

What to do about the high ALT picked up at the annual review

Dr Michael Yee

Consultant in Diabetes and Endocrinology

Mrs DC

52 year old cleaner

Raised ALT noted on blood tests in DM clinic

Previously had “bright” liver on ultrasound

HPC

No specific symptoms

No jaundice, no cholestatic symptoms or abdo pain

No significant alcohol intake

No major risk factors for viral hepatitis

Never smoked

PMH

Type 2 Diabetes (decades)

Regular retinal screening

No foot complications/neuropathy

No significant nephropathy

Obesity

Psoriasis

Never had methotrexate

Hypertension

Carpal Tunnel Syndrome

DH

Aspirin 75mg od

Irbesartan 300mg od

Doxazosin MR 8mg od

Indapamide MR 1.5mg od

Amlodipine 10mg od

Glimepiride 1mg od (previously 4mg od)

Exenatide 10ug bd

Simvastatin 40mg od

O/E

100.4 kg (BMI 40.2)

BP 123/74

No signs of chronic liver disease

CVS and Resp examinations unremarkable

Urine dip: NAD

Investigations

Na 138

K 4.4

Ur 6.0

Cr 55

ALT 30

AST 25

gGT 24

Bil 12

ALP 65

Alb 40

INR 1.0

HbA1c 7.1 (54)

Chol 5.33

HDL 1.06

TG 1.82

WCC 6.0

Hb 14.0

Plts 148

Investigations

USS (08/07/09):

1.3cm calculus in neck of
gallbladder

Normal liver parenchyma

Normal echotexture and
contour

CLD screen:

Hep B sAg Neg

Hep C Ab Neg

LAA Neg

α 1AT 1.3

Ferritin 8

TSH 1.9

NAFLD fibrosis score = **1.75**

<-1.455 = Low risk of advanced fibrosis

-1.455 to 0.676 = Indeterminant risk

>0.676 = High risk of advanced fibrosis

Algorithm based on:

AST, ALT, Alb, Plts, Age, BMI, presence of DM/IGT

Angulo et al. Hepatology 2007

- Fibroscan 25.1kPa

NAFLD

- Non-Alcoholic Fatty Liver Disease is an increasingly recognised condition that may progress to end-stage liver failure
- Ludwig in 1980 introduced the term “Non-Alcoholic Steatohepatitis”
- Prevalence is increasing worldwide with increasing obesity

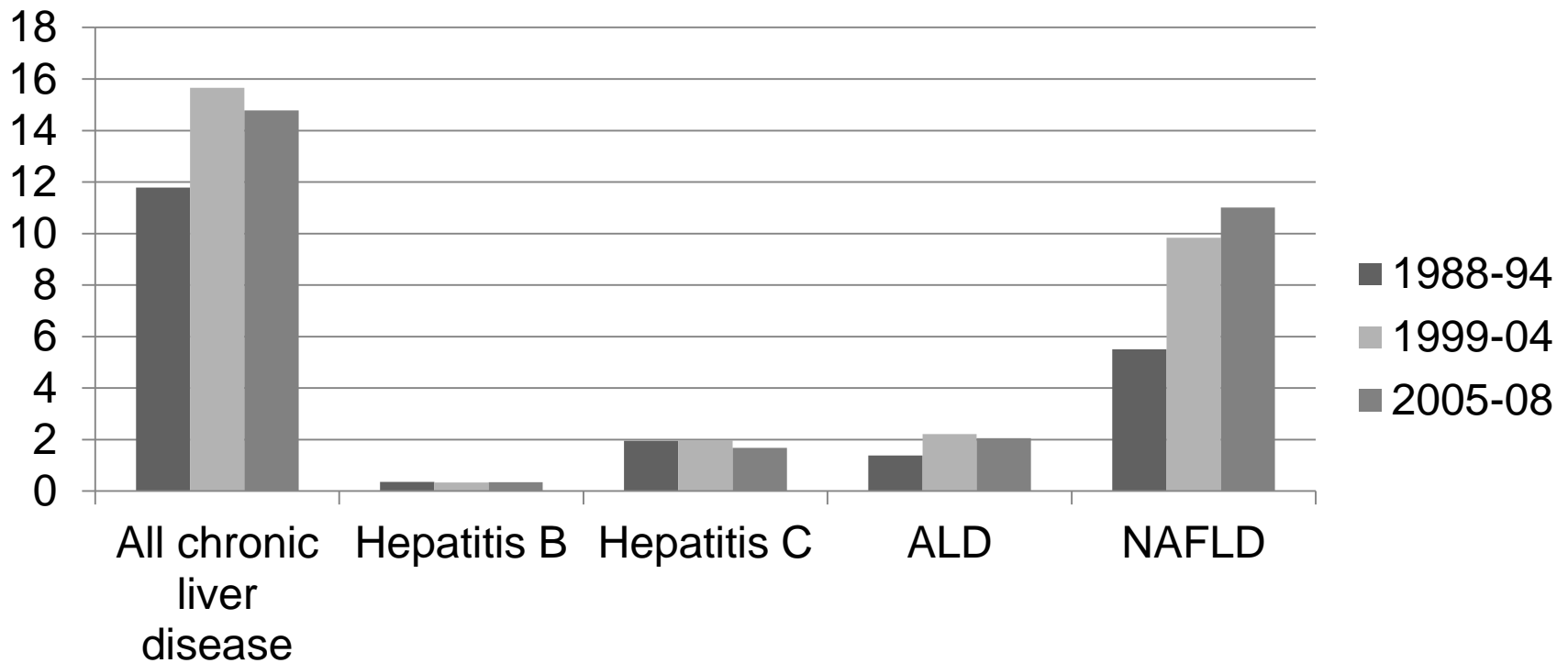
Prevalence of abnormal LFT's

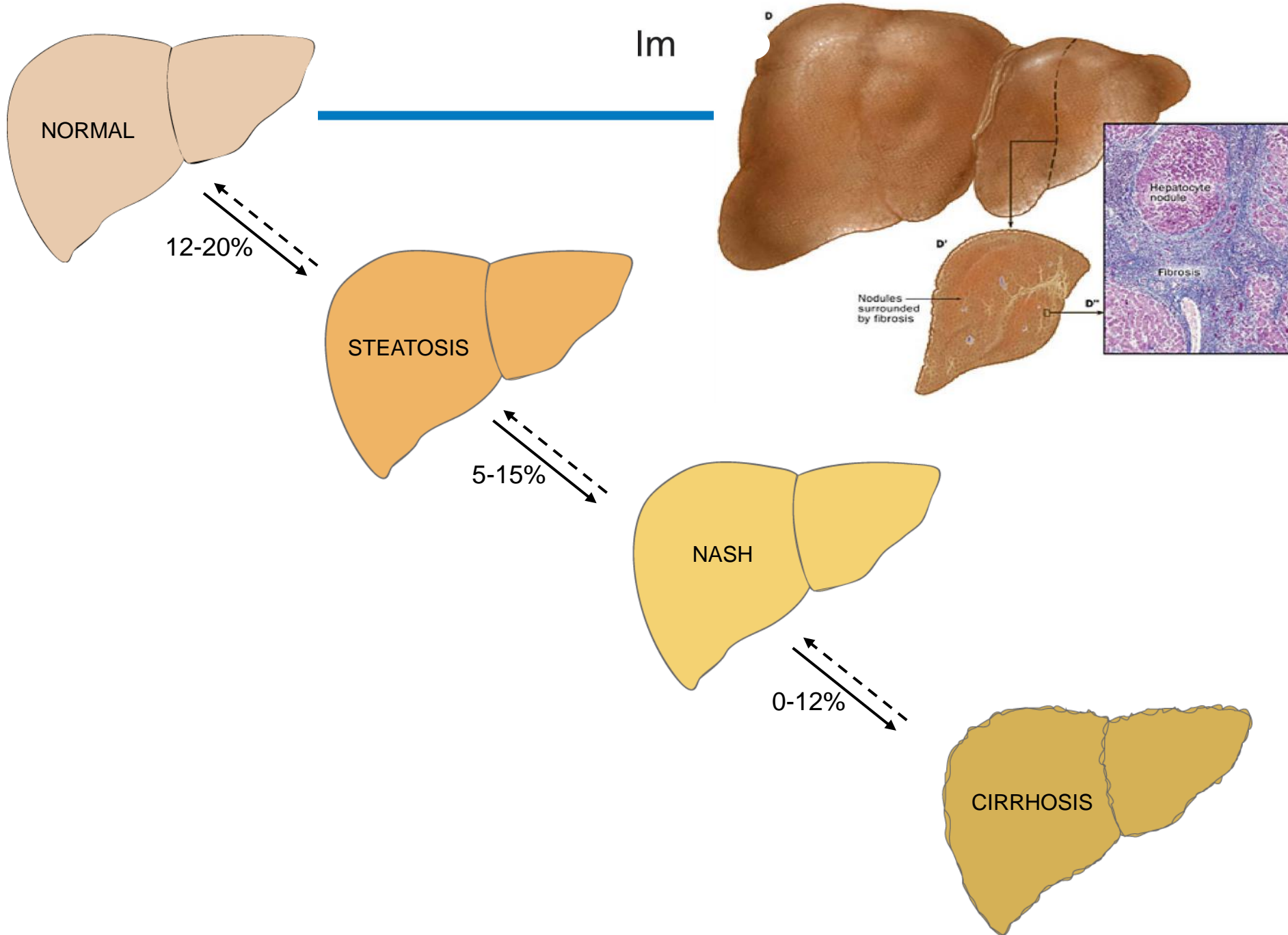
- Abnormal LFT's – 8% population (NHANES III)
- An identifiable cause was found in 31%
- Remainder probably had NAFLD

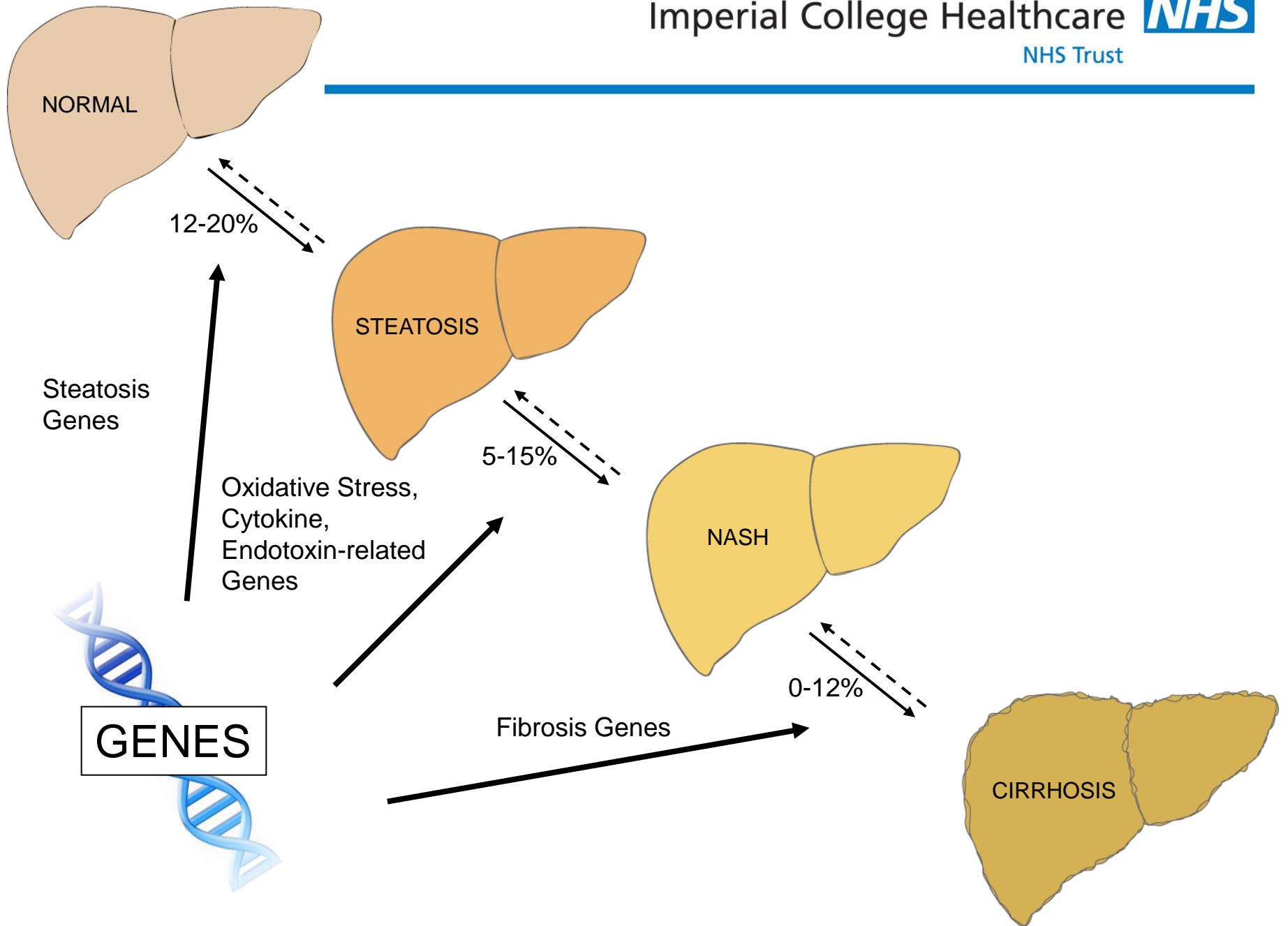
Prevalence

- Using traditional upper limits for ALT 3-5% of populations
- New lower ALT limits (men < 30; women <19) 12-14%
- Using ultrasound 20%
- (In obesity and diabetics 60-70%)

Prevalence of NAFLD in NHANES over 1988 – 2008





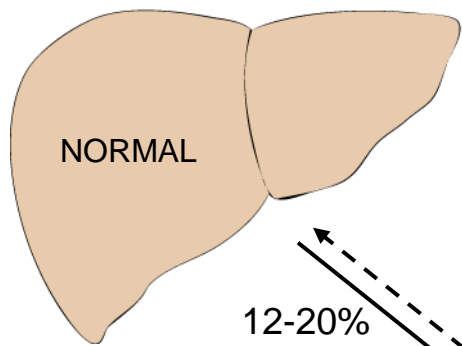


Genotypes

- PNPLA3 variant I148M
- TM6FS2 variant E167k

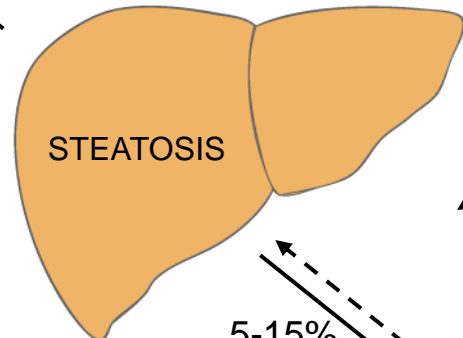


ENVIRONMENT

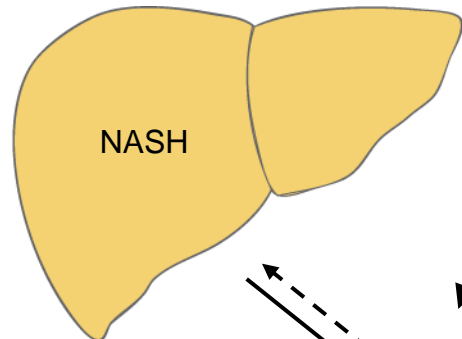


Diet, Obesity, DM

12-20%



5-15%



0-12%



SIBO,
Endotoxin,
TNF α ,
ROS

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ROS

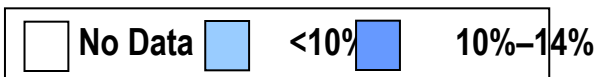
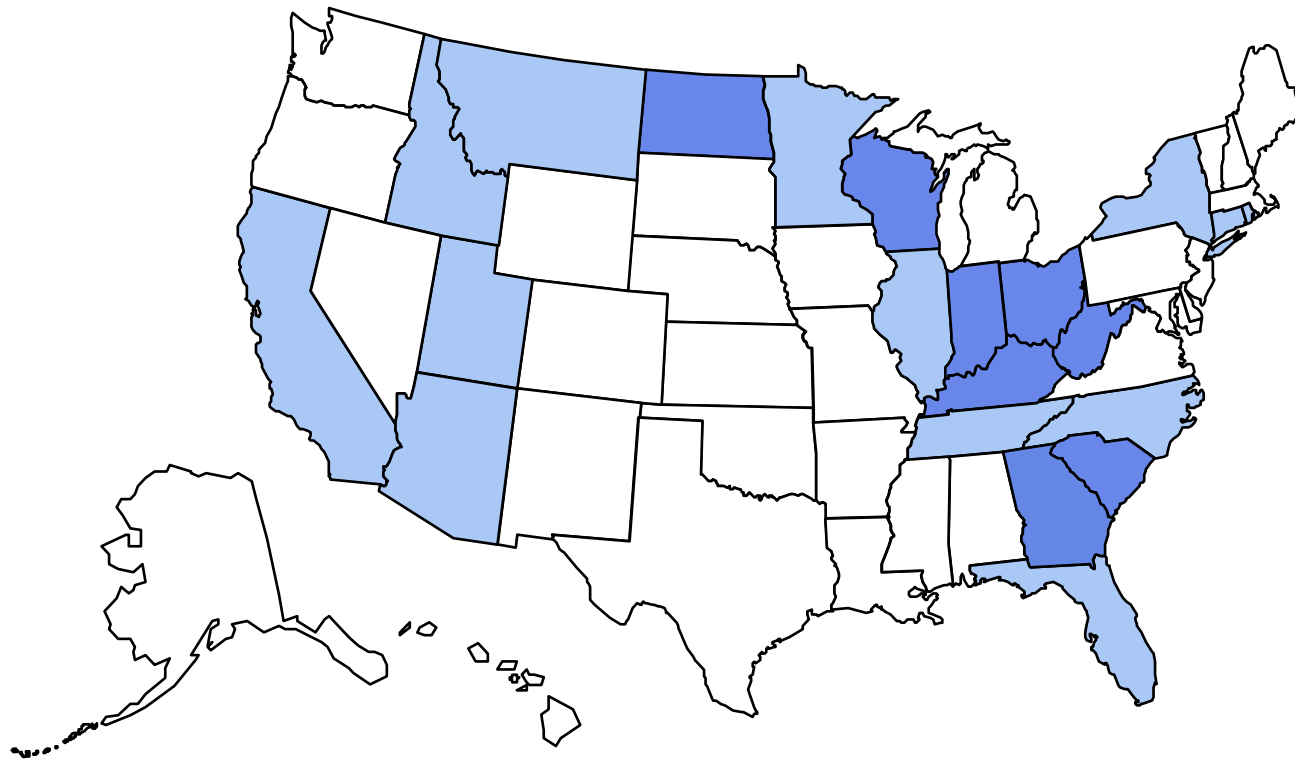
Environment

- Fructose
- Processed foods

Obesity Trends* Among U.S. Adults

BRFSS, 1985

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



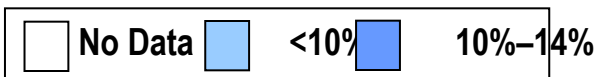
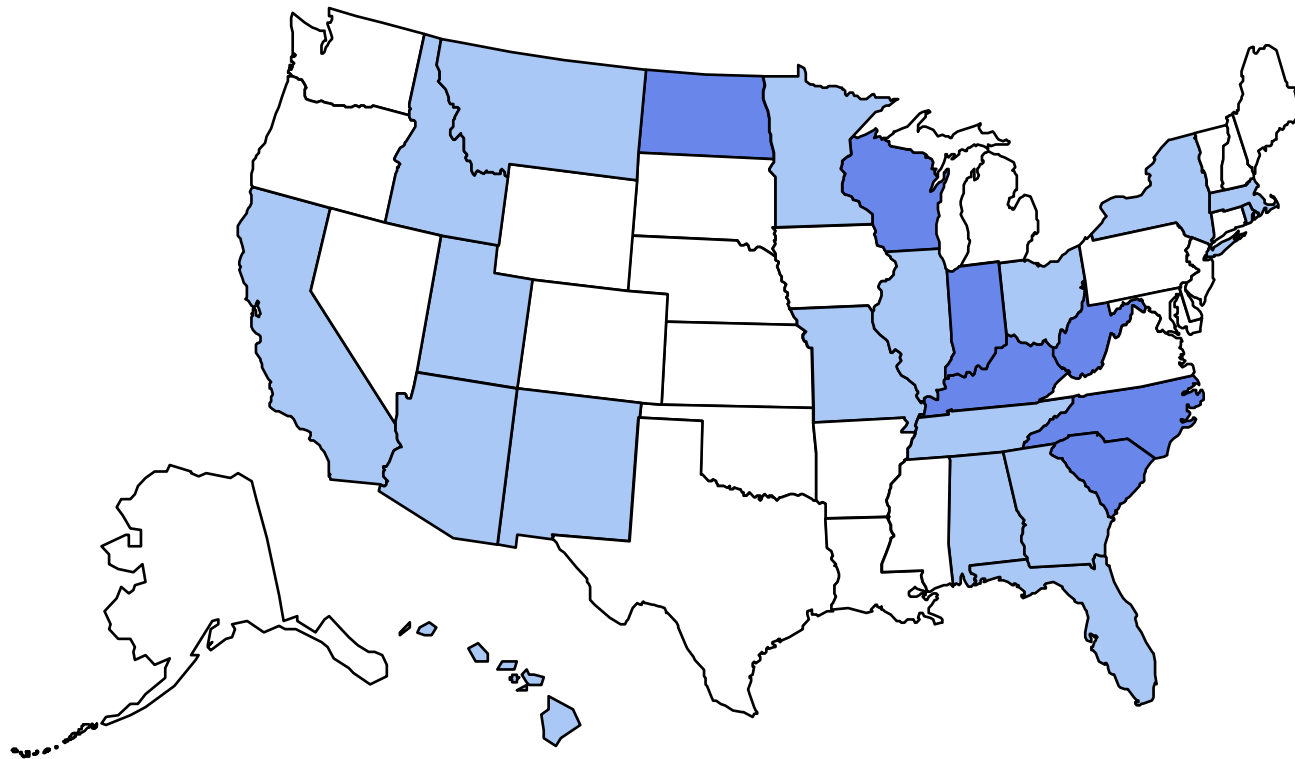
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 1986

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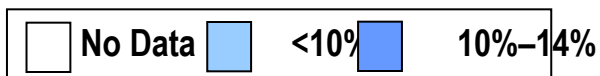
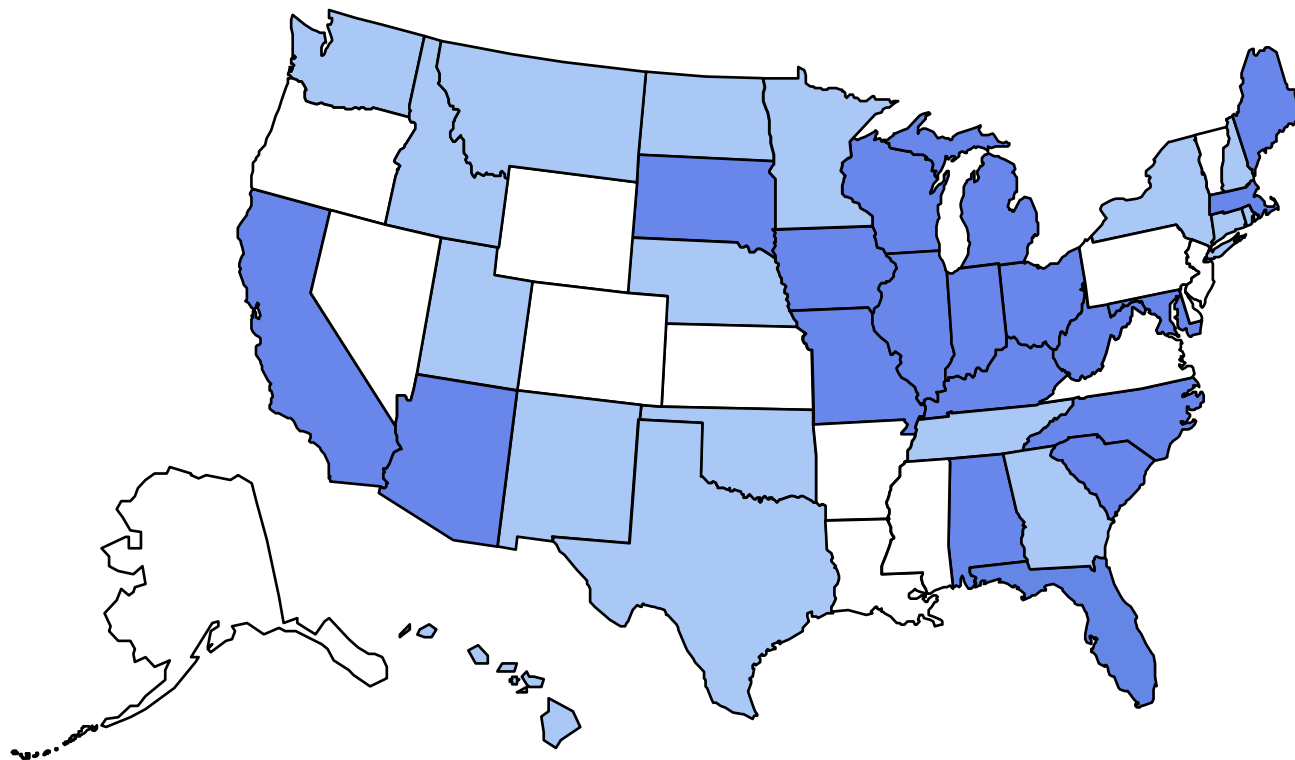
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 1988

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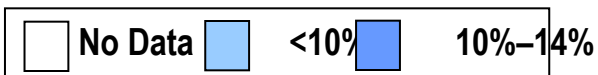
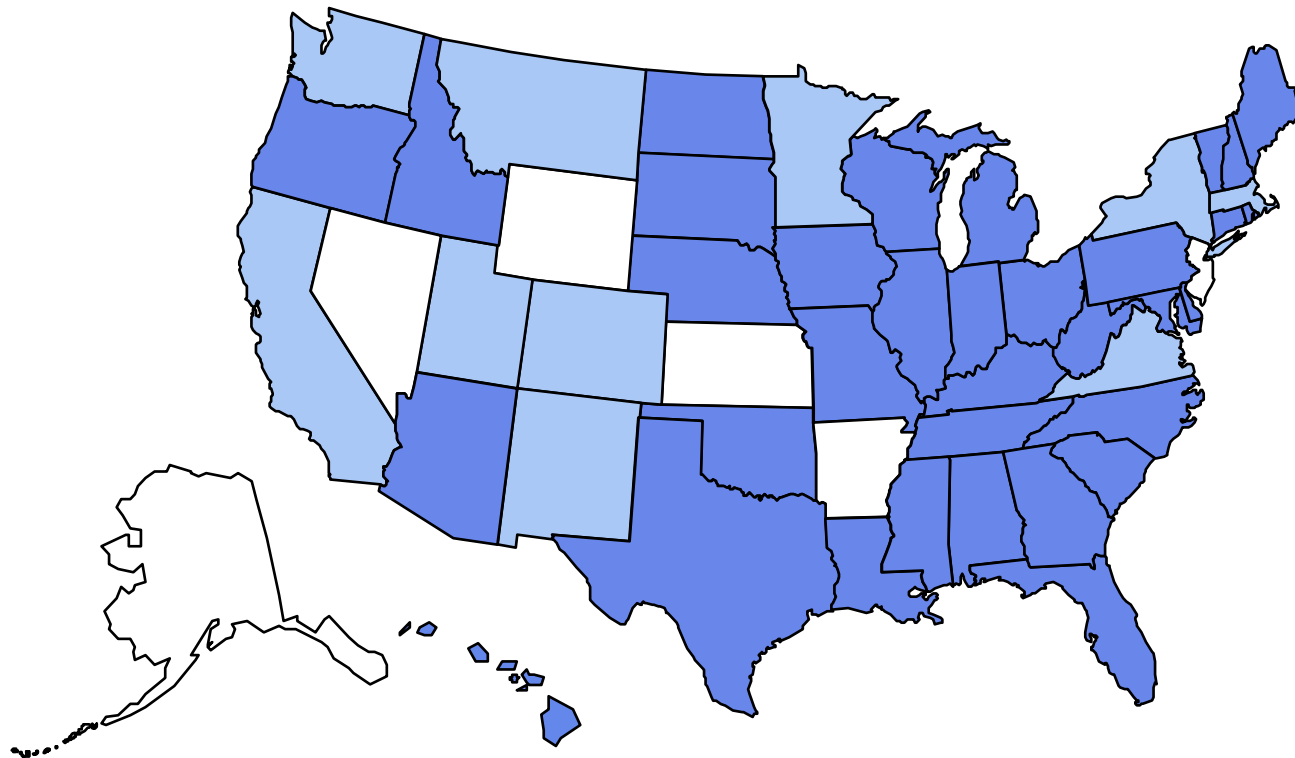
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 1990

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



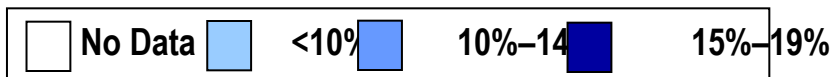
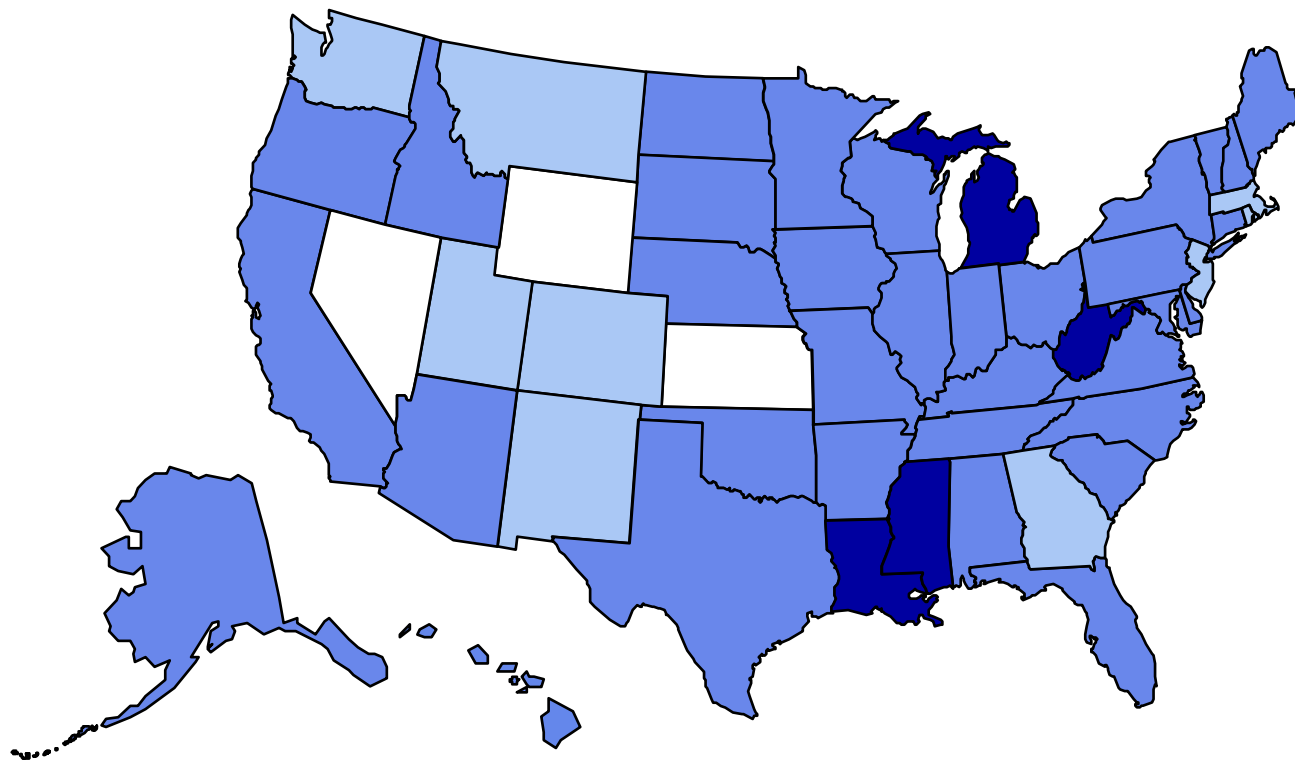
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 1991

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

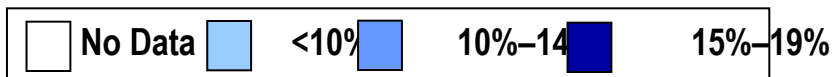
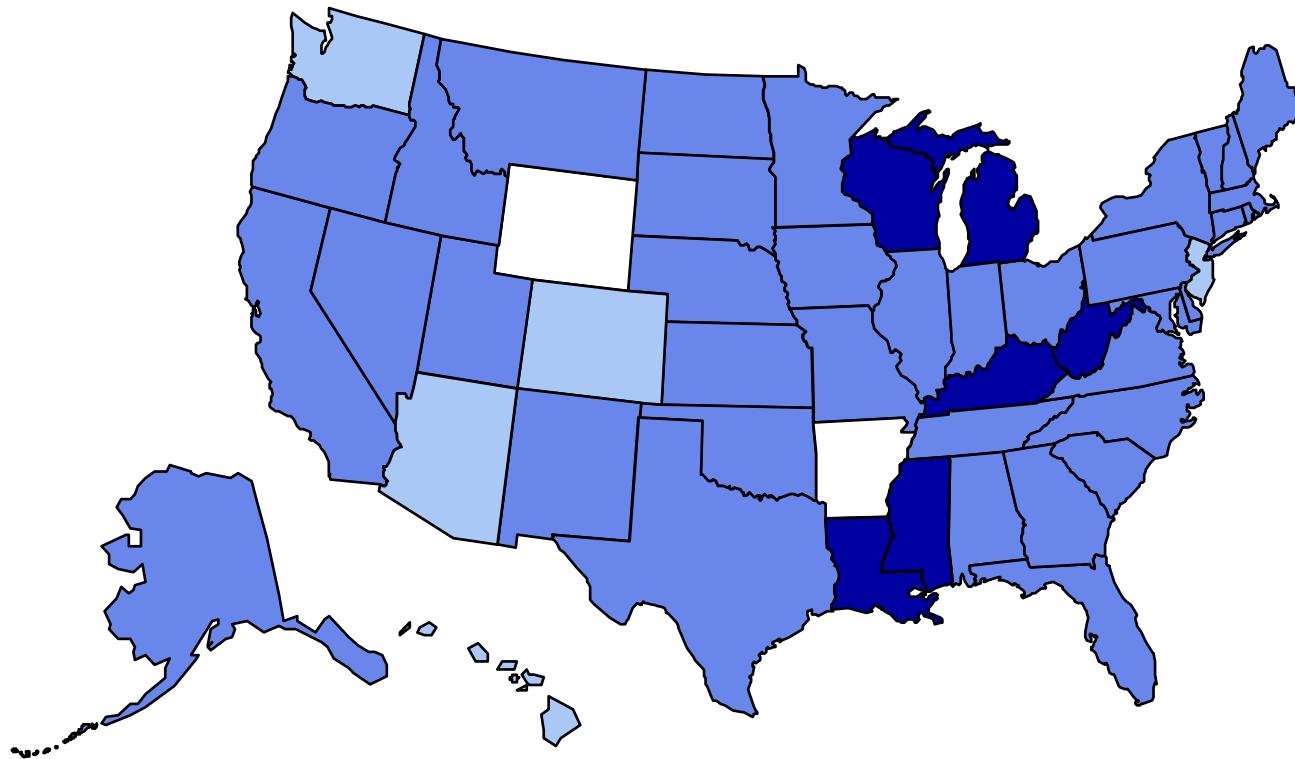


Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults

BRFSS, 1992

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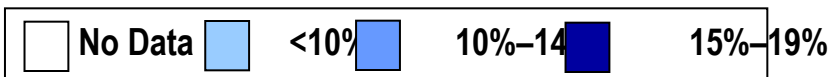
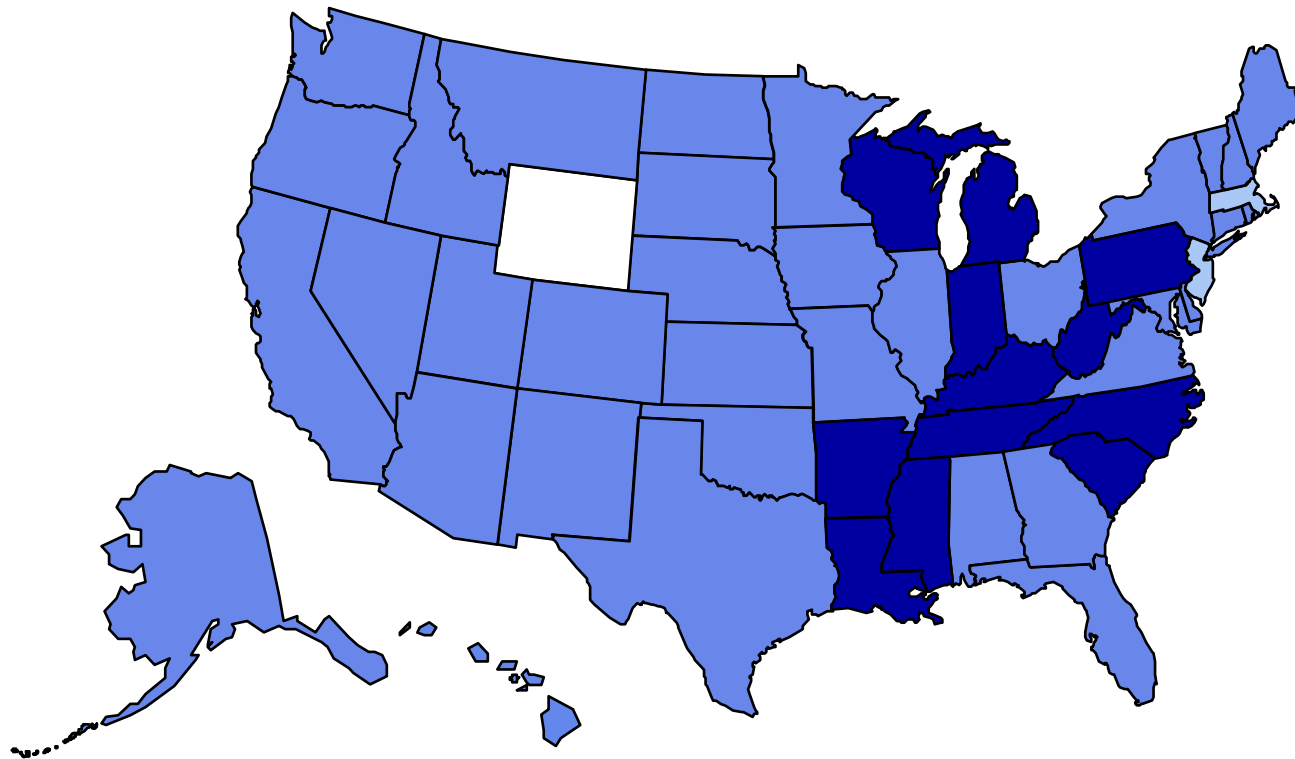
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 1993

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

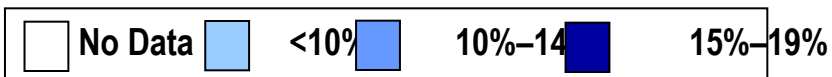
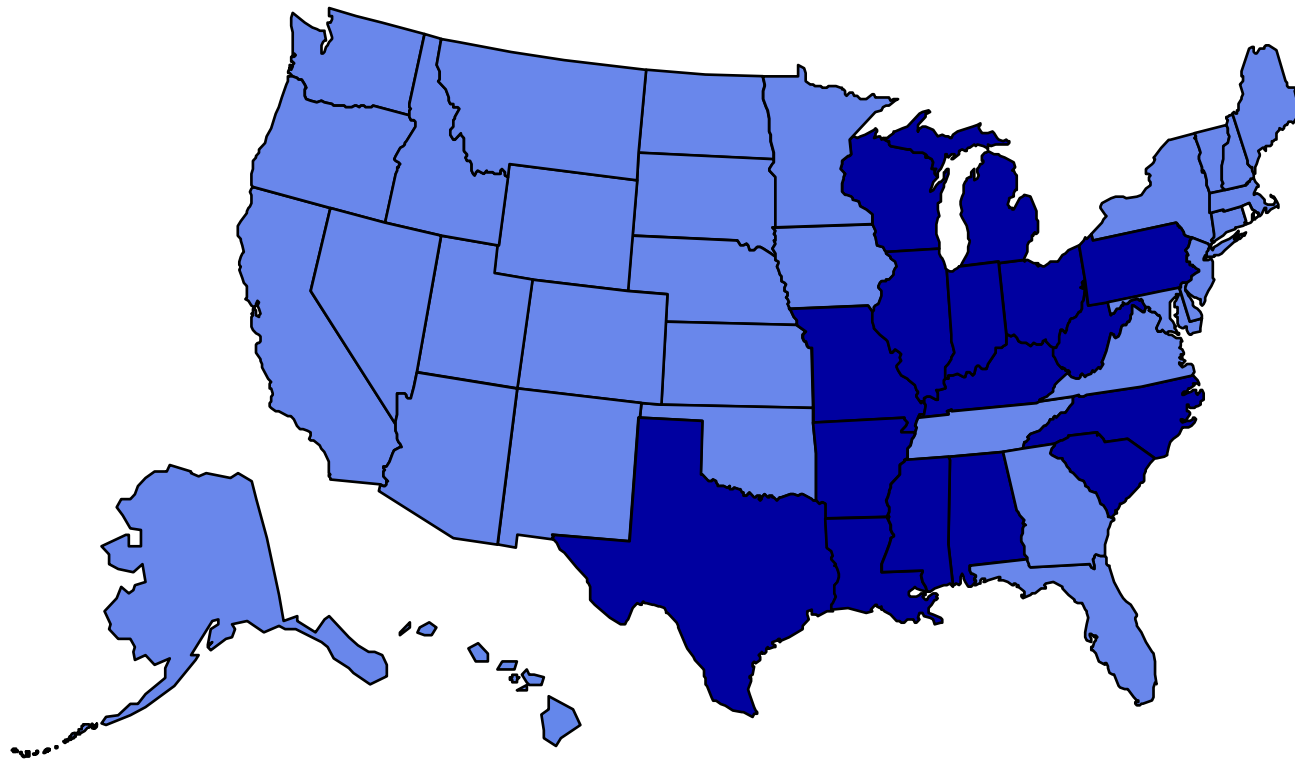


Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults

BRFSS, 1994

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

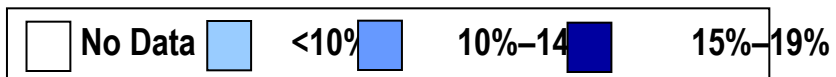
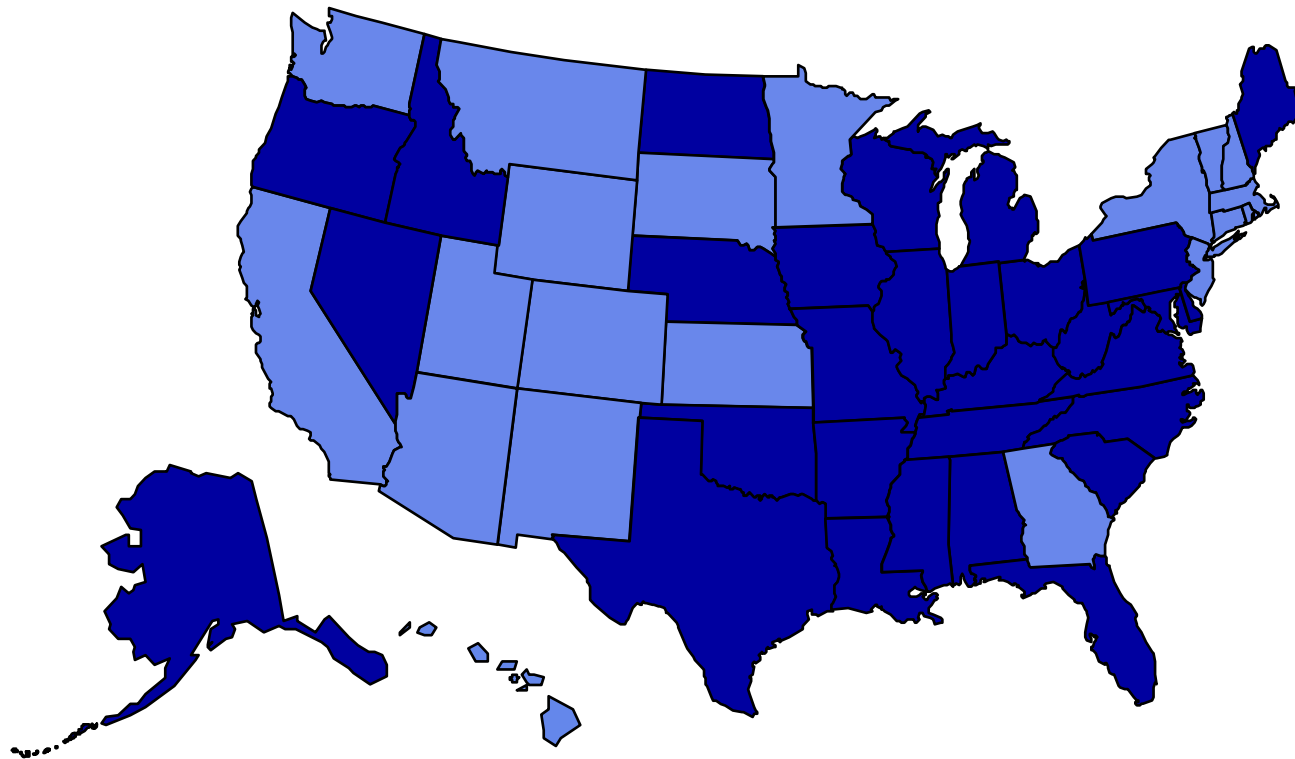


Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults

BRFSS, 1996

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



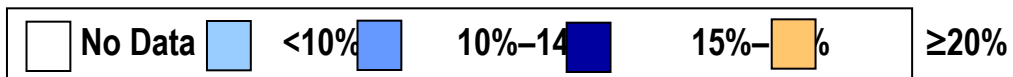
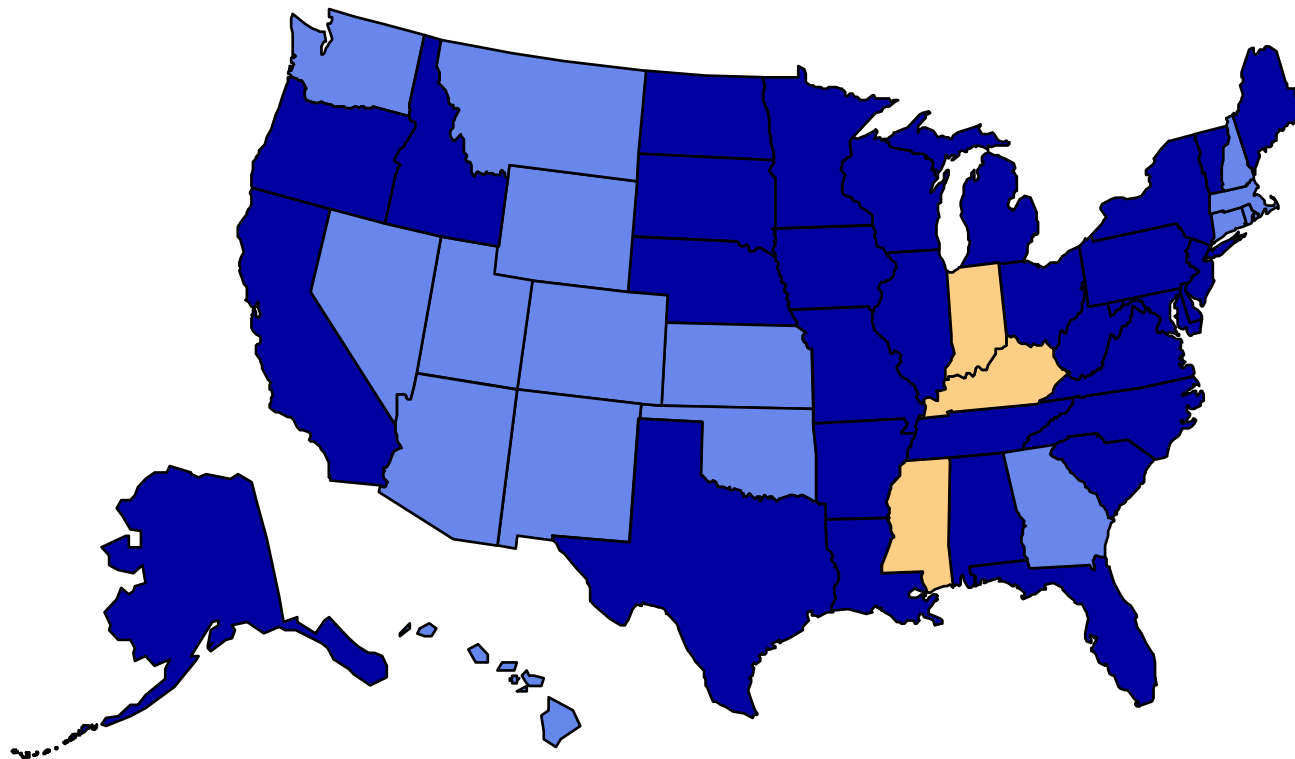
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 1997

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



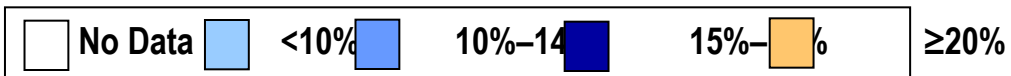
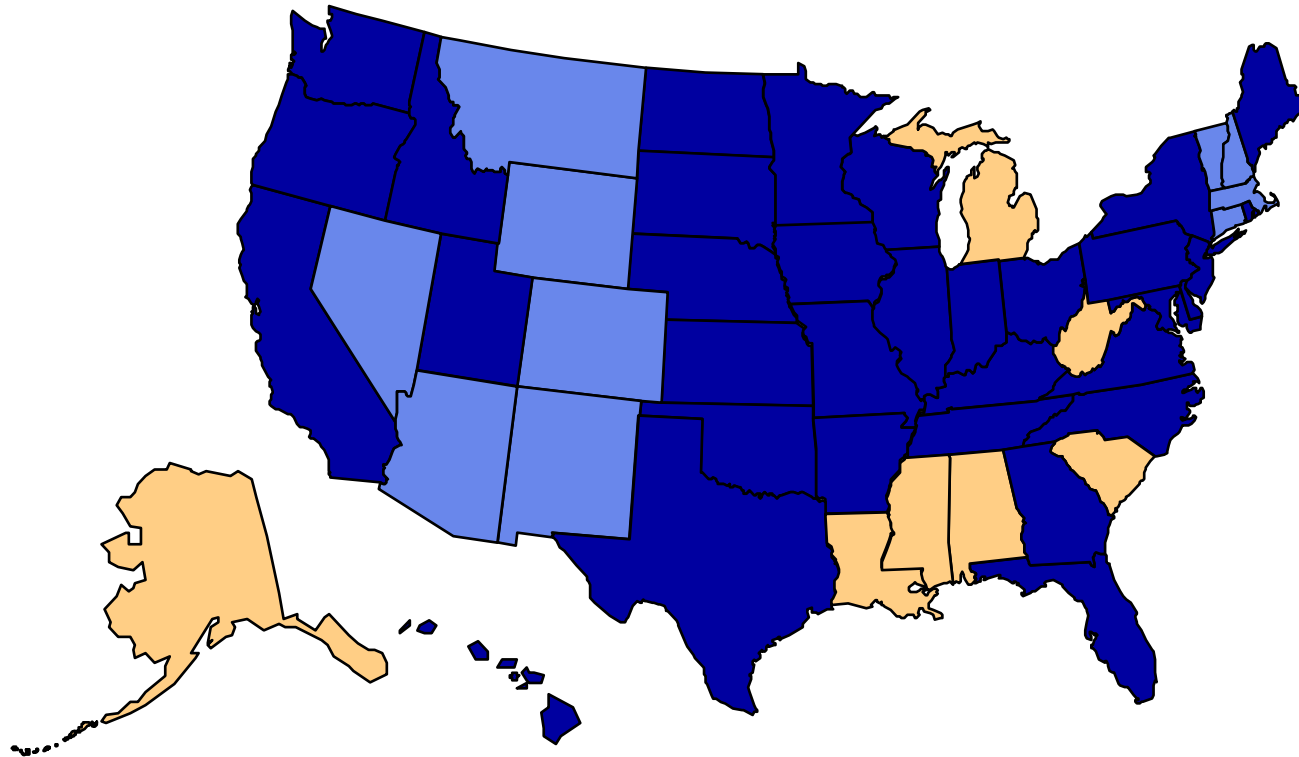
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 1998

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

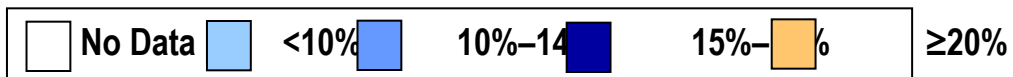
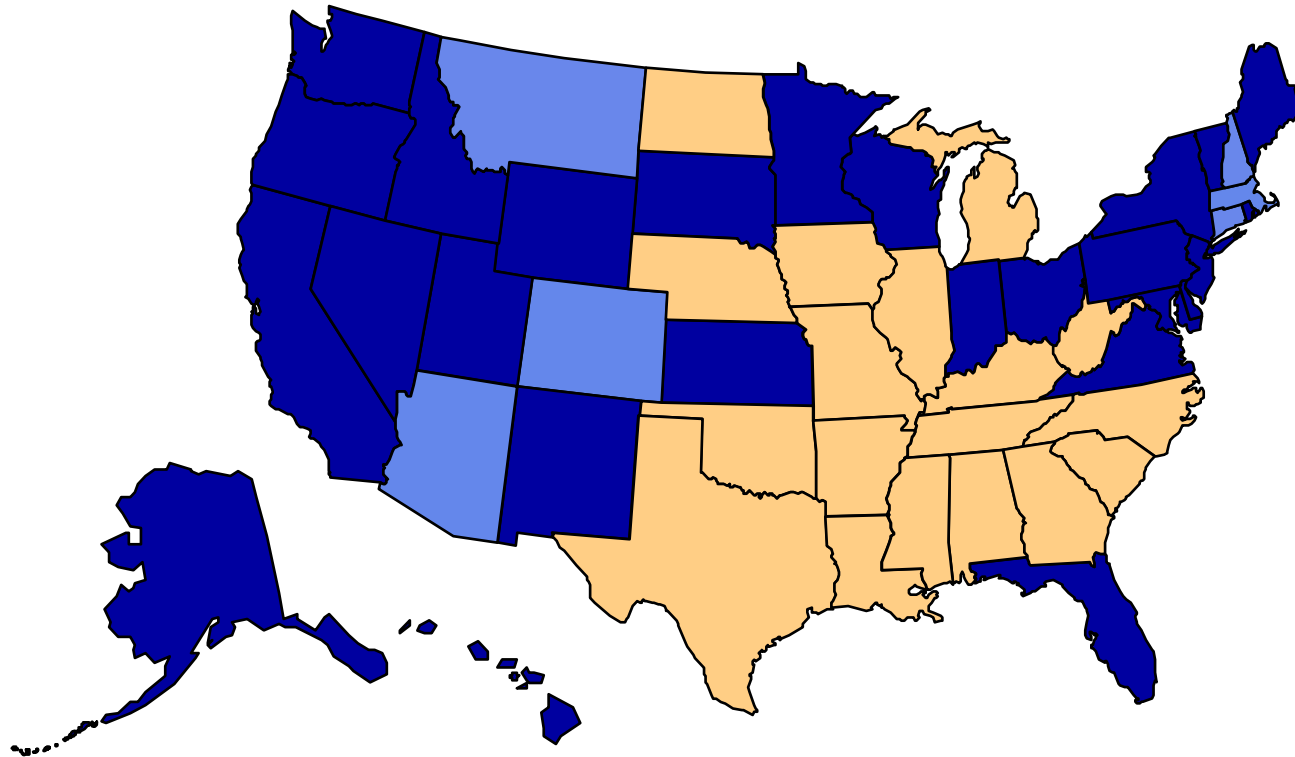


Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults

BRFSS, 1999

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



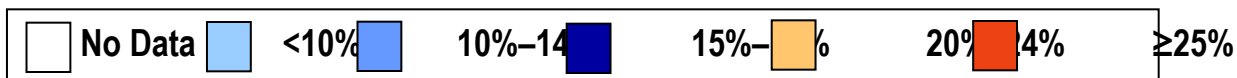
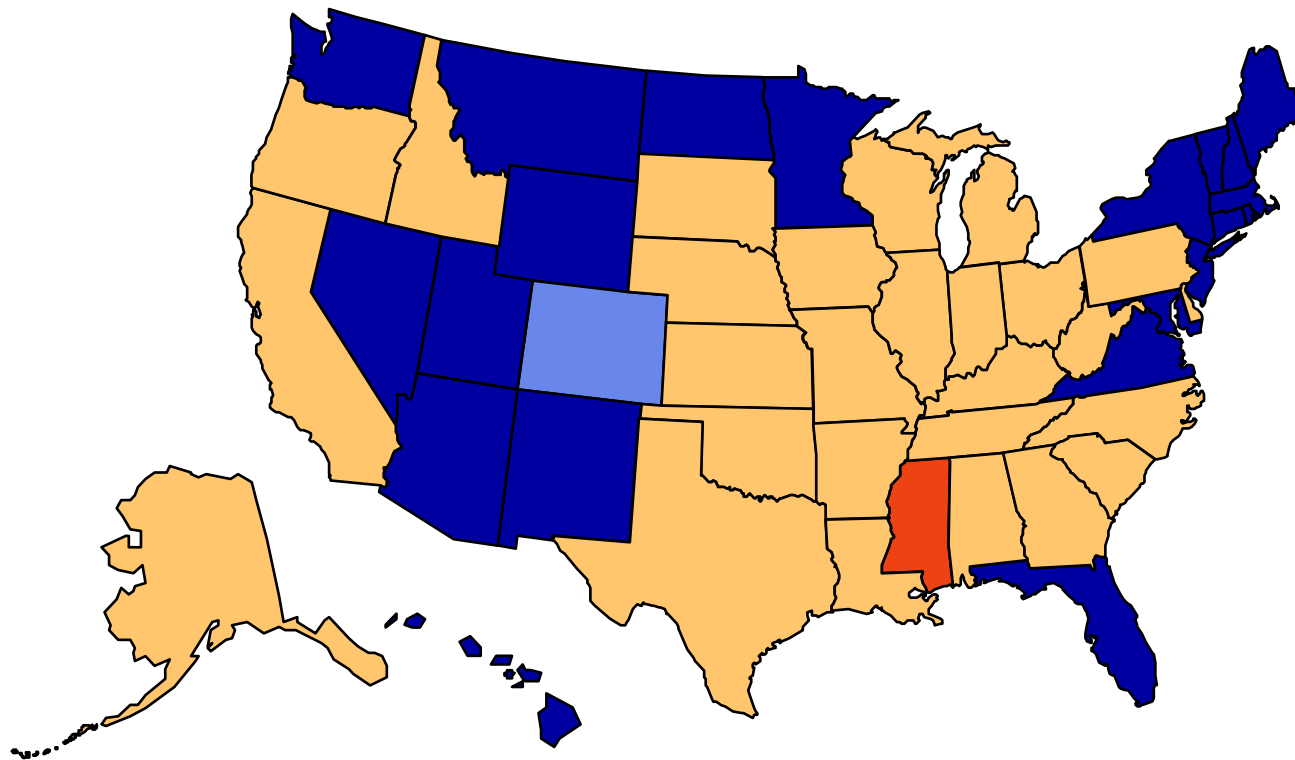
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 2001

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



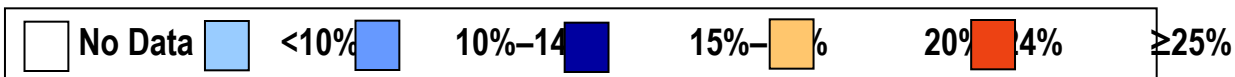
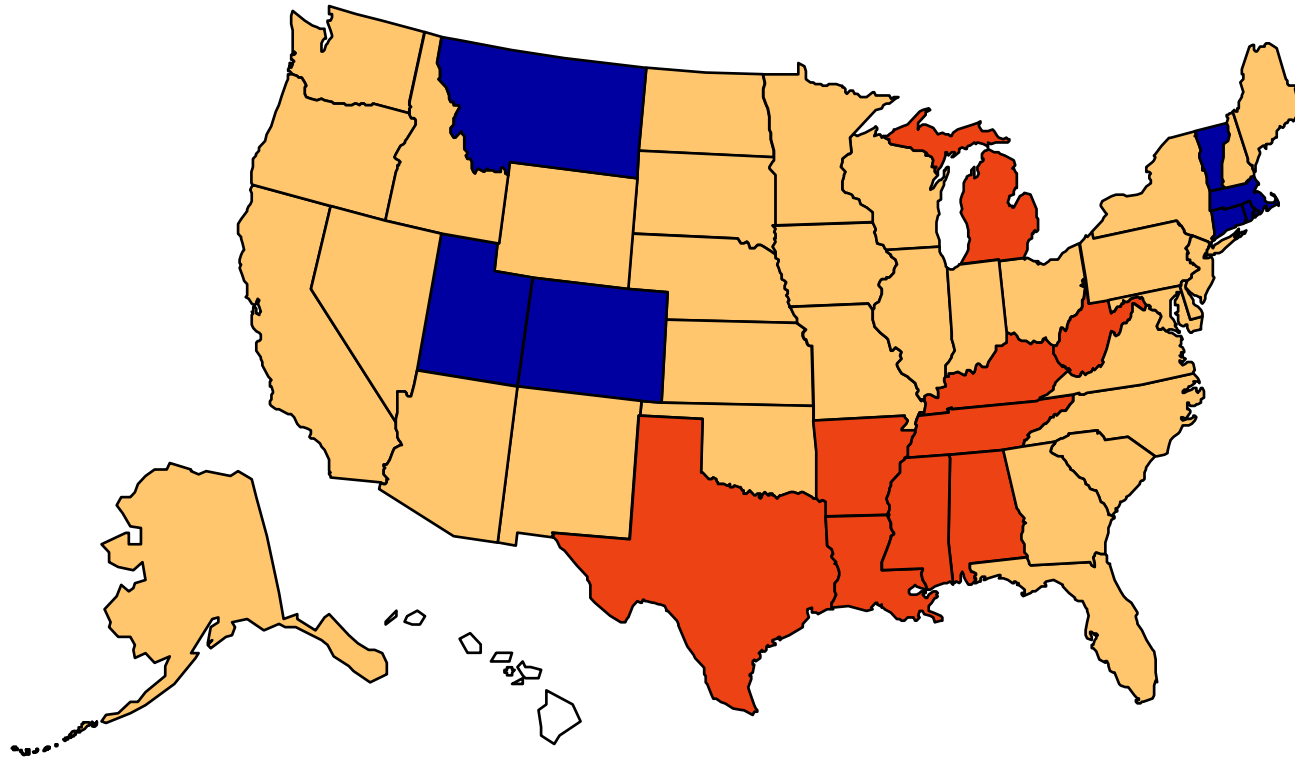
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 2004

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



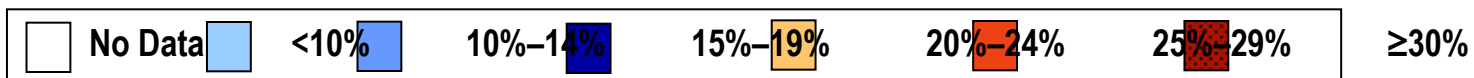
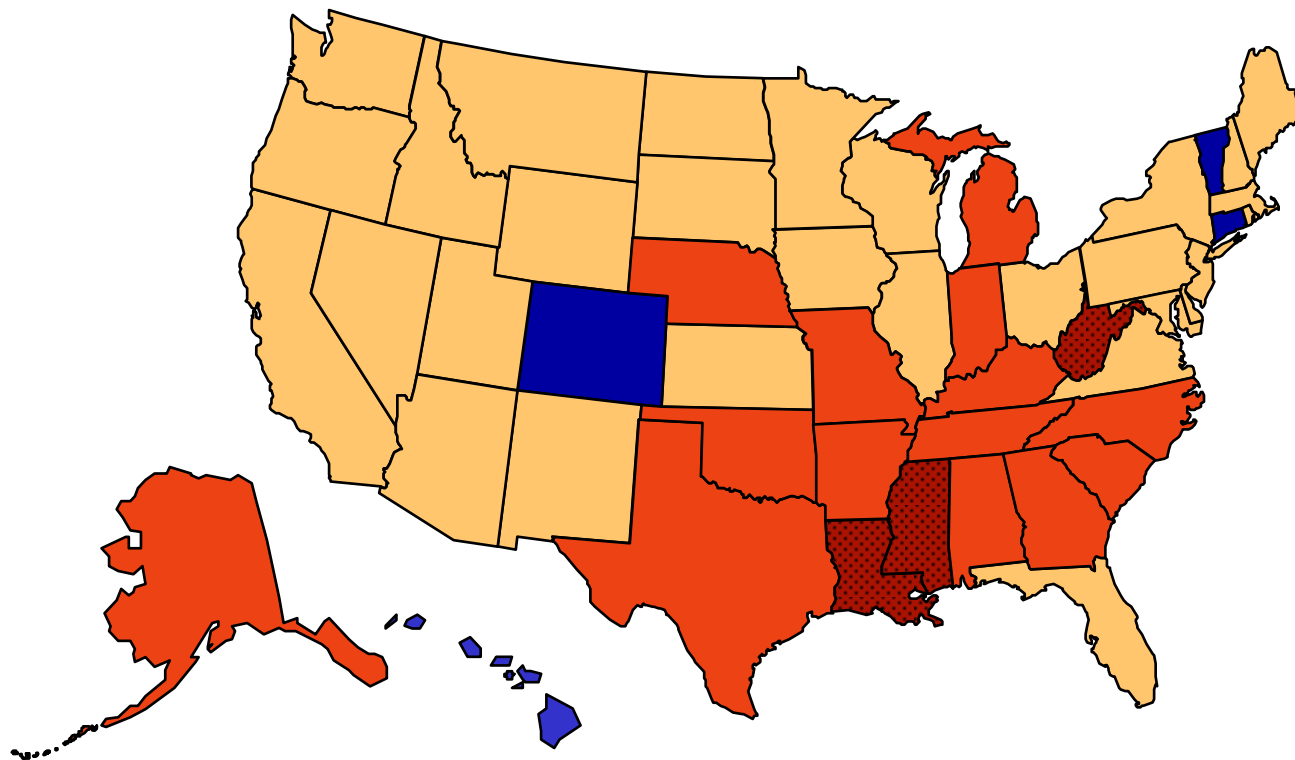
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 2005

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

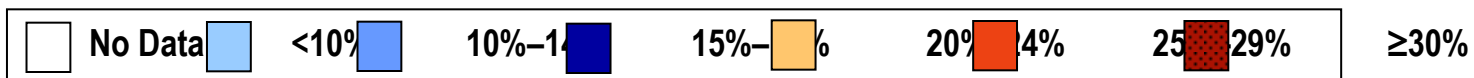
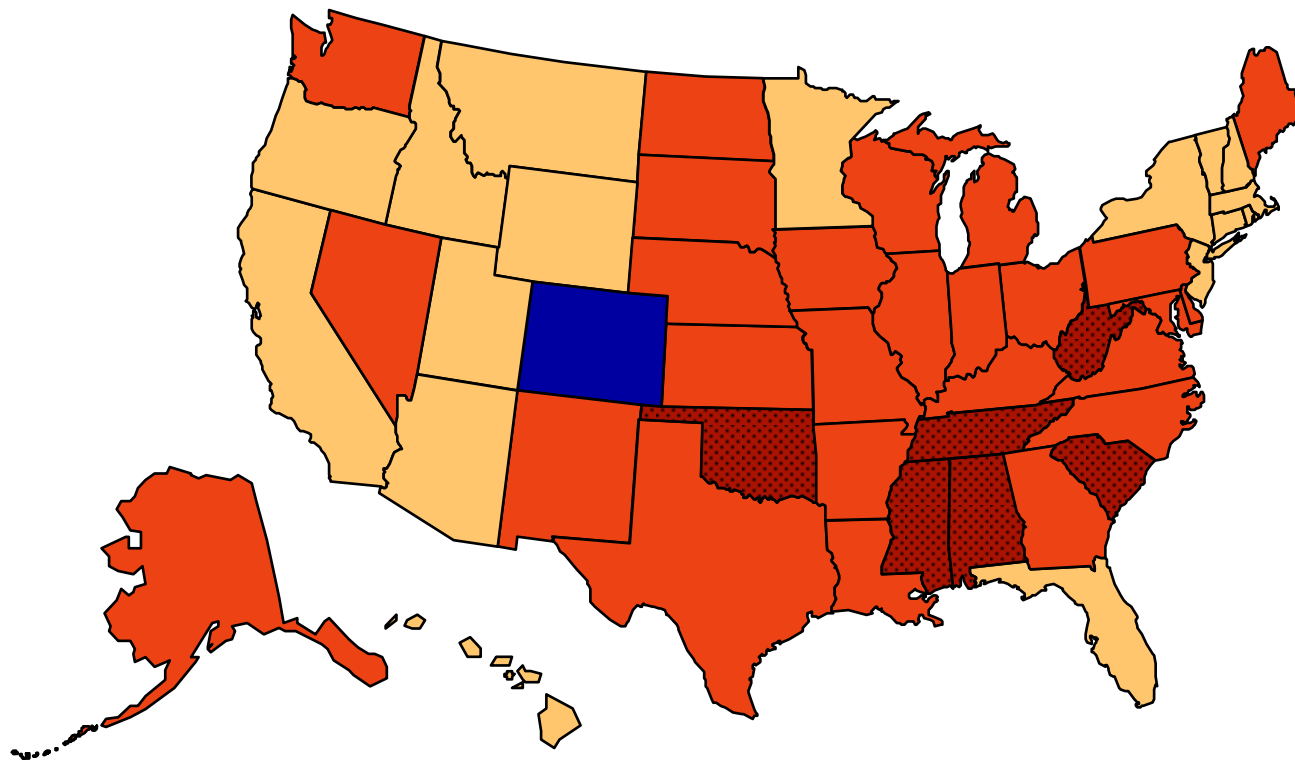


Source: Behavioral Risk Factor Surveillance System, CDC.

Obesity Trends* Among U.S. Adults

BRFSS, 2008

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



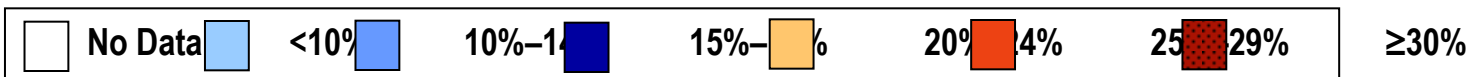
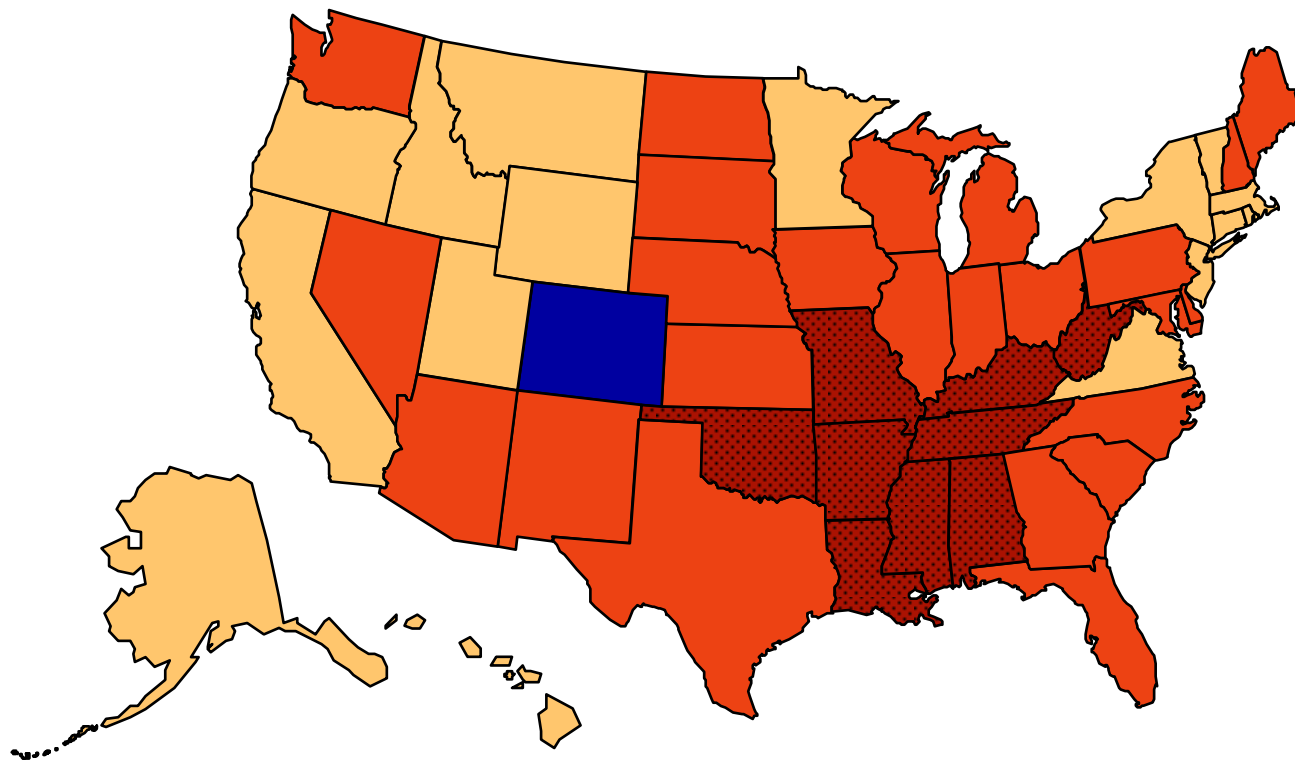
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 2009

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



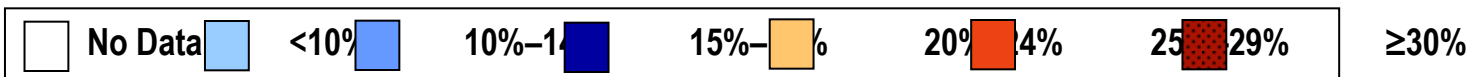
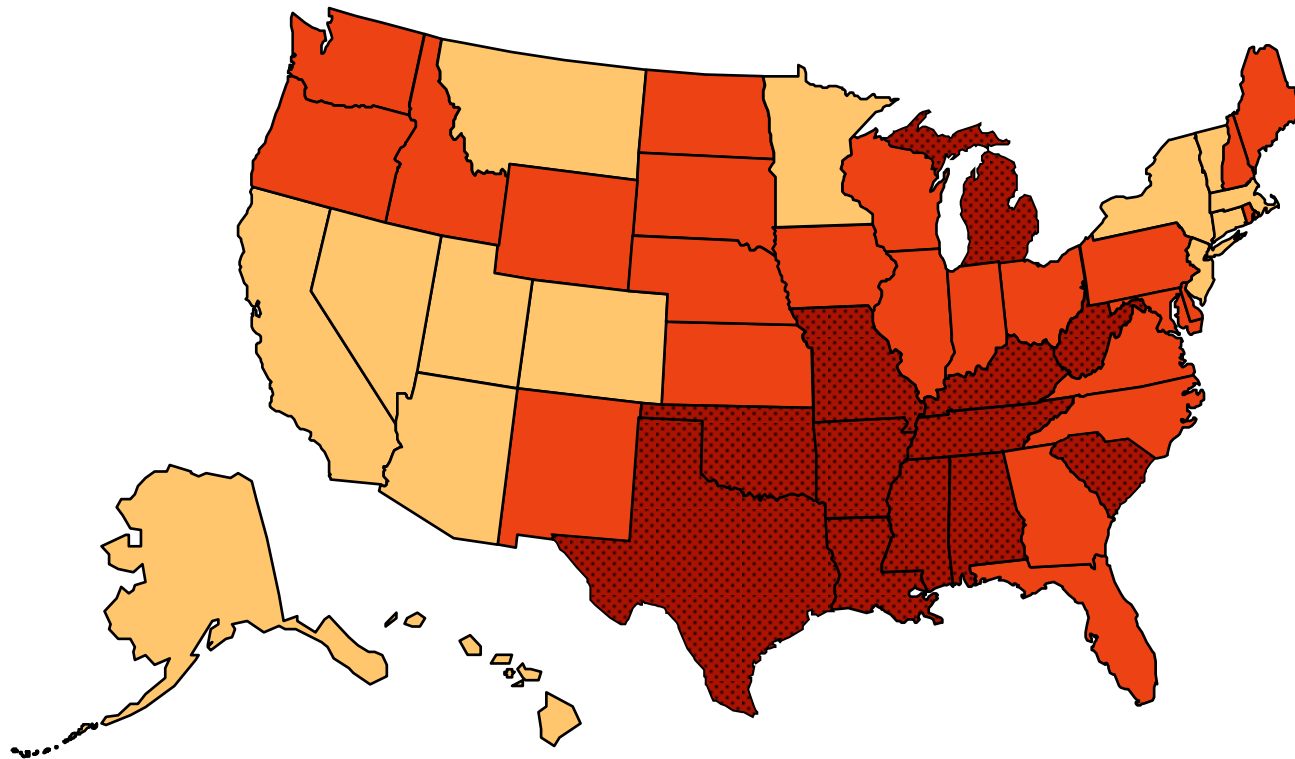
Source: Behavioral Risk Factor Surveillance System, CDC.



Obesity Trends* Among U.S. Adults

BRFSS, 2010

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



Source: Behavioral Risk Factor Surveillance System, CDC.



Pathogenesis

- Not well understood
- Insulin resistance – Obesity and Type 2 DM
- Oxidative stress

Clinical features

- Symptoms
 - Asymptomatic – 65%
 - Fatigue
 - Right upper quadrant pain
- Signs
 - Hepatomegaly
 - Acanthosis nigricans
 - Signs of chronic liver disease

Biochemistry

- Usually elevated ALT
- $AST/ALT < 1$
- GGT variable
- Platelets
- Clotting abnormalities

Diagnosis

- There are no diagnostic tests
- It is one of exclusion
 - ETOH < 14 units in women and <21 units in men
 - Viral hepatitis serology negative
 - Autoimmune screen negative
 - Iron and copper
 - Drugs

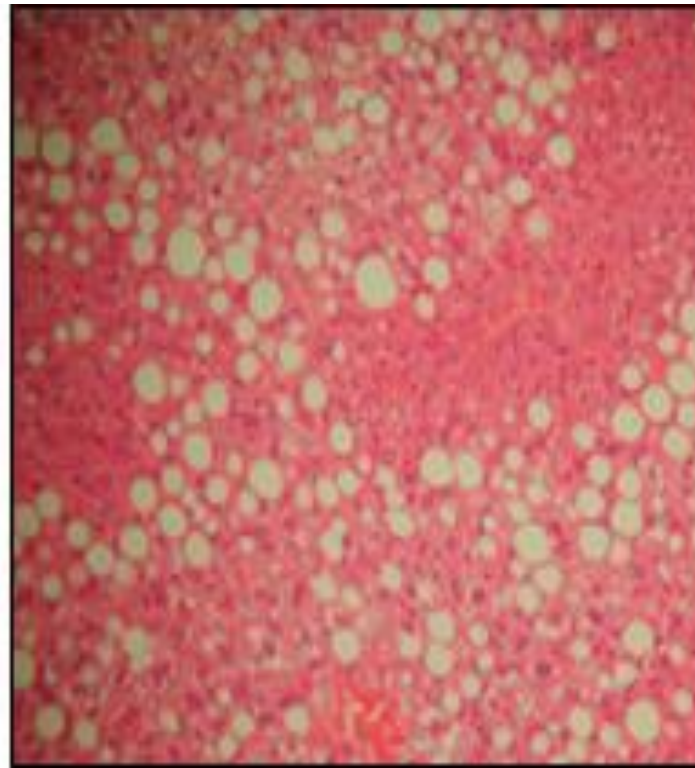
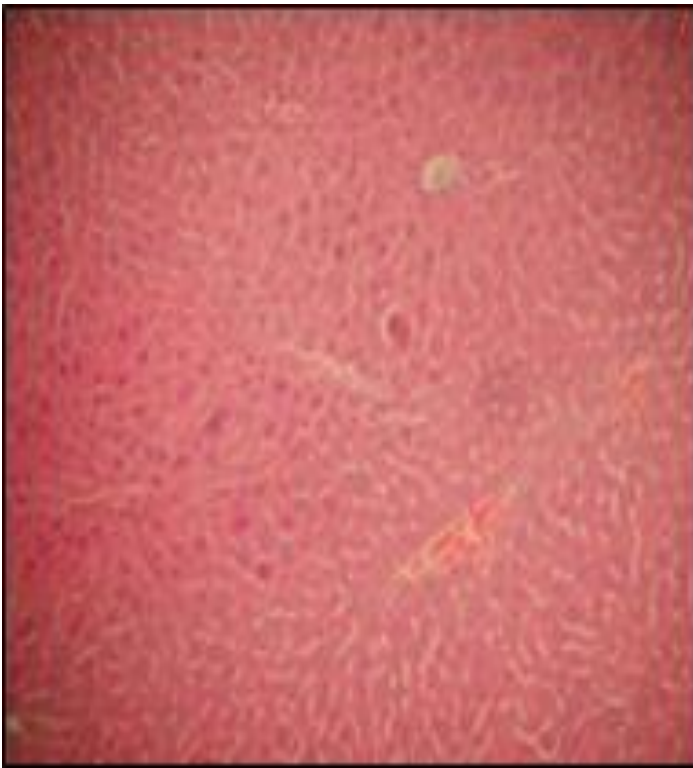
Imaging

- Ultrasound – Increased echogenicity to kidney
- CT – Low density to spleen
- MRI – In and Out Phase ECHO
- MRS – Quantative assessment of steatosis
- No imaging modality can differentiate the different stages of NAFLD

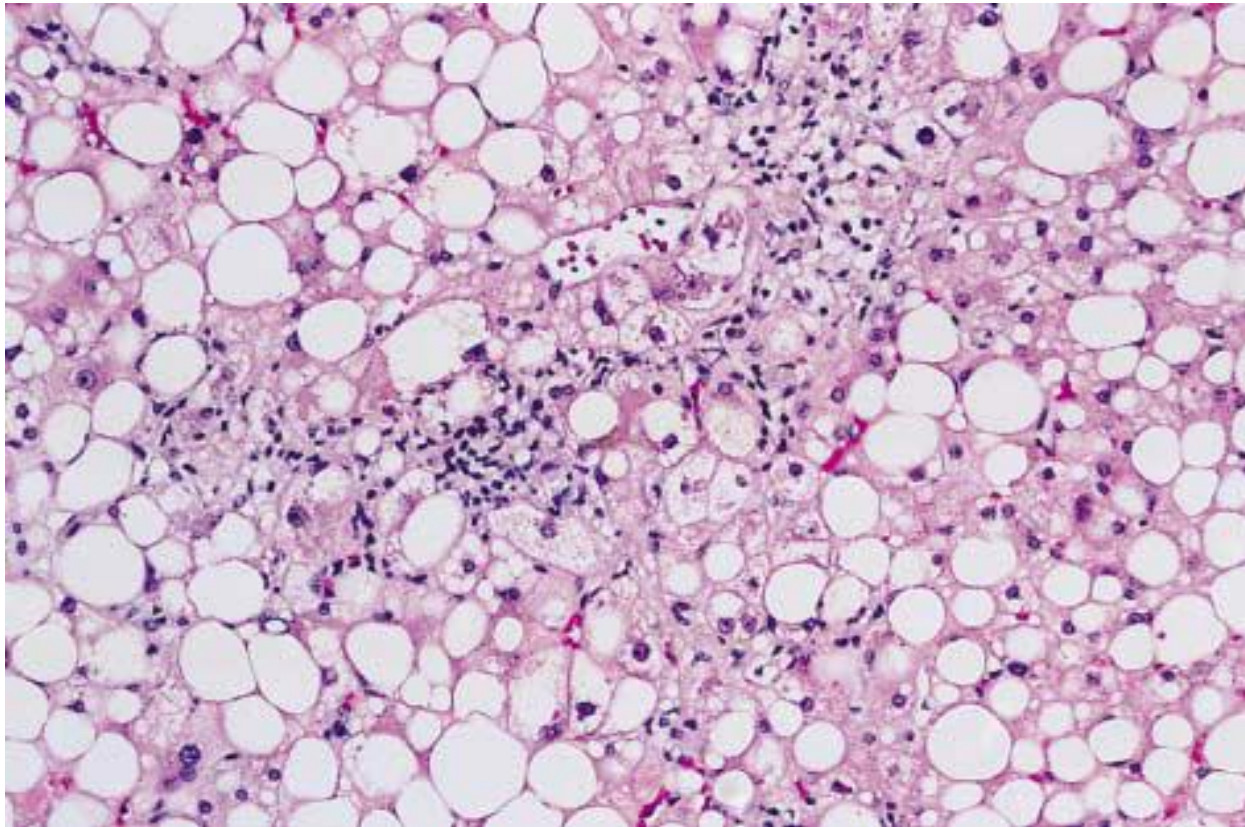
Liver Biopsy

- Confirm diagnosis
- Staging and Prognosis
- Management

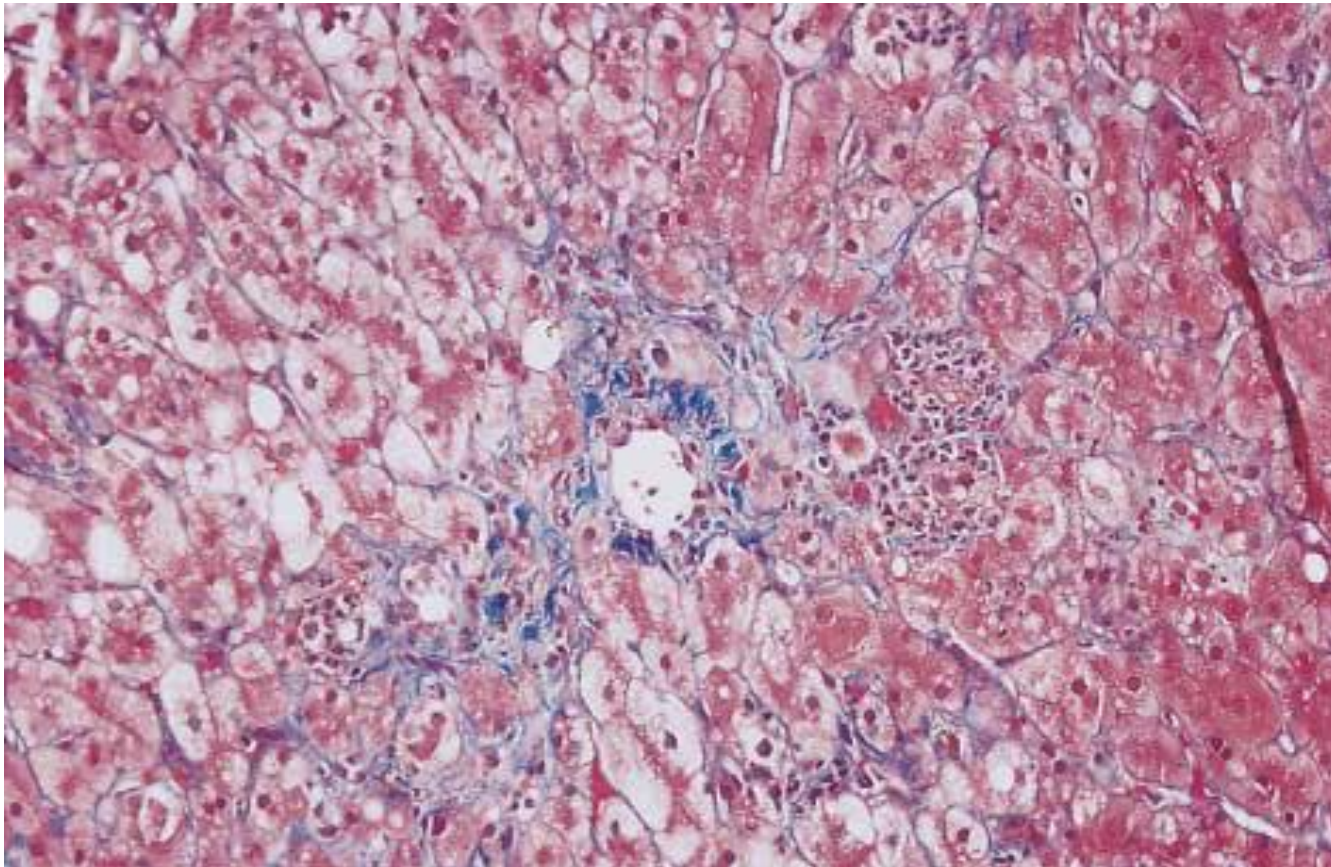
Liver Biopsy – Normal and Steatosis



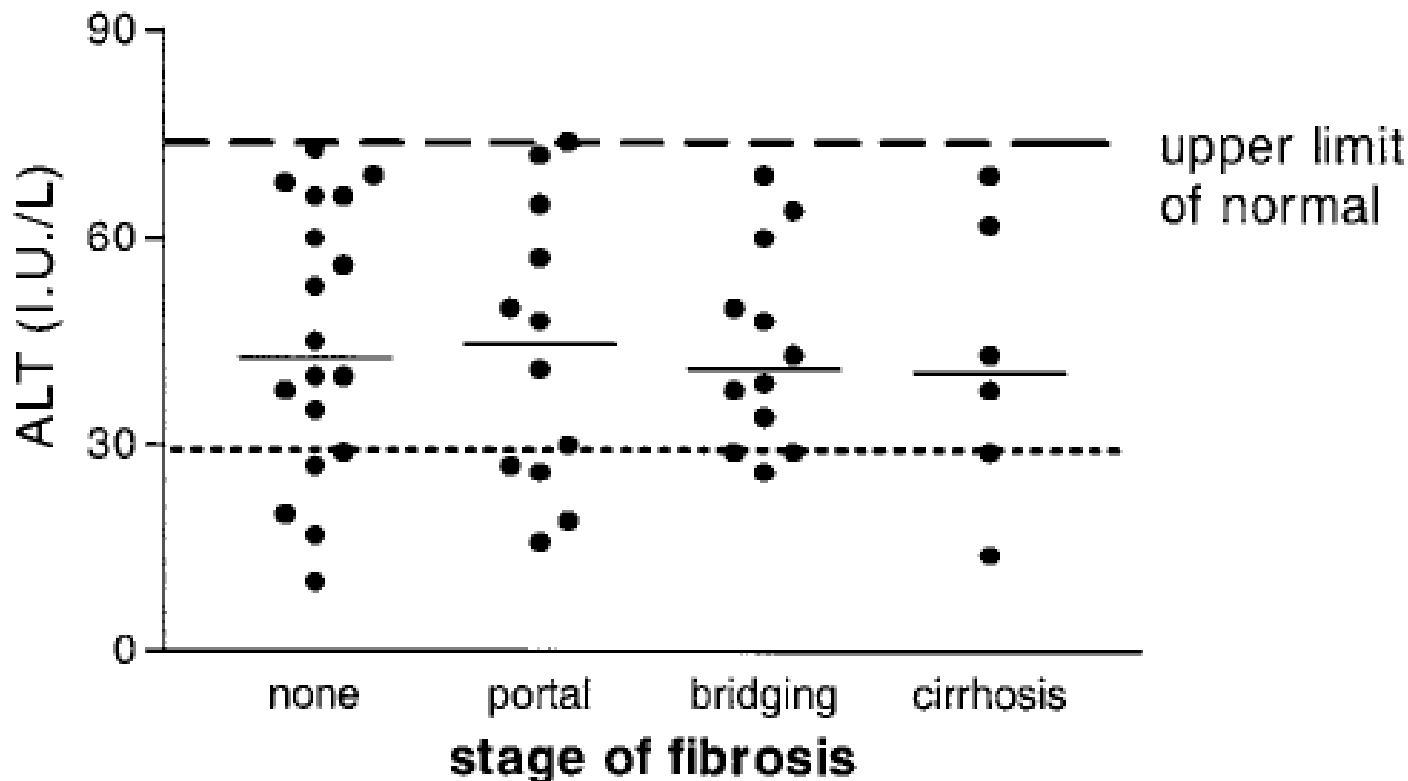
Liver Biopsy - Steatohepatitis



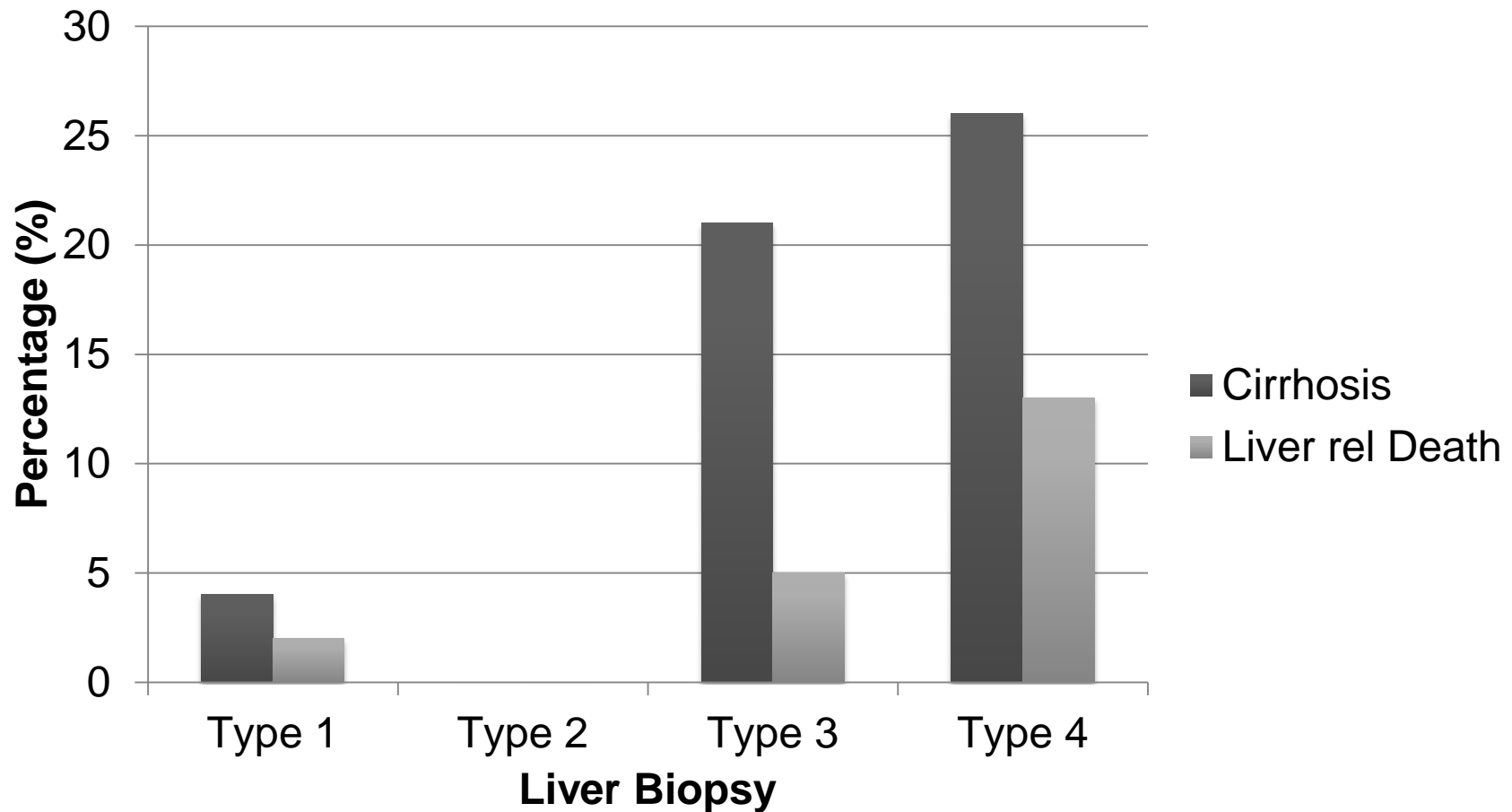
Liver Biopsy - Fibrosis



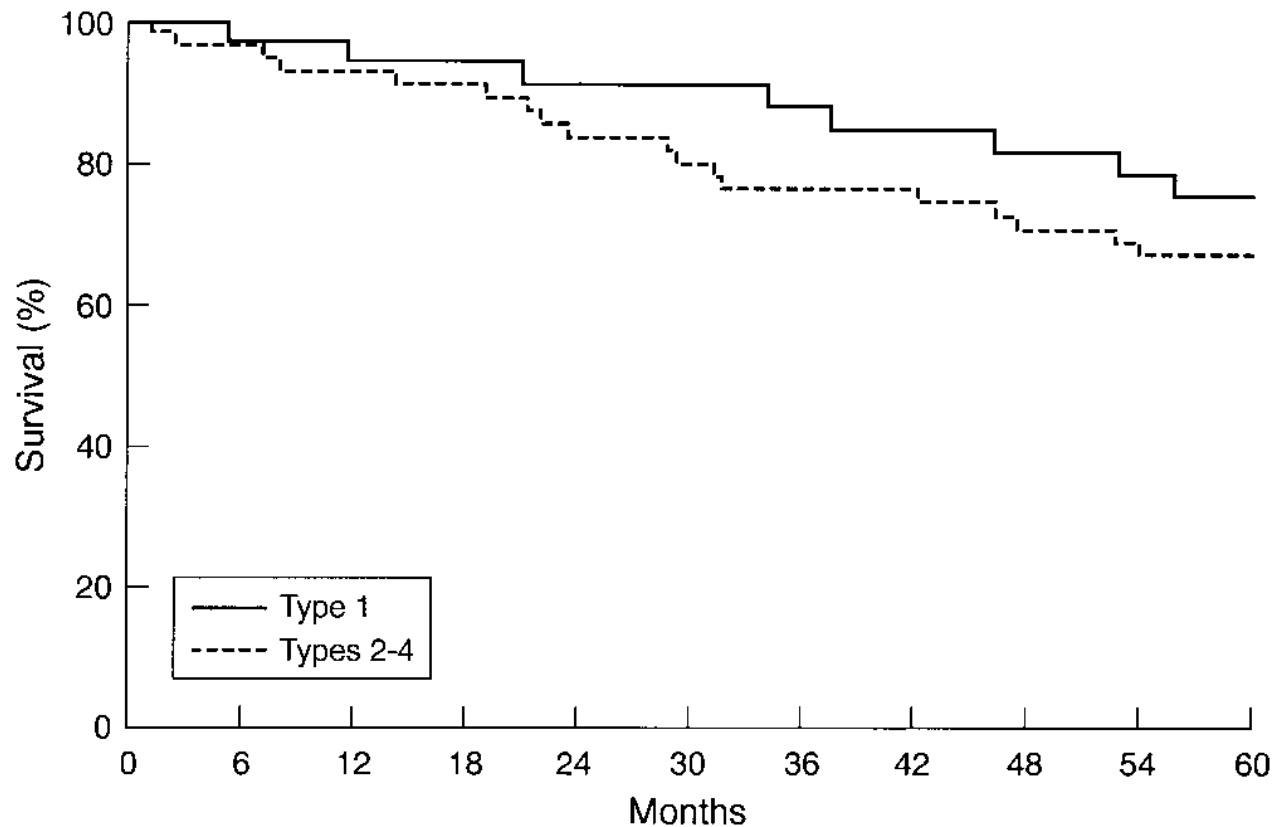
ALT may not be reliable marker of activity



Prognosis based on histology

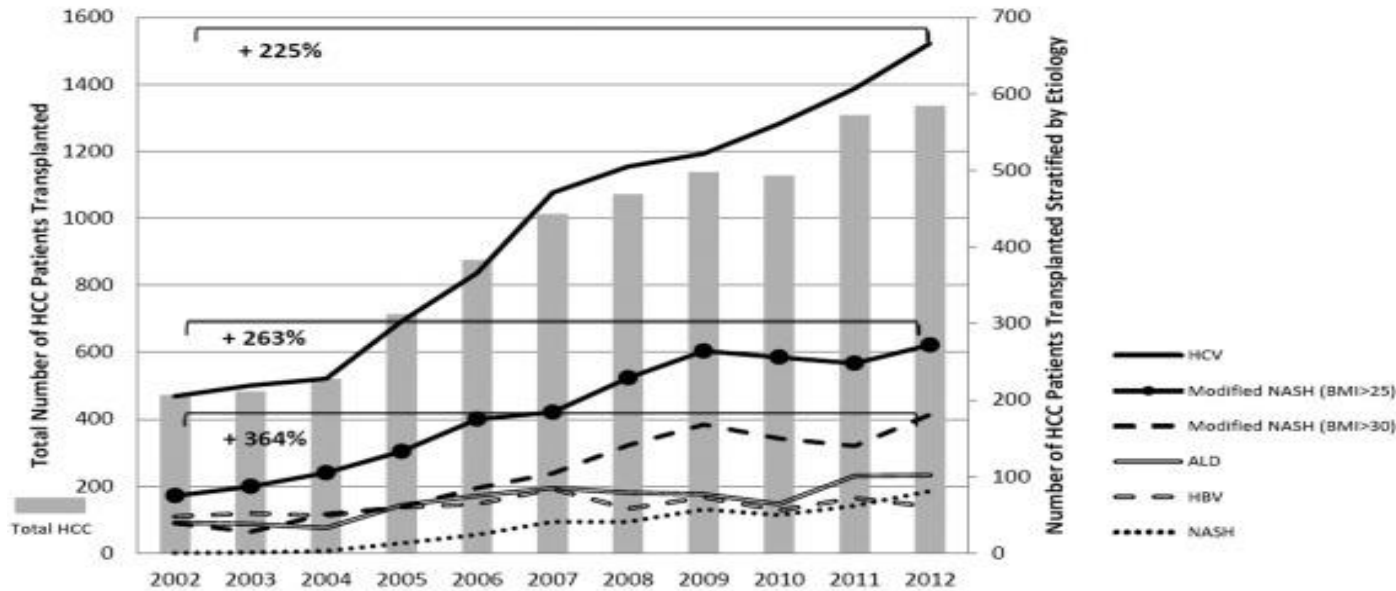


Survival rates based on liver histology



Hepatocellular carcinoma

Trends in HCC Liver Transplantation by Etiology of Liver Disease



Note: The percentages shown indicate the percent increase in the frequency of liver transplantations for each category from 2002 to 2012 and 2006 to 2012.

HCV-Hepatitis C virus, HBV-Hepatitis B virus, NASH-nonalcoholic steatohepatitis, ALD-alcoholic liver disease. Modified NASH (BMI > 25) includes NASH and patients with cryptogenic and unknown etiology with body mass index (BMI) ≥ 25 kg/m². Modified NASH (BMI > 30) includes NASH and patients with cryptogenic and unknown etiology with body mass index (BMI) ≥ 30 kg/m².

Simple Steatosis (12-40%)



NASH (15-25%)



Cirrhosis (7%)



Hepatic cellular carcinoma

Non-Invasive Methods of Staging

- Age > 45
- BMI > 30
- AST:ALT ratio > 1
- T2DM
- Obstructive sleep apnoea

Non-Invasive Methods of Staging

- NAFLD Fibrosis score
 - Age, AST/ALT ratio, BMI, platelets, albumin, glycaemia
- ELF Score
 - Hyaluronic acid, tissue inhibitor of matrix metalloproteinase 1, amino terminal peptide of pro-collagen III

Non-Invasive Methods of Staging

- Imaging techniques have limited use in early disease
- Transient elastography (Fibroscan) – BMI < 28
- Controlled attenuation parameter (CAP)

Weight management

- Lifestyle modification – Improvement in LFT's and a few studies shows histological improvement with gradual moderate (10%) wt loss (< 1.6kg/wk)
- Orlistat – Improvements in LFT's and U/S

Weight management

- Bariatric surgery
 - Significant weight loss 60%
 - Early techniques of jejuno –ileal bypass were associated with acute liver failure and massive steatosis
 - Newer surgical techniques are associated with histological improvements in liver biopsy

Insulin sensitiser

- Metformin – some conflicting evidence regarding benefits on steatosis
- Thiazolidendione – all studies have demonstrated improvements in steatosis in addition to histology.
 - Recent rosiglitazone meta-analysis
 - Stopping treatment leads to recurrence

Lipid Lowering Therapy

- Fibrates – Good animal data but limited human data. Improvements have been shown with gemfibrozil, but no significant changes with clofibrate
- Statins
 - No data on statins
 - Increased CVD risk
 - No evidence of increased hepatotoxicity

Anti-hypertensive agents

- Renin-Angiotensin System
 - Losartan has been demonstrated to improve liver fibrosis

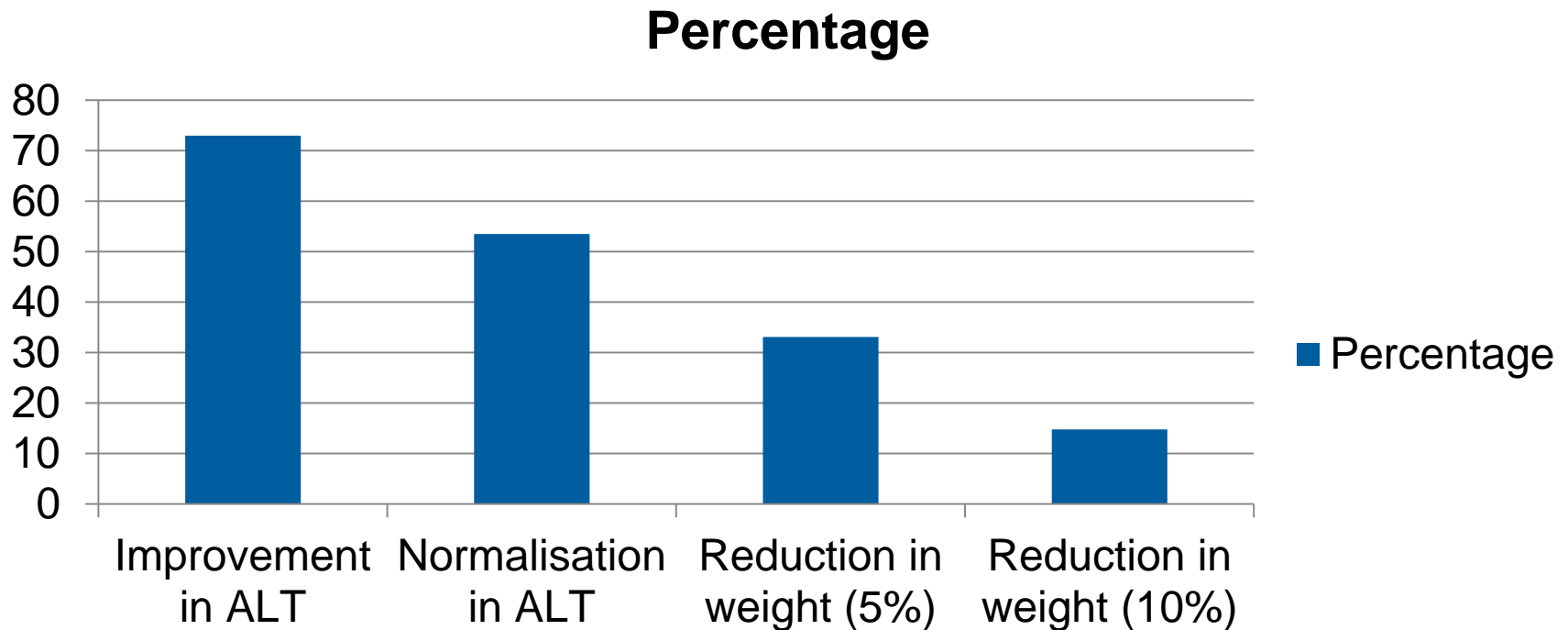
Liver directed treatment

- Ursodeoxycholic acid – promising data on LFT's and histology
- Anti-oxidants – no evidence of benefit from Vitamin C and E
- Rimonabant – in addition to effects from weight loss, inhibition of CB-1 receptor anti-fibrotic actions
- TNF α inhibitors (pentoxifylline) – promising results

Liver transplant

- Decompensated cirrhosis
- 50% have recurrence NASH in 4 years

Multidisciplinary clinics – 5 year follow up data



Clinical Guidelines

Clinical Practice Guidelines



EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease[☆]

European Association for the Study of the Liver (EASL)*, European Association for the Study
of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Summary

- NAFLD is increasingly prevalence
- It can lead to cirrhosis and HCC
- Treatments are currently limited but likely to increase

Specialist Metabolic and Hepatology Clinic

- Referrals to Dr Michael Yee (Metabolic Medicine Unit) or Dr Pinelopi Manousou (Hepatology Unit)
- Non-alcoholic and viral hepatitis negative