



Addressing Cardiometabolic Risk in Children and Adolescents: CHALLENGES AND SOLUTIONS

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Target Organ Damage Related to Cardiometabolic Disease in Children and Adolescents

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Presented at the

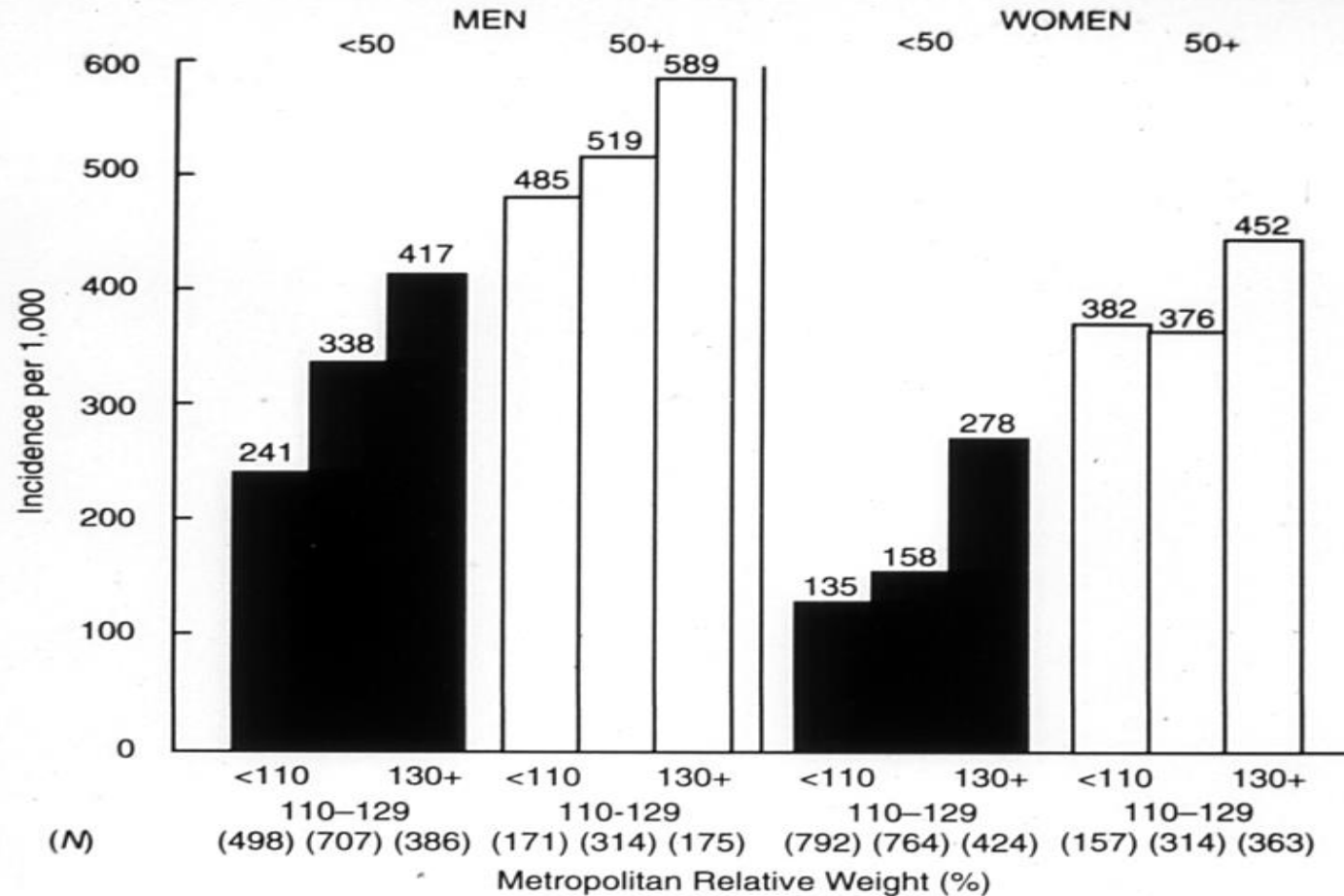
Target Organ Damage and Cardiometabolic Disease

- Obesity and cardiometabolic disease have a wide range of adverse health effects.

Target Organ Damage in Cardiometabolic Disease

- The relationship of obesity and increased risk for cardiovascular disease and all-cause mortality is well established in adults.

Target Organ Damage in Cardiometabolic Disease



Note: N = the number at risk for an event. Numbers above the bars give the actual incidence rates per 1,000.

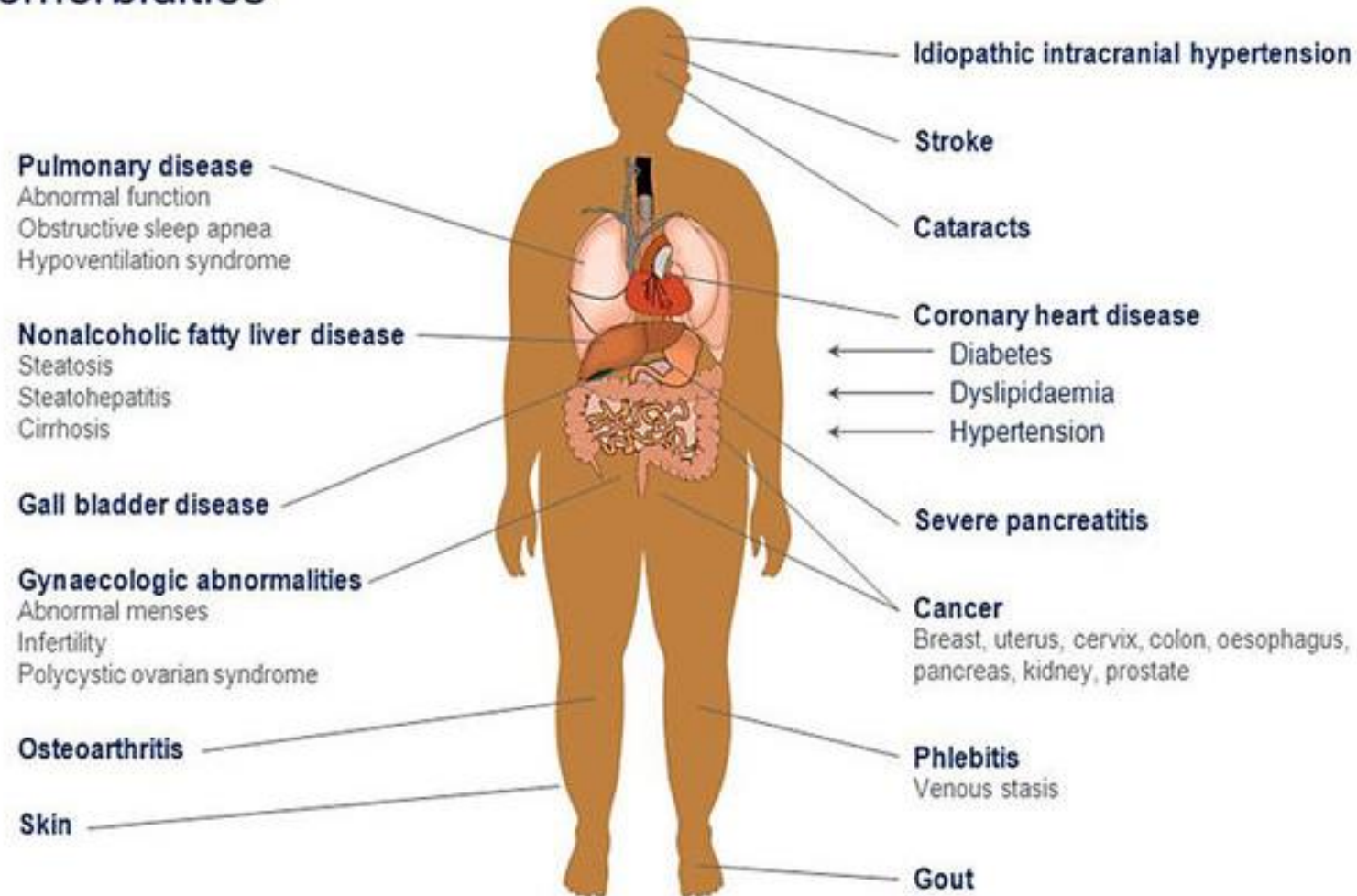
Figure 10-16 Incidence of Cardiovascular Disease in 26 Years' Follow-Up in Relation to Metropolitan Relative Weight among Men and Women above and below Age 50 at Entry, Framingham Heart Study. Source: Reprinted with permission from HB Hubert, M Feinleib, PM McNamara, and WP Castelli, *Circulation*, Vol 67, No 5, p 970, © 1983, American Heart Association.

Target Organ Damage in Cardiometabolic Disease

- Obesity and cardiometabolic disease can have an adverse impact on just about every organ system.

Target Organ Damage in Cardiometabolic Disease

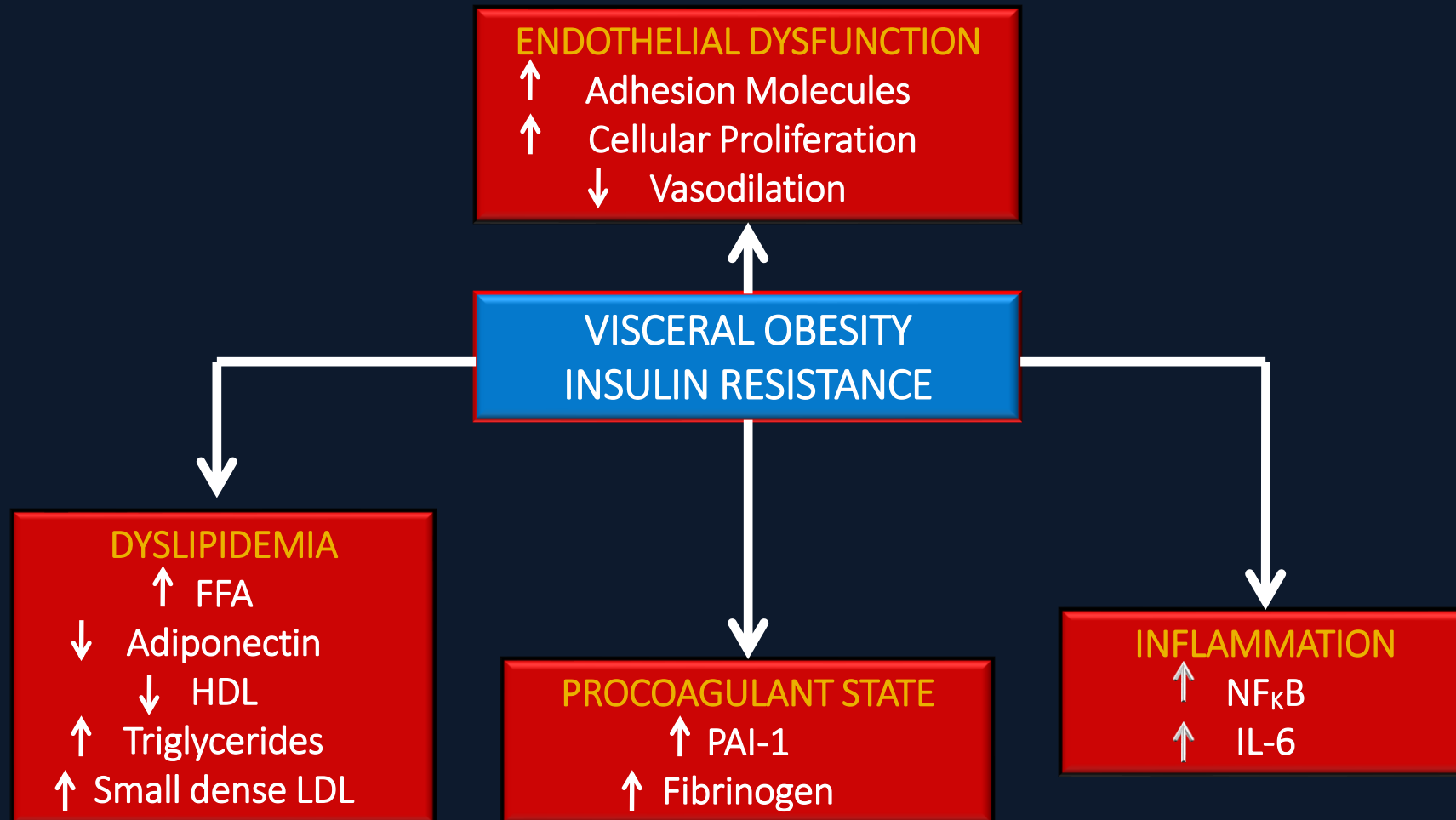
Obesity and comorbidities



Target Organ Damage in Cardiometabolic Disease

- There are multiple mechanisms associated with the adverse health effects of obesity and cardiometabolic disease.

Insulin Resistance and Associated Abnormalities



Target Organ Damage in Cardiometabolic Disease

- Cardiometabolic Disease can have a wide range of impacts across multiple organ systems.
- We will focus on those related to the cardiovascular system.
 - Outcomes include atherosclerosis leading to myocardial infarction and stroke.

Target Organ Damage

- Other important cardiovascular outcomes
- Left ventricular hypertrophy
 - Cardiac dysfunction
 - Heart failure
- Vascular structural and functional abnormalities
- Adverse neurocognitive outcomes

Target Organ Damage

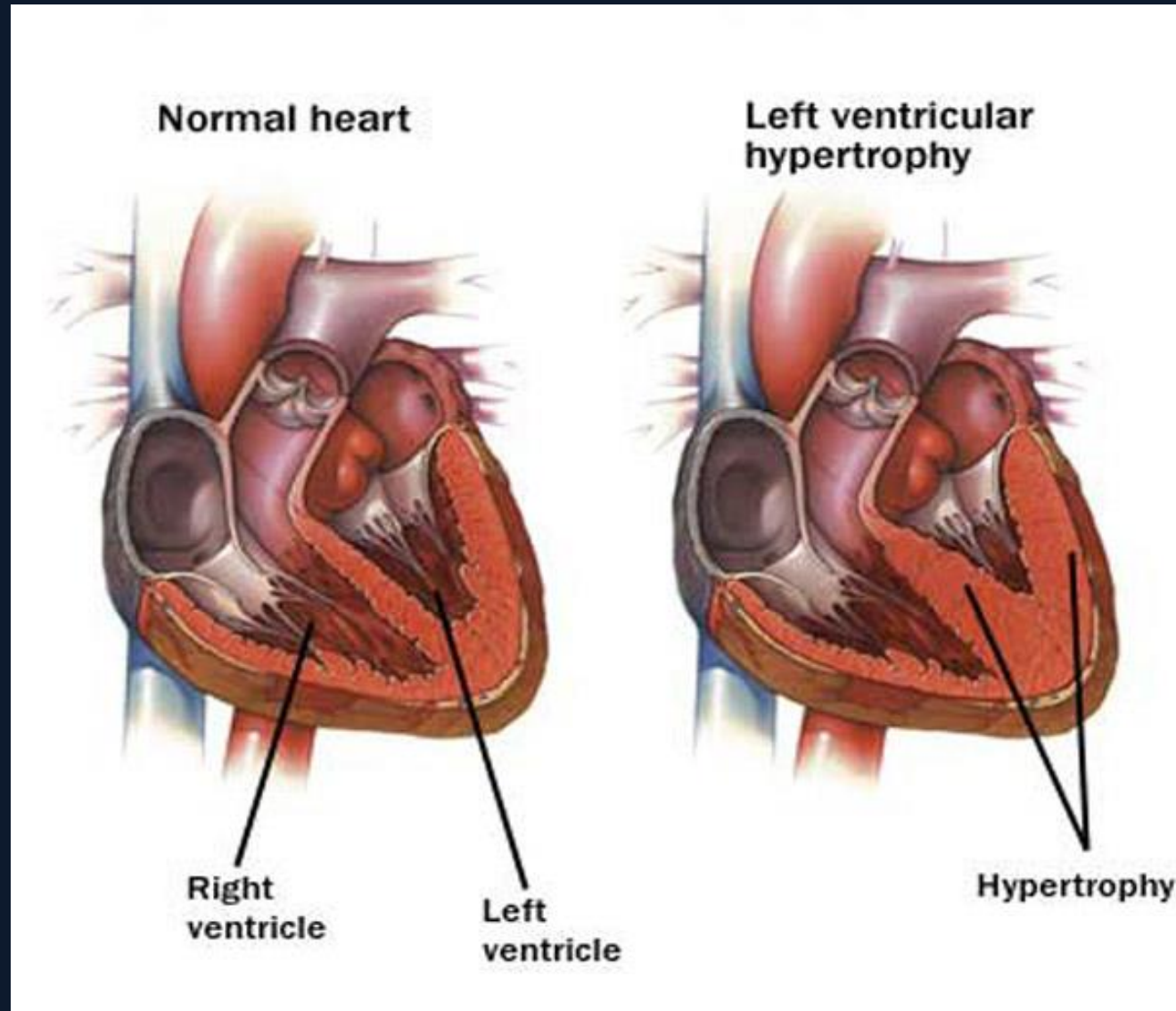
- While myocardial infarction and stroke occur largely in adults, other target organ damage can occur in childhood and adolescence.
- This may be progressive into adulthood.

Target Organ Damage in Cardiometabolic Disease

Obesity and Cardiovascular Disease

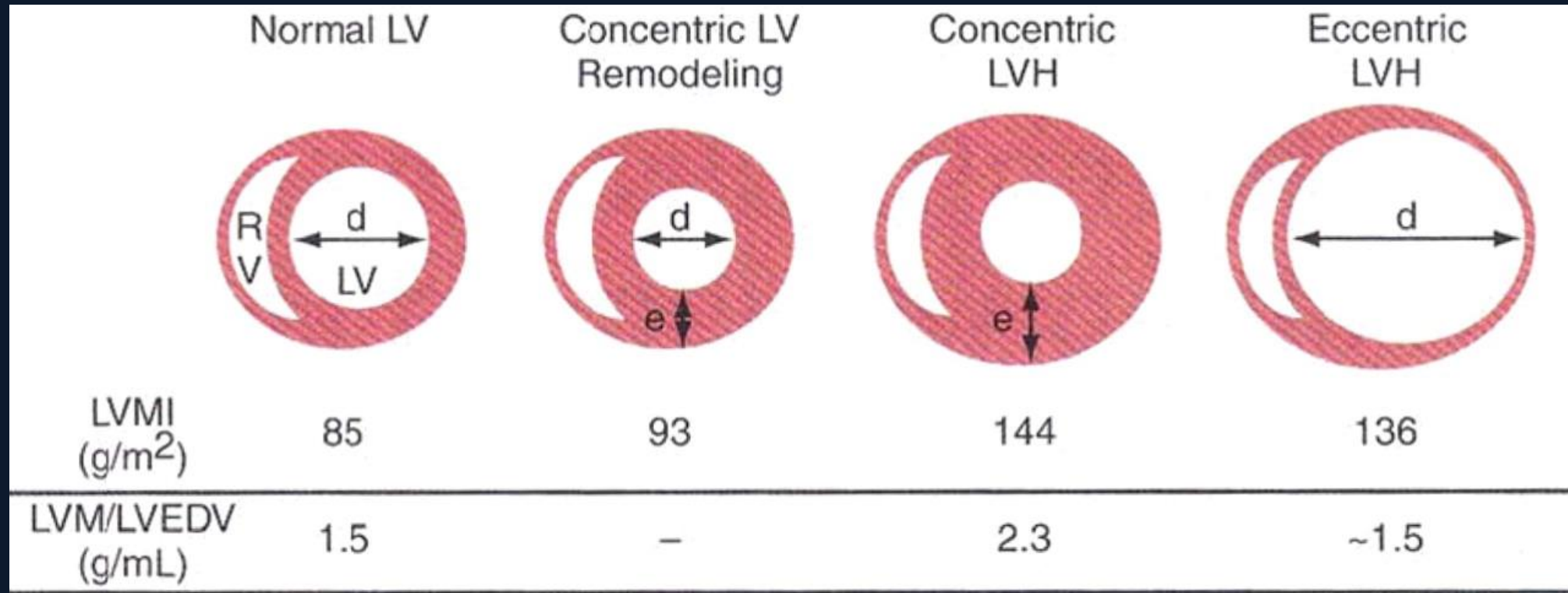
Left ventricular hypertrophy has been established as an important independent risk factor for adverse CVD outcomes in adults.

Target Organ Damage in Cardiometabolic Disease

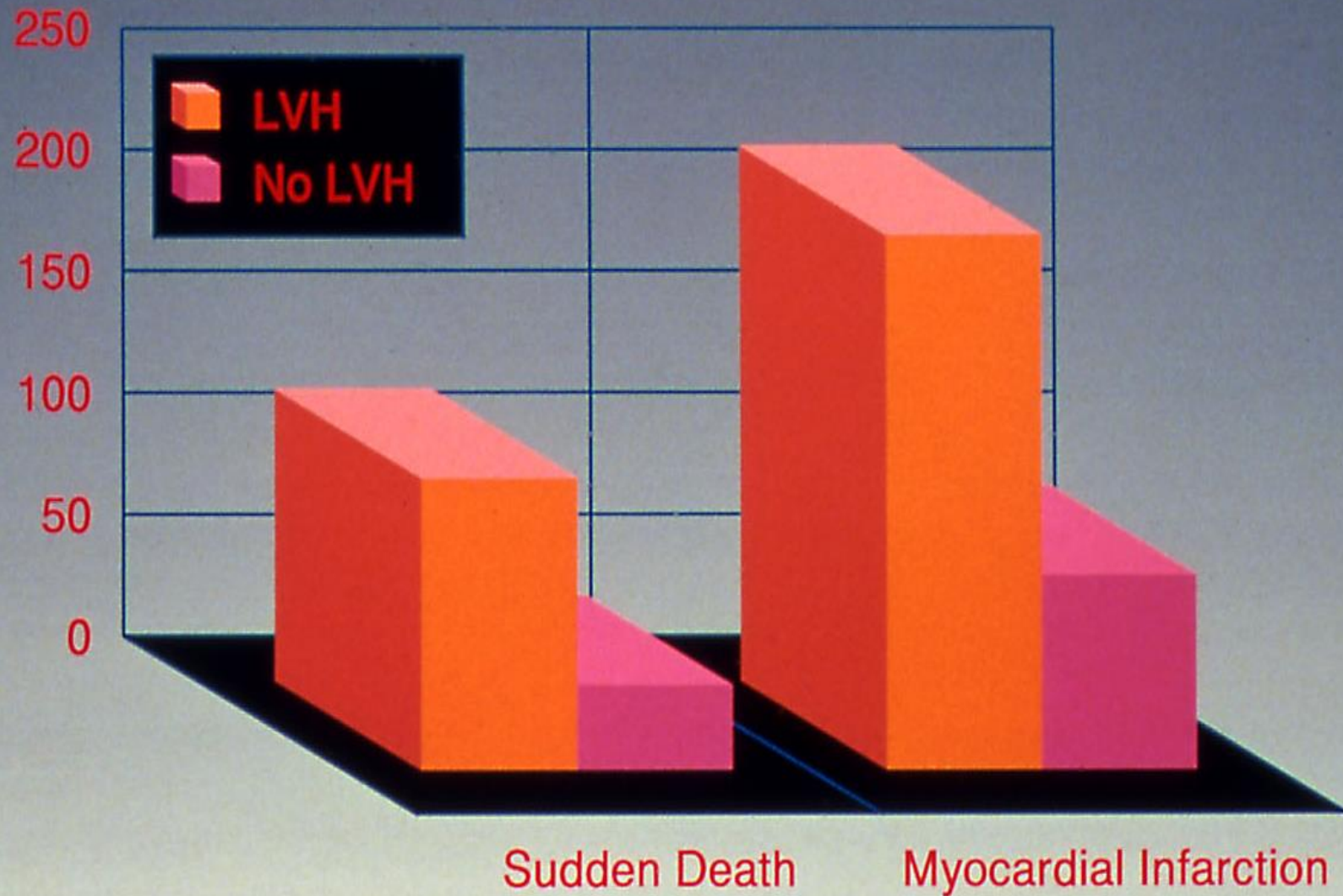


Target Organ Damage—Heart

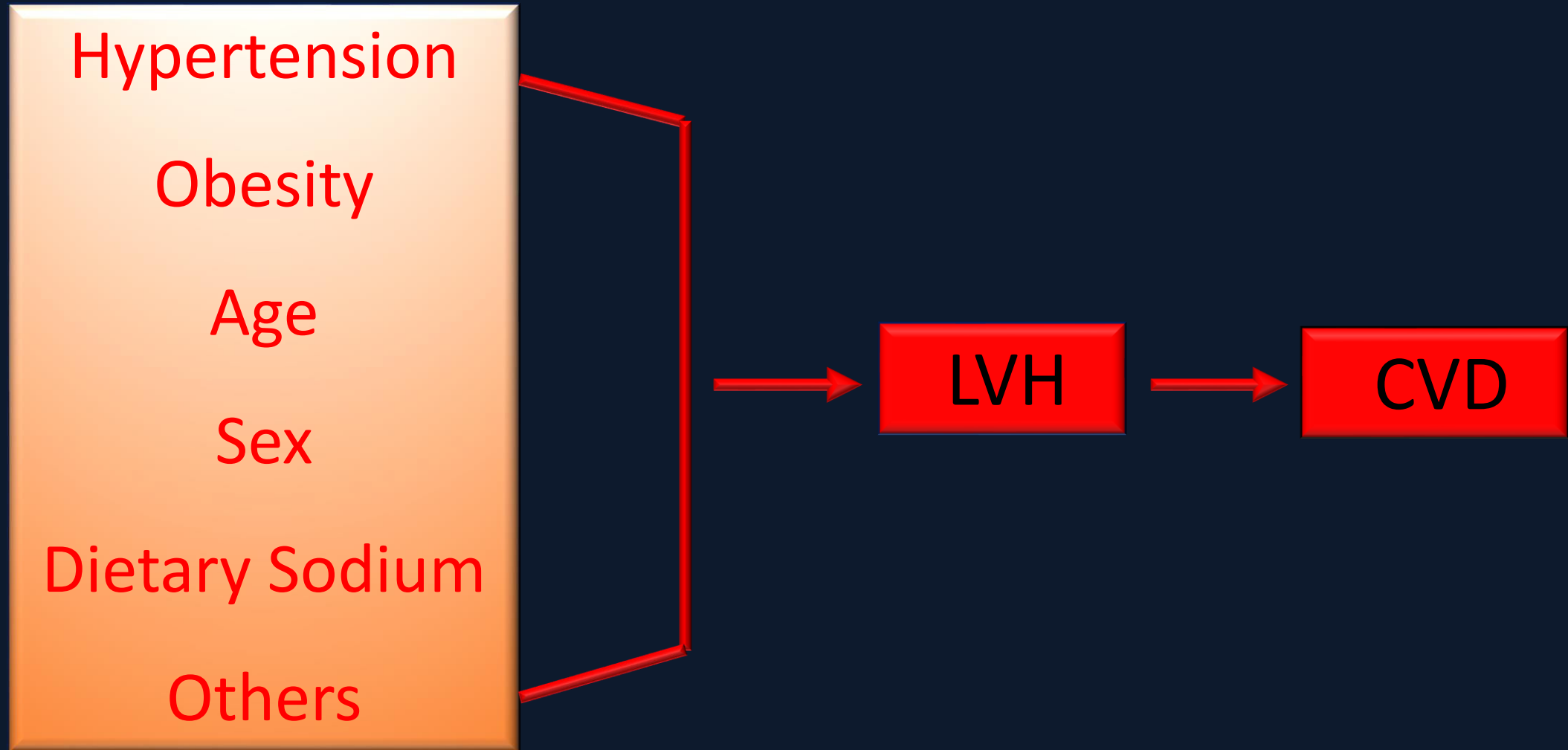
In addition to LV mass, LV geometry is also important.



Framingham Heart Study

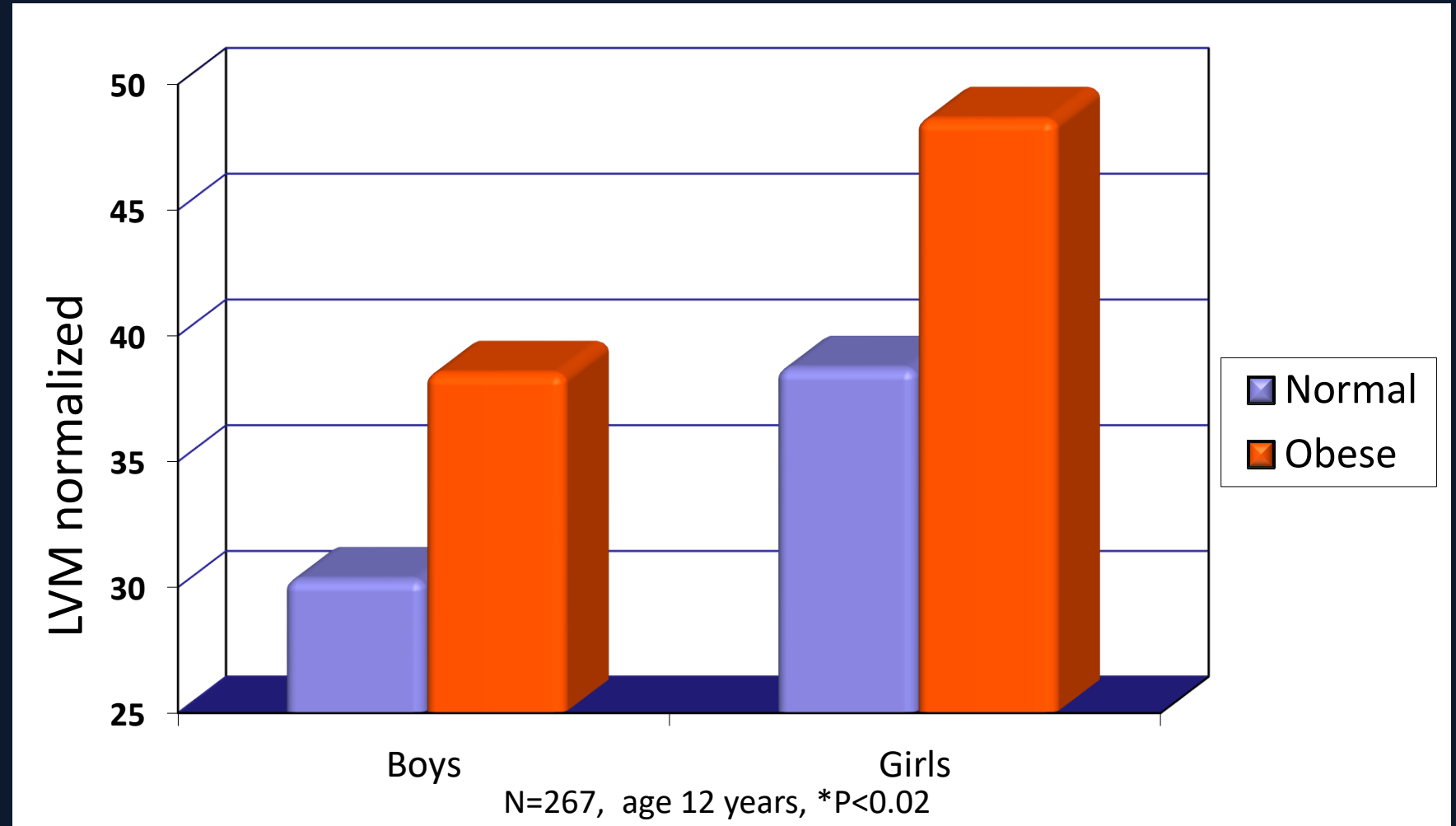


Target Organ Damage—Heart



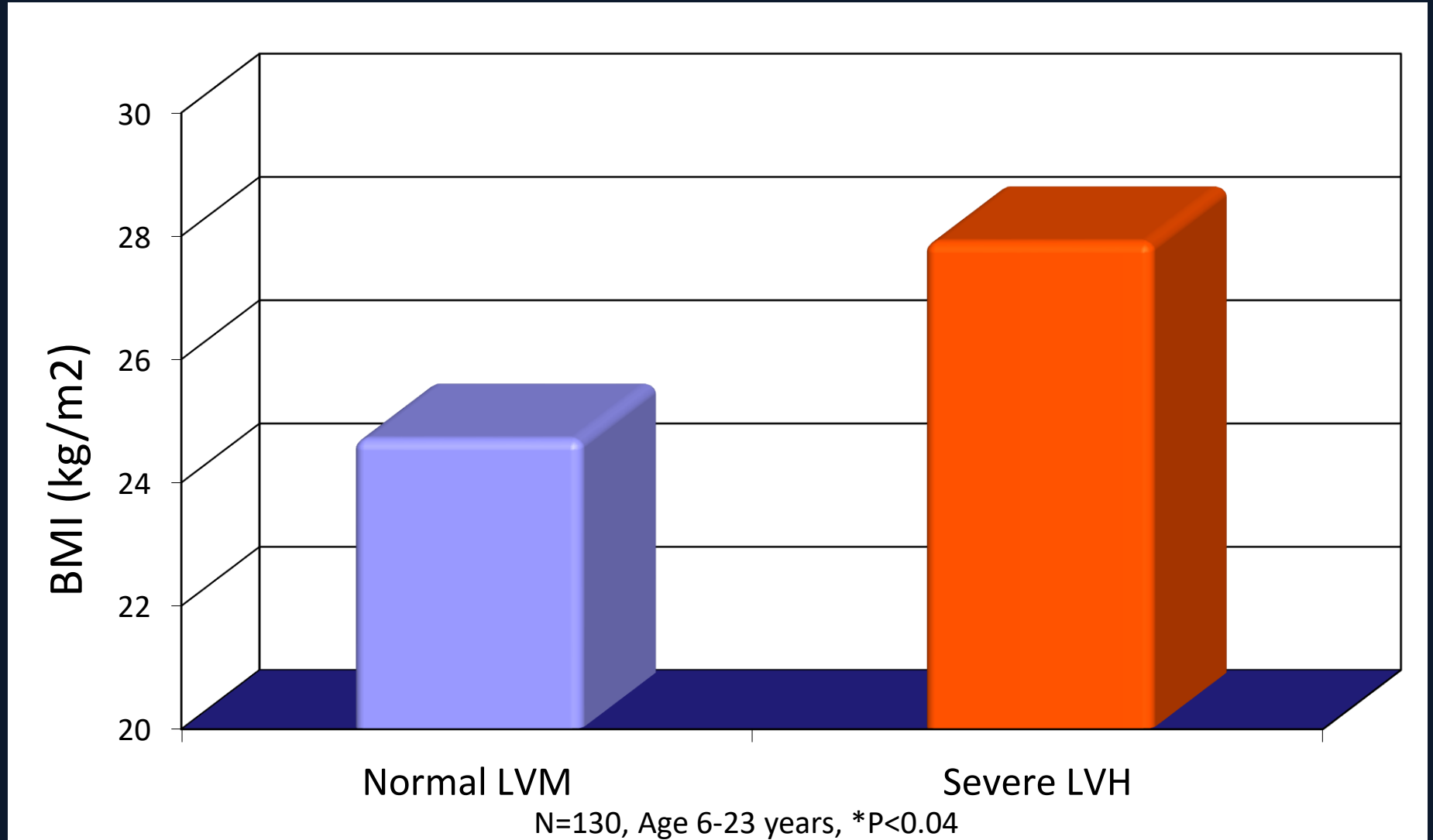
Target Organ Damage In Cardiometabolic Disease

LVM in
normal
and obese
children*



Target Organ Damage In Cardiometabolic Disease

BMI of
hypertensive
children
with and
without LVH*

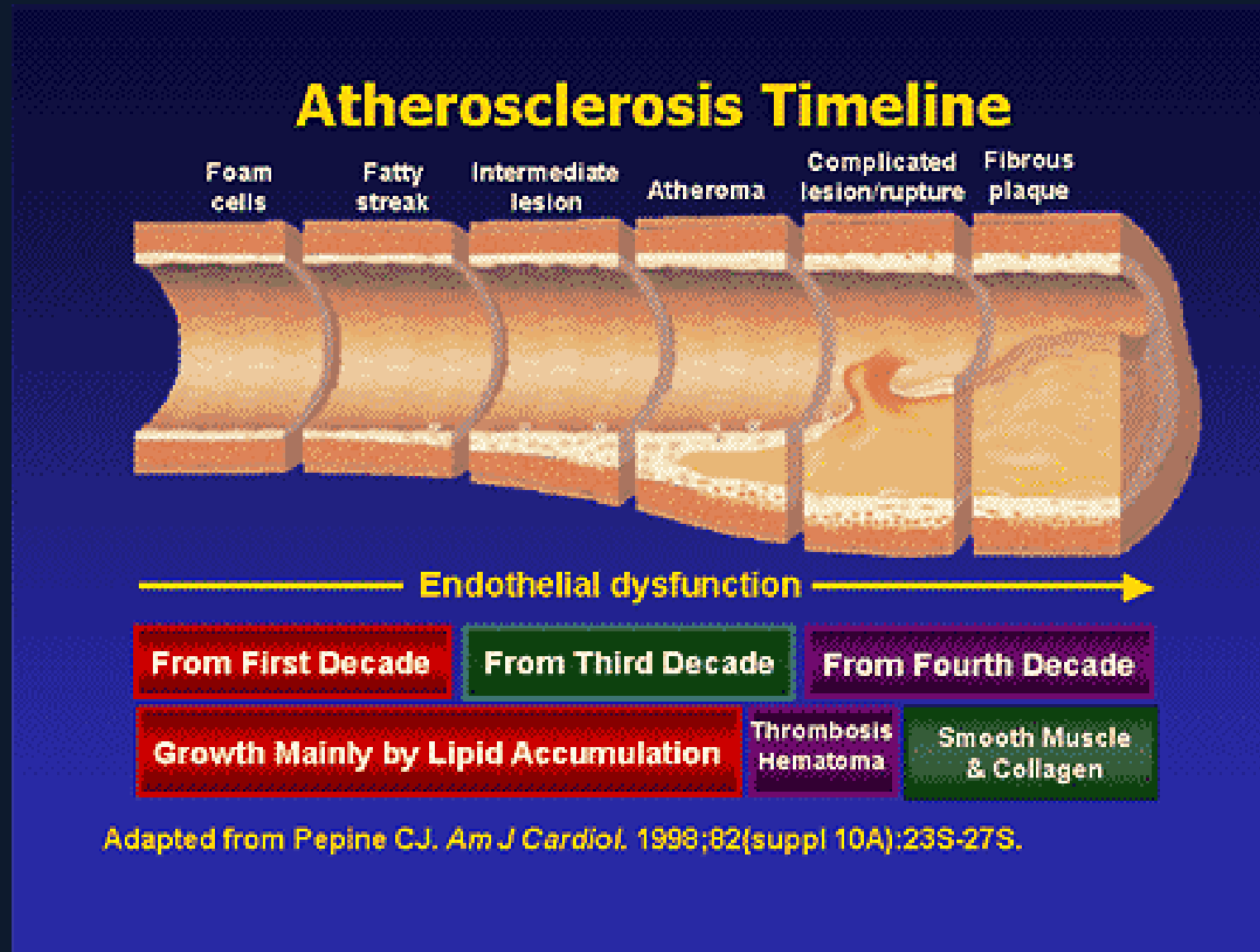


Target Organ Damage in Cardiometabolic Disease

Obesity and Cardiovascular Disease

Obesity in childhood is also associated with structural and functional abnormalities of the vasculature.

Target Organ Damage In Cardiometabolic Disease



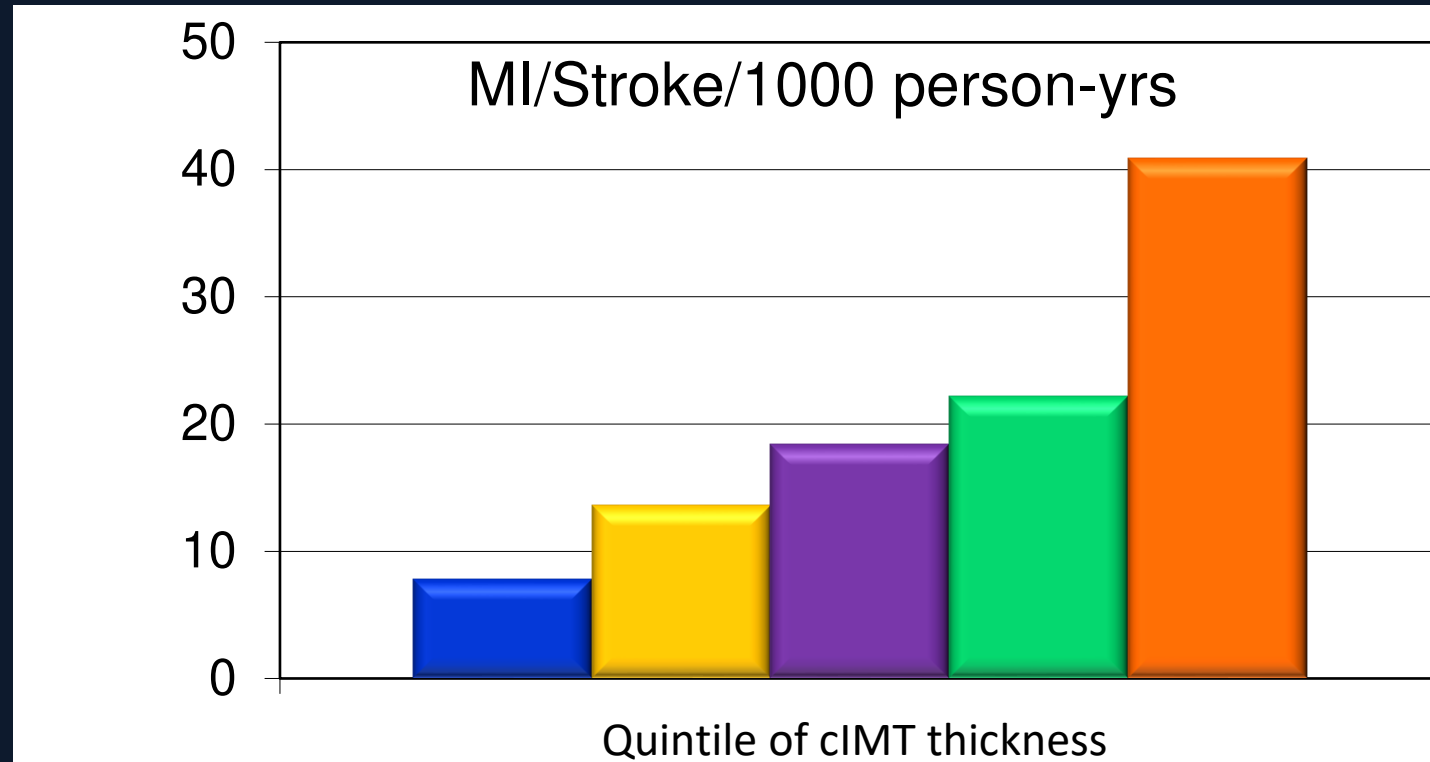
Target Organ Damage In Cardiometabolic Disease

Vascular Structure & Function

- Vascular structure
 - Measures of intima-media thickness of carotid, femoral arteries, abdominal aorta or other
- Arterial stiffness
 - Measures of intrinsic 'visco-elastic' properties of the arterial wall

Target Organ Damage In Cardiometabolic Disease

Higher Carotid IMT Predicts Hard CV Events

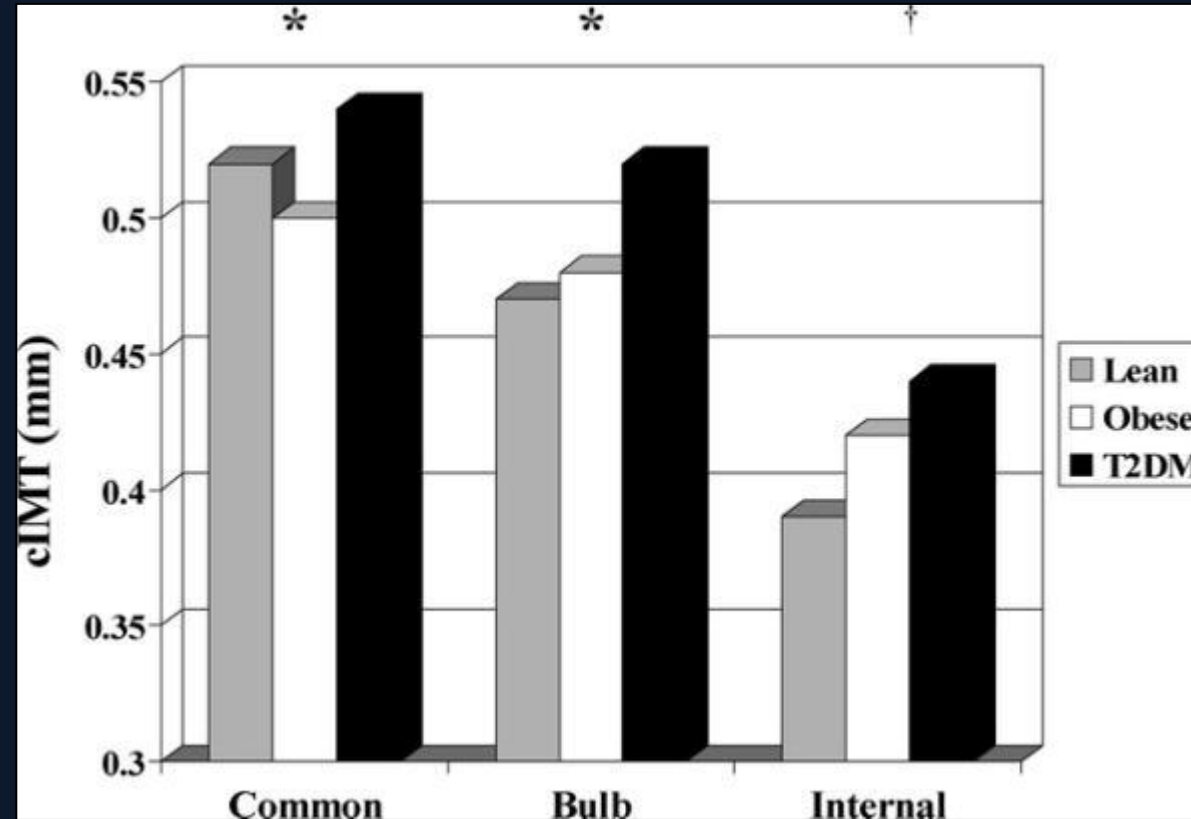


Incidence of stroke or myocardial infarction in adults increases with increasing carotid cIMT.

Target Organ Damage in Cardiometabolic Disease

Youth with obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function

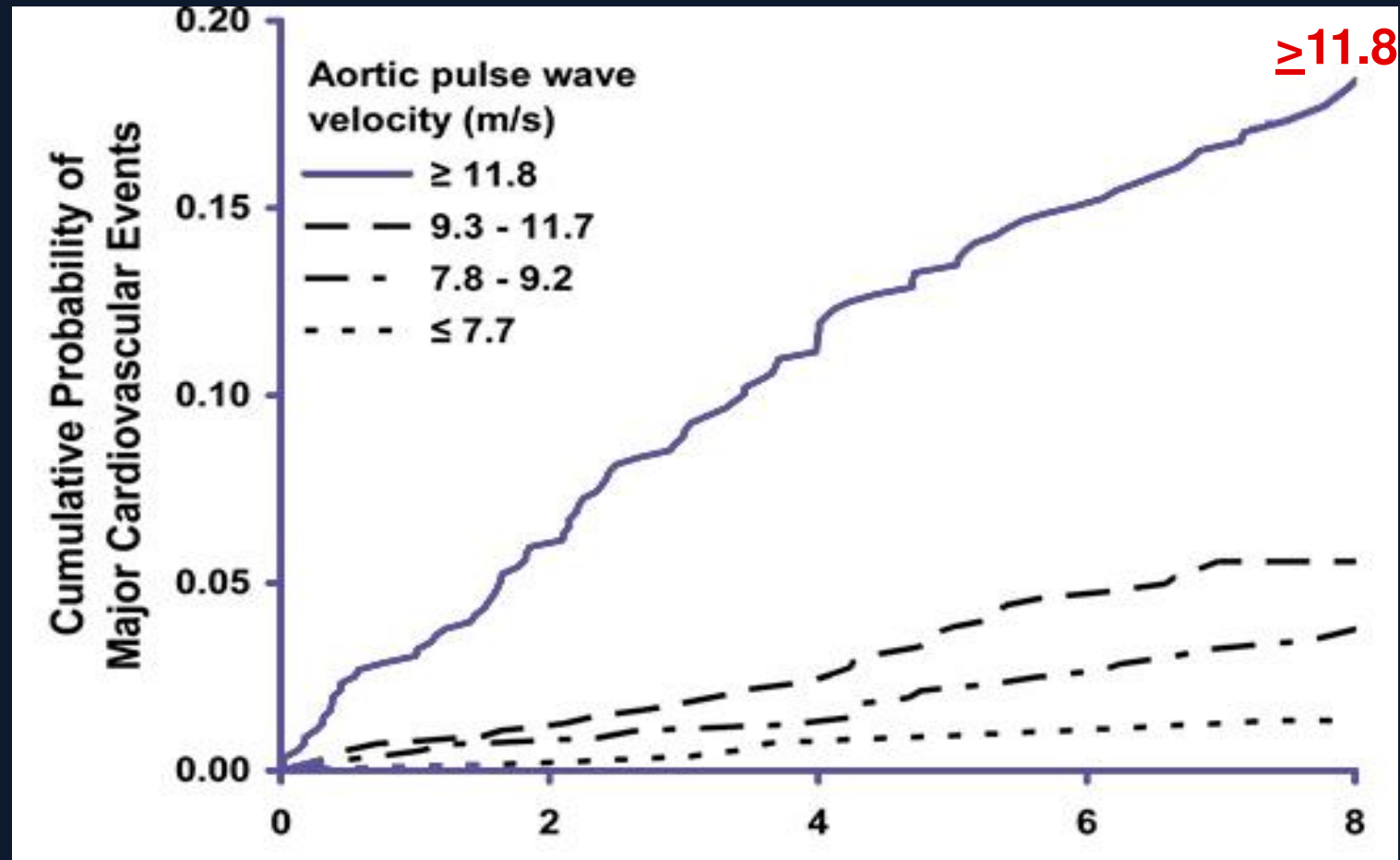
Figure 1.
cIMT by
group.
* $P < 0.05$,
lean < obese
and T2DM.



Urbina, Elaine; Kimball, Thomas; McCoy, Connie; Khoury, Philip; Daniels, Stephen, Dolan, Lawrence. Youth With Obesity and Obesity-Related Type 2 Diabetes Mellitus Demonstrate Abnormalities in Carotid Structure and Function. *Circulation*. 119(22):2913-2919, June 9, 2009. DOI: 10.1161/CIRCULATIONAHA.108.830380

Target Organ Damage in Cardiometabolic Disease

Elevated PWV *Predicts CV Events*



- PWV ≥ 11.8 m/sec at baseline associated with 48% increase in CVD risk even after adjustment for CV risk factors. N=2232, 63 years, 58% women.

Target Organ Damage in Cardiometabolic Disease

Higher PWV in youth with obesity and metabolic dysfunction

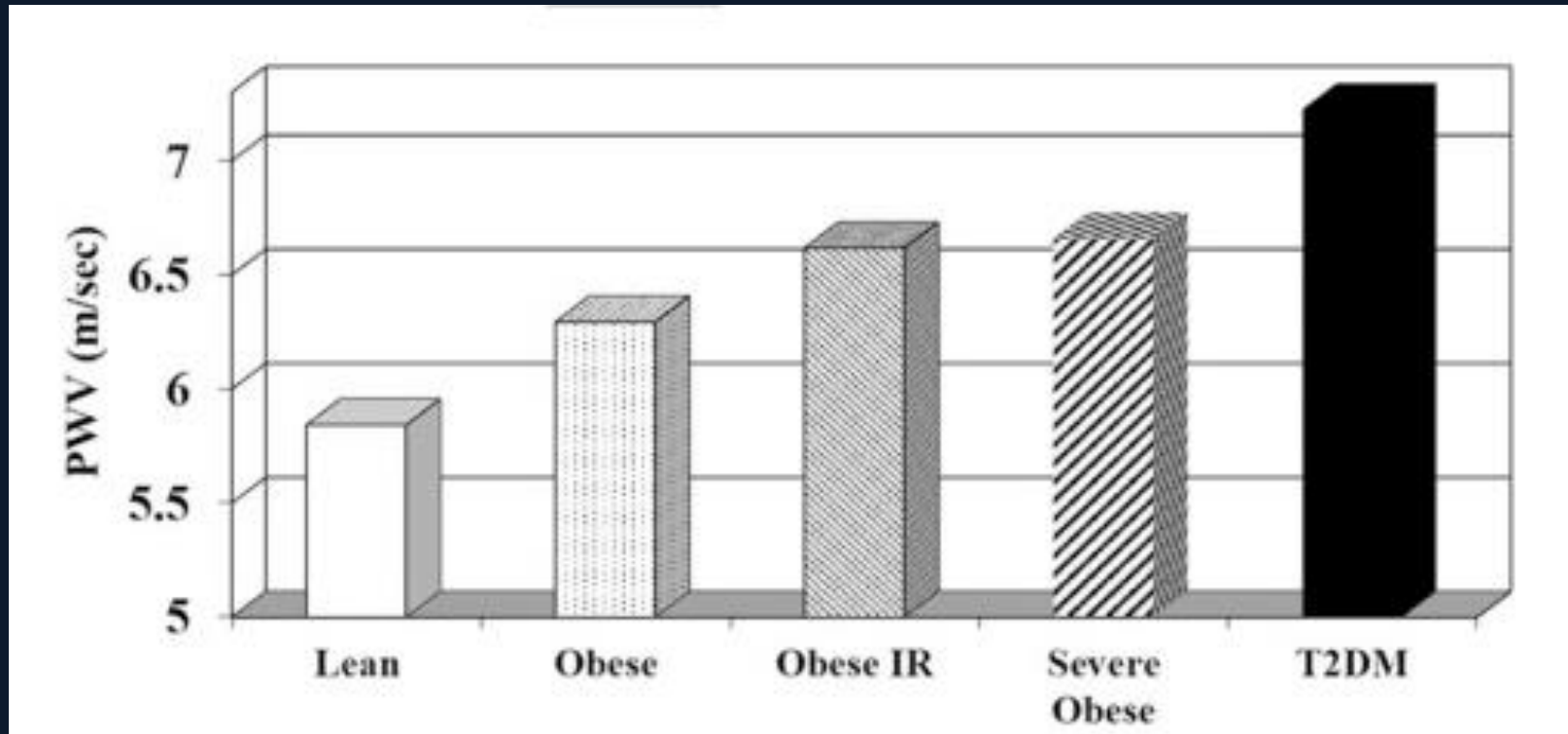
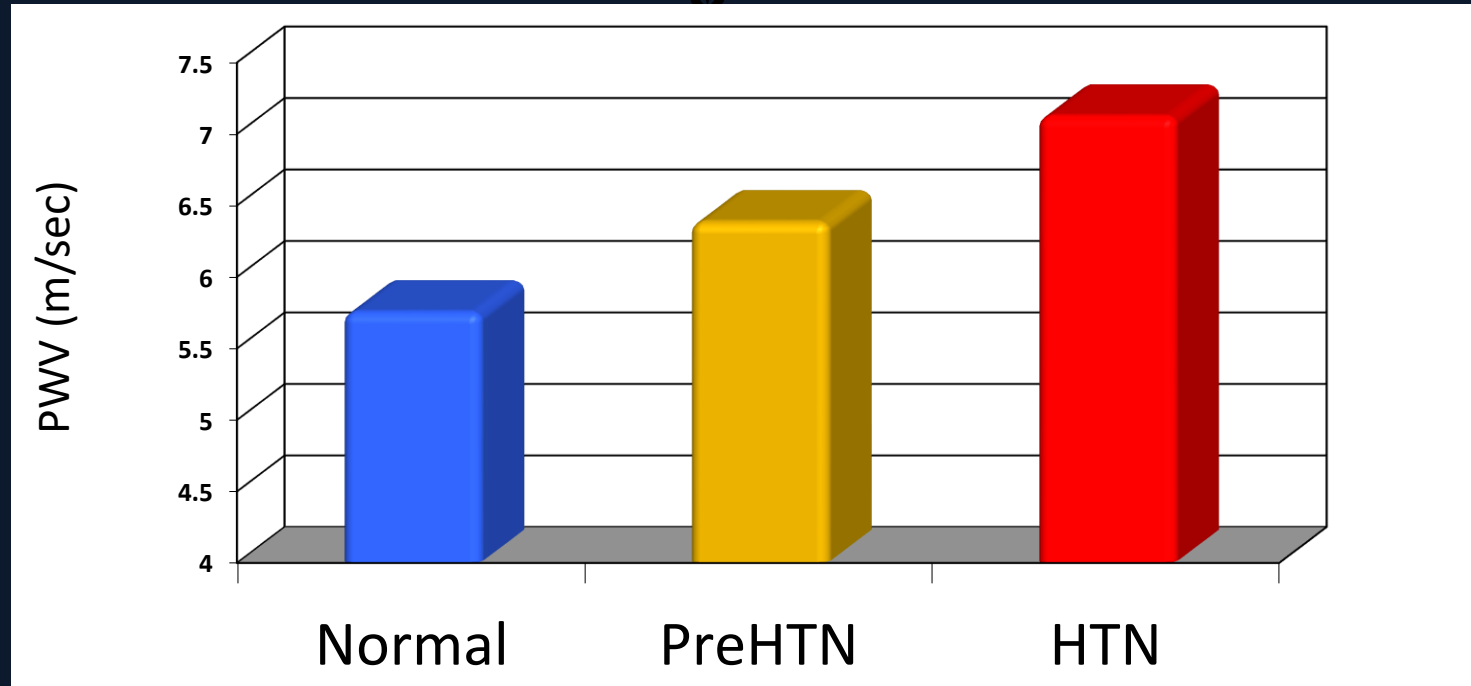


Figure 2

Higher PWV in youth with obesity and metabolic dysfunction. Comparing a spectrum of youth at risk, PWV is higher in youth with obesity, and further increases in youth with obesity and insulin resistance, youth with severe obesity, and youth with T2DM (unpublished data, adapted from Urbina et al and Shah et al).

Target Organ Damage in Cardiometabolic Disease

Increased PWV *with pre-HTN & HTN*



- Increased arterial stiffness (PWV) is also evident in youth with higher BP levels.
- In a study of over 700 adolescents, presence of Pre-HTN remained a significant predictor of PWV even after adjustment for other CV risk factors.
- Limitation: 1/3 cohort had T2DM so BP threshold for vascular TOD could not be determined.

Target Organ Damage In Cardiometabolic Disease

Neurocognitive Impairment in High Normal and Greater BP

- NHANES III Data
 - 6-16 yr.—5,077 kids
 - Prevalence SHtn 3.4% DHtn 1.6%
 - Groups $>$ or \leq 90%ile
- Wechsler Intelligence Scale for Children, Wide Range Achievement Test, Revised

Target Organ Damage in Cardiometabolic Disease

Table II. Average cognitive test scores for children with systolic BP \geq 90th percentile compared with scores for children with normal systolic BP

Cognitive Test	SBP <90th percentile	SBP \geq 90th percentile	P value
Block design	9.5 \pm 0.10	8.6 \pm 0.35	0.03
Digit span	8.7 \pm 0.08	7.9 \pm 0.24	0.01
Mathematics	93.8 \pm 0.54	89.6 \pm 1.4	0.01
Reading	92.1 \pm 0.53	89.5 \pm 2.3	NS
SBP, systolic BP; mean + SE			

Target Organ Damage In Cardiometabolic Disease

- We now have direct evidence of a link between obesity in youth and adult cardiovascular disease.

Target Organ Damage In Cardiometabolic Disease

Direct Evidence

- Cohort studies with long term follow up
- Childhood obesity → CVD morbidity and mortality

Target Organ Damage in Cardiometabolic Disease

Direct Evidence

Study of Native American Children

- 4,857 children without diabetes (mean age 11.3 years)
- Followed for death before age 55 years

Target Organ Damage In Cardiometabolic Disease

- 166 deaths from endogenous causes (3.4%) over median follow-up of 24 years
 - Factors associated with mortality:

	IRR	95% CI
Obesity	2.30	1.46 - 3.62
Glucose Intolerance	1.73	1.09 - 2.74
Hypertension	1.57	1.10 – 2.24

Target Organ Damage In Cardiometabolic Disease

Direct Evidence

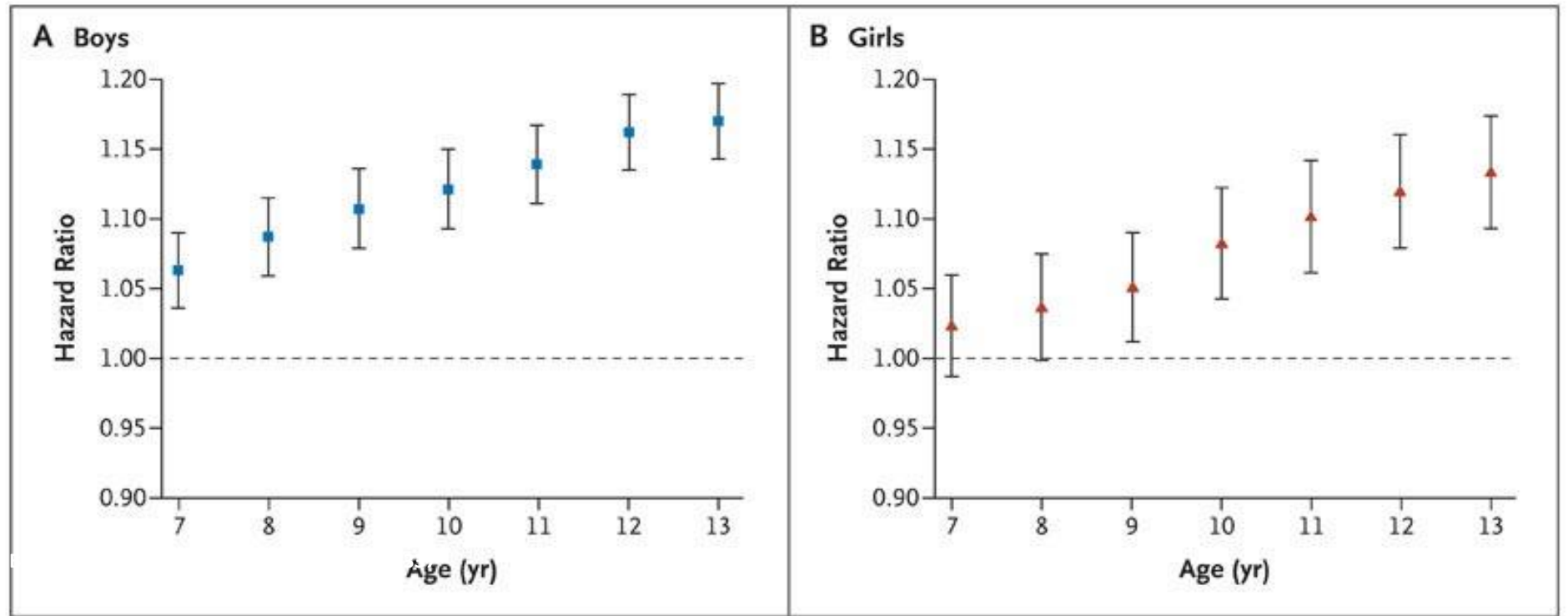
- Baker *et al* – Studied 276,835 Danish school children who were followed into adulthood.

Target Organ Damage in Cardiometabolic Disease

- Childhood BMI – age 7-13 years
- Adult CVD age 25-60 – from national registers
 - Nonfatal
 - Fatal

Target Organ Damage in Cardiometabolic Disease

Body-Mass Index (BMI) in Childhood and the Risk of Coronary Heart Disease (CHD) in Adulthood



The graphs depict the association between childhood BMI and the risk of having a CHD event (nonfatal or fatal) in adulthood. Hazard ratios and 95% confidence intervals are given for a 1-unit increase in BMI z score at each age from 7 to 13 years.

Target Organ Damage in Cardiometabolic Disease

Obesity and Cardiovascular Disease

- Higher BMI during childhood is associated with increased risk of CVD in adulthood.
- However, they did not have data on BMI in adulthood. This leaves the question of whether childhood obesity works through adult obesity or also has an independent effect.

Target Organ Damage in Cardiometabolic Disease

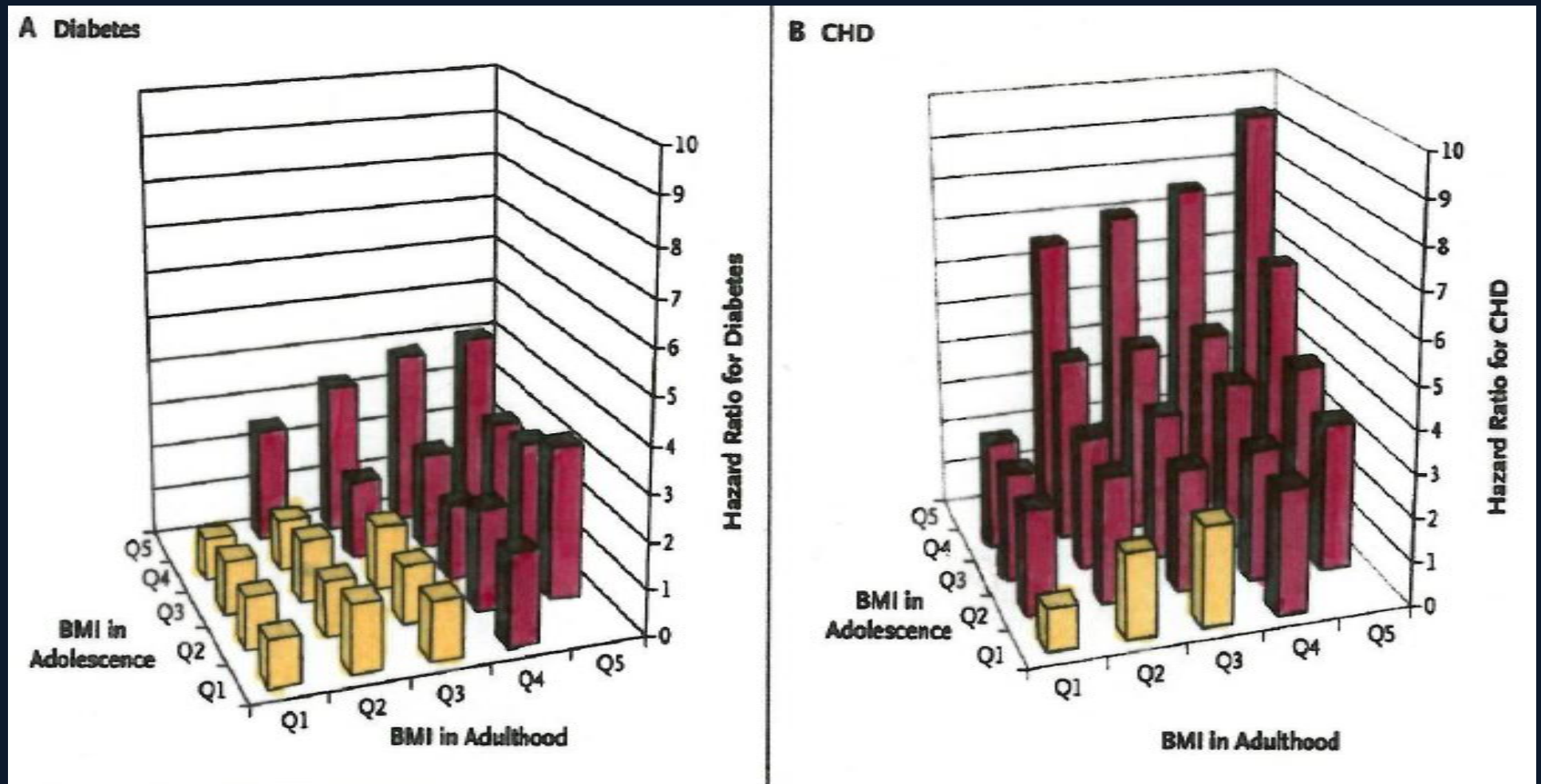
Obesity and Cardiovascular Disease

Direct Evidence

- Tirosh et al studied 37,674 apparently healthy Israeli men from adolescence (age 17) to adulthood. Outcomes were coronary heart disease and diabetes.

Target Organ Damage in Cardiometabolic Disease

Obesity and Cardiovascular Disease



Hazard Ratios for the Risk of Diabetes and Coronary Heart Disease among Apparently Healthy Young Adults, According to BMI in Adolescence and in Adulthood.

Target Organ Damage in Cardiometabolic Disease

Obesity and Cardiovascular Disease

- An elevated BMI in adolescence is an independent risk factor for CVD later in life.
- An elevated BMI in adulthood is an independent risk factor for both CVD and diabetes.

Obesity and Cardiovascular Disease

Direct Evidence

- Jacobs et al studied participants in 7 international cohorts (i3C)
- A total of 38,589 participants 3-19 years of age from the 1970s – 1990s were included.
- Outcomes were fatal and nonfatal cardiovascular events which were adjudicated via medical record review

Obesity and Cardiovascular Disease

Direct Evidence

- Childhood risk factors included body mass index, systolic blood pressure, total cholesterol, triglycerides, and cigarette smoking.
- A combined risk Z-score was calculated.

Obesity and Cardiovascular Disease

Table 2. Hazard Ratios for Adult Cardiovascular Events According to Childhood, Adult, or Childhood plus Adult Risk Scores.*

Variable	Hazard Ratio (95% CI) [†]	
	Fatal Event	Fatal or Nonfatal Event
Childhood risk factor		
Youth smoking: yes vs. no	1.61 (1.21–2.13)	1.70 (1.49–1.93)
z Score for body-mass index	1.44 (1.33–1.57)	1.45 (1.38–1.53) [‡]
z Score for systolic blood pressure	1.34 (1.19–1.50)	1.33 (1.24–1.42)
z Score for ln(triglycerides)	1.50 (1.33–1.70)	1.45 (1.34–1.56)
z Score for total cholesterol level	1.30 (1.14–1.47)	1.31 (1.22–1.42)
Combined-risk z score [§]	2.71 (2.23–3.29)	2.75 (2.48–3.06) [‡]

Obesity and Cardiovascular Disease

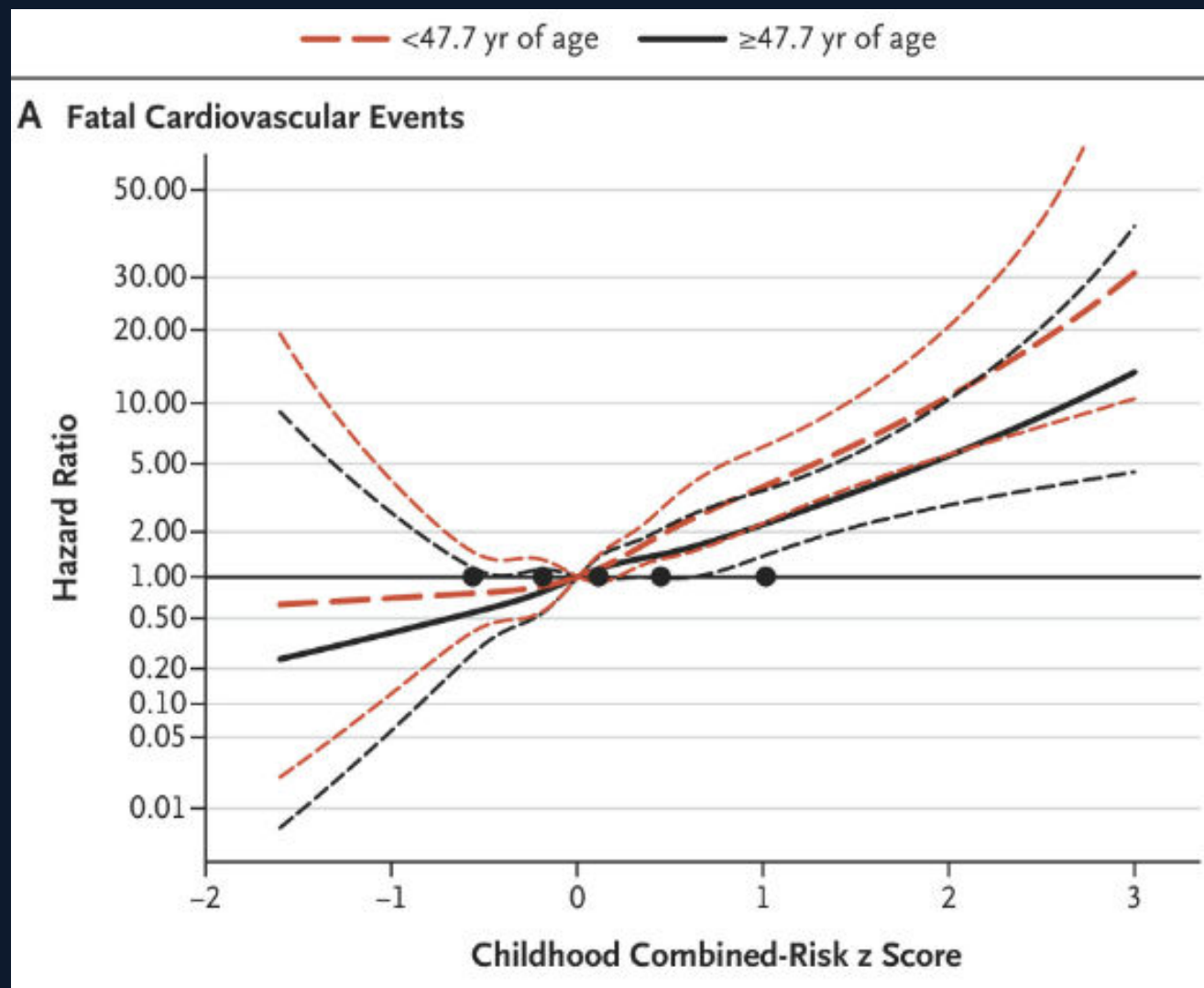


Figure 1. Hazard Ratios for Cardiovascular Events at Younger and Older Ages.

Panel A shows the hazard ratios for fatal cardiovascular events, and Panel B shows the hazard ratios for fatal or nonfatal cardiovascular events. The spline of the hazard ratio is presented on a logarithmic scale across the distribution of the childhood combined-risk z scores, with 95% confidence intervals (shorter dashed lines). Younger age (<47.7 years) includes all the participants, among whom there were 157 fatal events and a mean of 797 fatal or nonfatal events across imputations. The older age group includes only the participants who were followed and had no event or had events at or after 47.7 years of age (a total of 18,352 participants, among whom 162 had a fatal cardiovascular event and 1049 either had a fatal event due to other causes or were not followed past the age of 47.6 years; the 17,141 remaining participants had a mean of 766 fatal or nonfatal events across imputations). The black circles indicate knots placed at the 5th, 25th, 50th, 75th, and 95th percentiles of the combined-risk z score.

Obesity and Cardiovascular Disease

Direct Evidence

- Childhood risk factors both alone and in a combined risk score are associated with increased risk of both fatal and combined fatal or nonfatal cardiovascular outcomes.

Target Organ Damage In Cardiometabolic Disease

Obesity and Cardiovascular Disease

- An important issue is whether the impact of obesity in childhood on cardiovascular outcomes is fixed or can be altered.

Target Organ Damage In Cardiometabolic Disease

Obesity and Cardiovascular Disease

➤ Juonala *et al* combined data from the

- ✓ Bogalusa Heart Study
- ✓ Muscatine Study
- ✓ Cardiovascular Disease in the Young Finns Study
- ✓ Childhood Determinants of Adult Health Study (Australia)

to evaluate longitudinal data between childhood (BMI, CVD risk factors) and adulthood (BMI, CVD Risk Factors, carotid IMT)

Target Organ Damage in Cardiometabolic Disease

Obesity and Cardiovascular Disease

	Childhood	Adult
Group 1	Normal BMI	Non-obese
Group II	Obese	Non-obese
Group III	Obese	Obese
Group IV	Normal BMI	Obese

Target Organ Damage In Cardiometabolic Disease

Obesity and Cardiovascular Disease

- Children who were overweight or obese and remained obese in adulthood (Group III) had increased risk of T2DM, hypertension, dyslipidemia and increased carotid IMT
- Overweight or obese children who became non-obese by adulthood (Group II) were similar in CVD risk and carotid IMT to those who were never obese (Group I).

Target Organ Damage in Cardiometabolic Disease

Obesity and Cardiovascular Disease

This means that while prevention of obesity in childhood is optimal, treatment of those children who have become obese is also very important.

