

Maladie alcoolique et non alcoolique du foie La place des facteurs génétiques et environnementaux

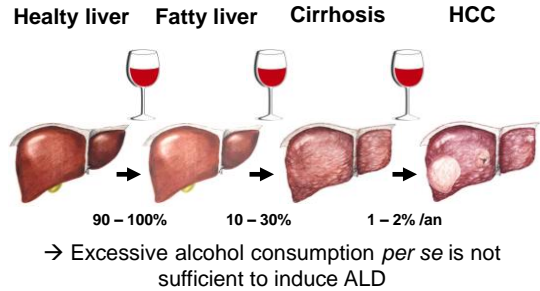
13^{ème} Journée d'automne d'actualités en Gastro-entérologie et Hépatologie

Pierre Deltenre

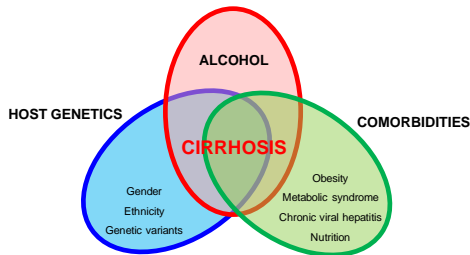
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Alcoholic liver disease

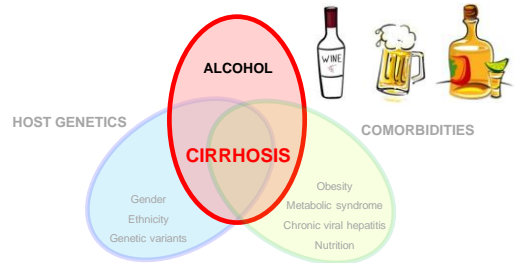


Risk factors for ALD progression



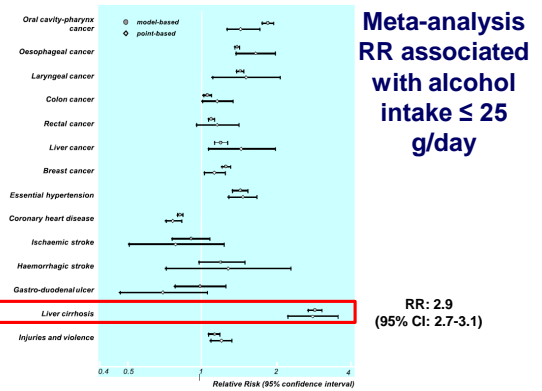
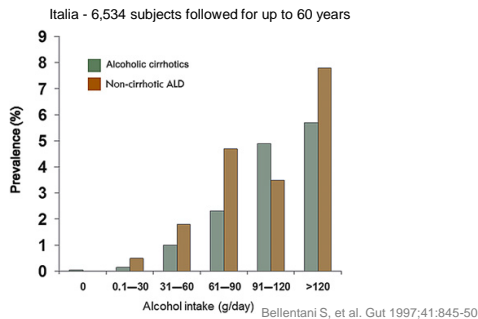
Adapted from Stickel F and Hampe J. Gut 2011;61:150-59

Risk factors for ALD progression



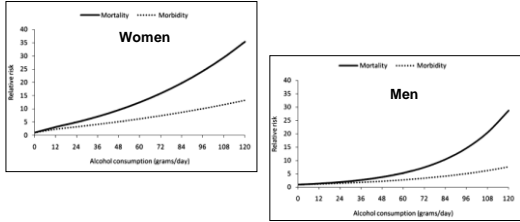
Adapted from Stickel F and Hampe J. Gut 2011;61:150-59

Relationship between the amount of alcohol and the likelihood of developing ALD



Meta-analysis dose of alcohol and risk of cirrhosis

Relative risk and meta-regression curve of liver cirrhosis associated with alcohol consumption



Rehm J, et al. Drug Alcohol Rev 2010;29:437-45

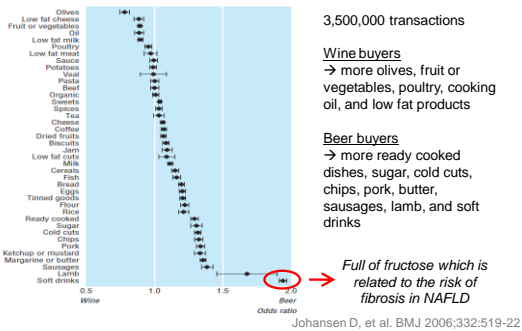
Meta-analysis dose of alcohol and risk of cirrhosis

	Mortality		Liver cirrhosis	
	RR	P-value	RR	P-value
Women				
0-12 g/d	1.9	0.013	0.4	0.105
12-24 g/d	5.6	< 0.001	1.0	0.981
24-36 g/d	7.7	< 0.001	2.4	< 0.001
Men				
0-12 g/d	1.0	0.991	0.3	
12-24 g/d	1.6	< 0.001	0.3	< 0.001
24-36 g/d	2.8	< 0.001	0.7	0.029
36-48 g/d	5.6	< 0.001	2.0	< 0.001

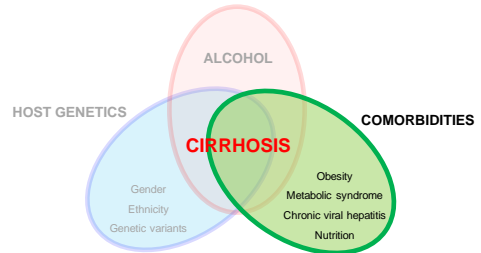
Lifetime abstainers were the reference group

Rehm J, et al. Drug Alcohol Rev 2010;29:437-45

Good or bad alcohol? Danish supermarket survey

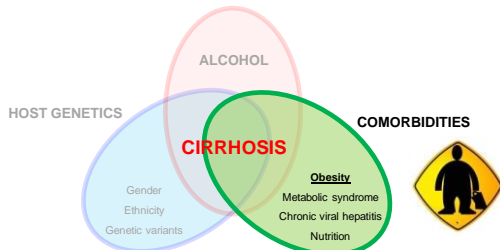


Risk factors for ALD progression



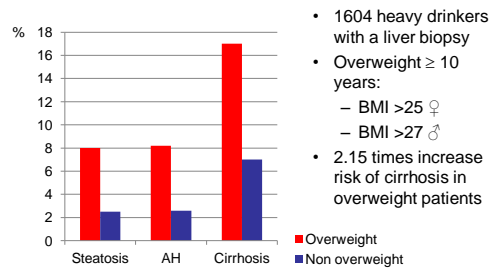
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Risk factors for ALD progression



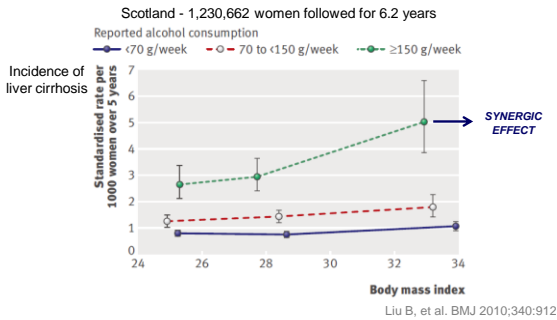
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ALD: the role of overweight

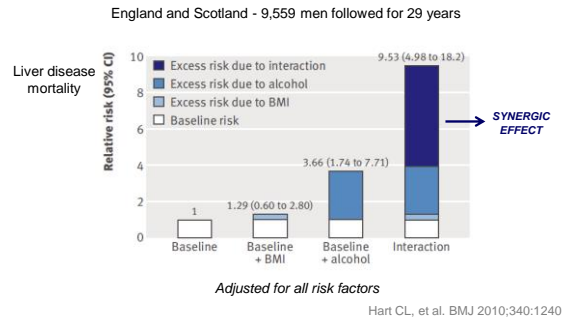


Naveau S, et al. Hepatology 1997;25:108-11

Standardized rates for liver cirrhosis over 5 years by BMI and alcohol consumption



Relative risks of contributions of BMI and alcohol to liver disease mortality



Independent risk factors for mortality in ALD

US - 15,886 participants followed for 13.3 years (235 patients with ALD)

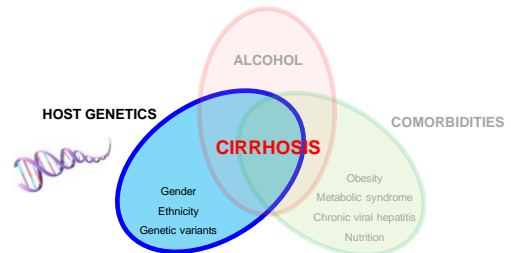
Variable/cohort	Overall mortality	Cardiovascular mortality	Liver-related Mortality
Age	1.06 (0.98 to 1.15)	0.91 (0.84 to 0.99)	1.15* (1.08 to 1.23)
Male gender	1.01 (0.41 to 2.48)	1.03 (0.40 to 2.64)	47.14* (5.46 to 406.93)
White	0.58 (0.20 to 1.65)	2.56 (0.13 to 49.01)	0.87 (0.19 to 4.12)
Smoking	3.38* (1.04 to 11.02)	6.60* (1.06 to 41.12)	2.26 (0.52 to 9.76)
Type 2 diabetes	3.00* (1.06 to 8.54)	19.91* (1.67 to 237.51)	3.60 (0.96 to 13.52)
Insulin resistance	3.21* (1.56 to 6.58)	6.43* (1.77 to 23.35)	2.43 (0.28 to 21.38)
Hypercholesterolaemia	0.79 (0.25 to 2.53)	3.34 (0.21 to 53.18)	0.04 (0.01 to 0.24)
Hypertension	1.76 (0.46 to 6.70)	7.55* (1.54 to 36.89)	1.77 (0.40 to 7.72)
Obesity	1.58 (0.57 to 4.40)	3.76 (0.54 to 26.14)	16.22* (1.91 to 137.68)
Metabolic syndrome	2.37 (0.50 to 11.18)	17.12 (0.94 to 311.08)	2.06* (1.21 to 3.31)

*p-Value for the adjusted HR (aHR) is ≤ 0.05.

→ Individuals with ALD and components of MS (type 2 diabetes, IR or elevated BMI) are at higher risk of mortality and/or liver-related mortality

Stepanova M, et al. Gut 2010;59:1410-15

Risk factors for ALD progression



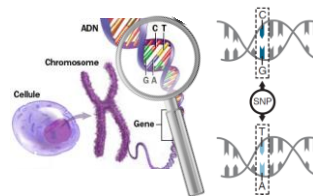
Adapted from Stickel F and Hampe J. Gut 2011;61:150-59

Lines of evidences for a genetic background in ALD

- Women are more susceptible to ALD following the consumption of similar amounts of alcohol
- Hispanic subjects are more prone to developing ALD than black and white subjects
- Monozygotic twins have a higher prevalence of alcoholic cirrhosis than dizygotic twins

Stickel F and Hampe J. Gut 2011;61:150-59

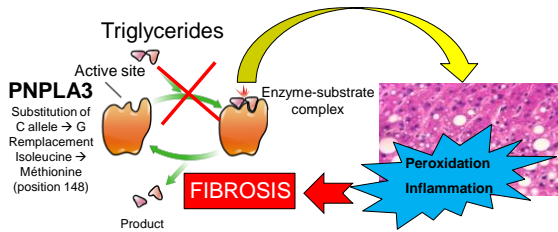
Numerous candidate genes in ALD



- Alcohol metabolism
- Oxydative stress
- Immune reactions
- Fibrosis
- Steatosis
- ...

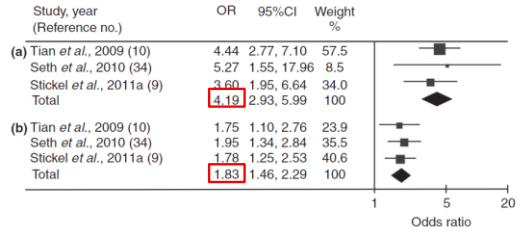
→ **PNPLA3: The strongest association**

PNPLA3 = Patatin-like phospholipase domain-containing protein 3



He et al., J Biol Chem 2010;285:6706-15

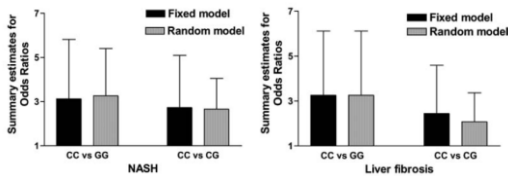
PNPLA3 and ALD



Patients with ALC as cases are compared with alcoholics without liver disease
(a) GG vs. CC genotypes (b) GC vs. CC genotypes

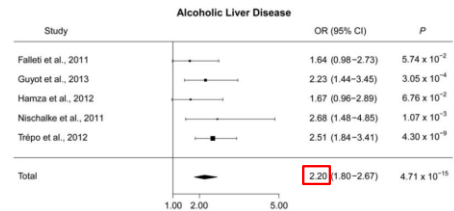
Chamorro AJ, et al. APT, in press

PNPLA3 and NAFLD



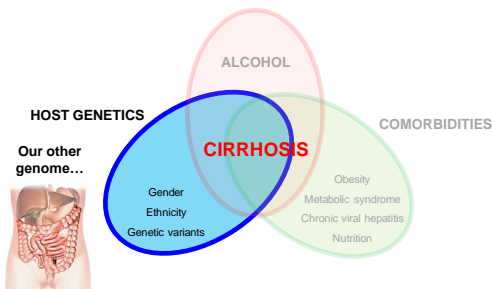
Sookoian S, et al. Hepatology 2011;53:1883-94

PNPLA3 and HCC



Trépo E, et al. Hepatology 2014;59:2170-77

Risk factors for ALD progression



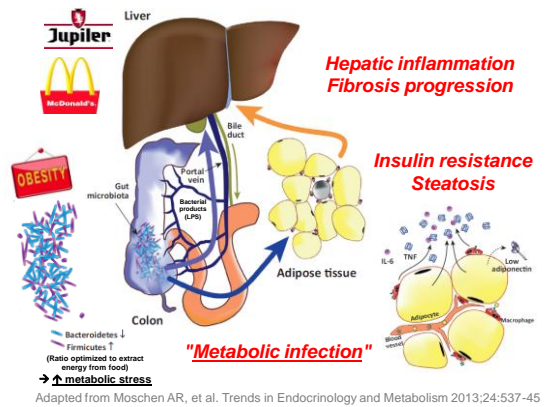
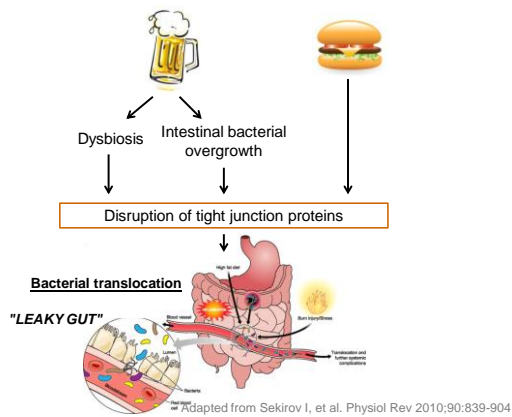
"Bad digestion is the root of all evil"

Hippocrates, 400 B.C.

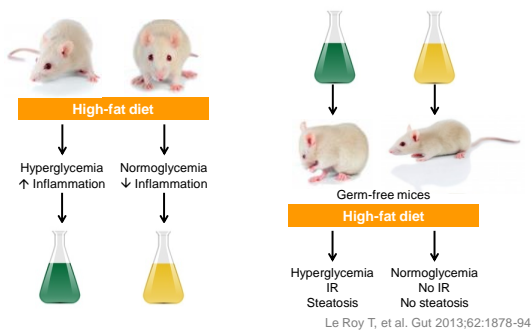
Gut microbiota

- The collection of microorganisms that live in peaceful coexistence with their hosts has been referred to as the microbiota, microflora, or normal flora
- It is estimated that the human microbiota contains as many as 10¹⁴ bacterial cells, a number that is 10 times greater than the number of human cells present in our bodies
- The colon alone is estimated to contain over 70% of all the microbes in the human body
- The human gut microbiota is dominated by only 2 phyla : the Bacteroidetes and the Firmicutes

Sekirov I, et al. Physiol Rev 2010;90:839-904



Intestinal microbiota determines the development of NAFLD



Conclusions

- Excessive alcohol consumption *per se* is not sufficient to induce ALD
- Environmental factors play an important role, mainly being overweight and having a metabolic syndrome
- Genetic background obvious – The best candidate gene is PNPLA3 rs738109 G
- Targeting the gut microbiota could be a new therapeutic approach for several liver diseases