

# COMPLEMENTARY MEDICINES – COMMON MYTHS, FALLACIES OR FACTS ?

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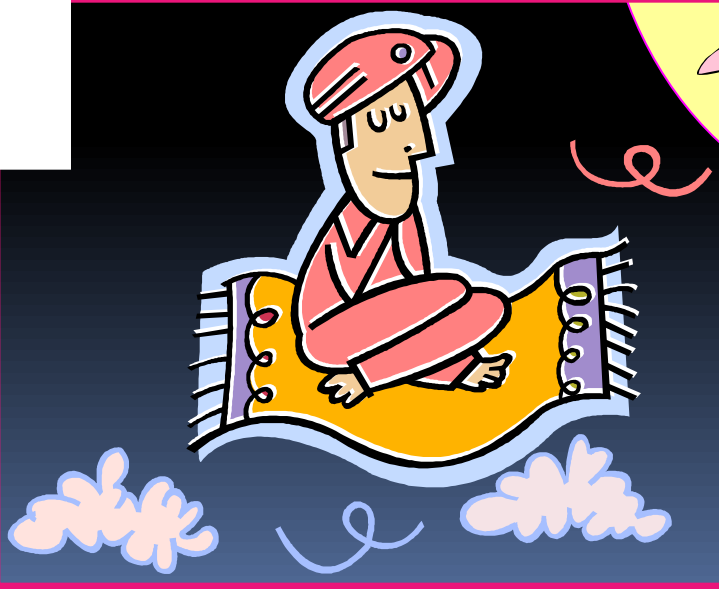


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# Fiction, fantasy...???





# Mum's advice

“Don't go out with wet hair...  
Or you'll catch a cold”

“Don't stand on a cold floor in bare feet...  
Because you'll catch a cold”

“Don't stand too close to the heater...  
because you'll get chilblains”

“Don't eat before you go swimming...  
because you will get a cramp/drown/sink...”

# Urban myths...a test



Coca cola used to contain cocaine

- A tooth left in a glass of CC overnight will dissolve
- Combining aspirin and CC will get you 'high'
- The Mormons own the CC company

- A mixture of Mentos and CC killed 2 Brazilian children



CC was originally intended as a patent medicine



- CC was originally green
- CC was invented in the late 19th century by a pharmacist

# For Today – 3 common misunderstandings & myths

- Vitamin C and kidney stones
- Vitamin E and increased mortality
- Do fish oils cause bleeding ?

# Vitamin C and kidney stones

- In humans some ascorbate - oxalate
- Oxalate is not further metabolised; it's excreted mainly in the urine
- \* Elevated urinary oxalate is a risk factor for calcium oxalate stone formation in susceptible individuals



# Dietary vitamin C



- In 1996, 5 yr prospective study men
- **No difference in relative risk** of symptomatic kidney stones with dietary vitamin C intake for any quintile
- Doses ranged from **under 250 mg/d (lowest) to more than 1,500 mg/d (highest)**
- Dietary vitamin C intakes **not associated** with increased incidence of kidney stones

# Ascorbate supplements ?



- **1994:** 1, 5, & 10 gm/d **increased** urinary oxalate from 34 mg/d to 41, 41, and 48 mg/d respectively ( $P < .05$ ) in 15 healthy people  
(Wandzilak et al)
- **1996:** 400 mg/d ascorbate **increased** urinary oxalate from 30 to 35 mg/d (ns), whereas a 1000 mg/d dose increased it to 40 mg per day ( $P < .02$ )  
(Levine et al)
- **1997:** 2 gm/d for 4 days **increased urinary oxalate only from 30 to 32 mg/d (ns) in 6 healthy subjects**  
(Liebman et al)
- **1998:** 4 gm/d for 5 days only **increased** urinary oxalate from 17.5 to 19.4 mg per day (ns) in 10 healthy men  
(Auer et al)

# Liebman et al.



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EFFECT OF SUPPLEMENTAL ASCORBATE AND ORANGE JUICE ON URINARY OXALATE<sup>1</sup>

Michael Liebman, PhD<sup>2</sup>, Weiwen Chai, MS, Ellen Harvey, BS, Laura Boenisch, BS  
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## ABSTRACT

The relationship between ascorbate intake, in supplemental form and naturally occurring in orange juice, and urinary oxalate was assessed in 6 healthy individuals. An experimental model which allowed a differentiation between endogenously- and exogenously-derived urinary oxalate was used. Twenty-four hour urine samples were collected the last day of baseline, supplemental ascorbate, and orange juice treatment periods. Oxalate load tests were administered the day following each experimental treatment. Oxalate loads consisted of 175 mg unlabeled and 18 mg 1,2-<sup>13</sup>C<sub>2</sub> oxalic acid. The orange juice treatment was associated with higher urinary excretion of endogenously-derived oxalate, citrate, and calcium, and a higher urinary pH. Since these urinary changes were not observed during the supplemental ascorbate period, the two sources of ascorbate differentially affected key urinary components which are related to calcium oxalate nephrolithiasis.

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Key Words: Oxalate, Ascorbate, Orange Juice

Found 2 gm  
ascorbate per  
day for 4 days  
increased  
urinary oxalate  
from 30 to  
32 mg per day  
(ns) in 6 healthy  
subjects

# Liebman et al...


Twenty-Four Hour Urinary Parameters\*

Parameter	Treatment	
	Baseline	Supplemental Ascorbate
Volume (ml)	2140 ± 533	2228 ± 652
Oxalate (mg)	30.0 ± 4.6	32.3 ± 3.1
Ascorbate (mg)	112 ± 43 <sup>a</sup>	1144 ± 138 <sup>b</sup>
Citrate (mg)	437 ± 35 <sup>a</sup>	397 ± 43 <sup>a</sup>
Calcium (mg)	221 ± 32	188 ± 38
Creatinine (mg)	1609 ± 195	1701 ± 217

\* $\bar{x} \pm SE$ ; n=6, Means within rows with different superscript letters are significantly different,  $P < 0.05$ .

# Bottom line...(vitamin C)

- Ascorbate **increases** urinary oxalate levels
  - Usually not significant at doses < 5gm/d
- The effect is **dose dependant**
- In people who do not form stones, vitamin C supplements and dietary C intake is **unlikely** to induce kidney stone formation
- In susceptible people, it is **not known** whether the minor increases in urinary oxalate will increase risk




# High dose vitamin E & mortality

Question:

- Do high dose vitamin E supplements increase mortality risk?

Why?

- Meta-analysis reported an increase with high dose supplements
  - Some later reviews still cite this caution
- 

# Where does the belief come from

- In 2005, a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality was undertaken using data from 19 RCTs consisting of a large study population (n=135 967)

(Miller, III and others 2005)

- A dose-response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality
- People should avoid doses of 400IU/d or higher

# Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality

Edgar R. Miller III, MD, PhD; Roberto Pastor-Barriuso, PhD; Darshan Dalal, MD, MPH; Rudolph A. Riemersma, PhD, FRCPE; Lawrence J. Appel, MD, MPH; and Eliseo Guallar, MD, DrPH

**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:** To perform a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality by using data from randomized, controlled trials.

**Patients:** 135 967 participants in 19 clinical trials. Of these trials, 9 tested vitamin E alone and 10 tested vitamin E combined with other vitamins or minerals. The dosages of vitamin E ranged from 16.5 to 2000 IU/d (median, 400 IU/d).

**Data Sources:** PubMed search from 1966 through August 2004, complemented by a search of the Cochrane Clinical Trials Database and review of citations of published reviews and meta-analyses. No language restrictions were applied.

**Data Extraction:** 3 investigators independently abstracted study reports. The investigators of the original publications were contacted if required information was not available.

**Data Synthesis:** 9 of 11 trials testing high-dosage vitamin E ( $\geq 400$  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 ( $\geq 400$  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 ( $\geq 400$  IU/d) vitamin E supplements may increase all-cause mortality and should be avoided.

# Looking closer at reality

- This meta-analysis has several serious flaws and been criticised on a number of accounts, inspiring over **40 letters** to the Editor and hundreds of emails and phone calls to the authors

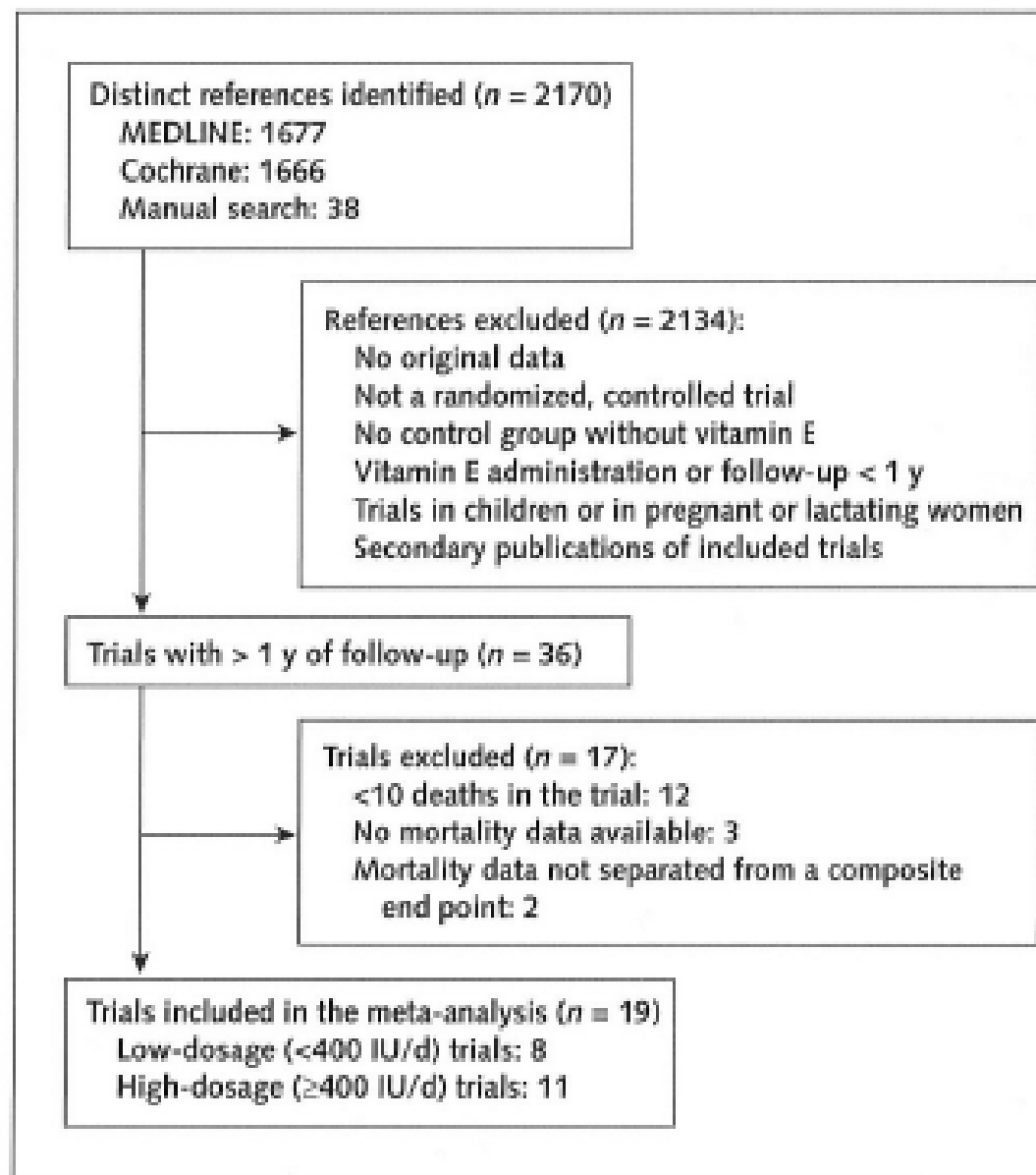


# 6 major flaws

1. Results from 12 clinical studies which reported **< 10 deaths each were excluded**
  - Gives artificial weight to studies in which more people died
2. Trials used **different** designs, treatment times, doses, combinations and endpoints
  - Pooling information from such heterogeneous studies is inappropriate
3. Subjects in many studies had **significant chronic disease** e.g. Parkinson's disease, end stage renal disease, coronary artery disease, diabetes mellitus and Alzheimer's dementia
  - This would have influenced/biased their mortality risk

# Study inclusion and exclusion criteria

Figure 1. Flow diagram of the trial selection process.



## 6 major flaws...cont'd

4. Studies used **different forms of vitamin E** (natural and synthetic) and sometimes **in combination** with other nutrients however all studies were pooled together and not separated out
5. Subject **adherence** to the treatment protocol was only considered in one study (the CHAOS study)
6. Some **statistical models** have been questioned

# Bottom line...(vitamin E)

- The results of this meta-analysis are **unreliable**
- Multiple confounding issues not properly addressed by authors
- Peer-review process flawed?
- Publication bias?
- Other?



# Tuna in Tokyo fish market



# Does fish oil cause bleeding?

## Expert Opinion: Omega-3 Fatty Acids and Bleeding—Cause for Concern?

William S. Harris, PhD

Omega-3 fatty acid ethyl esters have well-known triglyceride-lowering properties and were shown >30 years ago to inhibit platelet function. With the recent US Food and Drug Administration (FDA) approval of these agents for treating severe triglyceride elevations, concerns about excess bleeding naturally arise. However, an objective assessment of the evidence for clinically significant bleeding reveals that such concerns are unfounded. As such, the benefits of triglyceride lowering with omega-3 fatty acids more than outweigh any theoretical risks for increased bleeding. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:44C–46C)

Table 1  
Summary of reports of the effects of omega-3 fatty acids on bleeding complications

Procedure	EPA + DHA Dose (Product)	Pretreatment (days)	Duration (mo)	Patients (n)	Concomitant Medications	Bleeding Complications
CABG <sup>2</sup>	3.4 g (Omacor)*	2	12	610	Aspirin or warfarin	"The bleeding time increased moderately in both groups, and there was no group difference"
CABG <sup>3</sup>	4.3 g (unnamed) fish oil <sup>†</sup>	28	To surgery	30	Heparin during CABG	"The patients . . . did not have significantly increased bleeding at or after surgery compared to matched controls"
PTCA <sup>4</sup>	3.6 g (MaxEPA) <sup>‡</sup>	0	12	108	None	No patient had undesirable bleeding effects, and the combination appears quite safe
PTCA <sup>5</sup>	3.0 g (MaxEPA) <sup>‡</sup>	1–2	6	120	Aspirin, dipyridimole, CCB, nitrates	Only adverse events reported were: nausea (n = 4) and diarrhea (n = 1)
PTCA <sup>6</sup>	6.9 g (NIH Fish Oil) <sup>§</sup>	12–14	6	447	Aspirin	"No difference in clinically significant bleeding was noted. . . All bleeding times were within the normal range"
PTCA <sup>7</sup>	5.4 g (MaxEPA) <sup>‡</sup>	7	6	82	Aspirin and dipyridimole	"We did not observe a significant prolongation of bleeding time"
PTCA <sup>8</sup>	3.15 g (Ameu) <sup>  </sup>	0	4.5	204	Aspirin	"None of the patients demonstrated or reported on bleeding complications"
PTCA <sup>9</sup>	4.5 g (Promega) <sup>¶</sup>	0	6	194	Aspirin	No specific mention of bleeding, but stated that "six months of therapy appears safe"
PTCA <sup>10</sup>	5.4 g (MaxEPA) <sup>‡</sup>	6	4.5	814	Aspirin (all); 50% also taking low-molecular-weight heparin	"Bleeding less frequent in fish oil group"
PTCA <sup>11</sup>	3 g (MaxEPA) <sup>‡</sup>	1	4	108	Aspirin	"No patient suffered from bleeding complications"
PTCA <sup>12</sup>	3 g (MaxEPA)	4.3	6	107	Aspirin and CCB	"No patients suffered from bleeding complications during follow up"
PTCA <sup>13</sup>	4.5 g (MaxEPA) <sup>‡</sup>	21	6	205	Aspirin	"None of the patients reported bleeding . . . attributable to the fish oil supplements"
PTCA <sup>14</sup>	6 g (Super EPA 500 <sup>H</sup> or Promega <sup>  </sup> )	5.4	4.5	242	Aspirin and dipyridimole	4 events in 124 patients in the omega-3 group: at PTCA, 2 at puncture site; on study, 1 gastrointestinal bleed requiring transfusion and 1 heme-positive stool (nonsignificant vs placebo)
PTCA <sup>15</sup>	5.1 g (Omacor)*	14	6	388	Aspirin, nitrates, heparin, and nifedipine, all during procedure	Bleeding not mentioned: "no obvious adverse effects to the capsules were noted"
PTCA <sup>16</sup>	5.1 g before, 2.6 g after (Esapent)*	30	6	257	Aspirin	"Lack of any significant side effect [on] bleeding"
Endarterectomy <sup>17</sup>	1.4 g/day (MaxEPA) <sup>‡</sup>	42	Through surgery	170	Aspirin (100% of patients)	"No bleeding complications were noted during the intervention period or in the immediate period post-surgery" (P. Calder, personal communication)
Endarterectomy <sup>18</sup>	16–21 g/day (MaxEPA) <sup>‡</sup>	Median 30	Through surgery	29	None listed	"There were no clinically significant bleeding complications" (J. Rapp, personal communication)
Coronary angiography <sup>19</sup>	3.3 g for 3 mo; 1.6 g for 21 mo <sup>‡</sup>	None	24	223	Aspirin (91% of patients)	"Minor hematoma, but no other complication, was associated with the second episode of coronary angiography"
Coronary angiography <sup>20</sup>	4.8 g (Promega) <sup>H</sup>	None	28	59	Aspirin (95% of patients)	"There were no serious adverse events related to bleeding. This was not an issue for the cardiologists doing the cath" (F. Sacks, personal communication)



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Review

## Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives

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## 10. Decreased platelet aggregation

The antithrombotic potential of omega-3 fatty acids was one of the first effects reported in Greenlandic Eskimos, who consume large amounts of whale and seal meat. Omega-6

3 fatty acid levels is thus antithrombotic. Although EPA plus DHA have been associated with modest increases in bleeding times, no published studies have reported clinically significant bleeding episodes among patients treated with antiplatelet drugs and relatively high doses (3–7 g/day) of EPA plus DHA [79].

# Helping to create a myth?

## Putting information into context

- Is the source reliable? Credible? Recent?
  - Check the original report where possible
- When a new trial comes out, it should be interpreted in the light of 'what is already known'
  - Never a stand alone study
- In vitro and in vivo tests: know their strengths & limitations
  - Don't assume clinical significance
- N=1 and traditional evidence
  - A starting point, not an end point? Confounders?



