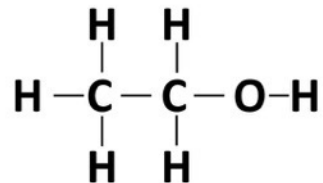


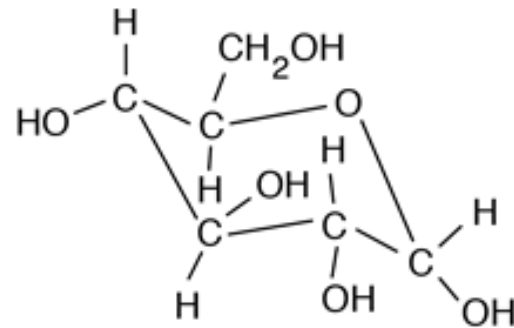
# Fat versus Alcohol: What Hurts the Most?

Mark Thursz

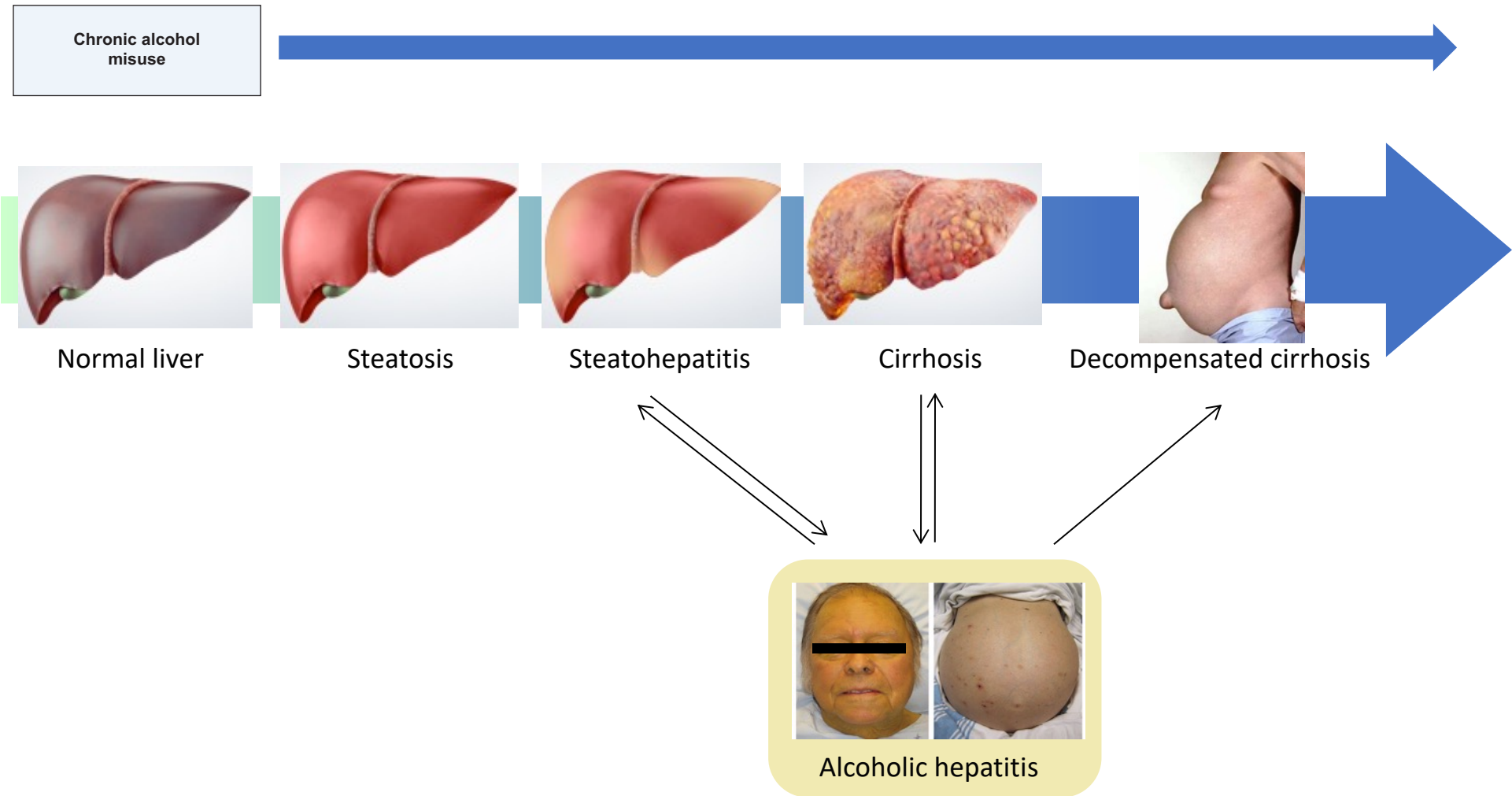
Imperial College London



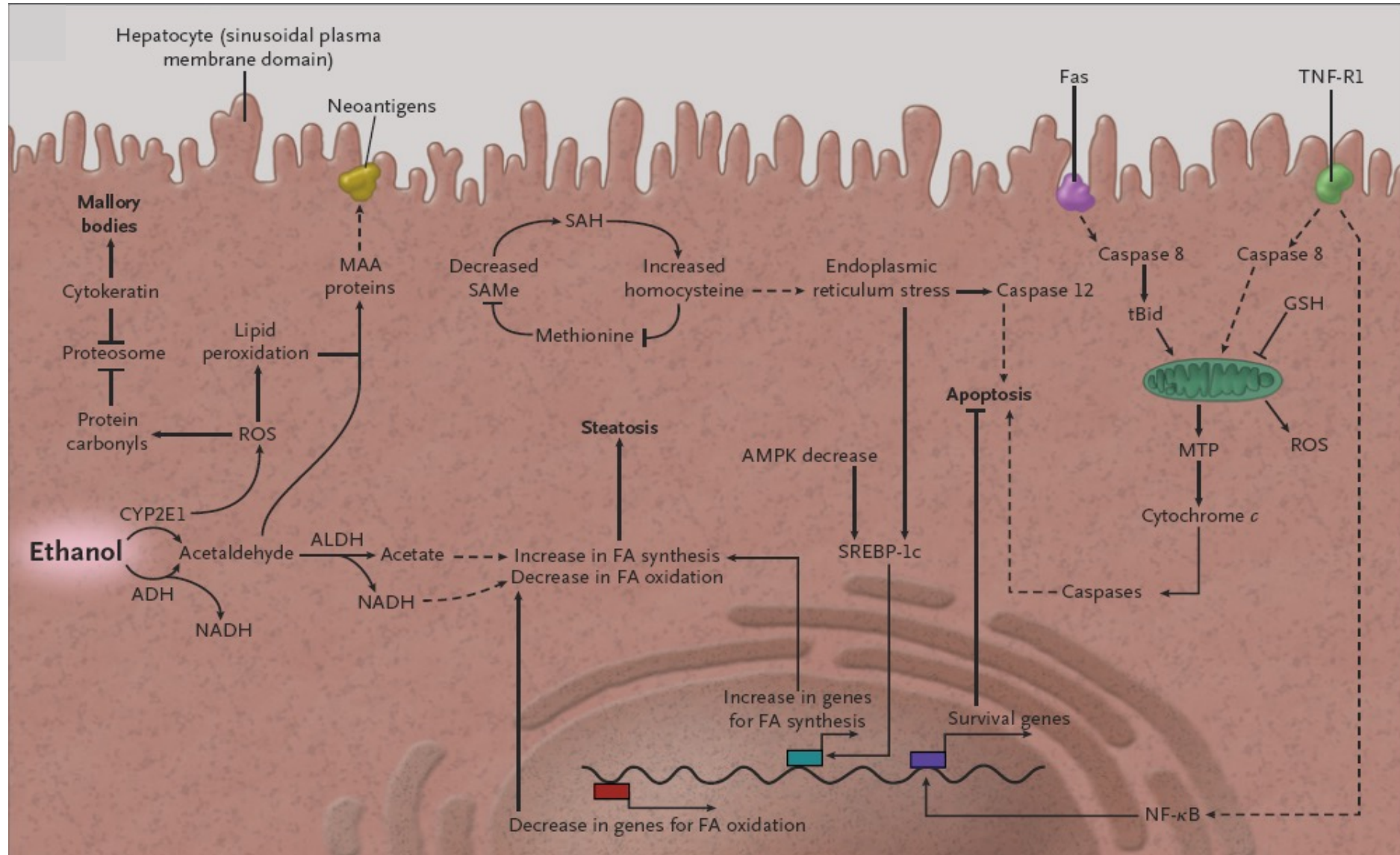
Versus

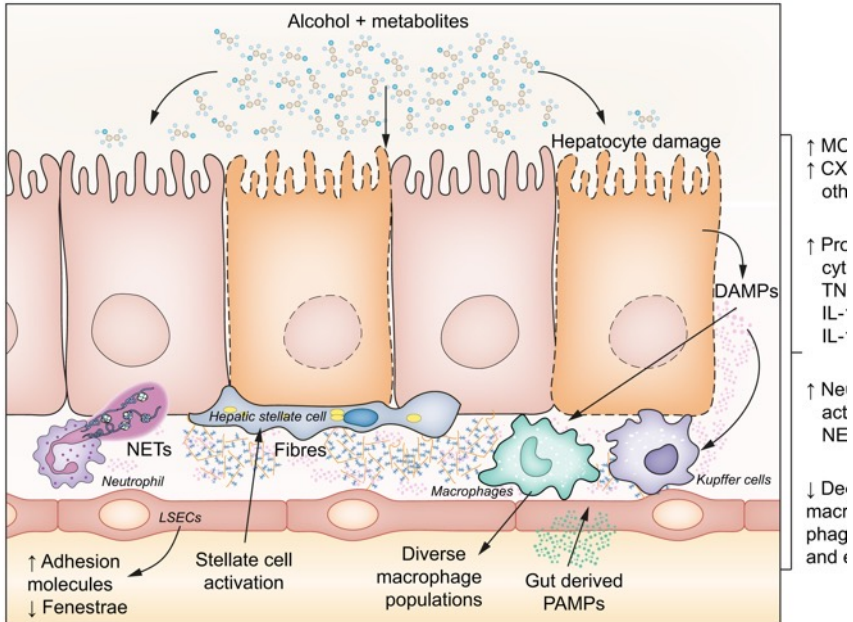
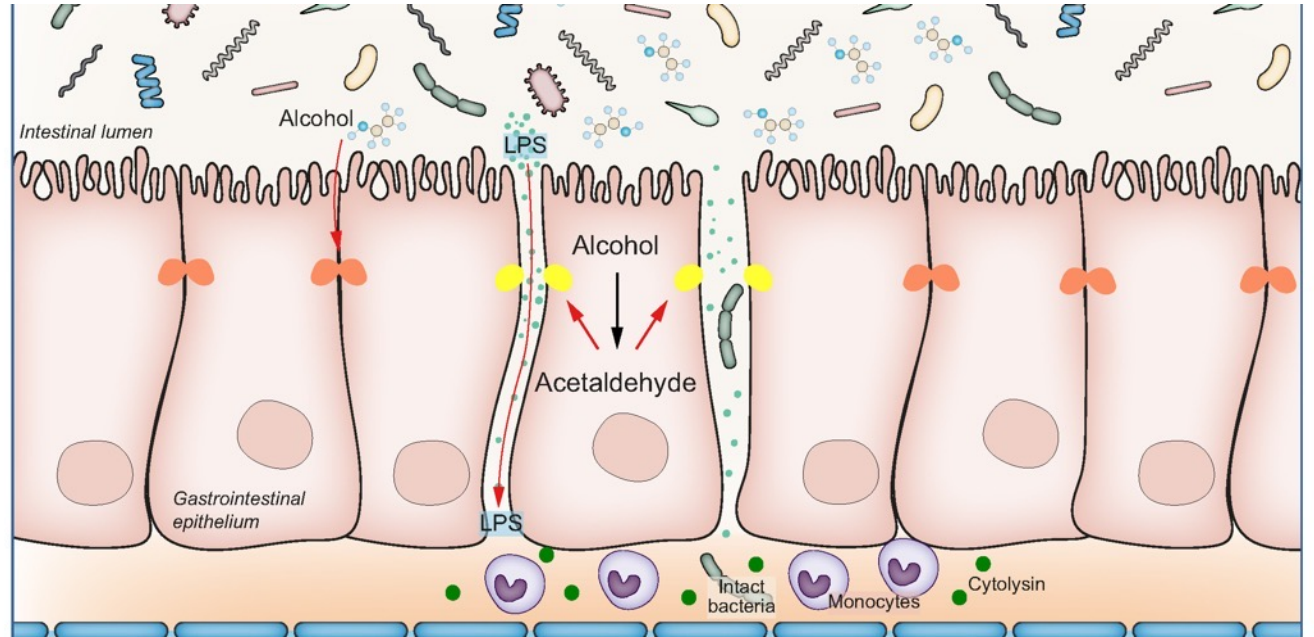


# Alcohol-Related Liver Disease: Alcohol Related Hepatitis



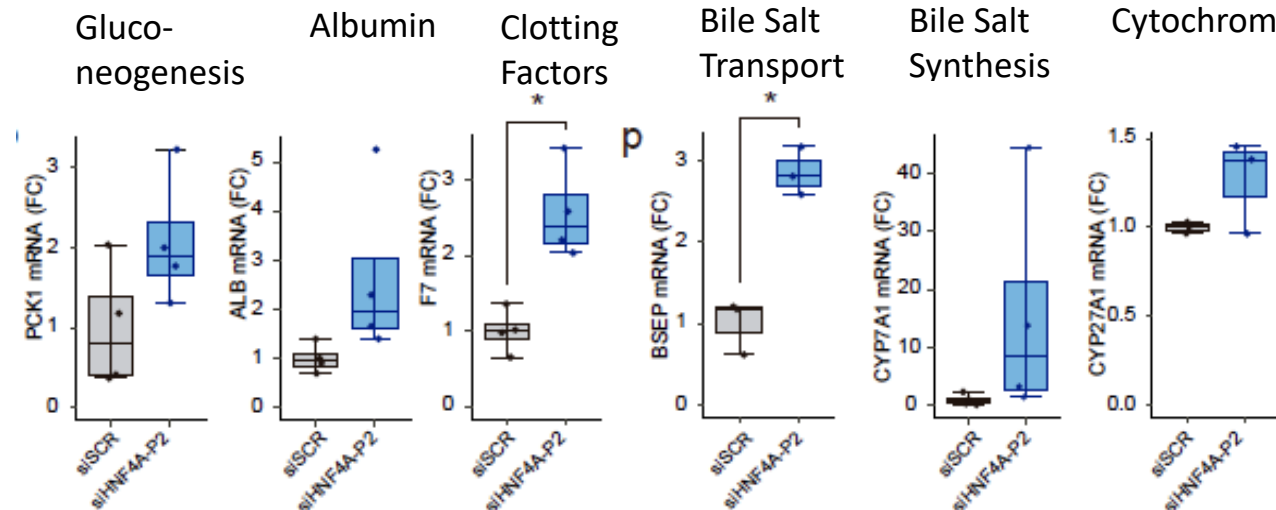
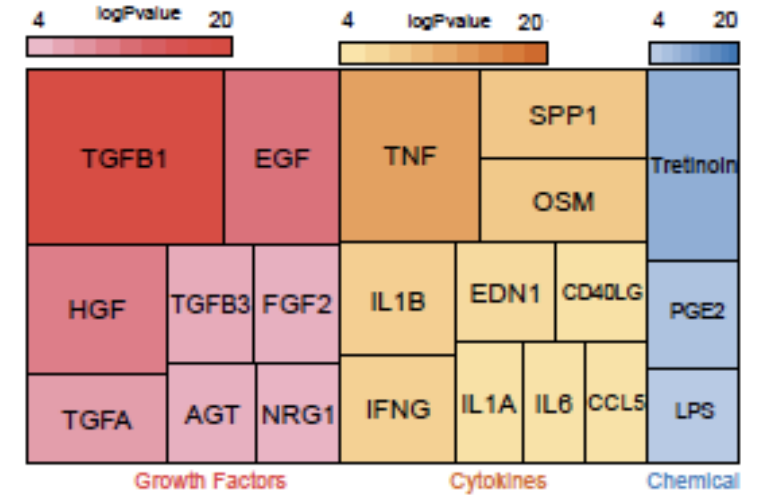
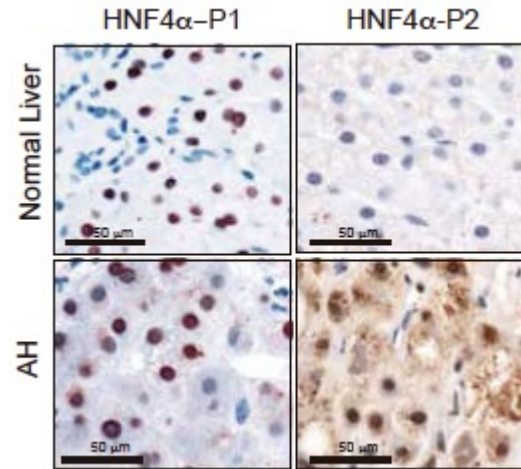
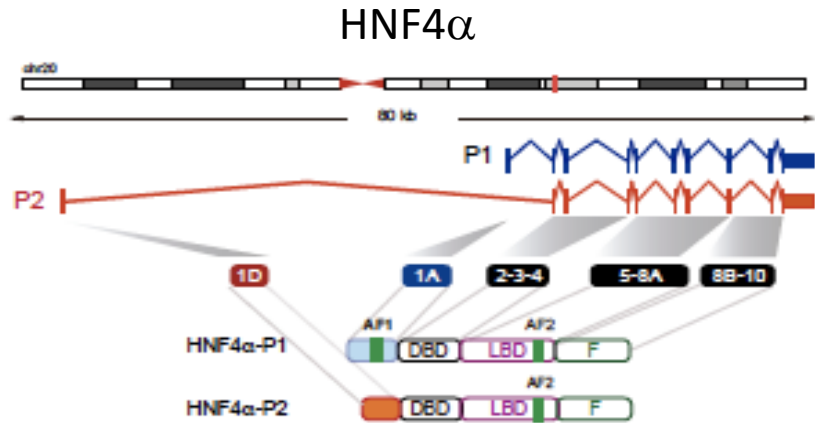
# Alcohol-Induced Cell Damage



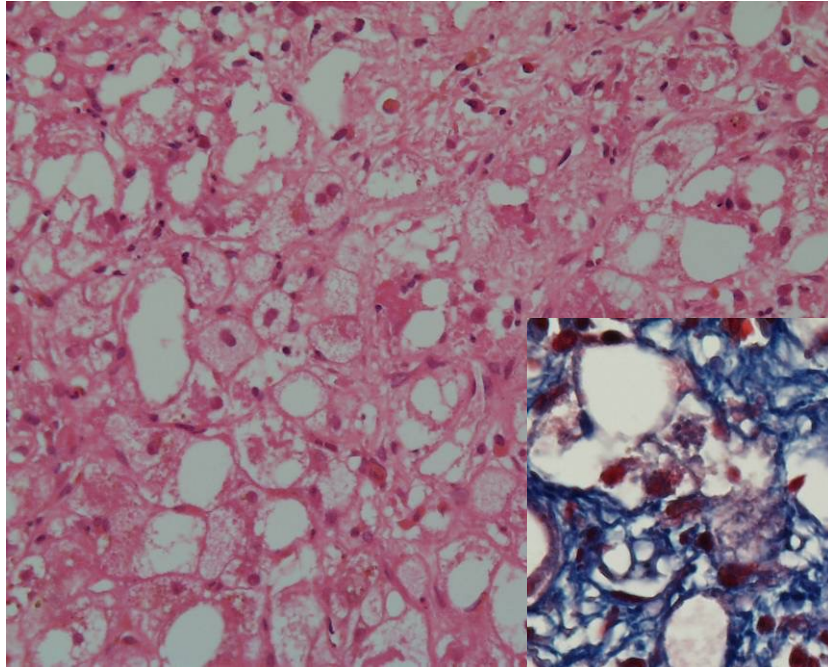


# Alcohol Causes Intestinal Damage and Liver Inflammation

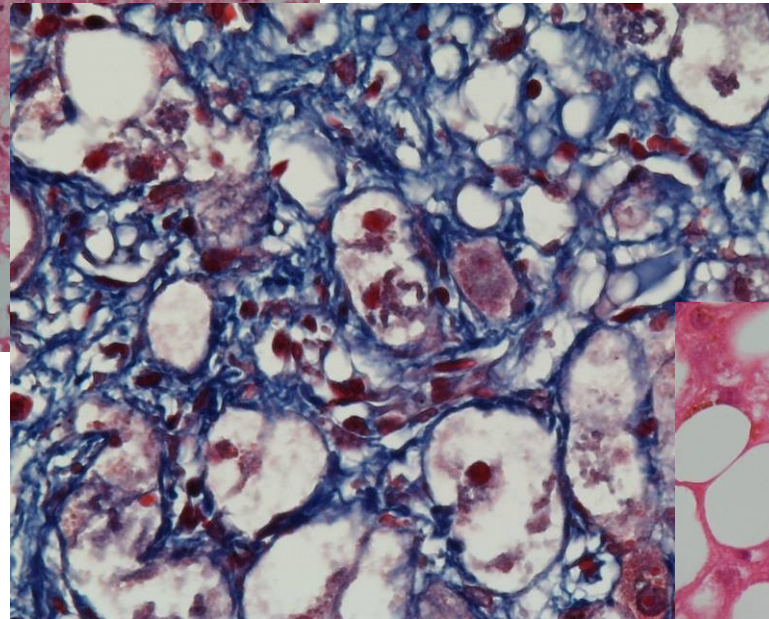
# Inflammation Epigenetics and Liver Dysfunction



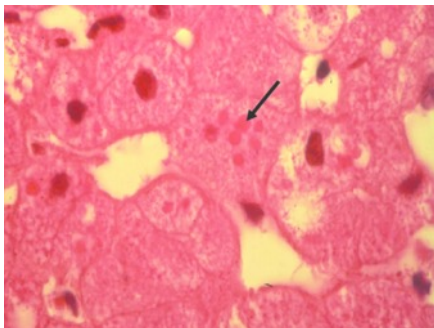
# Histological Appearance



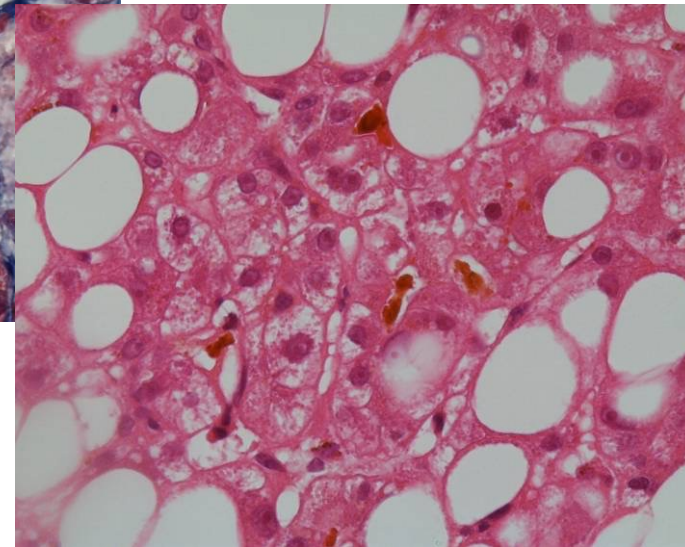
Steatosis  
Ballooning  
Mallory's Hyaline  
**Mega mitochondria**



Pericellular & perivenular  
fibrosis

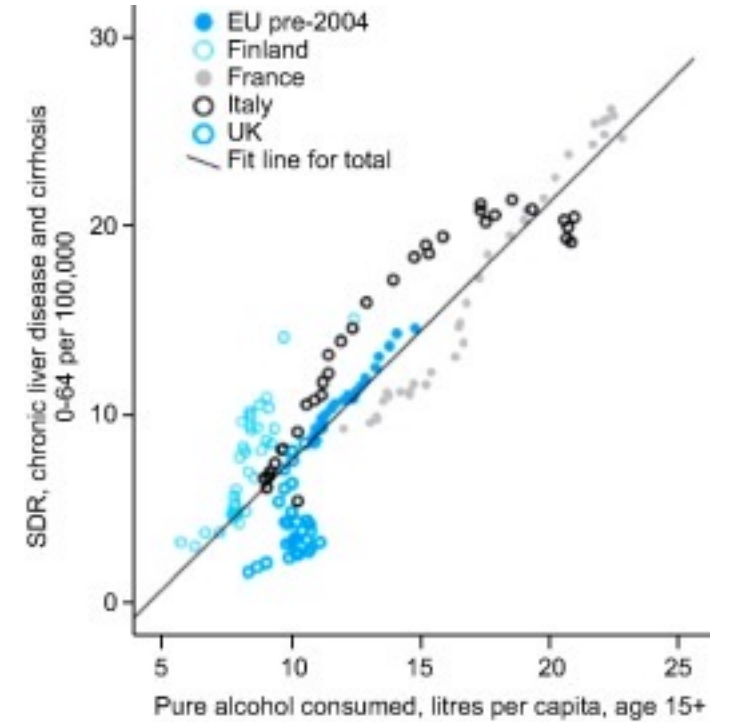
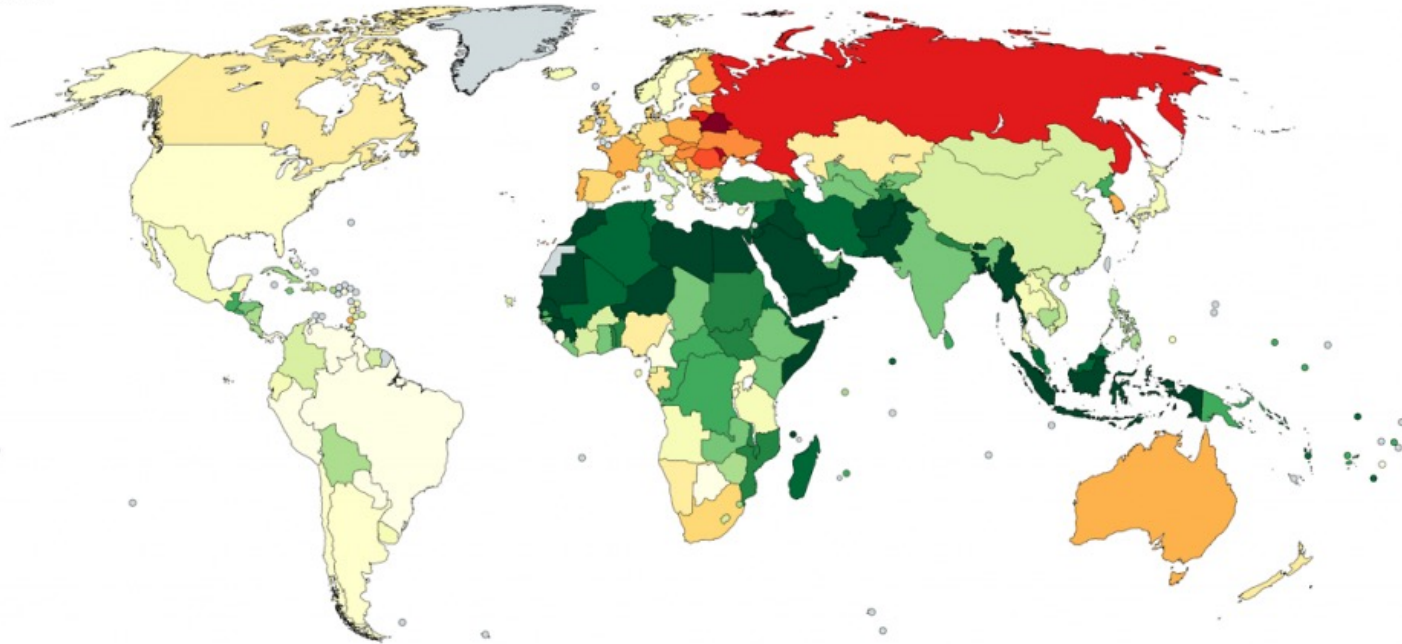
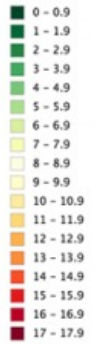


**Bile plugging**

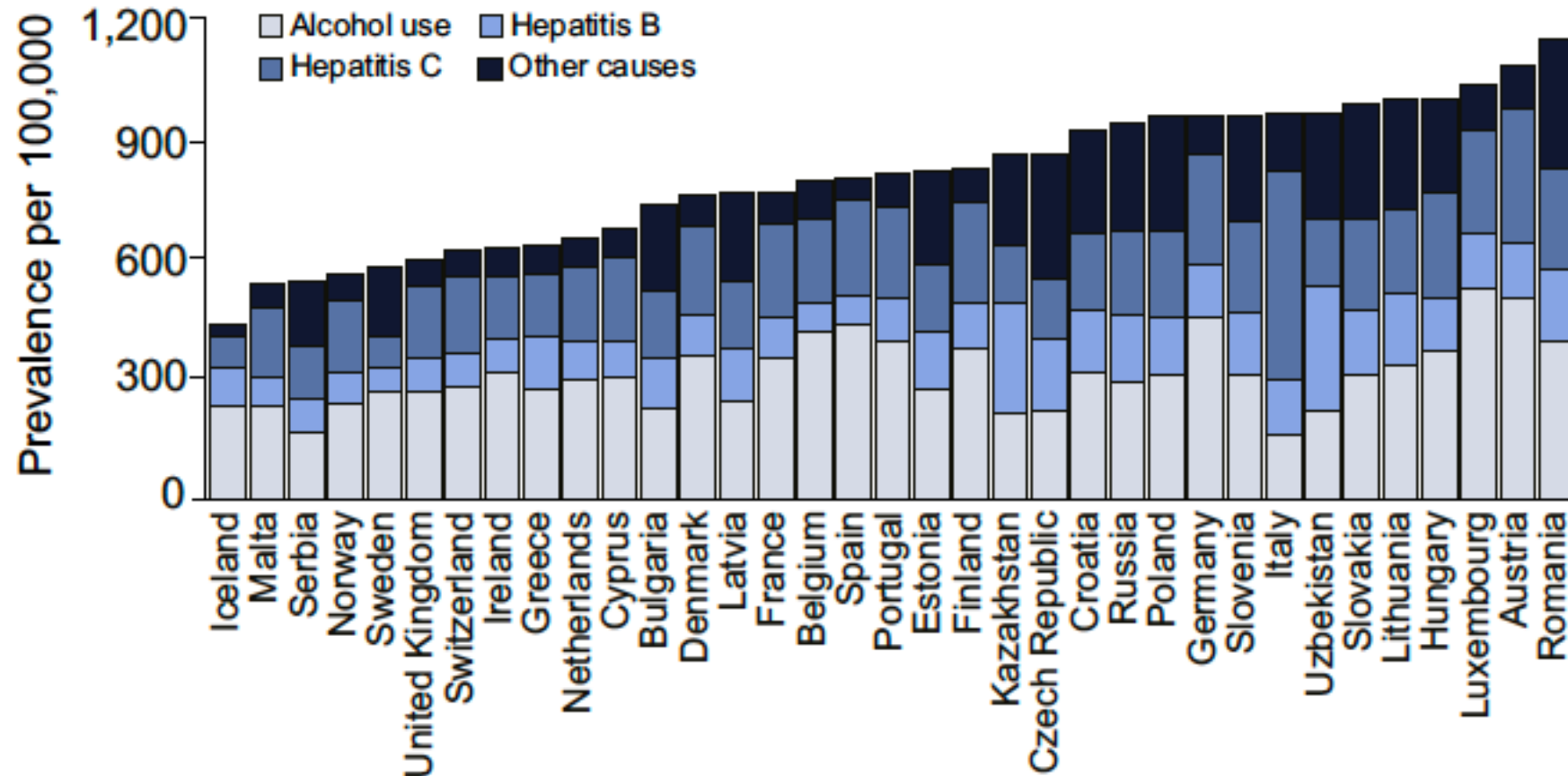


# Rate of Alcohol Consumption And Cirrhosis Deaths

Pure alcohol consumption among persons (age 15+) in liters per capita

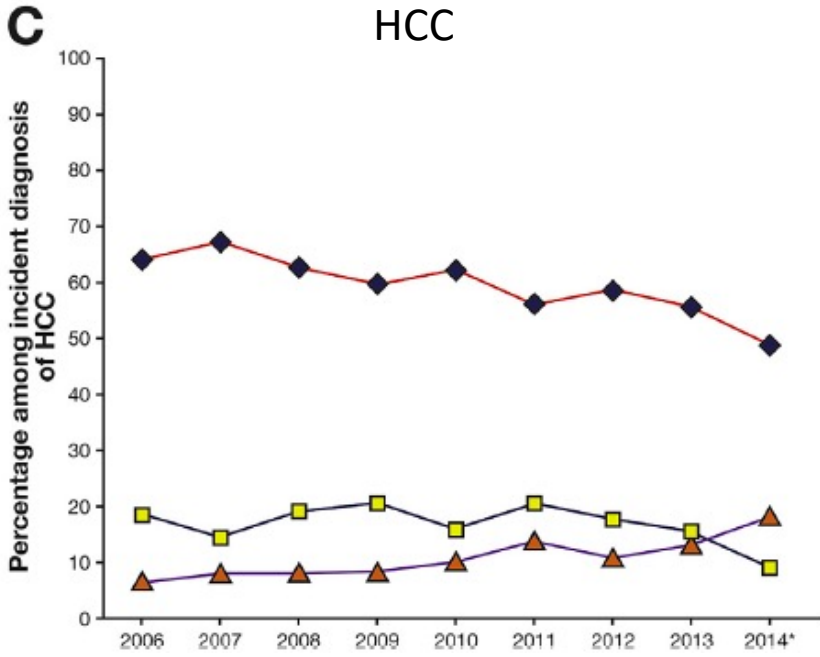
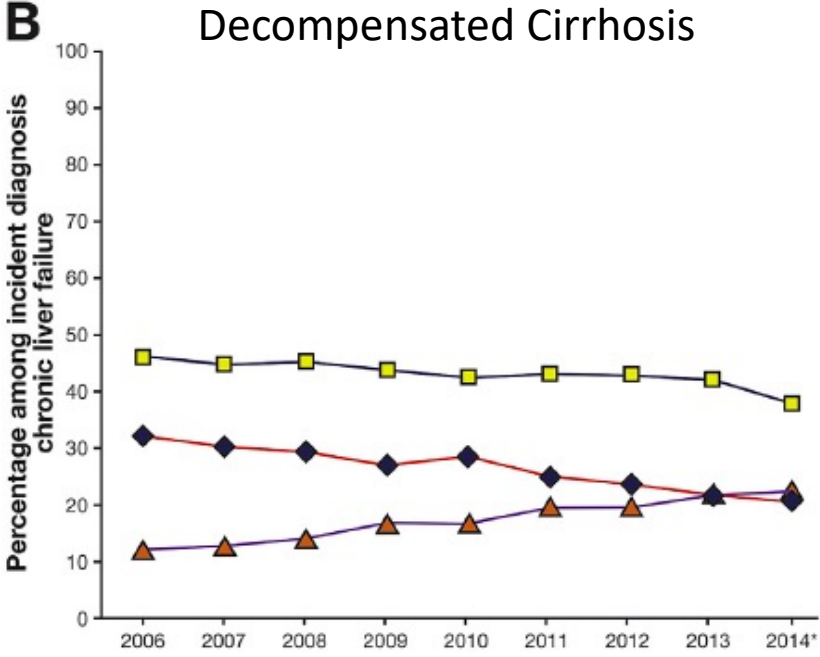
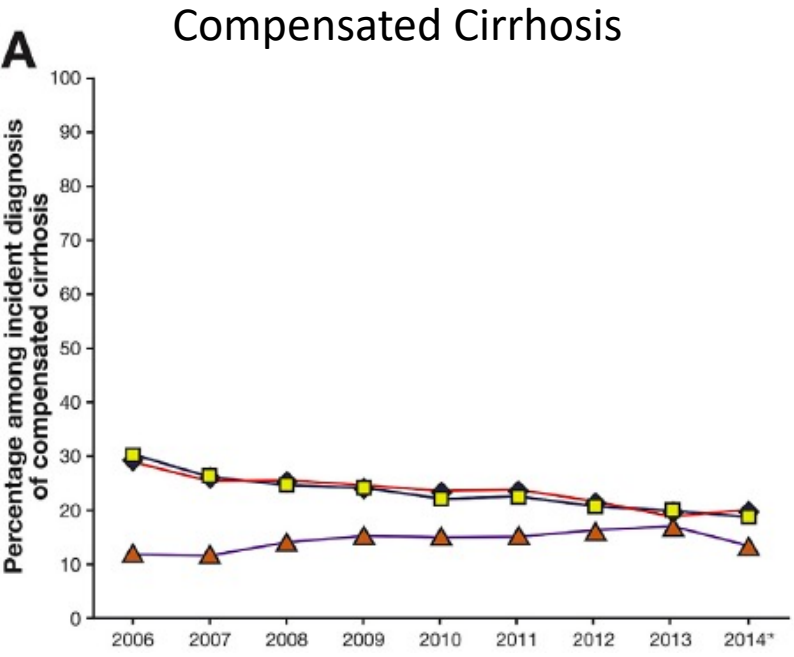




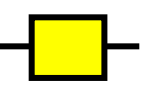
# Age Standardised Prevalence of Cirrhosis By Aetiology 2016



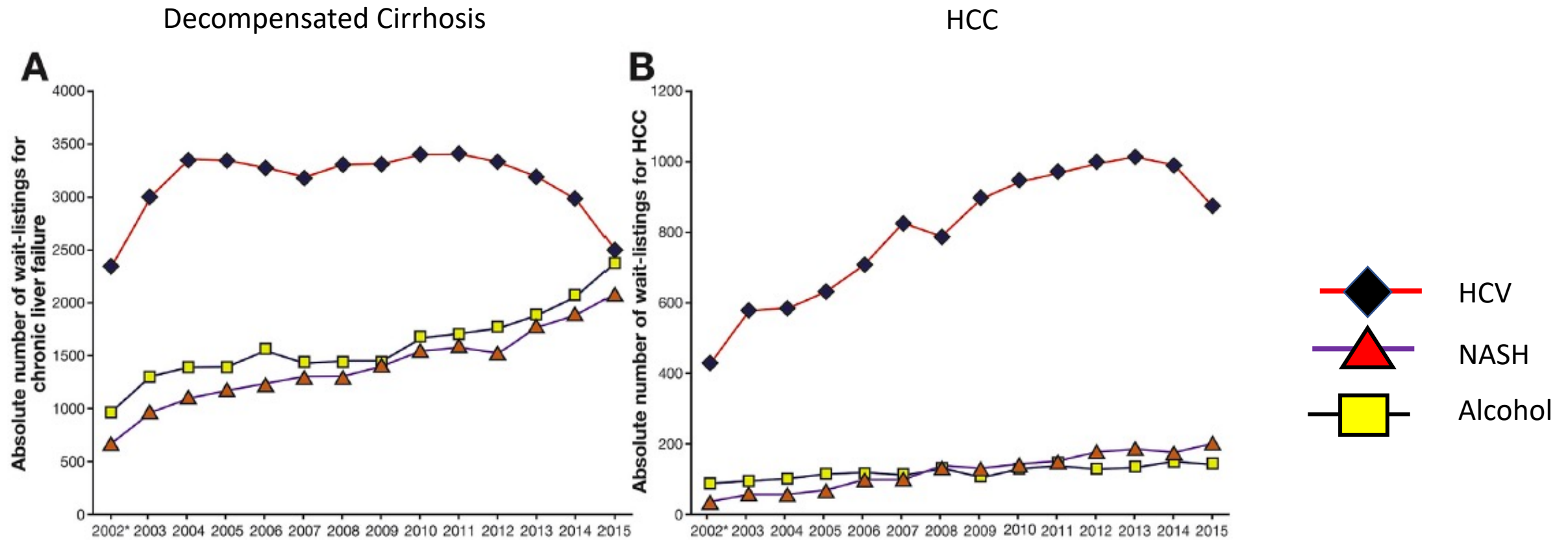


# US NHANES Incident Diagnoses By Aetiology



-  HCV
-  NASH
-  Alcohol

# US Transplant Waiting List By Aetiology

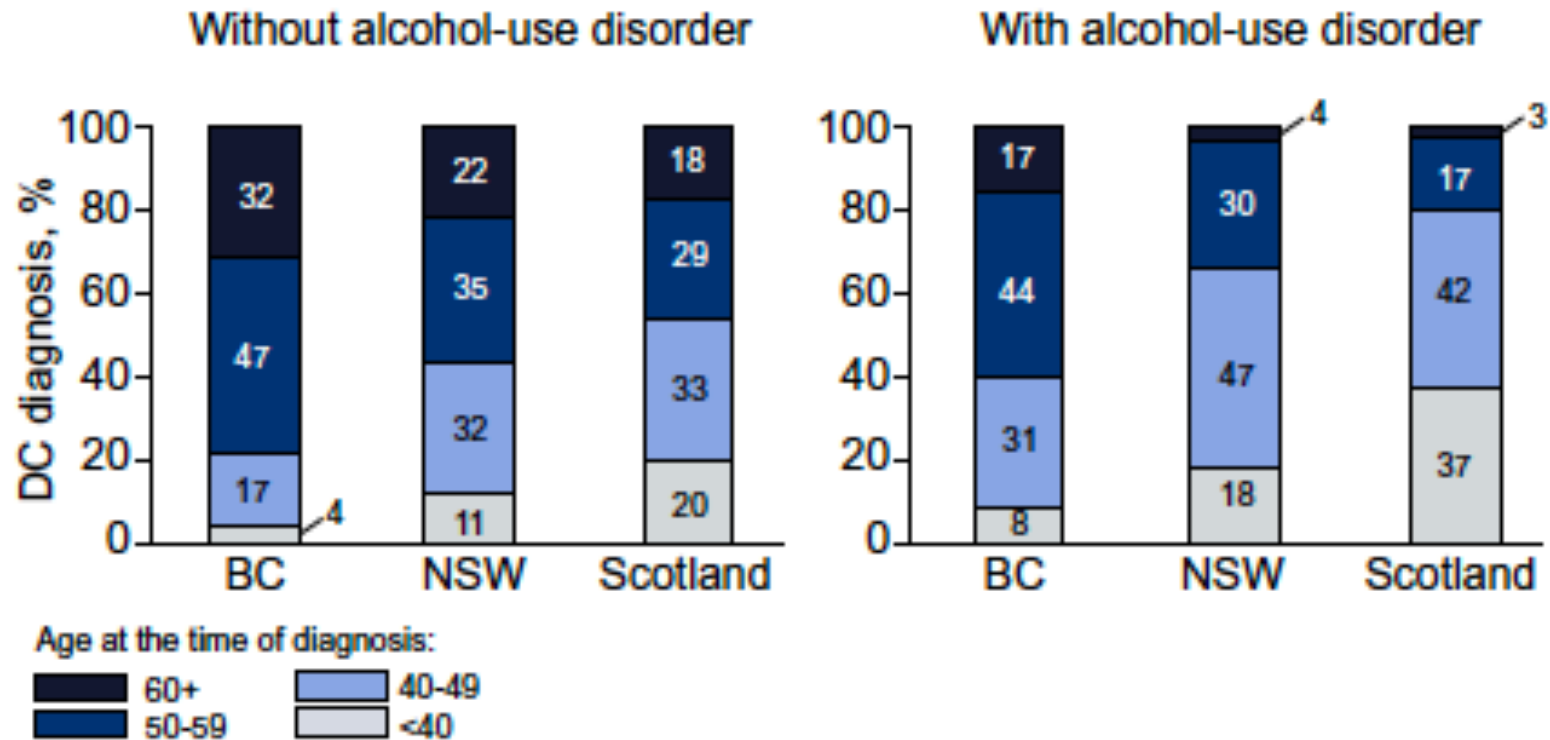


# Alcohol Makes a Major Contribution to Decompensated Cirrhosis amongst Patients with HCV

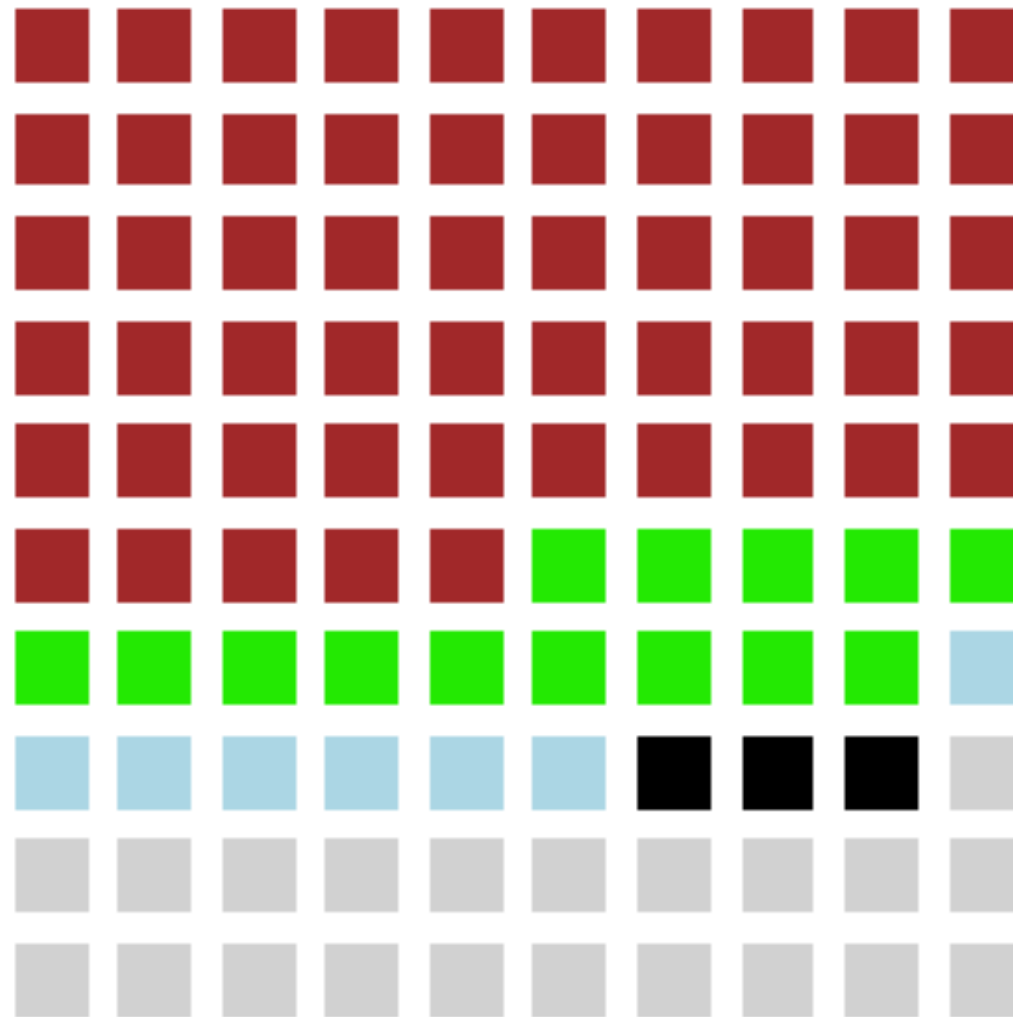
## Population Attributable Fraction

	<b>BC HCV notification, 1995–2011</b> N = 55,879 DC diagnosis 2001–2012, n = 2,443				<b>NSW HCV notification, 1995–2012</b> N = 82,526 DC diagnosis 2001–2013, n = 2,559				<b>Scotland HCV notification, 1995–2013</b> N = 30,746 DC diagnosis 2001–2014, n = 1,020			
	<b>Alcohol-use disorder, n</b>	<b>%</b>	<b>PAF<sup>α</sup></b>	<b>95% CI</b>	<b>Alcohol-use disorder, n</b>	<b>%</b>	<b>PAF<sup>α</sup></b>	<b>95% CI</b>	<b>Alcohol-use disorder, n</b>	<b>%</b>	<b>PAF<sup>α</sup></b>	<b>95% CI</b>
<b>All</b>	688	7	13	11–15	887	6	25	23–27	556	7	40	36–44
<b>Born ≥1965</b>	90	3	21	16–25	247	3	36	32–40	309	5	48	43–53
<b>Born &lt;1965</b>	598	9	12	10–14	640	13	22	20–24	247	12	33	28–37

# Age at Decompensation In Patients with HCV



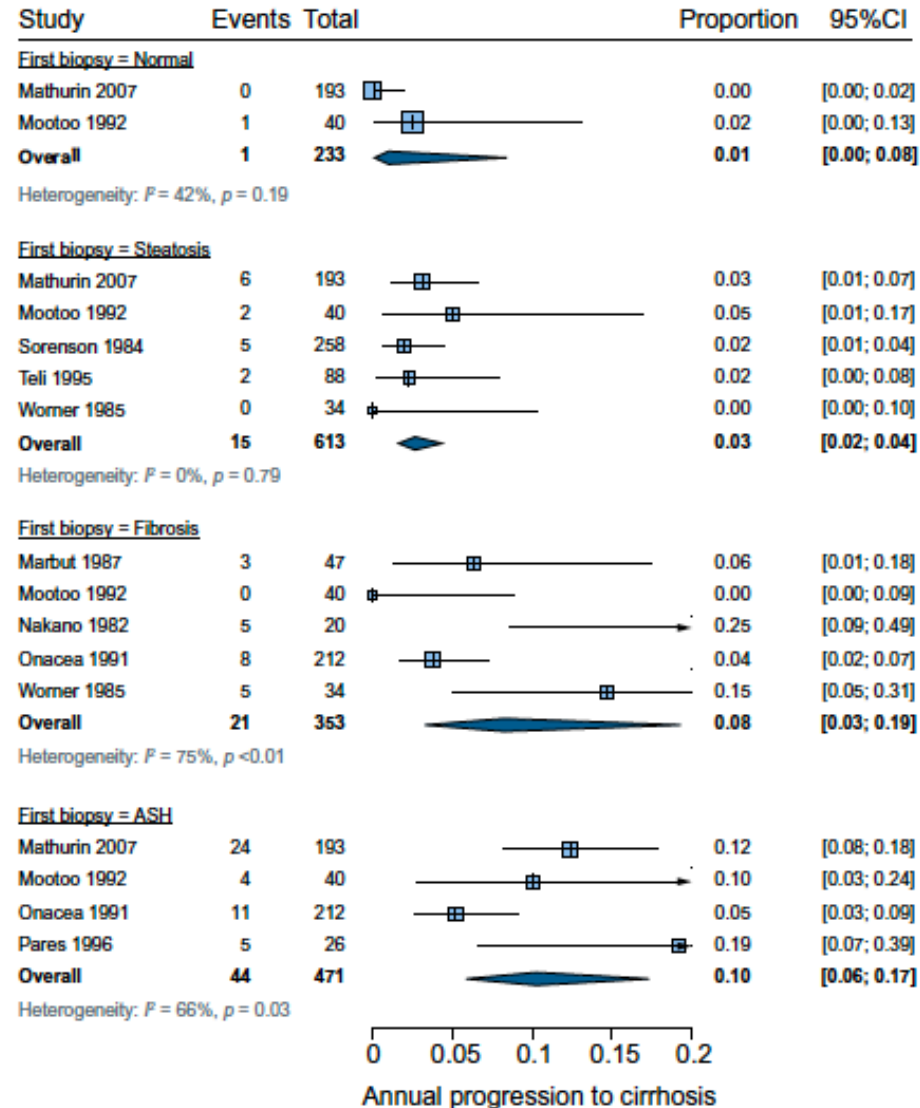
## Attributable risks of liver disease progression to a liver-related complications in a retrospective, in-hospital, cohort, of more than 50,000 T2D patients, 2010-2020



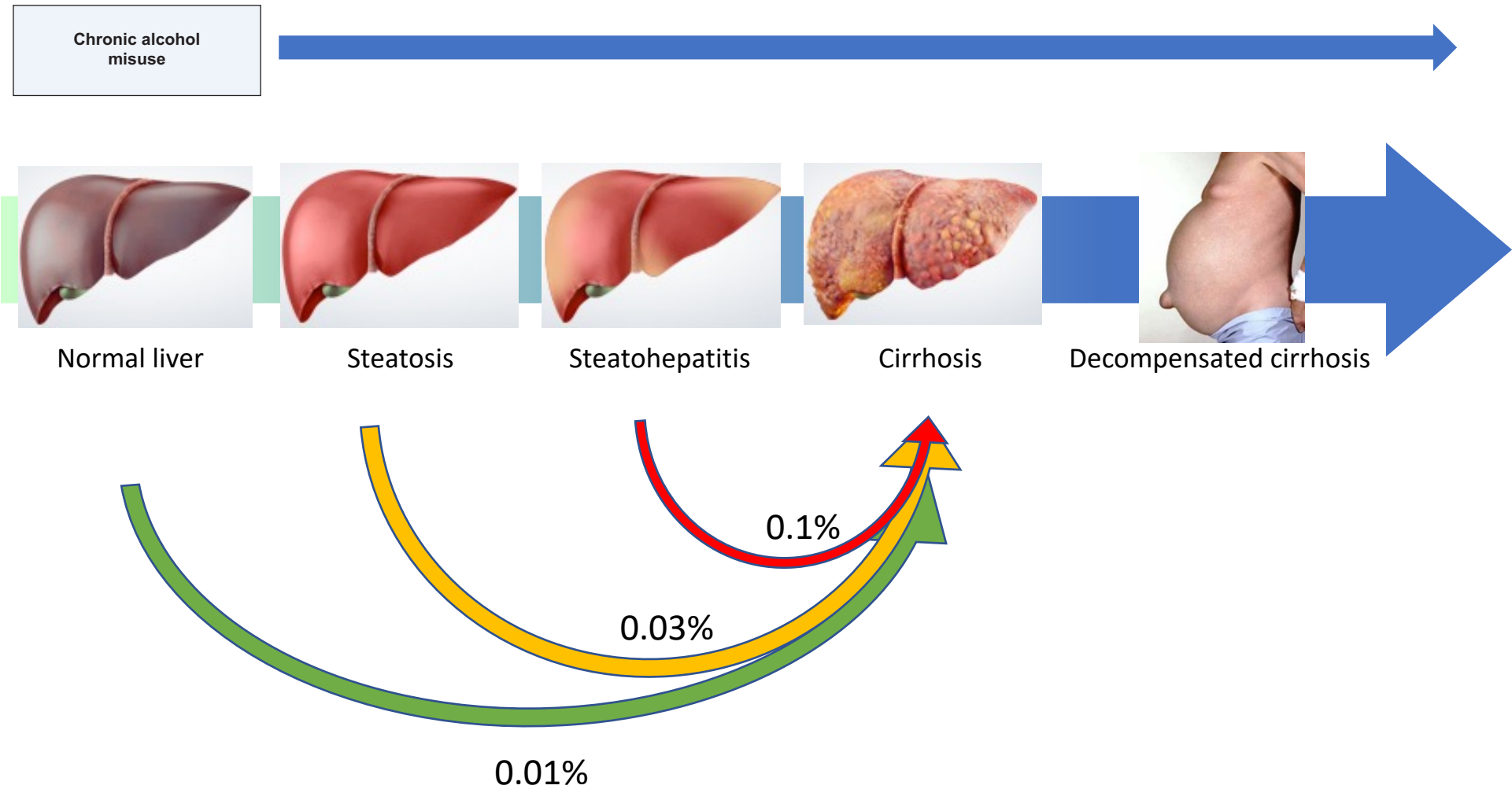
The attributable fraction reflects the number of liver events that would have been prevented in the absence of a risk factor. Attributable fractions were computed with Cox models stratified on sex with age as the time scale, and adjusted for alcohol use disorders, non-metabolic liver-related risk factors, obesity, and non-liver-related risk factors.

- Dark Red: Alcohol use disorders
- Green: Liver-related risk factors
- Light Blue: Obesity
- Black: Non-liver-related risk factors
- Grey: No risk factor identified

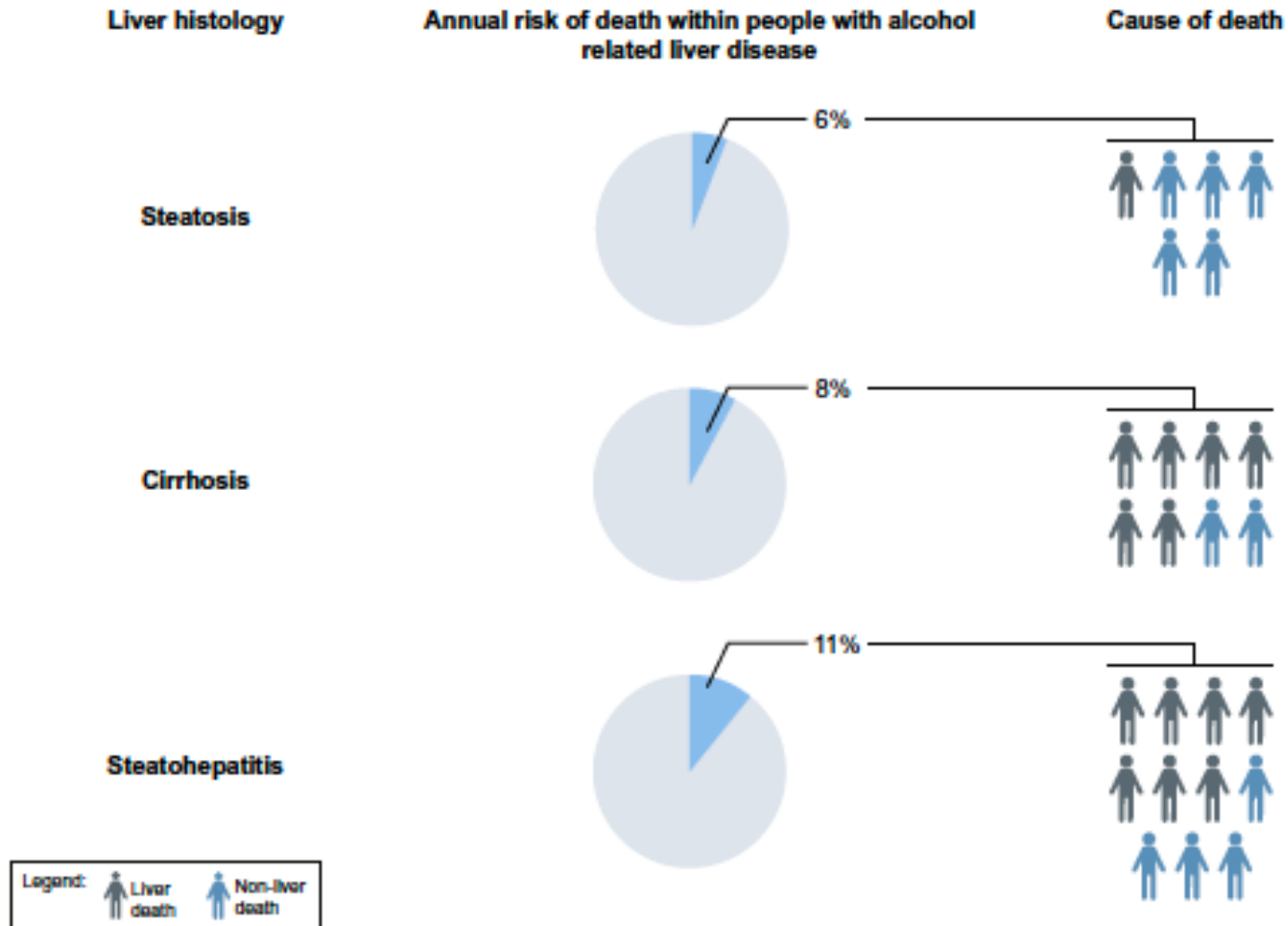
# Progression to Cirrhosis



# Alcohol-Related Liver Disease: Rate of Progression

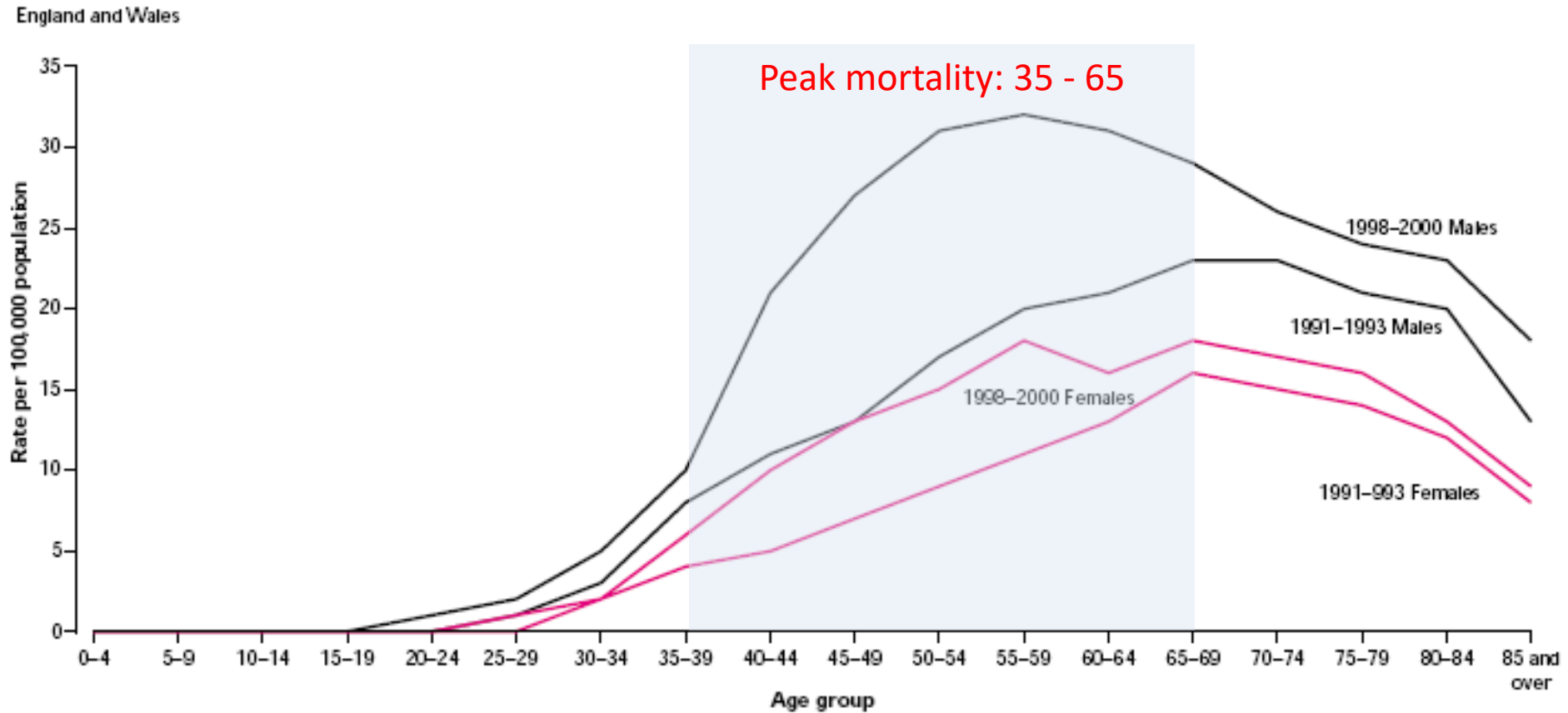


# ALD Mortality

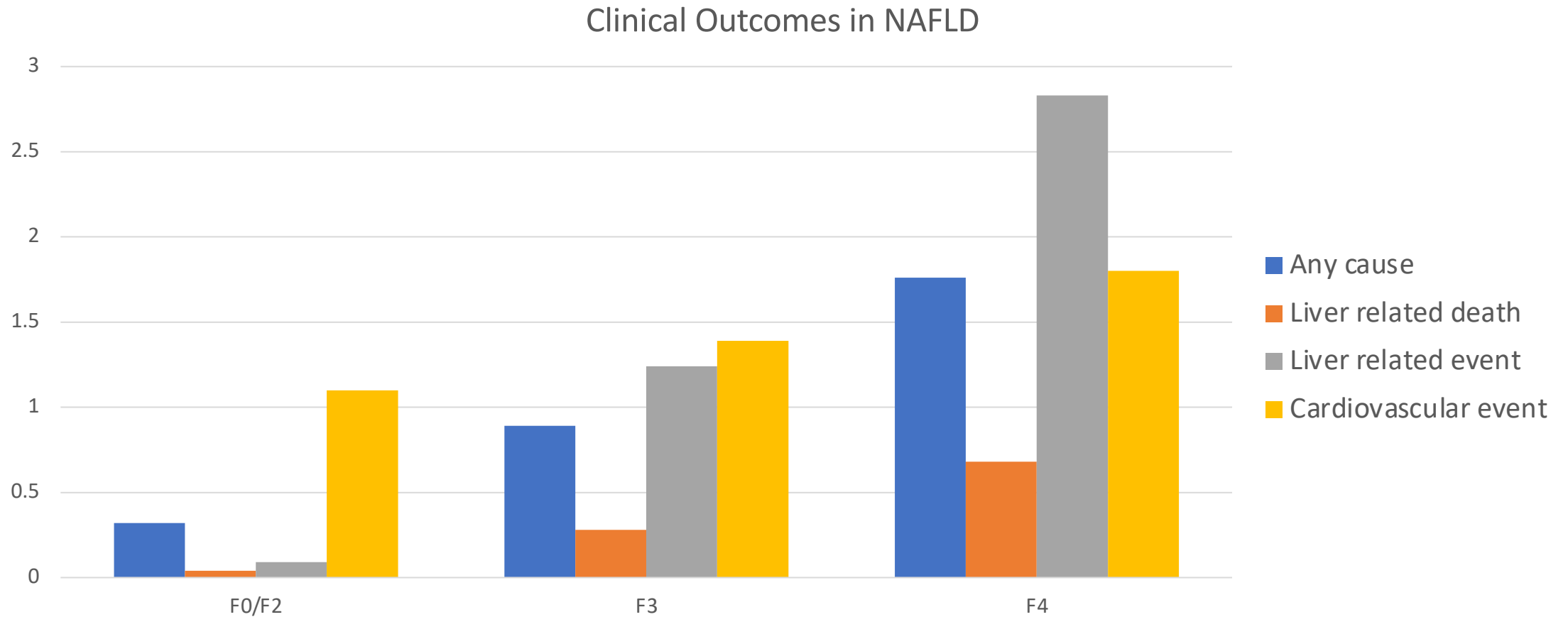




# Mortality and Age in ALD



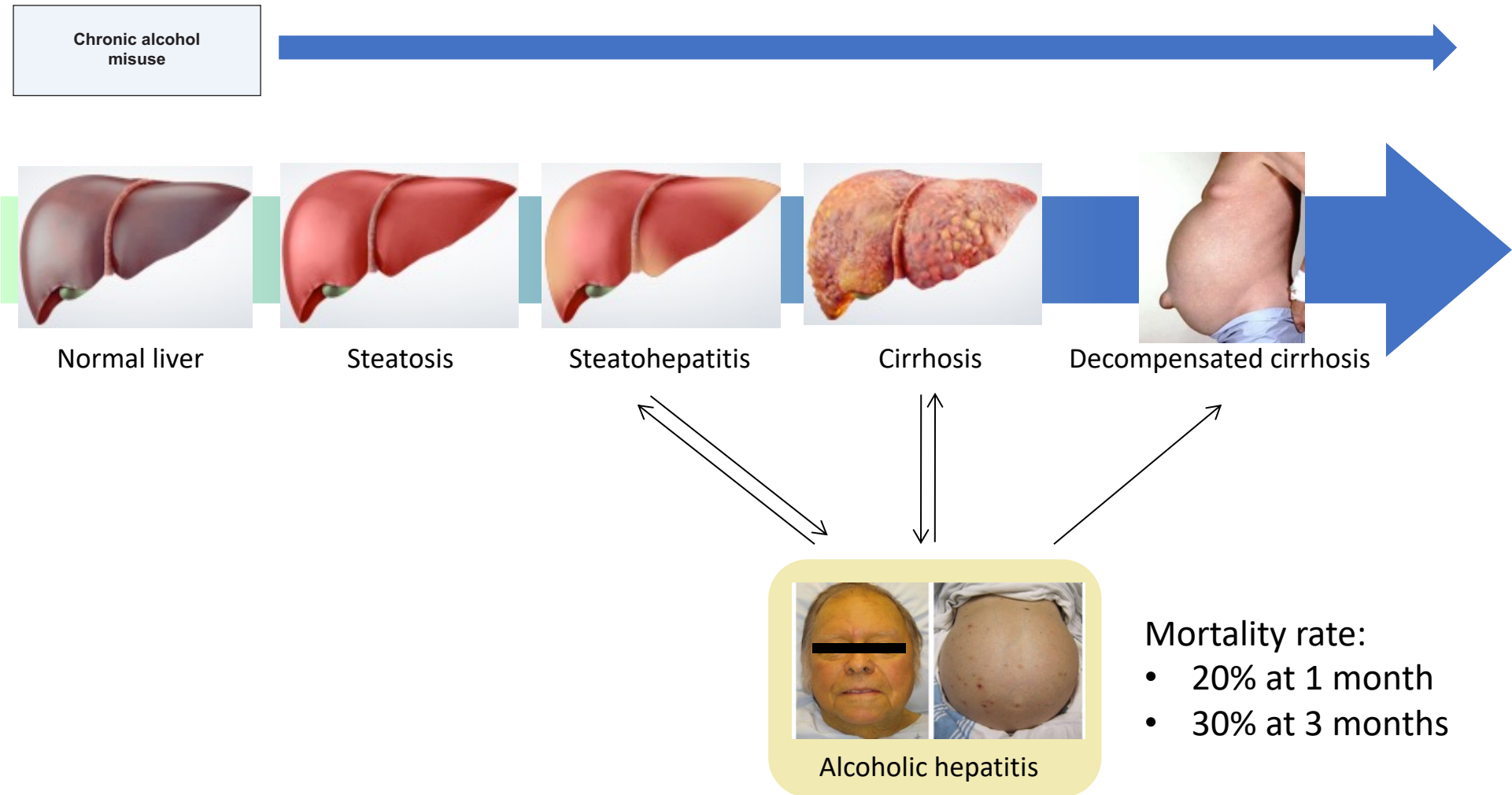
# Competing Causes of Morbidity & Mortality in NAFLD



1773 Adults with Biopsy – Staged NAFLD

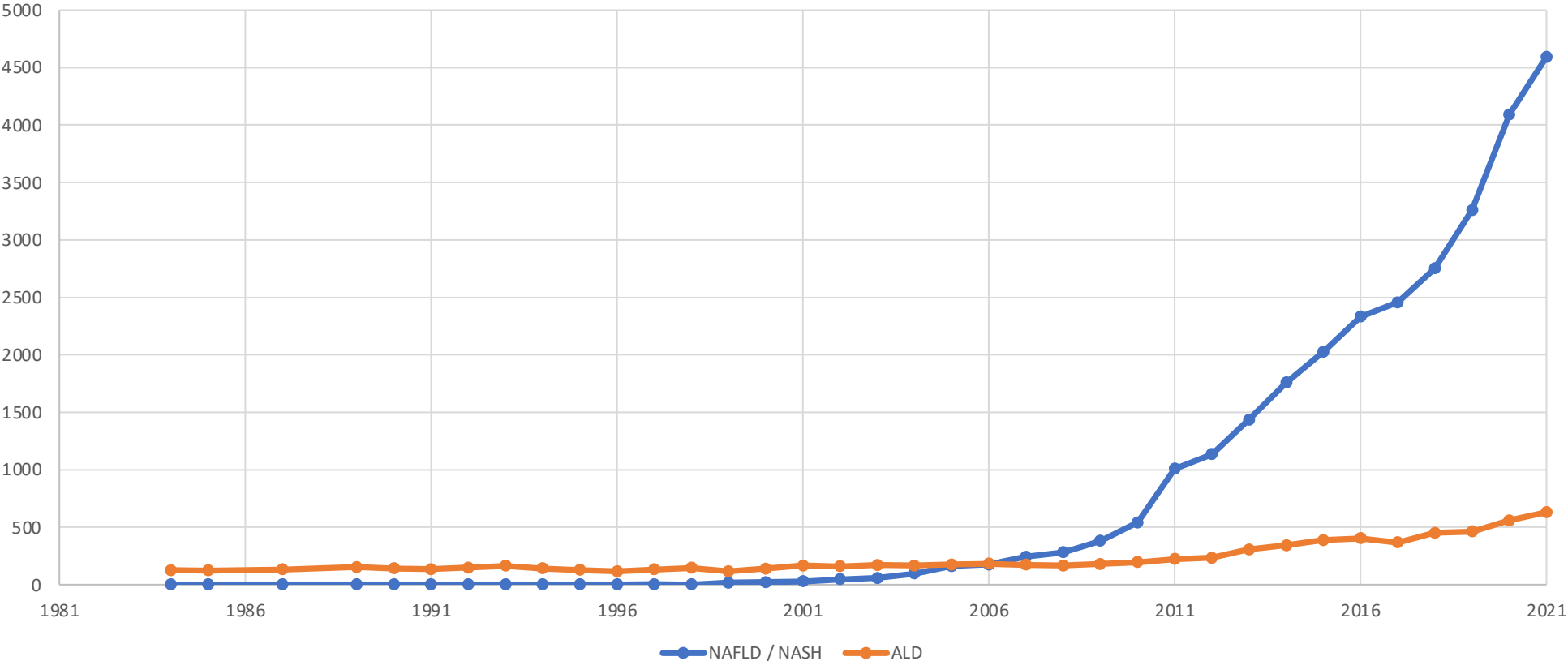
Sanyal NEJM 2021

# Alcohol-Related Liver Disease: Alcohol Related Hepatitis



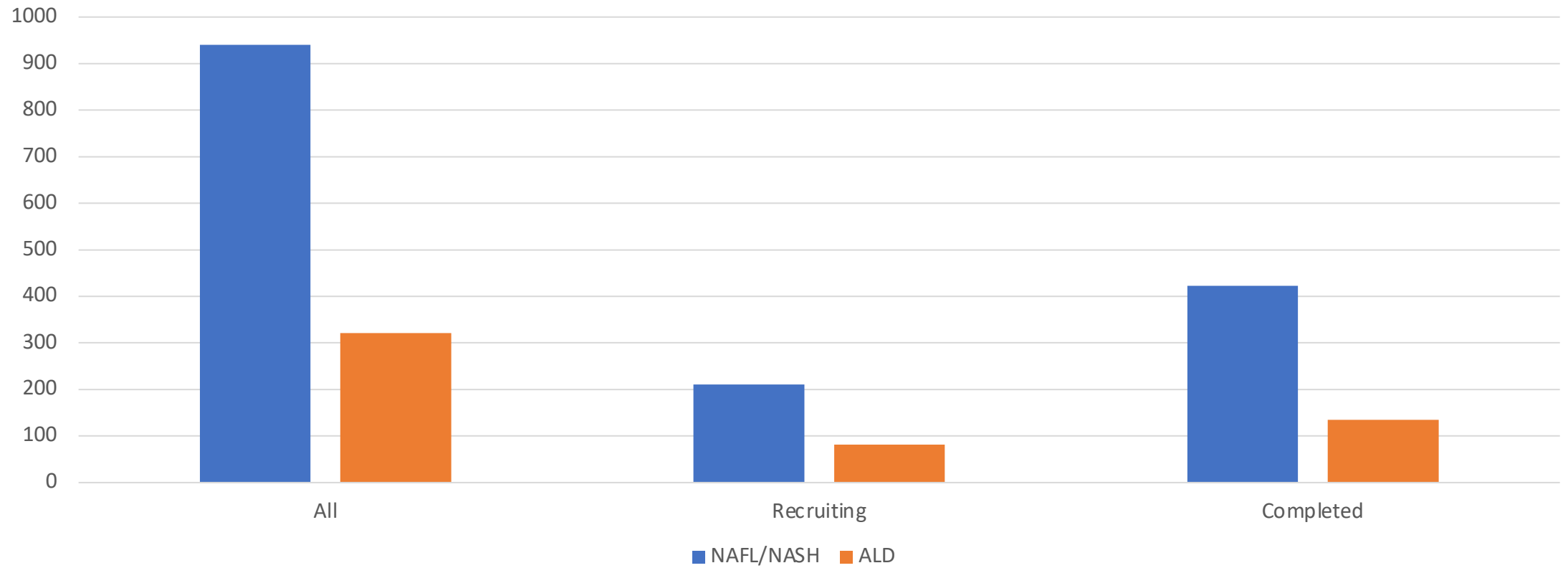
# Academic Endeavour

## PubMed Publications



# Clinical Trials

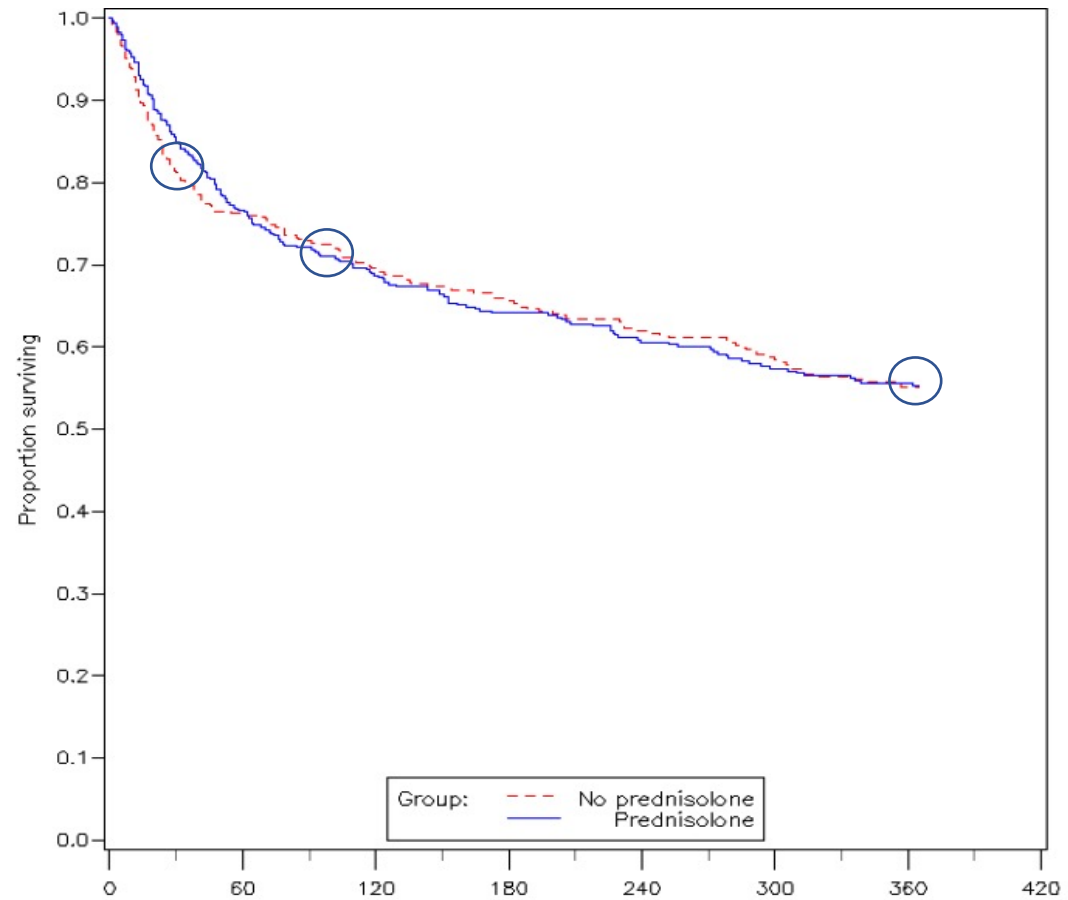
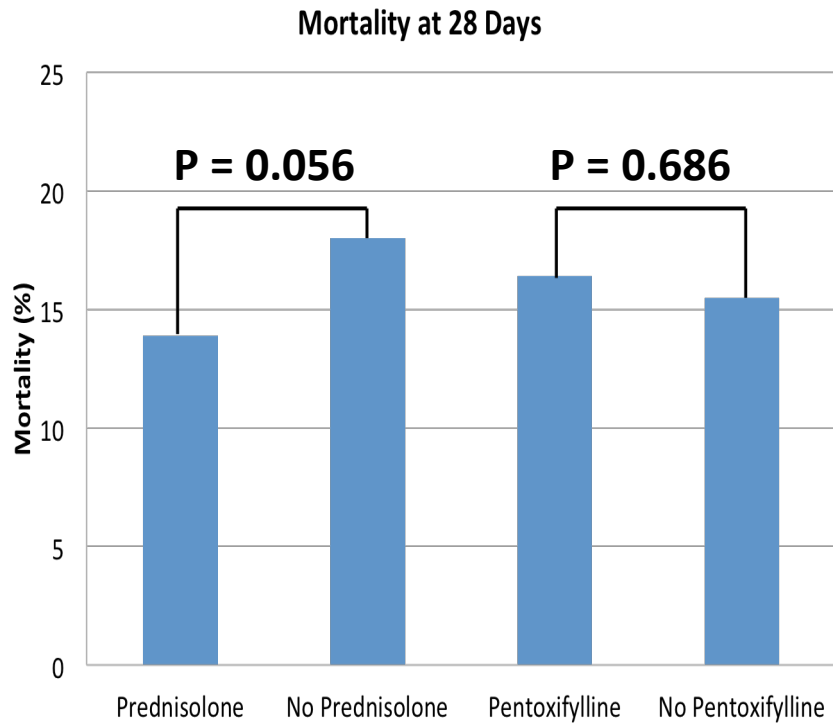
Studies on ClinicalTrials.Gov June 2022



# Treatments Available

- Alcohol-related Hepatitis (AH)
  - Specific drug therapy
  - Urgent transplantation
- Alcohol-related Cirrhosis
  - Treatment of Alcohol Use Disorder (AUD)
  - Transplantation
- Alcohol-related Liver Disease
  - Treatment of Alcohol Use Disorder (AUD)
- Treatment of Alcohol Use Disorder (AUD)

# Treatment of AH

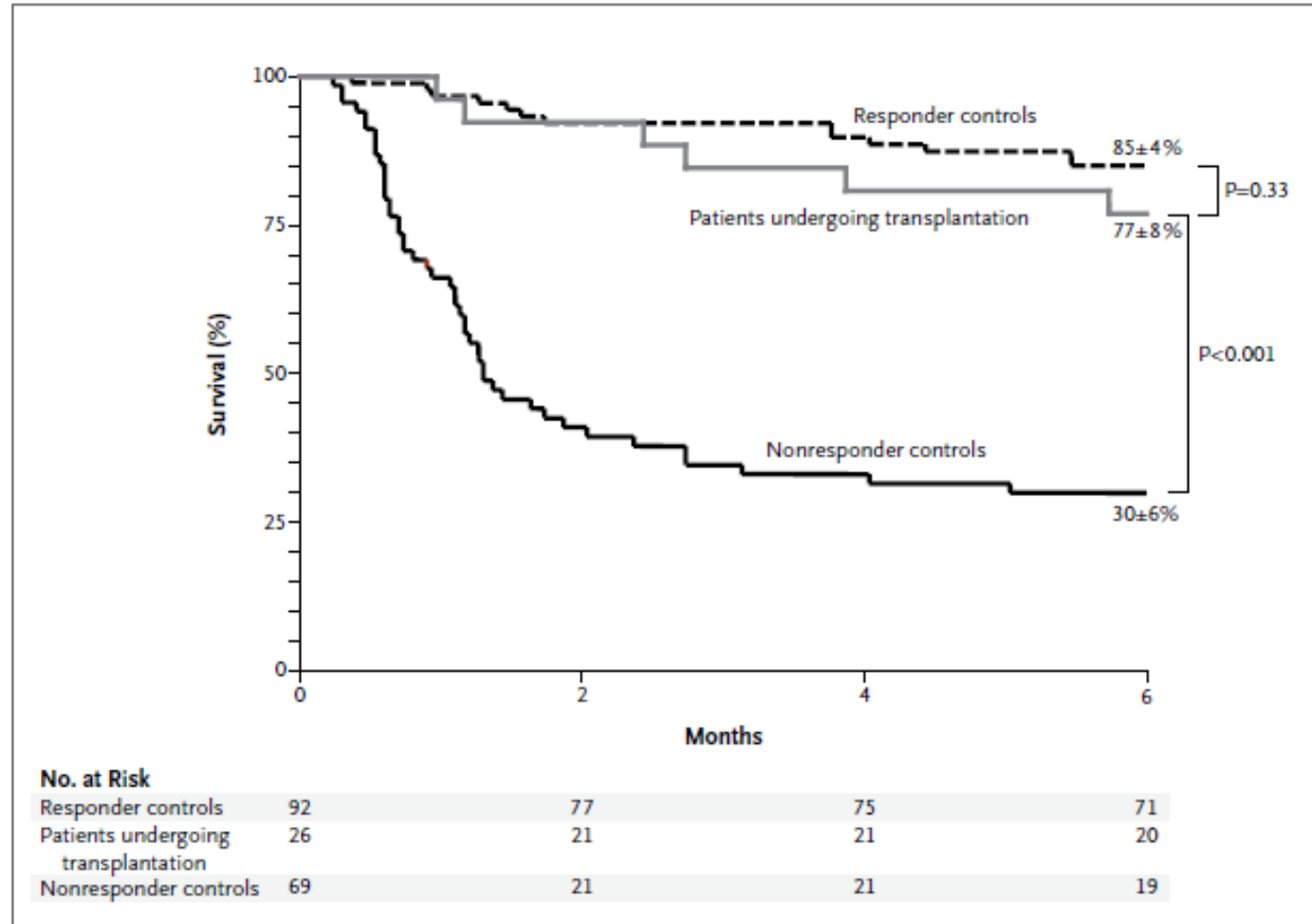


Patients at Risk

	0	60	120	180	240	300	360
No prednisolone	543	377	292	261	225	199	172
Prednisolone	546	383	296	253	217	192	168

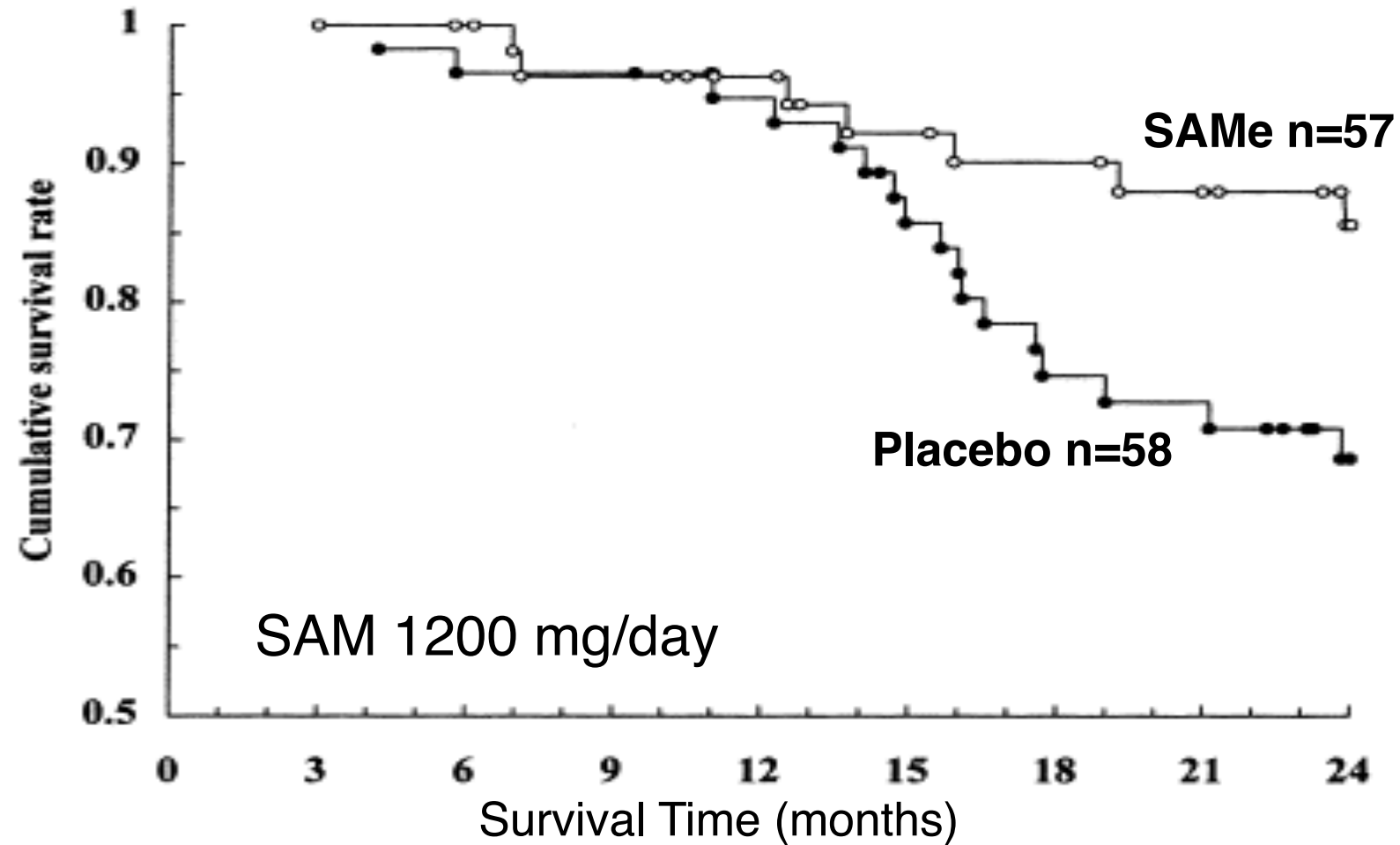
Days from start of treatment to death/last follow up

# Early Transplantation for Alcoholic Hepatitis





# S-Adenosyl Methionine in ALD Cirrhosis (Childs A & B)



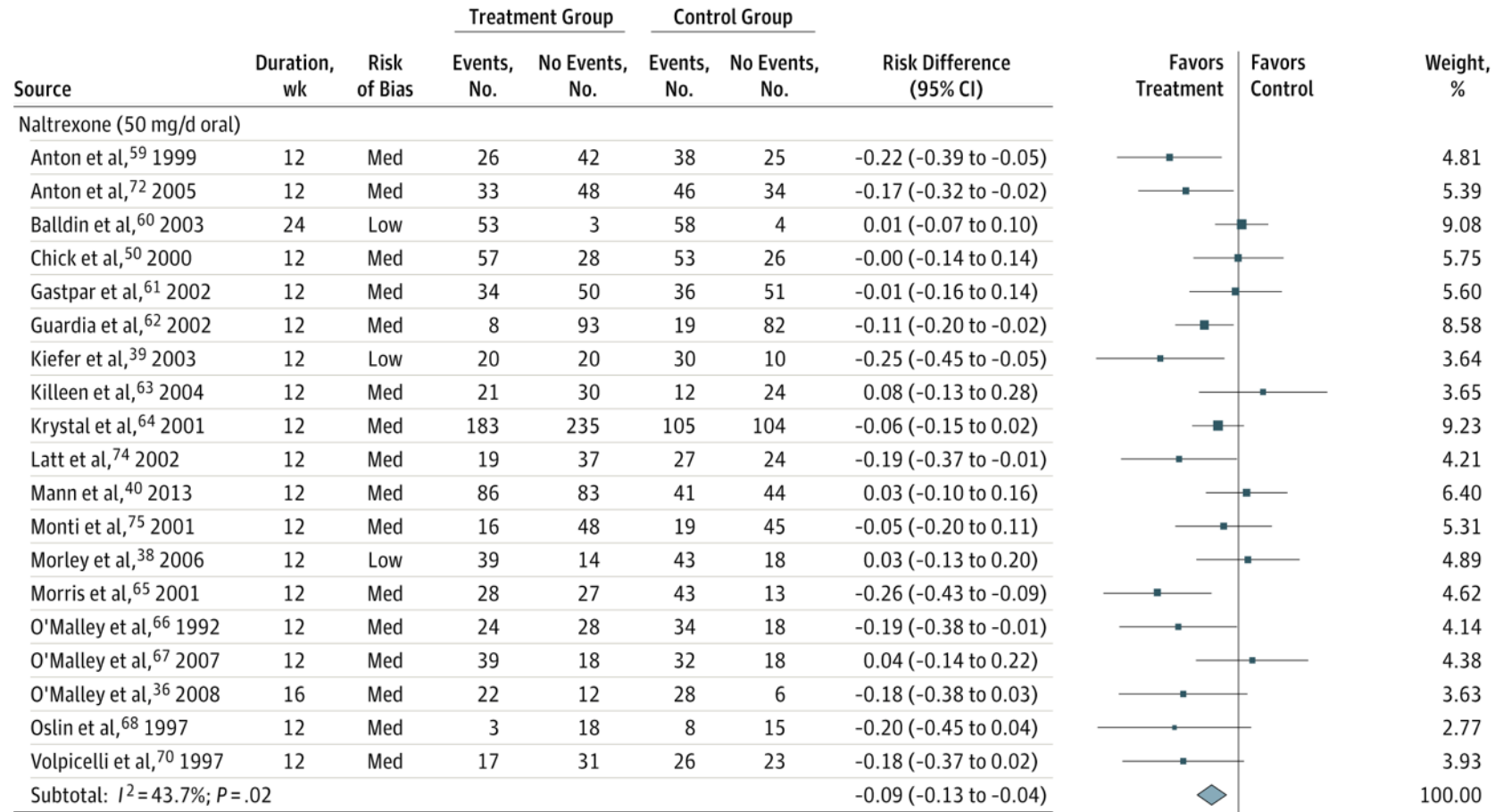
# Treatment of Alcohol Use Disorder

- Psychosocial Therapy
  - Brief Intervention
  - Motivational Interviewing
  - Cognitive Behavioural Therapy
  - Couples Therapy

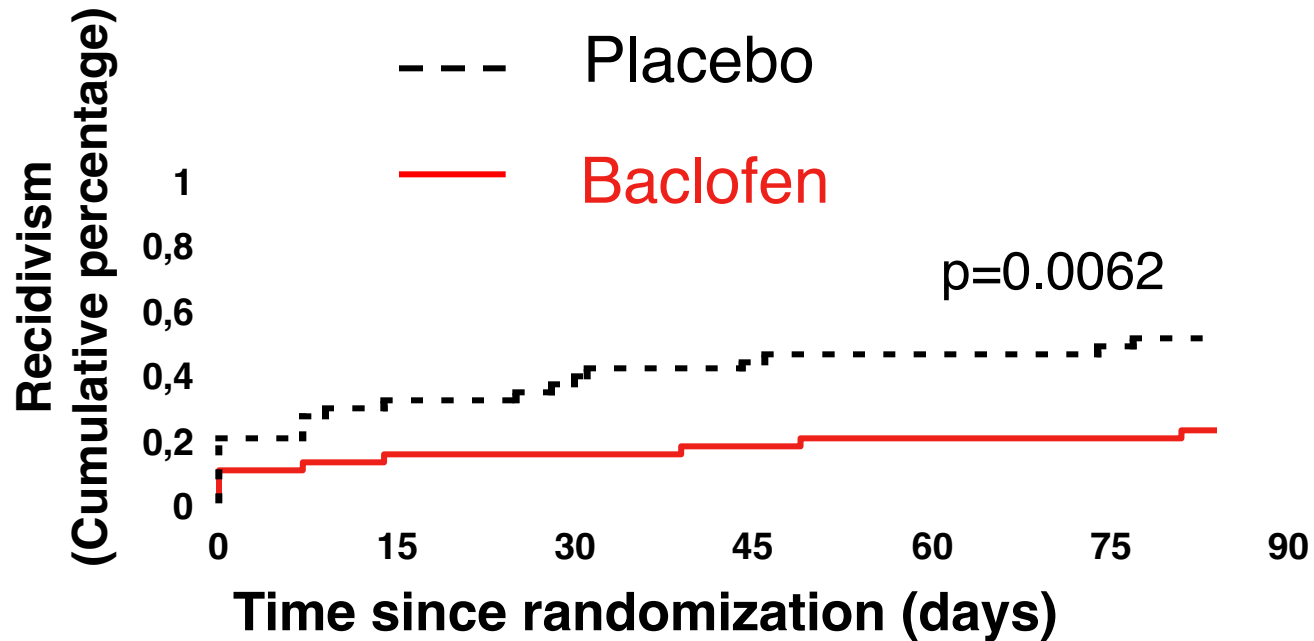
# Pharmacotherapy for AUD

Drug	Mechanisms of Action	Approved for AUD	Safety in advanced liver disease
Acamprosate	NMDA receptor	Yes	?
Baclofen	GABA receptors	No	Yes
Disulfiram	ALDH inhibition	Yes	No
Naltrexone	Opioid receptors	Yes	?
Nalmefene	Opioid receptors	Yes	?
Na Oxibate	GABA	Not yet	?
Topiramate	GABA receptors	No	?

# Naltrexone – Return to Any Drinking



# Baclofen in alcoholic cirrhosis

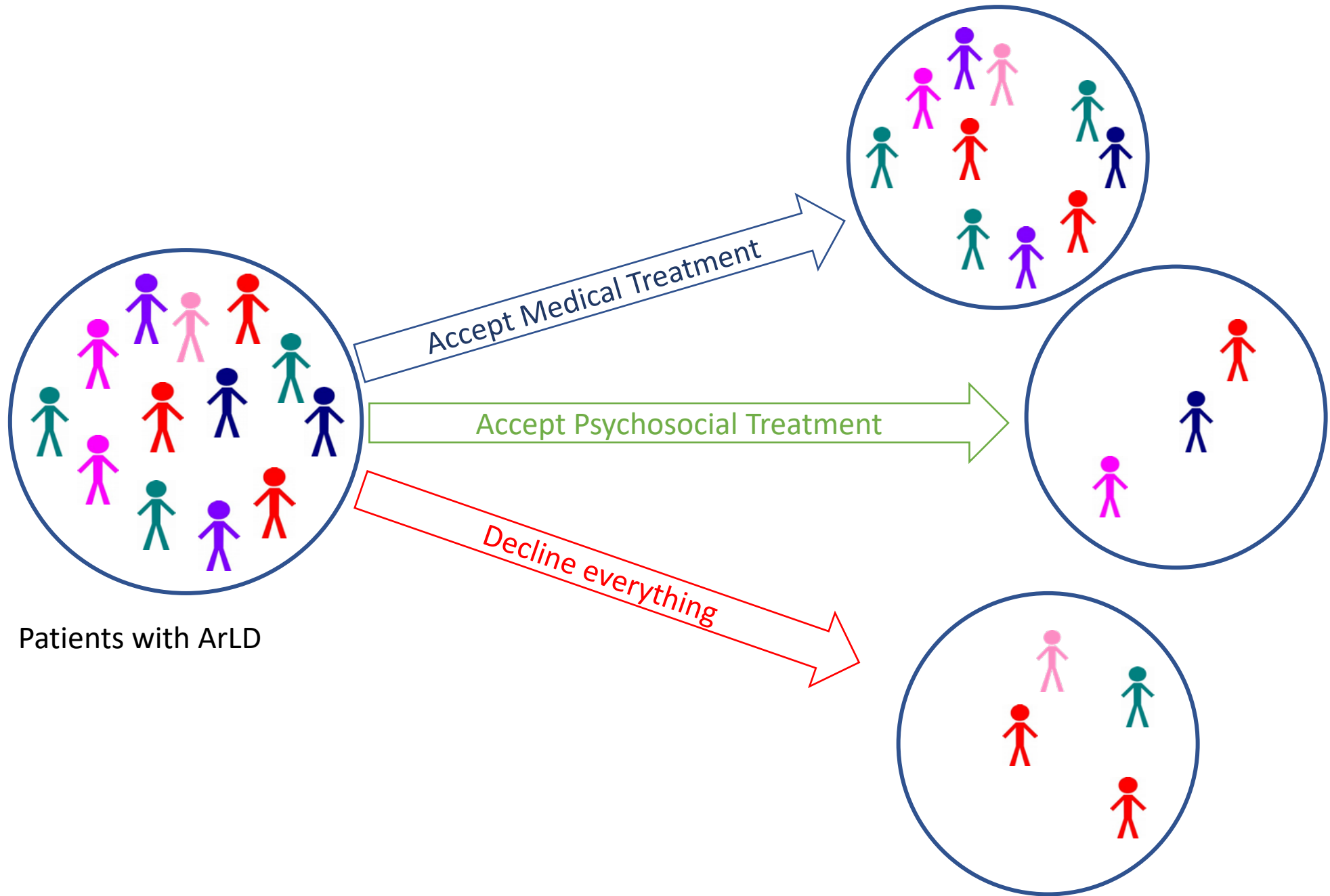


Addolorato G et al. Lancet 2007

Coming Soon

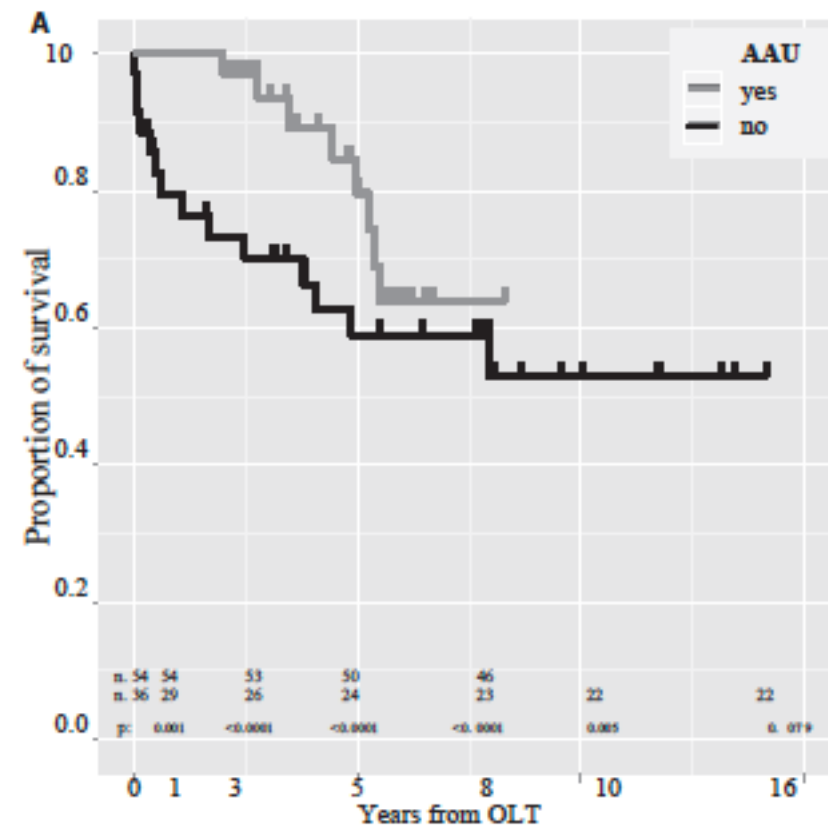
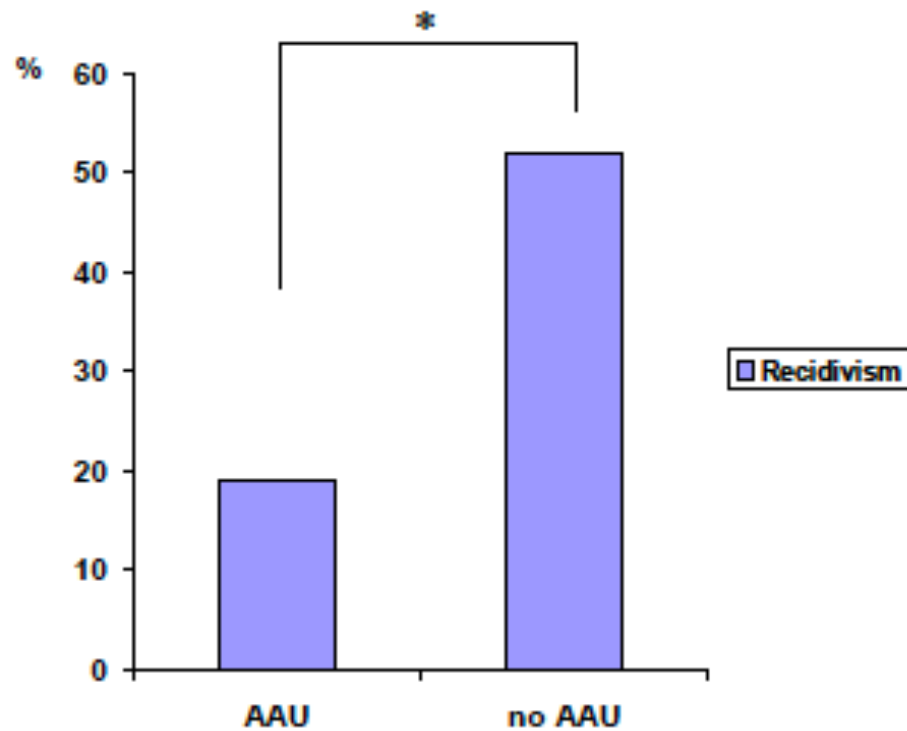
**BASIS Trial**

An adaptive-design randomised placebo-controlled trial of baclofen in the treatment of alcohol use disorder in patients with liver cirrhosis



Patients with ArLD

# Impact of Integrated ALD-AUD Service



# Stigmatisation

	Source of Stigma		
	Public	Self	Structural
Enacted	Individual discrimination and devaluation	Loss of self efficacy, self worth, shame	Discrimination in healthcare and resource allocation
Anticipated	Secrecy, help avoidance, delayed presentation, Social withdrawal	Denial. Misattribution of symptoms Delayed presentation	Non-disclosure in healthcare settings Avoidance of specialized addiction services
Results	Increased illness burden, Failure of delay seeking help. Poor quality healthcare. Negative health outcomes		



# Summary

- Alcohol drives liver disease through multiple pathways
- Amongst people with alcohol use disorder the risk of cirrhosis and liver-related mortality is high
- Alcohol is still the most important cause of liver-related mortality
- There are NO specific treatments for ALD
- Treatment of AUD is poorly effective and inaccessible
- Stigmatisation is a huge barrier to treatment and research