"ELIMINATION OF VIRAL HEPATITIS"
အသည်းရောင်ရောဂါ ပပျောက်ရေး
GI & LIVER FOUNDATION
GLF
(Myanmar)
"FIGHTING AGAINST GI CANCER"
"အစာအိမ်၊ အူလမ်းကြောင်းကင်ဆာရောဂါ တိုက်ဖျက်ရေး"

Masterclass in NASH

Zifam

Cardio-Metabolic Comorbidities of NAFLD- more than one disease?

PROF. KYAW SOE TUN (MYANMAR)

DISCLAIMER

- NOTHING TO DISCLOSE

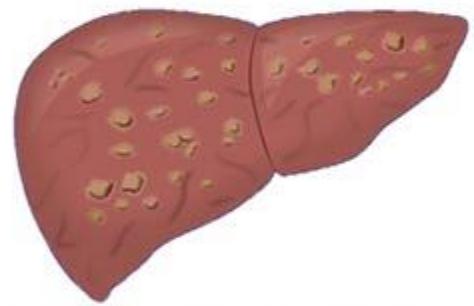
What is NAFLD?

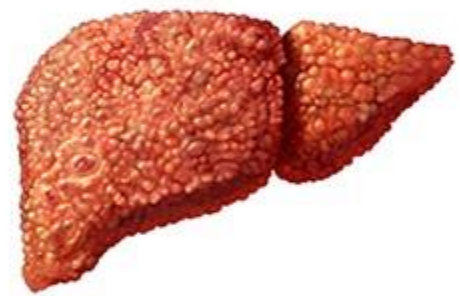
Name for a Spectrum of Liver Diseases

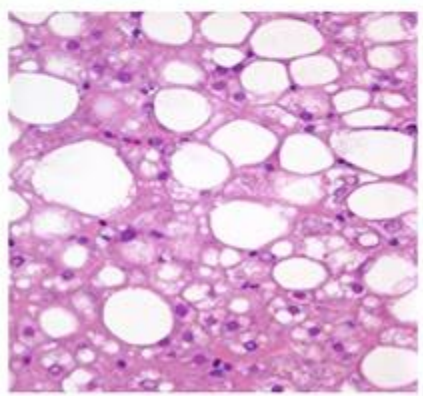
Steatosis

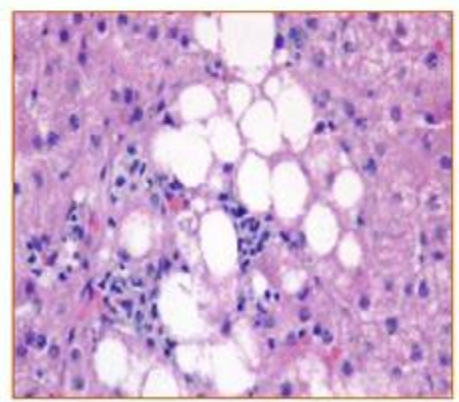
NASH
Non-Alcoholic Steatohepatitis

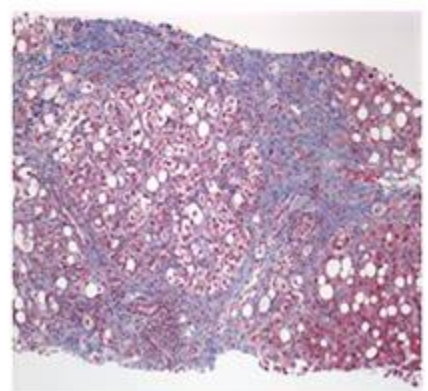
Cirrhosis



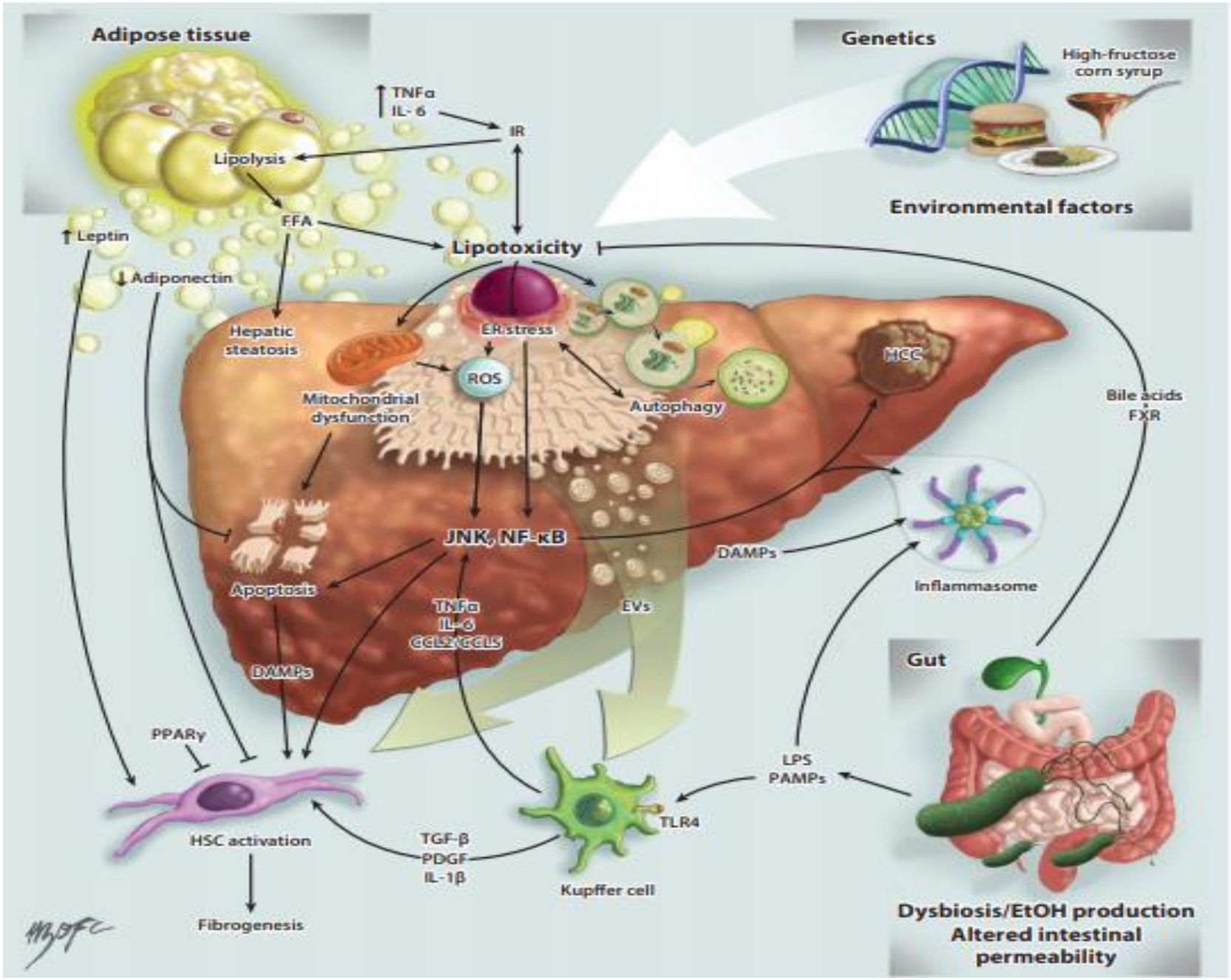




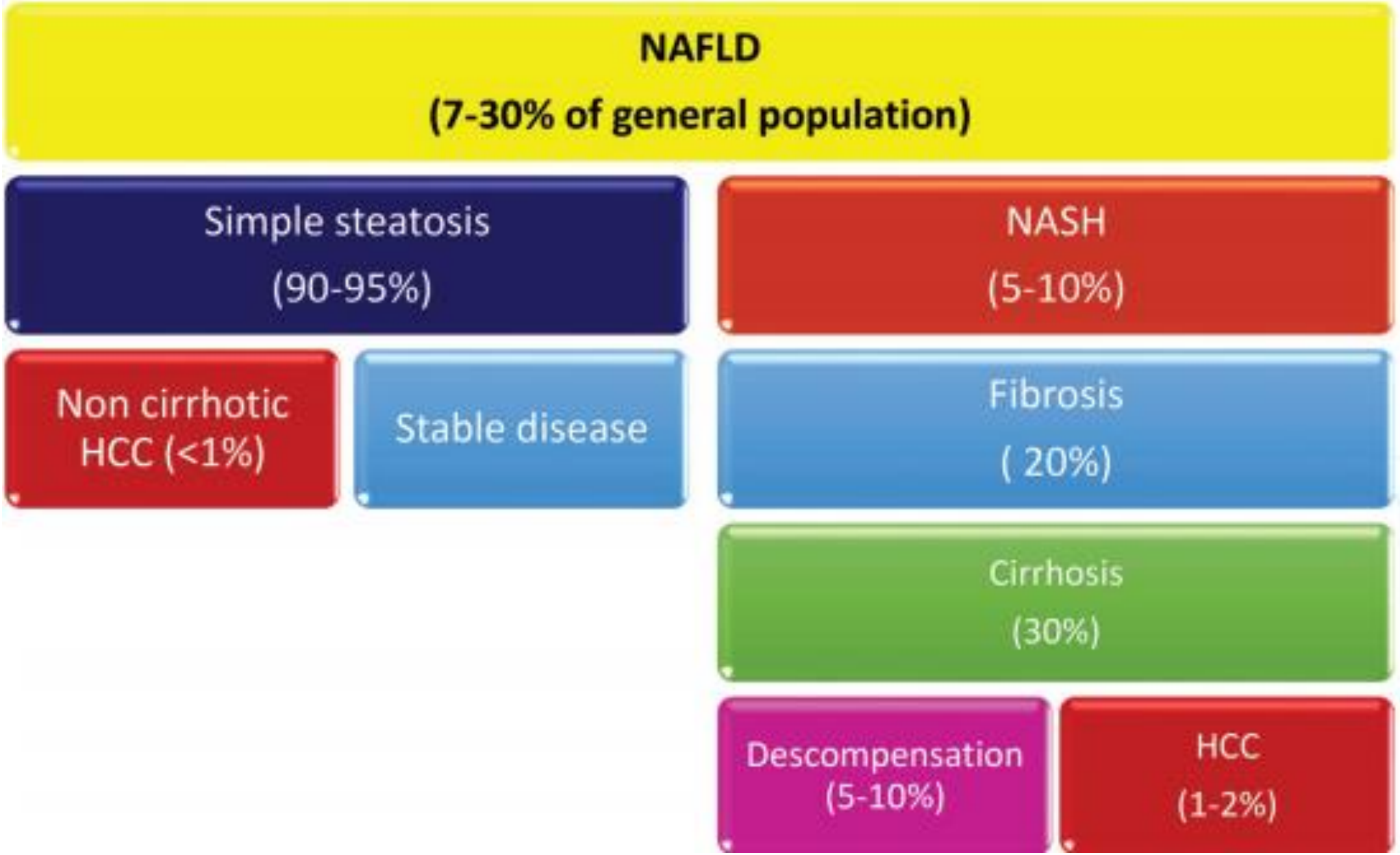




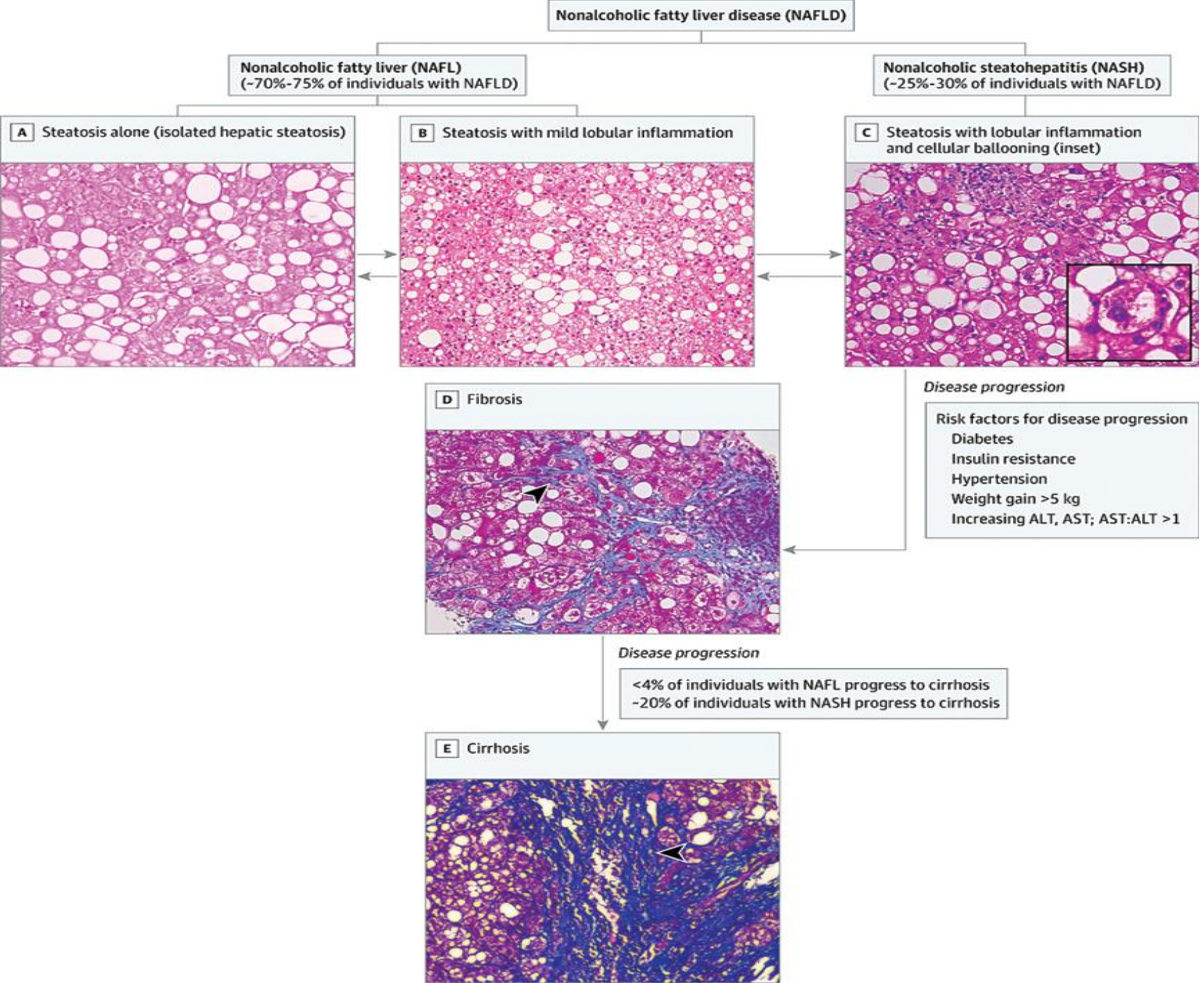
Schematic summary of NAFLD pathogenesis



Recent Insights into the Pathogenesis of Nonalcoholic Fatty Liver Disease ; Annu. Rev. Pathol. Mech. Dis. 2018. 13:321–50



Natural history of NAFLD



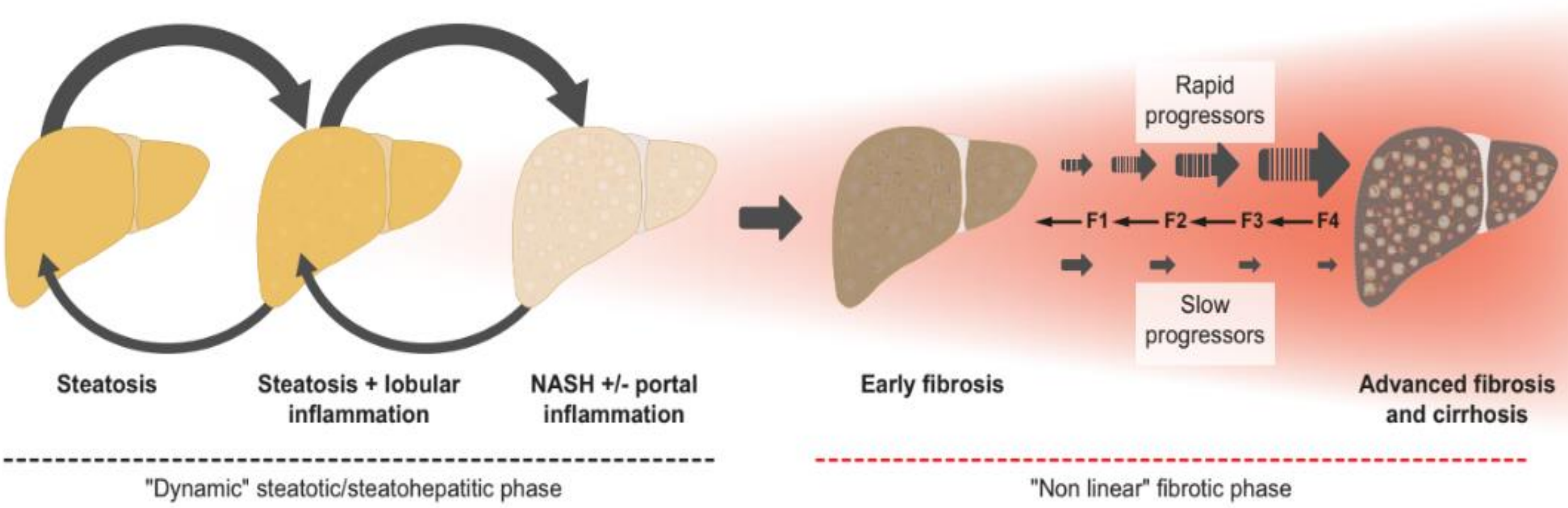
Histological Changes in Hepatic Steatosis With and Without Inflammation *(From Rinella ME: Nonalcoholic Fatty Liver Disease:*
A systematic Review. JAMA. 2015;313(22):2263-2273)16

Diagnostic criteria for different NAFLD stages, diagnostic methods/biomarkers and their limitations

	Clinical features	Histological definition	Diagnostic methods/limitations
Steatosis	Usually overweight and obese individuals in the absence of other causes of liver disease like excess alcohol consumption, hepatitis and iron overload	At least 5% liver fat accumulation with no evidence of hepatocellular injury	Hepatic ultrasound (widely available, very specific, but poor sensitivity for < 12% fat accumulation); liver computed tomography (widely available, good sensitivity, but implicates in radiation exposure), magnetic resonance imaging-proton density fat fraction-PDFF (limited by costs) and ^{1}H-magnetic resonance spectroscopy (highly sensitive for small amount fat accumulation but not widespread available)
Steatohepatitis (NASH)	Overweight and obese individuals + features of the metabolic syndrome + elevated aminotransferases, where other causes of liver disease were not encountered	Steatosis associated with liver inflammation and hepatocyte injury (ballooning) independent of fibrosis stage	Liver biopsy gold standard (limited by invasiveness, risk of complications and high cost); elevated aminotransferases have low sensitivity and specificity for NASH; Blood cytokeratin-18 (CK-18) fragments predictors of NASH (limited by non-commercial availability and poor reproducibility); NASH test (includes age, BMI, blood biomarkers like alpha-2 microgobulin) and NASH diagnostics panel (including CK-18 fragments) not so accurate
Fibrosis	Individuals older age 45, and type 2 diabetics have a greater risk of fibrosis	Presence of fibrosis (scarring): F1-portal fibrosis not affecting septa; F2-portal fibrosis with few septa; F3-bridging septa between central and portal veins; F4-cirrhosis	Non-invasive detection of liver stiffness (elasticity) by elastography: ultrasound transient elastography (limited in severe obese) and magnetic resonance elastography are preferred tests over blood biomarkers; "simple" blood biomarkers (ALT. AST, platelet counts), markers of hepatic dysfunction, derived Fibrosis–IV score may be useful but sensitivity declines with age; elevated ferritin in the absence of hemochromatosis might indicate a greater risk of cirrhosis; markers of elevated collagen turnover (e.g. hyaluronic acid, aminoterminal peptide of pro-collagen III) still under investigation

Atherosclerosis 282 (2019) 110–120

The dynamic natural history of NAFLD.



Current thinking based on longitudinal cohort studies and dual-biopsy cohorts is that the natural history of NAFLD is highly dynamic. The degree of steatohepatitis and therefore transition between NAFL and NASH is characterized by periods of waxing and waning. Similarly, fibrosis may progress or regress, and while most patients exhibit only slow progression, up to 20% of patients may be more rapid progressors. Risk of morbidity and mortality increases with fibrosis stage.

Mary E. Rinella, Frank Tacke, Arun J. Sanyal, Quentin M.Anstee; **Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD;** Journal of Hepatology 2019 vol. 71 j 823–833

Causes of Hepatic Steatosis

Macrovesicular steatosis

- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- Wilson's disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g. amiodarone, methotrexate, tamoxifen, corticosteroids)

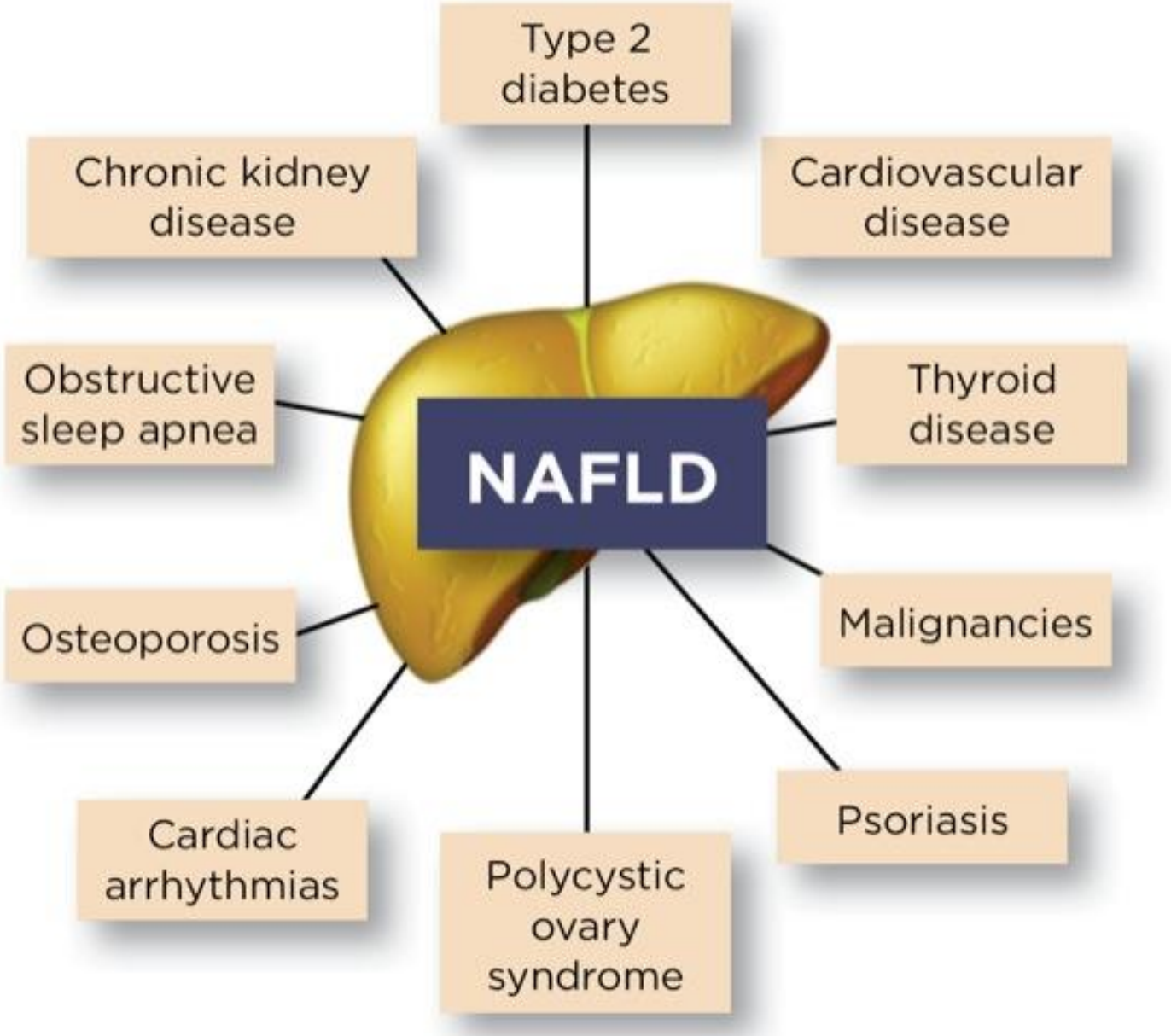
Microvesicular steatosis

- Reye's syndrome
- Medications (valproate, anti-retroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g. LCAT deficiency, cholesterol ester storage disease, Wolman disease)

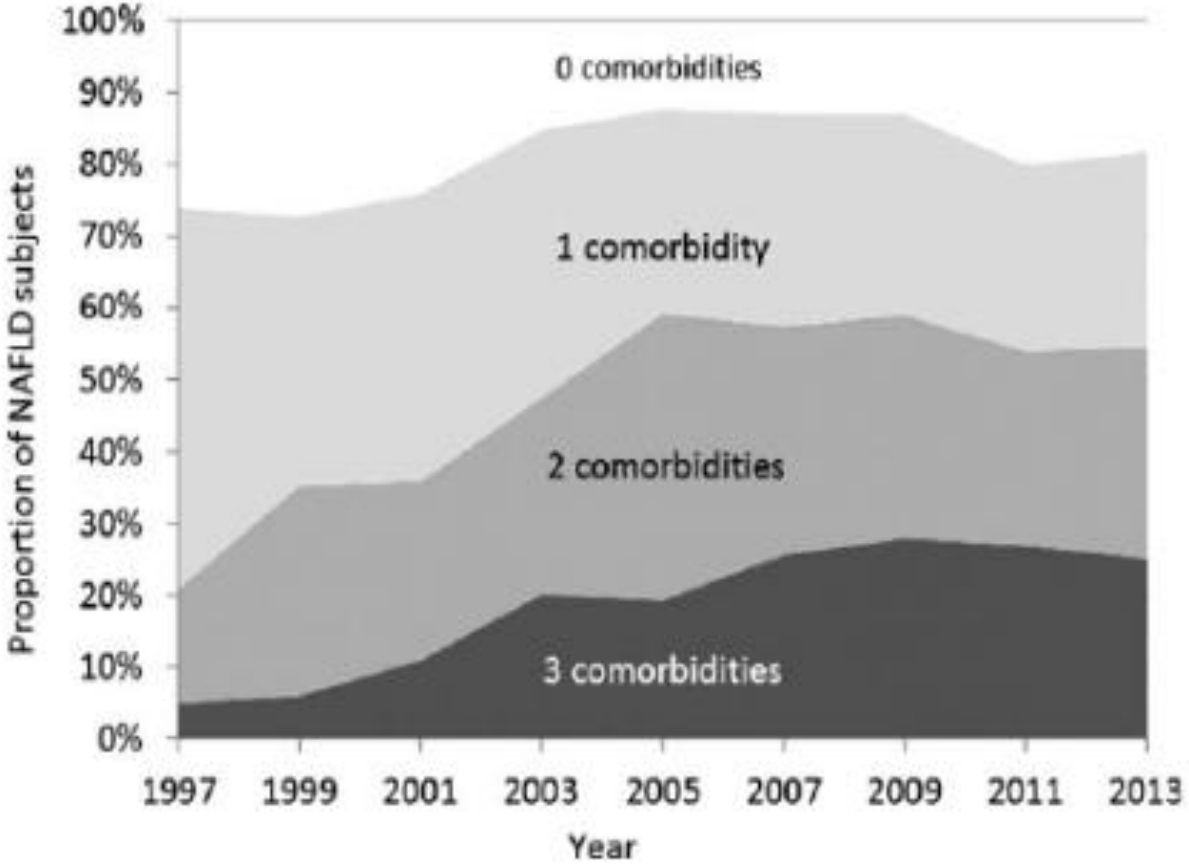
Causes of NAFLD in non-obese individuals.

1. **Genetic disorders:**
   a. Abetalipoproteinemia
   b. Lipodystrophies
   c. Cholesterol ester storage disease
   d. Wolman disease
   e. Wilson's disease
   f. *PNPLA3* mutation*
2. **Metabolic:**
   a. Insulin resistance and increased visceral adiposity (most common cause)
3. **Infectious-Inflammatory disorders:**
   a. Hepatitis C (especially genotype 3)
   b. HIV
   c. Celiac disease
   d. Small intestinal bacterial overgrowth
4. **Drugs:**
   a. Amiodarone
   b. Tamoxifen
   c. Diltiazem

Reported extrahepatic manifestations of NAFLD



Adams LA, et al. *Gut*. 2017;66(6):1138-1153



Proportion of NAFLD subjects with one, two, or three MCs (DM, HTN, or dyslipidemia) present at the time of diagnosis.

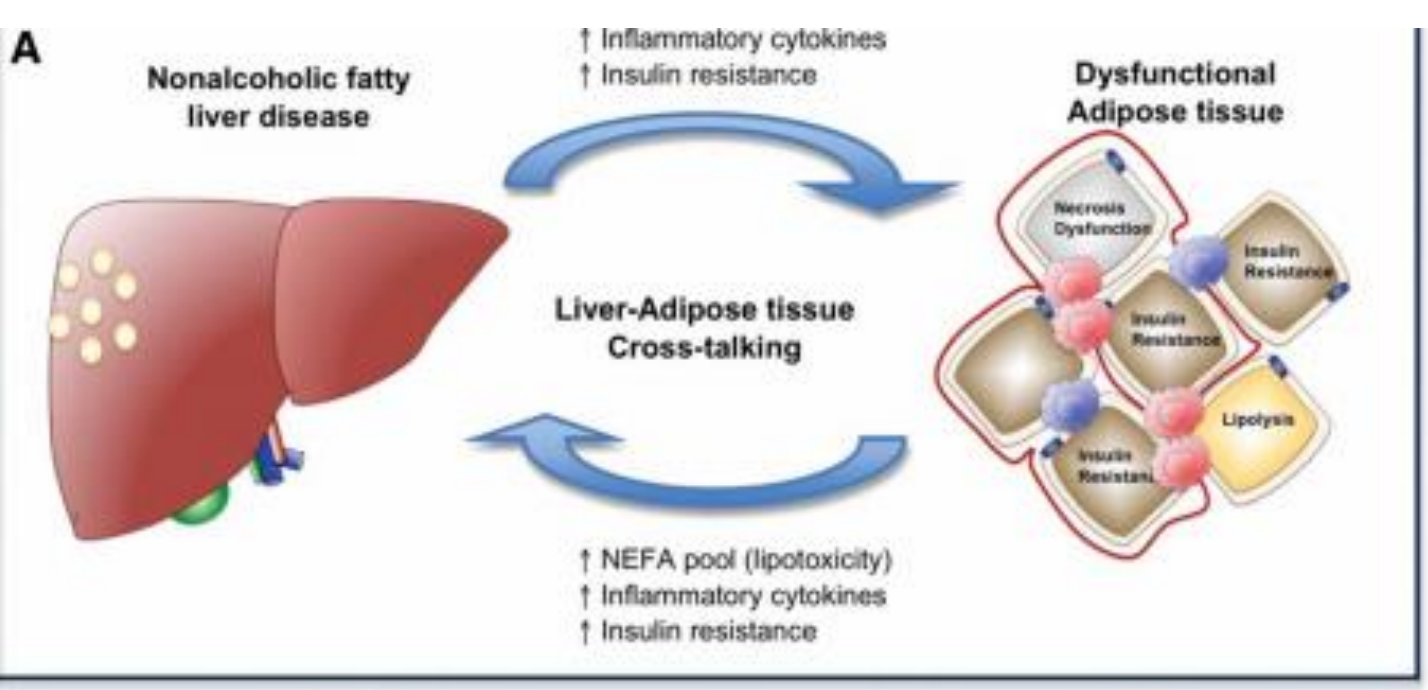
The proportion of subjects with multiple comorbidities atNAFLD diagnosis has increased since 1997

Adams LA, et al. *Gut*. 2017;66(6):1138-1153

Impact of NAFLD on incident MCs and mortality in reference to age- and sex-matched controls

Compared to controls, NAFLD subjects have a higher risk to develop incident dysmetabolic comorbidities (top row, horizontal arrows). The impact of NAFLD on mortality decreases as the number of dysmetabolic conditions increases (bottom row, vertical arrows).

A schematic of the putative mechanisms for the development of extrahepatic disease in patients with NAFLD



B **Atherosclerosis (CVD and CKD)**

- **Hepatic/peripheral insulin resistance**
  - Hyperglycemia
  - Hyperinsulinemia
- **Dyslipidemia**
  - ↑ LDL, triglycerides + VLDL
  - ↓ HDL
- **Pro-inflammatory mediators + oxidative stress**
  - ↑ CRP, IL-6, TNFα
  - ↑ Reactive oxygen species
  - ↓ Adiponectin
- **Hypercoagulation and hypofibrinolysis**
  - ↑ PAI-1, fibrinogen, factor VIII, vWF

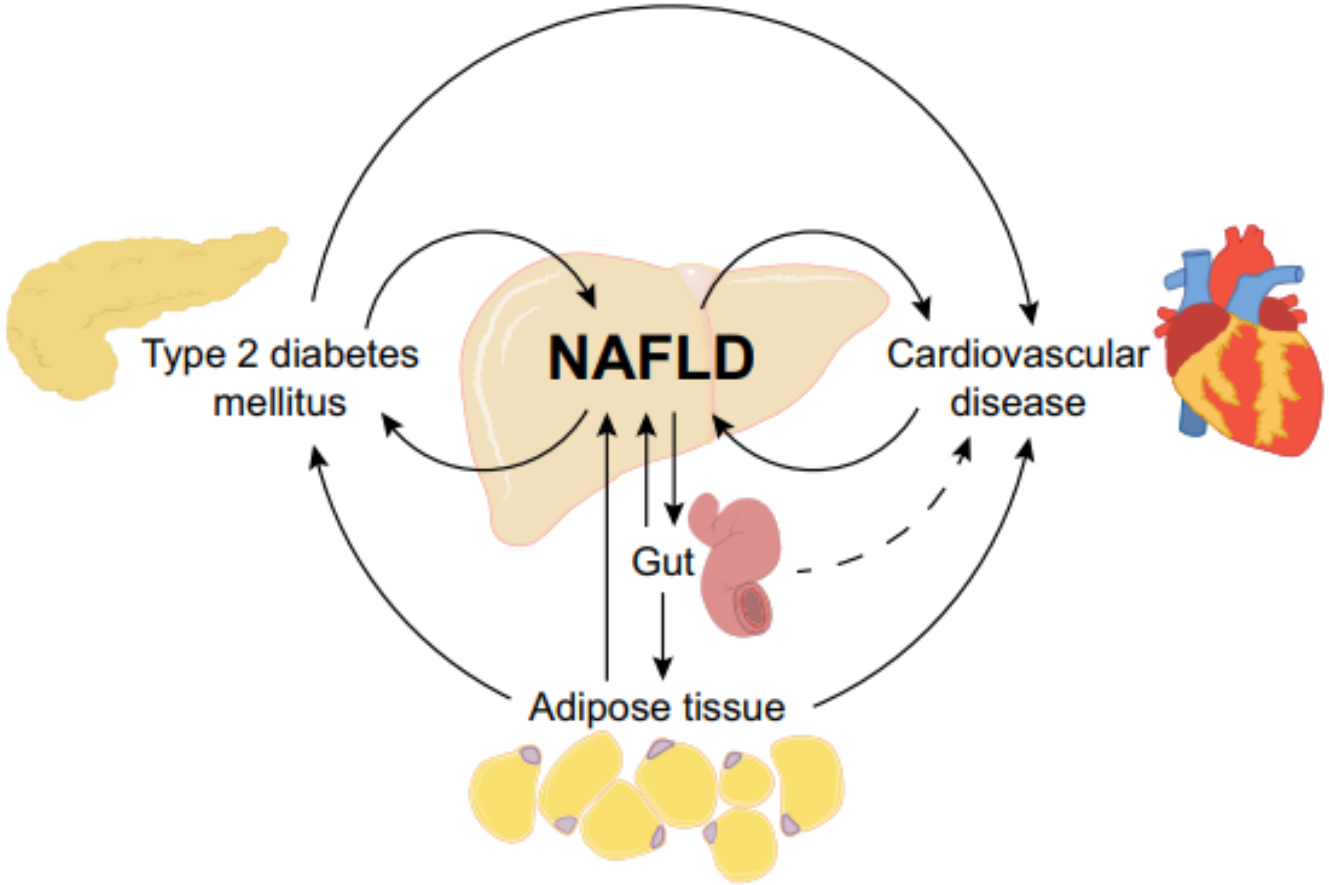
C **Type 2 Diabetes**

- **Hepatic/peripheral insulin resistance**
  - Hyperglycemia
  - Hyperinsulinemia
- **Pro-inflammatory mediators + oxidative stress**
  - ↑ CRP, IL-6, TNFα, OPN
  - ↑ Reactive oxygen species
  - ↓ Adiponectin
- **↑ Hepatokines that promote insulin resistance**
  - FGF-21
  - Fetuin-A
  - RBP-4

D **Extra-hepatic malignancy (colorectal cancer)**

- **Pro-inflammatory mediators (TNFα) ⇒ Angiogenesis**
- **Increased cancer cell growth + proliferation secondary to:**
  - ↓ Adiponectin + ↑Leptin
  - Hyperinsulinemia/insulin resistance
    - ↑ IGF-1
    - ↑ VEGF, ↓ p53 dependent apoptosis

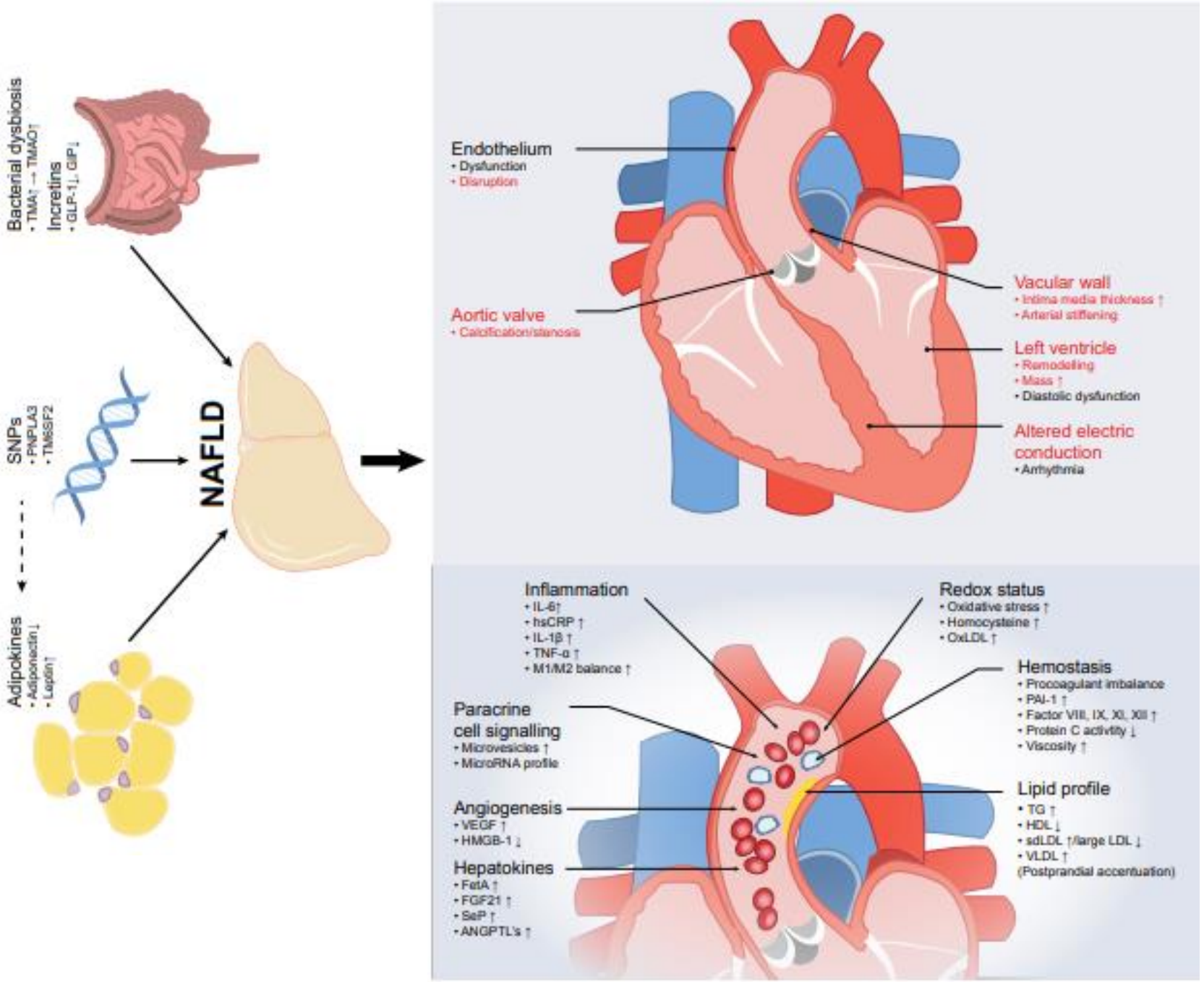
HEPATOLOGY, March 2014



Complex interplay of NAFLD and cardiovascular disease. The liver is centrally positioned in the metabolic syndrome, where NAFLD can be considered as the consequence of mechanism driven by the other components of the metabolic syndrome. However, reciprocal crosstalk exists, wherein the liver may actually drive diabetes mellitus or cardiovascular disease. These synergetic effects become more complex and create a vicious circle.

Journal of Hepatology 2016 vol. 65 j 425–443

Summary of potential pathophysiological mechanism responsible for increased CVD in NAFLD.



NAFLD drives multiple mechanisms that ultimately lead to cardiovascular disease. These mechanisms are summarised in this figure. Genetic background, adipose tissue and the gut all contribute, in part via the liver (direct effects also exists but are not within the scope of this review). The details about these mechanisms are described in the text. Structural alterations of the cardiovascular system are marked in red. ANGPTL, angiopoietin like proteins; FetA, fetuin-A; FGF21, fibroblast growth factor 21; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1; HDL, high-density lipoproteins; HMGB-1, high mobility group box 1; hsCRP, high sensitivity C-reactive protein; IL-1b, interleukin 1b; IL-6, interleukin 6; M1/M2, macrophage phenotype 1/2 ratio; OxLDL, oxidized low-density lipoprotein; PAI-1, plasminogen activator inhibitor 1; PNPLA3, patatin-like phospholipase domain containing protein 3; sdLDL, small dense low-density lipoproteins; SeP, selenoprotein P; SNP, single nucleotide polymorphism; TG, triglycerides; TM6SF2, transmembrane 6 superfamily member 2; TMA, trimethylamine; TMAO, trimethylamine-N-Oxide; TNF-a, tumor necrosis factor a; VEGF, vascular endothelial growth factor; VLDL, very low-density lipoproteins

Journal of Hepatology 2016 vol. 65 j 425–443

Potential pathophysiological mechanism responsible for increased CVD in NAFLD

Heart

LV remodelling and mass ↑

Diastolic dysfunction

Altered electric conduction/arrhythmia

Aortic valve calcifications

Vascular wall

Increased cIMT

Arterial stiffening

Endothelium

Endothelial dysfunction

Endothelium disruption

Redox status

Increased homocysteine
Unalterd homocysteine

Increased OxLDL (postprandial)

Increased oxidative stress

Lipid profile

Triglycerides ↑

HDL ↓

sdLDL ↑/large LDL ↓

VLDL ↑

Angiogenesis

Increased VEGF
Unaltered VEGF

HMGB-1 ↓

Hemostasis

PAI-1 ↑

Factor VIII, IX, XI, XII ↑

Protein C activtity ↓/ factor VII ↑

Whole blood viscosity ↑

Inflammation

IL-6 ↑

hsCRP ↑

IL-1β ↑

TNF-α ↑, CCL3 ↑, sICAM-1 ↑

M1/M2 balance ↑

Hepatokines

Fetuin A ↑
Fetuin A =

FGF21 ↑/FGF-resistance

SeP ↑

ANGPTL's ↑

Paracrine cell signaling

Microvesicles ↑

MicroRNA profile

Other mechanisms

Sarcopenia

Vitamin D ↓

Gut-liver axis

TMA ↑ >TMAO

Genetics

PNPLA3 mutation

TM6SF2 mutation

Journal of Hepatology 2016 vol. 65 j 425–443

Risk of Stroke Associated With Biochemical Markers of Inflammatory Nonalcoholic Fatty Liver Disease

Criterion for Biochemical Presence of Inflammatory Nonalcoholic Fatty Liver Disease	Prevalence of Biochemical Marker		Crude	Adjusted[a]
	Cases	Controls		
	No. (%)	No. (%)	OR (95% CI)	OR (95% CI)
Elevated alanine aminotransferase[b]				
Absent[c]	84 (82)	188 (94)	1.0	1.0
Present	19 (19)	12 (6)	3.5 (1.7–7.6)	3.3 (1.3–8.4)
Elevated aspartate aminotransferase[b]				
Absent[c]	90 (87)	190 (95)	1.0	1.0
Present	13 (13)	10 (5)	2.7 (1.2–6.5)	3.6 (1.1–11.0)
Elevated aspartate aminotransferase:alanine aminotransferase ratio <2.0				
Absent[c]	79 (77)	183 (92)	1.0	1.0
Present	24 (23)	17 (9)	3.3 (1.7–6.4)	3.1 (1.4–7.0)

[a]Adjusted for age (continuous in years), sex, current smoking, current heavy ethanol intake, history of hypertension, or current use of an antihypertensive agent, atrial fibrillation, LDL-cholesterol concentration (continuous in mmol/L), serum glucose concentration (continuous in mmol/L), and serum creatinine concentration (continuous in μmol/L).

[b]An alanine aminotransferase (40.0 U/L) or aspartate aminotransferase (37.5 U/L) concentration ≥95th percentile among controls.

[c]Reference category.

Epidemiology: January 2011 - Volume 22 - Issue 1 - p 129-130

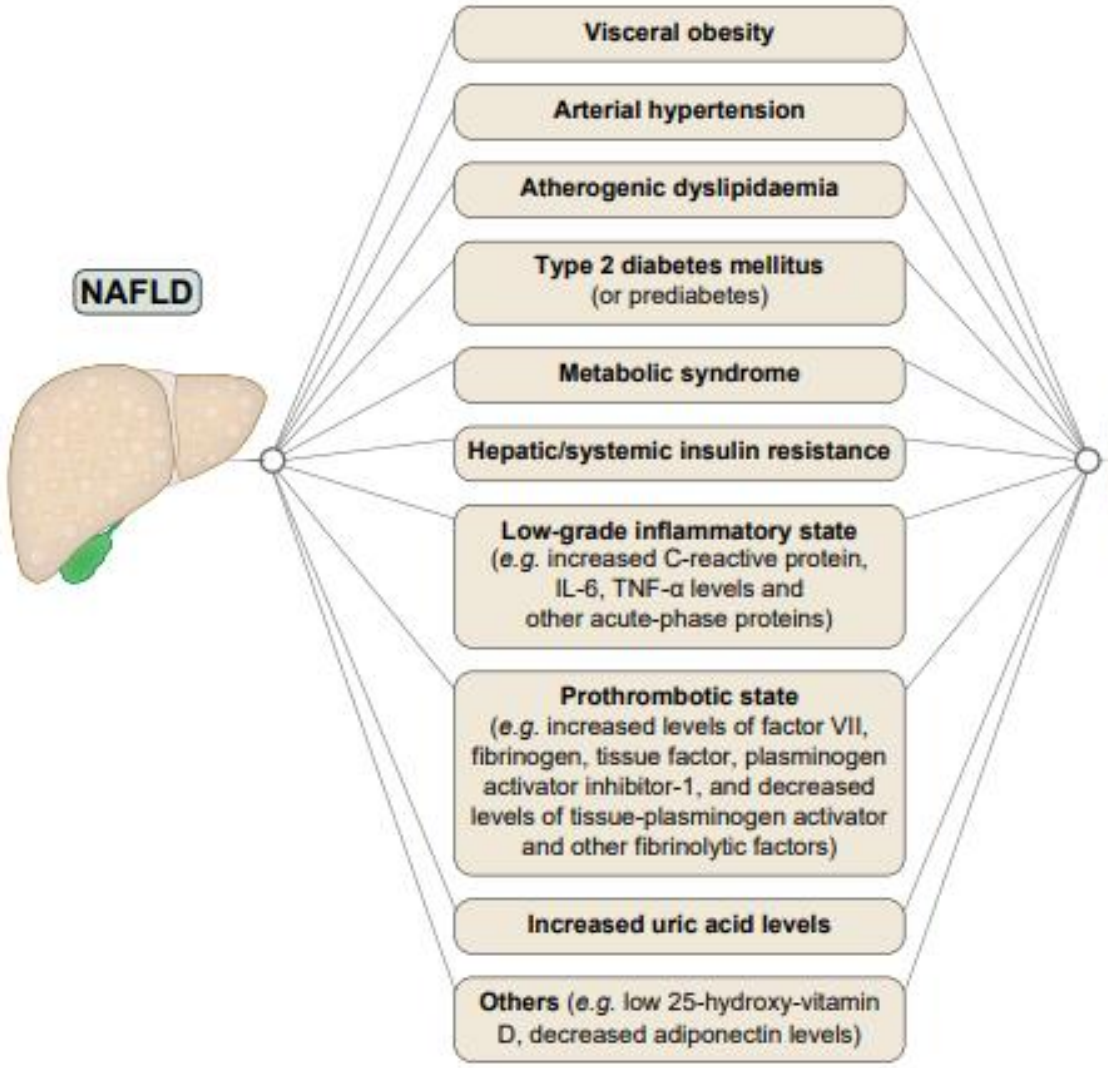
Diabetes and Family History of Diabetes on Histological Traits and Interaction Between Personal and Family History of Diabetes

Diabetes Status	N*	OR (95% CI)†	*P* Value‡
NASH			
No PH or FH diabetes	270	1.00 (–)	–
PH diabetes and no FH diabetes	76	2.48 (1.31-4.72)	**0.01**
FH diabetes and no PH diabetes	285	1.42 (1.02-1.98)	**0.04**
PH and FH diabetes	193	2.13 (1.38-3.30)	<**0.001**
Interaction between PH and FH diabetes	–	–	0.24
Any fibrosis			
No PH or FH diabetes	252	1.00 (–)	–
PH diabetes (yes versus no)	78	2.94 (1.49-5.81)	<**0.01**
FH diabetes (yes versus no)	269	1.40 (1.02-1.94)	**0.04**
PH and FH diabetes (yes versus no)	203	3.43 (2.11-5.56)	<**0.0001**
Interaction between PH and FH diabetes	–	–	0.58
Advanced fibrosis			
No PH or FH diabetes	85	1.00 (–)	–
PH diabetes (yes versus no)	52	6.03 (3.16-11.52)	<**0.0001**
FH diabetes (yes versus no)	92	1.24 (0.84-1.82)	0.28
PH and FH diabetes (yes versus no)	102	4.76 (2.96-7.64)	<**0.0001**
Interaction between PH and FH diabetes	–	–	0.13

Significant P values are shown in bold.
Abbreviations:
PH diabetes, personal history of diabetes; FH diabetes, family history of diabetes.
*N gives the number of patients with outcome and diabetes status.
†ORs and P values corresponding to PH diabetes, FH diabetes, and PH and FH diabetes were obtained from three separate logistic regression models adjusted for age at enrollment, gender, and BMI for each outcome. The control group for each model was individuals with no personal history or family history of diabetes.
‡P values corresponding to interaction between PH and FH diabetes were obtained using Wald's test

HEPATOLOGY, Vol. 56, No. 3, 2012

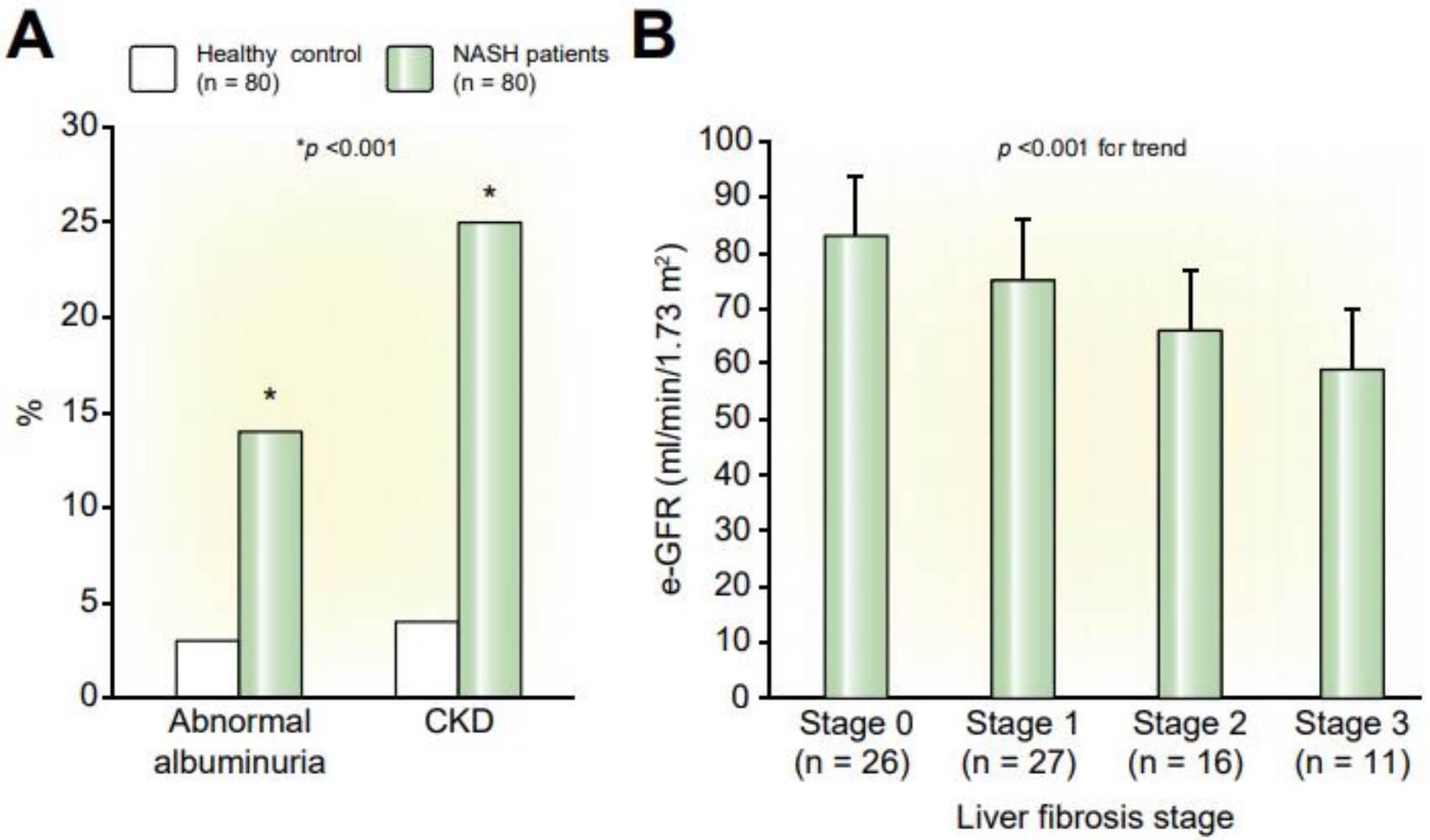
Risk factors in patients with NAFLD and CKD



Stages of CKD	Qualitative description	GFR (ml/min/1.73 m²)
1	Kidney damage with normal or elevated eGFR	≥90
2	Kidney damage with mild eGFR decrease	60-89
3A	Mild to moderate eGFR decrease	45-59
3B	Moderate to severe eGFR decrease	30-44
4	Severe eGFR decrease	15-29
5	Kidney failure	<15 or chronic dialysis

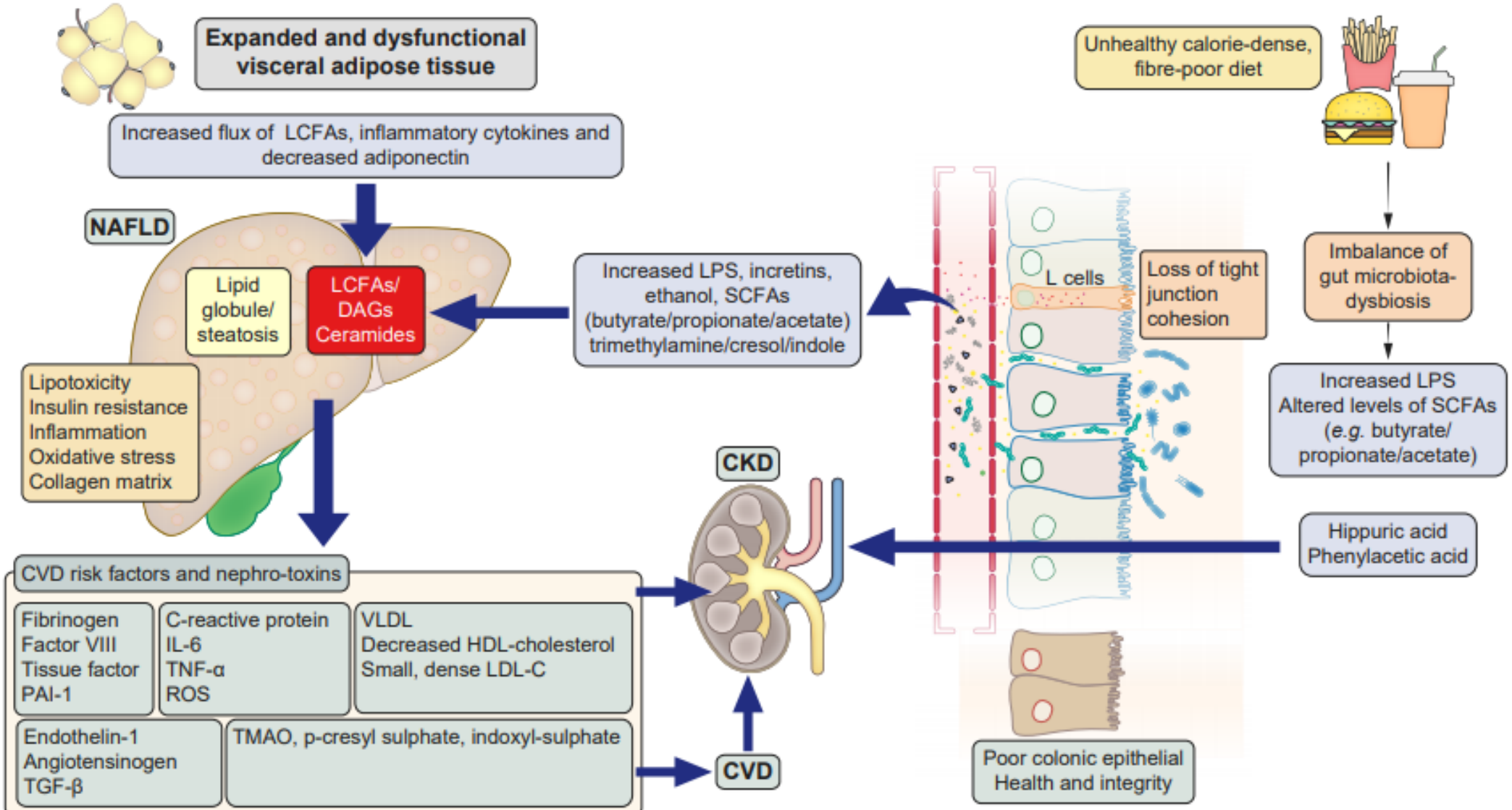
Journal of Hepatology 2020 vol. 72 j 785–801

Renal function parameters in patients with NASH and controls



Journal of Hepatology 2020 vol. 72 j 785–801

Potential mechanisms and factors linking intestinal dysbiosis, visceral adipose tissue dysfunction, NAFLD and CKD.



Journal of Hepatology 2020 vol. 72 j 785–801

Key Extrahepatic Manifestations of NAFLD

Extrahepatic manifestation	Key finding
Metabolic syndrome	Increasing prevalence of metabolic syndrome with progression of NAFLD, NASH, and severe fibrosis (18%–88%)
	Presence of metabolic syndrome associated with higher overall mortality in NAFLD
Visceral adiposity	Visceral adiposity carries a higher risk than subcutaneous adiposity for NAFLD
Type 2 diabetes	Insulin resistance is a common pathogenic mechanism for both type 2 diabetes and NAFLD, and more "severe" NAFLD is more likely to have incident diabetes
	Presence of type 2 diabetes in NAFLD increases mortality by 2.2-fold, and NAFLD increases the risk of microvascular diabetic complications
Cardiovascular disease	Cardiovascular disease is the primary cause of mortality in NAFLD, with multiple associations with cardiovascular disease events and subclinical markers
	More "severe" forms of NAFLD associated with higher risk of cardiovascular disease events and mortality
Chronic kidney disease	More "severe" NAFLD increases the likelihood of renal impairment, and improvement in hepatic disease may also improve renal function
Hypothyroidism	Subclinical and overt hypothyroidism link with NAFLD
Psoriasis	High prevalence of concurrent NAFLD and NASH in psoriasis
Polycystic ovarian syndrome	Polycystic ovarian syndrome and NAFLD share common risk factors in obesity and insulin resistance

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Li AA, et al: Extrahepatic Manifestations of Nonalcoholic Fatty Liver Disease

Key concepts of extra-hepatic manifestations of nonalcoholic fatty liver disease (NAFLD).

Established Linkages	
Type 2 diabetes	IR is the common pathogenic mechanism for both T2DM and NAFLD and the severity of NAFLD is directly proportional to incidence of T2DM [16–27]. The mortality of T2DM patients is increased 2-fold in the presence of NAFLD [13,28]. The risk of macro- and microvascular diabetic complications is increased by presence of NAFLD [29,30].
Cardiovascular Disease Atherosclerosis Heart failure Dysrhythmia	The primary cause of mortality in NAFLD is cardiovascular disease [2,44–48]. A higher risk of cardiovascular events is related to more "severe" forms of NAFLD [58–62]. Furthermore, in NAFLD patients, the frequency of aortic valve sclerosis and atrial fibrillation is higher [71–77].
Chronic Kidney Disease	The risk of renal impairment is increased by the presence of NAFLD [78,79]. Improvement in hepatic disease also improves renal function [90].
Obstructive Sleep Apnea	OSA is significantly associated with more "severe" forms of NAFLD and the treatment of OSA with CPAP therapy seems to improve the liver injury [103,104,110–119].
Endocrinopathies Polycystic ovarian syndrome Hypothyroidism	Obesity and IR are common risk factors for both PCOS and NAFLD [207–210]. The prevalence of NAFLD is higher in patients with hypothyroidism; furthermore, low thyroid function seems to worsen the progression of liver damage, while replacement therapy may improve liver function [187–189,194–197].
Emerging Linkages	
Osteoporosis	NAFLD is associated with a 2.5-fold risk of osteoporotic fractures [122,124,125].
Urolithiasis	NAFLD patients have an almost doubled risk of developing urolithiasis, both for urate and calcium stones [213,214].
Periodontitis	Periodontitis is significantly associated with the presence of NAFLD and common periodontal pathogens seem to be able to influence the development and alterations of NAFLD [179–184].
Psoriasis	IR is a common risk factor for both psoriasis and NAFLD. Patients with psoriasis have a 2-fold increased risk of suffering from NALFD [151–156].
Male sexual dysfunction	NAFLD is an emerging risk factor for the development of erectile dysfunction [200,201].

Int. J. Environ. Res. Public Health 2019, 16, 3415

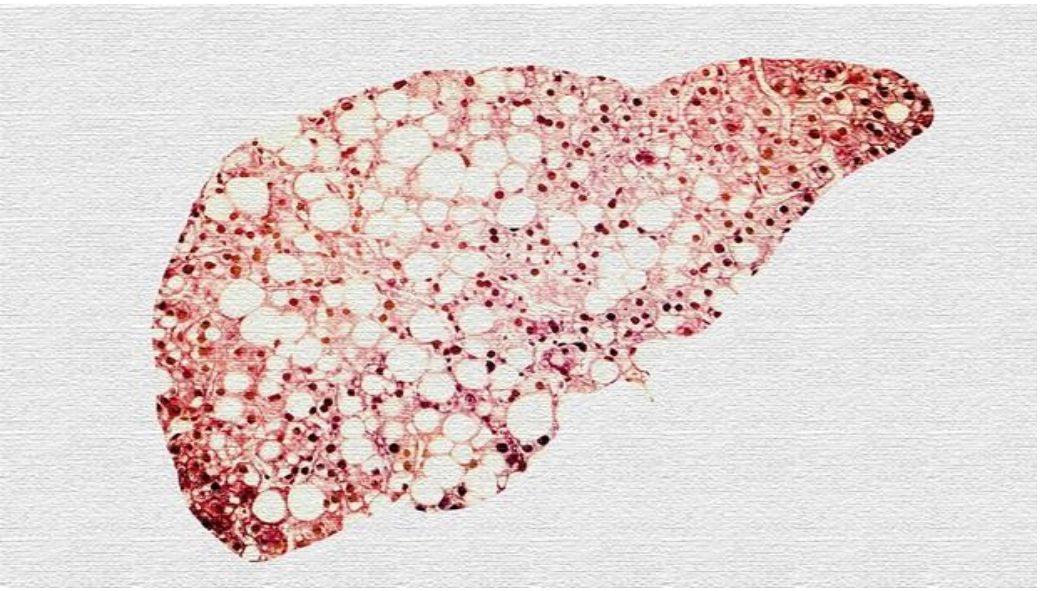
Putative mechanisms linking NAFLD and extra-hepatic cancers

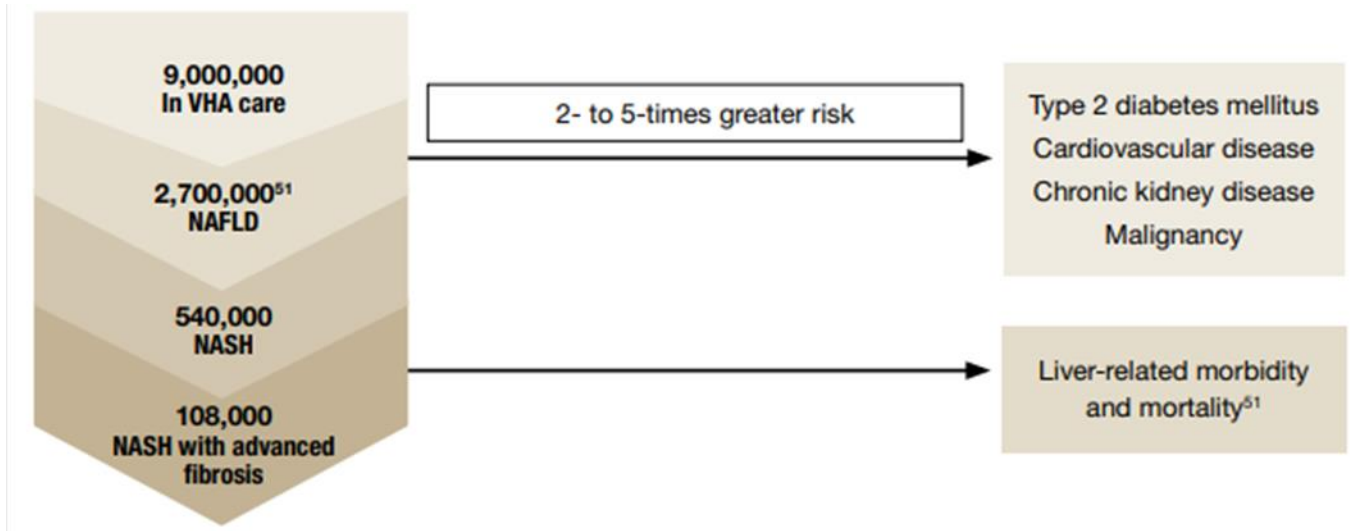
Mechanism	Effects	Extra-Hepatic Site
	Insulin resistance	
↑ IGF-1 axis	Proliferative and anti-apoptotic effects	Prostate/colorectal/lung/Breast cancers, Barrett's esophagus, esophageal adenocarcinoma
	Dysfunctional adipose tissue	
↓ adiponectin/caspase activation	Anti-apoptotic effects	Gastrointestinal and extra-intestinal cancer
↓ adiponectin/TNF-α	Proliferation and angiogenesis	Gastrointestinal and extra-intestinal cancer
↑ leptin/MAPK	Invasiveness, motility, lamellipodia formation	Colon/breast cancer, Barrett's esophagus, esophageal adenocarcinoma
↑ resistin/NF-κB		Breast/gastrointestinal and non-small cell lung cancers
	Inflammation	
IL-6/JAK/STAT3 and IL-6/MAPK	Proliferation	Renal/gastric/colorectal cancers
TNF-α/Wnt/β-catenin	Angiogenesis, differentiation and metastasis development	Colorectal cancer
	Gut microbiota	
MAMPs/TLRs	Inflammation	Colon cancer
Inflammasome-derived IL-18	Anti-apoptotic effects	Colon cancer

IGF-1, insulin growth factor-1; IL, interleukin; MAMPs, microorganism-associated molecular patterns; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κ B; STAT3, signal transducer and activator of transcription 3; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α.

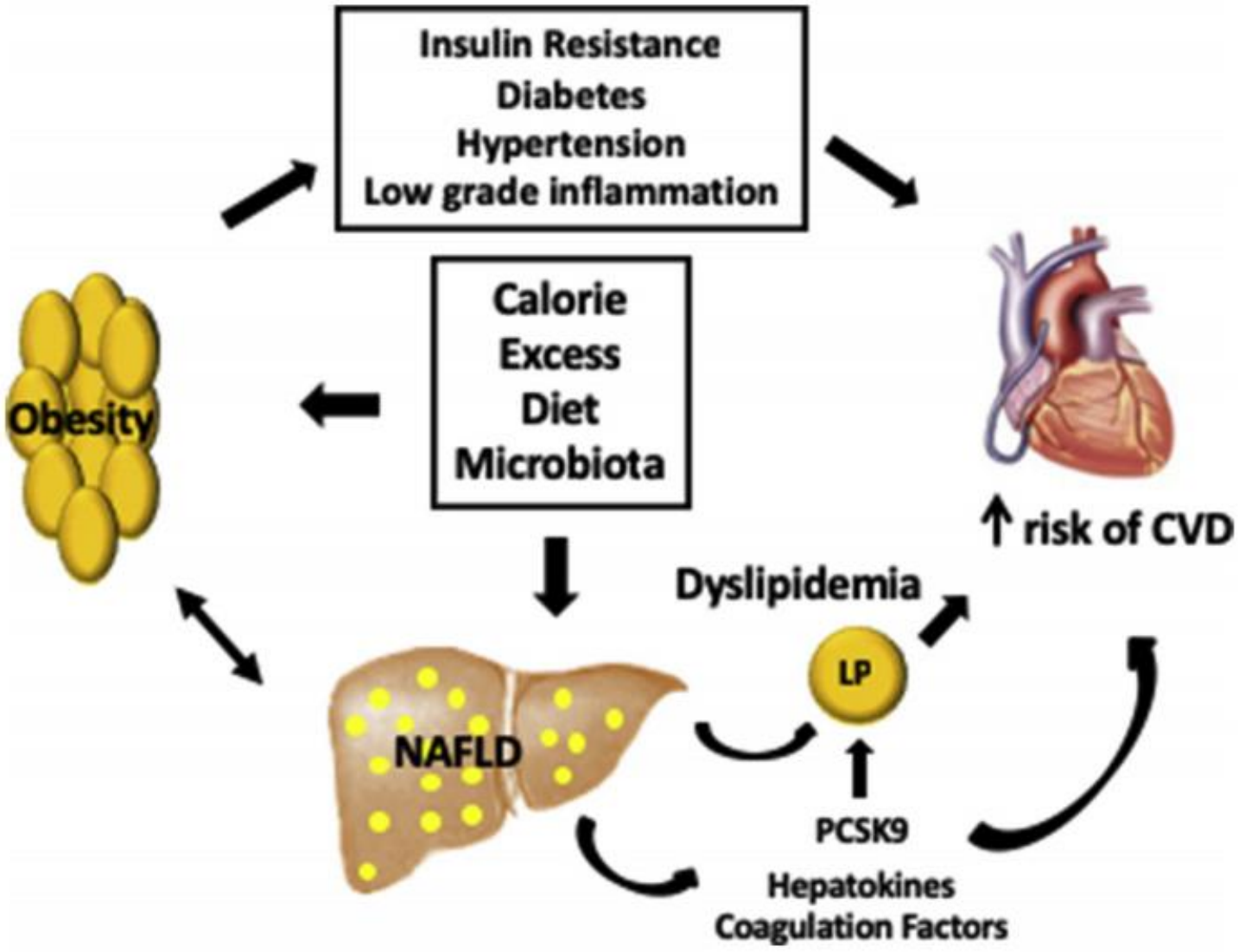
Int. J. Mol. Sci. 2016, 17, 717

NAFL
SINGLE DISEASE ?





Mechanisms of cardiovascular disease susceptibility due to excess of calorie intake



- A positive energy balance due to calorie excess or reduction in expenditure increases fat depot in the adipose and hepatic tissue.
- The fat in the adipose results in obesity, insulin resistance, T2D, hypertension and low-grade inflammation directly increasing the risk of cardiovascular events.
- The fat in the liver results in NAFLD, with consequent increased triglyceride-rich lipoproteins secretion causing dyslipidemia and increased risk of cardiovascular disease.
- NAFLD results also in changes in secretion of hepatic specific proteins including hepatokines, proprotein convertase subtilisin/kexin type 9 (PCSK9), coagulation factors inducing additional independent risk factors of cardiovascular disease.

LP-lipoproteins (VLDL); ASCVD-atherosclerotic cardiovascular disease; NAFLD-non-alcoholic fatty liver disease.

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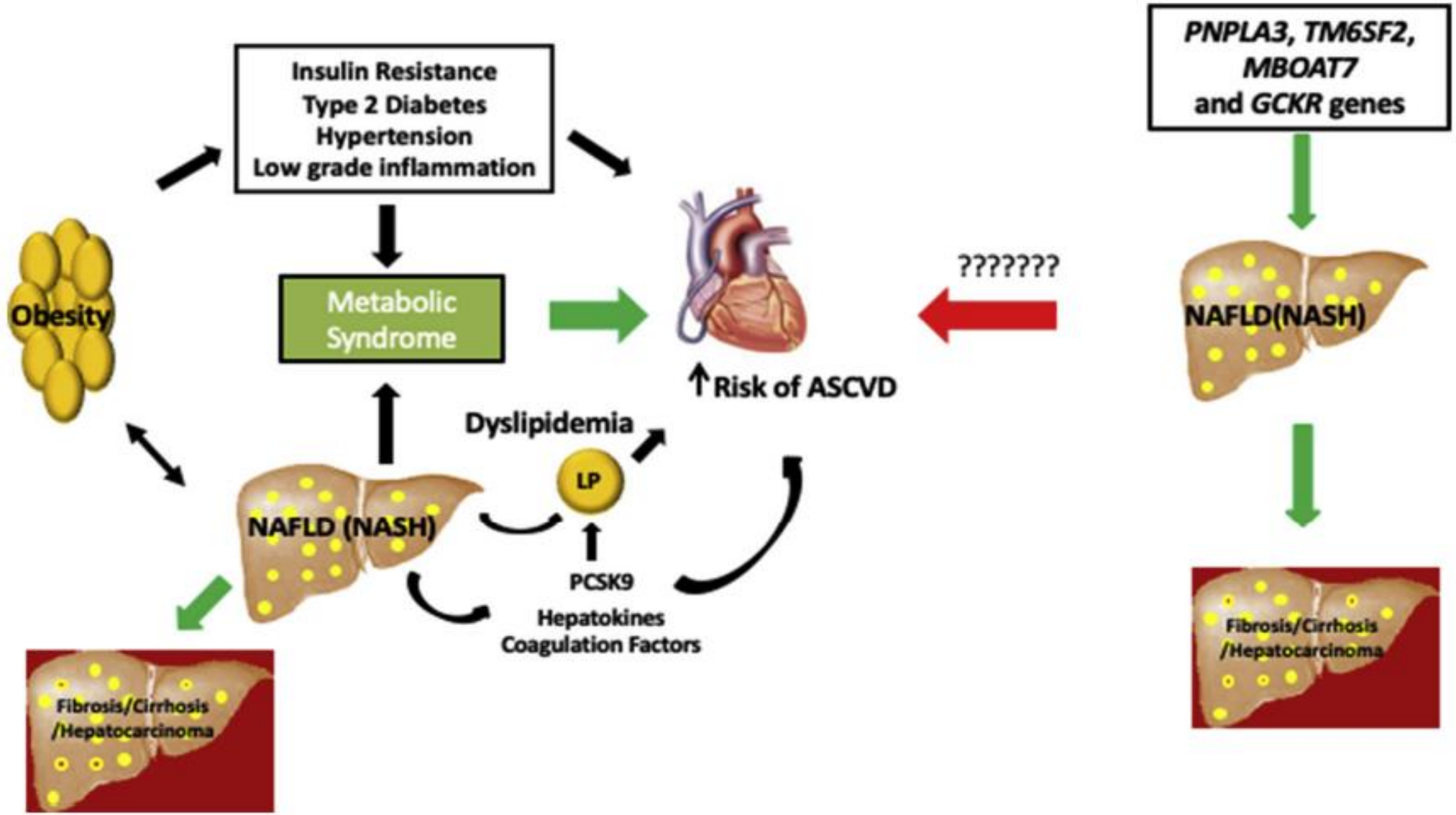
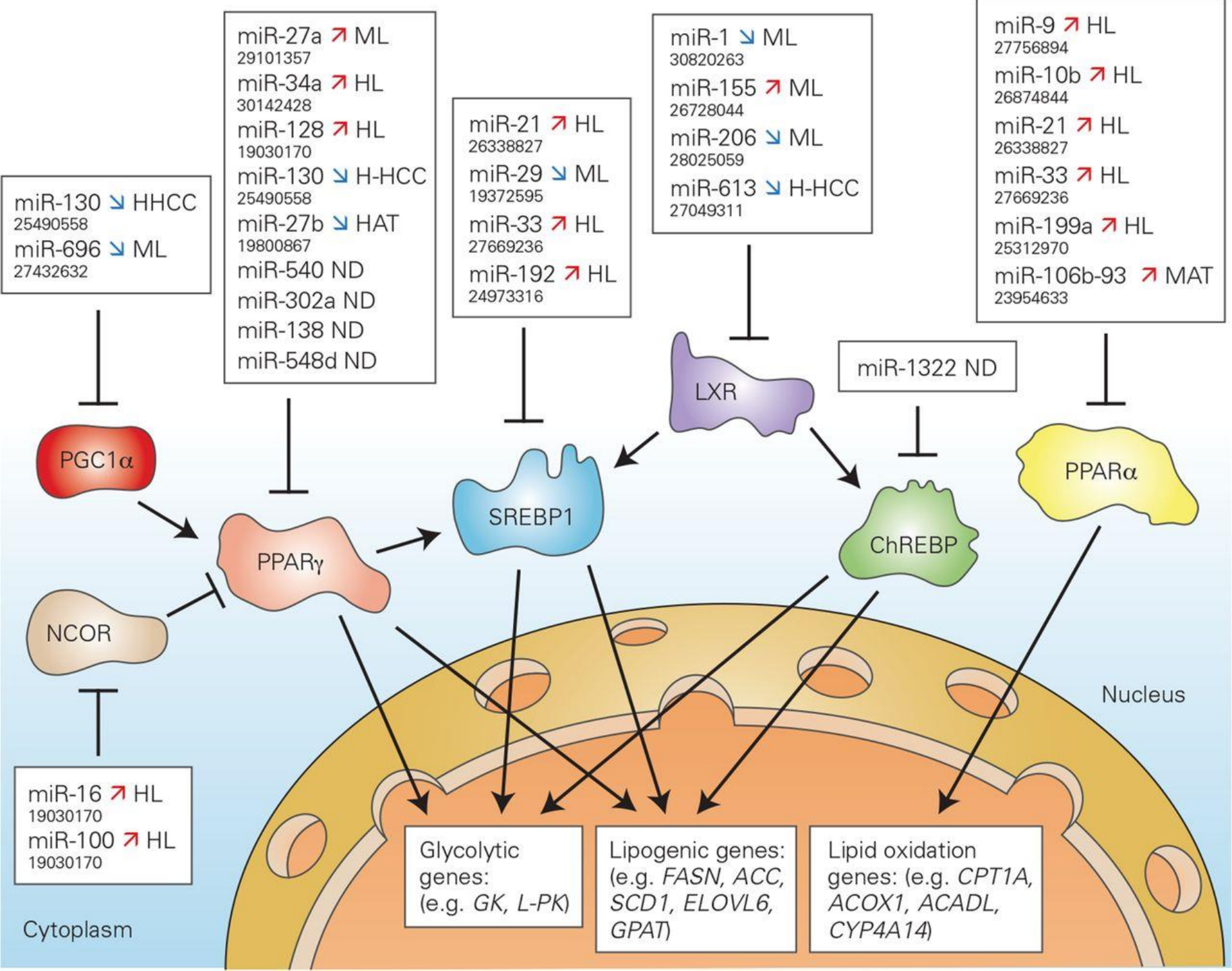
Summary of controversies of NAFLD as an independent cause of atherosclerotic cardiovascular disease

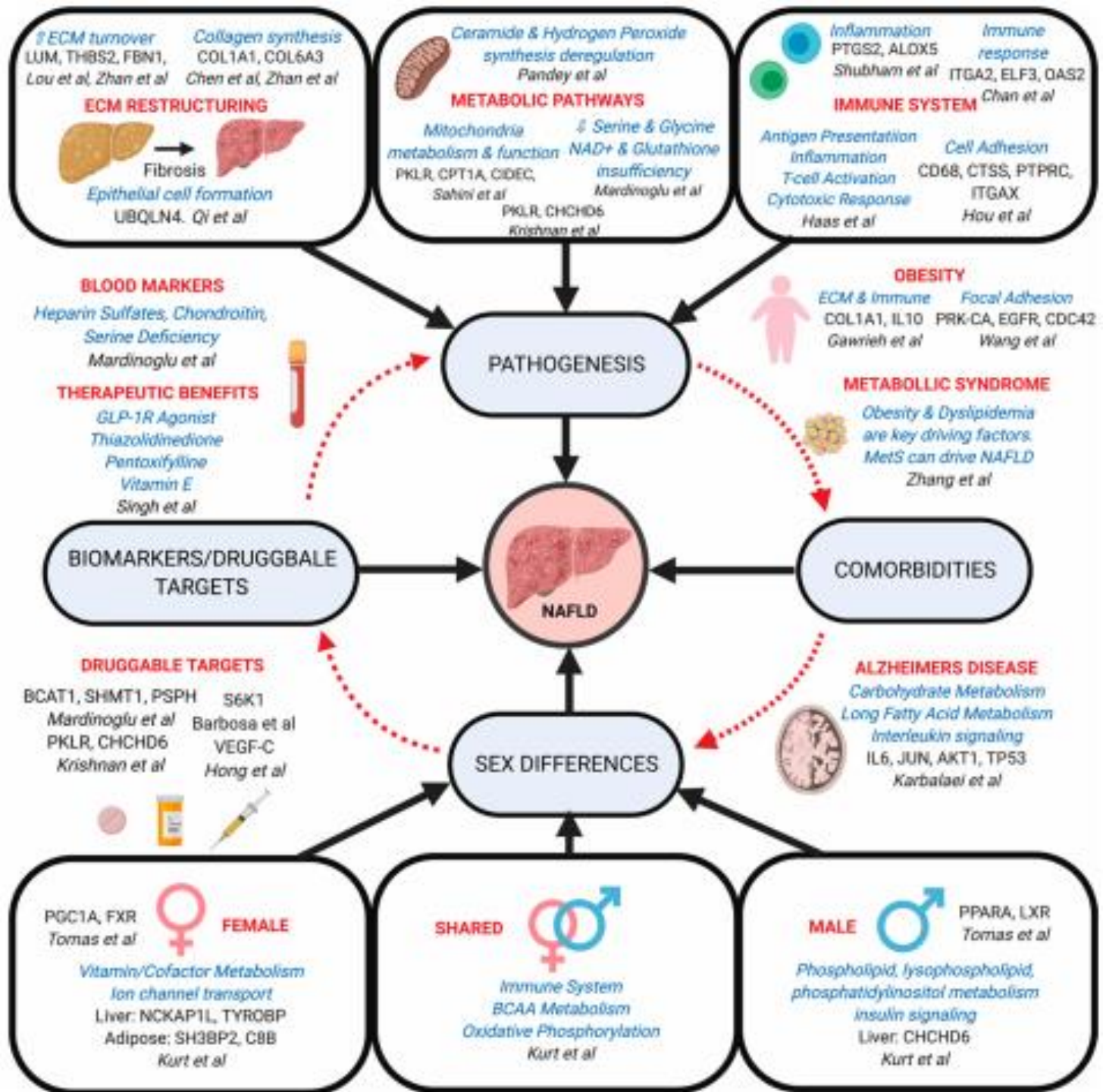


Genetic variants that predispose to NAFLD development have not been associated with atherosclerotic CVD development in the absence of overall obesity and the metabolic syndrome.

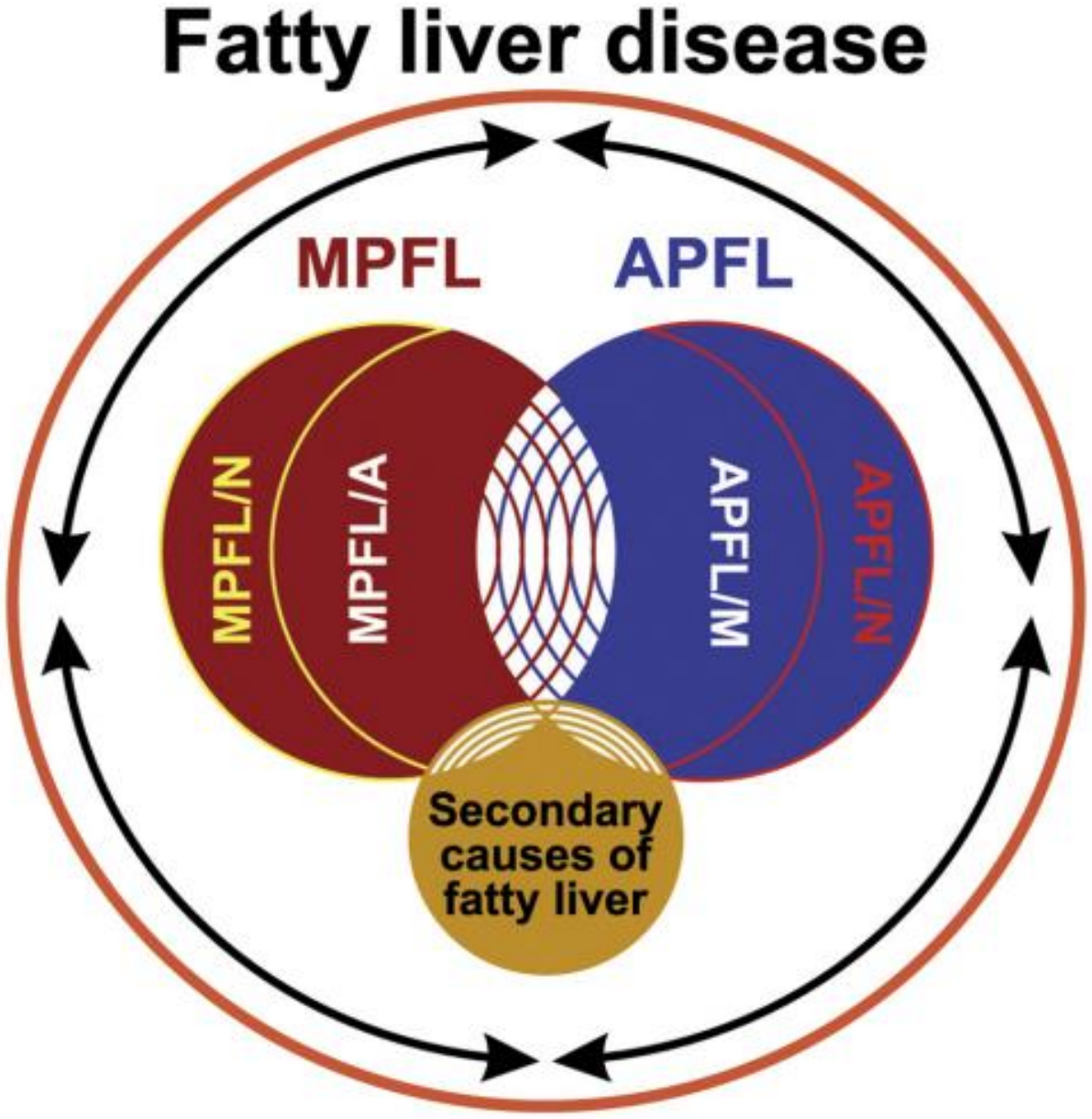
Atherosclerosis 282 (2019) 110–120



Monika Gjorgjieva, Cyril Sobolewski, Dobrochna Dolicka, Marta Correia de Sousa, miRNAs and NAFLD: from pathophysiology to therapy
http://orcid.org/0000-0001-7199-4135



Summary of findings from network-based studies to elucidate NAFLD progression, mechanisms, comorbidities, sex differences, biomarkers and druggable targets



CONCLUSION

Venn diagram illustrating the spectrum of fatty liver diseases and the overlap and distinction of the 2 main entities, namely, metabolic dysfunction predominant and alcohol predominant fatty liver. An updated and more appropriate nomenclature and classification system is required to reflect the nuances of disease etiology within the spectrum of fatty liver disease. The abbreviations are used to merely illustrate the various subgroups: MPFL: metabolic dysfunction predominant fatty liver; APFL, alcohol predominant fatty liver; MPFL/A and MPFL/N: metabolic dysfunction predominant fatty liver with, and without alcohol intake that is anything more than ceremonial; and APFL/M and APFL/N: alcoholic predominant fatty liver with metabolic dysfunction or with no metabolic dysfunction.

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