

Inflammation an oxidative stress in diabetes?



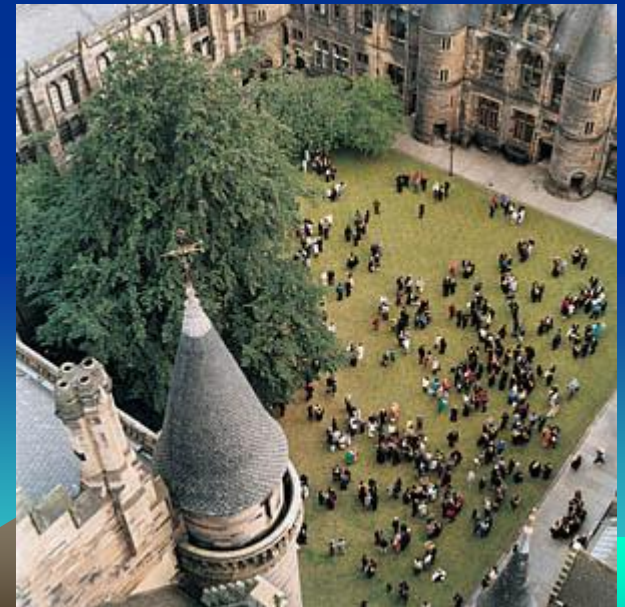
Naveed Sattar

Professor of Metabolic Medicine

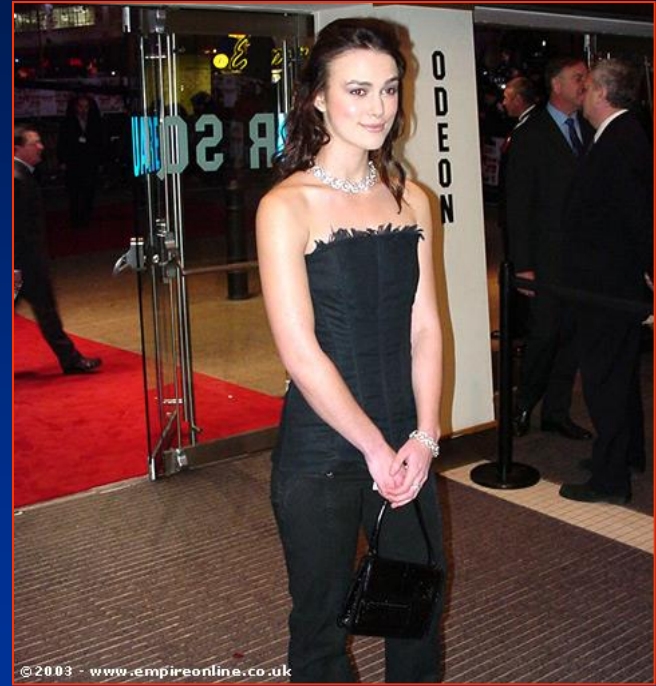
Hon. Consultant in Clinical Biochemistry



UNIVERSITY
of
GLASGOW







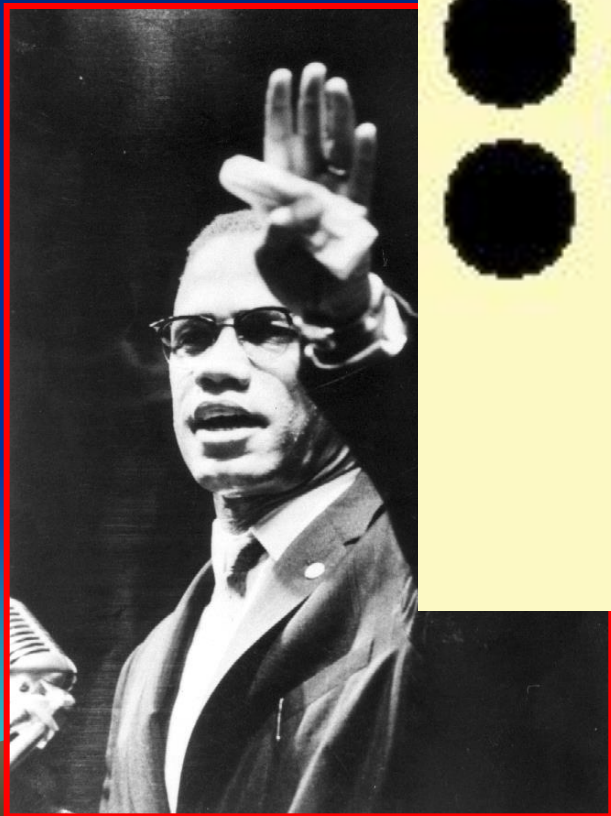
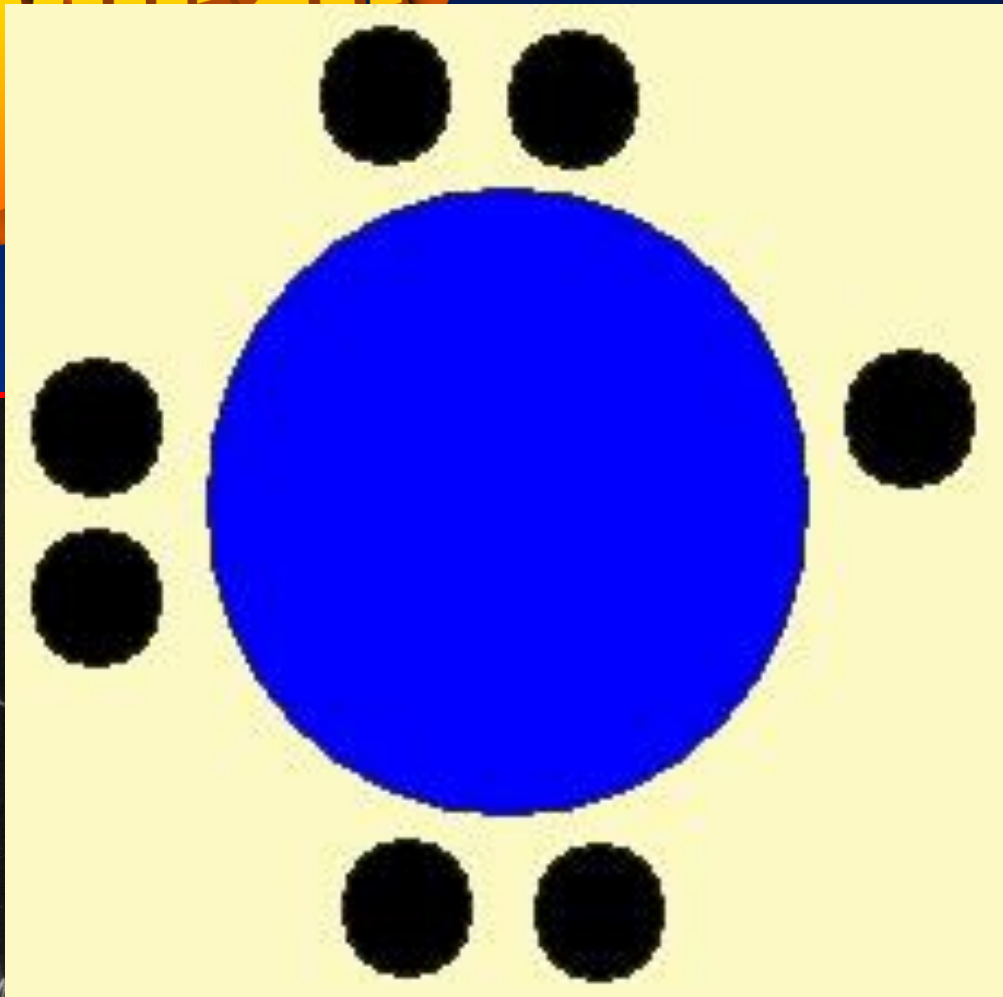
Outline

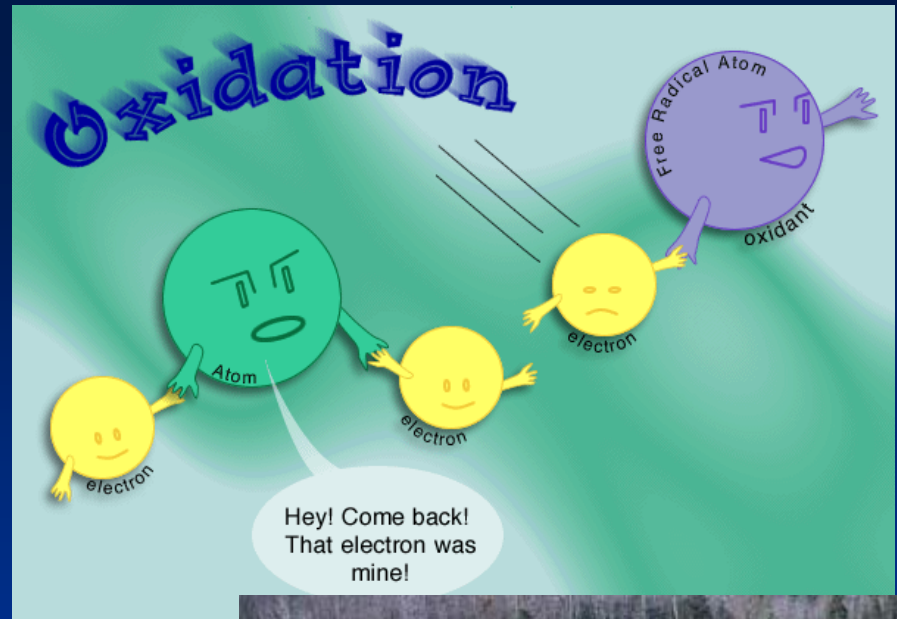
- Oxidative stress (free radicals)
 - Any clinical value of antioxidants
- Inflammation and diabetes
 - Any clinical use of CRP

- Light overview



Free radicals





Why does oxygen damage?

O_2 metabolism:

- Creates free radicals
- Not prejudicial

-Interact with nearest molecule

Not all free radical are bad!

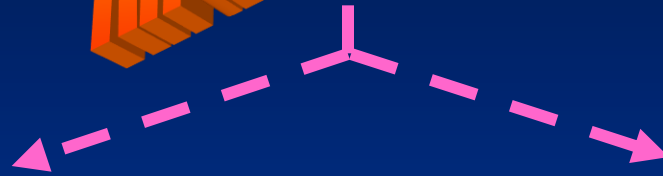
$NO\cdot$



So what protects us from oxidative stress?



Antioxidants



- **endogenous enzymes**

SOD

Catalase

- **circulating molecules**

albumin

urate

bilirubin

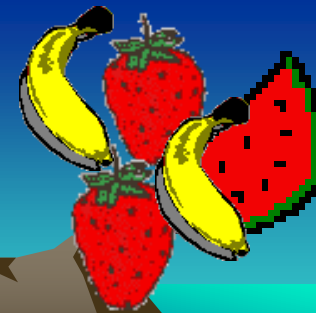
- **exogenous**

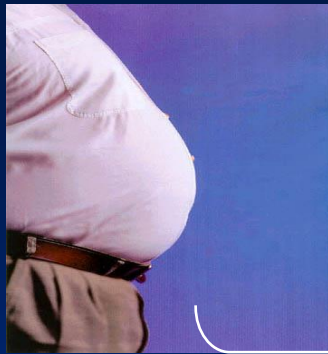
vitamin C

tocopherols

carotenoids

flavanoids





Oxidative stress

Protein lipid DNA carbohydrate

Oxidised LDL

mutations

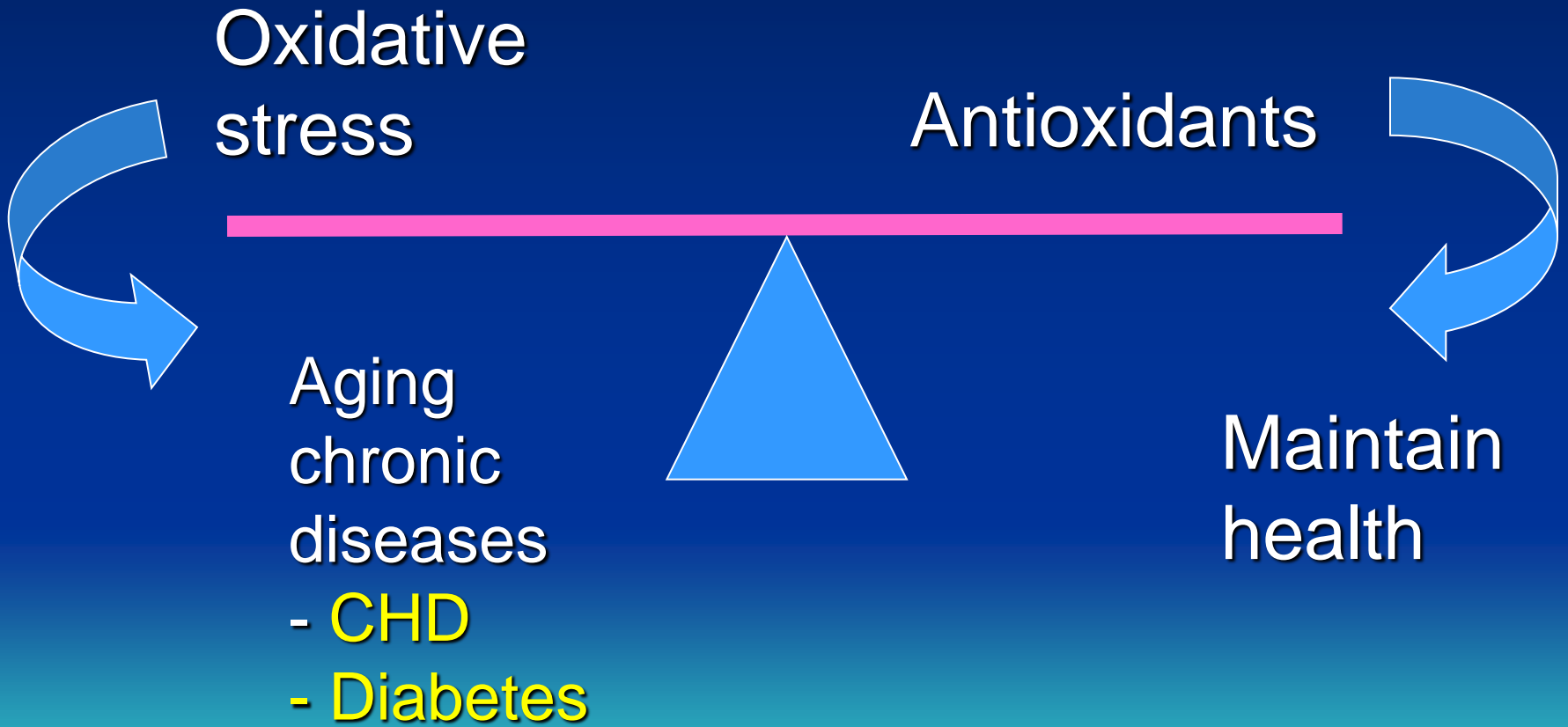
CHD

Cancer

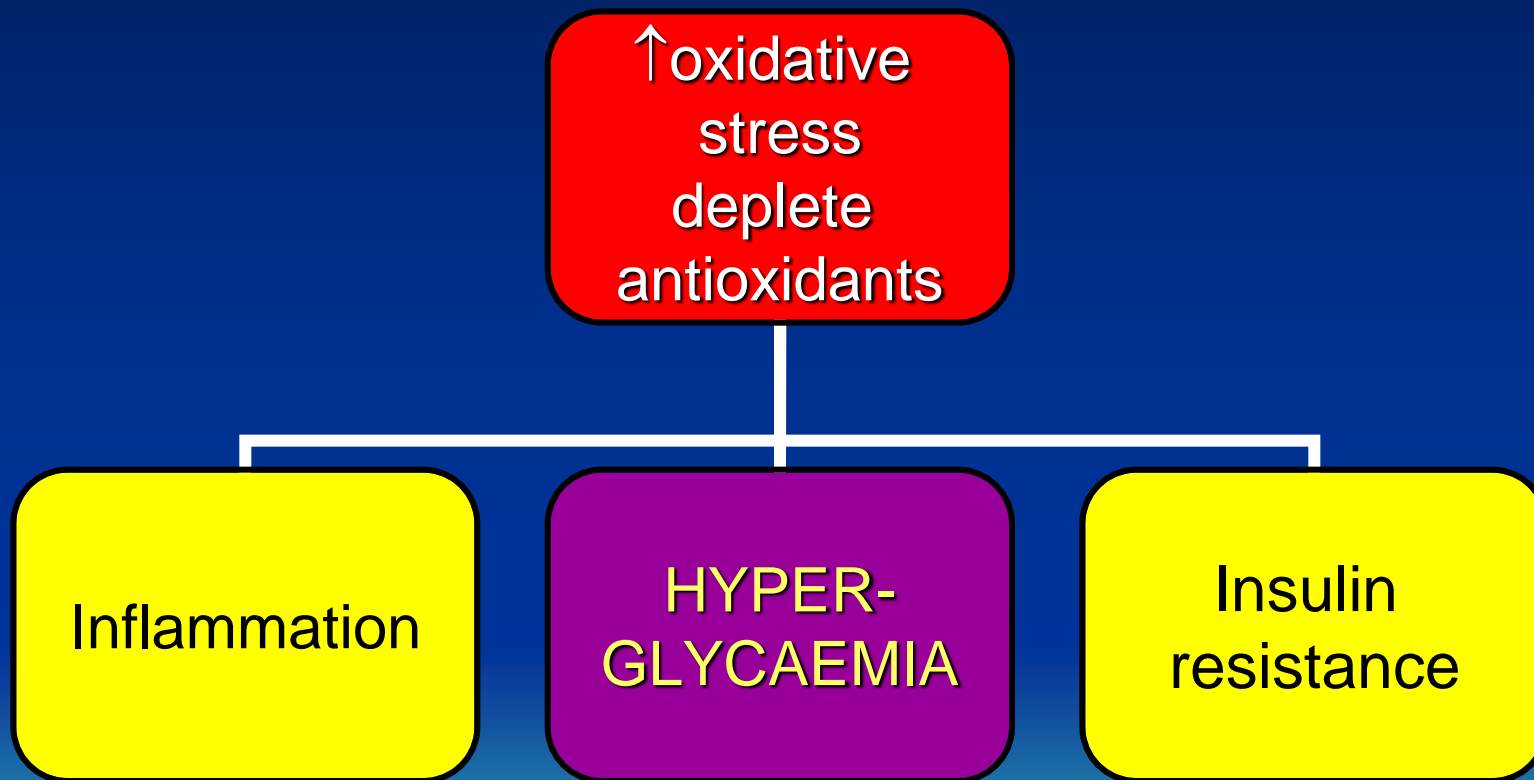
Aging process



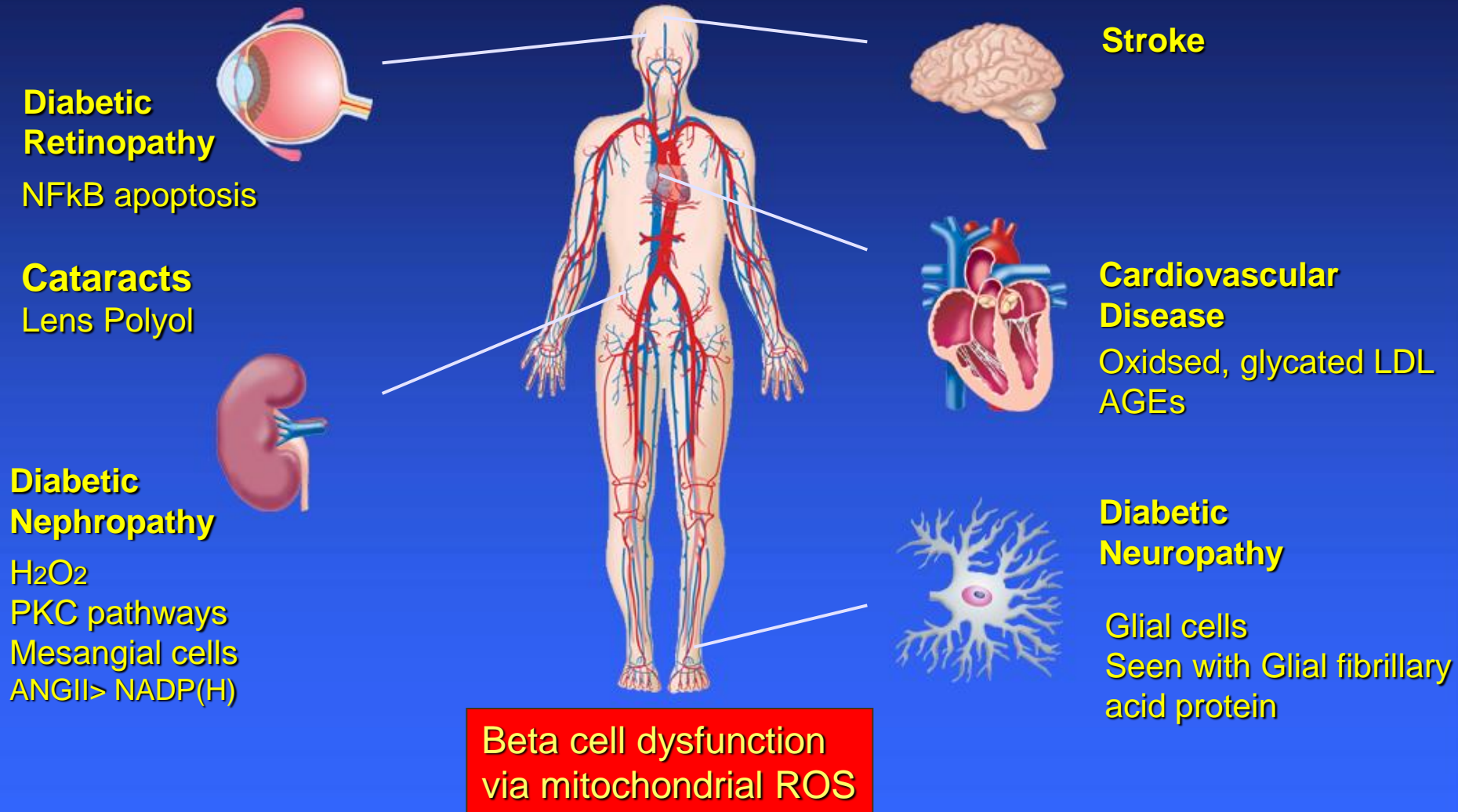
Homeostasis



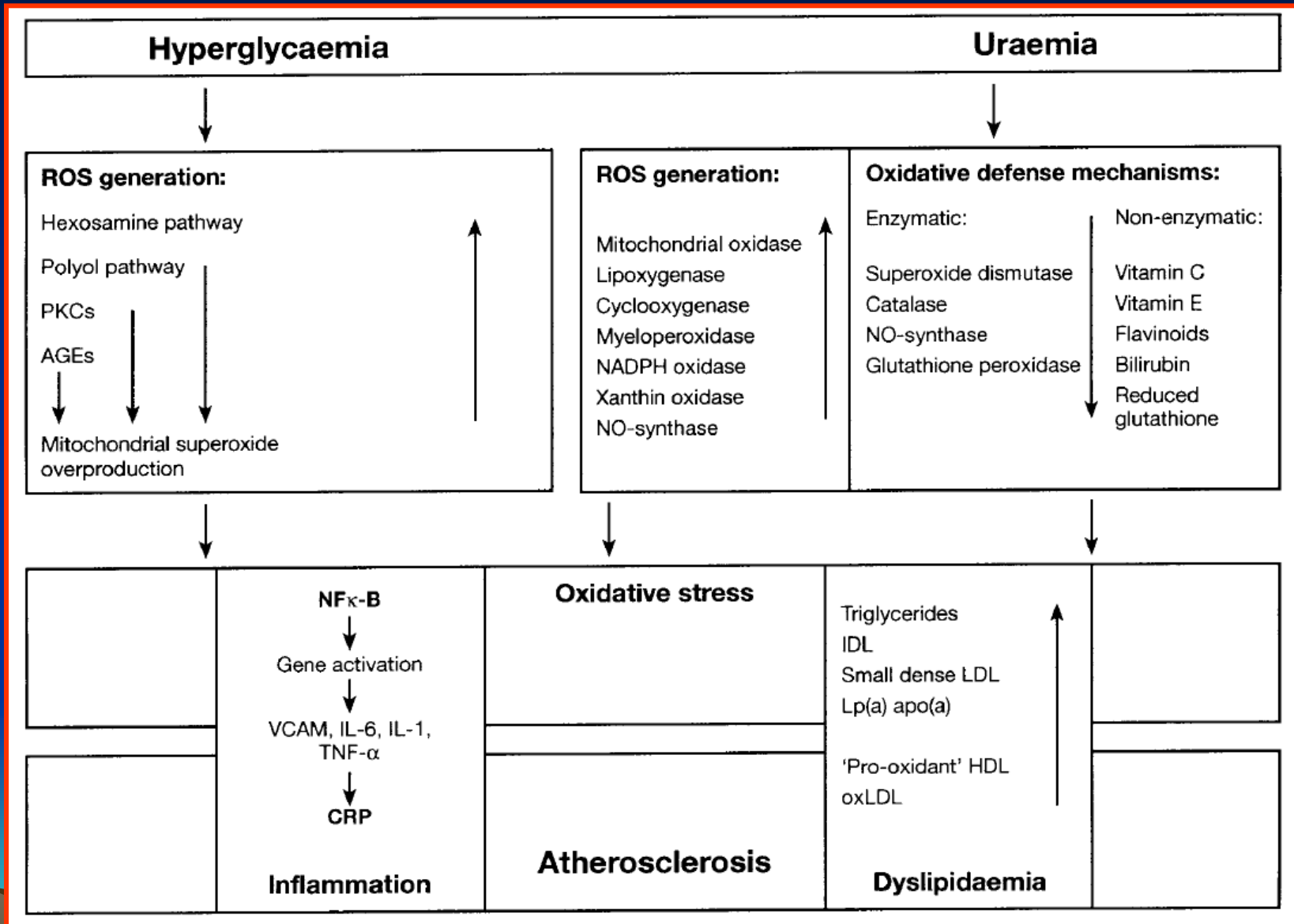
Why lots of oxidative stress in diabetes?

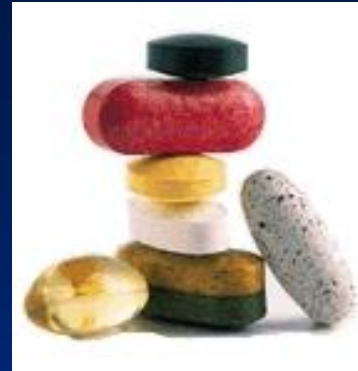


Oxidative stress linked to all diabetes complications



Hyperglycaemia with uraemia: double trouble





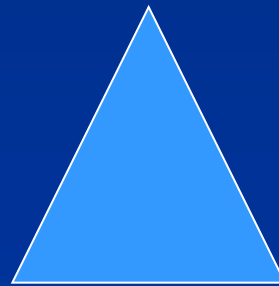
Oxidative stress

Antioxidants

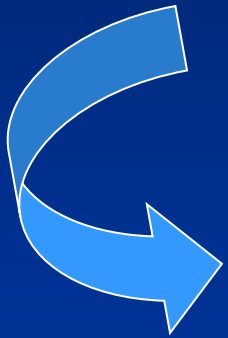


Aging
chronic
diseases

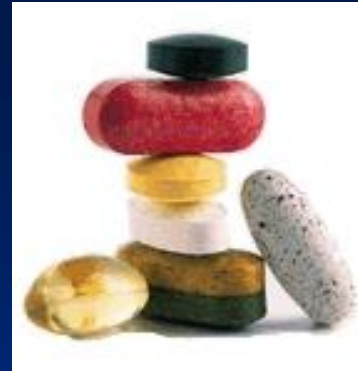
- CHD
- Diabetes



Maintain
health



Theory!



Vitamin supplements

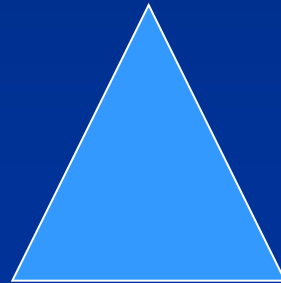
+

Oxidative stress

endogenous
antioxidants

↓ chronic
diseases

better
health



Uncontrolled prospective studies

US Nurses health study follow-up

>100 IU/d vitamin E for ≥ 2 years
significantly lowered risk of coronary events
in males and females



“Vitamin supplements for all”

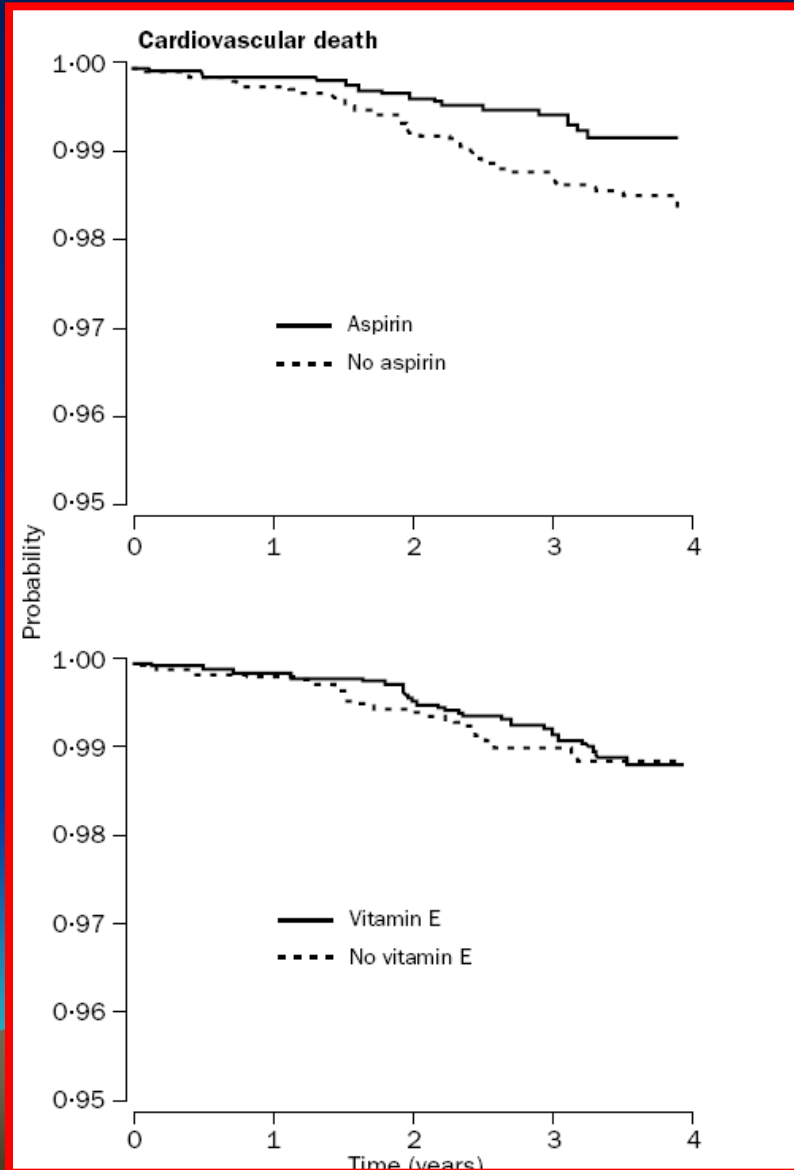


However!



Primary prevention Project - Italian [Lancet Jan 2001]

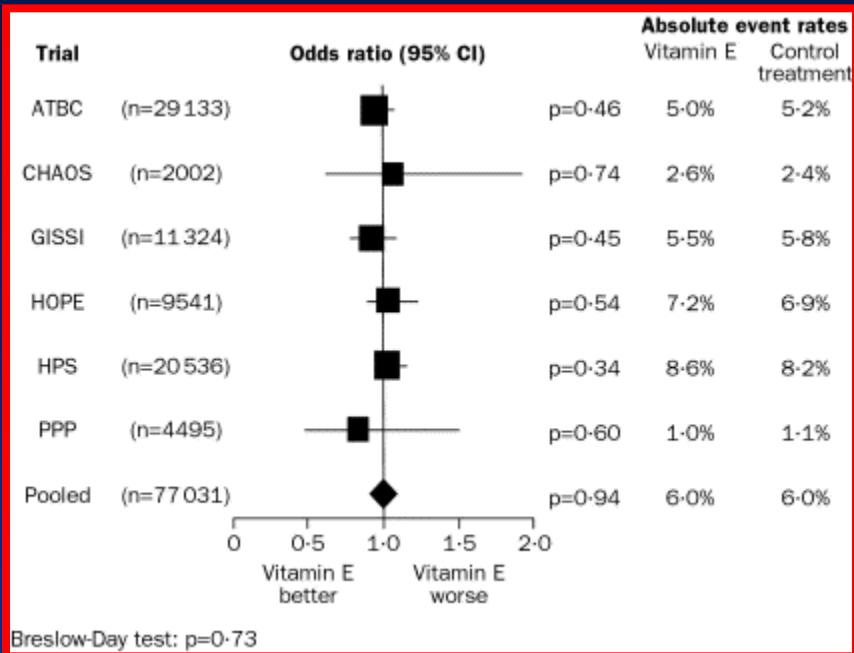
4495 age 64.4 with with CHD risk factors



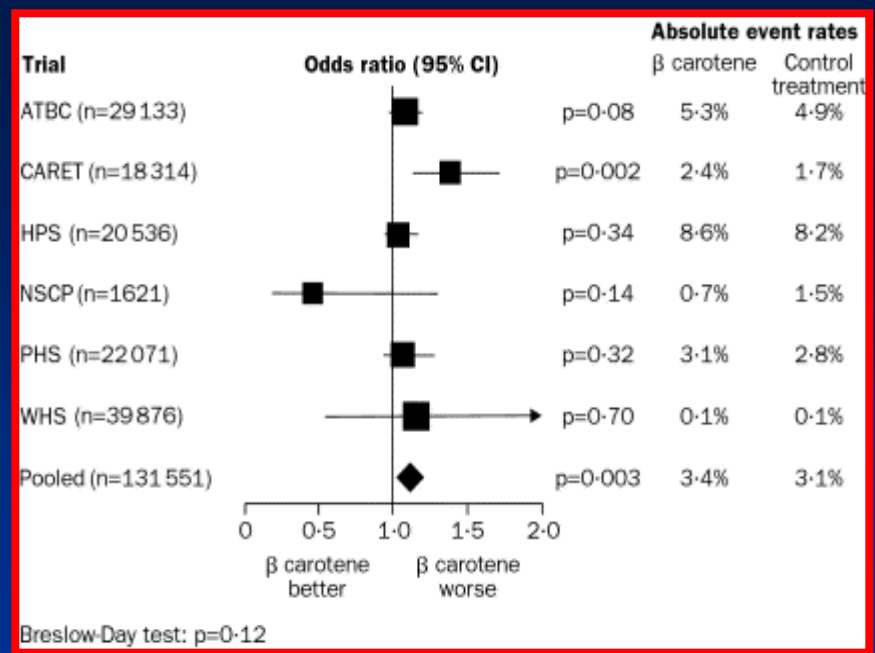
Aspirin

3.6 years

Vitamin E
300 mg/d

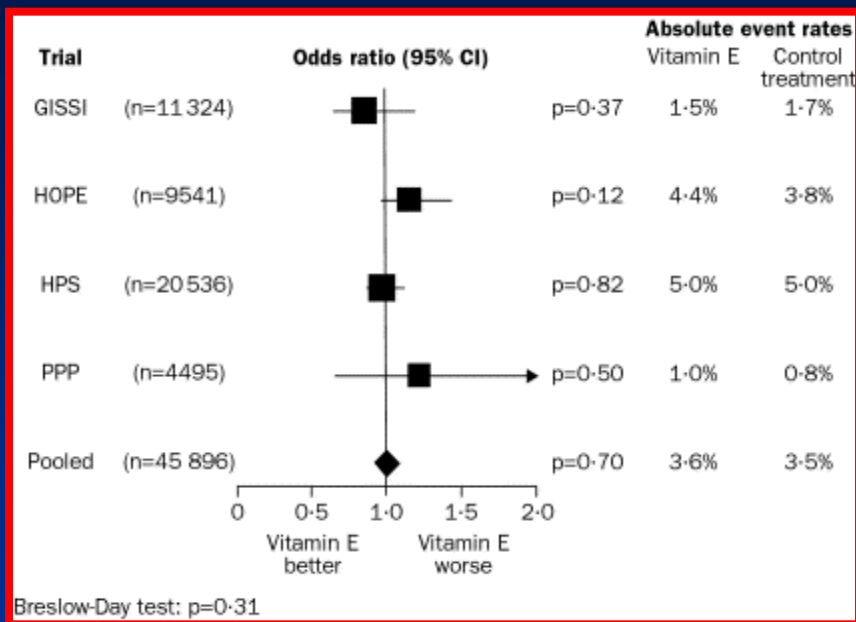


Vitamin E

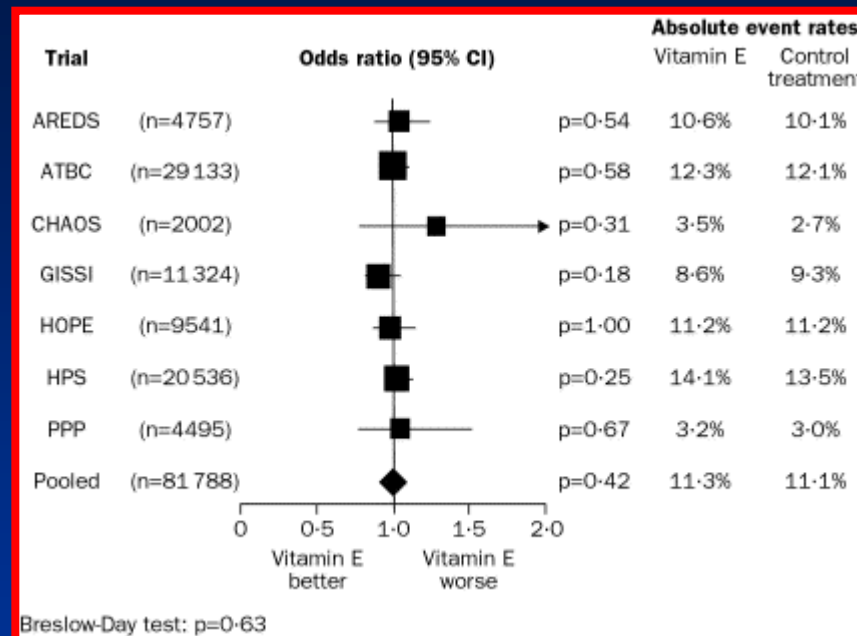


β carotene

CHD end-points



Stroke



All cause mortality

Other end-points

Specific studies of antioxidants in diabetes



Table 3. Clinical trials of antioxidants supplements in subjects with type 2 diabetes

<i>n</i>	Study population	Supplement	Dose	Results
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Peripheral neuropathy

Thioctic acid (α-lipoic) and diabetic neuropathy

- Water and lipid soluble
 - Disulphide bond
 - Works at level of mitochondria
 - Esp. well at peripheral nerves
- 7 trials: recent meta-analysis n=1258 in RCTs
 - Significant benefit
 - Methods sub-optimal
 - Large USA trial on the go – “NATHAN”

Where now for oxidation hypothesis?

“give earlier”

“higher doses”

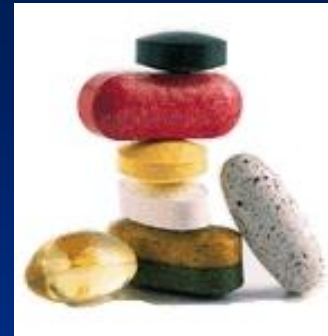
“give for longer”

“wrong choice of antioxidants”

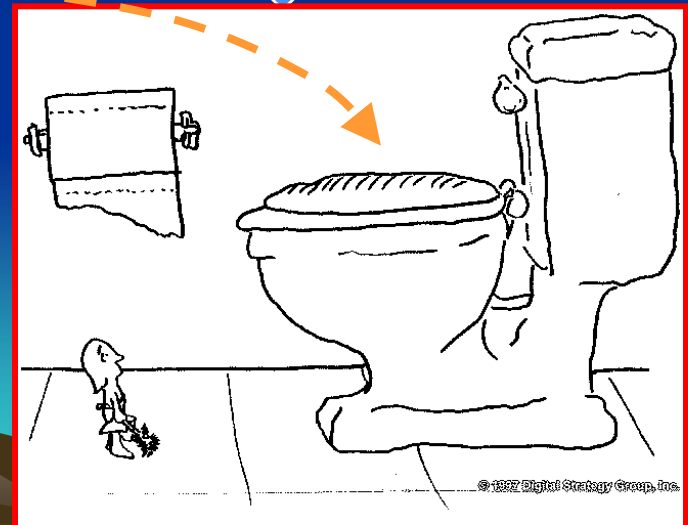


MAY work in some diseases

- pre-eclampsia (large trials ongoing)
- haemodialysis
- HIV
- Diabetic neuropathy?



Bypass
GI & renal tracts



Oxidative hypothesis – summary so far

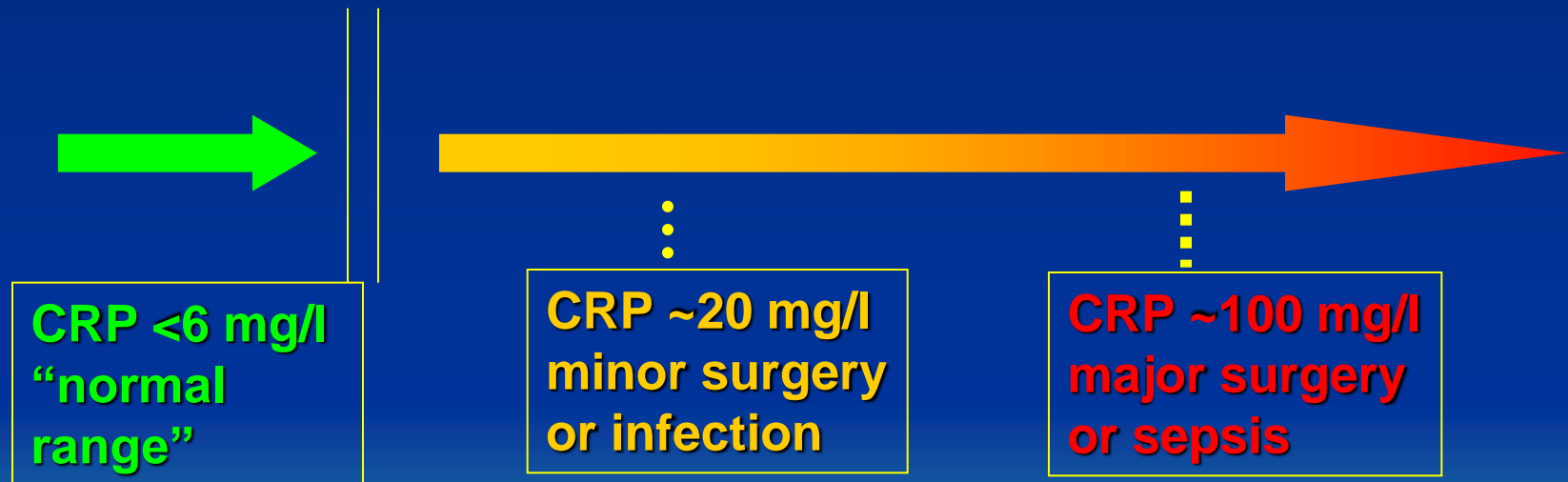
- ↑ oxidative stress in diabetes – downstream of other pathways
- Supplementation with antioxidants of unproven benefit
- Stick with glycaemic control, lifestyle improvements & proven therapies

Outline

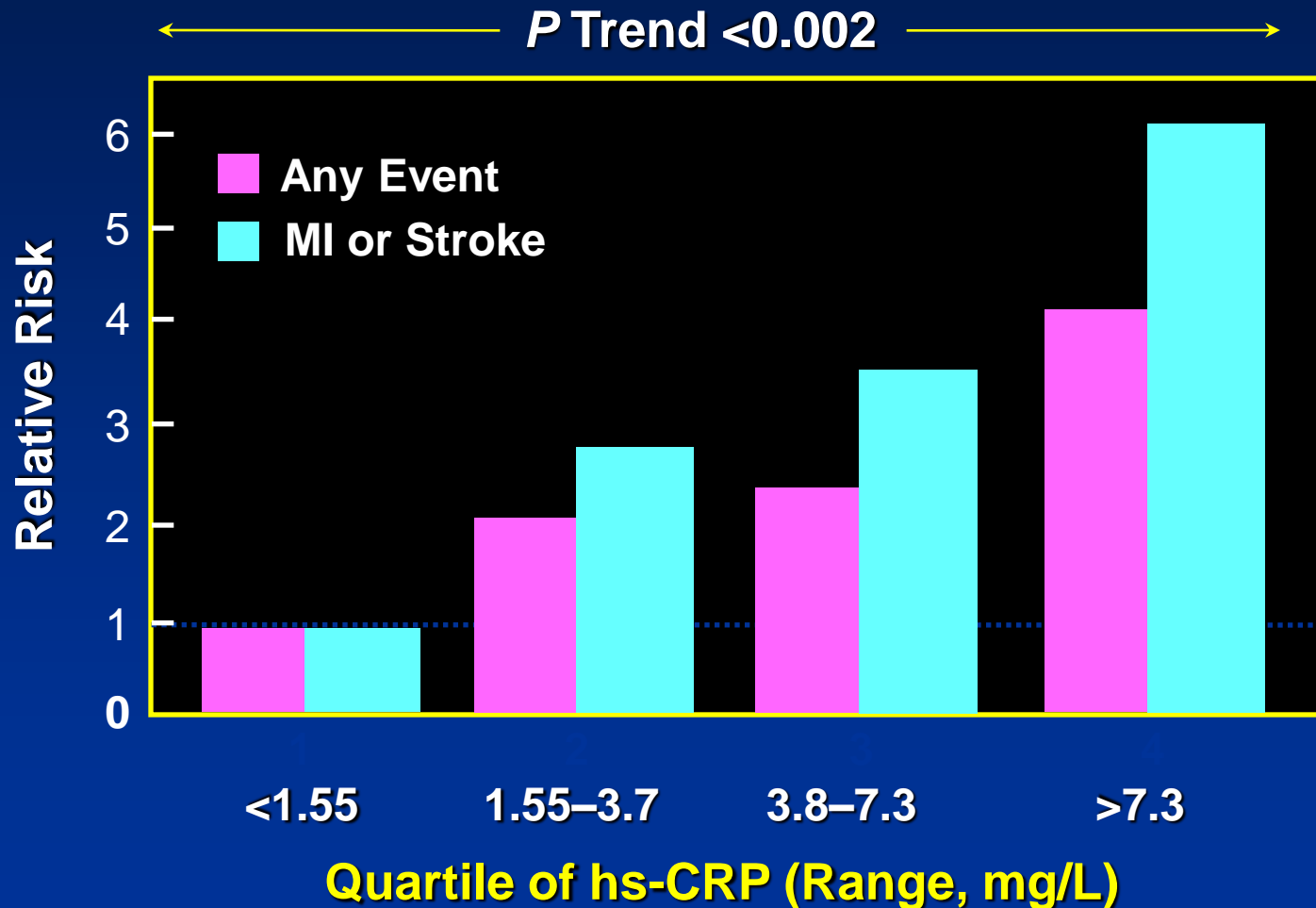
- Oxidative stress
 - Any clinical value of antioxidants
- Inflammation and diabetes
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Inflammatory marker in clinical use

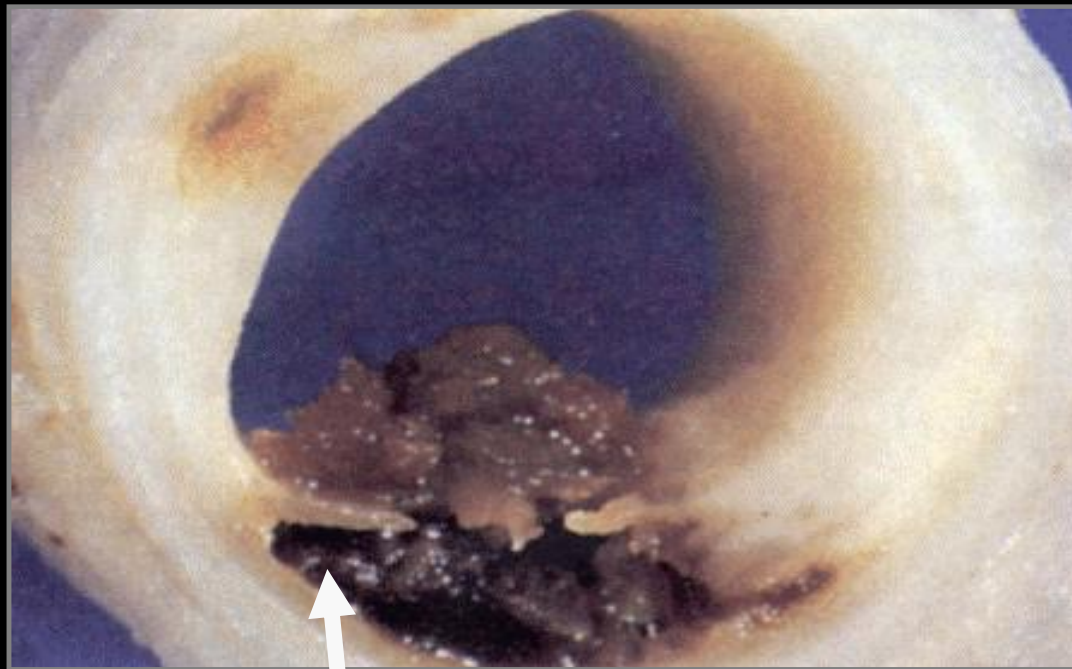
CRP as marker of inflammatory activity



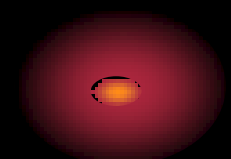
hs-CRP and Risk of Future Cardiovascular Events in Apparently Healthy Women



Cellular and molecular make-up of unstable plaques



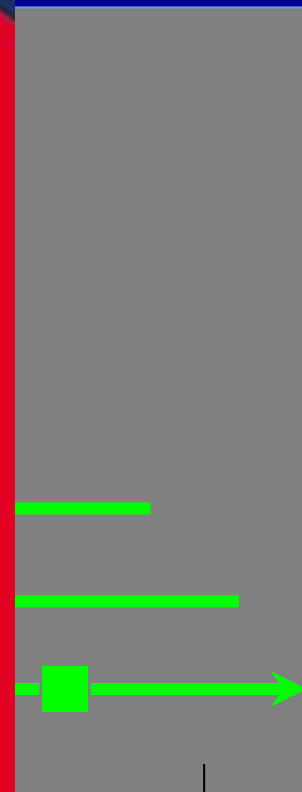
CRP, IL-6,
IL-15, IL-18, MMPs etc



Relative Risk
Middle-Age

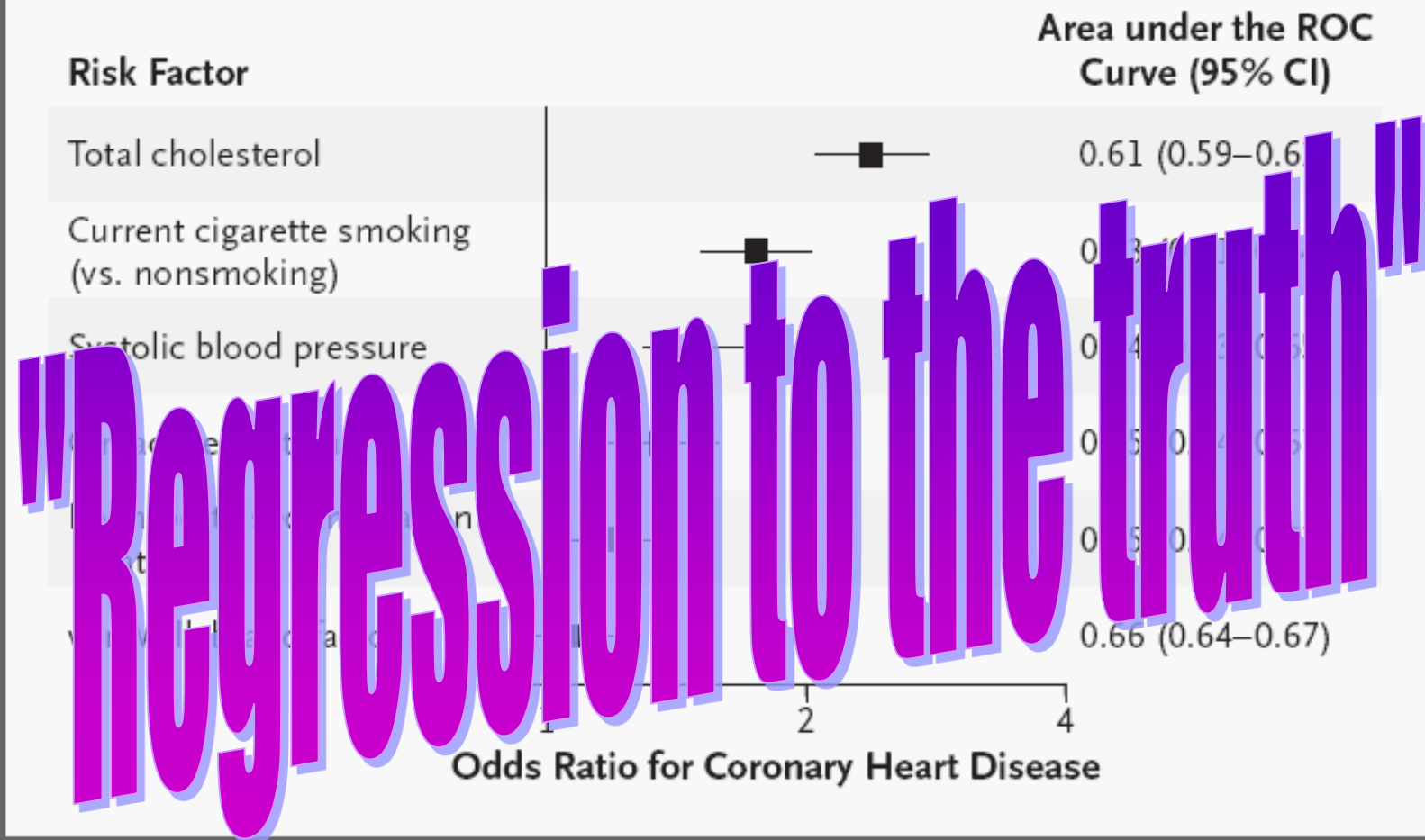
ntly Healthy

- Lipoprotein
- Homocyste
- Total Chole
- Fibrinogen
- tPA Antigen
- TC/HDL-C
- hs-CRP
- hs-CRP + T



6.0

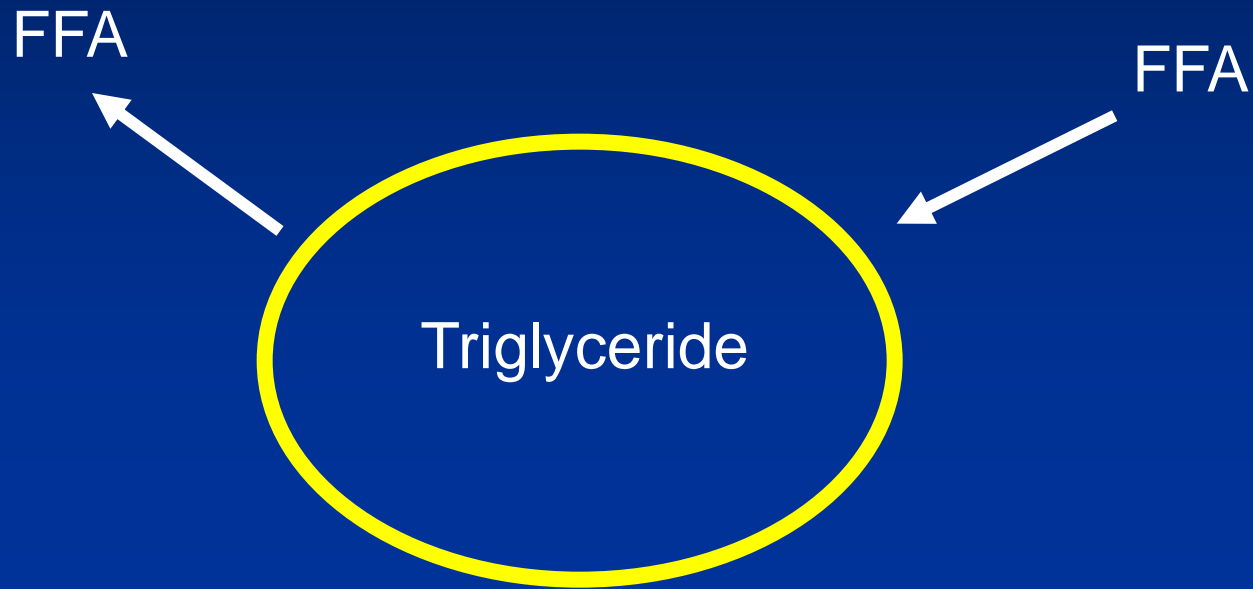
Adapted from Ric



John Danesh et al.

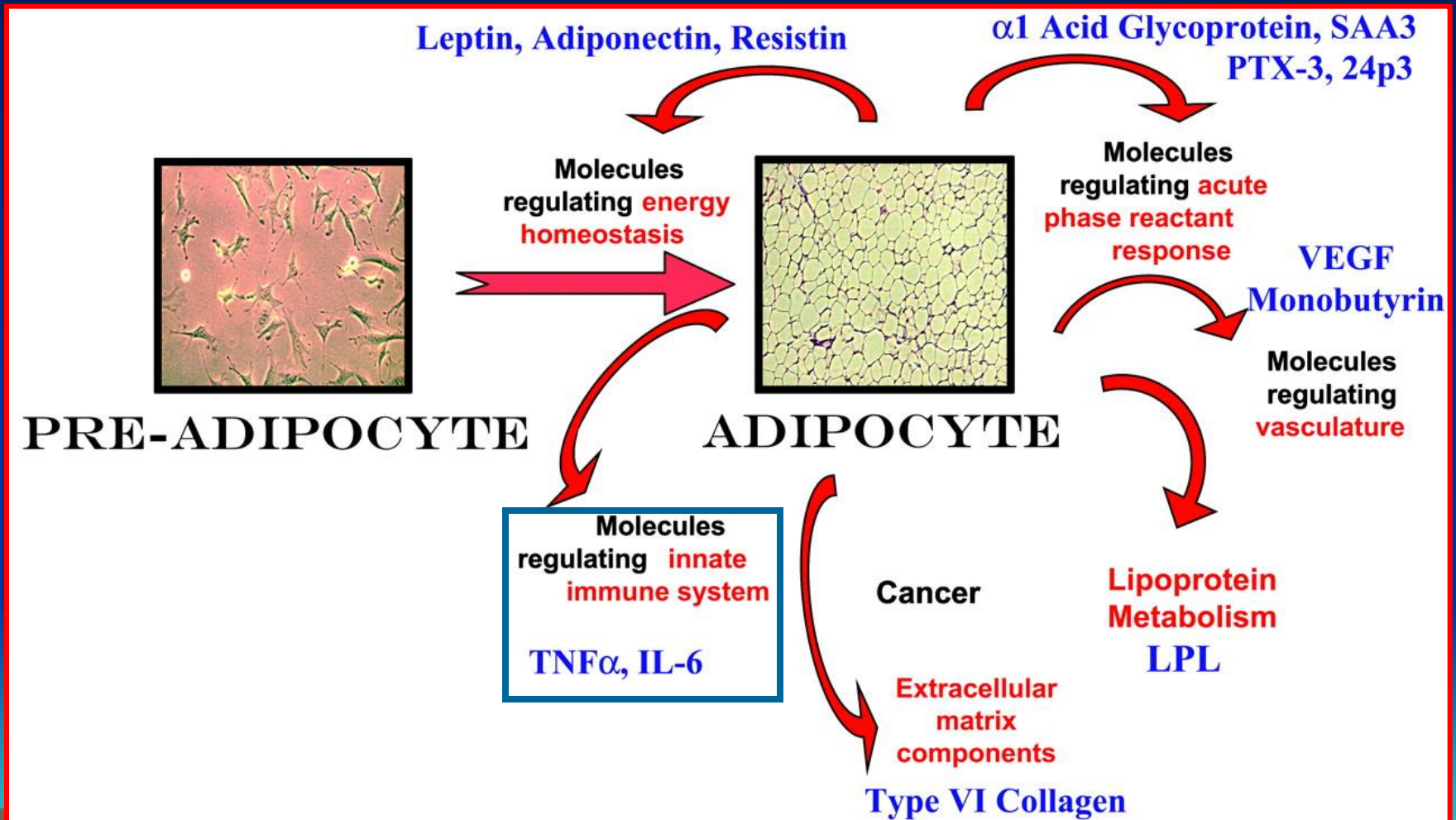
C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Heart Disease NEJM 2004

Confounding factors

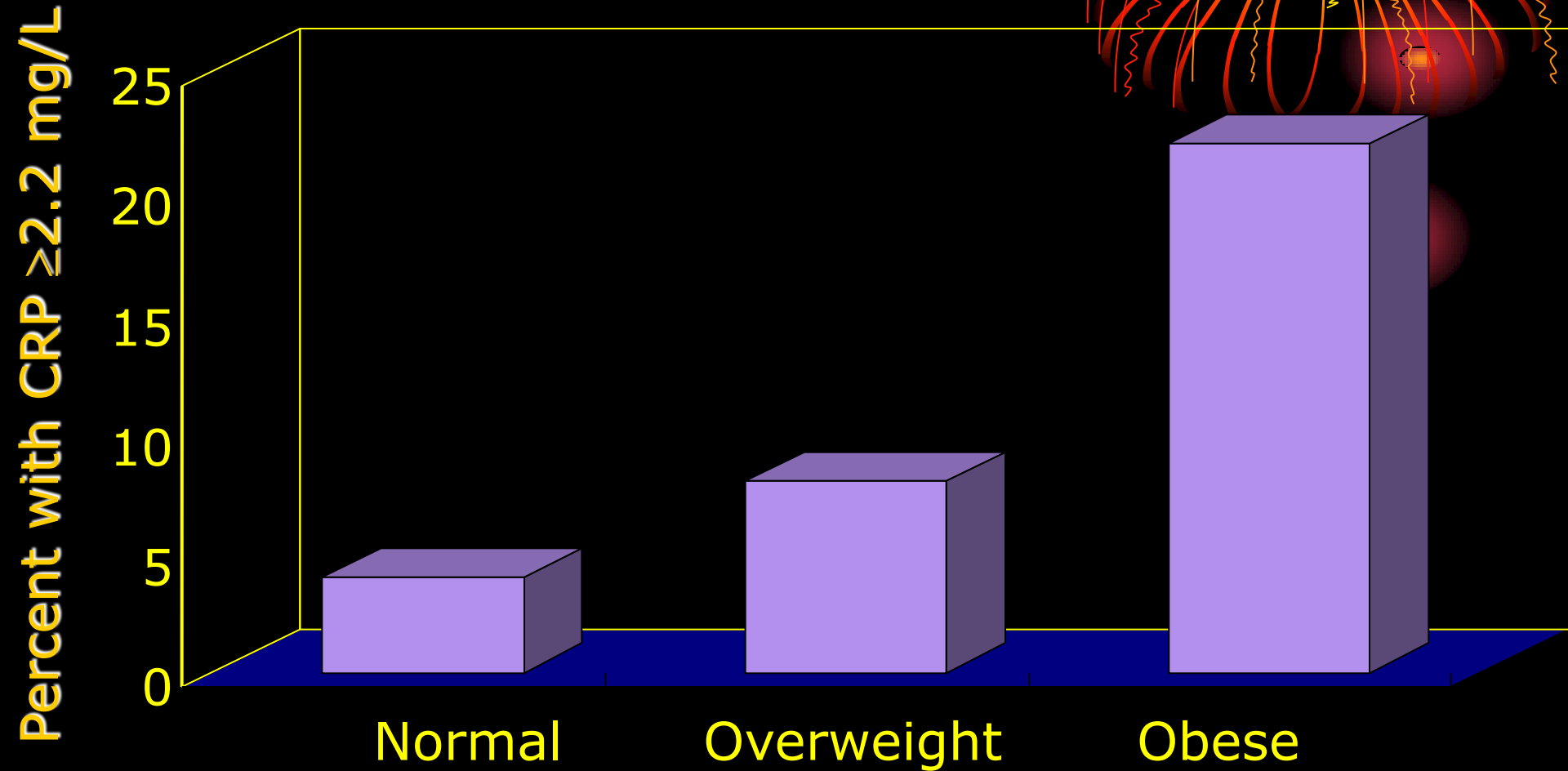


Adipocytes circa 1990

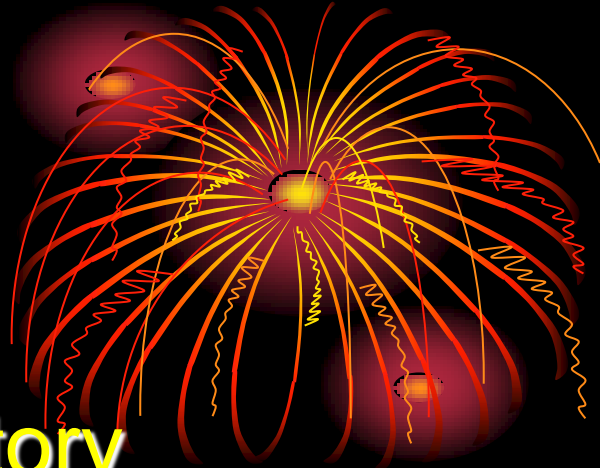
Adipocytes are sexy!



1. Obesity vs CRP levels



Visser M et al. *NHANES 1988-1994 JAMA* 1999;282:2131-2135.

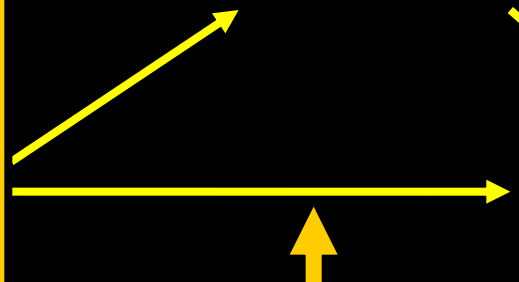


Inflammatory markers

- Lifestyle factors**
- Obesity
 - Sedentary behav.
 - Poor diet
 - Low social class
 - Race

CHD

Alternative Mechanisms
Lipids, BP, etc



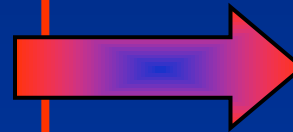
Inflammation and diabetes

- **Do inflammation markers predict diabetes?**
- **Any evidence that lessening inflammation improves insulin sensitivity?**



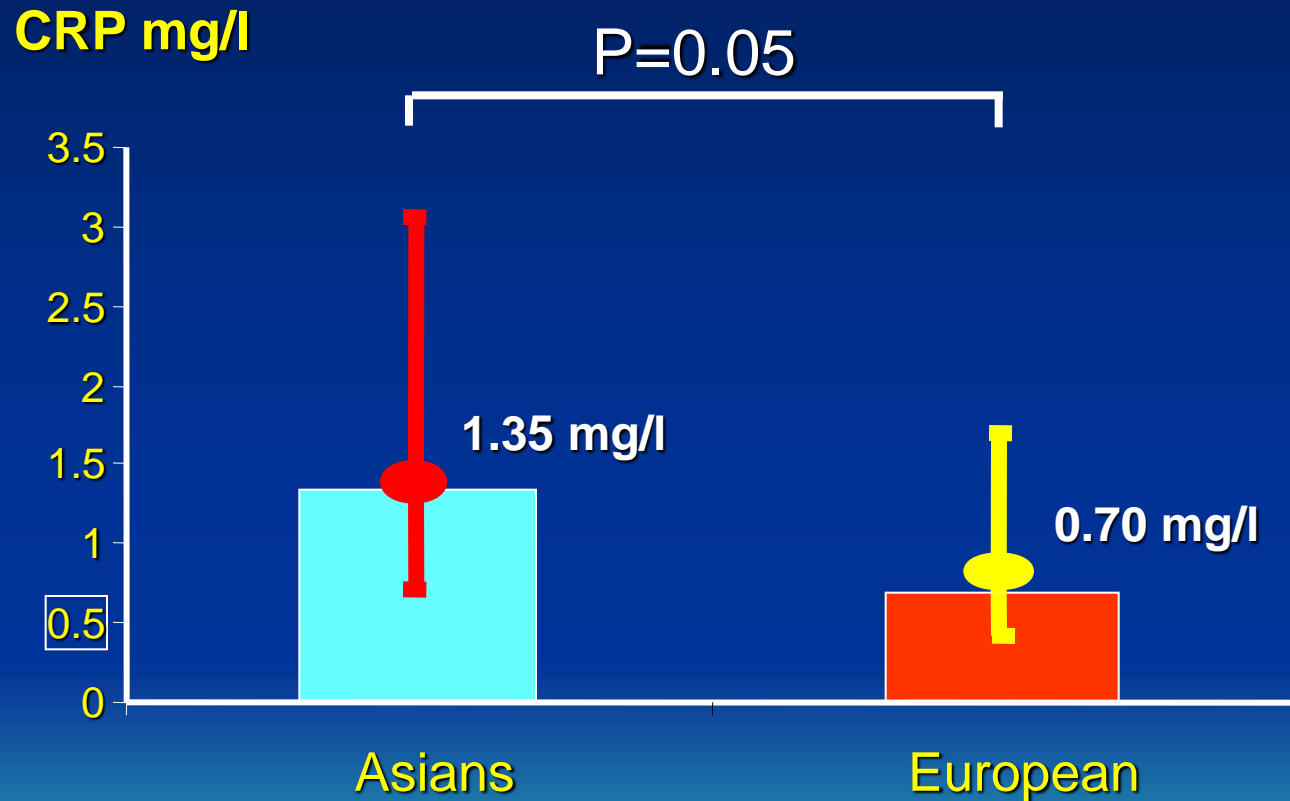
CRP goes up with:

- Age
- Obesity
- Low physical activity
- FH diabetes
- South Asians
- Others
 - PCOS
 - High GI diet



Diabetes

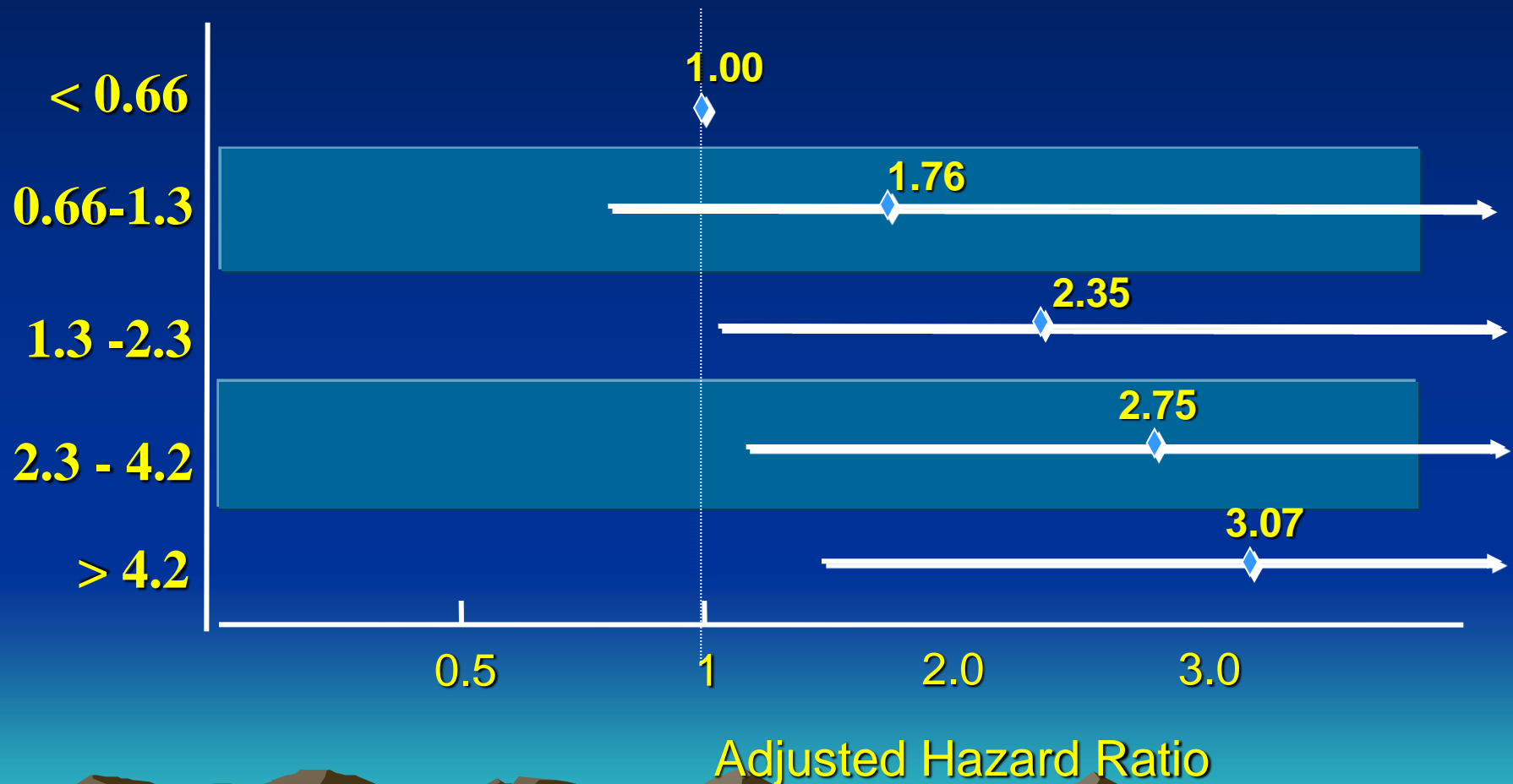
South Asians and CRP



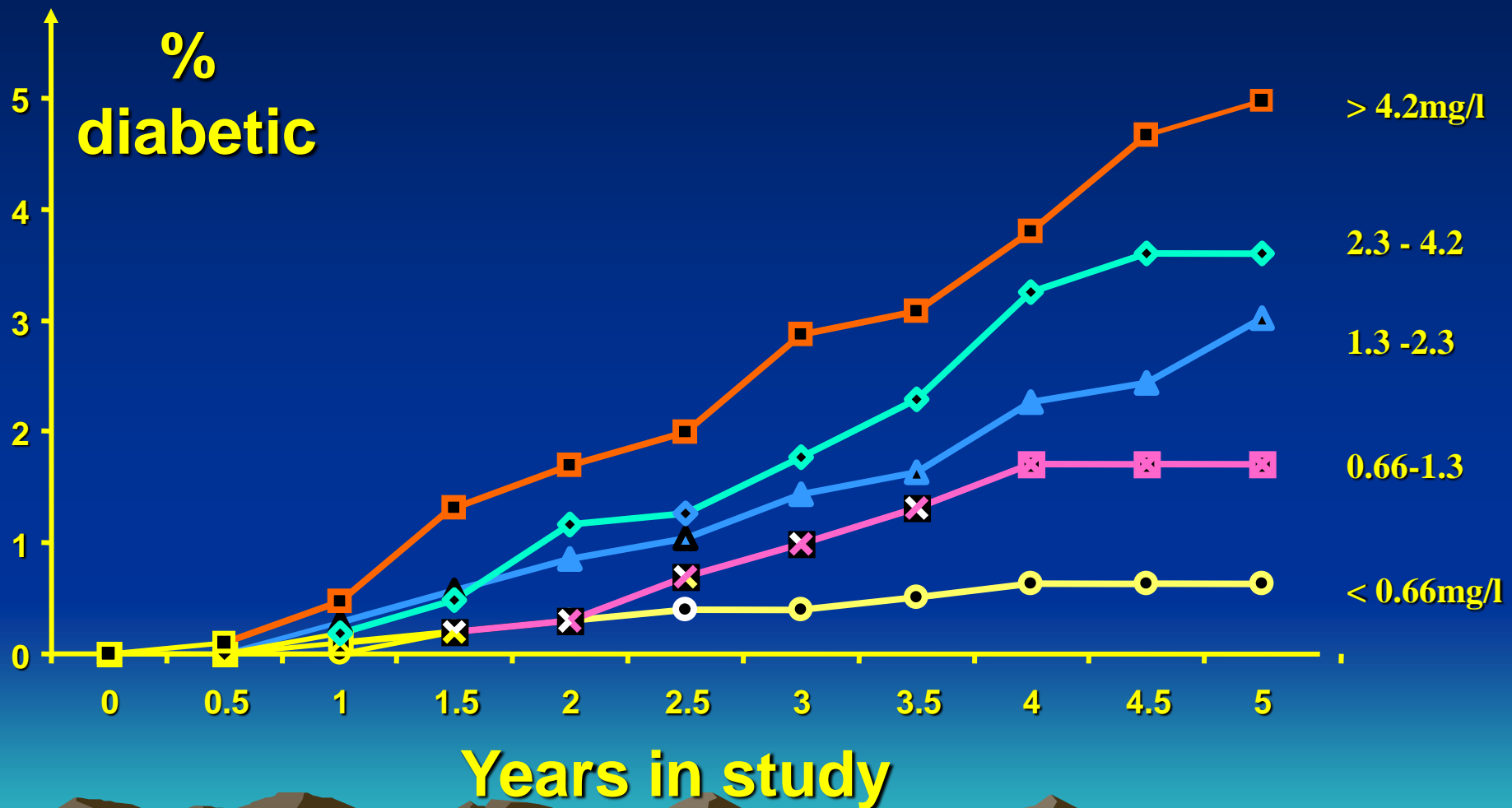
Does CRP predict new diabetes

	139 subsequent diabetes	All 5,974 subjects
Age (years)	55.6 (5.7)	55.2 (5.5)
Glucose (mmol/l)	5.49 (0.69)	4.72 (0.51)
Body Mass Index (kg/m ²)	27.7 (3.6)	25.9 (3.1)
Ln sensitive CRP [ln(mg/l)]	1.05 (0.90)	0.53 (1.08)

Diabetes risk by CRP quintiles (mg/l)



Kaplan-Meier curve



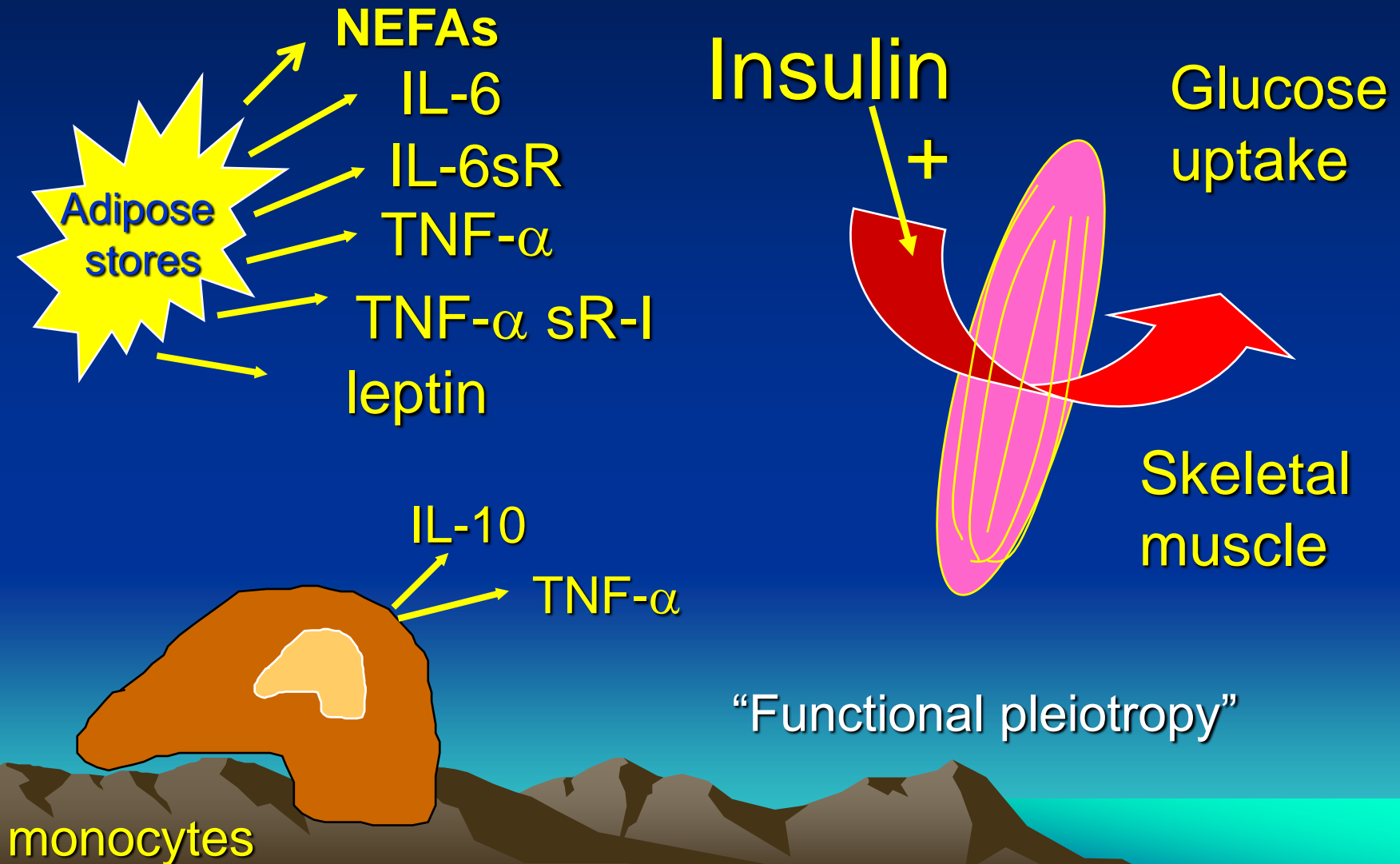
Multivariate Predictors of Diabetes in WOSCOPS



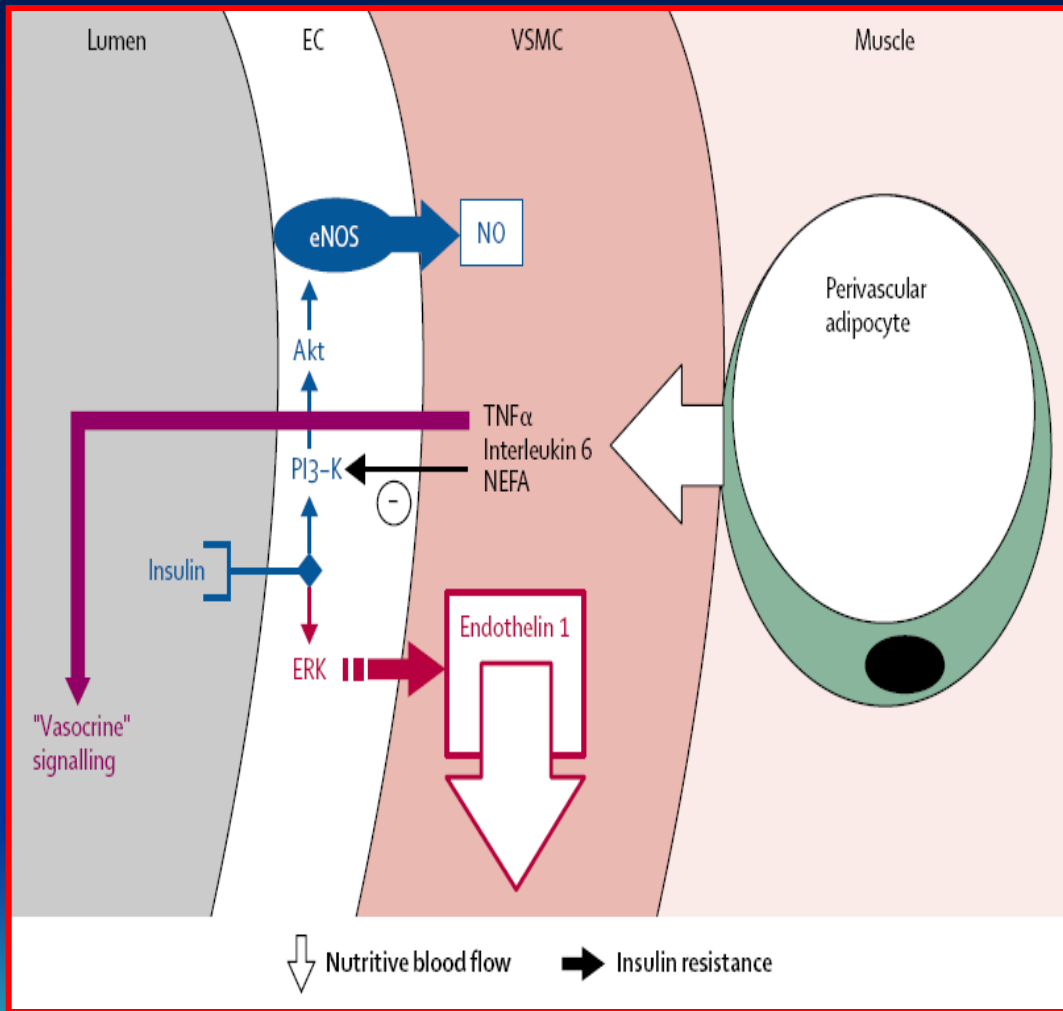
Inflammation ↔ IR?



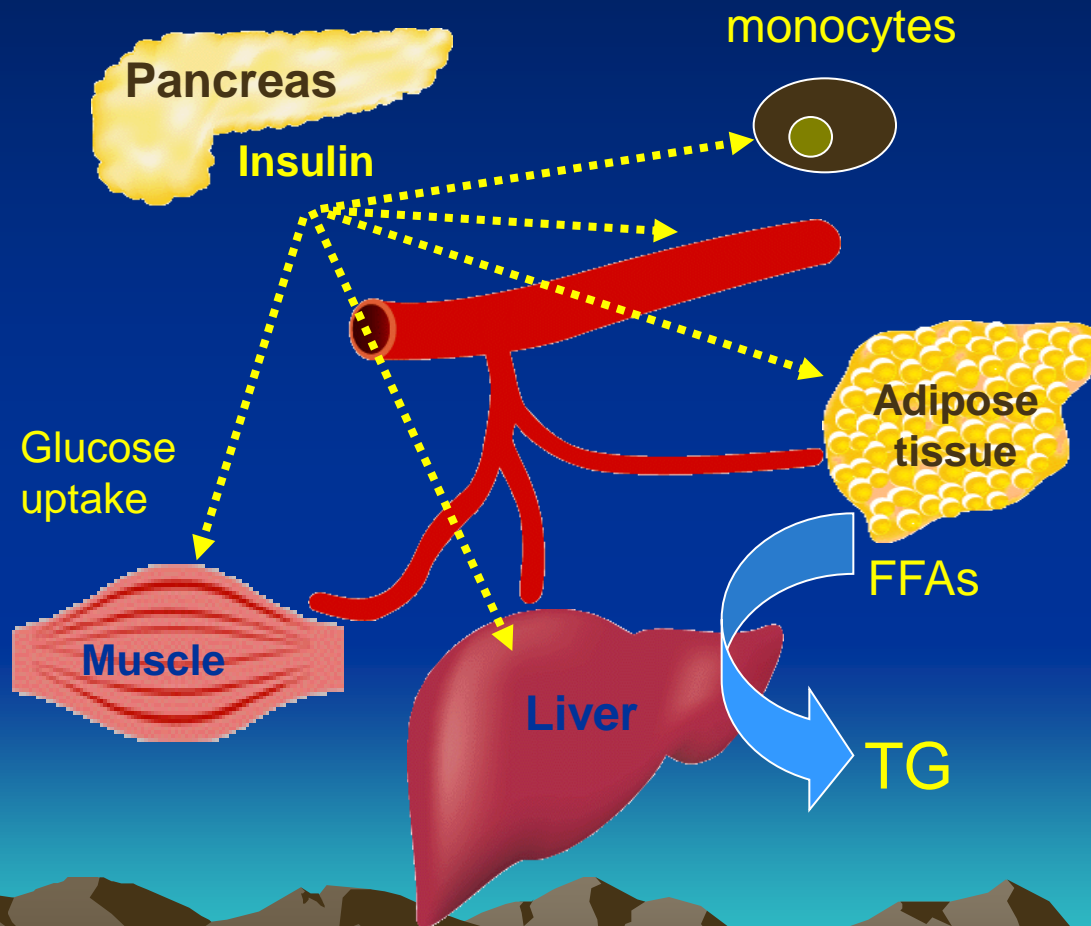
Plausible Mechanisms?

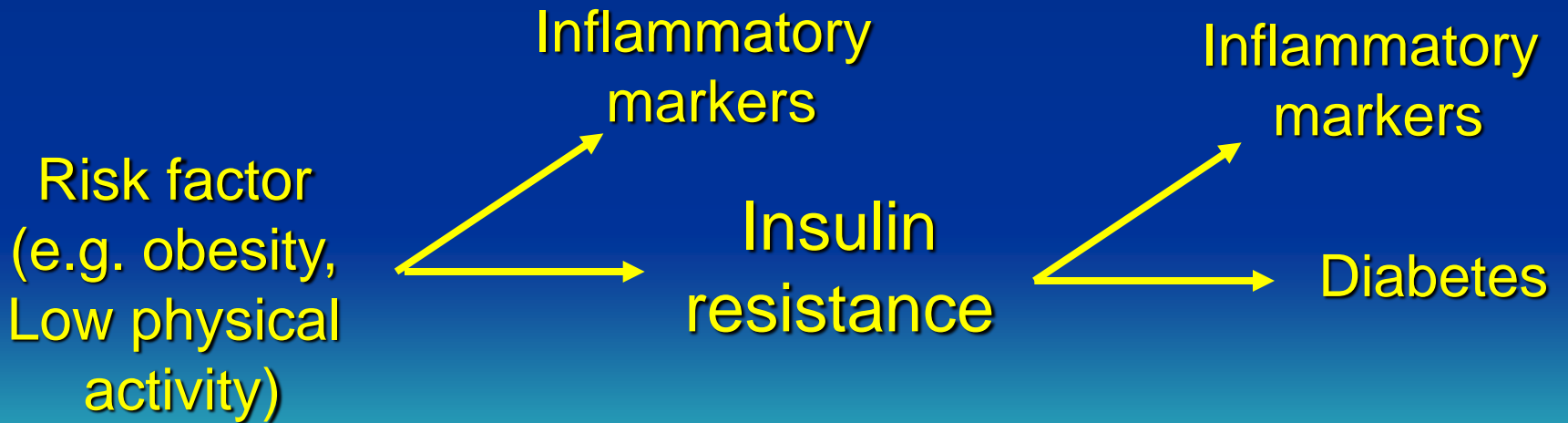
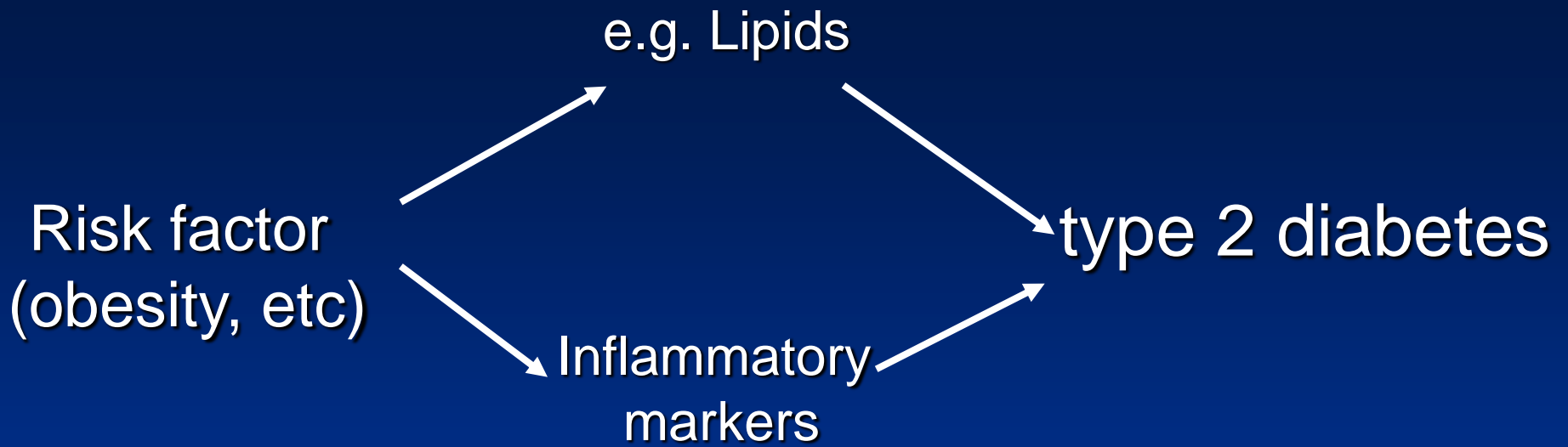


LOCAL FAT TO INFLAMMATON TO INSULIN RESISTANCE



Insulin resistance may lead to inflammation





Many existing vascular risk reduction modalities are anti-inflammatory

Lifestyle alterations

Weight loss

Exercise

Smoking cessation

Improved diet

Regular modest alcohol!

Pharmacological methods

Statins

Aspirin at high doses

ACE inhibitors

PPAR γ activators

Metformin

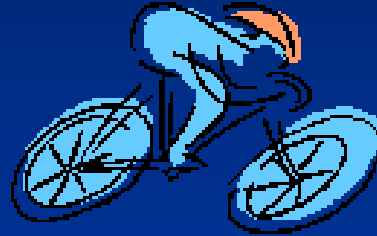
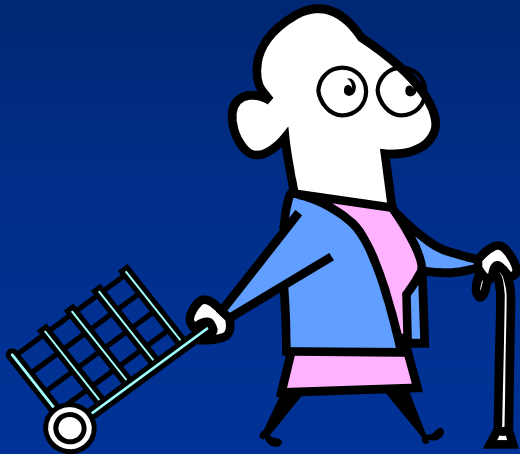


Conclusions on inflammatory markers

- Low grade inflammation (e.g. high CRP)
 - Linked to many factors, particularly obesity
 - predicts diabetes and metabolic derangement
 - Causality not established
- Future
 - trials of specific anti-inflammatory agents
 - genotype studies (G Davey-Smith et al Lancet)
 - may help dissect causality



Meantime



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