VIII CONGRESSO NAZIONALE

SINut
Società Italiana di Nutraceutica

Iperuricemia moderata: dal rischio cardiovascolare alla“soluzione” nutraceutica

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Alma Mater Stdiorum Università di Bologna

Recent references

- Cicero AF et al. Eur J Intern Med. 2018 Mar 23. pii: S0953-6205(18)30126-2. -> NAFLD
- Cicero AF et al. Int J Cardiol. 2018 Jun 15;261:204-208. -> LDL-oxidation
- Kuwabara M, Cicero AF et al. Int J Cardiol. 2018 Jun 15;261:183-188. -> Development high LDL cholesterol and hypertriglyceridemia
- Borghi C, Cicero AF. Int J Cardiol. 2018 Jan 1;250:62-63. -> SCA
- Borghi C, Cicero AF. Hypertension. 2017 Jun;69(6):1011-1013. -> Hypertension
- Cicero AF et al. Ann Med. 2017 Jun;49(4):275-282. -> Diabetes
- Cicero AF et al. Eur J Intern Med. 2017 Jan;37:38-42. -> Arterial stiffness
- Cicero AF et al. J Clin Hypertens. 2015 Oct;17(10):777-82. -> Maternal outcomes
- Cicero AF et al. Eur J Intern Med. 2015 May;26(4):255-8. -> ECG changes

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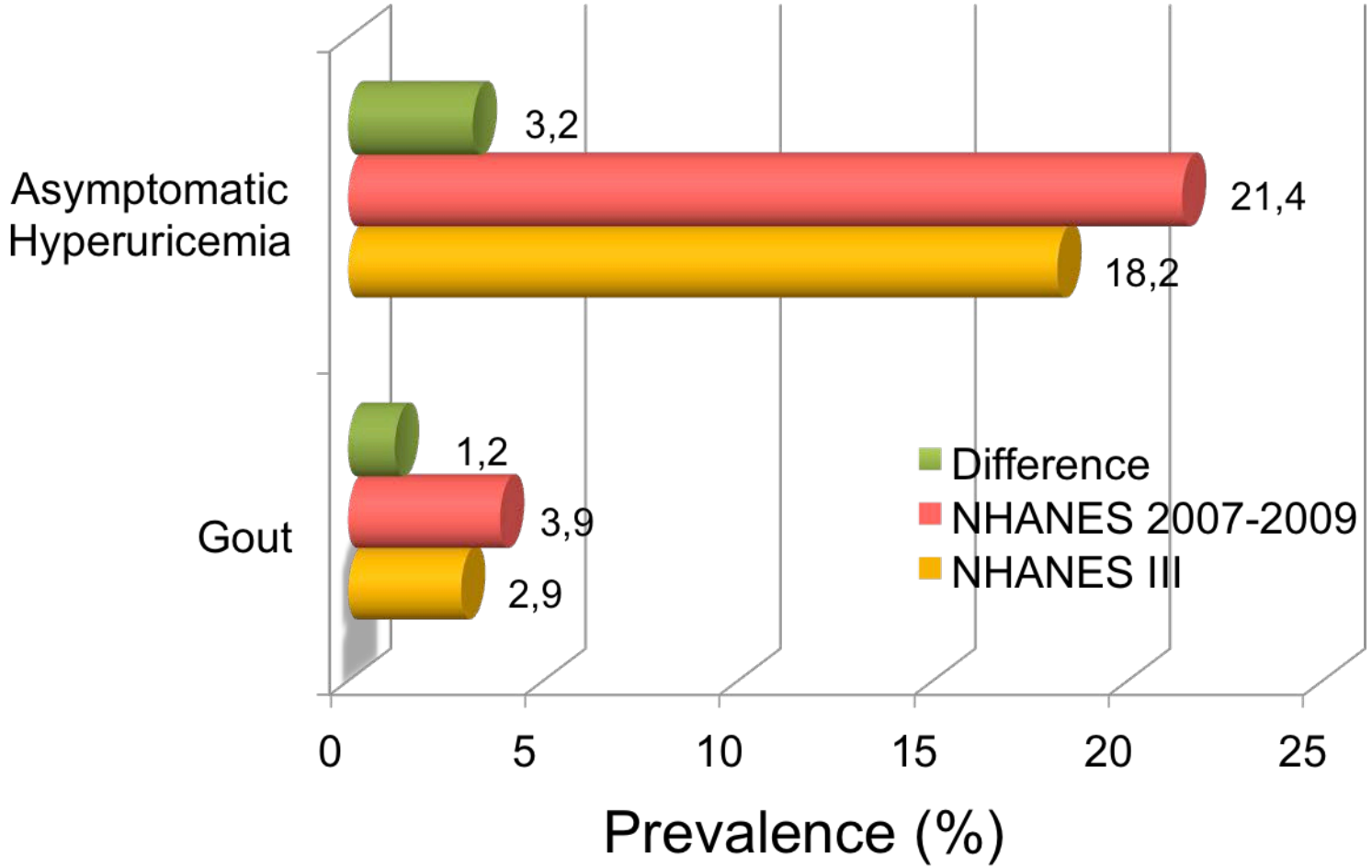
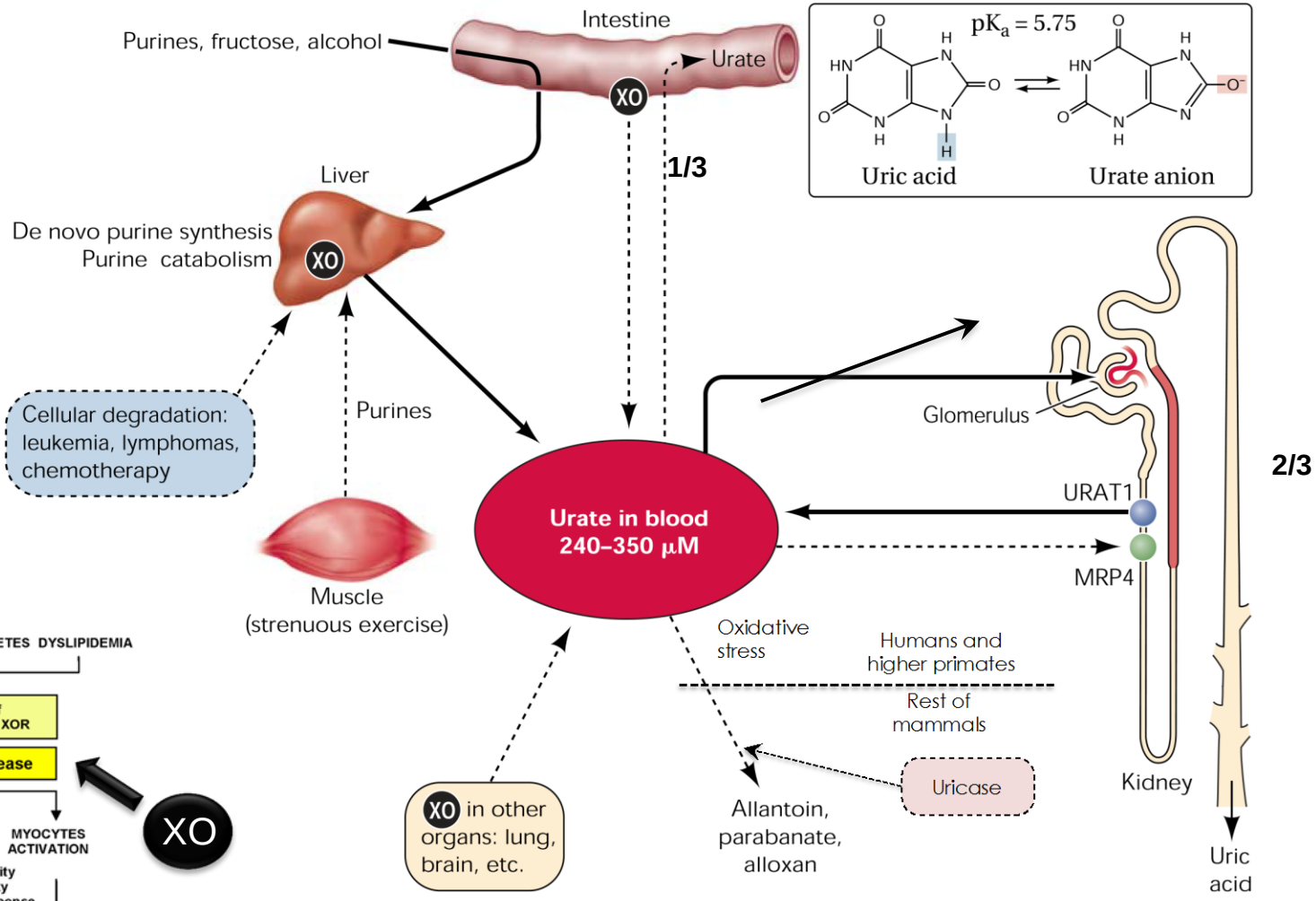
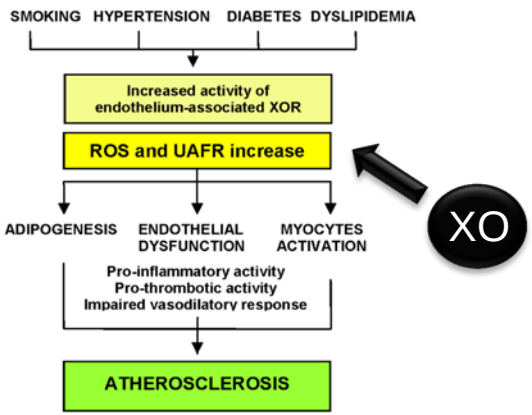
Comparison of the age-adjusted prevalence of gout and asymptomatic hyperuricemia among US adults, NHANES-III (1988-1994) vs. NHANES 2007-2008



Zhu Y et al, Arthritis Rheum 2011

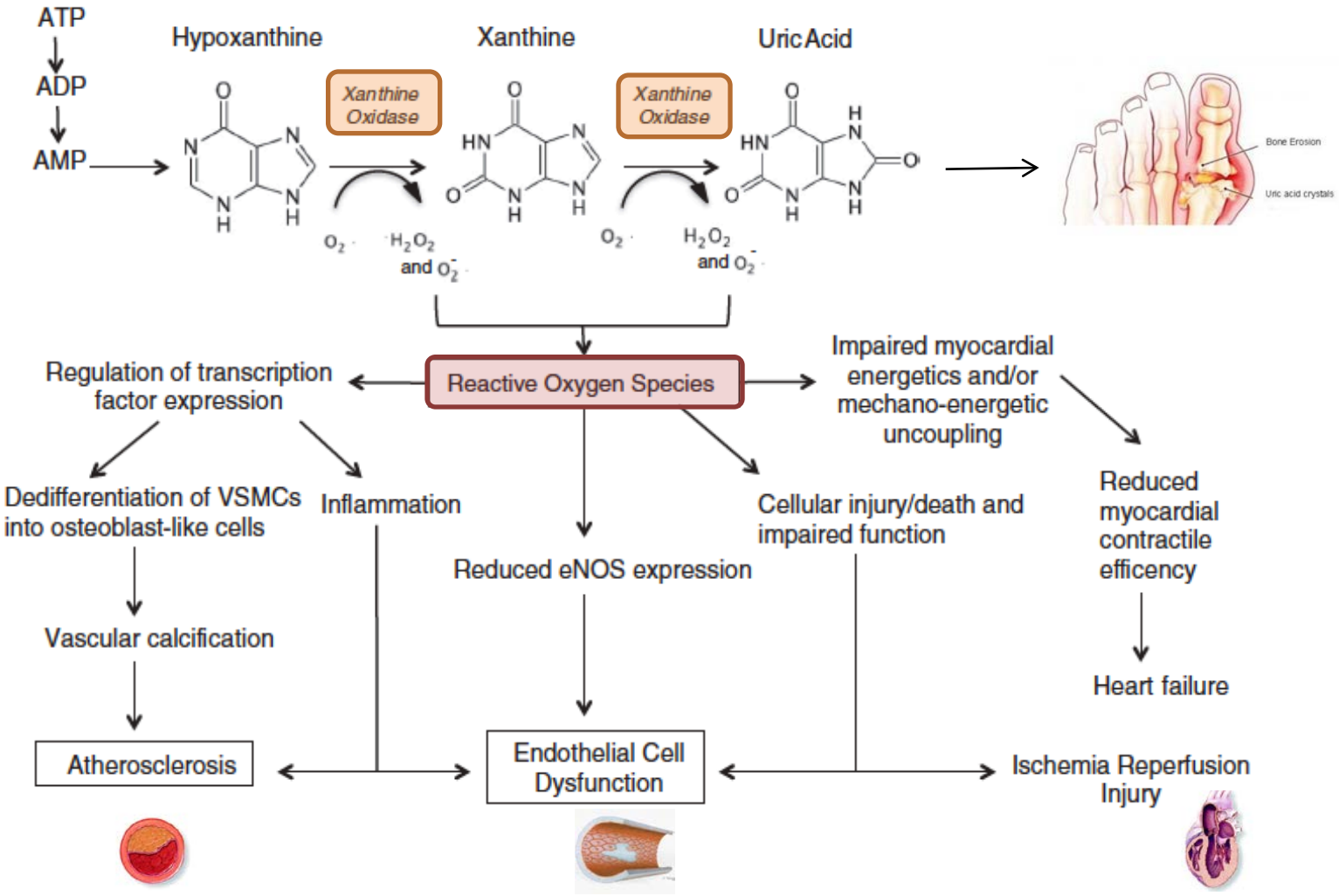
Human urate homeostasis





Hediger MA et al. Physiology (Bethesda). 2005 Apr;20:125-33.

Schematic overview of the uric acid metabolism and Xantine-Oxidase pathway



Okafor ON et al, Pharmacol & Ther 2016

URIC ACID

AS

A FACTOR IN THE CAUSATION OF DISEASE.

A CONTRIBUTION TO THE

PATHOLOGY OF HIGH ARTERIAL TENSION, HEADACHE, EPILEPSY, MENTAL DEPRESSION, GOUT, RHEUMATISM, DIABETES, BRIGHT'S DISEASE,

AND OTHER DISORDERS.

BY

ALEXANDER HAIG, M.A., M.D.Oxon., F.R.C.P.

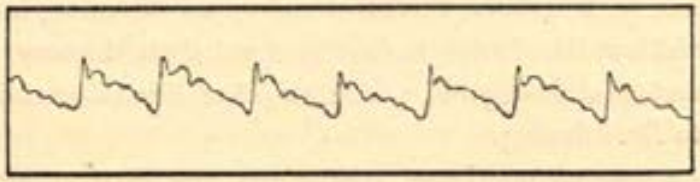


FIG. 14.—HIGH TENSION PULSE OF A URIC ACID HEADACHE. RATE 57.

Haig A, 1892

© 2011, American College of Rheumatology

Overall population

Males and females

Incident HTN rose by about
13% for any 1 mg/dl of SUA

Serum Uric Acid and Cardiometabolic Disease

Another Brick in the Wall?

Claudio Borghi, Arrigo Francesco Giuseppe Cicero

See related article, pp xxx–xxx

Several epidemiological and experimental studies have demonstrated a significant relationship between hyperuricemia and hypertension, metabolic syndrome, chronic kidney disease, and cardiovascular events.[1,2] This is confirmed in patients with gout,[3] as well as in those with asymptomatic hyperuricemia,[4] and may significantly contribute to the overall cardiovascular risk beyond the role of traditional risk factors. However, most of the studies assessing the role of elevated serum uric acid (SUA) in cardiovascular disease have been performed in patients with ≥1 interfering comorbidities. In the present issue of *Hypertension*, Kuwabara et al[5] have provided an interesting demonstration that hyperuricemia, per se, can be associated with an independent increase in the risk of cardiometabolic diseases in a large Japanese population. Specifically, after exclusion of all the patients with overt cardiometabolic disease at baseline, hyperuricemia was still associated with an increased incidence of hypertension, dyslipidemia, chronic kidney disease, and overweight/obesity. These results agree with those of the MRFIT (Multiple Risk Factor Intervention Trial)[6] and the PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni)[7] studies, showing a significant increase in the new onset of hypertension and metabolic syndrome in healthy subjects with elevated SUA levels after the adjustment for confounding risk factors associated with hyperuricemia.

The findings of Kuwabara et al[5] partially overcome one of the main obstacles in the evaluation of the pathogenetic role of elevated SUA levels in cardiovascular disease, namely the possible interference of other risk factors currently associated with hyperuricemia. This problem has usually been resolved with the application of multiple statistical adjustments, leading to a better definition of the importance of the different causative factors by excluding spurious correlations. However, data adjustment engenders an artificial interpretation of evidence because it is based on a presumed reciprocal interaction among causative factors without considering the sequential mechanistic approach. A typical example is the adjustment for baseline blood pressure values that were used by the Framingham investigators to exclude a causative role of SUA as a risk factor for cardiovascular disease.[8] At present, such adjustment seems difficult to justify in presence of many demonstrations of a significant effect of SUA over the new onset of hypertension.[1] Furthermore, although data adjustment can reasonably exclude the independent causative role of covariates, it cannot rule out their contributing effect to the physiological cascade, leading to a clinical phenotype. This seems to be the case for elevated levels of SUA. Elevated levels of SUA have been the object of extensive adjustment procedures, reaching different conclusions about its independent role as a risk factor for cardiometabolic disease. However, a proper definition of the role of SUA can be achieved by a direct evaluation of an appropriate population of subjects where any possible concurrent risk factors for cardiovascular disease can be reasonably excluded at baseline.

All these considerations support the notion that a correct interpretation of the pathogenetic role of SUA, in subjects at risk of cardiometabolic disease, cannot only consider the impact of hyperuricemia but should also take into account the heterogeneity of subjects apparently bearing the same levels of SUA (phenotypic profile).

A large body of evidence has demonstrated that a comparable level of SUA can be observed either as a consequence of an increased urate reabsorption or in response to an overproduction of the same compound. The second option may result from an excessive introduction/degradation of purine precursors or as a consequence of enhanced activation of xanthine oxidoreductase system.[9] This dual mechanism identifies 2 different types of patients but also 2 different approaches to the interpretation of data on SUA with respect to cardiovascular risk (Figure). The renal (entero-renal according with the distribution of URAT-1 [urate transporter-1]) predominance is more typical of patients with gout and might be associated with metabolic disorders, including obesity and insulin resistance, largely involved in the secondary increase in plasma levels of uric acid. In this subtype of patients, the adjustment of data for the possible confounding factors is more than justified and may provide a reliable estimate of the residual impact of hyperuricemia beyond that of the established cardiovascular risk factor. Conversely, the productive pathway is probably associated to the increased oxidative stress that accompanies the activation of xanthine oxidoreductase; this may cause a functional and structural change of the vascular system and neurohormonal control.[9] A hypothesis of a 2-component system controlling for the increased plasma levels of SUA has already been proposed in the literature[10] and could represent a reliable explanation for the clinical differences among subjects with comparable serum

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

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(*Hypertension*. 2017;69:00-00.
DOI: 10.1161/HYPERTENSIONAHA.117.09081.)
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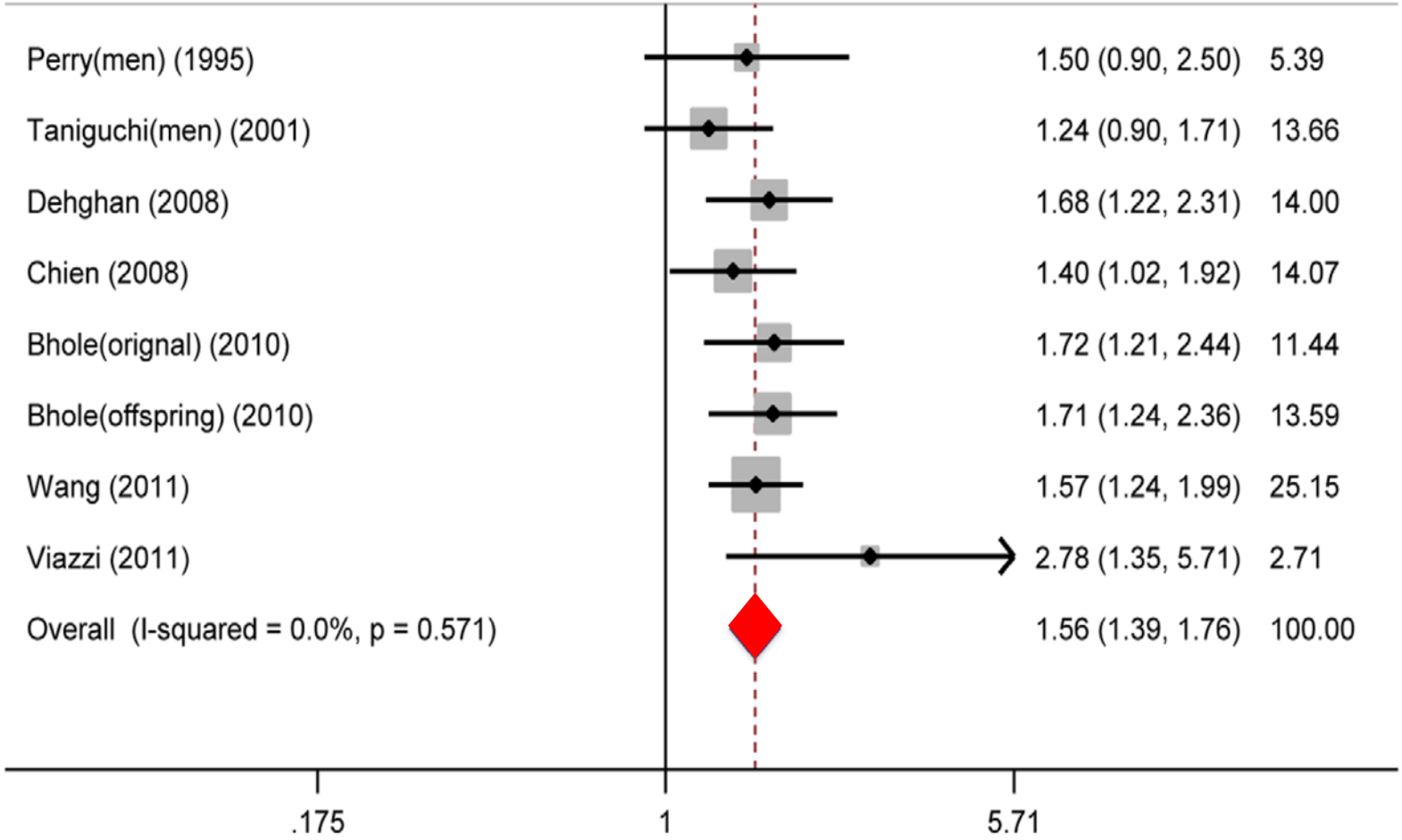
Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.117.09081

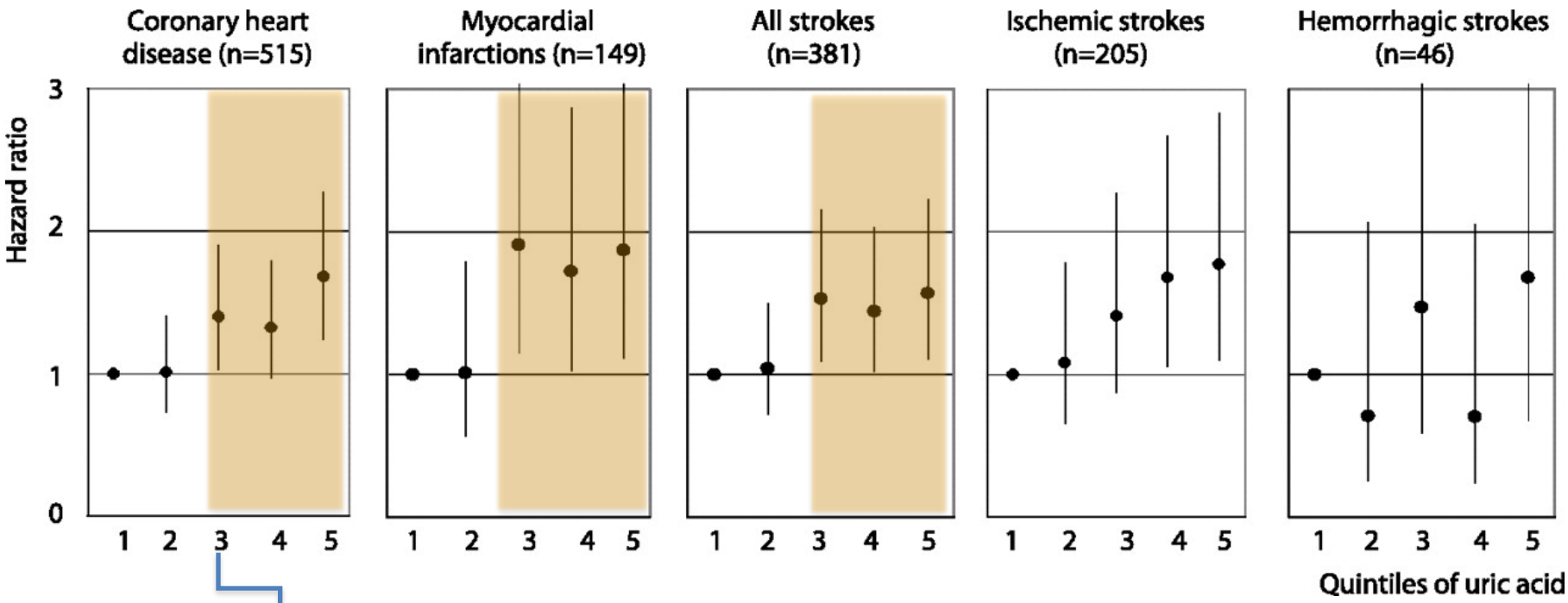
High SUA and Increased Risk of Type 2 DM: A Systemic Review and Meta-Analysis of Prospective Cohort Studies

7 eligible articles derived from 8 prospective cohort studies, involving a total of 32016 participants and 2930 incident type 2 diabetes



Qin Lv et al. February 2013 | Volume 8 | Issue 2 | e56864

Age and BP-adjusted HR for the associations between serum uric acid and cardiovascular disease: The Rotterdam Study



5.4 mg/dL

American Heart Association

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

OPEN ACCESS

Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies

Xue Li,[1] Xiangrui Meng,[1] Maria Timofeeva,[2] Ioanna Tzoulaki,[3] Konstantinos K Tsilidis,[3,4] P A Ioannidis,[5,6,7] Harry Campbell,[1] Evropi Theodoratou[1,2]

Summary of random-effects of cardiovascular impact of elevated SUA reported in meta-analysis of observational studies

Outcomes	N studies	N participants	N cases	Random-effect model	Relative risk (95%CI)
Cardiovascular outcomes					
Atrial fibrillation (AF)	6	426,159	7,595		1.49 (1.24, 1.79)
Atrial fibrillation recurrence (AF patients)	4	1,298	393		1.52 (1.19, 1.94)
CHD incidence	13	70,382	6,666		1.13 (1.05, 1.21)
CVD (Hypertention patients)	6	19,546	1,054		1.17 (1.07, 1.27)
Heart failure incidence	5	427,917	10,171		1.65 (1.41, 1.94)
Hypertension incidence	17	71,630	18,751		1.48 (1.33, 1.65)
Prehypertension	8	44,095	20,832		1.84 (1.42, 2.38)
LATH/LASEC (Patients with heart diseases)	6	2,361	241		1.59 (1.13, 2.23)
MACE (Patients after PCI)	2	3,054	–		1.78 (1.26, 2.52)
Medium term MACE (AMI patients)	4	4,299	1,240		1.93 (1.36, 2.74)
Short-term MACE (AMI patients)	7	6,470	787		2.46 (1.84, 3.27)
Stroke (Hypertention patients)	3	9,978	217		1.11 (0.98, 1.26)
Stroke incidence	5	24,548	1,290		1.22 (1.02, 1.46)

thebmj | BMJ 2017;357:j2376 | doi: 10.1136/bmj.j2376

The dual face of elevated SUA

Elevated SUA levels
(genes & diet)

Excretion vs. Production

↑☐ Tubular/intestinal transport systems
Urate deposition
Inflammation and vascular damage

Gout and beyond

Renal disease

Production vs. Excretion

↑☐ XO activity and genetics
Oxidative stress
Vascular damage

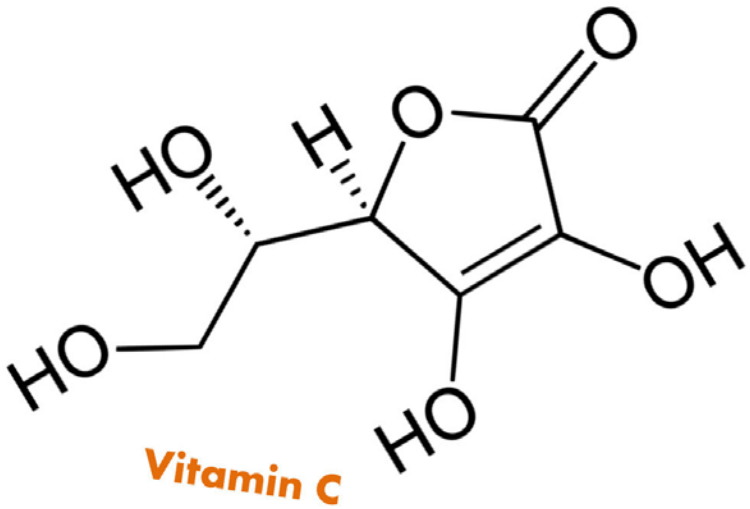
CV/metabolic disease

Esiste una dieta per la cura dell'iperuricemia?

Cicero AF et al. Synergie ed. 2018

- **Alimenti da limitare al massimo: birra, liquori, bibite dolcificate con fruttosio, fruttosio, molluschi, frattaglie (organi animali interni)**
- **Alimenti da limitare: carne rossa (specie se conservata o lavorata)**
- **Alimenti da preferire: acqua, tè, caffè, latticini magri, carboidrati (pane e analoghi, pasta, biscotti) prodotti con cereali integrali, verdure fresche, frutta fresca (preferendo quella meno dolce)**

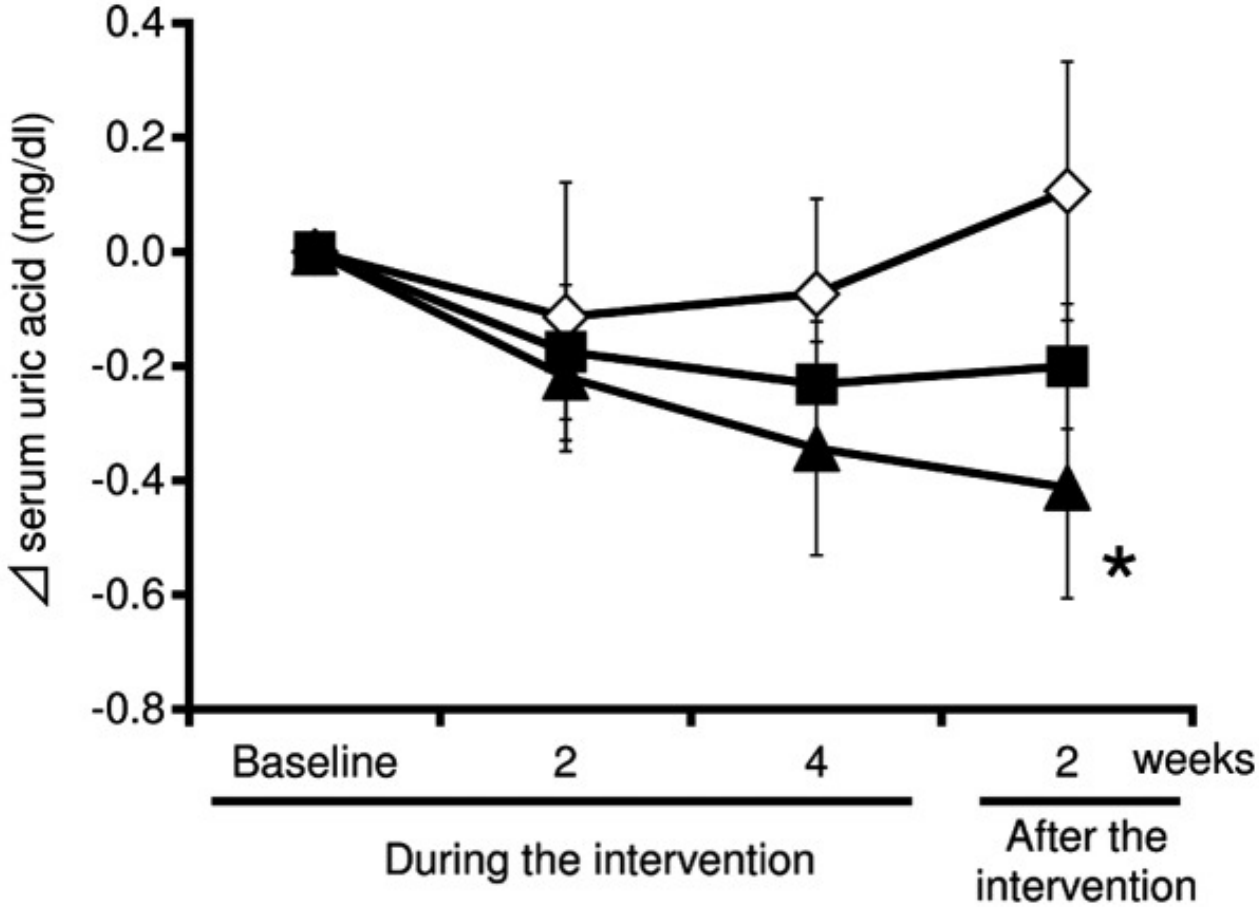
Vitamin C and SUA: the RCTs



- 10 small RCTs available
- Short-term
- Mead dosage: 500 mg/day
- Mild effect (-0.5-1 mg/dL)
- Probably related to improvement in FMD

Cochrane Database Syst Rev. 2014 Oct 7;(10):CD010156.

Changes of the SUA in the subjects of the placebo and test supplement (at low and high doses of tuna extract) groups during and subsequent to the intervention



Biomed Rep. 2016 Aug;5(2):254-258.

Consumption of cherries (280 gr) lowers plasma urate in healthy women: a pilot study

Plasma and urine biomarkers in healthy women before and after cherry consumption[1,2,3]

Biomarker	Baseline	1.5 h	3 h	5 h
Plasma urate, *μmol/L*				
Cherries[†]	214 ± 13	221 ± 22	203 ± 13	183 ± 15*
Grapes	278 ± 25	263 ± 26	257 ± 23	260 ± 21
Strawberries	286 ± 25	280 ± 20	277 ± 25	262 ± 29
Kiwifruit	285 ± 28	256 ± 21	257 ± 23	281 ± 19
Urinary urate, *μmol/mmol creatinine*	202 ± 13	278 ± 29*	350 ± 33*	260 ± 17*
Plasma				
C-reactive protein, *mg/L*	4.29 ± 2.18	ND	3.07 ± 1.26	3.59 ± 1.59
Nitric oxide, *μmol/L*	37.4 ± 5.2	ND	31.1 ± 2.9	31.6 ± 2.1
ORAC (lipophilic),[4] *μmol TE/L*	531 ± 37	628 ± 37*	681 ± 24*	711 ± 27*
FRAP, *μmol/L*	454 ± 23	432 ± 21*	403 ± 14*	414 ± 21*
Ascorbic acid, *μmol/L*	65.4 ± 5.6	74.5 ± 5.6*	71.8 ± 6.0*	68.2 ± 5.2

J Nutr. 2003 Jun;133(6):1826-9.

DOI 10.1002/mnfr.201700373 *Mol. Nutr. Food Res. 61, 11*, 2017, 1700373

RESEARCH ARTICLE

Effect of apple polyphenols on vascular oxidative stress and endothelium function: a translational study

Arrigo F.G. Cicero[1], Cristiana Caliceti[2,3], Federica Fogacci[1], Marina Giovannini[1],

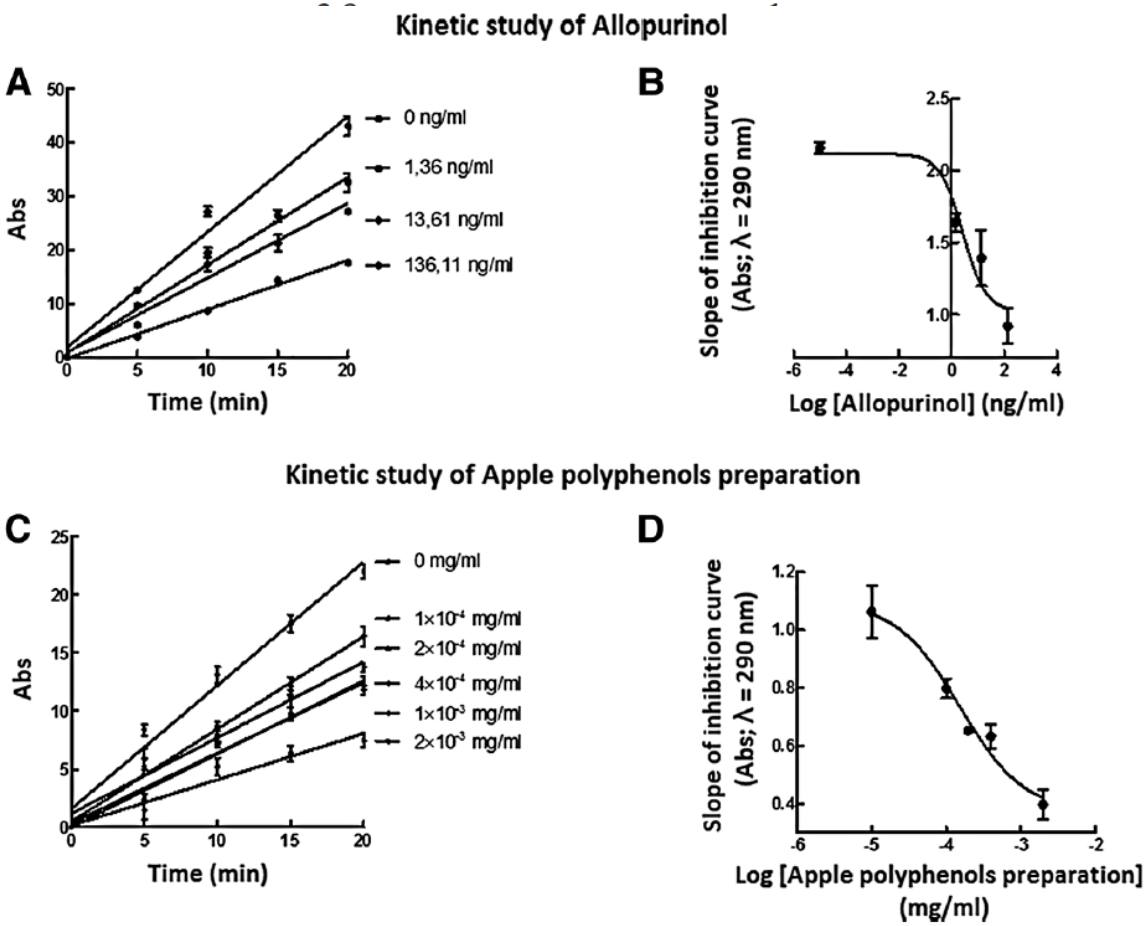


Figure 2. Vis-UV spectroscopic assay. (A) Kinetic study of uric acid production in presence of different concentrations of allopurinol (from 136.11–1.36 ng/mL) in borate buffer (pH 10.3) at 37°C for 20 min. The production of uric acid was monitored in time (0–20 min) by ultraviolet–visible (UV-vis) spectroscopy according to the increasing absorbance at 290 nm. Values are means of $n = 3$ with standard deviation (SD) indicated by vertical bars. (B) Dose-response curve obtained plotting kinetic curves slope *versus* log [allopurinol] in ng/mL. (C) Kinetic study of uric acid production in presence of different concentrations of apple polyphenols preparation (from 2×10^{-3} to 1×10^{-4} mg/mL) in borate buffer (pH 10.3) at 37°C for 20 min. The production of uric acid was monitored in time (0–20 min) by ultraviolet–visible (UV-vis) spectroscopy according to the increasing absorbance at 290 nm. Values are means of $n = 3$ with standard deviation (SD) indicated by vertical bars. (D) Dose-response curve obtained plotting kinetic curves slope versus log [apple polyphenols] in milligram per milliliter.

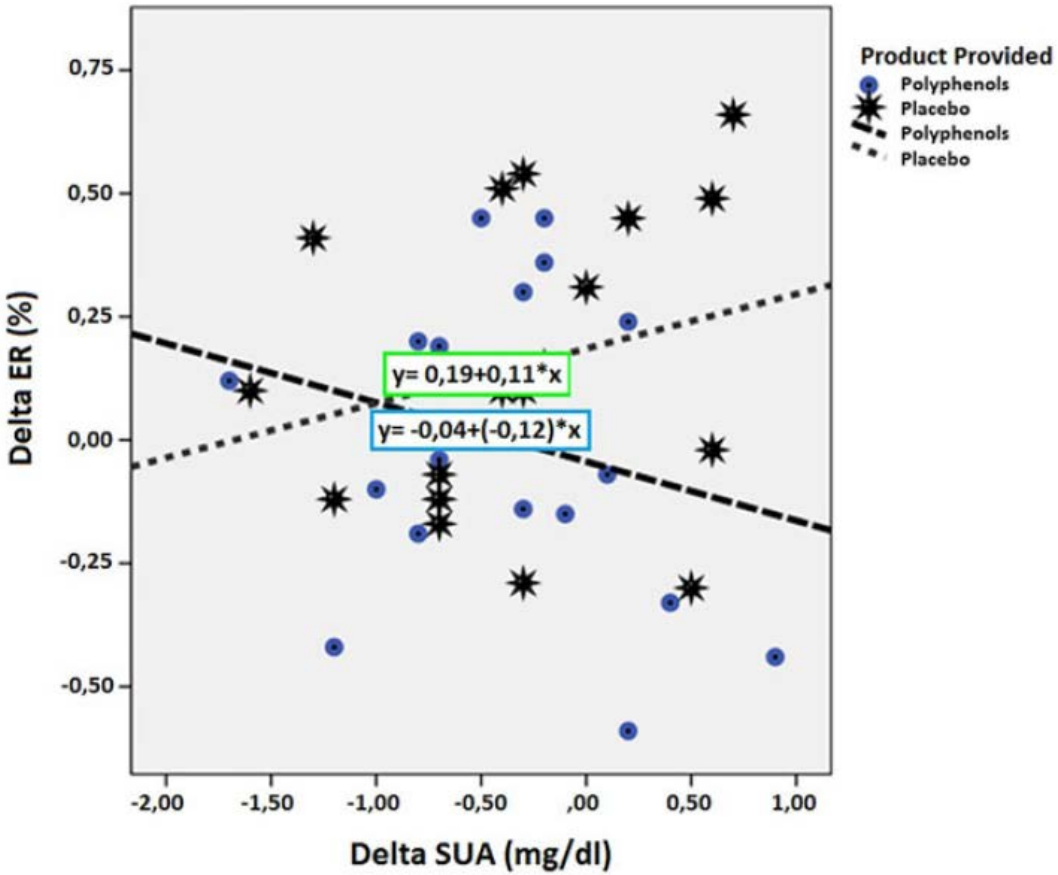
DOI 10.1002/mnfr.201700373 *Mol. Nutr. Food Res. 61, 11*, 2017, 1700373

RESEARCH ARTICLE

Effect of apple polyphenols on vascular oxidative stress and endothelium function: a translational study

Arrigo F.G. Cicero[1], Cristiana Caliceti[2,3], Federica Fogacci[1], Marina Giovannini[1], Donato Calabria[2,3], Alessandro Colletti[1], Maddalena Veronesi[1], Aldo Roda[2] and Claudio Borghi[1]

Relationship between SUA change and endothelial reactivity in subjects treated with apple polyphenols and placebo



A pilot clinical test on a nutraceutical fixed combination

- *Gingko biloba* leaf 250 mg (Kampferol 10 mg)
- *Scutellaria baicalensis* root 167 mg (Baicalin 50 mg)
- Green coffee seed 100 mg (Chlorogenic acid 10 mg, caffein 4.5 mg)
- Rutin 50 mg

ROS scaveging
XO inhibition

High Blood Press Cardiovasc Prev (2016) 23:381–386

The study results

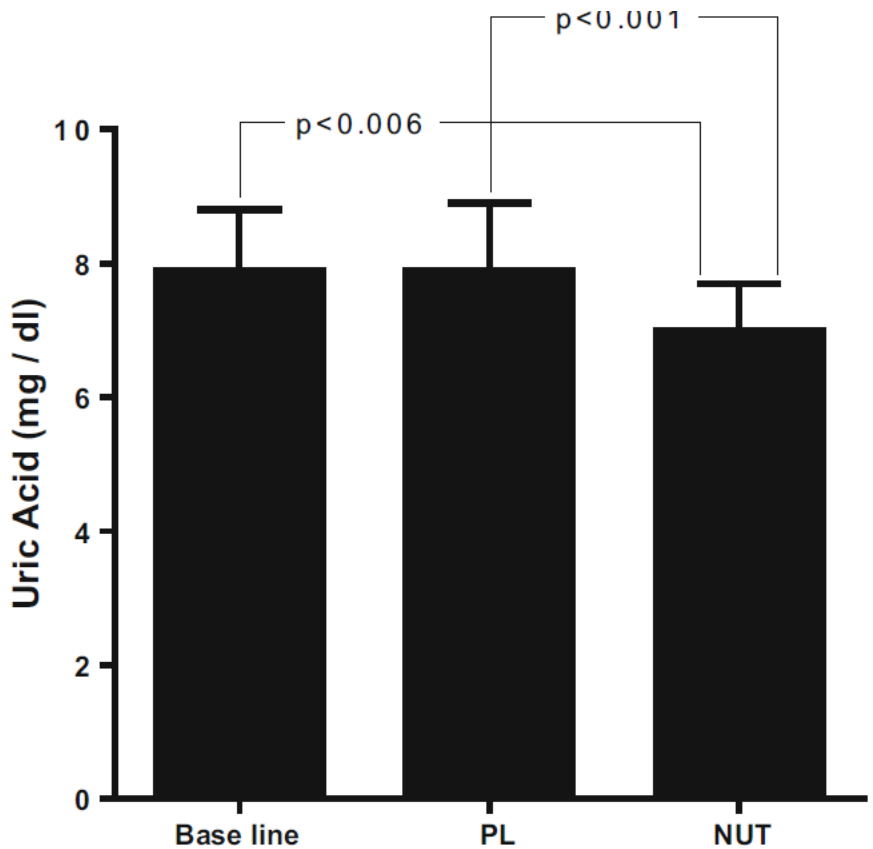


Fig. 1 Changes in serum uric acid (mean + SD) concentrations induced by 4 week placebo (PL) or ZinutriK® (NUT) treatments in asymptomatic hyperuricemic individuals

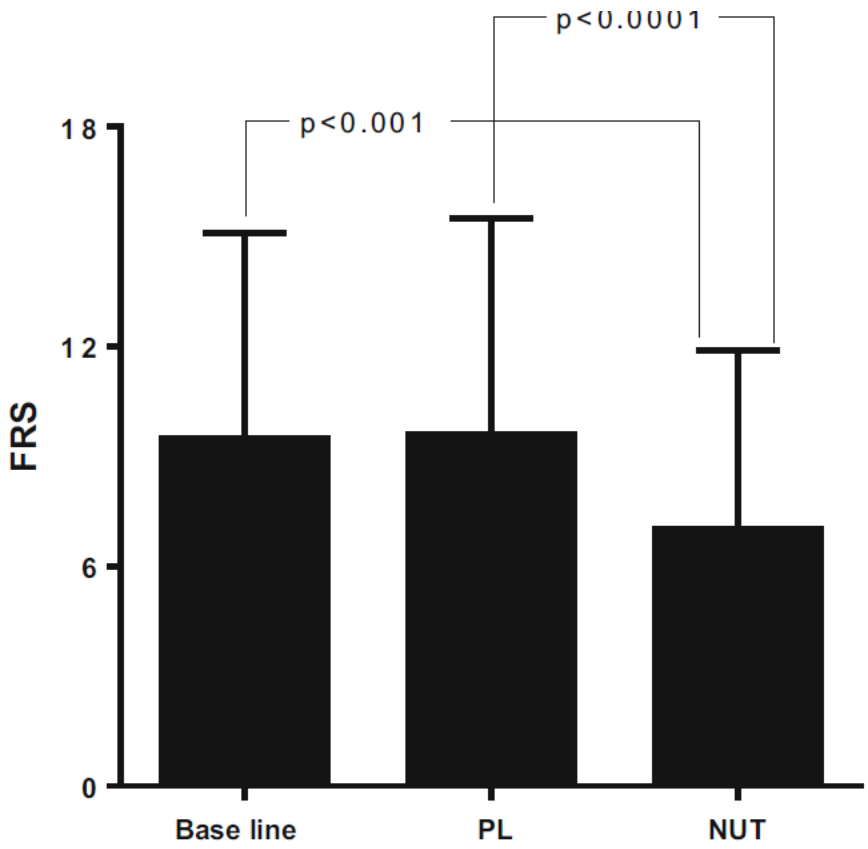


Fig. 2 Changes in the Framingham risk score (FRS) (mean + SD) induced by either placebo (PL) or ZinutriK® (NUT) treatments (4 weeks in both cases) in 16 individuals with asymptomatic hyperuricemia

High Blood Press Cardiovasc Prev (2016) 23:381–386

E ricordiamo l'antinutraceutico !!!