

State of the Science: *Multivitamin-Mineral Supplements and Chronic Disease Risk*

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Agenda

- Definitions
- Why MVM???
- AHRQ Evidence Report
 - ▶ Agency for Health Care Research on Quality
- SOS Committee Statement
 - ▶ State of the Science

- Implications for Dietitians

Multi-vitamin mineral supplement

- No standard definition
- Operational definition:
 - ▶ 3 or more V & M at doses $< UL$; no herbs, drugs, hormones
- Actually many MVM have 10 or more V and M and often other substances as well
- Small brands sold on internet often $\gg \%DV$

Why MVM?



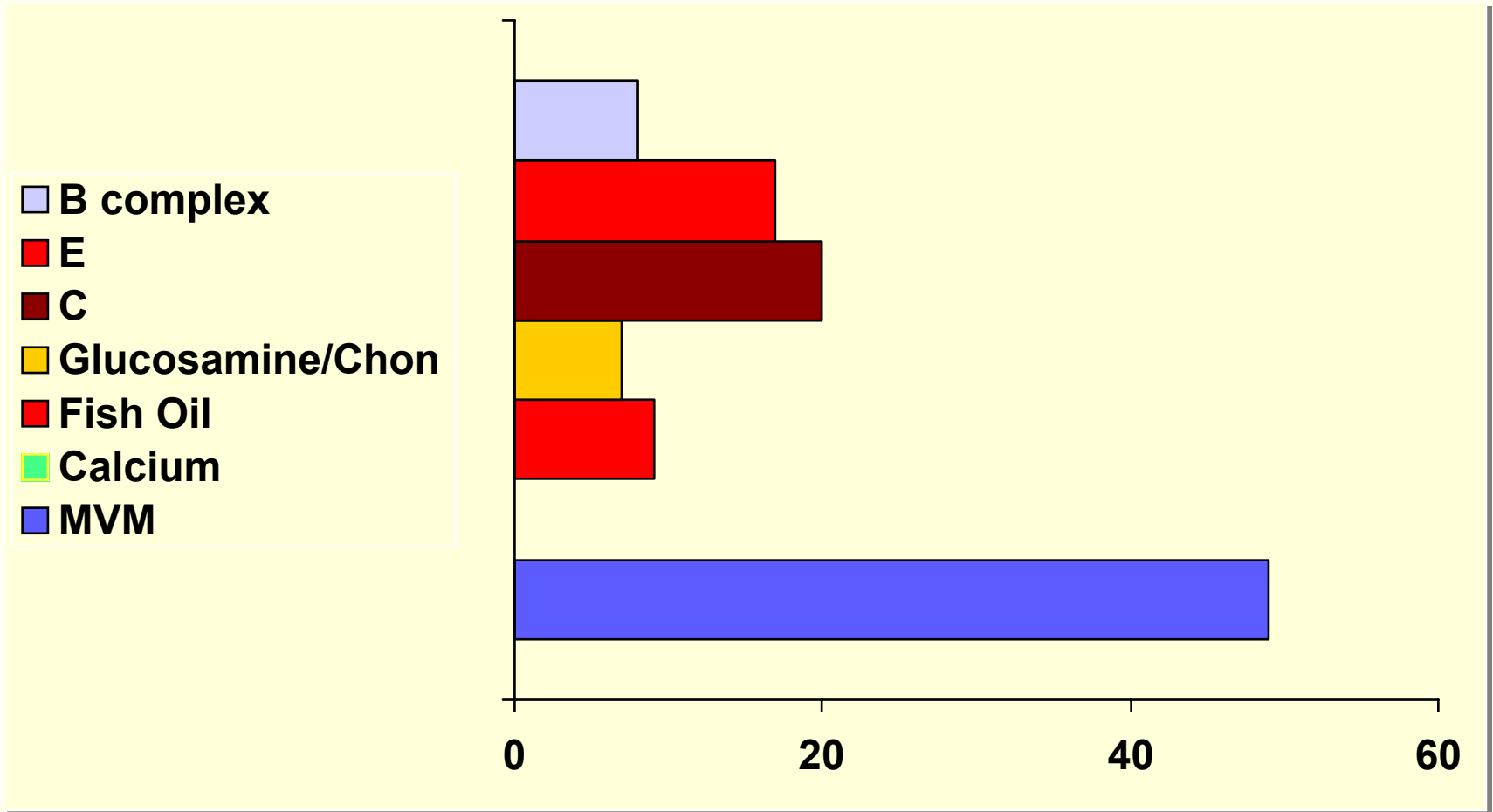
- High prevalence
- Few chemically determined values available
 - ▶ Only label declarations usually provided
- Most store brands fairly consistent and at DV levels but MVM in multilevel marketing vary widely in % DV
- ***Consumers and researchers may not be getting what they think***

Why MVM?

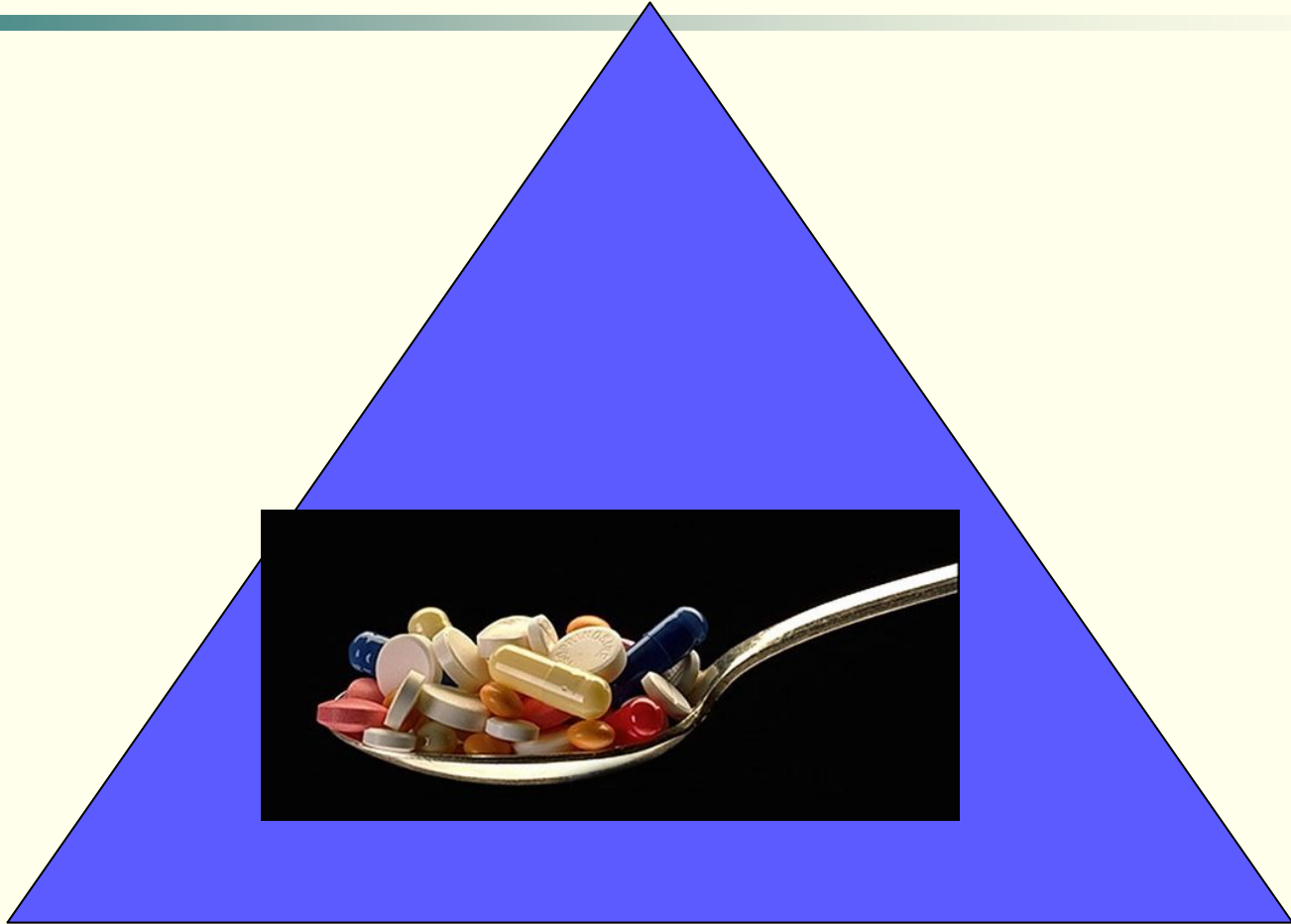
- 50% of adults take a dietary supplement; half of them take a MVM
- Most commonly used dietary supplement in USA
 - ▶ Consumer use for prevention or treatment of chronic disease
 - ▶ Not just nutritional adequacy

Adults 55+ Using Selected Dietary Supplement Products last 30 days, total population. 2004

NMI 2004 internet survey



Pharma Pyramid???



Is having all nutrients together in MVM good or bad?????

- Pros

- ▶ Convenient
- ▶ Functional relationships (Ca, D)
- ▶ May help fulfill some guidelines
 - ~ E.g. folic acid supplement during pregnancy

- Cons

- ▶ Bioavailability may be affected
- ▶ May increase risk of total intakes exceeding UL

Systematic Evidence-Based Review of the Literature



Diseases considered

- Cancers of breast, colon, lung, prostate, gastric
- Heart: Myocardial infarction and stroke
- Type 2 diabetes
- Parkinson's disease, dementia
- Cataracts and macular degeneration
- Memory loss
- Osteoporosis, Osteopenia, rheumatoid arthritis, osteoarthritis
- NASH, chronic nephrolithiasis
- HIV, Hepatitis C, TB
- COPD

Types of Studies

- **RCT:** Randomized controlled trial
 - ▶ allocation by chance to the treatment (MVM or none)

- **Observational:**
 - ▶ people allocate themselves to a treatment; choice, not assigned
 - Problems: confounding

MVM Evidence Report Questions

- For both MVM and single nutrients or functionally related nutrient pairs
 - ▶ Efficacy MVM for prevention of chronic disease in adults
 - ▶ Safety for adults and children

Nutrients studied for efficacy

- MVM*
 - FUNCTIONALLY RELATED PAIRS
 - ▶ Ca, D
 - ▶ Ca, Mg
 - ▶ Folic, B12
 - ▶ Folic, B6
 - SINGLE NUTRIENTS
 - ▶ A*, B1, B2, B6, B12
 - ▶ Niacin, folic acid
 - ▶ C,D*,E*
 - ▶ Ca*, Fe*, Zn, Mg,Se*
 - ▶ Beta carotene*
- ~ * = studied for safety also

Methods: Systematic reviews for

- **Efficacy**

- ▶ RCT or meta-analyses of RCT included

- **Safety**

- ▶ RCT & also observational studies

Finding the articles using search strategy and quality criteria

Search Strategy

Medline, Embase, Cochrane etc

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graph TD; A[Medline, Embase, Cochrane etc] --> B[63 articles meeting all criteria]
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63 articles meeting all criteria

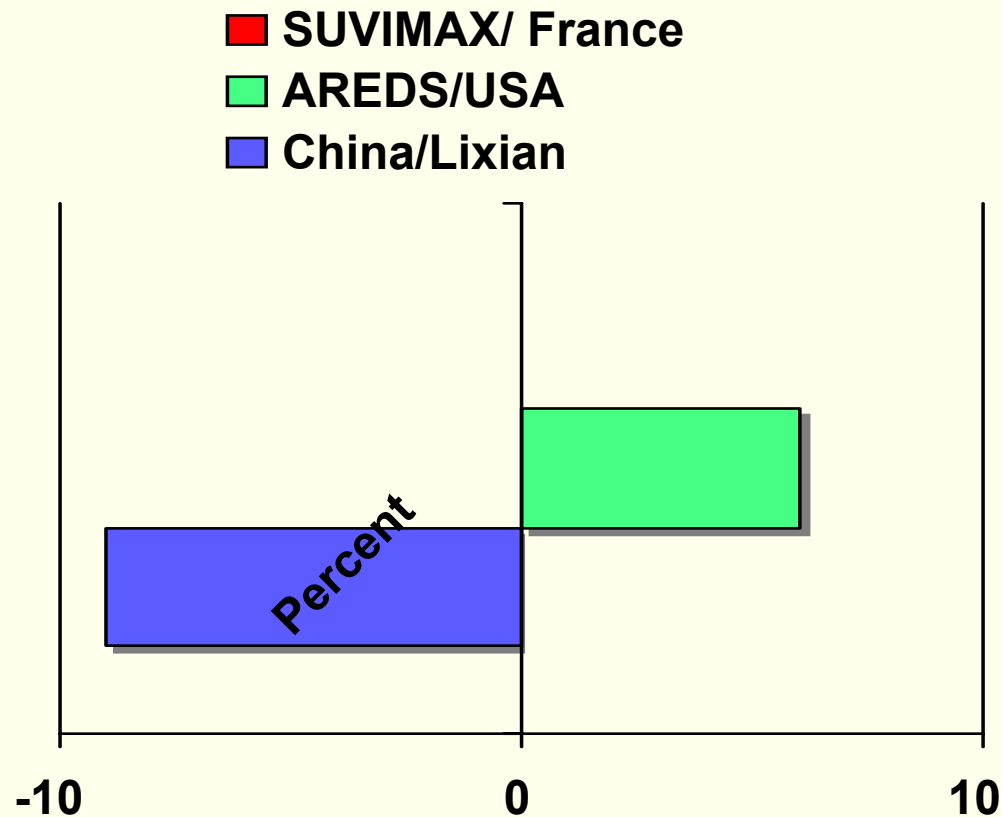
Evidence Report Findings

- Only 63 articles out of 11,324 citations to answer key questions
 - ▶ *Need more and better research*
- Few studies used most popular MVM on the market in USA
 - ▶ *Unclear if results apply to products in marketplace*

Evidence Report Findings

- For many diseases, no US Data available
 - ▶ Used studies in Europe and China as well
 - ▶ *Need more data*

Total Mortality and MVM: in some studies decreased risk, in others nsd



Disease Results

- Cancer:

- ▶ Decreased incidence mortality esophageal and gastric cancers in China (Linxian) with E beta carotene and Se supplement, and gastric noncardia with Zn and A
- ▶ France (Suvimax0 lower mortality and cancer incidence in men only with E,Se,C bata carotene and Zn

CVD

- No benefits of MVM use
- No harm

CATARACT

- What: 3 trials, RCT
- Time: 3-6 yr
- Where: USA, UK, China
- Results: inconsistent, modest benefits in 2 studies

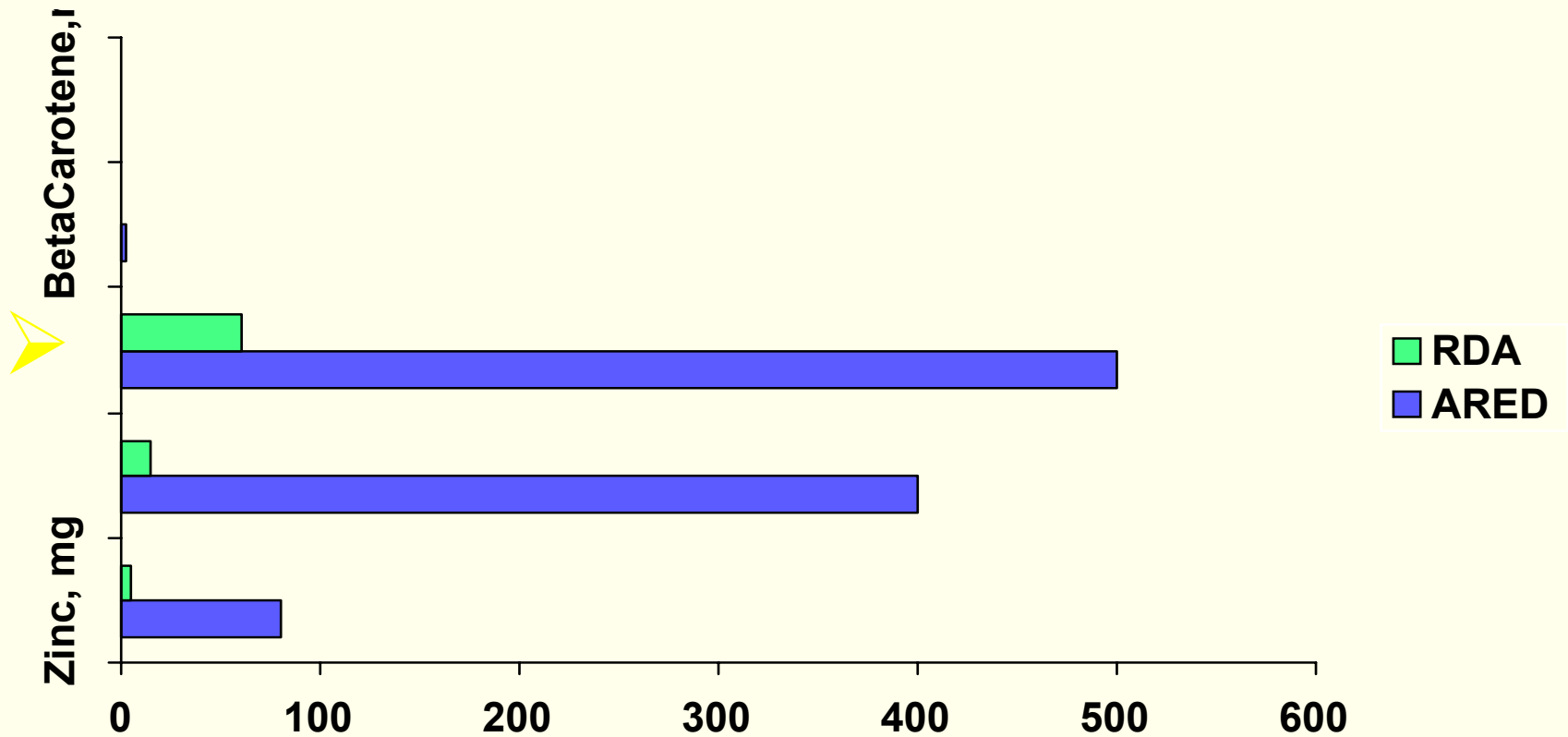


A R E D S

The Age-Related Eye Disease Study

Vision: Macular Degeneration

- **AREDS (age related eye disease study)**
randomized double blind clinical trial
n=4800
 - ~ C, E, beta carotene, Zn in doses many times DRI on AMD and cataract in patients with AMD
 - ~ 5 yr:
 - **Increased serum levels Zn, antioxidants**
 - **Some decreases in AMD due to Zn and antioxidants**

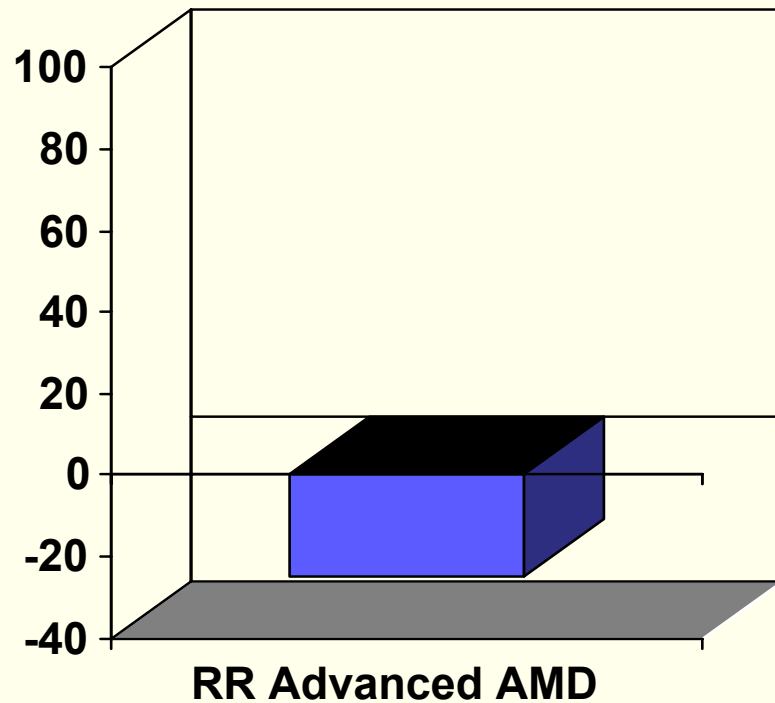


Macular Degeneration

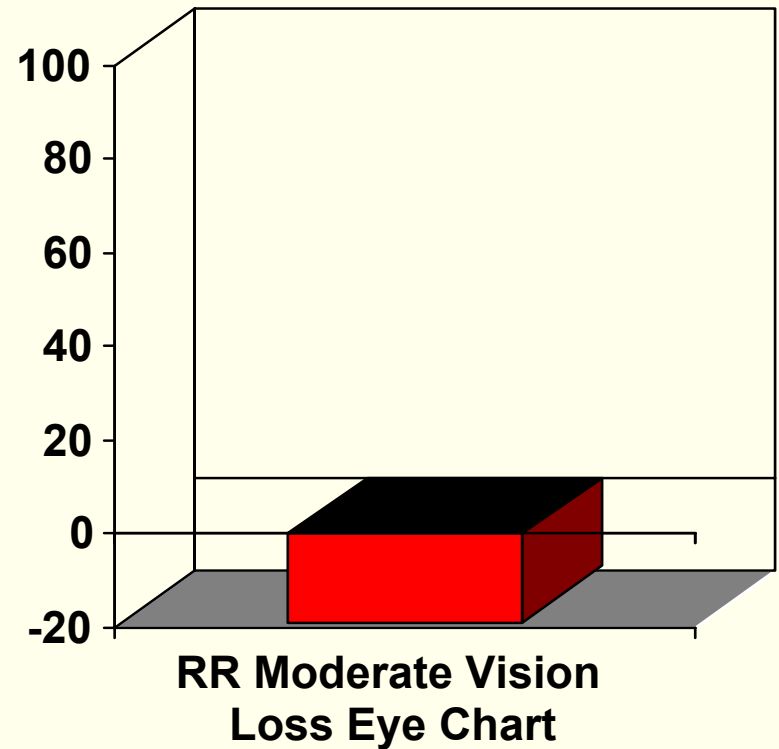
- What: 1 trial USA
- Time: 3-6 yr
- Where: USA
- AREDS (age related eye disease study)
 - ~ Dose 10X RDA Zn
 - ~ with or without antioxidants 5-15 times RDA
 - ~ Time 3-6 yr
 - ~ Results
 - **Benefit in those with intermediate macular degeneration or advanced macular degeneration**

AREDS 1

■ Moderate risk AMD at Baseline



■ Eye Chart



AREDS 2

- Enroll and follow for 5 years for progression
- Addition to AREDS 1 formula of
 - ▶ Lutein 10 mg + zeaxanthin 2 mg
 - ▶ And /or 1 gm omega 3 LCPUFA (DHA, EPA)

Beta Carotene Supplements (20,30, 50 mg doses)

- Efficacy: no protection vs. cancer, CVD, DM type 2, cataract, macular degeneration
- Safety:
 - ▶ Beta carotene with or without vitamin A increased lung cancer in smokers and asbestos workers and also increased total mortality

Vitamin A

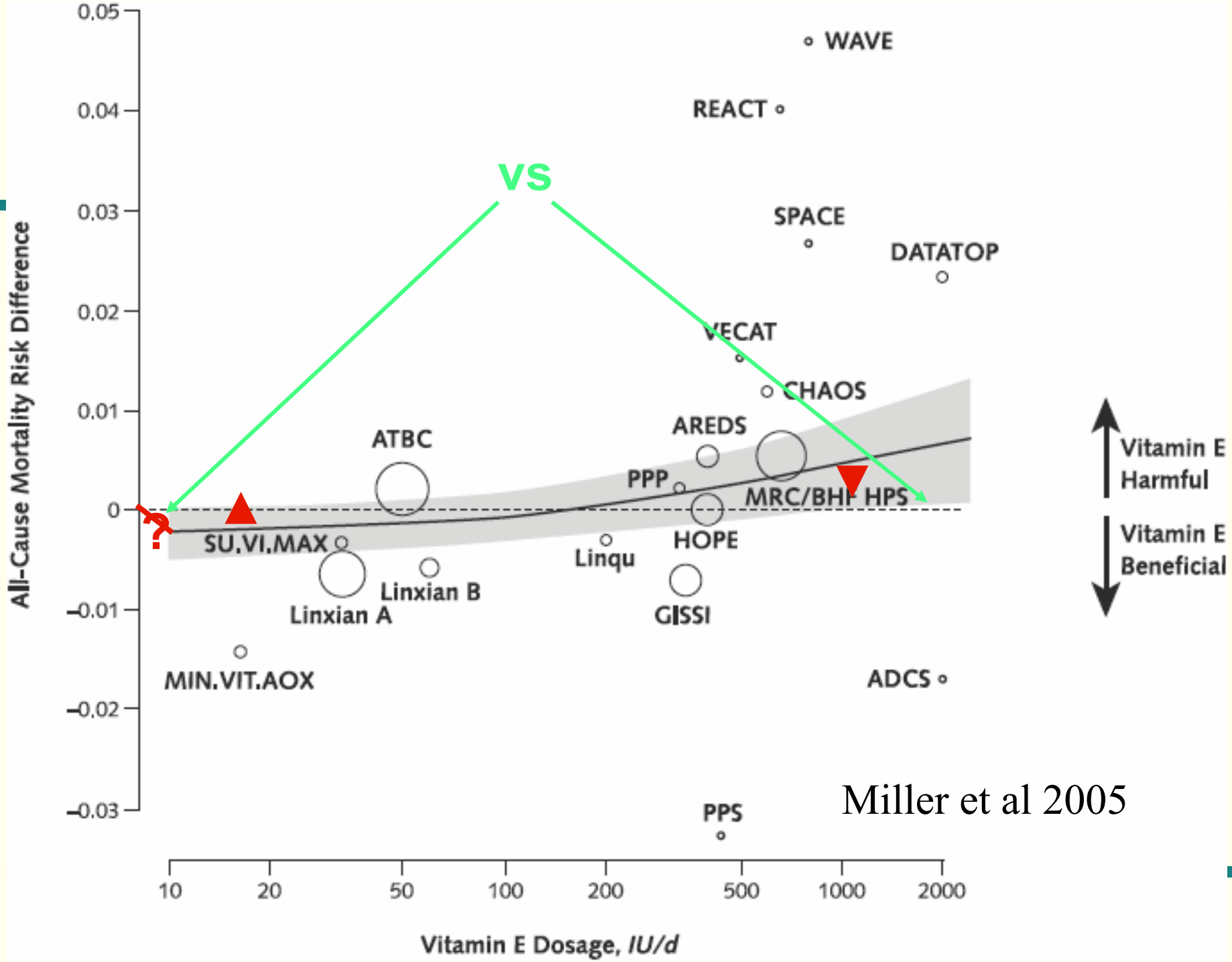
- Efficacy:
 - ▶ No RCT
 - ▶ not significant differences significant differences
 - ~ **Vit A and Zn or Vit. A and Beta carotene nsd in**
 - **stroke, cancer (esophageal, gastric)**
 - CVD, total mortality**
- Safety:
 - ▶ Vitamin A not safe with high dose beta carotene

Vitamin E

Dietary supplements of 50 mg alpha tocopherol or 300 IU, natural vit E at 500 IU or natural source E at 600 IU all examined

■ Efficacy

- ▶ In ATBC, Women's Health Study nsd on cancer CVD, cataract, age related eye disease, but
 - ~ 32% decrease in prostate cancer incidence and
 - ~ 41% decrease in prostate cancer mortality ATBC
 - ~ 22% decrease in colon cancer in smokers in ATBC
 - ~ Decrease in CVD in older women in WHS
 - ~ ? Stroke: increased in ATBC with low dose alpha tocopherol but decrease in WHS with higher dose



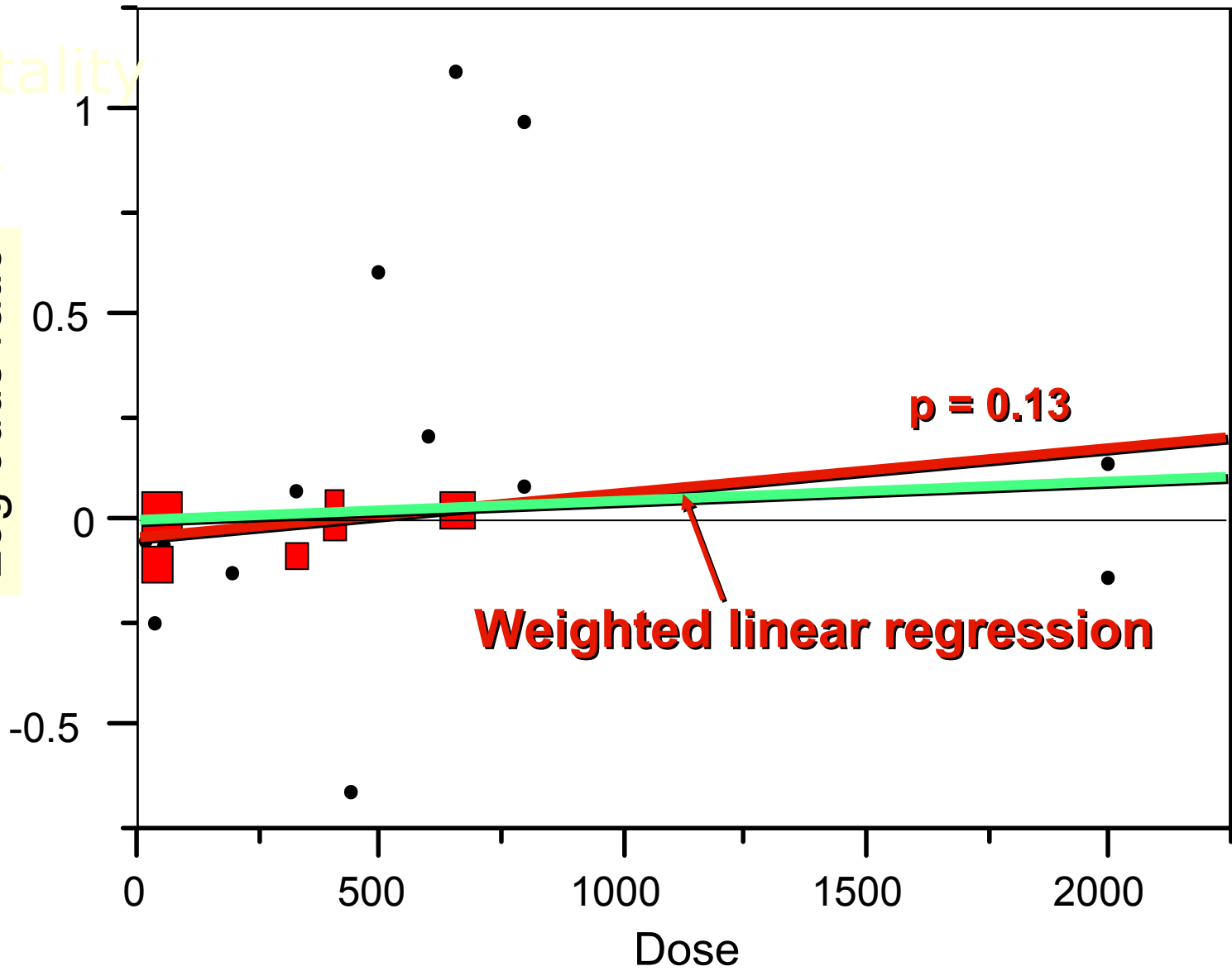
Random effects analysis—Confidence Bounds



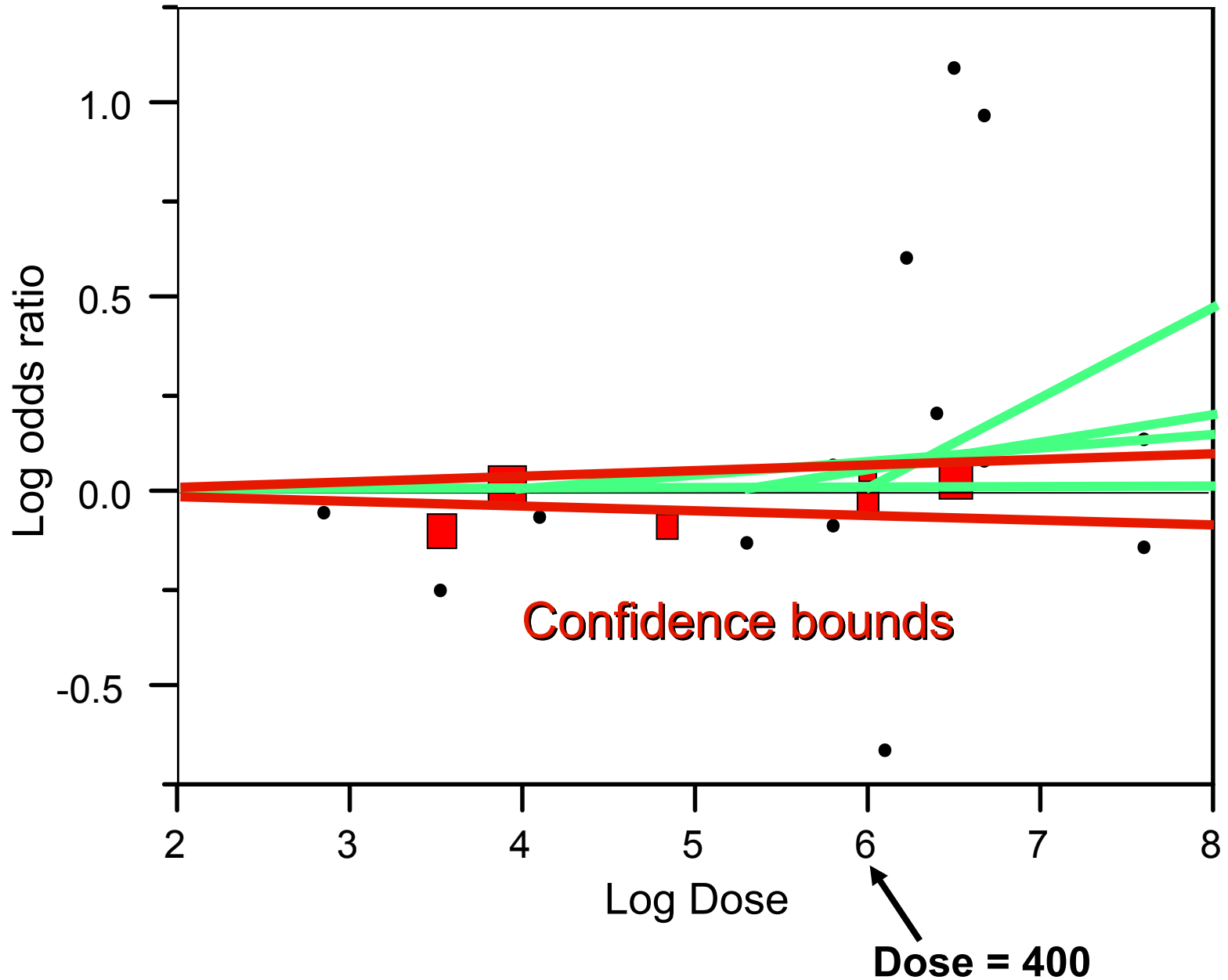
Simplest analysis of vitamin E studies of Miller et al (Dr. Barry Tx A& M)

Mortality
Risk

Log odds ratio



Random effects analysis—log dose (Dr. Barry Tx A& M)



MVM Trials difficult

- Can't determine which component responsible
- Controls also use MVM
- Very large sample sizes needed
- MVM supplement composition constantly changing

Folic Acid (based on prior EBR)

- Dose 0.75 mg or 30 mg with or without B12 or B6
- Time: 5-12 weeks
- Result not significant on cognitive function
- Trials: 5 small ones

Selenium

- Dose 200 micrograms
- Outcome skin cancer
- Result: prevention total mortality, lung, colon and prostate but nsd for CVD
 - ▶ Also, in Linxian, poorly nourished individuals had decreased risk of liver cancer on Se 200 micrograms 2 or more yr

Studies now in progress on E and Se in cancer prevention may clarify

- SELECT:
- Selenium and Vitamin E Cancer Prevention Trial
- Physicians' Health Study II

Calcium and D (used prior systematic reviews and new RCT)

- Calcium

- ▶ over short term (1 yr) benefit in BMD among postmenopausal women and may also protect vs. vertebral fractures

- D 700-800 IU and Ca 1000 mg

- ▶ Decreased hip and non- vertebral fractures with those with low D and Ca at baseline
- ▶ In WHI with 400 IU D and 1000 mg Ca over 7 yr
 - ~ 1.06% increase in hip bone density
 - ~ 12% decreased hip fracture
 - ~ no effect on colon cancer

Safety of MVM

- No consistent pattern of adverse events except skin (yellow) with MVM having high amounts of beta carotene
- NSD on mortality

Safety of Single Nutrients

- **Beta carotene** with or without A increased lung cancer in smokers & asbestos workers
- **A** slightly increased triglycerides
- **Ca** increased kidney stones
- **E** increased incidence of bleed but not with serious bleeding or hemorrhage
- **Iron:** decreased weight gain in non- anemic children

Future Research

- Better in vivo biomarkers
- More studies of effects of combinations and optimal doses
- More RCT
 - ▶ confounding and measurement error plaguing observational studies
- Include baseline intakes of dietary supplement in clinical trials and be sure to report dietary supplement intake

Future Research

- Find how efficacy varies by age, self selected dietary supplement use, dietary pattern, disease history, medication use, gene polymorphisms
- Develop a good adverse event reporting system
- More studies of cost effectiveness and risk benefit of MVM and other dietary supplements

MVM for infections

Stephen & Avenell J Hum Nutr
Deitet 19:179-90 2005

- Issue: is there support from RCT that MCM are effective in reducing infection?
- Search: Cochrane controlled trials register, EMBASE, MEDLINE, BIOSIS, CAB abstracts; found 20 acceptable studies, had to throw out 2 (Chandra and Jain)
- What : RCT or quasi RCT (assign by day of week) in adults with MVM defined as 2 or more vitamins or minerals or combinations

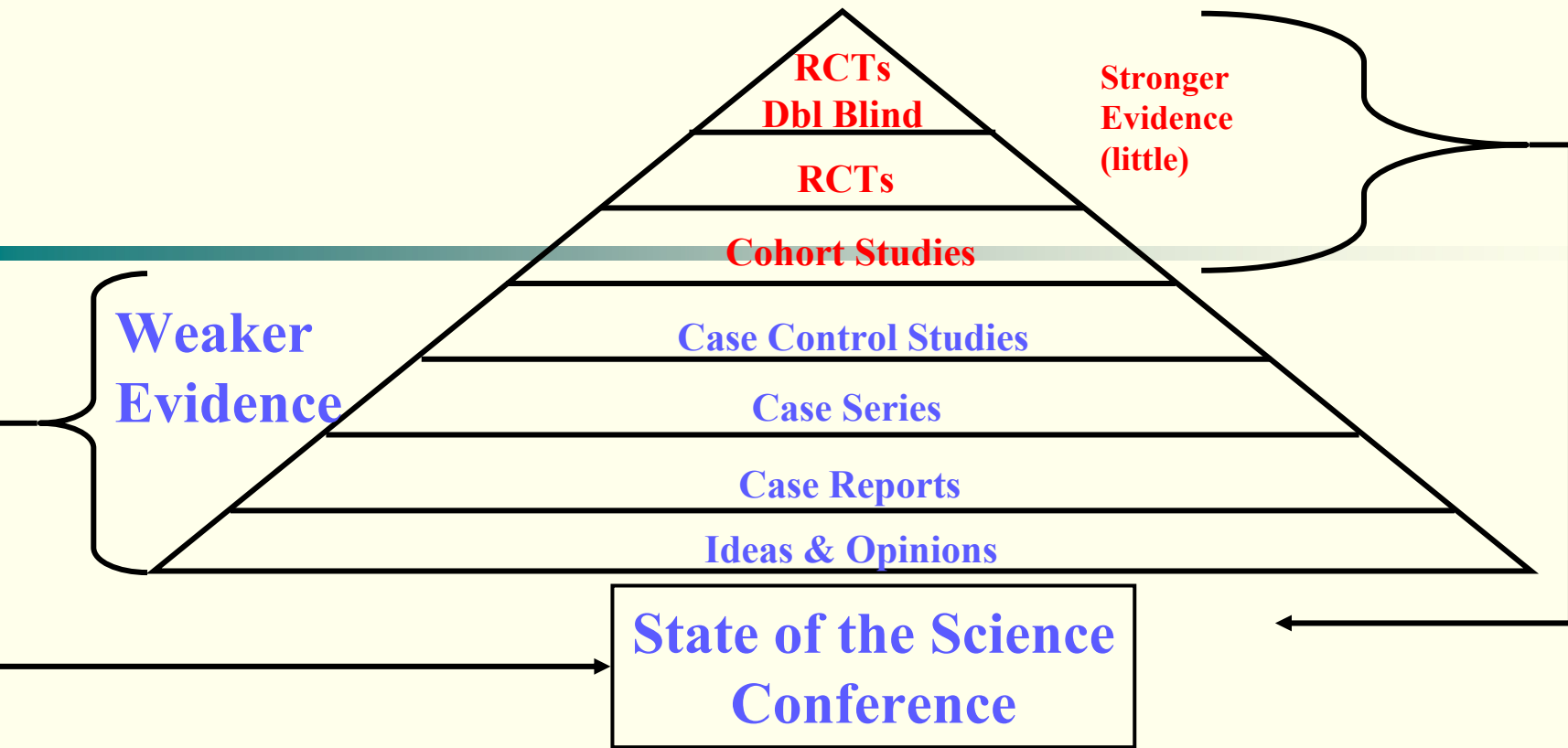
MVM for infections

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- Infections nsd in older adults with or without supplements
- Number of elders with or without DS having at least 1 infection: RR .98 CI .86 to 1.1 P<0.77
- At least one episode of infection in other adults between DS and non DS nsd
- BUT DS among >65 yr olds if undernourished or given DS for more than 6 mo may benefit:
 - ▶ Weighted mean difference -0.67 infections (CI -1.24 to -0.10) P= <.02

State of the Science Panel Report





Consensus Development Process: SOS

State of the Science Statement
Develop Research Agenda

Current patterns and prevalence use MVM varies

- Use DS high 50% adults, cost high \$23B DS and MVM major category of DS
- Users *different* than general population
 - ▶ Many F, elders, High SES, those with healthy lifestyles, lower BMI, live in West
 - ▶ Many with chronic illness or serious disease
 - ~ Make it difficult to draw conclusions from observational studies

Dietary intakes of MVM users vs nonusers vary

- **Dietary intake of MVM users vs. nonusers**
 - ▶ Those who have nutritional inadequacy and might benefit least likely to use
 - ▶ MVM users have increased dietary intakes of VM and thus may be at risk of exceeding UL
 - ▶ Intakes difficult to ascertain due to lack of good information on intake, lack of analytical database

Efficacy singles

- Efficacy of single vitamin mineral supplements in chronic disease prevention poorly documented and generalizable to US population
 - ▶ Many studies were reanalysed for outcomes that were not original study outcomes (thus power poor)





Efficacy singles and pairs

- **Few trials of individual or paired vitamins and minerals for Px of chronic disease produced beneficial effects**
 - ▶ Strong evidence for smokers to avoid beta carotene
 - ▶ Calcium and D have benefit on bone mineral density and fracture in postmenopausal women
 - ▶ Se may decrease prostate, lung and colon cancer
 - ▶ E may decrease CVD death in women and prostate cancer in male smokers
 - ▶ Trials of niacin, folate , B2, B6 and B12 no positive effects

Efficacy MVM

- Efficacy of MVM in chronic disease prevention in general population of adults
 - ▶ Cancer. Effects in China. In France, SUVIMAX with E, Se, C, Beta carotene and Zn decreased overall cancer but only in men, and no specific cancer went down, so was overall mortality in men, but no effects in women. Among men in French study intervention with MVM decreased prostate cancer in those with normal PSA levels.
 - ▶ CVD. No effects
 - ▶ Cataract. Modest, inconsistent effects
 - ▶ Macular degeneration: less progress in 2 study with C,E beta carotene and zinc.

Safety MVM

- Some single ingredients can produce adverse effects (like beta carotene and lung cancer, high D and Calcium and kidney stones, etc)
- Adverse effects due to exceeding UL can occur in individuals consuming a diet rich in fortified foods and also taking MVM
- Need better adverse event reporting, more information to consumers about avoiding exceeding the UL and how to report adverse events

Research Gaps Many

- Need more RCT and good observational studies
- Better DS reporting
- Better MVM databases and consumer information
- MVM nutrient and prescribed or OTC interactions
- Those at special risk and previously underrepresented
- basic mechanisms of effects of MVM
- RCT of individual supplements that are biologically plausible pairs.

Implications for Dietitians

- Ask about dietary supplement use
- Check nutrient containing supplements, esp high doses of single nutrients
- Check those already ill
- Check FDA websites for warnings

Implications for Dietitians

- Use of MVM best in levels not exceeding %DV
- No advantage to higher doses, may be disadvantages
- Benefits in chronic disease prevention not well documented except for Ca and D, Folic
- Little reason to recommend either for or against use to prevent chronic disease

Conclusions

- Supplement on Proceedings in American Journal of Clinical Nutrition this year
- Evidence report is in Annals of Internal Medicine
- Much research remains to be done

SOS on MVM and Chronic Disease Risk in Adults

- Evidence based review
 - ~ www.ahrq.gov/downloads/pub/br>evidence/pf/multivit.pdf
- Outside expert panel report
 - ~ <http://consensus.nih.gov/2006/MVMFINAL051706.pdf>
- AJCN supplement forthcoming



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