# "Dietary Supplements and Nutritional Products...now why would a toxicologist be interested?"

Association of Government Toxicologists
Wednesday, December 3, 2014

Council for Responsible Nutrition


# CRN is a trade association of dietary supplement, functional food and nutritional ingredient manufacturers and marketers, who join together to . . .


. . . sustain and enhance a climate for our member companies to responsibly develop, manufacture and market dietary supplements, functional foods and their nutritional ingredients.

# Some of Our Members:





































# Council for Responsible Nutrition (CRN)

- Scientific & International Affairs
- Scientific & Regulatory Affairs
- Communications
- Government Relations
- Membership Development

# CRN-International

- CRN-I is an international arm of the Council for Responsible Nutrition (CRN).
- CRN-I's mission is to provide science-based information to regulators, health care professionals and the media, particularly those outside the United States, supporting the safety and benefit of dietary ingredients and dietary/food supplements.
  - Promote sound nutrition and food safety

    policies well-grounded in science.

# CRN-International

- 2014 “A Quality Dietary Supplement: Before You Start and After It’s marketed” (*in progress*)
- 2013 " Bioactives: Qualitative Nutrient Reference Values for Life-stage Groups? A conference report" *European Journal of Nutrition*
- 2012 "Nutrient reference values for bioactives: new approaches needed? A conference report" *European Journal of Nutrition*
- 2011 "Nutrition issues in Codex: health claims, nutrient reference values and WTO agreements: a conference report" *European Journal of Nutrition*
- 2010 "Scientific issues related to Codex Alimentarius goals: A review of principles, with examples" *Regulatory Toxicology and Pharmacology*

# 2012 (SOT) Meeting

## DIETARY SUPPLEMENT ADULTERATION AND IMPACT ON HUMAN HEALTH

- Dietary Supplement Adulteration – A Clinician's Perspective
- Dietary Supplement Adulteration:  Canadian regulator's perspective
- US Regulatory Perspectives on the Intentional Adulteration of Dietary Supplements
- Quality standards; specifications on purity and authentic.

# 2013 (SOT) Meeting

## TRANSLATIONAL METHODS TO ASSESS THE SAFETY OF NATURAL HEALTH PRODUCTS, INCLUDING TRADITIONAL MEDICINES AND DIETARY SUPPLEMENTS

- In Silico Methods as Translational Tools for Supporting the Safety Assessment of Natural Health Products
  In vitro and in vivo approaches for assessing the safety of natural health products
- Computational Methods linking Traditional Chinese Medicine (TCM) and Western Therapeutics
- Herbogenomics as a Translational Method for the Safety Assessment of the Complex Mixtures in Traditional Chinese Medicines
- Evidence Based Reviews as a Method for Assessing the Safety of Dietary Supplements

# 2014 (SOT) Meeting

IMPROVING THE SAFETY OF DIETARY SUPPLEMENTS BY ASSESSING EFFECTS IN HUMANS.

- How Can Human Data, Generated Deliberately or Accidentally, Be Used to Advance the Understanding of Dietary Supplement Safety?
- A Clinician's Perspective on Accurate Adverse Event Knowledge in the Emergency Setting.
- Natural Product Post Market Surveillance: A Safety Net Designed to Detect Signals, Generate Hypotheses for Research, and Confirm Safety.
- Clinical Utility of Dietary Supplement Case Reports and Adverse Event Reports: A Pharmaceutical Scientist's Perspective
- Systematic Analyses of Kava's Hepatotoxic Risk – What We Know and What We Do Not Know
- Collection, Interpretation and Utilization of Adverse Event Data Within a Global Dietary Supplement Company

# 2013 (ToxForum) Meeting

## ADVERSE EVENTS AND CAUSALITY ASSESSMENT: A POTENTIAL FRAMEWORK FOR DIETARY SUPPLEMENTS AND FUCNTIONAL FOODS.

- Established causality assessment frameworks and criteria for foods and/or drugs.
- Vigilance of Health Products:  A Key Tool for Monitoring and Improving the Safety of Natural Health Products.
- Current approaches to causality assessment: Are they appropriate for dietary supplements?
- Clinical Utility of Dietary Supplement Case Reports and Adverse Event Reports: A Pharmaceutical Scientist's Perspective.

# 2014 (IFT) Meeting

## Adverse Events: When Unexpected Dietary Supplement Toxicity Sets Off an Alarm.

- Product Vigilance Activities as Critical Tools for Monitoring and Improving the Safety of Dietary Supplements in the Regulatory Context.
- Postmarket Surveillance and Adverse Event Reporting: Corporate Approaches to Signal Detection, Regulatory Reporting and Causality Assessment.
- Evidence-Based Safety Reviews for Dietary Supplements: USP Perspective.
- Responding to an AER Signal: Clinical and Public Health Context.

# Diverse Topics

- The Buzz on **Caffeine**: New Developments in the Safety and Regulation of Foods and Dietary Supplements.
- The need for a DRI-like process for **bioactives**; Rethinking the essential nutrient paradigm.
- **Spirulina**; Transition from Poor Man's Food to a Dietary Supplement.
- Helping to Ensure Product Quality: The **Black Cohosh** Story.
- Fifty Years of Change: Fate and Fortune of **Selenium and Mercury**.
- Limits for **elemental contaminants** in dietary supplements: Compendial perspectives.
- **Dietary Supplement Safety Assessment**: Past, Present, and Future.
- Quality and Safety of Functional Foods – From **naturals to designer molecules**, new challenges to keep the food supply chain safe.
- **Melamine**, Nitrogen and Protein Determination: A History and Path Forward.
- International Opportunities to Improve **Public Health** through Food and Dietary Supplement Ingredient Standardization: The Time is Ripe.
- The supportive relationship between current **Good Manufacturing Practices** (cGMPs) and quality specifications for dietary supplements/dietary ingredients.


Vitamin
and Mineral
Safety 3rd Edition
Council for Responsible Nutrition

# Less on Toxicology, More on Human Health….with maybe a bit of Psychology and Economics?!

# PSYCHOLOGY

A common and presumably simple question:

"Should I take a multivitamin?"

SCIENTIFIC AMERICAN™

# Multivitamins Are a Waste of Money, Doctors Say

**Annals of Internal Medicine**

ESTABLISHED IN 1927 BY THE AMERICAN COLLEGE OF PHYSICIANS

**Editorials** | 17 December 2013

## Enough Is Enough: Stop Wasting Money on Vitamin and Mineral Supplements FREE

Eliseo Guallar, MD, DrPH; Saverio Stranges, MD, PhD; Cynthia Mulrow, MD, MSc, Senior Deputy Editor; Lawrence J. Appel, MD, MPH; and Edgar R. Miller III, MD, PhD

CBSNEWS Video | US | World | Politics | Entertainment | Health | Mone

By RYAN JASLOW / CBS NEWS / December 16, 2013, 5:04 PM

## Multivitamin researchers say "case is closed" after studies find no health benefits

CNN Health

## Are multivitamins a waste of money? Editorial in medical journal says yes

By **Nadia Kounang**, CNN

updated 9:15 AM EST, Tue December 17, 2013

theguardian

## Vitamin supplements are waste of money, say scientists

Research suggests diet supplements taken by one in three B
have no clear health benefits and might even be harmful

al High-Dose Multivitamins and Minerals After
ocardial Infarction: A Randomized Trial

asio A. Lamas, MD; Robin Boineau, MD, MA; Christine Goertz, DC, PhD; Daniel B. Mark, MD, MPH; Yves
nberg, MD; Mario Stylianou, PhD; Theodore Rozema, MD; Richard L. Nahin, PhD, MPH; Lauren Lindblad,
Eldrin F. Lewis, MD; Jeanne Drisko, MD; Kerry L. Lee, PhD, for the TACT (Trial to Assess Chelation Therap
tigators*

ng-Term Multivitamin Supplementation and Cognitiv
nction in Men: A Randomized Trial

cine Grodstein, ScD*; Jacqueline O'Brien, ScD*; Jae Hee Kang, ScD; Rimma Dushkes, PhD; Nancy R. Co
; Olivia Okereke, MD; JoAnn E. Manson, MD, DrPH; Robert J. Glynn, PhD; Julie E. Buring, ScD; J. Michael
ano, MD, MPH; and Howard D. Sesso, ScD, MPH

itamin and Mineral Supplements in the Primary
revention of Cardiovascular Disease and Cancer: An
ated Systematic Evidence Review for the U.S.
entive Services Task Force FREE

P. Fortmann, MD; Brittany U. Burda, MPH; Caitlyn A. Senger, MPH; Jennifer S. Lin, MD, MCR; and Ev
P. Whitlock, MD, MPH

**Should I take a multivitamin – Ask the Internet!**

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Annals of Internal Medicine

ESTABLISHED IN 1927 BY THE AMERICAN COLLEGE OF PHYSICIANS

# Vitamin and Mineral Supplements in the Primary Prevention of Cardiovascular Disease and Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force FREE

Stephen P. Fortmann, MD; Brittany U. Burda, MPH; Caitlyn A. Senger, MPH; Jennifer S. Lin, MD, MCR; and Evelyn P. Whitlock, MD, MPH

**Conclusion:** Limited evidence supports any benefit from vitamin and mineral supplementation for the prevention of cancer or CVD. Two trials found a small, borderline-significant benefit from multivitamin supplements on cancer in men only and no effect on CVD.

**Primary Funding Source:** Agency for Healthcare Research and Quality.

- Specific systematic review based on heart disease and cancer prevention
- Conclusion is not that MVMs do not work, it is that there is **not enough qualifying studies to draw a firm conclusion for CVD and Cancer prevention**

This is a reviev
ideally suited t
not exposed to the medication. In a nutrient supplementation study, however, the control group is exposed to some level of the nutrient because it is designed to answer a different question: Does exposure to an optimal level of the nutrient produce better health outcomes than exposure to the usual level? To conduct this type of study, one must know both the usual and optimal level of exposure. In practice, however, exposure to the nutrient in the control group may change during the course of a trial as societal norms change, complicating interpretation of the trial results. Women in the WHI control group, for example, had twice the average calcium intake of that anticipated when the trial was designed, and the vitamin D dose was lower than many now think is necessary to achieve optimal blood levels.

- **Nutrients are not Drugs** – the studies evaluated were designed for drugs and may not be ideal for evaluating the effect of nutrients

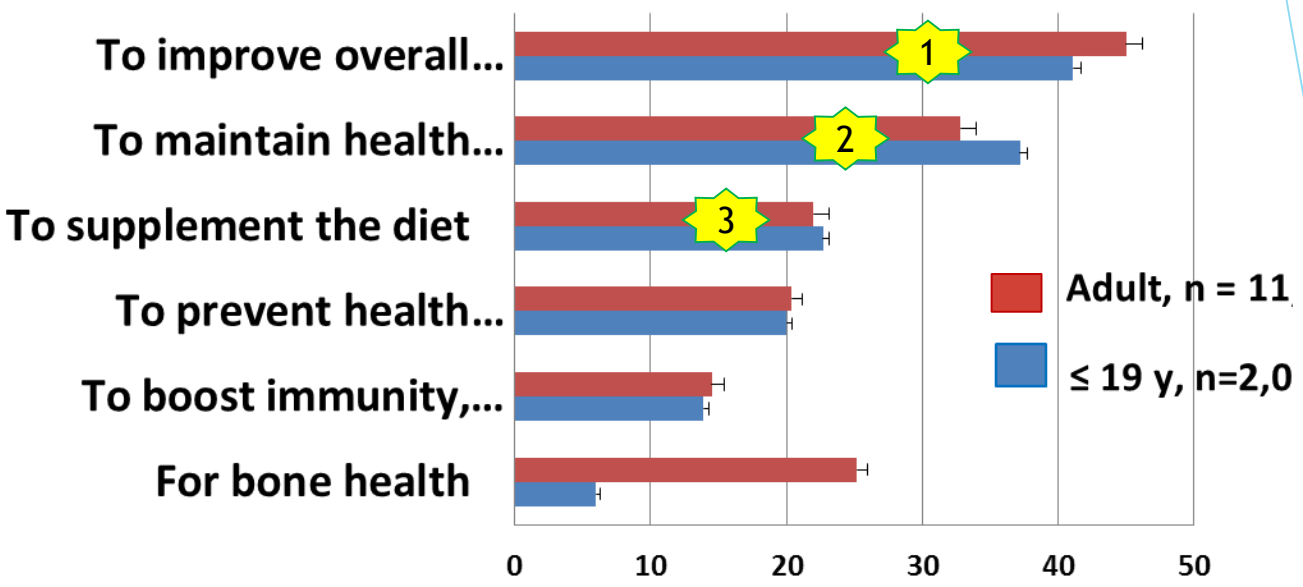
# Most people don't expect a simple multivitamin to prevent cancer or heart disease



**Dietary supplements are used as one component of a healthy lifestyle**

# Why use Dietary Supplements?

NHANES 2007-2010




Adult Data: Bailey, et al. *JAMA* 2013p;173:355

Child Data: Bailey, et al. *Ped Res 2013*;74:737

# Why don't all nutrition experts recommend a multivitamin?

Common reasons provided by experts that do not recommend multivitamins to fill nutrient gaps;

- People will use a multivitamin in place of a healthy diet or other healthy behaviors
- Safety: Supplementation may result in excess nutrient consumption

# Myth #1: People will use a multivitamin in place of other healthy behaviors

Psychol Sci. 2011 Aug;22(8):1081-6. doi: 10.1177/0956797611416253. Epub 2011 Jul 15.

**Ironic effects of dietary supplementation: illusory invulnerability created by taking dietary supplements licenses health-risk behaviors.**

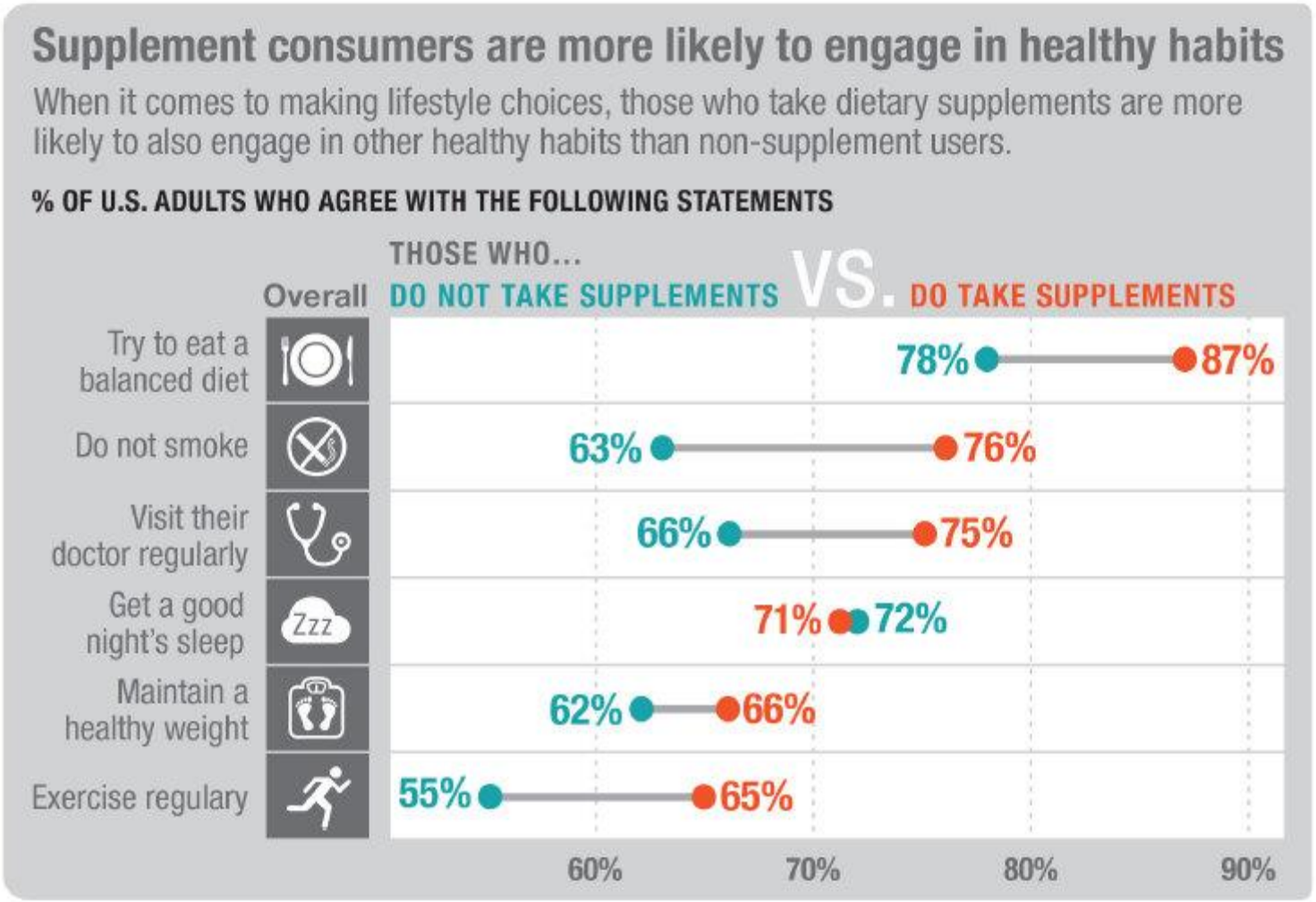
Chiou WB[1], Yang CC, Wan CS.

⊕ **Author information**

**Abstract**

The use of dietary supplements and the health status of individuals have an asymmetrical relationship: the growing market for dietary supplements appears not to be associated with an improvement in public health. Building on the notion of licensing, or the tendency for positive choices to license subsequent self-indulgent choices, we argue that because dietary supplements are perceived as conferring health advantages, use of such supplements may create an illusory sense of invulnerability that disinhibits unhealthy behaviors. In two experiments, participants who took placebo pills that they believed were dietary supplements exhibited the licensing effect across multiple forms of health-related behavior: They expressed less desire to engage in exercise and more desire to engage in hedonic activities (Experiment 1), expressed greater preference for a buffet over an organic meal (Experiment 1), and walked less to benefit their health (Experiment 2) compared with participants who were told the pills were a placebo. A mediational analysis indicated that perceived invulnerability was an underlying mechanism for these effects. Thus, a license associated with the use of dietary supplements may operate within cycles of behaviors that alternately protect and endanger health.

**The use of dietary supplements creates an illusory sense of invulnerability that disinhibits unhealthy behaviors, such as less desire to engage in exercise and more desire to engage in hedonic activities (e.g., casual sex, sunbathing, wild parties, excessive drinking, etc.).**

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# Increase in prevalence of dietary supplement use over time as shown in a series of NHANES surveys

| Survey | Prevalence of dietary supplement use |
|---|---|
| NHANES I, 1971-74 | 23% of adults |
| NHANES II, 1976-80 | 35% of adults |
| NHANES III, 1988-1994 | 42% of adults |
| NHANES 1999-2000 | 52% of adults |
| NHANES 2003-2006 | 54% of adults |
| NHANES 2007-2010 | 49% of adults |

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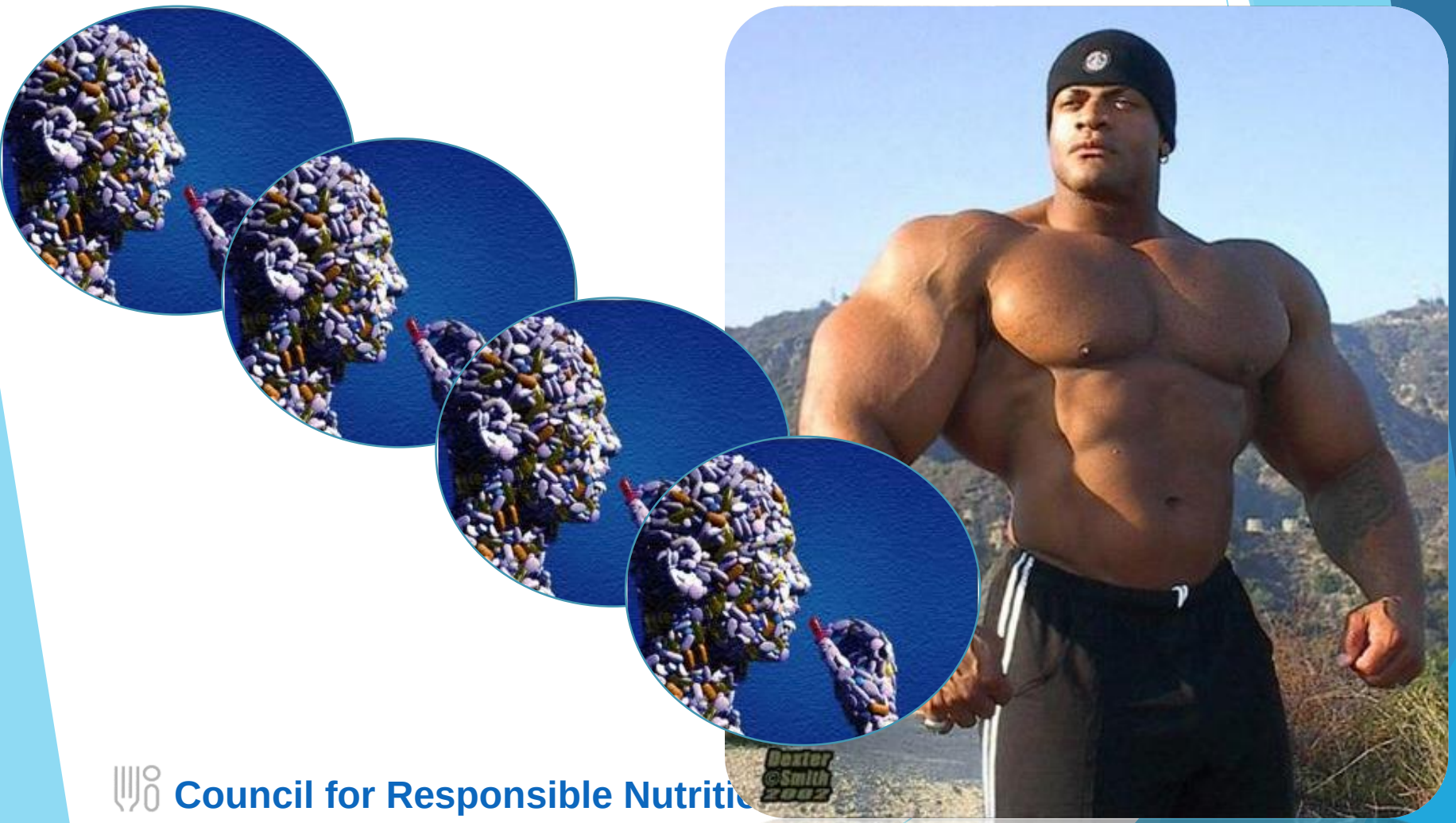
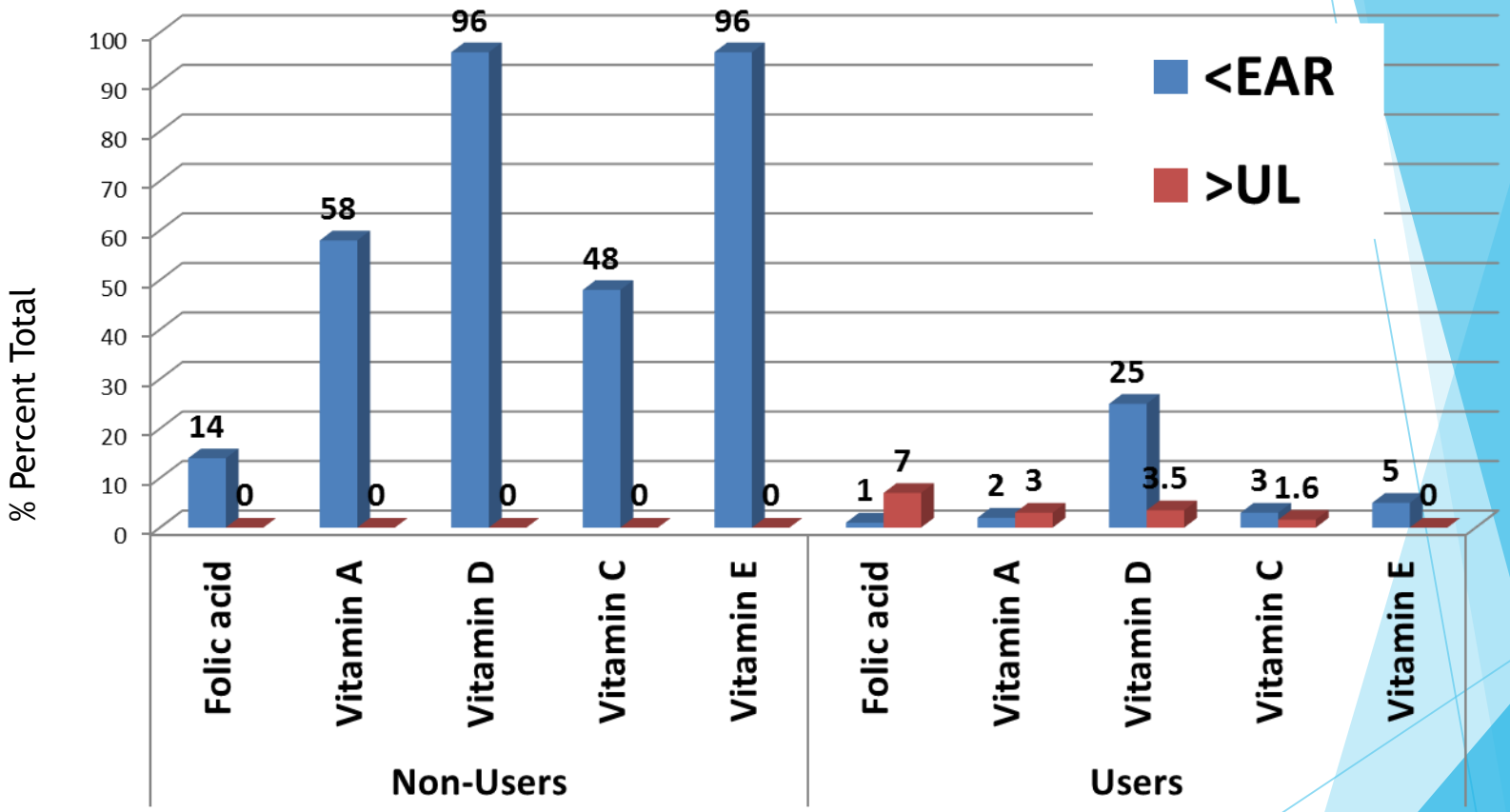
# Myth #2: Supplementation may result in unsafe consumption of excess nutrients



# Supplementation & Adult Nutrient Intakes

NHANES 2003-2006 (n = 8,860)

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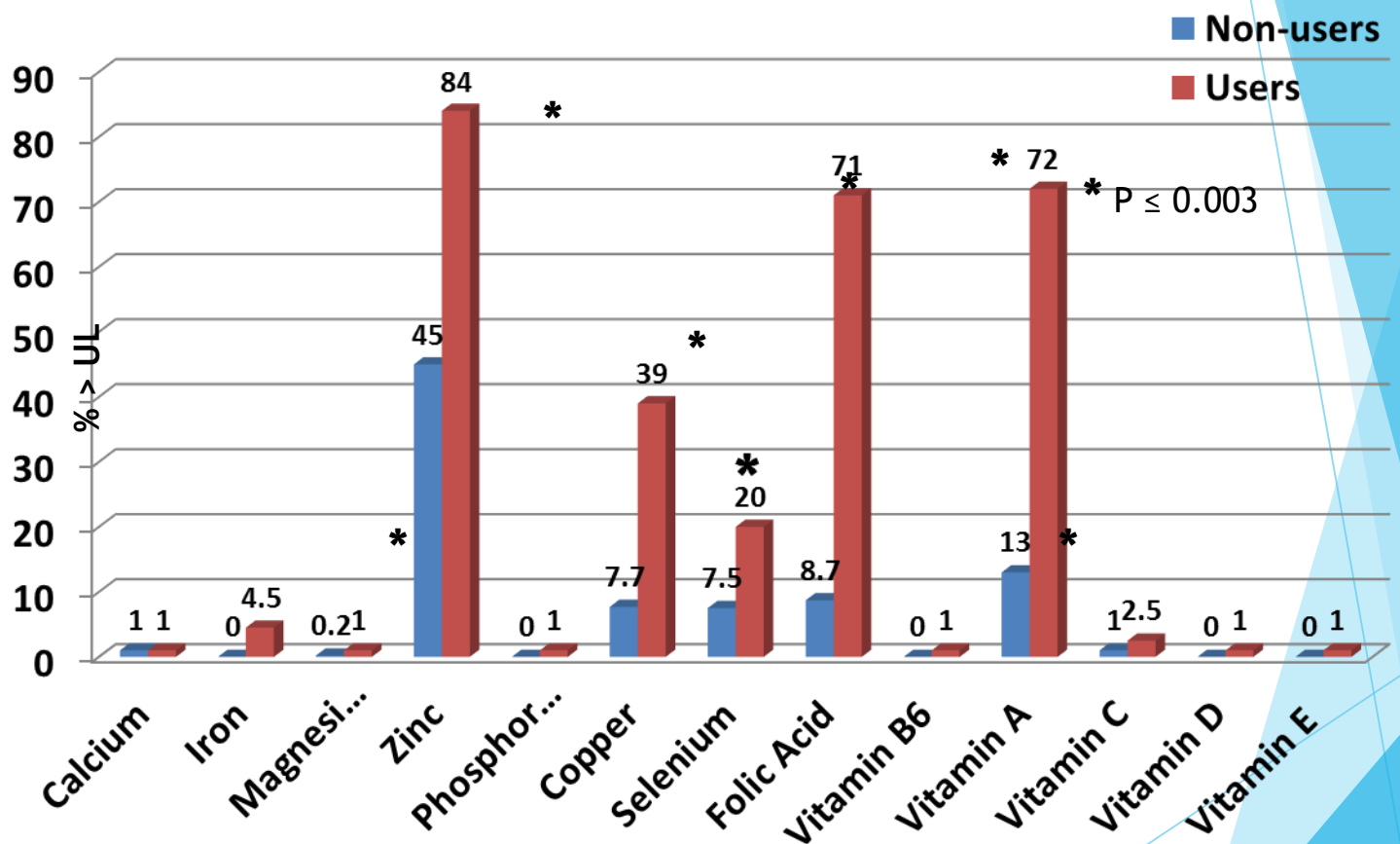
Source: Bailey et al. *JADA* 2012;112:657

# % US Children (2-8y) above UL

NHANES 2003-2006 (n=1,264)

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Source: Bailey et al. J Ped 2012;161:837

# Taking a multivitamin safely fills nutrient gaps

- Data show only a small percentage of Americans consume some nutrients at levels above the UL when contributions from diet, fortified food, and supplements are all taken into account
  - These levels have not been associated with harm.

- In the recent Physicians' Health Study II, over 14,000 male physicians took a daily multivitamin for over ten years
  - No serious adverse effects were found.
  - *Gaziano, et al. JAMA.* 2012;308:1871.

# ECONOMICS

A common and presumably simple question:

"Is an ounce of prevention worth a pound of cure?"

# Smart Prevention


CRN FOUNDATION

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# Americans spend too much money on healthcare.

- 75% of health care spending goes to addressing preventable diseases.
- Only 3% of every health care dollar spent is used for prevention.
- Numerous, rigorous studies demonstrate that the targeted use of certain dietary supplements can actually help to reduce the risk of some chronic diseases.

***What if dietary supplements could contribute to reducing overall healthcare expenditures?***

# The Hypothesis

We hypothesized that if the selected dietary supplement regimens were taken at the same preventive levels as used in the clinical research by those at-risk populations, there would be a cost savings to the health care system and to individual providers and payers from reduced medical expenses associated with those lower risks of disease.

# The Hypothesis

*In other words, using dietary supplements in certain cases to reduce this risk of disease would also reduce the attendant medical costs of those diseases - and save the health care system money.*

# The Plan of Action

This project looks at the cost of various combinations of preventative and treatment scenarios per the recommendations of the current state of science and examines prevention as an alternative course of action for a given at-risk population.

Objectives:

- To critically review the research literature which shows an association between dietary supplement intake and disease risk reduction to quantify the risk reduction; and then
- To determine the potential net health care cost savings from the use of certain dietary supplements as a result of avoided disease-related medical events.

# Research Scope

The disease conditions and dietary supplement combinations this report examines include:

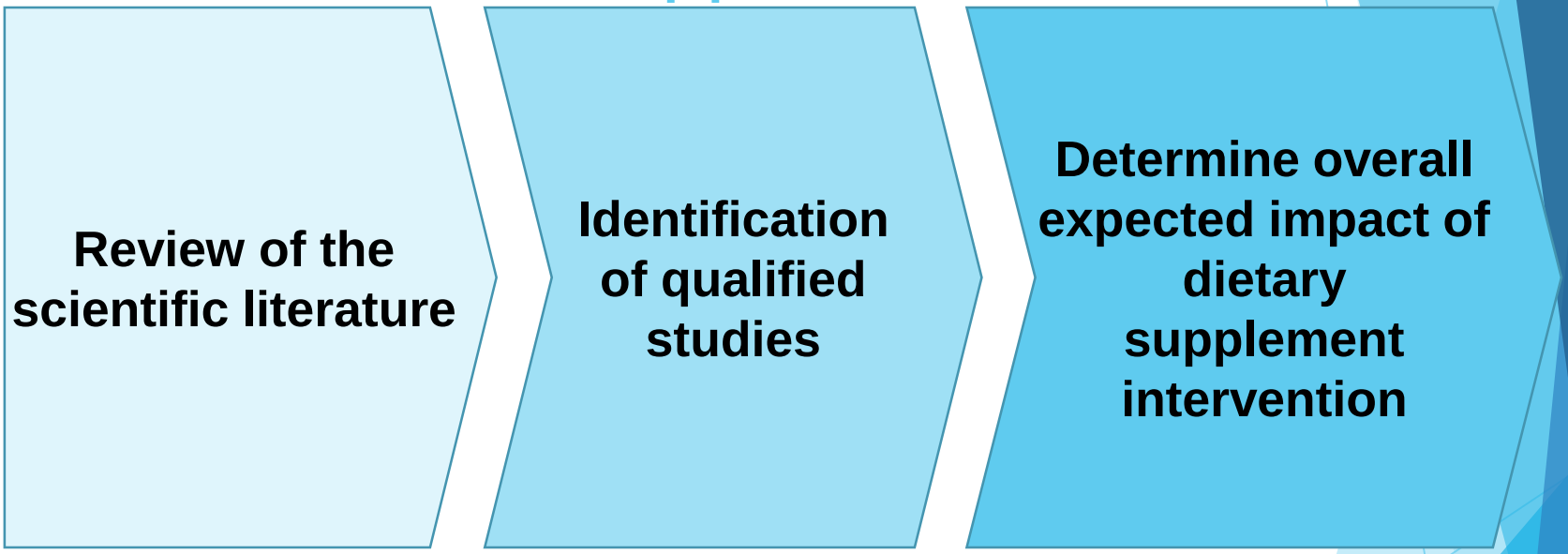
- Coronary heart disease (CHD) and the potential net health care cost savings when using **omega-3 fatty acids**, three **B vitamins** (folic acid, B6, and B12), **phytosterols** and **psyllium dietary fiber.**

- Diabetes and the potential net health care cost savings from diabetes-attributed CHD when using **chromium picolinate.**

- Osteoporosis and the potential net health care cost savings when using the combination of **calcium and vitamin D** or when using **magnesium.**

- Age-related eye disease (ARED), specifically age-related macular degeneration and cataracts, and the potential net health care cost savings when using **lutein and zeaxanthin.**

# Research Methodology—Part 1: Ascertain the Disease Risk Reduction from Supplement



# Osteoporosis


- 8.2 million women over 55 have osteoporosis.
- In 2012, there were 1.2 million fracture events related to osteoporosis.
- Average treatment cost in 2012 = $11,020 per event.
- More than $14 billion in annual direct health care costs.

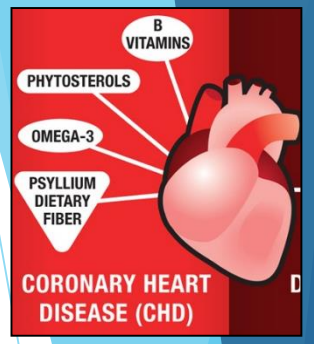
# Osteoporosis: Calcium & Vitamin D


- Preventive intake level (PIL) = 1,000 mg calcium and 800 *iu* vitamin D
- Median retail cost of calcium/vitamin D supplement = $.16 / day
- 18.6% relative risk reduction for falls and fractures;
- An average of 151,053 avoided events per year; and
- 1,208,422 avoided events accumulated from 2013 through 2020.

# Osteoporosis: Magnesium

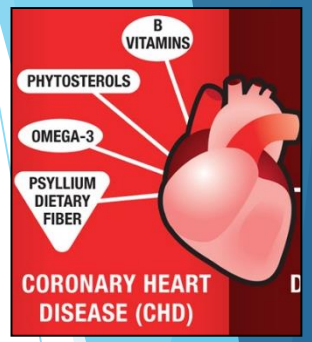

- Preventive intake level (PIL) = 100 mg.
- Median retail cost of magnesium supplement = $.09 / day
- 6% relative risk reduction for falls and fractures – 68,536 avoided events / year

# Coronary Heart Disease (CHD)



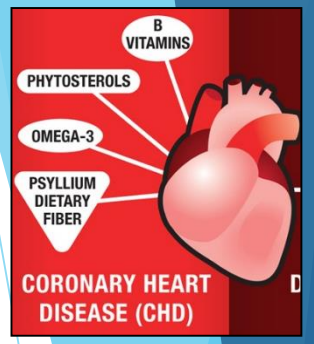

- 6.6% of U.S. adult population has CHD
- 16% of adults over 55 with CHD will experience a CHD-related medical event each year
- Average cost of CHD-related inpatient procedure or emergency room visit = $13,317
- Between 2013 and 2020, average direct health care costs related to CHD events among adults over 55 = $77.92 billion a year

# Coronary Heart Disease (CHD): Omega-3 fatty acids




- Preventive intake level (PIL) = 1,000 mg of omega 3s daily
- Median retail cost of omega 3s = $.25 / day
- 66 studies identified; subjects had pre-existing CHD or were at high risk
  - 6.9% relative risk reduction in CHD related medical events
  - An average of 137,210 avoided events per year
  - Cumulatively, 1,097,678 avoided events between 2013 and 2020

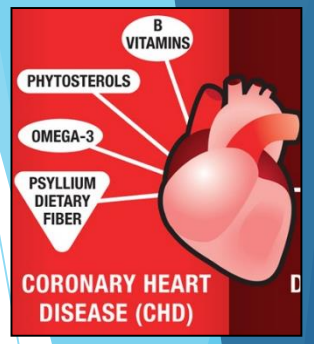
# Coronary Heart Disease (CHD): Phytosterols




**Phytosterol utilization yields:**

- Preventive intake level (PIL) = 2 grams
- Median daily retail cost = $.15 / day
- 11.2% relative risk reduction in CHD related medical events
- 283,389 avoided CHD events / year, or 2.2 million cumulatively between 2013 and 2020

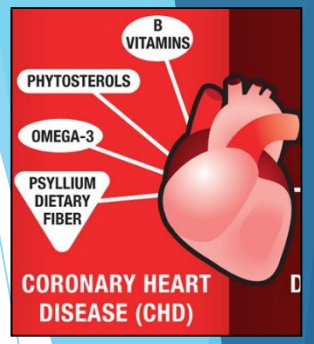
# Coronary Heart Disease (CHD): B vitamins




**B vitamin utilization yields:**

- Median daily retail cost = $.11 / day
- 3.3% relative risk reduction in CHD related medical events
- 101,028 avoided CHD events / year, or 808,225 events cumulatively between 2013 and 2020.

# Coronary Heart Disease (CHD): Psyllium dietary fiber




**Psyllium Dietary Fiber utilization yields:**

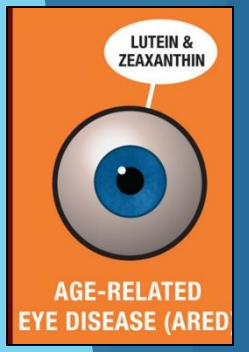
- Preventive intake level (PIL) = 10 grams
- Median daily retail cost = $.30 / day
- 11.5% relative risk reduction in CHD related medical events
- 292,165 avoided CHD events / year, or 2,337,318 events cumulatively between 2013 and 2020

# Diabetes-Related CHD


- Over 17 million U.S. adults have Type II Diabetes.
- Of them, over 6.9 million have diabetes-related CHD and 1.9 million experienced a diabetes-attributed CHD-related inpatient procedure and/or visited the emergency room in 2012.
- Average expenditure per person = $13,317.

- **Chromium picolinate utilization yields:**
  - 10.2% relative risk reduction.
  - An average of 81,243 avoided events per year.
  - 649,944 avoided events accumulated through 2020.

# Age-Related Eye Diseases (AREDs)




- Through 2020, an average of 4.8 million people over the age of 55 will experience an AMD or cataract event.
- Total cumulative health care costs related to ARED events: more than $164.4 billion—an average annual cost of nearly $20.60 billion.

- **Lutein and zeaxanthin utilization yields:**
  - 23.0% and 15.3% relative risk reduction of AMD and cataracts, respectively.
  - An average of 971,724 avoided AMD and cataract events per year.
  - 7,773,791 avoided events accumulated through 2020.

# Overarching Research Methodology—Part 2: Determination of Health Care Cost Savings

Once the expected risk reduction factor is derived from the literature review, the potential cost savings derived from increasing dietary supplement intake among a given high risk population can be calculated.

**Determine Hospital Utilization Costs in the Current State**

**−** **Avoided Hospital Utilization Costs Given 100% Use of Dietary Supplement Regimen at Preventive Intake Levels**

**=** **Revised Hospital Utilization Costs Accounting for Dietary Supplement Usage**

**+** **Costs of Dietary Supplement Utilization**

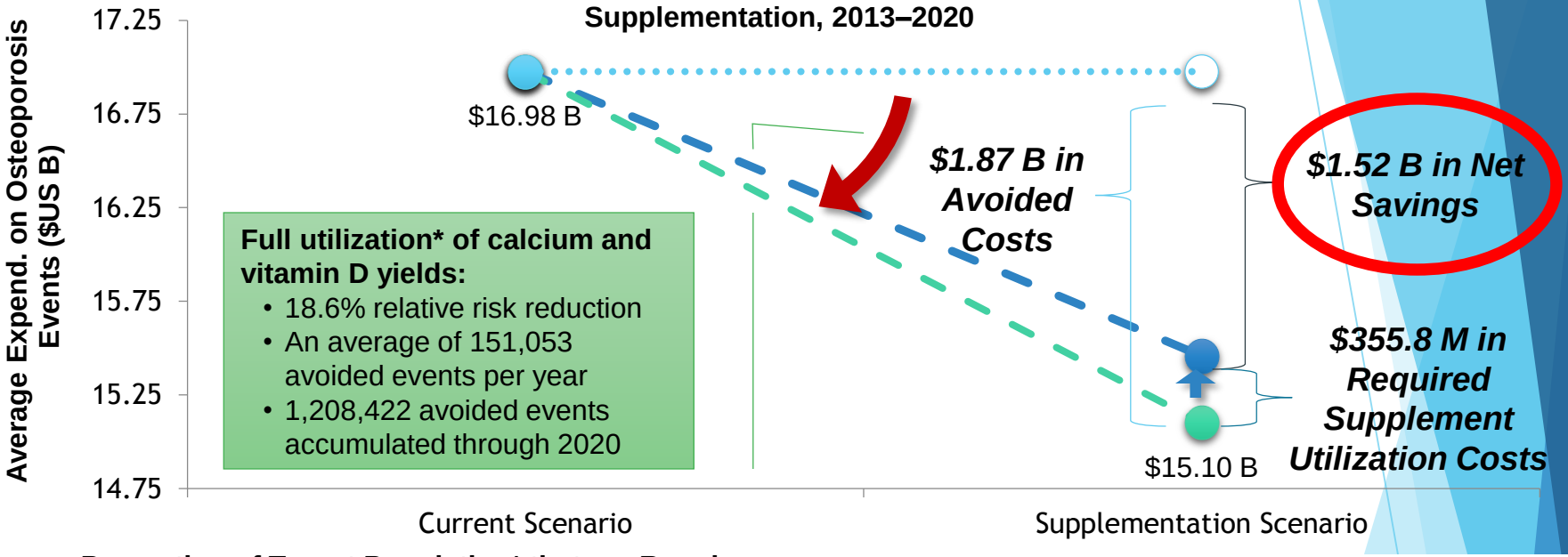
**=** **Combined Health Care Costs of Reduced Hospital Utilization and Cost of Dietary Supplement Utilization**

# Hypothetical:

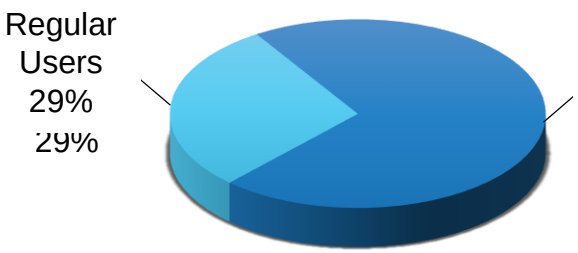
| | |
|---|---|
| Current Hospital Utilization | $100,000,000 |
| Avoided Costs of Medical Events with 100% Utilization of Dietary Supplement Based on Risk Reduction of Medical Events | - $15,000,000 |
| Revised Hospital Utilization | = $85,000,000 |
| Cost of Providing Supplement to 100% of Target Population | + $4,000,000 |
| Combined Health Care Cost of Dietary Supplement Utilization for Prevention and Revised Hospital Utilization | = $89,000,000 |

# Benefits of Calcium and Vitamin D—Potential Osteoporosis-attributed Cost Savings

**Net Annual Average Cost Savings due to Avoided Health Care Expenditures through Calcium and Vitamin D Supplementation, 2013–2020**




**Proportion of Target Population* that are Regular Users of Calcium and Vitamin D, 2012**




Source: Ipsos Public Affairs

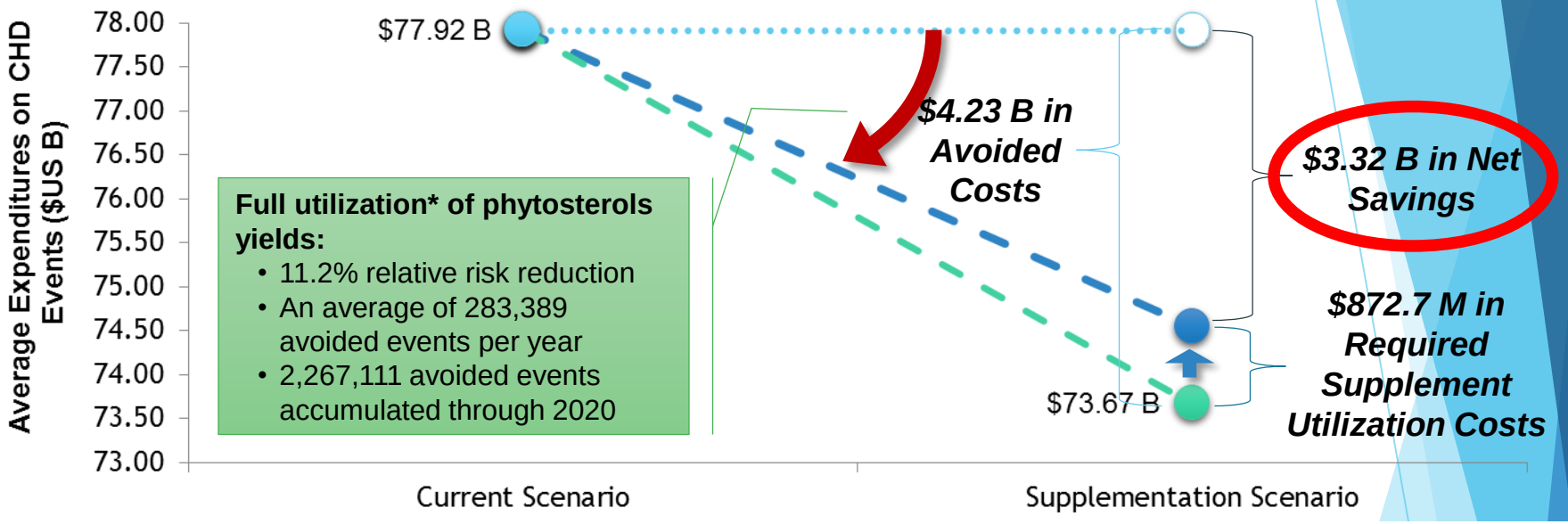
**Cost Savings Yet to Realized:**
- **107,248 avoided events per year**
- **$1.08 B in savings per year**

*Note: * Among all females over the age of 55 with Osteoporosis, **Time horizon = 2013 to 2020*
*Source: Frost & Sullivan analysis.*

Council for Responsible Nutrition

## Benefits of Phytosterols—Potential CHD Cost Savings

**Net Annual Average Cost Savings due to Avoided Health Care Expenditures through Phytosterols Intervention, 2013–2020**



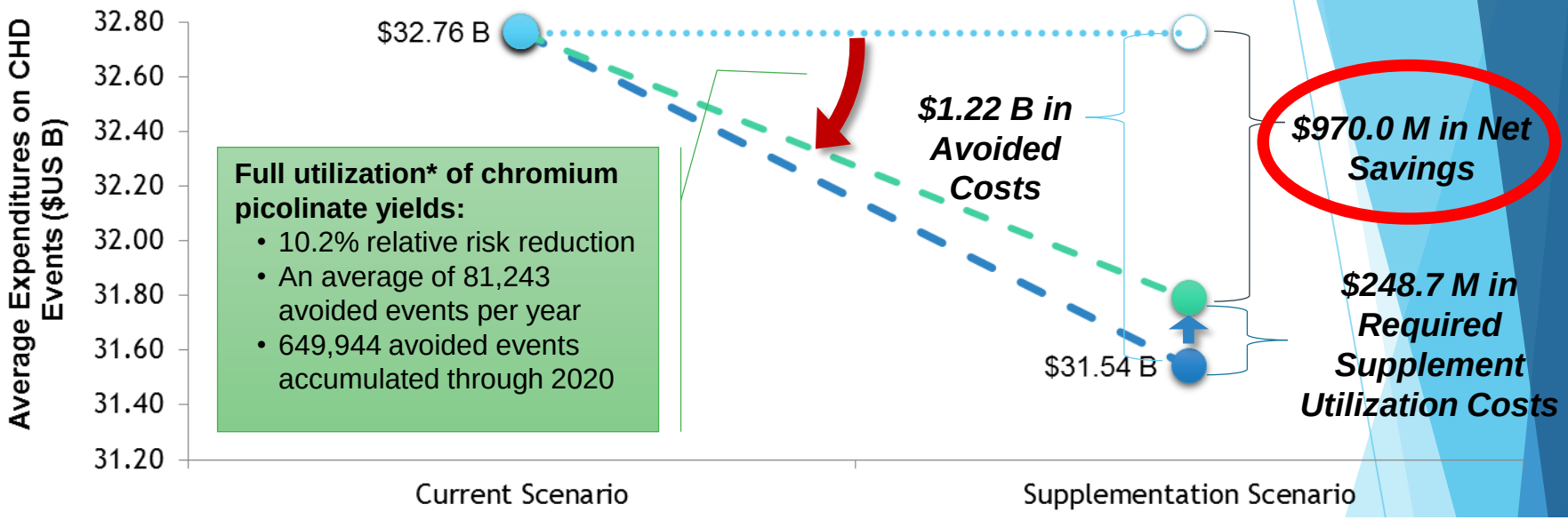

It is expected that less than 1% of adults over the age of 55 with CHD are already regular users of phytosterols, thus nearly all of the expected $3.32 B in potential net savings is yet to be realized.

*Note: * Among all adults over the age of 55 with CHD, **Time horizon = 2013 to 2020*

*Source: Frost & Sullivan analysis.*

## Benefits of Chromium Picolinate—Potential Diabetes-attributed CHD Cost Savings

**Net Annual Average Cost Savings due to Avoided Health Care Expenditures through Chromium Picolinate Intervention, 2013–2020**



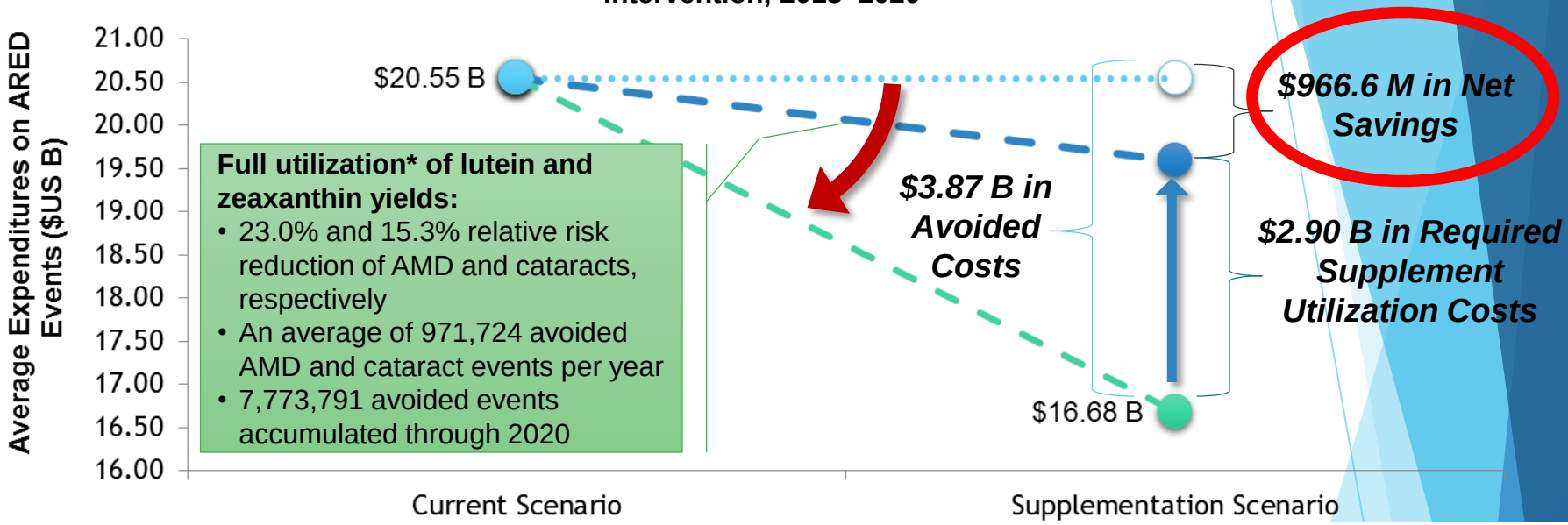

It is expected that less than 1% of adults over the age of 55 with CHD are already regular users are regular users of chromium picolinate, thus nearly all of the expected $970.0 B in potential net savings is yet to be realized.

*Note: * Among all diabetic adults over the age of 55 with CHD, **Time horizon = 2013 to 2020*

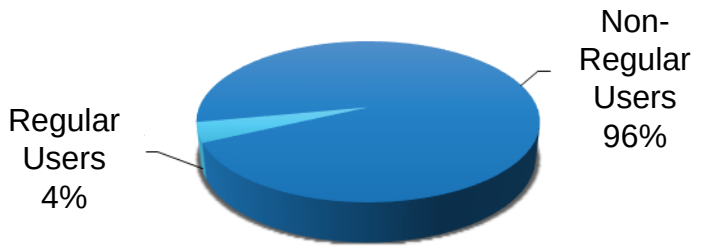
*Source: Frost & Sullivan analysis.*

# Benefits of Lutein and Zeaxanthin—Potential Age-related Eye Disease Cost Savings

**Net Annual Average Cost Savings due to Avoided Health Care Expenditures through Lutein and Zeaxanthin Intervention, 2013–2020**




**Proportion of Target Population* that are Regular Users of Lutein and Zeaxanthin, 2012**




Source: Ipsos Public Affairs

**Cost Savings Yet to Realized:**
- **932,855 avoided events per year**
- **$927.9 M in savings per year**

*Note: * Among all adults over the age of 55 with ARED, **Time horizon = 2013 to 2020. Includes Results of ARED II*
*Source: Frost & Sullivan analysis.*

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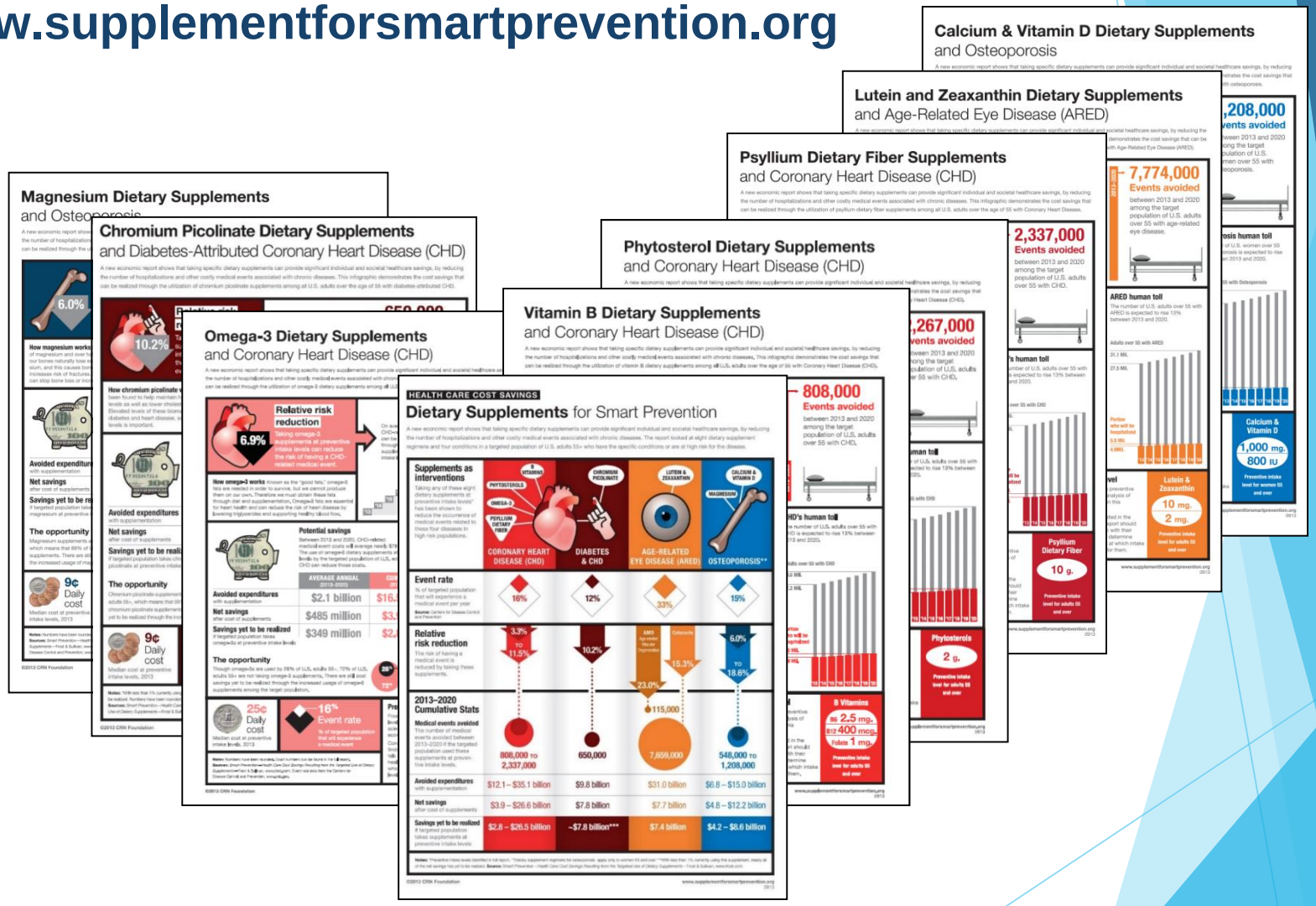
# Research Caveats

- The results from these eight regimens may not be generalizable to all supplements.
- This report is not intended to be a prescription for everyone to begin these eight regimens.
- Results of each supplement regimen should not be summed together for overall cost-savings effect.
- Results of each regimen are not comparable to one another for either:
  - Absolute savings, or
  - Cost/benefit ratio,

  although each regimen independently demonstrates significant cost savings for that supplement.

# www.supplementforsmartprevention.org

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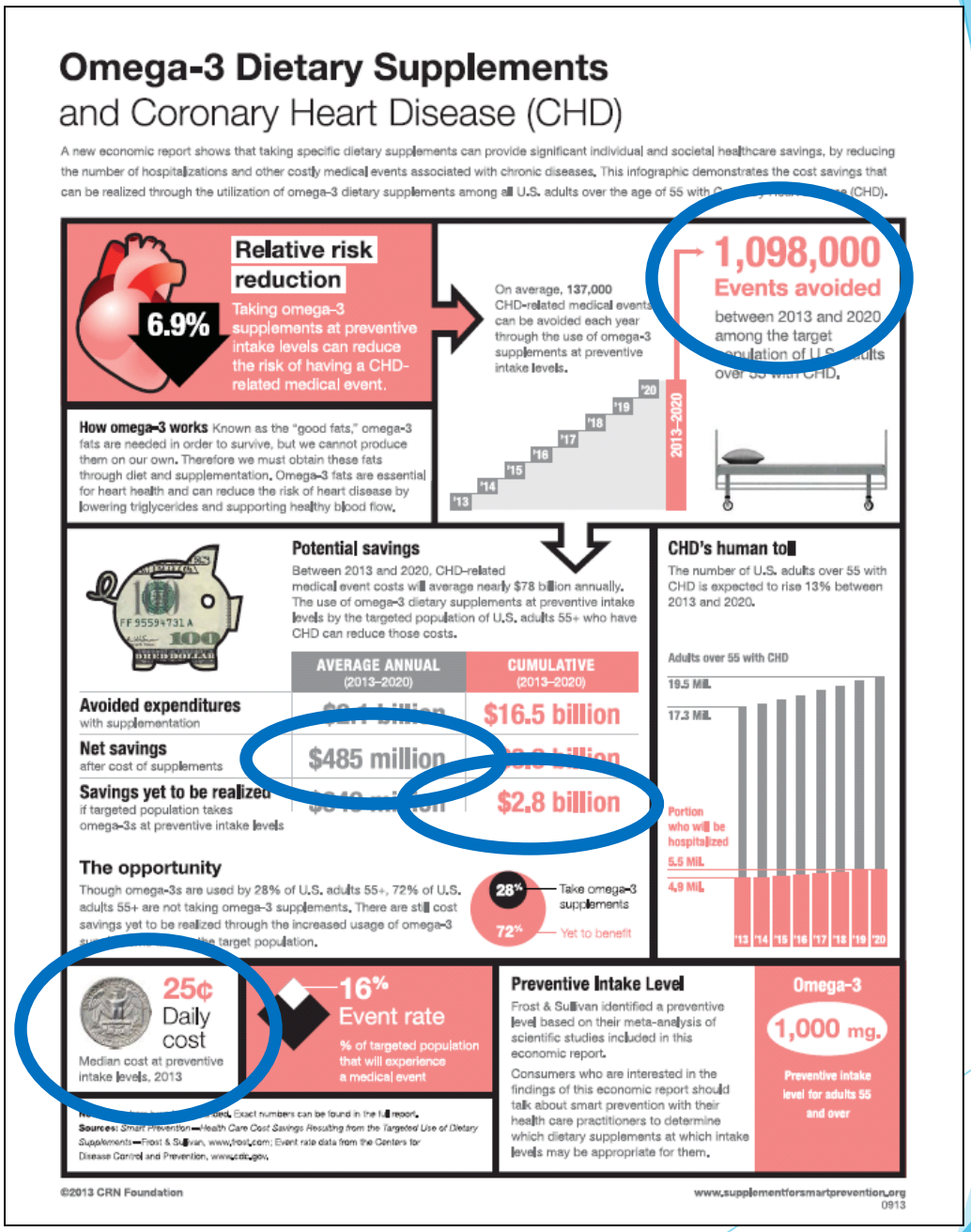


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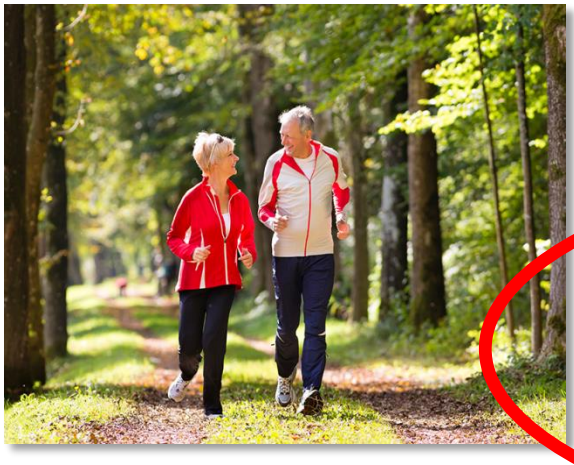
# Outcomes

Understanding the link between smart prevention and health care cost savings will help key stakeholders, including patients, health care professionals, governments, insurance companies and employers, make better-informed decisions on the best course of action that minimizes current and future health care costs and maximizes long term potential benefits.



- Disease events require costly treatment services, but until now there has been little effort to effectively calculate the cost-effectiveness of such supplement use.
- This report demonstrates that significant cost savings can be realized through the smart use of scientifically-substantiated dietary supplements among high risk populations.

# *Thank You!*

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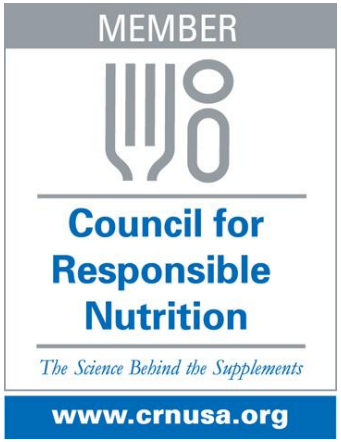


not-for-profit trade association representing the interests of the dietary supplement industry

# www.crnusa.org
# www.crn-i.ch

http://www.crnusa.org/CRNconsumersurvey/2014/CRN2014CCsurvey-infographic-pages.pdf
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