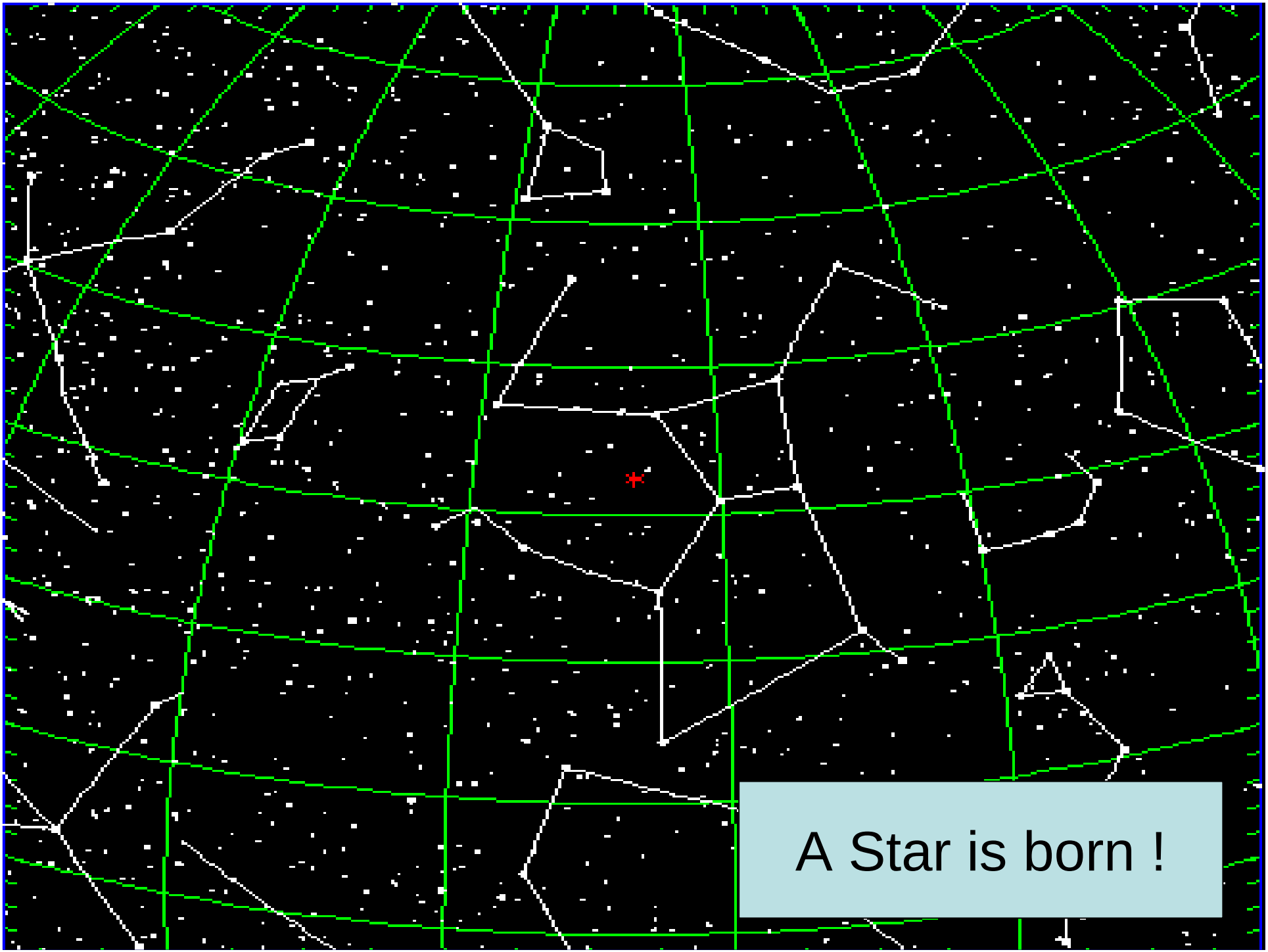
Traitement du syndrome métabolique

- Qui traiter?
- Pourquoi traiter?
- Comment traiter?

Reaven GM: Banting lecture 1988.
Role of insulin resistance in human disease.
Diabetes 37:1595–1607, 1988.


A Star is born !

Definition of metabolic syndrome

WHO guidelines

- Abdominal obesity : WHR >0.90 men
  >0.85 women
- Triglycerides >150 mg/100 ml
- HDL : <0.35 men , < 0.39 women
- BP >140/>90 mm Hg
- Fasting glucose : >110 mg/100ml, IR, DNID
- Microalbuminuria : >20 µg / min

ATP III: General Features of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in.)
Women	>88 cm (>35 in.)
Elevated triglycerides	≥150 mg/dL
Low HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Raised blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL

AHA/ NHLBI 2005

“Pre- metabolic syndrome”

AHA/ NHLBI 2005

- Waist : 94 – 100 cm ♂ 80-87 cm ♀

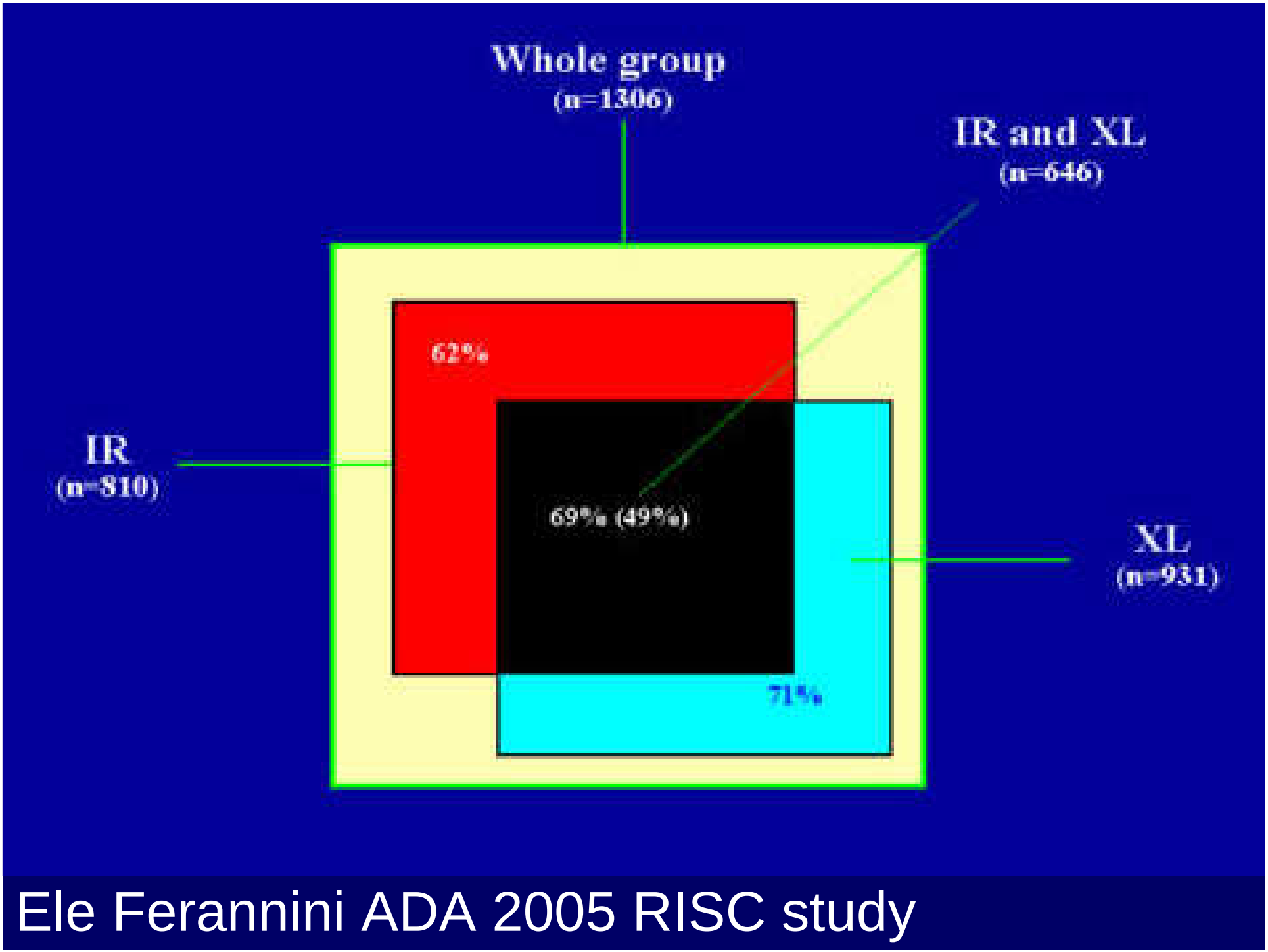
+ type 2 diabetes familial history before 60 y.
+ polycystic ovary
+ fatty liver
+ CRP > 3 mg/ l
+ impaired glucose tolerance
+ high Apo B
+ some populations.

Metabolic syndrome

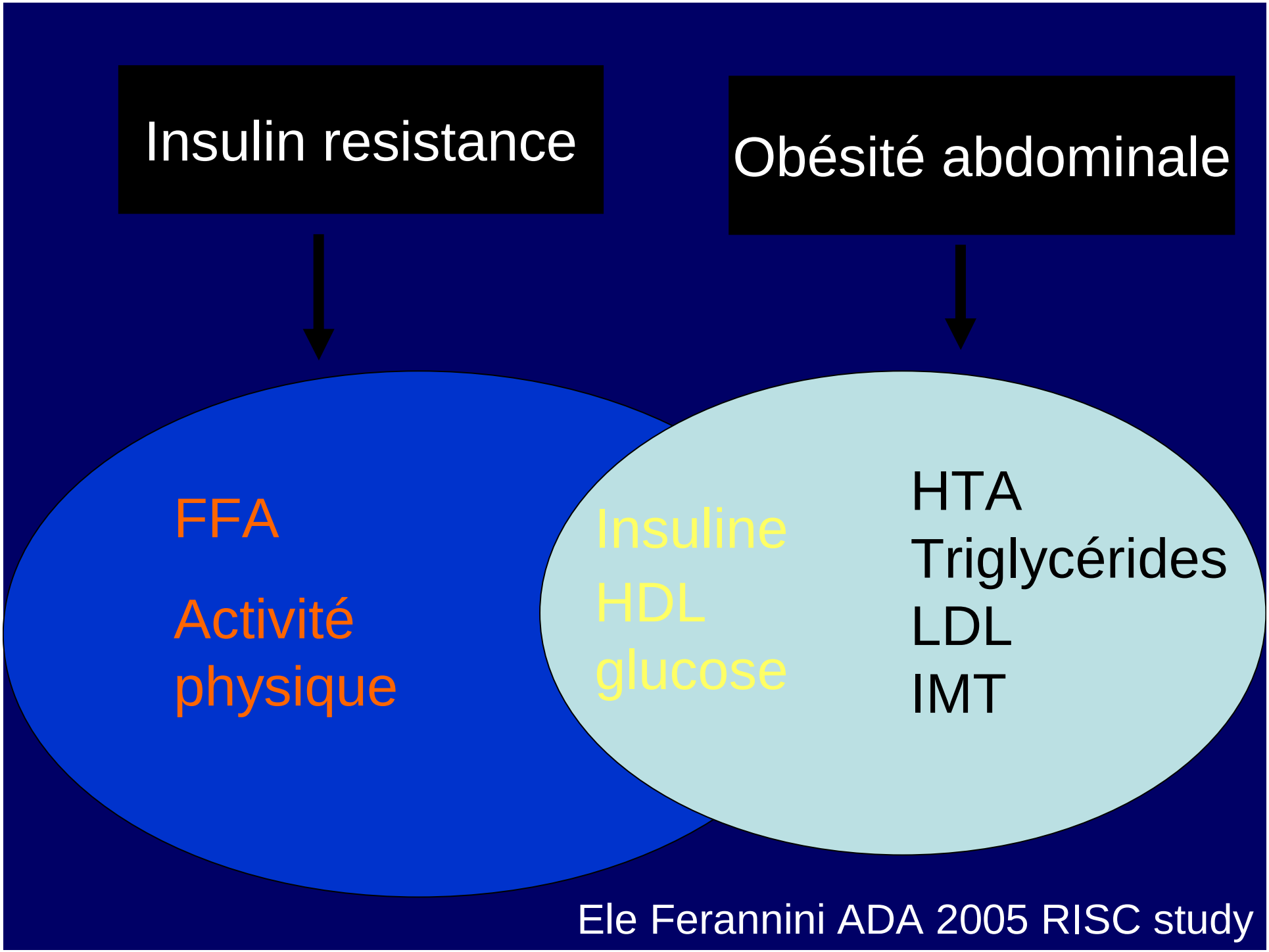
IDF définition

- Obésité centrale : > 94 cm ♂ ou 80 cm ♀
- Plus 2 des 4 facteurs:

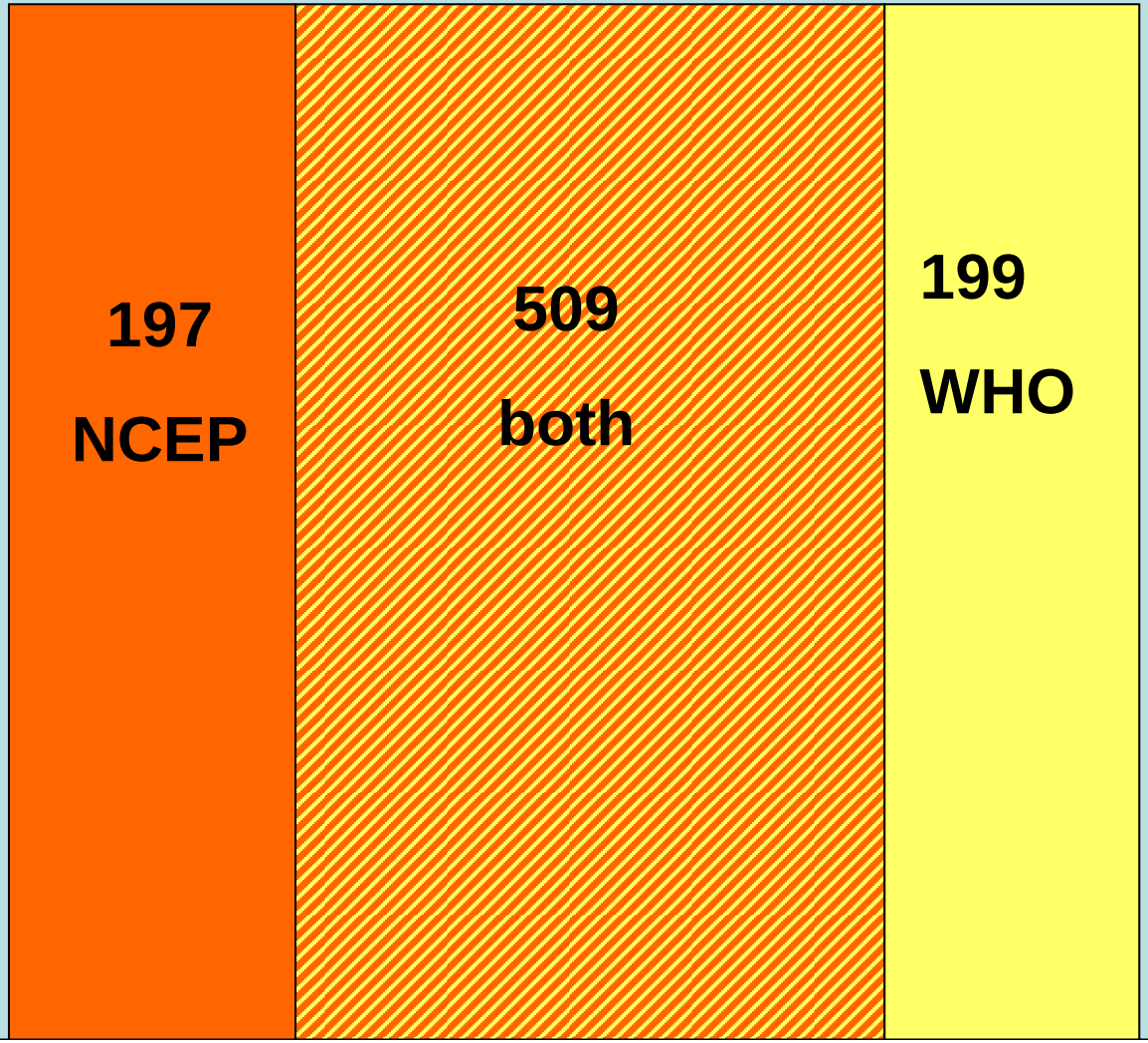
1. TG > 150 mg/100 ml
2. HDL < 40mg / 100 ml
3. sTA ≥ 130 mm Hg ou dTA ≥ 85 mm Hg
4. glycémie > 100 ml ou DNID



Ele Ferannini ADA 2005 RISC study

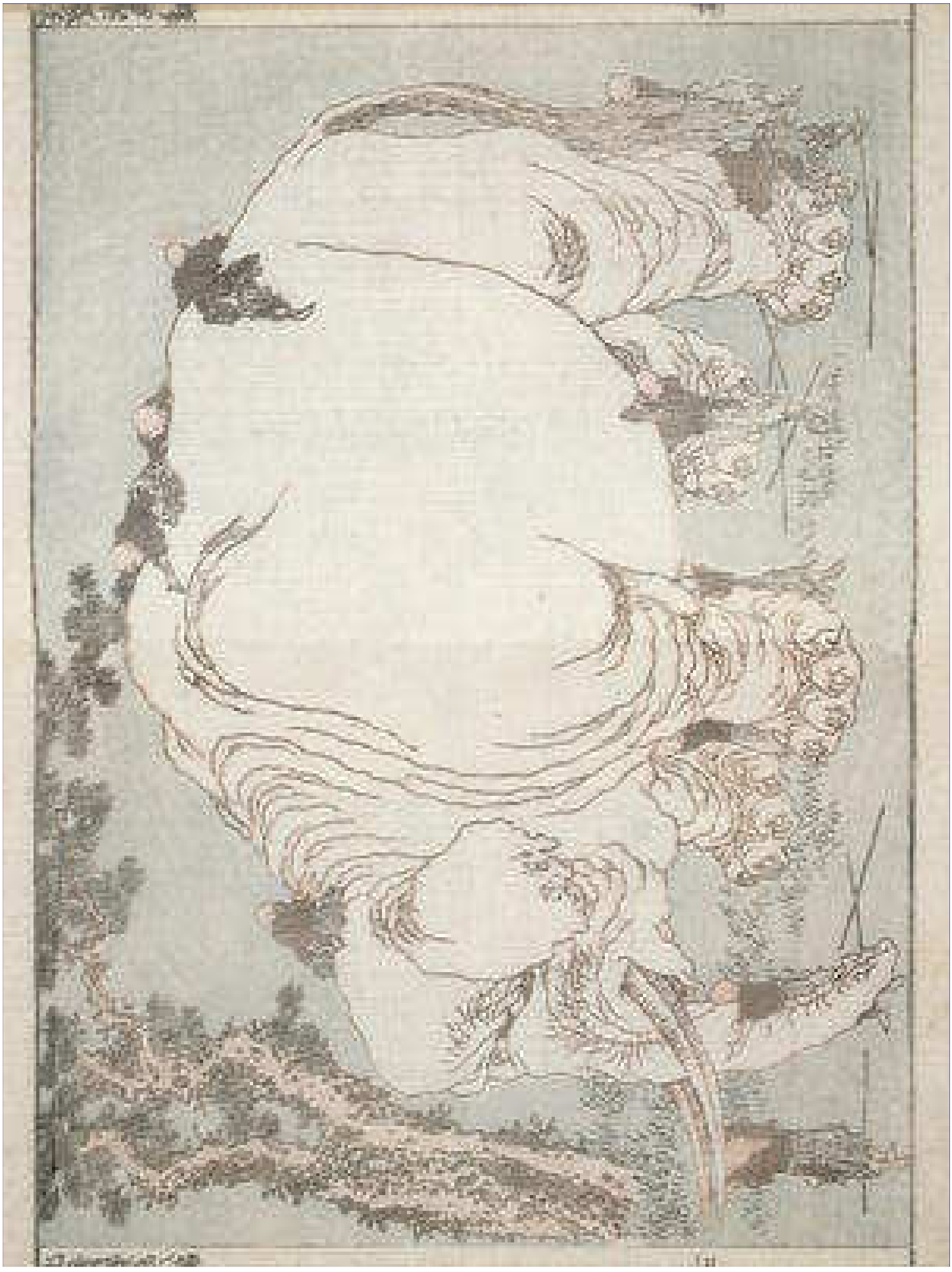

Insulin resistance
Obésité abdominale
FFA
Activité physique
Insuline
HDL
glucose
HTA
Triglycérides
LDL
IMT
Ele Ferannini ADA 2005 RISC study

San Antonio study Hunt Circulation 2004



	BMI (95% CI)*	Waist (95% CI)†	WHR (95%CI)‡
Overall	1·10 (1·07–1·13)	1·19 (1·16–1·22)	1·37 (1·34–1·41)
European	1·14 (1·09–1·20)	1·25 (1·19–1·31)	1·44 (1·36–1·51)
Chinese	1·19 (1·11–1·27)	1·24 (1·16–1·33)	1·08 (1·03–1·14)
South Asian	0·99 (0·93–1·05)	1·03 (0·97–1·10)	1·52 (1·41–1·64)
Other Asian	1·29 (1·17–1·43)	1·58 (1·41–1·78)	2·60 (2·25–3·01)
Arab	1·00 (0·93–1·07)	1·07 (0·99–1·16)	1·43 (1·31–1·57)
Latin American	1·12 (1·04–1·21)	1·20 (1·11–1·29)	1·43 (1·32–1·56)
Black African	1·29 (1·10–1·52)	1·57 (1·31–1·88)	1·36 (1·09–1·69)
Mixed-race African§	1·07 (0·94–1·22)	1·16 (0·99–1·34)	2·25 (1·79–2·84)

Yusuf Interheart study lancet 2005

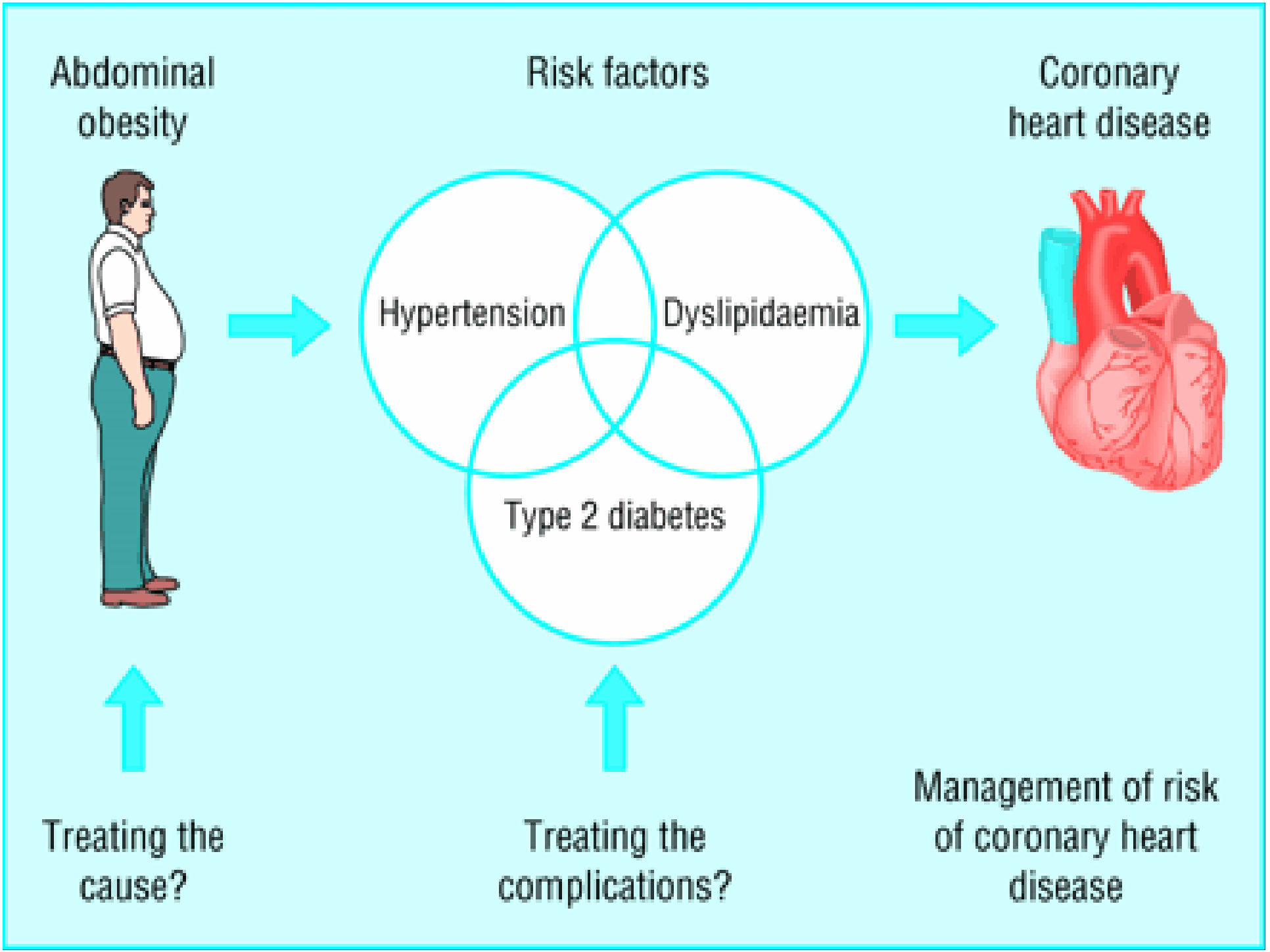


- Les critères de diagnostic du syndrome métabolique sont variables.
- Rôle de l'origine ethnique.
- La mesure de la circonférence de la ceinture est imprécise.
- Le diagnostic de syndrome métabolique ne permet pas d'envisager un mécanisme physiopathologique unique.

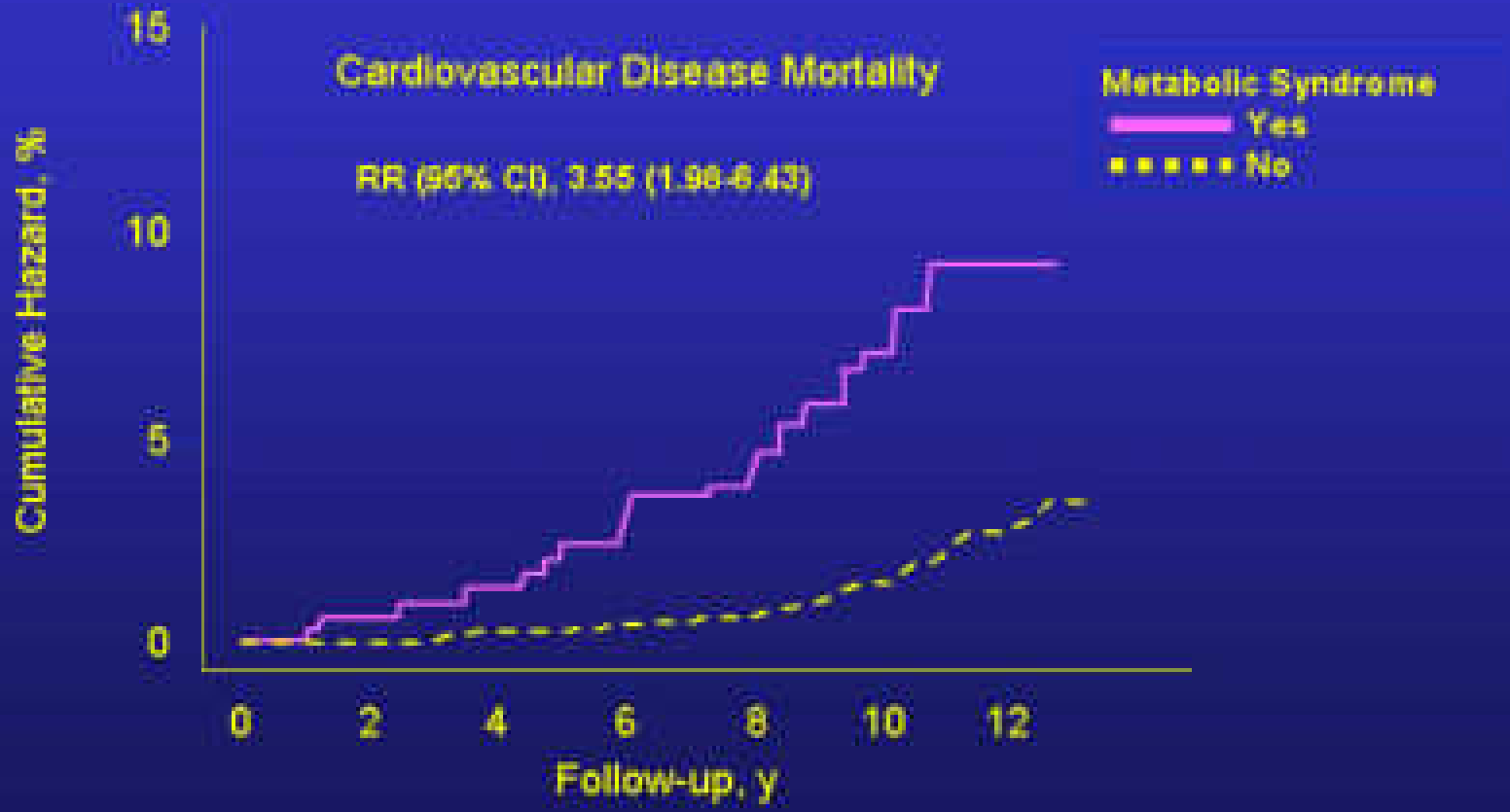
Traitement du syndrome métabolique

- Qui traiter?
- Pourquoi traiter?
- Comment traiter?


HYPERGLYCEMIA HYPERTENSION
TYPE 2 D.M.
MICROALBUMINURIA
HYPERURICEMIA
PAI-1
AMYLOID
I. R.
Hirsuitism
Hyperandrogenemia
Decreased FSH
^ LH
PCOS
REMODELING
Visceral Obesity
HYPERLIPIDEMIA
^TRIGS. dec. HDL^small dense LDL
Hyperinsulinemia
* AMYLIN


Abdominal obesity
Risk factors
Coronary heart disease
Hypertension
Dyslipidaemia
Type 2 diabetes
Treating the cause?
Treating the complications?
Management of risk of coronary heart disease

Cardiovascular Disease Mortality Increased in the Metabolic Syndrome



Metabolic Syndrome as a Risk Condition (Framingham Heart Study)

Cardiovascular disease

- Men: RR 2.50 x increased
- Women: RR 1.58 x increased

Type 2 Diabetes

- Men: RR 4.76 x increased
- Women: RR 5.66 x increased

Clinical syndromes associated with insulin resistance

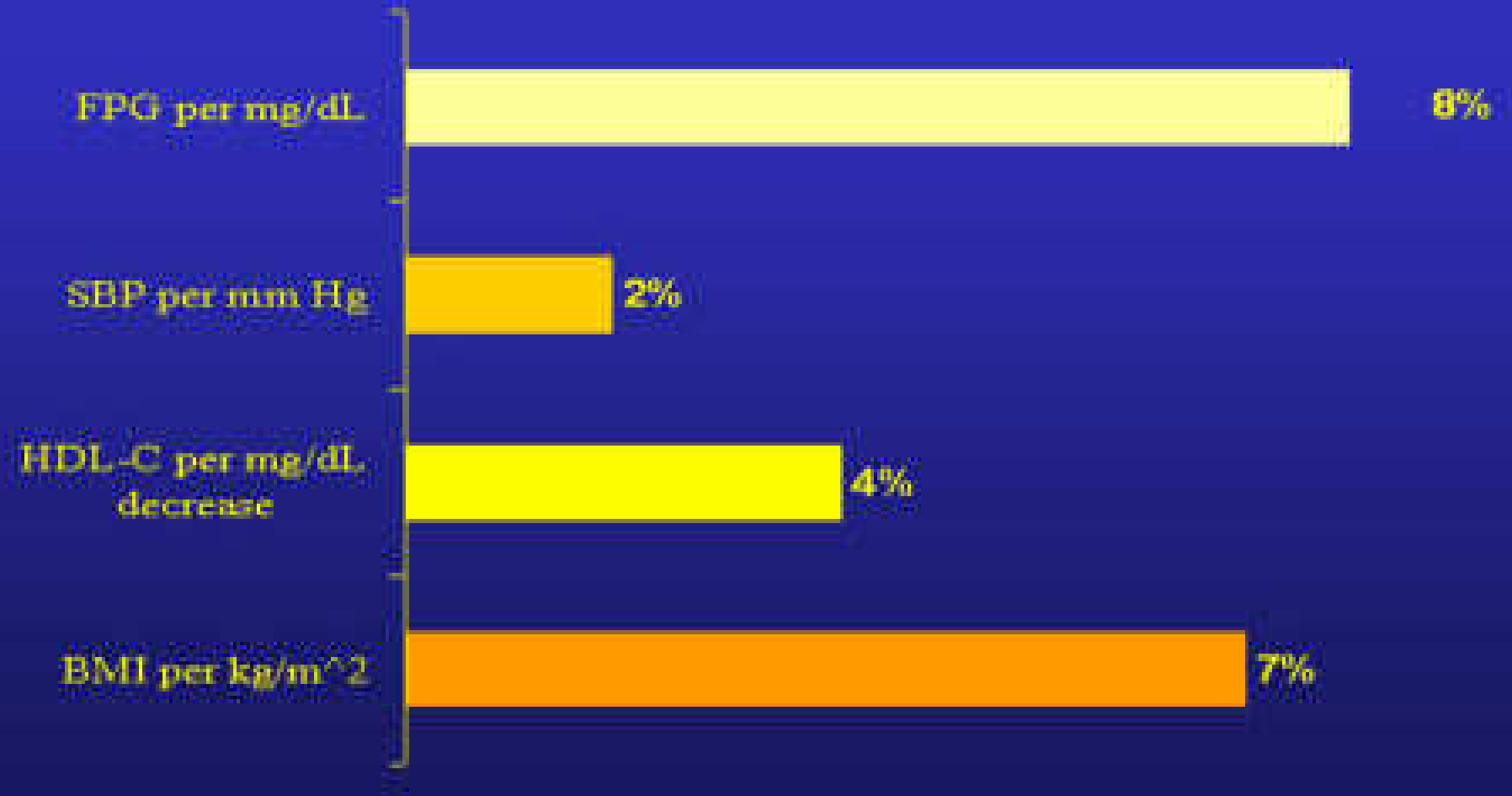
- Essential hypertension
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease
- Certain forms of cancer
- Sleep apnea
- Nephropathy and renal insufficiency

Reaven Clinical chemistry 2005

Syndrome Traits Don't Have Equal Predictive Power

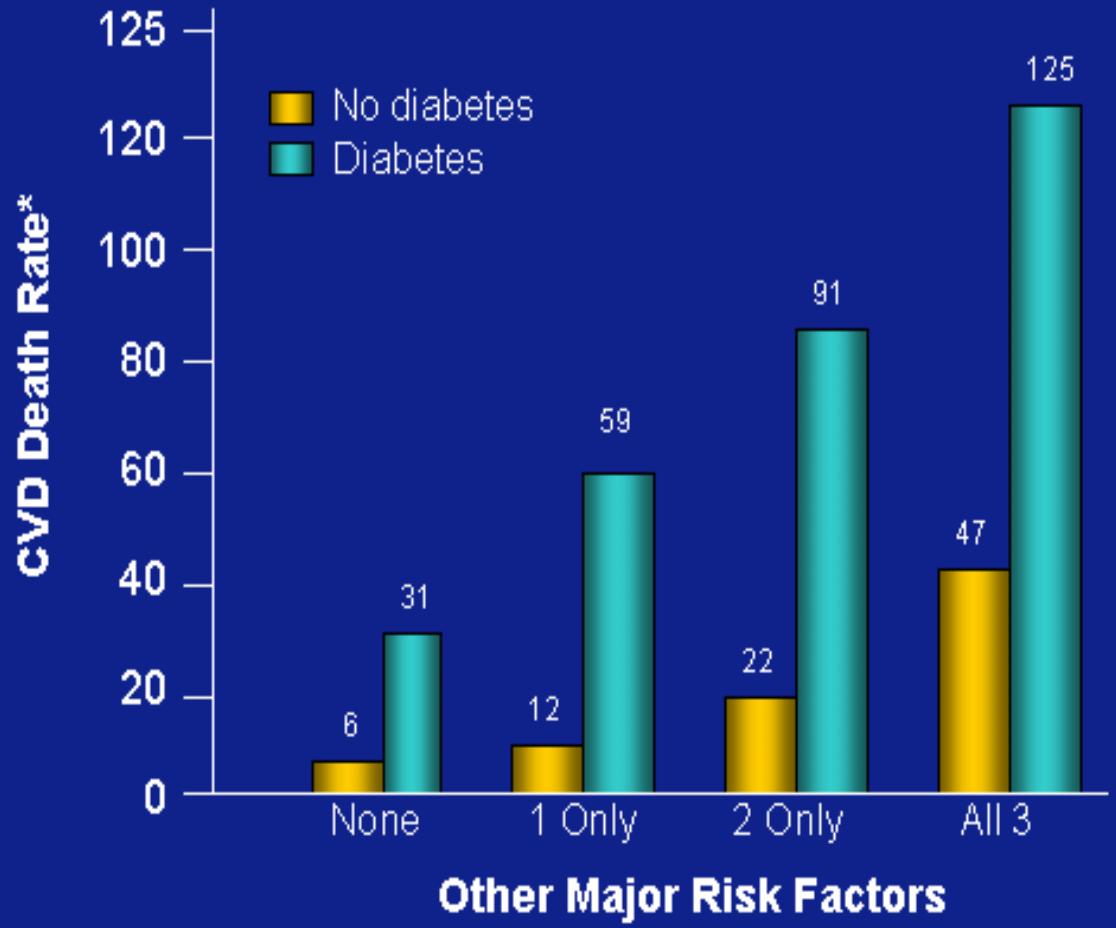
Risk of Type 2 Diabetes per Unit Change in Risk Trait Levels

San Antonio Heart Study



Stern et al Ann Intern Med 2002;136:575-81

Diabetes: A Strong Independent Risk Factor for CVD Mortality (MRFIT Study)



*Age-adjusted per 10,000 person-years.

Adapted from Stamler J, et al. *Diabetes Care*. 1993;16:434-444.

Prediction of CHD prevalence using multivariate logistic regression in NHANES

Variable*	Odds ratio
•Waist circumference	1.13
•Triglycerides	1.12
•HDL*	1.74
•Blood pressure*	1.87
•IFG	0.98
•diabetes*	1.55
•Metabolic syndrome	0.94

Alexander diabetes 2003

Odd ratio for prediction of diabetes and cardiovascular disease

Stern 2004

Diabetes care

Prediction of diabetes In the SAHS	univariate	multivariate
Metabolic syndrome	5.08	1.64
Diabetes risk score	6.46	5.50
Prediction of diabetes In MCDS	**univariate**	**multivariate**
Metabolic syndrome	2.63	1.15
Diabetes risk score	4.22	4.11

Odd ratio for prediction of diabetes and cardiovascular disease

Prediction of CVD In the SAHS	univariate	multivariate
Metabolic syndrome	3.95	1.14
Framingham risk Score	9.26	9.06

Stern 2004
Diabetes care

Hazard Ratios for Type 2 Diabetes among 13,163 Men According to Quintiles of Normal Fasting Plasma Glucose Levels

Table 2. Hazard Ratios for Type 2 Diabetes among 13,163 Men According to Quintiles of Normal Fasting Plasma Glucose Levels.*

Variable	Quintile 1 (N=2529)	Quintile 2 (N=2545)	Quintile 3 (N=2598)	Quintile 4 (N=2719)	Quintile 5 (N=2772)	P Value for Trend
Fasting plasma glucose levels (mg/dl)	50–81	82–86	87–90	91–94	95–99	—
Person-years of follow-up	13,830	13,969	14,631	15,637	16,242	—
No. of incident cases of diabetes	20	24	37	50	77	—
Adjusted risk ratio (95% CI)						
Age	1	1.47 (0.97–2.23)	1.81 (1.16–2.83)	2.33 (1.42–3.83)	3.05 (1.78–5.18)	<0.001
Age and body-mass index	1	1.35 (0.89–2.05)	1.65 (1.06–2.58)	2.17 (1.32–3.56)	2.68 (1.57–4.56)	<0.001
Age, triglyceride level, and body-mass index	1	1.30 (0.86–1.99)	1.58 (1.02–2.48)	2.05 (1.25–3.37)	2.40 (1.40–4.11)	<0.001
Multivariate†	1	1.43 (0.94–2.19)	1.82 (1.16–2.86)	2.64 (1.60–4.37)	2.84 (1.67–4.87)	<0.001

* CI denotes confidence interval. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† The multivariate Cox regression model was adjusted for age, body-mass index, and triglyceride levels as continuous variables; physical activity (≤60 or >60 minutes per week or missing information); family history of diabetes (positive, negative, or missing information); and smoking status (never smoked, former smoker, current smoker, or missing information).

Tirosh, A. et al. N Engl J Med 2005;353:1454-1462

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Relationship Between Metabolic Syndrome and Events

- Most studies show a relationship between MS and events
  - But the "whole is not greater than the parts"
- Most studies show "insulin resistance" is an independent risk factor
  - Many ways to measure IR
  - All are association studies

There are people who have:

BMI	-	>30
BP	-	>130 but <140
TRI	-	>150 but <200
FPG	-	>110 but <126
HDL	-	>40 but <60

Do they have increased CVD risk?

Do they have increased risk if they do NOT progress to frank disease?

Your input

What is your gender? **Male** **Female**

What is your age?
Input range: Male:35-65, Female:45-65 years

What is your LDL-cholesterol level?
Input range: 75-250 mg/dl

What is your HDL-cholesterol level?
Input range: 25-75 mg/dl

What is your fasting triglyceride level?
Input range: 50-400 mg/dl

What is your systolic blood pressure?
Input range: 100-225 mmHg

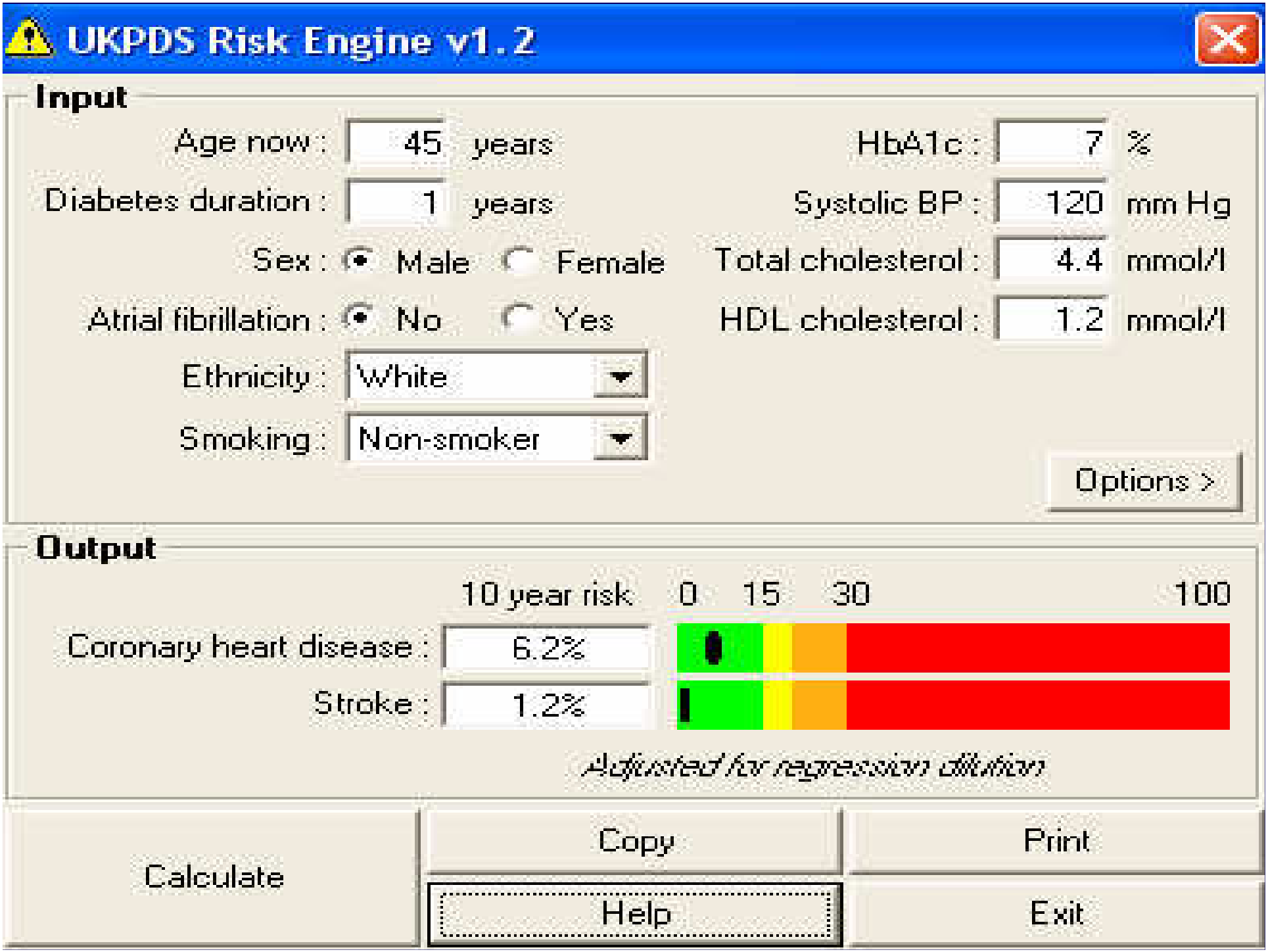
Have you smoked cigarettes at any time during the past 12 months? **No** **Yes**

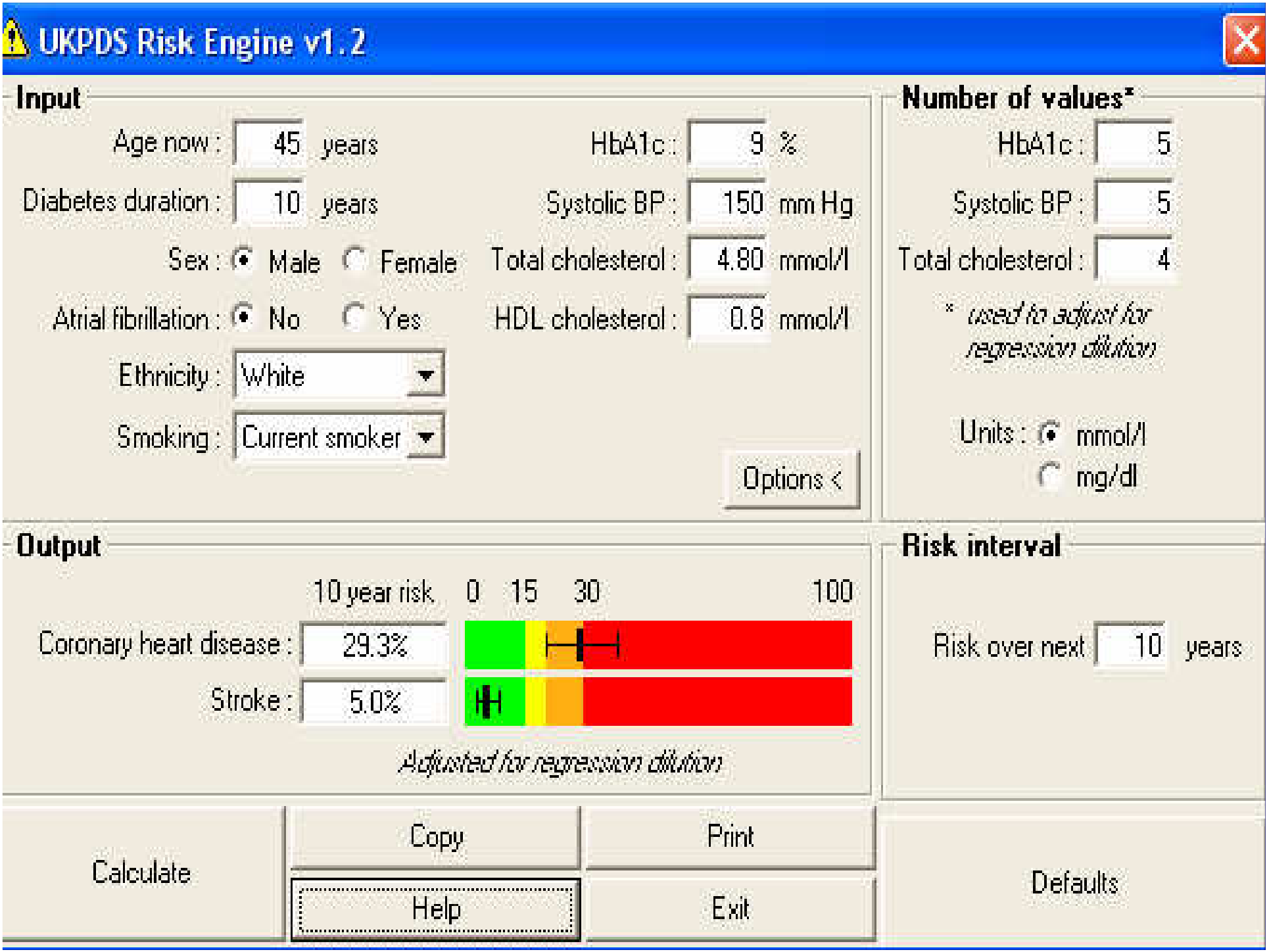
Do you suffer from diabetes mellitus? **No** **Yes**
Known diabetes mellitus or fasting blood glucose levels >=120 mg/dl

Did a first-degree relative (father, mother, brother, sister, son, daughter) suffer a heart attack (myocardial infarction) before the age of 60 years? **No** **Yes**

Your risk

	Age	LDL	HDL	Tg	DNID	hta	hxf	risk
P 1	45	150	30	240	non	oui	oui	9%
P 2	45	150	30	240	oui	non	oui	5%


UKPDS Risk Engine v1.2
Input
Age now : 45 years
Diabetes duration : 1 years
Sex : Male Female
Atrial fibrillation : No Yes
Ethnicity : White
Smoking : Non-smoker
HbA1c : 7 %
Systolic BP : 120 mm Hg
Total cholesterol : 4.4 mmol/l
HDL cholesterol : 1.2 mmol/l
Options >
Output
10 year risk
0 15 30 100
Coronary heart disease : 6.2%
Stroke : 1.2%
Adjusted for regression dilution
Calculate
Copy
Print
Help
Exit


UKPDS Risk Engine v1.2
Input
Age now : 45 years
Diabetes duration : 10 years
Sex : Male Female
Atrial fibrillation : No Yes
Ethnicity : White
Smoking : Current smoker
HbA1c : 9 %
Systolic BP : 150 mm Hg
Total cholesterol : 4.80 mmol/l
HDL cholesterol : 0.8 mmol/l
Options <
Number of values*
HbA1c : 5
Systolic BP : 5
Total cholesterol : 4
* used to adjust for regression dilution
Units : mmol/l
mg/dl
Output
10 year risk
0 15 30 100
Coronary heart disease : 29.3%
Stroke : 5.0%
Adjusted for regression dilution
Risk interval
Risk over next 10 years
Calculate
Copy
Print
Help
Exit
Defaults

The Metabolic Syndrome: Time for a Critical Appraisal

Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes care, diabetologia
septembre 2005

Summary of concern regarding the metabolic syndrome

1. Criteria are ambiguous or incomplete.
2. Value of including diabetes in definition is questionable
3. Insulin resistance as the unifying etiology is uncertain.
4. No clear basis for including/ excluding other risk factors
5. CVD risk value is variable and dependent on the specific risk factors present.

Summary of concern regarding the metabolic syndrome

6.The CVD risk associated with the syndrome appears to be no greater than the sum of its parts

7.Treatment of the metabolic syndrome is no different than the treatment for each of its parts

8. the medical value of diagnosing the syndrome is unclear

The Metabolic Syndrome: Requiescat in Pace Gerald M. Reaven

Clinical chemistry 2005

The myth of the metabolic syndrome

E. Gale
Diabetologia 2005

The concept of the metabolic syndrome appeared to be the best way to identify those persons in greatest need of clinical intervention"

Grundy SM. Clin Chem 2005

Diagnosis and Management of the Metabolic Syndrome

An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement

Grundy Circulation 2005


C’est une étoile filante !!!

Traitement du syndrome métabolique

- Qui traiter?
- Pourquoi traiter?
- Comment traiter?

Metabolic Risk

The epidemic

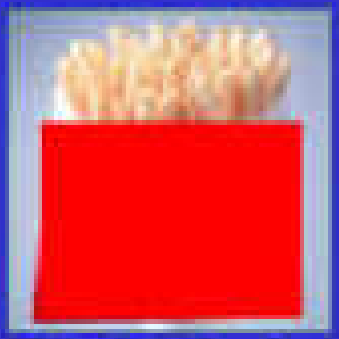
Awareness and prevention are the only ways to contain it.

Preventive measures

- Public awareness and education on metablolic risks
- Food labels and warning
- Remove of soda/vending machines in schools
- Physical activity compaigns
- Regular exercise progs in schools
- Maintain and reinforce these measures in high risk populations

FRENCH FRIES

20 Years Ago

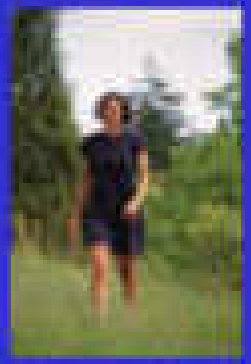


210 Calories
2.4 ounces

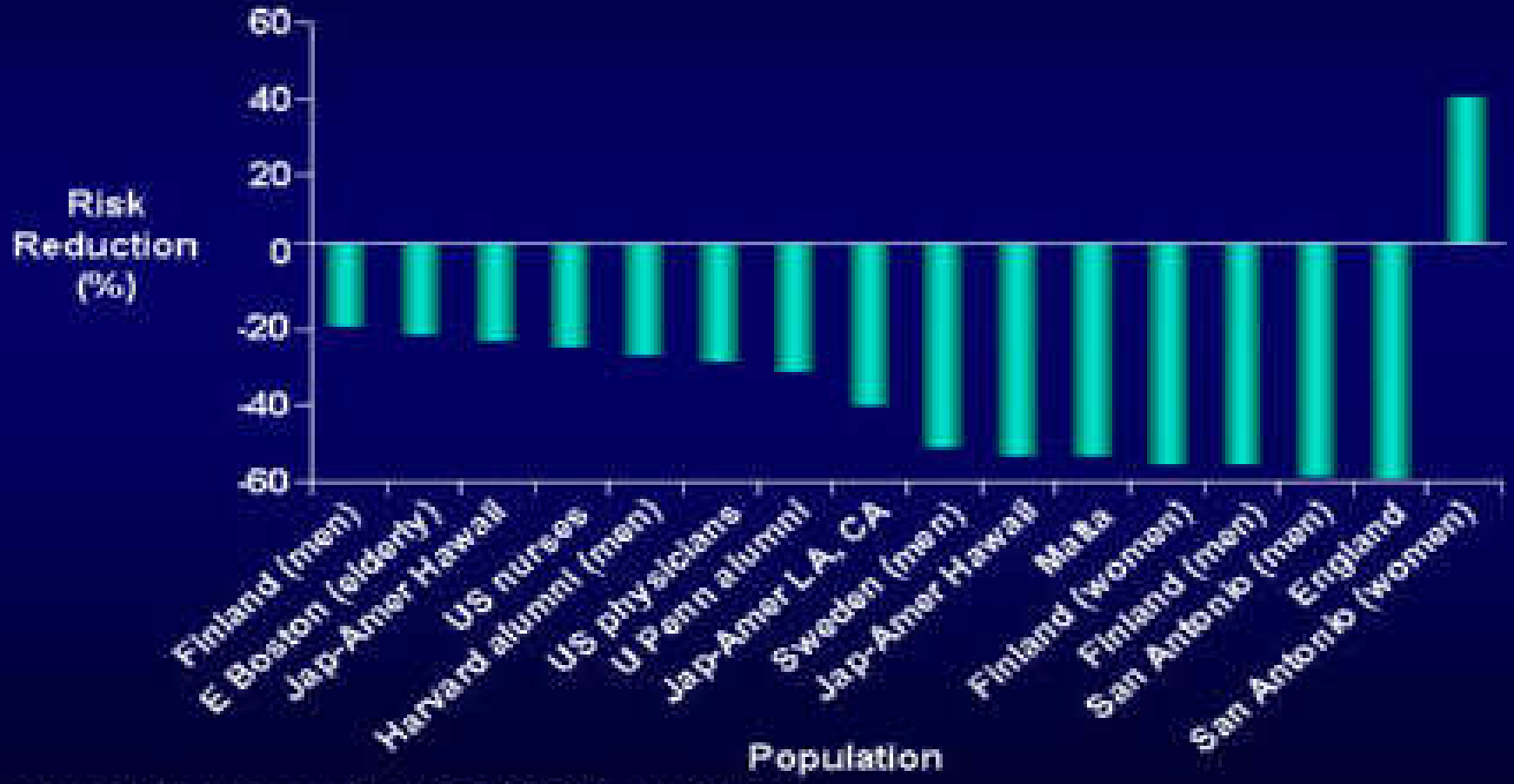
Today

610 Calories
6.9 ounces

Calorie Difference:
400 Calories=Walk
2hrs and 40 min

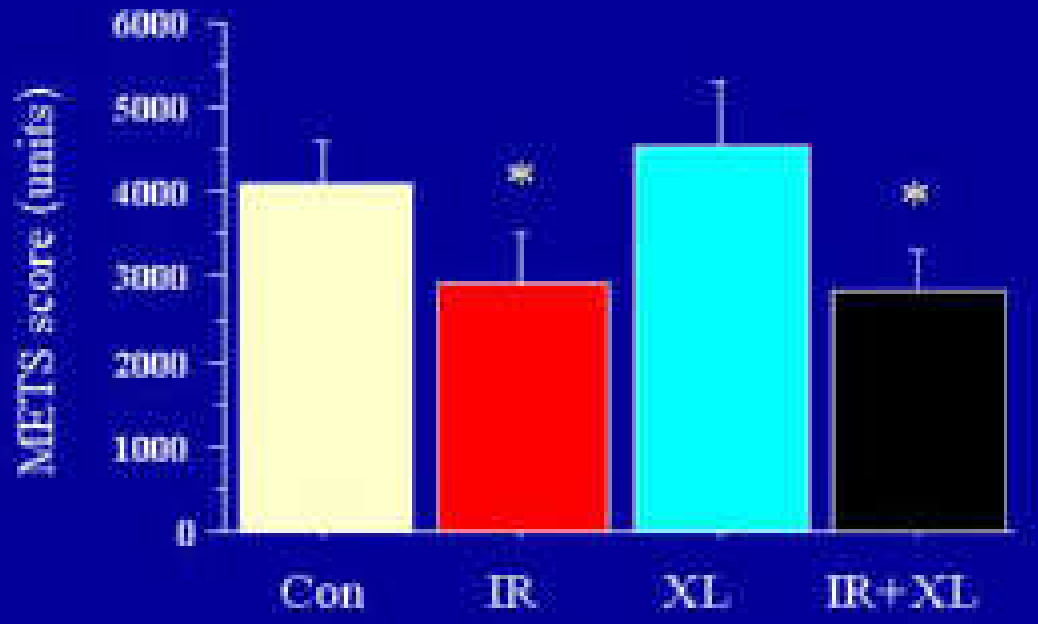


Exercise Reduces Risk of MS, DM



Adapted from Hamman R. *NCP*. 2003;(Suppl 134):29.

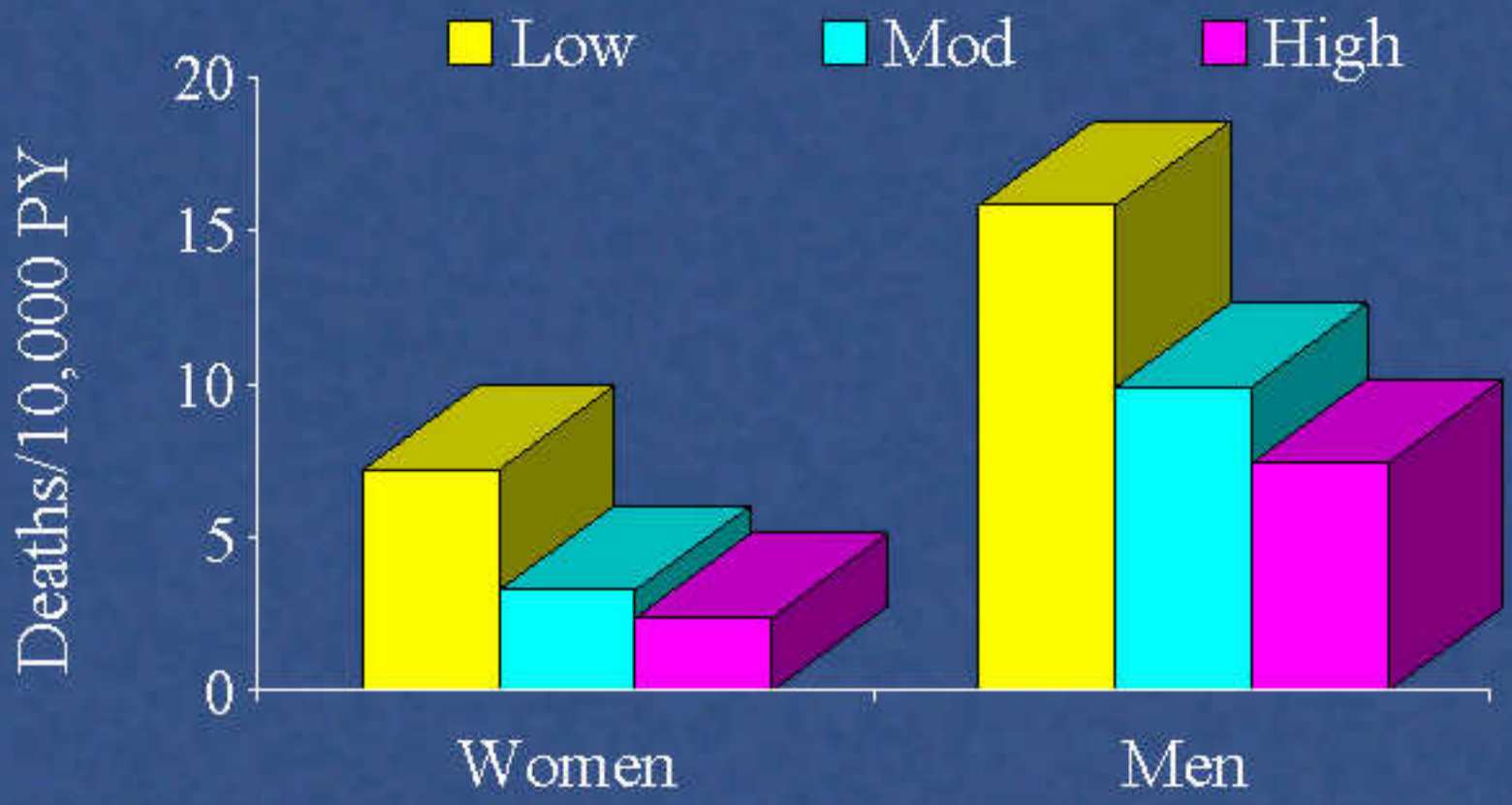
Physical activity



Ele Ferrannini ADA 2005 RISC study

The Cooper Institute
Dallas • Denver

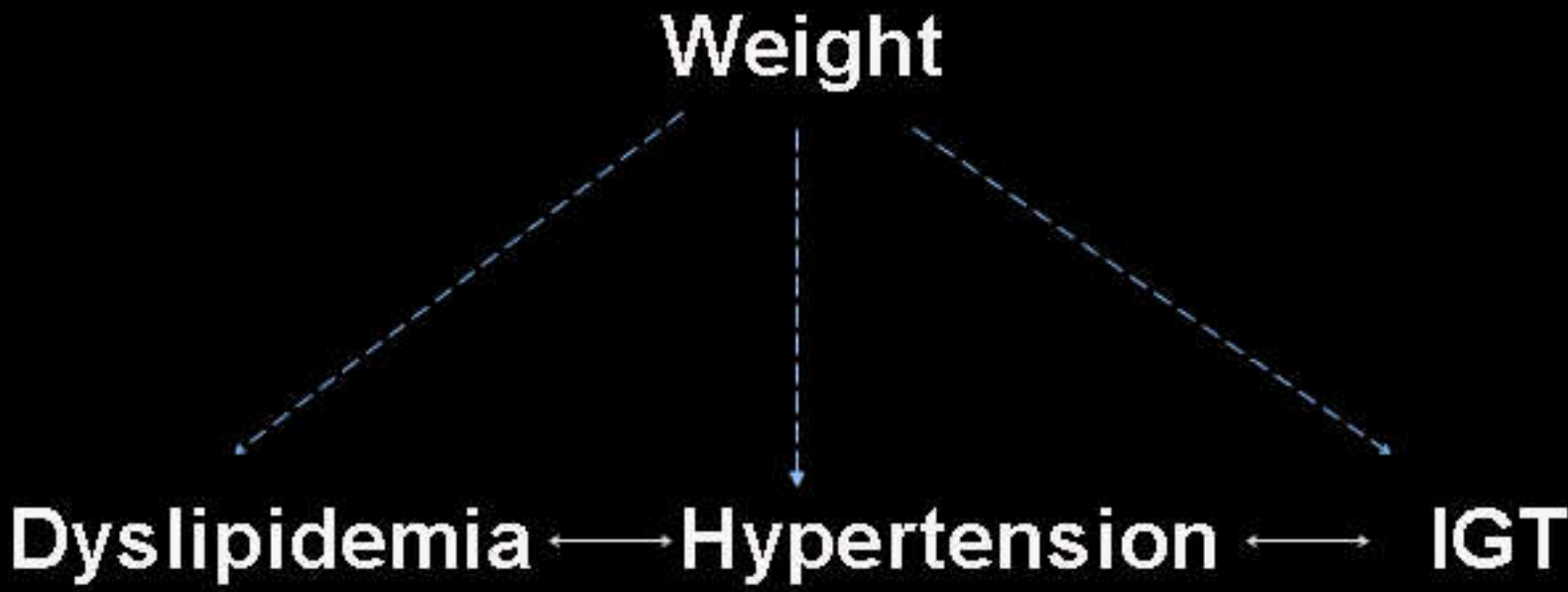
CVD Death Rates by Fitness, 7,080 Women & 25,340 Men



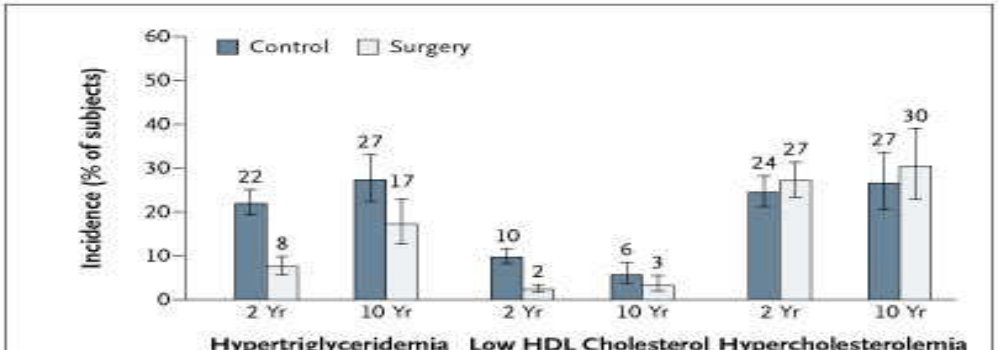
Adjusted for BMI, age, exam year, and other risk factors

New Treatment Paradigm

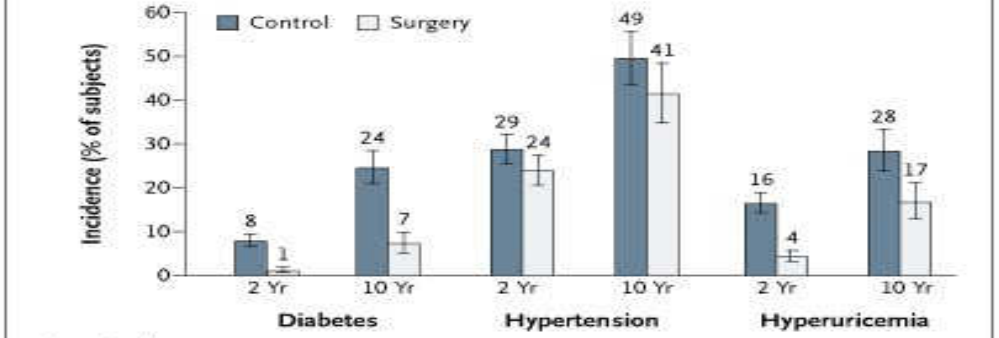
Management of weight first, followed by an integrated treatment approach



Incidence of Diabetes, Lipid Disturbances, Hypertension, and Hyperuricemia among Subjects in the SOS Study over 2- and 10-Year Periods



No. of subjects						
Control	801	281	1174	440	596	188
Surgery	731	225	1293	431	504	135
Odds ratio	0.29	0.61	0.21	0.57	1.27	1.16
95% CI	0.21–0.41	0.39–0.95	0.14–0.32	0.29–1.15	0.95–1.69	0.69–1.95
P value	<0.001	0.03	<0.001	0.12	0.11	0.57



No. of subjects						
Control	1402	539	770	279	1017	382
Surgery	1489	517	623	215	1044	342
Odds ratio	0.14	0.25	0.78	0.75	0.22	0.49
95% CI	0.08–0.24	0.17–0.38	0.60–1.01	0.52–1.08	0.15–0.31	0.34–0.71
P value	<0.001	<0.001	0.06	0.13	<0.001	<0.001

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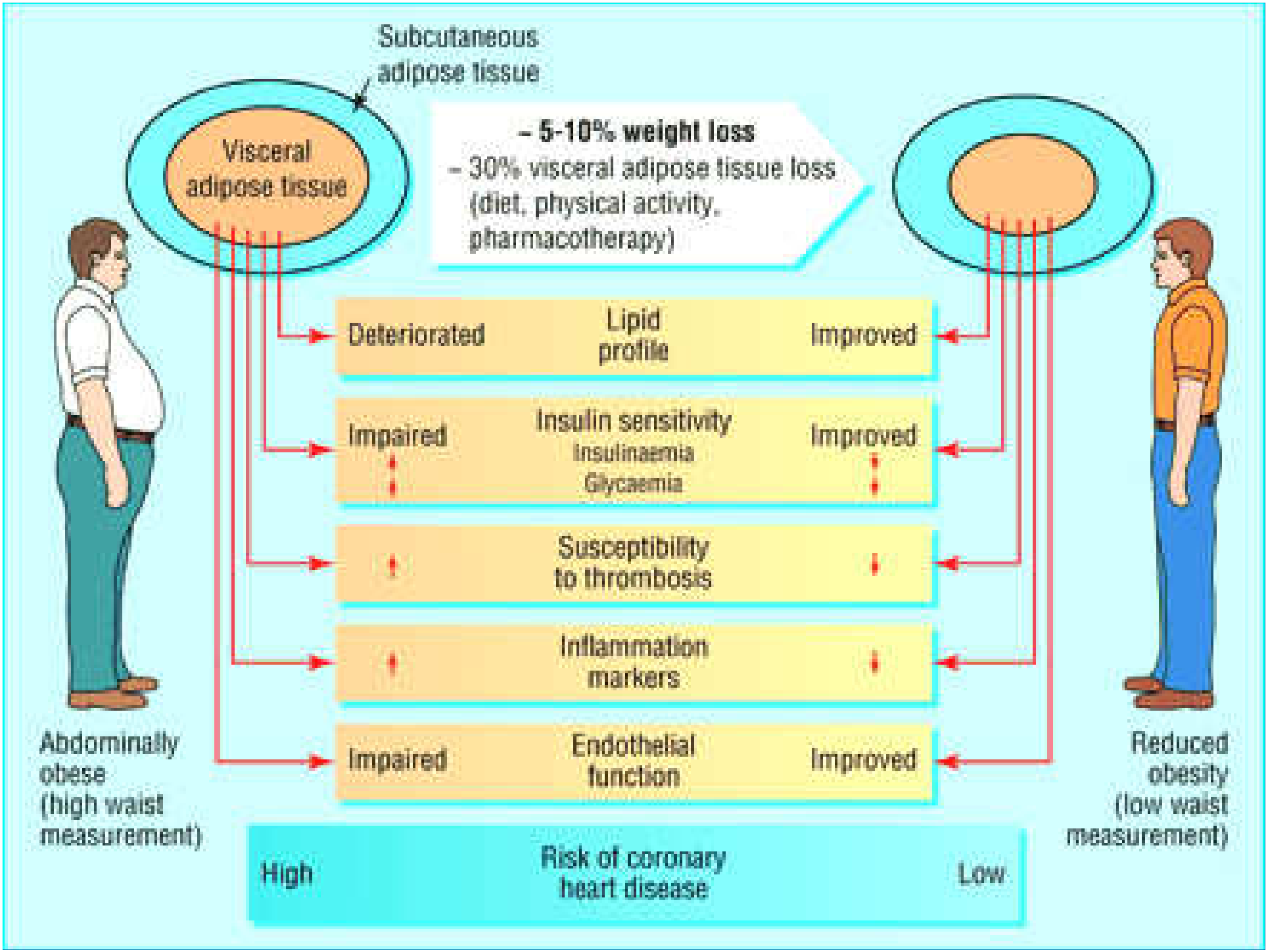

Subcutaneous adipose tissue
Visceral adipose tissue
– 5-10% weight loss
– 30% visceral adipose tissue loss (diet, physical activity, pharmacotherapy)
Deteriorated
Lipid profile
Improved
Impaired
Insulin sensitivity
Insulinaemia
Glycaemia
Improved
Susceptibility to thrombosis
Inflammation markers
Impaired
Endothelial function
Improved
Abdominally obese (high waist measurement)
Reduced obesity (low waist measurement)
High
Risk of coronary heart disease
Low

Therapeutics goals and recommendations

- Physical inactivity :
  - **Goal : regular moderate- intensity physical**
  - **Recommendations 30- 60 min moderate intensity exercise daily**

R.Ekel. Lancet 2005

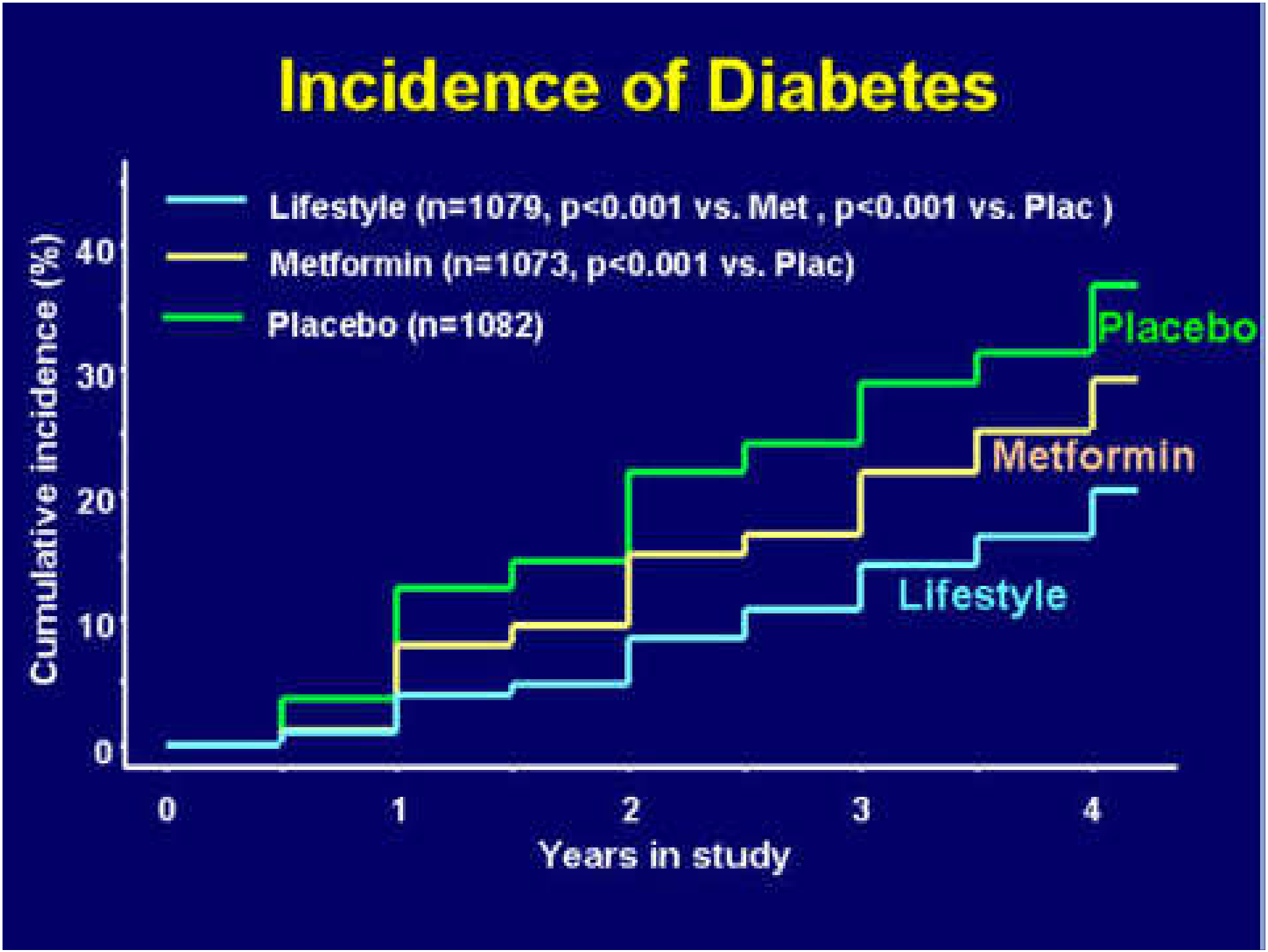
Therapeutics goals and recommendations

Anti atherogenic diet :

- **Goals : reduced intakes of saturated fats, trans fats and cholesterol**
- **Recommendations : saturated fats < 7% of total calories; reduce trans fats, dietary cholesterol < 200 mg daily; total fat < 25-45 % of total calories.**
- **simple sugars should be limited.**

R.Ekel. Lancet 2005

Incidence of Diabetes



Therapeutics goals and recommendations

- LDL-C levels:

  - **Goals : high risk patients : LDL< 100mg/100ml, optional < 70**

    moderately high risk : LDL< 130mg/ 100ml, optional < 100mg/ 100ml

    moderate risk patients : LDL < 130mg/ 100ml

  - **Recommendations : lifestyle therapies and LDL-cholesterol lowering drug to achieve recommended goal**

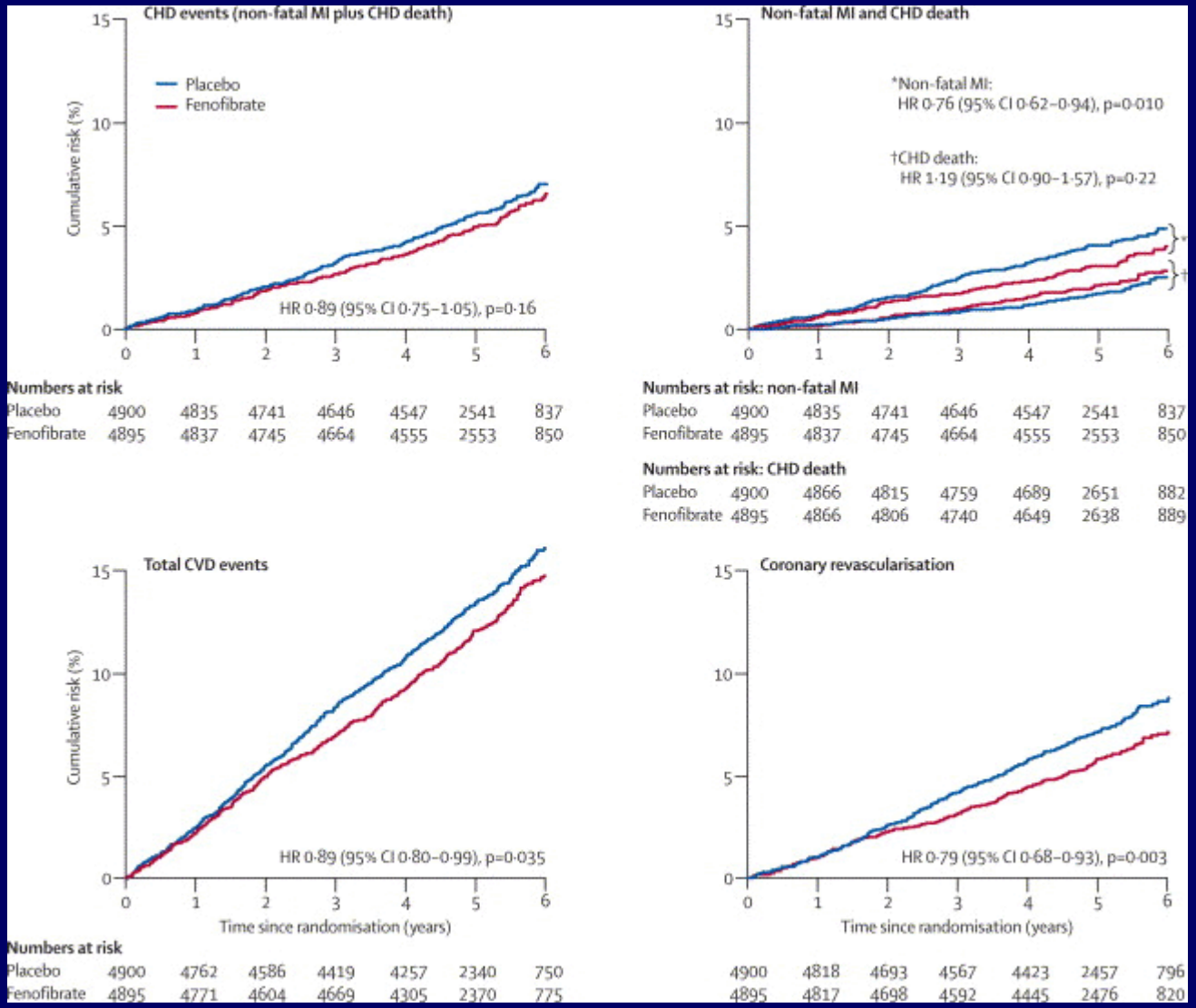
R.Ekel. Lancet 2005

Therapeutics goals and recommendations

- High triglyceride or/ and HDL-C :
  - **Goal : insufficient data to establish goal**
  - **Recommendations: high risk patients, consider adding fibrates (preferably fenofibrate), fish oil or nicotinic acid to LDL-lowering drug therapy**

R.Ekel. Lancet 2005

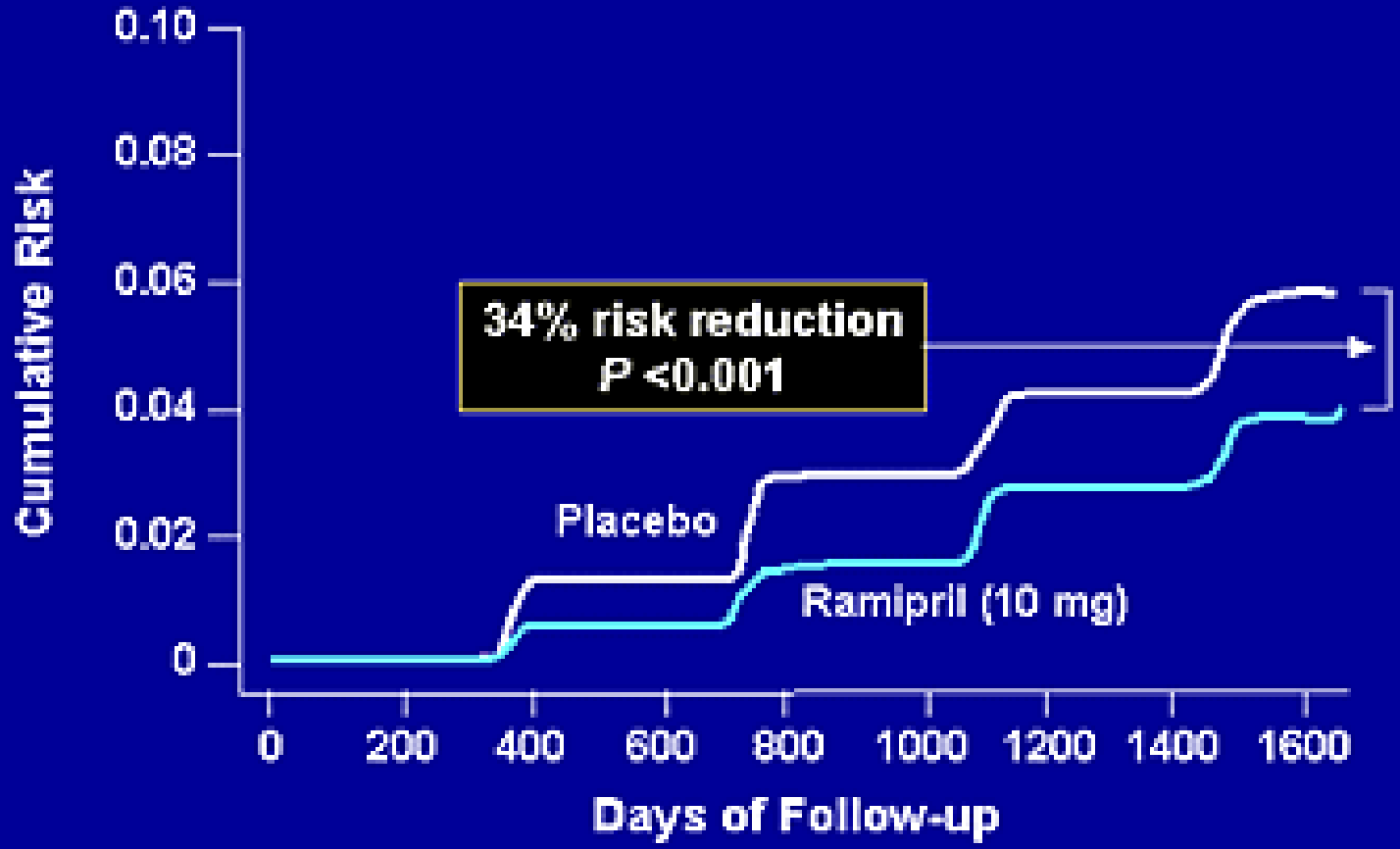
- AHA 2005
  - Fenofibrate is useful in primary prevention!
  - Fish oil is useful in secondary prevention?


CHD events (non-fatal MI plus CHD death)
Placebo
Fenofibrate
Cumulative risk (%)
HR 0·89 (95% CI 0·75–1·05), p=0·16
Numbers at risk
Placebo 4900 4835 4741 4646 4547 2541 837
Fenofibrate 4895 4837 4745 4664 4555 2553 850
Non-fatal MI and CHD death
*Non-fatal MI:
HR 0·76 (95% CI 0·62–0·94), p=0·010
†CHD death:
HR 1·19 (95% CI 0·90–1·57), p=0·22
Numbers at risk: non-fatal MI
Placebo 4900 4835 4741 4646 4547 2541 837
Fenofibrate 4895 4837 4745 4664 4555 2553 850
Numbers at risk: CHD death
Placebo 4900 4866 4815 4759 4689 2651 882
Fenofibrate 4895 4866 4806 4740 4649 2638 889
Total CVD events
Cumulative risk (%)
HR 0·89 (95% CI 0·80–0·99), p=0·035
Time since randomisation (years)
Numbers at risk
Placebo 4900 4762 4586 4419 4257 2340 750
Fenofibrate 4895 4771 4604 4669 4305 2370 775
Coronary revascularisation
HR 0·79 (95% CI 0·68–0·93), p=0·003
Time since randomisation (years)
4900 4818 4693 4567 4423 2457 796
4895 4817 4698 4592 4445 2476 820

High blood pressure

- Reduce BP to at least achieve BP of <140/90 mm Hg (or <130/80 mm Hg if diabetes present).
- Role of ARB and ACEI is debatable as first line.

HOPE: Reduction in New-Onset Diabetes



- Significantly fewer patients in the ramipril group presented with new-onset diabetes compared with patients in the placebo group.

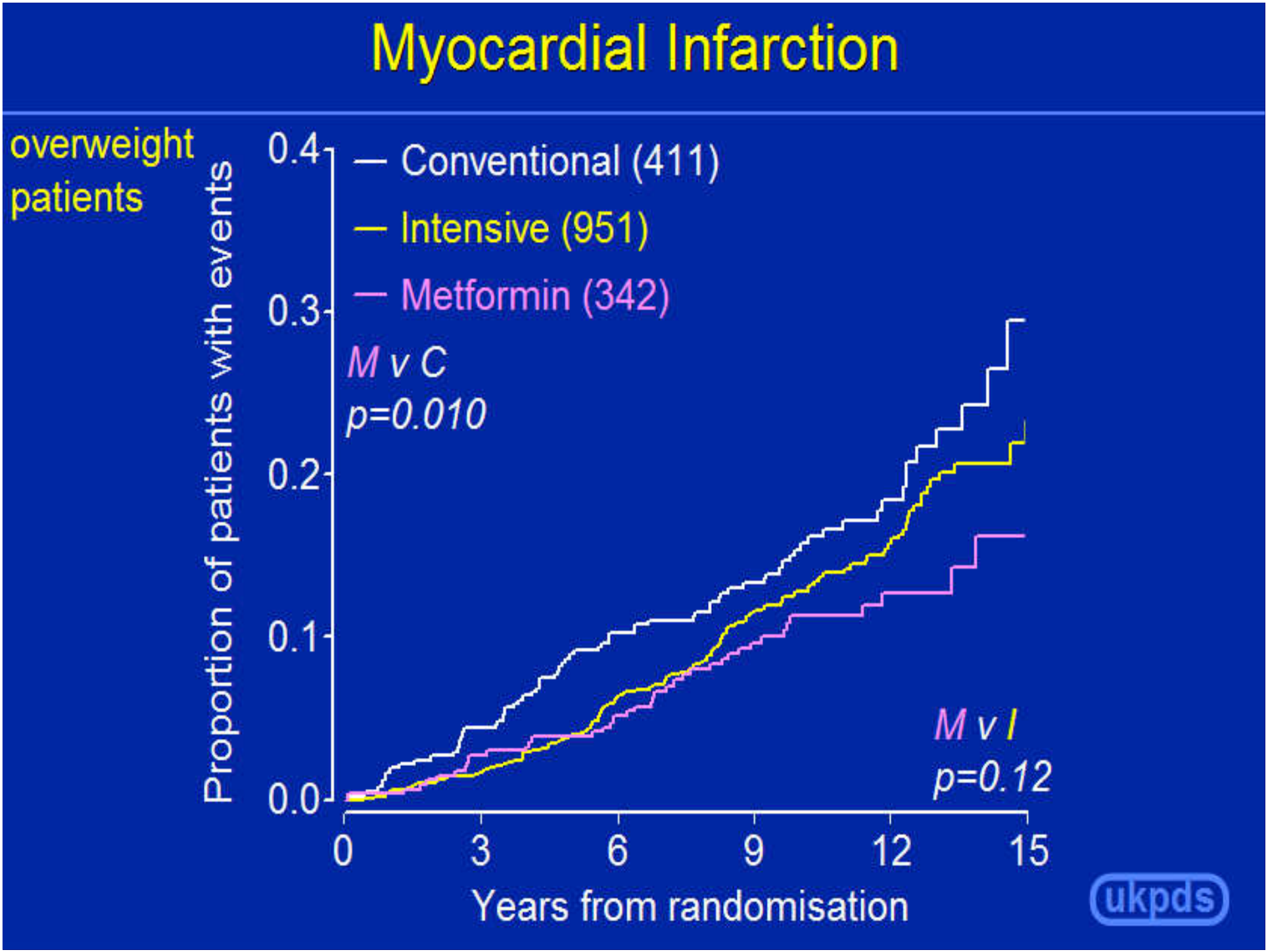
Yusuf S, et al. *JAMA*. 2001;286:1882–1885.

Therapeutics goals and recommendations

- Elevated glucose :
  - **Goals : maintenance or reduction in fasting glucose if >100mg/ 100 m. HbA1c < 7%**
  - **Recommendations : lifestyle therapies; add hypoglycemic agents as necessary to achieve goal fasting glucose or HbA1c. Use metformin or acarbose or glitazones in first line**
  - **Unsolved problems : treatment of IGT, treatment of insulin resistance??**

R.Ekel. Lancet 2005

Myocardial Infarction



STOP NIDDM

Time to Develop Diabetes

ITT

Primary objective:
Reduction in incidence of type 2 diabetes on Acarbose in IGT subjects

based on one positive OGTT

24.8 %

(p= 0.0015)

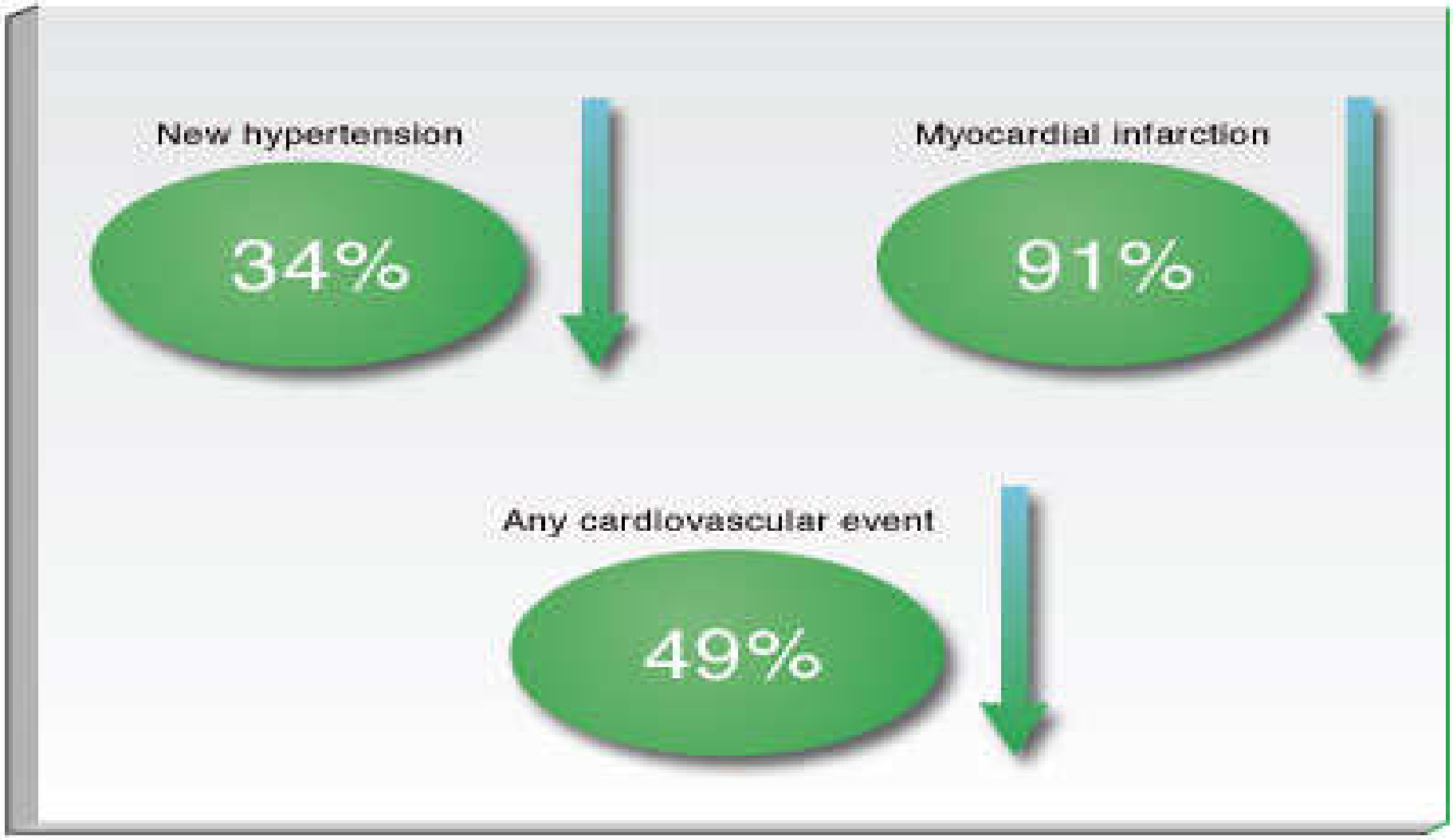
based on two consecutive positive OGTTs

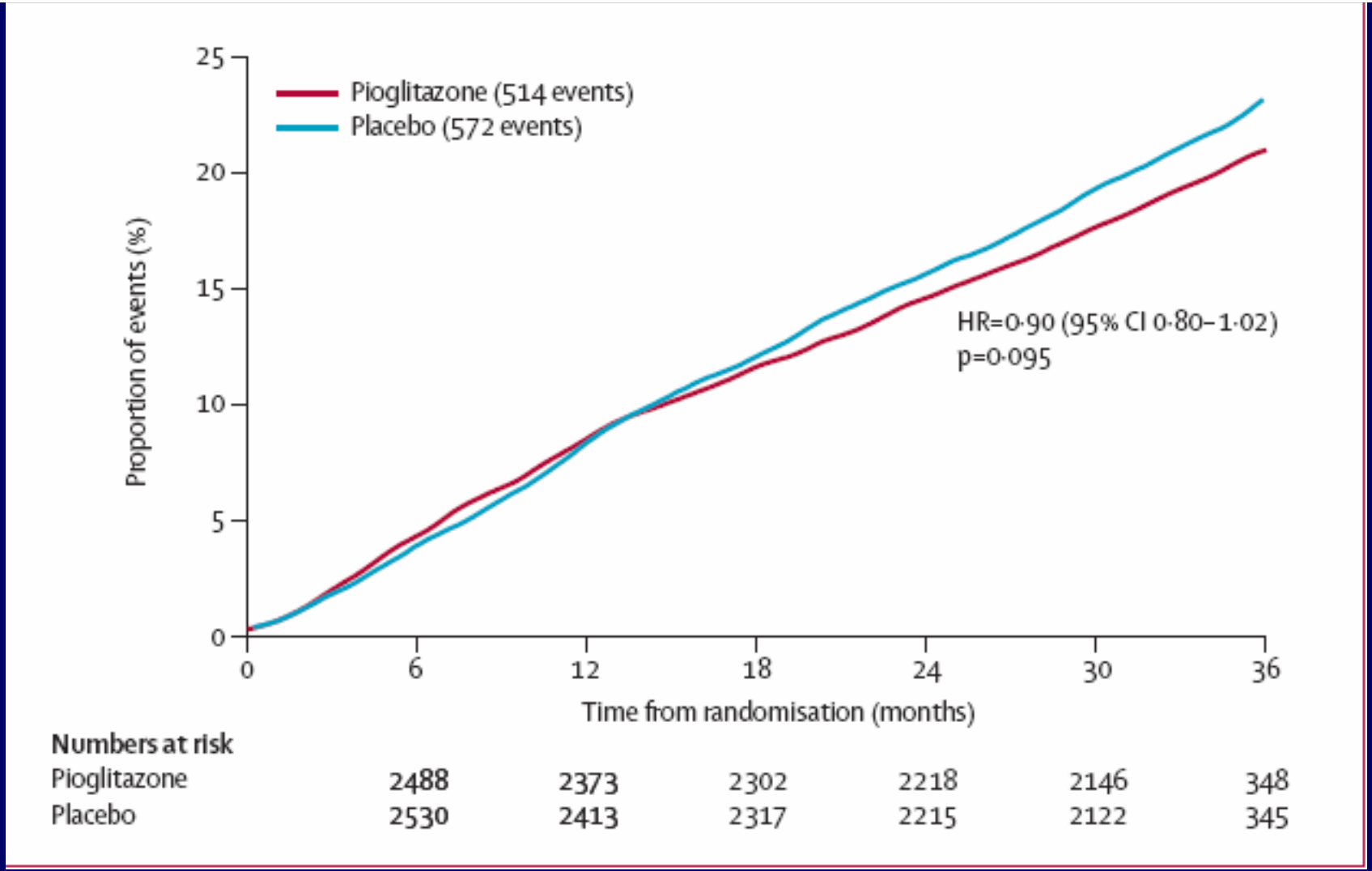
35.8 %

(p= 0.0017)

Chiasson J-L et al. Lancet (2002); 359: 2072-77

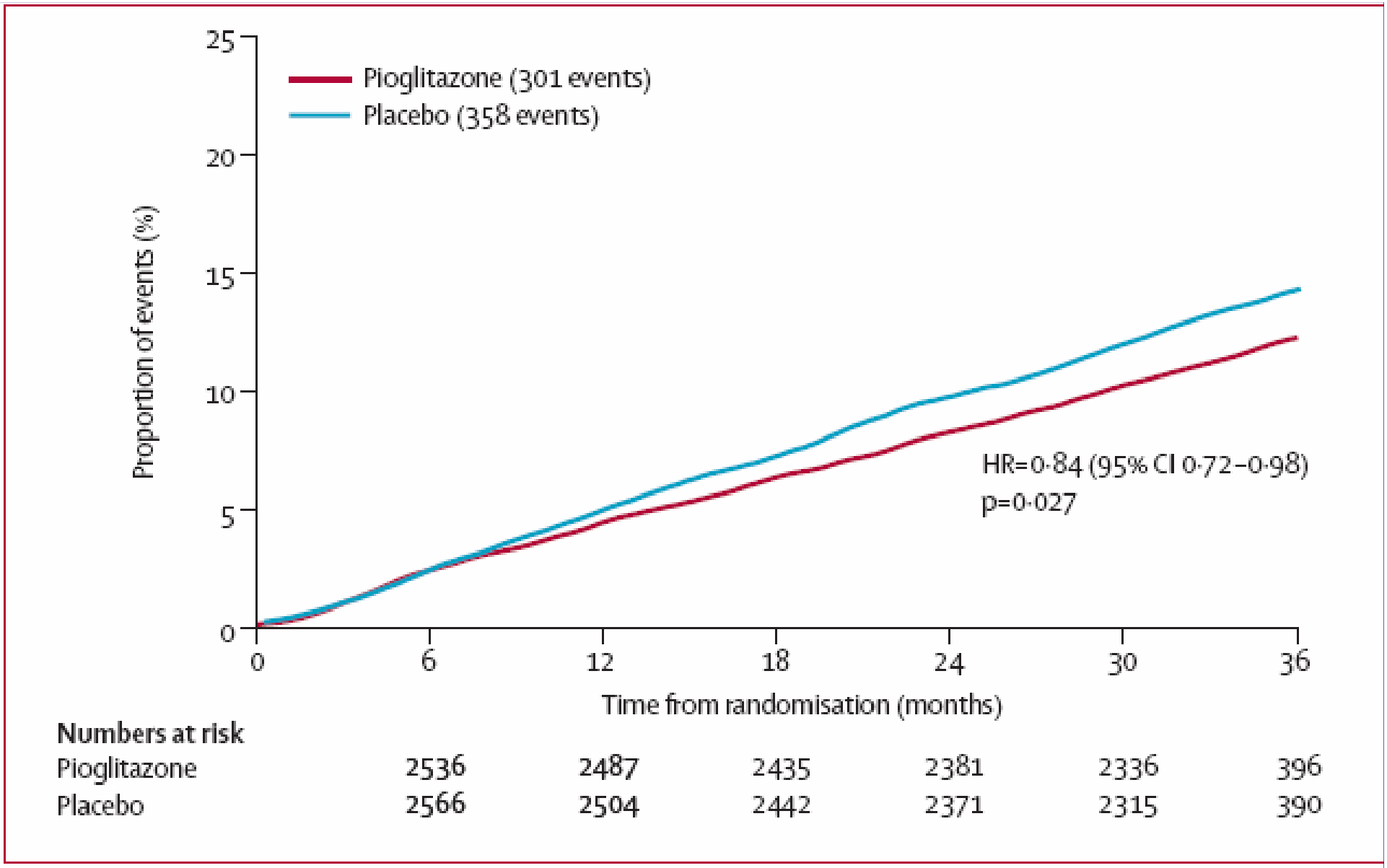
Acarbose significantly reduces the risk of cardiovascular disease.





PROspective pioglitAzone Clinical Trial In macroVascular Events

Lancet 2005



PROspective pioglitAzone Clinical Trial In macroVascular Events

Lancet 2005

Therapeutics goals and recommendations

- Prothrombotic state:
  - **Goal : reduction of prothrombotic state**
  - **Recommendations: high risk patients : initiate low-dose aspirin therapy; consider clopidogrel if aspirin is contraindicated**
  - **Moderately high-risk patients: considerlow dose aspirin**

R.Ekel. Lancet 2005

Therapeutic goals and recommendations

- Proinflammatory state :
  - **Goals and recommendations non specified**

R.Ekel. Lancet 2005

Conclusions and recommendations

- Adults with any major risk factor should be evaluated for the presence of other CVD risk factors.

- Patients with CVD risk variable above cutpoint for normal should receive counseling for life-style modification.

- At cutpoint indicative of frank disease (BP>140, glucose > 126 mg/100ml …), treatment should correspond to established guidelines

Conclusions and recommendations

- The label M.S. may help some health providers to research other risk factors, but we consider the risk engines more helpful (FHS, PROCAM, UKPDS).
- All CVD risk factors should be individually and aggressively treated.
- Until now, no appropriate pharmacological for the metabolic syndrome.
- The insulin sensitizers (metformin, acarbose, pioglitazone) appear reduce CVD in diabetics.

上医医未病之病

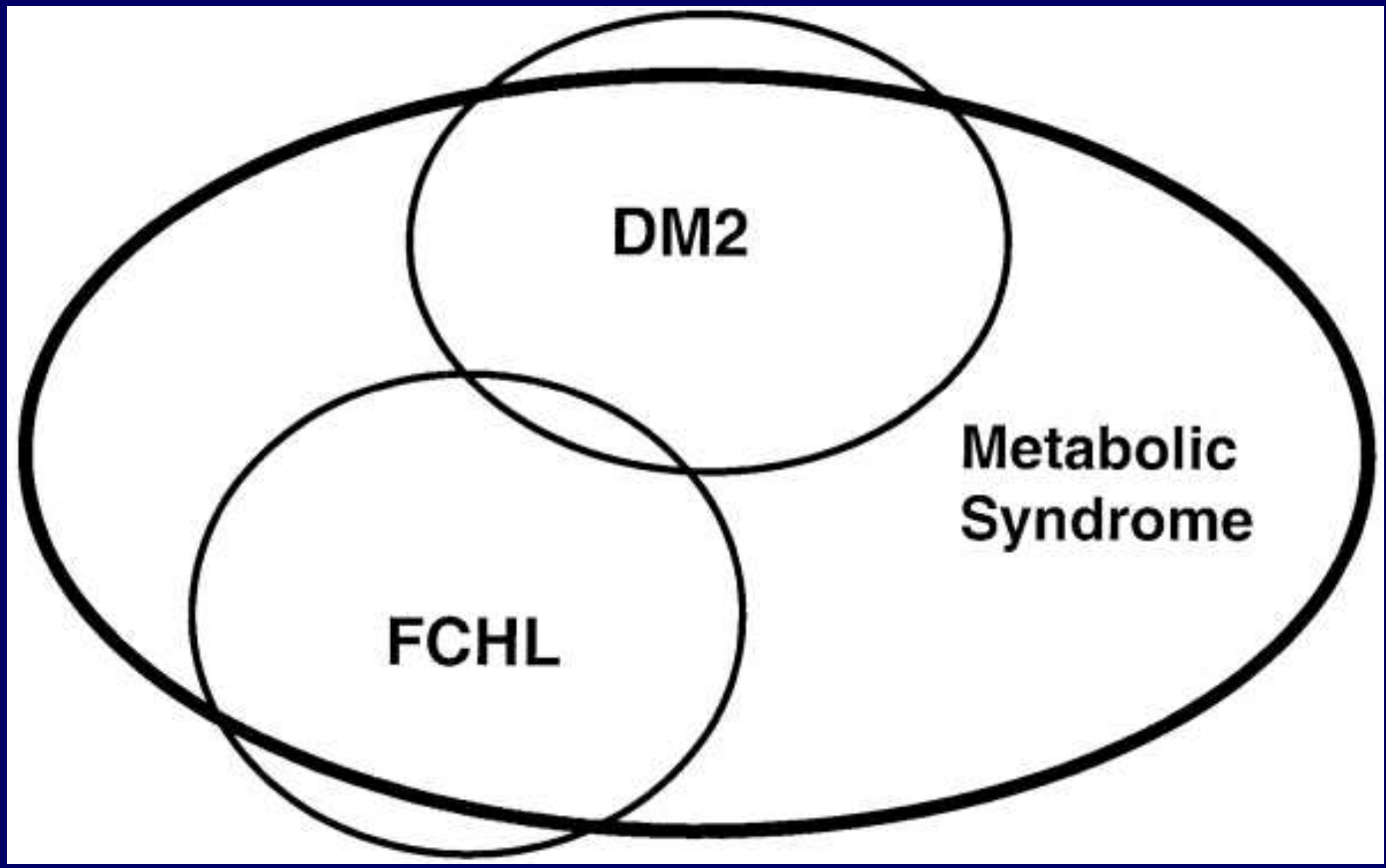
中医医将病之病

下医医已病之病

～黄帝：内経～

Superior doctors prevent the disease.
Mediocre doctors treat the disease before evident.
Inferior doctors treat the full blown disease.
–Huang Dee: Nai-Ching (2600 B.C. 1st Chinese Medical Text.)

FIG. 5. DM2 and FCHL share many of the phenotypic features of the metabolic syndrome (increased abdominal adiposity, insulin resistance, hypertension, and dyslipidemia), but appear to convey a greater risk of CAD than the metabolic syndrome alone



Carr, M. C. et al. J Clin Endocrinol Metab 2004;89:2601-2607

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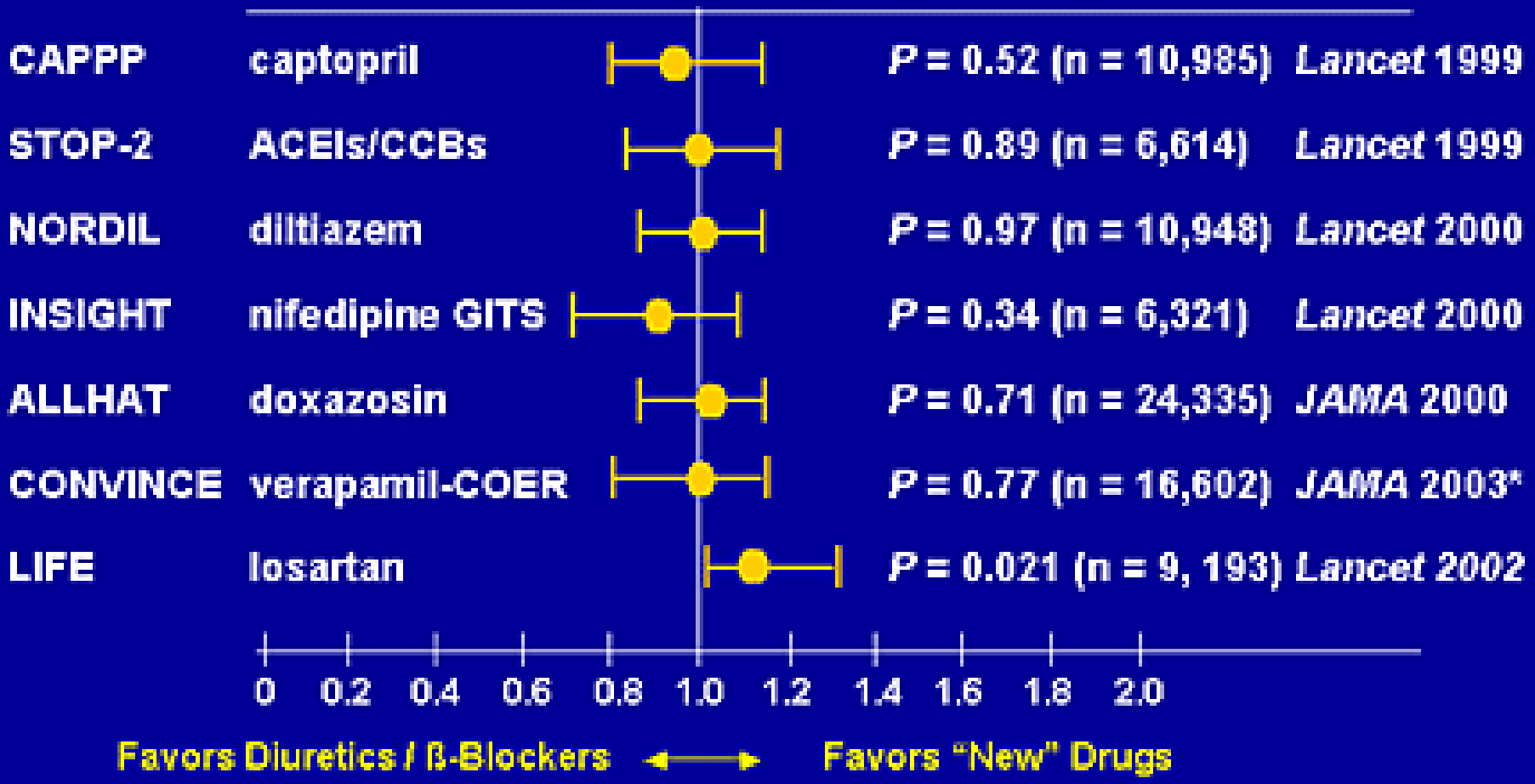
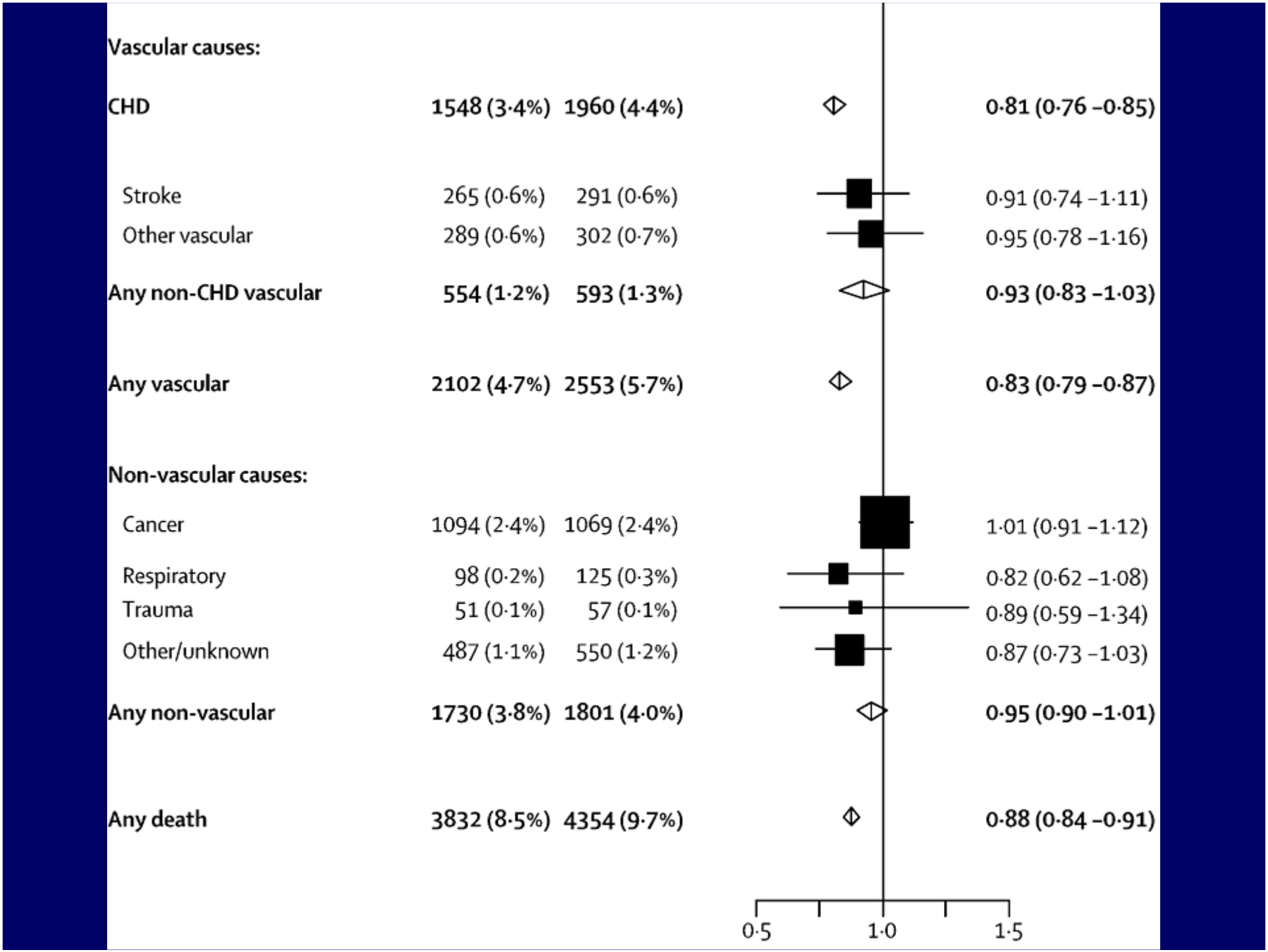
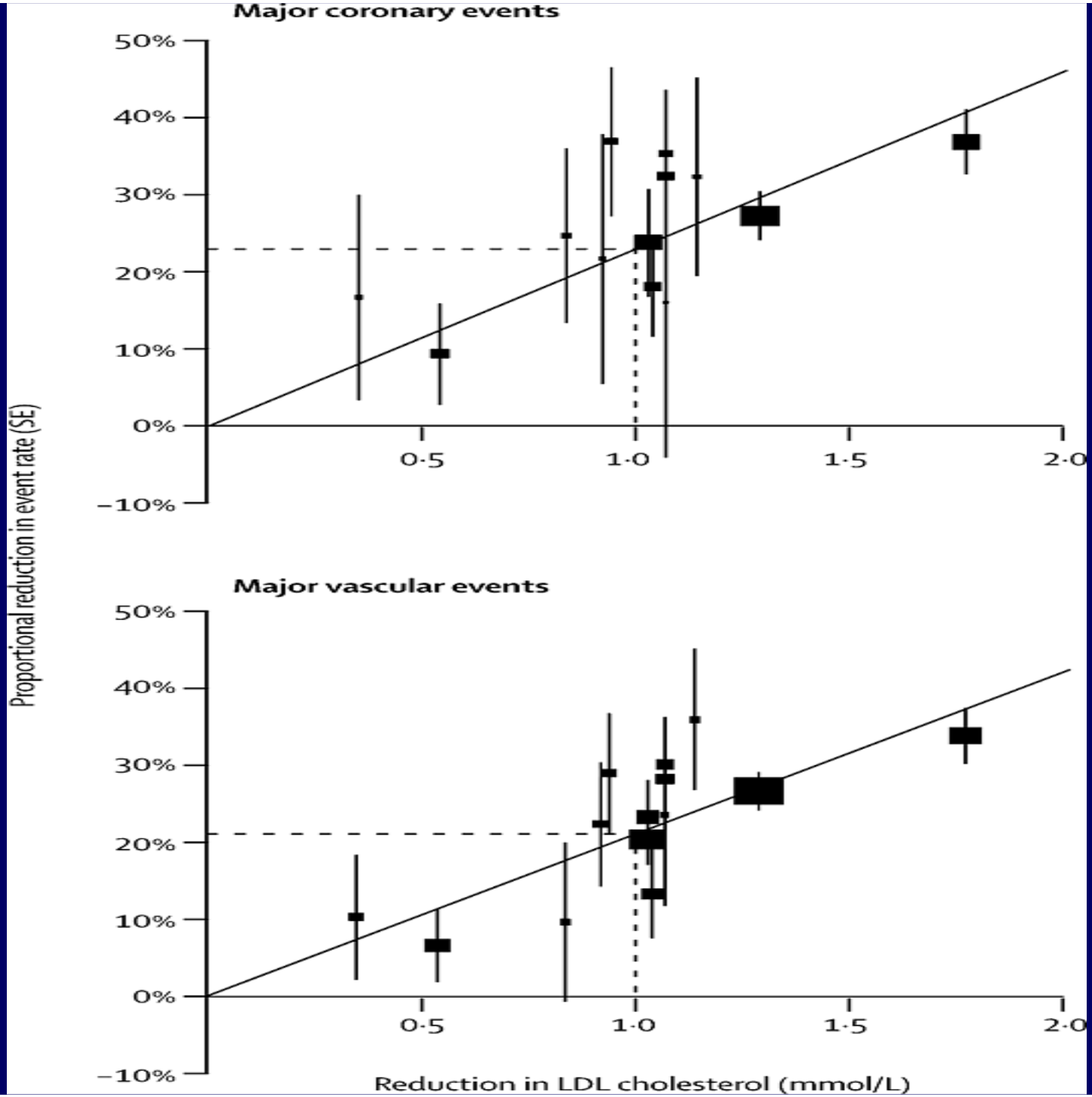
Recent Hypertension Trials With "New" Versus "Old" Drugs

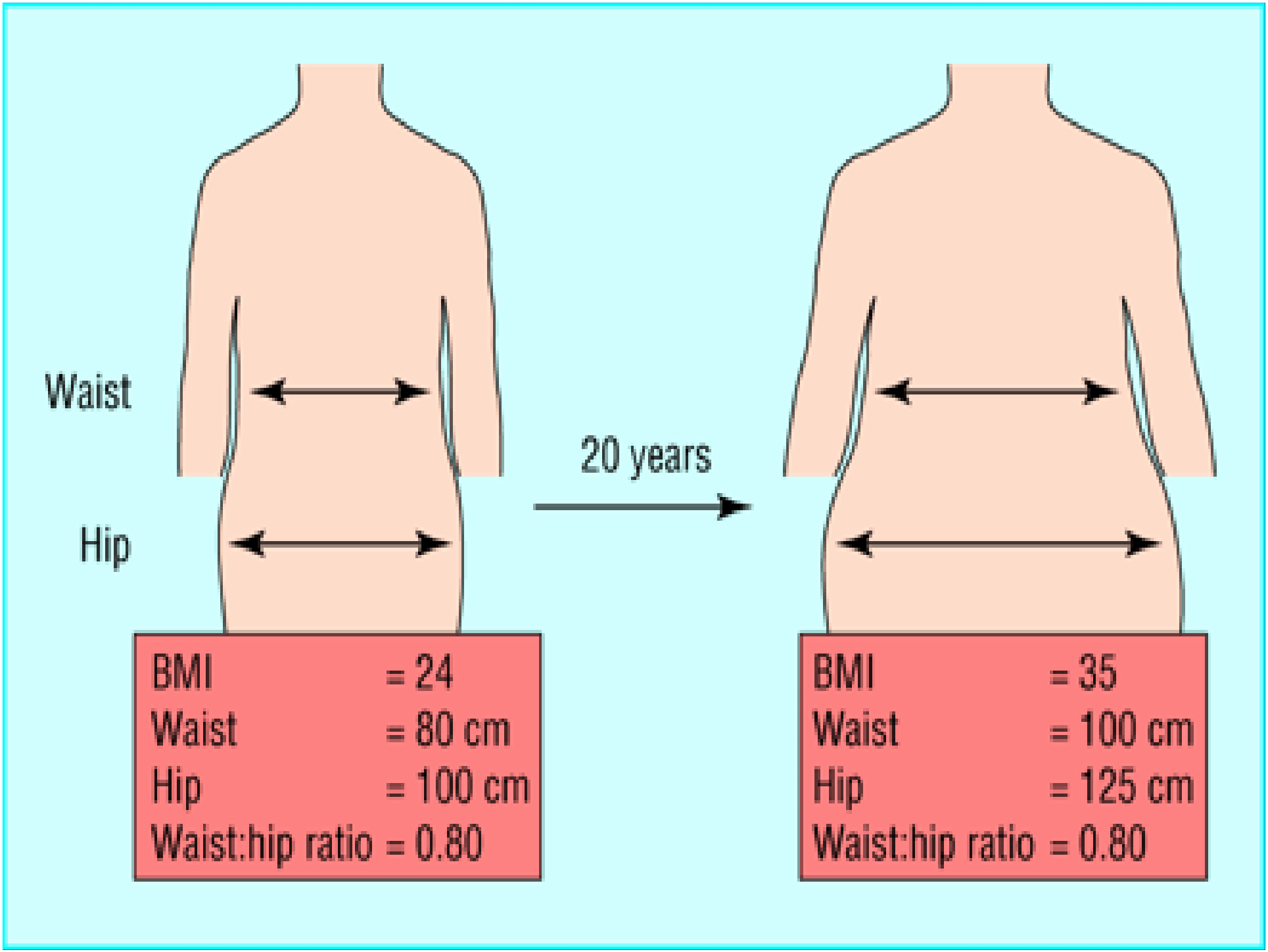


Kjeldsen SE, et al. *Lancet* 2000;356:1929-1930.

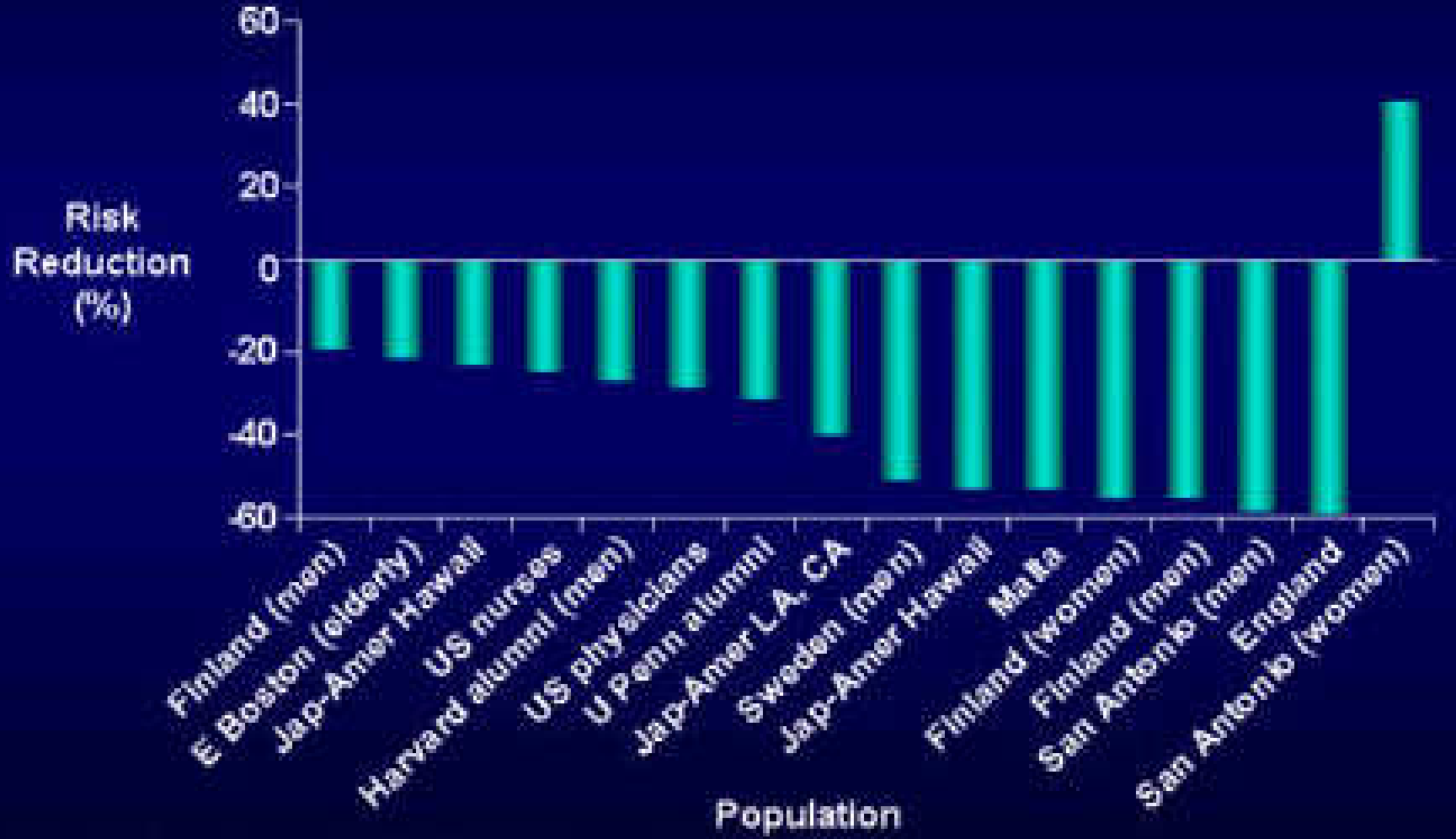
*Black HR, et al. *JAMA*. 2003;289:2073-2082.


Vascular causes:
CHD 1548 (3·4%) 1960 (4·4%) 0·81 (0·76 –0·85)
Stroke 265 (0·6%) 291 (0·6%) 0·91 (0·74 –1·11)
Other vascular 289 (0·6%) 302 (0·7%) 0·95 (0·78 –1·16)
Any non-CHD vascular 554 (1·2%) 593 (1·3%) 0·93 (0·83 –1·03)
Any vascular 2102 (4·7%) 2553 (5·7%) 0·83 (0·79 –0·87)
Non-vascular causes:
Cancer 1094 (2·4%) 1069 (2·4%) 1·01 (0·91 –1·12)
Respiratory 98 (0·2%) 125 (0·3%) 0·82 (0·62 –1·08)
Trauma 51 (0·1%) 57 (0·1%) 0·89 (0·59 –1·34)
Other/unknown 487 (1·1%) 550 (1·2%) 0·87 (0·73 –1·03)
Any non-vascular 1730 (3·8%) 1801 (4·0%) 0·95 (0·90 –1·01)
Any death 3832 (8·5%) 4354 (9·7%) 0·88 (0·84 –0·91)
0·5
1·0
1·5


Major coronary events
50%
40%
30%
20%
10%
0%
−10%
0·5
1·0
1·5
2·0
Major vascular events
50%
40%
30%
20%
10%
0%
−10%
0·5
1·0
1·5
2·0
Proportional reduction in event rate (SE)
Reduction in LDL cholesterol (mmol/L)


Waist
Hip
20 years
BMI = 24
Waist = 80 cm
Hip = 100 cm
Waist:hip ratio = 0.80
BMI = 35
Waist = 100 cm
Hip = 125 cm
Waist:hip ratio = 0.80

Exercise Reduces Risk of MS, DM



Adapted from Hamman R. *IJCP*. 2003;(Suppl 134):29.

Metabolic syndrome as predictor of CVD

- **MS increases risk of CHD**
- **MS predicts 25% of all new-onset CVD**
- **10-year risk of MS in men is between 10-20%**
- **Women with MS <10% of CVD risk**
- **No advantage above Framingham risk factors**

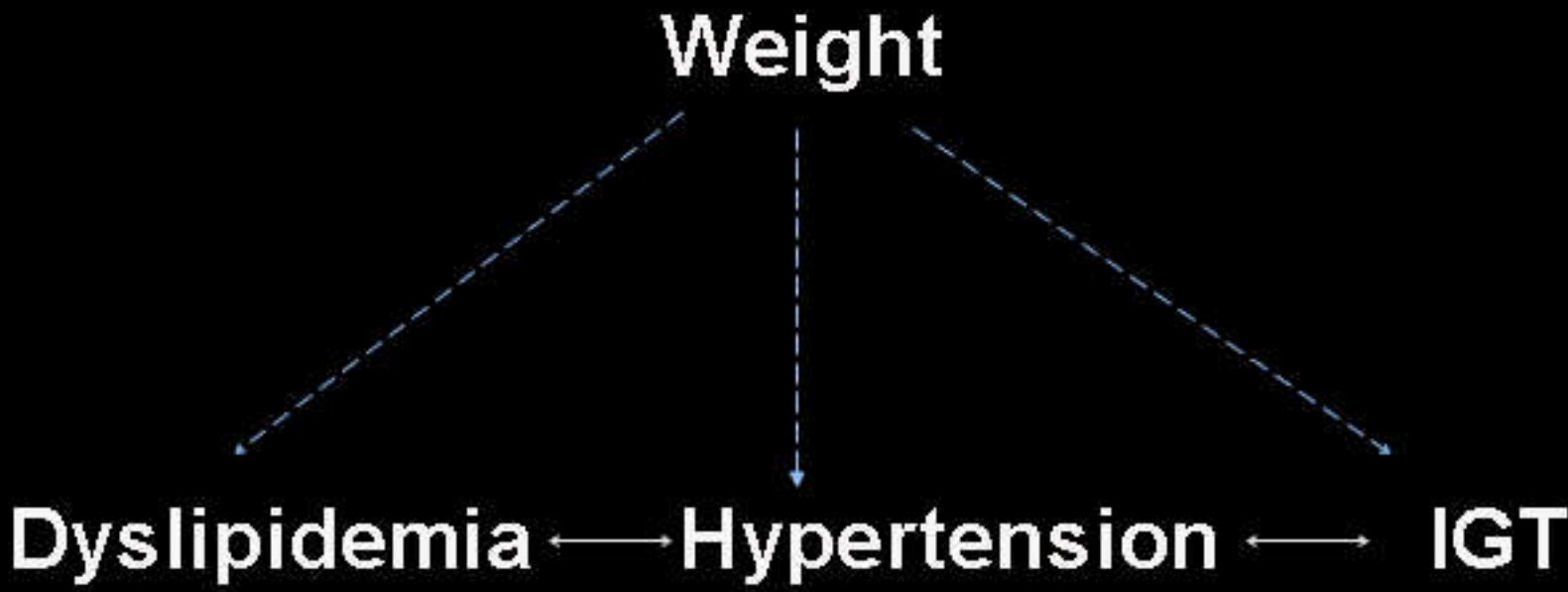
Treatment Approaches to Metabolic Syndrome

"All current guidelines on the management of the individual components of the metabolic syndrome emphasize that lifestyle modification (weight loss and physical activity) is first-line therapy."

Grundy SM, Hansen B, Smith SC, et al. Clinical Management of the metabolic syndrome. Report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association Conference on Scientific Issues Related to Management. *Circulation*. 2004;109:551-556

New Treatment Paradigm

Management of weight first, followed by an integrated treatment approach



Therapeutics goals and recommendations

- Abdominal obesity:
  - **Goal : 10% weight loss first year, threafter continued weight loss or maintain weight.**
  - **Recommendations : caloric restriction; regular exercise; behaviour modification.**

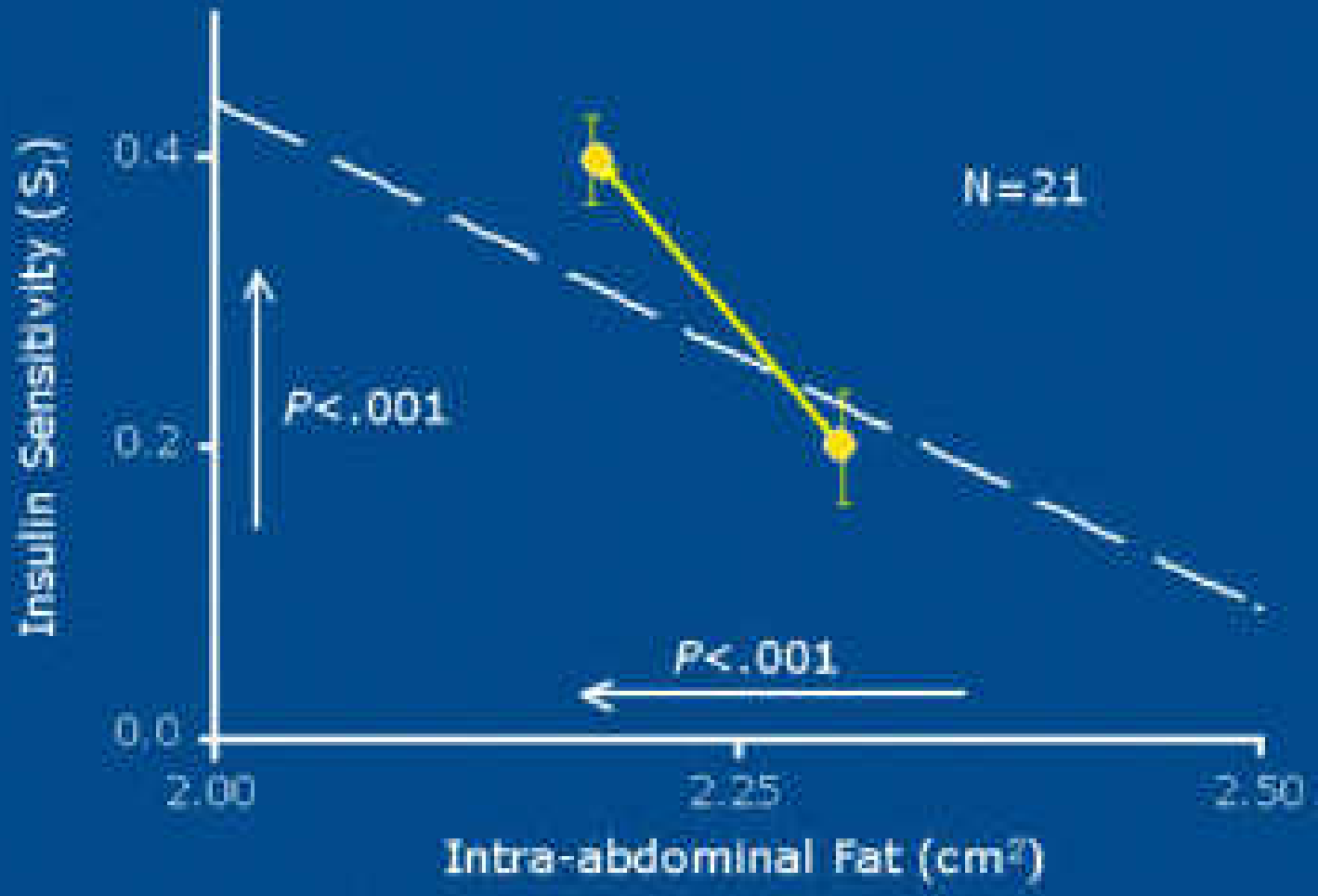
R.Ekel. Lancet 2005

Weight Loss Leads To ↓VAT

- Weight loss
  - Visceral fat turnover is much greater than that of subcutaneous fat:
    - A 10% weight loss may ↓VAT by 40%
- Alter the metabolism of VAT

VAT = visceral adipose tissue

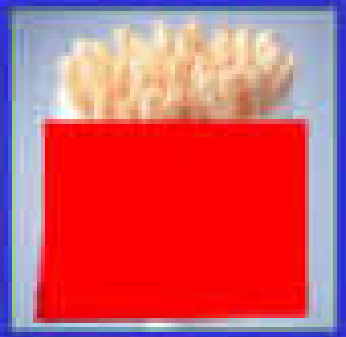
Insulin Sensitivity Improves After Weight Loss



Purnell JQ et al. *J Clin Endocrinol Metab*. 2000.

FRENCH FRIES

20 Years Ago

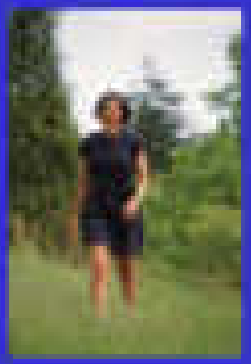


210 Calories
2.4 ounces

Today

610 Calories
6.9 ounces

Calorie Difference:
400 Calories=Walk
2hrs and 40 min

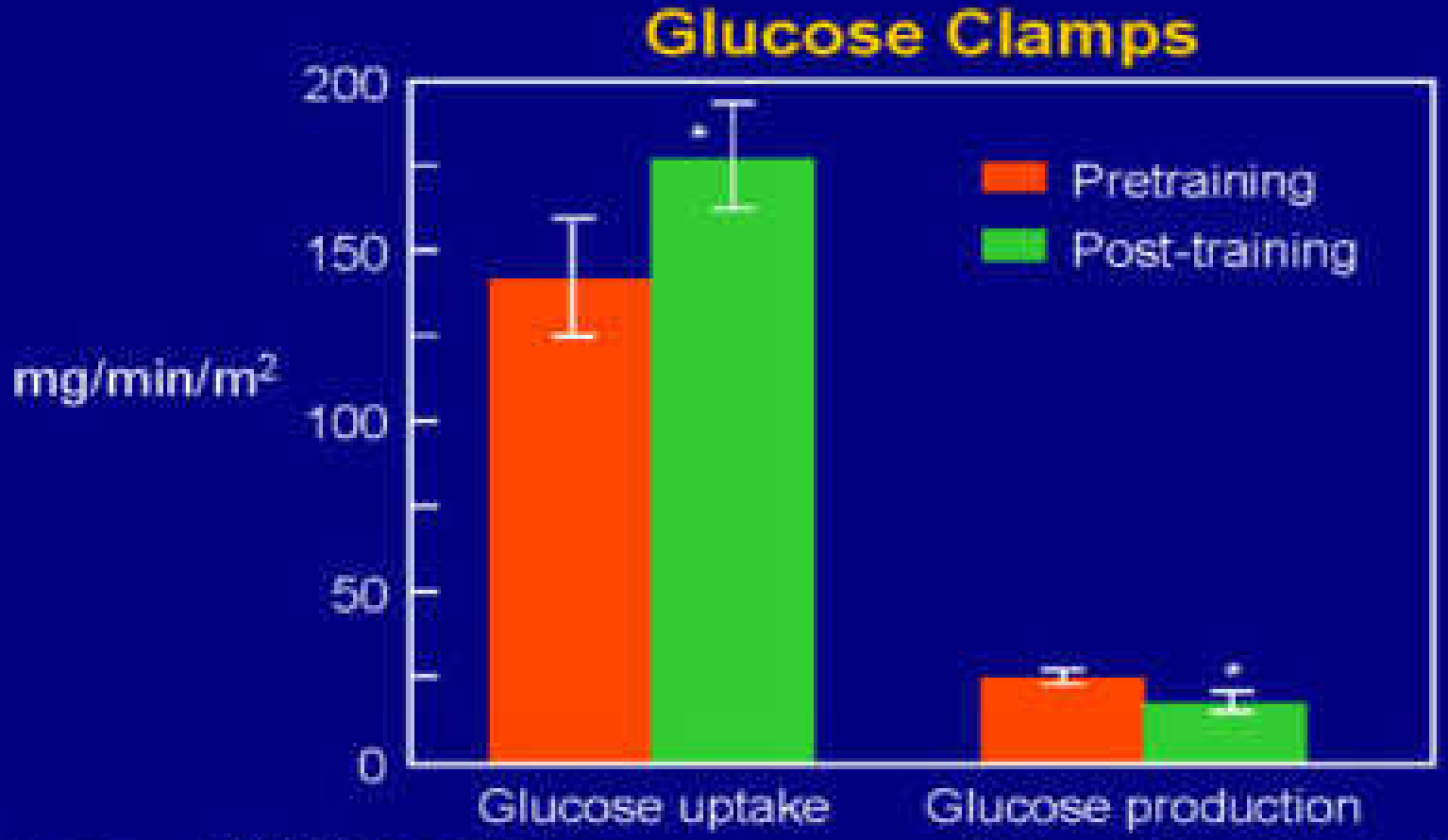


Therapeutics goals and recommendations

- Physical inactivity :
  - **Goal : regular moderate- intensity physical**
  - **Recommendations 30- 60 min moderate intensity exercise daily**

R.Ekel. Lancet 2005

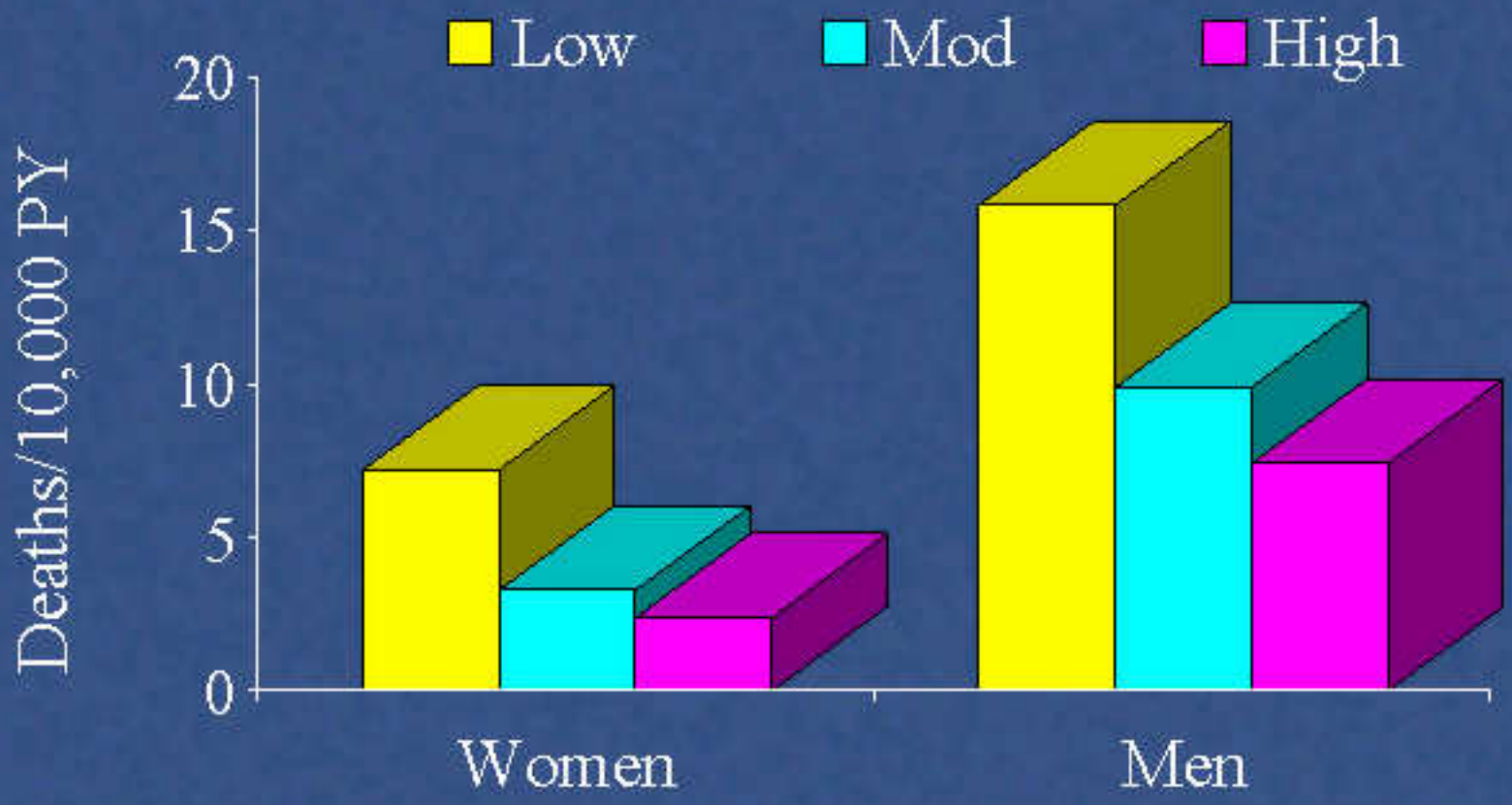
Aerobic Exercise Improves Insulin Sensitivity



DeFronzo R et al. *Diabetes*. 1987;36:1379-1385.

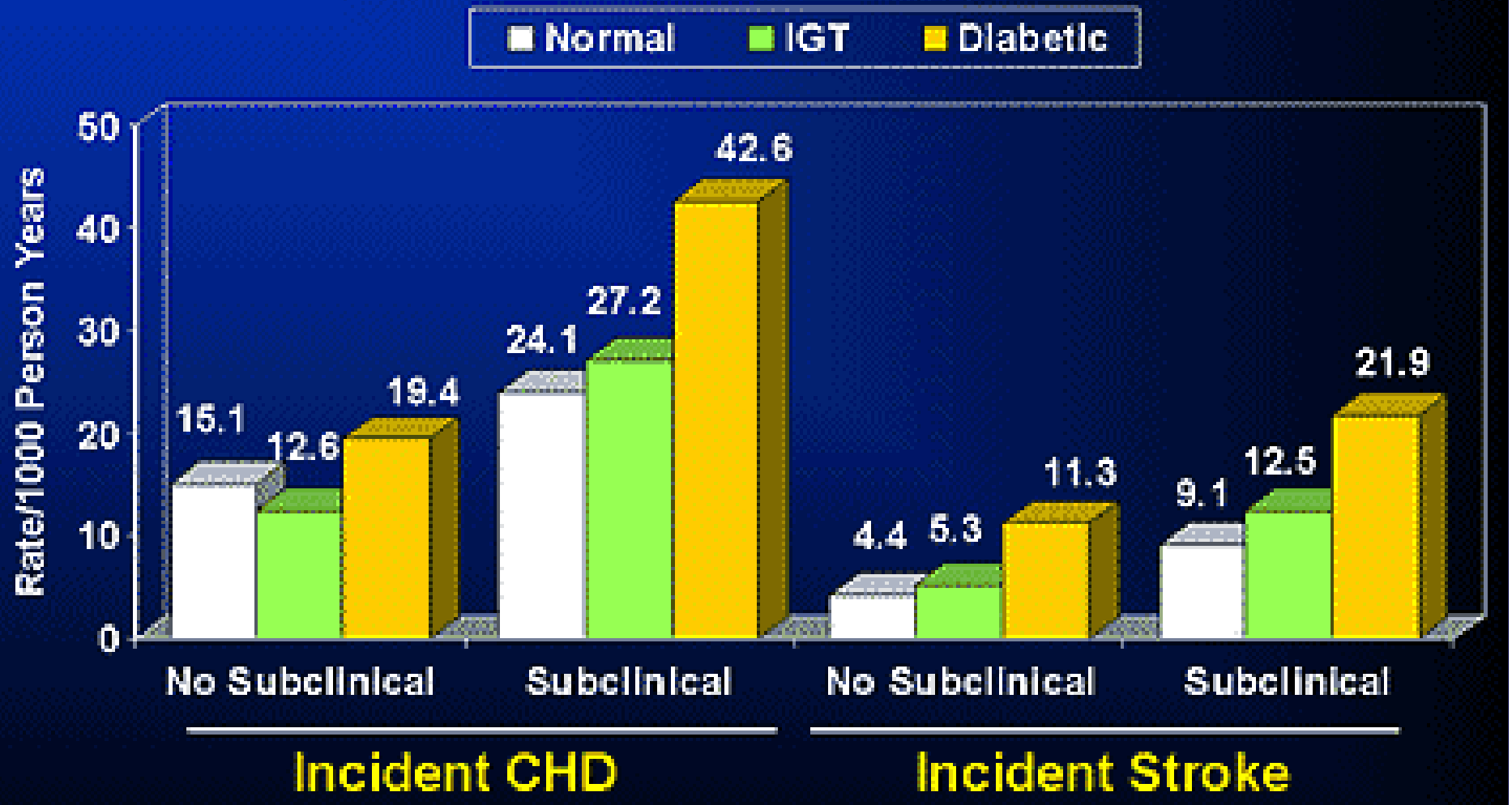
The Cooper Institute
Dallas • Denver

CVD Death Rates by Fitness, 7,080 Women & 25,340 Men



Adjusted for BMI, age, exam year, and other risk factors

Subclinical CVD With Impaired Glucose Tolerance Increases CVD Risks



Kuller et al. *Arterioscler Thromb Vasc Biol* 2000;20:823-9.

Prediction of CHD Prevalence using Multivariate Logistic Regression: NHANES

Variable	Odds Ratio	Lower 95% Limit	Upper 95% Limit
Waist Circumference	1.13	0.85	1.51
Triglycerides	1.12	0.71	1.77
HDL Cholesterol	1.74	1.18	2.58
Blood Pressure	1.87	1.37	2.56
Impaired Fasting Glucose	0.96	0.60	1.54
Diabetes	1.55	1.07	2.25
Metabolic Syndrome	0.94	0.54	1.68

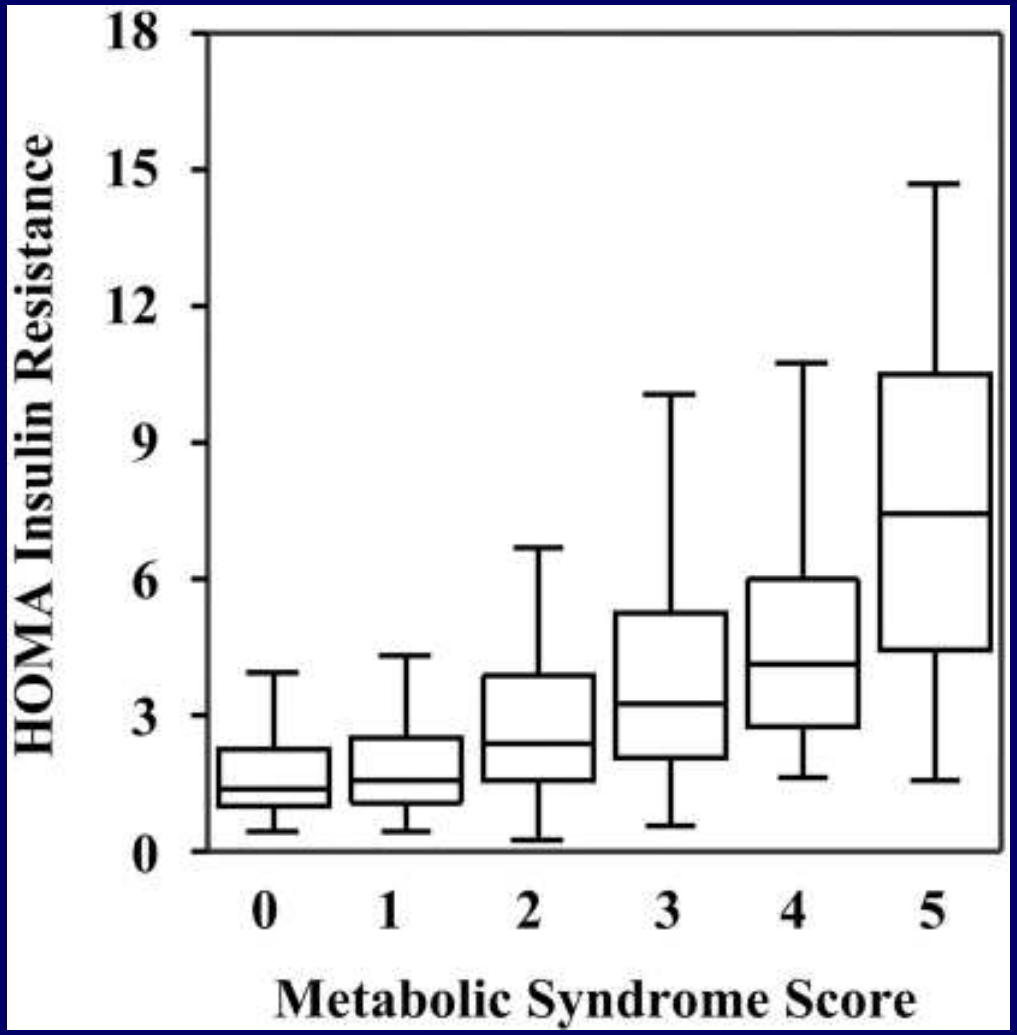
Significant predictors of prevalent CHD in red

Alexander C, et al. Diabetes 52: 1210-1214, 2003

	Cases	Controls
Patients	12 461	14 637
Females	3002	3786
Males	9459	10 851
Mean age (SD)	58·1 (12·2)	56·9 (12·2)
Prevalence of risk factors (%)		
Current smokers	45·2%	26·8%
Diabetes	18.5%	7.5%
Hypertension	39·0%	21·9%
Daily vegetable and fruit intake	35·8%	42·4%
Regular exercise*	14·3%	19·3%
Regular alcohol intake†	24·0%	24·5%
Median ApoB (IQ range)	0·95 (0·78–1·13)	0·90 (0·74–1·07)
Median ApoA (IQ range)	1·10 (0·96–1·26)	1·19 (1·03–1·37)
Median ApoB/Apo-A ratio (IQ range)	0·87 (0·70–1·05)	0·75 (0·60-0·93)

Yusuf lancet 2005

FIG. 1. Insulin resistance and MetS score



Saely, C. H. et al. J Clin Endocrinol Metab 2005;90:5698-5703

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

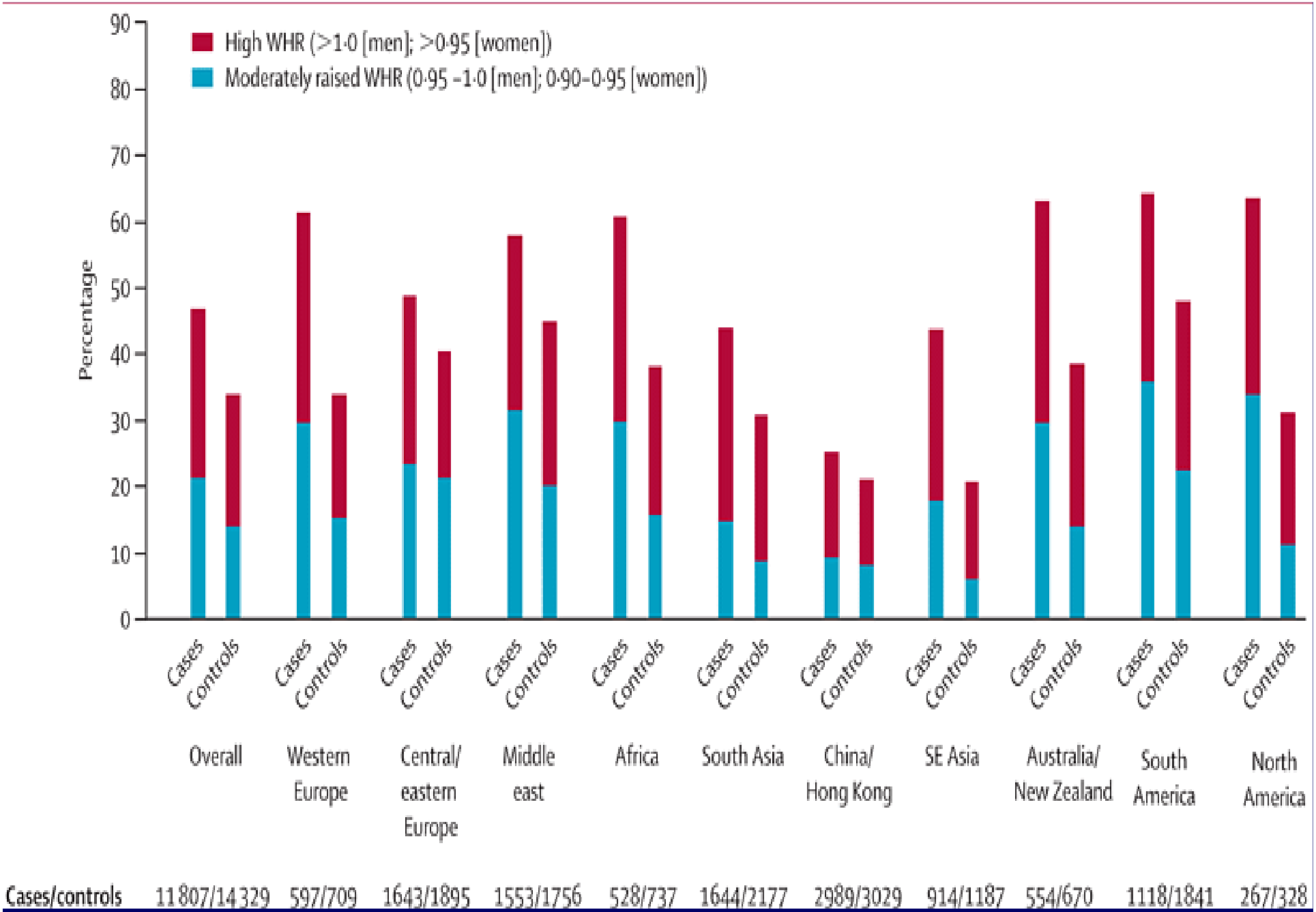
Clinical Outcomes of Metabolic Syndrome

Cardiovascular Disease

Type 2 Diabetes → CVD

Other conditions:

- Fatty liver
- Polycystic ovary disease
- Sleep disturbances
- Cholesterol gallstones



Yusuf lancet 2005

	Odds Ratio (95% CI)			Odds Ratio (95% CI)		
	1 SD	Adjusted for age, sex, and region	Additionally adjusted for WHR or BMI	1 SD (women/men)	Women	Men
Measure (units)						
BMI (kg/m²)	4·15	1·10 (1·07–1·13)	1·02 (0·99–1·04)*	4·70/3·89	1·04 (0·98–1·09)*	1·00 (0·97–1·04)*
Waist circumference (cm)	12·08	1·19 (1·16–1·22)	1·25 (1·21–1·30)†	12·97/11·58	1·40 (1·30–1·51)†	1·19 (1·14–1·24)†
Hip circumference (cm)	10·96	0·95 (0·94–0·99)	0·87 (0·84–0·89)†	12·18/10·36	0·92 (0·86–0·99)†	0·85 (0·82–0·89)†
Waist-to-hip ratio	0·085	1·37 (1·34–1·41)	1·37 (1·33–1·40)†	0·089/0·078	1·34 (1·27–1·42)†	1·35 (1·31–1·40)†
Waist-to-height	0·072	1·19 (1·16–1·22)	1·24 (1·20–1·28)†	0·082/0·066	1·39 (1·29–1·50)†	1·18 (1·13–1·23)†

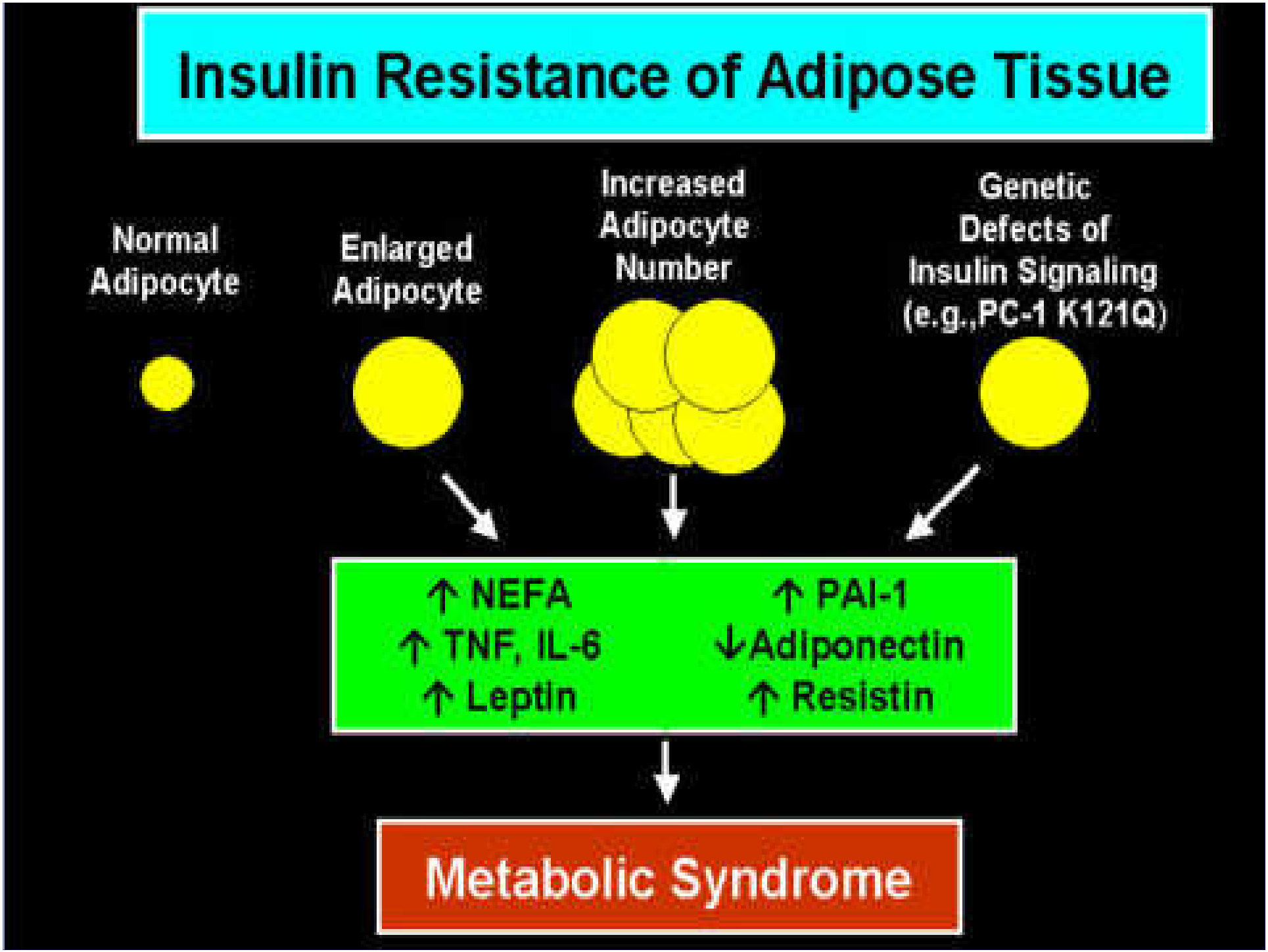
Yusuf lancet 2005

Intervention Therapies

- **Standard Lifestyle**
  - annual lifestyle counselling

- **Intensive Lifestyle**
  - weight loss target of ↓7%
    (↓5% achieved over 3 years)
  - low-fat diet and 150 min exercise per week
  - personal trainer and individual lifestyle program
  - behavior modification skills

- **Glucophage therapy.**
  - one 850 mg tablet twice a day


Insulin Resistance of Adipose Tissue
Normal Adipocyte
Enlarged Adipocyte
Increased Adipocyte Number
Genetic Defects of Insulin Signaling (e.g.,PC-1 K121Q)
↑ NEFA
↑ TNF, IL-6
↑ Leptin
↑ PAI-1
↓Adiponectin
↑ Resistin
Metabolic Syndrome

Weight Loss Leads To ↓VAT

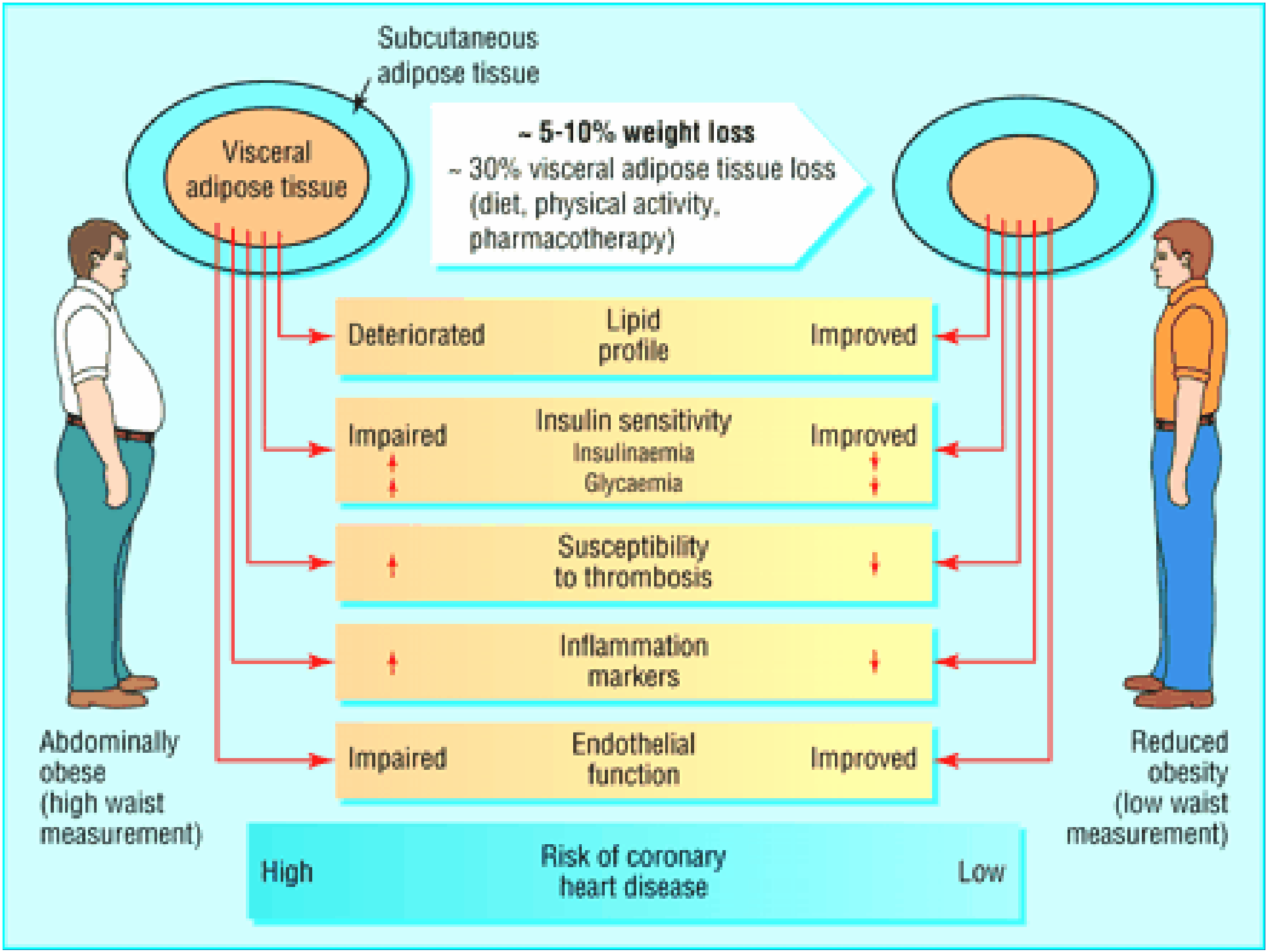
- Weight loss
  - Visceral fat turnover is much greater than that of subcutaneous fat:
    - A 10% weight loss may ↓VAT by 40%
- Alter the metabolism of VAT

VAT = visceral adipose tissue

Therapeutics goals and recommendations

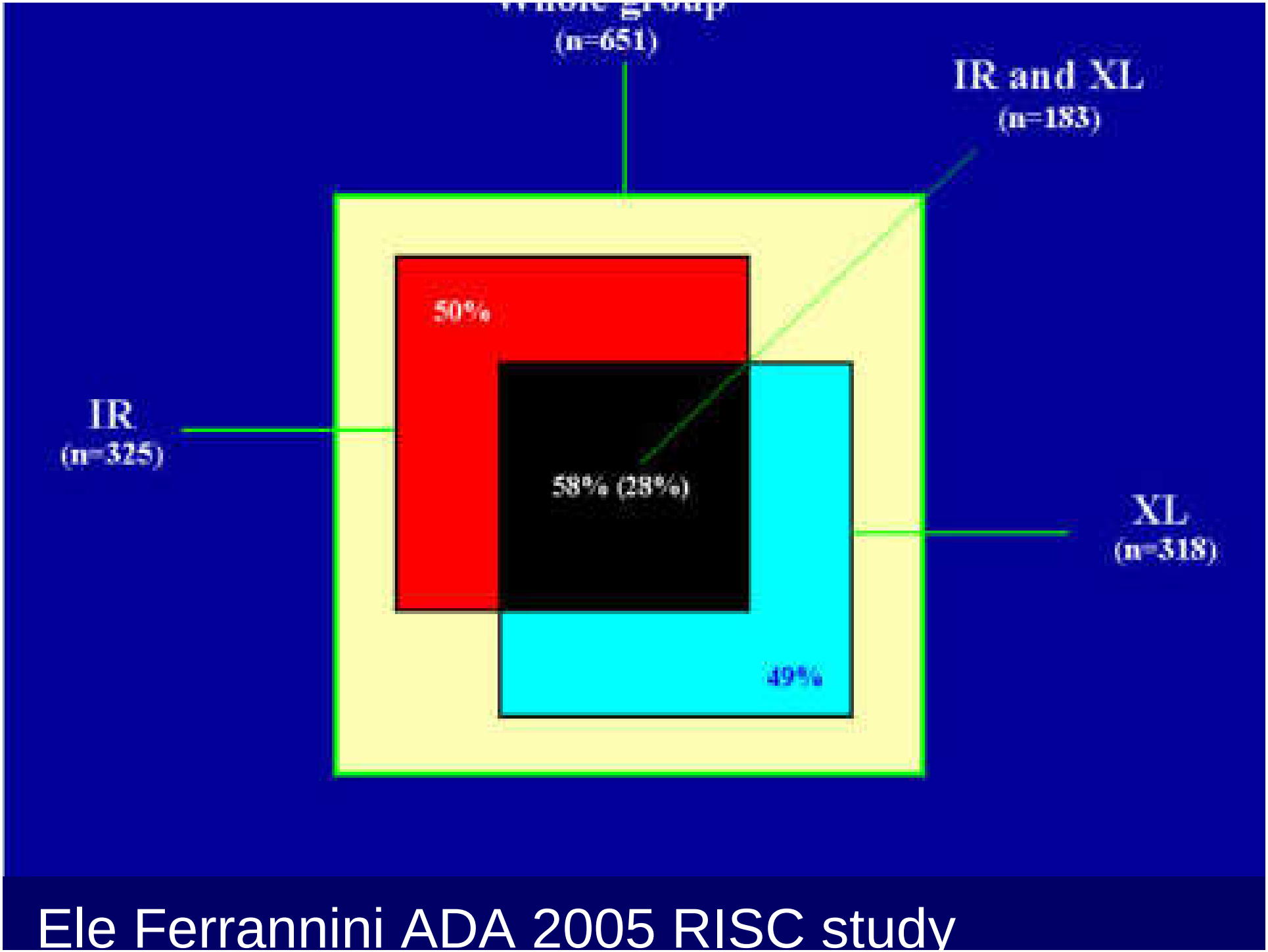
- Abdominal obesity:
  - **Goal : 10% weight loss first year, threafter continued weight loss or maintain weight.**
  - **Recommendations : caloric restriction; regular exercise; behavior modification.**

R.Ekel. Lancet 2005

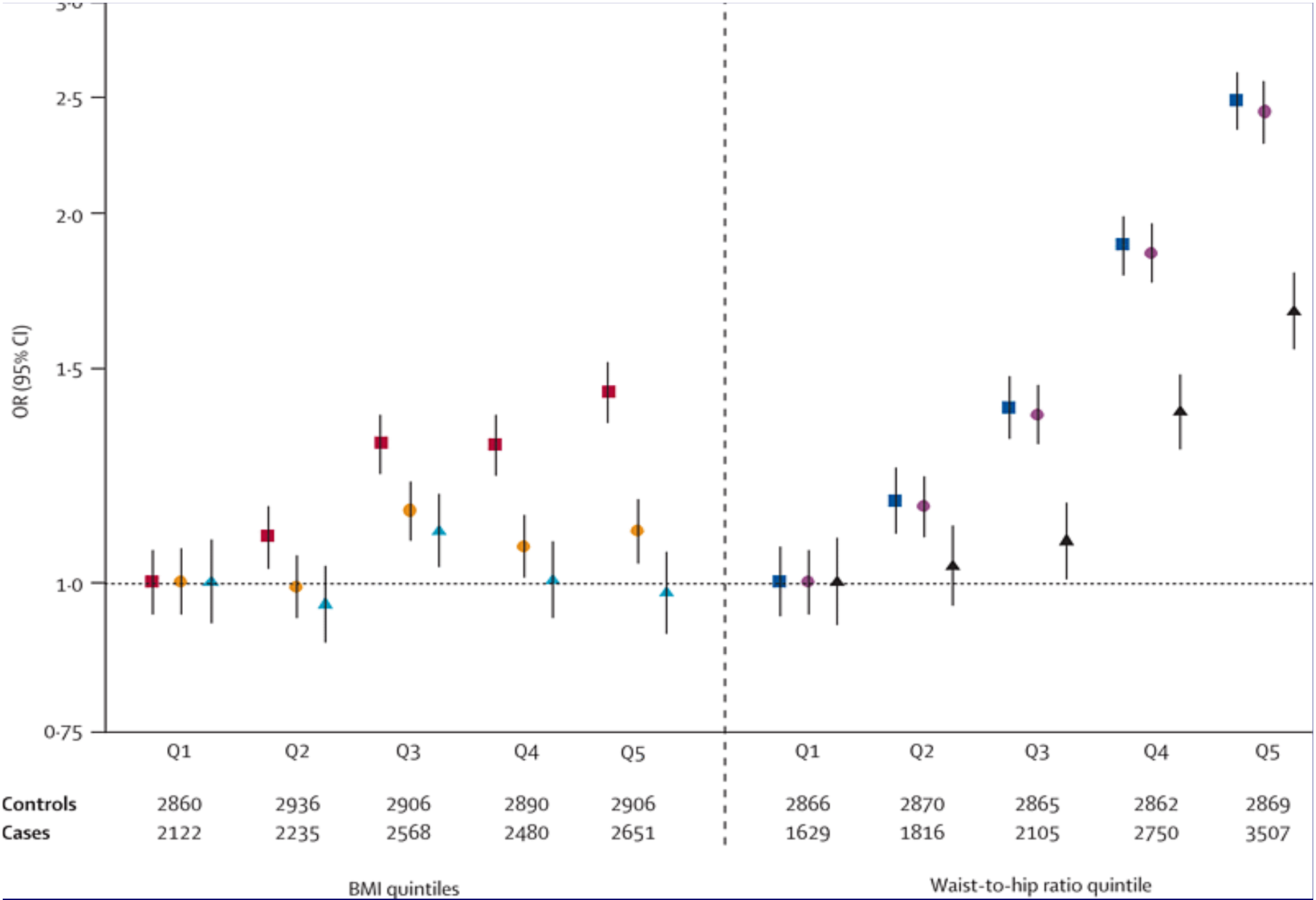

Subcutaneous adipose tissue
Visceral adipose tissue
~ 5-10% weight loss
~ 30% visceral adipose tissue loss (diet, physical activity, pharmacotherapy)
Deteriorated
Lipid profile
Improved
Impaired
Insulin sensitivity
Insulinaemia
Glycaemia
Improved
Susceptibility to thrombosis
Inflammation markers
Impaired
Endothelial function
Improved
Abdominally obese (high waist measurement)
Reduced obesity (low waist measurement)
High
Risk of coronary heart disease
Low

Critères métaboliques supplémentaires pour recherche

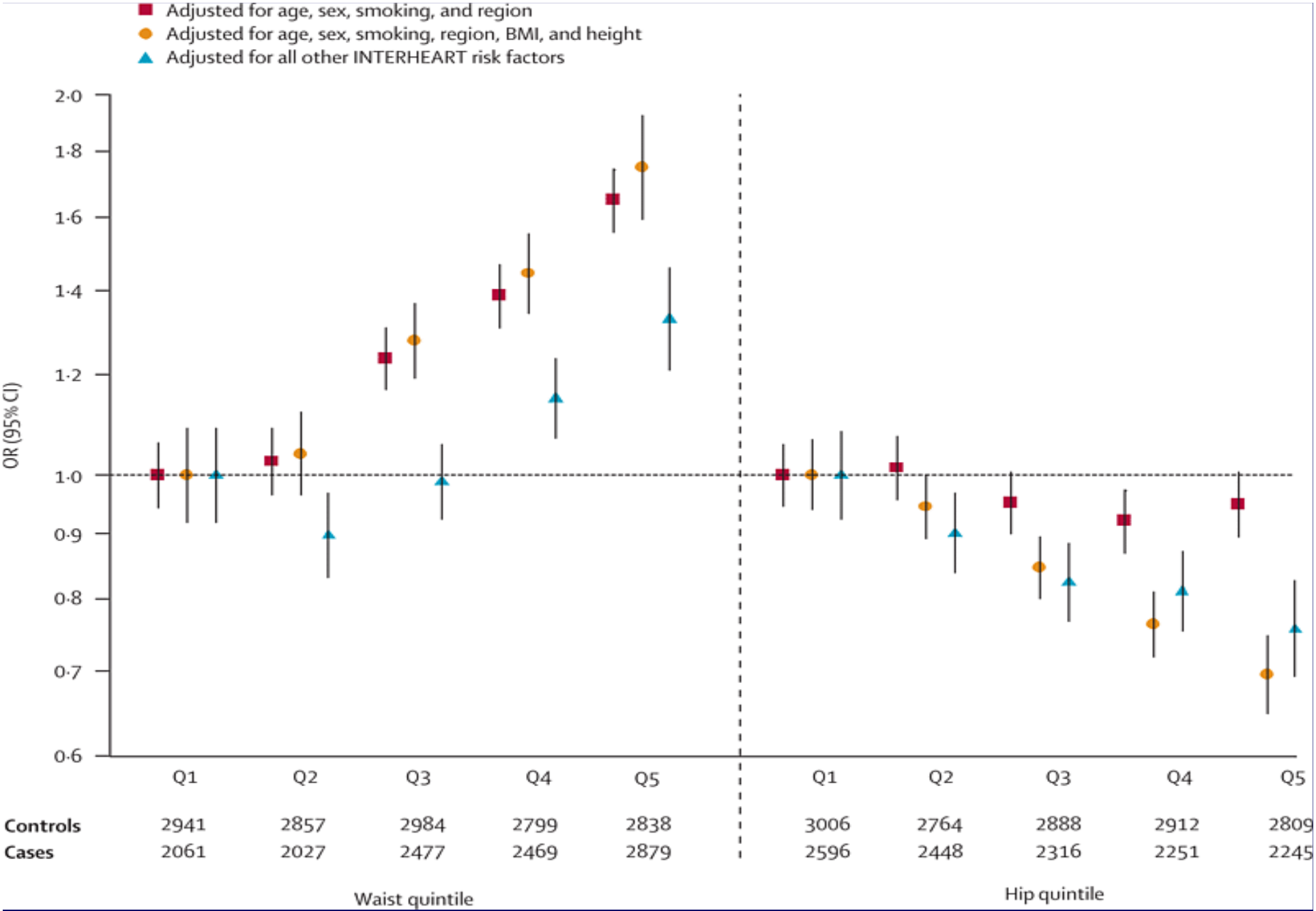
- Répartition anormale du tissu adipeux.
- Dyslipidémie athérogène: Apo B, LDL
- Dysglycémie
- Résistance à l'insuline. HOMA, clamp, Quicki
- Dysfonction vasculaire : microalbuminurie
- Etat inflammatoire.
- Etat prothrombotique
- Dysfonctionnement de l'axe hypothalamo – hypophyso - surrénalien.



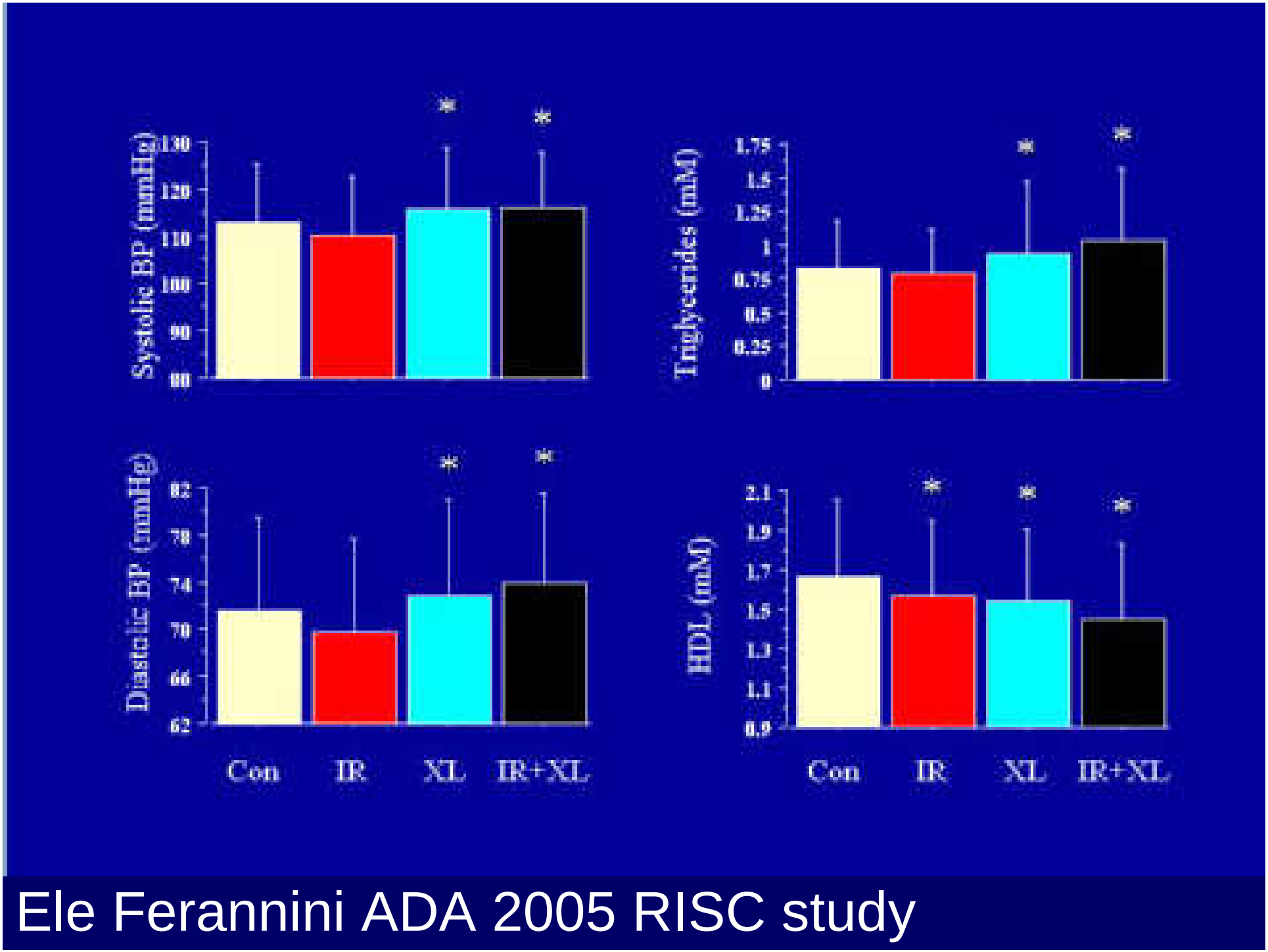
Ele Ferrannini ADA 2005 RISC study



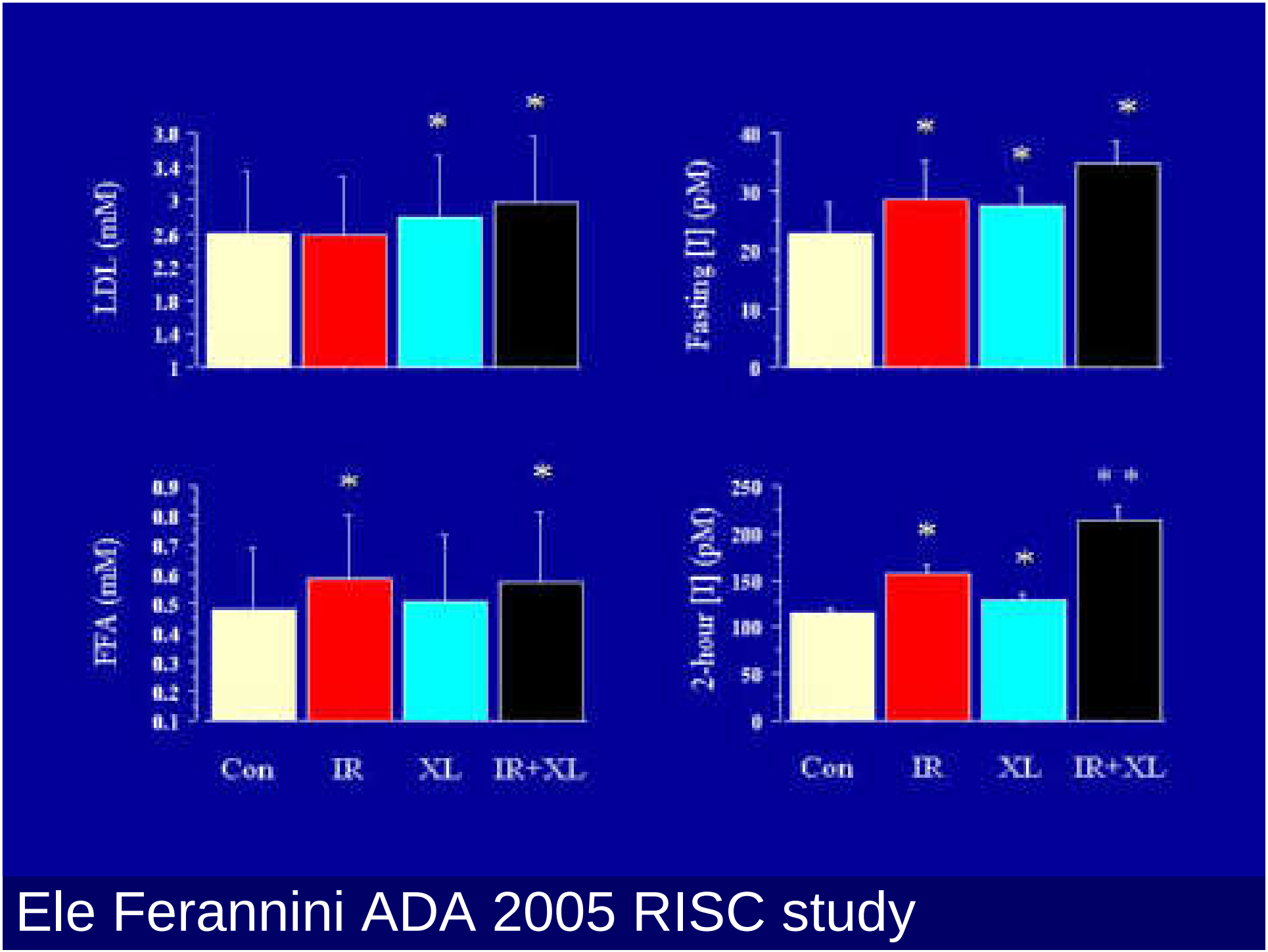
Yusuf lancet 2005



Yusuf lancet 2005

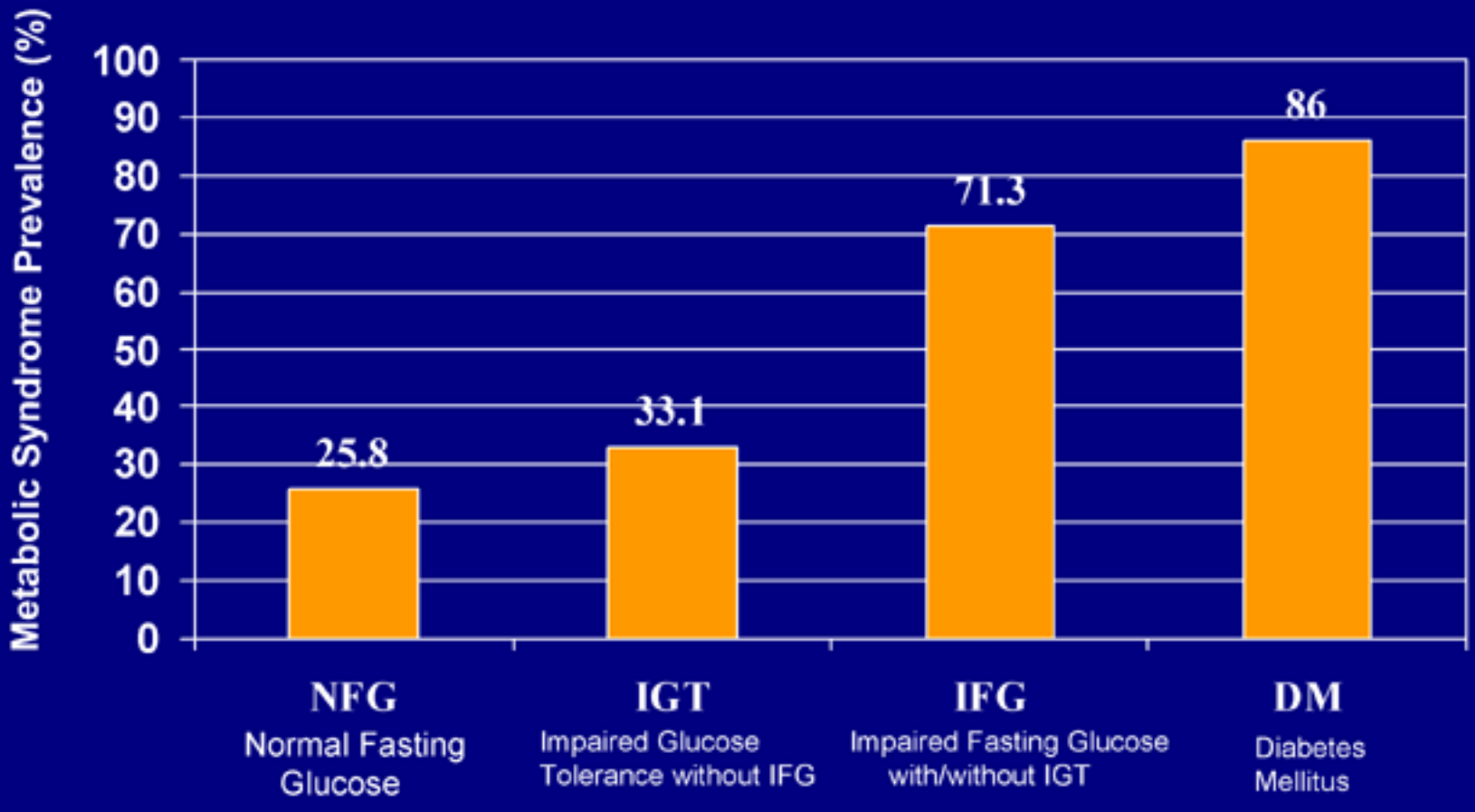


Ele Ferannini ADA 2005 RISC study



Ele Ferannini ADA 2005 RISC study

Prevalence by Glucose Intolerance



Source: Alexander CM et al NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 2003;52:1210-1214