A Systemic View of MASLD / MASH

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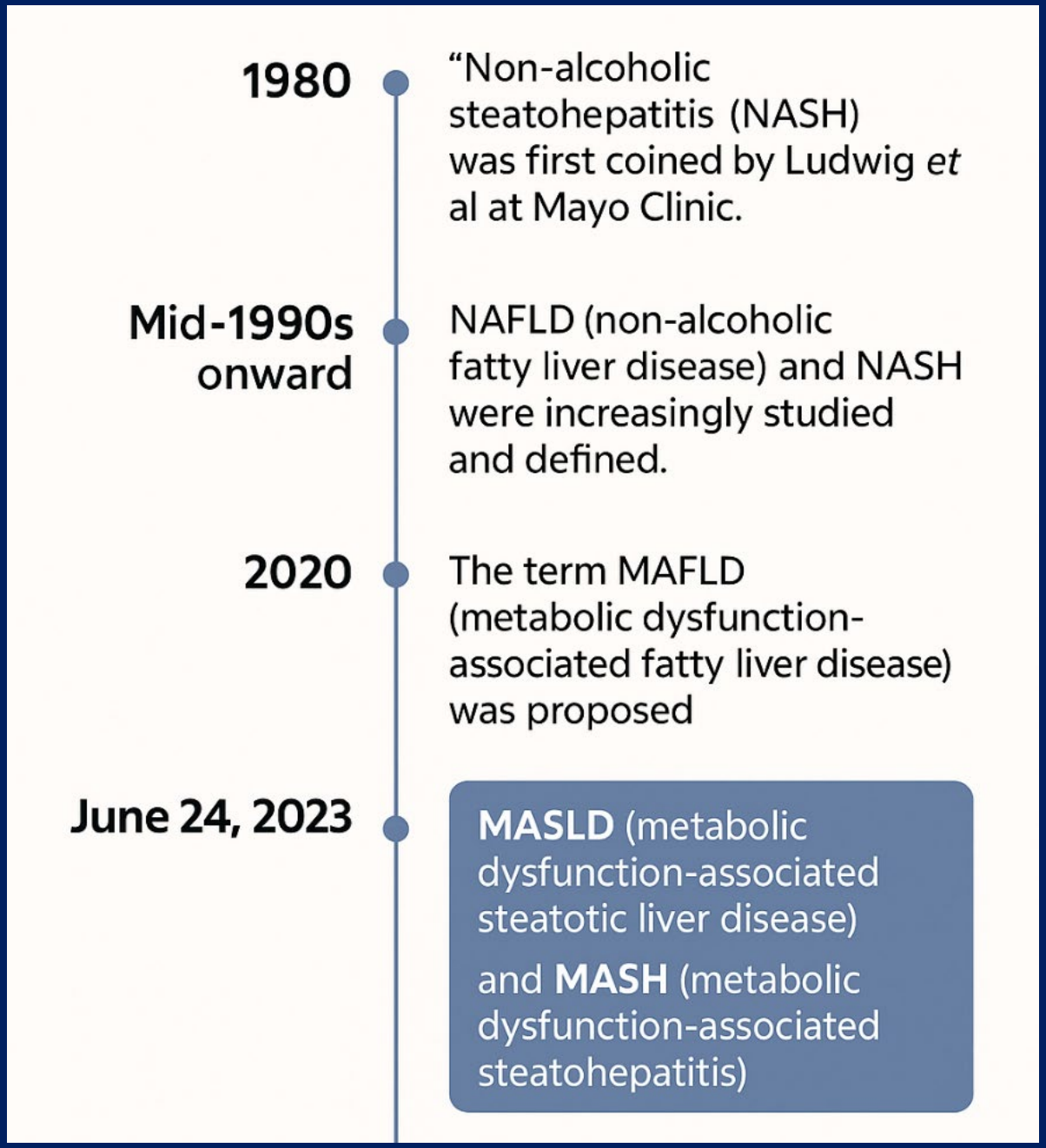
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Objectives

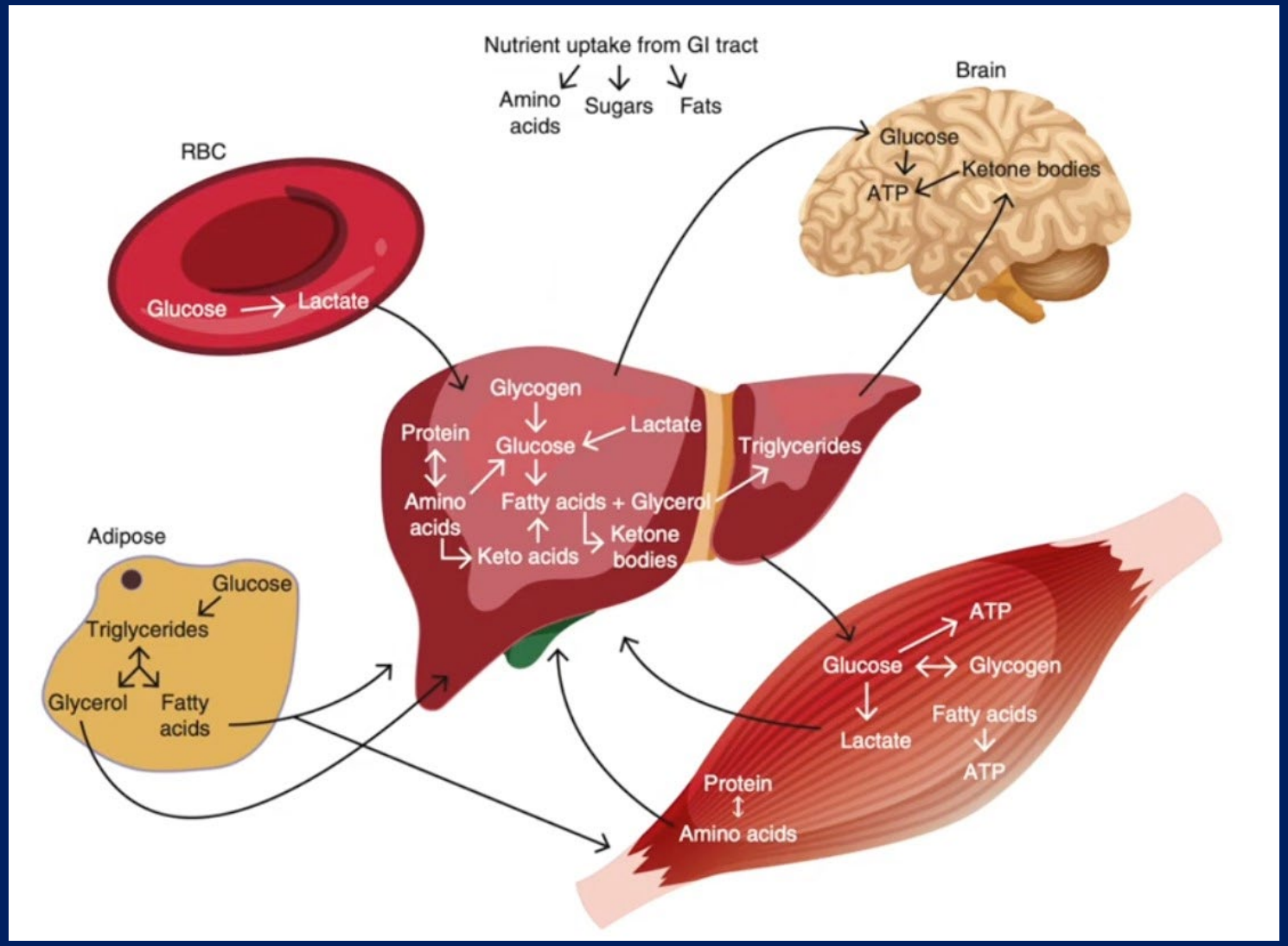
- Reframe MASLD/MASH as a systemic diseases.
- Highlight the impact on extrahepatic organs.
- Consider how this systemic view affects our approach to diagnosis and care.

Nomenclature Shift

Emphasis shifts from ruling out alcohol to recognizing metabolic dysfunction as the core driver



The Liver as a Metabolic Hub



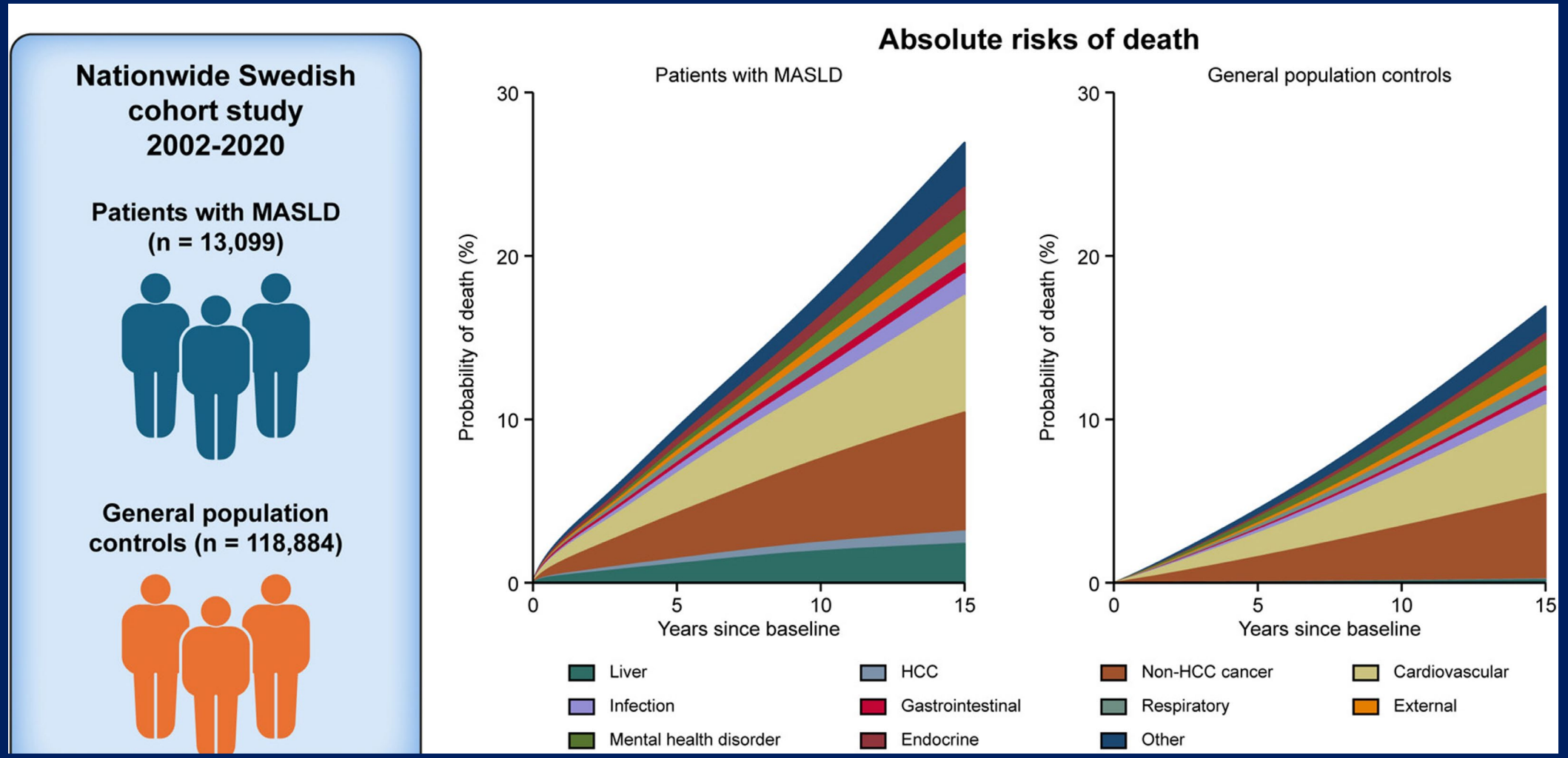
Case Vignette

A 50-year-old man has mildly elevated ALT, and prediabetes. Smokes 10 cigarettes per day. No alcohol. Atorvastatin prescribed by a cardiologist, but taken no more than 2 months ‘in fear of liver toxicity’. BMI:32 LDL:176 BP:145/90

Three years later, he dies suddenly of Acute MI.

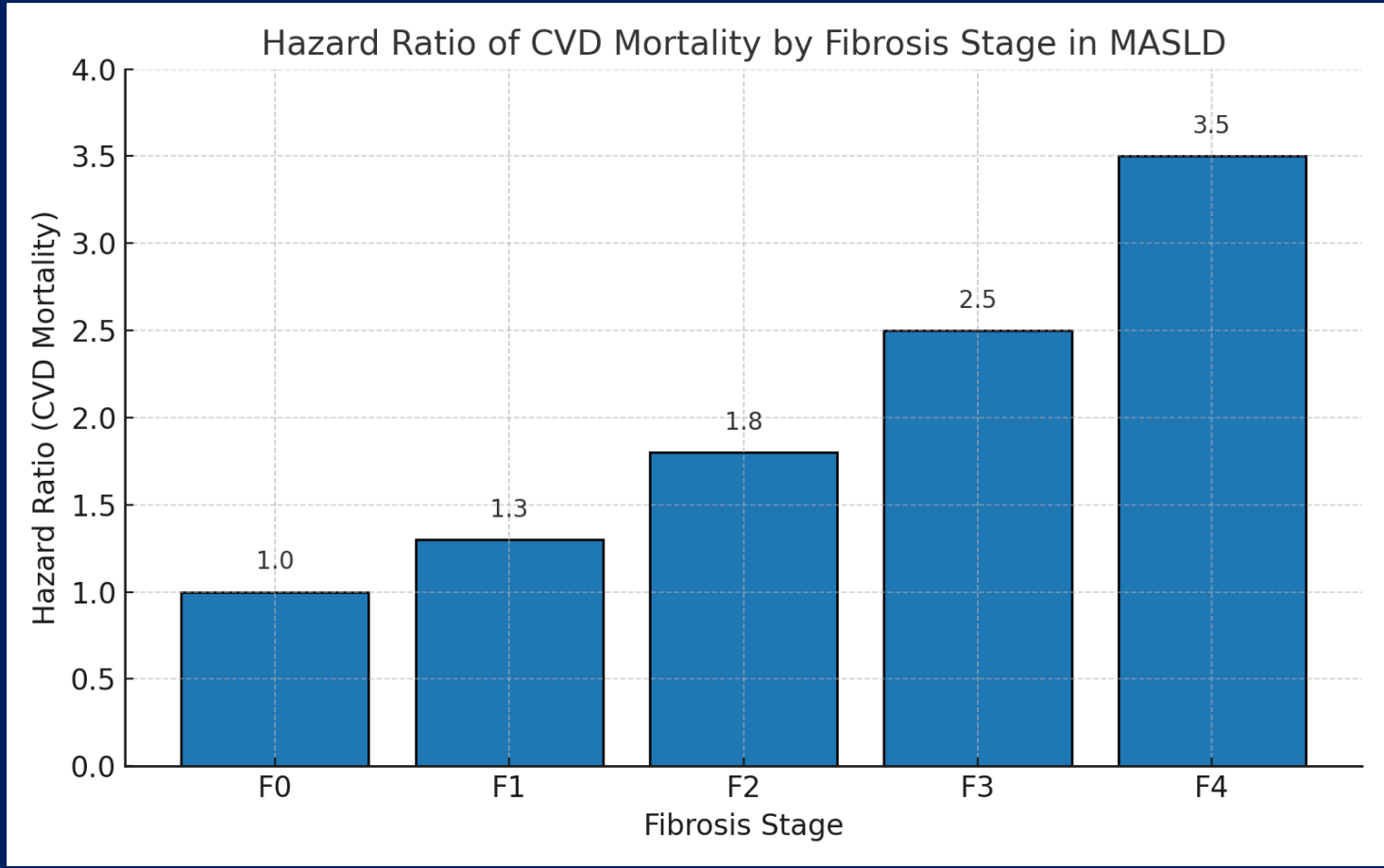
A Missed Opportunity for Systemic Intervention

Cause-specific mortality in MASLD



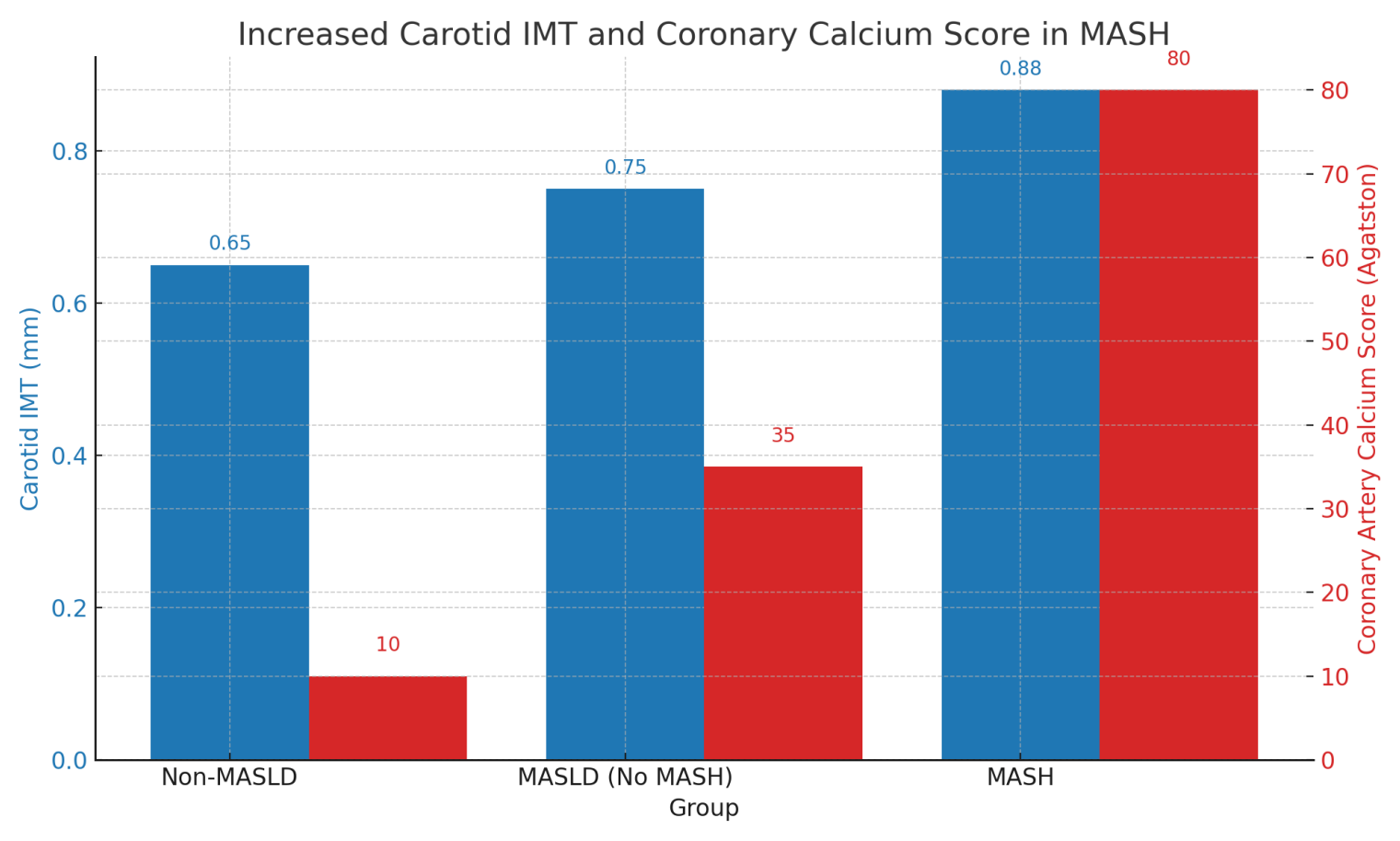
Issa, et al. J Hepatology, 2025

CVD is the #1 Killer in MASLD



Dulai, P. S., et al. Hepatology 65, 2017.

Atherosclerosis and MASH



Endocrine Associations

Hypothyroidism

- Impaired thyroid hormone receptor β signaling in the liver contributes to steatosis and inflammation.
- Resmetirom, a THR-agonist, shows promise in improving liver histology.

Polycystic Ovary Syndrome (PCOS)

- Women with hyperandrogenic PCOS are at high risk of MASLD.
- MASLD screening is recommended for all women with PCOS.

Endocrine Associations

Growth Hormone Deficiency (GHD)

- GH and IGF-1 regulate lipid metabolism and reduce hepatic fat accumulation.
- GHD increases MASLD risk and worsens fibrosis progression.

Panhypopituitarism

- Can lead to secondary MASLD with unique treatment needs.

Type 2 Diabetes & Insulin Resistance

- MASLD is highly prevalent in people with type 2 diabetes, especially when obesity is present.
- It increases risk for MASH, cirrhosis, and hepatocellular carcinoma (HCC).

Diabetes and MASLD

A Bidirectional Loop

Insulin Resistance ⇢ MASLD

↑Insulin Resistance ⇠ MASLD

Type2 DM ⇢ 3x ↑MASH/Cirrhosis

↑Diabetic Complications ⇠ MASH

Diabetes ⇢ ↑HCC in MASLD

Lipid Paradox in MASLD

Normal LDL-C, but high-risk lipoprotein profile:

- Small dense LDL
- Apolipoprotein B (apo-B)
- Remnant lipoproteins

More atherogenic than LDL-C alone

Risk calculators (e.g., ASCVD, Framingham) **may fail**

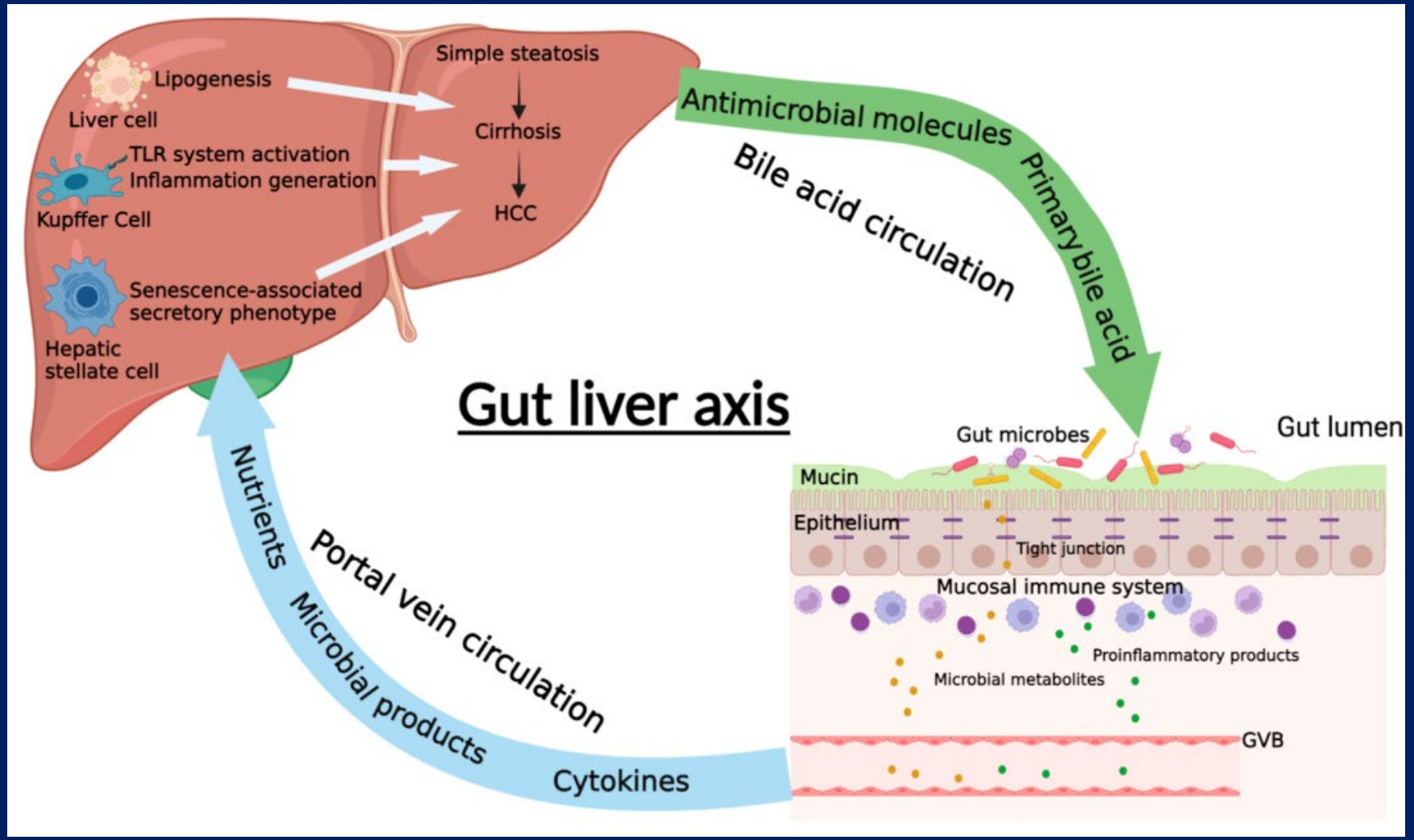
CKD and MASLD

- MASLD ⇢ ↑CKD risk
  - Independent of diabetes, hypertension, and BMI
  - Seen even in patients with preserved GFR and no albuminuria

- Advanced fibrosis (F3–F4) in MASLD strongly correlates with eGFR decline and incident CKD.

- Clinical Implication: **Monitor renal function proactively**

The Gut-Liver Axis



Central Nervous System

Patients with MASLD show higher risk of:

- Mild cognitive impairment (MCI)
- Slower processing speed
- Higher prevalence of depression and anxiety

Bidirectional relationship - Mood disorders worsen metabolic control

HCC with no Cirrhosis

Independent of fibrotic progression

- Chronic metabolic inflammation
- Oxidative stress
- Lipotoxicity

Surveillance Challenges

- No mention in guidelines
- Which MASLD pts are at risk?
- ↓Sono sensitivity in obesity/fatty liver
- ↓AFP reliability in early-stage HCC

Extrahepatic Malignancies

- Thyroid
- Colorectal
- Esophageal
- Stomach
- Breast
- Pancreas

Extrahepatic cancers are over 8x more frequent than hepatocellular carcinoma (HCC) in MASLD patients

- Proposed mechanisms:
  - Inflammation
  - insulin/IGF-1 axis
  - ? microbiome

Sarcopenia and MASLD

Up to 44% of MASLD patients may have sarcopenia.

Risk factors:

- Older age
- Female gender
- Obesity
- Low physical activity
- Smoking history
- Vitamin D deficiency

Smoking Accelerates MASLD Progression

- Downregulates AMPK signaling, a key regulator of fat metabolism ⇢ ↑hepatic lipid synthesis, TG accumulation, and insulin resistance.

- Activates hepatic stellate cells via the TGF-β/SMAD pathway, leading to extracellular matrix deposition and scarring.

- Induces epithelial–mesenchymal transition (EMT) in liver cells, accelerating fibrosis and cirrhosis.

Summary Slide: Multi-Organ Burden

Organ Involvement in MASLD/MASH: Mechanisms and Clinical Consequences

Organ/System	Mechanism(s)	Clinical Consequence(s)
Liver	Lipotoxicity, oxidative stress, insulin resistance, inflammation, fibrosis	Steatosis → SH → Fibrosis → Cirrhosis → HCC
Cardiovascular System	Atherogenic dyslipidemia, chronic inflammation, endothelial dysfunction	Accelerated atherosclerosis, coronary artery disease, heart failure
Pancreas	Insulin resistance, beta-cell dysfunction	Type 2 Diabetes Mellitus, impaired glucose tolerance
Kidneys	Systemic inflammation, endothelial dysfunction, altered RAAS	Chronic kidney disease, increased albuminuria
Intestines (Gut)	Dysbiosis, increased intestinal permeability ("leaky gut"), endotoxemia	Systemic inflammation, progression of liver injury
Adipose Tissue	Adipokine imbalance, inflammation, ectopic fat accumulation	Worsened insulin resistance, perpetuation of metabolic dysfunction
Muscle (Skeletal)	Insulin resistance, mitochondrial dysfunction	Sarcopenia, reduced glucose uptake, worsened metabolic profile
Brain (CNS)	Systemic inflammation, altered lipid signaling, insulin resistance	Increased risk of cognitive impairment, Alzheimer's disease-like changes
Endocrine System	Hormonal imbalance (e.g., leptin, adiponectin), insulin resistance	Polycystic ovarian syndrome (PCOS), hypogonadism, metabolic syndrome

Emerging Treatments (as of 2025)

Drug/Class	Mechanism of Action	Stage	Notes
Resmetirom (MGL-3196)	Selective thyroid hormone receptor-β (THR-β) agonist	✅ FDA Approved (2024–2025)	Improves liver fat and fibrosis; the first drug with regulatory approval
Lanifibranor	Pan-PPAR agonist (α, δ, γ)	Phase 3	Targets inflammation, steatosis, and fibrosis
Obeticholic acid (OCA)	FXR agonist	Phase 3 (REVERSE trial)	Improves fibrosis; pruritus is a common side effect
Aramchol	SCD1 inhibitor	Phase 3	Anti-steatotic and anti-fibrotic effects
Semaglutide (GLP-1 RA)	GLP-1 receptor agonist	Phase 2/3 for NASH	Strong metabolic effects; weight loss improves liver histology
Tirzepatide	Dual GIP/GLP-1 receptor agonist	Phase 2 (for MASH)	Promising weight loss and liver fat reduction
Pegbelfermin	FGF21 analogue	Phase 2	Improves liver steatosis and metabolic parameters
Aldafermin (NGM282)	FGF19 analogue	Phase 2 completed	Improves fibrosis and liver enzymes
Cenicriviroc	CCR2/CCR5 antagonist	Discontinued after Phase 3	Failed to meet primary endpoint in fibrosis
Volixibat	IBAT inhibitor (bile acid metabolism modulation)	Phase 2	May reduce liver fat via bile acid regulation

Noninvasive Stratification Tools

- Fibrosis stage as predictor of all-cause, CV, and renal mortality
- Should focus less on steatosis, more on fibrosis
- Fib-4, NFS, FAST score
- Fibroscan
- MR-Elastography
- Biomarkers - PRO-C3
- AI-based prediction

The Multidisciplinary Future

MASLD is no longer a hepatology-only issue.

- Cardiologist
- Nephrologist
- Endocrinologist
- Mental Health Specialist
- Dietitian
- Sports Specialist
- Bariatric Surgeon
- GI / Hepatologist
- Primary Care Practitioner

We Need Integrated Care Models

Core Elements of an Integrated MASLD Model:

- Risk stratification tools in primary care (e.g., FIB-4, liver stiffness).
- Shared decision-making across specialties.
- Standardized referral algorithms.
- Digital health platforms for tracking lifestyle, labs, and medication adherence.
- Patient education and engagement as a cornerstone.

Research Frontiers

Genetics & Precision Risk Stratification

- PNPLA3 (I148M)
  - ↑Steatosis, fibrosis
  - ↑HCC
  - ↑CV disease
- TM6SF2 (E167K)
- MBOAT7
- GCKR
- HSD17B13 (potential protective role)

Research Frontiers

Microbiome Modulation

- Fecal microbiota transplantation – early trials underway
- Next-generation probiotics and postbiotics
- Diet–microbiome interaction studies guiding personalized nutrition

Key Takeaways

- MASLD/MASH = systemic disease
- Fibrosis drives outcomes
- Systemic lens → better risk stratification and management
- Integrated Care Models are Needed