

# **Fueling the Disease:**

## **The Pandemic of Obesity and Diabetes**

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# Disclosures

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Echosens, Inventiva, Janssen, Nordic, Novo Nordisk,  
Poxel, Target-NASH, Zydus.

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Madrigal, Merck, Novo Nordisk, Pfizer, Poxel, Terns  
Pharma.

**Stock/Shareholder:** None

**Other:** None

# The Pandemics of Obesity and Diabetes

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## 1. Obesity

- Magnitude of the problem
- Obesity vs. diabetes as a risk factor

## 2. Diabetes

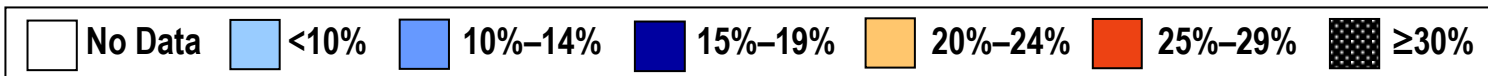
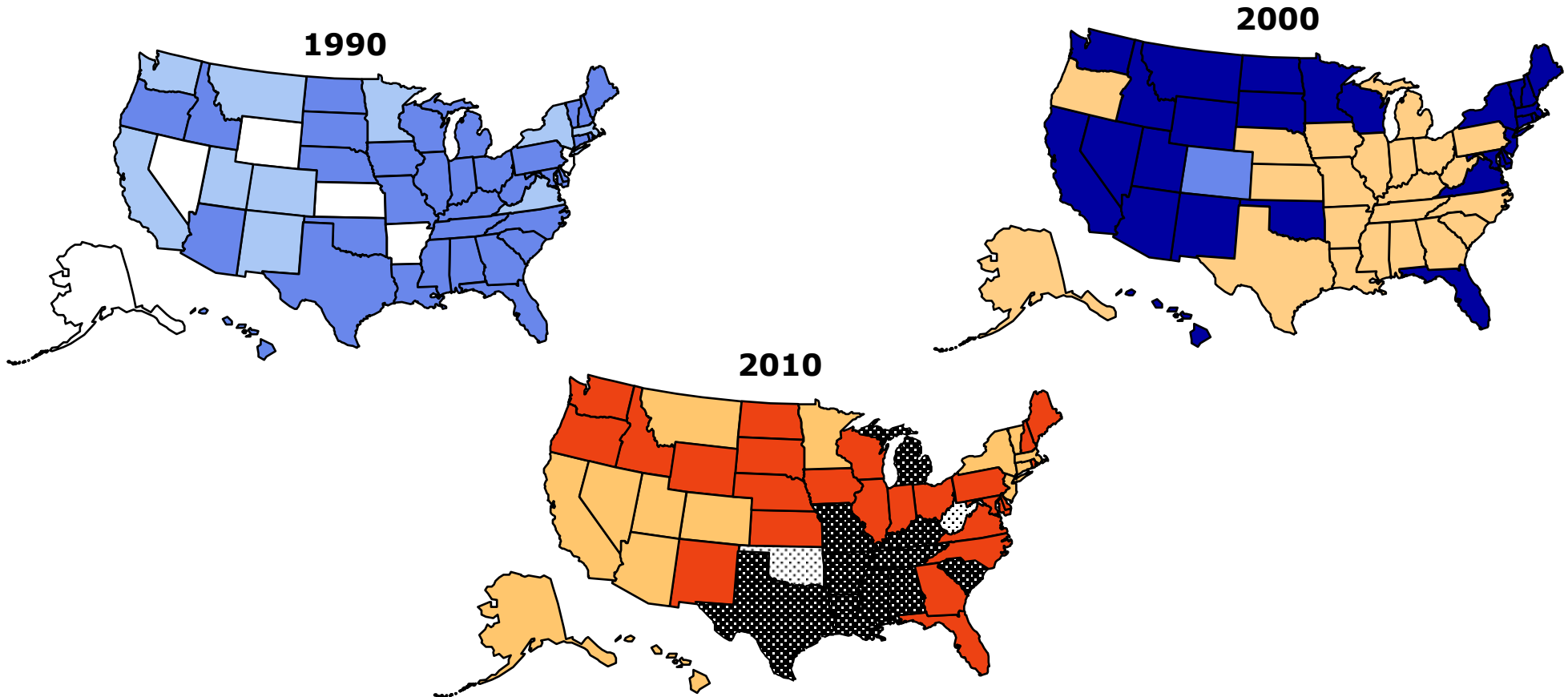
- Why diabetes is the problem
- Recent developments

## 3. The endocrinologist's view

- Why endocrinologists don't want to hear about NASH
- Some hope: 2021-2022 developments

# Obesity Trends\* Among U.S. Adults BRFSS, 1990, 2000, 2010

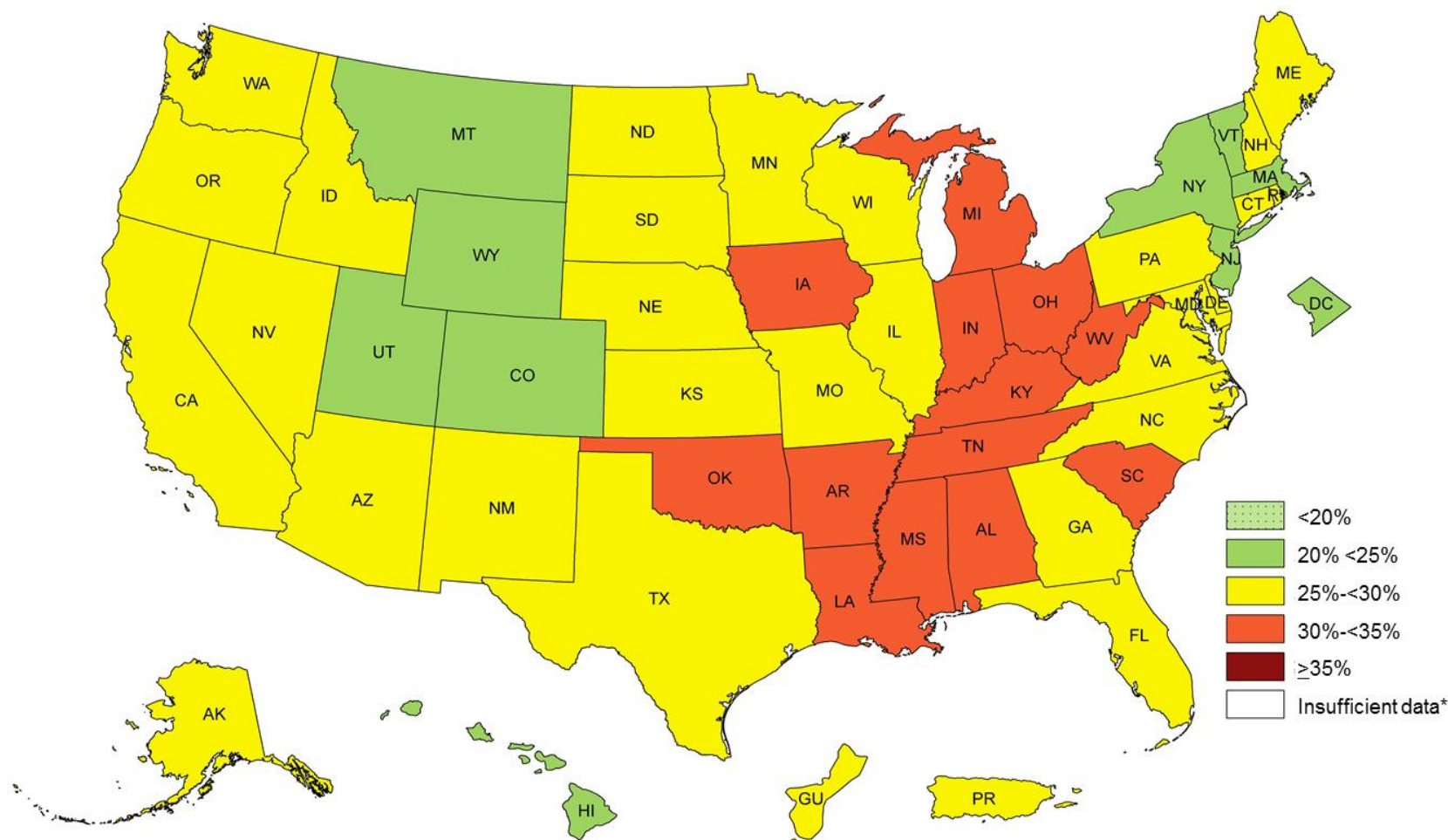
(\*BMI  $\geq 30$ , or about 30 lbs. overweight for 5'4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

# Prevalence<sup>¶</sup> of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2012

<sup>¶</sup> Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

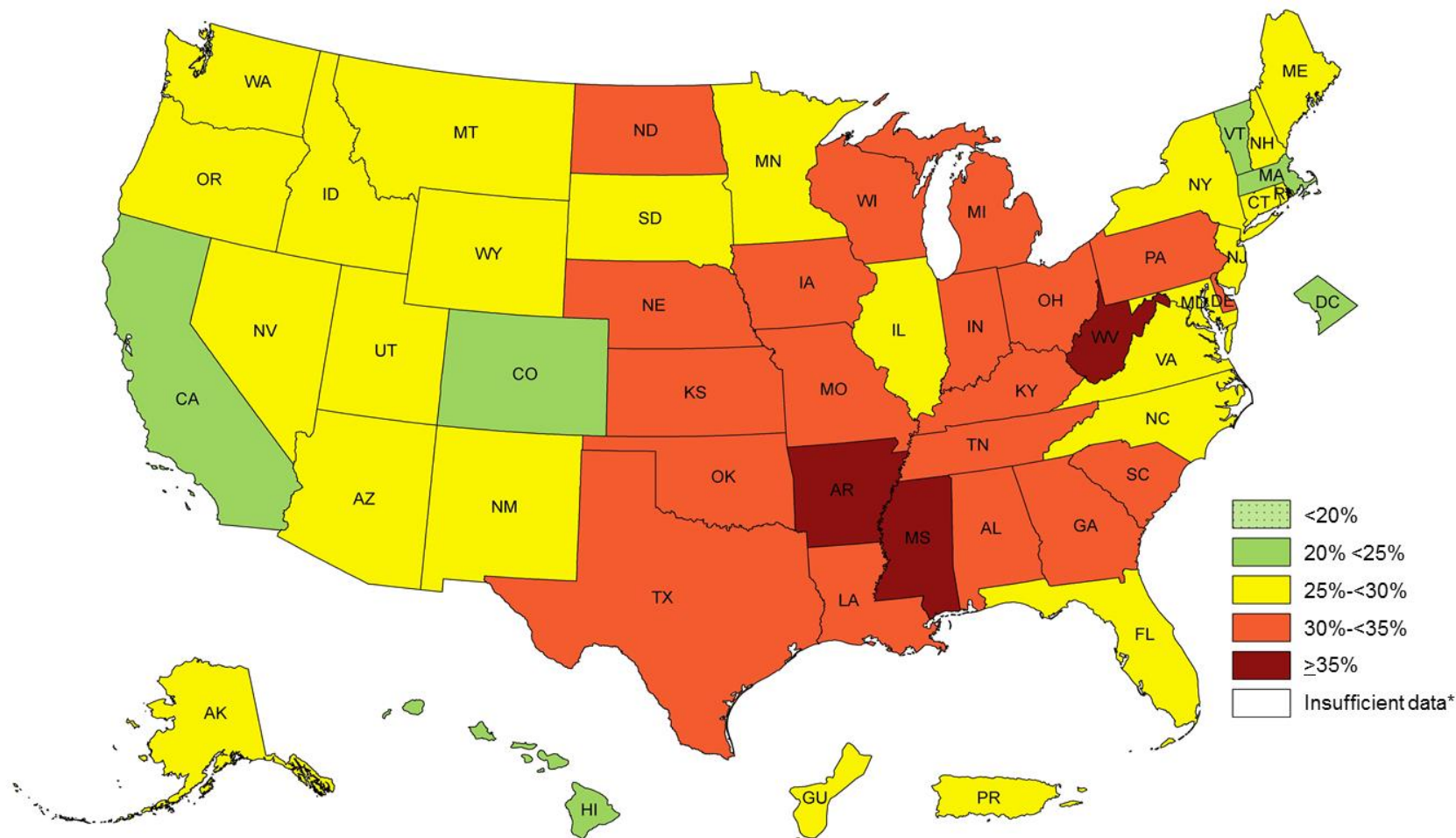


\*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.



# Prevalence<sup>1</sup> of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014

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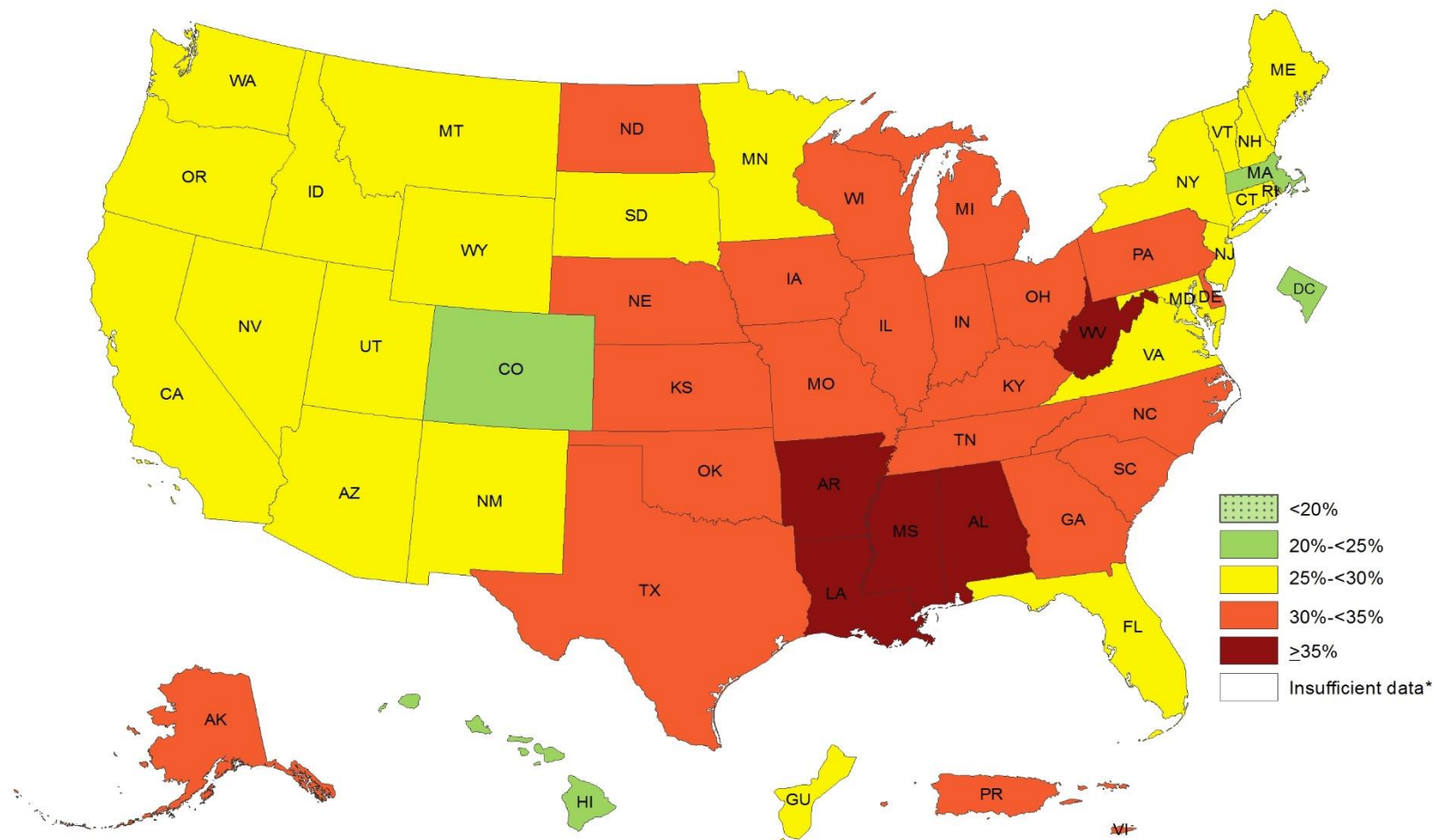


\*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.



# Prevalence<sup>1</sup> of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2016

<sup>1</sup> Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

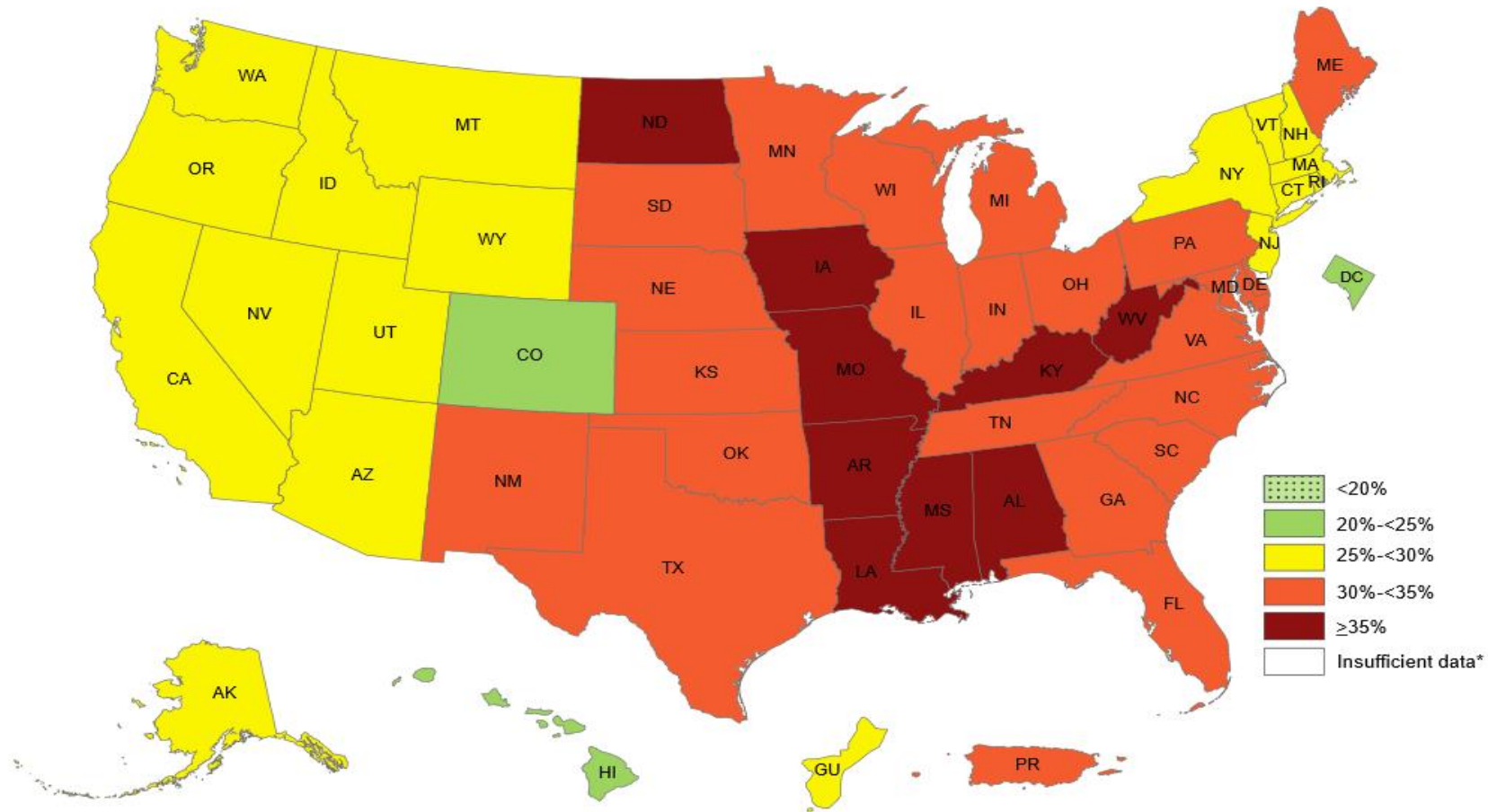


\*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.



# Prevalence<sup>†</sup> of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2018

<sup>†</sup> Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



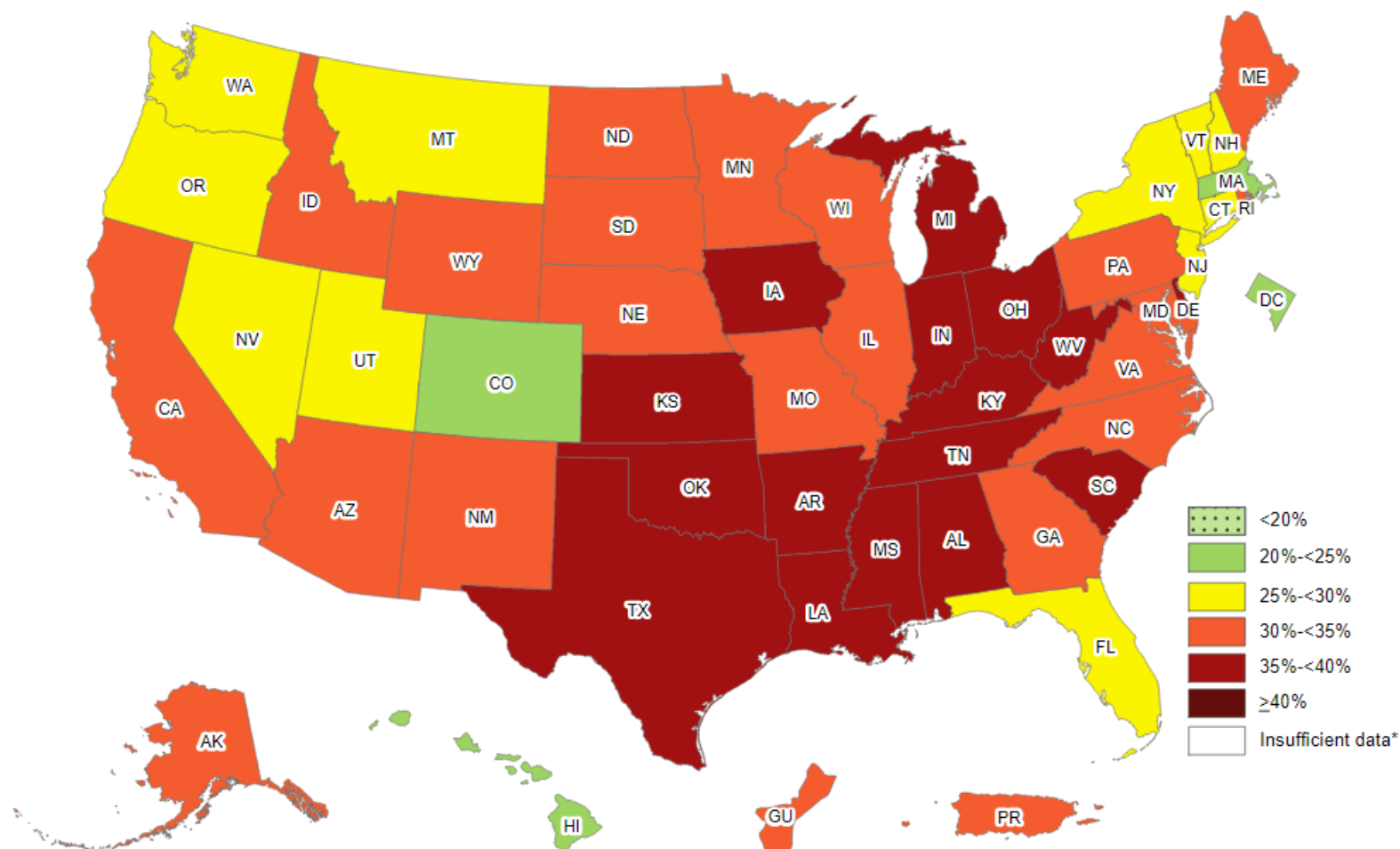
\*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.





# Prevalence<sup>†</sup> of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2020

<sup>†</sup> Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



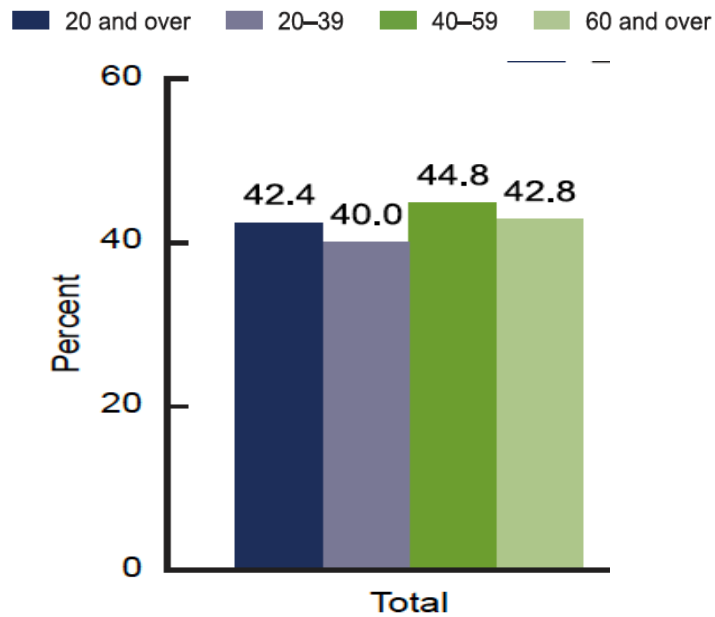
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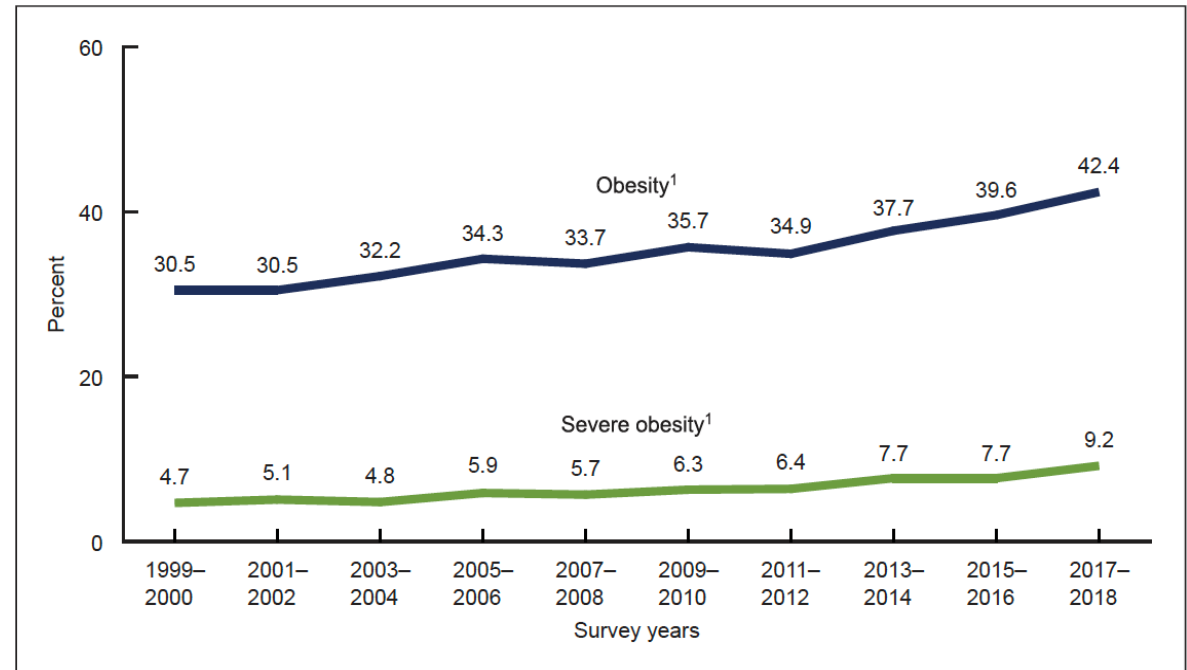
# Trends in age-adjusted obesity and severe obesity prevalence among adults aged 20 and over

United States, 1999–2000 through 2017–2018

## Prevalence of obesity in the United States

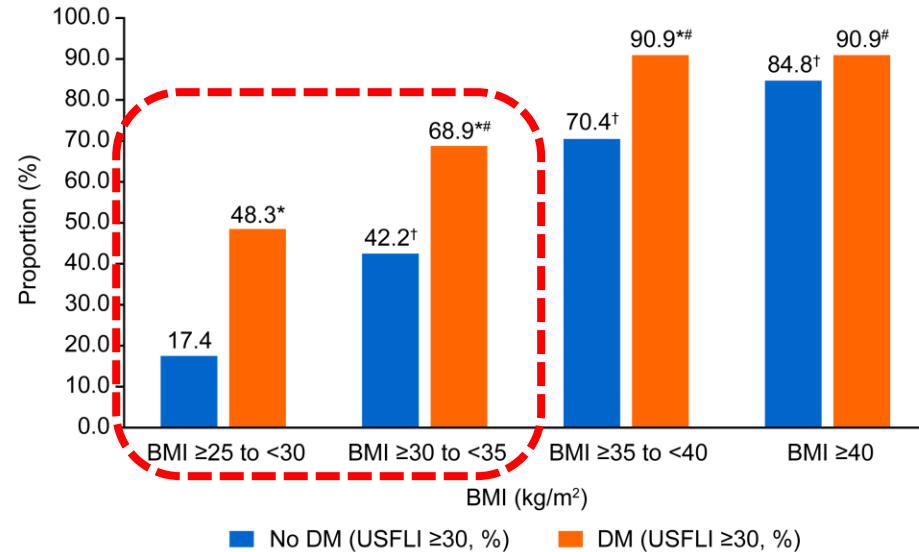


## Trends in obesity and severe obesity prevalence

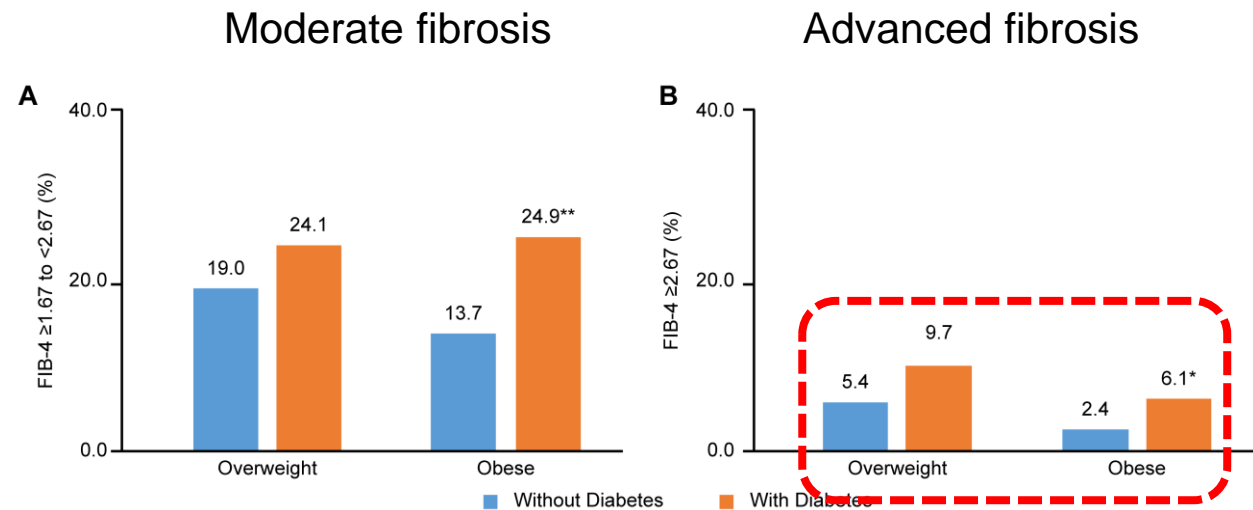


# Steatosis and Fibrosis in Individuals with Overweight or Obesity, with or without Diabetes

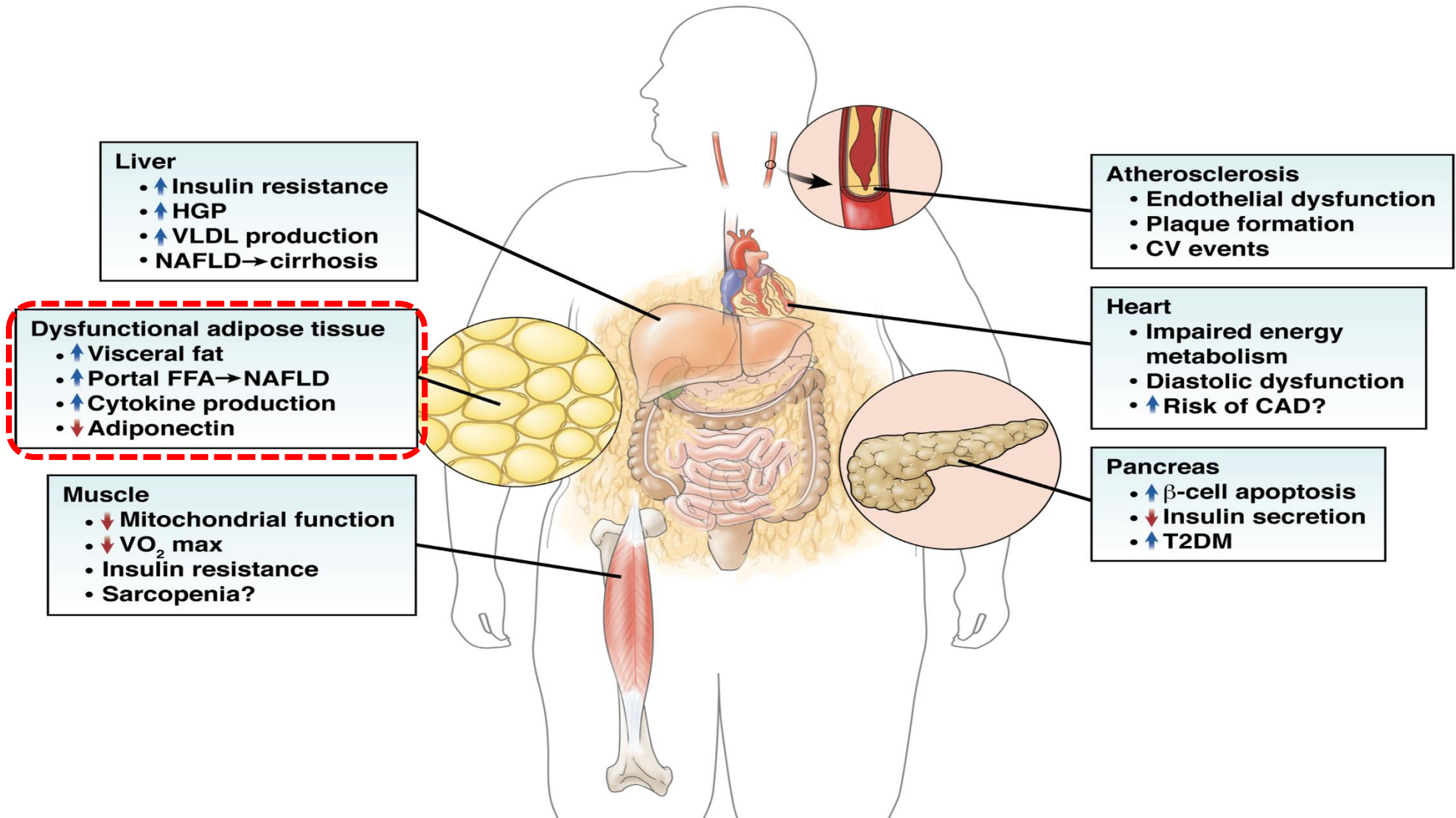
Prevalence of Steatosis:  
Role of obesity vs. diabetes



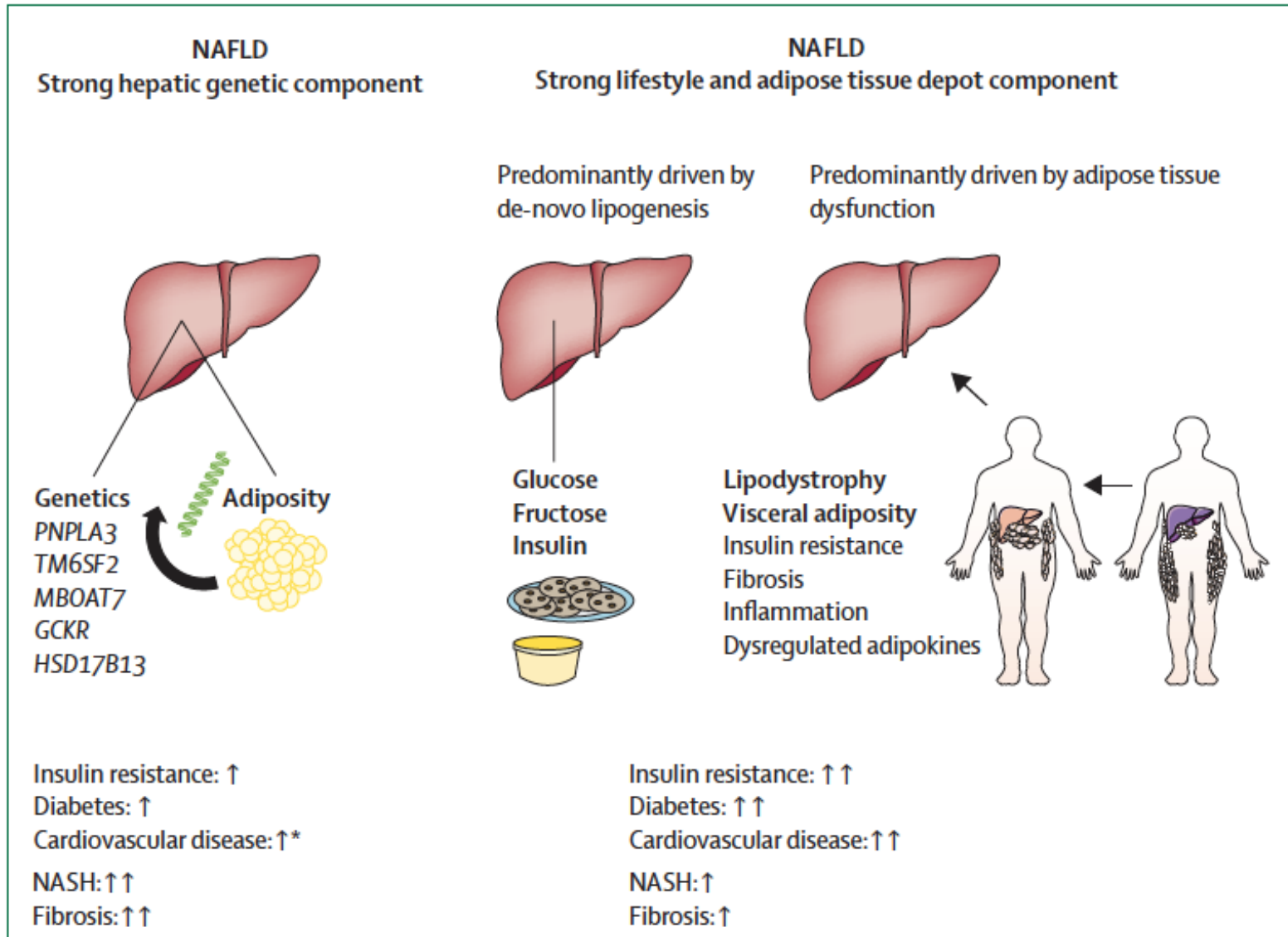
Prevalence of Fibrosis:  
Role of obesity vs. diabetes



# Insulin Resistance and Lipotoxicity in NAFLD



# Major Pathways Inducing NAFLD: Association with IR, T2DM, CVD, NASH and Fibrosis



# The Pandemics of Obesity and Diabetes

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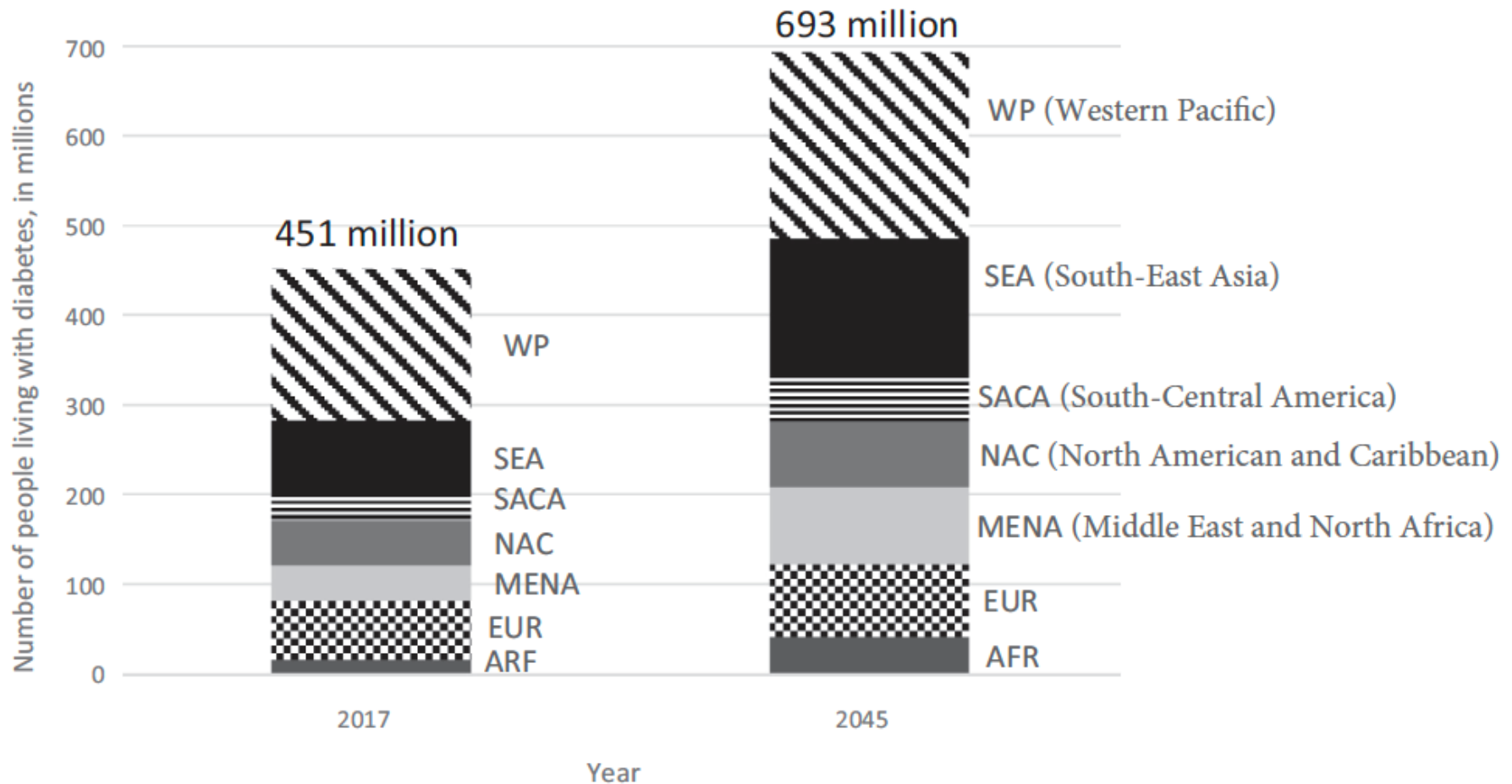
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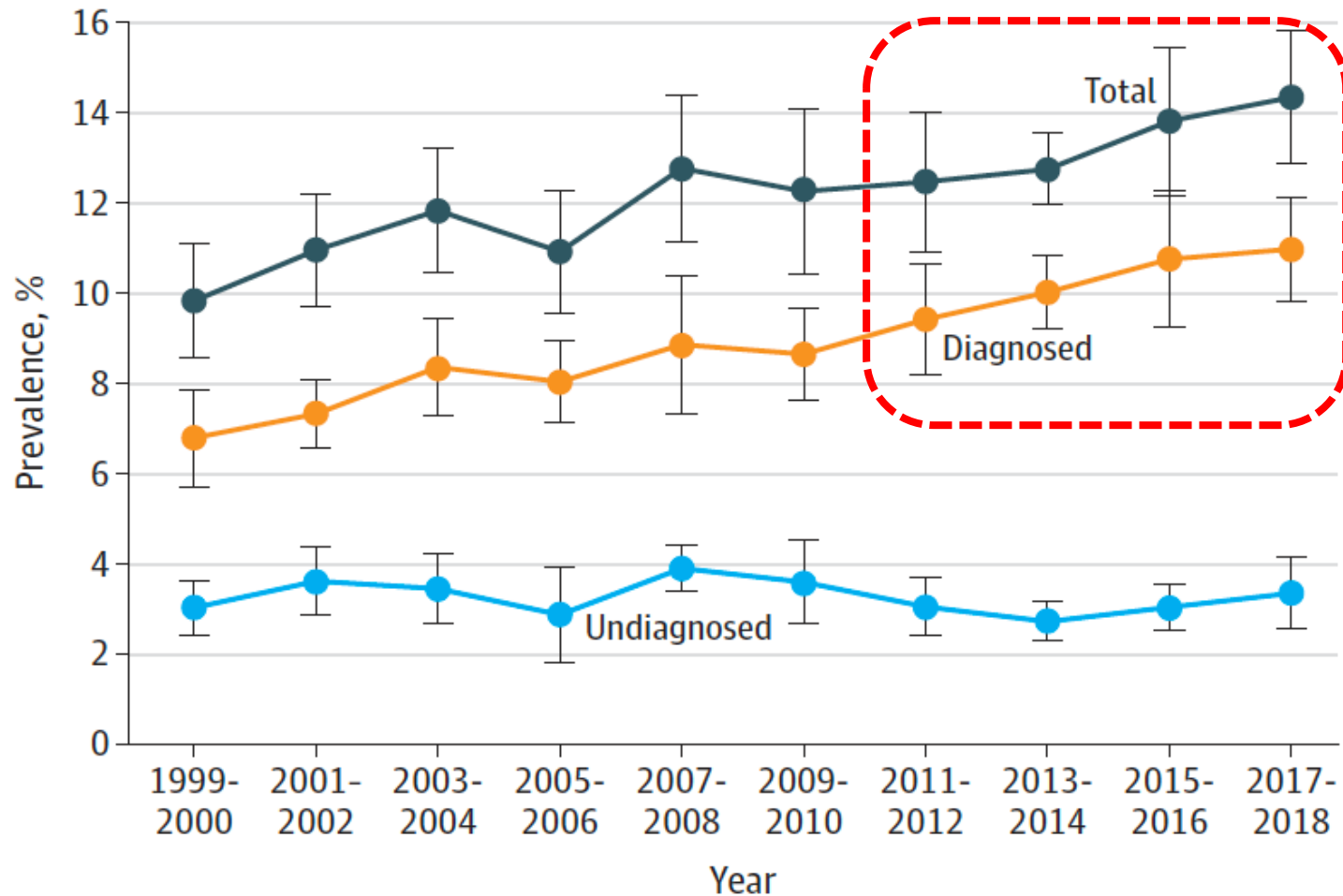
- Why diabetes is the problem
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# Global estimates of diabetes prevalence for 2017 and projections for 2045



# Trends in Prevalence of Diabetes in U.S. Adults, 1999–2018

**A** Diagnosed, undiagnosed, and total diabetes



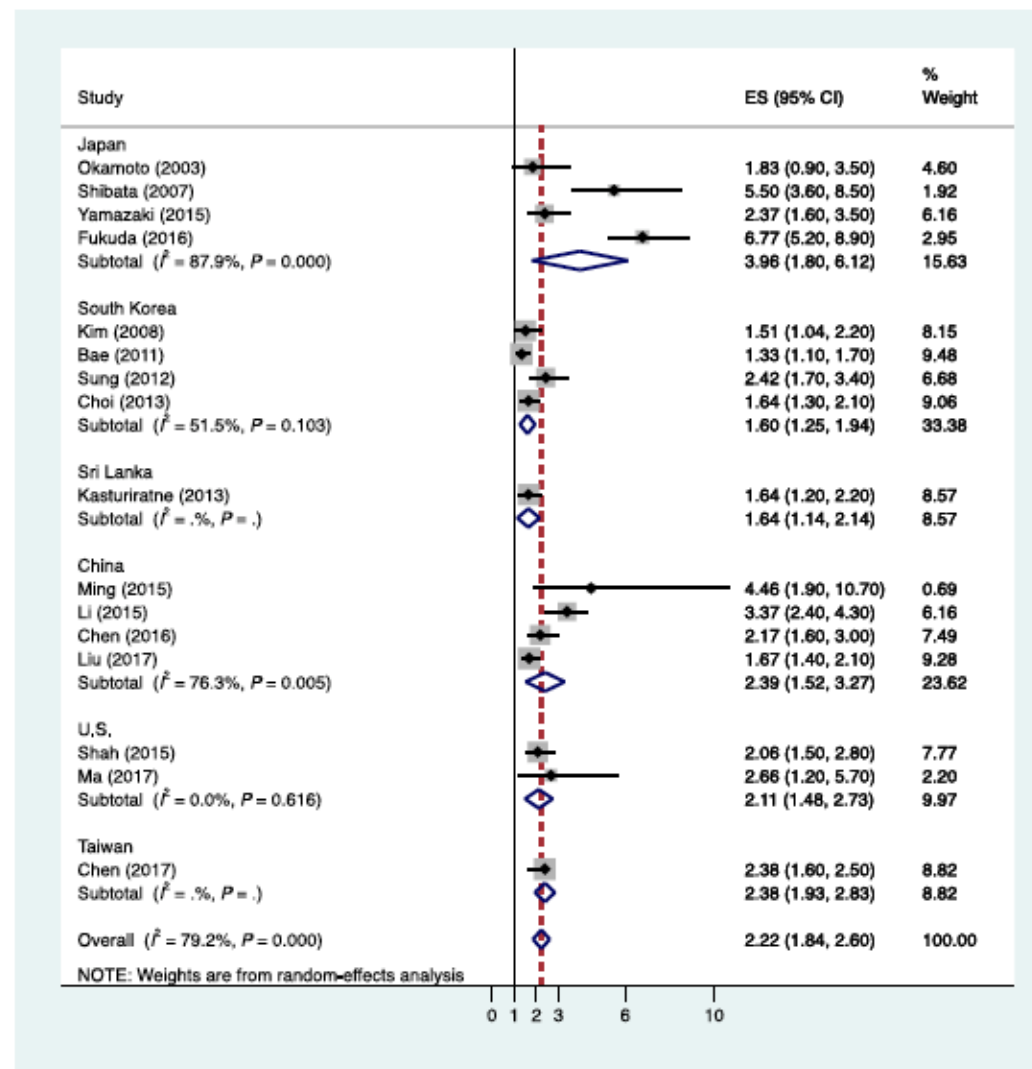


# Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis

- A total of 19 observational studies with 296,439 individuals (30.1% with NAFLD).
- Nearly 16,000 cases of incident diabetes.
- Follow-up median of 5 years.

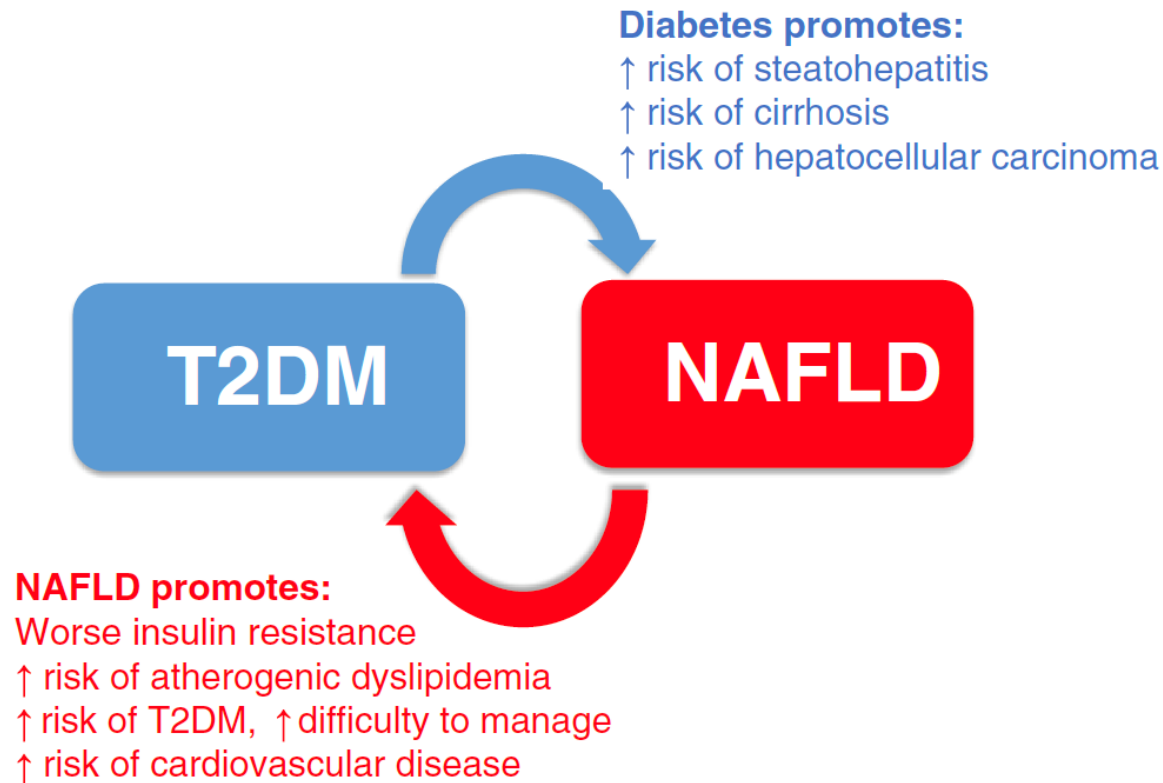
## Major findings:

- 2-fold greater risk of incident diabetes in patients with vs. without NAFLD ([HR] **2.22**, 95%CI 1.84–2.60).
- Patients with more “severe” NAFLD > incident diabetes (n = only 3 studies). (steatosis assessed only by US).
- In one study the risk greater in NAFLD pts with > NAFLD fibrosis score ([HR] 4.74, 95%CI 3.54–5.94).



# The Liver and Cardiometabolic Risk Reduction in T2DM

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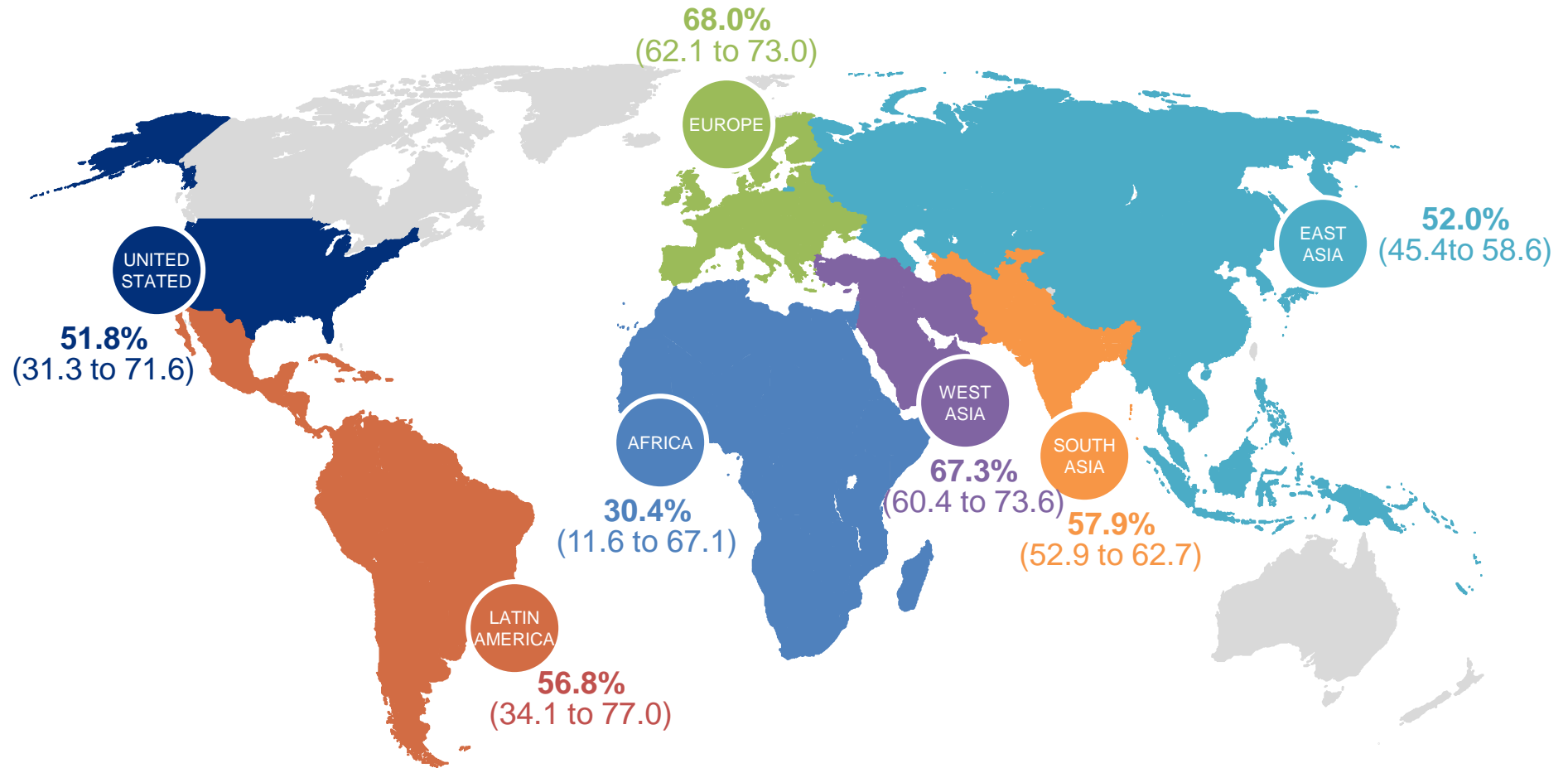


American Diabetes Association recommendation for NAFLD:

**Recommendation**

**4.14** Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

# Global Prevalence of NAFLD\* in T2DM: 55.5% (95% Confidence Interval: 47.3-63.7)

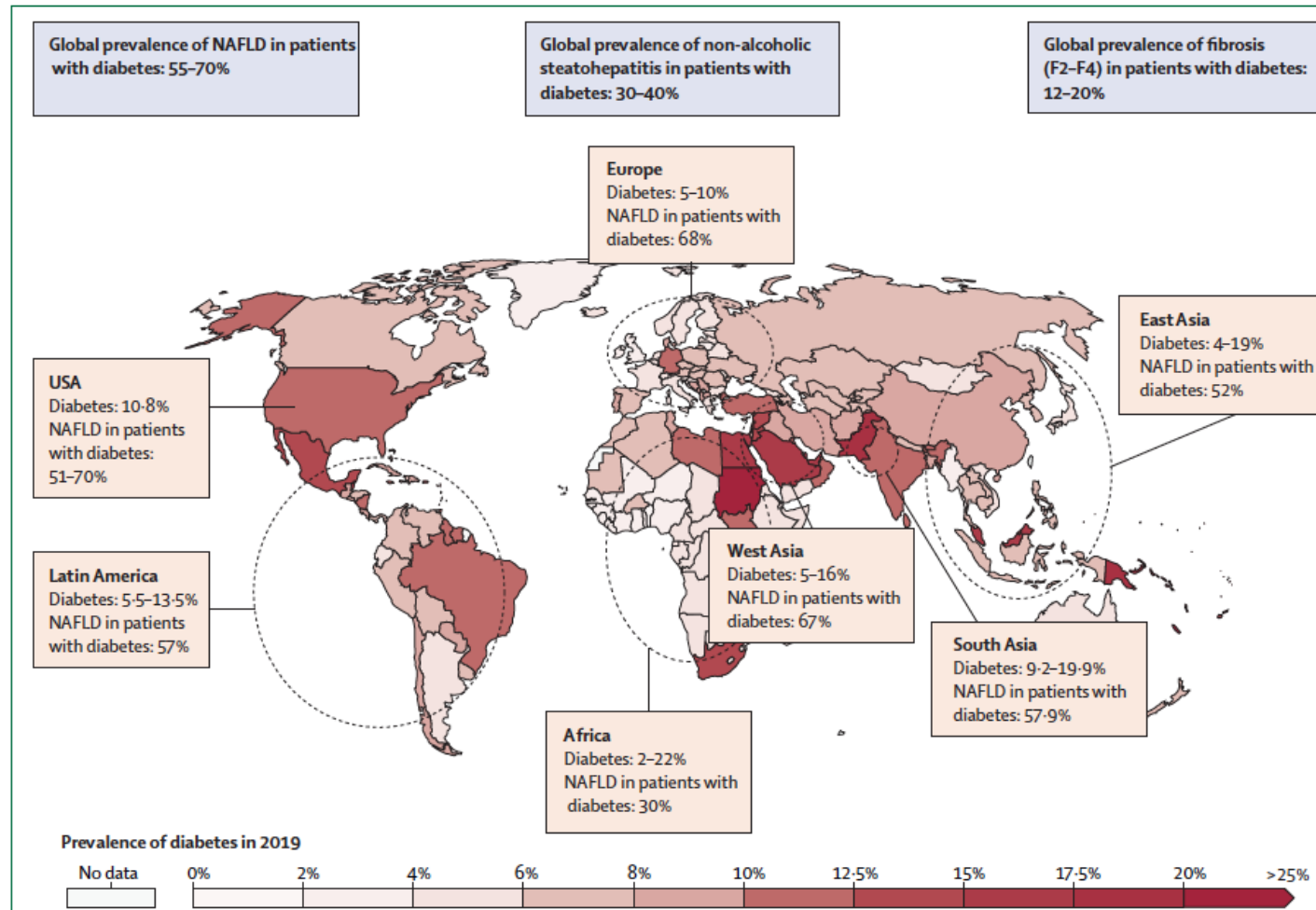


**NASH prevalence:**  
37.3% (10 studies)

# A global view of the interplay between non-alcoholic fatty liver disease and diabetes

Stefan N & Cusi K. Lancet Diabetes Endocrinol Feb 17, 2022.

Norbert Stefan, Kenneth Cusi





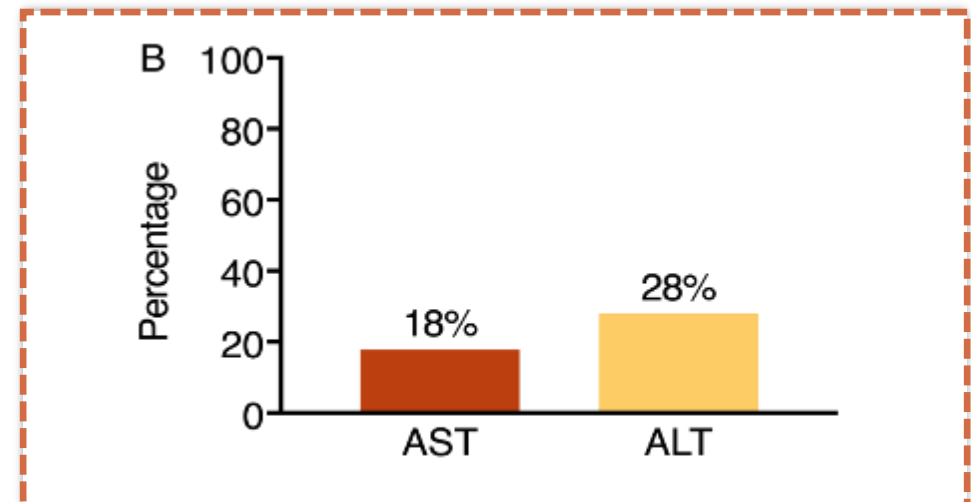
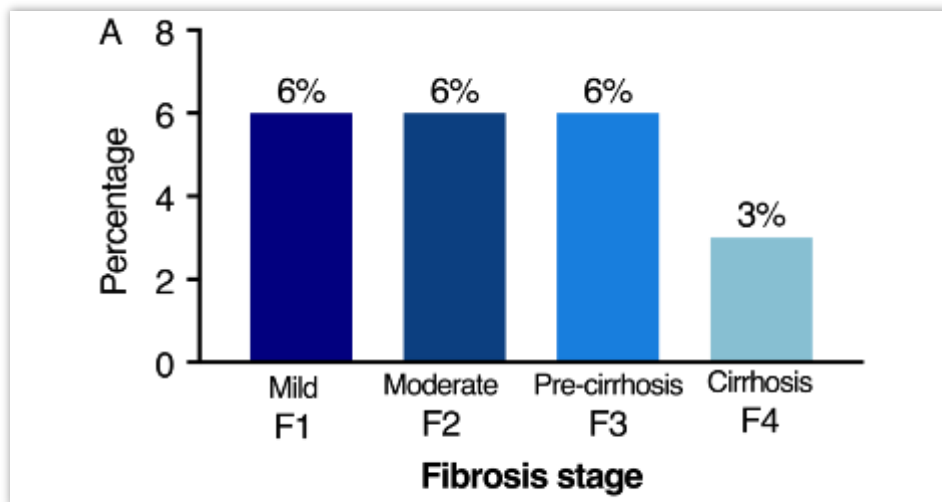
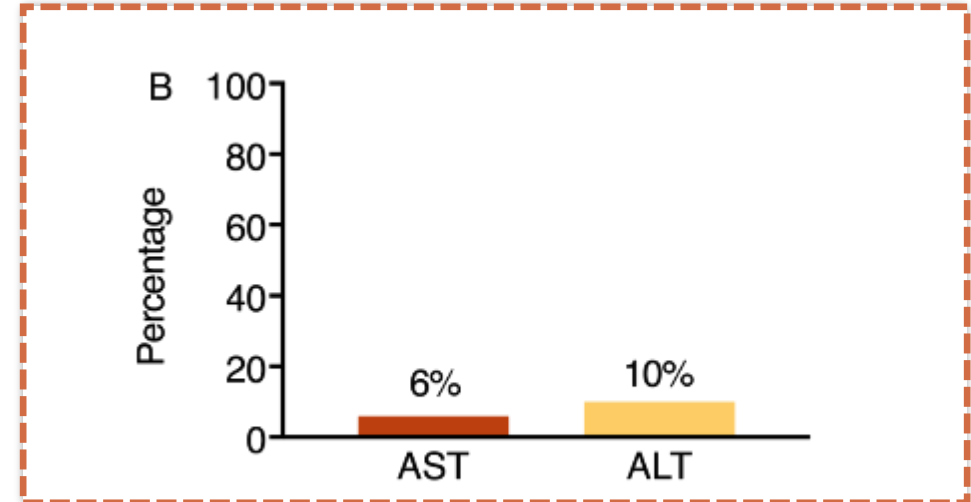
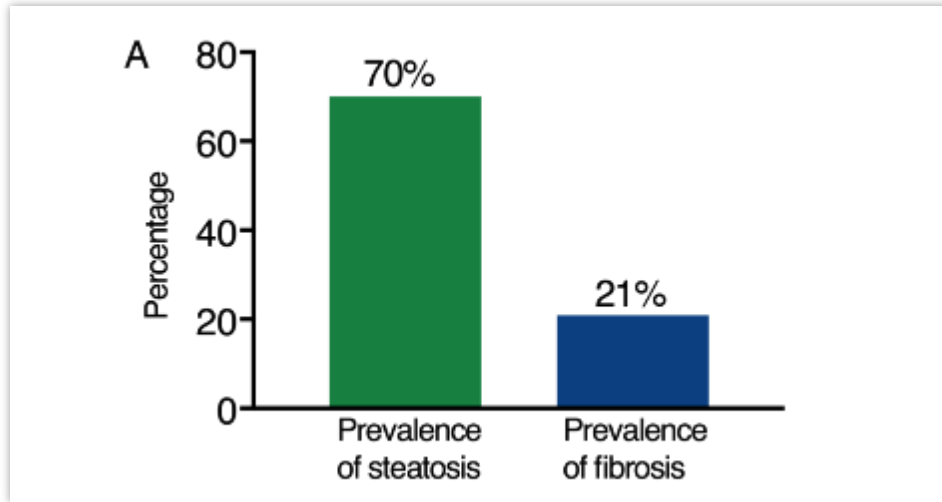
# Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening

*Diabetes Care* 2021;44:399–406 | <https://doi.org/10.2337/dc20-1997>

*Romina Lomonaco,<sup>1</sup>  
Eddison Godinez Leiva,<sup>1</sup> Fernando Bril,<sup>1</sup>  
Sulav Shrestha,<sup>1</sup> Lydia Mansour,<sup>1</sup>  
Jeff Budd,<sup>2</sup> Jessica Portillo Romero,<sup>2</sup>  
Siegfried Schmidt,<sup>3</sup> Ku-Lang Chang,<sup>3</sup>  
George Samraj,<sup>3</sup> John Malaty,<sup>3</sup>  
Katherine Huber,<sup>2</sup> Pierre Bedossa,<sup>4</sup>  
Srilaxmi Kalavalapalli,<sup>1</sup> Jonathan Marte,<sup>1</sup>  
Diana Barb,<sup>1</sup> Danielle Poulton,<sup>1</sup>  
Nada Fanous,<sup>1</sup> and Kenneth Cusi<sup>1,5</sup>*

# Prevalence of Elevated Plasma AST or ALT in Steatosis or Fibrosis in Patients with T2DM Unaware of Having NAFLD

N = 561 patients with type 2 diabetes



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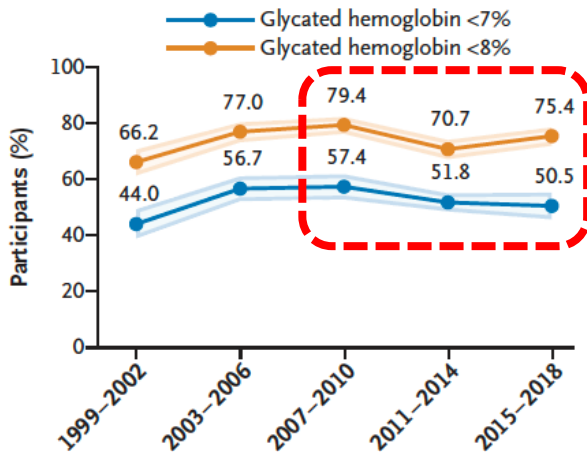
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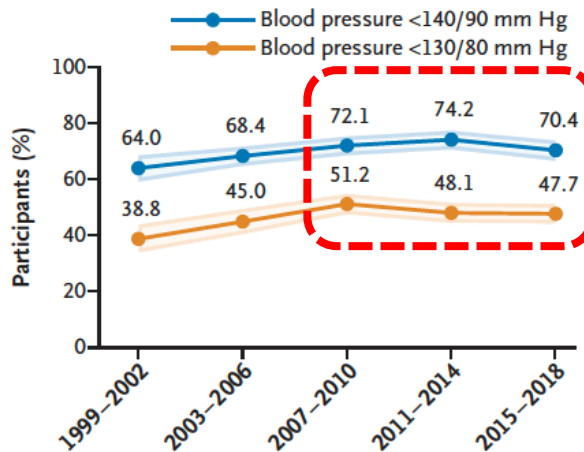
# Trends in Diabetes Control in U.S. Adults, 1999–2018

After progress from 1999 to the early 2010s, glycemic and blood-pressure control declined in adults with diabetes, while lipid control leveled off.

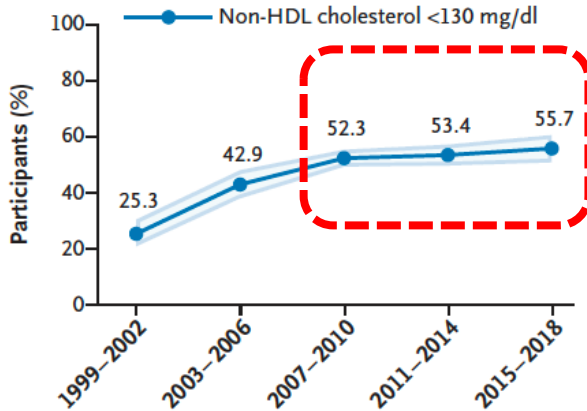
**A Glycemic Control**



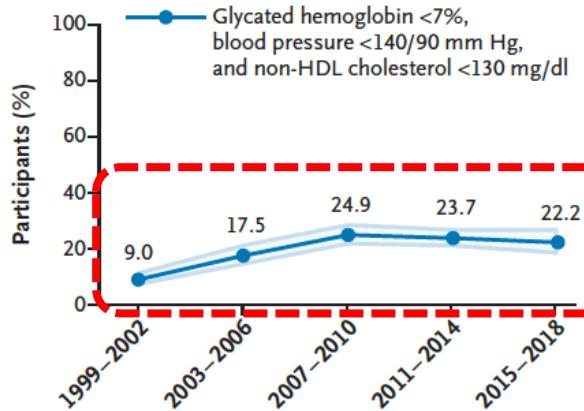
**B Blood-Pressure Control**



**C Lipid Control**



**D All Risk Factors Controlled**





## 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2019*

*Diabetes Care* 2019;42(Suppl. 1):S34–S45 | <https://doi.org/10.2337/dc19-S004>

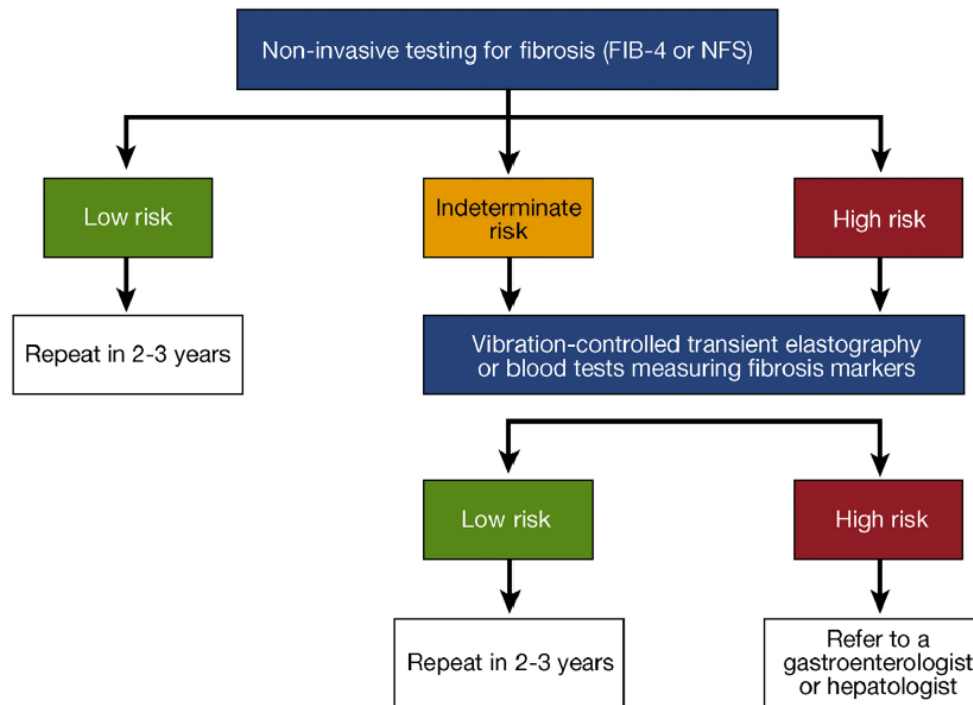
### **Recommendation**

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# Management of NAFLD in Primary Care

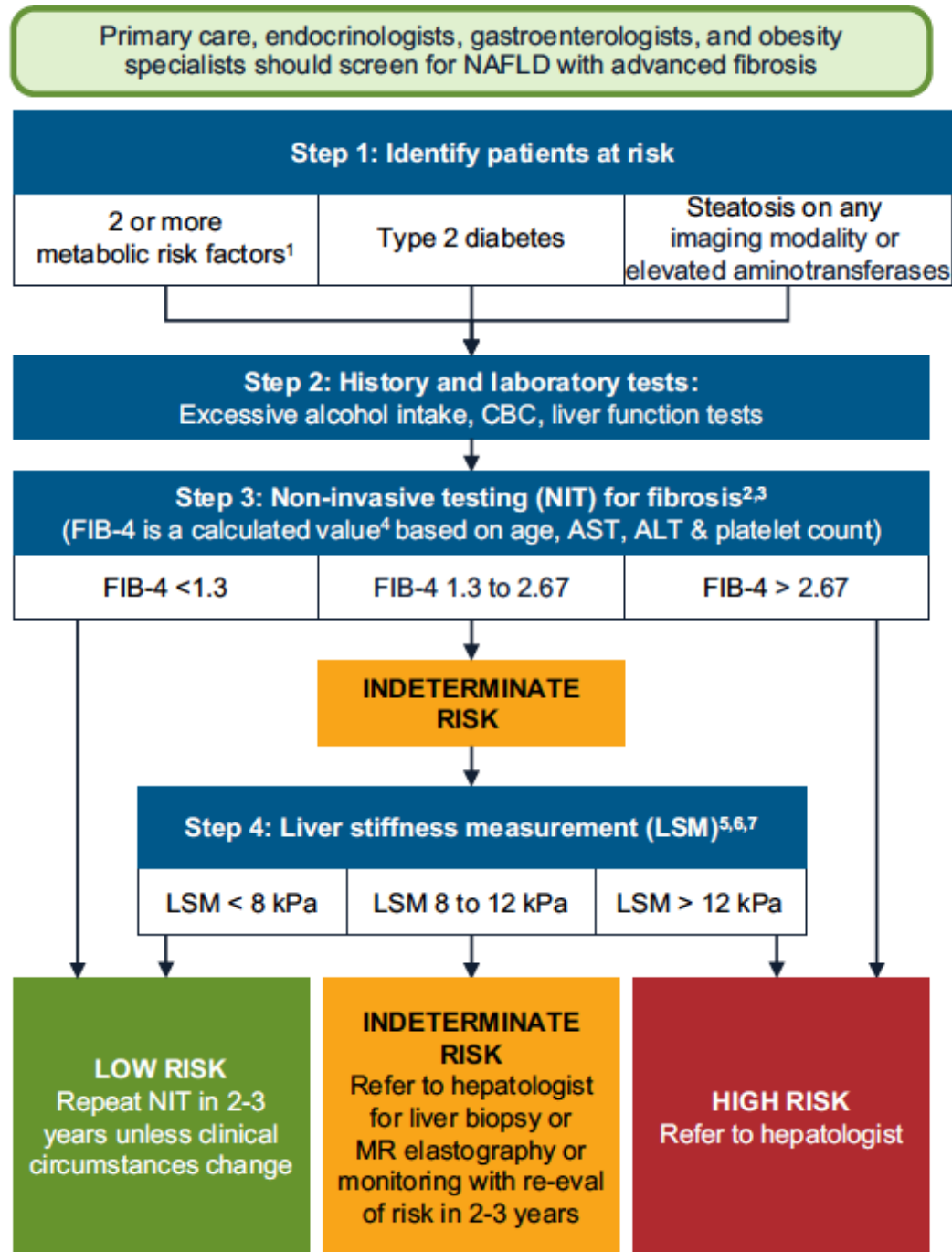
## Preparing for the NASH Epidemic: A Call to Action

Fasiha Kanwal,<sup>1</sup> Jay H. Shubrook,<sup>2</sup> Zobair Younossi,<sup>3</sup> Yamini Natarajan,<sup>4</sup> Elisabetta Bugianesi,<sup>5</sup> Mary E. Rinella,<sup>6</sup> Stephen A. Harrison,<sup>7</sup> Christos Mantzoros,<sup>8</sup> Kim Pfothenauer,<sup>9</sup> Samuel Klein,<sup>10</sup> Robert H. Eckel,<sup>11</sup> Davida Kruger,<sup>12</sup> Hashem El-Serag,<sup>13</sup> and Kenneth Cusi<sup>14</sup>



Algorithm for risk stratification in patients with NAFLD/NASH. FIB-4, Fibrosis-4 Index; NFS, NAFLD fib

# Clinical Care Pathway for the Diagnosis of NAFLD



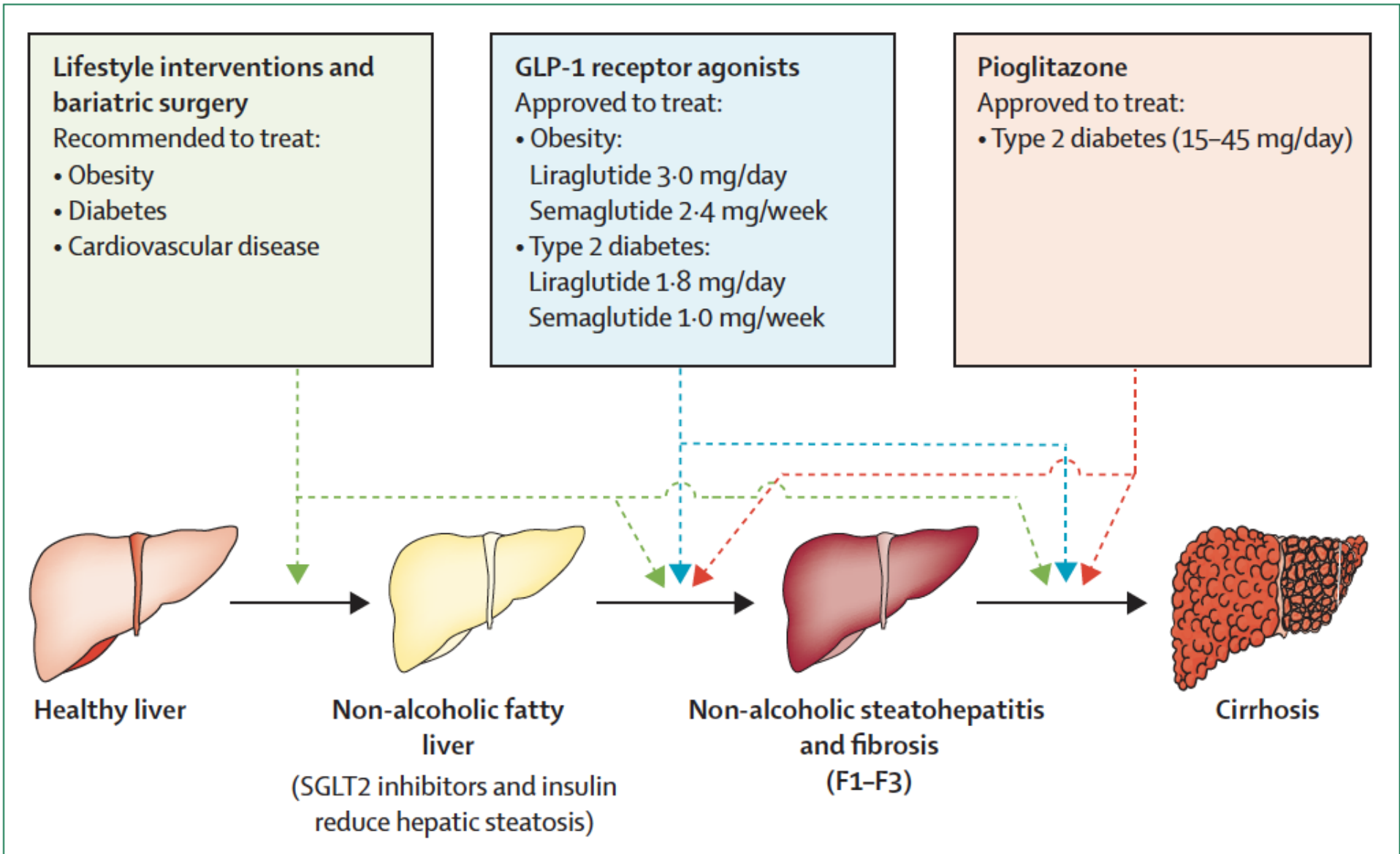
# Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease

Fasiha Kanwal,<sup>1,2</sup> Jay H. Shubrook,<sup>3</sup> Leon A. Adams,<sup>4</sup> Kim Pfothenauer,<sup>5</sup> Vincent Wai-Sun Wong,<sup>6</sup> Eugene Wright,<sup>7</sup> Manal F. Abdelmalek,<sup>7</sup> Stephen A. Harrison,<sup>8</sup> Rohit Loomba,<sup>9</sup> Christos S. Mantzoros,<sup>10</sup> Elisabetta Bugianesi,<sup>11</sup> Robert H. Eckel,<sup>12</sup> Lee M. Kaplan,<sup>10,13</sup> Hashem B. El-Serag,<sup>1,2</sup> and Kenneth Cusi<sup>14,15</sup>

## NAFLD Treatment

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK <sup>1</sup> FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention <sup>2</sup>	Yes	Yes	Yes
Weight loss recommended if overweight or obese <sup>3</sup>	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes <sup>4, 5, 6</sup>	Yes <sup>4, 5, 6, 7</sup>
CVD risk reduction <sup>8</sup>	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

# Treatments not approved for patients with NAFLD but that can be used for patients with obesity or diabetes



# Management Algorithm for Patients with NAFLD in Primary Care and Endocrinology Clinical Settings

High-risk groups for development of NAFLD

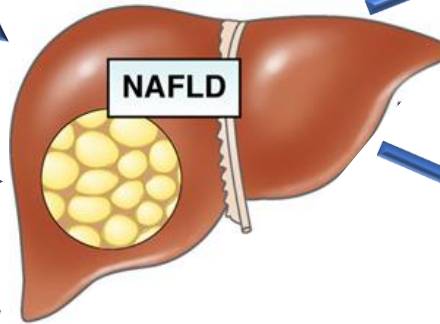
Prediabetes or T2DM

History and physical exam

2 or more metabolic risk factors

Hepatic steatosis or elevated AST or ALT (>30 u/L)

Rule out 2<sup>o</sup> causes



Prevention of Cardiovascular Disease

Prevention of Cirrhosis

Fibrosis Risk Stratification

Low Risk

Indeterminate Risk

High Risk

1. Obesity

2. Diabetes Management

3. Hypertension

4. Atherogenic Dyslipidemia

# Take Home Messages

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- **The dual obesity and diabetes epidemics will worsen** in the coming decade and will further fuel the epidemic of NASH and liver cirrhosis
- **NASH cirrhosis may be prevented** by early diagnosis in PCP and endocrinology clinics, but still significant clinical inertia
- **Diagnostic/management multidisciplinary algorithms are key** to increase awareness and early intervention
- **Current treatments remain underutilized to treat obesity and T2DM:** they reverse the fundamental defects associated with obesity (excess fat mass; GLP-1RAs) and with T2DM (dysfunctional adipose tissue, insulin resistance; PIO) that cause NAFLD.