METABOLIC SYNDROME CONTROVERSY

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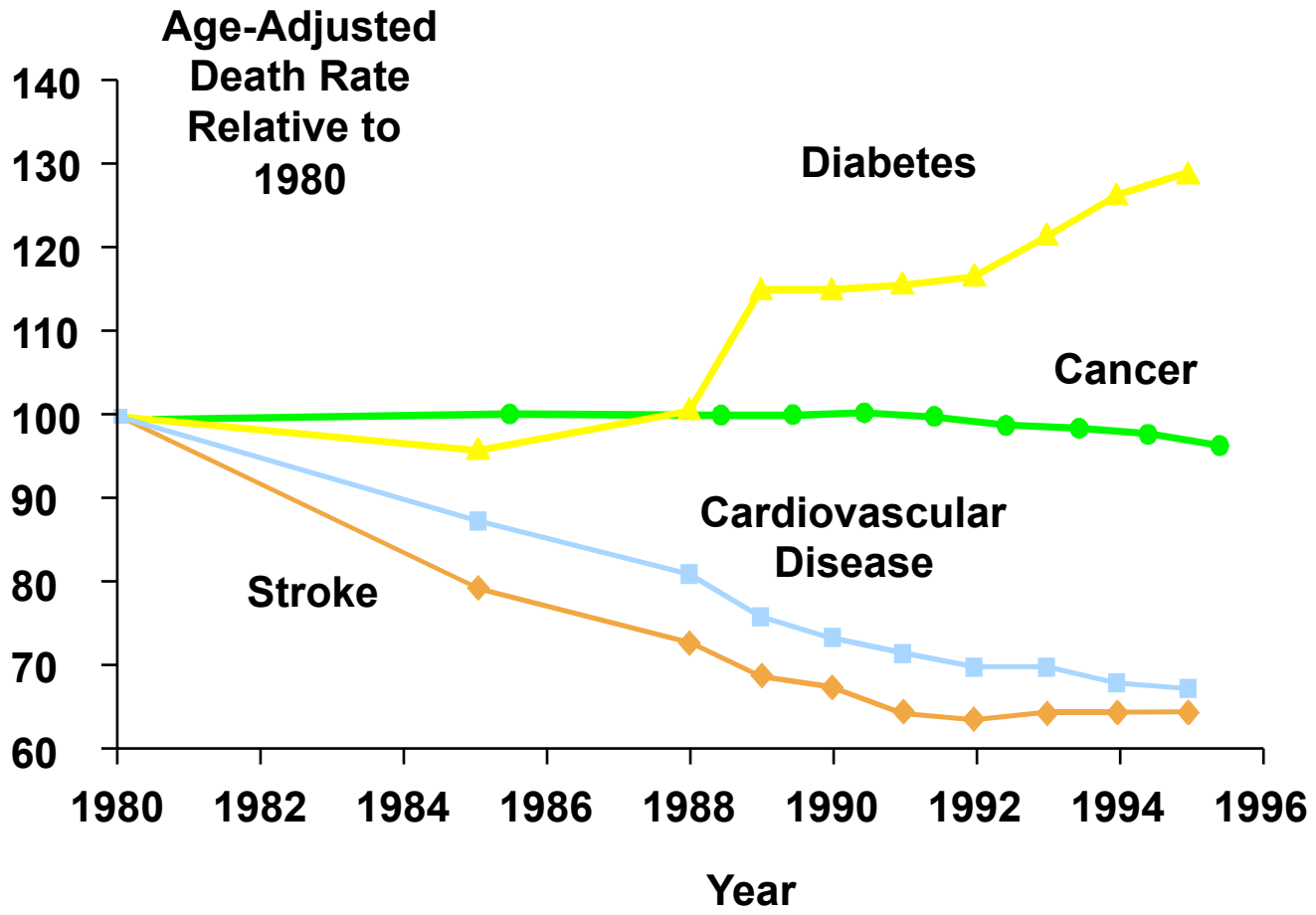
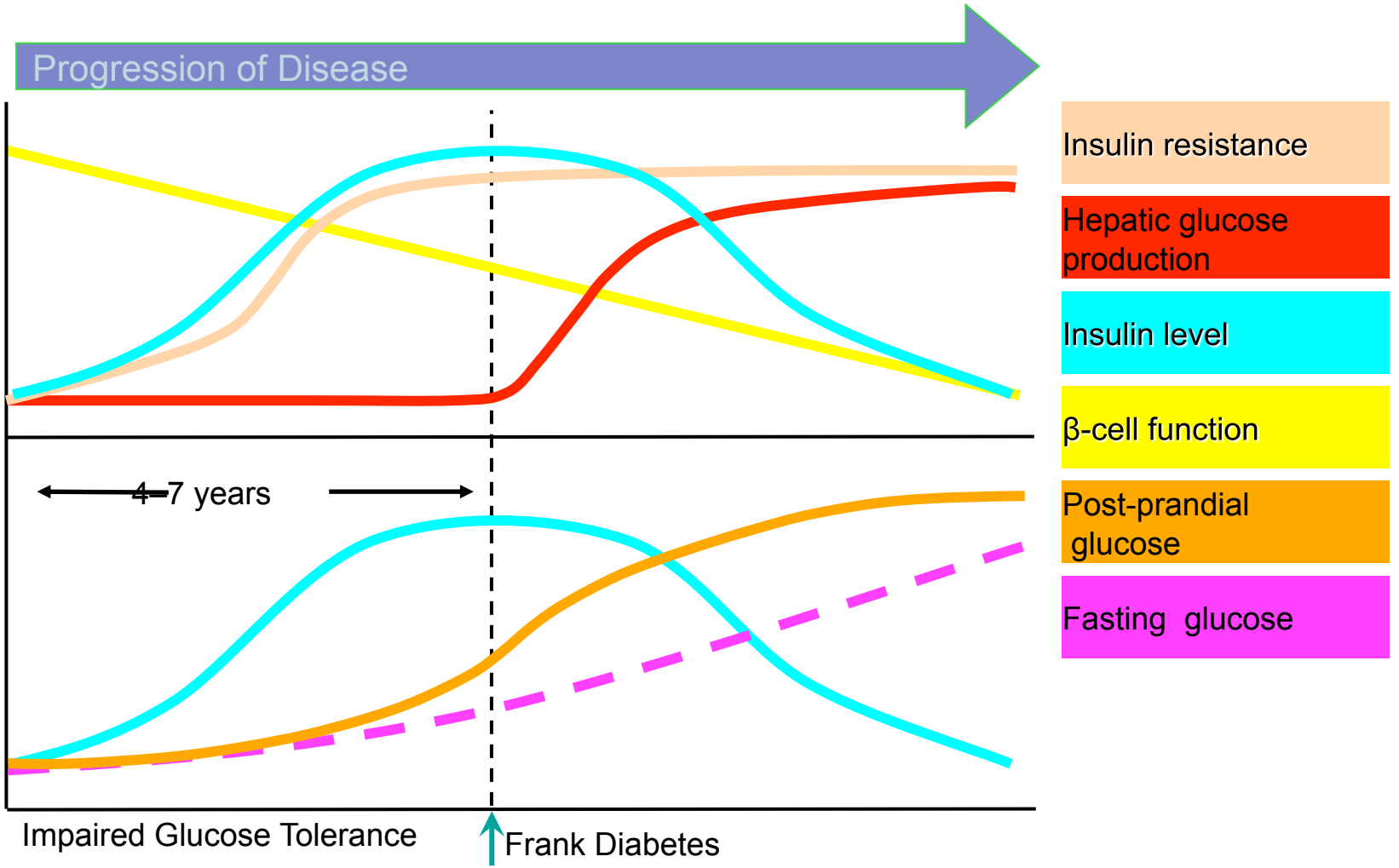
W.R 52 y Female

- BP =160/90
- WC =98 cm
- GLU = 250 mg/dl
- CHOL = 198 mg/dl
- TG = 258 mg/dl
- HDL = 28 mg/dl
- LDL = 107 mg/dl
- PROTEINURIA

Increasing Death Rate Due to Diabetes

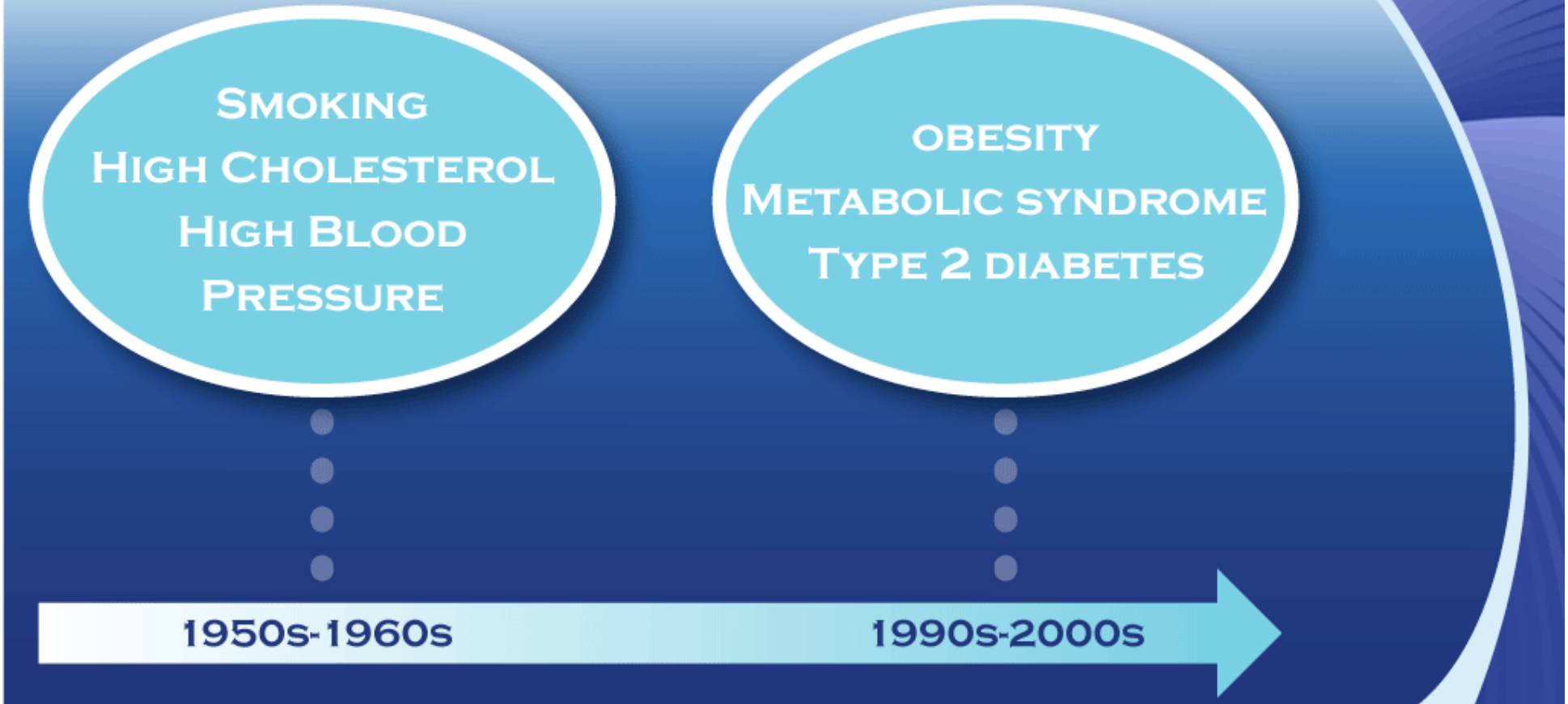


Progression of Disease



Reprinted from *Primary Care,* 26, Ra natural history of type 2 diabetes. Implications for clinical practice, 771–789, © 1999, with permission from Elsevier.

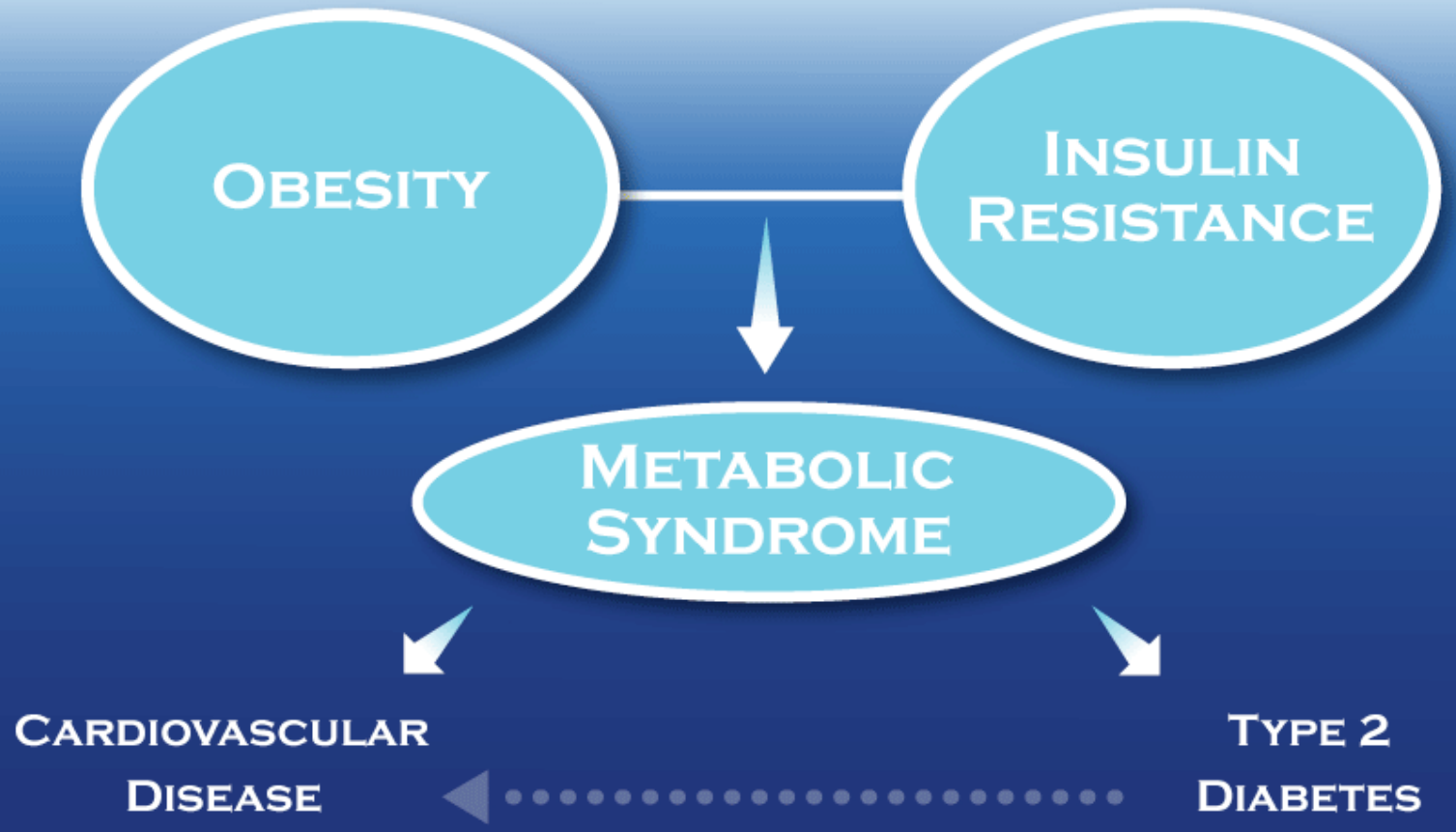
Cardiovascular Risk Factors: An Evolving Landscape



The Metabolic Syndrome Institute

Metabolic Syndrome

Dual Pathways: Dual Outcomes



The Metabolic Syndrome Institute

outline

- Metabolic syndrome name & definition?
- Is the metabolic syndrome important ?
- More than sum of its parts ?
- Clinical utility ?

Metabolic syndrome name

Syndrome derived from Greek:

syn = with or together

dromos = running stadium

Running together

Metabolic feature running together

CREPALDI'S SYNDROME

"seems to suggest a peculiar syndrome including hyperlipemia, obesity and diabetes. The development of ischaemic heart disease … and hypertension is often found in these patients."

Avogaro & Crepaldi, 1965

Conceptual Framework for the Metabolic Syndrome

- Environmental causes are responsible for the epidemic of the metabolic syndrome (NCEP)
- Insulin resistance is the underlying cause of the metabolic syndrome (Reaven, WHO)
- Abdominal Obesity is the underlying cause of the metabolic syndrome (IDF)

Environmental causes ATP III (2005)

- **High waist circumference (102/88 cm)**

  ↑ Triglycerides ≥ 150 mg/dL‡
- **↓ HDL cholesterol‡**
  - **Men < (40 mg/dL)**
  - **Women < (50 mg/dL)**
- **↑ Blood pressure ≥ 130 / ≥85 mm Hg‡**
- **↑ FPG ≥ 100 mg/dL, or diabetes**

Abdominal obesity - IDF

- **High waist circumference**

  Plus any two of

- **↑ Triglycerides ≥ 150 mg/dL‡**
- **↓ HDL cholesterol‡**
  - **Men < (40 mg/dL)**
  - **Women < (50 mg/dL)**
- **↑ Blood pressure ≥ 130 / ≥85 mm Hg‡**
- **↑ FPG ≥ 100 mg/dL, or diabetes**

Abdominal obesity and waist circumference thresholds

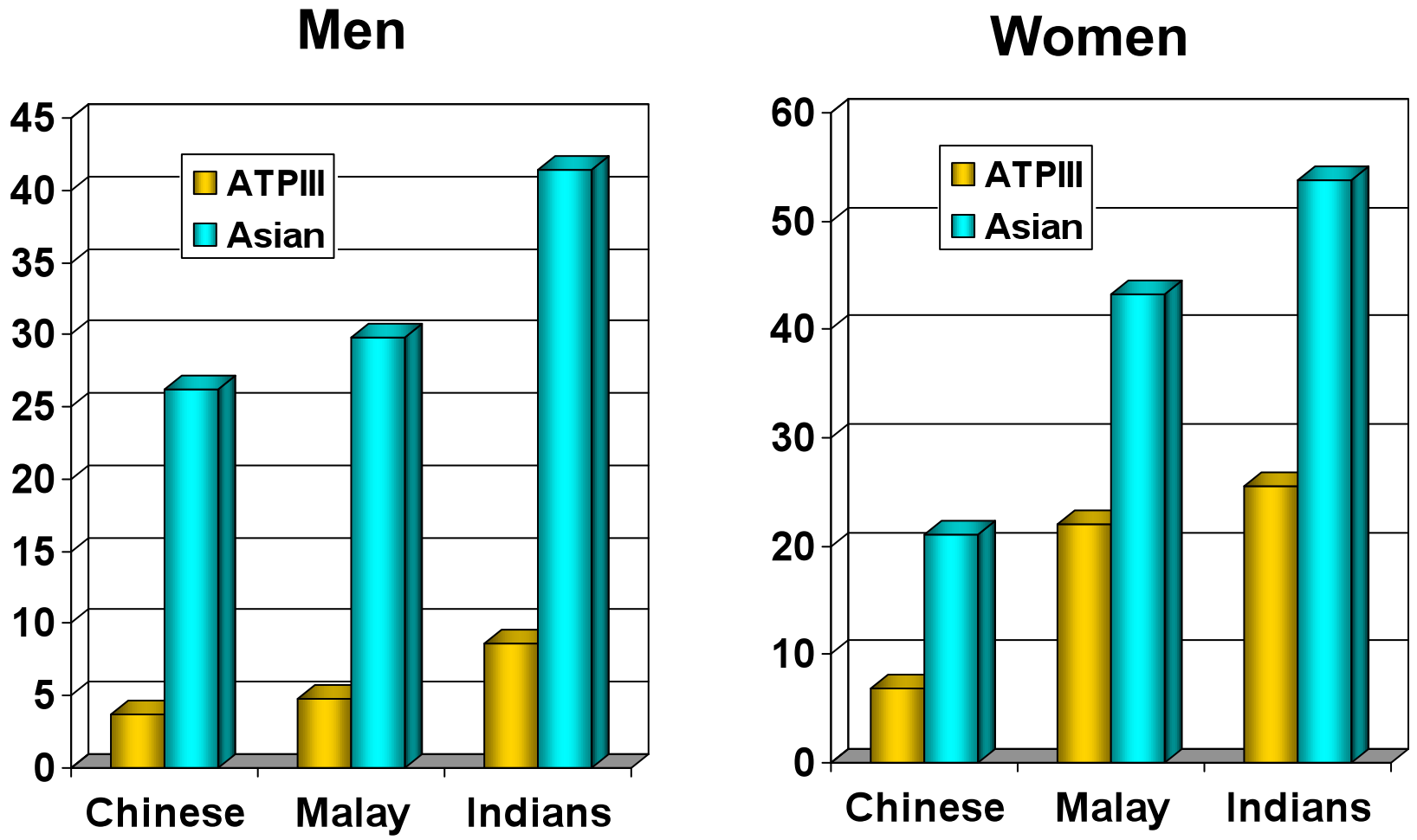
IDF criteria:

	Men	Women
Europid	≥94 cm (37.0 in)	≥80 cm (31.5 in)
South Asian	≥90 cm (35.4 in)	≥80 cm (31.5 in)
Chinese	≥90 cm (35.4 in)	≥80 cm (31.5 in)
Japanese	≥85 cm (33.5 in)	≥90 cm (35.4 in)

Current NCEP ATP-III criteria

- >102 cm in men, >88 cm in women

Prevalence of Central Obesity in Singapore



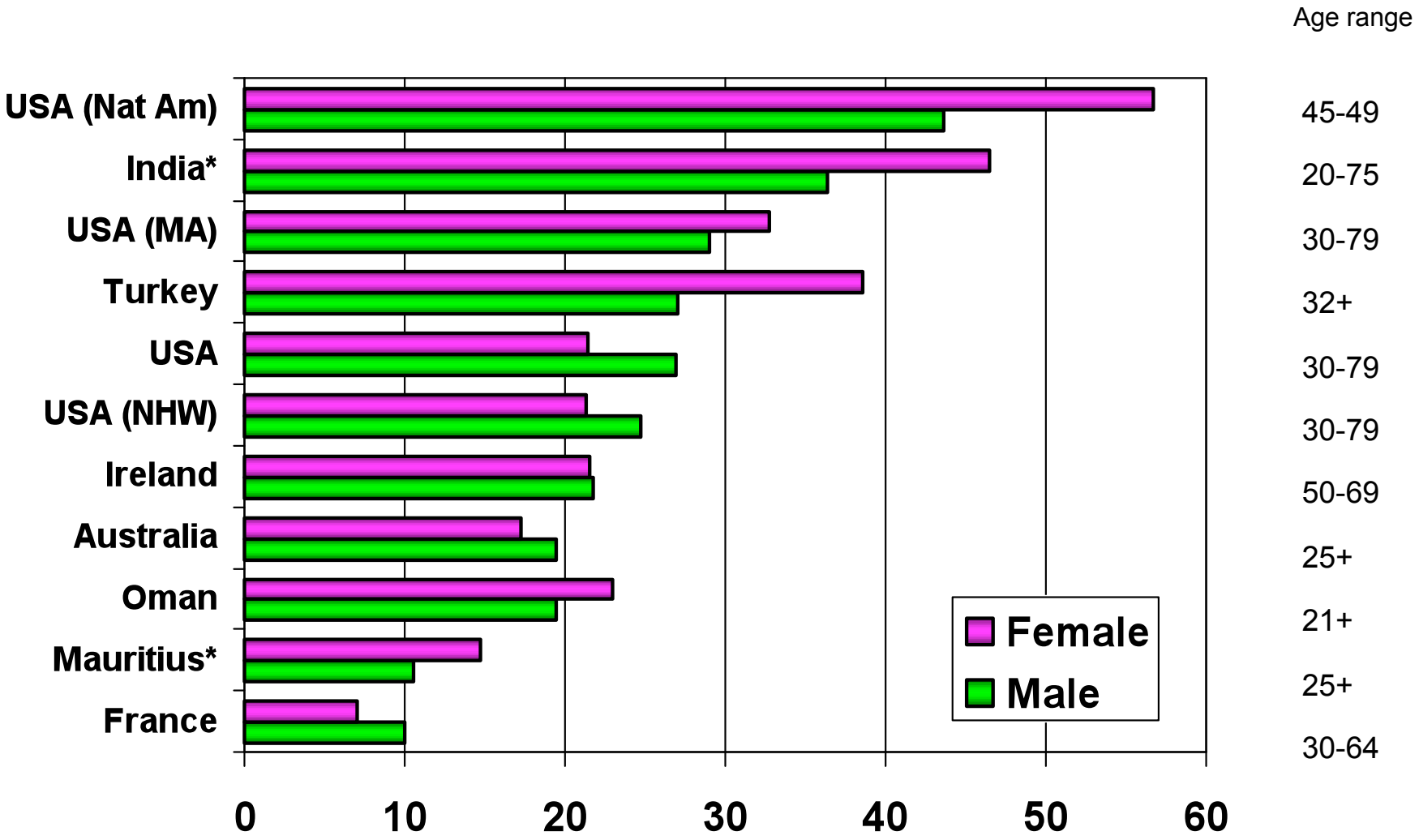
Women >88 cm (ATPIII) >80 cm (Asian)
Men >102 cm (ATPIII) >90 cm (Asian)

Tan CE et al Diabetes Care 2004

Criteria for Clinical Diagnosis of the Metabolic Syndrome - 2009

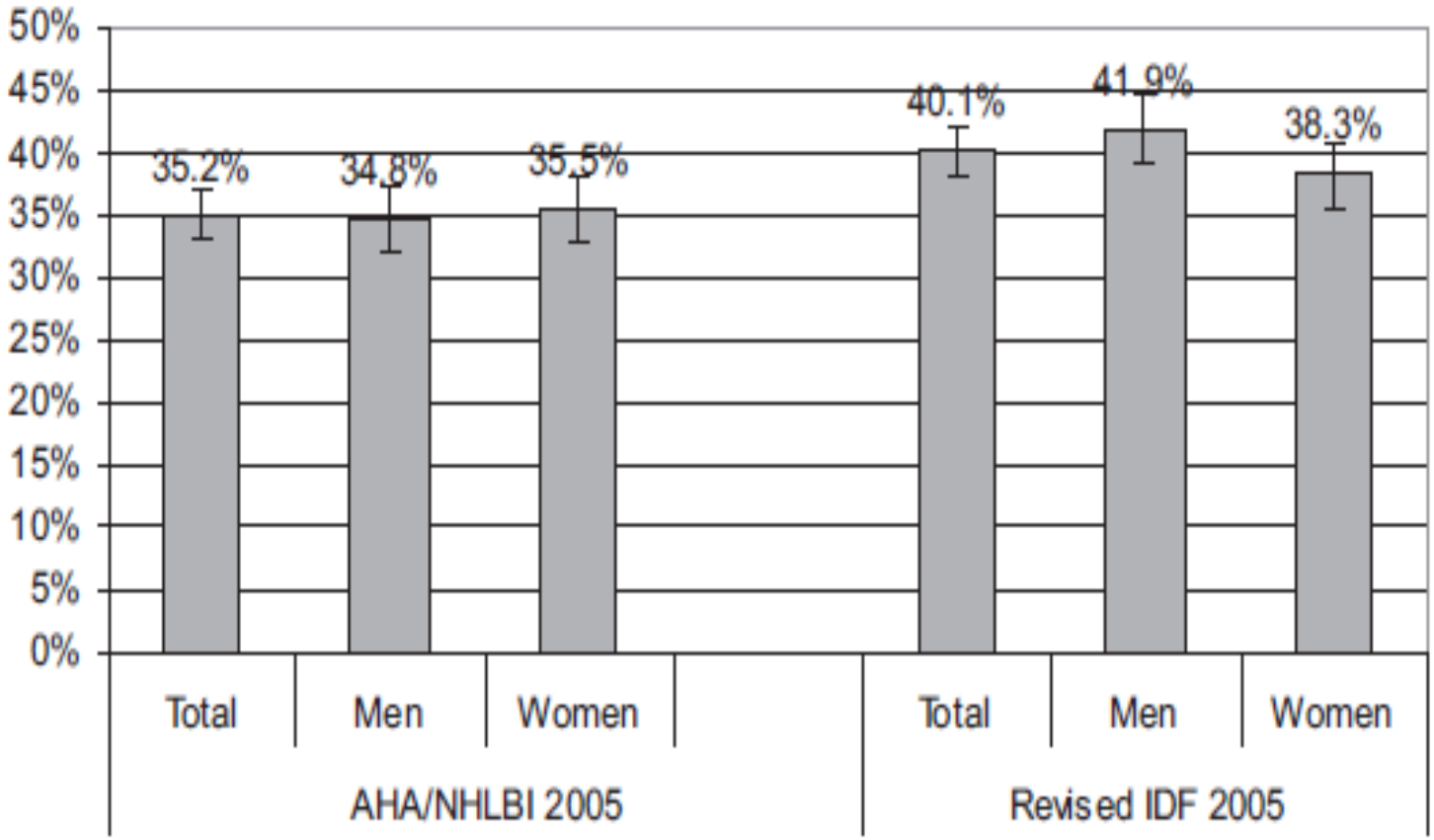
Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

Prevalence Of The Metabolic Syndrome According To ATP III Definition



*Obesity criteria adjusted to waist circumference appropriate for an Indian population

Unadjusted prevalence of the metabolic syndrome among US adults > 20 y



METABOLIC SYNDROME CONTROVERSY

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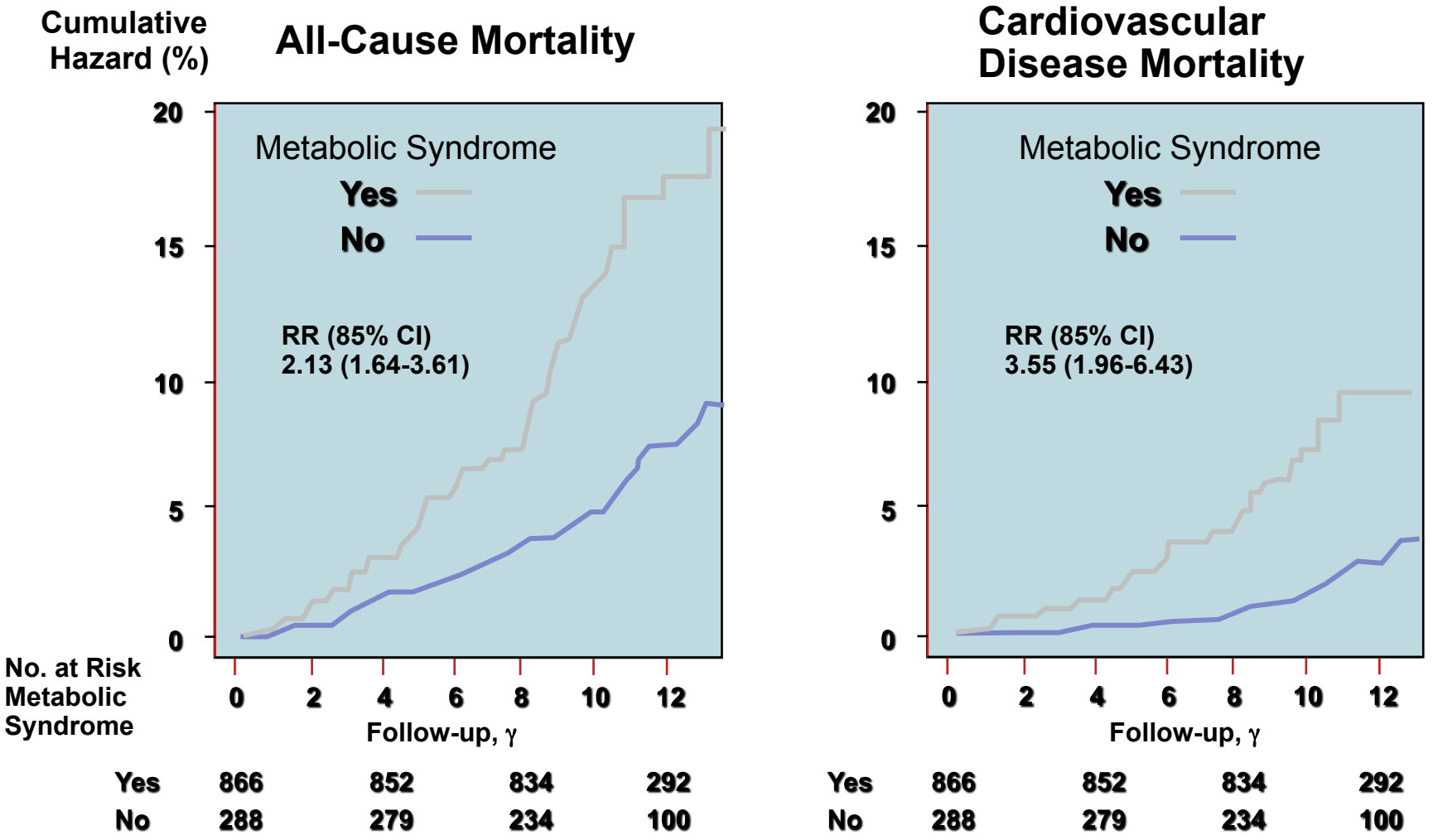
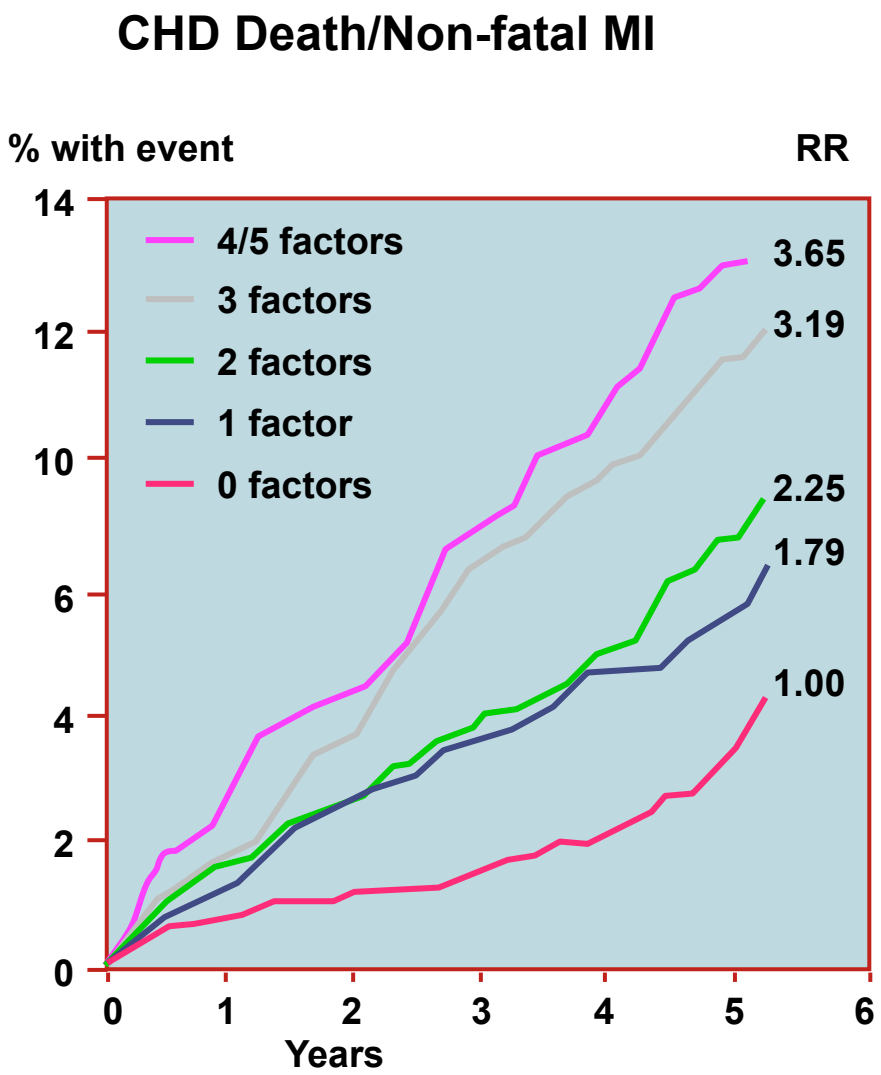
Metabolic Syndrome: Total and CV Mortality in Middle-Aged Men in Kuopio Heart Study

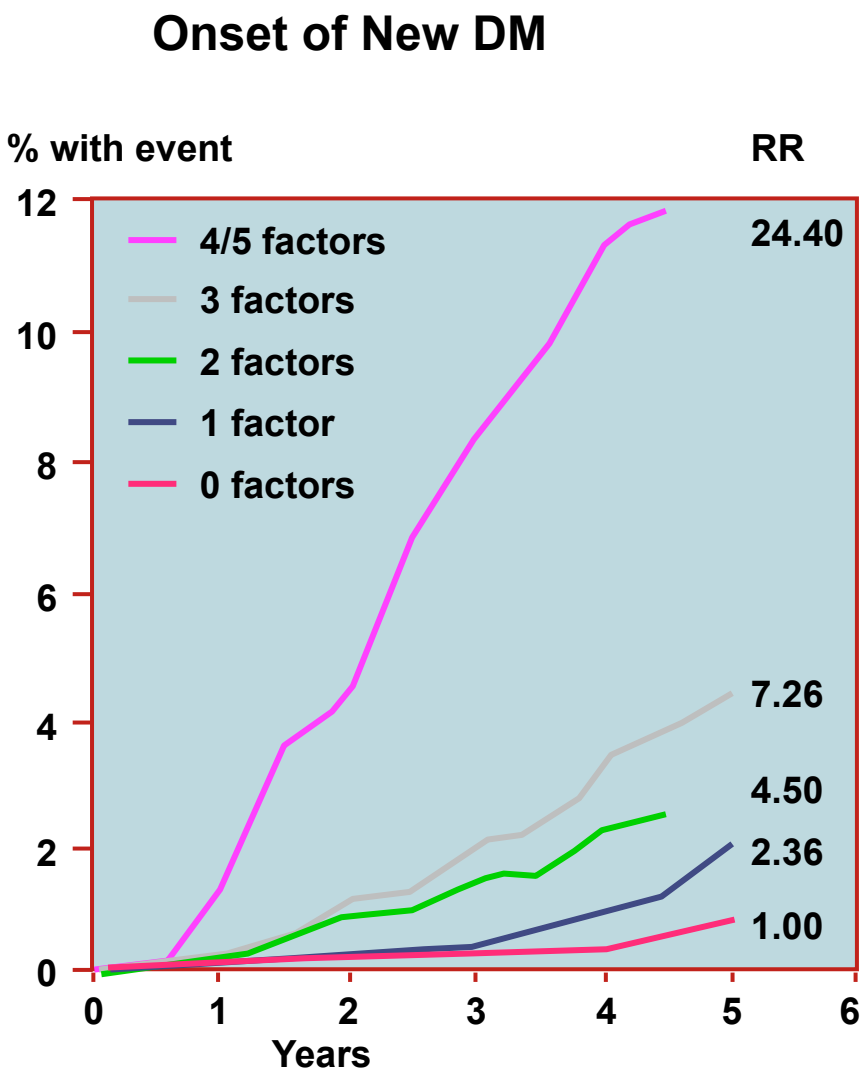


RR indicates relative risk; CI, confidence interval. Median follow-up (range) for survivors was 11.6 (9.1-19.7) years

Lokka, H-M, et al JAMA 2002; 288: 2709-2716

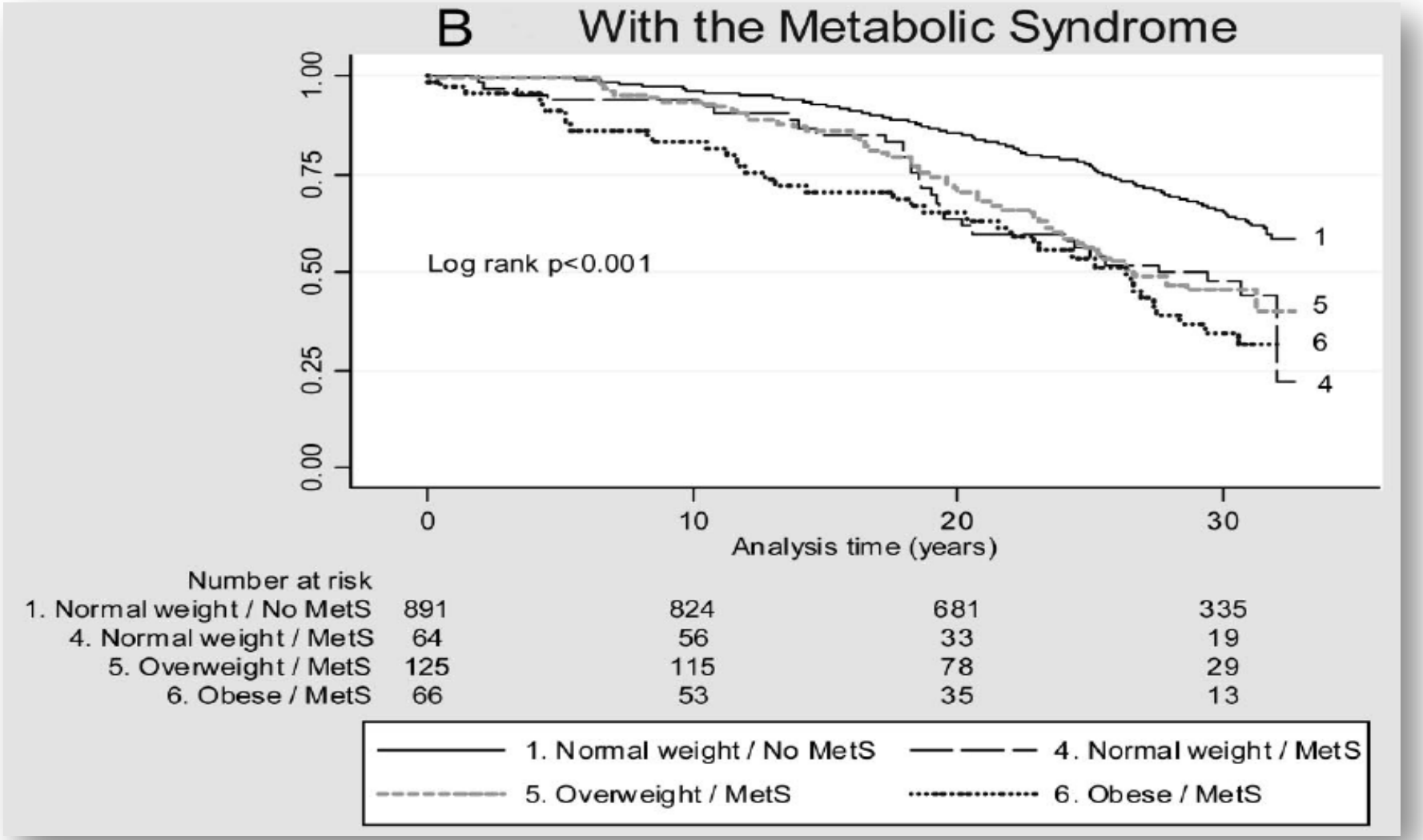
Metabolic Syndrome as a Predictor of CHD and Diabetes in WOSCOPS





Sattar N et al, Circ. 2003; 108: 414-419

Impact of Body Mass Index and the Metabolic Syndrome on the Risk of Cardiovascular Disease and Death in Middle-Aged Men



Ärnlöv J;*Circulation. 2010*

METABOLIC SYNDROME CONTROVERSY

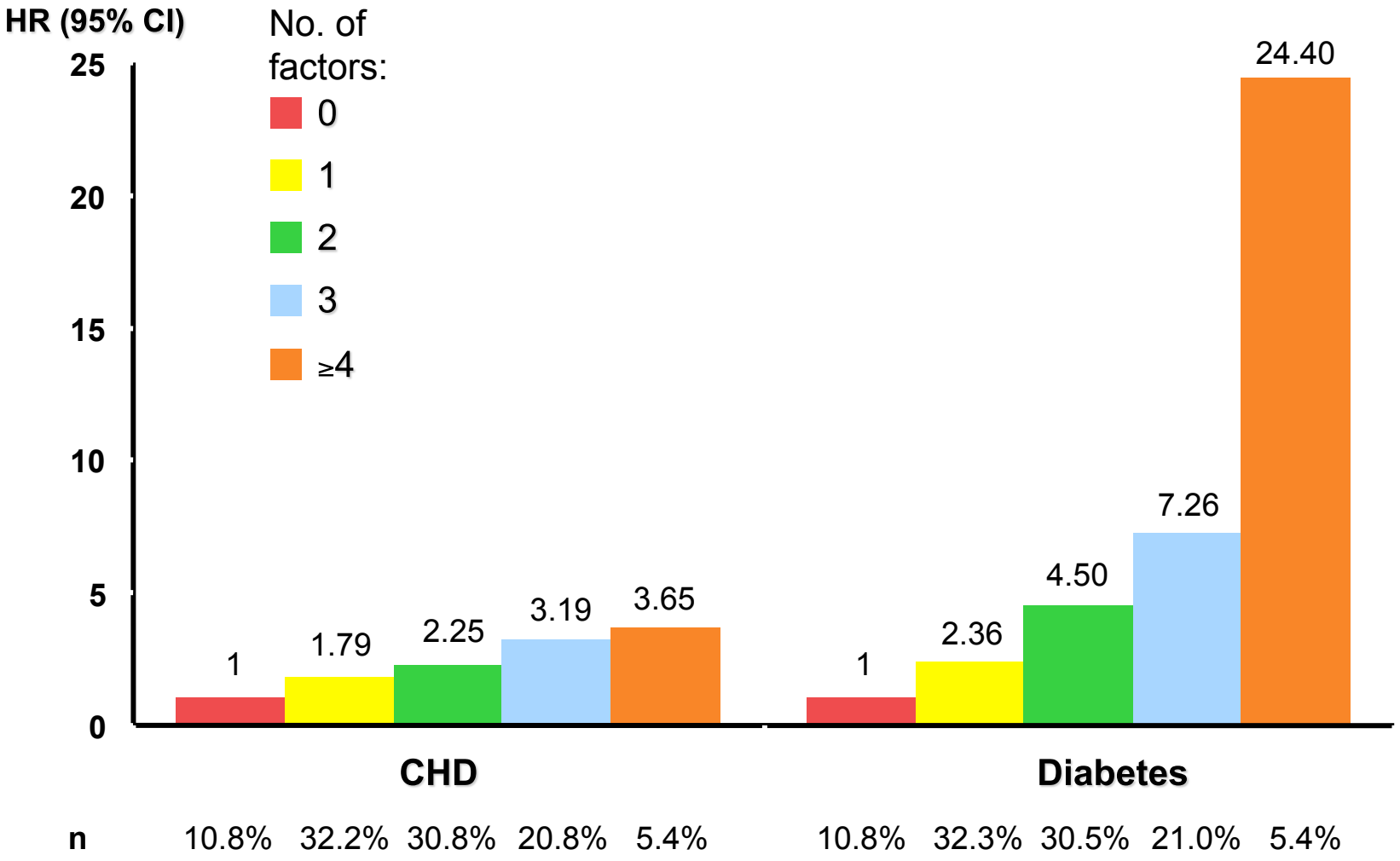
- Metabolic syndrome name & definition?
- Is the metabolic syndrome important ?
- More than sum of its parts ?
- Clinical utility ?

More than sum of its parts

- Multiplicative risk -Multiple risk factors rises geometrically.

- Hidden risk factors – Many MS risk factors are not measured.

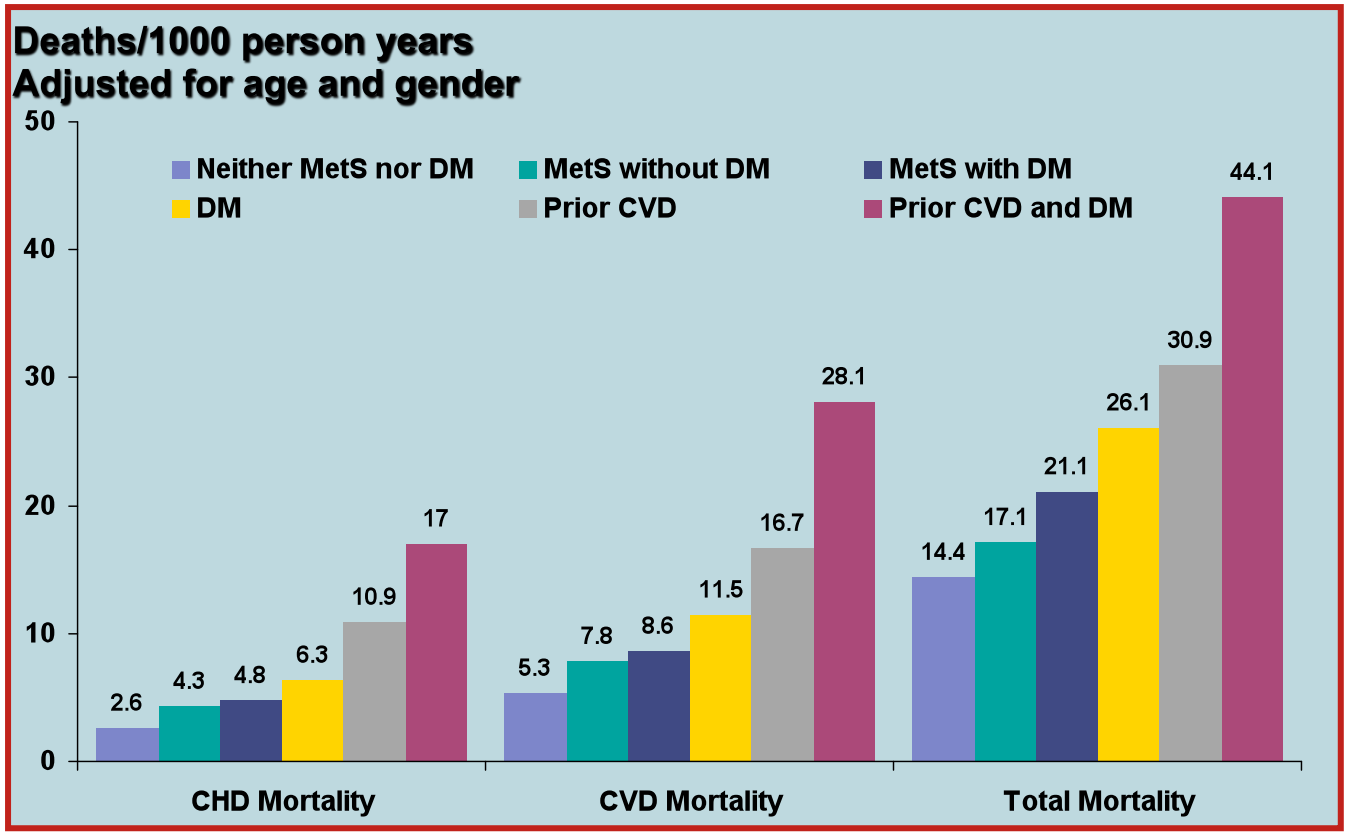
Risk for CHD and Diabetes Based on Number of Metabolic Syndrome Criteria



Sattar N et al. *Circulation*. 2003;108:414-419.

Impact of the Metabolic Syndrome on Mortality From CHD,CVD, and All Causes in US Adults: NHANES II

Prospective Cohort Study with 13 year F/U n=6255 ages 30-75 years



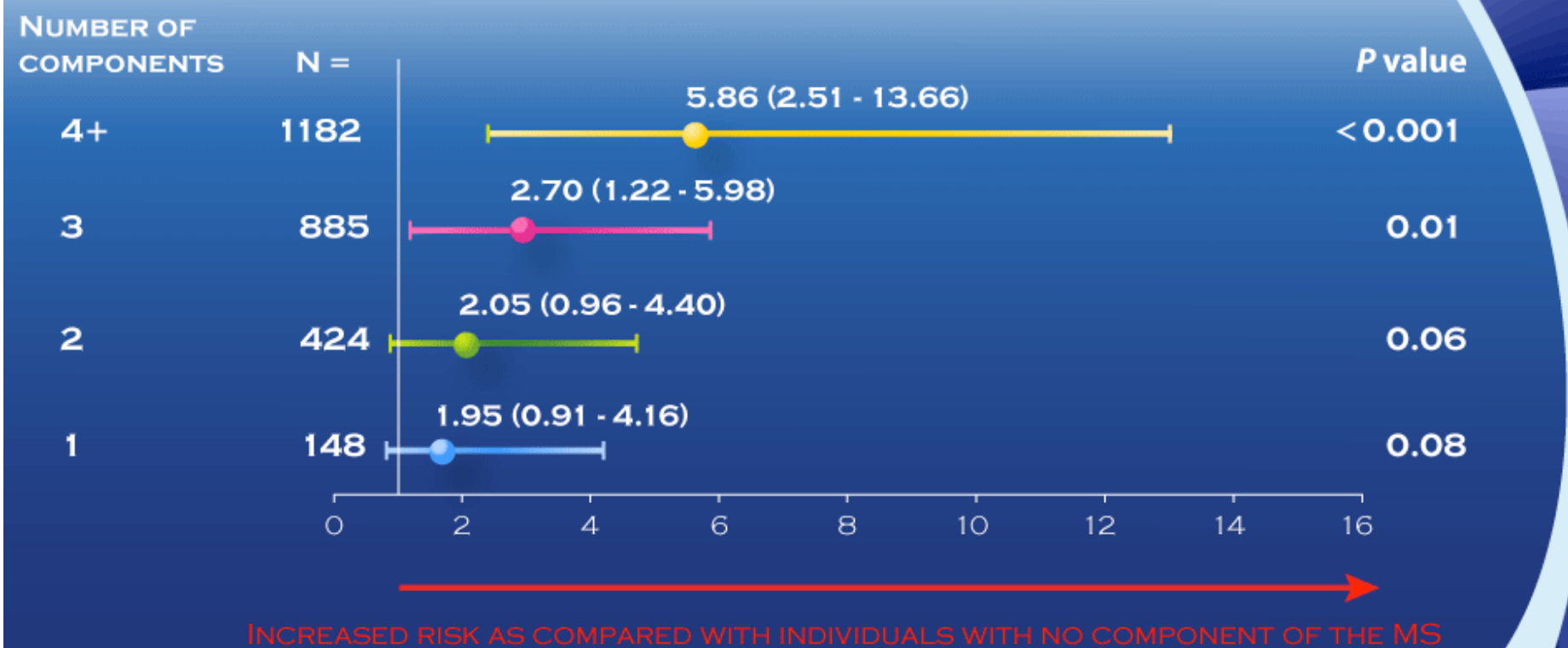
Hazard Ratio for CHD

No MetS RF	1.0
1-2 MetS RF	2.1
MetS	2.9
MetS+DM	5.0
CVD	6.8
DM+CVD	11.3

Metabolic Syndrome more strongly predicted CHD, CVD, and mortality than its individual components.

Malik, S et al. *Circulation*. 2004;110:1245-1250

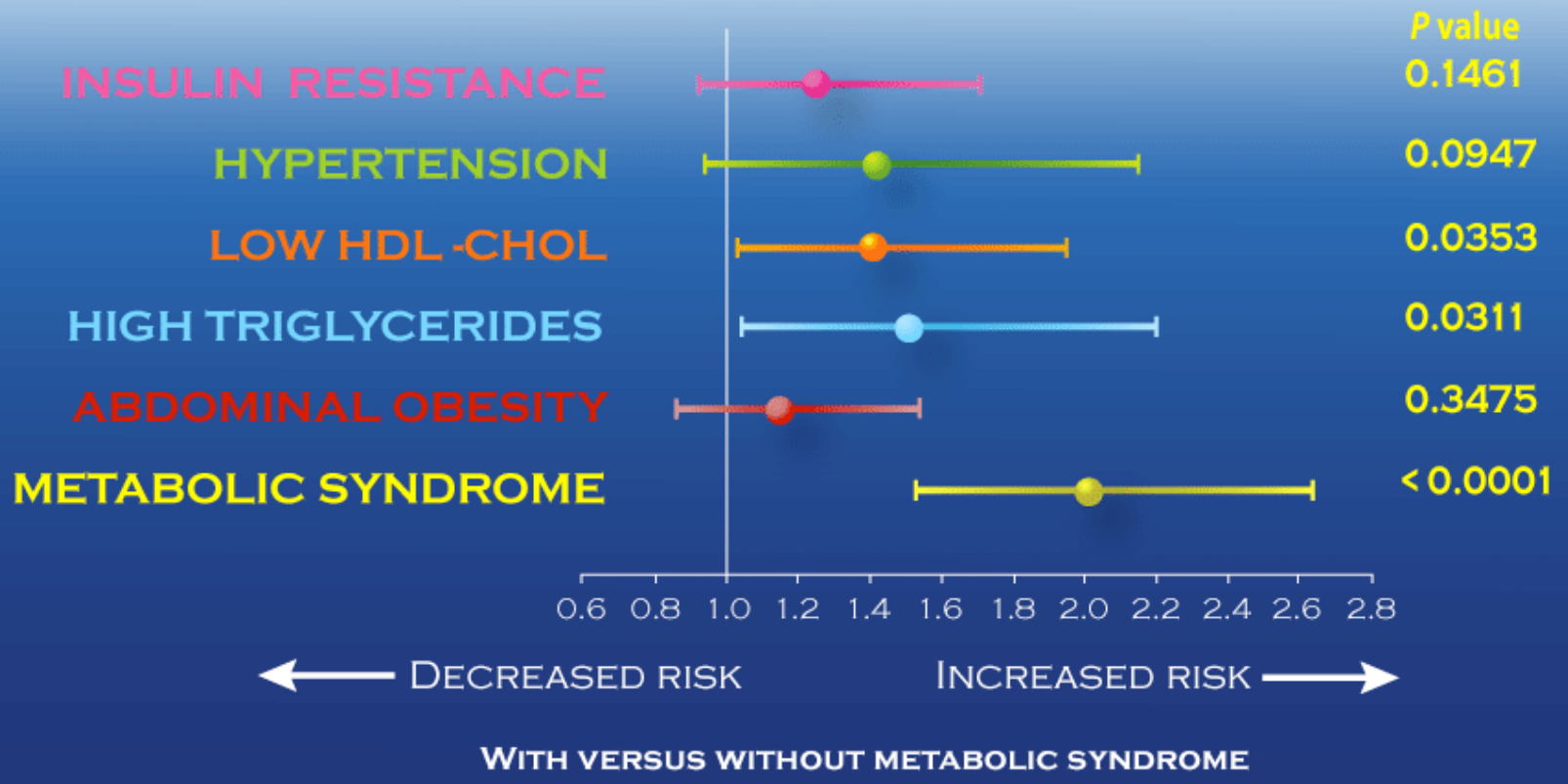
Association Between The Number of Metabolic Syndrome Components and Incident CVD



Klein BEK, et al. (Beaver Dam Study). Diabetes Care 2002;25:1790-1794.

The Metabolic Syndrome Institute

The Metabolic Syndrome Associates with a History of Myocardial Infarction Greater than any of its Individual Components



Ninomiya JK, et al. (NHANES III). *Circulation* 2004;109:42-6.

The Metabolic Syndrome Institute

More than sum of its parts

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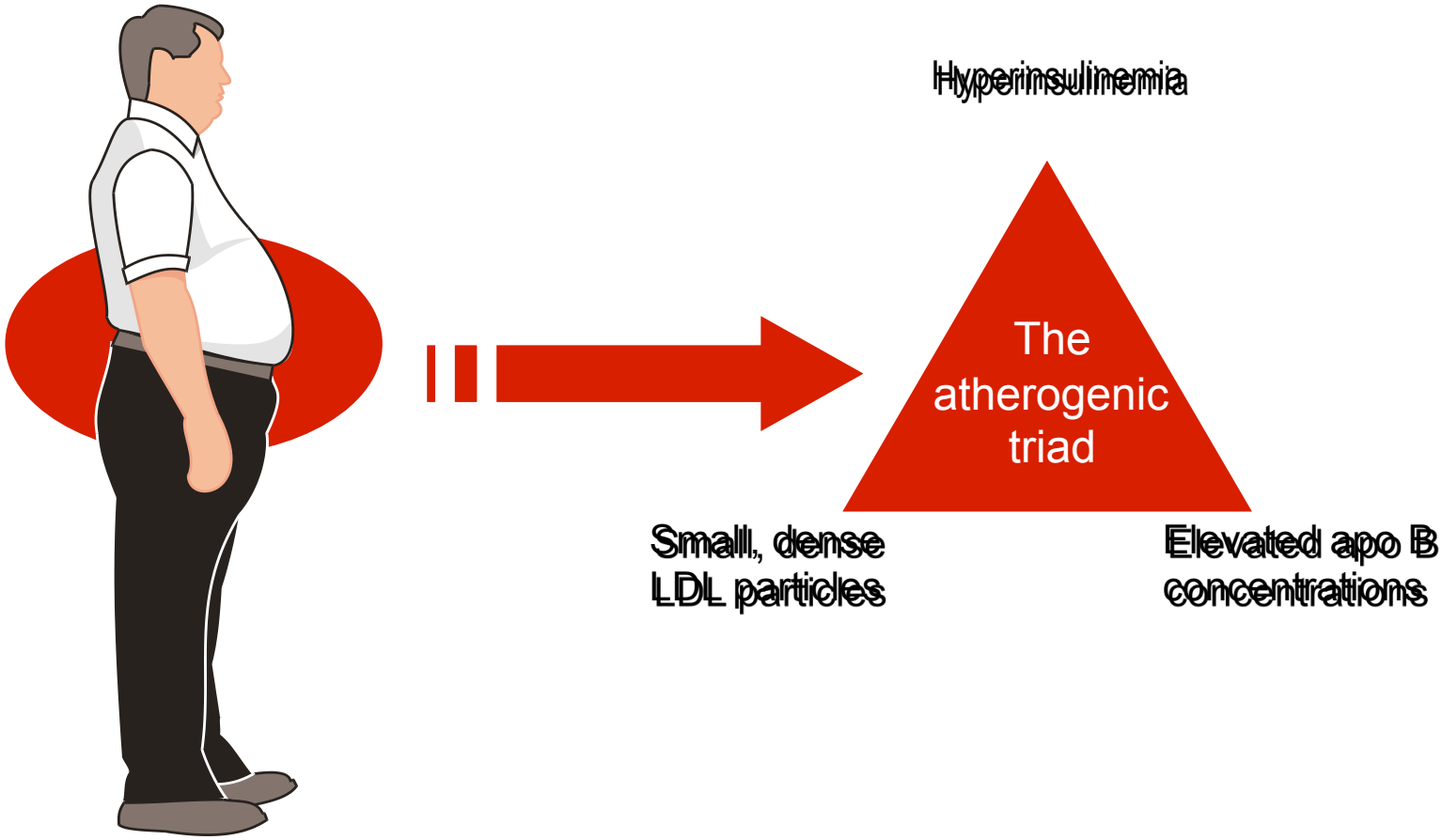
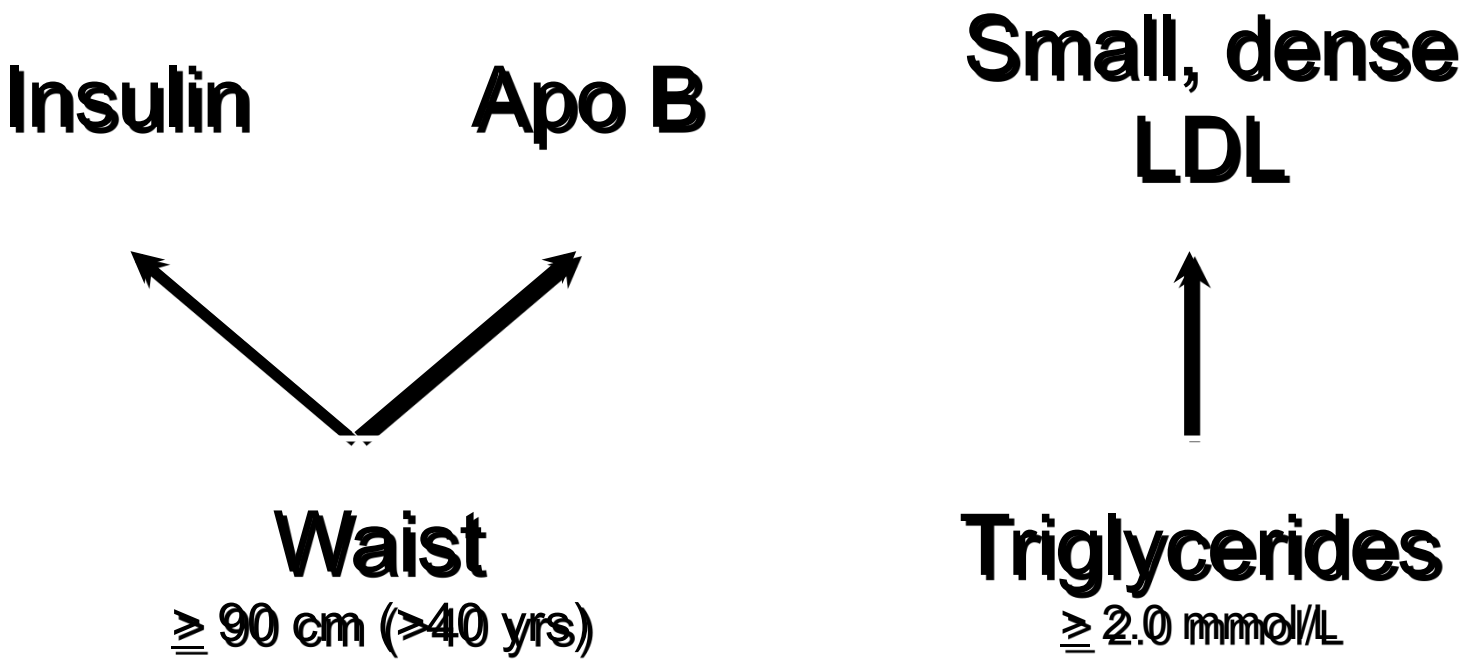
- Hidden risk factors – Many MS risk factors are not measured.

The atherogenic metabolic triad

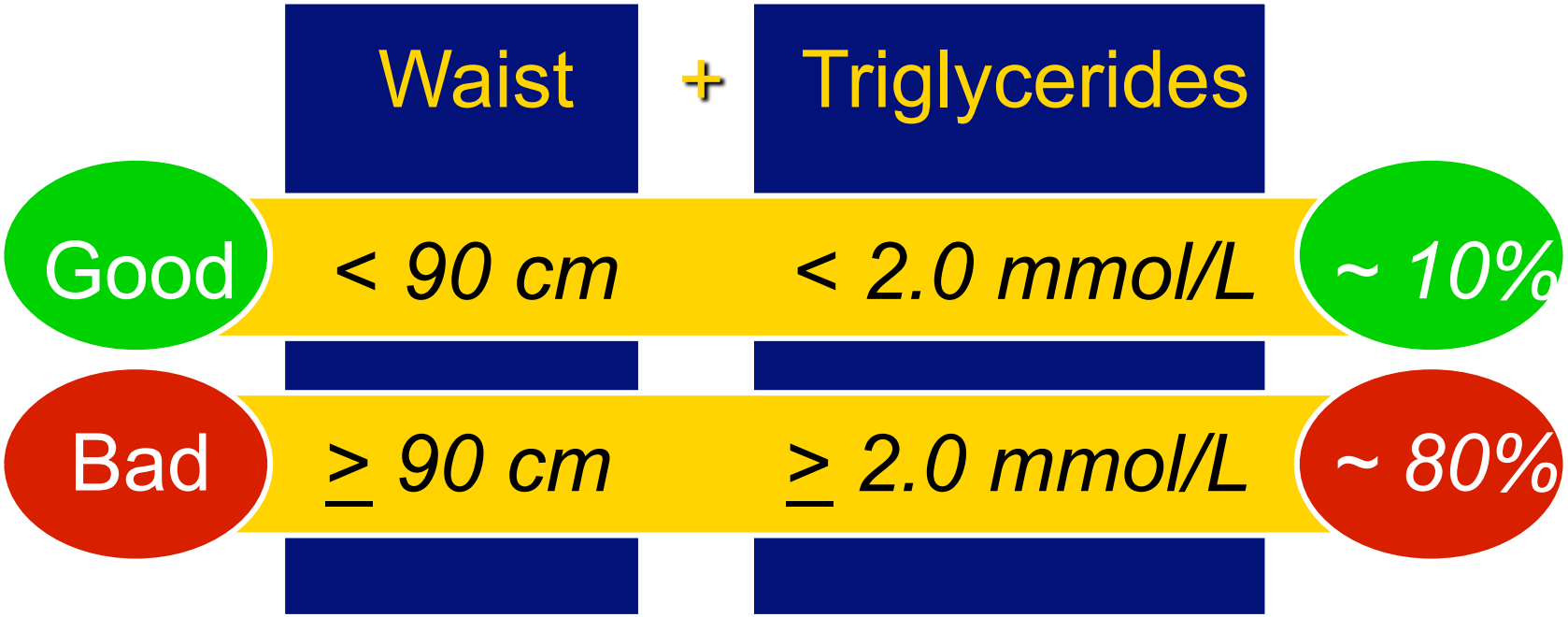


The Atherogenic Triad Anew Metabolic Risk Factor



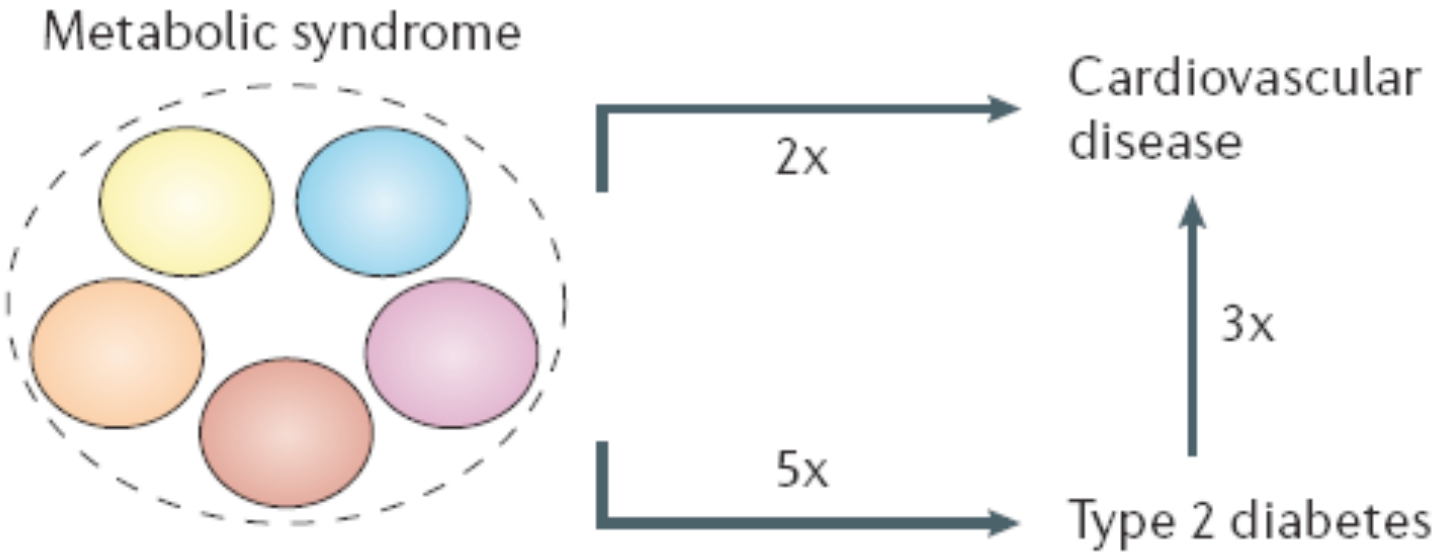
Adapted from Lemieux I et al.

Percentage of men with the constellation of risk factors of abdominal obesity



Adapted from Lemieux I et al. Circulation (2000) 102:179-184

More than sum of its parts



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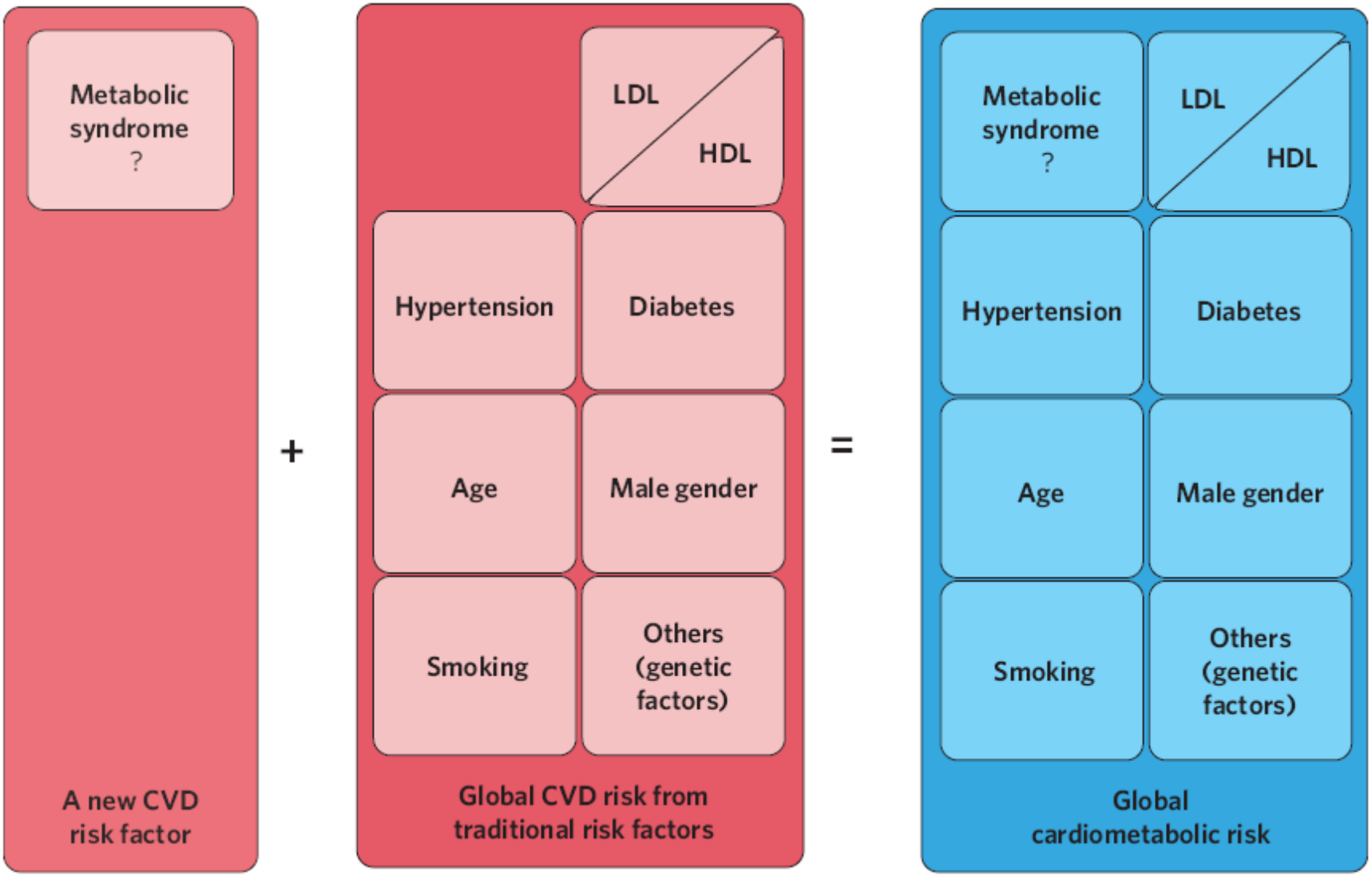
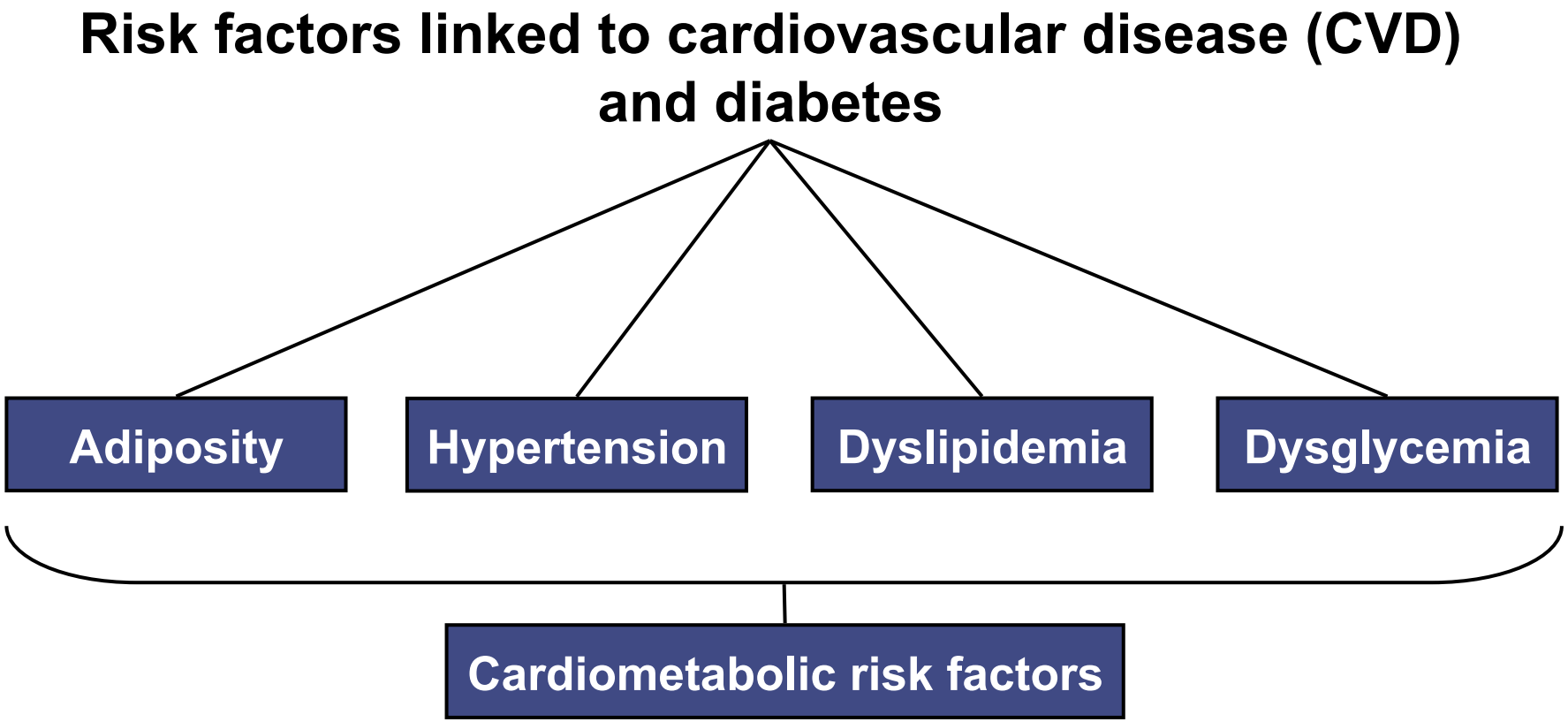
Global Cardiometabolic Risk



Defining cardiometabolic risk



Eckel RH et al. *Circulation.* 2006;113:2943-6.

Case study

- 45 y Male
- Non Smoker
- Total Cholesterol = **230** mg/dl
- HDL= **38** mg/dl
- LDL = **150** mg/dl
- TG = **180** mg/dl
- WC = **103** cm
- SBP = **133**
- Framingham = **8%**
- Cardiometabolic Risk = **16%**

JUPITER
Can we simplify guidelines for statin therapy

1. Strong recommendations for diet, exercise, and smoking cessation for any patient with or at risk for cardiovascular disease.

2. If there is prior MI, stroke, or known CVD, treat

3. If the patient is diabetic or has a very strong family history of premature atherothrombosis, treat

4. If LDLC > 160, TC:HDLC > 6, or hsCRP > 2, or MS treat

5. Beyond these recommendations, referral to lipid specialist or cardiologist for further evaluation.

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Metabolic Syndrome

- **High waist circumference (102/88 cm)**

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- **↓ HDL cholesterol‡**
  - **Men < (40 mg/dL)**
  - **Women < (50 mg/dL)**
- **↑ Blood pressure ≥ 130 / ≥85 mm Hg‡**
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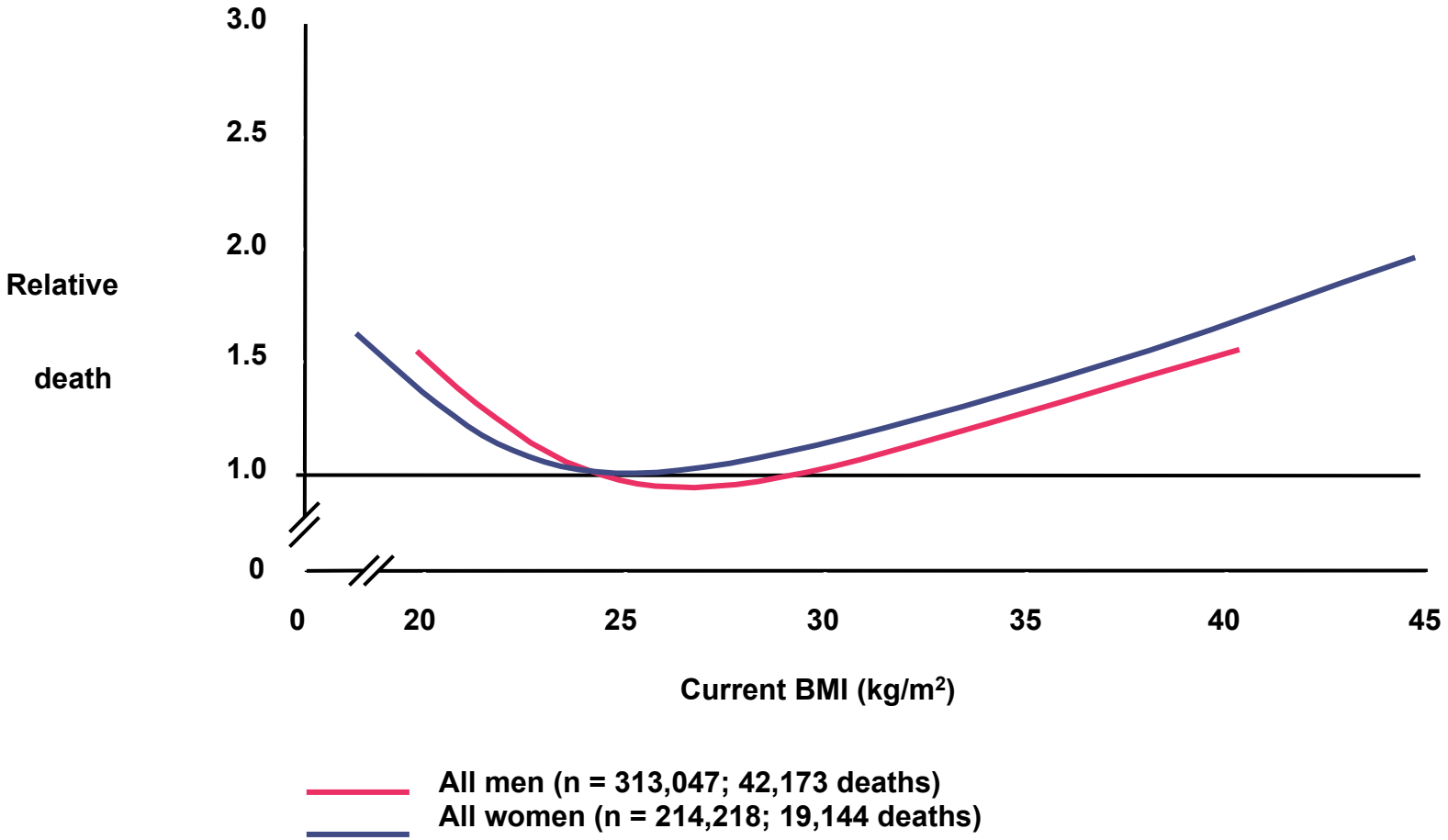
Adiposity predicts mortality



Adams KF et al. *New Engl J Med.* 2006;355:763-78.

Obesity is usually measured as body mass index (BMI)

$$\frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$$

Classification of Overweight and Obesity

BMI	Obesity
Overweight	25.0 - 29.9
Obesity I High	30.0 - 34.9
Obesity II High	35.0 - 39.9
Obesity III	≥40 Extremely

High High

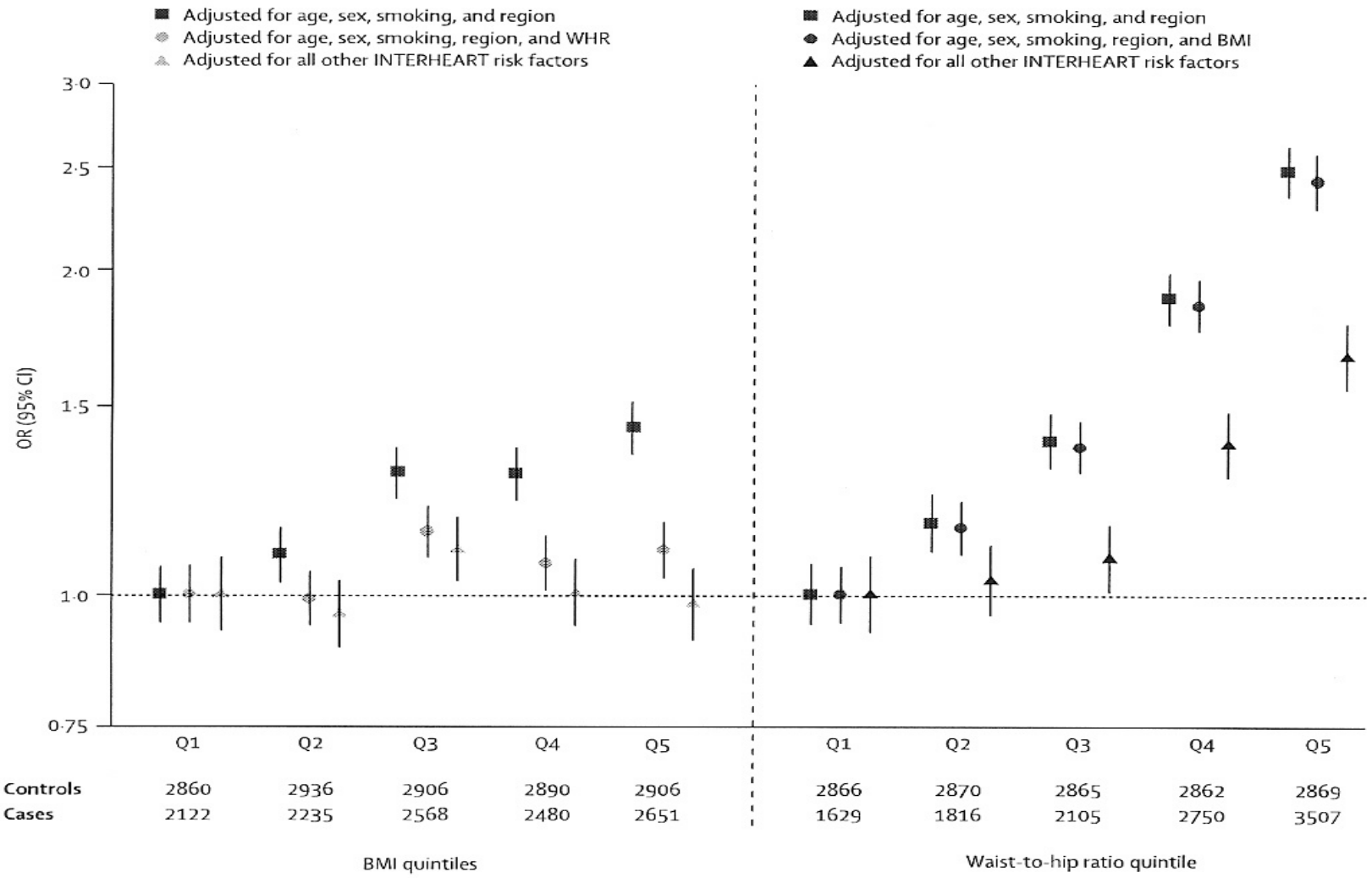
Body Mass Index Paradox

- 1.77 m
- 100.45 kg
- BMI = 32.09
- Obese???

Body Mass Index Paradox

- 1.77 m
- 100.45 kg
- BMI = 32.09
- Obese!!

Obesity and the risk of MI in 27000 participants from 52 countries: a case-control study



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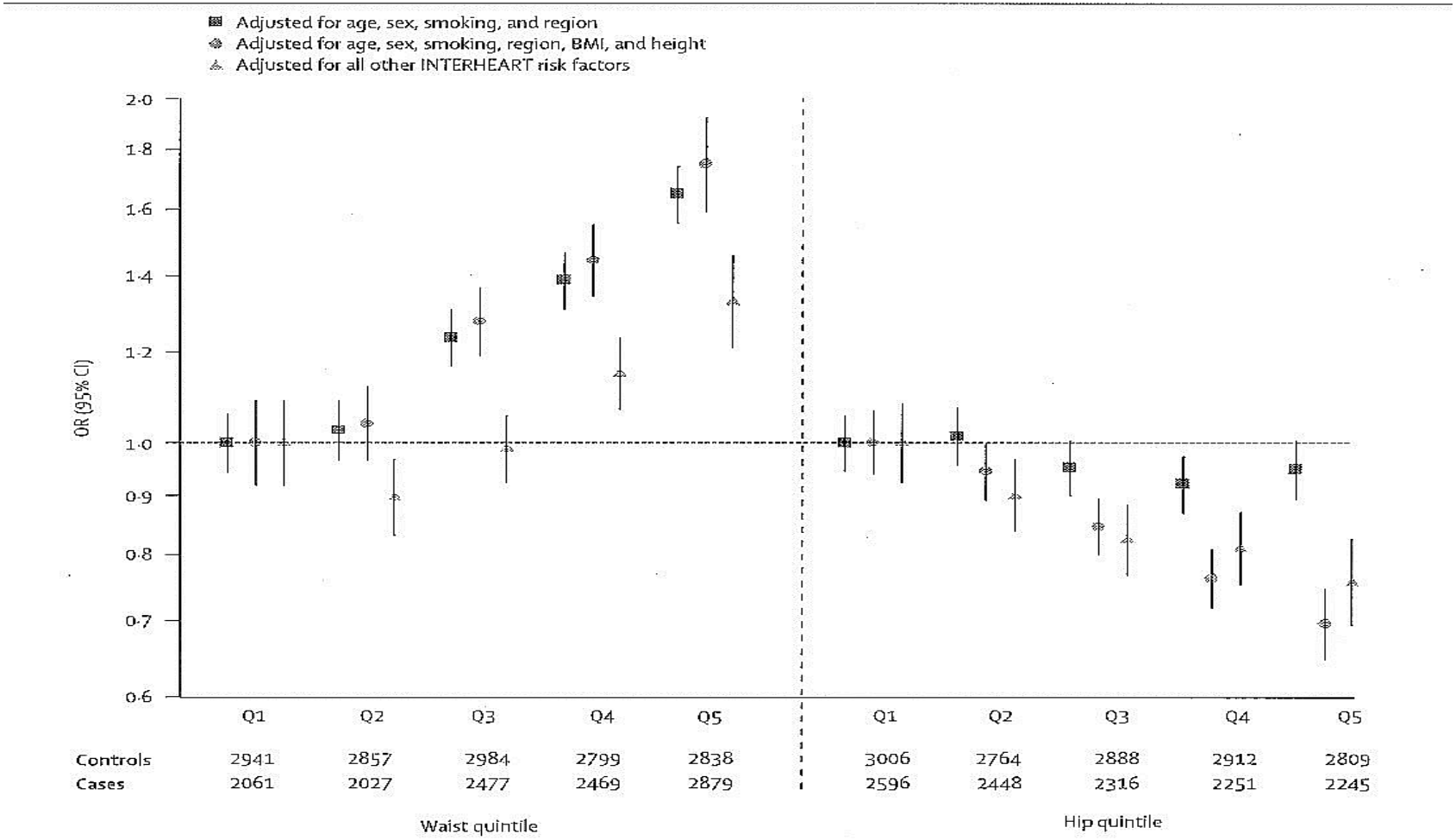
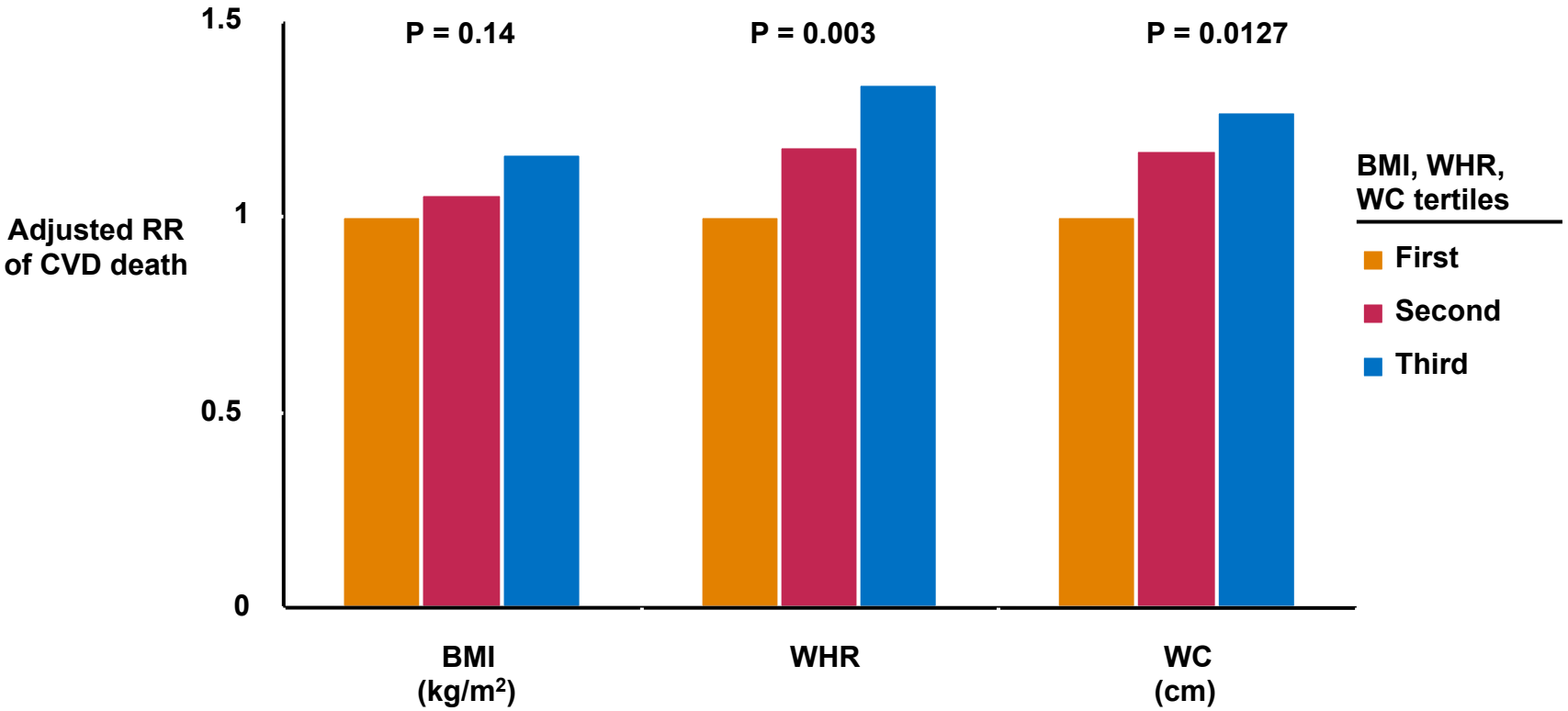


Central adiposity: Better marker of CVD than BMI

N = 8802 HOPE Study participants



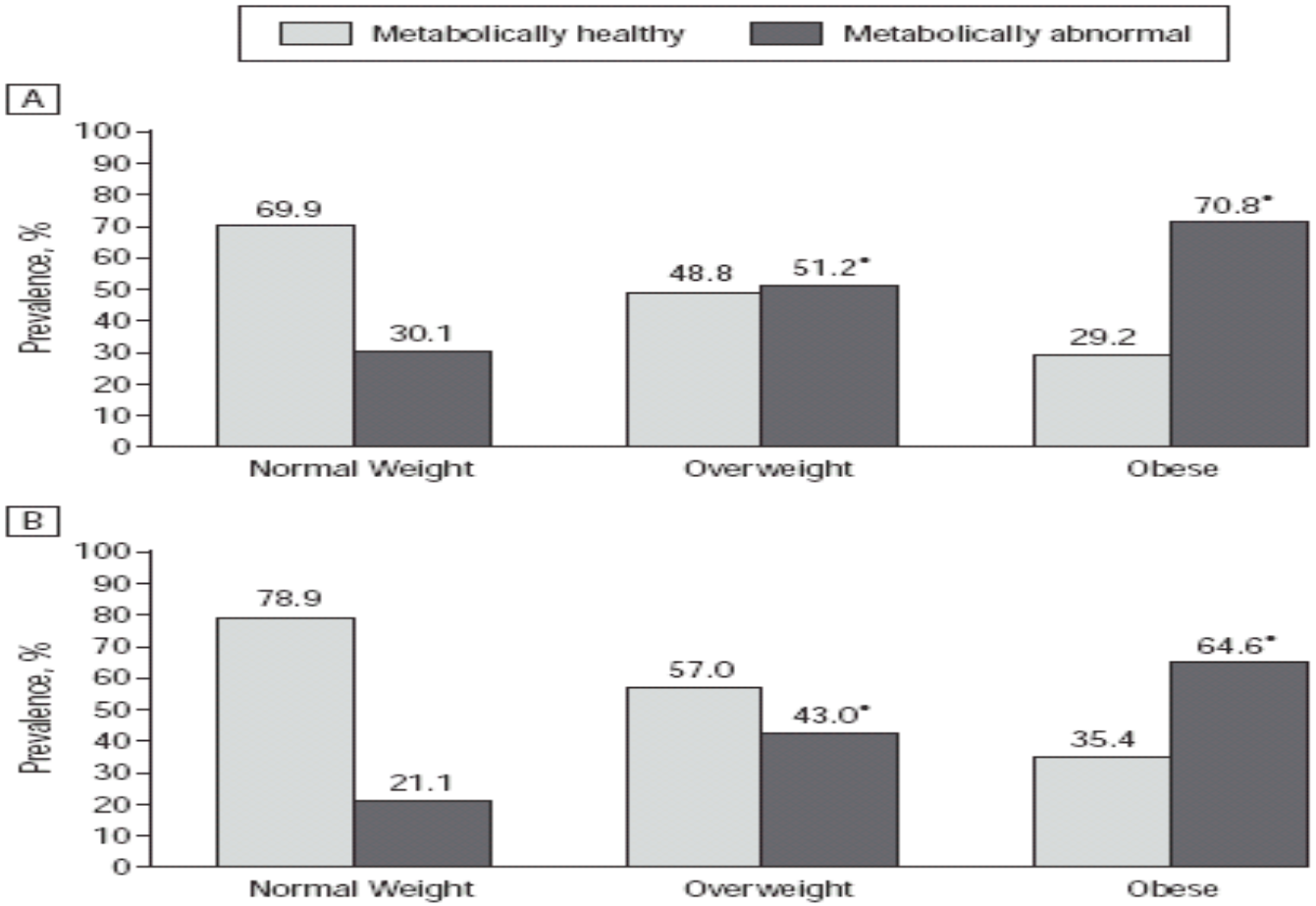
WC = waist circumference
WHR = waist/hip ratio

Dagenais GR et al. *Am Heart J.* 2005;149:54-60.

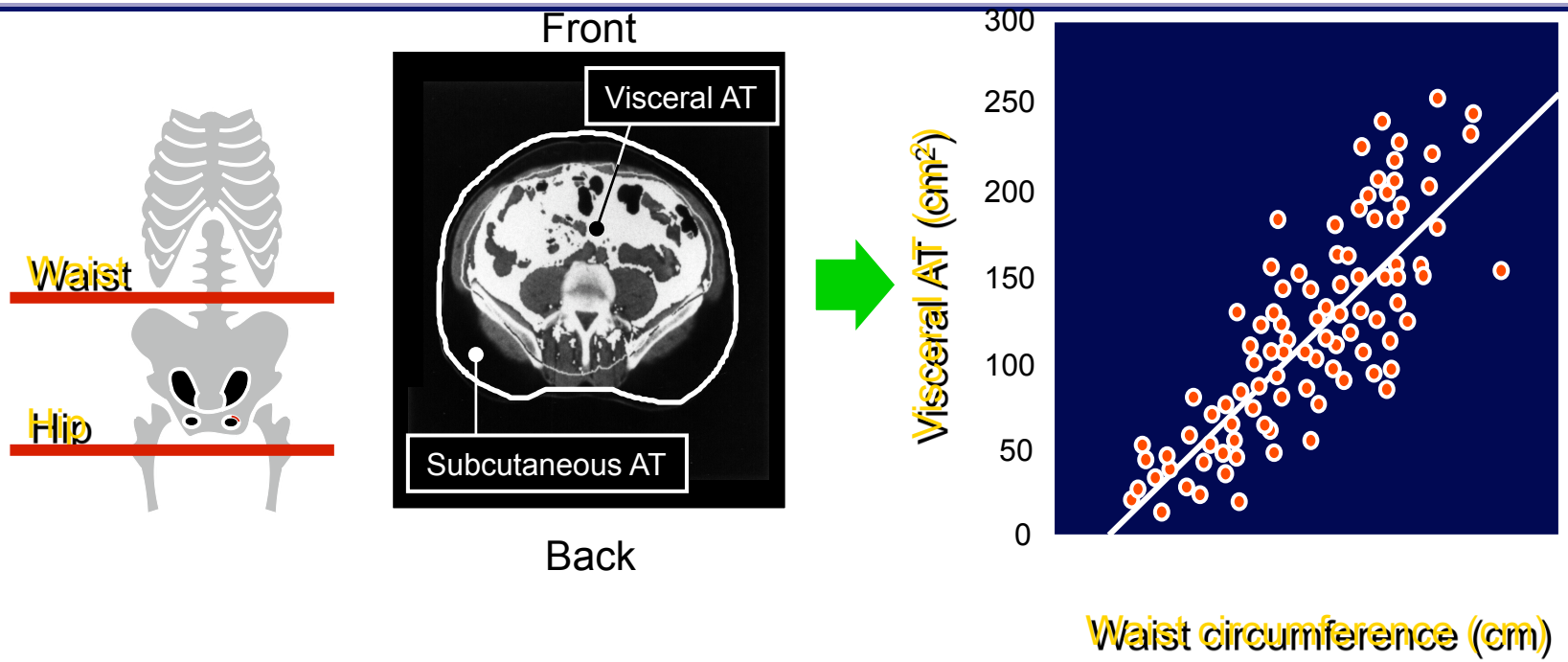
Classification of Overweight and Obesity

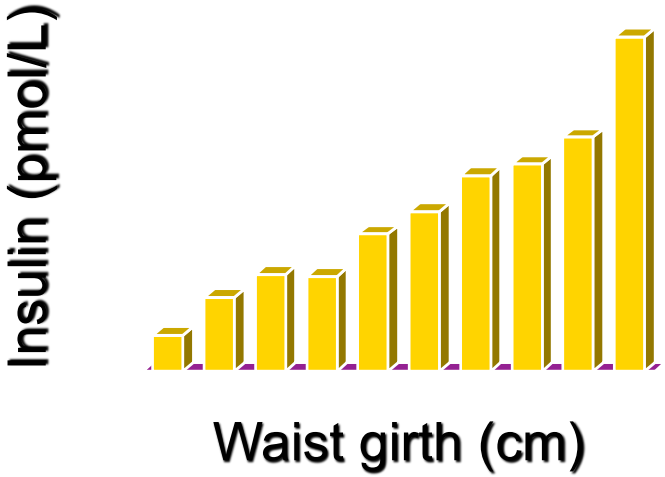
BMI	Obesity Class	Risk for Type 2 Diabetes, Hypertension and CVD (Waist Circumference)	
		Low	High
Overweight	25.0 - 29.9	Increased	High
Obesity I	30.0 - 34.9 I	High	Very High
Obesity II	35.0 - 39.9 II	Very High	Very High
Obesity III	≥40 III	Extremely High	Extremely High

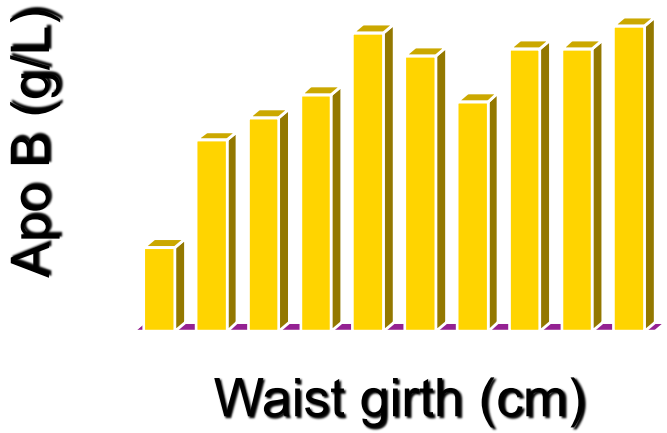
Age-standardized prevalence of cardiometabolic abnormalities by body size and sex (A, men; B, women).



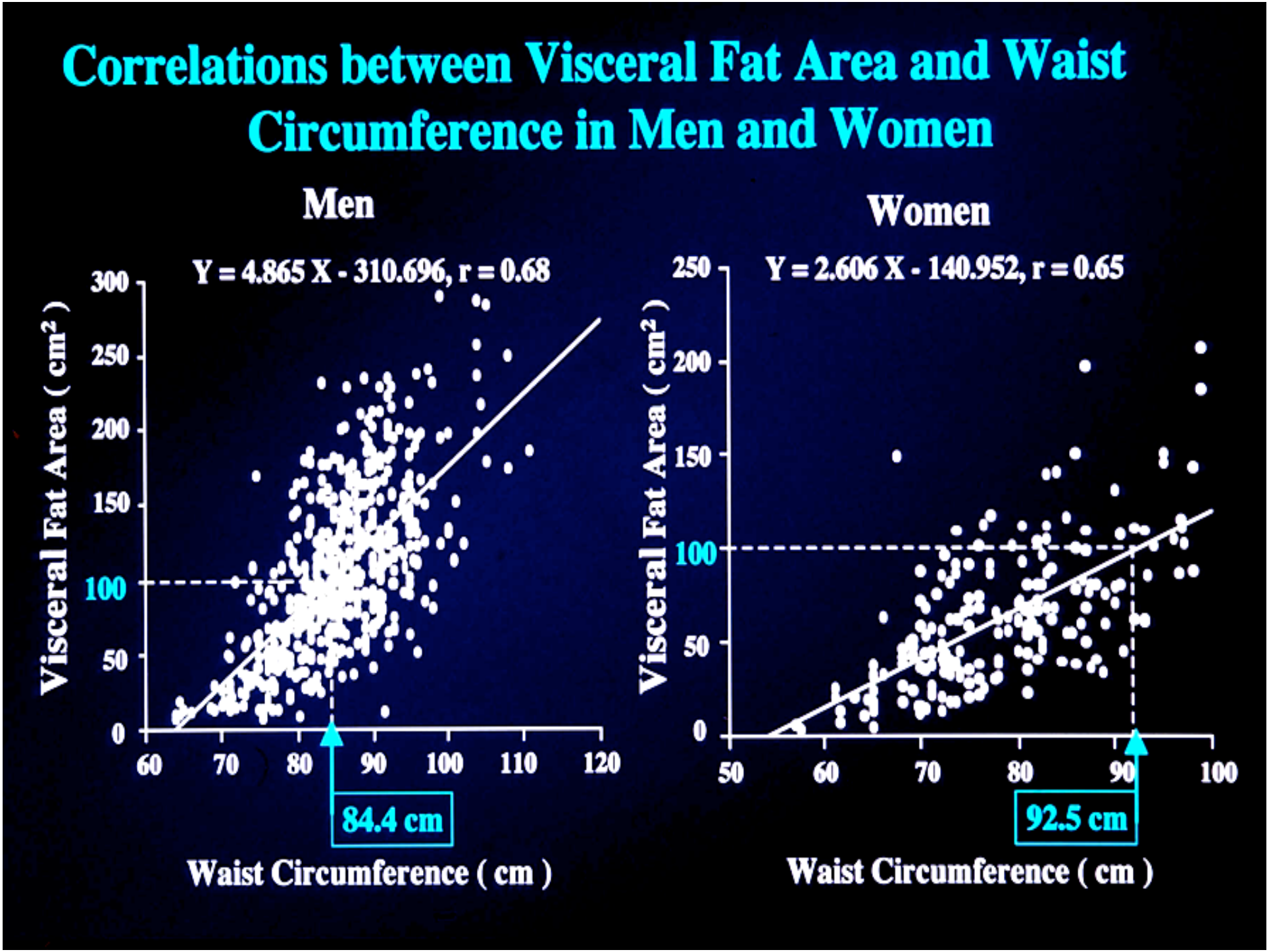
Relationship between waist circumference and visceral adipose tissue accumulation



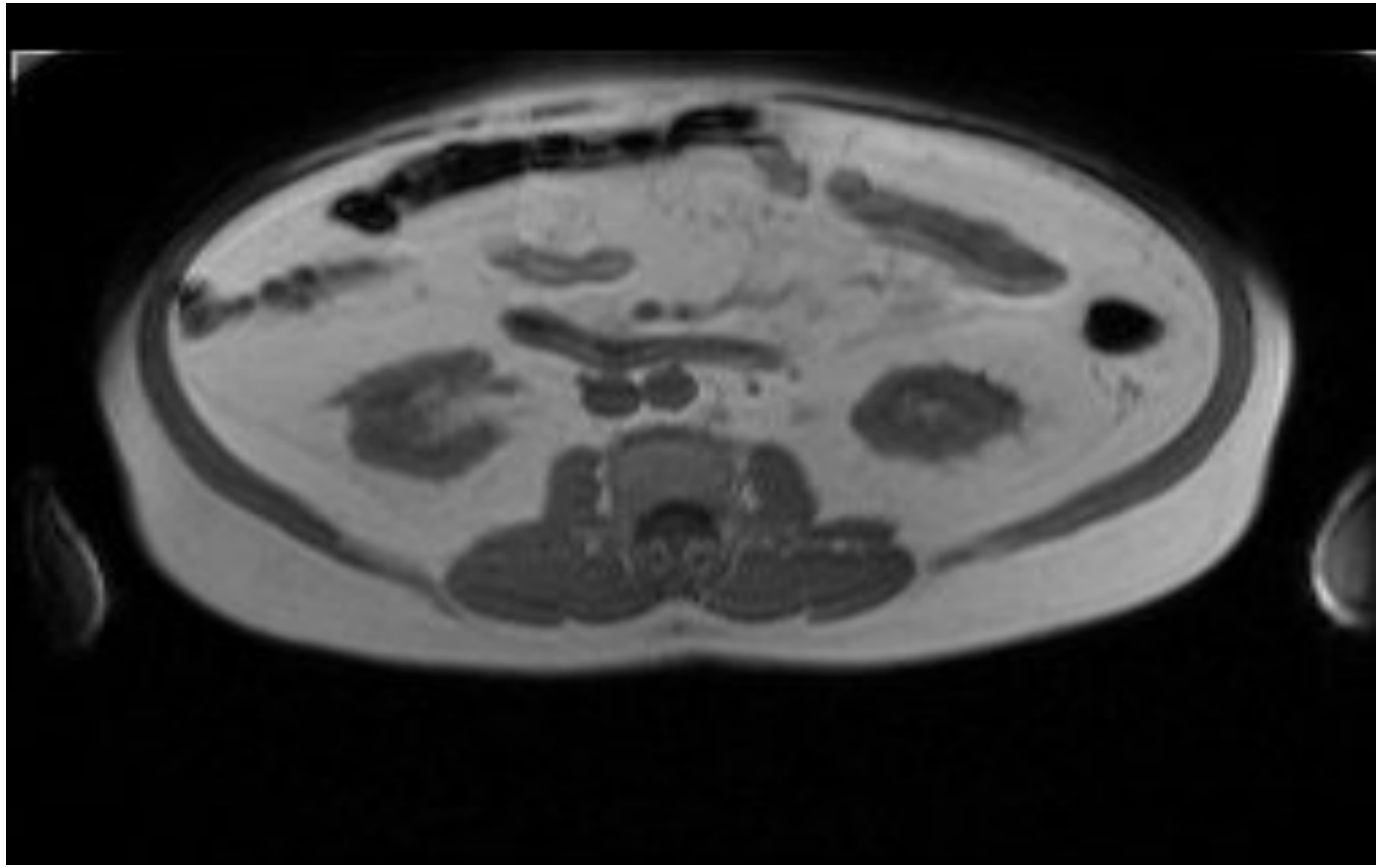




Correlations between Visceral Fat Area and Waist Circumference in Men and Women

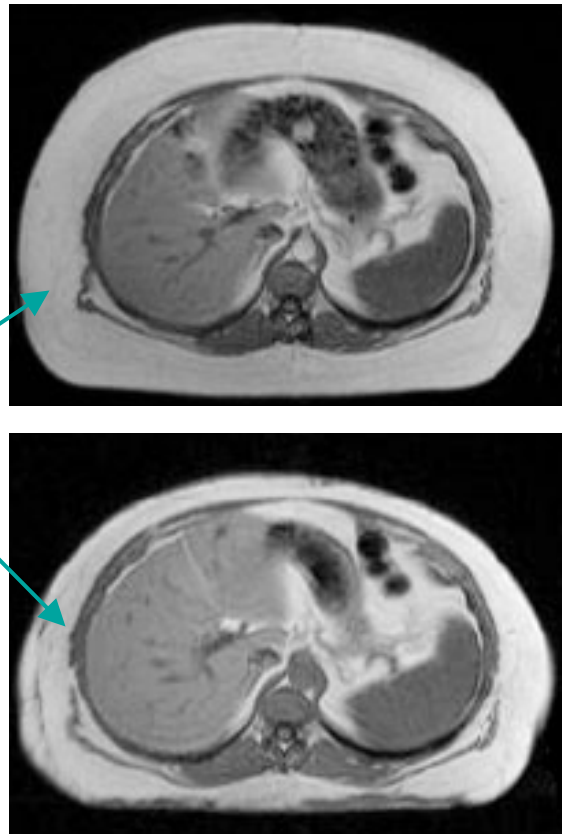


Abdominal (Visceral) Obesity



Neutral effect of liposuction on cardiometabolic risk factors

Magnetic resonance images

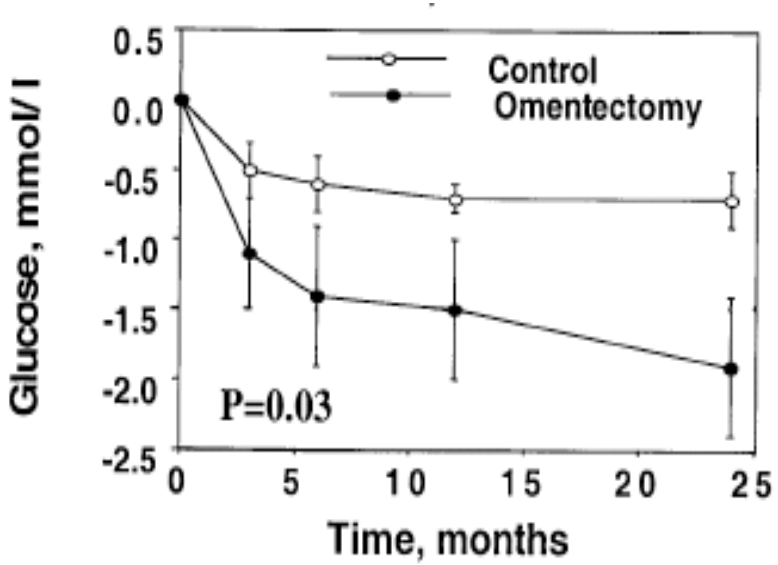


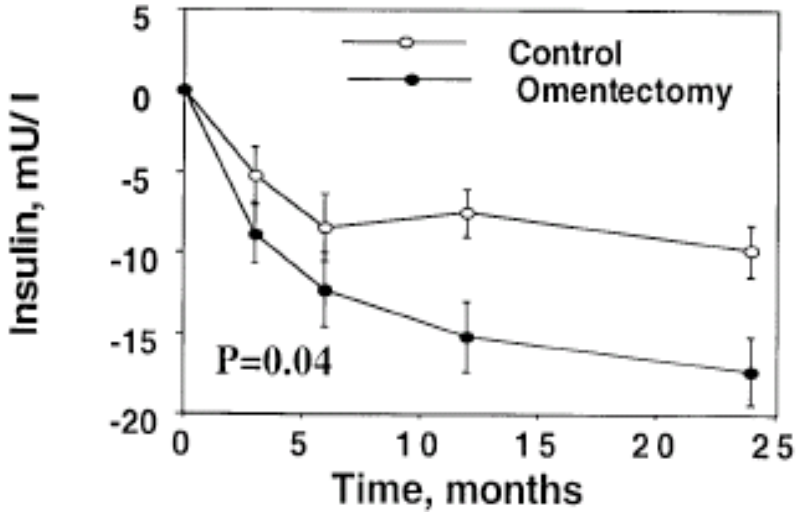
No significant change at 10-12 weeks

- BP
- Plasma glucose
- Plasma insulin
- Total-C, LDL-C, HDL-C, TG
- Adiponectin
- TNF-α
- IL-6
- CRP

Klein S et al. *N Engl J Med.* 2004;350:2549-57.

A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding





Omentectomy:

0.6 ± 0.3 Kg

◊TBW 0.8±0.4%

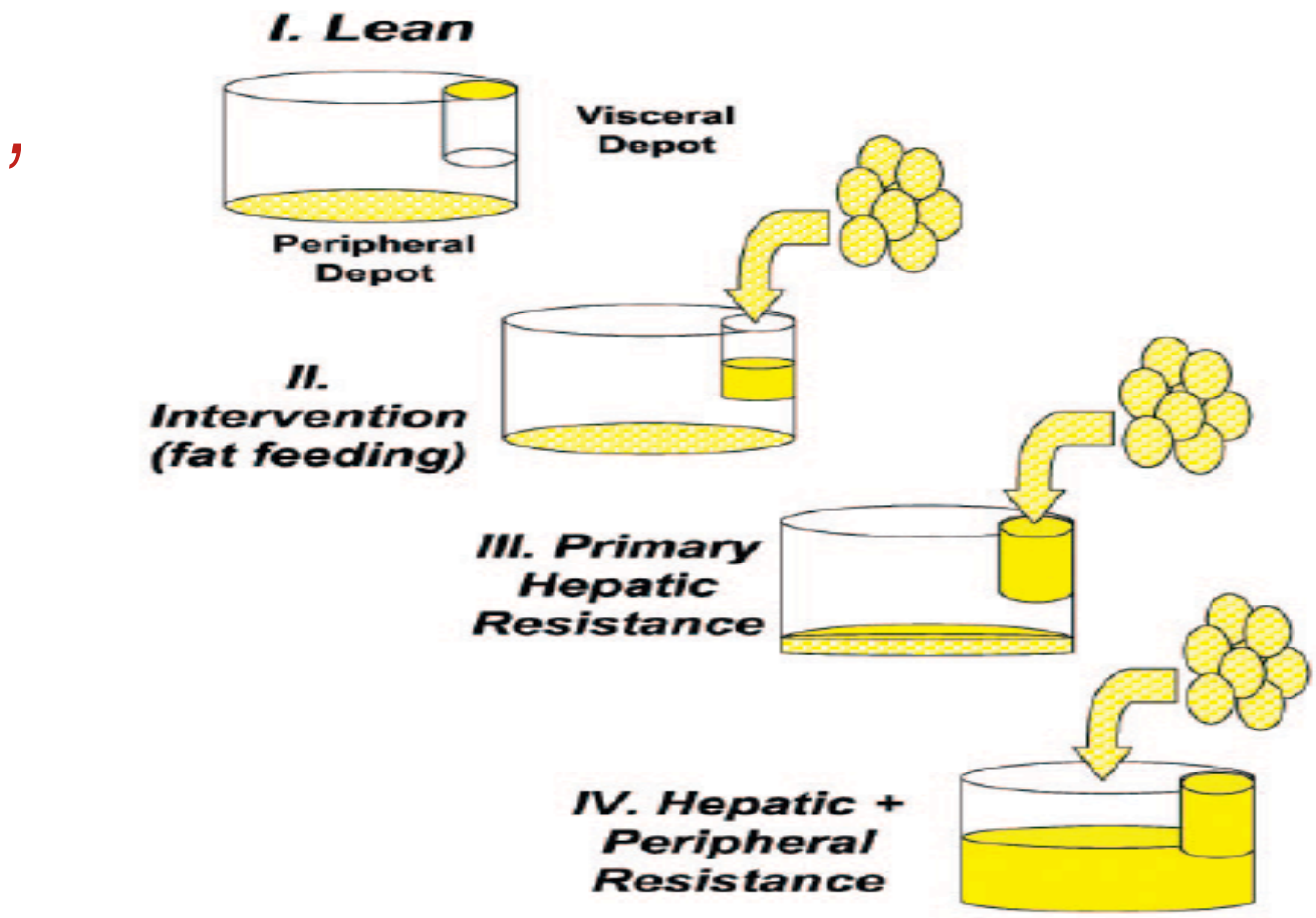
22 M, 28 W

2 Y FOLOW-UP

26% drop-out

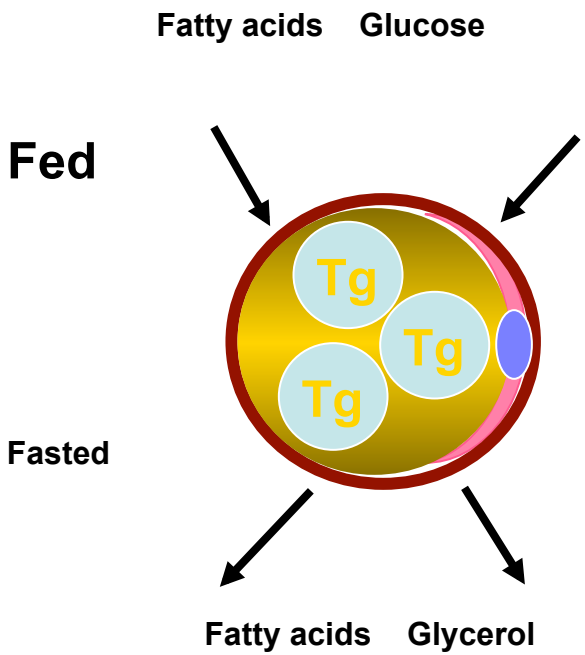
International Journal of Obesity (2002) 26, 193–199

Why Visceral Fat is Bad: Mechanisms of the Metabolic Syndrome

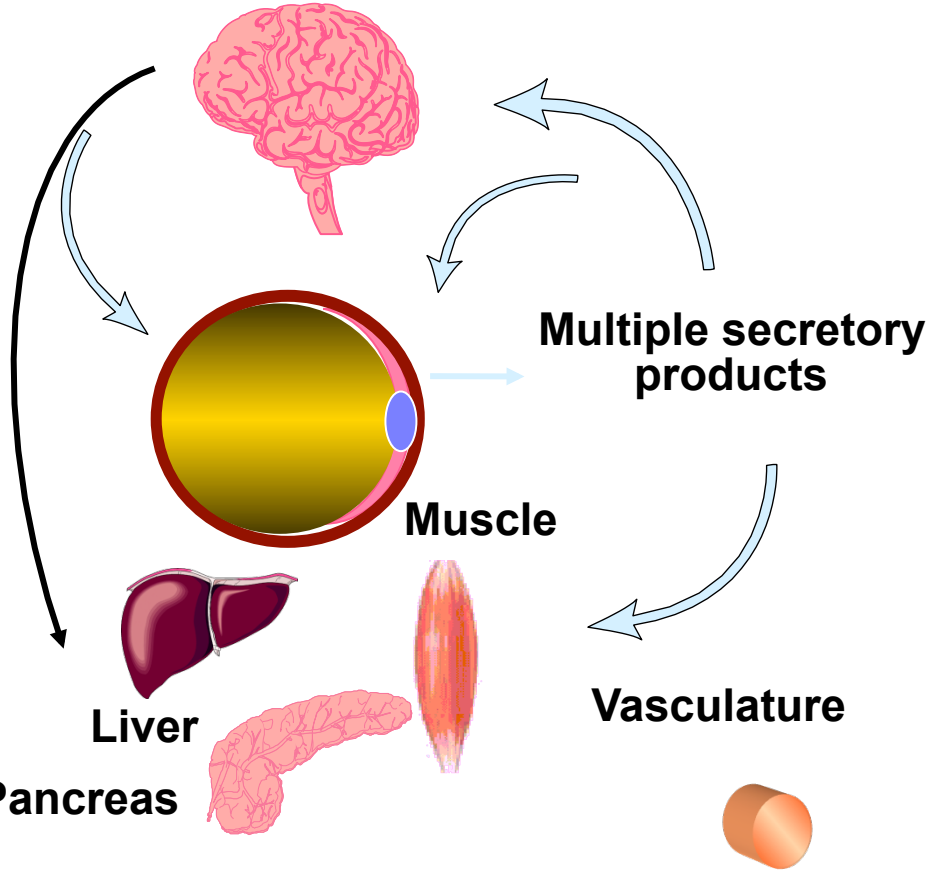


The evolving view of adipose tissue:an endocrine organ

Old View: inert storage depot

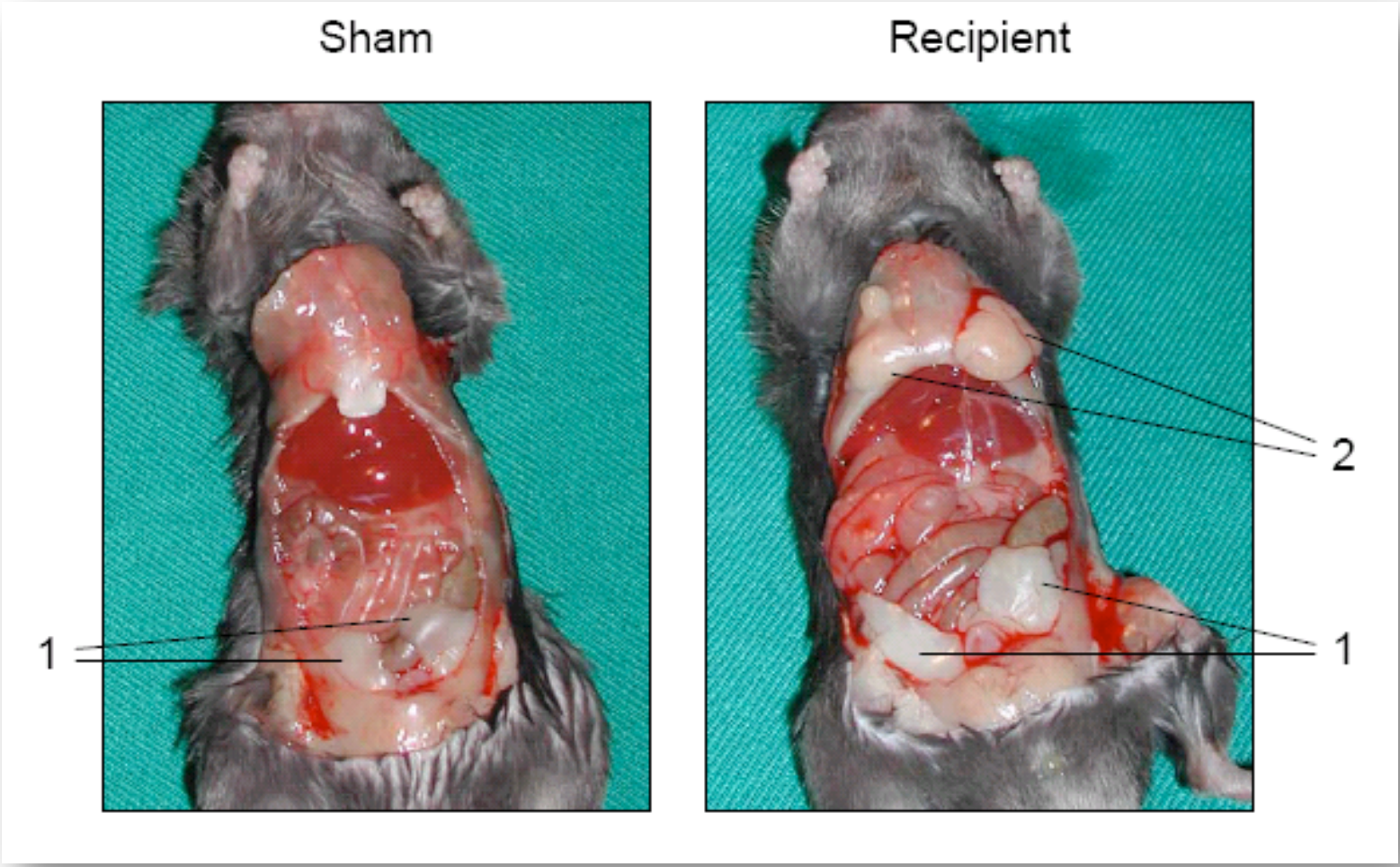


Current View: secretory/endocrine organ



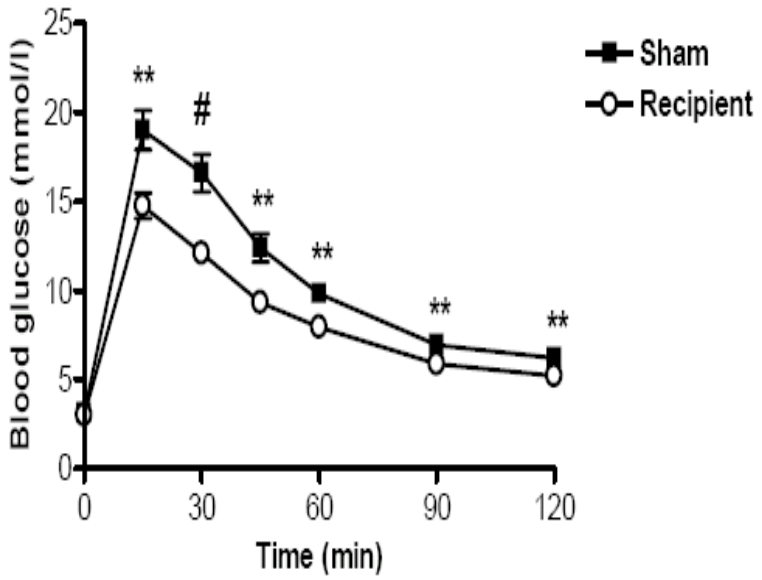
Lyon CJ et al 2003

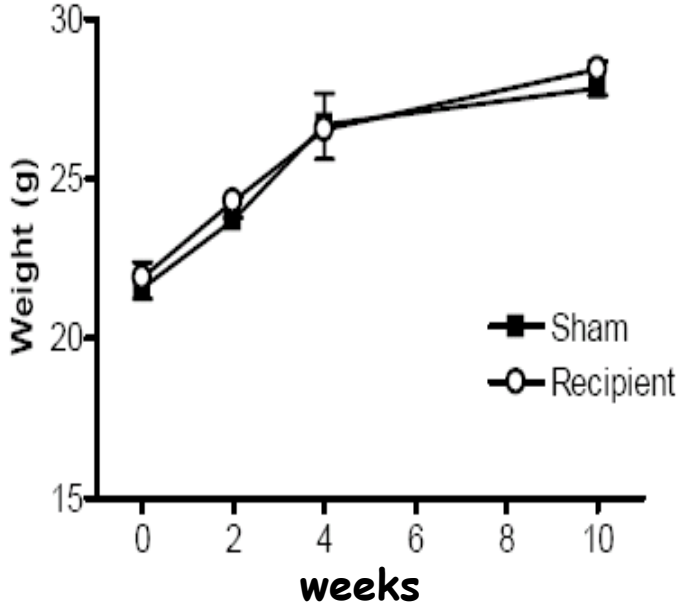
Dose implantation of normal abdominal fat mass (VAT) can cause cardiometabolic syndrome ?



Konrad et al. Diabetologia, 50:833-9, 2007

Dose implantation of normal abdominal fat mass (VAT) can cause cardiometabolic syndrome ?

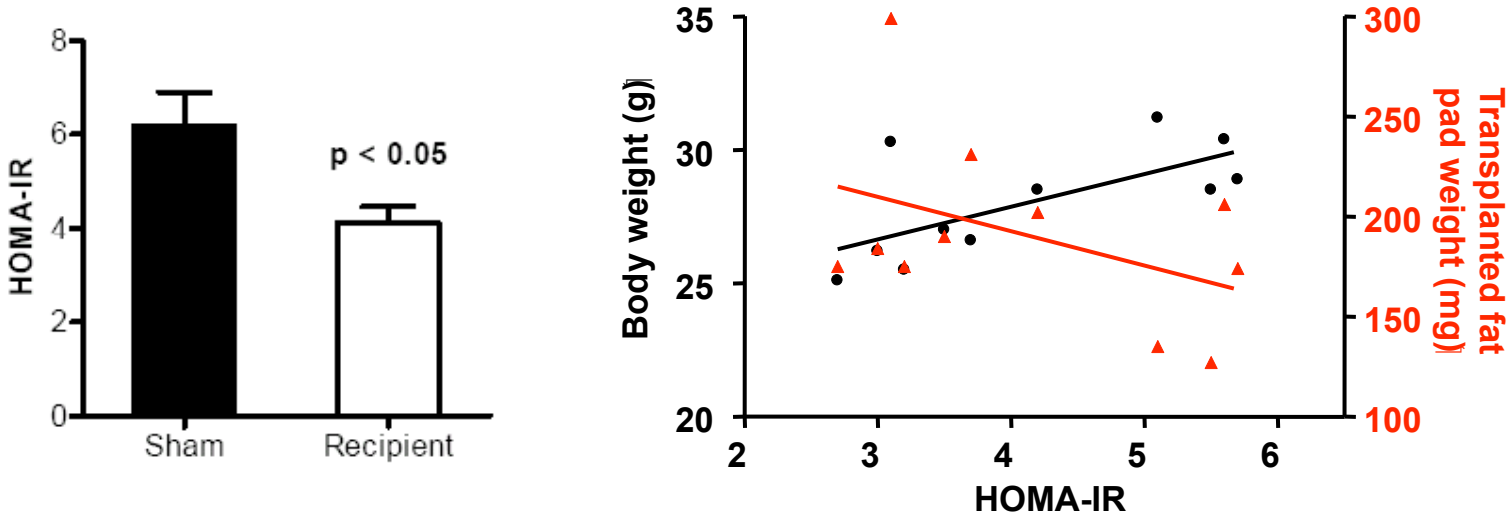




Konrad et al. Diabetologia, 50:833-9, 2007

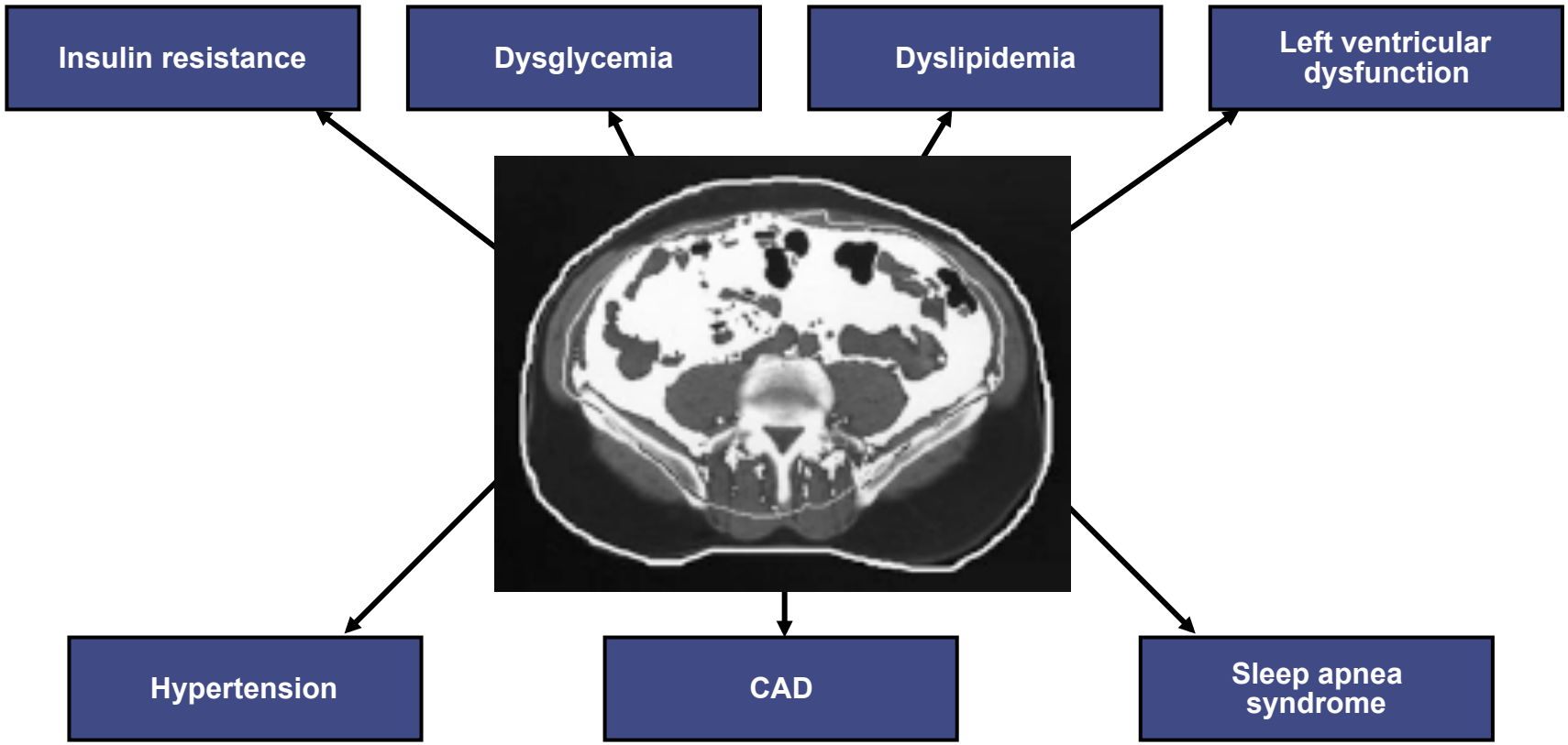
Dose implantation of normal abdominal fat mass (VAT) can cause cardiometabolic syndrome ?

Implantation of normal abdominal fat mass (VAT) promoted insulin sensitivity.



Konrad et al. Diabetologia, 50:833-9, 2007

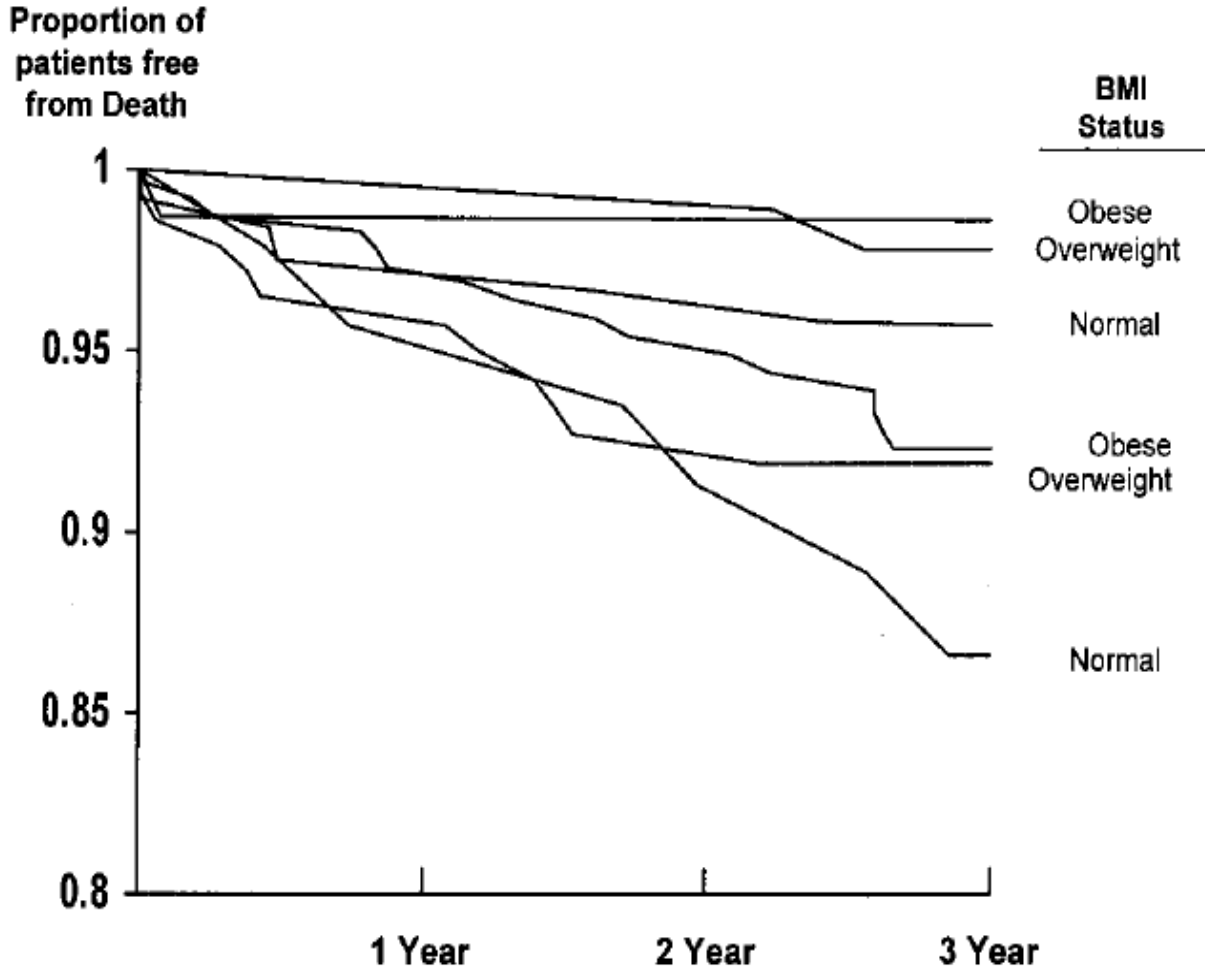
Associations of adiposity with CVD



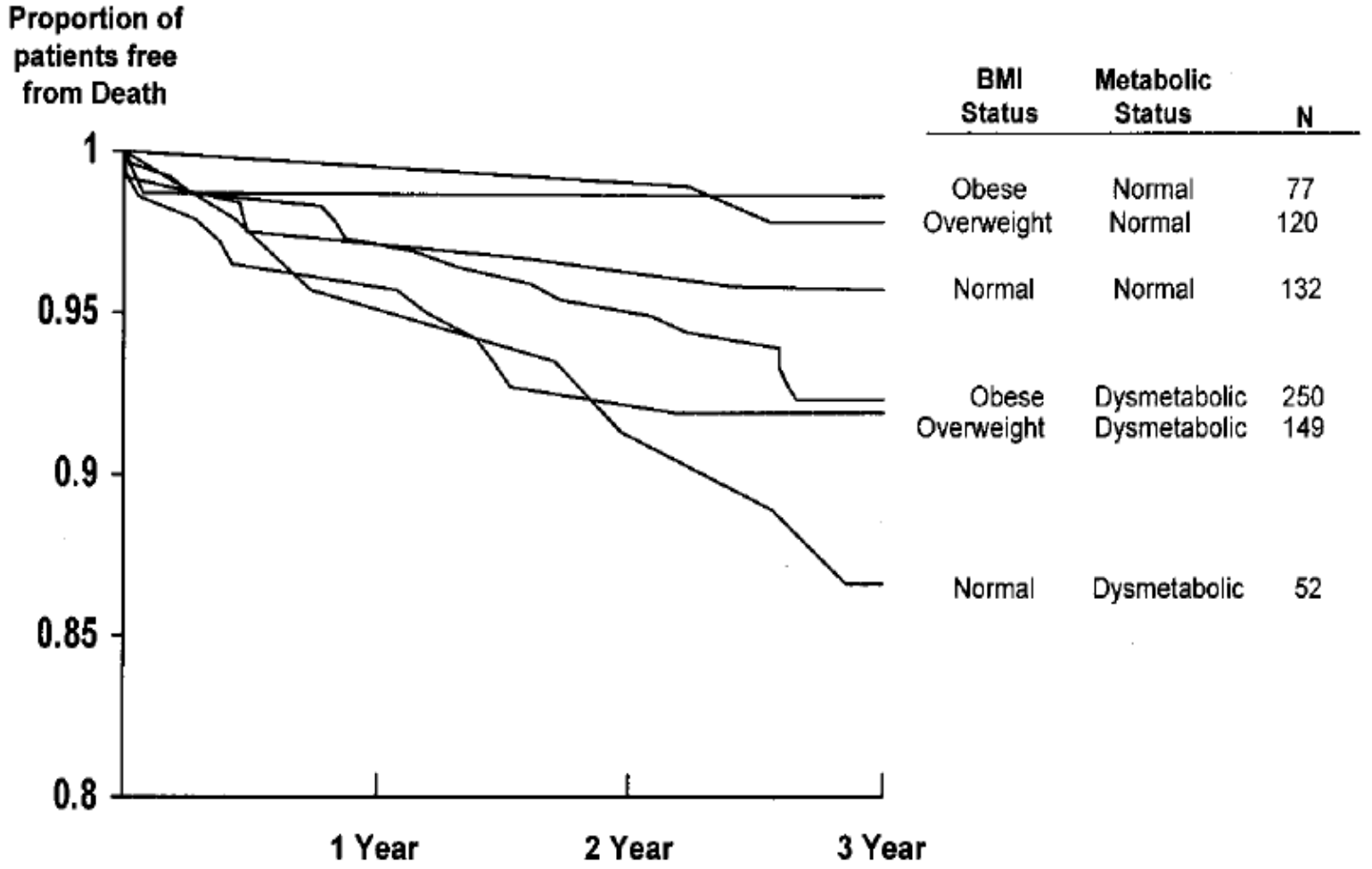
White = visceral fat area (VFA)
Black = subcutaneous (sc) fat

Matsuzawa Y. *Nat Clin Pract Cardiovasc Med*. 2006;3:35-42.

Kaplan-Meier curves of 3-year freedom from death by BMI and metabolic status at study entry. (WISE) study



Kaplan-Meier curves of 3-year freedom from death by BMI and metabolic status at study entry. (WISE) study



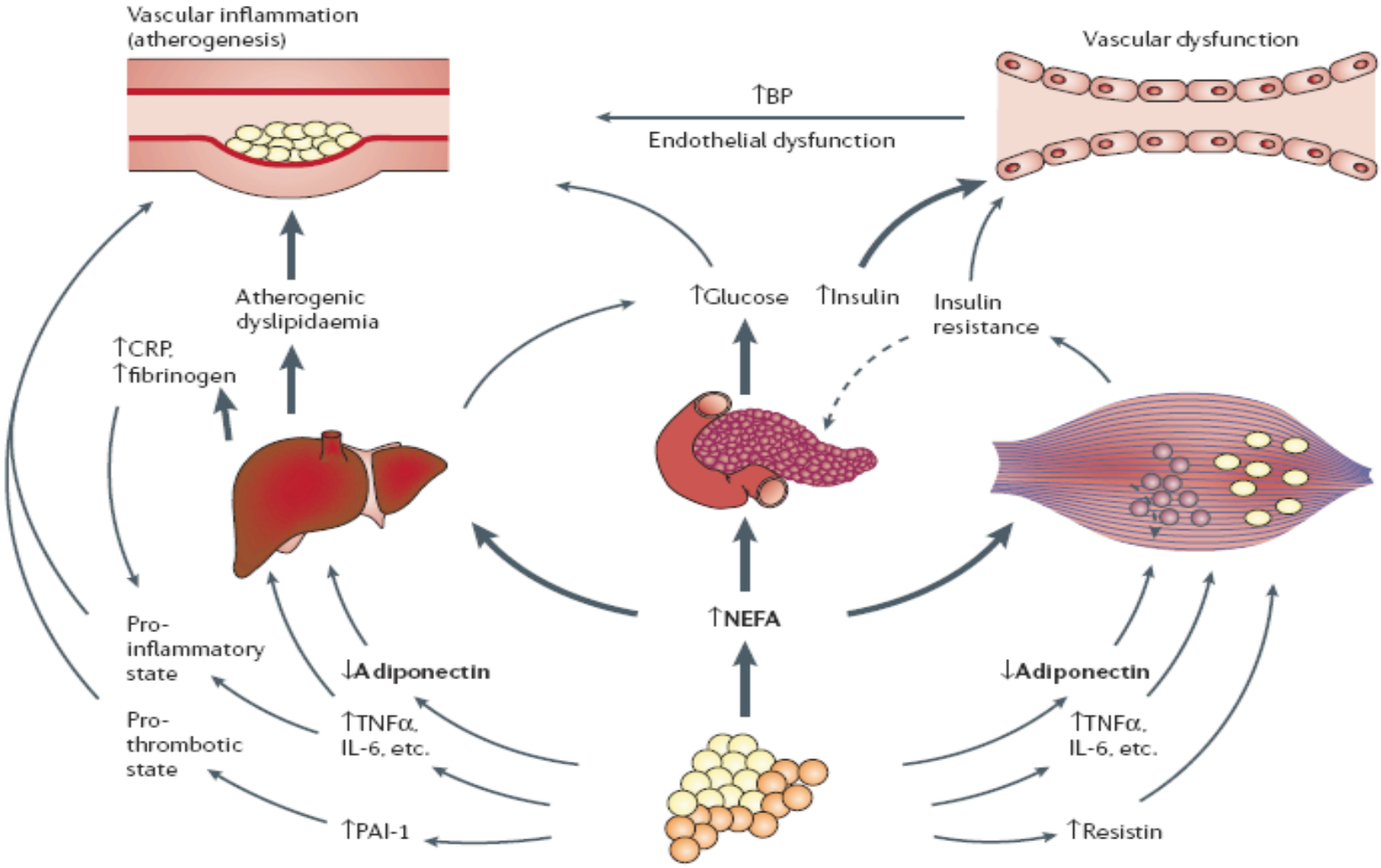
Metabolic Syndrome

- **High waist circumference (102/88 cm)**

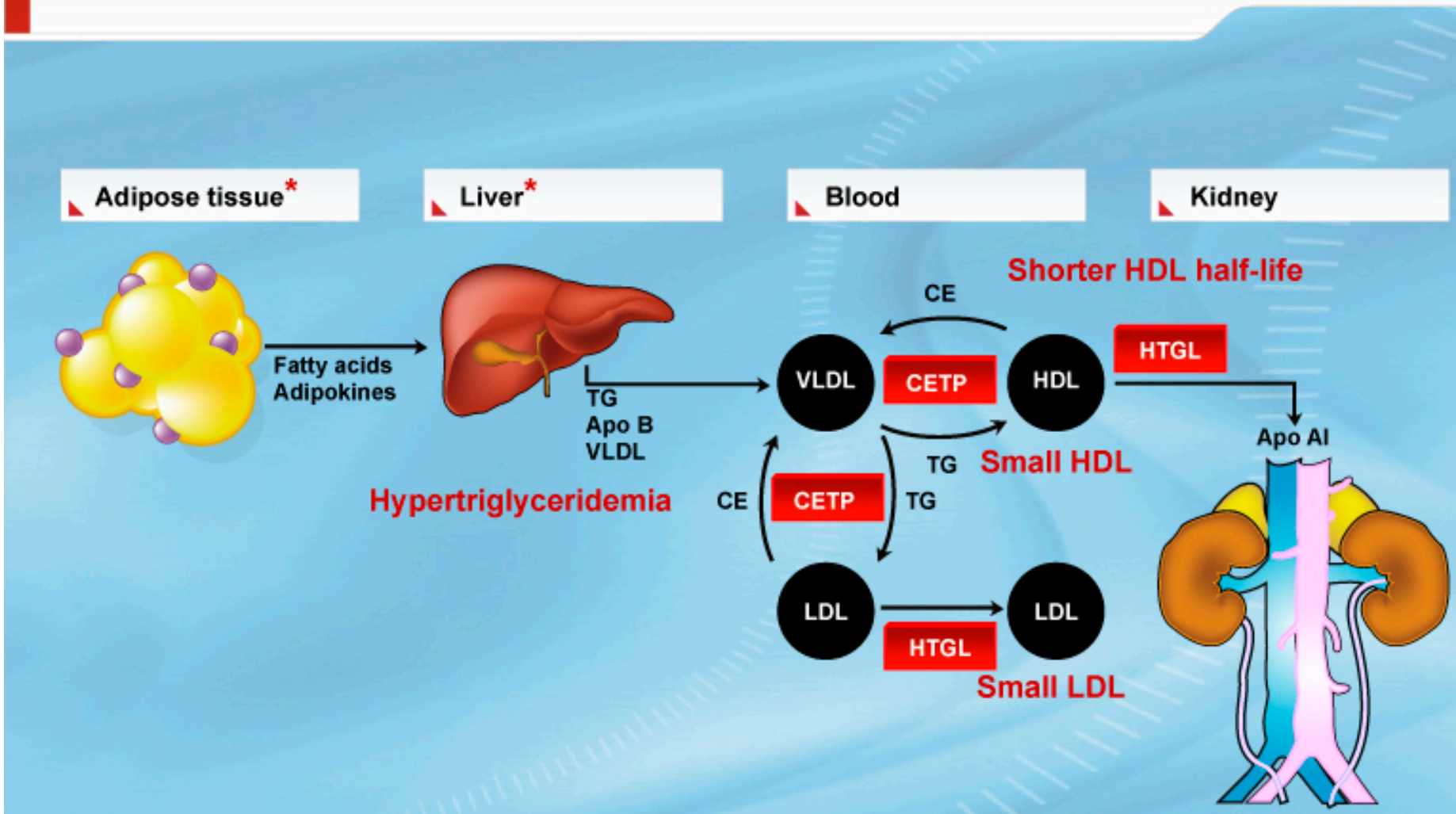
  ↑ Triglycerides ≥ 150 mg/dL‡

- **↓ HDL cholesterol‡**
  - **Men < (40 mg/dL)**
  - **Women < (50 mg/dL)**
- **↑ Blood pressure ≥ 130 / ≥85 mm Hg‡**
- **↑ FPG ≥ 100 mg/dL, or diabetes**

Obesity and the metabolic syndrome.



HOW INSULIN RESISTANCE AND DYSLIPIDEMIA ARE LINKED



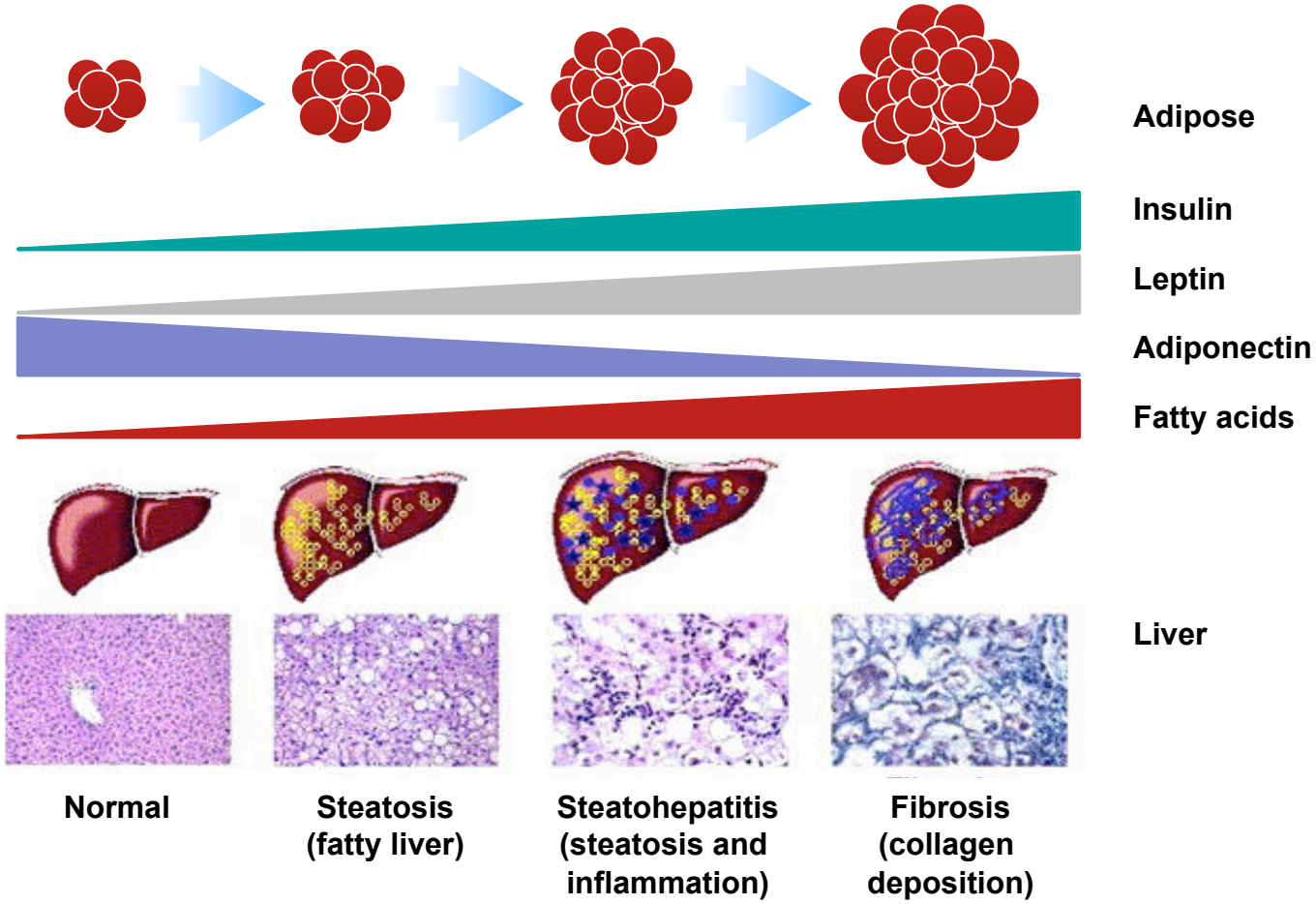
* *Insulin resistance*

Legend

CE = cholesteryl ester
CETP = cholesteryl ester transfer protein
HTGL = hepatic triglyceride lipase
TG = triglyceride

Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

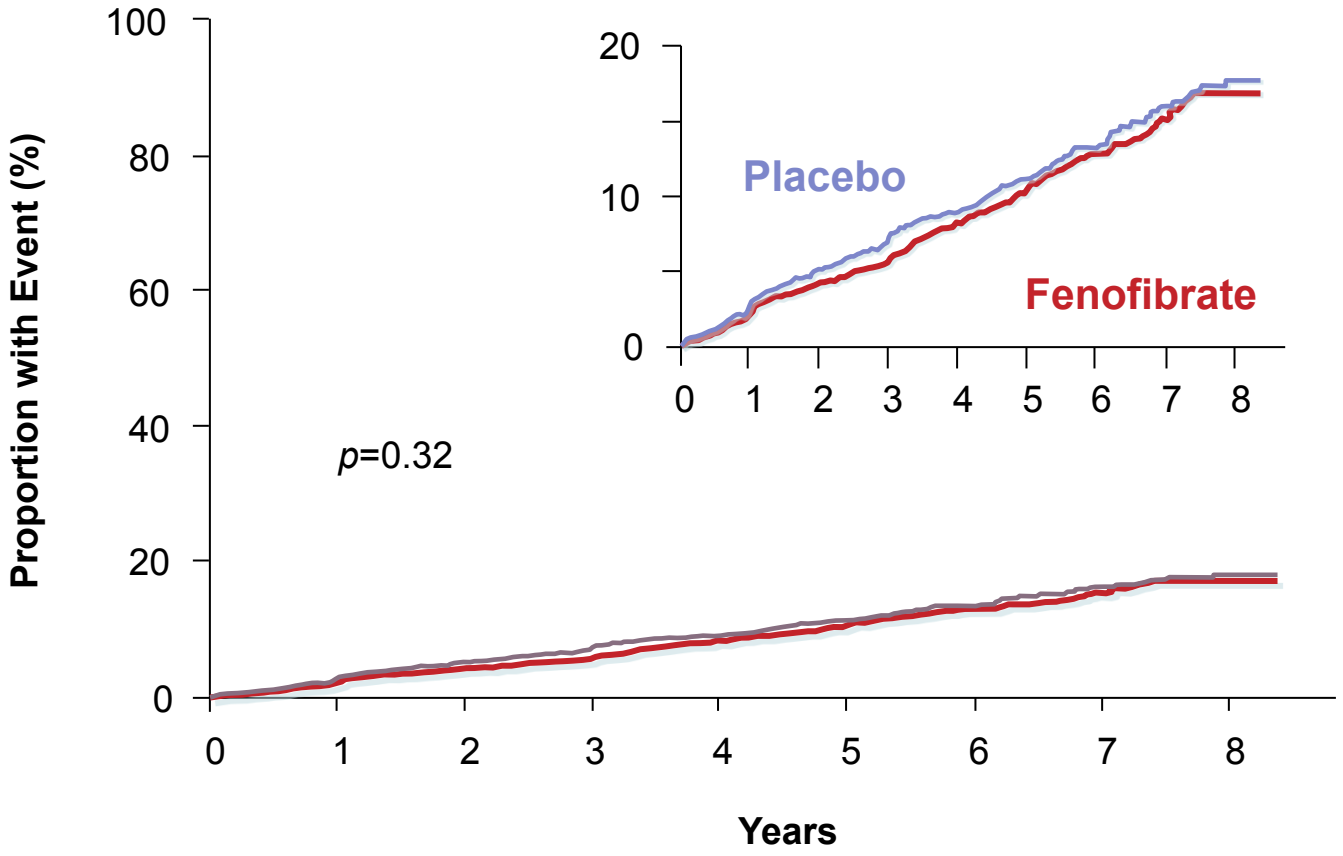
Adiposity in the development of NASH



Adapted from Ahima RS. *Gastroenterology.* 2007;132:444-6.
Angulo P. *N Engl J Med.* 2002;346:1221-31.

ACCORD: Simva with or without fenofibrate Lipid primary macrovascular outcome

(CV death + nonfatal MI + nonfatal stroke)



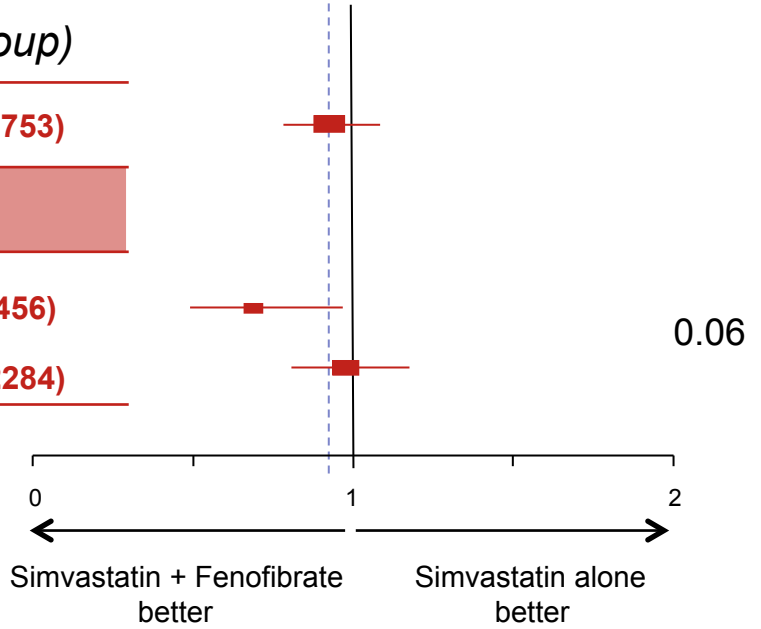
No. At Risk									
Fenofibrate	2765	2644	2565	2485	1981	1160	412	249	137
Placebo	2753	2634	2528	2442	1979	1161	395	245	131

ACCORD Study Group. *N Engl J Med* March 14, 2010. Epub.

ACCORD Lipid

31% reduction in events in patients with atherogenic dyslipidemia

Subgroup	Simvastatin + Fenofibrate	Simvastatin + Placebo	Hazard ratio (95% CI)	*p* value for interaction
	% of event (no. in group)			
Overall	**10.5 (2765)**	**11.3 (2753)**		
Triglyceride – HDL-C combination				
TG ≥204 mg/dL + HDL-C ≤34 mg/dL	**12.4 (485)**	**17.3 (456)**		0.06
All others	**10.1 (2264)**	**10.1 (2284)**		



- 20 patients with type 2 diabetes and atherogenic dyslipidemia needed to be treated for 5 years to prevent one CV event

ACCORD Study Group. *N Engl J Med* March 14, 2010. Epub.

ACCORD Lipid

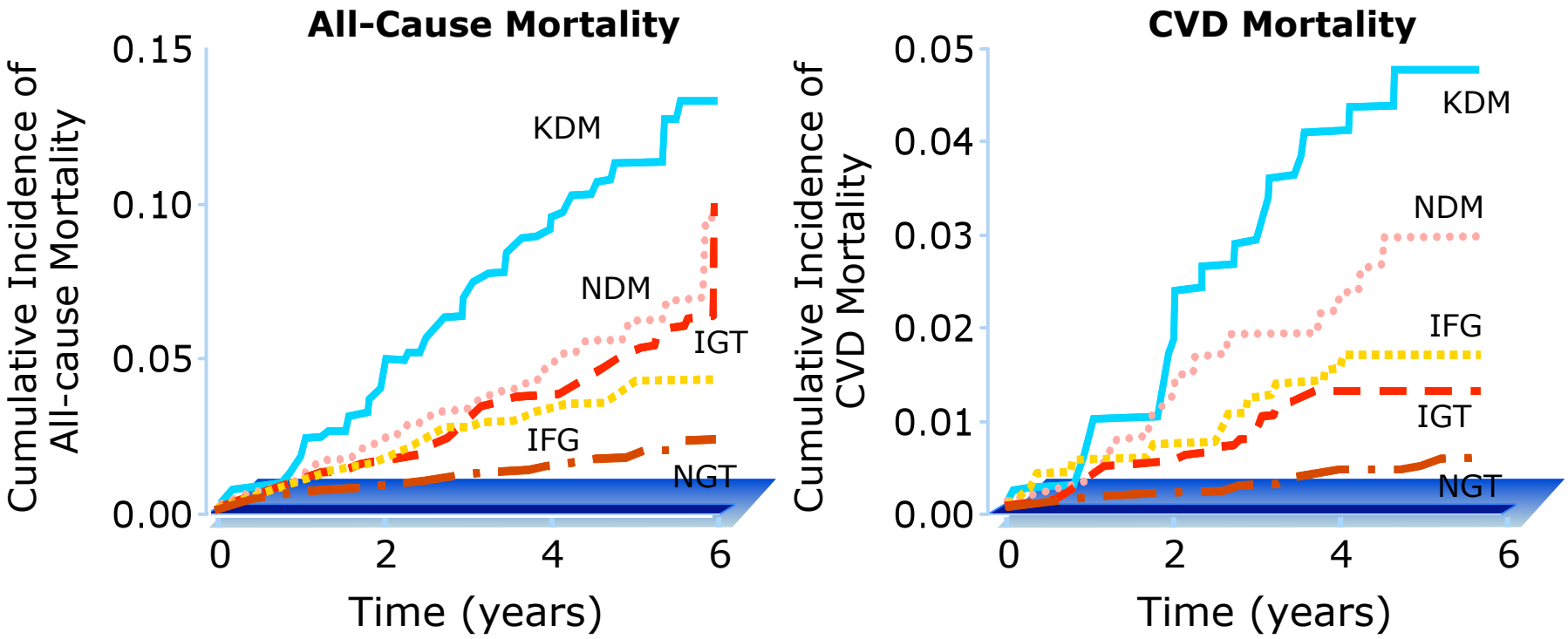
Comparison of subgroup results with those from prior landmark trials with fibrates

Trial (drug)	Primary endpoint: entire cohort (*p* value)	Lipid subgroup criterion	Primary endpoint: subgroup (*p* value)
HHS (gemfibrozil)	-34% (0.02)	TG > 200 mg/dL LDL-C/HDL-C > 5.0	Post-hoc -71% (0.005)
BIP (bezafibrate)	-7.3% (0.24)	TG ≥ 200 mg/dL	Post-hoc -39.5% (0.02)
FIELD (fenofibrate)	-11% (0.16)	TG ≥ 204 mg/dL HDL-C < 42 mg/dL	Post-hoc -27% (0.005)
ACCORD (fenofibrate)	-8% (0.32)	TG ≥ 204 mg/dL HDL-C ≤ 34 mg/dL	Prespecified -31%

Metabolic Syndrome

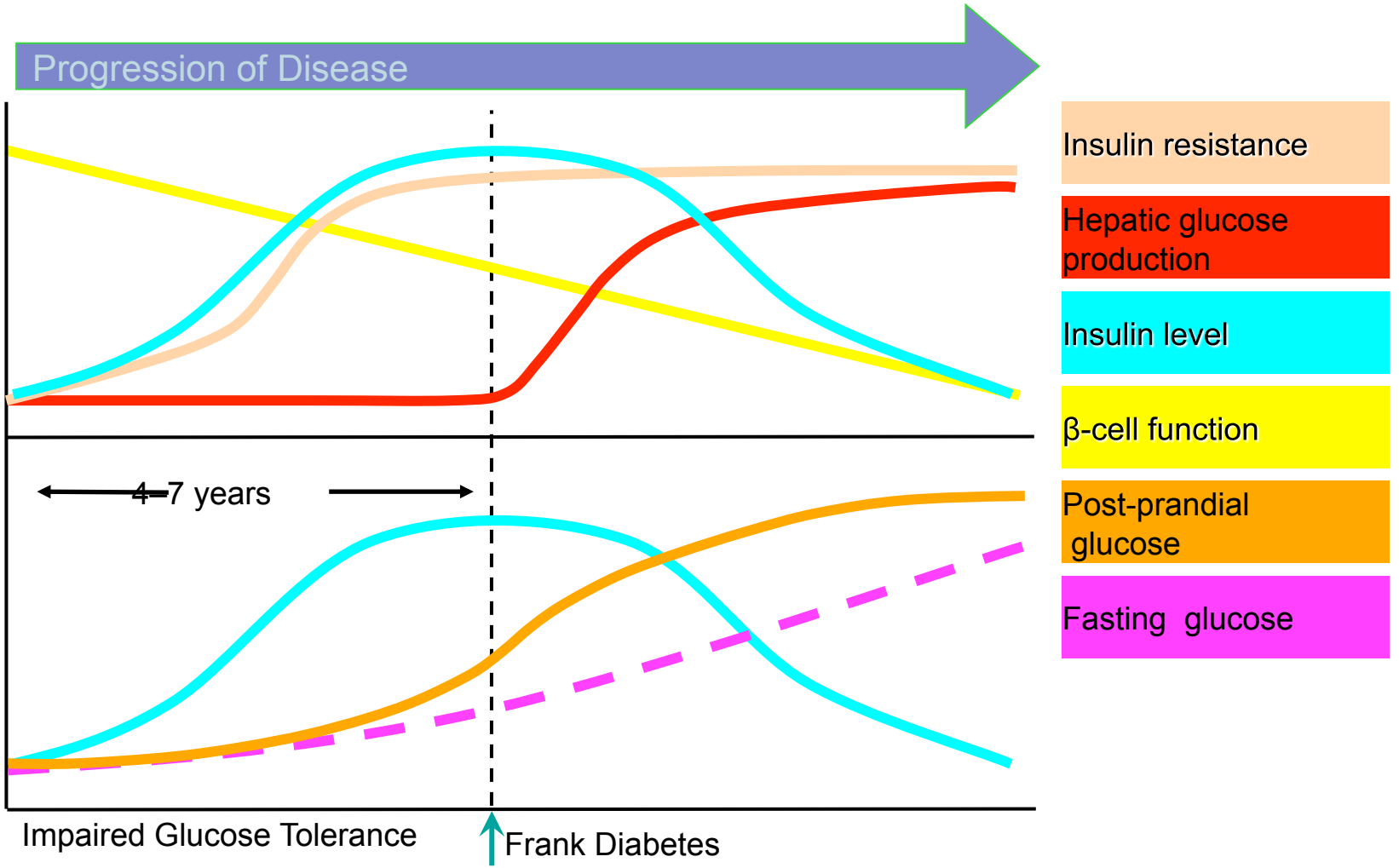
- **High waist circumference (102/88 cm)**
  ↑ Triglycerides ≥ 150 mg/dL‡
- **↓ HDL cholesterol‡**
  - **Men < (40 mg/dL)**
  - **Women < (50 mg/dL)**
- **↑ FPG ≥ 100 mg/dL, or diabetes**
- **↑ Blood pressure ≥ 130 / ≥85 mm Hg‡**

Unadjusted Mortality According to Glucose Metabolism: Data from AusDiab



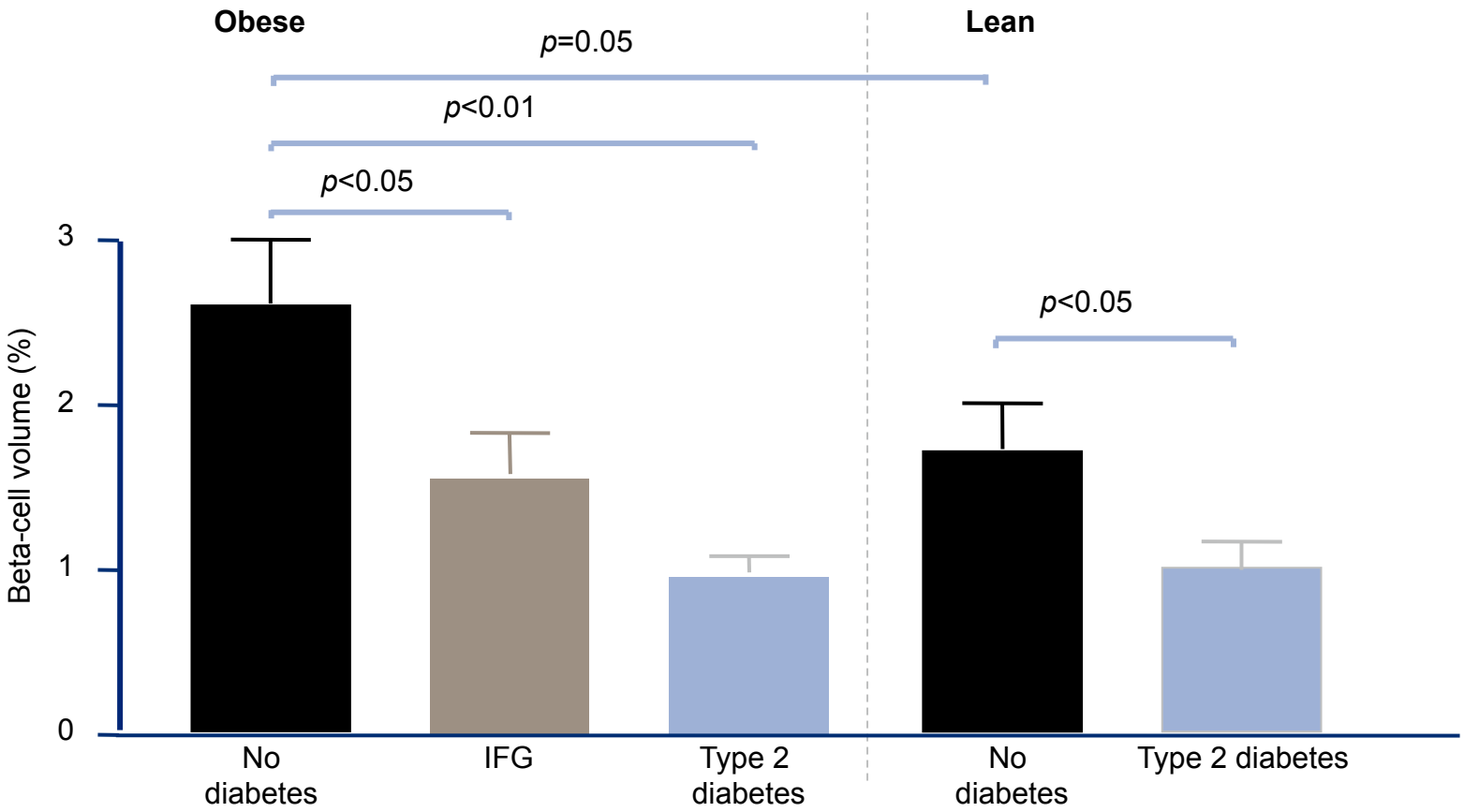
Reprinted from Barr EL, et al. *Circulation.* 2007;116:151–157, with permission from Lippincott Williams & Wilkins.

Progression of Disease



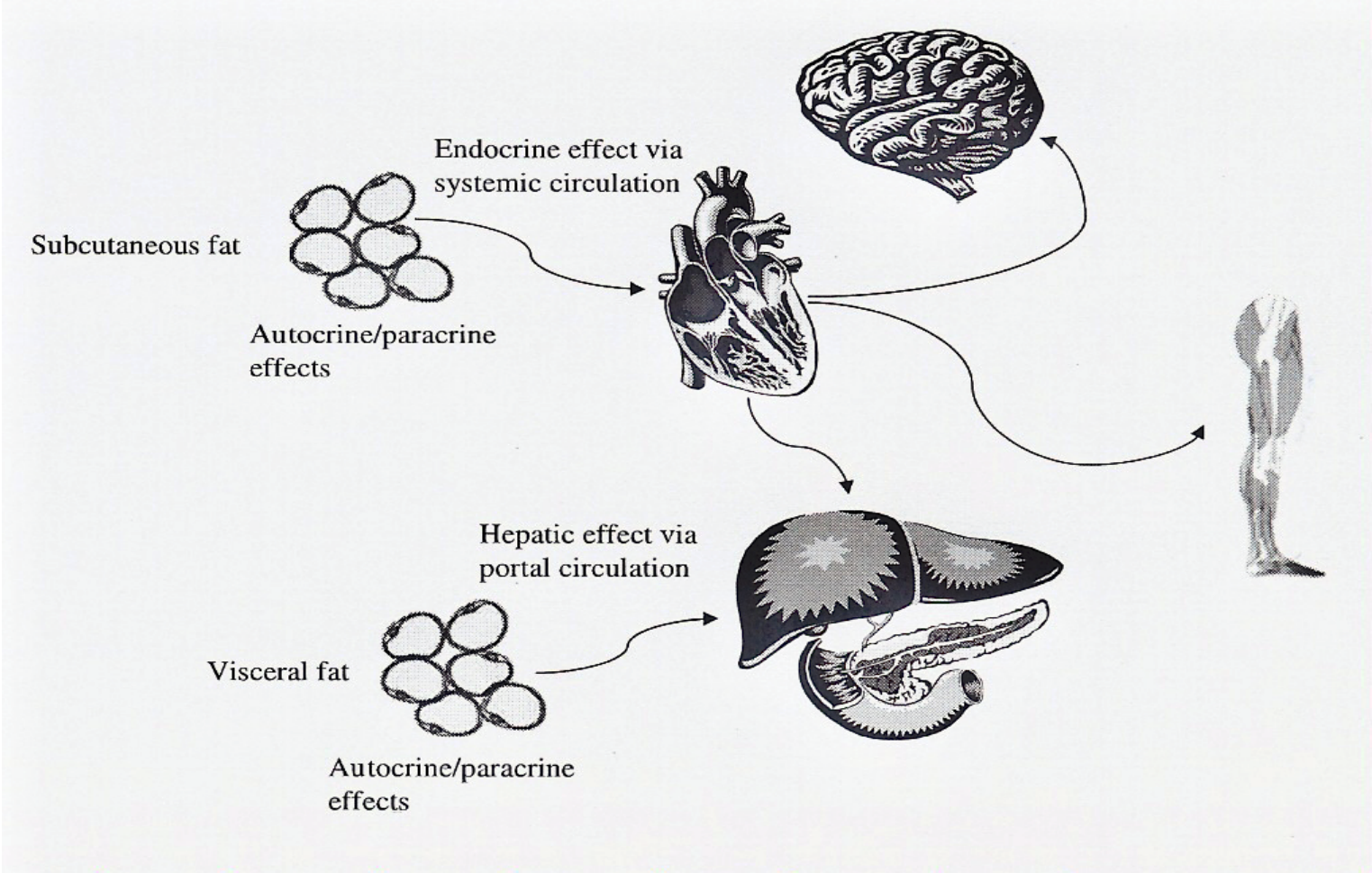
Reprinted from *Primary Care,* 26, Ra natural history of type 2 diabetes. Implications for clinical practice, 771–789, © 1999, with permission from Elsevier.

In humans, beta-cell mass increases with obesity, decreases with type 2 diabetes



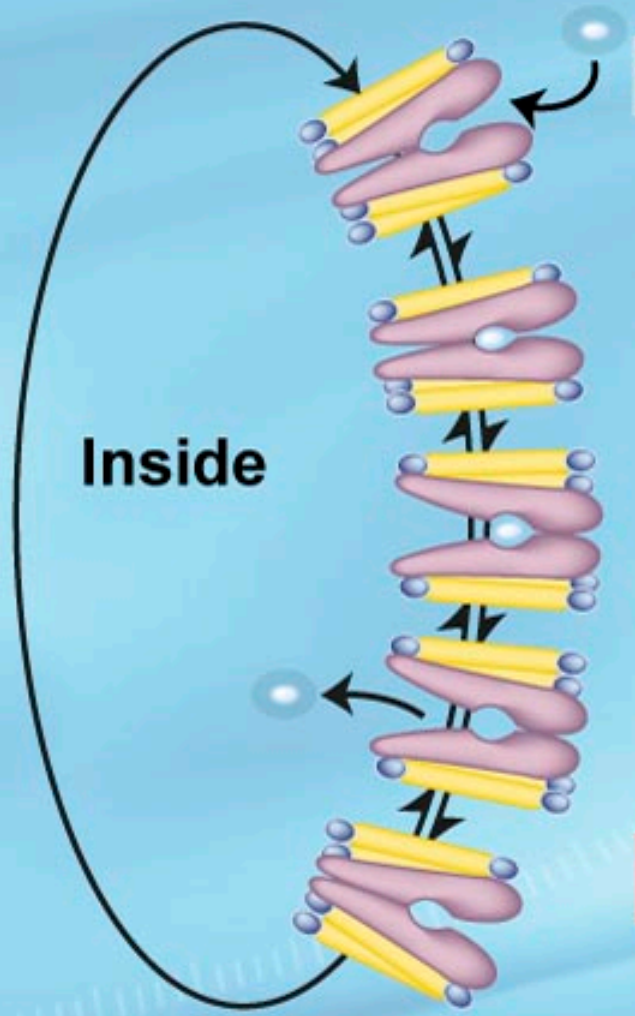
Adapted from Butler *et al. Diabetes* 2003;52:102–10
IFG, impaired fasting glucose. Data are mean±SE

Adipose tissue distribution and risk of metabolic disease



Yung X, Diabetologia 2007

GLUCOSE TRANSPORTERS (GLUT)



D-Glucose

Step 1

Step 2

Step 3

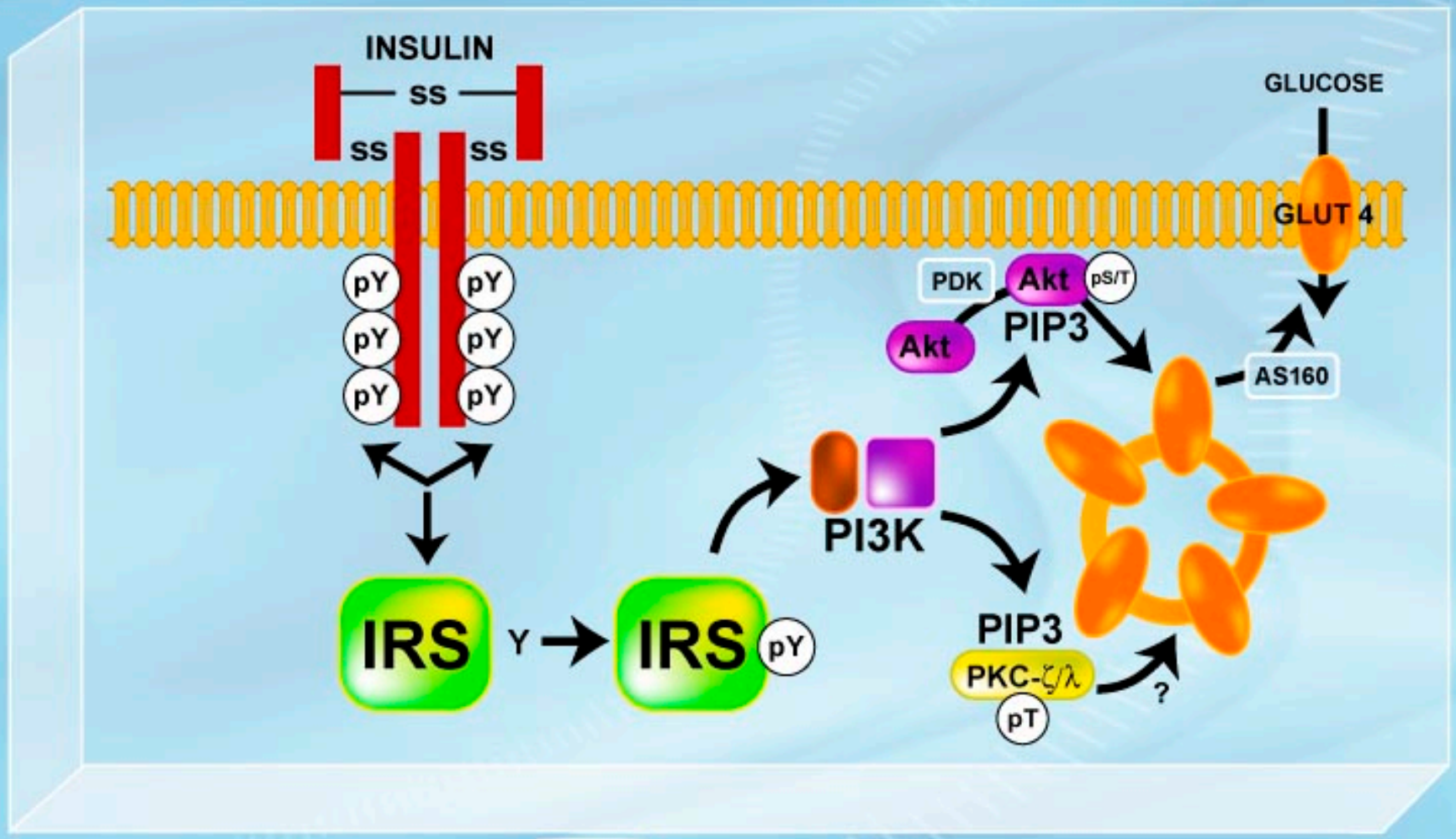
Step 4

Organ	Transporter
Blood-brain barrier	GLUT 1
Brain	GLUT 3
Intestine	GLUT 5
Liver	GLUT 2
Adipose tissue	GLUT 4* (GLUT 1)
Muscle	GLUT 4* (GLUT 1)
Pancreas	GLUT 2

* Insulin-sensitive

Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

SIMPLIFIED SCHEME OF INSULIN ACTION ON GLUCOSE TRANSPORT

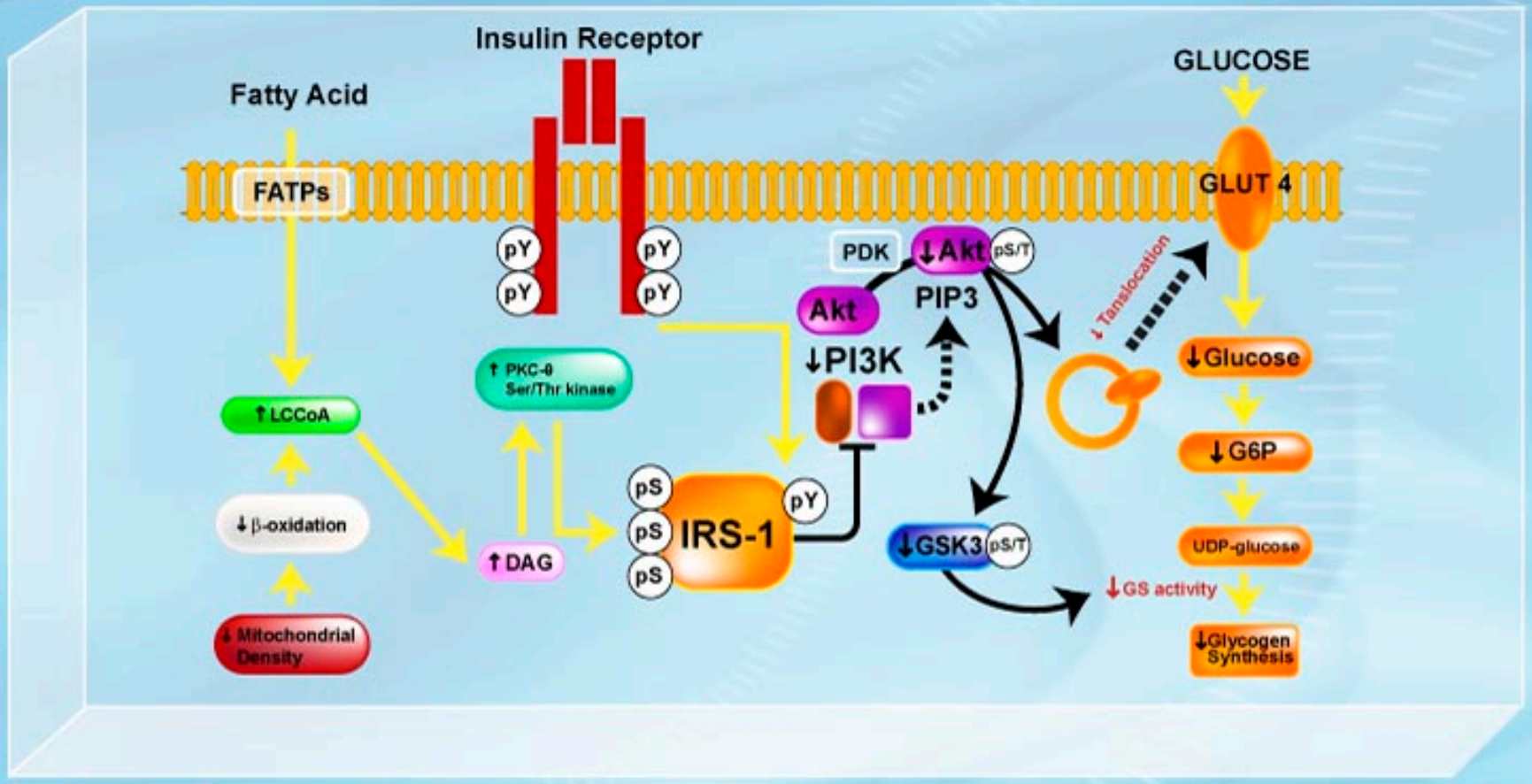


Legend

Akt= protein kinase
AS160 = Akt substrate of 160 kDa
GLUT = glucose transporter
IRS = insulin receptor substrate-1/2
PDK = phosphoinositide-dependent protein kinase
PIP3 = phosphatidylinositol 3 triphosphate
PI3K= phosphatidylinositol [3,4,5) kinase
PKC = protein kinase C
pS/T = serine/threonine phosphorylation
pT = threonine phosphorylation
pY = tyrosine phosphorylation

Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

MECHANISM OF FATTY ACID-INDUCED INSULIN RESISTANCE IN SKELETAL MUSCLE



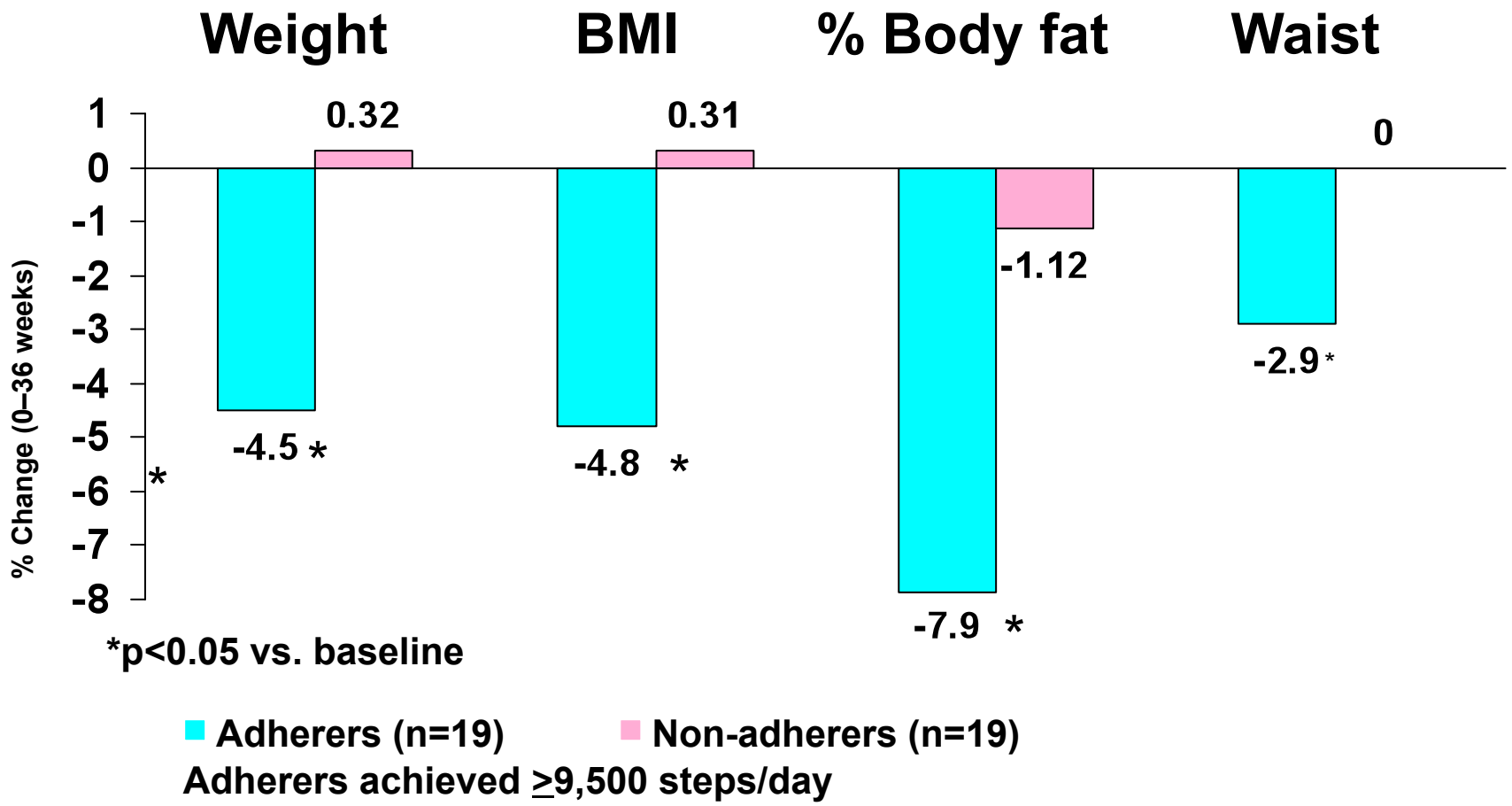
Legend

Akt = protein kinase B
DAG = diacylglycerol
FATPs = fatty acid transport proteins
G6P = glucose 6-phosphate
GLUT = glucose transporter
GS = glycogen synthase
GSK3 = glycogen synthase kinase-3
IRS-1 = insulin receptor substrate-1
LCCoA = long-chain acylcoenzyme A
PDK = phosphoinositide-dependent protein kinase
PKC = protein kinase C
PI3K = phosphatidylinositol [3,4,5] kinase
PIP3 = phosphatidylinositol 3 triphosphate
pS = serine phosphorylation
pS/T = serine/threonine phosphorylation
pY = tyrosine phosphorylation
Ser/Thr = serine/threonine
UDP = uridine diphosphate glucose

Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

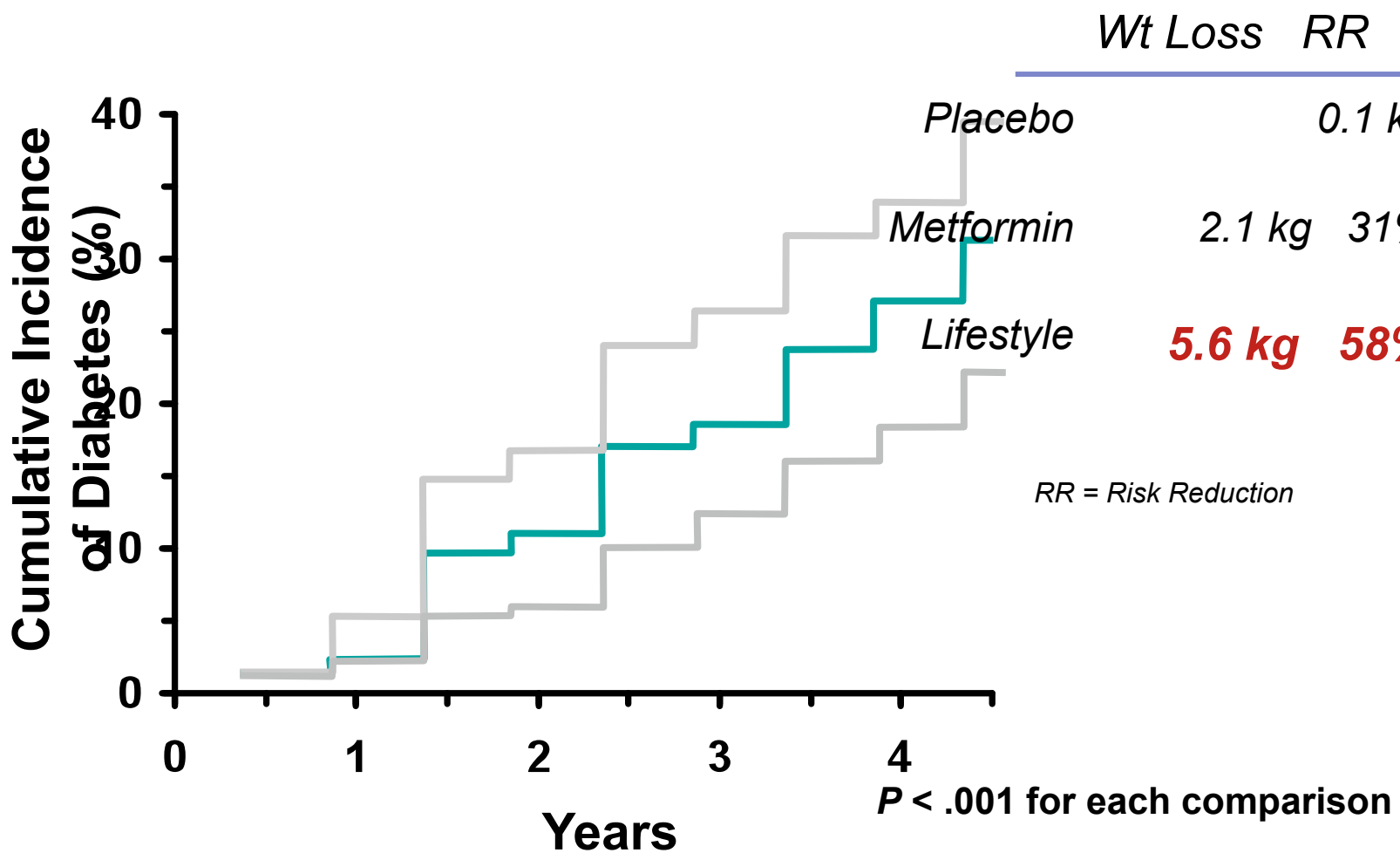
Adapted from Savage DB et al. Physiol Rev 2007; 87: 507-20

Benefits of a 36-week 10,000 steps per day exercise programme



Schneider PL et al. Am J Health Promot 2006;21:85-9.

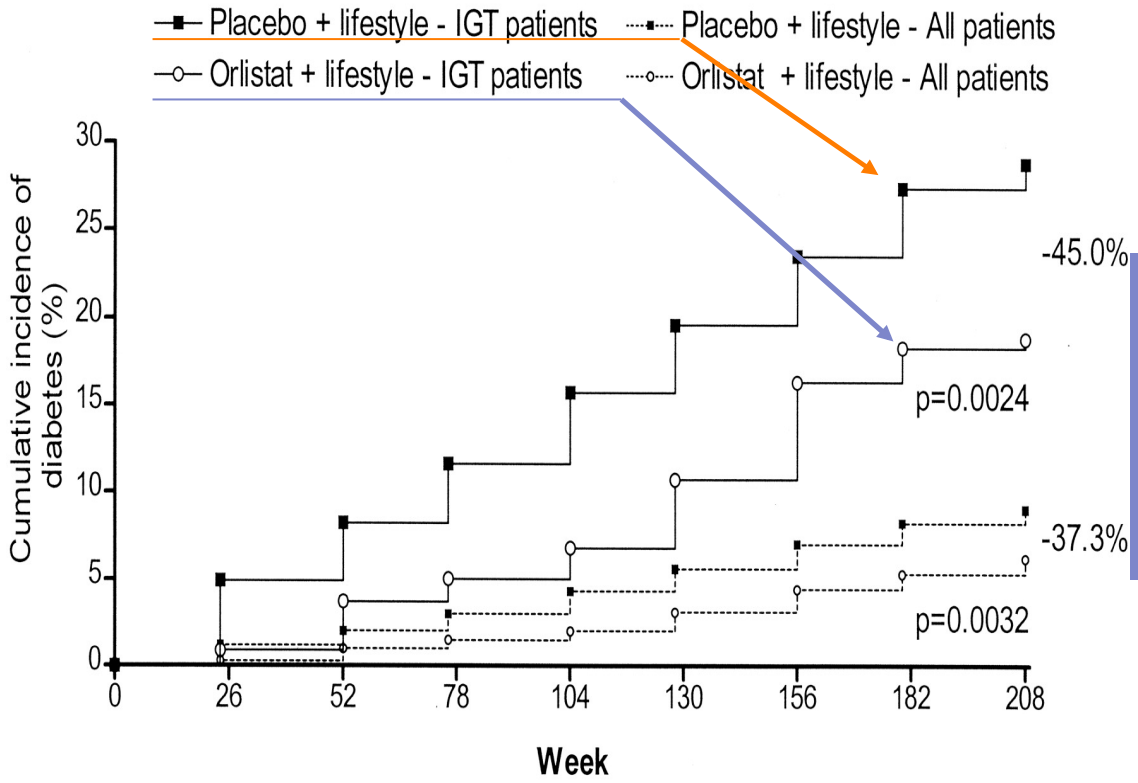
Modest Weight Loss Reduces the Incidence of New-Onset Diabetes In An At-Risk Population



Diabetes Prevention Program Research Group. *N Engl J Med.* 2002;346:393-403

4 year long RCT of orlistat as an adjunct to lifestyle for the prevention of type 2 diabetes in obese at-risk patient

Weight loss with orlistat+lifestyle reduced the risk of type 2 diabetes more than lifestyle alone



"DPP-like" intervention

Result "better than" DPP intervention

•Diabetes Care. 2004 Jan;27(1):155-61.

Metabolic Syndrome

- **High waist circumference (102/88 cm)**

  ↑ Triglycerides ≥ 150 mg/dL‡

- **↓ HDL cholesterol‡**
  - **Men < (40 mg/dL)**
  - **Women < (50 mg/dL)**
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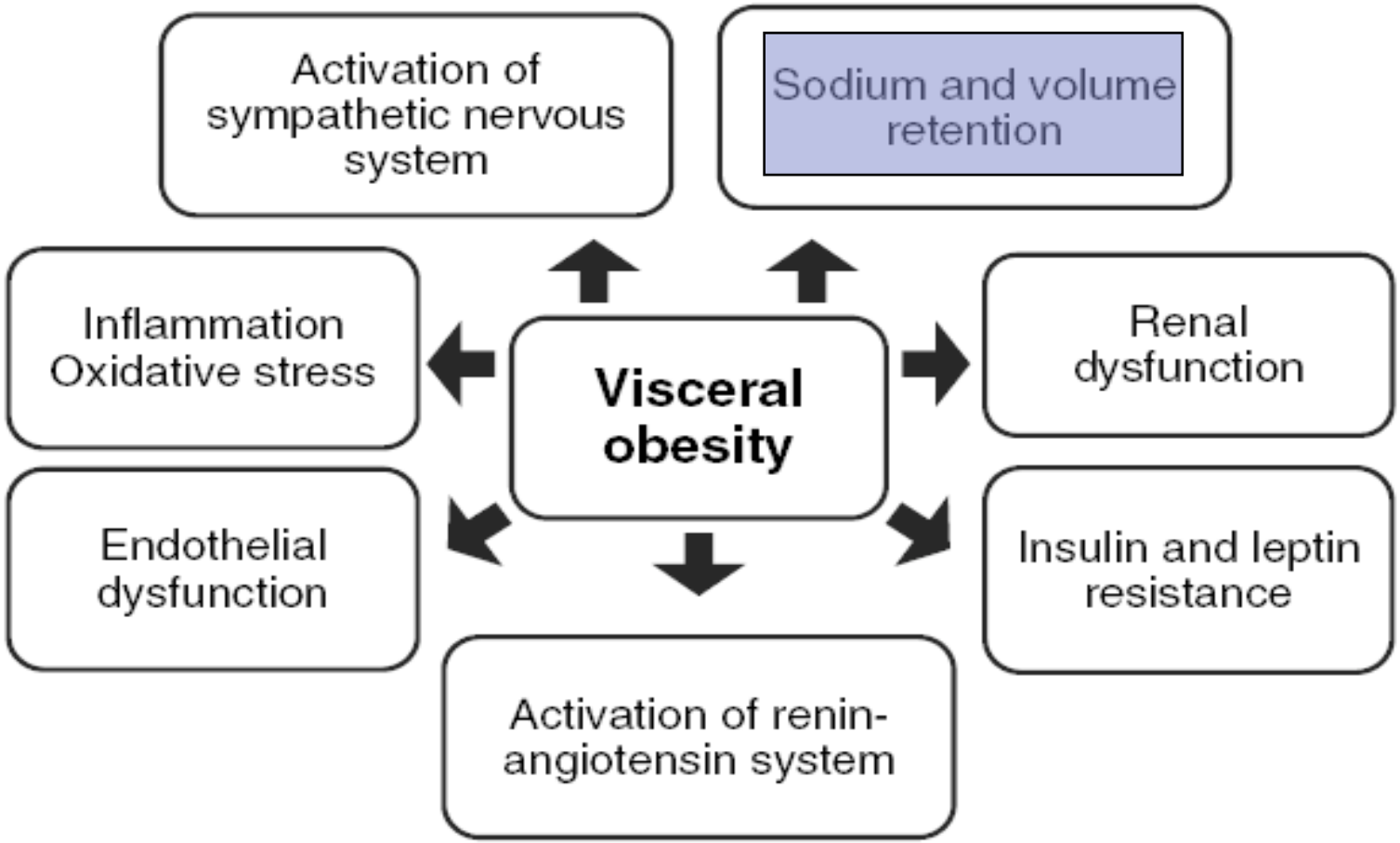
- **↑ Blood pressure ≥ 130 / ≥85 mm Hg‡**

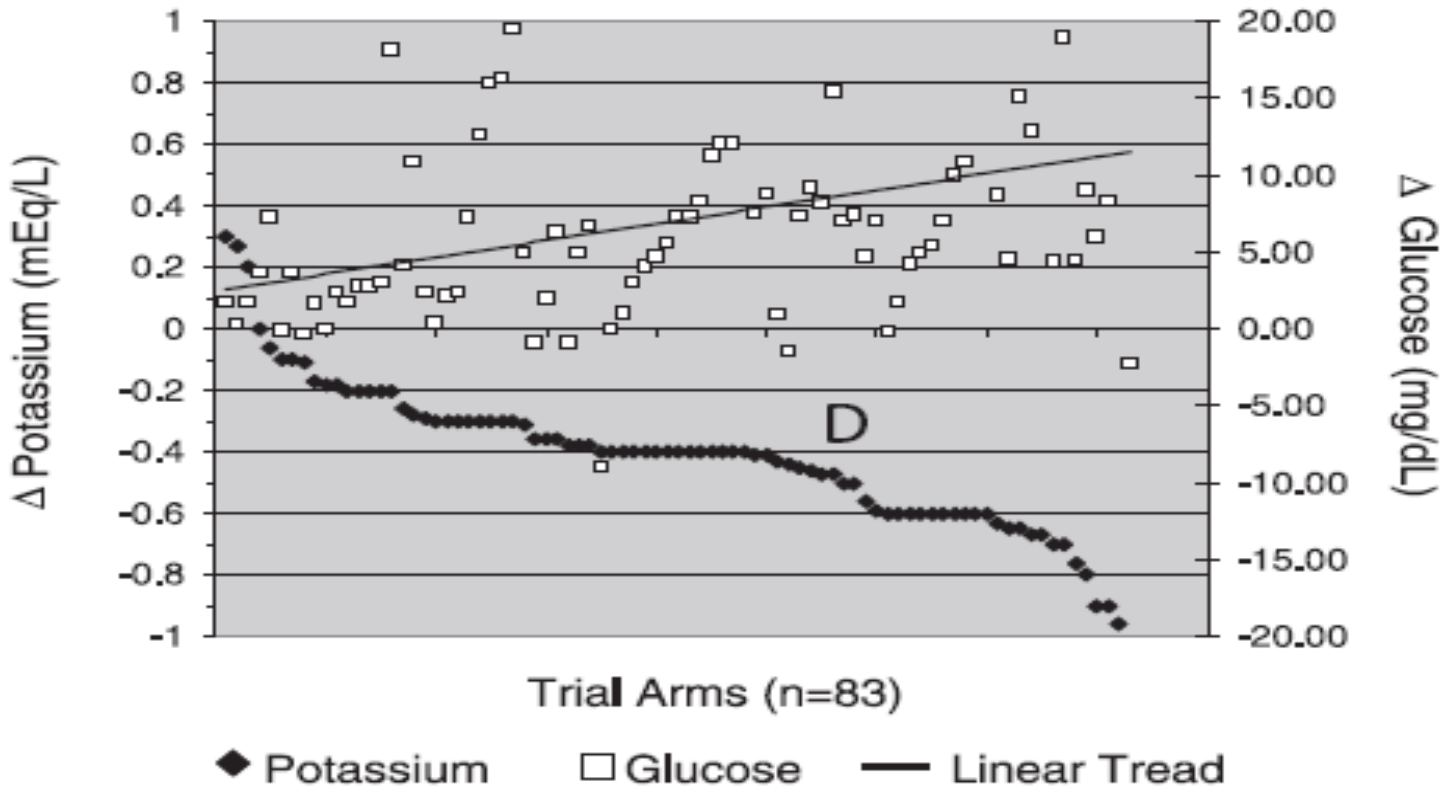
Potential mechanisms linking obesity to hypertension



K. Narkiewicz **Obesity** reviews (2006)

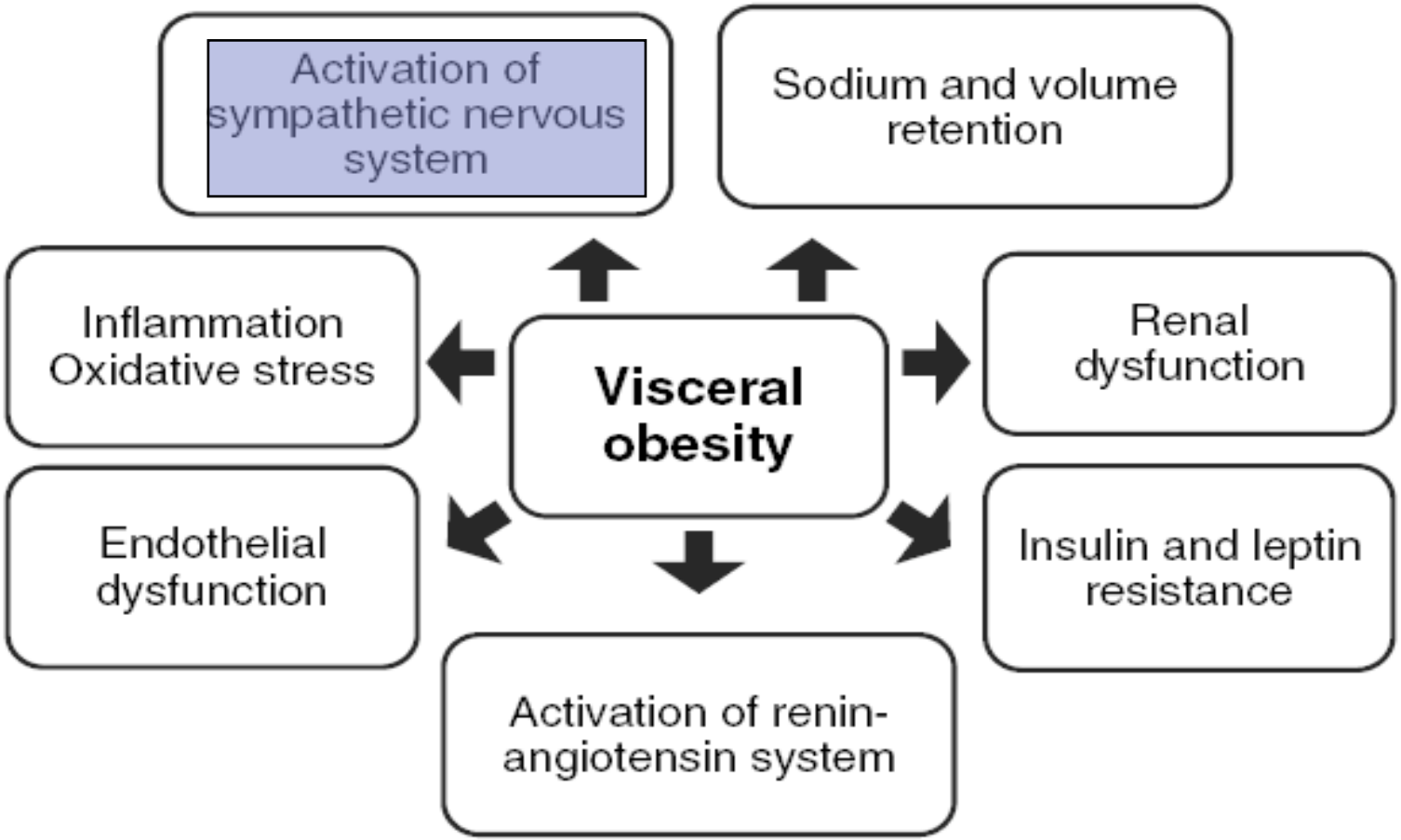
Thiazide Diuretics, Potassium, and the Development of Diabetes

A Quantitative Review



Alan J. Zillich, ***Hypertension. 2006***

Potential mechanisms linking obesity to hypertension

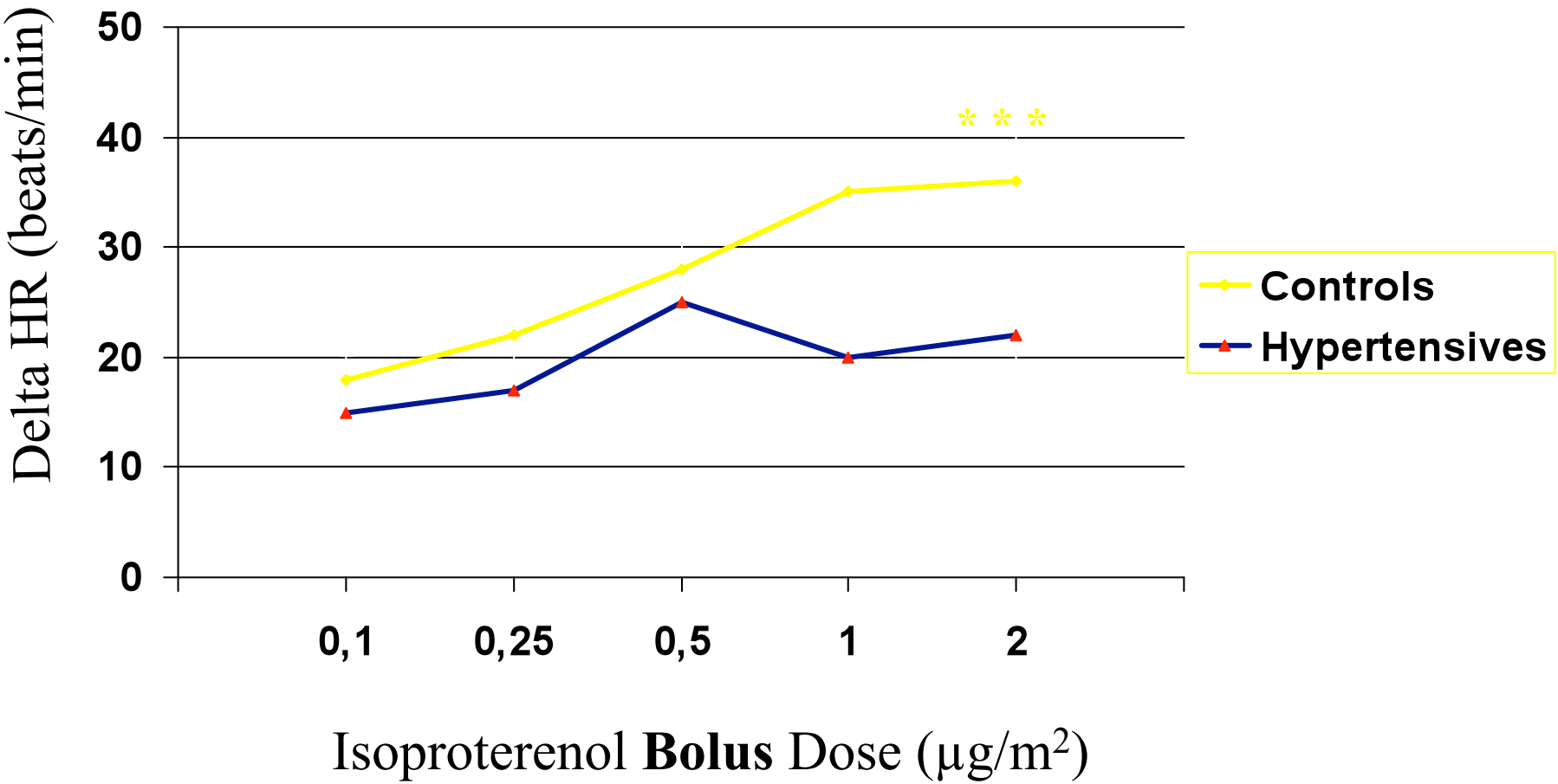


K. Narkiewicz **Obesity** reviews (2006)

HYPOTHESIS

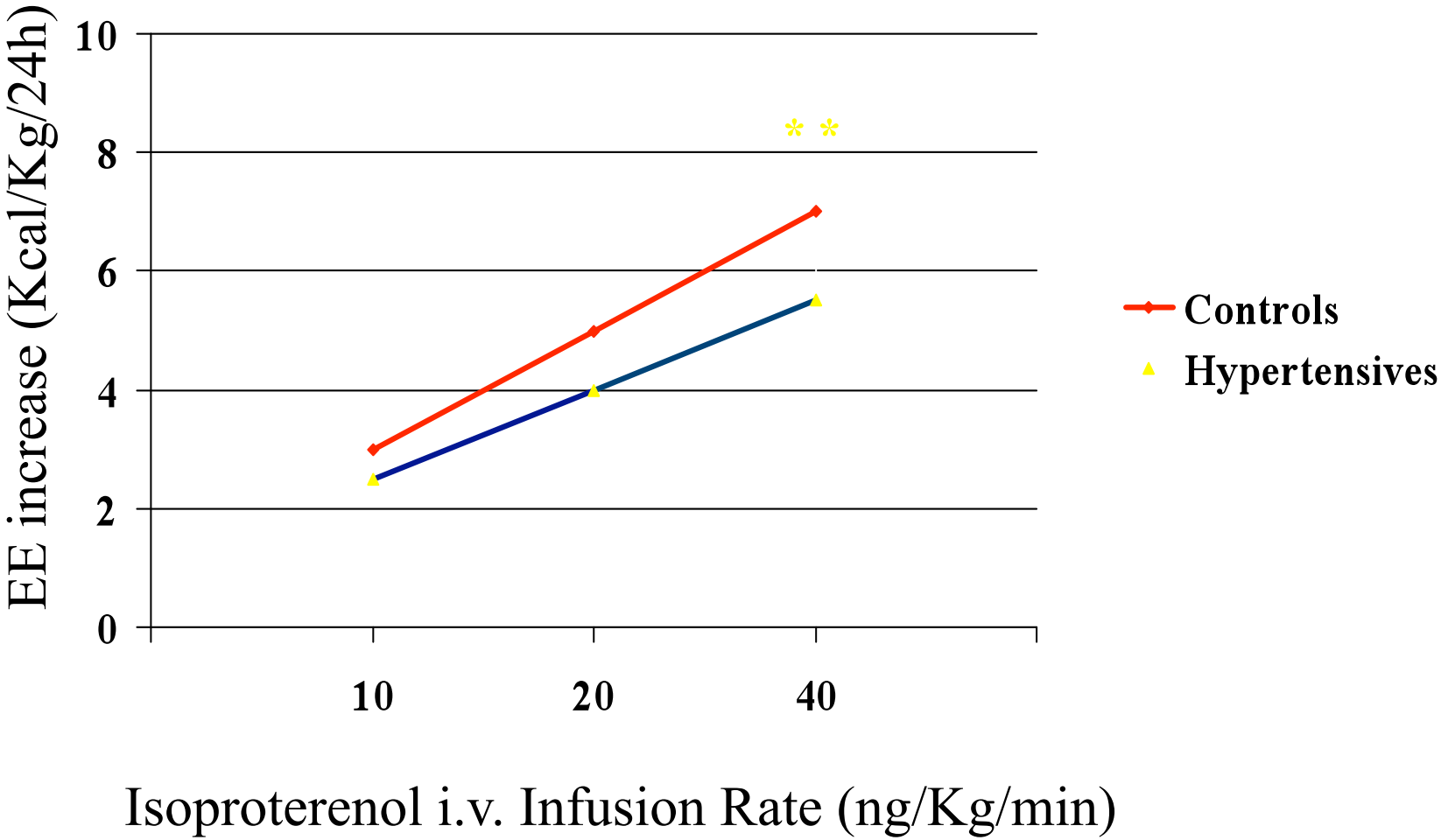
If in addition to cardiovascular responses, the metabolic responses were also decreased in hypertension, the patient's ability to dissipate calories would be diminished and they would gain more weight.

Heart rate response to isoproterenolol bolus is decreased in hypertension



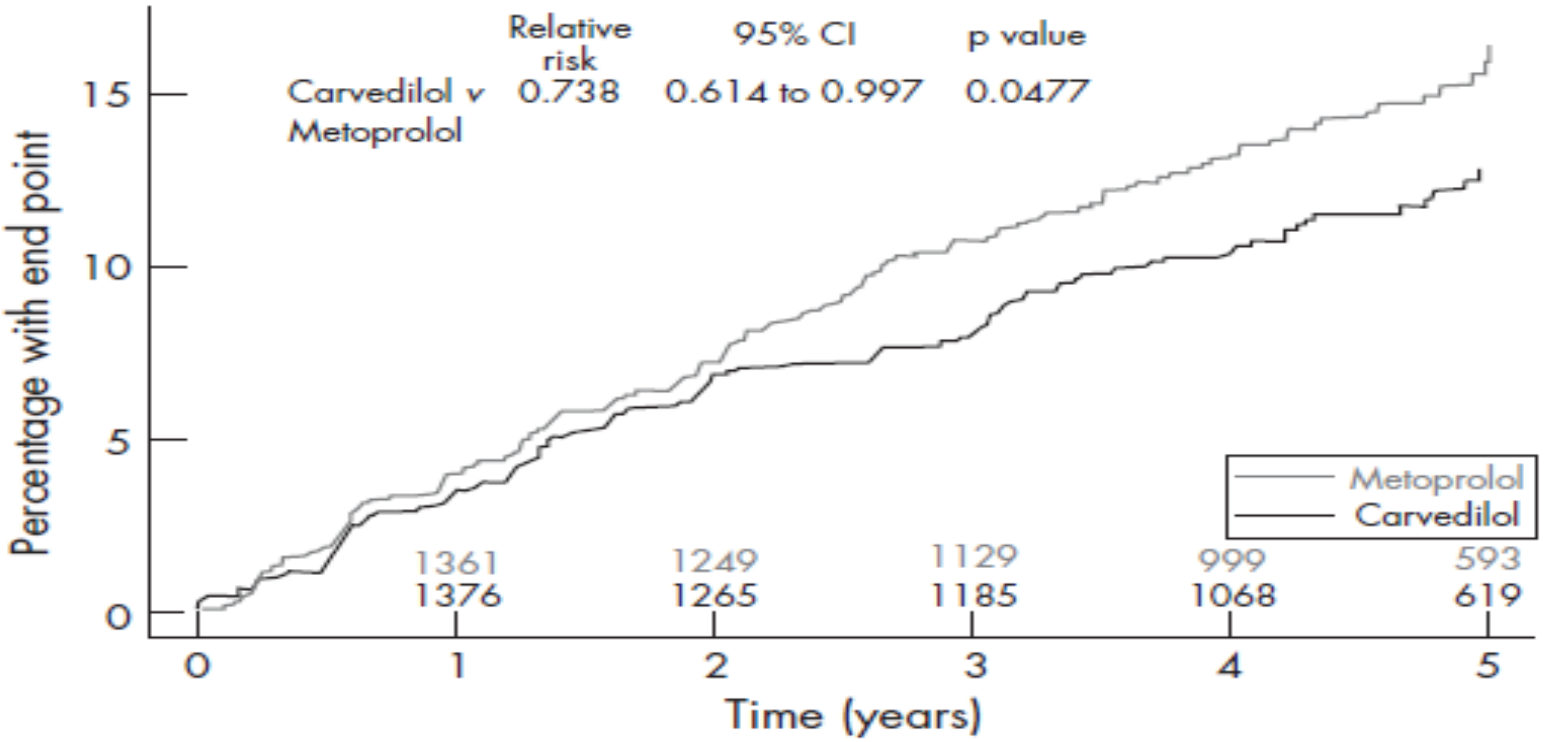
Valentini M, Julius S, et al, J of Hypertension 22:1999-2006, 2004

Energy expenditure response to isoproterenolol is decreased in hypertension.



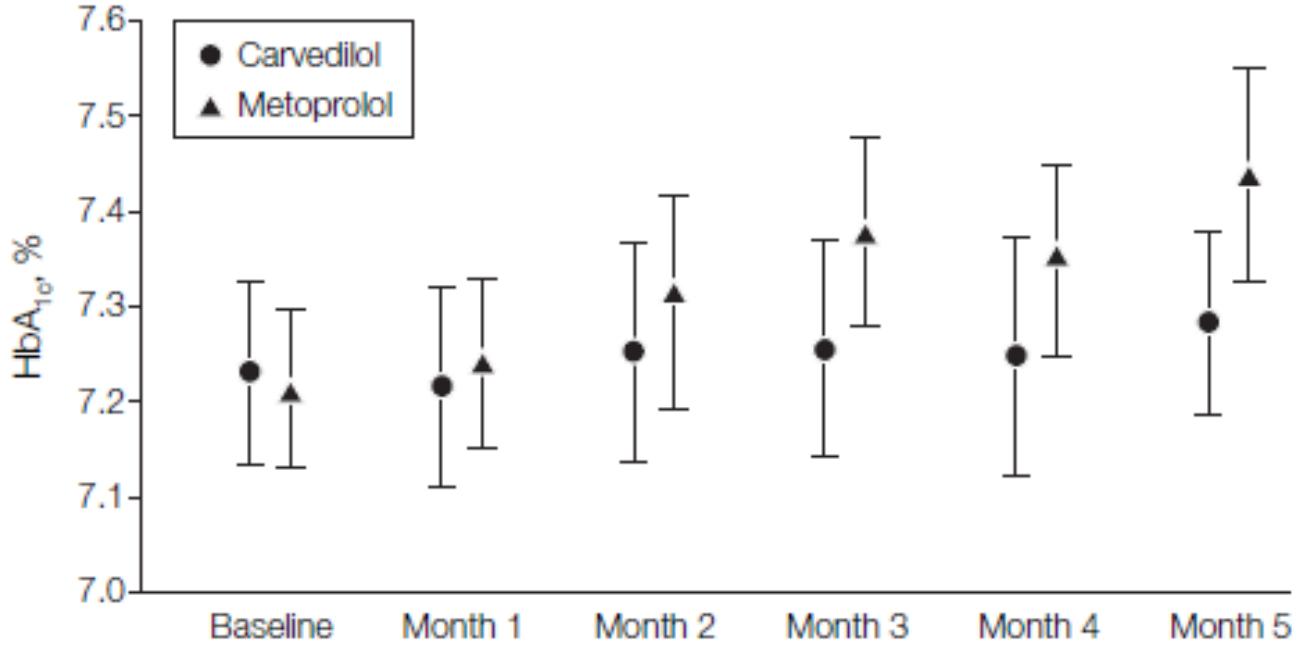
Valentini M, Julius S, et al, J of Hypertension 22:1999-2006, 2004

Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET)



Christian Torp-Pedersen; Heart 2007

Metabolic Effects of Carvedilol vs Metoprolol in Patients With Type 2 Diabetes Mellitus and Hypertension



No. of Participants						
Carvedilol	454	390	449	452	453	454
Metoprolol	654	550	643	655	655	657

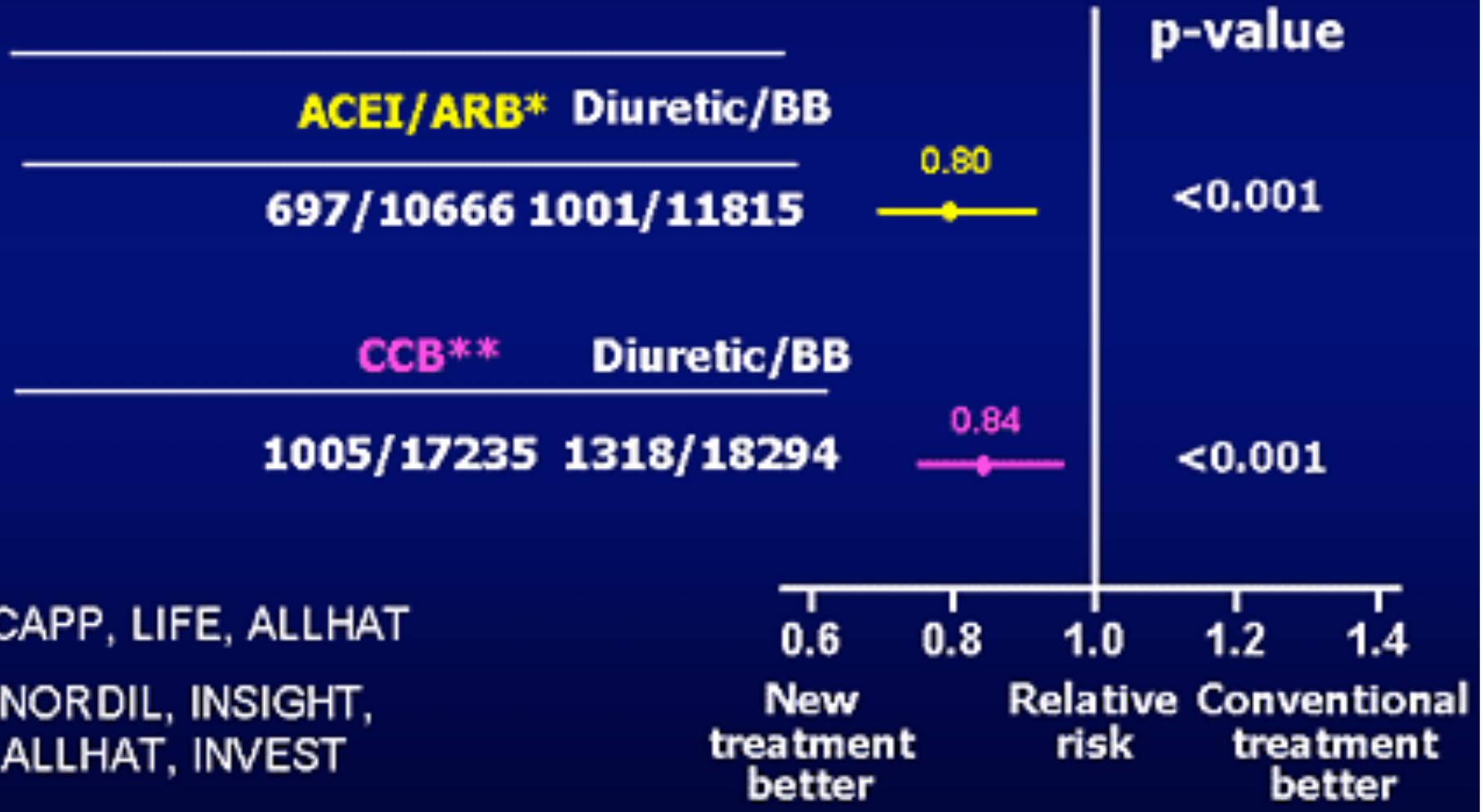
George L. Bakris, *JAMA. 2004*

Metabolic Effects of Carvedilol vs Metoprolol in Patients With Type 2 Diabetes Mellitus and Hypertension

Parameter	Carvedilol (n = 454) No. of Participants	Baseline	Maintenance Month 5 or Last Observation Carried Forward	% Change	Metoprolol (n = 657) No. of Participants	Baseline	Maintenance Month 5 or Last Observation Carried Forward	% Change	Treatment Difference % Change (95% CI)†	*P* Value
BP, mean (SE), mm Hg‡										
Systolic	454	149.4 (0.6)	131.3 (0.7)	−17.9 (0.7)	636	149.2 (0.5)	132.3 (0.6)	−16.9 (0.6)	−1.0 (−2.60 to 0.58)	.21
Diastolic	454	87.0 (0.4)	77.1 (0.4)	−10.0 (0.4)	636	86.3 (0.4)	76.8 (0.3)	−10.3 (0.3)	0.29 (−0.61 to 1.20)	.53
Heart rate/min, mean (SE)‡	454	73.7 (0.5)	67.6 (0.4)	−6.7 (0.4)	636	74.5 (0.4)	66.0 (0.4)	−8.3 (0.4)	1.6 (0.70 to 2.58)	<.001
Mean ACR, mg/g§	388	12.3	11.1	14.0	542	12.0	12.3	2.5	16.2 (−25.21 to −5.87)	.003
Mean HOMA-IR§	371	6.0	5.8	−9.1	540	5.8	6.2	−2.0	−7.2 (−13.8 to −0.2)	.004
Mean plasma glucose, mg/dL‡	419	147.0	154.7	6.6	607	147.4	158.6	10.6	−4.0 (−8.73 to 0.78)	.10
Mean serum insulin, μIU/mL‡	387	21.6	19.6	−19.4	561	21.2	20.2	−15.1	−4.2 (−16.7 to 8.24)	.51
Mean body weight, kg‡	456	98.2	97.2	0.17	650	97.0	98.2	1.2	−1.0 (−1.43 to −0.60)	<.001
Mean serum cholesterol levels, mg/dL§										
Total	433	185.6	181.7	−3.3	625	185.6	185.6	−0.4	−2.9 (−4.60 to −1.15)	.001
LDL	411	186.6	96.7	−4.0	572	100.5	96.7	−2.7	−1.3 (−4.31 to 1.78)	.40
HDL	432	46.4	42.5	−5.5	625	46.4	42.5	−5.7	0.2 (−1.68 to 2.12)	.83
Mean triglycerides, mg/dL§	433	159.4	168.3	2.2	625	168.3	186.0	13.2	−9.8 (−13.68 to −5.75)	<.001

It's Not Just ACE Inhibitors and ARBs That Reduce the Risk of Developing Diabetes

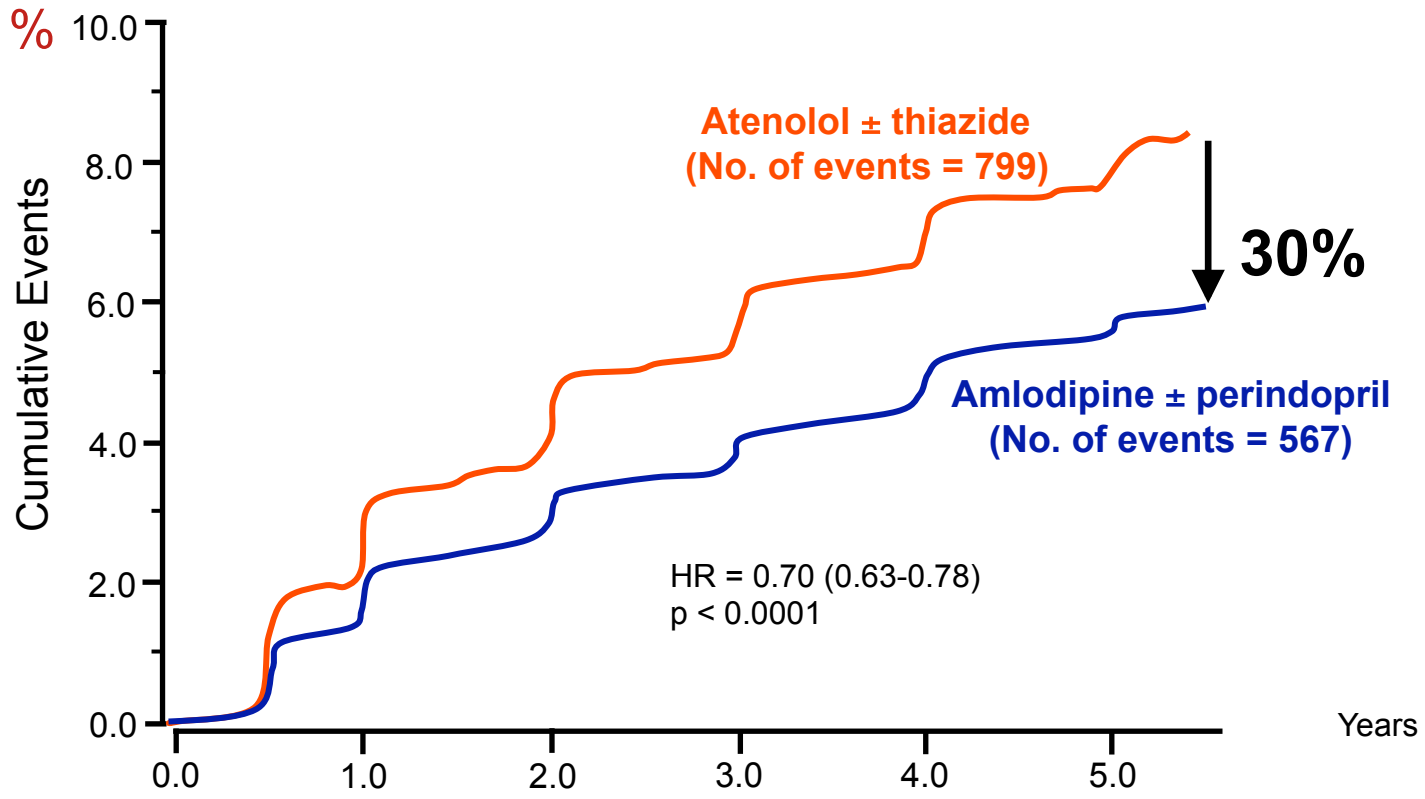
"New" *vs* "old" treatments for hypertension



*CAPP, LIFE, ALLHAT

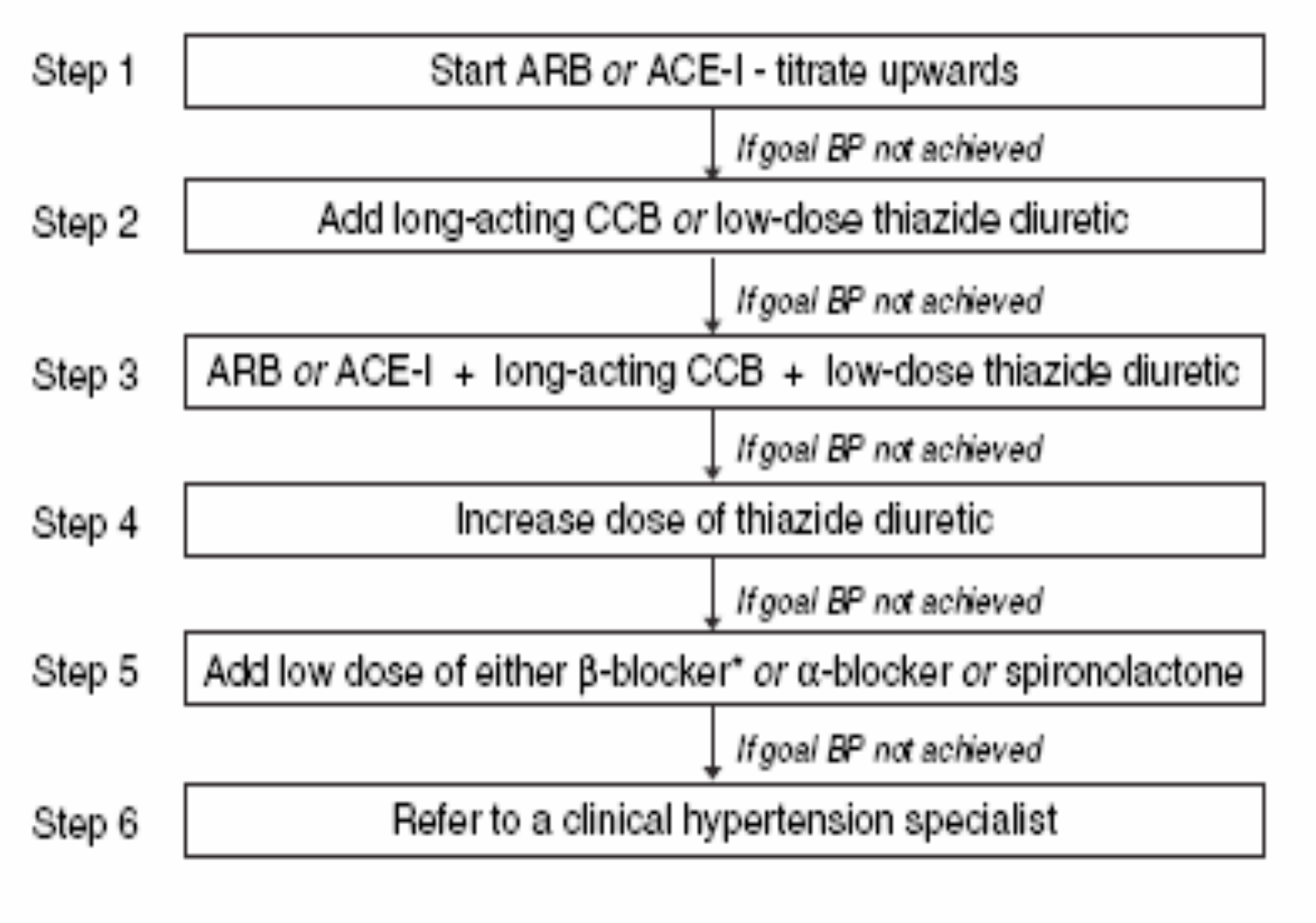
**NORDIL, INSIGHT, ALLHAT, INVEST

New-onset diabetes mellitus (ASCOT – BPLA)



Number at risk						
Amlodipine ± perindopril	9639	9383	9165	8966	8726	7618
Atenolol ± thiazide	9618	9295	9014	8735	8455	7319

Proposed algorithm for achieving target blood pressure goals in obese hypertensives



K. Narkiewicz **Obesity** reviews (2006)

Treatment

Combating The Metabolic Syndrome: Action Plan

- Which individual prevention?
- Which individual management?
  - Therapeutic objectives
  - First step: assessment of global cardiovascular risk in the patient
  - Second step: implementation of therapeutic lifestyle changes
  - Third step: using drug therapy to modify cardiovascular risk factors in high-risk patients

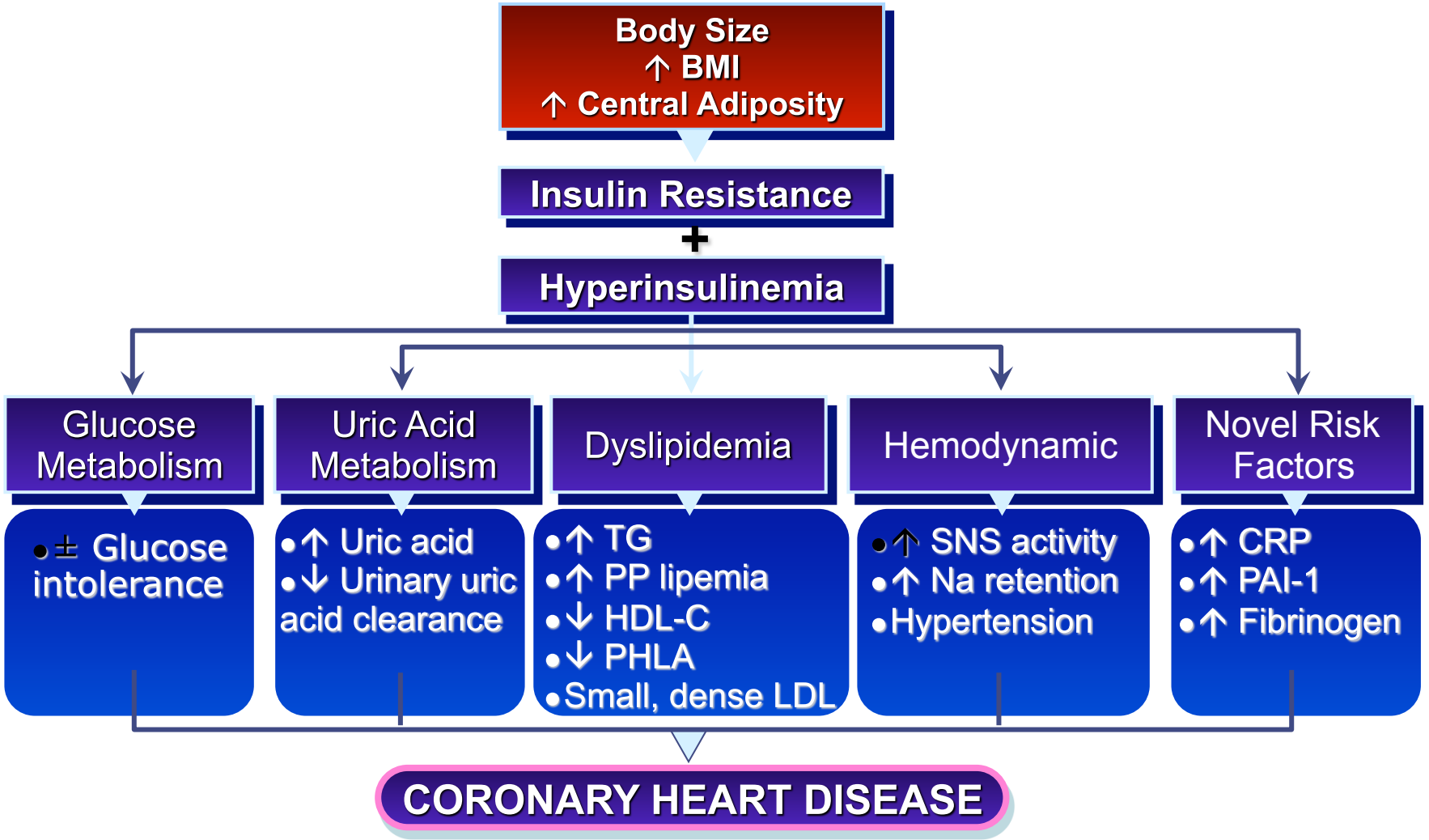
First Step: Assessment of Global Cardiovascular Risk

- High-risk patients: those with established cardiovascular disease, diabetes, or 10-year risk for CHD >20%
- Moderately high-risk patients:
  10-year risk for CHD =10-20%
- Moderate risk patients: those with metabolic syndrome but 10-year risk for CHD <10%

Combating The Metabolic Syndrome: Action Plan

- Which individual prevention?
- Which individual management?
  - Therapeutic objectives
  - First step: assessment of global cardiovascular risk in the patient
  - Second step: implementation of therapeutic lifestyle changes
  - Third step: using drug therapy to modify cardiovascular risk factors in high-risk patients

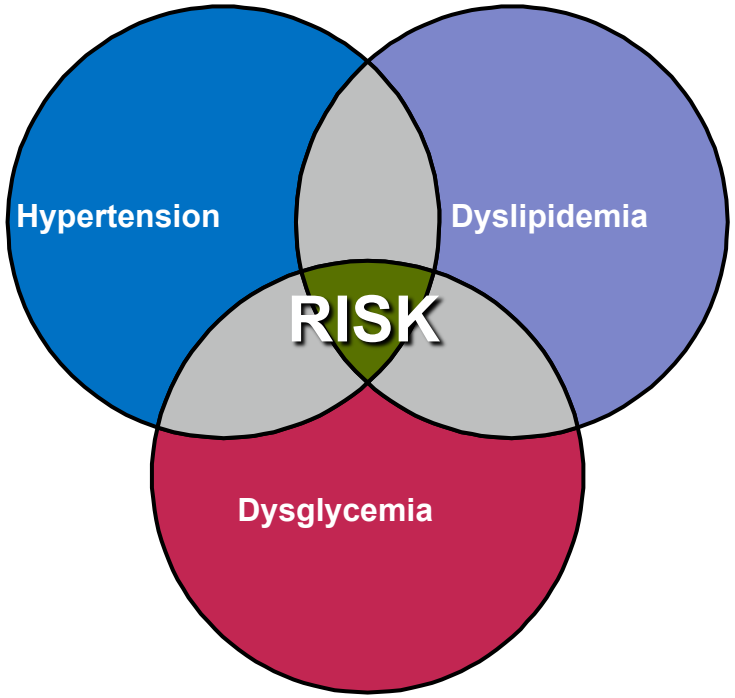
The Metabolic Syndrome: *Current Perspective*



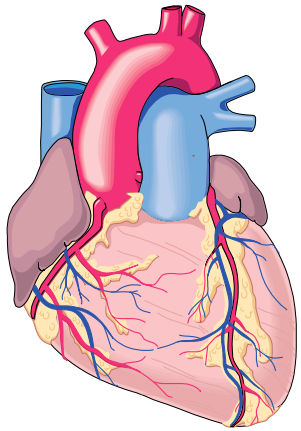
Adapted from Reaven G. Drugs. 1999;58 (suppl):19-20

A new vital sign: Waist circumference

Abdominal adiposity



Coronary heart disease



Adapted from Després J-P et al. *BMJ.* 2001;322:716-20.

New markers of CHD risk: what to look for?

Abdominal obesity

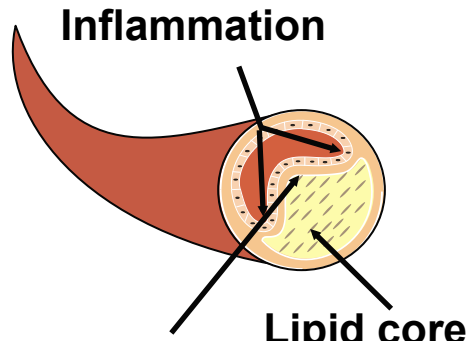
Atherogenic dyslipidemia
↑ Triglycerides
↓ HDL-cholesterol
↑ Cholesterol/HDL-cholesterol ratio
"Normal" LDL-cholesterol but ↑ apo B
Small, dense LDL and HDL
Postprandial hyperlipidemia

Insulin resistance
Insulin resistance
Hyperinsulinemia
Hyperglycemia
Type 2 diabetes

Thrombotic state
↑ PAI-1
↑ Fibrinogen

Inflammatory state
↑ CRP
↑ Cytokines

Metabolic risk factors



CORONARY ATHEROSCLEROSIS
UNSTABLE PLAQUE

↑ risk of acute coronary syndrome