Nutraceuticals and Medicine Conference

Tampa, FL – October 18, 2018

Hidden Hunger:
Challenges, Opportunities, and Solutions

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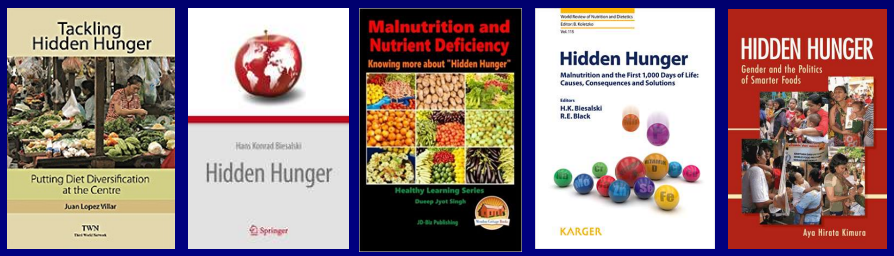
Hidden Hunger

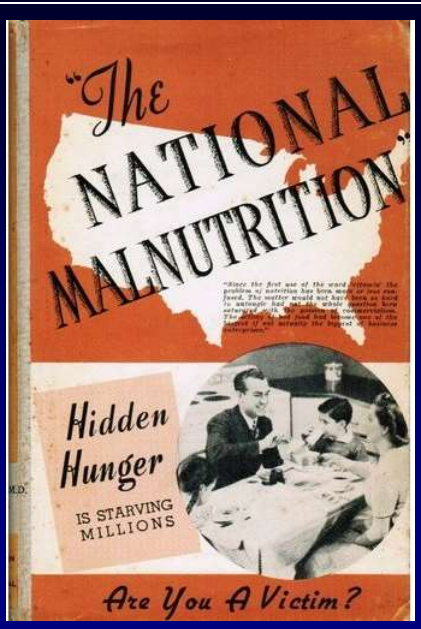
"Hidden Hunger" denotes a chronic lack of micronutrients – vitamins and minerals – whose effects may not be immediately apparent and whose consequences may be long-term and profound

The 'hidden hunger' due to micronutrient deficiency does not produce hunger as we know it. You might not feel it in the belly, but it strikes at the core of your health and vitality.

Kul C. Gautam
Past Deputy Executive Director, UNICEF



Hidden Hunger in America?!

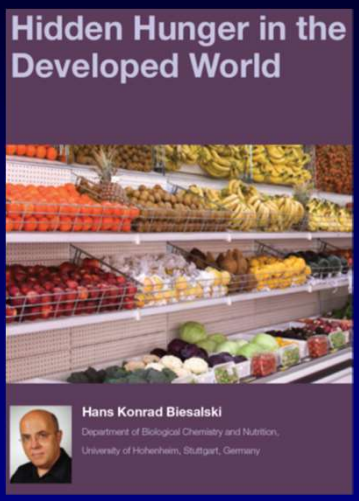


D.T. Quigley. The National Malnutrition 1943

Hidden Hunger in America?!

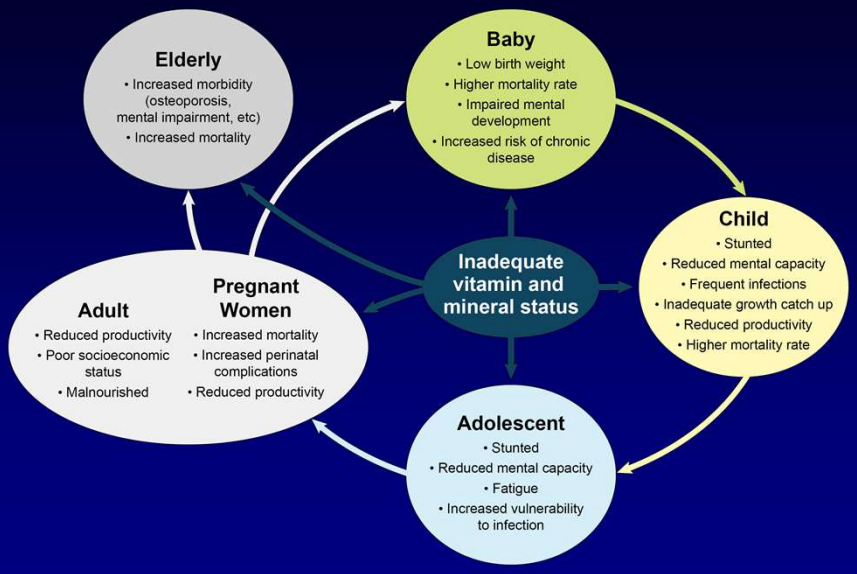
It is a popular perception that most people who live in the developed countries of the world enjoy a nutritionally sound diet and are not prey to hidden hunger. The reality is, however, different.

Micronutrient inadequacies are to be found in the developed world as well as in the developing world, and their current rate of growth in the developed world gives cause for concern.



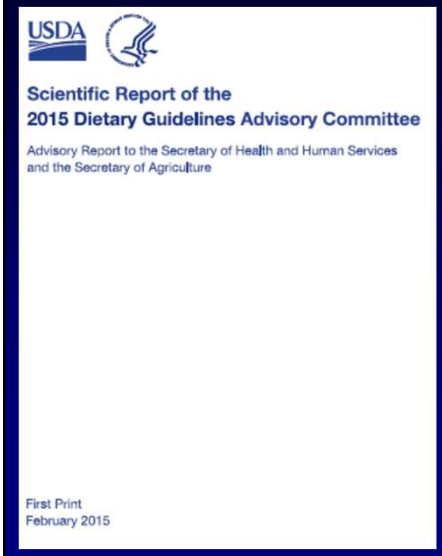
Eggersdorfer et al. The Road to Good Nutrition. Karger Publ. 2013

Impact of Hidden Hunger Across the Life Cycle



Bailey et al. *Ann Nutr Metab* 2015

2015 Dietary Guidelines Advisory Committee Underconsumed (Shortfall) Nutrients



	% <EAR
Potassium	97.0
Vitamin D	94.3
Choline	91.7
Vitamin E	88.5
Vitamin K	66.9
Magnesium	52.2
Calcium	43.0
Vitamin A	43.0
Vitamin C	38.9
Iron (women)	24.0
Folate	15.0
Fiber	95.0

2015 Dietary Guidelines Advisory Committee Underconsumed (Shortfall) Nutrients

USDA

Scientific Report of the
2015 Dietary Guidelines Advisory Committee

Advisory Report to the Secretary of Health and Human Services and the Secretary of Agriculture

"not of public health concern because their under-consumption has not been linked in the scientific literature to adverse health outcomes…"

First Print
February 2015

	% <EAR
Potassium	97.0
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~~Choline~~	~~91.7~~
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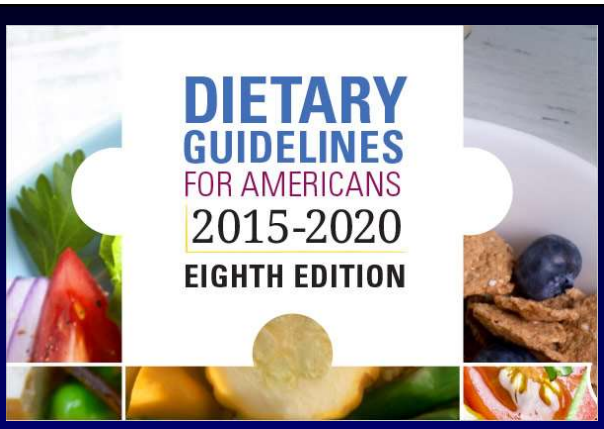

Although the majority of Americans consume sufficient amounts of most nutrients, some nutrients are consumed by many individuals in amounts below the Estimated Average Requirement or Adequate Intake levels. These include potassium, dietary fiber, choline, magnesium, calcium, and vitamins A, D, E, and C.

Healthy U.S.-Style Eating Pattern
Healthy Vegetarian Eating Pattern
Healthy Mediterranean-Style Eating Pattern

These healthy eating patterns are designed to meet the RDA and Adequate Intakes for essential nutrients, as well as AMDR set by the Food and Nutrition Board of the IOM. This eating pattern also conforms to limits set by the IOM or Dietary Guidelines for other nutrients or food components.

Theses patterns meet these standards for almost all nutrients.

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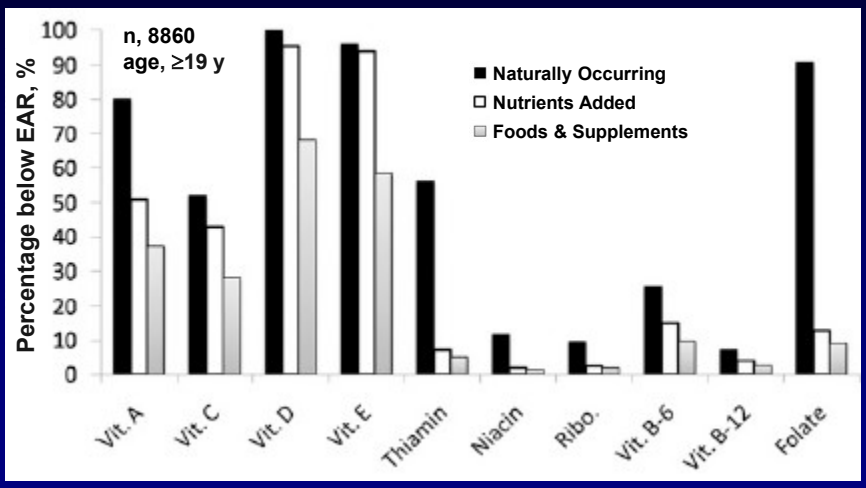
Theses patterns meet these standards for almost all nutrients. For a few nutrients (vitamin D, vitamin E, potassium, choline), amounts in the patterns are marginal or below the RDA or AI standard for many or all age-sex groups. In most cases, an intake of these nutrients below the RDA or AI is not considered to be of public health concern.

Where Do Americans Get Their Vitamins? Foods, Fortificants, and Supplements

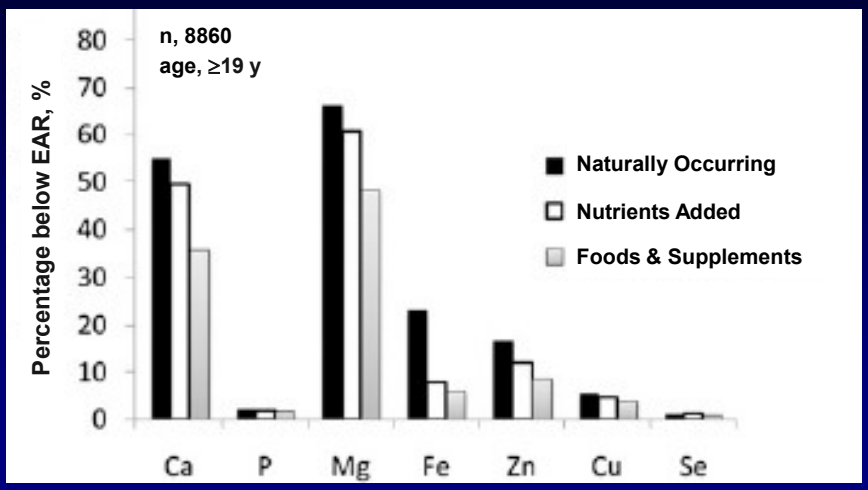
NHANES 2003-2006



Fulgoni et al. *J Nutr* 2011

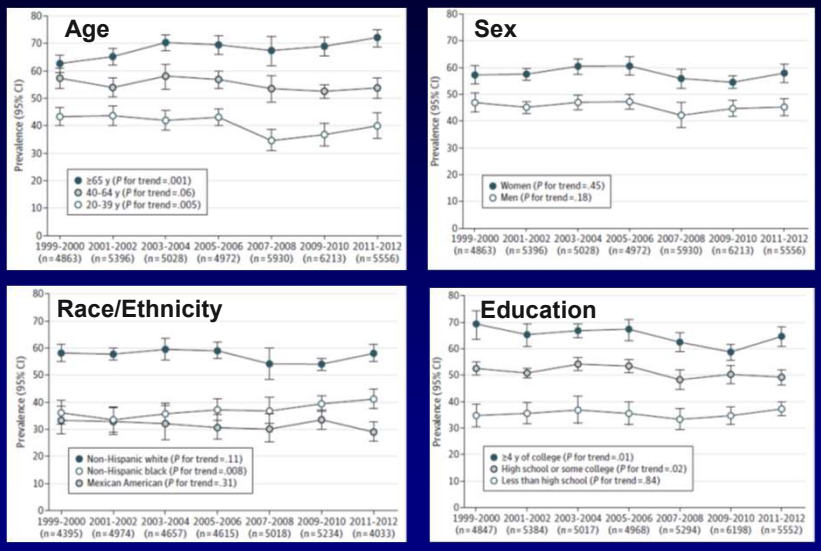
Where Do Americans Get Their Minerals? Foods, Fortificants, and Supplements

NHANES 2003-2006



Fulgoni et al. *J Nutr* 2011

Overall Use of Dietary Supplements Appears Stable: NHANES 1999-2012



Kantor et al. *JAMA* 2016

Trends in Use of MVMS Among Adults
NHANES 1999-2012

Year	n	30-d Prevalence of Use	95% CI
1999-2000	4862	37	35, 39
2001-2002	5396	38	35, 40
2003-2004	5028	38	36, 41
2005-2006	4972	40	38, 42
2007-2008	5930	33	30, 36
2009-2010	6213	32	31, 34
2011-2012	5556	31	29, 33

P Value for Trend <0.001

Kantor et al. *JAMA* 2016

EDITORIAL

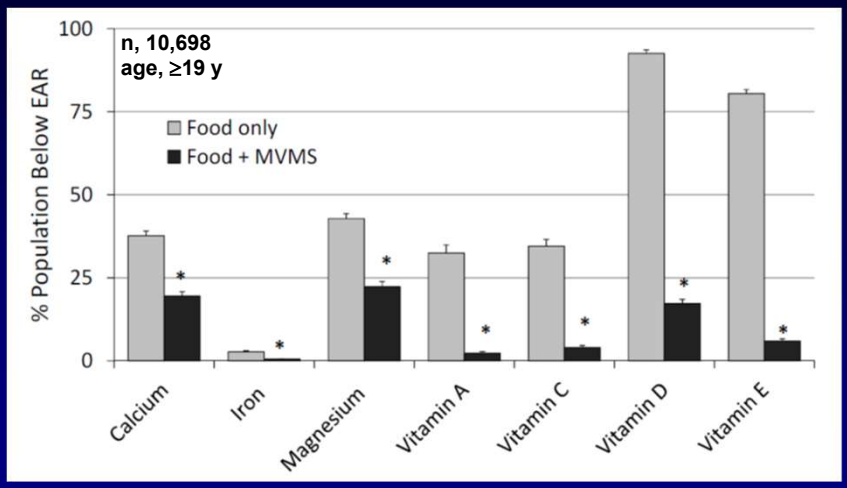
The Supplement Paradox
Negligible Benefits, Robust Consumption

For the majority of adults, supplements provide little, if any benefit. Why would consumers continue to use supplements after high-quality trials found many of these products to be no more effective than placebos?

Physicians can help remind patients that there is no benefit of obtaining vitamins from a pill rather than conventional food.

Cohen. *JAMA* 2016

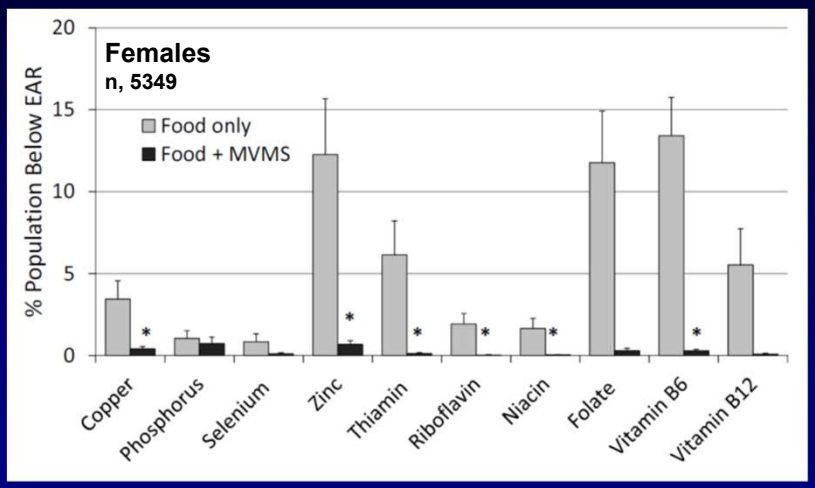
MVMS Reduce the Prevalence of Inadequacy for Underconsumed Nutrients
NHANES 2009-2012



Blumberg et al. *Nutrients* 2017

Inadequacy of Other Nutrients from Food and Food + MVMS

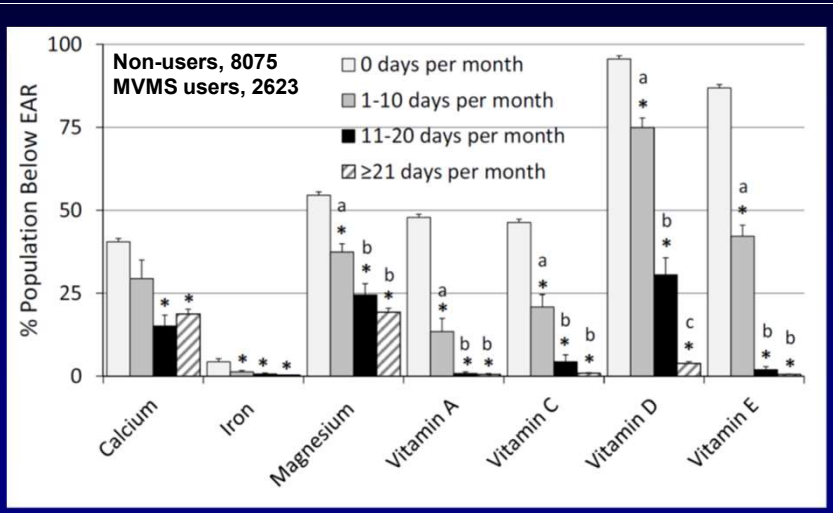
NHANES 2009-2012



Blumberg et al. *Nutrients* 2017

Inadequacy of Underconsumed Nutrients from Food and Food + MVMS by Frequency of Intake

NHANES 2009-2012



Blumberg et al. *Nutrients* 2017

Inadequacy of Other Nutrients from Food and Food + MVMS by Frequency of Intake

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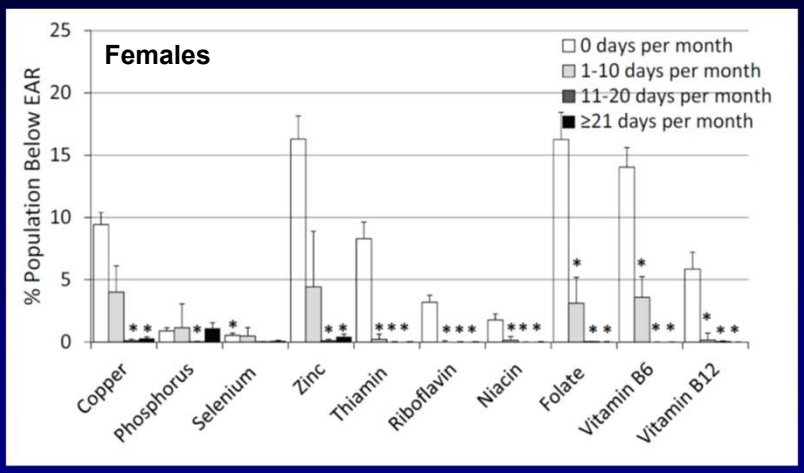
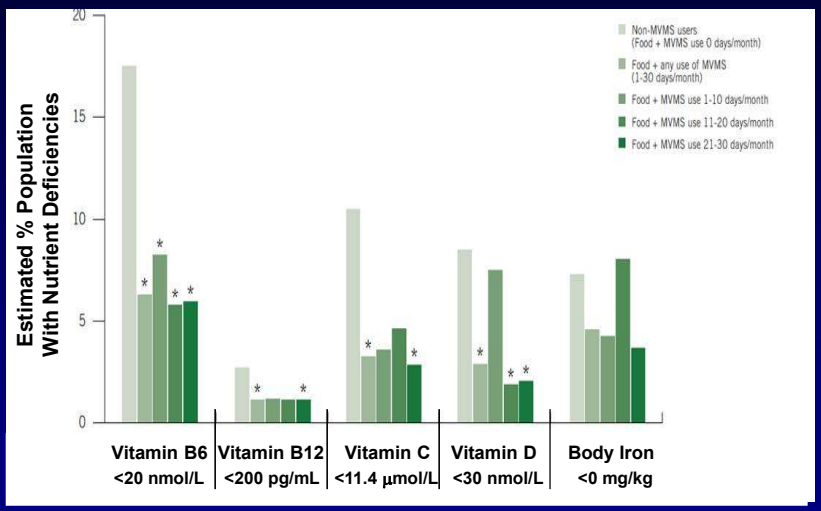


Blumberg et al. *Nutrients* 2017

MVMS Intake Frequency Reduces the Risk of Deficiency Based on Nutrient Status

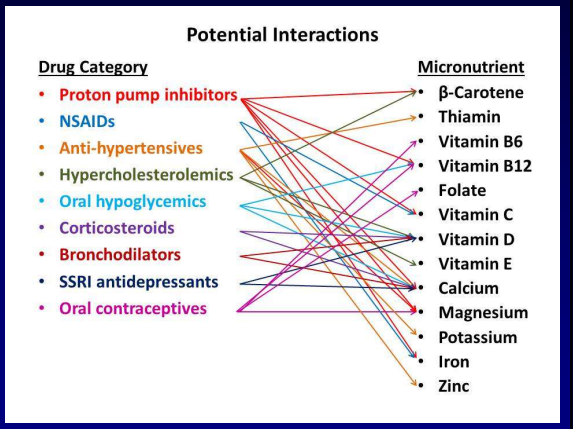
NHANES 2001-2012



Blumberg et al. *Nutrients* 2017

A Non-Food Cause of Hidden Hunger: Use of Rx Medicines

- 49.4% of ≥45 y took 1 to 4 drugs
- 39.7% of ≥65 y took ≥5 drugs

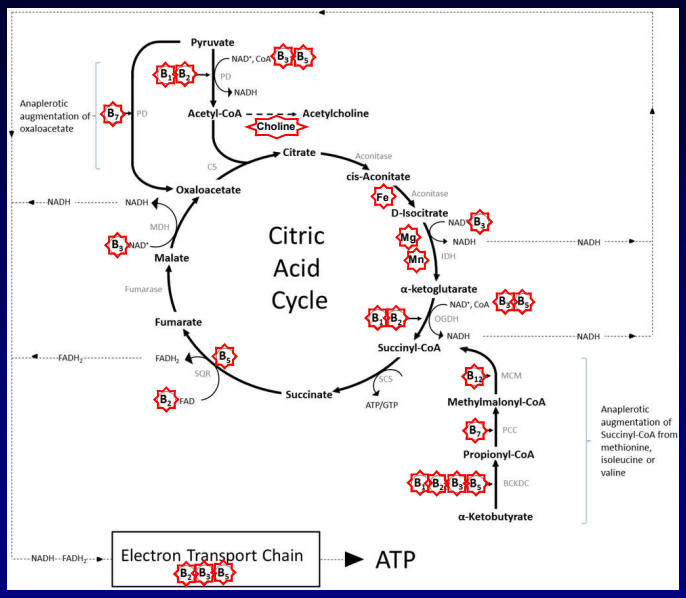


US DHHS CDC NCHS. Health United States 2013

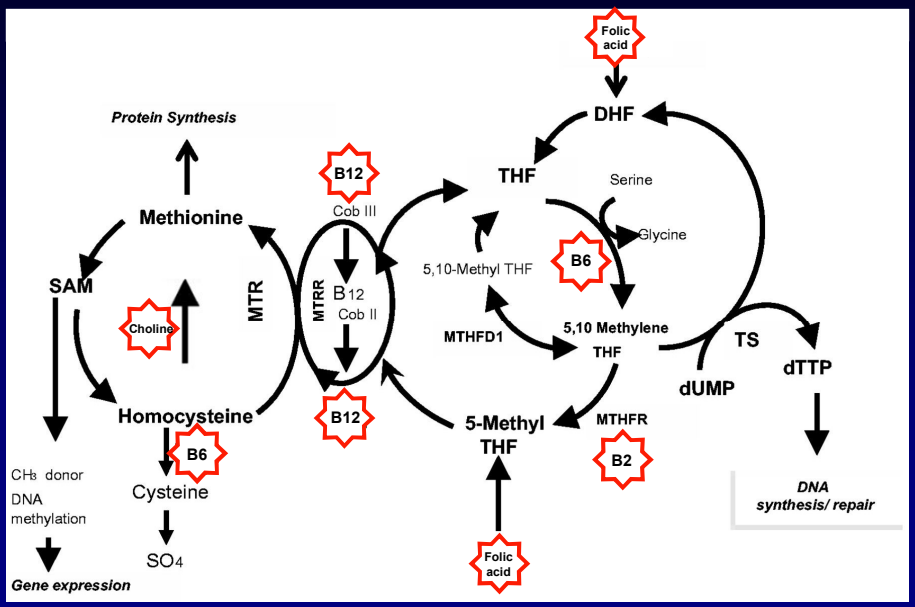
Functional and Health Consequences of Hidden Hunger

- Bone health: vitamins C, D, K; Ca, F, Mg, P
- Immune responsiveness: vitamins A, C, D, E; Fe, Se, Zn
- Cognitive performance: vitamins B12, C, D, E, choline; Ca, Mg, K
- Energy metabolism: vitamins B2, B6, B9, B12, C; Cu, Fe, P
- Blood pressure: vitamins C, D; Ca, Mg, K
- Oxidative stress: vitamins C, E; Cu, Mn, Se, Zn
- Epigenetic modification: vitamins B6, B9, B12, betaine, choline
- Hyperhomocysteinemia: vitamins B6, B9, B12, choline

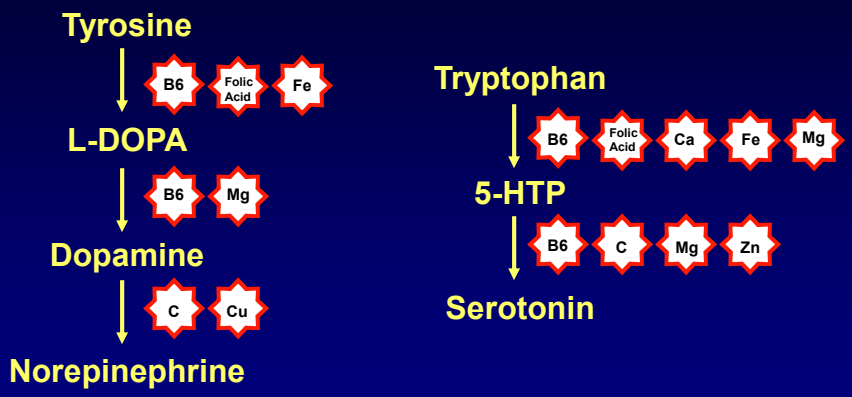
The Krebs (Citric Acid) Cycle



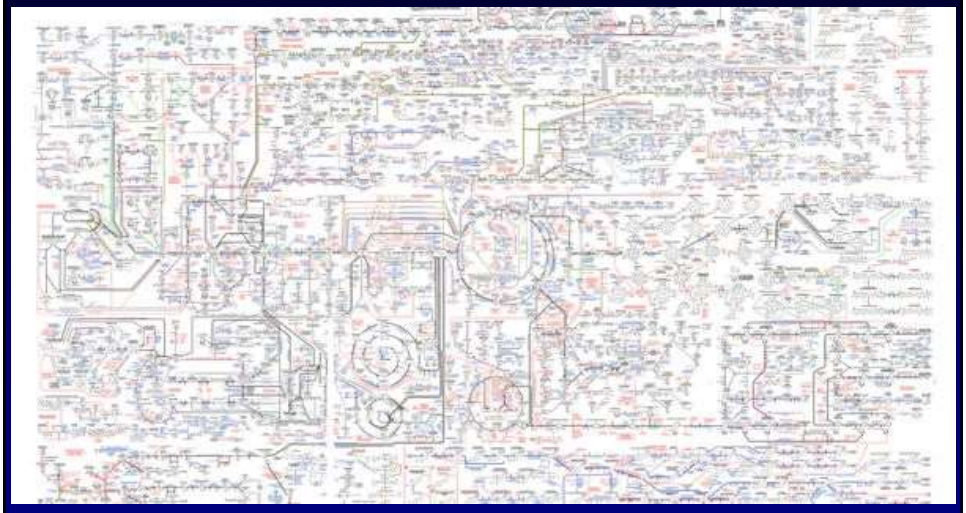
One Carbon Metabolism

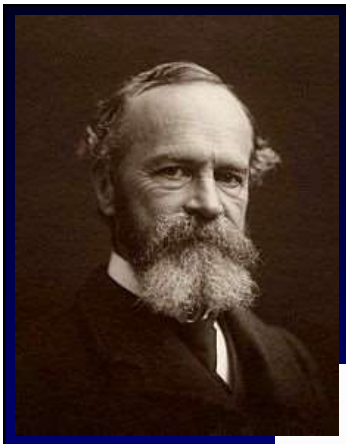


Neurotransmitter Synthesis



Metabolic Pathway of Life





A chain is no stronger than its weakest link, and life is after all a chain.

William James
1842-1910

Solving the Problem of Hidden Hunger

- Nutrition education

- Nutrition access

- Food enrichment

- Food fortification

- Dietary supplementation

Solving the Problem of Hidden Hunger

- Dietary supplementation ***advantages*** -

√ Rapid, reasonable, economic, and specific targeting of groups at risk for inadequacy

√ Increase nutrient intake and status but not calories

√ Massive changes in food supply are not required

√ May help reduce risk of some chronic diseases

√ Need some (but modest) nutrition educational efforts

Solving the Problem of Hidden Hunger

- Dietary supplementation ***limitations*** -

√ Cost to individual

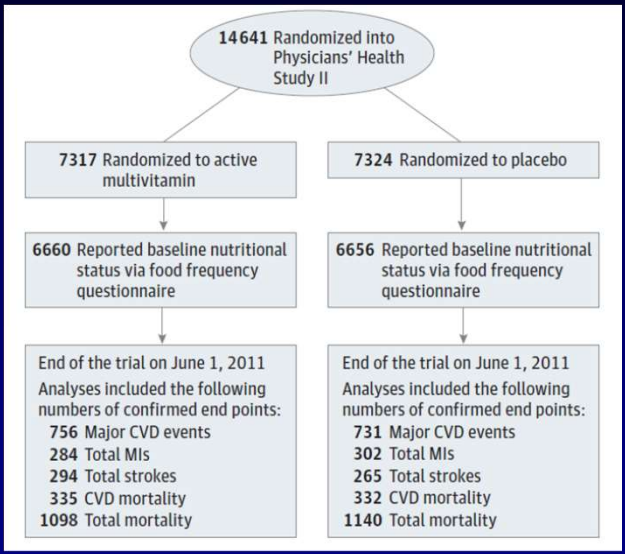
√ Volitional (adherence is required!)

√ Inability to reach some groups at risk

√ Some ingredients are difficult to formulate for technical or taste reasons

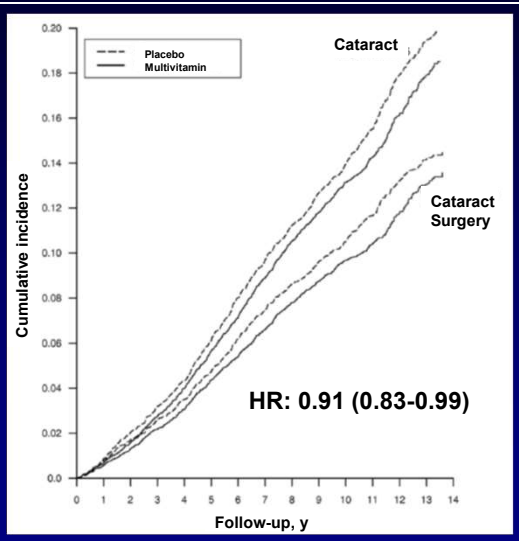
√ Need some (but modest) nutrition educational efforts

CONSORT Diagram of Men in the *Physician's Health Study II*



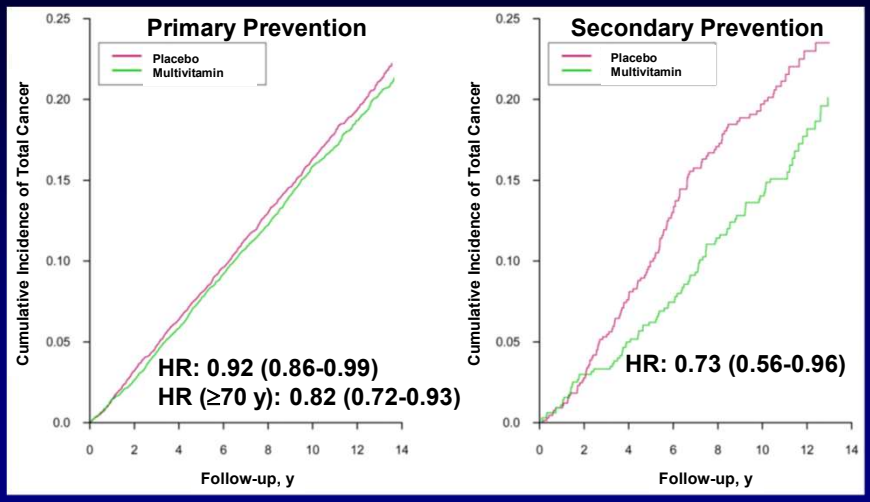
Rautiainen et al. *JAMA Cardiology* 2017

MVMS Reduce the Risk of Cataract and Cataract Surgery *Physician's Health Study II*



Christen et al. *Ophthalmology* 2014

MVMS Reduce the Risk of Total Cancer
Physicians' Health Study II



Gaziano et al. *JAMA* 2012

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Multiplicities in the Assessment of Multiple Vitamins

Is It Too Soon to Tell Men That Vitamins Prevent Cancer?

The PHS II study was a well-done, large-scale, blinded, randomized clinical trial with objective verification of cancer outcomes.

…the biological plausibility of the study hypothesis – that a multivitamin would be protective in a well-nourished population – is limited. This matters, because the chance that the study finding of a protective effect is true is intrinsically related (by Bayes theorem) to the plausibility of the hypothesis.

Bach and Lewis. *JAMA* 2012

EDITORIAL

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Multiplicities in the Assessment of Multiple Vitamins

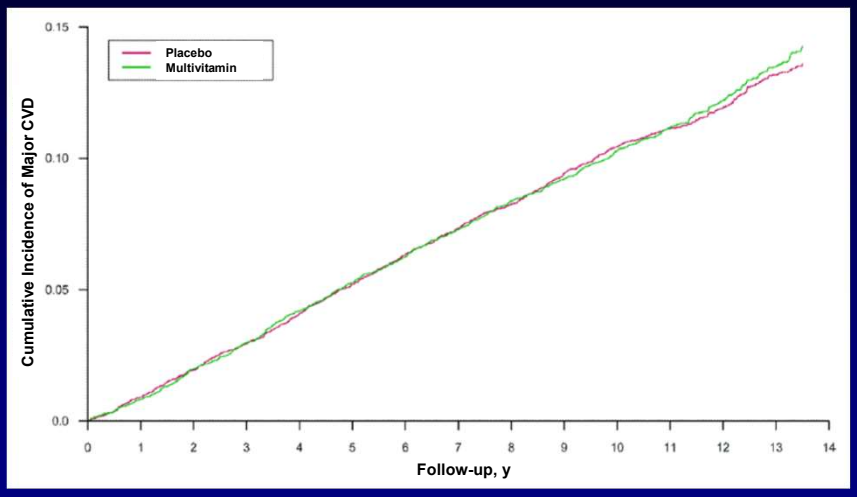
Is It Too Soon to Tell Men That Vitamins Prevent Cancer?

…Yet before drawing a definitive conclusion from this study that daily multivitamins reduce the risk of cancer in men, [we] must be convinced that the observed treatment effect is real and thus is likely to be reproduced in future experience, rather than a random event that is unlikely to recur.

Bach and Lewis. *JAMA* 2012

MVMS Do Not Reduce the Risk of Major Cardiovascular Events

Physician's Health Study II



Sesso et al. *JAMA* 2012

MVMS Reduces the Risk of Cardiovascular Disease in Men
Physicians Health Study I

Cardiac Revascularization (12.2 y F/U)			
n	No use: 1121	MVMS: 279	
HR (95% CI	1.00	0.86	0.75, 0.98

Ischemic Heart Disease (12.2 y F/U)			
n	No use: 1350	MVMS: 356	
HR (95% CI	1.00	0.89	0.79, 1.00

Major CVD Events (20 y F/U, self-report)			
n	No use: 1293	MVMS: 18	
HR (95% CI	1.00	0.56	0.24, 0.90

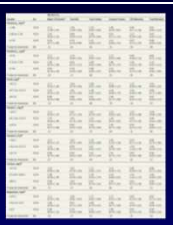
Rautianinen et al. *J Nutr* 2016

Effect of MVMS on Cardiovascular Disease: Prospective Cohort Studies

N	CVD	RR	95% CI	Reference
18,530	CVD	0.56	0.24-0.90	Rautiainen et al. *J Nutr* 2016
18,350	IHD	0.89	0.79-1.0	Rautiainen et al. *J Nutr* 2016
37,193	CAD	0.94	0.85-1.05	Rautiainen et al. *AJCN* 2015
21,132	MI	0.73	0.55-0.89	Rautiainen et al. *AJCN* 2010
381,553	IHD	0.82	0.71-0.94	Watkins et al. *Am J Epi* 2000
381,553	Stroke	0.81	0.67-0.98	Watkins et al. *Am J Epi* 2000
80,082	CHD	0.76	0.65-0.90	Rimm et al. *JAMA 1998*

MVMS Use and Baseline Nutrient Intake Have No Effect of CVD Events and Total Mortality

Physicians Health Study II



Except for

- Vitamin B6: total MI ($P_{interaction}$=0.01)
- Vitamin B12: CVD and total mortality ($P_{interaction}$=0.04)
- Vitamin D: CVD mortality ($P_{interaction}$=0.03)

"…a few potential exceptions that are more likely explained by chance and multiple testing…"

Rautiainen et al. *JAMA Cardiology* 2017

MVMS Use and Baseline Dietary Patterns Have No Effect on CVD Events and Total Mortality

Physicians Health Study II

		HR (95% CI)					
Variable	No.	Major CVD Events[a]	Total MIs	Total Strokes	Ischemic Strokes	CVD Mortality	Total Mortality
Alternate Healthy Eating Index[b]							
15.5 to <40.5	3391	1.15 (0.94-1.41)	1.09 (0.80-1.50)	1.34 (0.97-1.84)	1.36 (0.96-1.92)	0.96 (0.70-1.32)	0.95 (0.81-1.13)
40.5 to <49.5	3398	0.99 (0.80-1.21)	0.78 (0.57-1.06)	1.10 (0.78-1.56)	1.11 (0.77-1.62)	1.15 (0.84-1.58)	0.95 (0.80-1.13)
49.5 to 82.5	3606	0.96 (0.77-1.19)	0.88 (0.62-1.24)	0.98 (0.68-1.40)	0.90 (0.60-1.36)	0.97 (0.69-1.35)	1.04 (0.86-1.25)
P value for interaction	NA	.40	.32	.43	.33	.68	.74
Alternate Mediterranean Diet Score[b]							
0-2	3275	1.06 (0.86-1.30)	1.06 (0.76-1.48)	1.13 (0.81-1.57)	1.13 (0.80-1.60)	0.94 (0.69-1.27)	0.88 (0.75-1.03)
3-4	5114	1.02 (0.86-1.20)	1.03 (0.79-1.34)	1.04 (0.80-1.35)	1.07 (0.80-1.43)	0.99 (0.77-1.27)	1.05 (0.92-1.20)
5-9	4927	0.97 (0.82-1.15)	0.77 (0.59-1.00)	1.12 (0.85-1.49)	1.13 (0.82-1.56)	1.05 (0.82-1.35)	0.91 (0.79-1.05)
P value for interaction	NA	.81	.21	.89	.96	.84	.19

Rautiainen et al. *JAMA Cardiology* 2017

MVMS Use and Risk of Major CVD by Dietary Pattern: Trends

Physicians Health Study II

Tertile	Major CVD Events	Total MI	Total Stroke	Ischemic Stroke
AHEI 1	1.15	1.09	1.34	1.36
AHEI 3	0.96	0.88	0.98	0.90
AMEDS 1	1.06	1.06	1.13	1.13
AMEDS 3	0.97	0.77	1.12	1.13

Rautiainen et al. *JAMA Cardiology* 2017

MVMS Use and Risk of MI by Dietary Pattern in 3583 Men ≥70 y

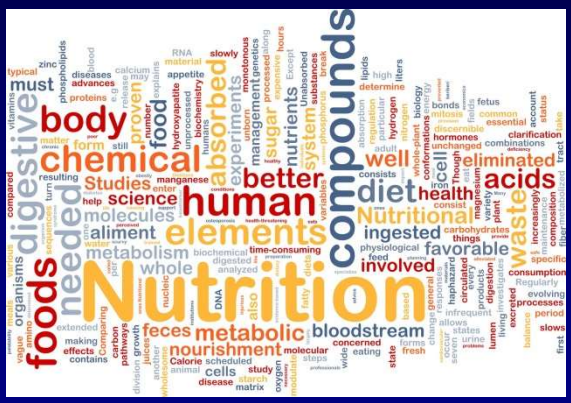
Physicians Health Study II

Diet Pattern	Tertile	HR	95% CI
AHEI	2	0.51	0.32-0.82
AMEDS	3	0.55	0.37-0.81

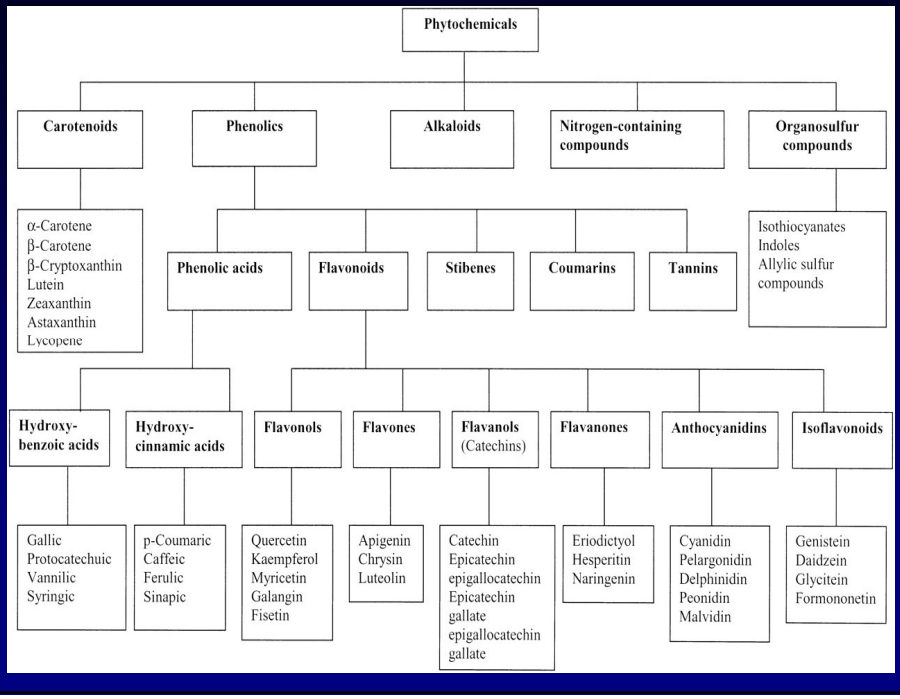
Rautiainen et al. *JAMA Cardiology* 2017

What About Dietary Bioactive Components?

Constituents in foods or dietary supplements, other than those needed to meet basic human nutritional needs, that are responsible for changes in health status



Office of Disease Prevention and Health Promotion, DHHS. *Fed Reg* 2004



Dietary Intake of Polyphenols in French Adults
SU.VI.MAX

Subclass	Mean intake mg/d/person	Main food contributors (%)
Flavanols	99 ± 116	tea (71), red wine (10), apples (6)
Flavonols	51 ± 28	tea (70), onions (23), spinach (13)
Flavones	33 ± 17	wheat flour (refined, 64; whole 20)
Flavanones	26 ± 29	oranges (50), OJ (44), red wine (3)
Anthocyanins	57 ± 47	red wine (41), cherries (23), strawberries (20)

Cohort XS
- n, 4942
- age, 45-60 y

Pérez-Jiménez et al. *Am J Clin Nutr* 2011

Anthocyanins Reduce the Risk of Incident Hypertension and Myocardial Infarction
Nurses Health Study II

n	87,242	93,600
Age, y	25-42	25-42
F/U, y	14	18
Q1 – Q5, mg/d	5.7-21.9	2.5-25.1

Quintile	iHT	MI
1	--	--
2	↓ 6%	↓ 20%
3	↓ 7%	↓ 29%
4	↓ 9%	↓ 15%
5	↓ 13%	↓ 32%
P_{trend}	*0.0001*	*0.047*

Cassidy et al. *Am J Clin Nutr* 2011 *Circulation* 2013

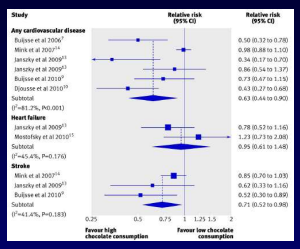
Proposed Criteria for a Bioactive to be Considered for Evaluation of DRI Framework

- Definition of the substance that is commonly used
- Method of analyzing the substance which is consistent with the definition
- Database of the amount of bioactives in foods
- Prospective cohort studies
- Clinical trials on digestion, absorption, activation, transport, and excretion of the substance
- Clinical trials on efficacy and dose-response
- Safety data at anticipated level of intake
- Systematic reviews and meta-analyses showing efficacy
- Plausible biological explanation for efficacy

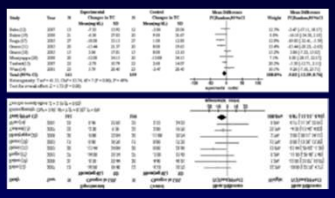
Lupton et al. *Eur J Nutr* 2014

Meta-analyses of Cocoa Flavanols

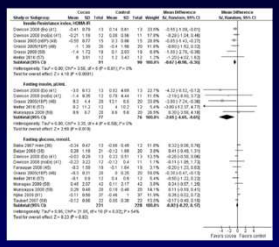
Cardiometabolic Disorders



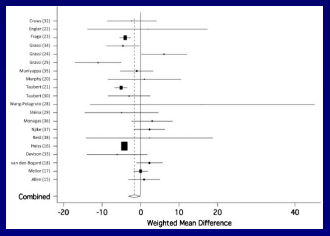
Total and LDL Cholesterol



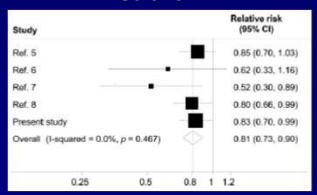
Insulin Sensitivity



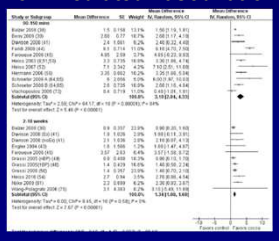
Systolic Blood Pressure



Stroke



Flow-Mediated Vasodilation



efsa
European Food Safety Authority

Scientific Opinion on the substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

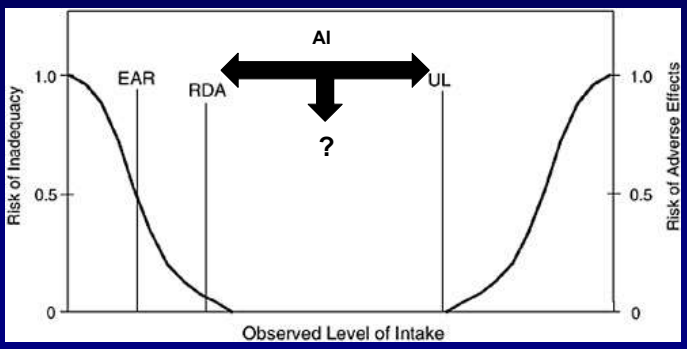
Cocoa flavanols help maintain endothelium-dependent vasodilation, which contributes to normal blood flow. In order to obtain the claimed effect, 200 mg of cocoa flavanols should be consumed daily. This amount could be provided by 2.5 g of high-flavanol cocoa powder or 10 g of high-flavanol dark chocolate, both of which can be consumed in the context of a balanced diet. The target population is the general population.

Agostoni et al. *EFSA J* 2012

Framework for Bioactive Reference Values

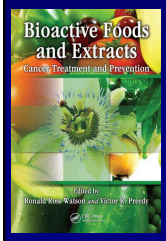
IOM framework – DRI: EAR, AI, RDA, UL
Codex framework – NRV

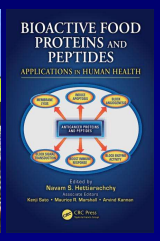
Adequate Intake: When sufficient evidence is not available to set an EAR, the AI is a goal for the intake of individuals. The AI is expected to cover the needs of most all people.

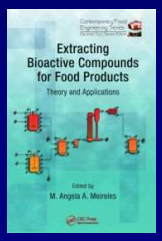


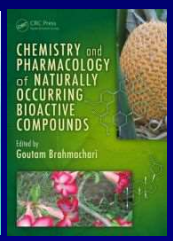
Accuse not Nature!
She has done her part;
Do Thou but Thine

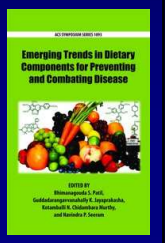
Milton, Paradise Lost 1667











Le mieux est
l'ennemi du bien

The perfect is
the enemy of the good

- Voltaire (François-Marie Arouet)
1694-1778