

Epidemiologia e storia naturale della NAFLD

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DISCLOSURE

IL SOTTOSCRITTO DICHIARA DI AVER
RICEVUTO NEGLI ULTIMI 2 ANNI I SEGUENTI
CONTRIBUTI :

- ✓ Per partecipazione e Corsi/Congressi :
 - ✓ Falk
 - ✓ Takeda
 - ✓ AbbVie
- ✓ Consulente per :
 - ✓ Nutrilinea srl Milan
 - ✓ Ideogen SA Svizzera

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

DEFINITION: IS TIME TO CHANGE NOMENCLATURE ?

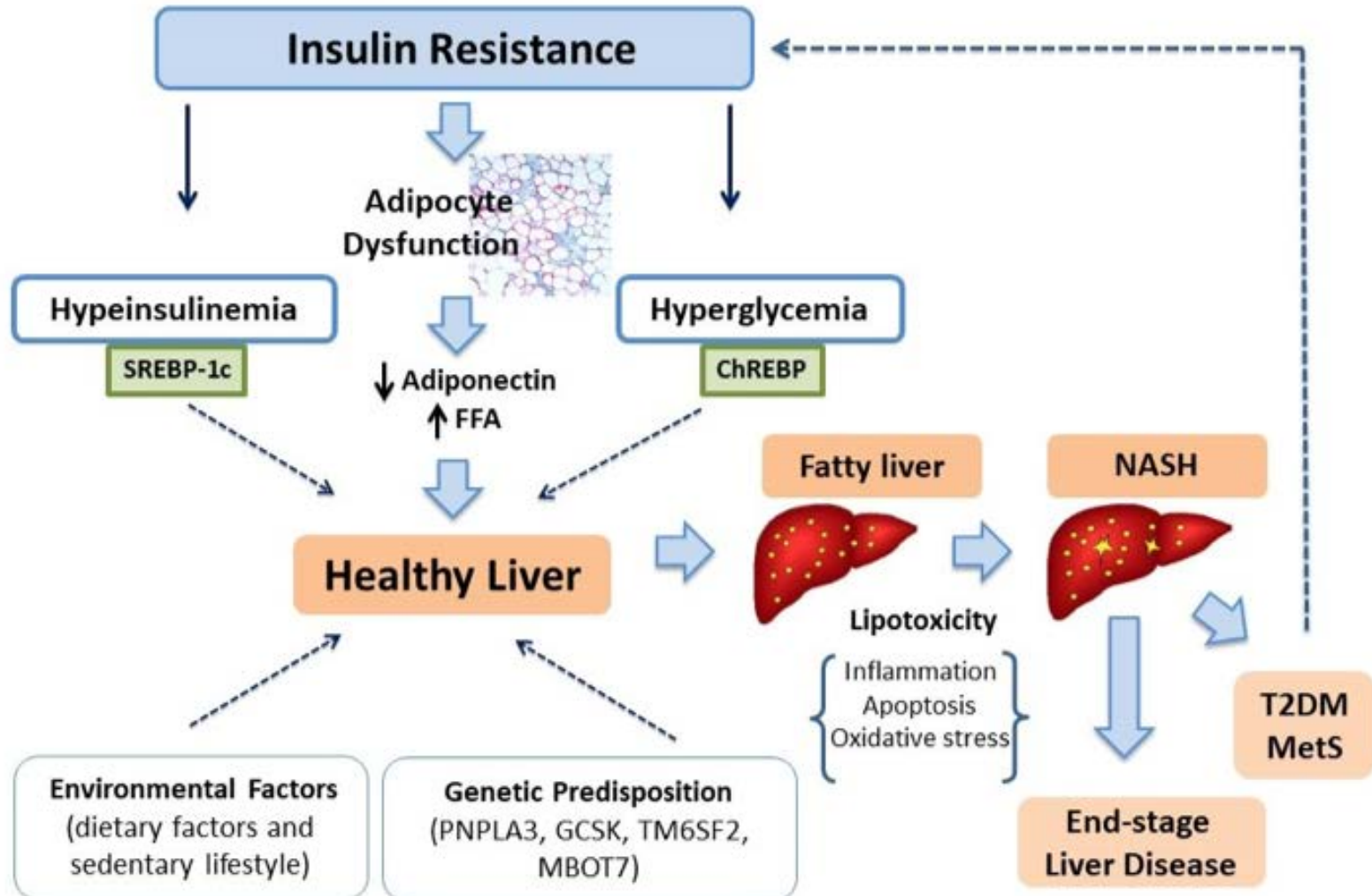
- From a «negative» to a «positive» definition
- Now NAFLD has a negative definition and is considered the hepatic manifestation of the Metabolic Syndrome
- NAFLD/NASH are associated to Metabolic Diseases such as T2DM, Obesity, dislipidemia, etc.
- We think that the definition and classification of primary NAFLD/ NASH must be revised and associated with the metabolic changes in the liver: MAFLD could be the right acronym, but a large consensus conference involving the main Scientific Societies.

- Bellentani S, Tiribell C. Lancet Gastroenterol Hepatol. 2017;2:547-548:
- Ana Ruth Araújo et al. Liver International. 2018;38(Suppl. 1):47–51.

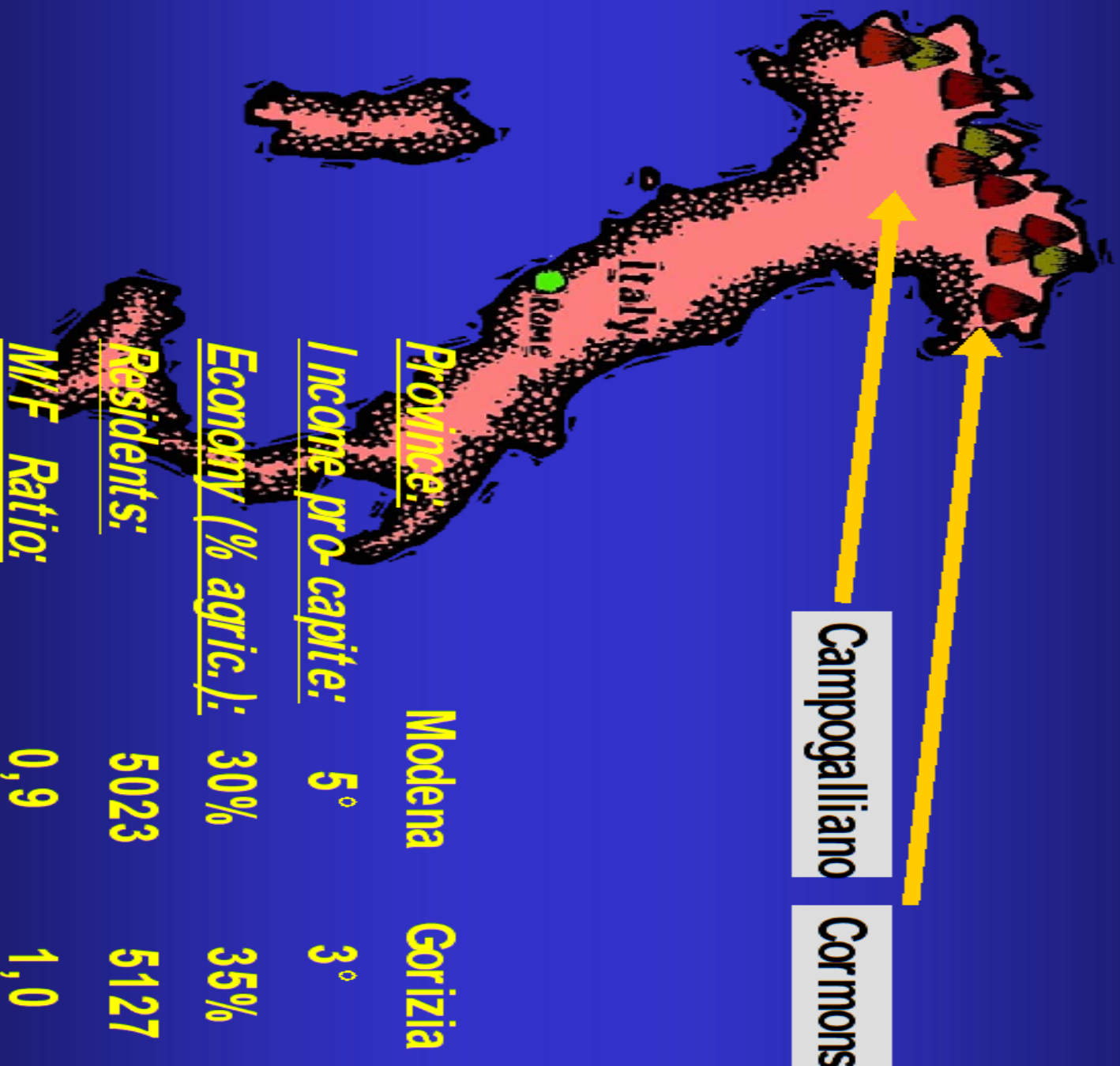
ARE WE READY TO CHANGE FROM A NEGATIVE DEFINITION (=NAFLD) TO A POSITIVE ONE (=MAFLD) ?

An International Consensus event is needed with these priorities :

Change the name from NAFLD/NASH to MAFL/MASH
(Metabolic Associated Fatty Liver and Metabolic
Associated Steato Hepatitis) ?
or simply Dis-metabolic Chronic Hepatitis (DCH).



The Dionysos Project



Studio Nutrizione e Fe (2005)

Nella popolazione generale di Campogallia

- La prevalenza di FL in soggetti appar
sani con alterazione degli enzimi epa
Italia è molto elevata (43-58%)
- La prevalenza della NAFLD è simile
con (25%) o senza (20%) sospetta ep
(transaminasi alterate)
- Il 50% dei casi di NAFLD viene pers
come criterio di screening l'alterazio
transaminasi

La prevalenza della NAFLD nei pazienti con
Sindrome Metabolica, Diabete Mellito, Obesità
e' almeno il doppio che nella popolazione
generale

Studio Nutrizione e Fegato (2005)

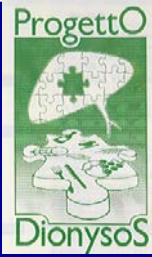


➤ L'alterazione delle ALT, la circonferenza fianchi e l'alterazione delle HDL non sono fattori predittivi di NAFLD

➤ Obesità, iperglicemia, iperinsulinemia, ipertrigliceridemia e la ipertensione arteriosa sistolica (cioè: “La sindrome metabolica”) sono fattori di rischio indipendenti per la NAFLD vs fegato normale

➤ Il sesso maschile e il rialzo delle GGT sono fattori di rischio indipendenti per AFLD vs NAFLD ma non per NAFLD vs fegato normale

Italy: The Dionysos Study



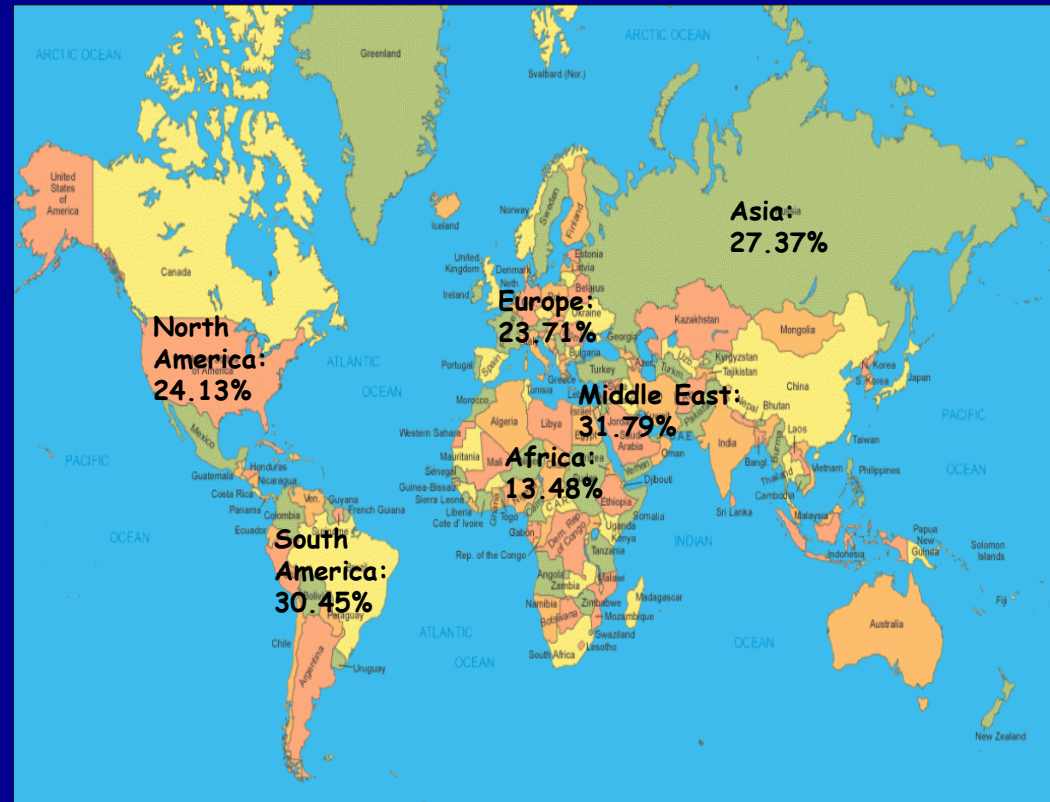
	<i>Condition Prevalence</i>	<i>Liver disease Prevalence</i>	
		<i>Among exposed</i>	<i>General Population</i>
HCV	3,2% (221/6917)	50% (110/221)	1,6% (110/6917)
HBV	1,2% (83/6917)	25% (21/83)	0,3% (21/6917)
Alcohol*	21% (1349/6917)	5,5% (74/1349)	1,1% (74/6917)
NAFLD	25% (1729/6917)	7,9-11,9% (138-207/1729) estimated	2-3% (138-207/6917) estimated

*Risk threshold for developing liver disease (> 30 gr/day x both sexes)

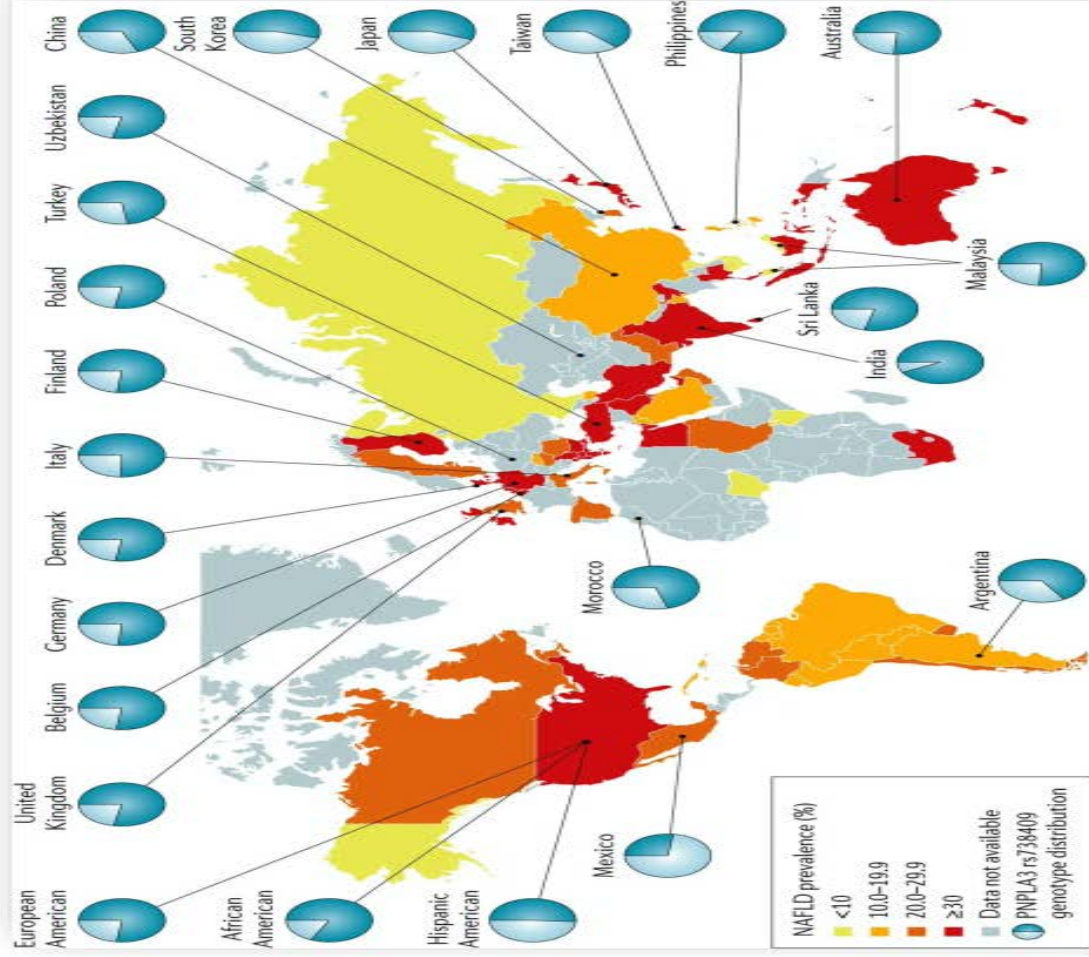
Bellentani S et al, Dig Dis 2010
 Bedogni G et al, Hepatology 2005
 Bellentani S et al, Gut 1999
 Bellentani S et al, Gut 1997
 Bellentani S et al, Hepatology 1994

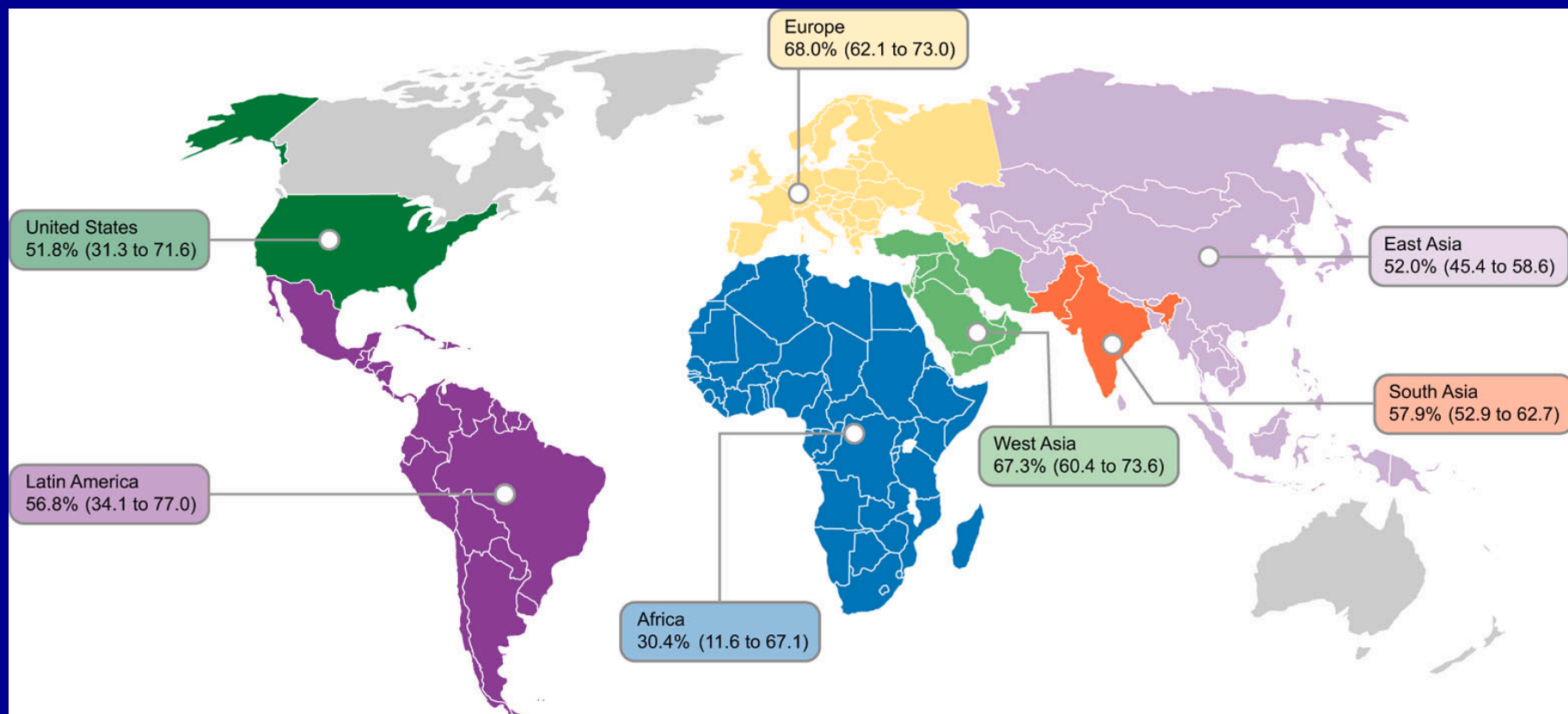
THE GLOBAL PREVALENCE OF NAFLD

- Pubmed and MEDLINE databases were searched from 1989-2015 for terms involving epidemiology and progression of NAFLD.
- Out of 729 studies, 86 were included with a sample size of 8,515,431 from 22 countries
- Global prevalence of NAFLD is **25.24% (22.10-28.65)** with highest prevalence in Middle East and South America and lowest in Africa



NAFLD affects one quarter of the global population

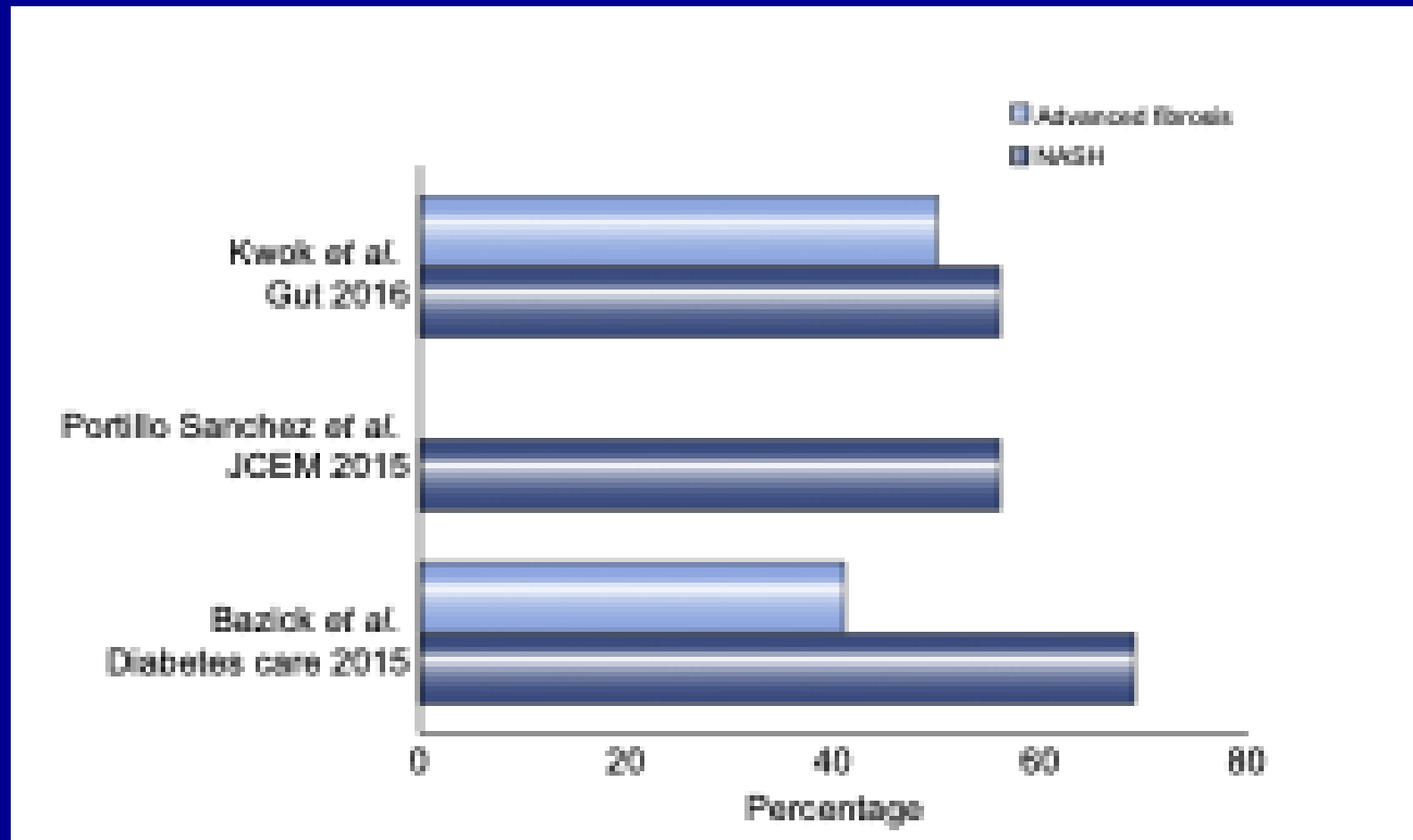




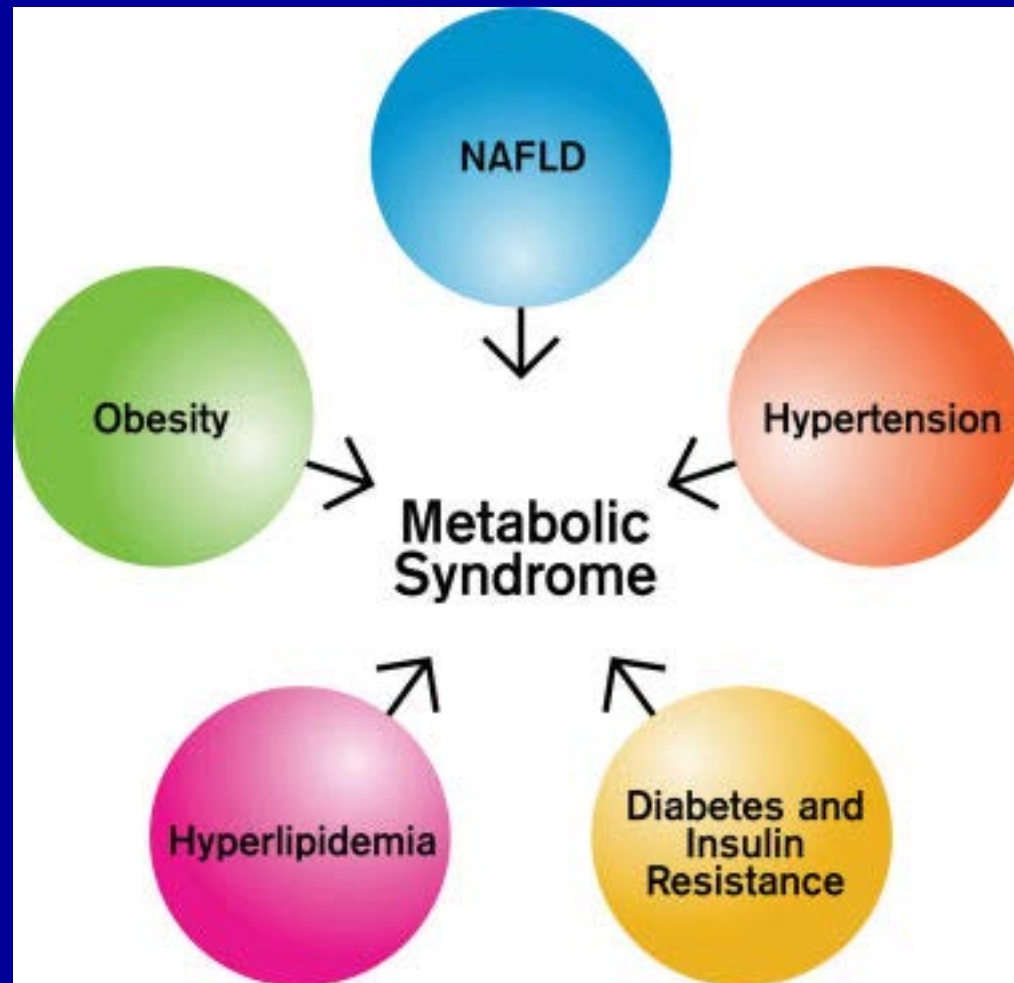
**Global prevalence of NAFLD among T2DM patients 55.5%
(95% confidence interval: 47.3-63.7)**

Younossi et al. J of Hepatology, 2019

PREVALENCE OF NASH AND ADVANCED FIBROSIS IN T2DM



Components of the Metabolic Syndrome



Moieties of NAFLD/NASH

Primary NAFLD

Secondary NAFLD

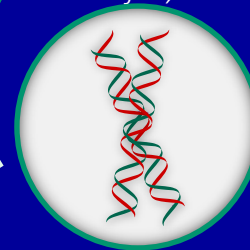


Insulin Resistance



Drugs:

Steroids,
Amiodarone,
Tamoxifen, etc.



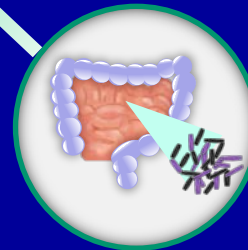
Metabolic or genetic alterations:

Lipodystrophy, LAL-D defic.
Dysbetalipoproteinemia,
Weber-Christian disease,
PNLPAA3 & TM6SF2



Nutritional:

TPN
Rapid weight loss
Bariatric surgery
Starvation



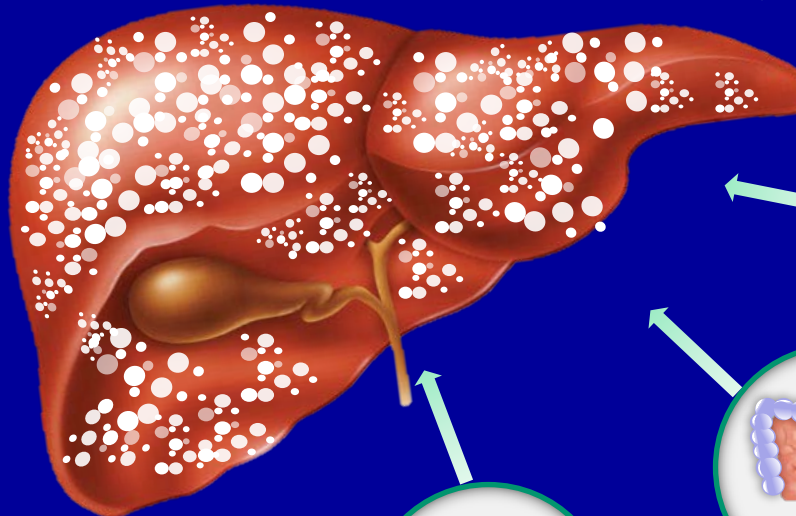
Small bowel diseases:

IBD
Bacterial overgrowth

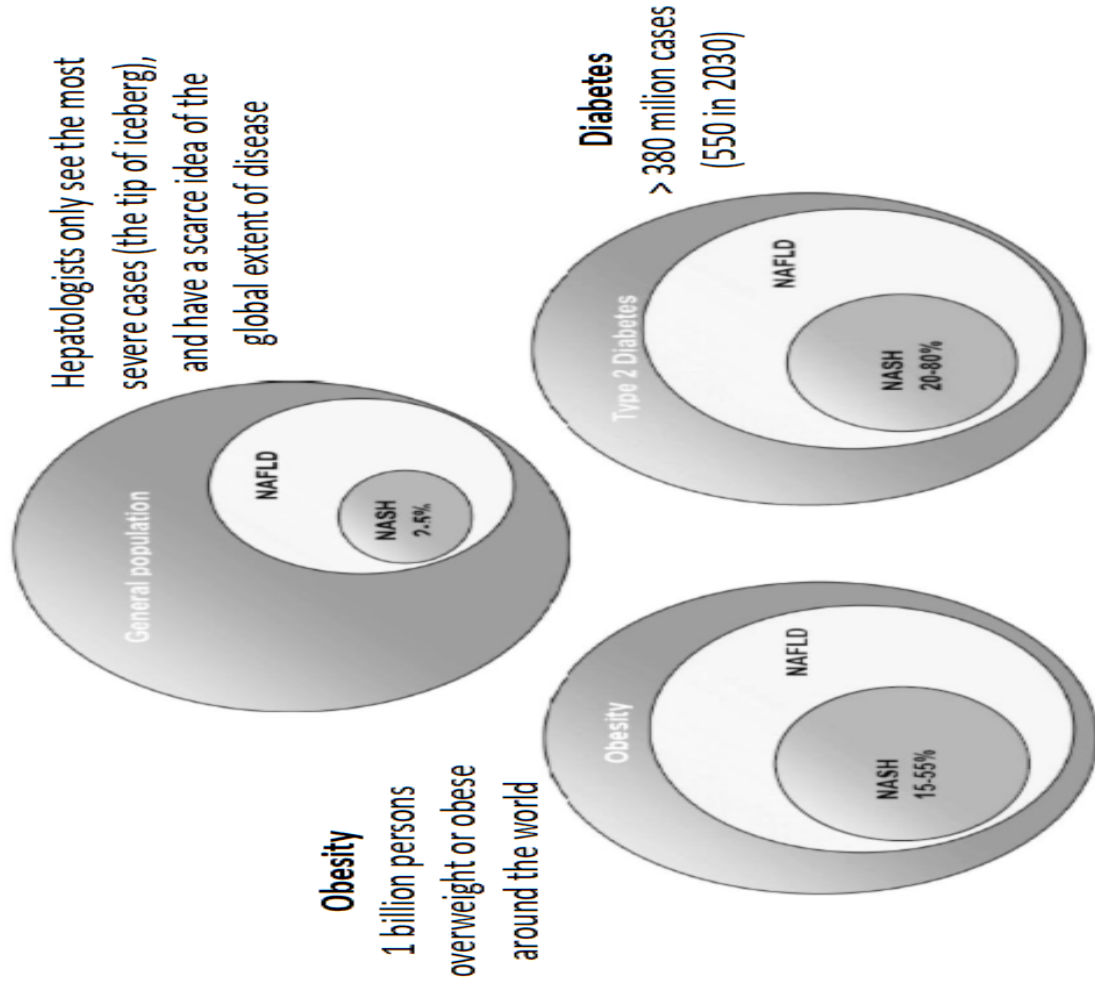


Environmental hepatotoxins:

Petrochemicals



NAFLD - The dimension of the problem

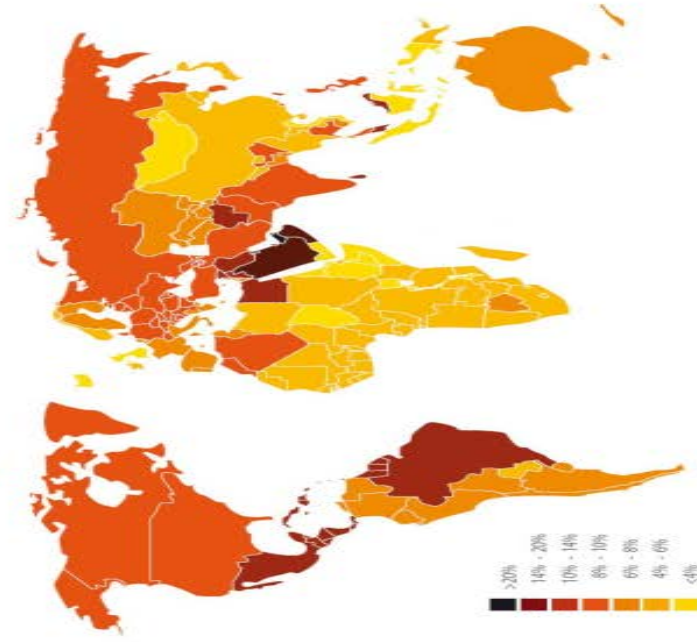


BHALLA et al, Curr Pharma Des 2013;19:5:69-

Diabetes in 2010

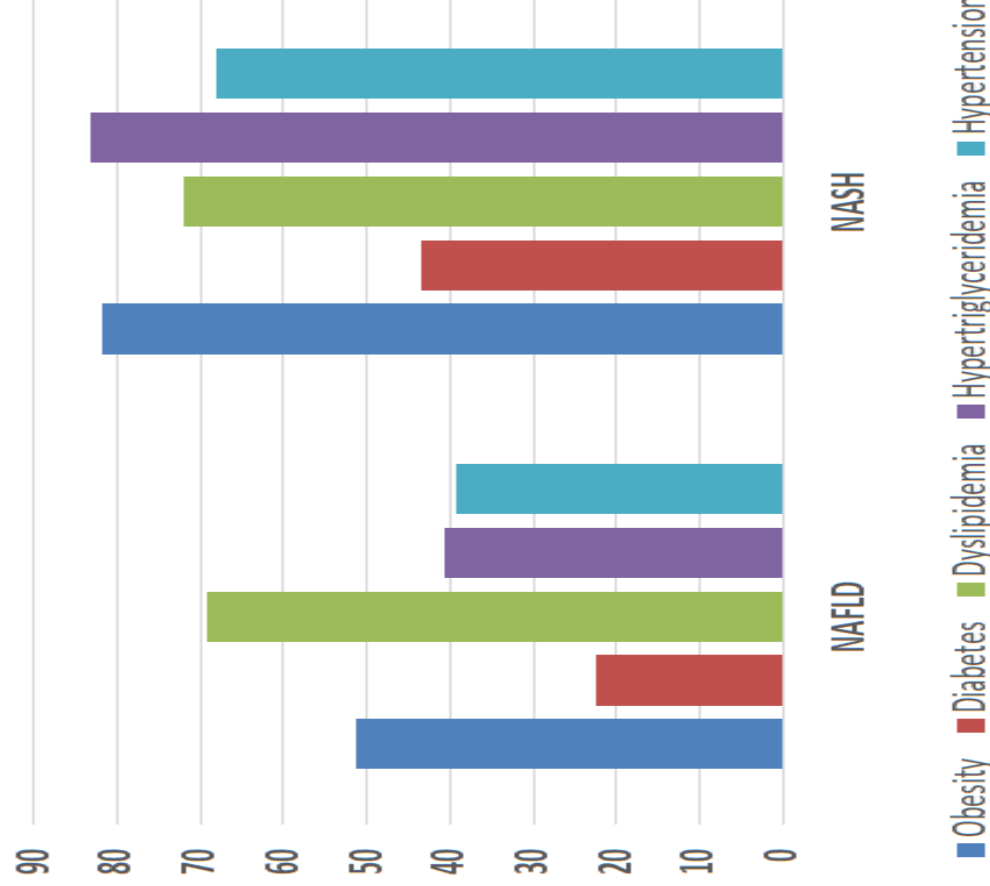


Diabetes in 2025



Proportion of patients with features of the metabolic syndrome among NAFLD vs. NASH cases

A meta-analytic assessment of prevalence, incidence, and outcomes



YOUNOSSI et al, Hepatology 2016;66:73-

PREVALENCE OF NAFLD IN T2DM

A recent meta-analysis by Younossi *et al.* including 80 observational studies for a total of nearly 49,500 individuals with T2DM (mean age: 58 years; mean body mass index: 28 kg/m²; percentage of men: 53%) shows:

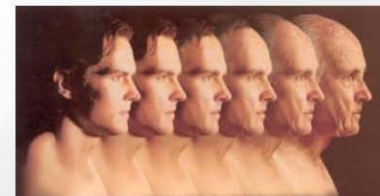
- Prevalence of NAFLD in patients with type 2 diabetes mellitus is more than 2-fold higher than in the general population
- The overall prevalence of **NAFLD** was approximately **55%**, the global prevalence of **NASH** was **37%**, and the prevalence of **advanced fibrosis** was **17%**.

Younossi et al. J of Hepatology, 2019

Gruppi ad alto rischio

ANZIANI

46%



Popolazione di 65 anni e più



13.219.074



21,7%
rispetto a
popolazione
totale



20.007.068



32,6%
rispetto a
popolazione
totale



Speranza di vita a 65 anni



#over65

Stili di vita e salute

Persone di 65-74 anni, valori percentuali anno 2014

In buona salute	36,2 44,0
Con almeno una malattia cronica	78,3 73,6
Consumatori di farmaci	76,9 75,0
Svolgono attività fisica con continuità	9,2 11,2
In sovrappeso	40,9 52,8
Consumano alcolici fuori pasto	7,2 29,2
Fumatori	9,4 16,4
Consumano 5 o più porzioni al giorno di verdure, ortaggi o frutta	5,6 4,8



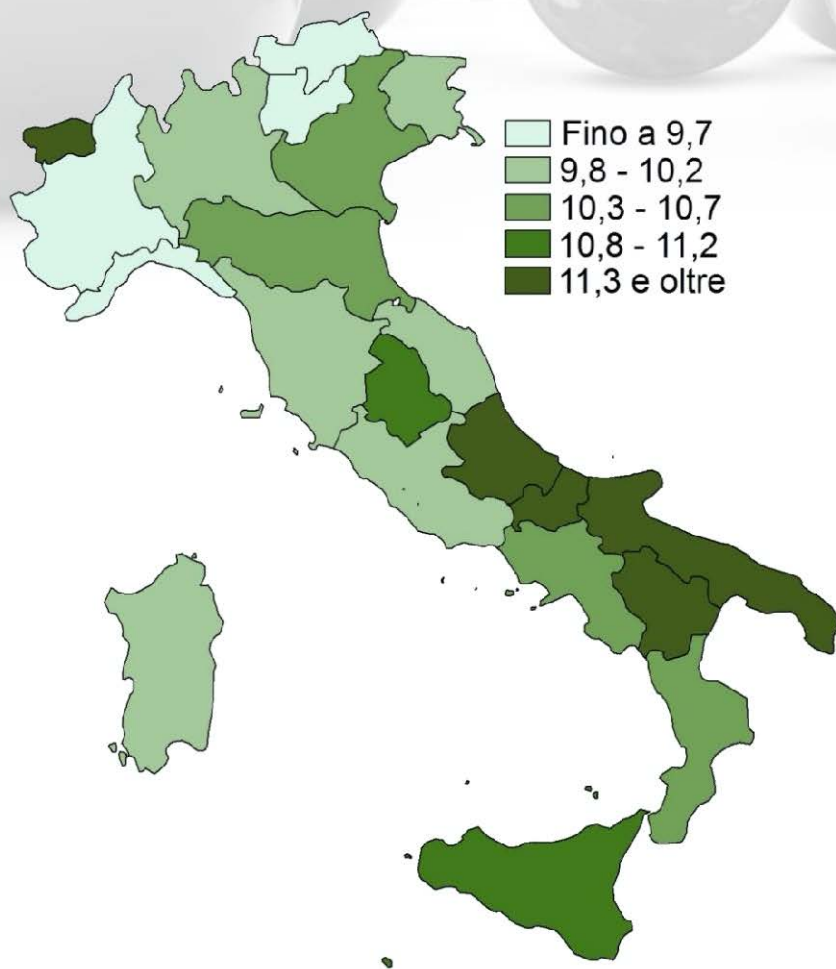
Donna Uomo

Dati ISTAT 2015

Gruppi ad alto rischio

OBESI

85%



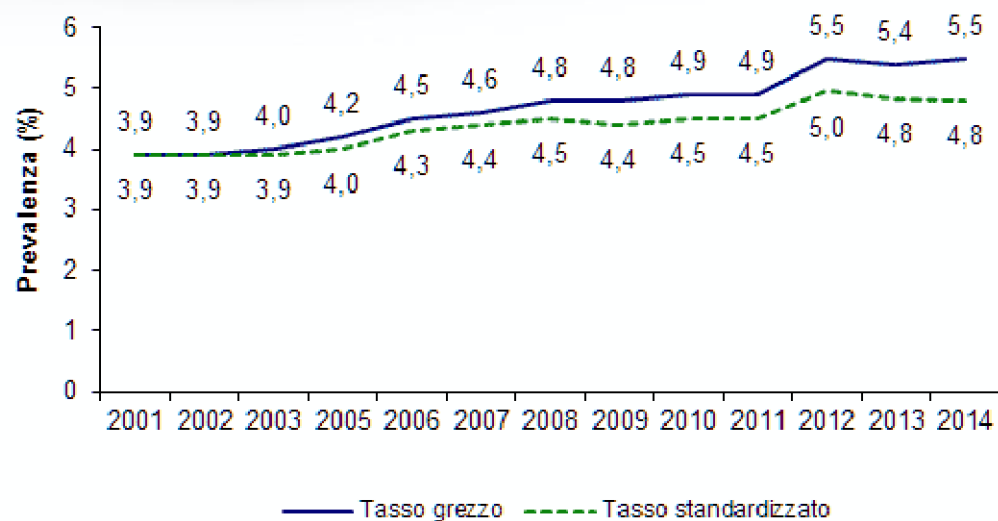
Dati ISTAT 2013

Italia = 10.3%

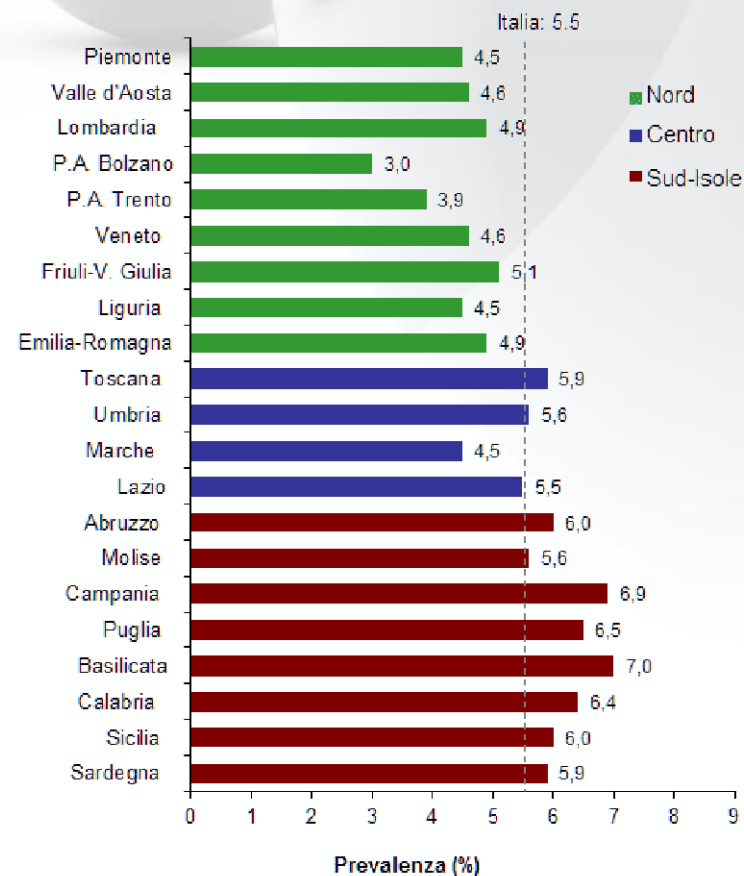
Gruppi ad alto rischio

DIABETICI

75%



Fonte ISTAT 2014, elaborazione ISS



Fonte ISTAT 2014, elaborazione ISS

PREVALENCE OF NAFLD/NASH

TAKE HOME MESSAGES 1

The global average prevalence in
general population:

ADULTS NAFLD=25-30%, NASH (20% of NAFLD =5-6%),

CHILDREN NAFLD=10-15%, NASH=5-17%

ADULT > 65 Y= 46%, NASH=9-10%

- Increases with age;
- Higher in males vs female;
- Higher in Caucasian and Hispanic;
- Increase trends in time (Big epidemic public health burden in the next future !)

ECONOMIC BURDEN OF NAFLD/NASH

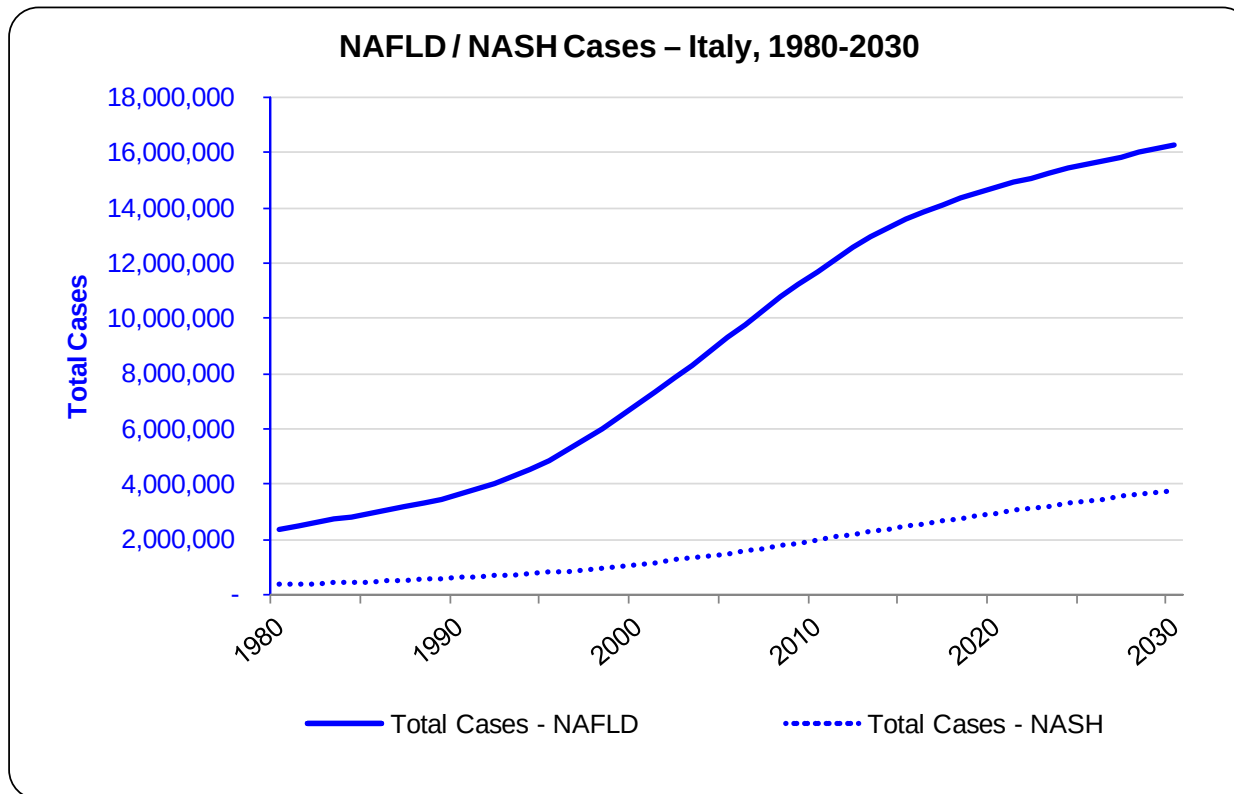
- In the US, over 64 million people with NAFLD, with annual direct medical costs of about \$103 bn [\$1,613 PP].
- In EU-4 countries ~52 million people with NAFLD with an annual cost of about € 35 billion (€ 354 to € 1,163 PP)
- Costs are highest in patients aged 45-65.
- Burden is higher when societal costs are included.

PREVALENCE OF NAFLD/NASH

TAKE HOME MESSAGES 2

- About one fourth of world's population have NAFLD
- The subgroup of NASH (5-6%) is progressive in 20-30% of the cases to cirrhosis/HCC
- In the US, NASH is the second leading indication for liver transplantation
- NAFLD is higher in patients with hypertension, diabetes, obesity or alteration of lipid metabolism
- The economic and public health burden of NAFLD is enormous and increasing especially in Children and adolescent

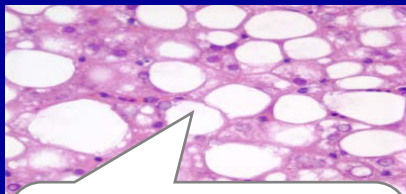
Relative Incidence of NAFLD (Italy)



- An estimated 13.6 million NAFLD cases in 2015 will increase to 16.2 million by 2030 .
- An estimated 2.5 million NASH cases in 2015 will increase to 3.8 million by 2030.

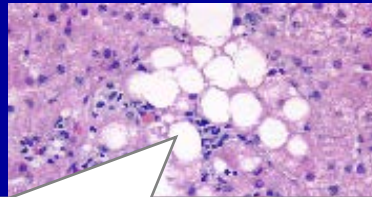
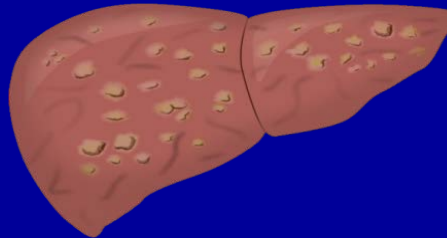
Natural history : Fatty Liver (FL)- NAFLD - NASH-Cirrhosis/HCC

Fatty Liver



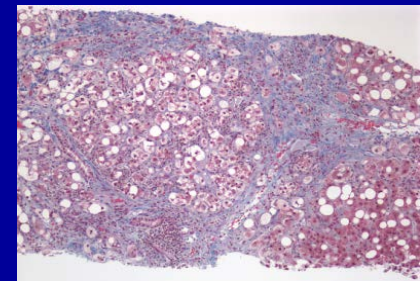
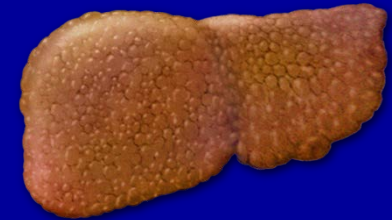
Fat infiltration >5%
with or without mild
inflammation

NASH

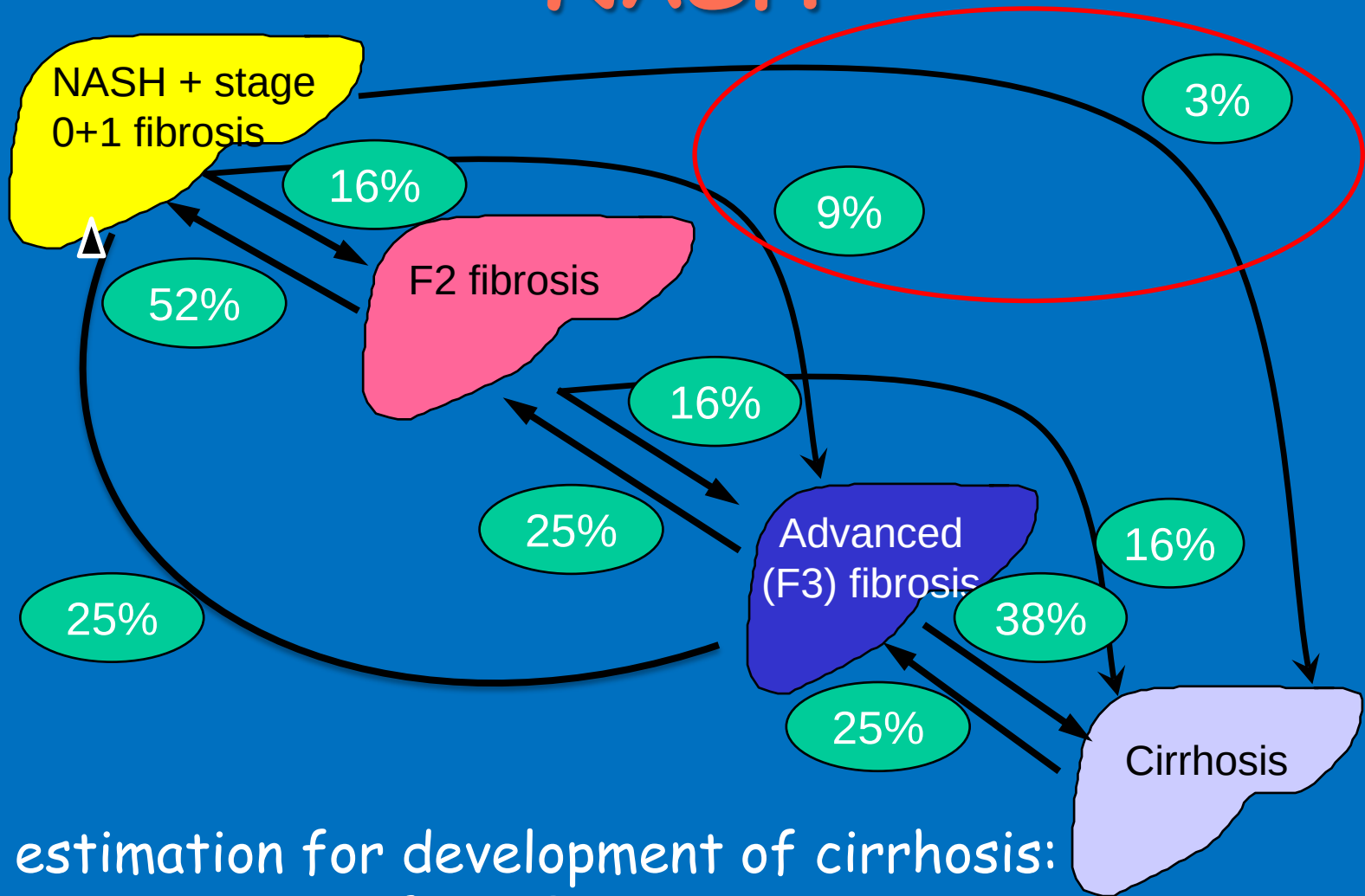


Steatosis + necro-inflammatory
changes (ballooning
degeneration, Mallory bodies,
megamitochondria)
and/or fibrosis

Cirrhosis



Natural history: Fibrosis-NASH



Time estimation for development of cirrhosis:
From NASH: 28 ys, from FL: 57 ys

NAFLD: main causes of mortality

Extrahepatic malignancies (28 % of all causes)



Breast and ovarian cancer (lifestyle, obesity, hormonal status)

Colorectal cancer (lifestyle, production of adipokines)

Ischemic heart diseases (25 % of all causes)

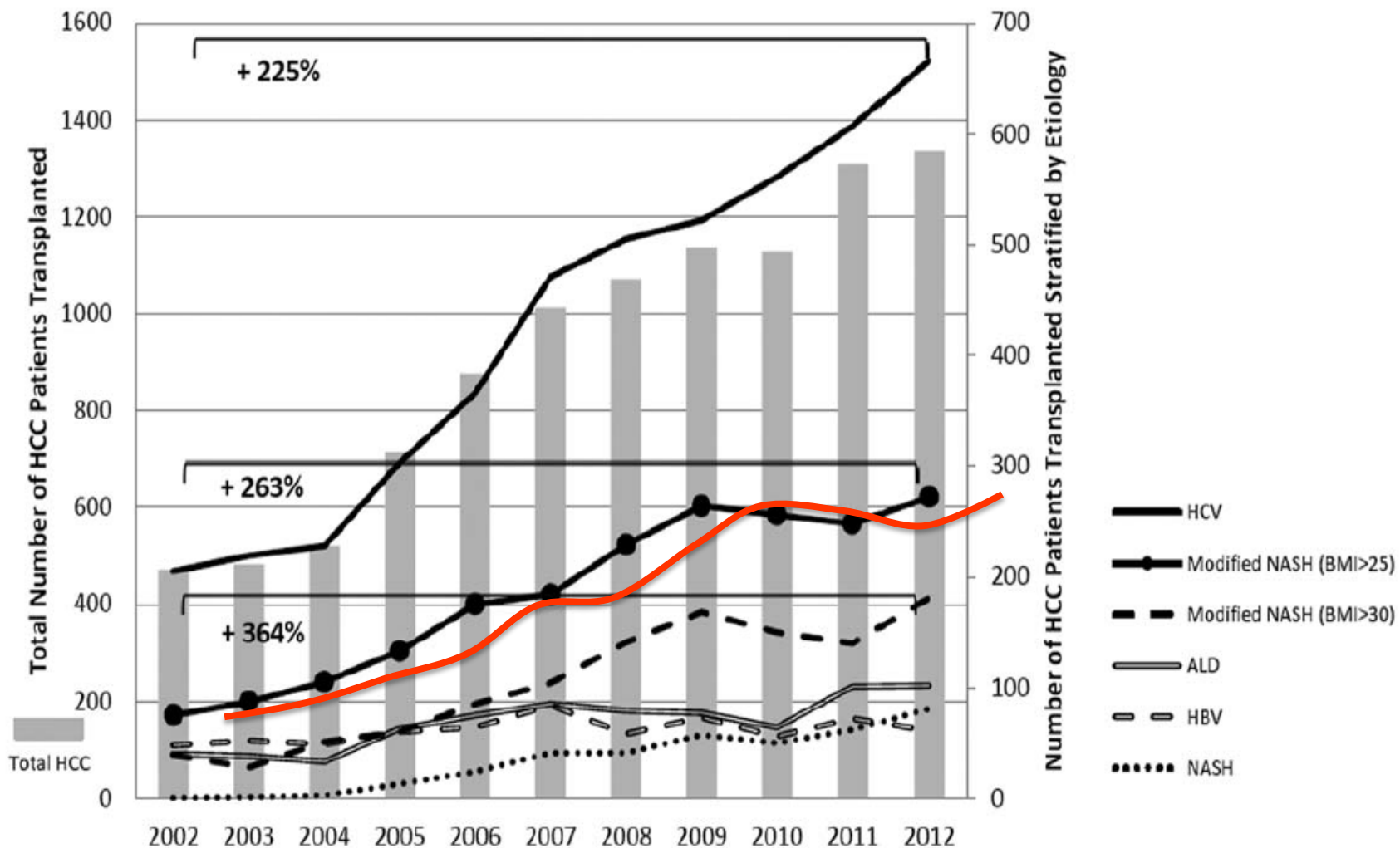
Liver-related diseases (13% of all causes)

The epidemiology of NAFLD/NASH-HCC

Study	Country	Study design	n (patients with HCC)	HCC caused by NAFLD (%)
Gonçalves <i>et al.</i> (2013) ¹⁴⁵	Brazil	Retrospective enrolment from Federal University of Espírito Santo Patients with diagnosis of HCC	1,516	4
Yang <i>et al.</i> (2012) ⁸	USA	Retrospective survey in Olmsted County Patients with diagnosis of HCC	47	11
Tokushige <i>et al.</i> (2011) ¹³	Japan	Retrospective nationwide survey Patients with diagnosis of HCC	14,530	2
Hucke <i>et al.</i> (2011) ⁹	Austria	Retrospective enrolment from Vienna General Hospital and Medical University Vienna Patients with diagnosis of HCC	850	5
Ertle <i>et al.</i> (2011) ¹⁰	Germany	Retrospective enrolment from Essen University Hospital Patients with diagnosis of HCC	162	22
Kawada <i>et al.</i> (2009) ¹²	Japan	Retrospective enrolment from Osaka Medical Center for Cancer and Cardiovascular Disease Patients submitted to hepatic resection	1,168	1
Malik <i>et al.</i> (2009) ¹¹	USA	Prospective enrolment from University of Pittsburg School of Medicine Patients with HCC submitted to liver transplantation	447	4
Guzman <i>et al.</i> (2008) ²⁵	USA	Retrospective enrolment from Chicago Medical Center Patients with diagnosis of HCC	50	10
Marrero <i>et al.</i> (2002) ¹⁴	USA	Prospective enrolment from Liver Clinic at Michigan University Patients with diagnosis of HCC	105	13

Nonalcoholic Steatohepatitis Is the Most Rapidly Growing Indication for Liver Transplantation in Patients With Hepatocellular Carcinoma in the U.S.

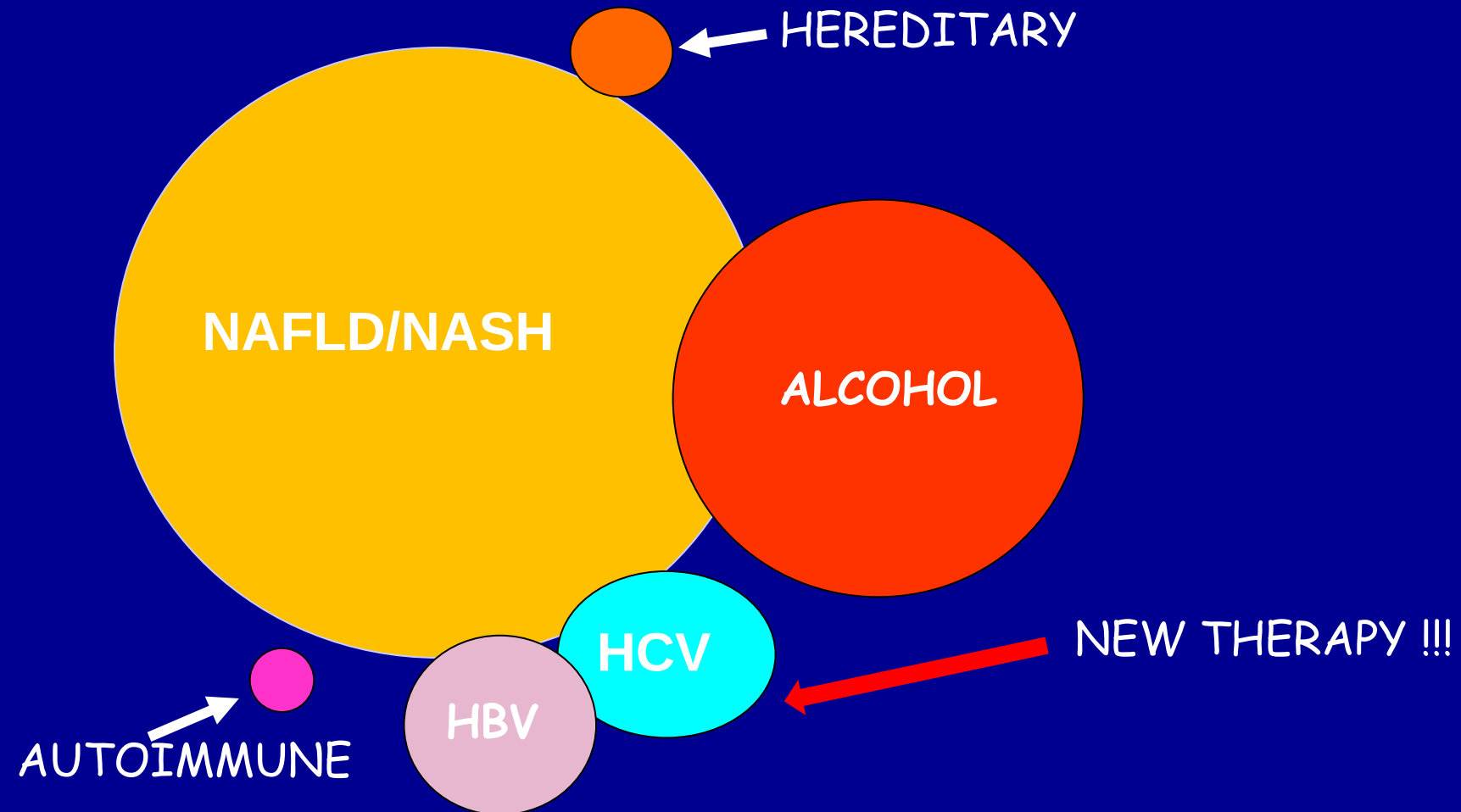
Robert J. Wong,^{1,2} Ramsey Cheung,^{1,2} and Aijaz Ahmed¹



NATURAL HISTORY AND PROGNOSIS OF NASH: TAKE HOME MESSAGES

- NAFLD/NASH warrants screening for cardiovascular diseases (proved increased mortality !!), colorectal and breast cancer, and progressive liver disease
- Progression to cirrhosis/HCC is slow
- HCC-NASH is associated with lifestyle risk factors and with metabolic diseases (obesity, diabetes, etc.),
- HCC-NASH could develop in the absence of cirrhosis (45%)
- Survival of treated HCC-NAFLD is similar to treated HCC-HCV
- Prevention and surveillance strategies for HCC-NAFLD are lacking

The Hepatologist Menu - 2030



THANK YOU FOR YOUR ATTENTION!

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Dott. STEFANO BELLENTANI

