The Copper - NAFLD connection: Role of hepatic copper deficiency

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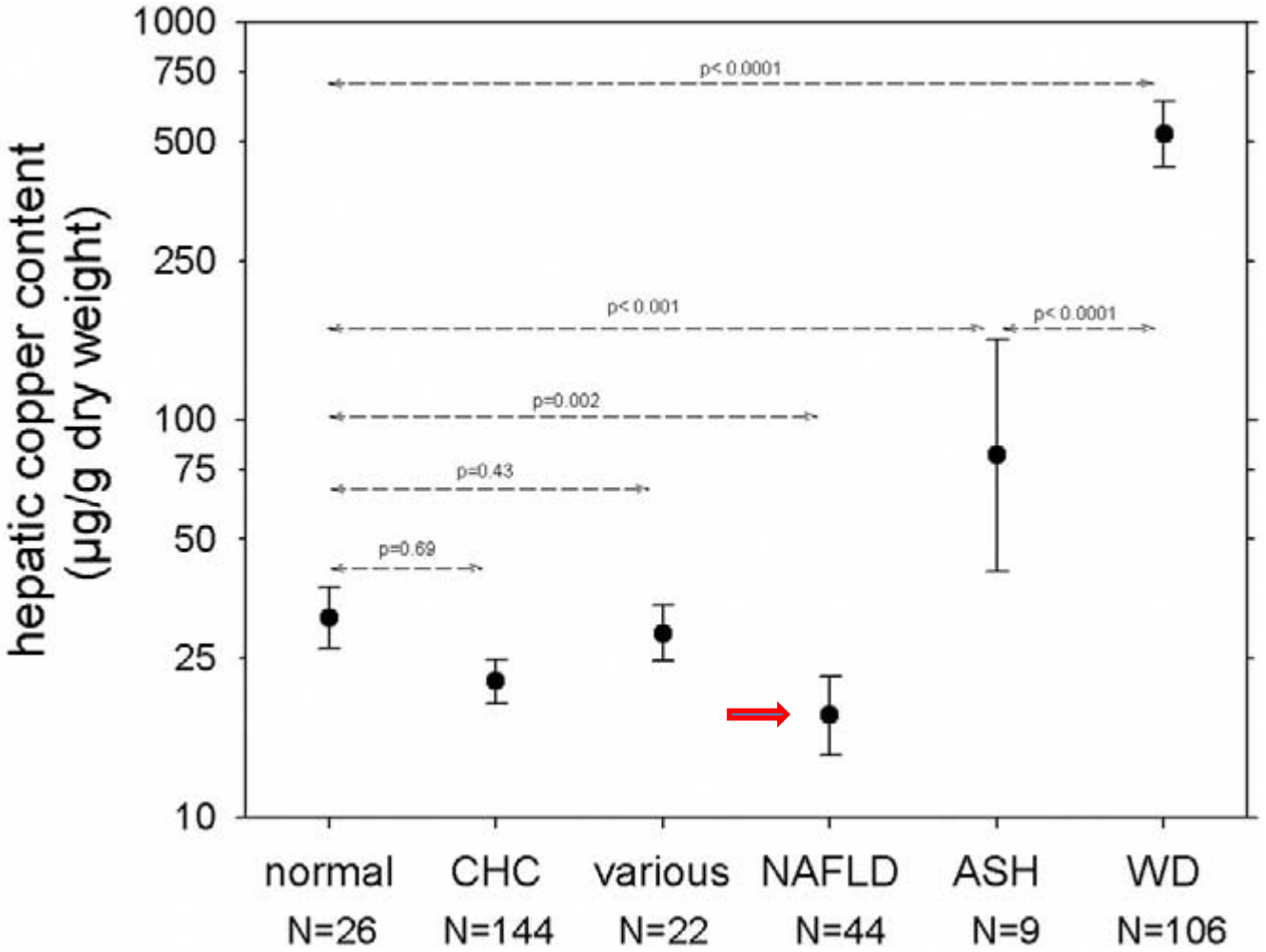
Hepatic copper content in patients with liver disease



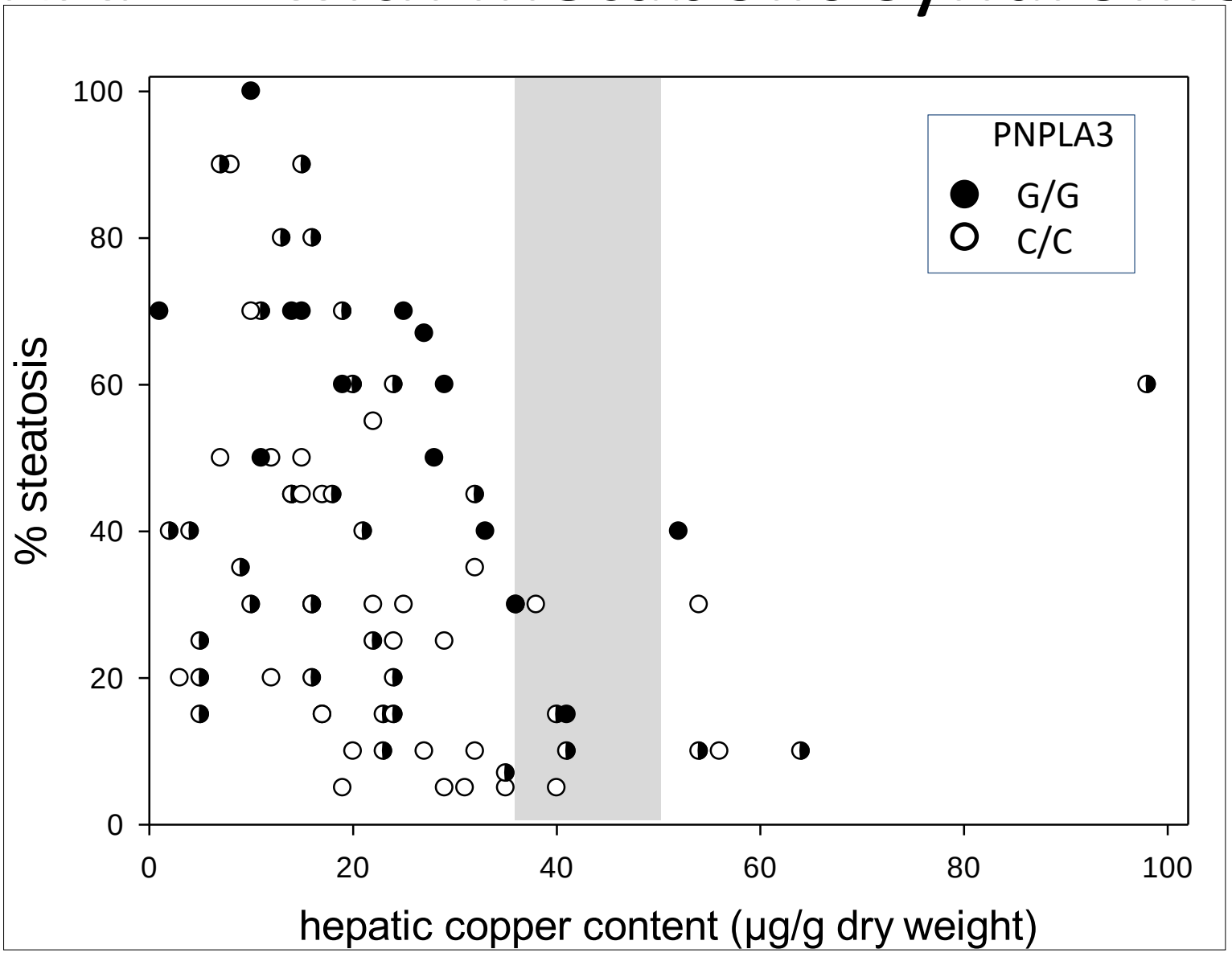
Ferenci et al, J, CGH 2005

NAFLD and hepatic copper content

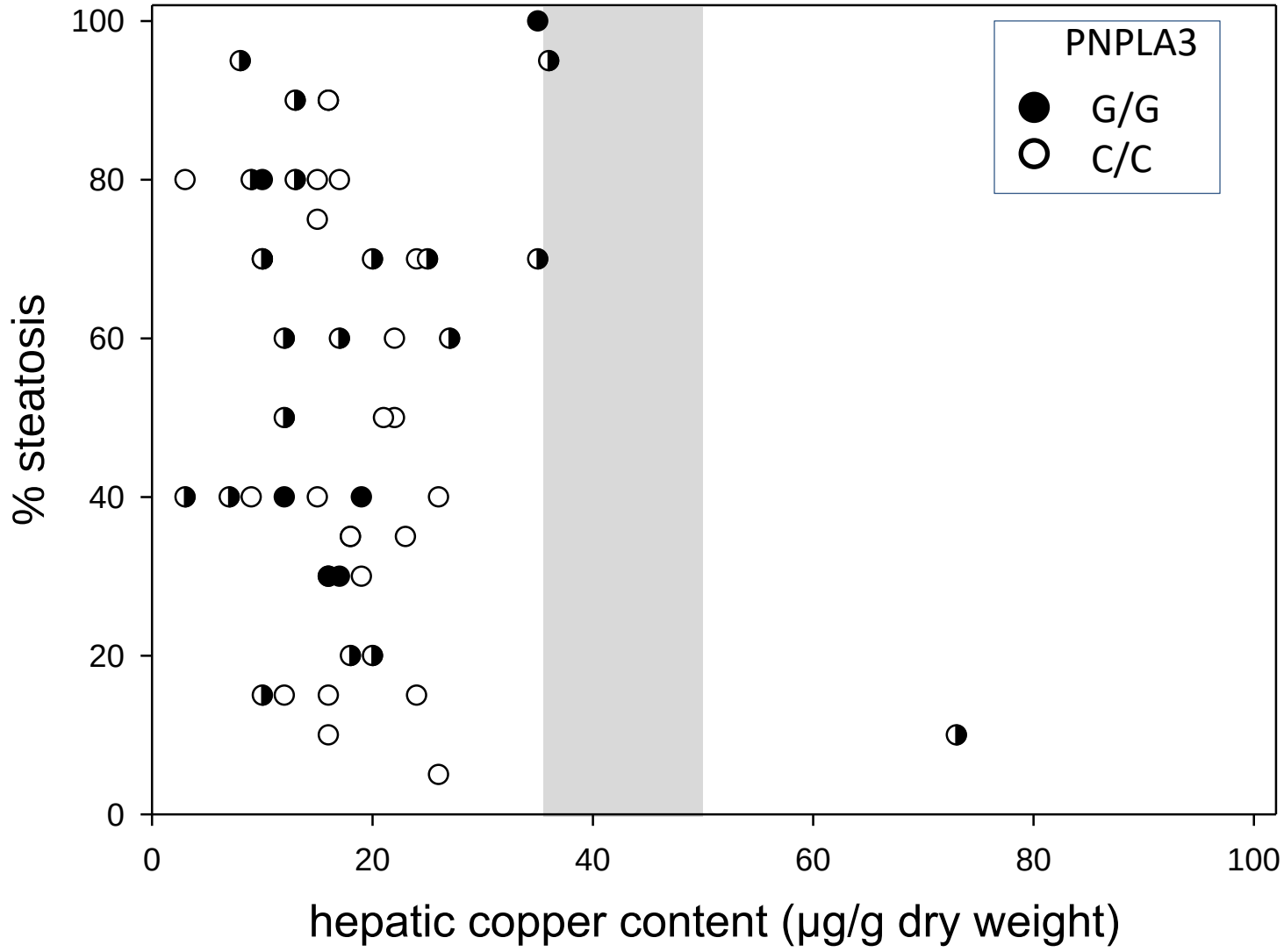
- 174 Caucasian patients with biopsy proven NAFLD/NASH (69% male, mean age 49a,mean BMI 30.2)
- Measurement of hepatic copper content (flame photometry)
- Semiquantitative assessment of hepatic steatosis
- Determination of *PNPLA3* and *TM6SF2*

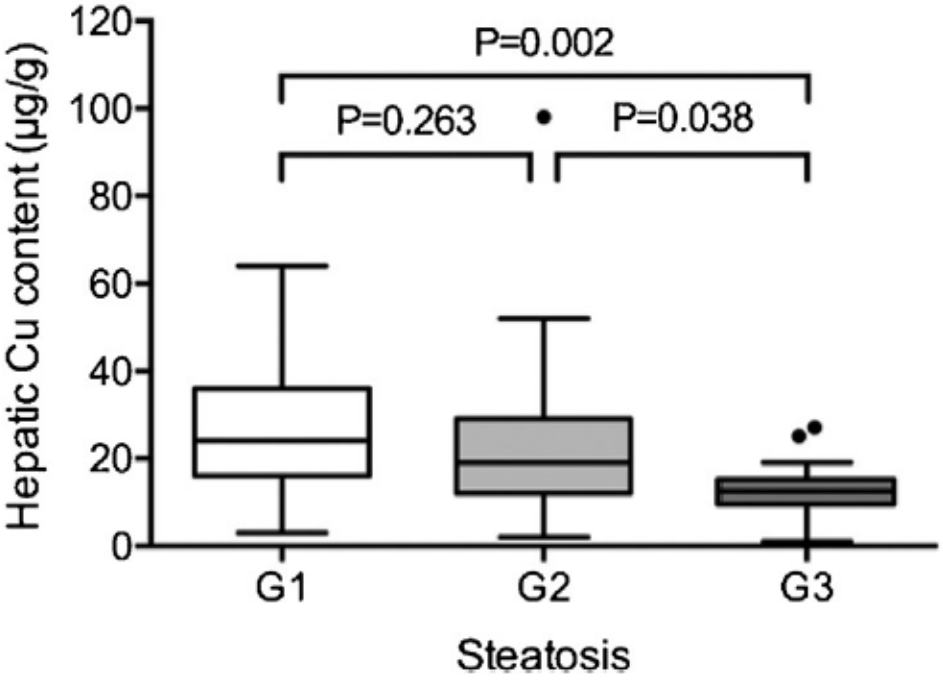
Stättermayer et al, J of Trace Elements in Medicine and Biology 2017

NAFLD with metabolic syndrome

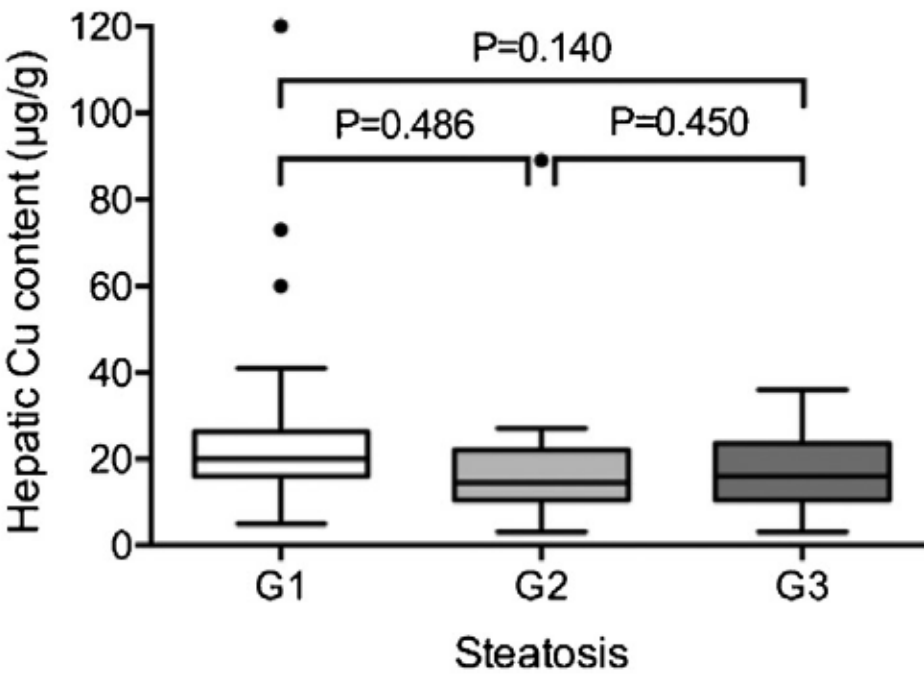


NAFLD without metabolic syndrome





Lean NAFLD

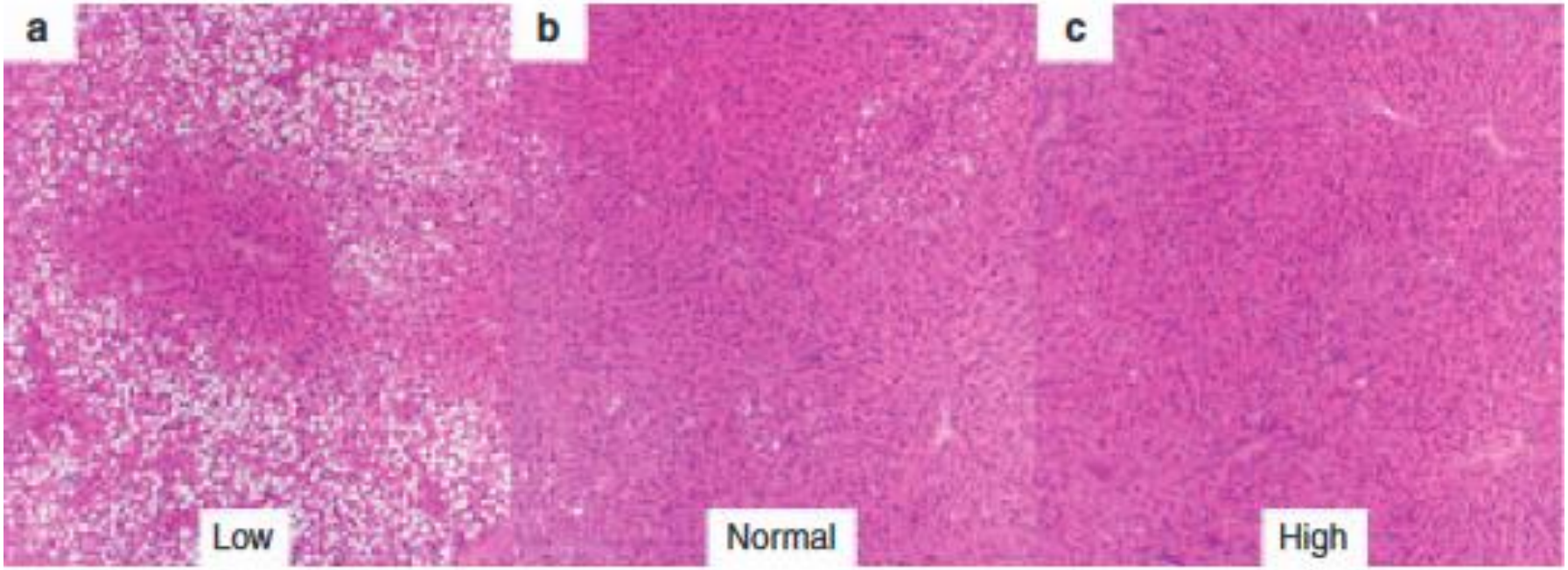


NAFLD in patients
with metabolic syndome

Stättermayer et al, J of Trace Elements in Medicine and Biology 2017

Experimental data

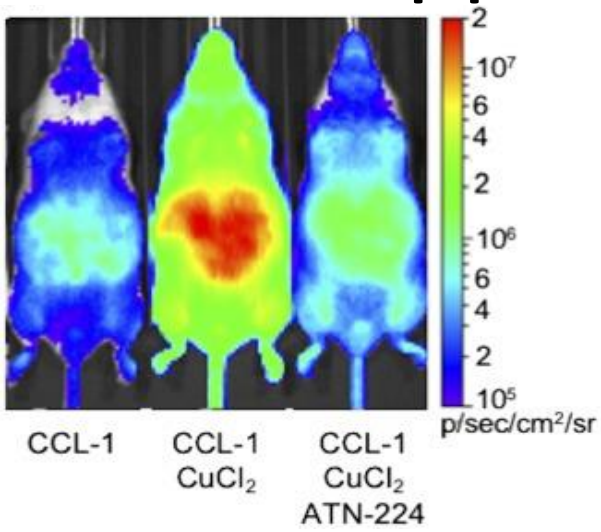
Effect of dietary copper on hepatic steatosis in rats

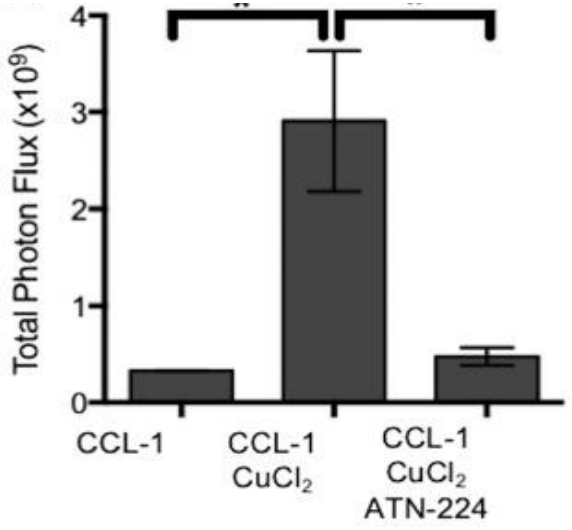


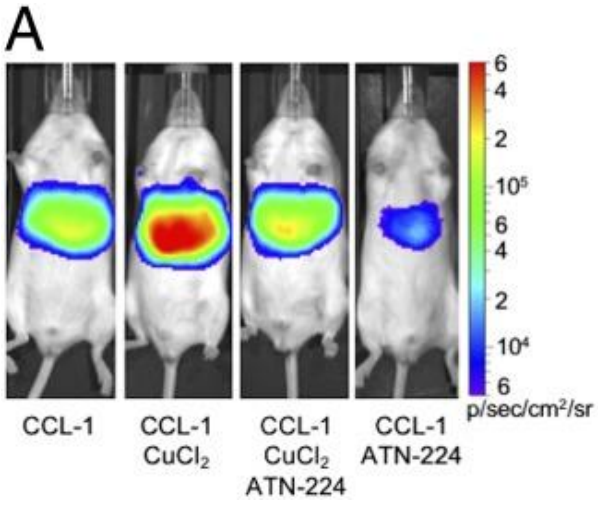
Copper in diet

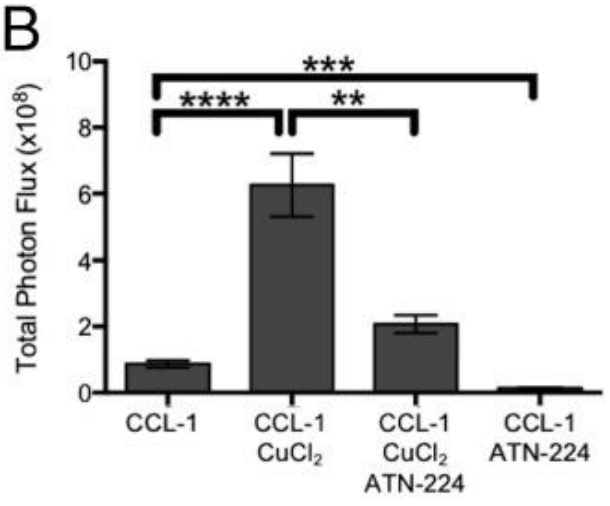
Aigner et al, Am J Gastro 2010

In vivo measurement of hepatic copper content



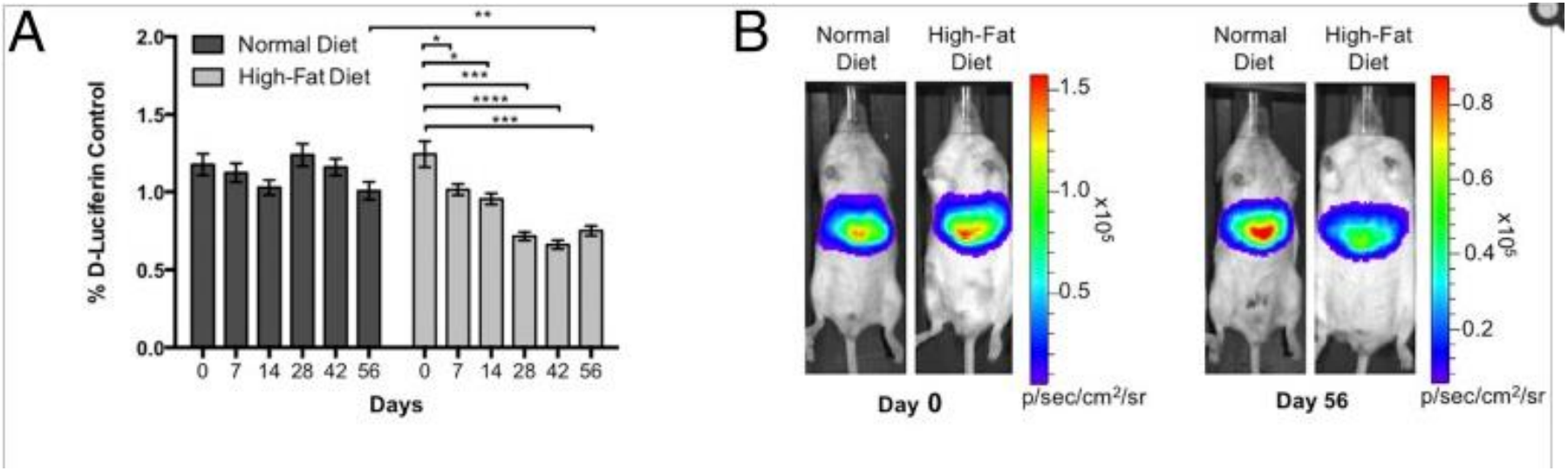






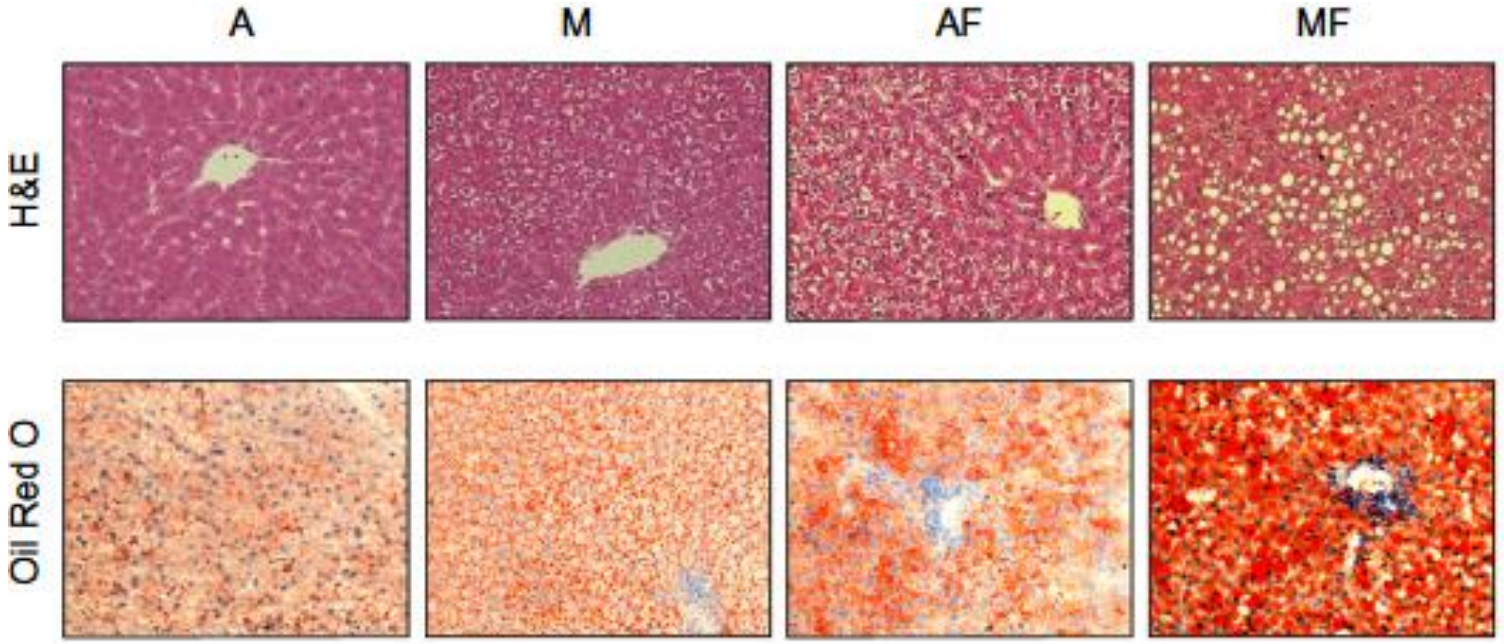
Heffern et al, PNAS 2016

Effect of a high fat diet on hepatic copper content



Heffern et al, PNAS 2016

Effect of high fructose feeding in rats

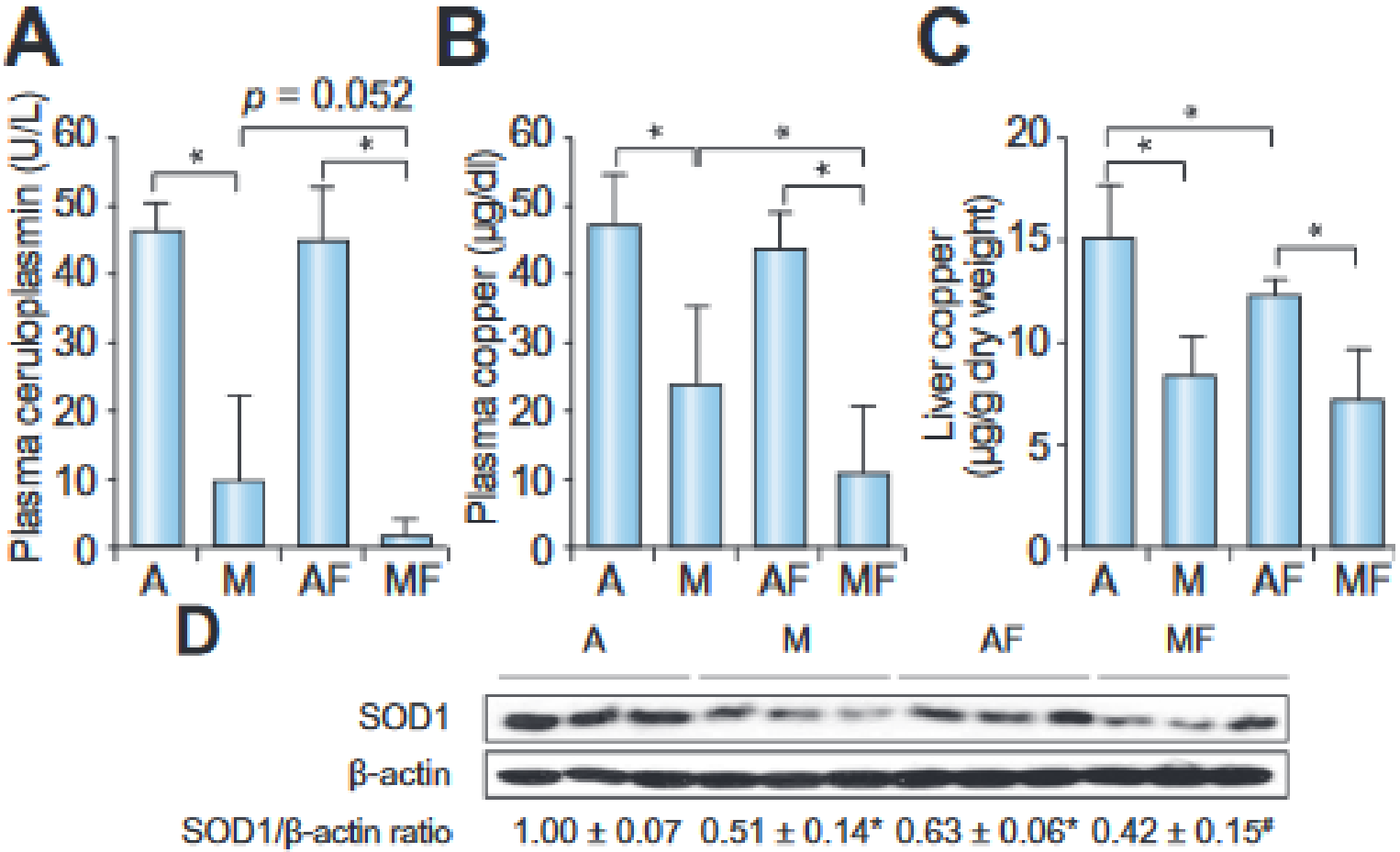


A: adaequate copper feeding
M: marginal copper feeding

AF: A+ 30% fructose
MF: M+30%fructose

Song et al, J, Hepatol 2012

Effect of high fructose feeding in rats



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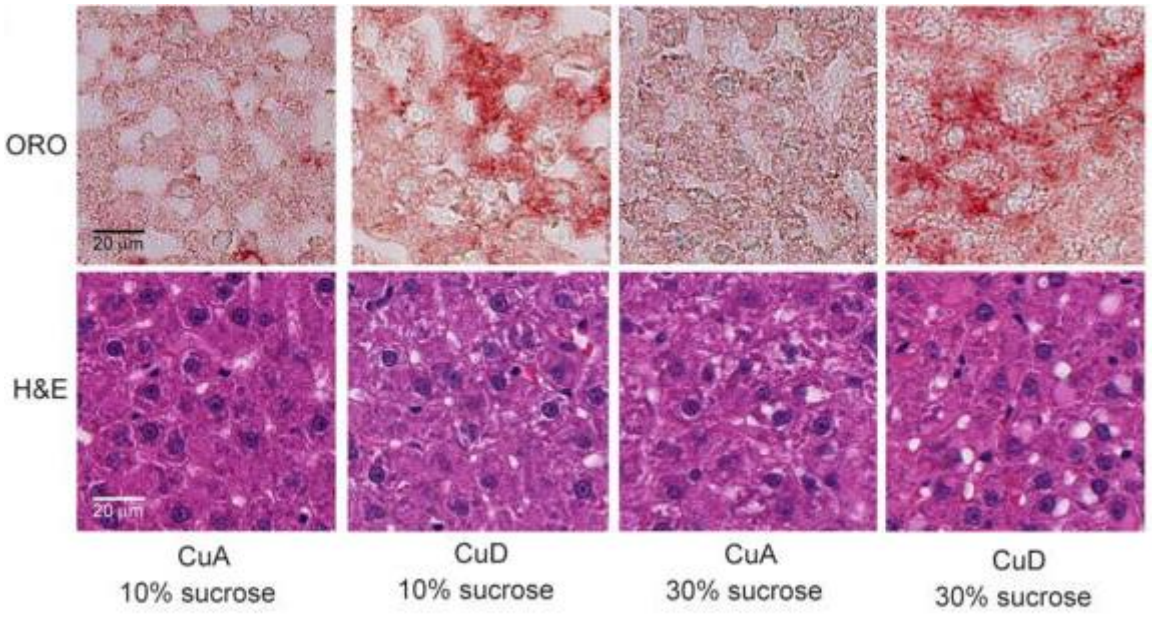
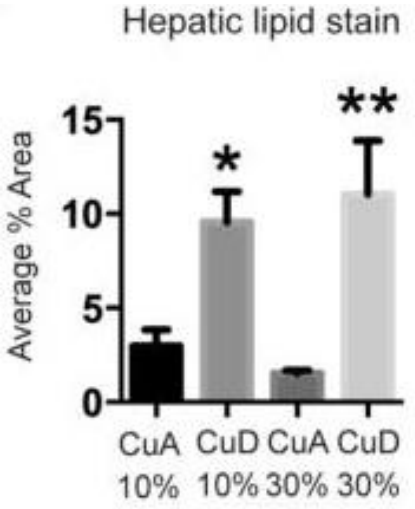




- Low dietary Cu and sucrose consumption promote inflammation and fibrosis gene expression changes consistent with NAFLD
- Low dietary Cu promotes steatosis as well as gene expression changes in lipid synthesis
- Cu deficiency and sucrose consumption promote NAFLD-like pathology

Tollino et al, J Nutr. Biochem 2015

Copper rich food

1) Beef liver

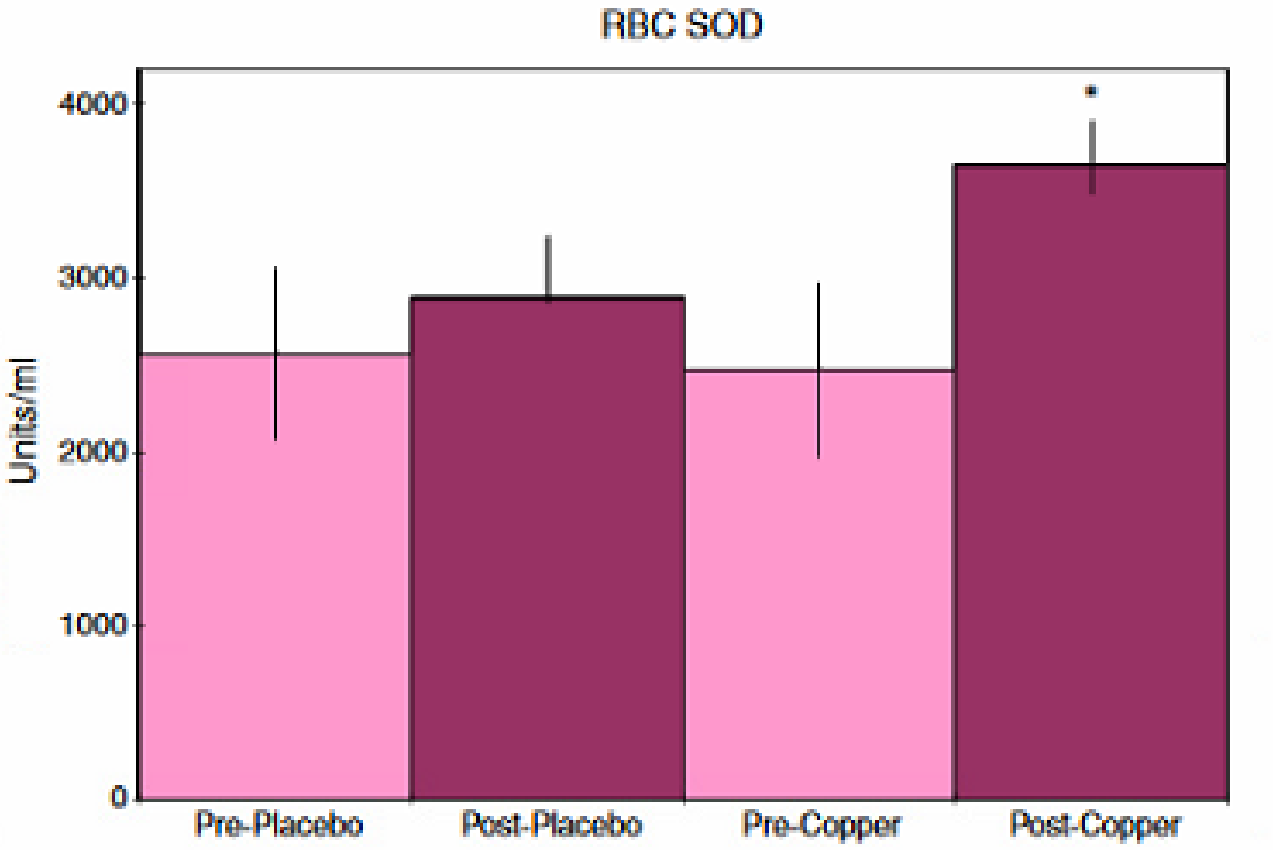
2) Sunflower seeds

3) Lentils

Diet of 25-50% US adults is copper deficient!

Copper content of a Big Mac™ 0.098 mg! (RDA 1-2 mg/d)

Effect of copper substitution (2mg/d as glycinate) on SOD



Marginal copper deficiency in US adults?

DiSilvestri et al, Metabolism 2012

NAFLD – copper connection

- Experimental:
  - Low copper diet leads to NAFLD
  - Low copper diet + high sucrose – highest degree of steatosis
  - High fat diet decreases hepatic copper content
- Patients:
  - Low hepatic copper content in (lean) NAFLD
  - Interaction with hepatic iron

Summary

- Hepatic copper content and PNPLA3 (SNP rs738409) are independently associated with moderate/severe steatosis and disease activity in patients with NAFLD with normal BMI.
- NAFLD is not a single disease entity
- Different pathogenetic mechanisms trigger hepatic steatosis and hepatocellular injury in patients with and without presence of MetS

Stättermayer et al, J of Trace Elements in Medicine and Biology 2017