Nutrition and Vitamin Supplements

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Learning Objectives

- Describe the role of common vitamins and minerals in normal physiology and disease
- Review the beneficial effects of vitamin and mineral supplements in the elderly
- Identify the potential toxic effects of vitamin and mineral supplements in the elderly
## Nutrient Content of a Multivitamin
Supplying the RDI

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Amount per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>5000 IU</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>60 mg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>400 IU</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>30 IU</td>
</tr>
<tr>
<td>Thiamine (B₁)</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Pyridoxine (B₆)</td>
<td>2 mg</td>
</tr>
</tbody>
</table>

## Nutrient Content of a Multivitamin
Supplying the RDA

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Amount per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riboflavin (B₂)</td>
<td>1.7 mg</td>
</tr>
<tr>
<td>Niacin</td>
<td>20 mg</td>
</tr>
<tr>
<td>Folic acid</td>
<td>400 mcg</td>
</tr>
<tr>
<td>Cyanocobalamin (B₁₂)</td>
<td>6 mcg</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>10 mg</td>
</tr>
</tbody>
</table>
Vitamin Considerations

- Vitamin deficiencies do happen!
- High-risk patients for deficiencies:
  - Liver and renal diseases
  - Undernourished
  - Malabsorption (e.g., IBD, SBS)
  - Substance abuse
  - Geriatrics
  - Chronic inflammatory disease

Vitamin A and Beta Carotene

- Retinol (vitamin A) is a member of the retinoid class while beta carotene is a carotenoid (a metabolic precursor of retinol)
- Retinol is found predominantly in foods of animal origin (meats, fish, dairy products)
- Primary food sources for beta carotene include fruits and vegetables
**Vitamin E**

- Functions: maintain normal cell structure; production of RBCs; antioxidant
- Signs of deficiency: increased platelet aggregation, neuropathy, hemolysis
- RDA: 8-10 mg α-TEs/day (PO)
- NAG-AMA: 10 IU (IV)
  
  \[(0.67 \text{ mg } \alpha-\text{Tes} = 1 \text{ IU})\]

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**Vitamin K**

- Functions: coagulation; skeletal development
- Signs of deficiency: bleeding (bruising to hemorrhage)
- RDA: 45-80 µg/day
Thiamine Deficiency (B₁):

- Thiamine: water-soluble vitamin which may be depleted within 2-3 weeks
- Involved in conversion of pyruvate to acetyl CoA, which enters Kreb’s cycle to yield ATP
- Increased delivery of glucose via PN accelerates consumption of thiamine stores
- Pyruvate is converted to lactic acid in the absence of thiamine
Development of Thiamine Deficiency

- Time period for development of lactic acidosis: 1-4 weeks
- Presentation forms of thiamine deficiency:
  - “Wet” beriberi (cardiovascular system)
  - “Dry” beriberi (nervous system)
  - Subclinical deficiency
Signs of Thiamine Deficiency

- “Wet” beriberi (cardiovascular system)
  - peripheral vasodilation and increased cardiac output
  - Na/H₂O retention leading to edema
  - venous congestive state, associated with increased RVEDP and PVP
  - Physical findings: tachycardia, cyanosis, cardiomegaly, neck vein distention

- “Dry” beriberi (nervous system)
  - peripheral neuropathy (distal segments of limbs)
  - Wernicke’s encephalopathy (eye palsies, ataxia)
  - Korsakoff’s syndrome (amnesia, inability to learn)

- Subclinical deficiency: irritability, frequent headaches, unusual fatigue
- RDA: 1-1.5 mg/day (PO)
- NAG-AMA: 3 mg/day (IV)
**Riboflavin (B<sub>2</sub>)**

- Functions: electron transport intermediary for oxidation-reduction rx, thus utilization of CHO, fats, and proteins; production of energy in cells
- Signs of deficiency: sore throat, cheilosis, magenta tongue
- RDA: 1-1.2 mg/day (PO)
- NAG-AMA: 3.6 mg/day (IV)

**Pyridoxine (B<sub>6</sub>)**

- Functions: essential cofactor for metabolism of protein & lipid, gluconeogenesis, CNS development, heme synthesis, and normal immune function
- Signs of deficiency: seborrheic dermatitis, microcytic anemia, angular stomatitis, glossitis
- RDA: 1.2-1.7 mg/day (PO)
- NAG-AMA: 4 mg/day (IV)
Cyanocobalamin (B\textsubscript{12})

- Functions: cofactor for CHO, protein, and fat metabolism
- Signs of deficiency: megaloblastic anemia, peripheral neuropathy, diarrhea, weight loss
- RDA: 2.4 μg /day (PO)
- NAG-AMA: 5 μg/day (IV)

Niacin

- Functions: metabolism of amino acids, fatty acids, CHO
- Signs of deficiency (pellegra): 3 D’s are dermatitis, diarrhea, and dementia
- RDA: 14-16 mg/day (PO)
- NAG-AMA: 40 mg/day (PO)
Folic Acid

- Functions: metabolism of amino acids and in nucleic acid synthesis
- Signs of deficiency: megaloblastic or macrocytic anemia
- RDA: 400 μg/day (PO)
- NAG-AMA: 400 μg/day (IV)

Ascorbic Acid (C)

- Functions: collagen synthesis, wound healing, immune function
- Signs of deficiency (scurvy): skin petechiae, bleeding gums, periungual hemorrhage
- RDA: 60 mg/day (PO)
- NAG-AMA: 100 mg/day (IV)
Biotin

- Functions: essential cofactor for fatty acid synthesis, gluconeogenesis, and BCAA metabolism
- Signs of deficiency: pallor, glossitis, hair loss, seborrheic dermatitis
- RDA: 25-30 µg/day (PO)
- NAG-AMA: 60 µg/day (IV)
Pantothenic Acid

- Functions: cofactor in amino acid and fatty acid metabolism; gluconeogenesis; heme and sterol synthesis
- Signs of deficiency: fatigue, malaise, sleep disturbances, N/V, paresthesias, hypoglycemia
- RDA: 5 mg/day (PO)
- NAG-AMA: 15 mg/day (IV)

Case Study 1

- 45 year-old healthy woman presents with complaints of tingling sensations in hands and feet. Also complains of stomach pain that is different from heartburn.
- In addition, she reports memory difficulty, extreme fatigue, aversion to the odor of cooking meat, decreased ability to taste food.
- She has no history of alcohol use, neurological disorders, diabetes, or GI surgery.
- Medication history is noncontributory; caloric intake is adequate
- Physical exam: reveals no recent weight changes; absence of reflexes in both arms with decreased reflexes in lower extremities
- Laboratory values: all chemistry tests within normal limits; autoimmune disorders ruled out. A nerve conduction study was performed and confirmed peripheral neuropathy of unknown origin.
- Referred to gastroenterologist. EGD performed that revealed gastritis, thinning of the gastric mucosa, \textit{H. pylori} infection
Case Study 1

• What vitamin/mineral deficiencies might you suspect?
• What additional biochemical tests would you recommend?

Case Study 1 Discussion

• Likely suffering from a vitamin B12 deficiency, as reflected by paresthesia of the hands and feet, poor memory, and irritability.
• Etiology may have been due to vitamin B12 malabsorption, secondary to the atrophic gastritis with hypochlorhydria or from adult onset pernicious anemia.
• H. pylori overgrowth can also contribute to vitamin B12 deficiency.
• The patient’s history of extreme fatigue could suggest anemia secondary to either folic acid or vitamin B12 or both.
• A zinc deficiency is also probable due to her report of decreased taste acuity and aversion to smells.
Case Study 1 Discussion

- Biochemical test results for vitamin and mineral status revealed the following:
  - red blood cell folate 300 ng/mL (normal range: 270 – 830 ng/mL)
  - serum vitamin B12 90 pg/mL (normal range: 200 – 835 pg/mL)
  - homocysteine level 29 μmol/L (normal range: 5 – 15 μmol/L)
  - serum methylmalonic acid 0.78 μmol/L (normal range: 0.08 – 0.56 μmol/L)
  - serum zinc 78 mcg/dL (normal range: 70 – 150 mcg/dL)
  - hemoglobin, hematocrit, MCV normal

- Interpretation:
  - Depressed vitamin B12 levels with elevated levels of homocysteine and serum MMA, and this is reflective of vitamin B12 deficiency

- Treatment:
  - Usually involves loading doses of daily to weekly B12 parenteral injections over a period of 1 – 3 months; can also use oral doses of 0.5 – 1 mg/day x 10 days
  - Initiate triple therapy for H. pylori infection (PPI, Clarithromycin, Amoxicillin)

He’s just going to keep talking until........

Don’t Shoot the Messenger of these recommendations!
Recommendations for MVs

- Given the greater likelihood of benefit than harm, a MV that does not exceed RDI of its component vitamins is reasonable for most adults.
- Daily MVs are especially important for:
  - Women who might become pregnant
  - People who consume 1-2 alcoholic drinks/day
  - Vegans who require supplemental vitamin B12 (because vitamin B12 is found in animal products only, such as meat, poultry, fish, eggs, and milk).

Recommendations for MVs

- Daily MVs are especially important for:
  - Poor urban residents who may be unable to afford adequate intake of fruits and veggies
  - Elderly (> 65 yrs) who tend to absorb vitamin B12 poorly and are often deficient in vitamin D
- Although commonly prescribed due to poor intake of vitamin B12 and D, do not recommend 2 MVs in the elderly because of:
  - the risk that increased vitamin A intake may increase the risk of hip fracture
  - Increased iron intake can increase risk of hemochromatosis in some people
Iron (Fe)
- An essential mineral and an important component of proteins involved in oxygen transport and metabolism
- Foods high in heme Fe are meat, fish, and poultry, and is absorbed very well
- Nonheme Fe is not as well absorbed as heme Fe, and is found in flours, cereals, and grain products

Iron absorption
- Dietary factors, such as meat proteins and vitamin C, can improve nonheme Fe absorption
- Ca+, polyphenols and tanins found in tea, and phytates, found in legumes, rice, and grains, can decrease the absorption of nonheme Fe

Populations at risk for Fe deficiency include women of childbearing age, pregnant women, older infants and toddlers, and teenage girls
Individuals with renal failure are at risk for Fe deficiency because of inability to synthesize erythropoietin
Common Vitamins/Minerals

- Iron supplements
  - Available in 2 forms: ferrous or ferric
  - Ferrous form is better absorbed
  - Adverse reactions include GI effects such as nausea, vomiting, constipation, dark colored stools, and/or abdominal pain.
  - To minimize GI side effects, start with half of recommended dose and gradually increase to full dose
  - Taking in divided doses with food may also help

Common Vitamins/Minerals

- Cautions with Fe supplements
  - Moderate to high potential for toxicity because very little Fe excreted from the body
  - Fe overload is associated with accumulation in liver
  - Acute toxicity can occur in children from overdoses of medicinal Fe; as few as 5-6 high-potency tabs can be fatal to a child of 22 lbs.
  - Fe supplements must be kept tightly capped and away from children’s reach
**RDI for Iron**

<table>
<thead>
<tr>
<th>Age</th>
<th>Infant/child</th>
<th>Males</th>
<th>Females</th>
<th>Pregnancy</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-12 mo</td>
<td>11 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 yrs</td>
<td>7 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-8 yrs</td>
<td>10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-13 y</td>
<td>8 mg</td>
<td>8 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-18 y</td>
<td>11 mg</td>
<td>15 mg</td>
<td>27 mg</td>
<td>10 mg</td>
<td></td>
</tr>
<tr>
<td>19-50 y</td>
<td>8 mg</td>
<td>18 mg</td>
<td>27 mg</td>
<td>9 mg</td>
<td></td>
</tr>
<tr>
<td>&gt; 50 y</td>
<td>8 mg</td>
<td>8 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Common Vitamins/Minerals**

- **Vitamin D**
  - Fat soluble vitamin, with major function to maintain normal blood concentrations of Ca+ and phosphorus
  - Promotes bone mineralization in concert with other vitamins, minerals and hormones.
  - Fortified food, such as milk, is a major source; naturally occurring foods such as fatty fish and fish oils contain significant amounts of vitamin D
  - Exposure to sunlight triggers vitamin D skin synthesis
Common Vitamins/Minerals

- Populations at risk for vitamin D deficiency:
  - Older Americans (> 50 yr) due to decreased skin synthesis and increased kidney disease
  - Homebound individuals living in the North
  - Fat malabsorption such as pancreatic enzyme deficiency, Crohn’s disease, cystic fibrosis, sprue, hepatic insufficiency, small bowel disease
  - Patients taking chronic corticosteroids

Common Vitamins/Minerals

- Cautions with Vitamin D supplements
  - Vitamin D toxicity can cause nausea, vomiting, poor appetite, constipation, weakness, and weight loss.
  - It can raise calcium blood concentrations, causing mental status changes.
  - Adequate intake of vitamin D is 200-400 IU (5-10 mcg) per day for adults 19-69 yrs and 600 IU (15 mcg) per day for age 70 + .
  - Doses of > 2000 IU (50 mcg) per day are not advised.
Common Vitamins/Minerals

- Magnesium (Mg)
  - Mineral that participates in > 300 biochemical reactions in the body
  - It helps maintain normal muscle/nerve function, normal sinus rhythm, and is critical for bone strength
  - Foods rich in Mg include green veggies, nuts, seeds, and whole grains
  - Refined foods, such as white bread, are usually low in Mg because Mg-rich germ and bran are removed when white flour is processed

Common Vitamins/Minerals

- Populations at risk for Mg deficiency:
  - Chronic use of medications such as loop diuretics (furosemide), chemotherapy agents (Cisplatin), immunosuppressants (cyclosporin A)
  - Excessive urinary wasting of Mg such as observed in poorly controlled diabetes or increased EtOH intake
  - GI disorders, such as Crohn’s disease, Ulcerative colitis, patients with small bowel resections, excessive diarrhea or vomiting
Common Vitamins/Minerals

- Signs of Mg deficiency include:
  - Neurological (confusion, disorientation)
  - Neuromuscular (muscle contractions, paraesthesias)
  - Cardiovascular (arrhythmias, coronary spasm)
- Recommended dietary intake:
  - Ages 14-18 yr: 360/410 mg (for females/males)
  - Ages 19-30 yr: 310/400 mg (for females/males)
  - Ages > 31 yr: 320/420 mg (for females/males)
- Mg Gluconate is the salt form least likely to cause diarrhea

Case Study 2

- 40 year-old male with a history of Crohn’s disease x 17 years
- He has known extensive small bowel and colonic involvement.
- He complains of muscle stiffness and cramps, easily fatigued with SOB.
- His BMI = 21 and he has apparent loss of muscle mass in his arms/legs.
- He is having 10-15 liquid bowel movements per day
- What nutrient deficiencies should be considered in this patient?
Case Study 2 Discussion

- Low BMI and apparent muscle loss is consistent with protein-calorie malnutrition
- Excessive GI losses could contribute to iron and B12 deficiencies. Ineffective absorption of iron and B12 is probably secondary to extensive malabsorption.
- What biochemical tests would you order?
  - Hemoglobin
  - Hematocrit
  - RBC folate
  - Serum ferritin
  - Serum vitamin B12, MMA, homocysteine

Case Study 2 Discussion

- Test results:
  - Hemoglobin 11 g/dL (normal range: 14 – 19 g/dL)
  - Hematocrit 34% (normal range: 40 – 54%)
  - RBC folate 500 ng/mL (normal range: 270 – 840 ng/mL)
  - Serum ferritin 10 ng/mL (normal range: 17 – 250 ng/mL)
  - Serum vitamin B12 100 pg/mL (normal range: 200 – 835 pg/mL)
  - Elevated homocysteine, MMA
- Interpretation: mixed microcytic/macrocytic anemia
- Treatment: oral iron sulfate supplementation (325 mg/day) and monthly B12 injections
Common Vitamins/Minerals

- Zinc (Zn)
  - Trace mineral essential for normal growth in children
  - Important for development of the GI tract, immune system, and the retina
  - Foods rich in Zn include meat, poultry, eggs, cheese, and whole grains
  - Humans easily absorb dietary Zn

Common Vitamins/Minerals

- Populations at risk for Zn deficiency include pregnant or breast feeding women, post-menopausal women on Ca+ supplements, and GI malabsorptive disorders (SBS, Crohn’s disease, sprue).
- Cautions with Zn:
  - High concentrations of Zn are known to lower HDL and increase LDL
  - Excess Zn can interfere with Cu absorption, causing deficiency
  - Excess Zn may suppress the immune system and impede wound healing
Folate and Neural Tube Defects

- Folate is necessary for embryogenesis.
- Multiple observational and randomized trials have demonstrated that folate supplementation reduces the risk of neural tube defects.
- Folate supplementation decreases the risk of first occurrence and recurrent neural tube defects.
- Intakes well above 400 mcg may be necessary to maximally reduce the risk of neural tube defects.

Definitions & Terminology

- Free radicals possess an unpaired electron in their outer orbit
- Unpaired electrons react to generate more stable species
- Most important free radicals are oxygen derivatives

Antioxidant Defense Network

Enzymatic Antioxidants

Superoxide $\xrightarrow{SOD} H_2O_2 \xrightarrow{catalase} GSH \xrightarrow{GSH} H_2O + O_2 \xrightarrow{H_2O + ROH + GSSH}$

- Trace elements (Mn, Cu, Zn, Se) serve as cofactors for these enzymatic reactions
- Deficiencies may impair activity of antioxidant enzymes
**Actions of Oxygen-Free Radicals**

- **Lipid peroxidation**
  - cyclic peroxides
  - TBARS assay

- **Alter ATP/DNA synthesis**
  - purine/pyrimidine base pairs
  - alter polymerases causing cell death

- **Interfere with cytokines**
  - prevent antitumor effects
  - increase NFκB activity

**Antioxidants**

Oxygen Radicals

Antioxidants
Vitamin A

- Function: vision, cellular differentiation, epithelial integrity
- Signs of deficiency: night blindness, conjunctival xerosis, anorexia
- RDA: 800-1000 μg RE/day (PO)
- NAG-AMA: 3300 IU/day (IV)
  \(1 \mu g \text{ RE} = 3.33 \text{ IU all-trans retinol}\)

Vitamin A and Beta Carotene

- Retinol (vitamin A) is a member of the retinoid class while beta carotene is a carotenoid (a metabolic precursor of retinol)
- Retinol is found predominantly in foods of animal origin (meats, fish, dairy products)
- Primary food sources for beta carotene include fruits and vegetables
Bitot’s spots, reflects vitamin A deficiency.
Dietary Carotenoids and Cardiovascular Disease*

<table>
<thead>
<tr>
<th>Quintile Carotene</th>
<th>Daily Intake (IU)</th>
<th>Relative Risk</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;5030</td>
<td>1.0</td>
<td>------</td>
</tr>
<tr>
<td>2</td>
<td>5030-7019</td>
<td>0.72</td>
<td>0.41-1.25</td>
</tr>
<tr>
<td>3</td>
<td>7020-9592</td>
<td>0.46</td>
<td>0.23-0.91</td>
</tr>
<tr>
<td>4</td>
<td>9593-14387</td>
<td>0.65</td>
<td>0.33-1.27</td>
</tr>
<tr>
<td>5</td>
<td>14388</td>
<td>0.30</td>
<td>0.11-0.82</td>
</tr>
</tbody>
</table>

*Data for current smokers

## Dietary Carotenoids and Lung Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Numbers</th>
<th>Years of Follow-Up</th>
<th>β-Carotene Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stehelin et al.</td>
<td>M: 68</td>
<td>12-14 yr</td>
<td>↓</td>
</tr>
<tr>
<td>Nomura et al.</td>
<td>M: 74</td>
<td>10 yr</td>
<td>↓</td>
</tr>
<tr>
<td>Menkes et al.</td>
<td>M+F: 99</td>
<td>9 yr</td>
<td>↓</td>
</tr>
<tr>
<td>Wald et al.</td>
<td>M: 50</td>
<td>3-10 yr</td>
<td>↓</td>
</tr>
</tbody>
</table>

Side effects of taking mega doses of vitamins!
Beta Carotene Supplementation


- Randomized, double-blind, placebo-controlled trial enrolling 29,133 Finnish males
- Treatment: Beta carotene 20 mg/d ± alpha-tocopherol 50 mg/d
- Average of 20 cigarettes/d for 35.9 years
- Primary endpoints: incidence of cancer and death

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### Beta Carotene Supplementation (alone or combination)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relative Risk (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>1.18 (1.03-1.36)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1.08 (1.01-1.16)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Beta Carotene Supplementation

CARET. NEJM 1996;334:1150-5

- Multicenter, randomized, double-blind, placebo-controlled trial enrolling 18,314 males & females
- Included current/former smokers, asbestos workers
- Treatment: 30 mg beta carotene + 25000 IU retinol
- Primary endpoints: incidence of lung cancer and mortality

### Estimated Relative Risk of Lung Cancer and Death

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Lung Cancer RR (95% CI)</th>
<th>Death RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>1.28 (1.04-1.57)</td>
<td>1.17 (1.03-1.33)</td>
</tr>
<tr>
<td>Asbestos workers</td>
<td>1.40 (0.95-2.07)</td>
<td>1.25 (1.01-1.56)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1.42 (1.07-1.87)</td>
<td>1.15 (0.96-1.56)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>0.08 (0.48-1.31)</td>
<td>1.06 (0.96-1.32)</td>
</tr>
</tbody>
</table>

Beta Carotene Supplementation


- Randomized, double-blind, placebo-controlled trial enrolling 22,071 male physicians
- Treatment: ASA 325 mg ± beta carotene 50 mg QOD
- 11% current smokers and 39% former smokers
- Average follow-up: 12 years (range 11.6-14.2)
- Primary end points: malignant neoplasms, cardiovascular disease, and death

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relative Risk (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant neoplasm</td>
<td>0.98 (0.91-1.06)</td>
<td>0.65</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0.96 (0.84-1.09)</td>
<td>0.50</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.96 (0.83-1.11)</td>
<td>0.60</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.09 (0.93-1.27)</td>
<td>0.28</td>
</tr>
<tr>
<td>Neoplasm death</td>
<td>1.02 (0.89-1.18)</td>
<td>0.79</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>1.02 (0.93-1.11)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Observational Studies of Carotenoids

- Individuals who consume more dietary carotenoids have a lower risk for lung & other cancers
- Individuals with higher plasma carotenoid concentrations have a lower risk for lung cancer and other chronic diseases.
- Taking beta carotene supplements have no benefits and may have adverse effects

Carotenoids and other Cancers

- Overall, beta carotene supplementation does not appear to reduce colorectal cancer risk.
- Beta carotene supplements may benefit regular alcohol users because their serum beta carotene concentrations appear to be lower.
- There is insufficient evidence to recommend beta carotene supplementation for prostate cancer prevention and some evidence of an increase in risk among alcohol users.
Vitamin E and Coronary Disease


- Randomized, double-blind, placebo-controlled
- 1035 patients assigned to α-tocopherol; first 546 patients received 800 IU/day and remaining patients received 400 IU/day
- 967 patients received identical placebo capsules
- Primary endpoints: cardiovascular death + non-fatal MI and non-fatal MI alone
Vitamin E and Coronary Disease

- Major CV events (non-fatal MI and CV deaths) were significantly reduced with α-tocopherol
- α-tocopherol significantly lowers the rate of non-fatal MI alone
- No change in CV deaths in response to α-tocopherol


Vitamin E (α-Tocopherols)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CHAOS</th>
<th>ATBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>population</td>
<td>CAD</td>
<td>smokers, -CAD</td>
</tr>
<tr>
<td>α-tocopherol</td>
<td>400-800 IU</td>
<td>50 mg</td>
</tr>
<tr>
<td>non-fatal MI</td>
<td>(NS)</td>
<td>ND</td>
</tr>
<tr>
<td>CV death</td>
<td>(NS)</td>
<td>ND</td>
</tr>
<tr>
<td>All mortality</td>
<td>(NS)</td>
<td>ND</td>
</tr>
</tbody>
</table>
Setbacks for Vitamin E

- Women’s Health Study (WHS): n=39876 healthy; 600 IU, vitamin E did NOT reduce CV ds or CA. 7/2005
- Heart Outcomes Prevention Evaluation – The Ongoing Outcomes (HOPE-TOO): n=9541 CVD or DM; 400 IU, vitamin E increased risk for heart failure, RR 1.13 [CI, 1.01 – 1.26] as well as hospitalization for heart failure, RR 1.21 [CI, 1.00 – 1.47]. It had no effect on incidence of CA, CVD, and mortality.


Setbacks for Vitamin E

- ADCSG study: n=769 Alzheimer ds (AD); vitamin E 2000 IU, donepezil 10 mg, placebo. Vitamin E had no effect on risk for developing AD nor slowed progression to AD.
- German Vitamin E study: n=160 ALS; vitamin E 5000 IU, vitamin E was NOT effective in slowing the progression of ALS.

Nonenzymatic Antioxidants

- Vitamin E
- Vitamin C
- Glutathione
- ROO•, RO•
- Tocopherol
- Tocopherol radical
- Ascorbate
- Semidehydroascorbate
- GSSG
- GSH
- ROOH, ROH

Geographical regions with medium-to-high coronary mortality have AA concentrations near borderline marginal deficiency (< 22.7 \( \mu \text{M} \)).

Low baseline concentrations of AA (36 \( \mu \text{M} \)) are significant for increased mortality from intestinal cancer (vs 47 \( \mu \text{M} \) in survivors).

Plasma concentrations of 50 \( \mu \text{M} \) to decrease risk of IHD and intestinal cancer may be reached with 100 mg AA/day.

Vitamin C (Ascorbic Acid)

- 30 separate randomized and non-randomized trials of AA taken to prevent or treat the common cold
- Doses of AA 1 gm/day for several months had no consistent beneficial effect for prevention of colds
- A modest benefit in reducing duration of cold symptoms (8-9% in symptom days) may be seen with AA ingestion.


Selenium

- Selenium is a component of glutathione peroxidase
- Protects against peroxide-induced damage
- Low Se concentrations are linked to an increased risk of cardiovascular disease
Plasma Selenium & Acute MI

- Subset of PHS in which baseline selenium plasma concentrations were obtained
- 251 physicians with acute MI were matched to 1 control with matching age and smoking habits
- Mean plasma selenium concentrations were nearly identical (114.4 ± 15.1 ng/g vs 113.3 ± 15.7, p = 0.35)
- No protective effect observed in patients with highest vs lowest selenium concentrations.

Salvini et al. Am J Cardiol 1995;76:1218-1221.

Influence of Selenium After Burns

- Prospective clinical trial enrolling 10 patients with 41 ± 9% TBSA burns
- One group received standard vs supplemented trace elements (92 vs 187 mcg/day Se, p < 0.001)
- Decreased STSG requirements and decreased hospitalization by 12 days, possibly due to immunological defense mechanisms.
Meta-analysis of Antioxidant Supplements

- Antioxidant supplements have been proposed for prevention of several diseases (i.e., GI cancer, cardiovascular, neurological, skin, ocular, renal, endocrinological, and rheumatoid diseases).
- All randomized trials involving adults comparing beta carotene, vitamin A, vitamin C, vitamin E, and selenium either singly or combined vs. placebo or vs. no intervention were analyzed.
- The effect of antioxidant supplements on all-cause mortality was analyzed with meta-analyses and reported as relative risk (RR) with 95% confidence intervals (CIs).


Antioxidant Supplements

- All antioxidants were given orally
- Dose and regimen of antioxidant supplements:
  - Beta carotene 1.2 – 50 mg (mean dose, 17.8 mg)
  - Vitamin A 1333 – 200000 IU (mean dose, 20219 IU)
  - Vitamin C 60 – 2000 mg (mean dose, 488 mg)
  - Vitamin E 10 – 5000 IU (mean dose, 569 IU)
  - Selenium 20 – 200 mcg (mean dose, 99 mcg)
- Above regimens taken daily or on alternate days
- Duration: 28 days to 12 years (mean 2.7 years)

Antioxidant Supplements

- A total of 68 randomized trials including 232,606 subjects were reviewed.
- Results were analyzed with respect to whether trials were of low or high methodological quality (pertaining to randomization, blinding, explanation for numbers/reasons of dropouts or withdrawals from groups).
- After exclusion of low quality studies, the following vitamins increased mortality given alone or in combination: beta carotene, 1.07 (1.02-1.11); vitamin A, 1.16 (1.10-1.24); vitamin E 1.04 (1.01-1.07).
- Vitamin C and selenium had no effect on mortality, given alone or in combination


Updated Meta-Analysis of Antioxidant Supplements

- 78 trials RCTs (296,707 subjects); mean age = 63 years; 46% women
- 26 trials assessed 215,900 healthy participants; 52 trials assessed 80,807 participants with stable, chronic diseases (CAD, DM, Alzheimer disease, age-related eye disease) between years 1977 - 2012
- All supplements were administered orally, alone or in combinations, as antioxidants with vitamins, minerals, or other interventions vs. placebo
- Antioxidant supplements included: beta carotene, vitamin A, vitamin C, vitamin E, and selenium
- Mean duration of supplementation = 3 years; included subjects from a variety of continents, such as Europe, North and South America, Asia, and Australia

In the 56 trials with a low risk of bias, results showed that antioxidant supplements were associated with a higher mortality vs. placebo (18,833 deceased per 146,320 participants [12.9%] vs. 10,320 deceased per 97,736 participants [10.6%]; RR, 1.04 [95% CI, 1.01-1.07]).

Beta carotene (RR, 1.05 [95% CI, 1.01-1.09]) and vitamin E (RR, 1.03 [95% CI, 1.00-1.05]) were associated with significantly higher mortality.

Vitamin A (RR, 1.07 [95% CI, 0.97-1.18]), vitamin C (RR, 1.02 [95% CI, 0.98-1.07]), and selenium (RR, 0.97 [95% CI, 0.91-1.03]) were not associated with higher or lower mortality.

However in a dose analysis evaluation, higher doses of vitamin A (20,000 IU) were associated with higher all-cause mortality (RR, 1.0006, [95% CI, 1.0002-1.001], p=0.002).

Bottom line: Higher mortality associated with beta carotene, vitamin E, and for higher doses of vitamin A. Vitamin C and selenium were associated with neither higher nor lower all-cause mortality.

Multivitamin-Mineral Use among U.S. Women

- The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States.
- Data from the NHANES III (1988-1994; n=8678; age ≥ 40 years) was analyzed to examine the association between multivitamin-mineral (MVM) or MV use and cardiovascular-specific mortality among U.S. adults without cardiovascular disease; matched with mortality data reported by National Death Index through 2011.
- MVM were defined as products with ≥ 3 vitamins and at least 1 mineral (e.g., calcium, magnesium, zinc, phosphorus, manganese, copper, iron, selenium, or chromium).
- MV were defined as vitamin combinations without minerals (e.g., antioxidant combinations or vitamin B complex products).
- Data is obtained on medication use and health history by questionnaire.
- Health data includes history of AMI, stroke, CHD, cancer, CVD, and DM.
- Social history information includes alcohol intake and cigarette smoking.
- Laboratory data included serum cotinine, serum cholesterol, HDL, BG.

Multivitamin-Mineral Use among U.S. Women

Results

- When all users of MVM or MVs were compared to nonusers, there was no significant association with CVD mortality.
- However, when users were classified by the reported length of time the products were used (< 1 year, 1-3 years, > 3 years), there was a significant association found with MVM use of > 3 years compared with nonusers (HR, 0.65; 95% CI, 0.49 – 0.85).
- This finding was primarily due to the significant association among women (HR, 0.56; 95% CI, 0.37 – 0.85) but not men (HR, 0.79; 95% CI, 0.44 – 1.42).
- Users did not differ from nonusers for age, BMI, alcohol intake, aspirin use, nor prevalence of high cholesterol, HTN, DM.

Antioxidants, Zinc, and Vision

- Age-related macular degeneration (AMD) is the leading cause of visual impairment in the US among people > 65 years or older
- Oxidative damage to the retina may be involved
- Objective of National Eye Institute (of NIH): evaluate effect of high-dose vitamin C (500 mg/day), vitamin E (400 IU/day), beta carotene (15 mg/day); zinc 80 mg/day and copper 2 mg/day; antioxidants + zinc; or placebo

Antioxidants, Zinc, and Vision

- Age-Related Eye Disease Study (AREDS) enrolled 3640 study patients (aged 55-80 years) and followed for an average of 6.3 years.
- Statistically significant odds reduction for the development of advanced AMD with antioxidants + zinc (OR=0.72; 99%CI 0.52-0.98).
- Concurrent study for age-related lens opacities and visual acuity loss, but antioxidants had no apparent effect on the 7-year risk development or progression for this disease.


Physical Performance in Elders

- InCHIANTI Study evaluated relationship between antioxidants and performance in 986 Italians ≥ 65 y.
- Plasma alpha- and gamma-tocopherol were associated with increased knee extension strength.
- Vitamin C and beta-carotene were significantly correlated with knee extension strength.
- Vitamin C was significantly associated with physical performance.

Potential Toxicity of Antioxidants

- Ascorbic acid
  - prooxidant when body iron stores high
  - increased iron in 10% whites / 30% African-Americans
  - can promote kidney stones
- α-Tocopherol
  - promote progression of autoimmune diseases
  - promote hemorrhagic strokes


Potential Harms of Vitamins

- Beta carotene:
  - 2 trials have reported increased risk for lung cancer and lung cancer mortality in smokers, especially heavy smokers. There is no increased risk for cancer in nonsmokers.
  - hypercarotenemia (yellowing of skin)
- MVs: rashes and minor bleeding events
- Vitamin A: increased incidence of hip fractures and hepatotoxicity (with mega doses)
- Folic acid: increased risk of prostate cancer
- Vitamin D and calcium: increased risk of kidney stones

“Supplements can help some people, harm others, and do nothing for most, so the bottom line is a wash.”

--- Victor Herbert, MD, Mount Sinai School of Medicine, Bronx, NY.

“The present evidence is insufficient to recommend either for or against the use of MVM supplements by the American public to prevent chronic disease”

--- Panel Statement from an NIH State-of-the-Science Conference held on 15-17 May 2006 at the NIH, Bethesda, Maryland
Antioxidant Nutrients and Health

Myths

● Antioxidant nutrient supplements are known to reduce the risk of disease in well-nourished populations
● More is better

Mayne ST, Yale University School of Medicine

Antioxidant Nutrients and Health

Facts

● The relationship between nutrients and disease prevention is complex, and more is not necessarily better
● Nutrients may not themselves account for reduced risk of disease but merely be present in the same foodstuffs that contain protective factors
Summary

• Inadequate folate status is associated with neural tube defects

• High-risk and healthy people should avoid taking mega doses of vitamin E (≥ 400 IU/day)

• Patients with intermediate or large pathological growths on the optic papilla, especially those with AMD should consider taking zinc + antioxidant supplements