



Sindrome Metabolica: un'entità complessa

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The Metabolic Syndrome: The Pioneers of the Past Century

Sweden: Kylin (twenties)

France: Vague (fifties)

Italy: Avogaro et al (sixties)

USA: Reaven (eighties)

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The Metabolic Syndrome:

Other names

- Syndrome X
- Insulin Resistance Syndrome
- Atherometabolic Syndrome
- Cardiometabolic Syndrome
- New World Syndrome, Deadly Quartet, GHO syndrome, etc.

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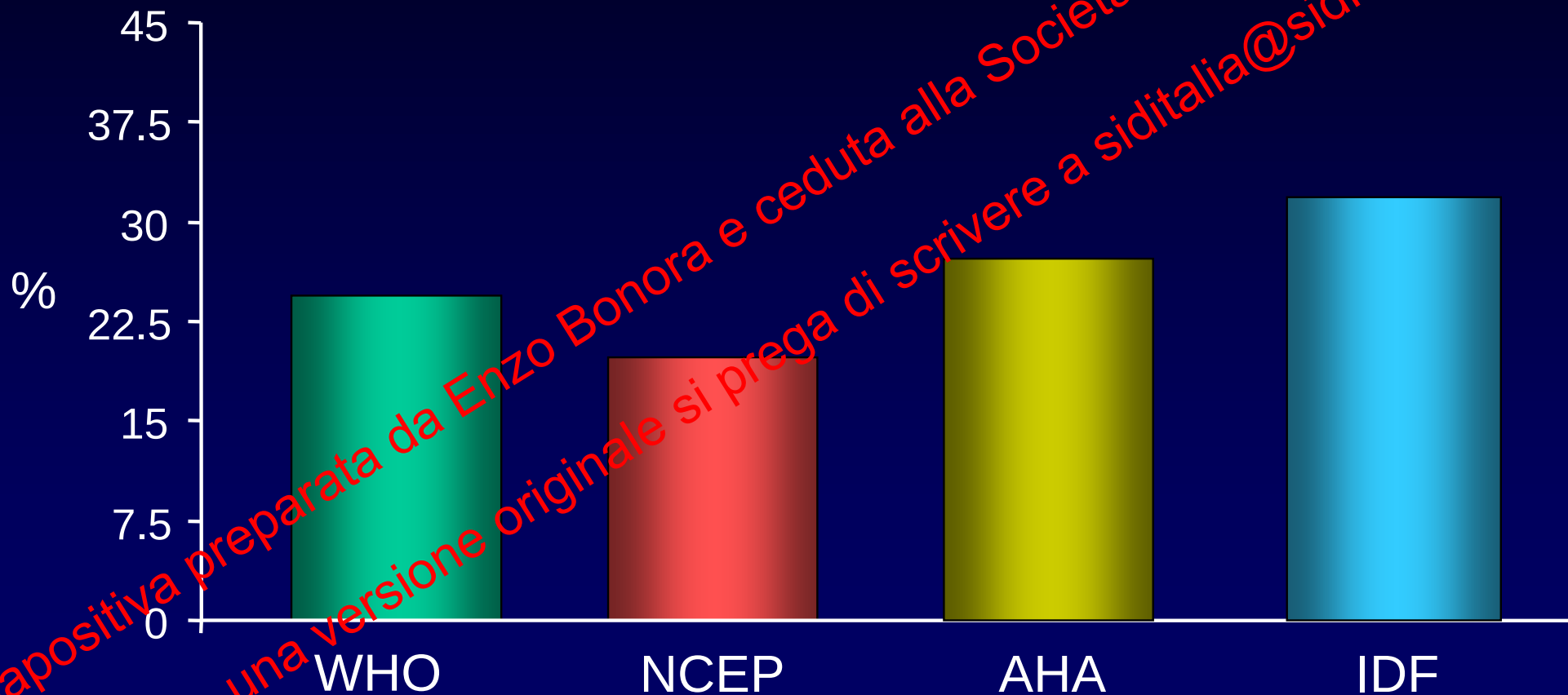
The Metabolic Syndrome: Size of Scientific Interest

- Date search: 21 May 2014
- MeSH term: Metabolic Syndrome X/epidemiology
6425 publications
- MeSH term: Metabolic Syndrome X/complications
4875 publications
- MeSH term: Metabolic Syndrome X/therapy
4008 publications

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(Bruneck Study; age 40-79; n=919; unpublished)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

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The Metabolic Syndrome: 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			

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Diagnostic Criteria of the Metabolic Syndrome

Three or more abnormalities among the following:

- Fasting glucose ≥ 100 mg/dl
- Triglycerides ≥ 150 mg/dl
- HDL < 40 mg/dl men, < 50 mg/dl women
- Hypertension ($\geq 135/85$ mmHg)
- Abdominal obesity (waist > 94 cm men, > 82 cm women)

The Metabolic Syndrome: Requiescat in Pace



Gerald M. Reaven

Clinical Chemistry 51: 931-938, 2005

“...it appears that making the diagnosis of the Metabolic Syndrome does not bring with it much in way of pathophysiologic understanding or clinical utility...”.

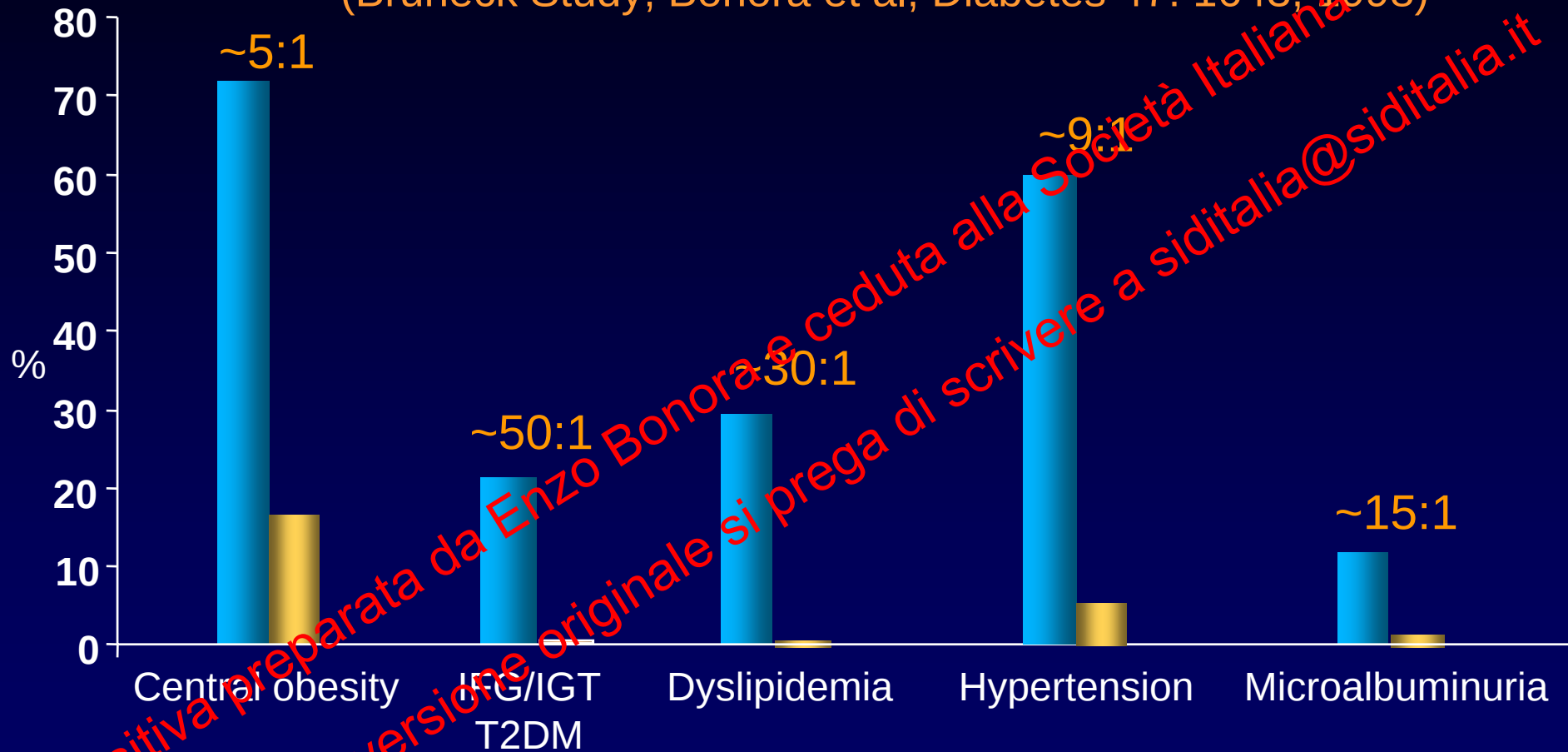
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Virtues of the Metabolic Syndrome (1)

- Prompts to seek carefully the other components when one is observed, prompt to seek other disorders featuring the cluster.
- Isolated disorders are rare; the phenotype is generally complex; the phenotype is rich of traditional and non-traditional CVD risk factors.

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

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

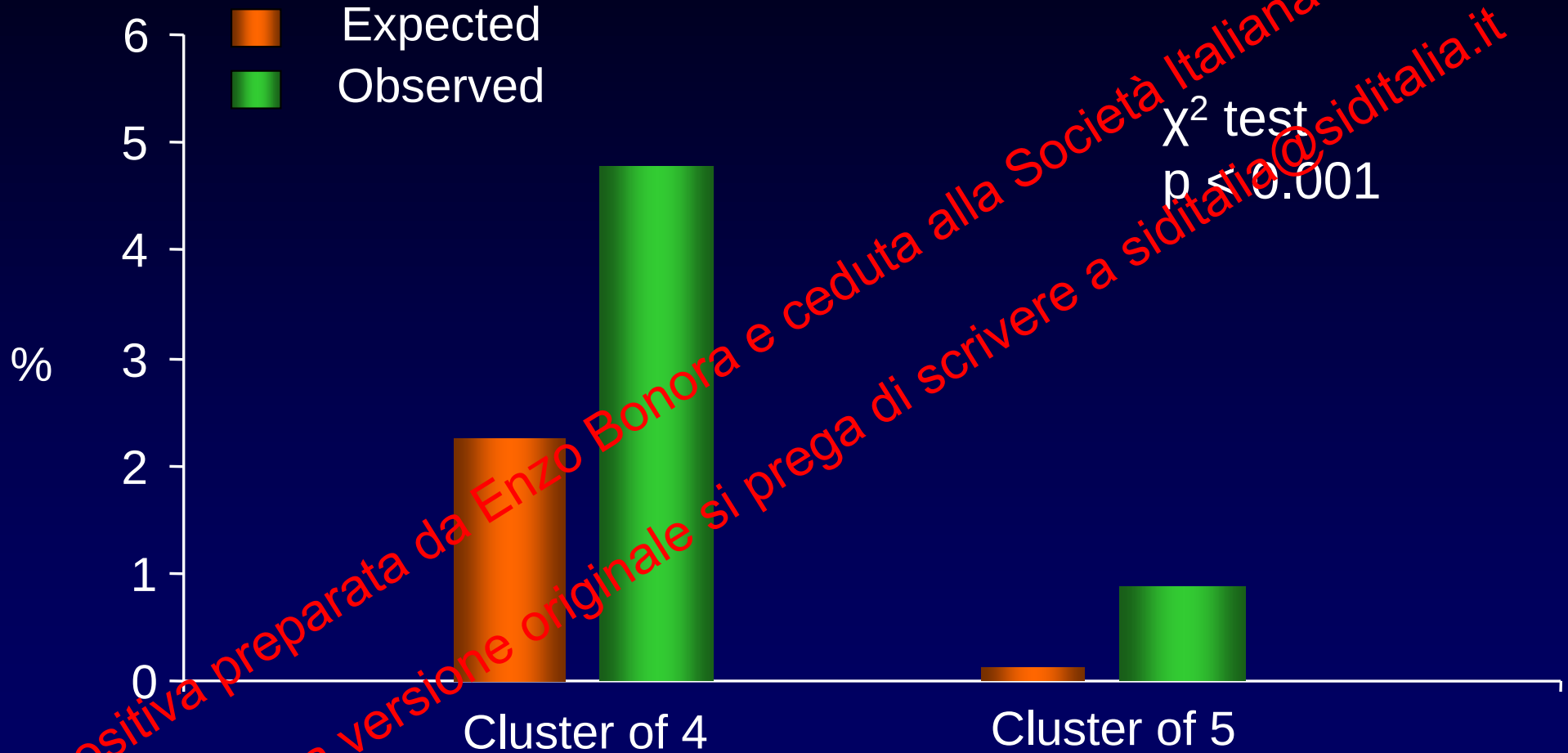


■ overall prevalence

■ prevalence of isolated disorders

Prevalence of More Complex Clusters in the General Population

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

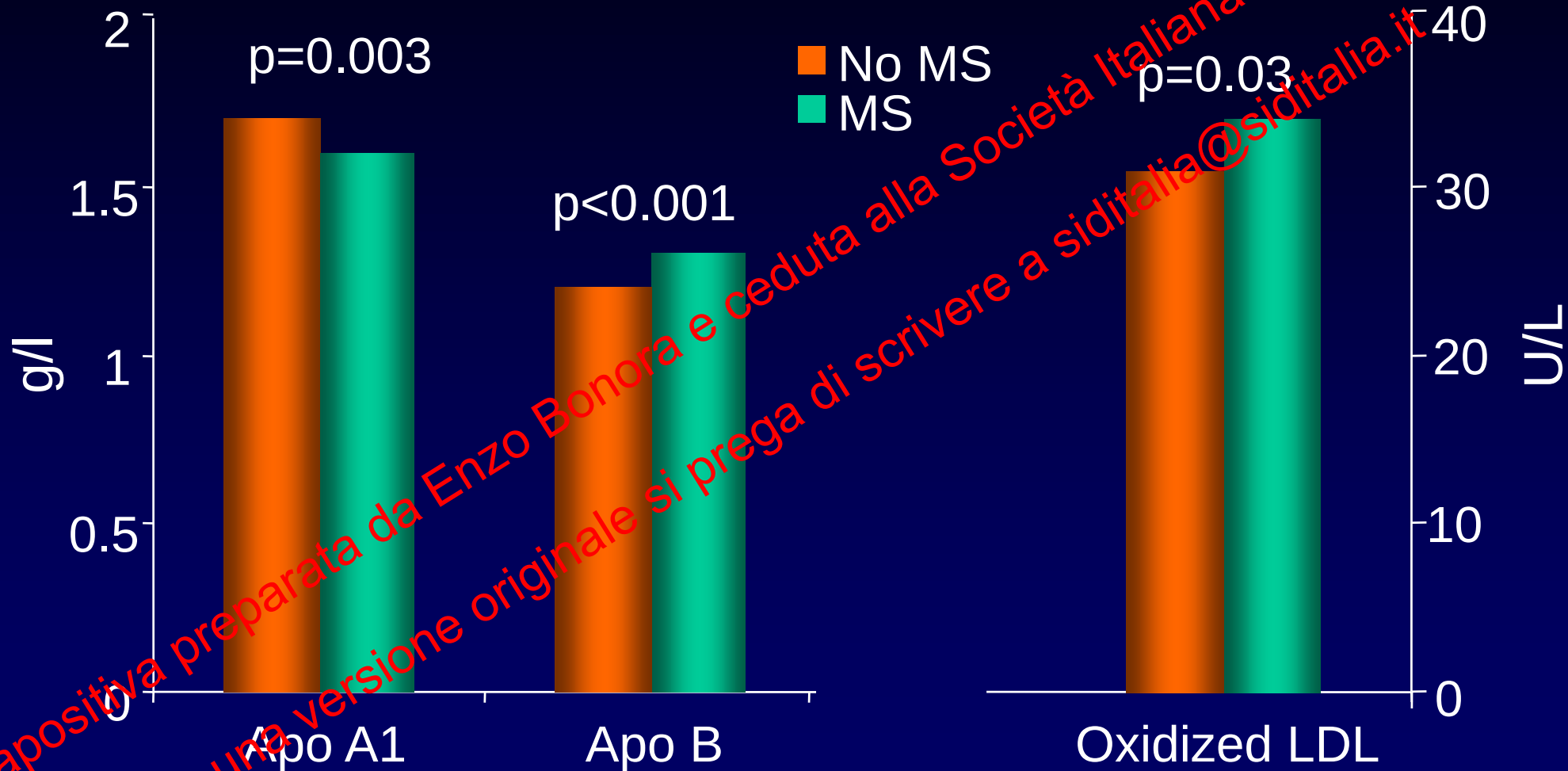


Possible traits in the cluster: dysglycemia, hypertension, high waist, high TG, low HDL-C

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

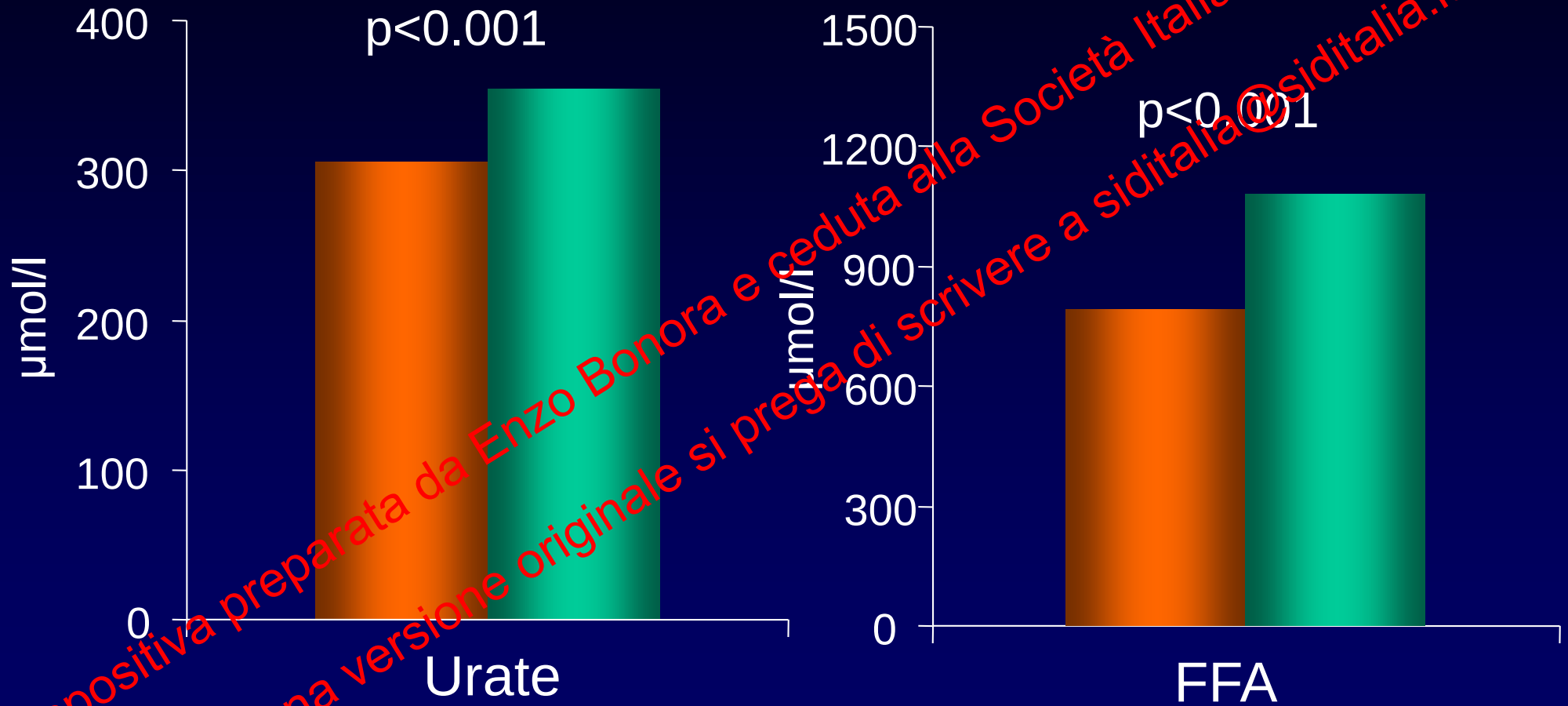
Ancillary Features of the Metabolic Syndrome

URATE AND FFA

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

■ No MS

■ MS

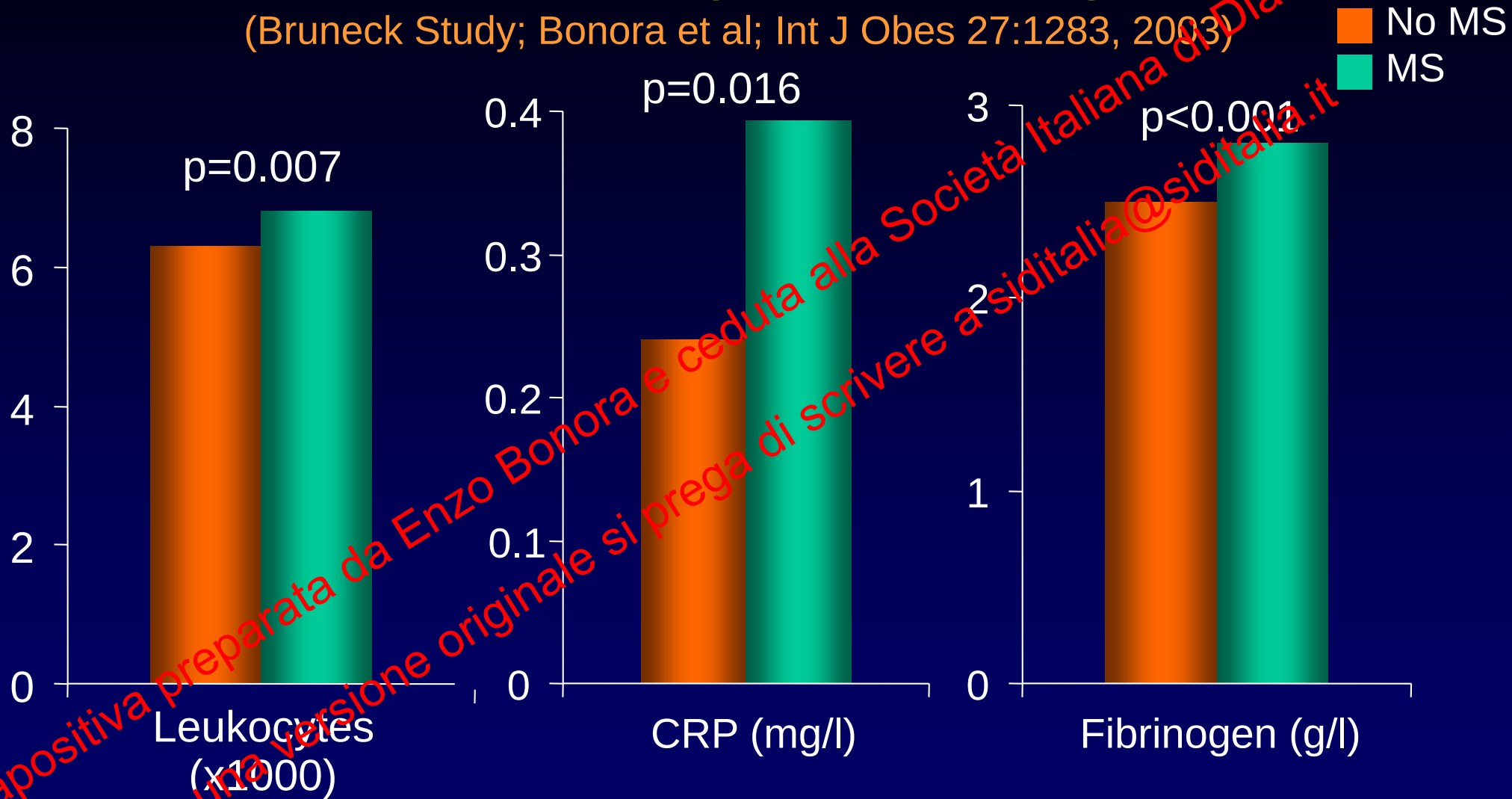


Adjusted for sex, age, smoking, alcohol, physical activity, social status

Ancillary Features of the Metabolic Syndrome

INFLAMMATORY MARKERS

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

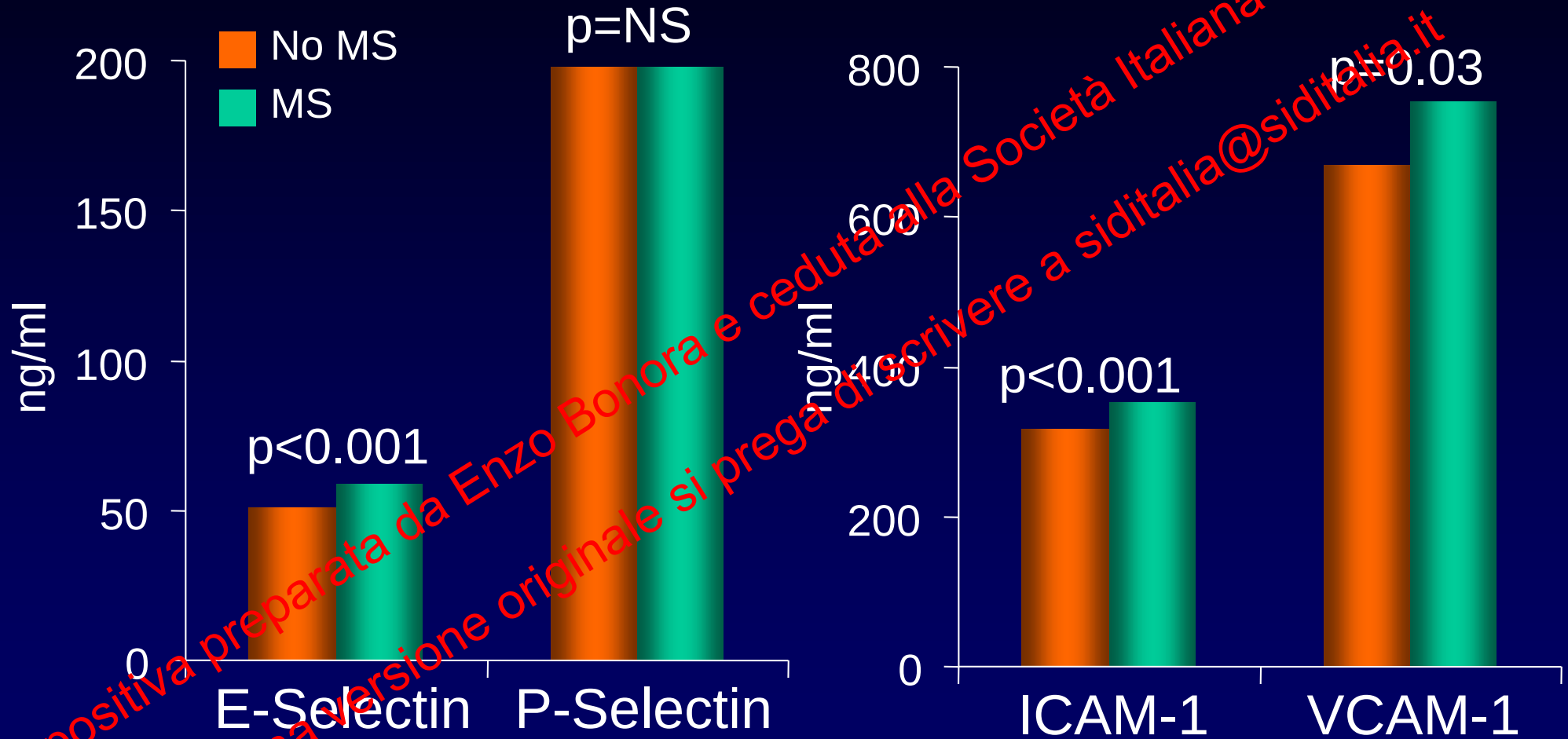


Adjusted for sex, age, smoking, alcohol, physical activity, social status

Ancillary Features of the Metabolic Syndrome

ENDOTHELIAL ADHESION MOLECULES

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

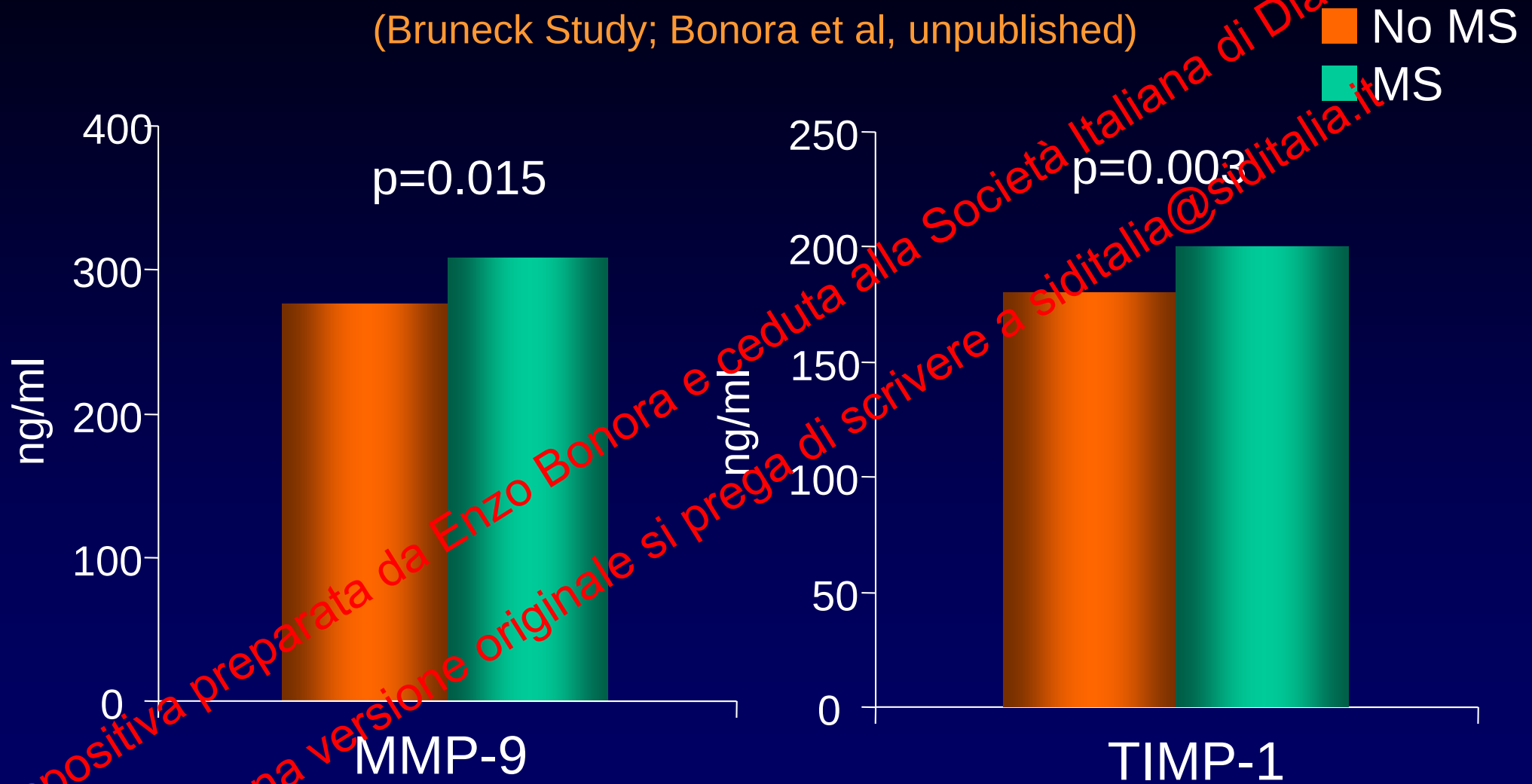


Adjusted for sex, age, smoking, alcohol, physical activity, social status

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

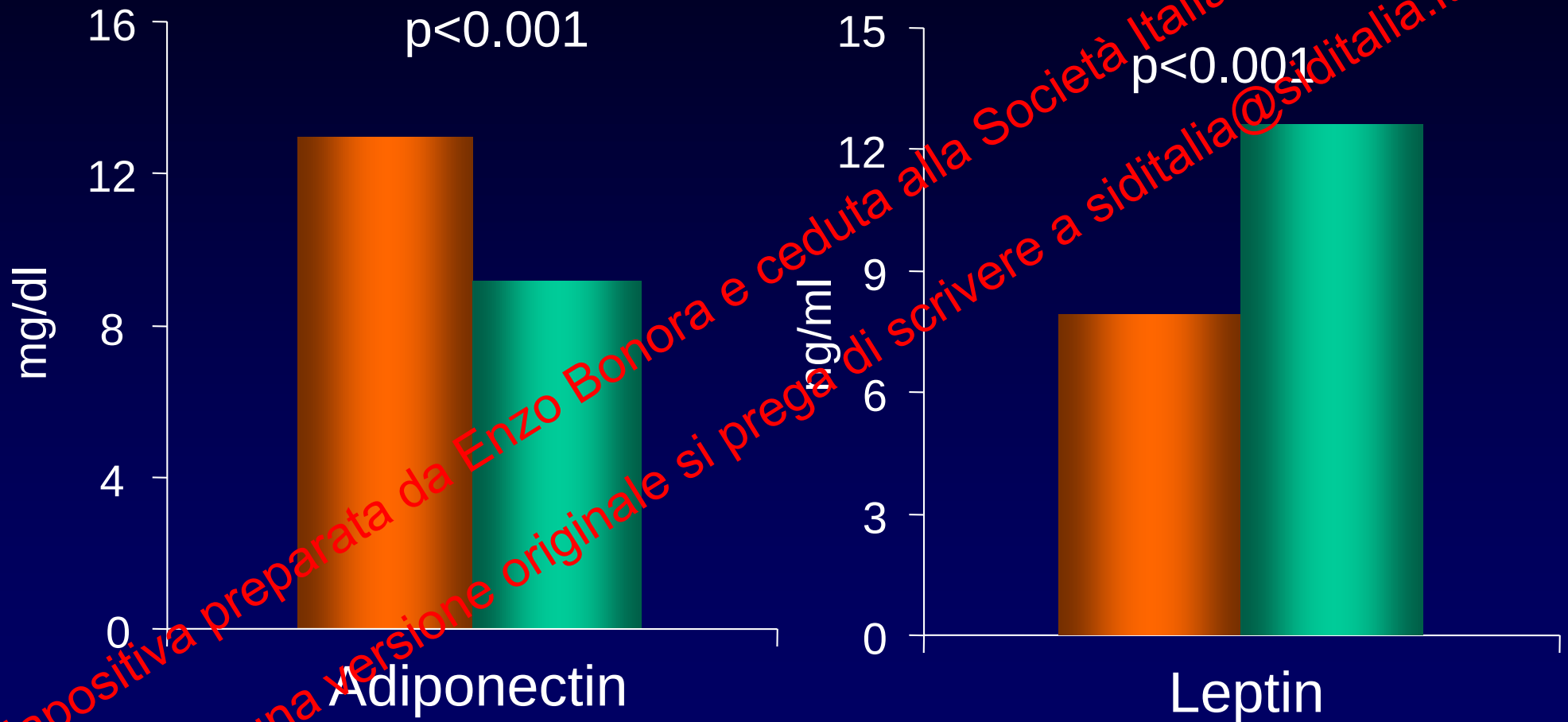
Ancillary Features of the Metabolic Syndrome

ADIPONECTIN AND LEPTIN

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

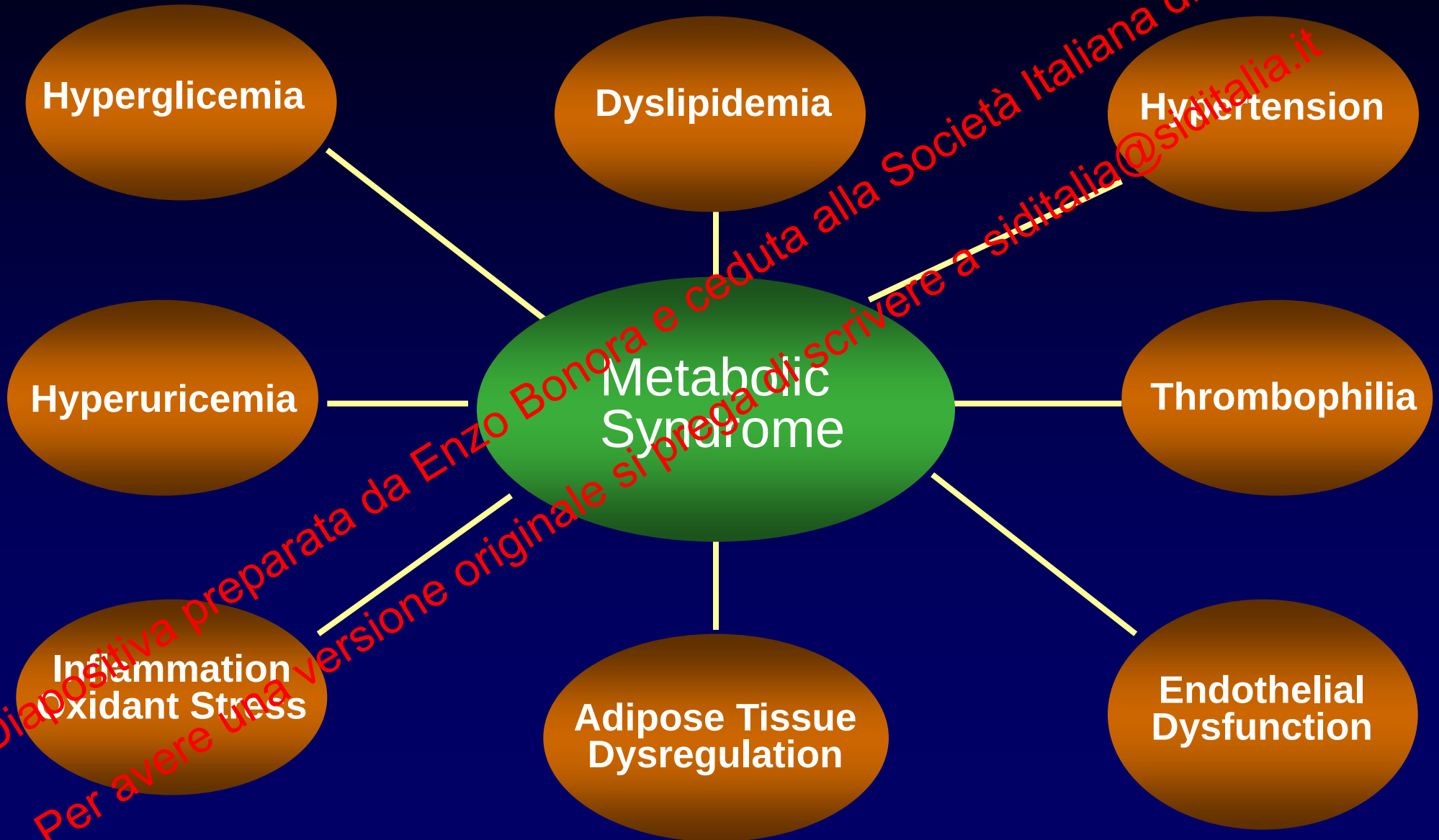
■ No MS

■ MS

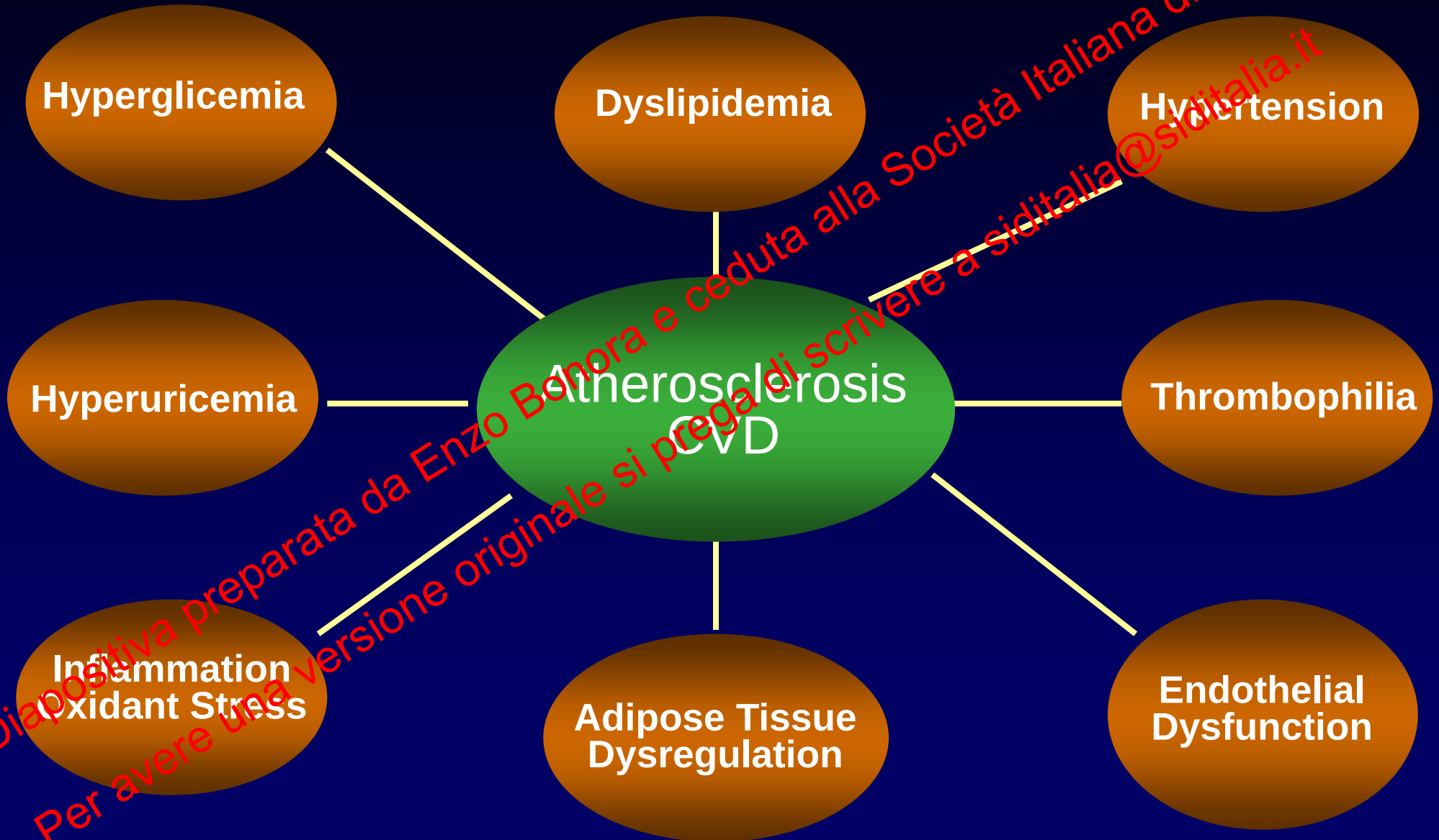


Adjusted for sex, age, smoking, alcohol, physical activity, social status

The Wide Spectrum of Disorders in the Metabolic Syndrome



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



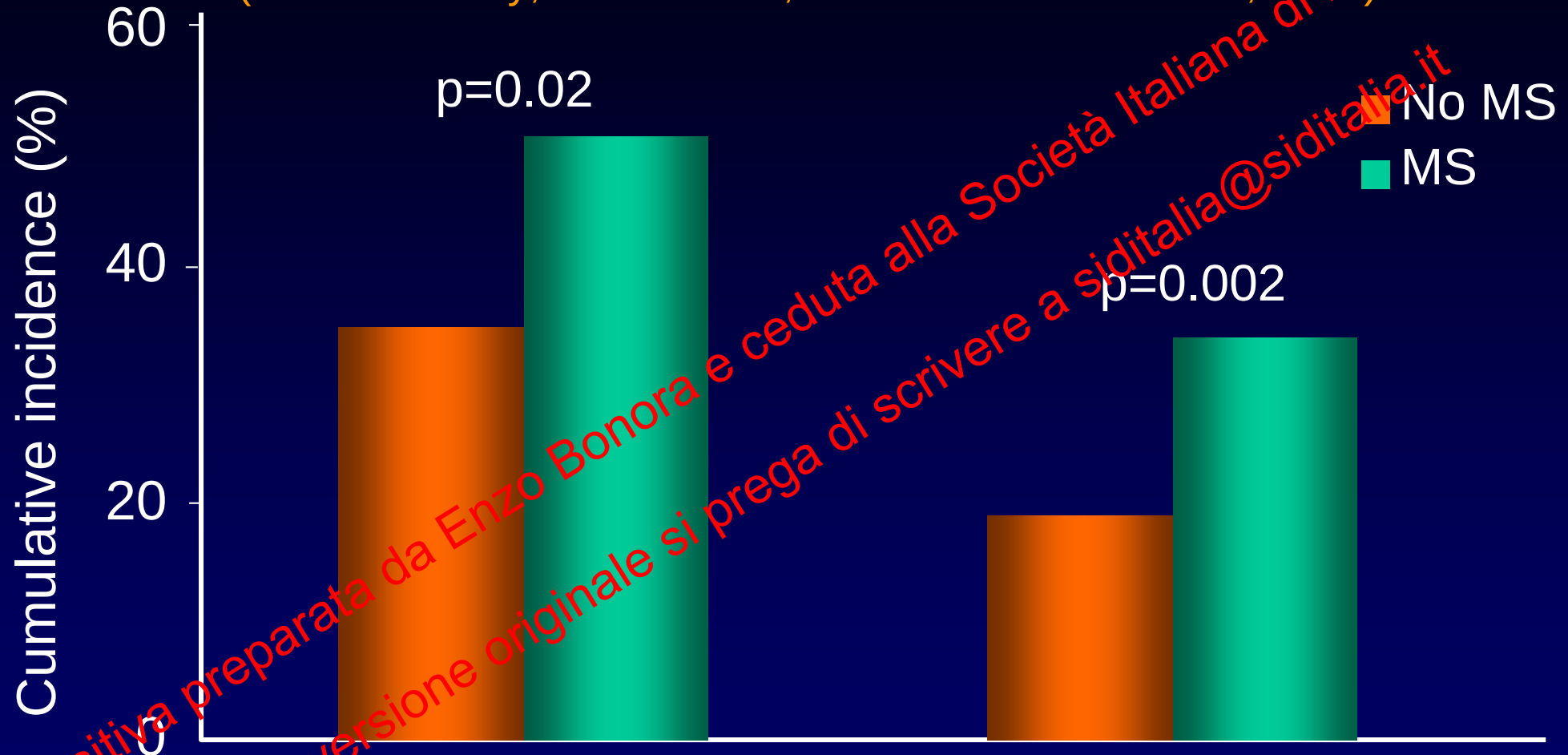
Virtues of the Metabolic Syndrome (2)

- Identifies subjects with high CV risk
- Subjects affected frequently develop CHD and stroke, and the risk is remarkably high

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5-yr Incidence of Carotid Atherosclerosis in the Metabolic Syndrome

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

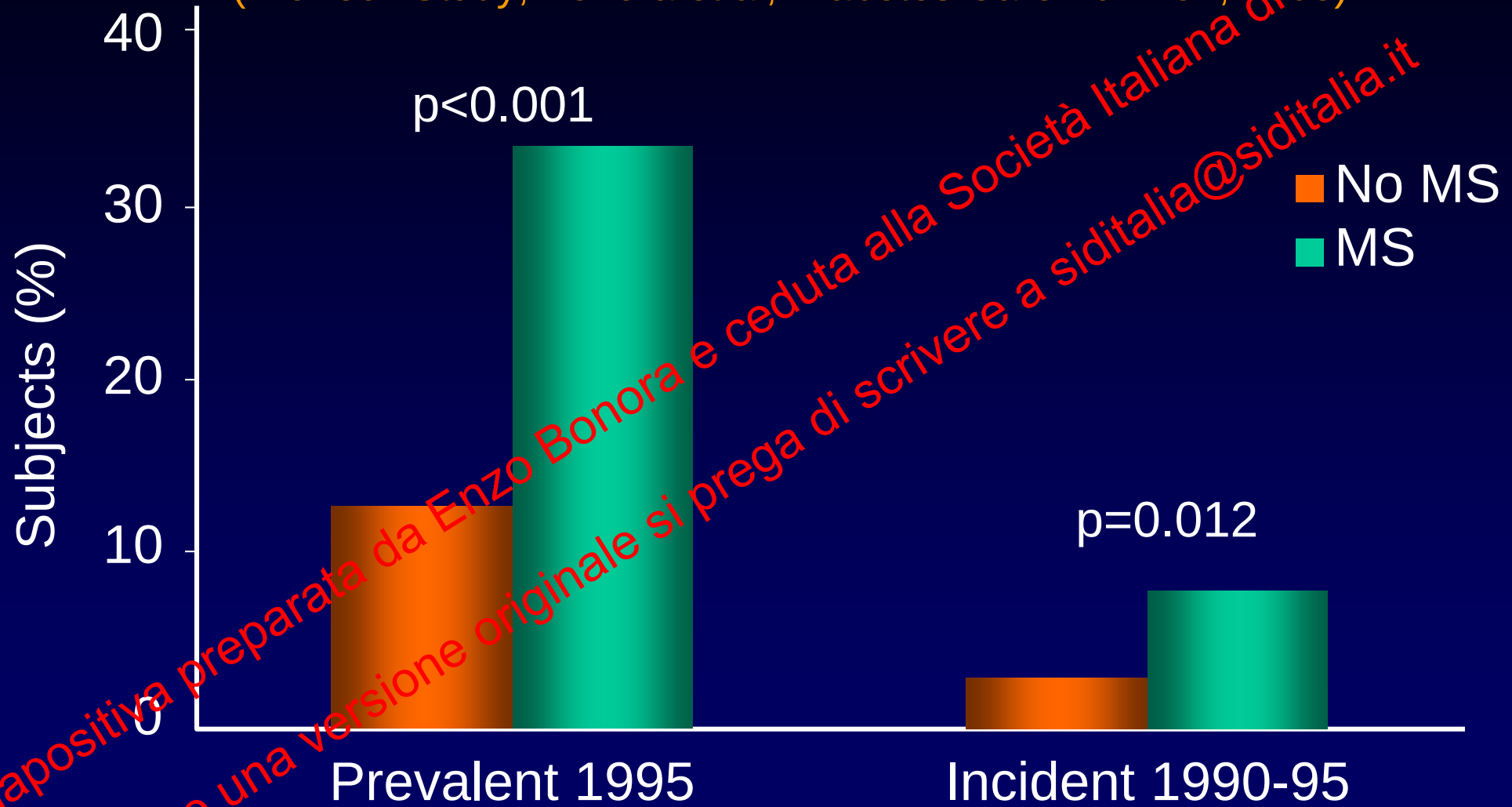


Incident plaques (1990-95) Incident stenosis (1990-95)

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

	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 activity, social status, LDL cholesterol, baseline atherosclerosis or CHD

Risk of CHD Morbidity 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

Meta-Analysis of Metabolic Syndrome and risk of incident cardiovascular events and death

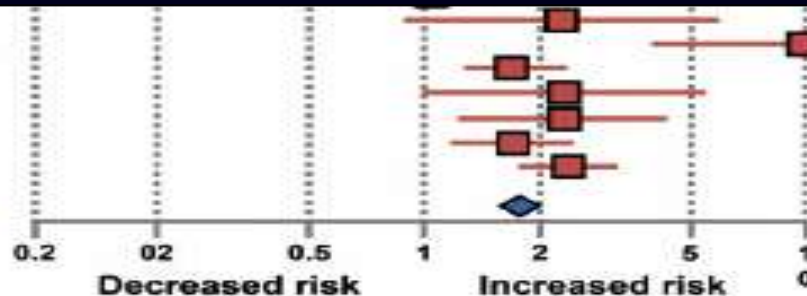
(Gami et al; JACC 2007; 49: 403-414)

Study	RR	95% CI
Godsland	1.28	0.86 1.90
Pyörälä	1.48	1.23 1.77
Wilson	2.87	1.96 4.20
Ford	1.37	1.02 1.85
Malik	2.71	1.76 4.17
Trevisan	2.66	1.82 3.90



Why the risk is not substantially greater than that conveyed by diabetes or hypertension?

Gimeno	1.30	0.90 5.90
Nakanishi	3.84	3.95 24.52
Holvén	1.69	1.29 2.34
Hsia	2.32	0.98 5.45
MacQuinn	2.32	1.24 4.33
Mat	1.71	1.18 2.47
Hu	2.38	1.78 3.19
Summary	1.78	1.58 2.00



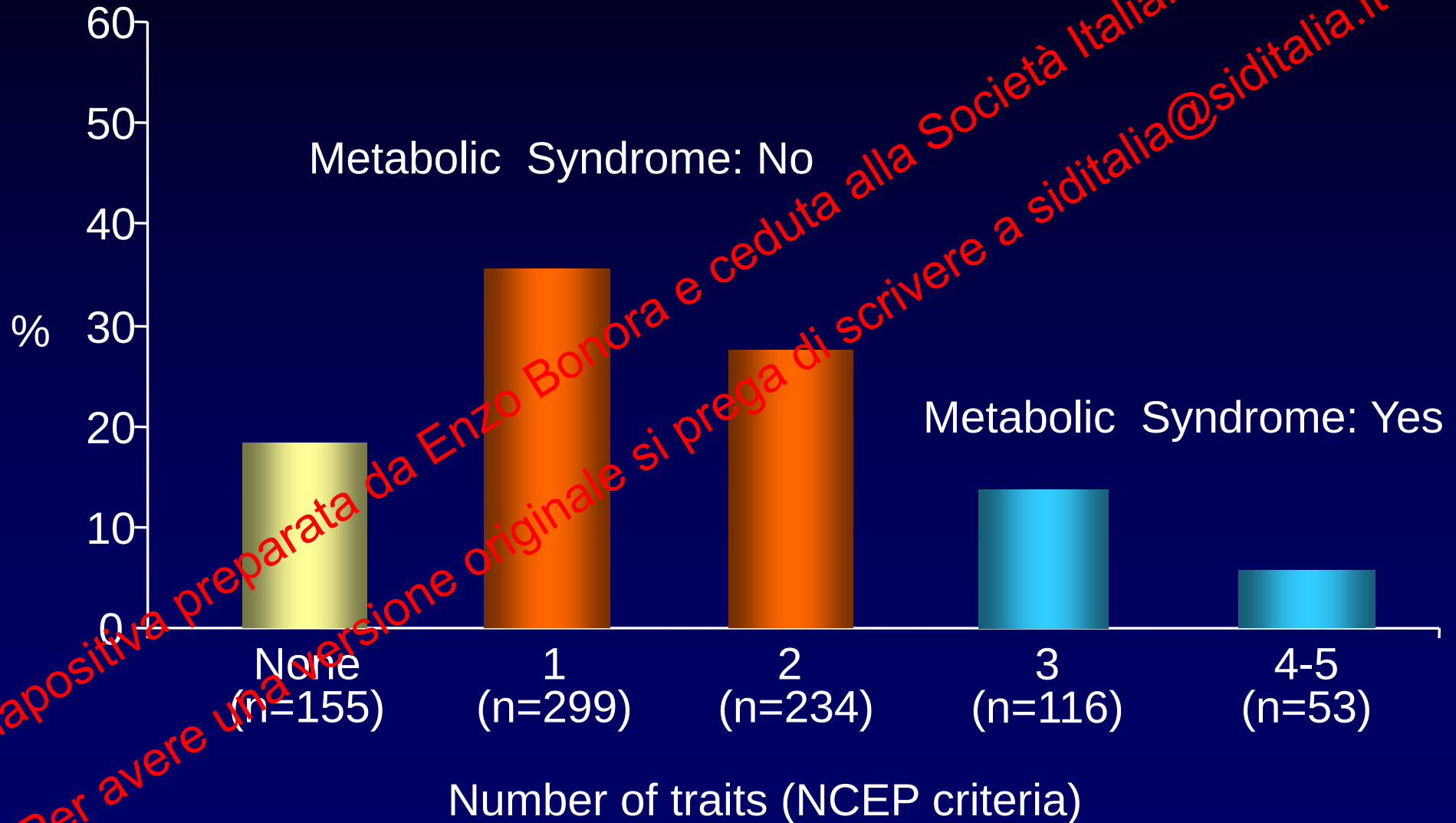
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The Metabolic Syndrome: What is the Correct Reference Category to Calculate the Risk?

- Subjects without the Metabolic Syndrome who often have isolated conditions or associations of two disorders (e.g. diabetes and hypertension or hypertension and dyslipidemia)?
- Subjects without any disorder (true healthy)?

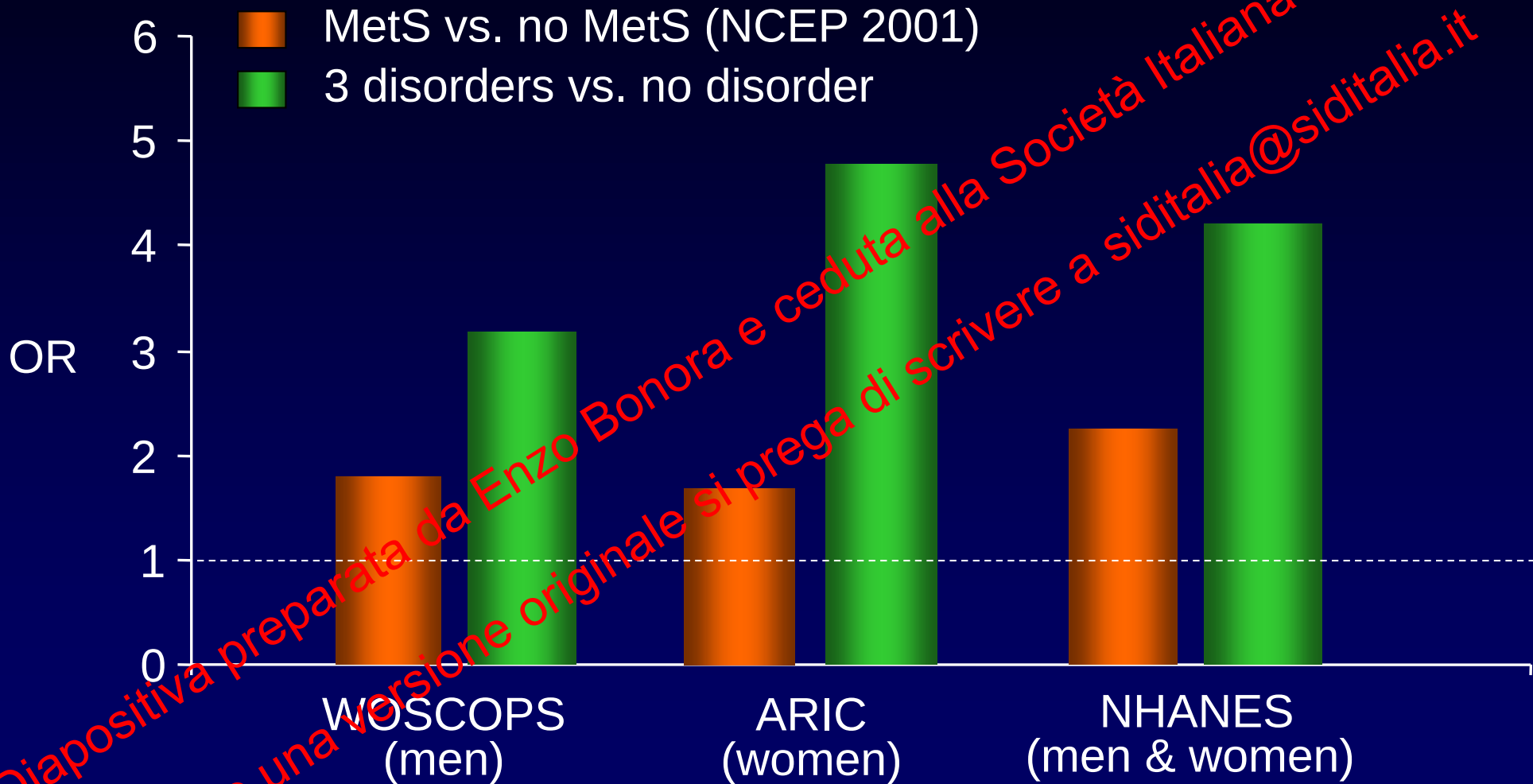
Prevalence of Traits of the Metabolic Syndrome in Subjects Aged 40-79 yr

(Bruneck Study; Bonora et al, Met Syndr Relat Disord 2011; 9:313)



Risk of CVD in Subjects with Metabolic Syndrome

Importance of the Reference Category



Sex- and age-adjusted

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

(Bruneck Study; Bonora et al, Met Syndr Relat Disord 2011; 9:313)



Adjusted for sex, age, smoking, LDL-C

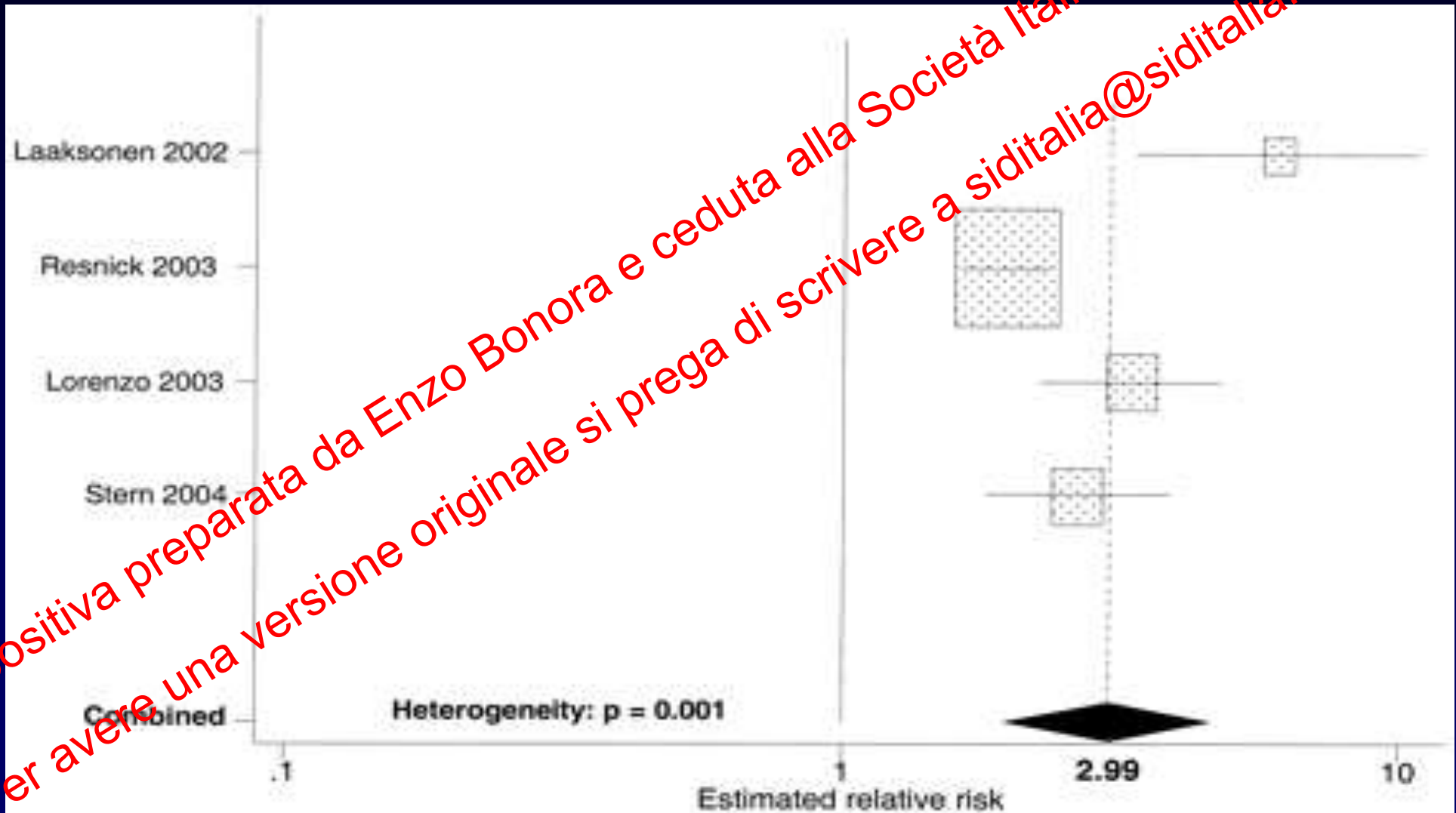
Virtues of the Metabolic Syndrome (3)

- Prompts to monitor the missing components.
- Phenotype is changing (e.g., type 2 diabetes occurs frequently).

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Summary of Prospective Studies of Metabolic Syndrome and Risk of T2DM

(Ford, EA; Diabetes Care 2005)



Risk of T2DM in Subjects Aged 40-79 yr with the Metabolic Syndrome According to NCEP 2001 Criteria

(Bruneck Study; age 40-79; unpublished)

*10-yr incident cases of T2DM 76

**OR MetS yes (n=169)
vs. no (n=688)

4.4

C.I. 2.7-7.2

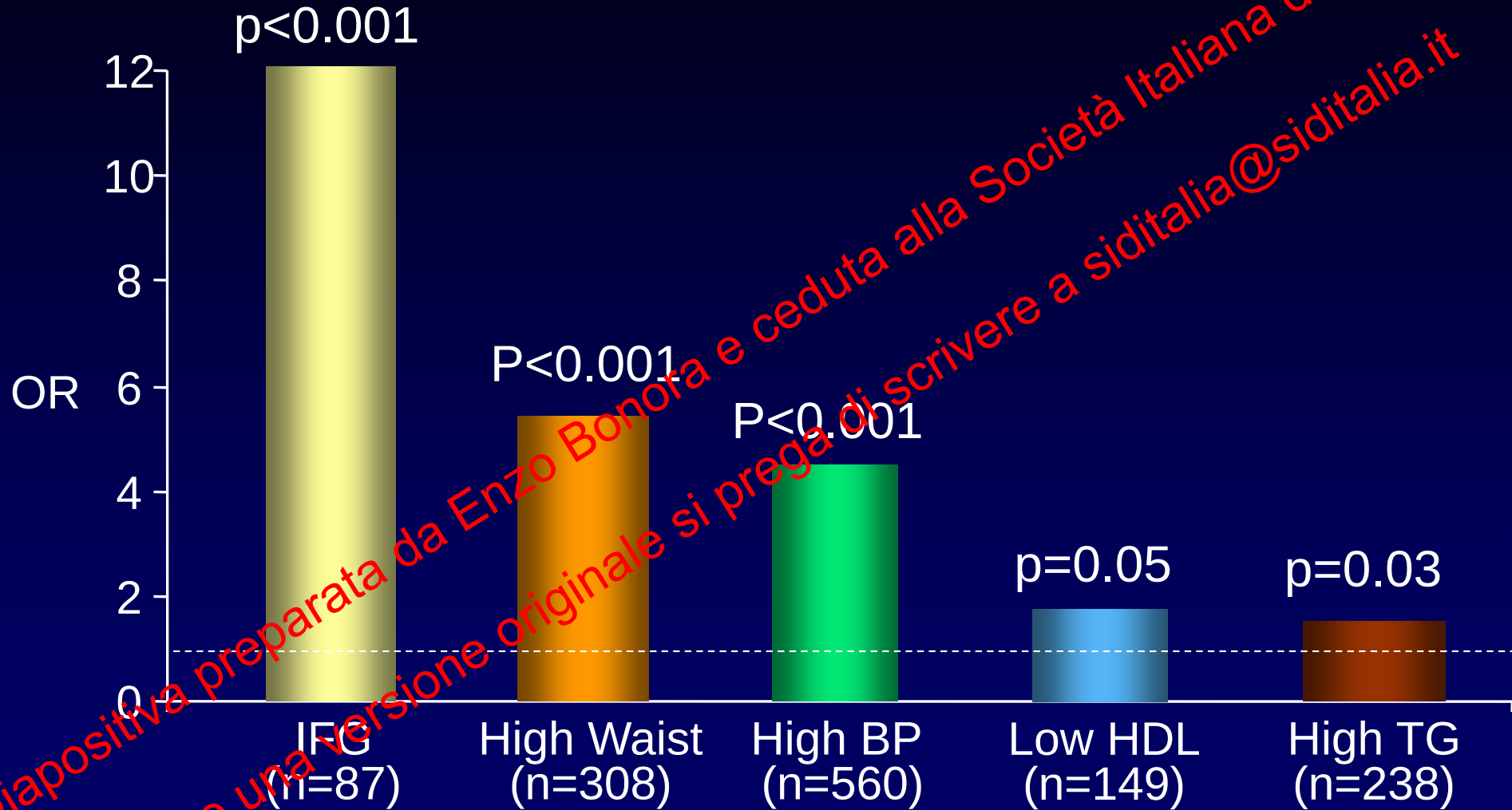
P<0.001

*ADA criteria (FPG only)

**Sex- and age-adjusted

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

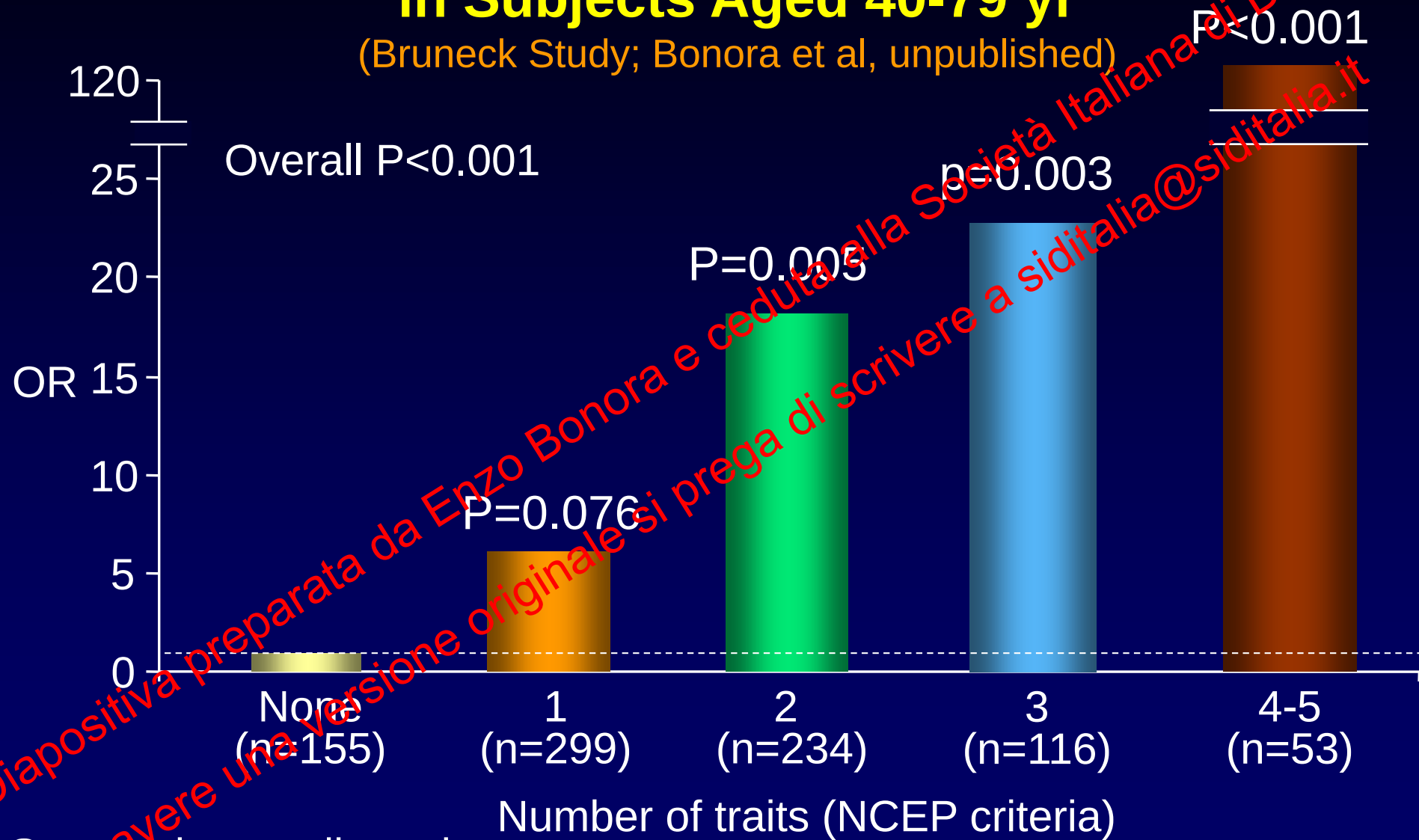
(Bruneck Study; Bonora et al, unpublished)



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

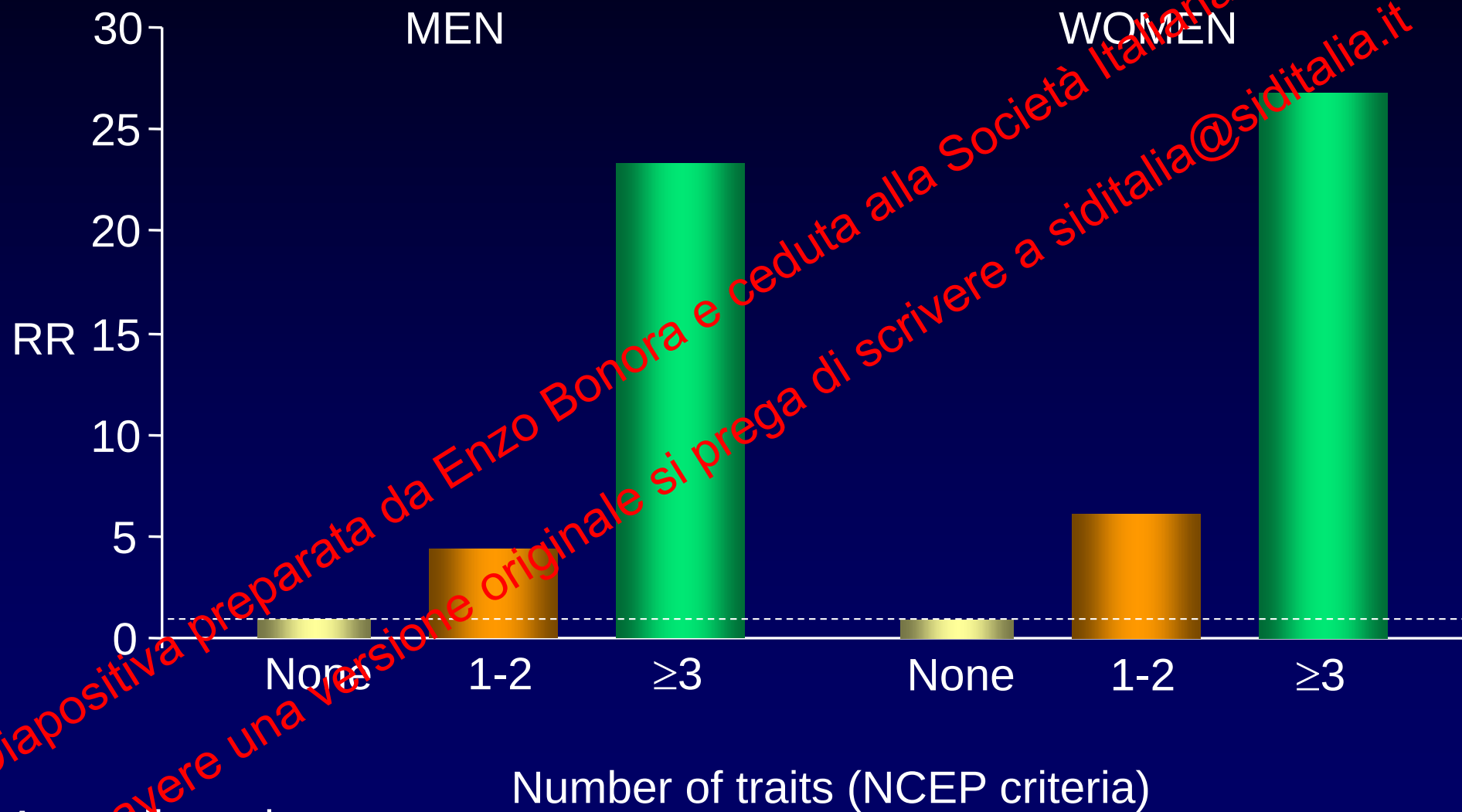
(Bruneck Study; Bonora et al, unpublished)



Sex- and age-adjusted

8-yr Risk of T2DM According to the Number of Traits of the Metabolic Syndrome

(Framingham Offspring Study; Wilson et al, Circulation 112: 3066, 2005)



Age-adjusted

Virtues of the Metabolic Syndrome (4)

- Draws attention to neglected risk factors and their cluster.
- Second lead risk factors (e.g., IFG, waist, triglycerides) carry an high CVD risk when they cluster.

Odds Ratio for 5-yr Incident CHD in Subjects without Diabetes and Definite Hypertension

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

Model 1 (individual putative risk factors)

IFG/IGT	1.7 (N.S.)
Insulin Resistance	1.4 (N.S.)
Central Obesity	1.1 (N.S.)
Dyslipidemia (low HDL and/or high TG)	1.3 (N.S.)
Mild hypertension	2.5 (N.S.)
Microalbuminuria	2.4 (N.S.)

Model 2

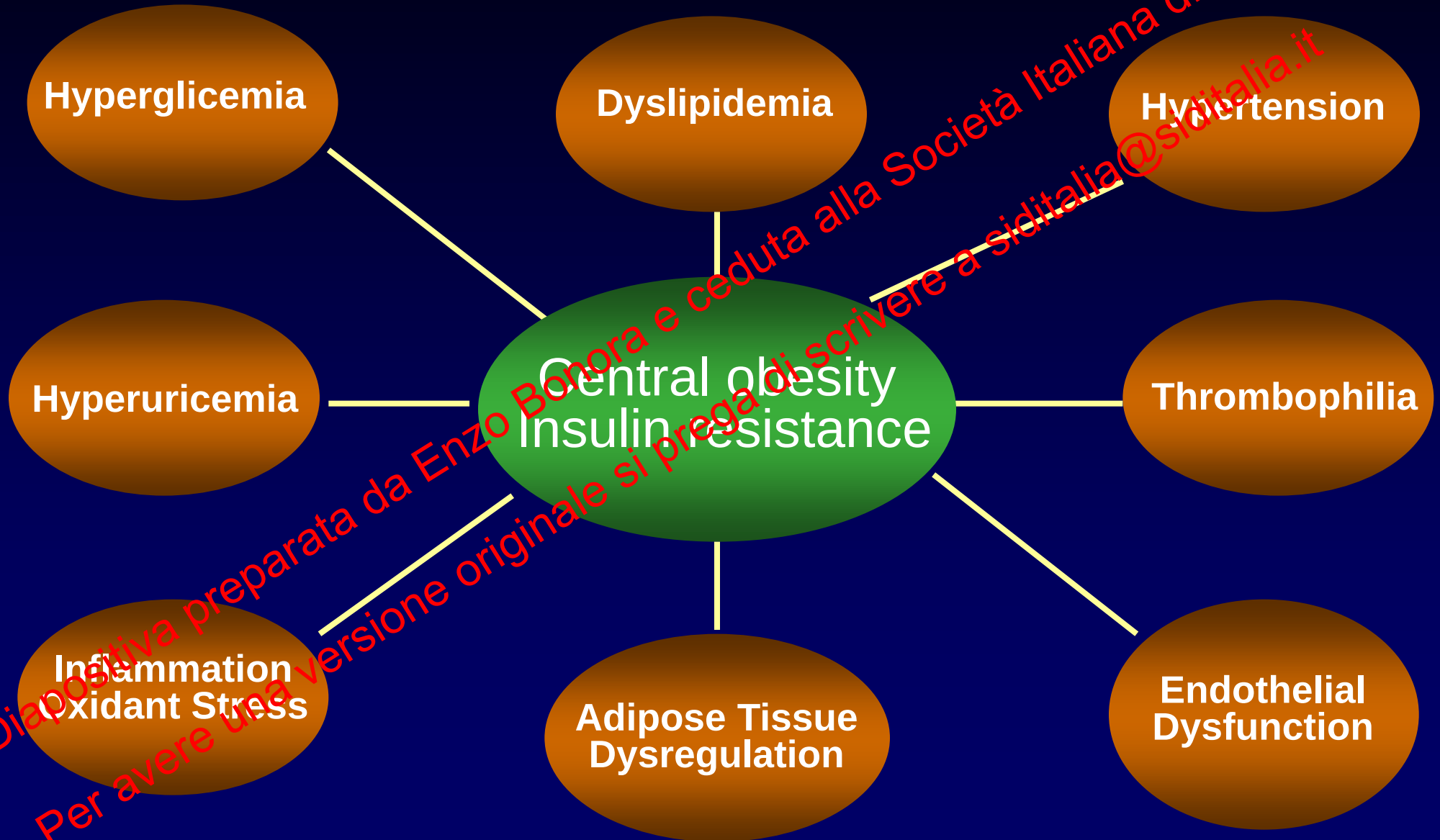
Metabolic Syndrome	3.7 (p<0.05)
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Adjusted for sex, age, life style factors, LDL cholesterol, baseline CHD

Virtues of the Metabolic Syndrome (5)

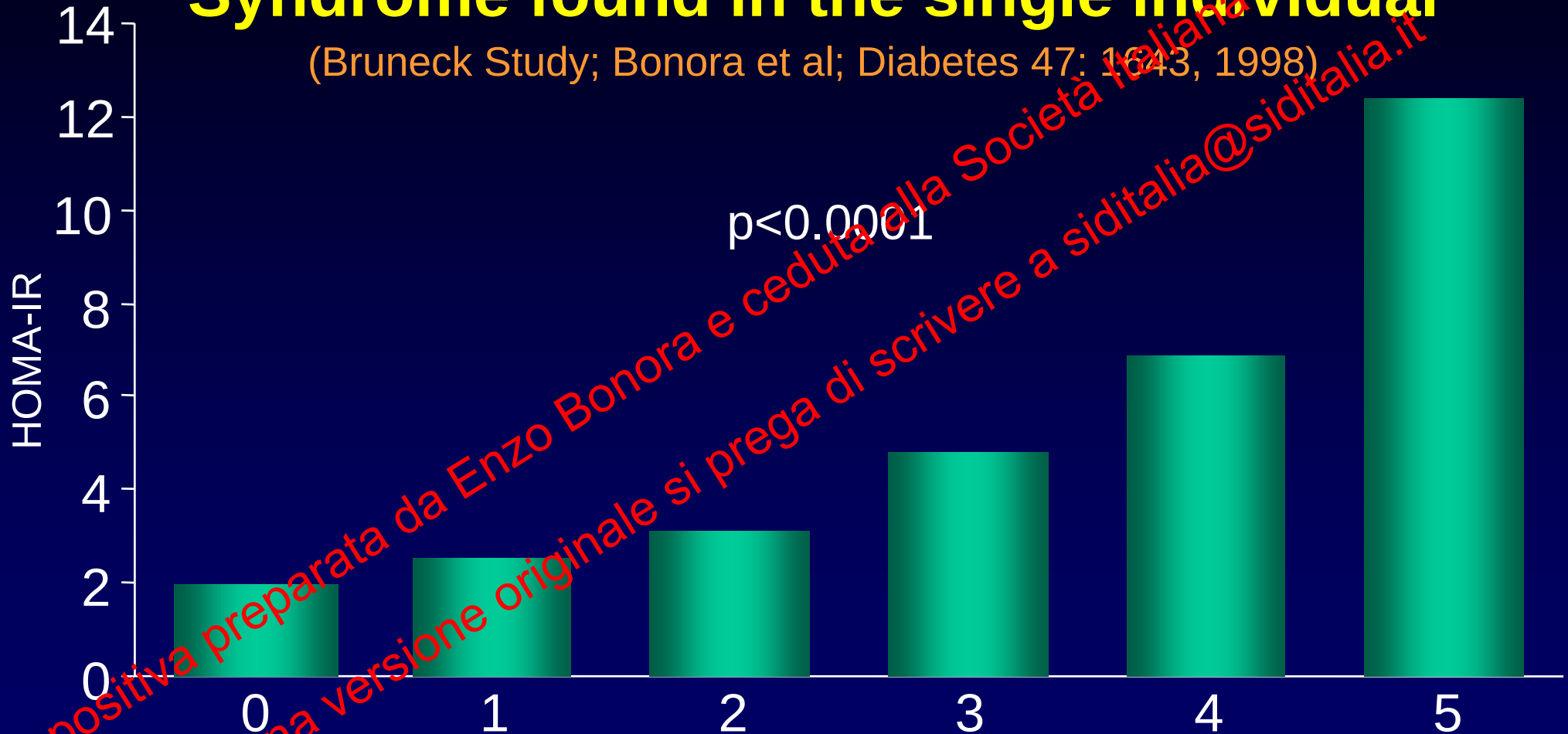
- Draws attention to underlying disorders that might be targeted with the purpose of ameliorating several risk factors with a single intervention.
- Treating an underlying disorder (“**olistic approach**”) might give a better or an additive advantage than treating individually each risk factor (“**fragmented approach**”).

The Two Underlying Disorders in the Metabolic Syndrome



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

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



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

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

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 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

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
Lp(a) (ng/ml)	6.7	14.8	0.001

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

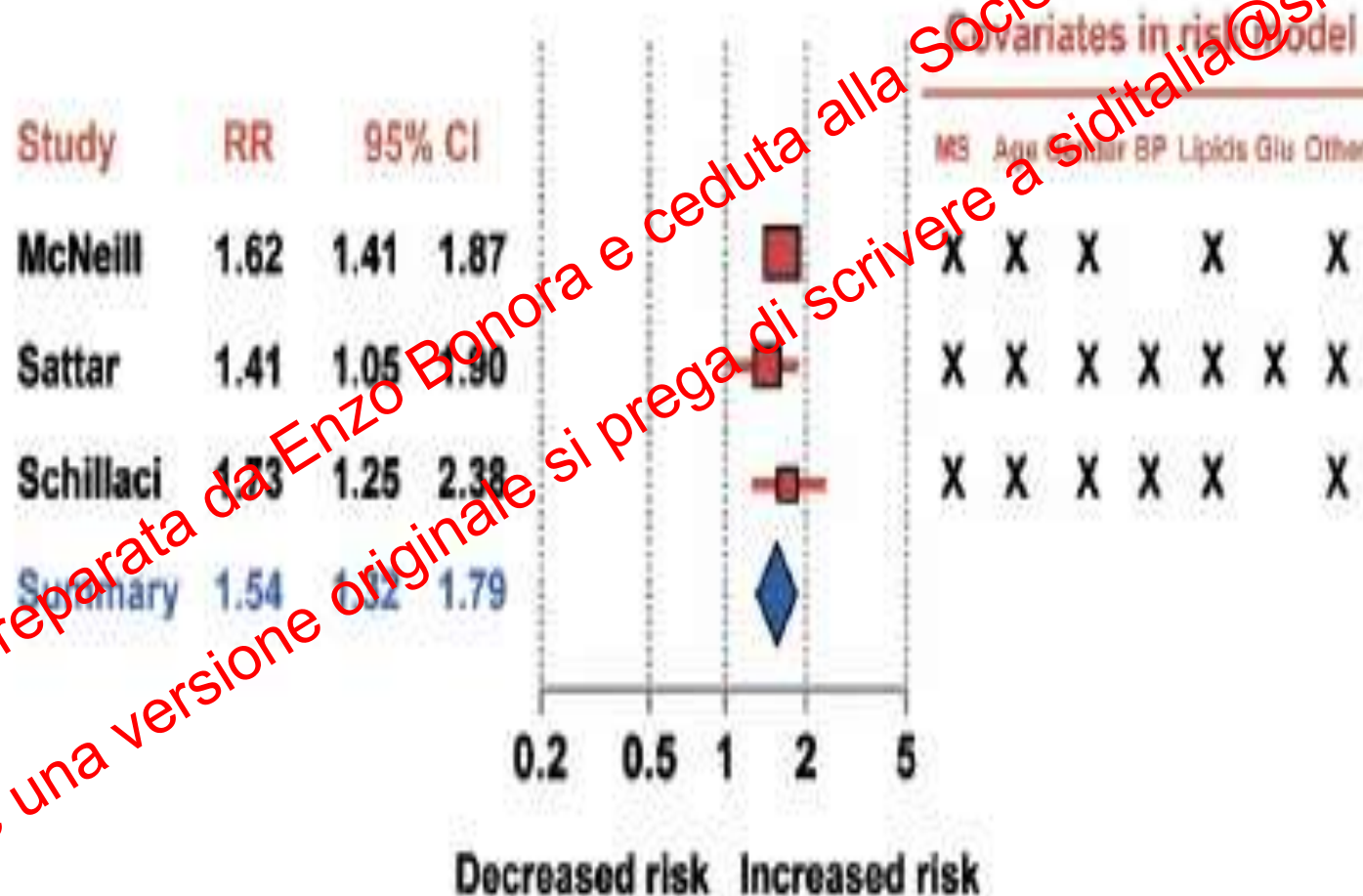
Virtues of the Metabolic Syndrome (5)

Provide information on CVD risk which beyond that defined by Framingham Risk Score or by classic risk factors

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Meta-Analysis of Metabolic syndrome and risk of incident cardiovascular events and death

(Gami et al; JACC 2007; 49: 403-414)



Hazard Ratio for CVD Events in Subjects with the Metabolic Syndrome

(CHS; Scuteri et al, Diabetes Care 28:882, 2005)

Model 1 (MetS only)

1.90 (1.60-2.26)

2) Synergism between risk factors and/or effect of non-traditional risk factors within the cluster (e.g., PAI-1, CRP, etc.)

Model 4 (+ individual components MetS-NCEP)

1.38 (1.07-1.79)

Risk of Cardiovascular Mortality in Subjects with the Metabolic Syndrome

(Sundstrom et al; BMJ 332: 878-882, 2006)

- 2332 men aged 50 yr, followed up to 33 years
- HR MetS vs. no MetS
2.21
p<0.001
- After adjustment for smoking, diabetes, cholesterol and hypertension
1.59
p<0.001

Estimating the CVD Risk: Metabolic Syndrome vs. Framingham Score

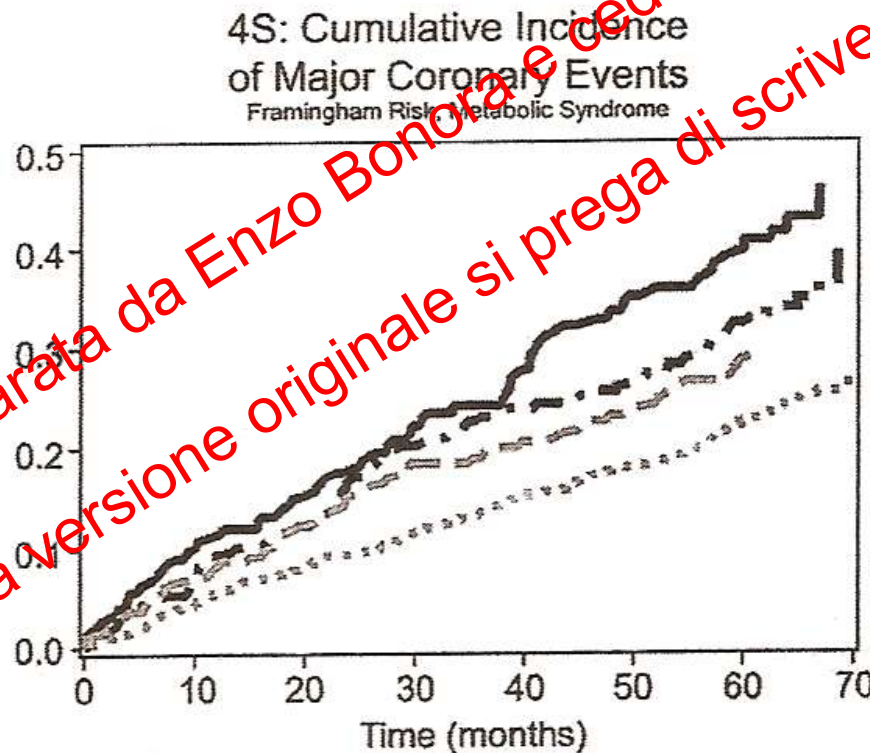
	Framingham	Met Syndr
Sex	✓	
Age	✓	
Smoking	✓	
LVH	✓	
Hypertension	✓	✓
Diabetes	✓	✓
LDL-cholesterol	✓	
HDL-cholesterol	✓	✓
Triglycerides		✓
Pre-diabetes (IFG, IGT)		✓
Insulin resistance		✓
Microalbuminuria		✓

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Cumulative incidence of CHD according to 10-year Framingham Score ($<20\%$, $\geq 20\%$) and Metabolic Syndrome (yes, no) in placebo-treated subjects from 4S

(Girman et al; Am J Cardiol 93:136, 2004)

prior CHD, moderate hypercholesterolemia



$\geq 20\%$, MetS

$\geq 20\%$, no MetS

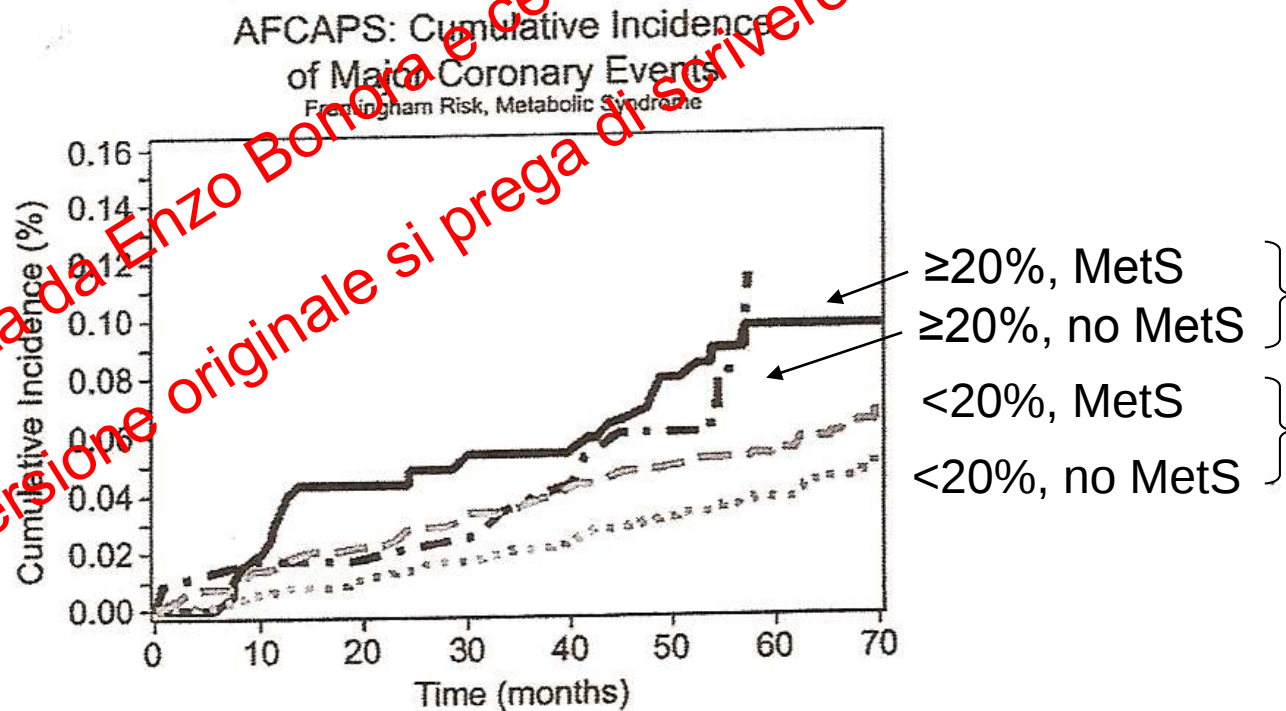
$<20\%$, MetS

$<20\%$, no MetS

Cumulative incidence of CHD according to 10-year Framingham Score ($<20\%$, $\geq 20\%$) and Metabolic Syndrome (yes, no) in placebo-treated subjects from AFCAPS

(Girman et al; Am J Cardiol 93:136, 2004)

no prior CHD, mild hypercholesterolemia and low HDL-C



Metabolic syndrome and risk of mortality in middle-aged versus elderly individuals: the HUNT study (Nord-Trondelag Health Study):

(Diabetologia, 2009; 52: 583-90)

Table 2 CVD and all-cause mortality according to presence or absence of the metabolic syndrome in the total sample and in the sub-sample without self-reported CVD at baseline

Variable	CVD mortality			All-cause mortality		
	40–59 years	60–74 years	75–89 years	40–59 years	60–74 years	75–89 years
Total sample (n=6,748)						
Deaths during follow-up, n	35	204	331	88	364	503
Metabolic syndrome						
Age ^a - and sex-adjusted HR	3.97 (2.66–7.88)	1.07 (0.82–1.39)	1.12 (0.90–1.40)	2.06 (1.35–3.13)	1.10 (0.90–1.36)	1.05 (0.88–1.25)
PAR (%) ^b	20.7	3.1	4.6	14.2	4.3	2.1
Multivariable HR ^c	1.95 (1.96–7.97)	1.03 (0.83–1.43)	1.11 (0.89–1.39)	2.14 (1.40–3.29)	1.14 (0.92–1.41)	1.05 (0.87–1.26)
No self-reported CVD (n=5,906)						
Deaths during follow-up, n	21	142	189	72	264	314
Metabolic syndrome						
Age ^a - and sex-adjusted HR	6.35 (2.46–16.4)	1.15 (0.82–1.61)	0.98 (0.74–1.31)	2.03 (1.28–3.23)	1.15 (0.90–1.47)	0.95 (0.76–1.19)
PAR (%) ^b	22.6	6.0	<0	12.6	6.0	<0
Framingham adjusted HR ^d	4.61 (1.74–12.2)	1.07 (0.75–1.51)	1.02 (0.75–1.37)	1.63 (1.01–2.63)	1.09 (0.84–1.41)	1.03 (0.82–1.30)
PAR (%) ^d	21.0	3.0	1.1	10.3	3.8	1.6

Virtues of the Metabolic Syndrome (6)

Absence of features of the Metabolic Syndrome is a marker of very low CVD risk

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15-yr Cumulative incidence of CHD in Subjects with the Metabolic Syndrome or No Trait of the Syndrome

(Bruneck Study; age 40-79; Bonora et al unpublished)

	Subjects at risk	CHD Incident cases	Percent cases
Metabolic Syndrome	228	31	13.6
No trait of Met S*	116	1	0.9

CHD=fatal and nonfatal IMA or angina confirmed by exercise ECG or angiography

*Current Smokers=25%; Total cholesterol >240 mg/dl=24%

Conclusions

- The Metabolic Syndrome is very common and it is featured by many clinical and biochemical abnormalities.
- Insulin resistance and central (visceral) obesity play a major pathogenic role in the Syndrome.
- The Syndrome is a very strong risk factor for type 2 diabetes mellitus.
- The Metabolic Syndrome is a strong risk factor for cardiovascular disease (on the top of Framingham Risk Score).

Multistep approach in the treatment of the Metabolic Syndrome

- Identification of subjects affected
- Definition of individual risk according to number and severity of components in the cluster as well as to additional risk factors (e.g., smoking, LDL-Cholesterol)
- Background treatment of underlying disorders: insulin resistance, excess (visceral) fat
- Specific additional treatment of single components, when necessary, and of associated risk factors (e.g. LDL-C)

Fine
Grazie

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