Vitamin D Deficiency and The Use of Supplements

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Disclosures

There are no financial relationships
or ties to industry
in relation to this presentation

Learning Objectives

- By the end of the session, participants will:
  - Understand the prevalence of vitamin D deficiency and the role for vitamin D in organ and system function, and disease states
  - Understand the assessment of vitamin D status and management of deficiency
  - Understand the prevalence of supplement use, misuse, benefits and harms

Vitamins: Hype or Real?

- Over past 30 years research has explored the use of nutritional supplements in the prevention of cancer, CVD, depression, DM, falls and other disorders
- Vitamin D has been seen as a strategy to prevent cancer and CVD, besides its perceived benefits for musculoskeletal health
- Several supplements consumed include vitamins C, D, B12, folic acid, beta- carotene, lycopene and others
- MVT mineral supplements: beneficial or misused?

Barry E L et al. Vitamin D as cancer therapy? JAMA.2019;321:1354-5

Manson JE, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Eng J Med. 2019;380:33-44

Vitamin D Screening and Supplementation in Primary Care

- Physicians and patients believe that identifying and correcting vitamin D deficiency improves health outcomes
- From 2000 to 2010 the volume of serum 25(OH)D tests reimbursed by Medicare Part B has increased 83 fold
- In 2000, four out of 1000 US Adults 70 and older reported taking daily vitamin D of 1000 IU, versus four of 10 in 2014: a 100 fold increase
- Further, physicians may misinterpret serum 25(OH)D levels of 20-30 ng/ml as representing a deficiency
- Kenneth W Lin. Am Fam Physician. 2018;97:226-7

Vitamin D Screening and Supplementation in Primary Care

- Is it time for clinicians and patients to curb enthusiasm for vitamin D screening and supplementation?
- Strategies to decrease unnecessary testing are being created (Choosing Wisely campaign) with a clinical decision support for ordering testing
- In Canada, the number of tests decreased by >90% during 12 months after publication of a paper and a requirement by physicians ordering the test to select one of several indications

Vit D: Levels and Dosing Not Clear

- There is controversy regarding optimal 25(OH)D serum levels for bone health
- The definition of deficiency is not clear
- Is the dosing regimen standardized for the healthy adult population and the fragile elderly at risk of falls?
- No consensus on the ideal regimen of supplementation: monthly vs daily vitamin D

Vitamin D: Hormone or Vitamin?

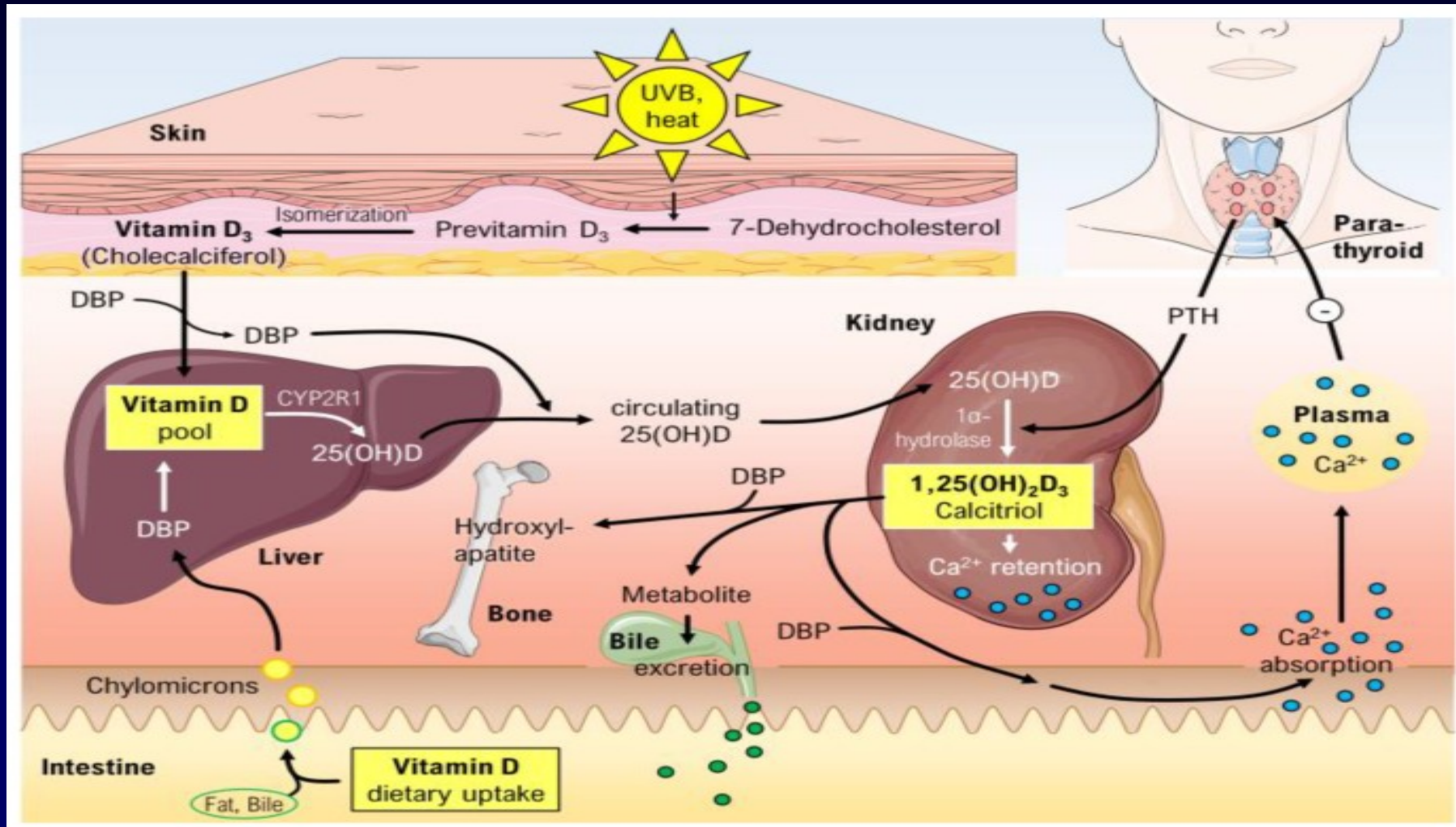
- Although labeled a fat-soluble vitamin, Vitamin D is a prohormone that is converted to active hormone with pleotropic functions
- Structure of 1,25 (OH)2D similar to steroid hormones

Osteomalacia: Definition

- Osteomalacia is defined as a metabolic bone disease where organic osteoid fails to become mineralized with calcium and phosphorus
- Osteomalacia from vitamin D deficiency denotes failure of mineralization in adults, who no longer have growing bones.
- Osteomalacia (unlike osteoporosis) is independent of bone mass

Vitamin D Metabolism

Legarth C. Int J Mol Sci.2018:19(2)

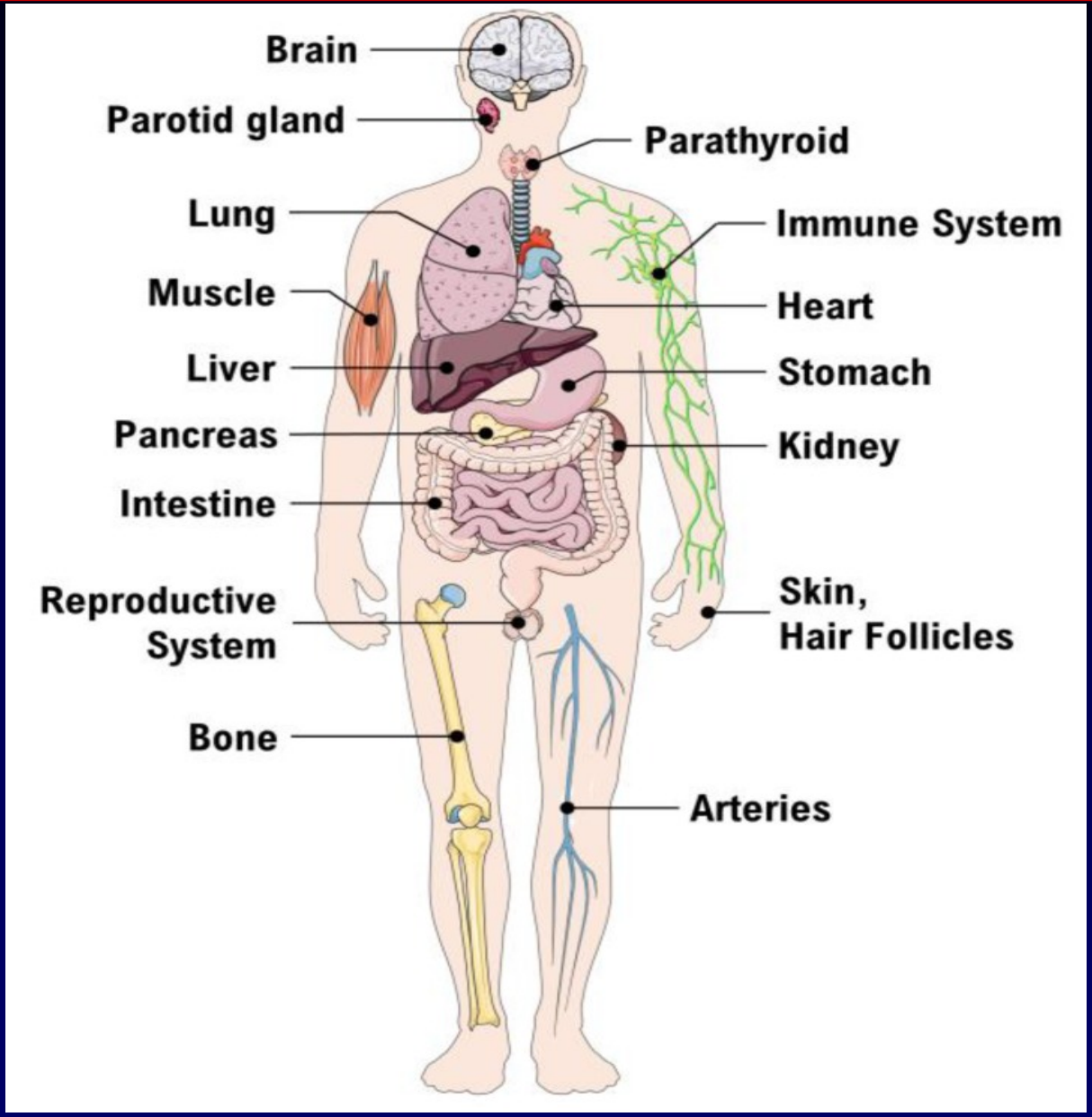


Vitamin D Metabolism

- D2 and D3 hydroxylated to 25-OH,D in liver
- 25-OH D3, bound to DBP, is converted to 1,25(OH)2D (calcitriol) in kidneys by a hydroxylase in the PCT: this is dependent on renal function, PTH, Ca, and Phos levels
- 1,25(OH)2D is 100 times potent than 25-OHD

Vitamin D Receptors (Recognize or Synthesize Vitamin D)

Legarth C. Int J Mol Sci.2018:19(2)



Vit D: Necessary for Calcium Absorption

- Vitamin D is required for small intestinal epithelium to synthesize calbindin, to promote Ca absorption
- Resistance occurs with age (↓ vitamin D gut receptors), typical after age 70
- Without vitamin D, only 10-15% dietary calcium and 60% phosphorus absorbed

Interaction of Vit. D, PTH and Calcium

- **When vit. D levels fall below 30 ng/mL, PTH levels increase in order to conserve Ca**
  - **PTH increases Ca re-absorption via the kidneys**
  - **Stimulates production of 1,25 dihydroxy D**
- **Osteomalacia results from low calcium phosphate product and poor mineralization**

Holick MF. Mayo Clin Proc. 2003;78:1457-9

Vitamin D Deficiency with Age: Factors

- **Inadequate intake** of vitamin D
  - Inadequate intake of fortified diary products or natural foods
- **Insufficient exposure to sunlight** in the aged
- **Aging skin less efficient** in synthesizing vitamin D
- Lesser dermal synthesis due to any of
  - Window glass, pigmentation, sunscreen, clothing
- **Fewer vitamin D receptors** in gut with age
- Decreased formation of end product in the kidney

Gloth III FM, Tobin JD. J Am Geriatr Soc. 1995; 43:822-8
MacLaughlin J, Holick MF. J Clin Invest. 1985;1536-8
Holick MF. Mayo Clin Proc. 2006; 82: 353-73

Effect of Latitude on Vitamin D Levels

- Does latitude and other factors such as sex, race, skin type and BMI affect vitamin D levels?
- 359 medical students from Bradenton, Florida and Erie, Pennsylvania; age 22-57 years; participants were provided surveys and blood tests
  - Mean levels: 34.5 in Bradenton and 28.1 in Erie
- **Latitude was statistically significant risk factor for vitamin deficiency; risk related to darker skin tone, overweight or obese status, and to lesser extent, male sex**
- A need to be cognizant of these risk factors

Leary PF et al. J Am Osteopathic Assoc. 2017;117:433-439

Forms of Vitamin D

- **Ergocalciferol (vitamin D2)**
  - From irradiation of yeast / plant sterol ergosterol
  - Primary commercial product
  - Half life of 25-OH D2 : 8-10 days
- **Cholecalciferol (vitamin D3)**
  - From oily fish and cod liver oil
  - In the body synthesized in the skin
  - Half life of 25-OH D3 : 25-30 days

Vitamin D levels: 25(OH) D

Levels above 20 ng/ml
are generally considered adequate
for bone and overall health
(National Institute of Health, 2011)

The Vitamin D Continuum

• Severe deficiency	< 10	ng / mL
• Deficiency	< 20	ng / mL
• Preferred range	30 - 60	ng / ml
• Reference range	20 - 100	ng / ml
• Intoxication	> 150	ng / ml

Sources: D2 and D3

- Humans get vitamin D from one of:
  - Exposure to sunlight: UV B radiation 290-315 nm
  - Diet, natural or fortified
  - Supplements

- Few foods naturally contain vitamin D
- Vitamin D supplements represents D2 or D3
- Ergocalciferol 70% potent as Cholecalciferol

Vitamin D Fortified Foods

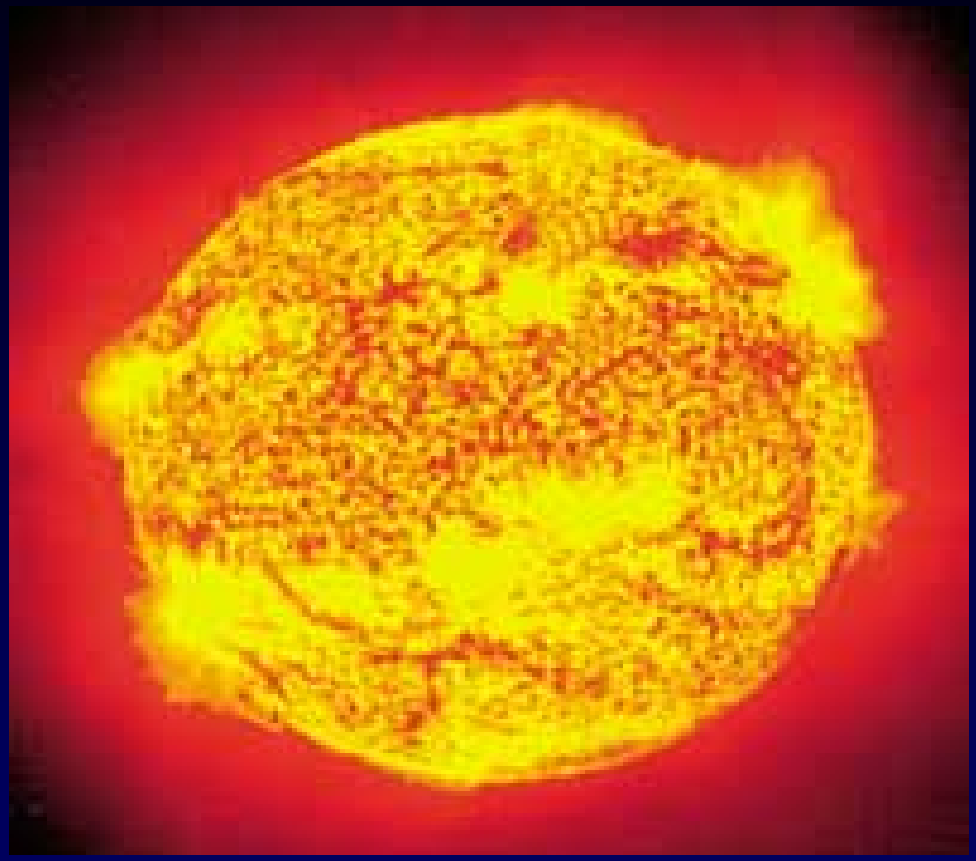
- **Milk is a source only when fortified**
- **Some brands of yogurt, cheese and orange juice are fortified**
- **Many cereals are fortified**
- **Read the labels!**

Dietary and Fortified sources of D2 and D3

- Natural:
  - Salmon, 3.5 oz: 300-1000 IU vit D3
  - Sardines 3.5 oz: 300 IU vit D3
  - Tuna 3.6 oz: 230 IU vit D3
  - Cod liver oil (1 tsp) 400-1000 IU vit D3
  - Shiitake mushroom 3oz 100-1600 IU vit D2
  - Egg yolk 20 IU vit D2 or D3

- Fortified foods:
  - Milk 8 oz: 100 IU vit D3
  - Orange juice 8 oz 100 IU vit D3
  - Yogurt 100 IU vit D3
  - Margarine 3.5 oz 430 IU IU vit D3
  - Fortified cereals 100 IU vit D3

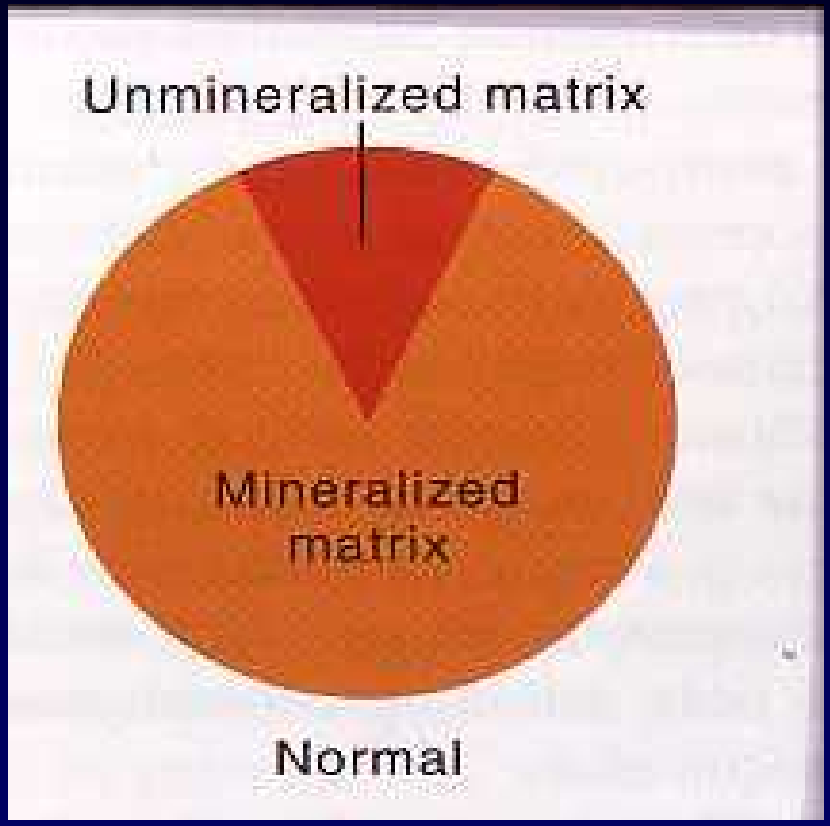
- Sunlight, UV B (0.5 erythema dose): 3000 IU D3

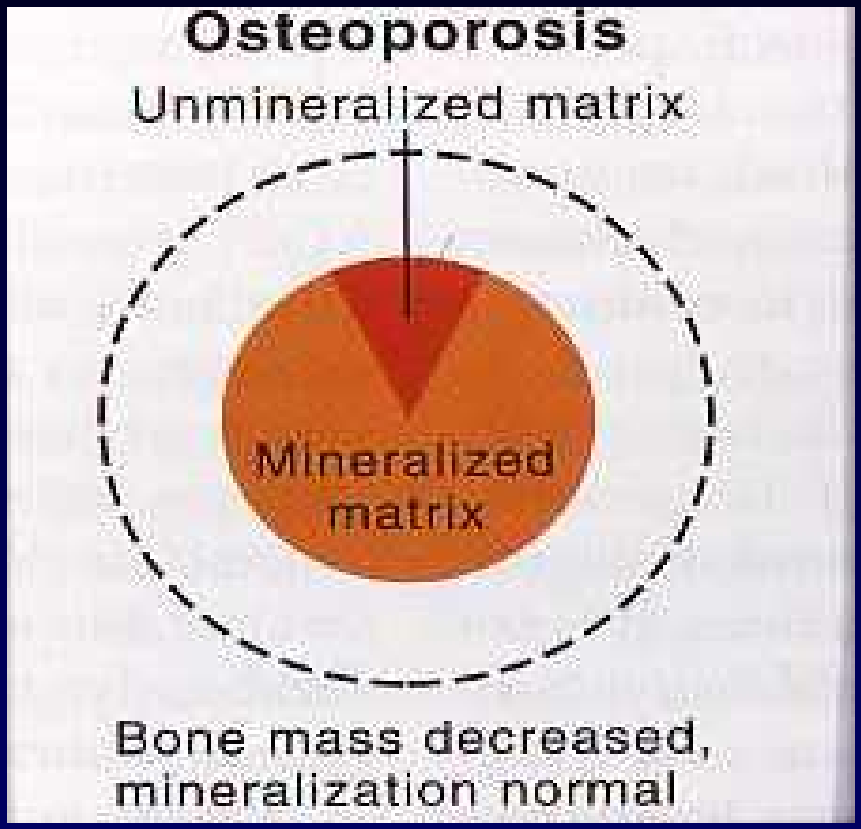


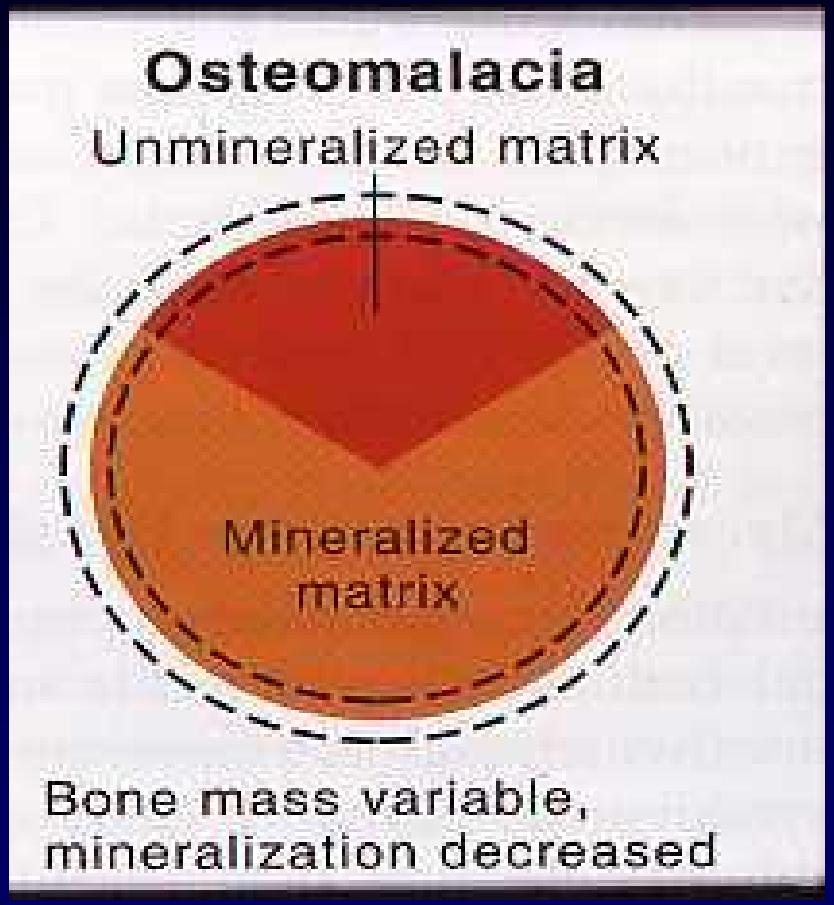
Sunlight (UV B rays, 290-315 nm)
A good source, and Free!

Vitamin D Deficiency:

Consequences


Unmineralized matrix
Mineralized matrix
Normal


Osteoporosis
Unmineralized matrix
Mineralized matrix
Bone mass decreased, mineralization normal


Osteomalacia
Unmineralized matrix
Mineralized matrix
Bone mass variable, mineralization decreased

Vit D Def: Musculoskeletal Consequences

- Deficiency leads to inhibition of mineralization at growth plates
- Unlike in osteoporosis, in osteomalacia, patients complain of isolated or generalized skeletal pain (aching, throbbing, elicited on P/E and pressure)
- Bilateral proximal muscle pain is typical (myalgia). Patients with fibromyalgia and chronic fatigue syndrome may have vitamin D deficiency

Holick MF. Mayo Clin Proc. 2006; 82: 353-73

Vitamin D and Falls: CPGs 2011, 2012

- **USPSTF Recommendation**
  - Provide intervention consisting of exercise of physical therapy and /or vitamin D supplementation to prevent falls (Grade B) (Ann Intern Med. 2012: 157)
- **Am Ger Soc / British Ger Soc Recommendation**
  - Vitamin D (800 IU) is recommended as a daily supplement for all older adults at risk of falls (2011)
  - Vitamin D is also recommended for all older adults with known vitamin D deficiency (Grade A)

Interventions to Prevent Falls in Older Adults: Updated Evidence and Systematic Review for USPSTF

JAMA 2018; 319: 1705-16

- 62 trials, 35058 patients
- Focus: 3 interventions: multifactorial (customized), exercise and vitamin D supplement
- Multifactorial (geriatric assessment, cognition, medications, CV health, environment etc.) and exercise interventions were associated with fall-benefit, evidence most consistent for exercise
- Vitamin D supplementation had mixed results; high dose was associated with higher fall-related outcomes

Interventions to Prevent Falls in Community Dwelling Older Adults: USPSTF Recommendation Statement (1)

JAMA 2018; 319: 1696-1704

- USPSTF recommends exercise interventions to prevent falls in community-dwelling adults 65 years or older (B)
- Clinicians should selectively offer multifactorial interventions in adults >65 years at risk of falls (balance, gait, vision, postural BP, medication, cognition, withdrawal or minimize psychoactive medications and address psychological health)
- Consider benefit and harms based on comorbidity and patient preferences
- Overall benefit of interventions is small

Interventions to Prevent Falls in Community Dwelling Older Adults: USPSTF Recommendation Statement (2)

JAMA 2018; 319: 1696-1704

- USPSTF found insufficient evidence for vitamin D or calcium supplementation to prevent fractures in men, premenopausal women at any dose and in post-menopausal women at doses >400 IU of vitamin D and >1000 mg calcium daily
- The USPSTF recommends against supplementation with <400 IU vitamin D or <1000 mg calcium in post-menopausal women
- The USPSTF recommends against vit D supplements to prevent falls in community adults 65 or older (D)
  - Overall harms of vitamin D supplements are small to moderate
  - At very high dosages, may be moderate

Vitamin D, Calcium or Combined Supplementation for the Primary Prevention of Fractures in Community Adults: Evidence and Systemic Review for USPSTF

JAMA 2018; 319: 1600 - 1612

- 11 RCTs, 51419 adults 50 or older, over 2 – 7 years
- Supplements of vitamin D alone or with calcium had no effect on total fracture incidence or hip fracture in those without vitamin D deficiency or osteoporosis
- Vitamin D alone or with calcium had no effect on all-cause mortality, or incident CV disease
- Vitamin D with calcium was associated with an increased incidence of kidney stones, but not an increase in cancer incidence

Vitamin D, Calcium or Combined Supplementation for the Primary Prevention of Fractures in Community Adults: USPSTF Recommendation Statement

JAMA 2018; 319: 1592-1599

- Current evidence is insufficient to assess the balance of benefits and harms of vitamin D and calcium, alone or combined for the primary prevention of fractures in adults (I)
- Evidence is insufficient to balance the benefits and harms of daily doses of >400 IU vitamin D and >1000 mg calcium (I)
- Recommends against daily supplements of vitamin D 400 IU or less and calcium 1000 mg or less for primary prevention of fractures in community adults

- The recommendations do not apply to persons with osteoporotic fractures, those with increased risk for falls or osteoporosis or vitamin D deficiency

Effect of Monthly High Dose Vitamin D on Falls and Non-vertebral Fractures: ViDA trial: A RCT

- **Vitamin D Assessment (ViDA) Study**: a RCT, double blind placebo controlled, NZ, 2011 – 2015
- 5110 participants to receive D3 or placebo
- Primary outcomes incident CVD.
- **Secondary outcomes**: respiratory illness & **fractures following falls,** and data is reported here.
- Oral D3 at 200,000 IU initial dose, then 100,000 monthly or placebo for mean of 3.3 years
- **Conclusion: Monthly high dose vitamin D did not prevent falls or fractures in this healthy, ambulatory population**

Khaw KT. Lancet Diabetes Endocrinol. 2017;5:438-447

Preventing Fractures and Falls : A Limited Role for Calcium and Vitamin D supplements?

Bischoff-Ferrari HA et al. JAMA 2018; 319: 1552-3

- Vitamin D and calcium are key nutrients to support bone metabolism. Vitamin D deficiency is a well-defined risk factor for falls and hip fractures.

- Fall prevention is important in prevention of fractures; but it is unclear if vitamin D and calcium supplementation is effective for the primary prevention of fractures in healthy community adults

- For those at risk for osteoporosis or vit D deficiency or both, it is reasonable to consider vit D supplements (800-1000 IU /d)
- For vulnerable populations (residents in institutions, those at high risk of fracture, impaired mobility or gait, or vitamin D deficiency), vitamin D supplements are beneficial

Vitamin D and Incident Type 2 Diabetes

- Blood 25(OH)D and Incident Type 2 Diabetes
- Meta-analysis of 21 studies, 76,220 participants, with 4996 incident type 2 diabetes
- Findings:
  - Inverse and significant association between circulating vitamin D levels & risk of type 2 diabetes
  - Seen across a broad range of blood 25(OH)D levels in diverse populations

Song Y et al. Diabetes Care. 2013; 36:1422-8

Vitamin D Supplementation Has No Effect on Insulin Sensitivity or Secretion In Vitamin D Deficient Overweight or Obese Adults

- Background: vitamin D supplement is a potential strategy to prevent type 2 diabetes
- 65 overweight or obese vitamin D deficient adults randomly assigned to receive vitamin D (bolus 100,000 + 4000 IU / d versus placebo for 16 weeks
- 54 completed the study
- Results non-significant for age, sex, physical activity
- Vitamin D supplementation does not improve insulin sensitivity or secretion in vitamin D deficient, overweight or obese adults despite using high dose
- Mousa A et al. Am J Clin Nutr. 2017; 105: 1372-81

Vitamin D deficiency and Non-lipid Biomarkers of Cardiovascular Risk

- Background: vitamin D deficiency has been associated with dyslipidemia and CVD; is there an association between deficiency and CVD?
- Cross sectional analysis; 4591 adults, mean age 60±14 yrs, 2009-2011 with measures of homocysteine, hs-CRP, cystatin C, creatinine, GGT, uric acid and HbA1c
- Calculated odds ratios of having high levels of each with 25OHD <20 ng/ml vs. optimal levels (>30 ng) adjusted for age, sex, and lipids
- Deficient 25OHD is associated with elevated levels of many biomarkers of CV risk, particularly in women

Faridi KF, et al. Arch Med Sci. 2017;13; 732-737

Vitamin D and Cardiovascular Disease

Postulate:

- Cardiac muscle has vitamin D receptors
- **Vitamin D deficiency: a role in pathogenesis of HF?**
- Lower vitamin D status may be associated with higher risk for hypertension and cardiovascular disease

Zitterman et al. J Am Coll Card. 2003; 42105-12
Holick MF. Mayo Clin Proc. 2006; 82: 353-73
Pittas AG et al. Ann Intern Med. 2010; 152: 307-14
Wang L et al. Ann Intern Med. 2010; 152: 315-23

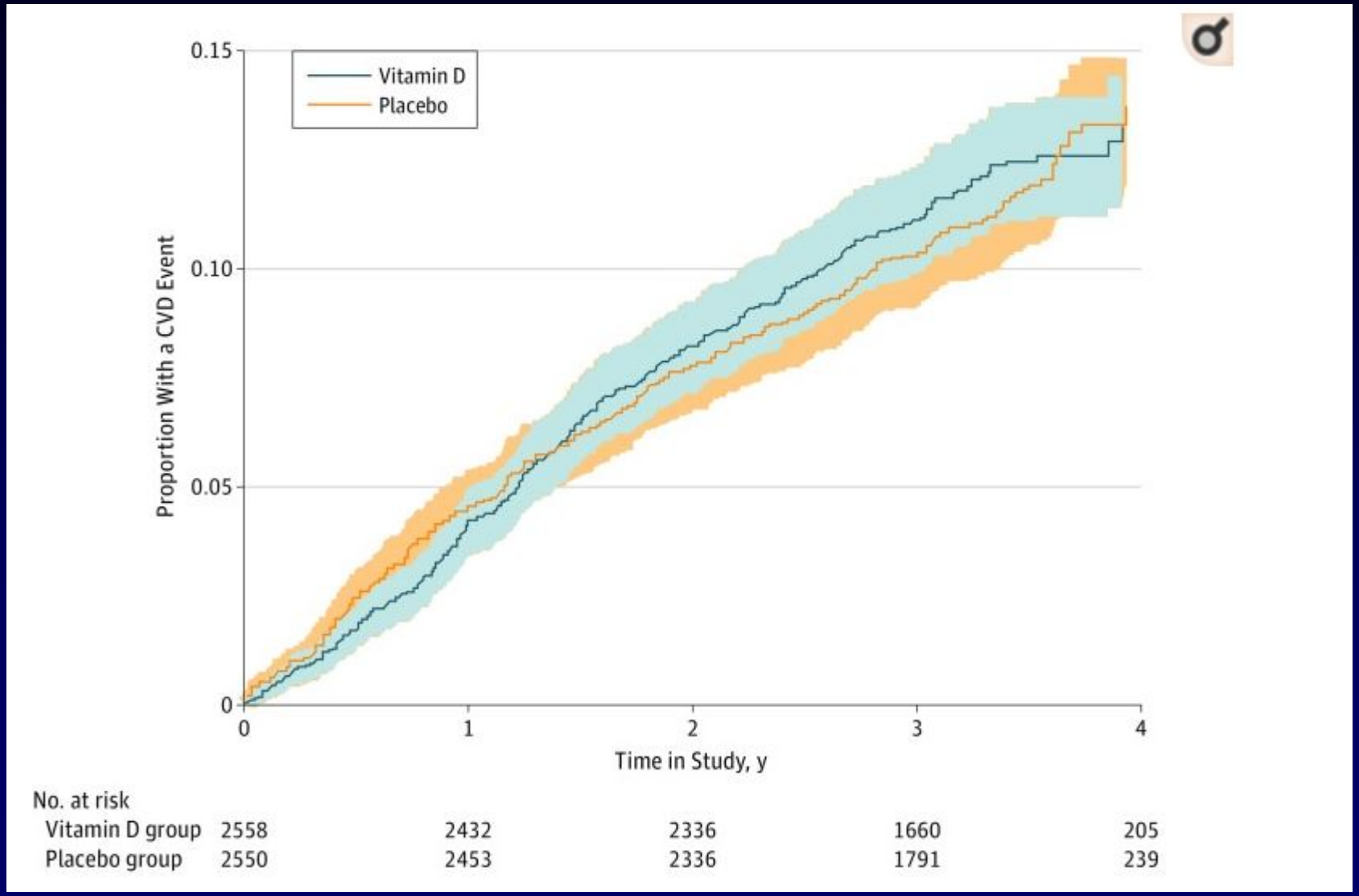
Effect of Monthly High Dose Vitamin D on CV Disease in the Vitamin D Assessment Study, a RCT

- Vitamin D Assessment Study: To examine if monthly high dose vitamin D prevents CVD; a RCT, double blind placebo controlled, Australia, NZ, 2011 –2015
- 47905 adults invited, 5110 participants to receive D3 or placebo; mean age 65.9 yrs; outcomes incident CVD and death. Secondary: MI, HF, HTN, stroke, arrhythmias, DVT
- Oral D3 200,000 IU initial dose, then 100,000 monthly or placebo for mean of 3.3 years
- Monthly high dose Vit D does not prevent CVD
- Similar results in those with baseline Vit D deficiency and for secondary outcomes
- The study does not support use of high dose vit D for CVD

Scragg R et al. JAMA Cardiol. 2017; 2: 608-616

Effect of Monthly High Dose Vitamin D on CV Disease in the Vitamin D Assessment Study

Scragg R et al. JAMA Cardiol. 2017; 2: 608-616



Association between Vitamin D Deficiency and Heart Failure Risk in the Elderly

Porto CM et al. ESC Heart Failure. 2017; doi: 10.1002/ehf2.12198 (ahead of print)

- Aim: evaluate the association between vitamin D def and risk of HF in elderly patients at cardiology OP clinics
- Cross-sectional study, 2015-2016; dependent variable risk of HF; independent variable was Vit D deficiency; intervening factors: age, gender, race, HTN, DM, hypothyroidism, CKD, dementia, smoking, dyslipidemia, obesity, alcoholism; logistic regression
- 137 elderly, 76% women, 65% deficient
- High prevalence of vit D deficiency; a strong association between deficiency and increased risk of HF noted

- Is vitamin D a risk factor for HF, a marker of HF disease severity or has a true pathophysiologic role?

Vitamin D Supplementation and Body Fat Mass

Golzarand M et al. Eur J Clin Nutr. 2018;doi:10.1038/s41430-018-0132-z (ahead of print)

- Studies suggest that 25(OH)D level is lower in obese than normal weight subjects
- Meta regression analysis indicate:
  - Age, baseline BMI, dose of vitamin D, female gender and baseline 25(OH)D are not source of heterogeneity
- Results suggest that 25(OH)D level is inversely correlated with PFM (% fat mass); vitamin D supplementation had no effect on fat mass

Vit D Supplementation in Obesity and During Weight Loss: A Review of RCTs

Bassatne A et al. Metabolism. 2019 (ahead of print)

- Vitamin D deficiency is common in obese individuals and during period of weight loss; in such patients higher doses are recommended vs. healthy adults
- Review of RCTs or oral Vit D supplementation in obese individuals without weight loss, those on medical weight loss and following bariatric surgery
- Vitamin D ≥ 1600 – 2000 IU/d may be needed to reach a conc. of 30 ng/ml in the obese & post bariatric surgery

- No clear benefit for vitamin D supplements in obese individuals as data on those with weight loss is scarce

Body Mass Index and Vitamin D

- BMI is inversely related to serum D levels
- Obese patients typically have lower vitamin D levels, in the range of 10-20 ng/ml
- This is partly due to lower levels of exercise and less sunlight exposure
- Additionally, vitamin D is also sequestrated in fat depots in these patients

Body Weight Impact on Determining Optimal Vit D dose

Zitterman A et al. Eur J Nutr. 2014; 53: 367-74

Body Weight (Kg)	30 Year Old	70 Year Old
50	1680 IU	960 IU
75	2520 IU	1460 IU
100	3360 IU	1960 IU

Vitamin D: Relationship to Bipolar Depression

- Vitamin D deficiency and DSM IV bipolar depression in double blind placebo controlled trial of 5000 IU versus placebo for 12 weeks
- Despite a greater rise in vitamin D levels in the supplemented group, no significant reduction in depressive symptoms, and no change in mood or anxiety symptoms

Marsh WE et al. J Psychiatr Res. 2017; 95:48-53

Vitamin D Status and Association with Season, and Depression in Stroke

Gu Y et al. Neurosci Lett. 2019;690:99-105

- Background: Vit D plays a key role in depression: assess the prevalence of vit D deficiency and assoc. with depression in patients with acute stroke
- Sept 2013 – May 2015; patients with acute stroke; assessed for depression 1 month after stroke (Hamilton Rating Scale); vitamin D levels categorized by month to reflect seasonal variation
- 442 patients; prevalence of vitamin D def (<30nmol/L) or insufficiency (30 – 49.99) was 46%
- Prevalence of depression significantly higher in vit D deficiency; vit D def and insufficiency had high rates in acute stroke; low levels of vitamin D were associated with depression in acute stroke
- Is vit D beneficial for depression in post-stroke pts?

Vitamin D levels in Schizophrenia

- Vitamin D deficiency is associated with schizophrenia, but is there a relationship with severity?
- 60 patients with schizophrenia classified as mild, moderate, markedly or severely ill vs 30 healthy controls.
- Patients with schizophrenia have low plasma vitamin D levels; they do not appear to be associated with the severity of schizophrenia and type of antipsychotics
- Regular screening for vitamin D status is suggested

Akinlade KS et al. Front Psychiatr. 2017; 8:105

Association between Mental Disorders, Cognitive Disturbances and Vitamin D level: Current state

- Background: Vitamin D deficiency is associated with development of several disorders; is there an association between vitamin D levels and cognition and mental disorders?
- Systematic research of PubMed, Medline and Cohrane database, 1995-2017
- 49937 articles, published over 22 years; 167 suitable
- An association between low vitamin D levels and mental disorders was found; but no clear consensus that addition of vitamin D improves or is beneficial to mental health
- Lerner PP et al. Clin Nutr ESPEN 2018: 89-102

Association Between Vitamin D concentration and Pain: Systematic review and Meta-analysis

- Search of electronic sources (MEDLINE, EMBASE, COCHRANE); a meta-analysis
- 81 studies, 50834 participants
- Compared to controls, 25(OH)D conc was significantly lower in patients with arthritis, muscle pain, and widespread pain, NOT with migraine and headache
- Conclusion:
  - A significantly lower 25(OH)D conc. was observed in patients with arthritis, muscle pain and chronic widespread pain compared with those without pain

Wu Z. Public Health Nutr. 2018; 1-16 (ahead of print)

Diagnosis of Osteomalacia: History and Clinical

- History
  - Dietary history (dairy products)
  - Unexplained pain
  - Medications: phenytoin, carbamazepine etc
  - Falls
  - Lack of exposure to sunlight
- Clinical findings
  - Musculoskeletal pain, often no apparent basis
  - Proximal muscle weakness
  - Waddling gait
  - Fractures
  - Hypocalcemia related: neuromuscular, cardiac

Vitamin D assays

- **25 (OH) D: is the standard clinical measure**
- Variations exist between labs, techniques
- Total 25 (OH) D includes 25(OH)D2 + 25(OH)D3
- A combined total is utilized

- 1,25 (OH)2 D is the active form but not a measure of vitamin D status (with exceptions, e.g. granulomas) and not routinely used to assess vitamin D status.

Holick MF. Mayo Clin Proc. 2006; 81: 353-73
Holick MF. NEJM. 2007; 357: 266-81

Diagnosis of Osteomalacia: Laboratory and Radiology

- **Laboratory:**
  - Low 25 hydroxy-vitamin D levels
  - Low (or normal) serum calcium, phosphorus
  - Elevated total or bone alkaline phosphatase
  - Low 24 hour urine calcium (in absence of thiazide)
  - Elevated PTH level
- **Radiology:**
  - Fractures, non traumatic (fragility)
  - Looser's zones (pseudo fractures)
  - Osteopenia (not diagnostic)
- **Bone biopsy**: definitive

Variable	Osteoporosis	Osteomalacia
Age of occurrence	older adults	young and old
Causative factors	age, endocrine, drugs, smoking, myeloma etc	Vit D or phosphorus deficiency, ↓ sunlight
Pathology	mineral to matrix: N	mineral to matrix: ↓
Bone volume	decreased	normal to decreased
Calcium, phos	normal	normal or decreased
Alk. phosphatase	normal	normal or increased
25 OH vitamin D	normal	low
Definite diagnosis	DEXA	Bone biopsy
DEXA	Below mean	Variable

Painful Bone or Muscle Disorders: Differential Diagnosis

- Osteomalacia
- Osteoporosis
- Adynamic bone disease
- Paget's disease
- Metastatic disease
- Multiple myeloma
- Hyperparathyroidism
- Polymyalgia rheumatica
- Fibromyalgia
- Late onset rheumatoid arthritis

IOM: Recommendations for Vit D

- No one doubts that vitamin D is essential to health
  - But the evidence has failed to translate consistently that an adequate level is associated with reduced risk for disease
  - The reports of health benefits are inconclusive
  - Risks are associated with both low and very high levels
- On the basis of available evidence most people are vitamin D sufficient with levels > 20 ng/ml (2010)

IOM Recommendations: Who is to be tested for vitamin D ?

- Dark skin
- Aging (decreased synthesis)
- Osteoporosis or prior skeletal fracture (radiographic)
- CKD (low synthesis)
- Nephrotic syndrome (loss of binding protein)
- Chronic musculoskeletal pain or weakness
- Malabsorption syndromes (celiac disease, IBS)
- Malnutrition
- Liver disease and liver failure
- Lab abnormalities: low urine Ca, low serum Ca or P, high alk phos
- Medications:
  - phenytoin, carbamazepine, corticosteroids, heparin, cholestyramine

Institute of Medicine: DRIs for Vitamin D

Nov 30, 2010

Life Stage Group	EAR IU/d	RDA IU/d	UL IU/d
19 – 30 years old	400	600	4000
31 – 50 years old	400	600	4000
51 – 70 year old Males	400	600	4000
51 – 70 year old Females	400	600	4000
> 70 years old	400	800	4000

Annual High dose Oral Vitamin D and Falls and Fractures in Older Women

- Study: 500,000 IU of cholecalciferol vs placebo to women 70+, in autumn or winter
- Assess the risk of falls and fracture
- Women in the vitamin D group had increased risk of falls and fractures
- High levels of vitamin D and calcium were observed in the treated group

Sanders KM et al. JAMA. 2010; 303:1815-22

High dose Vitamin D Supplementation
Too much of a Good Thing?

Dawson Hughes B. JAMA. 2010; 303: 1861-2

- Infrequent high doses are counterproductive and raise questions about the loading doses of 50,000 units weekly for 6-8 weeks
- No adverse effects noted with low doses; daily, weekly or monthly dosing better options?
- High doses intermittently may be metabolized and used differently from smaller daily doses

Current Thoughts on Dosing

Carbonare LD et al. Nutrients. 2017; 9, 652

- The most effective way to correct vitamin D deficiency is to administer a personalized loading dose, based on body weight and baseline 25(OH)D level to normalize status and then continue a supporting dose (daily, two weekly or monthly).
- Data suggests that the infrequent high dose approach improves adherence
- However, there is growing evidence that infrequent high dose vitamin D may be less effective or even harmful

Current Thoughts on Dosing

Carbonare LD et al. Nutrients. 2017; 9, 652
Bischoff-Ferrari et al. JAMA Int Med. 2016;176:657-666

- Those administered a personalized loading dose reached optimal levels within weeks, in contrast to the daily dose group
  - All studies did not replicate these findings
- A significant increase in falls was noted in the higher dose group (Bischoff-Ferrari, 2016)
- Daily admn. is the most physiological way to correct vitamin D deficiency, but less frequent admn. improves patient adherence to treatment
- Also, vitamin D3 appears significantly more effective than vitamin D2

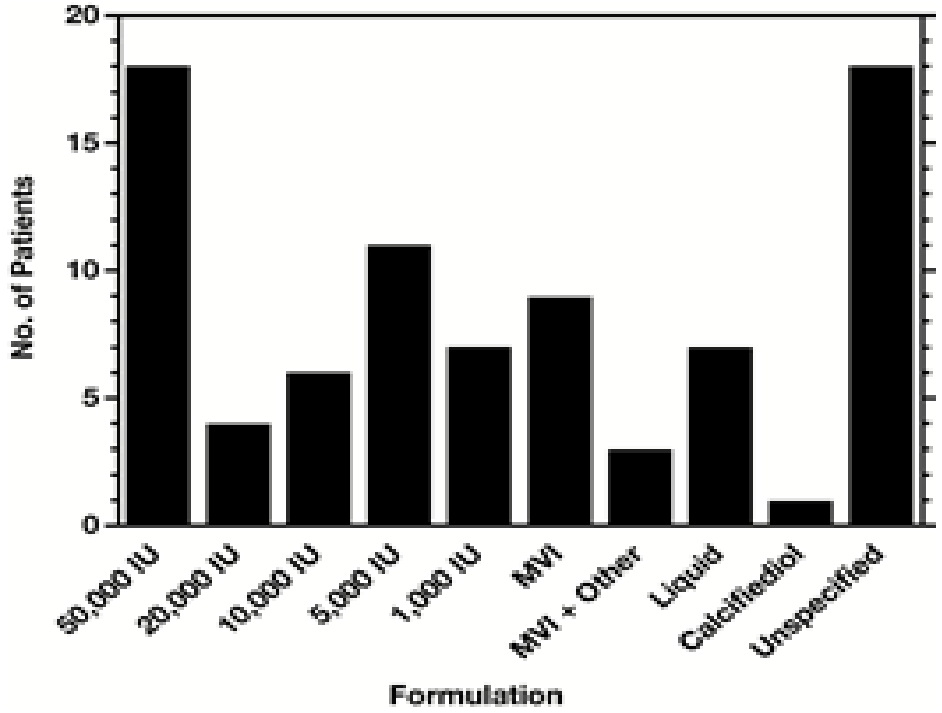
Vit D Toxicity: A 16 year Retrospective Study

Lee JP et al. Lab Med. 2018;19: 123-129

- Background: interest in vitamin D has increased over the past 2 decades and so also an increase in lab testing. Majority of tests displayed N or deficient levels
- 16 years study; 127,932 measures of 25(OH)D in 73779 patients, at University of Iowa Hospitals and Clinics
  - 780 patients exceeded 80 ng/ml, 89 exceeded 120 ng
  - Mean age 49 years, 11% below 18 years, highest 100
  - Only 4 patients showed symptomatic vitamin D toxicity, 3 of them from mis-dosing liquid formulations; manifest as poor balance, weakness, slurred speech
- Conclusions:
  - Symptomatic vitamin D toxicity is uncommon
  - Levels do not strongly correlate with clinical symptoms
  - Study highlights possible risk of liquid formulations

Vitamin D Dosage and Frequency

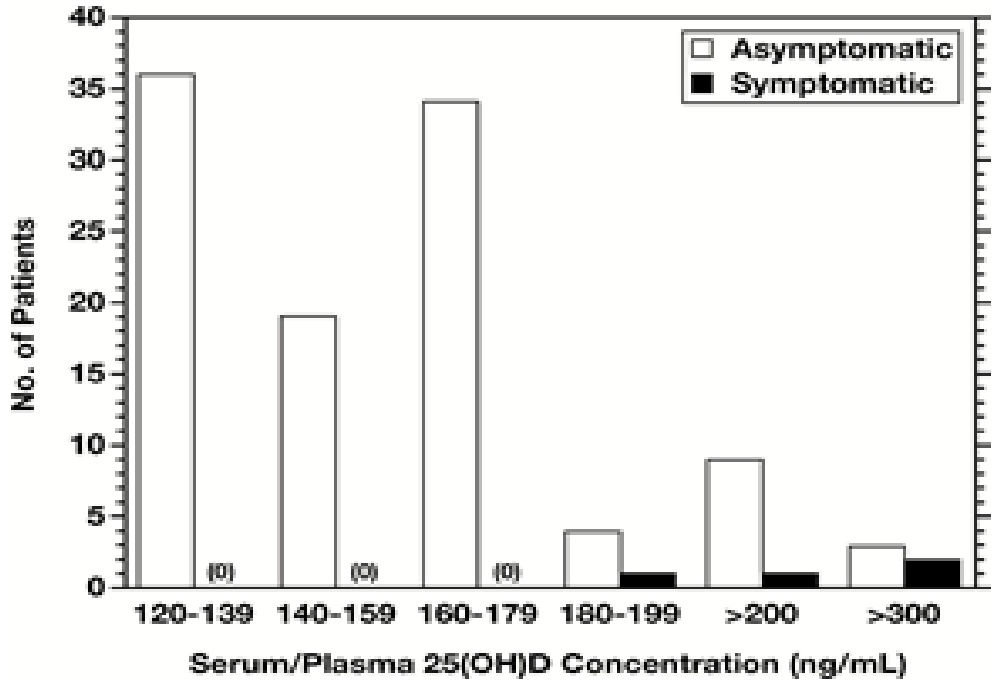
Figure 2 Varying vitamin D supplementation concentrations and their frequency among patients with elevated 25(OH)D ...



Laboratory Medicine, Volume 49, Issue 2, May 2018, Pages 123–129, https://doi.org/10.1093/labmed/lmx077

Vitamin D levels and Symptoms

Figure 1 Distribution of patients with and without symptoms at various vitamin D concentrations.



Laboratory Medicine, Volume 49, Issue 2, May 2018, Pages 123–129, https://doi.org/10.1093/labmed/lmx077

OXFORD
UNIVERSITY PRESS

Vit. D Supplement for Adults (Intl. Health Organizations)

Carbonare LD et al. Nutrients. 2017; 9, 652

Society	Vitamin D Supplementation
Institute of Medicine (2010)	600 IU / d, 18 -70 years 800 IU / d, over 70 years
Endocrine Society CPGs (2011)	1500 IU / d - 2000 IU / d, over age 19 years
Osteoporosis Australia (2016)	At least 600 IU / d, under 70 years At least 800 IU / d, over 70 years Sun avoiders or people at risk: 1000 – 2000 IU / d
National Osteoporosis Society Practical Guides (2013)	People >65 years, those not exposed to sun, pregnant and breast-feeding women: 400 IU / d
Italian Guidelines for Osteoporosis (2015)	If level <25 nmol/L: cumulative dose of 600,000, supporting dose 2000 IU/d If level 25 – 50 nmol/L, cumulative dose 400,000, supporting dose 1000 IU / d

Monitoring of Serum 25 Hydroxy Vit D

CMAJ. 2010; 182:1315-9

- In most , vitamin D supplements result in adequate blood levels with no need to test for vitamin D status
- Where malabsorption (e.g. celiac disease) is suspected, monitoring is required
- With standard supplements levels plateau in 3-4 mths
- Do not monitor sooner than 3 months

Administration of Vitamin D: Precautions

- Both vitamin D2 and D3 are best taken with a meal with fat to ensure maximal absorption
- Ergocalciferol capsules contain oil and can clog the feeding tube
- Cholecalciferol capsules / tabs in powder form may be used via the feeding tube
- Vitamin D as IM injection is painful and generally not preferred over the oral route

Institute of Medicine: DRIs for Calcium

Nov 30, 2010

Life Stage Group	EAR mg/d	RDA mg/d	UL mg/d
19 – 30 years old	800	1000	2500
31 – 50 years old	800	1000	2500
51 – 70 Year old males	800	1000	2000
51 – 70 Year old females	1000	1200	2000
> 70 years old	1000	1200	2000

Preferred Source of Calcium: Diet

- Must supplement calcium along with Vit D
- Counsel the patient on dietary sources
  - Yogurt : 400 mg per 8 oz
  - Milk : 300 mg per 8 oz
  - Orange juice (fortified): 300 mg / 8 oz
  - Cheese : 150 - 180 mg / oz
  - Cheddar cheese is particularly good source
  - Canned salmon with bones: 180 mg / 3 oz

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

ABSTRACT

BACKGROUND

It is unclear whether supplementation with vitamin D reduces the risk of cancer or cardiovascular disease, and data from randomized trials are limited.

METHODS

We conducted a nationwide, randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D_3 (cholecalciferol) at a dose of 2000 IU per day and marine n–3 (also called omega-3) fatty acids at a dose of 1 g per day for the prevention of cancer and cardiovascular disease among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were invasive cancer of any type and major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes). Secondary end points included site-specific cancers, death from cancer, and additional cardiovascular events. This article reports the results of the comparison of vitamin D with placebo.

RESULTS

A total of 25,871 participants, including 5106 black participants, underwent randomization. Supplementation with vitamin D was not associated with a lower risk of either of the primary end points. During a median follow-up of 5.3 years, cancer was diagnosed in 1617 participants (793 in the vitamin D group and 824 in the placebo group; hazard ratio, 0.96; 95% confidence interval [CI], 0.88 to 1.06; P=0.47). A major cardiovascular event occurred in 805 participants (396 in the vitamin D group and 409 in the placebo group; hazard ratio, 0.97; 95% CI, 0.85 to 1.12; P=0.69). In the analyses of secondary end points, the hazard ratios were as follows: for death from cancer (341 deaths), 0.83 (95% CI, 0.67 to 1.02); for breast cancer, 1.02 (95% CI, 0.79 to 1.31); for prostate cancer, 0.88 (95% CI, 0.72 to 1.07); for colorectal cancer, 1.09 (95% CI, 0.73 to 1.62); for the expanded composite end point of major cardiovascular events plus coronary revascularization, 0.96 (95% CI, 0.86 to 1.08); for myocardial infarction, 0.96 (95% CI, 0.78 to 1.19); for stroke, 0.95 (95% CI, 0.76 to 1.20); and for death from cardiovascular causes, 1.11 (95% CI, 0.88 to 1.40). In the analysis of death from any cause (978 deaths), the hazard ratio was 0.99 (95% CI, 0.87 to 1.12). No excess risks of hypercalcemia or other adverse events were identified.

CONCLUSIONS

Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259.)

From the Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (J.E.M., N.R.C., I.-M.L., W.C., S.S.B., S.M., H.G., D.G., T.C., D.D., G.F., C.R., V.B., E.L.G., W.C.W., J.E.B.), and the Departments of Epidemiology (J.E.M., N.R.C., I.-M.L., W.C.W., J.E.B.) and Nutrition (E.L.G., W.C.W.), Harvard T.H. Chan School of Public Health — all in Boston. Address reprint requests to Dr. Manson at the Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 900 Commonwealth Ave., 3rd Fl., Boston, MA 02215, or at jmanson@rics.bwh.harvard.edu.

*A complete list of the members of the VITAL Research Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 10, 2018, at NEJM.org.

N Engl J Med 2019;380:33-44.
DOI: 10.1056/NEJMoa1809944

Study Screening, Randomization

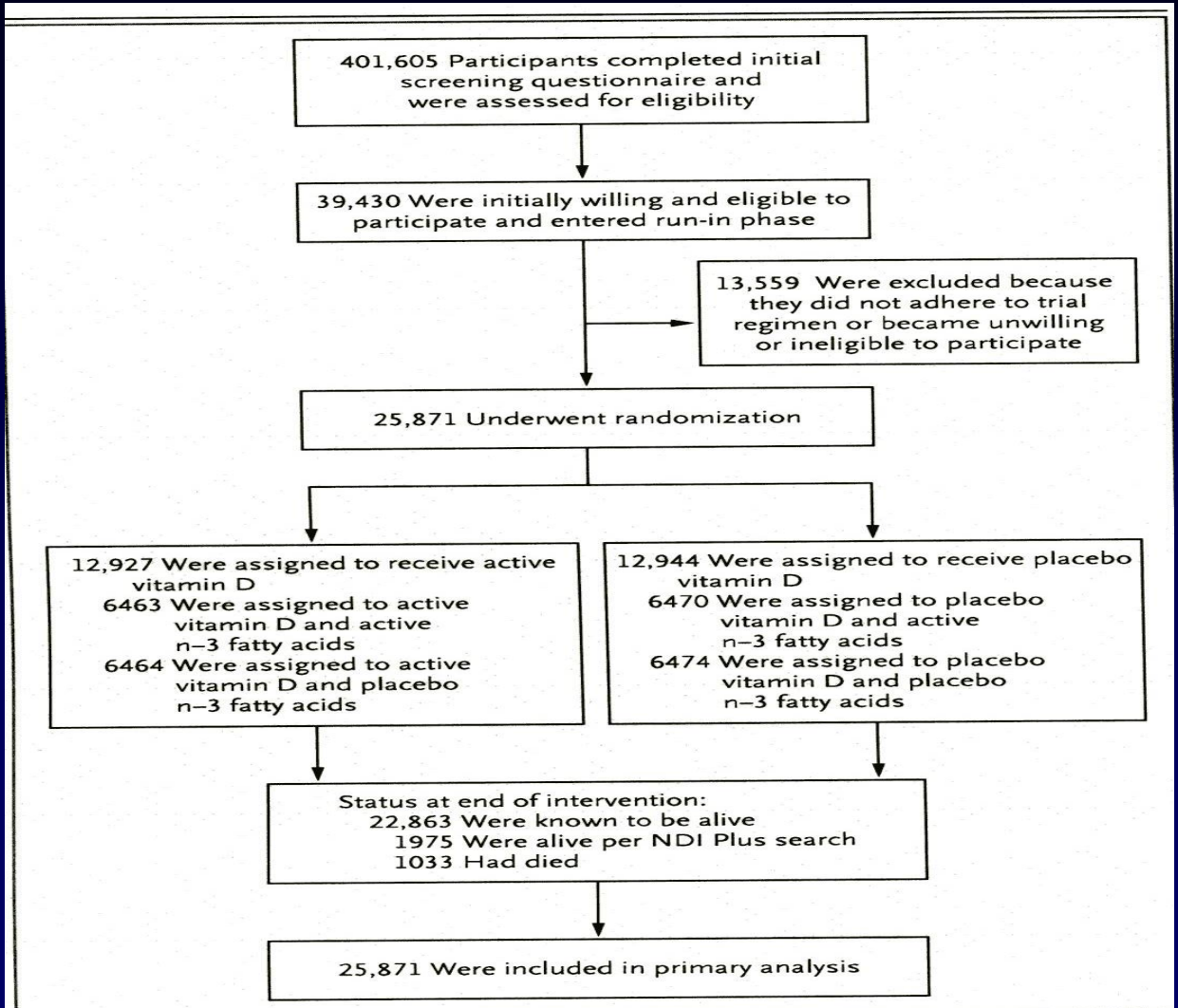
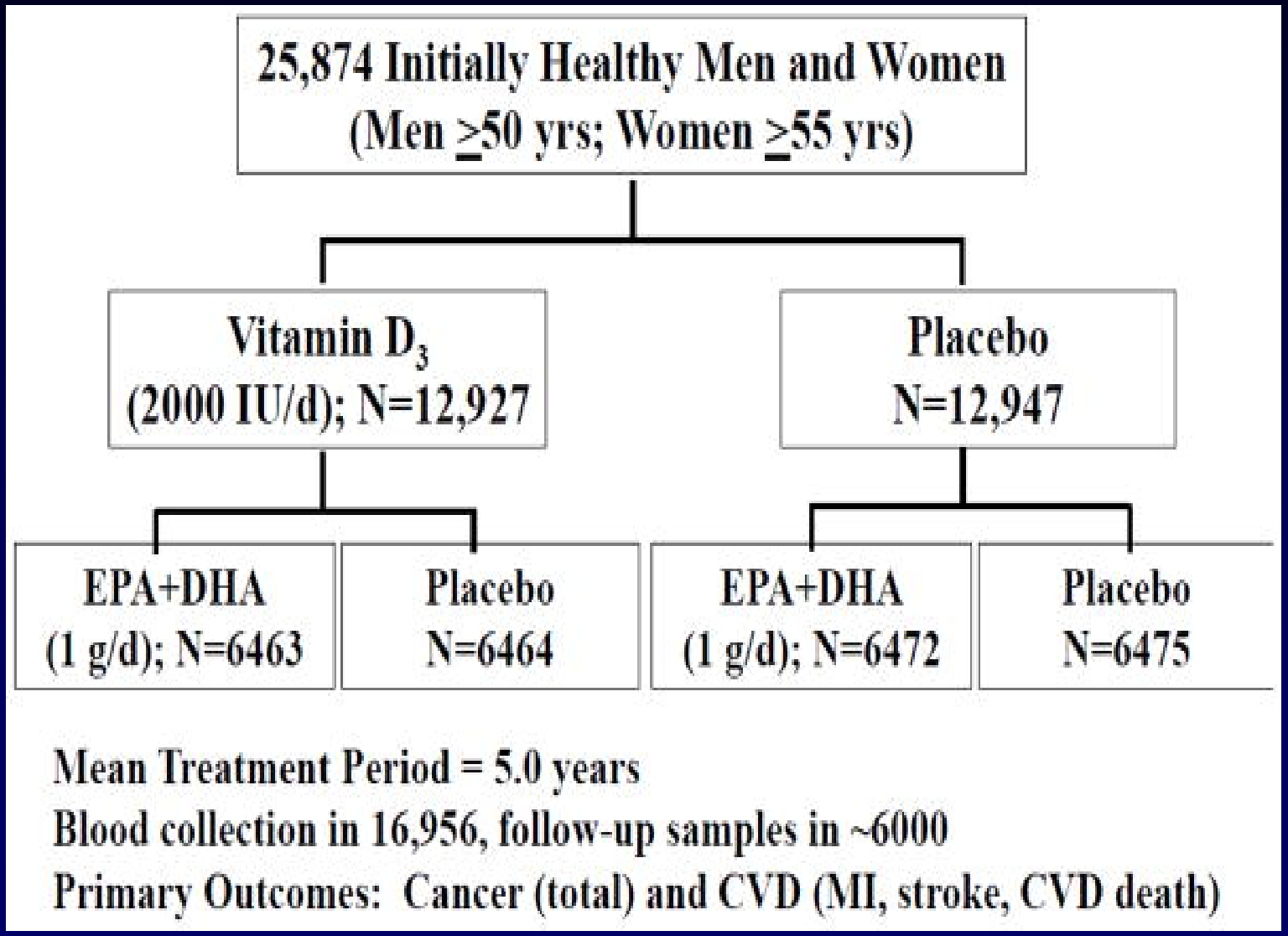


Figure 1. Screening, Randomization, and Follow-up of the Participants.
NDI denotes National Death Index.

ViTamin D and OmegaA-3 Trial (VITAL)



Participant Characteristics

Table 1. Characteristics of the Participants at Baseline, According to Randomized Assignment to Vitamin D or Placebo.*

Characteristic	Total (N = 25,871)	Vitamin D Group (N = 12,927)	Placebo Group (N = 12,944)
Female sex — no. (%)	13,085 (50.6)	6547 (50.6)	6538 (50.5)
Age — yr	67.1±7.1	67.1±7.0	67.1±7.1
Race or ethnic group — no./total no. (%)†			
Non-Hispanic white	18,046/25,304 (71.3)	9013/12,647 (71.3)	9033/12,657 (71.4)
Black	5106/25,304 (20.2)	2553/12,647 (20.2)	2553/12,657 (20.2)
Nonblack Hispanic	1013/25,304 (4.0)	516/12,647 (4.1)	497/12,657 (3.9)
Asian or Pacific Islander	388/25,304 (1.5)	188/12,647 (1.5)	200/12,657 (1.6)
Native American or Alaskan native	228/25,304 (0.9)	118/12,647 (0.9)	110/12,657 (0.9)
Other or unknown	523/25,304 (2.1)	259/12,647 (2.0)	264/12,657 (2.1)
Body-mass index‡	28.1±5.7	28.1±5.7	28.1±5.8
Current smoking — no./total no. (%)	1836/25,485 (7.2)	921/12,729 (7.2)	915/12,756 (7.2)
Hypertension treated with medication — no./total no. (%)	12,791/25,698 (49.8)	6352/12,834 (49.5)	6439/12,864 (50.1)
Current use of cholesterol-lowering medication — no./total no. (%)	9524/25,428 (37.5)	4822/12,700 (38.0)	4702/12,728 (36.9)
Diabetes — no./total no. (%)	3549/25,828 (13.7)	1812/12,903 (14.0)	1737/12,925 (13.4)

Cumulative Cancer and CV Events

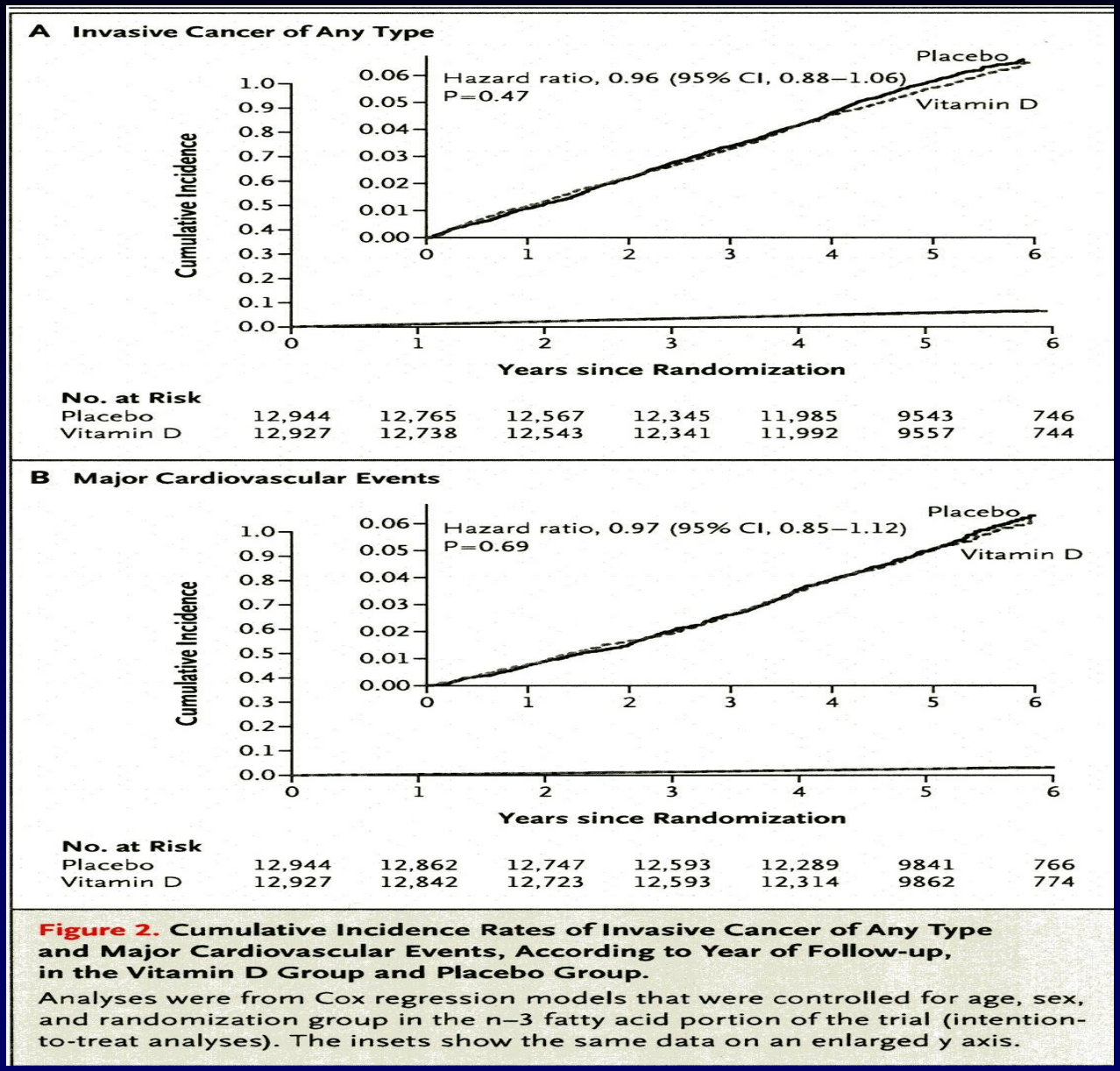


Figure 2. Cumulative Incidence Rates of Invasive Cancer of Any Type and Major Cardiovascular Events, According to Year of Follow-up, in the Vitamin D Group and Placebo Group.

Analyses were from Cox regression models that were controlled for age, sex, and randomization group in the n–3 fatty acid portion of the trial (intention-to-treat analyses). The insets show the same data on an enlarged y axis.

VITamin D and Omega-A 3 Trial (VITAL)

Manson JE et al. N Eng J Med. 2019;380:33-44

- **Background:**
  - Unclear if supplementation with vitamin D reduces risk of cancer or cardiovascular disease
  - Data from RCTs are limited
- **Conclusions**
  - Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo

Marine n-3 Fatty Acids and Prevention of CVD and Cancer (VITAL)

Manson JE et al. N Eng J Med. 2019;380:23-32

- **Background:**
  - Higher intake of marine n-3 (also termed omega-30 fatty acids) is associated with reduced risk of cancer and cardiovascular disease in observational studies
  - Data from RCTs are limited
- **Conclusions**
  - Supplementation with n-3 fatty acids did not result in a lower incidence of cancer or major cardiovascular events than placebo
  - No excess risks of bleeding or other serious adverse events were observed

VITAL signs for Dietary Supplementation to Prevent Cancer and Heart Disease (Editorial)

Keaney JF, Rosen CJ. N Eng J Med. 2019;380:91-93

- In the past decade the number of persons who supplement diets with fish oil increased by a factor of 10 and with vit D by a factor of 4
- The health benefits from these remain in doubt
- Compelling data that fish consumption is associated with protection from CVD exists
- Evidence from n-3 fatty acids may prevent CAD was based on 1 trial (in 1990, and the AHA recommendation for secondary prevention of CAD); since then no consistent benefit has been shown on use of n-3 fatty acids

VITAL signs for Dietary Supplementation to Prevent Cancer and Heart Disease (Editorial)

Keaney JF, Rosen CJ. N Eng J Med. 2019;380:91-93

- The recent AHA statement (opinion) is that use of n-3 fatty acids is reasonable (not recommended) in that use may prevent death from CAD in those with a recent MI (statement based on 1 meta-analysis).
- VITAL shows that n-3 fatty acids are not effective in preventing the combined end point of MI, stroke or death from CVD
- Adherence rates were high (80%); a good sample
- Data is also similar to the VIDA study (in New Zealand)
- But secondary end points: lower incidence of MI and death from MI with n-3 fatty acids and lower mortality form cancer with vitamin D, are noteworthy, although data need cautious interpretation

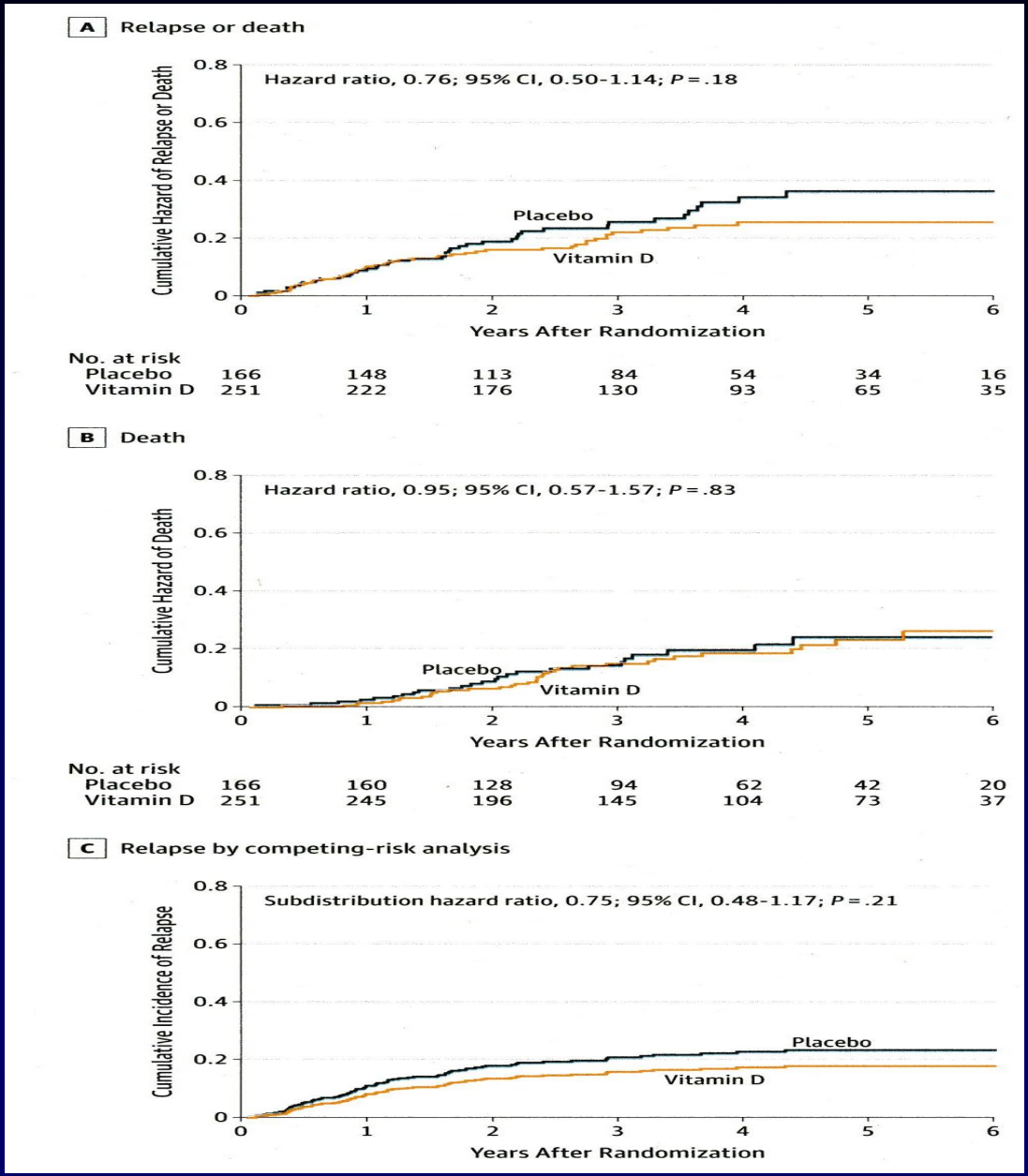
Vit D Supplements and Outcomes. AMATERASU Trial

JAMA 2019;321:1366

- **Question:**
  - Does vitamin D3 supplementation improve post-operative survival in patients with digestive tract cancers (esophagus to rectum)?
  - Vitamin D 2000 IU/d vs. placebo resulted in a 5 year relapse free survival of 77% vs 69%, not statistically significantly
- **Meaning**
  - In this RCT, vitamin D supplementation did not improve relapse free survival in patients with digestive tract cancers

Vit D Supplement and Outcomes. AMATERASU Trial

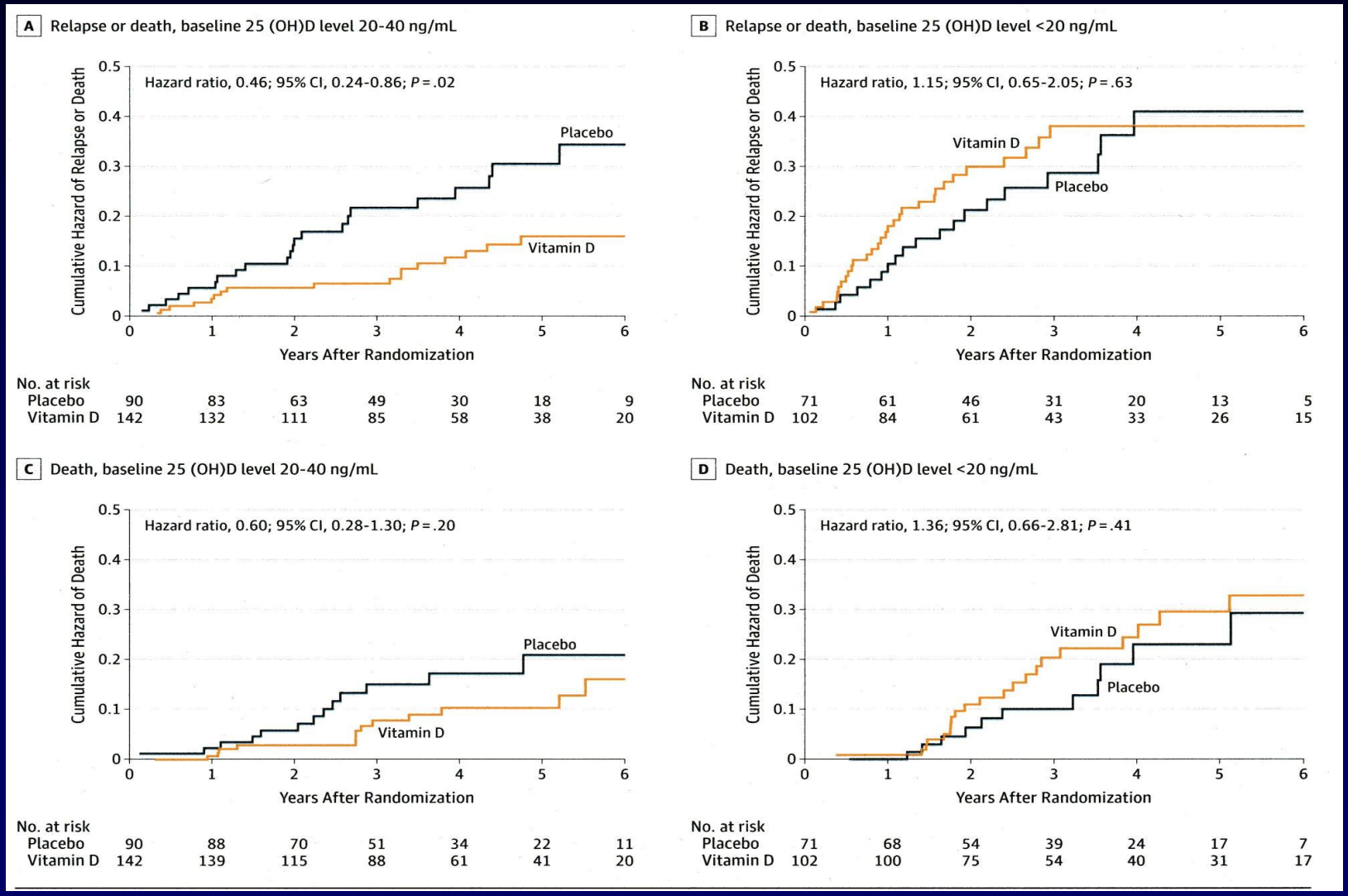
JAMA 2019;321:1366



Vit D Supplement and Outcomes. AMATERASU Trial
Relapse or Death and Vit D levels

JAMA 2019;321:1367

Vitamin D at 2000 IU/d did not improve relapse free survival with digestive tract cancer



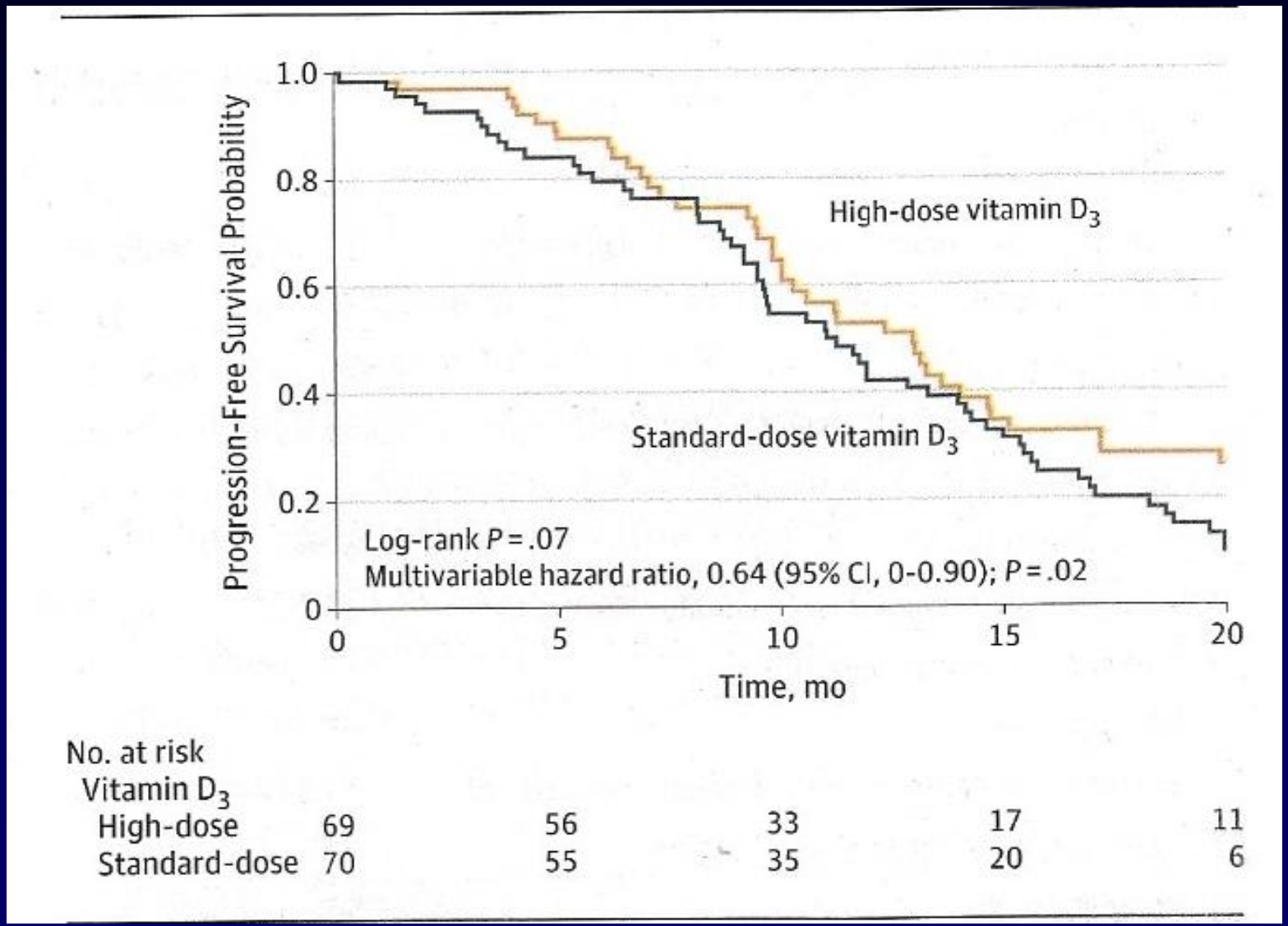
High Dose vs Standard Dose Vit D3 Supplements and Advanced Colorectal Cancer: The SUNSHINE Trial

JAMA 2019;321:1370-79

- **Question:**
  - Does high dose vitamin D3 supplement prolong progression free survival when added to standard chemotherapy for advanced or metastatic colorectal cancer?
  - High dose: 8000 IU/d for cycle 1, 4000 IU/d for subsequent cycles
  - Standard dose: 400 IU /d for all cycles
- **Meaning**
  - In this phase 2 RCT, the findings suggest a potential role for high dose vitamin D3 supplementation in tt of patients with advanced or metastatic colorectal cancer. Further large scale trials warranted

High Dose vs Standard Dose Vit D3 Supplements and Advanced Colorectal Cancer: The SUNSHINE Trial

JAMA 2019;321:1370-79



Effect of Vitamin D and Calcium Supplementation on Cancer Incidence in Older Women: a RCT

JAMA 2017; 317:1234-43

- **Question:**
  - Does dietary supplementation with vitamin D3 and calcium reduce the risk of all type cancer among older women?
  - 2903 healthy postmenopausal women, baseline vitamin D level of 32.8 ng/ml
  - Supplemented with vitamin D3 (2000 IU/d) and calcium (1500 mg/d), vs placebo for 4 years

- **Meaning**
  - Supplementation with vitamin D3 and calcium did not result in a significantly lower risk of cancer among healthy older women

MVT and Mineral Supplements

Dietary Supplement Use: Background

- **Definition:**
  - **MVMM (Multi Vitamin Multi Mineral) defined as use of any products containing 10 or more vitamins/minerals, as well as individual vitamins and nonvitamin, nonmineral (NVNM) supplements**
- **OTC supplements were used by 50 to 75% of US adults based on one study (CRN 2017)**
- **Based on NHANES data (1999 – 2012), the overall use of supplements remained stable during the period**
  - **Study of 37,958 non-institutionalized adults**
  - **52% reported use**

Kantor ED et al. Trends in supplement use among US adults from 1999-2012. JAMA. 2016;316:1464-74

Council for Responsible Nutrition. CRN 2017 Annual Survey on Dietary Supplements.

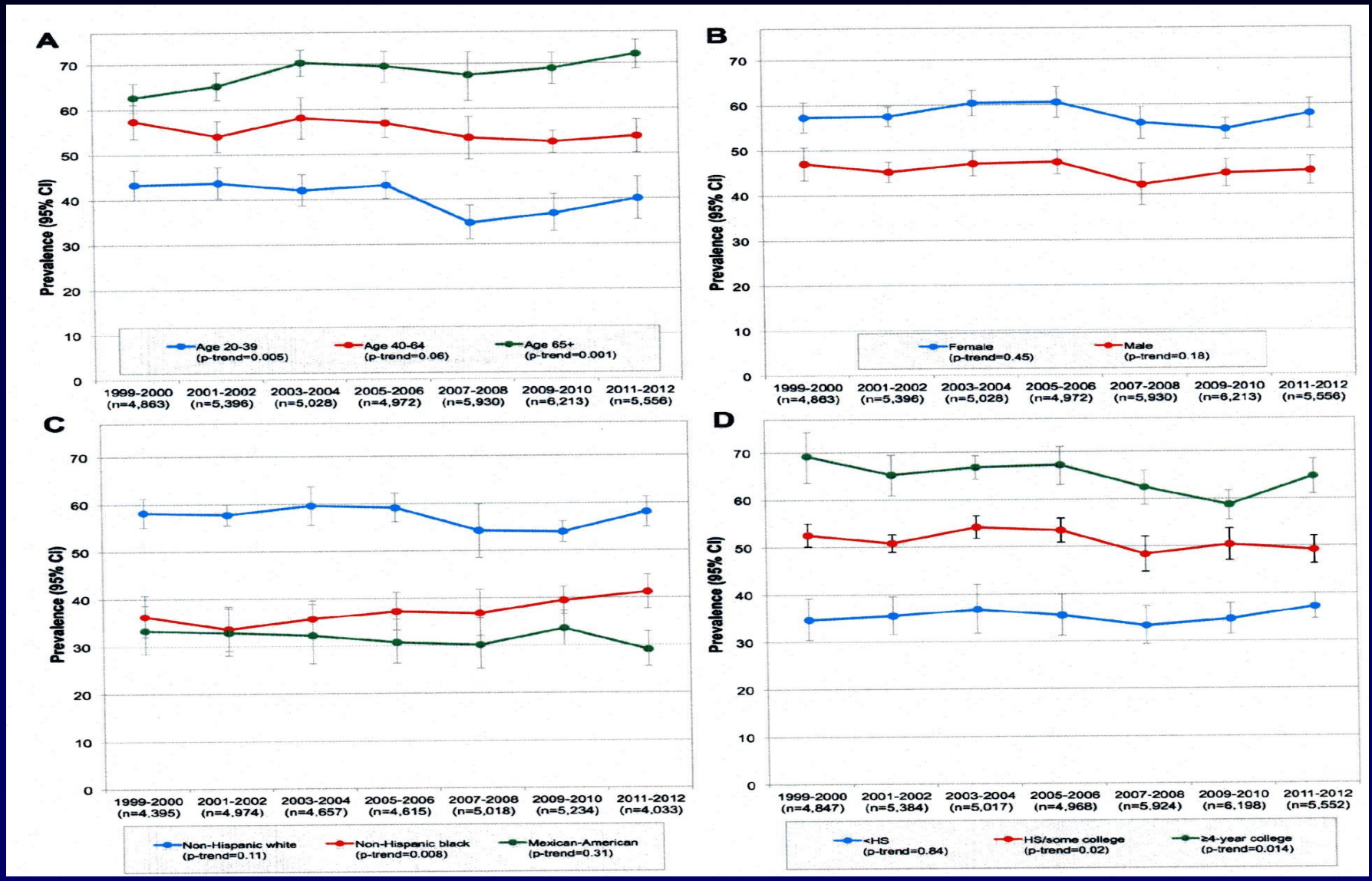
Dietary Supplement: Use and Misuse

- **Why are they used?**
  - To increase or replace some dietary constituents
  - To reduce risk of poor outcomes, esp. cancer and CVD
  - To improve sense of well being
  - Weight loss
  - Sexual enhancement
- **Why are we concerned?**
  - Adulteration by ingredients such as steroids, sildenafil, fluoxetine and more, with adverse health effects
  - Drug interactions with other medications
  - Not standardized, batch to batch, or even in each batch

Kantor ED et al. Trends in supplement use among US adults from 1999-2012. JAMA. 2016;316:1464-74
Tucker J et al. Unapproved pharmaceutical ingredients included in dietary supplements associated with US Food and Drug Admn. warnings. JAMA New Open. 2018; 1:e183337

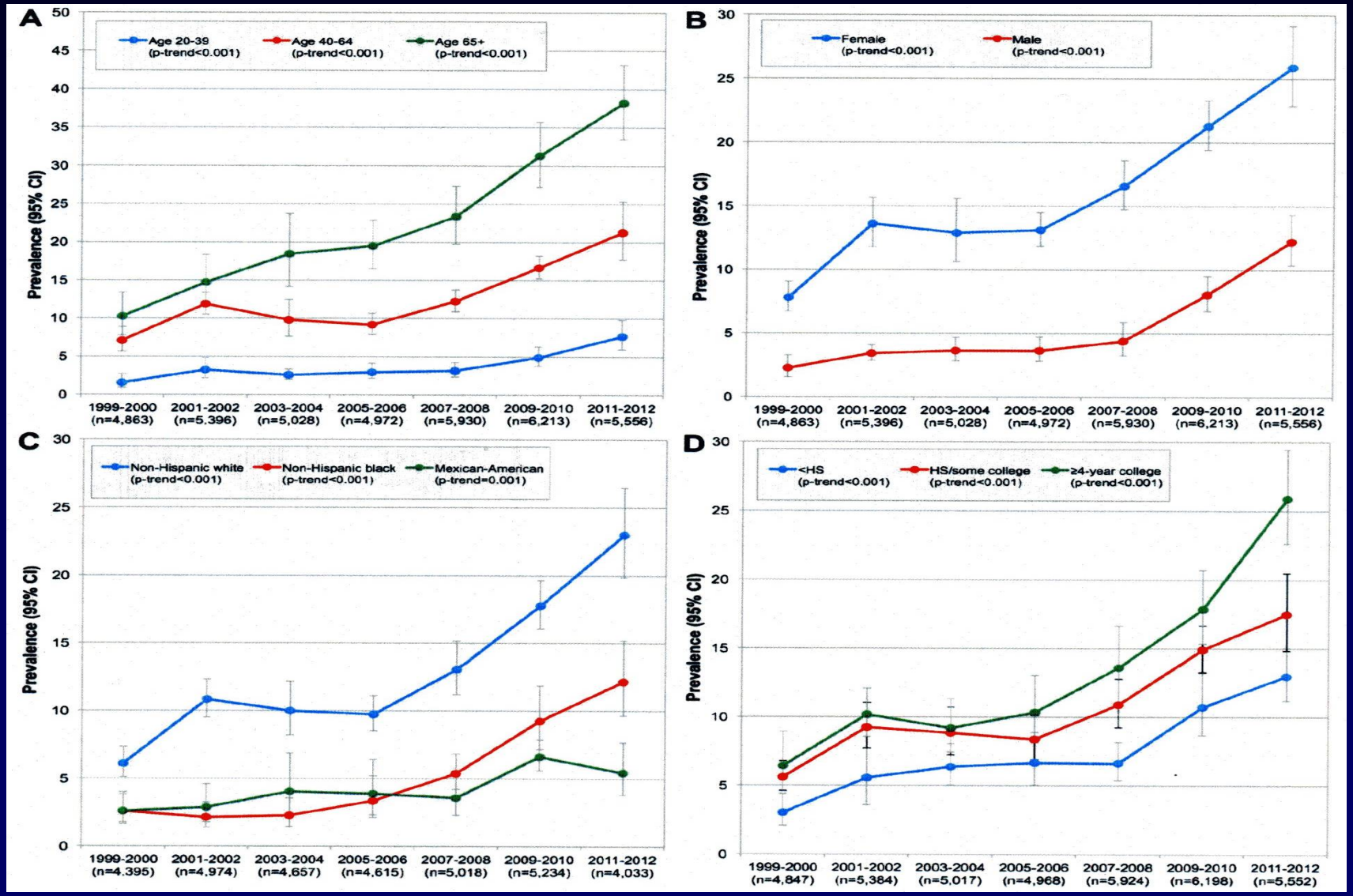
Trends in Any Supplement Use in U.S. Age (A), Gender (B), Race (C), Education (D)

JAMA.2016;316:1464-1474



Trends in Use of Vitamin D in U.S.
Age (A), Gender (B), Race (C), Education (D)

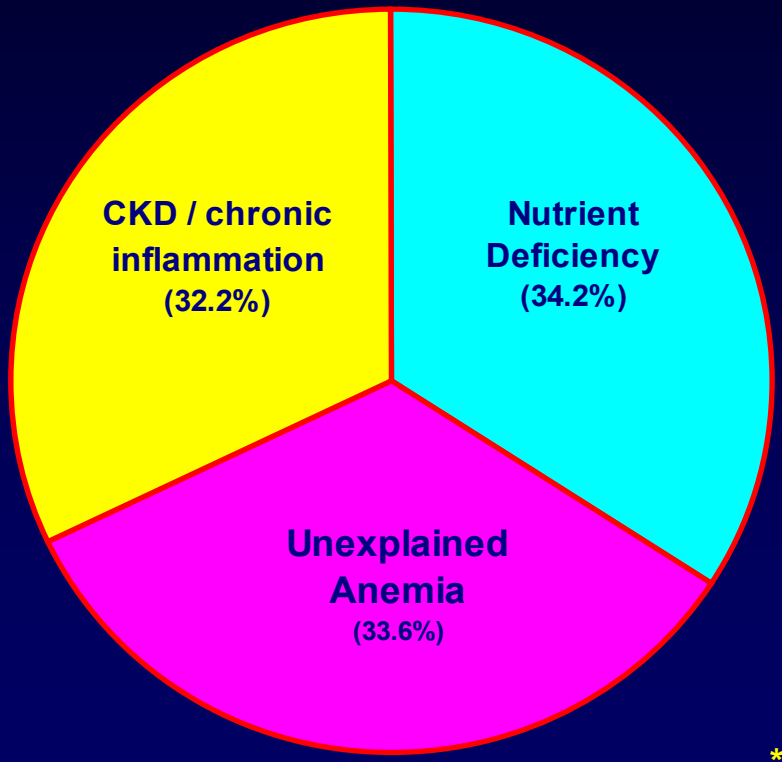
JAMA.2016;316:1464-1474



Supplement Use Trends in the U.S., 1999 - 2012

Stable Use	Increased Use	Decreased Use
Biotin	Lutein	Calcium
Calcium (excluding MVMM)	Lycopene (men only)	Copper, phosphorus
Iron (excluding MVMM)	Vitamin B12	Iron, magnesium, zinc
Lycopene (excluding MVMM)	Vitamin D (excluding MVMM)	Selenium
Vitamin A		Vitamin A
Vitamin D (in MVMM)		B1, B2, B3, B6, B12, folic acid
Vitamin K		Ginkgo biloba

Etiology of Anemia* (NHANES III, 1988-1994)



* WHO criteria for Anemia

Older Adults at Risk for B12 Deficiency

- Food - cobalamin malabsorption
- Atrophic gastritis, including H. pylori infection
- Prolonged use of acid lowering agents
- Pernicious anemia
- Gastric or ileal surgery
- Strict vegetarianism
- Bacterial overgrowth, blind loops
- Crohn's disease
- Chronic pancreatitis
- Medications: metformin, PPIs, etc

Carmel R. Am J Clin Nutr. 1997; 66:750-9

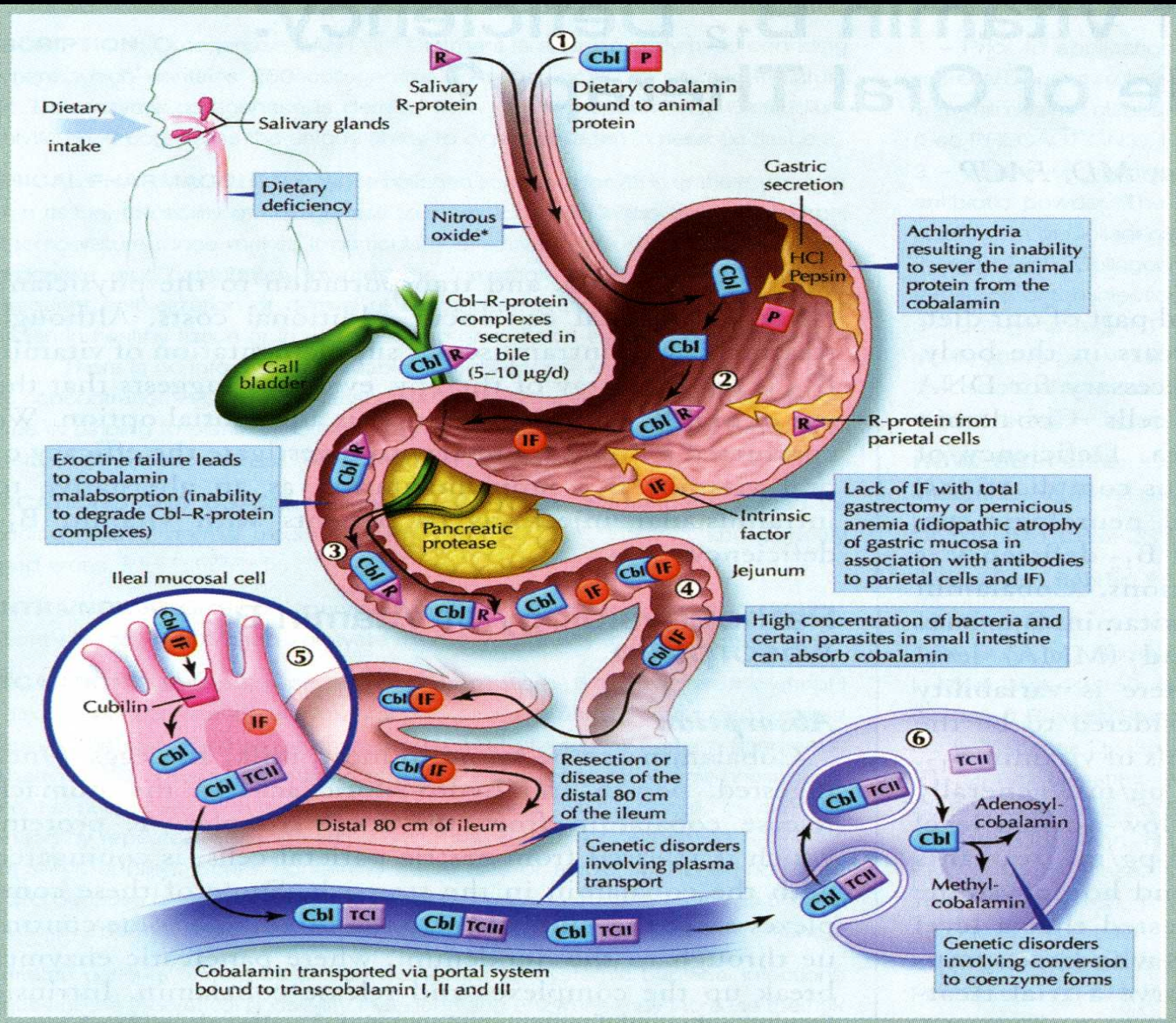


Figure 1. Cobalamin Metabolism and Corresponding Causes of Deficiency.

Vitamin B_{12} is unique among vitamins in that it is found almost exclusively in animal flesh and other animal-derived foods such as milk, cheese, and eggs. People who eat any or all of these foods are guaranteed an adequate intake. Strict vegetarians, however, must be sure to use vitamin B_{12}-fortified products such as fortified soy milk or take supplements.

Vegetables and B12

Fruits and B12

Metformin Related B12 Deficiency

- Diabetics may slow intestinal transit and bacterial overgrowth and malabsorption
- B12-IF complex uptake by ileal cell membrane receptors is calcium dependent
- Metformin affects Ca dependent membrane action
  - Value for screening for B12 status if on metformin

Kin Wah Liu et al. Age and Aging. 2006; 35: 200-1

Principles of Management

- Consider treatment when B12 levels are clearly low or if marginal, with ↑ MMA and/or Hcys
- With deficiency and no symptoms, oral or injection B12
- With deficiency + complications (neurological), initiate by injection therapy to rapidly correct status
- Maintenance with oral B12 possible with large doses
- No B12 toxicity reported with high doses
- While on injection therapy, do not measure levels
- Treatment is usually for life
- Individualize approach to patient preferences and cost

Carmel R. How I treat cobalamin (B12) deficiency. Blood. 2008; 112: 2214-21

Stabler SP. Screening the older population for cobalamin (B12) deficiency. J Am Geri Soc. 1995;43: 1290-98

Dharmarajan TS et al. An algorithmic approach to screening for vitamin B12 status and treatment of identified deficiency. In Herbert V, ed. Vitamin B12 deficiency. Royal Society of Medicine Press. 1999; 49-51

Treatment of B12 Deficiency

- **Intramuscular**
  - Commonly used, safe, reliable, inexpensive
  - Initiation and maintenance: 100-1000 mcg, Q 1-3 months
- **Intranasal**
  - Weekly instillation of intranasal gel 500 μg
- **Oral** (500-2000 μg daily)
  - Useful in strict vegans, with or without IF
  - Large doses effective even in pernicious anemia (no IF)
  - Least reliable, compliance influences results
- **Sublingual**
  - Effective, convenient alternative form of administration
  - Dose: Cobalamin nuggets 2000 μg daily

Delpre et al. Lancet, 1999;354:740-1
Andres E et al. Efficacy of oral cobalamin (vit B12) therapy. Expert Opin Pharmacother 2010. 11: 249-56
Carmel R. How I treat cobalamin (B12) deficiency. Blood. 2008; 112: 2214-21

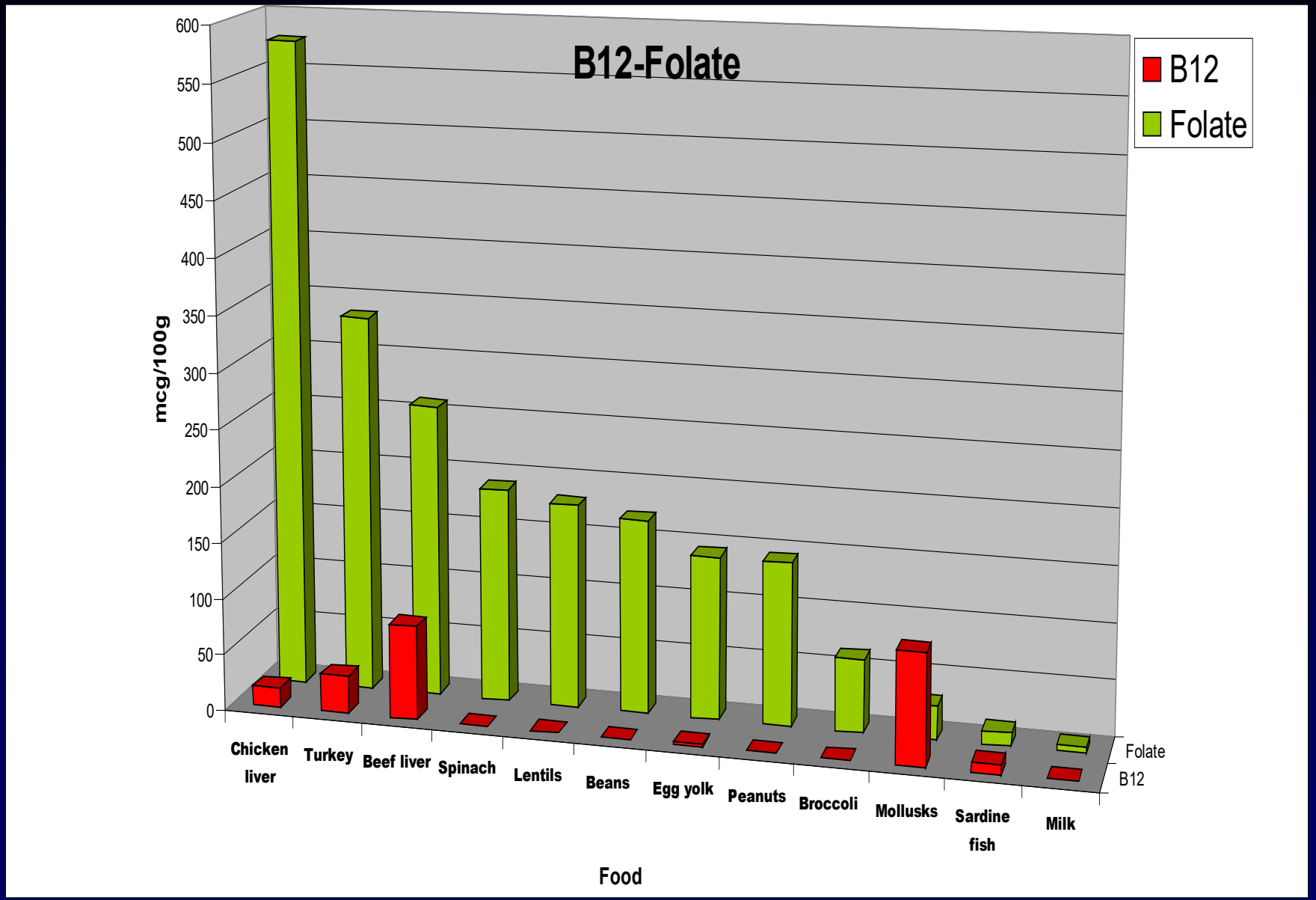
Folic Acid or Folate?

- Terminolgy: **Folic acid or folate?**
  - Folic acid is the form in supplements, 100% bioavailability
  - Folate in food: availability is <50%, > half lost in frying or boiling
  - Red cell or serum folate: RBC folate stable, fluctuates little

- **Folate is present in virtually all foods**
  - Dairy, poultry, meat (liver, kidney), seafood, fruits, veggies, nuts
  - Highest: yeast, spinach, liver, peanuts, kidney beans
  - Fortification of cereals and grains mandated in the U.S.

- RDA: 400 µg /d

Carmel R. Folic Acid. Modern Nutrition in Health and Disease. 2006; 470-81


B12-Folate
B12
Folate
mcg/100g
600
550
500
450
400
350
300
250
200
150
100
50
0
Chicken liver
Turkey
Beef liver
Spinach
Lentils
Beans
Egg yolk
Peanuts
Broccoli
Mollusks
Sardine fish
Milk
Folate
B12
Food

Folate Deficiency: Causes

- **Nutritional:** malnutrition, malabsorption
- **Excess utilization**: psoriasis, hemolysis
- **Excess loss:** dialysis, CHF, liver disease
- **Alcohol**: inhibits entero-hepatic circulation
- **Drug interactions;**
  - phenytoin, methotrexate, trimethoprim, triamterene

Snow CF. Arch Intern Med. 1999;159: 1289-98
Smith RL. J Am Med Dir Assn. 2001; 2: 230-8

Vitamins A, C and E

- **Vitamin A:**
  - Excessive use causes liver toxicity, decline in bone density
  - Raised intracranial pressure (pseudotumor cerebri)
  - Beta carotene (vitamin A precursor): predisposes to lung cancer in tobacco users and linked to CVD
- **Vitamin C**
  - Taken in excess, causes increase in urinary oxalate excretion and renal stone risk
- **Vitamin E**
  - Serum vitamin E may be a predictor of hemorrhagic events in atrial fib if on warfarin
  - Linked to colorectal adenoma, prostate cancer and higher overall mortality
- Moyer VA. Vitamin, mineral and MVT supplements for primary prevention of CVD and cancer. USPSTF statement. Ann Intern Med. 2014;160:558-64

Vitamin D, Summary

- Vitamin D deficiency is common in all ages, and especially in older adults
- Evidence is pending for the roles of vitamin D beyond skeletal health, for other organs / systems
- Routine use of vit D and / or calcium for prevention of fractures and falls is perhaps not beneficial
- For those with osteoporosis, vitamin D deficiency and for vulnerable adults, it may be prudent to supplement vitamin D
- In the Omega 3 Trial, supplementing vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events versus placebo

Dharmarajan TS. Current Opin Gastroenterol. 2015; 31: 143-52

CURRENT OPINION

Is vitamin supplementation appropriate in the healthy old?

T.S. Dharmarajan[a,b,c]

Purpose of review
Vitamin supplements are used by large numbers of older adults. Although vitamins serve several functions in the body, the benefits or harm of routine supplementation are far from clear. Data from studies over the last decade are reviewed to enable an understanding.

Recent findings
Summarized data from studies conducted over the last few years, pertinent to the use of vitamins, as multivitamin combinations and as individual vitamins specifically A, D, E, C, and the B group are presented. This review targets the benefits and harm of multivitamins when used to lower the risk of cancer, cardiovascular and cerebrovascular disease, visual disorders (e.g., cataracts and age-related macular degeneration), and bone disease. The effects of vitamins on total mortality are discussed. In addition, isolated or multiple vitamin deficiencies, their predisposing settings and manifestations from mild-to-life-threatening illness are discussed.

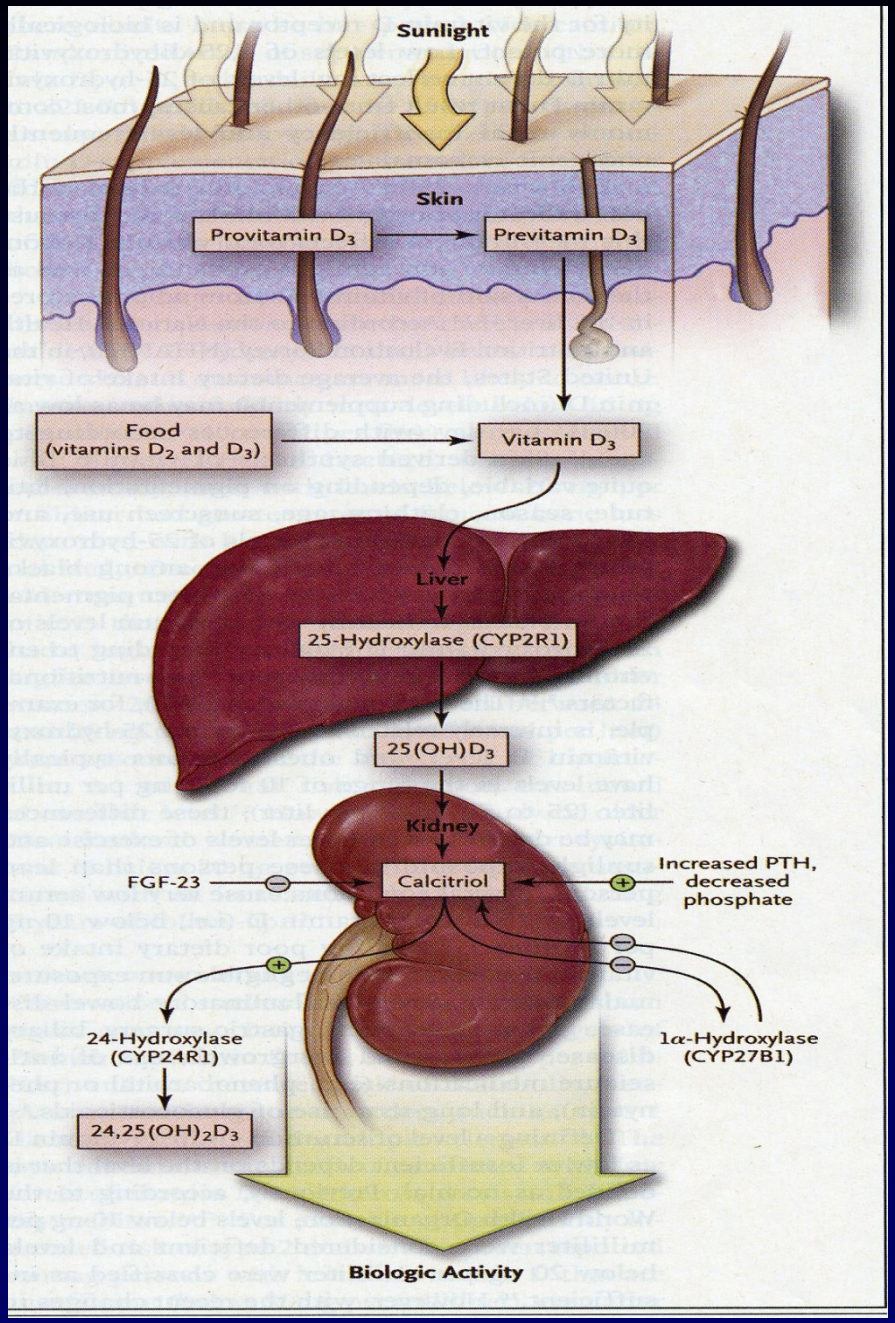
Summary
Data from studies demonstrate considerable variations, most confirming little to no benefit following supplementation in healthy adults. However, clear roles exist for vitamin supplementation in states of deficiency and in subgroups of older adults at high risk for deficiency from specific or multiple vitamins. In these settings, vitamin supplements help prevent or correct deficiency and related manifestations.

Vitamin Supplementation In the Healthy Old

- Data suggests little to no benefit for routine supplements of vitamins / minerals in healthy old
- A balanced diet similar to the Mediterranean diet will likely provide most essential nutrients
- Data on reduction of risk for cancer, vascular disease, cognitive decline and mortality are not supported by the use of MVTs / supplements
- Consumed in excess, there may even result harm
- Subgroups on restricted diets, poor intake and nutrient deficiencies from illness (e.g. vit D, B12, calcium, iron etc) may benefit from replacement
- MVT / supplements are never a replacement for a healthy and balanced diet

Thank You !

Figure from: Rosen CJ.
N Eng J Med 2011;364:248-54



Meeting Vitamin D Requirements

- **Exposure of the skin to UVB**
  - Consider sunlight, portable UVB device e.g. Sperti lamp, tanning bed
- Diet or supplements
- **Treatment of Deficiency**
  - Vitamin D2 or D3 at 50,000 IU weekly or monthly
  - Daily vitamin D at 600, 800, 1000 or 2000 IU
- **In CKD:**
  - In CKD stage I-III, test for status and use vitamin D
  - In CKD stage IV-V, consider analogues: calcitriol, paricalcitol, or doxercalciferol, under guidance of a nephrologist

Holick MF. Mayo Clin Proc. 2006; 81: 353-73
Holick MF. New Eng J Med. 2007; 357: 266-81
Bischoff-Ferrari HA. Adv Exp Med Bio. 2008;624: 55-71