Investing in one treatment, applying to multiple diseases

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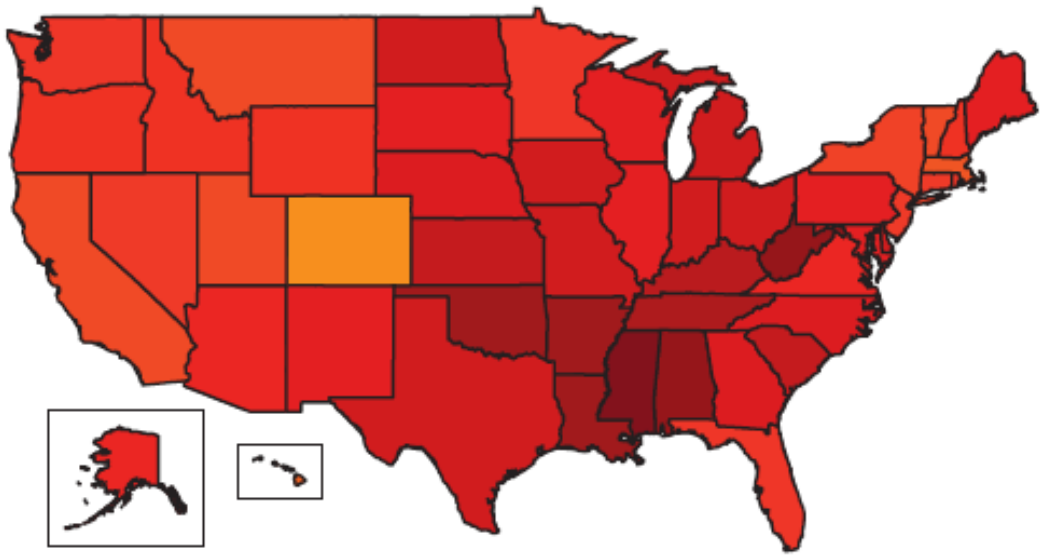
Eli Lilly and Company

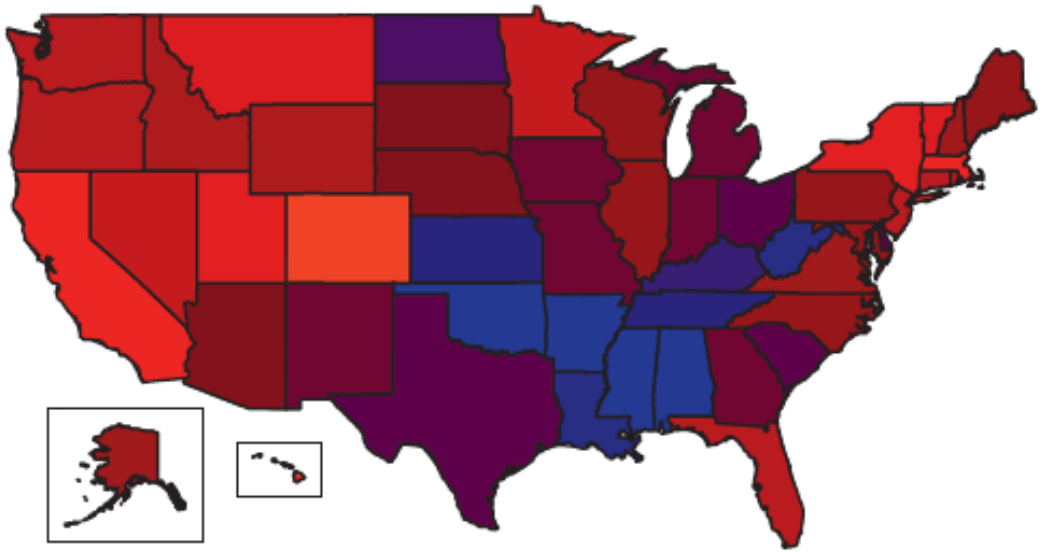
Obesity, a Key Risk Factor for the Development of T2DM

Projected U.S. State-Level Prevalence of Adult Obesity

2020



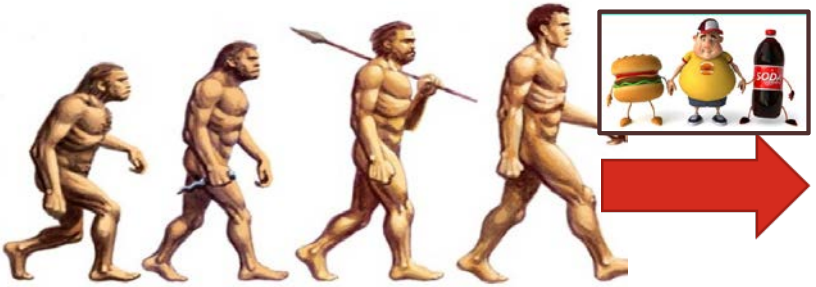
2030

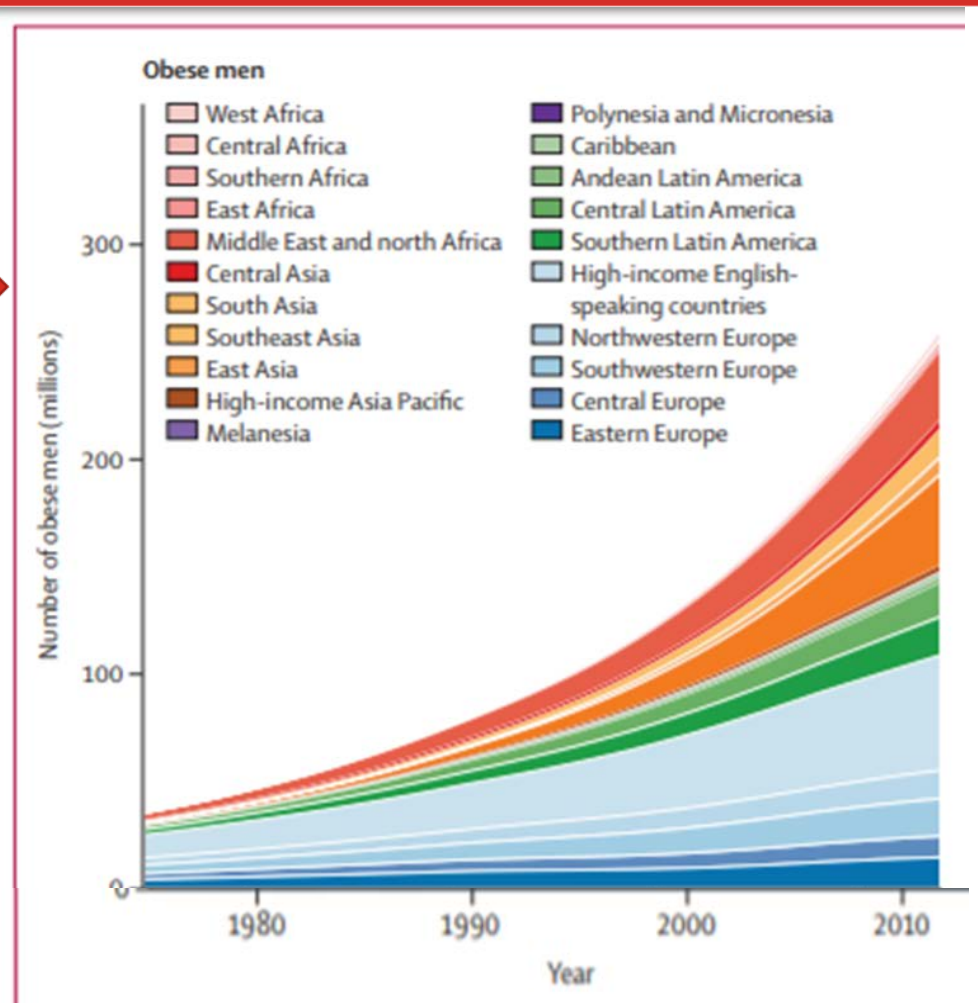


Ward et al., New Engl Journal of Medicine 2019

Metabolic Syndrome
The origin and consequences

Human phenotype in the 1970's ------ and after 1970





Insulin resistance
Hypertension
Dyslipidemia
Beta-cell Dysfunction
Fatty Liver
Low-grade inflammation

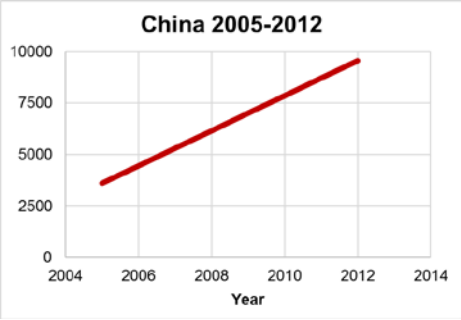
CVD
Hyperglycemia
NASH
Cancer
Cognitive Decline
CKD
Arthritis

NCD Risk Factor Collaboration (NCD-RisC) Lancet 2016; 387: 1377–96

https://hubpages.com/politics/Why-Are-There-Still-Apes

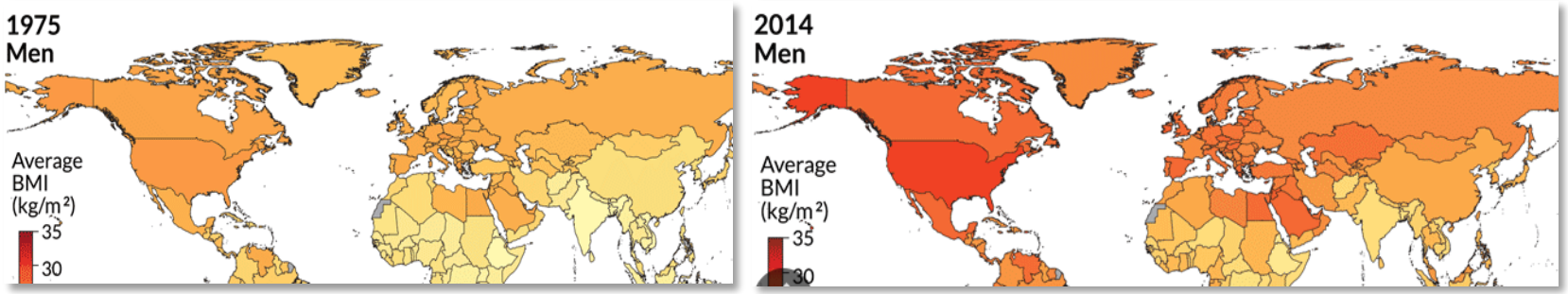
China Exemplifies the Common Soil Origin of Diabetes and Co-Morbidities: Fast Food – Obesity – Diabetes – CVD - NASH

Fast Food outlets



From Xue et al., *Prev Med* 2017 102; 79–85

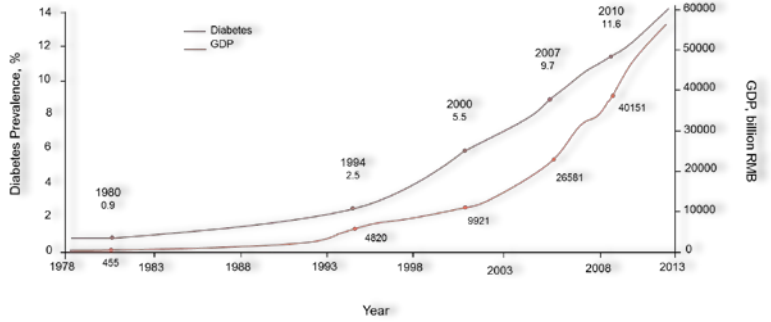
BMI:1975-2014



From NCD Risk Factor Collaboration, *Lancet* 2016; 387: 1377-96 http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)30054-X.pdf https://creativecommons.org/licenses/by/4.0/

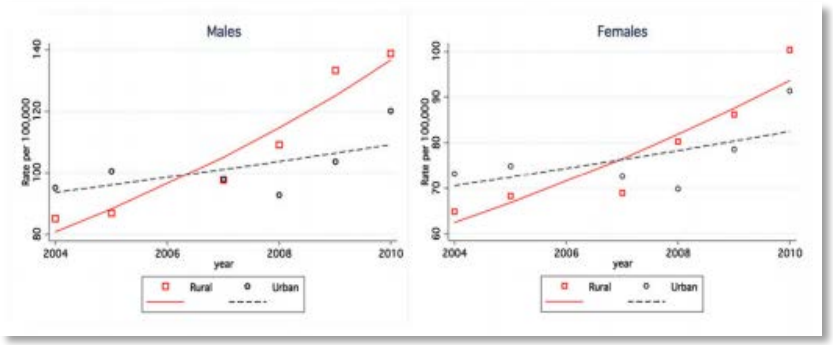
Diabetes prevalence

increased from 0.9% in 1980 to ~12% 2010



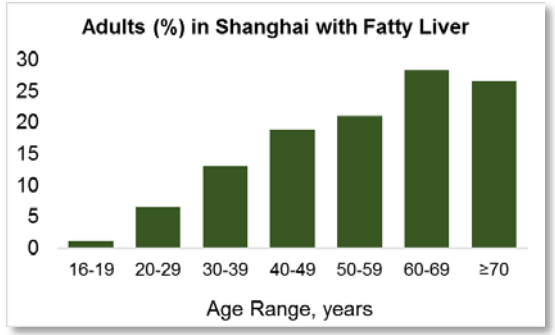
From Chan et al., *Lancet Diabetes Endocrinol* 2014; 2: 969–79

Ischemic Heart Disease Mortality:2004-10



Xiaofei Z. et al.European Heart Journal – Quality of Care and Clinical Outcomes 2017:3, 47–52

NAFLD prevalence



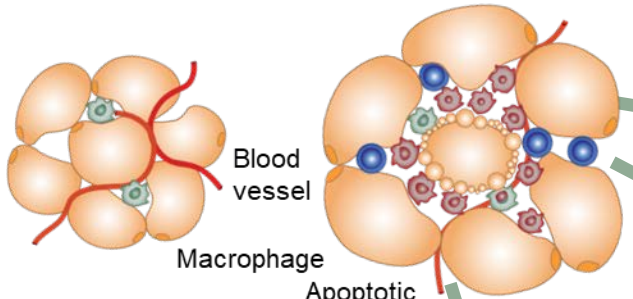
From Fan et al., *J Hepatol* 2005; 43: 508–514

"Ectopic or Bad Fat" Related Metabolic Disorders: The Common Origin of Many Non-Communicable Diseases

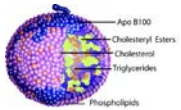
Genes + Environment

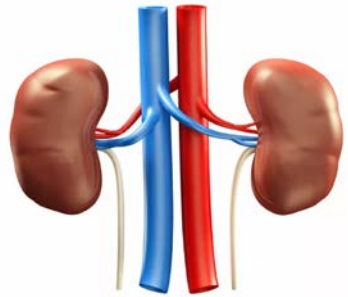
Lean adipose tissue

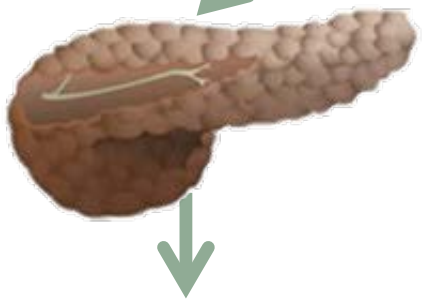
Obese adipose tissue



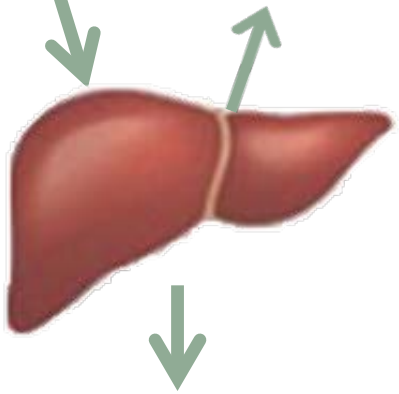
Dyslipidemia
High TG + ApoB, low HDL







✓ T2DM



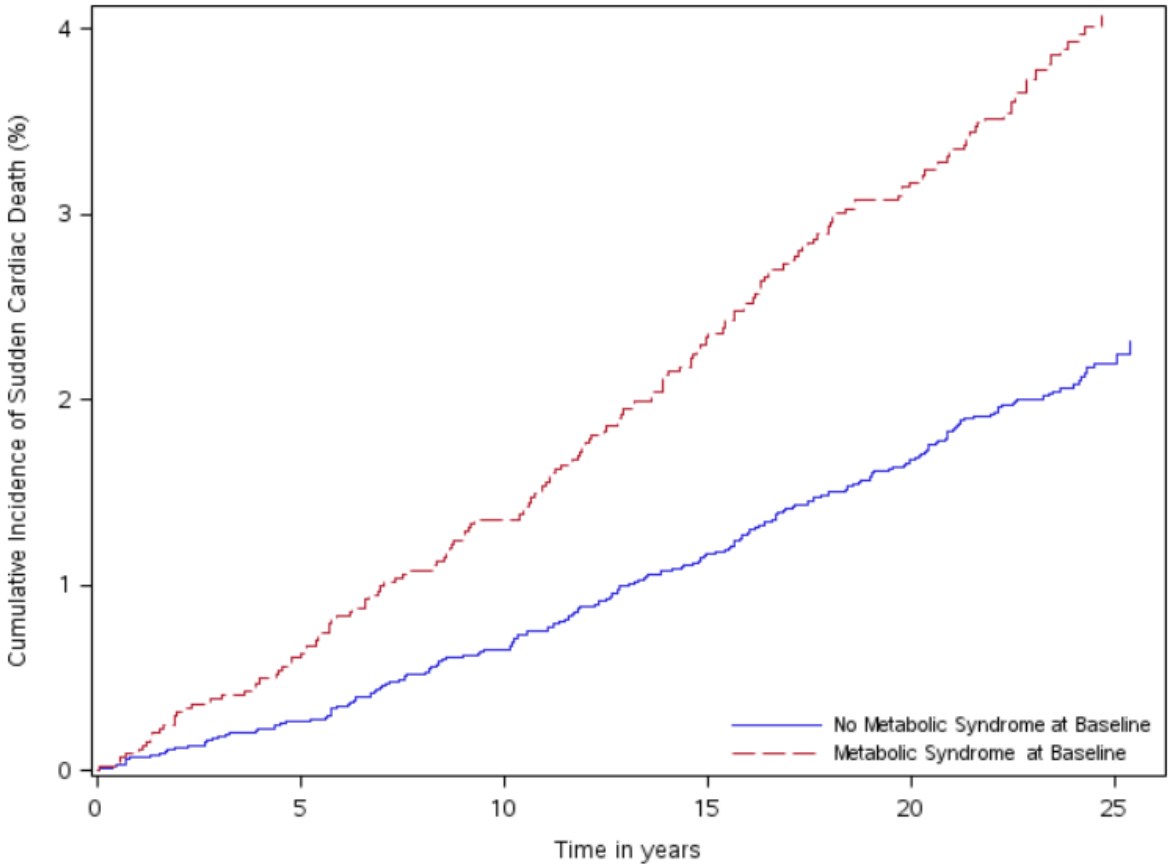
✓ NASH
✓ Fibrosis
Cirrhosis
Hepatocellular Carcinoma (HCC)

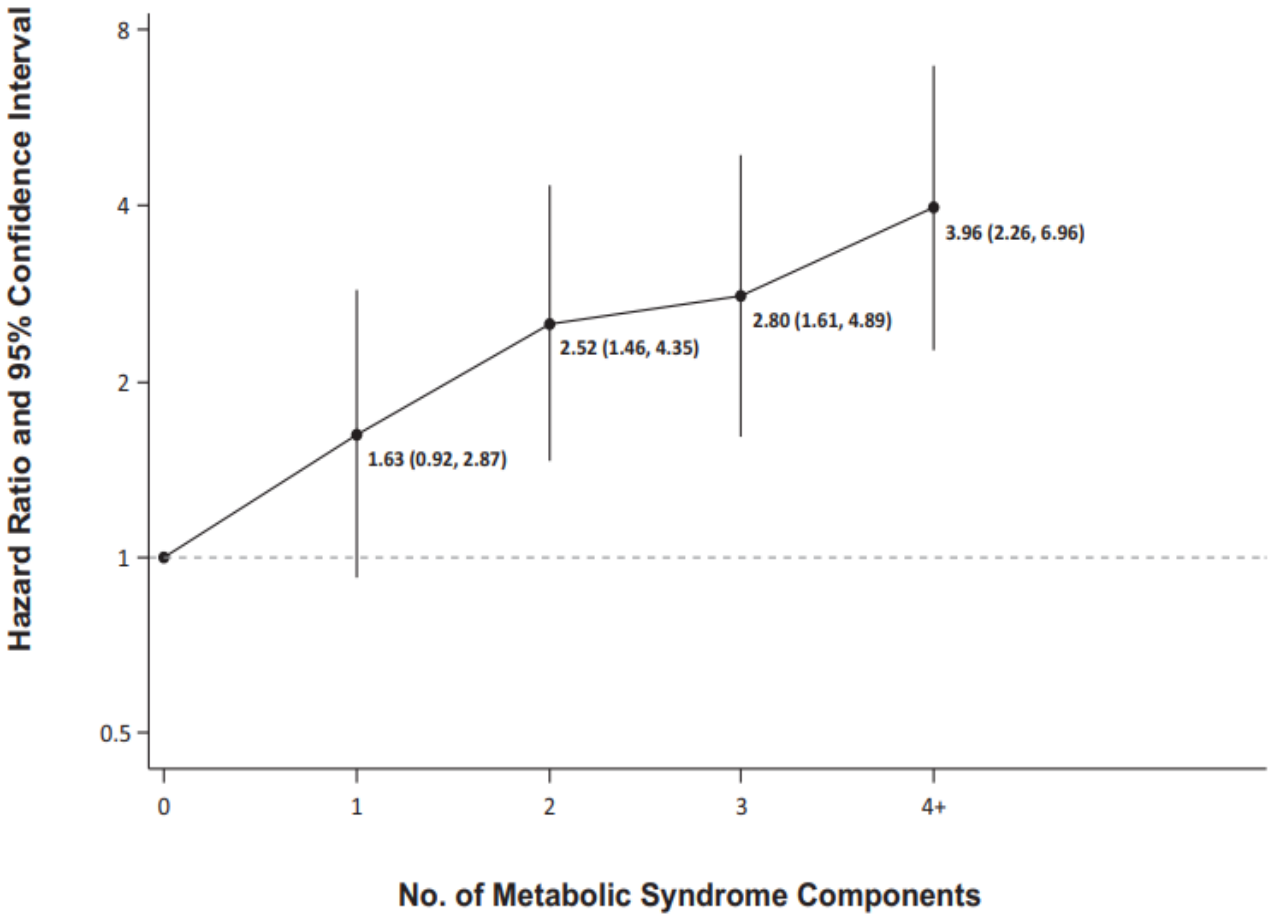
✓ Atherosclerosis
✓ Heart failure

Hypertension
Chronic Kidney Disease (CKD)

https://myheartsisters.org/2011/12/07/what-your-body-fat-really-looks-like

Risk of Sudden Cardiac Death according to the Number of Metabolic Syndrome Criteria. The ARIC Study Cohort 1987 to 2012.

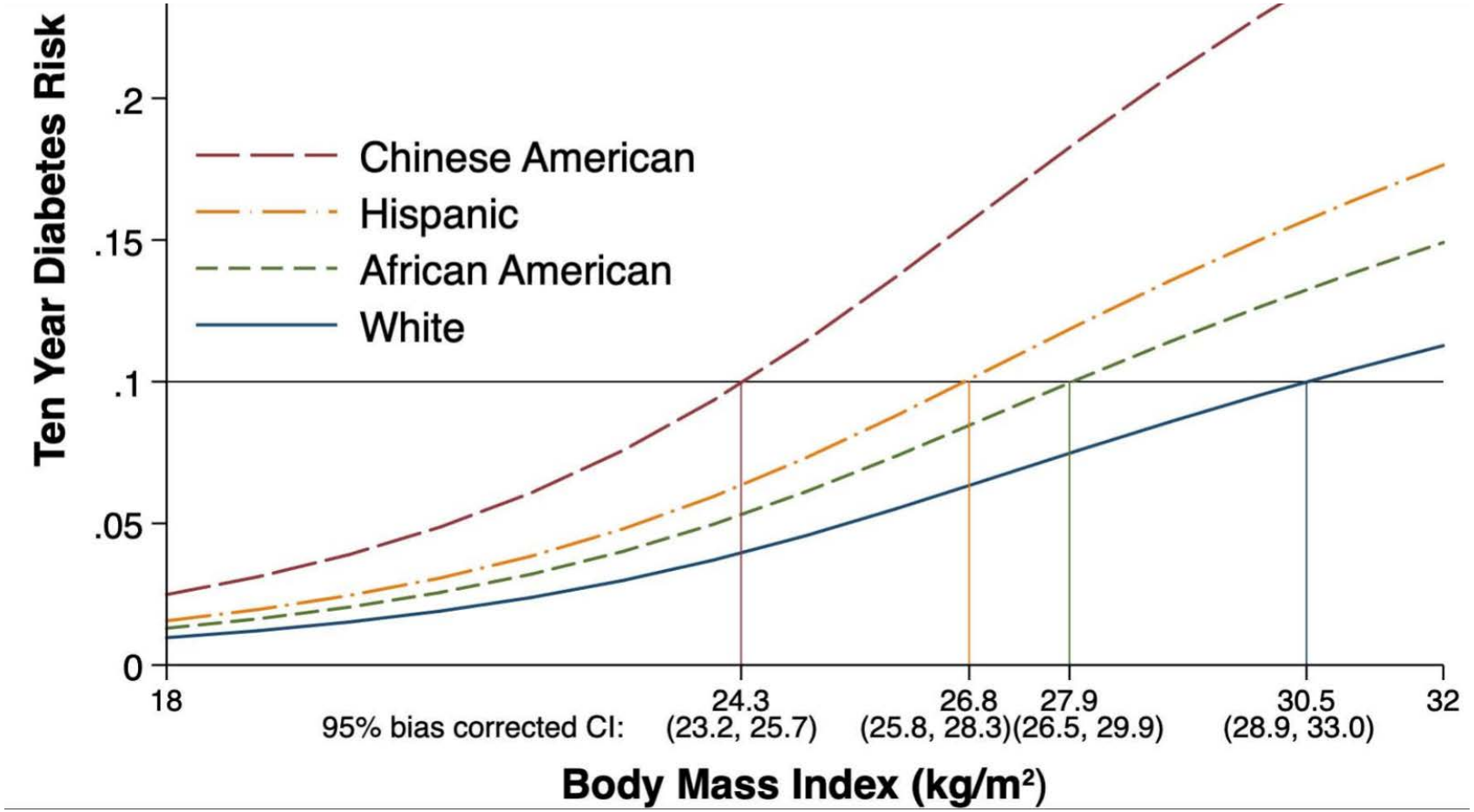




MS: 3 or more of the following: **waist circumference** ≥35 inches (88 cm) for women or ≥40 inches (102 cm) for men**; FBG** ≥100 mg/dL (5.5 mmol/L); **SBP** ≥130 or diastolic blood pressure ≥85 mm Hg; **serum TG** ≥150 mg/dL (1.7 mmol/L) and **HDL-C**<40 mg/dL (1.0 mmol/L) in men or <50 mg/dL (1.3 mmol/L) in women.

J Am Heart Assoc. 2017;6:e006103. DOI: 10.1161/JAHA.117.006103.)

BMI Levels Associated with a 10% Diabetes Risk over 10 years in Middle Aged Adults in the Multi-Ethnic Study of Atherosclerosis (MESA)



Rodriguez LA et al. Diabetic Med.2020, in press: https://doi.org/10.1111/dme.14377

Metabolic Health

- The aspirational goal is to establish metabolic health in persons with metabolic disorders associated with weight gain/obesity in order to prevent major clinical events
  - (Pre-)Diabetes
  - Metabolic Syndrome: a cluster of cardiovascular disease risk factors associated with insulin resistance
- Clinical endpoints may include:
  - CVD
  - CKD
  - HF
  - Diabetes
  - NASH
  - Osteoarthritis
  - Sleep apnea
  - Some cancers
  - Clinical Depression
  - Impaired Cognition
  - PCOS

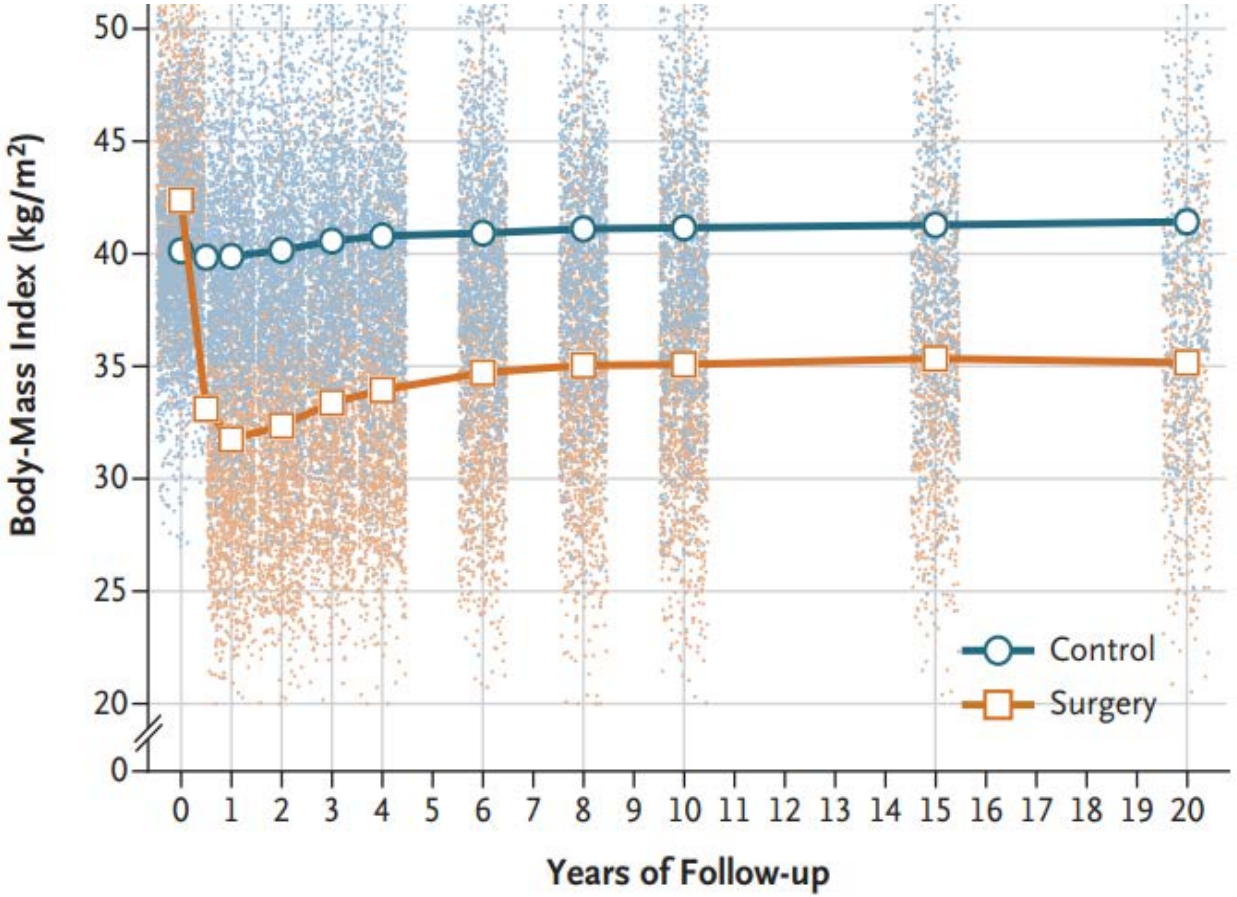
	Cutoff points
Normal triglyceride concentrations	<150 mg/dL or <1·7 mmol/L and not on drug treatment for elevated triglyceride concentration
Normal HDL cholesterol concentrations	
Men	≥40 mg/dL or ≥1·05 mmol/L
Women	≥50 mg/dL or ≥1·25 mmol/L and not on drug treatment to increase HDL cholesterol
Normal blood pressure	<130/85 mm Hg and not on antihypertensive drug treatment
Normal fasting glucose	<100 mg/dL or <5·6 mmol/L and not on drug treatment for hyperglycaemia

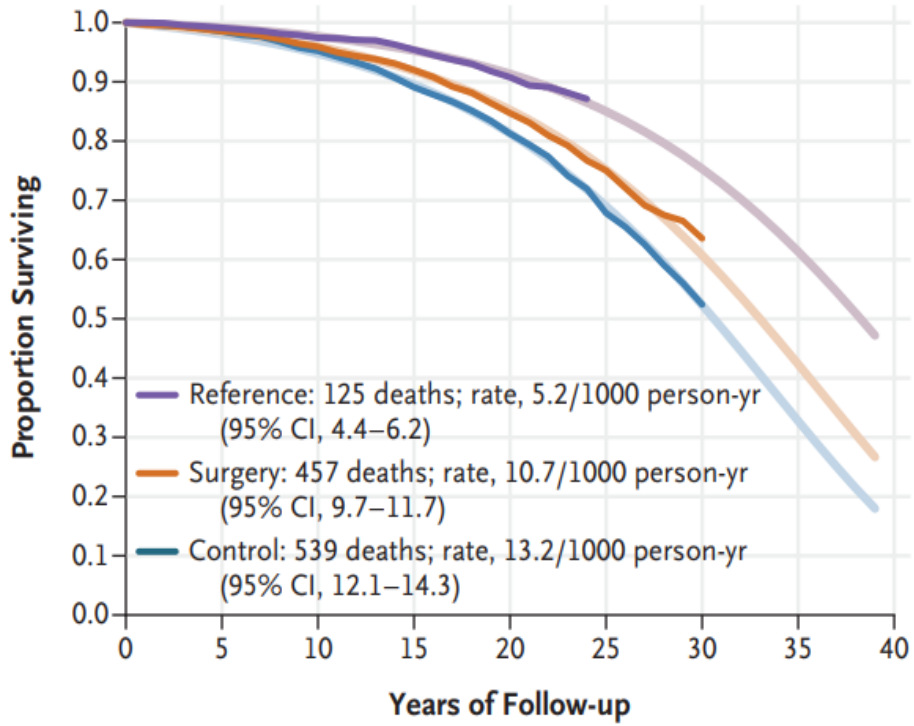
These measures are those most frequently used to define metabolic syndrome in studies that evaluate subgroups of obese people with regard to cardiovascular risk, according to a systematic review.[22] Cutoff points refer to definitions of metabolic syndrome components according to the National Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP-III) update from 2005.[23]

***Table*: Cutoff points for triglycerides, HDL cholesterol, blood pressure, and fasting glucose to define metabolic health**

- Norbert S et al. Lancet Diabetes Endocrinol 2018; 6: 249–58

BMI and Mortality following Bariatric Surgery

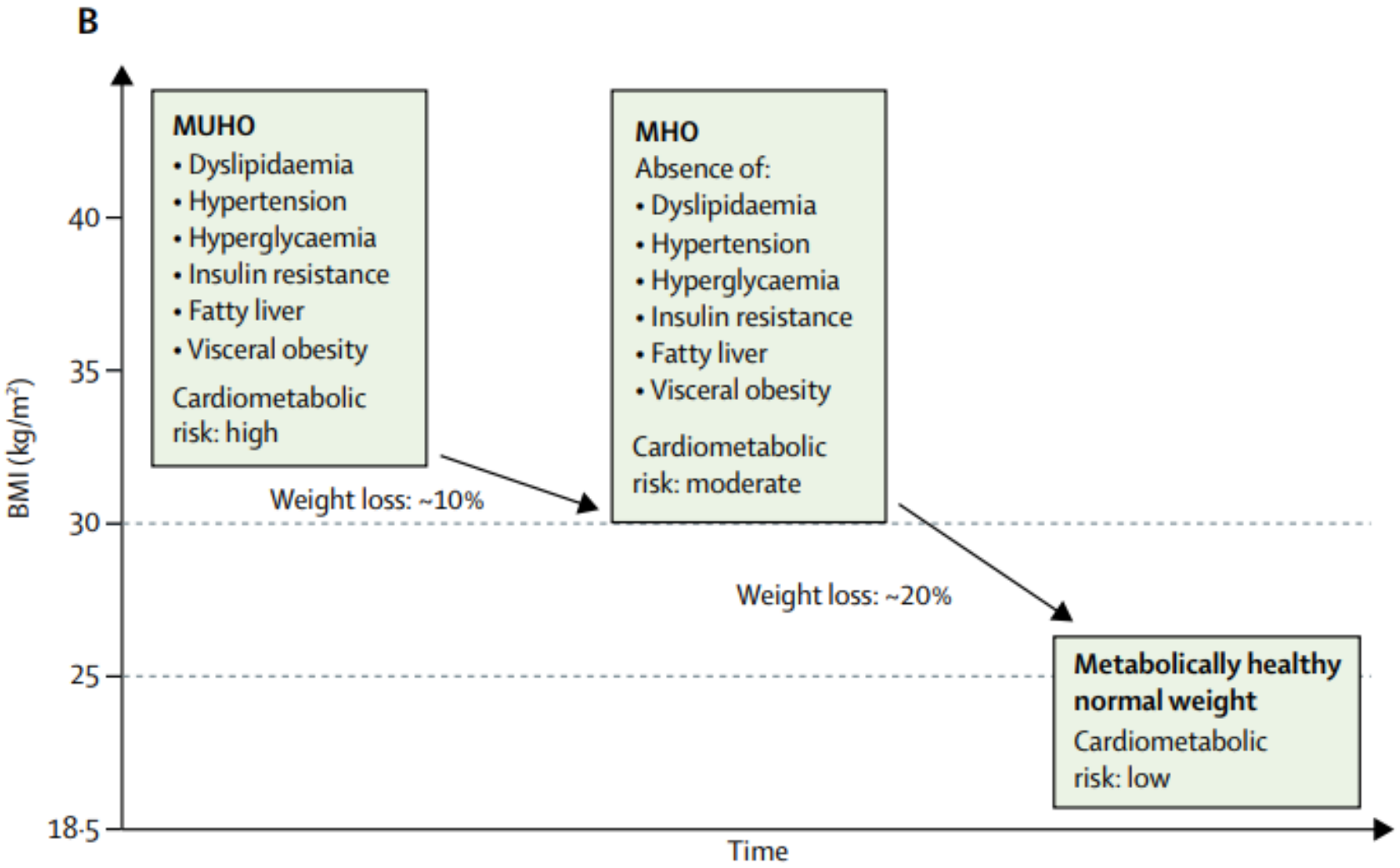




No. at Risk								
Reference	1135	1125	1106	1083	905	0	0	BMI: 25.2±3.8
Surgery	2007	1915	1837	1744	1390	580	34	
Control	2040	1961	1815	1589	1238	488	26	

Carlsson LMS, et al. N Engl J Med 2020;383:1535-43.

Moderate Weight Loss Provides Metabolic Health Benefits



Norbert S. et al.Lancet Diabetes Endocrinol 2018; 6: 249–58

How to Invest in One Treatment and How to Apply it to Multiple Diseases

Opportunities:

1. "Excess body fat increases the risk of death and major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers" (FDA)
2. Weight gain associated diseases very prevalent around the globe

Challenges:

1. The Bar is HIGH: very competitive science and drug development
2. Obesity and related disorders perceived as a public health issue and as a personal responsibility (stigma)
3. High Risk and costly development program; several pharmaceutical companies have left this therapeutic area
4. Identifying the right patient for the right therapy (health economics)

Path forward?

1. Drug development should be focused on total disease burden, not only on separate indications, in patients at high risk
2. Affordability of a development program can be achieved by allowing Real World Evidence and pragmatic trials focused on the effectiveness of novel medicines to reduce disease burden for registration purposes