Penn Nursing
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Shared genetic and metabolic risks of liver disease with dementia and Alzheimer's Disease

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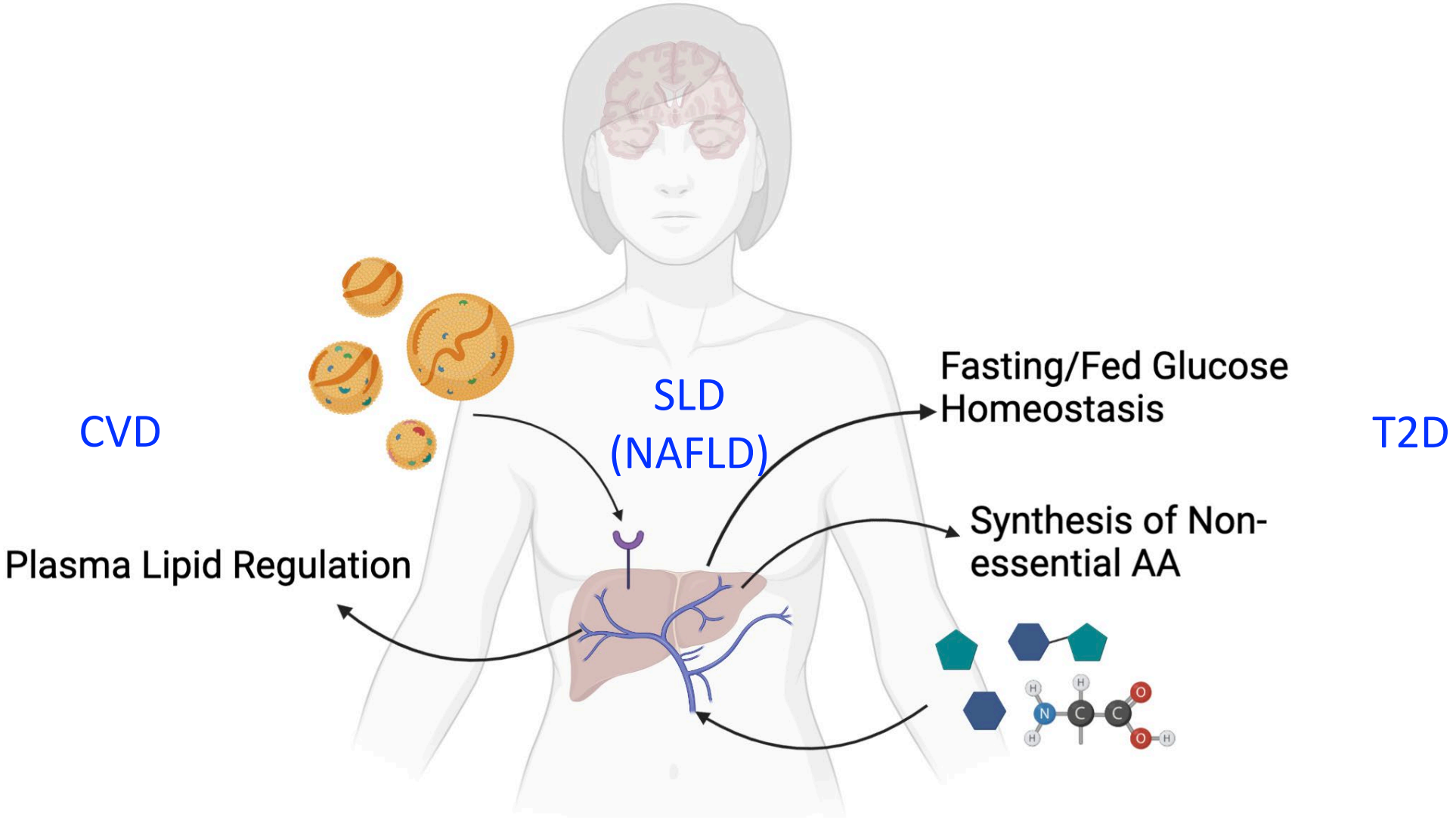
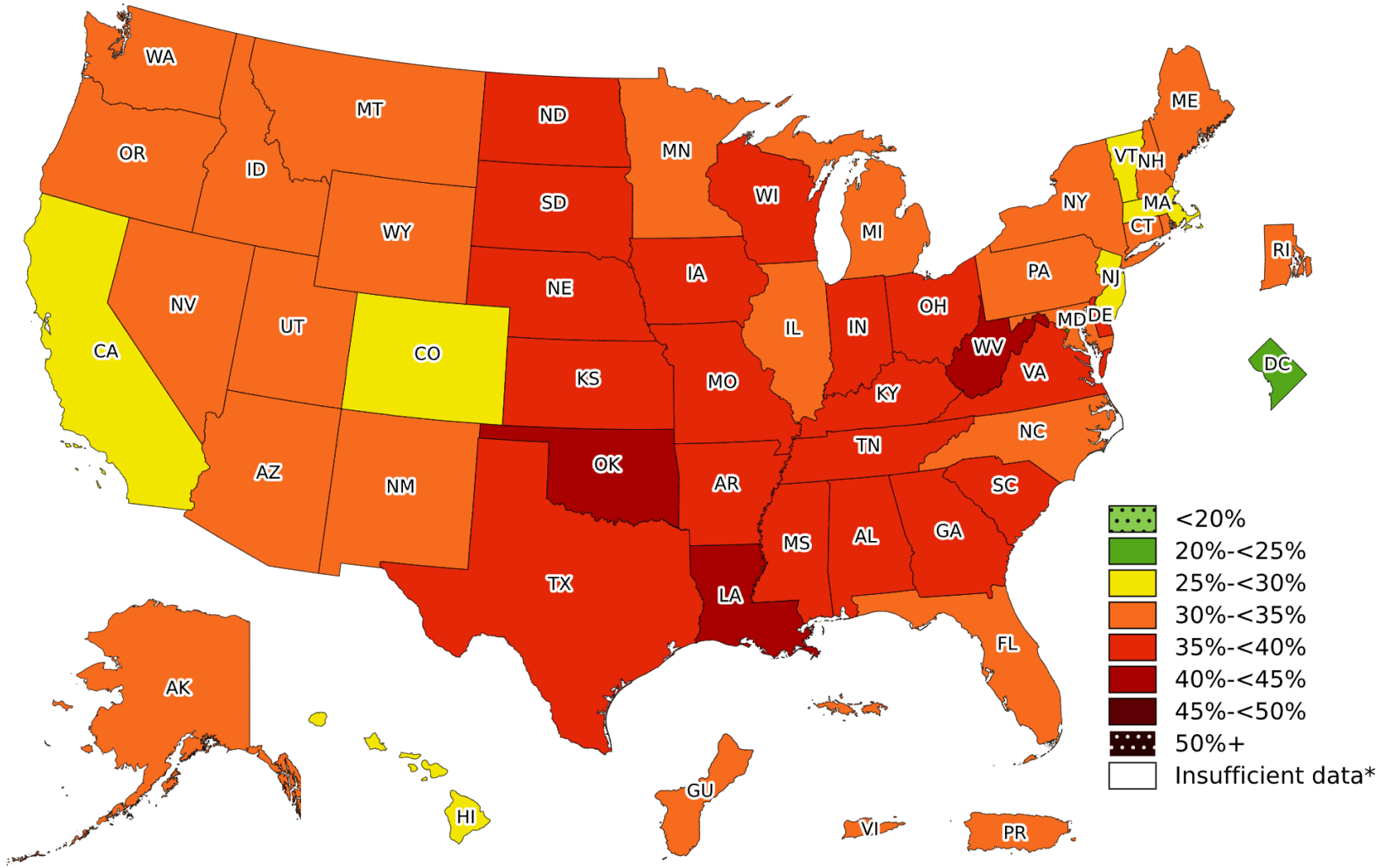
RCCN Workshop on Nutrition and Aging Biology

Liver is central to metabolism and health



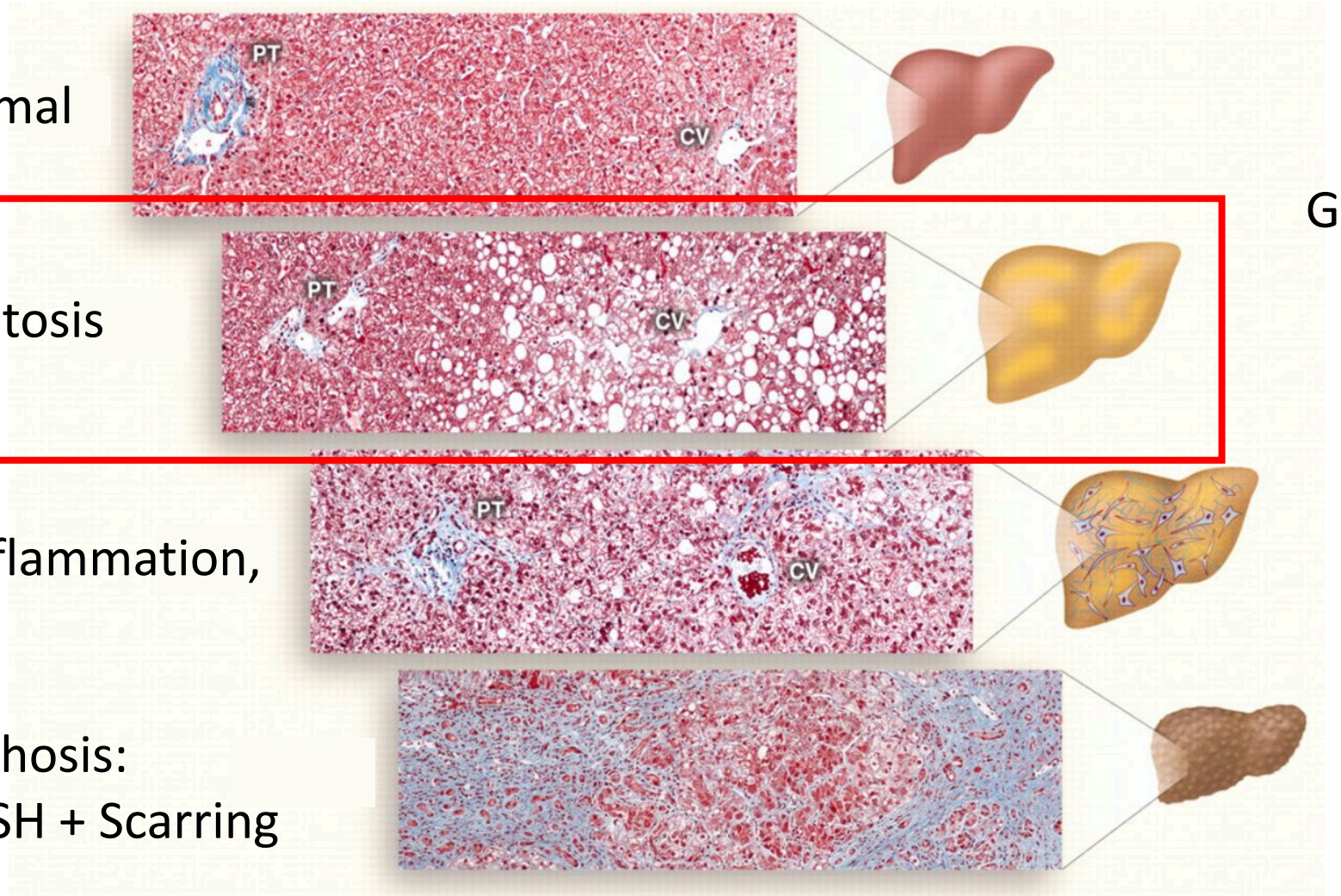
SLD is a growing public health concern

SLD:
Obesity: 30-90%
Severe Obesity: >90%



cdc.gov

NAFLD is a spectrum of liver pathologies



Normal

T2D
CVD

Steatosis

NASH:
Steatosis + Inflammation,
Fibrosis

Cirrhosis:
NASH + Scarring

General Population:

25-30% (~100M)

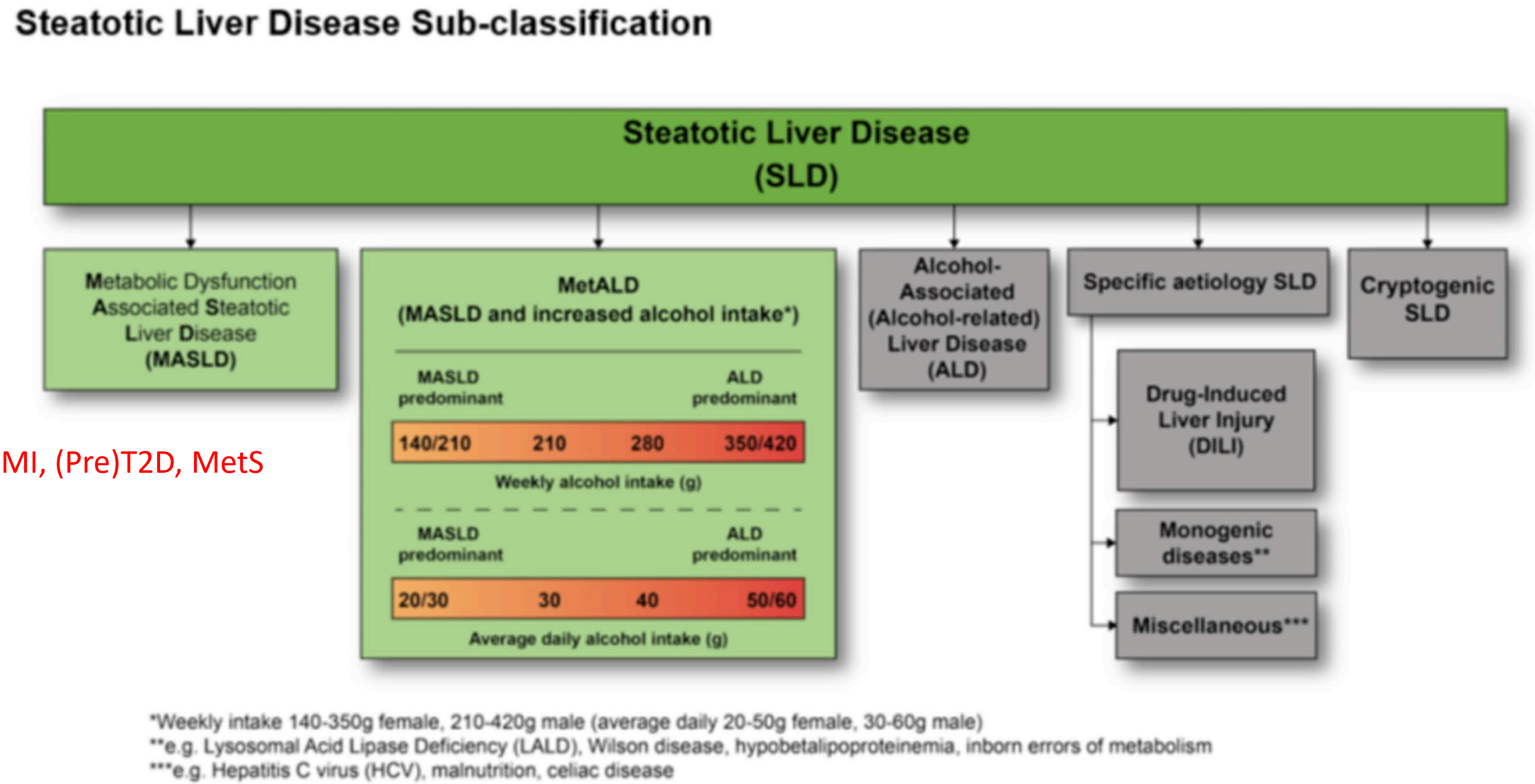
15-20% (~20M)

10-20% (~4M)

HCC
~10%

Adapted from Cohen et al. *Science* 2011

New Nomenclature: MASLD



Adapted from Rinella et al. *Hepatology* 2023

Common Features of MASLD and Alzheimer's Disease

MASLD Comorbidities

- Obesity
- T2D
- HTN
- Dyslipidemia
- Liver manifestation of MetS

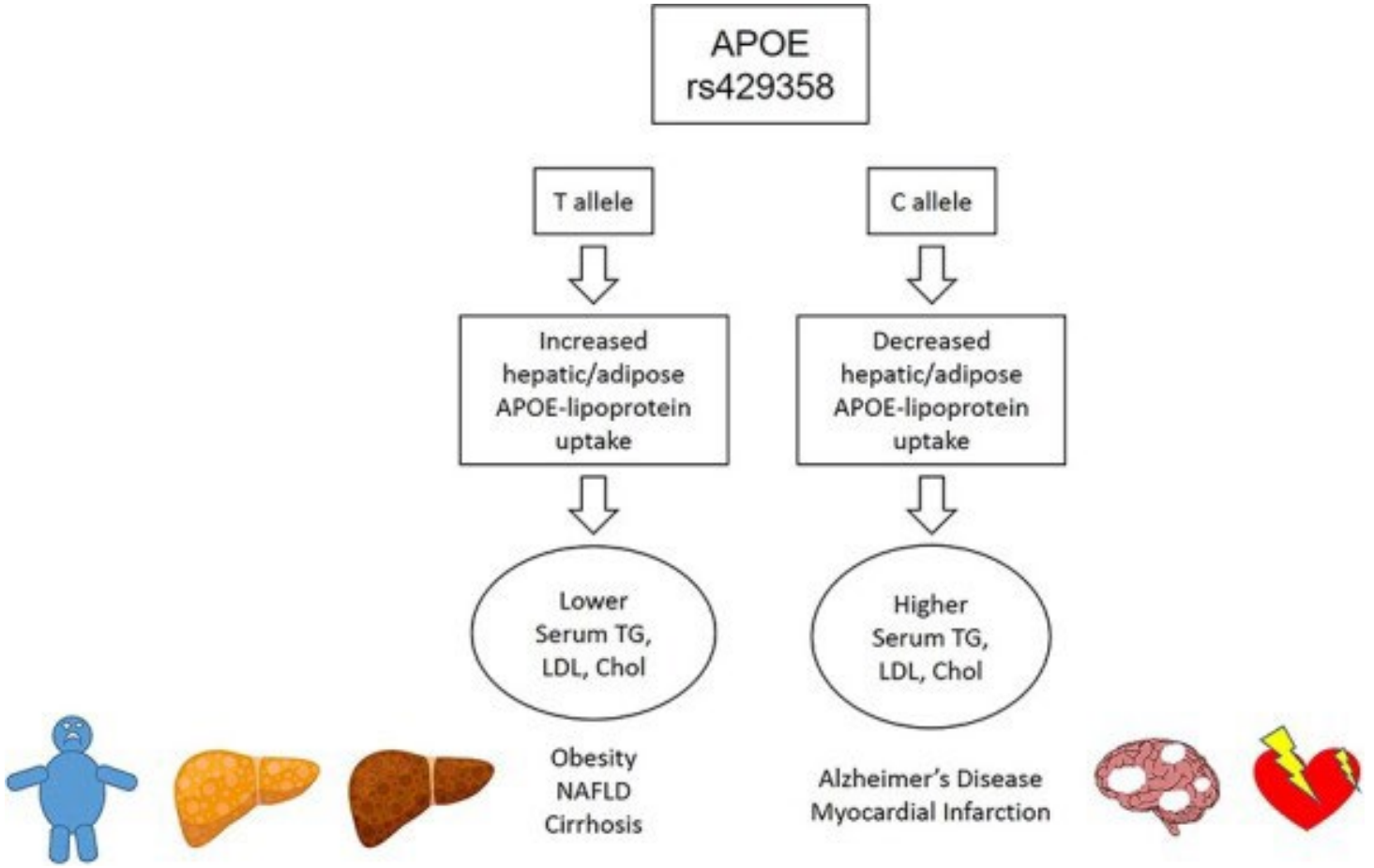
AD Risk Factors

- Obesity
- T2D
- HTN
- Dyslipidemia
- Metabolic Syndrome (MetS)

High hereditability:

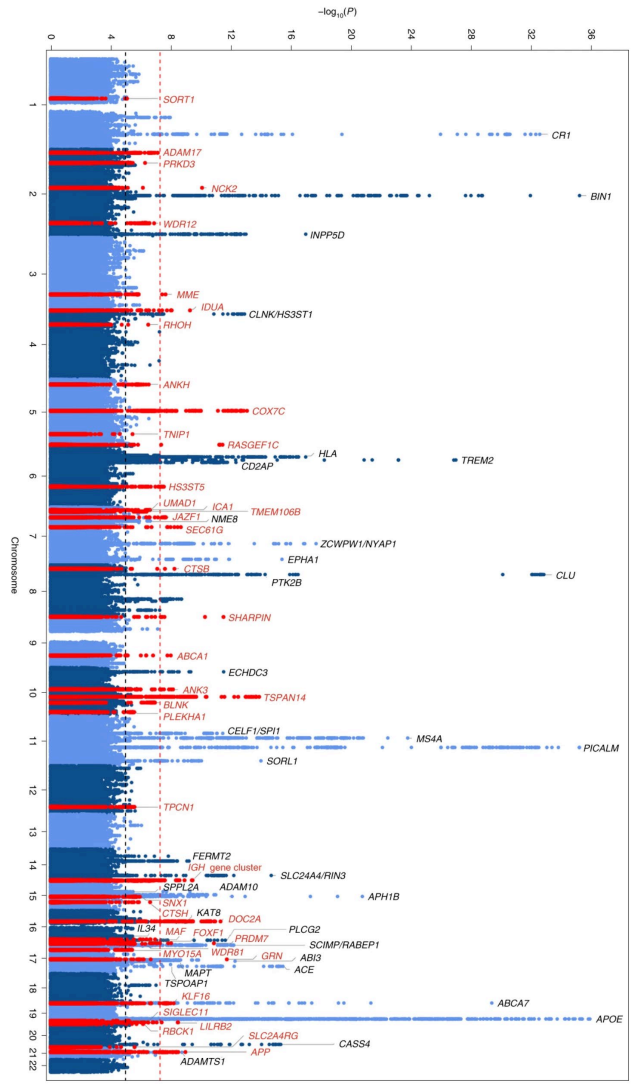
**Numerous shared risk genes between NAFLD/MASLD and AD*

APOE genetic associations with AD and NAFLD/MASLD



Palmer et al. *Hum Mol Genet* 2021

AD GWAS risk loci with liver metabolic functions



SORT1 → Liver lipid accumulation/TG secretion

JAZF1 → Glucose homeostasis/T2D

CLU/APOJ → Liver-derived hepatokine/Glucose metabolism

ABCA1 → HDL metabolism

ABCA7 → HDL metabolism

APOE → NAFLD/MASLD

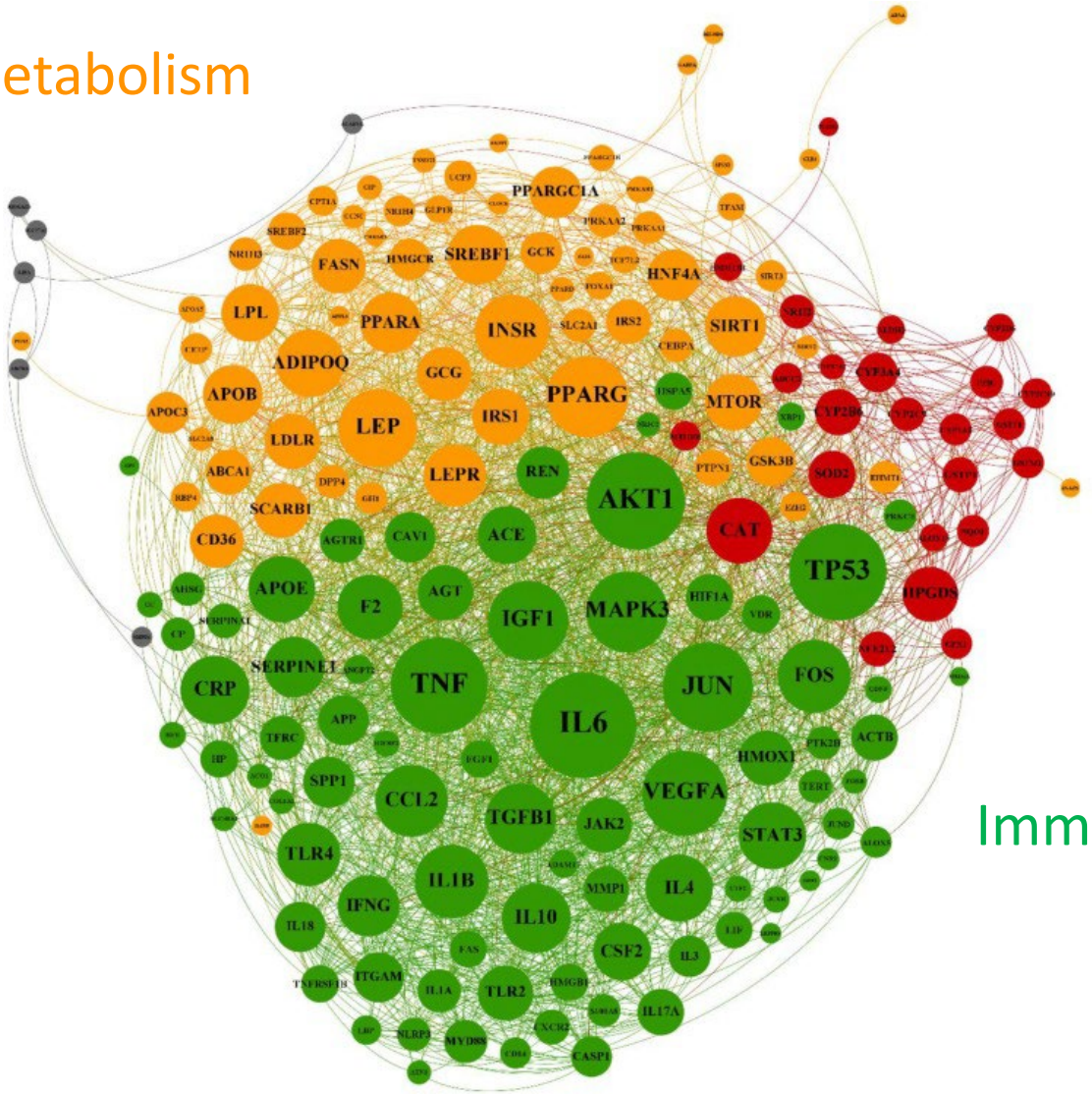
Bellenguez *et al. Nat Genet* **54**, 412–436 (2022)

Novel associations = Red

Replicated associations = Black

Network of genes common to AD and NAFLD

Carbohydrate metabolism



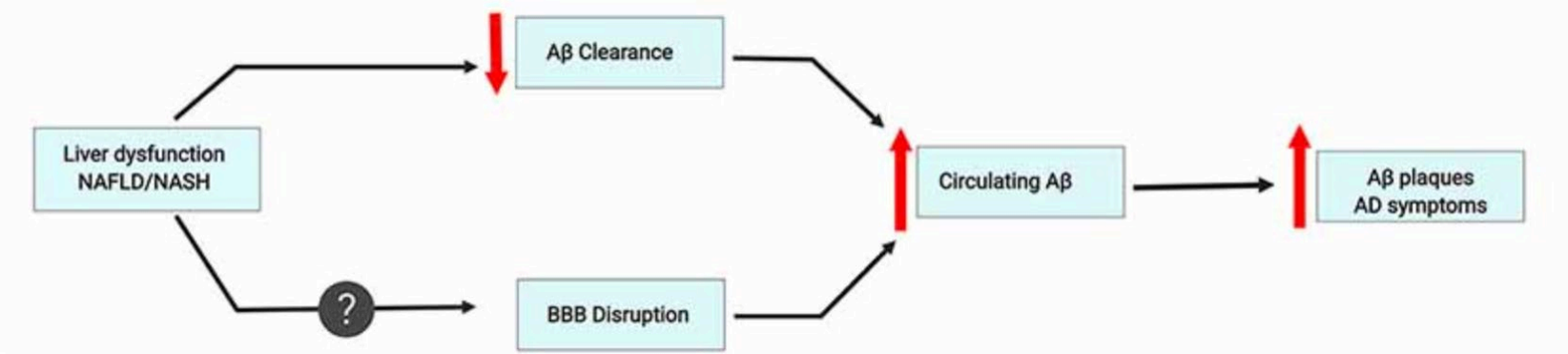
Lipid metabolism

Immune/Inflammation

Karbalaei et al. *Gastro Hepatol Bed Bench* 2018

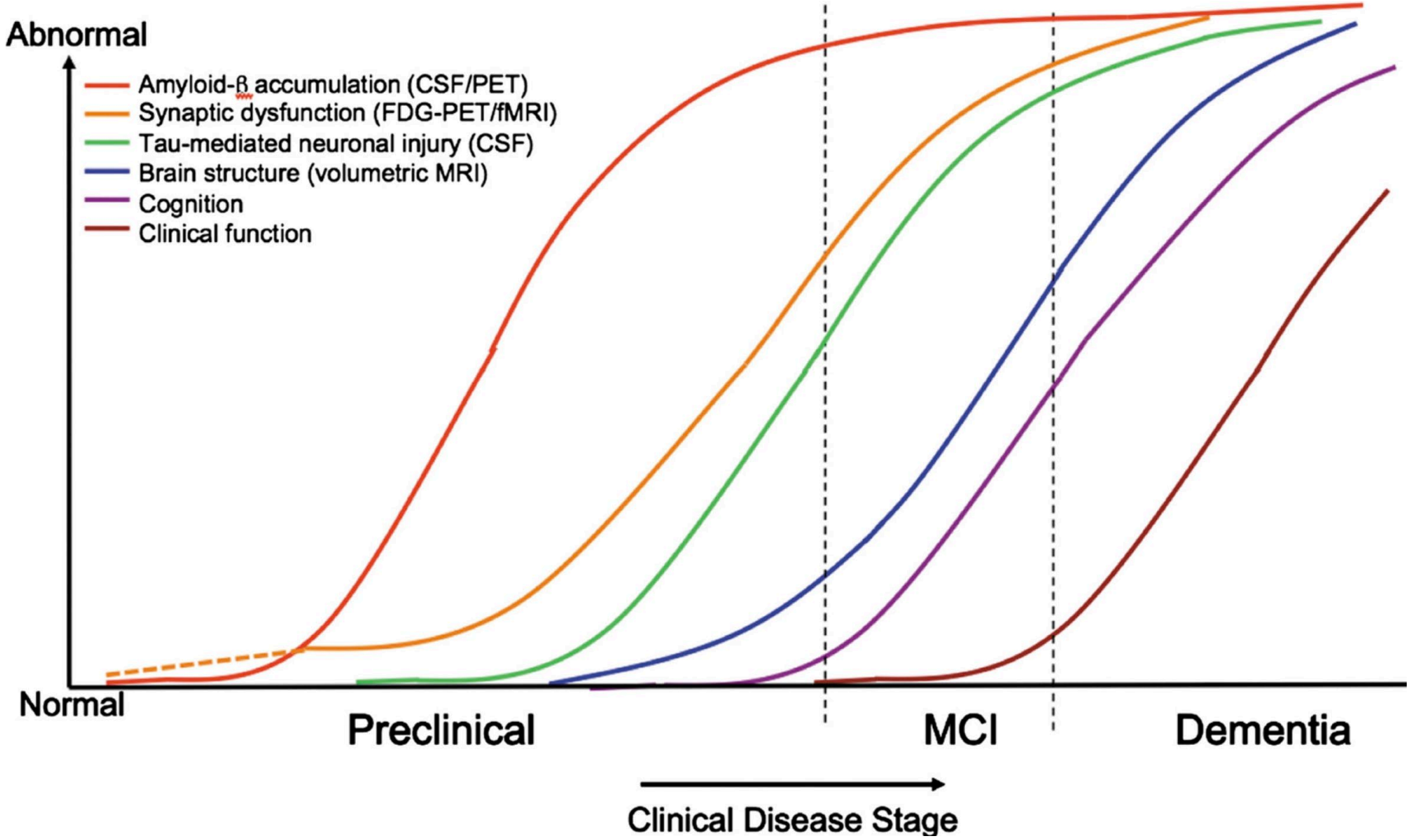
Does MASLD directly increase risk of AD?

- Aβ is produced in normal brain but accumulates in AD
- Aβ passes through BBB to peripheral circulation; cleared by liver, kidneys
- MASLD may inhibit peripheral clearance and contribute to neural accumulation



Estrada et al., *Front. Aging Neurosci.*, 2019

Neurotoxic proteins accumulate decades before dementia



Sperling et al. Alz Dement. 2011