# EPIDEMIOLOGY OF NAFLD/NASH

Stefano Bellentani, M.D., Ph.D.
Chief of Gastroenterology and Hepatology Service
Clinica Santa Chiara – Locarno – Switzerland &

Fondazione Italiana Fegato (FIF), Bassovizza (Trieste), Italy

e.mail: bellentanistefano@gmail.com

10TH ANNIVERSARY

2017

10th PARIS HEPATOLOGY CONFERENCE

**30 & 31 January 2017**
PARIS - Palais des Congrès

**International Conference
on the Management of Liver Diseases**

Organised by Pr Patrick Marcellin,
APHC

Organising Committee
Michelle Martinot-Peignoux, Monelle Muntlak
Hôpital Beaujon, APHP - INSERM CRI - Université Paris-Diderot

Scientific Committee
Marc Bourlière, Massimo Colombo, Rafael Esteban,
Graham Foster, Michael Fried, Michael Manns

Conflict of interest (period 2015-2016) : Consultant for ROTTAPHARM-MEDA

# OUTLINES OF MY SPEACH

- Definition
- Prevalence
- Incidence
- Risk factors
- Natural History
- The future of Hepatology……

# Forms and etiology of NAFLD/NASH

✓ **"Primary" NAFLD/NASH: Associated with the metabolic syndrome**

✓ **"Secondary" NAFLD: Associated with different conditions**

    Drugs: Steroids, Amiodarone, Tamoxifen, anti-HIV drugs, etc.

    Metabolic or genetic alterations: Lipodystrophy, Dysbetalipoproteinemia, Weber-Christian disease

    Nutritional: TPN, Rapid weight loss, Bariatric surgery, Starvation

    Small bowel diseases: IBD, Bacterial overgrowth

    Environmental hepatotoxins: e.g. Petrochemicals

✓ **Steatosis accompanying other forms of liver disease**

# Components of the Metabolic Syndrome
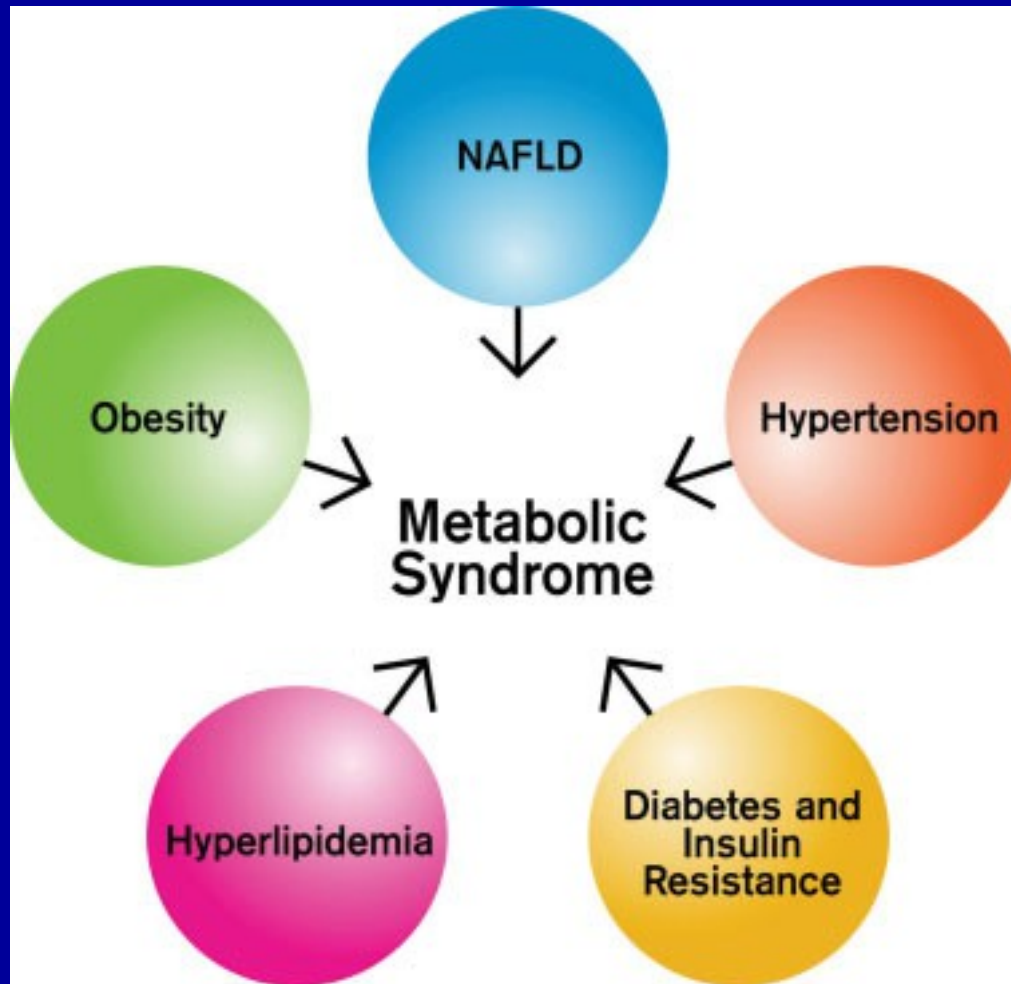
# Similar entities: different names and acronyms

NASH   Non Alcoholic Steatohepatitis

ASH    Alcoholic steatohepatitis

BASH   Both alcoholic and non alcoholic steatohepatisis
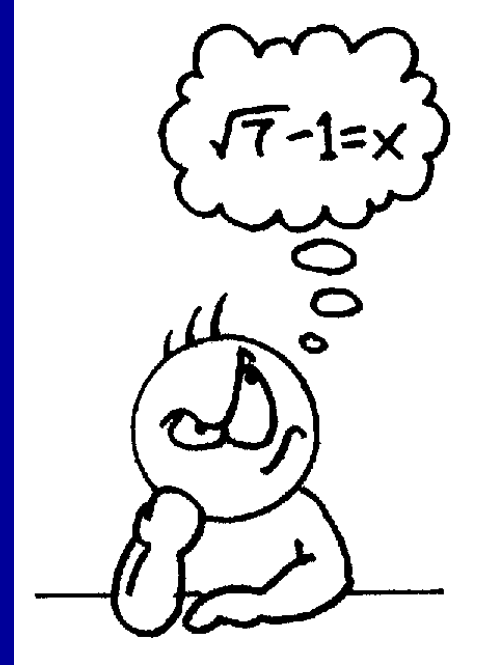
DASH   Drug induced steatohepatitis

CASH   Chemotherapy associated steatohepatitis

PASH   PNPLA3 associated steatohepatitis

# NAFLD/NASH Prevalence

**Diagnosis ? Different series..**

- Liver Biopsy
- Post-mortem studies
- Cryptogenic cirrhosis
- Surrogate alteration LFT (GGT, ALT, etc.)
- Surrogate indexes (FLI, USFLI)

# Italy: The Dionysos Study

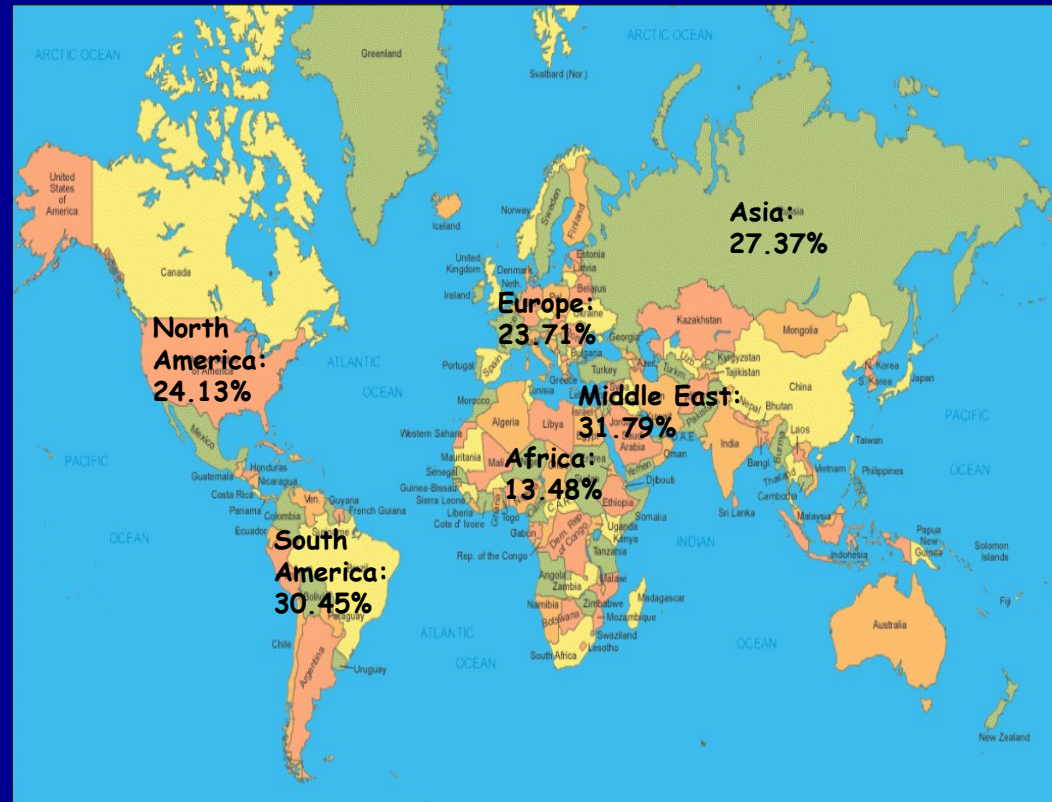| | Condition Prevalence | Liver disease Prevalence | |
| --- | --- | --- | --- |
| | | Among exposed | General Population |
| **HCV** | **3,2%** (221/6917) | 50% (110/221) | **1,6%** (110/6917) |
| **HBV** | **1,2%** (83/6917) | 25% (21/83) | **0,3%** (21/6917) |
| **Alcohol\*** | **21%** (1349/6917) | 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)*
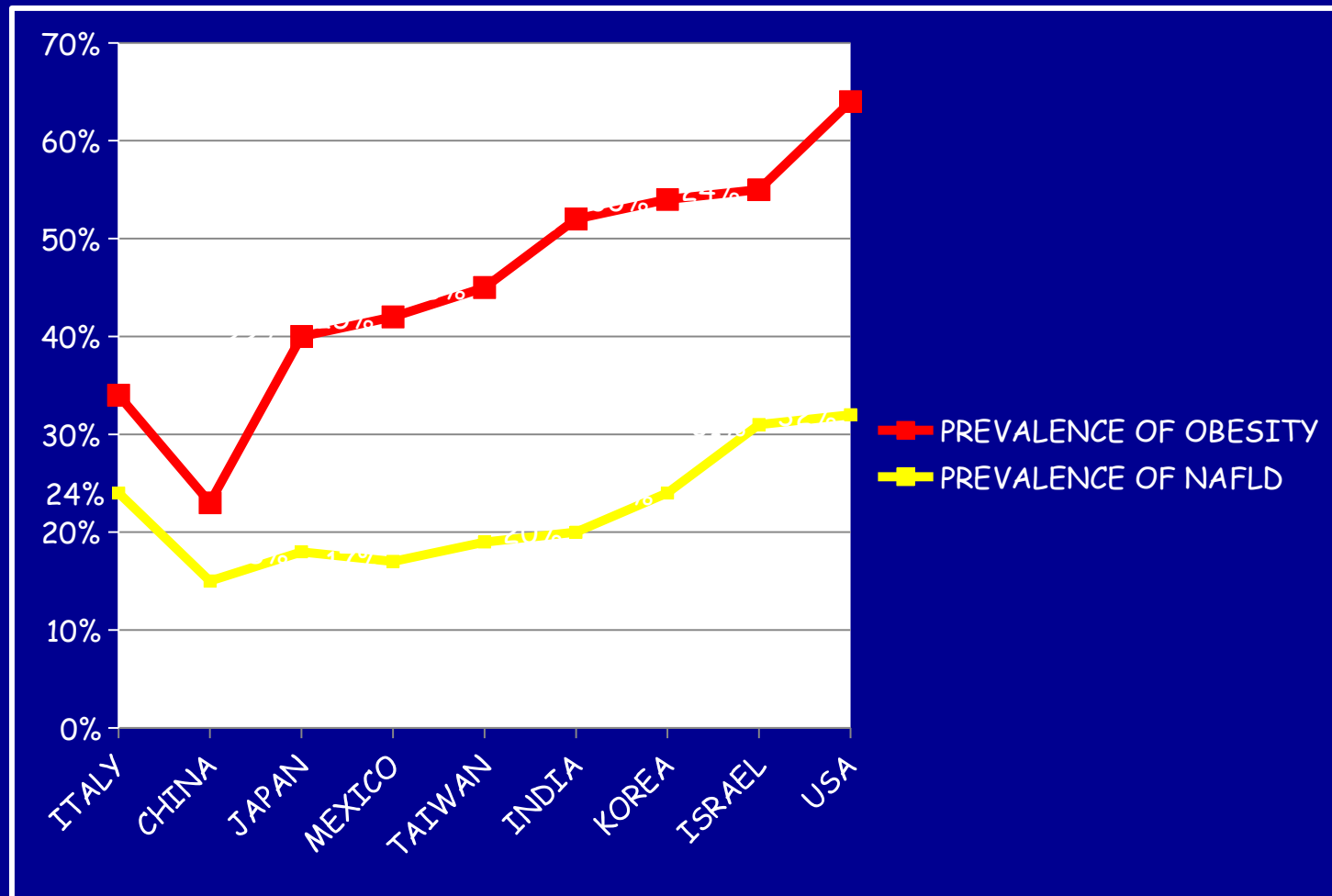
Bellentani S et al, Dig Dis 2010
Bedogni G et al, Hepatology 2005
Bellentani S et al, Gut 1999
Bellentani S et al, Gut 1997
Bellentani S et al, Hepatology 1994

# 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



North America: 24.13%

South America: 30.45%

Europe: 23.71%

Middle East: 31.79%

Africa: 13.48%

Asia: 27.37%

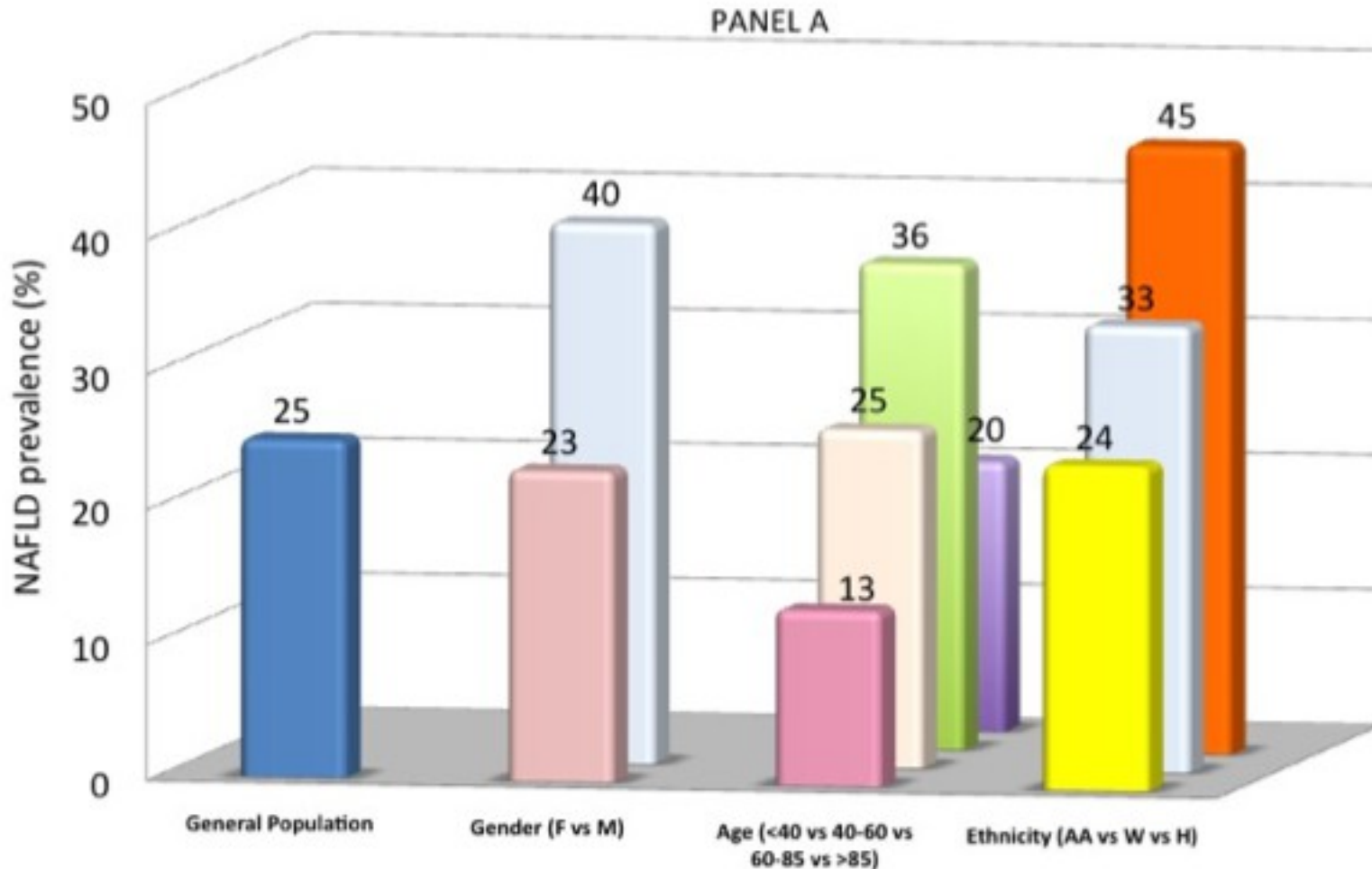Younossi Z, et al. *Hepatology* 2015

Prevalence of NAFLD as a function of obesity in different part of the world

*From Lazo et al. Semin.Liver Dis., 2008 modified*

# PREVALENCE OF NAFLD/NASH IN DIFFERENT POPULATIONS



Lonardo A, Bellentani S, et al., DLD 2015

# Prevalence NASH and advanced fibrosis in children/adolescents

| Time Intervals | NAFLD P (%) | NASH P (%) |
|---|---|---|
| 1998-1994 | 3.3 | 0.74 |
| 1999-2004 | 8.8 | 3.1 |
| 2005-2010 | 10.1 | 3.4 |

Selvakumar et al. :AASLD 2016 Abstr. n. 202

# 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.

Younossi Z, et al. *Hepatology* 2016

# 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=8-10%, NASH=2-5%

- 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 !)

# 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 hyperthension, diabetes  or alteration of lipid metabolism

- The economic and public health burden of NAFLD is enormous and increasing

# RISK FACTORS FOR NAFLD/NASH



PANEL B

Lonardo A, Bellentani S, et al., DLD 2015
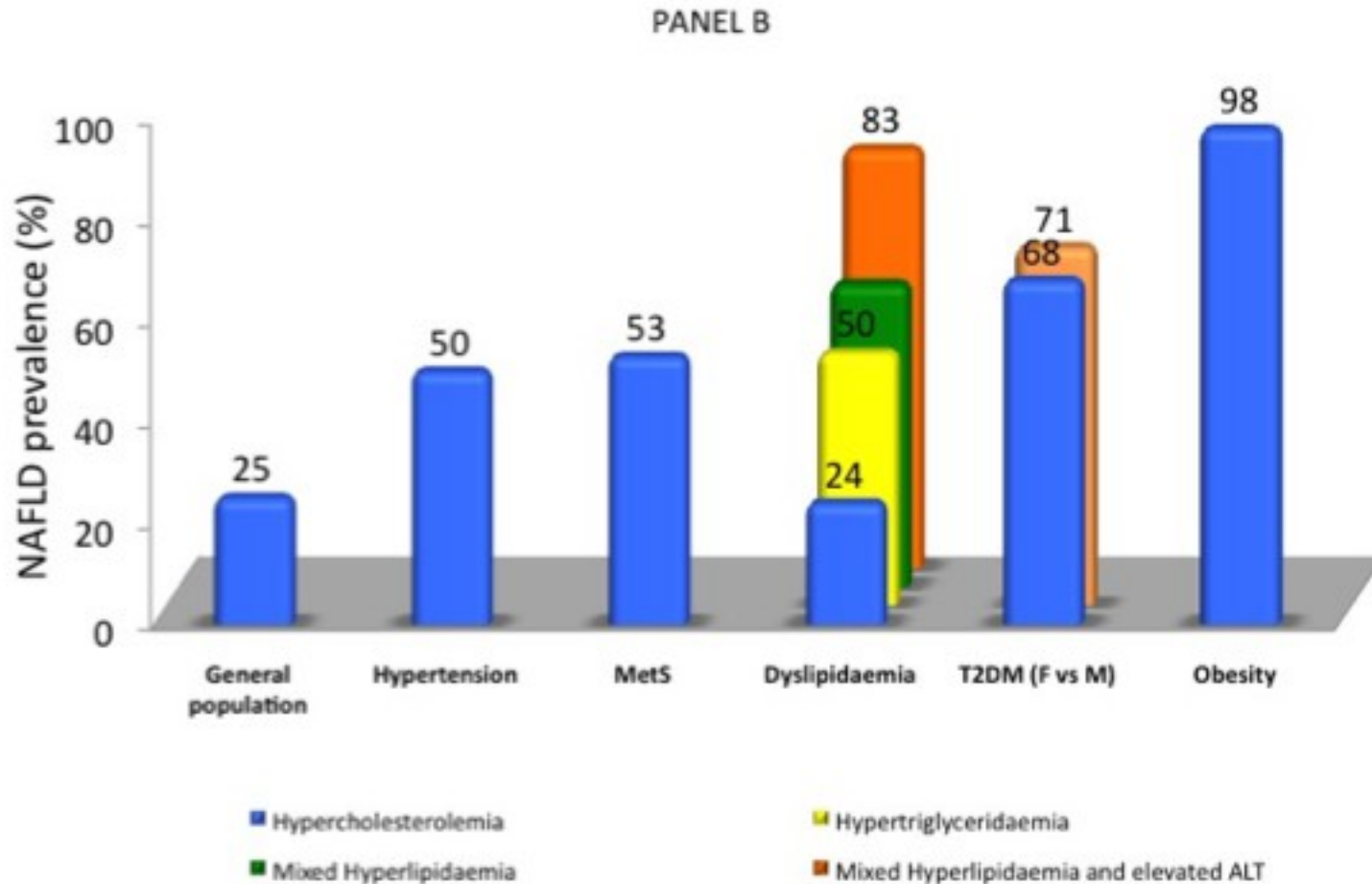
# EATING HABITS MODIFIES THE RISK OF NAFLD

Consuming a greater percentage of the daily calories in the morning decreased the odds of steatosis by 14% and 21%. Conversely, the odds of steatosis were 20% greater when morning and midday meals were skipped or when meals were consumed late in the night (73%). Late eating also increased the probability of developing significant fibrosis (61%).

CONCLUSIONS: Eating breakfast and lunch, and avoiding Latenight meals, reduce the risk of NAFLD

Esteban J et al.,AASLD 2016 Abstr. n. 34

# RISK FACTORS OF NAFLD TAKE HOME MESSAGES

Prevalence of NAFLD/NASH is higher in:
- Obese subjects (36-78%)
- Pts. with hyperglicemia or diabetes (43-62%)
- Pts. with hyperlipemia (45-65%)
- Pts. with hypertension (35-45%)
- Pts. with metabolic syndrome
- Pts. with  HCV infection (55%)
- Pts. consuming artificial fructose in the diet (soft drinks and junk food) and NOT consuming coffee
- Pts. consuming late-night meals and skipping breakfast and lunch

# NAFLD: main causes of mortality

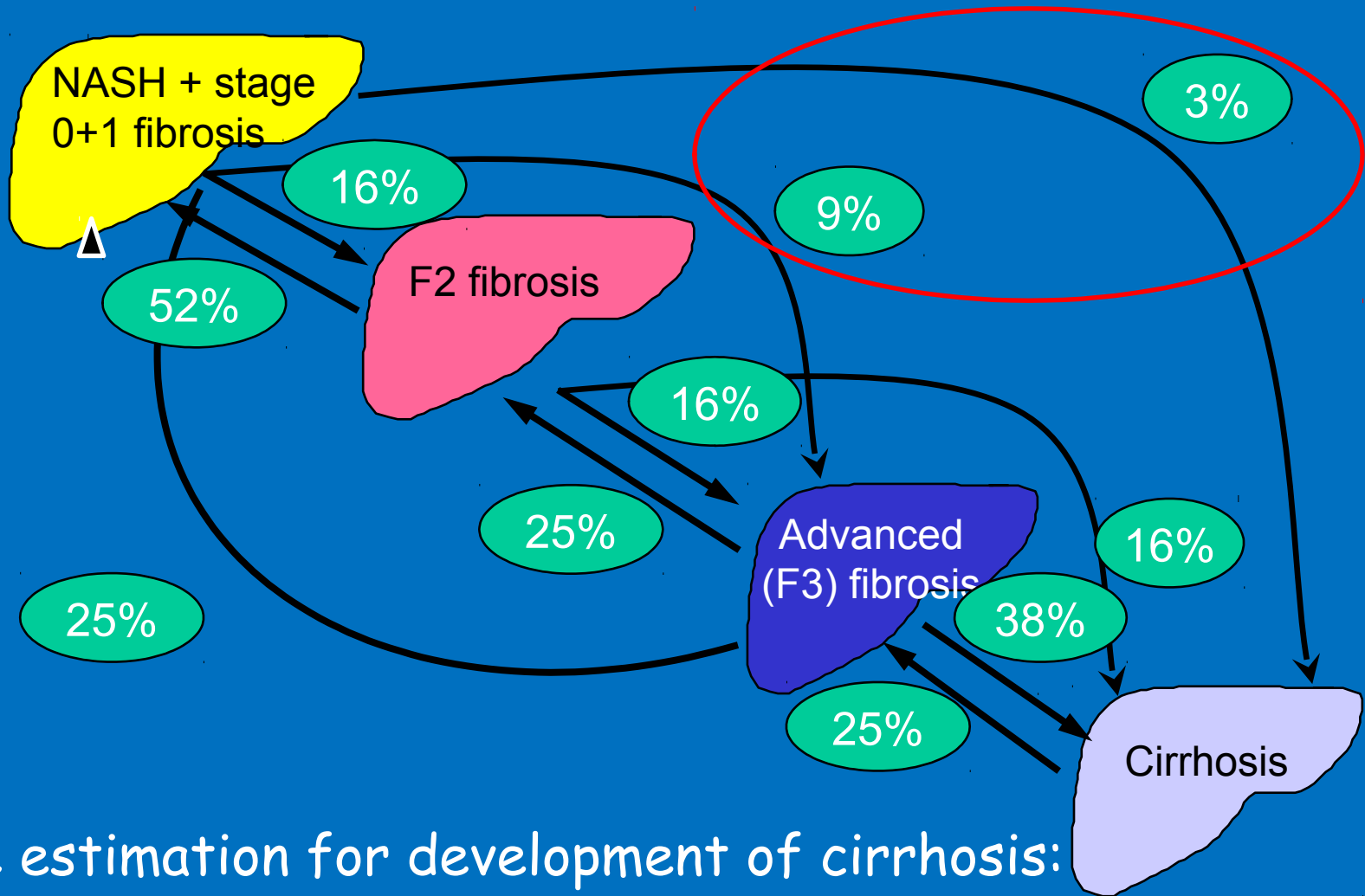Extrahepatic malignancies (28 % of all causes)

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

Colorectal cancer (lifestyle, production of adipokines)

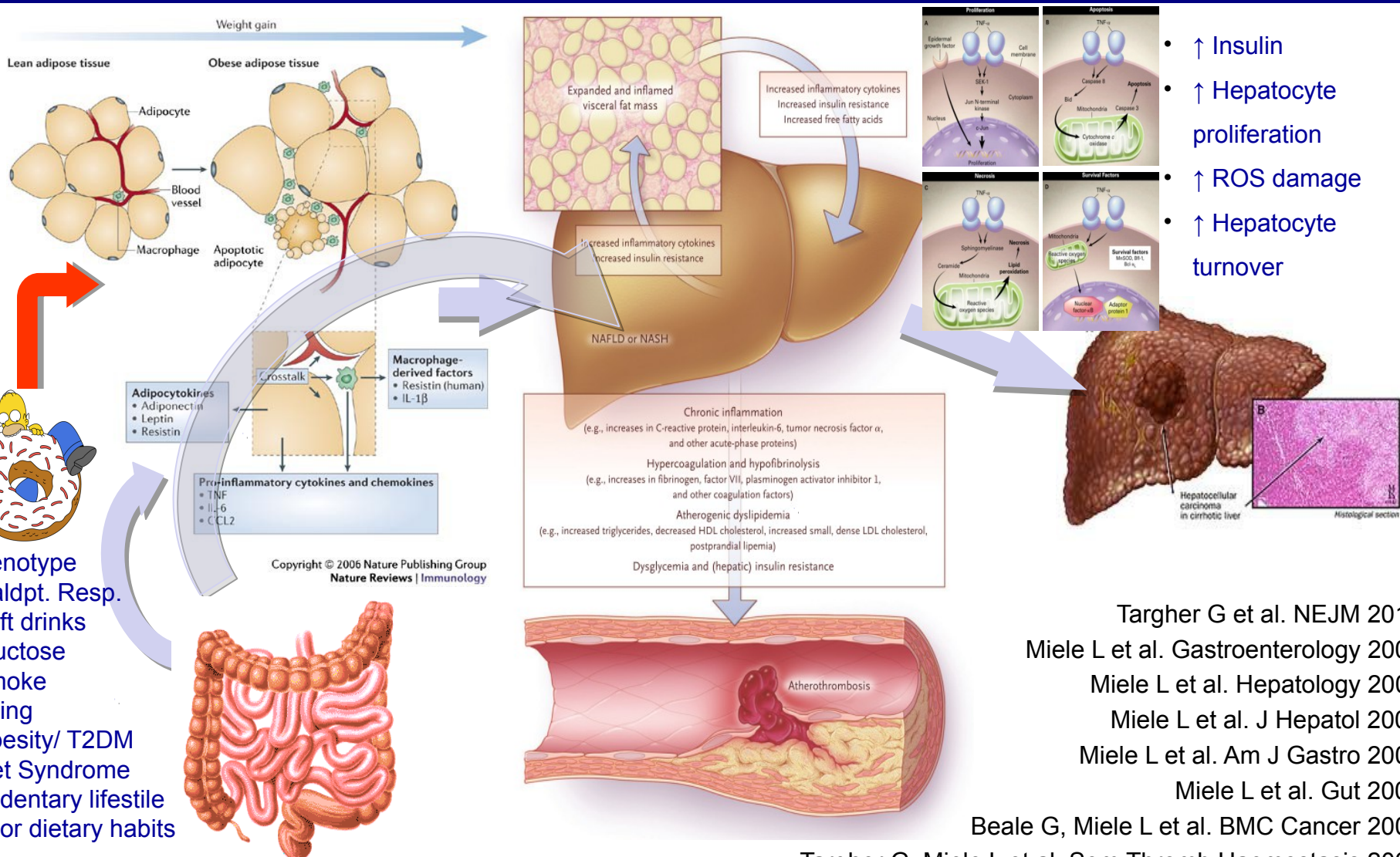Ischemic heart diseases (25 % of all causes)

Liver-related diseases (13% of all causes)

# Progression of fibrosis in NASH



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

# Progression of fatty liver and increased incidence of cardiovascular disease and HCC



- ↑ Insulin
- ↑ Hepatocyte proliferation
- ↑ ROS damage
- ↑ Hepatocyte turnover

Genotype
Maldpt. Resp.
Soft drinks
Fructose
Smoke
Aging
Obesity/ T2DM
Met Syndrome
Sedentary lifestile
Poor dietary habits

Targher G et al. NEJM 2010
Miele L et al. Gastroenterology 2008
Miele L et al. Hepatology 2009
Miele L et al. J Hepatol 2009
Miele L et al. Am J Gastro 2003
Miele L et al. Gut 2001
Beale G, Miele L et al. BMC Cancer 2009
Targher G, Miele L et al. Sem Thromb Haemostasis 2008

# THE BURDEN OF NAFLD/NASH AND NASH-RELATED CIRRHOSIS AND PREVALENCE OF HCC IN THE GENERAL POPULATION
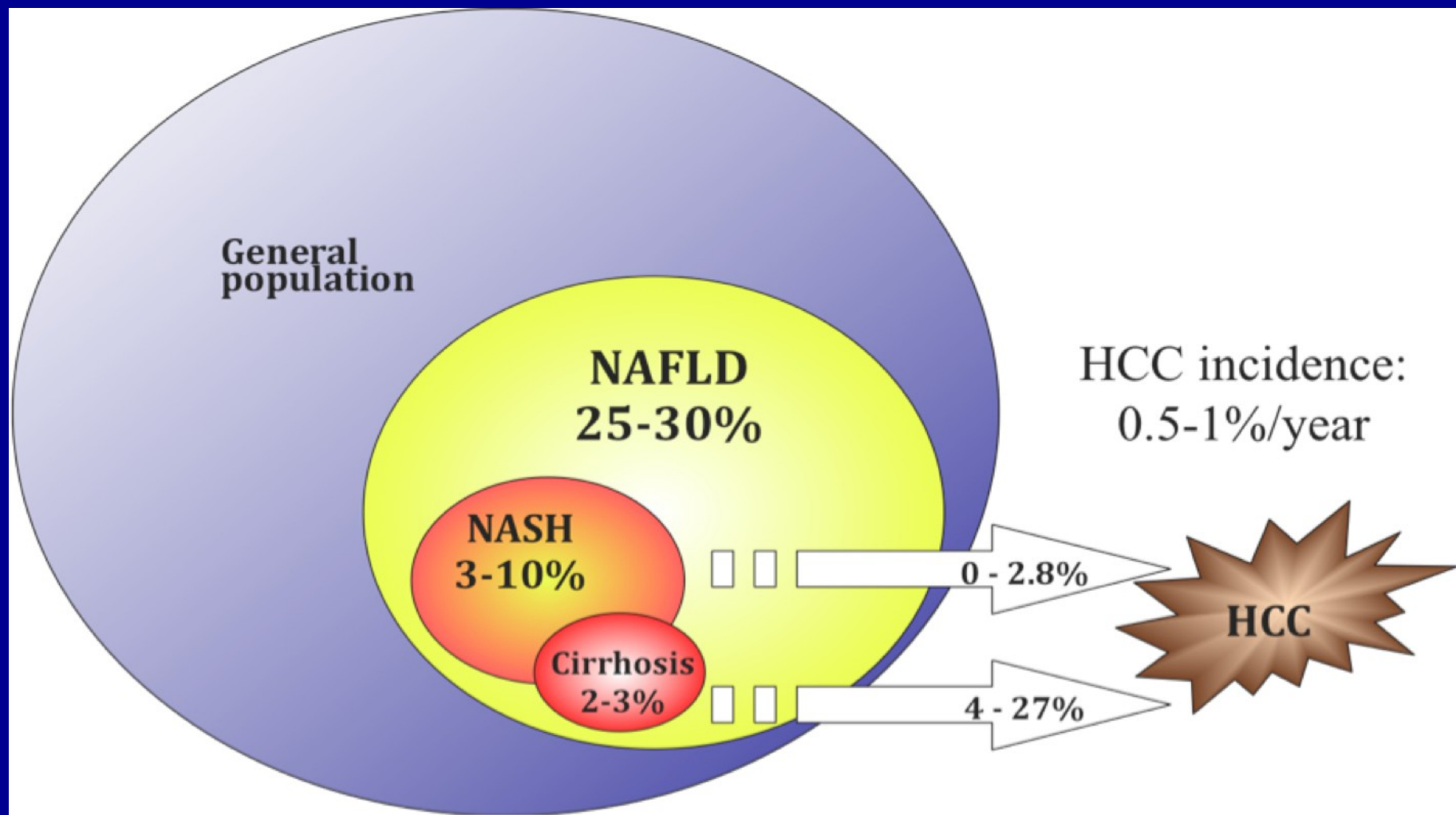
# CLINICAL PATTERNS OF HEPATOCELLULAR CARCINOMA (HCC) IN NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD): A MULTICENTER PROSPECTIVE STUDY

756 patients with either HCC-NAFLD (145) or HCC-HCV (611) were enrolled in Secondary Care Italian Centers

## RESULTS    HCC-NAFLD vs HCC-HCV:

- Significantly increased volume, more often  an infiltrative pattern
- Cirrhosis was present in only  about 55% vs 95% in HCC-HCV
- Propensity score analysis showed no significant difference in survival.
- Additionaly, no difference in survival between the 2 groups in patients within Milan criteria (38.6 vs 41.0 months, p=n.s.)

Piscaglia F et al. Hepatology, 2016

# 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 FUTURE:
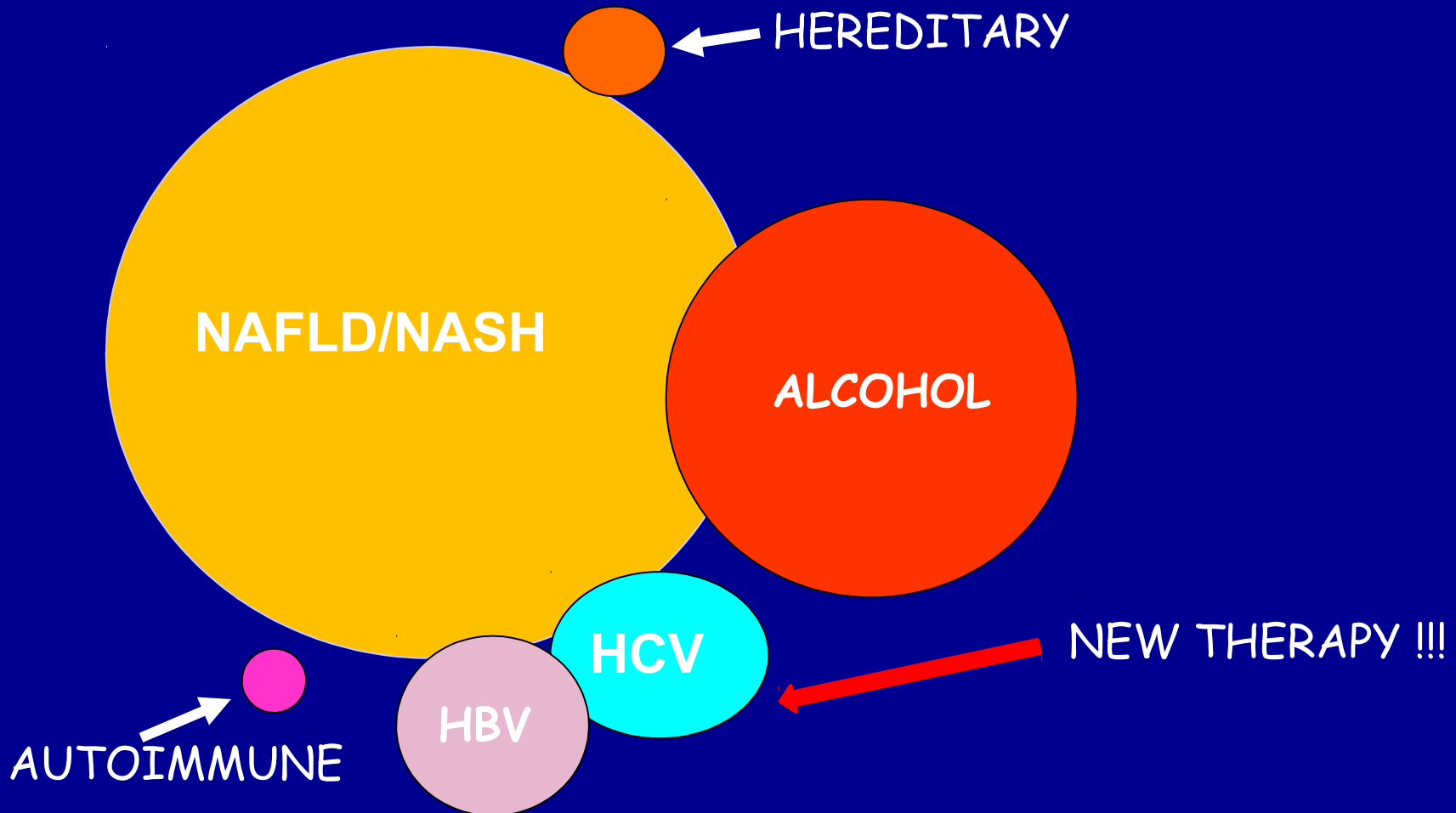
# Modeling NAFLD in Italy and US

April, 2016

# 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.

# The Hepatologist Menu - 2017

HEREDITARY

HCV

NAFLD

ALCOHOL

HBV

AUTOIMMUNE
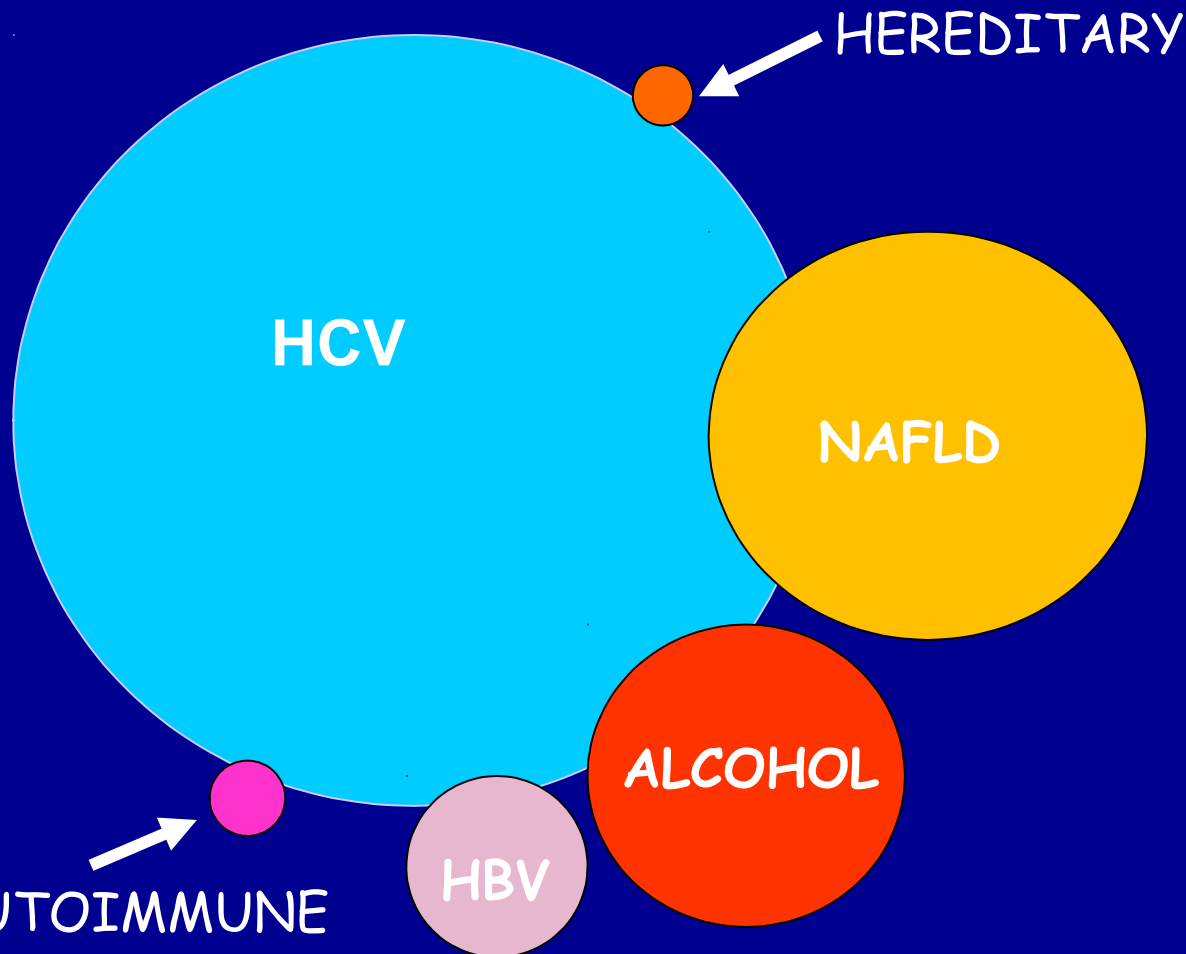
The Hepatologist Menu - 2030

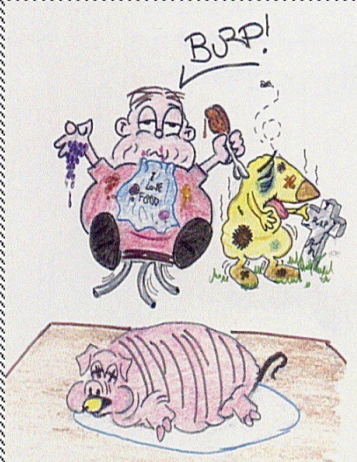# ARE WE READY TO CHANGE FROM A NEGATIVE DEFINITION (=NASH) TO A POSITIVE ONE ?

An International Consensus event is needed with these priorities :

1- Change the name from NASH to MESH
(MEtabolic Steato Hepatitis) ?
or simply Dis-metabolic Chronic Hepatitis (DCH).

2- Develop new protocols for the diagnosis, treatment
of patients with NASH and new policies
for the surveillance of patients with NASH
at risk to progress to cirrhosis and HCC

# THANK YOU VERY MUCH FOR YOUR ATTENTION !
## Stefano Bellentani, MD, PhD
bellentanistefano@gmail.com