



NUTRACEUTICA, FITONUTRIENTI INTEGRATORI E RISCHIO CARDIOVASCOLARE NEL PAZIENTE DIABETICO TIPO 2

*La voce dell'EBM:
“I CONTRO”*

Riccardo Candido

Centro Diabetologico Distretto 3

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[Botanical origin of dietary supplements labeled as "Kwao Keur", a folk medicine from Thailand.](#)

1. Maruyama T, Kawamura M, Kikura-Hanajiri R, Goda Y.
 J Nat Med. 2013 May 16. [Epub ahead of print]
 PMID: 23677774 [PubMed - as supplied by publisher]
[Related citations](#)

[Sources of Vitamin A in the Diets of Pre-School Children in the Avon Longitudinal Study of Parents and Children \(ALSPAC\).](#)

2. Cribb VL, Northstone K, Hopkins D, Emmett PM.
 Nutrients. 2013 May 15;5(5):1609-21. doi: 10.3390/nu5051609.
 PMID: 23676550 [PubMed - in process]
[Related citations](#)

[Health-promoting components of fruits and vegetables in the diet.](#)

3. Liu RH.
 Adv Nutr. 2013 May 1;4(3):384S-92S. doi: 10.3945/an.112.003517.
 PMID: 23674808 [PubMed - in process]
[Related citations](#)

[National athletic trainers' association position statement: evaluation of dietary supplements for performance nutrition.](#)

4. Smith JJ, Franklin D, Brackley J, Deussen ME, Leavelle MA, Gardner RH, et al.

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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR THE CLINICAL USE OF
DIETARY SUPPLEMENTS AND NUTRACEUTICALS

The task force was **impressed** by the **vastness of the available literature** and the **variability of extant data** on the subject of dietary supplements and nutraceuticals

La piramide dell'evidenza



EBM e i livelli dell'evidenza

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- English

- [Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial.](#)
1. Awasthi S, Peto R, Read S, Clark S, Pande V, Bundy D; DEVTA (Deworming and Enhanced Vitamin A) team.
Lancet. 2013 Apr 27;381(9876):1469-77. doi: 10.1016/S0140-6736(12)62125-4. Epub 2013 Mar 14.
PMID: 23498849 [PubMed - indexed for MEDLINE] [Free PMC Article](#)
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- [Effect of vitamin D supplementation on blood pressure in blacks.](#)
2. Forman JP, Scott JB, Ng K, Drake BF, Suarez EG, Hayden DL, Bennett GG, Chandler PD, Hollis BW, Emmons KM, Giovannucci EL, Fuchs CS, Chan AT.
Hypertension. 2013 Apr;61(4):779-85. doi: 10.1161/HYPERTENSIONAHA.111.00659.
PMID: 23487599 [PubMed - indexed for MEDLINE]
[Related citations](#)
- [Argan oil and postmenopausal Moroccan women: impact on the vitamin E profile.](#)
3. El Monfalouti H, Charrouf Z, El Hamdouchi A, Labraimi H, Chafchaoui-Moussaoui I, Kartah B, El Kari K, Bensouda Y, Derouich A, Dodin S, Denhez C, Guillaume D, Agnaou H.
Nat Prod Commun. 2013 Jan;8(1):55-7.
PMID: 23472459 [PubMed - indexed for MEDLINE]

REVIEW

A.E.G. Cicero • G. Derosa • A. Gaddi

What do herbalists suggest to diabetic patients in order to improve glycemic control? Evaluation of scientific evidence and potential risks

Rank	Remedy	Herbalists, n (%)
Herbal medicines		
1	Gymnema (<i>Gymnema silvestre</i>)	131 (19.1)
2	Psyllium (<i>Plantago isphagula</i>)	112 (16.4)
3	Fenugreek (<i>Trigonella foenumgraecum</i>)	99 (14.5)
4	Bilberry (<i>Vaccinium myrtillus</i>)	87 (12.7)
5	Garlic (<i>Allium sativum</i>)	80 (11.7)
6	Chinese ginseng (<i>Panax ginseng</i>)	73 (10.7)
7	Dandelion (<i>Taraxacum officinale</i>)	34 (5.0)
8	Burdock (<i>Arctium lappa</i>)	27 (3.9)
9	Prickly pear cactus (<i>Opuntia fulginosa</i>)	22 (3.2)
10	Bitter melon (<i>Momordica charantia</i>)	15 (2.2)
-	Others	5 (0.7)
Dietary supplements		
1	Biotin	91 (13.3)
2	Vanadium	88 (12.9)
3	Chromium	82 (12.0)
4	Vitamin B6 (pyridoxine)	78 (11.4)
5	Vitamin C (ascorbic acid)	75 (11.0)
6	Vitamin E (α -tocopherol)	69 (10.0)
7	Zinc	57 (8.3)
8	Selenium	51 (7.4)
9	α -Lipoic acid (thioctic acid)	46 (6.7)
10	Fructooligosaccharides (FOS)	40 (5.8)
-	Others	8 (1.2)

Characteristics of herbal remedies commonly recommended for the control of glycemia

Herbal remedy	Efficacy	Precautions	Common or serious adverse events
Bilberry (<i>Vaccinium myrtillus</i>)	Adults, possibly effective	Use of antidiabetic drugs	Undefined gastrointestinal complaints
Bitter melon (<i>Momordica charantia</i>)	Adults, possibly effective	Pregnancy, use of antidiabetic drugs	Bitter taste; hypoglycemia, abdominal pain and diarrhea with juice or dried juice powder; increased appetite and headache with seeds
Burdock (<i>Arctium lappa</i>)	Animal data only	Use of antidiabetic drugs	None reported
Dandelion (<i>Taraxacum officinale</i>)	Animal data only	Use of antidiabetic drugs	Allergic reactions
Fenugreek (<i>Trigonella foenumgraecum</i>)	Adults, possibly effective	Hypersensitivity or history of allergic reaction to fenugreek, pregnancy, use of antidiabetic drugs	Allergic reactions, minor transient diarrhea and flatulence, decreased absorption of co-assumed drugs
Gymnema (<i>Gymnema silvestre</i>)	Adults, possibly effective	Use of antidiabetic drugs	Bitter taste
Ginseng (<i>Panax ginseng</i>)	Adults, possibly effective	Hypersensitivity to ginseng, use of antidiabetic drugs, stimulants, monoamine oxidase inhibitors, anticoagulants	Nervousness, gastrointestinal upset or diarrhea, insomnia, edema, dizziness, headache, euphoria, vaginal bleeding, and skin eruptions
Garlic (<i>Allium sativum</i>)	Adults, possibly effective	Pregnancy, lactation, hypersensitivity to garlic, use of antiaggregant or anticoagulant drugs, surgery	Abdominal discomfort, nausea, vomiting, diarrhea, anemia, headache, myalgia, fatigue, fullness, increased liver enzymes in plasma, hyperuremia, body odor, halitosis, garlic smell
Prickly pear cactus	Adults, possibly effective	None reported	None reported in man, increased plasma creatinine and urea concentrations in rats
Psyllium (<i>Plantago isphagula</i>)	Adults, possibly effective	Hypersensitivity to psyllium, diverticulosis (seeds)	Reduced absorption of co-assumed drugs, esophageal or intestinal obstruction, flatulence and abdominal distention

Characteristics of dietary supplements commonly recommended for the control of glycemia

Dietary supplement	Efficacy	Precautions	Common or serious adverse events
Alpha-lipoic acid (thioctic acid)	Adults, inconclusive	Hypersensitivity to α -lipoic acid, neonates, concurrent use of antihyperglycemic drugs and cisplatin	Hypoglycemia, temporary worsening of neuropathy and paresthesia, allergic skin reactions
Biotin	Animal data only	None reported	Gastrointestinal upset
Chromium	Adults, possibly effective	Concurrent use of antihyperglycaemic drugs	Weight loss, anemia, thrombocytopenia, liver dysfunction, renal failure, insomnia, irritability
Fructooligosaccharides (FOS)	Adults, inconclusive	Concurrent use of antihyperglycaemic drugs	Flatulence, bloating, abdominal discomfort
Vanadium	Adults, effective	Hypersensitivity to vanadium, pregnancy, gastrointestinal illnesses, manic-depressive disorders, concurrent use of antihyperglycemic drugs, iron supplementation	Gastrointestinal upset with primary symptoms of diarrhea, cramps, black stools; hemolysis, greenish tongue, increased blood urea, high blood pressure, fatigue, manic-depressive disorder, weight loss
Vitamin B6 (pyridoxine)	Adults, possibly effective	Hypersensitivity to vitamin B6, neonatal seizures, co-treatment with L-DOPA, amiodarone, phenytoin	Peripheral sensory neuropathy, nausea and other gastrointestinal complaints
Vitamin C (ascorbic acid)	Adults, inconclusive	Pre-existing kidney stone disease, pre-existing renal insufficiency, patients with erythrocyte G6PD deficiency, hemochromatosis, thalassemia, sideroblastic anaemia, co-assumption of aluminium-containing antacids, cyanocobalamin, anticoagulants	Diarrhea
Vitamin E (alpha-tocopherol)	Adults, possibly effective	Co-assumption of anticoagulants	None reported for oral route

Ranking System for the Levels of Scientific Evidence for Herbal Medicines and Nutraceuticals

Ranking	Level of Scientific Evidence	Intervention and Scientific Evidence
1	High	A systematic review A randomised controlled trial
2	Medium	A pseudo-randomised controlled trial A comparative study with concurrent controls A comparative study without concurrent controls
3	General	Case series
4	Animal studies	<i>In vivo</i> studies
5	Cellular studies	<i>In vitro</i> studies
6	Chemical studies	Pharmaceutics, biochemical, nutritional, microbiological, phytochemical and quality analysis studies

Therapeutic Goods Administration. Guidelines for Levels and Kinds of Evidence to Support Indications and Claims For Non- Registerable Medicines, including Complementary Medicines, and other Listable Medicines 2001.

Herbal Medicines and Nutraceuticals for Diabetic Vascular Complications: Mechanisms of Action and Bioactive Phytochemicals

Eshaifol A. Omar^{a,1}, Antony Kam^{a,1}, Ali Alqahtani^a, Kong M. Li^b, Valentina Razmovski-Naumovski^{a,d}, Srinivas Nammi^{a,c}, Kelvin Chan^{a,d}, Basil D Roufogalis^a and George Q. Li^{a,*}

Aloe (Aloe vera), Andrographis paniculata, Astragalus membranaceus, baical skullcap (Scutellaria baicalensis), bilberry (Vaccinium myrtillus), bitter melon (Momordica charantia), cinnamon (Cinnamomum zeylanicum), clove (Syzygium aromaticum), evening primrose oil (Oenothera biennis), fenugreek (Trigonella foenum graecum), fish oil, flaxseed oil (Linum usitatissimum), garlic (Allium sativum), ginger (Zingiber officinale), ginkgo (Ginkgo biloba), ginseng (Panax ginseng), goldenseal (Hydrastis canadensis), grape seed (Vitis vinifera), green tea (Camellia sinensis), Gymnema montanum, hawthorn (Crataegus monogyna), honey, licorice (Glycyrrhiza glabra), oats (Avena sativa), olive (Olea europaea), psyllium (Plantago ovata), turmeric (Curcuma longa), wild yam (Dioscorea opposita), Withania somnifera and wolfberry (Lycium barbarum), gotu kola (Centella asiatica), pomegranate (Punica granatum) and propolis.

Herbal Medicines and Nutraceuticals for Diabetic Vascular Complications: Mechanisms of Action and Bioactive Phytochemicals

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A series of highest level of clinical have recently been carried out for several different pharmacological strategies for 10 natural products with promising results for the management of diabetic complications including: *Capsicum frutescens*, *Centella asiatica*, fish oil, *Ginkgo biloba*, *Linum usitatissimum*, *Pinus pinaster*, *Salvia hispanica*, *Salvia miltiorrhiza*, *Tinospora cordifolia* and *Vitis vinifera*, as well as a naturally occurring phytochemical, γ -linolenic acid.

Herbal Medicines and Nutraceuticals for Diabetic Vascular Complications: Mechanisms of Action and Bioactive Phytochemicals

Eshaifol A. Omar^{a,1}, Antony Kam^{a,1}, Ali Alqahtani^a, Kong M. Li^b, Valentina Razmovski-Naumovski^{a,d}, Srinivas Nammi^{a,c}, Kelvin Chan^{a,d}, Basil D Roufogalis^a and George Q. Li^{a,*}

- In reality **most research studies** on herbal medicines and nutraceuticals **are dominated by animal, cellular and chemical works**, while there is **limited clinical evidence available at present**.
- This may influence current perceptions of these medicines and hence **limit the future development of herbal medicines and nutraceuticals**.
- Incorporating the valuable evidence from animal, cellular and chemical studies into the existing system should be **important adjunctive evidence to clinical evidence**, providing a valuable approach in recognizing and further developing the potential health benefits of herbal medicines and nutraceuticals.

Meta-analysis of the effect of herbal supplement on glycemic control in type 2 diabetes.

Suksomboon N, Poolsup N, Boonkaew S, Suthisisang CC

Study or Subgroup	Treatment			Control			Weight	Mean Difference IV, Random, 95% CI	Year	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total				
1.1.1 Cinnamomum cassia										
Suppapitipom 2006	7.76	0.95	20	7.87	0.96	40	23.9%	-0.11 [-0.62, 0.40]	2006	
Blevins 2007	7.4	0.88	29	7.2	0.85	28	31.0%	-0.20 [-0.25, 0.65]	2006	
Mang 2006	6.83	0.83	33	6.68	0.7	32	45.0%	-0.15 [-0.22, 0.52]	2006	

CONCLUSIONS: The current evidence suggests that supplementation with Ipomoea batatas, Silybum marianum, and Trigonella foenum-graecum may improve glycemic control in type 2 diabetes. Such effect was not observed with Cinnamomum cassia. **Given the limitations of the available studies and high heterogeneity of the study results for milk thistle and fenugreek, further high quality, large controlled trials using standardized preparation are warranted to better elucidate the effects of these herbs on glycemic control in type 2 diabetes patients.**

Test for overall effect: $Z = 2.67$ ($P = 0.008$)

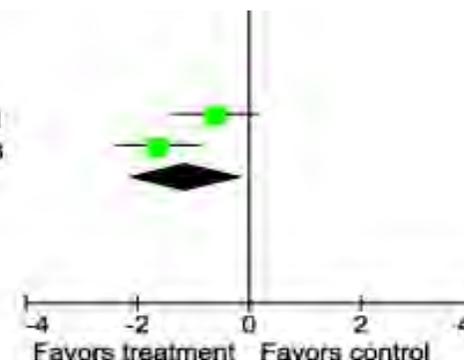
1.1.4 Trigonella foenum-graecum

Gupta 2001	7.54	0.9	12	8.14	1.1	13	49.5%	-0.60 [-1.39, 0.19]	2001	
Lu 2008	6.56	0.95	46	8.2	1.73	23	50.5%	-1.64 [-2.40, -0.88]	2008	
Subtotal (95% CI)			58			36	100.0%	-1.13 [-2.14, -0.11]		

Heterogeneity: $\tau^2 = 0.39$; $\text{Chi}^2 = 3.49$, $df = 1$ ($P = 0.06$); $I^2 = 71\%$

Test for overall effect: $Z = 2.16$ ($P = 0.03$)

Mean difference (95% confidence interval) in HbA_{1c} between the treatment and the placebo groups.





A Review of the Hypoglycemic Effects of Five Commonly Used Herbal Food Supplements

Ruitang Deng*

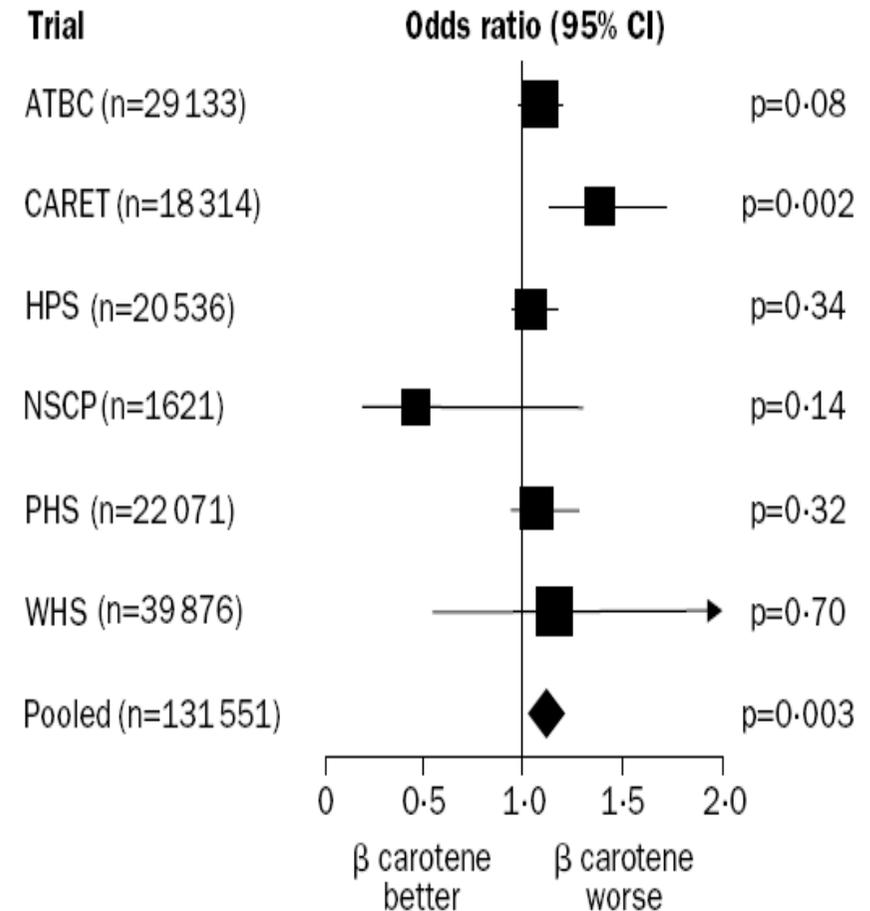
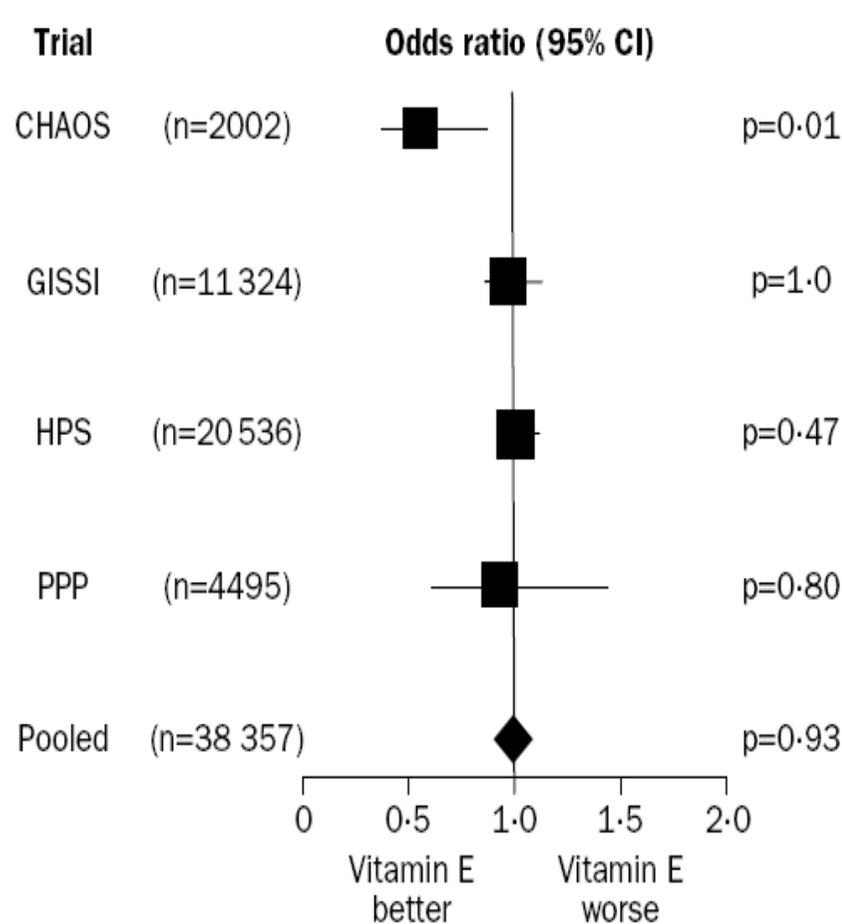
Abstract

Hyperglycemia is a pathological condition associated with prediabetes and diabetes. The incidence of prediabetes and diabetes is increasing and imposes great burden on healthcare worldwide. Patients with prediabetes and diabetes have significantly increased risk for cardiovascular diseases and other complications. Currently, management of hyperglycemia includes pharmacological interventions, physical exercise, and change of life style and diet. Food supplements have increasingly become attractive alternatives to prevent or treat hyperglycemia, especially for subjects with mild hyperglycemia. This review summarized current patents and patent applications with relevant literature on five commonly used food supplements with claims of hypoglycemic effects, including emblica officinalis (gooseberry), fenugreek, green tea, momordica charantia (bitter melon) and cinnamon. The data from human clinical studies did not support a recommendation for all five supplements to manage hyperglycemia. Fenugreek and composite supplements containing emblica officinalis showed the most consistency in lowering fasting blood sugar (FBS) or glycated hemoglobin (HbA1c) levels in diabetic patients. The hypoglycemic effects of cinnamon and momordica charantia were demonstrated in most of the trials with some exceptions. However, green tea exhibited limited benefits in reducing FBS or HbA1c levels and should not be recommended for managing hyperglycemia. **Certain limitations are noticed in a considerable number of clinical studies including small sample size, poor experimental design and considerable variations in participant population, preparation format, daily dose, and treatment duration. Future studies with more defined participants, standardized preparation and dose, and improved trial design and size are warranted.**

🌐 Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials

Lancet 2003; **361**: 2017–23

Deepak P Vivekananthan, Marc S Penn, Shelly K Sapp, Amy Hsu, Eric J Topol





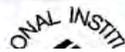
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Author Manuscript

Conclusion: There were no overall effects of vitamins C, E or beta-carotene on cardiovascular events among women at high risk for CVD.

in the Secondary Prevention of Cardiovascular Events in Women:

Results from the Women's Antioxidant Cardiovascular Study (WACS)



NIH Public Access

CONCLUSION: Over the longest follow-up recorded thus far, a combination of folic acid/vitamin B6/vitamin B12 did not reduce a combined endpoint of total cardiovascular events among high-risk women despite significant homocysteine lowering.

Cardiovascular Disease: A Randomized Trial



NIH Public Access

Conclusions: In this large, long-term trial of male physicians, neither vitamin E nor C supplementation reduced the risk of major cardiovascular events. These data provide no support for the use of these supplements for the prevention of CVD in middle-aged and older men.

Men: The Physicians' Health Study II Randomized Trial

[Ann Intern Med.](#) 2005 Jan 4;142(1):37-46.

Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality.

[Miller ER 3rd](#), [Pastor-Barriuso R](#), [Dalal D](#), [Riemersma RA](#), [Appel LJ](#), [Guallar E](#).

Abstract

BACKGROUND:

Experimental models and observational studies suggest that vitamin E supplementation may prevent cardiovascular disease and cancer. However, several trials of high-dosage vitamin E supplementation showed non-statistically significant increases in total mortality.

PURPOSE:

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mortality

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comparisons

[Biofactors.](#) 2009 Nov-Dec;35(6):469-73.

No evidence supports vitamin E indiscriminate supplementation.

[Dotan Y](#), [Lichtenberg D](#), [Pinchuk I](#).

Department of Physiology and Pharmacology, Tel Aviv University, Sackler Medical School, Tel Aviv, Israel.

9 of 11 trials testing high-dosage vitamin E (> or =400 IU/d) showed increased risk (risk difference > 0) for all-cause mortality in comparisons of vitamin E versus control. The pooled all-cause mortality risk difference in high-dosage vitamin E trials was 39 per 10,000 persons (95% CI, 3 to 74 per 10,000 persons; P = 0.035). For low-dosage vitamin E trials, the risk difference was -16 per 10,000 persons (CI, -41 to 10 per 10,000 persons; P > 0.2). A dose-response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/d.

LIMITATIONS:

High-dosage (> or =400 IU/d) trials were often small and were performed in patients with chronic diseases. The generalizability of the findings to healthy adults is uncertain. Precise estimation of the threshold at which risk increases is difficult.

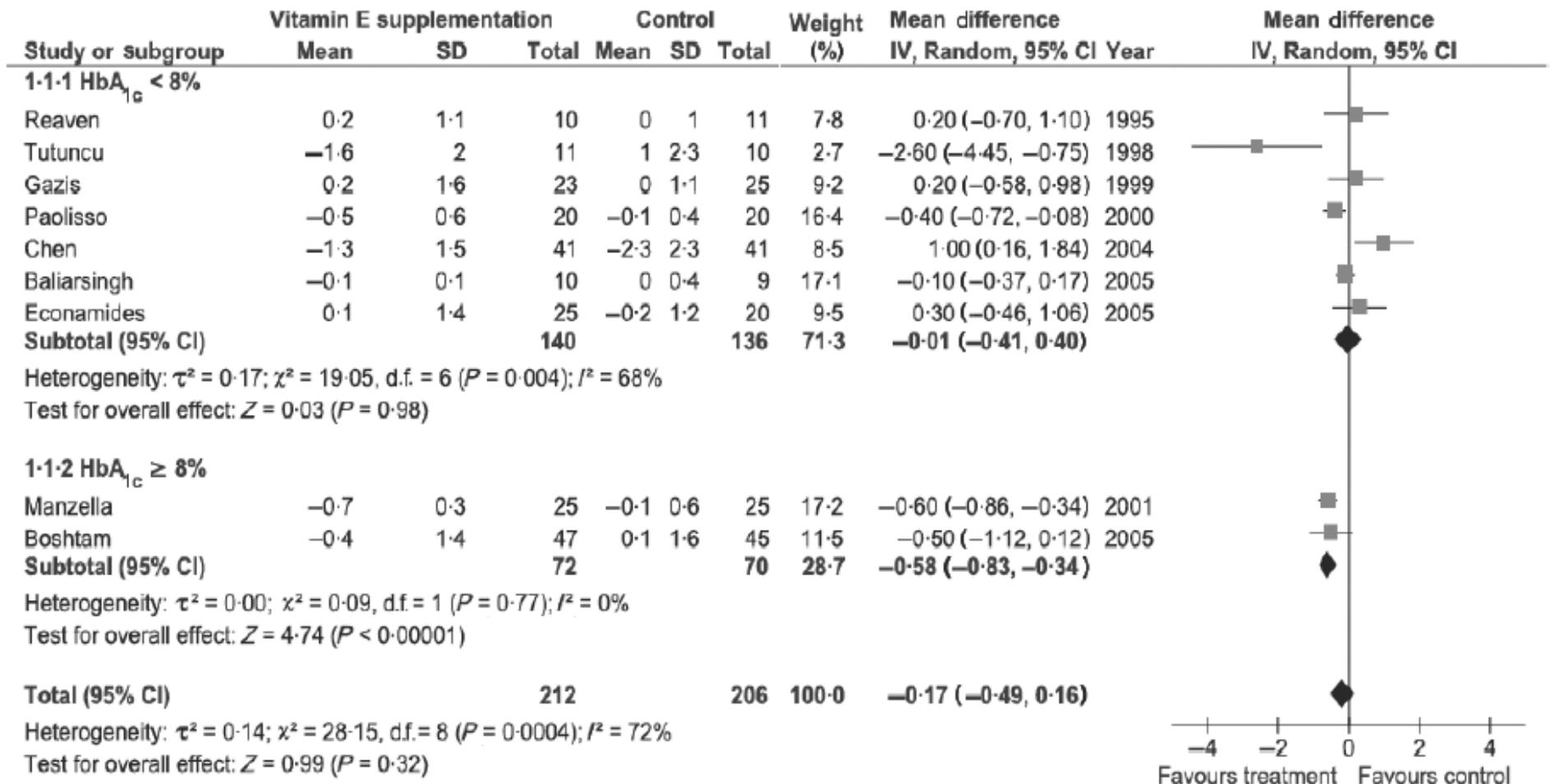
CONCLUSION:

High-dosage (> or =400 IU/d) vitamin E supplements may increase all-cause mortality and should be avoided.

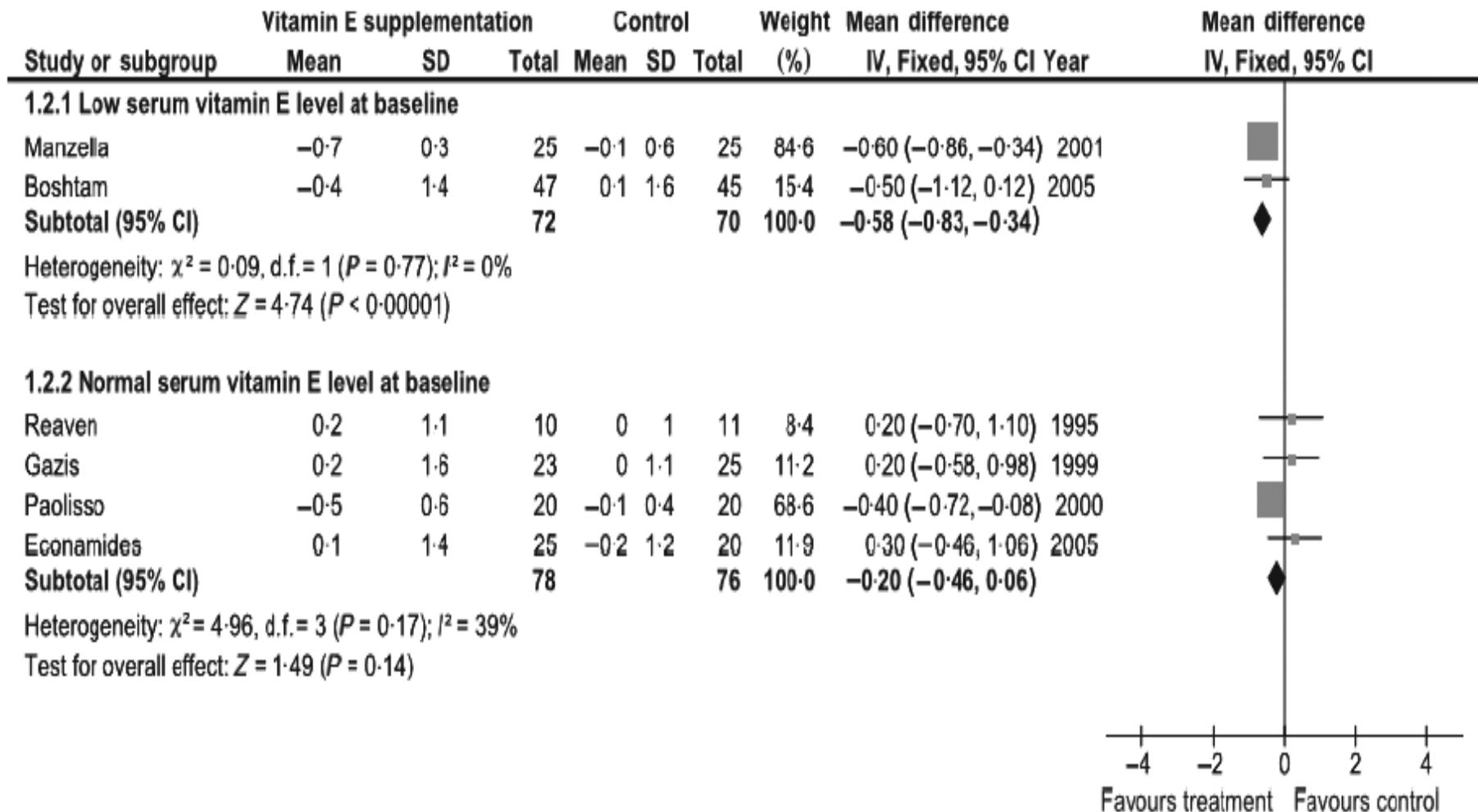
ORIGINAL ARTICLE

Effects of vitamin E supplementation on glycaemic control in type 2 diabetes: systematic review of randomized controlled trials

N. Sukomboon* PharmD PhD, N. Poolsup† PhD and S. Sinprasert* MSc in Pharm



Mean difference (95% confidence interval) in the change of HbA1c for vitamin E supplementation and control in patients with low and normal serum vitamin E levels at baseline.



- The evidence suggests **no beneficial effect of vitamin E supplementation** in improving glycaemic control in unselected patients with type 2 diabetes.
- **HbA1c may decrease with vitamin E supplementation in patients with inadequate glycaemic control or low serum levels of vitamin E.** This shows the importance of targeting therapy.
- **Due the limitations of the published data, adequate sample size, high quality, randomized controlled trials with standard protocols for vitamin E supplementation are warranted.**
- **Safety and long-term benefit of such supplements remain to be determined** before its clinical benefit can be established unequivocally.



Published in final edited form as:

Pharmacogenomics. 2010 May ; 11(5): 675–684. doi:10.2217/pgs.10.17.

Vitamin E reduces cardiovascular disease in individuals with diabetes mellitus and the haptoglobin 2-2 genotype

- Haptoglobin genotype & diabetic cardiovascular disease:

- The haptoglobin (Hp) genotype is an independent determinant of susceptibility to cardiovascular disease in individuals with diabetes mellitus (DM).
- Individuals with the Hp 2-2 genotype and diabetes have an increased risk of myocardial infarction (MI), cardiovascular death and stroke.

- Pharmacogenomic application of the Hp genotype:

- Vitamin E has not been shown to provide benefit to genetically unselected populations of individuals with diabetes, and may have increased mortality.
- Retrospective analysis of the **Heart Outcomes Prevention Evaluation (HOPE)** study demonstrated a significant reduction in cardiovascular disease (CVD) death and MI in individuals with the Hp 2-2 genotype who received vitamin E.



Published in final edited form as:

Pharmacogenomics. 2010 May ; 11(5): 675–684. doi:10.2217/pgs.10.17.

Vitamin E reduces cardiovascular disease in individuals with diabetes mellitus and the haptoglobin 2-2 genotype

- **Israel Cardiovascular Events Reduction with vitamin E (ICARE)**, a prospective study in which Hp 2-2 DM individuals were randomized to vitamin E or placebo, demonstrated a significant reduction in CVD death, MI and stroke in Hp 2-2 DM individuals who received vitamin E.
- Extrapolation of the results of the ICARE and HOPE studies to a real-life population over 50 years demonstrates that a **pharmacogenomic algorithm of administering vitamin E to Hp 2-2 DM individuals would prolong life** by approximately 3 years in these individuals.

- Conclusion:

- The Hp genotype identifies those **DM individuals at exceptionally high risk of CVD**.
- The Hp genotype appears to identify very large subgroups of DM individuals (~a third of the DM population) who may receive **great clinical benefit from vit. E**.



Published in final edited form as:

Metabolism. 2009 April ; 58(4): 469–478. doi:10.1016/j.metabol.2008.11.003.

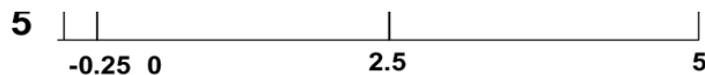
The Response of Gamma Vitamin E to Varying Dosages of Alpha Vitamin E plus Vitamin C

35

High

1.9

- Our results suggest that all prospective cardiovascular clinical trials that utilized vitamin E supplementation actually suppressed the beneficial antioxidant gamma isomer of vitamin E.
- No beneficial effects on several potential cardiovascular risk factors were observed, even when the vitamin E was supplemented with vitamin C.
- If a standardized preparation of gamma vitamin E (without the alpha isomer) becomes available, the effects of gamma vitamin E on atherosclerotic risk will warrant additional studies.



Hours Post Meal



Hours Post Meal

J Lipid Res. 2013 Mar 15. [Epub ahead of print]

Vitamin E in the Prevention of Cardiovascular Disease- the Importance of Proper Patient Selection

Moshe Vardi, Nina S. Levy, Andrew P Levy

Does vitamin E protect against the development of CV disease?

Conclusions:

1)The answer appears to be a resounding no when one provides vitamin E indiscriminately to unselected populations.

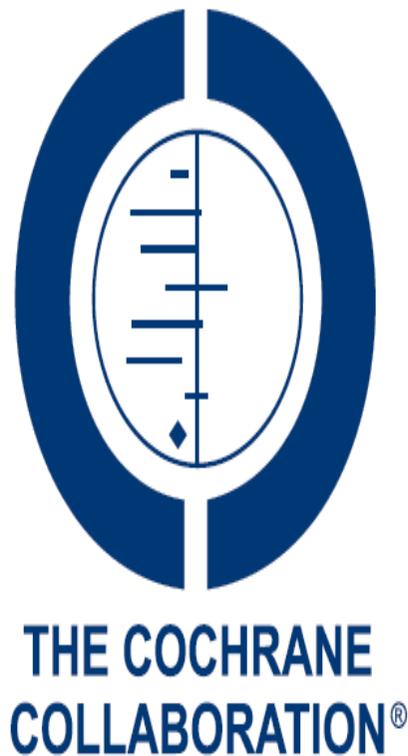
2)Vitamin E has been shown to be cardio-protective in certain patient subgroups under high levels of oxidative stress such as those individuals on hemodialysis (SPACE) or in diabetic individuals with the Hp 2-2 genotype (ICARE). A plausible biological rational has been provided.

3)The adoption of a pharmacogenomic approach to the use of vitamin E appears to identify a subgroup of individuals for whom vitamin E provides significant clinical benefit.

Selenium supplementation for the primary prevention of cardiovascular disease (Review)

Rees K, Hartley L, Day C, Flowers N, Clarke A, Stranges S

Cochrane Database Syst Rev 2013 Jan 31;1:CD009671.

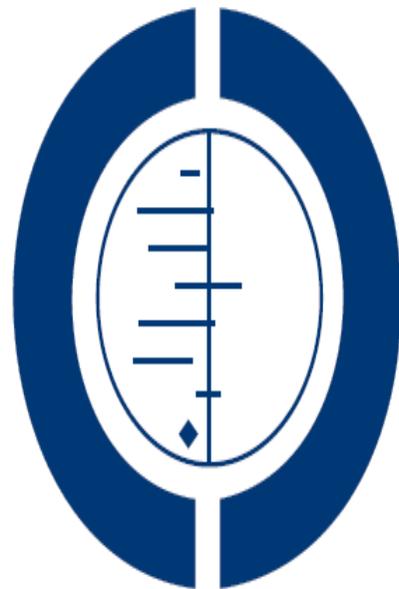


Authors' conclusions

- There were **no statistically significant effects** of selenium supplementation on all cause mortality, CVD mortality, non-fatal CVD events or all CVD events (fatal and non-fatal).
- There was a **small increased risk of type 2 diabetes with selenium supplementation** but this did not reach statistical significance.
- The limited trial evidence that is available to date **does not support the use of selenium supplements in the primary prevention of CVD.**

Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases (Review)

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C
Cochrane Database Syst Rev. 2012 Mar
14;3:CD007176. doi



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Authors' conclusions

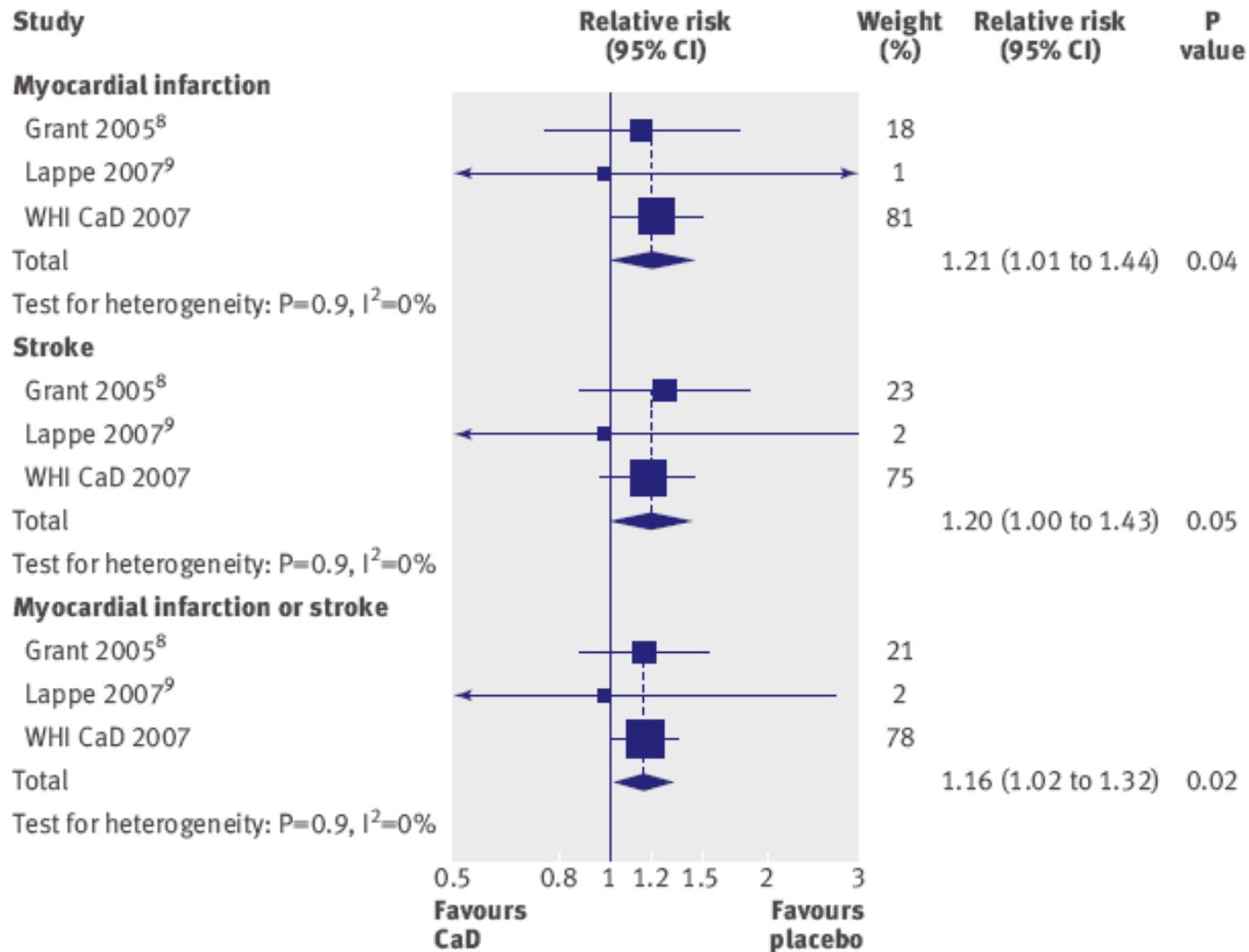
- We found **no evidence to support** antioxidant supplements for primary or secondary prevention.
- Vitamin A, beta-carotene, and vitamin E **may increase mortality**.
- **Future randomised trials** could evaluate the potential effects of vitamin C and selenium for primary and secondary prevention.
- Such trials should be closely monitored for **potential harmful effects**.
- Antioxidant supplements need to be considered **medicinal products** and should undergo **sufficient evaluation before** marketing.

Systematic Review: Vitamin D and Cardiometabolic Outcomes

Anastassios G. Pittas, MD, MS; Mei Chung, MPH; Thomas Trikalinos, MD; Joanna Mitri, MD; Michael Brendel, BA; Kamal Patel, MPH; Alice H. Lichtenstein, DSc; Joseph Lau, MD; and Ethan M. Balk, MD, MPH

- **A lower 25(OH)D concentration or vitamin D intake may be associated with higher risk for incident hypertension and cardiovascular disease, but the association with diabetes-related outcomes remains unclear.**
- **As a whole, the trials showed no statistically significant effect of vitamin D supplementation on cardiometabolic outcomes.**
- **The available data are inadequate to support the contention that cardiometabolic outcomes can be improved by increasing vitamin D intake or serum or plasma 25(OH)D concentrations.**
- **Adequate randomized trials, conducted in well-defined populations are needed to test the potential role of vitamin D in primary prevention or therapy.**
- **Vitamin D remains a promising, although unproven, new element in the prevention and management of cardiometabolic disease.**

Effect of calcium and vitamin D on CVD events



CaD = calcium and vitamin D

Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis

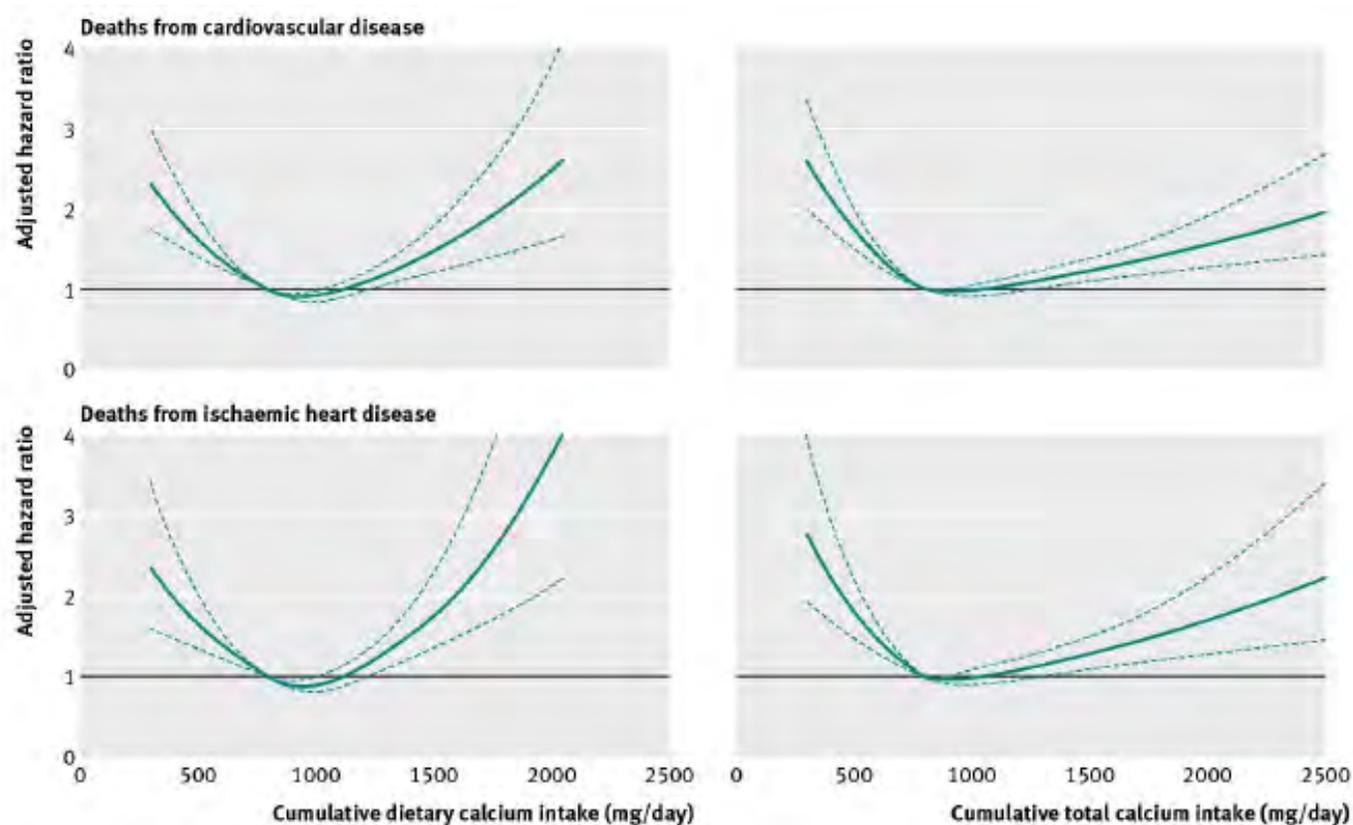
Mark J Bolland, senior research fellow,¹ Andrew Grey, associate professor,¹ Alison Avenell, clinical research fellow,² Greg D Gamble, research fellow,¹ Ian R Reid, professor of medicine and endocrinology¹

... in our analysis, treating 1000 patients with calcium or calcium and vitamin D for five years would cause an additional six myocardial infarctions or strokes (number needed to harm of 178) and prevent only three fractures (number needed to treat of 302).

Meta-analyses of trials involving 29 000 people found that calcium supplements used with or without vitamin D modestly increase cardiovascular risk, suggesting their use in osteoporosis management should be reassessed

Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study

Karl Michaëlsson *professor*¹, Håkan Melhus *professor*², Eva Warensjö Lemming *researcher*¹, Alicja Wolk *professor*³, Liisa Byberg *associate professor*¹



Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study

Karl Michaëlsson *professor*¹, Håkan Melhus *professor*², Eva Warensjö Lemming *researcher*¹, Alicja Wolk *professor*³, Liisa Byberg *associate professor*¹

What is already known on this topic

A low calcium intake is associated with higher fracture rates in elderly people and a higher risk of stroke and fatal ischaemic heart disease

Meta-analyses of some randomised studies have, however, shown a higher risk of incident ischaemic heart disease and stroke with calcium supplement use

In observational studies, use of calcium supplements has been associated with both lower overall and cardiovascular mortality rate, as well as higher incidence of cardiovascular disease

What this study adds

In this Swedish cohort study of women, high intakes of calcium (>1400 mg/day) were associated with higher mortality

The increase was moderate with a high dietary calcium intake without supplement use, but more pronounced with a high dietary calcium intake with calcium tablet use

For most women with lower calcium intakes only modest differences in risk were observed

Alpha-lipoic acid as a dietary supplement: Molecular mechanisms

and therapeutic potential

Biochim Biophys Acta. 2009 October ; 1790(10): 1149–1160.

Kate Petersen Shay¹, Régis F. Moreau¹, Eric J. Smith^{1,2}, Anthony R. Smith¹, and Tory M. Hagen^{1,2}

Punti da chiarire:

- 1. Quale è la isoforma più efficace clinicamente (enantiomero R? enantiomero S? combinazione dei due?)**
- 2. La somministrazione e.v. è più efficace di quella orale**
- 3. Aumento dello stress ossidativo a dosaggi elevati**
- 4. Le evidenze attuali derivano da studi animali e pochissimi sono gli RCT**

What Is New for an Old Molecule? Systematic Review and Recommendations on the Use of Resveratrol

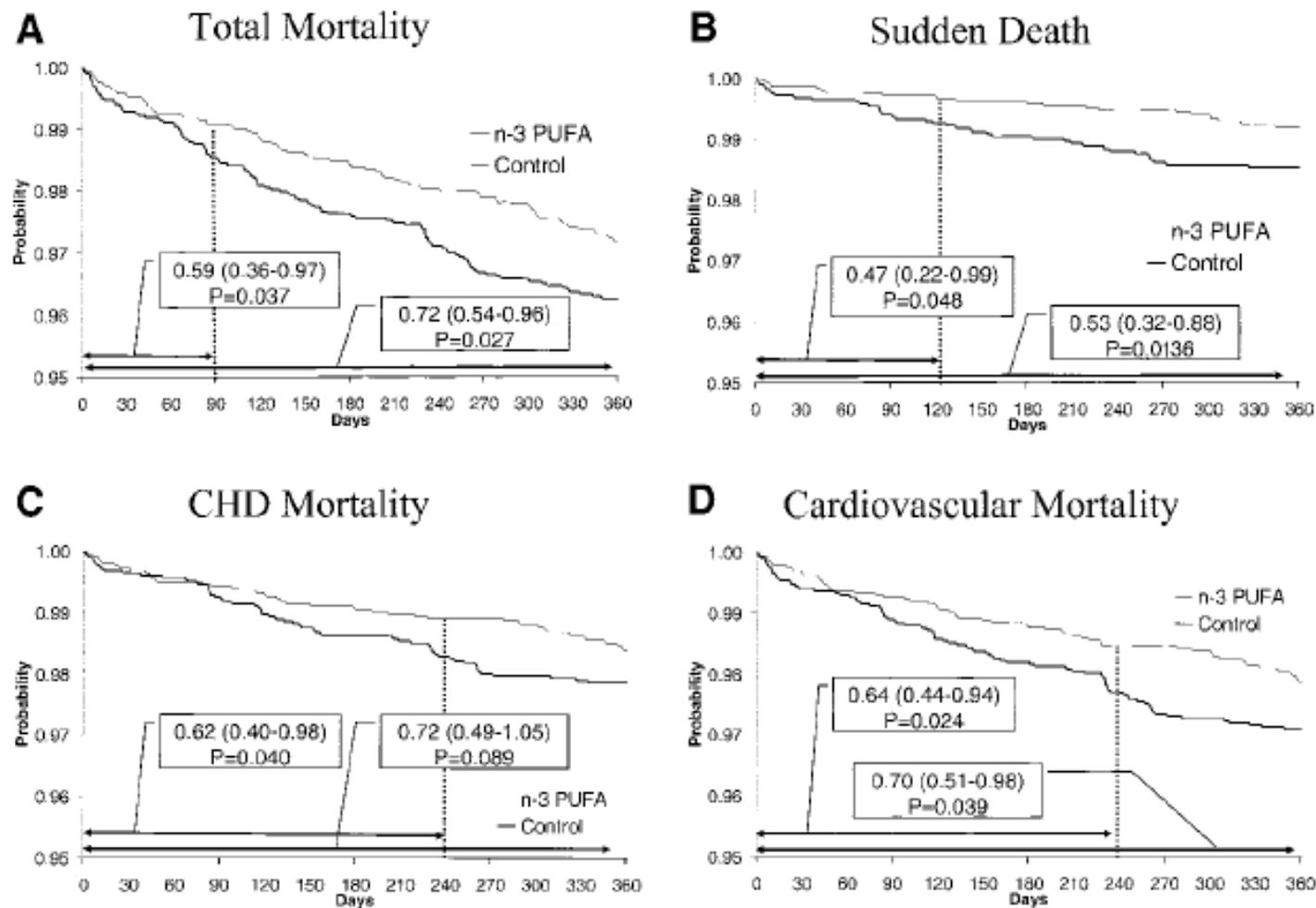
Ole Vang^{1*}, Nihal Ahmad², Clifton A. Baile³, Joseph A. Baur⁴, Karen Brown⁵, Anna Csiszar⁶, Dipak K. Das⁷, Dominique Delmas⁸, Carmem Gottfried⁹, Hung-Yun Lin¹⁰, Qing-Yong Ma¹¹, Partha Mukhopadhyay¹², Namasivayam Nalini¹³, John M. Pezzuto¹⁴, Tristan Richard¹⁵, Yogeshwer Shukla¹⁶, Young-Joon Surh¹⁷, Thomas Szekeres¹⁸, Tomasz Szkudelski¹⁹, Thomas Walle²⁰, Joseph M. Wu²¹

Overall conclusions for the use of resveratrol

- 1 Published evidence today is not sufficiently strong to justify recommendation for the chronic administration of resveratrol to human beings, beyond the dose which can be obtained from dietary sources.
 - 2 Animal data are promising and indicate the need for further human clinical trials.
-

Early Protection Against Sudden Death by n-3 Polyunsaturated Fatty Acids After Myocardial Infarction

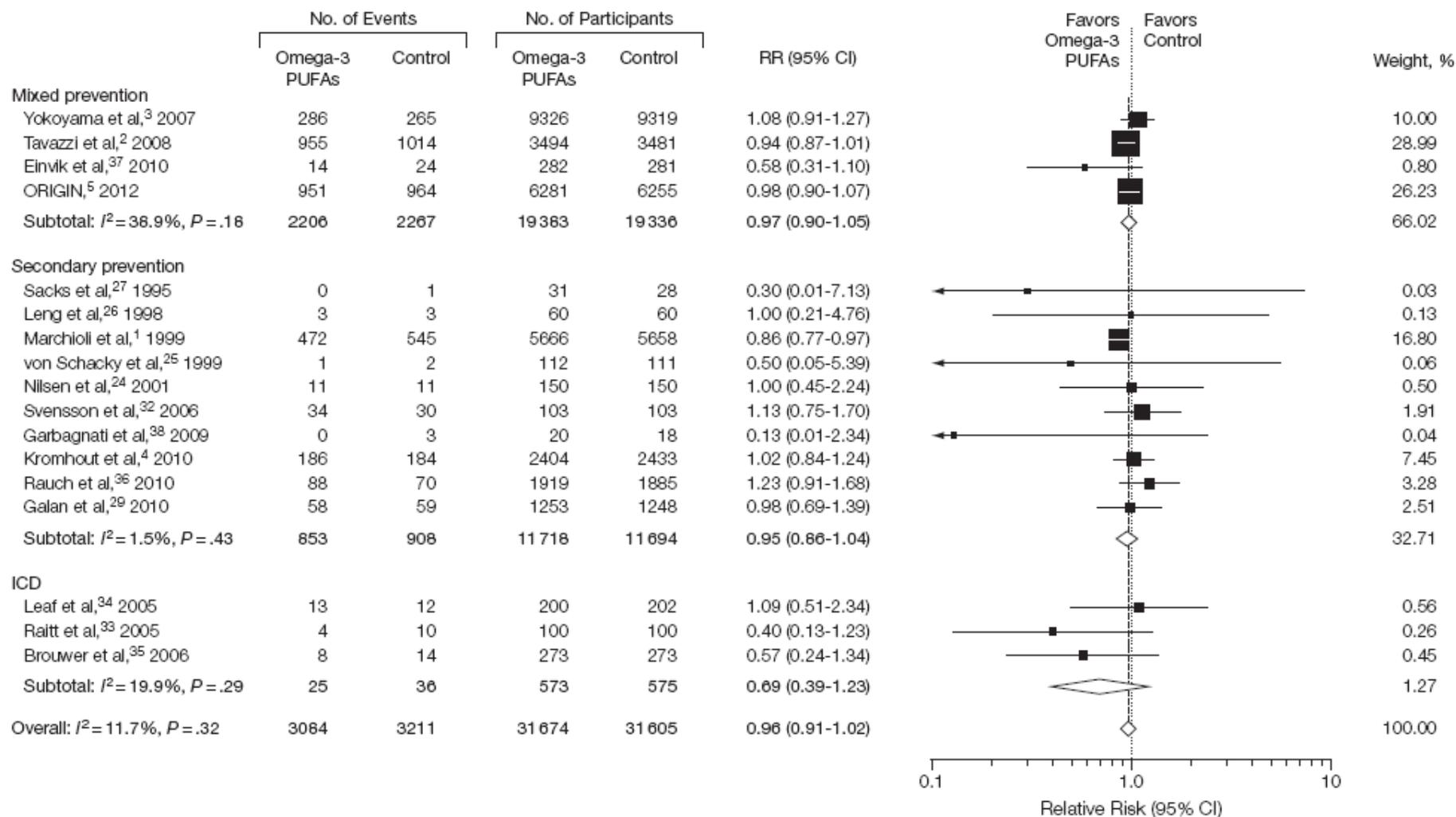
Time-Course Analysis of the Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione



Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events

A Systematic Review and Meta-analysis

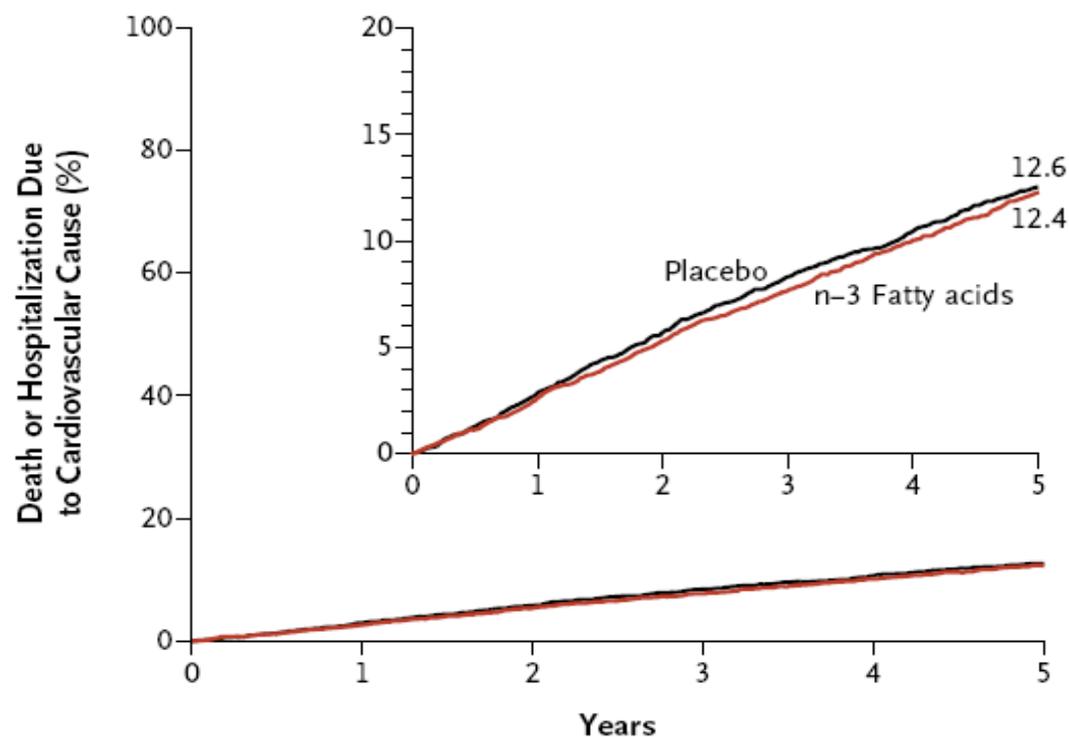
Figure 4. Meta-analysis of Omega-3 Supplements for All-Cause Mortality



n-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors

The Risk and Prevention Study Collaborative Group*

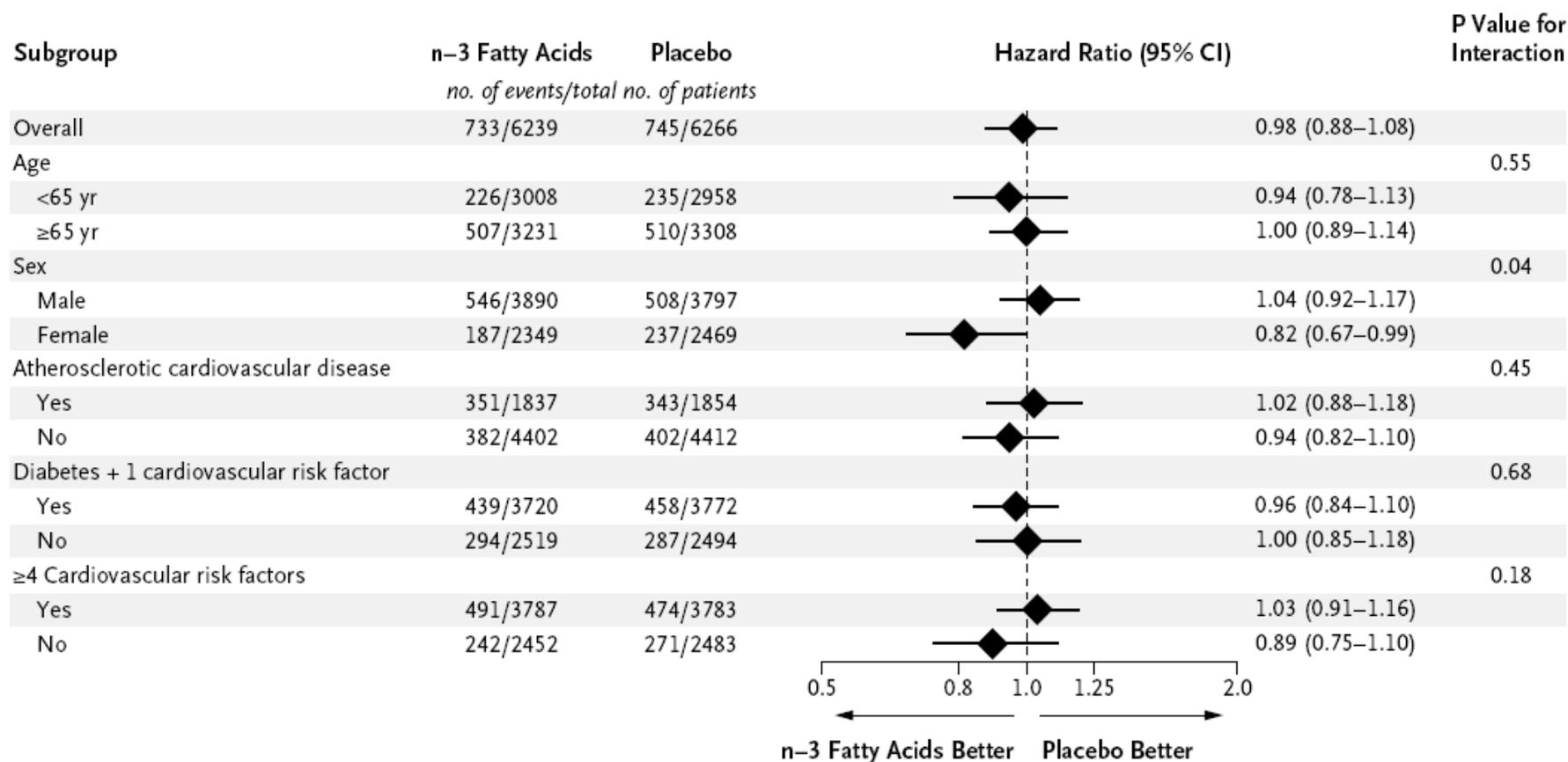
Kaplan–Meier Curves for Death or First Hospitalization Due to Cardiovascular Cause



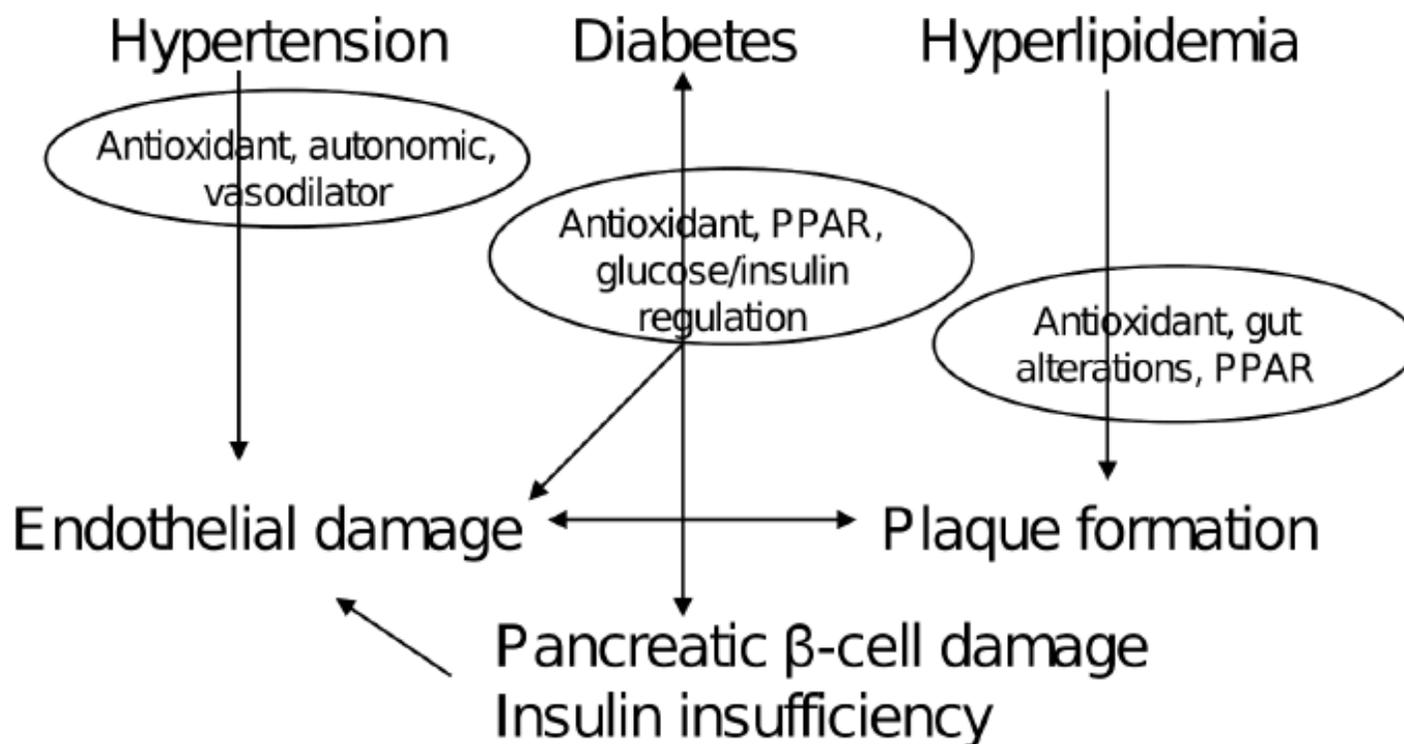
No. at Risk						
n-3 Fatty acids	6239	5910	5566	5216	4863	2992
Placebo	6266	5908	5528	5137	4780	2926

n-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors

The Risk and Prevention Study Collaborative Group*



Flavonoids and Age Related Disease: Risk, benefits and critical windows





Flavonoids and Age Related Disease: Risk, benefits and critical windows

- The **strongest evidence for the benefits** of flavonoids in diseases of aging relates to their effect on **components of the metabolic syndrome**.
- Flavonoids from soy, grape seed, kudzu and other sources all lower arterial pressure, concentration of lipids and plasma glucose in **animal models and in a limited number of tests in humans**.
- The underlying mechanisms appear to include antioxidant actions, central nervous system effects, gut transport alterations, fatty acid sequestration and processing, PPAR activation and increases in insulin sensitivity.



Flavonoids and Age Related Disease: Risk, benefits and critical windows

- In animal models of disease, dietary flavonoids also demonstrate a protective effect against cognitive decline, cancer and metabolic disease.
- Flavonoids can be detrimental in some settings and, therefore, are not universally safe (mutagenic effects, drug interactions, hepato-toxicity, worsen bone loss).
- It is important to determine the impact of these agents on prevention/attenuation of disease, including optimal exposure (intake, timing/duration) and potential contraindications.

[J Am Coll Nutr.](#) 2009 Oct;28(5):517-24.

The effect of adding plant sterols or stanols to statin therapy in hypercholesterolemic patients: systematic review and meta-analysis.

[Scholle JM](#), [Baker WL](#), [Talati R](#), [Coleman CI](#).

Abstract

OBJECTIVE:

To characterize the effect of plant sterols/stanols on serum lipids in hypercholesterolemic patients on concurrent statin therapy, we conducted a systematic review and meta-analysis.

METHODS:

A systematic literature search of MEDLINE and Cochrane Comprehensive Database was conducted. Studies included in the analysis if they were randomized controlled trials in combination with statins in hypercholesterolemic patients. The mean difference (WMD) of the change in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides was calculated as the difference between treatment and control groups using a random-effects model.

RESULTS:

Eight studies (n = 306 patients) met the inclusion criteria. Plant sterols/stanols in combination with statin therapy significantly reduced total cholesterol (WMD, -9.37 mg/dL [95% CI, -13.26 to -5.48], p < 0.0001) and LDL cholesterol (WMD, -13.26 mg/dL [95% CI, -17.34 to -9.18], p < 0.0001) but not HDL cholesterol or triglycerides.

CONCLUSIONS:

Based upon the current literature, we can only say that plant sterols/stanols, when administered in addition to statins, favorably affect total and LDL cholesterol with 95% confidence. Randomized trials examining the impact of plant sterols/stanols in combination with statins on patient morbidity and mortality are needed.

- Based upon the current literature, we can only say that plant sterols/stanols, when administered in addition to statins, favorably affect total and LDL cholesterol.

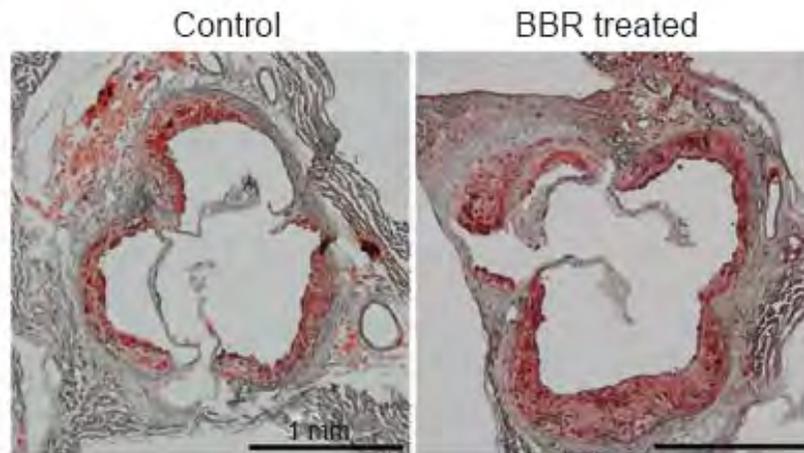
- Randomized trials examining the impact of plant sterols/stanols in combination with statins on patient morbidity and mortality are needed.

Berberine promotes the development of atherosclerosis and foam cell formation by inducing scavenger receptor A expression in macrophage

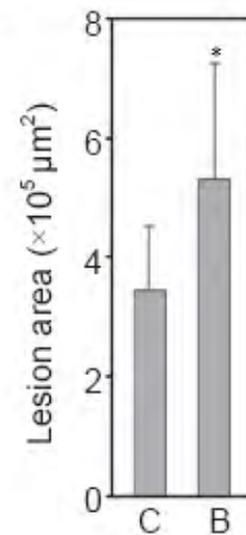
Ke Li^{1,*}, Wenqi Yao^{1,*}, Xiudan Zheng¹, Kan Liao¹

Cell Research (2009) 19:1006-1017.

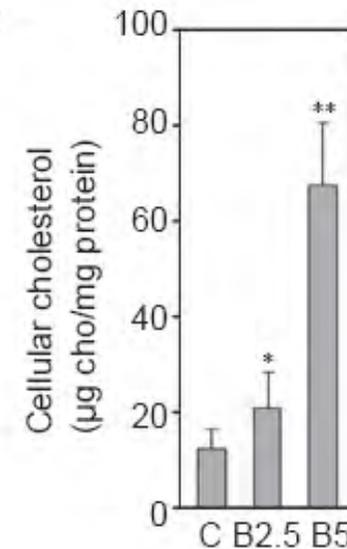
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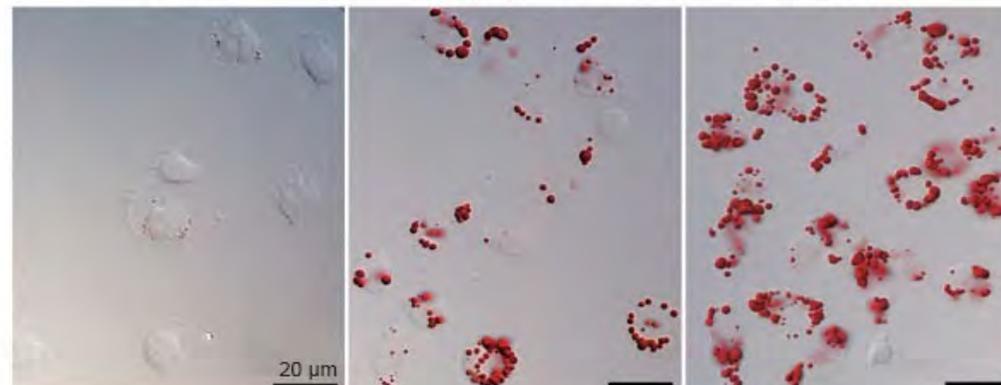
F



Control

2.5 mg/kg/day BBR

5 mg/kg/day BBR

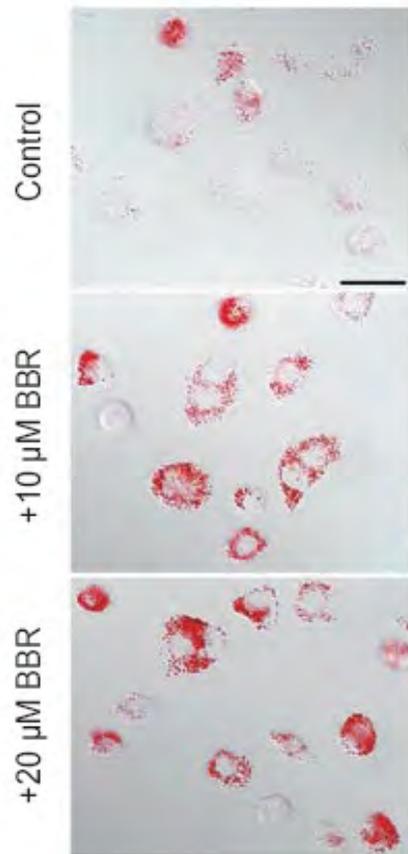


Berberine promotes the development of atherosclerosis and foam cell formation by inducing scavenger receptor A expression in macrophage

Ke Li^{1,*}, Wenqi Yao^{1,*}, Xiudan Zheng¹, Kan Liao¹

Cell Research (2009) 19:1006-1017.

Berberine induced foam cell formation in human primary macrophage



Conclusions:

- Our results suggest that to evaluate the potential of a cholesterol-reducing compound in alleviating atherosclerosis, its effect on the cells involved in atherosclerosis development, such as macrophages, should also be considered.
- Promotion of foam cell formation could counter-balance the beneficial effect of lowering serum cholesterol.



Supplementi

- ▶ La supplementazione routinaria con antiossidanti, come la vitamina E e C e β -carotene non è consigliata in mancanza di prove di efficacia e di sicurezza a lungo termine. (**Livello della prova I, Forza della raccomandazione D**)
- ▶ L'introduzione di cibi naturalmente ricchi di antiossidanti, microelementi e altre vitamine deve essere incoraggiata. Per questo l'introduzione giornaliera di frutta e vegetali deve essere promossa nelle persone con il diabete. (**Livello della prova III, Forza della raccomandazione B**)

Standards of Medical Care in Diabetes—2013

AMERICAN DIABETES ASSOCIATION

DIABETES CARE, VOLUME 36, SUPPLEMENT 1, JANUARY 2013

- Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety. (A)

The following NHPs lowered A1C by $\geq 0.5\%$ in trials lasting at least 3 months in adults with type 2 diabetes:

- *Coccinia cordifolia*
- *Ganoderma lucidum*
- *Salacia reticulata*
- Soybean-derived pinitol extract
- Touchi soybean extract
- *Pterocarpus marsulium* (vijayasar)
- *Gynostemma pentaphyllum*
- Marine collagen peptides
- Silymarin
- *Citrullus colocynthis*
- *Trigonella foenum-graecum* (fenugreek)

These products are promising and merit consideration and further research, but, as they are mostly single, small trials, it is premature to recommend their widespread use.

The following NHPs failed to lower A1C by $\geq 0.5\%$ in trials lasting at least 3 months in adults with type 2 diabetes:

- *Tinospora crispa*
- French maritime pine bark
- Soy phytoestrogens
- *Agaricus blazei*
- Antioxidants (fruit/vegetable extract, pomegranate extract)
- *Camellia sinensis*
- *Cinnamomum* spp (cinnamon)
- *Momordica charantia* (bitter melon or bitter gourd)
- Flaxseed oil
- Ginseng
- Coenzyme Q10
- Vitamin C
- Vitamin D
- Vitamin E

It should be noted that, in many cases, small sample sizes made the trials insufficiently powered to establish a significant benefit from NHP interventions.

- The following NHPs have demonstrated conflicting effects on A1C in trials lasting at least 3 months in adults with type 2 diabetes:
 - *Ipomoea batatas* (cayapo)
 - Chromium
 - Magnesium
 - L-carnitine

- It should be noted that vanadium, a trace element that is commonly used to treat type 2 diabetes, has not been studied in trials evaluating glycemic control over a period of 3 months or longer.

Recommendations

1. Natural health products are not recommended for glycemic control for individuals with diabetes as there is insufficient evidence, at this time, regarding efficacy and safety [Grade D, Consensus].
2. Healthcare providers should ask about the use of natural health products [Grade D, Consensus].