



Medicina  
Biorreguladora  
de Sistemas

by -Heel

# Aprendan de Matrix. !

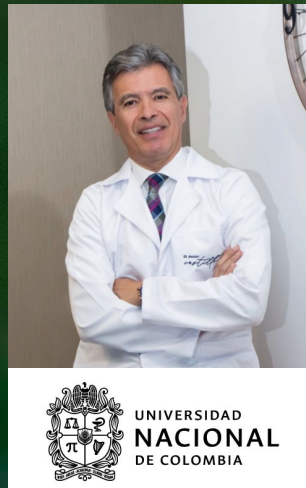
Dra Myriam Lucia Velandia Romero Biol.MSc.PhD  
Insituto de Virologia . Universidad El Bosque  
Colombia

# El Imbalance metabólico...

## inicia en el hígado

# Castillo Jorge

Especialista en Endocrinología  
Los Cobos Medical Center  
Bogotá, Colombia



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Healthcare designed by nature

[www.eldoctorcastillo.com](http://www.eldoctorcastillo.com)


THERAPEUTIC ADVANCES in  
*Chronic Disease*

---

# Association of NAFLD with cardiovascular disease and all-cause mortality: a large-scale prospective cohort study based on UK Biobank

Wen Ma\*, Wentao Wu\*, Weixing Wen, Fengshuo Xu, Didi Han, Jun Lyu and Yuli Huang 

El FLI genera una puntuación de 0 a 100: 

- **FLI < 30**: Regla la presencia de hígado graso (alta sensibilidad).
- **FLI ≥ 60**: Indica una alta probabilidad de hígado graso (alta especificidad). 

n=215.24

5

*Ther Adv Chronic Dis* 2022, Vol. 13: 1–19

Association of NAFLD with cardiovascular disease and all-cause mortality: a large-scale prospective cohort study based on UK Biobank

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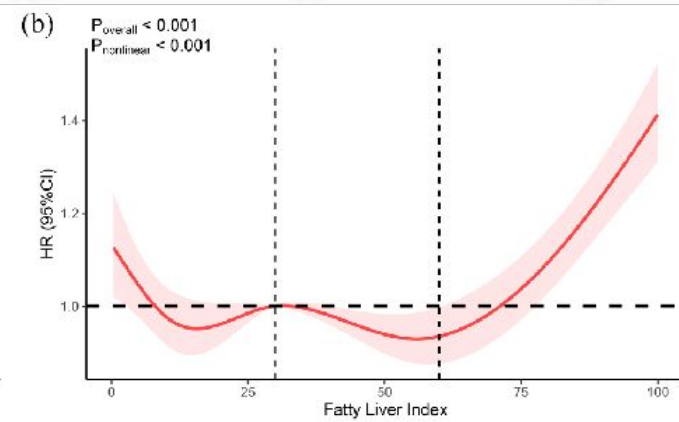
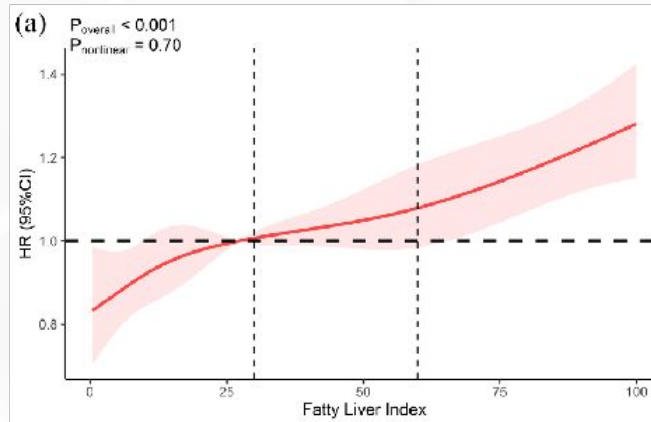
MACE

Mortalidad x ECV

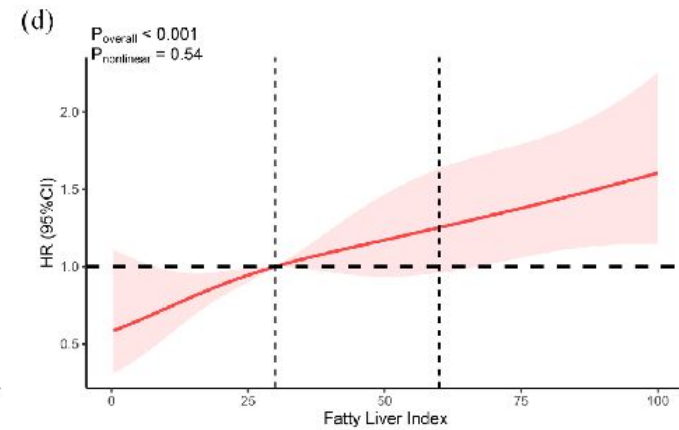
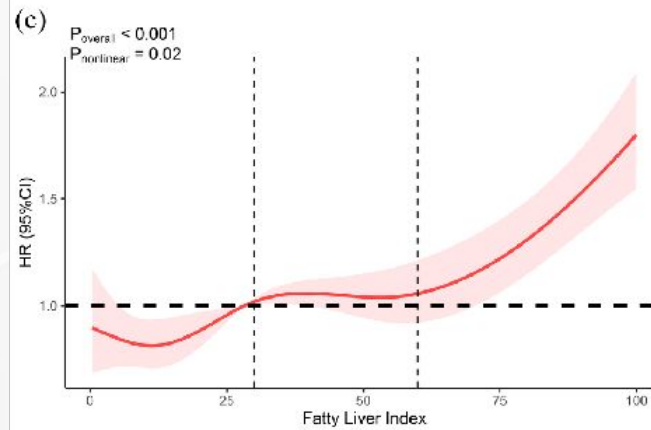
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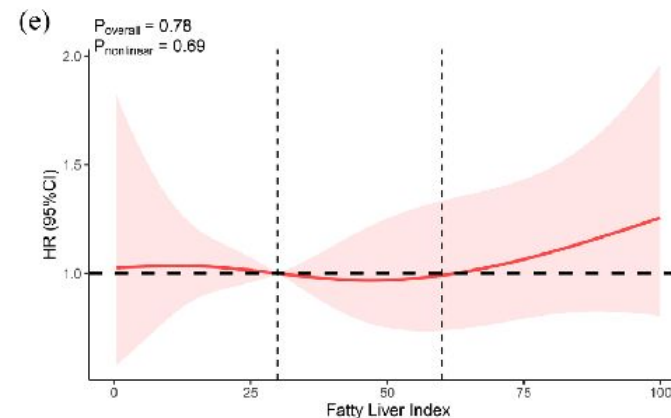
n=215.24  
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Mortalidad Total



IAM



Mortalidad x Stroke

**Association of NAFLD with cardiovascular disease and all-cause mortality: a large-scale prospective cohort study based on UK Biobank**

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n=215.24  
5

MACE	1.25 (1.14 – 1.36)
Mortalidad Total	1.14 (1.08 – 1.20)
Mortalidad x ECV	1.61 (1.42 – 1.82)
IAM	1.58 (1.19 – 2.11)
Mortalidad x Stroke	1.18 (0.85 – 1.64)

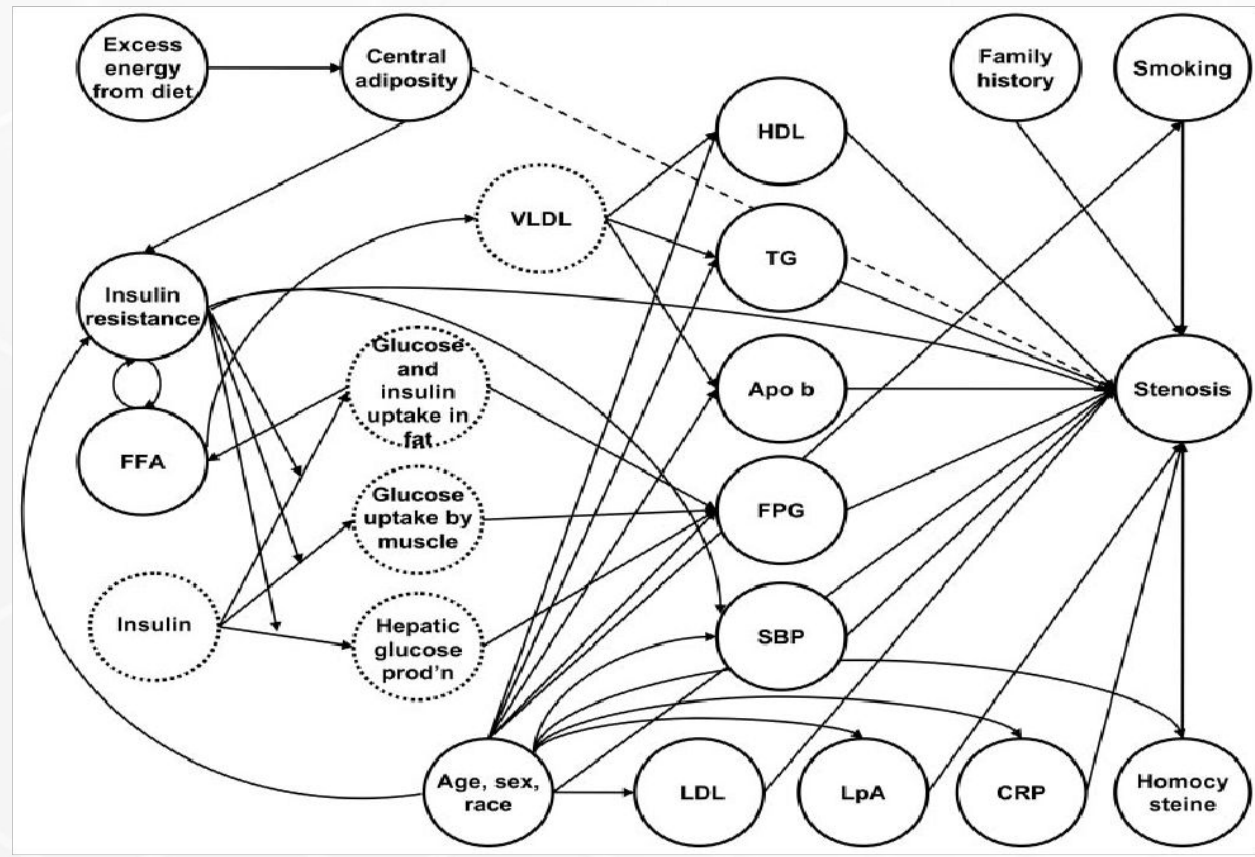


# Relationship of Insulin Resistance and Related Metabolic Variables to Coronary Artery Disease: A Mathematical Analysis

DAVID EDDY, MD, PHD<sup>1</sup>  
LEN SCHLESSINGER, PHD<sup>1</sup>  
RICHARD KAHN, PHD<sup>2</sup>

BARBARA PESKIN, PHD<sup>1</sup>  
RICK SCHIERINGER, MD<sup>3</sup>

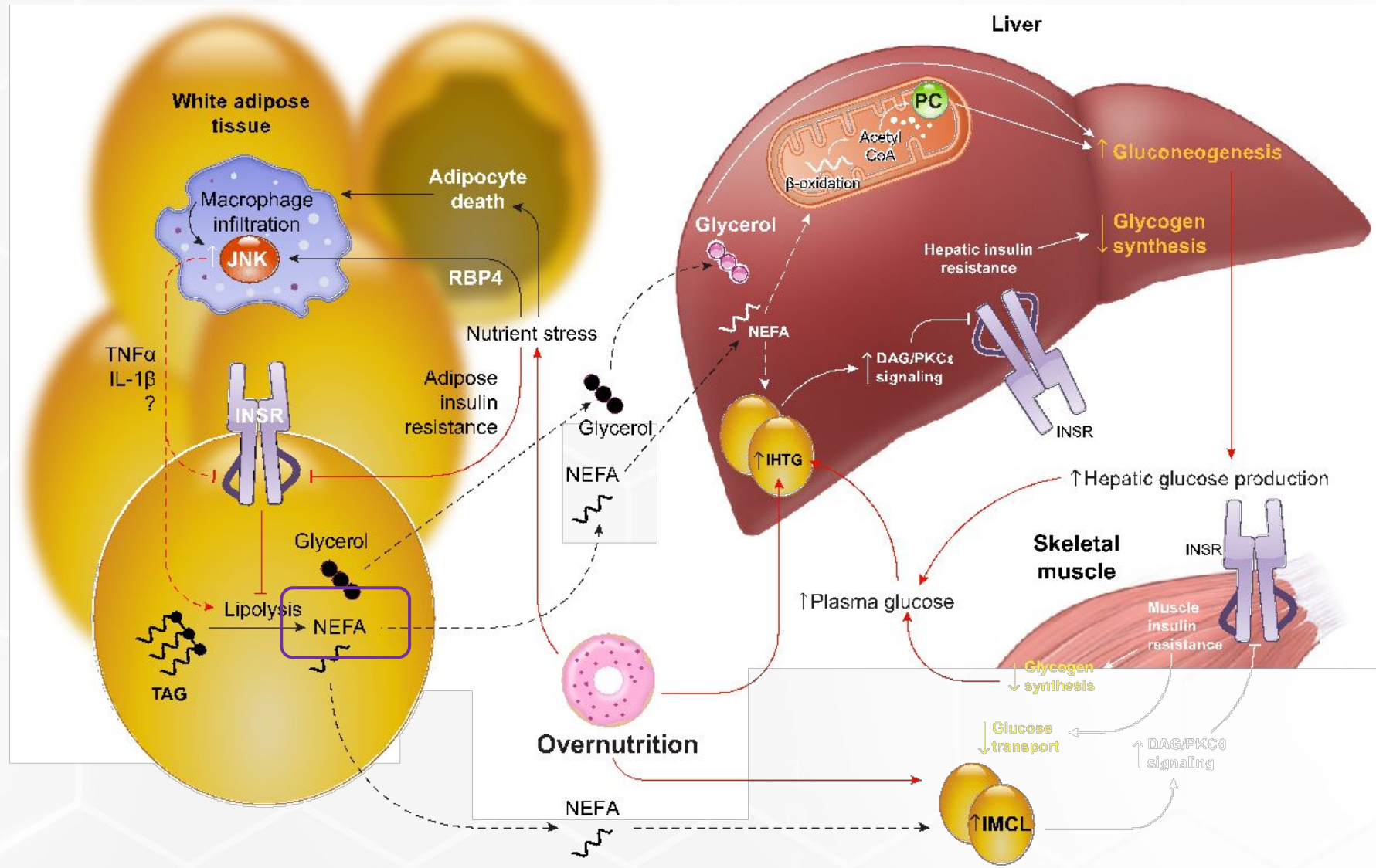
tion of CAD is caused by other risk factors such as LDL cholesterol, C-reactive protein, and blood pressure and by nonmetabolic risk factors such as age, sex, and

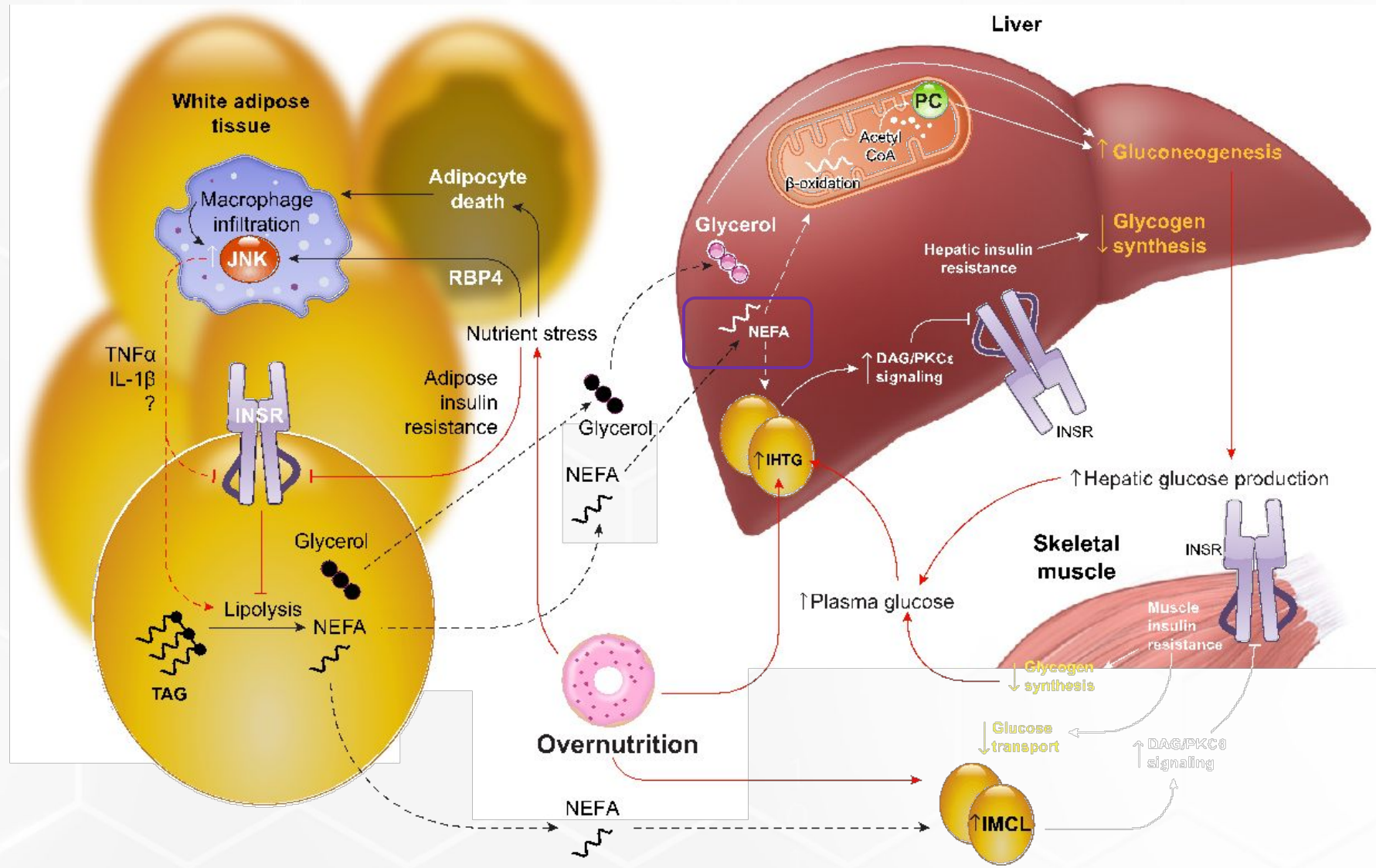


**Figure 1**—Variables and pathways in the Archimedes model pertinent to coronary artery disease. Variables in solid circles are calculated for this analysis. CRP, C-reactive protein; prod'n, production; TG, triglyceride.

**Table 1—Treatment targets for variables and percent decrease in incidence of MIs as a result of normalizing variable values to reach treatment targets**

	Target for normalization	Decrease in incidence of MIs (fatal and nonfatal)
Insulin resistance	Average value at ages 20–30 years	42
SBP (mmHg)	114	36
HDL cholesterol (mg/dl)	46 (men), 54 (women)	31
BMI (kg/m <sup>2</sup> )	22.5	21
LDL cholesterol (mg/dl)	108	16
Triglycerides (mg/dl)	108	10
FPG (mg/dl)	86	9
Smoking	Never smoke	9
Family history	No family history	4
Causality not established		
FFA (mg/dl)	20	18
C-reactive protein (mg/dl)	0.32	10
ApoB (mg/dl)	85	9
Lipoprotein(a) (mg/dl)	57 (blacks), 21.5 (nonblacks)	9
Homocysteine (μmol/l)	7.0	5
All variables	NA	94

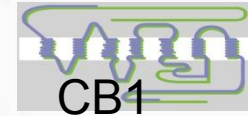








**Dieta  
Crasa**

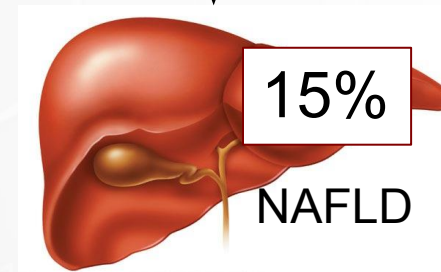
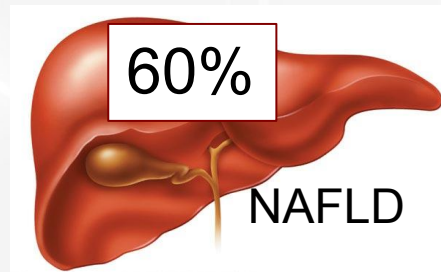


CB1



**SERBP**

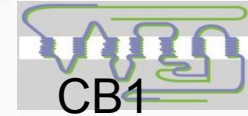
Sterol Regulatory Element  
Binding Proteins





Lipogenesis  
Hepática  
de Novo

Dieta  
Grasa

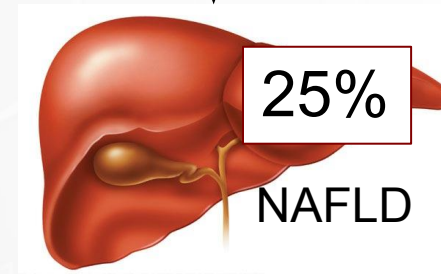
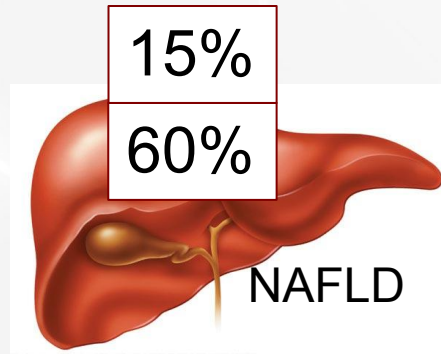


R. Insulina

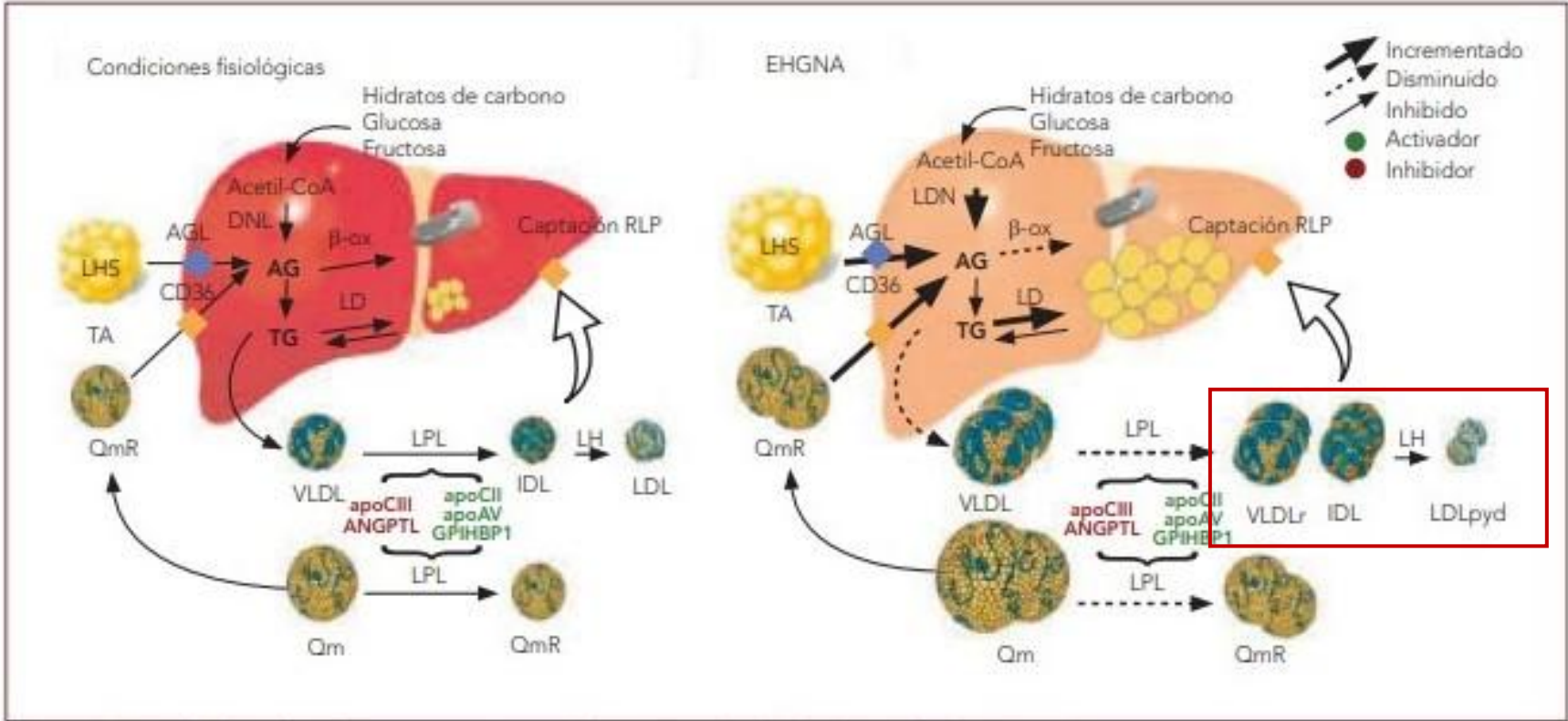


SERBP

Sterol Regulatory Element  
Binding Proteins



# Lipogénesis Hepática de Novo



## Management Algorithm for NAFLD – Overview

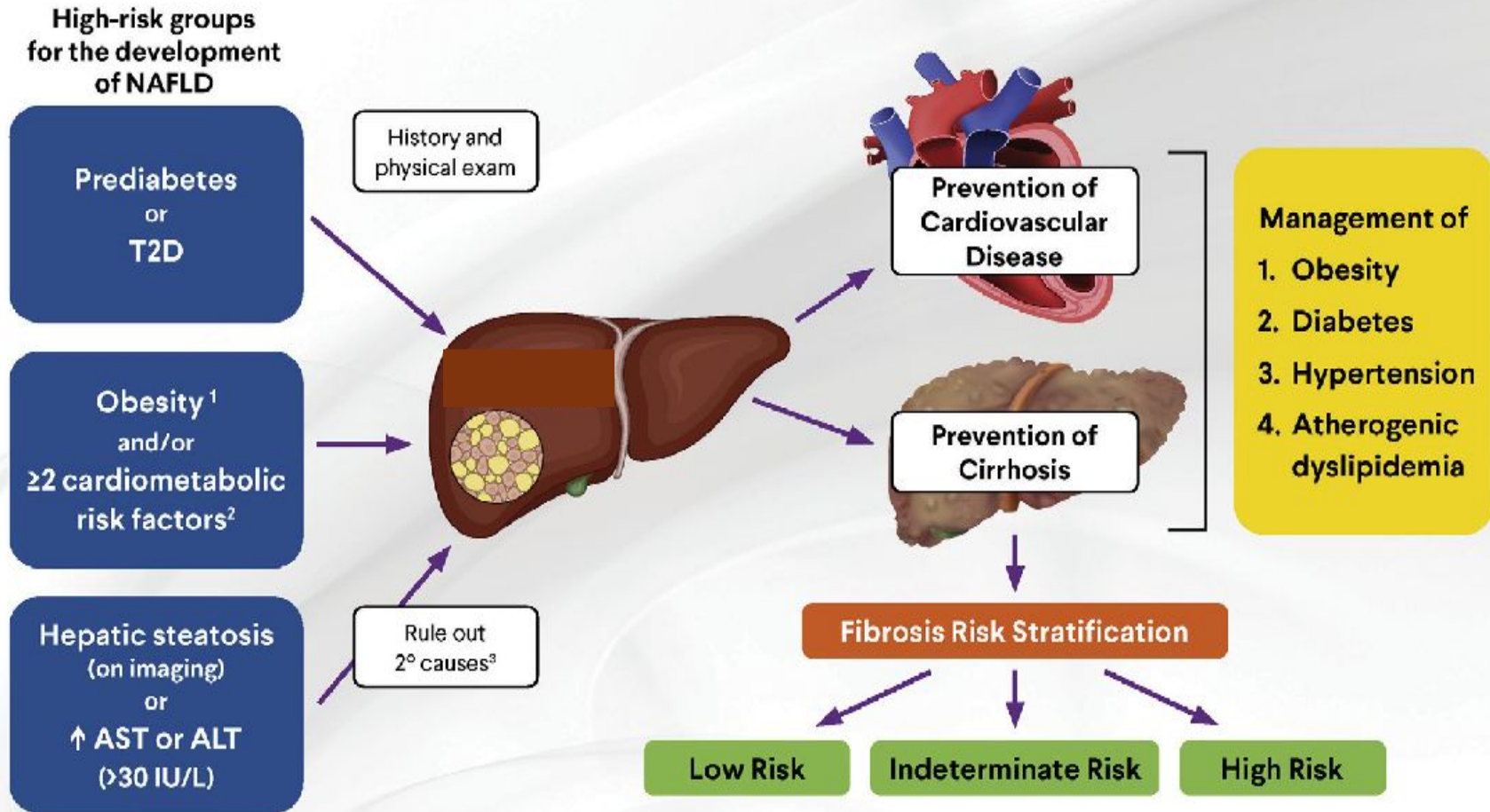
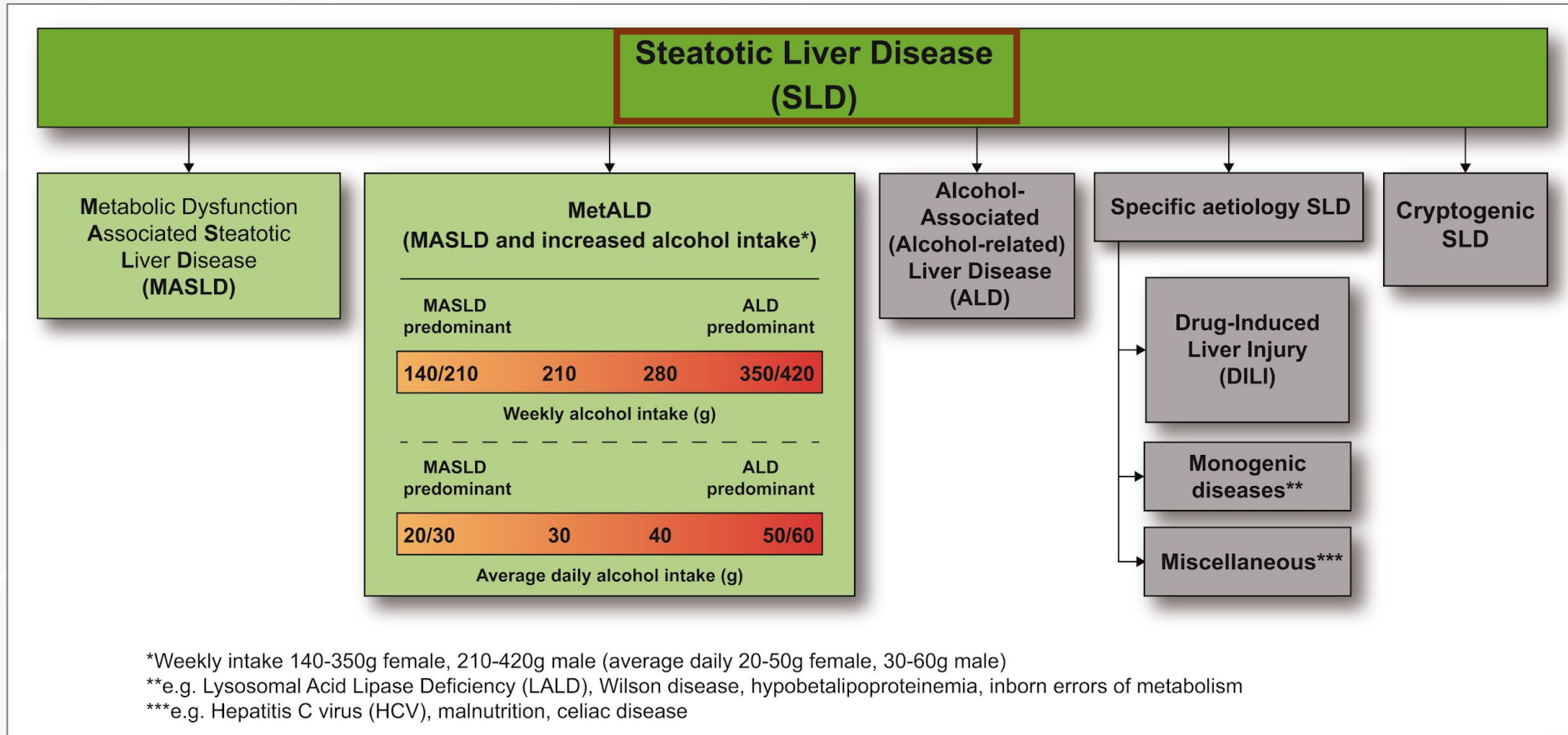


FIGURE 5

Esteatosis: "cambio graso"

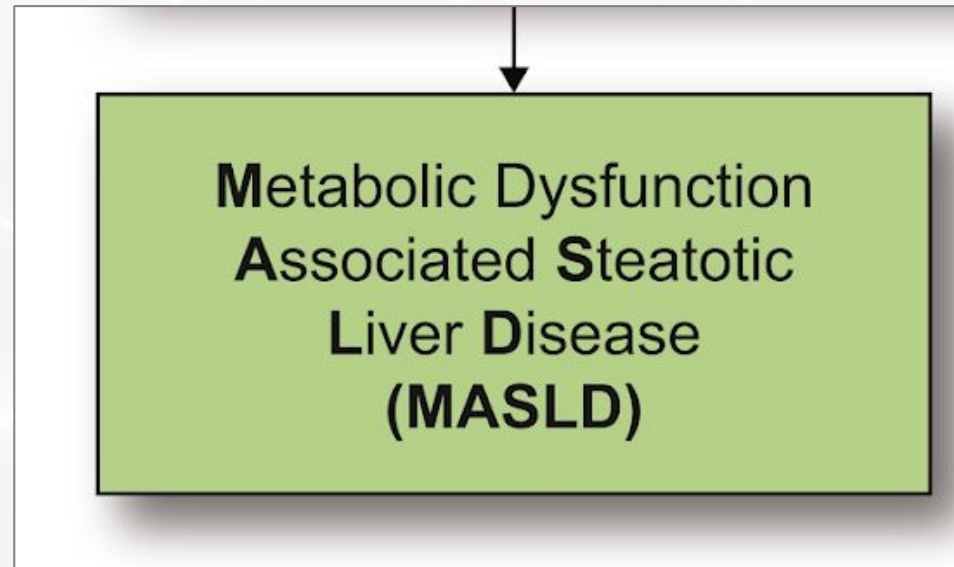


## FIGURE 5

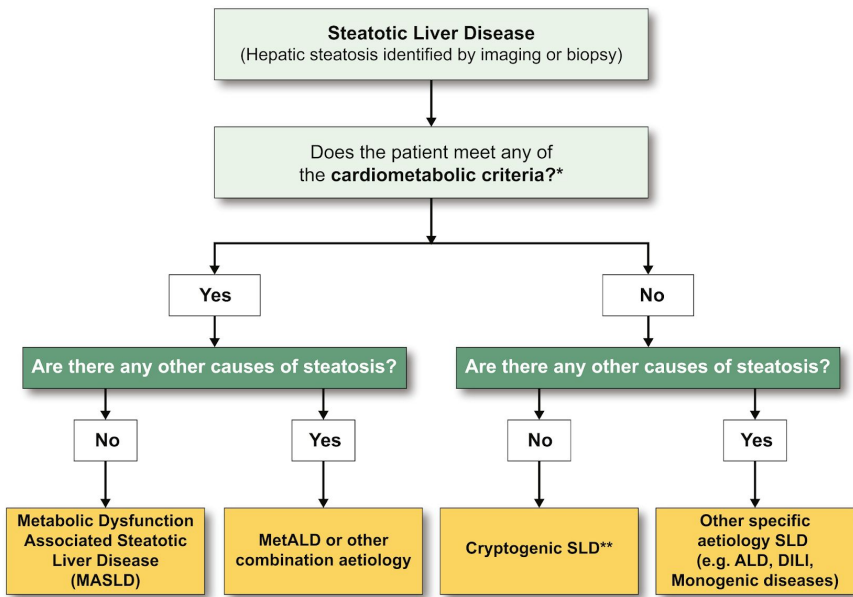
A multi-society Delphi consensus  
statement on new fatty liver disease  
nomenclature

Hepatology : June 24, 2023

doi: 10.1097/HEP.0000000000000520



Hepatology Publish Ahead of Print  
DOI:10.1097/HEP.0000000000000520



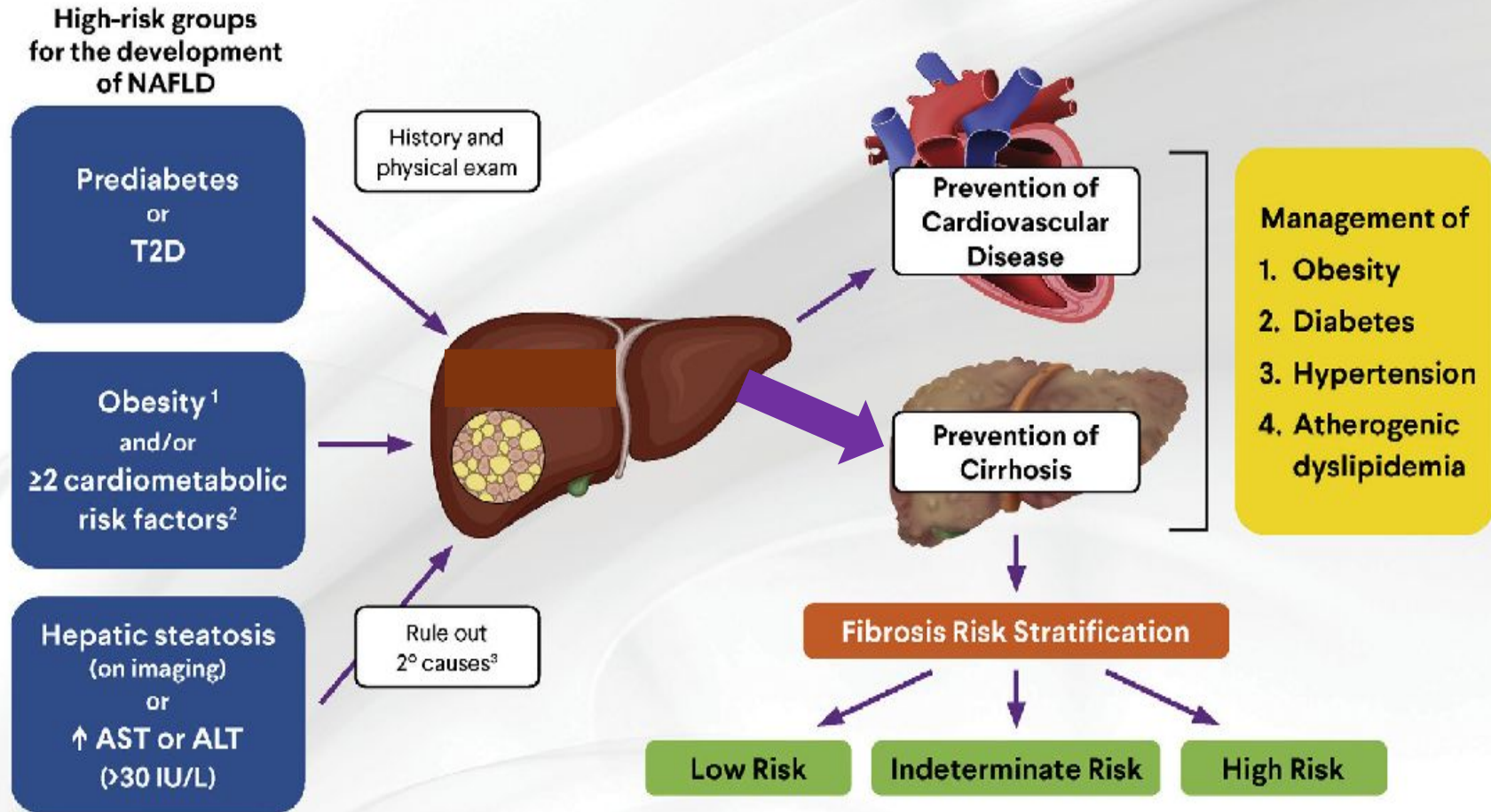
ALT > AST

\*Cardiometabolic criteria

Adult Criteria	Pediatric Criteria
<p>At least 1 out of 5:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> BMI <math>\geq 25 \text{ kg/m}^2</math> [23 Asia] OR WC <math>&gt; 94 \text{ cm}</math> (M) 80 cm (F) OR ethnicity adjusted</li> <li><input type="checkbox"/> Fasting serum glucose <math>\geq 5.6 \text{ mmol/L}</math> [100 mg/dL] OR 2-hour post-load glucose levels <math>\geq 7.8 \text{ mmol/L}</math> [<math>\geq 140 \text{ mg/dL}</math>] OR HbA1c <math>\geq 5.7\%</math> [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes</li> <li><input type="checkbox"/> Blood pressure <math>\geq 130/85 \text{ mmHg}</math> OR specific antihypertensive drug treatment</li> <li><input type="checkbox"/> Plasma triglycerides <math>\geq 1.70 \text{ mmol/L}</math> [150 mg/dL] OR lipid lowering treatment</li> <li><input type="checkbox"/> Plasma HDL-cholesterol <math>\leq 1.0 \text{ mmol/L}</math> [40 mg/dL] (M) and <math>\leq 1.3 \text{ mmol/L}</math> [50 mg/dL] (F) OR lipid lowering treatment</li> </ul>	<p>At least 1 out of 5:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> BMI <math>\geq 85^{\text{th}}</math> percentile for age/sex [BMI z score <math>\geq +1</math>] OR WC <math>&gt; 95^{\text{th}}</math> percentile OR ethnicity adjusted</li> <li><input type="checkbox"/> Fasting serum glucose <math>\geq 5.6 \text{ mmol/L}</math> [<math>\geq 100 \text{ mg/dL}</math>] OR serum glucose <math>\geq 11.1 \text{ mmol/L}</math> [<math>\geq 200 \text{ mg/dL}</math>] OR 2-hour post-load glucose levels <math>\geq 7.8 \text{ mmol/L}</math> [140 mg/dL] OR HbA1c <math>\geq 5.7\%</math> [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes</li> <li><input type="checkbox"/> Blood pressure age <math>&lt; 13\text{y}</math>, BP <math>\geq 95^{\text{th}}</math> percentile OR <math>\geq 130/80 \text{ mmHg}</math> (whichever is lower); age <math>\geq 13\text{y}</math>, 130/85 mmHg OR specific antihypertensive drug treatment</li> <li><input type="checkbox"/> Plasma triglycerides <math>&lt; 10\text{y}</math>, <math>\geq 1.15 \text{ mmol/L}</math> [<math>\geq 100 \text{ mg/dL}</math>]; age <math>\geq 10\text{y}</math>, <math>\geq 1.70 \text{ mmol/L}</math> [<math>\geq 150 \text{ mg/dL}</math>] OR lipid lowering treatment</li> <li><input type="checkbox"/> Plasma HDL-cholesterol <math>\leq 1.0 \text{ mmol/L}</math> [<math>\leq 40 \text{ mg/dL}</math>] OR lipid lowering treatment</li> </ul>

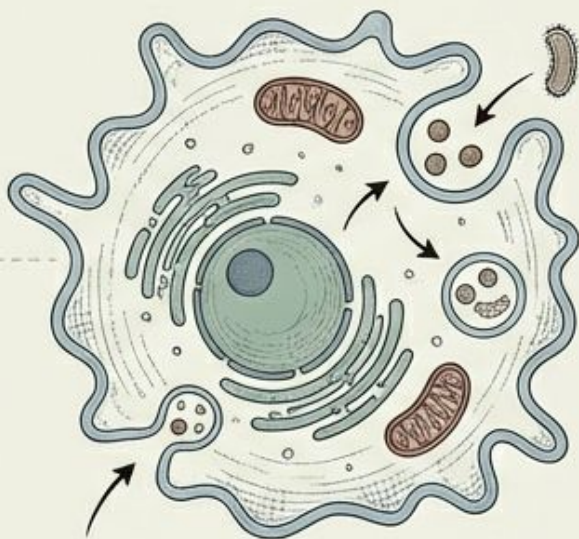
Hepatology Publish Ahead of Print  
DOI:10.1097/HEP.0000000000000520

## Management Algorithm for NAFLD – Overview



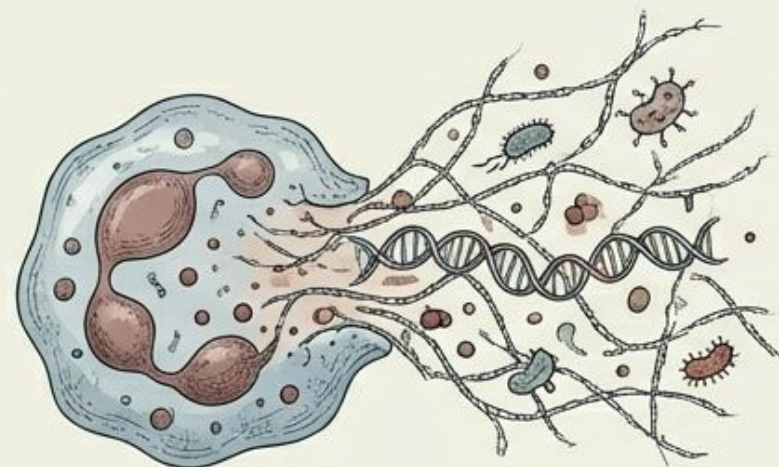
# Inmunidad Innata: La Primera Línea de Defensa

## Macrófagos / Kupffer



- **Origen:** Residentes (Embrionarias) vs. Reclutadas (Monocitos).
- **Acción:** Fagocitosis y liberación de TNF- $\alpha$ .
- **Polarización:** M1 (Pro-inflamatorio) vs M2 (Reparador).

## Neutrófilos

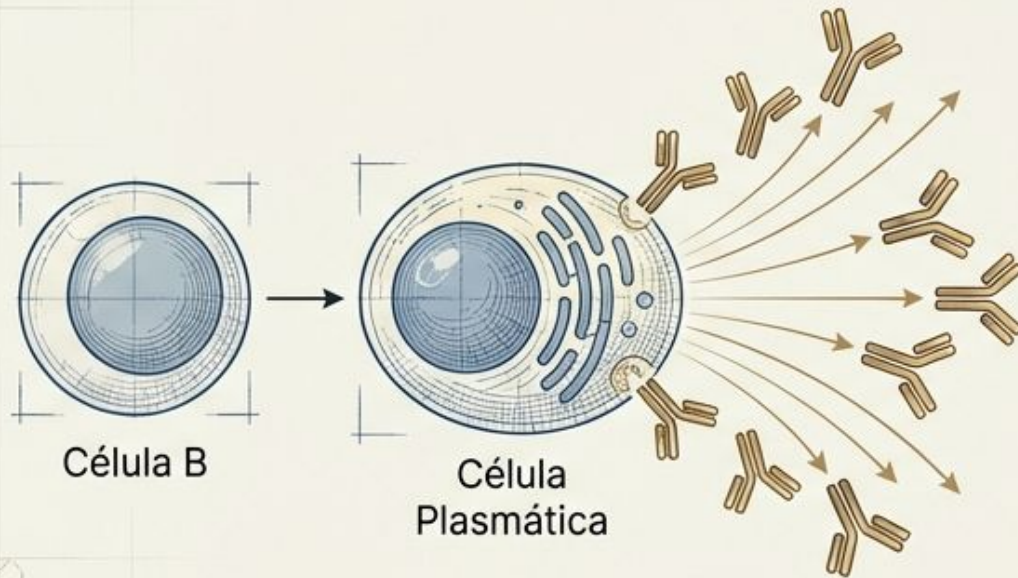


**NETs**  
(Trampas Extracelulares)

- **Mecanismo:** NETs (Trampas Extracelulares).
- **Efecto:** Redes de ADN/Histonas.
- **Daño:** Atrapan patógenos pero causan lesión tisular y trombosis.

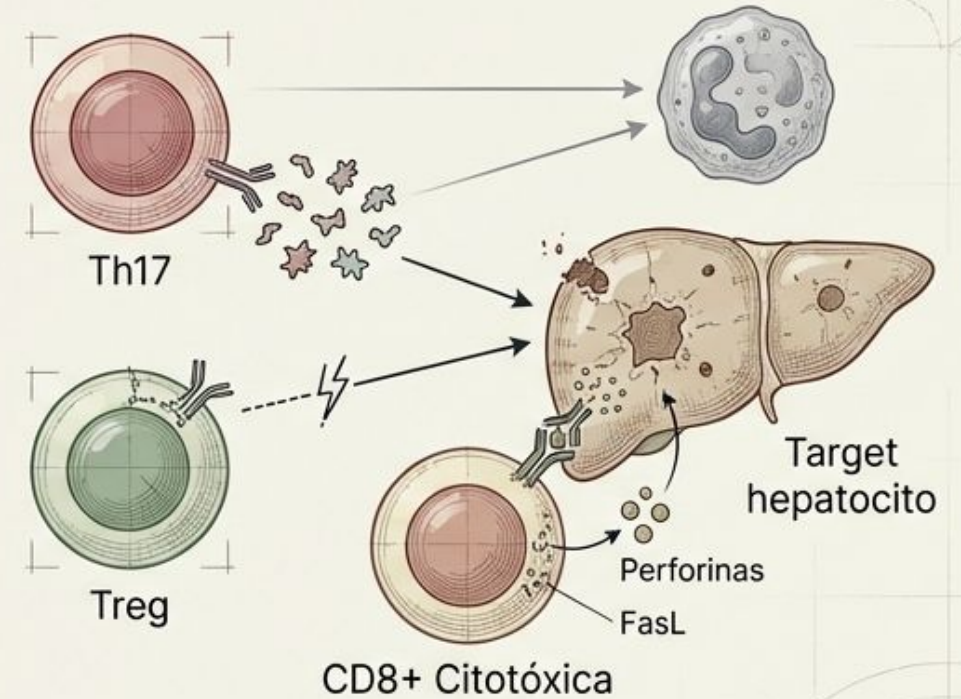
# Inmunidad Adaptativa: Respuesta Específica y Daño Crónico

## Células B y Plasmáticas

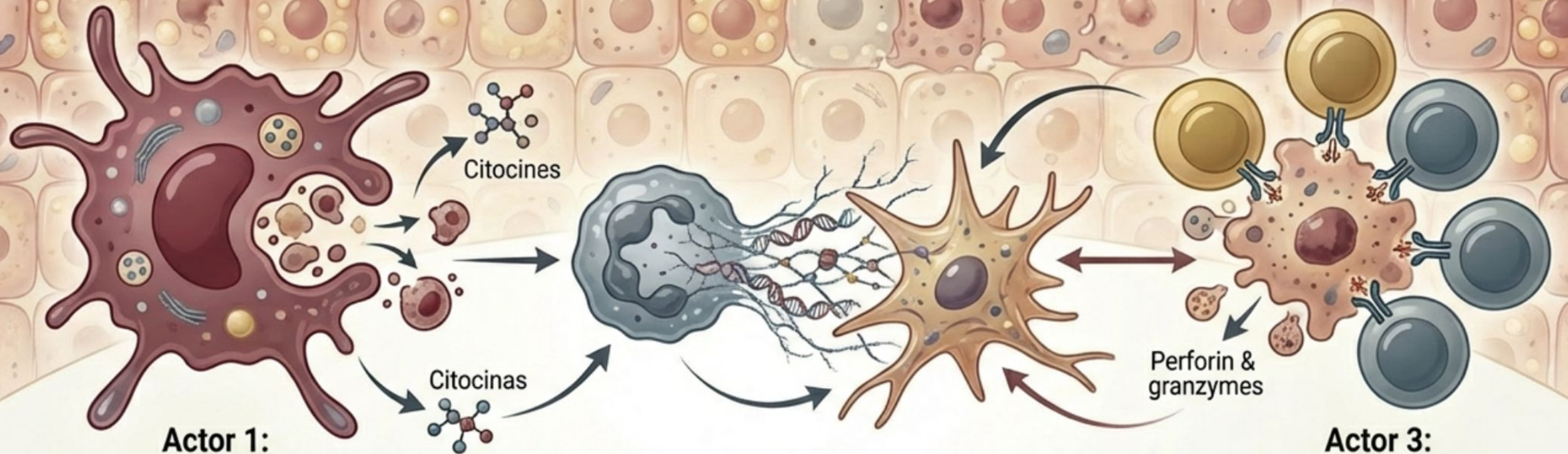


- Aumento de IgA secretora
- Producción de Autoanticuerpos
- Activación de Fibroblastos

## Células T (Desequilibrio)



- **Th17:** Pro-inflamatorio (Recruta neutrófilos)
- **Treg:** Pérdida de tolerancia (Disfuncionales)
- **CD8+ Citotóxicos:** Asesinos de hepatocitos (Perforinas/FasL)



**Actor 1:  
Macrófagos  
(Células de Kupffer)**

Fenotipo TREM2+S100A9+.  
Detectan estrés y liberan  
IL-17A y TNF.

**Actor 2  
Neutrófilos y NETs**

Trampas Extracelulares de  
Neutrófilos (NETs). Inducen la  
activación de células estrelladas.

**Actor 3:  
Linfocitos T  
(Inmunidad Adaptativa)**

Infiltración de CD8+ y Th17.  
Correlación directa entre cantidad  
de CD8+ y grado de daño hepático.

**Consecuencia:** Cascada de citocinas (TNF, TGF- $\beta$ , IL-1 $\beta$ ) que perpetúa la inflamación crónica.

The NEW ENGLAND JOURNAL of MEDICINE

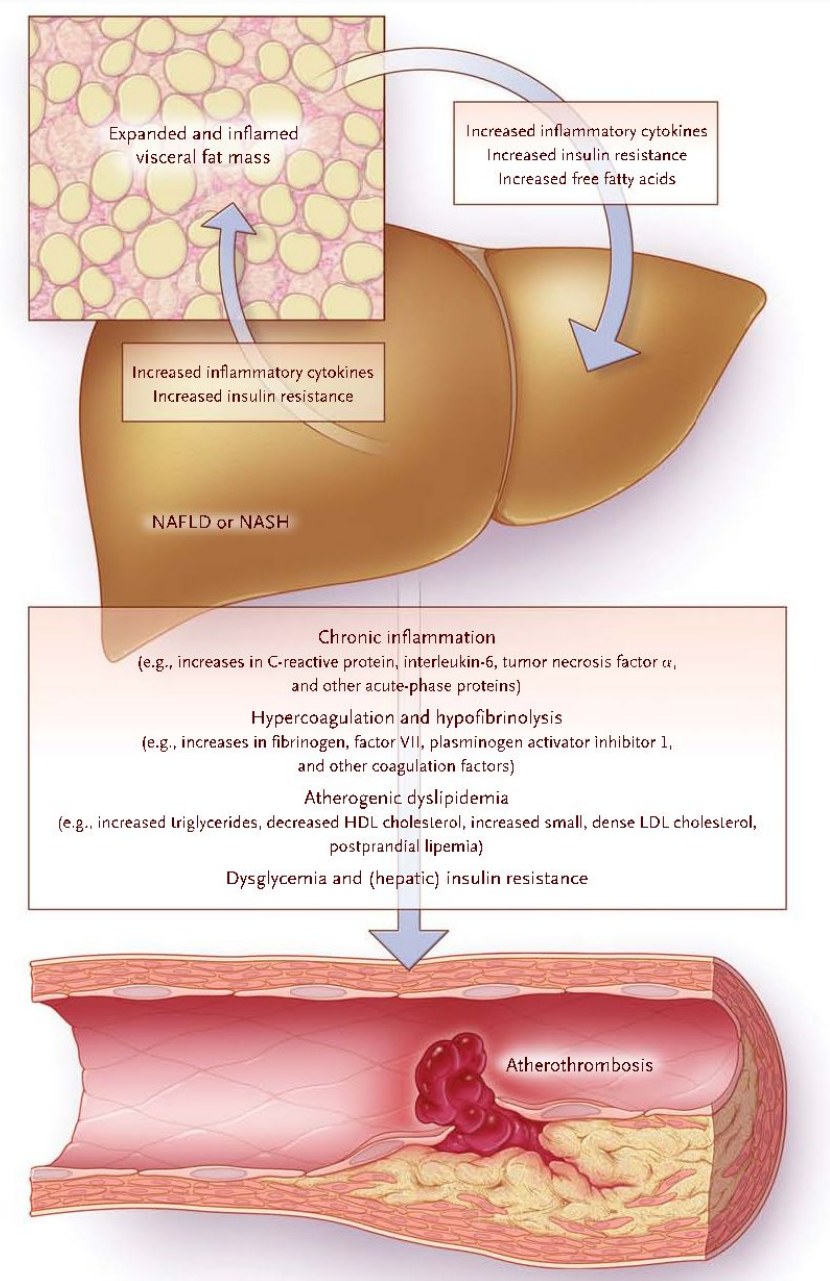
REVIEW ARTICLE

CURRENT CONCEPTS

# Risk of Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease

Giovanni Targher, M.D., Christopher P. Day, M.D., Ph.D.,  
and Enzo Bonora, M.D., Ph.D.

N Engl J Med 2010;363:1341-50.



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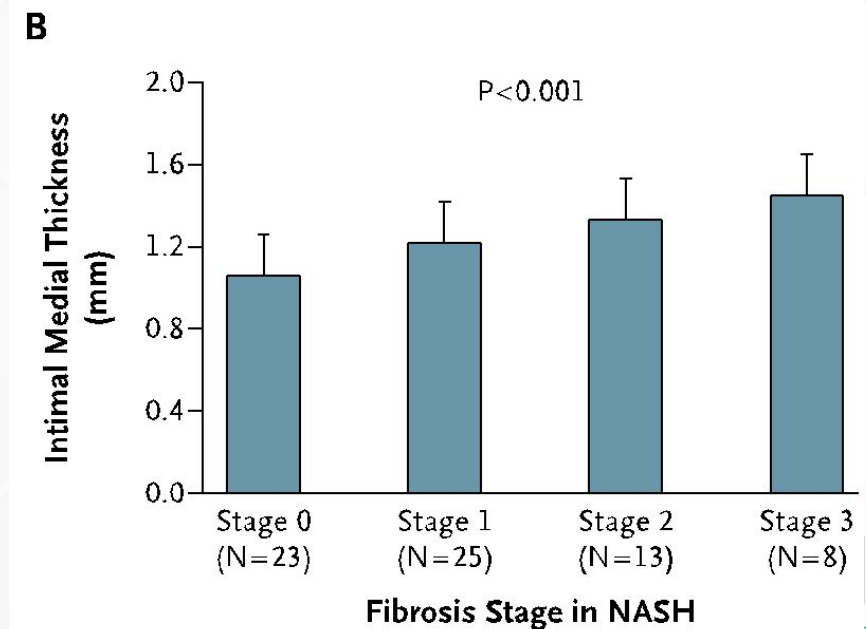
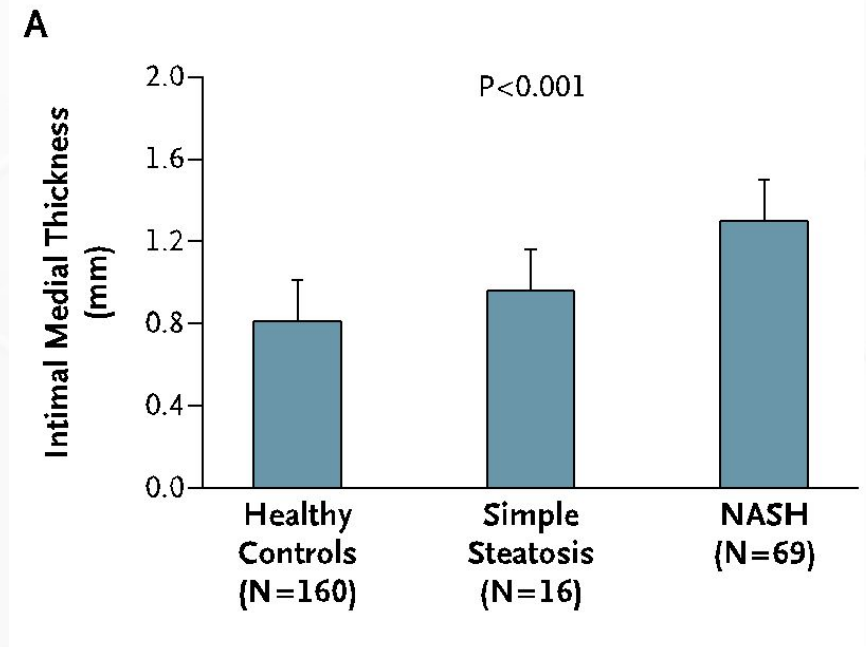
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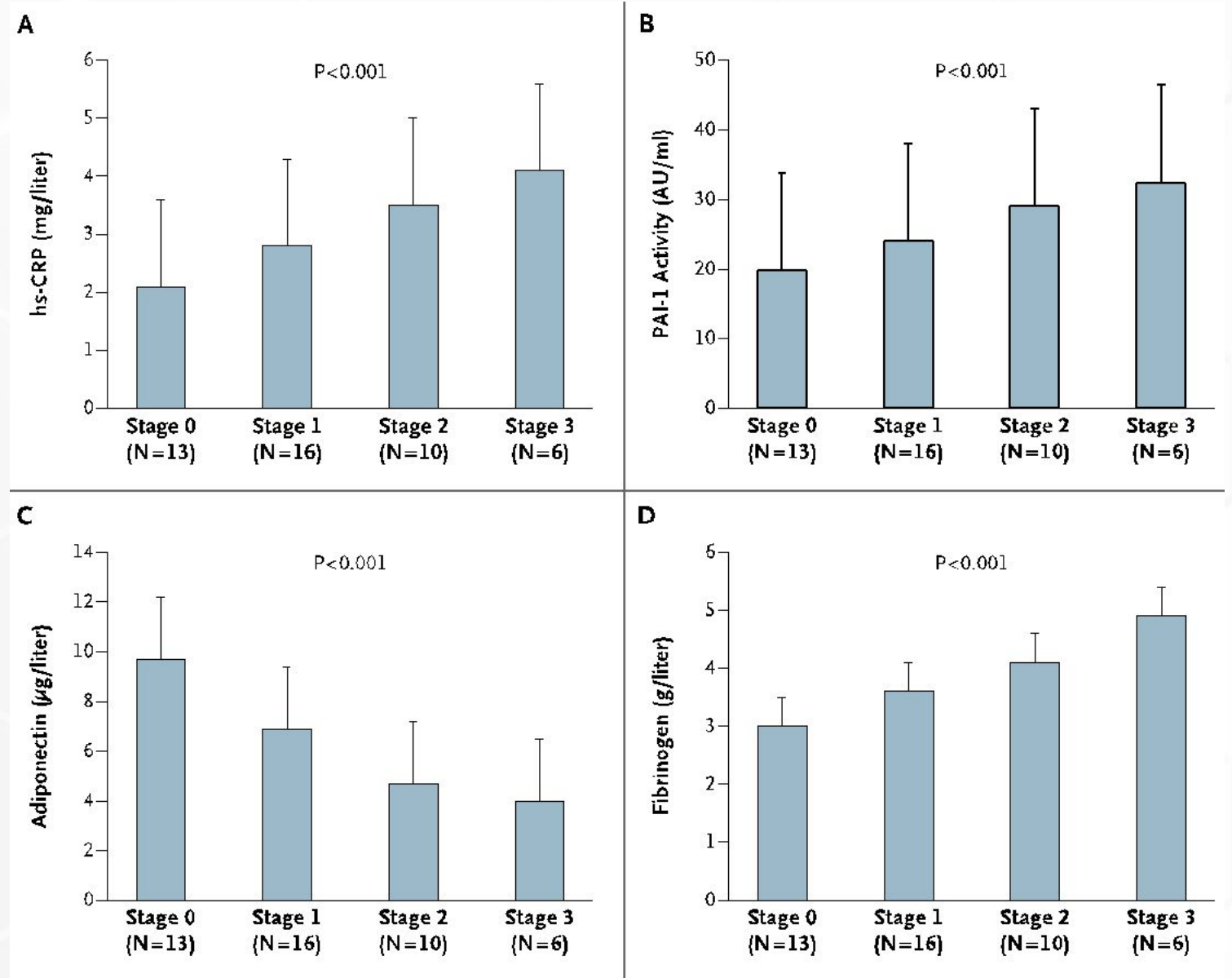
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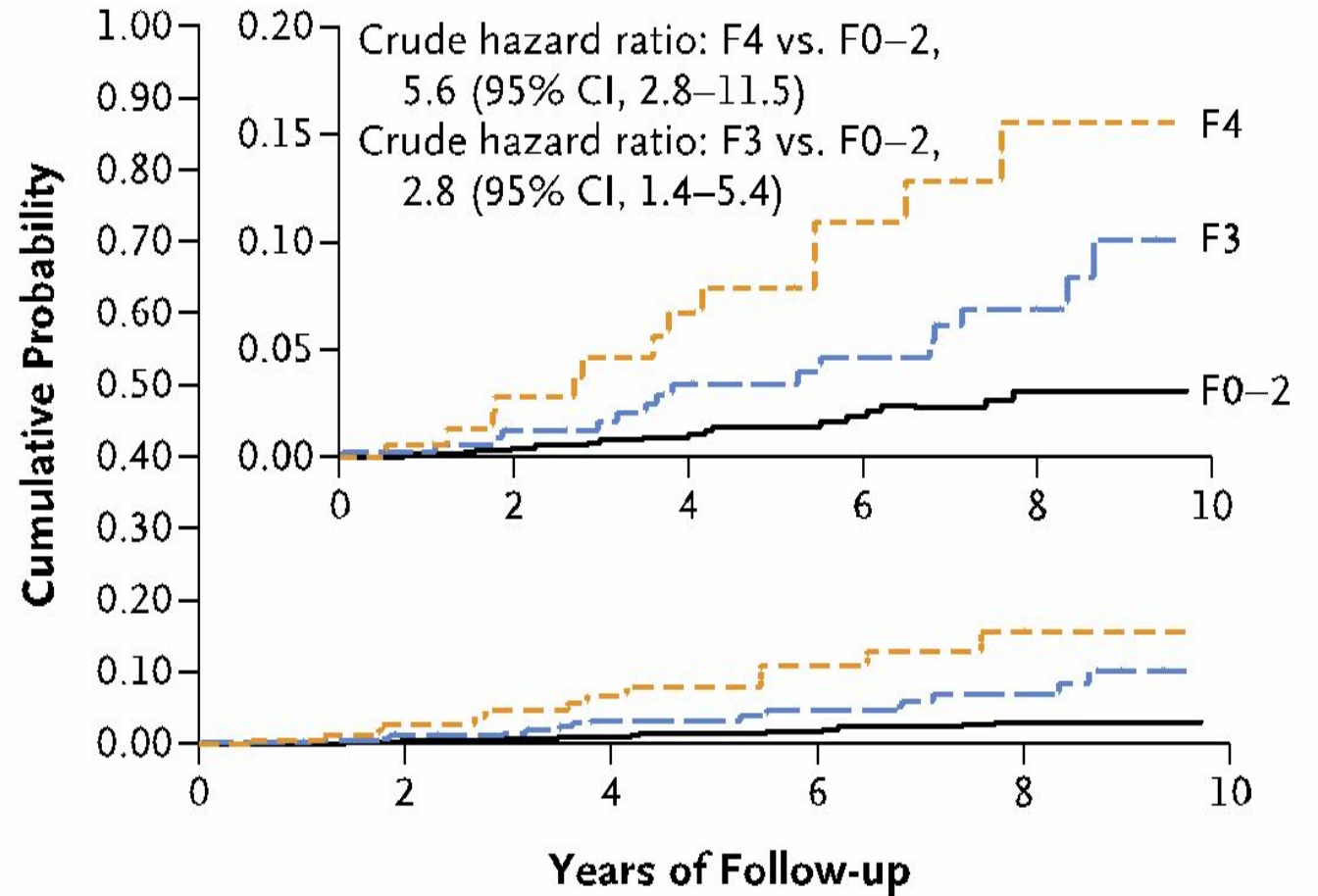
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prospective Study of Outcomes in Adults  
with Nonalcoholic Fatty Liver Disease

N Engl J Med 2021;385:1559-69

### A Death from Any Cause



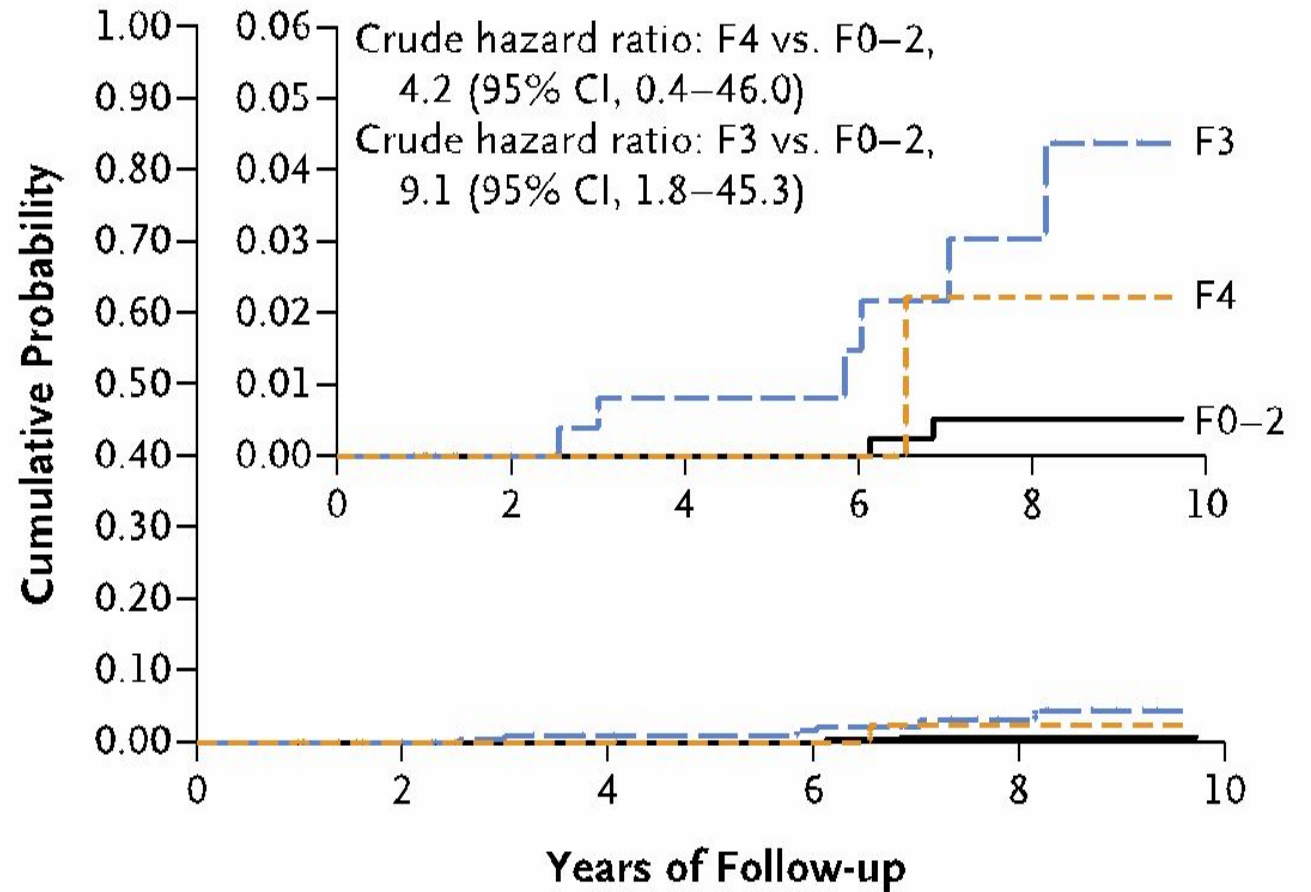
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ORIGINAL ARTICLE

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### C Hepatocellular Carcinoma



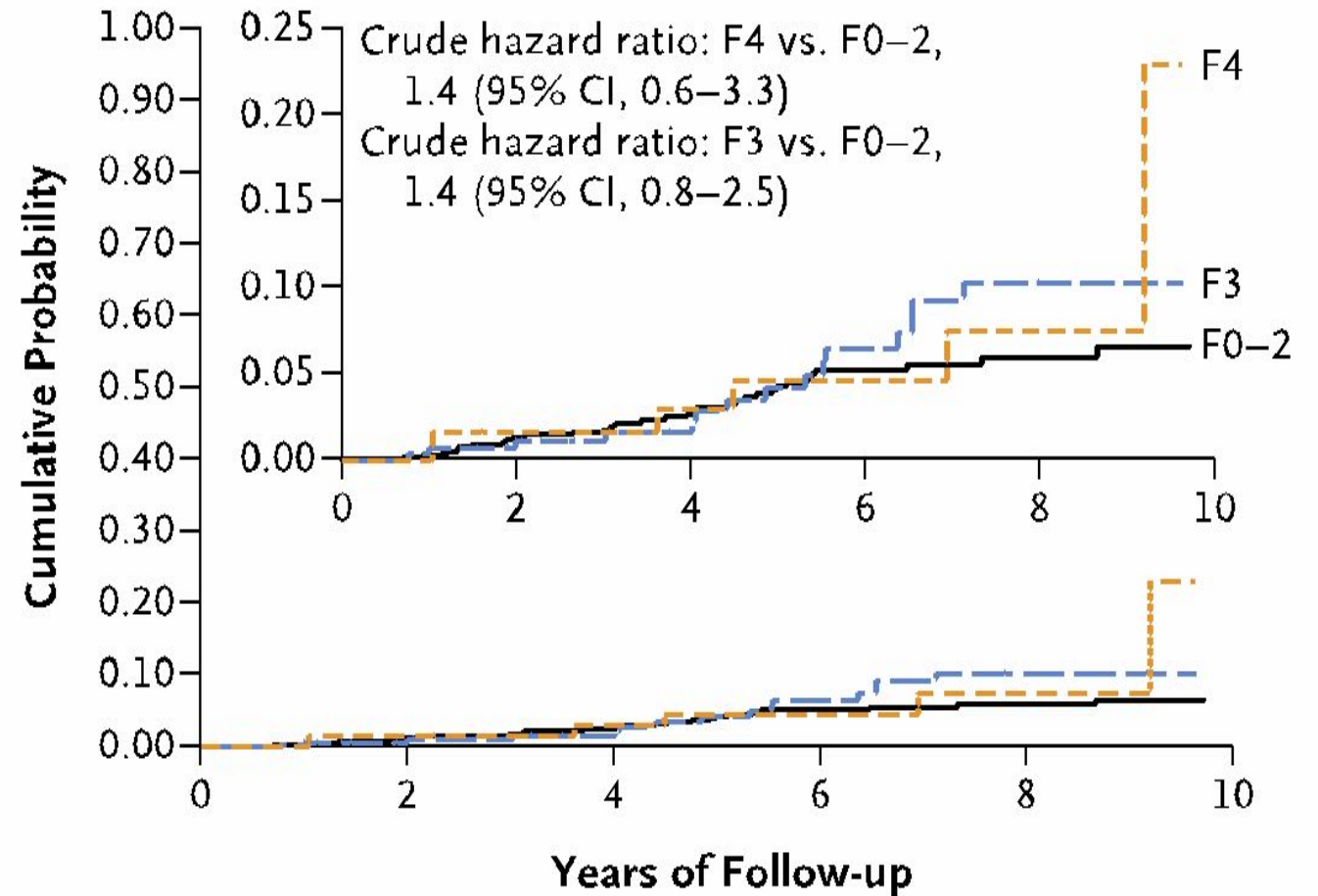
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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## D Extrahepatic Cancer

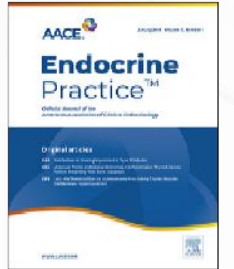


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## Endocrine Practice

journal homepage: [www.endocrinepractice.org](http://www.endocrinepractice.org)

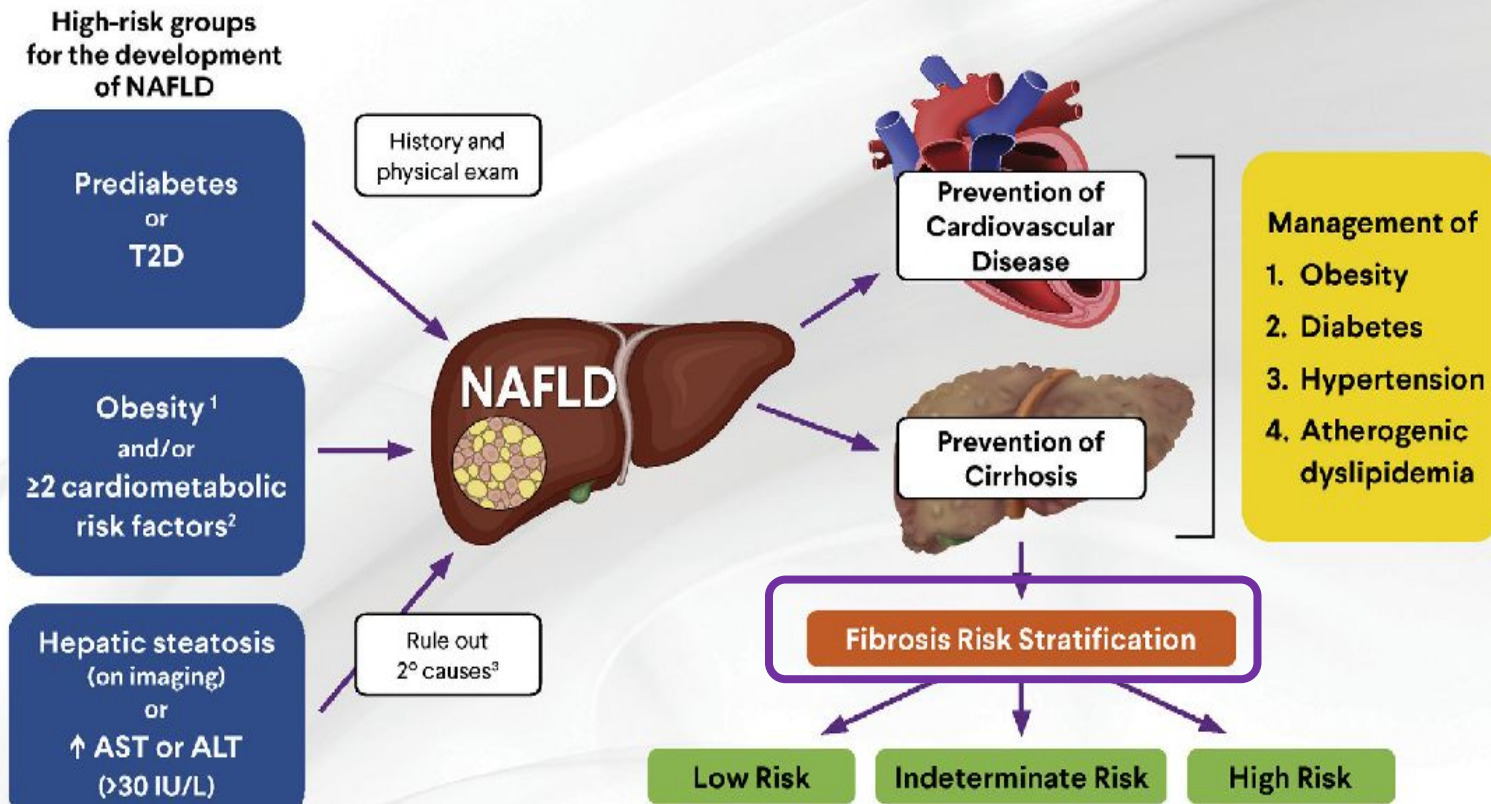


Clinical Practice Guidelines

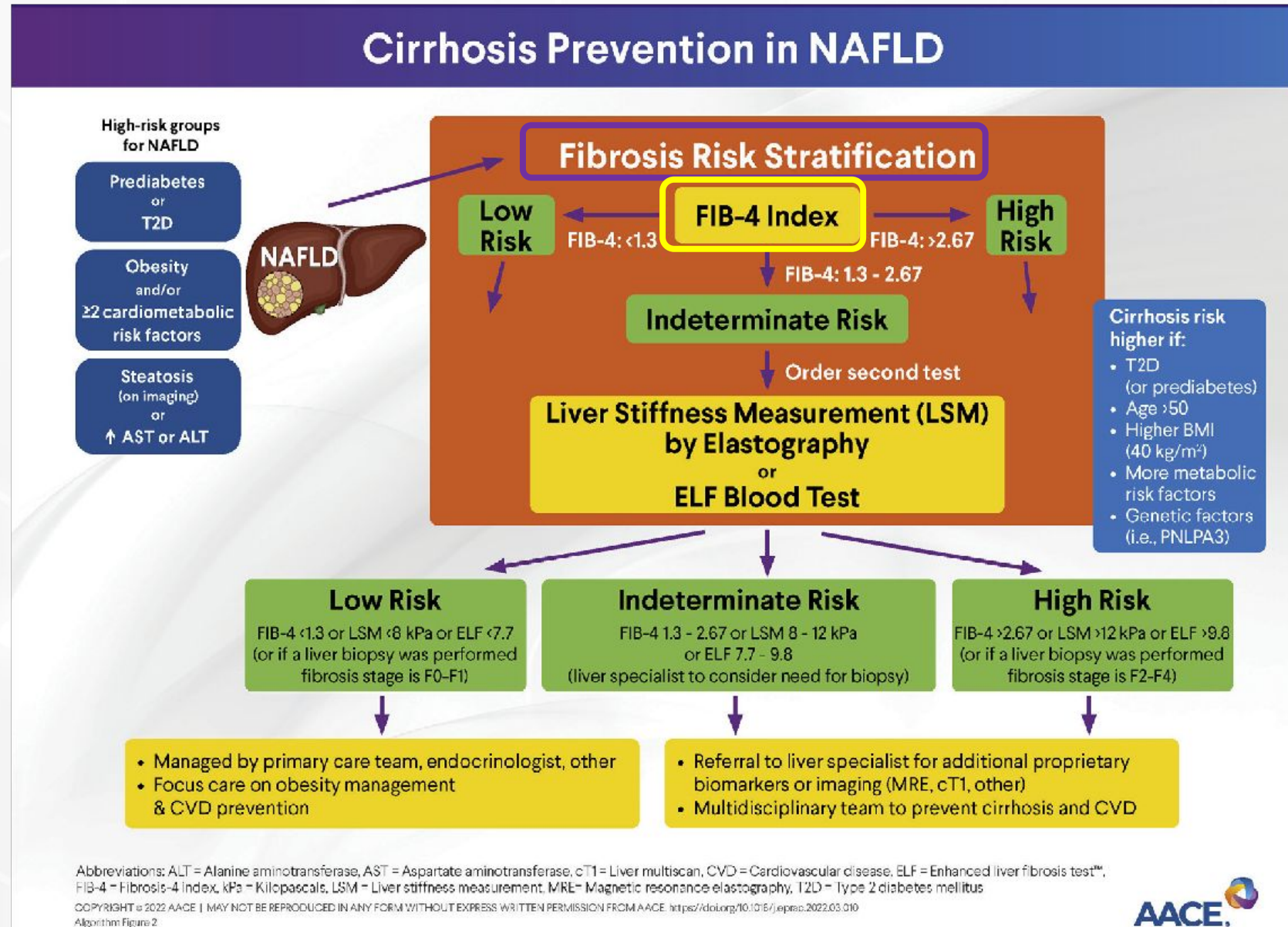
**American Association of Clinical Endocrinology Clinical Practice  
Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver  
Disease in Primary Care and Endocrinology Clinical Settings**  
Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)



## Management Algorithm for NAFLD – Overview



# Cirrhosis Prevention in NAFLD



**[1.3 -  
2.67]**  
F4

- El uso de FIB-4 con un umbral inferior de  $< 1,3$  (para descartar fibrosis avanzada) y un umbral superior de  $\geq 2,67$  (para descartar fibrosis avanzada) proporciona:
- sensibilidad del **82 %**
- especificidad del **93 %** para discriminar la fibrosis avanzada.

TIGO 14:45 50 %

### Kalkulator fibroze 4 (FIB-4)

Starost Starost pacijenta	<input type="text" value="godine"/>	Edad
Vrijednost AST Aspartat aminotferaza	<input type="text" value="U/l"/>	
Vrijednost ALT Alanin aminotferaza	<input type="text" value="U/l"/>	
Broj trombocita PLT x 10 <sup>9</sup> /l	<input type="text" value="x10&lt;sup&gt;9&lt;/sup&gt;/l"/>	Plaquetas

Izračunati

Aplikacija je kreirana uz podršku  
**PRO.MED.CS**  
Praha a.s.  
Predstavništvo Sarajevo

BA/URS/23/01/23

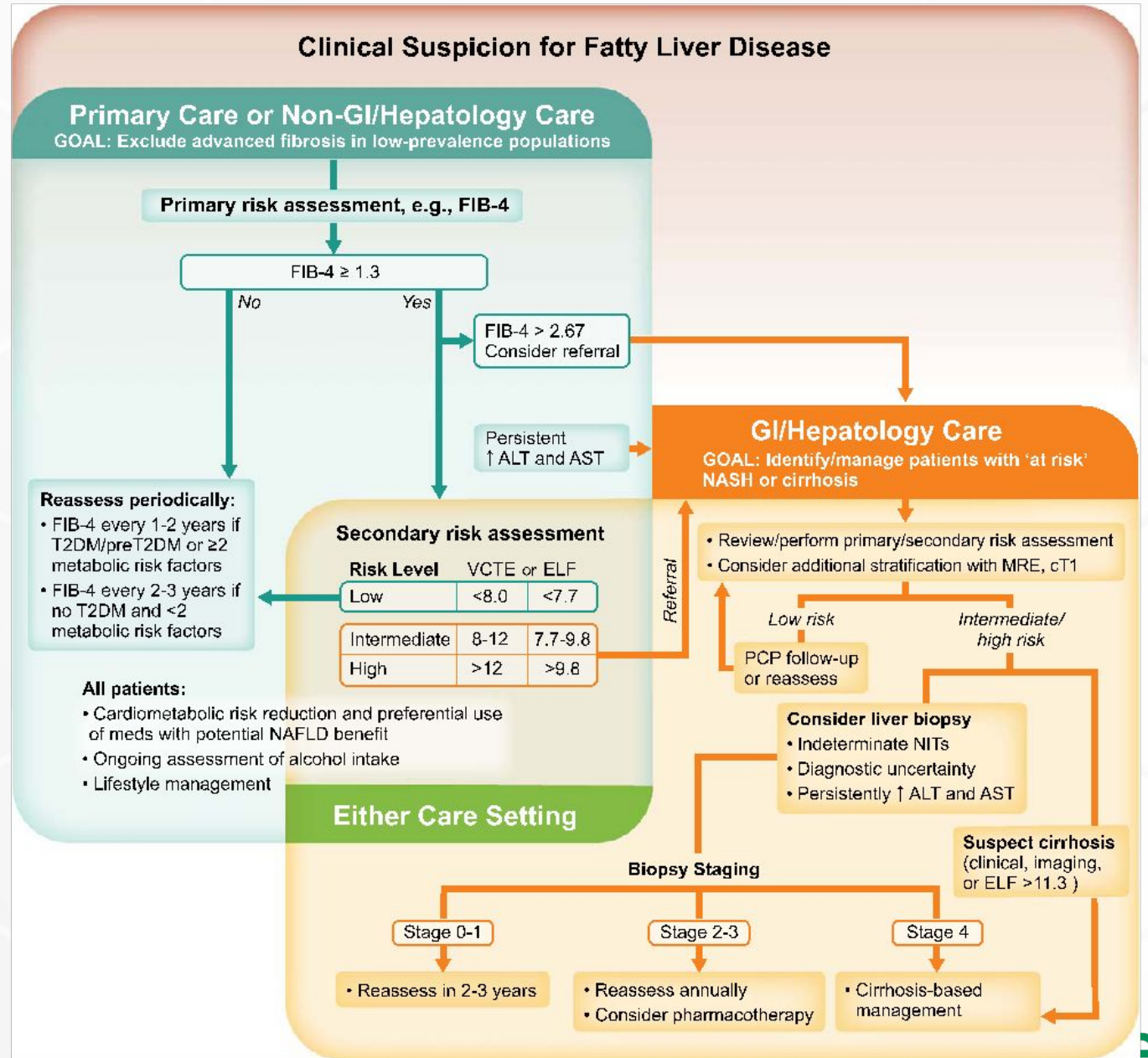


## FIB-4 Score<sup>[c]</sup>

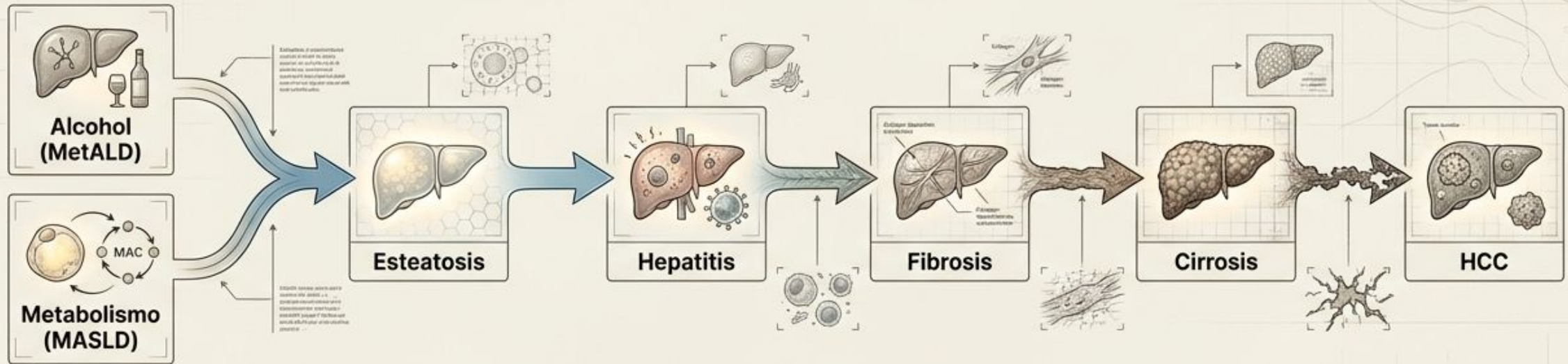
$$\frac{\text{Age (years)} \times \text{AST level (U/L)}}{\text{Platelet count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = \boxed{\phantom{000}}$$

PRACTICE GUIDANCE

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease






# El Espectro de la Enfermedad: Convergencia Patológica



# Conclusiones y Perspectivas Futuras

## Key Takeaways

-  **Complejidad Sistémica:** SLD es una patología inmune multisistémica, no solo metabólica.
-  **Interconexión:** El triángulo Intestino-Adiposo-Hígado es inseparable.
-  **El Futuro:** Terapias Combinadas (Antioxidante + Modulador) y Medicina de Precisión basada en el perfil inmune.

**El objetivo: No solo suprimir la inflamación, sino restaurar la homeostasis.**

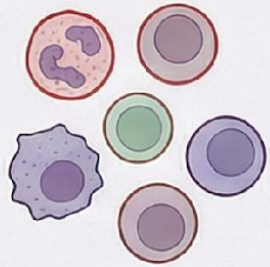
# Hepar compositum (HC-24): Un enfoque multicomponente contra la inflamación y fibrosis hepática

El estudio investiga el potencial de Hepar compositum (HC-24) en un modelo agresivo de MASLD/MASH, demostrando que actúa directamente sobre la inflamación y la formación de cicatrices (fibrosis) de manera independiente a la acumulación de grasa.

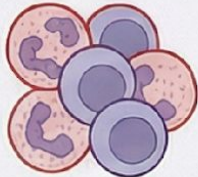
## Control de Enfermedad (Modelo Agresivo)

### Inflamación Hepática

Puntaje de actividad NAFLD (NAS)  
Mediana: 5.0



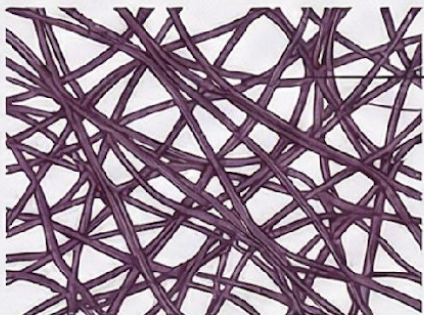
Neutrófilos (GR-1+) y  
Células T colaboradoras (CD4+)



y Células T colaboradoras (CD4+)  
Células T (CD4+): 9.5

### Fibrosis y Cicatrización

Área Fibrótica Total (Sirius Red %): 1.2%



Depósito de Colágeno Tipo I y III

## Efecto con HC-24 (Tratamiento Recuperador)

### Reducción de la Inflamación Hepática



**Disminución de infiltrados inmunes clave:** Reduce significativamente la presencia de neutrófilos (GR-1+) y células T colaboradoras (CD4+) en el hígado.



**Mejora del puntaje de actividad NAFLD (NAS):** El tratamiento con HC-24 redujo la puntuación NAS de un nivel medio de 5.0 a 3.0. (NAS Mediana: 3.0)



**Acción independiente del colesterol:** Su efecto antiinflamatorio funciona incluso sin alterar los niveles de colesterol libre intrahepático.  
Células T (CD4+): 2.9

### Acción Antifibrótica y Reparadora



**Reducción del área fibrótica total:** Disminución significativa del área positiva teñida con Sirius Red en el tejido hepático. (Fibrosis Sirius Red %: 0.8%)



**Inhibición de colágenos específicos:** Reduce cualitativamente el depósito sinusoidal de colágeno tipo I y tipo III.



**Protección sin pérdida de peso:** Los efectos antifibróticos ocurren sin afectar el peso corporal o los niveles de glucosa.

# Gracias



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