **0.0001** A vs B **0.0001**
Triglycerides (mg/dL)	32.16% (-)	21% (-)	2.8% (+)	A vs C **0.001** B vs C **0.002** A vs B 0.935
Total cholesterol (mg/dL)	14.8% (-)	17% (-)	9.3% (+)	A vs C **0.0001** B vs C **0.0001** A vs B 0.626
LDL-C (mg/dL)	15% (-)	9% (-)	29% (-)	A vs C 0.217 B vs C 0.234 A vs B 0.705
HOMA-IR	6.2% (+)	43% (-)	46% (+)	A vs C **0.021** B vs C **0.001** A vs B **0.0001**
TyG index	3.3% (-)	1.2% (-)	1% (+)	A vs C **0.020** B vs C **0.010** A vs B 0.131
FL index	19% (-)	27% (-)	4.7% (+)	A vs C **0.017** B vs C **0.0001** A vs B 0.626
TE	21% (-)	27% (-)	8.7% (+)	A vs C **0.001** B vs C **0.0001** A vs B 0.053

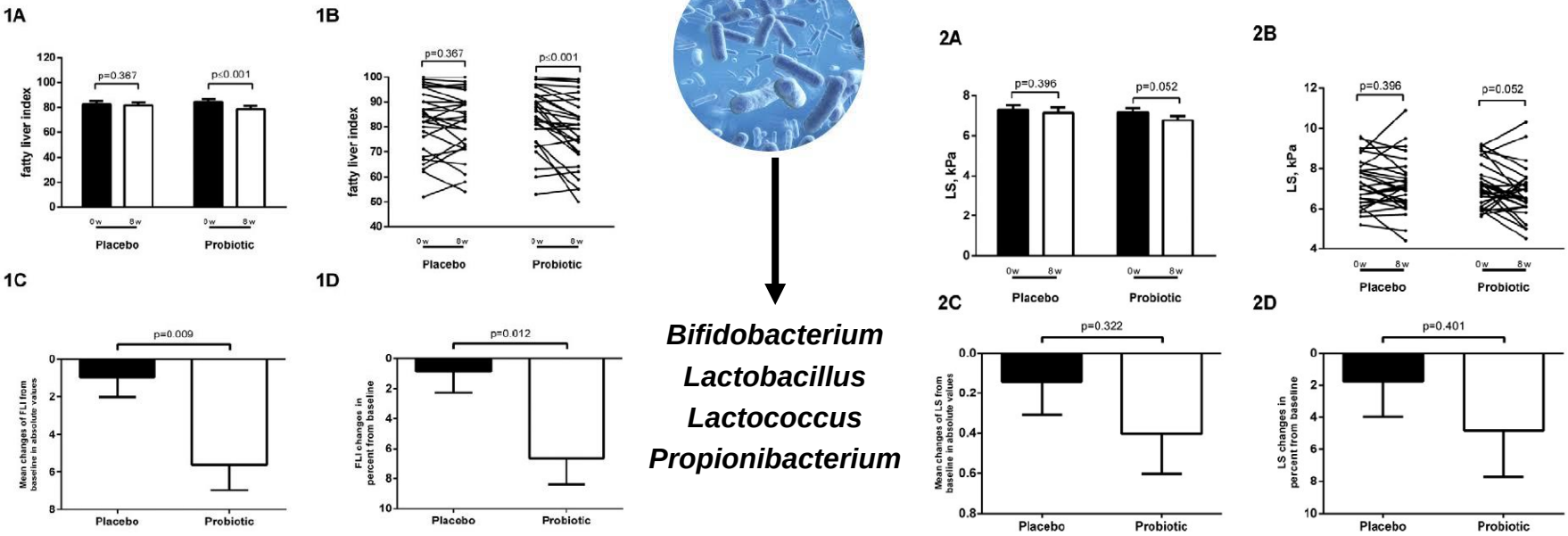
PROBIOTICS AND NAFLD

ORIGINAL PAPER

Available from: http://www.jgld.ro/wp/archive/y2018/n1/a8
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.271.kby

A Multi-strain Probiotic Reduces the Fatty Liver Index, Cytokines and Aminotransferase levels in NAFLD Patients: Evidence from a Randomized Clinical Trial

Nazarii Kobyliak[1], Ludovico Abenavoli[2], Galyna Mykhalchyshyn[1], Liudmyla Kononenko[1], Luigi Boccuto[3], Dmytro Kyriienko[1,4], Oleg Dynnyk[5]



PROBIOTICS AND NAFLD

first hit

second hit

INSULIN RESISTANCE

hyperinsulinism

hyperglycaemia

peripheral lipolysis

STEATOSIS

overloaded mitochondrial β-oxydation

CYP2E1-induction

small intestinal bacterial overgrowth

intestinal permeability

gut-derived endotoxins (LPS, NH3, acetaldehyde)

Kupffer cells (activation of NF-kB)

TNF-α, IL6 iNOS, COX-2

INFLAMMATION

↑ ROS

OXIDATIVE STRESS

stellate cells

lipid peroxidation

TGF-β, α-SMA collagen MMPs

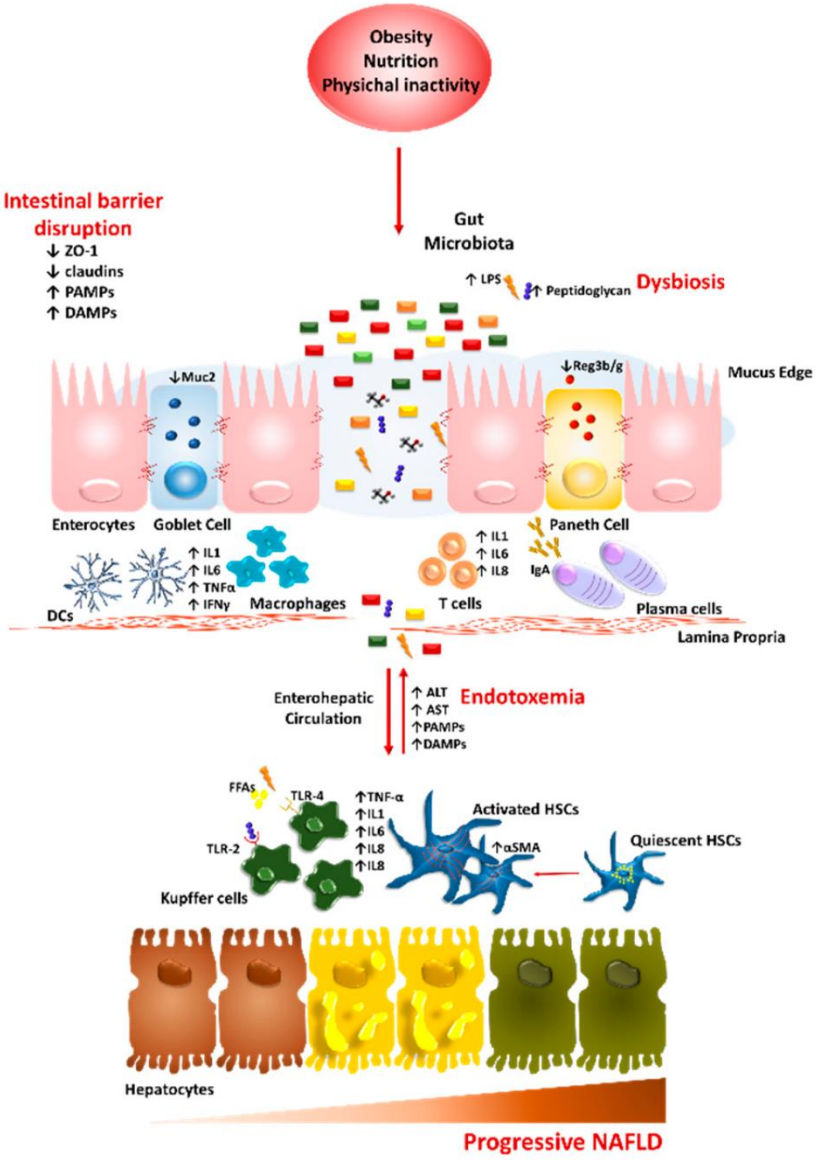
NECROSIS

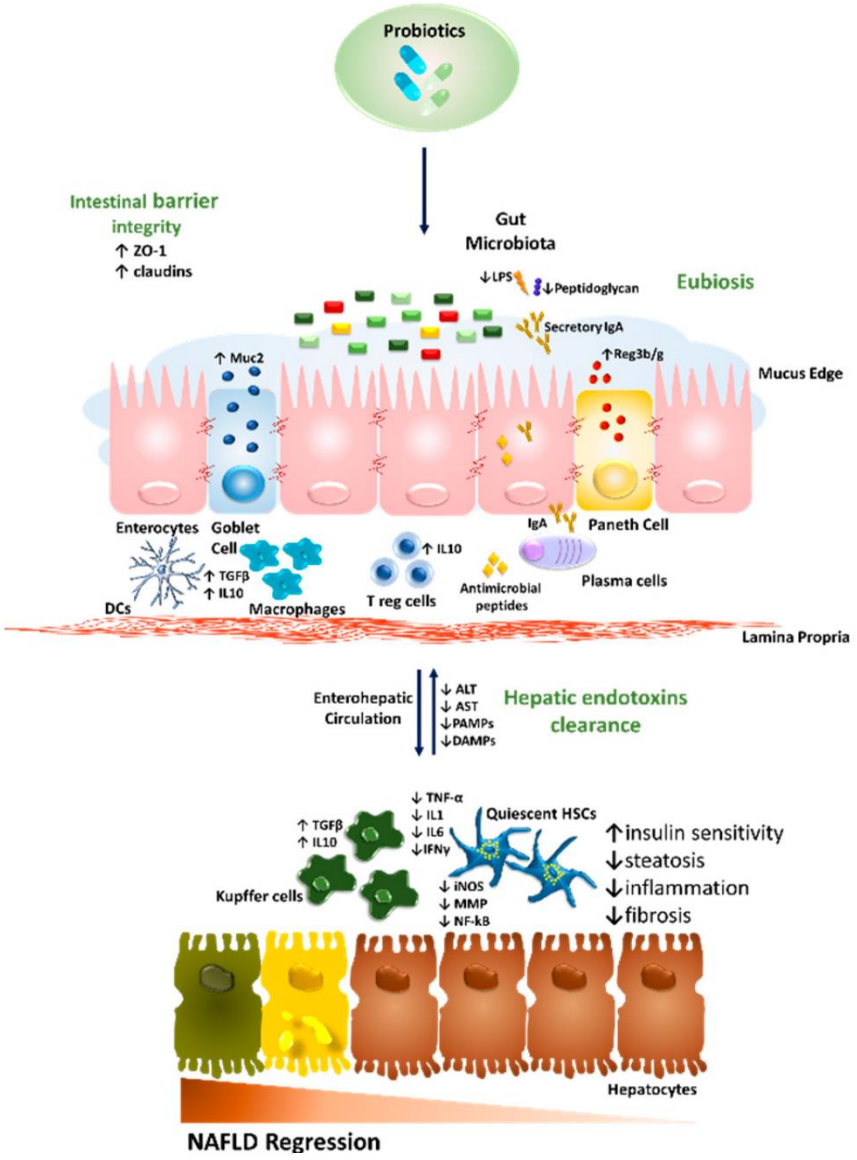
STEATO-HEPATITIS

FIBROSIS

neutrophils

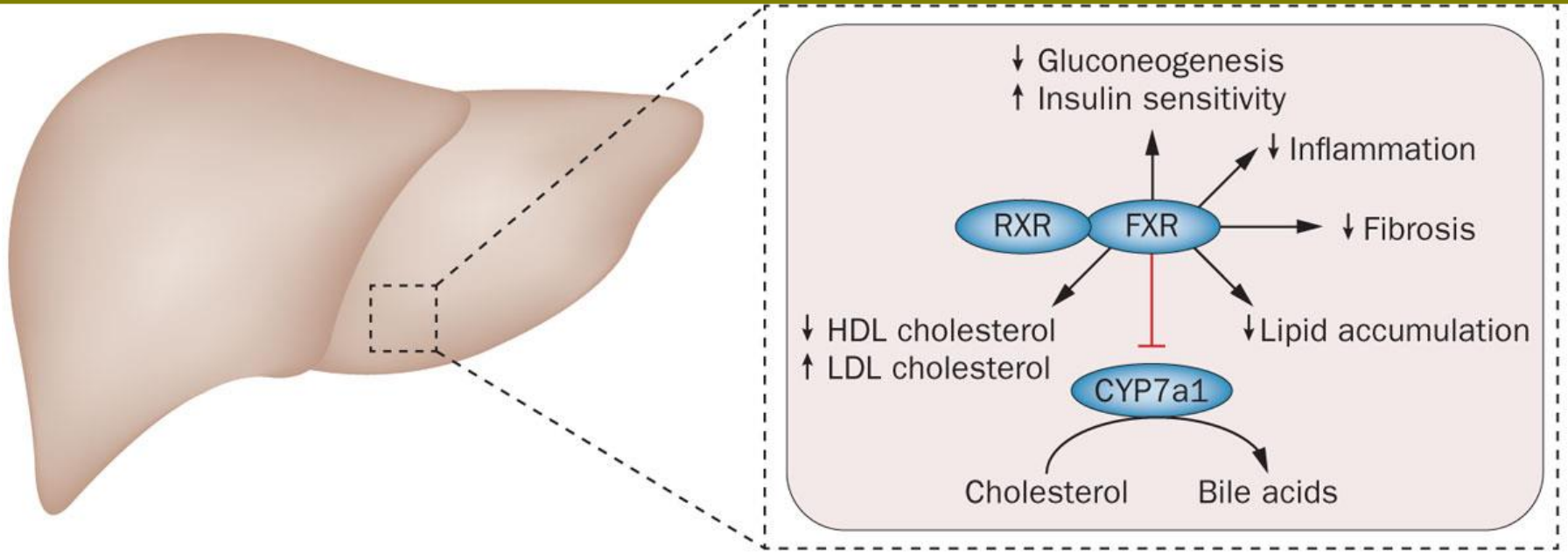
PROBIOTICS AND NAFLD





Meroni et al. Nutrients; 2019

OBETICHOLIC ACID AND NAFLD



Rinella and Sanyal. Nat Rev Gastroenterol Hepatol; 2014

The farnesoid X receptor (FXR) is a metabolic nuclear receptor expressed in the liver, involved in the regulation of the expression and function of genes involved in bile acids synthesis, uptake and excretion

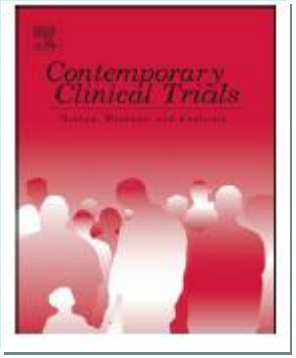
Obeticholic acid, a semi-synthetic bile acid ligand for FXR, 100× more potent than its natural ligand, might be able to ameliorate several metabolic derangements seen in NASH by inhibiting hepatic stellate cell activity

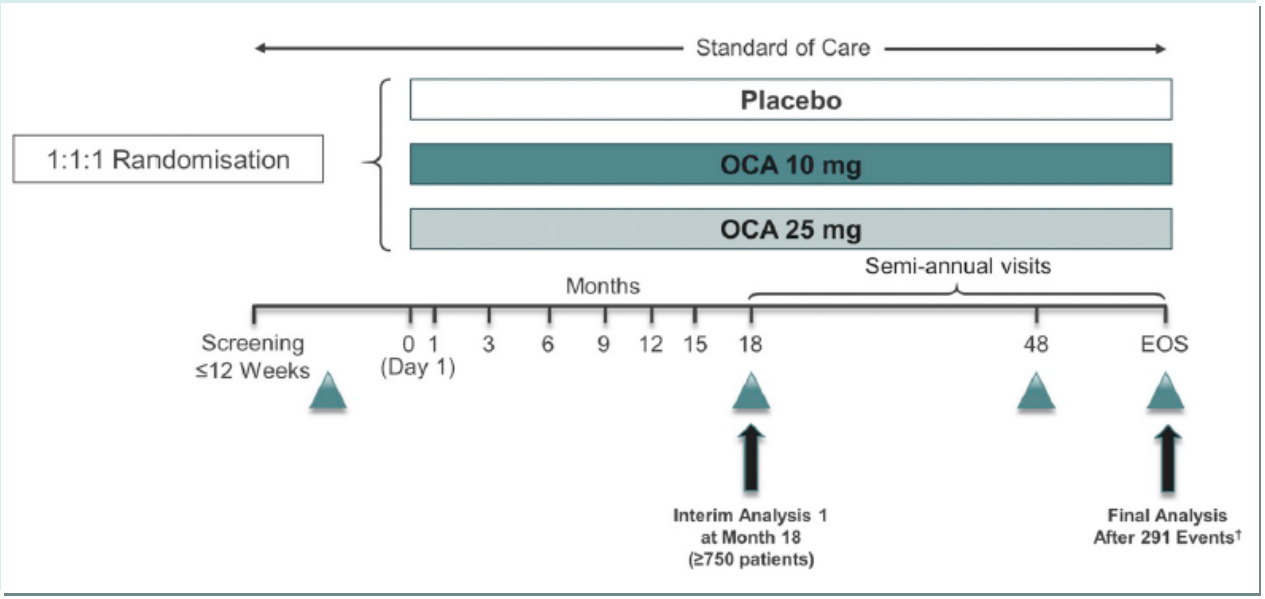
OBETICHOLIC ACID AND NAFLD

Authors	Phase/ Status	Patient population	Duration	Primary/ Secondary Endpoints	Intervention dosage/ Subjects	Findings
FLINT study (NCT01265498)	III / Completed	Biopsy proven NASH	72 weeks	Histological Improvement in NAS (no worsening in fibrosis; and decrease in NAFLD Activity Score (NAS) of at least 2 points	25 mg OCA (n=141) Placebo (n=142)	Primary endpoint was achieved in 45% of the patients receiving OCA and 21% of those receiving placebo
Mudaliar et al. (NCT00501592)	II / Completed	Type 2 diabetes patient with presumed NAFLD	6 weeks	Assessing changes in insulin resistance and glucose homeostasis / Hepatocellular function	25 mg OCA (n=20) 50 mg OCA (n=21) Placebo (n=23)	Administration of 25 or 50 mg OCA increased insulin sensitivity, and reduced markers of liver inflammation and fibrosis
REVERSE study (NCT03439254)	III / Recruitment	Patient with compensated cirrhosis due to NASH	12 months	% subjects with improvement in fibrosis by at least 1 stage with no worsening of NASH, using NASH CRN/ % subjects with improvement in fibrosis by at least 2 stage or with NASH resolution	10 mg OCA 10 up to 25 mg OCA Placebo Totally (n=540)	
RE-GENERATE study (NCT02548351)	III / Recruitment	Patient with non-cirrhotic NASH with liver fibrosis	18 months	% patients that achieve at least one stage of liver fibrosis improvement with no worsening of NASH, or NASH resolution with no worsening of liver fibrosis / liver-related clinical outcomes	10 mg OCA 25 mg OCA Placebo Totally (n=2370)	
CONTROL study (NCT02633956)	II / Recruitment completed	Biopsy proven NASH with fibrosis stage 1-4	16 weeks	Effect on LDL and LDL particle concentration, LDL particle size	5mg OCA/20mg Atorvastatin (n=20) 10mg OCA/20mg Atorvastatin (n=21) 25mg OCA/20mg Atorvastatin (n=22) Placebo/20mg Atorvastatin (n=21)	

REGENERATE: Design of a pivotal, randomised, phase 3 study evaluating the safety and efficacy of obeticholic acid in patients with fibrosis due to nonalcoholic steatohepatitis

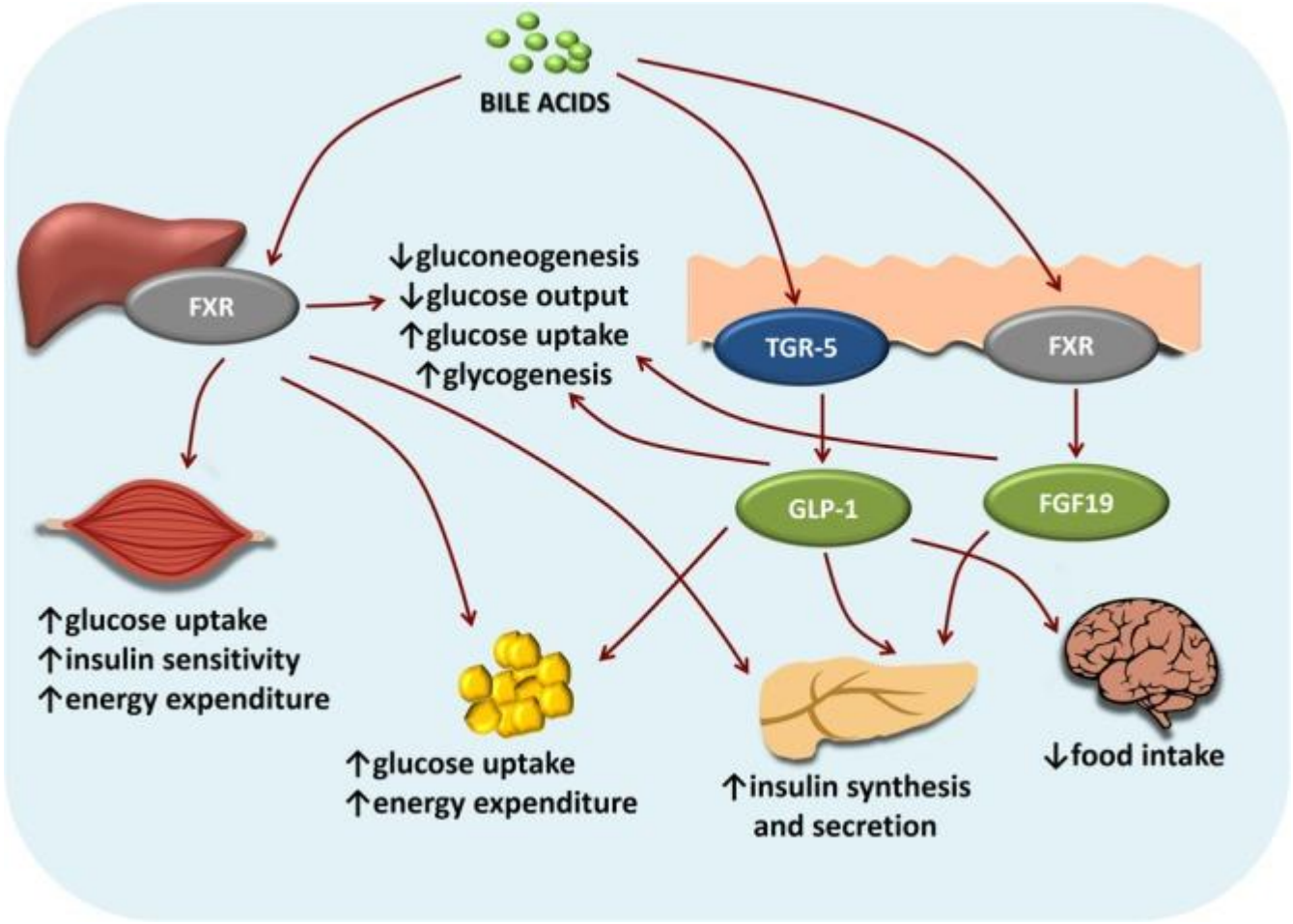
Vlad Ratziu[a,*], Arun J. Sanyal[b], Rohit Loomba[c], Mary Rinella[d], Stephen Harrison[e], Quentin M. Anstee[f], Zachary Goodman[g], Pierre Bedossa[h], Leigh MacConell[i], Reshma Shringarpure[i], Amrik Shah[i], Zobair Younossi[g]





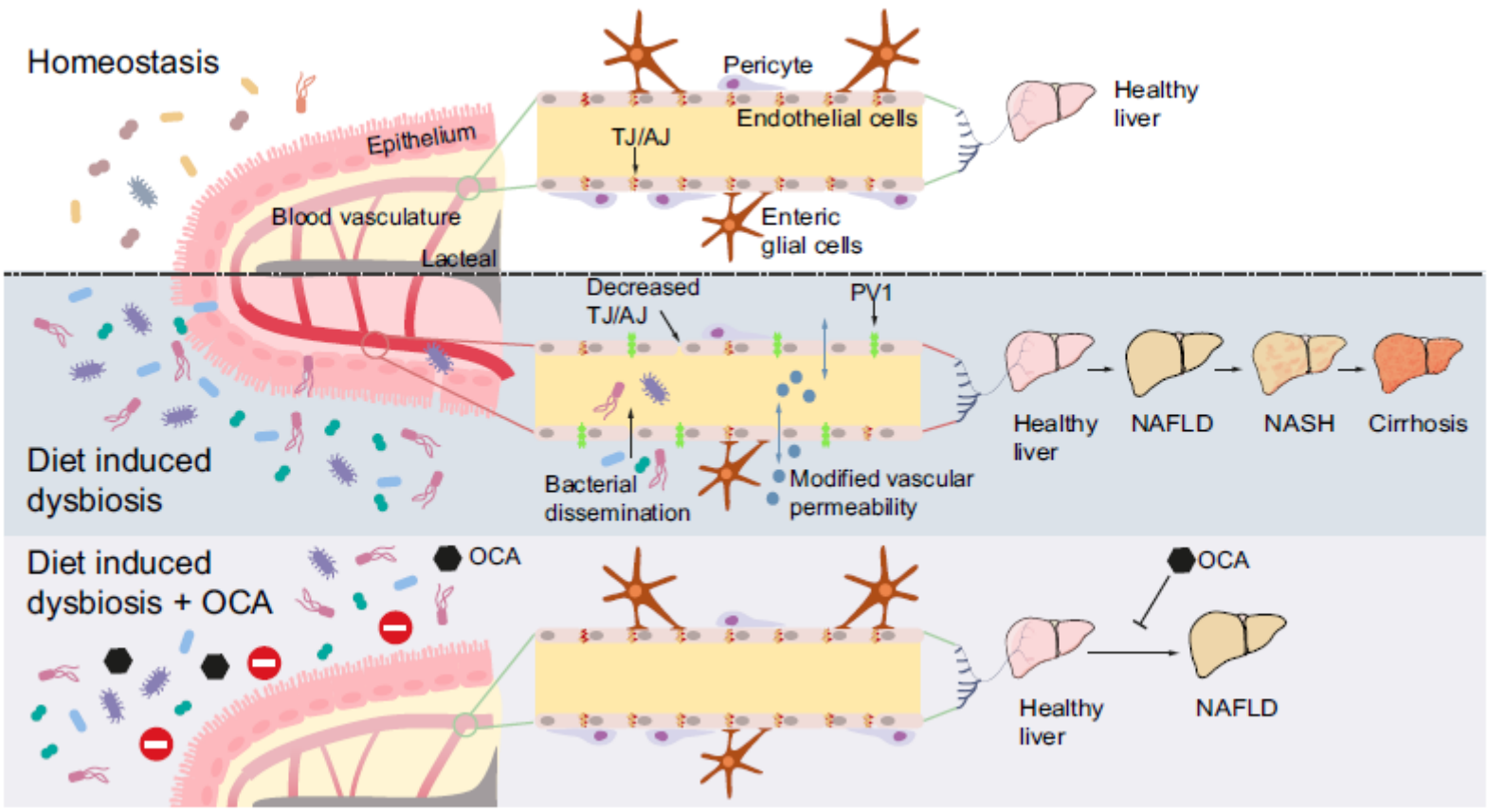
Month 18 interim analyses (All patients)	
Primary objectives	Assessment (Based on liver biopsy using NASH CRN criteria)
Improvement in fibrosis with no worsening of NASH	A ≥ 1-stage reduction in fibrosis and no increase in hepatocellular ballooning, lobular inflammation, or steatosis from baseline
Resolution of NASH with no worsening of fibrosis	NASH resolution defined as the overall histopathologic interpretation of I) "no fatty liver disease" or II) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAS of 0 for ballooning and 0–1 for inflammation with no increase in fibrosis stage from baseline

OBETICHOLIC ACID AND NAFLD



Danic et al. Front Pharmacol; 2018

OBETICHOLIC ACID AND MICROBIOTA



Mouries et al. J Hepatol; 2019

OLT AND NAFLD

- **NASH is the second most common indication for LT in USA (21.5%) and Europe (8.4%), after alcohol-related cirrhosis**

- **During the past 10 years, the prevalence of NAFLD as an indication for LT has increased by 170%**

- **NASH is the second leading etiology for HCC in adults requiring LT in USA**

Pais et al. J Hepatol; 2016
Loomba and Adams. Hepatology; 2019

NAFLD: THE CHALLENGES

NAFLD represents the most common form of chronic liver disease worldwide

Pts with NAFLD should be screened for the different components of MS

The development of new therapeutic strategies of NAFLD is mandatory

In this way, gut microbiota modulation is a promising area for medical research

AND A DIET COKE PLEASE…

THANK YOU

…I DONT WANT TO GET FAT!!!