



ROMA

10 OTTOBRE 2019

CORRETTA
GESTIONE
DEL PAZIENTE
CON **DIABETE TIPO
AD ALTO RISCHIO
CARDIOVASCOLARE** 2

Inquadramento e
quantificazione del
rischio cardiovascolare
nel paziente con
diabete di tipo 2

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Diapositiva preparata da GIUSEPPE PUGLIESE e ceduta alla Società Italiana di Diabetologia.
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Dichiaro altresì il mio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

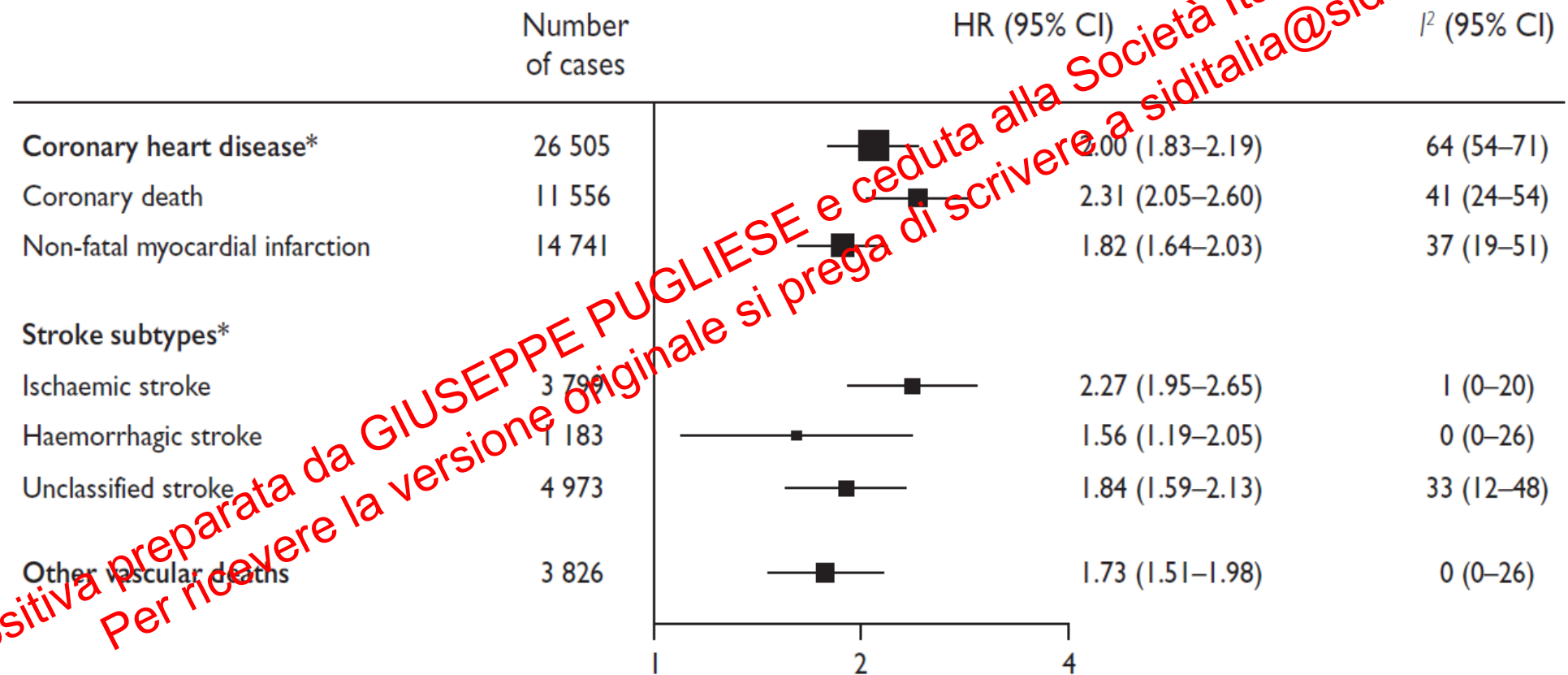
In fede

Giuseppe Pugliese

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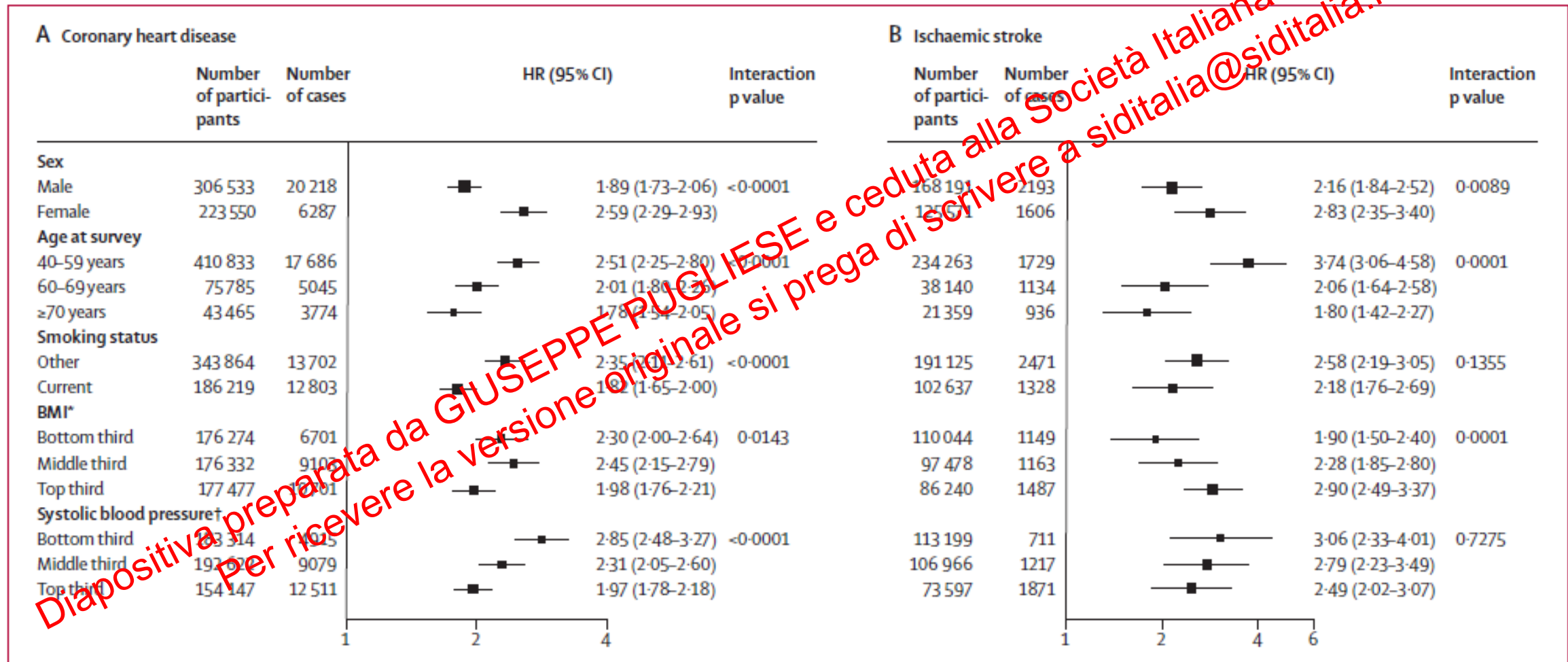
Collaborative meta-analysis of 102 prospective studies

(n=698,782; 52,765 non-fatal or fatal vascular outcomes; 8.49 million person-years at risk)



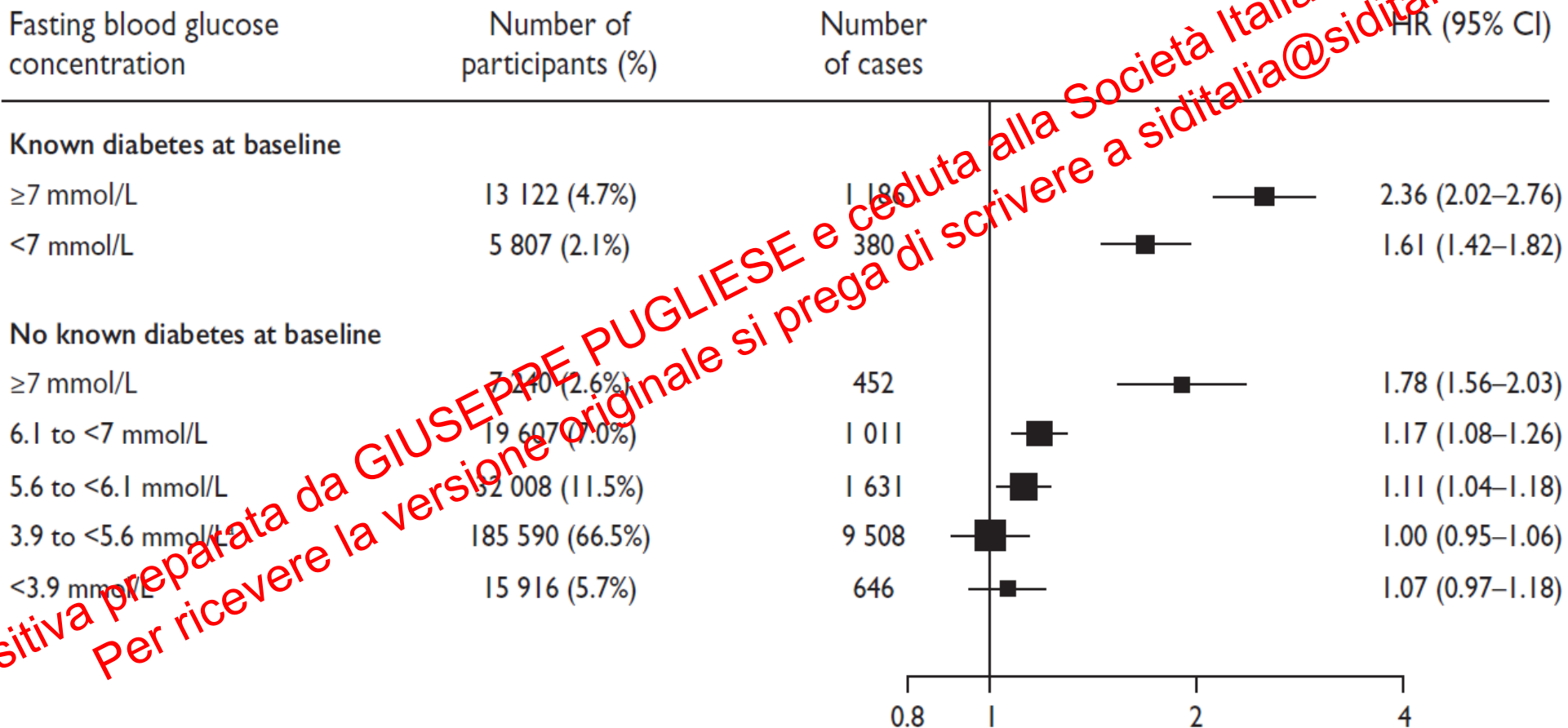
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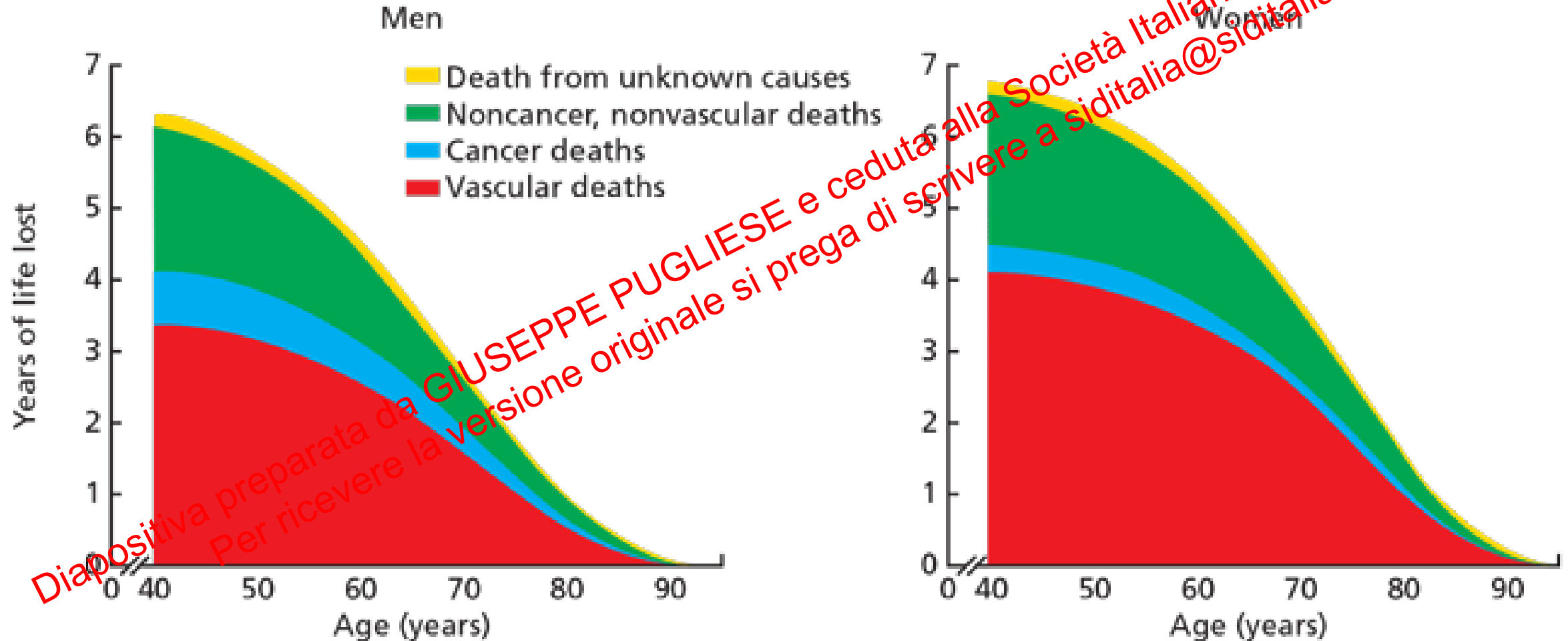


Collaborative meta-analysis of 102 prospective studies

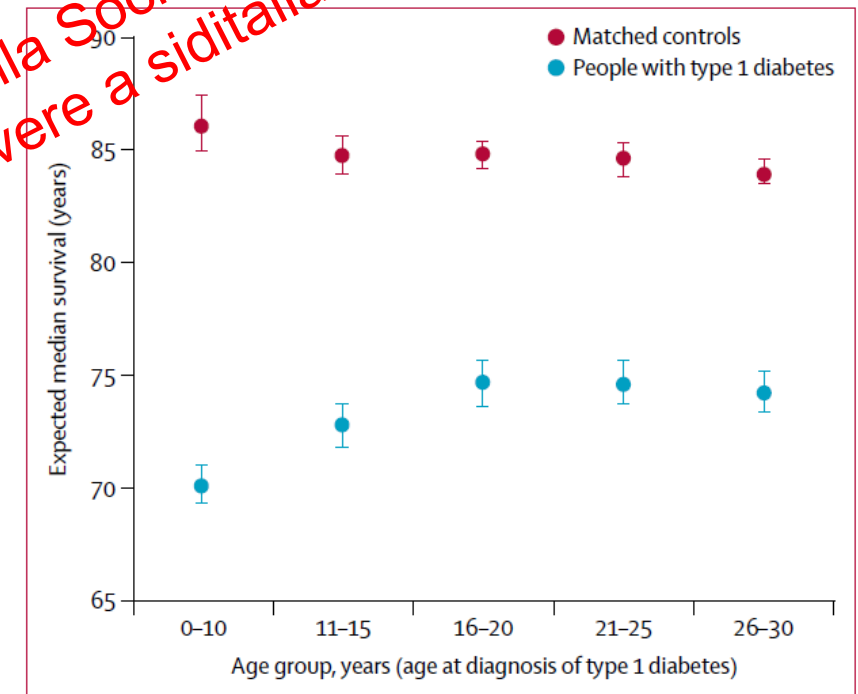
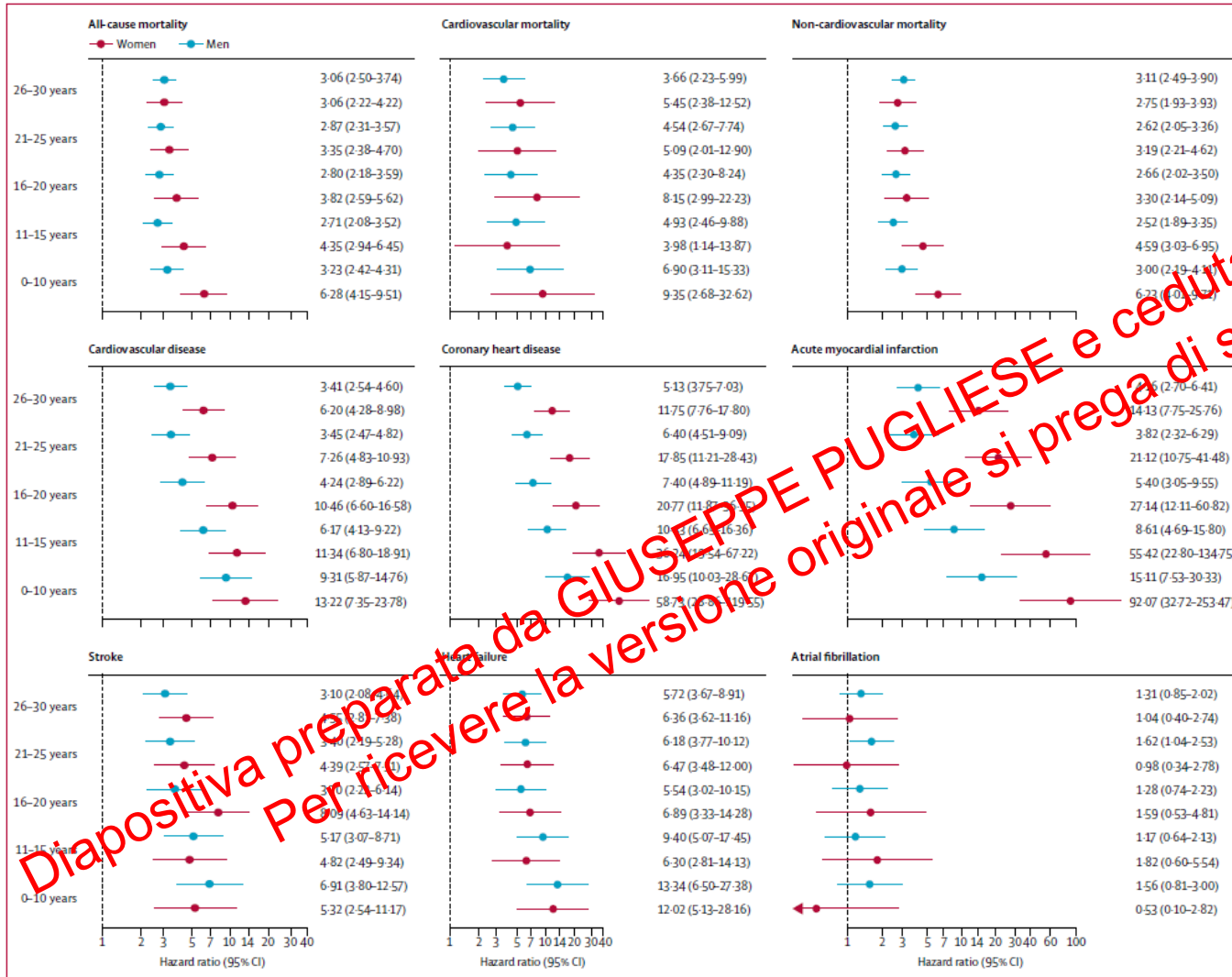
(n=698,782; 52,765 non-fatal or fatal vascular outcomes; 8.49 million person-years at risk)



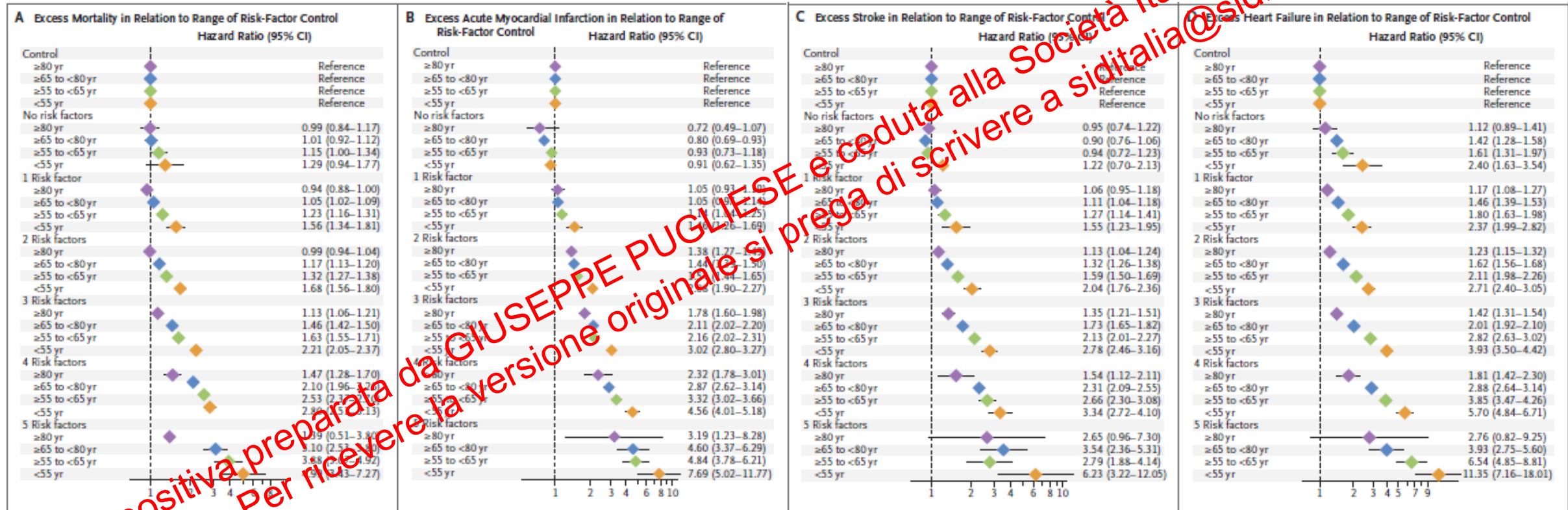
Collaborative meta-analysis of individual-participant data from 97 studies
(n=820,900 with and without diabetes; 123,205 deaths)



Cohort study of individuals with type 1 diabetes in the Swedish National Diabetes Register (n=27,195 individuals with type 1 diabetes, 959 deaths, and 135,178 matched controls, 1,501 deaths; median follow-up 10 years)



Cohort study of individuals with type 2 diabetes in the Swedish National Diabetes Register
(n=271,174 individuals with type 2 diabetes and 1,355,870 matched controls; median follow-up 5.7 years)



2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

CV risk assessment

Resting ECG is recommended in patients with DM with hypertension or suspected CVD

Carotid or femoral ultrasound should be considered for plaque detection as CV risk modifier

Screening for CAD with coronary CT angiography and functional imaging may be considered

CAC scoring may be considered as risk modifier

ABI may be considered as risk modifier

Key messages

- Routine assessment of microalbuminuria should be carried out to identify patients at risk of developing renal dysfunction and/or CVD.
- A resting electrocardiogram (ECG) is indicated in patients with DM and hypertension, or if CVD is suspected.
- Other tests, such as transthoracic echocardiography, coronary artery calcium (CAC) score, and ankle–brachial index (ABI), may be considered to test for structural heart disease as risk modifiers in those at moderate or high risk of CVD.
- Routine assessment of novel biomarkers is not recommended for CV risk stratification.

Gaps in the evidence

- The prognostic value of advanced imaging techniques, such as strain imaging or CV magnetic resonance with tissue characterization, needs validation in prospective cohorts.
- Asymptomatic subjects with significant atherosclerosis burden (i.e. CAC score >400) may be referred for functional imaging or CTCA; however, identification of the presence of significant coronary artery stenoses has not been shown to be better than aggressive medical treatment for CVRFs.
- Sex-specific differences in the diagnosis of CAD require further investigation.
- The uptake of CV risk assessment in different ethnic groups requires evaluation.

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Cardiovascular risk categories in patients with diabetes^a

Very high risk

10-year risk of CV death >10%

Patients with DM **and** established CVD
or other target organ damage^b
or three or more major risk factors^c
or early onset T1DM of long duration (>20 years)

High risk

10-year risk of CV death 5-10%

Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor

Moderate risk

10-year risk of CV death <5%

Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

^aModified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.²⁷

^bProteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy.

^cAge, hypertension, dyslipidemia, smoking, obesity.

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Recommendations	Class ^a	Level ^b
Routine assessment of microalbuminuria is indicated to identify patients at risk of developing renal dysfunction or at high risk of future CVD. ^{27,38}	I	B
A resting ECG is indicated in patients with DM diagnosed with hypertension or with suspected CVD. ^{38,39}	I	C
Assessment of carotid and/or femoral plaque burden with arterial ultrasonography should be considered as a risk modifier in asymptomatic patients with DM. ^{60–62}	IIa	B
CAC score with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic patients with DM at moderate risk. ^{c 63}	IIb	B
CTCA or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac magnetic resonance imaging, or exercise or pharmacological stress echocardiography) may be considered in asymptomatic patients with DM for screening of CAD. ^{47,48,64,65,67–70}	IIb	B
ABI may be considered as a risk modifier in CV risk assessment. ⁷⁶	IIb	B
Detection of atherosclerotic plaque of carotid or femoral arteries by CT, or magnetic resonance imaging, may be considered as a risk modifier in patients with DM at moderate or high risk CV. ^{c 75,77}	IIb	B
Carotid ultrasound intima–media thickness screening for CV risk assessment is not recommended. ^{62,73,78}	III	A
Routine assessment of circulating biomarkers is not recommended for CV risk stratification. ^{27,31,35–37}	III	B
Risk scores developed for the general population are not recommended for CV risk assessment in patients with DM.	III	C

ABI = ankle–brachial index; CAC = coronary artery calcium; CAD = coronary artery disease; CT = computed tomography; CTCA = computed tomography coronary angiography; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiogram.

^aClass of recommendation.

^bLevel of evidence.

GS

Age: 68 years

Gender: male

Ethnicity Caucasian

Former smoker (nonsmoker for 10 years)

Diabetes duration: 14 years

HbA_{1c}: 8.3% (67 mmol/mol)

Triglycerides: 189 mg/dl (2.14 mmol/l)

Total cholesterol: 210 mg/dl (5.44 mmol/l)

HDL cholesterol: 52 mg/dl (1.35 mmol/l)

LDL cholesterol: 120.2 mg/dl (3.11 mmol/l)

Blood pressure: 135/85 mmHg



Treatment: Metformin 1000 mg bid, Gliclazide 60 mg qd, Ramipril 5 mg + Hydrochlorothiazide 25 mg qd, Amlodipine 5 mg qd, Simvastatin 10 mg qd

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Cardiovascular risk stratification using available algorithms



NATIONAL CHOLESTEROL EDUCATION PROGRAM

Third Report of the Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack

The risk assessment tool below uses information from the Framingham Heart Study to predict a person's chance of having a heart attack in the next 10 years. This tool is designed for adults aged ≥ 20 who do not have heart disease or diabetes. To find your risk score, enter your information in the calculator below.

Age:

years

Gender:

☐ Female ☒ Male

Total cholesterol:

mg/dL

HDL cholesterol

mg/dL

Smoker:

☒ No ☐ Yes

Systolic blood pressure:

mm/Hg

Are you currently on any medication to treat high blood pressure.

☐ No ☒ Yes

Calculate your 10-year risk

16%



Total cholesterol: is the sum of all the cholesterol in your blood. The higher your total cholesterol, the greater your risk for heart disease.

<200 mg/dL: 'desirable' level that puts you at lower risk for heart disease. A cholesterol level of 200 mg/dL or greater increases your risk.

200 to 239 mg/dL: 'borderline-high.'

≥ 240 mg/dL: 'high' blood cholesterol. A person with this level has more than twice the risk of heart disease compared to someone whose cholesterol is <200 mg/dL.



High density lipoprotein (HDL) cholesterol: is the 'good' cholesterol. HDL carry cholesterol in the blood from other parts of the body back to the liver, which leads to its removal from the body. So HDL help keep cholesterol from building up in the walls of the arteries.

<40 mg/dL: a major risk factor for heart disease

40 to 59 mg/dL: the higher your HDL, the better

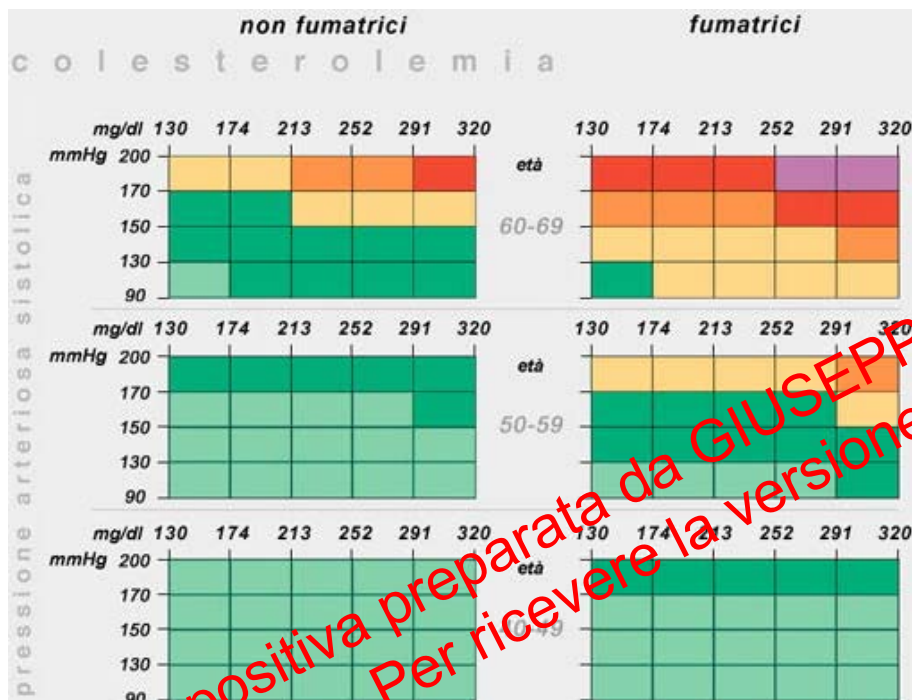
≥ 60 mg/dL: an HDL of 60 mg/dL and above is considered protective against heart disease.



Smoker: select "yes" if you have smoked any cigarettes in the past month.



Systolic blood pressure: is the first number of your blood pressure reading. For example, if your reading is 120/80 (120 over 80), your systolic blood pressure is 120.



livello di rischio a 10 anni

rischio MCV V	oltre 30%
rischio MCV IV	20% - 30%
rischio MCV III	15% - 20%
rischio MCV II	10% - 15%
rischio MCV I	5% - 10%
rischio MCV I	meno 5%





Sesso

Età

Abitudine al fumo di sigaretta (si intende chi fuma regolarmente ogni giorno, anche una sola sigaretta, oppure ha smesso di fumare da meno di 12 mesi)

Qual è il valore della pressione sistolica? (misurazione, espressa in mmHg)

Qual è il valore della pressione sistolica? (misurazione, espressa in mmHg)

Qual è il valore della colesterolemia totale? (espressa in mg/dl)

Qual è il valore della colesterolemia HDL? (espressa in mg/dl)

È mai stato diagnosticato il diabete? (oppure due determinazioni successive di glicemia a digiuno superiori o uguali a 126 mg/dl)

Presenza di ipertensione arteriosa per cui il medico ha prescritto farmaci anti-ipertensivi (si considera sotto trattamento chi assume regolarmente questi farmaci)

27%

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AMERICAN
COLLEGE of
CARDIOLOGY

2013 Guideline on the Assessment of Cardiovascular Risk



American
Heart
Association.

Heart Risk Calculator

Age (years)

Gender ☒ Male ☐ Female

Race ☐ African American ☒ Other

Total cholesterol (mg/dL)

HDL cholesterol (mg/dL)

Systolic blood pressure (mmHg)

Diastolic blood pressure (mmHg)

Treated for high blood pressure ☐ No ☒ Yes

Diabetes ☐ No ☒ Yes

Smoker ☒ No ☐ Yes

35,1%

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Input

Age now : 68 years HbA1c : 8.3 %
Diabetes duration : 14 years Systolic BP : 135 mm Hg
Sex : ☒ Male ☐ Female Total cholesterol : 210 mg/dl
Atrial fibrillation : ☒ No ☐ Yes HDL cholesterol : 52 mg/dl
Ethnicity : White
Smoking : Non-smoker

Options >

Output

10 year risk 0 15 30 100

CHD :	34,7%	
Fatal CHD :	27,8%	
Stroke :	18,1%	
Fatal stroke :	2,6%	

Adjusted for regression dilution

Calculate Copy Print
Help Exit

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What available algorithms do not consider

Classical algorithms to quantify total CV risk consider (some) traditional risk factors (age, gender, ethnicity, hypertension, dyslipidemia, smoking), but pay limited or no attention to other risk factors (traditional and nontraditional) and particularly to search/detection of (subclinical) organ damage

Overweight and
(central) obesity

C-reactive protein and
fibrinogen
(inflammatory markers)

Macrovascular

Physical inactivity &
sedentary behavior

hsTnT and NT-proBNP
(markers of myocardial
injury)

Microvascular

GS

Age: 68 years

Gender: male

Ethnicity Caucasian

Former smoker (nonsmoker for 10 years)

Diabetes duration: 14 years

Physically inactive (~30 min/wk mod-vig PA)

Sedentary (~12 h/day sitting or reclined)

HbA_{1c}: 8.3% (67 mmol/mol)

Triglycerides: 189 mg/dl (2.14 mmol/l)

Total cholesterol: 210 mg/dl (5.44 mmol/l)

HDL cholesterol: 52 mg/dl (1.35 mmol/l)

LDL cholesterol: 120.2 mg/dl (3.11 mmol/l)

Blood pressure: 135/85 mmHg

BMI: 33.9 kg/m²

Waist circumference: 116 cm



ACR: 26 mg/g

eGFR: 42 mL/min/1.73 m²

Fundus examination: mild NPDR

WPT great toe: 26 mV

ECG: 85 beats/min, sinus rhythm, LVH

Echocardiogram: LVH (LV mass indexed to BSA 133 g/m²), preserved LVEF (58), diastolic dysfunction (E/A 0.7), LA dilation (42 mm)

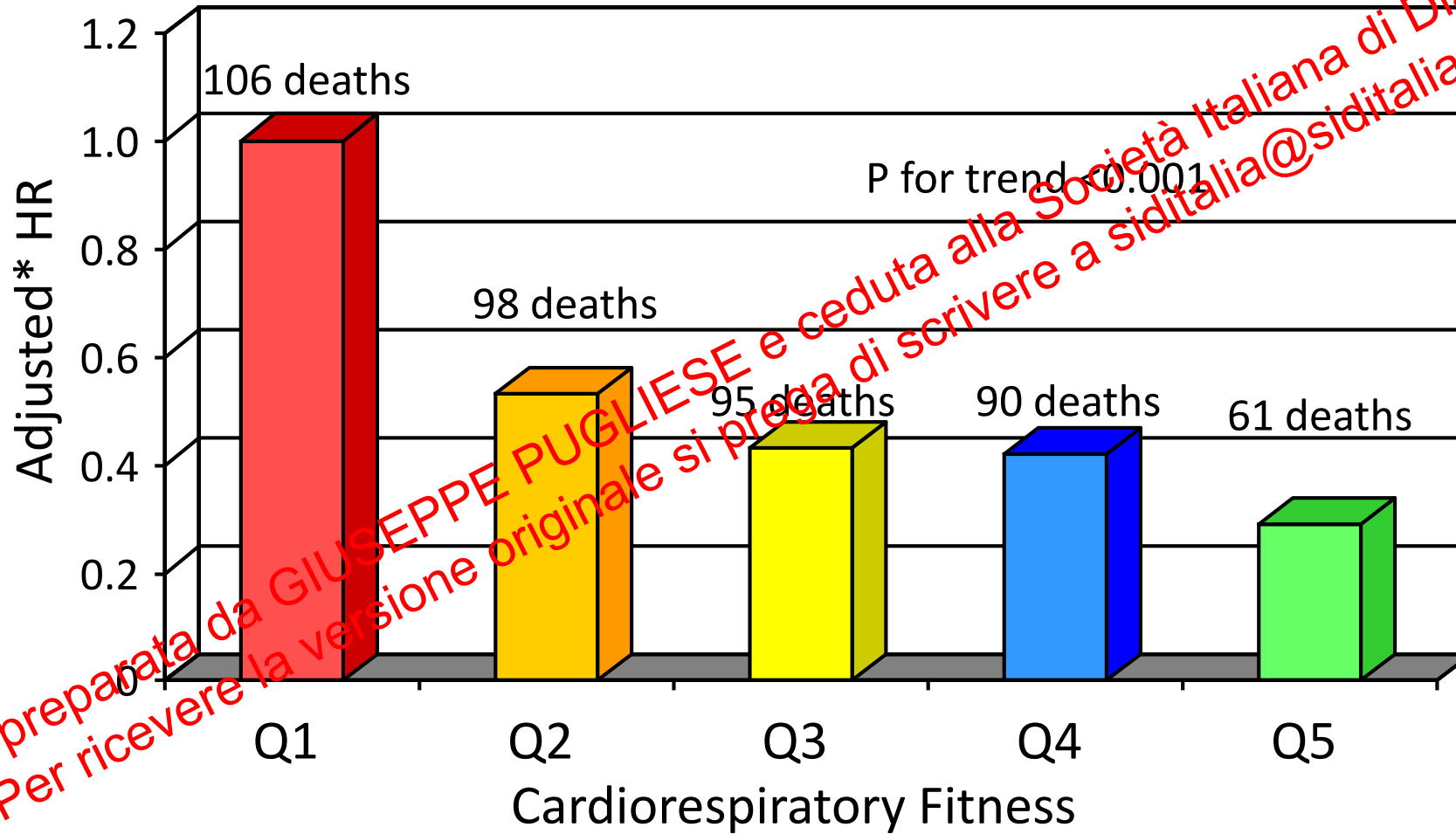
CAC score: 276

ABI: 0.85

Carotid US: no plaque

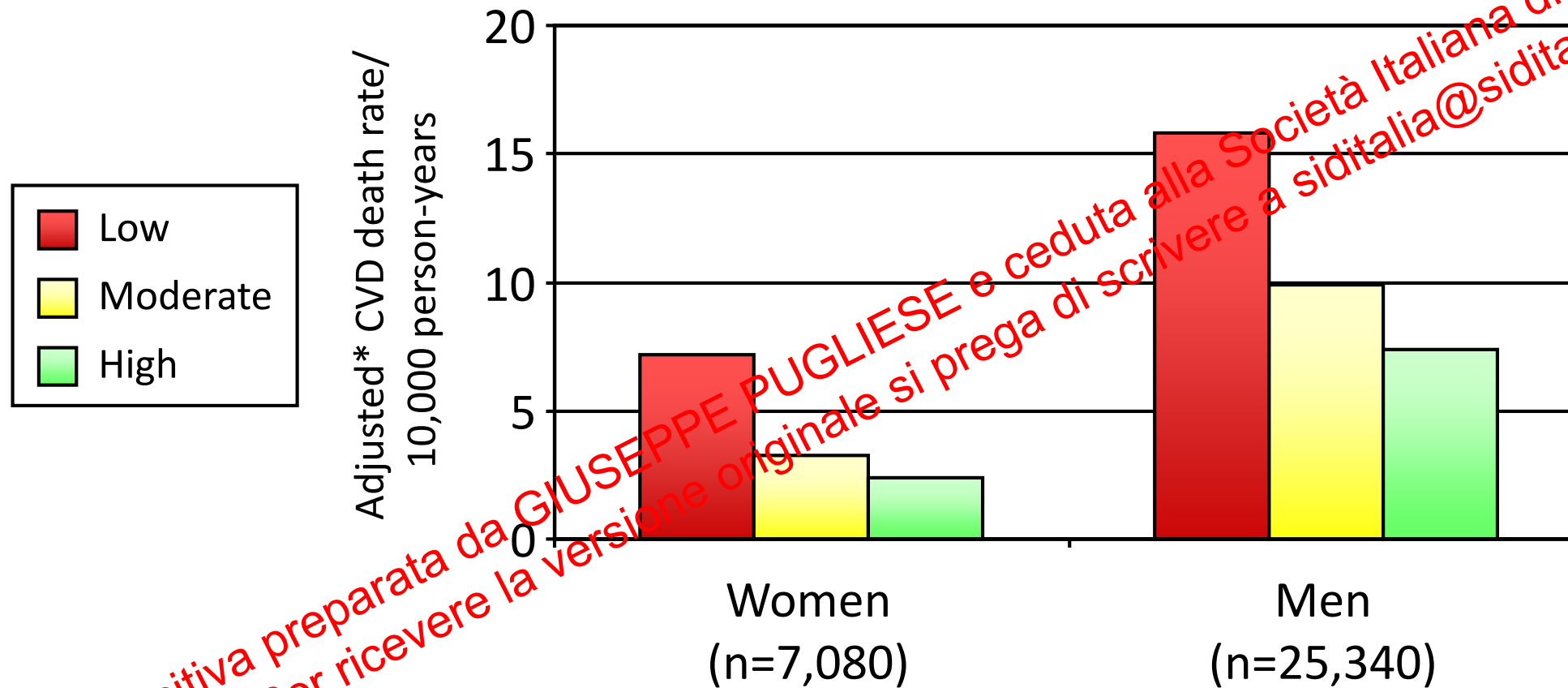
Treatment: Metformin 1000 mg bid, Gliclazide 60 mg qd, Ramipril 5 mg + Hydrochlorothiazide 25 mg qd, Amlodipine 5 mg qd, Simvastatin 10 mg qd

The Aerobics Center Longitudinal Study (ACLS)



2,603 adults aged ≥ 60 yrs. *Adjusted for age, exam year, smoking, abnormal exercise ECG, baseline health conditions.

The Aerobics Center Longitudinal Study (ACLS)



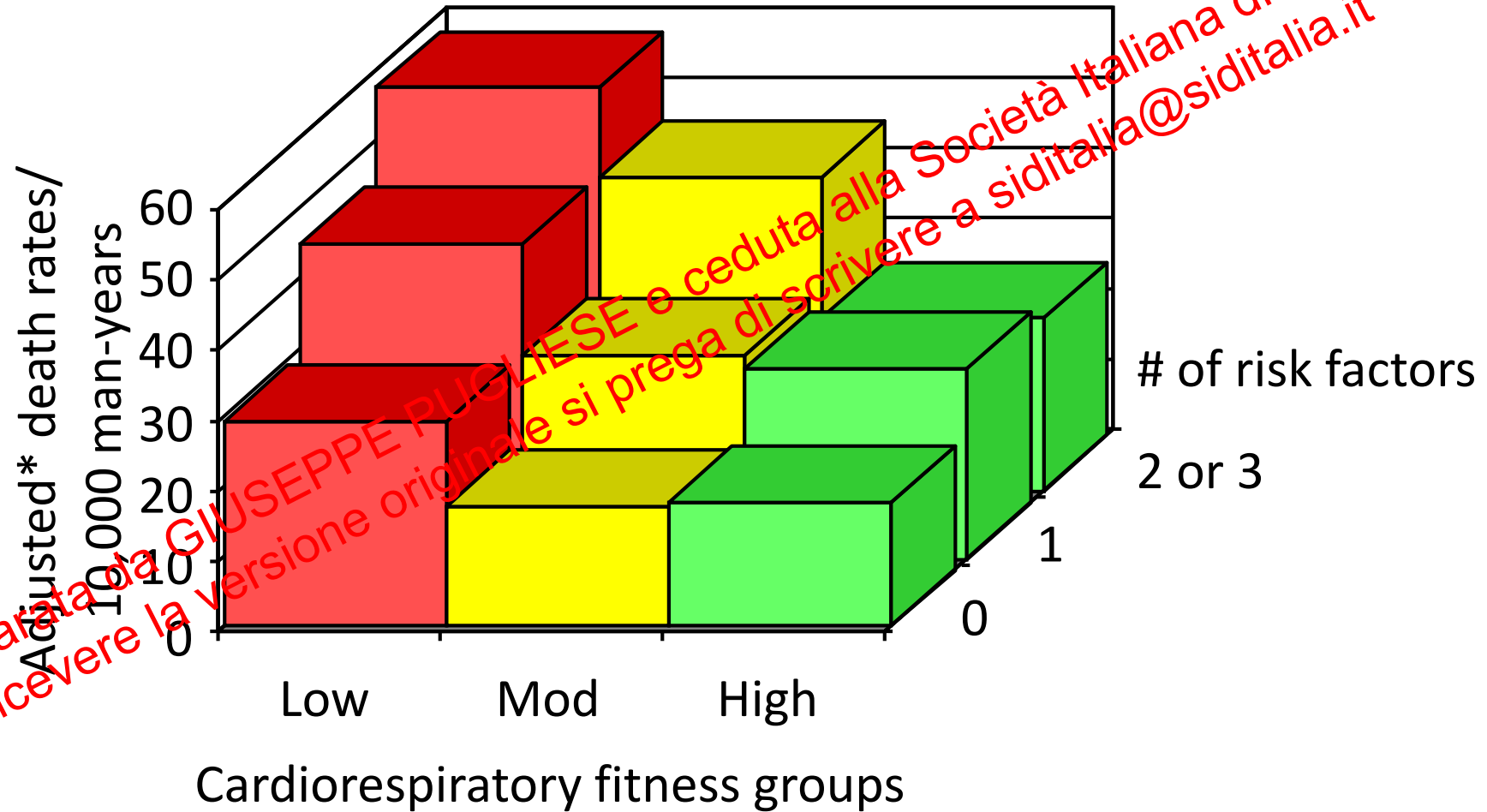
*Adjusted for age, exam year, and other risk factors

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The Aerobics Center Longitudinal Study (ACLS)

Risk factors:
Current smoking
SBP ≥ 140 mmHg
Chol ≥ 240 mg/dl

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

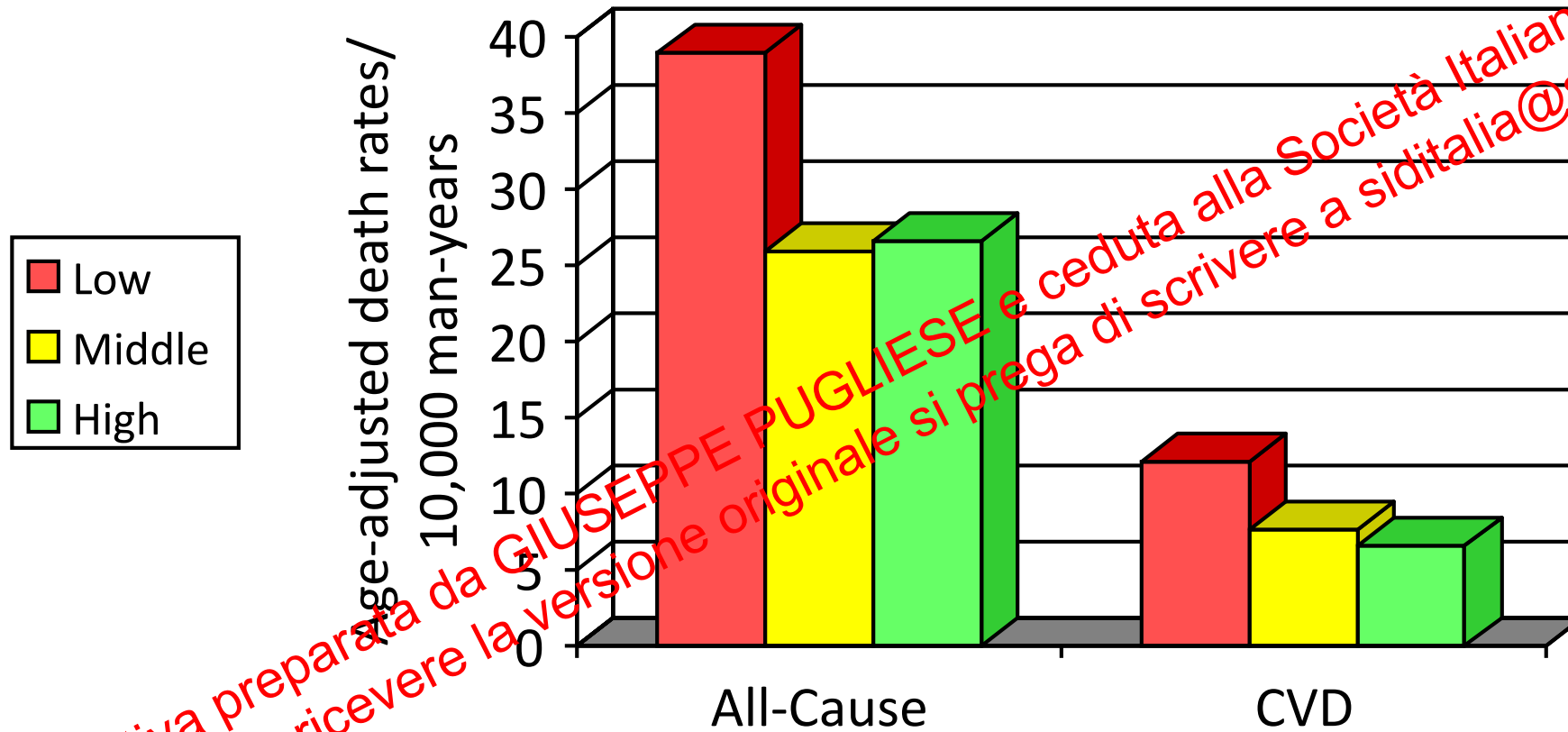


The Aerobics Center Longitudinal Study (ACLS)

	Age-adjusted death rates/10,000 man-years	
Fitness group	All-cause	CVD
Never fit	122	65
Improvers	68	31
Always fit	40	14

	All-cause death rates/10,000 man-years by age group			
Fitness group	20-39 yrs	40-49 yrs	50-59 yrs	≥60 yrs
Never fit	101	109	470	826
Improvers	23	73	129	414
Always fit	10	51	62	199

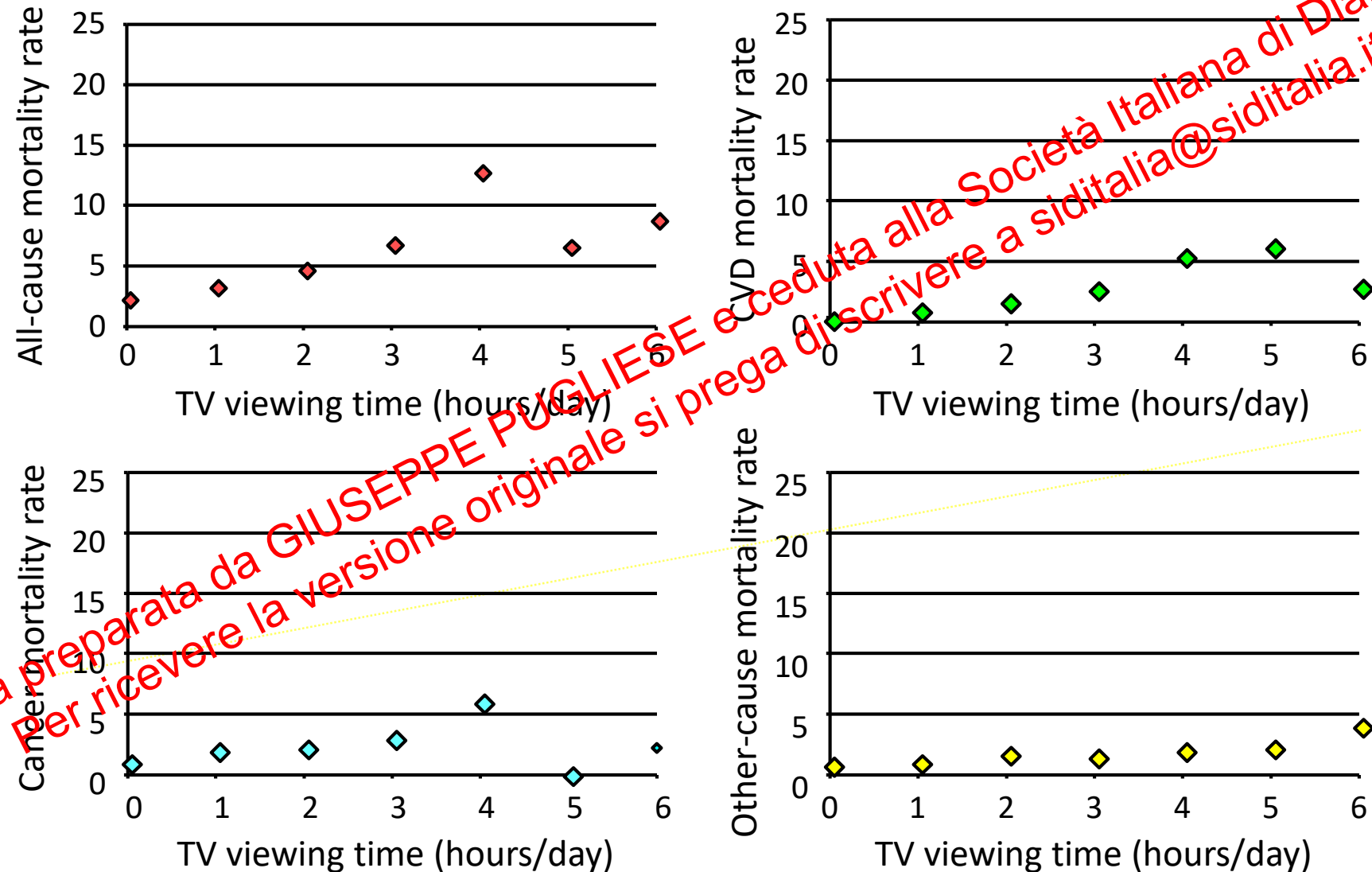
The Aerobics Center Longitudinal Study (ACLS)



503 deaths (145 CVD) in 8,762 men during average follow-up of 18.9 yrs

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Australian Diabetes, Obesity and Lifestyle Study (AusDiab)



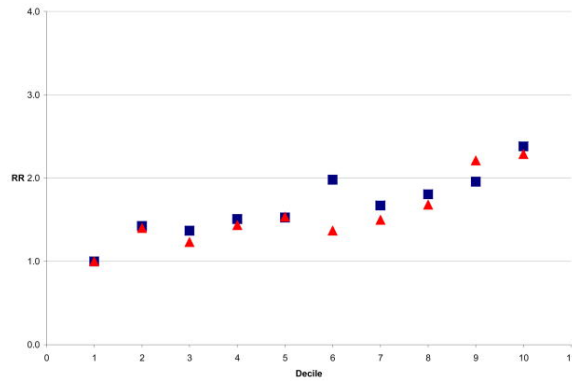
Systematic review and harmonised meta-analysis of individual level data from 8 registries
(n=36,383; mean age 62.6 years; 72.8% women, with median follow-up of 5.8 years, range 3.0-14.5 years, and 2,149, 5.9% deaths)

Variables	Hazard ratios (95% CI) for all cause mortality*; No of participants; No of deaths			
	First quarter (least active)	Second quarter	Third quarter	Fourth quarter (most active)
Model A				
Total physical activity (cpm)	1 (ref) (n=9189; 1301)	0.47 (0.42 to 0.53) (n=9225; 506)	0.35 (0.26 to 0.47) (n=9201; 177)	0.28 (0.22 to 0.34) (n=9231; 220)
Physical activity intensity:				
Light (min/d)	1 (ref) (n=9191; 1188)	0.58 (0.52 to 0.64) (n=9214; 547)	0.42 (0.36 to 0.49) (n=9212; 171)	0.36 (0.28 to 0.46) (n=9235; 237)
Low light (min/d)	1 (ref) (n=9182; 1100)	0.64 (0.57 to 0.72) (n=9224; 552)	0.46 (0.38 to 0.56) (n=9229; 376)	0.41 (0.35 to 0.50) (n=9217; 276)
High light (min/d)	1 (ref) (n=9166; 1261)	0.53 (0.47 to 0.60) (n=9241; 517)	0.35 (0.31 to 0.42) (n=9207; 290)	0.36 (0.25 to 0.51) (n=9227; 236)
Moderate to vigorous (min/d)	1 (ref) (n=9095; 1221)	0.54 (0.48 to 0.60) (n=9296; 525)	0.40 (0.29 to 0.56) (n=9235; 311)	0.35 (0.28 to 0.44) (n=9226; 247)
Sedentary (min/d)	1 (ref) (n=9219; 339)	1.32 (1.14 to 1.54) (n=9223; 432)	1.97 (1.59 to 2.30) (n=9201; 598)	3.22 (2.49 to 4.15) (n=9190; 935)
Model B†				
Total physical activity (cpm)	1 (ref) (n=9096; 1187)	0.48 (0.43 to 0.54) (n=9105; 463)	0.34 (0.26 to 0.45) (n=9096; 265)	0.27 (0.23 to 0.32) (n=9086; 214)
Physical activity intensity:				
Light (min/d)	1 (ref) (n=9073; 1089)	0.62 (0.54 to 0.68) (n=9101; 511)	0.44 (0.38 to 0.51) (n=9090; 320)	0.38 (0.28 to 0.51) (n=9119; 229)
Low light (min/d)	1 (ref) (n=9066; 1010)	0.66 (0.56 to 0.77) (n=9106; 518)	0.47 (0.38 to 0.58) (n=9112; 353)	0.42 (0.34 to 0.52) (n=9099; 268)
High light (min/d)	1 (ref) (n=9054; 1159)	0.55 (0.49 to 0.63) (n=9120; 483)	0.38 (0.30 to 0.48) (n=9088; 278)	0.37 (0.32 to 0.46) (n=9113; 229)
Moderate to vigorous (min/d)	1 (ref) (n=9000; 1139)	0.54 (0.55 to 0.74) (n=9153; 468)	0.55 (0.40 to 0.74) (n=9123; 305)	0.52 (0.43 to 0.61) (n=9105; 237)
Sedentary (min/d)	1 (ref) (n=9102; 331)	1.28 (1.09 to 1.51) (n=9105; 417)	1.71 (1.36 to 2.15) (n=9096; 562)	2.63 (1.94 to 3.56) (n=9080; 843)
Model C†				
Total physical activity (cpm)	1 (ref) (n=8971; 1122)	0.54 (0.48 to 0.61) (n=9004; 458)	0.41 (0.32 to 0.51) (n=8972; 259)	0.34 (0.29 to 0.41) (n=8985; 208)
Physical activity intensity:				
Light (min/d)	1 (ref) (n=8944; 1030)	0.66 (0.58 to 0.74) (n=8979; 485)	0.51 (0.44 to 0.57) (n=8992; 308)	0.44 (0.34 to 0.59) (n=9017; 224)
Low light (min/d)	1 (ref) (n=8939; 959)	0.70 (0.62 to 0.79) (n=8997; 490)	0.54 (0.48 to 0.63) (n=8999; 338)	0.48 (0.40 to 0.57) (n=8997; 260)
High light (min/d)	1 (ref) (n=8919; 1086)	0.63 (0.56 to 0.71) (n=8990; 467)	0.46 (0.39 to 0.54) (n=8985; 269)	0.45 (0.31 to 0.65) (n=9028; 225)
Moderate to vigorous (min/d)	1 (ref) (n=8875; 1077)	0.69 (0.58 to 0.81) (n=9041; 441)	0.62 (0.48 to 0.80) (n=9009; 297)	0.61 (0.50 to 0.75) (n=9007; 232)
Sedentary (min/d)	1 (ref) (n=9001; 317)	1.21 (1.02 to 1.42) (n=9006; 403)	1.56 (1.24 to 1.98) (n=8969; 536)	2.18 (1.61 to 2.95) (n=8956; 791)

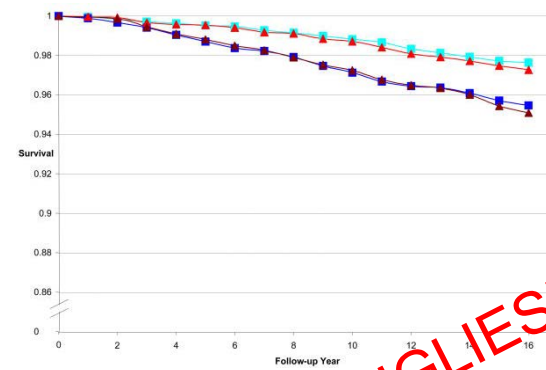
cpm=counts per minute.
Model A adjusted for sex (when applicable), age, and wear time (n=36852, 2304 deaths). Model B adjusted for sex (when applicable), age, body mass index, socioeconomic position, and wear time (n=36383, 2149 deaths). Model C additionally adjusted for covariates listed in table 1 (n=35932, 2047 deaths).
*By Cox regression.
†Moderate-to-vigorous physical activity and sedentary time are mutually adjusted.

The Health Professionals Follow-up Study (HPFS)

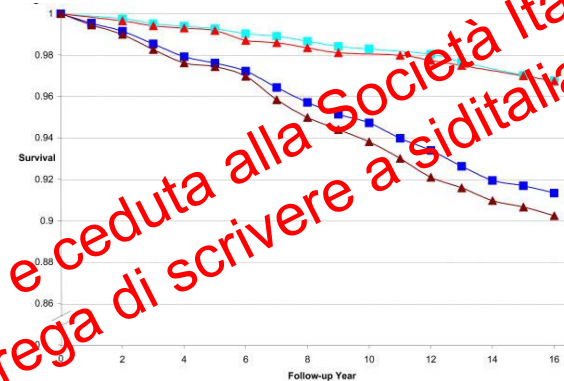
♂



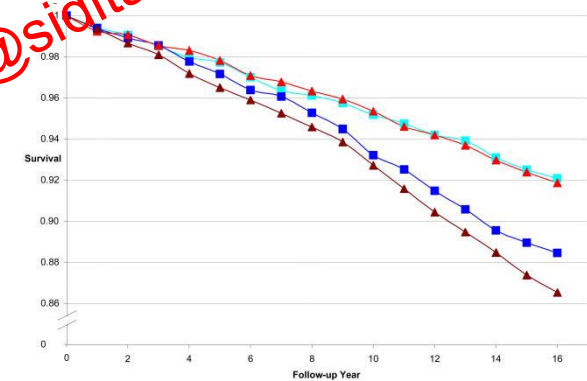
<55 years



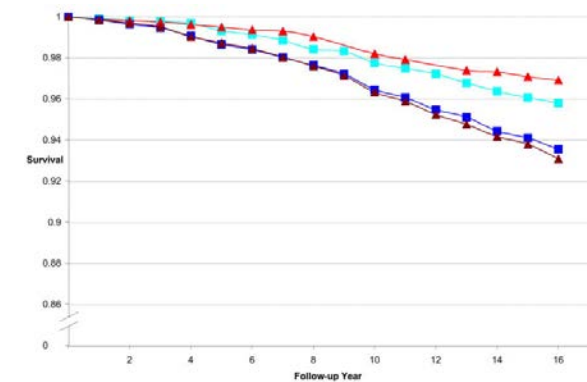
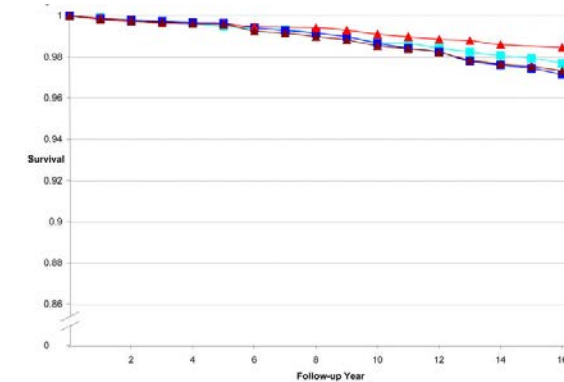
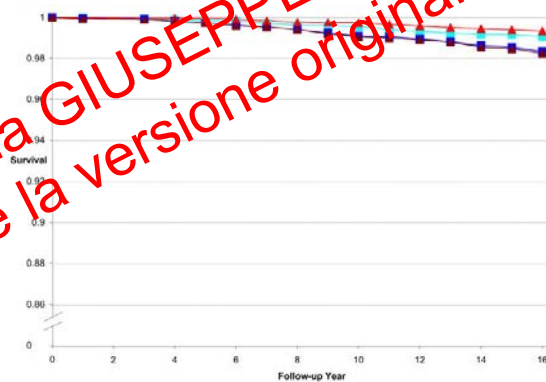
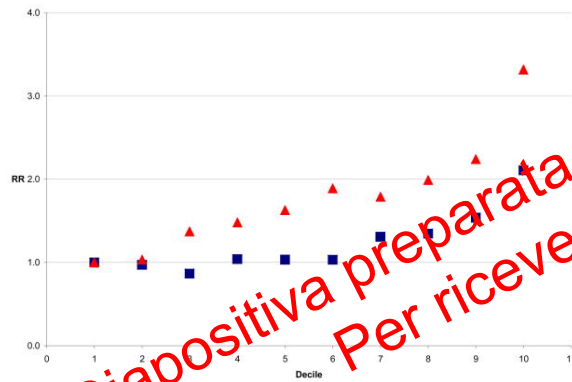
55-59 years



≥60 years



♀

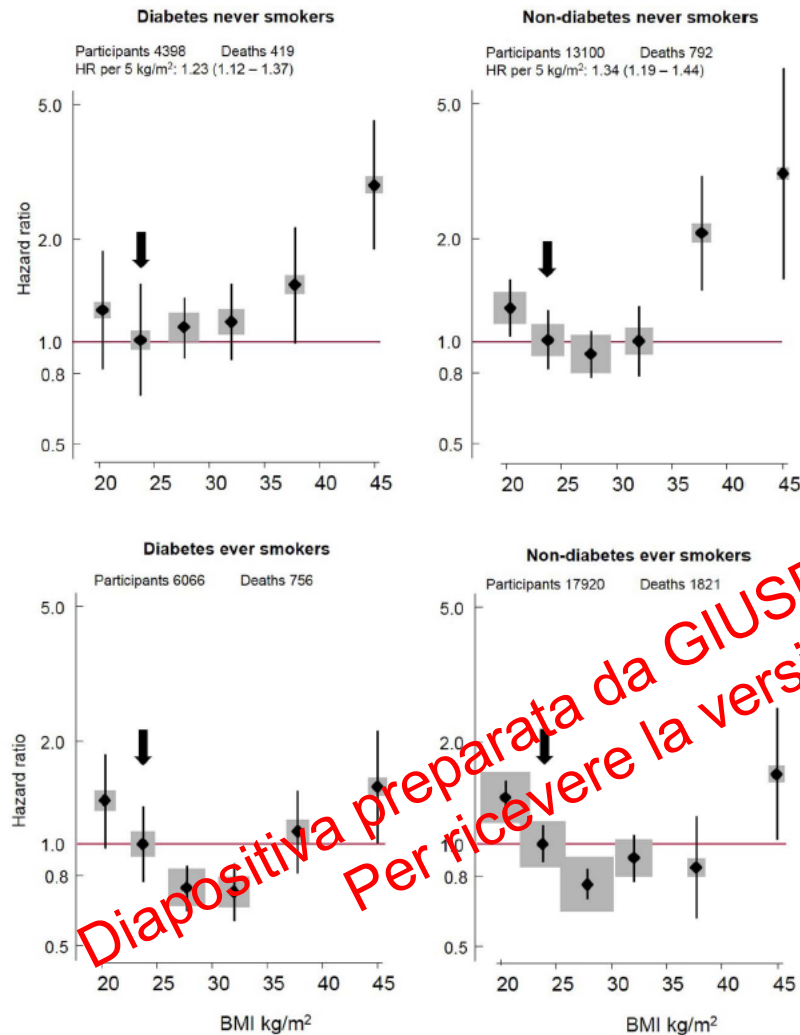


■ BMI
▲ WC

■ Q1 BMI ▲ Q1 WC
■ Q5 BMI ▲ Q5 WC

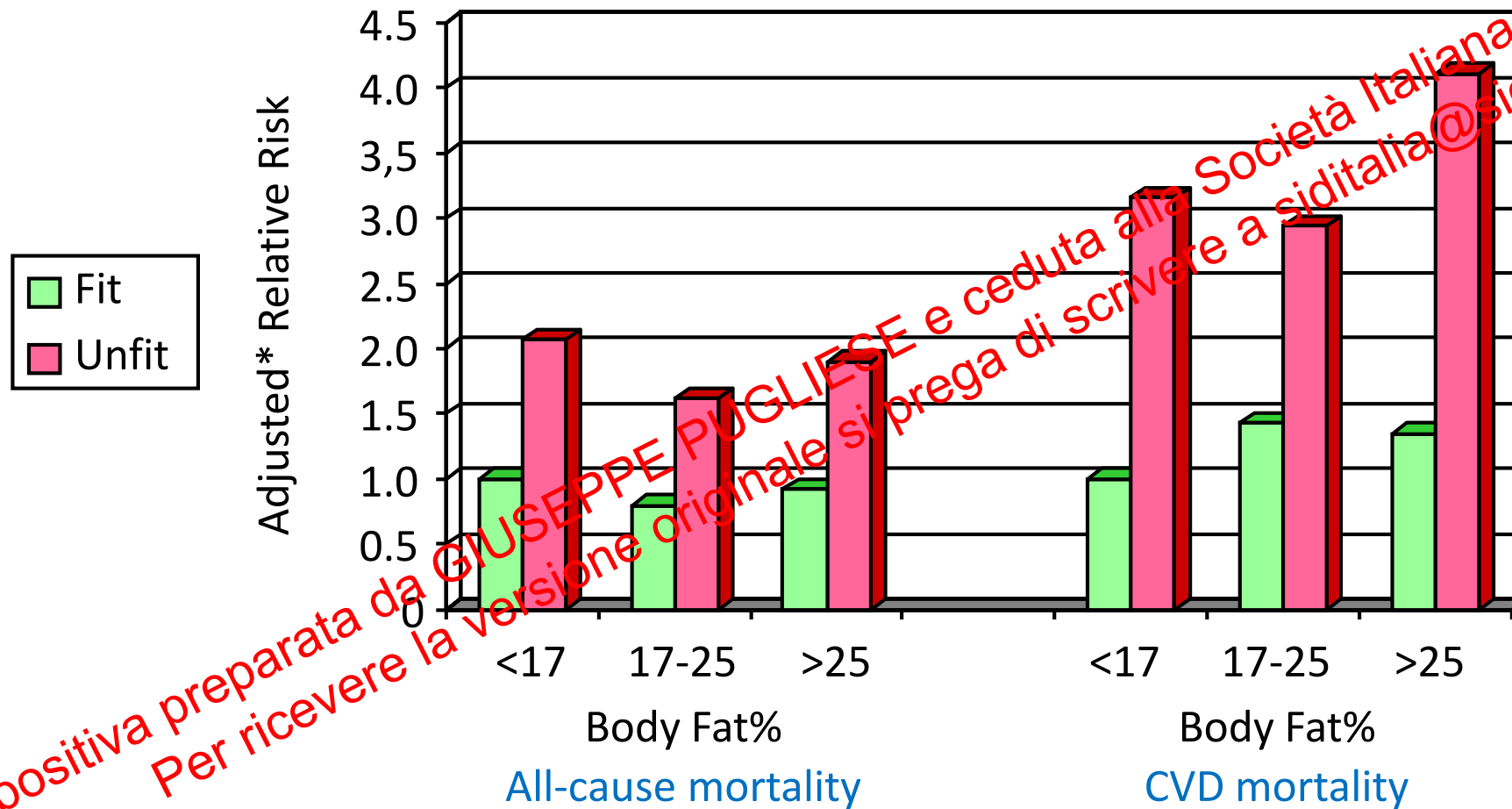
Diapositiva preparata da GIUSEPPE PUGLIESE e ceduta alla Società Italiana di Diabetologia. Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Matched population-level cohort study using primary care records from Salford, UK

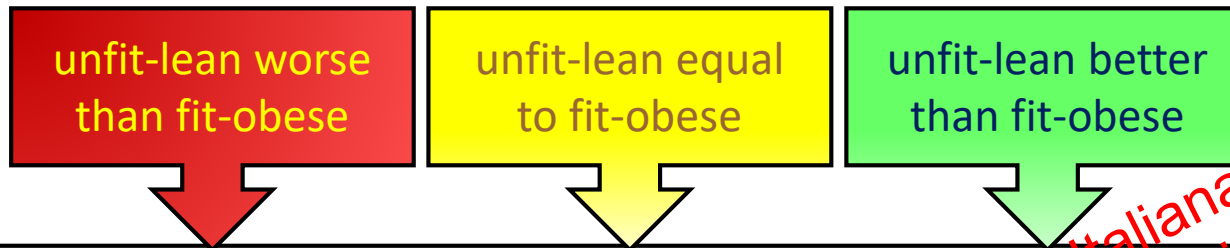


	BMI (kg/m ²) category						
	18.5–22.49	22.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	40.0–59.9	Total
Never smokers							
Type 2 diabetes							
No. of deaths	42	47	154	96	43	37	419
No. of individuals	205	374	1408	1269	667	475	4398
Risk estimates: adjusted for age and sex (95% CIs)	1.23 (0.81 to 1.86)	1.00 (referent)	1.08 (0.78 to 1.50)	1.12 (0.79 to 1.60)	1.45 (0.95 to 2.21)	2.87 (1.84 to 4.49)	
Never diabetes							
No. of deaths	183	169	270	113	44	13	792
No. of individuals	1775	2631	5287	2366	751	290	13 100
Risk estimates: adjusted for age and sex (95% CIs)	1.25 (1.01 to 1.55)	1.00 (referent)	0.92 (0.76 to 1.12)	1.02 (0.80 to 1.29)	1.98 (1.40 to 2.81)	3.31 (1.87 to 5.86)	
Ever smokers							
Type 2 diabetes							
No. of deaths	64	104	288	170	83	47	756
No. of individuals	263	514	2105	1795	853	536	6066
Risk estimates: adjusted for age and sex (95% CIs)	1.34 (0.98 to 1.83)	1.00 (referent)	0.74 (0.59 to 0.92)	0.72 (0.56 to 0.92)	1.09 (0.81 to 1.46)	1.48 (1.03 to 2.11)	
Never diabetes							
No. of deaths	468	415	598	254	54	32	1821
No. of individuals	3002	3508	7145	3060	884	321	17 920
Risk estimates: adjusted for age and sex (95% CIs)	1.34 (1.17 to 1.53)	1.00 (referent)	0.75 (0.66 to 0.85)	0.91 (0.78 to 1.07)	0.82 (0.61 to 1.10)	1.69 (1.18 to 2.43)	

The Aerobics Center Longitudinal Study (ACLS)



*adjusted for age, exam year, smoking, alcohol, & parental history

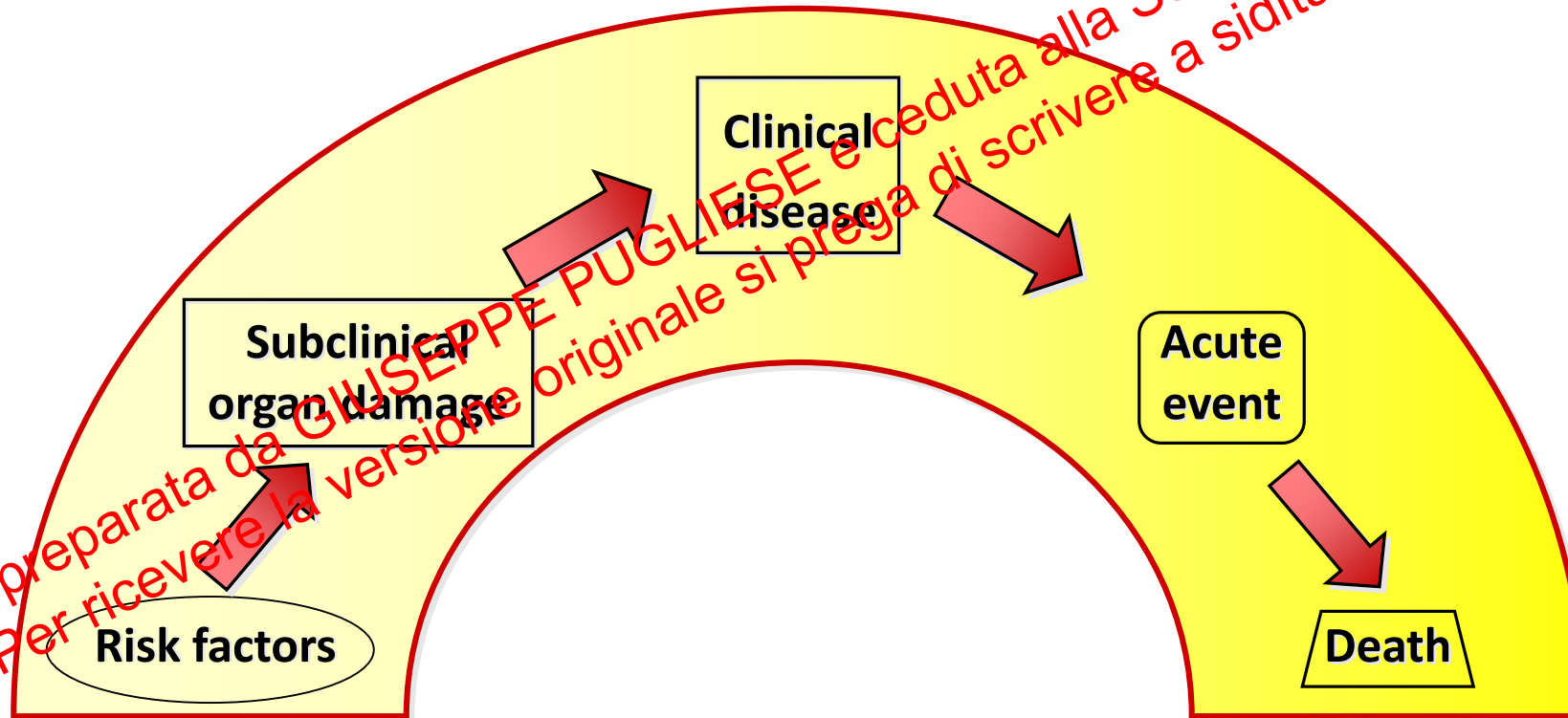


Outcome (fitness or PA as exposure)	Poor fitness or low PA in physically unfit individuals is a greater health risk than obesity in physically fit individuals	Poor fitness or low PA physically unfit individuals and obesity in physically fit individuals are similar health risks	Poor fitness or low PA in physically fit individuals is a smaller health risk than obesity in physically fit individuals	P (χ ²)
Total mortality				
Fitness	<u>X</u> <u>X</u> <u>X</u> <u>X</u> x	<u>X</u> x		0.07
Physical activity	<u>x</u> x	<u>X</u>	<u>X</u>	0.78
Cardiovascular mortality				
Fitness	<u>X</u> <u>X</u> <u>X</u> x x x	<u>X</u>		0.01
Physical activity	<u>x</u>	<u>X</u> <u>X</u> <u>X</u> <u>x</u> <u>x</u>	<u>X</u>	0.10
Cardiovascular disease				
Fitness	<u>x</u>			0.37
Physical activity	<u>X</u> x x x	<u>x</u> <u>x</u>	<u>X</u> <u>X</u>	0.61
Type 2 diabetes				
Fitness		x	<u>X</u> <u>X</u>	0.37
Physical activity		<u>x</u> <u>x</u>	<u>X</u> x x x x x	0.03
Cardiovascular and type 2 diabetes risk factors				
Fitness	<u>x</u>	<u>X</u> <u>x</u>	x (waist)	0.78
Physical activity		x	<u>X</u> <u>X</u> <u>X</u> <u>x</u> <u>x</u> x (waist) x (fat mass)	0.005

Unless indicated, BMI was used to identify obesity.
X = difference between normal-weight and unfit/inactive vs. obese and fit/active was verified by confidence intervals.
x = difference between normal-weight and unfit/inactive vs. obese and fit/active was not verified by confidence intervals.
Underlining refers to studies using BMI 30 as the cut-off point for obesity; other studies used cut-offs BMI 25–28.
BMI, body mass index; PA, physically active.

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Intermediate subclinical and clinical endpoint(s) with evidence of prognostic (and therapeutic) importance in terms of prediction of non-fatal and fatal events



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Systematic review and meta-analysis of 8 studies

(n=7,604 patients with type 2 diabetes, DME 4.6%, PDR 7.4%; 1,203 incident CVD events, including 916 CHD cases; mean follow-up of 5.9 years)

Outcome, DR Type	Model 1 ^a				Model 2 ^b				Model 3 ^c			
	Studies, No.	Participants, No.	Events, No.	IRR (95% CI)	Studies, No.	Participants, No.	Events, No.	IRR (95% CI)	Studies, No.	Participants, No.	Events, No.	IRR (95% CI)
First CVD												
DME	7	5553	910	1.65 (1.24-2.19)	6	4662	810	1.46 (1.04-2.05)	4	2285	427	1.48 (0.76-2.87)
PDR	7	5514	1016	1.28 (1.03-1.58)	4	3106	604	1.29 (1.00-1.66)	3	2506	430	1.21 (0.85-1.72)
VTDR	8	6343	1100	1.39 (1.16-1.67)	5	3872	635	1.34 (1.07-1.69)	4	2396	451	1.26 (0.92-1.73)
Fatal CVD												
DME	5	3719	176	2.85 (1.43-5.68)	5	3606	162	3.05 (1.43-6.43)	4	2278	101	3.53 (1.35-9.25)
PDR	5	3552	14	1.85 (1.04-3.28)	4	3106	164	2.05 (1.03-4.07)	3	2036	99	1.50 (0.56-4.03)
VTDR	6	4309	258	2.33 (1.49-3.67)	5	4012	185	2.40 (1.44-4.02)	4	2389	101	2.20 (1.10-4.39)
First CHD												
DME	7	4950	740	1.51 (1.16-2.14)	6	3426	468	1.80 (1.00-3.26)	4	2156	359	1.45 (0.73-2.88)
PDR	6	4580	743	1.39 (1.09-1.88)	4	2884	477	1.36 (1.02-1.81)	3	1898	357	1.20 (0.82-1.76)
VTDR	7	5288	802	1.47 (1.20-1.79)	5	3648	504	1.44 (1.11-1.87)	4	2256	375	1.32 (0.94-1.85)
Fatal CHD												
DME	5	3519	150	3.55 (1.76-7.15)	5	3411	136	3.80 (1.77-8.18)	3	1810	89	3.77 (1.39-10.21)
PDR	5	3287	208	2.11 (1.19-3.76)	4	2884	139	2.33 (1.17-4.66)	3	1898	89	1.70 (0.63-4.60)
VTDR	6	4076	218	2.74 (1.74-4.32)	5	3633	142	2.81 (1.67-4.74)	3	1898	89	2.47 (1.21-5.06)

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; DME, diabetic macular edema; DR, diabetic retinopathy; IRR, incidence rate ratio; PDR, proliferative diabetic retinopathy; VTDR, vision-threatening diabetic retinopathy.

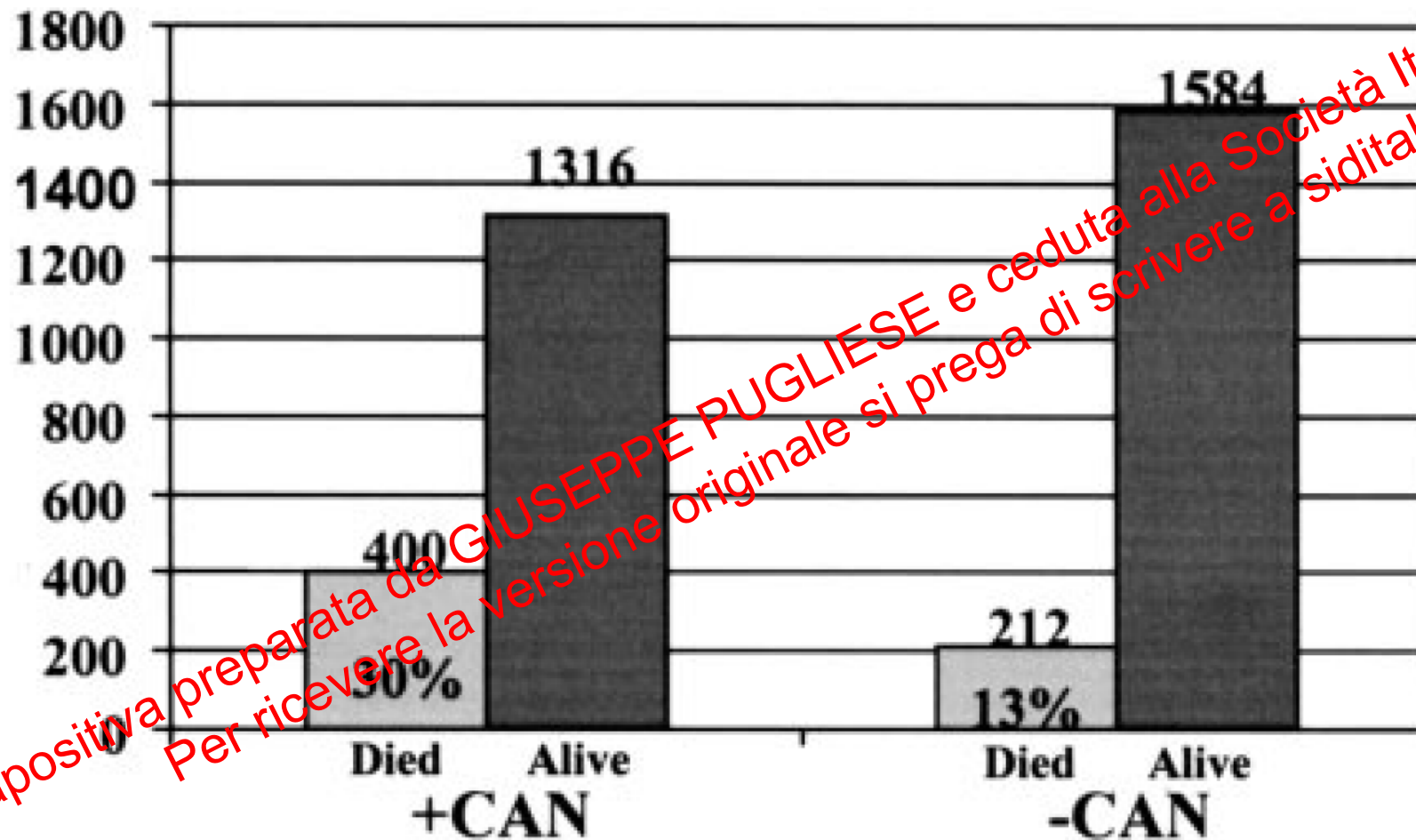
^a Model 1: adjusted for age, sex, and race/ethnicity.

^b Model 2: model 1 additionally adjusted for current smoking, systolic blood pressure, use of hypertension medication, total cholesterol level, and body mass index.

^c Model 3: model 2 additionally adjusted for duration of diabetes, use of treatment for diabetes, and hemoglobin A_{1c} level.

Meta-analysis of 15 studies

(n=3,512; follow-up of 1-16 years)



RR ≥ 1 test 2.14 (95% CI 1.83-2.51), $P < 0.0001$

RR ≥ 2 test 3.65 (95% CI 2.66-4.47), $P < 0.0001$

National Kidney Foundation's (NKF's) Kidney Disease Outcomes Quality Initiative (KDOQI)

				Albuminuria (mg/g)				
				A1 (normo)		A2 (micro)	A3 (macro)	
				Optimal	High-normal	High	Very high	Nephrotic
				<10	10-29	30-299	300-1999	>2000
eGFR, ml/min/1.73 m ²	G1	High	>105	No CKD	Stage 1			
		Optimal	90-104					
	G2	Mild	75-89		Stage 2			
			60-74					
	G3a	Mild-moderate	45-59	Stage 3				
	G3b	Moderate-severe	30-45					
	G4	Severe	15-29	Stage 4				
	G5	Kidney failure	<15	Stage 5				

CKD3bNA

Nonalbuminuric renal impairment

Kidney Disease: Improving Global Outcomes (KDIGO)

				Albuminuria (mg/g)				
				A1 (normo)		A2 (micro)	A3 (macro)	
				Optimal	High-normal	High	Very high	Nephrotic
				<10	10-29	30-299	300-1999	>2000
eGFR, ml/min/1.73 m ²	G1	High	>105					
		Optimal	90-104					
	G2	Mild	75-89					
		60-74						
	G3a	Mild-moderate	45-59					
	G3b	Moderate-severe	30-45					
	G4	Severe	15-29					
	G5	Kidney failure	<15					

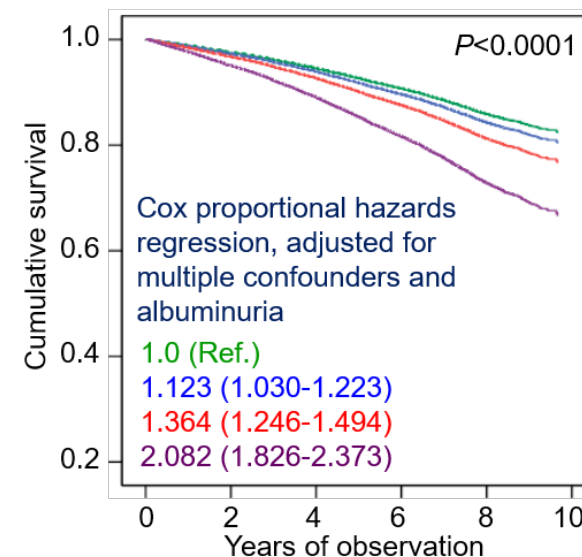
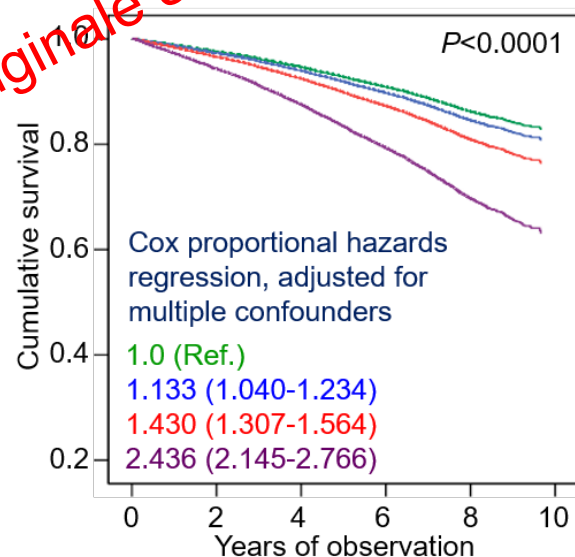
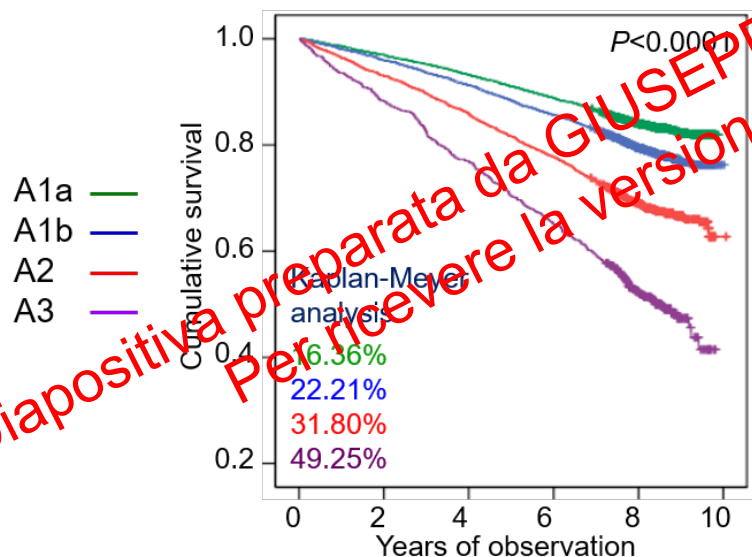
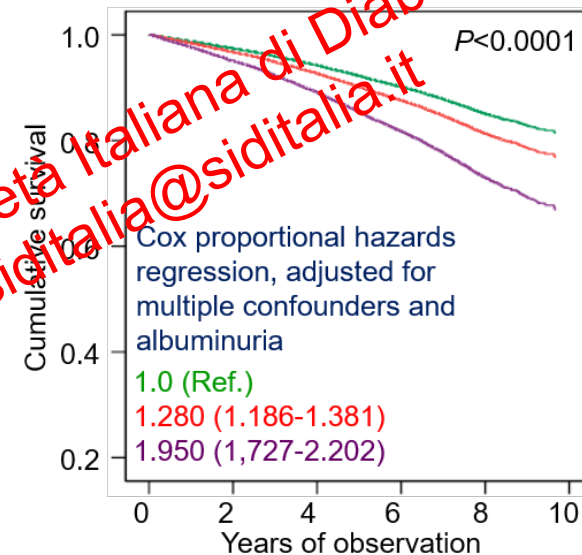
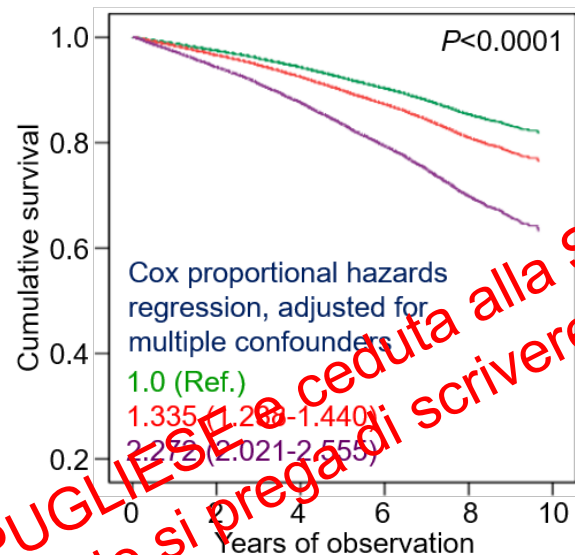
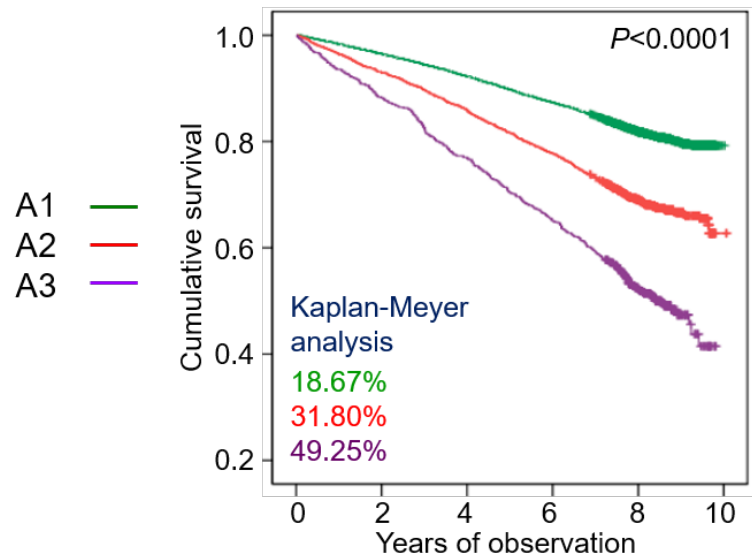
G3bA1(b)

The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

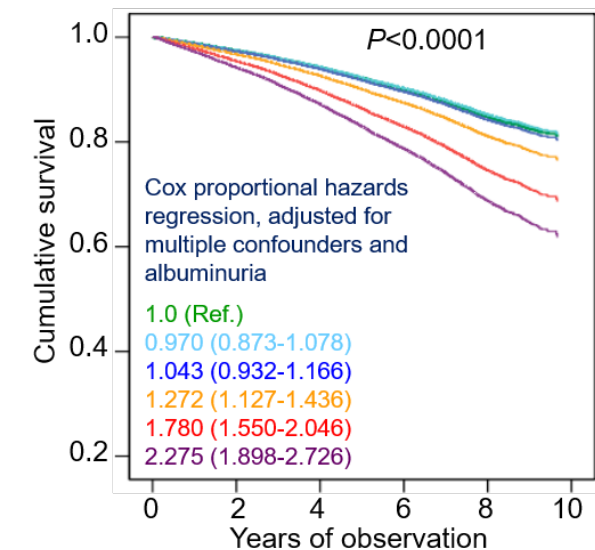
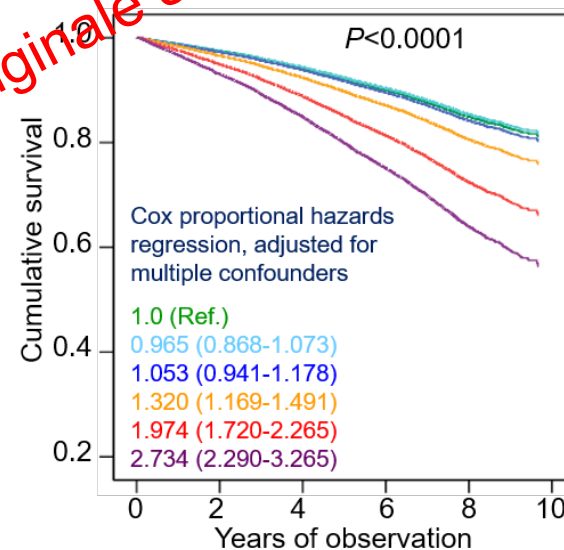
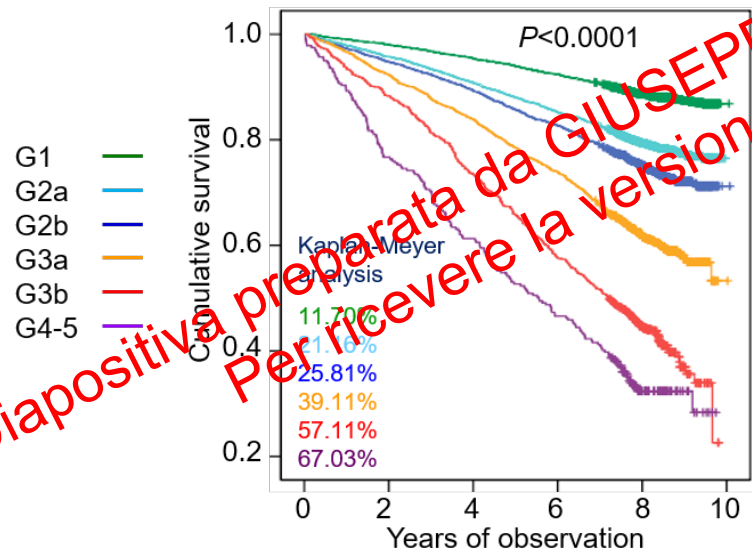
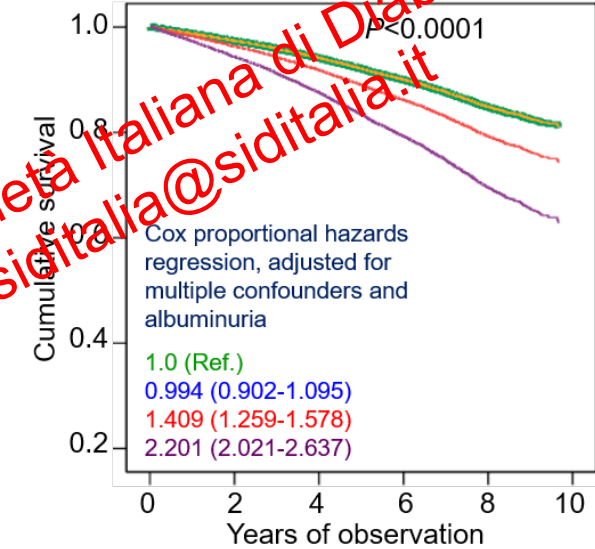
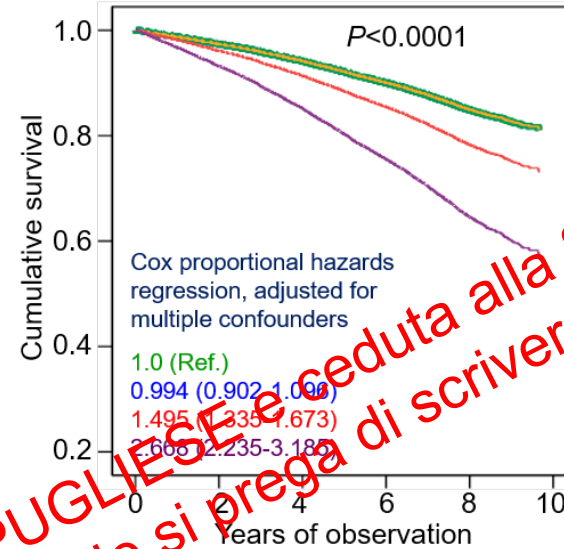
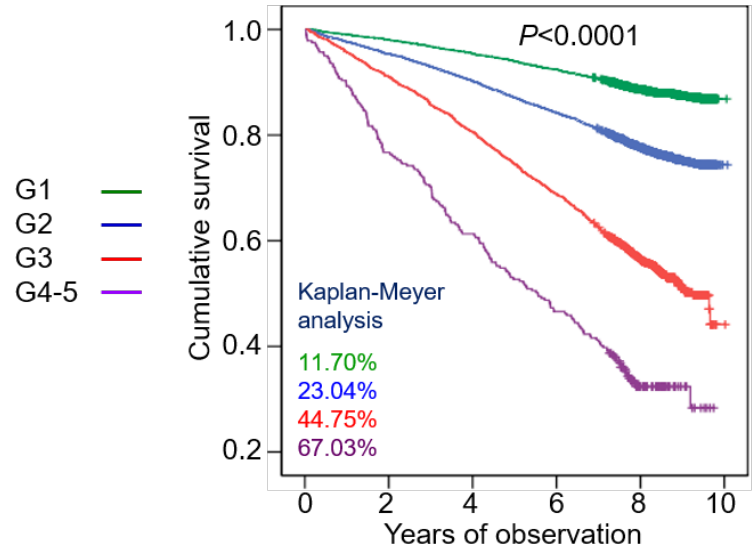
Categories		Age categories			
		<55 years	55-64 years	65-74 years	>75 years
Albuminuria	Reference	1.00	1.00	1.00	1.00
	A1a	1.90 (1.39-2.60)	1.93 (1.66-2.24)	1.56 (1.42-1.71)	0.93 (0.86-1.00)
	A1b	2.88 (2.15-3.86)	2.09 (1.79-2.44)	1.91 (1.75-2.09)	1.14 (1.07-1.21)
	A2	5.14 (3.85-6.86)	3.42 (2.92-4.01)	2.94 (2.70-3.20)	1.59 (1.51-1.68)
	A3	10.69 (7.02-16.29)	8.62 (7.06-10.52)	5.32 (4.68-6.04)	2.42 (2.24-2.61)
eGFR	Reference	1.00	1.00	1.00	1.00
	G1	2.53 (2.09-3.11)	2.33 (2.07-2.62)	1.61 (1.44-1.80)	0.78 (0.64-0.94)
	G2a	2.53 (1.57-4.07)	2.51 (2.12-2.96)	1.75 (1.59-1.92)	0.97 (0.90-1.05)
	G2b	6.10 (3.75-9.95)	1.99 (1.53-2.60)	1.96 (1.76-2.17)	1.15 (1.07-1.23)
	G3a	13.42 (8.42-21.38)	3.21 (2.26-4.56)	3.08 (2.75-3.46)	1.35 (1.26-1.44)
	G3b	10.19 (4.24-25.00)	8.70 (6.36-11.92)	5.60 (4.96-6.33)	1.95 (1.82-2.09)
	G4	36.30 (21.21-62.09)	11.30 (7.71-16.57)	6.85 (5.71-8.20)	3.00 (2.76-3.25)
	G5				

Excess mortality versus the general population in 15,656 patients with type 2 diabetes by age category according to albuminuria and eGFR levels

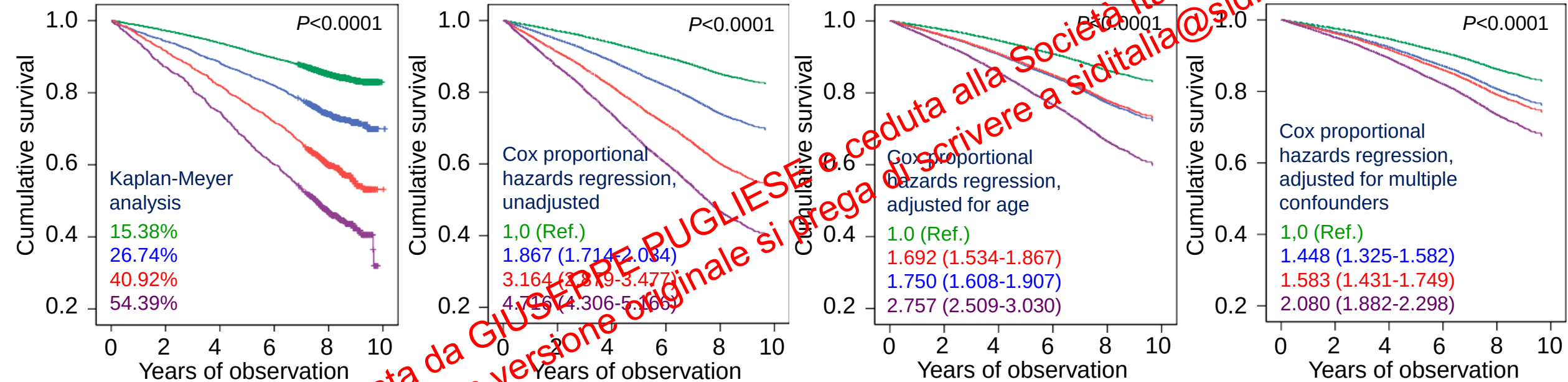
The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study



The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study



The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study



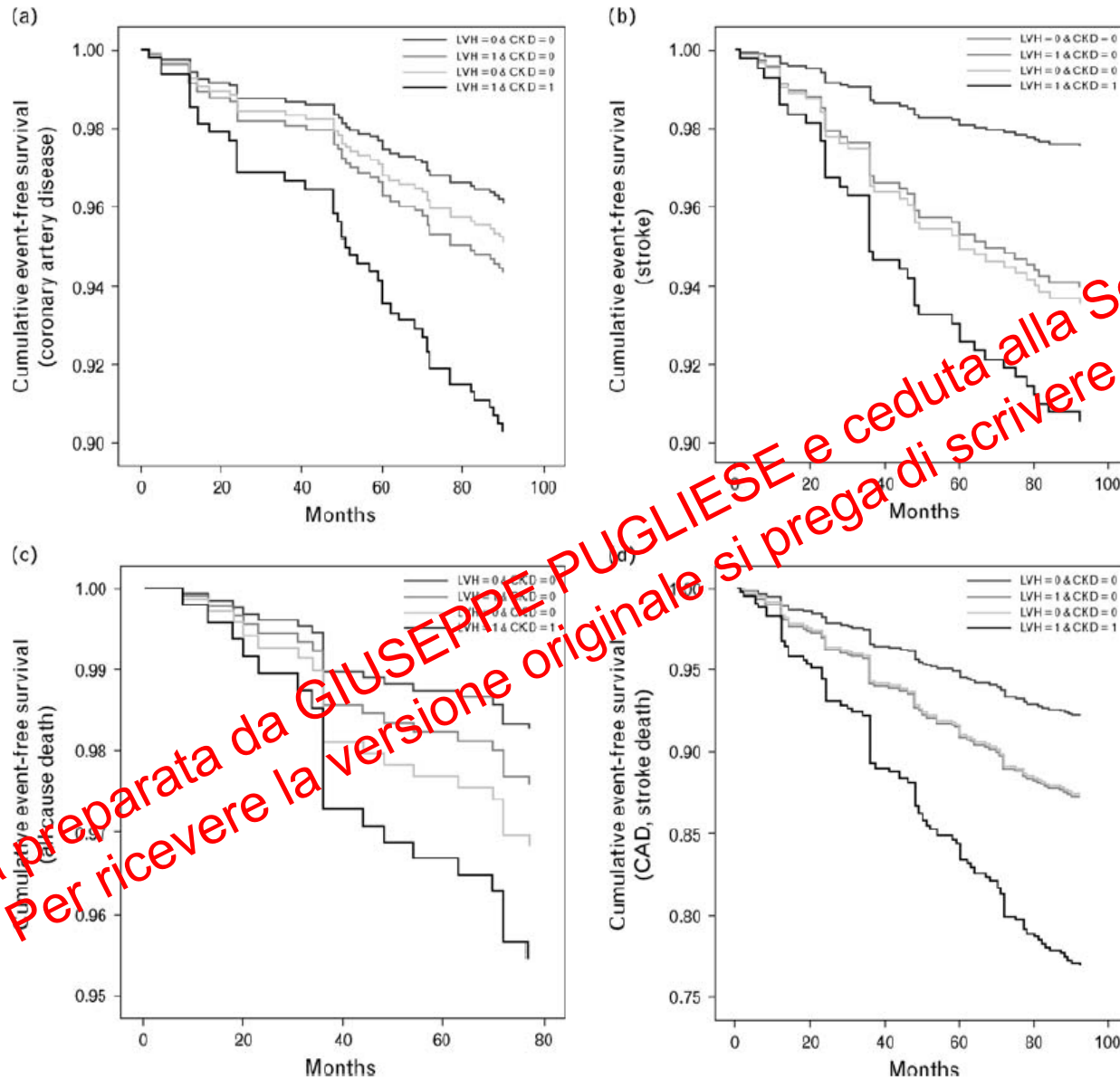
Alb-/eGFR- — Alb+/eGFR- —

Alb-/eGFR+ — Alb+/eGFR+ —

The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

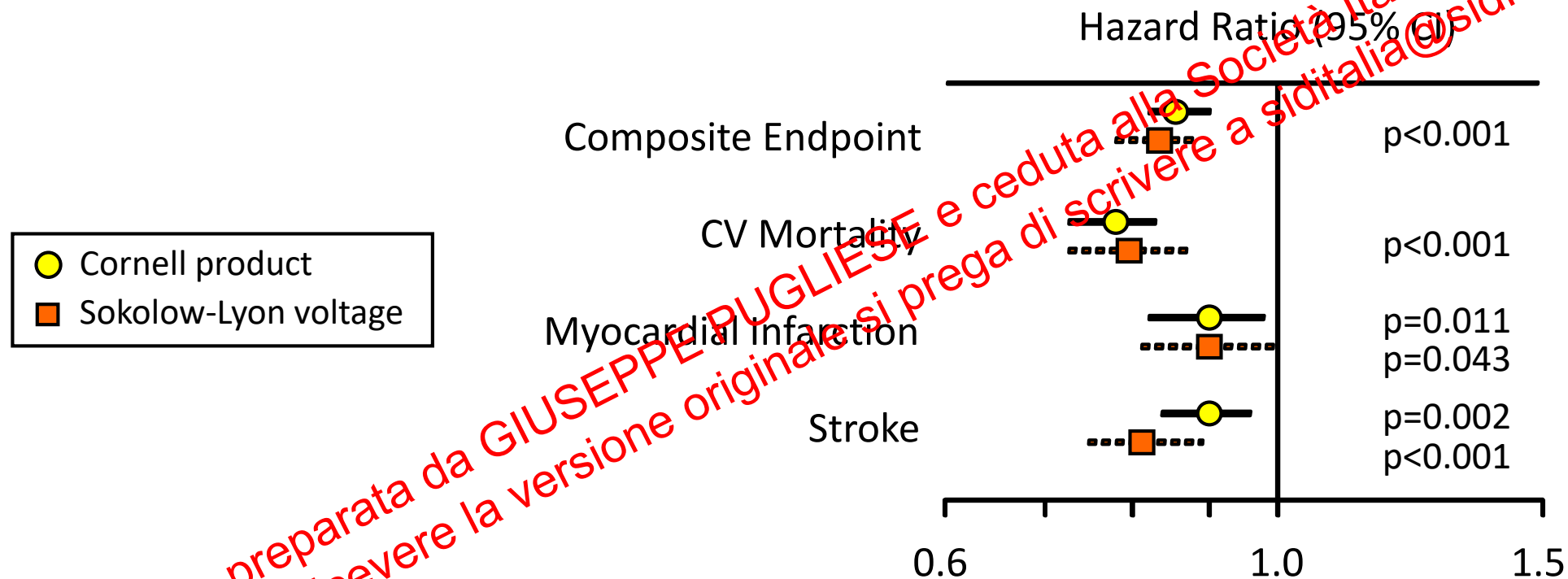
KDIGO categories	A1a	A1b	A2	A3
G1	1 (Ref.)	0.936 (0.780-1.124)	1.313 (1.079-1.599)	2.192 (1.546-3.108)
G2a	0.798 (0.667-0.956)	1.050 (0.885-1.246)	1.310 (1.089-1.575)	2.477 (1.816-3.379)
G2b	1.104 (0.833-1.120)	1.057 (0.879-1.273)	1.388 (1.148-1.678)	1.706 (1.232-2.362)
G3a	1.316 (1.071-1.617)	1.389 (1.138-1.694)	1.482 (1.218-1.804)	2.263 (1.708-3.000)
G3b	1.847 (1.400-2.438)	2.248 (1.791-2.821)	2.089 (1.686-2.590)	2.784 (2.136-3.629)
G4-5	1.613 (0.876-2.968)	2.245 (1.494-3.374)	2.785 (2.094-3.703)	4.662 (3.590-6.054)

Cox proportional hazards regression, adjusted for multiple confounders



1652 hypertensive patients free of CVD
(mean age 54.3 years, 696 male
patients, office blood pressure
147/93mmHg, mean period of 6 years)

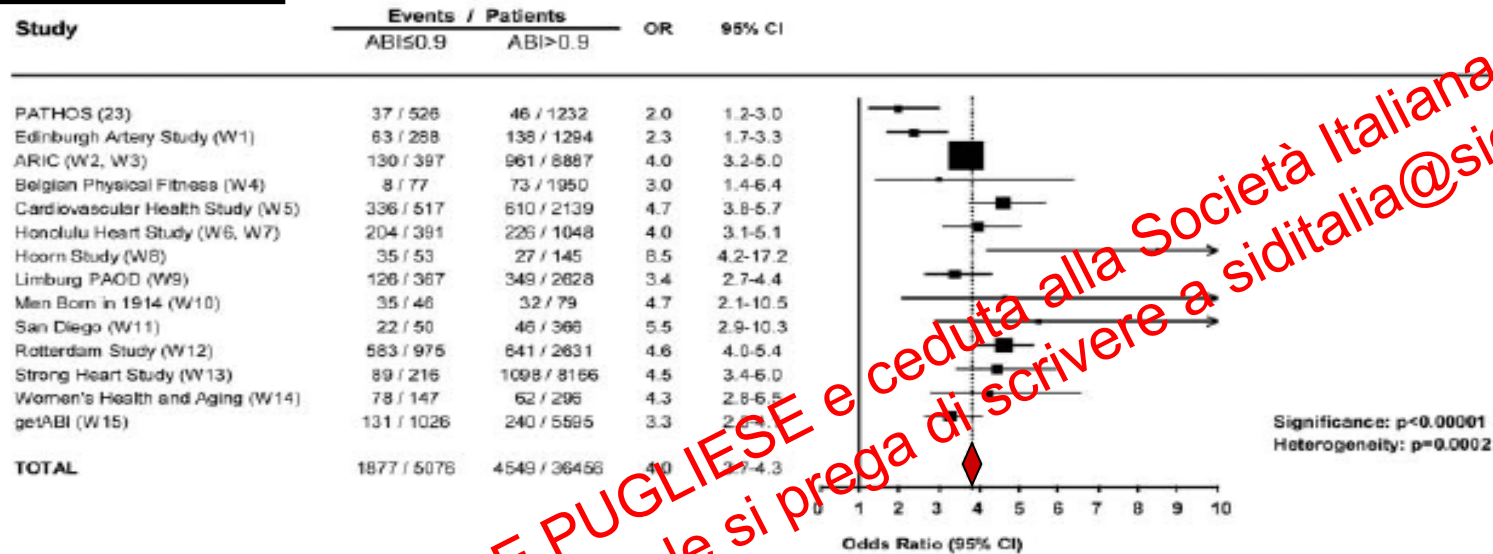
Double-blind, randomized, parallel-group study conducted in 1995-2001 among 9,193 men and women with hypertension aged 55-80 years (mean, 67 years)



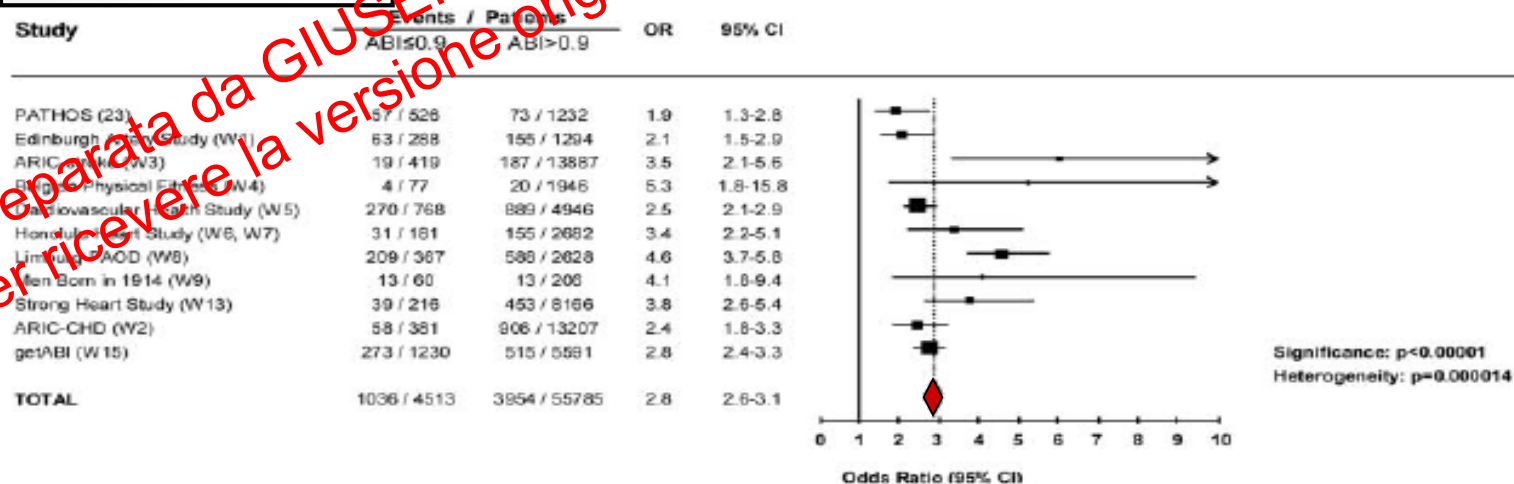
Multivariate Cox models, adjusted for treatment effect, baseline Framingham risk score, baseline and in treatment systolic and diastolic BPs; hazard ratios calculated for a 1 SD decrease in Cornell product and Sokolow-Lyon voltage

Meta-analysis of 16 studies

All-cause mortality

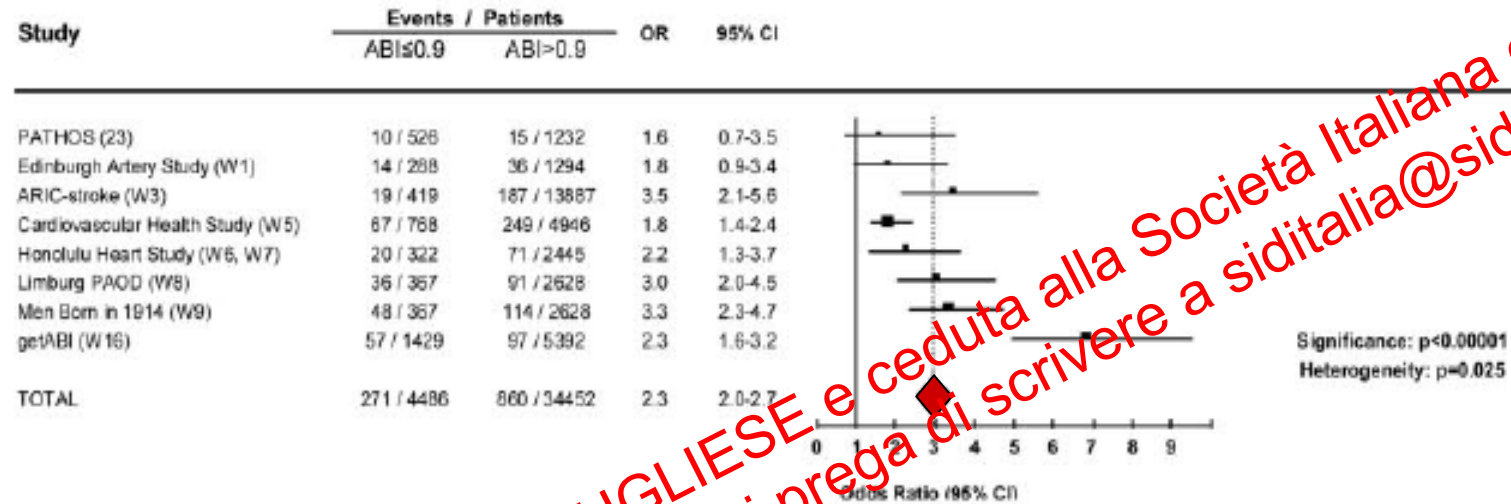


Total cardiovascular events

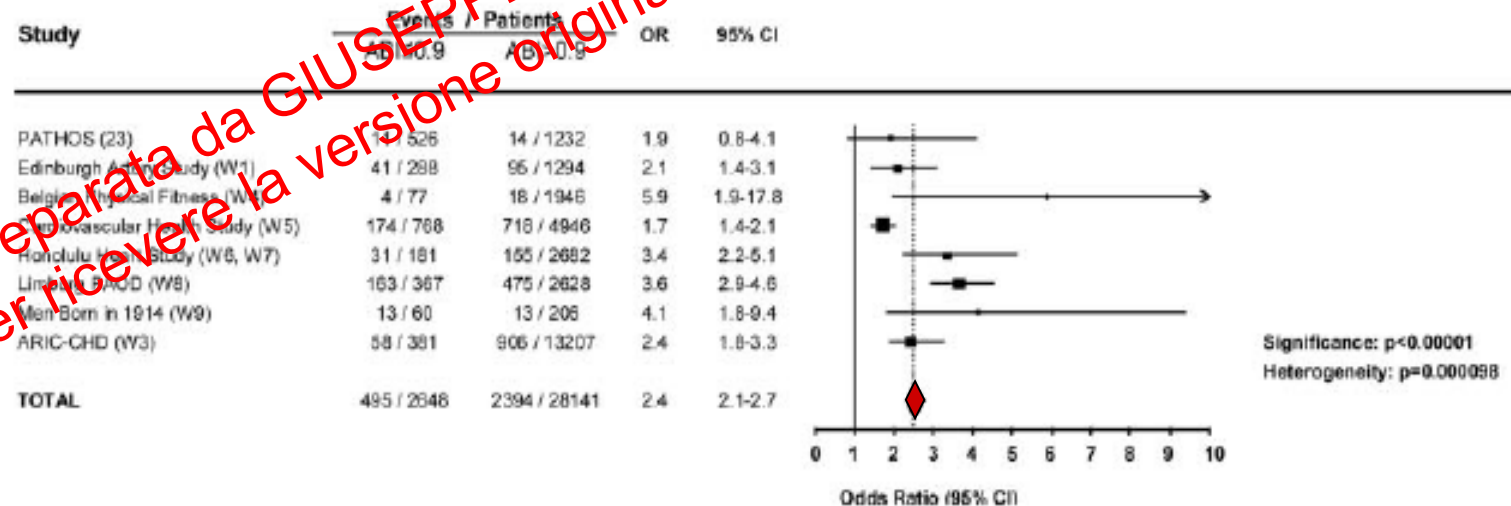


Meta-analysis of 16 studies

Stroke/TIA



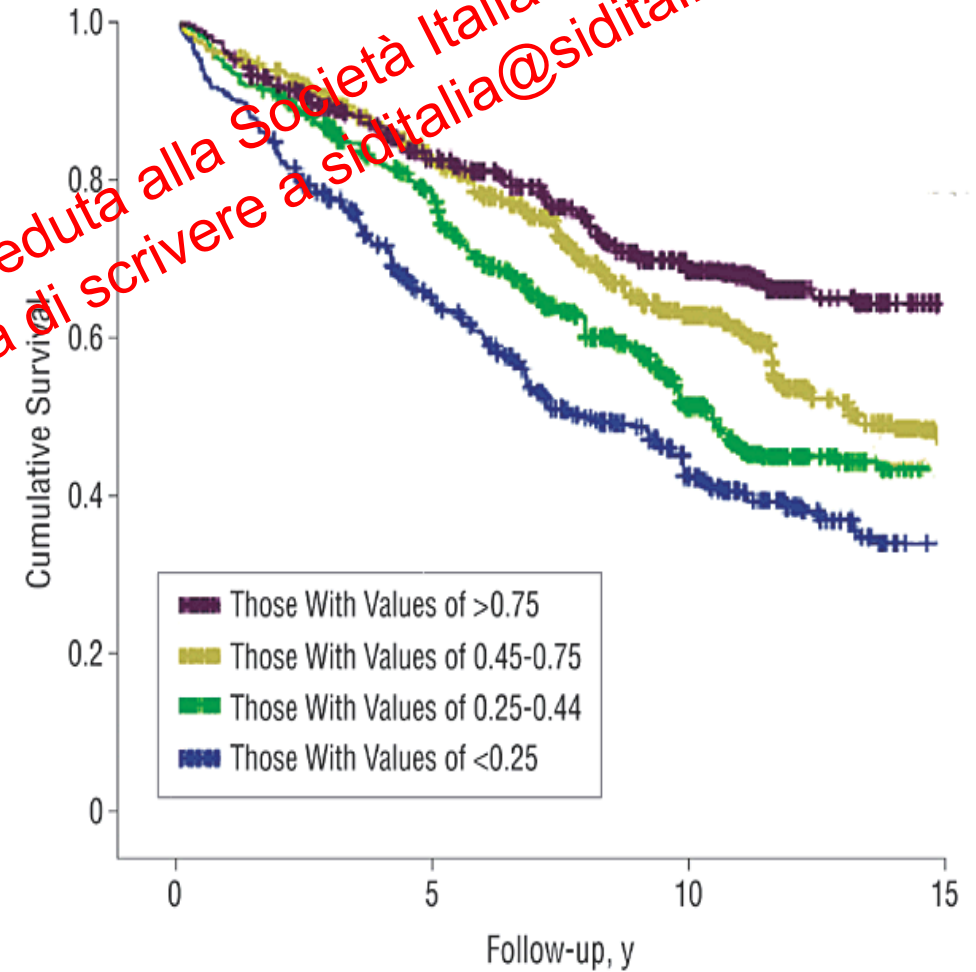
Coronary artery disease



3,209 patients (mean age 63 ± 12 years; 71.1% male; mean follow-up 8 years [IQR 4-11 years])

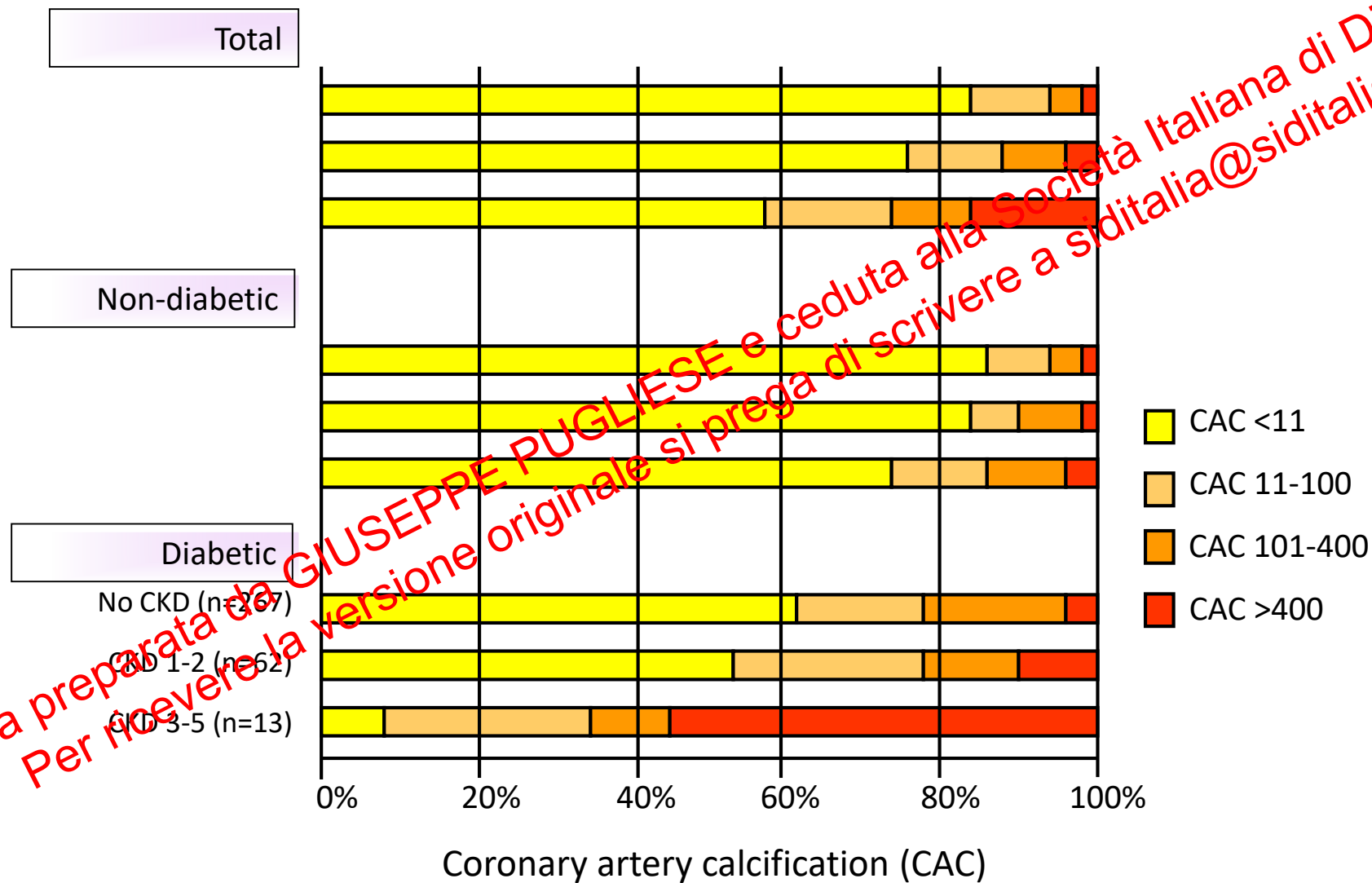
Resting

Post-exercise



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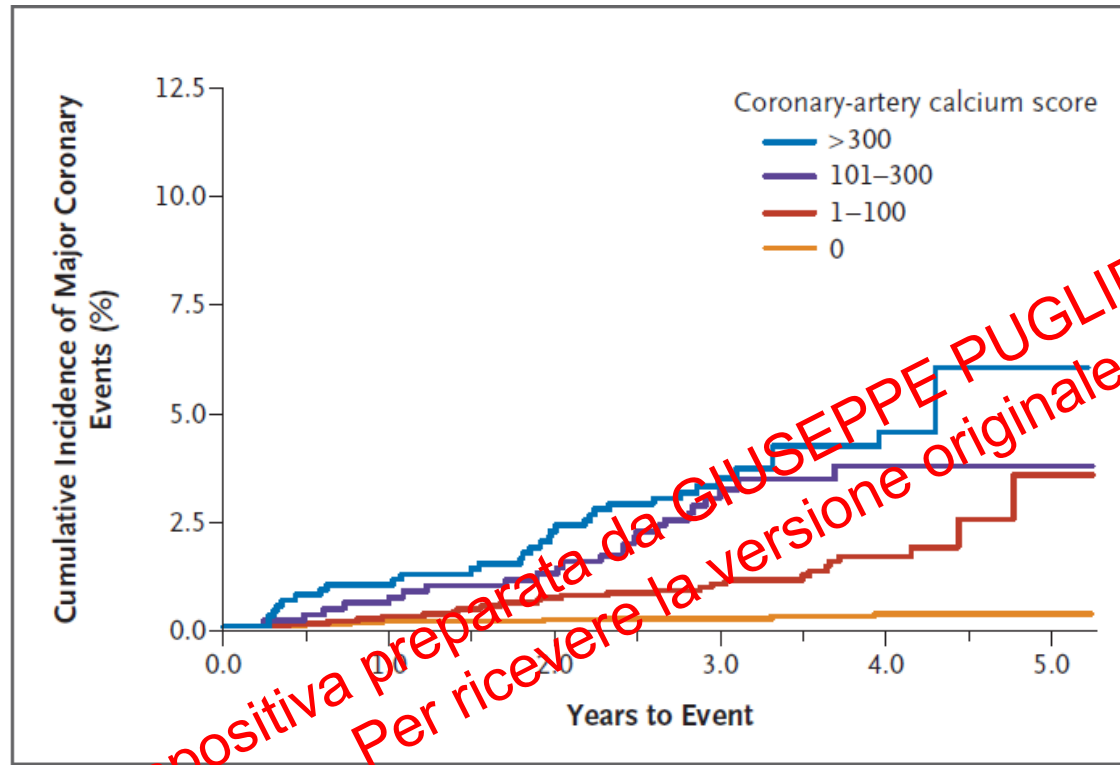
The Dallas Heart Study



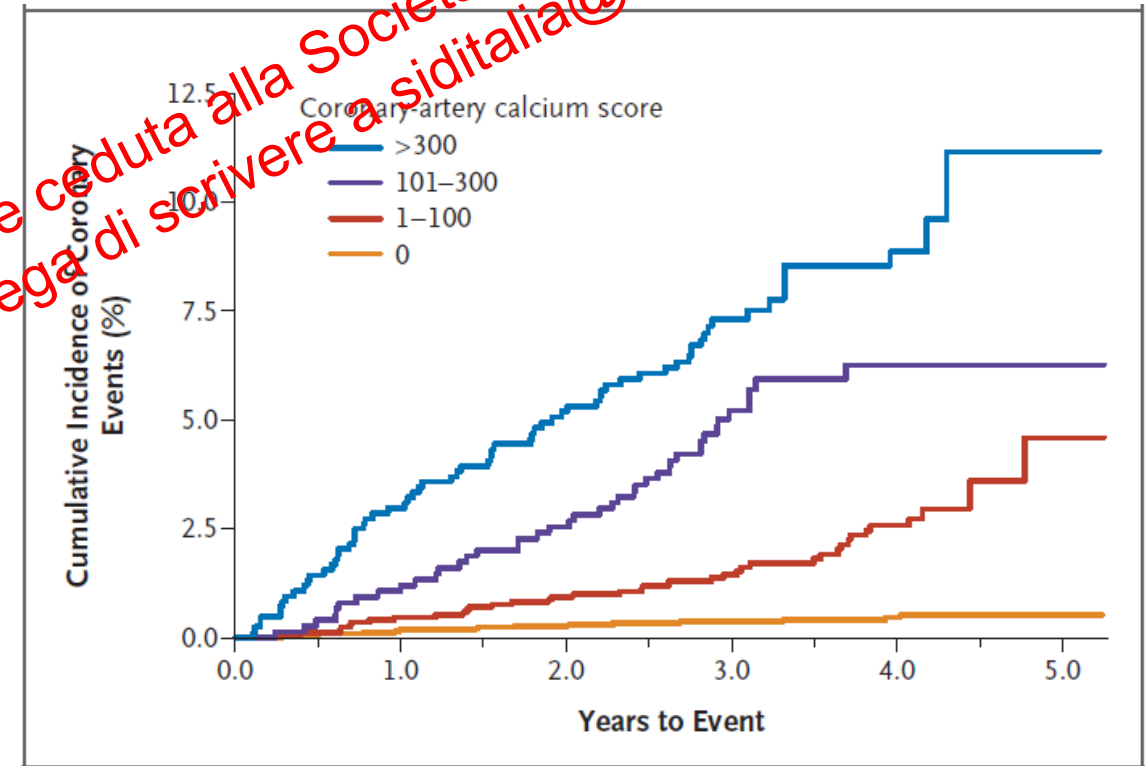
Population-based sample of 6,722 men and women

(38.6% white, 27.6% black, 21.9% Hispanic, and 11.9% Chinese, with no clinical CVD at entry; median follow-up of 3.8 years)

Major coronary events
(MI and death from CHD)



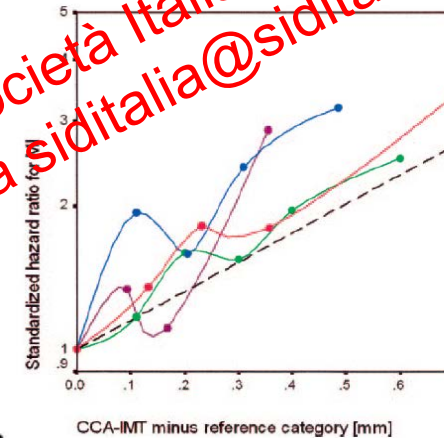
Any coronary event



Systematic review and meta-analysis of 8 studies (n=37,197)

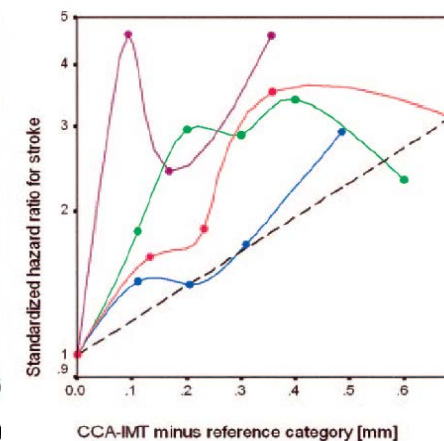
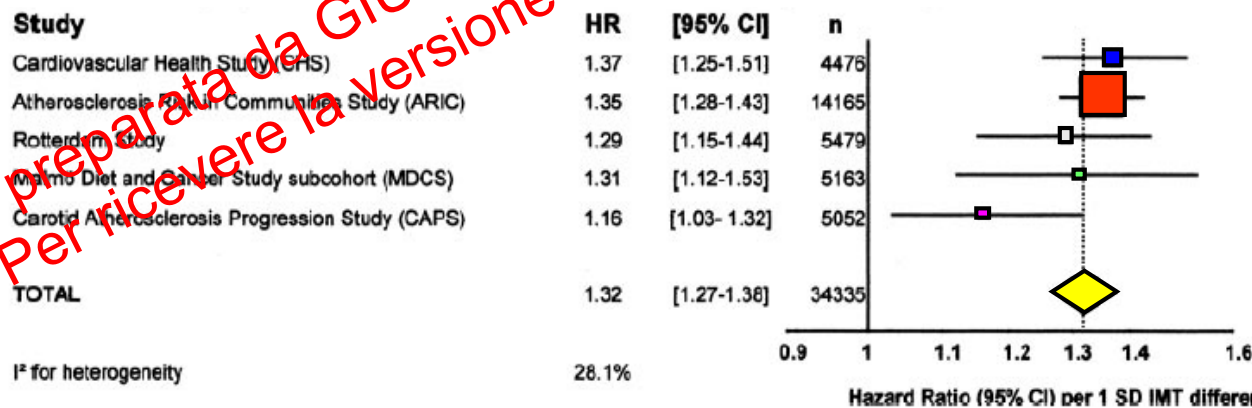
Myocardial infarction

Hazard ratio (HR) per 1 SD difference in CCA-IMT, adjusted for sex and age



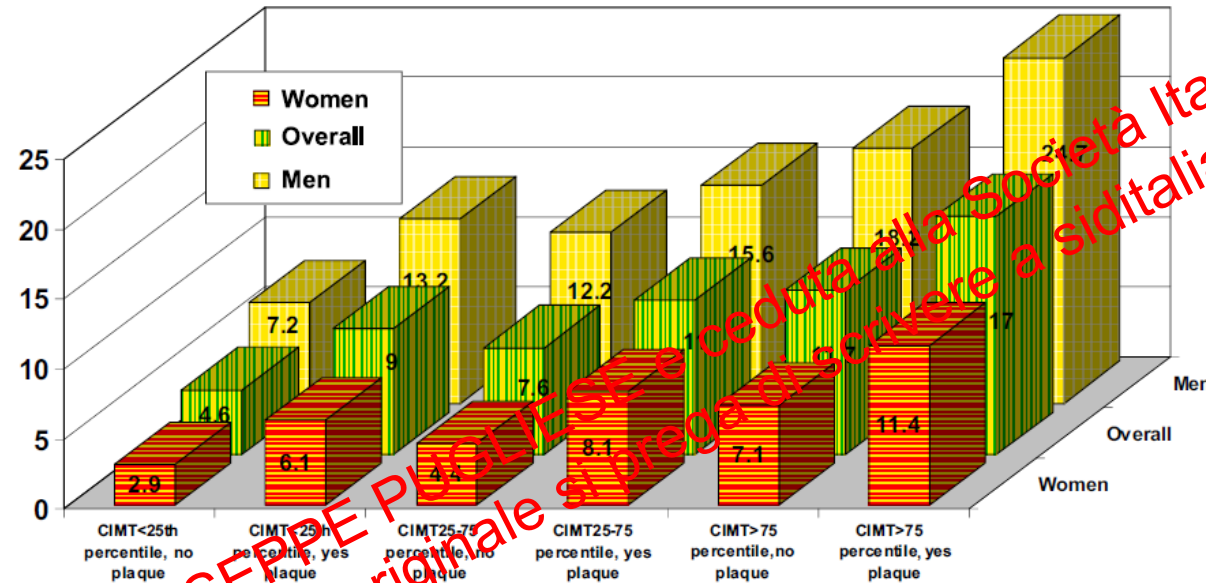
Stroke

Hazard ratio (HR) per 1 SD difference in CCA-IMT, adjusted for sex and age



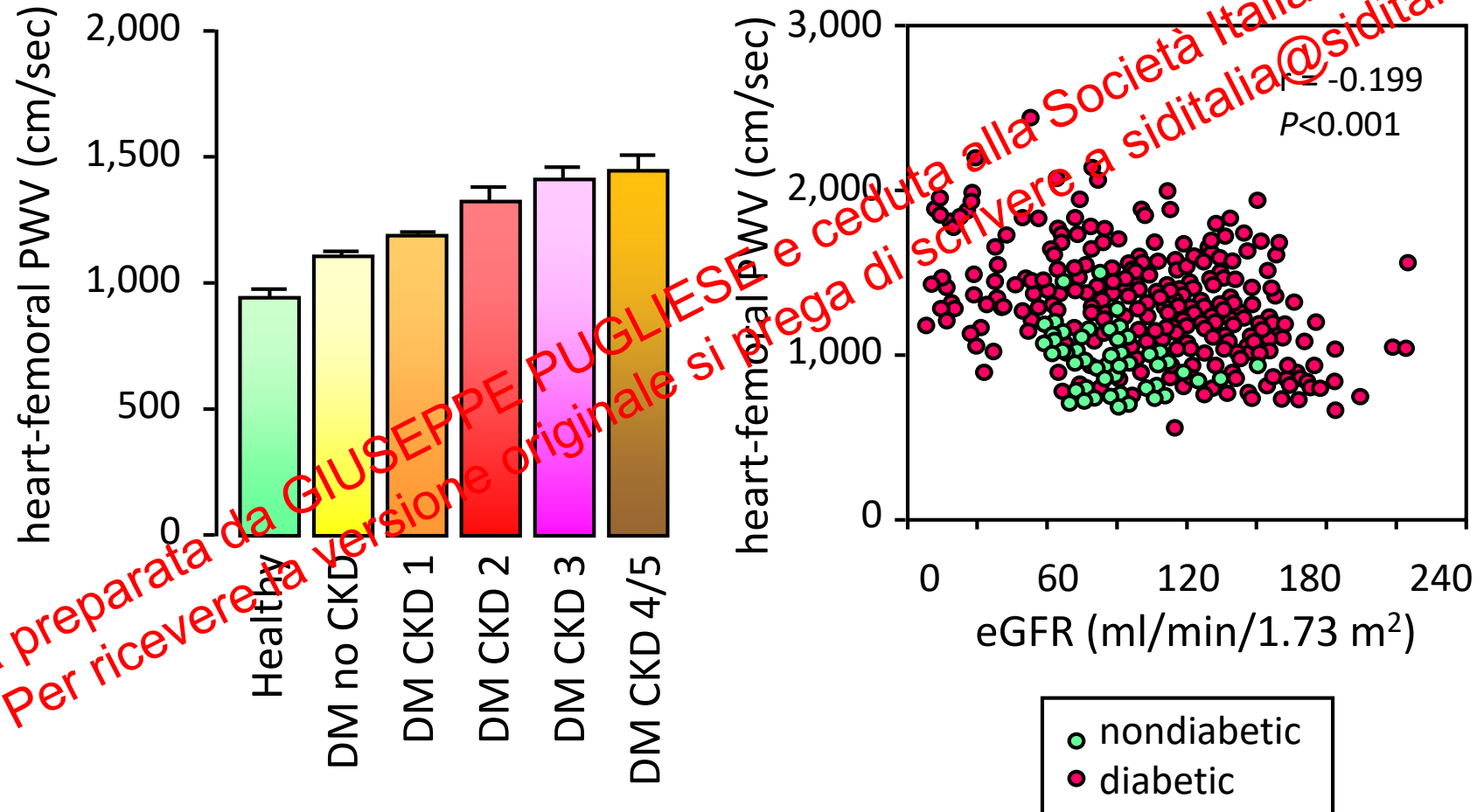
The Atherosclerosis Risk In Communities (ARIC) Study

(n=13,145; 5,682 men, 7,463 women)



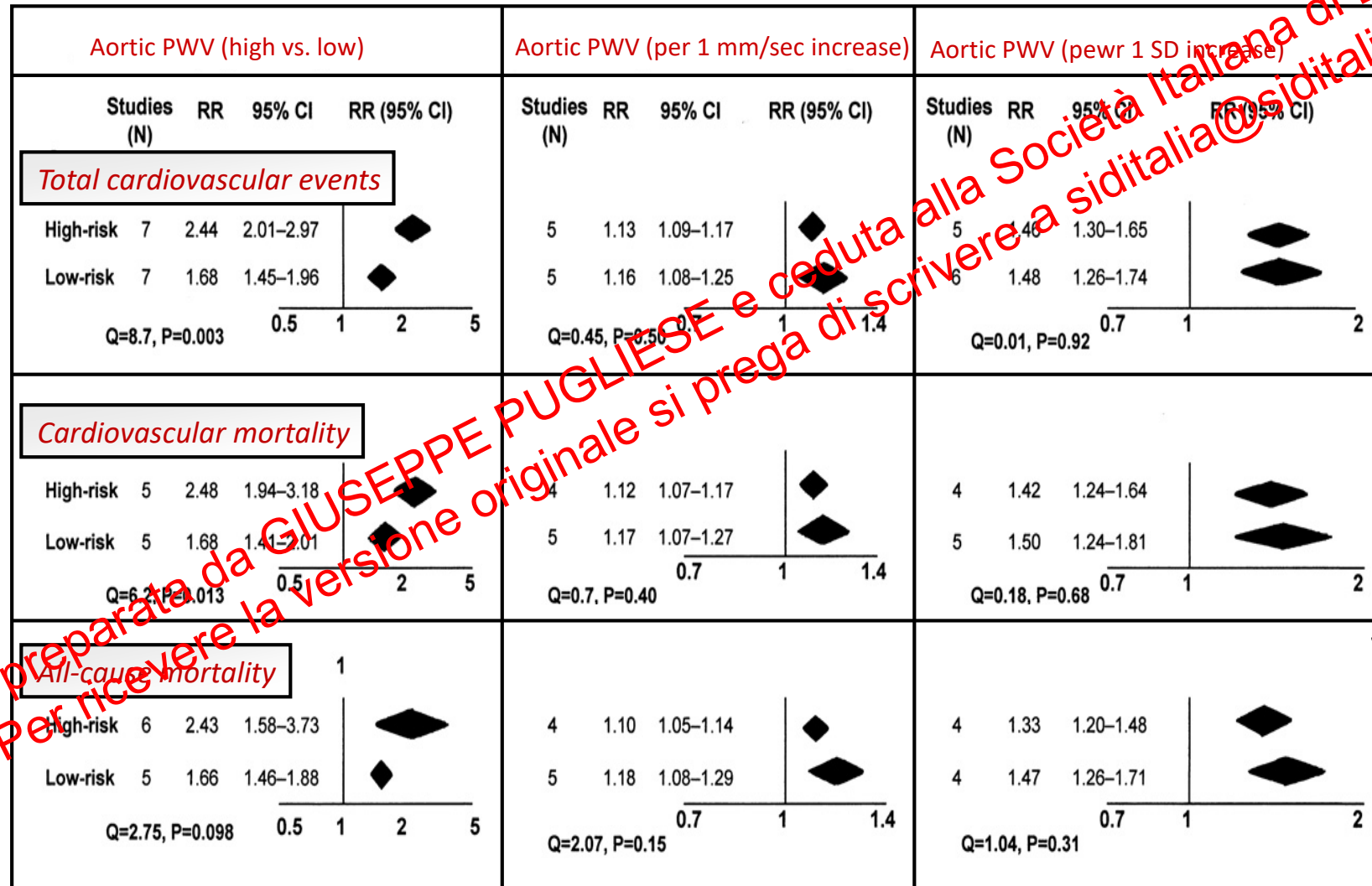
CHD Risk by TRF + CIMT + Plaque					
CHD Risk by TRF only	<5%	5%–10%	10%–20%	>20%	All
≤5%, low risk	5,585 (91.4)	523 (8.6)	0 (0.00)	0 (0.00)	6,108 (46.5)
	2	5	—	—	2
5%–10%, low-intermediate risk	839 (22.4)	2,340 (62.5)	563 (15.1)	0 (0.00)	3,742 (28.5)
	5	7	17	—	8
10%–20%, high-intermediate risk	0 (0.00)	627 (24.8)	1,560 (61.7)	340 (13.5)	2,527 (19.2)
	—	11	15	24	15
>20%, high risk	0 (0.00)	0 (0.00)	165 (21.5)	603 (78.5)	768 (5.8)
	—	—	14	31	27
All	6,264 (48.9)	3,490 (26.6)	2,288 (17.4)	943 (7.2)	13,145 (100.0)
	2	7	15	28	7

434 patients had type 2 diabetes, and there were 192 healthy control subjects

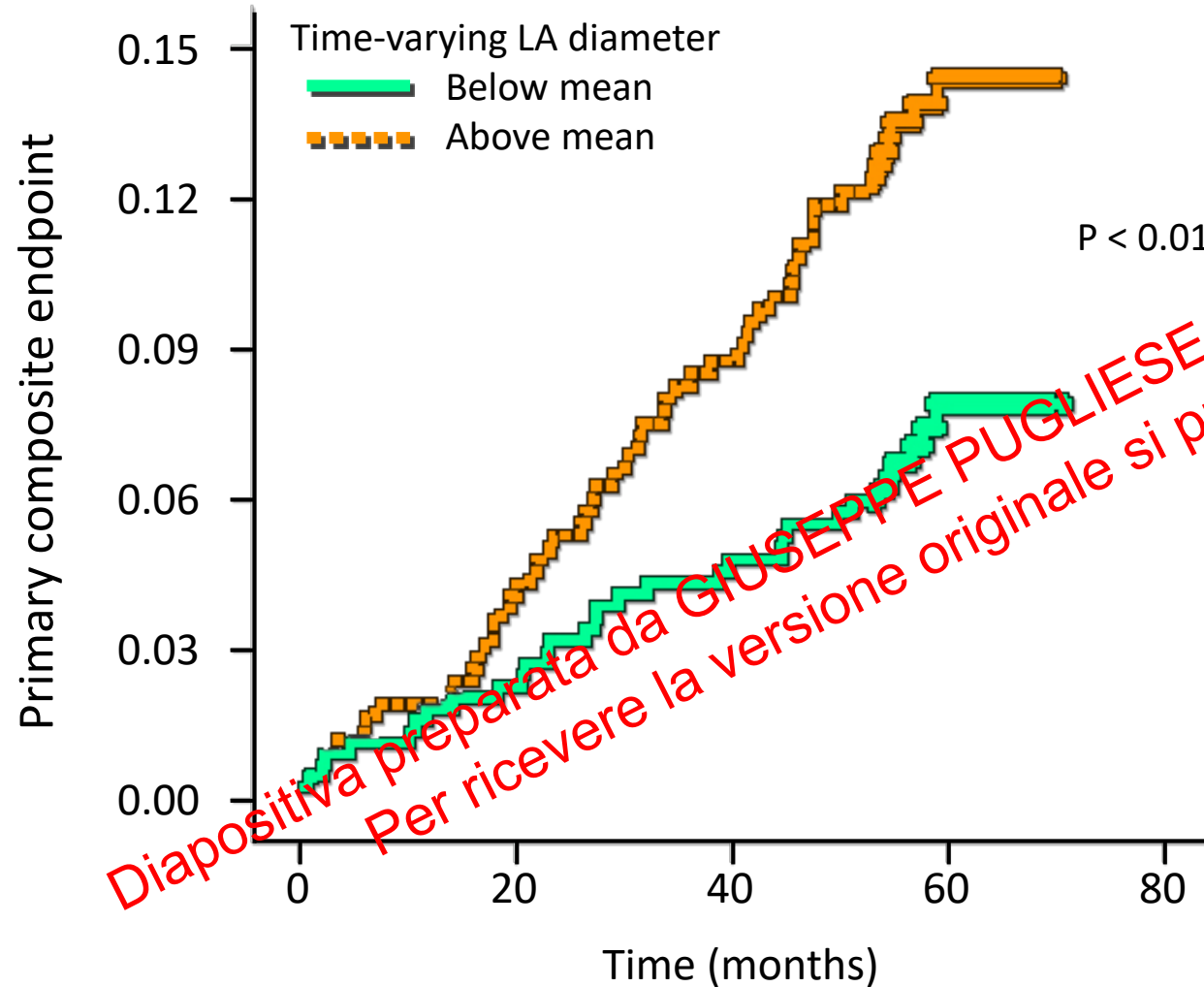


Meta-analysis of 17 longitudinal studies

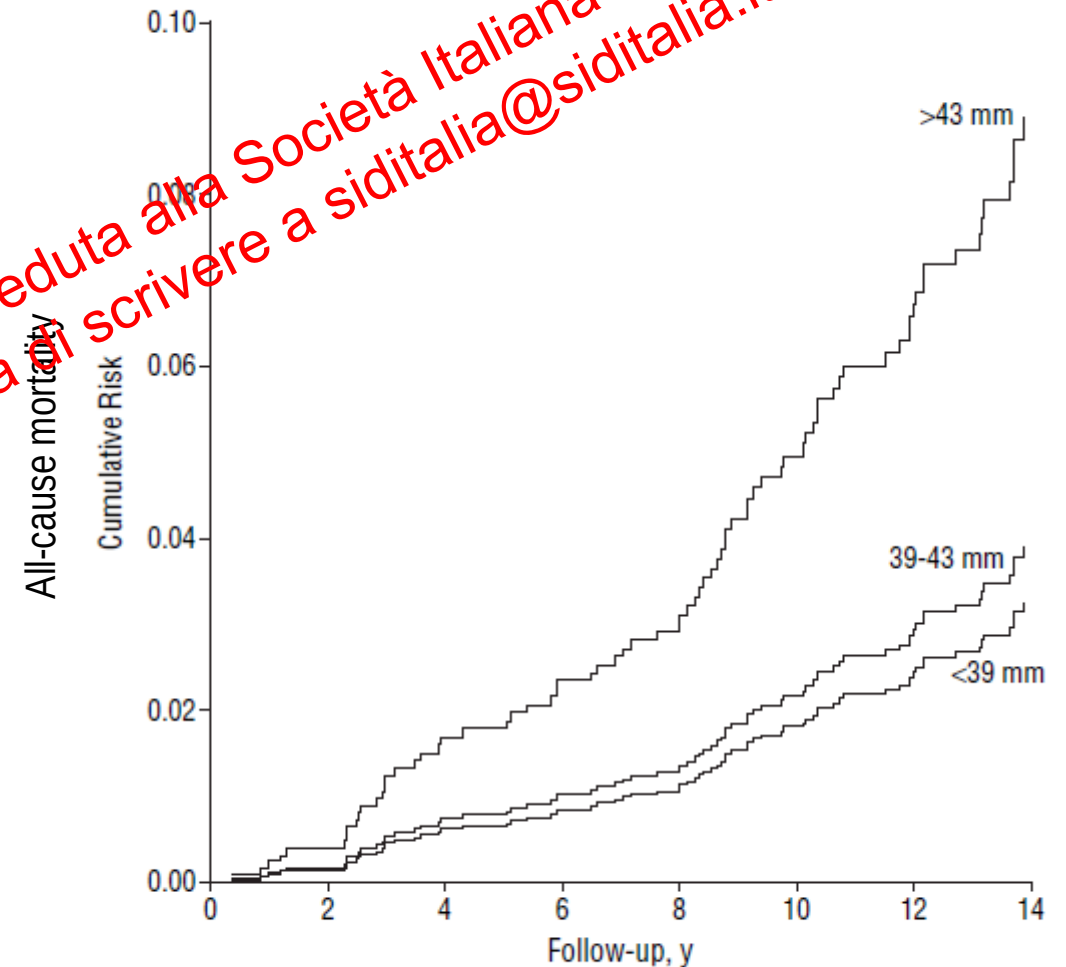
(n=15,877; mean follow-up of 7.7 years)



132 patients (mean age 63 ± 8 years, 56% women) with stable angina and non-obstructive CAD diagnosed as $<50\%$ stenosis by CCTA



830 men (age 42-61 years) from eastern Finland (54 deaths due to CVD; mean follow-up of 13 years)



GS

Screening for CAD with coronary CT angiography and functional imaging ?

Age: 68 years

Gender: male

Ethnicity Caucasian

Former smoker (nonsmoker for 10 years)

Diabetes duration: 14 years

Physically inactive (~30 min/wk mod-vig PA)

Sedentary (~12 h/day sitting or reclined)

HbA_{1c}: 8.3% (67 mmol/mol)

Triglycerides: 189 mg/dl (2.14 mmol/l)

Total cholesterol: 210 mg/dl (5.44 mmol/l)

HDL cholesterol: 52 mg/dl (1.35 mmol/l)

LDL cholesterol: 120.2 mg/dl (3.11 mmol/l)

Blood pressure: 135/85 mmHg

BMI: 33.9 kg/m²

Waist circumference: 116 cm



ACR: 26 mg/g

eGFR: 42 mL/min/1.73 m²

Fundus examination: mild NPDR

WPT great toe: 26 mV

ECG: 85 beats/min, sinus rhythm, LVH

Echocardiogram: LVH (LV mass indexed to BSA 133 g/m²), preserved LVEF (58), diastolic dysfunction (E/A 0.7), LA dilation (42 mm)

CAC score: 276

ABI: 0.85

Carotid US: no plaque

Treatment: Metformin 1000 mg bid, Gliclazide 60 mg qd, Ramipril 5 mg + Hydrochlorothiazide 25 mg qd, Amlodipine 5 mg qd, Simvastatin 10 mg qd

- ❖ CV risk assessment and stratification using existing algorithms is based on (some) traditional risk factors and risk estimates vary according to the prediction model used (endpoint, population, year).
- ❖ Further stratification of CV risk should consider other traditional risk factors (physical inactivity/sedentary behavior, BMI/waist circumference), but not nontraditional risk factors, the additive predictive power of which has not been proven yet.
- ❖ Target organ damage (CKD, retinopathy, autonomic neuropathy, LVH, abnormal ABI, non-zero CAC score, plaque detected at carotid or femoral US) should be evaluated and considered as risk modifier.
- ❖ Screening for CAD with coronary CT angiography and functional imaging may be considered in asymptomatic individuals at very high risk.