

Metabolic Syndrome Overview: Easy Living, Bitter Harvest

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Evolution of Metabolic Syndrome

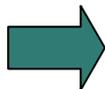
- 1923: Kylin describes clustering of hypertension, gout, and hyperglycemia



- ▼ 1988: Reaven describes “Syndrome X” – hypertension, hyperglycemia, glucose intolerance, elevated triglycerides, and low HDL cholesterol



- ▼ 1998: World Health Organization defines “Metabolic Syndrome” as clustering of insulin resistance/ glucose intolerance + (2/3) abdominal obesity (WHI, BMI, WC), low HDL, hypertriglyceridemia, or hypertension
- ▼ 1999: EGIR as above but excluded Type 2 diabetes, used only WC



**2002:
NCEP
ATP III**

Clinical Identification of the Metabolic Syndrome: NCEP-ATP III (3/5 traits)

Risk Factor	Defining Level
Abdominal Obesity (Waist Circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
TG	≥ 1.70 mmol/L (150 mg/dL)
HDL-C	
Men	<1.0 mmol/L (40 mg/dL)
Women	<1.30 mmol/L (50 mg/dL)
Blood Pressure	≥ 130/85 mm Hg
Fasting Glucose	≥ 6.1 mmol/L (110 mg/dL)

International Diabetes Federation Criteria (2004)

Risk Factor	Defining Level
Abdominal Obesity (Waist Circumference) Men Women	 >102 cm (>40 in)* >88 cm (>35 in)*
PLUS	
TG HDL-C Men Women Blood Pressure Fasting Glucose	 ≥ 1.70 mmol/L <1.0 mmol/L <1.30 mmol/L ≥ 130/85 mm Hg ≥ 5.6 mmol/L (or T2DM)

Ethnic group

Waist circumference

Europids*

Men

94 cm

Women

80 cm

South Asians

Men

90 cm

Women

80 cm

Chinese

Men

90 cm

Women

80 cm

Japanese

Men

85 cm

Women

90 cm

Ethnic South and Central
Americans

Use South Asian recommendations

Sub-Saharan Africans

Use European data

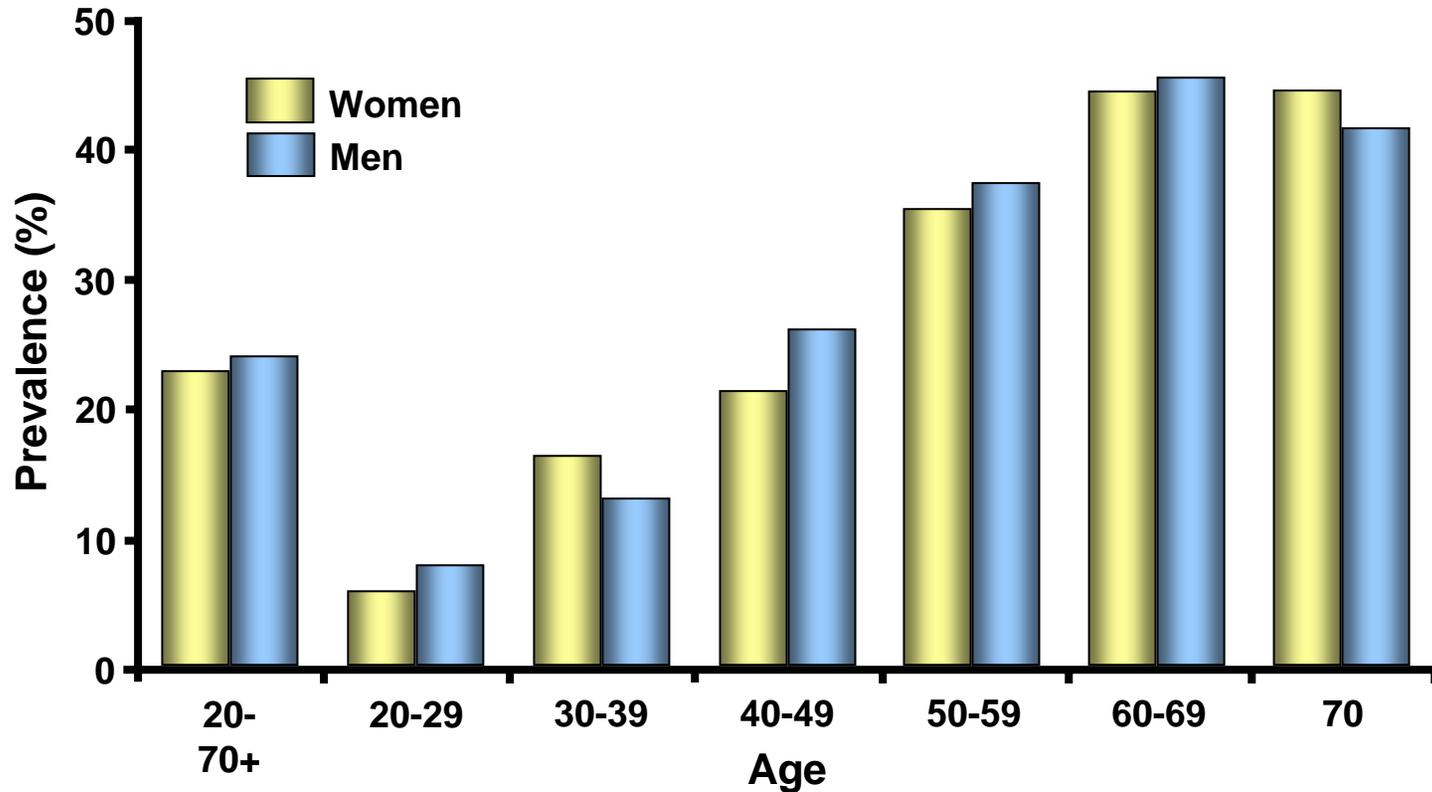
Eastern Mediterranean and
middle east (Arab) populations

Use European data

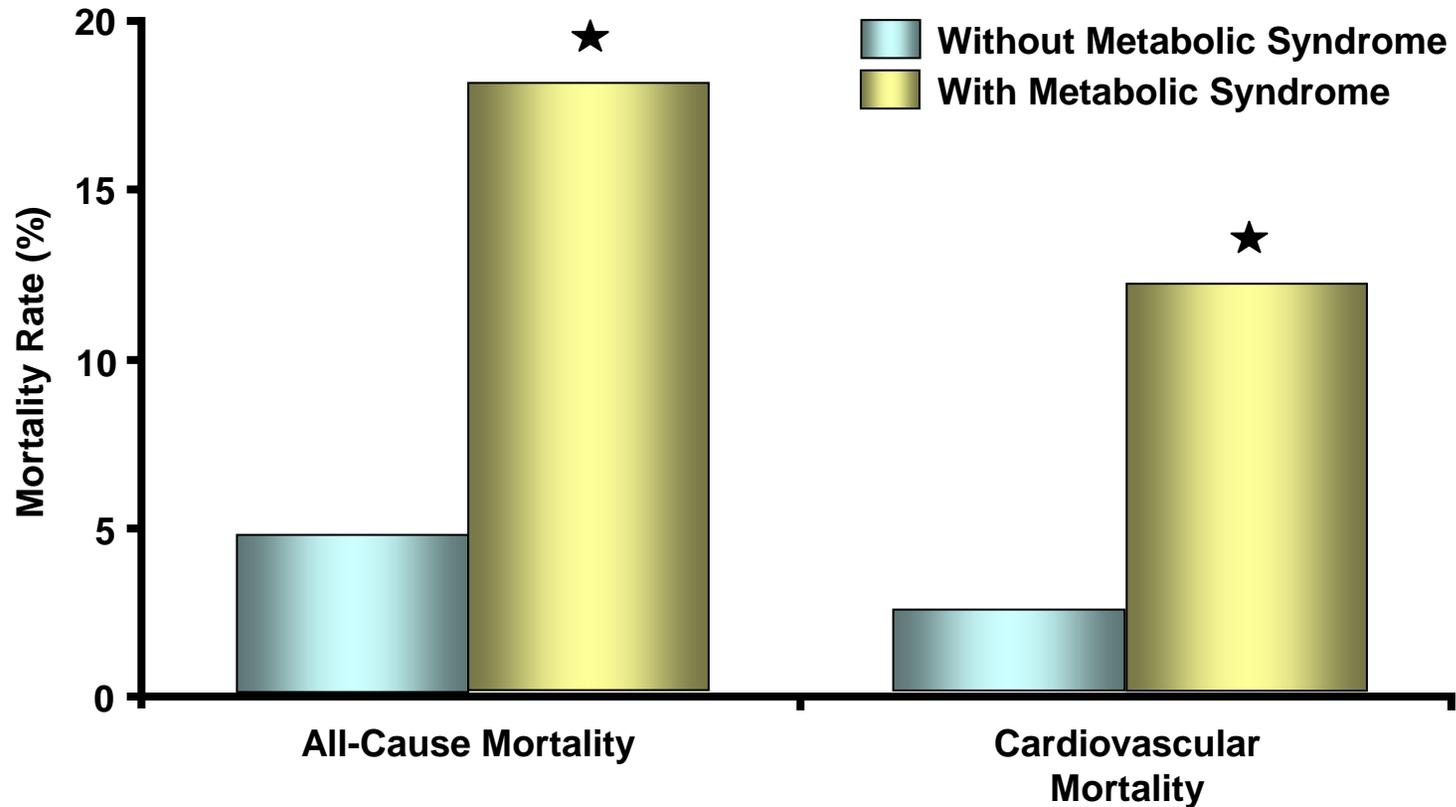
Comparing the Criteria

- Overlap by 93% in different populations using the different criteria
- Not all agree that diabetes should be included as this syndrome predicts risk
- Other markers?
- Variable prevalence rates in children and adolescents

Increasing Prevalence of NCEP Metabolic Syndrome with Age (NHANES III)



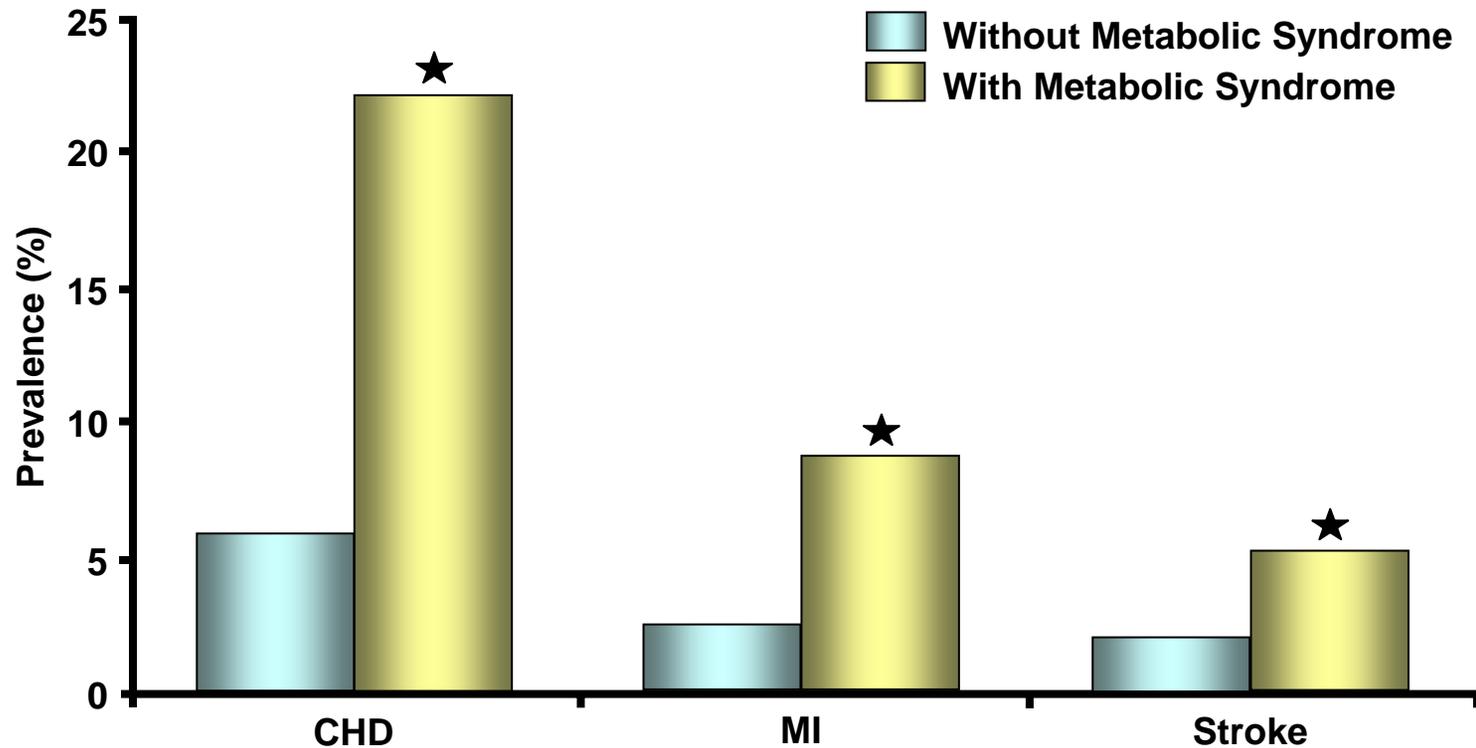
Metabolic Syndrome: Impact on Mortality



*P < 0.001

Isomaa B, et al. *Diabetes Care* 2001; 24:683-9

Metabolic Syndrome: Impact on Cardiovascular Health



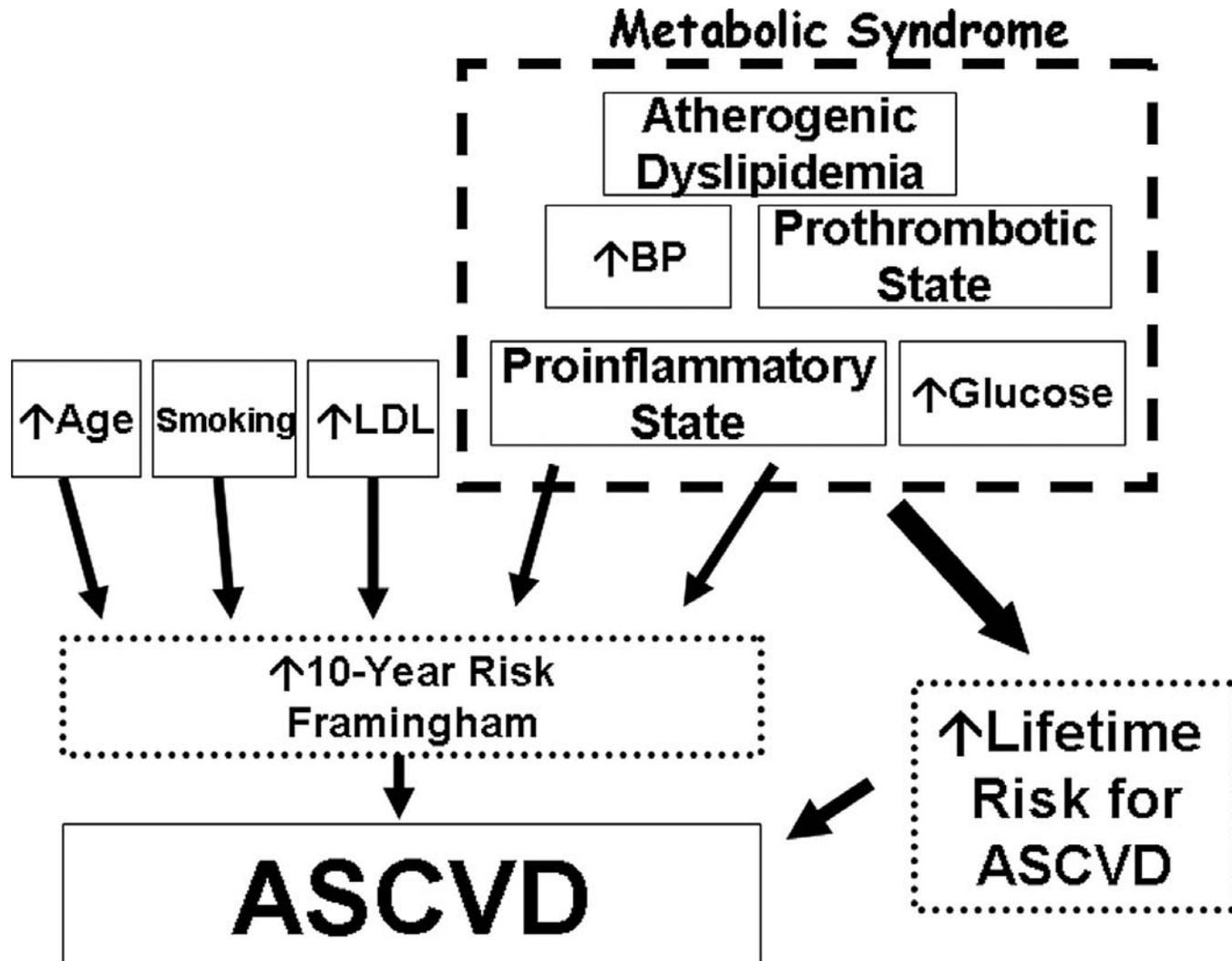
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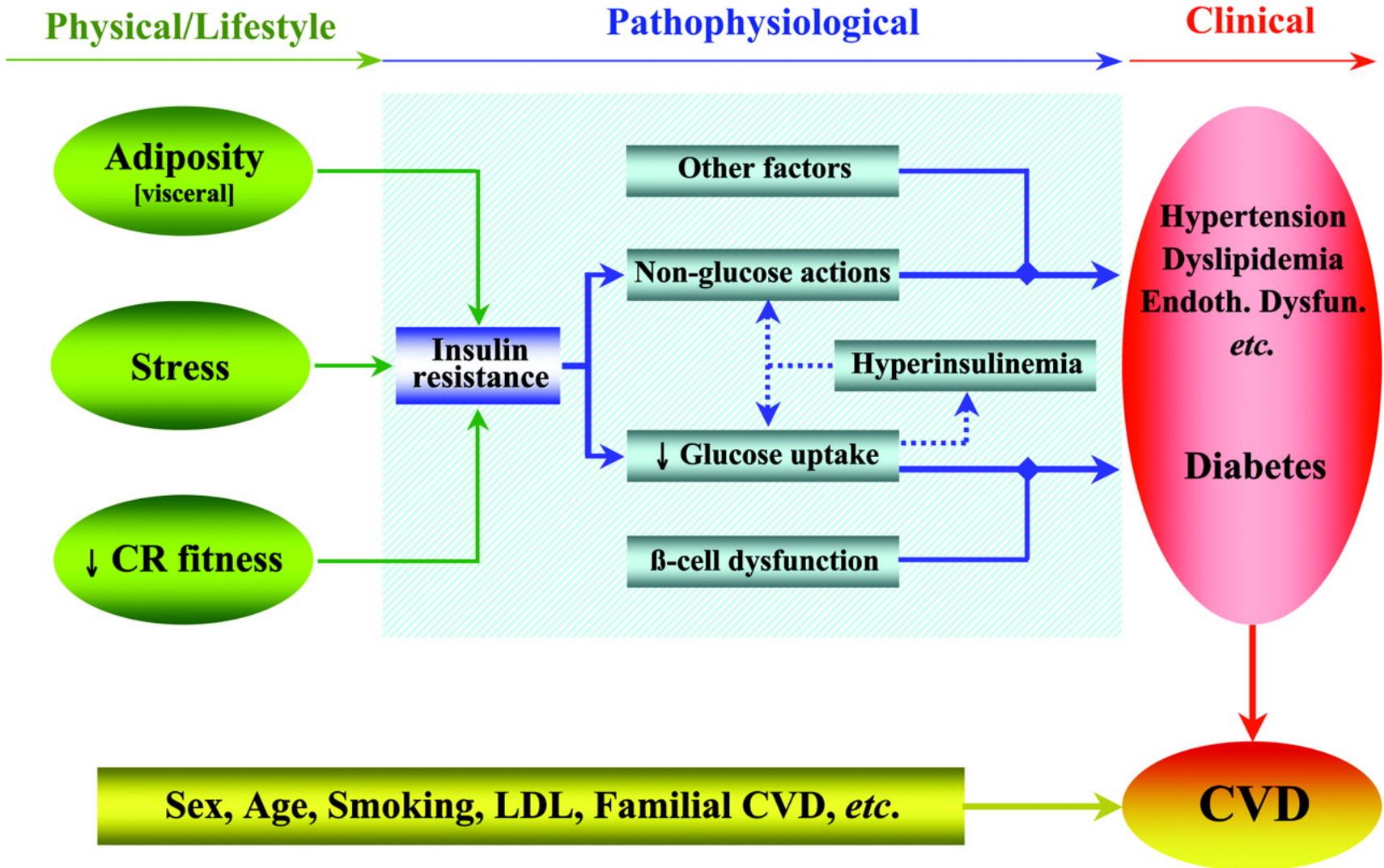
Other Associated Disorders..

- Fatty liver
- Polycystic Ovary Syndrome
- Sleep apnea
- Gout
- CKD

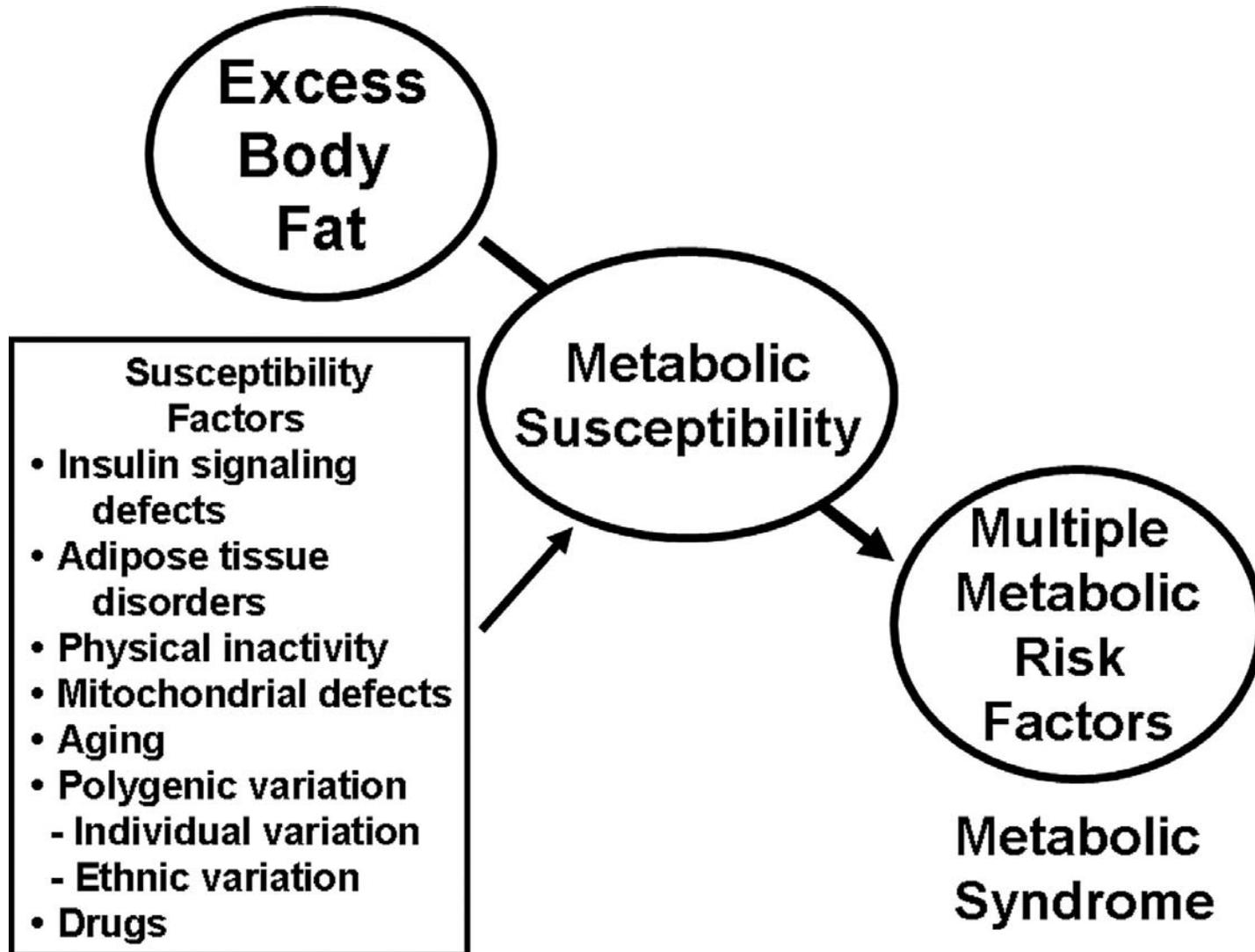
Metabolic Syndrome as a multiplex cardiovascular risk factor.



Domains of the Syndrome



Proposed scheme for pathogenesis of Metabolic Syndrome



Metabolic Syndrome – a progressive disorder

- Increased age
- Stiffening of arterial tree
- Decline in pancreatic beta-cell function
- Mitochondrial dysfunction
- Inflammatory changes in adipose tissue



- Diabetes mellitus and CVD

Objective of Management of Metabolic Syndrome

Reduce Underlying Causes

- Weight reduction
- Increased physical activity

Reduce Risk

- Antihypertensives
- Aspirin (patients with CHD)
- Lipid-lowering agents
- Antihyperglycemics
- ? insulin sensitizers

Goals of Therapy

- Reduce lifetime risk of ASCVD
- Reduce short-term risk as estimation of risk into three categories of 10-yr risk of CHD:
 - lower-moderate (<10%)
 - Intermediate (10-20%)
 - High (>20%)

Risk factor 10-yr risk for coronary heart disease	Lower-to-moderate risk (<10%)	Moderately high risk (10–20%)	High risk (>20%)¹
MetS as a whole	Reduce lifetime risk for ASCVD and diabetes	Reduce both lifetime and short-term risk	Reduce short-term risk
Obesity	10% reduction in body weight (preference to lifestyle therapy) BMI < 25	10% reduction in body weight (consider weight loss drugs) BMI < 25	10% reduction in body weight (consider weight loss drug) BMI < 25
Atherogenic diet	Maximal antiatherogenic diet (<7% sat FA; <1% trans FA)	Maximal antiatherogenic diet (<7% sat FA; <1% trans FA)	Maximal antiatherogenic diet (<7% sat FA; <1% trans FA)
Physical inactivity	Exercise 30 min/d - 60 min/d	Exercise 30 min/d - 60 min/d	Exercise 30 min/d - 60 min/d
Atherogenic dyslipidemia: (LDL cholesterol)	LDL cholesterol < 3.3 mmol/L <2.6mmol/L (with lifestyle)	LDL cholesterol < 3.3 mmol/L (with drugs if necessary) <2.6 mmol/L	LDL cholesterol < 2.6 mmol/L <1.8 mmol/L (in CHD patients)
Atherogenic dyslipidemia: HDL cholesterol	Raise HDL (lifestyle therapy)	Raise HDL (lifestyle therapy)	Raise HDL (consider drug therapy)

Risk factor 10-yr risk for coronary heart disease	Lower-to-moderate risk (<10%)	Moderately high risk (10–20%)	High risk (>20%)¹
BP	BP < 140/90 mm Hg (with drugs if necessary) 130/80 (with lifestyle therapies)	BP < 140/90 mm Hg (with drugs if necessary) 130/80 (with lifestyle therapies)	BP < 140/90 mm Hg (with drugs if necessary) 130/80 (with drugs in diabetes and chronic renal failure)
Elevated FBG (prediabetes)	FBG < 5.5 mmol/L (with lifestyle therapy)	FBG < 5.5 mmol/L (with lifestyle therapy)	FBG < 5.5 mmol/L (consider insulin sensitizer)
Elevated FBG (diabetes)	HbA1c 6–7%	HbA1c 6–7%	HbA1c 6–7%
Prothrombotic state	No drug	Consider antiplatelet drug (ASA 81mg/d)	Antiplatelet drug (ASA 81mg/d)
Proinflammatory state	Complete smoking cessation	Complete smoking cessation	Complete smoking cessation

Problems with the current paradigm of Metabolic Syndrome and potential solutions

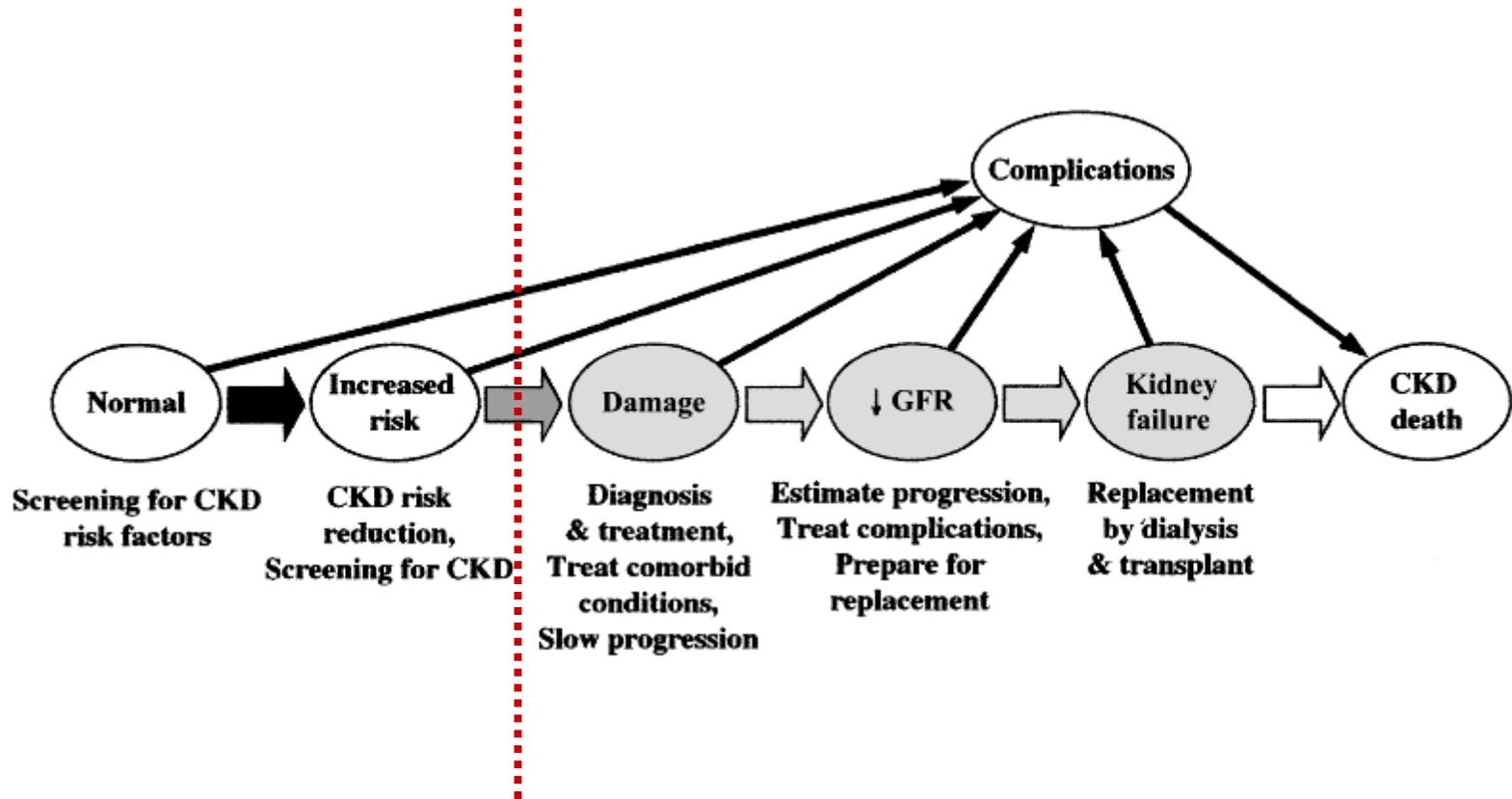
Problem	Possible solution
Uncertain purpose for outcome	Specified purpose
Ill-defined criteria	Well-defined criteria
Data for cutt-offs?	Continuous variables
Linear modeling (direct 1:1 effects of each factor vs MS)	Nonlinear modeling
No weighting of criteria	Weighted variables (scores)
Unclear pathogenesis	Further study
Exclusion of established predictors	Inclusion of established predictors

METABOLIC SYNDROME AND CKD

Dr. Caroline Stigant, BC Nephrology Days 2007

- MS – A Risk Factor for CKD
- Data review
 - Cross-sectional
 - Prospective
- Pathogenesis
 - How do MS components cause kidney injury?
- Significance of MS to Kidney Care Providers

MS: NEW PARADIGM FOR CV / KIDNEY RISK REDUCTION



CKD: MORE PREVALENT IN INDIVIDUALS WITH METABOLIC SYNDROME

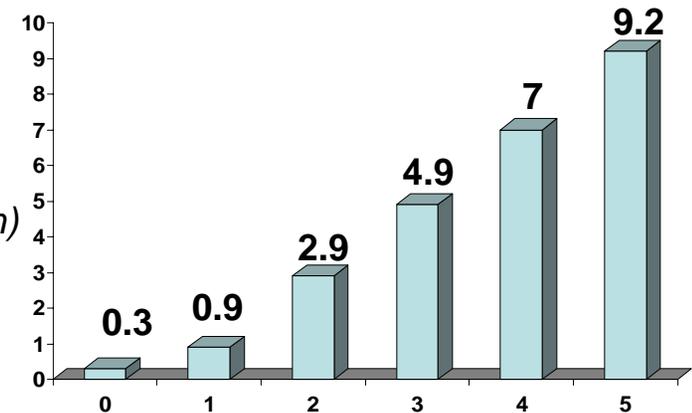
Overall adjusted
OR of developing
CKD MS vs no MS

2.60

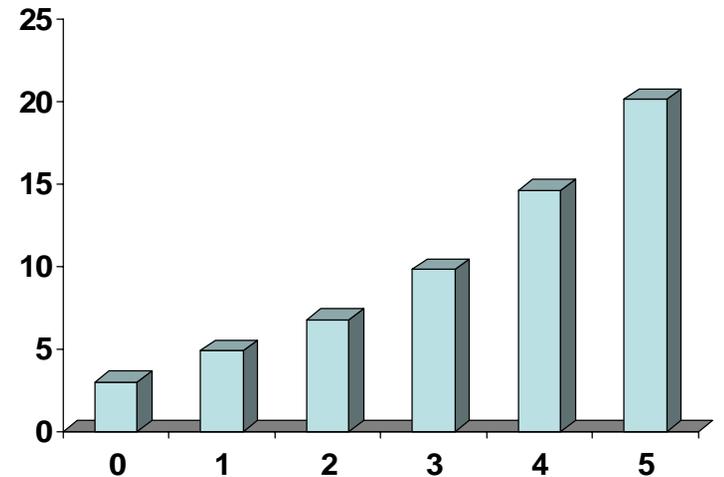
Overall adjusted OR of
developing MAU MS vs
no MS

1.89

% CKD
(GFR <60 mL/min)



% MAU
(Urine ACR 30-300
mg/g)



of MS Risk Factors

MS: INCREASED RISK OF DEVELOPING CKD

	ARIC	Tehran Lipid & Glucose Study	Hisayama
n	10,096	4607	1440
Population	U.S.	Iranian Adults s/ DM or CKD	Japanese adults
Follow-up (yrs)	9	3	5
MS (%)	21%	21.9%	
CKD Prev MS+	6%	2%	10.6%
CKD Prev MS-	10%	3.4%	4.8%
Adjusted OR	1.43 (1.18-1.73)	1.88 (1.26-2.8)	2.08 (1.23-3.52)

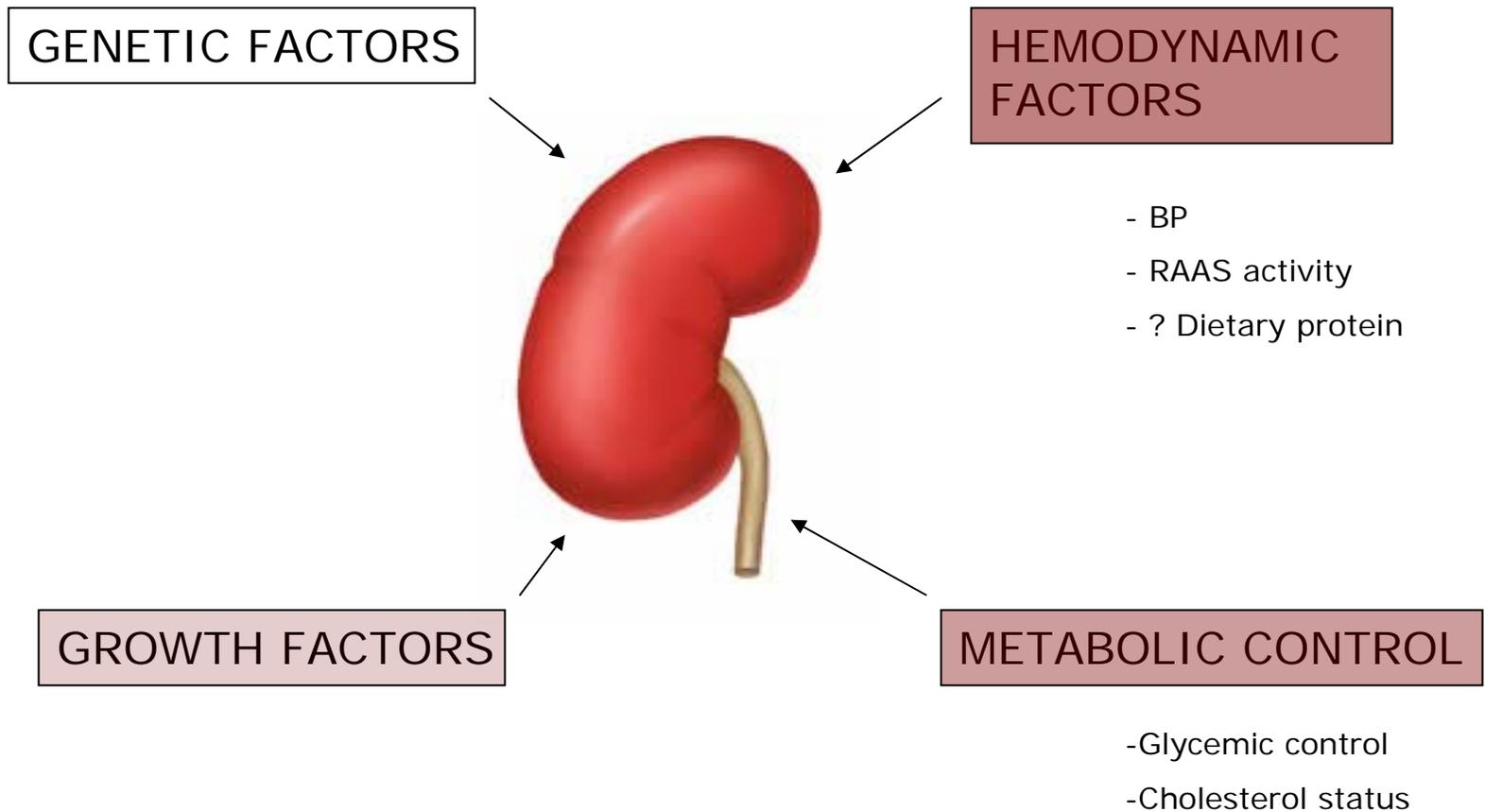
Increasing Risk of CKD by MS Trait



<u># of Traits</u>	<u>Adjusted RR (95% CI)</u>
0	0
1	1.13 (0.89-1.45)
2	1.53 (1.18-1.98)
3	1.75 (1.32-2.33)
4	1.84 (1.27-2.67)
5	2.45 (1.32-4.54)

Individual traits conferring greatest risk: HTN, hyperglycemia

PATHOGENESIS OF PROGRESSIVE NEPHROPATHY



SIGNIFICANCE

- MS confers renal risk across populations
 - Summary:
 - MAU: 2x risk
 - CKD: 1.5-2.5x risk
 - If 20-30% of the population has MS, huge numbers at risk of CKD!
- MAU and CKD confer cardiovascular risk
- MS paradigm allows us to focus earlier on risk factors
- MS components are TREATABLE

