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HEPATOLOGY  
CONFERENCE

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on the Management of Liver Diseases

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# WORLDWIDE EPIDEMIOLOGY OF NASH

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**PARIS, 11th International PHC**

**15-16 January 2018**

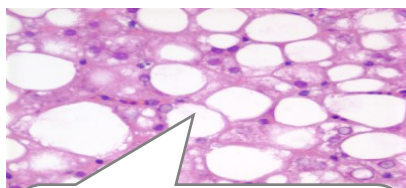
# OUTLINES OF MY SPEECH

- Definition
- Prevalence
- Incidence
- The future of Hepatology.....

# Non Alcoholic Fatty Liver Disease (NAFLD)

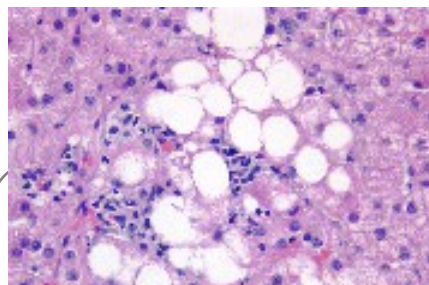
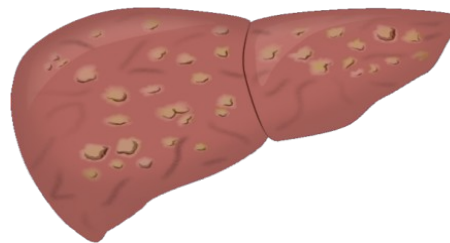
Alcohol intake < 20-30g/day

Fatty Liver



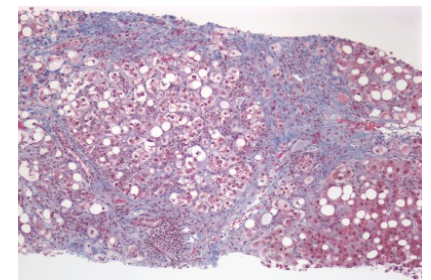
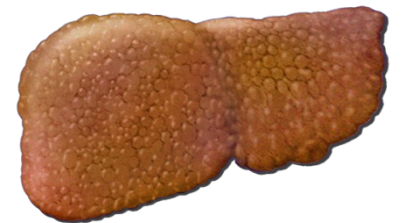
Fat infiltration >5%  
with or without mild  
inflammation

NAFLD/NASH



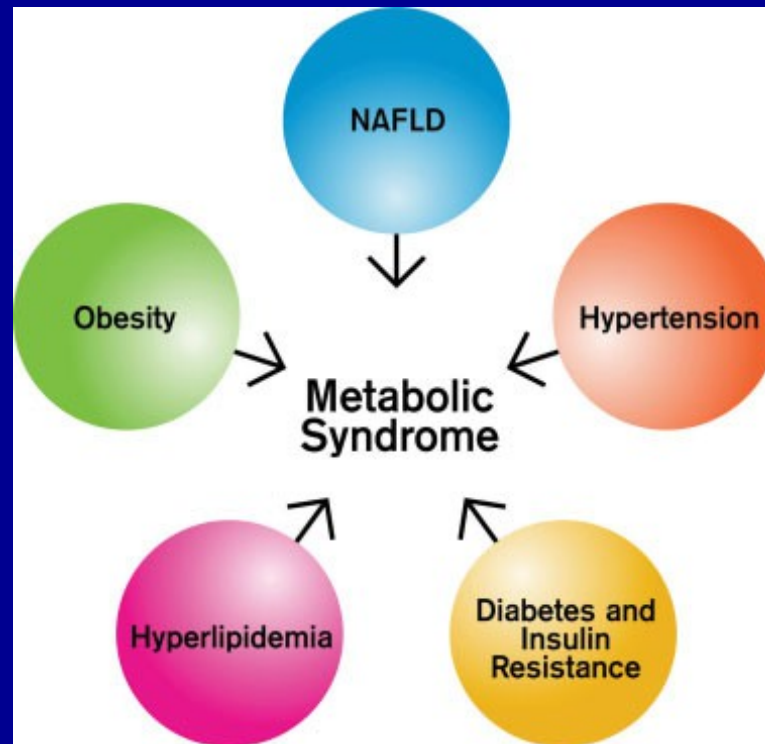
megamitochondria)  
and/or fibrosis

Cirrhosis/HCC

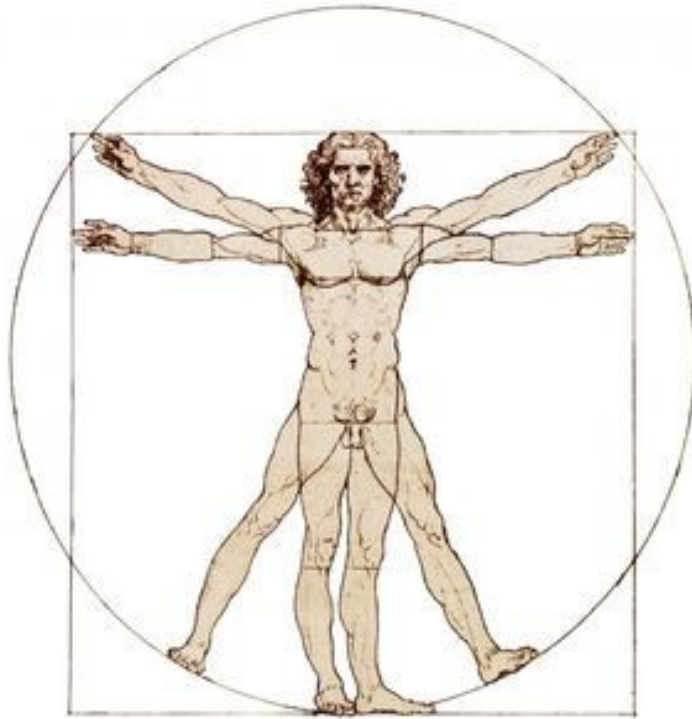


# What is Non-Alcoholic Fatty Liver Disease (NAFLD) ?

- NAFLD is a chronic liver condition characterized by hepatic fat accumulation in the absence of ethanol abuse (<20g/day) & other identifiable causes
- NAFLD is always associated to insulin resistance
- NAFLD is considered the hepatic manifestation of Metabolic Syndrome



# Non-alcoholic fatty liver disease NAFLD : a multi-system disease



## Hepatic

cirrhosis,  
HCC

## Metabolic

Central obesity,  
Insulin resistance,  
Type 2 diabetes

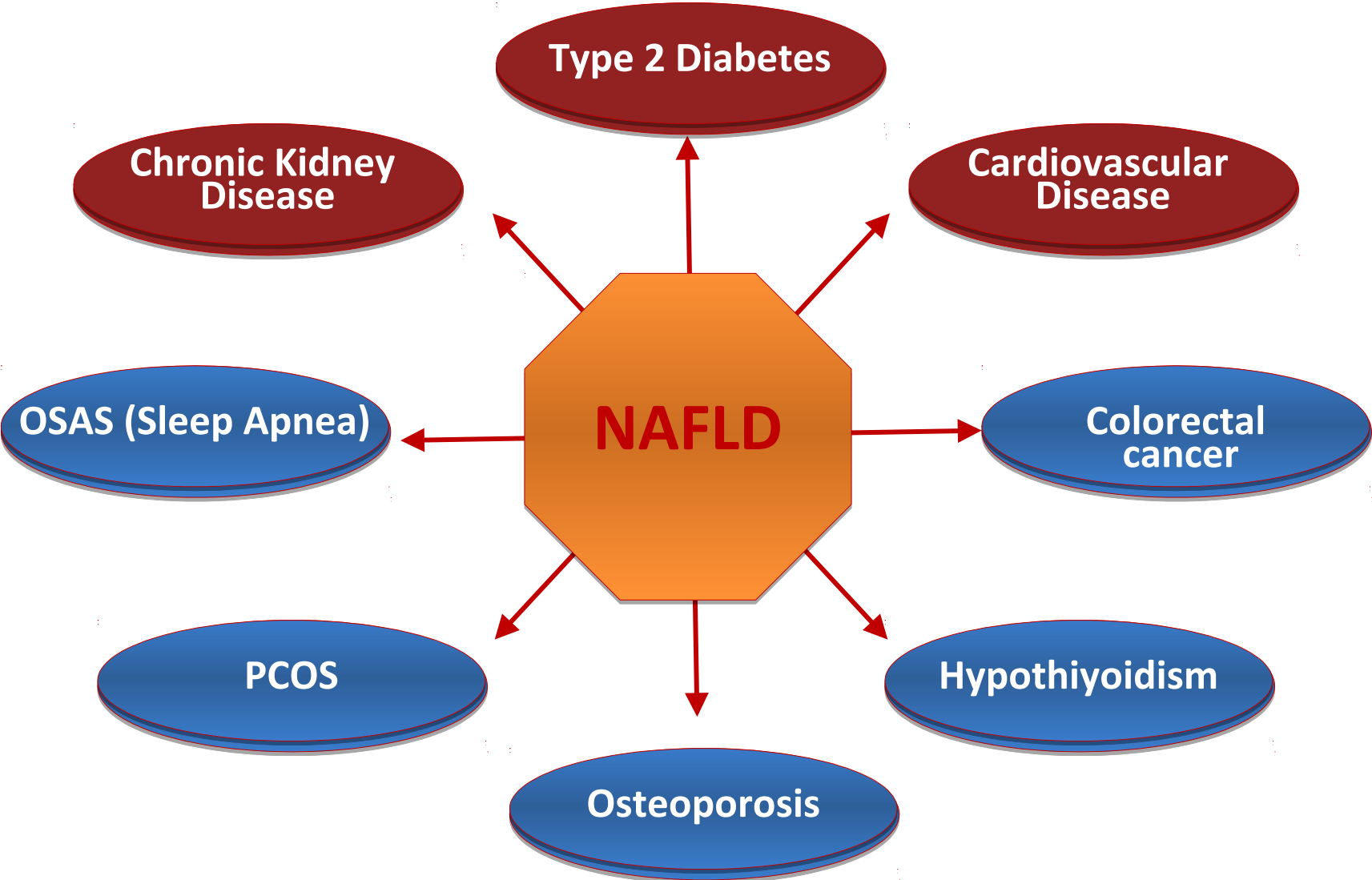
## Cardiovascular

Dyslipidemia,  
Hypertension  
Cardiovascular Disease (CVD)

# The spectrum of NAFLD

- **Insulin-resistant NAFLD subjects**
  - Obesity (visceral)
  - Environmental (High fructose diet; high fat diet)
  - Metabolically Obese Normal Weight (MONW) Subjects
  - Congenital and acquired lipodistrophy
- **Non insulin resistant NAFLD subjects**
  - Genetic (PNPLA3 NAFLD)
  - Congenital defects of metabolism
    - Familial Hypobetalipoproteinemia (FHLB)
    - Lysosomal acid lipase deficiency (LAL-D)
- **Association with endocrine disorders**
  - PCOS
  - hypothyroidism
  - GH deficiency
- **Secondary causes**
  - Drug-related (amiodarone, methotrexate, tamoxifen, corticosteroids..)
  - Jejunioileal bypass, starvation, TPN

# Extrahepatic manifestations of NAFLD

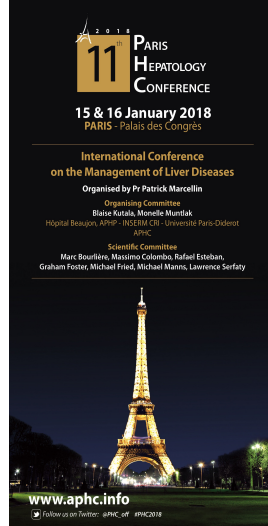


# DEFINITION OF NAFLD: IT IS TIME TO CHANGE !

Actual definitions of the difference between AFLD vs NAFLD have significant methodological biases:

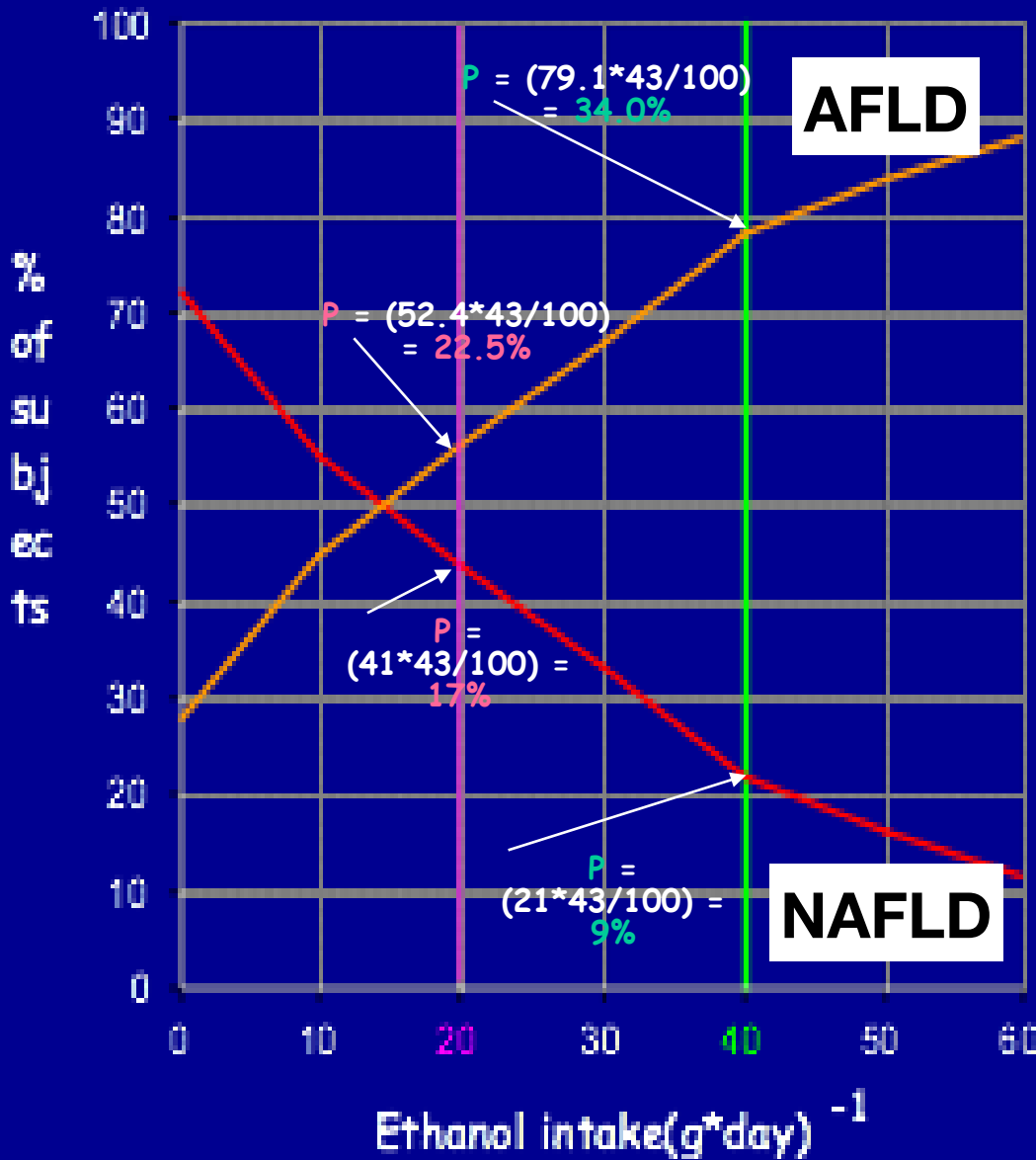
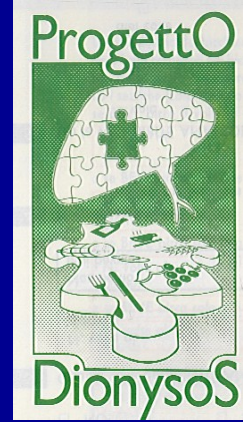
- 1- Inadequate adjustment for confounding factors
- 2- Different ways of calculating alcohol consumption
- 3- Failure to measure lifetime use or pattern of alcohol intake.

These biases influence the calculation of the real prevalence and incidence of NAFLD and NASH which varies greatly in the general population.





# NAFLD and AFLD in the Nutrition and Liver Dionysos Study (Bellentani et al., Hepatology, 2005)



Prevalence FL = 43-56%

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# Italy, the Dionysos Study: 2005



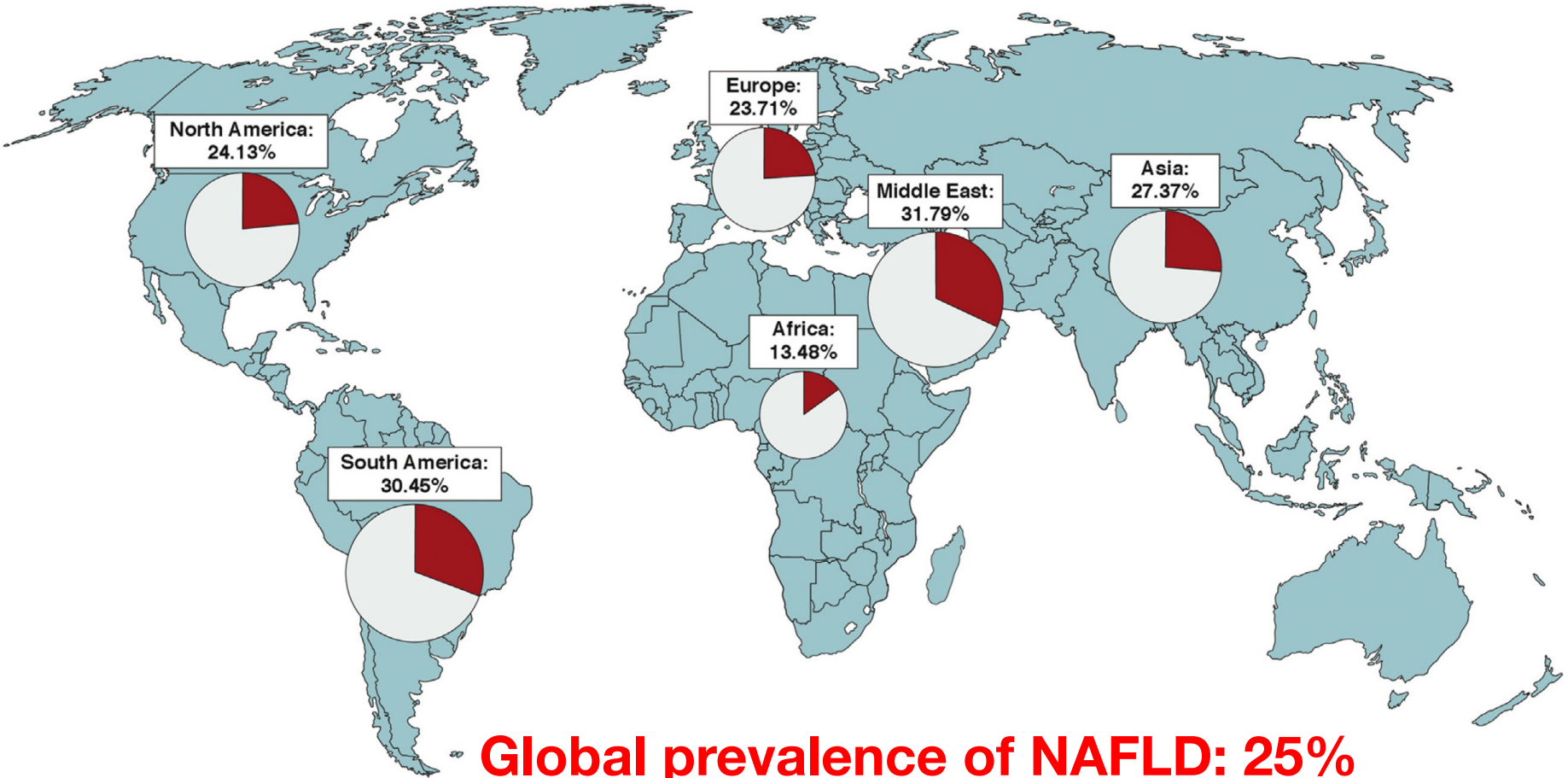
	<i>Condition Prevalence</i>	<i>Liver disease Prevalence</i>	
		<i>Among exposed</i>	<i>General Population</i>
<b>HCV</b>	<b>3,2%</b> (221/6917)	50% (110/221)	<b>1,6%</b> (110/6917)
<b>HBV</b>	<b>1,2%</b> (83/6917)	25% (21/83)	<b>0,3%</b> (21/6917)
<b>Alcohol*</b>	<b>21%</b> (1349/6917)	5,5% (74/1349)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

# Global prevalence of NAFLD

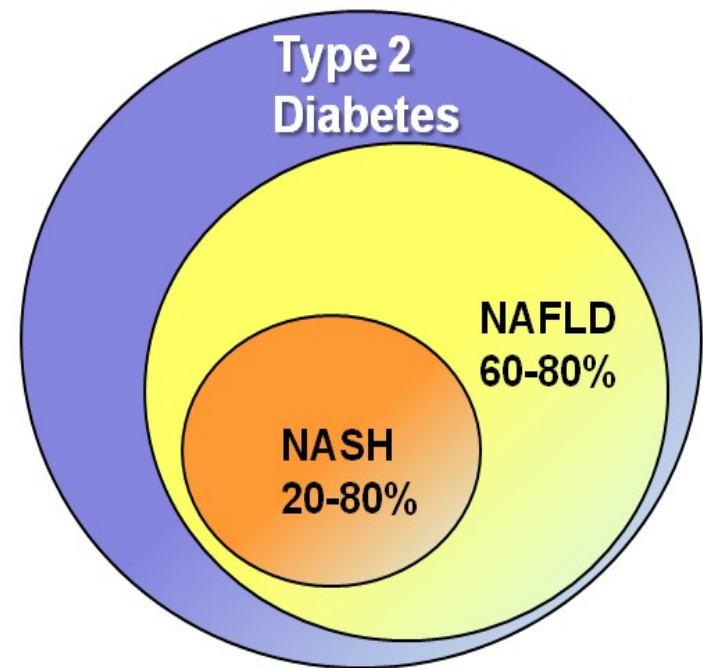
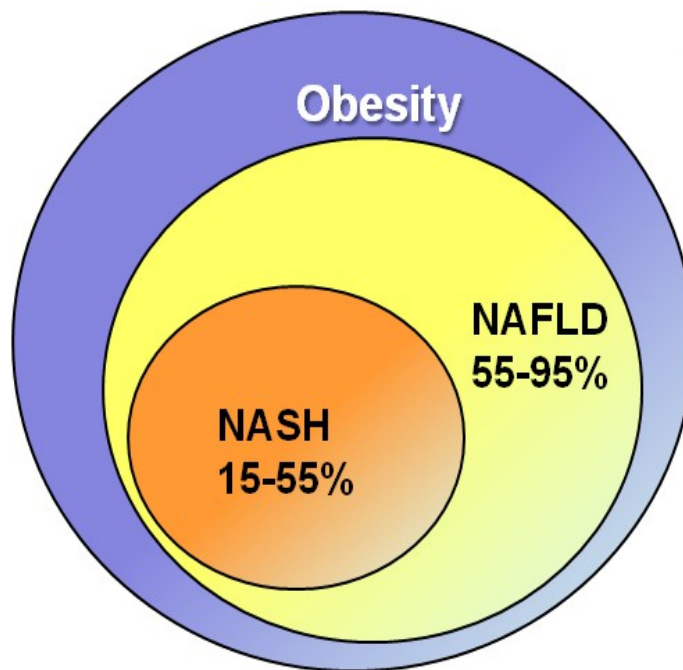
Global prevalence of overweight and obesity: 39%



# Prevalence of NAFLD and NASH in high-risk groups

Obesity: 1 billion subjects overweight or obese around the world

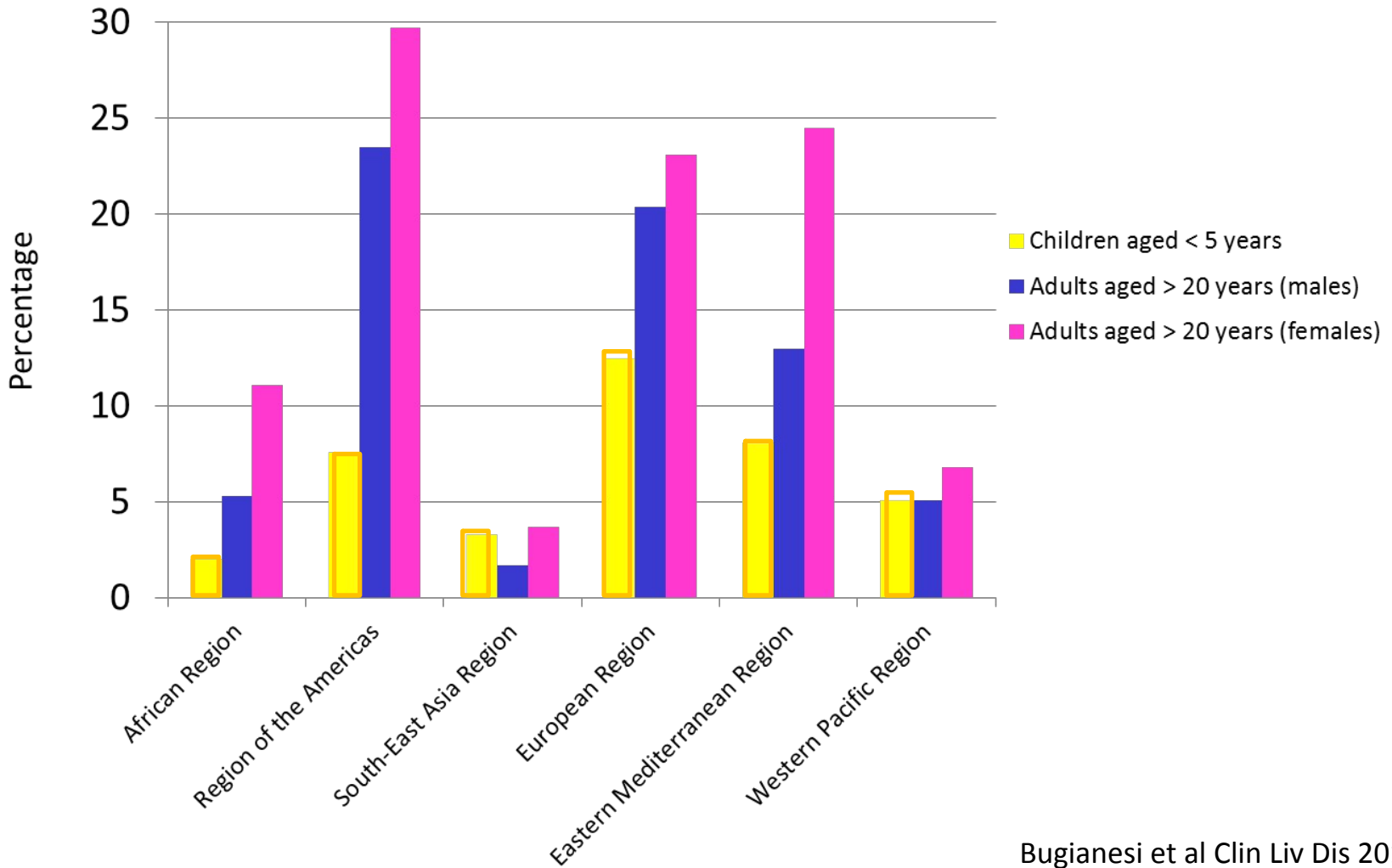
Diabetes: over 380-million cases, but 550 in 2030



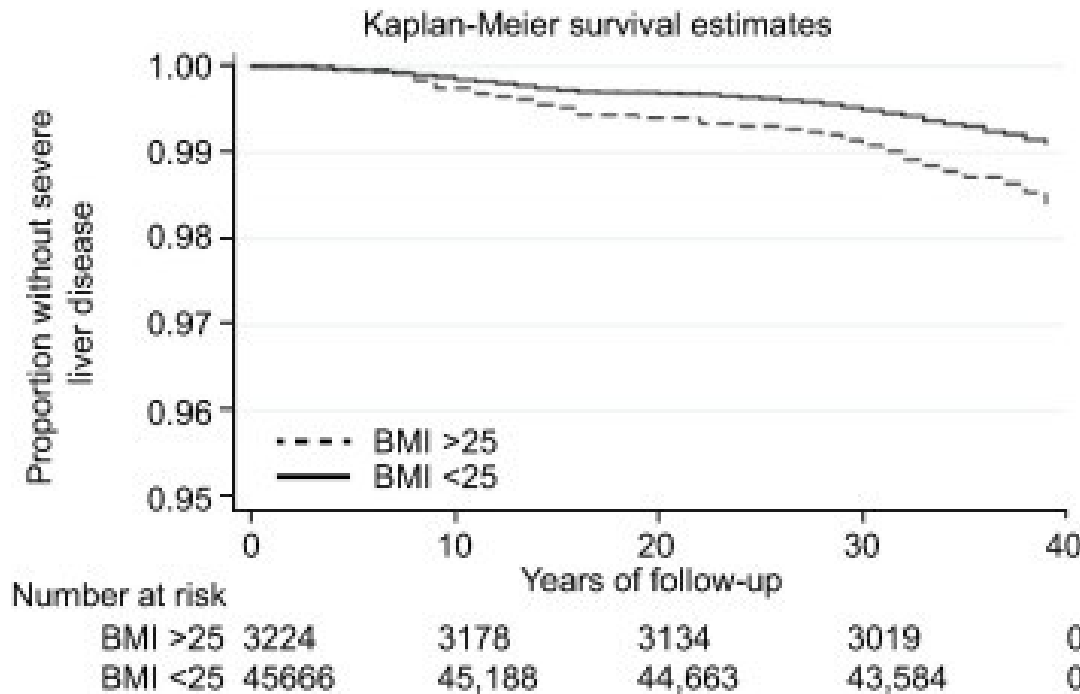
Hepatologists only see the most severe cases (the tip of iceberg), and have a scarce idea of the global extent of disease

# Global burden of increased BMI (>25) in children and of obesity in adults.

Data from World Health Organization



# Overweight in late adolescence predicts development of severe liver disease later in life: A 39 years follow-up study



Kaplan-Meier curve for the development of severe liver disease, stratified on overweight status.

BMI in late adolescence is a strong and independent predictor of liver-related mortality later in life after adjustment for alcohol, narcotics, smoking, high blood pressure, physical activity

being overweight at 18-20 yrs increased the risk of liver related outcomes by 64% compared to a low-normal range BMI

liver-related outcomes were increased by 5% for each unit increase in BMI

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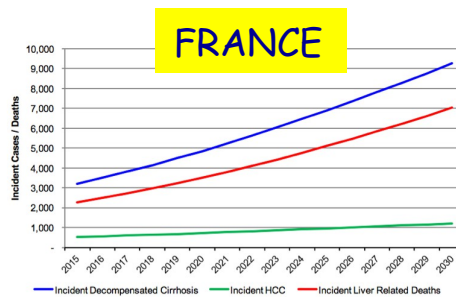
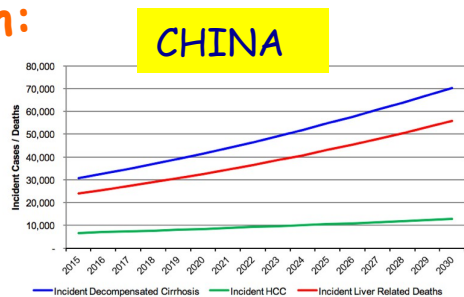


# Relative Incidence of NAFLD (Italy)

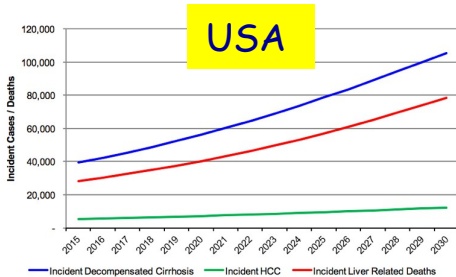
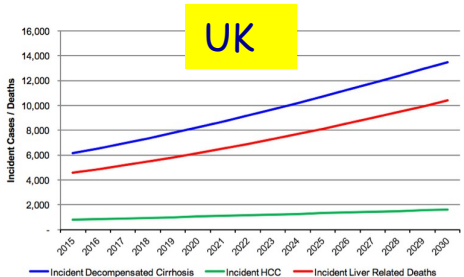
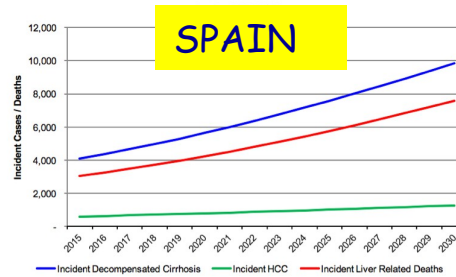
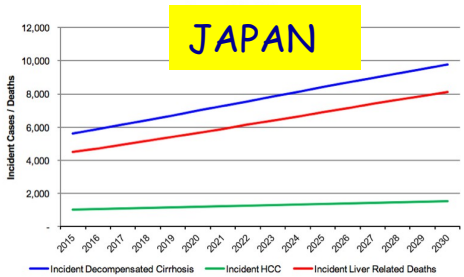
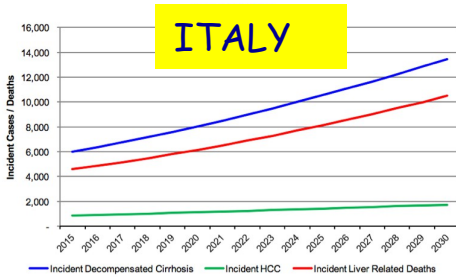
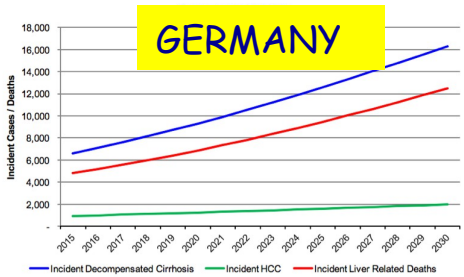
- An estimated 13.6 million NAFLD cases in 2015 will increase to 16.2 million by 2030 .
- An estimated 2.5 million NASH cases in 2015 will increase to 3.8 million by 2030.

# Incident Trend Decompensated Cirrhosis, HCC and Liver-Related Deaths among Prevalent NAFLD

NAFLD Population:  
2015-2030



INCIDENT DEC. CIRRHOSIS  
DEATH  
HCC

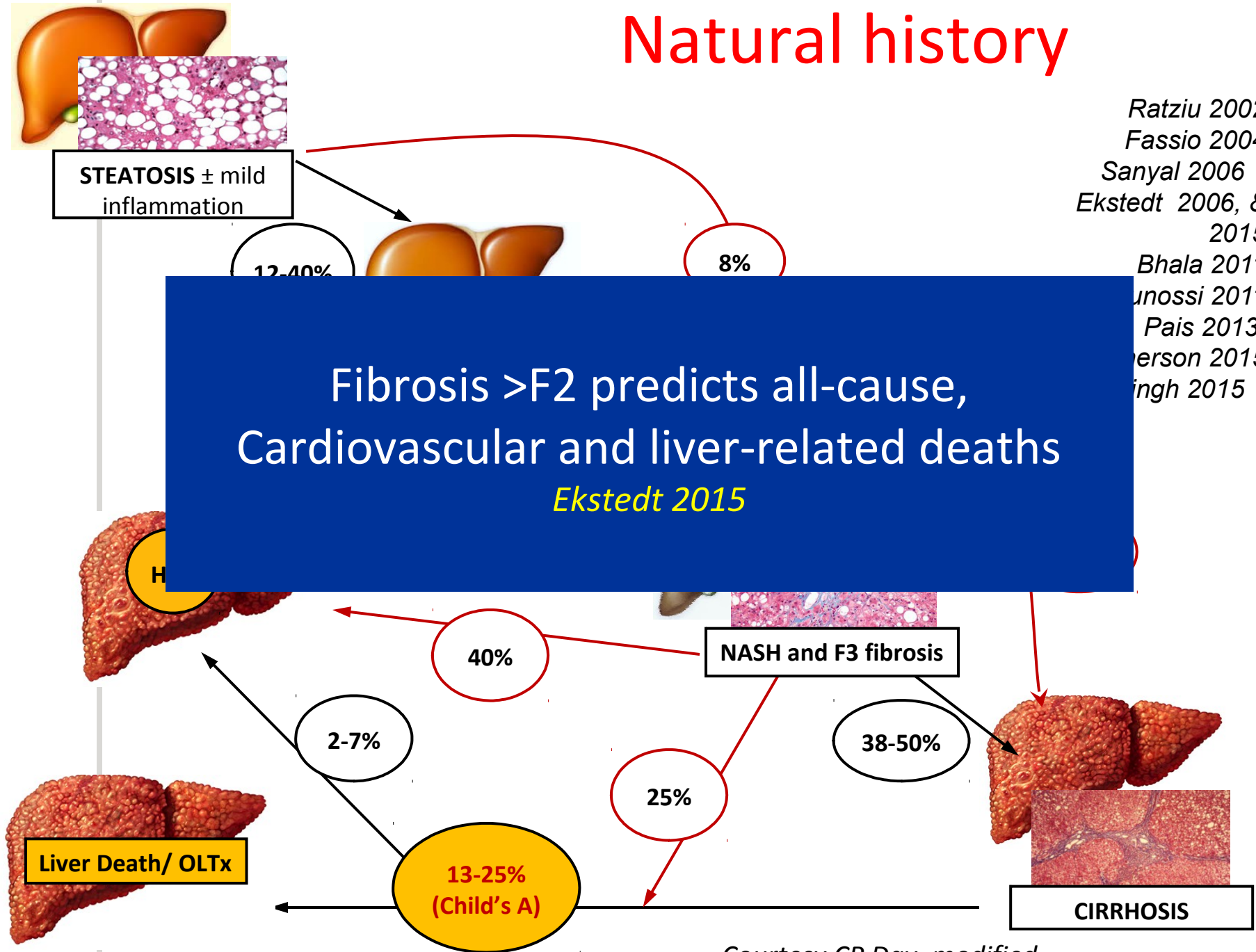


2016

2030

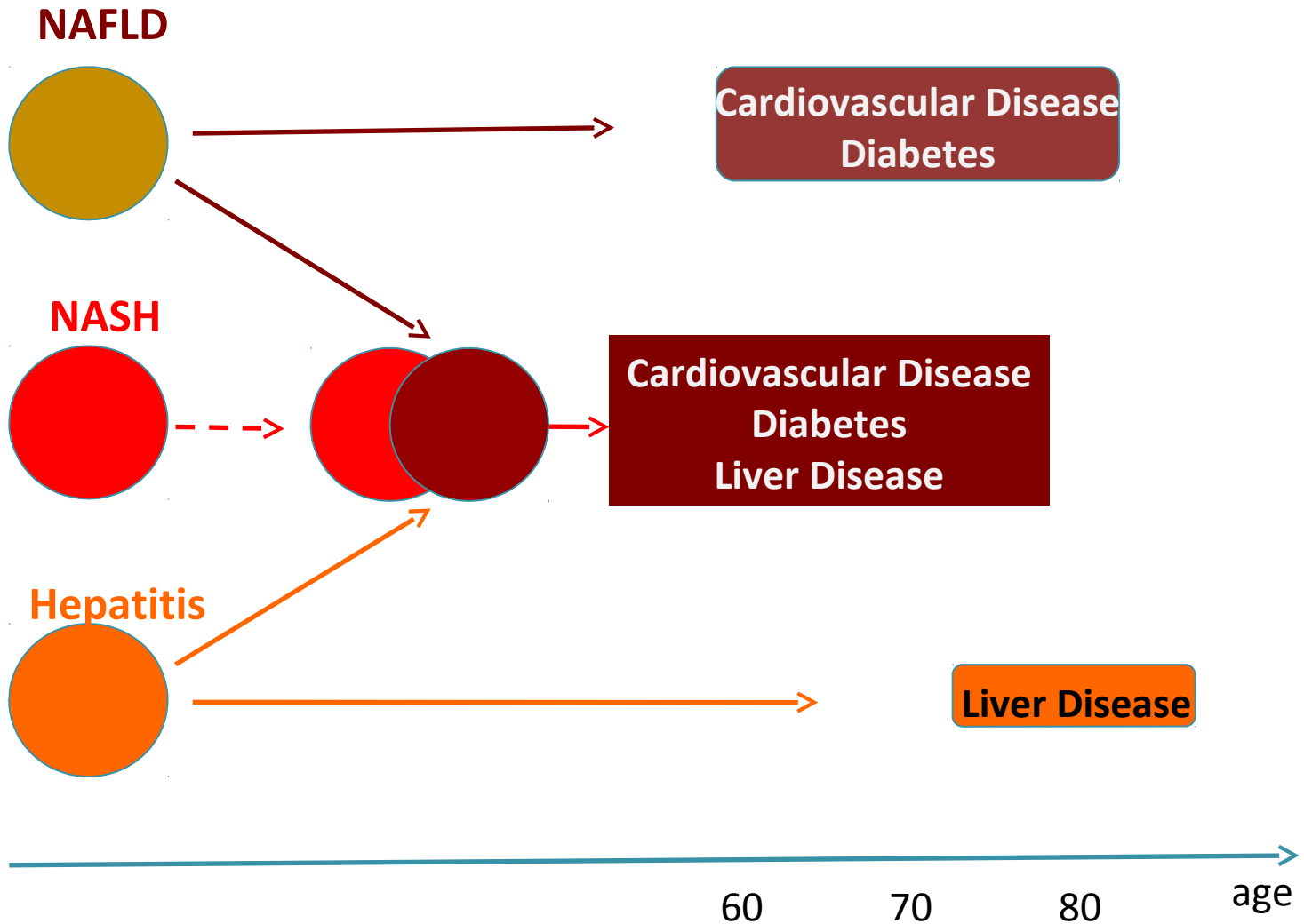
# Natural history

Ratziu 2002  
Fassio 2004  
Sanyal 2006  
Ekstedt 2006, &  
2015  
Bhala 2011  
Innessi 2011  
Pais 2013  
Person 2015  
Singh 2015



Fibrosis >F2 predicts all-cause,  
Cardiovascular and liver-related deaths  
*Ekstedt 2015*

# Death Risks in NAFLD



# Clinical outcomes (Mortality) of subjects with NAFLD/NASH

Population	Outcome	Incidence Rate Per 1000 PYs	N	95% CI	I <sup>2</sup> (%)	Follow-up (years)
NAFLD	CVD-Specific Mortality	4.79	6	(3.43 - 6.7)	91.17	12.96
NAFLD	HCC	0.44	3	(0.29 - 0.66)	0.00	5.82
NAFLD	Liver-Specific Mortality	0.77	7	(0.33 - 1.77)	91.84	13.17
NAFLD	Overall Mortality	15.44	7	(11.72 - 20.34)	97.17	13.17
NASH	HCC	5.29	1	(0.75 - 37.56)	NA	4.50
NASH	Liver-Specific Mortality	11.77	3	(7.1 - 19.53)	0.00	8.08
NASH	Overall Mortality	25.56	2	(6.29 - 103.8)	73.85	6.17
NAFLD	Annual Fibrosis Progression Rate	0.06	4	(0.03 - 0.09)	64.4	7.06
NASH	Annual Fibrosis Progression Rate	0.09	2	(0.06 - 0.12)	0.0	4.01

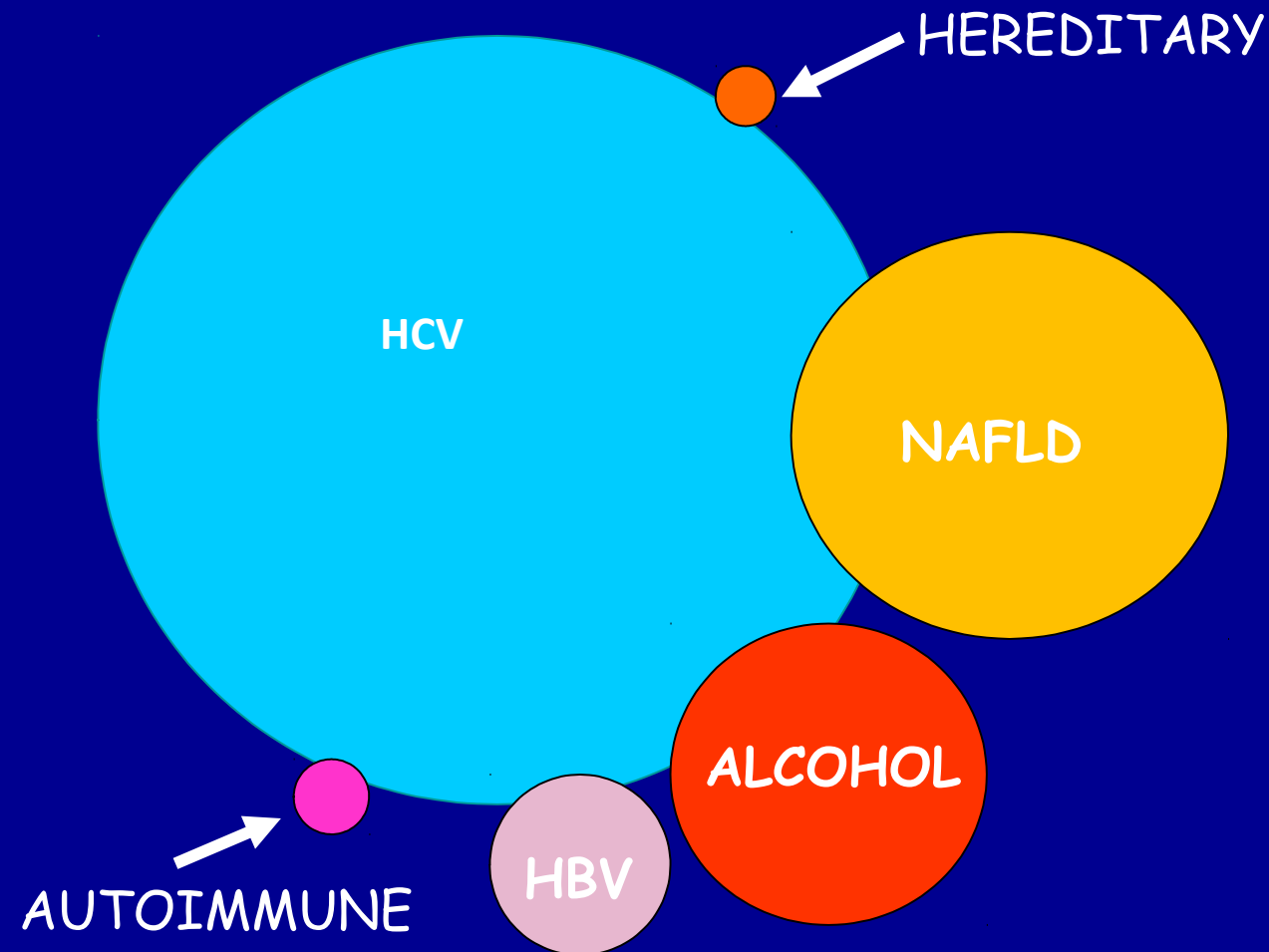
## Main causes of death

- Cardiovascular Disease (2 x compared to the general population)
- Cancer
- Liver disease (10 x compared to the general population)

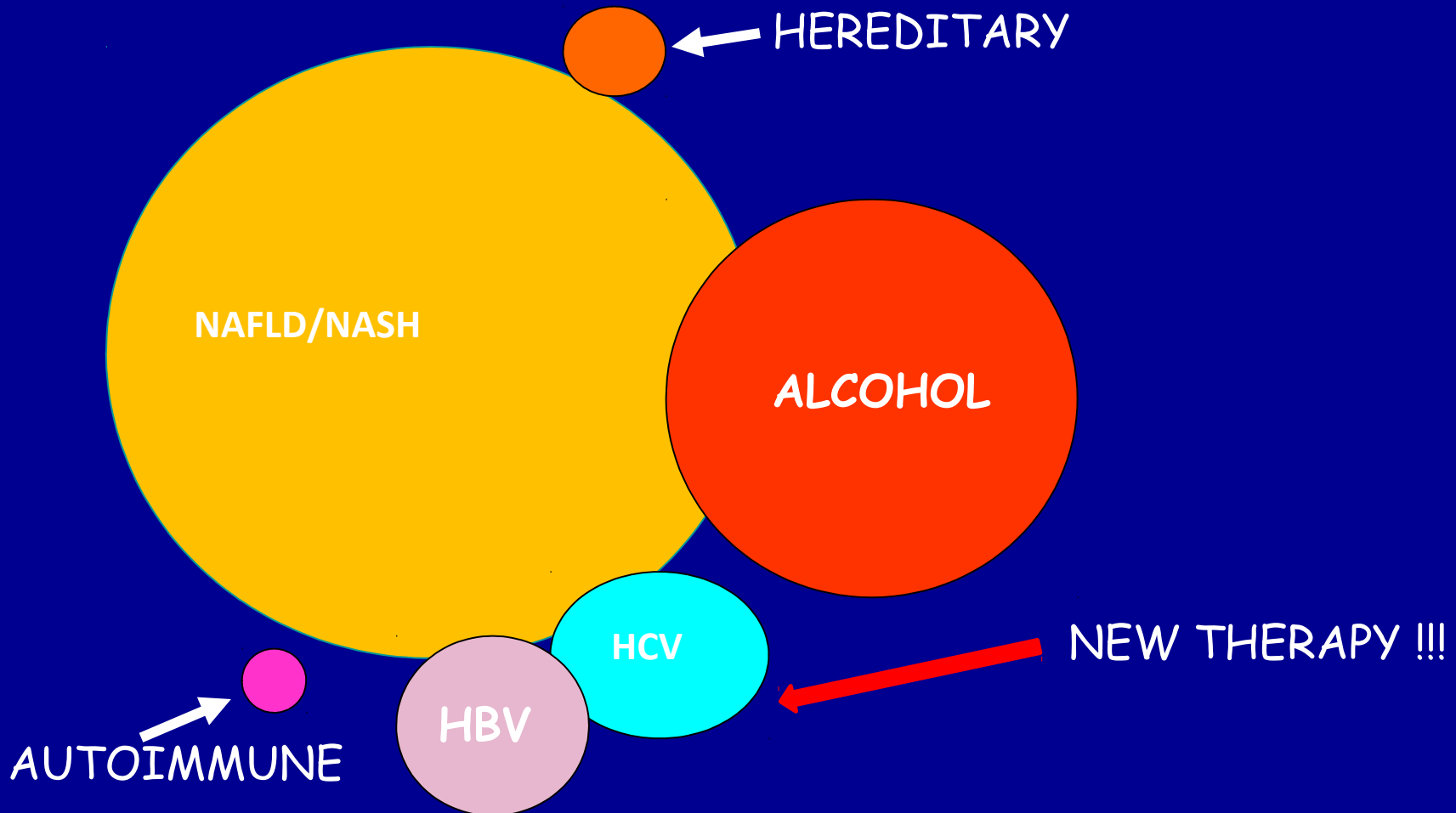
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# The Hepatologist Menu - 2018



# The Hepatologist Menu - 2030





# Similar entities: different names and acronyms

## *ACRONYM*

## *SIGNIFICANCE*

**NASH**

NonAlcoholic SteatoHepatitis

**ASH**

Alcoholic SteatoHepatitis

**BASH**

Both Alcoholic and NonAlcoholic SteatoHepatitis

**GASH**

Genetic Associates SteatoHepatitis

**CASH**

Chemotherapy Associated SteatoHepatitis

**DASH**

Drug Associated SteatoHepatitis

**PASH**

PNPLA3 associated steatohepatitis

## Actual Classification NAFLD/NASH

### Moving from a negative definition of primary NAFLD and NASH

Primary Insulin-resistant NAFLD/NASH	Primary Non insulin resistant NAFLD/NASH	Secondary NAFLD/NASH
Metabolically Healthy Obesity (MHO) (visceral obesity)	Genetic [PNPLA3 and TM6SF2 genes involved]	Associated with endocrine disorders: <ul style="list-style-type: none"> <li>- Polycystic Ovary Syndrome (PCOS)</li> <li>- Hypothyroidism</li> <li>- GH deficiency</li> </ul>
Metabolically Obesity Normal Weight (MONW)	Hypobetalipoprotein syndrome	Environmental (High fructose diet; high fat diet)
Type 2 Diabetes Mellitus (T2DM)	Metabolically Obesity Normal Weight (MONW) (Probably Genetic, too)	Drug-related (amiodarone, methotrexate, tamoxifen, corticosteroids..)
Congenital Lipodistrophy	Unknown causes (Cryptogenic)	Jejunioileal bypass
Lysosomal Acid Lypase Deficiency (LALD or Non-Obese Fatty Liver)		Total Parenteral Nutrition (TPN), Starvation
		Associated with other hepatic diseases [viral, autoimmune, alcoholic steatohepatitis (ASH), etc.]

# New proposed classification NAFLD/NASH

Moving to a positive definition of NASH: MAFL (Metabolic Associated Fatty Liver) and MASH (Metabolic Associated SteatoHepatitis) thus revising the old definition and classification

Primary MAFL/MASH	Secondary MAFL/MASH
Metabolically Healthy Obesity (MHO) (visceral obesity)	Associated with endocrine disorders: <ul style="list-style-type: none"><li>- Polycystic Ovary Syndrome (POS)</li><li>- Hypothyroidism</li><li>- GH Deficiency</li></ul>
Metabolically Obesity Normal Weight (MONW) (Probably Genetic, too)	Environmental (High fructose diet; high fat diet)
Type 2 Diabetes Mellitus (T2DM)	Drug-related (amiodarone, methotrexate, tamoxifen, corticosteroids..)
Genetic [PNPLA3 and TM6SF2 genes involved]	Jejunioileal bypass
Hypobetalipoprotein syndrome	Total Parenteral Nutrition (TPN), Starvation
Congenital Lipodistrophy	Associated with other hepatic diseases [viral, autoimmune, alcoholic steatohepatitis (ASH), etc.]
Lysosomal Acid Lypase Deficiency (LALD or Non-Obese Fatty Liver)	
Unknown causes (Cryptogenic)	

# Case definitions for inclusion and analysis of endpoints in clinical trials for NASH through the lens of regulatory science

M. Shadab Siddiqui and the Case Definition Working Group  
Hepatology Jan.2018, Open Acces online

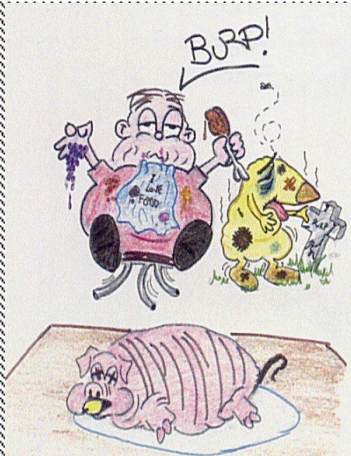
**Table 4:** Standardized format for comparison of study populations across trials

Phenotype	Disease Activity	Disease Stage	Etiology/Associations
1. Steatosis 2. Steatohepatitis 3. Indeterminate	<b>NAS:</b> - Steatosis - Lobular inflammation - Ballooning  <b>SAF:</b> - Steatosis - Lobular inflammation - Ballooning - Fibrosis	<b>Fibrosis:</b> - <b>Stage 0:</b> No fibrosis - <b>Stage 1a:</b> Mild peri-sinusoidal - <b>Stage 1b:</b> Moderate peri-sinusoidal - <b>Stage 1c:</b> Portal/Peri-portal - <b>Stage 2:</b> Peri-sinusoidal and portal/peri-portal - <b>Stage 3:</b> Bridging - <b>Stage 4:</b> cirrhosis	1. Insulin resistance 2. Alcohol 3. Lean NASH 4. PNPLA3+ 5. Drugs 6. Inherited disorders e.g. Weber-Christian, hypobetalipoproteinemia 7. Lipodystrophy 8. Short bowel 9. TPN 10. Jejunio-ileal bypass

**Note:** Many include one or more subsets from each of the columns. This provides a standardized format for comparison of study populations across trials.  
NAS, NAFLD activity score; SAF, Steatosis-Activity-Fibrosis Score.

# THANK YOU VERY MUCH FOR YOUR ATTENTION!

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