The Liver Forum

Compensated NASH Cirrhosis: Risk Stratification

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&

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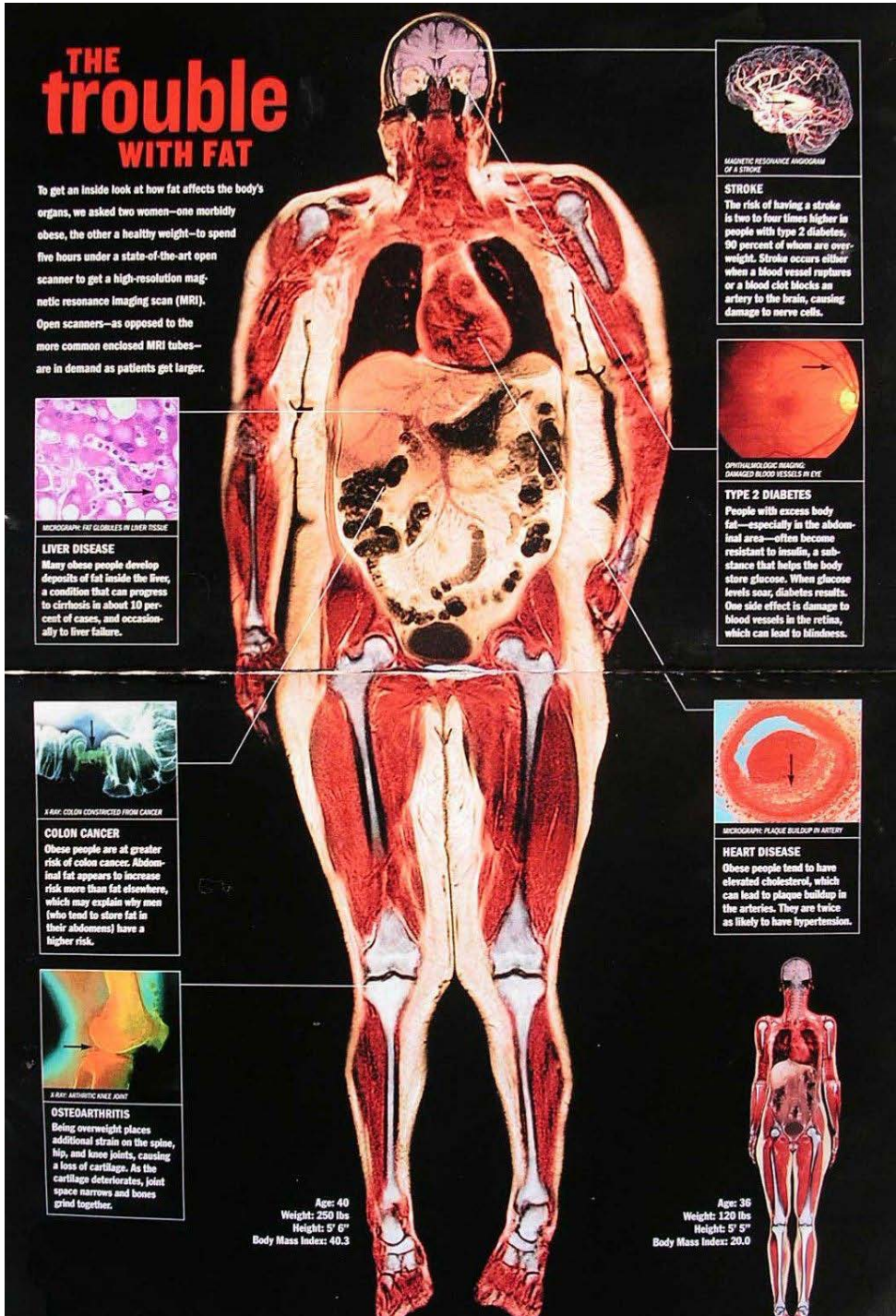
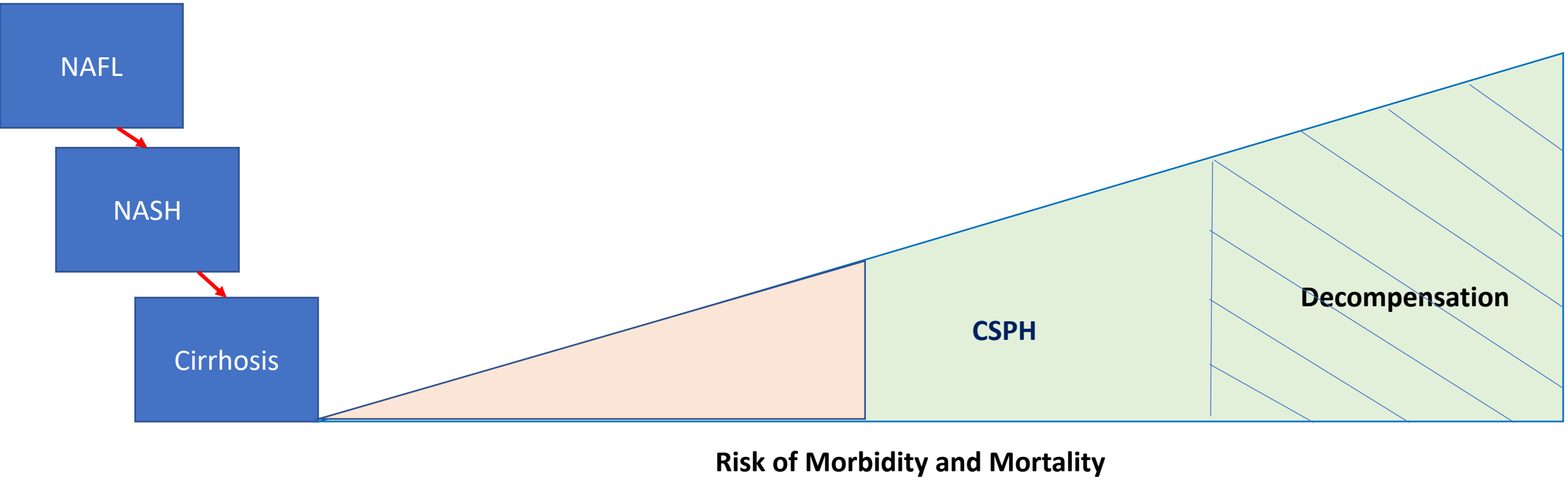
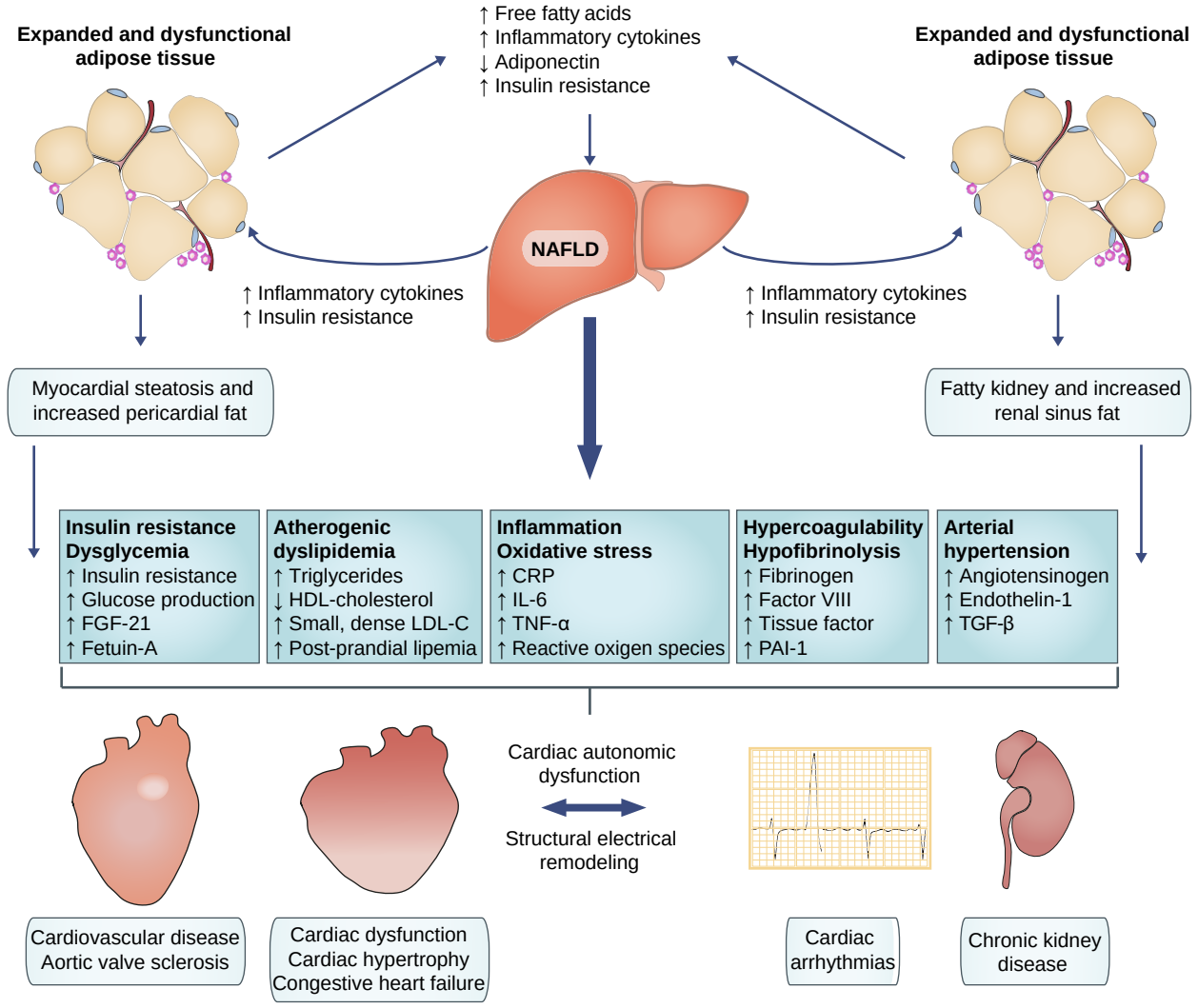


NASH Cirrhosis Risk Stratification: Different Lenses to be Used?

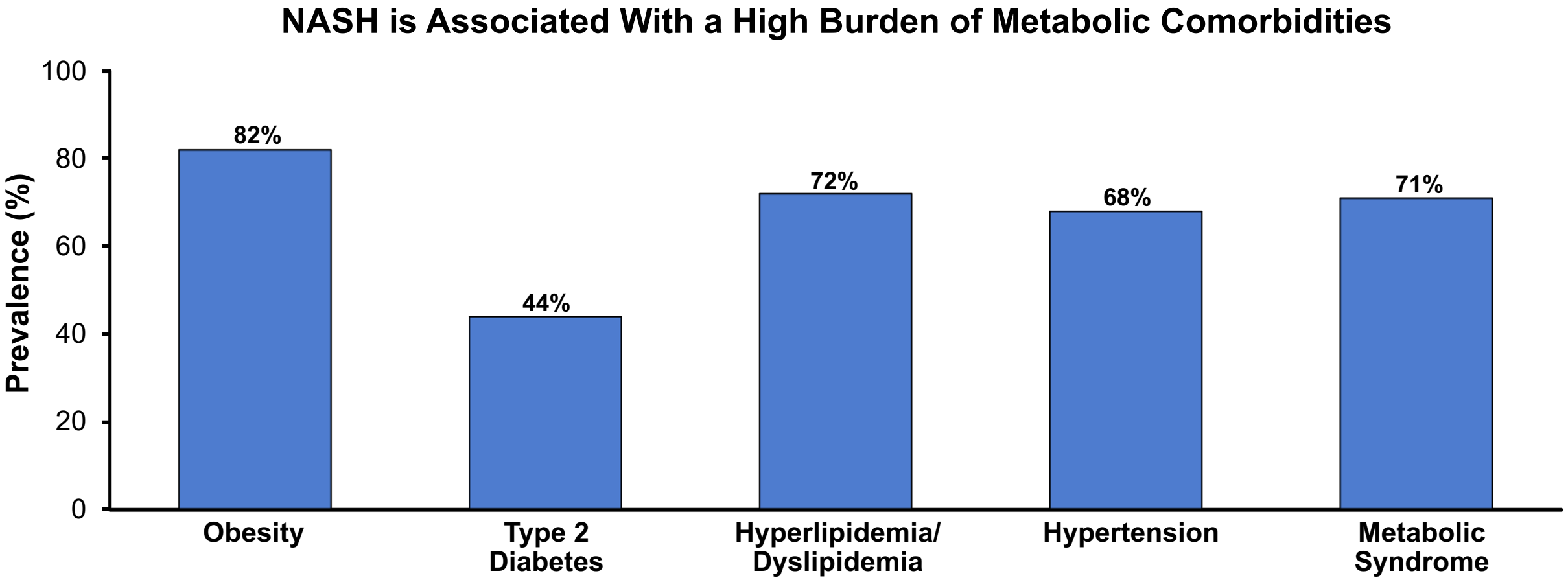


NAFLD A Multisystem Disease



Byrne and Targher; J Hep 2015

Comorbidities Associated With NASH:



Meta-analysis: data from studies that diagnosed NAFLD by imaging (US, CT, MRI/SPECT) and NASH by histology in NAFLD patients.
Number of studies reporting for NASH: obesity (n=4); type 2 diabetes (n=9); hyperlipidemia/dyslipidemia (n=4); hypertension (n=4); metabolic syndrome (n=2).

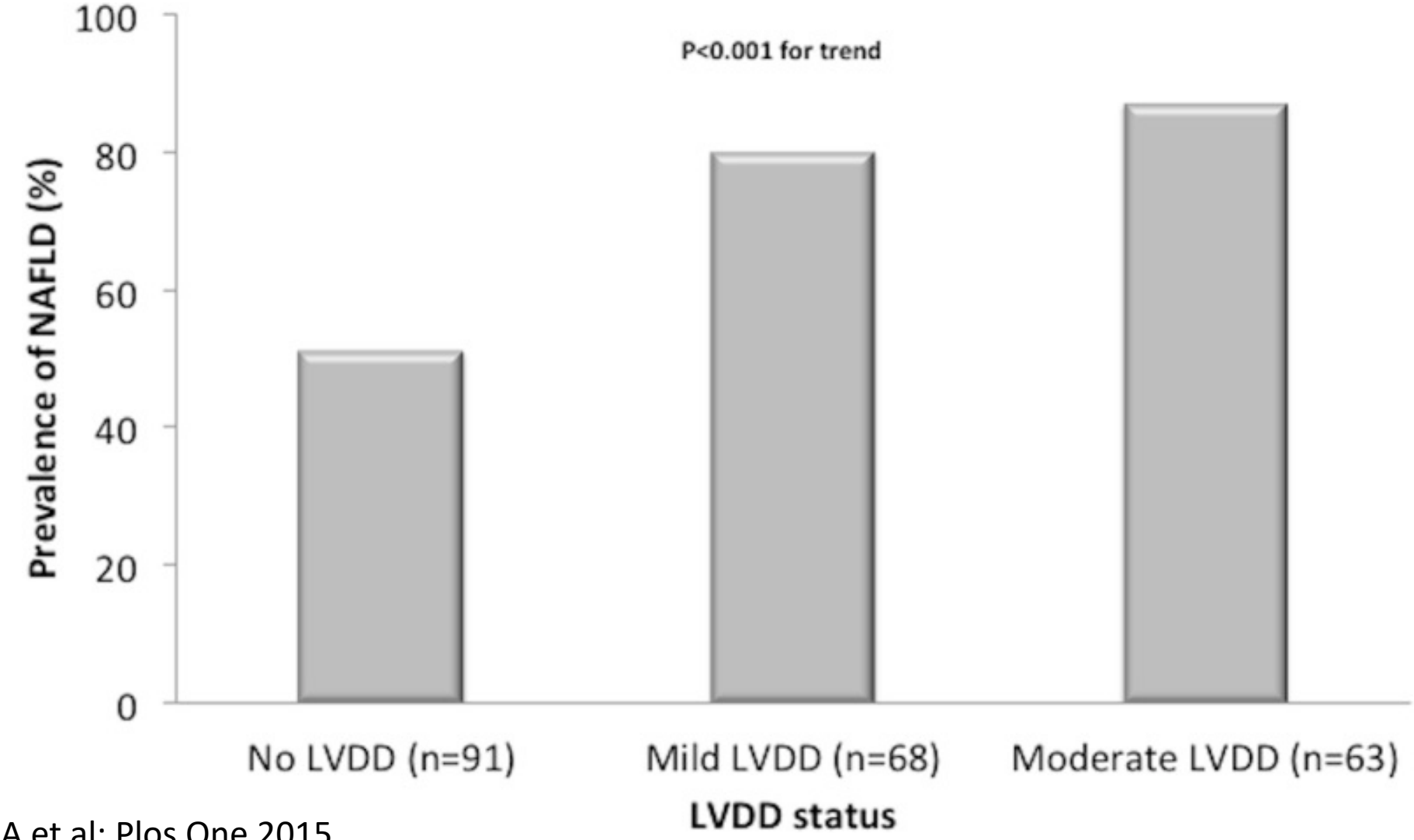
Younossi ZM, et al. *Hepatology.* 2016;64:73-84.

NAFLD and Cardiac Associations

- NAFLD is associated with
  - Endothelial dysfunction
  - Increased carotid artery intima thickness
  - Increased arterial stiffness and elevated coronary calcium scores
  - Coronary artery disease (CAD)
  - Aortic valve sclerosis
  - Cardiac arrhythmias, such as atrial fibrillation
  - Diastolic dysfunction

Byrne et al; J Hep 2015
Targher et al; J Hep 2016
Mantovani A et al; Plos One 2015
Käräjämäki AJ et al; Plos One 2015

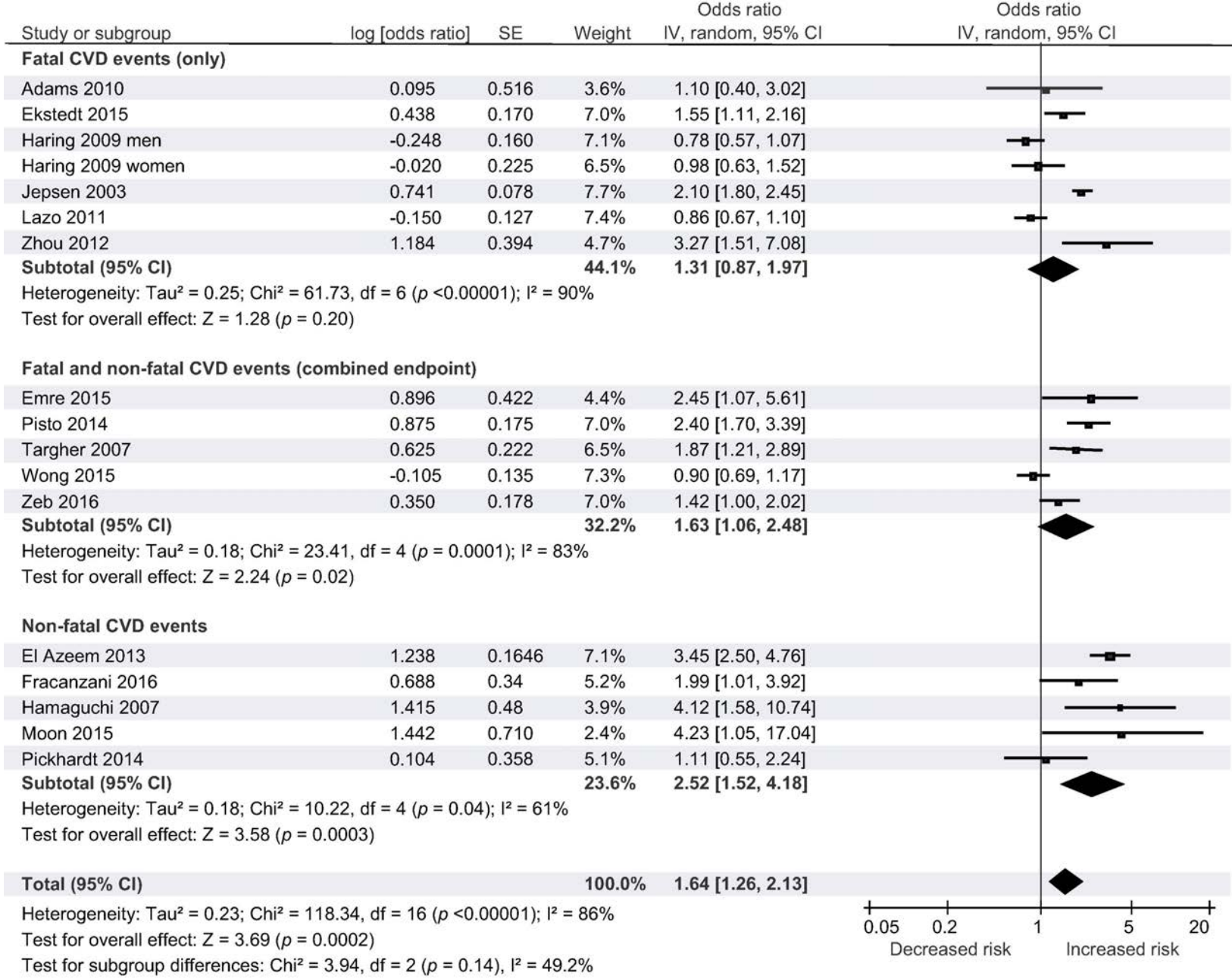
Diastolic dysfunction is three times more common in patients with NAFLD



Mantovani A et al; Plos One 2015

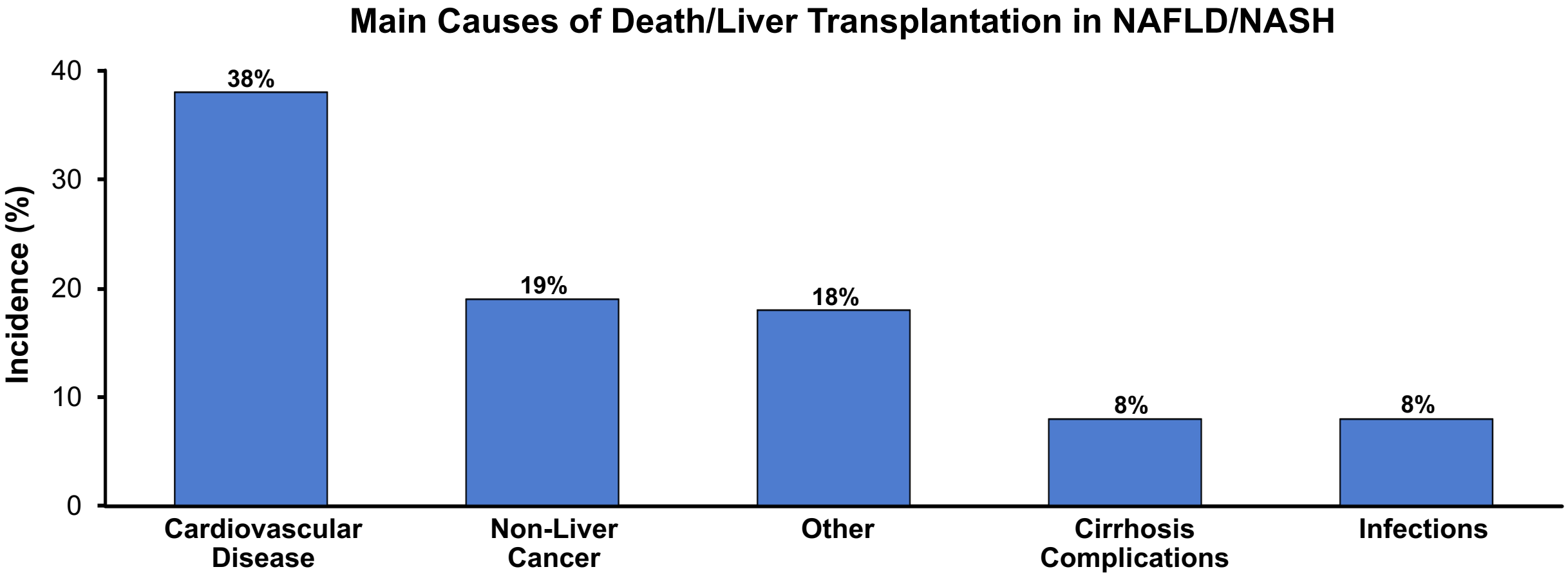
NAFLD is associated with fatal and non-fatal incidence of cardiovascular events

risk appeared to increase with greater severity of NAFLD



Targher et al; J Hep 2016

Cardiovascular Disease Is the Most Common Cause of Death/Liver Transplantation in NAFLD/NASH



PRELHIN: Prognostic Relevance of Liver Histology In NAFLD (retrospective, longitudinal NAFLD/NASH cohort (n=619; 1975-2005) in the US, Europe, and Thailand. Overall mortality/liver transplantation (193/619).

Angulo P, et al. *Gastroenterology.* 2015;149:389-397.

Association of NAFLD with CKD

- Accumulating evidence indicates that the presence and severity of NAFLD is strongly associated with an increased prevalence of CKD
- 20% to 55% , compared to 5–30% in those without NAFLD.
- The presence and severity of NAFLD predicts the development of incident CKD, independent of traditional cardiorenal risk factors
- Despite the growing evidence linking NAFLD to CKD, whether a causal association exists has not been definitively established

Targher et al; Nature Rev Neph 2017
Targher et al, Diab Care 2014

Meta-Analysis: CKD and NAFLD

- A total of 9 observational studies with 96,595 adult individuals (34.1% with NAFLD)
- Predominantly Asian descent, and 4653 cases of incident CKD stage ≥3
- Median of 5.2 years
- Patients with NAFLD had a significantly higher risk of incident CKD than those without NAFLD ([HR] 1.37, 95% CI 1.20–1.53; I2 = 33.5%).
- Patients with more 'severe' NAFLD (according to ultrasonography and non-invasive fibrosis markers) were also more likely to develop incident CKD (HR 1.50, 95% CI 1.25–1.74; I2 = 0%); this risk appeared to be even greater among those with ultrasound- diagnosed NAFLD and a high-intermediate NAFLD fibrosis score (n = 1 study; random-effects HR 1.59, 95% CI 1.31–1.93).

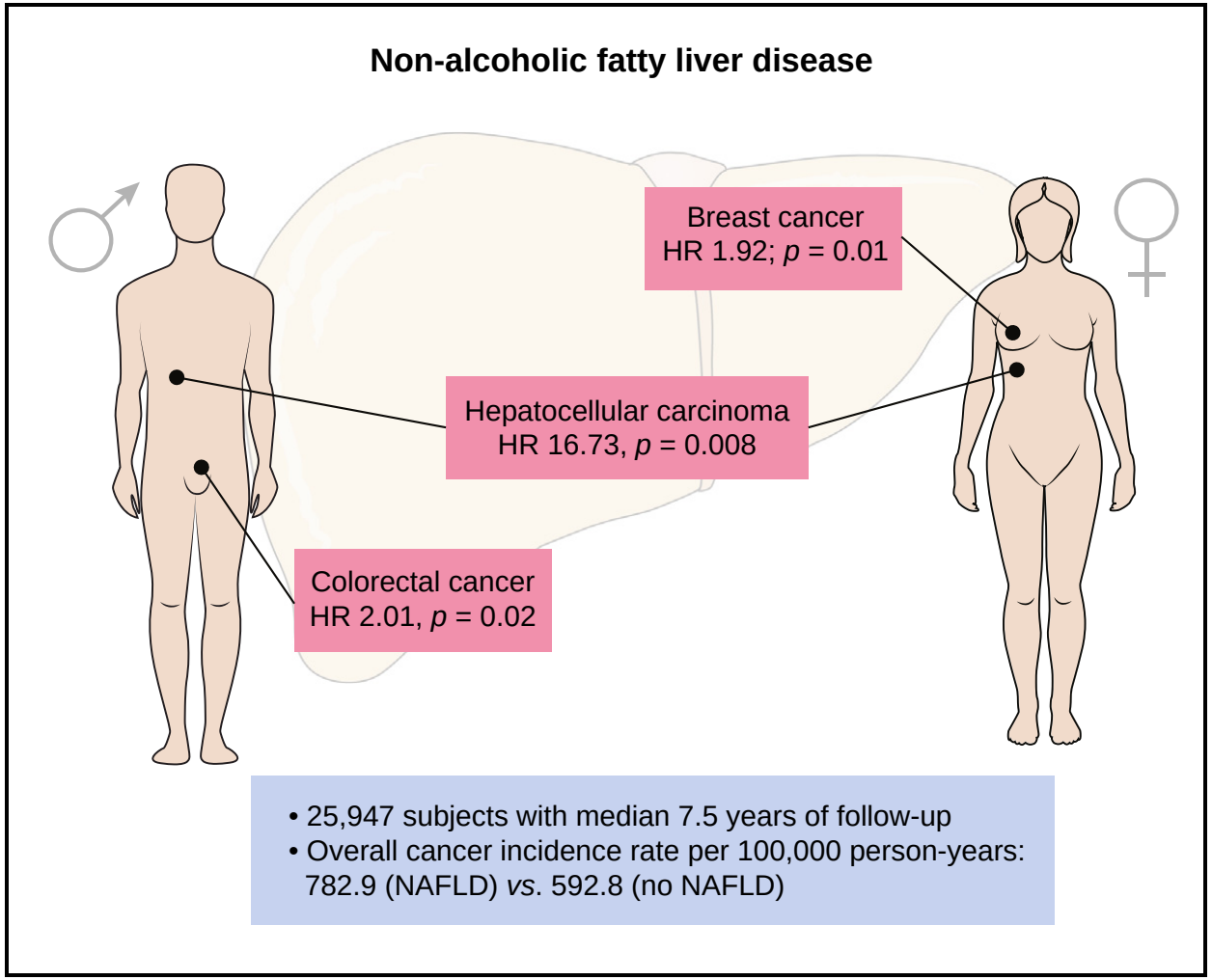
Mantovani et al; Metabolism 2017

In the Context of NASH cirrhosis

- NAFLD is also the most rapidly growing indication for simultaneous liver–kidney transplantation .
- In the US, more than 10% of the adult population (and more than 25% of individuals older than 65 years) have CKD.
- NAFLD and CKD share risk factors
- Hepatorenal syndrome, can develop in cirrhotic patients with portal hypertension.

Singal et al; Transplantation 2016
McCullough, K. et al. Nephrol. Dial. Transplant 2012

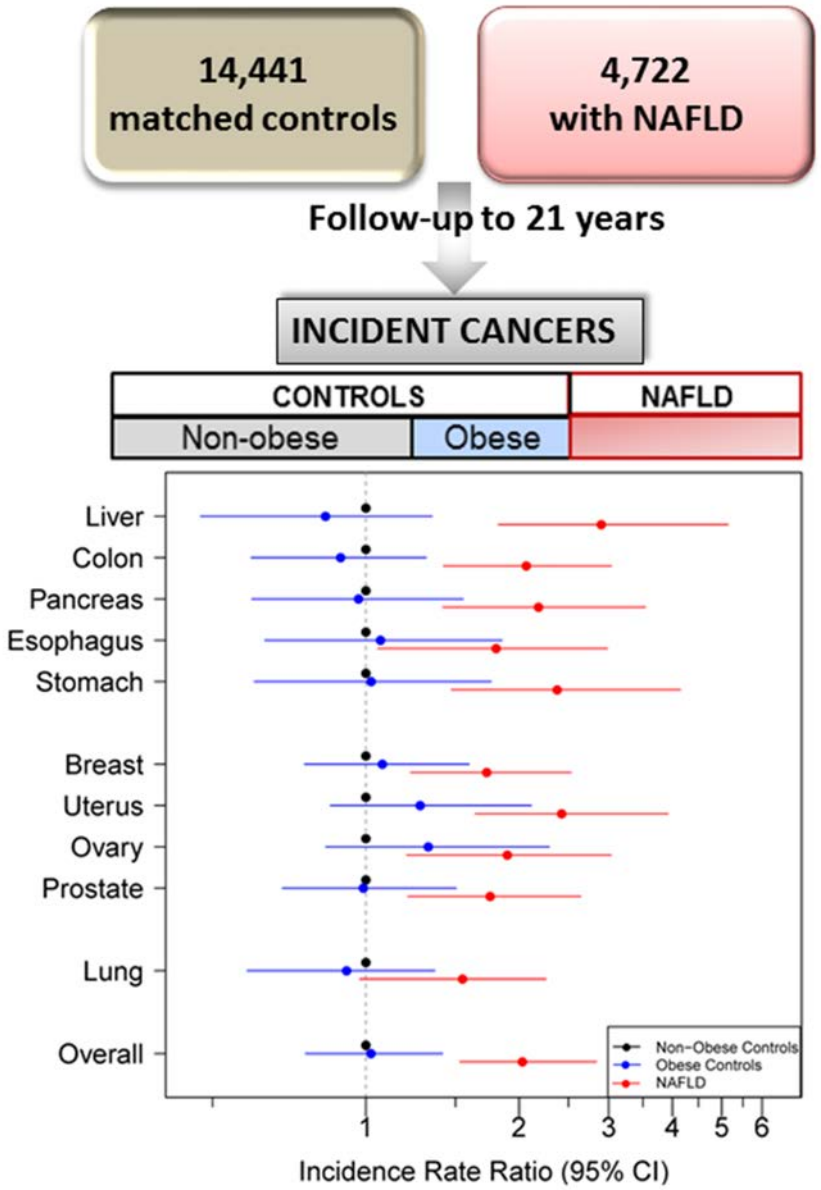
NAFLD & CA



Kim et al; J Hep 2017

NAFLD & CA

- NAFLD was associated with 90% higher risk of malignancy IRR= 1.9 (95%CI 1.3, 2.7).
- The highest risk increase was noted in **liver cancer**, IRR=2.8 followed by **uterine** IRR=2.3 **stomach** IRR=2.3, **pancreas** IRR=2.0 (95%CI 1.2, 3.3) and **colon cancer** IRR=1.8
- In reference to non-obese controls, NAFLD was associated with higher risk of incident cancers (IRR=2.0) while obesity alone was not (IRR=1.0).



Allen et al; J Hep 2019

NAFLD is Associated with Many Other Risk Factors

Common Comorbidities With Established Association

- Obesity
- Type 2 diabetes
- Dyslipidemia
- Metabolic syndrome*
- Polycystic ovary syndrome

Other Conditions Associated With NAFLD

- Hypothyroidism
- Obstructive sleep apnea
- Hypopituitarism
- Hypogonadism
- Psoriasis
- Sarcopenia
- Psychological

*ATP III definition (requires the presence of ≥3 of the following features):
(1) waist circumference >102 cm in men or >88 cm in women; (2) triglyceride level ≥150 mg/dL; (3) HDL cholesterol level <40 mg/dL in men and <50 mg/dL in women; (4) SBP ≥130 mm Hg or DBP ≥85 mm Hg; and (5) fasting plasma glucose level ≥110 mg/dL.

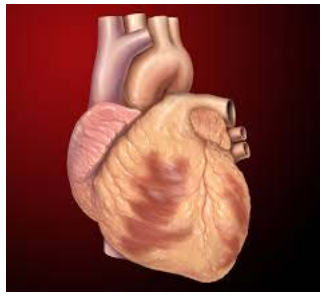
Chalasani N, et al. *Hepatology.* 2018;67:328-357.

Considerations in NASH Cirrhosis Trials

Kidneys

NASH/NAFLD →	NASH (F2) →	NASH with compensated Cirrhosis →	NASH with Decompensated Cirrhosis
Proteinuria	Proteinuria CKD	CKD	CKD ESRD
1) Medications may affect GFR 2) Cr is being used for inclusion/exclusion 3) If GFR is used, cr formulas are usually used	1) Medications may affect GFR 2) Cr is being used for inclusion/exclusion 3) If GFR is used, cr formulas are usually used	1) Medications may affect GFR 2) Cr is being used for inclusion/exclusion 3) If GFR is used, cr formulas are usually used 4) GFR is not accurately calculated in obese/cirrhotics	1) Medications may affect GFR 2) Cr is being used for inclusion/exclusion 3) If GFR is used, cr formulas are usually used 4) GFR is not accurately 5) calculated in obese/cirrhotics 6) Development of HRS 7) Use of diuretics and ascites issues in this population

Considerations in NASH Cirrhosis Trials

	NASH/NAFLD →	NASH (F2) →	NASH with compensated Cirrhosis →	NASH with Decompensated Cirrhosis
Cardiac 	• **Endothelial dysfunction** • **Increased arterial stiffness and elevated coronary calcium scores**	• **Endothelial dysfunction** • **Increased arterial stiffness and elevated coronary calcium scores** • **Diastolic dysfunction** • **Hx of CVD/MIs**	• **Increased arterial stiffness and elevated coronary calcium scores** • **Diastolic dysfunction** • **Hx of CVD/MIs** • **Cirrhosis cardiomyopathy**	• **Increased arterial stiffness and elevated coronary calcium scores** • **Diastolic dysfunction** • **Hx of CVD/MIs** • **Cirrhosis cardiomyopathy**
	1) Cardiac function is not assessed 2) Some medications may worsen lipid profile 3) Some trials exclude patients with history of cardiac events	1) Cardiac function is not assessed 2) Some medications may worsen lipid profile 3) Some trials exclude patients with history of cardiac events	1) Cardiac function is not assessed 2) Some medications may worsen lipid profile) 3) Some trials exclude patients with history of cardiac events	1) Cardiac function is not assessed 2) Some medications may worsen lipid profile 3) Some trials exclude patients with history of cardiac events 4) Development of HPS, PPH…

Examples of Risk Stratification from Similar Systemic Diseases

Kings Criteria used in Obesity

	Stage 0 Normal health	Stage 1 At risk of disease	Stage 2 Established disease	Stage 3 Advanced disease
A) Airway	Normal Neck<43cm	Mild OSA Neck≥43cm Asthma/COPD	Requires CPAP	
B) BMI		35-39.9 kg/m2	40-50 kg/m2	>50 kg/m2
C) CV risk	<10%	10-19%	≥20% Stable CAD	
D) Diabetes	FPG < 5,6 HbA1 < 5,7	IFG HbA1c 5.7-6.4%	DM2 HbA1c < 9%	DM2 HbA1c ≥ 9%
E) Economic complications	None	None	Workplace disadvantage	Disabled
F) Functional Limitation	≥3 h moderate physical activity/week	1-2 h moderate physical activity/week	<1 h moderate physical activity/week	
G) Gonadal Dysfunction	Normal	Hyperandrogenemiac	PCOS	Infertility
H) Health status	Normal	Anxiety/depression without medication	Moderate depression	Severe Depression
I) Image	Normal	Does not like looking in mirror	Avoid mirrors/body image dysphoria	Severe eating disorder

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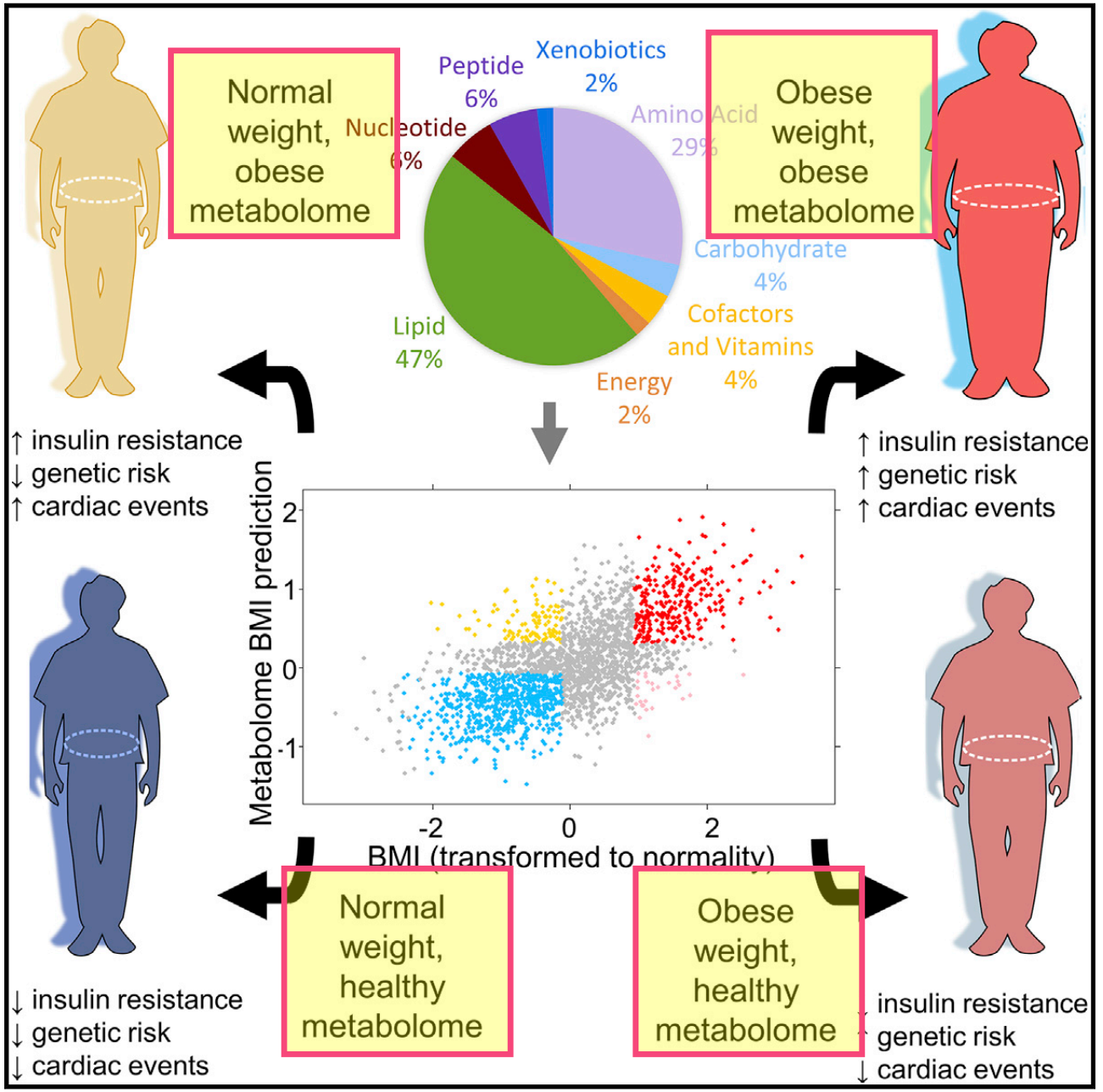
K) Kidney	Normal	GFR <60 mL/min	GFR <30 mL/min	GFR <15 mL/min
M) Malignancies	None	HCC	Others	Metastatic
S) Sarcopenia (need modification)	Normal			SMI < 50 cm2/m2 in men and < 39 cm2/m2 in women)

Obesity is not the Same In ALL

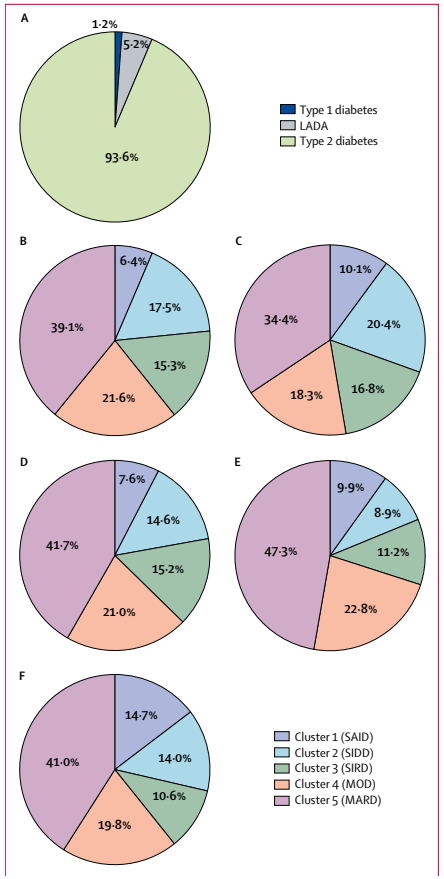
- Obesity is a heterogeneous and complex disease that is imprecisely measured by BMI.
- UK study
- Obesity results in a profound perturbation of the plasma metabolome
- At any given BMI, abnormal metabolomes associate with different health outcomes
- At any given BMI, different genetic obesity risks do not change the metabolome
- A metabolome signature effectively tracks changes in obesity

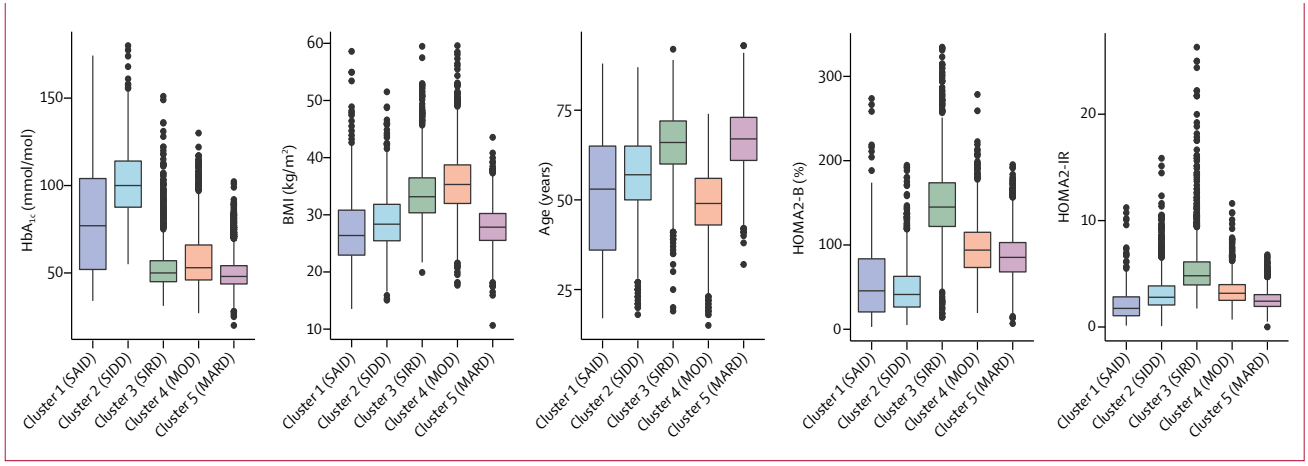


Cirulli et al; Cell Metabolism 2019

Diabetes Cluster Classification

- 8980 from the Swedish All New Diabetics in Scania cohort.
- Clusters were based on six variables
  - (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA_{1c}, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance),
- Related to prospective data from **patient records on development of complications and prescription of medication**.
- Replication was done in three independent cohorts: the Scania Diabetes Registry (n=1466), All New Diabetics in Uppsala (n=844), and Diabetes Registry Vaasa (n=3485).

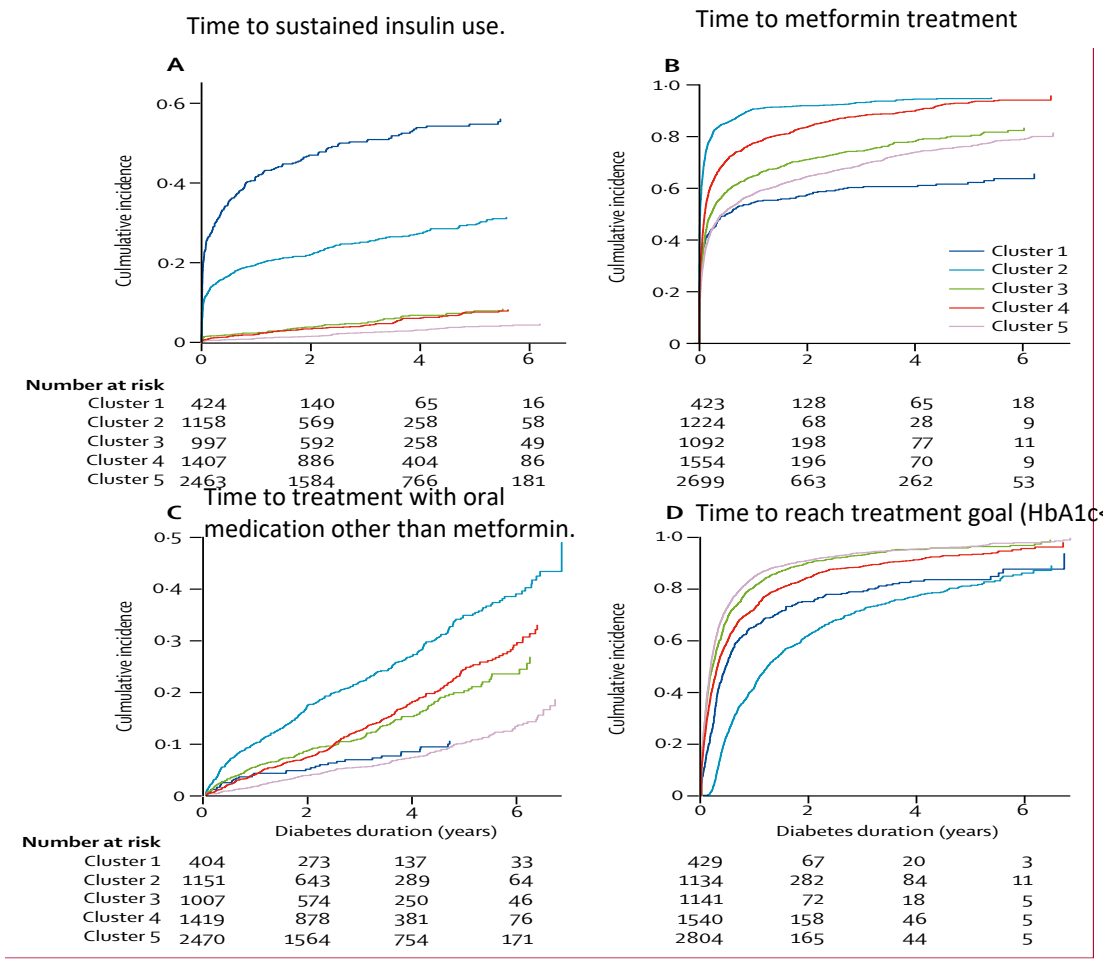




Ahlqvist et al; Lancet Diabetes-Endocrinology 2019

Diabetes Cluster Classification

- Cluster 3 (most resistant to insulin) had significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5, but had been prescribed similar diabetes treatment.
- Cluster 2 (insulin deficient) had the highest risk of retinopathy.
- In support of the clustering, genetic associations in the clusters differed from those seen in traditional type 2 diabetes.



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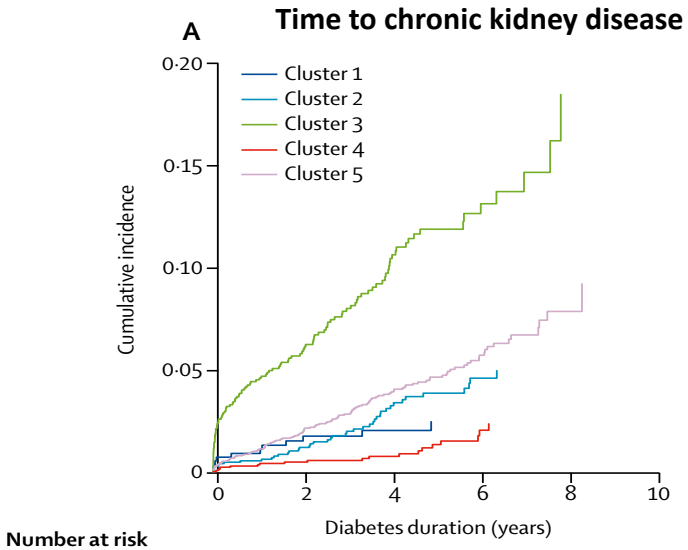
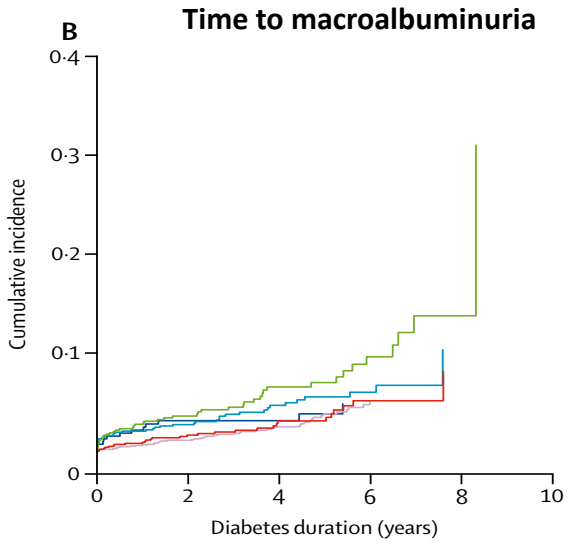
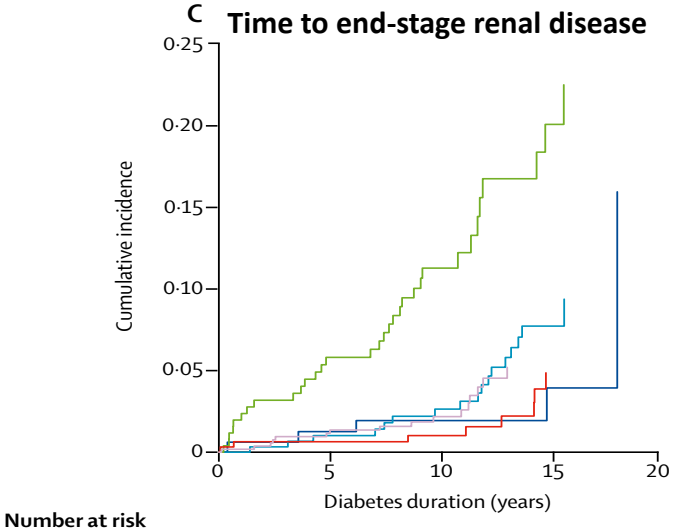


Number at risk

Cluster 1	496	362	220	82	11
Cluster 2	1325	912	511	180	17
Cluster 3	1061	669	337	105	13
Cluster 4	1607	1082	596	206	27
Cluster 5	2880	1968	1128	414	55

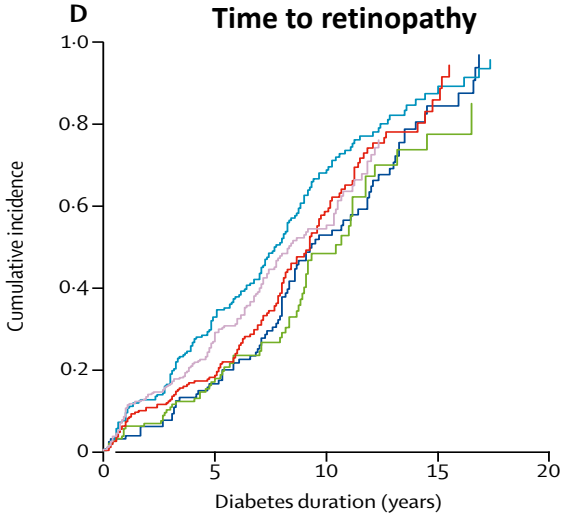


333	213	117	39	5
388	513	266	81	5
664	384	193	62	7
922	546	268	79	7
1665	1034	541	172	16



Number at risk

Cluster 1	158	123	70	22
Cluster 2	298	248	153	40
Cluster 3	239	166	81	21
Cluster 4	307	261	157	43
Cluster 5	514	381	184	42



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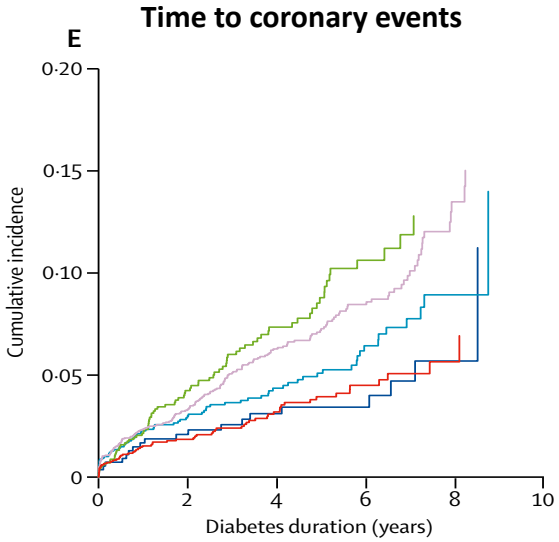
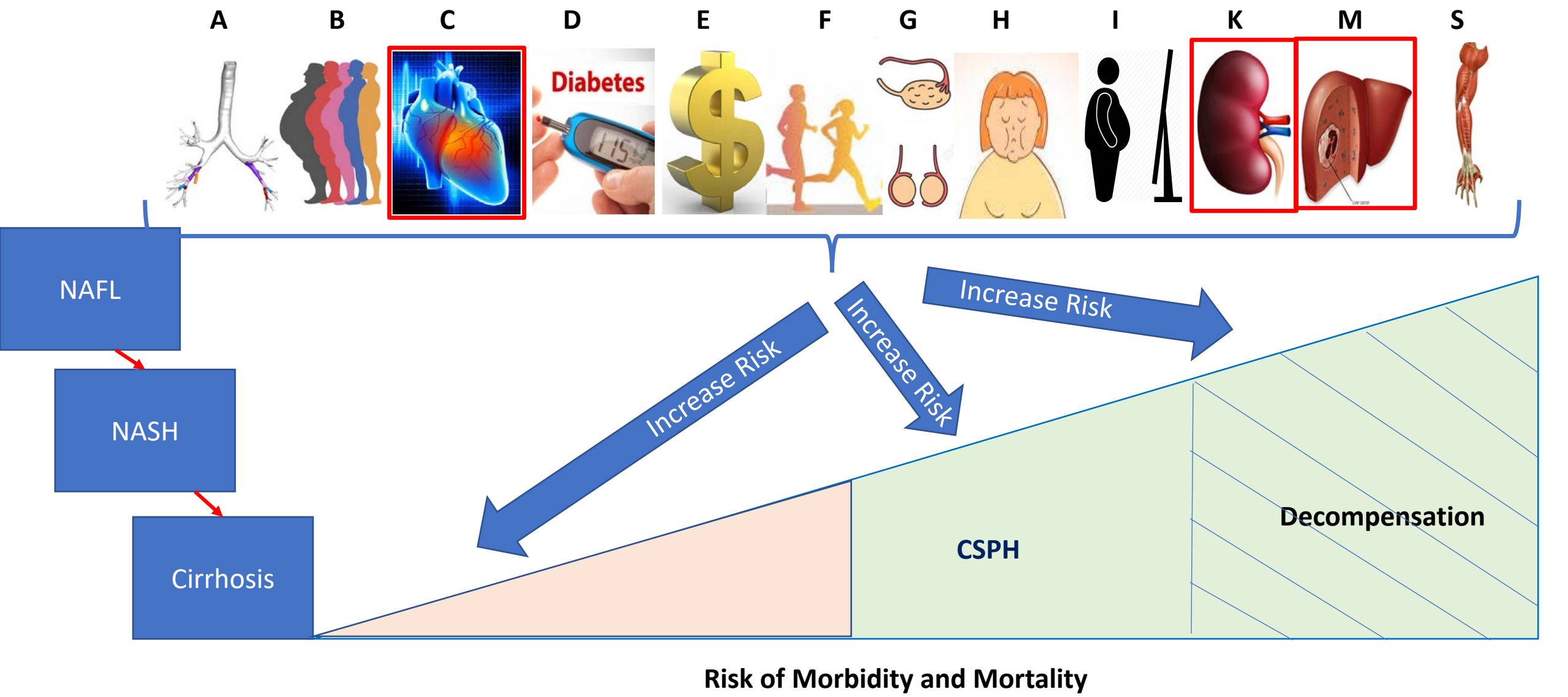


499	376	245	106	16
1325	936	557	215	32
996	658	349	118	20
1594	1115	647	252	43
26415	18450	1095	444	77

The Point to Make

- Other systemic diseases have considered long term complications and response to treatment for risk stratification
- This is logical especially that these complications may worsen the disease course and lead to mortality


A
B
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M
S
Diabetes
NAFL
NASH
Cirrhosis
Increase Risk
Increase Risk
Increase Risk
CSPH
Decompensation
Risk of Morbidity and Mortality

Unmet Needs

- Drugs Development
- NITs

Multisystem Disease

- Risk stratification
- More research

Alina	Allen	Mayo Clinic
Frank	Anania	U.S. Food and Drug Administration
Quentin	Anstee	Newcastle University
David	Assis	Yale University School of Medicine
Jasmohan	Bajaj	Virginia Commonwealth University
Pierre	Bedossa	University of Paris Diderot
Annalisa	Berzigotti	Inselspital, University of Bern
Pascal	Birman	GENFIT SA
Jaime	Bosch	Inselspital, University of Bern
Cliff	Brass	Novartis Pharma AG
Ashley	Brower	Novartis
Dania	Calboli	Novartis Pharma AG
Naga	Chalasani	Indiana University School of Medicine
Jean	Chan	Conatus Pharmaceuticals, Inc.
Edgar	Charles	Bristol-Myers Squibb
Chuhan	Chung	Gilead Sciences, Inc.
Ingrid	Delaet	Intercept Pharmaceuticals, Inc.
Adrian	Di Bisceglie	HighTide Therapeutics
Klara	Dickinson	CymaBay
Lara	Dimick-Santos	U.S. Food and Drug Administration
Judith	Ertle	Boehringer Ingelheim
Gregory	Everson	HepQuant
James	Featherstone	Syneos Health
Claudia	Filozof	Covance
Laurent	Fischer	Allergan
Mikael	Forsgren	AMRA Medical
Sven	Francque	Antwerp University Hospital
Scott	Friedman	Icahn School of Medicine at Mount Sinai
Michael	Fuchs	McGuire VA Medical Center
Guadalupe	Garcia-Tsao	Yale University School of Medicine
Juan	Gonzalez-Abraldes	University of Alberta
Katherine	Barradas	The Forum for Collaborative Research
Hans-Juergen	Gruss	Syneos Health
Mark	Hartman	Eli Lilly
Suneil	Hosman	GENFIT SA
Dean	Hum	GENFIT SA
Joanne	Imperial	Blade Therapeutics
Rajiv	Jalan	University College London
Lijuan	Jiang	Enanta Pharmaceuticals, Inc.
David	Jones	Novartis Pharma AG
Marko	Korenjak	European Liver Patients' Association
Gadi	Lalazar	The Rockefeller University
Lois	Lee	Intercept Pharmaceuticals, Inc.
Olof Dahlqvist	Leinhard	AMRA Medical
Patricia	Lopez	Novartis Pharma AG
Eduardo	Martins	Allergan
Brian	McColgan	Gilead Sciences, Inc.
Sophie	Megnien	Summit Clinical Research
Ruby	Mehta	U.S. Food and Drug Administration
Peter	Mesenbrink	Novartis Pharmaceuticals
Veronica	Miller	The Forum for Collaborative Research
Andrea	Mospan	TARGET PharmaSolutions
Rob	Myers	Gilead Sciences, Inc.
Mazen	Noureddin	Cedars Sinai Medical Center
Stephanie	Omokaro	U.S. Food and Drug Administration
Marcos	Pedrosa	Novartis Pharma AG
Veronica	Pei	U.S. Food and Drug Administration
Margaret	Powell	TARGET PharmaSolutions
Vlad	Ratziu	Hôpital Pitié Salpêtrière
Arie	Regev	Eli Lilly
Robert	Riccio	Syneos Health
Gerardo	Rodriguez	Allergan
Arun	Sanyal	Virginia Commonwealth University
Elmer	Schabel	BfArM
Suna	Seo	U.S. Food and Drug Administration
Sudha	Shankar	Medimmune/AstraZeneca
David	Shapiro	Intercept Pharmaceuticals, Inc.
Mohammad Shadab	Siddiqui	Virginia Commonwealth University
Claude	Sirlin	University of California, San Diego
Alastair	Smith	Syneos Health
Peter	Szitanyi	Charles University
Mette	Thomsen	Novo Nordisk
Peter	Traber	Alacrita Consulting
William	Treem	Takeda Pharmaceuticals
Raj	Vuppalanchi	Indiana University School of Medicine
Christian	Weyer	Intercept Pharmaceuticals, Inc.
Robert	White	Novartis Pharma AG
Jose	Willemse	Dutch Liver Patients Association

Thank you