

# ***Age-dependent comorbidity profiles and genetic disorders in real world MASLD cohorts***

***Sept 8 2025***

***Paris, France***

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**Karolinska  
Institutet**

# Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease

## *Histology:*

- Steatosis
- Mallory Bodies
- Necrosis
- Inflammation
- Fibrosis

*Obesity*

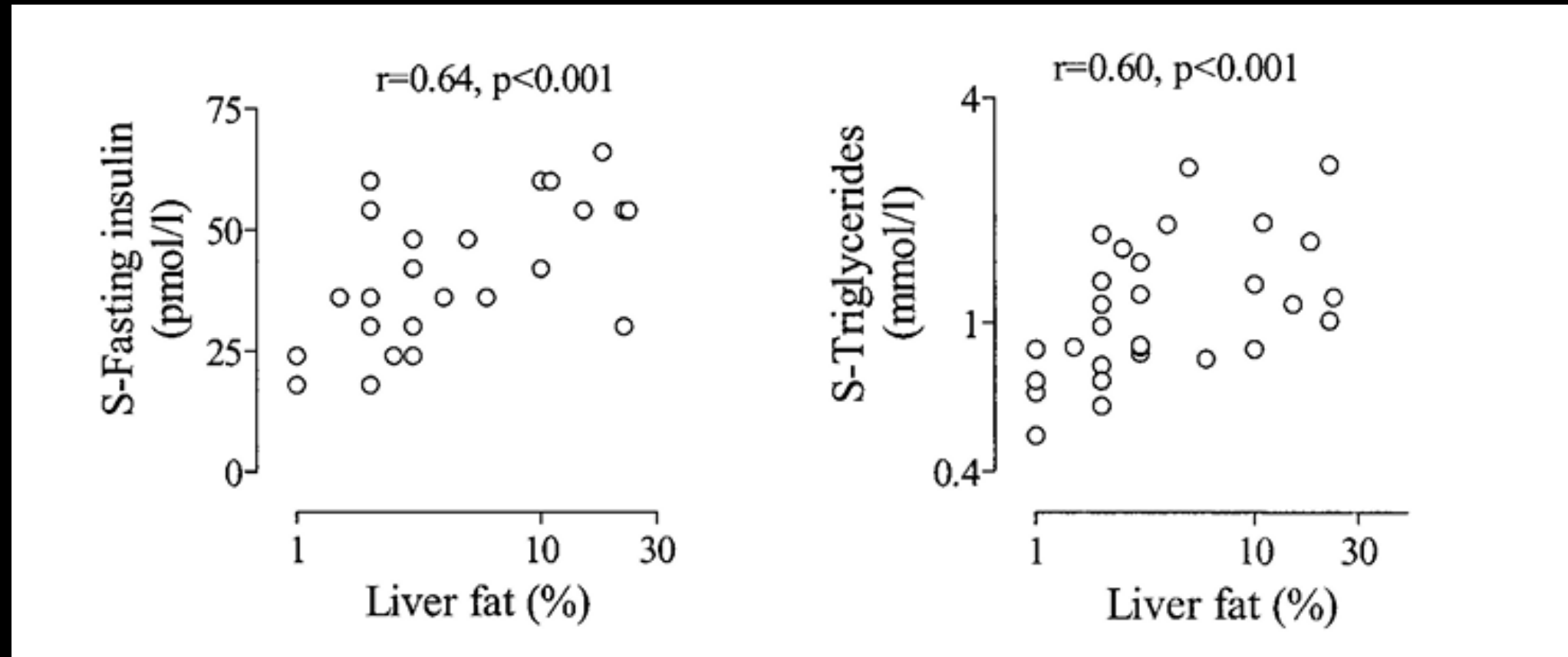
*Women*

*ALT*

**Diabetes**

*dyslipidemia*

# Hepatic triglyceride content directly correlates with fasting insulin and serum triglyceride in normoglycemic men



# MASLD is an independent risk factor for diabetes

	All participants ( <i>n</i> = 3,074)				Men ( <i>n</i> = 1,866)		Women ( <i>n</i> = 1,208)	
	Crude		Multivariate adjusted		Multivariate adjusted		Multivariate adjusted	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
NAFLD at baseline	6.05 (4.45–8.22)	<0.001	2.37 (1.60–3.52)	<0.001	2.27 (1.47–3.51)	<0.001	3.01 (1.18–7.68)	0.021
Age (continuous)	—	—	1.04 (1.02–1.07)	<0.001	1.04 (1.01–1.07)	0.0022	1.05 (1.00–1.11)	0.073
Women	—	—	0.91 (0.61–1.35)	0.63	—	—	—	—
BMI (continuous)	—	—	1.11 (1.04–1.17)	0.0010	1.12 (1.04–1.20)	0.0017	1.05 (0.94–1.18)	0.37
IFG	—	—	4.11 (2.93–5.77)	<0.001	3.62 (2.47–5.32)	<0.001	6.12 (3.09–12.14)	<0.001
Family history of diabetes	—	—	2.16 (1.50–3.13)	<0.001	2.03 (1.32–3.13)	0.0013	2.76 (1.33–5.78)	0.0066
DL	—	—	1.68 (1.18–2.39)	0.0040	1.73 (1.15–2.59)	0.0084	1.45 (0.68–3.11)	0.34
HT	—	—	1.08 (0.71–1.63)	0.73	1.06 (0.67–1.67)	0.81	1.16 (0.43–3.08)	0.77
Physical exercise	—	—	0.54 (0.31–0.95)	0.034	0.55 (0.28–1.06)	0.074	0.47 (0.15–1.51)	0.21
Logistic regression models were used to estimate the ORs, 95% CIs, and <i>P</i> values.								

# Liver Steatosis is an Independent Predictor of Atherosclerosis

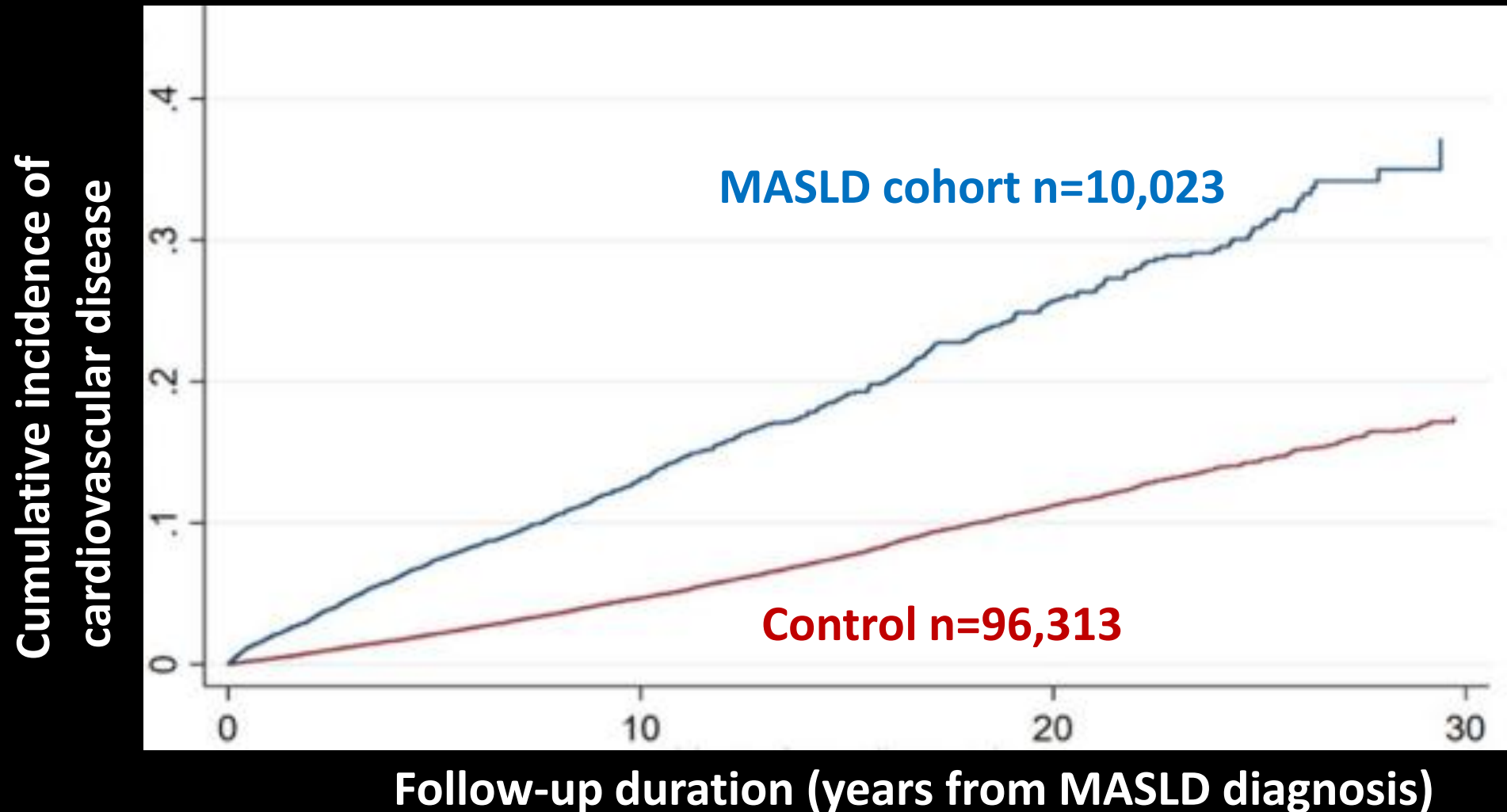
	C-IMT		CAC	
	Beta	<i>P</i>	Beta	<i>P</i>
Age	0.445	< 0.001	0.226	< 0.001
Type 2 diabetes	0.034	0.066	0.039	0.053
High blood pressure	0.105	< 0.001	0.048	0.023
Tobacco	0.052	0.004	0.008	0.690
hsCRP	−0.018	0.329	−0.045	0.023
Steatosis*	0.065	0.001	0.091	< 0.001

*Case (n=930) vs. control (n=1,624) study from high risk individuals for CAD from Paris, France*

\*steatosis measured by fatty liver index and included as a continuous variable in the model

C-IMT=carotid intima-media thickness; CAC=coronary artery calcification; hsCRP=hultra sensitive c reactive protein

# MASLD predicts of cardiovascular mdisease risk



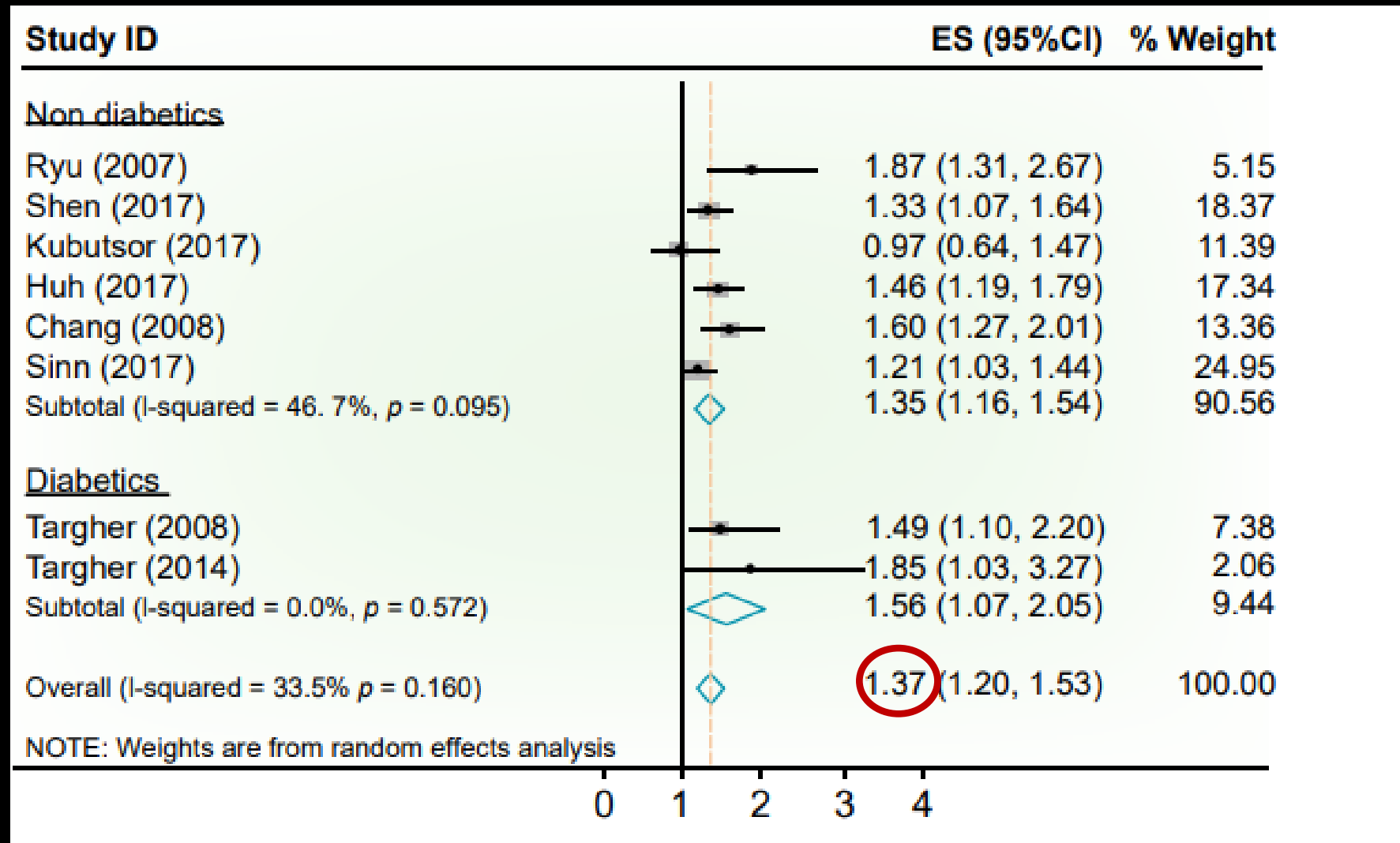
# MASLD is a risk factor for Heart Failure

	N	Event	Duration, PY	IR, 1000 PY	HR (95% CI)			
					Model 1	Model 2	Model 3	Model 4
HF incidence								
No SLD	789,654	42,824	5400244.7	7.93	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
MASLD	1,008,394	53,929	6934888.4	7.78	0.98 (0.97, 0.99)	1.11 (1.09, 1.12)	1.11 (1.09, 1.12)	1.11 (1.09, 1.13)
MetALD	147,192	6,178	1005630.2	6.14	0.78 (0.76, 0.80)	1.15 (1.12, 1.18)	1.11 (1.08, 1.14)	1.14 (1.10, 1.17)
ALD with HD	46,369	2,338	314081.5	7.44	0.95 (0.91, 0.99)	1.36 (1.30, 1.42)	1.30 (1.25, 1.36)	1.32 (1.26, 1.38)

Model 1: Non-Adjusted; Model 2: Age, Sex; Model 3: Age, Sex, Income, Smoking, Regular exercise, CCI Score; Model 4: Age, Sex, Income, Smoking, Regular exercise, CCI Score, Fasting glucose, DM Duration, Insulin, OHA, CKD, Statin, BMI

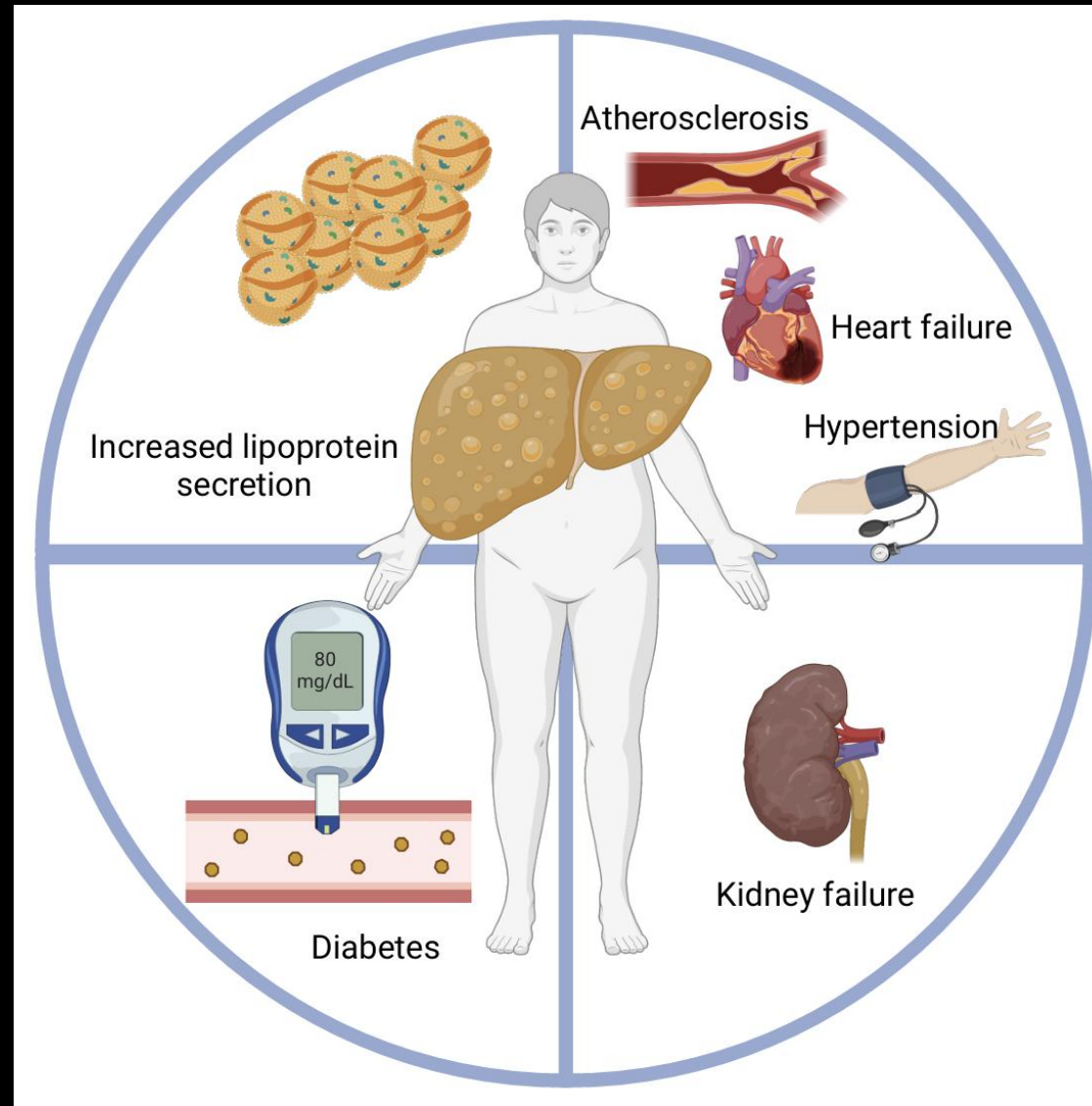
IR, incidence rate; PY, person years; HR, hazard ratio; CI, confidence interval; SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic alcohol-associated liver disease; ALD with MD, alcohol-associated liver disease with metabolic dysfunction; VH, viral hepatitis; CV, cardiovascular; HF, heart failure;

# MASLD clusters with Chronic Kidney Disease

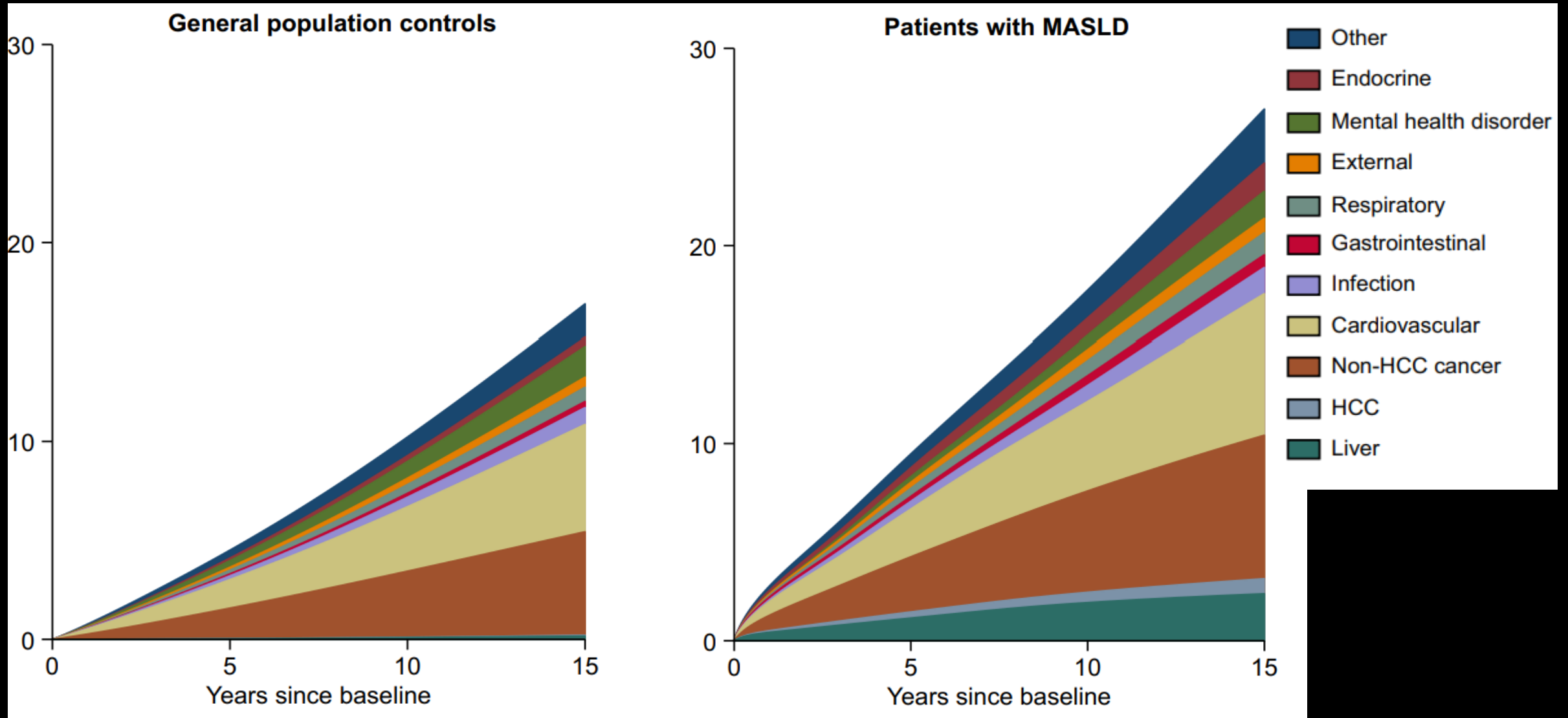




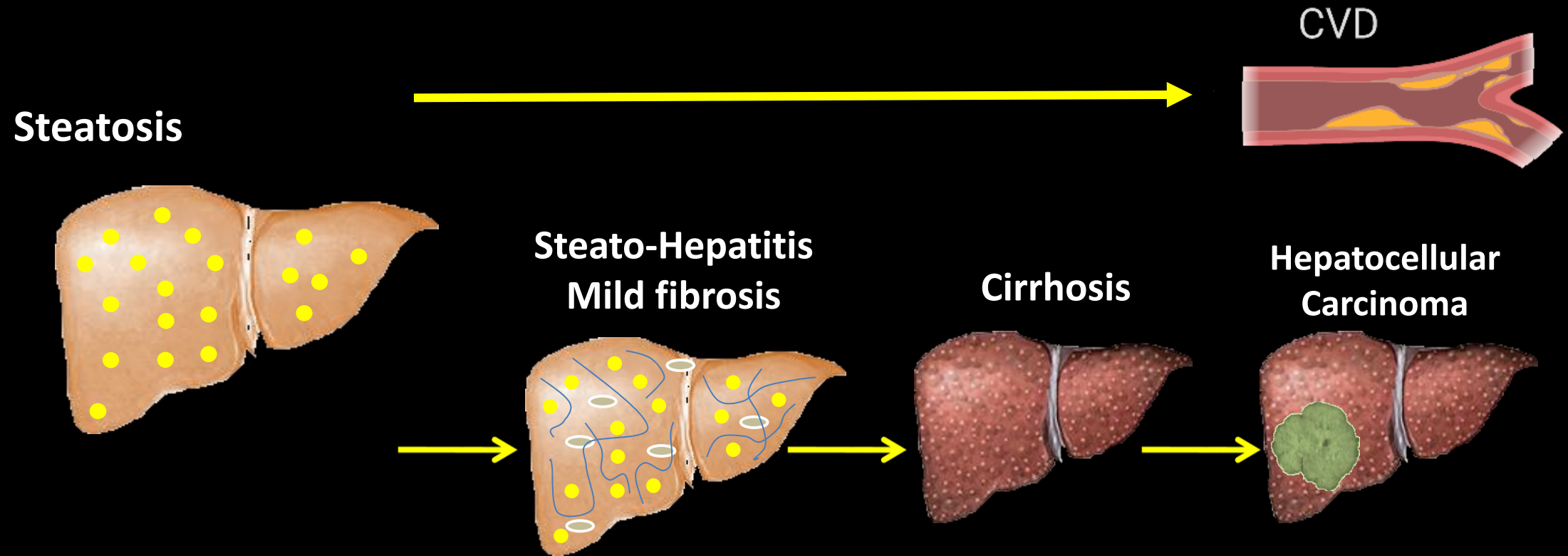
# Systemic MASLD



# All cause mortality in MASLD



# MASLD Clinical trajectories



# Human Genetics of Steatotic Liver Disease

## *Inborn*

Common

**PNPLA3**

**TM6SF2**

**MBOAT7**

**GCKR**

**GPAM**

**MARC1**

**APOE**

**PSD3**

**COBLL1**

**FTO**

**SREBP1C**

**PNPLA2**

**INSR**

Rare

**APOB**

**MTTP**

**CIDEB**

## *Inborn*

Common

**PNPLA3**

**HSD17B13**

**ATG7**

**HFE**

Rare

**ATG7**

**HFE**

## *Inborn*

Common

**STRN**

**KLB**

**SHROOM3**

**TOR1B**

**HKDC1**

**SH2B3**

**APOH**

**TM4SF4**

**ACVR1C**

**TNFSF10**

## *Acquired*

**GPAM**

**FOX1**

**CIDEB**

## *Acquired*

**TERT**

**TP53**

**CTNNB1**

**AXIN1**

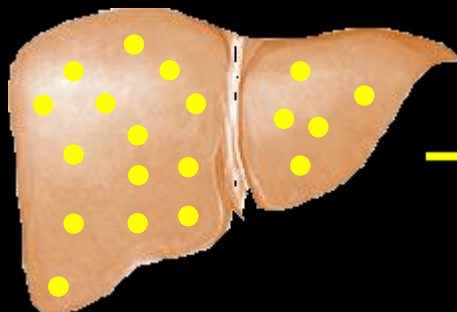
**RAS, ARID1A**

**ARID2, KMT2C**

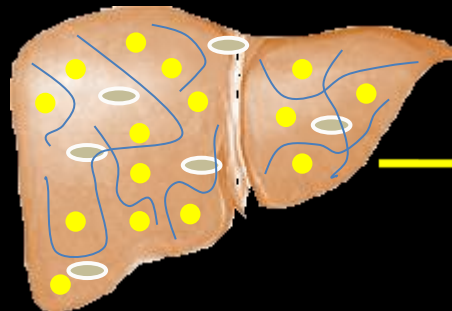
**MAPK, AKT**

**mTOR, MET**

**Steatosis**



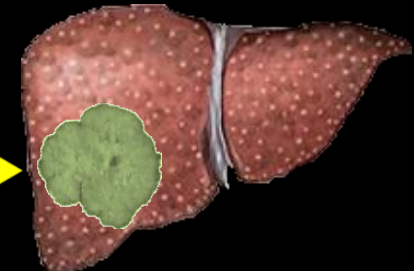
**Steato-Hepatitis**



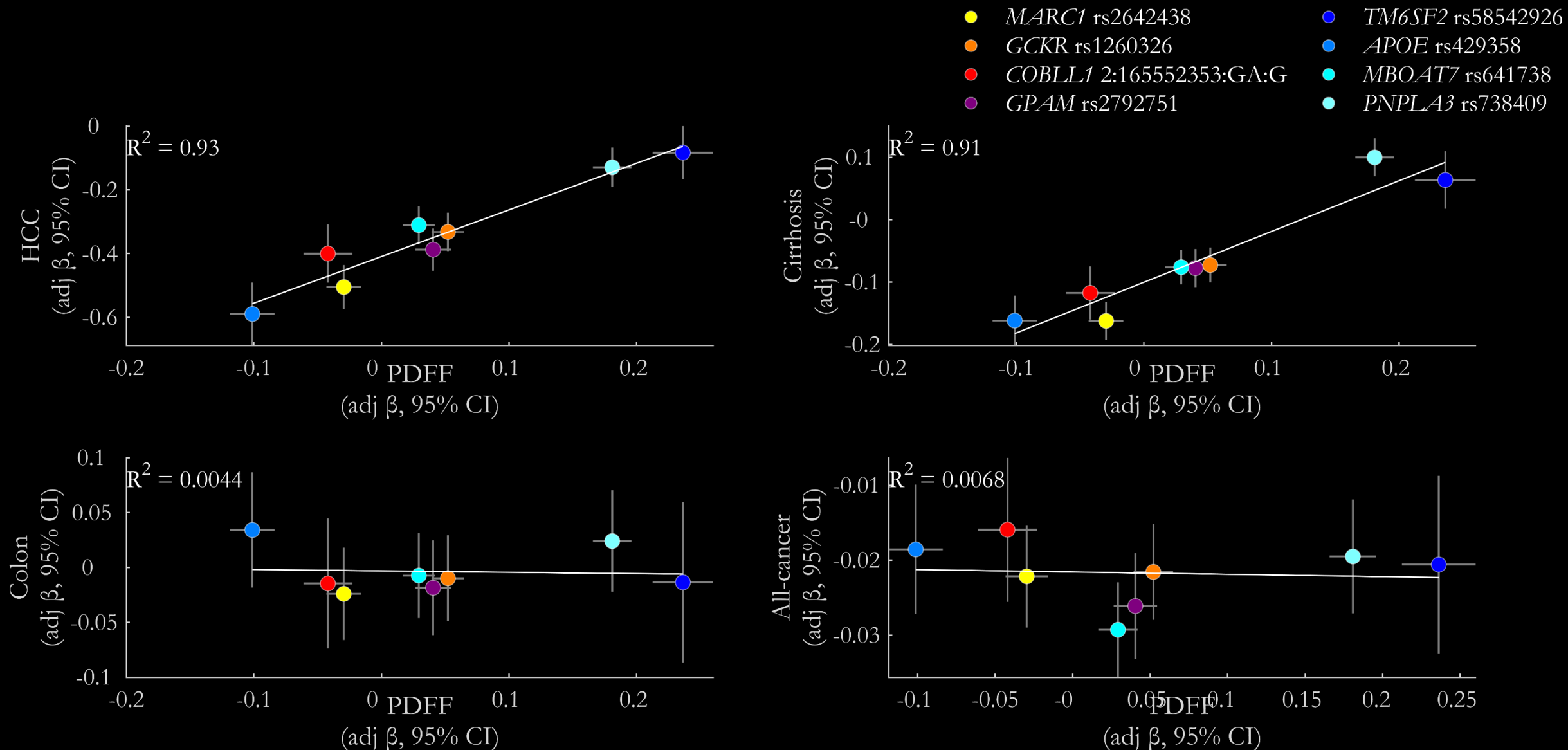
**Cirrhosis**



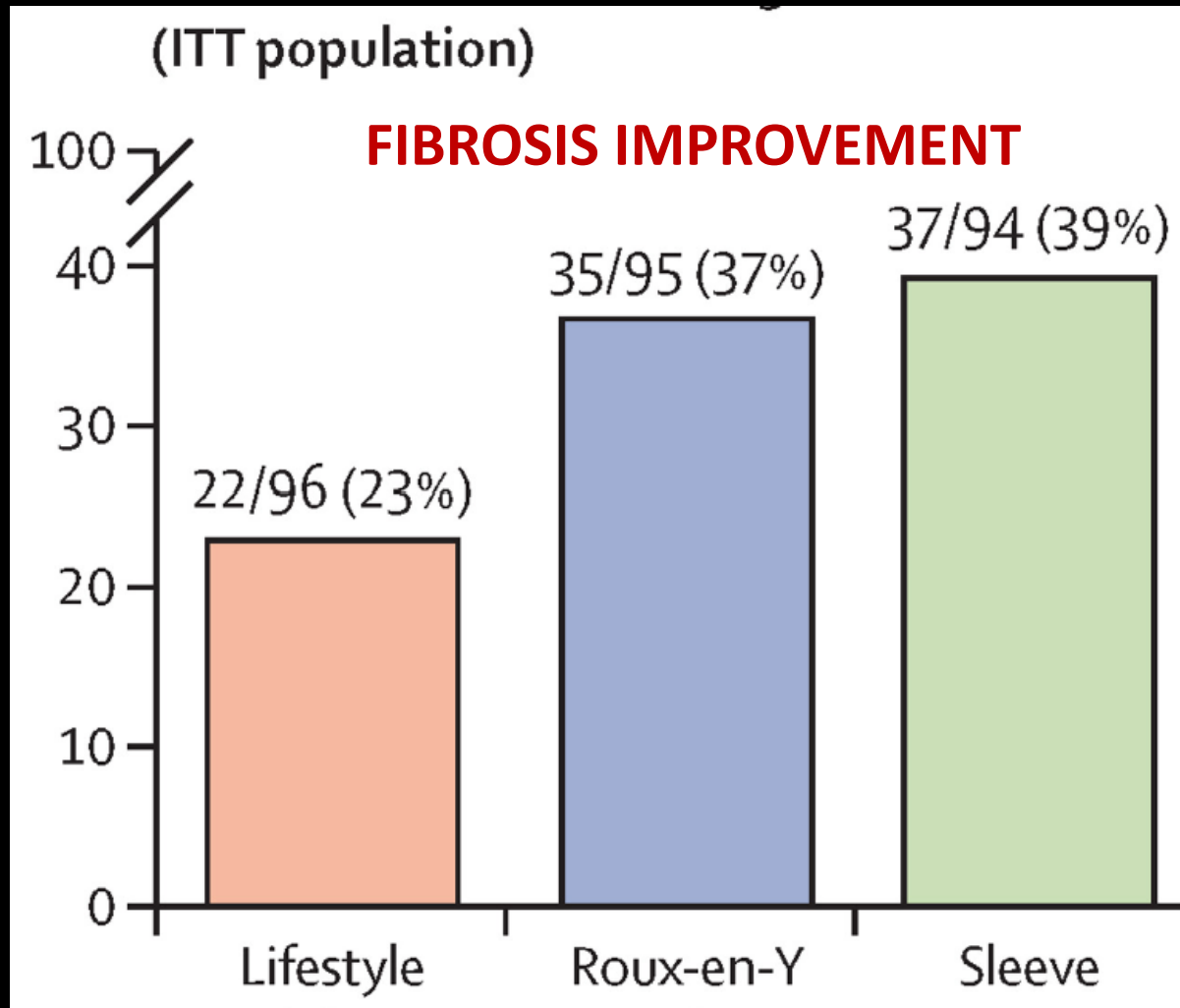
**Hepatocellular  
Carcinoma**



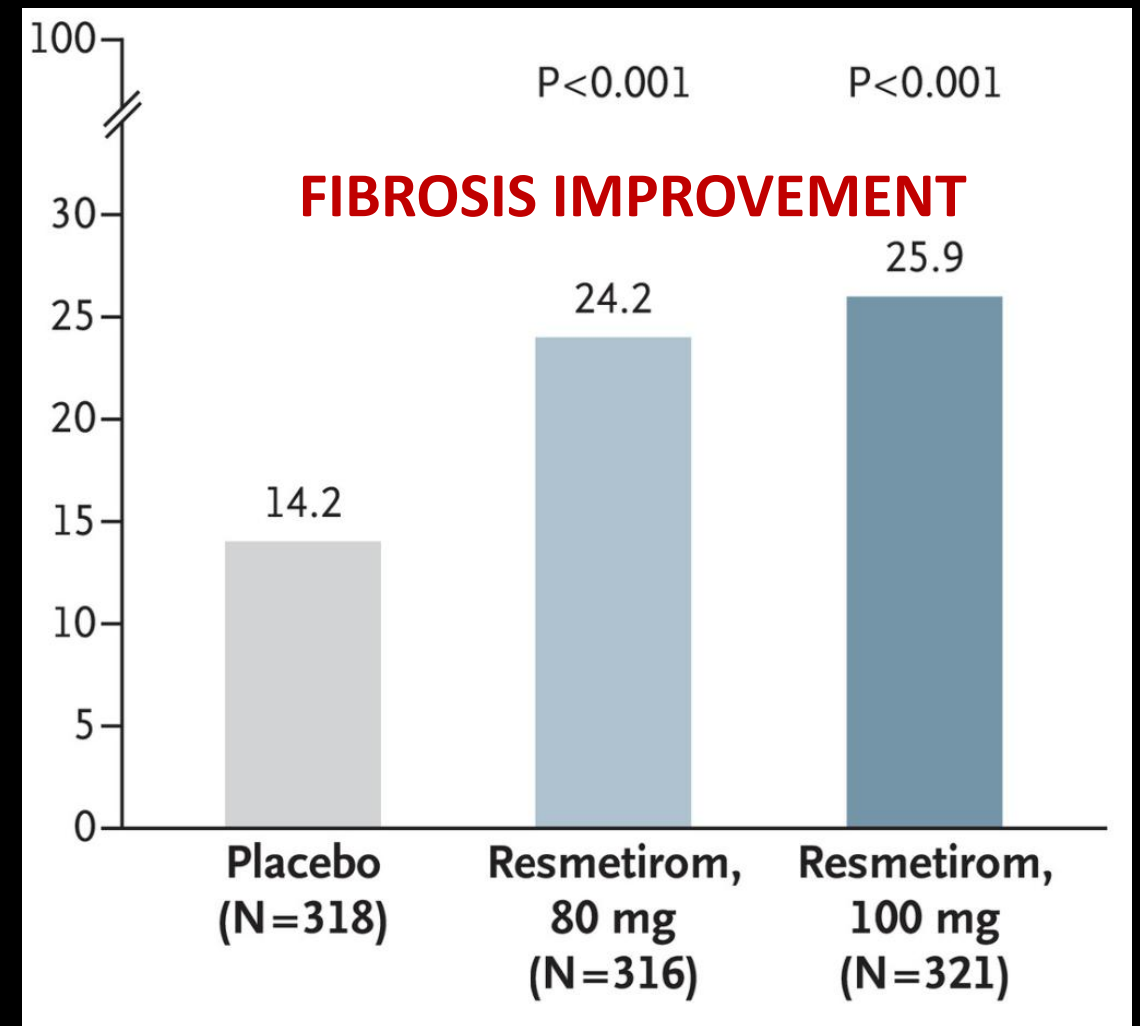
# Linear relationship between liver fat, cirrhosis and HCC



# Lowering Liver Triglycerides Reduces Fibrosis



*Verrastro O Lancet 2023*



*Harrison NEJM 2024*

# Human Genetics of Steatotic Liver Disease

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**TNFSF10**

## Acquired

**GPAM**

**FOX1**

**CIDEB**

## Acquired

**TERT**

**TP53**

**CTNNB1**

**AXIN1**

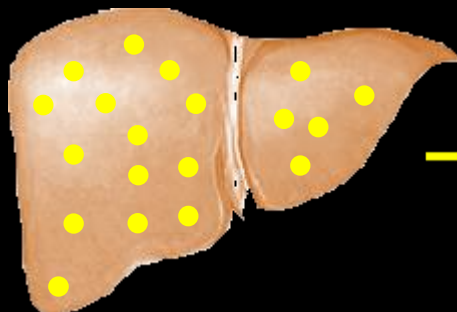
**RAS, ARID1A**

**ARID2, KMT2C**

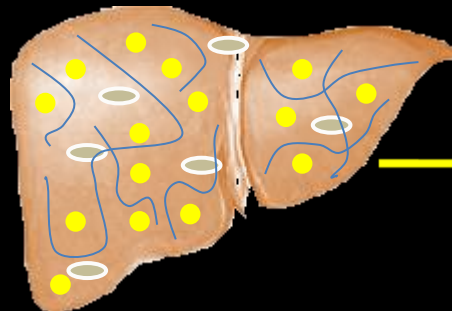
**MAPK, AKT**

**mTOR, MET**

**Steatosis**



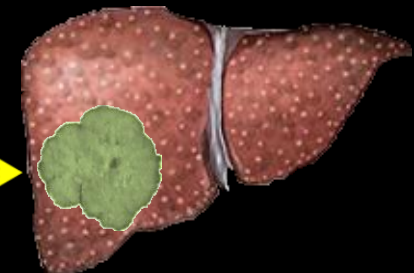
**Steato-Hepatitis**



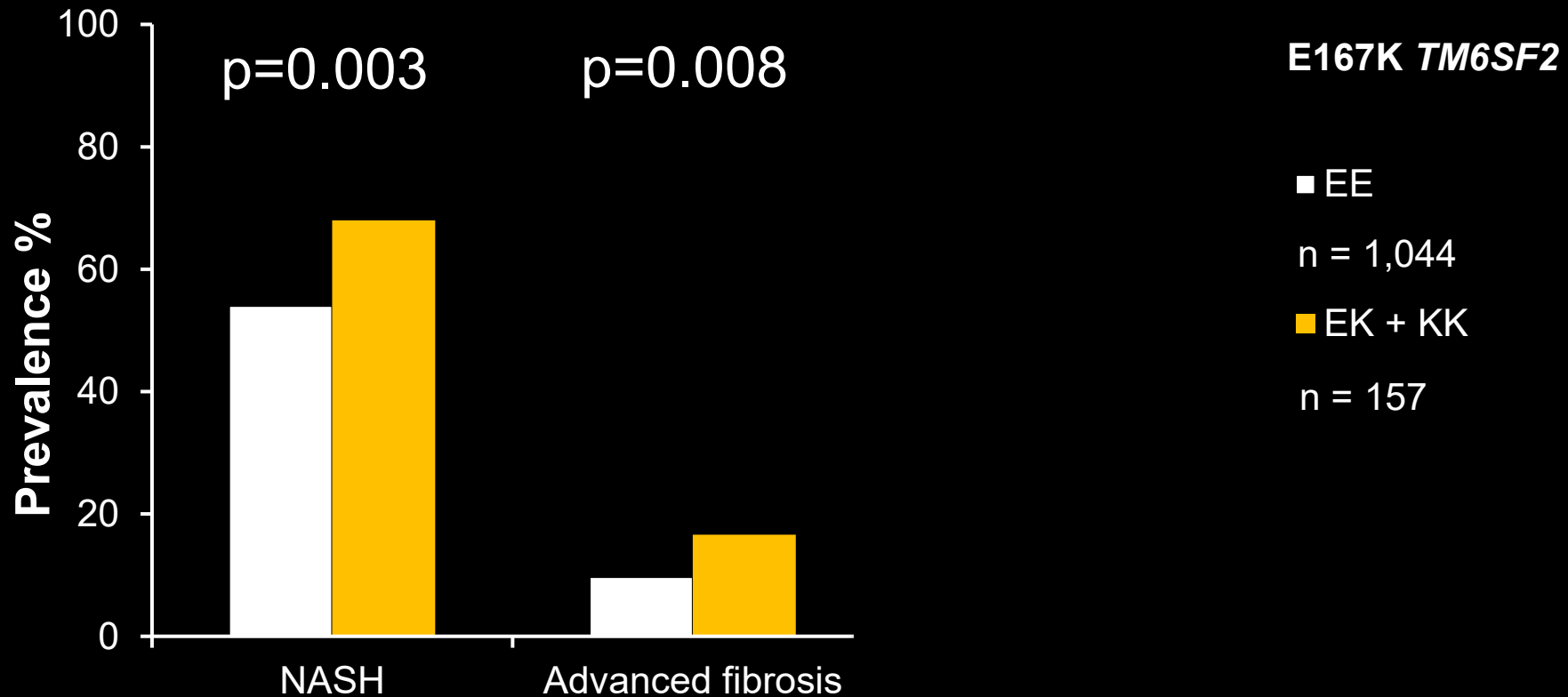
**Cirrhosis**



**Hepatocellular Carcinoma**

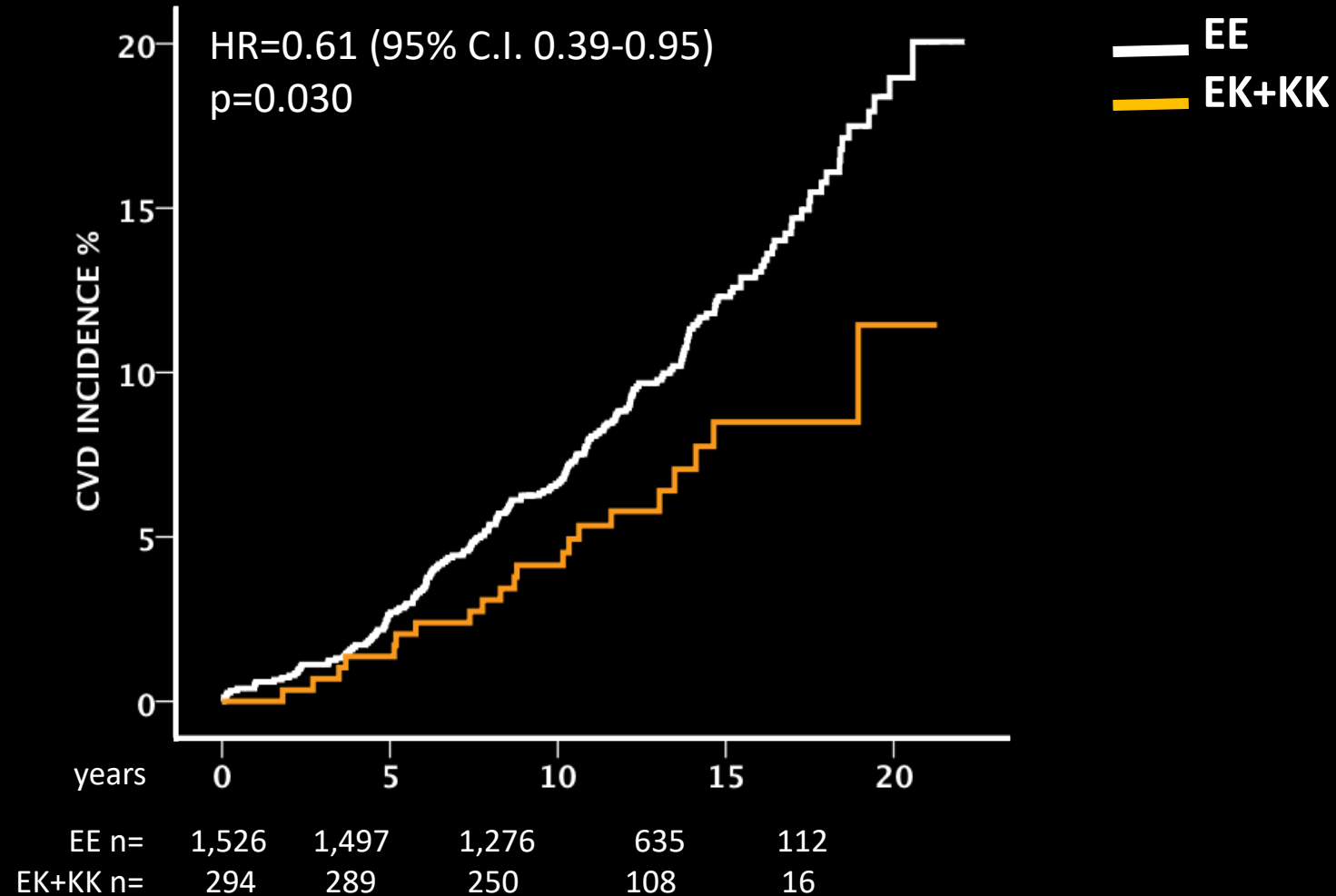


# TM6SF2 E167K increases liver inflammation and fibrosis





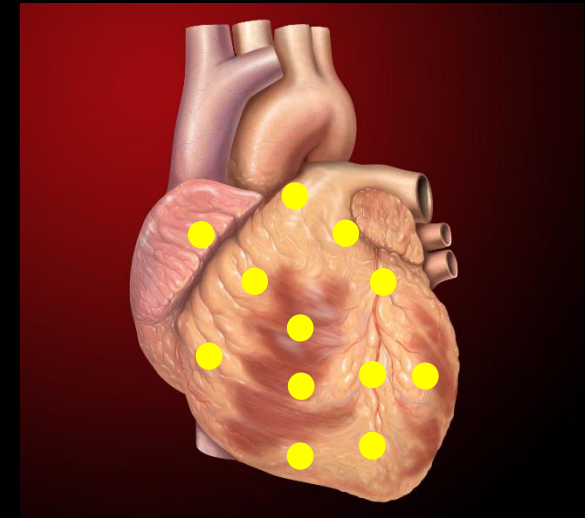
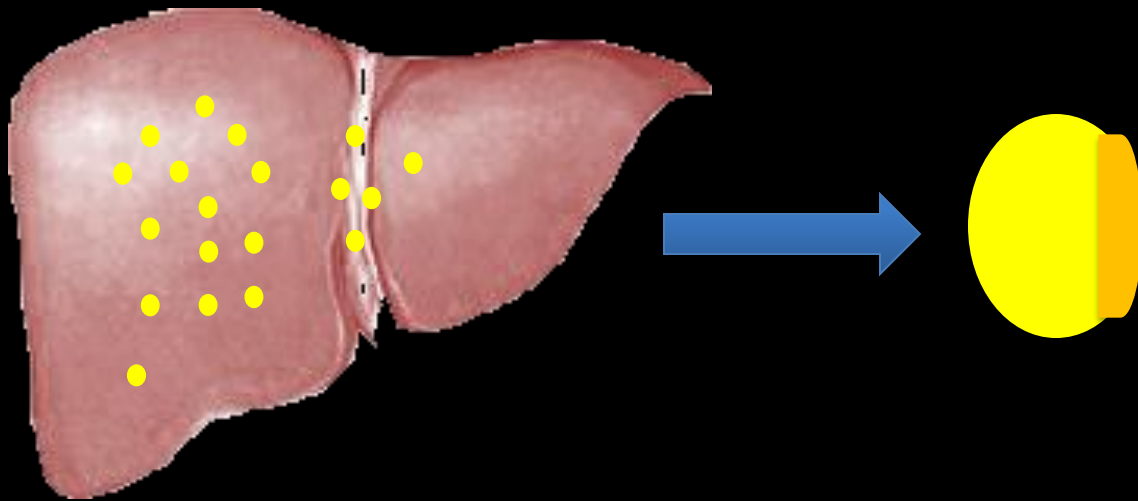
# TM6SF2 E167K decreases the incidence of cardiovascular disease in the SOS study



# TM6SF2 Carriers have lower plasma APOB and TGs in the SOS Study

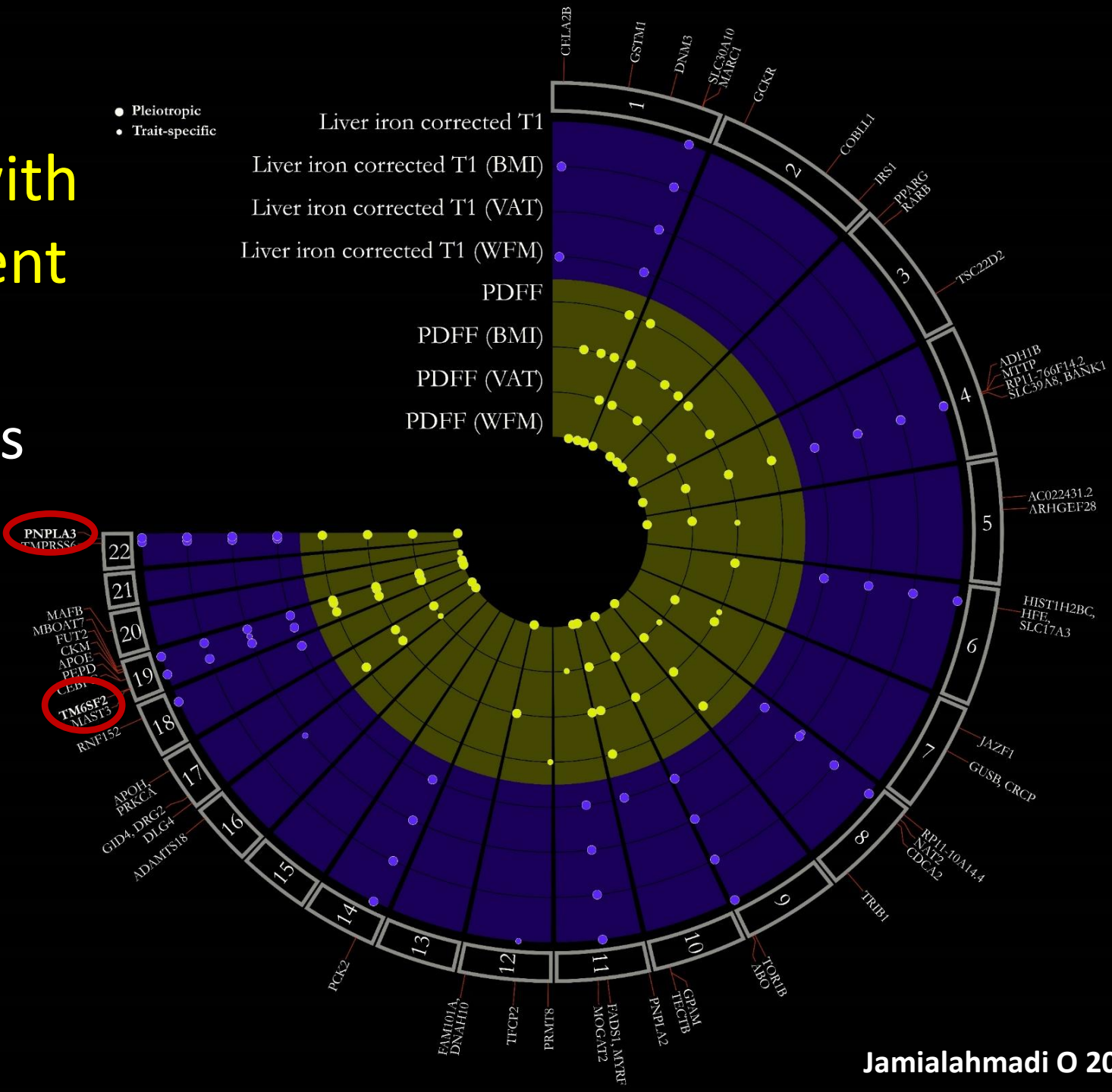
	Non Carriers (n=1,525)	Carriers E167K (n=294)	P Value
Triglycerides (mmol/L)	2.1 $\pm$ 1.5	1.8 $\pm$ 1.0	0.006
APOB (g/L)	1.24 $\pm$ 0.3	1.19 $\pm$ 0.3	0.003
HDL-C (mmol/L)	1.3 $\pm$ 0.3	1.3 $\pm$ 0.3	0.48

**TM6SF2 E167K carriers are protected from cardiovascular disease at the cost of liver disease**



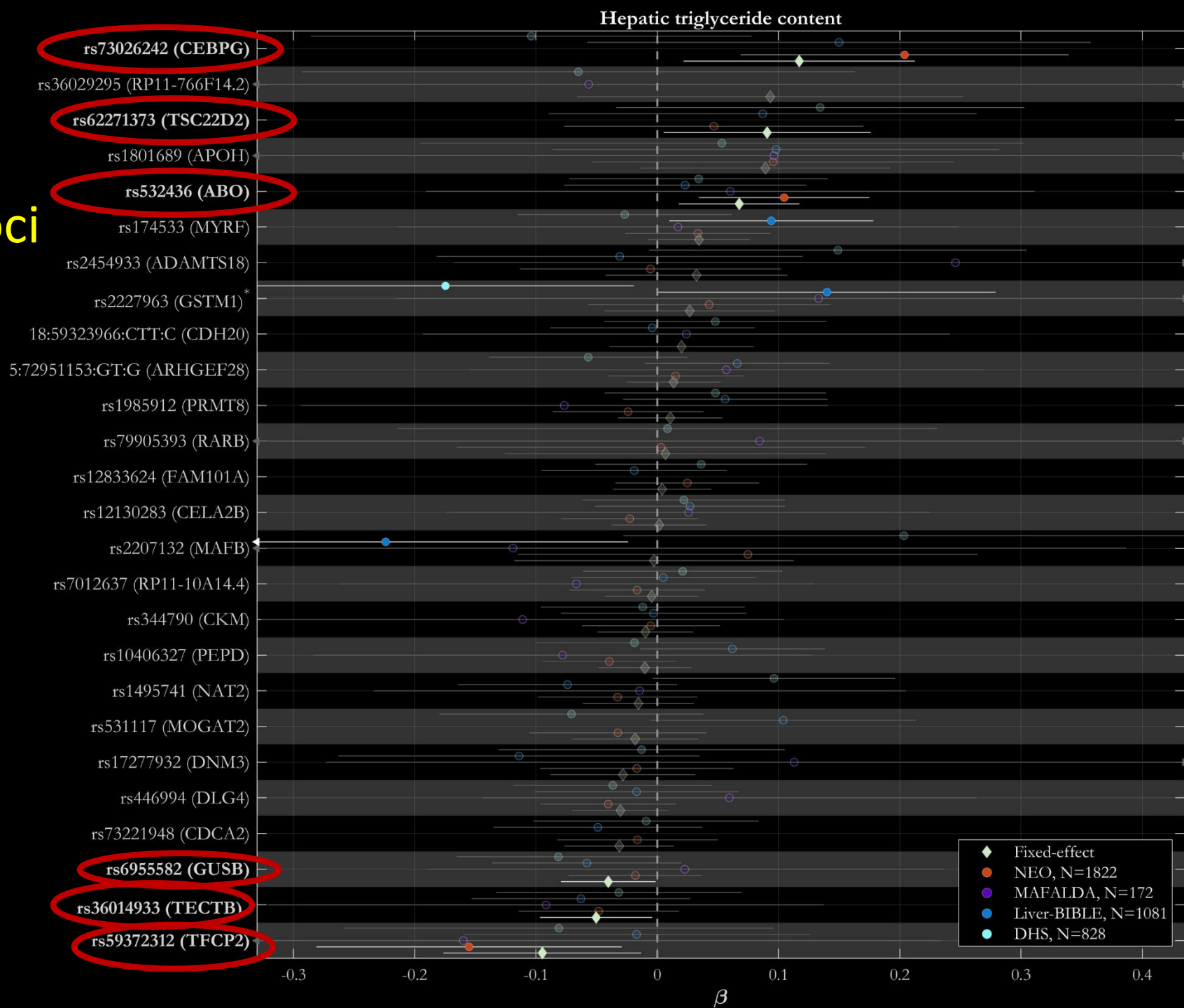
# GWAS on liver fat content with different adiposity adjustment

- 37 loci for liver triglycerides
- 17 loci for liver inflammation

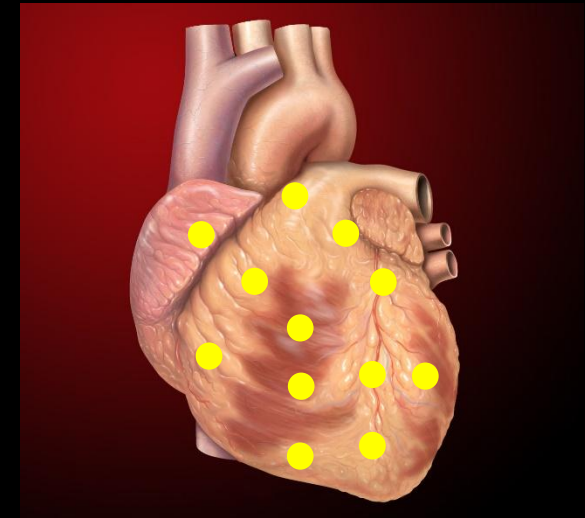
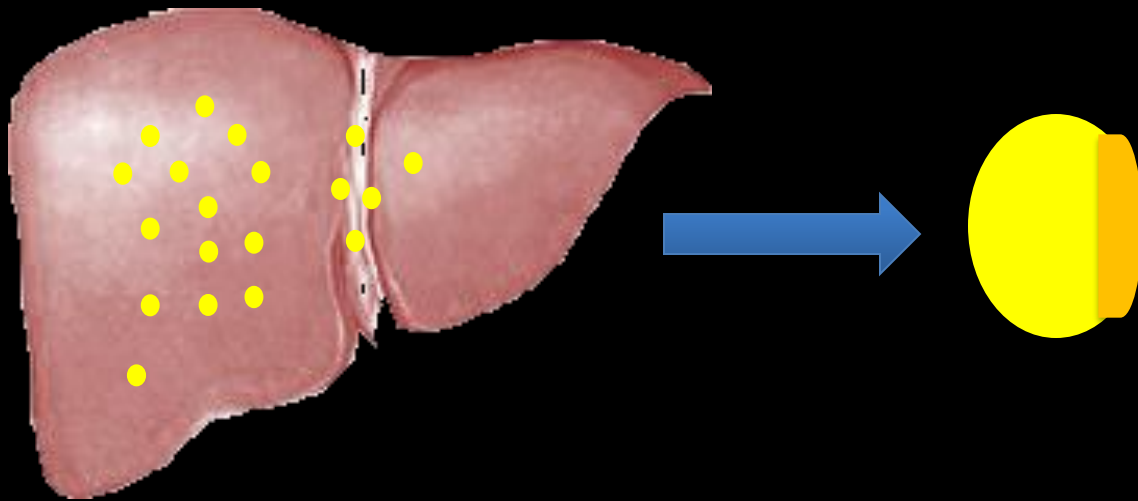


For a total of 26 novel loci associated with MASLD

6 were replicated in independent cohorts

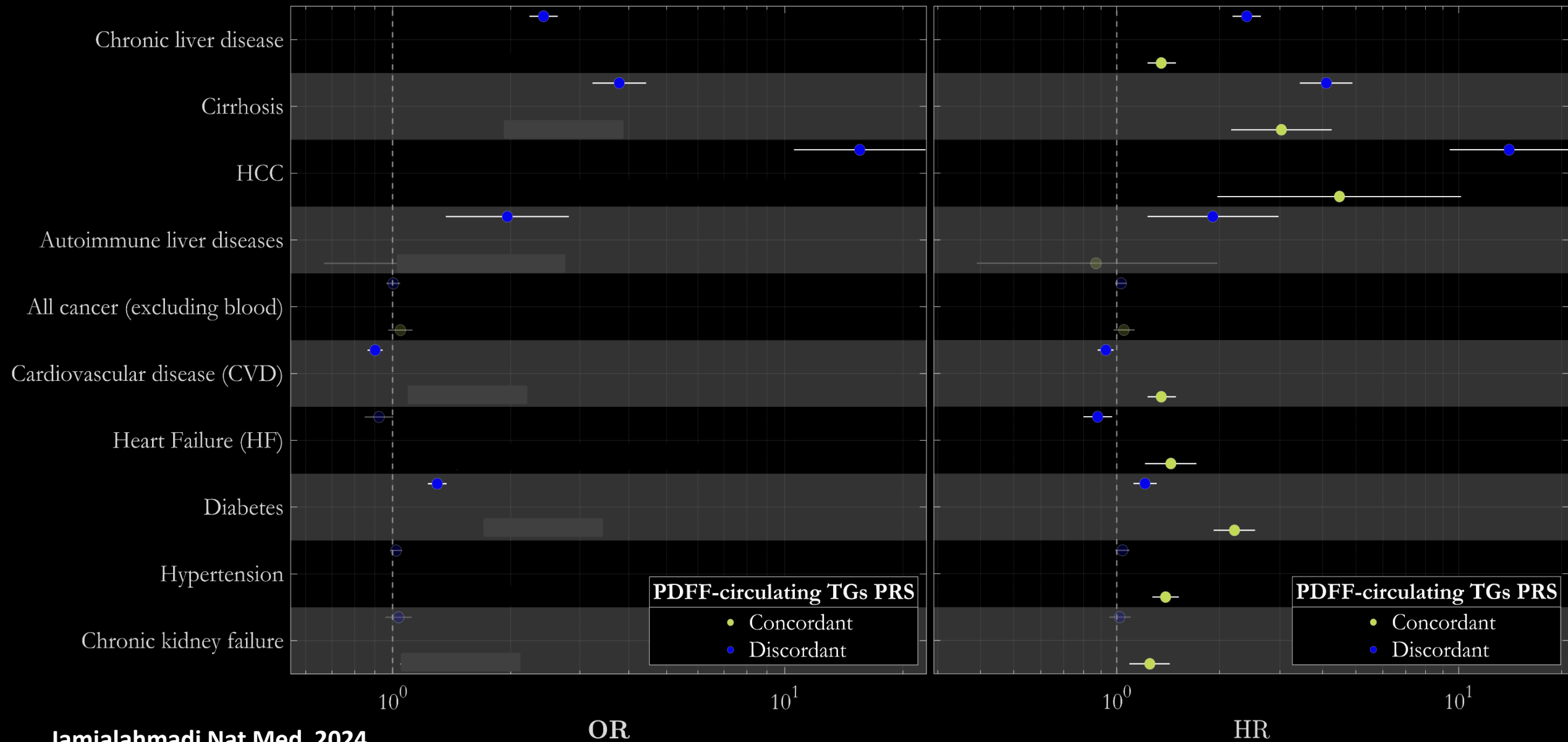


# Liver lipoprotein retention as a paradigm for chronic liver disease



***2 Partitioned Polygenic risk score (pPRS) with variant predicted to cause lipoprotein retention***

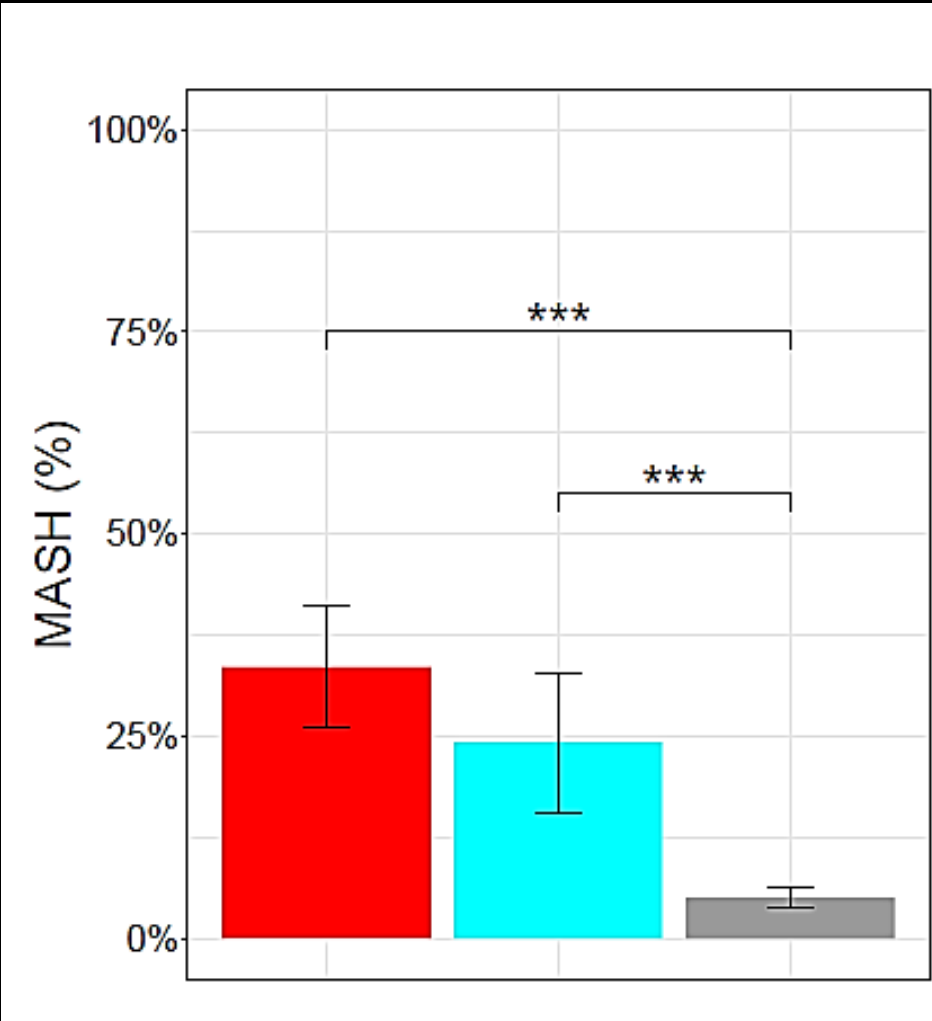
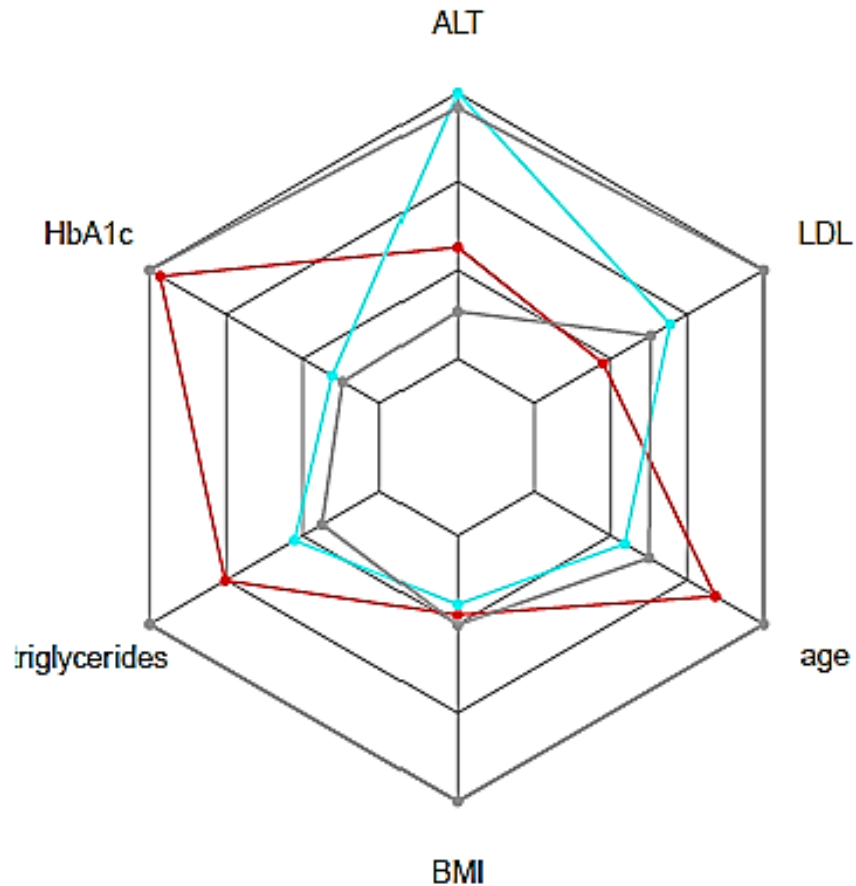
# pPRS dissects 2 types of MASLD: a liver specific (discordant) and a systemic (concordant)



# Unsupervised Clustering identifies two types of MASLD with different metabolic features in people with obesity

**ABOS cohort** (n=1389)

- Cardiometabolic (n=158)
- Liver specific (n=99)
- Controls (n=1132)

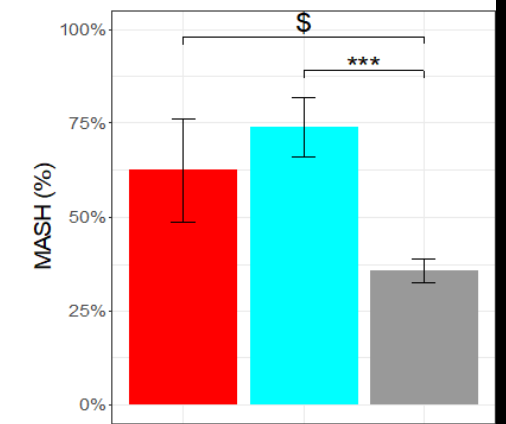
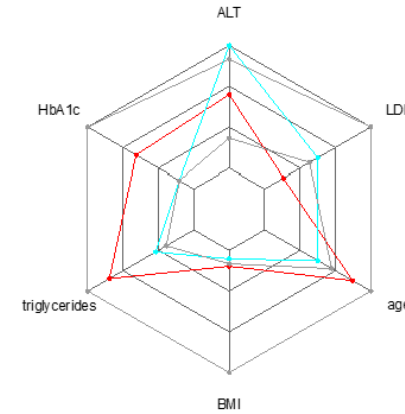
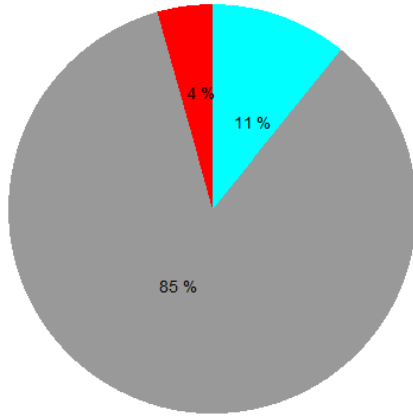




# Replication in Independent cohorts

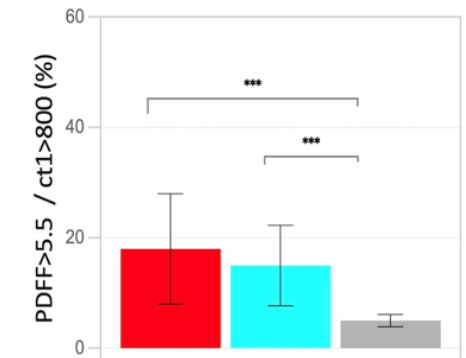
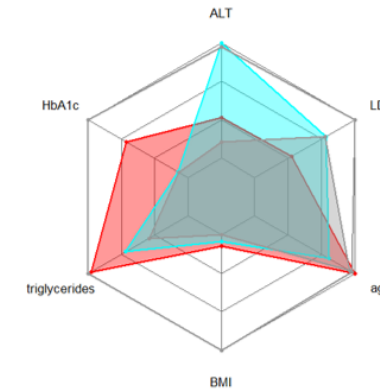
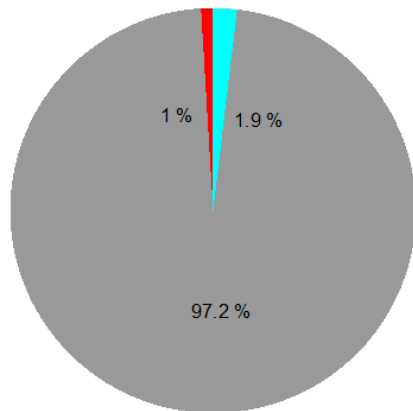
## Validation cohort (n=1,099)

- Cardiometabolic (n=48)
- Liver-specific (n=119)
- Control (n=932)



## UK Biobank MRI cohort (n=6,792)

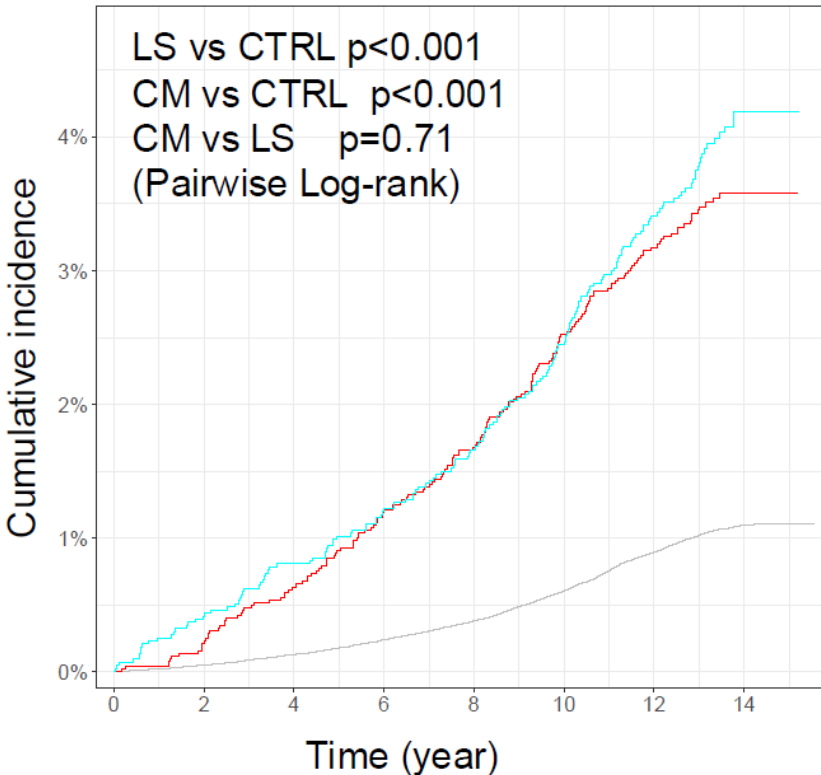
- Cardiometabolic (n=65)
- Liver-specific (n=128)
- Control (n=6,599)



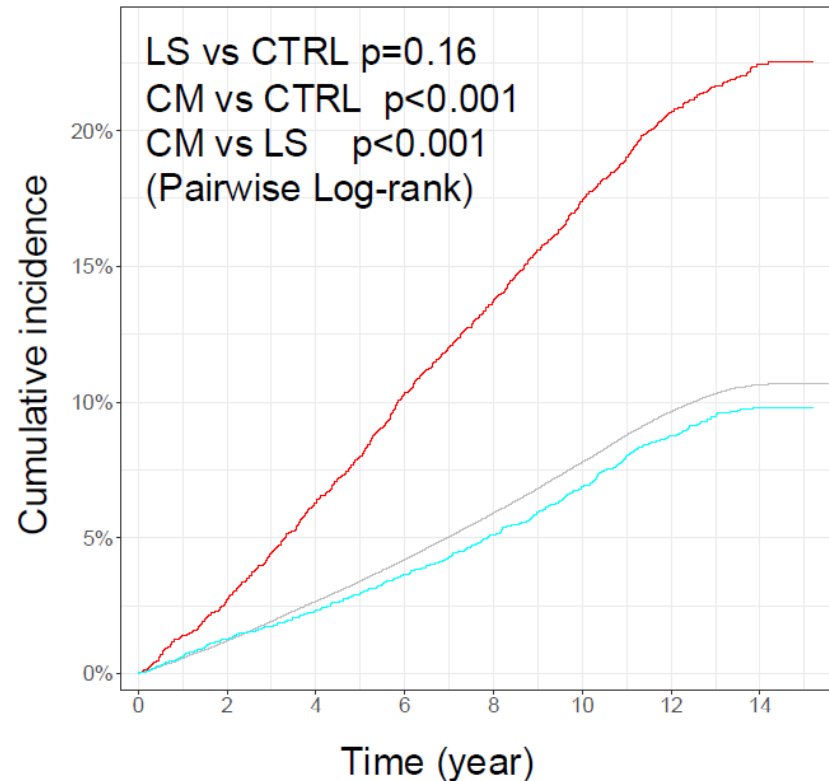
# MASLD with different clinical trajectories for CVD and diabetes

- Cardiometabolic (n=158)
- Liver specific (n=99)
- Controls (n=1132)

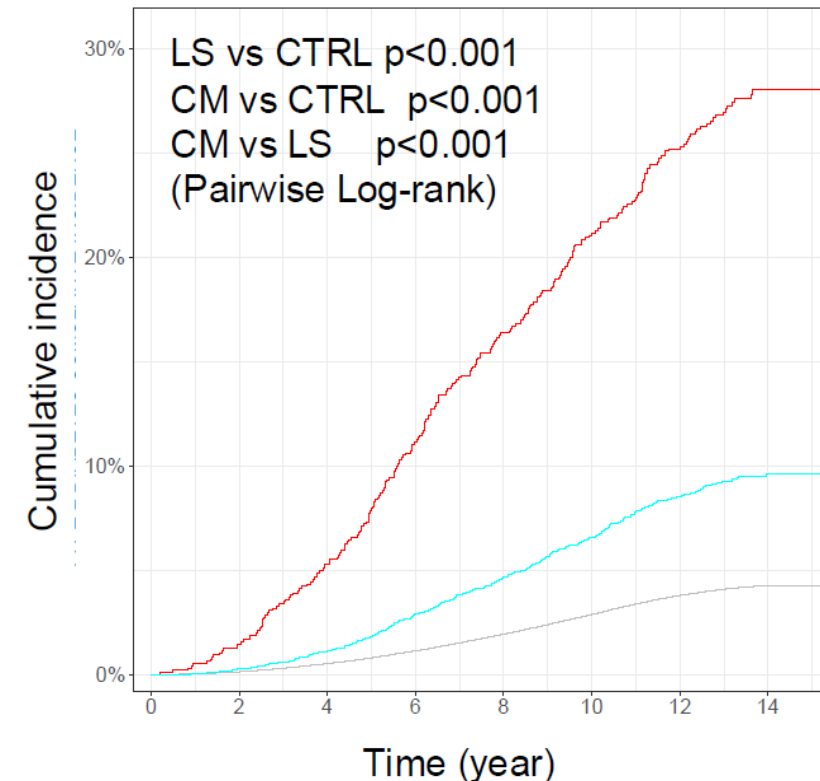
## Chronic liver disease



## Cardiovascular disease



## Type 2 diabetes



# MASLD Clusters

nature  
medicine

Age:

48

BMI:

35

hba1c %:

7,8

ALT in IU/L:

23

Triglycerides in  
mmol/L:

4

Cholesterol LDL  
in mmol/L:

3

Compute

**Age:** 48

**BMI:** 35

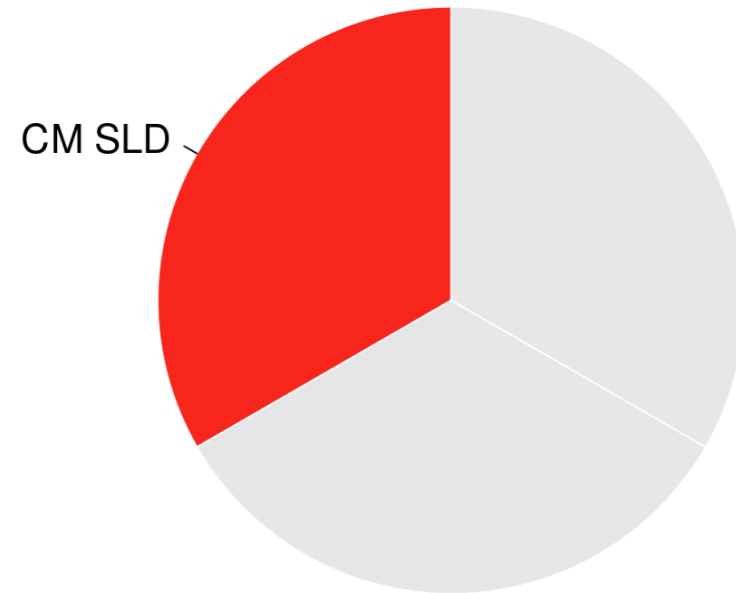
**hba1c %:** 7.8

**ALT in IU/L:** 23

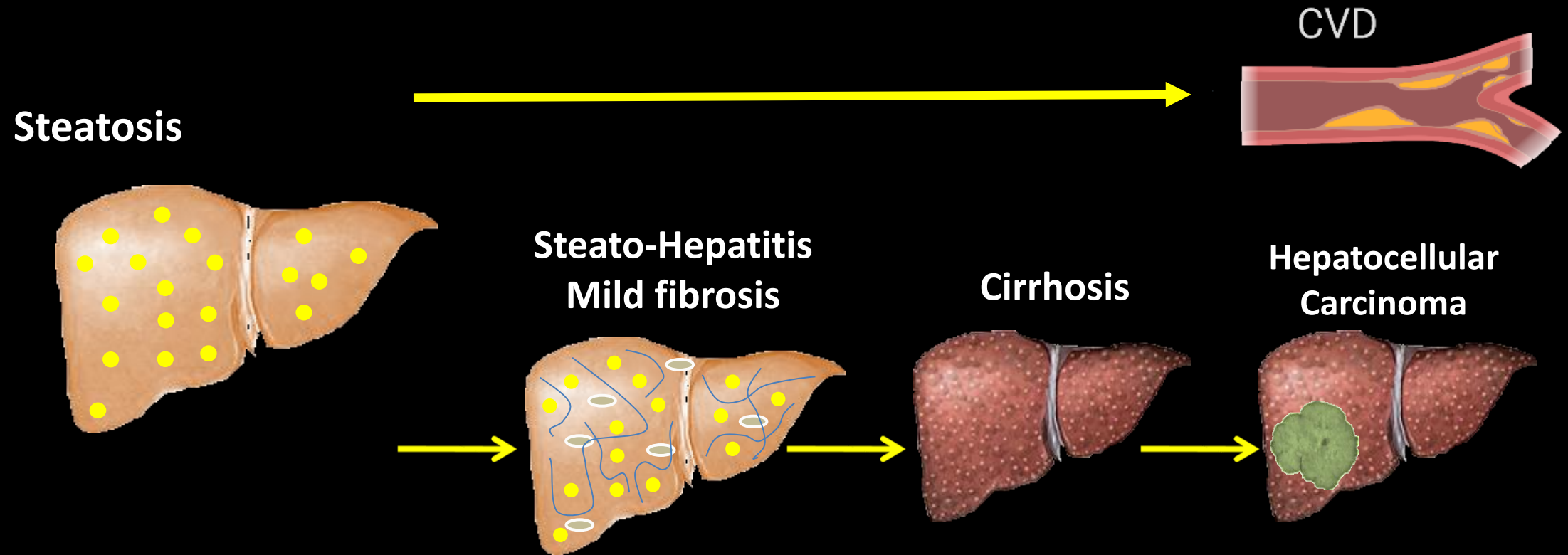
**Triglycerides in mmol/L:** 4

**Cholesterol LDL in mmol/L:** 3

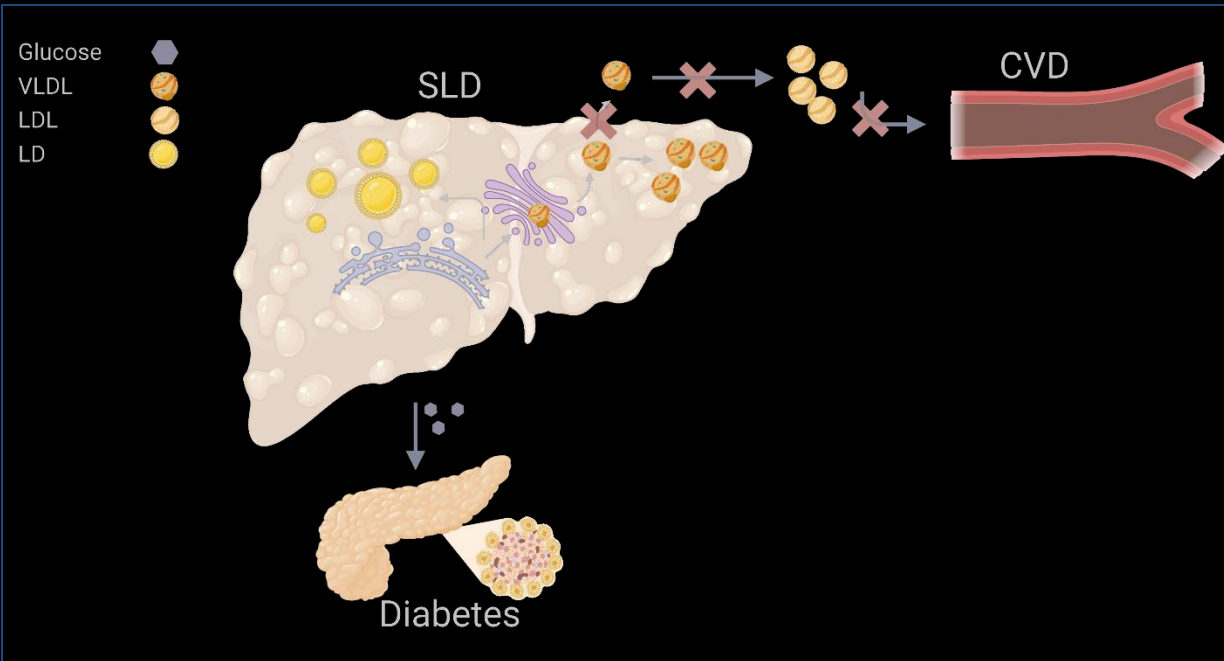
**Cluster:** Cardiometabolic  
(CM) SLD



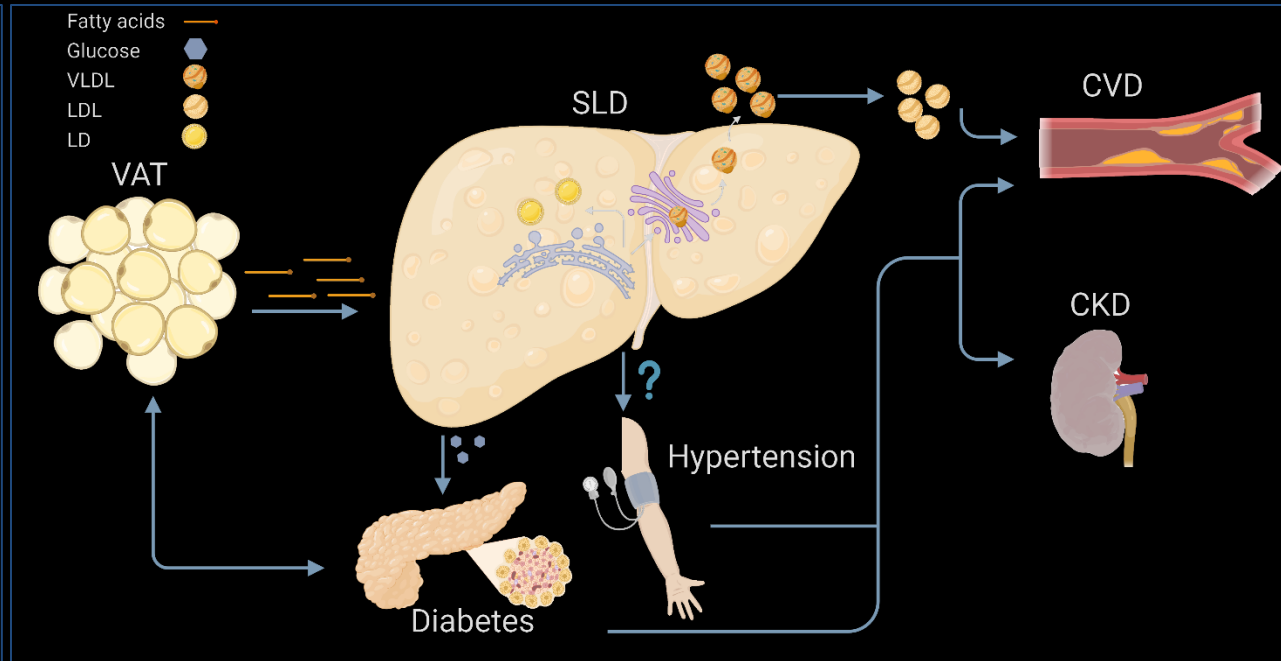
# MASLD Clinical trajectories



# Liver specific MASLD



# Systemic MASLD





ESC













European Society  
of Cardiology

European Heart Journal (2025) 00, 1–29  
<https://doi.org/10.1093/eurheartj/ehaf314>

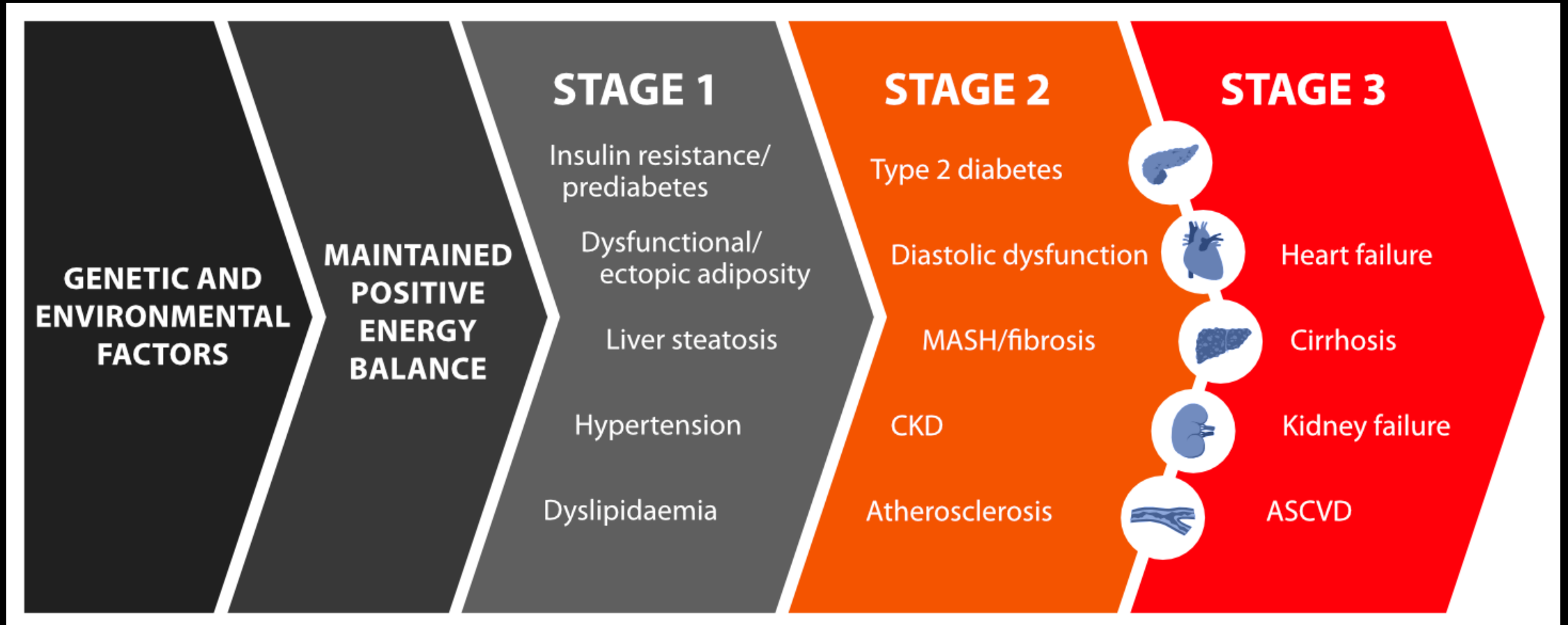
**SPECIAL ARTICLE**

*Diabetes and metabolic disorders*

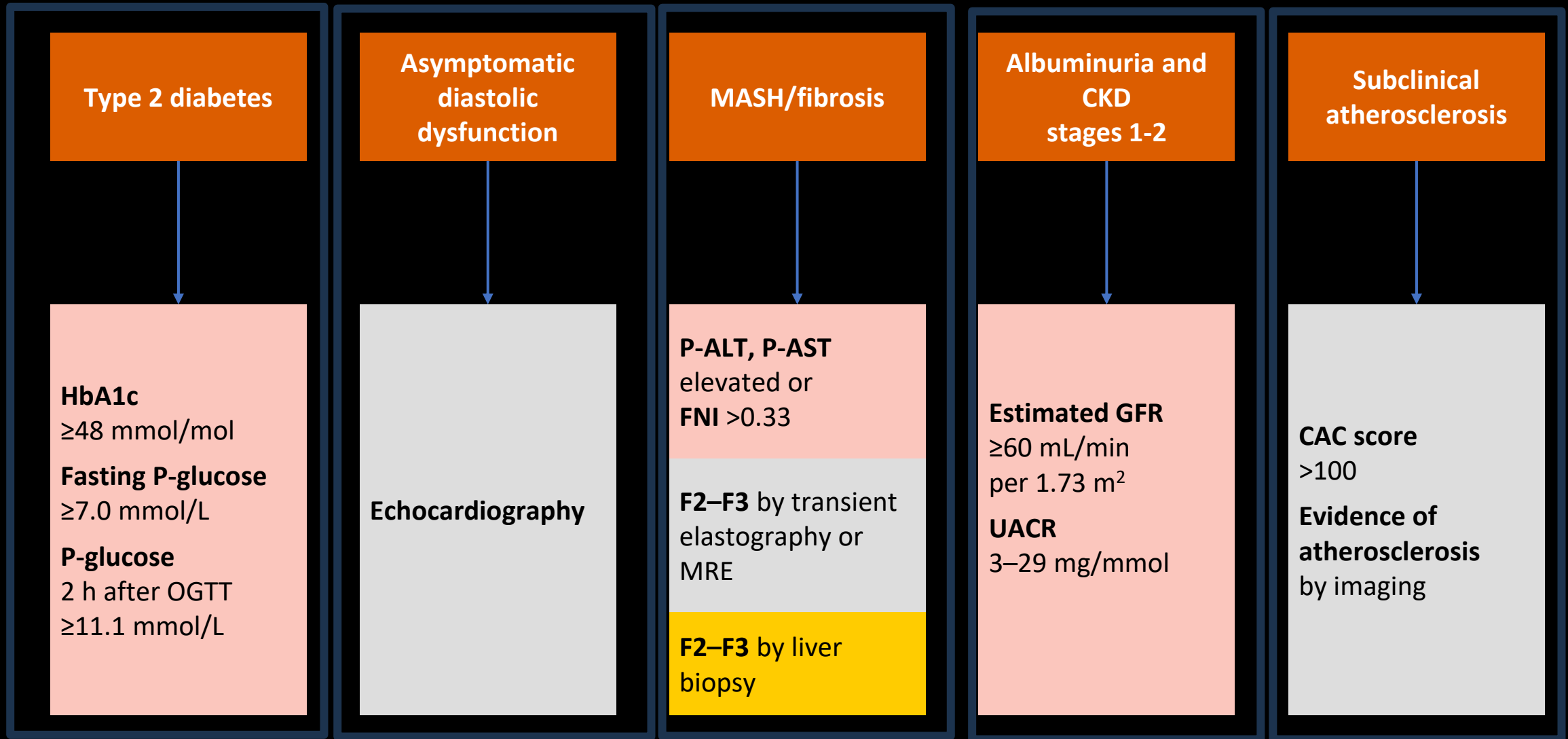
# Clinical staging to guide management of metabolic disorders and their sequelae: a European Atherosclerosis Society consensus statement

Stefano Romeo <sup>1,2,3,4,5,\*</sup>, Antonio Vidal-Puig<sup>6,7,8,\*</sup>, Mansoor Husain<sup>9,\*</sup>,  
Rexford Ahima<sup>10</sup>, Marcello Arca<sup>11,12</sup>, Deepak L. Bhatt<sup>13</sup>, Anna Mae Diehl<sup>14</sup>,  
Luigi Fontana <sup>15,16</sup>, Roger Foo <sup>17,18</sup>, Gema Frühbeck<sup>19,20,21,22</sup>,  
Julia Kozlitina <sup>23,24,25</sup>, Eva Lonn<sup>26,27</sup>, Francois Pattou<sup>28</sup>, Jogchum Plat<sup>29</sup>,  
Susan E. Quaggin<sup>30,31</sup>, Paul M. Ridker <sup>32</sup>, Mikael Rydén<sup>33</sup>, Nicola Segata<sup>34,35</sup>,  
Katherine R. Tuttle<sup>36,37</sup>, Subodh Verma <sup>38</sup>, Jeanine Roeters van Lennep <sup>39</sup>,  
Marianne Benn <sup>40,41</sup>, Christoph J. Binder <sup>42</sup>, Oveis Jamialahmadi <sup>3</sup>,  
Rosie Perkins <sup>3</sup>, Alberico L. Catapano<sup>43,44,†</sup>, Lale Tokgözoğlu<sup>45,†</sup>, and  
Kausik K. Ray <sup>46,‡</sup>; on behalf of the European Atherosclerosis Society Consensus

# Systemic Metabolic Disorders

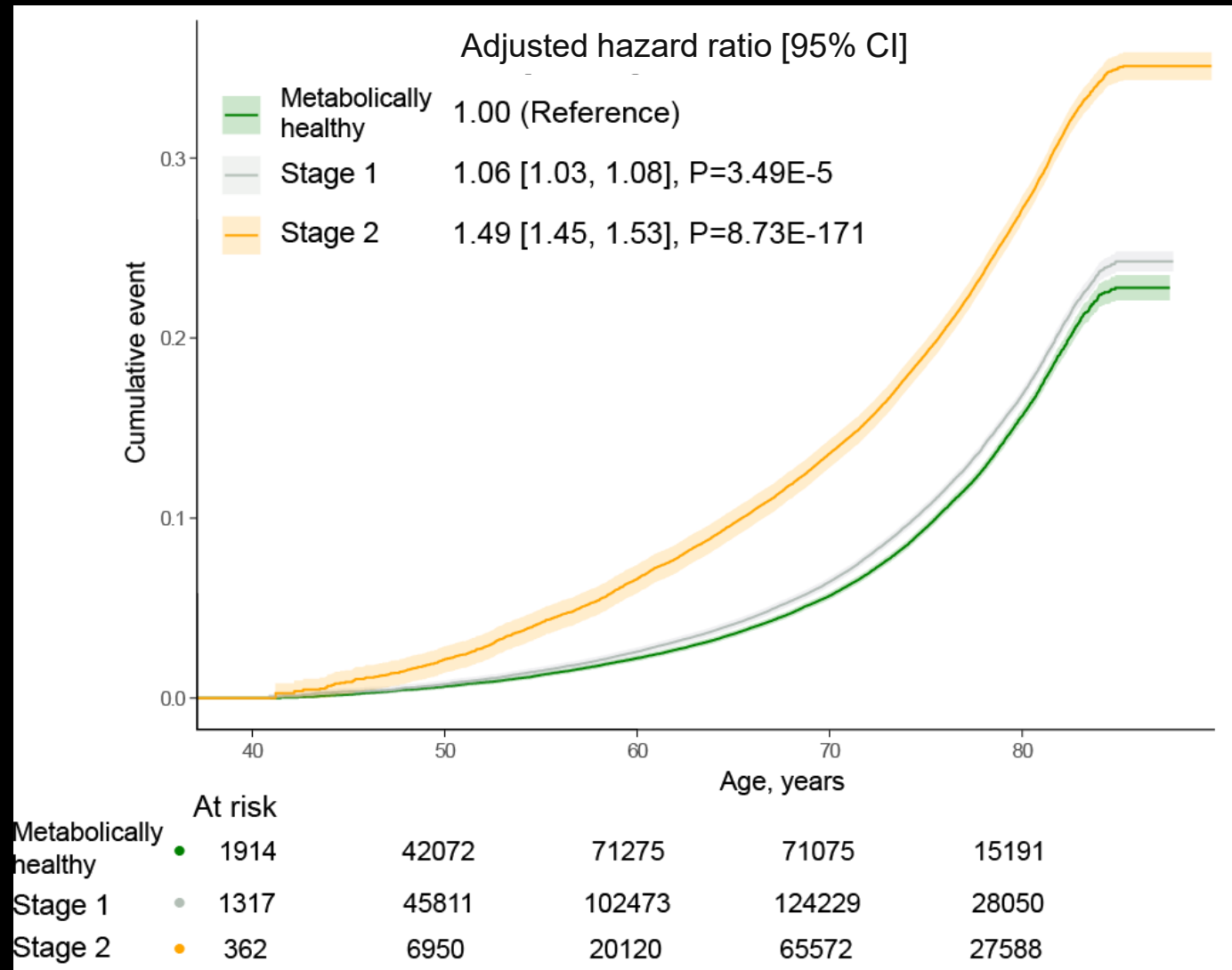


# Defining criteria for systemic metabolic disorder Stage 2





# All-cause mortality with Stage 1 or 2 in UKB participants



**Daniel  
Linden**



**Jussi Pihlajamäki**



Russia

**Nozomu Kono**

Canada



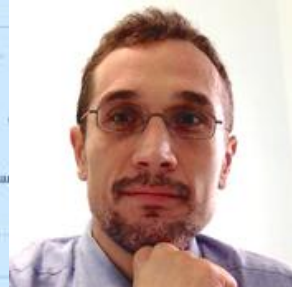
**Université  
de Lille**



**GÖTEBORG  
UNIVERSITY**

UNIVERSITY  
OF EASTERN  
FINLAND

**Francois Pattou**



**Umberto  
Vespasiani Gentilucci**



**Luca Valenti**

FONDAZIONE IRCCS CA' GRANDA  
OSPEDALE MAGGIORE POLICLINICO



UNIVERSITÀ DEGLI STUDI  
DI MILANO

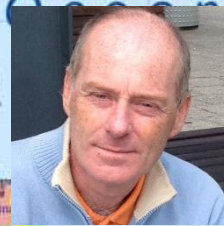


**Antonio De Vincentis**



**UTSouthwestern  
Medical Center**

**Julia Kozlitina**



**Arturo Pujia**



UNIVERSITÀ  
DEGLI STUDI  
DI PALERMO



**Salvatore Petta  
Stefania Grimaudo**

Indian



# The Labs



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novonordiskfonden

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Hjärt  Lungfonden

AstraZeneca 