# Ernährung 2007

## Vitamine und Spurenelemente – Indikationen Kontraindikationen?

Neue Ergebnisse aus der Forschung –
Neue Indikationen Kontraindikationen?

# Ernährung 2007

## Vitamine und Spurenelemente – Was ist evidence based?

Neue Ergebnisse aus der Forschung –
Neue Indikationen Kontraindikationen?

## Evidence-Based Medicine: Grades of Evidence
## Hierarchy of Research Designs

I. Properly randomized, controlled trial

II.1 Well-designed controlled trial without randomization

II.2 Well-designed cohort or case-control analytic study

II.3 Multiple time series with or without intervention

III. Opinions of respected authorities; descriptive studies or case reports; reports of expert committees

US Preventive Services Task Force 1996

EDITORIALS

# Surviving Antioxidant Supplements

Goran Bjelakovic, Christian Gluud

?

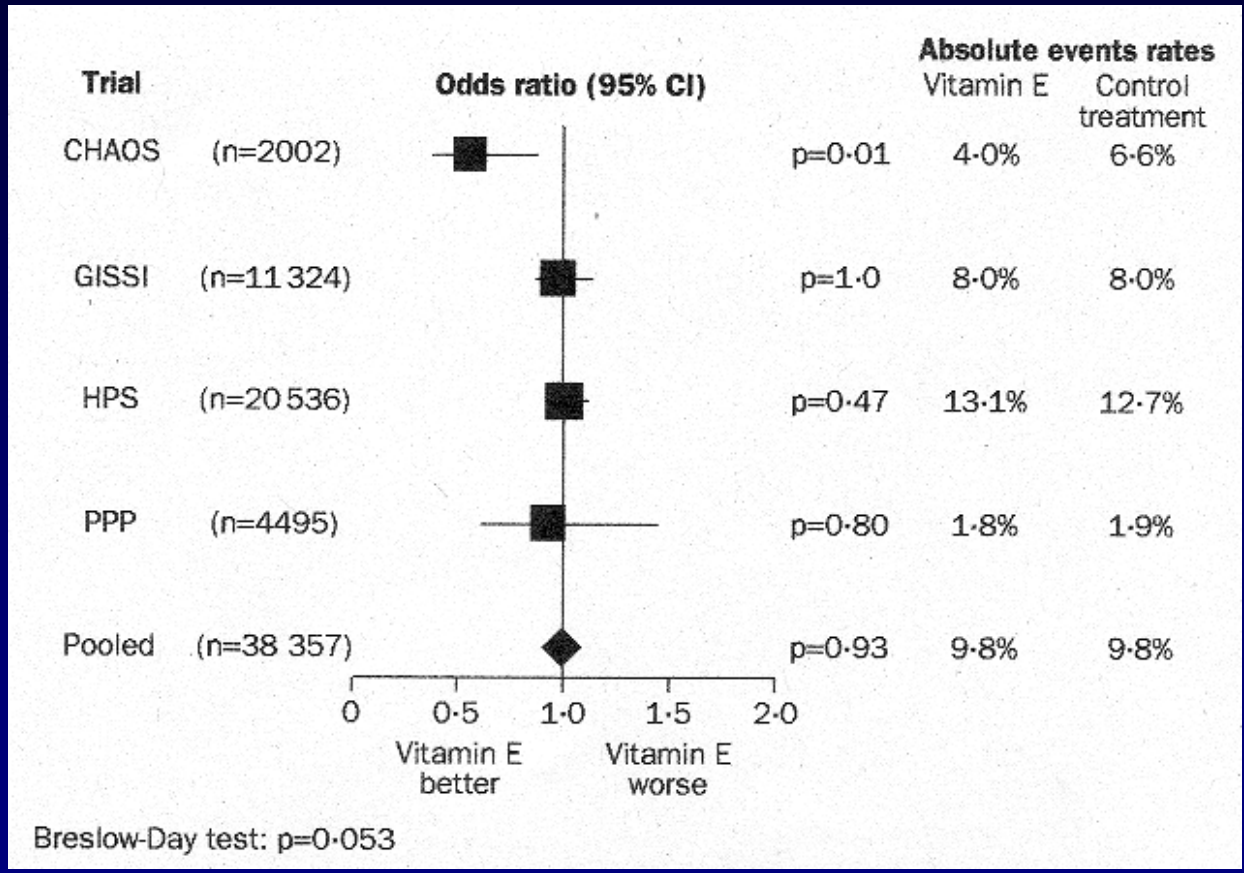
**D. Vivekananthan et al., Lancet Vol 348 June 14 2003**

**Use of antioxidant vitamins for the prevention of cardiovascular disease: meta analysis of randomised trials.**

**The lack of a salutary effect was seen consistently for various doses of vitamins in diverse populations.**

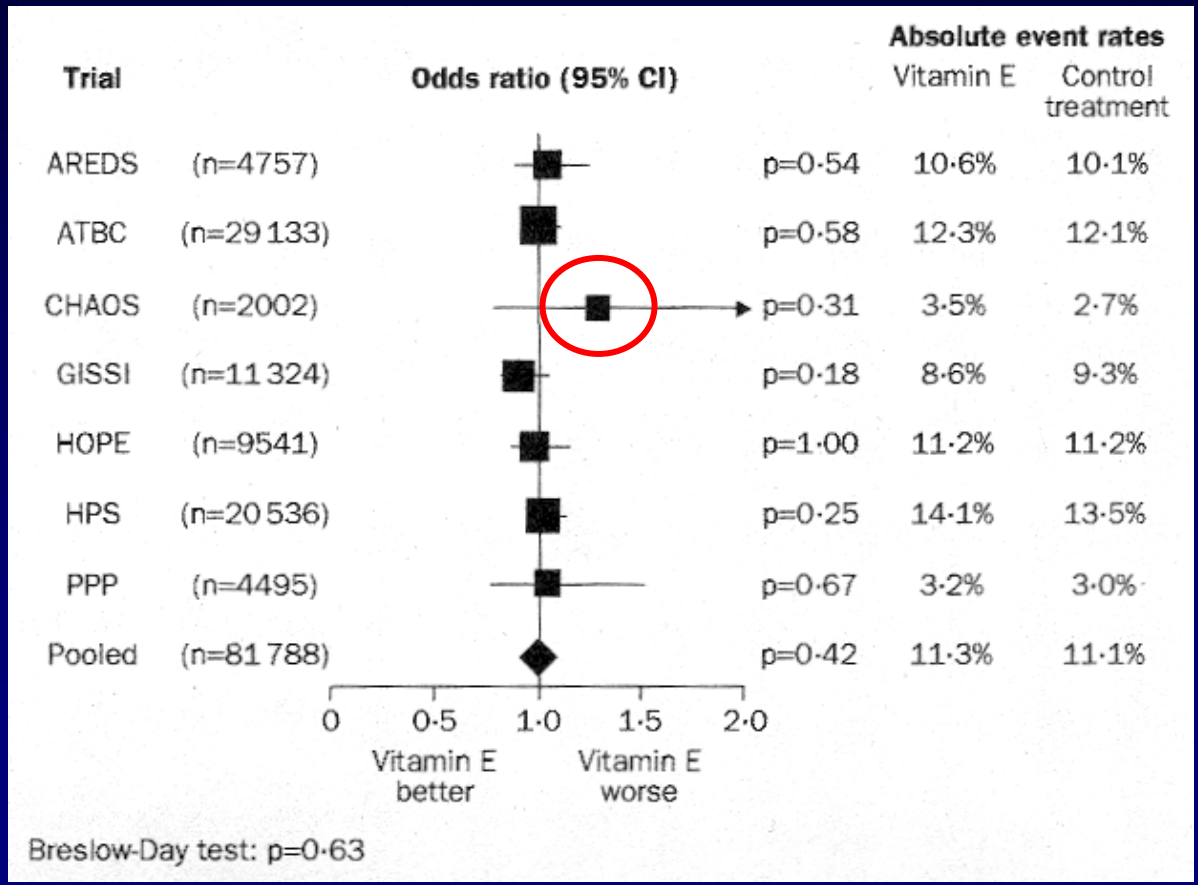
**Our results combined with the lack of mechanistic data for efficacy of vitamin E, do not support the routine use of vitamine E.**

**Odds ratios (95% CI) of the combined endpoint of cardiovascular death or non-fatal MI for individuals treated with vitamin E or control therapy.**



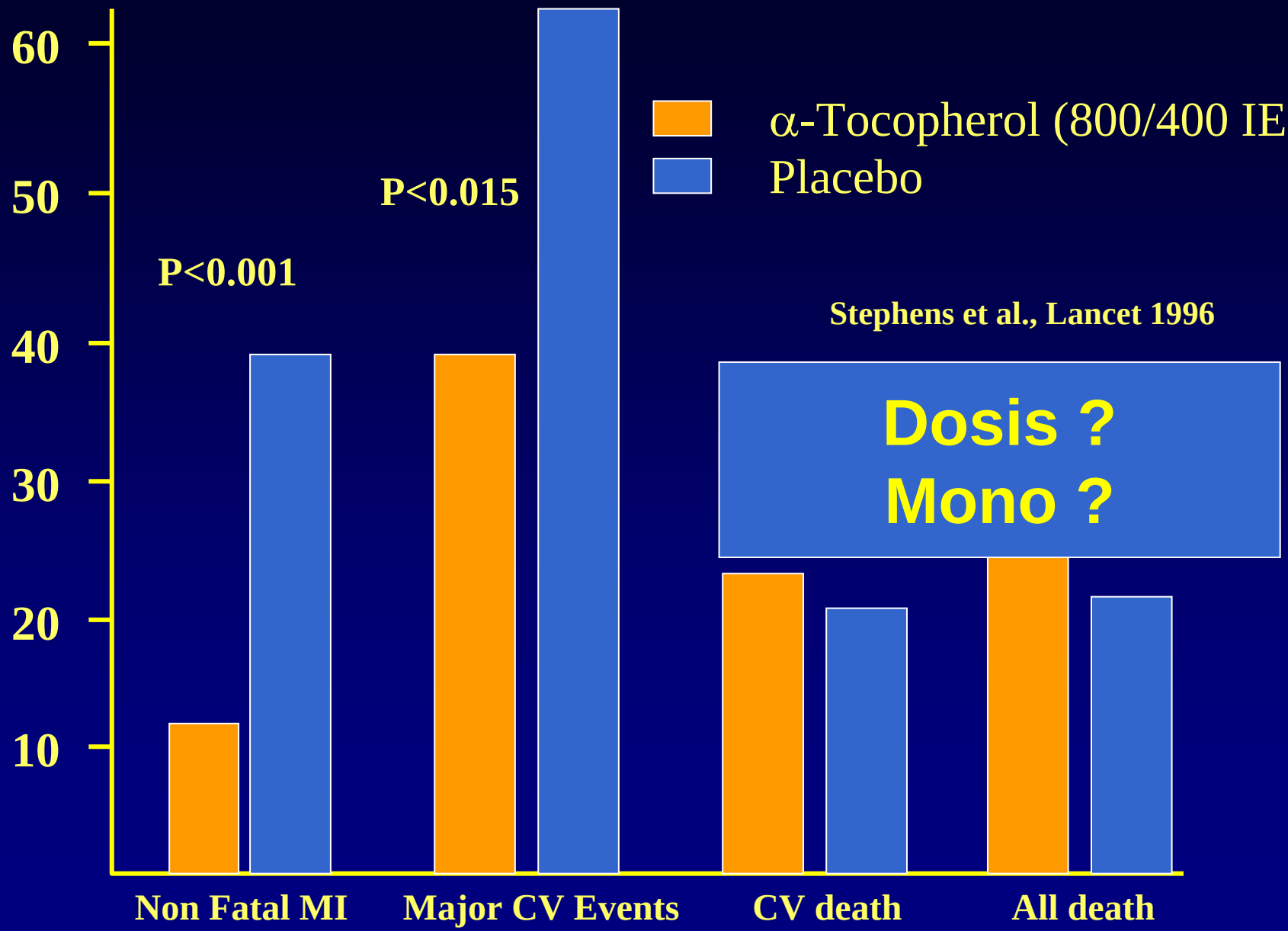

**Source:** Vivekananthan DP, The Lancet 361, 2003

# Odds ratios (95% CI) of all-cause mortality for individuals treated with vitamin E or control therapy.



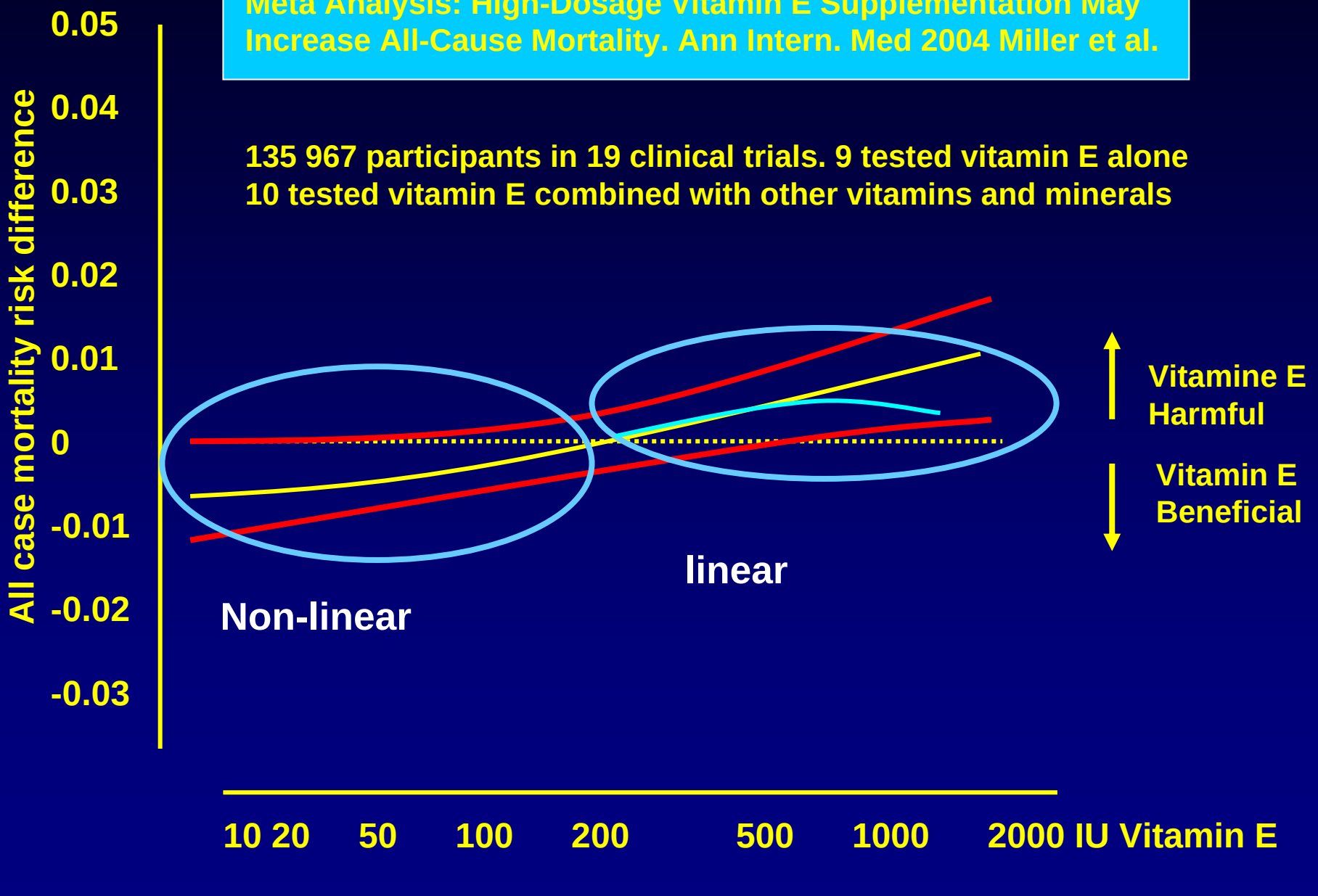

**Source:** Vivekananthan DP, The Lancet 361, 2003

# Number of events in the CHAOS-Study



**Meta Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality. Ann Intern. Med 2004 Miller et al.**

**135 967 participants in 19 clinical trials. 9 tested vitamin E alone**
**10 tested vitamin E combined with other vitamins and minerals**



# AREDS showed a 25% reduction of late AMD using antioxidants

N.M. Bressler et al. *ARVO 2002*

„U.S. Public Health Impact of AREDS results“

- 6 Mio  55 - 80 Y. with risk for late AMD
- 1.2 Mio will develop late AMD within 5 years
- 25 % Riskreduction within 5 years

$\Rightarrow$ > 300.000 would have no pogression into a late AMD

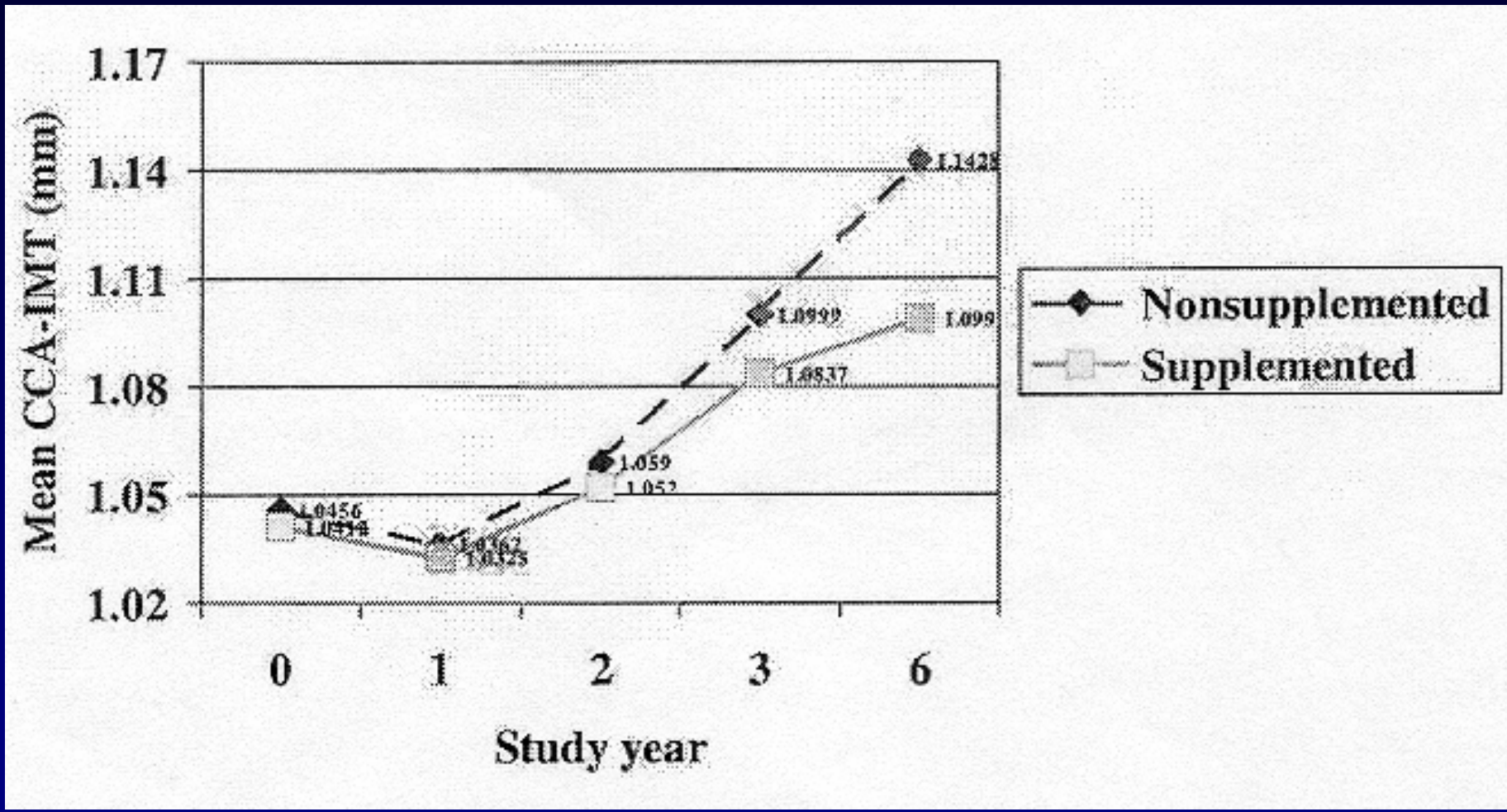
**Six year effect of combined vitamin C and E supplementation on atherosclerotic progression.**

**Salonen et al. Circulation 107: 2003**

**3 years supplementation with 136mg vitamin E and 250mg vitamin C twice daily slowed down progression of carotid atherosclerosis in men but not in women.**

**Further slow down of progression in hypercholesteronemic persons.**

# The mean CCA-IMT* in the annual assessments in male participants randomized to supplementation and to no supplements.




Source: Salonen RM, Circulation, 2002

* Common-carotid artery-intima media thickness

**Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis.**

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C.

## CONCLUSIONS:

**Treatment with beta carotene, vitamin A, and vitamin E may increase mortality.**

**Bjelkovic et al., 2007:**

**Keine Zunahme der Mortalität in 68 RCT**

**Low risk of bias: 5% Zunahme der Mortalität in 47 Studien**

**13 Studien mit mehr als 1000 TN: 1% Risiko Reduktion**

**High risk of bias: signifkante Abnahme der Mortalität**

**21 von 68 gaben Mortalität an**

**Mittlere Dauer der Vitamin Einnahme 2.7 Jahre**

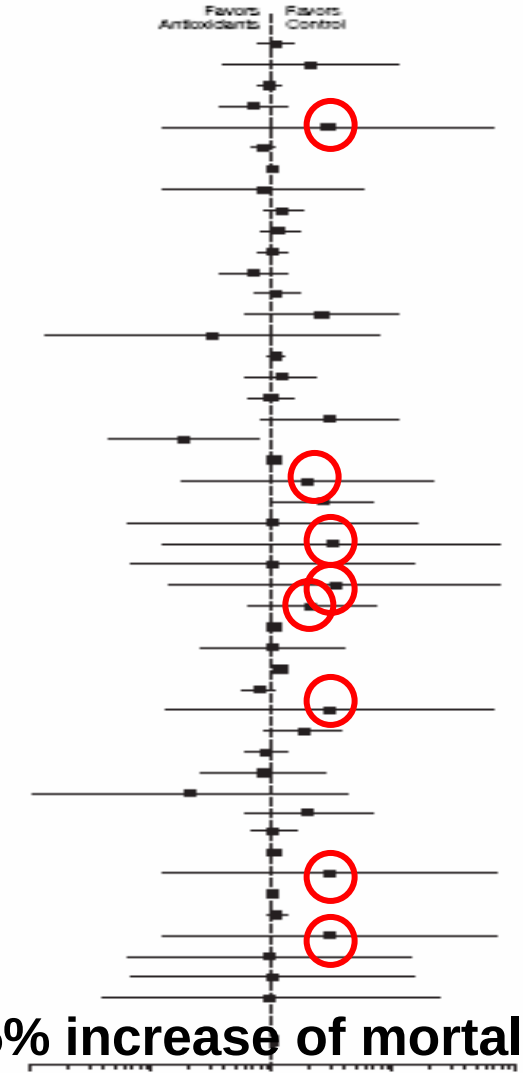
# Intervention effect of antioxidant supplements vs placebo on mortality in trials with low risk of bias



**Figure 2.** Intervention Effect of Antioxidant Supplements vs Placebo on Mortality in Trials With Low Risk of Bias

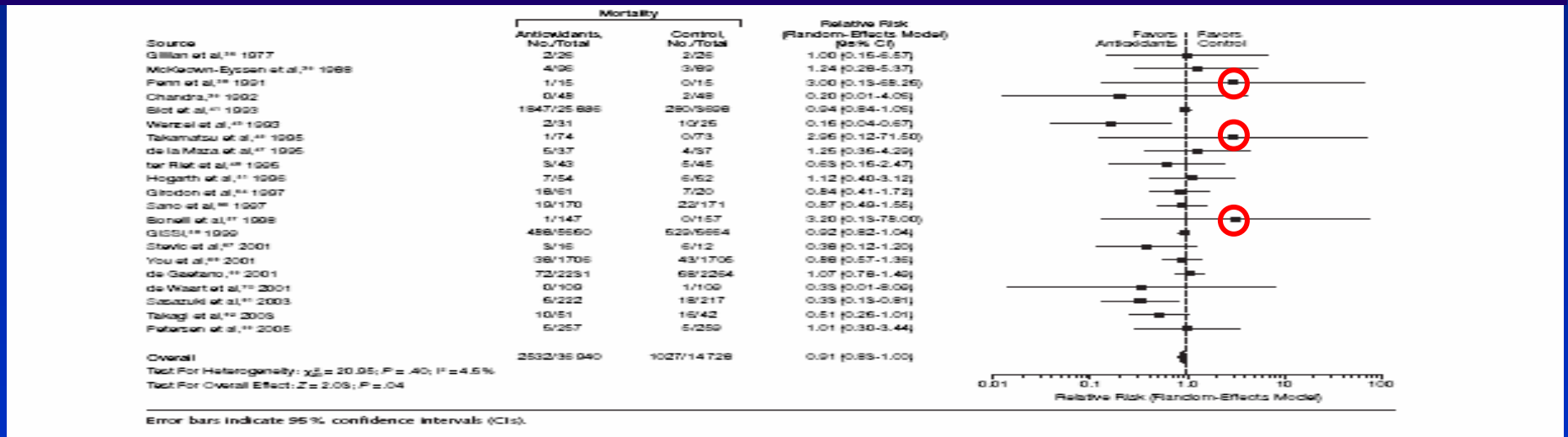
| Source | Mortality: Antioxidants, No./Total | Mortality: Control, No./Total | Relative Risk (Random-Effects Model) (95% CI) |
|---|---|---|---|
| Greenberg et al,[37] 1990 | 79/913 | 72/892 | 1.07 (0.79-1.46) |
| Murphy et al,[42] 1992 | 4/55 | 2/56 | 2.11 (0.40-11.05) |
| Li et al,[43] 1993 | 157/1657 | 167/1661 | 0.94 (0.77-1.16) |
| Greenberg et al,[44] 1994 | 50/650 | 14/214 | 0.71 (0.38-1.31) |
| Pike et al,[45] 1995 | 1/24 | 0/23 | 2.89 (0.12-67.29) |
| Clark et al,[46] 1996 | 108/655 | 129/659 | 0.84 (0.67-1.07) |
| Hennekens et al,[51] 1996 | 979/11035 | 968/11035 | 1.01 (0.93-1.10) |
| Richer,[52] 1996 | 2/39 | 2/32 | 0.82 (0.12-5.50) |
| Stephens et al,[53] 1996 | 68/1035 | 52/957 | 1.22 (0.85-1.73) |
| Moon et al,[54] 1997 | 62/1157 | 55/1140 | 1.15 (0.81-1.65) |
| Girodon et al,[19] 1999 | 155/543 | 51/182 | 1.02 (0.78-1.33) |
| Green et al,[20] 1999 | 15/801 | 22/820 | 0.70 (0.36-1.34) |
| Boaz et al,[21] 2000 | 31/97 | 29/99 | 1.09 (0.72-1.66) |
| Correa et al,[22] 2000 | 16/759 | 2/237 | 2.57 (0.59-11.08) |
| Jacobson et al,[23] 2000 | 0/57 | 1/55 | 0.32 (0.01-7.74) |
| AREDS,[24] 2001 | 251/2370 | 240/2387 | 1.06 (0.89-1.25) |
| Brown et al,[25] 2001 | 17/84 | 13/76 | 1.18 (0.62-2.27) |
| Desmuelle et al,[26] 2001 | 34/144 | 35/144 | 0.97 (0.64-1.47) |
| Chylack et al,[71] 2002 | 9/149 | 3/148 | 2.98 (0.82-10.79) |
| Graat et al,[72] 2002 | 3/499 | 5/153 | 0.18 (0.04-0.76) |
| Heart Protection Study,[73] 2002 | 1445/10269 | 1389/10267 | 1.04 (0.97-1.11) |
| Hodis et al,[74] 2002 | 2/177 | 1/176 | 1.99 (0.18-21.73) |
| Waters et al,[75] 2002 | 16/212 | 6/211 | 2.65 (1.06-6.65) |
| White et al,[76] 2002 | 1/50 | 1/50 | 1.00 (0.06-15.56) |
| Wiluka et al,[77] 2002 | 1/67 | 0/69 | 3.09 (0.13-74.50) |
| Collins et al,[78] 2003 | 1/26 | 1/26 | 1.00 (0.07-15.15) |
| Prince et al,[79] 2003 | 1/29 | 0/32 | 3.30 (0.14-77.95) |
| Salonen et al,[80] 2003 | 10/300 | 5/130 | 2.11 (0.63-7.02) |
| Virtamo et al,[81] 2003 | 8225/21846 | 2605/7287 | 1.06 (1.02-1.09) |
| Albup et al,[84] 2004 | 4/81 | 4/83 | 1.02 (0.27-3.99) |
| Goodman et al,[85] 2004 | 1865/9420 | 1509/8804 | 1.16 (1.09-1.23) |
| Herdberg et al,[86] 2004 | 76/6481 | 98/6536 | 0.78 (0.58-1.05) |
| Manuel-y-Keenoy et al,[87] 2004 | 1/12 | 0/12 | 3.00 (0.13-67.05) |
| McNeil et al,[88] 2004 | 20/595 | 11/598 | 1.83 (0.88-3.78) |
| Meydani et al,[89] 2004 | 59/311 | 44/306 | 0.87 (0.58-1.30) |
| Mezey et al,[90] 2004 | 4/25 | 5/26 | 0.83 (0.25-2.75) |
| Richer et al,[91] 2004 | 0/30 | 2/31 | 0.21 (0.01-4.13) |
| Avenell et al,[92] 2005 | 8/466 | 4/454 | 1.99 (0.60-6.57) |
| Graf et al,[93] 2005 | 31/89 | 29/77 | 1.03 (0.68-1.54) |
| Lee et al,[94] 2005 | 636/19937 | 615/19939 | 1.03 (0.93-1.15) |
| Limburg et al,[18] 2006 | 1/180 | 0/180 | 3.00 (0.12-73.16) |
| Lonn et al,[95] 2005 | 709/4761 | 801/4780 | 1.00 (0.92-1.10) |
| Mamas et al,[97] 2005 | 154/399 | 142/401 | 1.09 (0.91-1.31) |
| Mooney et al,[98] 2005 | 1/142 | 0/142 | 3.00 (0.12-73.03) |
| Tam et al,[100] 2005 | 1/20 | 1/19 | 0.95 (0.06-14.13) |
| Witte et al,[101] 2005 | 1/16 | 1/16 | 1.00 (0.07-14.64) |
| Rayman et al,[102] 2006 | 1/380 | 0/121 | 0.96 (0.04-23.43) |
| Overall | 15366/99026 | 9131/81843 | 1.05 (1.02-1.09) |

Test for Heterogeneity: $\chi^2_{44} = 49.47$; $P = .34$; $I^2 = 7.0\%$




**5% increase of mortality**

# Intervention effect of antioxidant supplements vs placebo or no intervention on mortality in trials with high risk of bias



# Multivitamin Use and Risk of Prostate Cancer in the National Institutes of Health–AARP Diet and Health Study

Karla A. Lawson, Margaret E. Wright, Amy Subar, Traci Mouw, Albert Hollenbeck, Arthur Schatzkin, Michael F. Leitzmann

These results suggest that regular multivitamin use is not associated with the risk of early or localized prostate cancer. The possibility that men taking high levels of multivitamins along with other supplements have increased risk of advanced and fatal prostate cancers is of concern and merits further evaluation.

J Natl Cancer Inst 2007;99:754–64

# Multivitamin Use and Risk of Prostate Cancer in the National Institutes of Health–AARP Diet and Health Study

Karla A. Lawson, Margaret E. Wright, Amy Subar, Traci Mouw, Albert Hollenbeck, Arthur Schatzkin, Michael F. Leitzmann

Methode der Evaluierung:

Fragebogen zur Häufigkeit der Einnahme in den letzten 12 Monaten bei 10.241 Männern mit Prostata Krebs

Ergebniss: Betroffen vor allem die Gruppe, die angaben neben Multivitaminen (>7/Woche) zusätzlich Selen einzunehmen

(RR 5.8 für fatal Prostata Krebs n=8) sowie Personen

mit positiver Familienanamnese (RR 16.41 n=3)

**Genetik ?**

# Multivitamin Use and Risk of Prostate Cancer in the National Institutes of Health–AARP Diet and Health Study

Karla A. Lawson, Margaret E. Wright, Amy Subar, Traci Mouw, Albert Hollenbeck, Arthur Schatzkin, Michael F. Leitzmann

**3 Fälle mit wahrscheinlicher Genetik tragen zur Gesamtrisikoerhöhung von Teilnehmern mit Multivitamin Einnahme > 7/Tag auf 1.33 zu 75% bei.**

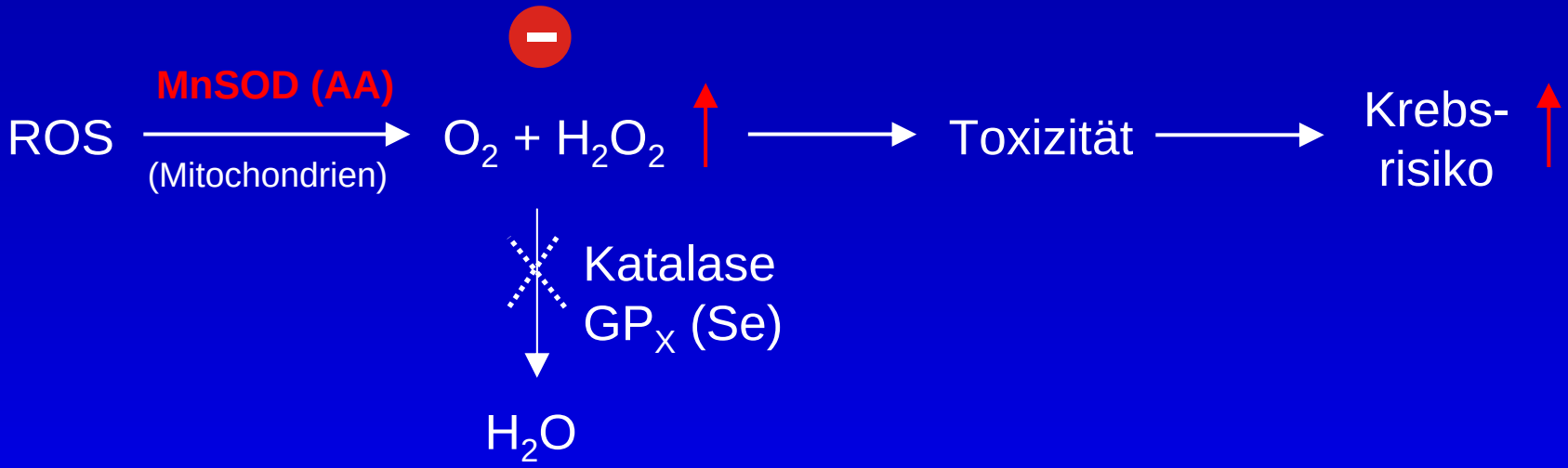
# MnSOD-Polymorphismus und Prostatakrebs

(Haojie et al. Cancer Research 65(6): 2498-2504; 2005)


- AA-Genotyp: MnSOD-Aktivität und Transfer in Mitochondrien ist gesteigert
- Häufigkeit des A-Allels liegt bei Japanern bei 12% und bei Kaukasiern bei 41-55%
- AA-Genotyp hat ein stark erhöhtes Risiko für Prostatakrebs (und andere Krebsarten) aber nur dann, wenn der allgem. Antioxidantienstatus im Plasma gering war

# MnSOD-Polymorphismus und Prostatakrebs

Antioxidantien:
Lycopin, Vitamin E, Se, ß-Carotin ….

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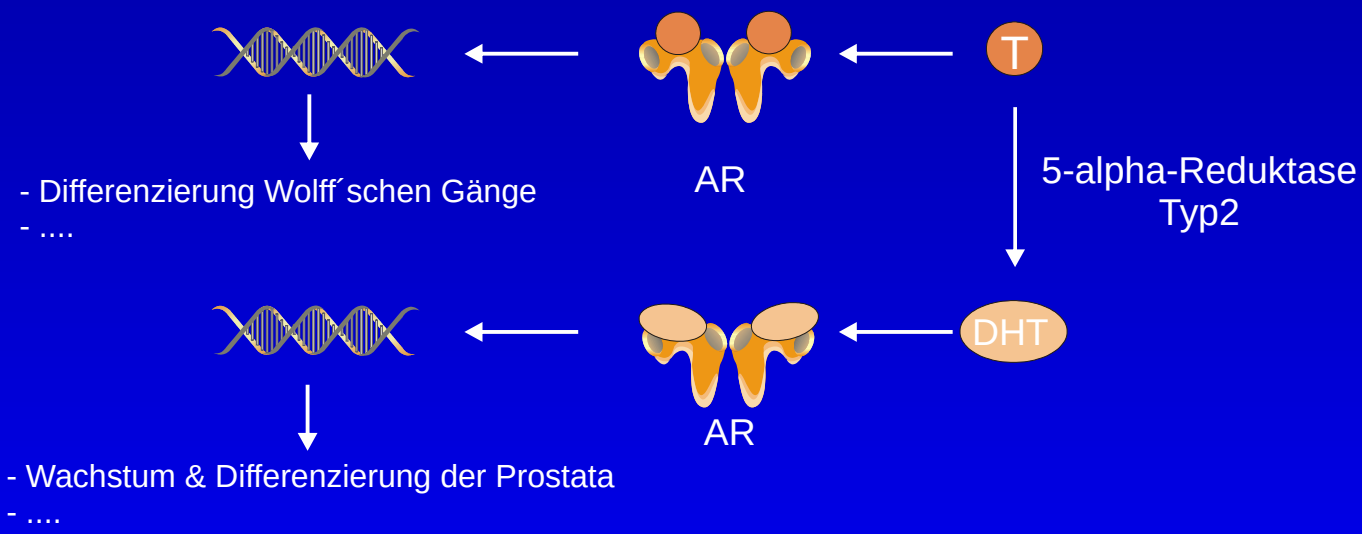
(Haojie et al.: MnSOD Polymorphism, Prediagnostic Antioxidant Status, and Risk of Clinical Significant Prostate Cancer. *Cancer Research 65(6): 2498-2504; 2005*)

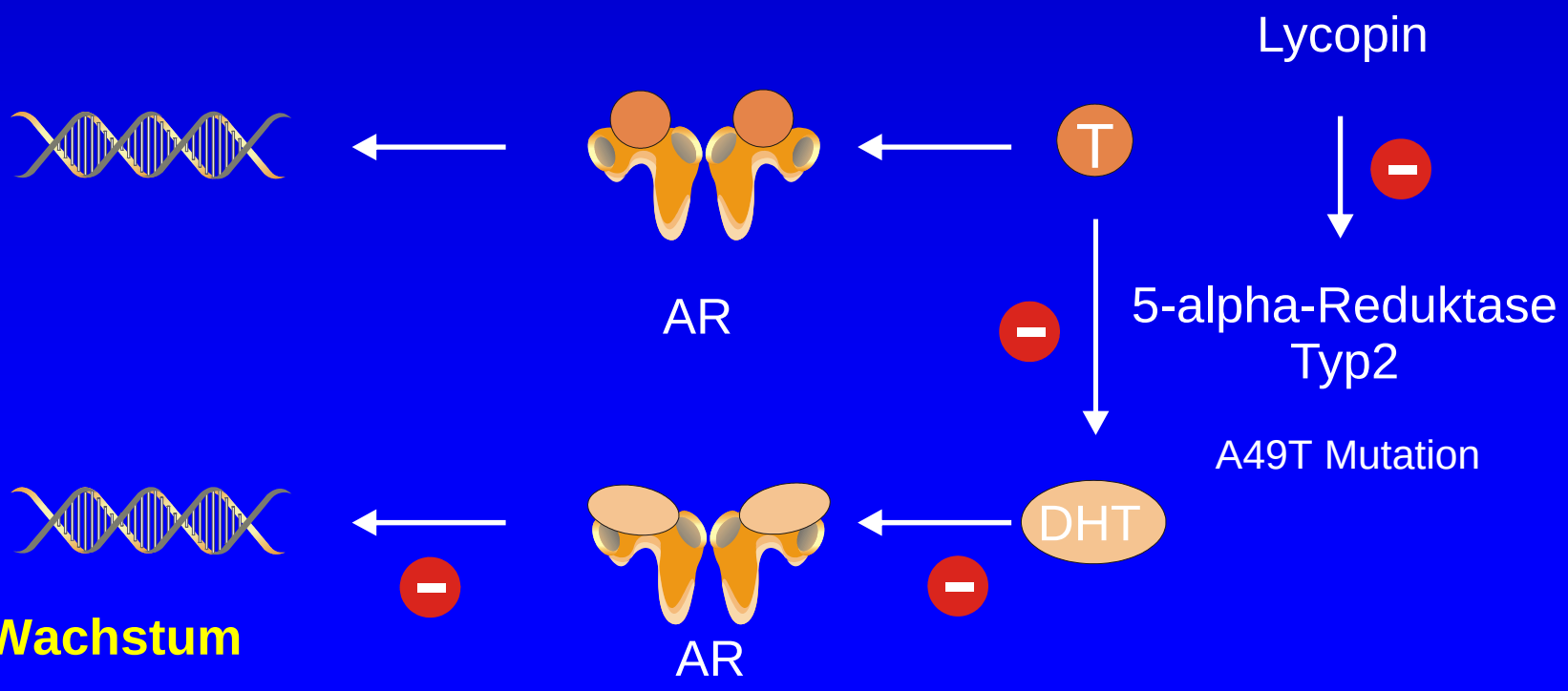
# Genetik

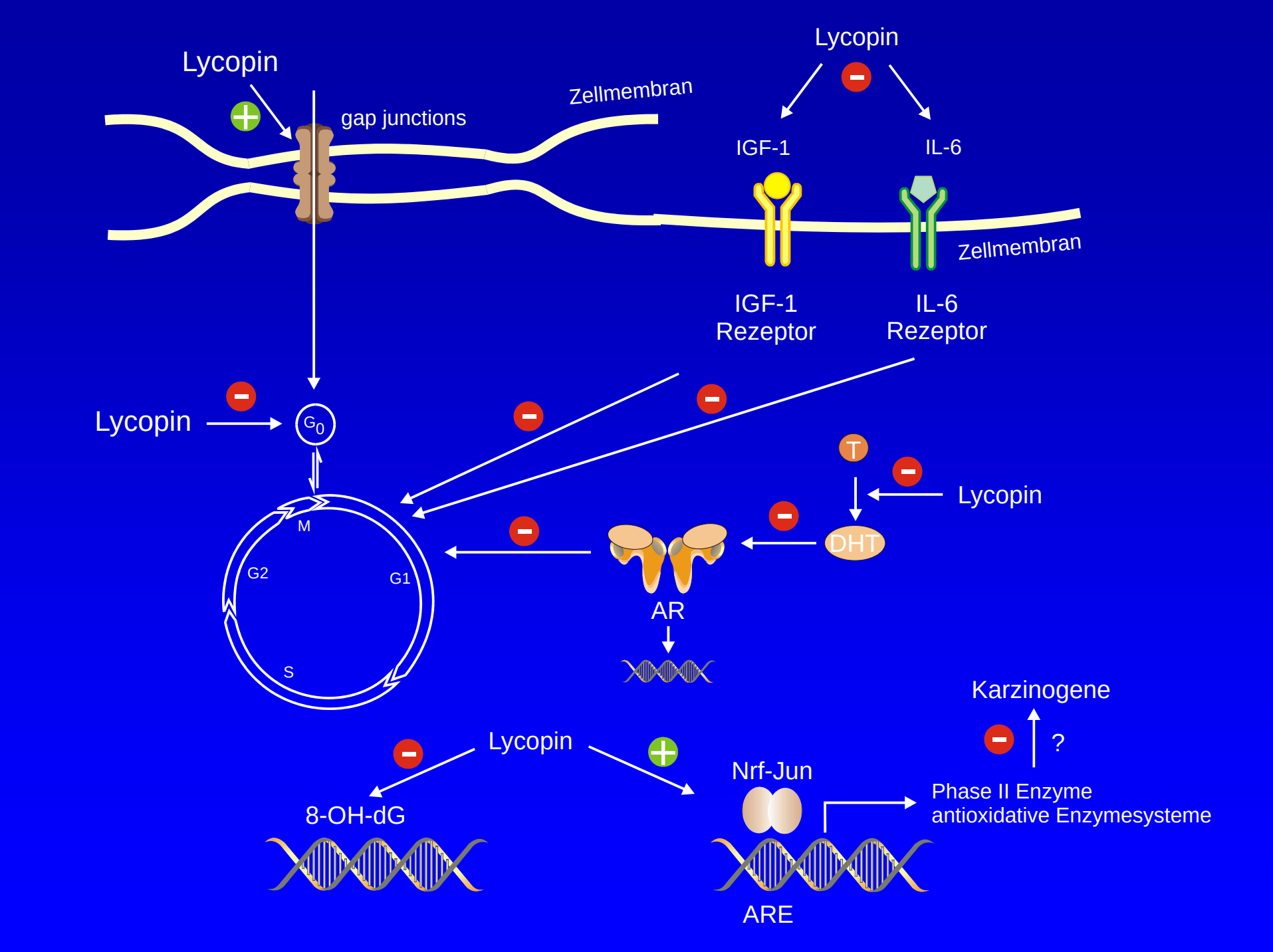



- Junge Japaner haben eine niedrigere 5-alpha-Reduktase Aktivität als junge Kaukasier
- Das DHT : Testosteron Verhältnis ist bei jungen Kaukasiern höher als bei jungen Japanern
- Ergebnisse korrespondieren mit dem Prostatakrebsrisiko

Profitieren vorwiegend die Menschen von Lycopin, die eine gesteigerte 5-alpha-Reduktase Aktivität (A49T Mutation) aufweisen ?

- **Junge Japaner haben eine niedrigere 5-alpha-Reduktase Aktivität als junge Kaukasier**
- **Das DHT : Testosteron Verhältnis ist bei jungen Kaukasiern höher als bei jungen Japanern**
- **Ergebnisse korrespondieren mit dem Prostatakrebsrisiko**




Lycopin
Zellmembran
gap junctions
Lycopin
IGF-1
IL-6
Zellmembran
IGF-1
Rezeptor
IL-6
Rezeptor
Lycopin
G0
M
G2
G1
S
T
Lycopin
DHT
AR
Karzinogene
?
Lycopin
8-OH-dG
Nrf-Jun
Phase II Enzyme
antioxidative Enzymesysteme
ARE

The Journal of Nutrition - Research Article

**Lycopene Inhibits Disease Progression in Patients with Benign Prostate Hyperplasia**a,b

Silke Schwarz1*, Ute C. Obermüller-Jevic2*, Eva Hellmis3, Winfried Koch4, Günther Jacobi3, Hans-Konrad Biesalski1

TABLE 4

*Results from clinical examinations and IPSS index*

| | Placebo | | Lycopene | |
|---|---|---|---|---|
| | Baseline Mean ± SD | After 6 months Mean ± SD | Baseline Mean ± SD | After 6 months Mean ± SD |
| **DRE *(mL)*** | **43.6 ± 12.1 (40.0)** | **55.3 ± 25.6 (50.0)§§** | **47.4 ± 15.2 (40.0)** | **49.7 ± 13.0 (50.0)** |
| **TRUS *(g)*** | **40.5 ± 13.0 (36.9)** | **50.1 ± 21.1 (46.5)[a]** | **42.2 ± 14.3 (37.0)** | **43.4 ± 11.9 (43.0)** |
| IPSS (points) | 12.4 ± 2.0 (12.5) | 10.1 ± 4.8 (9.5)[a] | 12.0 ± 2.4 (12.0) | 10.3 ± 4.0 (10.0)[b] |
| IPSS, obstruction-related[1] | 7.3 ± 0.9 (7.0) | 5.6 ± 3.1 (5.0)[a] | 7.2 ± 1.6 (7.0) | 5.9 ± 2.9 (6.0)[b] |
| IPSS, irritation-related[2] | 5.2 ± 1.5 (5.0) | 4.5 ± 2.2 (4.0) | 4.8 ± 1.1 (4.0) | 4.4 ± 1.5 (4.0) |
| IPSS, quality of life | 1.8 ± 0.7 (2.0) | 2.2 ± 1.0 (2.0) | 2.1 ± 0.6 (2.0) | 2.1 ± 0.8 (2.0) |

No significant differences between lycopene and placebo groups.
Significantly different from baseline: $p<0.05$[a], $p<0.01$[b]
[1]IPSS questions No. 1, 3, 5 and 6
[2]IPSS questions No. 2, 4 and 7

**Unter 6-monatiger Lycopin Behandlung (15mg/Tag) kommt es zu keiner weiteren Hyperplasie der Prostata im Gegensatz zur Placebo Gruppe, bei der ein signifkantes Wachstum vorliegt.**

The Journal of Nutrition - Research Article

**Lycopene Inhibits Disease Progression in Patients with Benign Prostate Hyperplasia**[a,b]

Silke Schwarz1*, Ute C. Obermüller-Jevic2*, Eva Hellmis3, Winfried Koch4, Günther Jacobi3, Hans-Konrad Biesalski1

**TABLE 3**

*Primary and secondary endpoints*

| | Placebo | | Lycopene | |
|---|---|---|---|---|
| | Baseline Mean ± SD (median) | After 6 months Mean ± SD (median) | Baseline Mean ± SD (median) | After 6 months Mean ± SD (median) |
| *Primary endpoint* | | | | |
| **PSA, total (ng/mL)[1,2]** | **6.85 ± 2.3 (6.31)** | **6.81 ± 4.7 (5.07)** | **6.56 ± 2.3 (5.87)** | **5.82 ± 1.8 (5.57)[a]** |
| PSA, free (ng/mL)[2] | n/a | 0.98 ± 0.53 (0.87) | n/a | 0.93 ± 0.33 (0.85) |
| *Secondary endpoints* | | | | |
| Lycopene (µmol/L)[2] | 0.46 ± 0.24 (0.38) | 0.54 ± 0.25 (0.60) | 0.43 ± 0.22 (0.42) | 1.24 ± 0.31 (1.23)[b,d] |
| Lycopene in prostate (µmol/g) | 0.45 ± 0.25 (0.43) | n/a | 0.51 ± 0.30 (0.43) | n/a |
| Lycopene in BMC (pmol/µg DNA) | 0.06 ± 0.07 (0.05) | 0.17 ± 0.14 (0.11)[a] | 0.06 ± 0.1 (0.00) | 0.59 ± 0.58 (0.38)[b, c] |
| IGF-1 (µg/L)[2] | 160.2 ± 54.5 (157.5) | 150.0 ± 57.4 (147.5) | 163.8 ± 61.6 (165.0) | 164.6 ± 51.9 (161.0) |
| IGFBP-3 (mg/L)[2] | 4.5 ± 1.0 (4.4) | 4.2 ± 1.0 (4.2) | 4.9 ± 1.2 (4.8) | 4.8 ± 0.8 (4.8) |

Significantly different from baseline: $p<0.05$[a], $p<0.0001$[b]

Change from baseline significantly different from placebo group: $p<0.01$[c], $p<0.0001$[d]. Adjusted for age, BMI and baseline values.

n/a = not applicable

[1] Total PSA determined during screening instead of baseline (visit 1), see explanation in Materials and Methods

[2] Plasma concentrations

**Der PSA-Wert nimmt in der behandelten Gruppe signifikant ab.**

**Vitamine und Spurenelemente – Indikationen und Kontraindikationen**

**Ein Vitamin Supplement wird man zur Vermeidung von Defiziten empfehlen. Dies kann zu einer besseren Lebens-Qualität beitragen.**

**Keinesfalls beabsichtigt man damit das Leben zu verlängern!**

**Vitamine und Spurenelemente –**
**Indikationen und Kontraindikationen**

**Unter dem Aspekt der adaequaten Versorgung mit Mikronährstoffen gibt es eine Reihe von Risikogruppen:**

**Alte Menschen**
**Menschen mit konsumierenden Erkrankungen**
**Bei Reduktionsdiäten bzw. niedriger Energiezufuhr**
**Schwangerschaft**

# Vitamine und Spurenelemente – Indikationen und Kontraindikationen

Unter dem Aspekt der adaequaten Versorgung mit Mikronährstoffen gibt es einige isolierte Substanzen in der Praevention:

Folsäure
Vitamin B12
Vitamin E
Vitamin A
Eisen
Jod
Selen

**Vitamine und Spurenelemente – Indikationen und Kontraindikationen**

**Kontraindikationen bestehen für Dosierungen Innerhalb des 1-3-fachen der Empfehlungen nicht.**

**Hochdosierte Einzelpräparate oder Kombinationen sollten nur bei entsprechender Indikation und nicht während der Krebstherapie eingesetzt werden**

# Contributions from Different Research Strategies

| Strategy | Approaches | Features |
|---|---|---|
| Basic research | Cell culture | + Precise |
| | Animal model | + Lifespan |
| | | - Extrapolation |
| Clinical observation | Experience with patients | + Hypothesis generation |
| | | - Anecdotal |

# Contributions from Different Research Strategies

| Strategy | Approaches | Features |
|---|---|---|
| Epidemiology | Descriptive | + Multiple endpoints |
| | Analytical | + Various nutrients |
| | | + Long duration |
| | | - Inexact |
| | | - Confounded |
| Intervention studies | Clinical trial | + Exact |
| | | - Limited doses |
| | | - Duration |
| | | - Expensive |

There is no clinical trial which can mimic the epidemiological data

# Primary vs. Secondary Prevention

**For a common chronic disease, a 20% reduction in risk by primary prevention has the potential to avoid hundreds of thousands of cases while a 20% reduction in secondary prevention, tens of thousands of cases.**

**Vivekananthan and co workers mixed intervention studies and prevention studies**

**Intervention studies do not deal with prevention**

**There is no epidemiological study which documented a beneficial effect of vitamins E and C on clinical endpoints In any disease in high risk groups**

**So far the beneficial effect of vitamines E and C has only been proven in epidemiological studies dealing with nutriton and some (retrospective) with supplements**

# RCT, Observational Studies and the Hierarchy of Research Designs

**"The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and education of health care professionals."**

**Concato et al. *N Engl J Med* 2000**

# Comparison of 136 Observational Studies and RCT

**“We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtain in randomized, controlled trials.”**

**Benson & Hartz. *N Engl J Med* 2000**

# Nutrition, Chronic Disease, and the Problem of Proof

**“The randomized controlled trial, which has become the gold standard for establishing the efficacy of pharmacologic agents, is poorly suited to the evaluation of nutritional effects, a fact that I believe many have been reluctant to acknowledge.”**

**Heaney. *Am J Clin Nutr* 2006**

# Meta-Analysis of Five Interventions According to Research Design

| Clinical Topic | Studies | N | Summary Estimate (95% CI) |
|---|---|---|---|
| Bacille Calmette-Guérin | 13 RCT | 359,922 | 0.49 (0.34-0.70) |
| vaccine and tuberculosis | 10 CC | 6,511 | 0.50 (0.39-0.65) |
| Mammography and mortality | 8 RCT | 429,043 | 0.79 (0.71-0.88) |
| from breast cancer | 4 CC | 132,456 | 0.61 (0.49-0.77) |
| Cholesterol levels and death | 6RCT | 36,910 | 1.42 (0.94-2.15) |
| due to trauma | 14 C | 9,377 | 1.40 (1.14-1.66) |
| Treatment of hypertension | 14 RCT | 36,894 | 0.58 (0.50-0.67) |
| and stroke | 7 C | 405,511 | 0.62 (0.60-0.65) |
| Treatment of hypertension | 14 RCT | 36,894 | 0.86 (0.78-0.96) |
| and coronary heart disease | 9 C | 418,343 | 0.77 (0.75-0.80) |

RCT = Randomized controlled trial
CC = Case-control; C = Cohort

Concato et al *N Engl J Med* 2000

# Strengths of Observational Studies

- More likely to include broad representation of the population at risk
- Closer relationship to “real world” use of foods and supplements
- When the relative risk is large in size (RR <0.70)
- When the required duration of exposure is long
- Sometimes only feasible or ethical approach

# U.S. Preventive Services Task Force Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease

**"…evidence is insufficient to recommend for or against the use of supplements of vitamins A, C or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease."**

**US PSTF *Ann Intern Med* 2003**

# U.S. Preventive Services Task Force Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease

***Excluded:***

- **Supplementation in patients with known or potential nutritional deficiencies (including pregnant and lactating women, children, elderly, patients with chronic illness)**
- **Supplementation in specific populations not widely generalizable**
- **Secondary outcomes**
- **Case-control studies**

**US PSTF *Ann Intern Med* 2003**

# U.S. Preventive Services Task Force Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease

**"Dietary supplements may be appropriate for people whose diet does not provide the recommended dietary intake of specific vitamins."**

**US PSTF *Ann Intern Med* 2003**

# NIH State-of-the Science Conference Multivitamin/Mineral Supplements and Chronic Disease Prevention

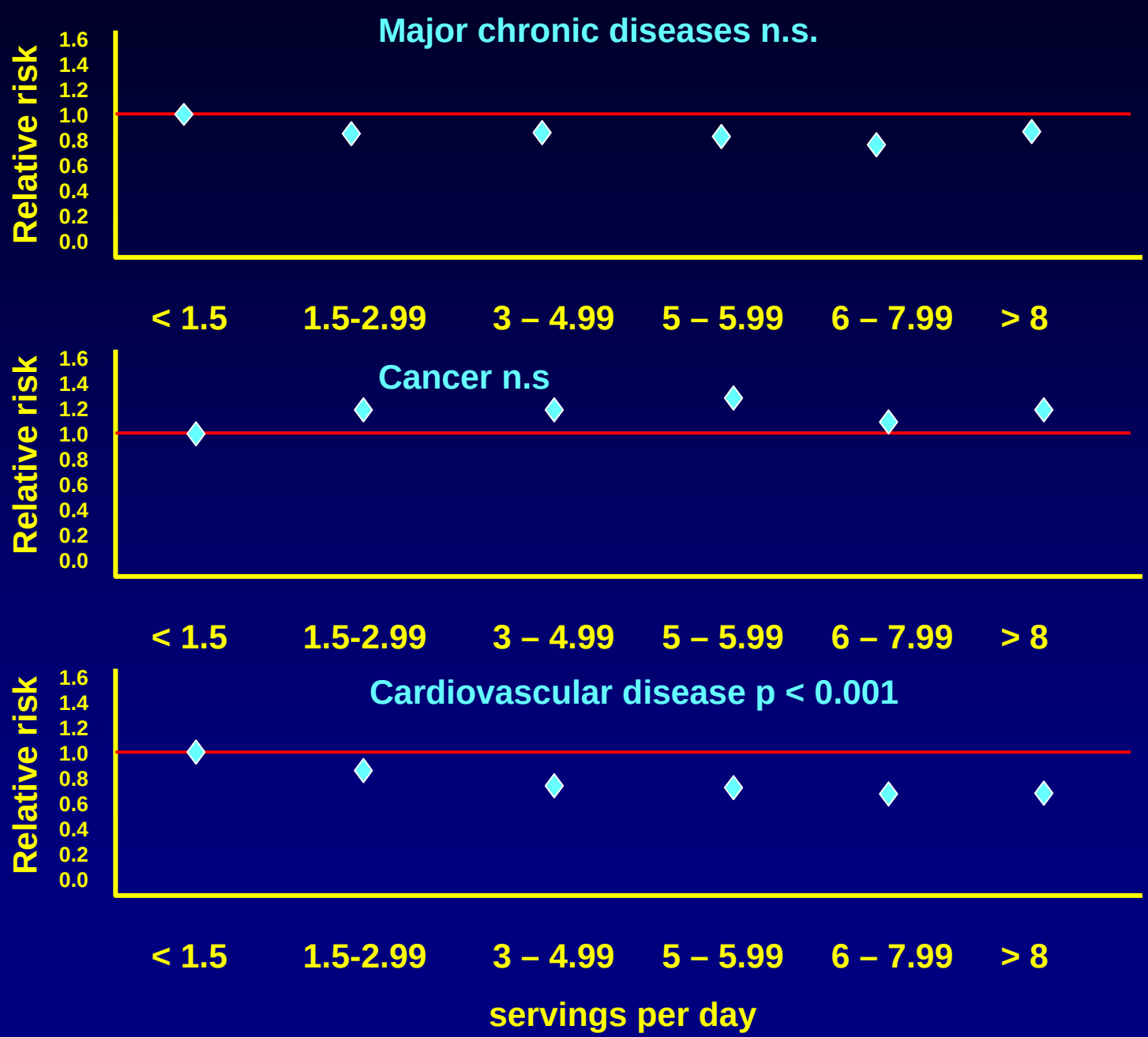
**Literature search process identified 11,324 citations (1996-February 2006) potentially relevant to the Key Questions through MEDLINE, EMBASE, Cochrane database, etc.**

**AHRQ Publication No. 06-E012, May 2006**

# Antioxidants

**The worse the message – the better**

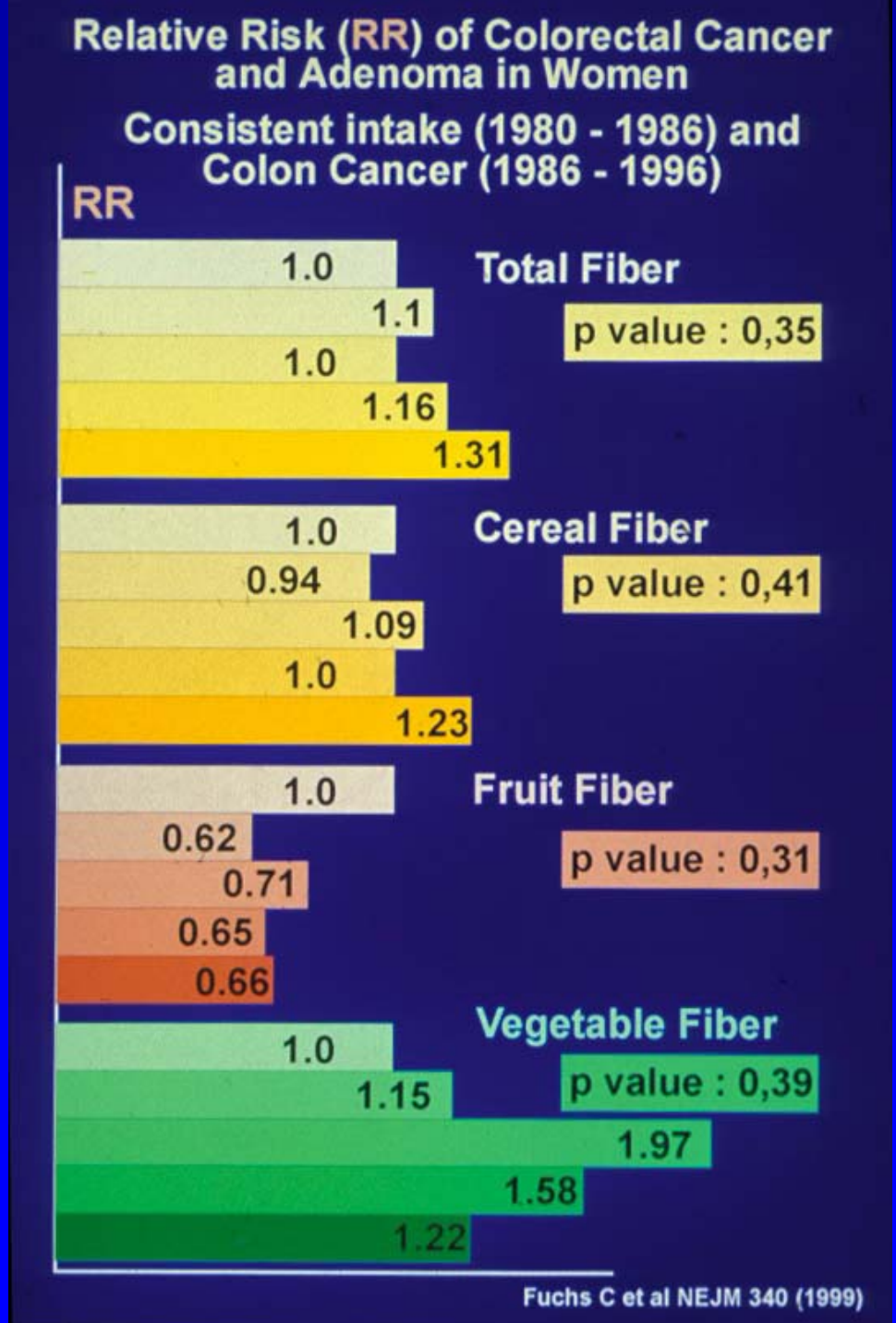
# Fruit and vegetable intake and risk of major chronic disease




71 910 part. from NHS and 37 725 part. from PHS Dietary quest. in 1984, 1986, 1990, 1996

Observation May 1998 Jan 1998

Hung et al JNCI 2004


Relative Risk (RR) of Colorectal Cancer and Adenoma in Women
Consistent intake (1980 - 1986) and Colon Cancer (1986 - 1996)
RR
1.0
Total Fiber
1.1
p value : 0,35
1.0
1.16
1.31
1.0
Cereal Fiber
0.94
p value : 0,41
1.09
1.0
1.23
1.0
Fruit Fiber
0.62
p value : 0,31
0.71
0.65
0.66
Vegetable Fiber
1.0
1.15
p value : 0,39
1.97
1.58
1.22
Fuchs C et al NEJM 340 (1999)

# Evidence for Preventive Nutrition: Observational Studies or RCT?

- Both necessary, neither is perfect
- Neither can answer all questions
- Best approach depends on what question being asked, to what population answer being applied
- When findings discrepant, learn from it
- Need for innovative designs, not just methods of analysis
- Need for large samples, adequate duration, real time data, ability to examine subgroups
- Must be able to move forward and make decisions

**Conclusion**

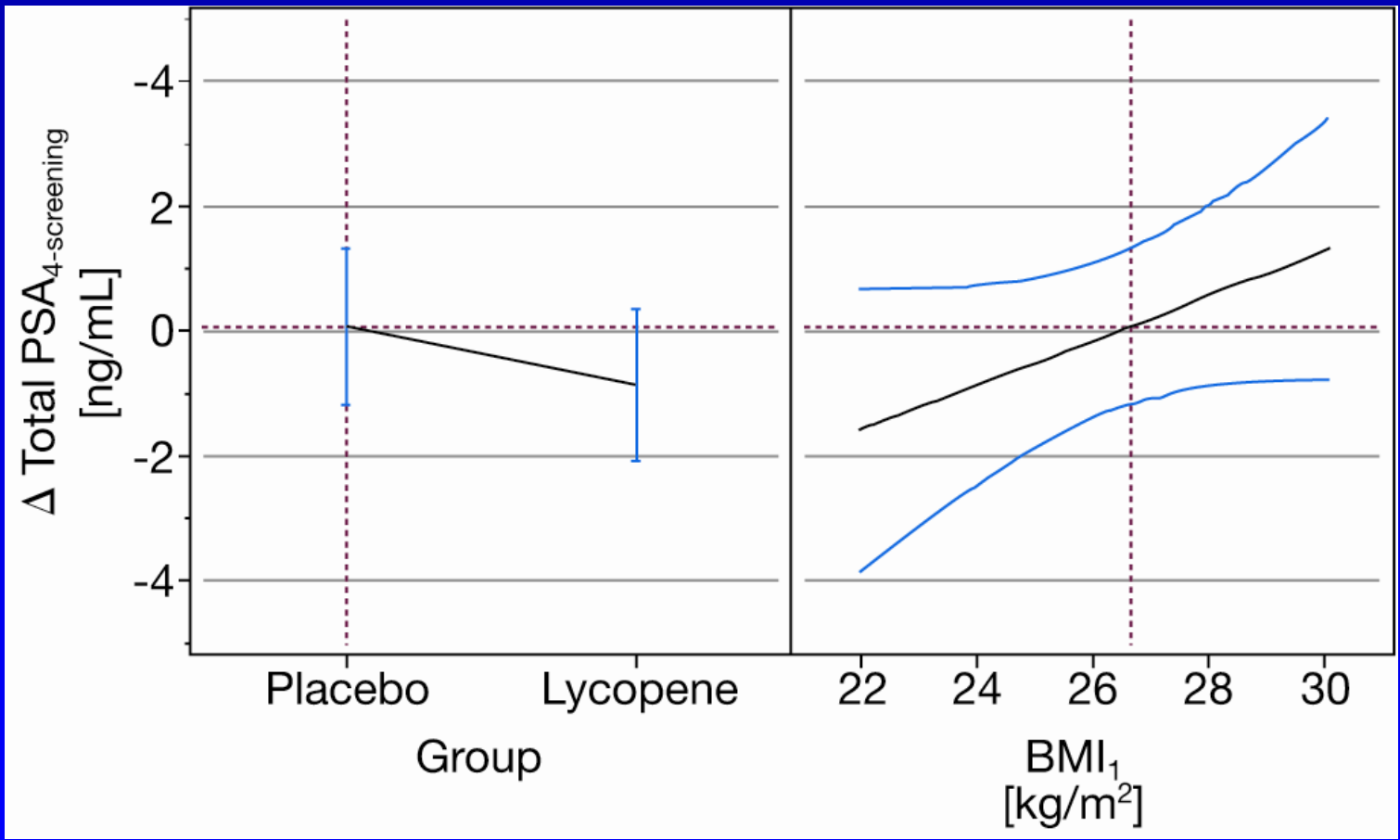
**To elucidate evdience based benefit/risk of nutraceuticals we need other instruments than in cases of xenobiotics.**

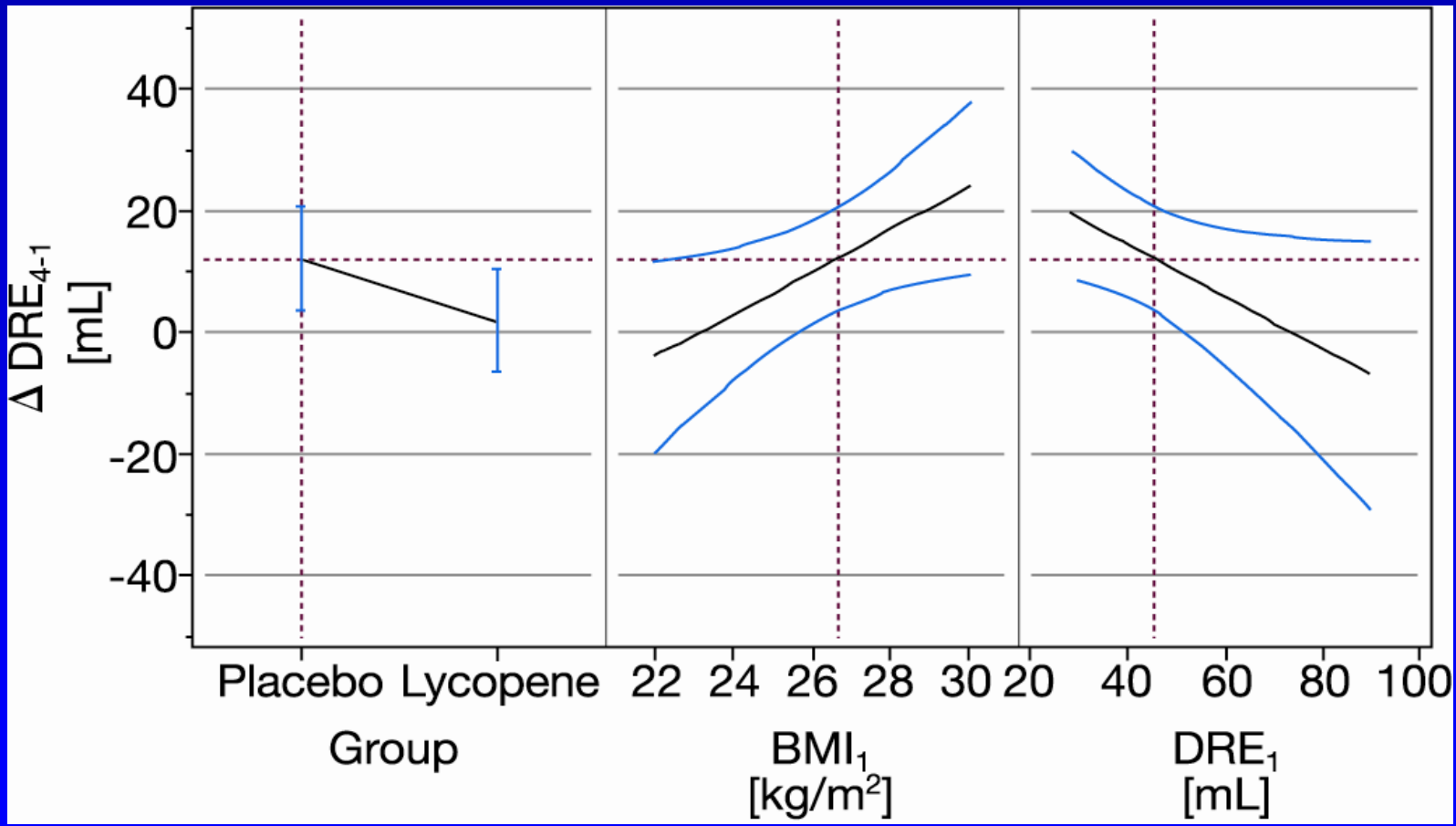
**Clear cut discrimination between primare prevention and Intervention**

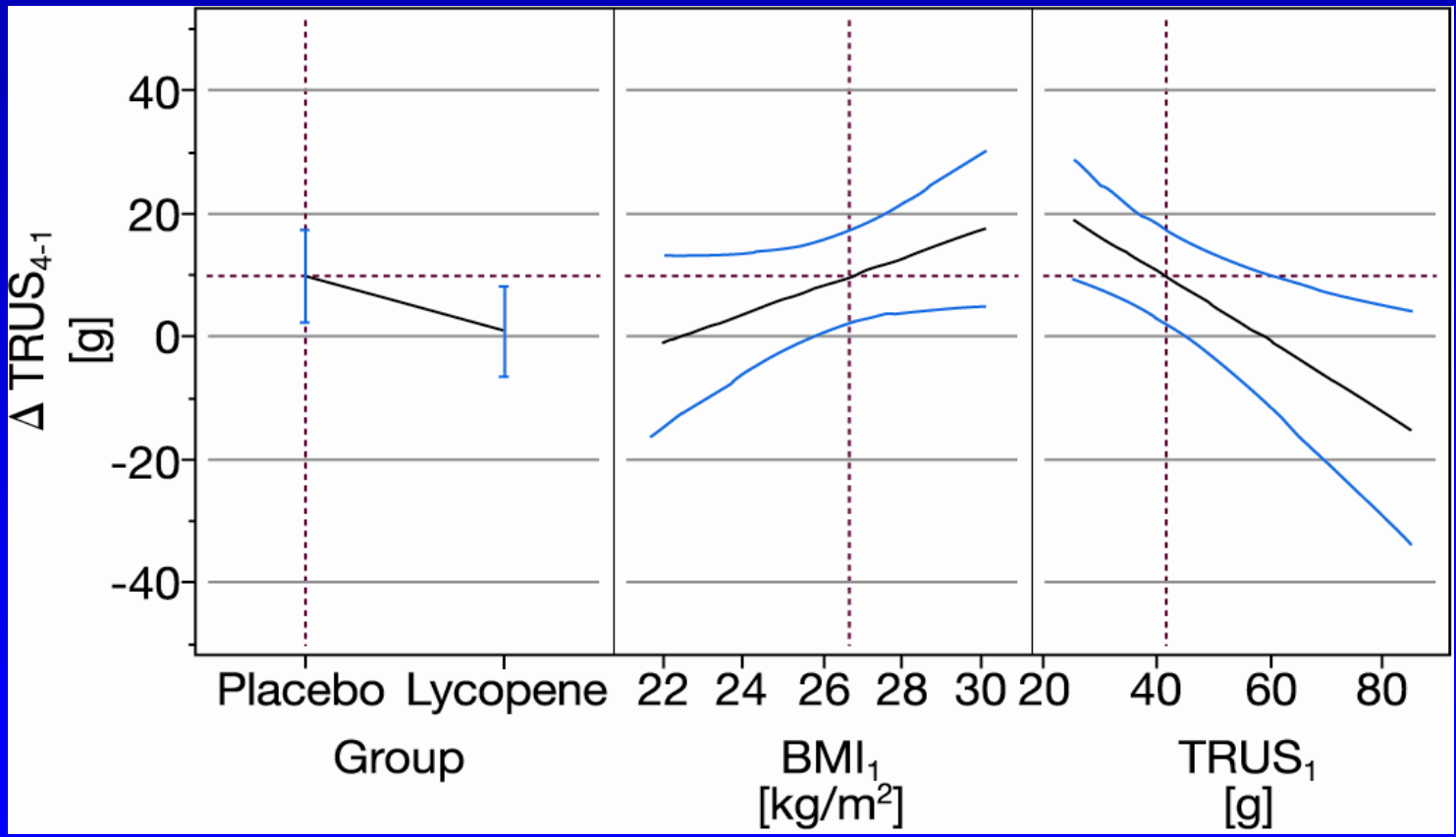
**Consideration of major differences in bioavailability and organ distribution**

**Network and interactions of micronutrients**

**Specific biomarkers and pre-clinical endpoints**


Δ Total PSA4-screening [ng/mL]
-4
2
0
-2
-4
Placebo
Lycopene
Group
22
24
26
28
30
BMI1 [kg/m2]


Δ DRE4-1 [mL]
40
20
0
-20
-40
Placebo
Lycopene
Group
22
24
26
28
30
BMI1 [kg/m2]
20
40
60
80
100
DRE1 [mL]


Δ TRUS4-1 [g]
40
20
0
-20
-40
Placebo
Lycopene
Group
22
24
26
28
30
BMI1 [kg/m2]
20
40
60
80
TRUS1 [g]

# Drugs vs. Nutrients: Limits of RCT as a Research Strategy in Preventive Nutrition

- **Chronic diseases have long latency and multifactorial causation**
- **Absence of no exposure group (only different levels of intake)**
- **Nutrients possess ≥1 threshold activities**
- **Most nutrients have beneficial effects on multiple tissues (RCT designed for single outcomes)**

# NIH State-of-the Science Conference Multivitamin/Mineral Supplements and Chronic Disease Prevention

**"The present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease."**

www.consensus.nih.gov August 2006

# Selected Exclusion Criteria

- not written in English
- contained no human data
- only pregnant women
- only infants
- only subjects ≤18 years (except safety)
- only patients with chronic diseases
- only patients receiving treatment for chronic disease
- only patients in long-term care facilities
- only studied nutritional deficiency
- contained no useful information for Key Questions
- did not address supplements separately from dietary intake
- did not cover the defined disease endpoints
- was an editorial, commentary or letter
- was not a RCT (except safety)

# NIH State-of-the Science Conference Multivitamin/Mineral Supplements and Chronic Disease Prevention

**The review process for eligibility and study quality assessment excluded consideration of 11,261 reports, so final report is based on 63 articles.**

**AHRQ Publication No. 06-E012, May 2006**

# NIH State-of-the Science Conference Multivitamin/Mineral Supplements and Chronic Disease Prevention

**"The present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease."**

**"Limiting the focus of our statement to RCTs has some inherent limitation".**

www.consensus.nih.gov August 2006