INTERNATIONAL SEMINAR

REPOSI 2015

Milan, Italy

24-25 September

TARGETING THE BURDEN OF POLYPHARMACY IN THE ELDERLY

The role of nutrition and nutraceuticals in older adults on polypharmacy: opportunities and concerns

UNIVERSITÀ CATTOLICA del Sacro Cuore

Graziano Onder
Centro Medicina dell'Invecchiamento
Università Cattolica del Sacro Cuore
Rome - Italy

Outline

- Nutrition and nutraceuticals (definition and effects)
- Opportunites → therapeutical effects of nutrition and nutraceuticals
- Concerns when used with drugs
  - →Interactions
  - → Regulations

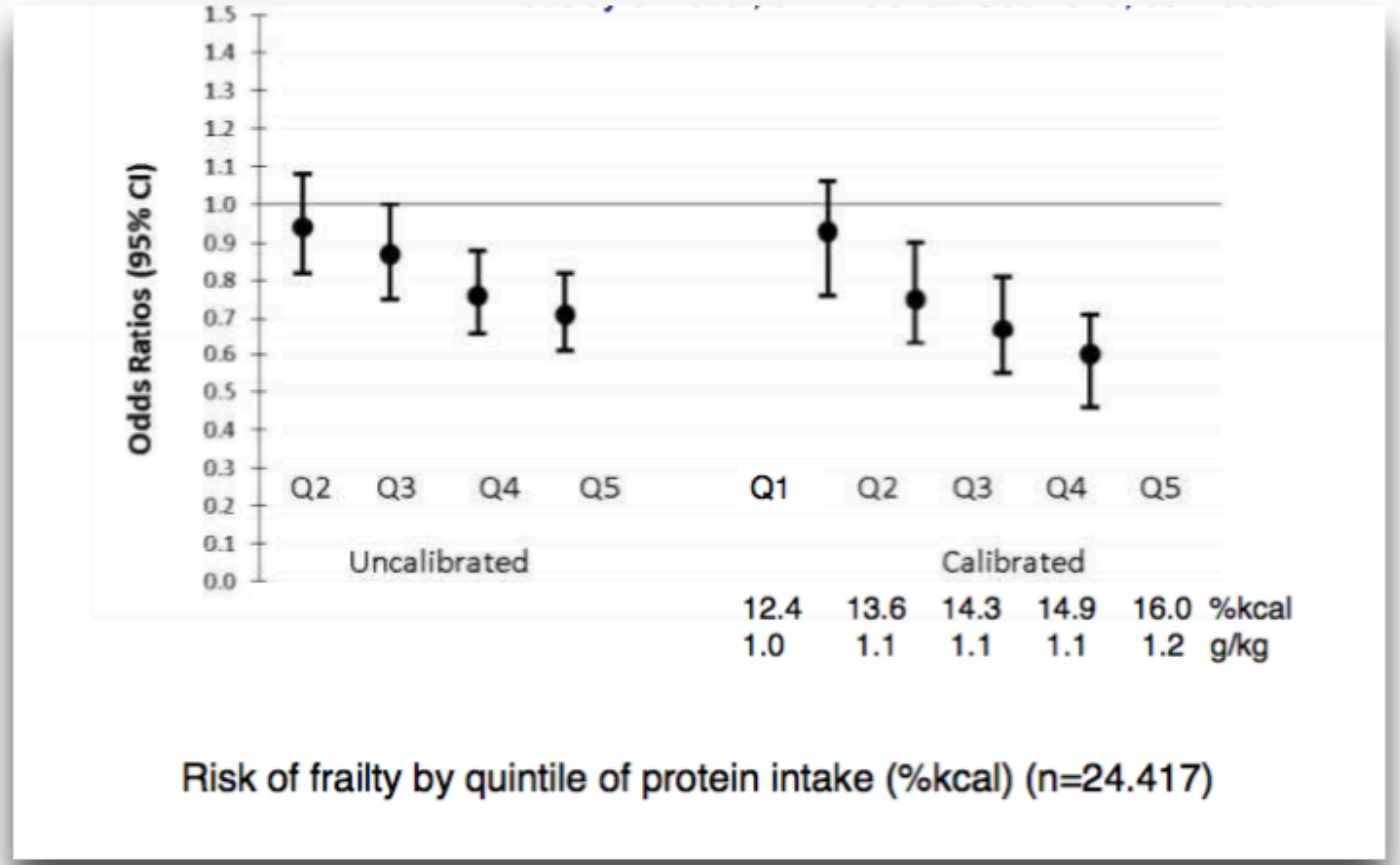
Outline

- **Nutrition and nutraceuticals (definition and effects)**

Beneficial effects of

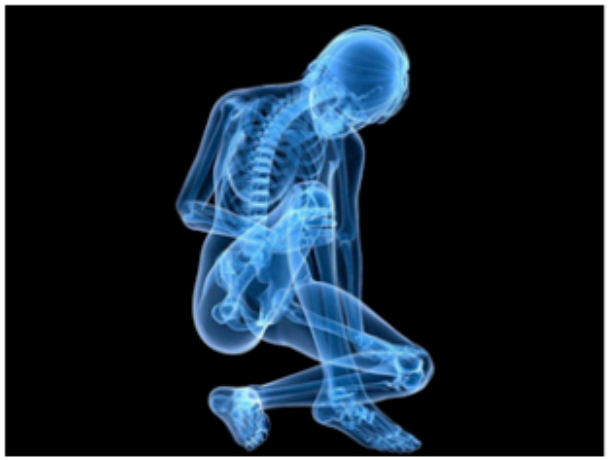
- Nutrition
  - ✓Proteins +

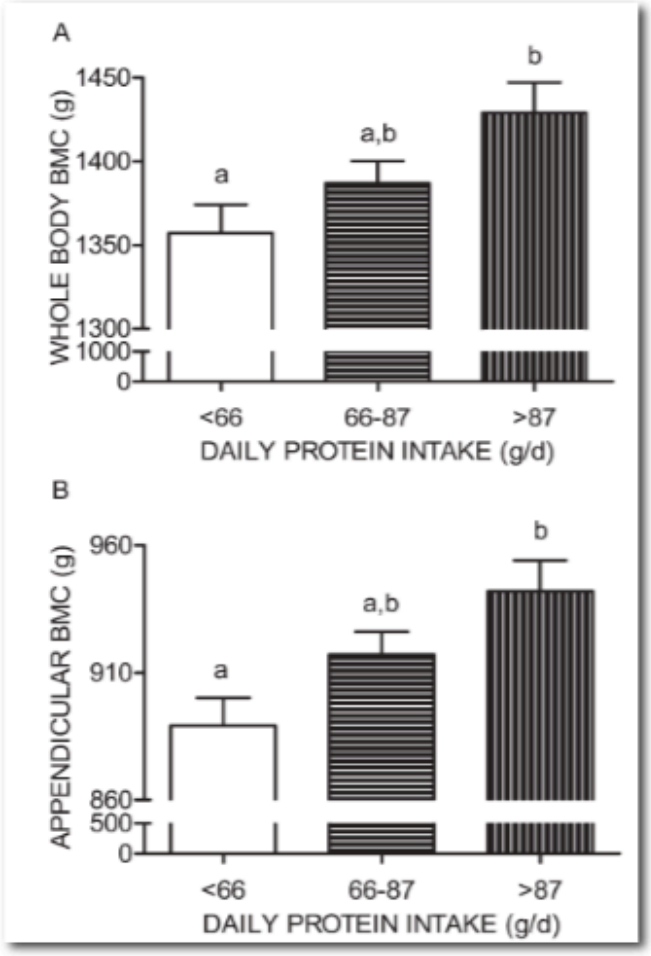
Reduced protein intake predicts incident frailty



Houston D K et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. Am J Clin Nutr 2008

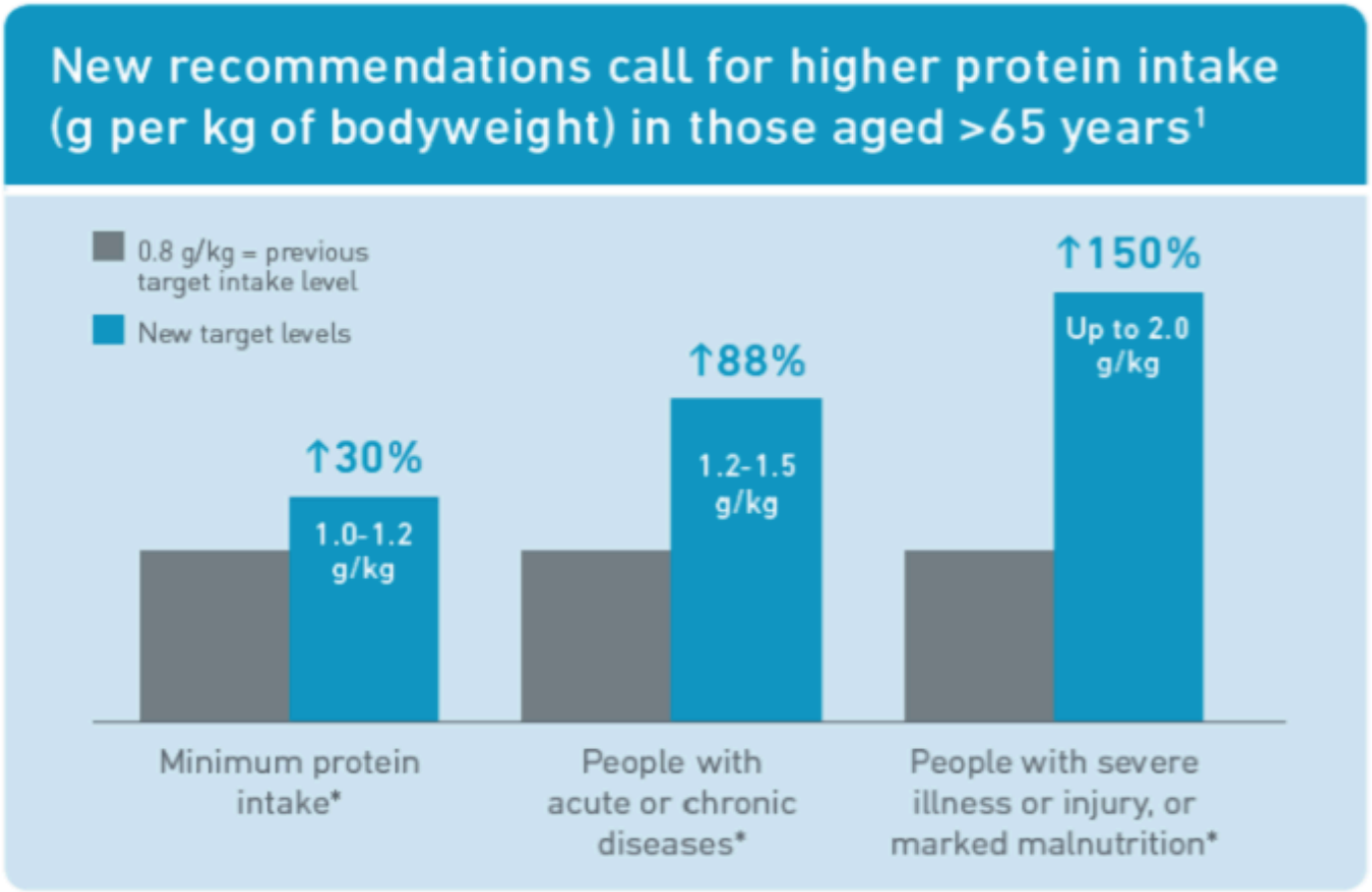
Low protein intake predicts low bone mass



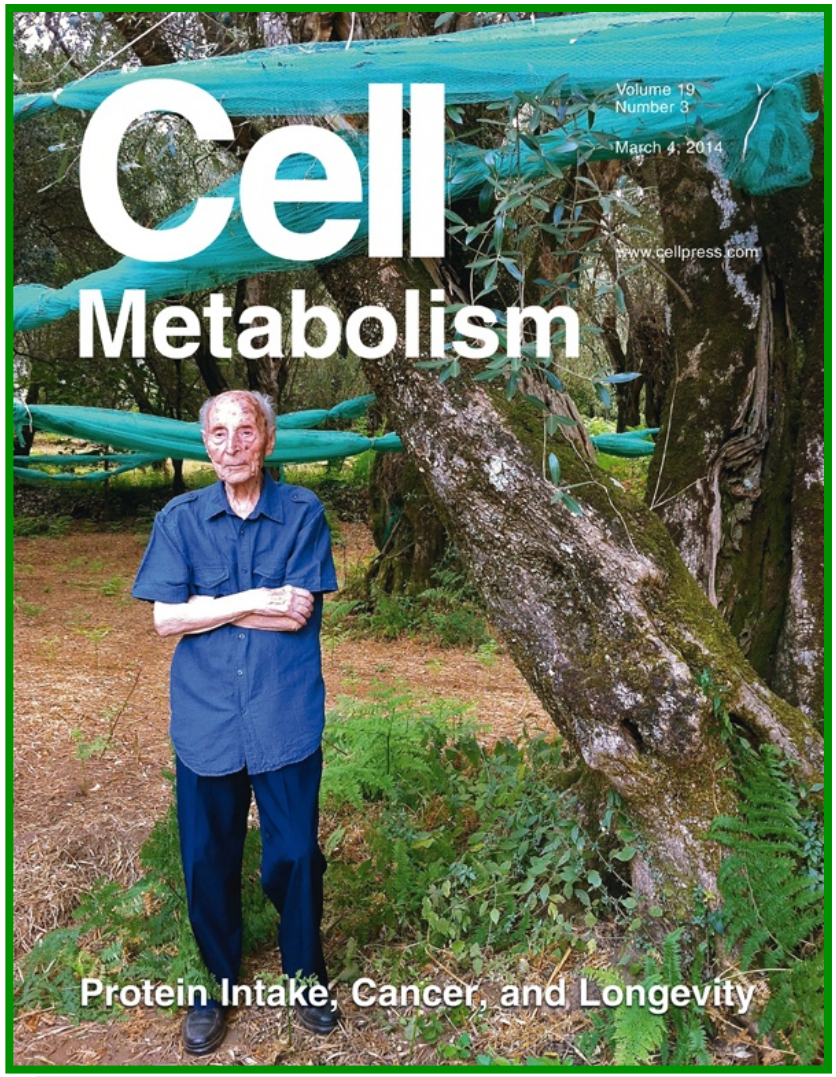


Meng X et al. A 5-year cohort study of the effects of high protein intake on lean mass and BMC in elderly postmenopausal women. J Bone Miner Res. 2009

PROT-AGE summary



*Caution needed among those with severe kidney disease (i.e. estimated Glomerular Filtration Rate <30mL/min/1.73m²), calculating their needs differently.



Low Protein Intake Is Associated with a Major Reduction in IGF-1, Cancer, and Overall Mortality in the 65 and Younger but Not Older Population

Morgan E. Levine,[1,11] Jorge A. Suarez,[1,2,11] Sebastian Brandhorst,[1,2] Priya Balasubramanian,[1,2] Chia-Wei Cheng,[1,2] Federica Madia,[1,3] Luigi Fontana,[4,5,6] Mario G. Mirisola,[1,2,7] Jaime Guevara-Aguirre,[8] Junxiang Wan,[1,2] Giuseppe Passarino,[9] Brian K. Kennedy,[10] Min Wei,[1,2] Pinchas Cohen,[1,2] Eileen M. Crimmins,[1] and Valter D. Longo[1,2,*]

Mice and humans with growth hormone receptor/IGF-1 deficiencies display major reductions in age-related diseases. Because protein restriction reduces GHR-IGF-1 activity, we examined links between protein intake and mortality. Respondents aged 50–65 reporting high protein intake had a 75% increase in overall mortality and a 4-fold increase in cancer death risk during the following 18 years. These associations were either abolished or attenuated if the proteins were plant derived. Conversely, high protein intake was associated with reduced cancer and overall mortality in respondents over 65, but a 5-fold increase in diabetes mortality across all ages. Mouse studies confirmed the effect of high protein intake and GHR-IGF-1 signaling on the incidence and progression of breast and melanoma tumors, but also the detrimental effects of a low protein diet in the very old. These results suggest that low protein intake during middle age followed by moderate to high protein consumption in old adults may optimize healthspan and longevity.

The Ratio of Macronutrients, Not Caloric Intake, Dictates Cardiometabolic Health, Aging, and Longevity in Ad Libitum-Fed Mice

Samantha M. Solon-Biet,[1,2,3,4,13] Aisling C. McMahon,[1,2,3,13] J. William O. Ballard,[5] Kari Ruohonen,[6] Lindsay E. Wu,[7] Victoria C. Cogger,[1,2,3] Alessandra Warren,[1,2,3] Xin Huang,[1,2,3] Nicolas Pichaud,[5] Richard G. Melvin,[8] Rahul Gokarn,[2,3] Mamdouh Khalil,[3] Nigel Turner,[9] Gregory J. Cooney,[9] David A. Sinclair,[7,10] David Raubenheimer,[1,4,11,12] David G. Le Couteur,[1,2,3,*] and Stephen J. Simpson[1,4,*]

Cell Metabolism *19*, 407–417, March 4, 2014

Beneficial effects of

- Nutrition
  - ✓Proteins +
- Nutraceuticals

THE FOUNDATION FOR INNOVATION IN MEDICINE

P.O. Box 1220, Mountainside, N.J. 07092
Telephone (908) 272-2967
www.fimdefelice.org

The NutraCeutical Revolution: Fueling a Powerful, New International Market

Stephen L. DeFelice, M.D.
Chairman
The Foundation for Innovation in Medicine

A nutraceutical is any substance that is a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease. Such products may range from isolated nutrients, **dietary supplements** and specific diets to genetically engineered designer foods, **herbal products**, and processed foods such as cereals, soups and beverages.

Trends in Food Science & Technology, February 1995, Vol. 6

Beneficial effects of

- Nutrition
  - ✓Proteins **+**
- Nutraceuticals
  - ✓Herbal supplements **+/-**

Herbal Medication – JAMA Patient Page

Medication	Disease	Effect
St John's wort	Depression	+
Cranberry	UTI	+
Echinacea	Cold	-
Ginseng	Memory	-
Gingko biloba	Dementia	-
Garlic	CV	-
Ginger	Nausea	-
Soy	Menopause	-

Onder G et al. Submitted

Beneficial effects of

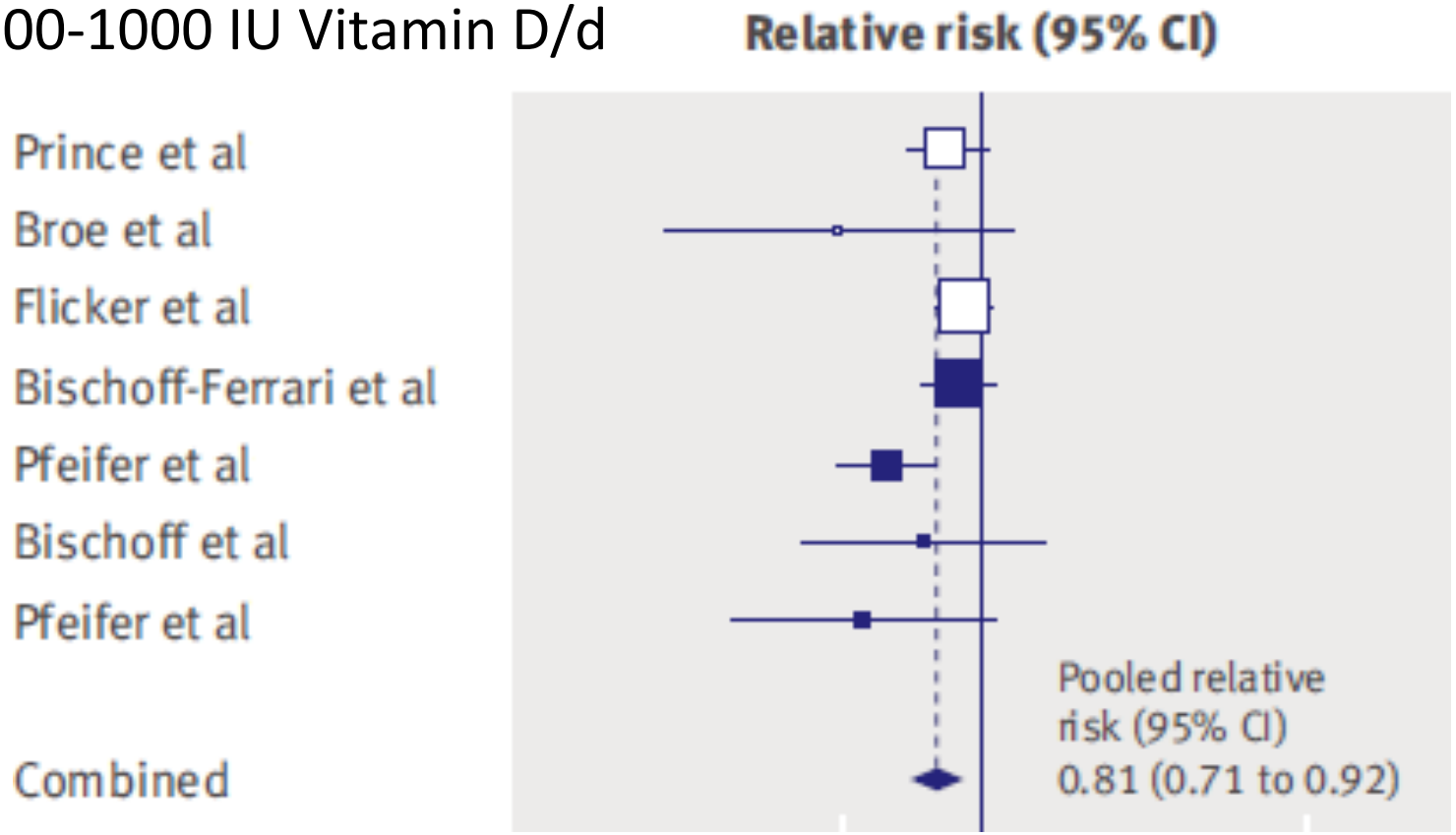
- Nutrition
  - ✓Proteins **+**
- Nutraceuticals
  - ✓Herbal supplements **+/-**
  - ✓Vitamins **+/-**

RCTs: Vitamin D and Physical Performance

Bischoff et al. 2003	122 ♀ 85,3 y NH	800 IU D3/d +Ca vs. Ca, p.o. 3 months	+ Strength M. quadriceps, Handgrip, TUG
Latham et al. 2003	243 ♀♂ 79,1 y Rehab	300000 IU D3 vs. Placebo, p.o. 3/6 months	- Strength M. quadriceps, TUG, Balance
Dhesi et al. 2004	139 ♀♂ 76,6 y Amb	600000 IU D2 vs. Placebo, i.m. 6 months	+ Physical performance, Reaction time, Body sway - Strength
Pfeifer et al. 2009	242 ♀♂ 77 y Amb	800 IU D3/d +Ca vs. Ca, p.o. 12 months	+ Strength M. quadriceps, TUG, Body sway
Zhu et al. 2010	302 ♀ 77 y Amb, VD deficient	1000 IU D3/d +Ca vs. Ca, p.o. 12 months	+ Strength hip extensor and adductor, TUG, Body sway

Meta-analysis: Prevention of falls

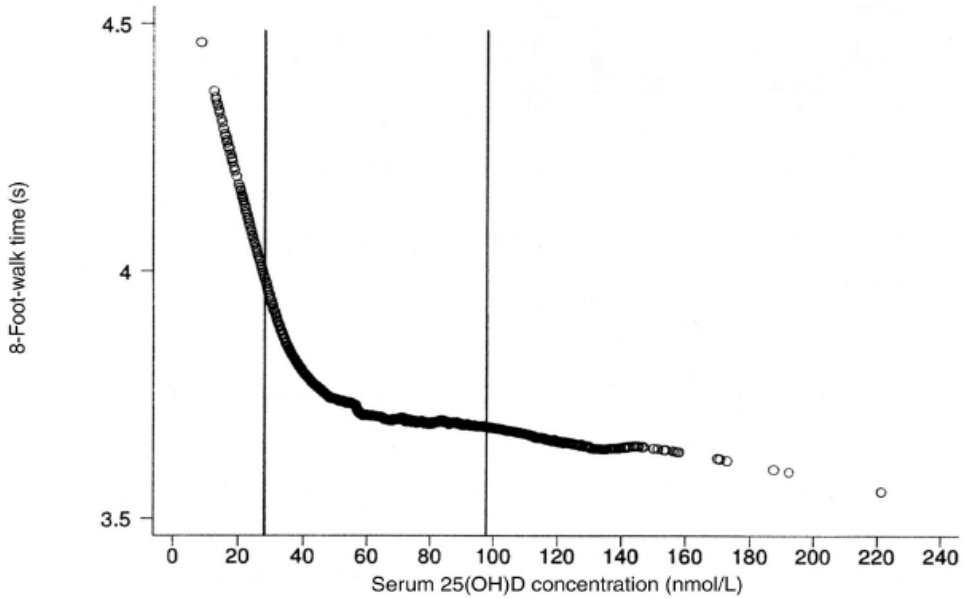
700-1000 IU Vitamin D/d



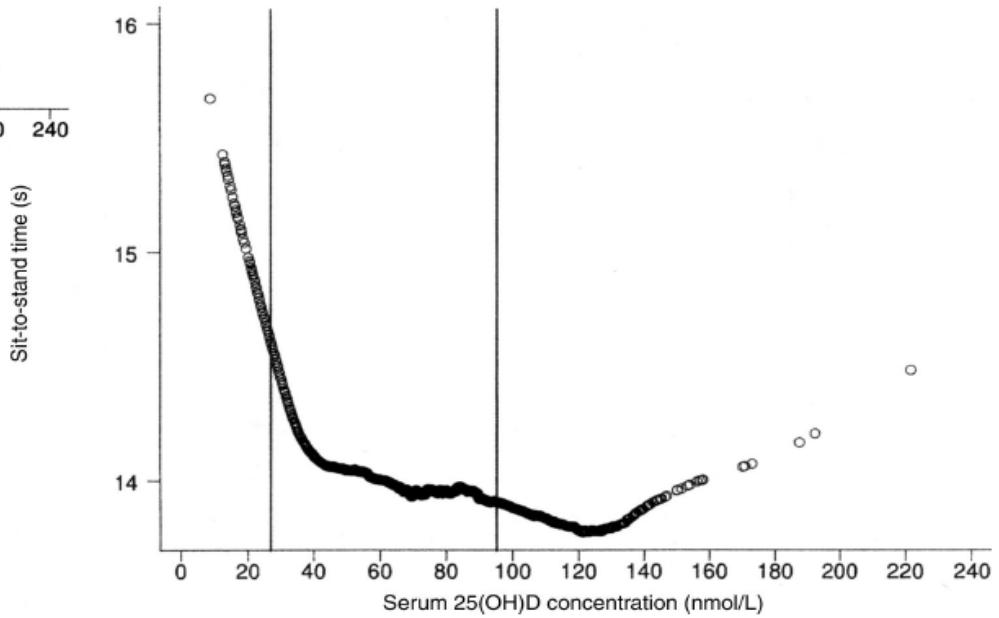
n=1921

Bischoff-Ferrari *et al.* BMJ 2009

Vitamin D – Optimal serum concentration



The most advantageous serum concentrations of 25(OH)D begin at 75 nmol/L (30 ng/mL), and the best are between 90 and 100 nmol/L (36–40 ng/mL).



Bishoff-Ferrari *et al.* AJCN 2006

Vitamin E and prostate cancer

	Placebo (n = 8696)	Vitamin E Alone (n = 8737)	Selenium Alone (n = 8752)	Vitamin E + Selenium (n = 8702)
No. of prostate cancers				
October 2008	416	473	432	437
July 2011	529	620	575	555
Hazard ratio, (99% CI)				
October 2008		1.13 (0.95-1.35)	1.04 (0.87-1.24)	1.05 (0.88-1.25)
P value		.06	.62	.52
July 2011		1.17 (1.004-1.36)	1.09 (0.93-1.27)	1.05 (0.89-1.22)
P value		.008	.18	.46
Absolute risk[a]	9.3	10.9	10.1	9.7
Gleason ≥7, No.	133	155	161	164
Hazard ratio (99% CI)		1.16 (0.86-1.58)	1.21 (0.90-1.63)	1.23 (0.91-1.66)
P value		.20	.11	.08

[a]Prostate cancers per 1000 person-years.

Klein EA et al. JAMA. 2011;306(14):1549-1556.

Beneficial effects of

- Nutrition
  - ✓Proteins **+**
- Nutraceuticals
  - ✓Herbal supplements **+/-**
  - ✓Vitamins **+/-**
  - ✓Antioxidants **-/?**
  - ✓Nutritional supplements **+/-**

Outline

- Nutrition and nutraceuticals (definition and effects)
- **Opportunites → therapeutical effects of nutrition and nutraceuticals**

Opportunities

Disease	Treatment
Sarcopenia/frailty	Proteins (leucine), vit D
Falls	vit D
Depression	St John's wort
Osteoporosis	vit D
UTI	Cranberry
Neuropathy	vit b12

Outline

- Nutrition and nutraceuticals (definition and effects)
- Opportunites → therapeutical effects of nutrition and nutraceuticals
- **Concerns when used with drugs**

→ **Interactions**

Older people are more susceptible to food-drug interactions

Physiological changes related to aging

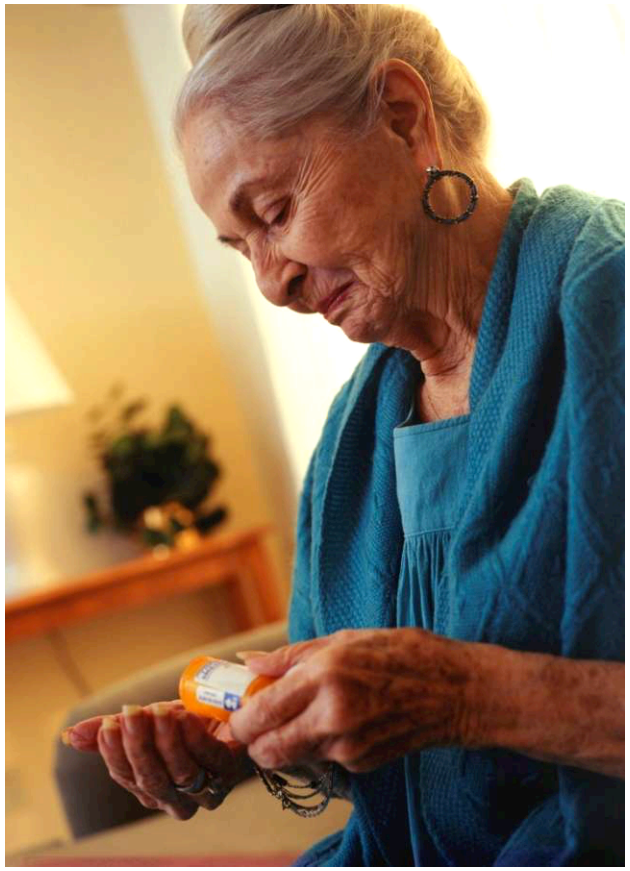
- Slowed metabolism
- Altered hepatic/renal function

Multi-morbidity and polypharmacy

Non-compliance/drug errors

Poor intake/nutritional status

Enteral or parenteral nutrition



Mariscal O, et al. *Feeding, Nutrition and Health in the Elderly*. Medical Publishers; 1999.

Interactions

- Drug alters nutrient absorption or has anti-nutrient effects
- Food changes drug's pharmacodynamic or pharmacokinetic properties

Interactions

- **Drug alters nutrient absorption or has anti-nutrient effects**
- Food changes drug's pharmacodynamic or pharmacokinetic properties

Polypharmacy and nutrition

- **Drug–nutrient interactions leading to decreased absorption of essential nutrients**

Drug use in Italy (n=15,931,642)

	% medication use in according to age group (years)									
Medication	All	65-69	70-74	75-79	80-84	85-89	90-94	≥94	**65-89**	**≥90**
Proton pump inhibitors	**40.9**	**34.1**	**39.6**	**44.5**	**47.6**	**47.0**	**42.2**	**18.9**	**41.3**	**37.3**
Platelet aggregation inhibitors	32.8	22.1	30.2	37.1	41.5	42.2	38.7	17.1	32.6	34.1
HMG CoA reductase inhibitors	26.1	24.5	29.2	30.9	28.5	21.6	12.1	2.6	27.4	10.1
Beta blocking agents, selective	19.7	17.3	20.2	22.2	22.6	20.4	15.4	5.0	20.3	13.2
Fluoroquinolones	19.2	17.3	19.3	20.6	21.1	20.4	18.8	9.1	19.5	16.7
ACE inhibitors, plain	17.9	14.5	17.1	19.3	21.1	21.2	19.2	8.3	18.0	16.9
Dihydropyridine derivatives	17.6	13.3	17.1	20.3	21.6	20.2	16.7	6.9	17.8	14.6
Combinations of penicillins	15.9	17.5	16.7	15.8	15.3	14.5	13.3	6.4	16.3	11.9
Angiot. II antagonists and diuretics	14.5	12.7	15.2	16.9	16.5	13.7	10.1	3.4	15.0	8.7
Propionic acid derivatives	14.3	14.0	15.2	15.9	15.1	12.8	10.1	4.1	14.8	8.8
Glucocorticoids	14.2	13.4	14.1	14.9	15.2	14.8	13.7	6.9	14.3	12.3
Sulfonamides, plain	13.9	6.1	9.2	14.1	20.3	25.7	27.6	14.3	13.0	24.8
Angiotensin II antagonists, plain	13.6	12.0	13.8	15.0	15.5	14.5	11.9	4.5	13.9	10.3
Acetic acid derivatives	12.9	12.2	13.6	14.6	14.0	11.9	9.3	3.8	13.3	8.2

Onder G et al. JAMDA in press

PPI and vitamin b12

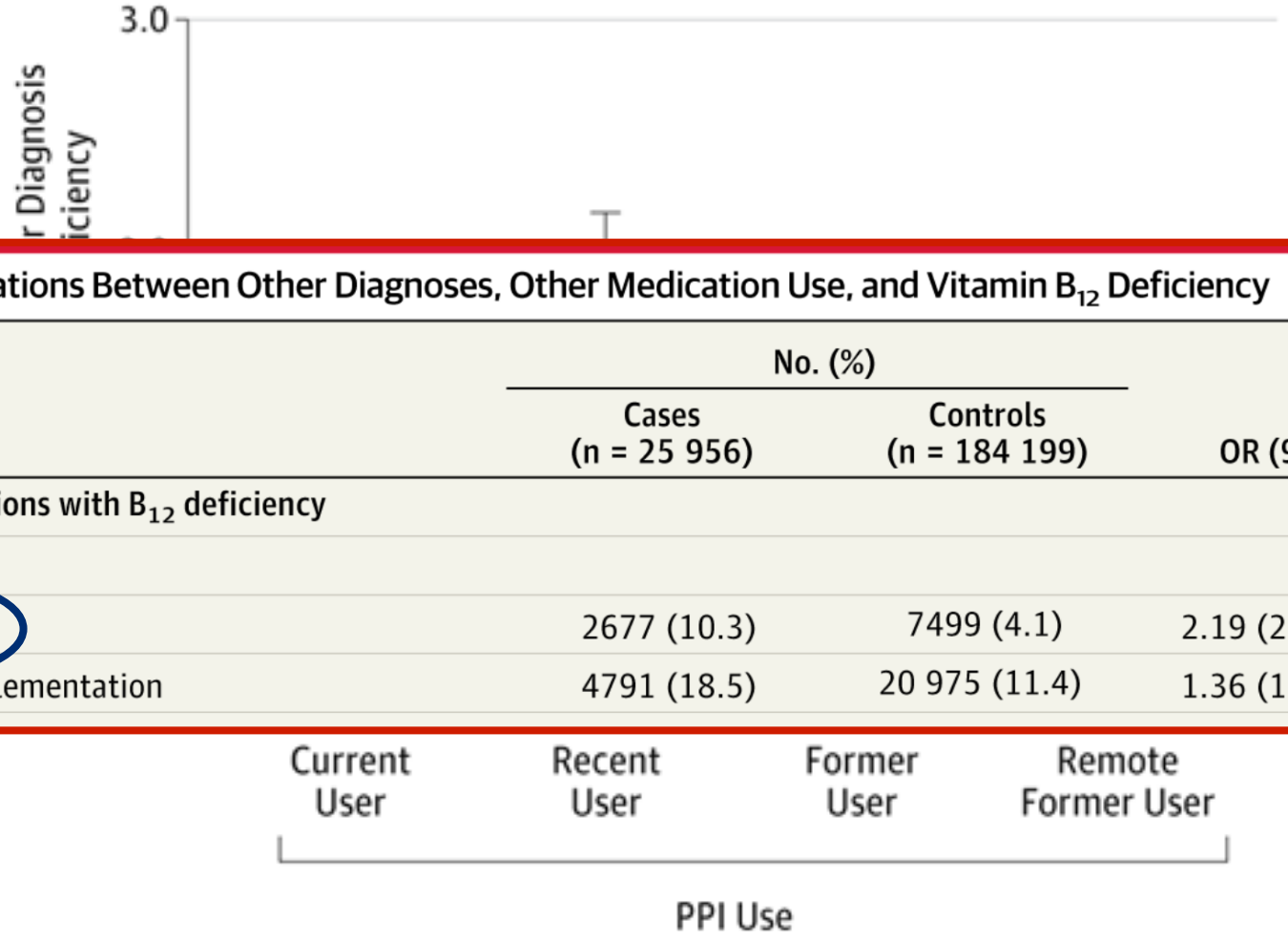


Table 4. Associations Between Other Diagnoses, Other Medication Use, and Vitamin B_{12} Deficiency

	No. (%)		
	Cases (n = 25 956)	Controls (n = 184 199)	OR (95% CI)[a]
Known associations with B_{12} deficiency			
Medications[b]			
Metformin	2677 (10.3)	7499 (4.1)	2.19 (2.06-2.33)
Thyroid supplementation	4791 (18.5)	20 975 (11.4)	1.36 (1.28-1.46)

Lam JR et al. JAMA. 2013;310(22):2435-2442

Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications

Ther Adv Drug Saf

(2013) 4(3) 125–133

DOI: 10.1177/2042098613482484

© The Author(s), 2013.
Reprints and permissions:
http://www.sagepub.co.uk/journalsPermissions.nav

Joel J. Heidelbaugh

Abstract: Proton pump inhibitors (PPIs) remain the superior choice worldwide in antisecretory therapy in the evidence-based treatment of upper gastrointestinal disorders including gastroesophageal reflux disease, erosive esophagitis, dyspepsia and peptic ulcer disease. PPI overutilization in ambulatory care settings is often a result of failure to re-evaluate the need for continuation of therapy, or insufficient use of on-demand and step-down therapy. Nonjudicious use of PPIs creates both preventable financial as well as medical concerns. PPIs have been associated with an increased risk of vitamin and mineral deficiencies impacting vitamin B_{12}, vitamin C, calcium, iron and magnesium metabolism. While these risks are considered to be relatively low in the general population, they may be notable in elderly and malnourished patients, as well as those on chronic hemodialysis and concomitant PPI therapy. No current evidence recommends routine screening or supplementation for these potential vitamin and mineral deficiencies in patients on either short- or long-term PPI therapy. Reducing inappropriate prescribing of PPIs can minimize the potential risk of vitamin and mineral deficiencies.

PPI and calcium

… stomach acid and the slightly acidic milieu of the proximal duodenum are required to free ingested calcium from the food matrix making it available for absorption. Without an acidic environment in the stomach and upper small bowel, *calcium may be retained in its food matrix preventing absorption*…

Insogna KL . Am J Gastroenterol 2009

Study	Type of study	No. of individuals	PPI–fracture association	
			Hip	Other sites
Yang et al. [58]	Case–control	13,556 cases; 153,386 controls	OR=1.44; 1.30–1.59	Not reported
Vestergaard et al. [59]	Case–control	124,655 cases; 373,962 controls	OR=1.45; 1.28–1.65	OR=1.60; 1.25–2.04 (spine); OR=1.18; 1.12–1.43 (any site)
Targownik et al. [98]	Case–control	15,792 cases; 47,289 controls	OR=1.62; 1.02–2.58[a]	OR=1.92; 1.16–3.18[a] (any site)
Yu et al. [55]	Prospective cohort study	721 PPI users; 10,373 controls	RH=1.16; 0.80–1.67 (women); RH=0.62; 0.26–1.44 (men)	RH=1.34; 1.10–1.64 (women, non-spine); RH=1.21; 0.91–1.62 (men, non-spine)
Roux et al. [99]	Cohort	61 PPI users; 1,150 controls	Not reported	RR=3.50; 1.14-8.44
Gray et al. [56]	Prospective cohort study	3,396 PPI users; 127,756 controls	HR=1.00; 0.71–1.40	HR=1.47; 1.18–1.82 (spine); HR=1.26; 1.05–1.51 (wrist); HR=1.25; 1.15–1.36 (total)
Corley et al. [60]	Case–control	33,752 cases; 130,471 controls	Yes[b]	Not reported
Yu et al. [61]	Meta-analysis	62,210 PPI users; 1,084,560	RR=1.30; 1.19–1.43	RR=1.56; 1.31–1.85 (spine); RR=1.16; 1.04–1.30 (any site)
Khalili et al. [62]	Prospective cohort study	5,341 PPI users; 74, 558 controls	HR=1.35; 1.13–1.62	Not reported
Fraser et al. [63]	Prospective cohort study[c]	261 PPI users; 9,162 controls	HR=1.52; 0.99–2.35	Adjusted HR=1.33; 1.15–1.56

Keller J et al. Osteoporosis Int 2013

Polypharmacy and nutrition

- Drug–nutrient interactions leading to decreased absorption of essential nutrients
- **Side-effects of various drugs may also affect the nutrient intake:**
  - **anorexia**
  - **gastrointestinal problems**

Drug-related anorexia

- Examples of drug-induced anorexia:
  - Amphetamine and methamphetamine
  - Antidepressants
  - **Metformin**
  - **Opiates**
  - MAOIs (tranylcypromine, moclobemide): fermented food
  - Orlistat: fat
  - Anti-vitamin effect: folate – methotrexate
  - **Ace inhibitors**

Heuberger RA. Drugs Aging. 2011;28:315-323.

Captopril-induced dysgeusia

SIR,—Captopril and other angiotensin-converting enzyme inhibitors are established for the treatment of hypertension, cardiac failure, and left ventricular dysfunction.[1,2] The most common adverse effects are headache, dizziness, fatigue, and cough. Dysgeusia is rare.[2,3] A patient is presented in whom oral administration of captopril-hydrochlorothiazide combination was associated with the development of severe dysgeusia, characterised by a repugnant sweet taste persisted for nearly 11 months. In this follow-up period the patient lost 27 kg of body weight. Oral administration of zinc was without effect, but selenium-methionine caused impressive improvement with disappearance of dysgeusia.

A 59-year-old man was admitted to another hospital in January, 1992, because of exertional dyspnoea and cough. He had smoked 20–40 cigarettes daily for forty years, and had been drinking 2–3 beers daily for 20 years. He weighed 92 kg, height 170 cm (body mass index 32). Clinical examination and lung function tests revealed obstructive bronchitis, left and right ventricular dysfunction on echocardiography, mild hypertension, and clinically silent alcoholic liver cirrhosis. He was discharged on captopril 25 mg with hydrochlorothiazide 25 mg (half a tablet twice daily), inhaled steroids, and bronchodilators. 12 days later he complained that stewed steak with red peppers tasted sweet. Over the following days, all food tasted nauseatingly sweet, and the patient, after checking the indications and adverse effects of captopril, discontinued therapy 19 days after starting. Despite withdrawal of captopril, sweet hypergeusia persisted for nearly 11 months. As a result the patient lost his appetite.

In November, 1992, he came to our hospital. He was treated as an outpatient with oral zinc sulphate heptahydrate 200 mg daily for 14 days without effect. A week later, selenium methionine 250 µg twice a day was started. 9 days later he was admitted for 2 days because of lack of appetite and weight loss. He weighed 65 kg (body mass index 22·5). Serum zinc (69·7 µg/dL) was low (normal 68–136), selenium was 95·2 µg/L (normal 70–130 µg/L). Laryngological examination excluded organic causes of persistent dysgeusia. 2 weeks after starting selenium methionine, he improved and a week later dysgeusia had disappeared. Recognition thresholds for the four basic tastes have remained normal, appetite has returned, and the patient regained 3 kg over 6 weeks.

In trials with many thousands of patients on captopril, the frequency of dysgeusia was 0·1–3%.[1,3] The effect appears to be dose-related and is associated with certain structural features of this drug, especially the sulphydryl group.[4,5] Zinc deficiency, reported in cirrhosis and chronic liver diseases,[6] may be a predisposing factor for chemosensory taste dysfunction. However, zinc therapy may provide no benefit in taste dysfunction,[7] as in our patient. In patients with alcoholic and non-alcoholic liver cirrhosis, selenium concentrations are reduced in serum and liver tissue.[8,9] The impressive improvement of repugnant sweet dysgeusia after oral selenium methionine suggests that selenium metabolism may be altered in taste dysfunction.

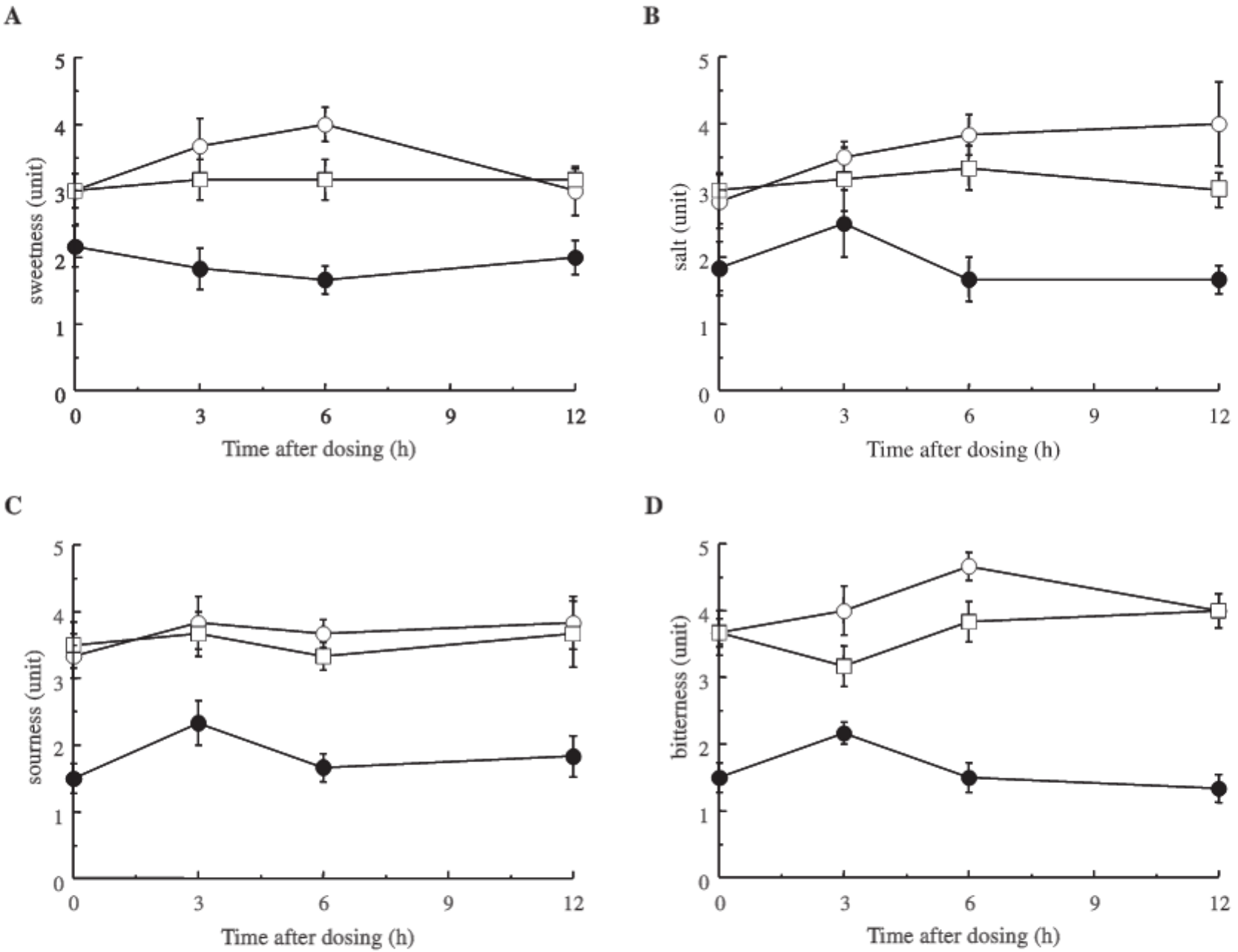
II Department of Medicine,
General Hospital Linz,
Linz 4020, Austria

JAN ZAZGORNIK
WILHELM KAISER
GEORG BIESENBACH

1. Pfeffer MA, Braunnwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. *N Engl J Med* 1992; **327:** 669–77.
2. The SOLVD investigators effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991; **325:** 292–302.
3. Brogden RN, Todd PA, Sorkin EM. Captopril: an update of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. *Drugs* 1988; **36:** 540–600.
4. Girard M. The safety of angiotensin-converting enzyme (ACE) inhibitors in moderate hypertension. *Adverse Drug React Toxicol Rev* 1991; **10:** 169–85.
5. Heel RC, Brogden RN, Speight TM, Avery GS. Captopril: a preliminary review of pharmacological properties and therapeutic efficacy. *Drugs* 1980; **20:** 409–52.
6. Halsted JA, Smith JC. Plasma zinc in health and disease. *Lancet* 1970; i: 322–24.
7. Deems DA, Doty RL, Settle RG, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch Otolaryngol Head Neck Surg* 1991; **117:** 519–28.
8. Dworkin BM, Rosenthal WS, Stahl RE, Panesar NK. Decreased hepatic selenium content in alcoholic cirrhosis. *Dig Dis Sci* 1988; **33:** 1213–17.
9. Thulurath PJ, Triger DR. Selenium in chronic liver disease. *J Hepatol* 1992; **14:** 176–82.

THE LANCET VOL 341: JUNE 12, 1993

Prevalence: 0.1-3%



● placebo ○ losartan □ perindopril

J Clin Pharmacol 2005;45:1319-1323

Drug-related anorexia

- Examples of drug-induced anorexia:
  - Amphetamine and methamphetamine
  - Antidepressants
  - **Metformin**
  - **Opiates**
  - MAOIs (tranylcypromine, moclobemide): fermented food
  - Orlistat: fat
  - Anti-vitamin effect: folate – methotrexate
  - **Ace inhibitors**

Polypharmacy

Heuberger RA. Drugs Aging. 2011;28:315-323.

Polypharmacy and nutritional status

	Nutrition (MNA-SF)		
	β (SE)	p-value	95%CI
Intercept	16.73 (1.39)	<0.001	13.98–19.47
Time of measuring			
2004	Ref.		
2005	−0.28 (0.11)	0.011	−0.50–(−0.06)
2006	−0.42 (0.11)	<0.001	−0.65–(−0.20)
2007	−0.37 (0.11)	0.001	−0.60–(−0.15)
Polypharmacy status			
Non-polypharmacy	Ref.		
Polypharmacy	−0.12 (0.13)	0.333	−0.37–0.13
Excessive polypharmacy	−0.62 (0.18)	0.001	−0.98–(−0.27)
Age	−0.04 (0.02)	0.016	−0.08–(−0.01)
Gender			
Female	Ref.		
Male	0.11 (0.16)	0.471	−0.20–0.42

Jyrkka et al. Pharmacoepidemiol Drug Saf 2011 May;20(5):514-22.

Polypharmacy and vitamins

Ann Nutr Metab. 2011;58(2):118-25. doi: 10.1159/000327351. Epub 2011 Apr 29.

Intake of medication and vitamin status in the elderly.

Fabian E[1]

⊕ Auth

Abstra

BACKG
This stu

METHO
determin
glutathio
RIA.

RESUL
and K, r
was, ho
per day
status o

CONCL
medicat
fulfilled.

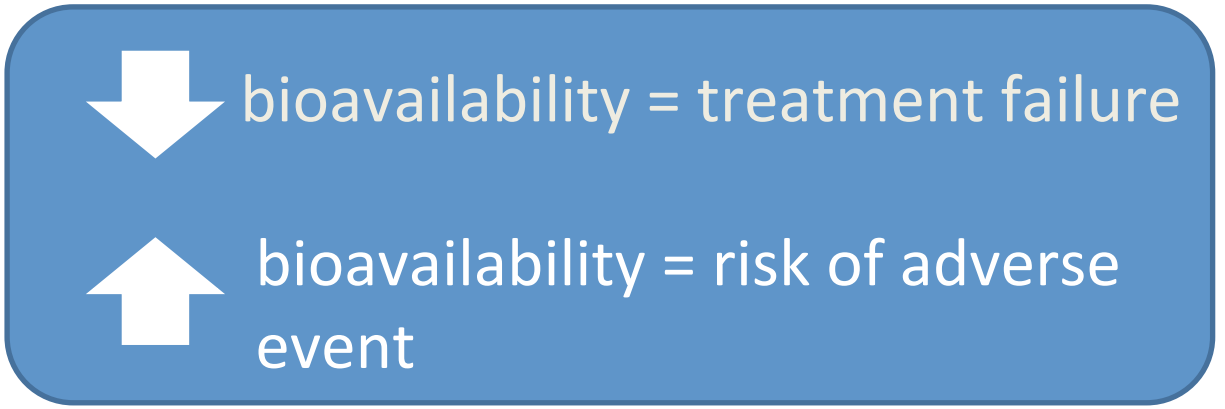
Parameter	Total (n = 102)	≤2 drugs per day (n = 56)	≥3 drugs per day (n = 46)
Fat-soluble vitamins			
Vitamin A, μmol/l[2]	2.2 ± 0.6	2.1 ± 0.5	2.3 ± 0.6
Vitamin E, μmol/l[3]	31 ± 8	30 ± 6	32 ± 10
Vitamin D, nmol/l	33 ± 13	36 ± 14*	29 ± 11
Vitamin K, nmol/l	0.60 ± 0.51	0.70 ± 0.53**	0.48 ± 0.45
Water-soluble vitamins			
Vitamin B_1, TPP effect[4], %	15 ± 7	15 ± 7	14 ± 6
Vitamin B_2, FAD effect[5], %	26 ± 12	27 ± 13	25 ± 11
Vitamin B_6, α-EGOT[6]	1.71 ± 0.26	1.64 ± 0.22*	1.78 ± 0.28
Folate, nmol/l	21 ± 18	23 ± 20**	16 ± 9
Vitamin B_{12}, pmol/l	183 ± 60	182 ± 63	184 ± 56
Vitamin C, μmol/l	70 ± 22	72 ± 22	68 ± 21

Interactions

- Drug alters nutrient absorption or has anti-nutrient effects
- **Food changes drug's pharmacodynamic or pharmacokinetic properties**

Pharmacokinetic interactions: LADME

- Food components can effect drug pharmacokinetics
  - Changing drug plasma concentration
  - Altering therapeutic activity
- Interaction occurs in any of the LADME processes
  - **L** (Liberation)
  - **A** (Absorption)
  - **D** (Distribution)
  - **M** (Metabolism)
  - **E** (Excretion)



1. Genser D. *Ann Nutr Metab.* 2008;52 Suppl. 1:29-32.
2. Schmidt LE, et al. *Drugs.* 2002;62:1481-1502.

Interactions: absorption

Food influence drug absorption

- Delay gastric emptying
- Increase motility
- Stimulate secretions
- Affect pre-systemic hepatic drug clearance

Food can influence drug bioavailability

- Casein and calcium present in milk decrease the absorption of ciprofloxacin and tetracycline
- Proteins can decrease absorption of L-DOPA

Laitinen K, et al. *Bone.* 2000;27:293-296.

Interactions: distribution

- Drugs bind plasma proteins post-absorption
- Drugs released from proteins at sites of action or metabolism
- Free-drug levels are high when:
  - Drug is displaced from plasma proteins (e.g., by food components)
  - Plasma protein levels are low (e.g., with malnutrition)

McCabe BJ, et al., eds. *Handbook of Food-Drug Interactions*. CRC Press; 2003.

Interactions: distribution

- When level of free-drug rises, drug activity is higher
- When interactions occur, a drug with a high plasma-protein binding rate and a narrow therapeutic index (NTI) poses high risk to patient
  - Anti-vitamin K
  - Anti-epileptic drugs
  - Digoxin
  - Lithium

Drug binding change + NTI = High risk

Body Composition and Drugs

- Older adults generally weigh less and have a smaller amount of water and a larger proportion of fat than younger adults.
- The amount of a drug concentration will often be much higher in an older adult than it would be if the same amount of the drug were given to a younger person.
- Drugs that concentrate in fat tissue may stay in the body longer because there is more fat for them to accumulate in.

Interactions: metabolism cytochrome system effects

- **Grapefruit juice**
  - Irreversible inhibitor of intestinal cytochrome P450 3A4
  - Increases the bioavailability, plasma concentration, and side effects of more than 85 drugs
    - e.g., simvastatin, lovastatin, atorvastatin, tacrolimus, cyclosporine, verapamil, felodipine, carbamazepine, triazolam, sildenafil

1. Bailey DG, et al. *CMAJ.* 2013;185:309-316.
2. Hanley MJ, et al. *Expert Opin Drug Metab Toxicol.* 2011;7:267-286.

Serious adverse events related to grapefruit–drug interaction

Serious adverse event	Drug	Amount of grapefruit consumed
Torsade de pointes	Amiodarone[18]	Juice, 1–1.5 L/d on a regular basis
	Quinine in tonic water[19]	Juice, high volume during preceding days
Complete heart block	Verapamil[20]	Juice, high volume during preceding days
Rhabdomyolysis	Atorvastatin[21,22]	Juice, 1–2 glasses/d for 5 d; juice from fresh grapefruit daily for 2 mo
	Simvastatin[23]	Whole fruit, 1 fruit/d for 2 wk
Nephrotoxicity	Tacrolimus[24]	Marmalade, 1.5 kg eaten during preceding 1 wk
Myelotoxicity	Colchicine[25]	Juice, 1 L/d for preceding 2 mo
Venous thrombosis	Ethinylestradiol[26]	Whole fruit, 1 fruit/d for breakfast for preceding 3 d

Bailey DG, et al. *CMAJ.* 2013;185:309-316.

Interactions

- Drug alters nutrient absorption or has anti-nutrient effects
- Food changes drug's pharmacodynamic or pharmacokinetic properties
- **Herbal medications**

Interactions – Herbal medications

Herb and drug(s)	Results of interaction	Comments
Betel nut (*Areca catechu*)		
Flupenthixol and procyclidine	Rigidity, bradykinesia, jaw tremor[5]	Betal contains arecoline, a cholinergic alkaloid.
Fluphenazine	Tremor, stiffness, akithesia[5]	
Prednisone and salbutamol	Inadequate control of asthma	Arecoline challenge caused dose-related bronchoconstriction in six asthma patients.[6]
Chilli pepper (*Capsicum* spp)		
ACE inhibitor	Cough[7]	Capsaicin depletes substance P.
Theophylline		
Danshen (*Salvia miltiorrhiza*)		
Warfarin		
Devil's claw (*Harpagophytum procumbens*)		
Warfarin		
Dong quai (*Angelica sinensis*)		
Warfarin	Increased INR[15,16] and widespread bruising[16]	Dong quai contains coumarins.
Eleuthero or Siberian ginseng (*Eleutherococcus senticocus*)		
Digoxin	Raised digoxin conce	
Garlic (*Allium sativum*)		
Warfarin	Incr d INR	
Ginkgo (*Ginkgo biloba*)		
Aspirin	Spontaneous hyphem	
Paracetamol and ergotamine/caffeine	Bilateral subdural ha	and subdural haematoma[27] have been reported with the use of ginkgo alone.
Warfarin	Intracerebral haemorrhage[28]	
Thiazide diuretic	Hypertension[18]	This effect may be an unusual adverse reaction to the drug or herb; ginkgo alone has not been associated with hypertension.
Ginseng (*Panax* spp)		
Warfarin	Decreased INR[29]	In rats, concomitantly administered ginseng had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin.[30]
Phenelzine	Headache and tremor,[31] mania[32]	Patient with mania also ingested bee pollen, and had previously had unipolar depression.
Alcohol	Increased alcohol clearance[33]	In mice, ginseng increases the activity of alcohol dehydrogenase and aldehyde dehydrogenase.
Guar gum (*Cyamopsis tetragonolobus*)		
Metformin, phenoxymethylpenicillin, glibenclamide	Slows absorption of digoxin, paracetamol, and bumetanide; decreases absorption of metformin, phenoxymethylpenicillin, and some formulations of glibenclamide[18]	Guar gum prolongs gastric retention.

Subarachnoid haemorrhage associated with *Ginkgo biloba*

Extracts of *Ginkgo biloba* and bleeding or haemorrhage

THE LANCET
FULL-TEXT ARTICLE

Herb and drug(s)	Results of interaction	Comments
Karela or bitter melon (*Momordica charantia*)		
Chlorpropamide	Less glycosuria[34]	Karela decreases glucose concentrations in blood.[35]
Liquorice (*Glycyrrhiza glabra*)		
Prednisolone	Glycyrrhizin decrease	
	increases AUC,[36] incr	
	concentrations predn	
Hydrocortisone	Glycyrrhetinic acid po	
	vasoconstrictor respe	
Oral contraceptives	Hypertension, oedem	
Papaya (*Carica papaya*)		
Warfarin	Increased	
Psyllium (*Plantago ovata*)		
Lithium	Decreased lithium co	
St John's wort (*Hypericum perforatum*)		
Paroxetine	Lethargy/incoherenc	
Trazodone	Mild serotonin syndr	
Sertraline	Mild serotonin syndr	
Nefazodone	Mild serotonin syndr	
Theophylline	Decreased theophylli	
Digoxin	Decreased AUC, dec	
	concentrations[46]	
Phenprocoumon	Decreased AUC[48]	
Cyclosporin	Decreased concentra	
Combined oral contraceptive (ethinyloestradiol and desogestrel)	Breakthrough bleedir	
Saiboku-to (Asian herbal mixture)		
Prednisolone	Increased prednisolo	
Shankhapushpi (Ayurvedic mixed-herb syrup)		
Phenytoin	Decreased phenytoin	
	seizure control[51]	
		effect of phenytoin.[51] Shankhapushpi is used to treat seizures.
Sho-saiko-to or xiao chai hu tang (Asian herb mixture)		
Prednisolone	Decreased AUC for prednisolone[50]	Contains liquorice (*Glycyrrhiza glabra*), *Bupleurum falcatum, Pinellia ternata, Scutellaria baicalensis, Zizyphus vulgaris, Panax ginseng,* and *Zingiber officinale.*
Tamarind (*Tamarindus indica*)		
Aspirin	Increased bioavailability of aspirin[52]	Tamarind is used as a food and a medicine.
Valerian (*Valeriana officinalis*)		
Alcohol	A mixture of valepotriates reduces adverse effect of alcohol on concentration[53]	
Yohimbine (*Pausinystalia yohimbe*)		
Tricyclic antidepressants	Hypertension[54]	Yohimbine alone can cause hypertension, but lower doses when combined with tricyclic antidepressants. Effect is str than normotensive individuals.[55]

Given the widespread use of hypericum extracts,[1,2] the implications of the emerging evidence of adverse reactions are potentially serious. In many countries such as the USA, UK, and Sweden, extracts of St John's wort are marketed as food supplements. Even though the interaction data are preliminary, attention to three precepts seem prudent. First, doctors should be aware that administration (or discontinuation) of hypericum extracts may significantly affect blood concentrations of many prescribed medicines. Second, patients must be encouraged to discuss their use of herbal remedies with their physician, and the prevalent misconception that natural always equates with harmless must be effectively refuted. The mass media have an important responsibility in this respect. Third, regulatory bodies should perhaps take a fresh look at whether herbal medicines need regulation, since the perception of "risk free" may reflect incomplete understanding.

THE LANCET
FULL-TEXT ARTICLE

U.S. Department of Health & Human Services | National Institutes of Health

NIH National Center for Complementary and Integrative Health

NIH...Turning Discovery Into Health

Search

Follow NCCIH

Home | Health Info | Research | Grants & Funding | Training | News | About NCCIH

Cranberry

Common Names: cranberry, American cranberry, bog cranberry
Latin Name: *Vaccinium macrocarpon*

© Steven Foster

On this page:

- What the Science Says
- Side Effects and Cautions
- For More Information
- Key References

Download PDF
Health Topics A–Z
Medical Dictionary

SHARE THIS PAGE:

1 Like

There are some indications that cranberry should be used cautiously by people who take blood-thinning drugs (such as warfarin), medications that affect the liver, or aspirin.

https://nccih.nih.gov/health/herbsataglance.htm

Outline

- Nutrition and nutraceuticals (definition and effects)
- Opportunites → therapeutical effects of nutrition and nutraceuticals
- Concerns
  - →Interactions
  - → **Regulations**

THE SUPPLEMENT SLEUTH

Some dietary supplements are spiked with drugs. Pieter Cohen is out to expose the hazards

53%
of U.S. adults report taking at least one dietary supplement.

34%
of U.S. adults report taking both a dietary supplement and a prescription medication.

18%
of U.S. adults report taking at least one natural product (not including vitamins and minerals).

$36 billion
The amount that Americans spend a year on dietary supplements

Tainted supplements

Prescription and illegal drugs are routinely found in supplements. Here's a sampling of more than 50 culprits from 2015.

PRODUCT NAME	CATEGORY	HIDDEN INGREDIENT
Smart Lipo	Weight loss	Sibutramine (a withdrawn weight loss drug); phenolphthalein (unapproved laxative ingredient)
Xcel	Weight loss	Fluoxetine (brand name Prozac)
Extreme Diamond 3000	Sexual enhancement	Desmethyl carbodenafil (unapproved, structurally similar to Viagra's active ingredient)
King of Romance	Sexual enhancement	Sildenafil (brand name Viagra)
Asihuri Plus Forte	Joint and nerve pain	Dexamethasone a (corticosteroid); phenylbutazone (discontinued NSAID)

SCIENCE Aug 21, 2015 • VOL 349 ISSUE 6250

Conclusions

- Nutrition and nutraceuticals can represent a valuable treatment for several conditions
- They might also have negative health effects, including drug interactions

“natural” does not always mean “safe”

- Drug use may impact on nutritional status
- Nutritional status should always be evaluated before prescribing