Alcohol-Associated Liver Disease (ALD) vs. Metabolic Dysfunction-Associated Steatohepatitis (MASH):

Two etiologies, one disease

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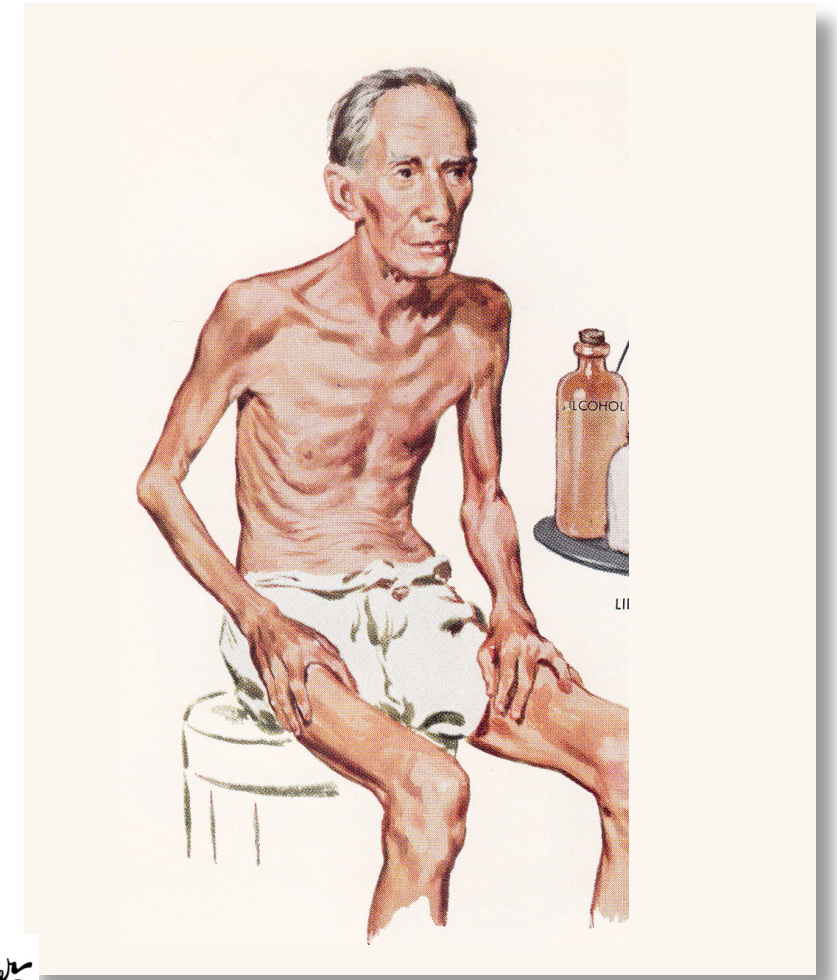
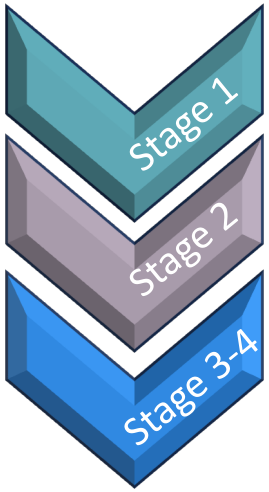
The Road to A Healthier Liver

Fatty Liver: Evolving Concept of a Disease Spectrum

Alcohol



Synergism



MASH

F. Netter M.D.

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Common Pathways in the Pathogenesis of MASH & ALD

Overlapping mechanisms of MASH and ALD

Insulin resistance

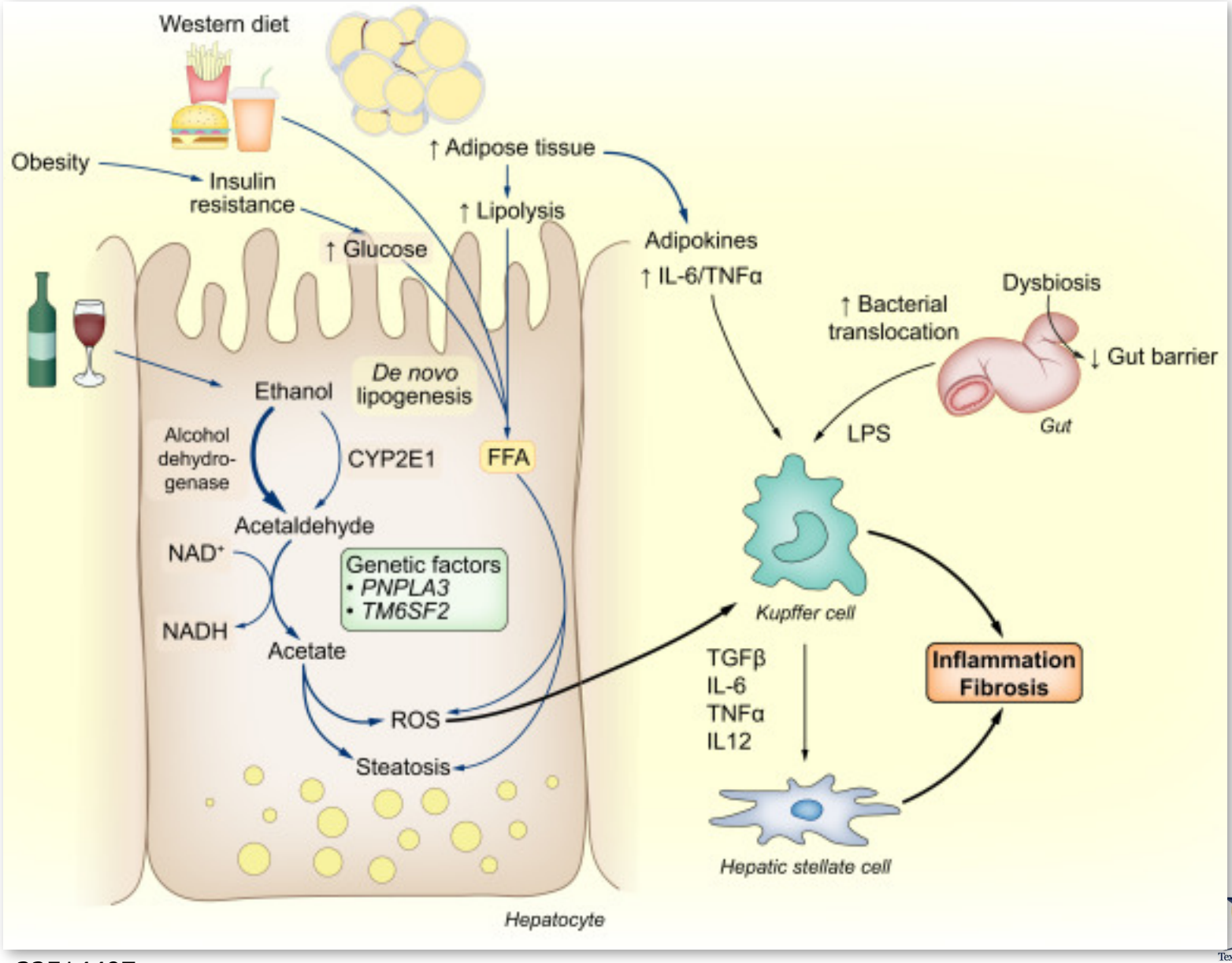
Increased peripheral lipolysis

Increased *de novo* lipogenesis

Impaired lipoprotein export from the hepatocytes

Mitochondrial dysfunction

Gut dysbiosis



Ntandja Wandji LC, et al. JHEP Rep. 2020. PMID: 32514497

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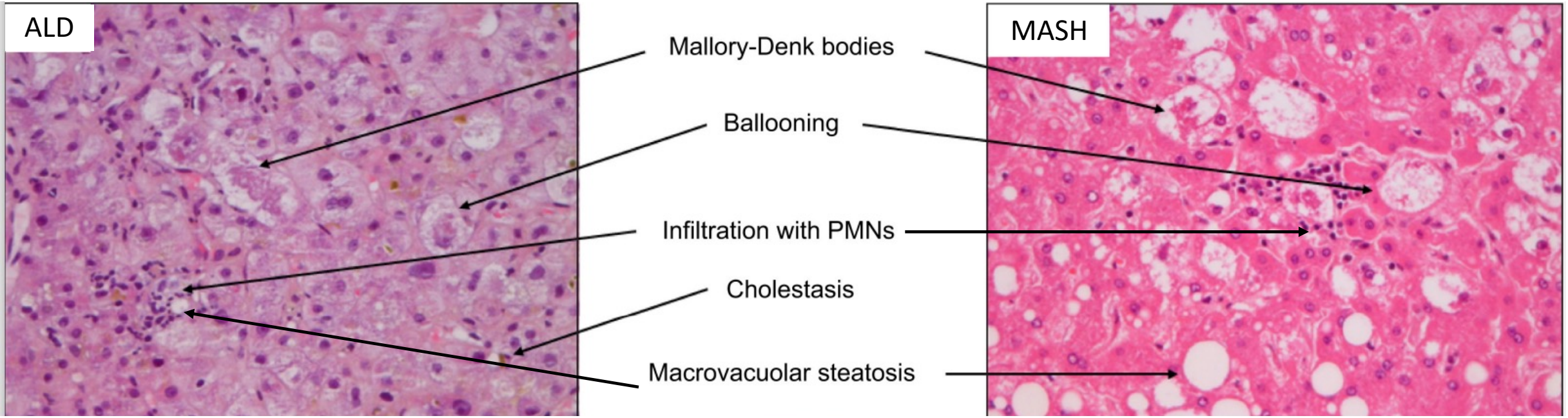
Common Histology Features in MASH and ALD



Histology findings reported more frequently in ALD than in MASH:
Portal acute inflammation, larger numbers of neutrophils, sclerosing hyaline necrosis, cholestasis, fibro-obliterative lesions of the outflow veins, foamy degeneration of hepatocytes.

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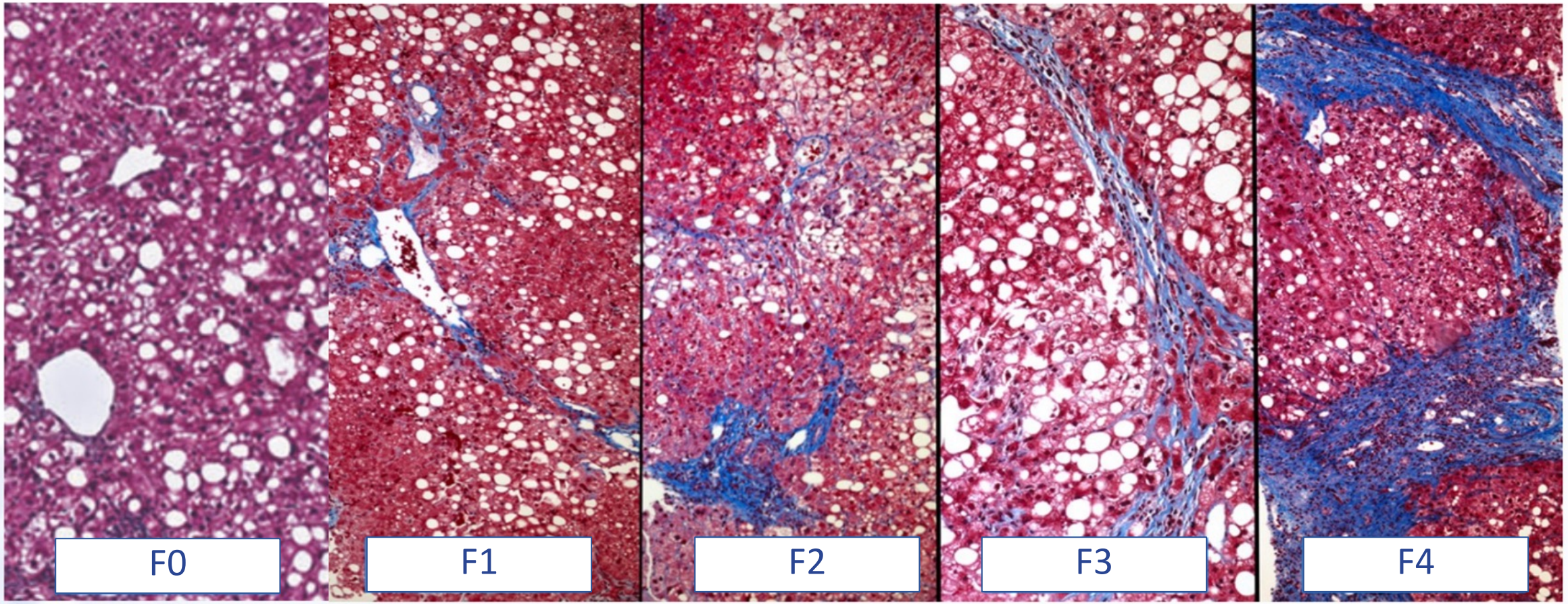
Ntandja Wandji LC, et al. JHEP Rep. 2020. PMID: 32514497

Fibrosis Progression in MASH and ALD



Estes et al., Hepatology 2018 :123-133

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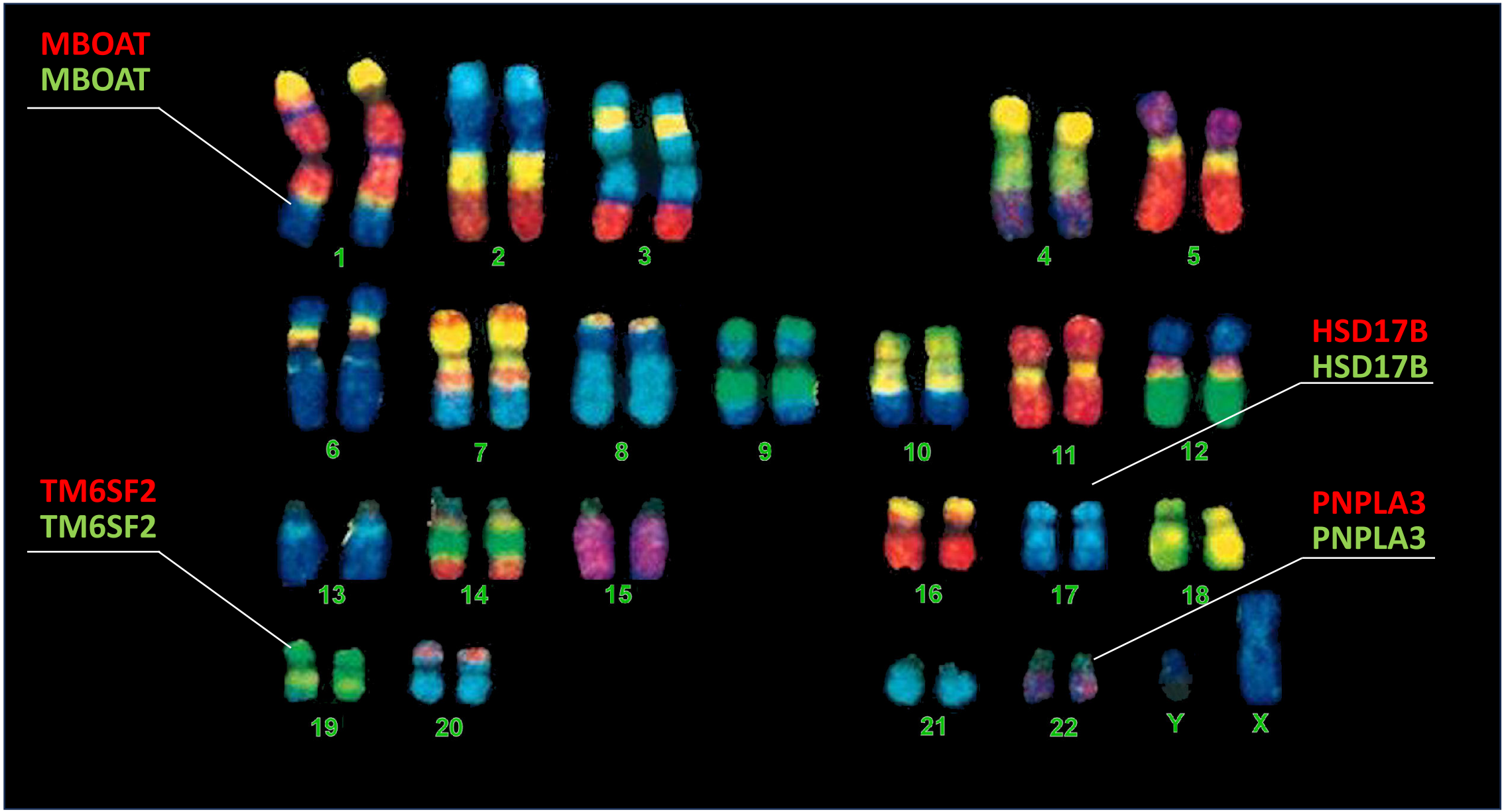
Common Genetic Determinants in MASH and ALD



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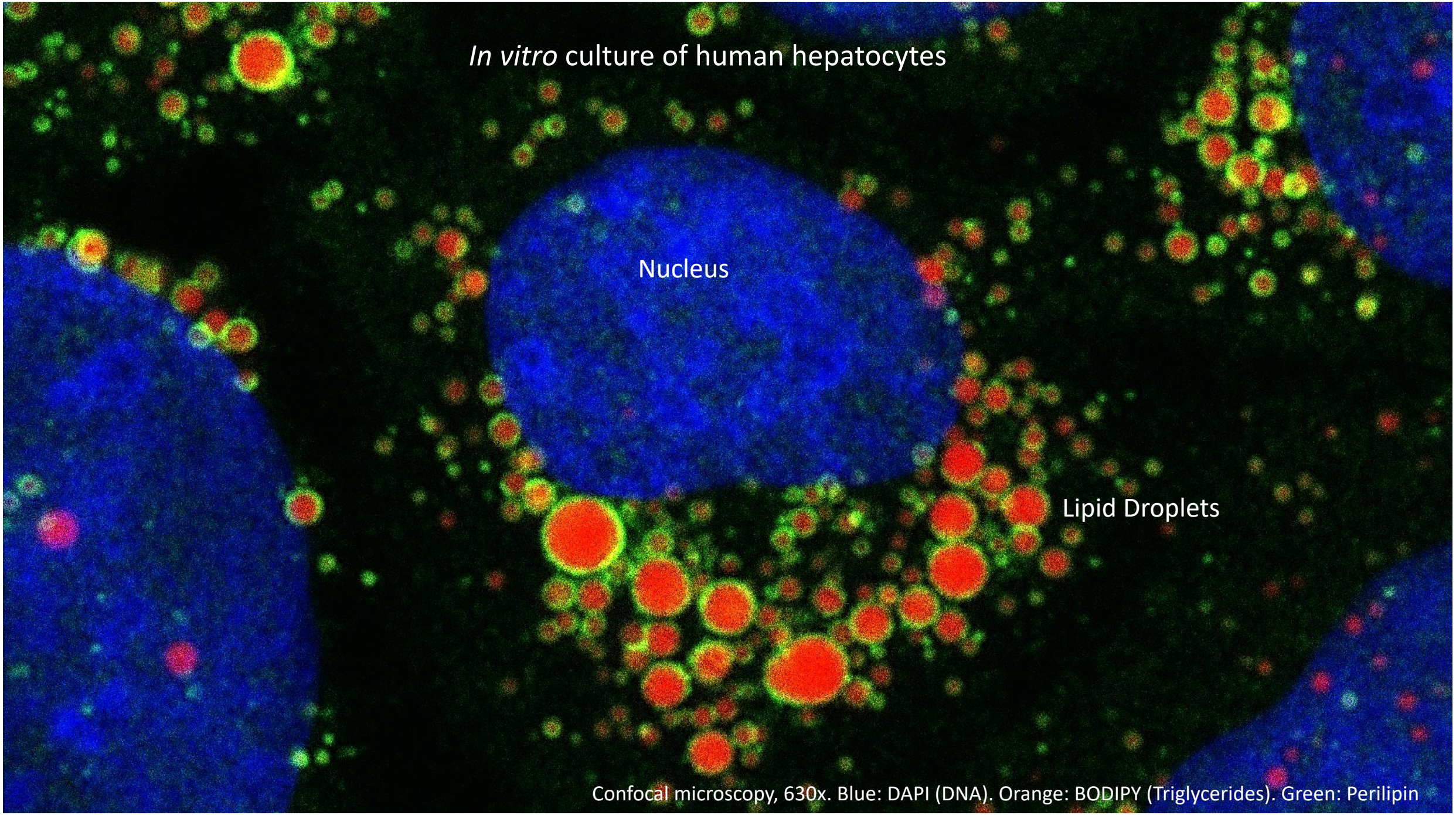
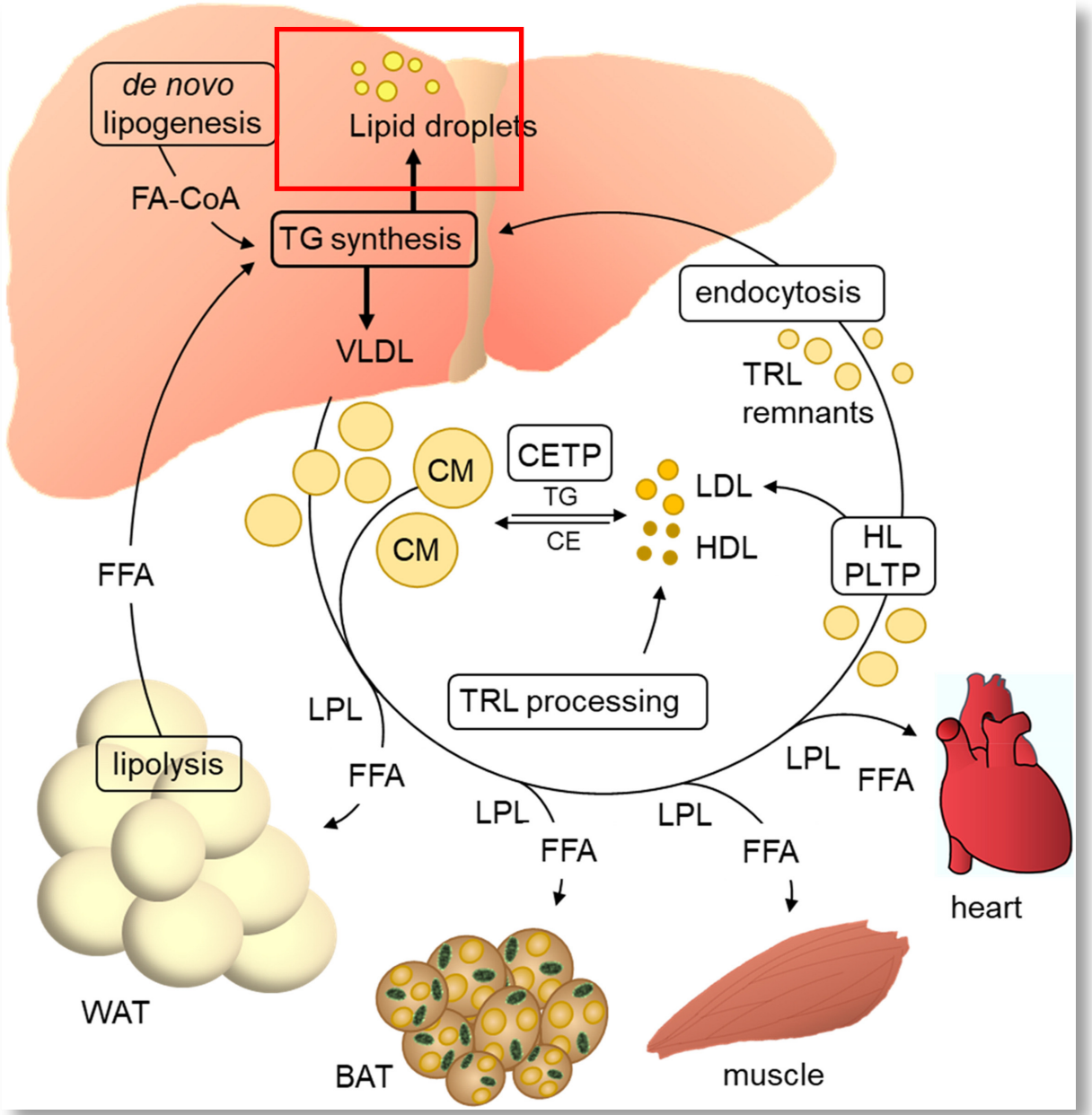

In vitro culture of human hepatocytes
Nucleus
Lipid Droplets
Confocal microscopy, 630x. Blue: DAPI (DNA). Orange: BODIPY (Triglycerides). Green: Perilipin

Abnormal Lipid Flux Defines MASH & ALD

The tankless water heater model



Ntandja Wandji LC, et al. JHEP Rep. 2020.

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Overlapping Causes of Impaired Lipid Flux in the Liver

Fatty acids = main form of excess energy supply (from lipolysis and DNL)

↓

Abnormal lipid flux causes build-up of Fatty acids in the liver

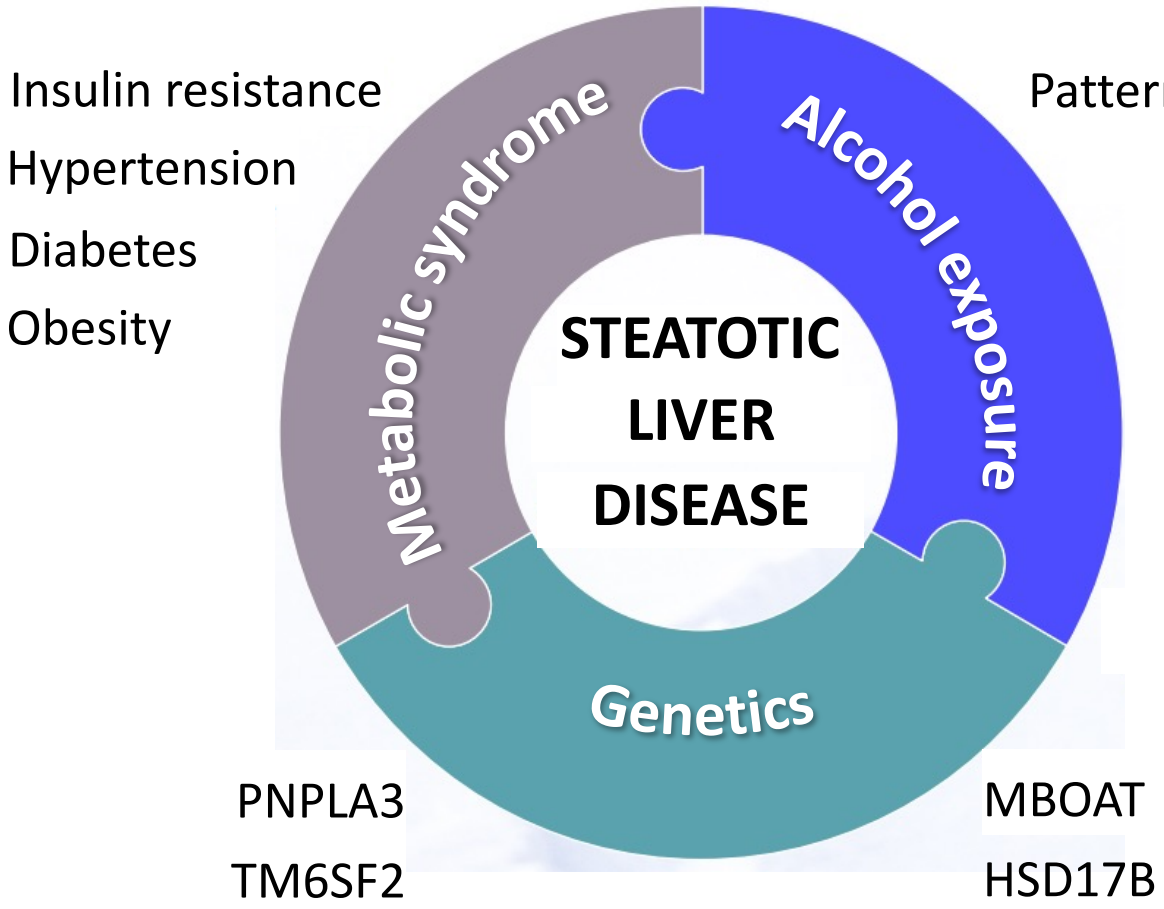
↓

Lipotoxic Species

↓

Liver Injury

Endoplasmic reticulum stress
Mitochondrial Dysfunction
Inflammatory cytokines release
Apoptosis



Hobbs et al., Nat Genet. 2008 Dec;40(12):1461-5; Nat Genet. 2014 Apr;46(4):352-6; Abul-Hushn et al., Engl J Med. 2018 Mar 22;378(12):1096-1106, Harrison et al., Nature Med. 2023:562-573

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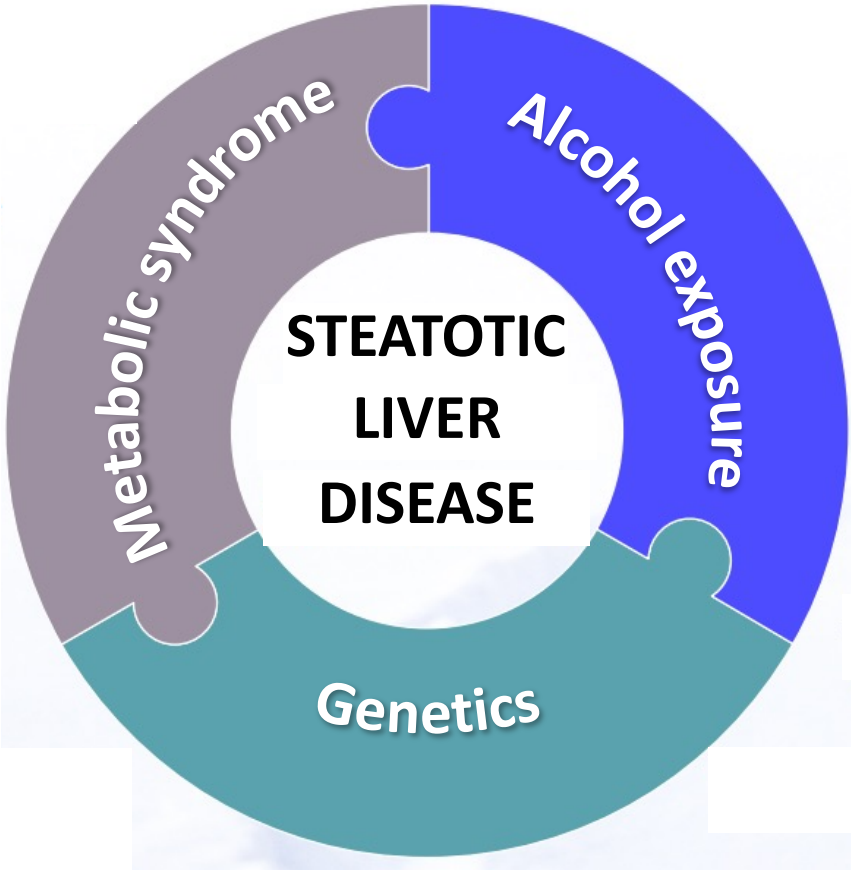
Overlapping Causes of Impaired Lipid Flux in the Liver

1. Threshold effect of alcohol
2. Genetics x MASH interaction
3. Genetics x ALD interaction
4. Alcohol x Diabetes interaction
5. Alcohol x Metabolic Syndrome
6. Integrative model (pilot studies)



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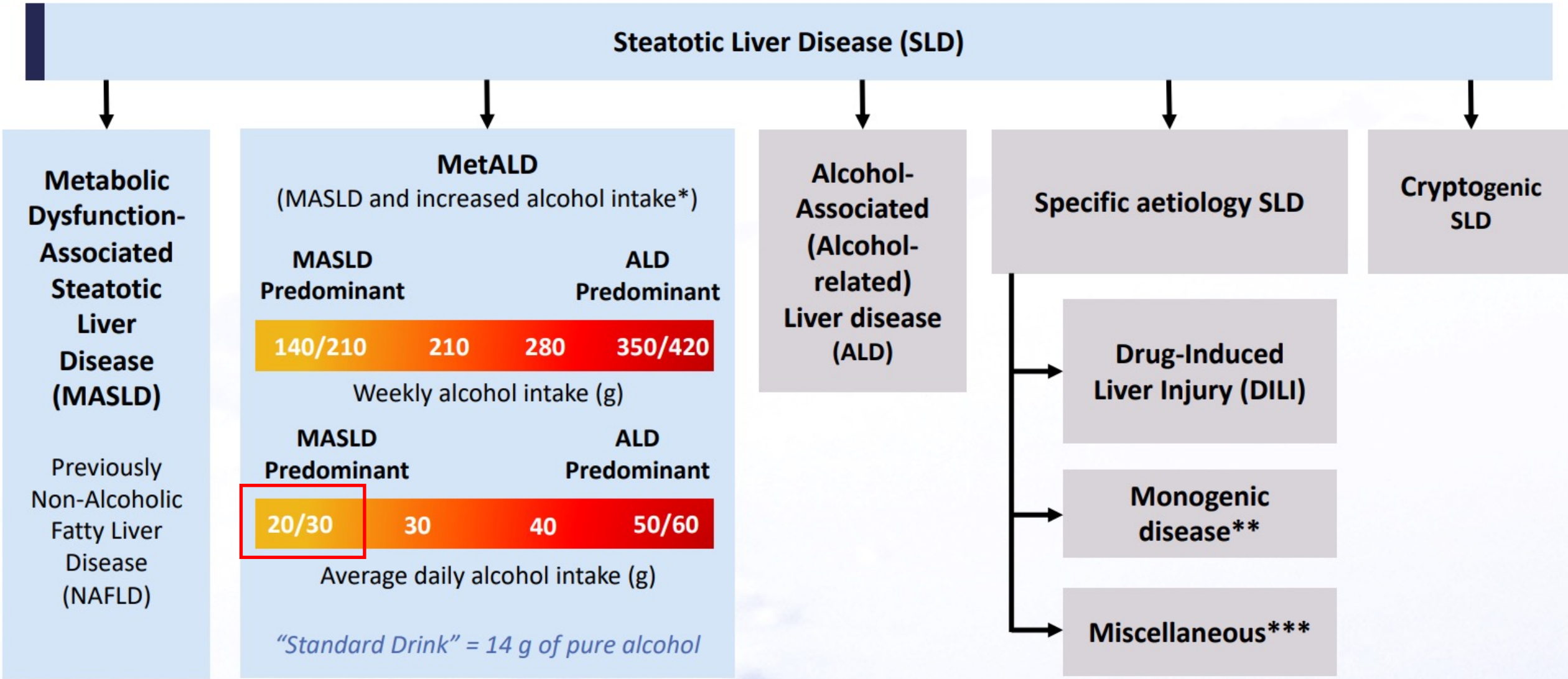
2023 Fatty Liver Disease Nomenclature



*) Average daily 20 - 50 g (1.4 – 3.6 drinks) female, 30 - 60 g (2.1 – 4.3 drinks) male
**) Lysosomal Acid Lipase Deficiency, Wilson disease, inborn errors of metabolism
***) HCV, malnutrition, celiac disease

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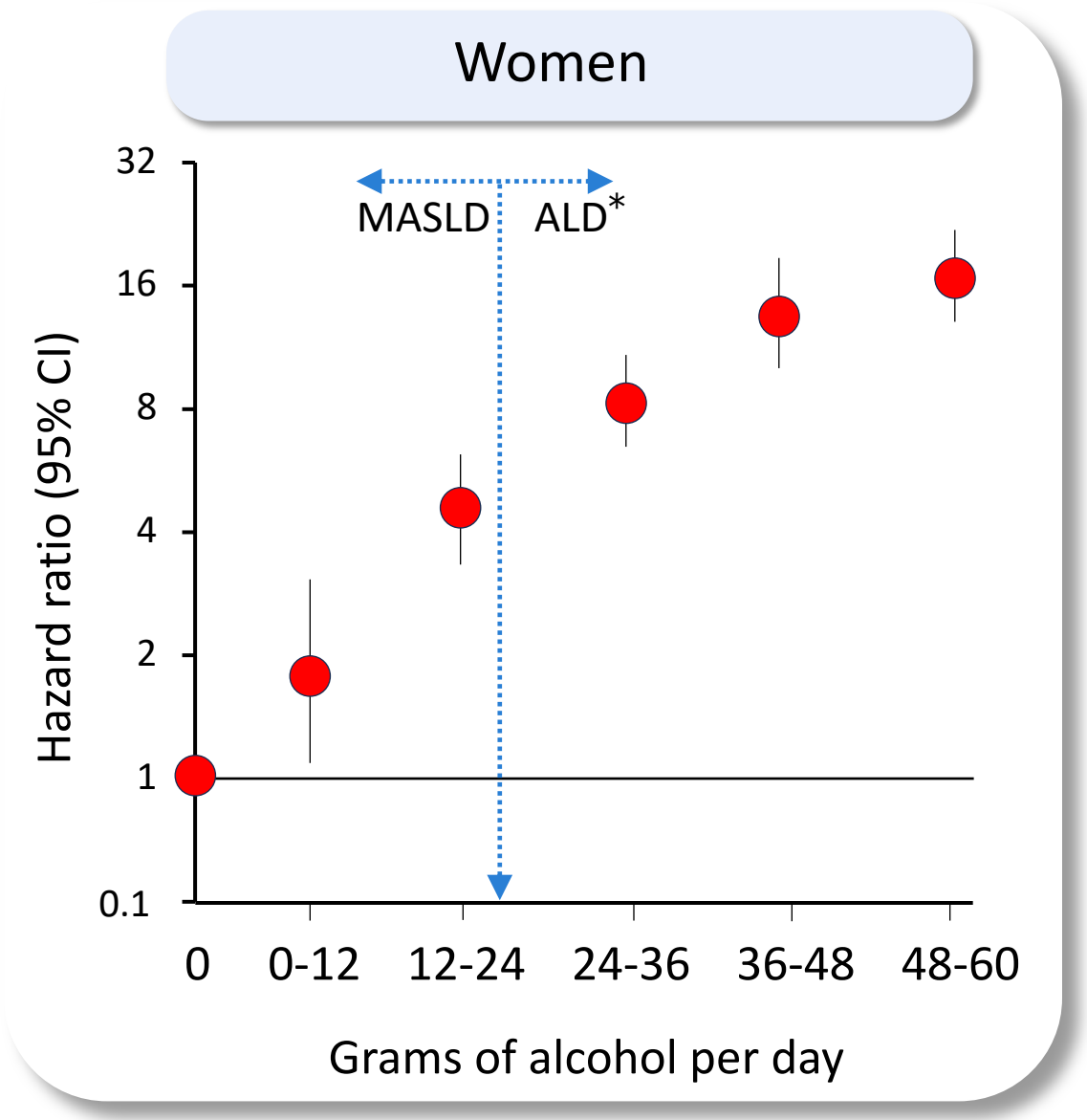
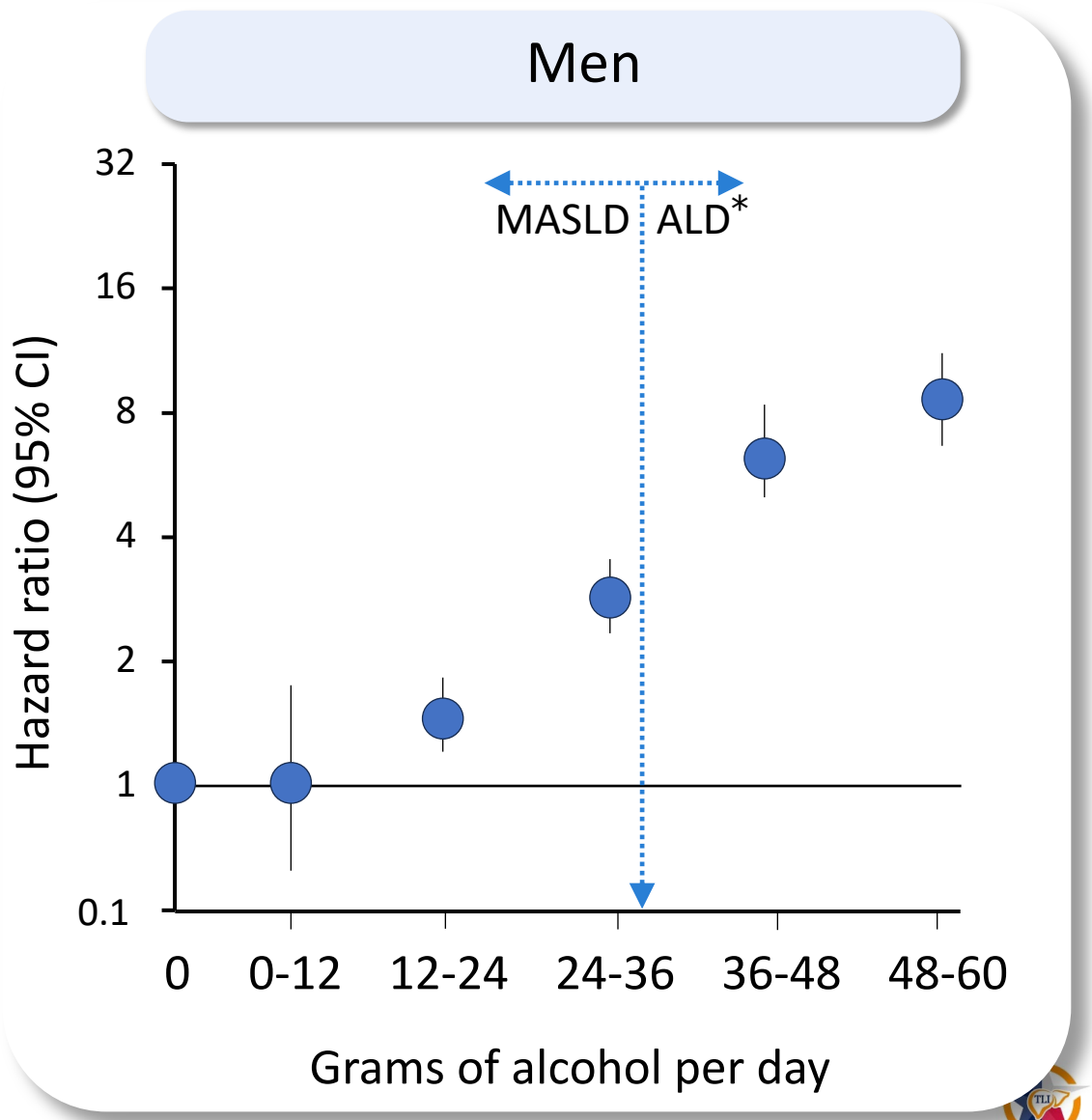
Rinella ME. Hepatology. 2023 Jun 24: PMID: 37363821

Alcohol Dose and Risk of Cirrhosis: Every Gram Matters





*) 2023 consensus threshold differentiating MASLD from MetALD

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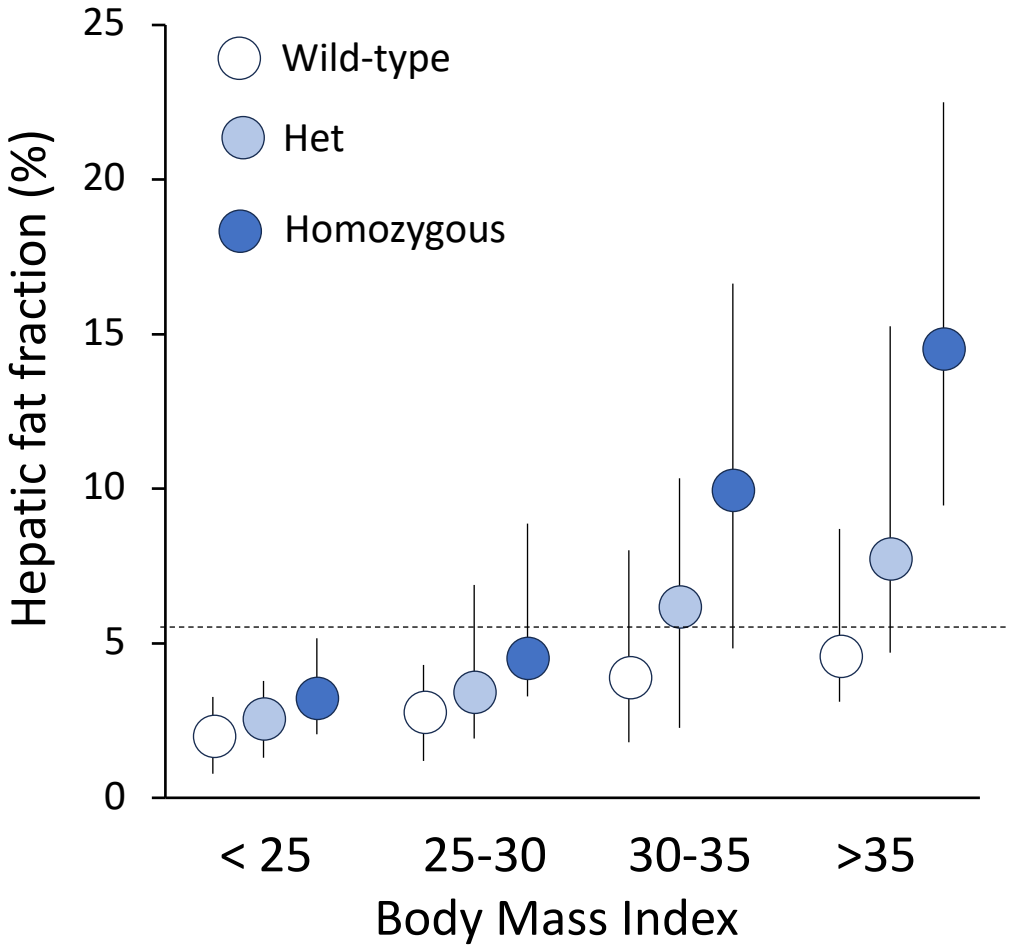
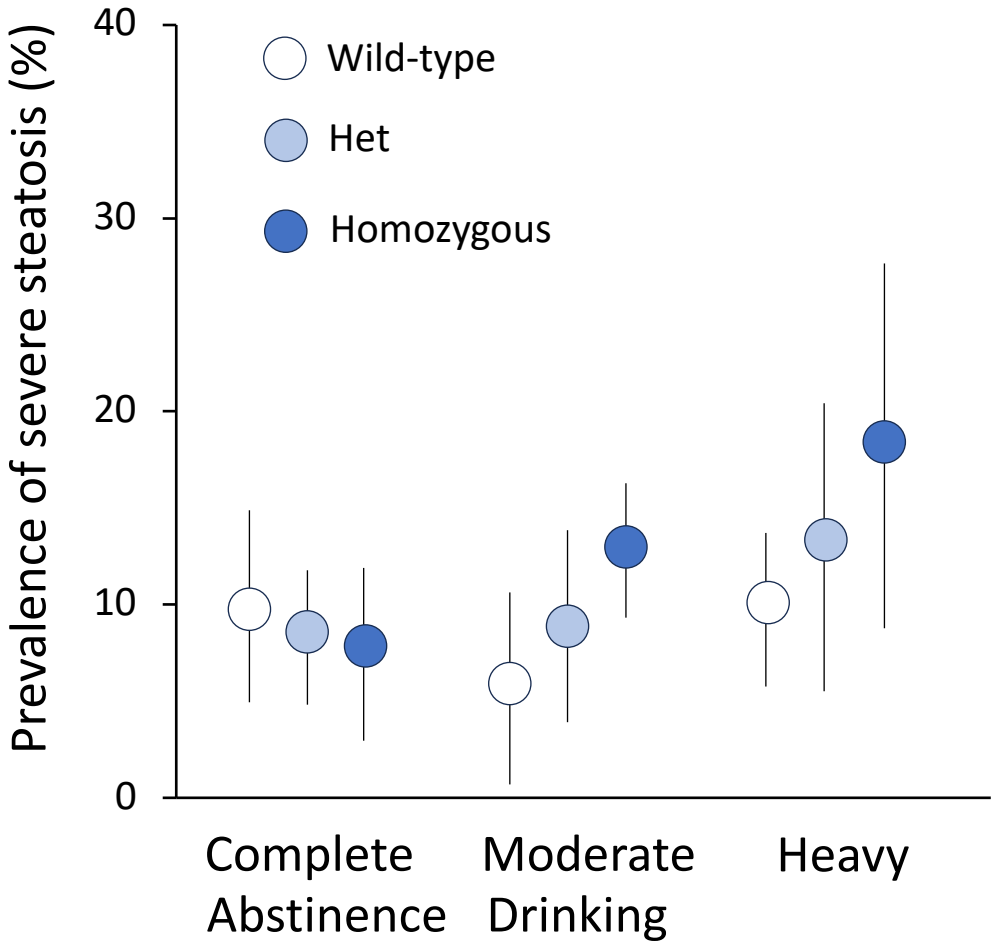
Rehm et al., Drug and Alcohol Review 2010;437-445

Gene-Environment Interactions in MASH and ALD

PNPLA3 I148M variant: a major genetic determinant of steatosis in Hispanic > Caucasian > African American populations





Kozlitina et al., Nat Genet. 2017 Jun;49(6):842-847; Lazo et al., CGH 2021;2606-2614

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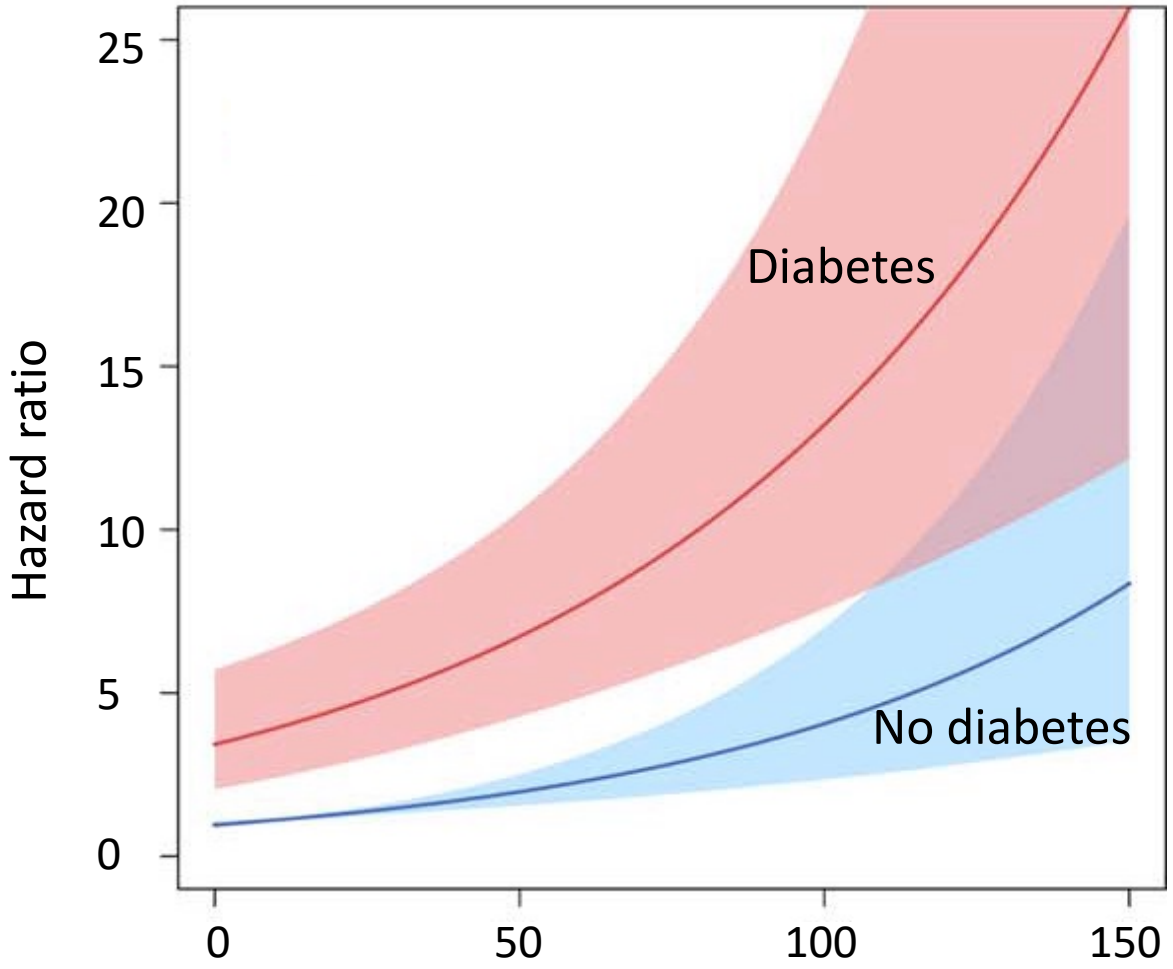
Interaction Between Alcohol and Diabetes in Fatty Liver Disease

Finnish registry study, N ~ 7000. Liver-related admissions, mortality, and liver cancer.



Aberg et al. Hepatology 2018:2141-2149

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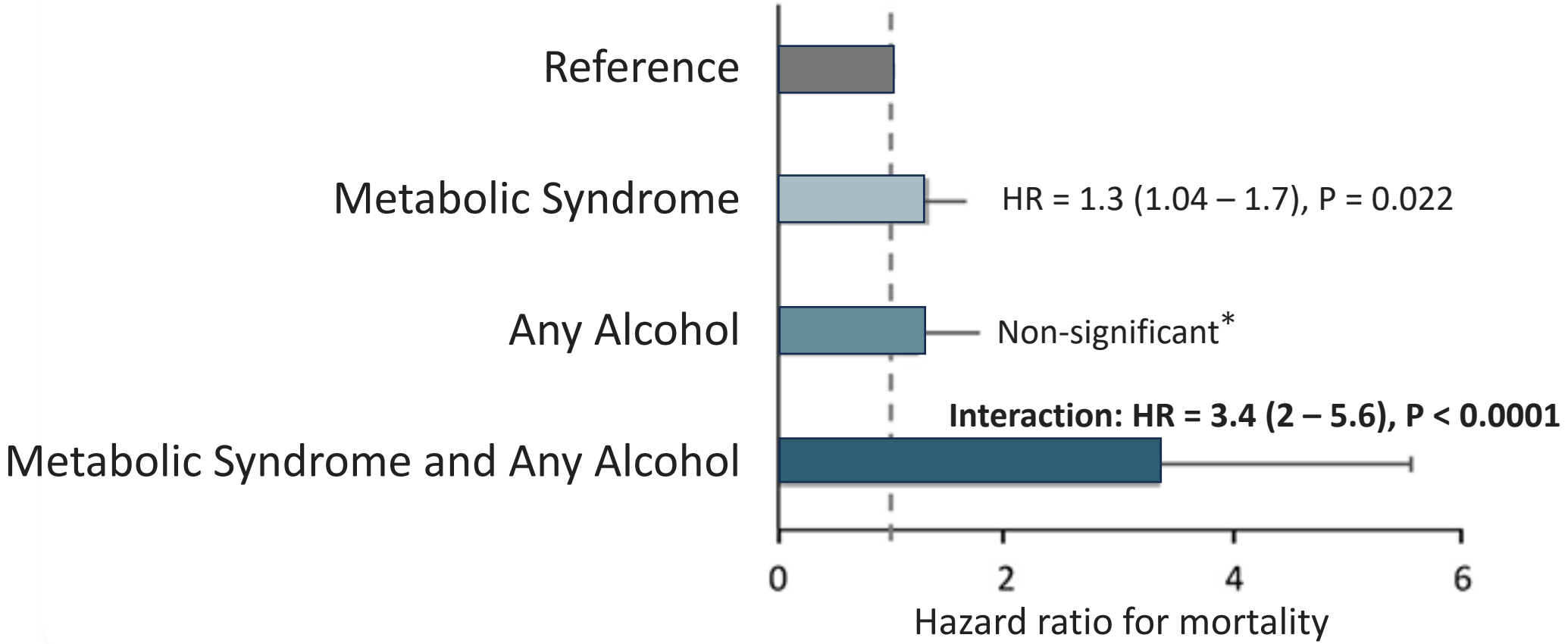
Interaction Between Alcohol and Metabolic Syndrome in MAFLD

NHANES data, 4264 individuals with any steatosis on liver ultrasound.



*) Excessive alcohol consumption was statistically significant (men >3 drinks/day, for women was >1.5 drinks/day)

Younossi et al., Clin Gastro Hepatol 2019;1625-1633

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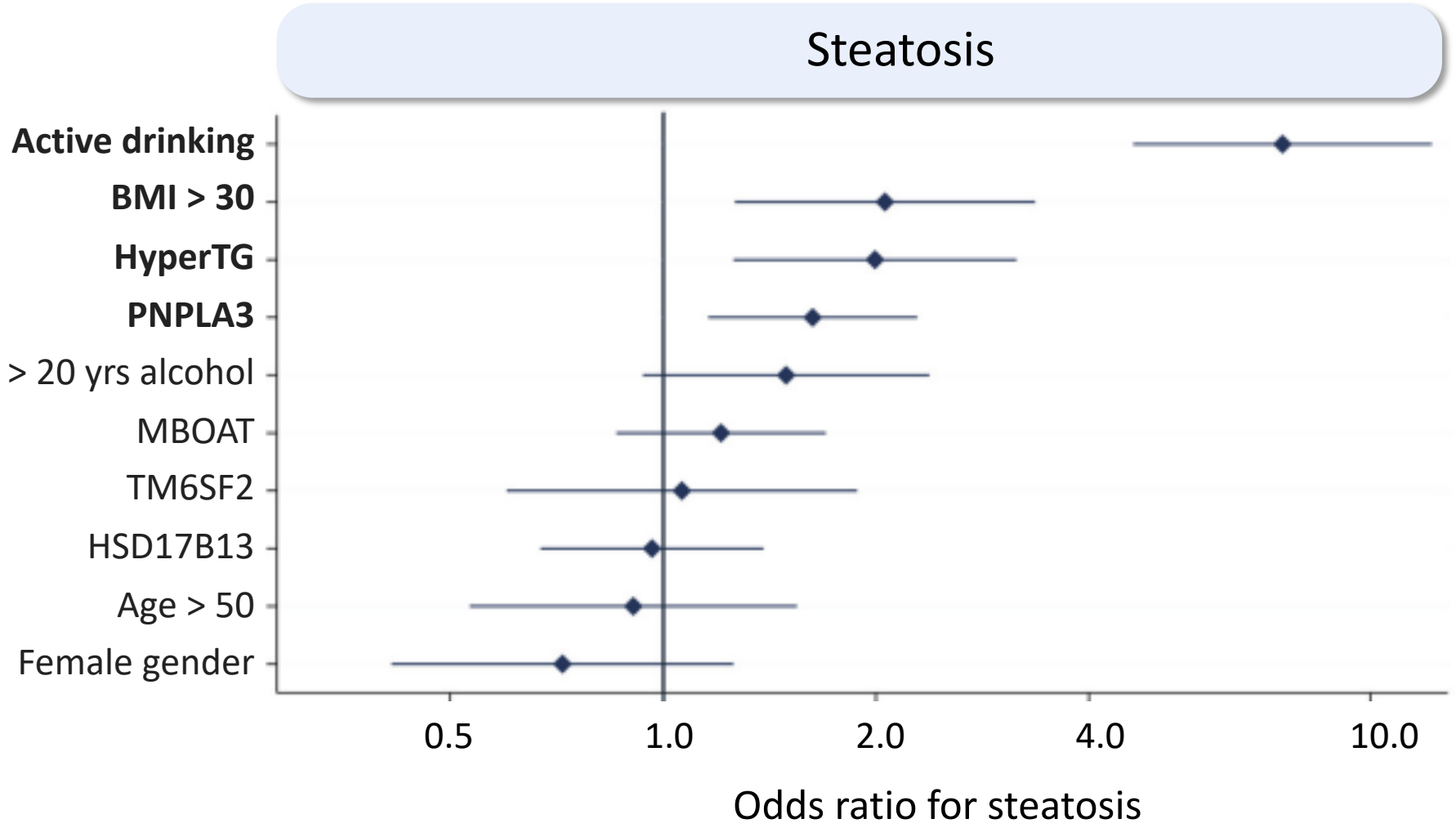
Risk Factors for Steatosis in ALD

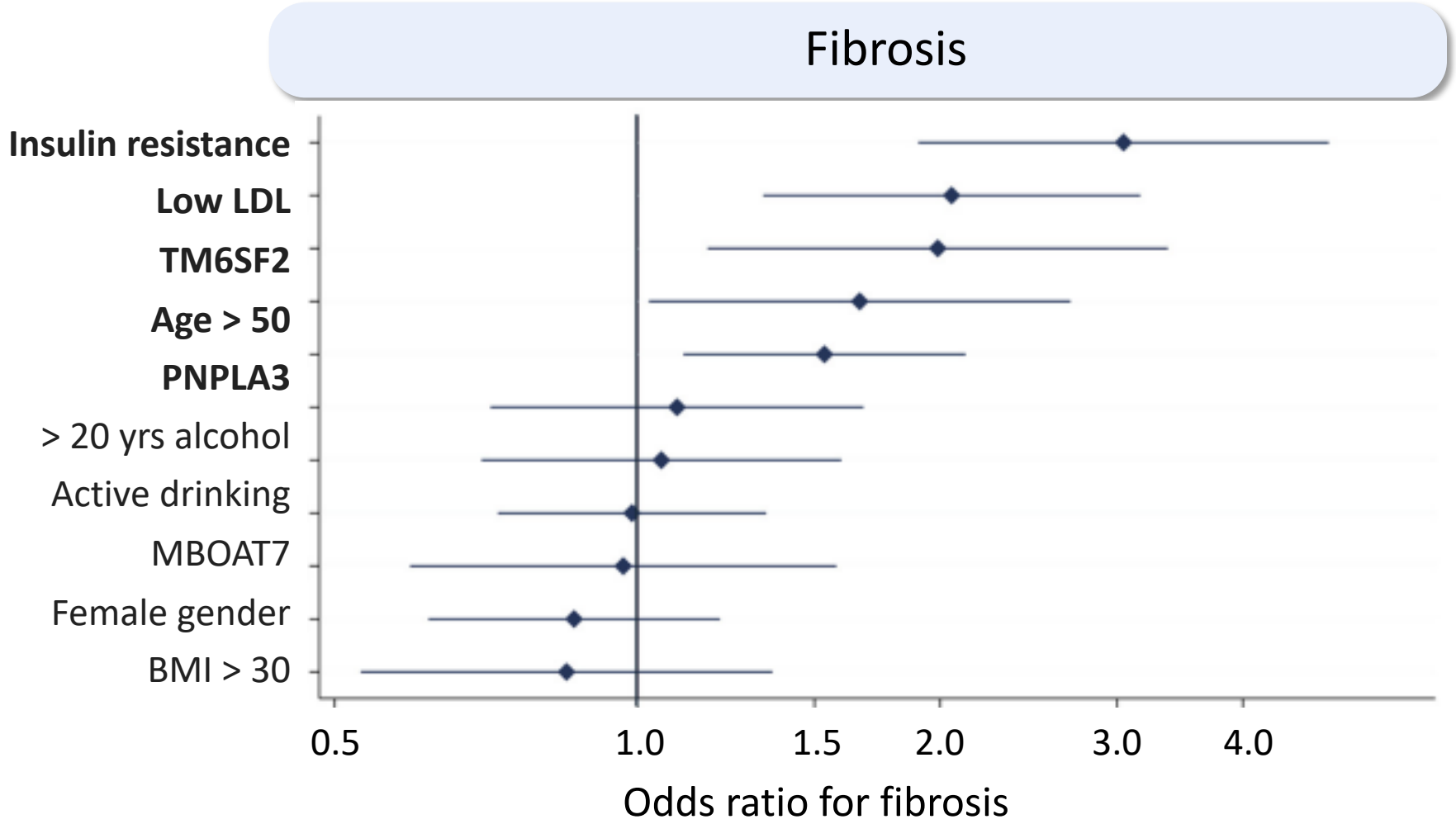
325 patients with ALD. Biopsy-based, cross-sectional study.



Israelson et al., Clin Gastro Hepatol 2022;20:1784–1794

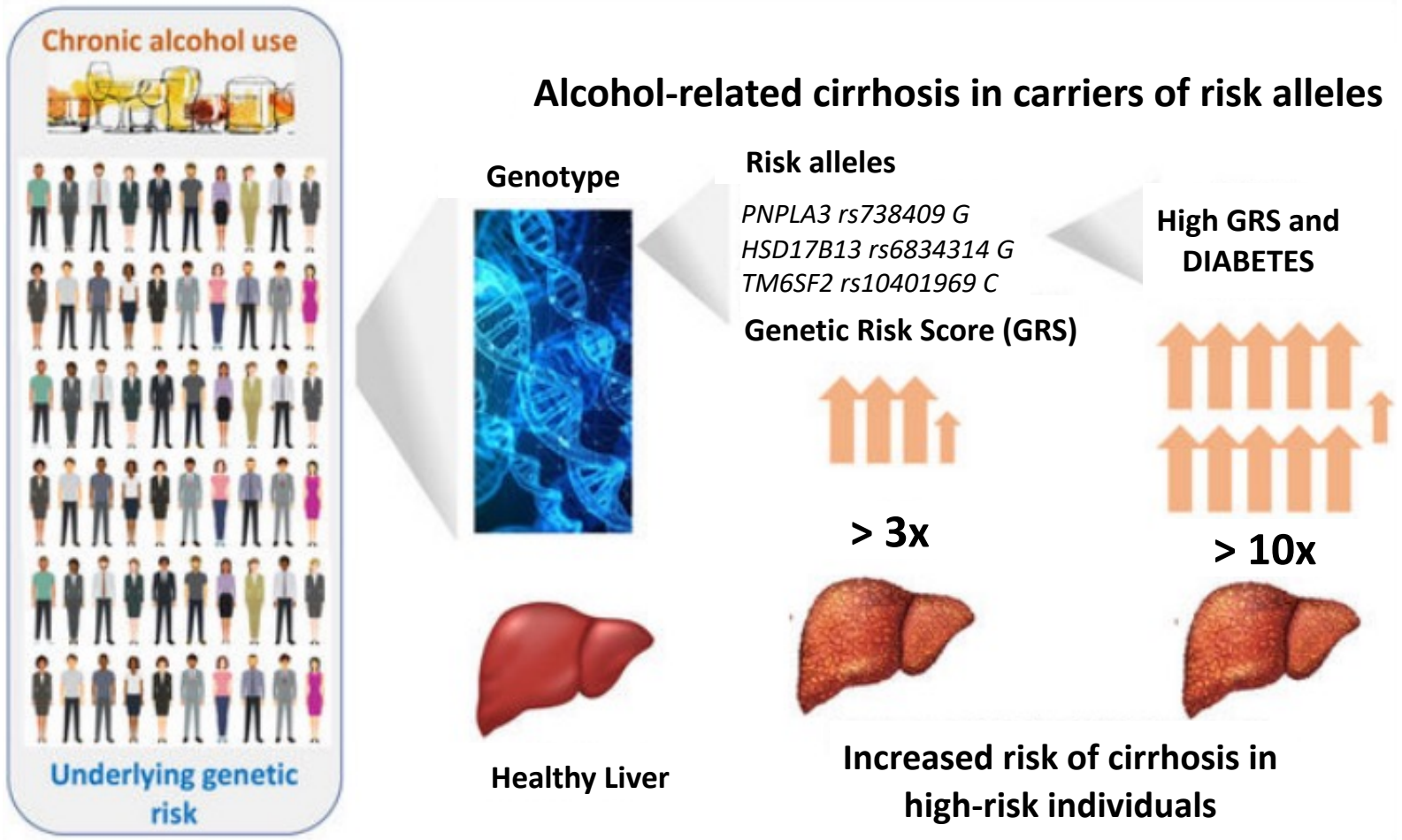
Risk Factors for Fibrosis in ALD

325 patients with ALD. Biopsy-based, cross-sectional study.



Israelson et al., Clin Gastro Hepatol 2022;20:1784–1794

A Genetic Risk Score Predicts Development of ALD Cirrhosis in Drinkers



Whitfield et al., *Journal of Hepatology* 2022:275-282

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A Genetic Risk Score Predicts Development of ALD Cirrhosis in Drinkers

1. Calculate the risk score as:

(0.7839*__PNPLA3__ rs738409 G dosage) + (0.5423*__TM6SF2__ rs10401969 C dosage) – (0.4463*__HSD17B13__ rs6834314 G dosage)

2. Assign the patient to the appropriate stratum of risk, as follows:

	Score less than 0 Low risk	Score above 0.7 High risk
Relative risk if not diabetic	1 (reference)	3-fold
Relative risk if diabetic	3-fold	Over 10-fold

Patients with scores between 0 and 0.7 are at intermediate risk.

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Whitfield et al., *Journal of Hepatology* 2022:275-282

Conclusions

- ALD and MASH have overlapping pathogenesis, genetics, histology, and clinical course.
- Patients who drink in excess often have metabolic syndrome.
- Alcohol is additive with metabolic syndrome in the development and progression of fatty liver disease.
- Insulin resistance and genetic susceptibility have considerable, independent impact on progression of liver disease.
- In patients with steatotic liver disease, safe limits of alcohol use concerning liver risk may not exist.

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Q&A/Panel Discussion

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15 Minute Break

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