Il diabete in Italia: Aspetti epidemiologici e modelli assistenziali

L'instabilità della glicemia, del peso e della pressione sistolica: importante fattore di rischio per il diabetico anziano

Giuseppe Verlato, Giacomo Zoppini

Sezione di Epidemiologia e Statistica Medica, Dipartimento di Medicina e Sanità Pubblica, Università degli Studi di Verona

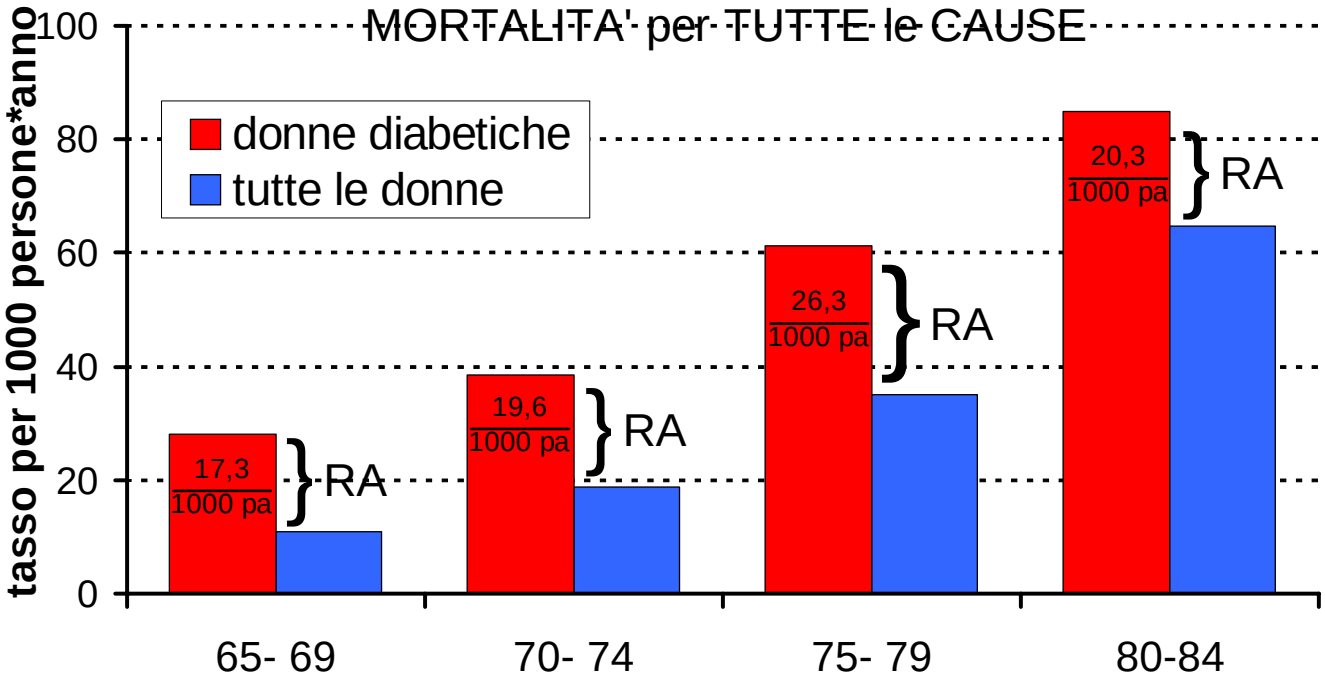
Endocrinologia e Malattie del Metabolismo, Dipartimento di Scienze Biomediche e Chirurgiche, Università di Verona

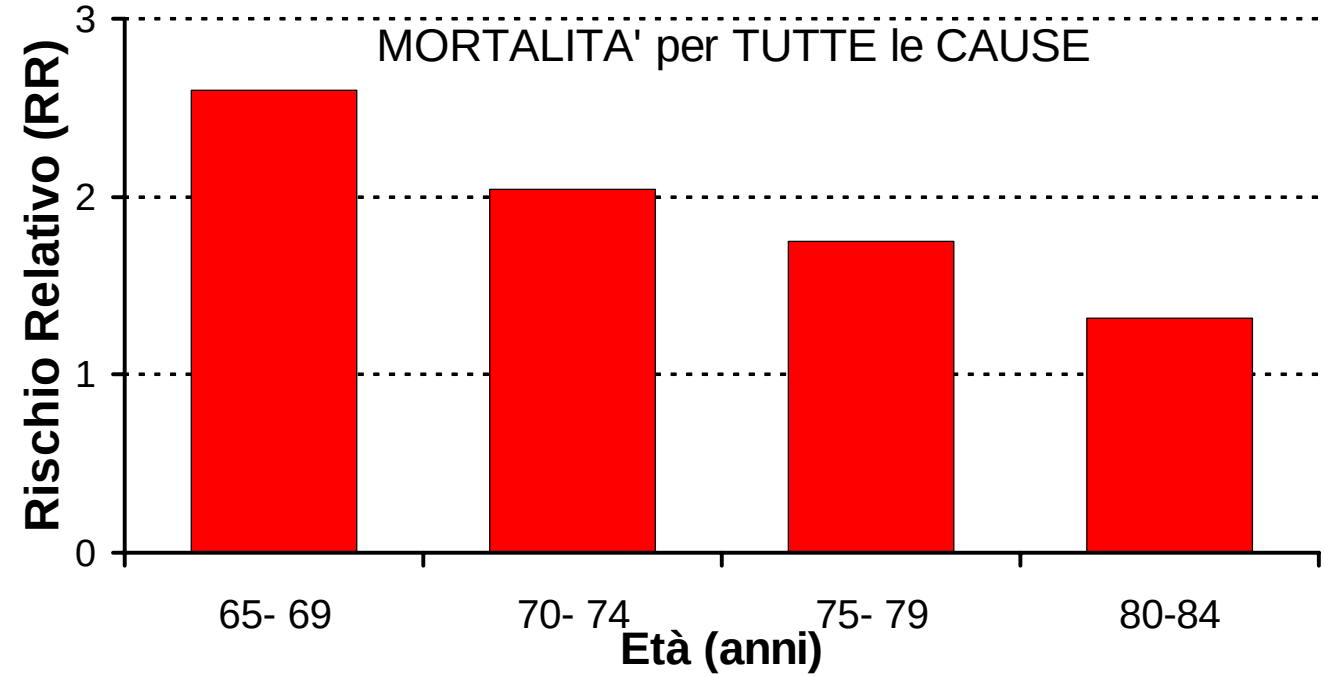
CARATTERISTICHE DEGLI ANZIANI

I soggetti anziani vanno incontro alla perdita dell'omeostasi, ovvero della capacità di mantenere costante le condizioni dell'ambiente interno [Resnick, 1998].

Questo fenomeno, detto omeostenosi (*homeostenosis*), è un fattore prognostico negativo per i soggetti anziani.

Negli anziani la forza dell'associazione tra un fattore di rischio e un outcome sanitario, misurata in termini di Rischio Relativo, spesso diminuisce.


MORTALITA' per TUTTE le CAUSE
tasso per 1000 persone*anno
donne diabetiche
tutte le donne
100
80
60
40
20
0
17,3
1000 pa
RA
19,6
1000 pa
RA
26,3
1000 pa
RA
20,3
1000 pa
RA
65- 69
70- 74
75- 79
80-84


MORTALITA' per TUTTE le CAUSE
Rischio Relativo (RR)
3
2
1
0
65- 69
70- 74
75- 79
80-84
Età (anni)

RAZIONALE

Nei diabetici anziani l'importanza di alcuni fattori di rischio diminuisce con l'avanzare dell'età. L'obesità si associa ad un eccesso di mortalità nei giovani ma non negli anziani, sia nei diabetici [Zoppini et al, 2003] che nella popolazione generale [Stevens et al, 1998].

Negli anziani con diabete di tipo 2 la variabilità della glicemia (coefficiente di variazione intra-individuale) è un fattore di rischio più importante della glicemia media [Muggeo et al, 1995, 1997, 2000].

La variabilità è stata valutata tramite il coefficiente di variazione che è poco correlato con la media a differenza della deviazione standard.

Coefficiente di variazione (CV) - 2

Per rispondere a queste domande è necessario calcolare il **coefficiente di variazione: CV = (deviazione standard / media) * 100**. La deviazione standard viene cioè espressa in percentuale della media.

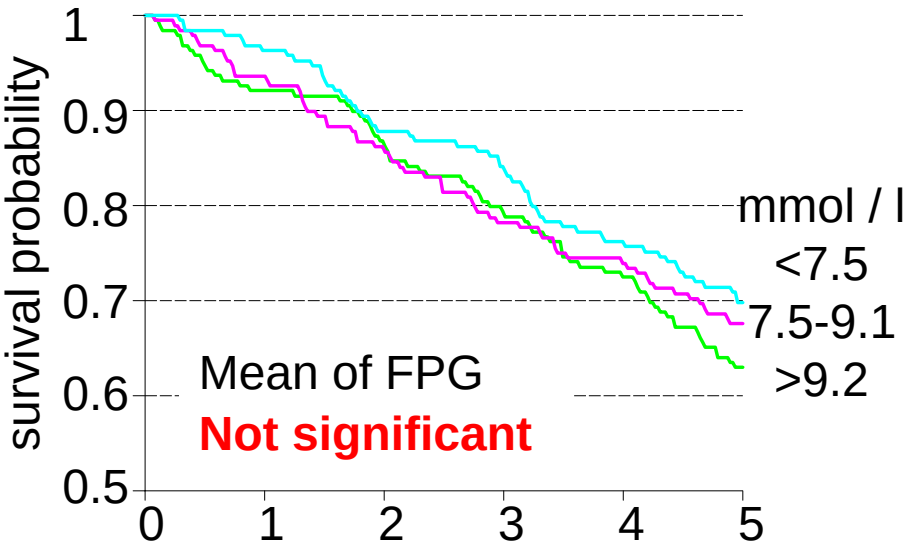
	Media	Dev. standard	CV
Neonati	4 Kg	1 Kg	**25 %**
Bambini 1 anno	11 Kg	1 Kg	**9,1 %**

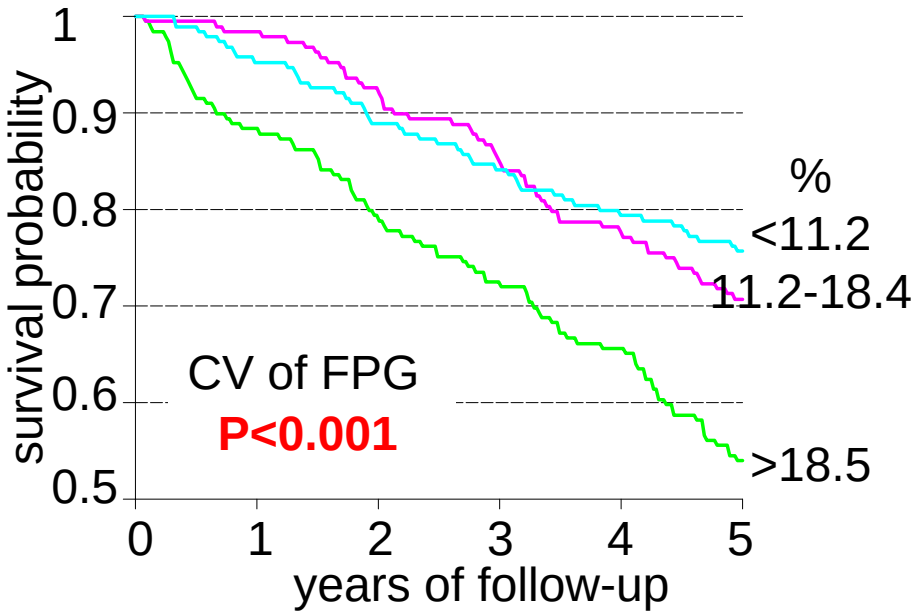
La variabilità del peso è maggiore nei neonati.

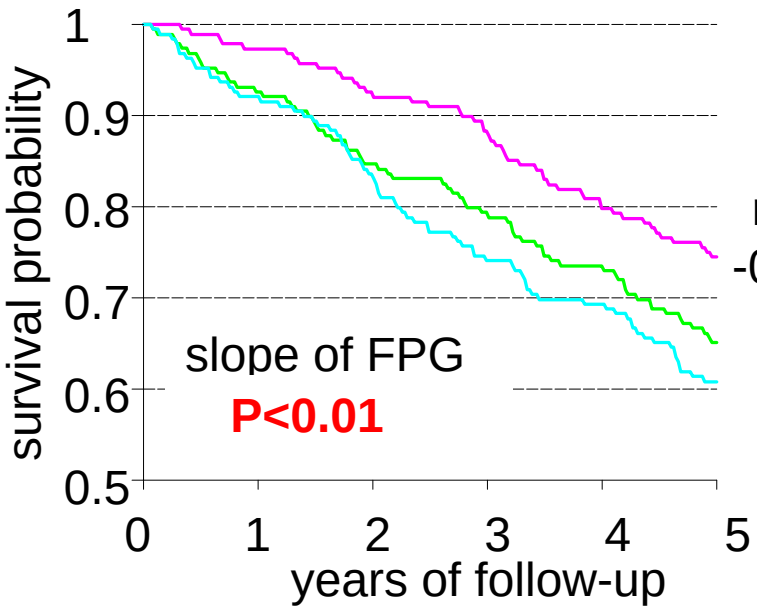
	Media	Dev. standard	CV
Peso	55,1 Kg	5,7 Kg	**10,3 %**
Statura	166,1 cm	6,1 cm	**3,7 %**

La variabilità del peso è maggiore della variabilità della statura.

Kaplan-Meier estimates of survival probability in 566 elderly **(>=75 yrs)** type 2 diabetic patients from Verona, grouped in tertiles according to mean, coefficient of variation and slope of fasting plasma glucose over time.





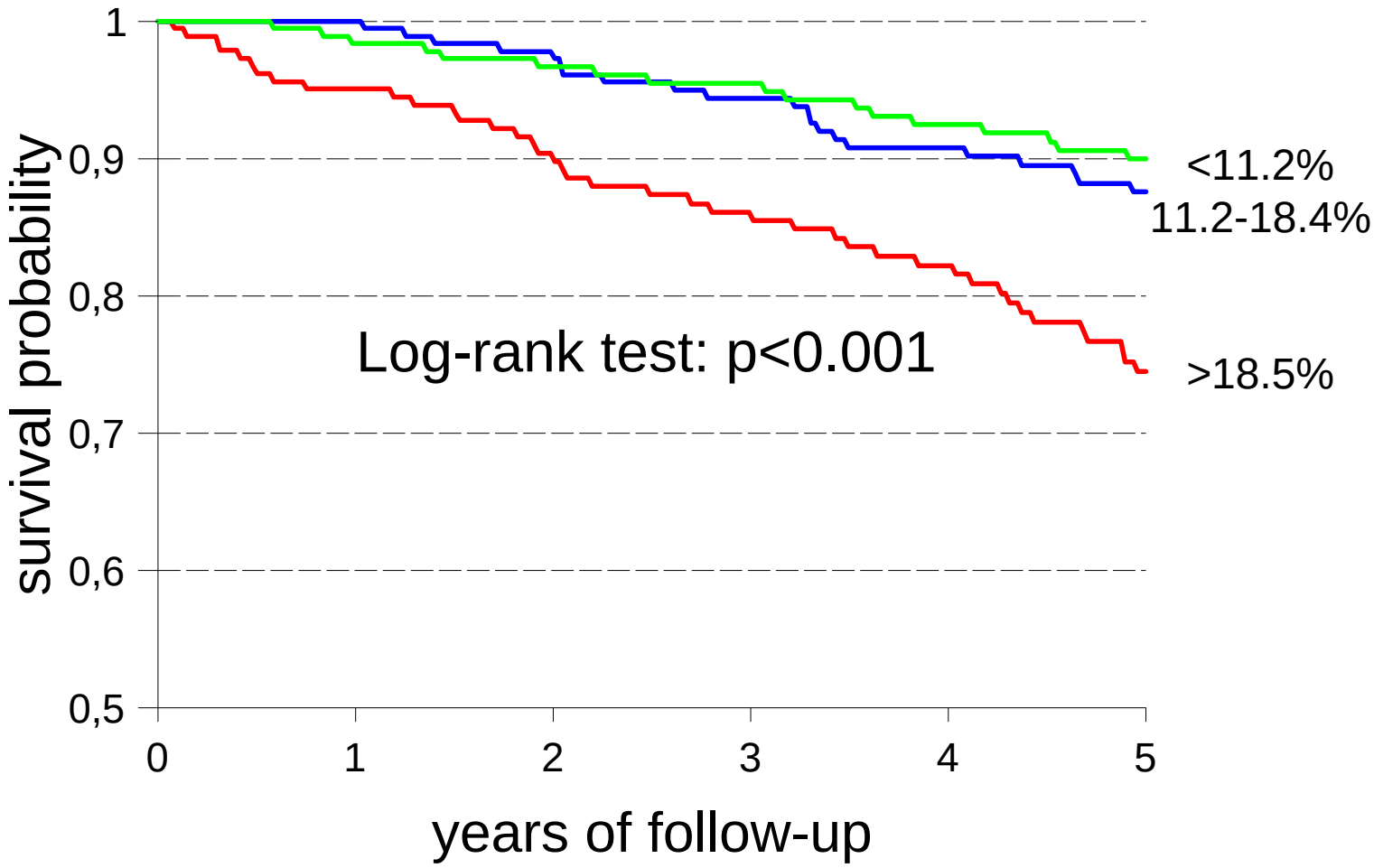


Muggeo M, Verlato G, Bonora E, Ciani F, Moghetti P, Eastman R, Crepaldi G, de Marco R (1995) Long-term instability of fasting plasma glucose predicts mortality in elderly NIDDM patients. The Verona Diabetes Study. *Diabetologia*, 38: 672-679

	Relative Risk	
	Controlling for sex and age	Adjusting also for all other variables
Mean FPG: II vs I tertile	1.06 (0.74-1.53)	0.91 (0.63-1.32)
III vs I tertile	1.31 (0.92-1.87)	0.94 (0.64-1.39)
CV-FPG: II vs I tertile	1.22 (0.83-1.81)	1.16 (0.77-1.74)
III vs I tertile	2.18 (1.52-3.12)	1.91 (1.28-2.85)
Slope-FPG: II vs I tertile	0.58 (0.40-0.83)	0.75 (0.51-1.13)
III vs I tertile	0.85 (0.61-1.19)	0.91 (0.65-1.28)

Adjusting for sex, age, diabetes duration, insulin treatment and statistics of fasting plasma glucose

Kaplan-Meier estimates of survival probability when considering **cardiovascular mortality** as the end-point in 566 elderly **(>=75 yrs)** type 2 diabetic patients from Verona, grouped in tertiles according to coefficient of variation of fasting plasma glucose



Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R (1997) Long-term instability of fasting plasma glucose: a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus. The Verona Diabetes Study. *Circulation*, 96: 1750-1754

	Relative Risk	
	CV-FPG: II vs I tertile	CV-FPG: III vs I tertile
Mortality due to diabetes	1.43 (0.51-4.00)	1.41 (0.49-4.04)
Mortality from malignancies	1.15 (0.50-2.61)	1.74 (0.75-4.01)
Cardiovascular mortality	1.20 (0.62-2.33)	2.40 (1.28-4.53)

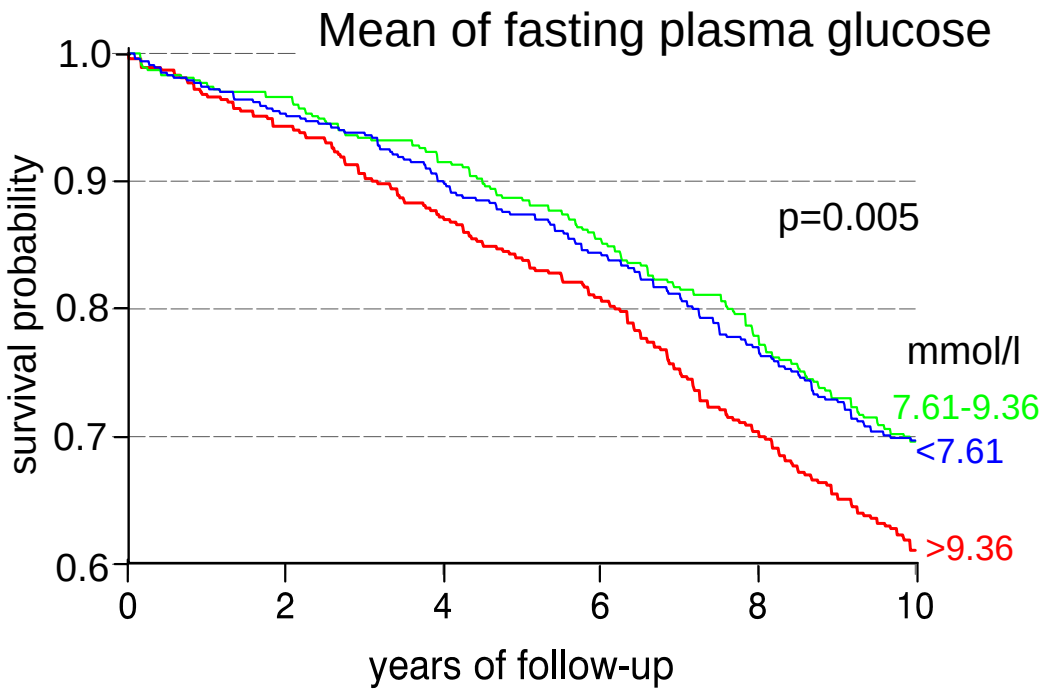
Adjusting for sex, age, diabetes duration, insulin treatment and statistics of fasting plasma glucose

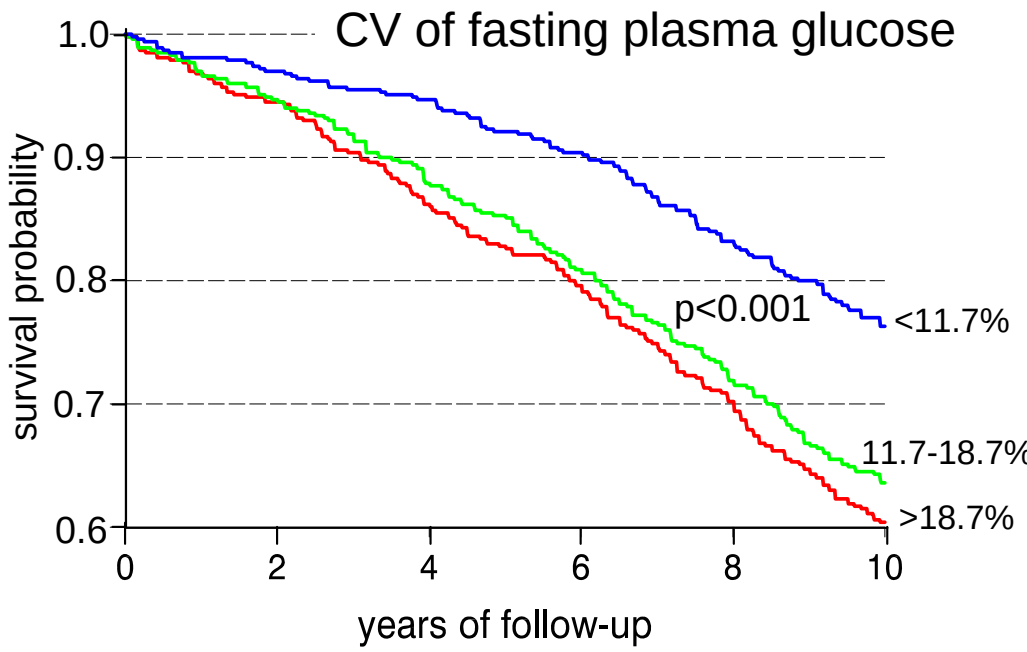
These results are consistent with the results of an American study performed in hypertensive diabetic subjects aged >60 years [Frost et al, Circulation 1996].

	Hazard Ratio	
	Frost et al, 96	Muggeo et al,97
RR of cardiovascular mortality for a 1 SD- increase in FPG	1.22 (1.08-1.36)	1.21 (0.99-1.49)

Relative risks were computed in univariable analysis

Kaplan-Meier estimates of survival probability in 1,409 type 2 diabetic patients from Verona, **aged 56-74 yrs**, 1 Jan 1987 through 31 Dec 1996. Patients were grouped into tertiles according to mean FPG and CV of FPG during the 3 years (1 Jan 1987 through 31 Dec 1986) preceding the mortality follow-up.





Muggeo M, Zoppini G, Bonora E, Brun E, Bonadonna RC, Moghetti P, Verlato G (2000) Fasting plasma glucose variability predicts 10-year survival of Type 2 diabetic patients. The Verona Diabetes Study. *Diabetes Care*, 23:45-50

Glucose variability is a significant predictor of morbidity and mortality in **intensive care units**, both for children [Wintergerst et al, Pediatrics, 2006] and for adults [Egi et al, Anesthesiology, 2006].

"… within-day and between-day variability in blood glucose around a patient's mean value has no influence on the development or progression of either retinopathy (P=0.18 and P=0.72, respectively) or nephropathy (P=0.32 and P=0.57)" in patients with type 1 diabetes [Kilpatrick et al, Diabetes Care, 2006].

Cell culture studies demonstrates that constant high glucose levels injure cells differently from fluctuating high and low glucose levels [Li et al, 1996]. In particular intermittent high glucose enhances apoptosis in human endothelial cells in vitro to a larger extent than constant high concentrations of glucose [Risso et al, 2001]. Hence, fluctuating levels of risk factors may damage by specific underlying mechanisms.

SCOPI della presente indagine

Verificare se è possibile generalizzare queste osservazioni.

In particolare, confrontare il significato prognostico del valore medio e della variabilità di alcuni fattori di rischio (indice di massa corporea, pressione sistolica e glicemia a digiuno) nei diabetici con età inferiore o maggiore di 65 anni.

METODI

Nell'ambito del *Verona Diabetes Study* sono stati studiati tutti i diabetici di tipo 2, che avevano almeno una misurazione all'anno per i 3 fattori di rischio considerati nel triennio 1984-86. I pazienti sono stati seguiti nei 10 anni successivi (1987-96).

	numerosità	deceduti 1987-96	età (anni) media ±DS
pazienti <65 anni	565	98	56.6 ± 7.7
pazienti >=65 anni	754	340	72.7 ± 5.3

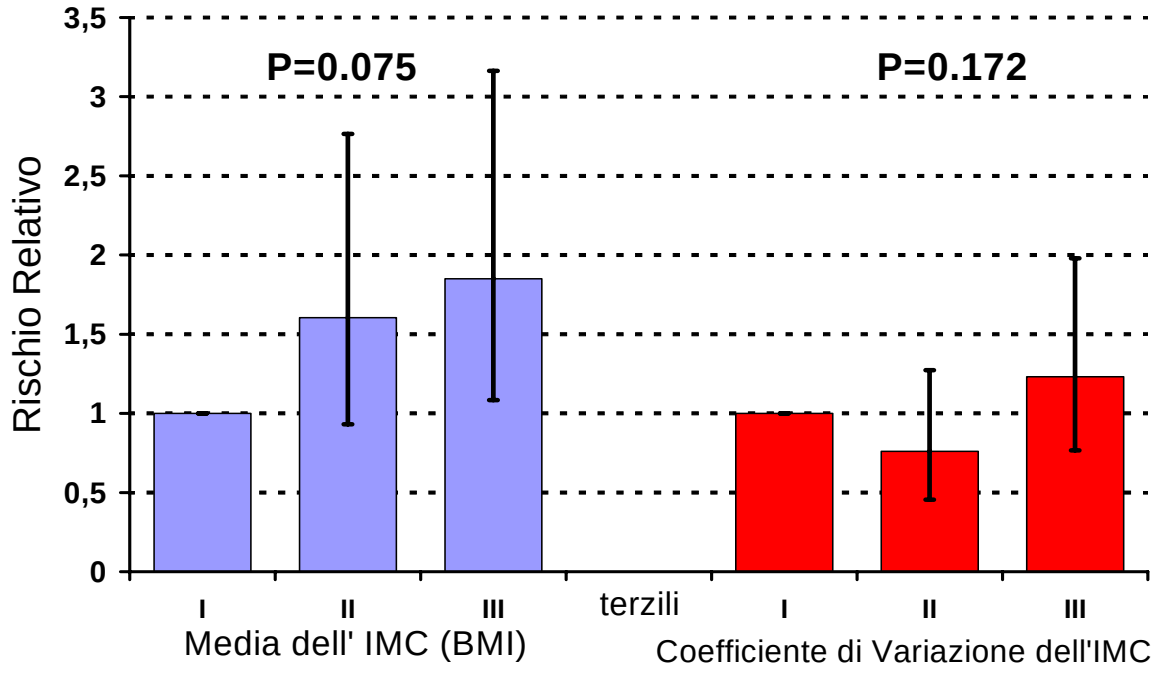
L'analisi della sopravvivenza è stata effettuata con un modello di Cox, controllando per sesso, età, fumo, tempo dalla diagnosi, e trattamento.

	≤ 65 years (n=565)	>65 years (n=754)	P value	All subjects
Age (years)	56.6±7.7	72.7±5.3	-----	65.9±10.3
Sex (M/F)	276/289 (49/51)	280/474 (37/63)	<0.001	556/763 (42/58)
Time since diagnosis (yrs)	10.6±6.0	13.3±6.7	<0.001	11.9±6.3
Therapy			0.137	
Diet	24 (5)	41 (6)		65 (5)
Oral Hypoglycemic Agents	418 (81)	620 (84)		1038 (83)
Insulin	72 (14)	77 (10)		149 (12)
Mean BMI (Kg^2 /m)	27.7±4.5	27.2±3.8	0.017	27.4±4.1
Mean Systolic Pressure (mmHg)	148.3±10.5	156.7±9.2	<0.001	153.1±10.6
Mean Fasting Plasma Gluc. (mmol/l)	9.8±2.7	8.8±2.2	0.001	9.3±2.5
CV - BMI (%)	3.4±2.1	3.3±1.8	0.355	3.4±1.9
CV - Systolic Pressure (%)	6.0±2.3	6.2±2.8	0.150	6.1±2.6
CV Fasting Plasma Glucose (%)	21.4±11.3	18.5±9.7	<0.001	19.8±10.5

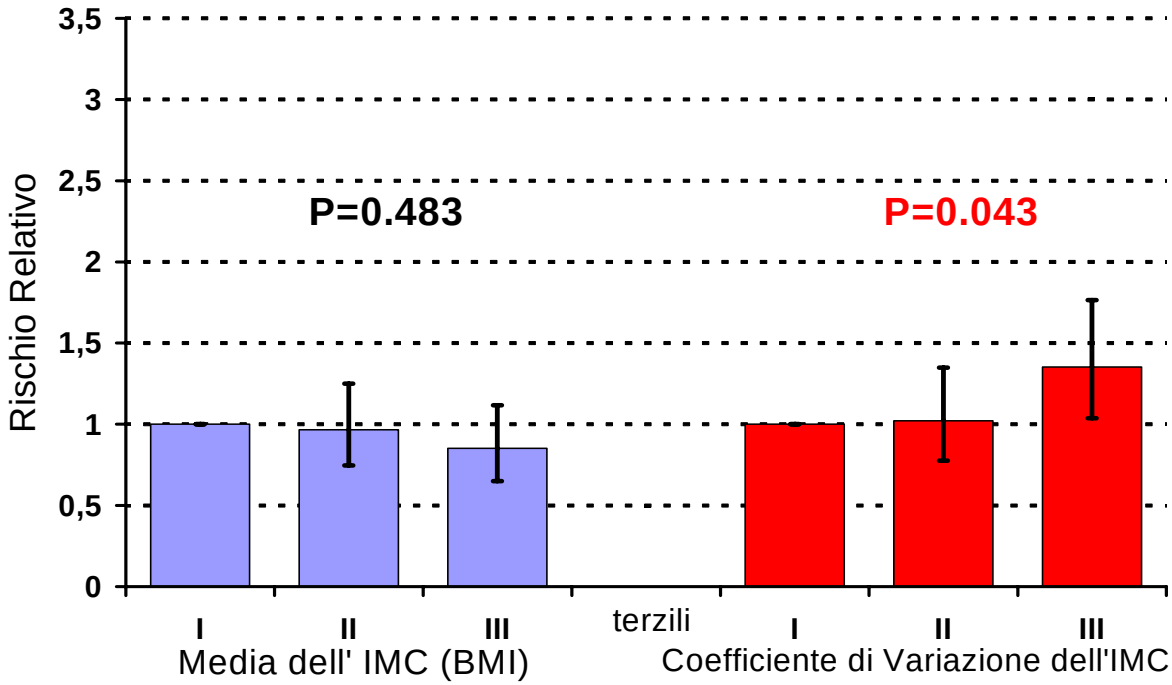
La media e il coefficiente di variazione dei fattori di rischio sono stati ricodificati in terzili usando i seguenti valori (*cutoff)*:

	Pazienti <65 anni		Pazienti >=65 anni	
	I	II	I	II
Media IMC (kg/m^2)	25.4	29.1	25.4	28.5
CV IMC (%):	2.4	3.7	2.4	3.6
Media pressione sistolica (mmHg)	145.0	152.5	152.6	159.2
CV pressione sistolica (%):	4.9	6.6	4.9	6.7
Media glicemia a digiuno (mmol/l):	8.27	10.33	7.67	9.54
CV glicemia a digiuno (%):	15.1	23.7	13.0	20.7

Pazienti diabetici
<65 anni

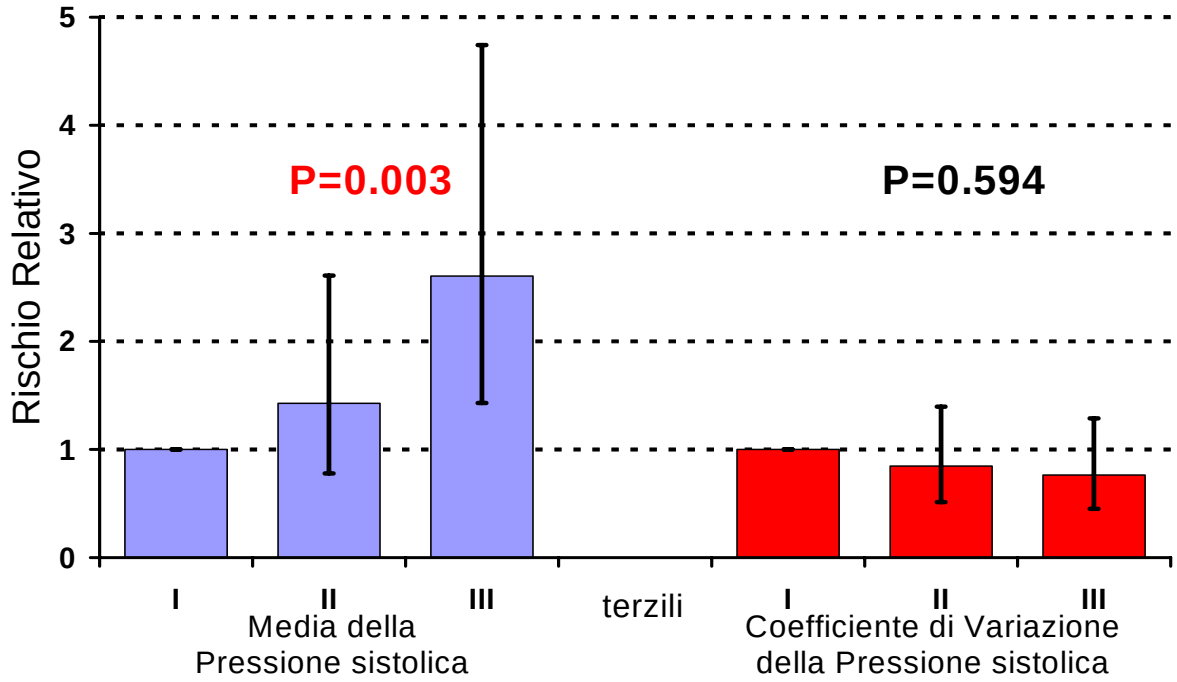


Pazienti diabetici
>=65 anni

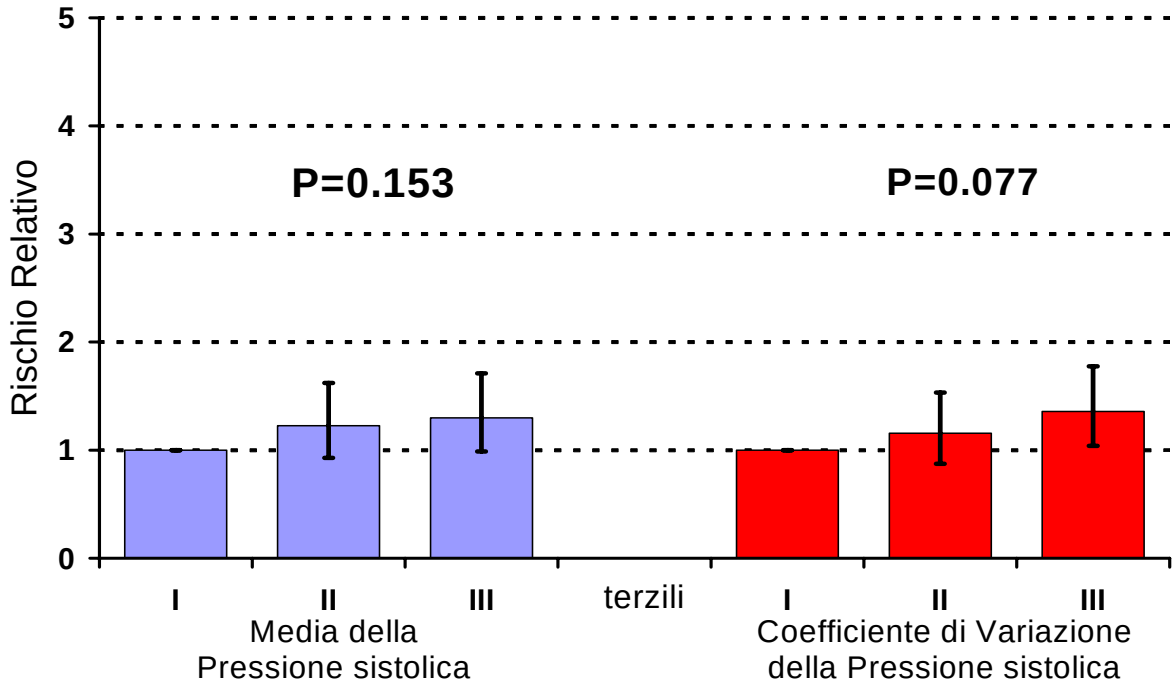


Zoppini et al, Int J Obesity, 03

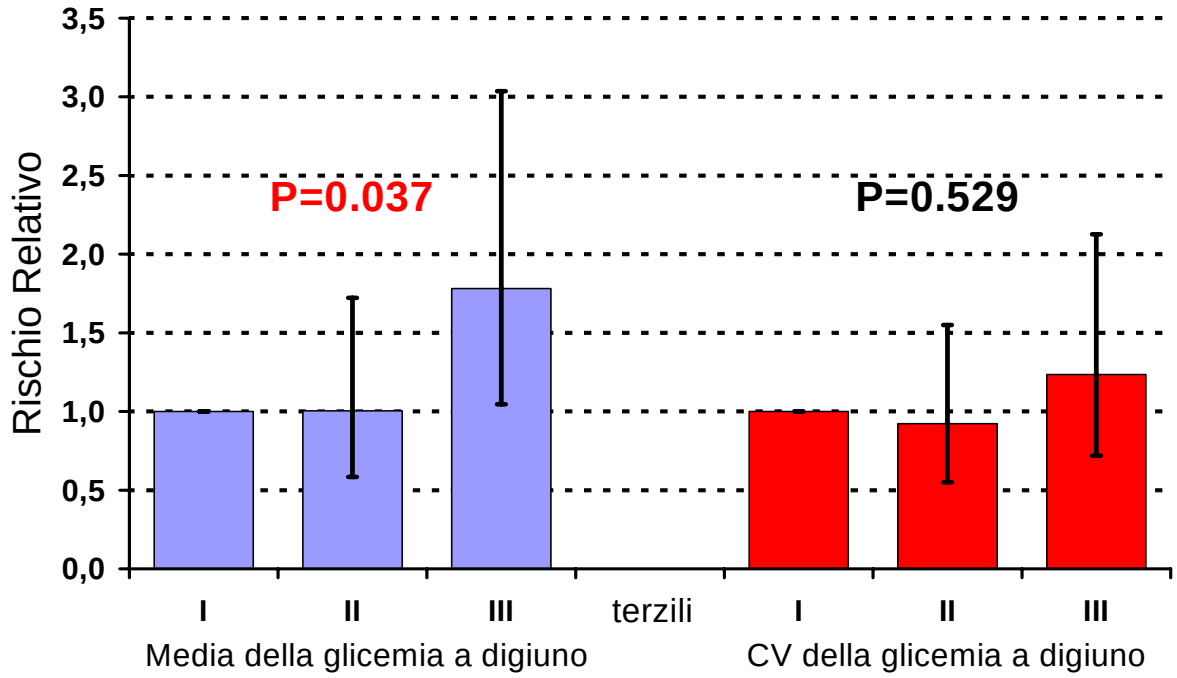
Pazienti diabetici
<65 anni



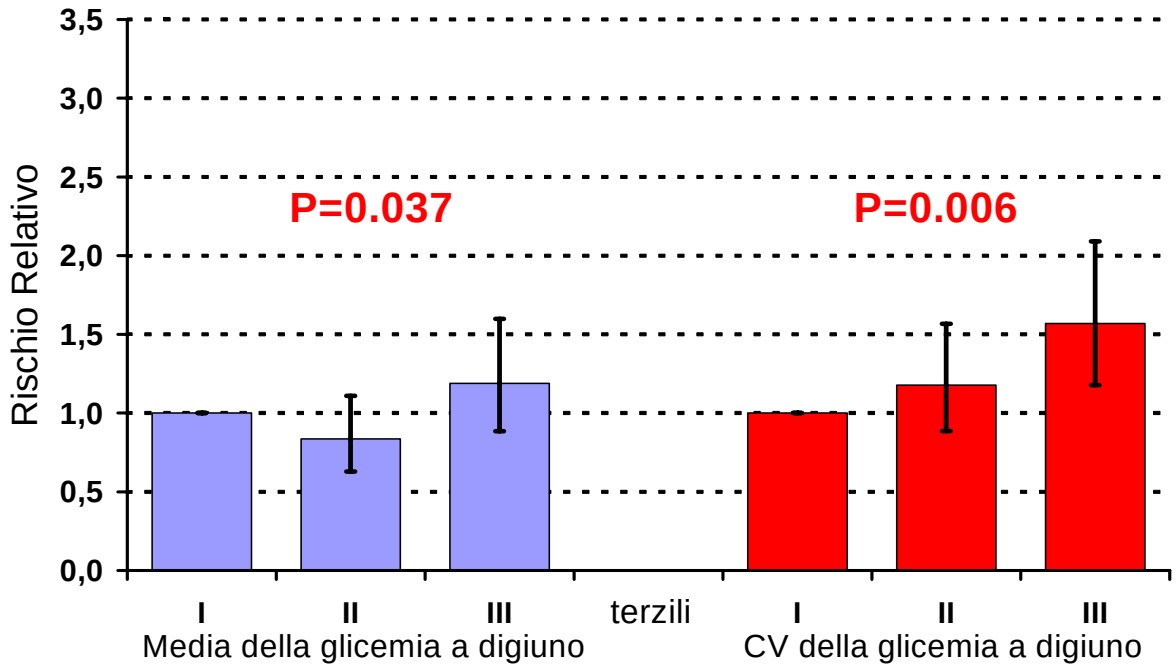
Pazienti diabetici
>=65 anni



Pazienti diabetici
<65 anni



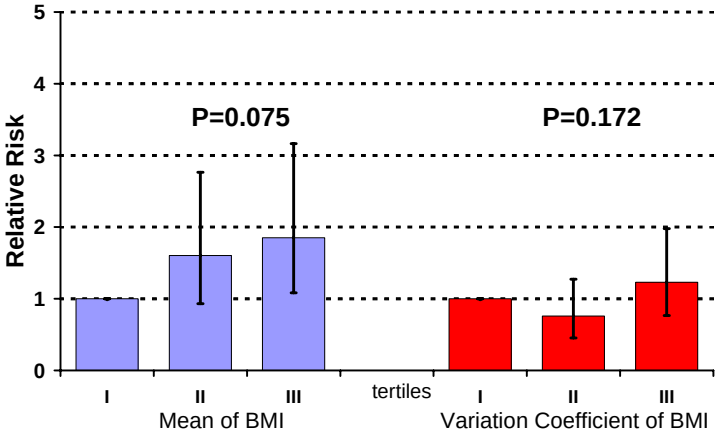
Pazienti diabetici
>=65 anni

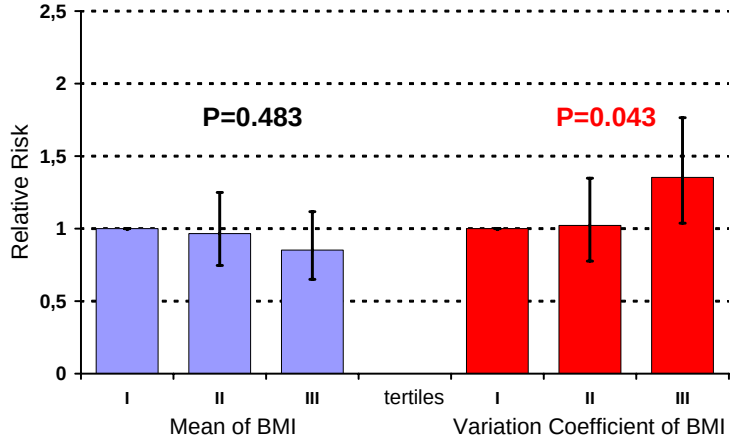


Aged under 65 years

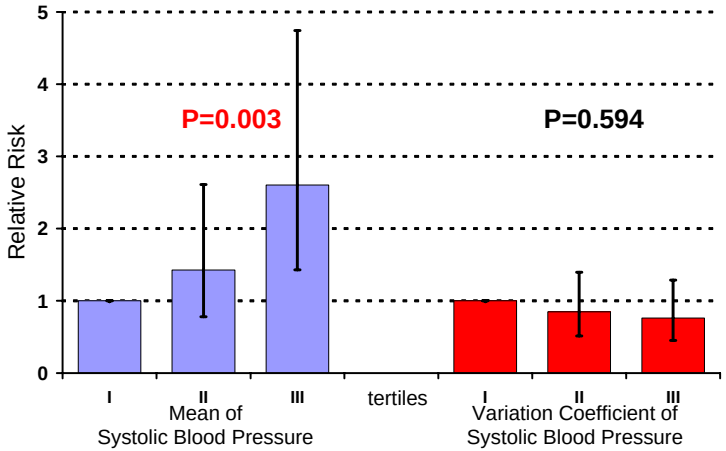
Aged 65 years or more

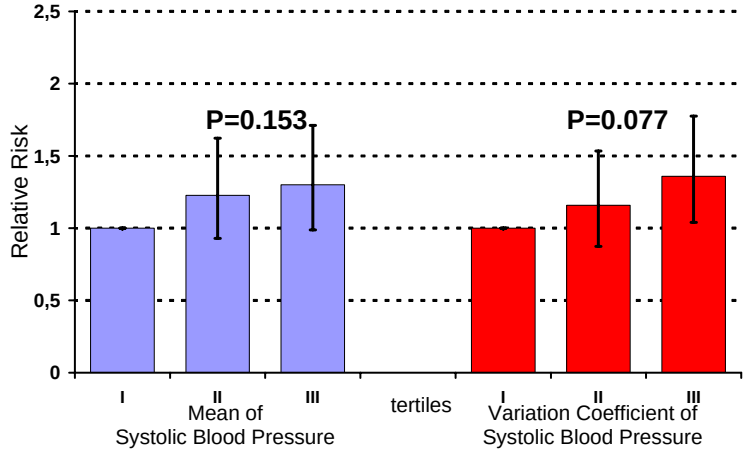
BMI



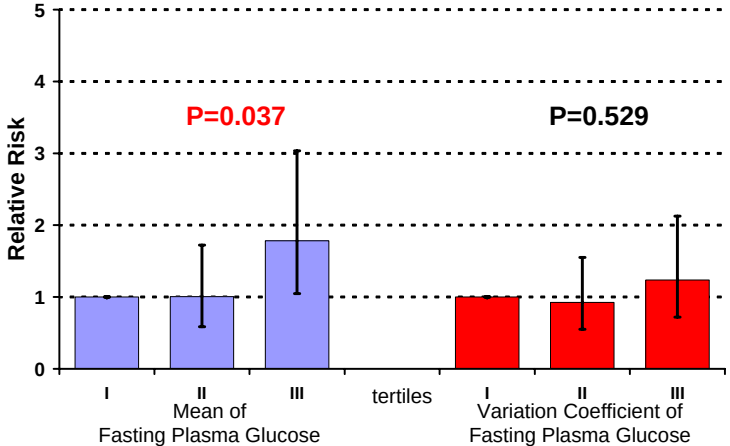


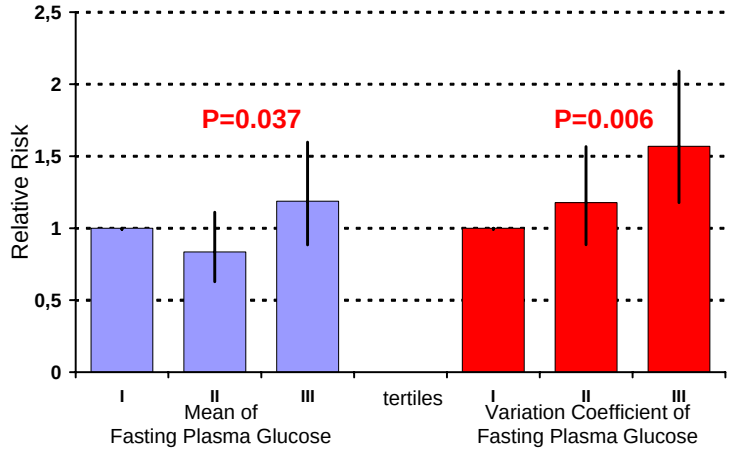
Systolic pressure





Fasting plasma glucose





RISULTATI

Sotto i 65 anni di età, il livello medio dei fattori di rischio ha notevole importanza prognostica, ma non la loro variabilità.

Infatti, il rischio di morte tende ad aumentare dal I al III terzile dell'Indice di Massa Corporea (P=0.075), della pressione sistolica (P=0.003) e della glicemia a digiuno (P=0.037).

Una situazione opposta è stata rilevata nei pazienti anziani, in cui la variabilità (coefficiente di variazione intra-individuale) diventa il fattore prognostico più importante.

Il rischio di morte tende ad aumentare dal I al III terzile del CV dell'Indice di Massa Corporea (P=0.043), della pressione sistolica (P=0.077) e della glicemia a digiuno (P=0.006).

CONCLUSIONI

Si conferma che i soggetti anziani vanno incontro alla perdita dell'omeostasi, ovvero della capacità di mantenere costante le condizioni dell'ambiente interno [Resnick, 1998].

Questi dati suggeriscono che nei diabetici di tipo 2 più giovani la terapia dovrebbe mirare a ridurre il livello medio dei fattori di rischio, mentre nei soggetti anziani il clinico dovrebbe cercare anche di ridurre la variabilità di questi fattori.

BIBLIOGRAFIA

1) Bruno G, Merletti F, Boffetti P, Cavallo-Perin P, Bargero G, Gallone G, Pagano G (1999a) Impact of glycaemic control, hypertension and insulin treatment on general and cause-specific mortality: an Italian population-based cohort of Type II (non-insulin-dependent) diabetes mellitus. *Diabetologia* 42: 297-301

2) Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB (1988) Mortality among diabetics in a national sample. *Am J Epidemiol* 128: 389-401

3) Muggeo M, Verlato G, Bonora E, Bressan F, Girotto S, Corbellini M, Gemma ML, Moghetti P, Zenere M, Cacciatori V, Zoppini G, de Marco R (1995a) The Verona Diabetes Study: a population-based survey on known diabetes mellitus prevalence and 5-year all-cause mortality. *Diabetologia* 38: 318-325

4) Muggeo M, Verlato G, Bonora E, Ciani F, Moghetti P, Eastman R, Crepaldi G, de Marco R (1995) Long-term instability of fasting plasma glucose predicts mortality in elderly NIDDM patients. The Verona Diabetes Study. Diabetologia, 38: 672-679

5) Muggeo M, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R (1997) Long-term instability of fasting plasma glucose, a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus. The Verona Diabetes Study. Circulation, 96: 1750-1754

6) Muggeo M, Zoppini G, Bonora E, Brun E, Bonadonna RC, Moghetti P, Verlato G (2000) Fasting plasma glucose variability predicts 10-year survival of Type 2 diabetic patients. The Verona Diabetes Study. Diabetes Care, 23: 45-50

7) Panzram G (1987) Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 30: 123-131

8) Panzram G, Zabel-Langhennig R (1981) Prognosis of diabetes mellitus in a geographically defined population. *Diabetologia* 20: 587-591

1) Resnick NM (1998) Geriatric medicine. In: Harrison's Principles of Internal Medicine. 14th Edition, pp.37-46

2) Stevens JS, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL (1998) The effect of age on the association between body mass index and mortality. New Engl J Med, 338: 1-7

3) Stengard JH, Tuomilehto J, Pekkanen J, Kivinen P, Kaarsalo E, Nissinen A, Karvonen MJ (1992) Diabetes mellitus, impaired glucose tolerance and mortality among elderly men: the Finnish cohorts of the seven countries study. *Diabetologia* 35: 760-765

4) Tan HH, McAlpine RR, James P, Thompson P, McMurdo MET, Morris AD, Evans JMM, for the DARTS/MEMO Collaboration (2004) Diagnosis of type 2 diabetes at an older age - Effect on mortality in men and women. *Diabetes Care* 27: 2797-99

5) Waugh NR, Dallas JH, Jung RT, Newton RW (1989) Mortality in a cohort of diabetic patients: Causes and relative risks. *Diabetologia* 32: 103-104

6) Wong JSK, Pearson DWM, Murchison LE, Williams MJ, Narajan V (1991) Mortality in diabetes mellitus: Experience of a geographically defined population. *Diabet Med* 8: 135-139

7) Zoppini G, Verlato G, Leuzinger C, Zamboni C, Brun E, Bonora E, Muggeo M (2003) Body mass index and the risk of mortality in type 2 diabetic patients from Verona. *Int J Obesity* 27:281-285

Il "Verona Diabetes Study"

1) **Muggeo M**, Verlato G, Bonora E, Bressan F, Girotto S, Corbellini M, Gemma ML, Moghetti P, Zenere M, Cacciatori V, Zoppini G, de Marco R (1995) The Verona Diabetes Study: a population-based survey on known diabetes mellitus prevalence and 5-year all-cause mortality. *Diabetologia*, 38: 318-325 (I.F. 95 = 4.525)

2) **Muggeo M**, Verlato G, Bonora E, Ciani F, Moghetti P, Eastman R, Crepaldi G, de Marco R (1995) Long-term instability of fasting plasma glucose predicts mortality in elderly NIDDM patients. The Verona Diabetes Study. *Diabetologia*, 38: 672-679 (I.F. 95 = 4.525)

3) Verlato G, **Muggeo M**, Bonora E, Corbellini M, Bressan F, de Marco R (1996) Attending the Diabetes Center is associated with increased 5-year survival probability of diabetic patients. The Verona Diabetes Study. *Diabetes Care*, 19: 211-213 (I.F. 96=3.457)

4) **Muggeo M**, Verlato G, Bonora E, Zoppini G, Corbellini M, de Marco R (1997) Long-term instability of fasting plasma glucose: a novel predictor of cardiovascular mortality in elderly patients with non-insulin-dependent diabetes mellitus. The Verona Diabetes Study. *Circulation*, 96: 1750-1754 (I.F. 97=9.762)

5) de Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, **Muggeo M** (1999) Cause-specific mortality in Type 2 diabetes. The Verona Diabetes Study. *Diabetes Care*, 22: 756-761 (I.F. 99 = 5.076)

6) Zoppini G, Verlato G, Bonora E, **Muggeo M** (1999) Attending the Diabetes Center is associated with reduced cardiovascular mortality in Type 2 diabetic patients: the Verona Diabetes Study. *Diabetes Metab Res Rev*, 15: 170-174 (I.F. 99 = 2.417)

7) **Muggeo M**, Zoppini G, Bonora E, Brun E, Bonadonna RC, Moghetti P, Verlato G (2000) Fasting plasma glucose variability predicts 10-year survival of Type 2 diabetic patients. The Verona Diabetes Study. *Diabetes Care*, 23:45-50 (I.F. 00 = 4.992)

8) Brun E, Nelson RG; Bennett PH, Imperatore G, Zoppini G, Verlato G, **Muggeo M** (2000) Diabetes duration and cause-specific mortality in the Verona Diabetes Study. *Diabetes Care*, 23: 1119-1123 (I.F. 99 = 4.992)

9) Verlato G, **Muggeo M** (2000) The capture-recapture method in the epidemiology of Type 2 diabetes mellitus – A contribution from the Verona Diabetes Study. *Diabetes Care*, 23: 759-764 (I.F. 00 = 4.992)

10) Zoppini G, Verlato G, Leuzinger C, Zamboni C, Brun E, Bonora E, **Muggeo M** (2003) Body mass index and the risk of mortality in type 2 diabetic patients from Verona. Int J Obesity, 27:281-285 (IF 03=2.794)

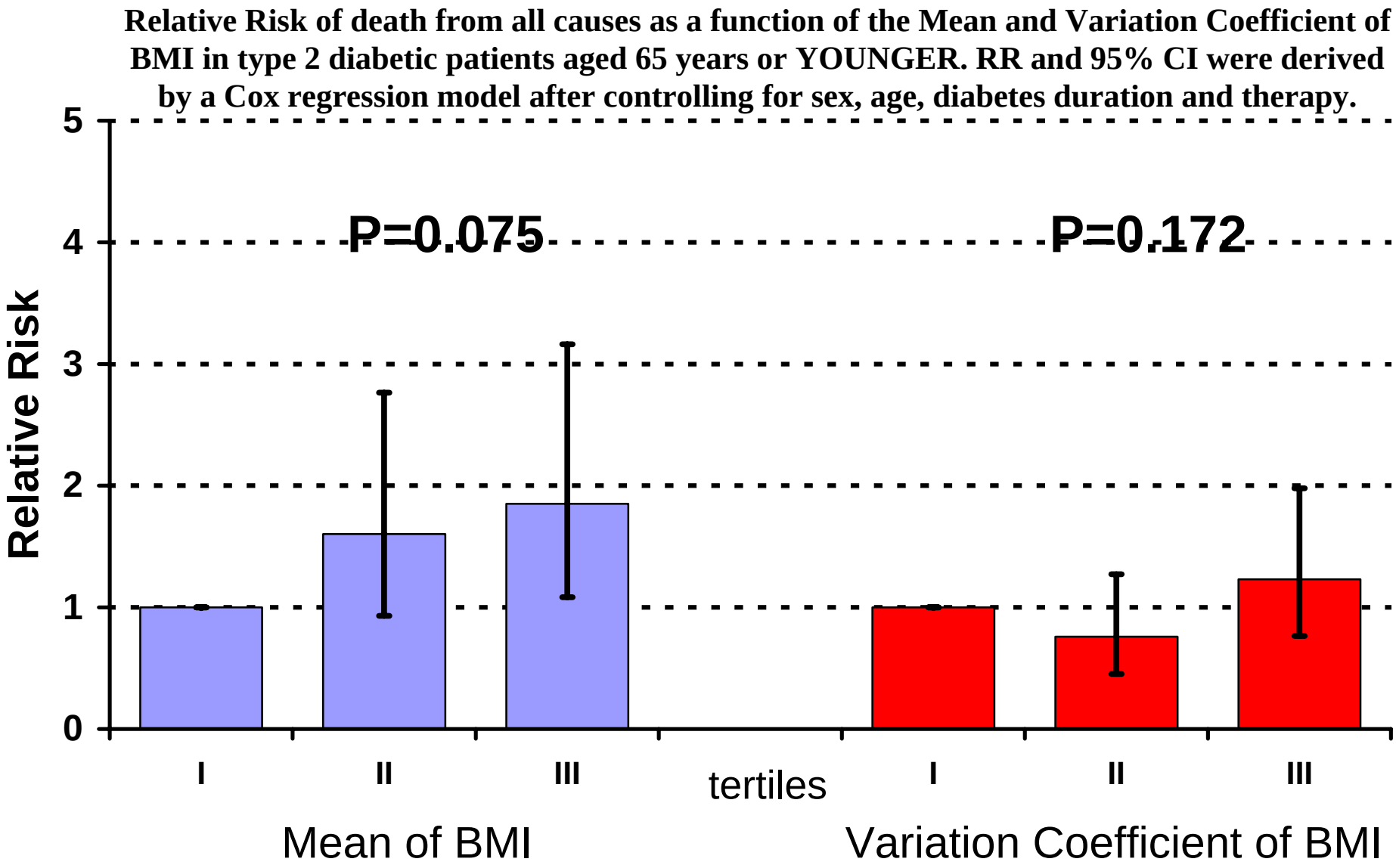
11) Verlato G, Zoppini G, Bonora E, **Muggeo M** (2003) Mortality from site-specific malignancies in type 2 diabetic patients from Verona. Diabetes Care, 26:1047-1051 (IF 03=7.501)

12) Zoppini G, Verlato G, Zamboni C, Venturi C, Gennaro N, Biasi V, Bonora E, **Muggeo M** (2006) Pulse pressure and mortality from cardiovascular diseases in type 2 diabetic patients. The Verona Diabetes Study. *Cerebrovascular Diseases*, 23: 20-26 (IF 05 = 2.319)

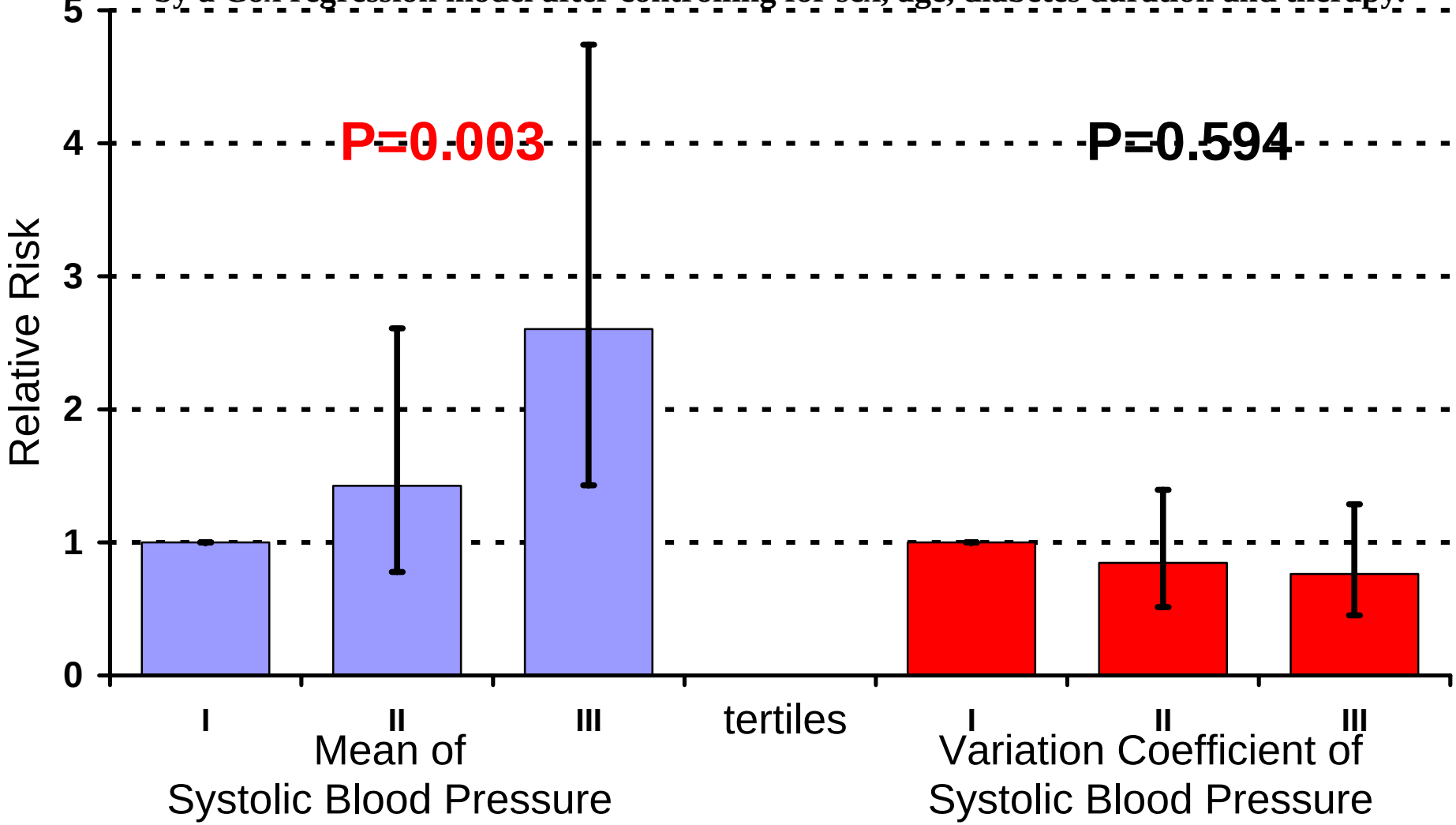
In adults it is still debated whether weight cycling has adverse effects. “Mortality in middle-aged men with sustained weight loss and weight fluctuation (cycling) is determined to a major extent by disadvantageous lifestyle factors and preexisting disease” [Wannamethee et al, Arch Internal Med 2002; Folsom et al, Int J Obesity 1996]. Weight cycling does not independently affect cardiovascular risk profile [Graci et al, Int J Obesity, 2004].

In the Nineties the Verona Diabetes Study reported that in the elderly mortality from all causes [Muggeo et al, 1995] and from cardiovascular diseases [Muggeo et al, 1997] was related to the variability of fasting glycemia rather than to mean glycemia.

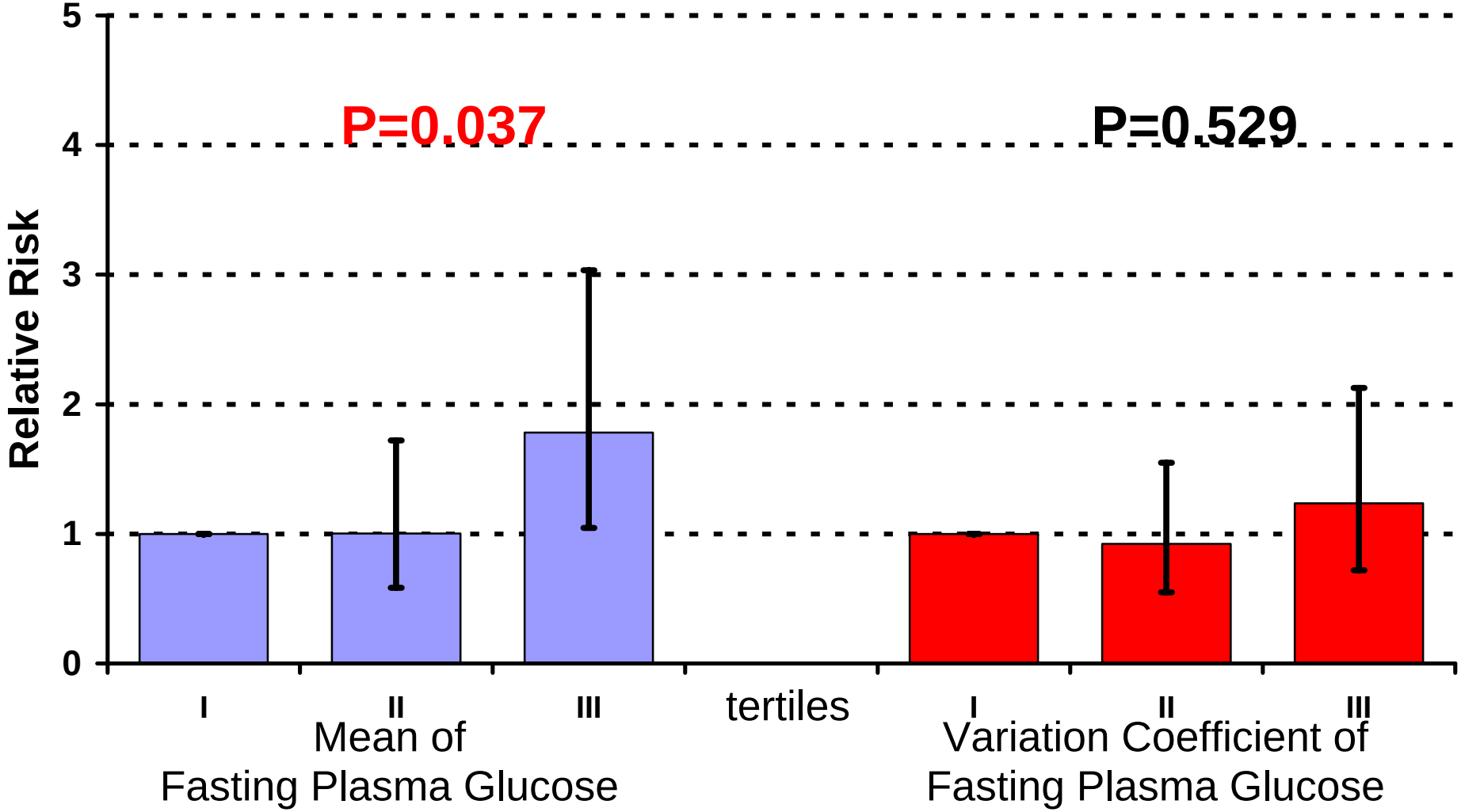
This observation prompted us to study in more detail the prognostic significance of long-term variability of other cardiovascular risk factors in type 2 diabetes.


Relative Risk of death from all causes as a function of the Mean and Variation Coefficient of BMI in type 2 diabetic patients aged 65 years or YOUNGER. RR and 95% CI were derived by a Cox regression model after controlling for sex, age, diabetes duration and therapy.
Relative Risk
0
1
2
3
4
5
P=0.075
P=0.172
I
II
III
tertiles
I
II
III
Mean of BMI
Variation Coefficient of BMI

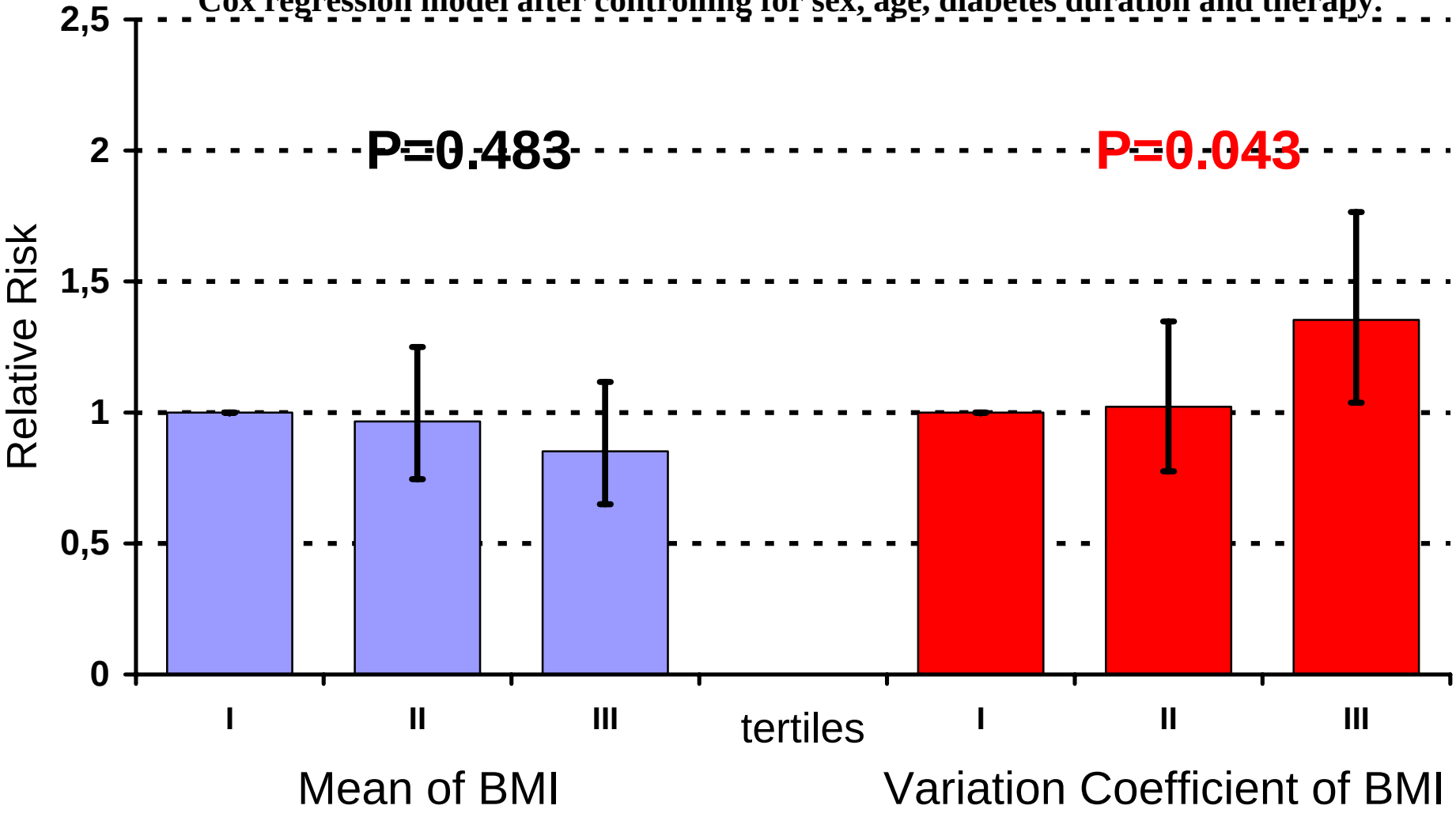
Relative Risk of death from all causes as a function of the Mean and Variation Coefficient of Systolic Blood Pressure in type 2 diabetic patients aged 65 years or YOUNGER. RR and 95% CI were derived by a Cox regression model after controlling for sex, age, diabetes duration and therapy.



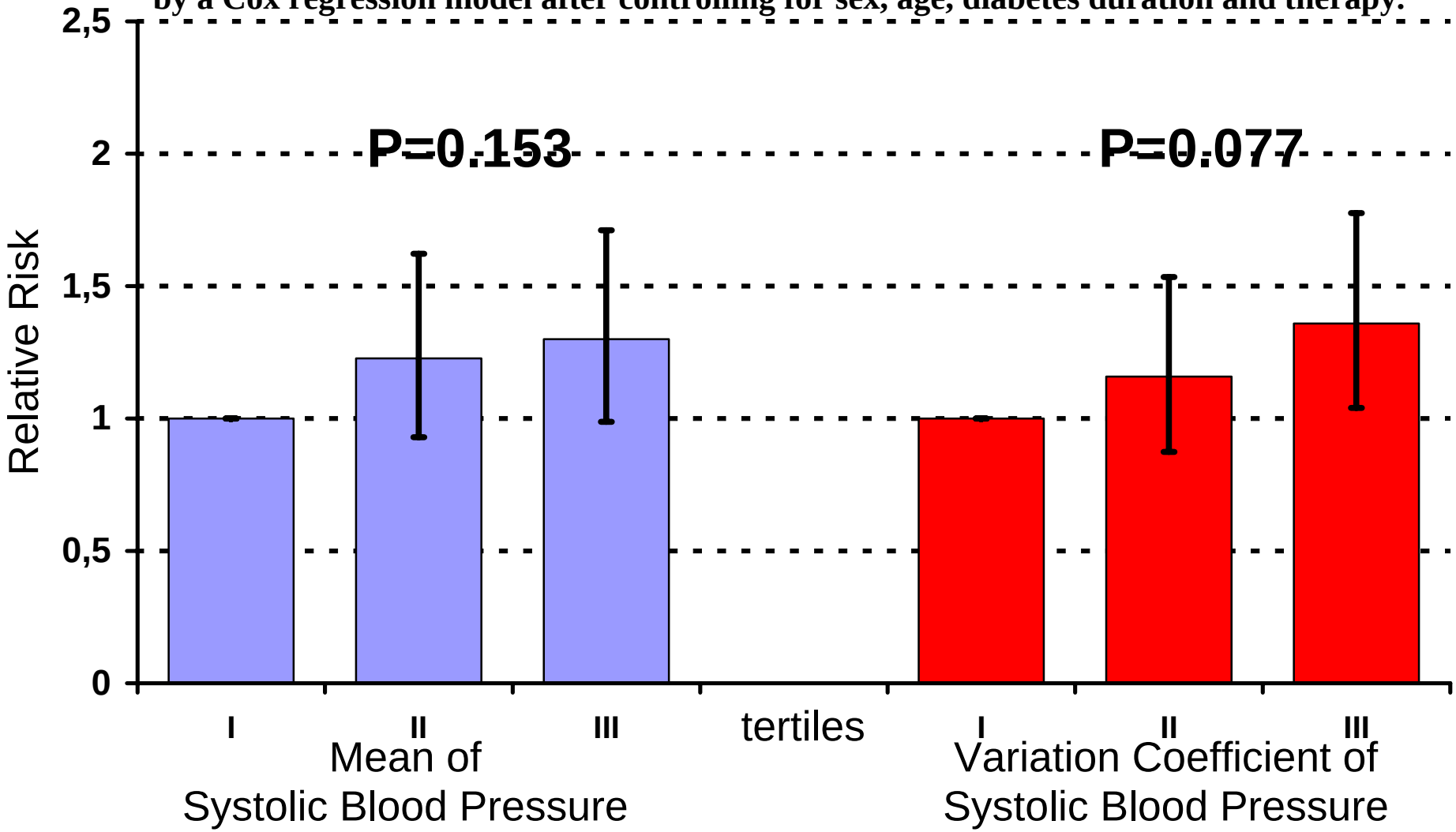
Relative Risk of death from all causes as a function of the Mean and Variation Coefficient of Fasting Plasma Glucose in type 2 diabetic patients aged 65 years or YOUNGER. RR and 95% CI were derived by a Cox regression model after controlling for sex, age, diabetes duration and therapy.



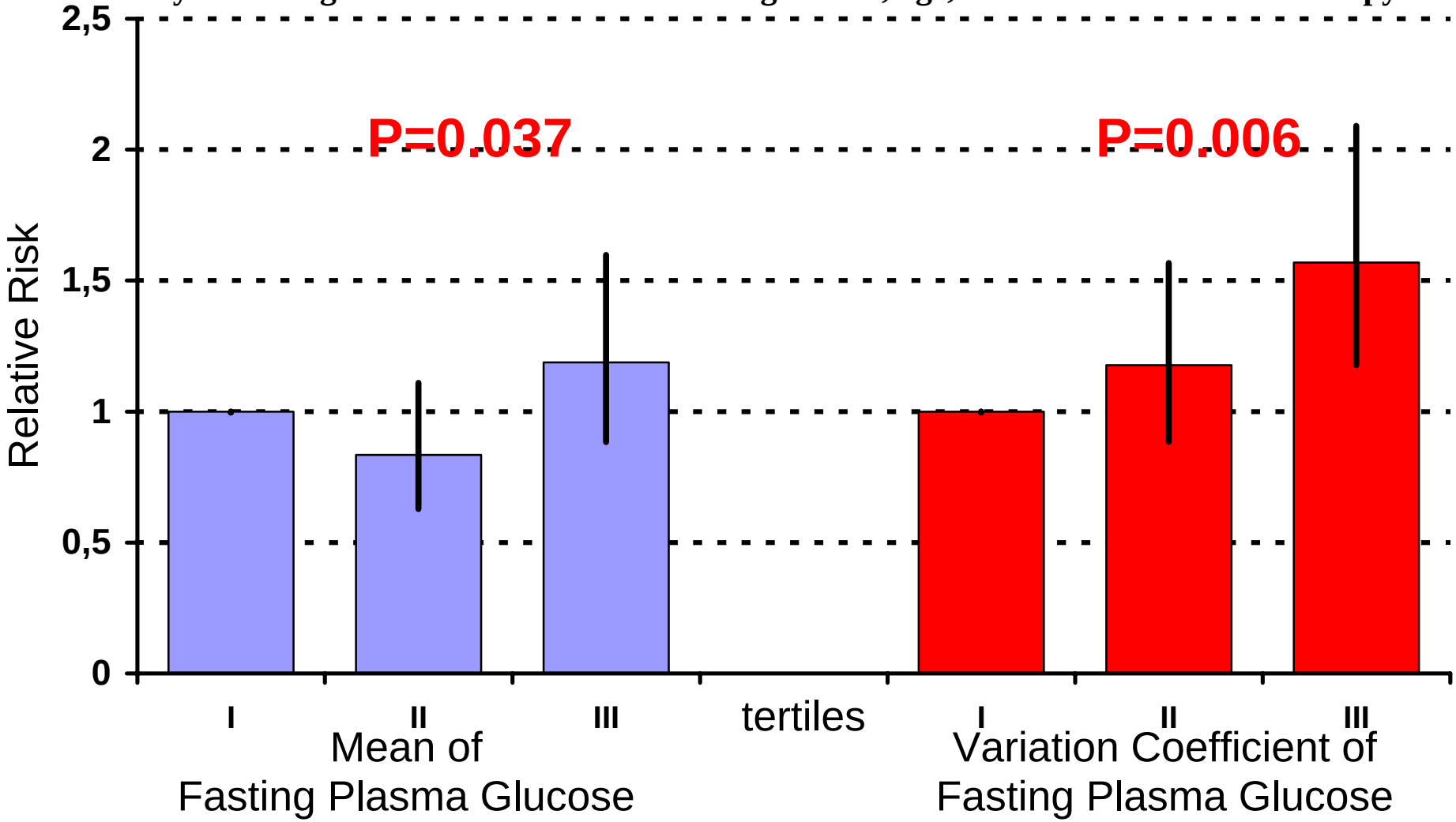
Relative Risk of death from all causes as a function of the Mean and Variation Coefficient of BMI in type 2 diabetic patients OLDER than 65 years. RR and 95% CI were derived by a Cox regression model after controlling for sex, age, diabetes duration and therapy.



Relative Risk of death from all causes as a function of the Mean and Variation Coefficient of Systolic Blood Pressure in type 2 diabetic patients OLDER than 65 years. RR and 95% CI were derived by a Cox regression model after controlling for sex, age, diabetes duration and therapy.



Relative Risk of death from all causes as a function of the Mean and Variation Coefficient of Fasting Plasma Glucose in type 2 diabetic patients OLDER than 65 years. RR and 95% CI were derived by a Cox regression model after controlling for sex, age, diabetes duration and therapy.



CONCLUSIONI

I soggetti anziani vanno incontro alla perdita dell'omeostasi, ovvero della capacità di mantenere costante le condizioni dell'ambiente interno [Resnick, 1998].

Questo fenomeno, detto omeostenosi (*homeostenosis*), è un fattore prognostico negativo per i soggetti anziani.

Questi dati suggeriscono che nei diabetici di tipo 2 più giovani la terapia dovrebbe mirare a ridurre il livello medio dei fattori di rischio, mentre nei soggetti anziani il clinico dovrebbe cercare anche di ridurre la variabilità di questi fattori.