NON-ALCOHOLIC FATTY LIVER DISEASE IN CHILDREN (NAFLD)

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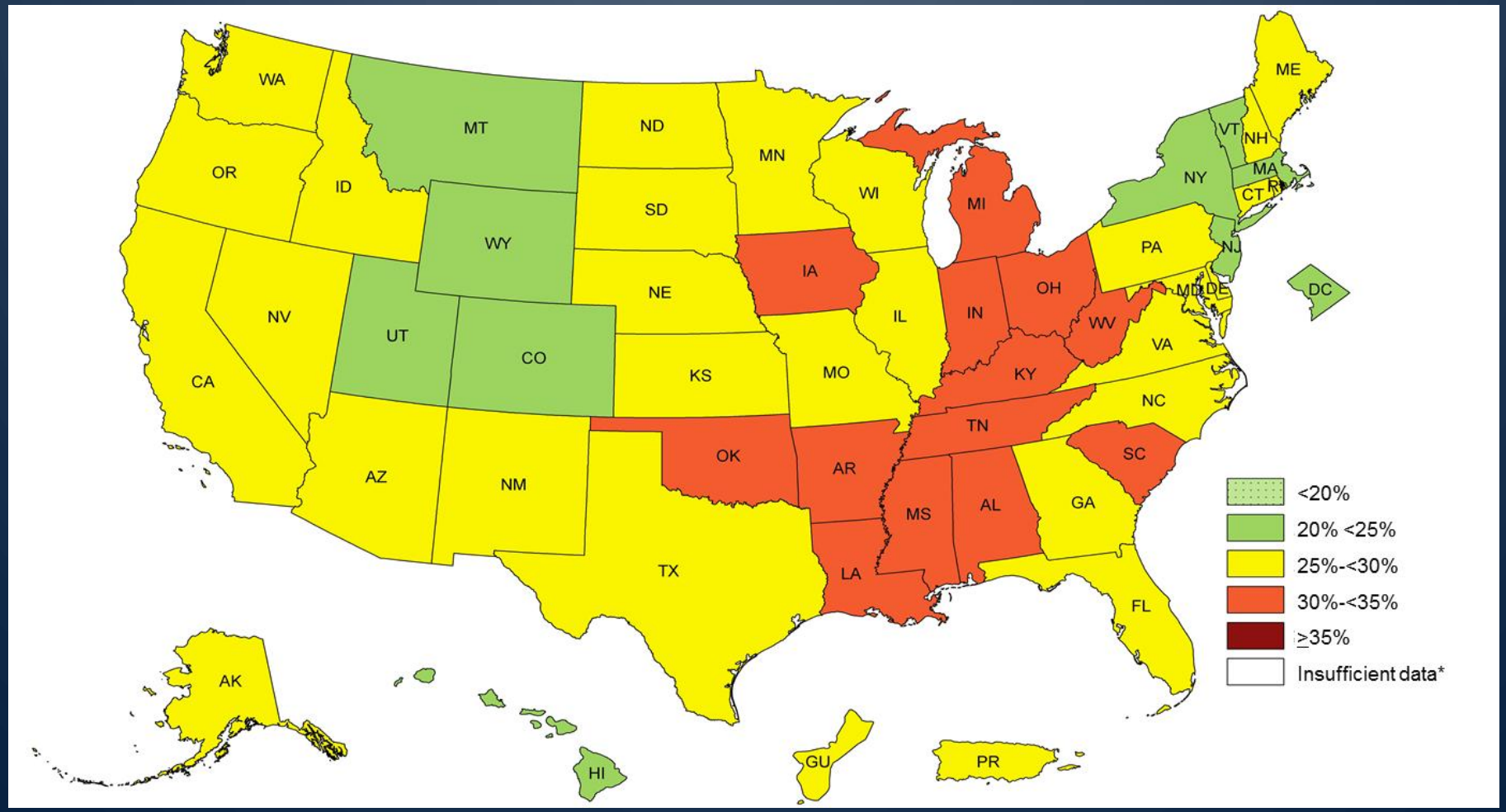
NAFLD

- Pediatric NAFLD is inclusive term referring to the full spectrum of disease Indicates fatty infiltration of the liver in children (18 years or younger), which is not secondary to genetic/ metabolic disorders, infections, use of steatogenic medications, ethanol consumption, or malnutrition.
- Fatty infiltration is typically defined as fat >5% of the liver by imaging, direct quantification, or histologic estimation

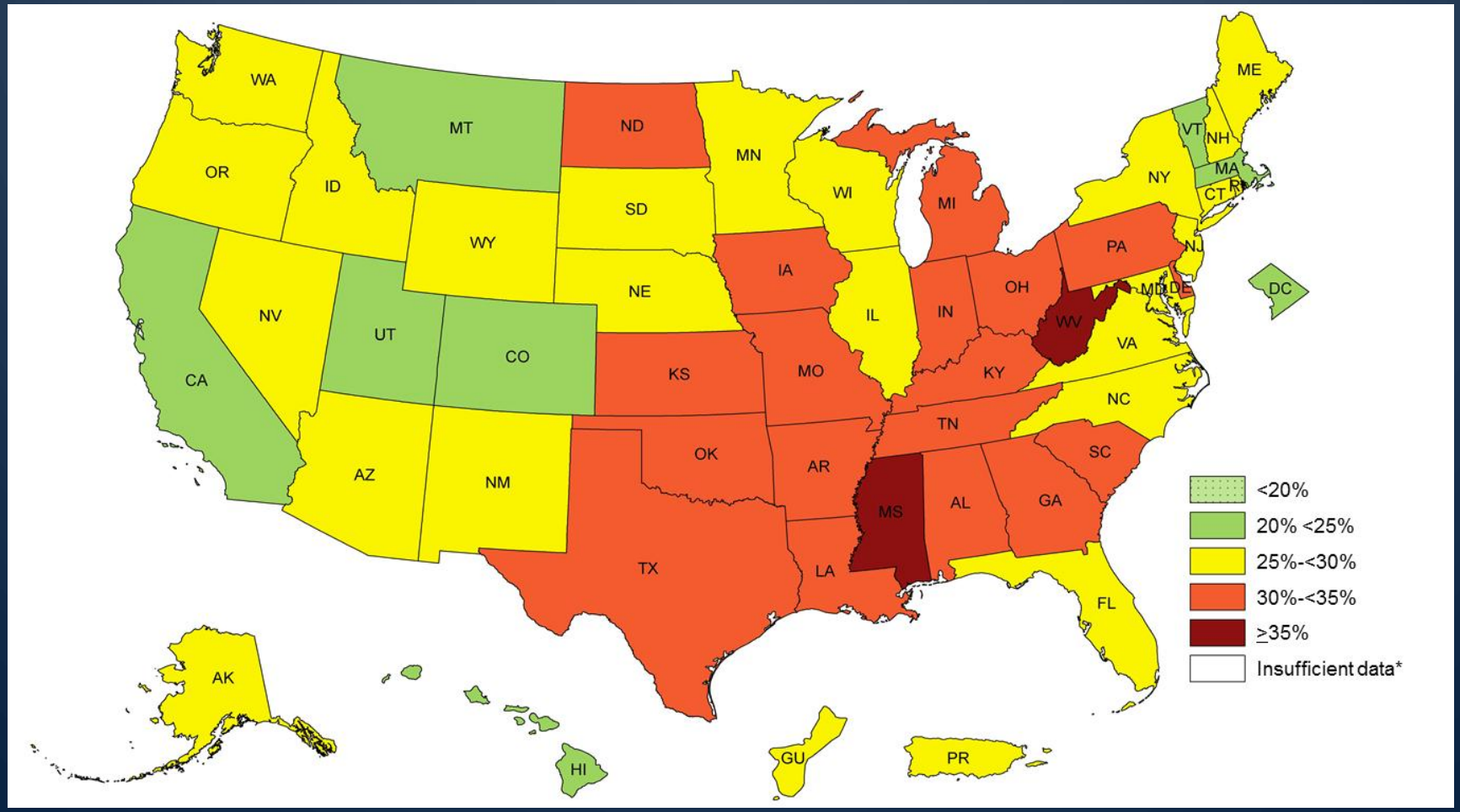
EPIDEMIOLOGY

- The first case of pediatric nonalcoholic fatty liver disease was reported in 1983.
- The prevalence of NAFLD in children ranges between 4.2% to 9.6%, increasing up to 38% in the obese subpopulation.
- NAFLD prevalence ranges from 0.7% in young children ages 2 to 4.
- Most patients are diagnosed after nine years of age.
- This has become the most common etiology of chronic liver disease in children and adolescents in most industrialized countries.
- (NAFLD) affects up to 70% of children with obesity and has become the number one etiology for liver transplant in the United States
- The prevalence of NAFLD is estimated to be 30% in Western populations and up to 90% in patients with insulin resistance, obesity, dyslipidemia, hypertension, and genetic predispositions .

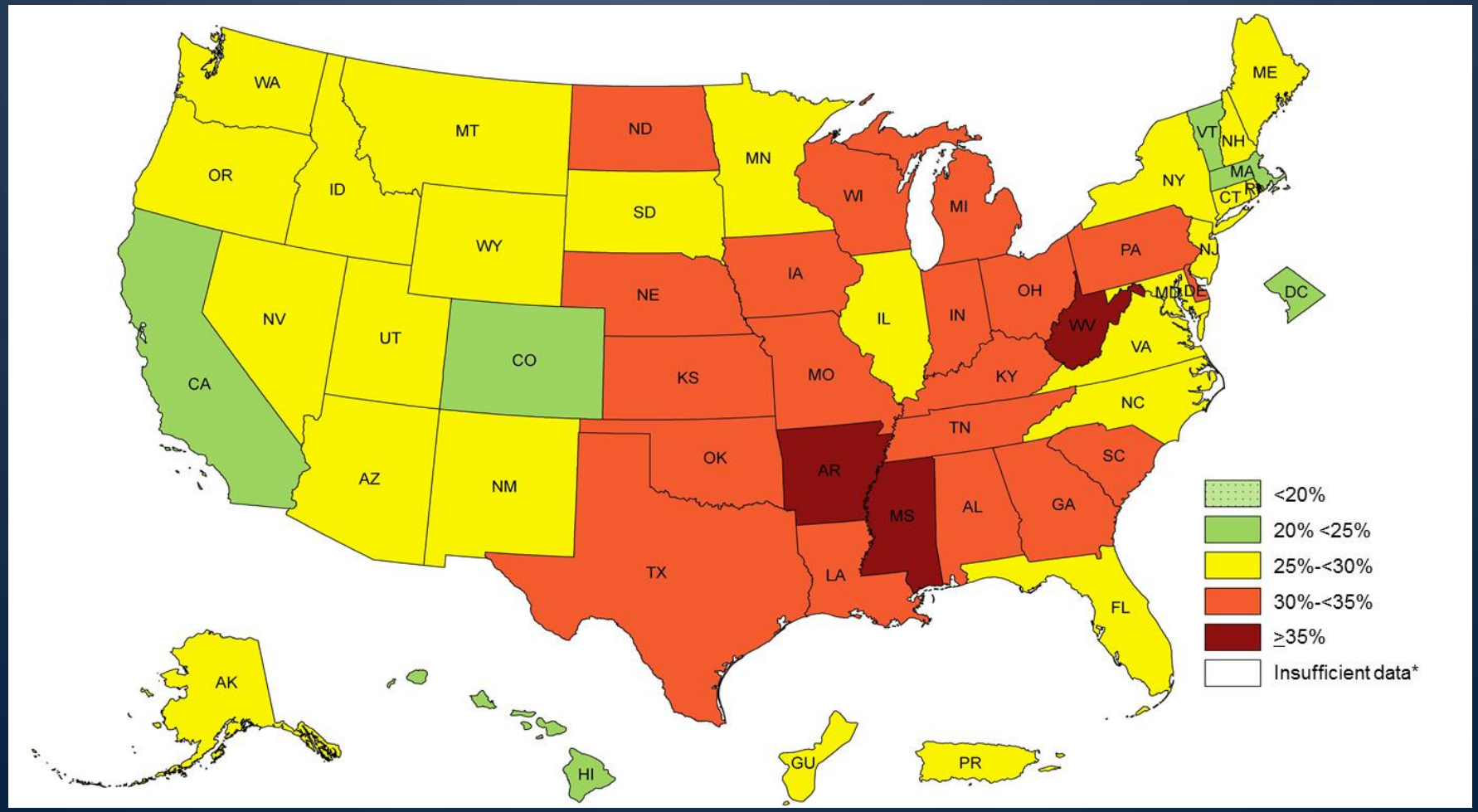
PREVALENCE¶ OF SELF-REPORTED OBESITY AMONG U.S. ADULTS BY STATE AND TERRITORY, BRFSS, 2012



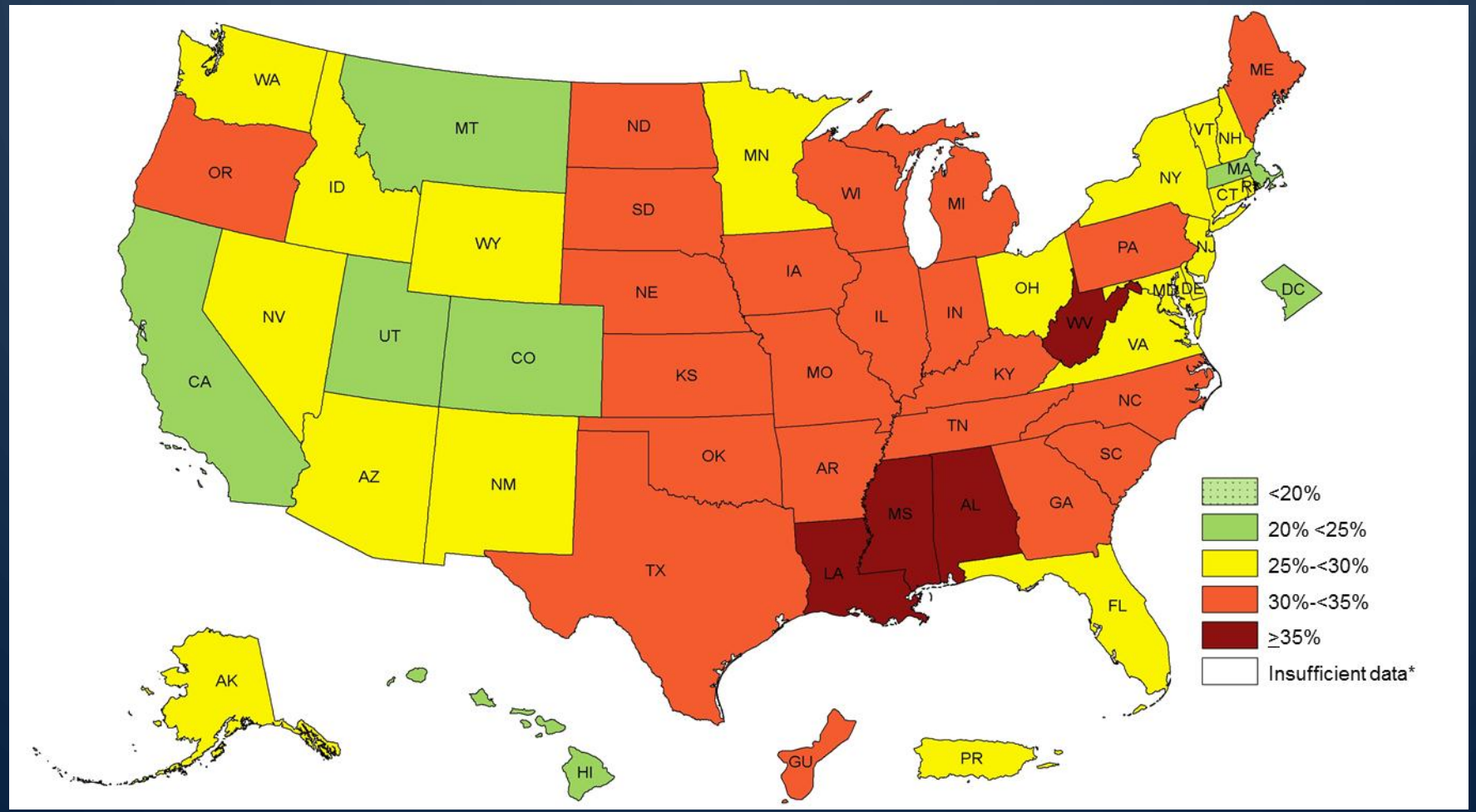
Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2013



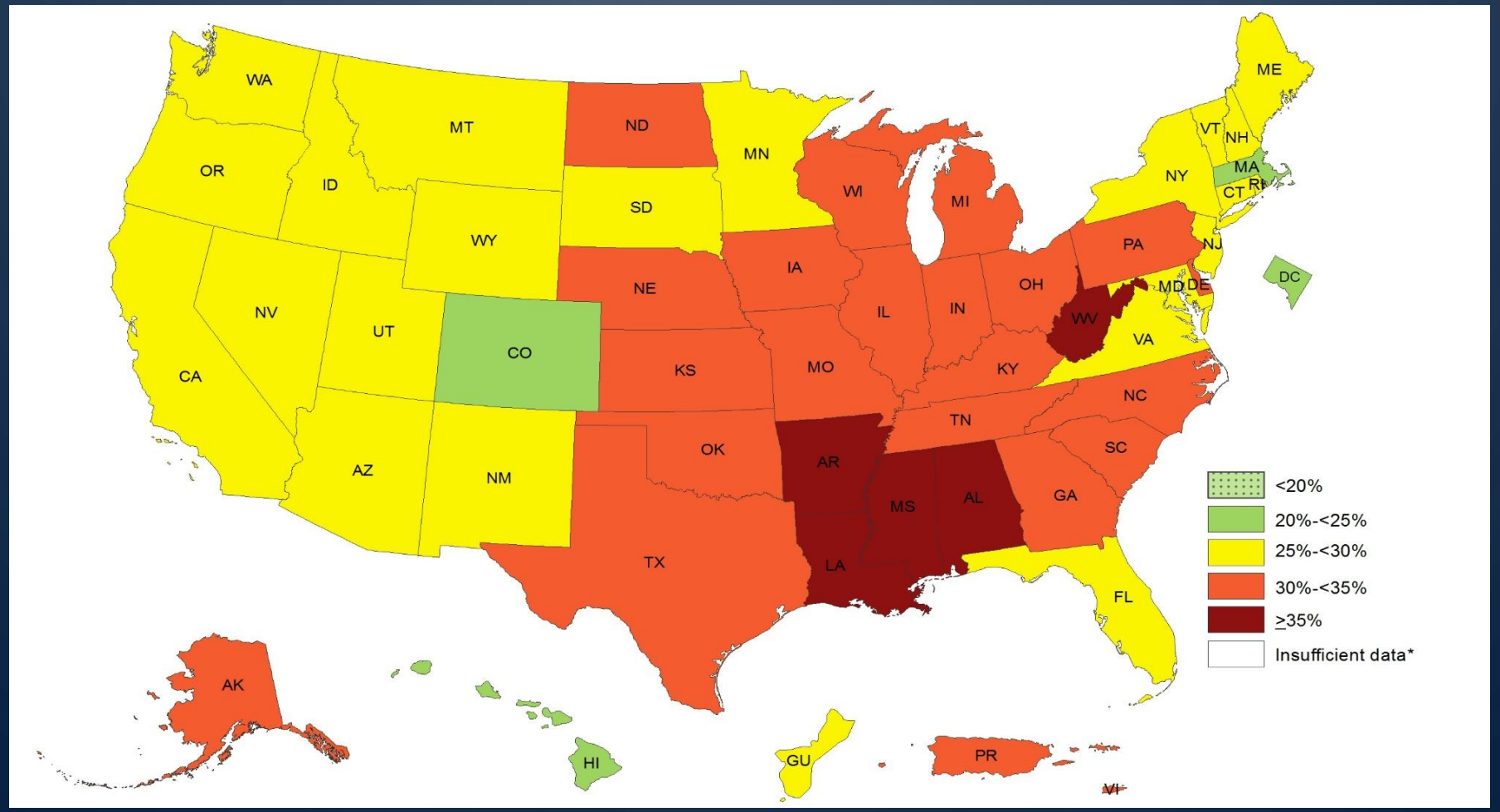
Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014

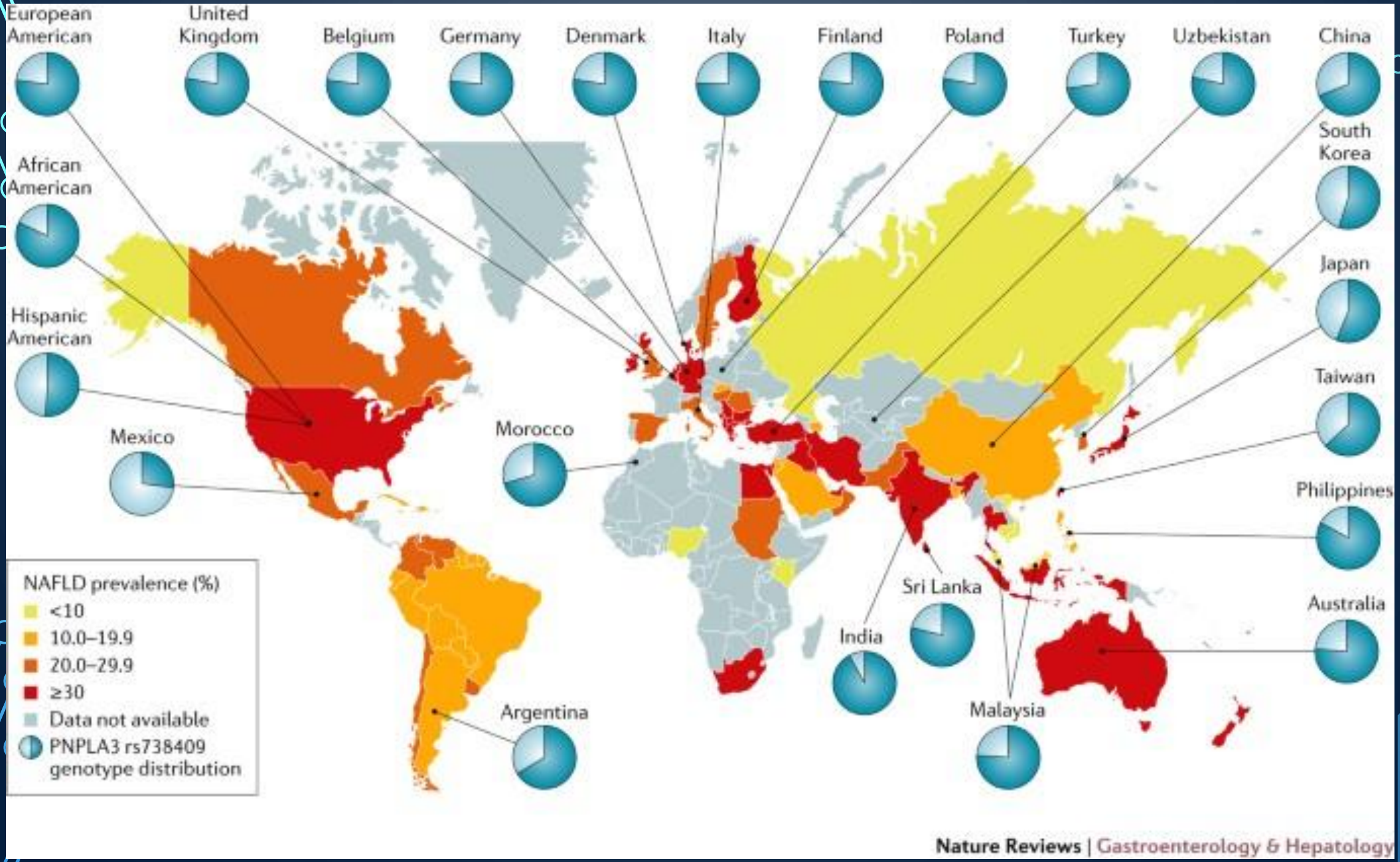


Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2015



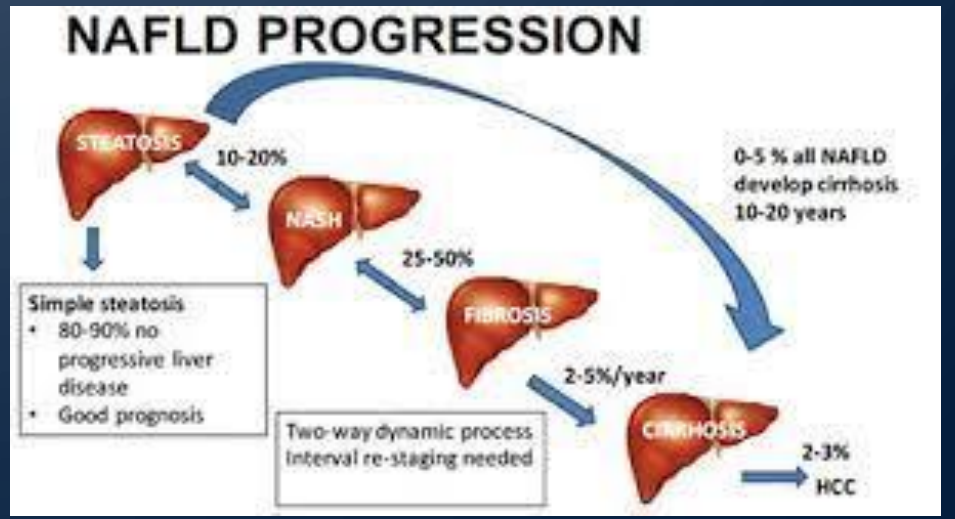
Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2016

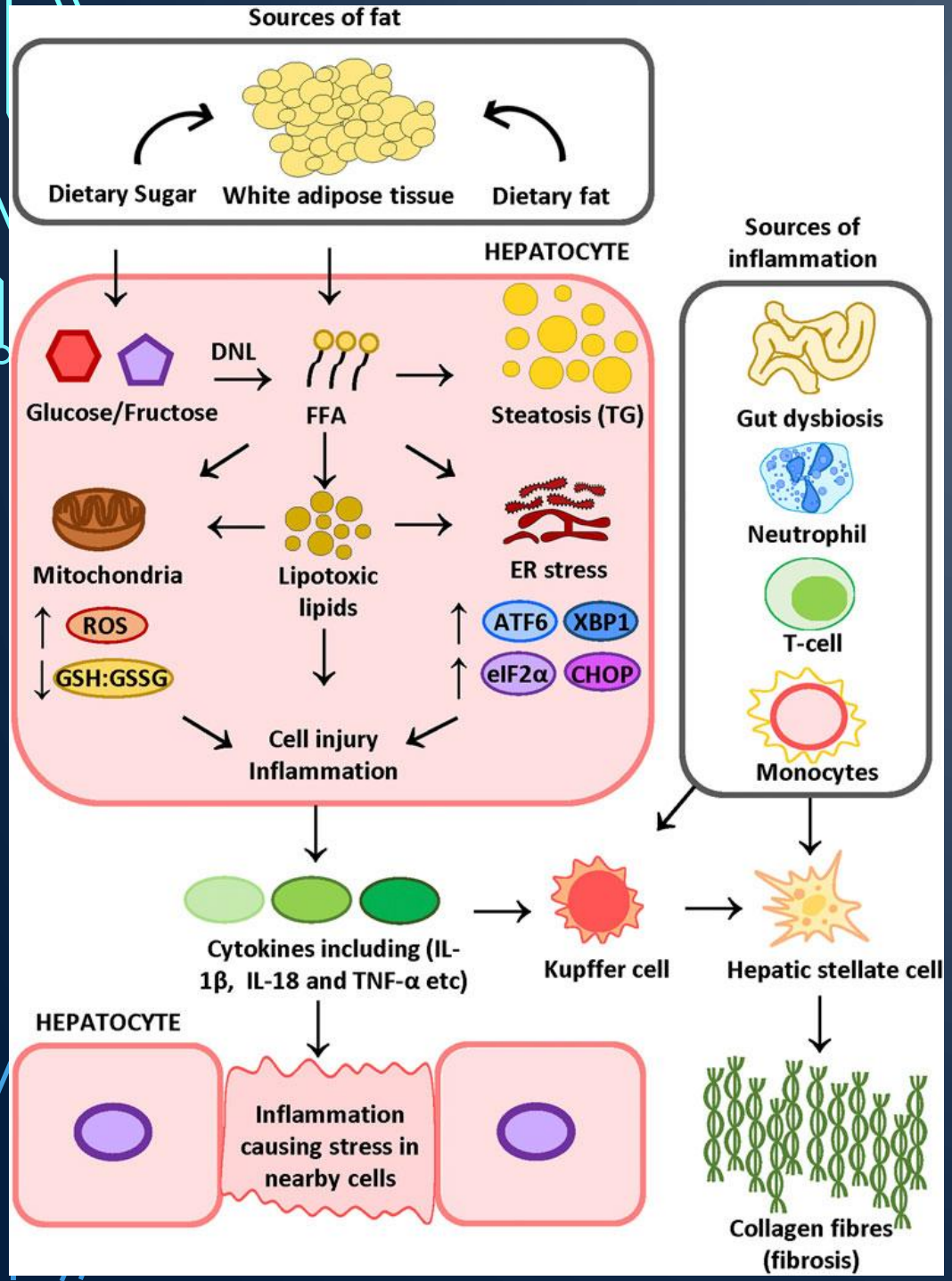


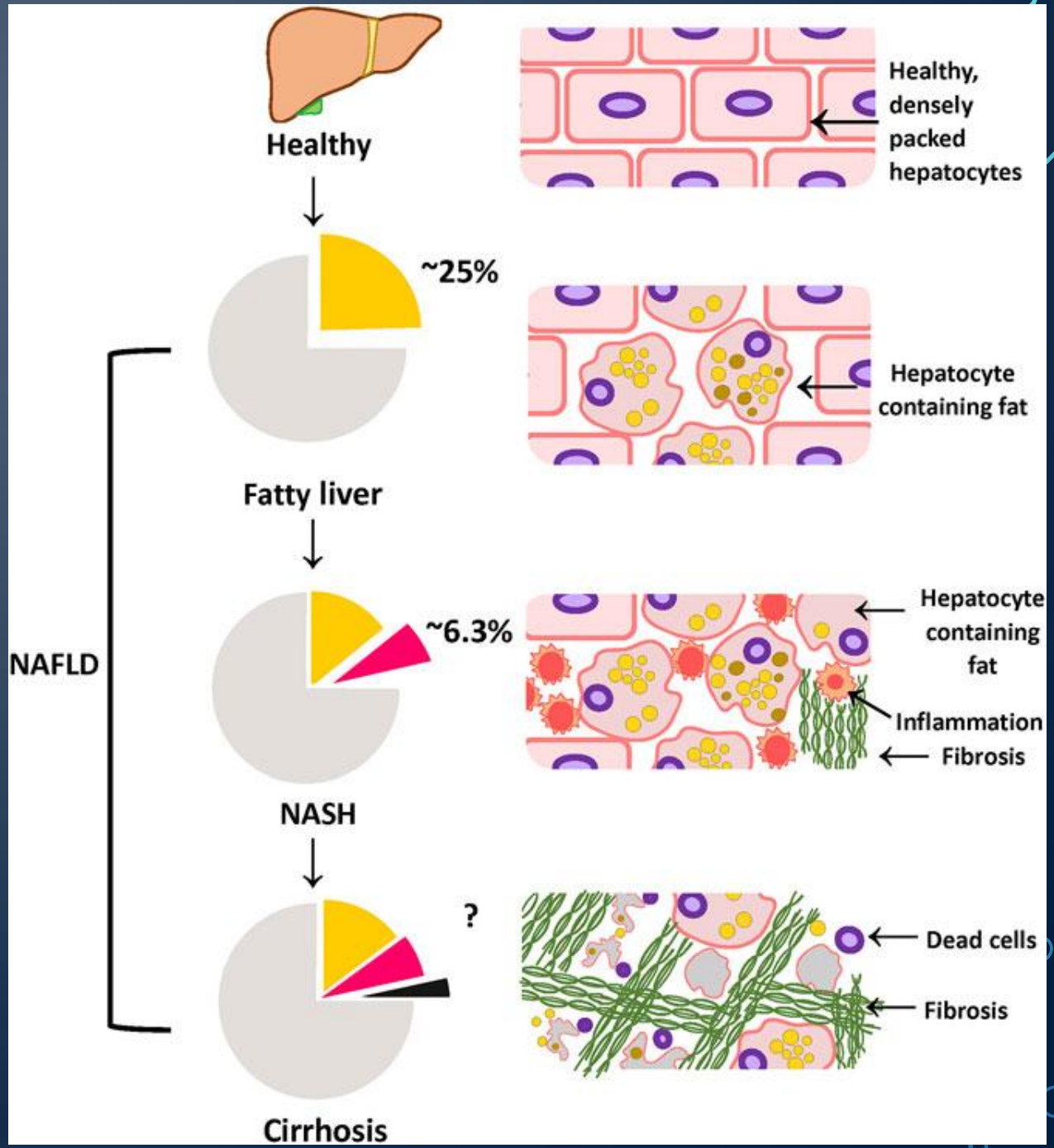

European American
United Kingdom
Belgium
Germany
Denmark
Italy
Finland
Poland
Turkey
Uzbekistan
China
South Korea
African American
Japan
Hispanic American
Taiwan
Mexico
Morocco
Philippines
Sri Lanka
Australia
India
Argentina
Malaysia
NAFLD prevalence (%)
<10
10.0–19.9
20.0–29.9
≥30
Data not available
PNPLA3 rs738409 genotype distribution
Nature Reviews | Gastroenterology & Hepatology

NAFLD

- NAFL
  - Steatosis without specific changes to suggest steatohepatitis, with or without fibrosis
- Pediatric NASH
  - Hepatic steatosis with inflammation, with or without ballooning injury to hepatocytes and fibrosis Zone 3 (venule) centered injury pattern or confluent pattern typically with ballooning Portal predominant (zone 1) centered injury pattern often without ballooning
- NAFLD with fibrosis
  - NAFL or NASH with periportal, portal, or sinusoidal or bridging fibrosis
- NAFLD with cirrhosis
  - Cirrhosis in the setting of NAFLD



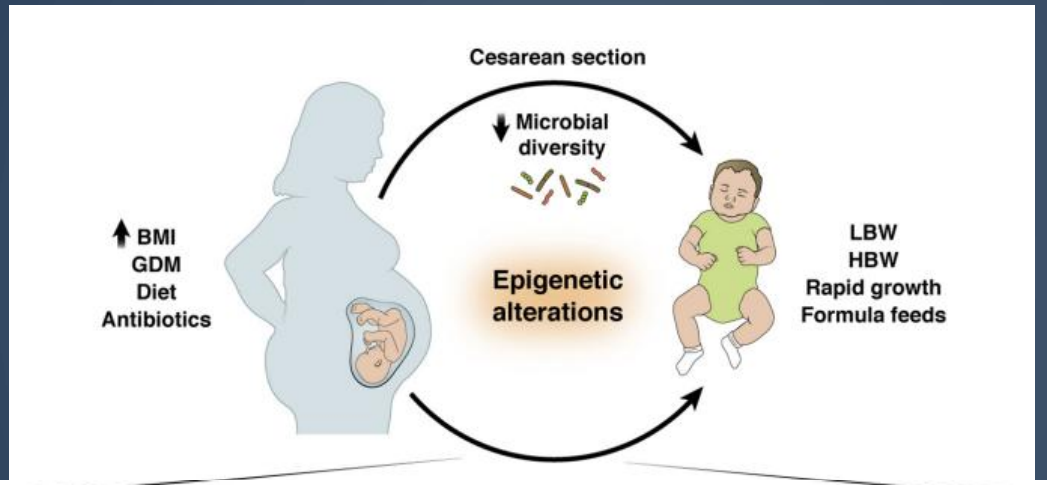

Sources of fat
Dietary Sugar
White adipose tissue
Dietary fat
HEPATOCYTE
Sources of inflammation
DNL
Glucose/Fructose
FFA
Steatosis (TG)
Gut dysbiosis
Neutrophil
Mitochondria
Lipotoxic lipids
ER stress
ROS
GSH:GSSG
ATF6
XBP1
eIF2α
CHOP
T-cell
Cell injury
Inflammation
Monocytes
Cytokines including (IL-1β, IL-18 and TNF-α etc)
Kupffer cell
Hepatic stellate cell
HEPATOCYTE
Inflammation causing stress in nearby cells
Collagen fibres (fibrosis)

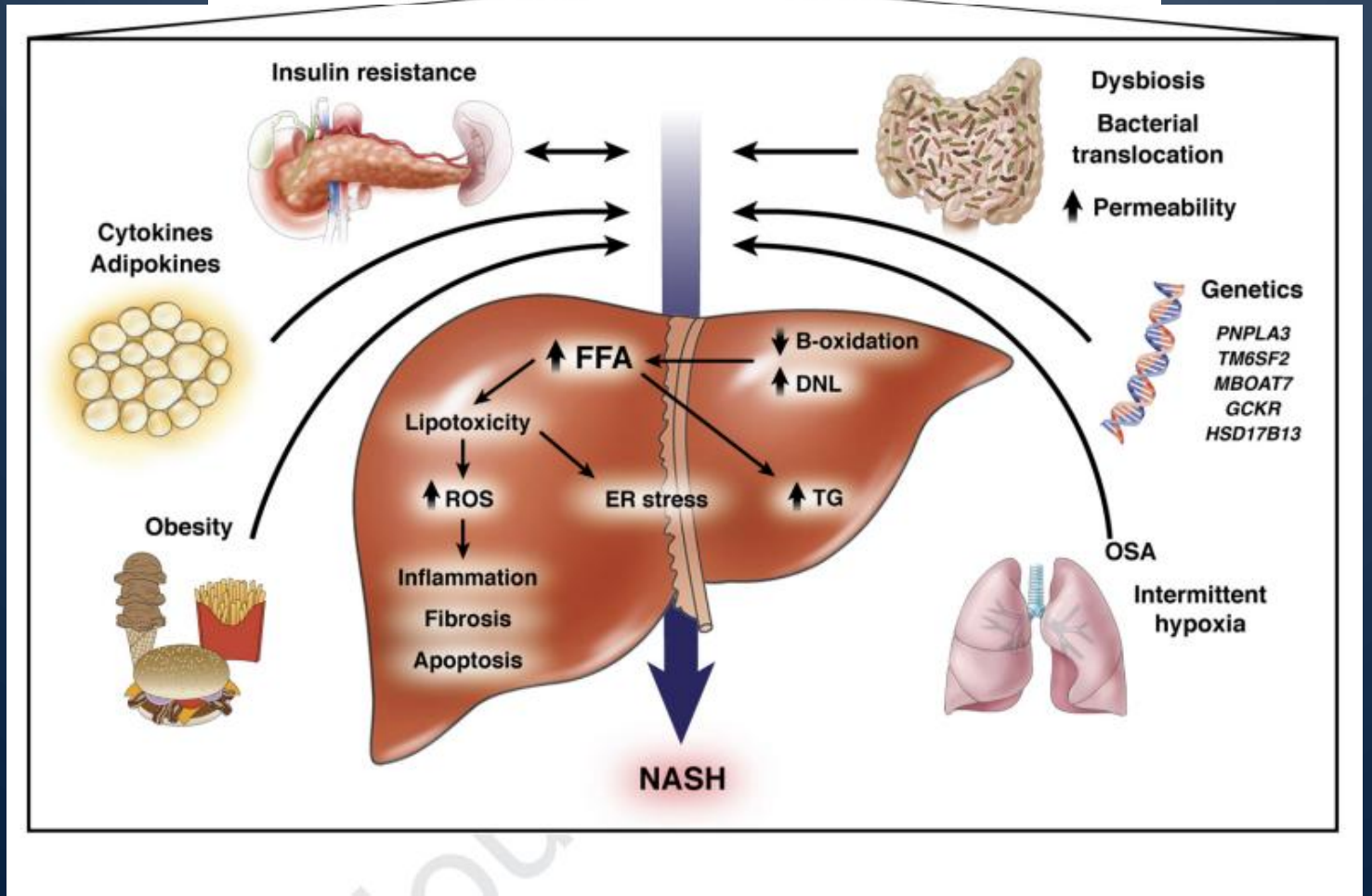

Healthy
Healthy, densely packed hepatocytes
~25%
Hepatocyte containing fat
Fatty liver
NAFLD
~6.3%
Hepatocyte containing fat
Inflammation
Fibrosis
NASH
?
Dead cells
Fibrosis
Cirrhosis

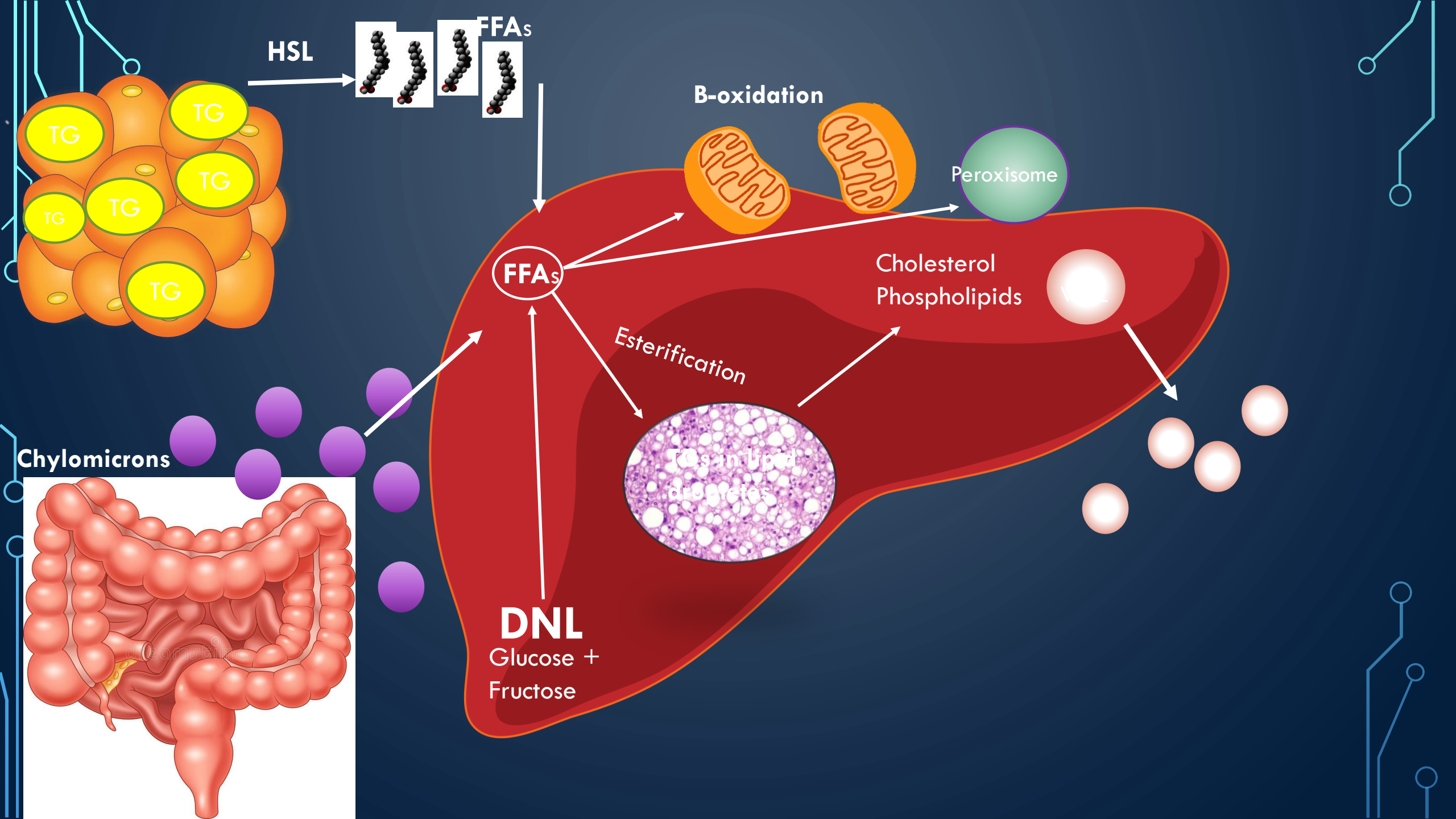
"MULTI-HIT" HYPOTHESIS

- 1. Adipose tissue inflammation
- 2. De novo Lipogensis (DNL)
- 3. Insulin Resistance
- 4. Lipotoxicity
- 5. Mitochondrial Dysfuntion
- 6. Oxidative Stress
- 7. Endoplasmic Reticulum Stress
- 8. Microbiota Associated Mechanism
- 9. Short-Chain Fatty Acids (SCFAs) Relevant Mechanism
- 10. Dietary Choline Mechanism
- 11. Bile Acid Pool Related Mechanism
- 12. Endogenous Alcohol Theory
- 13. Intestinal Permeability and Endotoxemia
- 14. Saturated Fatty Acids
- 15. Fructose 16. Genetics 17. PNPLA3 (Patatin-Like Phosopholipase Domain Containing 3)
- 18. TM6SF2 (Transmembrane 6 Superfamily Member 2) Interplay between Diet, Microbiota, and Host Genetics

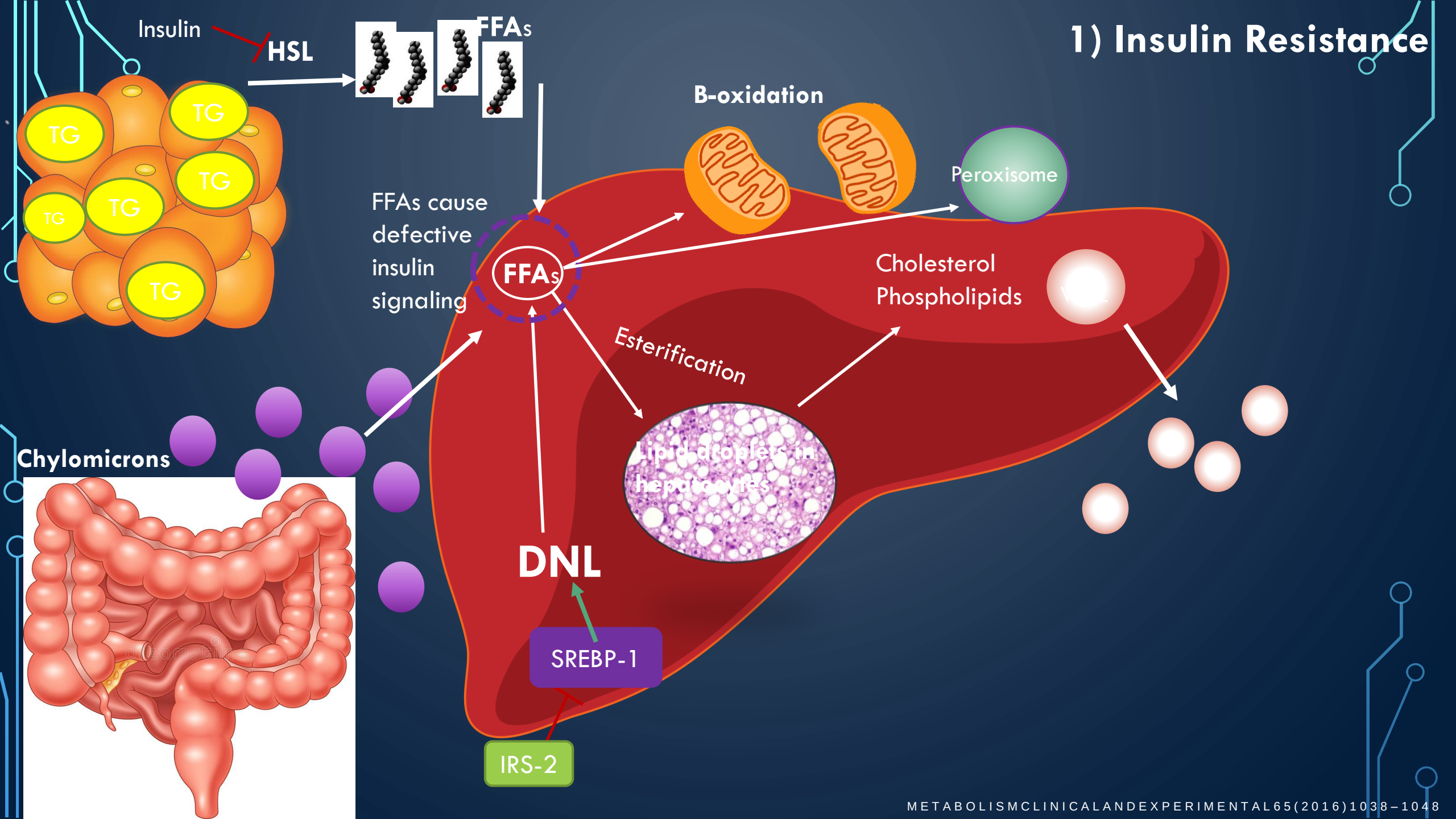
- Gastroenterology Research and Practice Volume 2016, Article ID 2862173, 13 pages "Multi-hit" Hypothesis


Cesarean section
Microbial diversity
BMI
GDM
Diet
Antibiotics
Epigenetic alterations
LBW
HBW
Rapid growth
Formula feeds


Insulin resistance
Dysbiosis
Bacterial translocation
Permeability
Cytokines
Adipokines
Genetics
PNPLA3
TM6SF2
MBOAT7
GCKR
HSD17B13
FFA
B-oxidation
DNL
Lipotoxicity
ROS
ER stress
TG
Obesity
Inflammation
Fibrosis
Apoptosis
OSA
Intermittent hypoxia
NASH


HSL
FFAs
TG
TG
TG
TG
TG
TG
B-oxidation
Peroxisome
FFAs
Cholesterol
Phospholipids
VLDL
Esterification
TGs in lipid droplets
DNL
Glucose +
Fructose
Chylomicrons

1) Insulin Resistance



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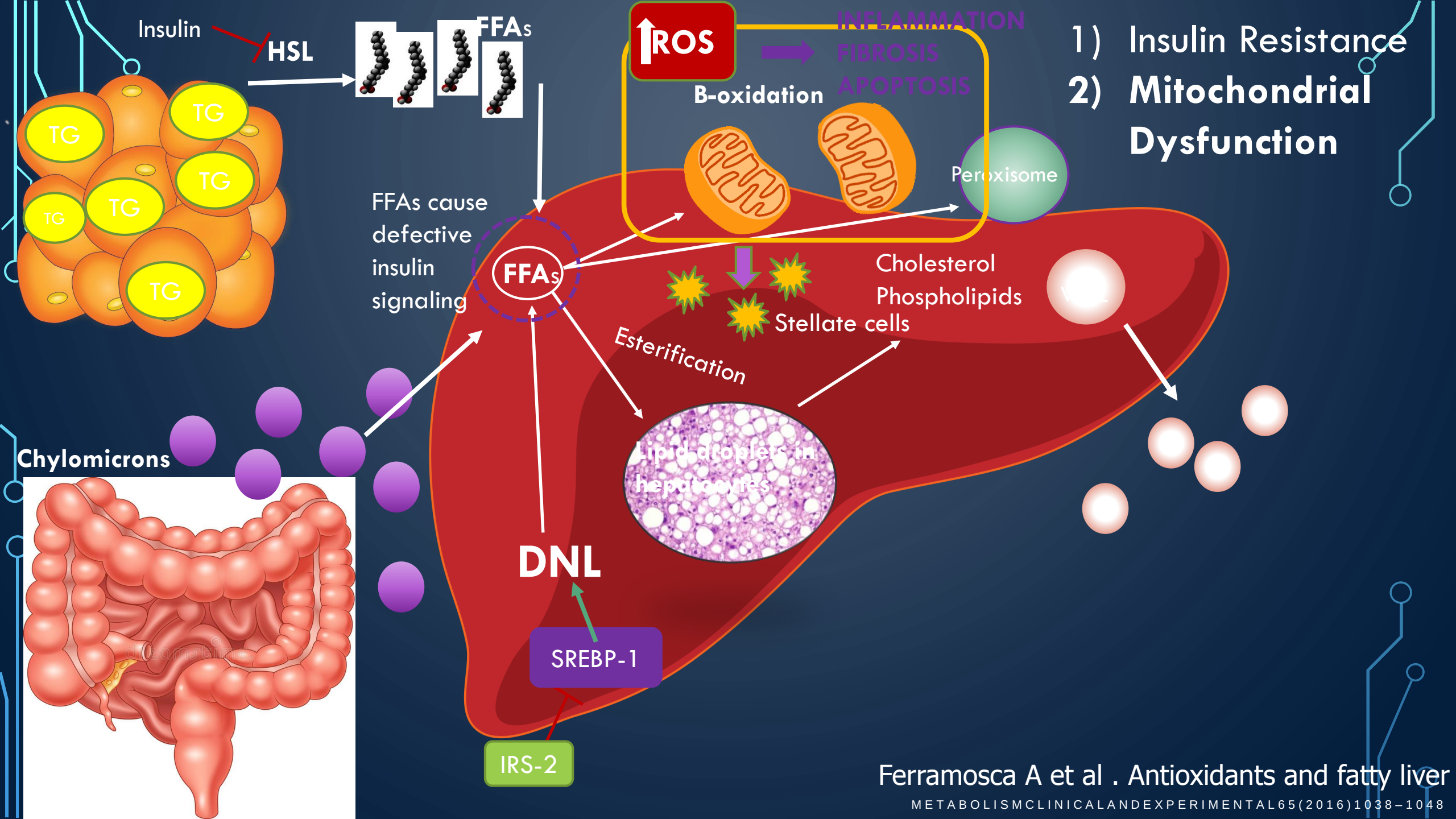

Ferramosca A et al . Antioxidants and fatty liver

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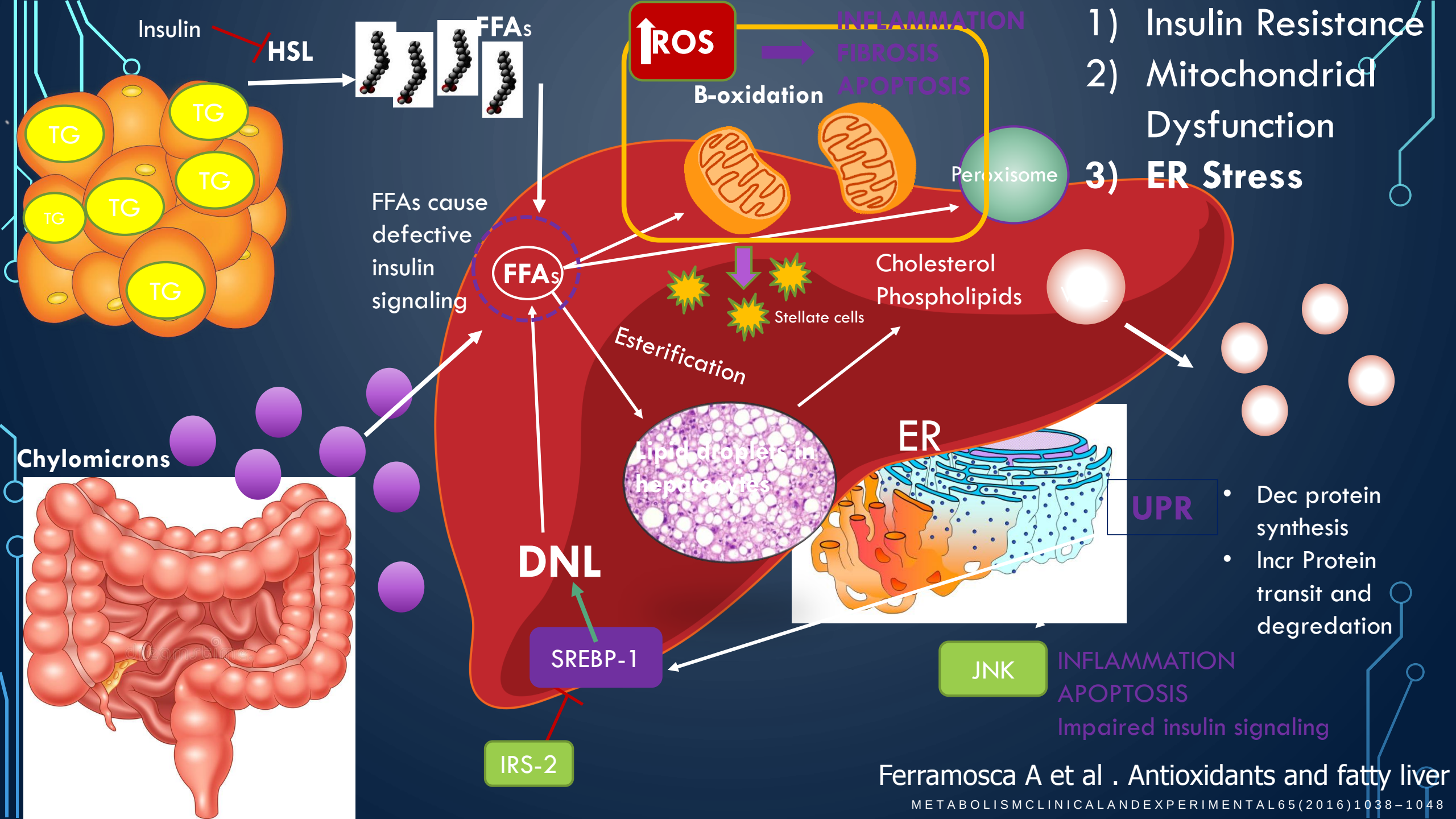

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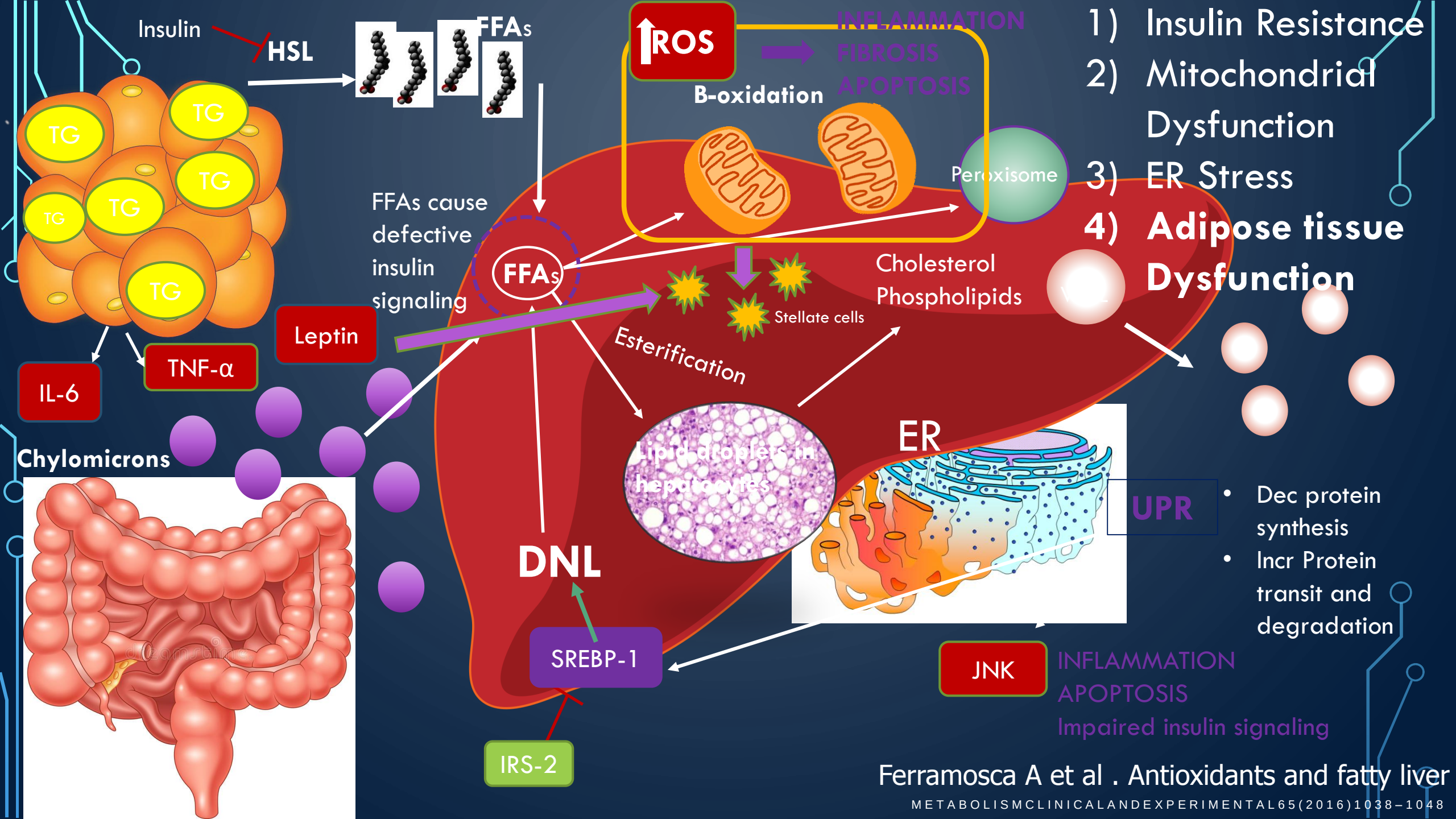

1) Insulin Resistance
2) Mitochondrial Dysfunction
3) ER Stress
4) **Adipose tissue Dysfunction**

- Dec protein synthesis
- Incr Protein transit and degradation

Ferramosca A et al . Antioxidants and fatty liver

METABOLISMCLINICALANDEXPERIMENTAL65(2016)1038–1048

1) Insulin Resistance
2) Mitochondrial Dysfunction
3) ER Stress
4) Adipose tissue Dysfunction
5) Dysbiosis

Insulin
HSL
FFAs
TG
TG
TG
TG
TG
TG
TG
IL-6
TNF-α
Leptin
Chylomicrons
LPS
FFAs cause defective insulin signaling
FFAs
ROS
INFLAMMATION
FIBROSIS
APOPTOSIS
B-oxidation
Peroxisome
Cholesterol
Phospholipids
Stellate cells
Esterification
Lipid droplets in hepatocytes
DNL
SREBP-1
IRS-2
ER
UPR
JNK
INFLAMMATION
APOPTOSIS
Impaired insulin signaling

- Dec protein synthesis
- Incr Protein transit and degradation

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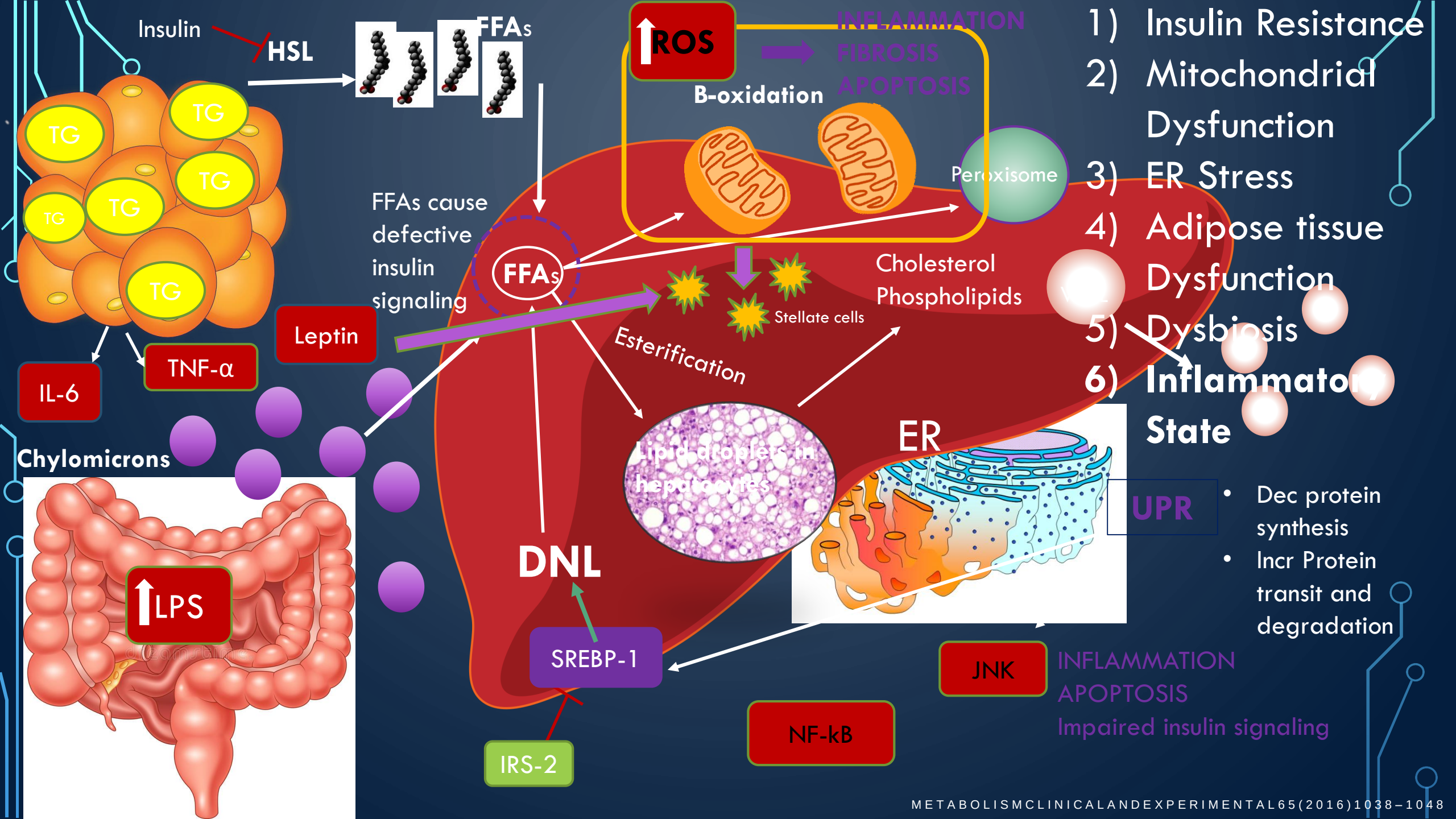

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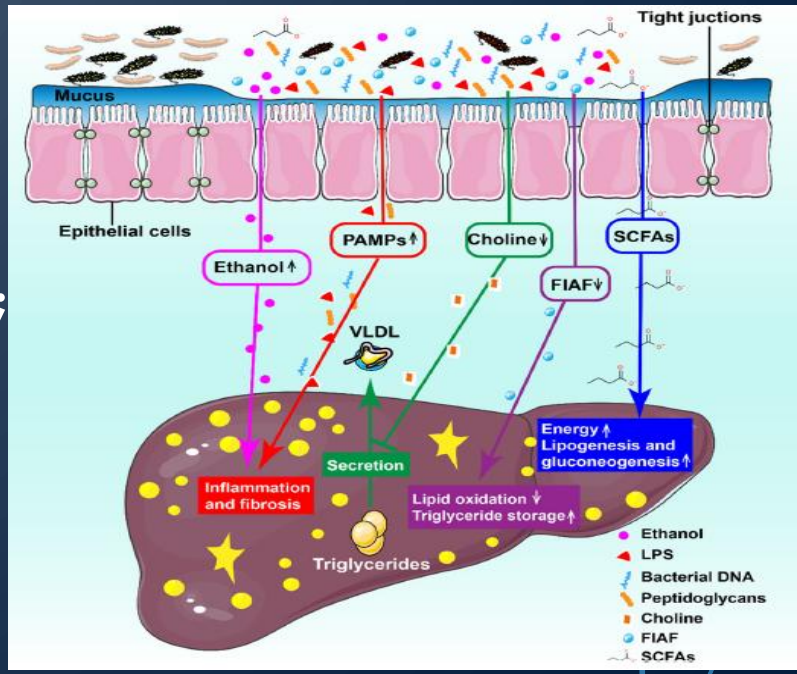
METABOLISMCLINICALANDEXPERIMENTAL65(2016)1038–1048

MICROBIOTA ASSOCIATED MECHANISM

Gut microbiota may contribute to the pathogenesis of NAFLD through several mechanisms

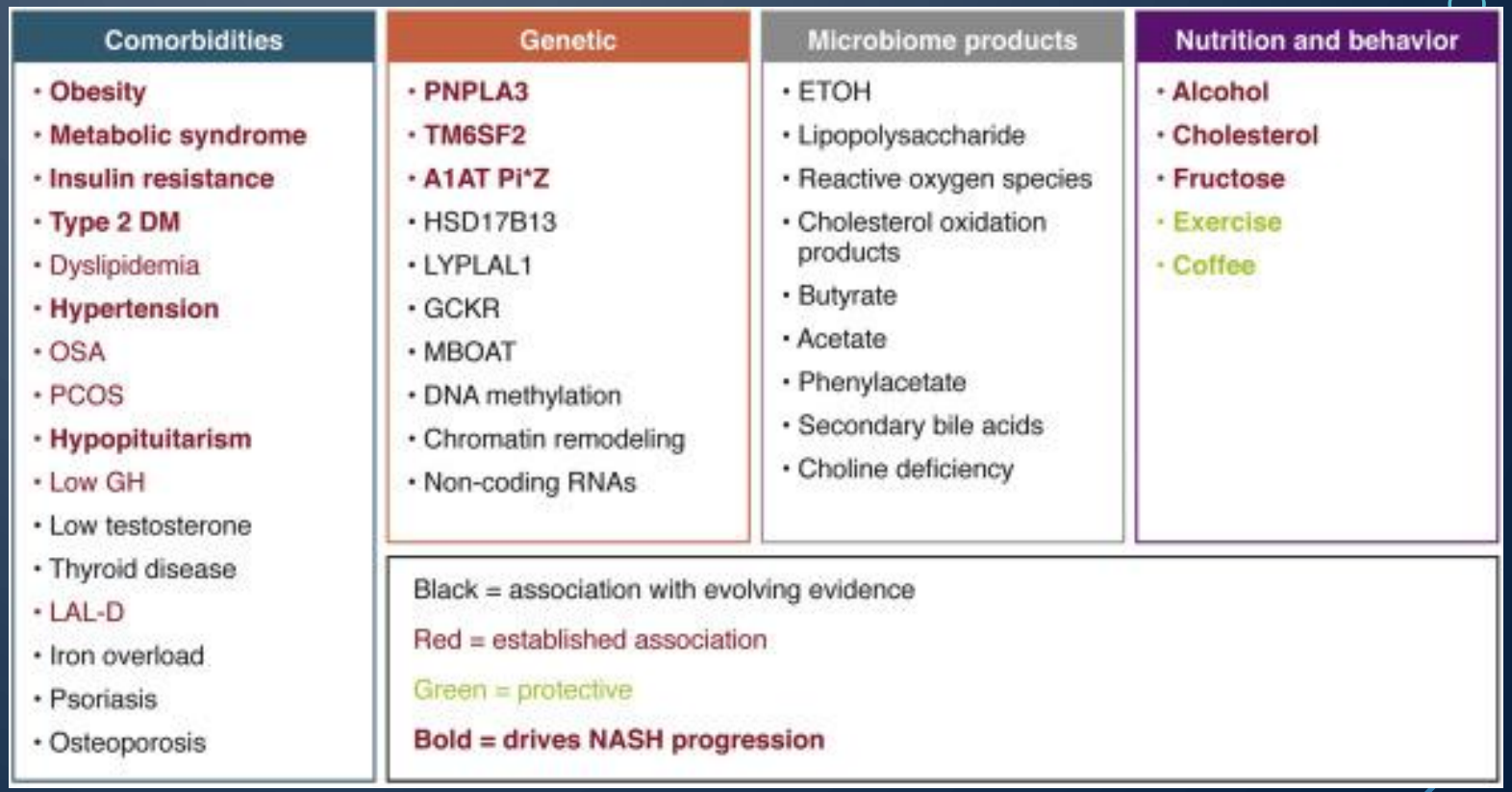
- ✓1. Increased production and absorption of gut short-chain fatty acids;
- ✓2. Altered dietary choline metabolism by the microbiota;
- ✓3. Altered bile acid pools by the microbiota;
- ✓4. Increased delivery of microbiota-derived ethanol to liver;
- ✓5. Gut permeability alterations and release of endotoxin;
- ✓6. Interaction between specific diet and microbiota.



• P. Lin, J. Lu, Y. Wang et al., "Naturally occurring stilbenoid TSG reverses non-alcoholic fatty liver diseases via gut- liver axis," PLoS ONE, vol. 10, no. 10, Article ID e0140346, 2015

RISK FACTOR

- Obese children
- Metabolic syndrome
- Male children
- Caucasian, Asian, Hispanic
- Prediabetes
- Diabetes
- Obstructive sleep apnea(OSA)
- Panhypopituitarism

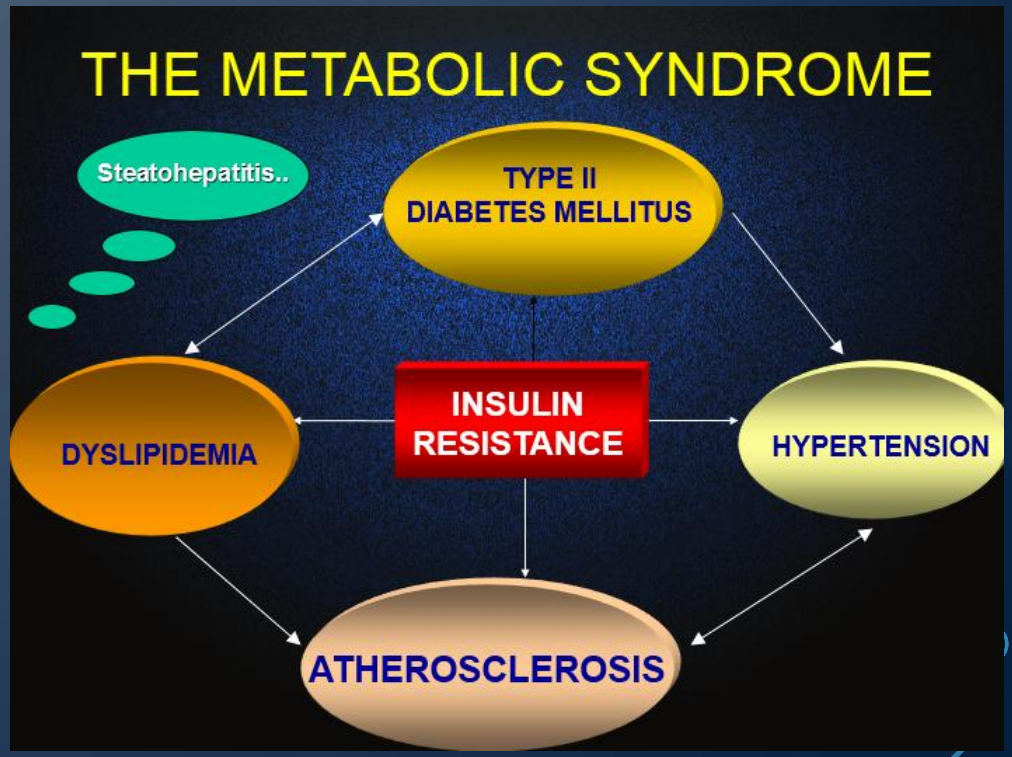


LEAN NAFLD

- NAFLD that develops in patients with a body mass index (BMI) < 25 kg/m2.
- In these subjects, given the absence of classical risk factors, steatosis is often underrecognized.
- The higher prevalence of lean NAFLD is in some rural areas of Asian countries .
- Lean NAFLD is not a simple benign condition.
- Lean NAFLD were more likely to develop severe liver disease; older age, fibrosis stage and cardiovascular mortality.

MAFLD

- ✓ Insulin resistance was proposed as a major NAFLD risk factor (increased hepatic gluconeogenesis, impaired glucose uptake by muscle, and increased release of free fatty acids and inflammatory cytokines from peripheral adipose tissues)
- ✓ Authors have long debated whether NAFLD was the hepatic feature of the metabolic syndrome (MetS)
- ✓ In 2020, the definition of "metabolic dysfunction-associated fatty liver disease MAFLD has been firstly proposed to identify fatty liver condition associated to metabolic disorders



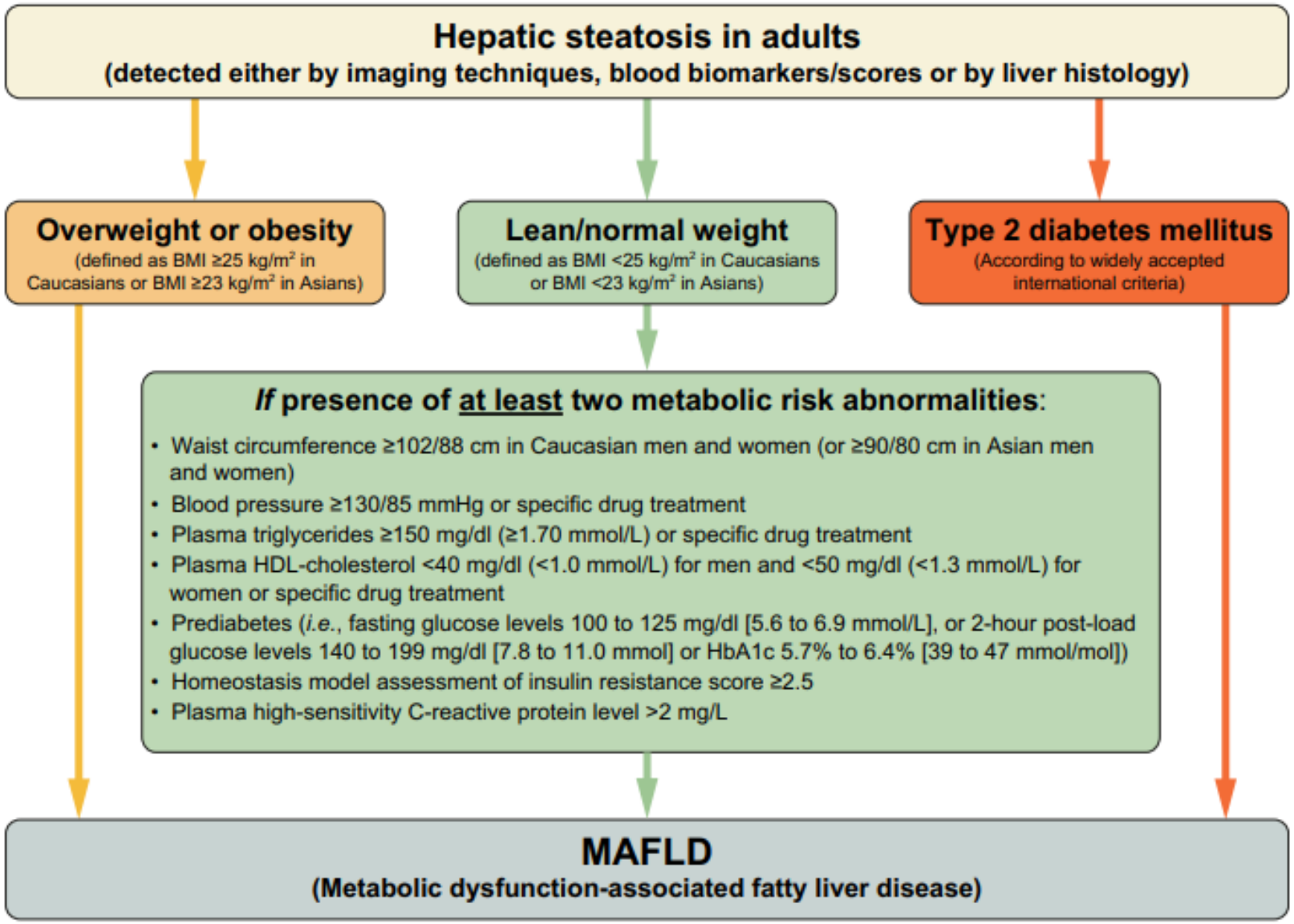
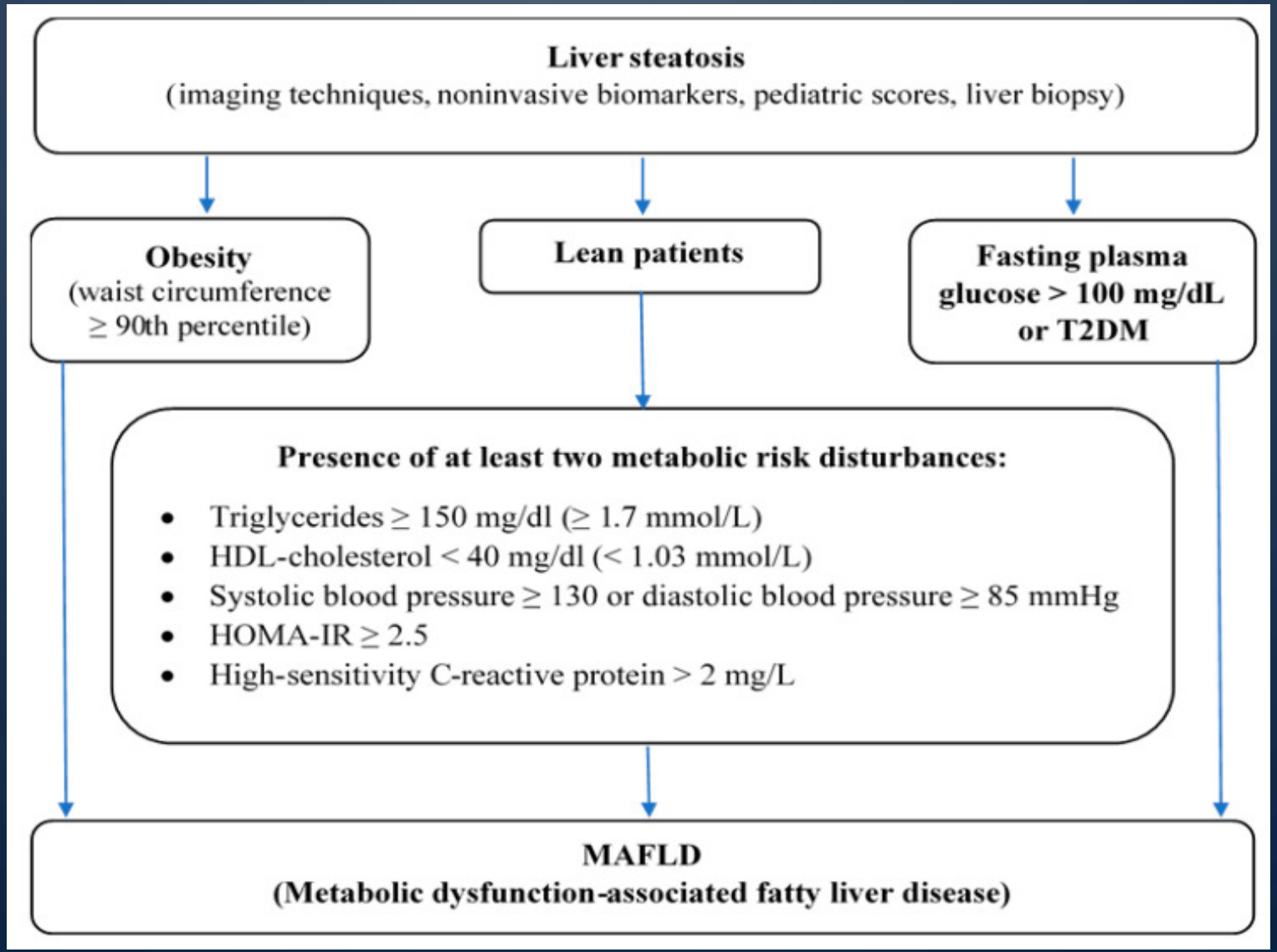


Fig. 1. Flowchart for the proposed "positive" diagnostic criteria for MAFLD.

A PROPOSED DIAGNOSTIC CRITERIA FOR MAFLD IN PATIENTS AGED 10–16 YEARS OLD (ADOPTED FROM ESLAM ET AL.)



CLINICAL PRESENTATION

- Most patients with NAFLD are ***asymptomatic***
- Right upper quadrant pain
- Abdominal discomfort
- Fatigue
- Obesity-associated comorbidities
  - gastroesophageal reflux disease, constipation, functional abdominal pain, or slipped capital femoral epiphysis
- Rarely have signs of end-stage liver disease
  - palmar erythema, spider angiomata, muscle wasting, jaundice, or encephalopathy
- Hepatomegaly and/or splenomegaly
- Acanthosis nigricans

EXTRAHEPATIC COMPLICATIONS

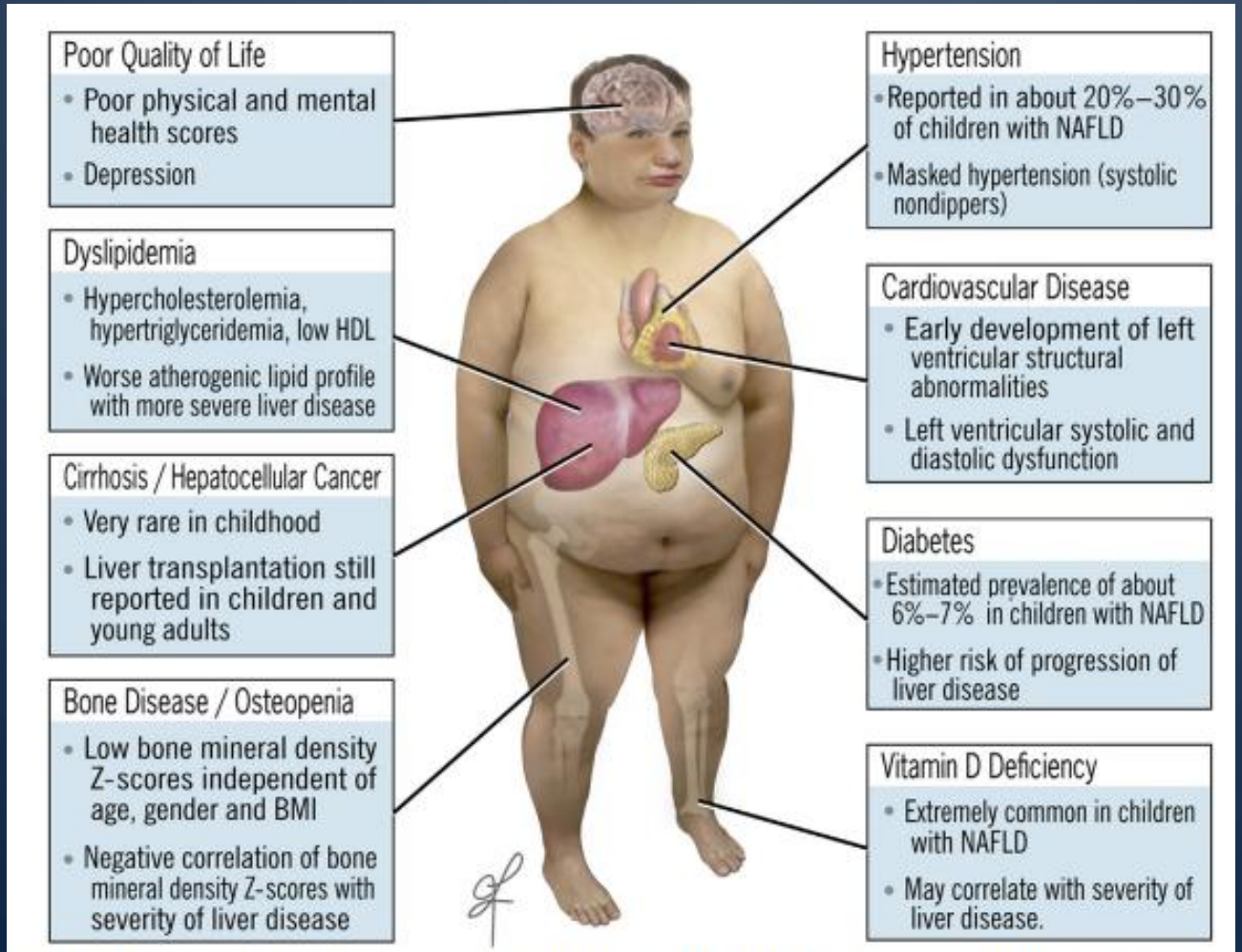


Fig. 1. Extrahepatic complications in children with NAFLD. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2016. All Rights Reserved).

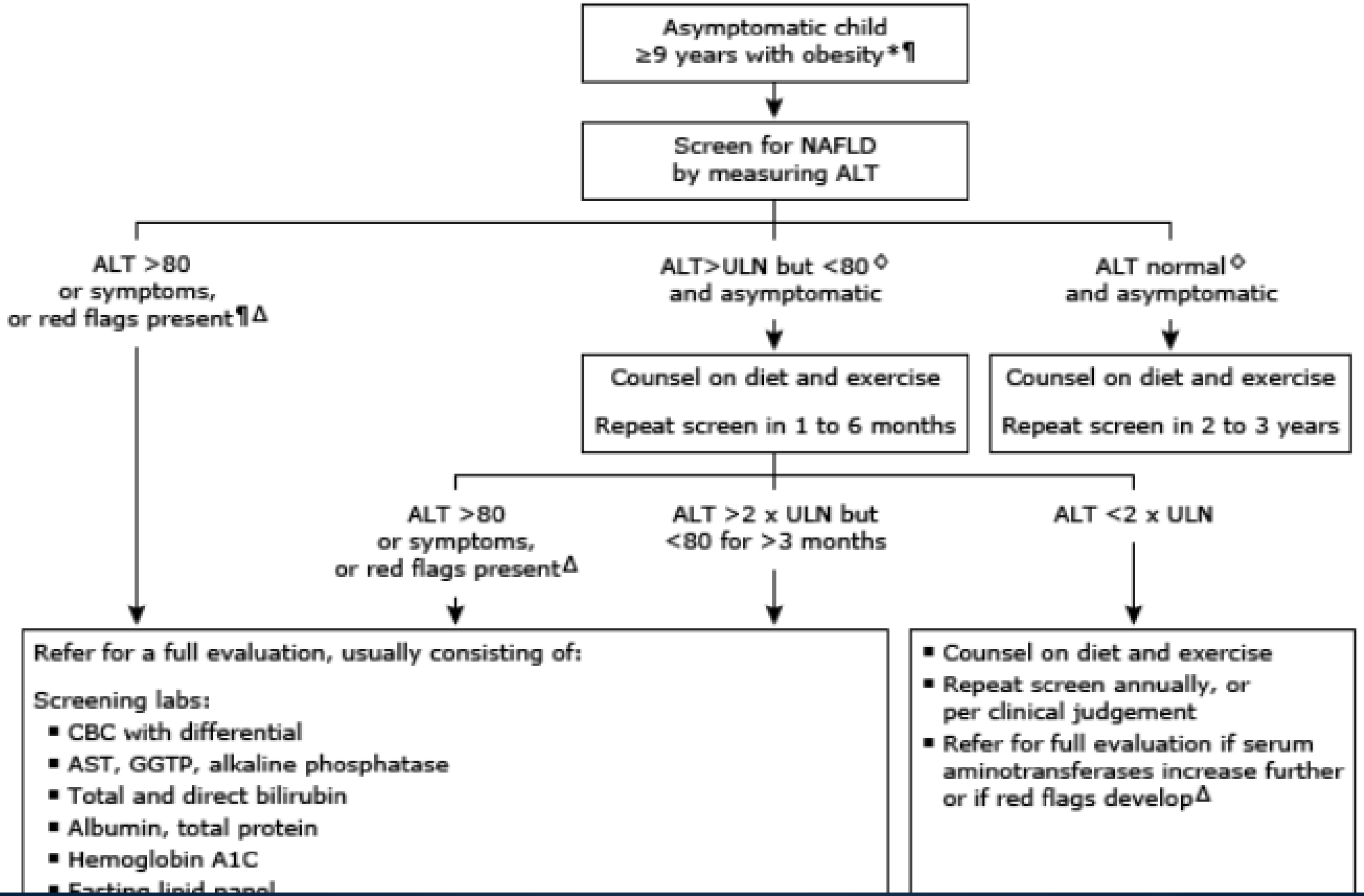
SCREENING
AT-RISK POPULATIONS

- Begin screening for NAFLD between 9 and 11 years
- Screen all children with obesity (body mass index [BMI] ≥95 percentile);
- Screen overweight children (BMI ≥85 percentile) if other risk factors are present (eg, signs of insulin resistance or a family history of NAFLD).
- Earlier screening can be considered in younger patients with risk factors such as severe obesity, family history of NAFLD/ NASH, or hypopituitarism
- Consider screening of siblings and parents of children with NAFLD if they have known risk factors for NAFLD (obesity, Hispanic ethnicity, insulin resistance, prediabetes, diabetes, dyslipidemia)

SCREENING

- Screening consists of measurement of serum alanine aminotransferase (ALT).
- For ALT interpretation, use the upper limit of normal (ULN) of 22 units/L for girls and 26 units/L for boys(although somewhat higher thresholds in younger children and a transient rise peripubertally)
- Imaging and Ultrasonography to detect hepatic steatosis is not recommended as screening for NAFLD.

Screening and evaluation for nonalcoholic fatty liver disease in children



ALT >80 or symptoms, or red flags present[Δ]

ALT >2 x ULN but <80 for >3 months

Refer for a full evaluation, usually consisting of:

Screening labs:

- CBC with differential
- AST, GGTP, alkaline phosphatase
- Total and direct bilirubin
- Albumin, total protein
- Hemoglobin A1C
- Fasting lipid panel

Laboratory evaluation for other specific causes of liver disease:

- Infection (HAV, HBV, HCV, other chronic viral infections if indicated by history)
- Celiac disease
- Hypothyroidism
- Autoimmune liver disease
- Genetic liver diseases (Wilson disease, hypobetalipoproteinemia and alpha 1 antitrypsin deficiency, lysosomal acid lipase deficiency)[§¥]

Consider liver biopsy[‡]

- To assess for steatosis, inflammation/steatohepatitis, and fibrosis; with copper measurement if Wilson disease is suspected

Imaging[†]

- Abdominal ultrasound to rule out anatomical abnormalities and assess for portal hypertension
- Possibly MRI-PDFF to measure liver fat

RED FLAGS

- ✓ Chronic fatigue,
- ✓ Gastrointestinal (GI) bleeding,
- ✓ Jaundice,
- ✓ Splenomegaly,
- ✓ Firm liver on examination,
- ✓ Enlarged left lobe of the liver
- ✓ Low platelets,
- ✓ Low white blood cell count,
- ✓ Elevated direct bilirubin,
- ✓ Elevated international normalized ratio (INR),
- ✓ Long history of elevated liver enzymes (>2 years).

Table 6. Noninvasive serologic tests for the diagnosis of NAFLD.

Serologic Test	Component of the Test	Clinical Utility
Aminotransferases [86]	ALT and AST	May be elevated in NAFLD patients
Cytokeratin-18 [87]	Cytokeratin-18	Elevated levels in NASH patients
AST/platelet ratio index (APRI) [88]	AST and platelets	Predicting fibrosis
NAFLD fibrosis score (NFS) [89,90]	Age, BMI, blood glucose levels, aminotransferase levels, platelet count, and albumin	Predicting advanced fibrosis and clinical outcomes in NAFLD patients
FIB-4 index [90,91]	Age, AST, ALT and platelet count	Predicting advanced fibrosis and clinical outcomes in NAFLD patients
FibroTest [92–94]	Age, sex, alpha-2-macroglobulin, haptoglobin, gamma globulin, apolipoprotein A1, gamma glutamyl transferase and total bilirubin levels	Predicting extent of fibrosis
ActiTest [93,94]	Age, sex, alpha-2-macroglobulin, haptoglobin, gamma globulin, apolipoprotein A1, gamma glutamyl transferase and total bilirubin and ALT levels	Predicting necroinflammatory activity
Enhanced Liver Fibrosis panel (ELF) [95,96]	Matrix metalloproteinase 1 (MMP-1), HA and amino-terminal propeptide of type III collagen level	Predicting extent of fibrosis
FibroSpect II [97]	Hyaluronic acid, tissue inhibitor of metalloproteinase-1 (TIMP-1), and alpha-2-macroglobulin.	Predicting extent of fibrosis

4.3. Indirect Markers of Fibrosis

Table 7. Imaging modalities for the diagnosis of NAFLD.

Imaging Modality	Clinical Utility	Limitations
Ultrasound Abdomen [98]	Widely available and convenient Sensitivity and specificity for diagnosing fatty liver disease is 85% and 94% respectively	Operator dependent Lacks sensitivity in NAFLD patients with less than 30% steatosis on liver biopsy
CT abdomen [99]	Limited clinical utility in diagnosing NAFLD	Radiation hazard, introduces contrast-related risks, has low sensitivity for hepatic fat mapping
Magnetic resonance spectroscopy [99–101]	Allows for quantification of hepatic fat	Not available on all scanner
Transient Elastography (Fibroscan) [102,103]	Sensitivity of 88% with a negative predictive value of 90% in detecting advanced fibrosis	Presence of ascites, obese patients or presence of acute inflammation
Magnetic Resonance elastography [104,105]	Sensitivity of 86% and specificity of 91% for diagnosing advanced fibrosis	Limited availability, expertise to interpret the results, cost of the procedure, presence of metal implants, patient's size and claustrophobia
Shear wave elastography (SWE) [106]	Sensitivity of 90% and the specificity of 88% in detecting advanced fibrosis	Limited evidence available current and needs further research on its clinical utility

ULTRASOUND

- Ultrasound has a sensitivity of approximately 80% and specificity of approximately 50% to 60% for hepatic steatosis .
- Decreased sensitivity in patients with mild steatosis.
- Ultrasound cannot accurately distinguish between simple steatosis and NASH or fibrosis.
- Although recent imaging techniques are more accurate than conventional ultrasound, their use is currently limited because of cost and the lack of validated cut-off values in children.

TREATMENT

- The only proven treatment for NAFLD
  - Lifestyle modification
  - Weight loss
  - Exercise

Lifestyle changes	• Avoidance of sugar-sweetened beverages • Consumption of healthy, well balanced diet • Moderate- to high-intensity exercise daily • Less than 2 hour/day of screen time

WEIGHT LOSS

- Weight loss of at least 3%-5% of body weight improve steatosis
- Weight loss (7%-10%) improve the majority of the histopathological features of NASH, including fibrosis

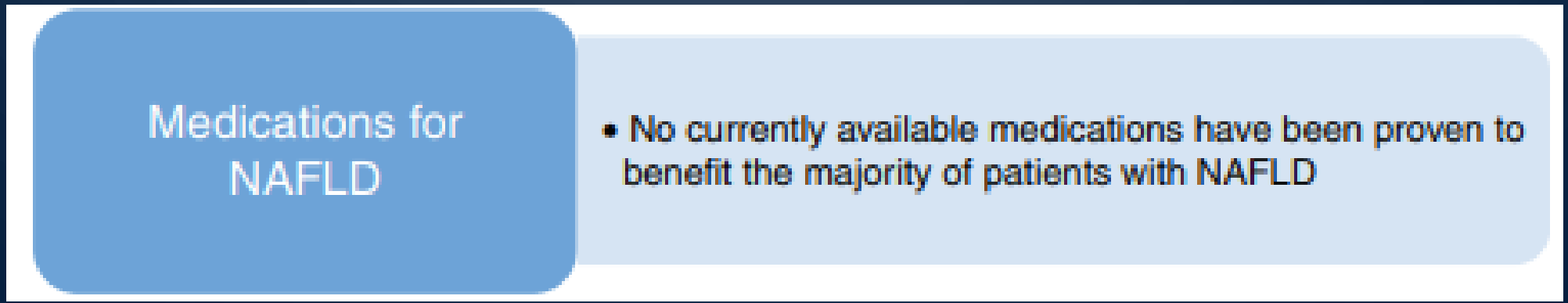
TREATMENT

No medications have been proven to benefit the majority of patients with NAFLD

Vitamin E is the only medical therapy that has offered histological benefits to children with biopsy-proven NASH in a large placebocontrolled, multi-center RCT, and its use is supported by the AASLD Guidelines for children with biopsy-proven NASH.

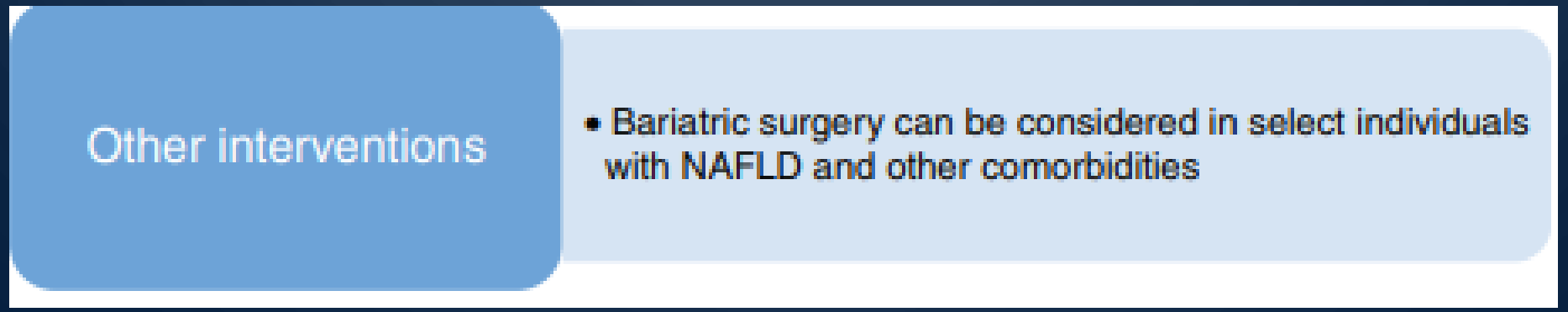
TREATMENT *(NOT RECOMMENDED)*

- Metformin
- omega-3-fatty acids(250 or 500 mg DHA)
- Probiotics(Lactobacillus GG and VSL 3)
- Ursodeoxycholic acid



TREATMENT

- Bariatric surgery is not recommended as a specific therapy for NAFLD given lack of outcome data in adolescents.
- Bariatric surgery may be considered for selected adolescents with BMI >35 kg/m2 , who have noncirrhotic NAFLD and other serious comorbidities (eg, T2DM, severe sleep apnea, idiopathic intracranial hypertension) that are likely to improve with WLS.



GRADING

Sonography

Grade 0	Normal parenchymal liver ecogenicity
Grade 1	Increased liver echogenicity without haziness of vessel walls
Grade 2	Increased liver echogenicity with haziness of vessel walls
Grade 3	Increased liver echogenicity leading to loss of normal contrast between liver and diaphragm

Pathology

Grade of NAFLD

Macrovesicular steatosis

Grade 0: No steatosis

Grade 1: < 33% steatosis

Grade 2: < 33–66% steatosis

Grade 3: > 66% steatosis

Necroinflammatory activity

Grade 1 (mild) steatosis up to 66%; occasional ballooned hepatocyte (mainly zone 3); scattered intra-acinar neutrophil (PMN) lymphocytes, no or mild portal inflammation.

Grade 2 (moderate) steatosis of any degree; obvious zone-3 ballooning degeneration; intra-acinar PMNs; zone-3 perisinusoidal fibrosis may present mild to moderate, portal and intra-acinar inflammation.

Grade 3 (severe) panacinar steatosis; widespread ballooning; intra-acinar inflammation; PMNs associated with ballooned hepatocyts, mild to moderate portal inflammation.

Stage of NAFLD

Stage 1: zone 3 perisinusoidal/pericellular fibrosis; focally or extensively present.

Stage 2: zone 3 perisinusoidal/pericellular fibrosis with focal or extensively periportal fibrosis.

Stage 3: zone 3 perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis.

Stage 4: cirrhosis.

PROGRESSION

NASH survival rates in comparison with simple steatosis and
patitis (ASH)

Survival	Simple steatosis	NASH	ASH
5-year	Normal	67%	59%
10-year	Normal	38%	15%

Population studied	Prevalence of disease progression
NAFLD → NASH	
General population	10–20%
No inflammation or fibrosis	5%
High-risk, severe obesity	37%
NAFLD → cirrhosis	
Simple steatosis	0–4% over 10–20 y
NASH → fibrosis	
Patients at tertiary referral centers	25–33% at diagnosis
High-risk, severe obesity	23%
NASH → cirrhosis	
High-risk, severe obesity	5.8%
Patients at tertiary referral centers	10–15% at diagnosis
General population	3–15% over 10–20 y
General population	5–8% over 5 y
NASH → liver failure	
Cirrhosis	38–45% after 7–10 y
NASH → hepatocellular carcinoma	
Cirrhosis	2–5% per year

FOLLOW UP

- Liver fibrosis progresses at a rate of approximately one stage per decade, suggesting that F2 fibrosis will progress to cirrhosis within 20 years.
- A decrease in ALT is commonly used as a marker of improvement in histology of NAFLD.
- It is recommended to follow children with NAFLD on a yearly basis at a minimum to monitor for progression of disease and provide treatment.
- Exposures to Liver Toxins
  - ✓ Prolonged cigarette smoking
  - ✓ Binge drinking
- Prevention of Hepatitis A and B
- Initiation and Monitoring of Potentially Hepatotoxic Medications


با تشکر از توجه شما
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