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ADME in NAFLD: Genes and Big Jeans Increase the Risk of Adverse Drug Reactions

Nathan J. Cherrington, Ph.D.

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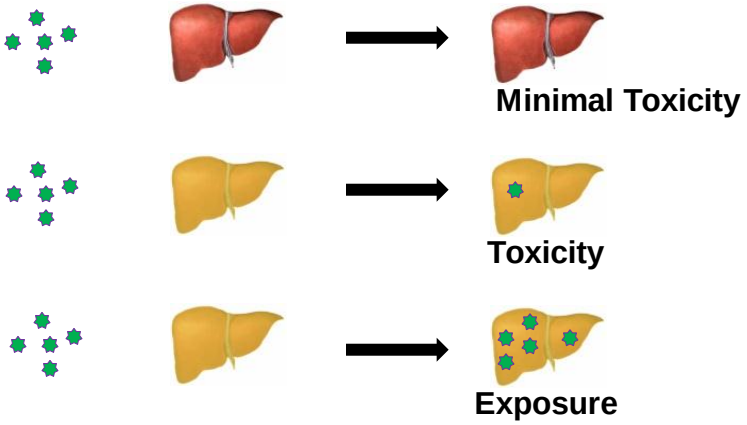
Drug-Induced Liver Injury



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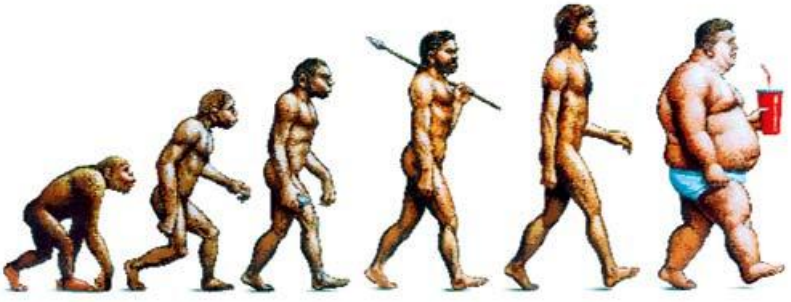
Obesity: An Increasing Health Crisis



Dec 11th, 2003 *The Economist*

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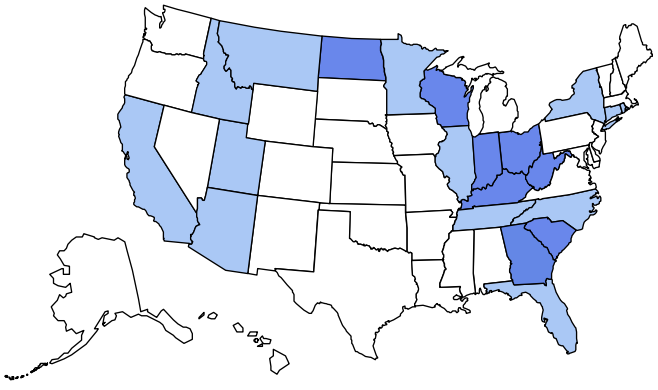
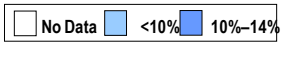
Obesity Trends* Among U.S. Adults
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)





http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

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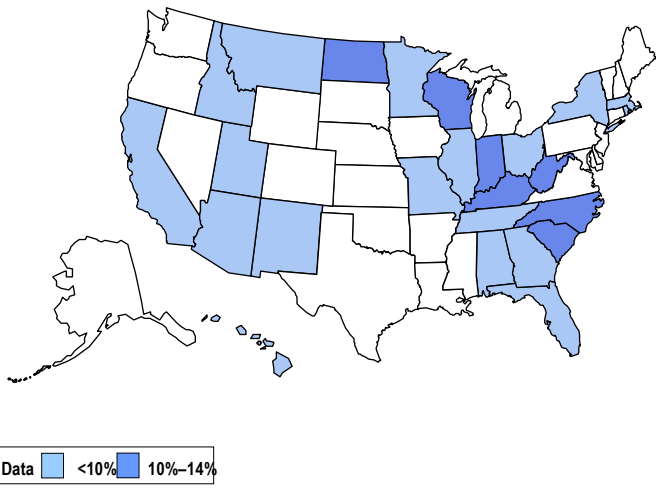
Obesity Trends* Among U.S. Adults
BRFSS, 1986

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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Obesity Trends* Among U.S. Adults
BRFSS, 1987

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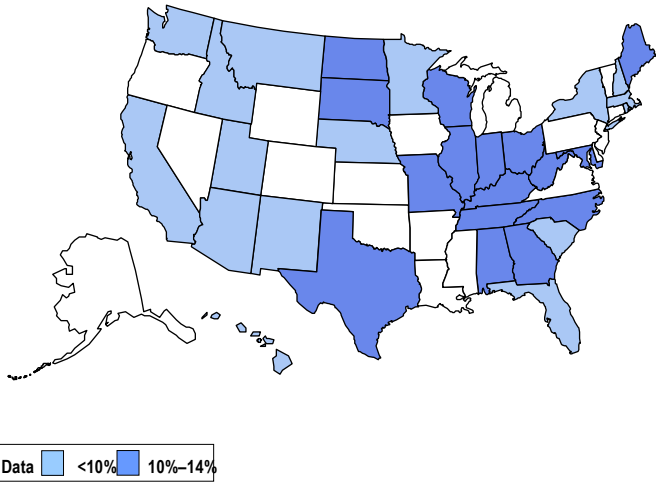

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Obesity Trends* Among U.S. Adults
BRFSS, 1988

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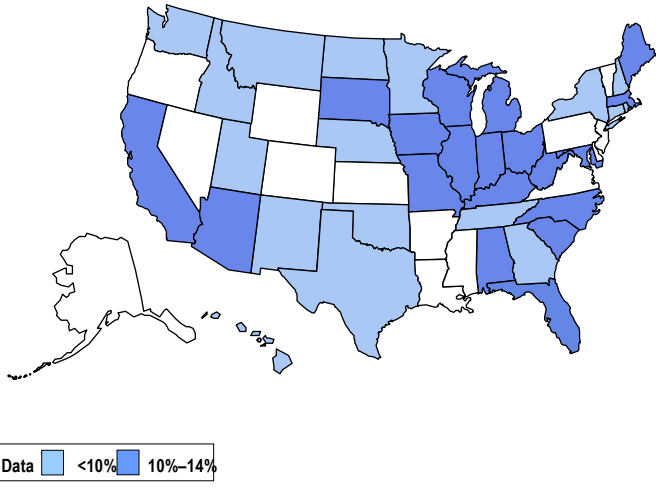

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Obesity Trends* Among U.S. Adults
BRFSS, 1989

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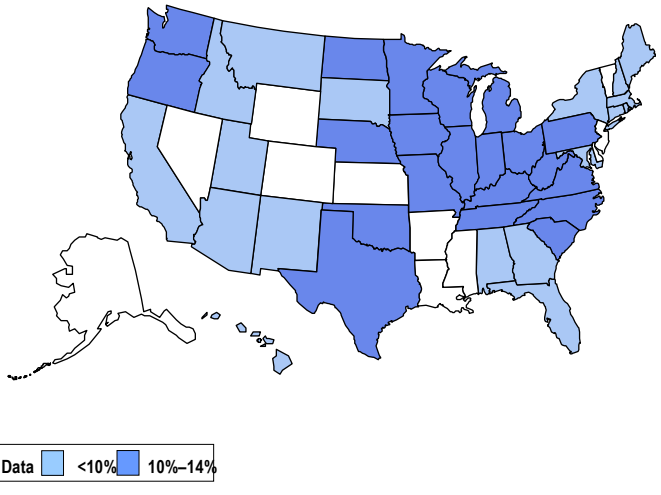

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BRFSS, 1990

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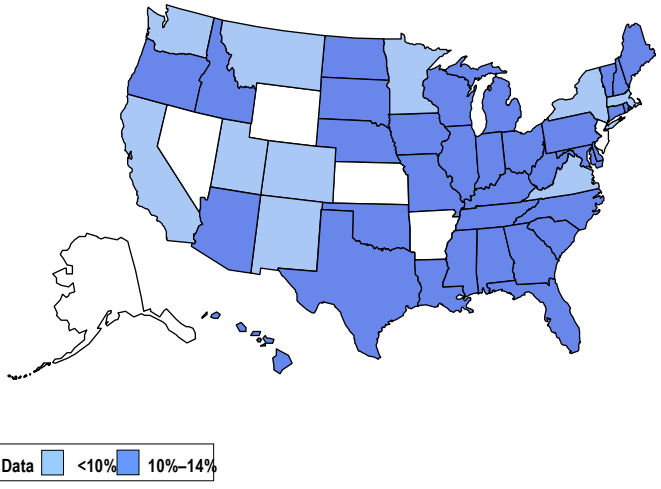

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Obesity Trends* Among U.S. Adults
BRFSS, 1991

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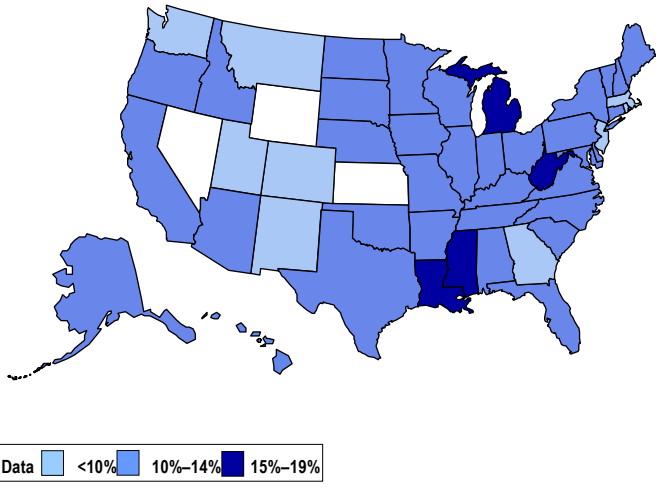

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BRFSS, 1992

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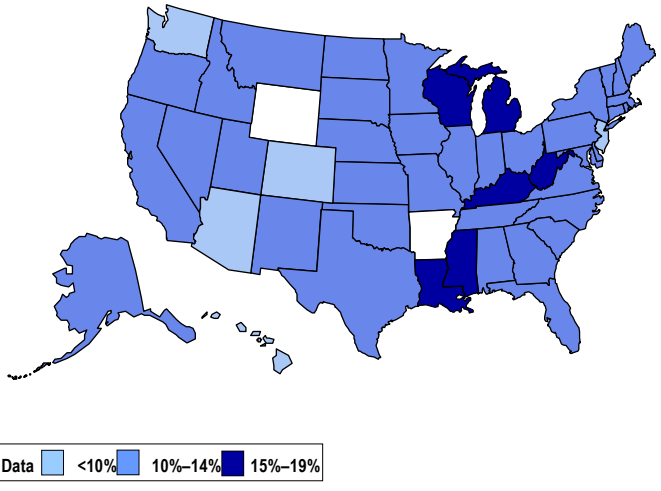

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Obesity Trends* Among U.S. Adults
BRFSS, 1993

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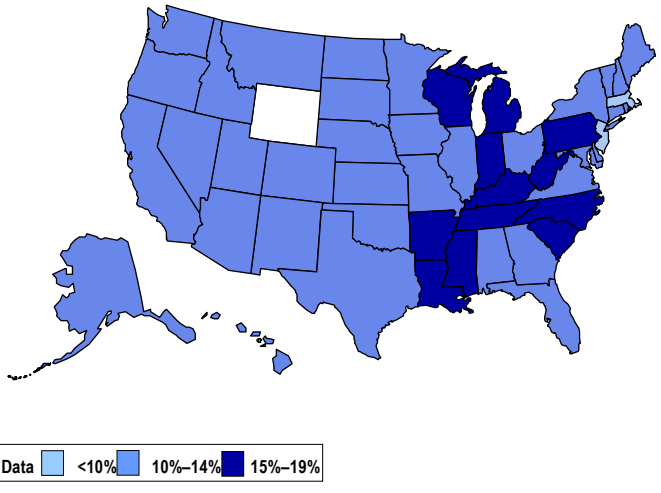

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Obesity Trends* Among U.S. Adults
BRFSS, 1994

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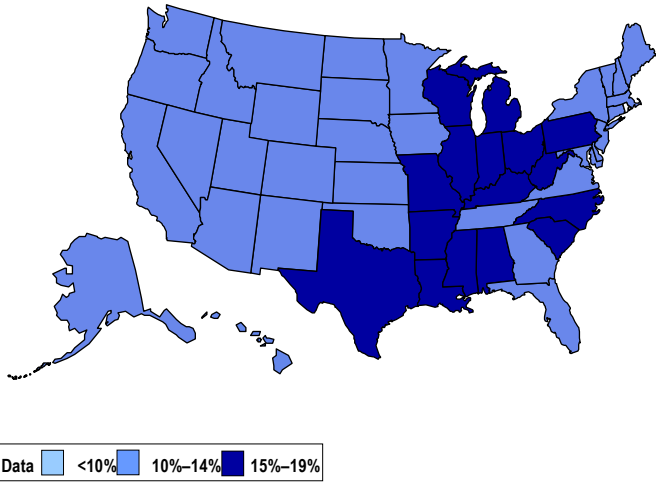

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Obesity Trends* Among U.S. Adults
BRFSS, 1995

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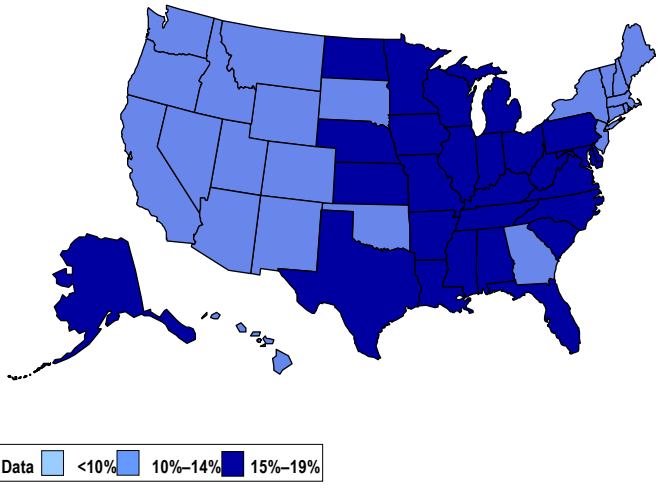

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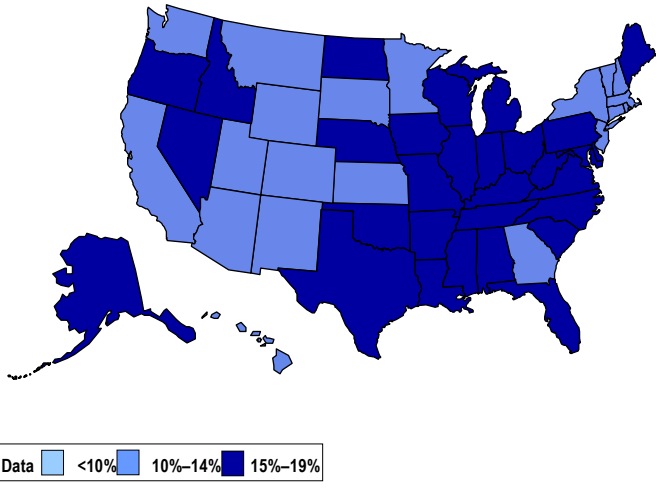
Obesity Trends* Among U.S. Adults
BRFSS, 1996

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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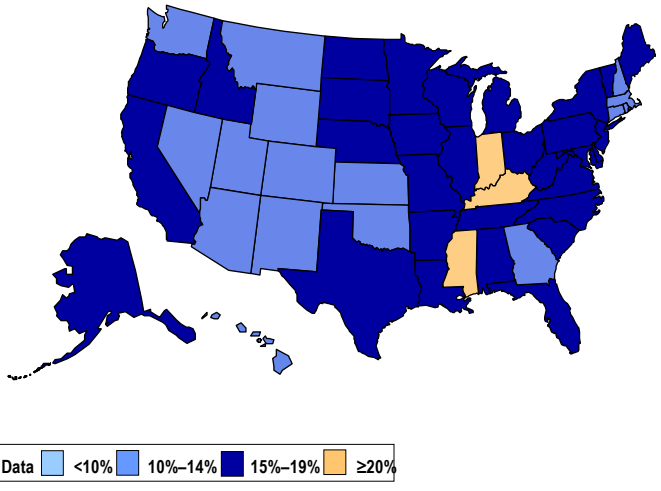
Obesity Trends* Among U.S. Adults
BRFSS, 1997

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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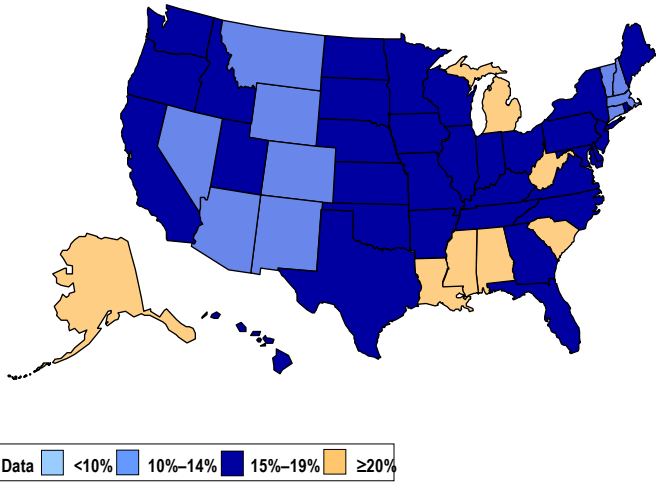
Obesity Trends* Among U.S. Adults
BRFSS, 1998

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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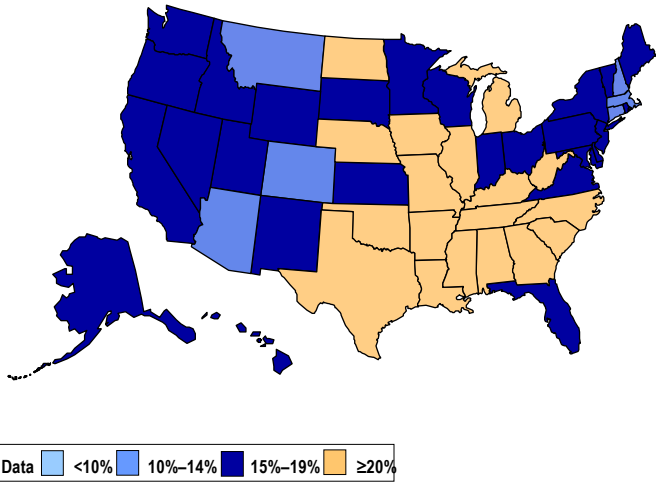
Obesity Trends* Among U.S. Adults
BRFSS, 1999

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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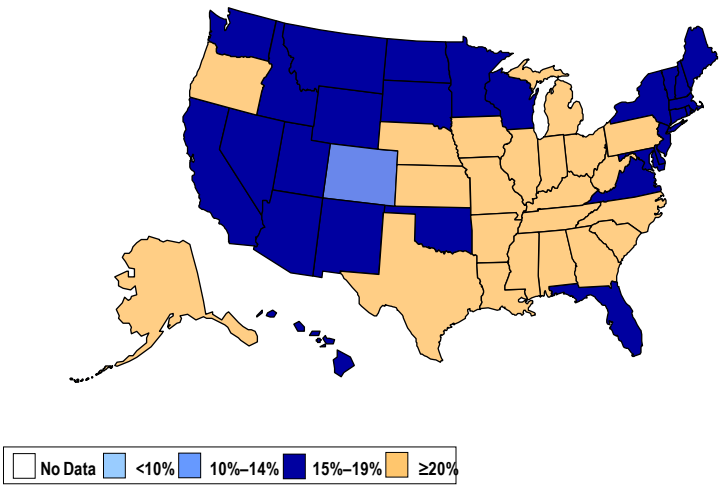
Obesity Trends* Among U.S. Adults
BRFSS, 2000

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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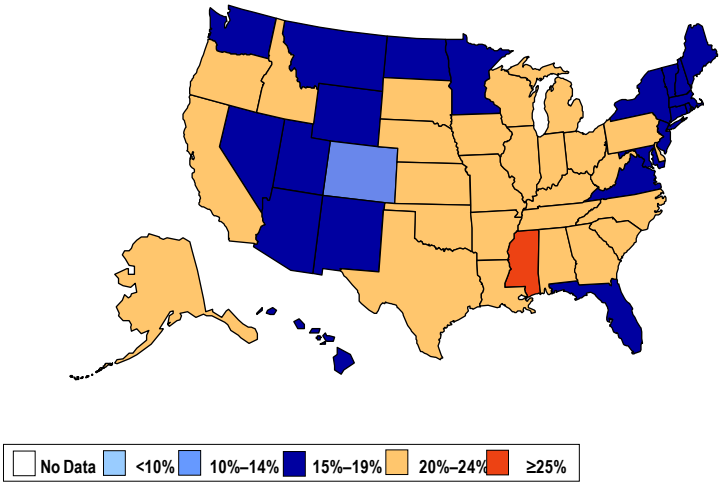
Obesity Trends* Among U.S. Adults
BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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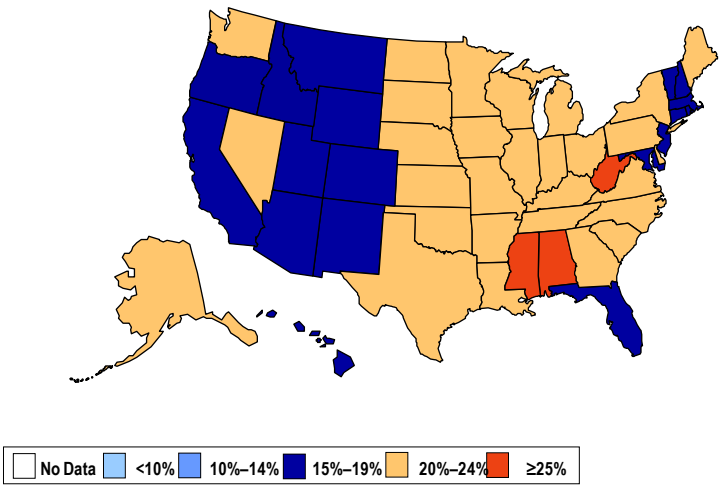
Obesity Trends* Among U.S. Adults
BRFSS, 2002

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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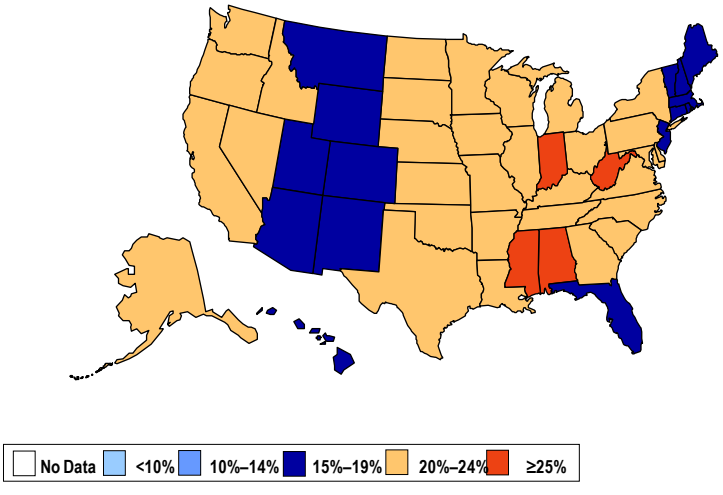
Obesity Trends* Among U.S. Adults
BRFSS, 2003

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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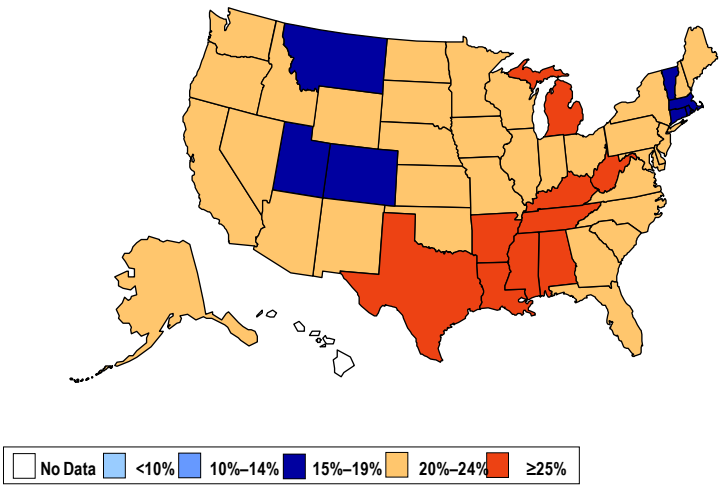
Obesity Trends* Among U.S. Adults
BRFSS, 2004

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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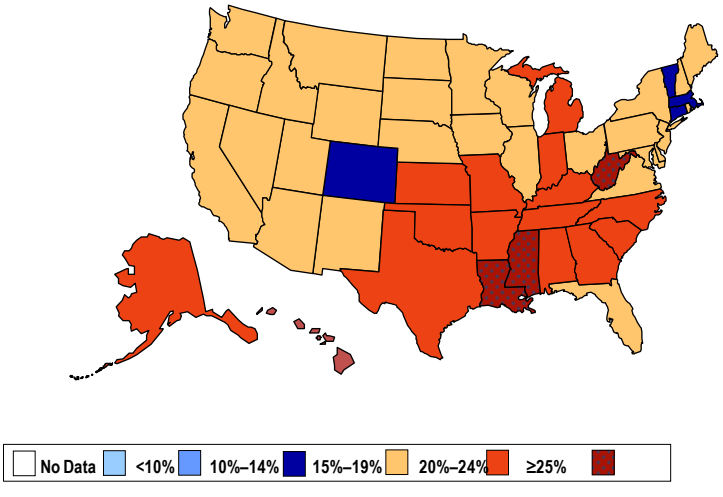
Obesity Trends* Among U.S. Adults
BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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Obesity Trends* Among U.S. Adults
BRFSS, 2006

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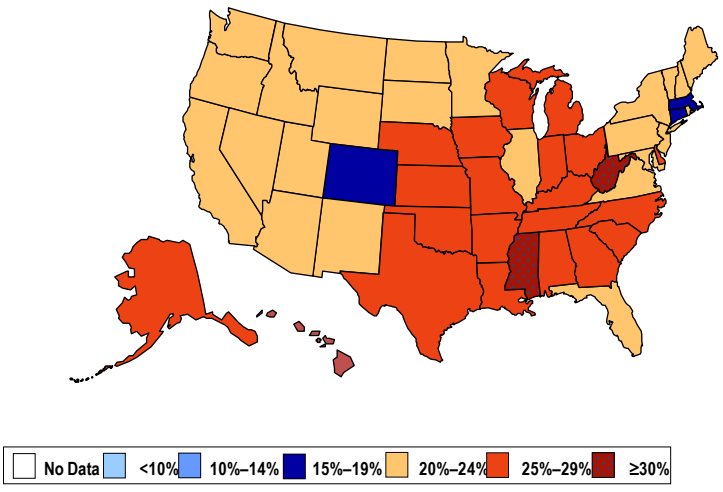

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Obesity Trends* Among U.S. Adults
BRFSS, 2007

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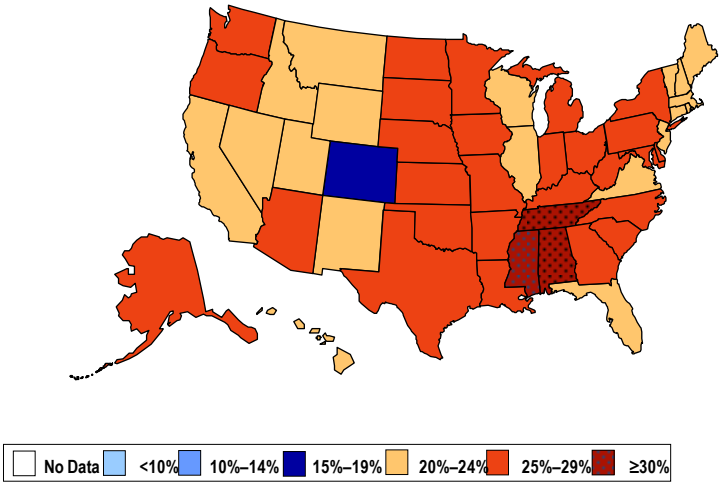

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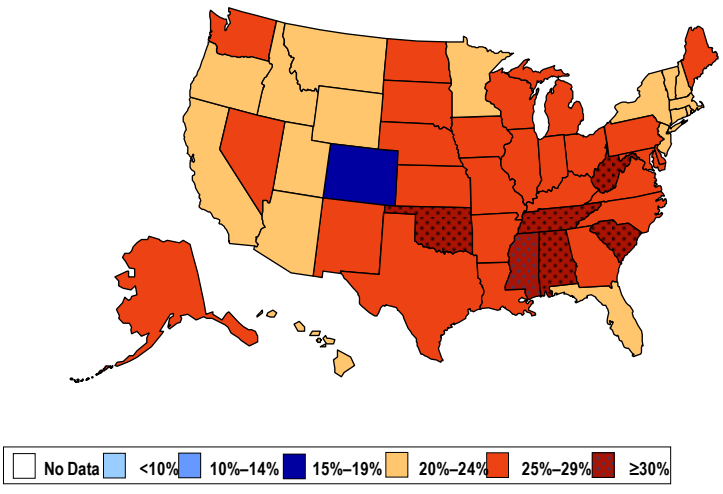
Obesity Trends* Among U.S. Adults
BRFSS, 2008

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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Obesity Trends* Among U.S. Adults
BRFSS, 2009

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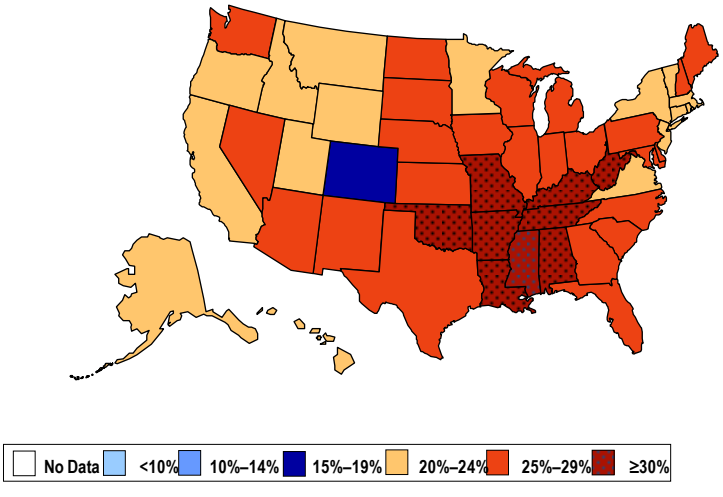

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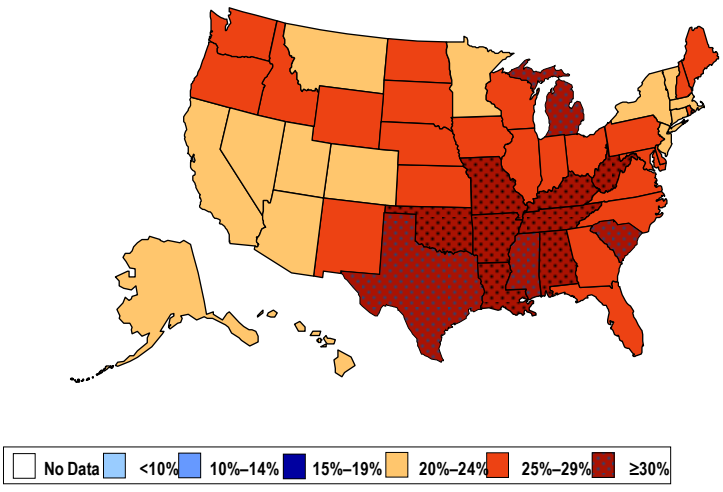
Obesity Trends* Among U.S. Adults
BRFSS, 2010

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



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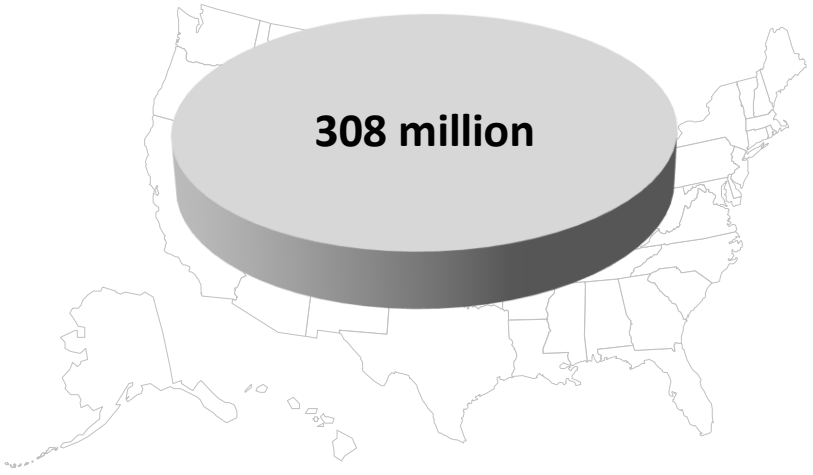
Prevalence of Nonalcoholic Fatty Liver Disease in U.S.



Ref: Ali & Cusi, Ann Med. 2009;41(4):265-78
McCullough et al. J Clin Gastroenterol. 2006 Mar;40 Suppl 1:S17-29

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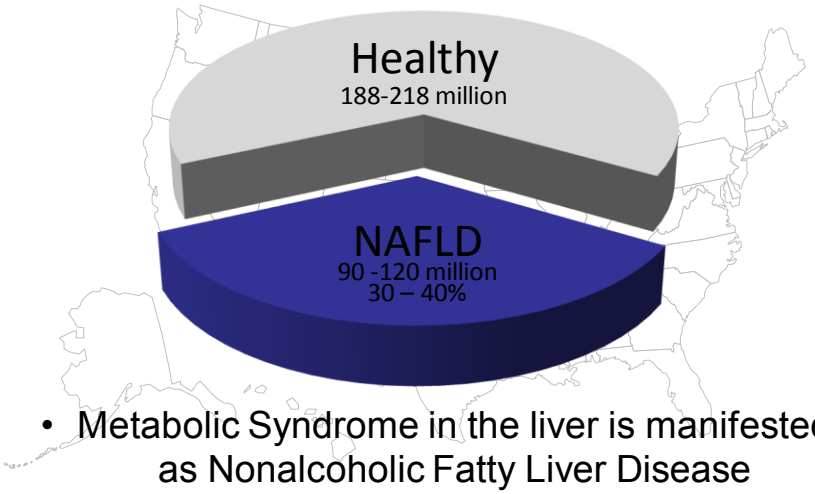

- Metabolic Syndrome in the liver is manifested as Nonalcoholic Fatty Liver Disease

Ref: Ali & Cusi, Ann Med. 2009;41(4):265-78
McCullough et al. J Clin Gastroenterol. 2006 Mar;40 Suppl 1:S17-29

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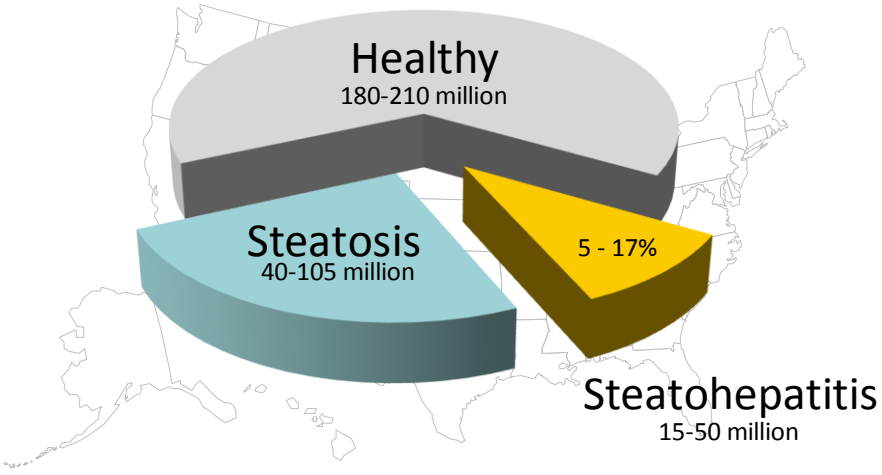

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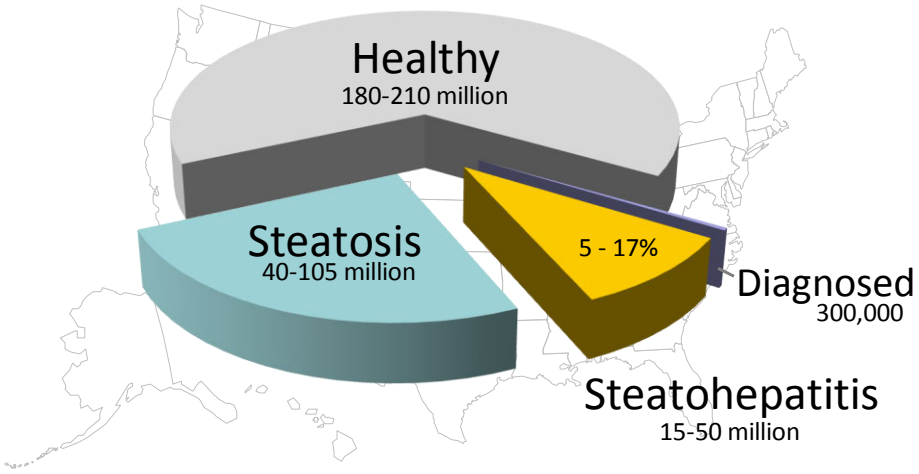

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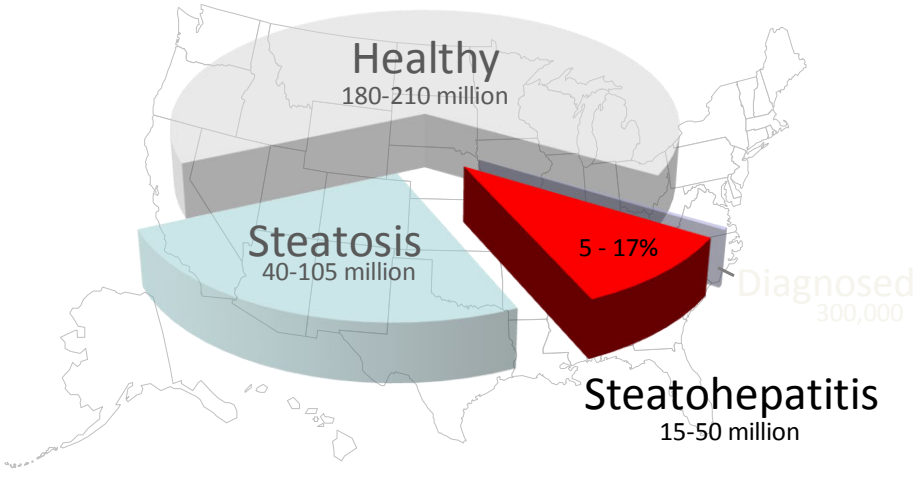

Ref: Ali & Cusi, Ann Med. 2009;41(4):265-78
McCullough et al. J Clin Gastroenterol. 2006 Mar;40 Suppl 1:S17-29

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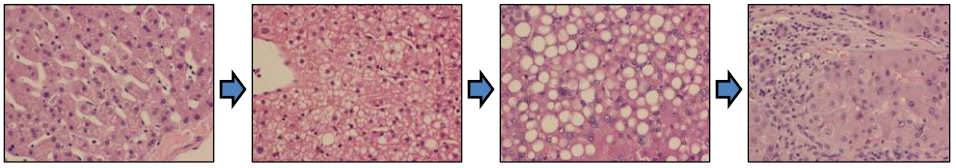
NAFLD Comprises a Spectrum of Pathologic Severity



Healthy liver | Steatosis | NASH w/fat | NASH not fatty (Cirrhosis)

- benign
- reversible

- steatosis
- inflammation
- progressive fibrosis

- irreversible scarring
- end-stage

NAFLD = Nonalcoholic Fatty Liver Disease
NASH = Nonalcoholic Steatohepatitis

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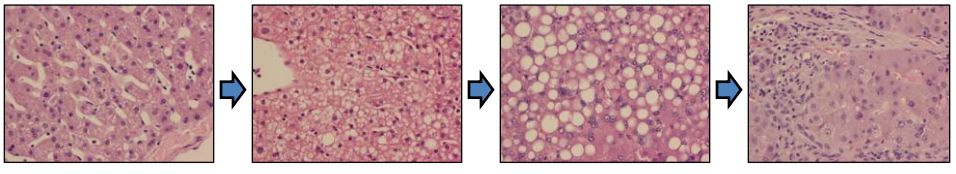
NAFLD Comprises a Spectrum of Pathologic Severity



Healthy liver | Steatosis | NASH w/fat | NASH not fatty (Cirrhosis)

19 | 1316 | 1

- **2nd hit includes Inflammation and oxidative stress :**
  - Macrophage and Stellate cell activation
  - Cytokine and ROS production
  - Mitochondrial dysfunction
  - Lipid peroxidation

Global Gene Expression Analysis
33,252 genes- Affymetrix Genechip Human 1.0 ST Array

NAFLD = Nonalcoholic Fatty Liver Disease
NASH = Nonalcoholic Steatohepatitis

0.01 Significance Level

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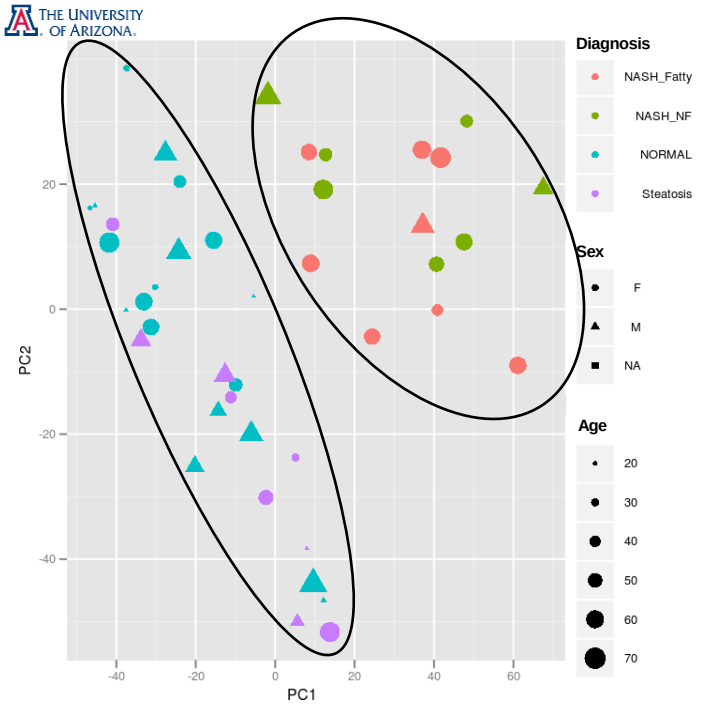

PCA Cluster by Diagnosis

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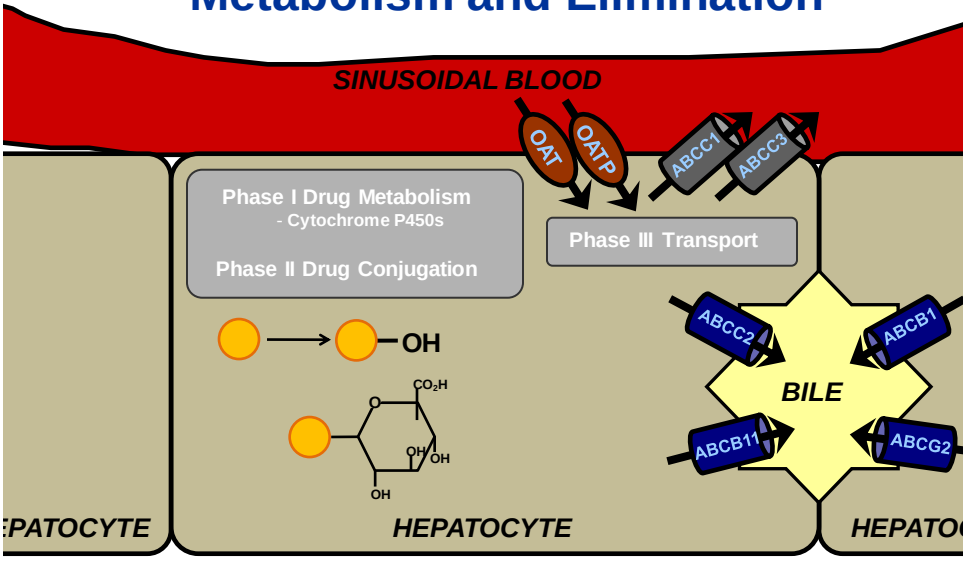
The Liver is the Major Organ of Drug Metabolism and Elimination



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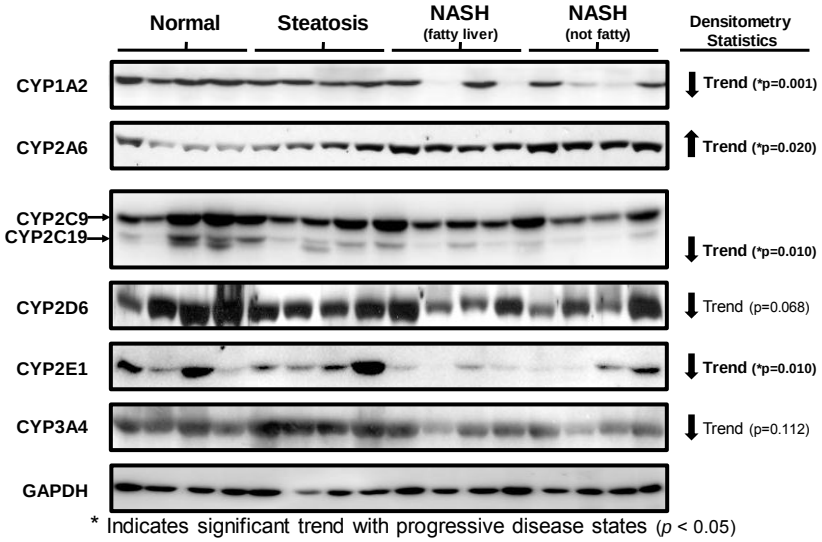
Drug Metabolizing Enzyme Protein Expression in NAFLD Patients



* Indicates significant trend with progressive disease states ($p < 0.05$)

Ref: Fisher *et al.* DMD. 2009: 37(10):2087-94

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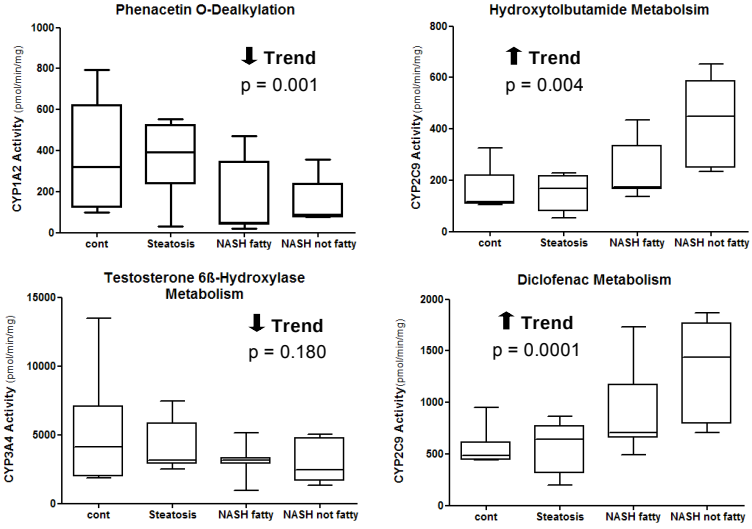
Drug Metabolizing Enzyme Activity in NAFLD Patients



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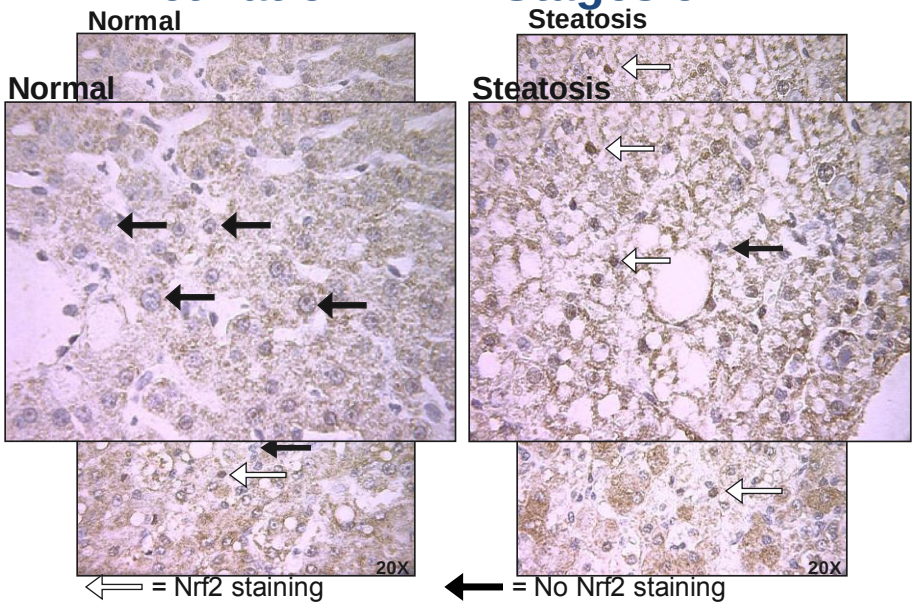
Nrf2 Activation in All Stages of NAFLD



Ref: Hardwick *et al.* DMD. 2010: 38(12):2293-301

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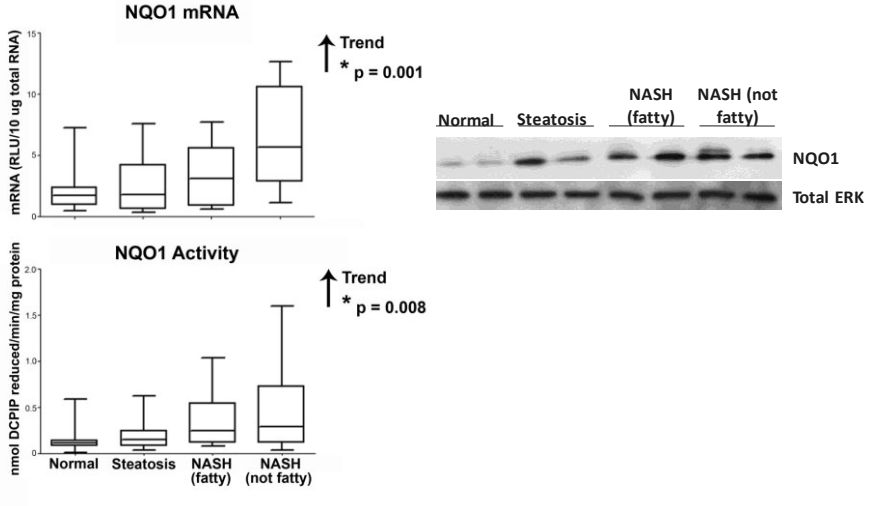
The Affect of NAFLD on NQO1



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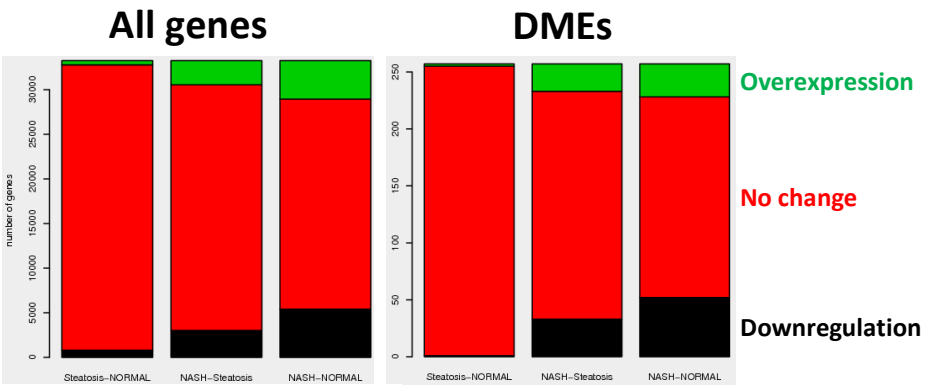
Global Gene Expression



33,252 genes-Affymetrix Genechip Human 1.0 ST Array

Ref: Lake *et al.* DMD. 2011: 39(10):1954-60

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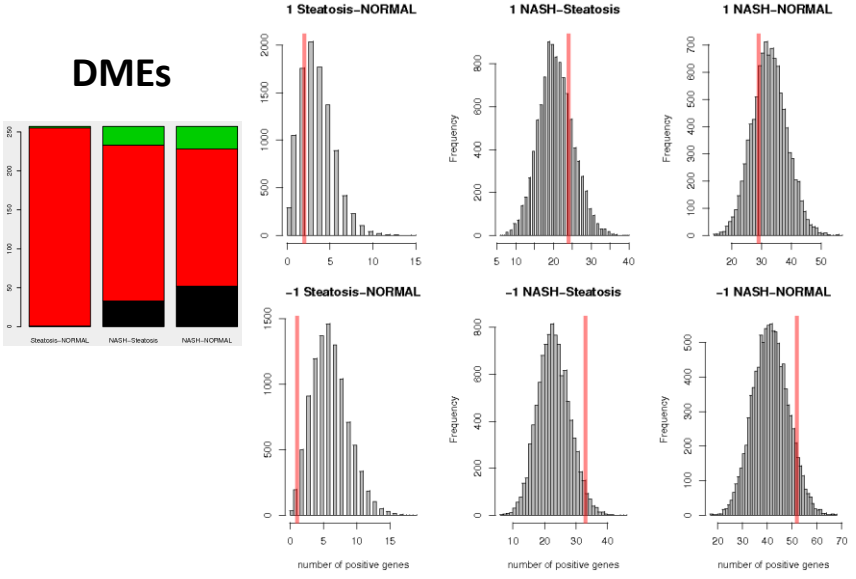
Global Gene Expression



Ref: Lake *et al.* DMD. 2011: 39(10):1954-60

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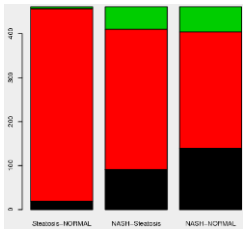
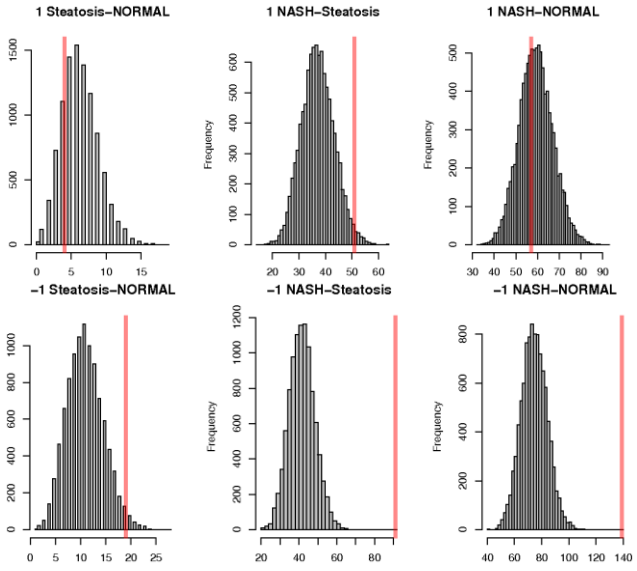
Global Gene Expression

Transporters





Ref: Lake *et al.* DMD. 2011: 39(10):1954-60

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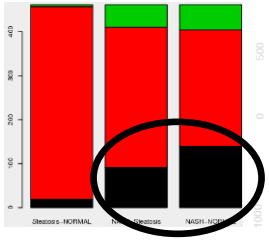
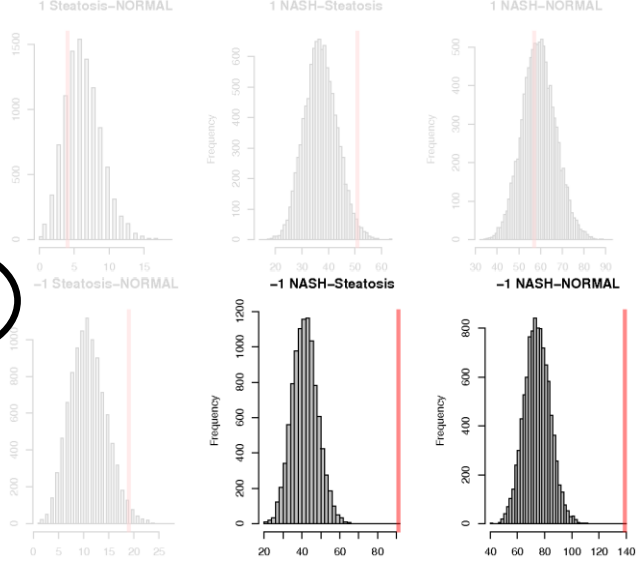
Global Gene Expression

Transporters





Ref: Lake *et al.* DMD. 2011: 39(10):1954-60

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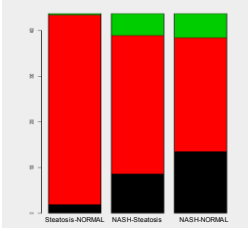
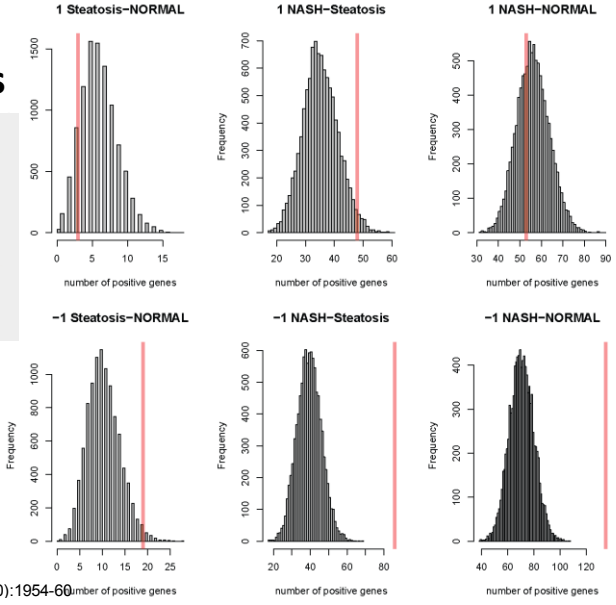
Global Gene Expression

Uptake Transporters





Ref: Lake *et al.* DMD. 2011: 39(10):1954-60

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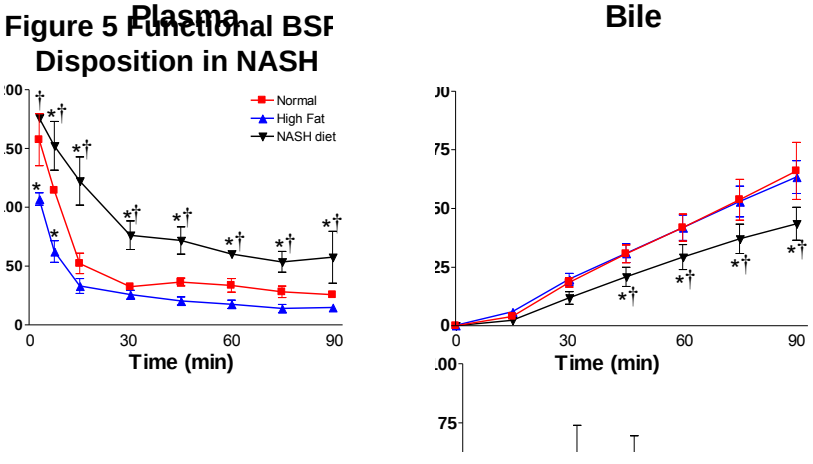
NAFLD Alters BSP Clearance

Figure 5 Functional BSP Disposition in NASH



Ref: Fisher *et al.* Eur J Pharmacol. 2009: 613(1-3):119-27

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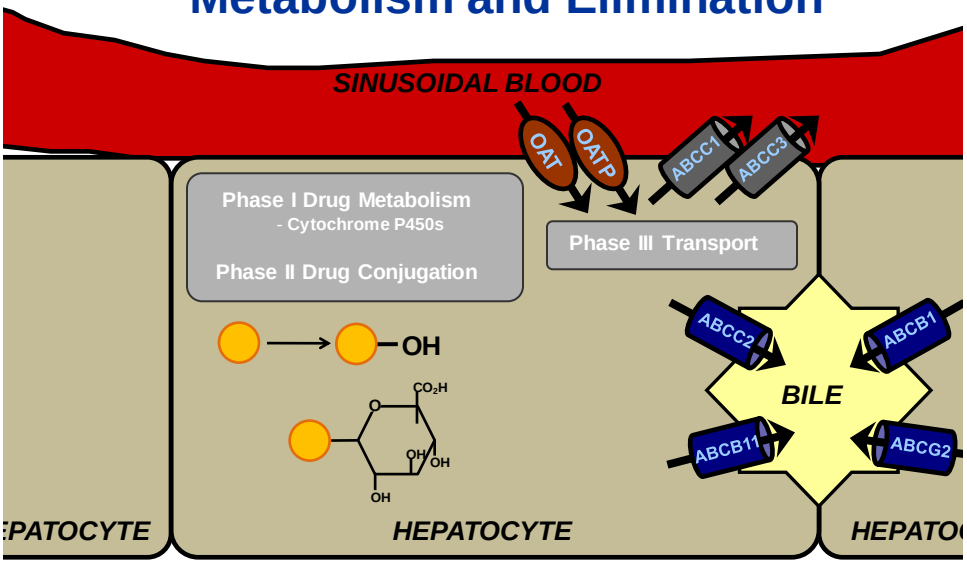

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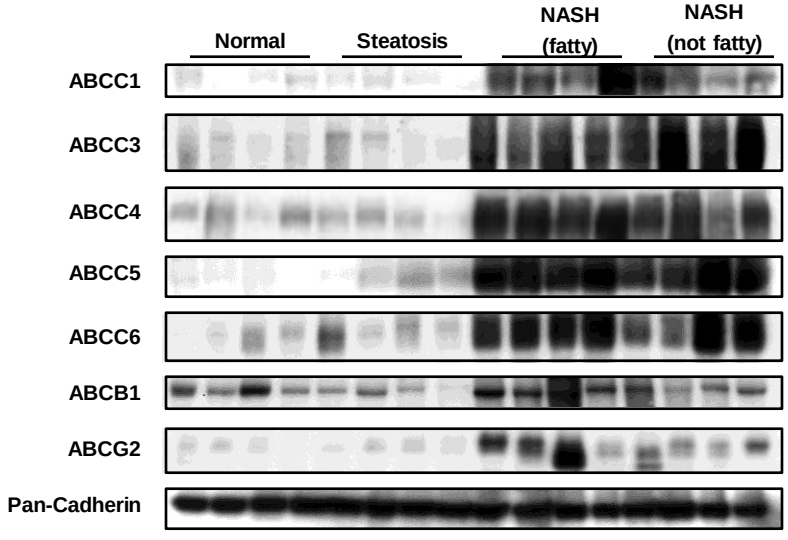
Efflux Transporter Protien Expression



Ref: Hardwick *et al.* DMD. 2011: Epub ahead of print

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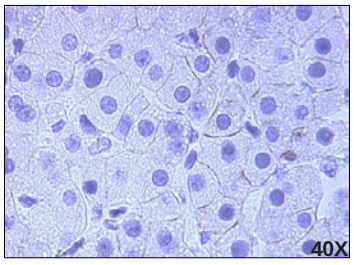
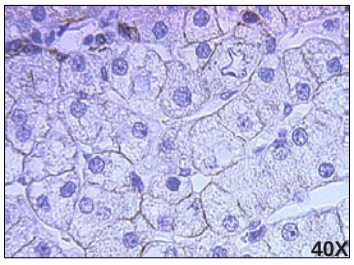
ABCC3 Immunohistochemistry

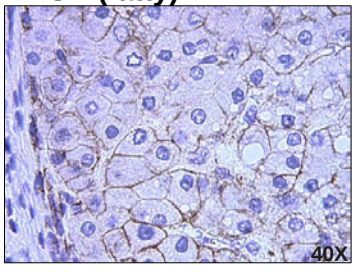
Normal



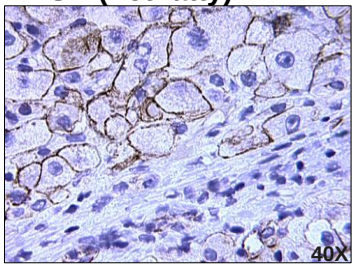
Steatosis



NASH (fatty)



NASH (not fatty)



51

Ref: Hardwick *et al.* DMD. 2011: Epub ahead of print

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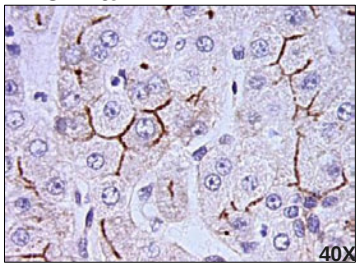
Cellular Localization of ABCC2

Normal



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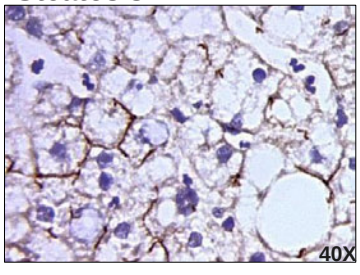
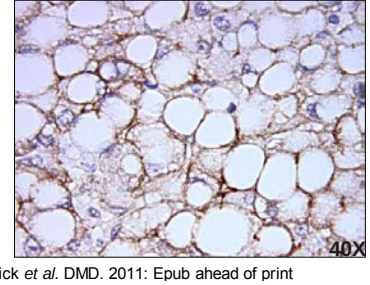
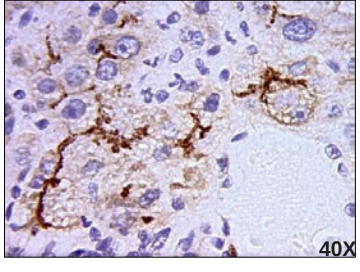


NASH (fatty)



NASH (not fatty)



Ref: Hardwick *et al.* DMD. 2011: Epub ahead of print

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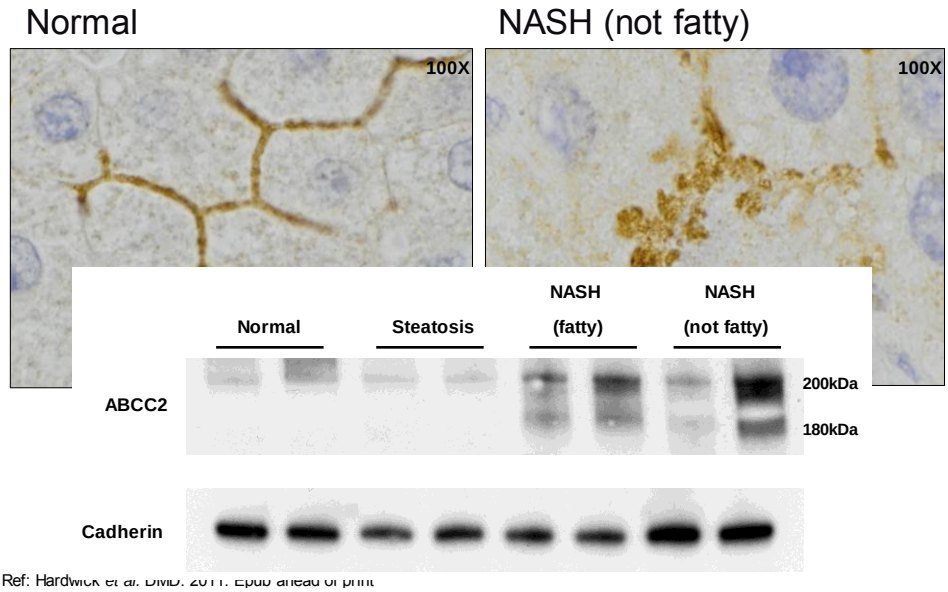
Cellular Localization of ABCC2



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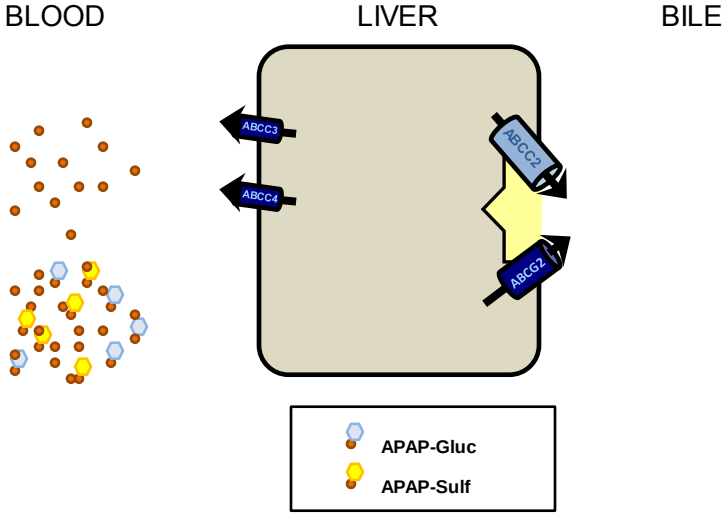
APAP Elimination in Normal Liver



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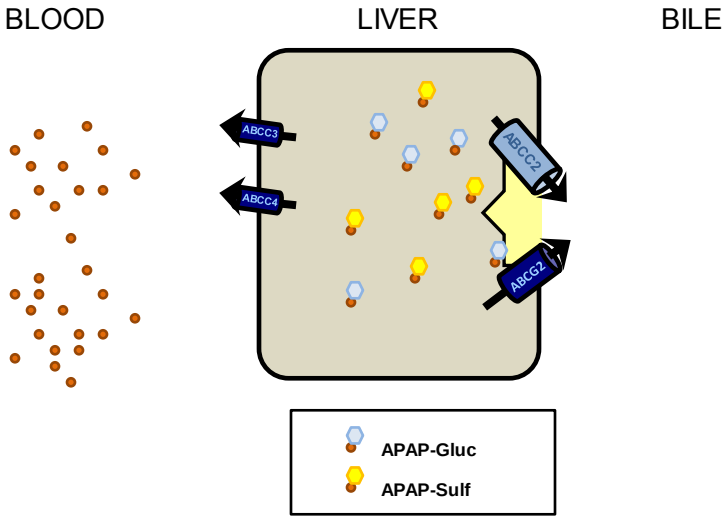
APAP Elimination in Normal Liver



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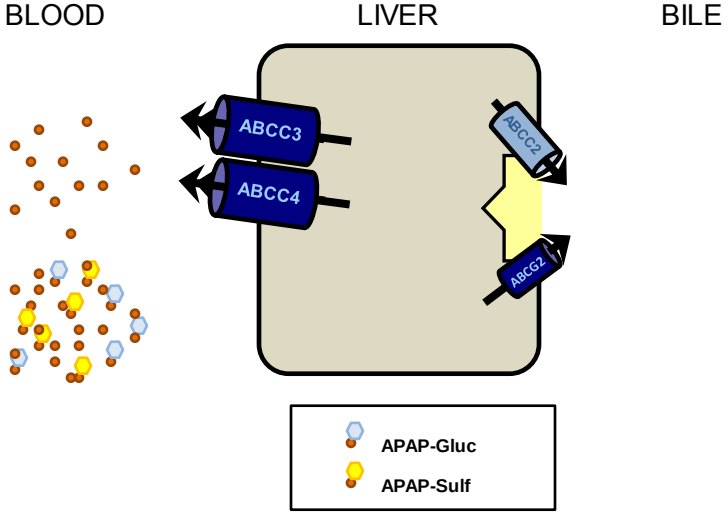
APAP Elimination in NASH



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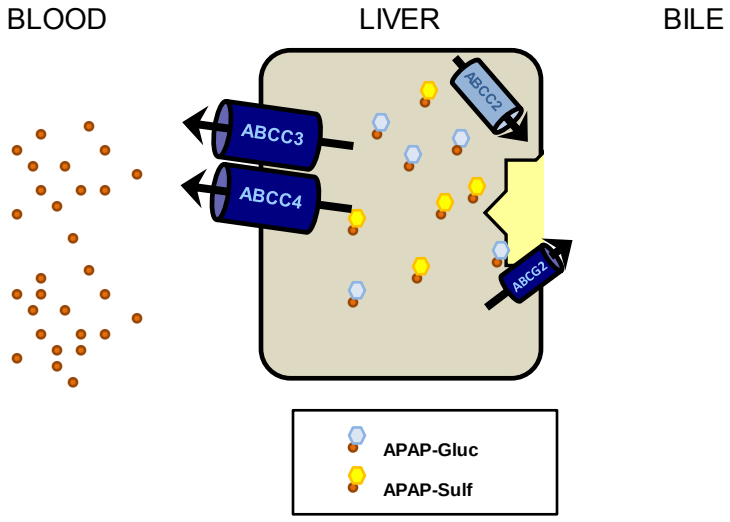
APAP Elimination in NASH



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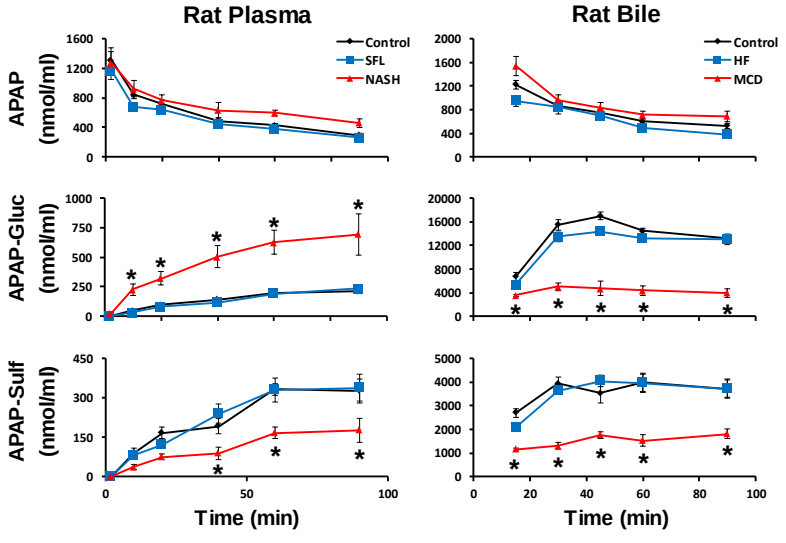
APAP Disposition



APAP = Acetaminophen

* $p < 0.05$ significant vs. Control

Ref: Lickteig *et al*. DMD. 2007: 35(10):1970-8

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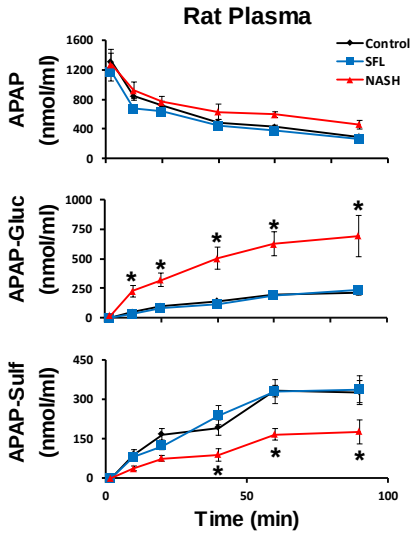
APAP Disposition



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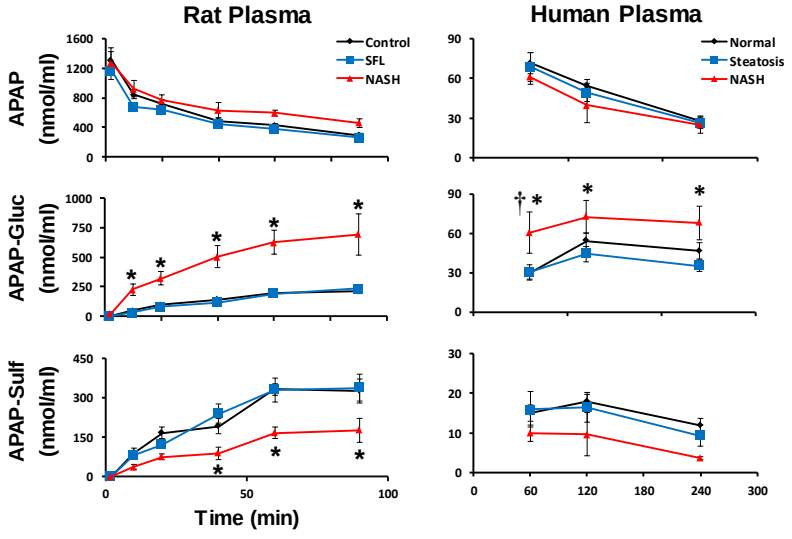
APAP Disposition



APAP = Acetaminophen

** p < 0.05 significant vs. Control*

Ref: Merrell *et al*. unpublished data

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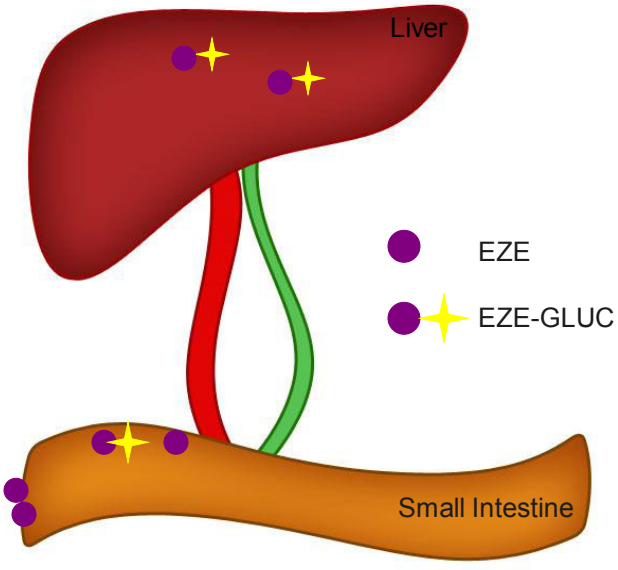
Ezetemibe Disposition



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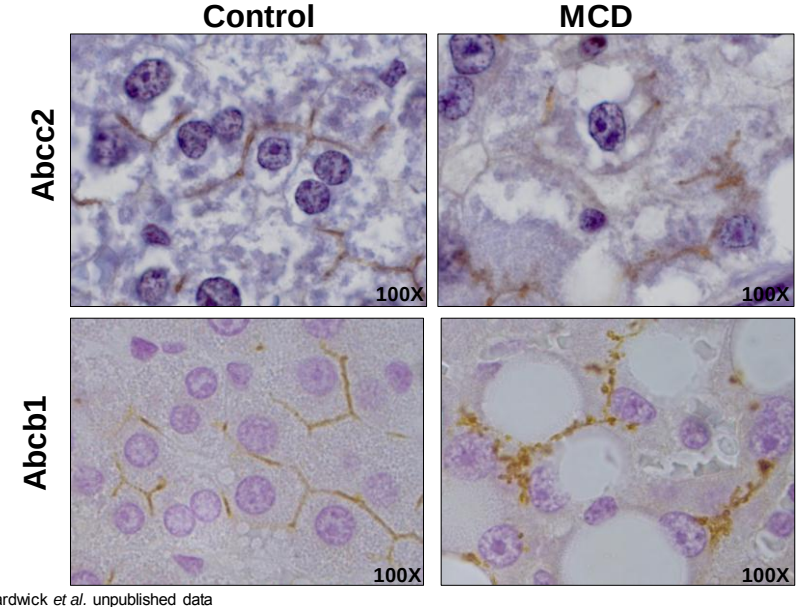
Abcc2 and Abcb1 Localization



Ref: Hardwick *et al.* unpublished data

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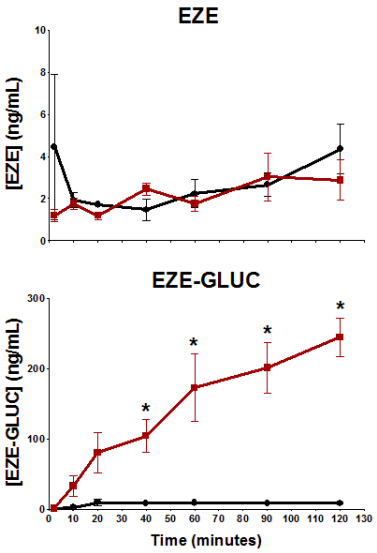
EZE and EZE-Gluc Disposition

Plasma



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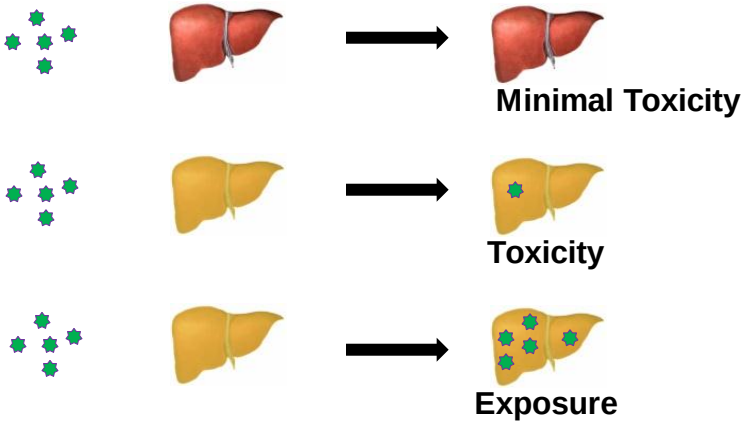
Drug-Induced Liver Injury



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Summary

- Drug Metabolizing Enzyme and Transporter expression changes occur during the transition from simple fatty liver to NASH
- Mechanisms of regulating DME and Transporter function during NASH may be controlled at the transcription, post-translational modification, and cellular localization levels
- Changes in the expression of the ADME battery of genes results in altered disposition and exposure of numerous drugs and xenobiotics
- Understanding inter-individual variation in drug metabolism may help lead to “personalized medicine”