Università di Verona
Corso di Laurea in Medicina e Chirurgia
Corso di Endocrinologia e Malattie del Metabolismo
Anno Accademico 2008/2009

Sindrome Metabolica

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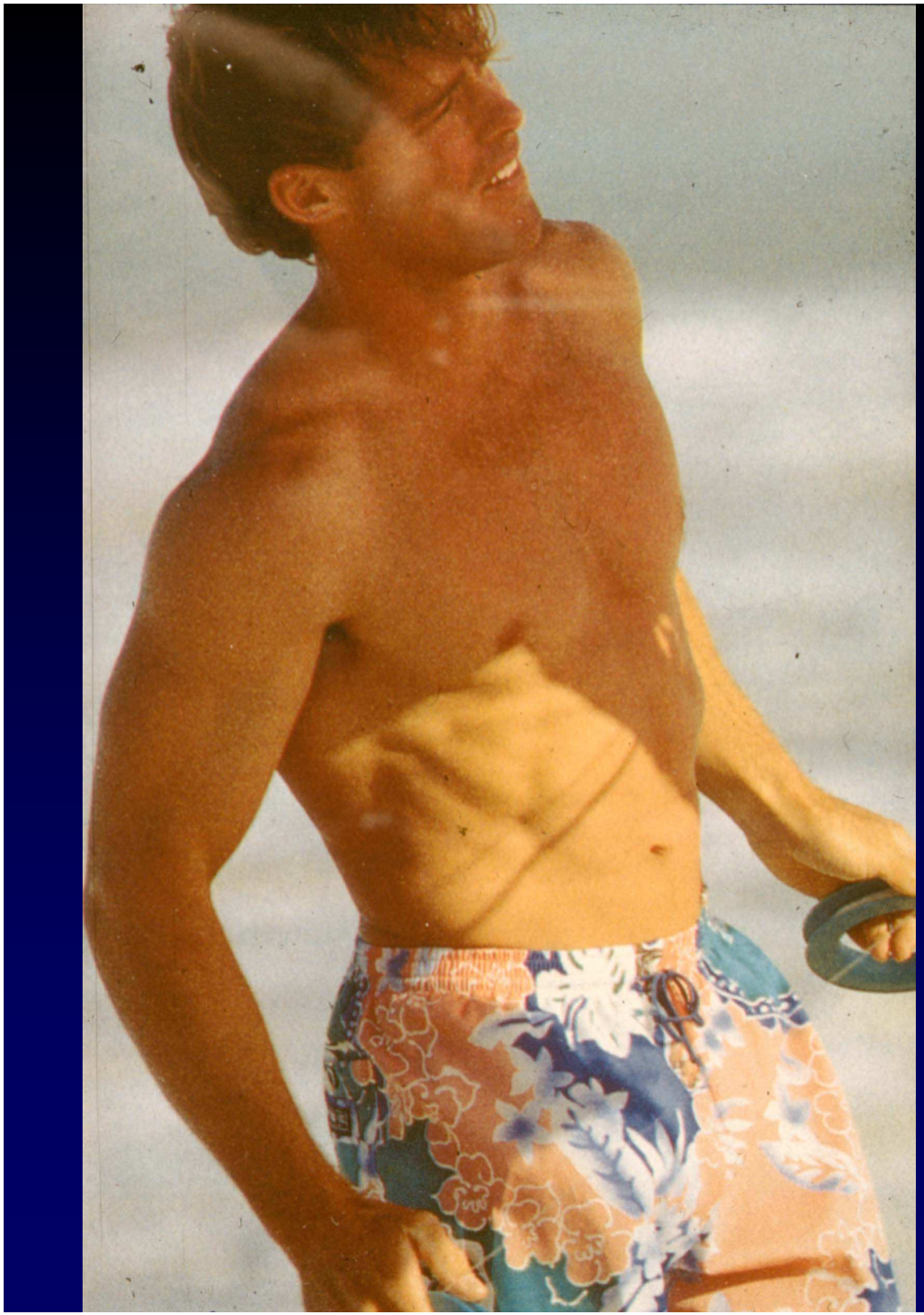
SINDROME METABOLICA

- Condizione clinica nota da molto tempo
- Dignità nosografica in anni recenti
- Criteri diagnostici ancora dibattuti
- Molto diffusa nella popolazione
- Stretta relazione con insulinoresistenza
- Elevato rischio cardiovascolare

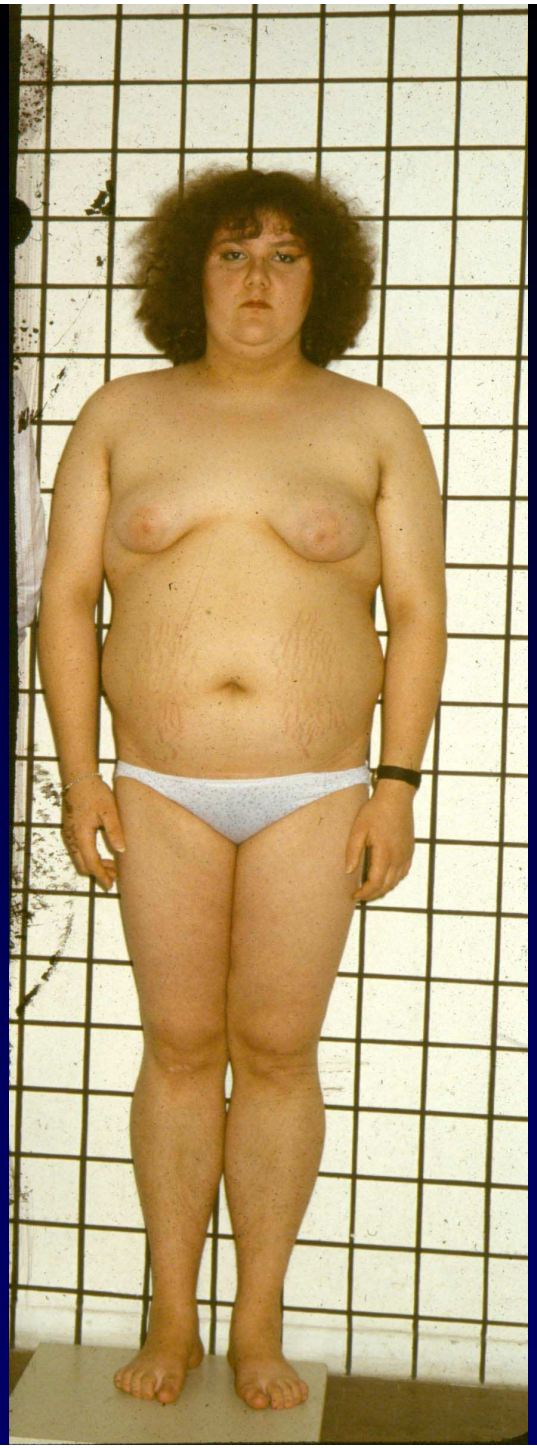


Caso n°1

• Sesso	Maschile
• Età	48 anni
• Peso	108 kg
• Altezza	181 cm
• BMI	33 kg/m^2
• Glicemia	132 mg/dl
• Colesterolo totale	254 mg/dl
• Colesterolo HDL	28 mg/dl
• Trigliceridi	303 mg/dl
• Uricemia	7.9 mg/dl
• Pressione arteriosa	160/100 mmHg

Caso n°2

Sesso	Femminile
Età	33 anni
Peso	94 kg
Altezza	171 cm
BMI	32 kg/m^2
Glicemia	112 mg/dl
Glicemia dopo glucosio orale (2h)	174 mg/dl
Colesterolo totale	204 mg/dl
Colesterolo HDL	31 mg/dl
Trigliceridi	241 mg/dl
Uricemia	6.6 mg/dl
Pressione arteriosa	145/95 mmHg



Diagnosi A (“frammentaria”)

Soggetto con diabete tipo 2 (o ridotta tolleranza glucidica), obesità,ipertensione arteriosa, dislipidemia e iperuricemia

Diagnosi B (“unitaria”)

Sindrome metabolica

SINDROME METABOLICA

I molti nomi:

- Sindrome X (Reaven)
- Sindrome dell'insulinoresistenza (De Fronzo)
- Sindrome metabolica (Ferrannini)
- Sindrome GDH (glucose intolerance, dyslipidemia, hypertension) (Zimmett)
- Sindrome GHO (glucose intolerance, hypertension, obesity) (Modan)
- Quartetto mortale ("deadly quartet") (Kaplan)
- Sindrome Dismetabolica (Amer Ass Clin Endocr)

SINDROME X

(Reaven, 1988)

- Insulinoresistenza
- Iperinsulinemia
- Intolleranza glucidica (IGT o NIDDM)
- Ipertrigliceridemia
- Basso HDL colesterolo
- Ipertensione

LE MOLTI SINDROMI METABOLICHE

	Obesità	IGT o NIDDM	Dislipidemia	Ipertensione	Iperuricemia	Insulino-resistenza
Sindrome X		+	+	+		+
Sindrome IR	+	+	+	+		+
Sindrome metabolica	+/-	+/-	+/-	+/-		+
Sindrome GDH	+/-	+	+	+		
Sindrome GHO	+	+		+		+
Sindrome plurimetabolica	+/-	+	+	+	+	+/-

W.H.O. Diagnostic Criteria of the Metabolic Syndrome

Impaired glucose regulation (IFG, IGT or DM)

or

Insulin resistance (bottom quartile M-clamp)

and at least two of:

- Impaired glucose regulation
- Insulin resistance
- Dyslipidemia (TG ≥150 mg/dl and/or HDL <35 mg/dl men, <39 mg/dl women)
- Hypertension (≥140/90 mmHg)
- Obesity (BMI >30) and/or central fat distribution (WHR >0.9 men, >0.85 women)
- Microalbuminuria (AER ≥20 µg/min or ACR ≥30 mg/g)

NCEP-ATP III Diagnostic Criteria of the Metabolic Syndrome

Three or more abnormalities among the following:

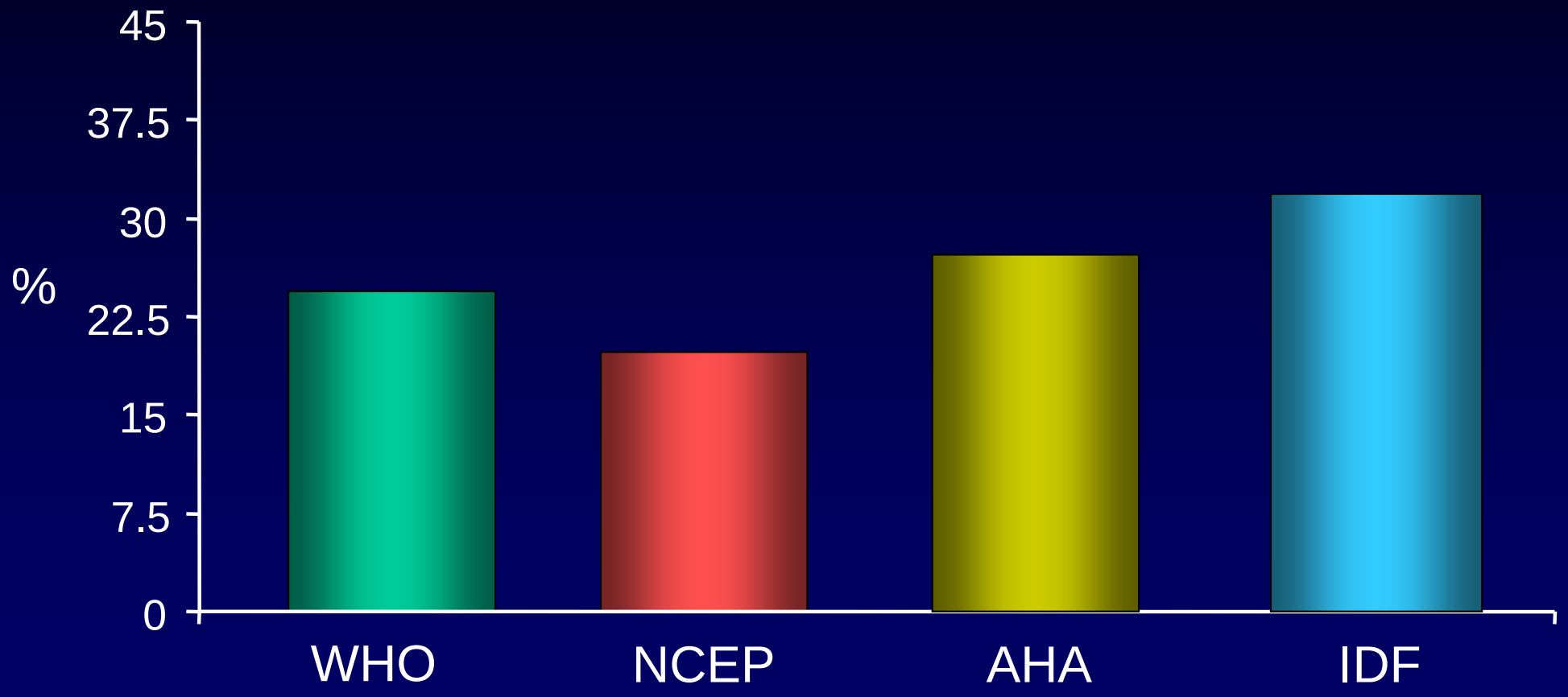
- Fasting glucose ≥110 mg/dl
- Triglycerides ≥150 mg/dl
- HDL <40 mg/dl men, <50 mg/dl women
- Hypertension (≥135/85 mmHg)
- Abdominal obesity (waist >102 men, >88 women)

The Metabolic Syndrome: Recommended Diagnostic Criteria

	WHO 1+2	NCEP Any 3	IDF 1+2	AHA Any 3
High glucose or insulin resist.	necessary			
High glucose		V	V	V
Low HDL-C or high TG	V			
Low HDL-C		V	V	V
High TG		V	V	V
High BP	V	V	V	V
Obesity or high waist	V			
High waist		V	necessary	V
Microalbuminuria	V			

The Metabolic Syndrome: Size of the Problem

(Bruneck Study; age 40-79; n=919; unpublished)

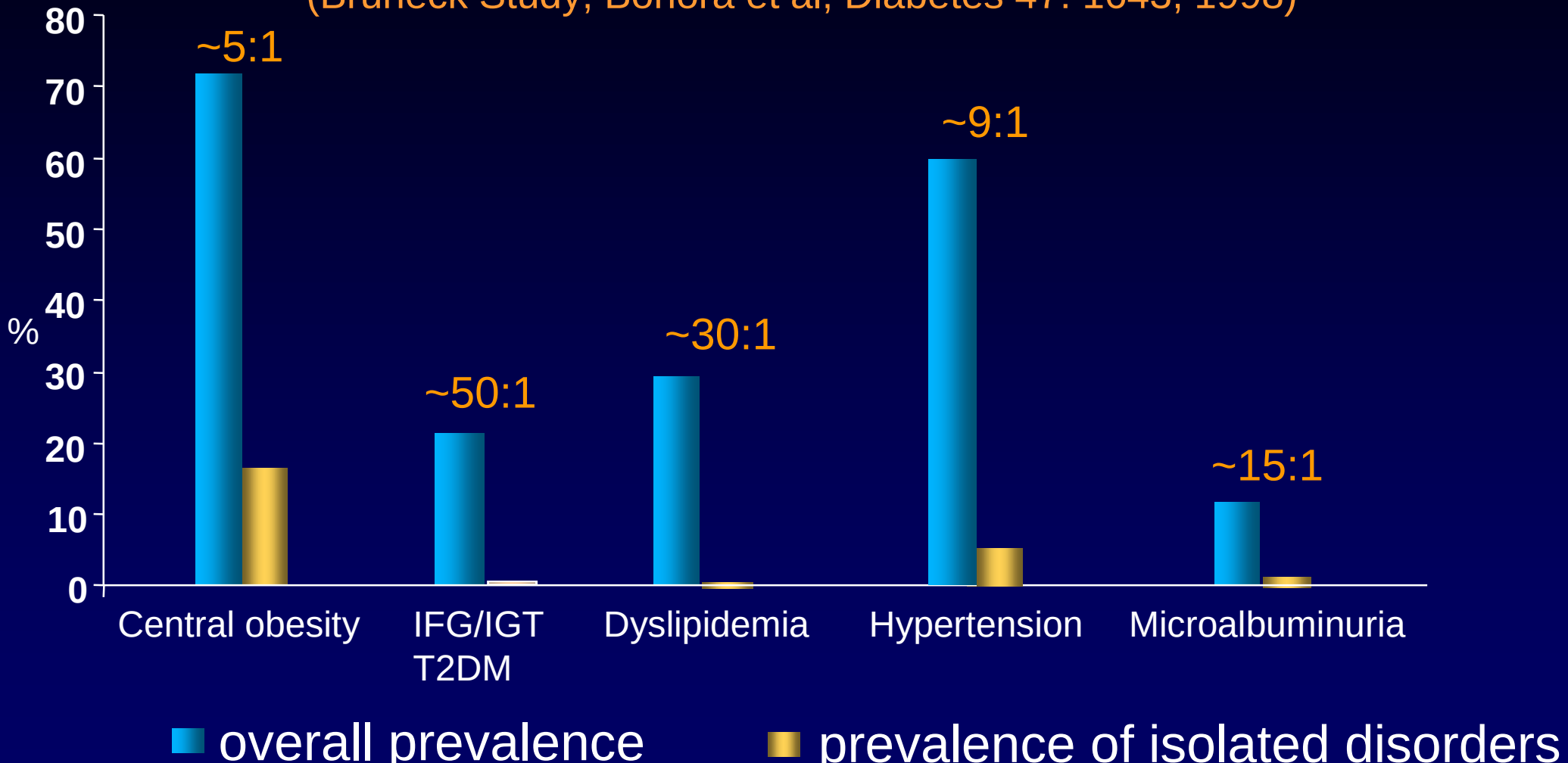


Subjects Aged 40-79 yr in Italy with the Metabolic Syndrome

Four to eight millions

Prevalence of the Main Clinical Disorders Featuring the Metabolic Syndrome: Overall vs. Isolated

(Bruneck Study; Bonora et al; Diabetes 47: 1643, 1998)



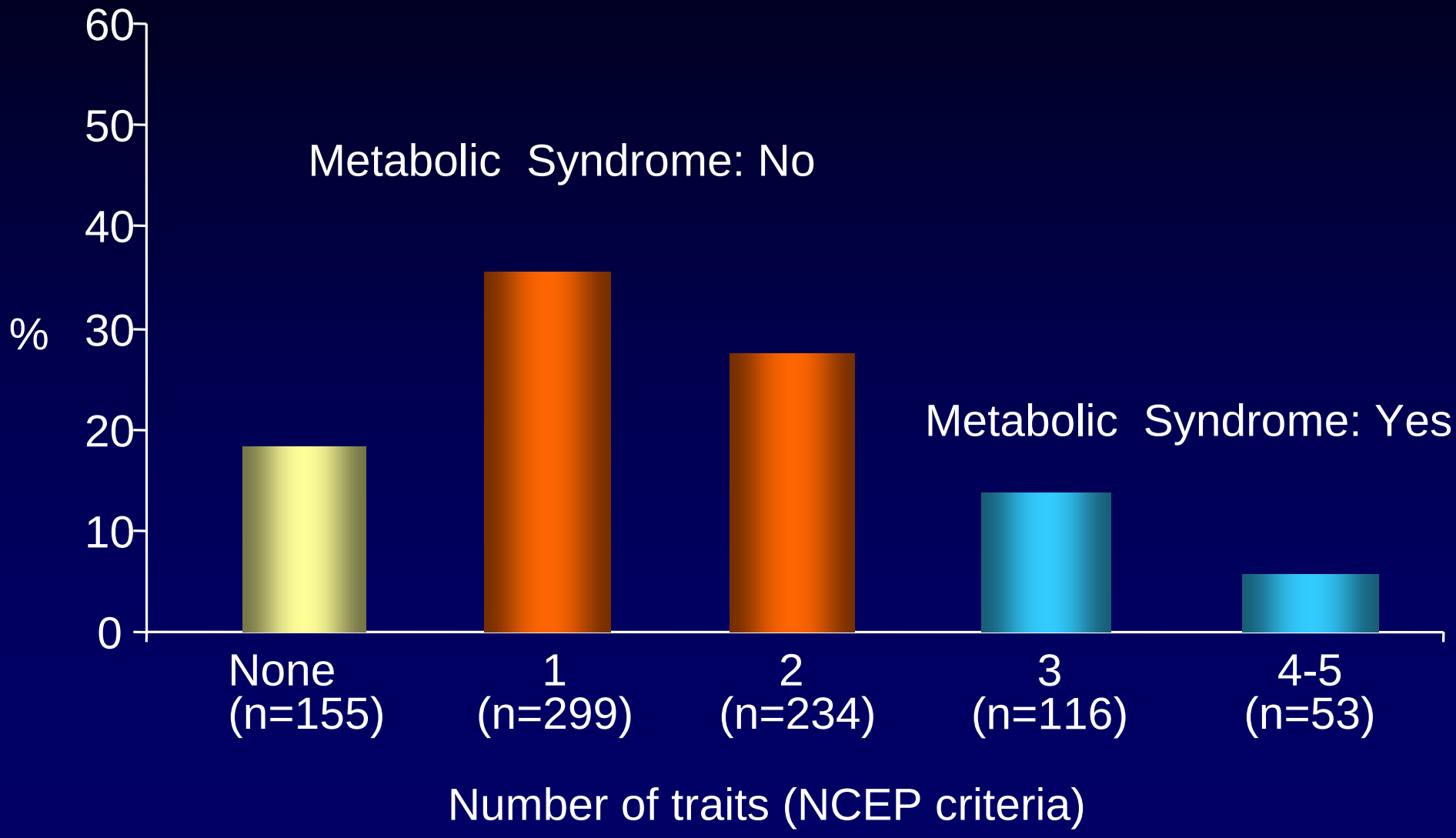
Prevalence of More Complex Clusters in the Genereal Population

(Bruneck Study, age 40-79 years, n=919; unpublished)

Possible traits in the cluster: dysglycemia, hypertension, high waist, high TG, low HDL-C

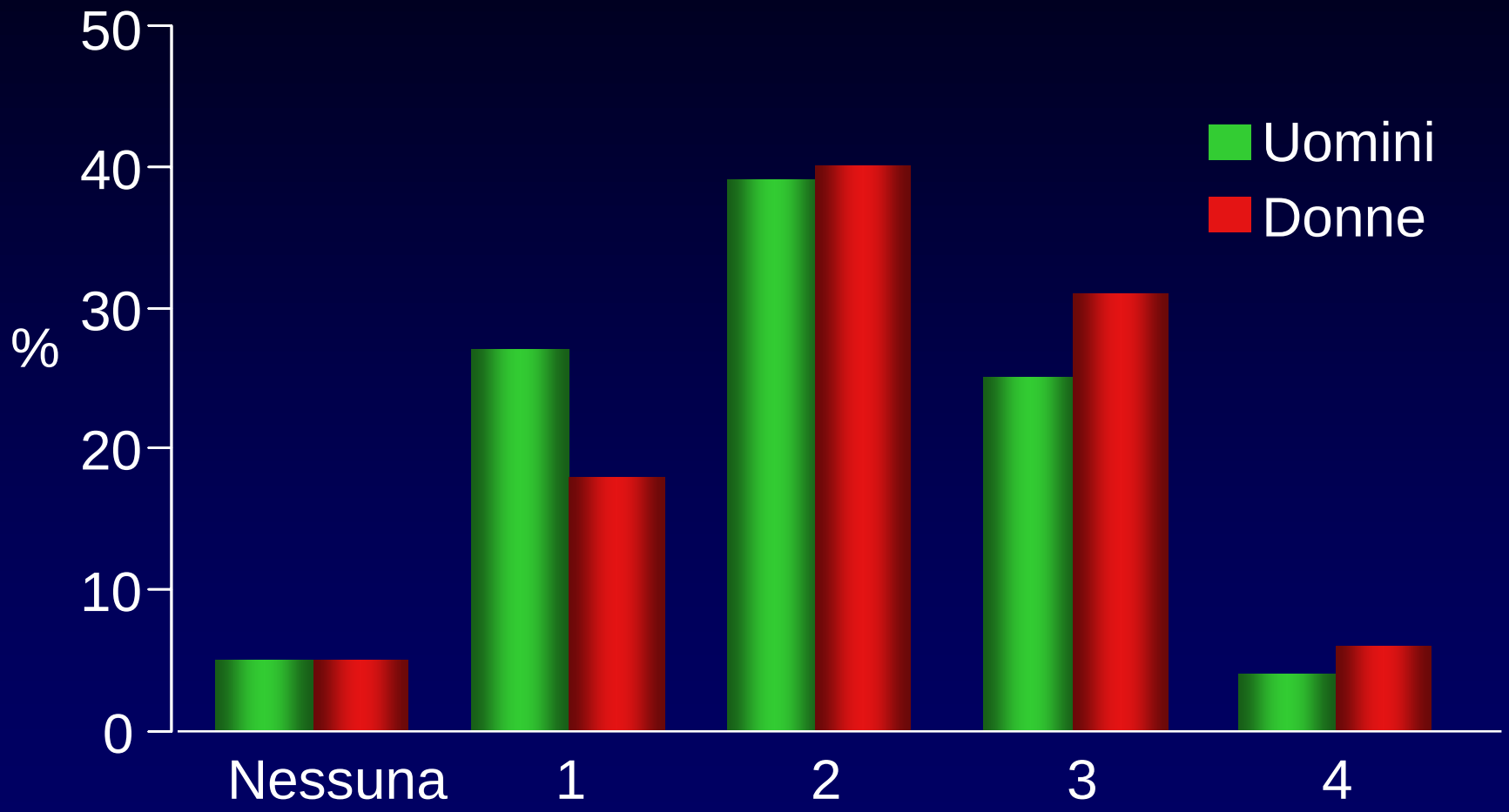
Prevalence of Traits of the Metabolic Syndrome in Subjects Aged 40-79 yr

(Bruneck Study; Bonora et al, unpublished)



PREVALENZA DI ALTERAZIONI METABOLICHE MULTIPLE NEL DIABETE TIPO 2

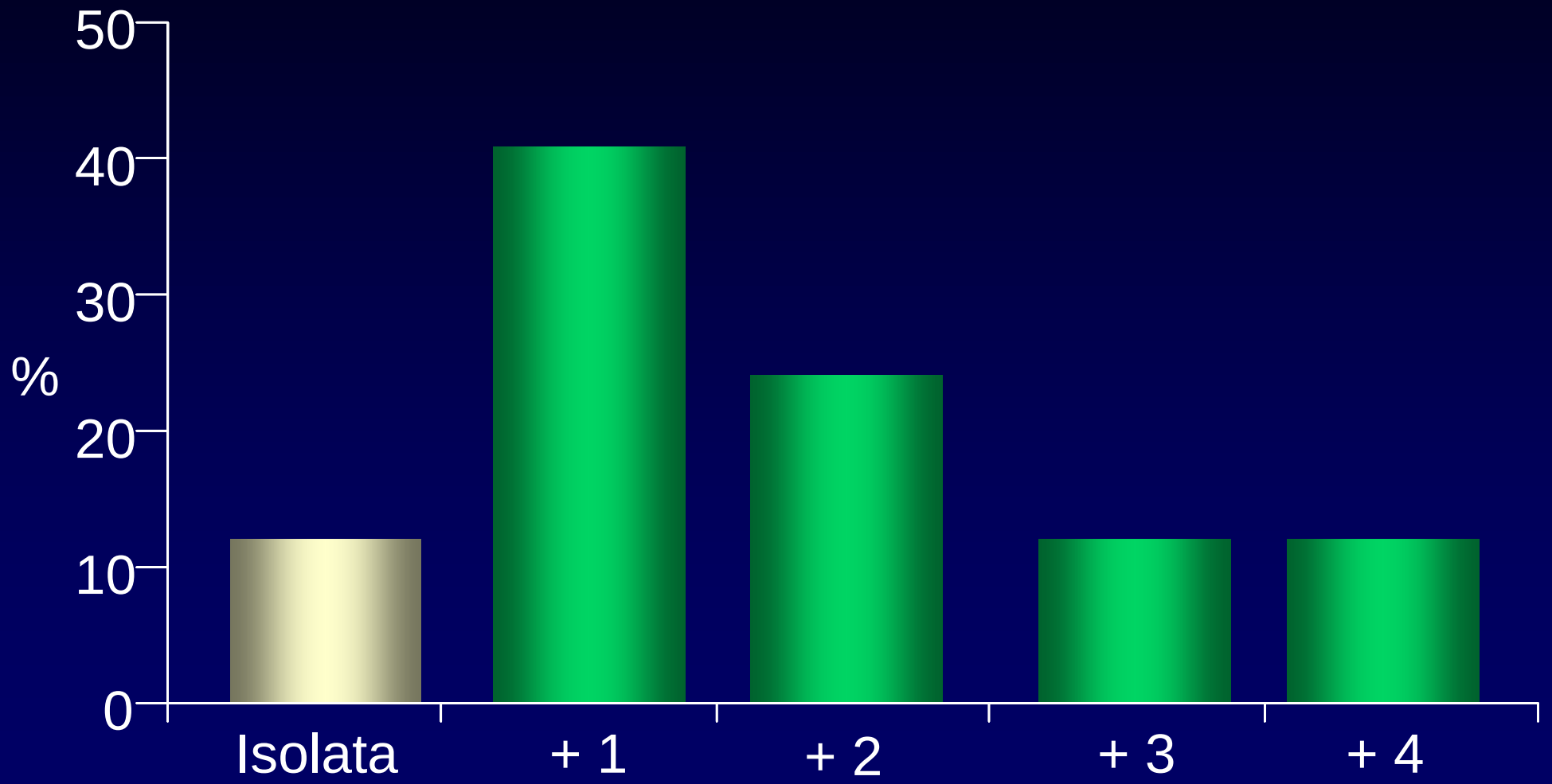
(Verona Diabetes Complications Study; n=1780)



Alterazioni metaboliche: sovrappeso - dislipidemia - ipertensione - iperuricemia

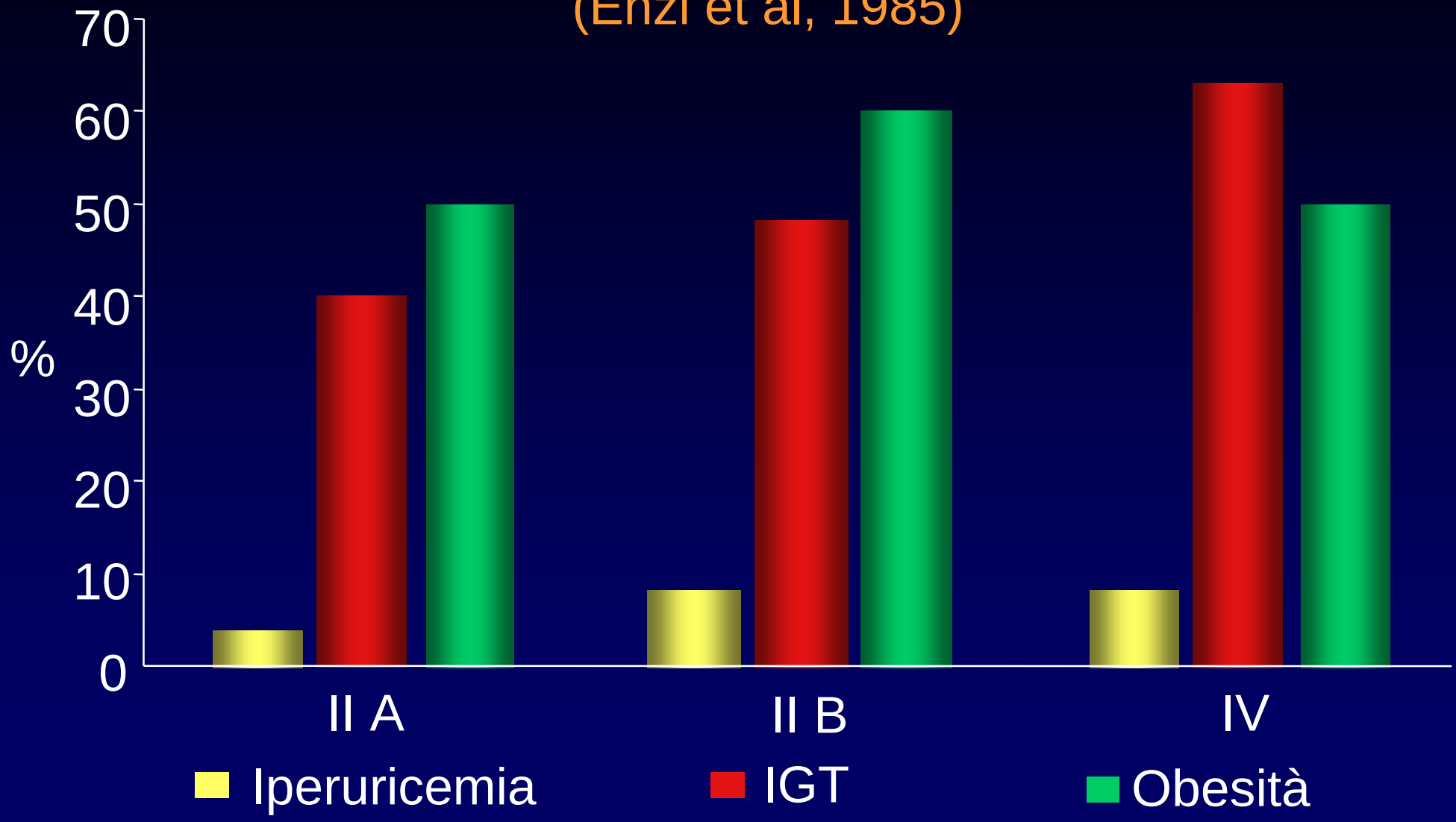
IPERURICEMIA PRIMITIVA ISOLATA E ASSOCIATA AD ALTRE ALTERAZIONI METABOLICHE

(obesità, diabete, dislipidemia, ipertensione)



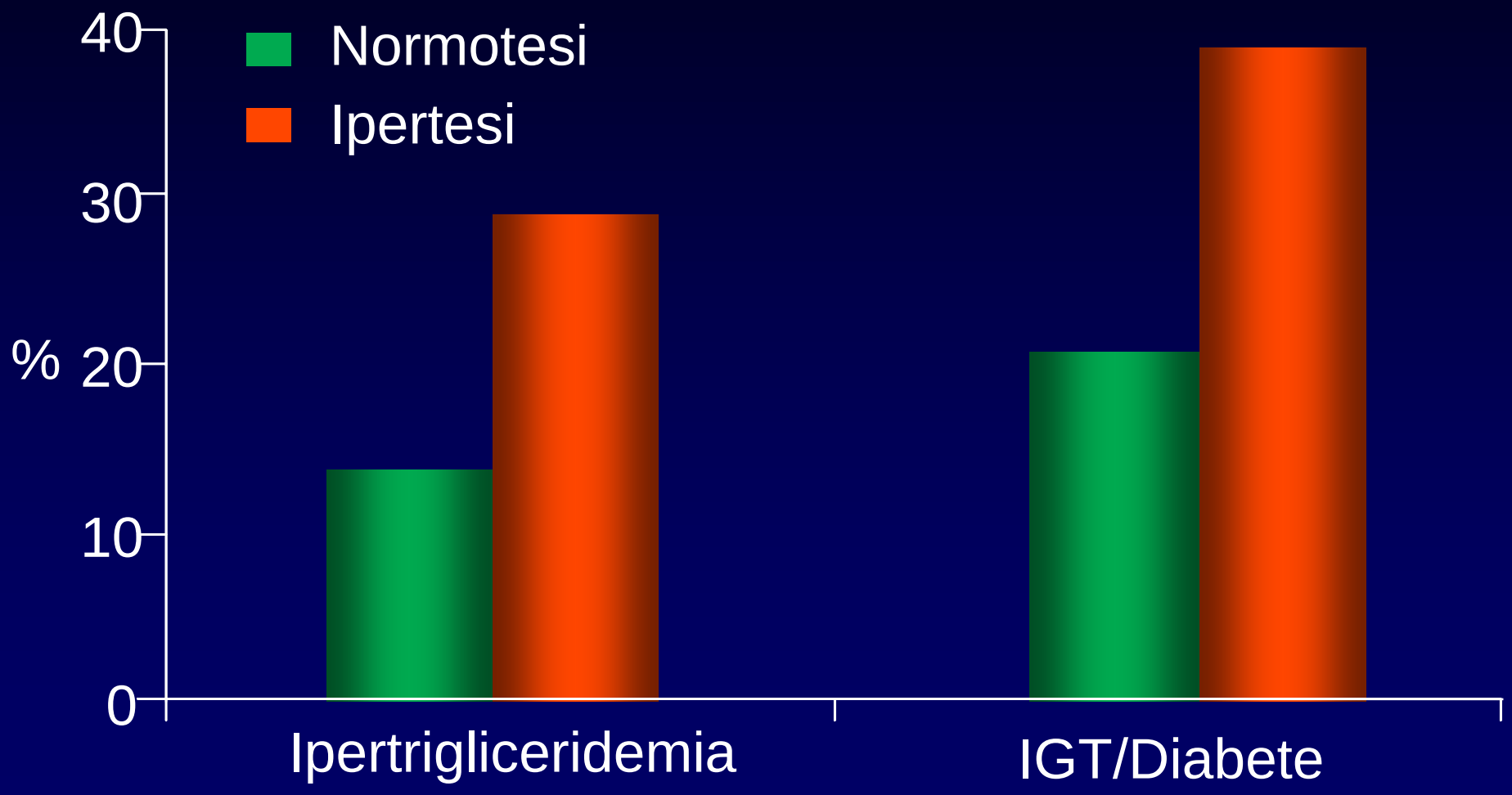
PREVALENZA DI OBESITA', IGT E IPERURICEMIA IN SOGGETTI CON IPERLIPIDEMIA

(Enzi et al, 1985)



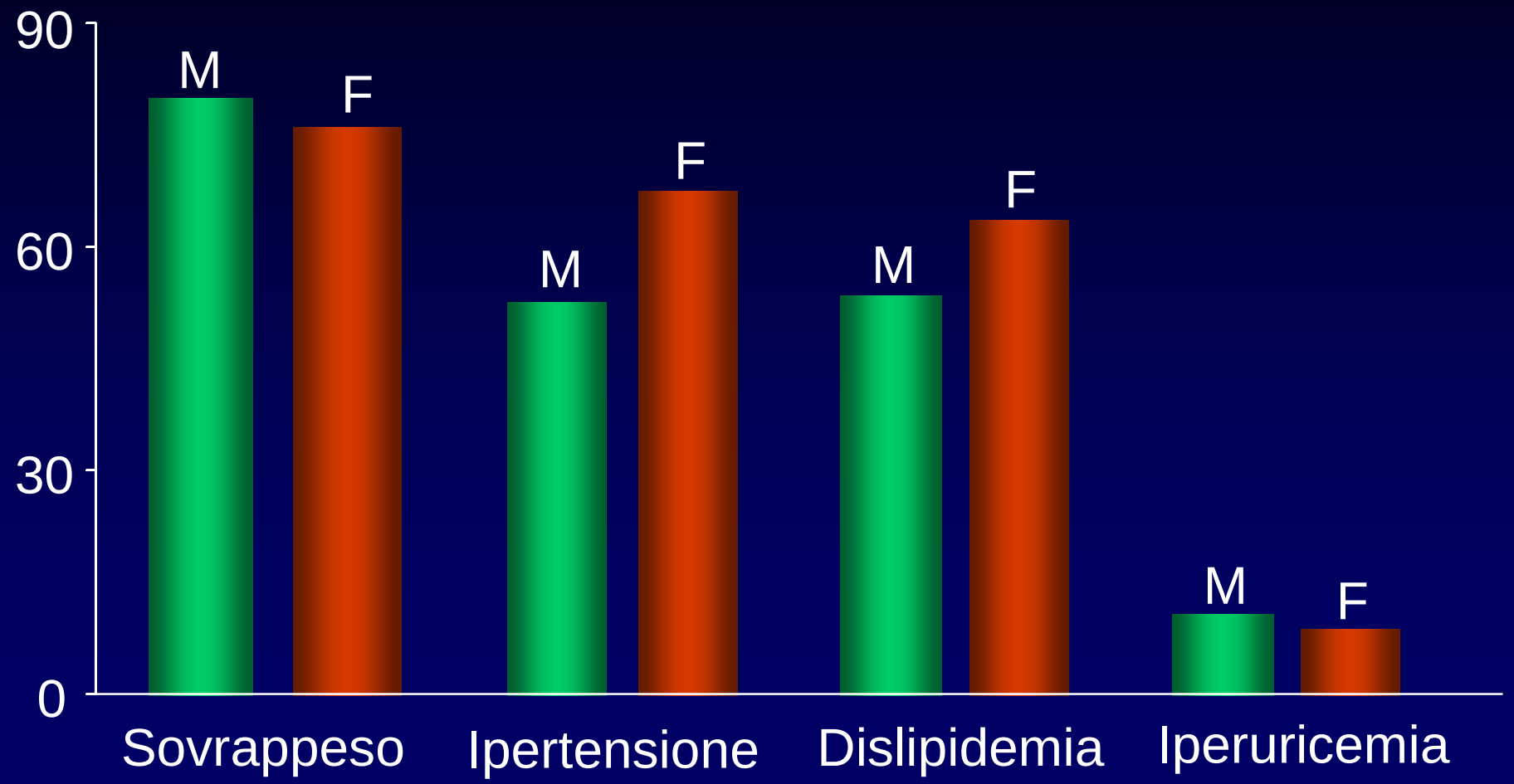
PREVALENZA DI ALTERAZIONI METABOLICHE NELL'IPERTENSIONE ESSENZIALE

(Goteborg Study)

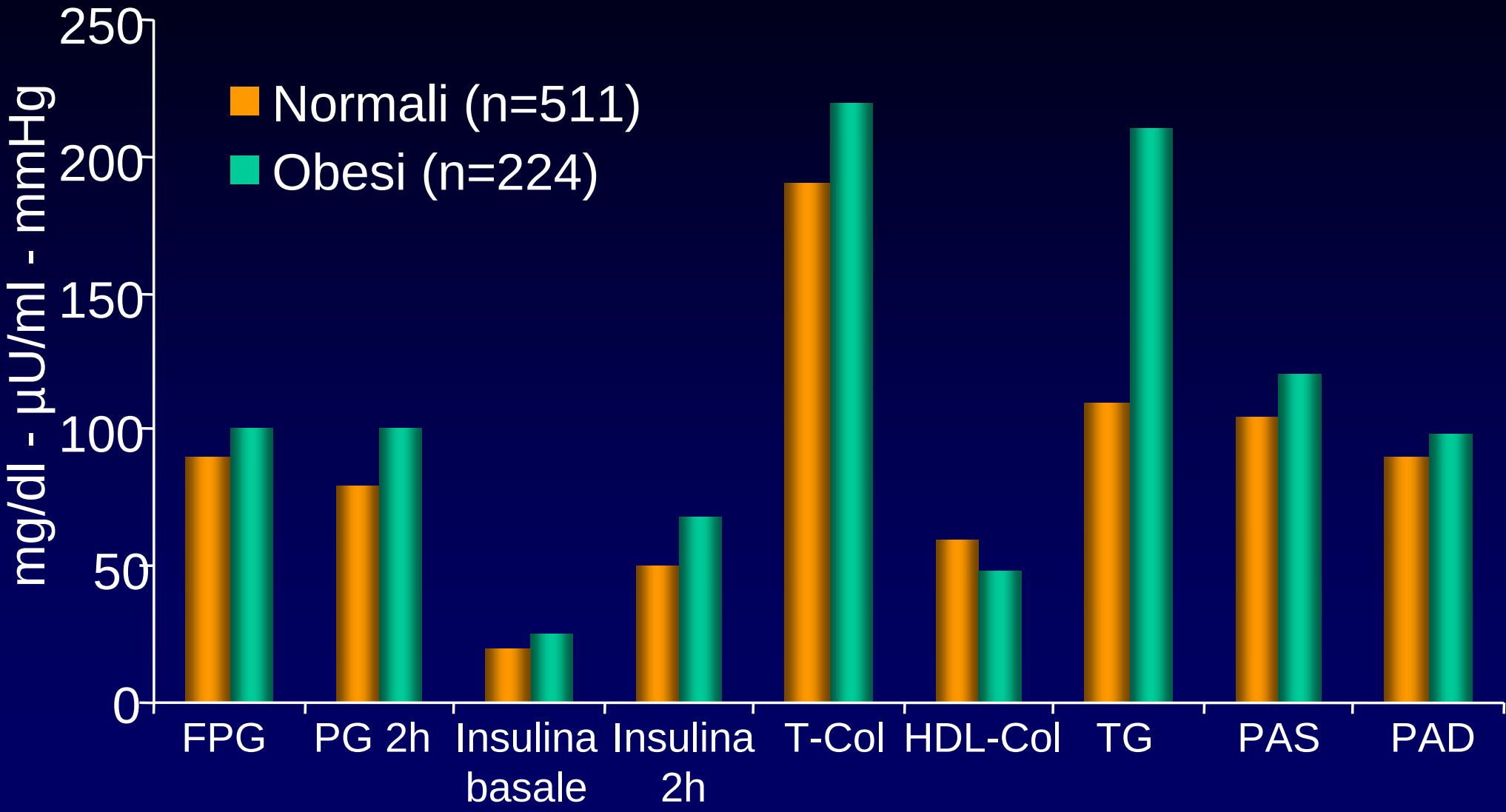


PREVALENZA DI ALTERAZIONI METABOLICHE NEL DIABETE NON INSULINO-DIPENDENTE

(Verona Diabetes Complications Study; n=1780)



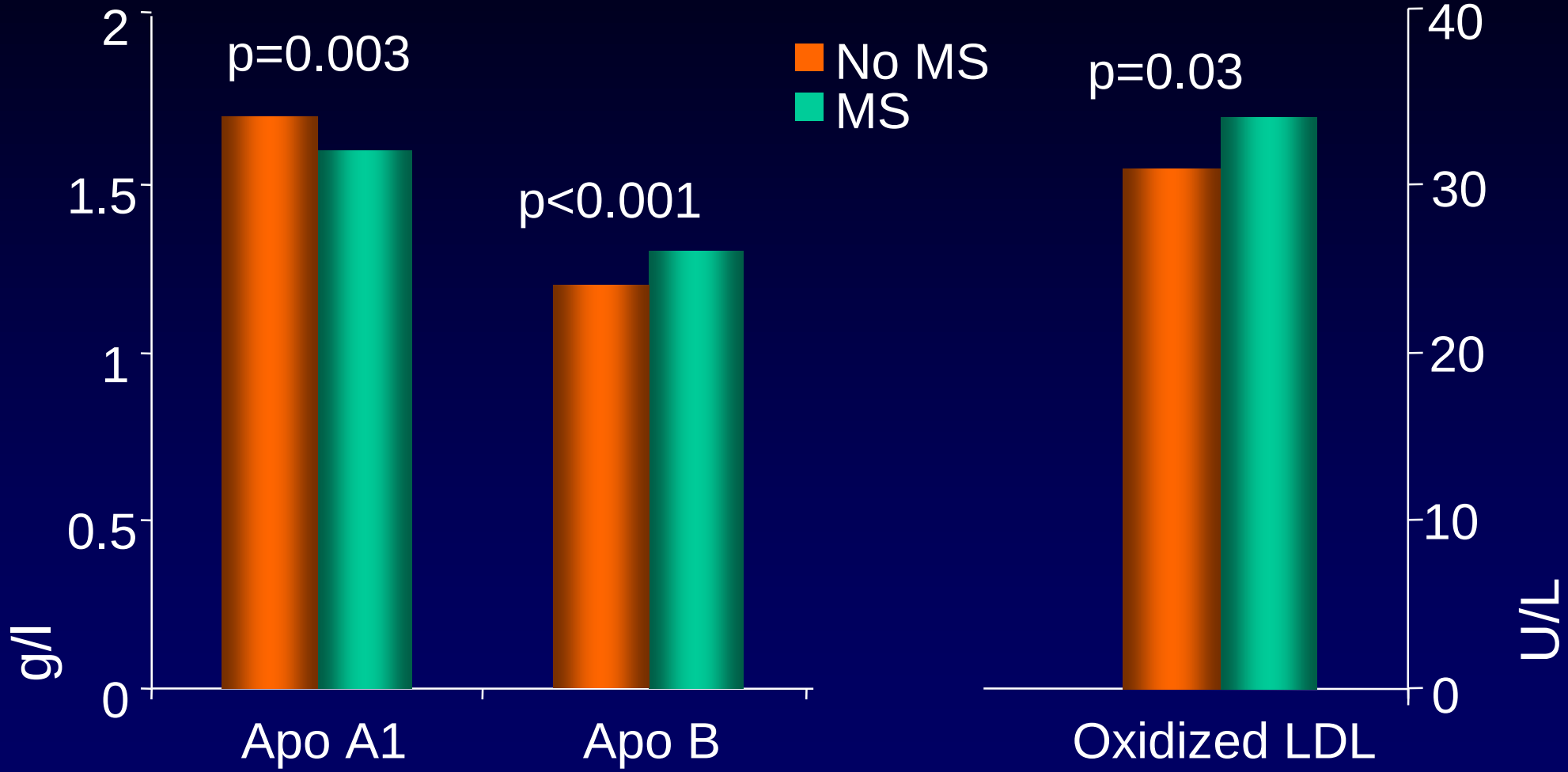
FATTORI DI RISCHIO METABOLICI ED EMODINAMICI NELL'OBESITA'



Ancillary Features of the Metabolic Syndrome

APOPROTEINS AND OXIDIZED LDL

(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)

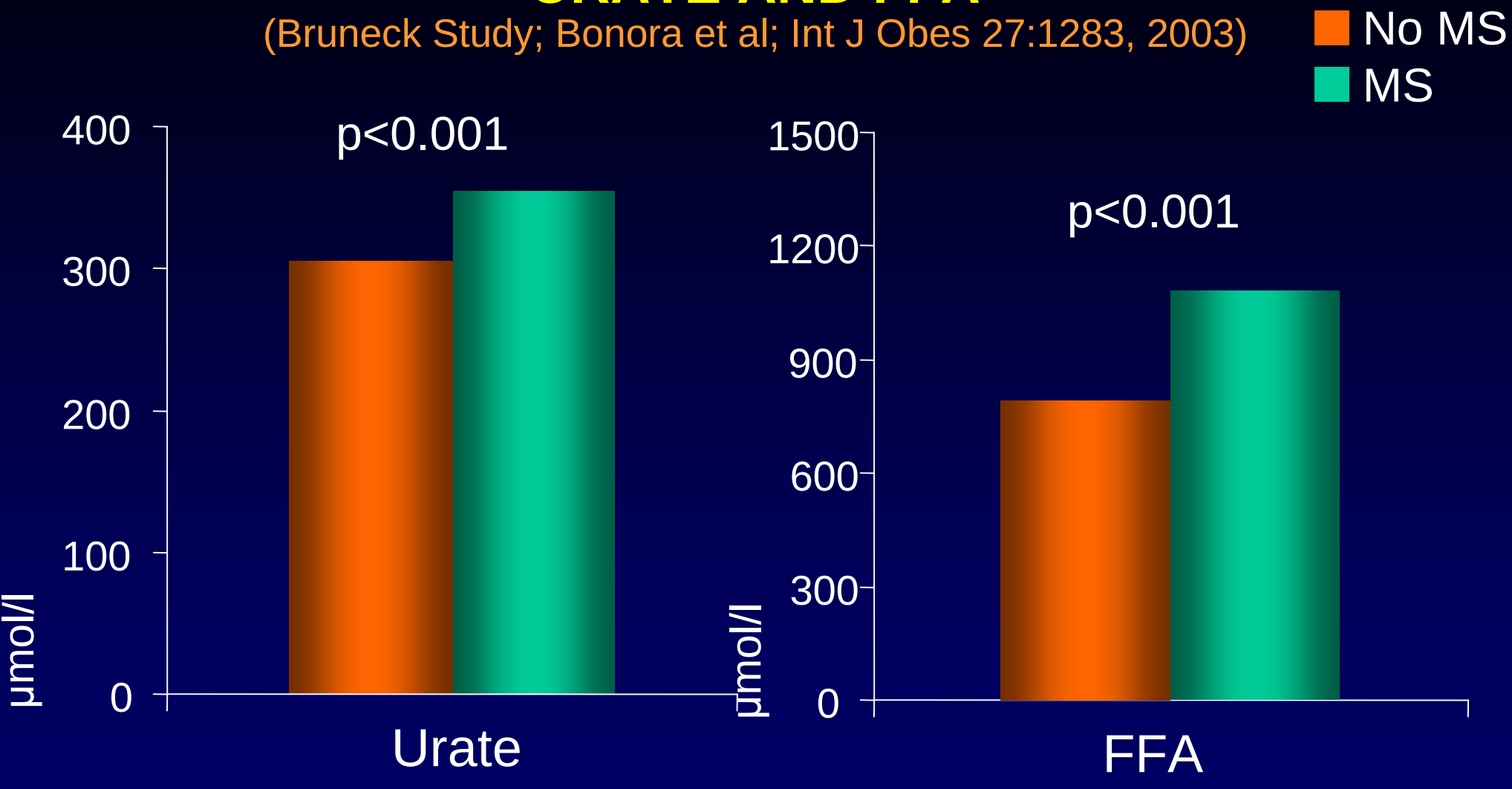


Adjusted for sex, age, smoking, alcohol, physical activity, social status

Ancillary Features of the Metabolic Syndrome

URATE AND FFA

(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)

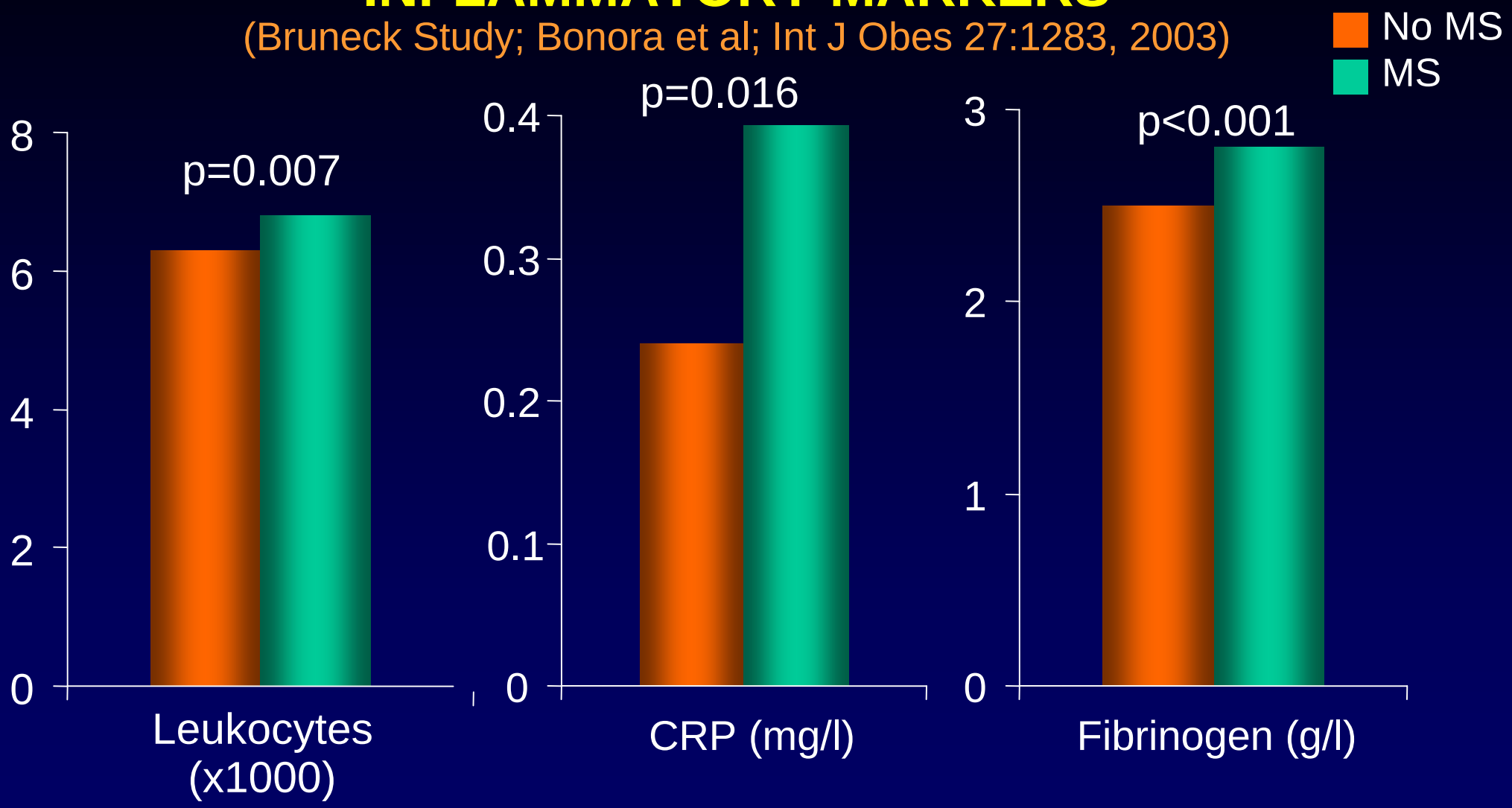


Adjusted for sex, age, smoking, alcohol, physical activity, social status

Ancillary Features of the Metabolic Syndrome

INFLAMMATORY MARKERS

(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)

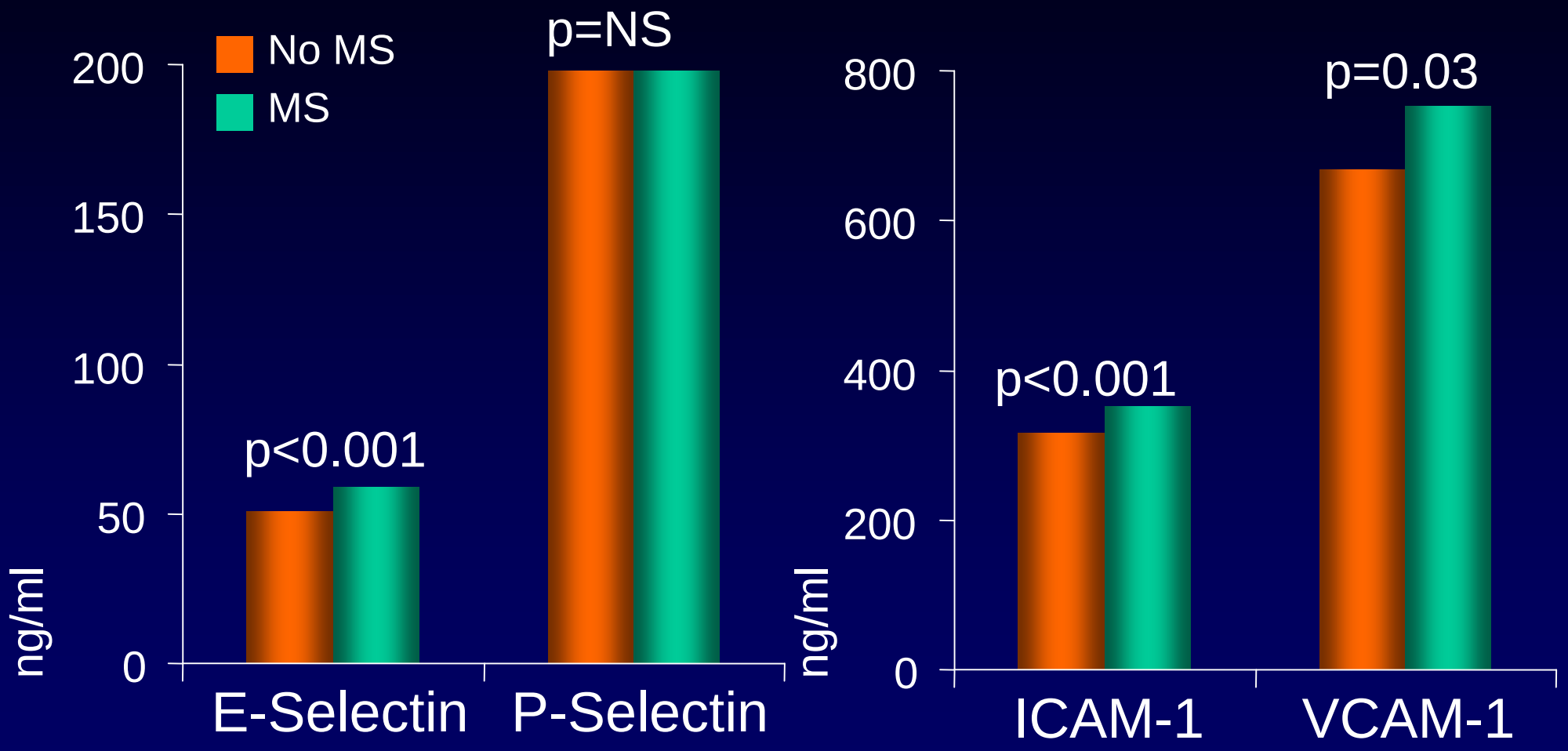


Adjusted for sex, age, smoking, alcohol, physical activity, social status

Ancillary Features of the Metabolic Syndrome

ENDOTHELIAL ADHESION MOLECULES

(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)

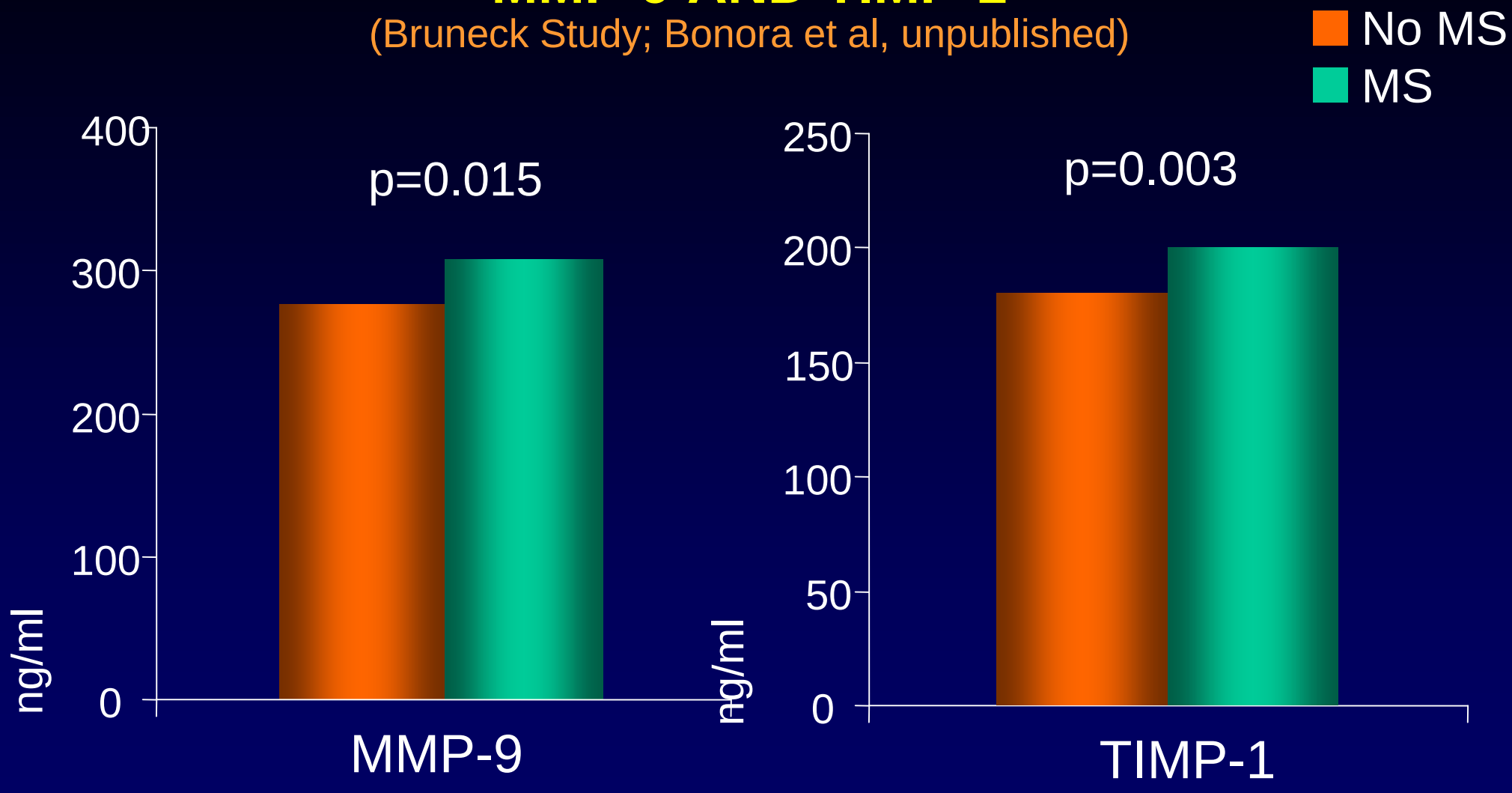


Adjusted for sex, age, smoking, alcohol, physical activity, social status

Ancillary Features of the Metabolic Syndrome

MMP-9 AND TIMP-1

(Bruneck Study; Bonora et al, unpublished)

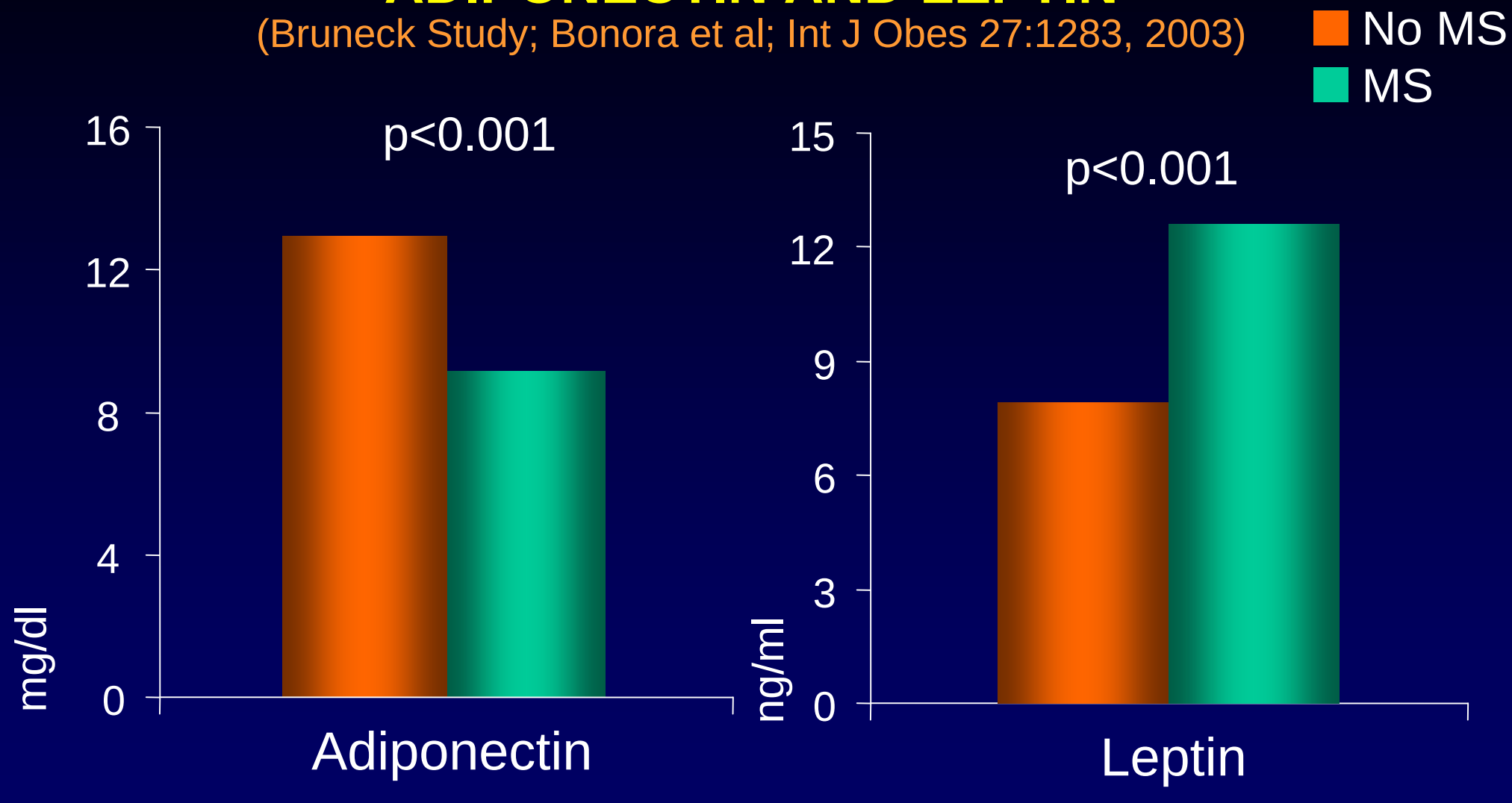


Adjusted for sex, age, smoking, alcohol, physical activity, social status

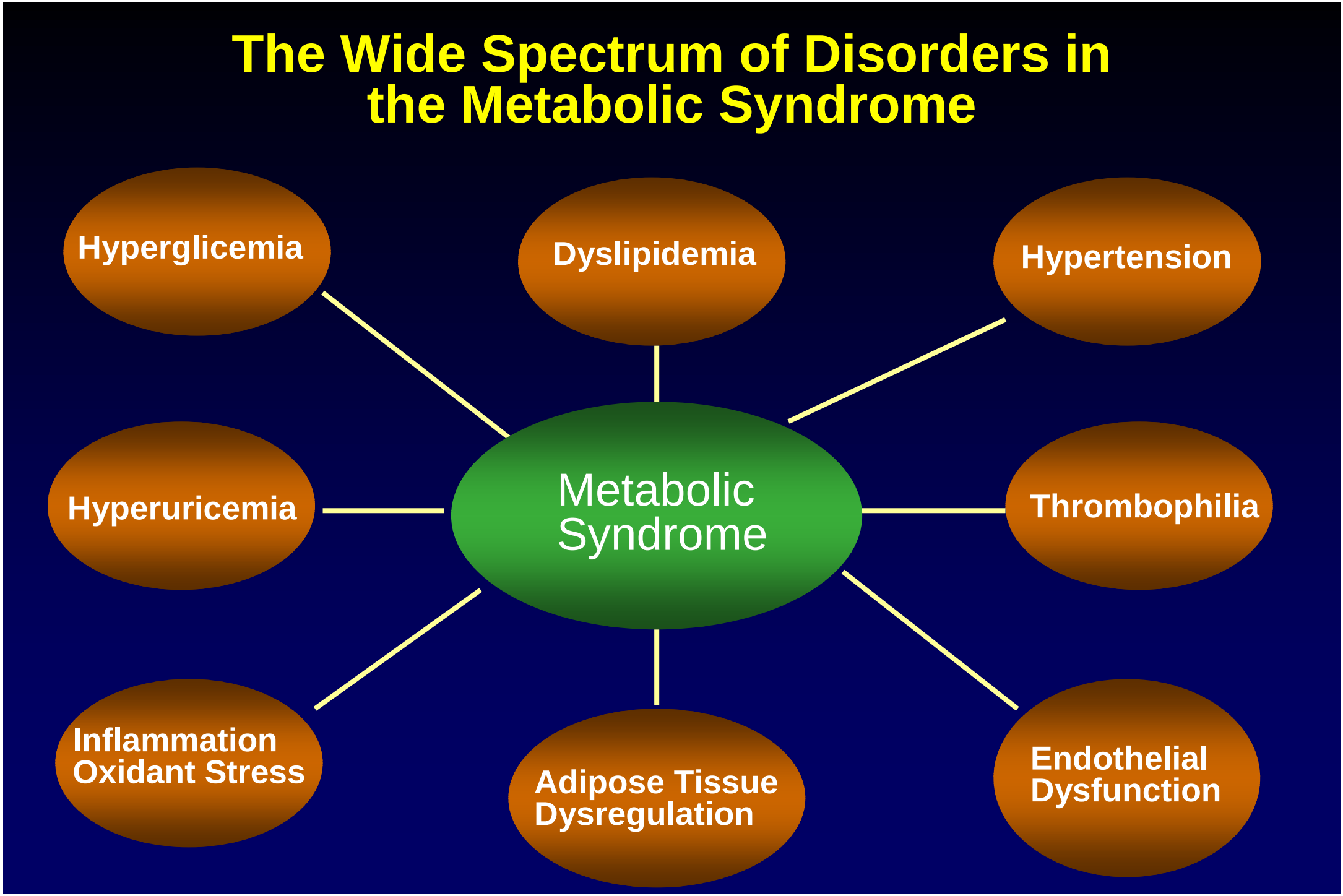
Ancillary Features of the Metabolic Syndrome

ADIPONECTIN AND LEPTIN

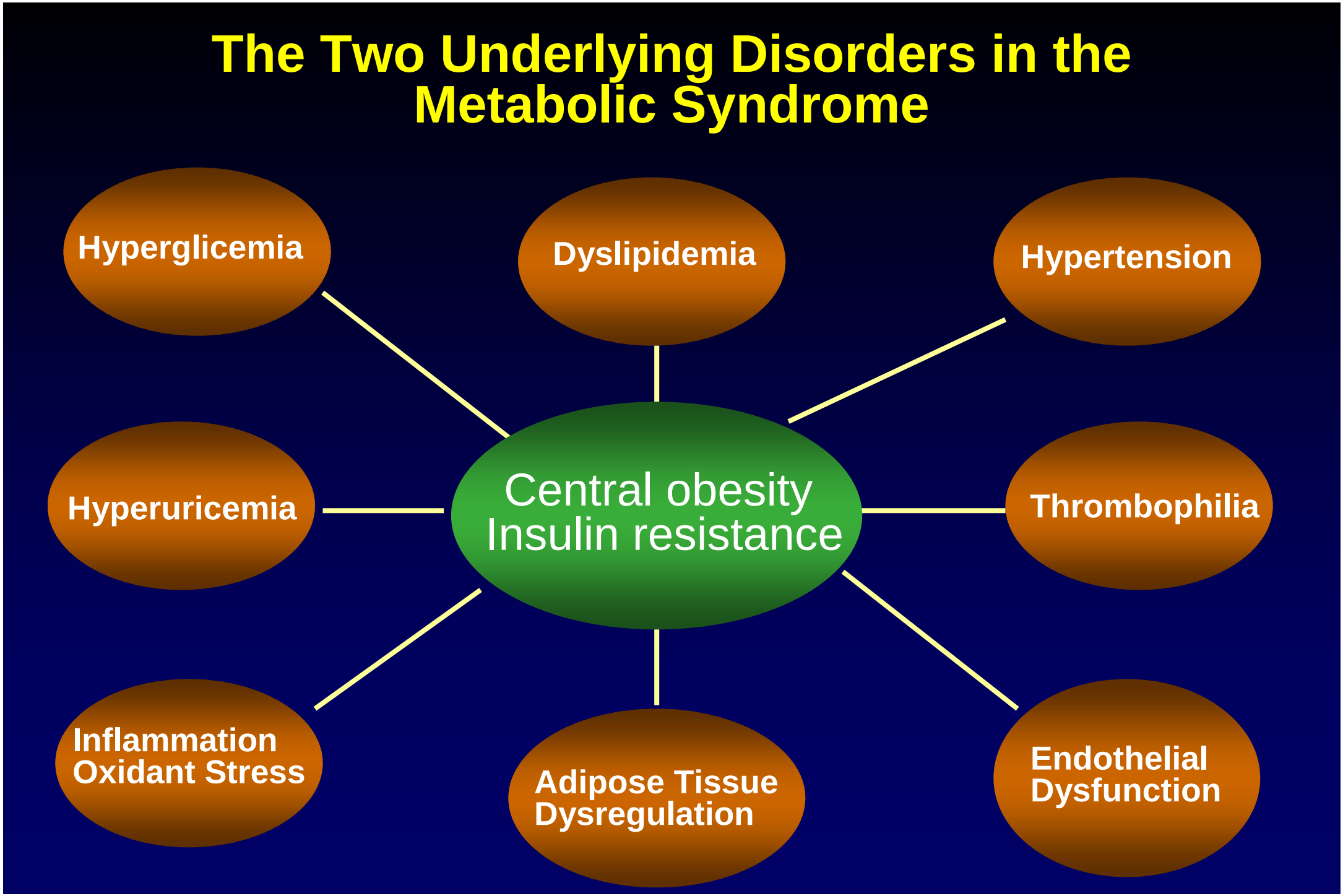
(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)



Adjusted for sex, age, smoking, alcohol, physical activity, social status


The Wide Spectrum of Disorders in the Metabolic Syndrome
Hyperglicemia
Dyslipidemia
Hypertension
Hyperuricemia
Metabolic Syndrome
Thrombophilia
Inflammation Oxidant Stress
Adipose Tissue Dysregulation
Endothelial Dysfunction

The Two Underlying Disorders in the Metabolic Syndrome



Classic CVD Risk Factors According to Waist Circumference

(Bruneck Study; Bonora et al, unpublished)

	Waist (Q1)	Waist (Q4)	p
Systolic blood pressure (mmHg)	139	154	0.001
2-h OGTT glucose (mg/dl)	95	112	0.001
Apo B (mg/dl)	113	127	0.001
HDL cholesterol (mg/dl)	63	52	0.001
Triglycerides (mg/dl)	114	157	0.001

Data adjusted for sex, age, smoking and HOMA-IR

Non-traditional CVD Risk Factors According to Waist Circumference

(Bruneck Study; Bonora et al, unpublished)

	Waist (Q1)	Waist (Q4)	p
Uric acid (mg/dl)	4.7	5.9	0.001
Fibrinogen (mg/dl)	249	277	0.001
Ferritin (mg/dl)	127	176	0.010
E-selectin (ng/ml)	49	60	0.001
Leptin (ng/ml)	6.7	14.8	0.001

Data adjusted for sex, age, smoking and (ln)HOMA-IR

Classic CVD Risk Factors According to HOMA-estimated Insulin Resistance

(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)

	HOMA-IR (Q1)	HOMA-IR (Q4)	p
Systolic blood pressure (mmHg)	144	150	0.001
HbA1c (%)	5.46	5.71	0.001
LDL cholesterol (mg/dl)	133	141	NS
HDL cholesterol (mg/dl)	56	51	0.001
Triglycerides (mg/dl)	124	183	0.001

Data adjusted for sex, age, waist

Non-traditional CVD Risk Factors According to HOMA-Estimated Insulin Resistance

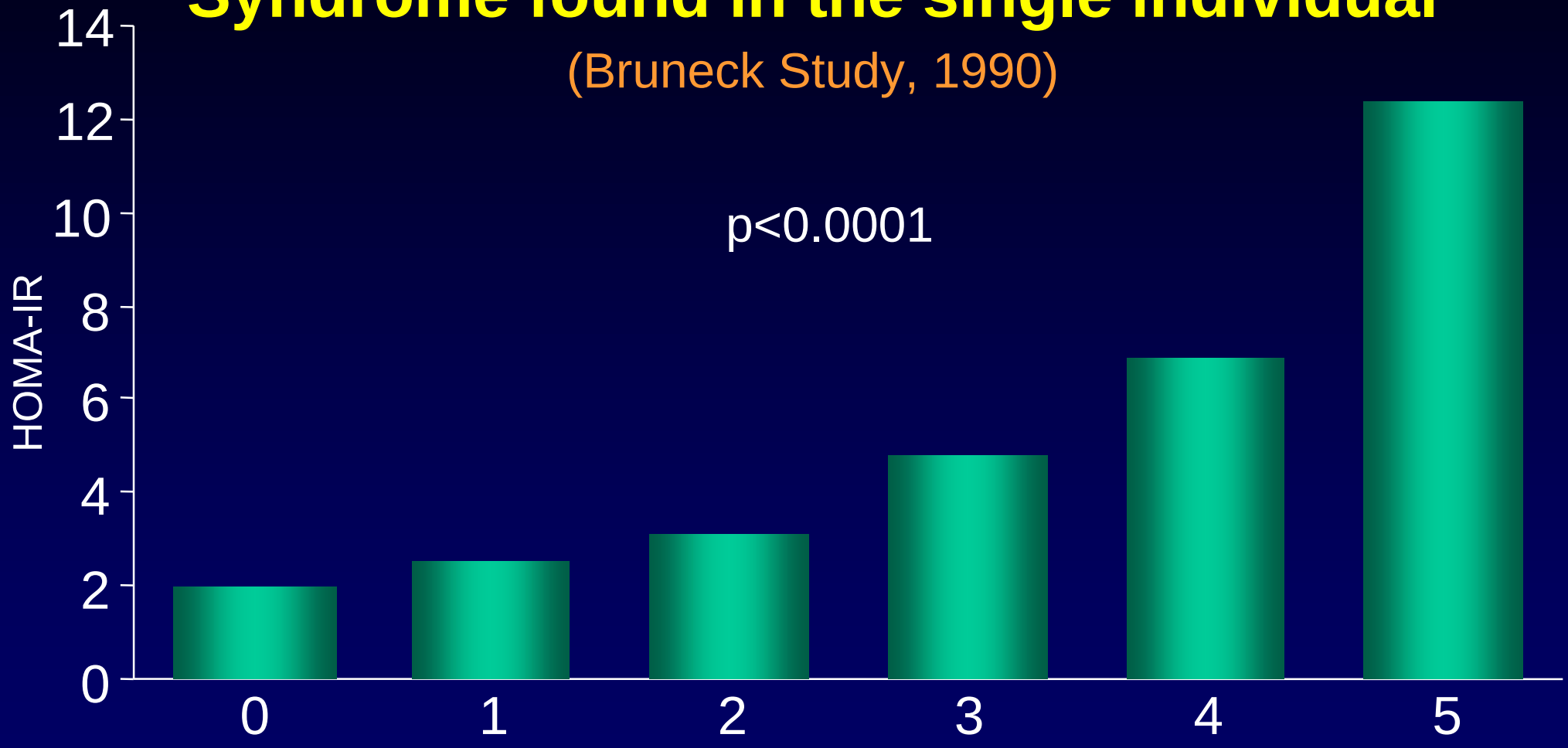
(Bruneck Study; Bonora et al; Int J Obes 27:1283, 2003)

	HOMA-IR (Q1)	HOMA-IR (Q4)	p
Fibrinogen (mg/dl)	255	273	0.001
Ferritin (mg/dl)	151	194	0.036
Leukocytes	6155	7256	0.001
Adiponectin (mg/dl)	13	10	0.001
Ox-LDL (U/l)	31	36	0.001

Data adjusted for sex, age, waist

Insulin Resistance according to the Number of Abnormalities composing the Metabolic Syndrome found in the single individual

(Bruneck Study, 1990)



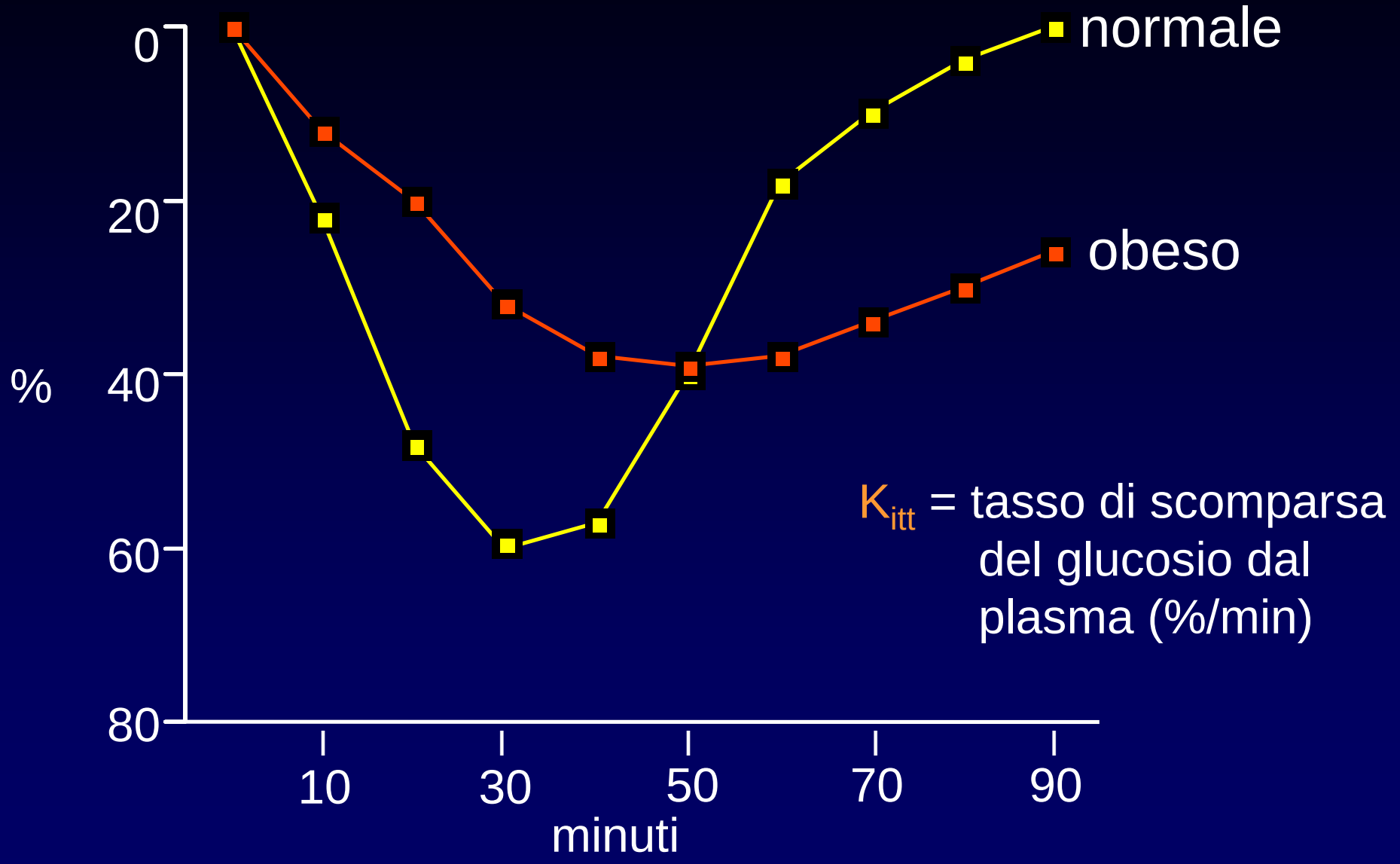
Abnormalities: impaired glucose regulation (IFG,IGT,DM), hypertension, dyslipidemia, obesity or central fat distribution, microalbuminuria
Sex-and age-adjusted

INSULINO-RESISTENZA

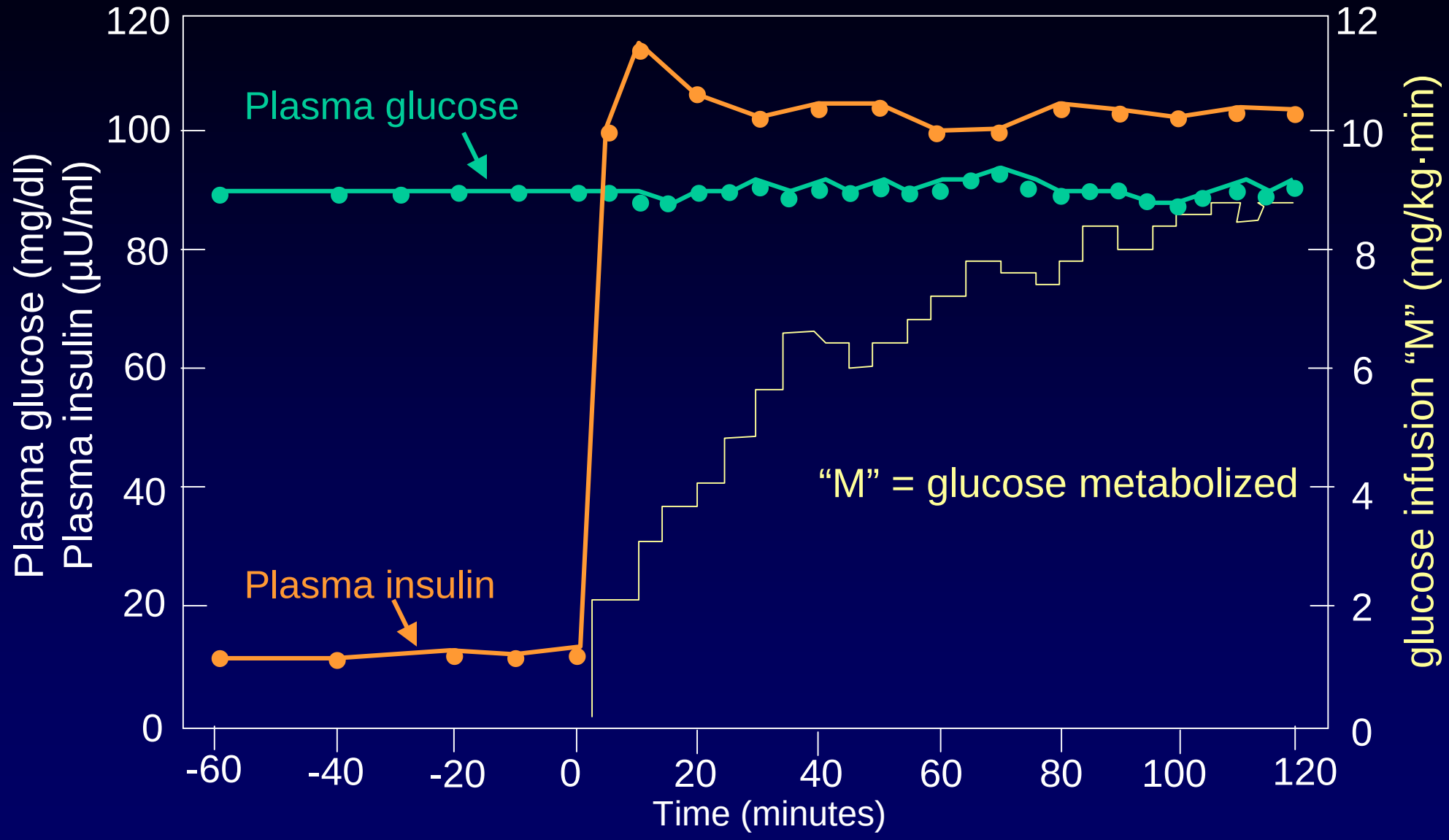
Condizione clinica in cui l'insulina esercita un effetto biologico inferiore al normale.

- Organismo intero
- Singolo organo
- Singolo tipo cellulare
- Singolo processo biologico

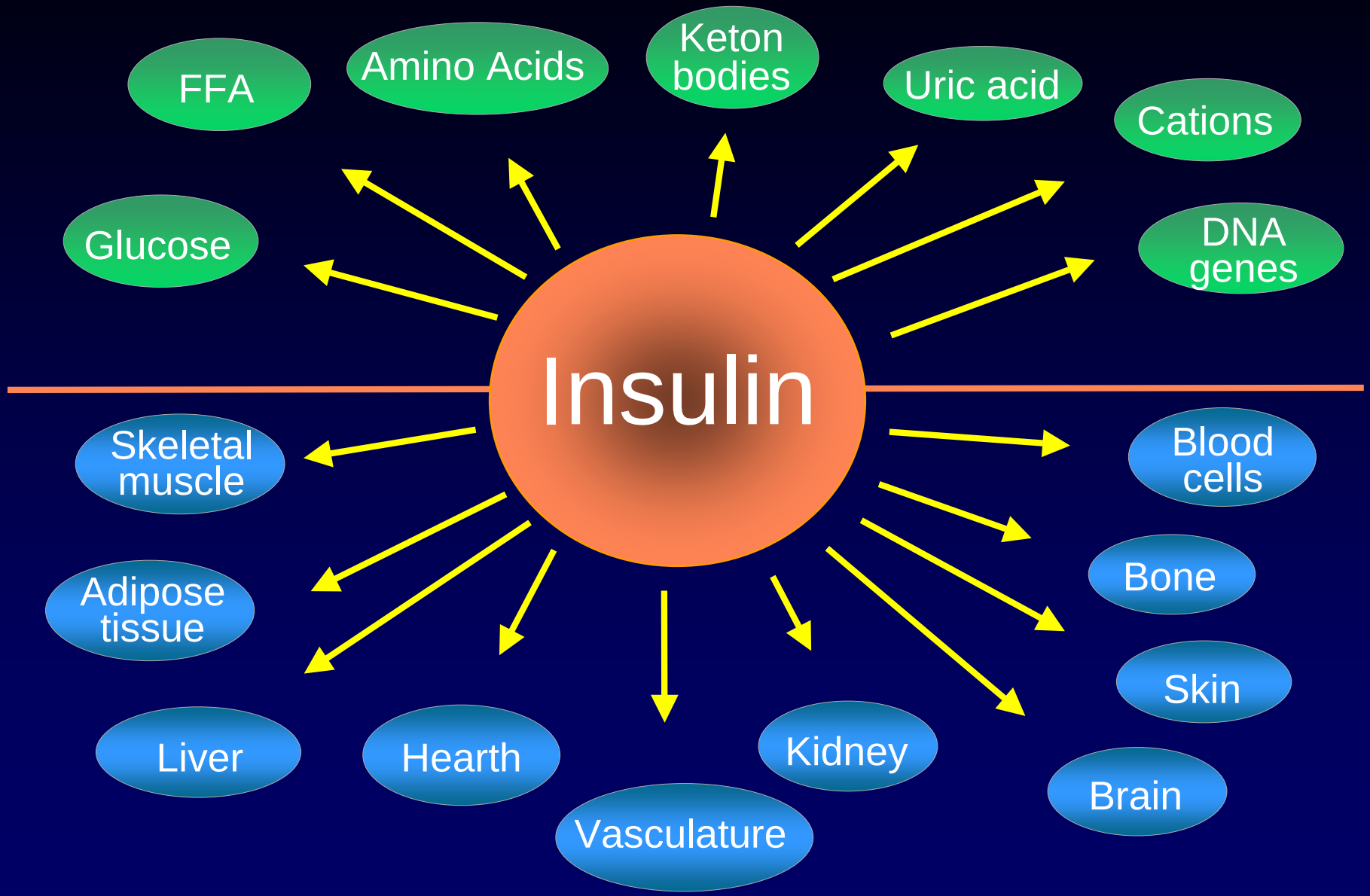
DECREMENTO GLICEMICO DOPO INSULINA E.V.



La tecnica del clamp del glucosio (“glucose clamp”)



THE WIDE SPECTRUM OF INSULIN BIOLOGICAL EFFECTS



INSULINO-RESISTENZA

NELLA FISIOLOGIA

- Pubertà
- Gravidanza
- Invecchiamento

NELLA PATOLOGIA

- Diabete mellito tipo 2 e antecedenti (IFG/IGT)
- Obesità
- Dislipidemia (fenotipi IIB e IV)
- Ipertensione arteriosa essenziale
- Epatopatie croniche
- Uremia
- Policistosi ovarica
- Acromegalia, ipercorticismo, altre endocrinopatie
- Sindromi genetiche (es. leprecaunismo)

INSULIN RESISTANCE IN HUMAN DISEASES

	Approximate % with IR when the condition is isolated
Type 2 diabetes mellitus	70-80
IGT/IFG	50-60
Obesity	40-50
Dyslipidemia (II B, IV)	40-50
Essential hypertension	20-30
Hyperuricemia	20-30
PCOS	20-30
Endocrine diseases	quite common
Other chronic diseases	quite common
Apparently healthy subjects	10-20

EPIDEMIOLOGIA DELL'INSULINO-RESISTENZA

- diabete mellito tipo 2
- obesità
- dislipidemia (alti TG e/o basso HDL)
- ipertensione essenziale
- altre condizioni cliniche

Prevalenza = 30-40%

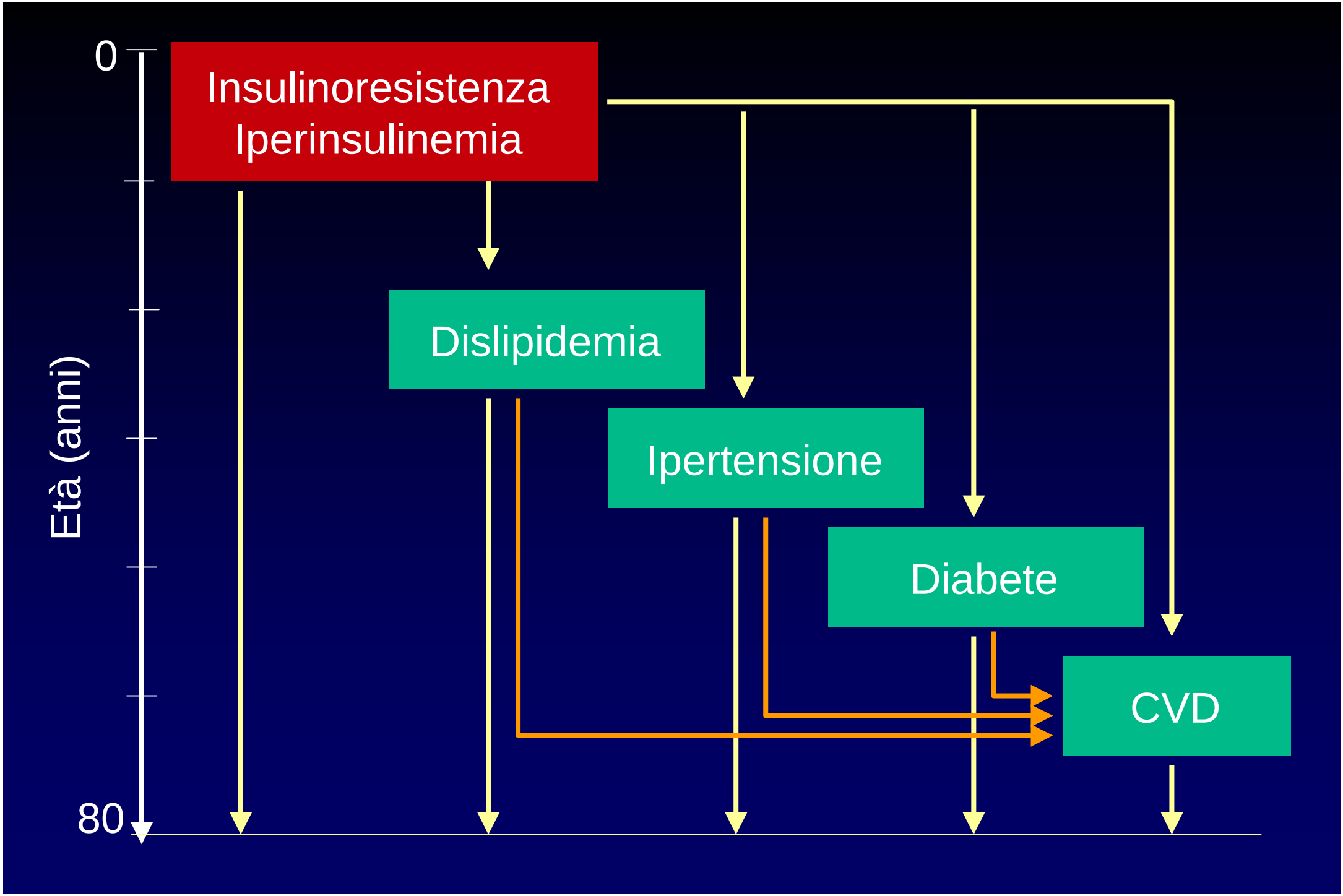
SUBJECTS WITH INSULIN RESISTANCE IN THE WORLD

Type 2 diabetes - IFG/IGT - Obesity (overweight) - Dyslipidemia - Hypertension - Hyperuricemia - Endocrine Diseases - Non-Metabolic Diseases - Healthy subjects

Hundreds of millions people

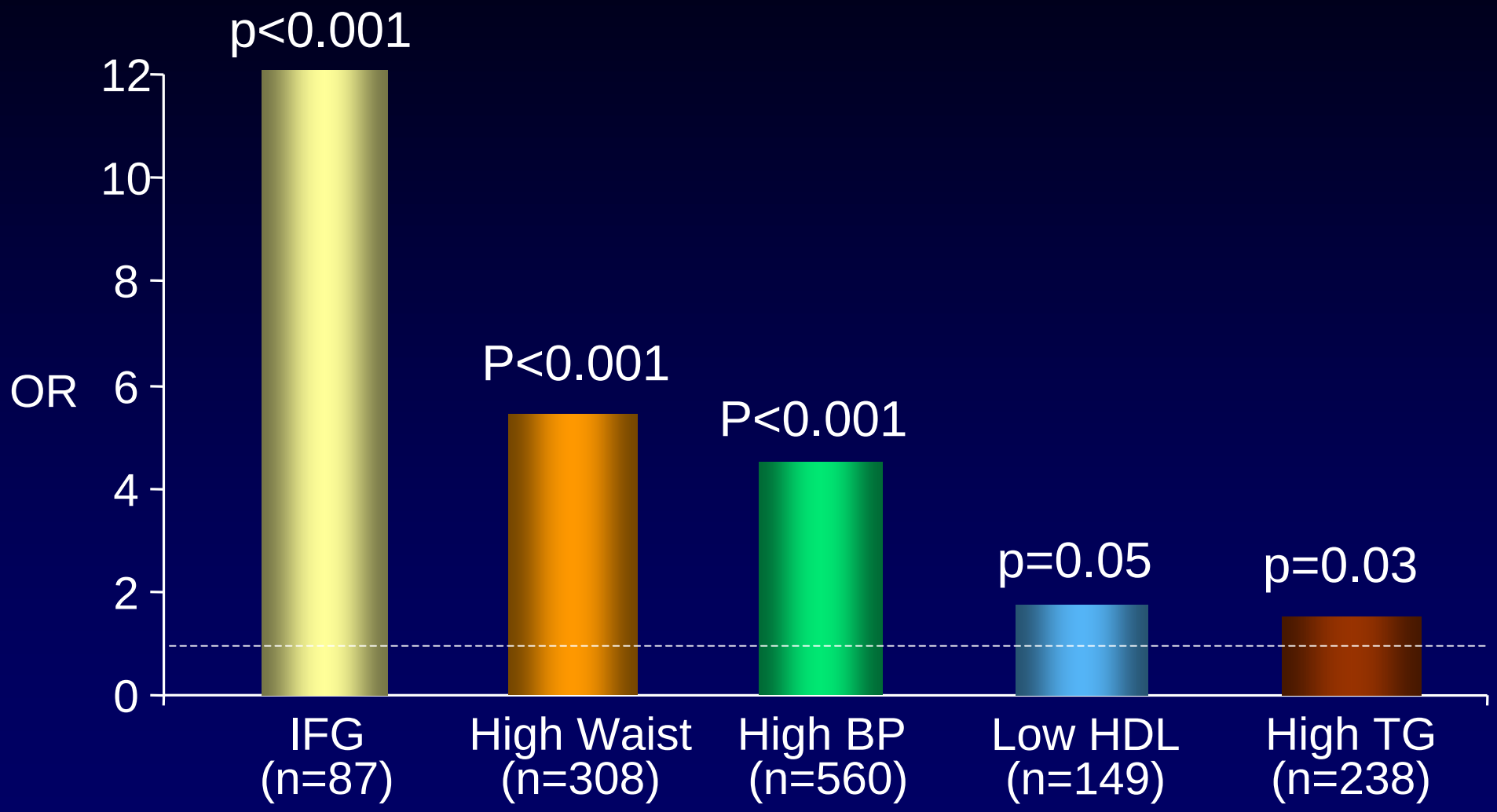
SINDROME METABOLICA

- Dinamicità del quadro clinico
- Eterogeneità del quadro clinico nei consanguinei
- Forte impatto dei fattori ambientali sul fenotipo
- Notevole suscettibilità genetica


0
Insulinoresistenza
Iperinsulinemia
Dislipidemia
Ipertensione
Diabete
CVD
Età (anni)
80

Traits of the Metabolic Syndrome as Risk Factors of T2DM in Subjects Aged 40-79 yr

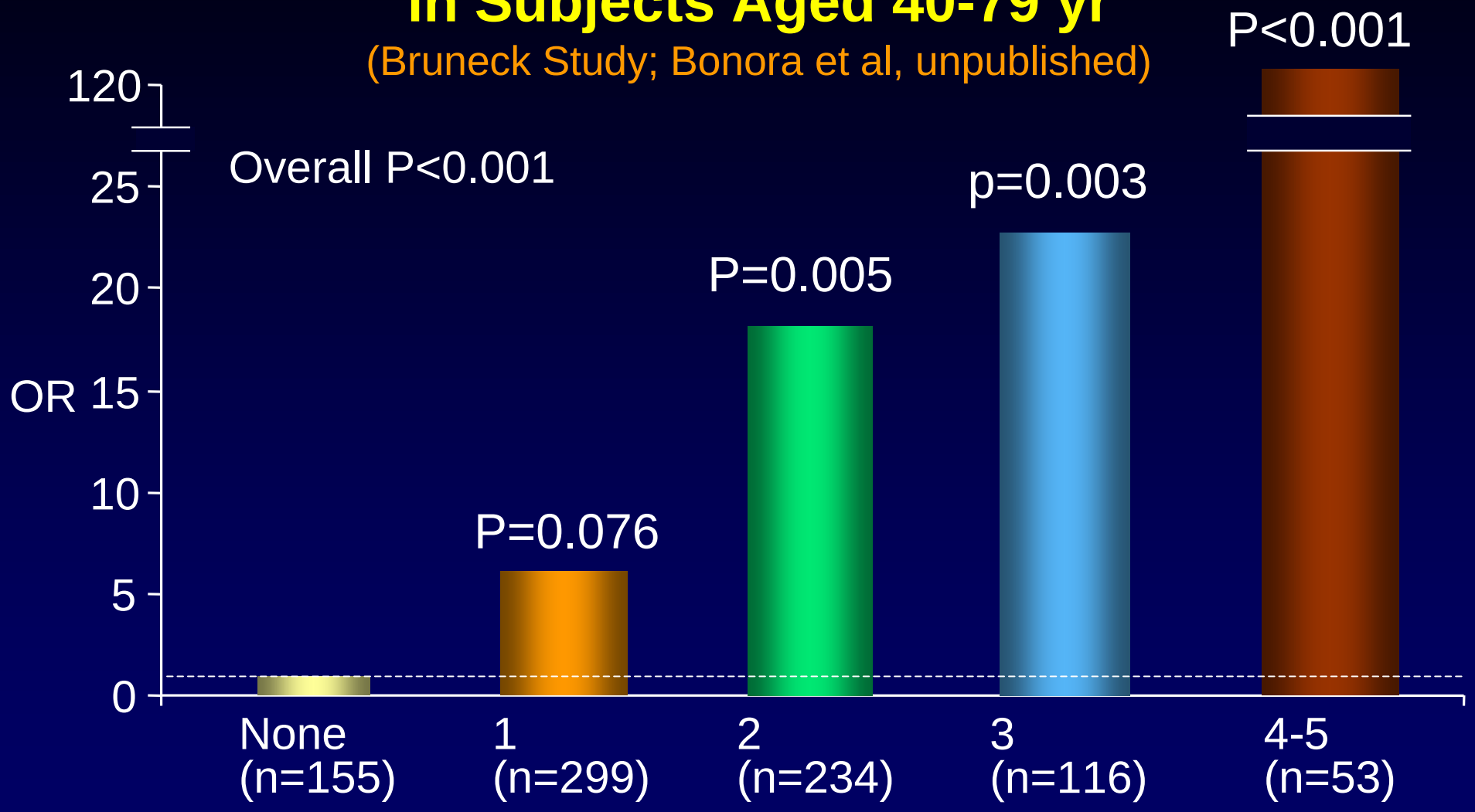
(Bruneck Study; Bonora et al, unpublished)



Sex- and age-adjusted ORs vs. subjects without the given disorder.

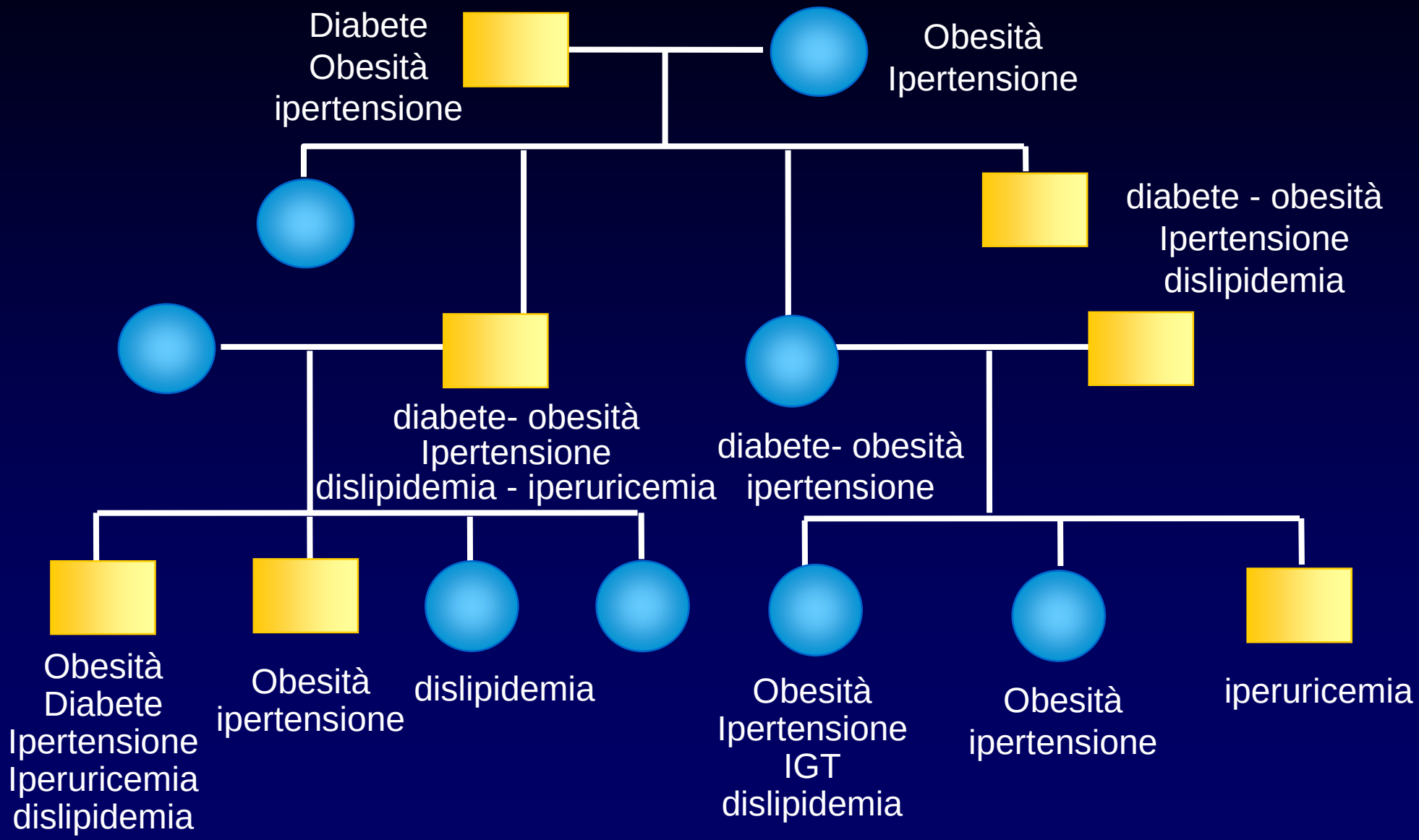
10-yr Risk of T2DM According to the Number of Traits of the Metabolic Syndrome Occurring in Subjects Aged 40-79 yr

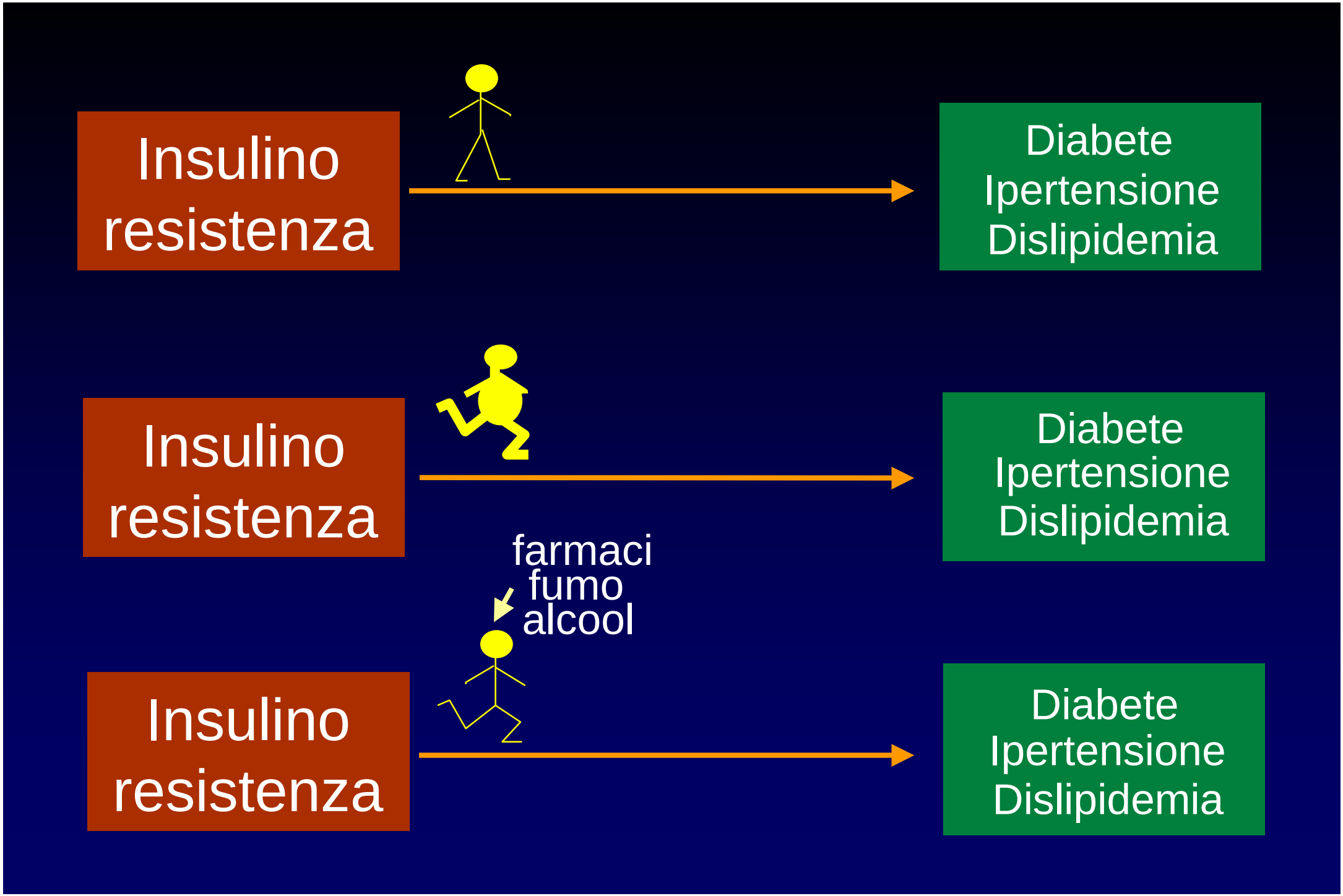
(Bruneck Study; Bonora et al, unpublished)



Sex- and age-adjusted

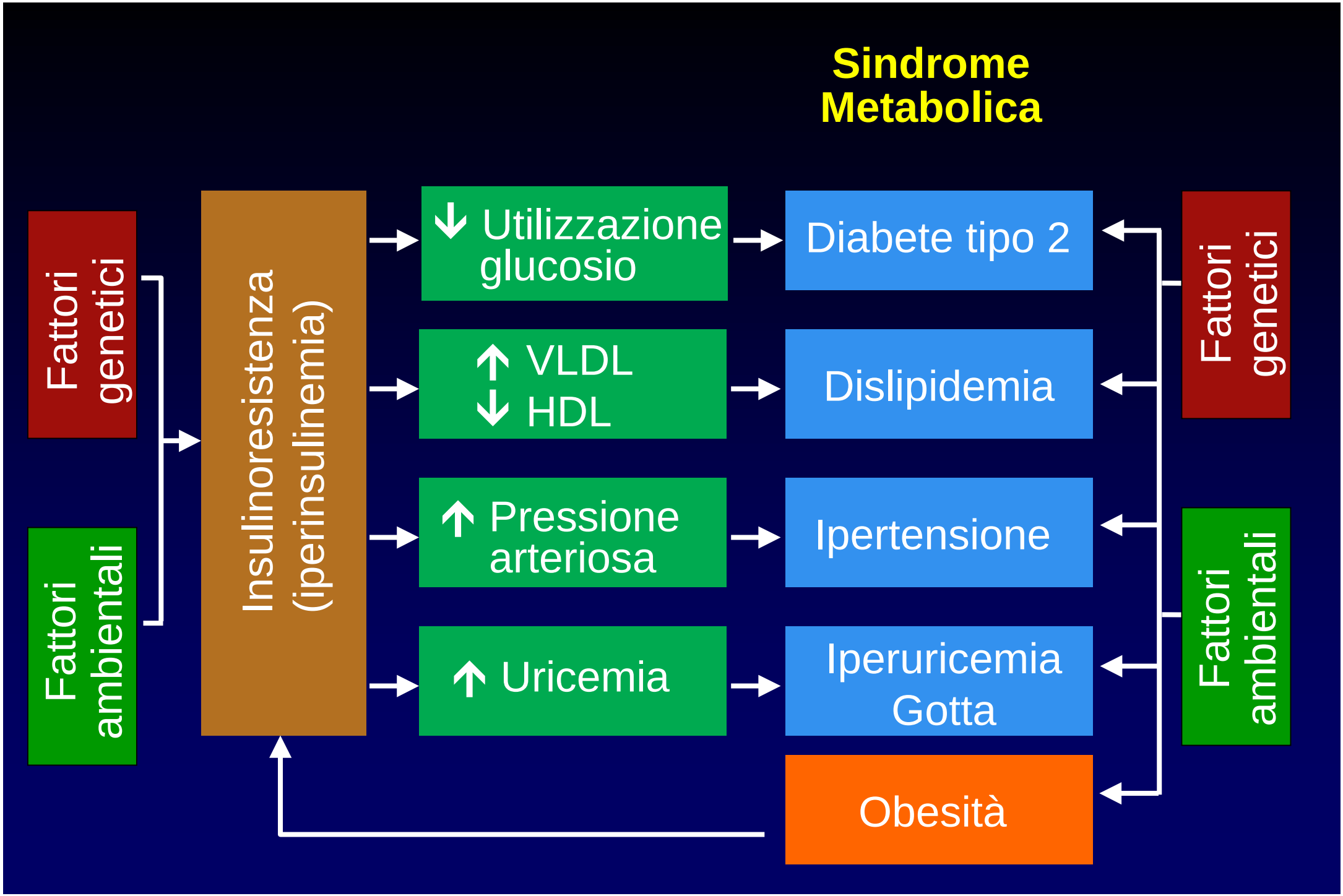
GENEALOGIA NELLA SINDROME METABOLICA




Insulino resistenza
Diabete Ipertensione Dislipidemia
Insulino resistenza
Diabete Ipertensione Dislipidemia
farmaci
fumo
alcool
Insulino resistenza
Diabete Ipertensione Dislipidemia

SINDROME METABOLICA

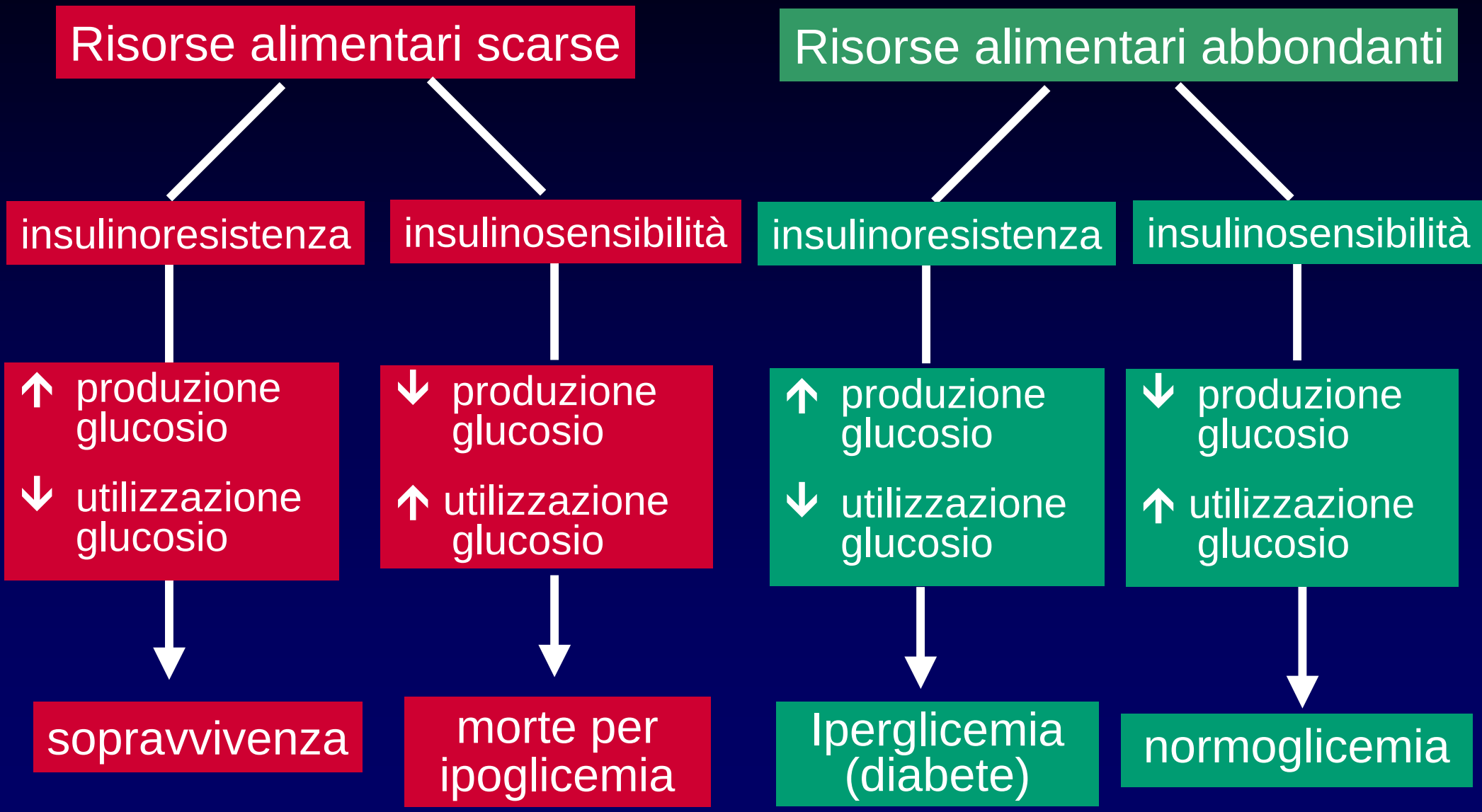
Interazione fra geni di suscettibilità e fattori ambientali


Sindrome Metabolica
Fattori genetici
Fattori ambientali
Insulinoresistenza (iperinsulinemia)
↓ Utilizzazione glucosio
↑ VLDL
↓ HDL
↑ Pressione arteriosa
↑ Uricemia
Diabete tipo 2
Dislipidemia
Ipertensione
Iperuricemia Gotta
Obesità
Fattori genetici
Fattori ambientali

S. METABOLICA IN POPOLAZIONI CHE NE ERANO ESENTI

- Indiani americani
- Aborigeni australiani
- Polinesiani
- Giapponesi migrati negli USA
- Cinesi migrati alle Is. Mauritius

RISORSE ALIMENTARI E INSULINORESISTENZA COME ELEMENTI DI SOPRAVVIVENZA E CAUSA DI DIABETE



SELEZIONE NATURALE E INSULINORESISTENZA

INSULINOSENSIBILI

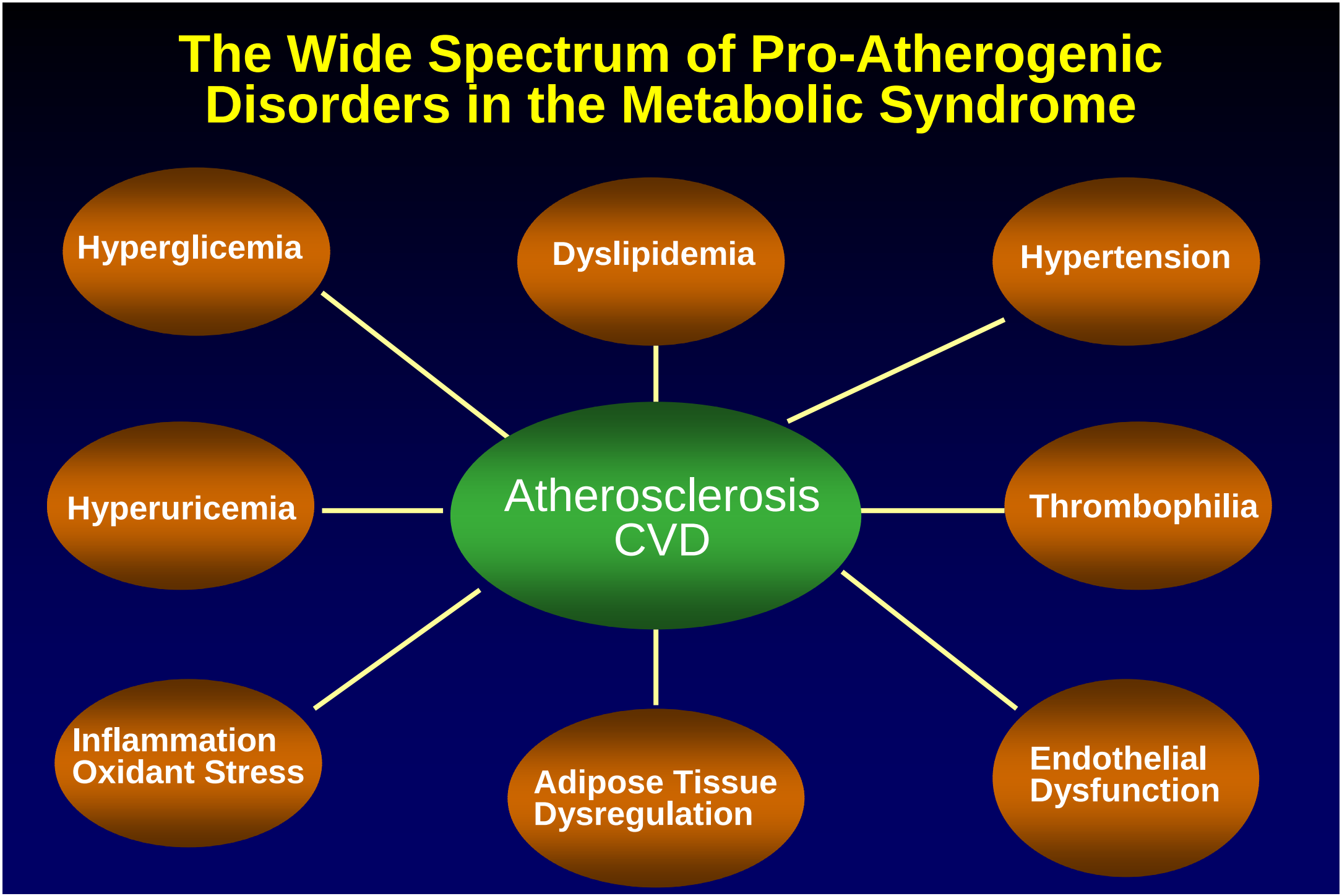
INSULINORESISTENTI

Storia dell'umanità (millenni)

Perché identificare i soggetti con sindrome metabolica ?

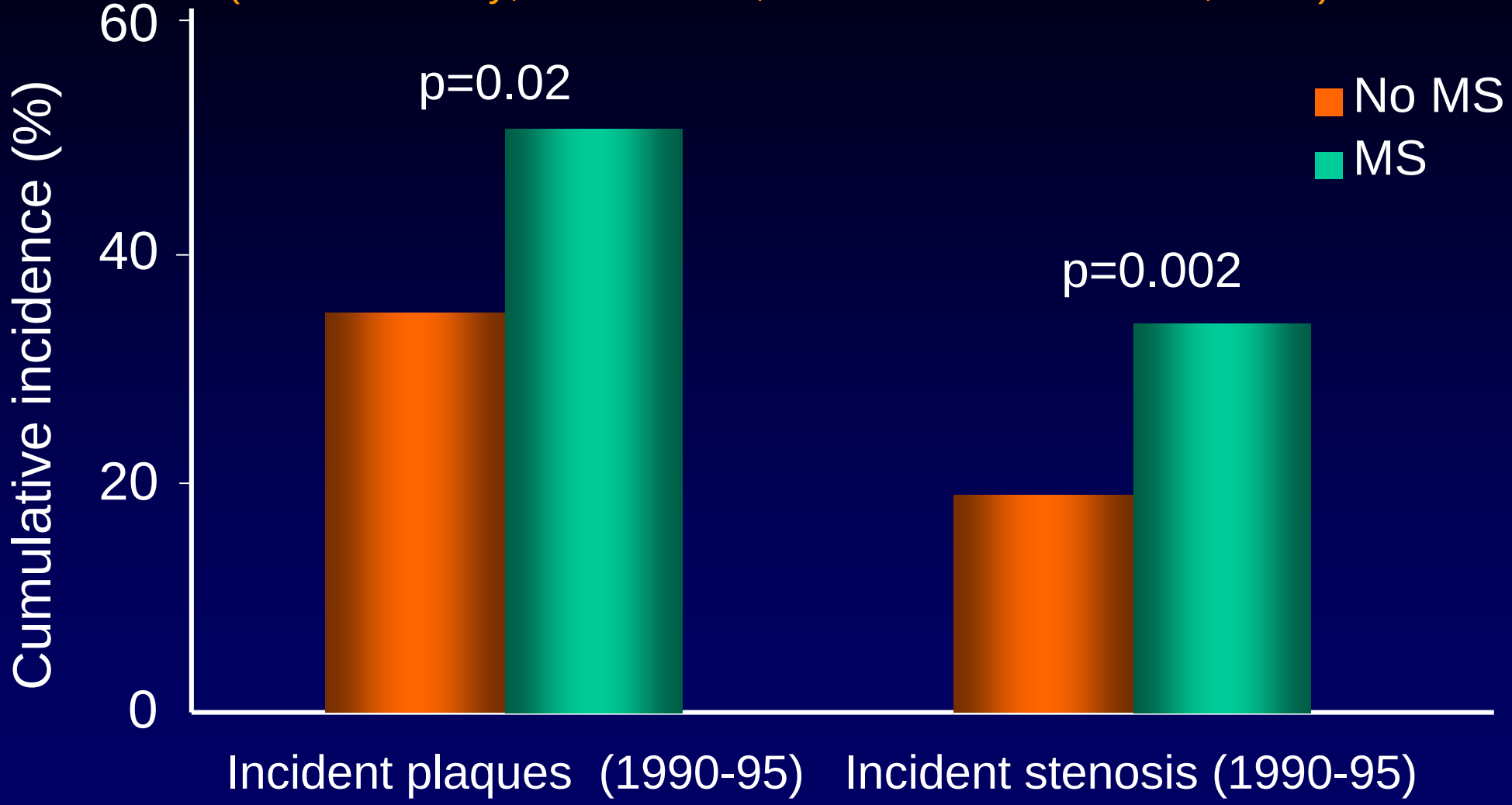
Elevata probabilità di sviluppare malattie cardiovascolari (infarto, ictus) per aggregazione di molteplici fattori di rischio.

The Wide Spectrum of Pro-Atherogenic Disorders in the Metabolic Syndrome



5-yr Incidence of Carotid Atherosclerosis in the Metabolic Syndrome

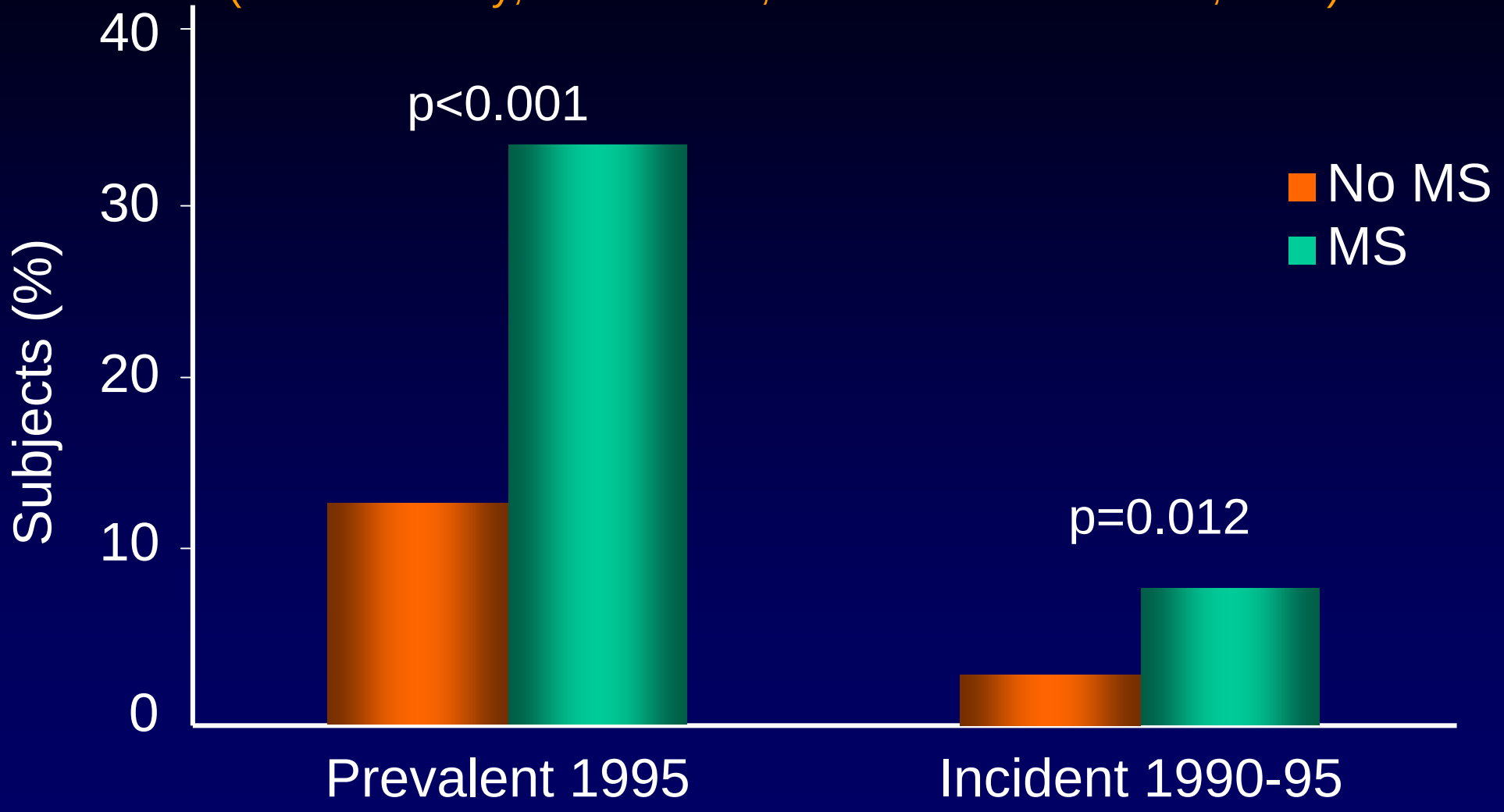
(Bruneck Study; Bonora et al, Diabetes Care 26:1251, 2003)



Adjusted for sex, age, smoking, alcohol, physical activity, social status, LDL-cholesterol, baseline atherosclerosis

Prevalent and Incident Coronary Heart Disease in the Metabolic Syndrome

(Bruneck Study; Bonora et al, Diabetes Care 26:1251, 2003)



Adjusted for sex, age, smoking, alcohol, physical activity, social status, LDL cholesterol, baseline CHD

Odds Ratio for Incident Carotid Atherosclerosis and CHD in subjects with the Metabolic Syndrome

(Bruneck Study, 1990-1995)

	OR	95% C.I.	p
Incident carotid plaques	1.5	1.1-2.1	0.02
Incident carotid stenosis	2.4	1.3-4.1	0.01
Incident CHD	2.3	1.2-4.3	0.01

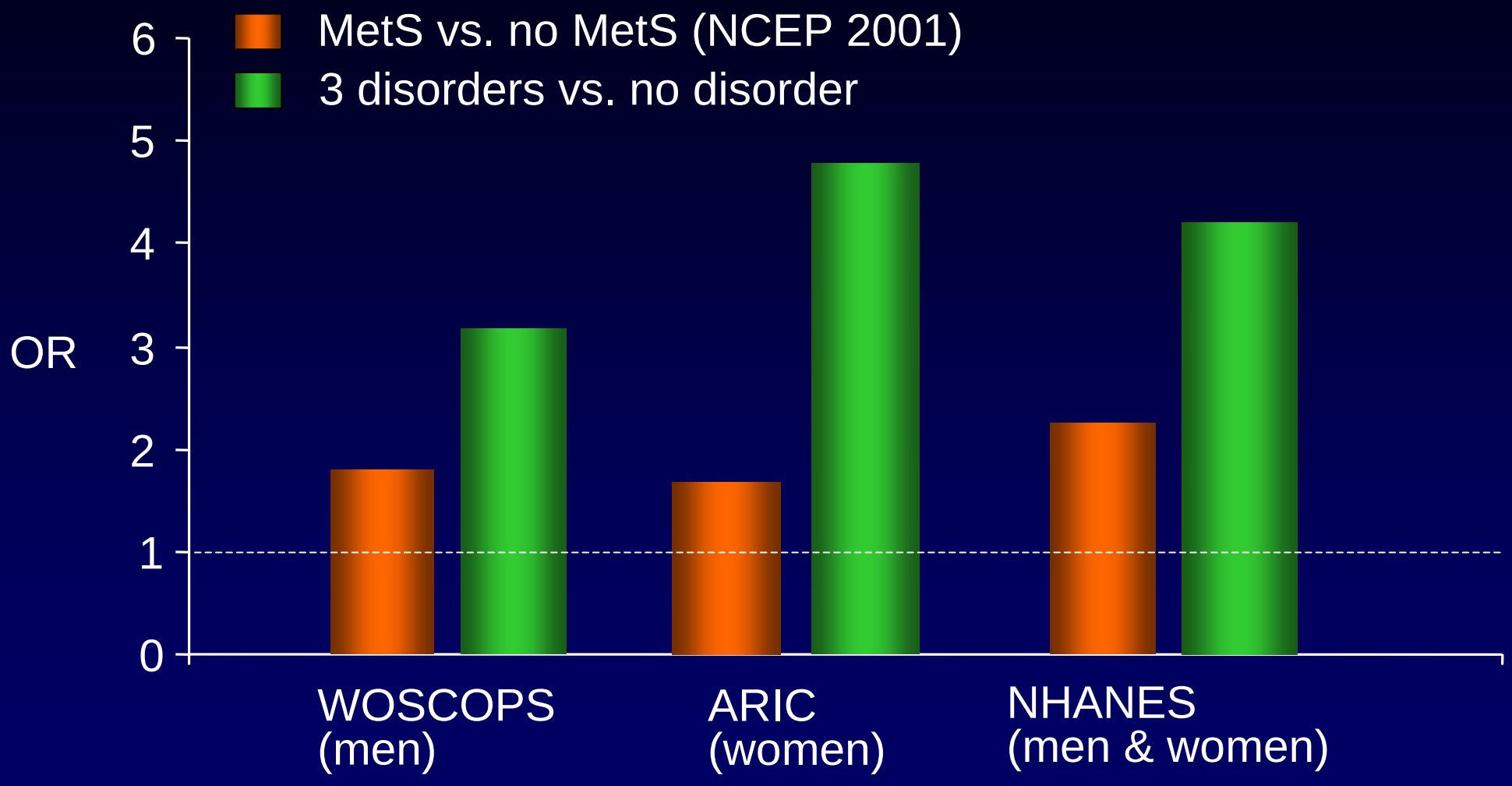
Adjusted for sex, age, smoking, alcohol, physical acitivity, social status, LDL cholesterol, baseline atherosclerosis or CHD

Risk of CHD Morbility or Mortality in Subjects with the Metabolic Syndrome. Comparison of Literature Data

First Author	Country of study	Number of subjects	Years of Follow-up	WHO crit. OR/HR	NCEP crit. OR/HR
Bonora	Italy	888	5	2.0	1.5
Isooma	Finland	2401	7	3.0	-
Lakka	Finland	1209	11	3.3	4.3
Hu	Europe	11512	9	2.8-2.3	-
Sattar	UK	6447	5	-	1.3
McNeill	USA	3215	5	-	2.0-1.5
Hunt	USA	2815	13	2.8-1.1	4.6-1.8
Malik	USA	6255	13	-	2.2-1.9

Women, Men

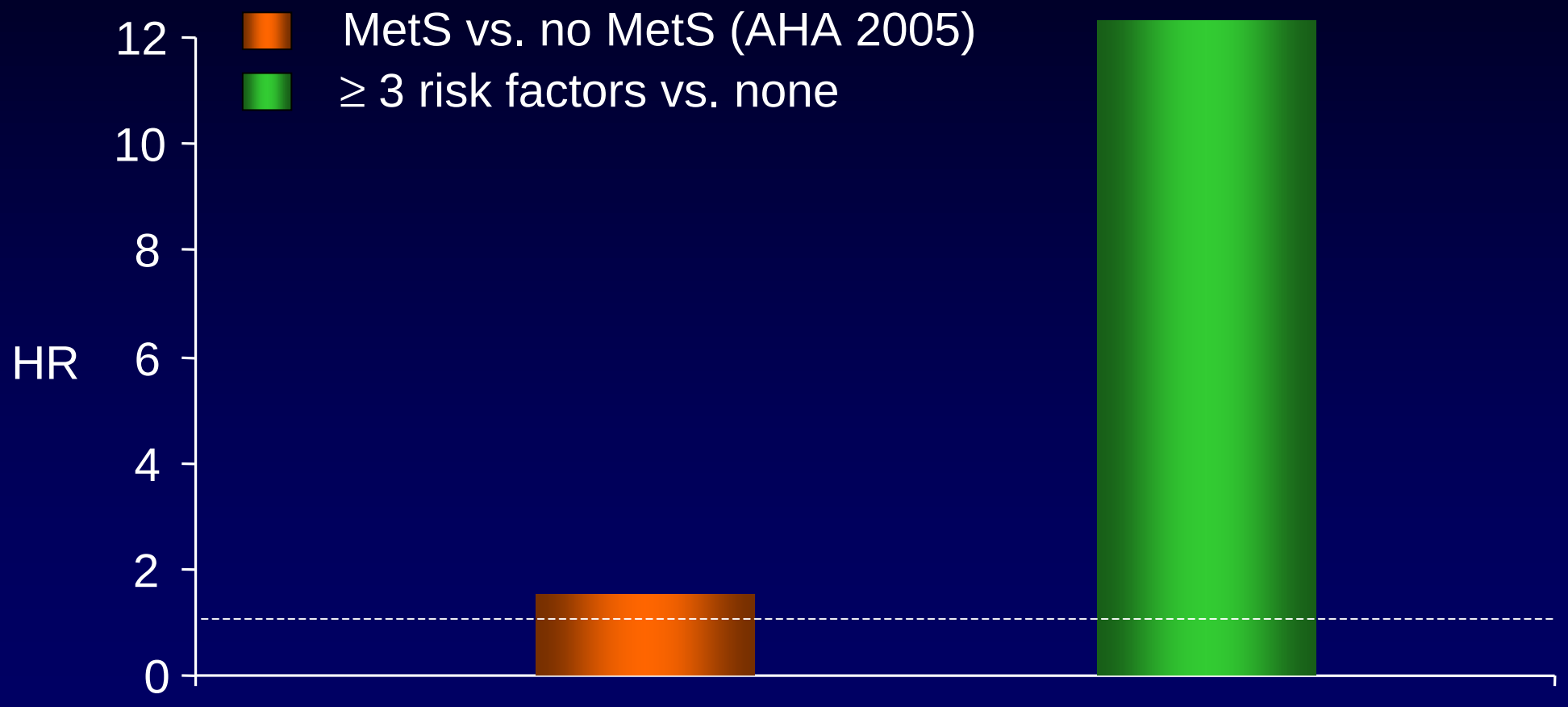
Risk of CVD in Subjects with Metabolic Syndrome: Importance of the Reference Category



Sex- and age-adjusted

Risk of CHD in Subjects with Metabolic Syndrome: Importance of the Reference Category

(Bruneck Study; age 40-79, unpublished)



Adjusted for sex, age, smoking, LDL-C