Cardiovascular Disease After Spinal Cord Injury: Achieving Best Practice

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February 12, 2010

National Rehabilitation Hospital

MedStar Health

CAVEAT LECTOR

CVD-related Mortality in Aging SCI

- GU complications accounted for 43% of SCI-related deaths in the ‘40s and ‘50s
- GU mortality was reduced to 10% in the ‘80s and ’90s
- CVD-related diseases are now the most frequent cause of death long-term
  - 46% of those surviving 30 years
  - 35% of those older than 60 years

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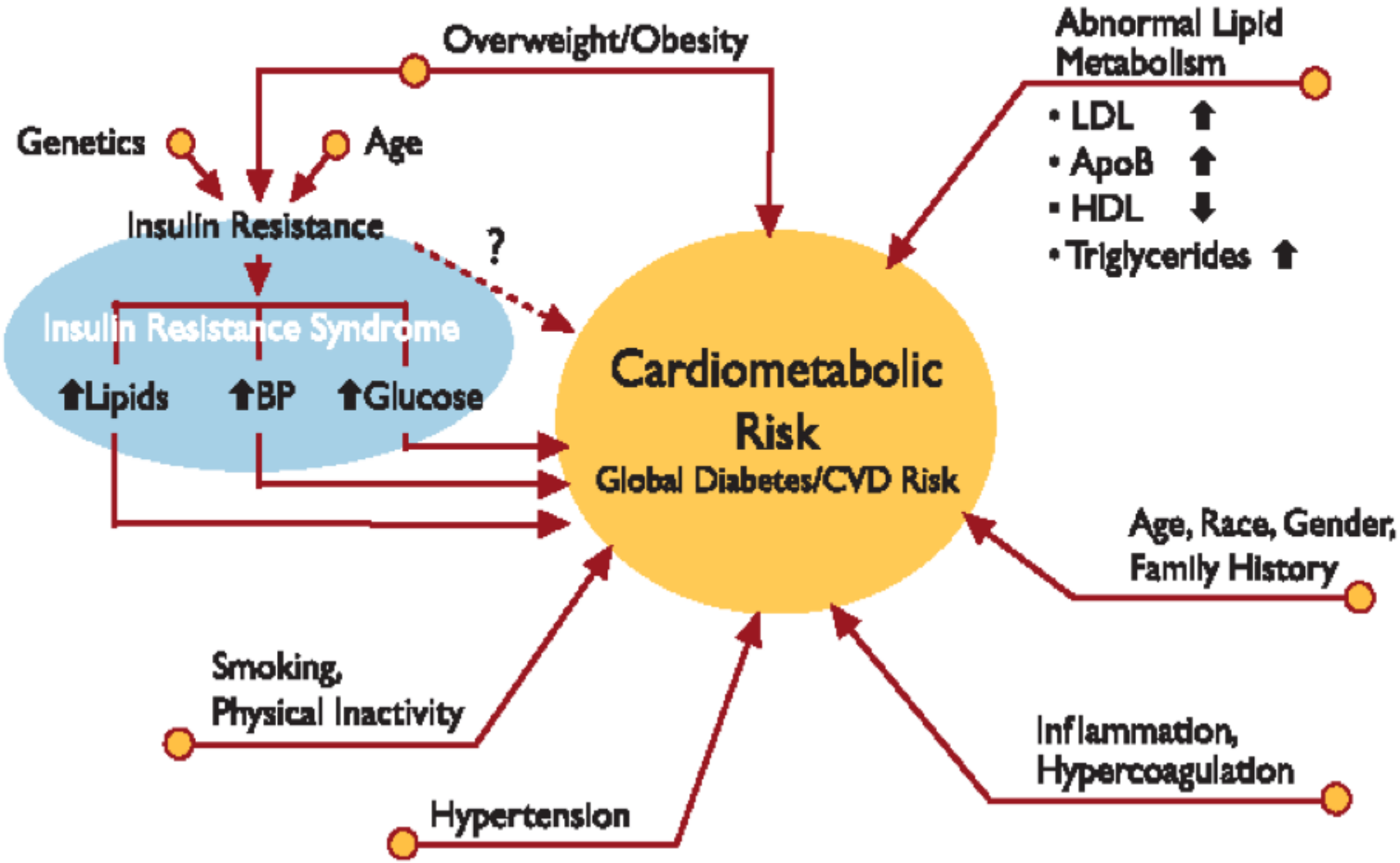
Cardiometabolic Risk Clustering

- 'Metabolic syndrome' has been supplanted by 'cardiometabolic risk'
- Better defines CVD and endocrine risks
- Clustering is the unique combinations of risk factors in populations that may impart a health hazard
  - Risk clustering linked to CVD-related morbidity and mortality, which worsens non-linearly with identification of additional risk factors

Factors Contributing to Cardiometabolic Risk



EVALUATING RISK FACTORS SMOKING

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Smoking in the U.S.

- Healthy People 2010 goal
  - 12%
- Most recent CDC data
  - 19.8%
  - Down from 23% (1998)
  - “Non smoking” states
    - Utah, CA, CT
  - Smoking states
    - KY, WV, OK

Tobacco Use after SCI

- 19-22% in the community
- Veterans have a similar or slightly higher prevalence

Banerjea, 2009; Johnston, 2005; Weaver, 2007

EVALUATING RISK FACTORS
BLOOD PRESSURE

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Hypertension in the U.S.

- 1 in 3 adults
- Cause in 90-95% unknown
- Death due to hypertension
  - Rate increased 25.2%
  - Number of deaths increased by 56.4%
- At risk groups
  - Non-Hispanic blacks
    - Middle-aged or older
    - Less educated
    - Overweight or obese
    - Physically inactive
    - Comorbid diabetes

Hypertension after SCI

- Well-known decrease in BP after SCI
- More pronounced with higher and more complete injuries
- Hypertension clearly more prevalent in paraplegia compared with tetraplegia
- Hypertension more likely in those with incomplete injuries

Questions Related to Hypertension

- But……is hypertension more common than in the U.S. population?
- Is hypotension ‘protective’ for CVD?
- What is hypertension in tetraplegia?

Autonomic Dysregulation

- Autonomic dysreflexia
- 10% of people with chronic SCI have AD
- Much AD is silent
- 2.5% incomplete paraplegia
- 3% complete paraplegia
- 12% incomplete tetraplegia
- 22.5% complete tetraplegia

EVALUATING RISK FACTORS OVERWEIGHT/OBESITY

Obesity

- High body fat relative to lean body mass (>22% body fat)
- Waist circumference
  - Men > 42 in
  - Women > 35 in
- Waist to hip ratio (WHR)
  - Waist Circ / Hip Circ
  - Men < 0.9 safe; > 1 at risk
  - Women < 0.8 safe; > 1 at risk

NHLBI Obesity Education Initiative

- Body mass index (kg/m^2)
- BMI >= 30
- Obesity is a defining component of CMR

Category	BMI
Underweight	<18.5
Normal	18.5-24.9
Overweight	25.0-29.9
Obesity I	30.0-34.9
Obesity II	35.0-39.9
Obesity III	≥40.0

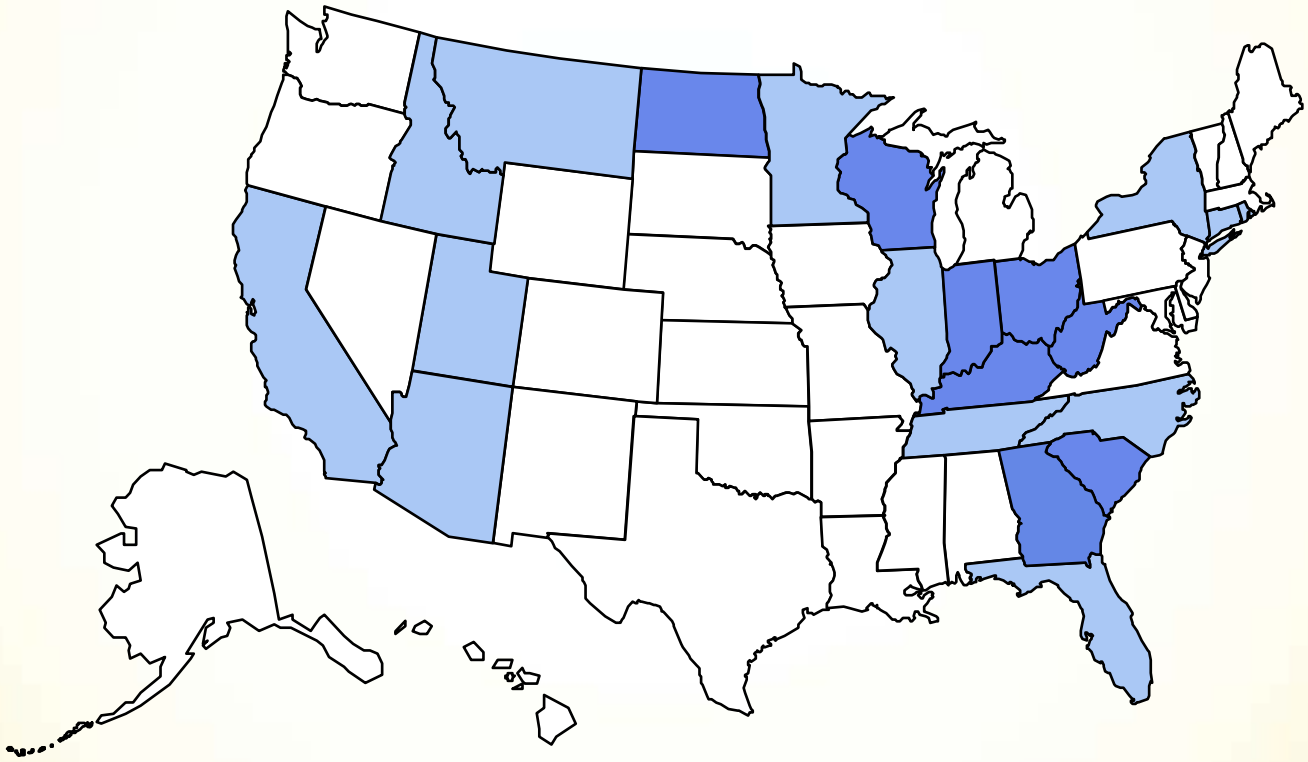
Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (1998)

UNITED STATES OBESITY TRENDS

Obesity Trends* Among U.S. Adults

BRFSS, 1985

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



Obesity Trends* Among U.S. Adults

BRFSS, 1986

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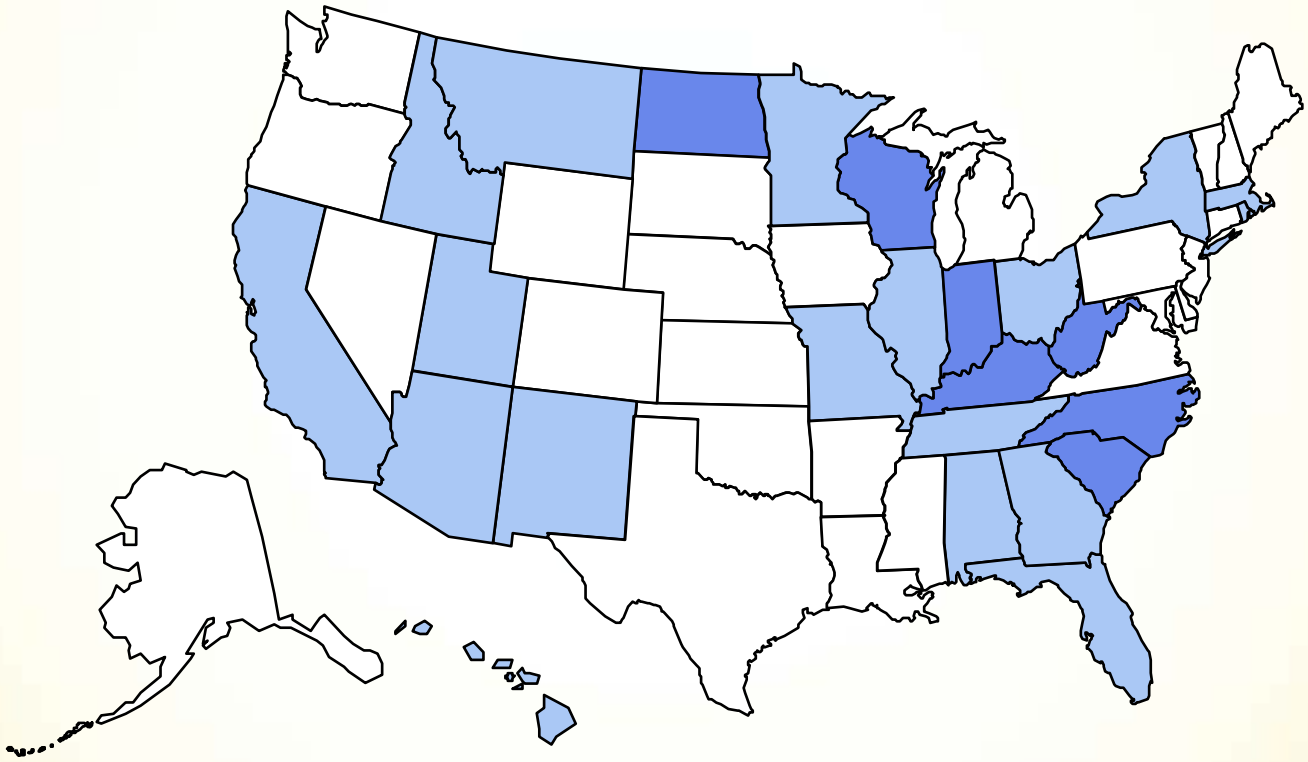

Obesity Trends* Among U.S. Adults

BRFSS, 1987

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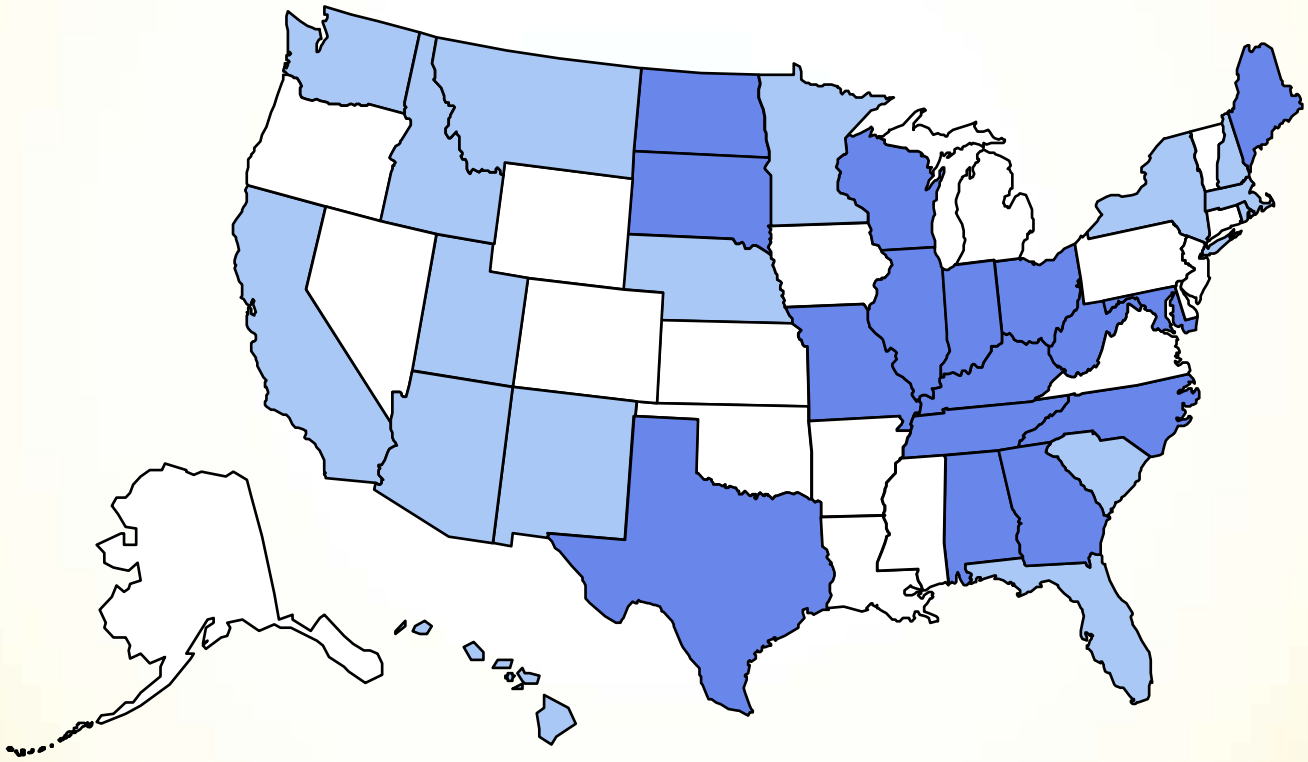

Obesity Trends* Among U.S. Adults

BRFSS, 1988

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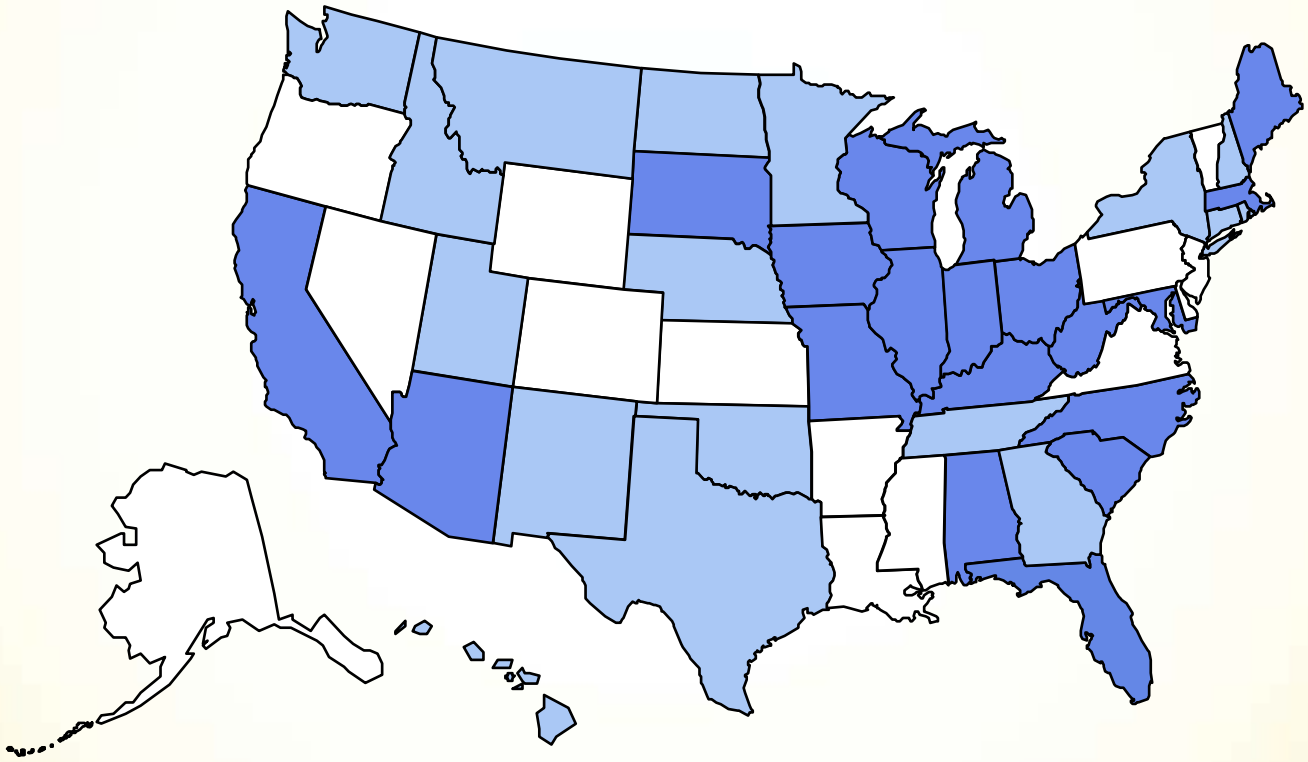

Obesity Trends* Among U.S. Adults

BRFSS, 1989

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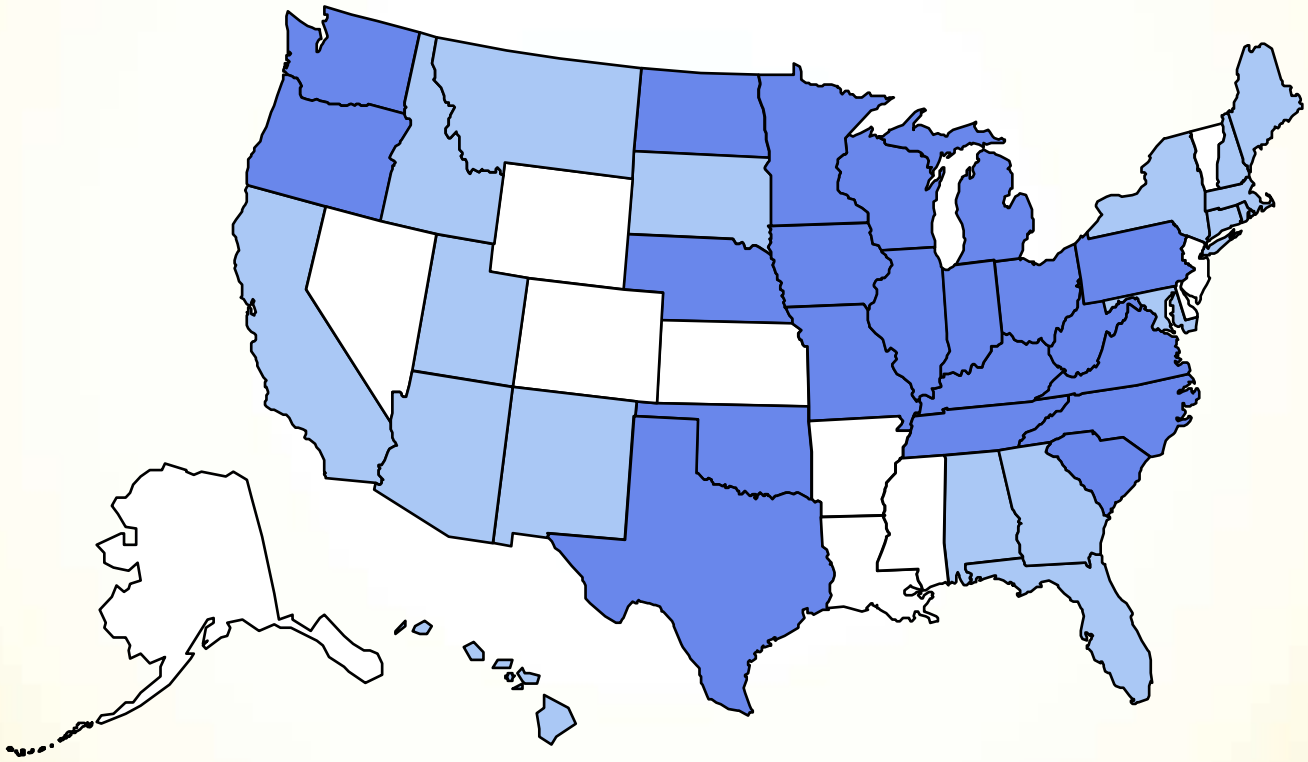

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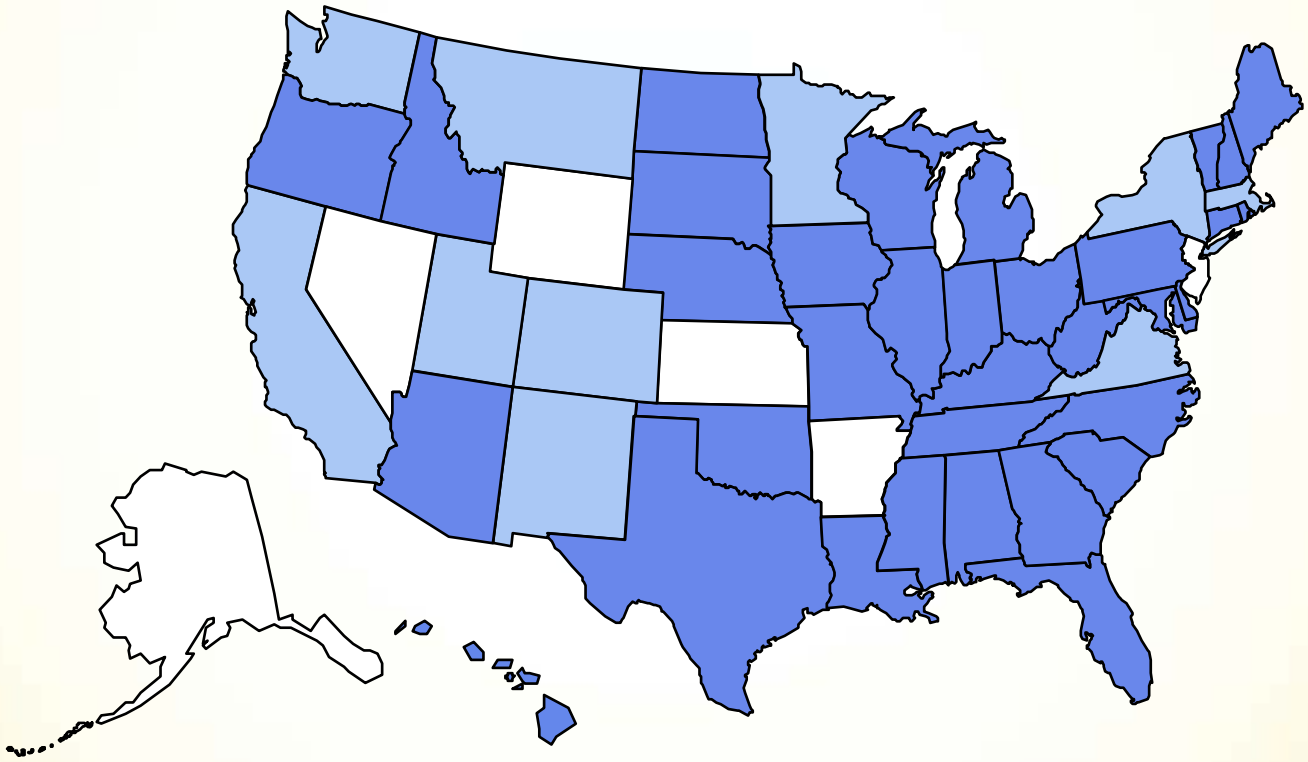

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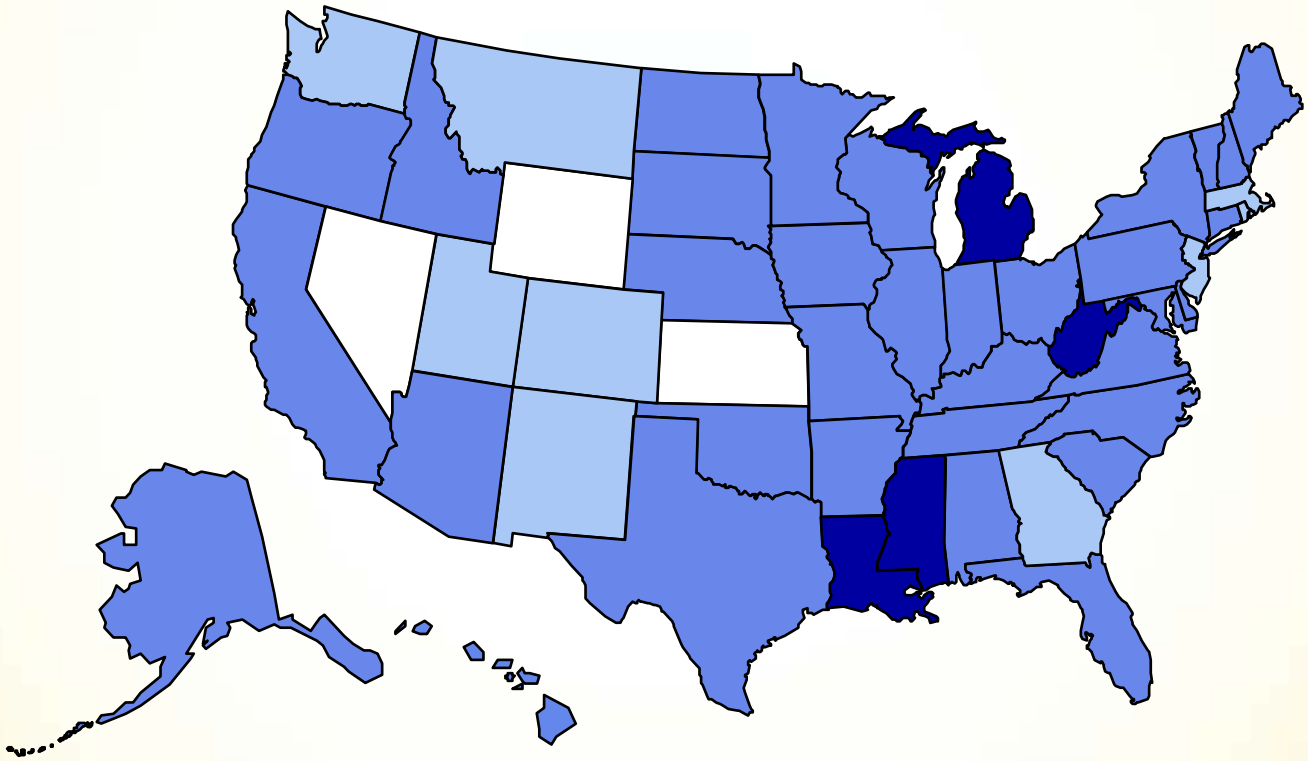

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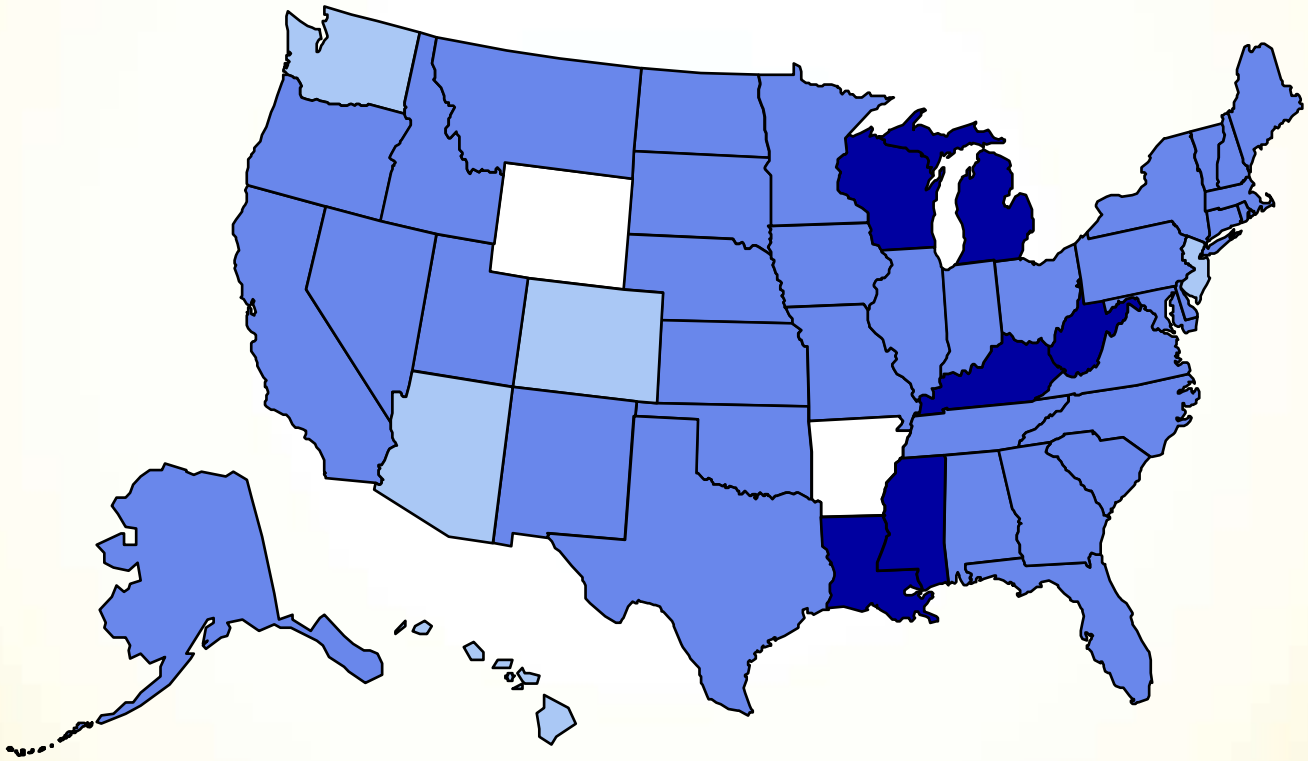

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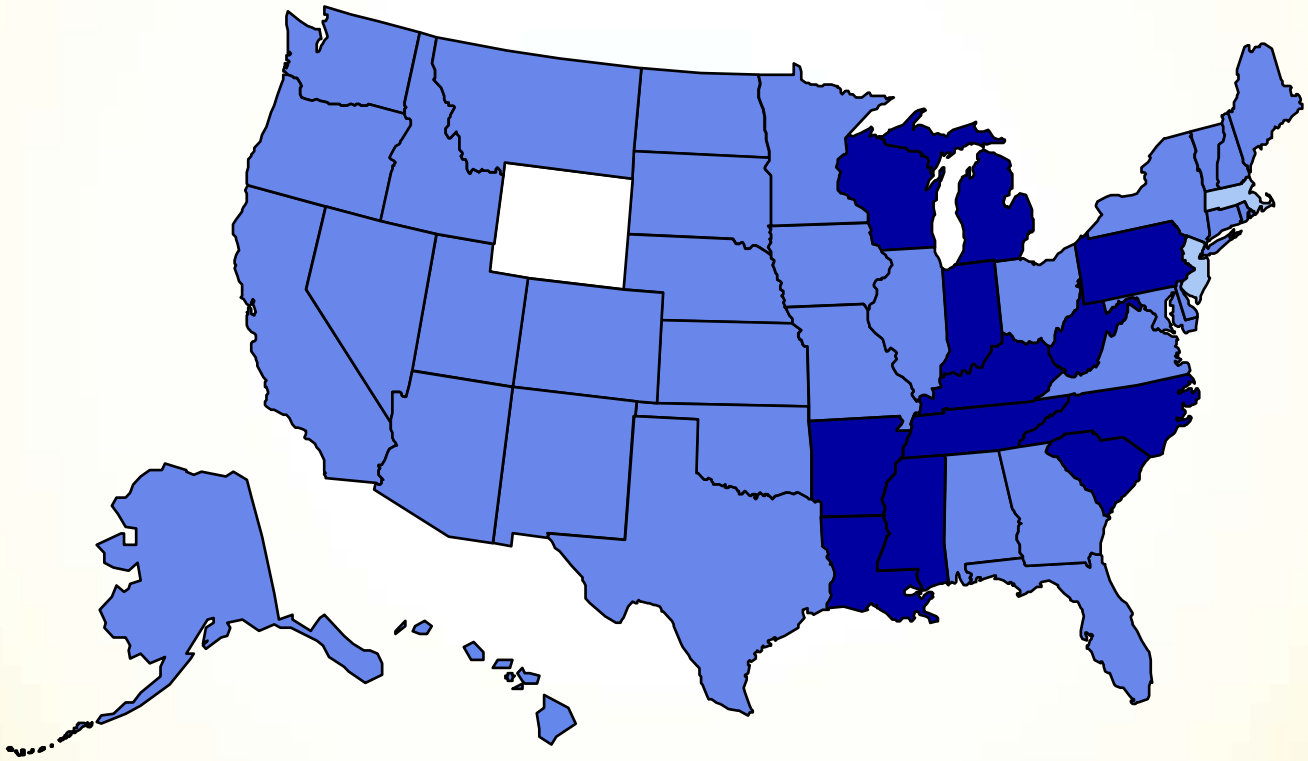

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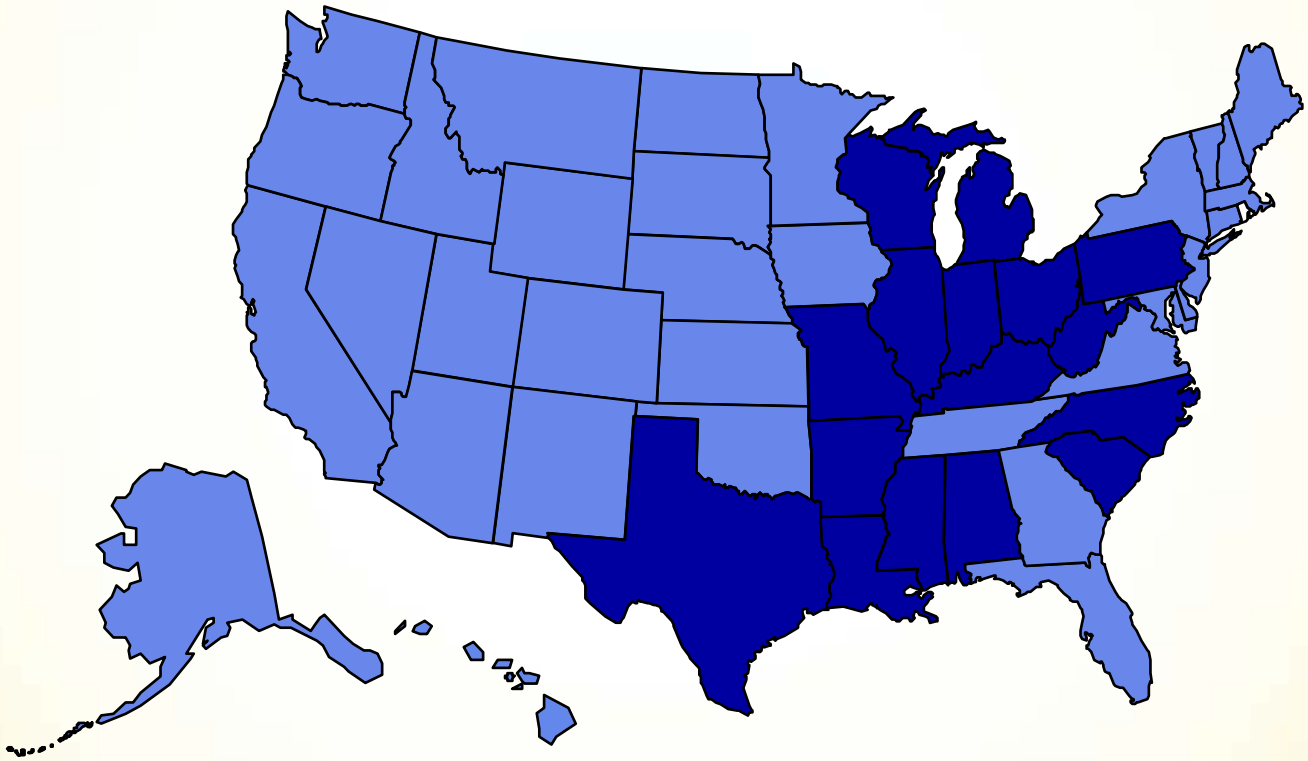

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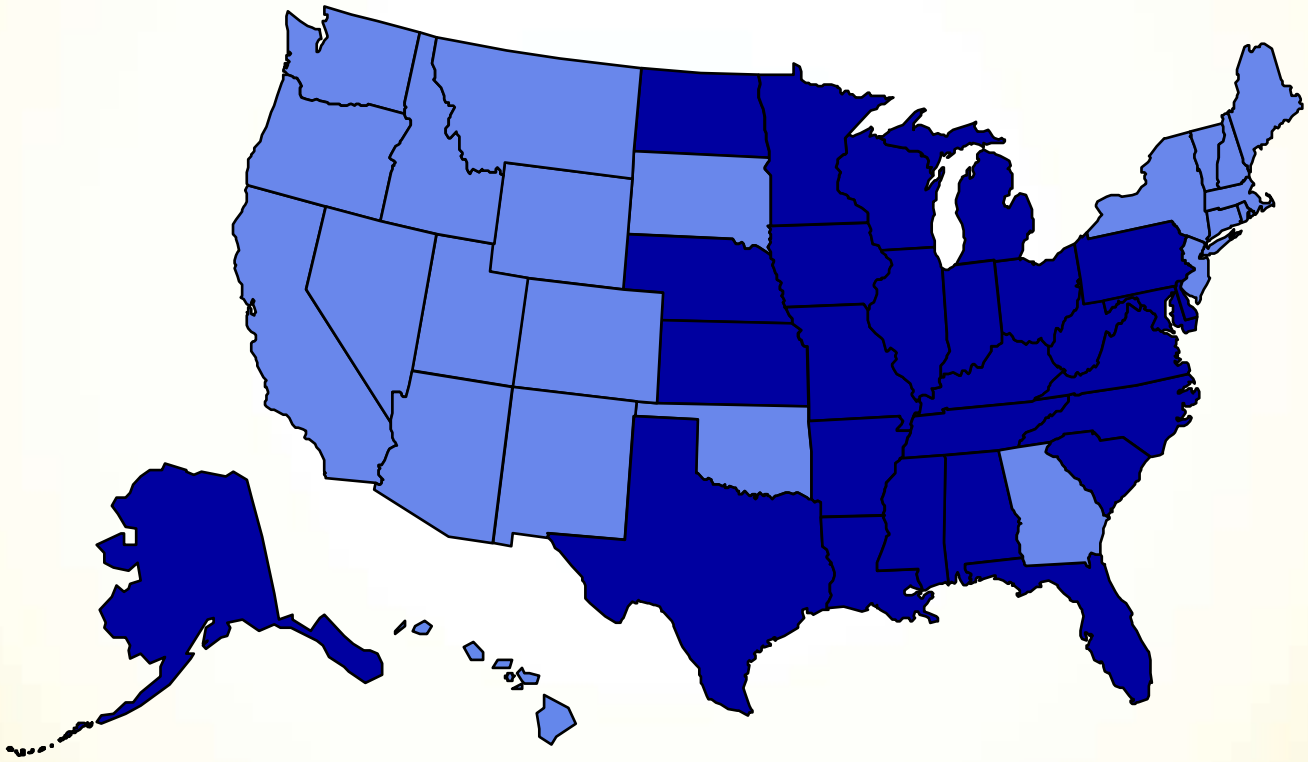

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BRFSS, 1996

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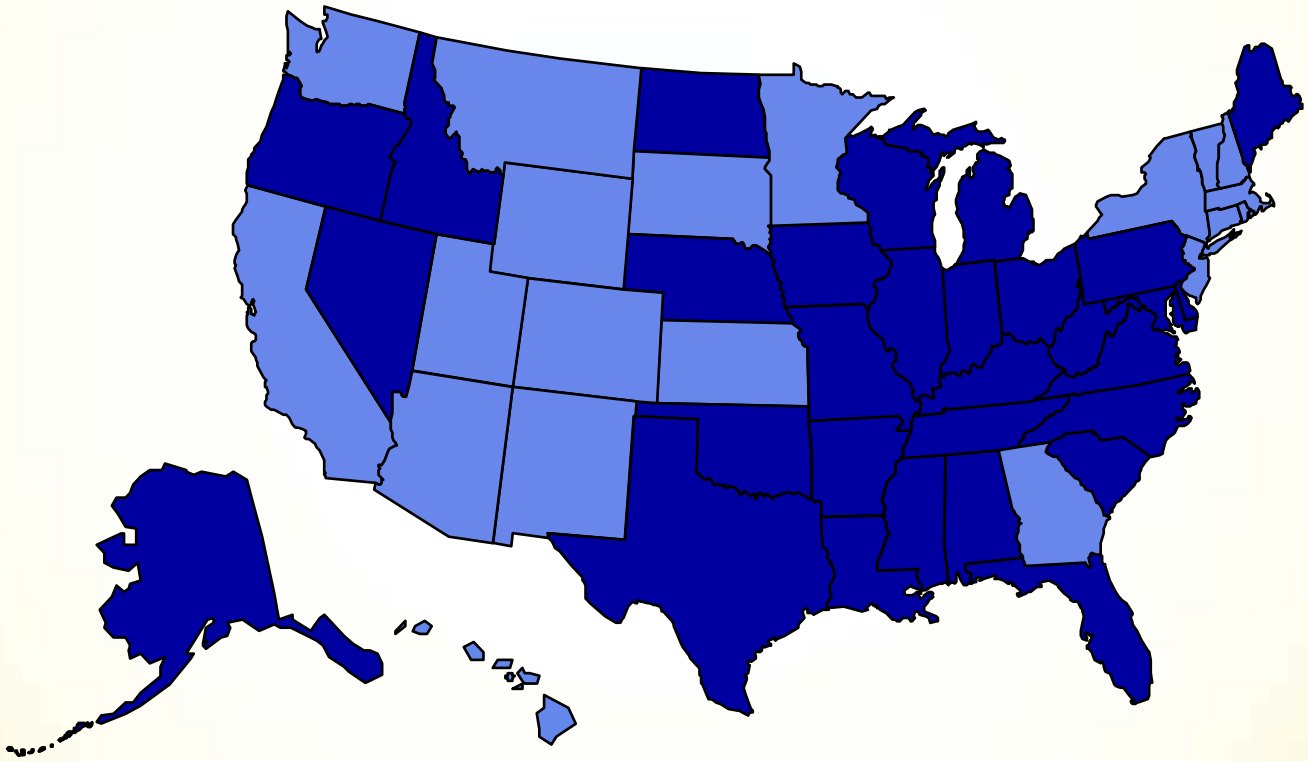

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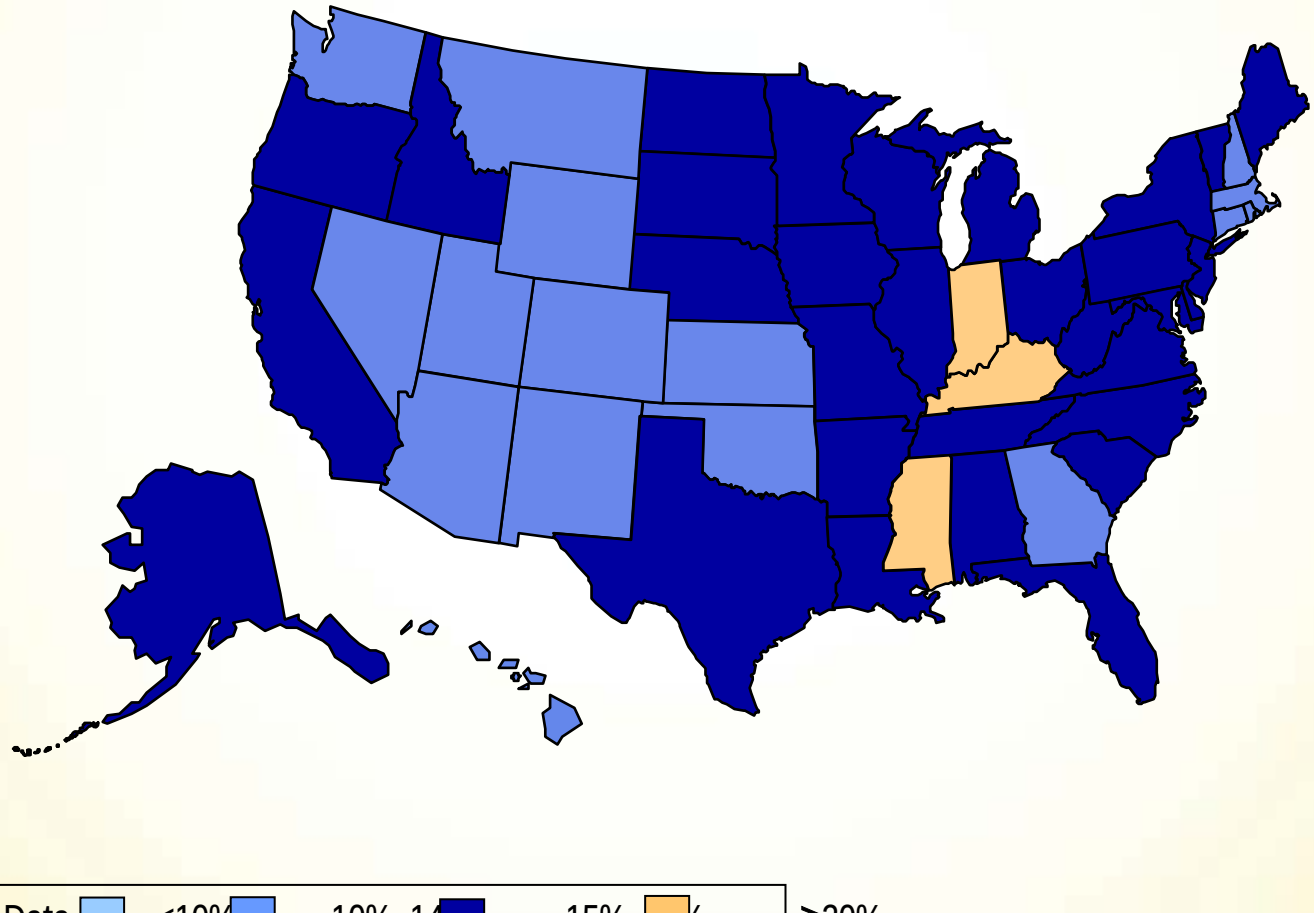

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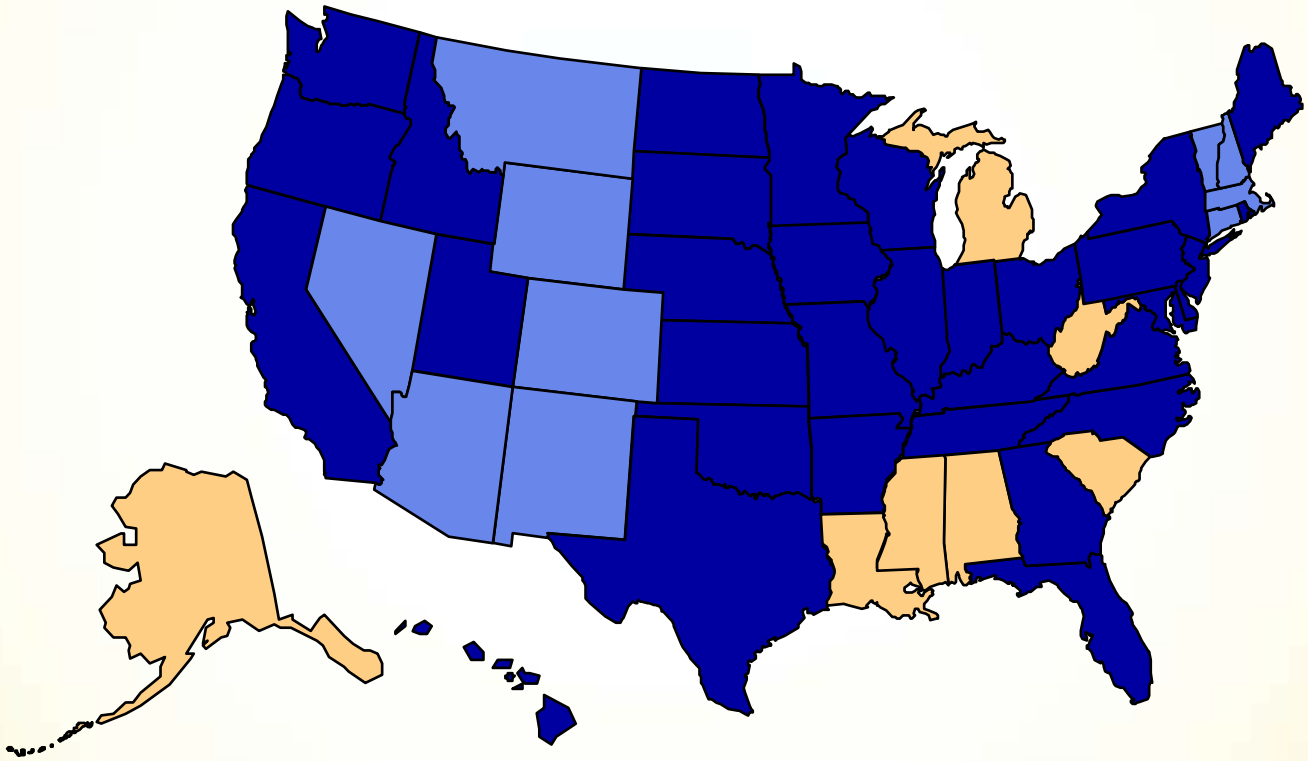

Obesity Trends* Among U.S. Adults

BRFSS, 1999

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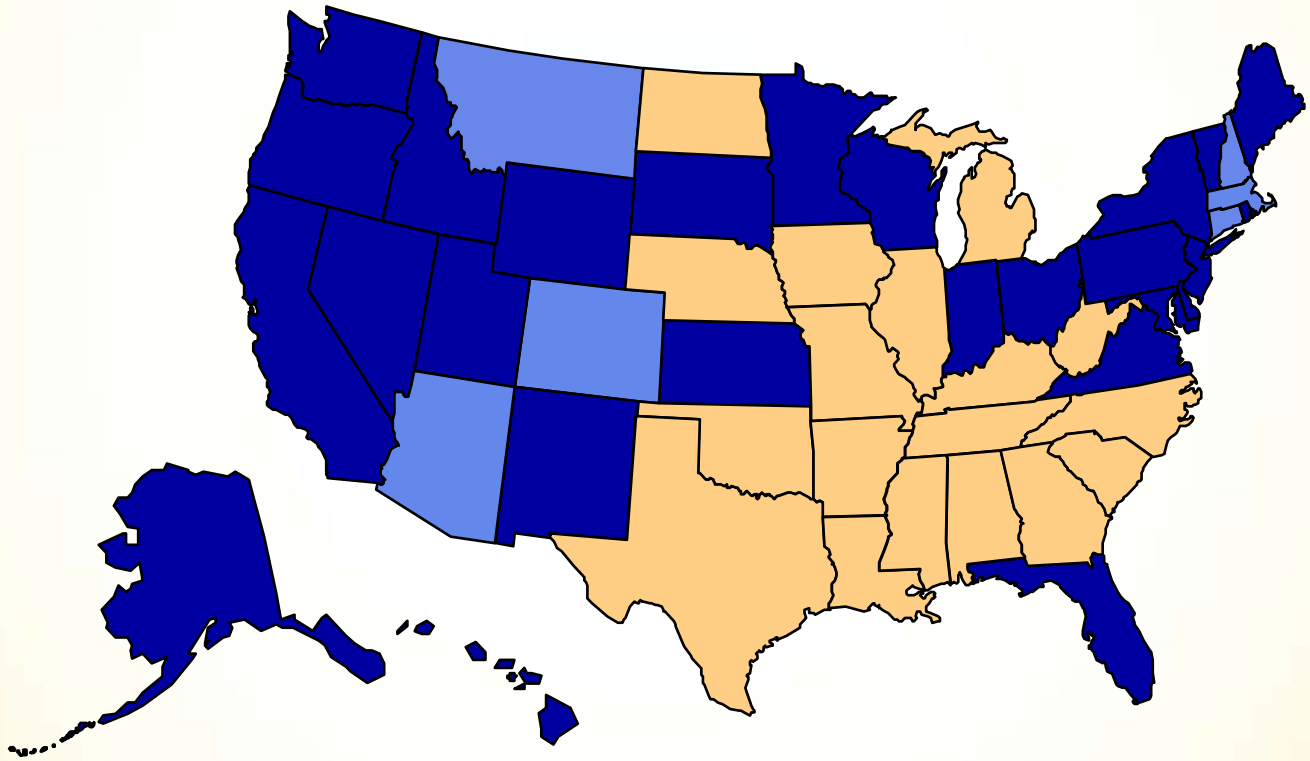
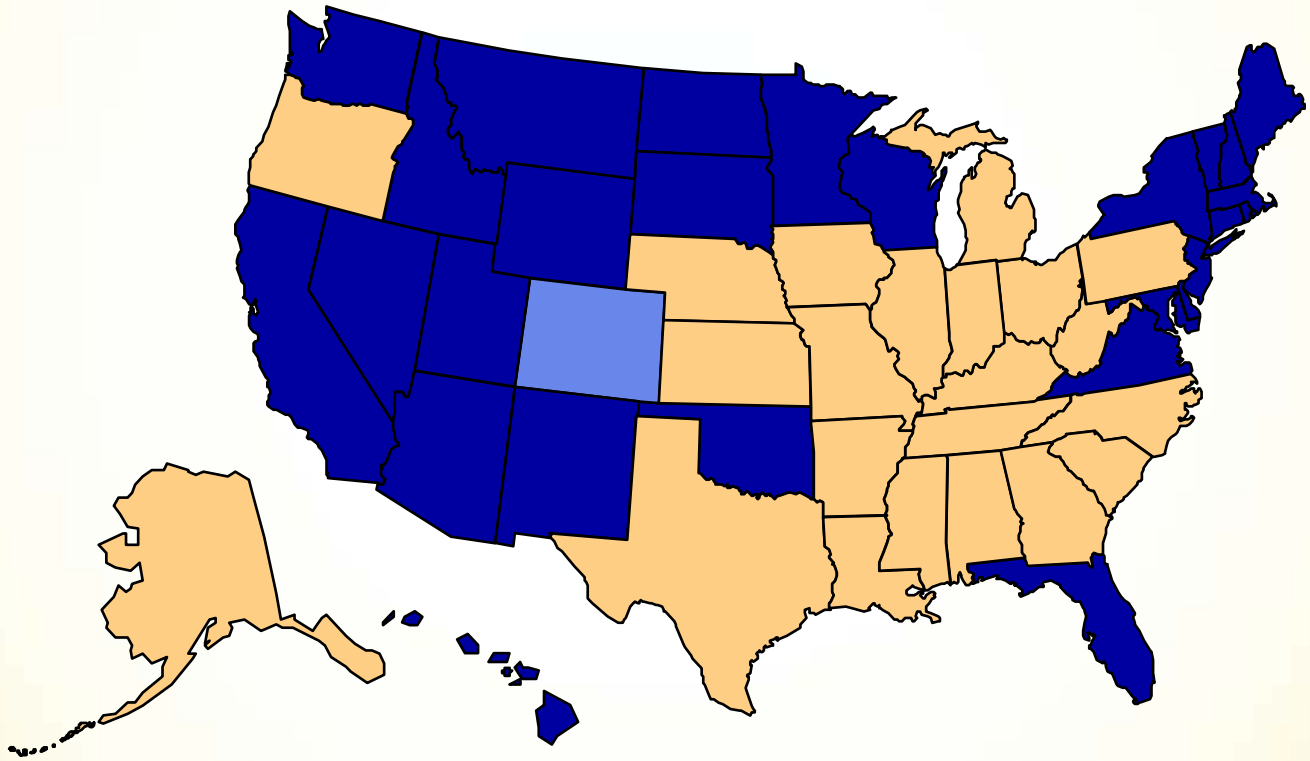


Obesity Trends* Among U.S. Adults

BRFSS, 2000

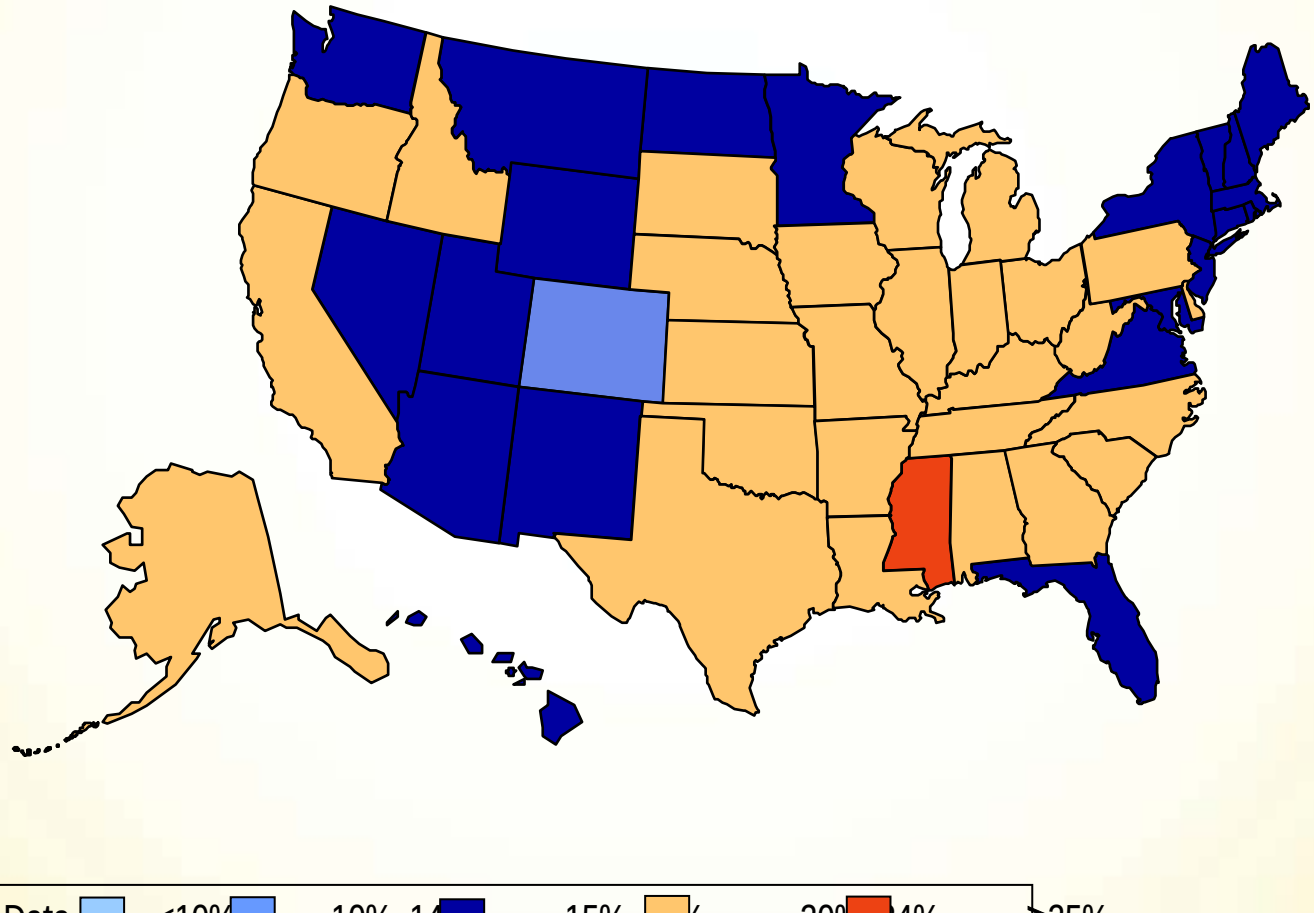
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 2001

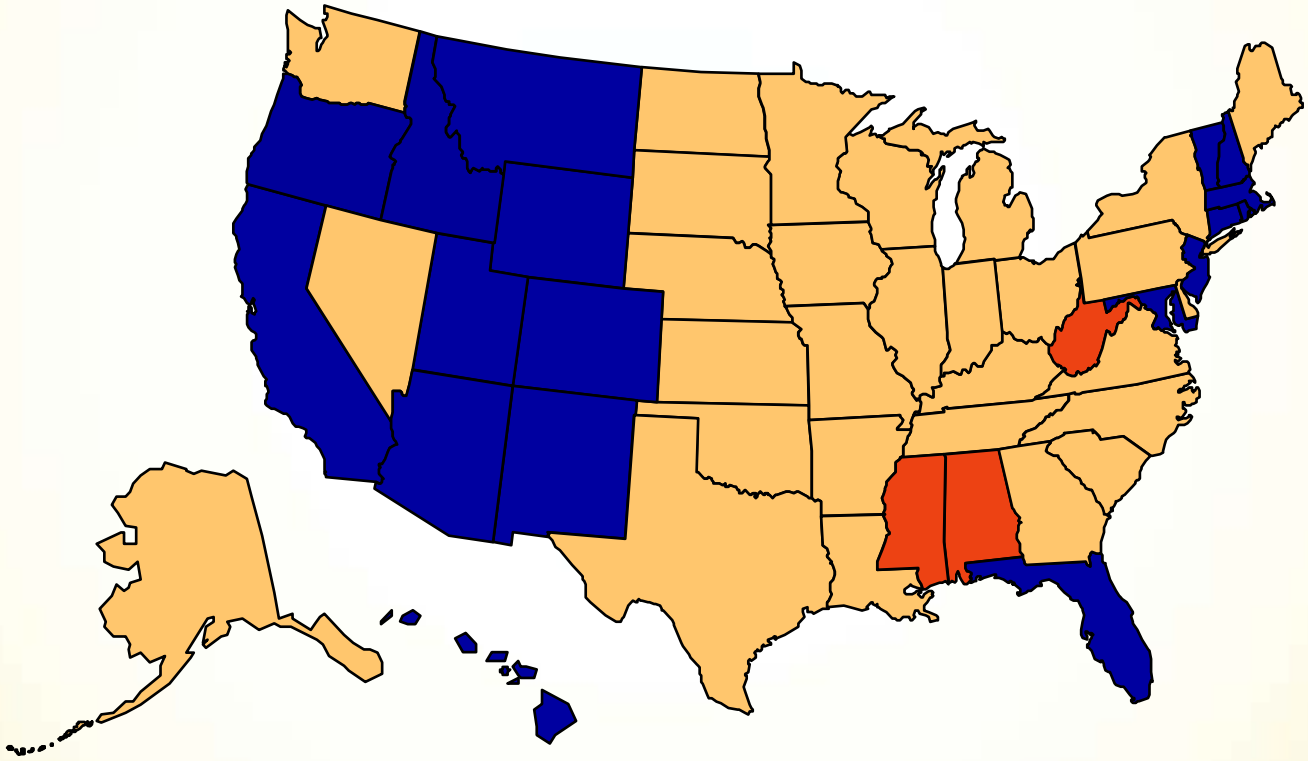
(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends* Among U.S. Adults

BRFSS, 2002

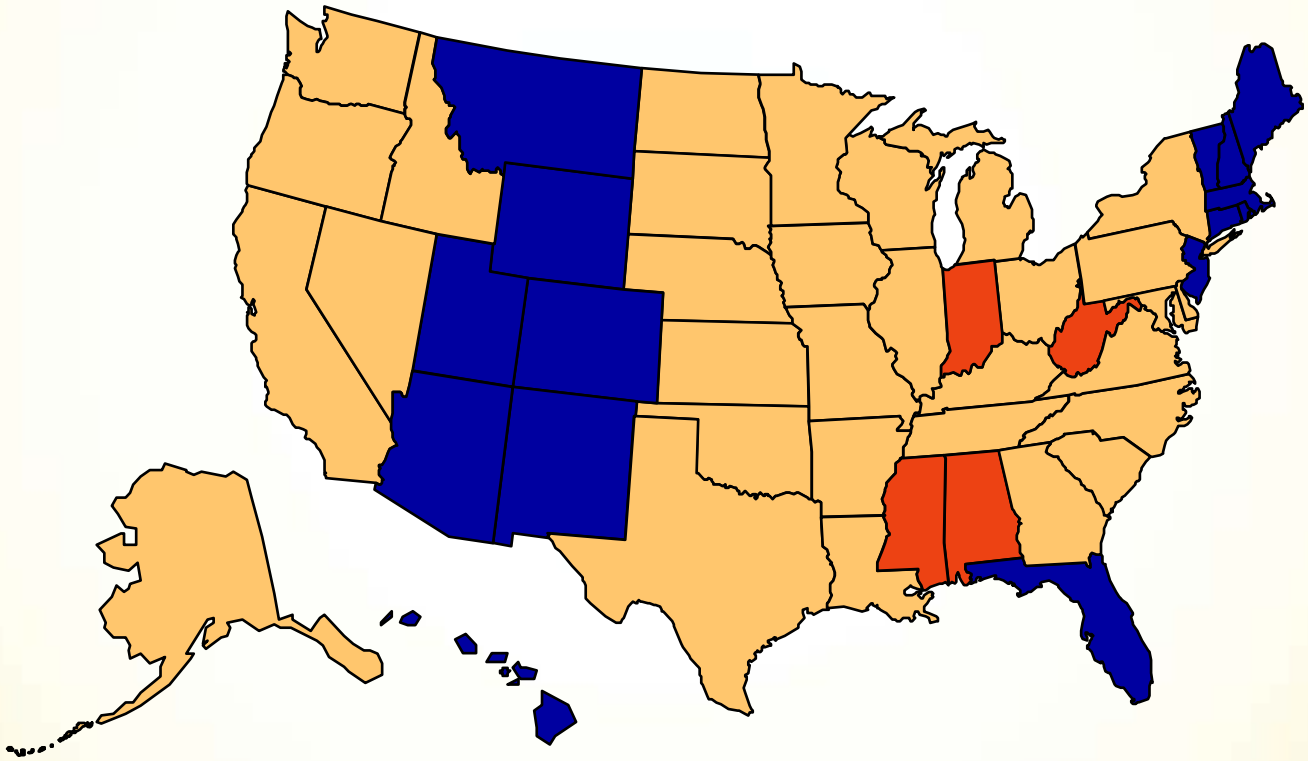
(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends* Among U.S. Adults

BRFSS, 2003

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



Obesity Trends* Among U.S. Adults

BRFSS, 2004

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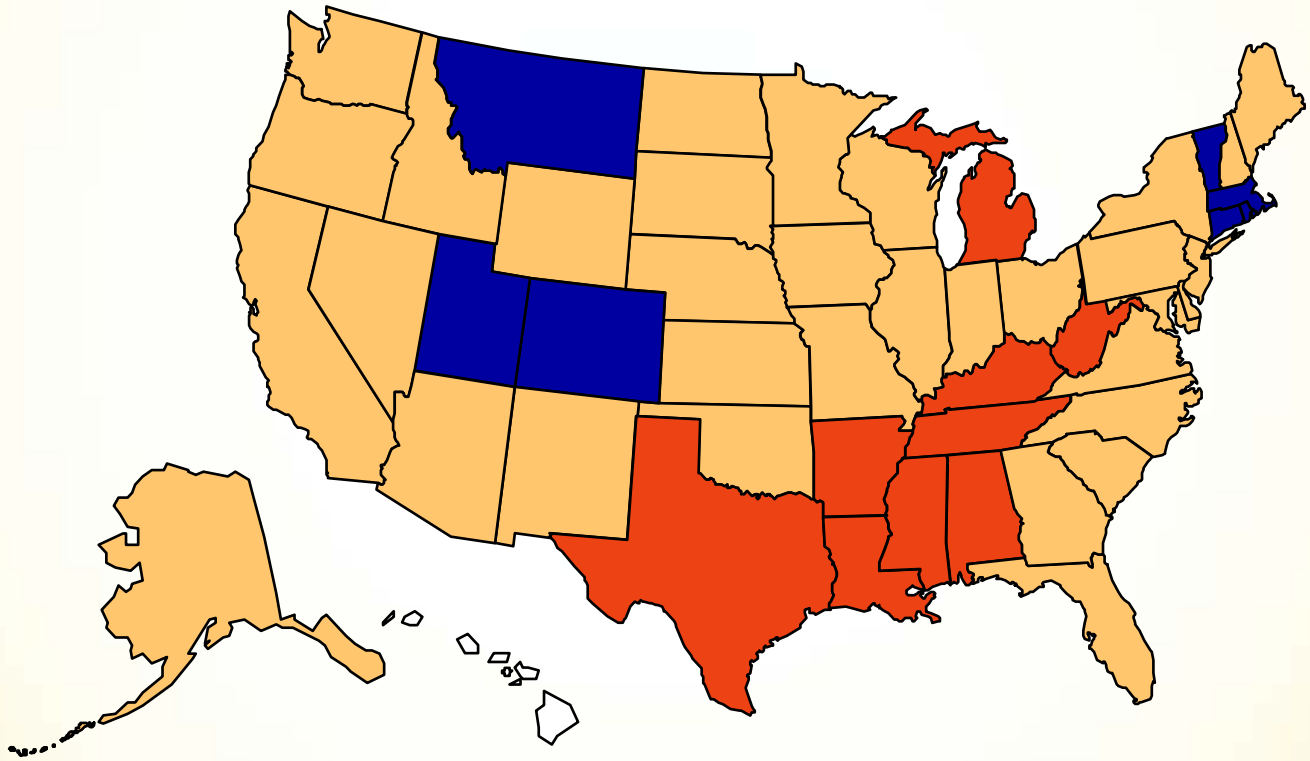

Obesity Trends* Among U.S. Adults

BRFSS, 2005

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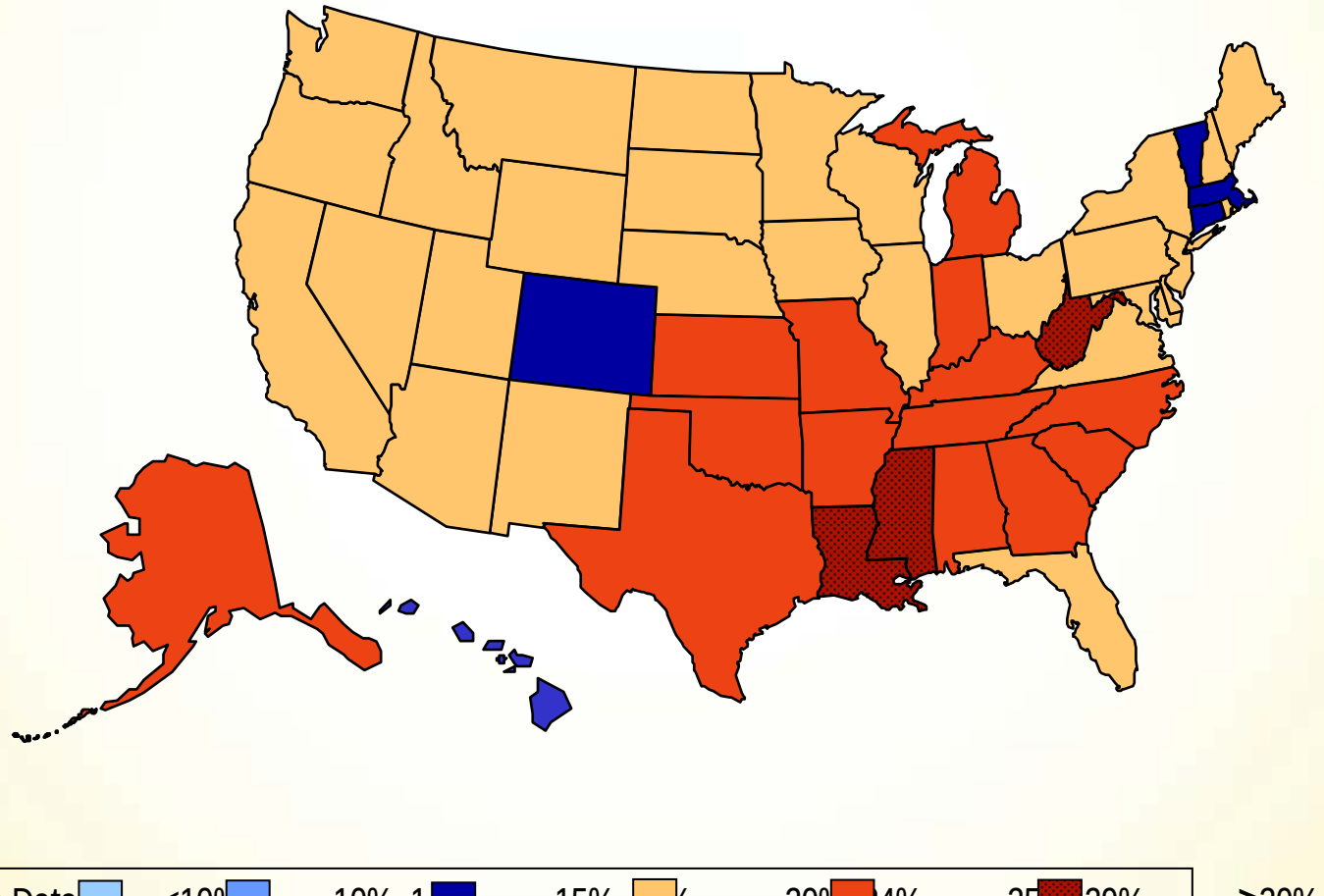
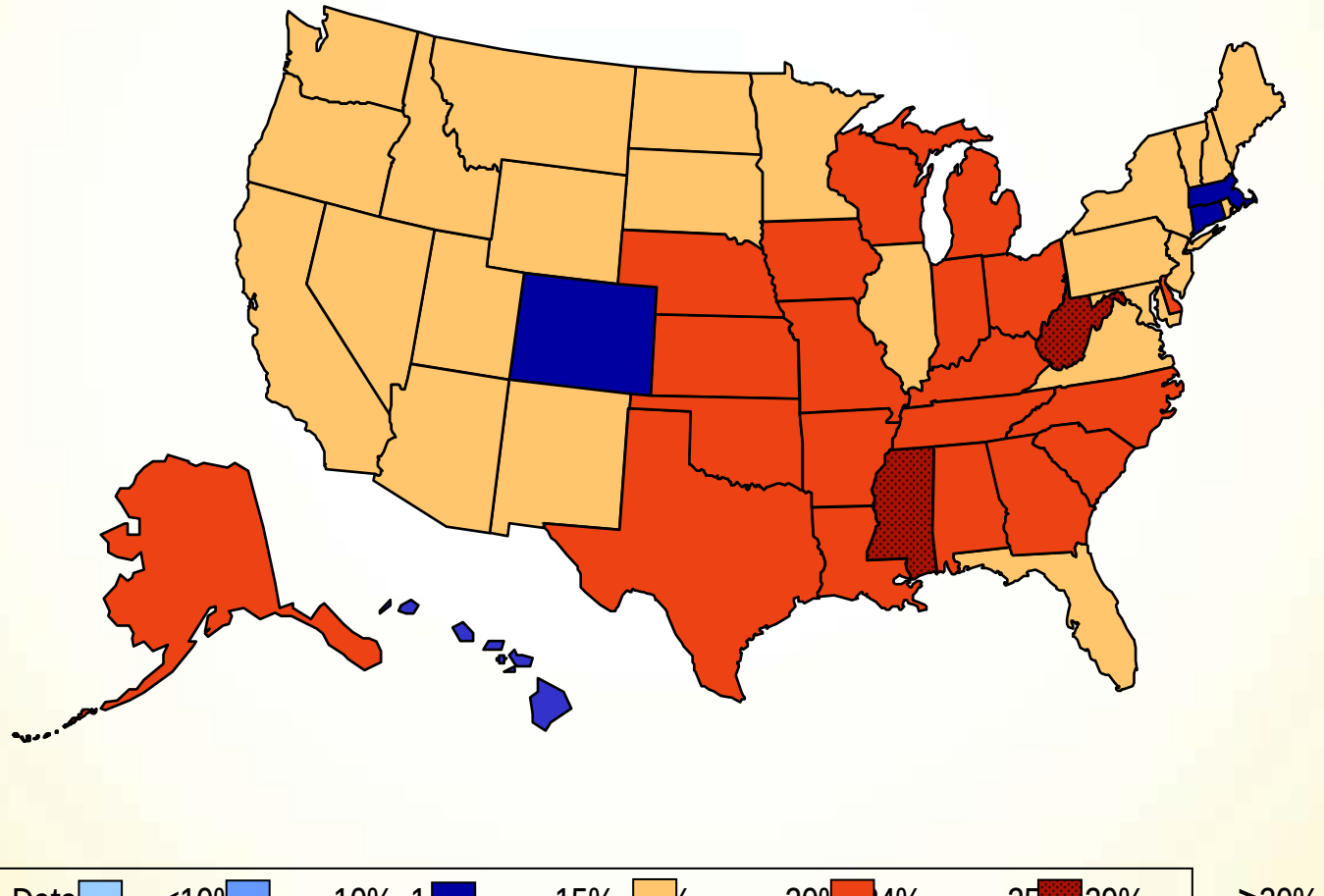


Obesity Trends* Among U.S. Adults

BRFSS, 2006

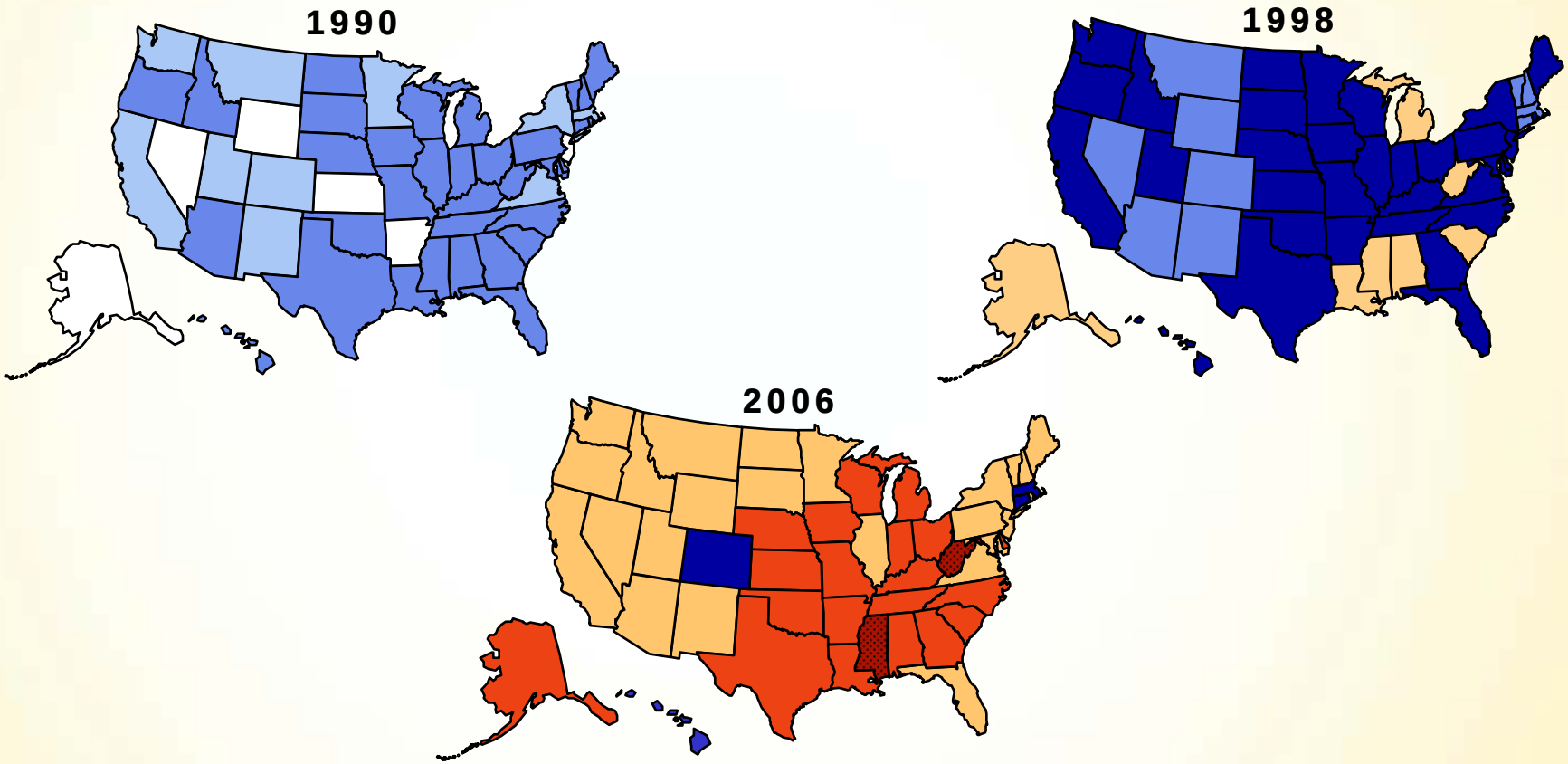
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)



Obesity Trends* Among U.S. Adults

BRFSS, 1990, 1998, 2006

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



Body Composition

Authors	#	SCI	Gender	Age	BMI	SCI %BF	AB % BF	Method
Buchholz, 2003	28	Para	M/F	29	23.5	30.8	22.8	H20 Dil
Bulbanian, 1987	22	Para	M	27.5	22.3	22.4	11.3	Hydro
Clasey, 2006	13	Para	M/F	37	24.3	27.7	NA	4-C
George, 1988	15	P/T	M/F	31	22.3	25.5	20.2	Hydro
Jones, 2003	20	P/T	M	16-52	23.1	27.5	18.1	DXA
Lussier, 1983	2	Para	F	30.5	17.9	30.5	NA	Hydro
Maggioni, 2003	13	Para	M	34	25.7	31.1	20.8	DXA
Spungen, 2000	8	Para	M	40	22.3	33.5	26.3	DXA
Spungen, 2003	66	Tetra	M	40	25.4	36.3	24.2	DXA

Body Habitus After SCI – Routine BMI Tables

BMI (Population Guidelines)	Males				Females			
	U.S. Men[34]	All SCI Men	Tetra		U.S. Women[34]	All SCI Women	Tetra	
Recommended < 25	29.2%	39.3%	37.5%	40.5%	38.2%	75.0%		81.8%
Overweight 25.1 – 29.9		49.2%	50.0%	48.6%		16.7%		18.2%
Obesity 30.0 – 39.9	31.1%	11.5%	12.5%	10.8%	33.2%			
Extreme Obesity > 40	2.8%	0%	0%	0%	6.9%	8.3%	100%	
Overweight or Obese	70.8%	60.7%	62.5%	59.5%	61.8%	25%	100%	18.2%

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Groah, 2009

Body Habitus After SCI

- Adjusting for SCI, 74% of the SCI population studied were overweight or obese
- Using standard BMI tables, 59.5% of males and 18.2% of females were overweight or obese

Groah, 2009

Obesity After SCI

- Obesity is at epidemic proportions
- Obesity is due to
  - Obligatory sarcopenia
  - Blunted anabolism
  - Blunted sympathetic NS
  - Positive energy balance
- Obesity is UNDERestimated by BMI in people with SCI

Obesity After SCI

- Obesity mediates
  - Insulin resistance
  - Hypertension
  - Dyslipidemia
  - Thromboembolism
  - Coronary artery disease

Fat is not Benign!

- Adipocytes:
  - Secretes inflammatory mediators
    - Interleukin-6
    - Tumor necrosis factor
  - Secretes fibrinolysis inhibitors
    - Increase thrombus risk
  - Mediates CRP and hsCRP
  - Reduce vasodilation and promote atherogenesis
    - Hypertension
  - Cause insulin resistance

EVALUATING RISK FACTORS PHYSICAL ACTIVITY

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Motivators and Deterrents to Exercise

- 26 adults with SCI were polled from a survey of 596 with SCI
- All were active prior to injury and expressed an interest in being physically active
- 15 exercisers and 11 non-exercisers

Kehn & Kroll, 2008

Motivators and Deterrants to Exercise

- No differences between the groups in age, gender, marital status, education, income, employment, injury level, or completeness
- Duration of injury was associated with exercising
- Barriers to exercise
  - Limited return on investment
  - Time, motivation, lack of knowledge of equipment

Kehn & Kroll, 2008

EVALUATING RISK FACTORS: ATHEROGENIC DYSLIPIDEMIA

National Cholesterol Education Panel Guidelines

- HDL < 40 is abnormal
- LDL 130 – 159 is borderline high
- LDL > 160 is high
- LDL “target” is 100
- Triglyceride 150-199 is borderline high
- Triglyceride < 150 is normal

HDL-C Roles

- HDL-C function includes protection against development of vascular disease
- HDL-C is directly related to insulin sensitivity

HDL-Cholesterol After SCI

- Nonveterans with SCI and matched sedentary controls
  - HDL-C was lower in the SCI population
  - 39 mg/dl vs. 45 mg/dl
- HDL-C and race
  - Caucasians and Latinos with SCI have lower HDL-C than AB controls
  - AA with or without SCI had higher HDL-C when matched on ethnicity and SCI
  - AA with SCI do not have HDL-C levels significantly different from non-SCI AA

Atherogenic Lipid Profile

- Normal total cholesterol
- Normal or elevated LDL
- Normal or elevated triglycerides
- Consistently low HDL
- Significantly elevated TC:HDL ratio

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Bauman, 1992; 1992; 1999; Bostom 1991; Zlotolow 1992

EVALUATING RISK FACTORS INSULIN RESISTANCE

Diagnostic Criteria for Disorders of Carbohydrate Metabolism

	FPG (mg/dL)	OGTT 120 min (mg/dL)
Normal (NGT)	<100	<140
Impaired (IGT)	100*-125	140-199
Diabetic (DM)	≥126	≥200

Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: *Diabetes Care* 20:1183-1197, 1997.
*Updated from 110, *Diabetes Care* 2003

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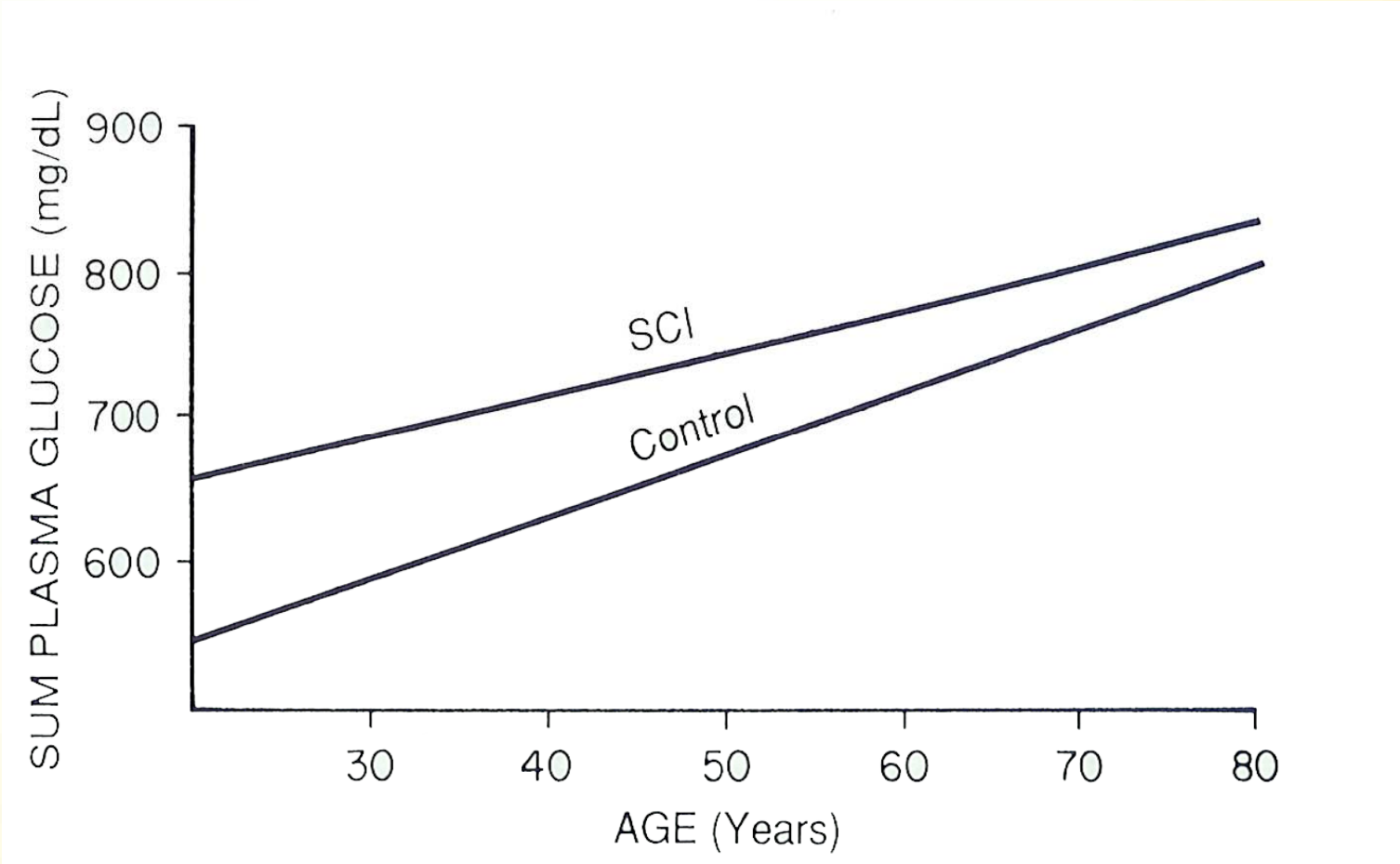
Glucose Intolerance in SCI

- Hyperinsulinemia
  - 34% of SCI had IGT
  - Impaired glucose tolerance
    - 73% complete tetra
    - 44% incomplete tetra
    - 24% complete para
    - 31% incomplete parad

Bauman, 1994; Bauman 1999

Relationship of Age with Glucose Tolerance in Veterans



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Bauman WA and Spungen AM. *Metabolism*. 43: 749-756, 1994

Insulin Resistance

- Peak Glucose correlated with:
  - Highest level of lesion
  - Older age at time of injury
  - Increased TB %fat
- Peak Insulin correlated with:
  - Male gender
  - Increased TB %fat

Bauman WA, Adkins RH, Spungen AM, Waters RL. The effect of residual neurological deficit on oral glucose tolerance in persons with chronic spinal cord injury. *Spinal Cord*. 1999; 37: 765-771.

CHO Metabolism Summary

- Increased prevalence of IGT and DM
- The more severe the neuro impairment, the worse the CHO metabolism
- Peak Glucose is independently related to %fat, neuro, age at time of injury, and male gender
- Hyperinsulinemia: >50% Tetra and >30% Para
- OGTT ↔ to diagnose early disease (IGT, mild DM, and hyperinsulinemia)

ALL OF THESE FACTORS RELATE TO CARDIOMETABOLIC RISK

Cardiometabolic Risk

- Central obesity (WC)
  - European men >94cm (37”)
    - Or US men > 102 cm (40”)
  - European women > 80 cm (31.5”)
    - Or US women > 88 cm (34.5”)
  - Plus any 2 of the following:
    - TG >= 150 md/dl
    - Low HDL-C
    - High BP
    - Fasting glucose >= 100 md/dl

Metabolic Syndrome after SCI

- N=487 vets with SCI
- Mean age 55.2 yrs; 48.7% tetra
- 63.4% HDL < 40
- 56.5% BMI > 25 kg/m2
- 56.5 % htn
- 44.8% IDF metabolic syndrome
- 37% dyslipidemia

Castillo, 2007 (JSCM)

EVALUATING RISK FACTORS INFLAMMATION

Evidence that CRP is a Strong Predictor of Future Cardiac Events

- CRP has strong prognostic value for detection of 1st vascular events, even after adjustment for all traditional CVD risks[1]
- hs-CRP levels are strongly correlated with future CHD mortality.[2] Baseline hs-CRP levels are significantly higher among men who subsequently sustain MI.[3]
- Combined modeling with hs-CRP and Total Cholesterol (TC) improved forecasting of future MI by TC alone.[3]
- Meta-analyses consistently find CRP a significant CVD risk marker.

[1] Women's Health Study (WHS), [2] Multiple Risk Factor Intervention Trial (MRFIT), [3] Physicians Health Study (PHS)

Relative Risk Categories for hs-CRP Levels: Two Stratification Methods

Low	< 1 mg/dL
Moderate	1-3 mg/dL
High	> 3 mg/dL

Disease Risk Stratification by Cutpoints of the American Heart Association – Centers for Disease Control and Prevention

Quintile of TC:HDL-C ratio			Quintile of hs-CRP (mg/L)				
			1	2	3	4	5
	Male	Female	< 0.7	0.7-1.1	1.2-1.9	2.0-3.8	3.9-15
1	< 3.4	< 3.4	1	1.2	1.4	1.7	2.2
2	3.4-4.0	3.4-4.1	1.4	1.7	2.1	2.5	3.0
3	4.1-4.7	4.2-4.7	2.0	2.5	2.9	3.5	4.2
4	4.8-5.5	4.8-5.8	2.9	3.5	4.2	5.1	6.0
5	> 5.5	>5.8	4.2	5.0	6.0	7.2	8.7

RR's

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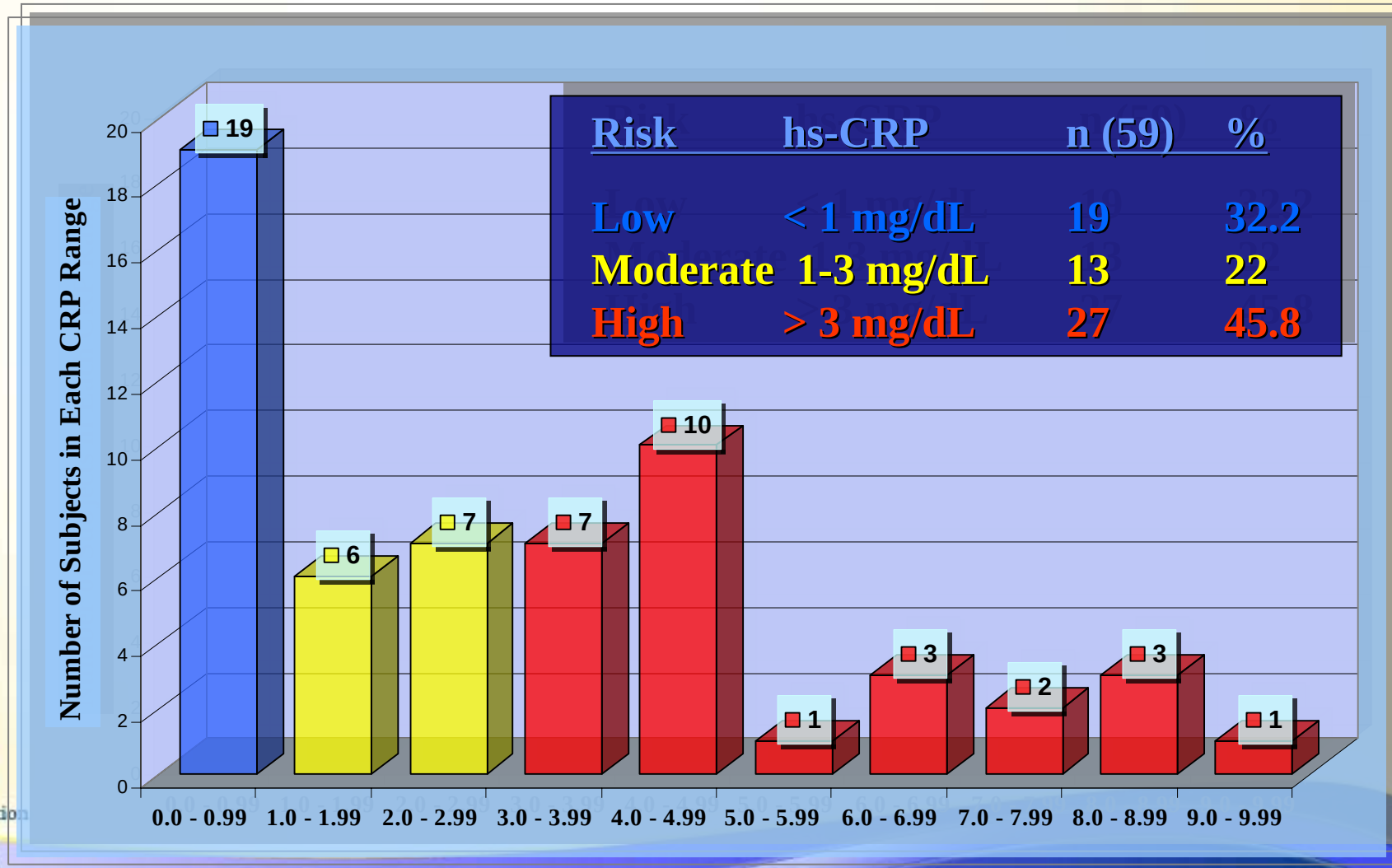
Combined: Physicians Health Study and Women's Health Study RCTs

CVD Risk Based Upon Tertiles of hs-CRP:
45.8% of Population at 2x or Greater Risk



Risk	hs-CRP	n (59)	%
Low	< 1 mg/dL	19	32.2
Moderate	1-3 mg/dL	13	22
High	> 3 mg/dL	27	45.8

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Homocysteine and C-Reactive Protein Summary

- 44% of SCI patients studied in a large sample had a homocysteine level associated with an increased mortality ratio
- 62% of SCI pts studied had moderate to high CRP levels
- When applying risk assessment methods (Physicians Health Study), 78%, 56%, and 46% had double, triple or quadruple the normal risk

Ridker, 2000; Nash, 2006

CARDIOMETABOLIC RISK CLUSTERING

Framingham Risk Scores

- 121 (97 male, 24 female)
- Age 18-73 (mean 37 years)
- Duration of injury (mean 11 years)
- Paraplegia (N=73) and tetraplegia (N=48)

Groah, 2010

CMR Clustering

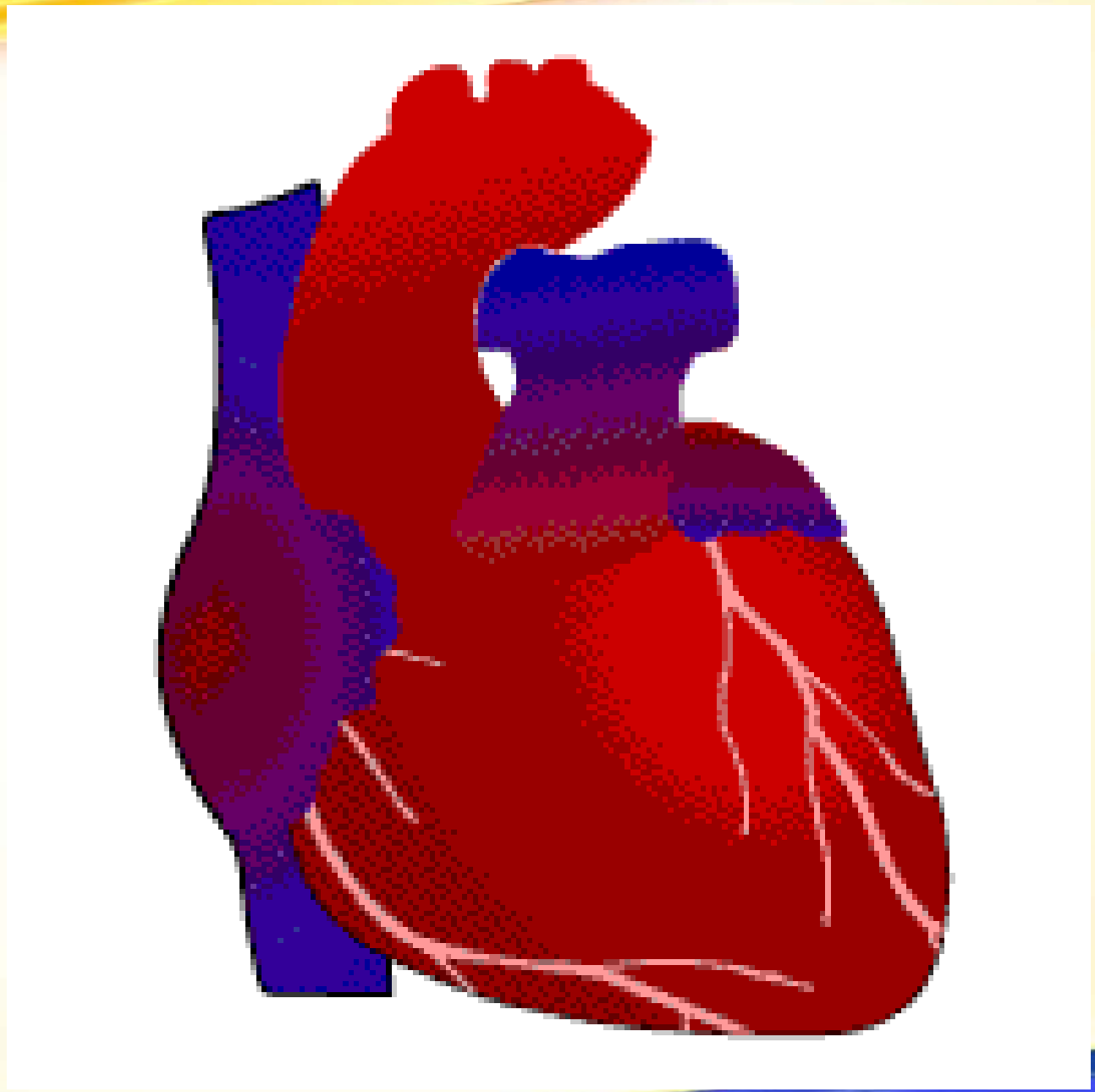
- 90%, 8.3% and 1.7% were in low, medium and high risk groups
- Most prevalent CMR
  - Overweight/obesity (74%)
  - Elevated LDL (64%)
  - Low HDL (53%)
  - Elevated sBP (33%)
  - Elevated TC (30%)
- In addition, TG, FI, HgbH1c, HOMA-IR were all associated with Framingham Risk

Groah, 2010

CMR Clustering

- Paraplegia vs. Tetraplegia
  - Paras had higher sBP
  - Tetras had higher 2-hour glucose
  - Tetras had higher 2-hour insulin

Groah, 2010



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SUMMARIZING THE EVIDENCE

AHRQ Evidence Report

- Carbohydrate and Lipid Disorders After SCI

AHRQ Evidence Report Results

- "the quality of evidence regarding the prevalence, impact, and outcomes of carbohydrate and lipid disorders in adults with chronic SCI is weak. Evidence is limited by relatively few studies, small sample size, lack of appropriate control groups, failure to adjust for known confounding variables, and variation in reported outcomes.

AHRQ Evidence Report Results

- "However, the existing evidence does not indicate that adults with SCI are at a markedly greater risk for carbohydrate and lipid disorders or subsequent cardiovascular morbidity and mortality than AB adults. Body mass index is not reliable for assessing body composition, especially percent body fat, in adults with SCI. There are no high quality studies evaluating the impact of exercise, diet, or pharmacologic therapies on these disorders."

AHRQ Evidence Report Conclusions

- "Evidence does not support using different thresholds to define or treat abnormal lipid and carbohydrate measures or to incorporate other markers to assess risk (e.g. insulin resistance, impaired fasting glucose, or impaired glucose tolerance) for individuals with SCI compared with AB adults. Due to physiologic differences between adults with SCI and AB individuals, caution may be required when extrapolating data."

ACHIEVING BEST PRACTICE: WHAT DOES THE CLINICIAN DO WHEN A SYSTEMATIC REVIEW DEVIATES FROM PREVIOUSLY HELD BELIEFS OR EVIDENCE?

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Systematic Review Appraisal

Evidential Hierarchy(s) ***Levels of Evidence***

Category I: Evidence from at least one properly randomized controlled trial.

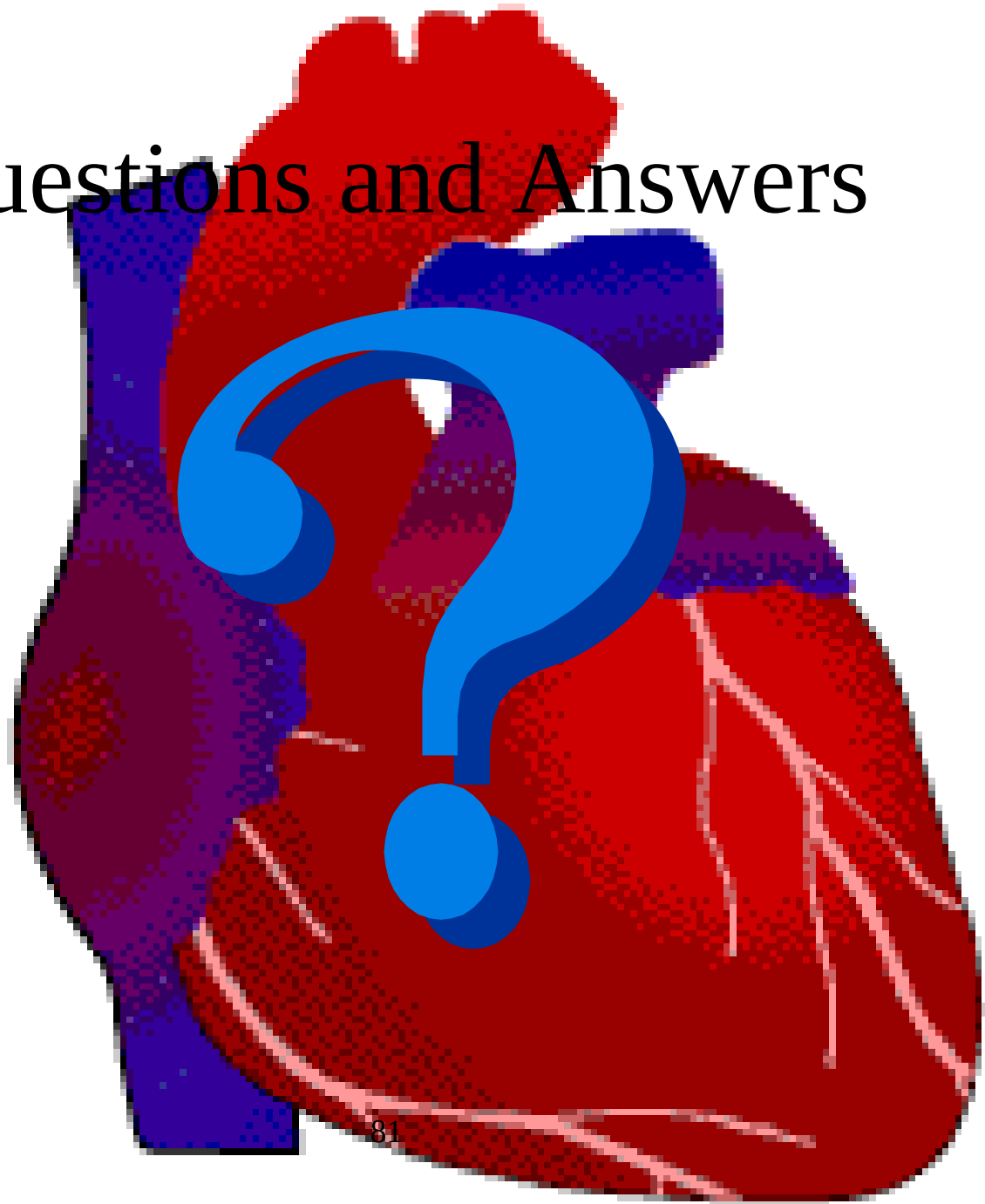
Category II-1: Evidence from well-designed controlled trials without randomization.

Category II-2: Evidence from well-designed cohort or case-control analytic studies

Category II-3: Evidence from multiple times series with or without intervention and uncontrolled

Category III: Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Questions and Answers



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