

Rev. Stephen Hales, 1733

# Nutraceutica e pressione arteriosa: risultati di trial clinici e metanalisi

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# Gazzetta Medica di Torino

## SOMMARIO

Comunicazioni originali: SCIPIONE RIVA-ROCCI: Un nuovo sfigmomanometro.  
 Accademie e Società: Reale Accademia di medicina di Torino (Sedute 13 e 27 novembre 1896).  
 Note cliniche e terapeutiche: Un caso di tic faciale in un orologiaio. — L'urticaria delle vie respiratorie. — Un caso di spasmo fonico guarito coll'elettricità. — Il kefir al creosolat e al carbonato di guaiacolo.  
 Bollettino della mortalità di Torino (3<sup>a</sup> decade del mese di novembre).

## COMUNICAZIONI ORIGINALI

CLINICA MEDICA PROPEDEUTICA DI TORINO (Prof. C. FORLANINI)

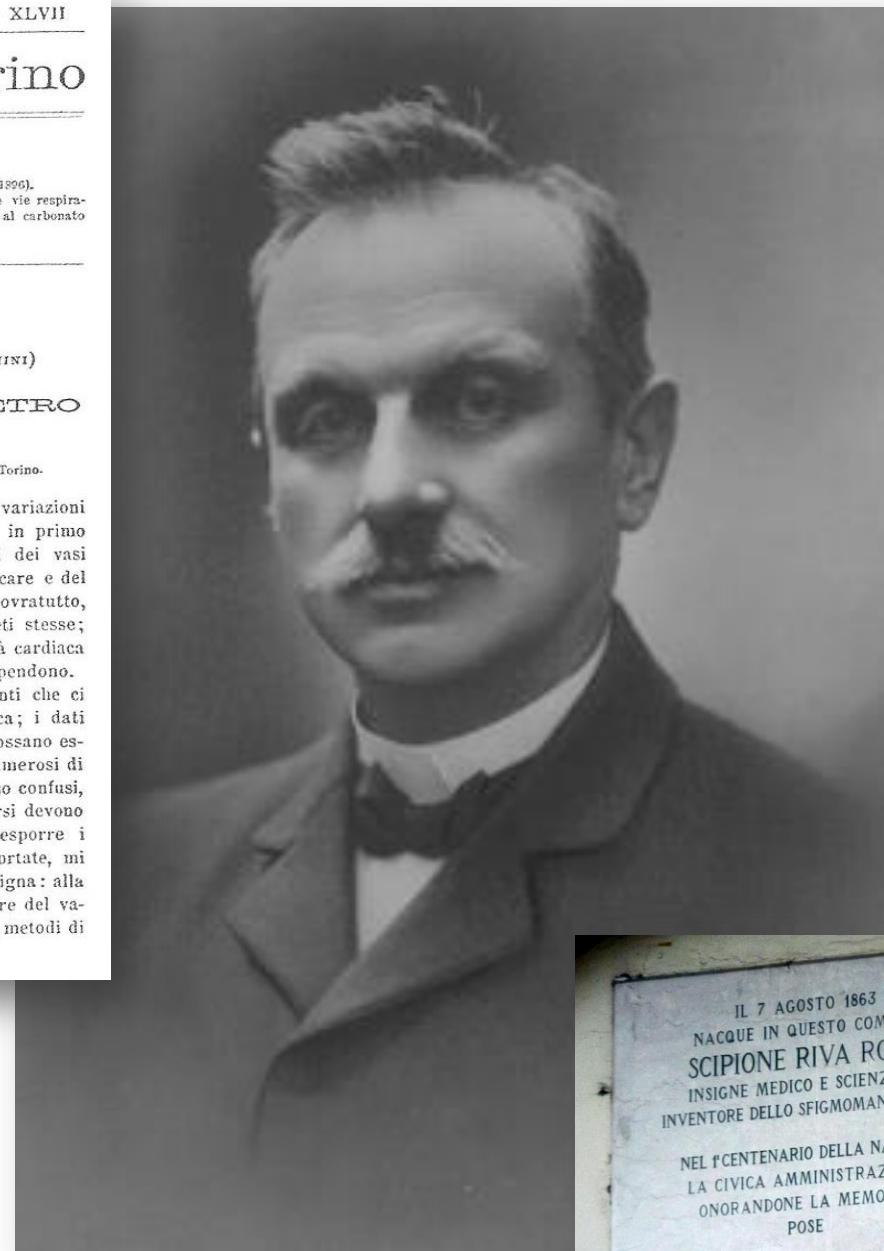
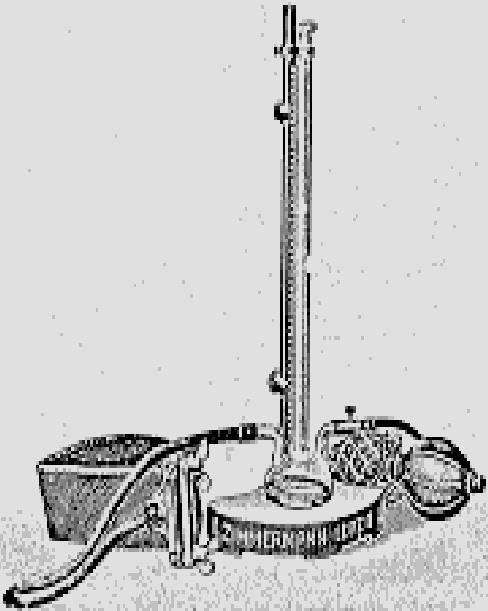
### UN NUOVO SFIGMOMANOMETRO

Nota del Dott. SCIPIONE RIVA-ROCCI

Aiuto alla Clinica Med. Prop. — Docente di Patologia Medica nella R. Univ. di Torino.

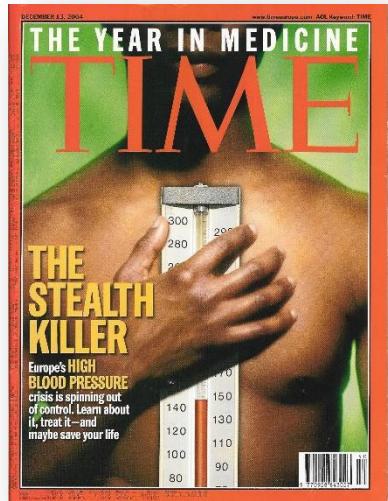
Dal punto di vista clinico noi ricerchiamo il valore e le variazioni della pressione sanguigna arteriosa per due scopi principali: in primo luogo per conoscere lo sforzo che essa esercita sopra le pareti dei vasi e quindi sui tessuti circostanti, cosa che ci dà modo di giudicare e del grado di resistenza di queste pareti vasali e di questi tessuti, e, soprattutto, della maggiore o minore probabilità di una rottura delle pareti stesse;

in qualche modo la potenzialità cardiaca datorie e biologiche, che ne dipendono. amo ora nè metodi, nè strumenti che ci lo esatto i postulati della clinica; i dati nano però abbastanza perchè possano esserica. Ma siccome nei metodi numerosi di scopi fondamentali vennero spesso confusi, terminarsi ed il metodo da seguirsi devono so e nell'altro, così, prima di esporre i che modificazioni che vi ho apportate, mi intendiamo per pressione sanguigna: alla mentali potremo meglio giudicare del va- rfezioni dei singoli strumenti e metodi di



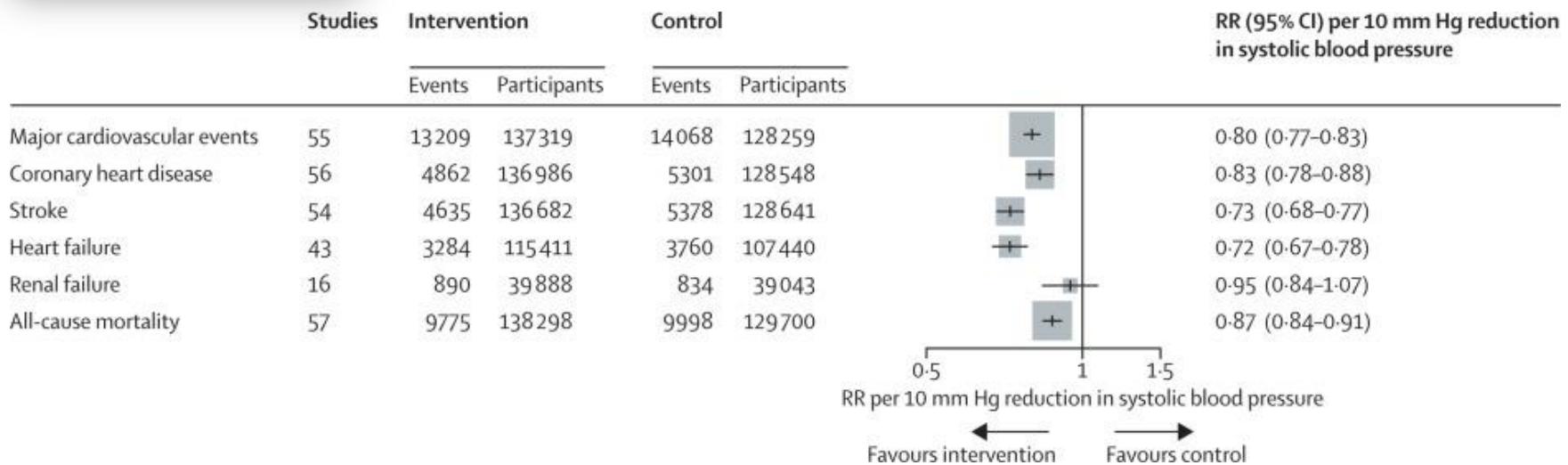


# How manage the blood pressure problem?

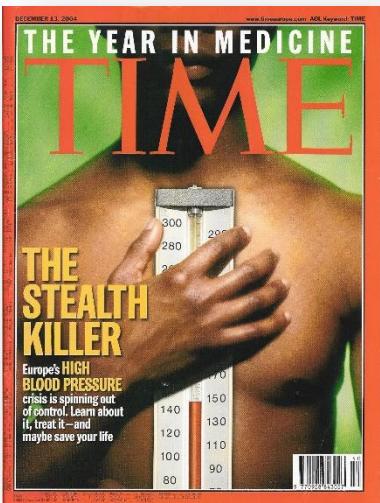


# Standardised effects of a 10 mm Hg reduction in systolic blood pressure.

A systematic review and metanalysis of 123 studies and 613.815 patients

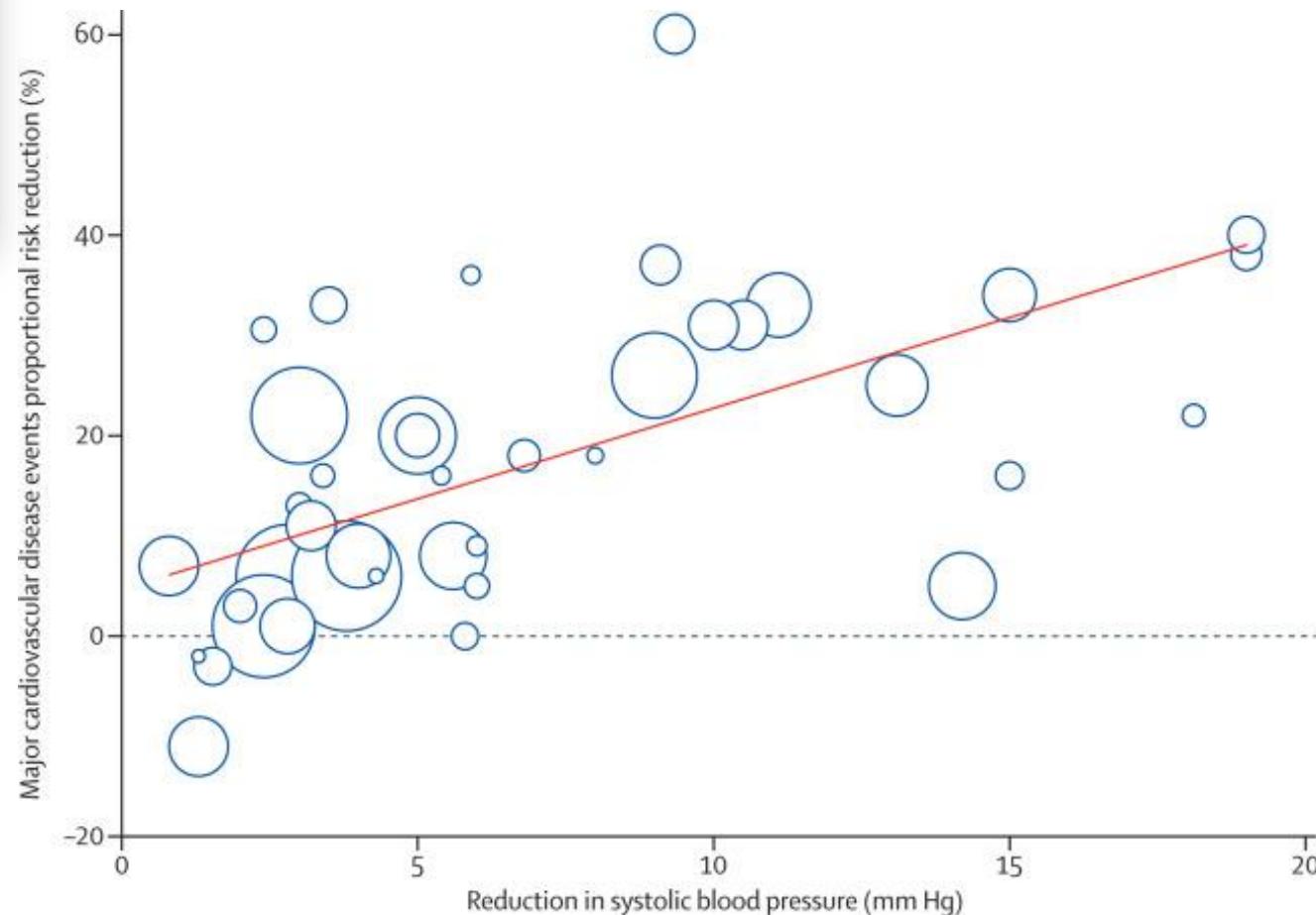


Ettehad E et al, Lancet 2015



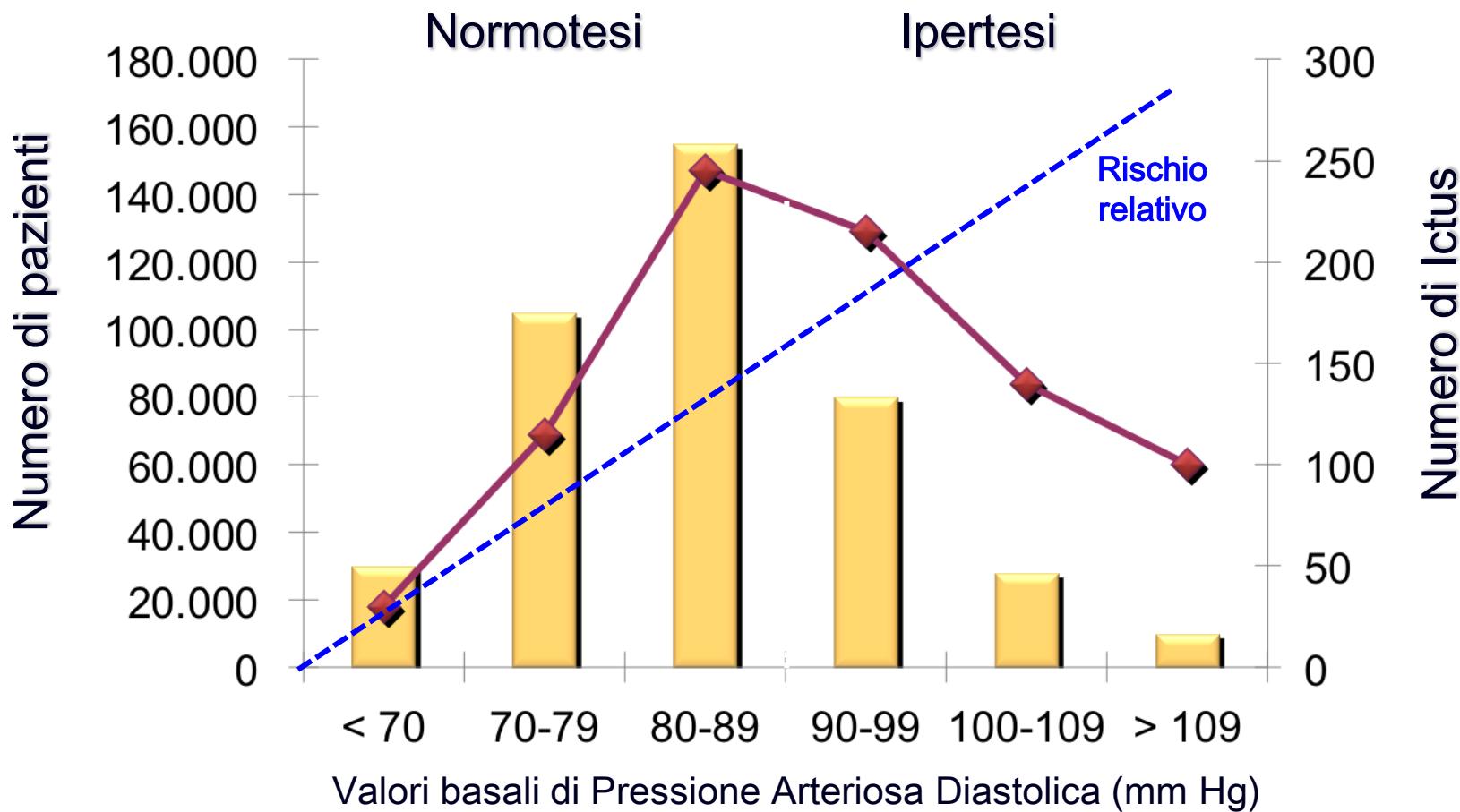
# Meta-regression plot and % of risk reduction in major CV events regressed against the difference in achieved SBP between study treatment groups.

A systematic review and metanalysis of 123 studies and 613.815 patients



Ettehad E et al, Lancet 2015

# Rischio di Ictus nella popolazione generale



MacMahon S et al, *J Hypertens*, 1994,

# Factors affecting the “*blood pressure burden*” in the general population



- Increase with age
- Increase % with “high-normal” BP
- Raised BP in children/adolescents
- New risk factors for BP increase  
(air pollution, noise, geo-magnetic instability, intestinal microbiota, etc)



**Is nutraceutical approach  
a possible solution?**



## Possible impact of nutraceutical approach to BP

- No expectations for “*massive*”BP decreases
- Influence on BP values in the population
- Interference with the progression of BP values (elderly, adolescents-young adults)
- Integrated effect with BP lowering drugs

# Natural Antihypertensive Compounds Categorized By Antihypertensive Class

## *Diuretics*

Hawthorne berry

Mg<sup>2+</sup>

Vitamin B6  
(pyridoxine)

Ca<sup>2+</sup>  
Taurine

Protein

Celery

Fiber

GLA

Co-Q-106

Vitamin C (ascorbic acid)  
L-Carnitine

## *CCBs*

$\alpha$ -Lipoic acid

Hawthorne berry

Vitamin C (ascorbic acid)

Celery

Vitamin B6 (pyridoxine)

$\omega$ -3 FAs (EPA and DHA)

Magnesium (Mg<sup>2+</sup>)

Calcium

NAC

Garlic

Vitamin E

## *$\beta$ -Blockers*

Hawthorne berry

## *Central $\alpha$ Agonists*

Taurine

Vitamin C2.

K<sup>+</sup>

Vitamin B6

Zn

Co-Q-10

Na<sup>+</sup> restriction

Celery

Protein

GLA/DGLA

Fiber

Garlic

## *Direct vasodilators*

$\omega$ -3 FAs

Flavonoids

MUFAs ( $\omega$ -9 FAs)

Vitamin C

K+11. Vitamin E

Mg<sup>2+</sup>

Co-Q-10

Ca<sup>2+</sup>

L-Arginine

Soy

Taurine

Fiber

Celery

Garlic

ALA

## *ACEIs*

Garlic

Geletin

Seaweed-various (Wakame, etc)

Sake

Tuna protein/muscle, Sardine protein/muscle

EFA ( $\omega$ -3 FAs)

Chicken egg yolks

Hawthorne berry

Zein

Bonito fish (dried), Dried salted fish

Pycnogenol

Fish sauce

Casein, Zn

Hydrolyzed whey protein

Hydrolyzed wheat germ isolate

Sour milk

## *ARBs*

Potassium (K<sup>+</sup>)

Fiber

Garlic

Vitamin C

Vitamin B6 (pyridoxine)

Co-Q-10

Celery

GLA and DGLA

## REVIEW-THEMED ISSUE

## Nutraceuticals with a clinically detectable blood pressure-lowering effect: a review of available randomized clinical trials and their meta-analyses

Dietary supplement/ nutraceutical	Level of evidence	Potential mechanisms involved in blood pressure regulation
Aged garlic extract	Meta-analysis of randomized controlled trials	↑ NO production; ↑ H <sub>2</sub> S; ↑ bradykinin; ↓ catecholamine sensitivity; ACE inhibition; calcium channel blocking
Beetroot juice	Meta-analysis of randomized controlled trials	↑ NO availability
Calcium (in pregnancy)	Meta-analysis of randomized controlled trials	Unknown
Chelated magnesium	Meta-analysis of randomized controlled trials	Calcium channel blocking; ↑ PGE; ↑ NO synthesis
Cocoa flavonoids	Meta-analysis of randomized controlled trials	Antioxidation; free radical scavenging; ↑ NO production and endothelial function; ↓ inflammation; ↓ ROS production (NADPH oxidase inhibition)
Coenzyme Q10 (high dosage in hypertensive patients)	Meta-analysis of randomized controlled trials	Antioxidation; free radical scavenging; ↑ vitamin and antioxidant regeneration; acts as a cofactor and coenzyme in mitochondrial oxidative phosphorylation; ↑ LDL and lipid oxidation
Controlled-release melatonin (night hypertension)	Meta-analysis of randomized controlled trials	↑ NO production; protection of vessels from oxidation; regulation of circadian rhythms
Fish peptides	Various small randomized controlled trials	ACE inhibition
Isoflavones	Meta-analysis of randomized controlled trials	ACE inhibition?
L-arginine (high dosages)	Meta-analysis of randomized controlled trials	↑ NO availability
Lactotripeptides	Meta-analysis of randomized controlled trials	ACE inhibition?
Lycopene	Meta-analysis of randomized controlled trials	Antioxidation; free radical scavenging
Polyunsaturated fatty acids (high dosages)	Meta-analysis of randomized controlled trials	↓ TXA2 and inflammation; ↑ vasodilator PGs; ↑ NO synthase; ↓ insulin resistance; ↓ RAAS
Potassium	Different randomized controlled trials	↑ Natriuresis; ↑ baroreflex sensitivity modulation; ↑ Na <sup>+</sup> -K <sup>+</sup> -ATPase; ↑ insulin sensitivity; ↓ ATII; ↓ catecholamine sensitivity; ↓ ADMA; ↓ oxidative stress; ↓ TGF-β production
Probiotics	Meta-analysis of randomized controlled trials	ACE inhibition?
Pycnogenol	Meta-analysis of randomized controlled trials	↑ NO production; ↓ ACE; ↑ endothelial function; ↓ myeloperoxidase activity; ↓ urinary albumin excretion
Resveratrol	Meta-analysis of randomized controlled trials	↑ NO production; protection of vessels from oxidation; ↓ vascular inflammation; ↓ platelet aggregation
Vitamin C	Meta-analysis of randomized controlled trials	↓ adrenal steroid production and serum aldehydes; ↓ binding affinity of the ATIR for ATII; ↑ Na <sup>+</sup> -K <sup>+</sup> -ATPase; ↑ natriuresis; ↑ superoxide dismutase; ↑ cyclic GMP; ↑ NO and PG <sub>E2</sub>

ACE, angiotensin-converting enzyme; ADMA, asymmetric dimethylarginine; ATIR, angiotensin II type 1 receptor; ATII<sub>α</sub>, angiotensin II; H<sub>2</sub>S, hydrogen sulfide; LDL, low-density lipoprotein; NO, nitric oxide; PG, prostaglandin; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TX, thromboxane.

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Keywords blood pressure, BP, clinical evidence review, dietary supplements, hypertension, nutraceuticals

## Dietary supplements and nutraceutical with a clinically relevant effect on blood pressure

*Promossi*

*Bocciati  
(Rimandati)*

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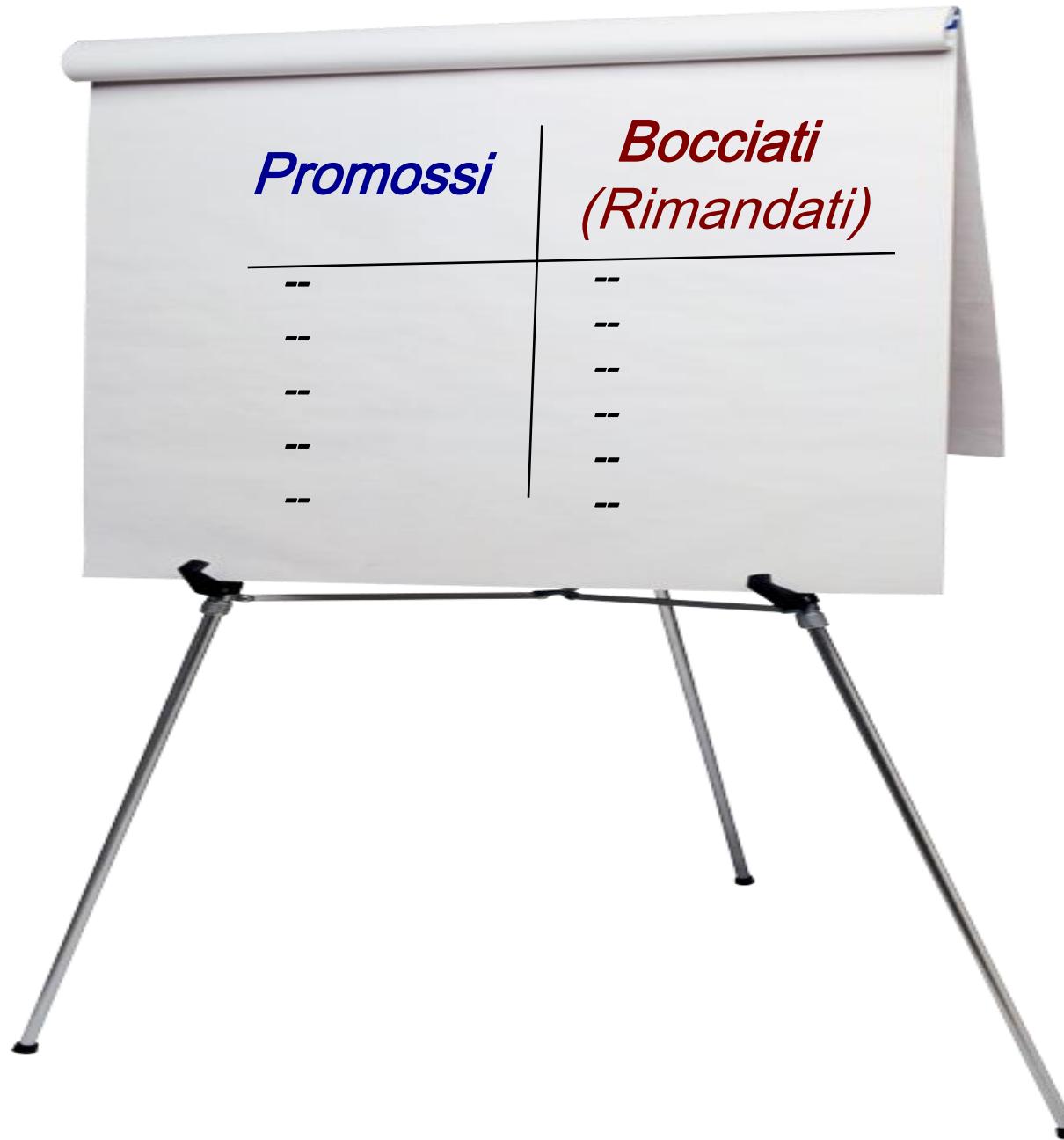
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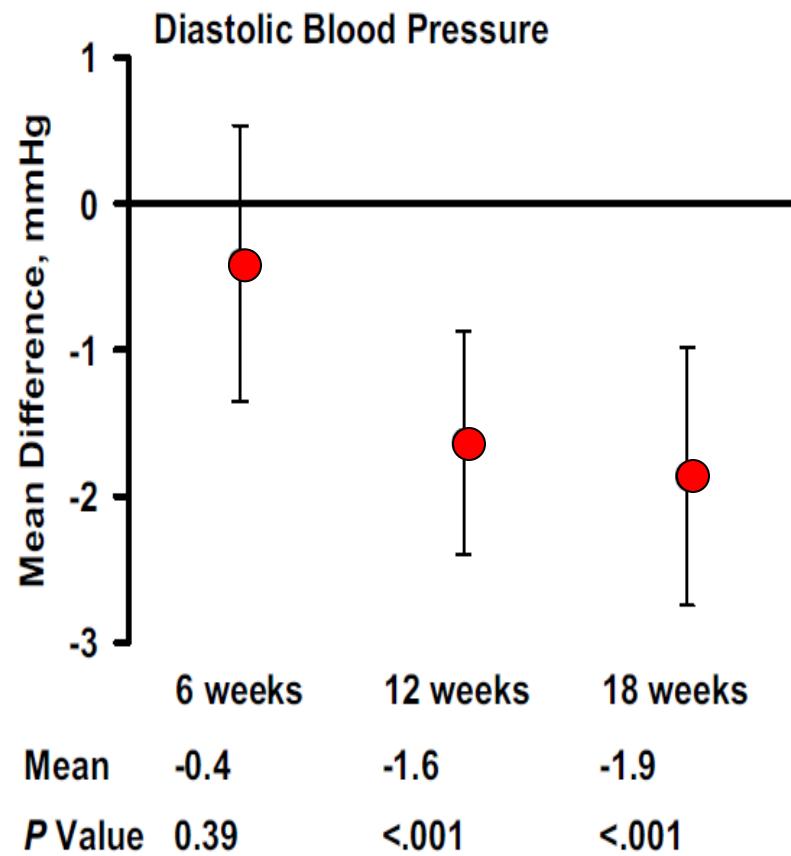
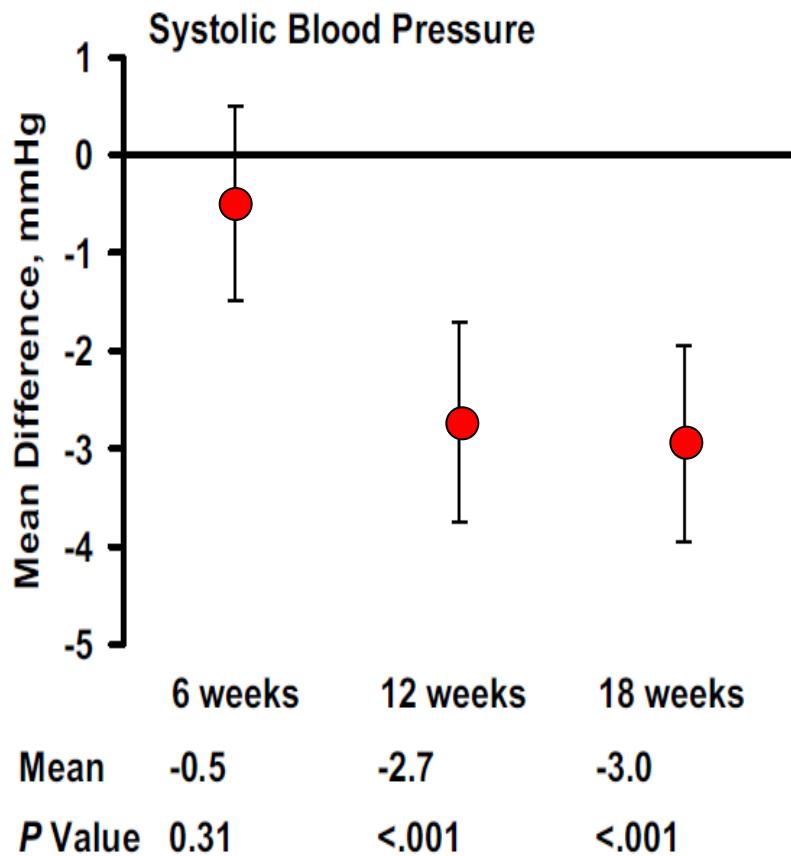
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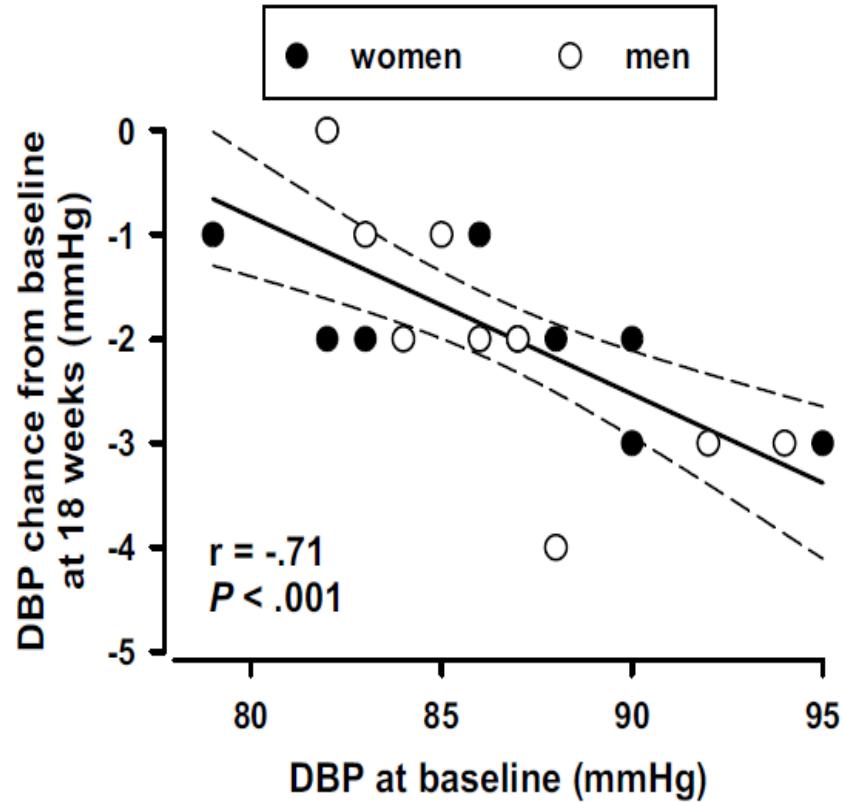
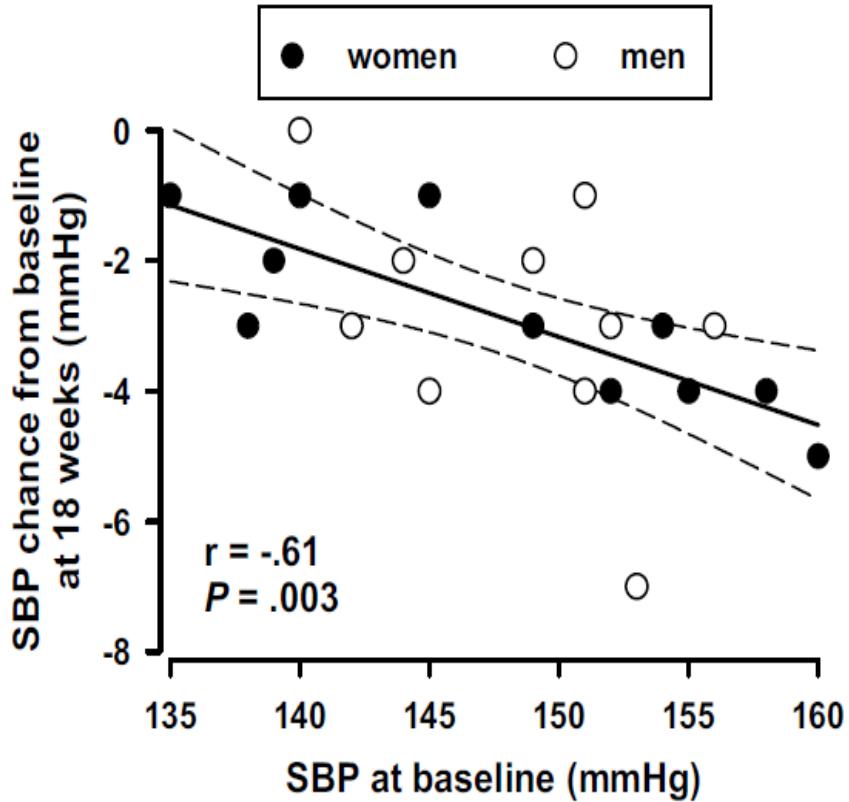


# Effects of Habitual Cocoa Intake on Blood Pressure in untreated upper-range pre-hypertension or stage 1 HTN



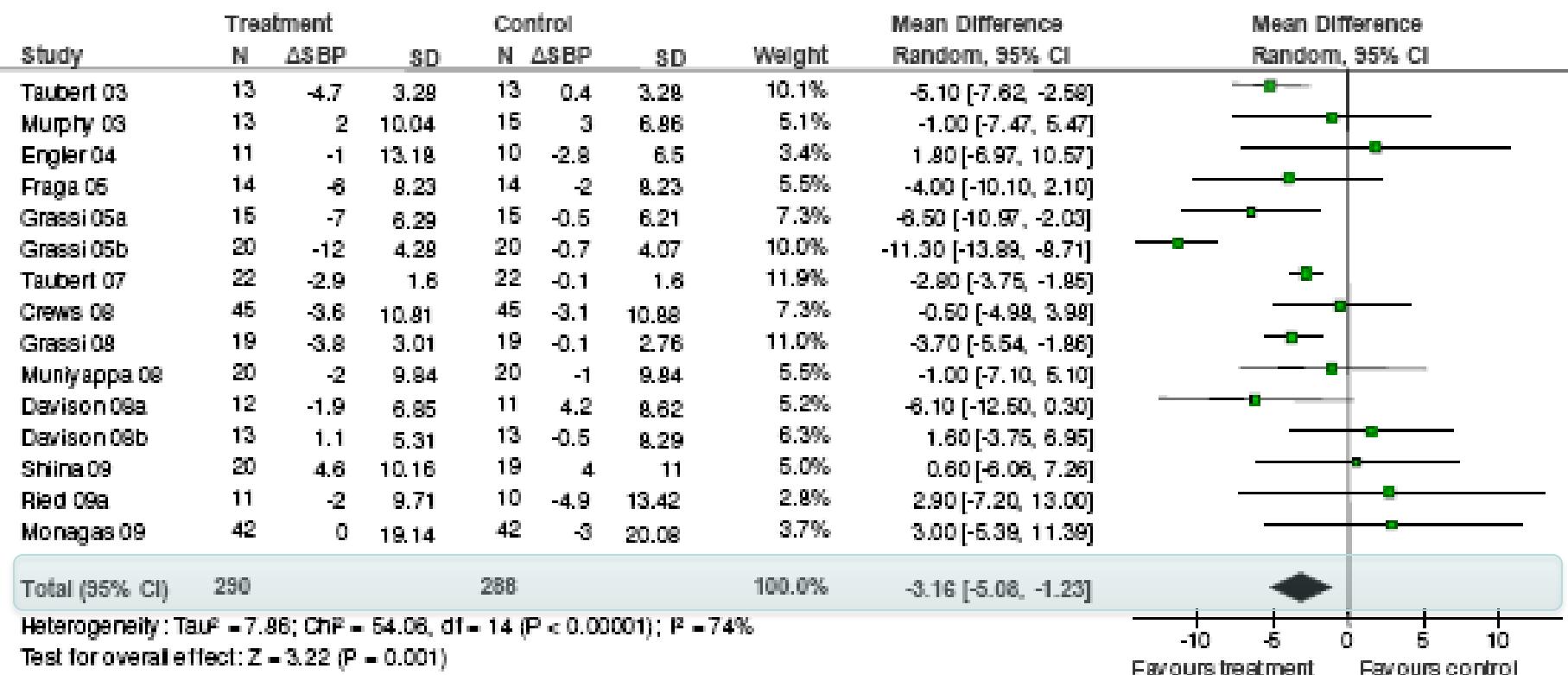
Taubert et al. JAMA 2007;298(1):49-60

# Blood Pressure Reductions after 18 Weeks of Dark Chocolate in Relation to Baseline Blood Pressure



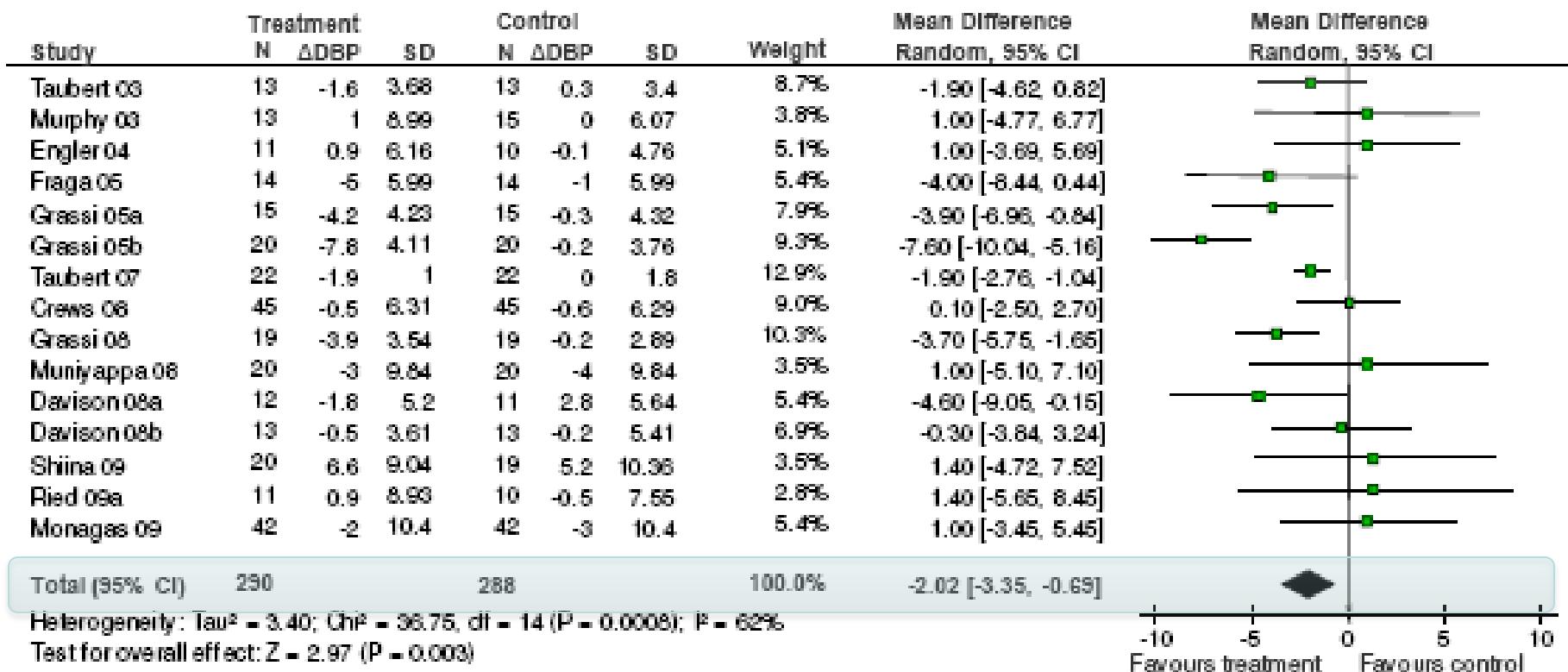
Taubert et al. JAMA 2007;298(1):49-60

# Cioccolato e pressione sistolica



Ried K et al. *BMC Medicine* 2010, 8:39

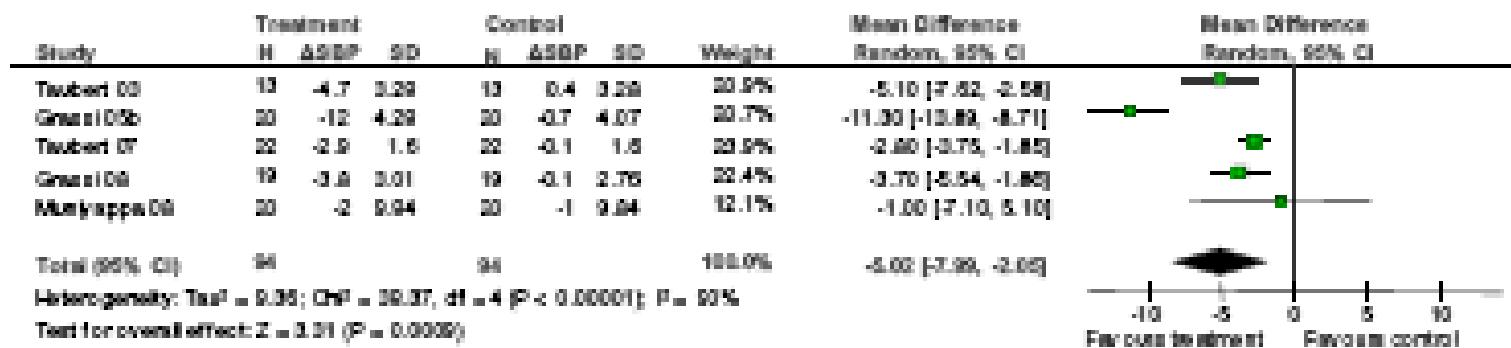
# Cioccolato e pressione diastolica



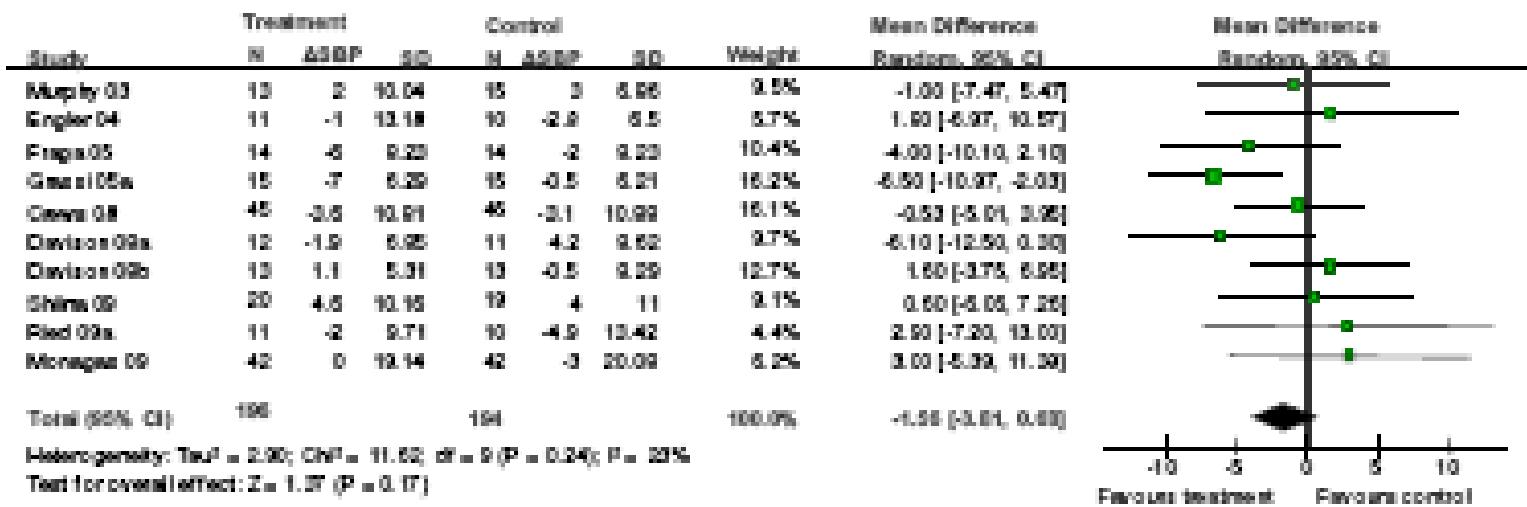
Ried K et al. *BMC Medicine* 2010, 8:39

# Cioccolato, PAS basale e riduzione pressoria

## A) SBP hypertensive subgroup ( $\geq 140$ mm Hg)



## B) SBP normotensive subgroup ( $< 140$ mm Hg)





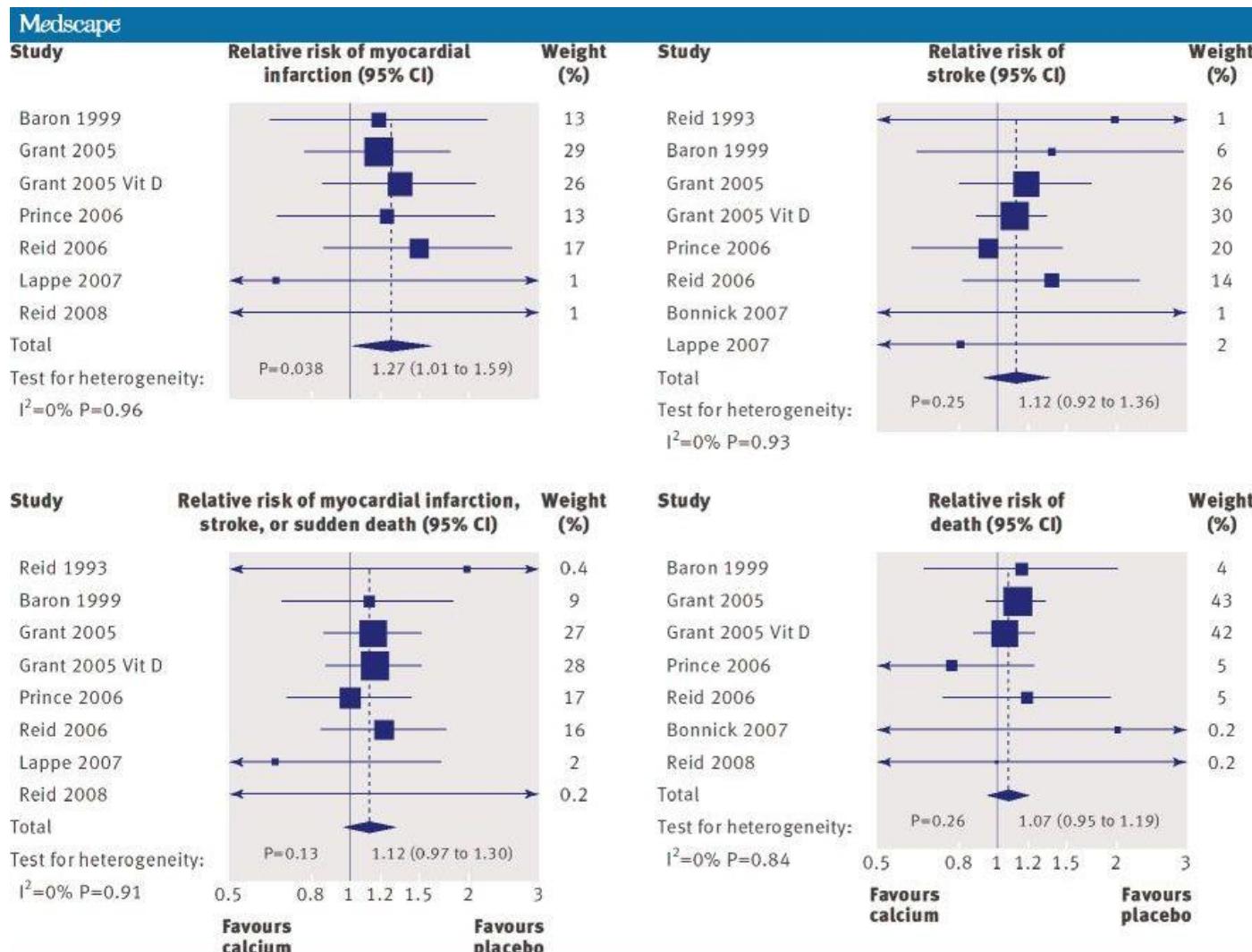
# The effect depends on age !

THE COCHRANE  
COLLABORATION®

	< 50yrs	> 50yrs
Mean difference SBP (95% CI)	-4.57 (7.41, -1.73) mm Hg, p=0.002, n=10	-0.96 (-3.44, 1.52) mm Hg, p=0.45, n=10
Mean difference DBP (95% CI)	-3.85 (-5.45, -2.26) mm Hg, p<0.001, n=9	-0.89 (-1.80, 0.01) mm Hg, p=0.05, n=10

*Cochrane Database of Systematic  
Reviews 2012, Issue 8. Art. No.: CD008893.*

# Effetti della somministrazione di Calcio nella popolazione generale



Source: BMJ © 2010 BMJ Publishing Group Ltd

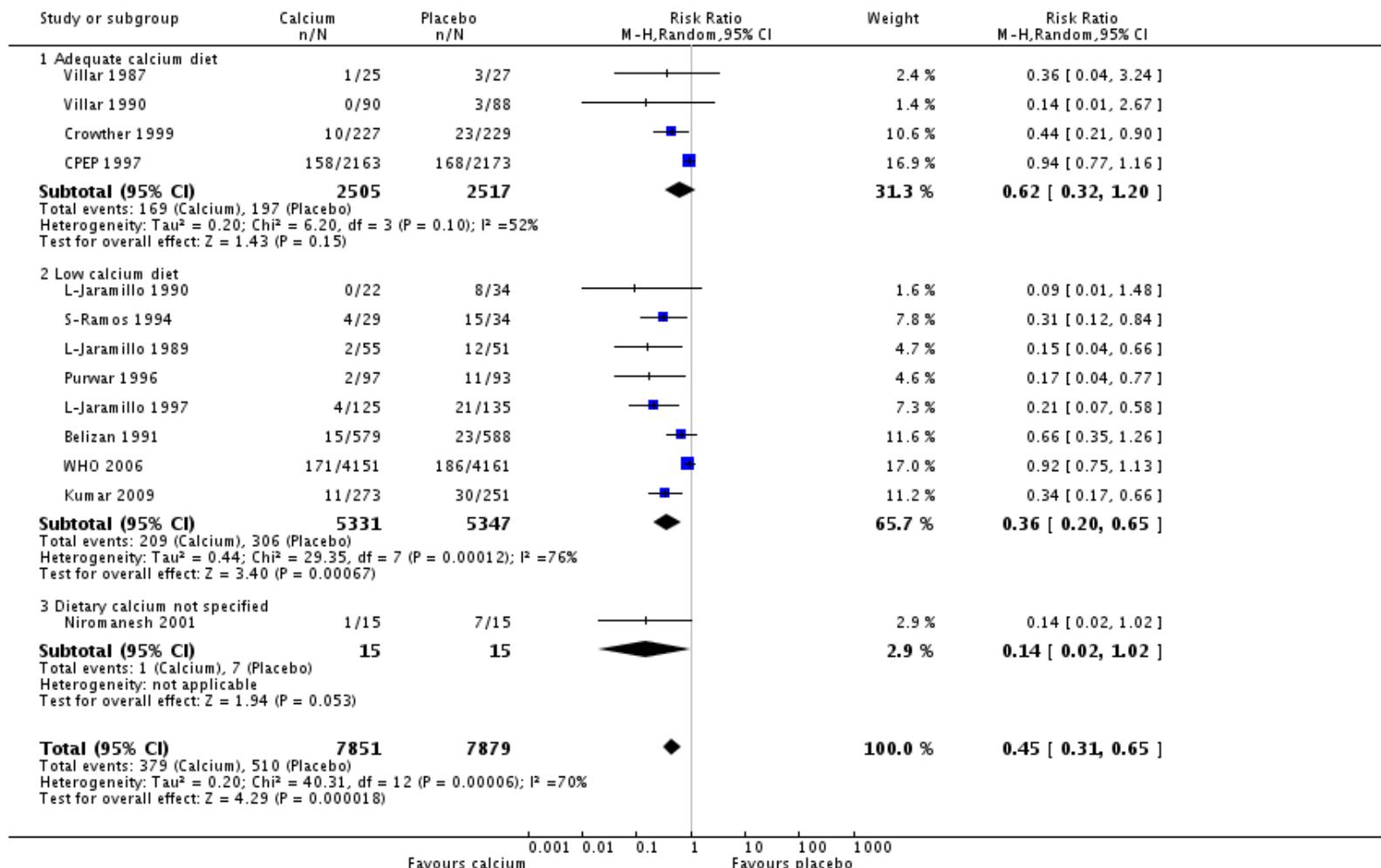
Bolland MJ et al. BMJ 2010; 341:c3691

# Calcium supplementation and *pre-eclampsia* by dietary calcium intake

Review: Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems

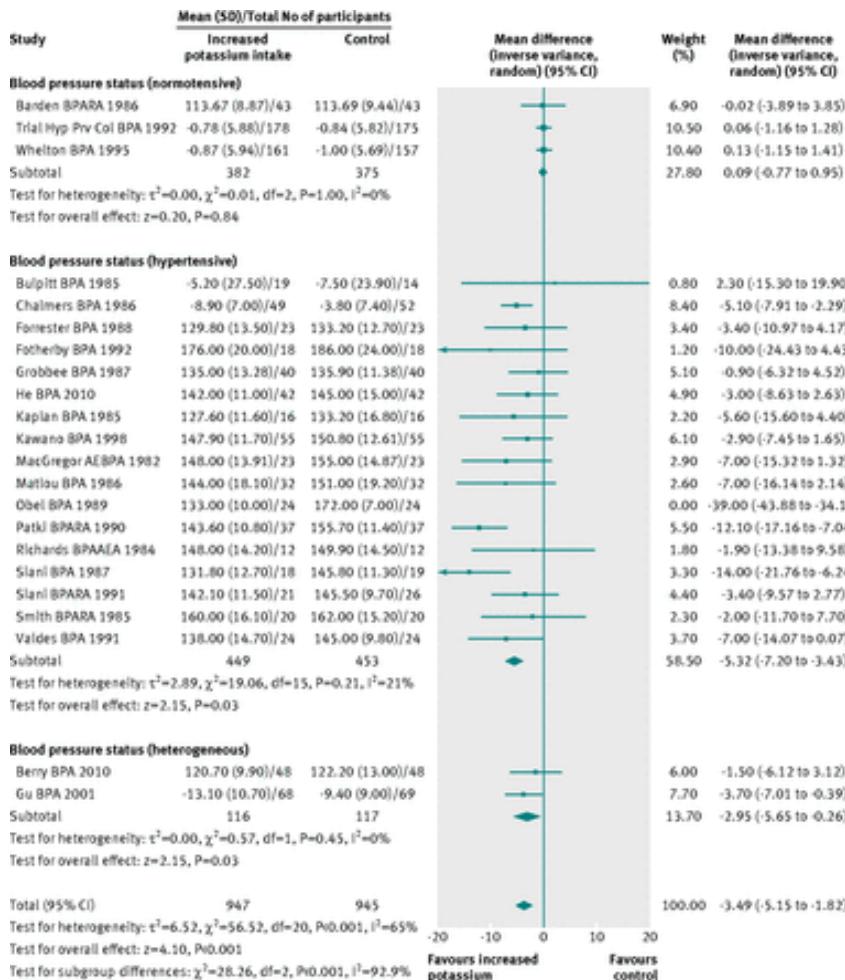
Comparison: 1 Routine calcium supplementation in pregnancy by baseline dietary calcium

Outcome: 2 Pre-eclampsia

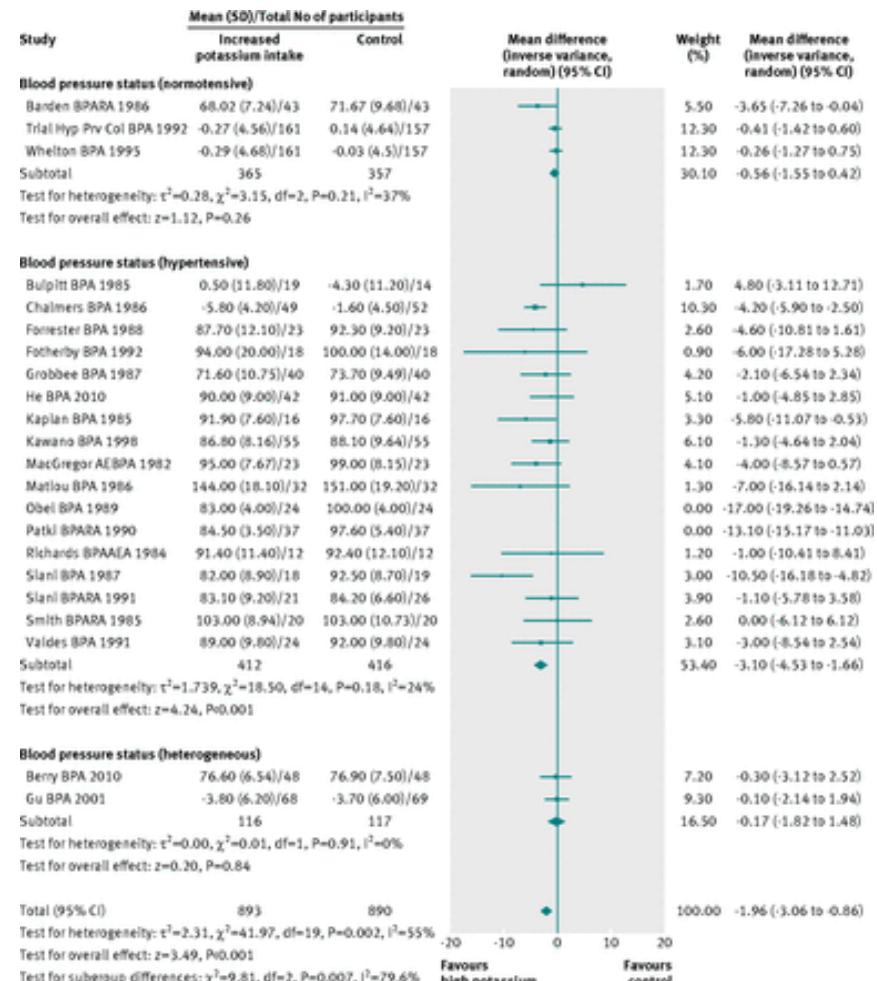


# Effect of increased K intake on HPT: meta-analyses and subgroup analysis

SBP



DBP



## ORIGINAL ARTICLE

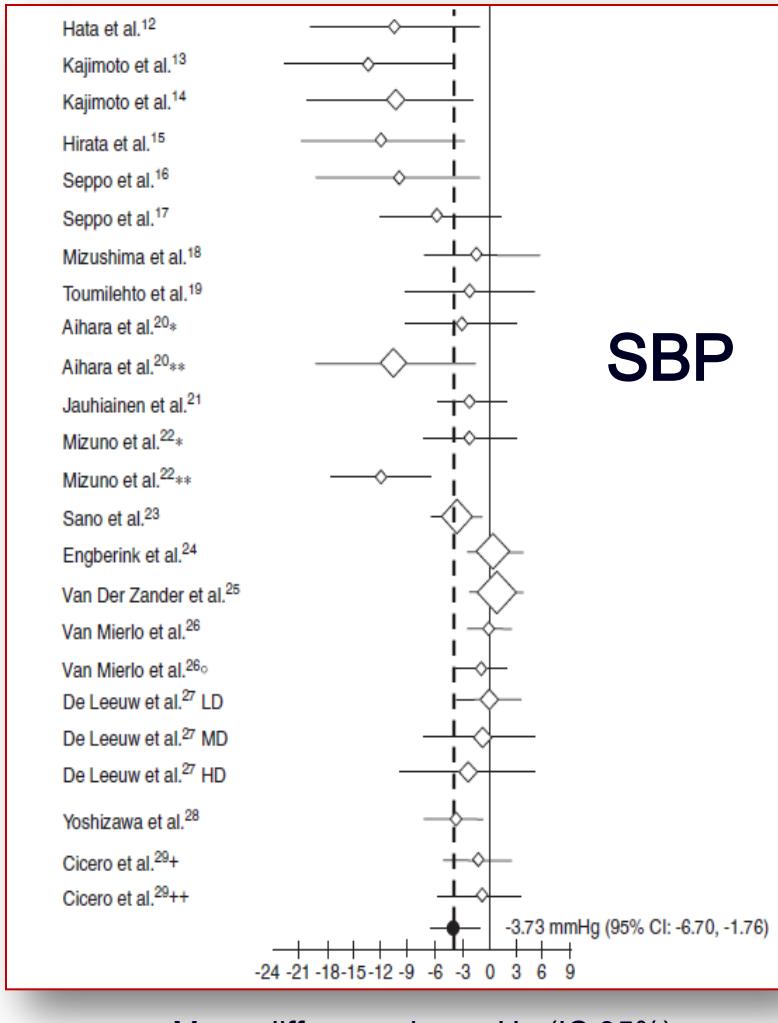
# Blood pressure lowering effect of lactotripeptides assumed as functional foods: a meta-analysis of current available clinical trials

AFG Cicero, B Gerocarni, L Laghi and C Borghi

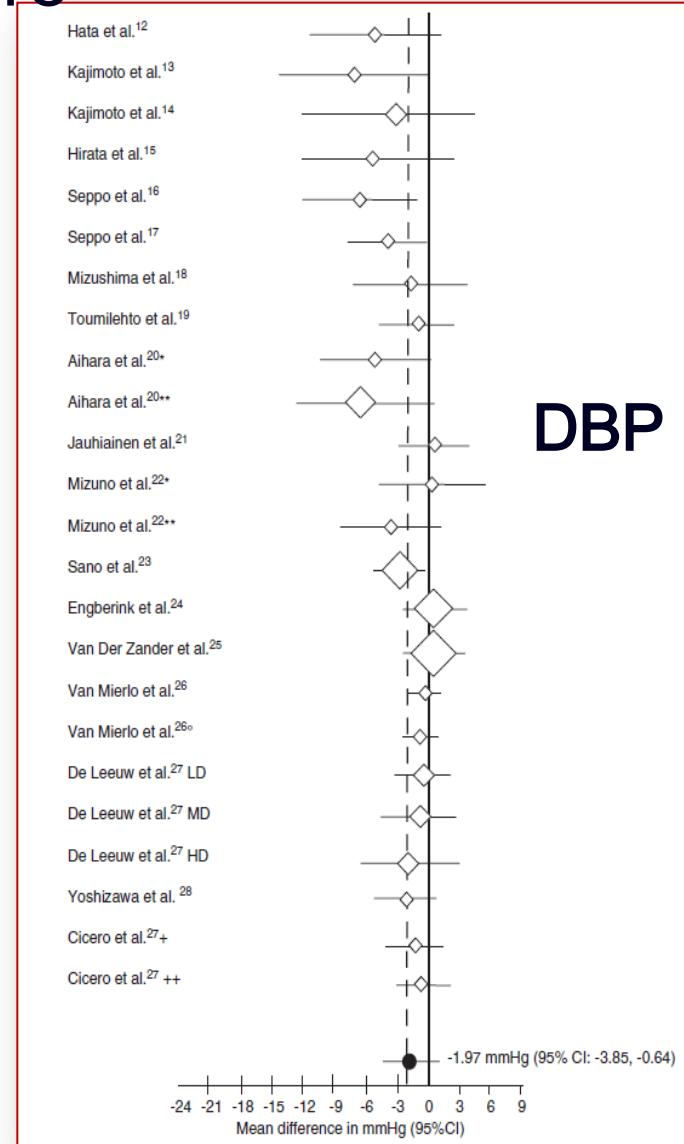
*Internal Medicine, Aging and Kidney diseases Department, Sant'Orsola-Malpighi University Hospital,  
University of Bologna, Bologna, Italy*

# Meta-analysis of RCTs on LTPs and Blood Pressure

PAS (Heterogeneity: P = 0,03, test di Egger: P = 0,38)



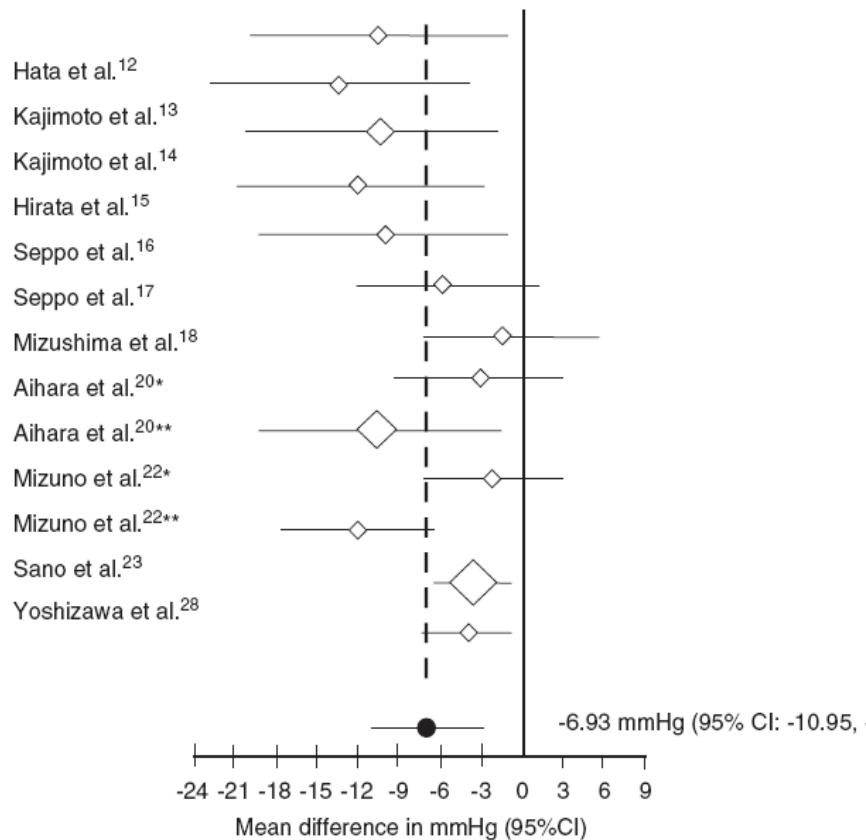
PAS (Heterogeneity: P = 0,04, test di Egger: P = 0,29)



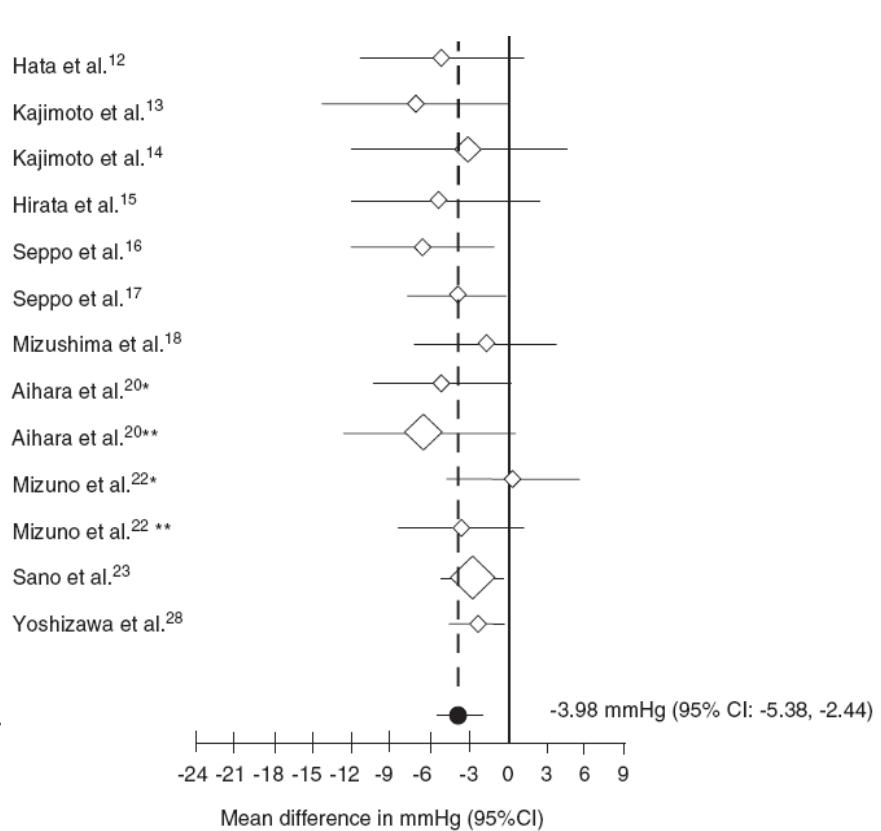
\*High-normal BP  
\*\* Mild HBP

# Is the effect significantly higher in Asian subjects? Results of metanalysis

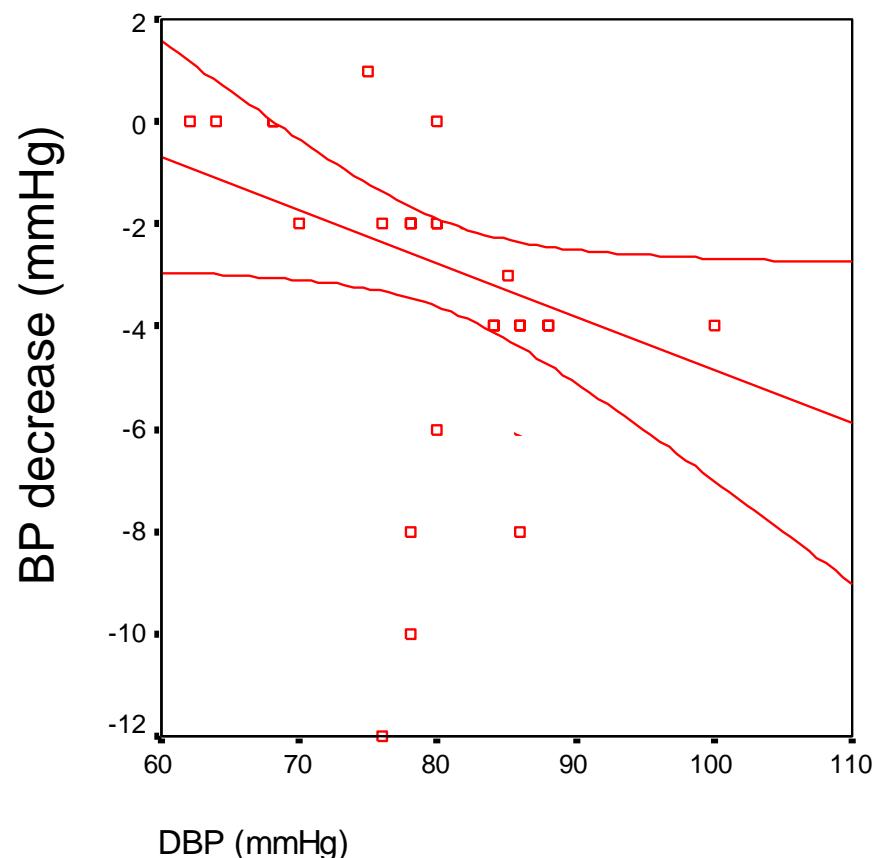
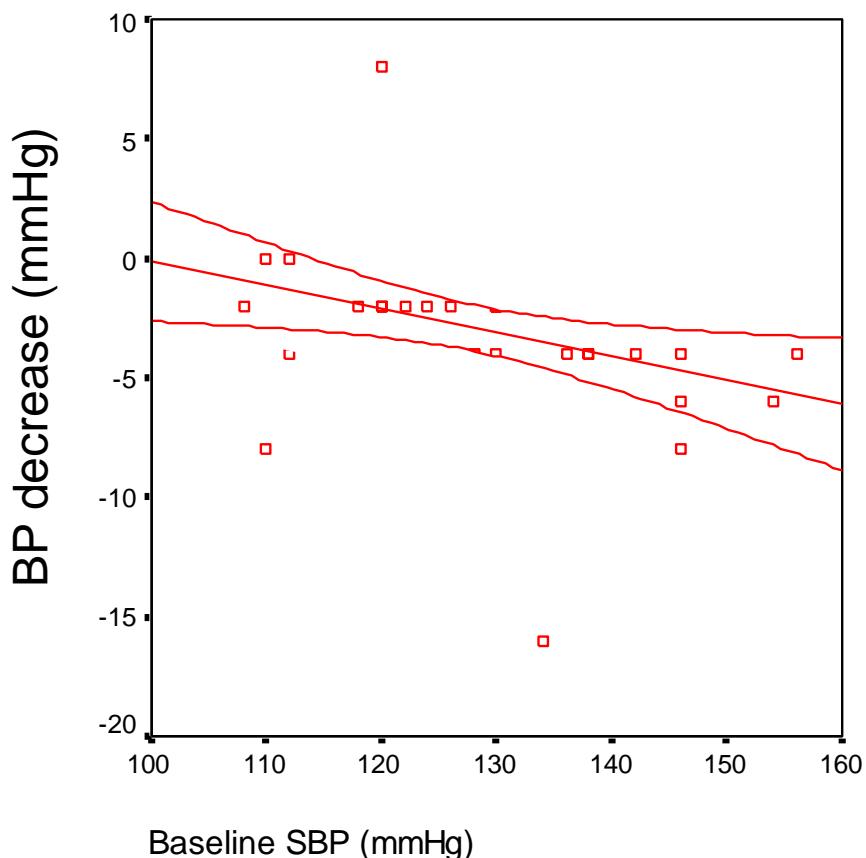
- 7 mmHg



- 4 mmHg



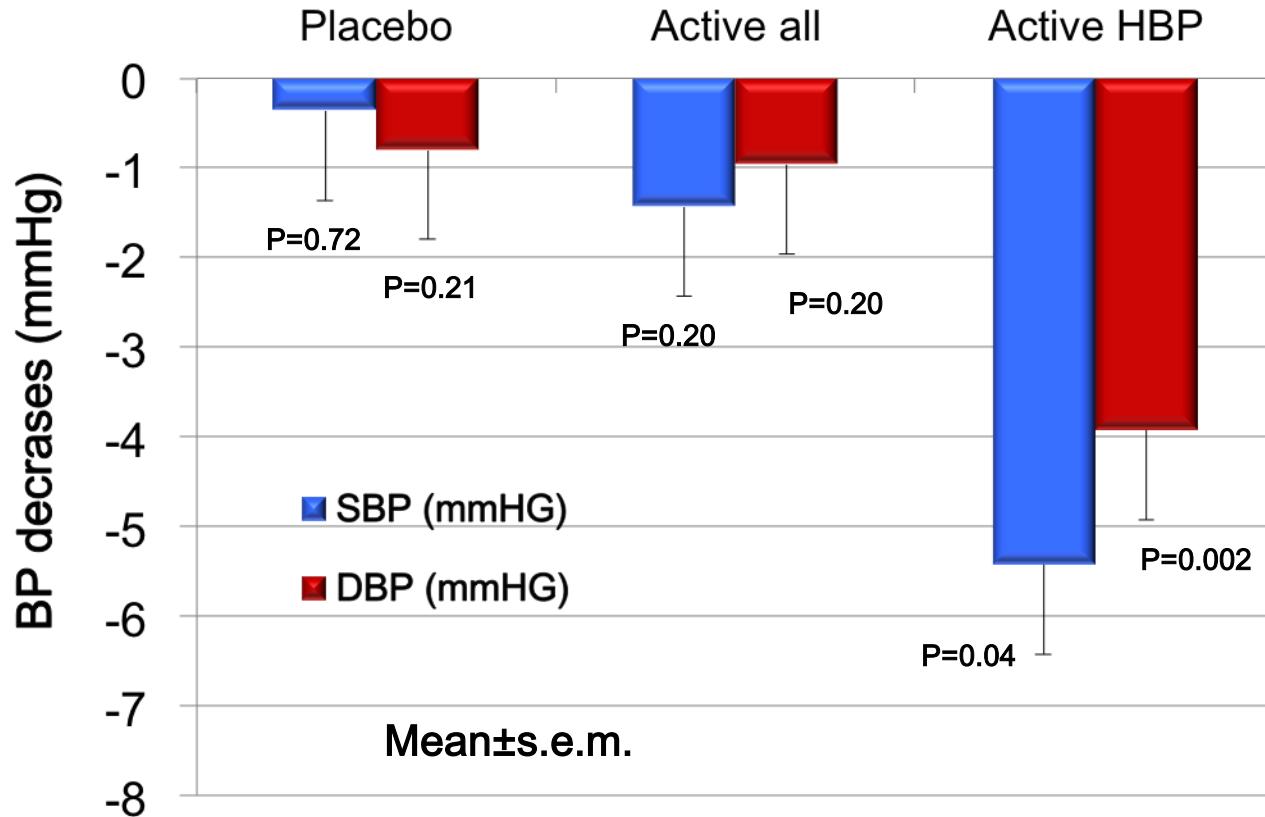
# Relationship between BP decrease and baseline Systolic and Diastolic blood pressure in subjects treated with Ile-Pro-Pro/Val-Pro-Pro lactopeptide



Cicero AFG et al, J Hum Hypertens 2010

# Effects of a lactotripeptide-enriched juice on ABPM in 50 patients with normal and high-normal HBP

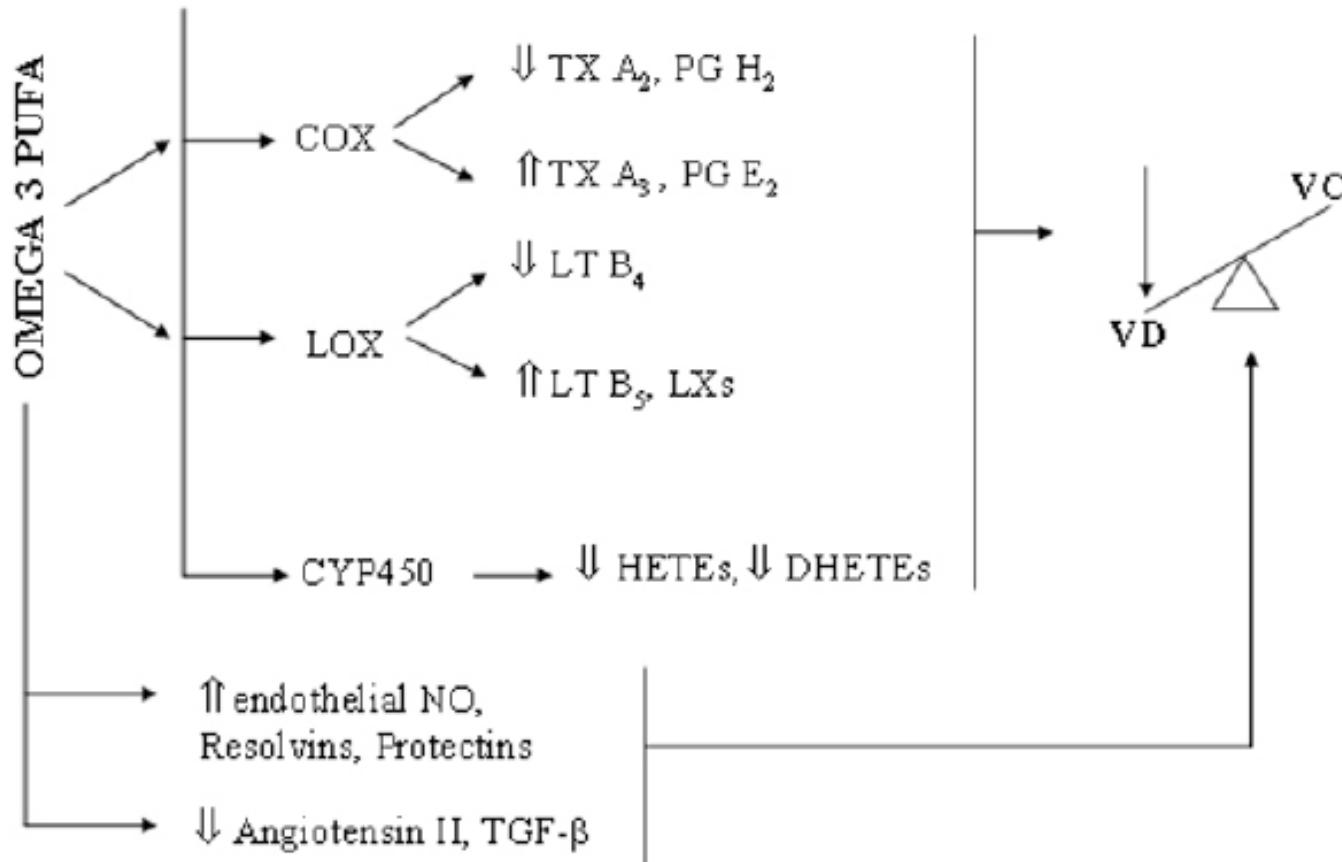
A double-blind, cross over study



Cicero AFG et al, 2010

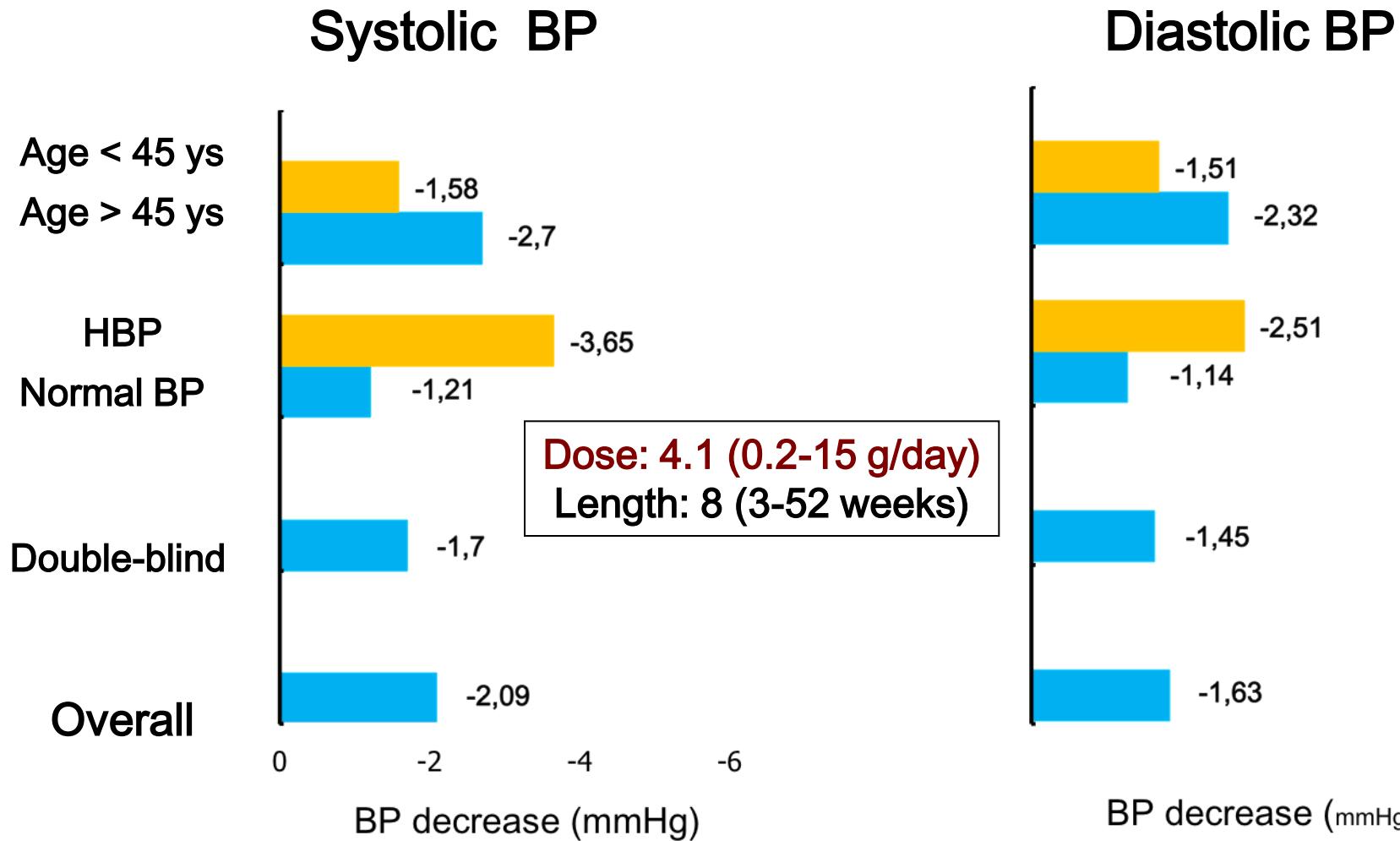
# Omega 3 PUFAs and BP

## ARACHIDONIC ACID



-3 mmHg  
SBP  
- 2.5  
mmHg  
DBP

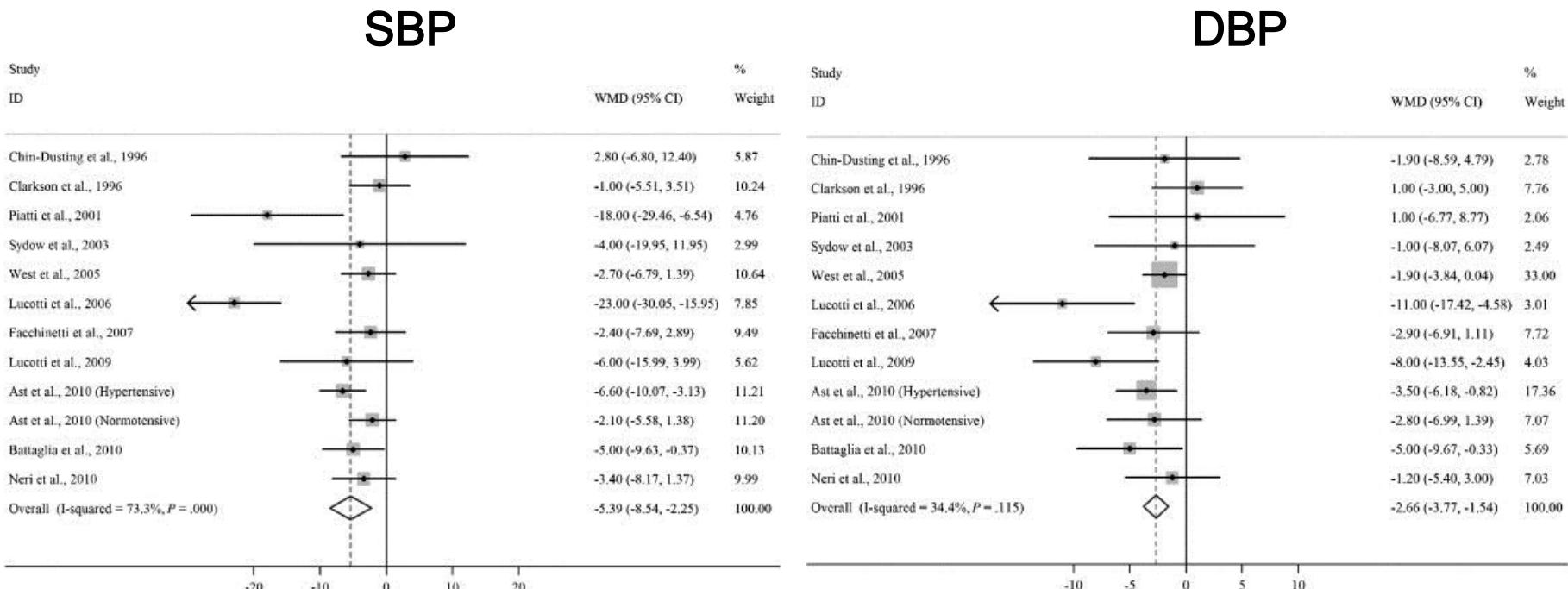
# Metanalysis of 36 different randomized and controlled trials assessing the effects of n-3 PUFA on blood pressure



Geleijnse et al, 2001

# Effect of oral L-arginine supplementation on BP: A meta-analysis of RCTs

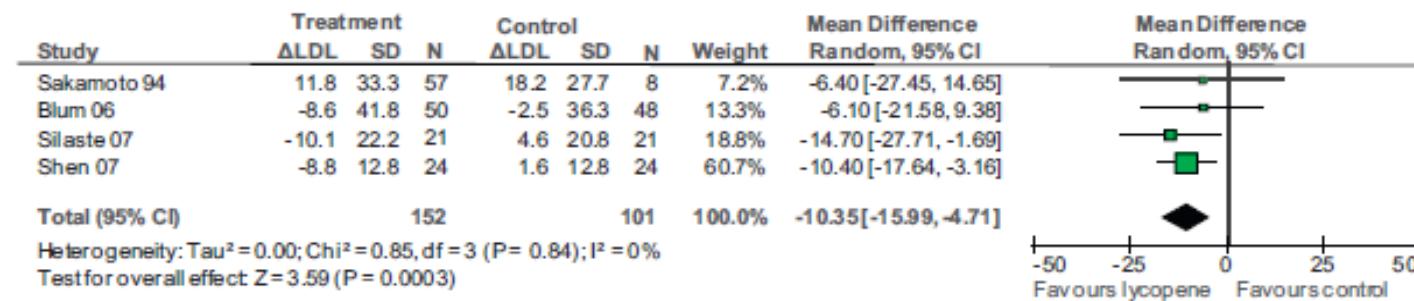
Dose ranging from 4 to 24 gr/day



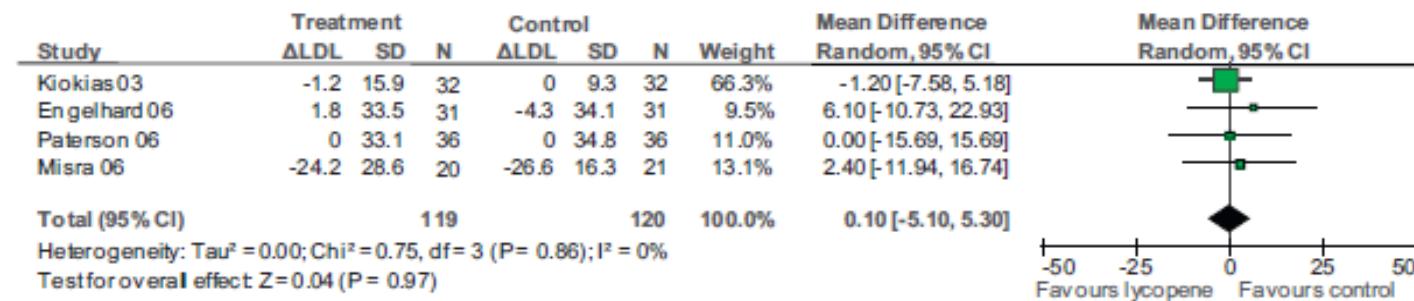
Dong et al. Am Heart J 2011;162:959-65

# Lycopene, LDL-C and BP: a meta-analysis of RCTs

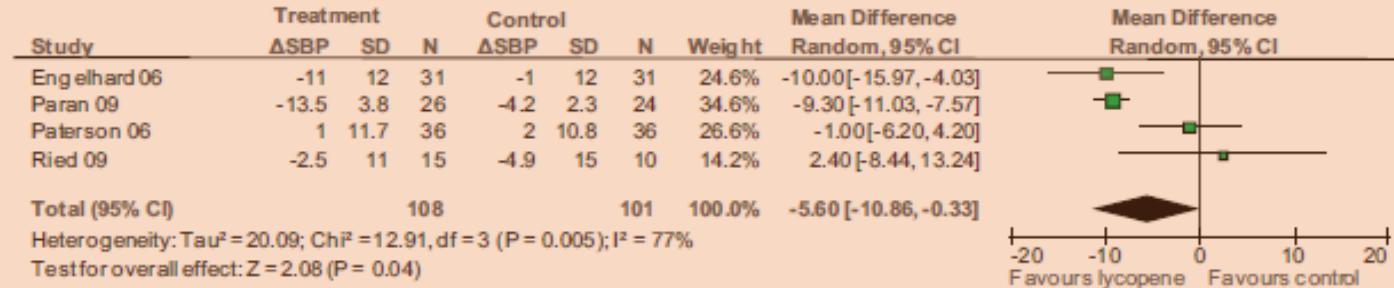
## C LDL cholesterol, high dose lycopene



## D LDL cholesterol, low dose lycopene



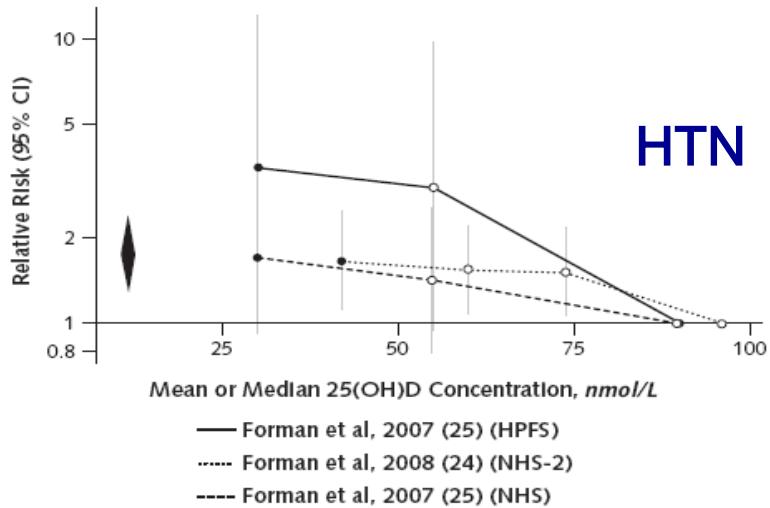
## A SBP all studies



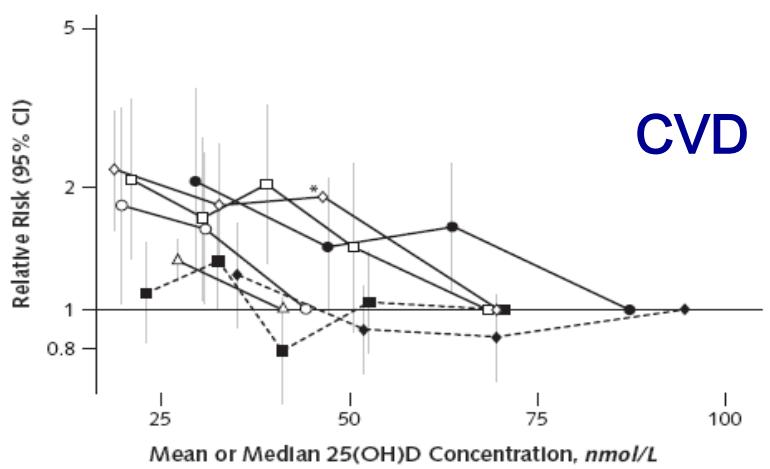
*Promossi*

*Bocciati  
(Rimandati)*





HTN

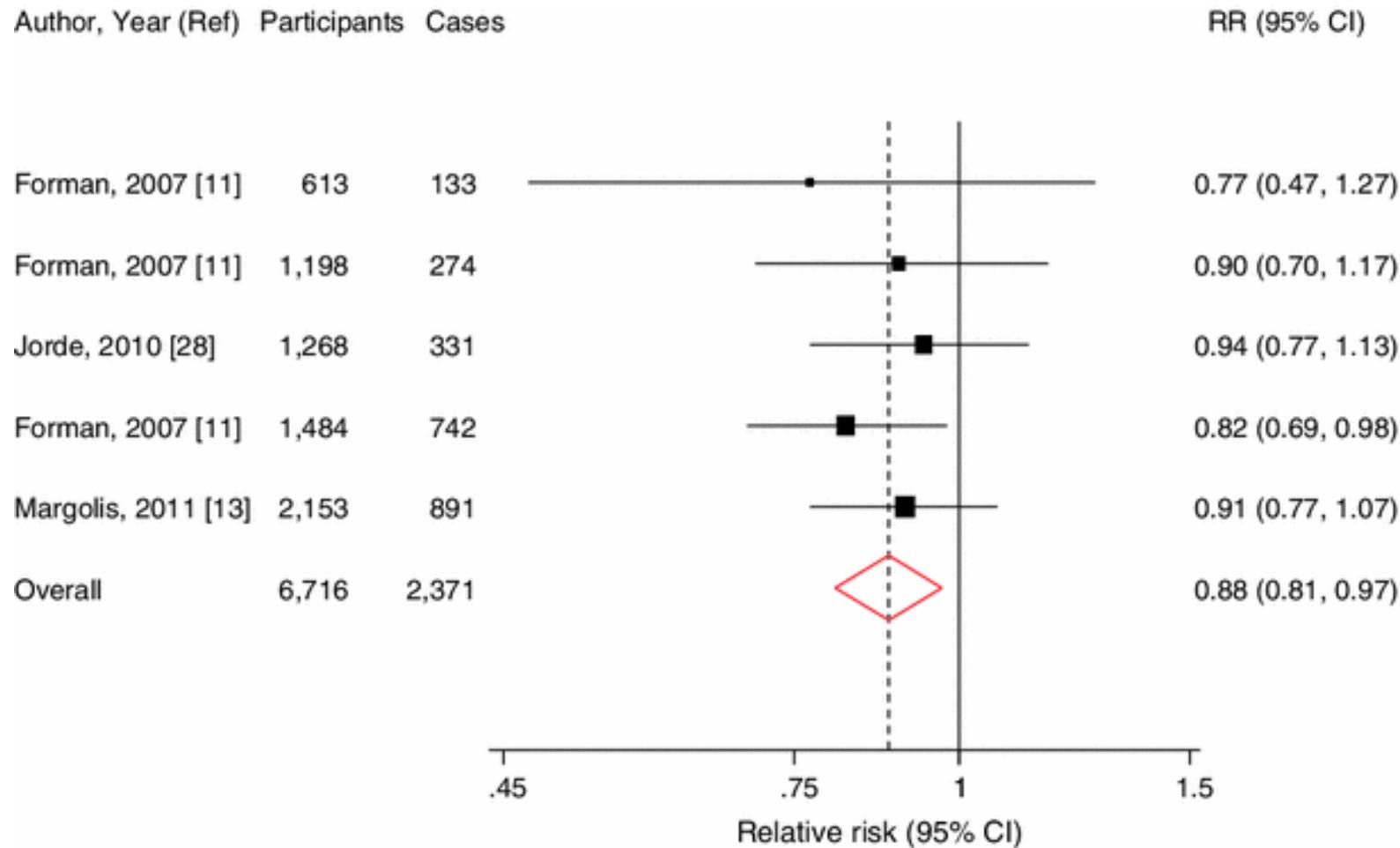


CVD

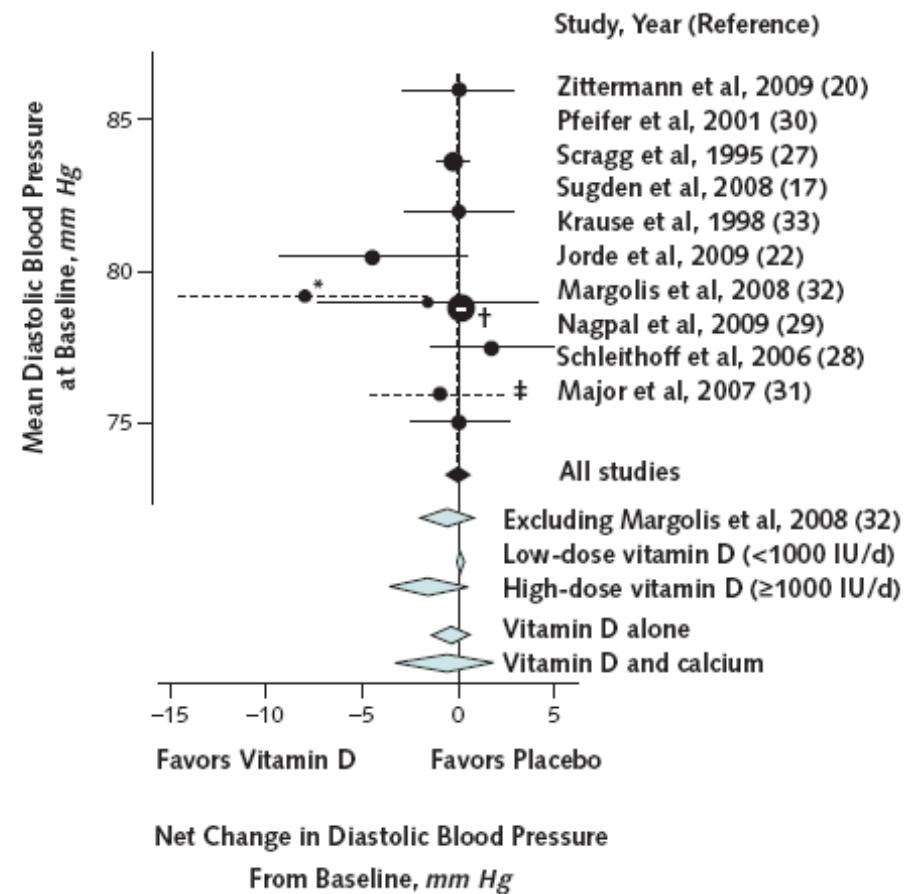
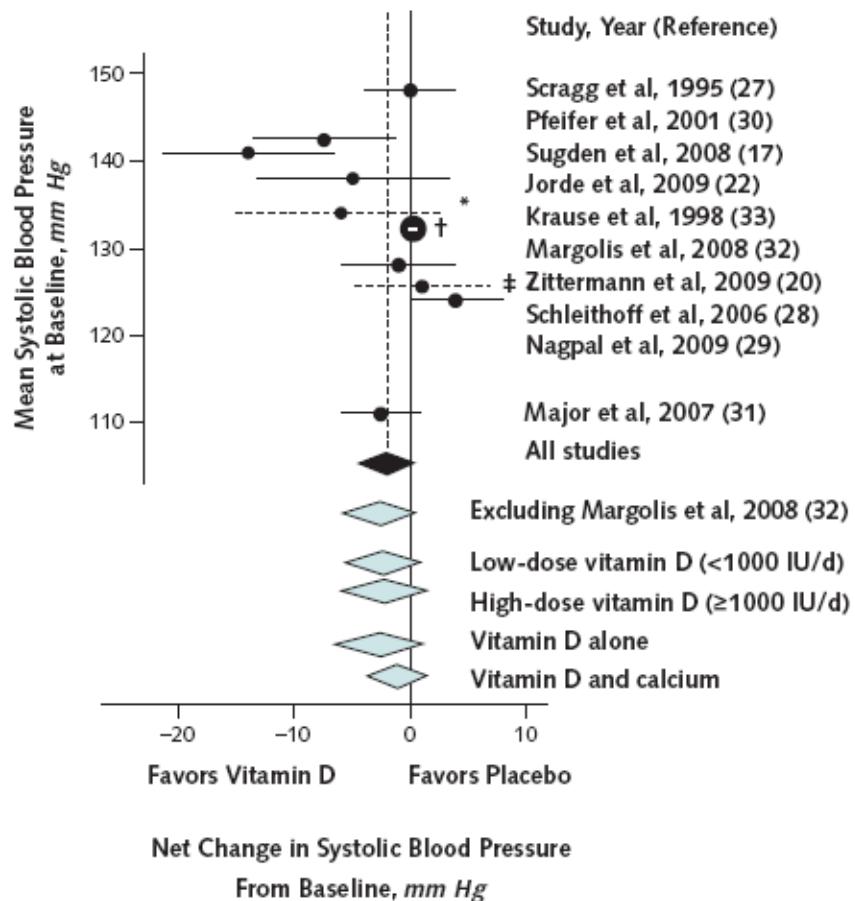
# Concentrazione sierica di Vitamina D ed incidenza di ipertensione e malattia cardiovascolare in studi epidemiologici

*Pittas et al. Ann Intern Med.*  
2010;152:307-314

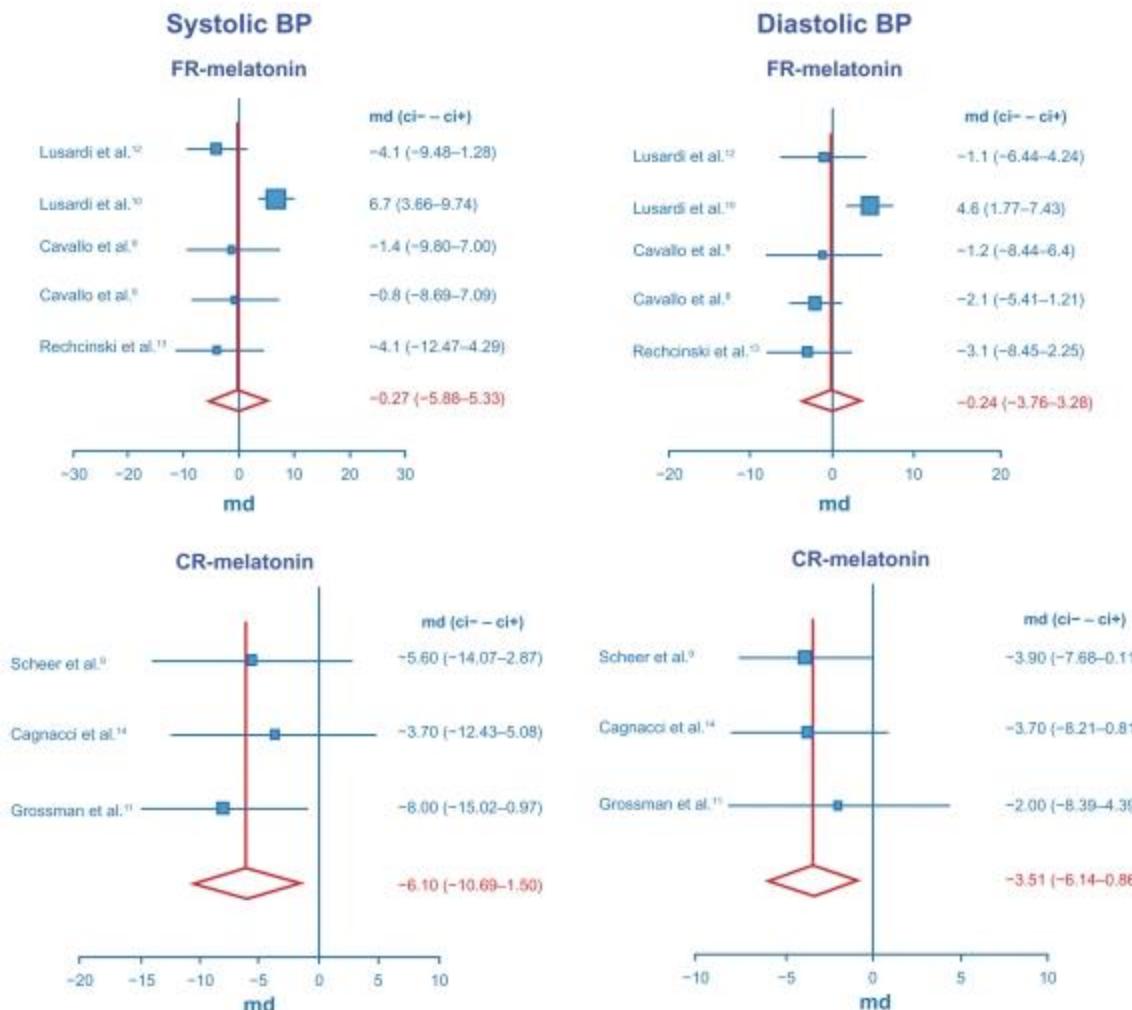
# RR for hypertension per 10 ng/mL increment in 25(OH) D levels



# Metanalisi degli studi di intervento

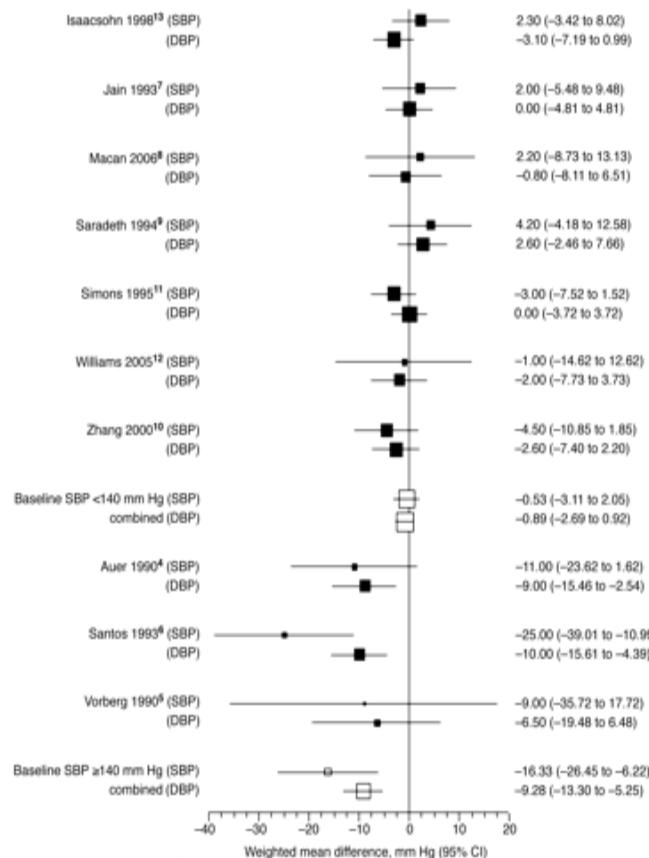


# Effect of fast-and controlled-release melatonin on nocturnal BP: meta-analysis of RCTs



## Effects of Garlic on Blood Pressure in Patients With and Without Systolic Hypertension: A Meta-Analysis

Kurt M Reinhart, Craig I Coleman, Colleen Teevan, Payal Vachhani, and C Michael White



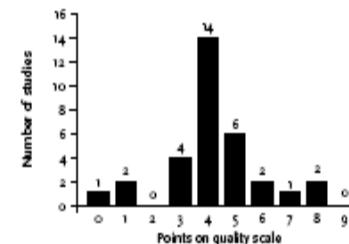
10 000 µg of allicin per day, the amount contained in 4 cloves of garlic (4 g), is required to achieve a significant BP-lowering effect.  
In human beings, the average reduction in SBP is 5 to 8 mm Hg (3 studies/30!).

## A systematic review on the influence of trial quality on the effect of garlic on blood pressure

S. Simons\*, H. Wollersheim\*, T. Thien†

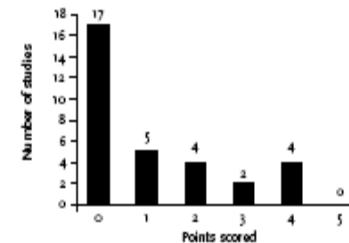
Departments of <sup>1</sup>Pulmonary Diseases and <sup>2</sup>General Internal Medicine, and <sup>3</sup>Scientific Institute on Quality of Healthcare, Radboud University Medical Centre, PO Box 9101, 6500 HB Nijmegen, the Netherlands, \*corresponding author: tel: +31 (0)24-361 4579, fax: +31 (0)24-361 03 24, e-mail: S.Simons@long.umcn.nl

Figure 2. Spread of quality scores on the methodology of the selected clinical trials (n=32)



No points indicates a high suspicion of bias. The quality criteria are mentioned in table 2.

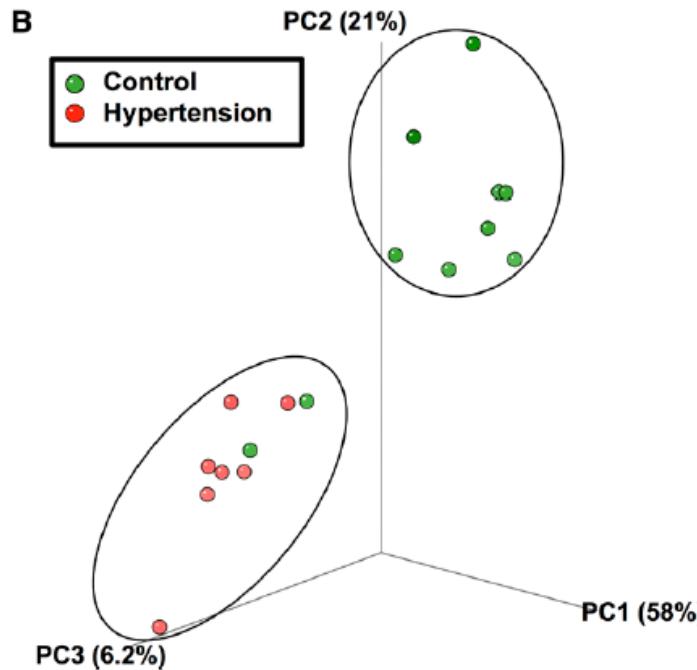
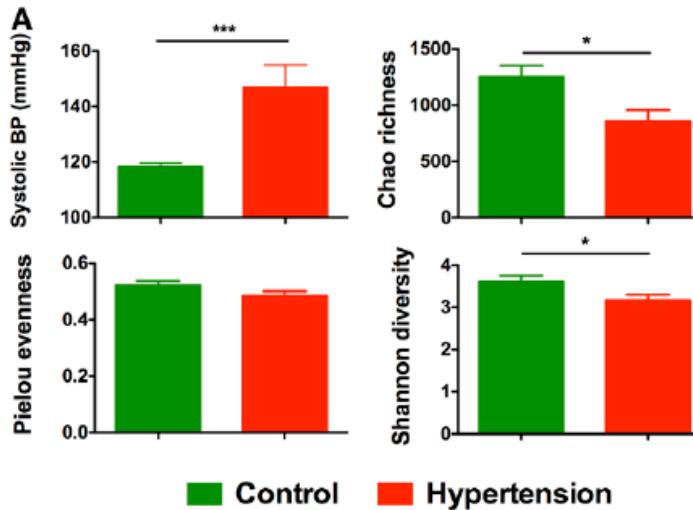
Figure 3. Spread of scores of the quality of blood pressure measurement as reported in the selected clinical trials (n=32)



The 5 criteria are depicted in table 3.

Score: 0-9

Score: 0-5



## Microbiota and Hypertension

### Gut Dysbiosis Is Linked to Hypertension

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**Abstract**—Emerging evidence suggests that gut microbiota is critical in the maintenance of physiological homeostasis. This study was designed to test the hypothesis that dysbiosis in gut microbiota is associated with hypertension because genetic, environmental, and dietary factors profoundly influence both gut microbiota and blood pressure. Bacterial DNA from fecal samples of 2 rat models of hypertension and a small cohort of patients was used for bacterial genomic analysis. We observed a significant decrease in microbial richness, diversity, and evenness in the spontaneously hypertensive rat, in addition to an increased Firmicutes/Bacteroidetes ratio. These changes were accompanied by decreases in acetate- and butyrate-producing bacteria. In addition, the microbiota of a small cohort of human hypertensive patients was found to follow a similar dysbiotic pattern, as it was less rich and diverse than that of control subjects. Similar changes in gut microbiota were observed in the chronic angiotensin II infusion rat model, most notably decreased microbial richness and an increased Firmicutes/Bacteroidetes ratio. In this model, we evaluated the efficacy of oral minocycline in restoring gut microbiota. In addition to attenuating high blood pressure, minocycline was able to rebalance the dysbiotic hypertension gut microbiota by reducing the Firmicutes/Bacteroidetes ratio. These observations demonstrate that high blood pressure is associated with gut microbiota dysbiosis, both in animal and human hypertension. They suggest that dietary intervention to correct gut microbiota could be an innovative nutritional therapeutic strategy for hypertension. (*Hypertension*. 2015;65:1331-1340. DOI: 10.1161/HYPERTENSIONAHA.115.05315.) • Online Data Supplement

Key Words: butyrate ■ dysbiosis ■ hypertension ■ microbiota ■ minocycline

# Diversity of microbial richness and in patients with hypertension

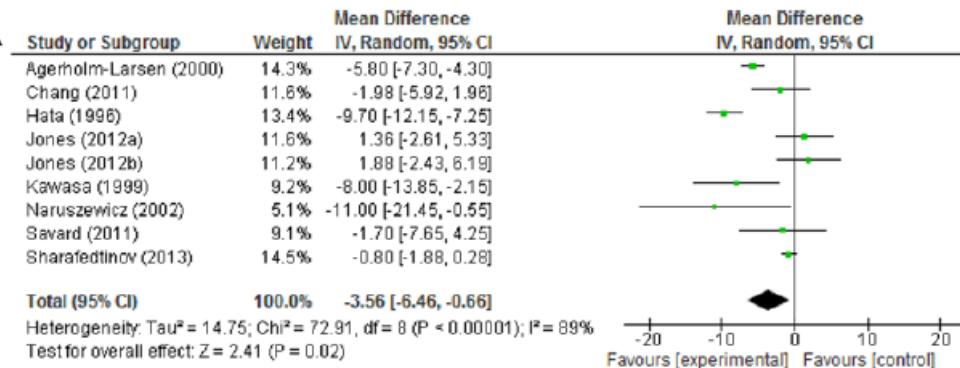
Yang T. et al. *Hypertension*. 2015 Jun;65(6):1331-40

## Effect of Probiotics on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials

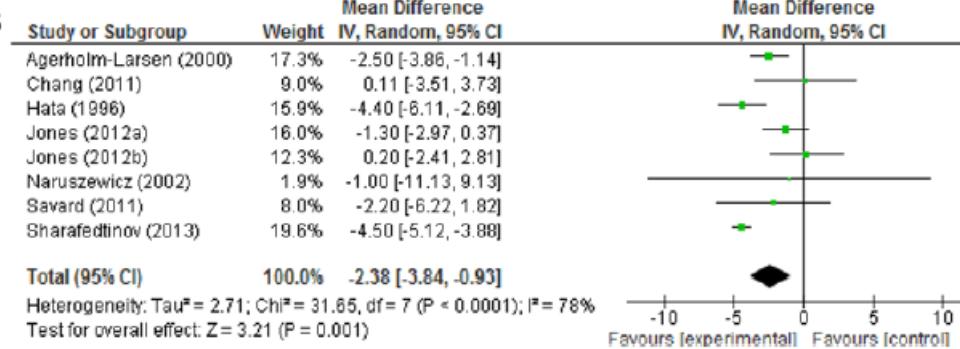
Saman Khalesi, Jing Sun, Nicholas Buys and Rohan Jayasinghe

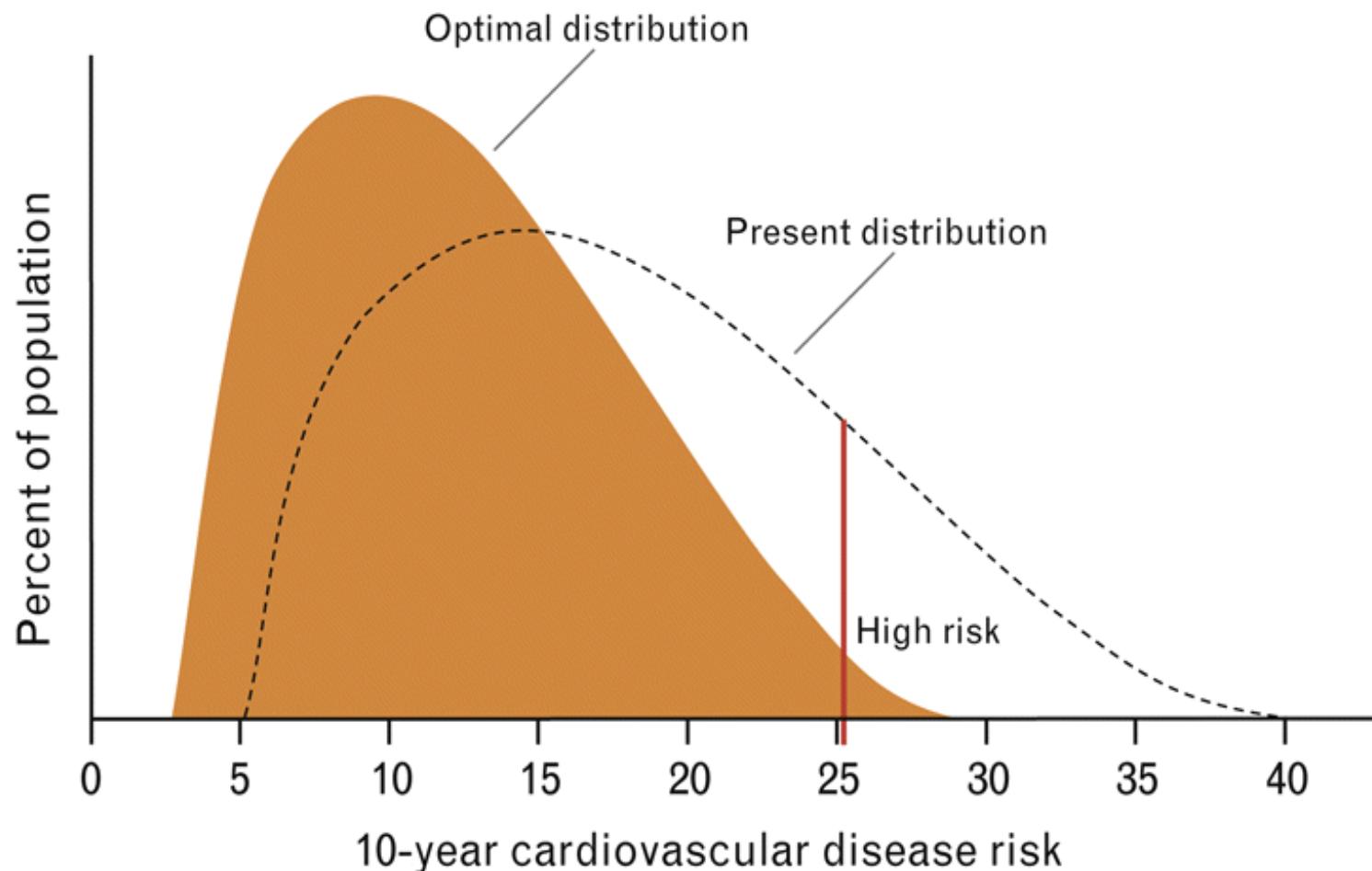
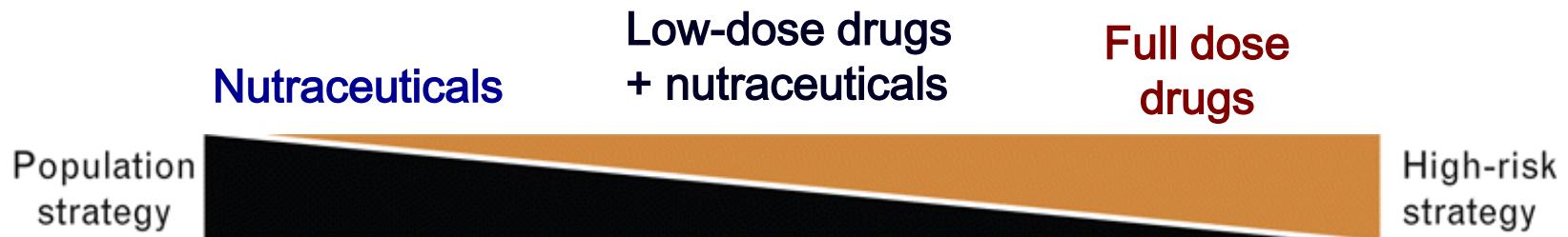
*Hypertension.* 2014;64:897-903; originally published online July 21, 2014;

**A**



**B**





From Mendis S et al J Vasc Health Risk Manage 2009;1:15-18 (mod)