
Metabolic Syndrome: Bad for the Heart and Bad for the Brain?

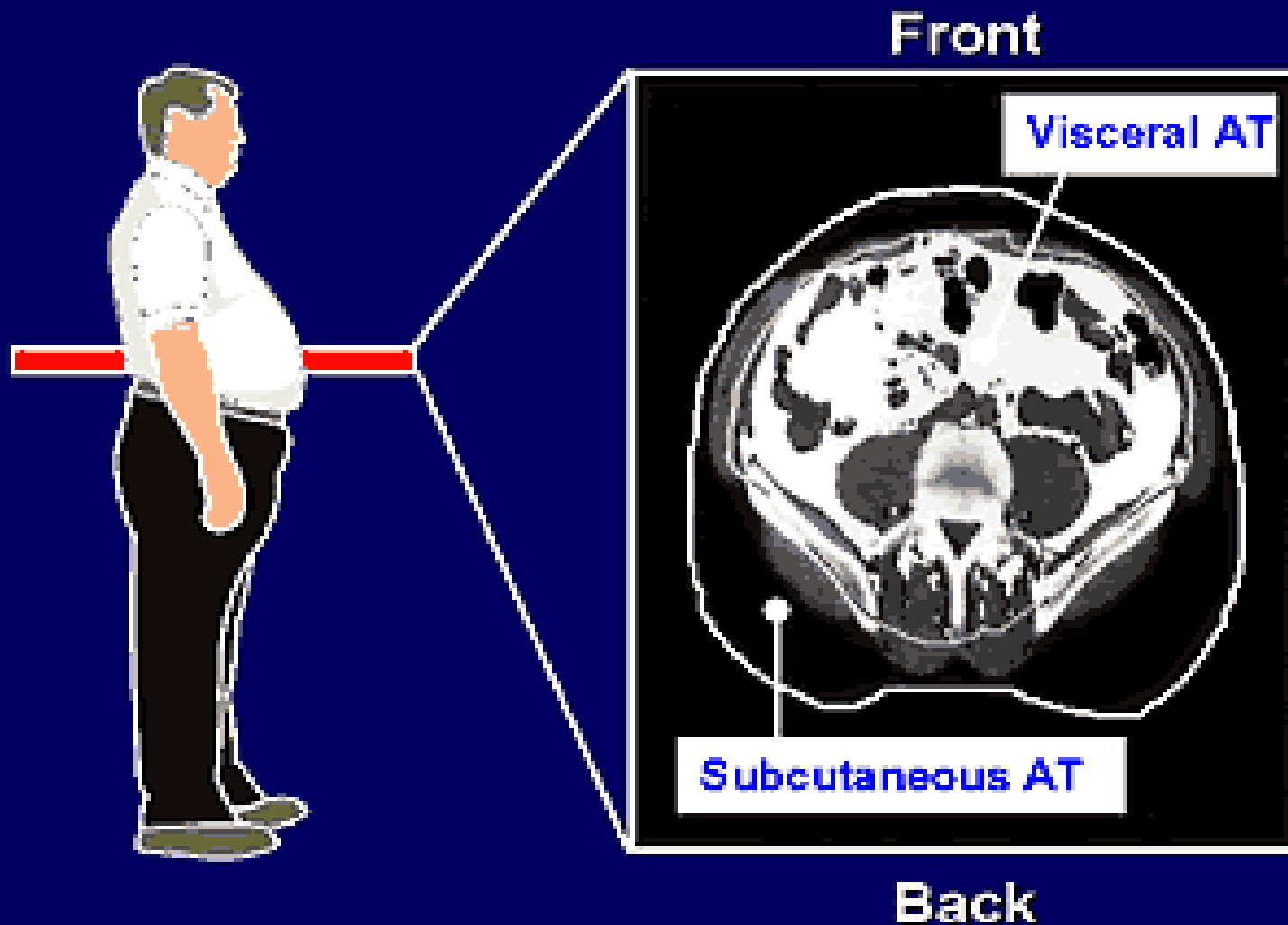
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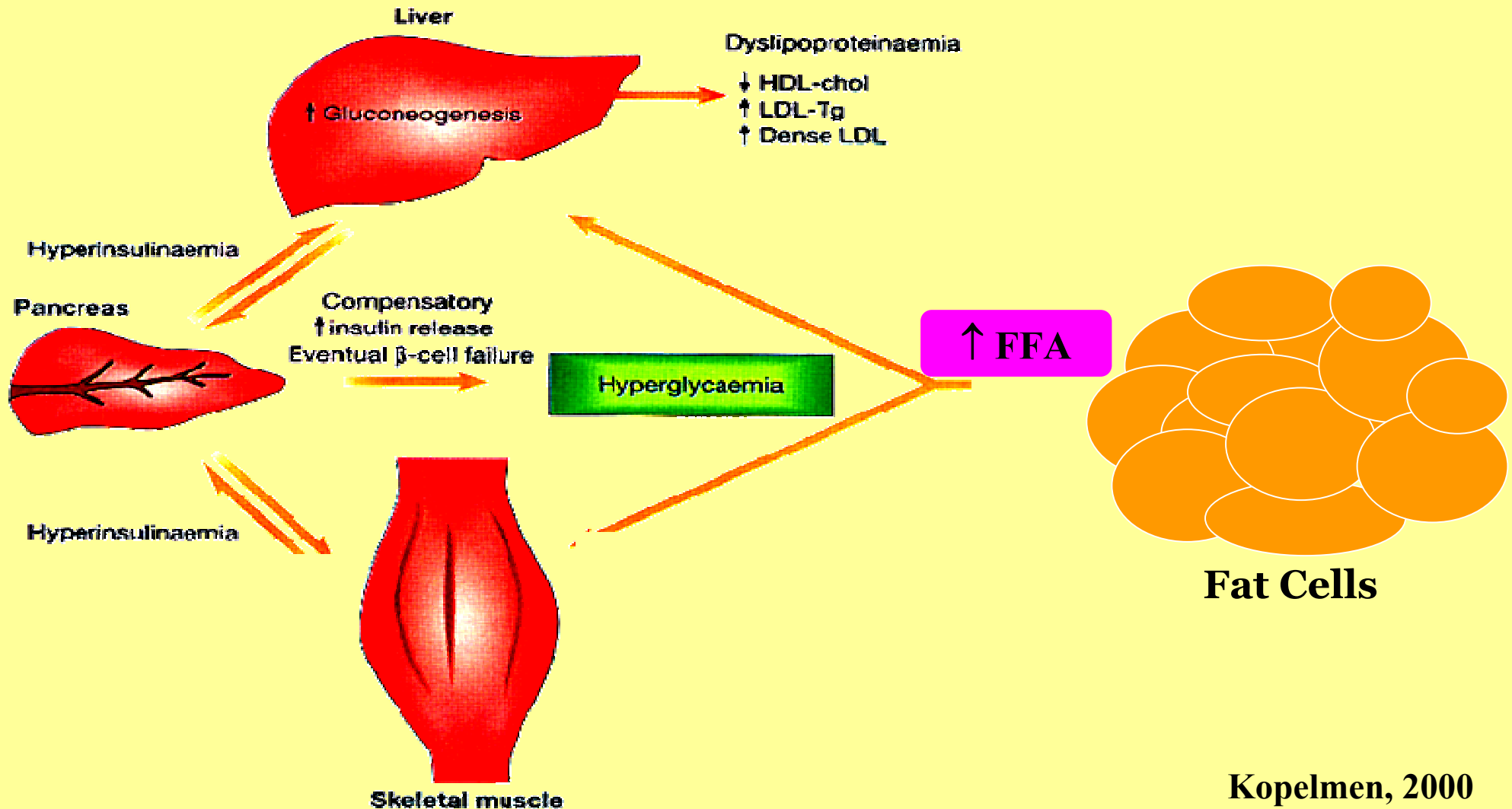
Why would diabetes and obesity be bad for the brain?

- Insulin receptors in brain
- Insulin degrading enzyme regulates β amyloid level in CNS; insulin resistance could be a predisposition to AD
- PPAR γ agonists (increase insulin sensitivity) may improve cognitive function and regulate β amyloid
- Increase in micro and macro vascular disease

Visceral Fat



Why is visceral fat so bad?



What it secretes...

Lipoproteins

- LPL
- CETP
- Apo E
- PLTP

Complement Factors

- Adipsin
- C3

Growth Factors

- TGF- β
- IGF-1
- VEGF

Hormones

- Leptin
- Cortisol
- Estradiol

Peptides

- Adiponectin
- PAI-1
- Angiotensinogen
- Resistin
- Visfatin

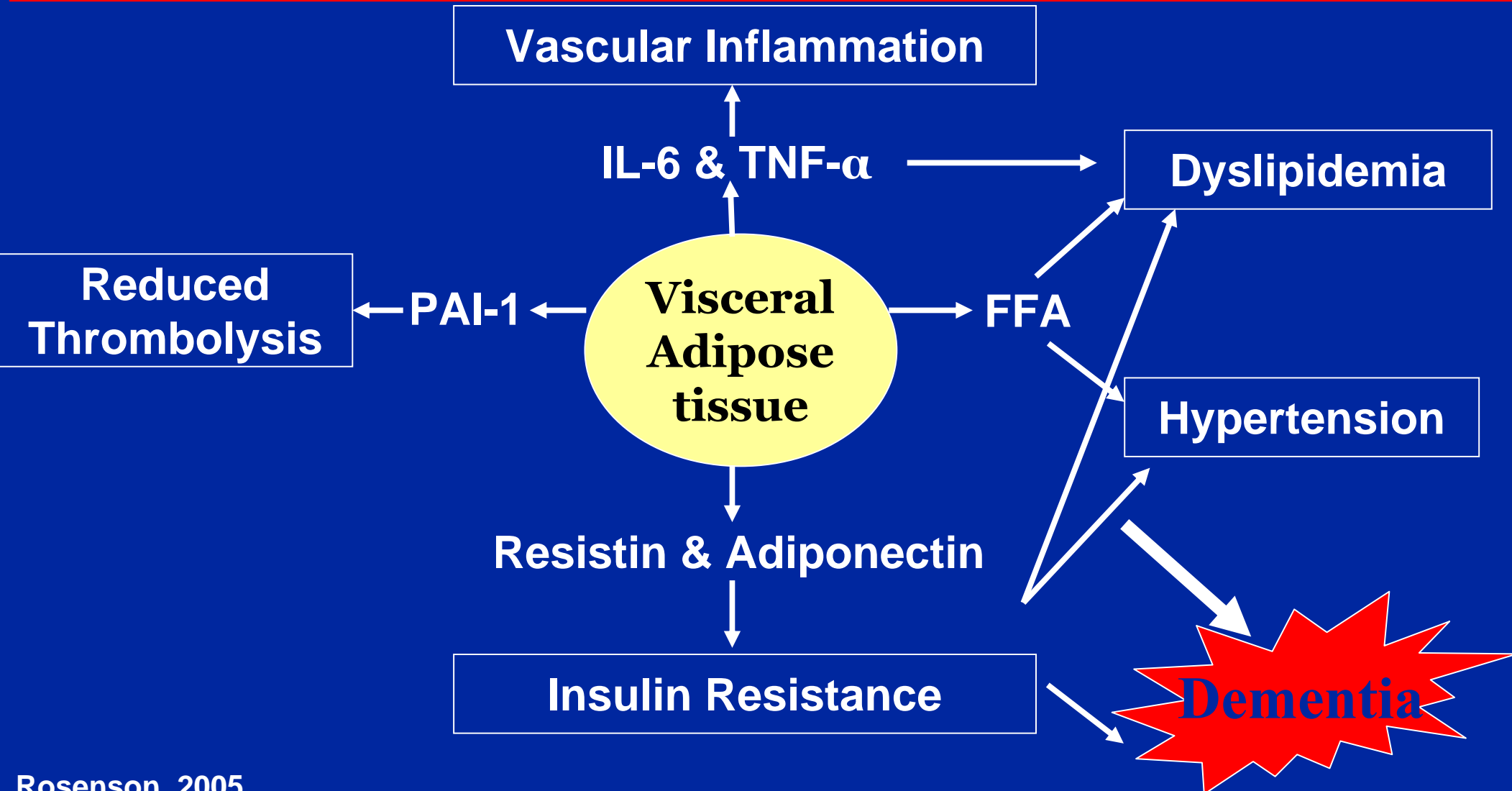
Cytokines

- TNF α
- IL-6

**Adipose
Tissue**



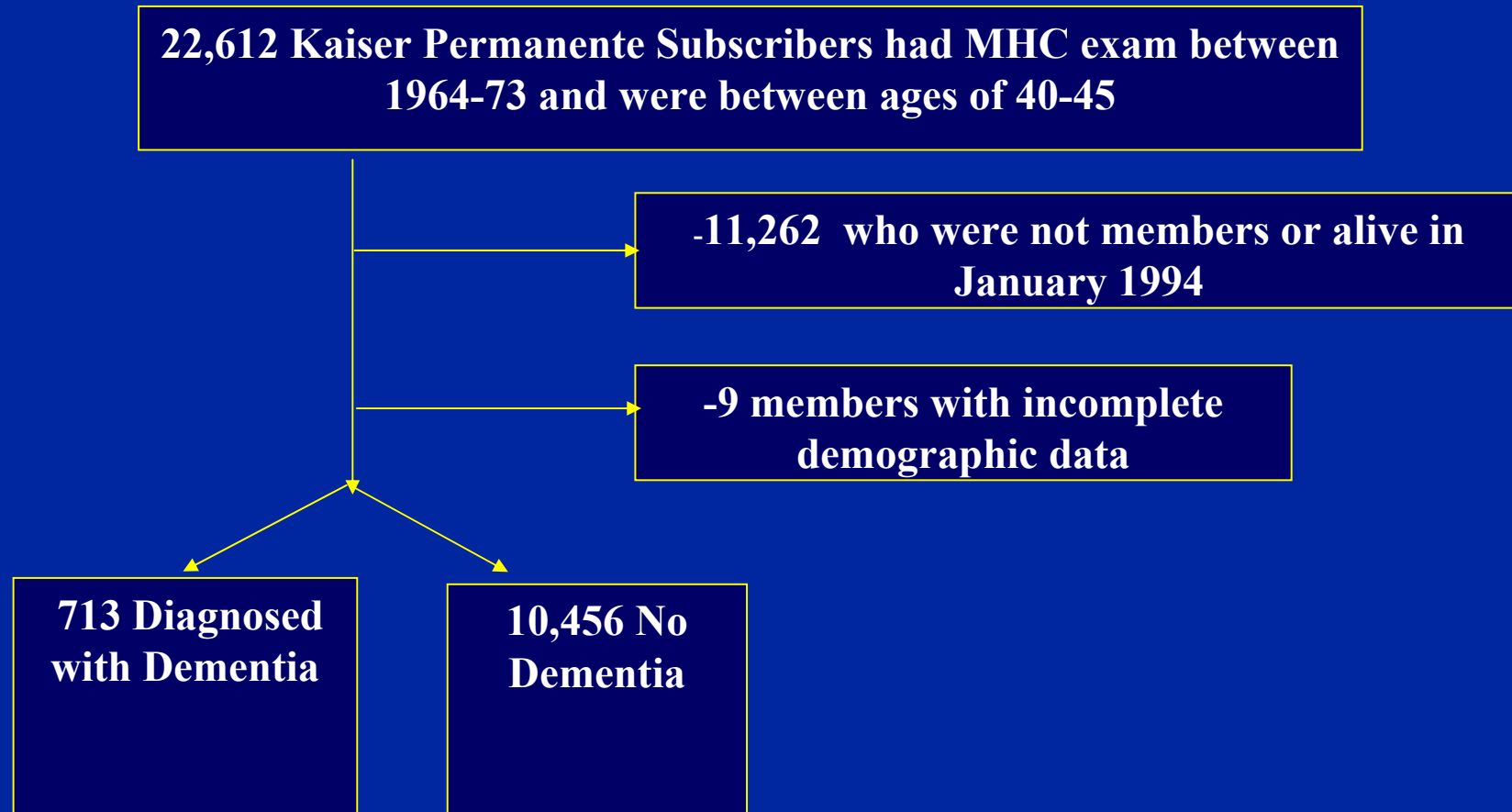
Proposed Mechanisms for Dementia



Association between Obesity & Dementia

- 11,341 men and women enrolled in Kaiser
- Attended Multiphasic Health Check-up between 1964-73 and were ages 40-45 at time of exam
- Alive, and still Kaiser members as of January 1, 1994
- OSCAR (computer charts) implemented in 1994

Kaiser Sample Selection



Obesity and Risk of Dementia

<u>Body Mass Index- All**</u>	Adjusted for age at midlife exam and education	Adjusted for age at midlife exam, age at case ascertainment, education, race, marital status & sex	Adjusted for all + midlife & late life co morbidity*
	Hazards Ratio (95 % Confidence Interval)	Hazards Ratio (95% Confidence Interval)	Hazards Ratio (95% Confidence Interval)
Obese	1.38(1.10 to 1.72)	1.56(1.24 to 1.96)	1.74(1.34 to 2.26)
Overweight	1.16(1.01 to 1.34)	1.22(1.04 to 1.42)	1.35(1.14 to 1.60)
Underweight	1.41(0.82 to 2.39)	1.46(0.84 to 2.54)	1.24(0.70 to 2.21)

Whitmer R, ...Yaffe K; BMJ, 2005.

Metabolic Syndrome: Background

- The metabolic syndrome, a constellation of related cardiovascular risk factors, has been reported to be associated with CV disease, mortality and other poor health outcomes
- Individual components of the metabolic syndrome such as hypertension & diabetes are associated with cognitive decline
- Few have investigated the association between the metabolic syndrome and cognitive decline

The 'Metabolic Syndrome'

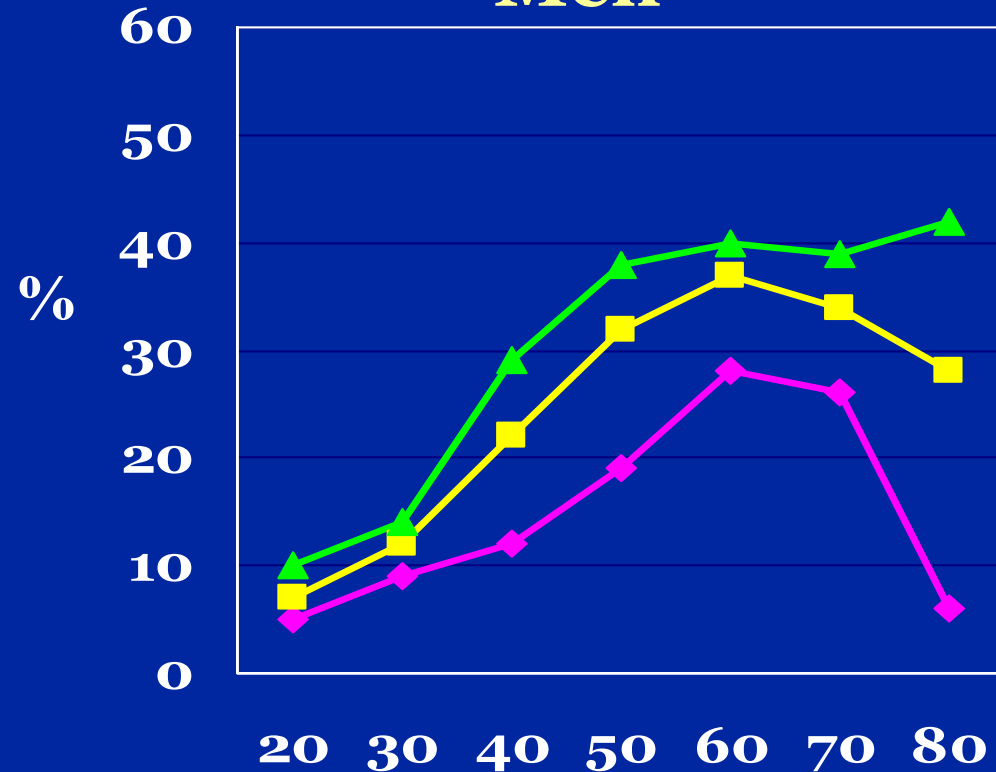
Also known as:

- **Syndrome X**
- **Insulin Resistance Syndrome**
- **The Deadly Quartet**
- **The Dysmetabolic Syndrome**

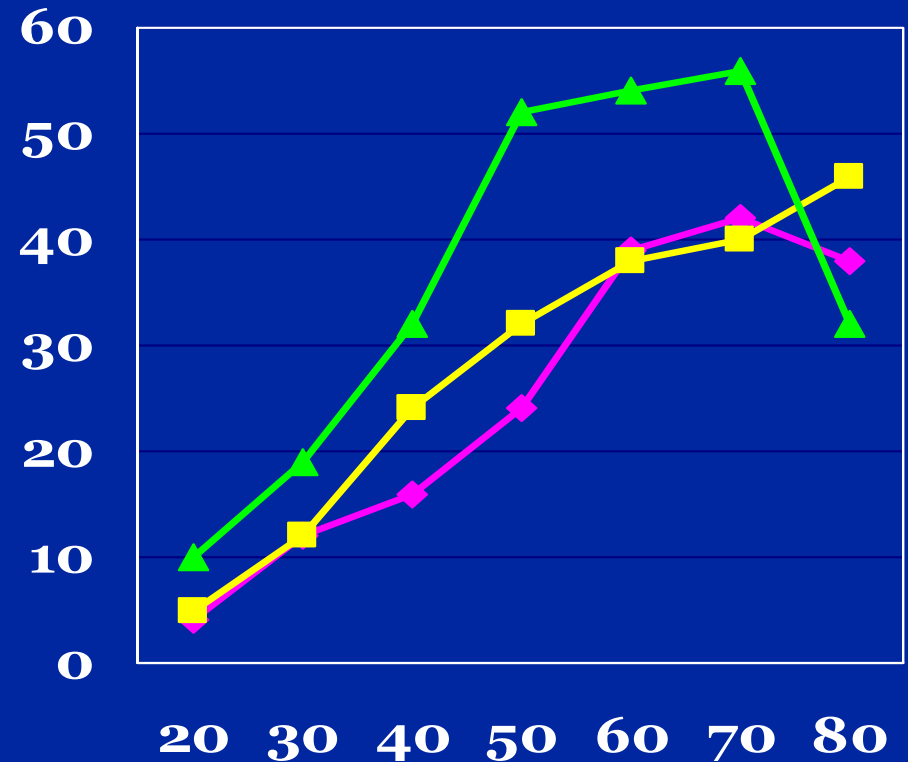


Metabolic Syndrome Prevalence

Men



Women



◆ Black ■ White ▲ Mex. Am

Study 1 Health ABC

- Participants were part of the Health, Aging, and Body Composition Study (Health ABC)
 - Prospective cohort study of 3,075 well-functioning community dwelling elders
 - Aged 70-79
 - Living in Memphis, TN and Pittsburgh, PA
 - 43% Black
 - 2949 subjects with all measurements for this study; 2498 with 4-year follow-up

Metabolic Syndrome Definition

- Fulfill ≥ 3 criteria (NCEP guidelines):
 - Waist: > 102 cm ♂ , > 88 cm ♀
 - HDL: < 40 for men, < 50 for women
 - Triglycerides: ≥ 150 mg/dL
 - BP: $\geq 130/ \geq 85$ (or med use)
 - Fasting glucose: ≥ 110 mg/dL (or med use)

Cognitive Outcomes in Health ABC

- Modified Mini-Mental (3MS) at baseline and biannually
- Cognitive Decline
 - ≥ 5 point decline with logistic regression
 - 4-year change using Random Effects
- Interaction with Inflammation ($>$ median IL-6 and CRP at baseline)

Metabolic Syndrome & Cognitive Decline

Health ABC

	High Inflammation N=618	Low Inflammation N=1880
No Metabolic Syndrome N=1534	1.0	1.0
Metabolic Syndrome N=964	1.94 (1.25-3.00)	1.13 (0.87-1.47)

P for interaction = 0.04

Yaffe et al, *JAMA*, 2004

Study 2 SALSA

- Participants were part of the Sacramento Area Latino Study of Aging (SALSA)
 - community-based cohort of elderly Latinos (aged ≥ 60 y) from Sacramento area
 - 1,624 participants followed over 5 years
- Cognition measured by the 3MS and the Delayed Word-List Recall (DelRec)
- Inflammation measured with CRP

Metabolic Syndrome & Cognitive Decline

SALSA

	3MS Score		DelRec Score	
	Beta	P-value	Beta	P-value
All	-0.40	0.04	-0.07	0.18
CRP \geq Median	-0.65	0.03	-0.08	0.34
CRP < Median	-0.26	0.45	-0.02	0.79

Adjusted for age, gender, education, born in the USA, depression, stroke, & alcohol

Yaffe et al, submitted

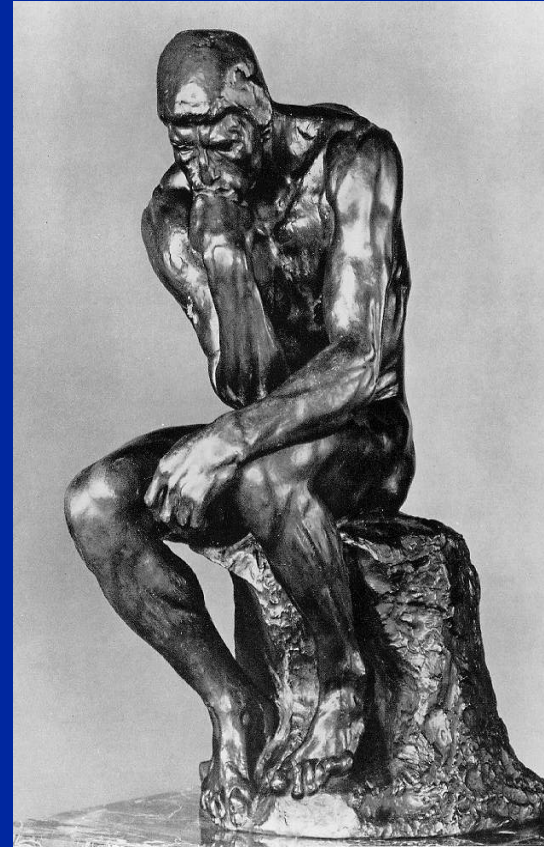
Conclusions:

Metabolic Syndrome

- Subjects with metabolic syndrome had an increased risk of developing cognitive impairment and decline over time
- Especially for those with high inflammation
- Results in Latino elders as well as in Black and White elders
- Need to determine if reducing metabolic syndrome or inflammation could prevent cognitive decline

Future Directions

- Markers of metabolism eg leptin
- Polymorphisms related to adiposity eg PPAR γ
- Trials of weight loss and treating metabolic syndrome



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