L’acido urico, questo sconosciuto

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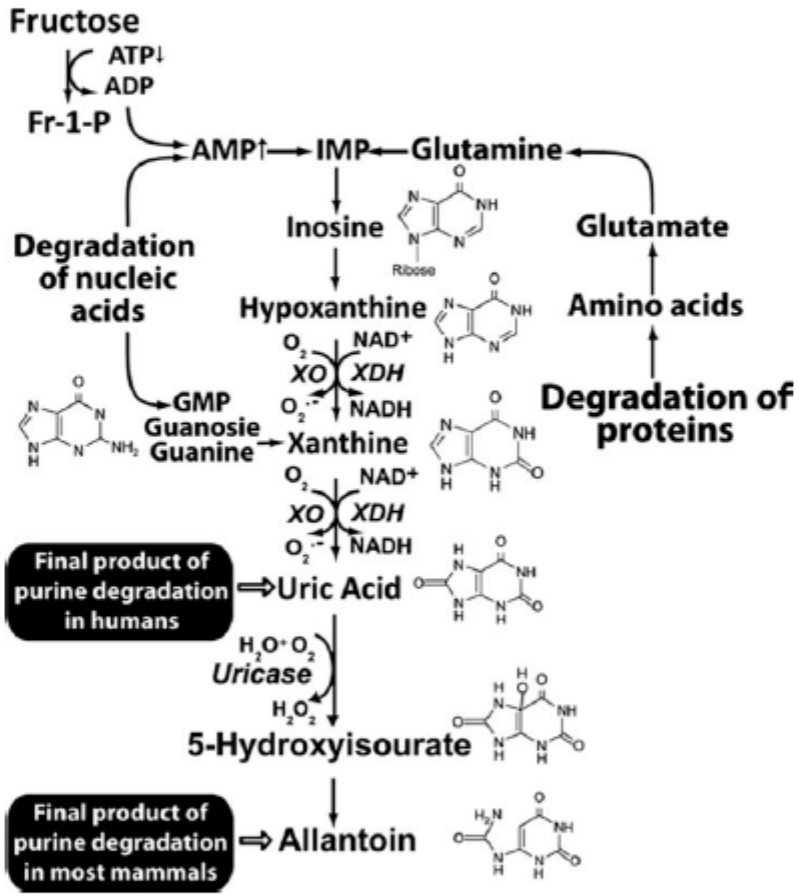
Dichiarazione di conflitto di interessi

Negli ultimi due anni nessun rapporto diretto di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

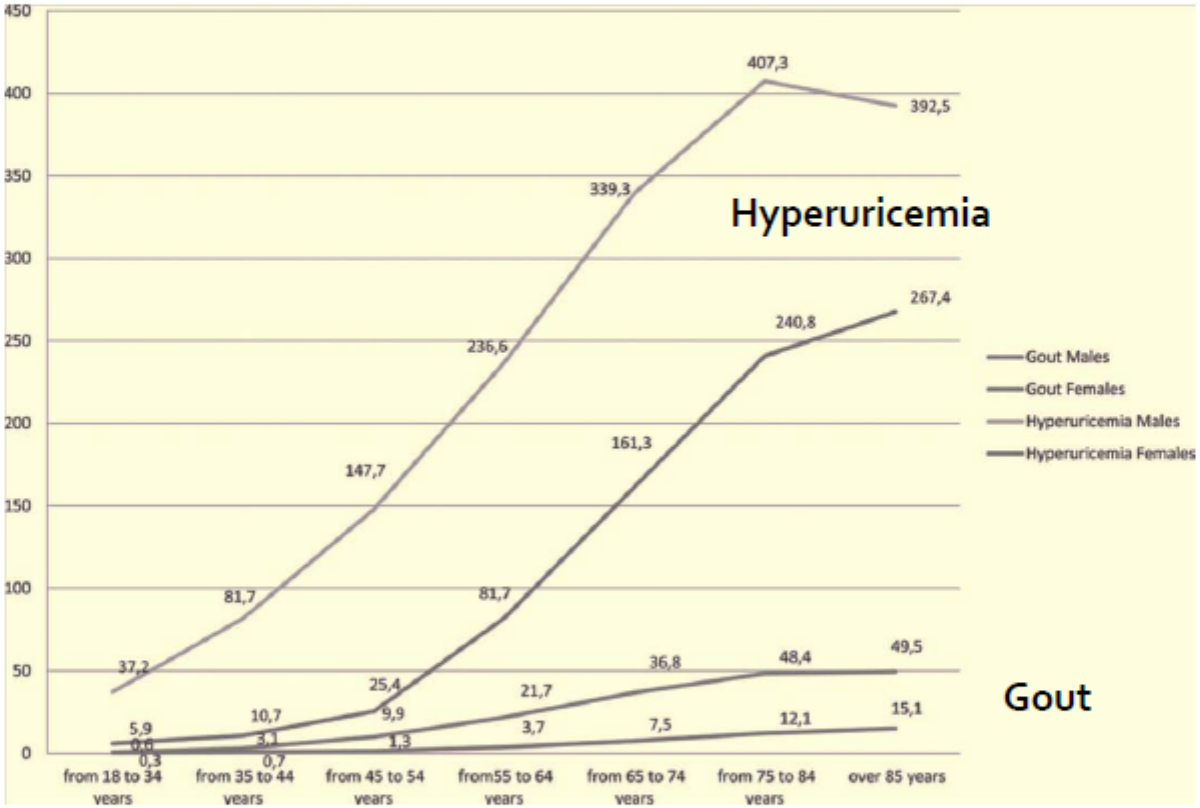
Uric acid metabolism.



American Heart Association
Learn and Live

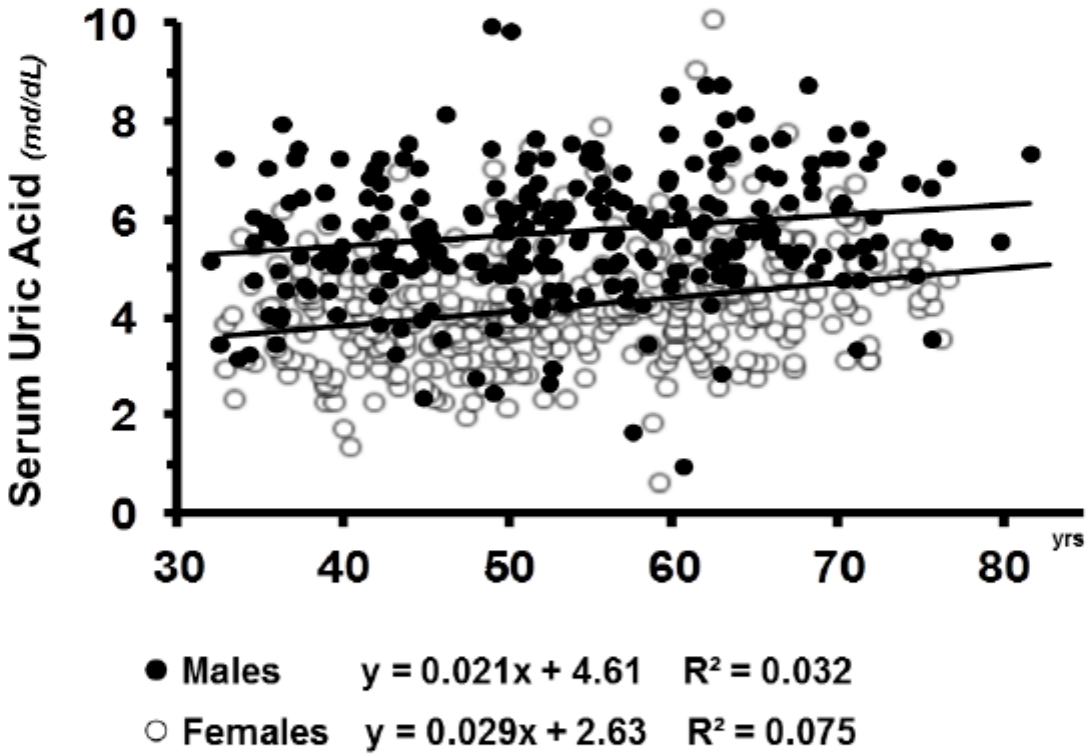
Johnson R J et al. Hypertension 2013;61:948-951

Prevalence of gout and hyperuricaemia (serum uric acid >6 mg/dl) per 1000 inhabitants by gender and age groups in 2009



Trifirò G ey al, Ann Rheum Dis.2012

Relationship between age and SUA in the cohort of the Brisighella Heart Study



Borghi C et al, J Hypertens 2013 , in press

2. Epidemiologia

- Frequenza dell'iperuricemia: 20 – 25% della popolazione
- Iperuricemia : gotta = 10 : 1
- Frequenza della gotta: 1 – 3% (paesi occidentali)
- Apice: negli uomini tra 40 - 50 a.
  nelle donne tra 50 - 60 a. (estrogeni → secrezione ↑)
- M : F = 3,6 : 1 (effetto uricosurico degli estrogeni)
- Il rischio di presentare un attacco di gotta cresce con l'aumento della concentrazione di acido urico:
  - 390-420 µmol/l → **< 2%**
  - Ca. 480 µmol/l → ca. **40%**
  - > 540 µmol/l → quasi **100%** (entro 1 – 1 ½ anno)

Myth: Gout is common among men but rare among women

Reality

- Increases substantially after menopause & rises with age
- In kidney, URAT1 responsible for reabsorbtion of uric acid from proximal tubule
- Estrogen has a direct effect on expression

Enomoto et al. Nature. 2002; 417.

3. Eziologia e patogenesi (1)

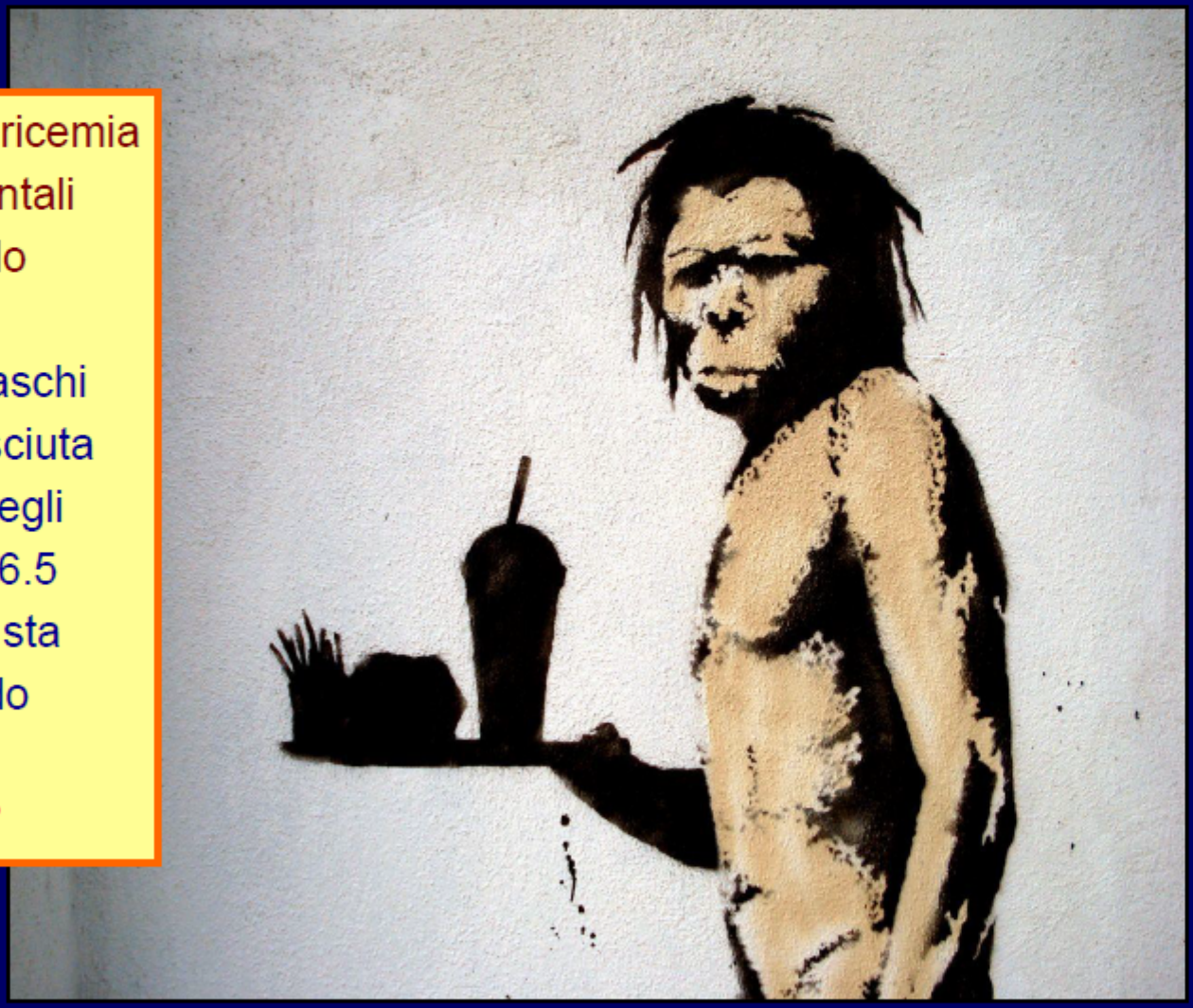
- L'acido urico è il prodotto terminale del metabolismo delle purine
  - Endogeno (2/3): prodotto terminale del metabolismo cellulare nell'organismo
  - Esogeno (1/3): prodotto di scomposizione delle purine assunte con l'alimentazione
- Viene secreto per lo più per via renale (70-90%), mentre il resto viene secreto attraverso il tratto digestivo.

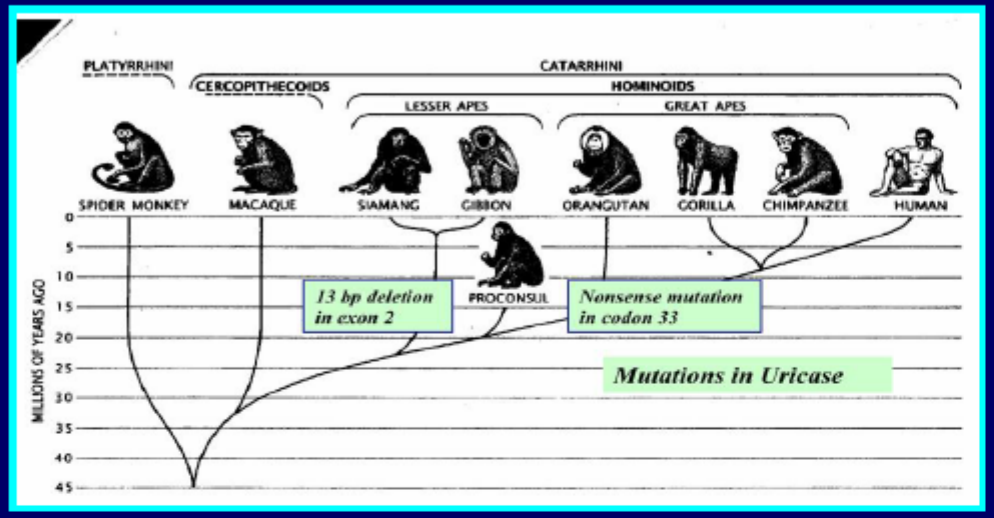
⇒ Gotta: « bilancio dell'acido urico positivo »

L'evoluzione sociale negli umani avviene molto più velocemente di quella genetica

I valori medi di uricemia nei paesi occidentali stanno crescendo gradualmente :
l'uricemia nei maschi americani è cresciuta da <3.5 mg/dL negli anni 20 , a 6.0 -6.5 mg/dL nei 70s e sta ancora crescendo

PERCHE'?





Circa 15 milioni di anni fa , un ominide nostro antenato subì una mutazione del gene dell'uricasi ,l'enzima epatico che degrada l'ac.urico in allantoina.

Come conseguanza gli uomini e i grandi primati hanno livelli di uricemia più elevati degli altri mammiferi.

La mutazione ha alterato la capacità di regolare l'uricemia e quindi ,variazioni della dieta possono causare grandi variazioni dei livelli di ac.urico che, negli umani, può variare da 2 mg/dL fino a 12 mg/dL.

Questa grande variabilità è determinata dal bilancio tra introduzione di purine con la dieta e produzione di urati da un lato, e eliminazione renale ed extrarenale dell'ac.urico dall'altro.

Ma perchè tutto ciò è avvenuto?

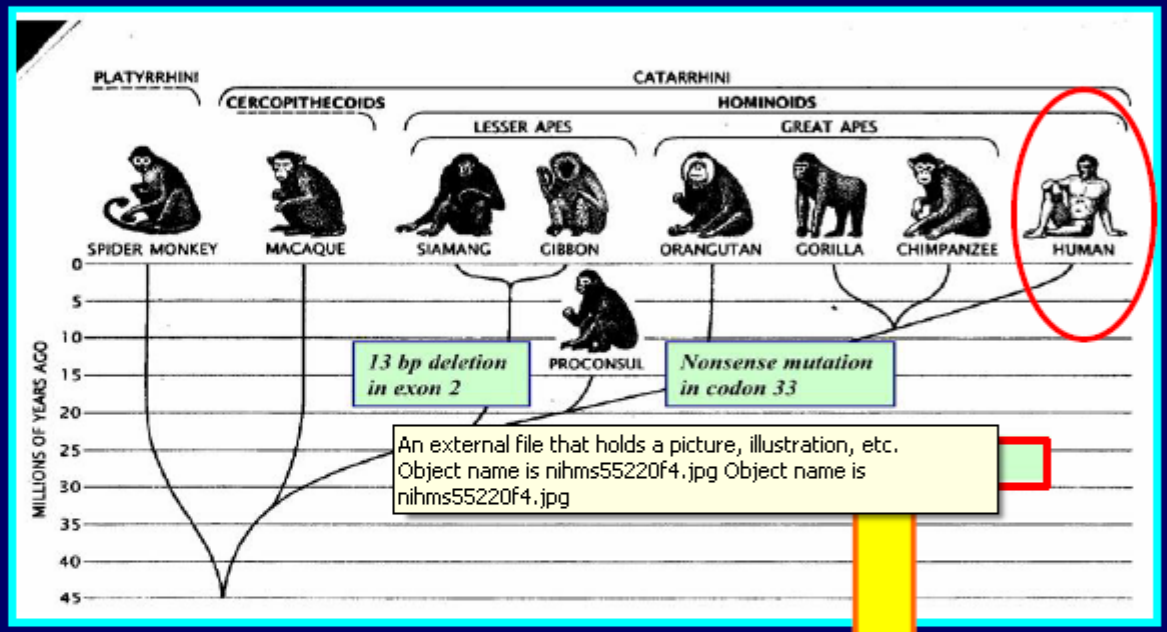
Uric Acid & Evolution

- UA is the end prod of purine metab in humans due to loss of uricase activities
- What are the evolutionary advantages of uric acid?
  - Anti – oxidant → inc life expect
  - BP control in times of low salt ingestion
  - Intelligence
  - Neurodegenerative protective effects

The Two Faces of Uric Acid

- Uric acid highest [ ] anti-oxidant in blood
- Provide > 50% of total anti-oxidant
- Anti-oxidant effect complex
  - Doesn't react with some oxidants, e.g SO
- Effects in AS, CVA & MI?
  - Protective (compens) rxn vs primary cause
  - Acitivated by oxidative stress
  - Metab derangements - Cu++ & Fe++

Mutazioni dell'uricasi durante l'evoluzione



Maggiore sopravvivenza in carenza di nutrienti, acqua e sali

↑ Neuroprotezione

↑ Acido urico

↑ Pressione arteriosa

↑ Sodiosensibilità

↑ Insulinoresistenza

Obesità centrale

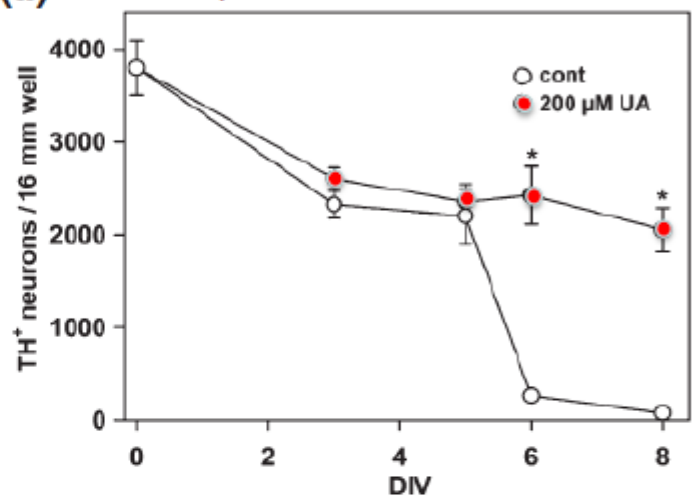
Iperuricemia, gotta e malattia – i nuovi concetti

La scomparsa dell'uricasi – unico enzima in grado di degradare l'acido urico in allantoina – sarebbe stata un vantaggio durante il miocene, consentendo lo sviluppo neuronale e, soprattutto, l'eliminazione renale di una maggiore quantità di acido urico e, quindi, di scorie azotate, senza variare l'apporto idrico (e la quantità di urina)

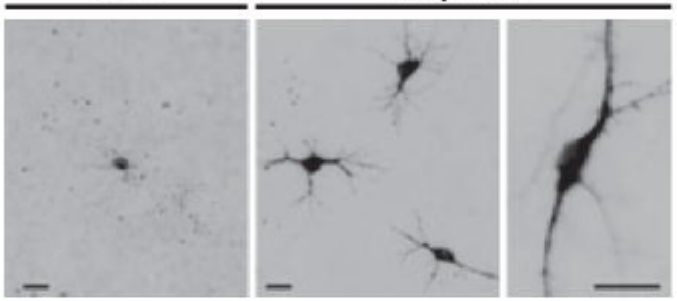
Stesso genotipo ?

Effetti dell'Ac.Urico sulle cellule nervose dopaminergiche

(a) Sopravvivenza in coltura

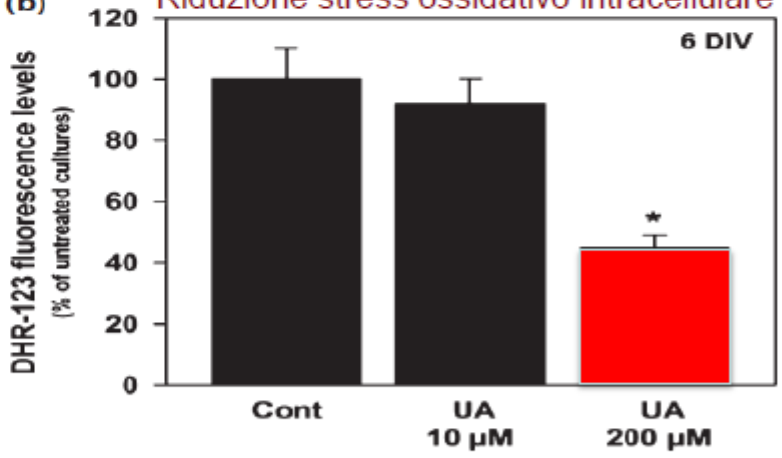


(c)



Dimensioni cellulari

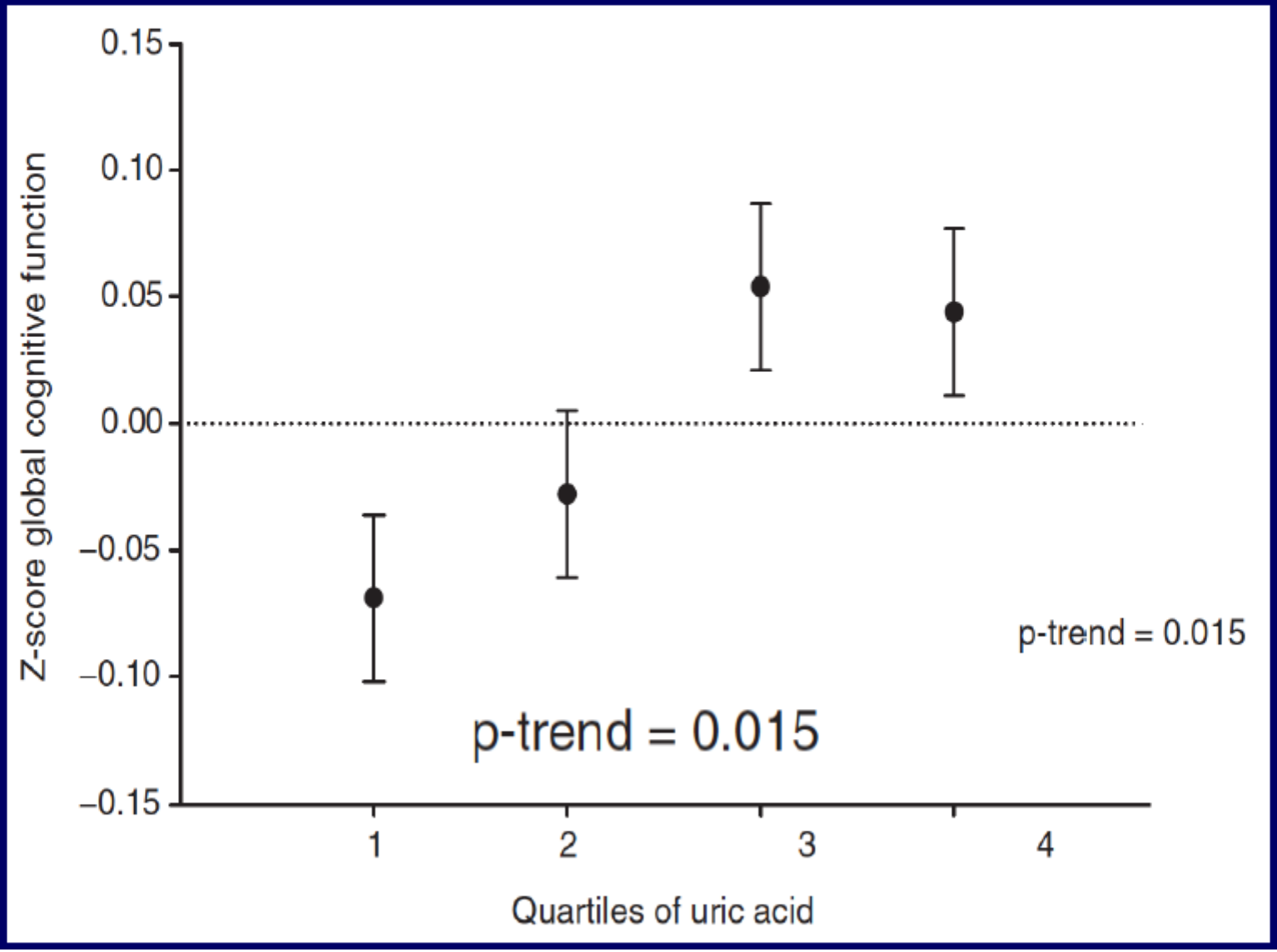
(b) Riduzione stress ossidativo intracellulare



JOURNAL OF NEUROCHEMISTRY | 2009 | 109 | 1118–1128

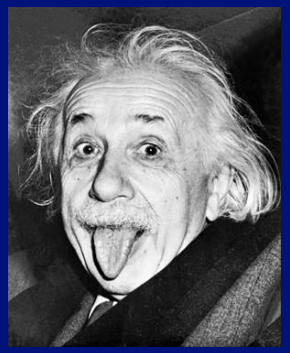
Serum uric acid and cognitive function and dementia

1.724 subjects (age 64.1±5.7 years)



Uric Acid

The Good

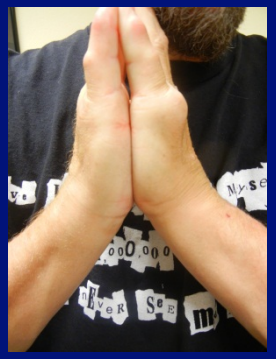


Intelligence

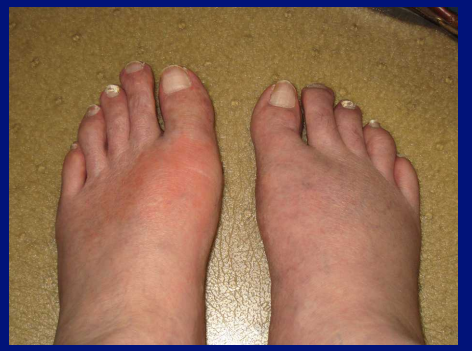
Alzheimer's

Parkinson's Disease

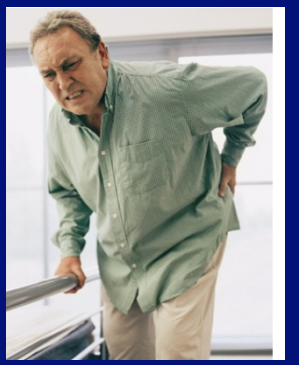
The Bad



Tophi

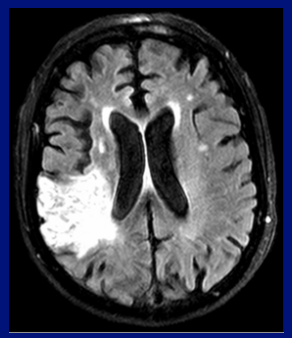


Gout



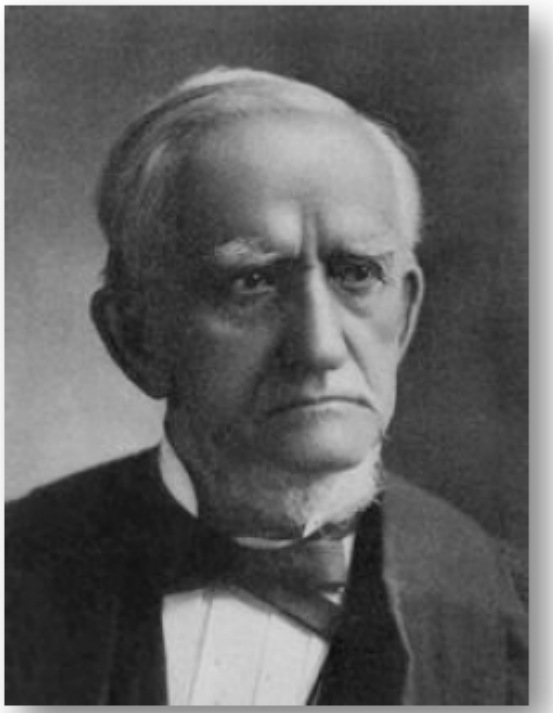
Stone

The Ugly



CVA

MI

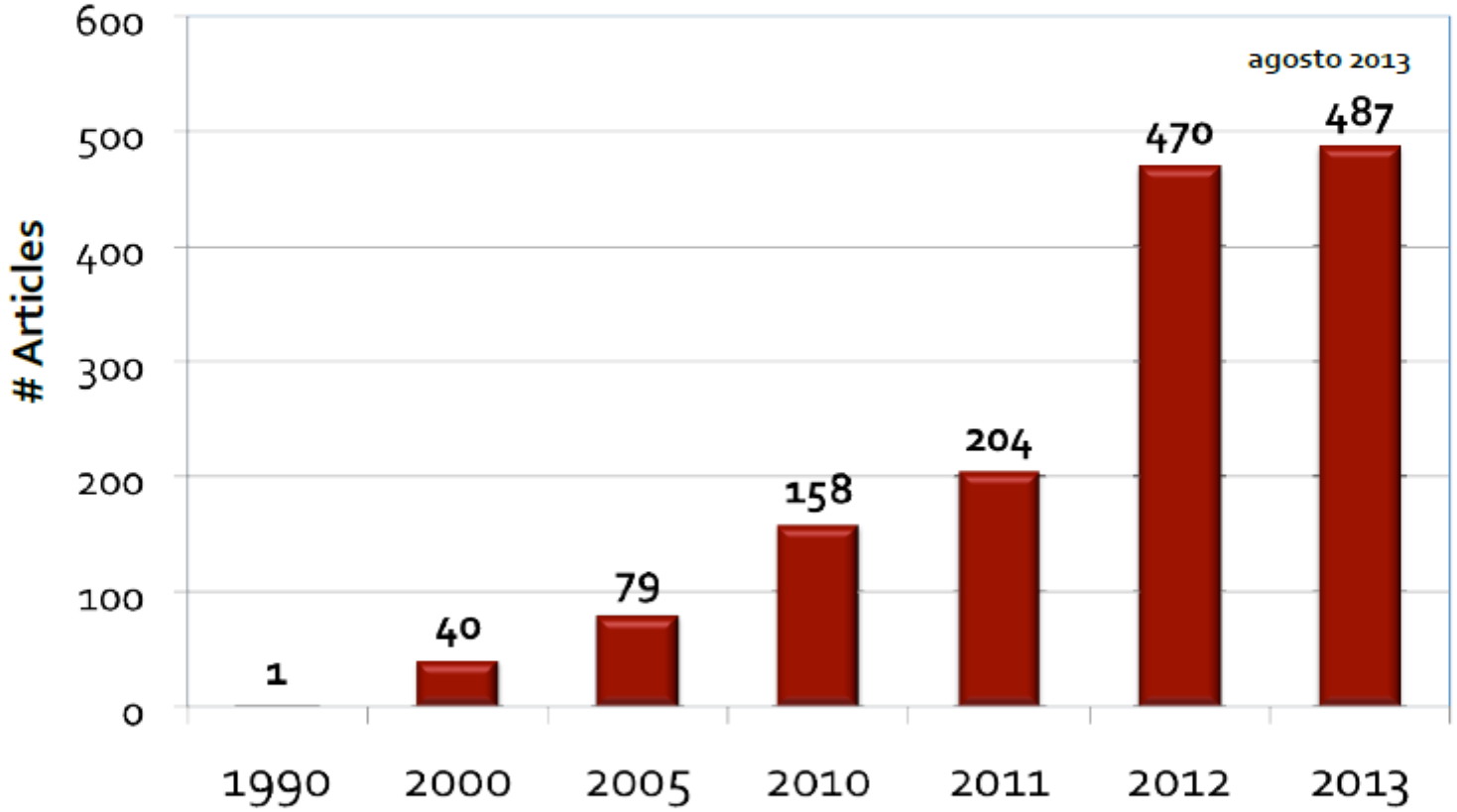


January 9, 1817 – June 16, 1904

1897, American Medical Association
Dal discorso presidenziale di
Nathan Smith Davis

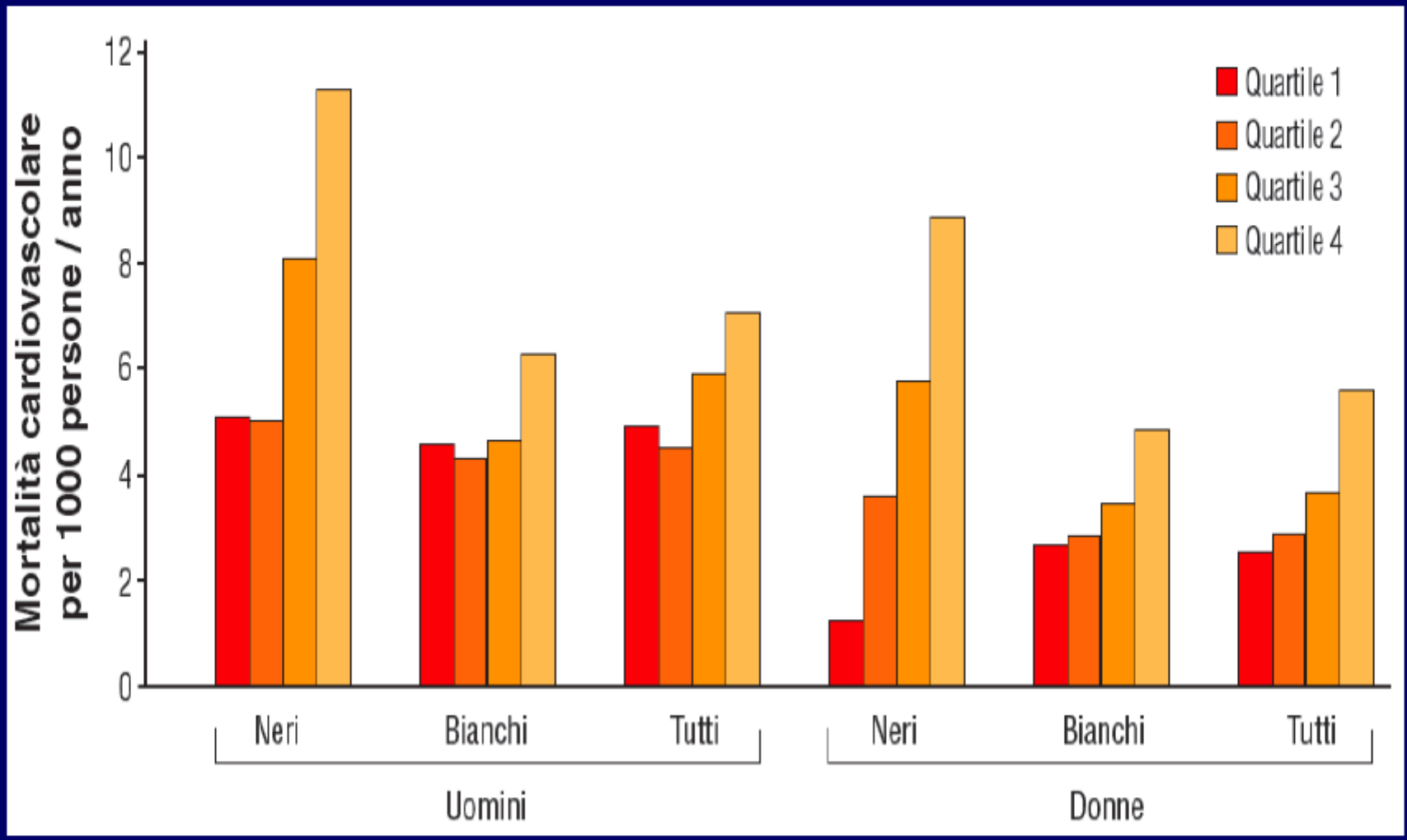
"High arterial tension in gout is due in part to uric acid or other toxic substances in the blood which increase the tonus of the [renal] arterioles"

Published Articles Linking Uric Acid to Cardiovascular Outcomes



Mortalità cardiovascolare per quartile di uricemia. The NHANES I Epidemiologic Follow-up Study (1971-1992)

5926 soggetti, età 24-75 anni, follow-up medo 16.4 anni



Resurrection of Uric Acid as a Causal Risk Factor in Essential Hypertension

Richard J. Johnson, Dan I. Feig, Jaime Herrera-Acosta, Duk-Hee Kang

In his landmark paper describing the entity of essential hypertension, Frederick Akbar Mahomed observed that many hypertensive subjects came from gouty families, leading him to suggest uric acid as a causal factor in the blood pressure response.[1] Ten years later this hypothesis was championed by Haig, who proposed low purine diets as a means to prevent hypertension and vascular disease.[2] During the same period the French academician, Henri Huchard, noted that renal arteriolosclerosis (the histological lesion of hypertension) was primarily observed in 3 groups: those with gout or lead poisoning or those with a diet enriched in fatty meat, all conditions associated with hyperuricemia.[3]

During the early 1900s there continued to be reports linking uric acid with hypertension.[4] In the 1960s and 1970s, at a time when hyperuricemia was present in ~5% of the US population,[5] an elevated uric acid level was observed in 40% to 60% of hypertensive subjects[6]; similarly, hypertension was observed in 50% to 65% of subjects with gout.[7] Cannon et al reported that hyperuricemia was observed in 25% of untreated hypertensive subjects, 50% of those on treatment, and 75% to 100% of those with malignant hypertension or renal dysfunction.[8] Population-based studies also found an increased frequency of hypertension with stepwise increases in serum uric acid levels in both blacks and whites.[9]

Whereas these studies confirmed initial impressions of a close association of uric acid with hypertension, the studies did not address causality. Indeed, most authorities proposed that the presence of hyperuricemia in the hypertensive subject likely reflected the fact that an elevated renal vascular resistance (which is present in hypertension) may favor increased reabsorption of urate and because the hypertensive phenotype often carries similar characteristics as the patient with gout (with increased frequency of obesity, alcohol use, renal dysfunction, male gender, black race, and diuretic use).[10] As a consequence, uric acid levels are largely ignored in medical practice, the uric acid measurement was removed from the routine laboratory (SMAC-20) panel, uric acid is not considered a risk factor for hypertension by either the American Heart Association[11] or the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[12] and asymptomatic hyperuricemia is currently considered benign and not requiring treatment.[13]

A key experiment that had not been performed was to determine the effect of mild hyperuricemia on blood pressure in animals. In this regard, most mammals have a low serum uric acid level because of the presence of uricase, a hepatic enzyme that degrades uric acid to allantoin. However, in humans the uricase gene is mutated, resulting in uric acid levels that are both higher and less regulatable than in other mammals. Interestingly, when mild hyperuricemia was induced in rats by the administration of a uricase inhibitor, they became hypertensive.[14] Further studies showed that the hypertension in this model was mediated by 2 mechanisms. The first mechanism resulted from uric acid–induced renal vasoconstriction mediated by endothelial dysfunction with reduced NO levels and by activation of the renin-angiotensin system.[14,15] This hypertension type is salt-resistant in that it occurs even in the presence of a low-salt diet, and it responds to lowering of uric acid.[14] Later, however, the hyperuricemia causes progressive renal microvascular disease (a lesion resembling arteriolosclerosis), and once sufficient narrowing of the arteriolar lumen occurs, a component of the hypertension becomes salt-driven, renal-dependent, and independent of uric acid levels.[16] Finally, further studies demonstrated that this microvascular disease resulted from direct effects of uric acid, in that the urate was shown to enter into the vascular smooth muscle cell where it caused cell proliferation, activated the local renin-angiotensin system, and stimulated the production of various inflammatory mediators including CRP and monocyte chemoattractant protein-1 (reviewed in Reference 17).

The identification of a biological mechanism by which uric acid could cause hypertension in humans has led to a renewed interest in the role of uric acid in hypertension. Indeed, there are now 9 studies that have examined whether an elevated uric acid level predicts the development of hypertension, and all found uric acid predictive (Table 1).[18–26] In all studies the risk for the development of hypertension was consistent and dose-dependent, and in the 8 studies in which multivariate analysis was performed to control for variables such as obesity, uric acid was always found to be an independent predictor (Table 1). Two of these studies are published in this issue. The first study, the Bogalusa Heart Study, found that uric acid levels in childhood predict the development of diastolic hypertension 10 years later.[25] The second study,

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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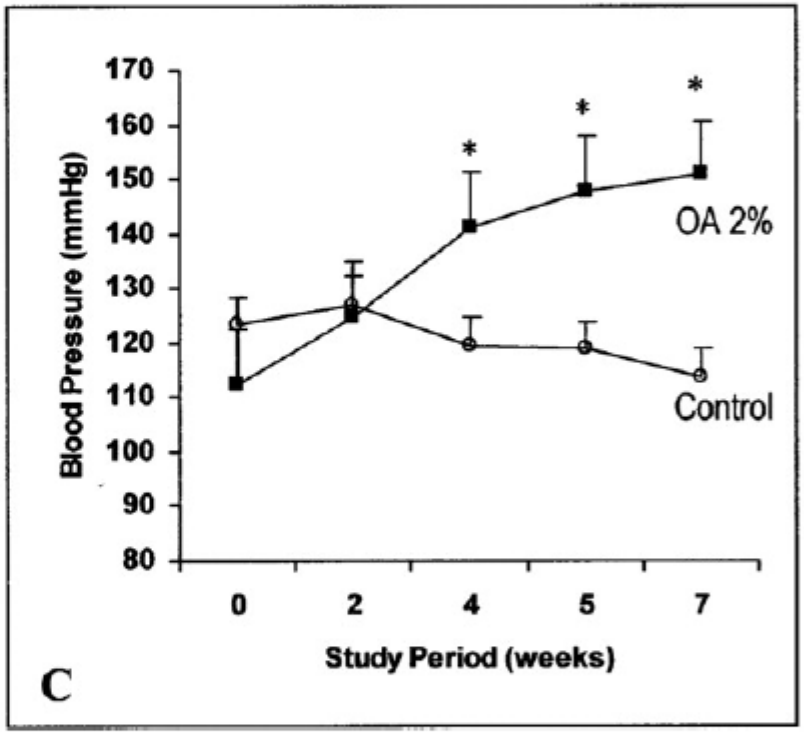
(*Hypertension*. 2005;45:18-20.)

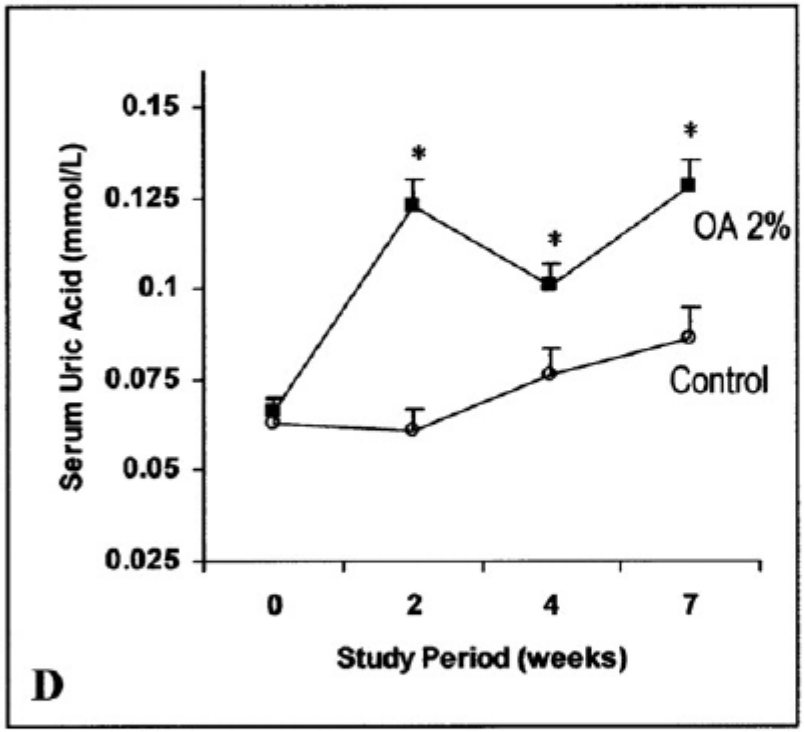
Hypertension is available at http://www.hypertensionaha.org

Hyperuricemia and development of HBP

Study	No. of Patients	Relative Risk of Hypertension	95% CI
Kaiser Permanente, 1990[53]	2062 adults	2.1 times greater at 6 yr (high vs. low quintile)	1.20–3.98
University of Utah, 1991[44]	1482 adults	1.44 times greater per SD increment at 7 yr	1.03–2.01
Olivetti Heart, 1994[46]	619 men	1.23 times greater per 1 mg/dl increase at 12 yr	1.07–1.39
CARDIA, 1999[42]	5115 men	1.21 times greater per SD increment at 10 yr	1.03–1.41
Osaka Health Survey, 2001[56]	6356 men	2 times greater at 10 yr (high vs. low quintile)	1.56–2.60
Hawaii–Los Angeles–Hiroshima, 2001[45]	140 men	2.0 times greater at 15 yr (high vs. low quartile)	1.02–3.9
Osaka Factory, 2003[48]	433 men	1.0 mg/dl, increased 27 mm Hg SBP at 5 yr	Not calculated
Osaka Health Survey, 2003[51]	2310 men	1.13 times greater per SD increment at 6 yr	1.06–1.21
Okinawa, 2004[50]	4489 adults	1.46 times greater for men (uric acid ≥7 mg/dl) and 1.94 for women (uric acid ≥6 mg/dl) at 13yr	1.09–2.03 1.05–3.57
Bogalusa Heart, 2005[41]	679 children	Increased risk for diastolic hypertension at 11 yr	Not calculated
Framingham Heart, 2005[55]	3329 adults	1.17 times greater per SD increment at 4 yr	1.02–1.33
Normative Aging, 2006[52]	2062 men	125 times greater at 21 yr (uric acid >6.5 mg/dl)	1.08–1.34
ARIC, 2006[49]	9104 adults	1.1 times greater per SD increment at 9 yr	1.02–1.14
Beaver Dam Health Survey, 2006[54]	2520 adults	1.65 times greater at 10 yr (high vs. low quintile)	1.41–1.93
Health Professionals' Follow-up, 2006[43]	750 men	1.02 times greater per SD increment at 8 yr	0.92–1.13
MRFIT, 2007[47]	3073 men	1.1 times greater per SD increment at 6 yr	1.02–1.19

Hyperuricemia and Blood pressure in rats

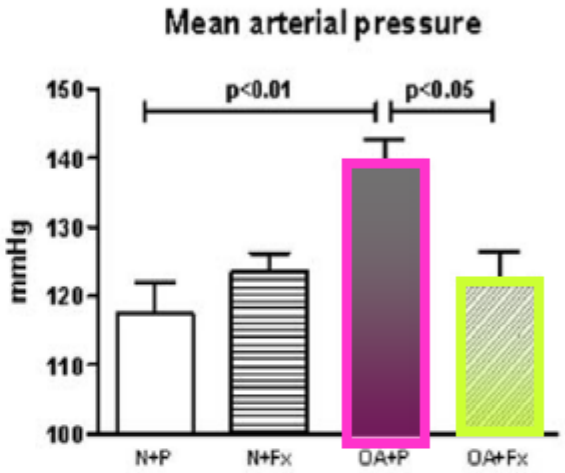


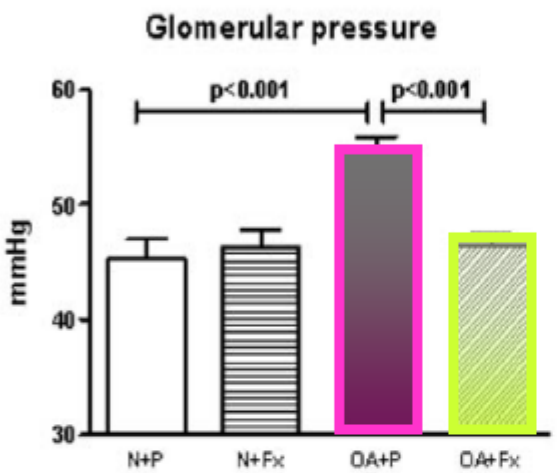


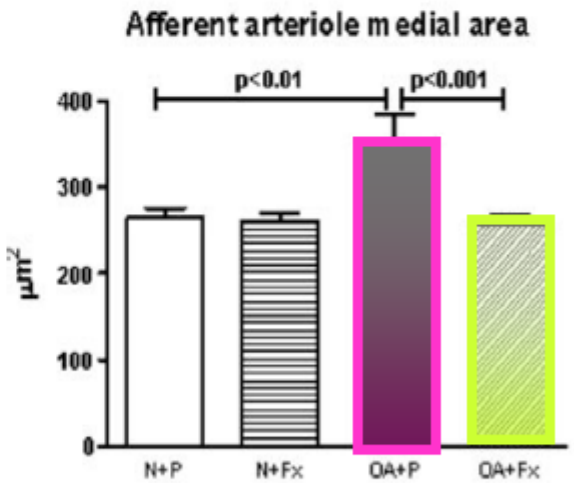
American Heart Association
Learn and Live

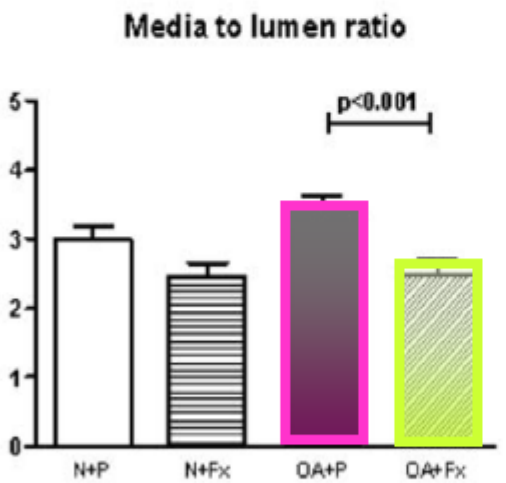
Mazzali M et al. Hypertension 2001;38:1101-1106

Febuxostat attenuates arteriolosclerosis and systemic and glomerular hypertension in rats





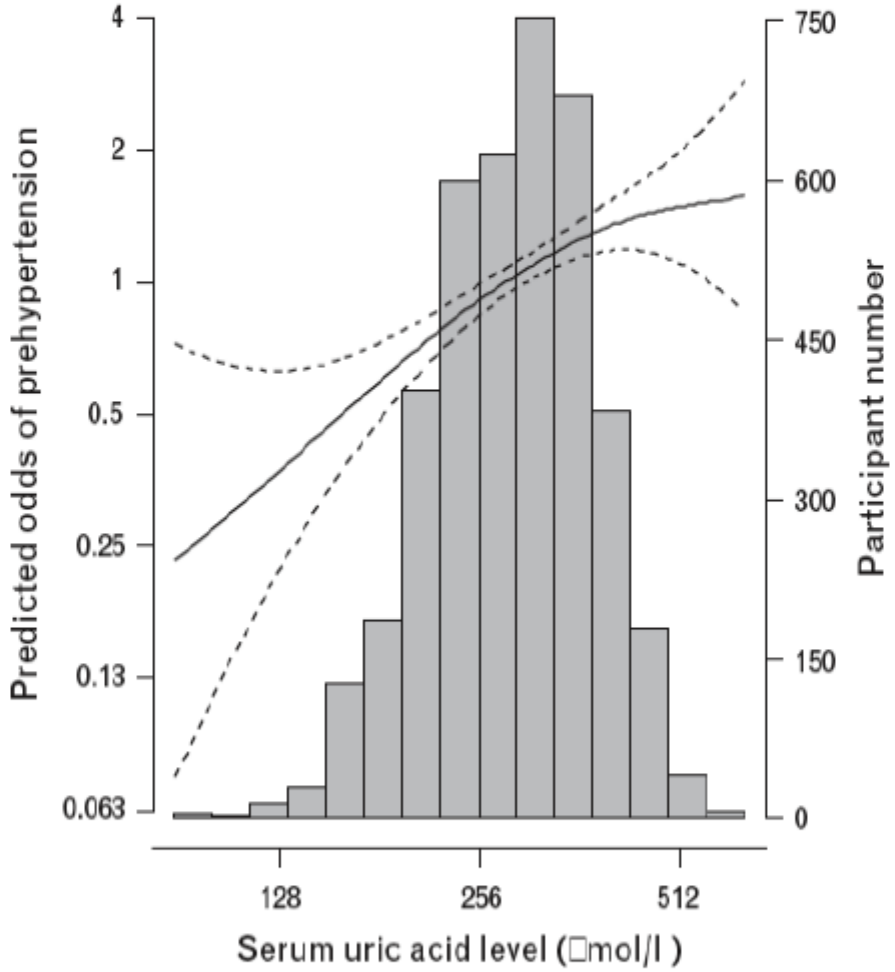




Sanchez-Lozada LG, NDT 2008

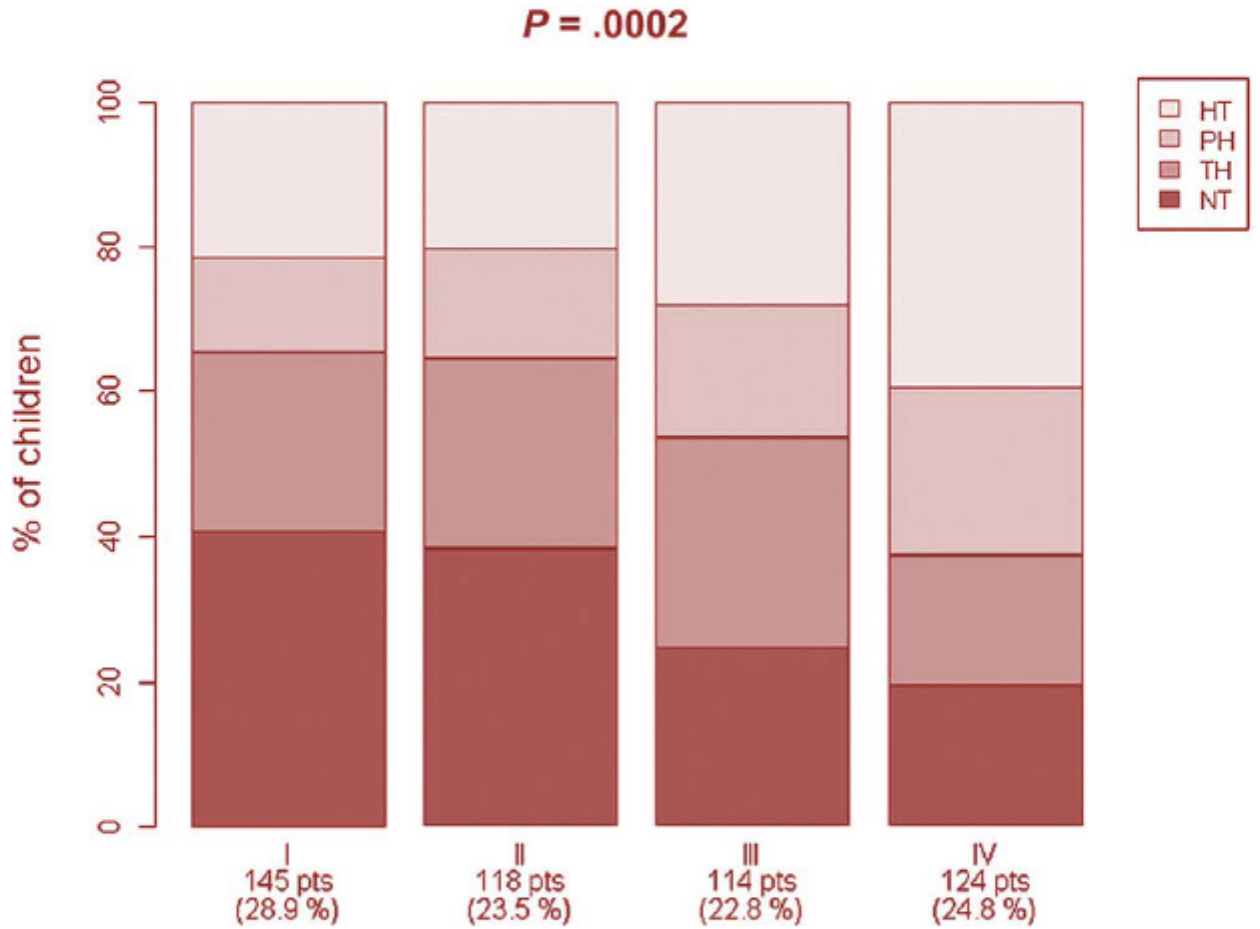
Association between serum uric acid and prehypertension among US adults

Shirmila Syamala[a], Jialiang Li[b] and Anoop Shankar[a]



Syamala S et al, J Hypertens 2007

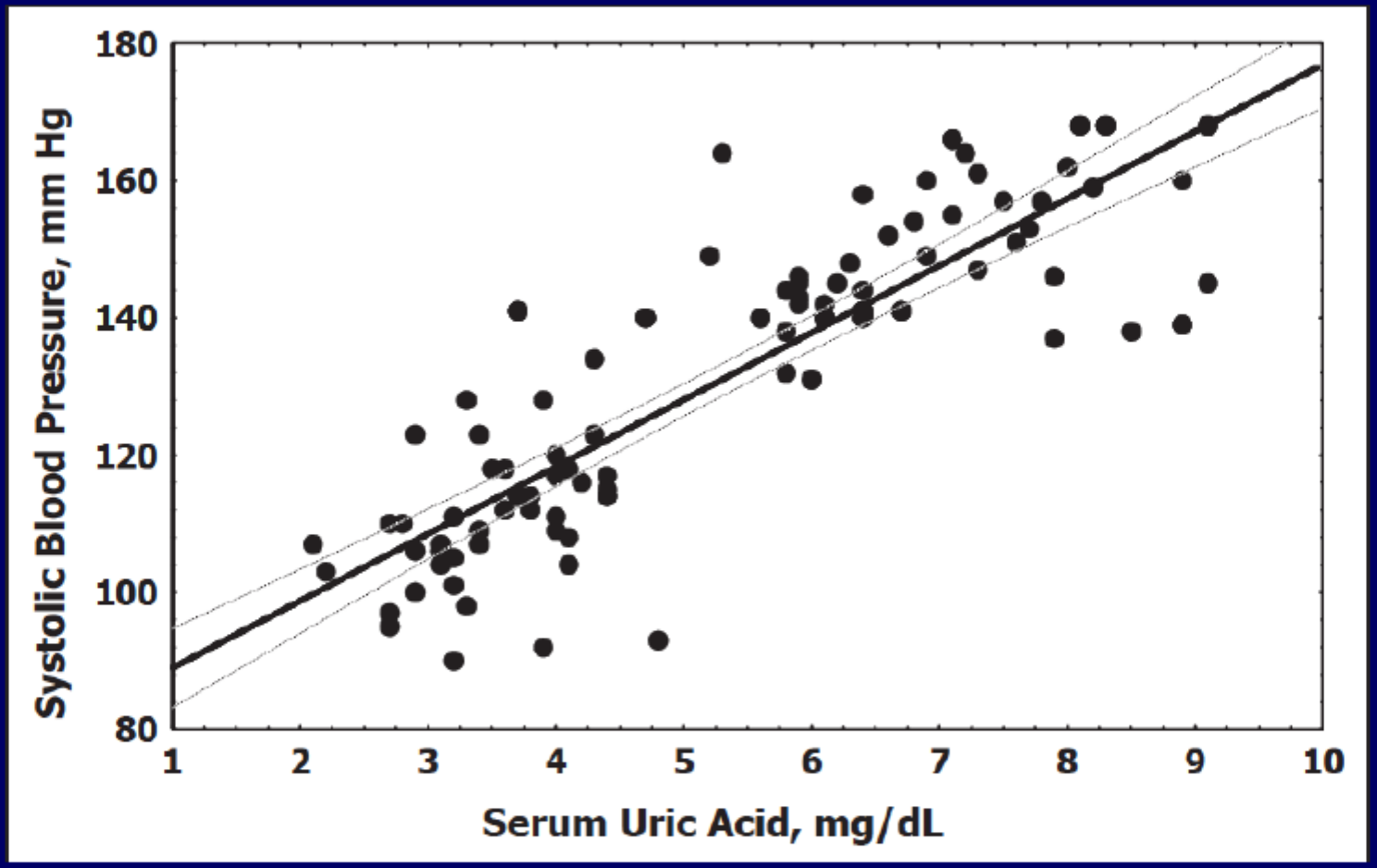
Distribution of BP categories according to UA quartiles in pediatric population (501 subjects 6-18 ys)



Viazzi F et al. Pediatrics 2013;132:e93-e99

PEDIATRICS

Rapporto tra uricemia e PA sistolica in bambini normotesi e con ipertensione essenziale



Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension. 2003;42:247–252.

Childhood Uric Acid Predicts Adult Blood Pressure

The Bogalusa Heart Study

Arnold B. Alper Jr, Wei Chen, Lillian Yau, Sathanur R. Srinivasan, Gerald S. Berenson, L. Lee Hamm

Abstract—Uric acid has been proposed as an important risk factor in the development of primary hypertension in humans. However, limited information is available linking childhood uric acid levels and blood pressure levels in adulthood. This study examined 334 whites and 243 blacks enrolled in the Bogalusa Heart Study as children aged 5 to 17 years and as adults aged 18 to 35 years. The average follow-up period was 12 years. Childhood uric acid was significantly correlated with childhood and adult blood pressure, both systolic and diastolic. In a multivariate regression analysis, adjusting for age, sex, race, childhood body mass index, childhood uric acid levels, and change in levels of uric acid were significant predictors of adult diastolic blood pressure, whereas change in uric acid was a significant predictor of adult systolic blood pressures. In conclusion, elevated childhood serum uric acid levels are associated with increased blood pressure beginning in childhood and higher blood pressure levels that persist into adulthood, in males and females, whites and blacks, suggesting that early elevations in serum uric acid levels may play a key role in the development of human hypertension. **(*Hypertension*. 2005;45:34-38.)**

Predictors of adult HBP

Independent Variable	Regression Coefficient	*P* Value
SBP		
Race	2.36	0.002
Sex	−5.95	<0.001
Childhood age	−0.58	<0.001
Δ Age	0.59	<0.001
Childhood BMI	0.37	<0.001
Childhood SBP	0.48	<0.001
Childhood uric acid	0.63	0.067
Δ Uric acid	5.85	0.025
DBP		
Race	0.62	0.36
Sex	−2.38	0.002
Childhood age	−0.058	0.63
Δ Age	0.61	<0.001
Childhood BMI	0.23	0.002
Childhood DBP	0.23	<0.001
Childhood uric acid	0.79	0.008
Δ Uric acid	6.27	0.011

Δ uric acid indicates change in serum uric acid levels from childhood to adulthood; Δ age, change in age between baseline and follow-up.

Uric Acid Level and Elevated Blood Pressure in US Adolescents

National Health and Nutrition Examination Survey, 1999–2006

Lauren F. Loeffler, Ana Navas-Acien, Tammy M. Brady, Edgar R. Miller III, Jeffrey J. Fadrowski

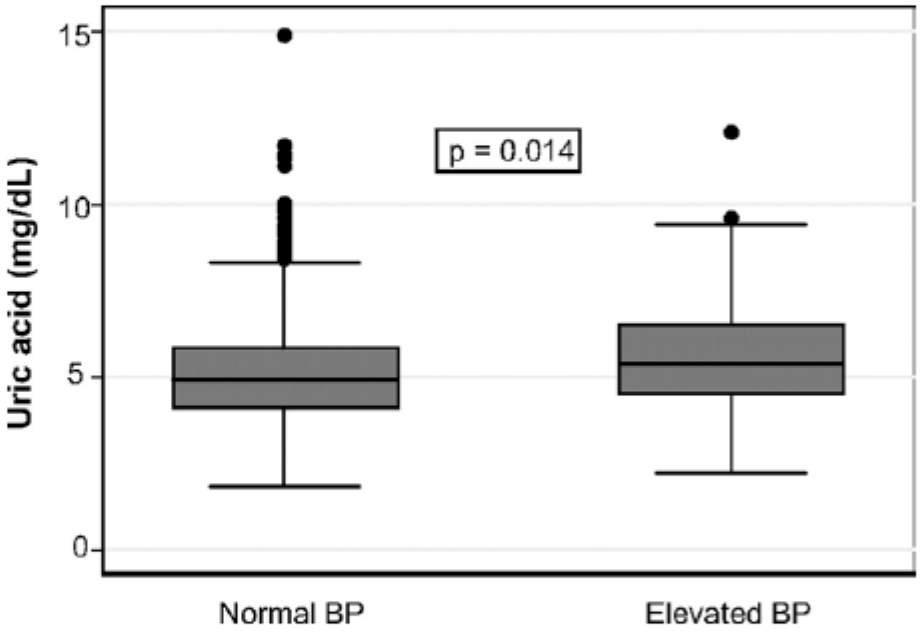


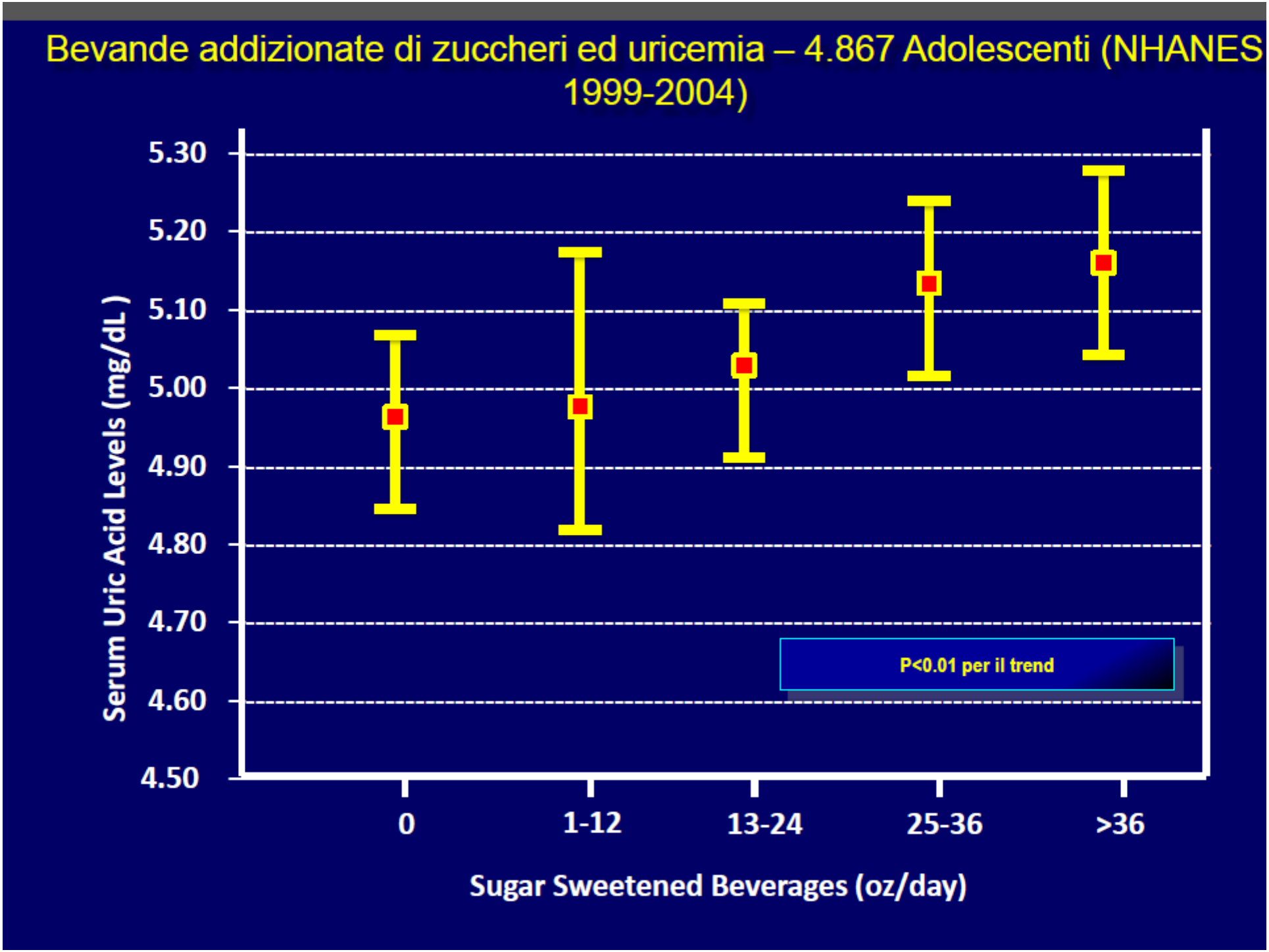
Table 1. Demographic and Clinical Characteristics Among Adolescents With Normal and Elevated Blood Pressure, National Health and Nutrition Examination Survey 1999–2006

Characteristic*	Normal Blood Pressure, N=5827 (96.7%)	Elevated Blood Pressure, N=209 (3.3%)	*P*
Age, y	14.5 (0.04)	14.4 (0.1)	0.22
Sex, % male	51	52	0.82
Uric acid ≥5.5 mg/dL, %			
Overall	33	50	<0.001
Males	53	76	0.002
Females	12	22	0.02
eGFR, mL/min/1.73 m^2	144 (0.8)	143 (1.8)	0.59

OR for HBP (> 5.5 mg/dL) =2.03 (95% CI 1.38-3.0)

Loeffler L F et al. Hypertension 2012;59:811-817

American Heart Association
Learn and Live


Bevande addizionate di zuccheri ed uricemia – 4.867 Adolescenti (NHANES 1999-2004)
Serum Uric Acid Levels (mg/dL)
5.30
5.20
5.10
5.00
4.90
4.80
4.70
4.60
4.50
P<0.01 per il trend
0
1-12
13-24
25-36
>36
Sugar Sweetened Beverages (oz/day)

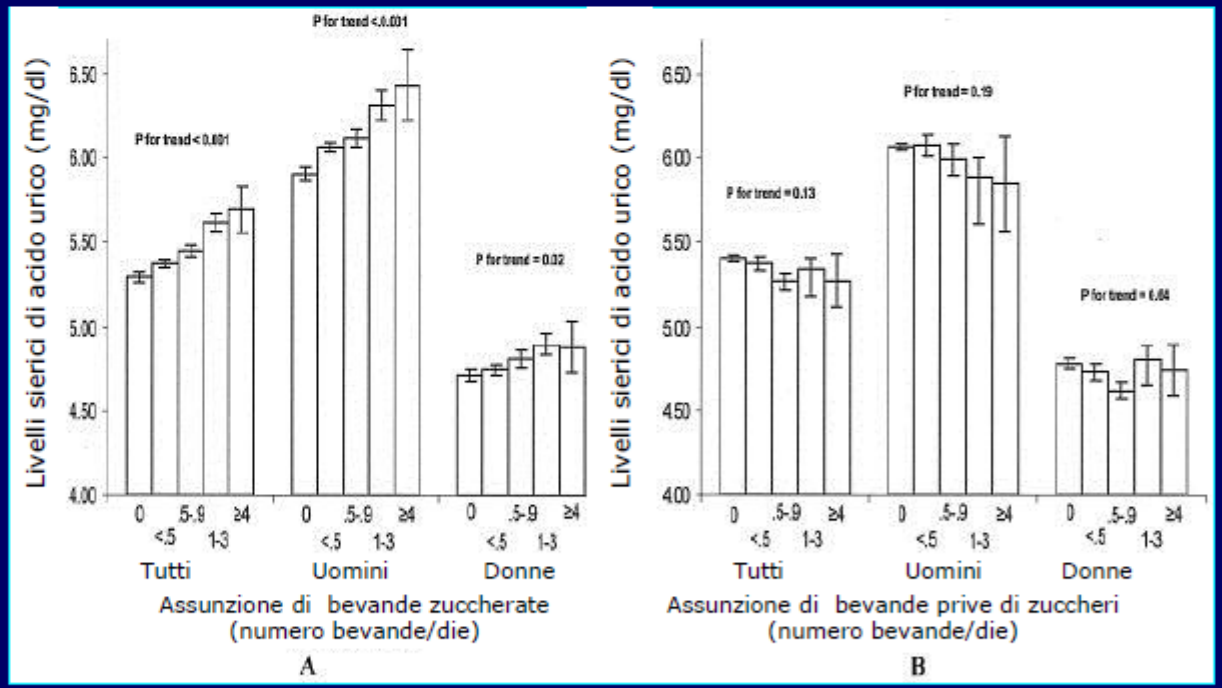
Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: The third national health and nutrition examination survey

FRUTTOSIO →

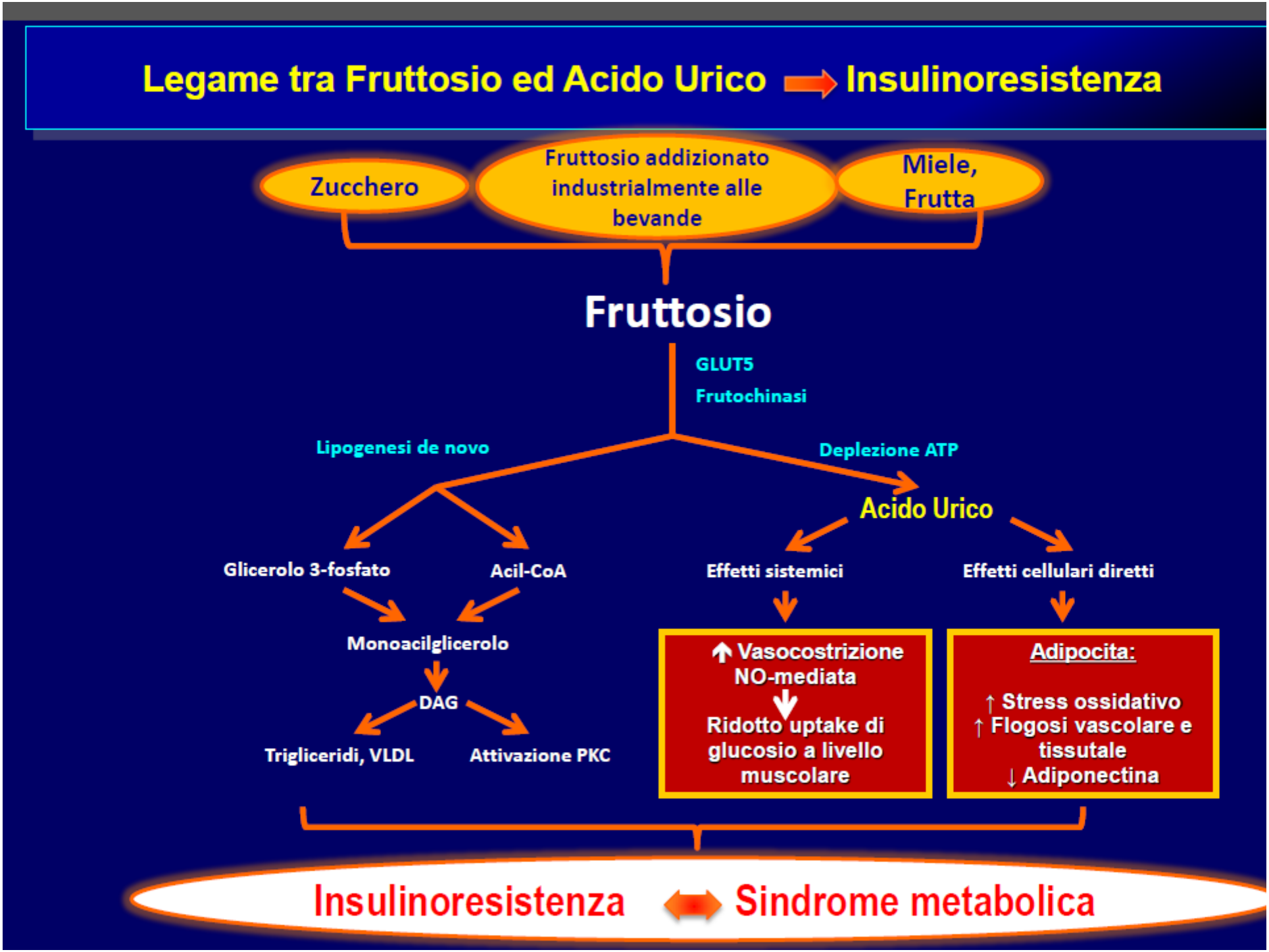
- Frutta
- Verdura

e ...

- Bevande zuccherate
- Dolcificanti
- Dolci e cibi raffinati industrialmente



Nel Third National Health and Nutrition Examination Survey (1988-1994) condotto in 14.761 soggetti sani (età ≥ 20 anni) si è evidenziata una correlazione diretta tra assunzione di bevande zuccherate ricche in fruttosio e livelli sierici di acido urico (A), correlazione che viceversa non è emersa in seguito ad assunzione di bevande prive di zuccheri (B).

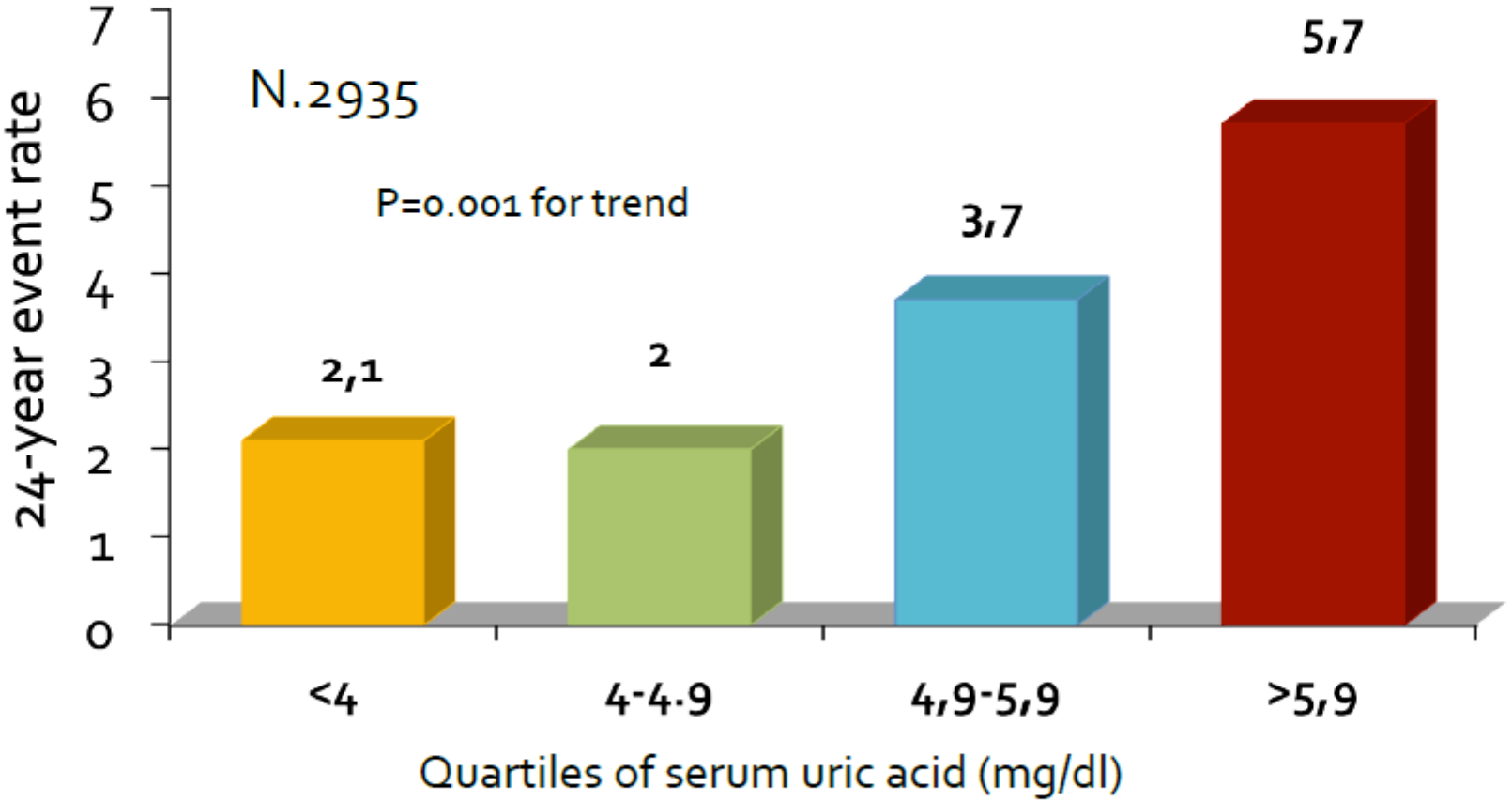

Legame tra Fruttosio ed Acido Urico
Insulinoresistenza
Zucchero
Fruttosio addizionato industrialmente alle bevande
Miele, Frutta
Fruttosio
GLUT5
Frutochinasi
Lipogenesi de novo
Deplezione ATP
Acido Urico
Glicerolo 3-fosfato
Acil-CoA
Monoacilglicerolo
DAG
Trigliceridi, VLDL
Attivazione PKC
Effetti sistemici
Effetti cellulari diretti
↑ Vasocostrizione NO-mediata
Ridotto uptake di glucosio a livello muscolare
Adipocita:
↑ Stress ossidativo
↑ Flogosi vascolare e tissutale
↓ Adiponectina
Insulinoresistenza
Sindrome metabolica

Relationship between SUA and CV-TOD

A relationship has been demonstrated between:

- SUA and LV mass and structure, *Tze-Fan Chao et al, In J Cardiol 2013*
- SUA and IMT, *Borghi C et al, J Hypertens 2013*
- SUA and PWV, *Borghi C et al, J Hypertens 2013*
- SUA and microalbuminuria, *Viazzi F, et al. Am J Hypertens 2007*
- SUA and Renal Vascular Resistance, *Viazzi F, et al. Am J Hypertens 2007*

Multivariate analysis of SUA and CV event rate in the overall population of the Brisighella Heart Study

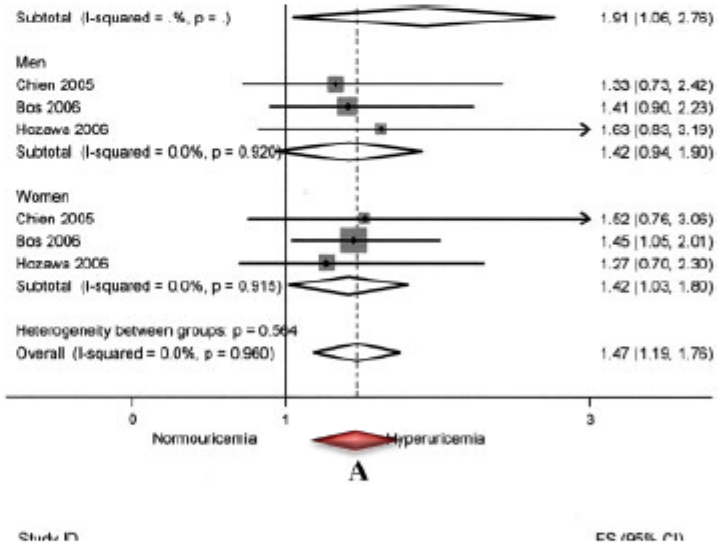


Borghi C et al Clinical Lipidology 2011

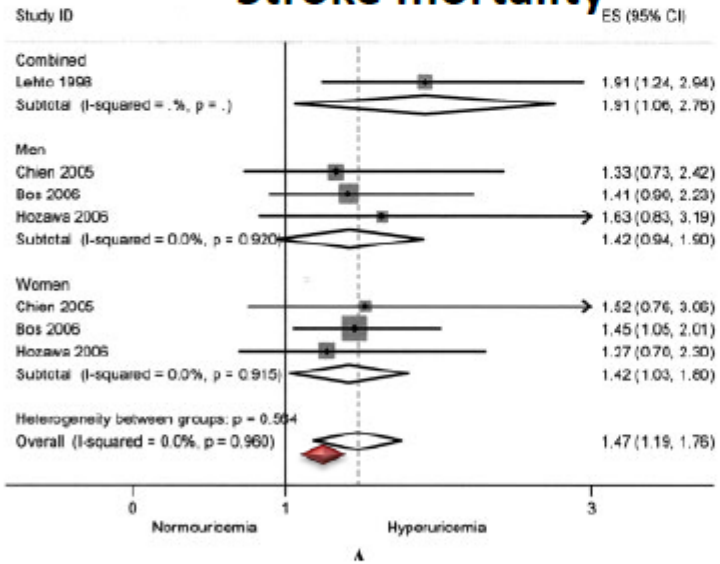
tis Care & Research)
Vol. 61, No. 7, July 15, 2009, pp 885–892
DOI 10.1002/art.24612

ORIGINAL ARTICLE

Stroke incidence

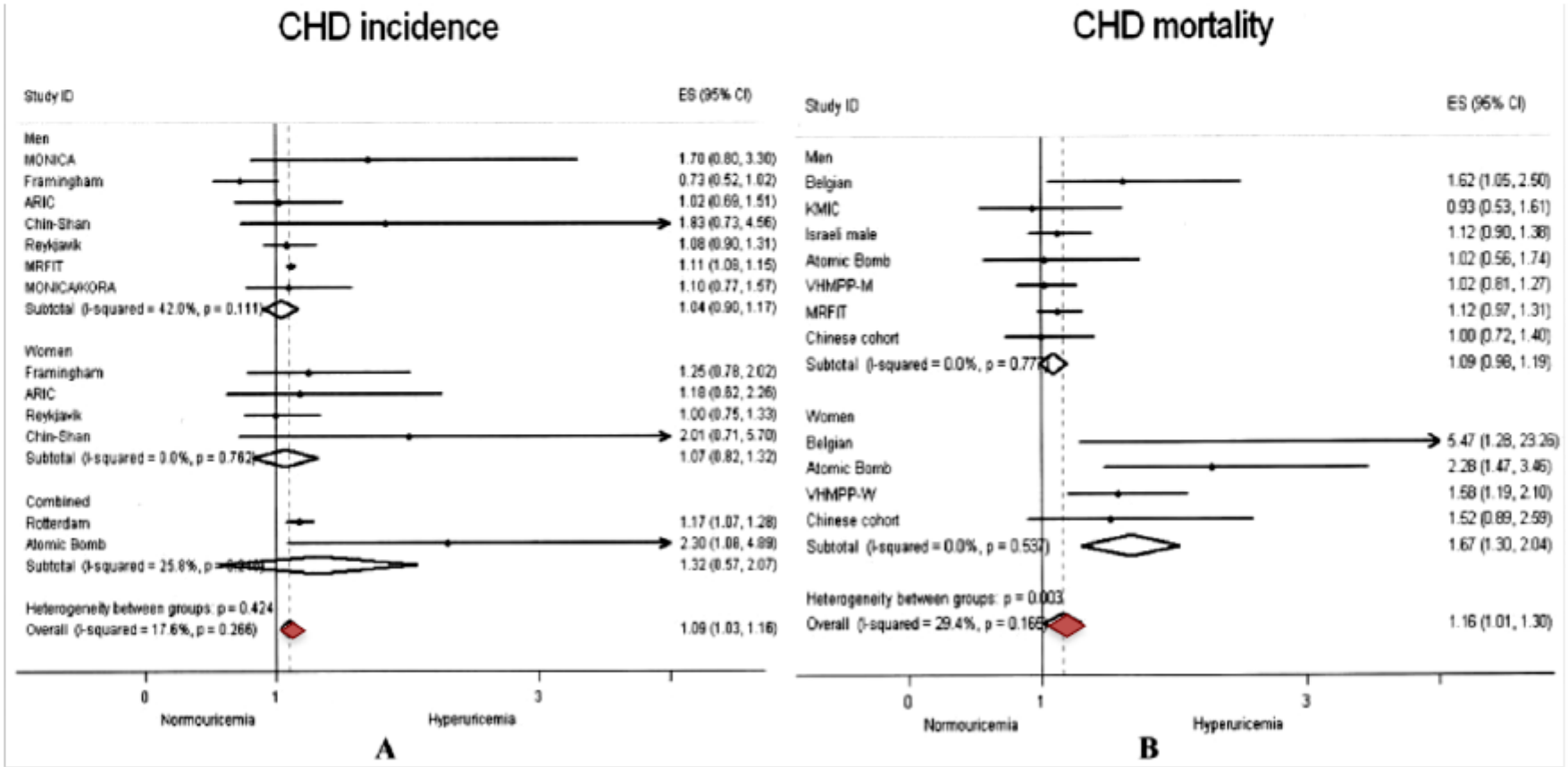


Stroke mortality



o. 2, February 2010, pp 170–180
DOI 10.1002/acr.20065

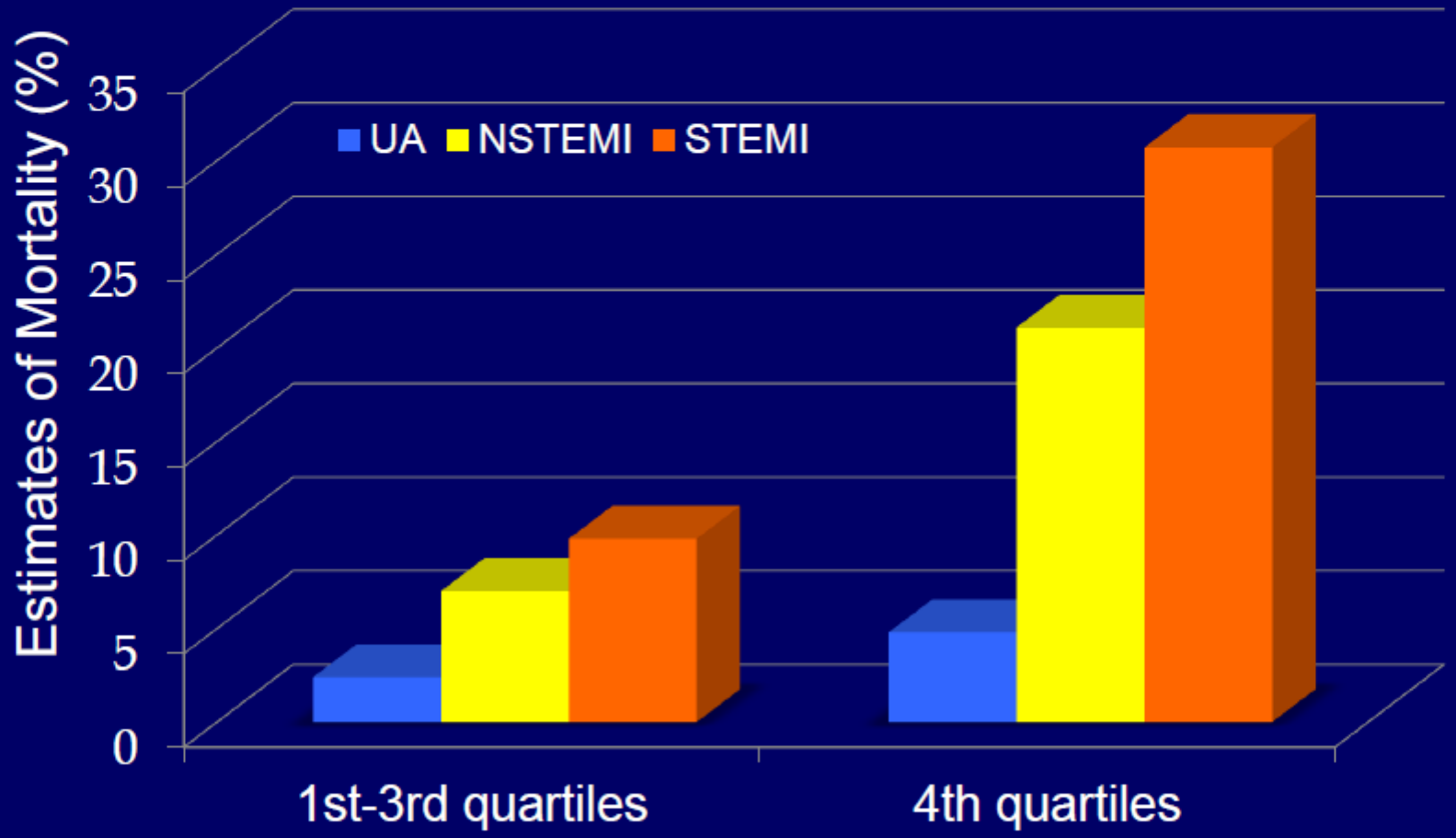
ORIGINAL ARTICLE



Prognostic Value of Uric Acid in Patients With Acute Coronary Syndromes

1.629 STEMI, 1.332 NSTEMI, 2.163 UA

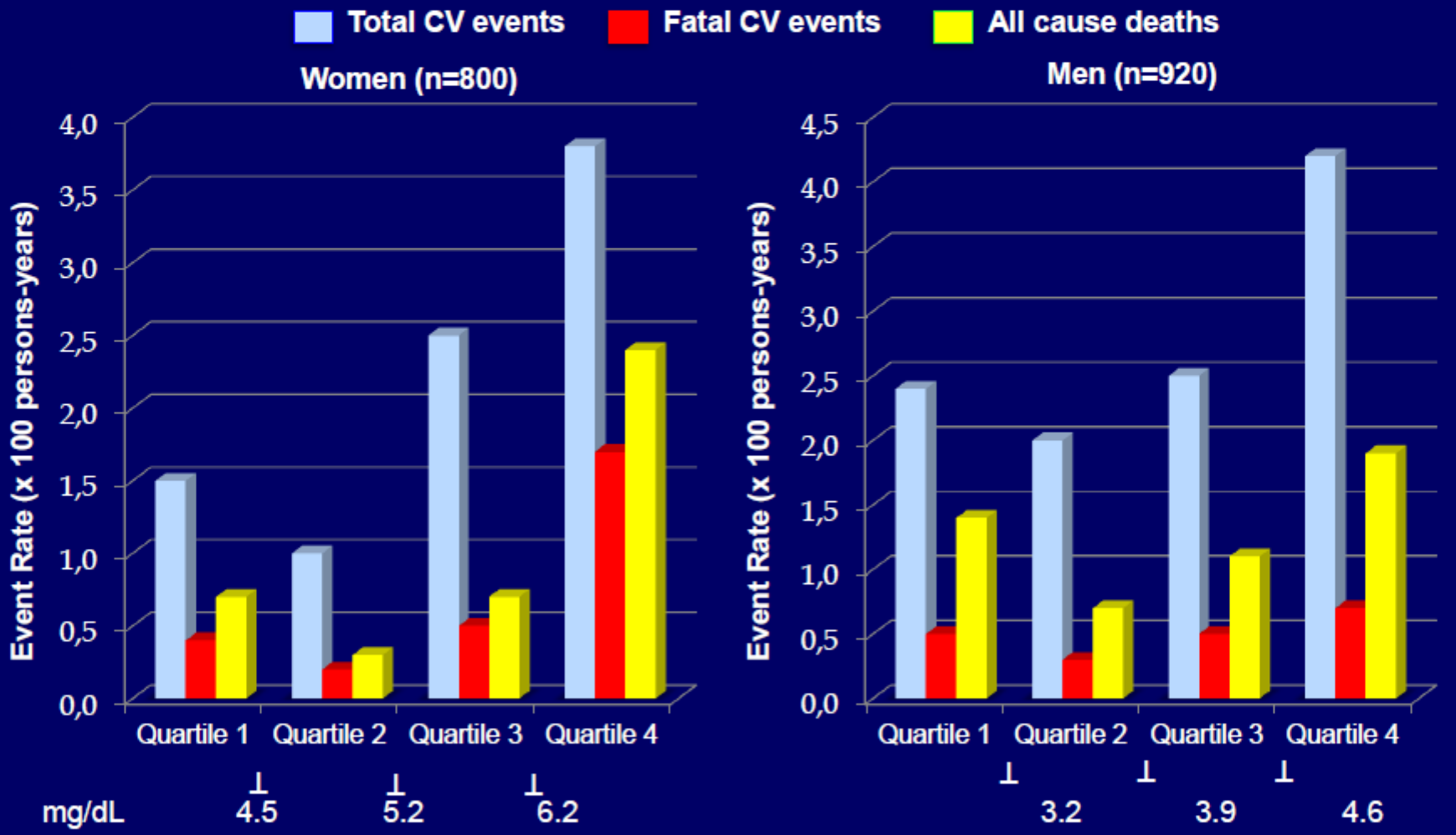
12% increase in the adjusted risk for 1-year mortality for every 1 mg/dL increase in SUA



Ndrepepa G et a Am J Cardiol 2012;109:1260 –1265l.

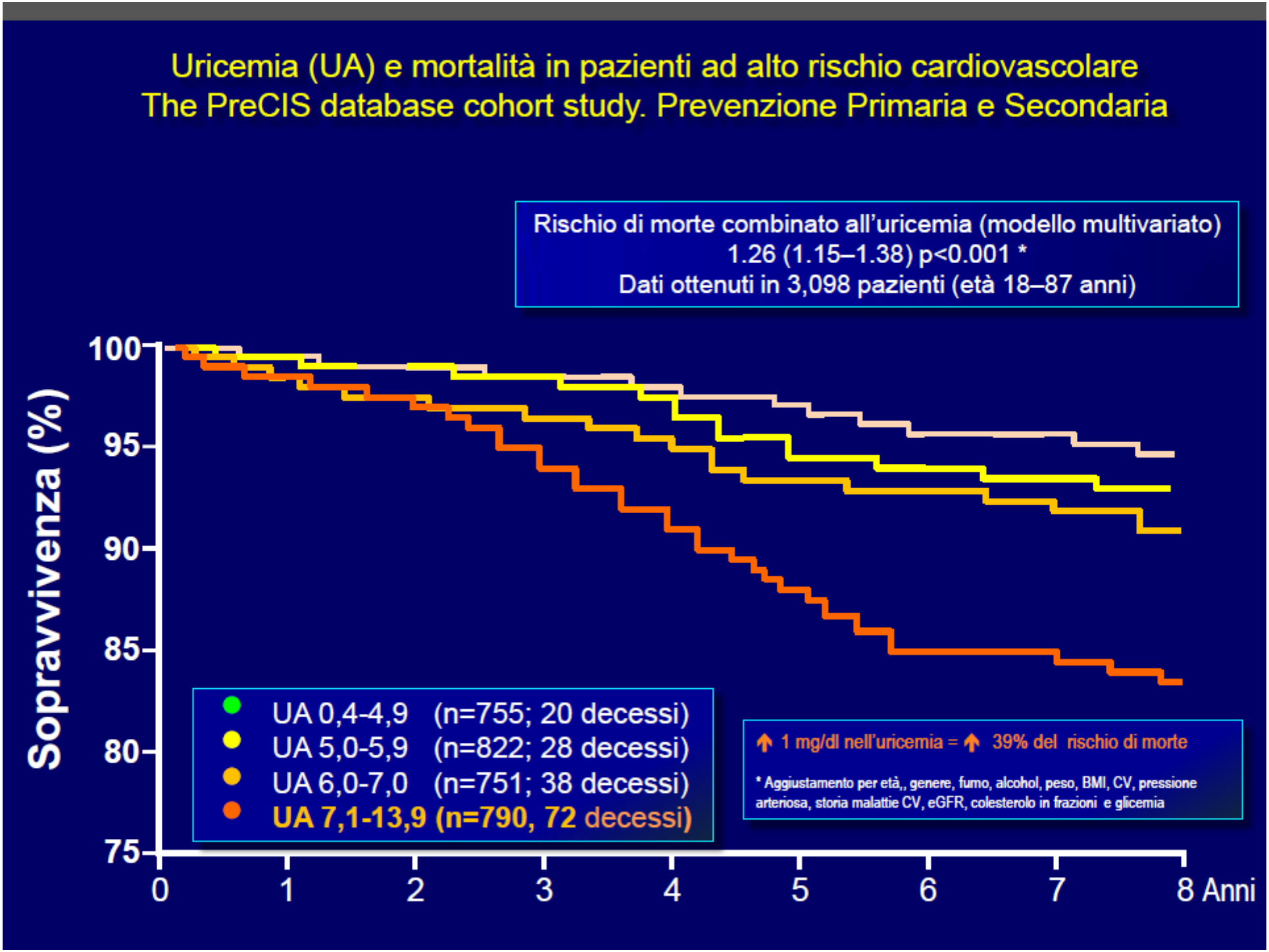
Relation Between Serum Uric Acid and Risk of CVD in Essential Hypertension: The PIUMA Study

1720 subjects with EH, untreated, screened for absence of cardiovascular disease, renal disease, cancer, and other important disease. Follow-up up to 12 years (mean, 4.0) we followed

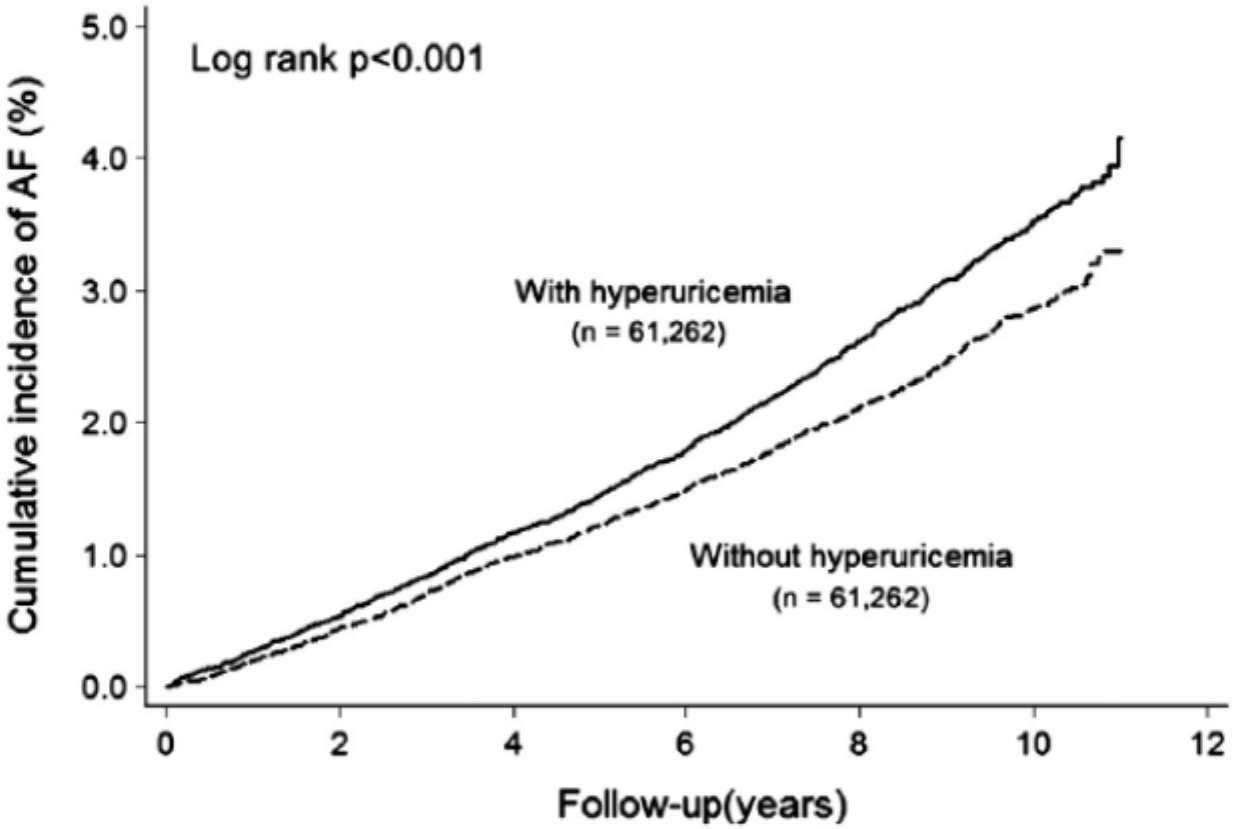


Verdecchia P et al. Hypertension. 2000;36:1072-1078.)

Uricemia (UA) e mortalità in pazienti ad alto rischio cardiovascolare
The PreCIS database cohort study. Prevenzione Primaria e Secondaria



Cumulative incidence of AF in patients with and without elevated SUA in the NHIRD cohort (Taiwan).



Tze-Fan Chao et al, In J Cardiol 2013

Summary of studies investigating the relationship between UA and AF

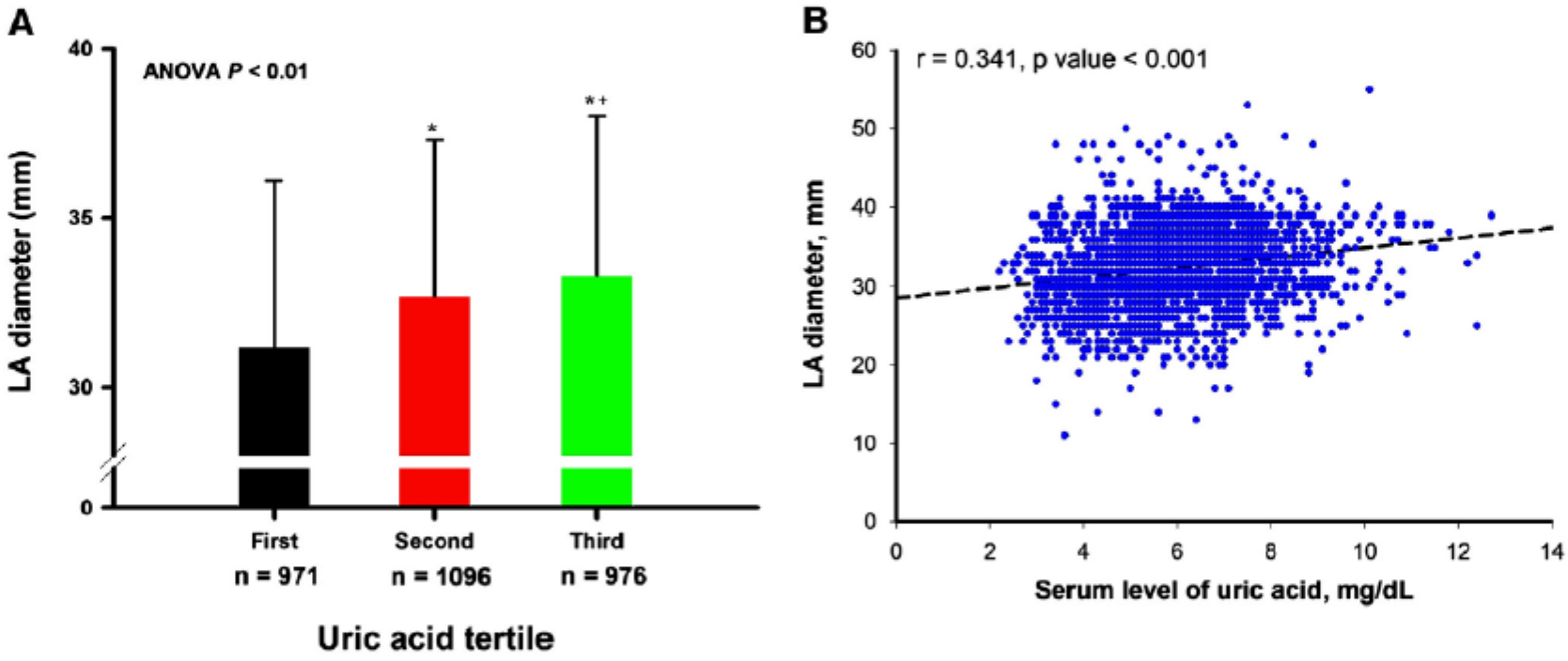
Table 5
Summary of the studies investigating the relationship between UA and AF.

Author (year)	Study design	Patient number	Age, years	Main findings
Letsas et al. [17]	Cross-section	Paroxysmal AF: 45 Persistent AF: 41 Non-AF: 86	Paroxysmal AF: 67.4 ± 8.8 Persistent AF: 71.9 ± 9.9 Non-AF: 61.3 ± 14.7	UA level was associated with permanent AF (OR = 2.712; 95% CI = 1.327–3.555; p = 0.002).[a]
Liu et al. [18]	Cross-section	451 patients with hypertension — AF: 50 Non-AF: 401	AF: 61.8 ± 9.2 Non-AF: 54.9 ± 12.1	Independent association between UA level and AF was noted (OR = 1.008; 95% CI = 1.003–1.013; p = 0.002).[b]
Tamariz et al. [19]	Longitudinal cohort	15,382 AF-free patients (1085 cases of new-onset AF during the median follow-up duration of 16.8 years)	45–64 years at enrollment	Baseline UA level was a predictor of AF (HR = 1.16; 95% CI = 1.06–1.26 per 1 standard deviation of increasing UA level; p < 0.01).[c] Subgroup analyses showed that baseline UA levels were associated with AF in blacks and women, but not in whites and men.
Suzuki et al. [20]	Cross-section	AF: 1131 Non-AF: 6024	Male: 57.1 ± 13.8 Female: 60.7 ± 15.2	Adjusted OR for AF was 1.176 (95% CI = 0.935–1.478) in males and 1.888 (95% CI = 1.278–2.790) in females.[d]

AF = atrial fibrillation; CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HR = hazard ratio; OR = odds ratio; RAS = renin–angiotensin system; UA = uric acid.

Tze-Fan Chao et al, In J Cardiol 2013

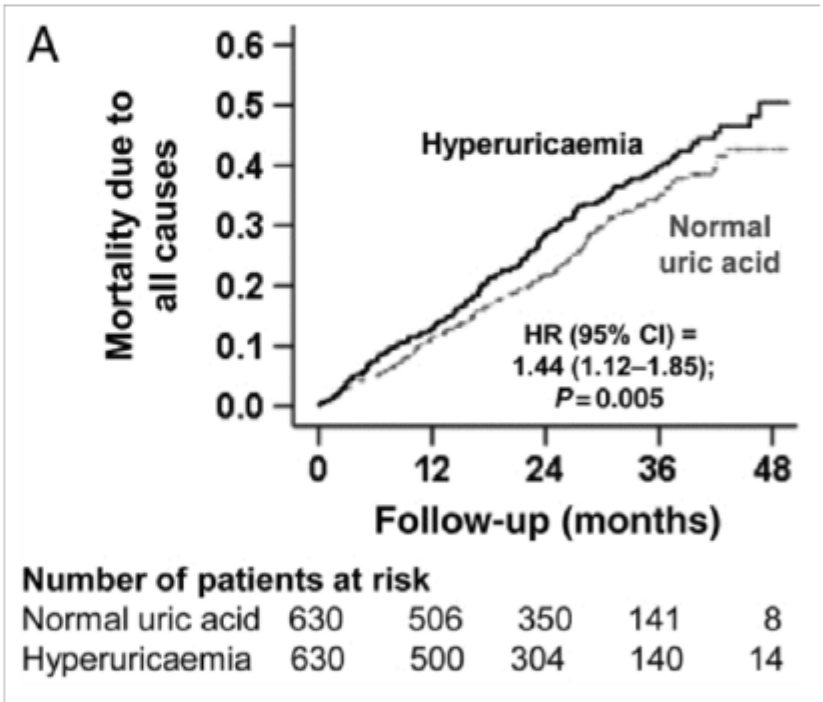
Relationship between LA diameter and SUA in patients with elevated SUA



Tze-Fan Chao et al, In J Cardiol 2013

Kaplan-Meier plots for all-cause mortality and HF hospitalization in patients with CHF

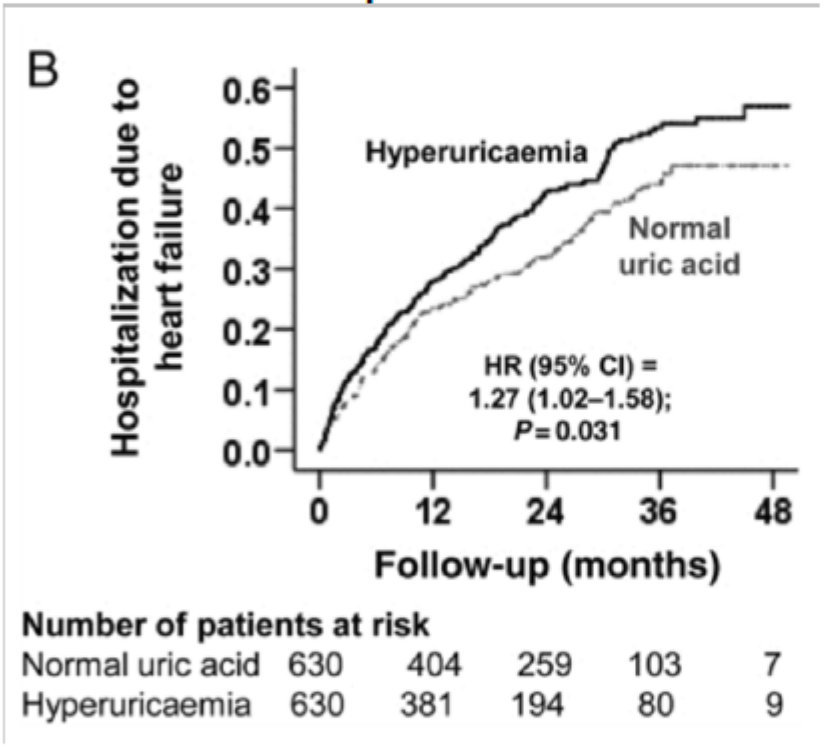
All-cause mortality



Number of patients at risk

Normal uric acid	630	506	350	141	8
Hyperuricaemia	630	500	304	140	14

Hospitalization for HF

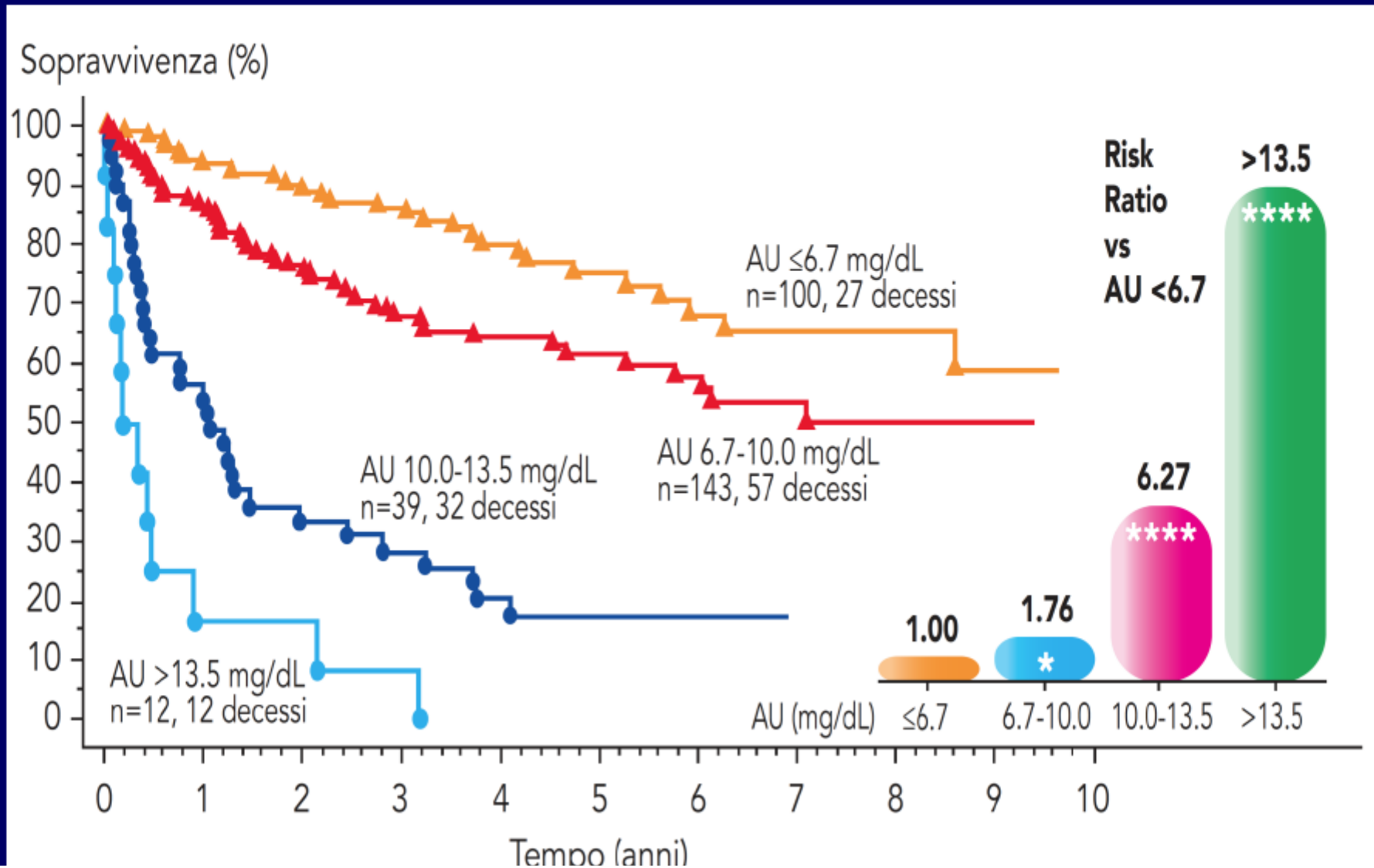


Number of patients at risk

Normal uric acid	630	404	259	103	7
Hyperuricaemia	630	381	194	80	9

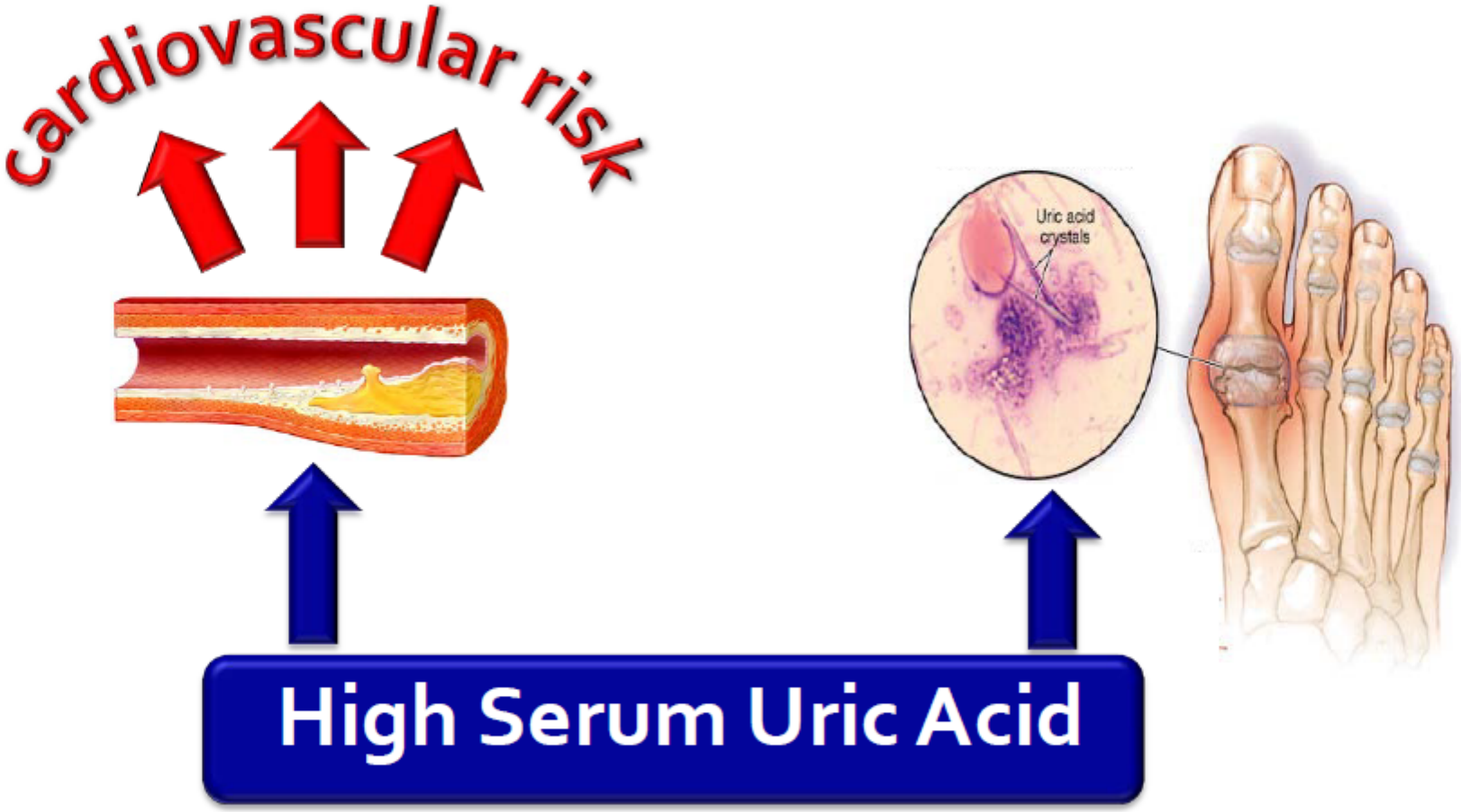
Filippatos GS et al, Eur Heart J, 2011

Curve di sopravvivenza di Kaplan-Meier distinte per livelli di acido urico in pazienti con scompenso cardiaco lieve-moderato

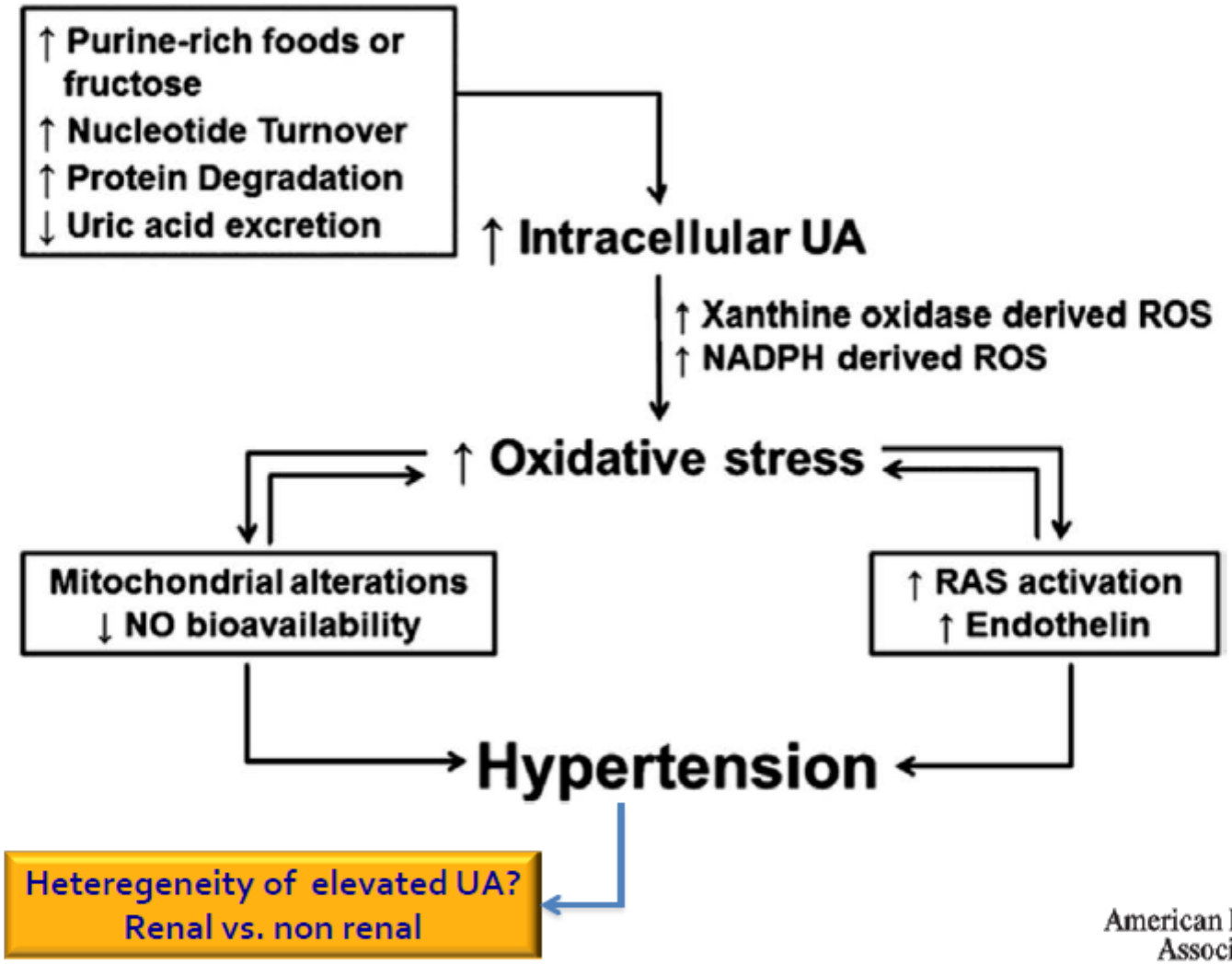


SUA and CV disease: what is the mechanism(s)?

SUA, tissue deposition and CV risk



Proposed mechanisms leading from UA to HBP & CVD

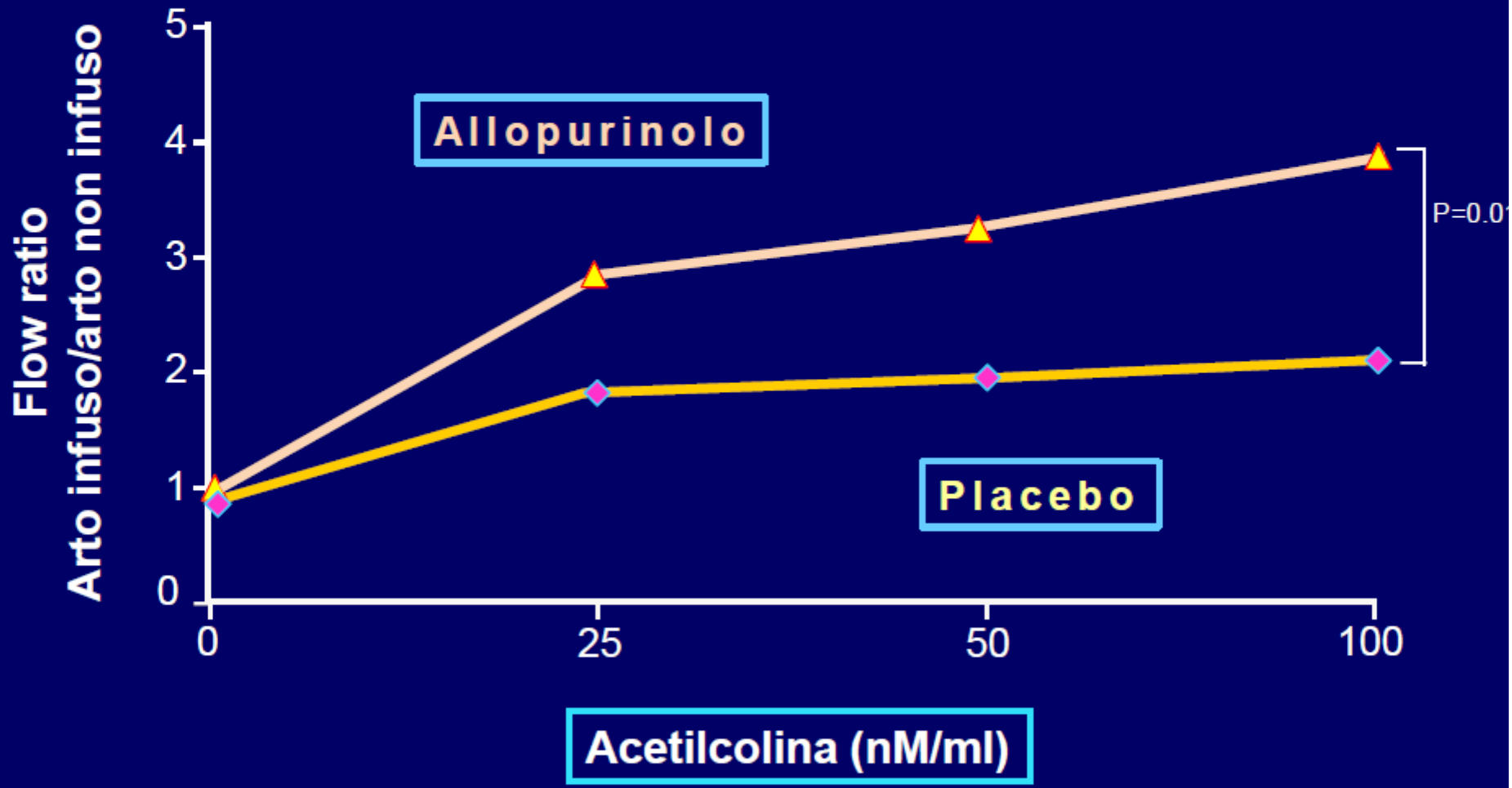


Johnson R J et al. Hypertension 2013;61:948-951

American Heart Association
Learn and Live

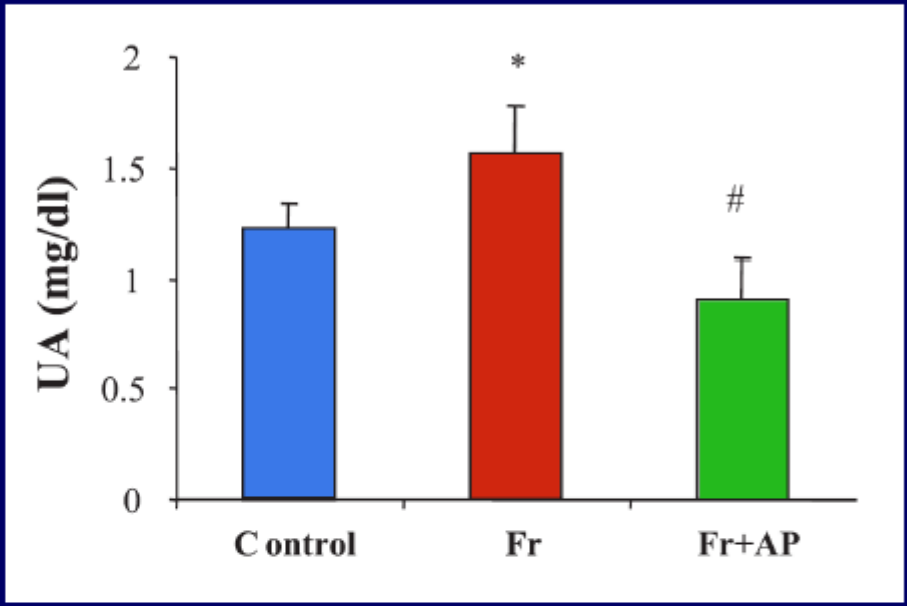
La riduzione dell'uricemia migliora la biodisponibilità di NO nel *diabete di tipo 2*

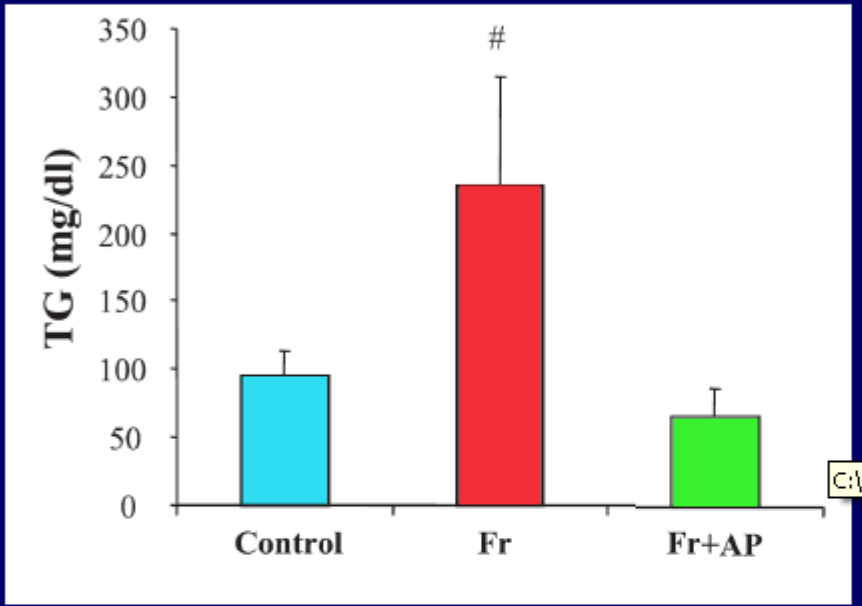
La riduzione dell'uricemia, malgrado l'allopurinolo non abbia propri effetti vascolari, induce vasodilatazione NO-mediata.
Ciò dimostra che l' acido urico riduce la biodisponibilità di NO

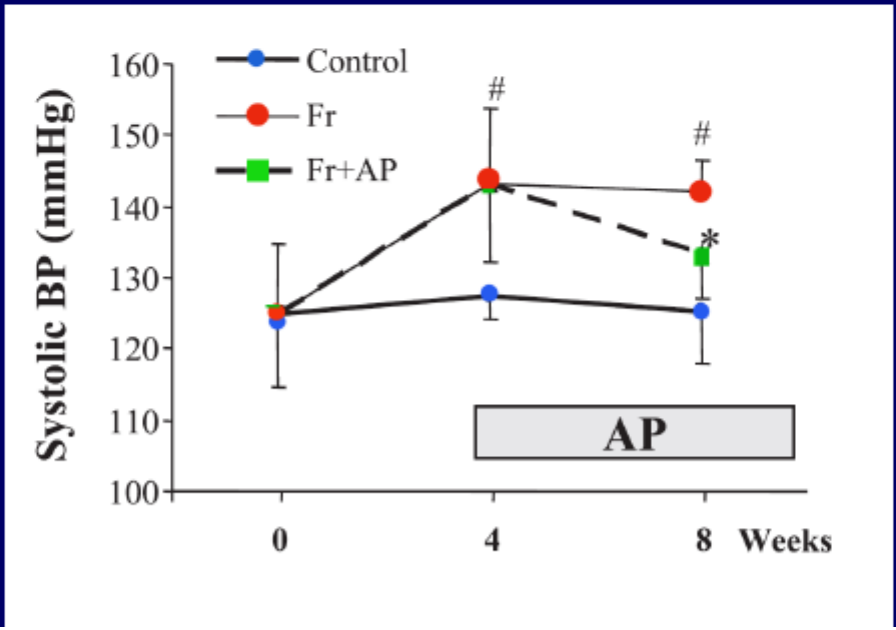


Therapeutic evidence

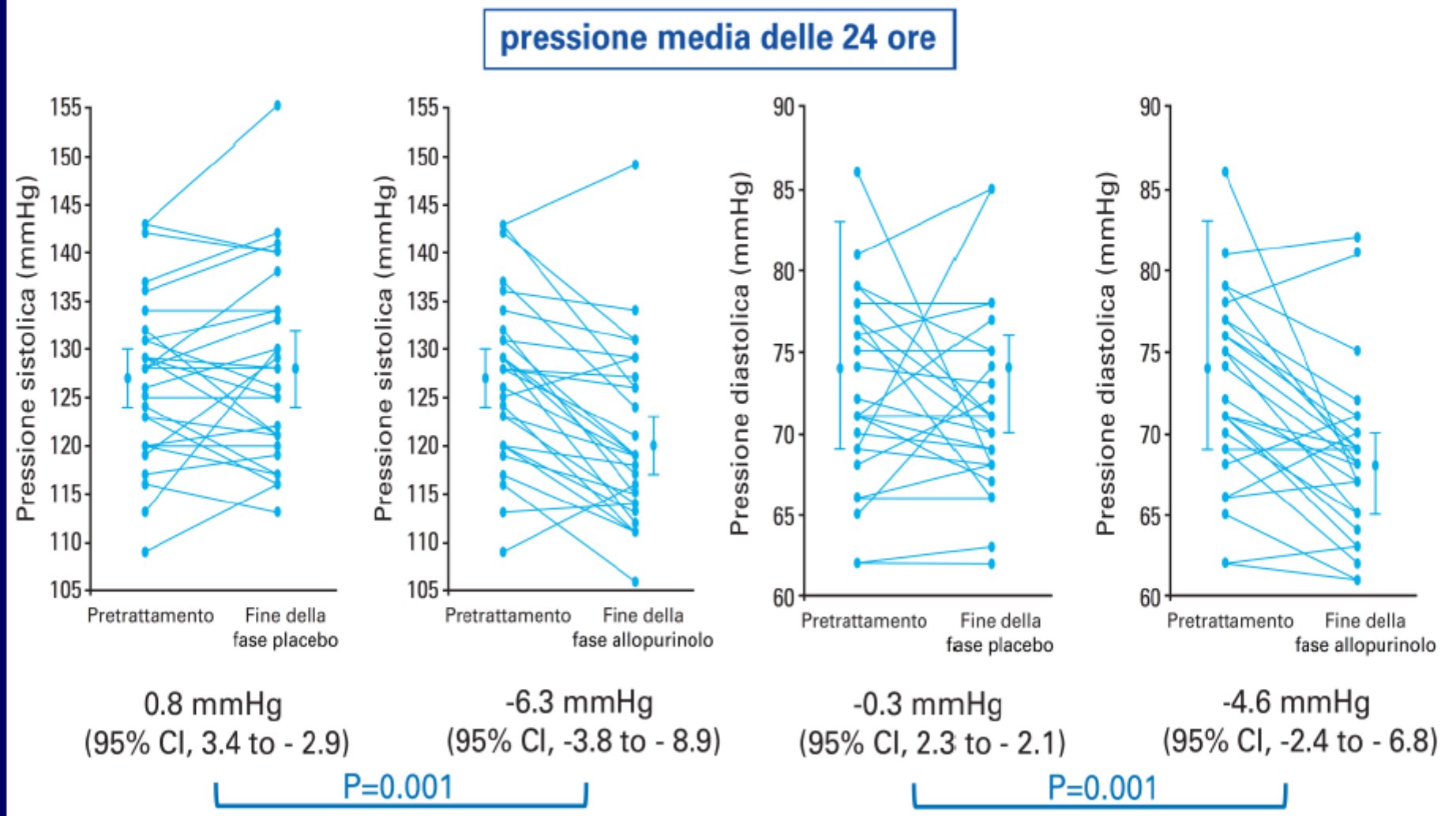
Effetti del fruttosio e della concomitante somministrazione di allopurinolo su acido urico (UA) Triglicerdi (TG) e Pressione sistolica nei ratti



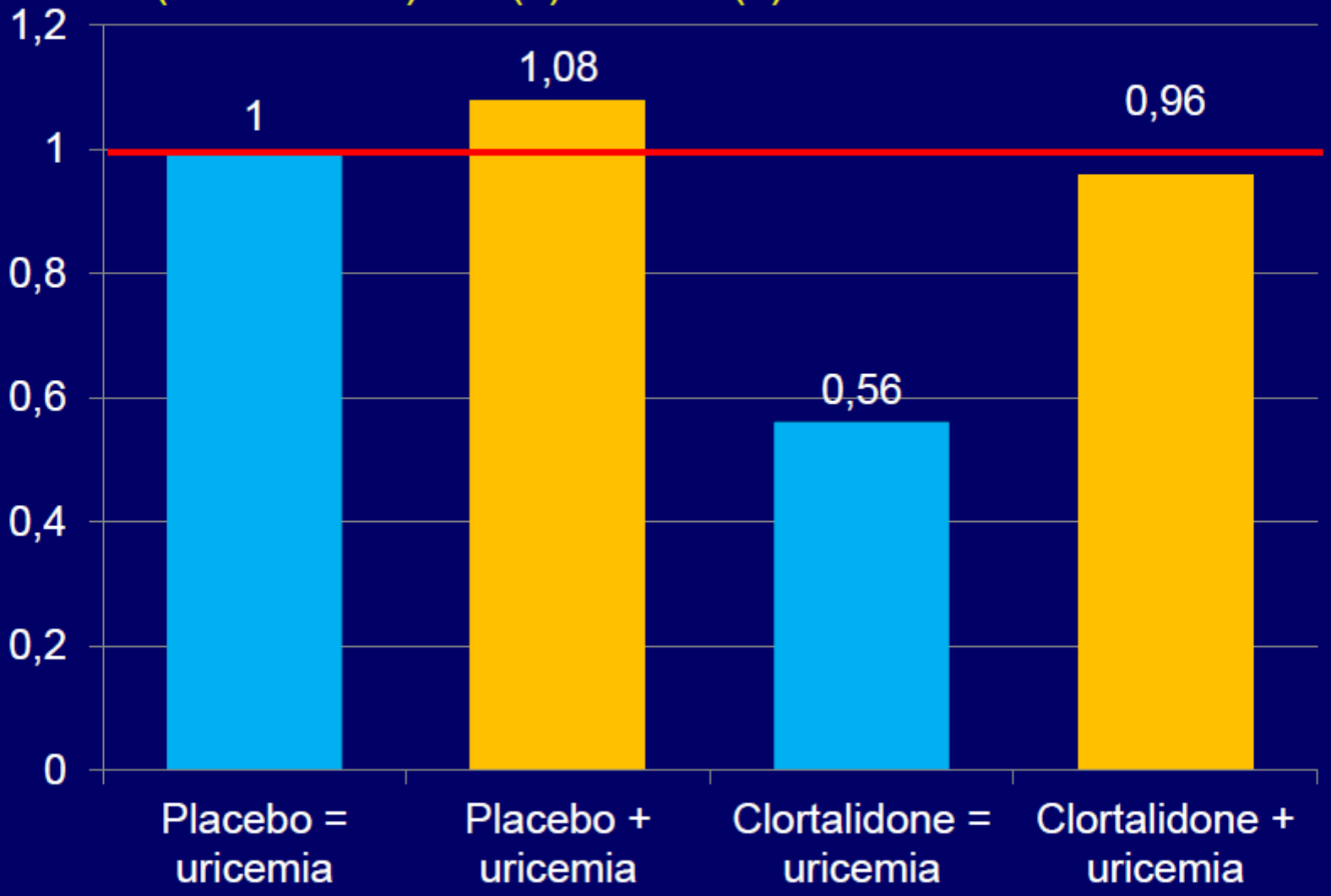




Effetto del trattamento ipouricemizzante sulla pressione ateriosa in adolescenti ipertesi iperuricemici

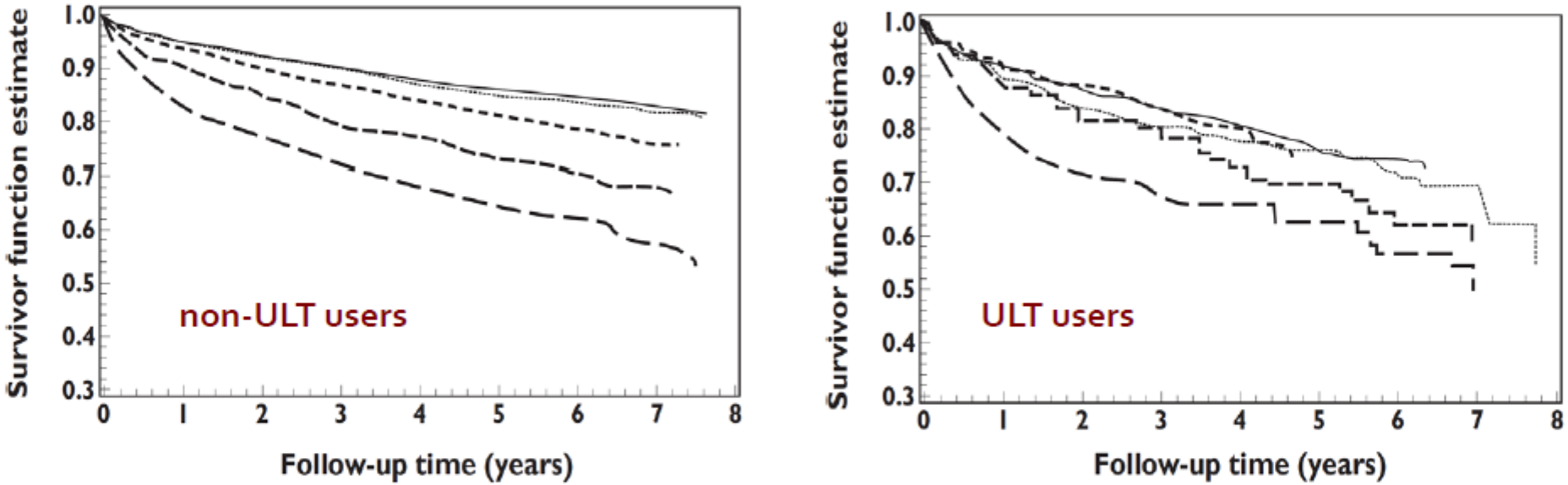


Rischio di eventi coronarici rispetto alle variazioni in 1 anno della uricemia (1 mg/dl) nei pazienti ipertesi e trattati con clortalidone (studio SHEP) con (+) e senza (=) aumento dell'uricemia



J Hypertens 2000; 18:1149-1154 &

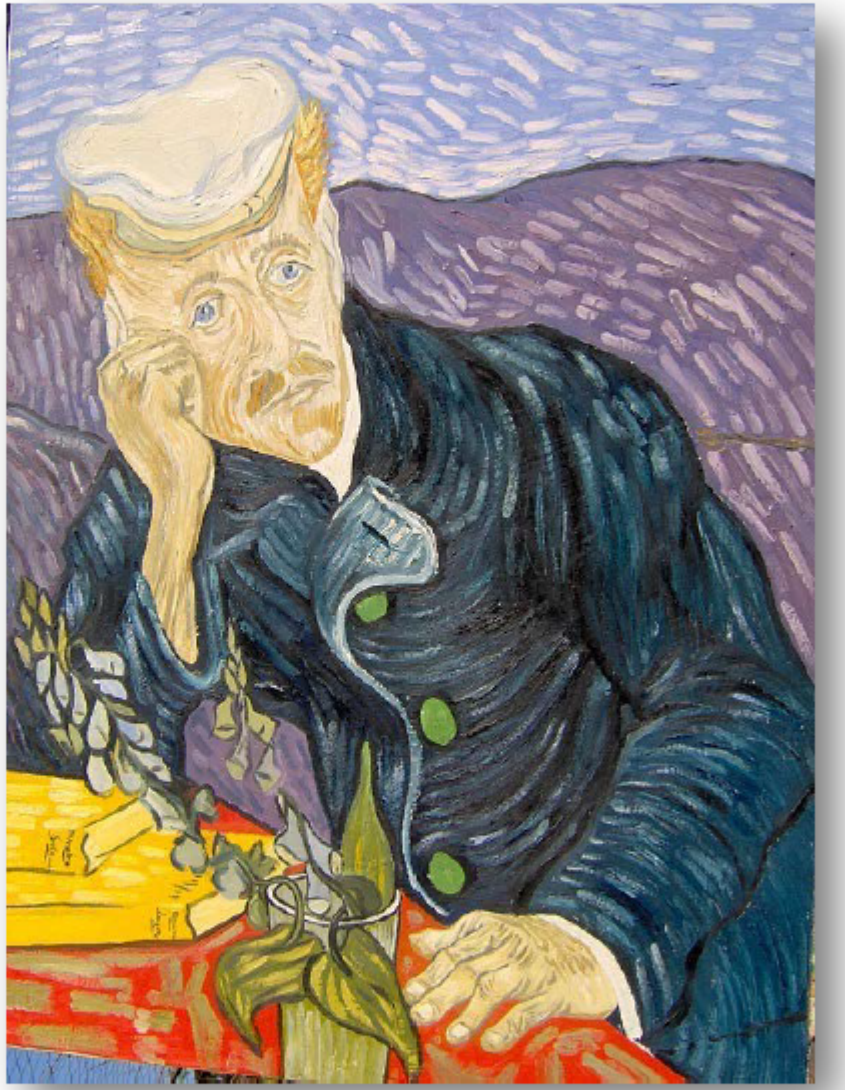
Impact of allopurinol use on urate concentration and cardiovascular outcome



ULT=Urate Lowering Treatment

Wei L, et al. Br J Clin Pharmacol 2001;71(4): 600–607

Conclusion



- The plasma levels of SUA appear related to CV disease
- The relationship may be mediated by onset of HBP
- The CV impact of SUA can be already detected early in life
- The cut-off levels for CV disease might be lower than those that define hyperuricemia
- The preventive effect of UA lowering treatment is currently not defined and RCT (with XO-inhibitors) are warranted for the future

Grazie per l’attenzione

Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study

- Compared losartan to atenolol for reduction in CV morbidity & mortality
- Losartan interferes with urate reabsorbtion
- > 9000 pts w HBP & LVH followed for ~ 4.8 yrs
- Pts. generally not hyperuricemic on entry
- Baseline SUA found to be signif assoc with inc CV events
- Inc. SUA in atenolol gp signif > losartan gp (P<.0001)
- Estimated contribution of SUA to CV death, non-fatal & fatal MI, & fatal & non-fatal stroke was 29%
- Attenuating SUA reduces CV events in high risk gps

Hoieggen A et al. The Impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int. 2004;65:1041-1049.

Myth: The uric acid is normal, it can't be gout

Reality

- 339 pts (2 studies) comparing tx with etoricoxib or indometh for acute gout
- 14% uric acid < 6.0 mg/dL at baseline
- 32% < 8.0 mg/dL during acute attack
- A change in uric acid is a better predictor of acute gout than inc sua

Schlessinger et al. J Rheum 2009; 36(6).

Uric Acid is a Risk Factor for Myocardial Infarction & Stroke

- 4385 participants in Rotterdam, 1990-1993 were > 55 yoa, free from CVA & CHD
- Average f/u was 8.4 yrs
- Relationship betw SUA & risk of CVD is linear
- High SUA levels assoc with risk of MI & CVA
- Age & sex adjusted hazard ratios for highest vs lowest quintile of UA were
  - 1.68 CVD
  - 1.87 MI
  - 1.57 CVA
- SUA is a strong risk factor for MI & stroke

Bos MJ et al. Stroke. 2006;37:1503-1507.

Social evolution or social involution?

Sweetened Drinks and Gout

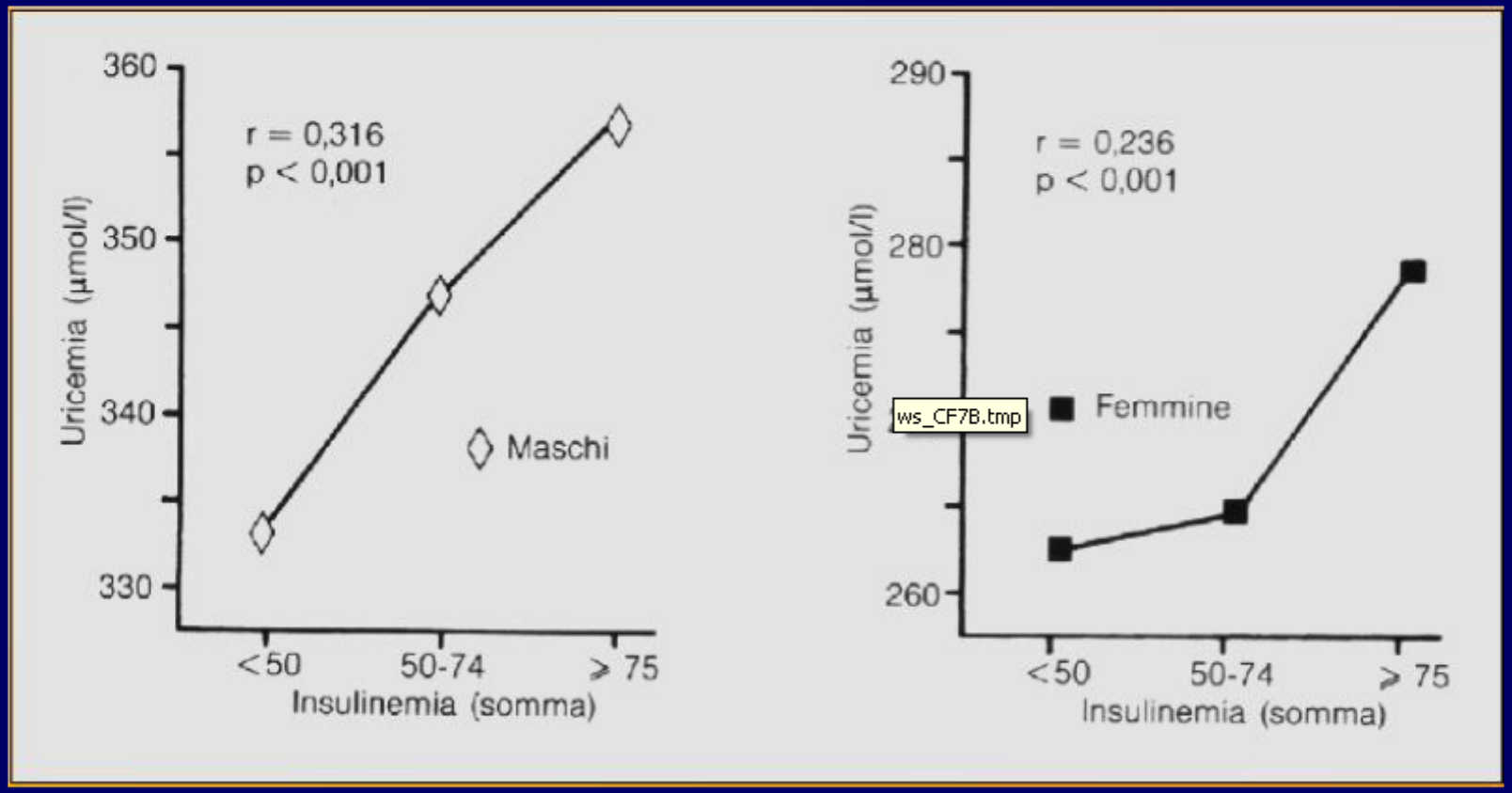
Author, year	Study design	N / sex	Quality	Outcome	Predictors/ Intervention	Effect
Choi, 2008	Prospective cohort	46.393 m		Incident gout	**Sweetened soft drinks** (vs < 1/month): 1/month-1/week 2-4/week 5-6/week 1/day ≥2/day	RR (95% CI): 1.00 (0.84 – 1.20) 0.99 (0.77 – 1.29) 1.29 (1.00 – 1.68) 1.45 (1.02 – 2.08) 1.85 (1.08 – 3.16)
Choi, 2010	Prospective cohort	78.906 f		Incident gout	**Sugar sweetened soda** (servings): 1/day vs ≤1/month ≥2/day vs ≤1/month	RR (95% CI): 1.74 (1.19 – 2.25) 2.39 (1.34 – 4.26)
Merriman 2011 (ABS)	Case-control	1.386 m/f		Gout	**Sweetened beverages** (servings/day) 1-1.99 vs 0 2-3.99 vs 0 ≥4 vs 0	OR (95% CI): 1.05 (0.51 – 2.15) 1.67 (0.66 – 4.24) 4.48 (1.22 – 16.5)

L’iperuricemia non è ufficialmente riconosciuta come un fattore di rischio cardiovascolare: ma…

Arthur Schopenhauer (1788–1860) ha detto:

“Ogni verità passa attraverso tre stadi
- Primo: viene ridicolizzata
- Secondo: viene contrastata con violenza
- Terzo: viene accettata per la sua propria evidenza.”

Correlazione uricemia / insulinemia



Modan M & al., *Diabetologia* 1987

Risk of death for CV causes and tertiles of SUA

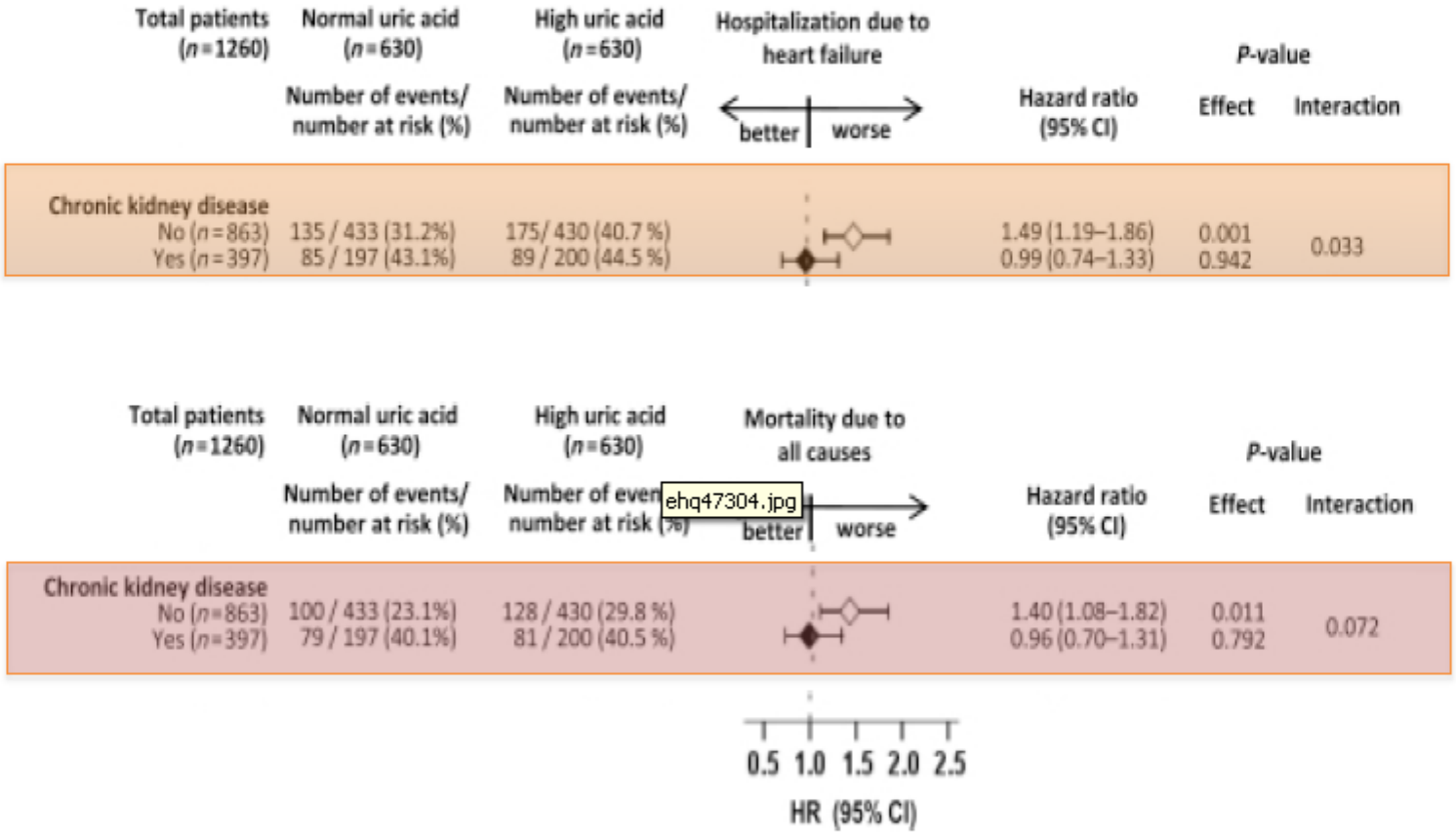
Tertile	Model 1	Model 2	Model 3
	Relative Risks (95% CI) for Death From CVD		
1 (3.03-5.04 mg/dL)	1 (Reference)	1	1
2 (5.05-5.88 mg/dL)	2.69 (1.20-6.04)	3.29 (1.30-8.34)	4.98 (1.61-15.4)
3 (5.89-9.58 mg/dL)	2.69 (1.21-5.98)	3.73 (1.42-9.83)	4.77 (1.50-15.1)
Trend over tertiles, *P*	.02	.01	.01
	Relative Risks (95% CI) for Death From Any Cause		
1 (3.03-5.04 mg/dL)	1 (Reference)	1	1
2 (5.05-5.88 mg/dL)	1.32 (0.85-2.03)	1.53 (0.96-2.45)	1.74 (1.05-2.88)
3 (5.89-9.58 mg/dL)	1.66 (1.10-3.08)	1.82 (1.12-2.97)	1.85 (1.08-3.17)
Trend over tertiles, *P*	.01	.02	.03

Abbreviations: CI, confidence interval; CVD, cardiovascular disease.
SI conversion: To convert uric acid levels to micromoles per liter, multiply by 59.48.
*Model 1 was age-adjusted; model 2, adjusted for age, examination year, smoking (cigarettes per day), low-density lipoprotein cholesterol level, family history ır coronary heart disease, systolic blood pressure, use of diuretics, use of β-blockers, use of other blood pressure medications, body mass index, alcohol intake erum creatinine level, and adult socioeconomic class; model 3, adjusted for the covariates in model 2 and fasting serum insulin, triglyceride, and high-density

Niskanen LK et al Arch Int Med 2004

Association of hyperuricemia, HF hospitalization and all-cause mortality in matched CHF patients.

Role of Chronic Kidney Disease



Filippatos GS et al, Eur Heart J, 2011