

# **The Vital Fat-Soluble Vitamins**

**Presented by Chris Masterjohn, PhD**

September, 2013 Regional Wise Traditions Conference  
Portland, OR

This content of this talk is the independent work of Chris Masterjohn and does not necessarily represent the positions or opinions of the University of Illinois.

# The Major Sources of Vitamins A and D



**Liver – Vitamin A**



**Sunshine – Vitamin D**

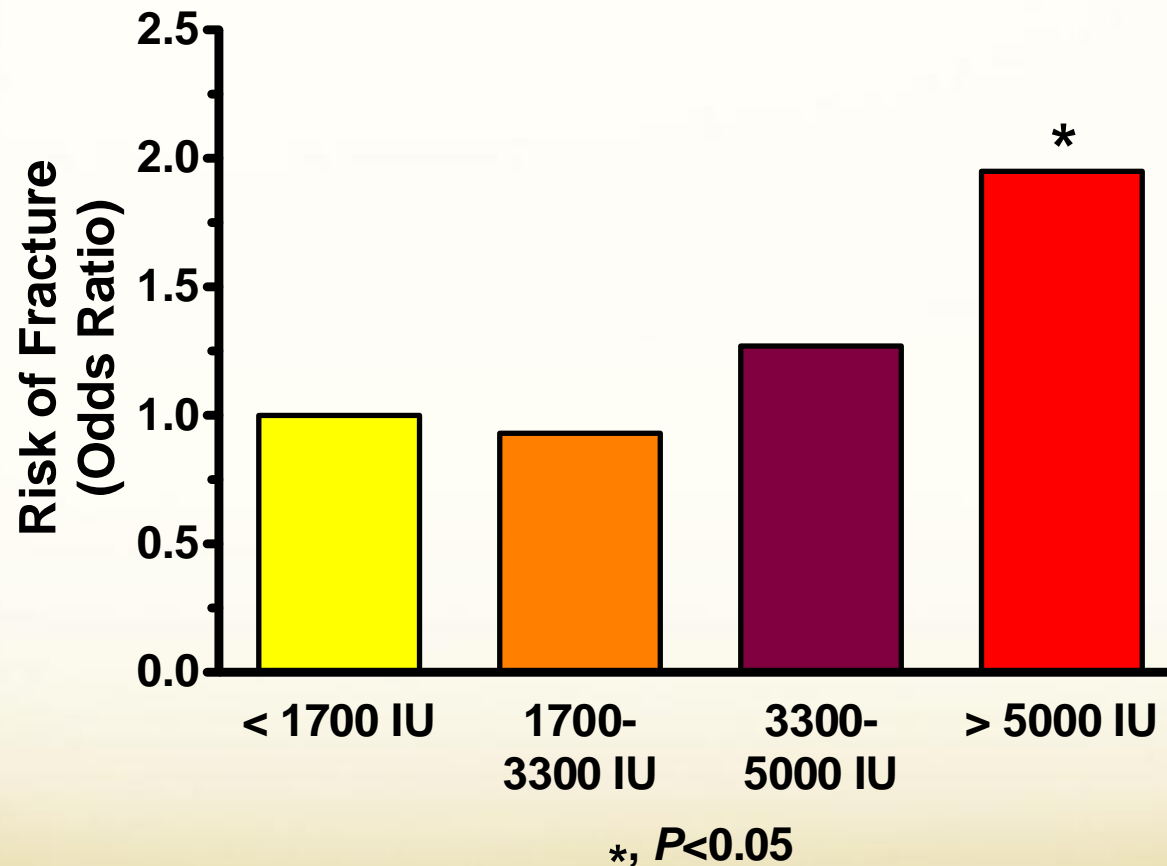


**Cod Liver Oil –  
Vitamins A and D**

## ***My Wise Traditions Articles Through Spring, 2007***

- **Fall, 2004** – Vitamin A: The Forgotten Bodybuilding Nutrient
- **Spring, 2005** – The China Study
- **Fall, 2005** – Dioxins in Animal Foods: A Case for Vegetarianism?
- **Winter, 2005/Spring, 2006** – Vitamin A on Trial: Does Vitamin A Cause Osteoporosis?
- **Fall, 2006** – From Seafood to Sunshine: A New Understanding of Vitamin D Safety
- **Spring, 2007** – On the Trail of the Elusive X-Factor: A 62-Year Mystery Finally Solved

# Vitamin A Intake Greater Than 5,000 IU Associated With the Risk of Hip Fracture in Sweden

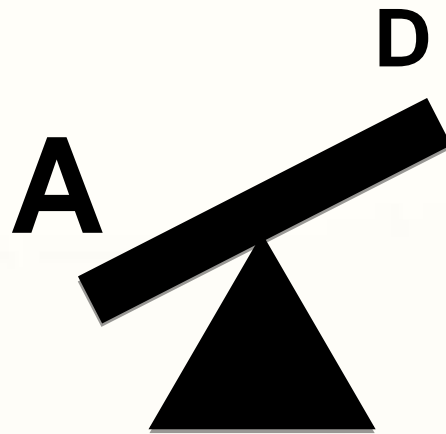


Melhus et al. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. Ann Intern Med. 1998;129(10):770-8.

# **Vitamins A and D Protect Against Each Other's Toxicity and Increase the Need for Each Other**

- Massive doses of vitamin A cause bone loss in animals, but massive doses of vitamin D offer complete protection.
- Massive doses of vitamin D cause soft tissue calcification in animals, but massive doses of vitamin A offer complete protection.
- Even modest amounts of one vitamin can deplete the storage supply of the other.
- These interactions occur even if vitamin D is provided by ultraviolet light or both vitamins are provided by injection.

# **Vitamin A Contributes to Bone Loss Only When Vitamin D Is Limiting**



**Elevated Phosphorus  
Depressed Calcium**



**Bone Loss**

# The Major Sources of Vitamins A and D



**Liver – Vitamin A**



**Sunshine – Vitamin D**



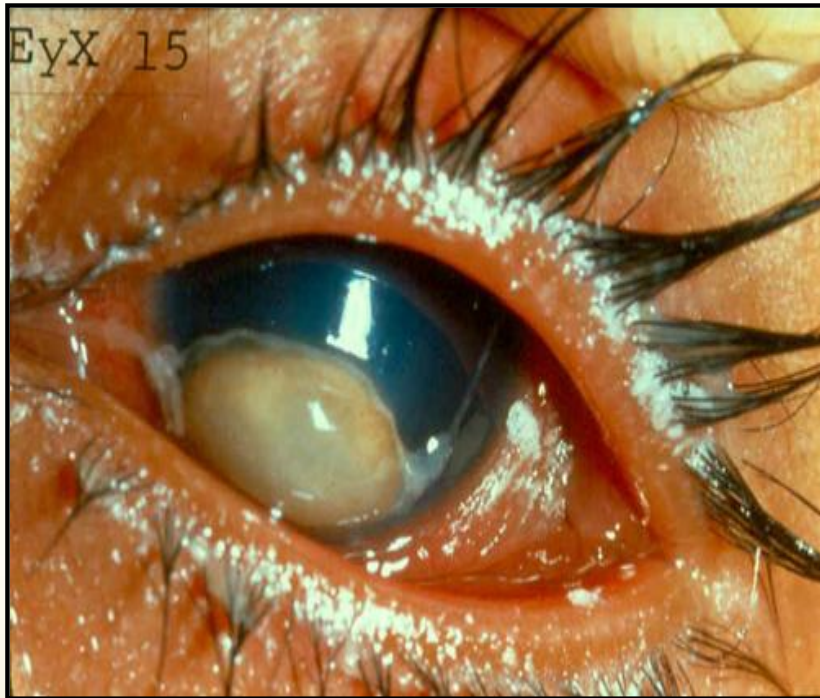
**Cod Liver Oil –  
Vitamins A and D**

**Good Vitamin, Bad Vitamin:**

**Repeating A Historical  
Mistake?**

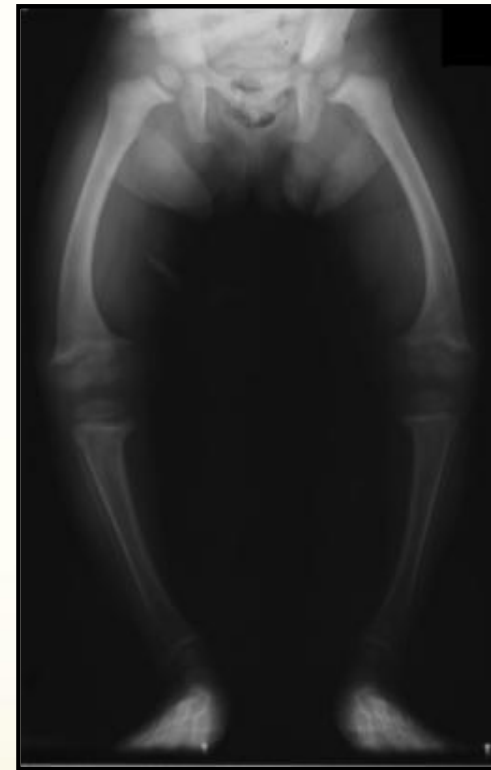


# Cod Liver Oil Prevented and Cured Deficiencies of Both Vitamins A and D



Corneal ulceration due to **xerophthalmia**,  
prevented by vitamin A..

This is rare!



Bowed and poorly mineralized legs due to  
**rickets**, prevented by vitamin D.

This is important!

# Dogs Fed Vitamin A-Deficient Diets Developed Pneumonia



**Olive Oil**



Soft bones, bronchial pneumonia.



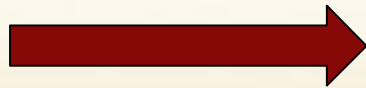
**Butter (A)**



Soft bones, free of infection.



**Cod Liver Oil (A+D)**



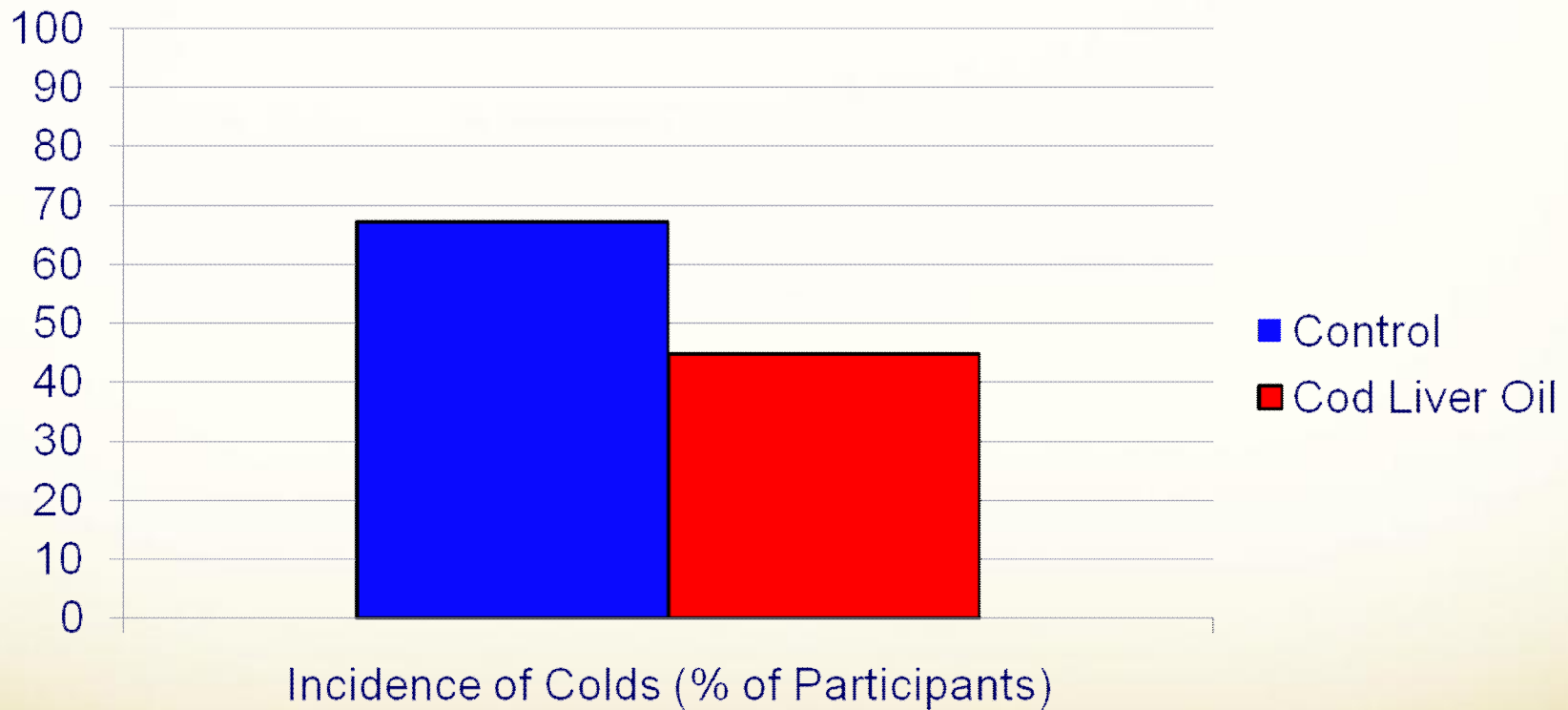
Well mineralized bones, free of infection.

# Vitamin A, Not Vitamin D, Protected Against Infection in Rats

"The importance of vitamin D has attracted great attention recently, and it has even been suggested that preparations of vitamin D can be safely substituted for cod-liver oil in medical treatment. The work above described shows that this teaching is erroneous, and that, although vitamin D controls, probably absolutely, the calcification of bones and teeth, it has no direct power to promote resistance to infection in the same way as vitamin A. If a substitute for cod-liver oil is given it ought to be at least as powerful as this oil in its content of both vitamins A and D."

*Vitamin A Is the Anti-Infective Vitamin!*

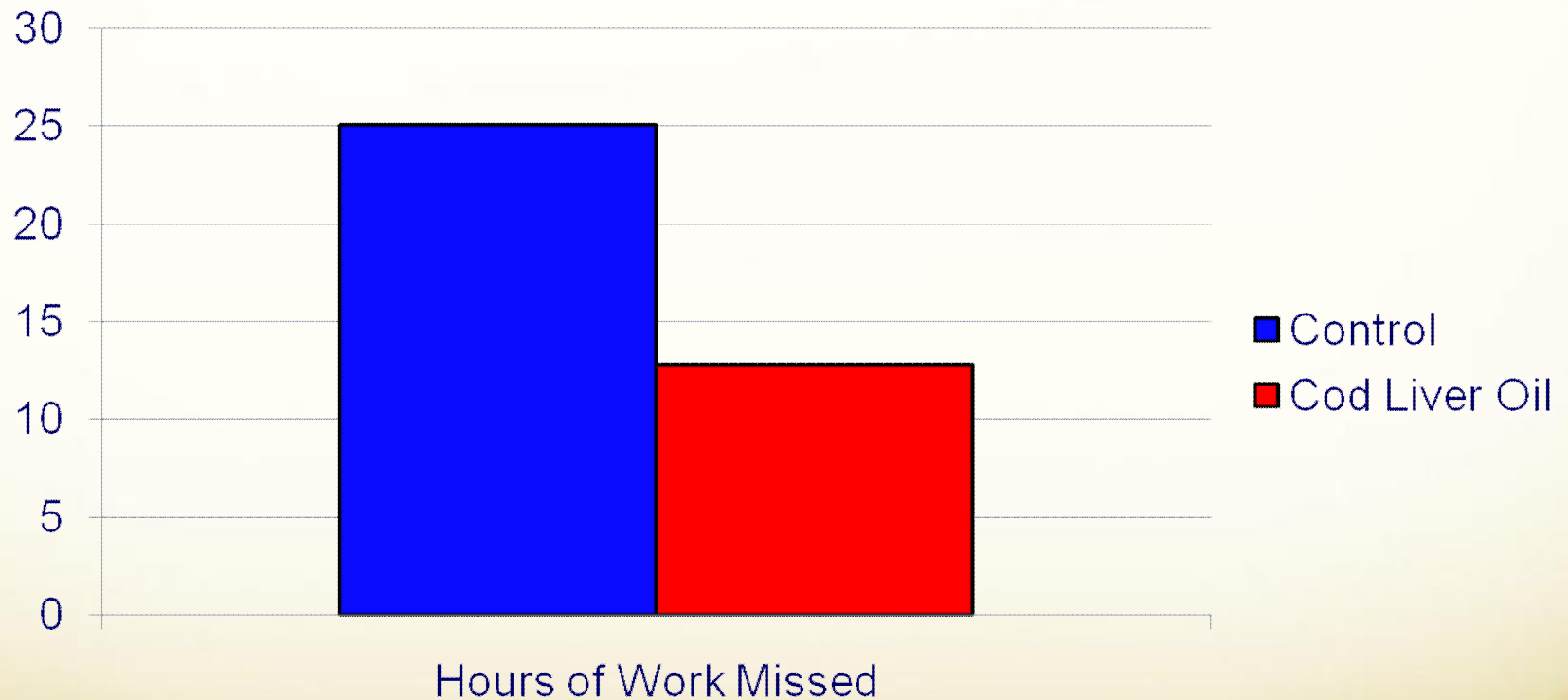
# Cod Liver Oil Decreases the Incidence of Colds



One tbsp CLO (15,000 IU A; 2,000 IU D) per day, Dec-March, n=313.

Holmes AD, Pigott MG, Sawyer WA, Comstock L. Vitamins Aid Reduction of Lost Time in Industry. *Indust Eng Chem.* 1932;24:1058-60.

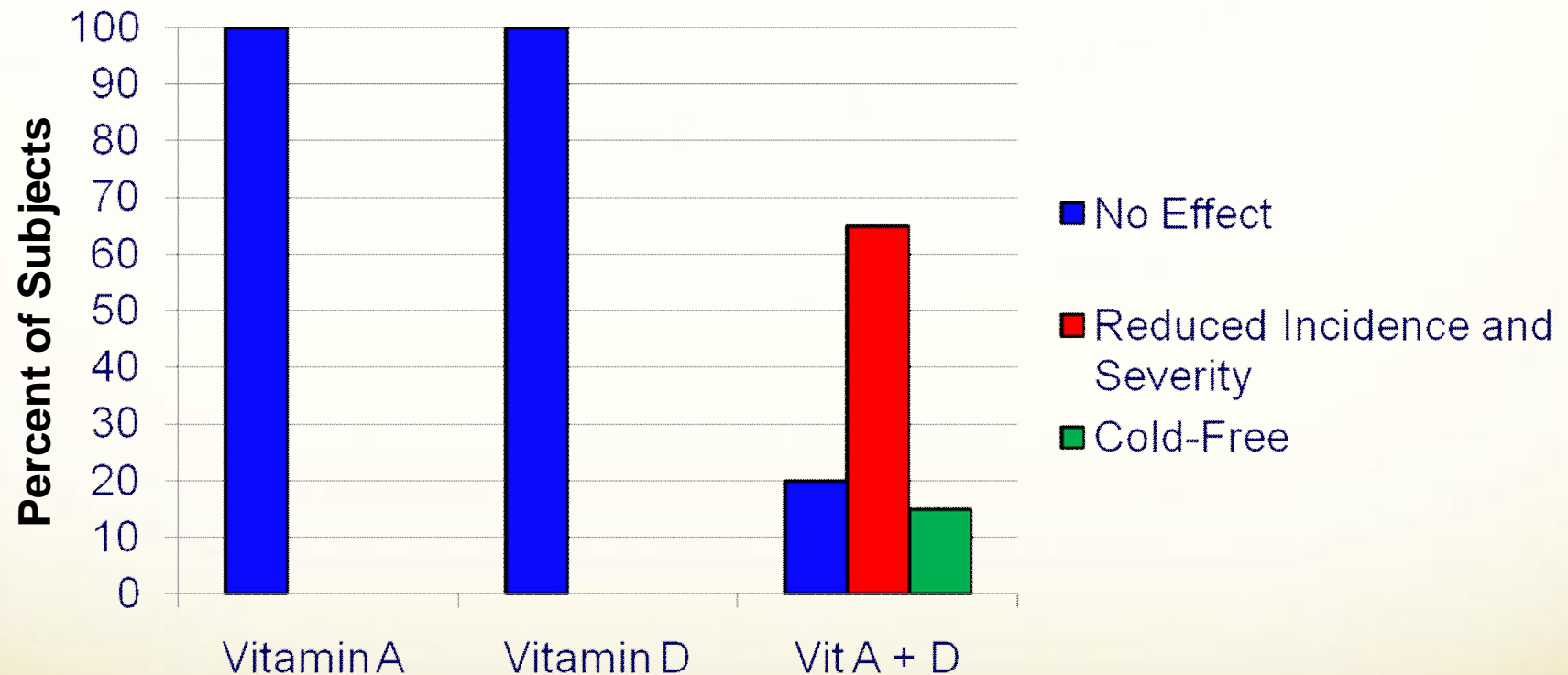
# Cod Liver Oil Decreases Time Missed From Work



One tbsp CLO (15,000 IU A; 2,000 IU D) per day, Dec-March, n=313.

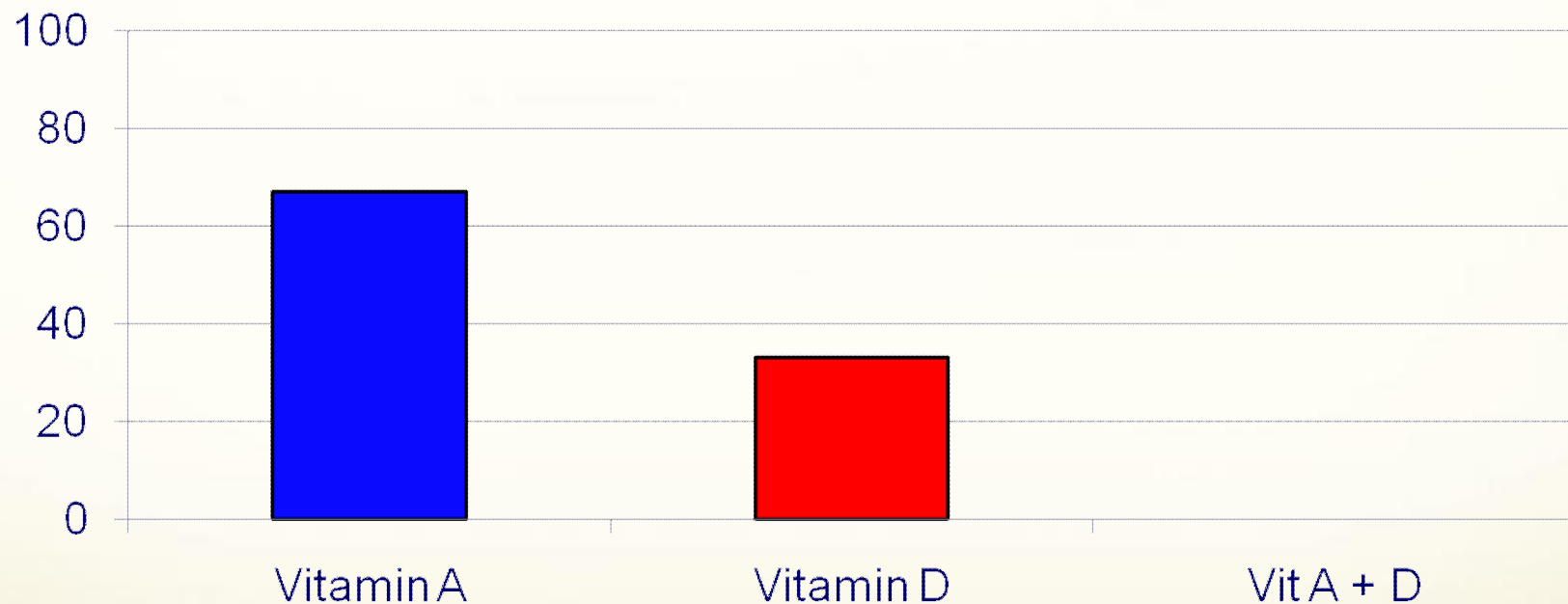
Holmes AD, Pigott MG, Sawyer WA, Comstock L. Vitamins Aid Reduction of Lost Time in Industry. *Indust Eng Chem.* 1932;24:1058-60.

# Vitamins A and D Only Protect Against Colds When Combined



54 “chronic or frequent cold sufferers” aged 7-49 given 9,000-40,000 IU A, 120,000-300,000 IU D, or both, daily Sept-June for three years.

# Vitamins A and D Proved Toxic Alone But Not in Combination



**Percentage of Subjects Who Developed Symptoms of Toxicity**

54 “chronic or frequent cold sufferers” aged 7-49 given 9,000-40,000 IU A, 120,000-300,000 IU D, or both, daily Sept-June for three years.

Spiesman IG. Massive doses of vitamins A and D in the prevention of the common cold. Arch Otolaryngol.1941;34(4):787-791.

# Two Models of Synergy

**Vitamin A**



**Molecular  
Process**



**Clinical  
Outcome**

**Vitamin D**



**Molecular  
Process**



**Vitamin A**



**Vitamin D**



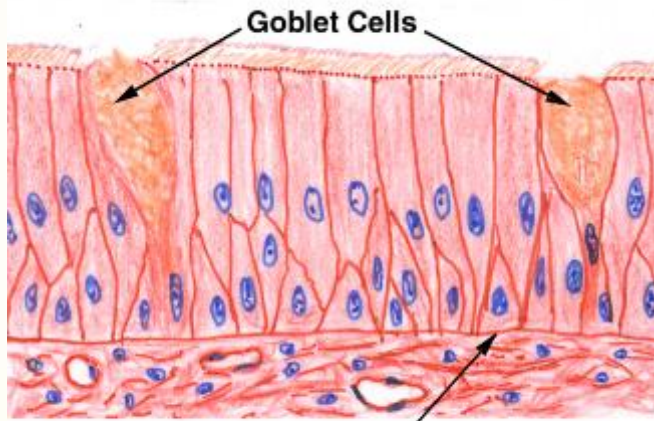
**Molecular  
Process**



**Clinical  
Outcome**



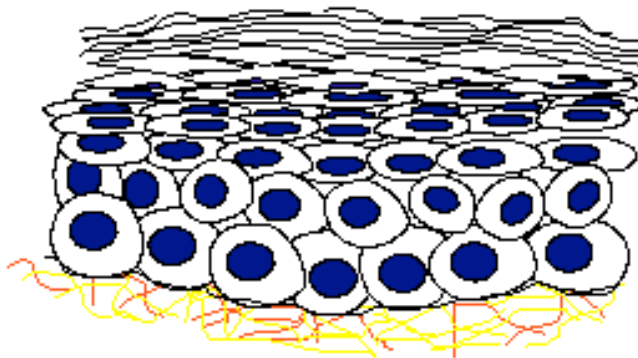
# Vitamin A Deficiency: Replacement of Normal Epithelial Tissue With Keratinized Tissue Sabotages Defense Against Pathogens



## Normal Pseudo-stratified Columnar

- Ciliated
- Goblet cells produce mucous
- Defense against pathogens

keratinized stratified squamous  
dead, keratinized cells at surface



cells flatten  
toward surface  
↑  
mitotic divisions

## Replacement w/ Keratinized In Deficiency

- Hyperkeratosis
- Loss of normal tissue function, including the first line of immune defense.
- Xerophthalmia

# **Vitamin A Supports the Immune System in Many Ways**

**Vitamin A also does the following:**

- **Supports Natural Killer Cell Activity**
- **Enhances T Cell Proliferation**
- **Supports Killer T Cell Function**
- **Supports Helper T Cell Activity**
- **Regulates Activation, Proliferation, and Survival of B Cells**
- **Increases Production of Zinc-Dependent Metalloproteinases**

# Vitamin D Stimulates Production of Antimicrobial Peptides

Cathelicidins and their derivatives are also effective against:

- *Candida albicans*
- *Streptococcus aureus*
- Group A *Streptococcus* (*S. pyogenes* or GAS)
- *E. faecalis*
- *Pseudomonas aeruginosa*
- *E. coli*
- lentiviruses and retroviruses (e.g. HIV)

# Activation of Vitamins A and D

Vitamin A  
(Retinol)



Retinal



*All-Trans*

Retinoic Acid  
(ATRA)



*9-Cis*

Retinoic Acid  
(9CRA)

Vitamin D

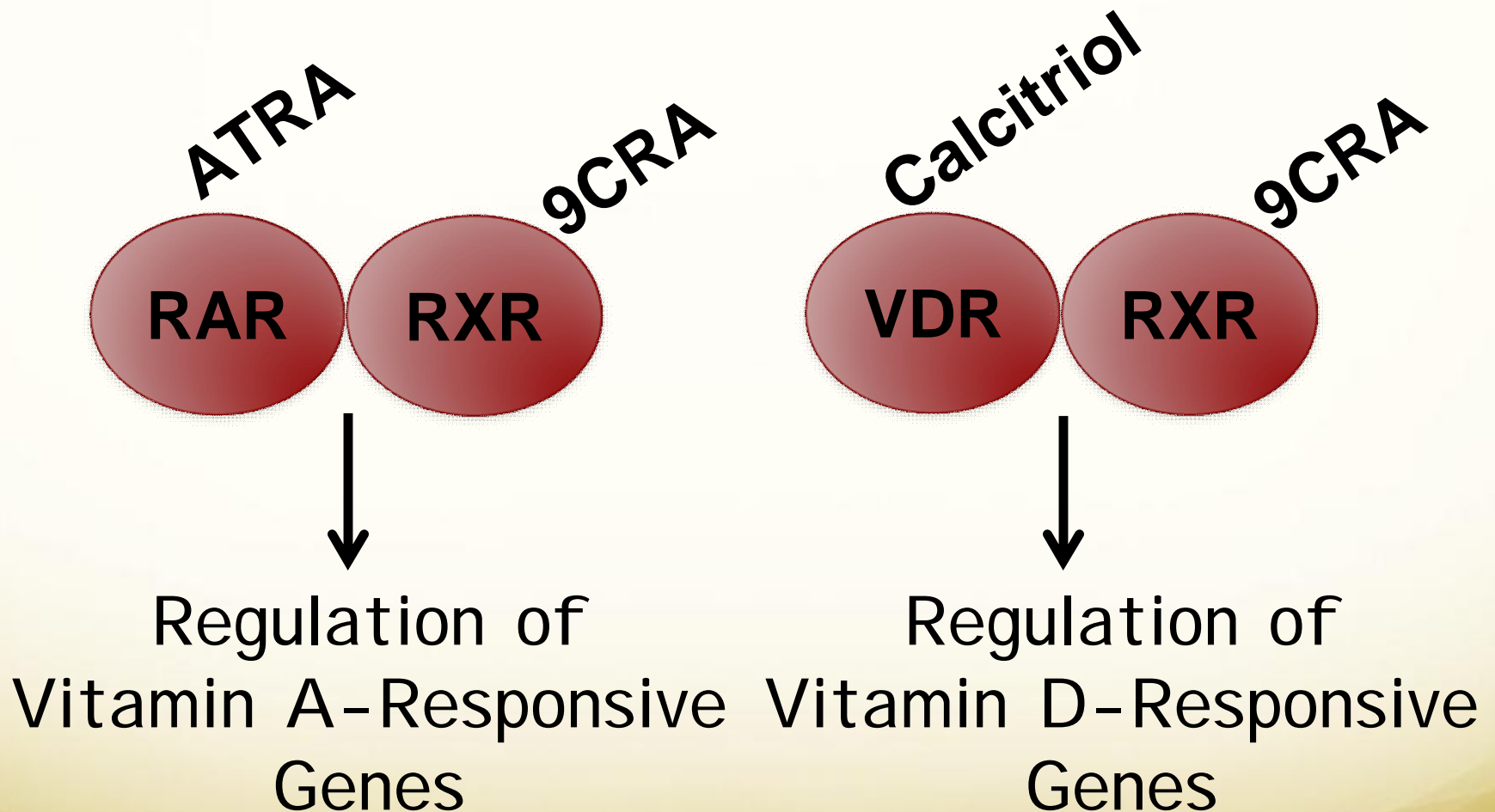


Calcidiol  
25(OH)D



Calcitriol  
1,25(OH)<sub>2</sub>D

# Vitamins A and D Are Molecular Partners



RAR – Retinoic Acid Receptor; VDR – Vitamin D Receptor; RXR – Retinoid X Receptor

# Two Models of Synergy

**Vitamin A**



**Molecular  
Process**



**Clinical  
Outcome**

**Vitamin D**



**Molecular  
Process**



**Clinical  
Outcome**

**Vitamin A**



**Molecular  
Process**

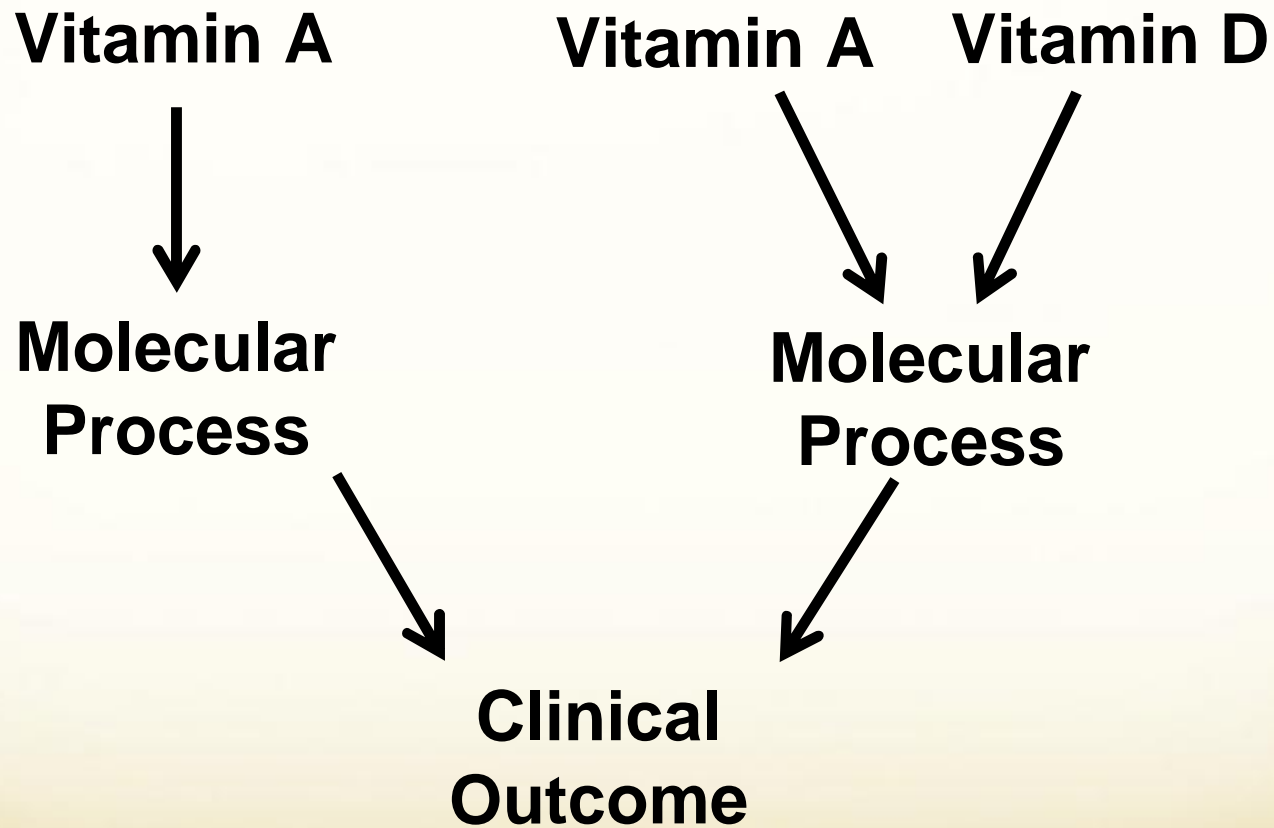


**Clinical  
Outcome**

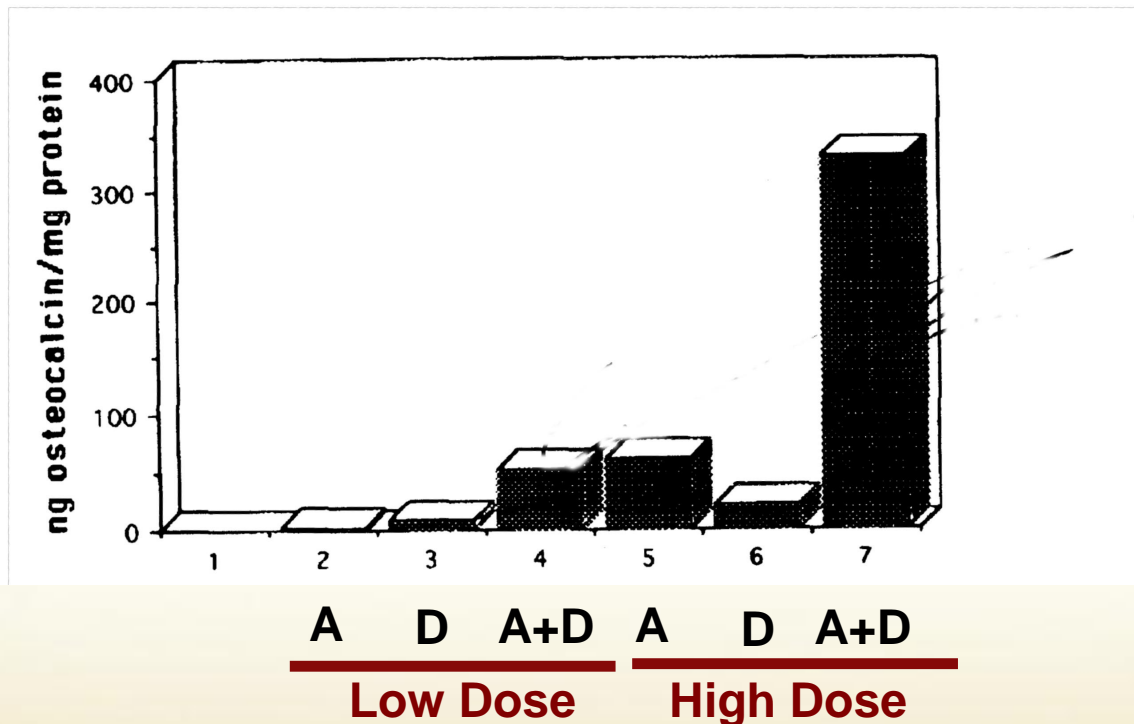
**Vitamin D**



# A Revised Model of Synergy

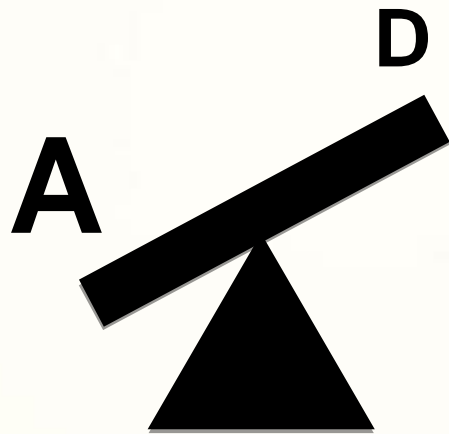


# Vitamins A and D Synergistically Increase the Production of Osteocalcin





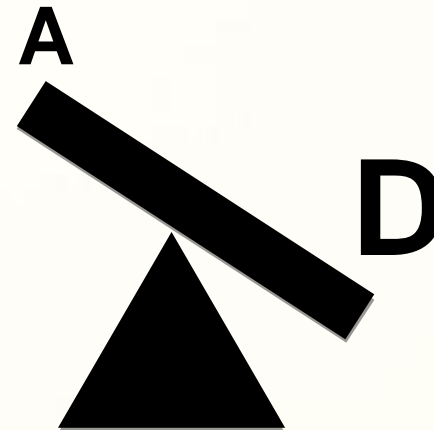
# Is the Mechanism of Vitamin D Toxicity Similar to That of Vitamin A But Reversed?



**Elevated Phosphorus  
Depressed Calcium**



**Bone Loss**



**Hypercalcemia**

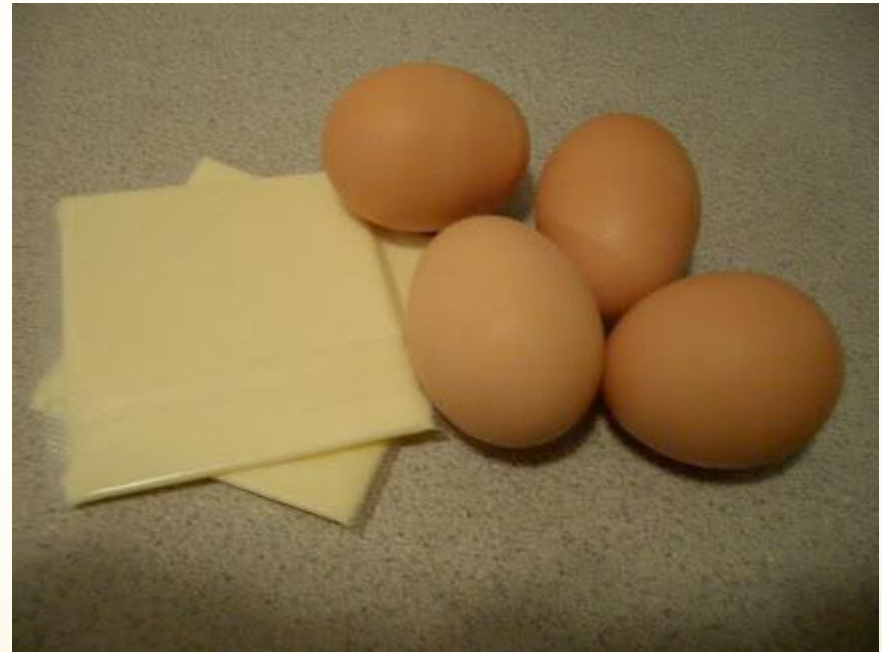


**Soft Tissue  
Calcification**

# A Third Synergistic Partner: Vitamin K<sub>2</sub>!

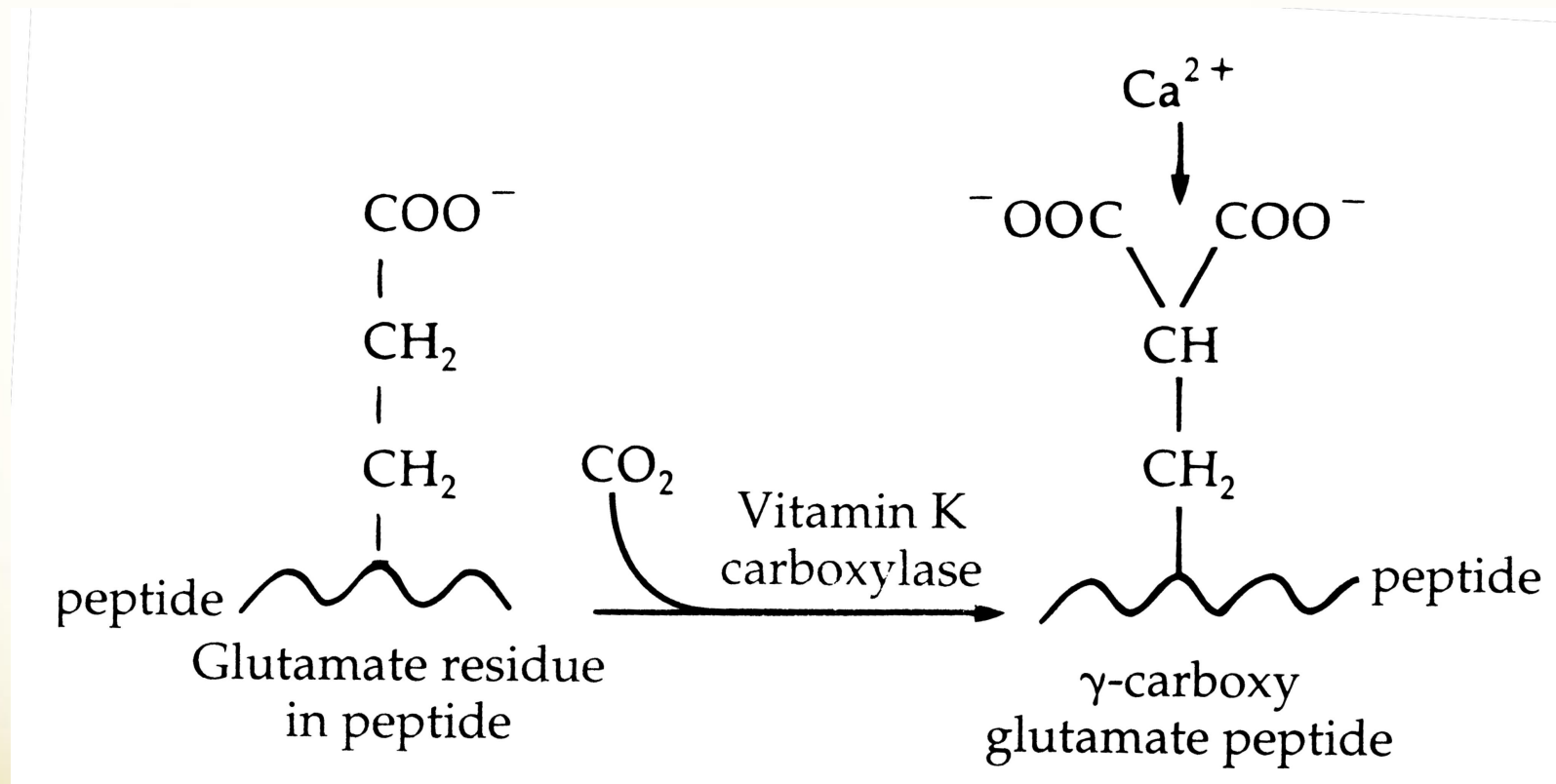


**Leafy Greens – Vitamin K<sub>1</sub>**

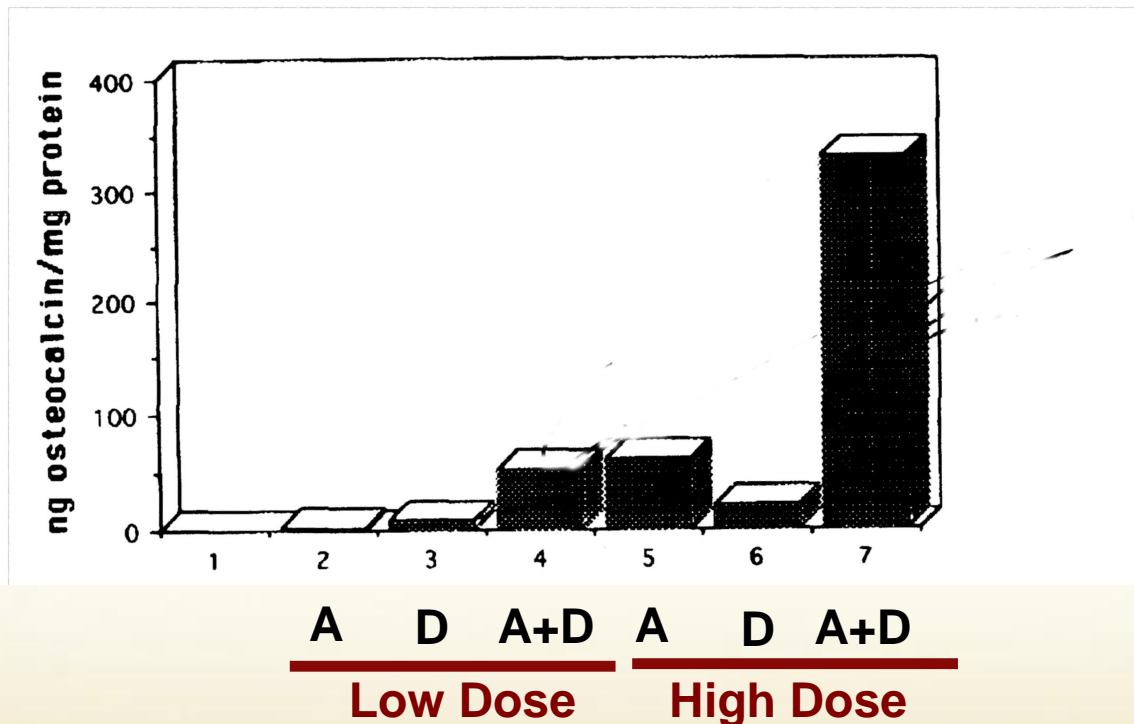


**Animal Fats and  
Fermented Foods – Vitamin K<sub>2</sub>**

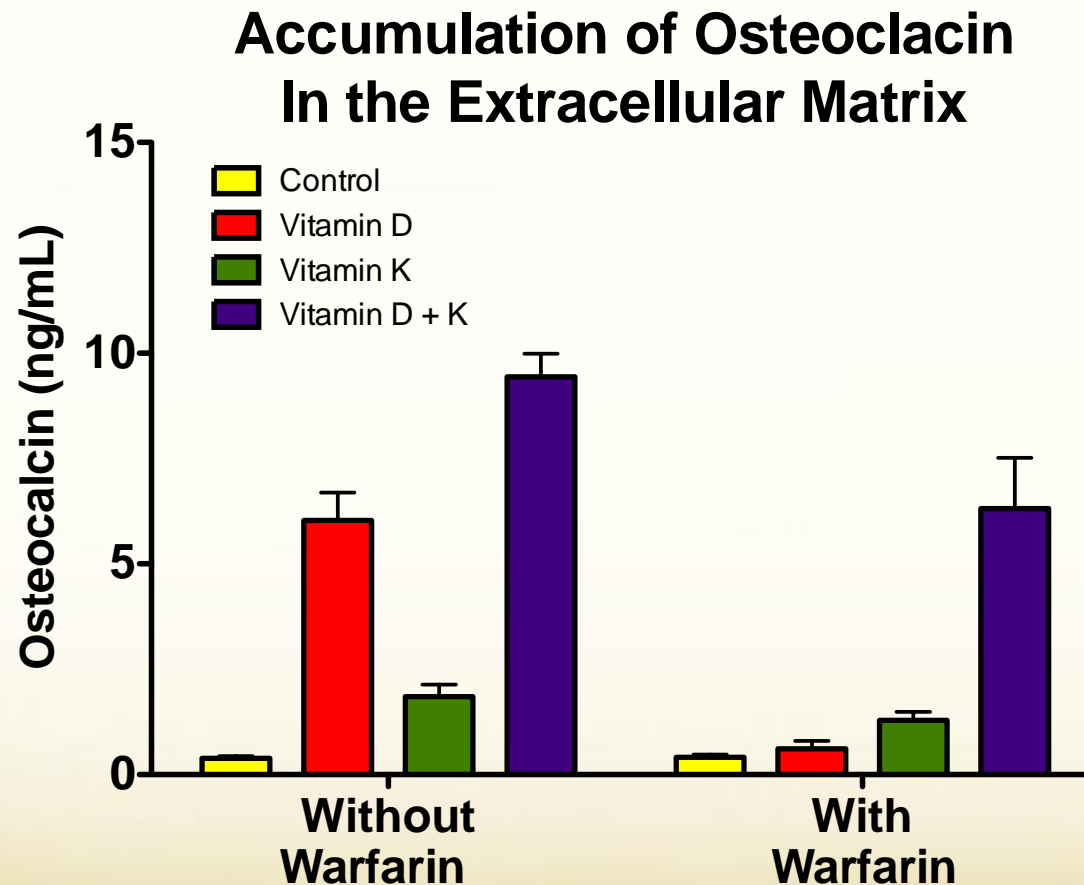
# Vitamin K Activates Proteins By Giving Them the Ability to Bind Calcium



# Vitamins A and D Synergistically Increase the Production of Osteocalcin



# Osteocalcin Only Accumulates in Bone Matrix After Activation by Vitamin K



# Vitamin K<sub>2</sub> Protects Against Calcification of Blood Vessels and Heart Valves

## *Nutritional Epidemiology*

### **Dietary Intake of Menaquinone Is Associated with a Reduced Risk of Coronary Heart Disease: The Rotterdam Study<sup>1</sup>**

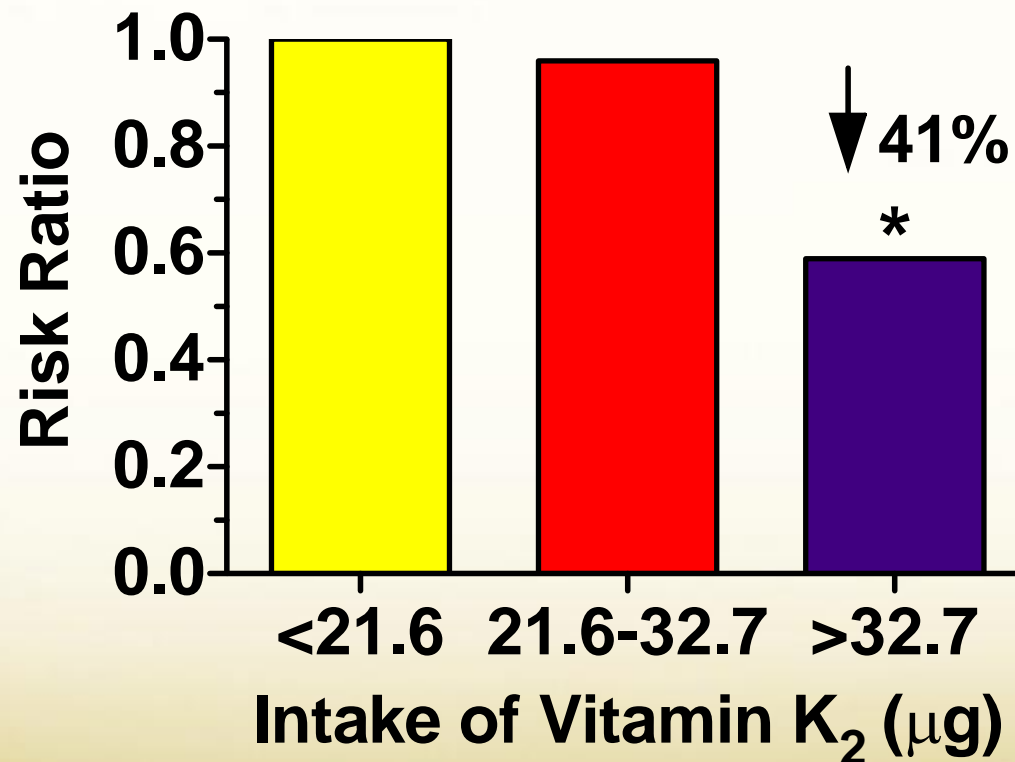
Johanna M. Geleijnse,<sup>\*†</sup> Cees Vermeer,<sup>\*\*</sup> Diederick E. Grobbee,<sup>‡</sup> Leon J. Schurgers,<sup>\*\*</sup> Marjo H. J. Knapen,<sup>\*\*</sup> Irene M. van der Meer,<sup>\*</sup> Albert Hofman,<sup>\*</sup> and Jacqueline C. M. Witteman<sup>\*2</sup>

*\*Department of Epidemiology & Biostatistics, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; †Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands; \*\*Department of Biochemistry, Cardiovascular Research Institute Maastricht, University of Maastricht, Maastricht, The Netherlands; and ‡Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands*

**ABSTRACT** Vitamin K-dependent proteins, including matrix Gla-protein, have been shown to inhibit vascular calcification. Activation of these proteins via carboxylation depends on the availability of vitamin K. We examined whether dietary intake of phylloquinone (vitamin K-1) and menaquinone (vitamin K-2) were related to aortic calcification and coronary heart disease (CHD) in the population-based Rotterdam Study. The analysis included 4807 subjects with dietary data and no history of myocardial infarction at baseline (1990–1993) who were followed until January 1, 2000. The risk of incident CHD, all-cause mortality, and aortic atherosclerosis was studied in tertiles of energy-adjusted vitamin K intake after adjustment for age, gender, BMI, smoking, diabetes, education, and dietary factors. The relative risk (RR) of CHD mortality was reduced in the mid and upper tertiles of dietary menaquinone compared to the lower tertile [RR = 0.73 (95% CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively]. Intake of menaquinone was also inversely related to all-cause mortality [RR = 0.91 (0.75, 1.09) and 0.74 (0.59,

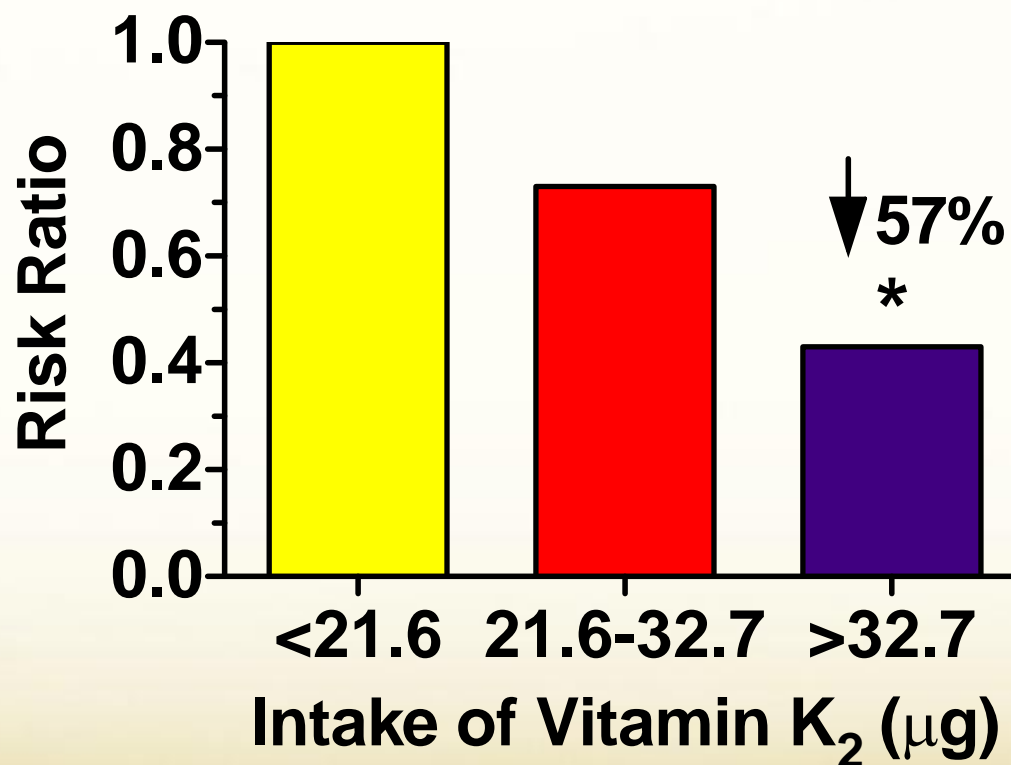
# Vitamin K<sub>2</sub> Intake Is Associated With a Reduced Incidence of CHD

## Coronary Heart Disease Incidence



# Vitamin K<sub>2</sub> Intake Is Associated With a Reduced Incidence of CHD

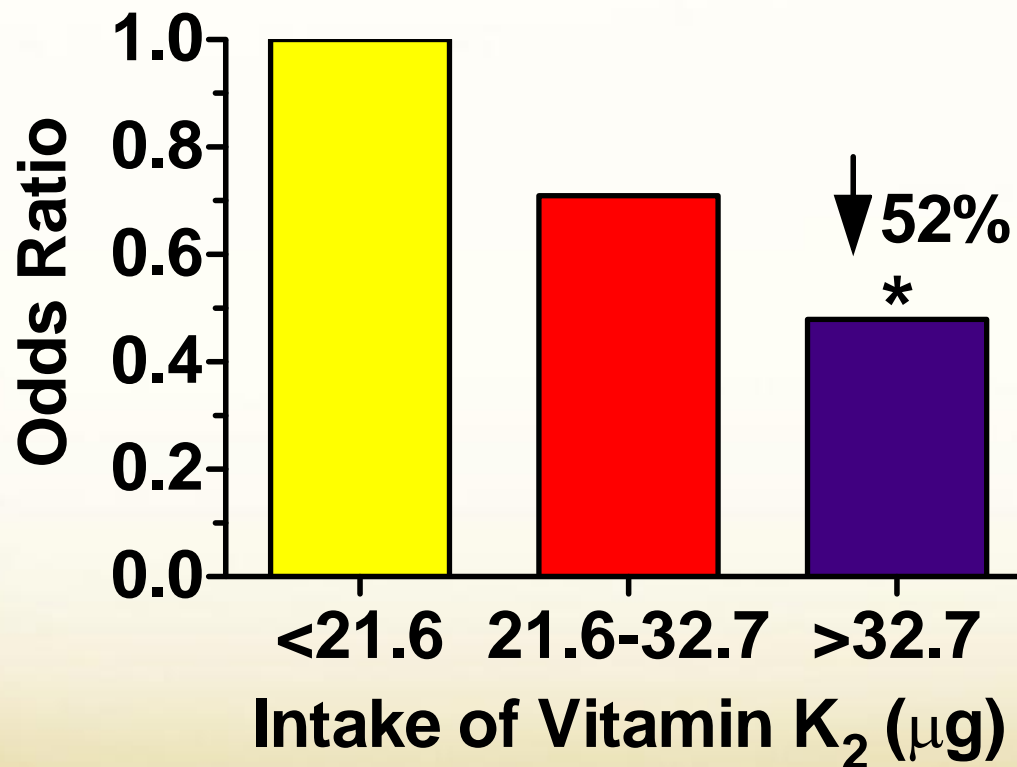
## Coronary Heart Disease Mortality





# Vitamin K<sub>2</sub> Intake Is Associated With Reduced Aortic Calcification

Likelihood of Having Severe Aortic Calcification



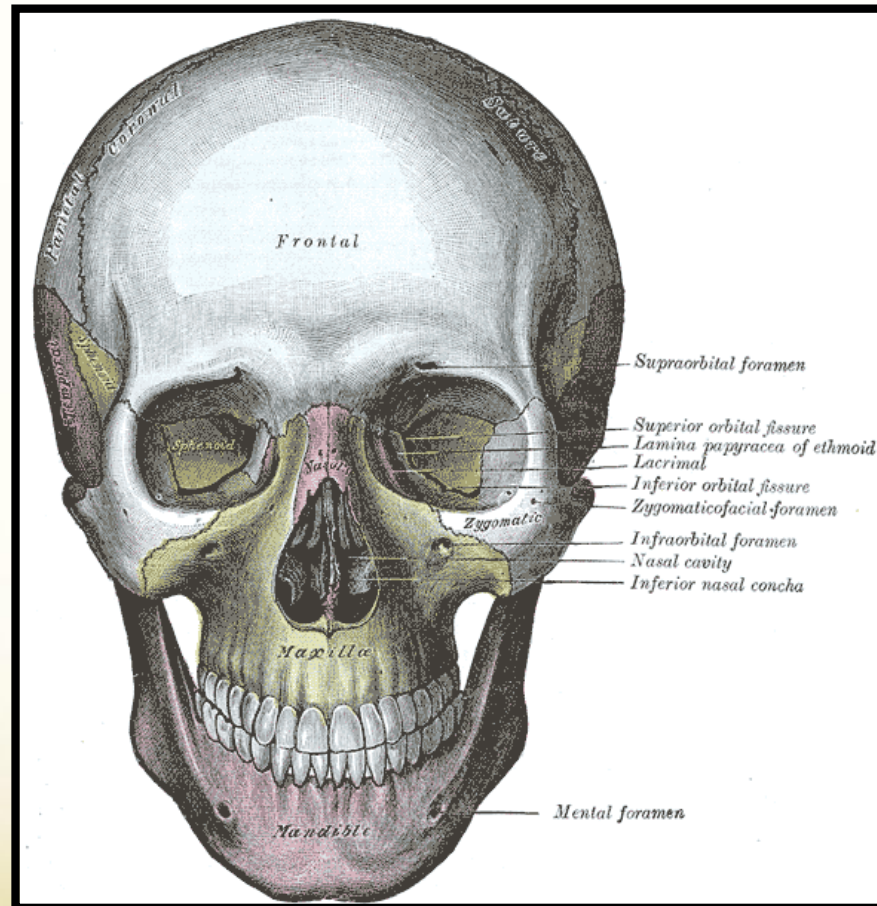
# MGP Knockout Mouse Is Shorter In Stature Than Normal Mouse and Suffers From Soft Tissue Calcification and Spontaneous Fractures



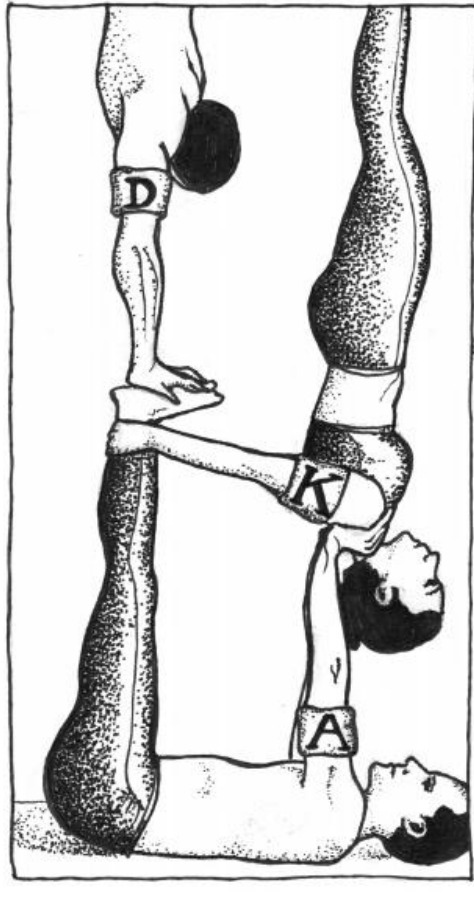
# Warfarin During Pregnancy Causes Underdevelopment of Middle Third of the Face



# The Maxilla Constitutes the “Middle Third of the Face”



# Synergy Between Vitamins A, D, and K<sub>2</sub>



- Vitamins A and D cooperate to tell cells which proteins to make, and how much of them to make.
- Vitamin K2 activates those proteins by giving them the ability to bind calcium.

# Redefining Vitamin D Toxicity

Medical Hypotheses (2007) 68, 1026–1034



ELSEVIER

medical  
hypotheses

<http://intl.elsevierhealth.com/journals/mehy>

## Vitamin D toxicity redefined: Vitamin K and the molecular mechanism

Christopher Masterjohn \*

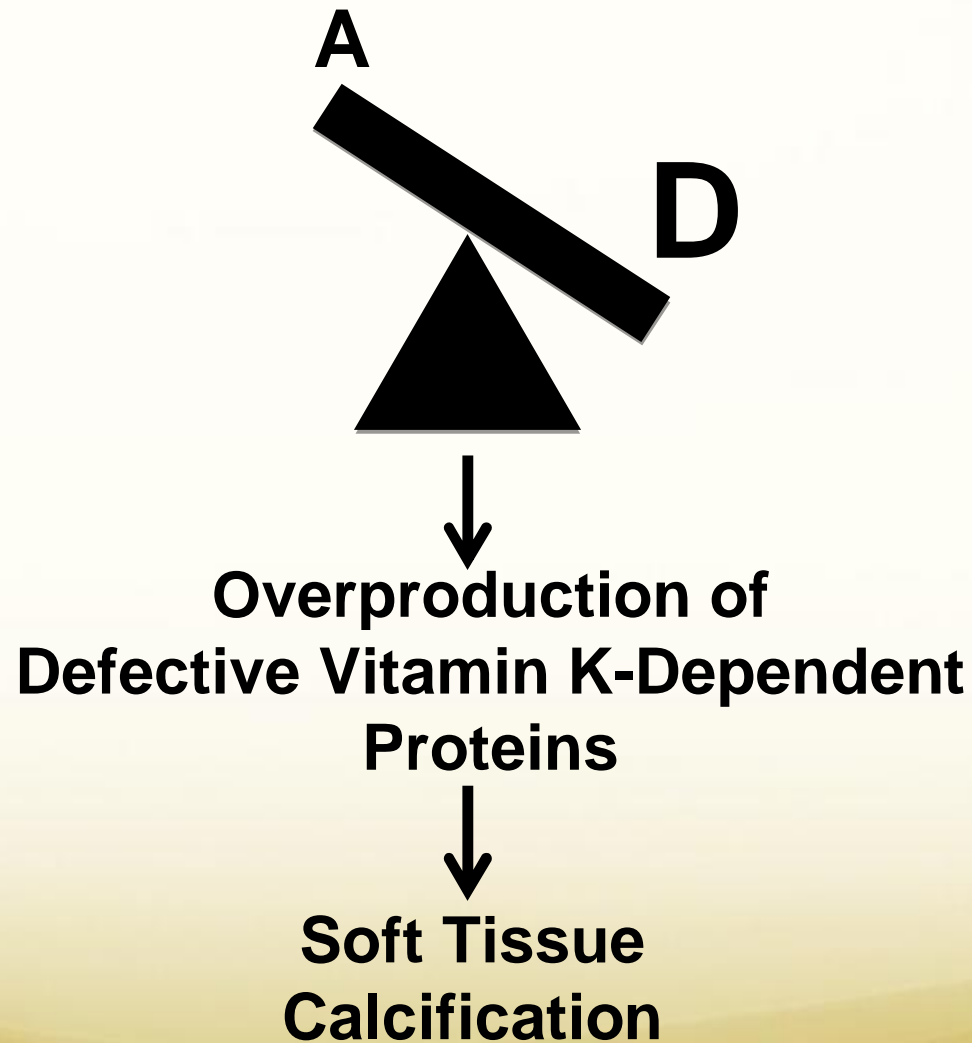
*Weston A. Price Foundation, 4200 Wisconsin Ave., NW, Washington DC 20016, United States*

Received 13 September 2006; accepted 14 September 2006

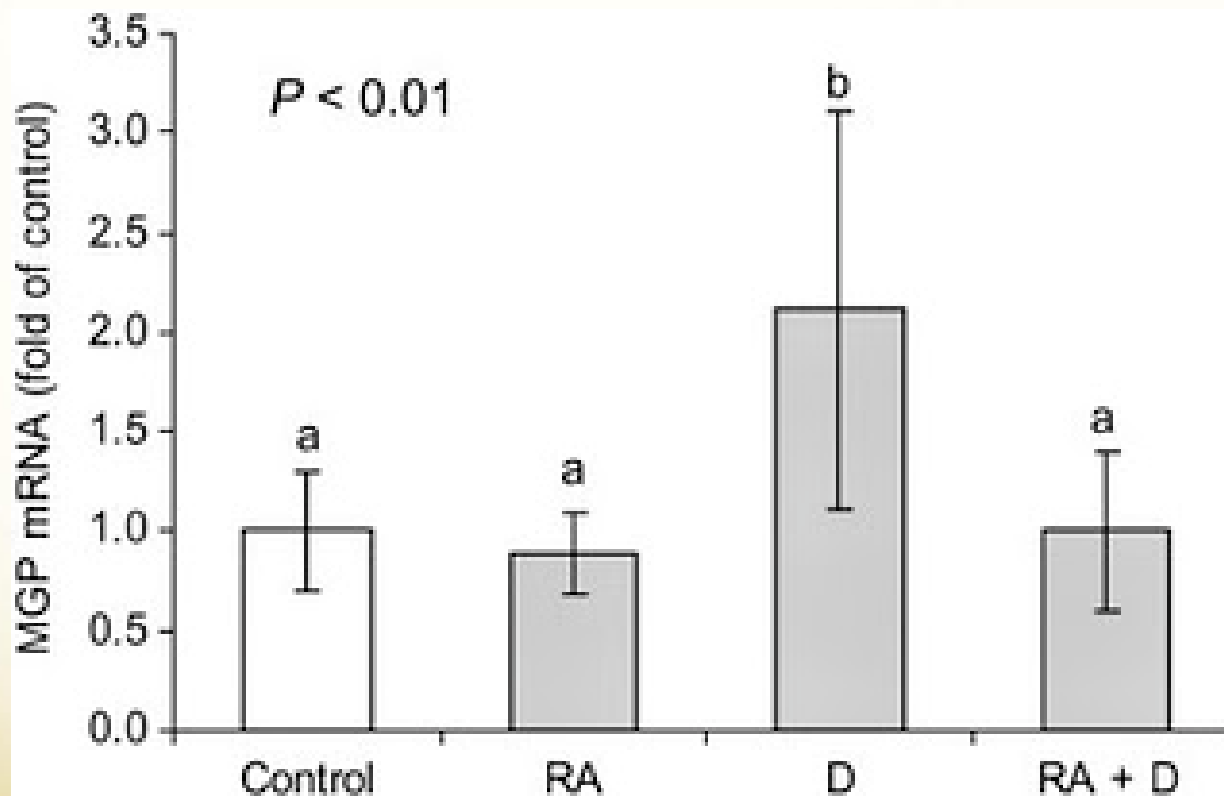
---

**Summary** The dose of vitamin D that some researchers recommend as optimally therapeutic exceeds that officially recognized as safe by a factor of two; it is therefore important to determine the precise mechanism by which excessive doses of vitamin D exert toxicity so that physicians and other health care practitioners may understand how to use optimally therapeutic doses of this vitamin without the risk of adverse effects. Although the toxicity of vitamin D has

# My Hypothesis



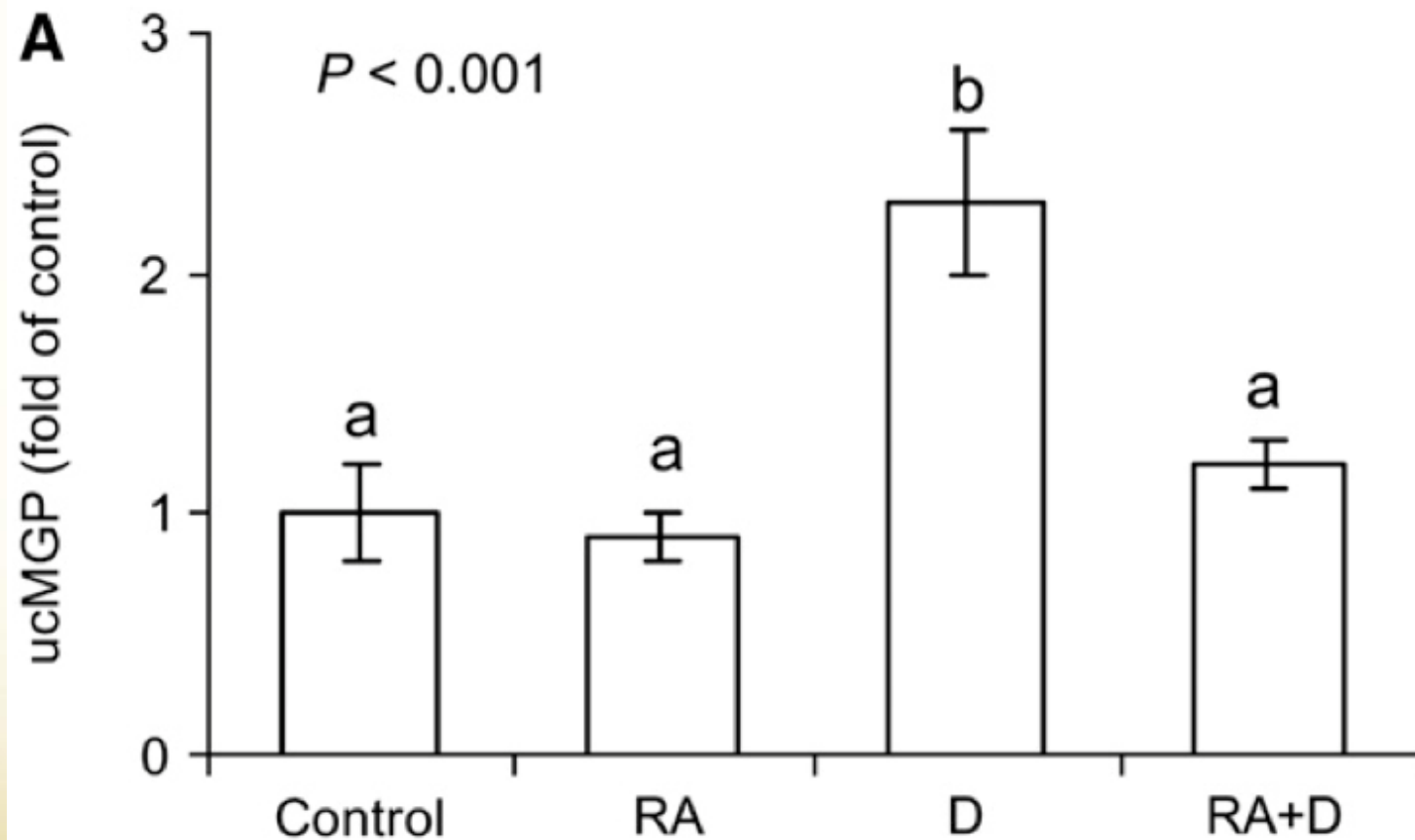
# Tufts Confirms: Vitamin A Curbs The Excessive Production of Vitamin K-Dependent Proteins Otherwise Induced by Vitamin D



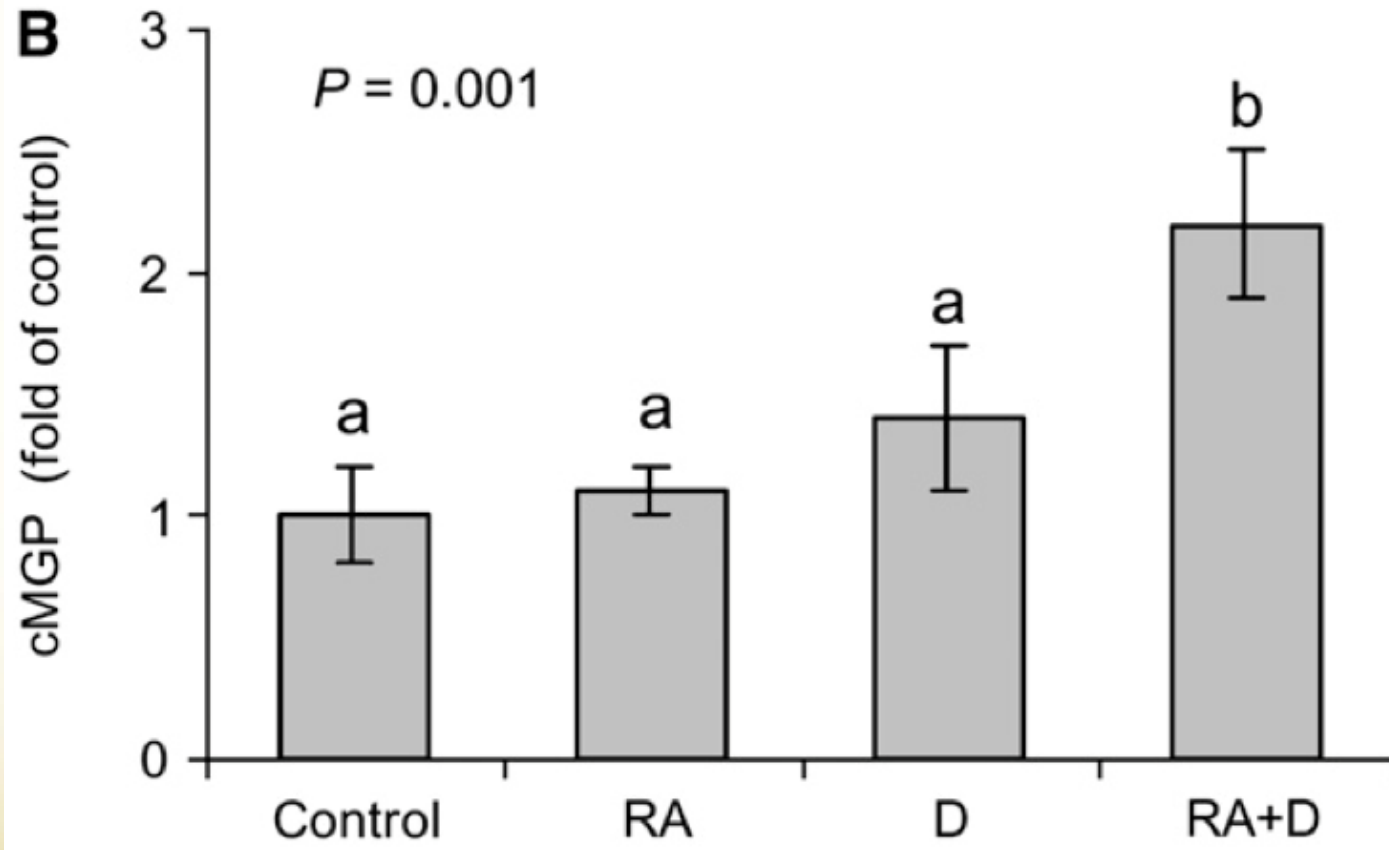
Fu et al. 9-Cis Retinoic Acid Reduces 1 $\alpha$ ,25-Dihydroxycholecalciferol-Induced Renal Calcification by Altering Vitamin K-Dependent gamma-Carboxylation of Matrix gamma-Carboxyglutamic Acid Protein in A/J Male Mice. J Nutr. 2008;138:2337-2341.



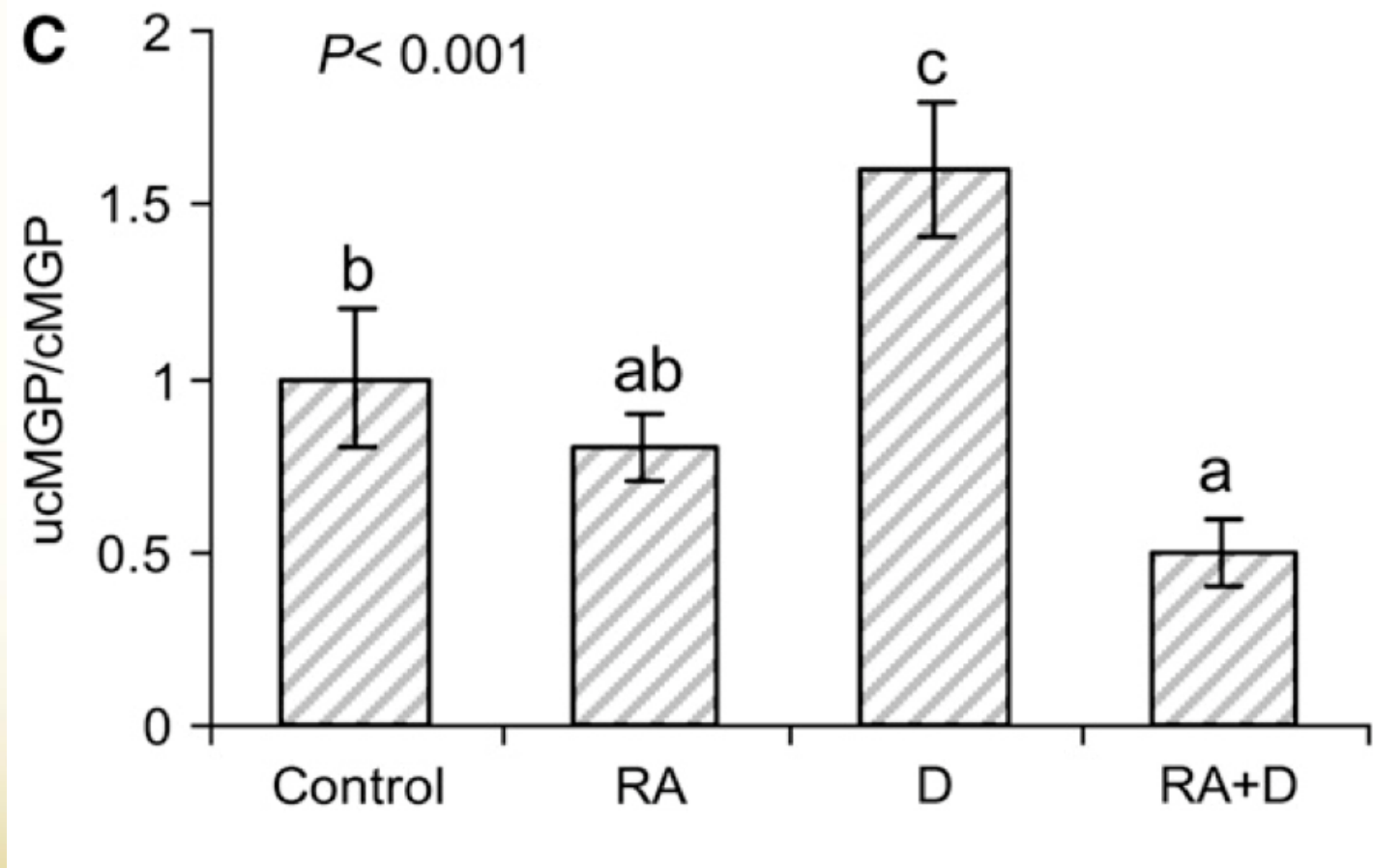
# Vitamin A Normalizes the Production of Defective MGP That Otherwise Increases With Vitamin D



# Vitamins A and D Synergize to Maximize the Amount of Active MGP Produced

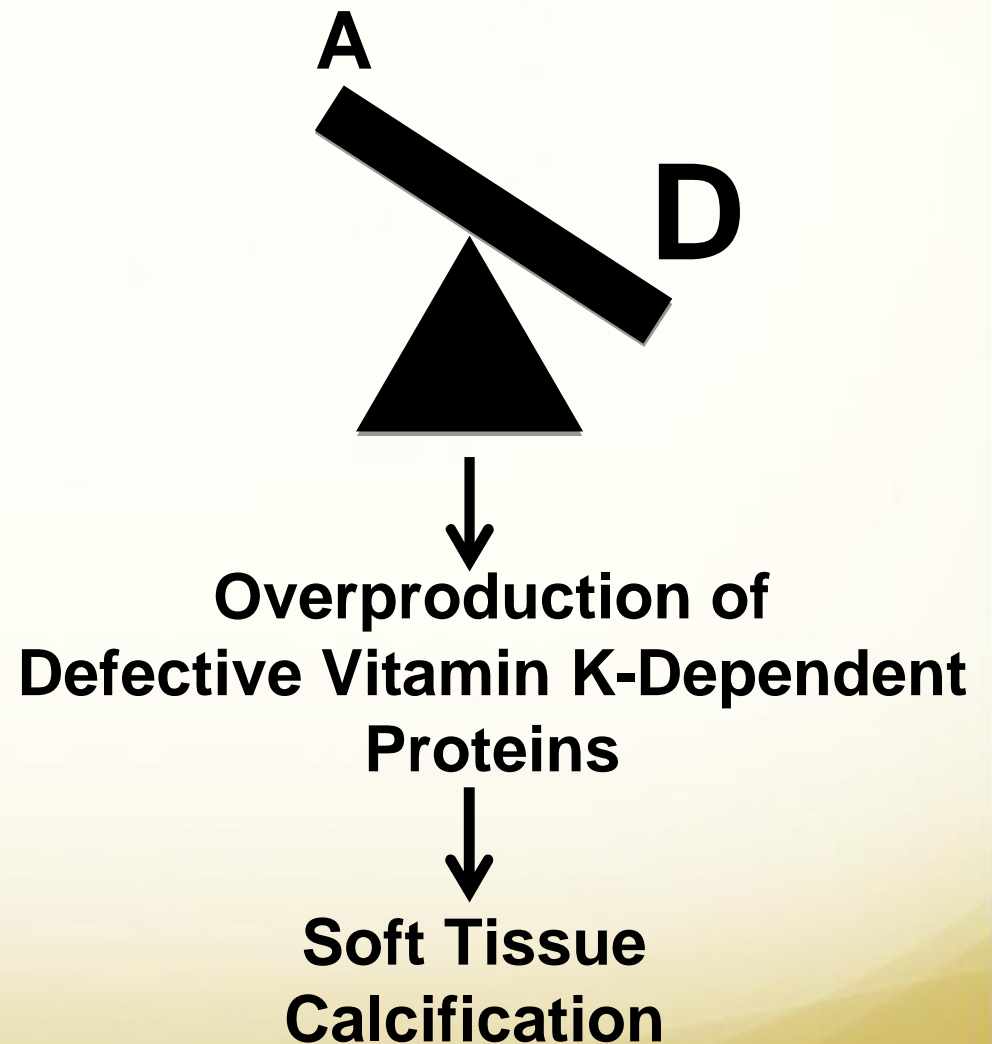
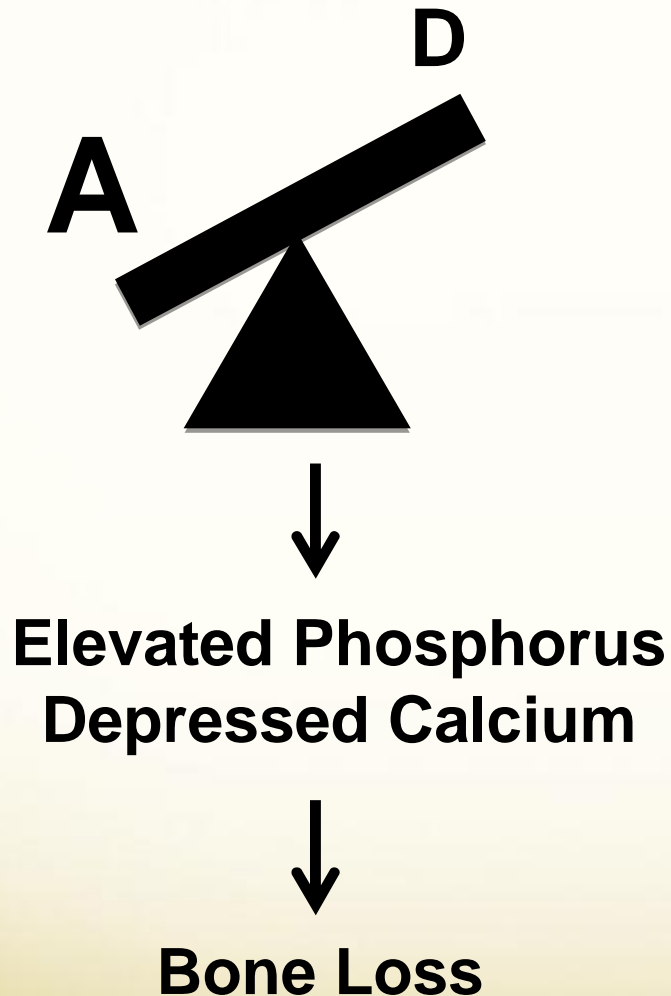


## Vitamins A and D Synergize to Minimize the Proportion of MGP That Is Defective

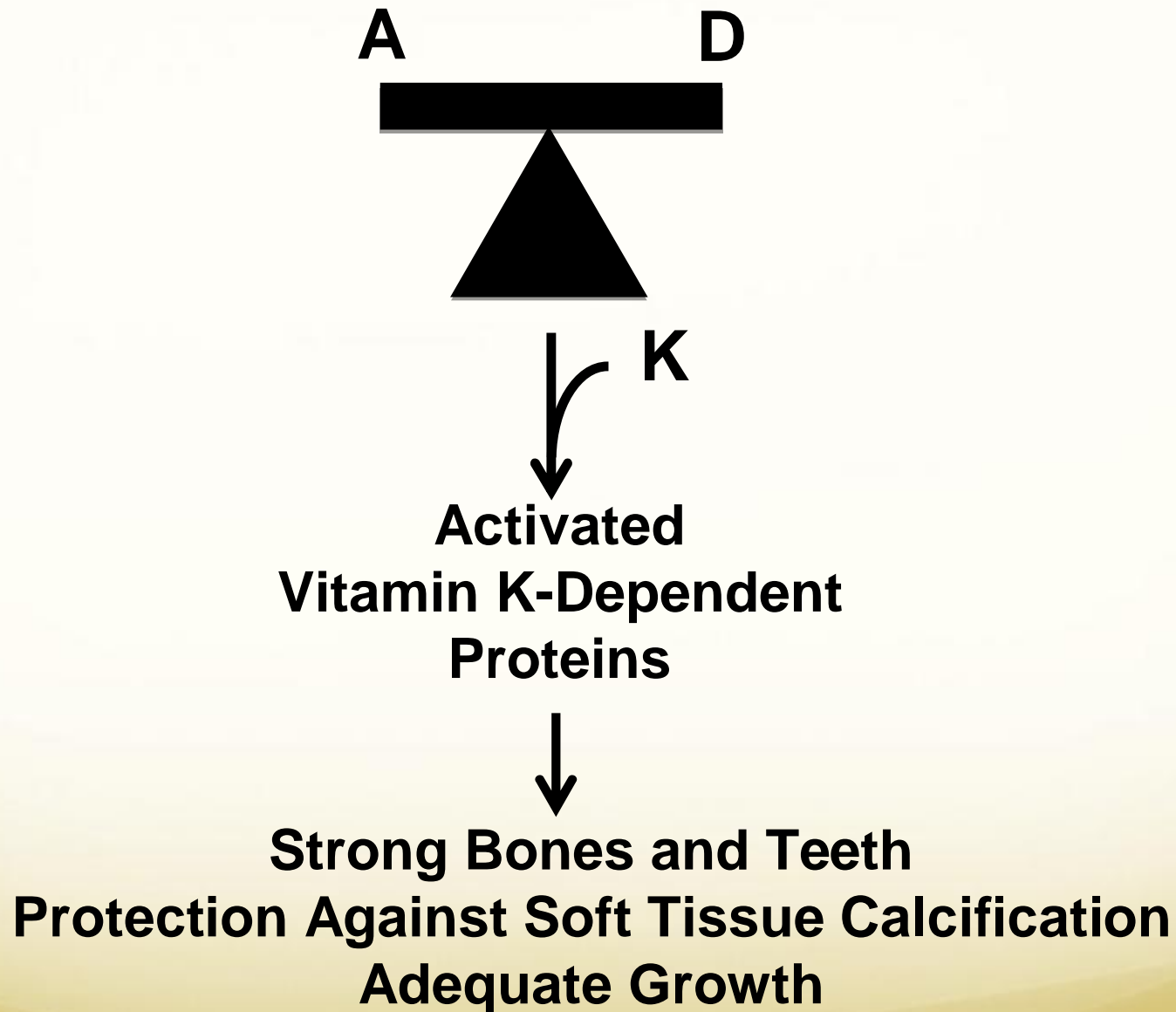


# **A New Model of Vitamin D Toxicity**

## **Toxicity of Vitamins A and D Due to Imbalance**



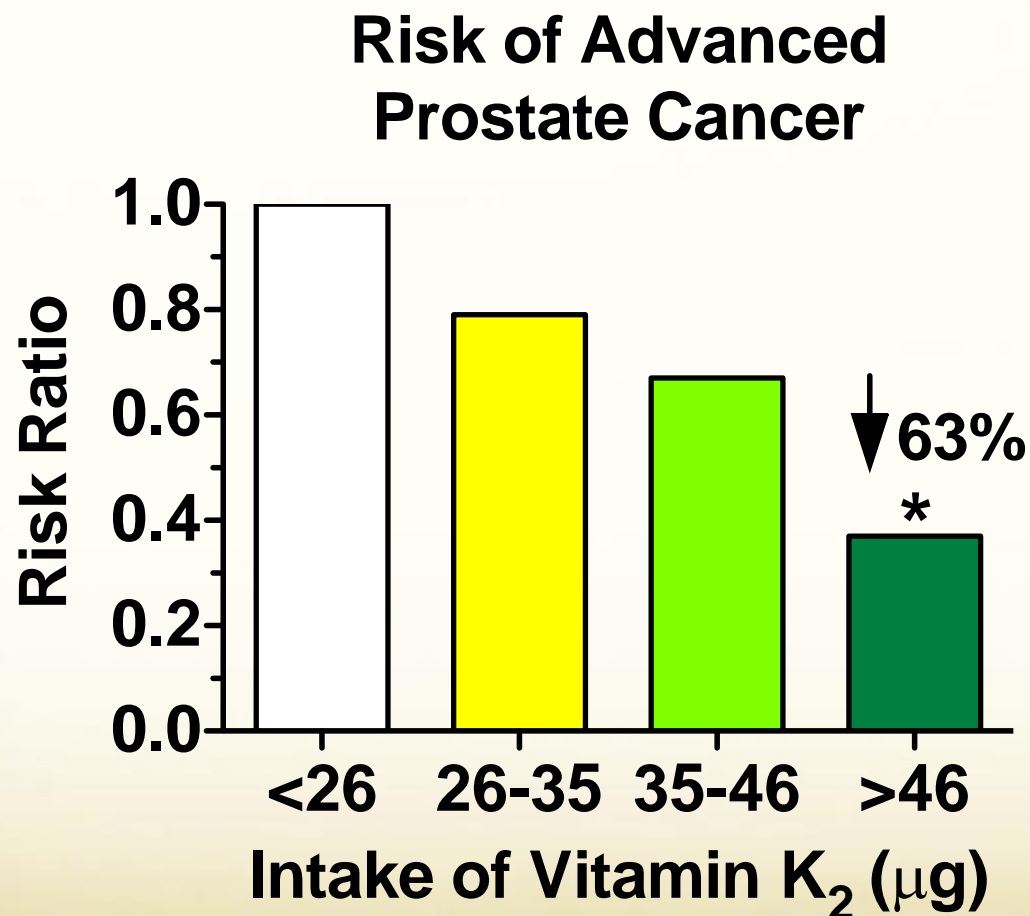
# Synergy Between Vitamins A, D, and K<sub>2</sub>



# Unanswered Questions

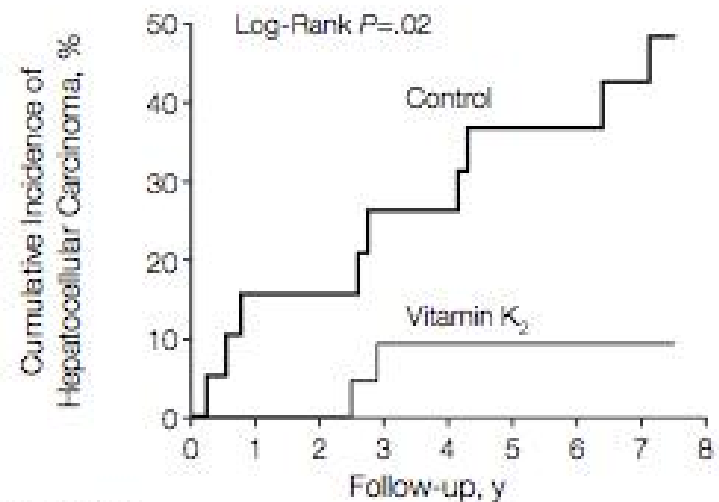
- Can the mechanistic understanding generated by the Tufts study be replicated in a study using dietary vitamins rather than the activated hormone forms?
- Does vitamin K protect against vitamin D toxicity like vitamin A does? Or is it the vitamin K-dependent enzyme rather than the amount of vitamin K that is limiting?
- Can this be replicated in other species?

# Vitamin K<sub>2</sub> Intake Associated With a Reduced Risk of Advanced Prostate Cancer



# Vitamin K<sub>2</sub> Reduces the Risk of Liver Cancer in Women by 87%

**Figure 2.** Cumulative Incidence of Hepatocellular Carcinoma Diagnosed in Women Treated With Vitamin K<sub>2</sub>



No. at Risk	0	1	2	3	4	5	6	7	8
Control	19	16	16	14	14	12	12	5	0
Vitamin K <sub>2</sub>	21	21	21	19	19	19	19	9	0

Habu et al. Role of Vitamin K<sub>2</sub> in the Development of Hepatocellular Carcinoma in Women With Viral Cirrhosis of the Liver. JAMA. 2004;292:358-61.



# The Many Functions of Vitamin A

- Essential to good vision, especially night vision.
- Essential to male and female reproduction.
- Essential to proper development of organs and tissues.
- Aids in the production of steroid hormones.
- Protects against kidney stones.
- May protect against asthma.
- Supports dopamine signaling; may protect against depression and support focused, goal-oriented behavior.
- Protects against fatty liver disease.
- Protects against oxidative stress and exposure to environmental toxins.

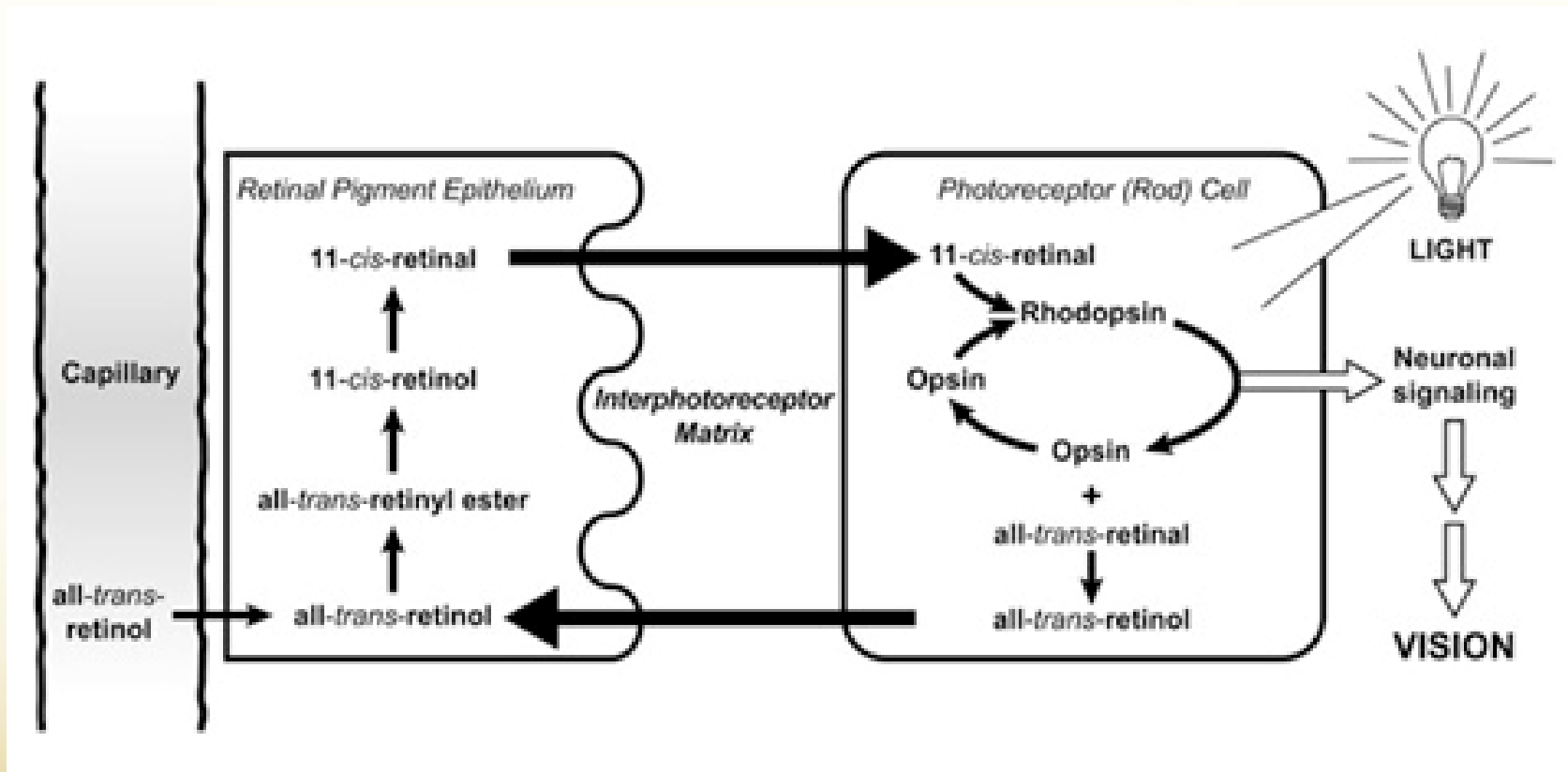
# Many Roles for Vitamin D?

- Rickets and osteomalacia
- Hypocalcemia
- Convulsions, tetany and heart failure in the newborn
- Osteoporosis
- Heart Disease
- High blood pressure
- Obesity
- Arthritis
- Mental Illness
- Chronic Pain
- Muscular weakening
- Radiation poisoning
- Diabetes
- Multiple sclerosis
- Other autoimmune diseases

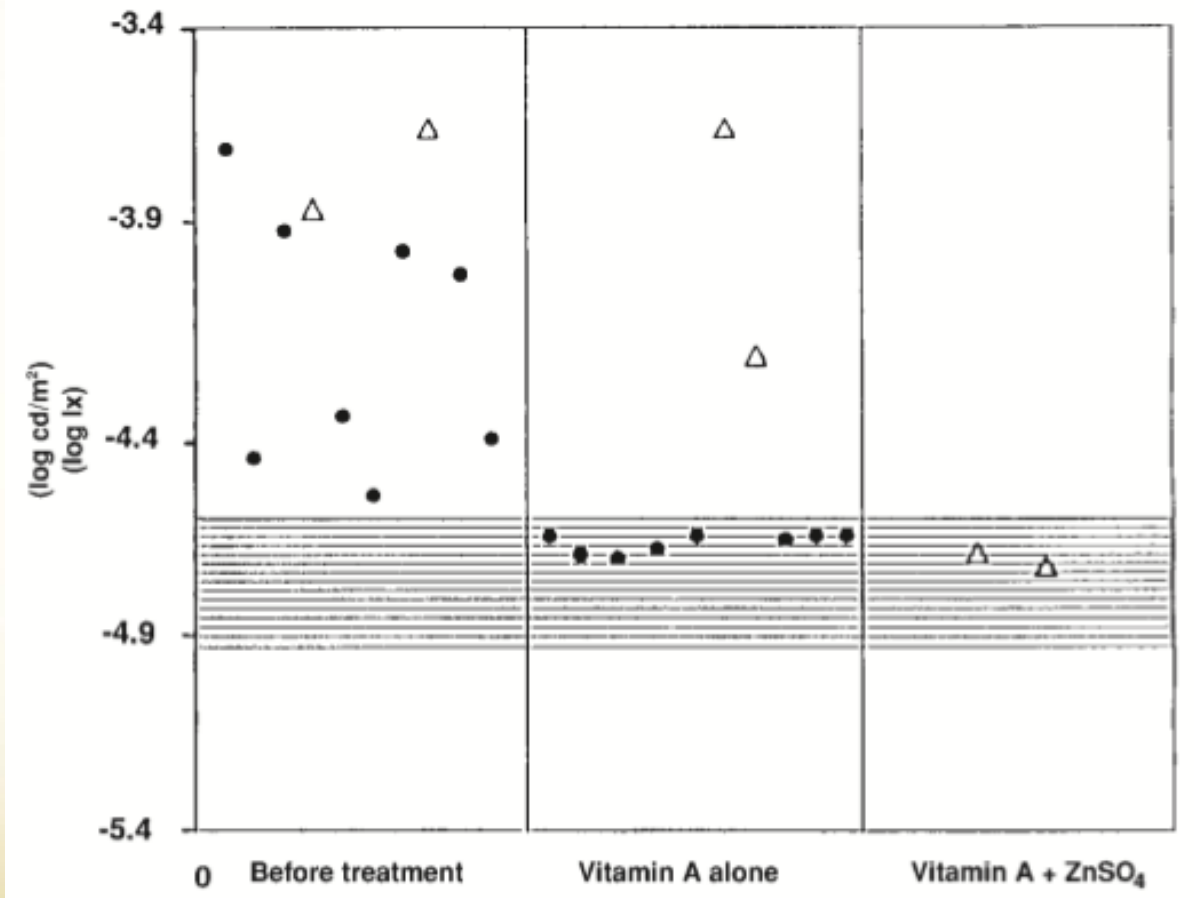
**Making the Most of the Fat-  
Soluble Vitamins:  
Zinc, Magnesium, Fat, Carbs,  
Carbon Dioxide, and Thyroid!**

**(Oh my!)**

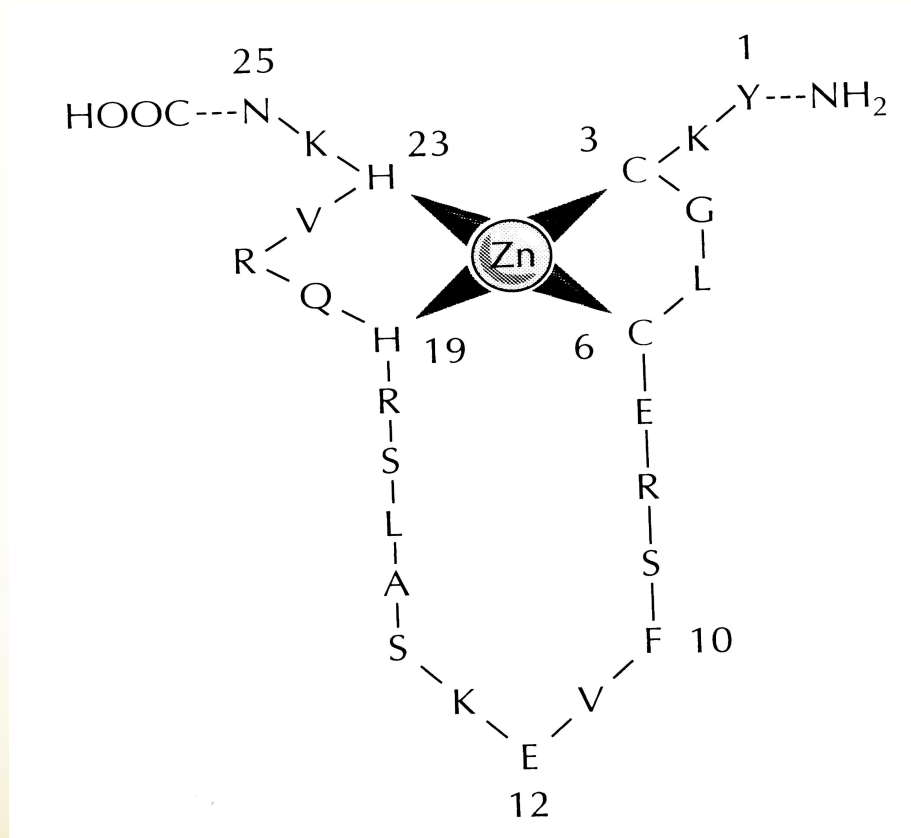
# Vitamin A Helps Convert Impulses of Light Into Visual Images



# Zinc Is Sometimes Necessary to Correct Vitamin A-Related Visual Function

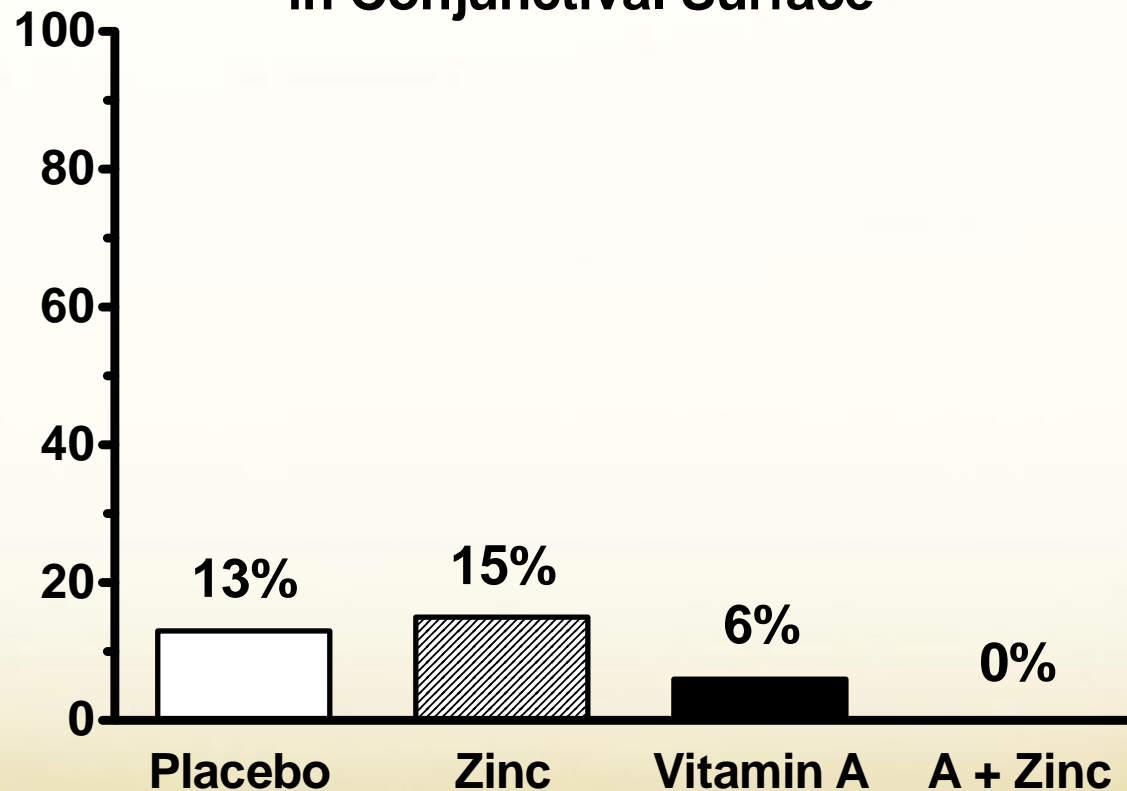


# A “Zinc Finger Motif” Activates the Nuclear Receptors For the Fat-Soluble Vitamins



# Zinc Is Needed For Vitamin A to Promote Proper Eye Development

Percent of Children With Abnormalities in Conjunctival Surface



# Zinc is Found Most Abundantly in Oysters, Beef, and Cheese

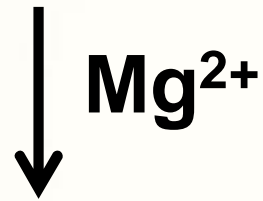
Food	Zinc (mg/100 g)
Oysters	17-91
Ground Beef	3.9-4.1
Liver	3.1-3.9
Cheese	2.8-3.2
Chicken	1.0-2.0
Eggs	1.1
Legumes	0.6-1.0
Milk	0.4
Grains and Cereals	0.3-1.0
Vegetables	0.1-0.7
Fruit	<0.1

From Groff and Gropper, *Advanced Nutrition and Human Metabolism*, 2005.



# The Role of Magnesium

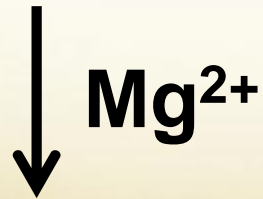
Vitamin D



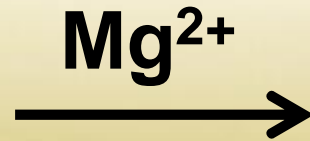
25(OH)D



1,25(OH)<sub>2</sub>D



Calcium  
Absorption



Distribution of Calcium to  
Blood, Bones, Teeth, and  
Storage Vesicles

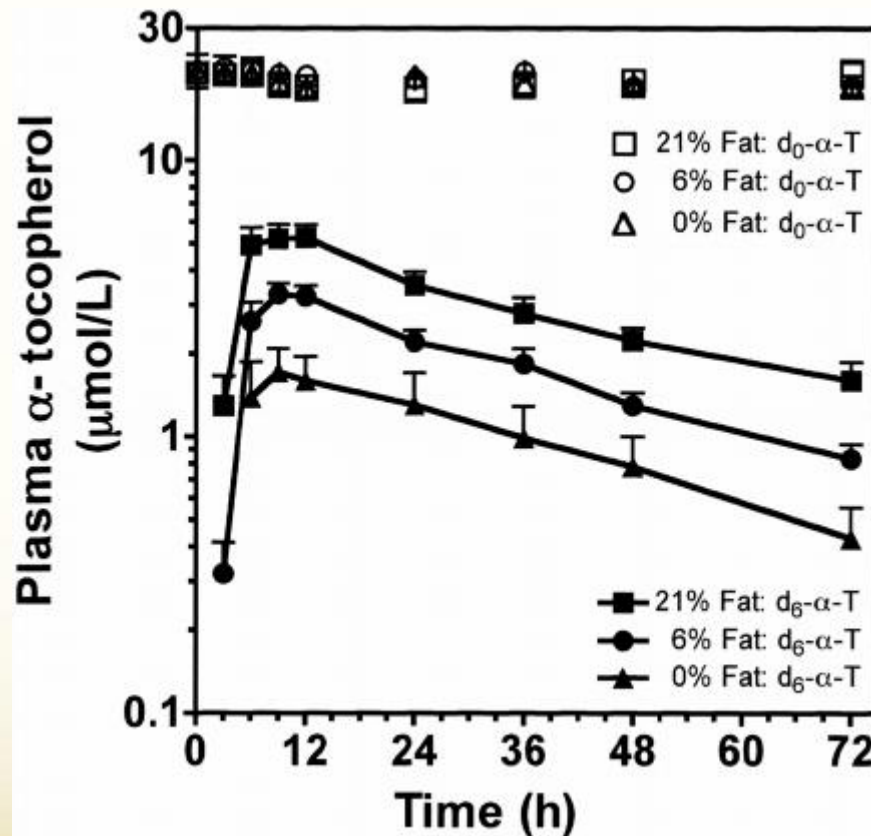


Parathyroid  
Gland

# Magnesium is Rich in Many Foods, But Not Meat Or Refined Carbs

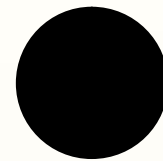
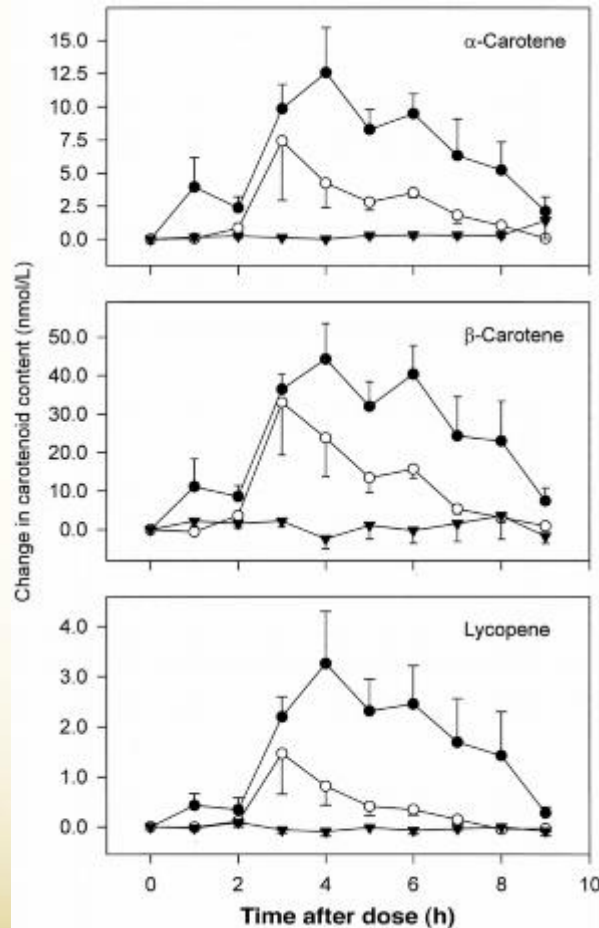
Food	Magnesium (mg/100 g)
Pumpkin and Squash Seeds	534
Brazil Nuts	376
Caviar	300
Buckwheat	231
Tomatoes	194
Kidney Beans	140
Whole Wheat	126
Hamburger	27
Liver	18
Enriched White Flour	16
Table Sugar	9

# Butterfat Increases the Absorption of Vitamin E

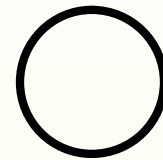


Bruno et al. Human vitamin E requirements assessed with the use of apples fortified with deuterium-labeled alpha-tocopherol acetate. *Am J Clin Nutr.* 2006;83(2):299-304.

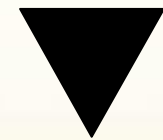
# Canola Oil Increases Absorption of Carotenenes From Salad



28 grams of fat



6 grams of fat

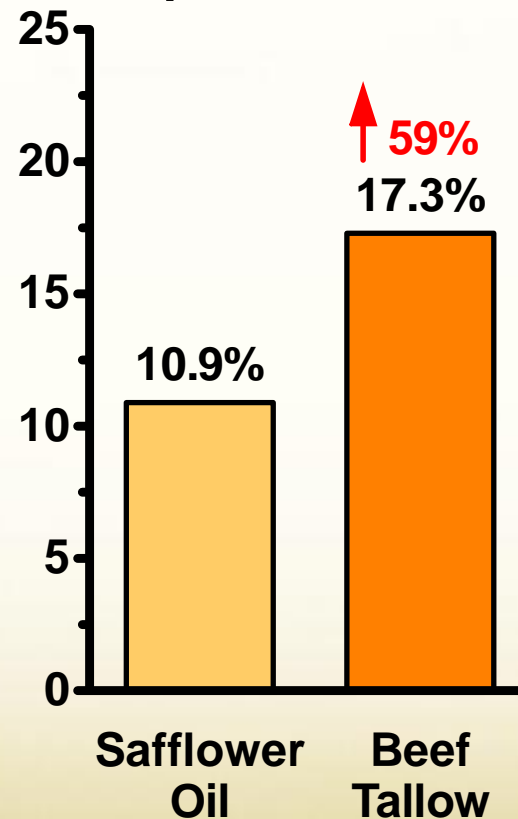


0 grams of fat

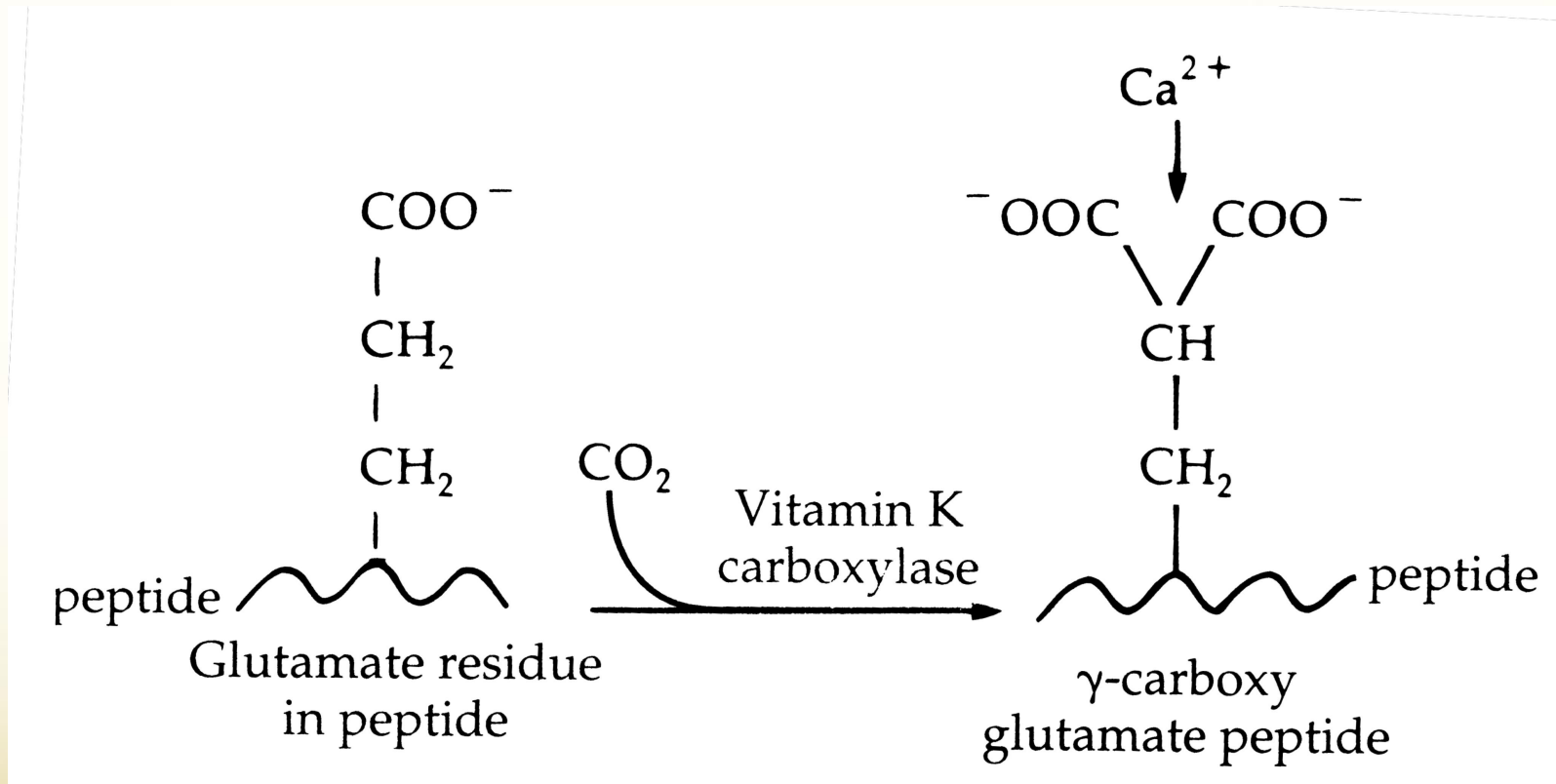
Brown et al. Carotenoid bioavailability is higher from salads ingested with full-fat than with fat-reduced salad dressings as measured with electrochemical detection. Am J Clin Nutr. 2004;80(2):396-403.

# Saturated Fats Are Superior At Promoting Fat-Soluble Vitamin Absorption

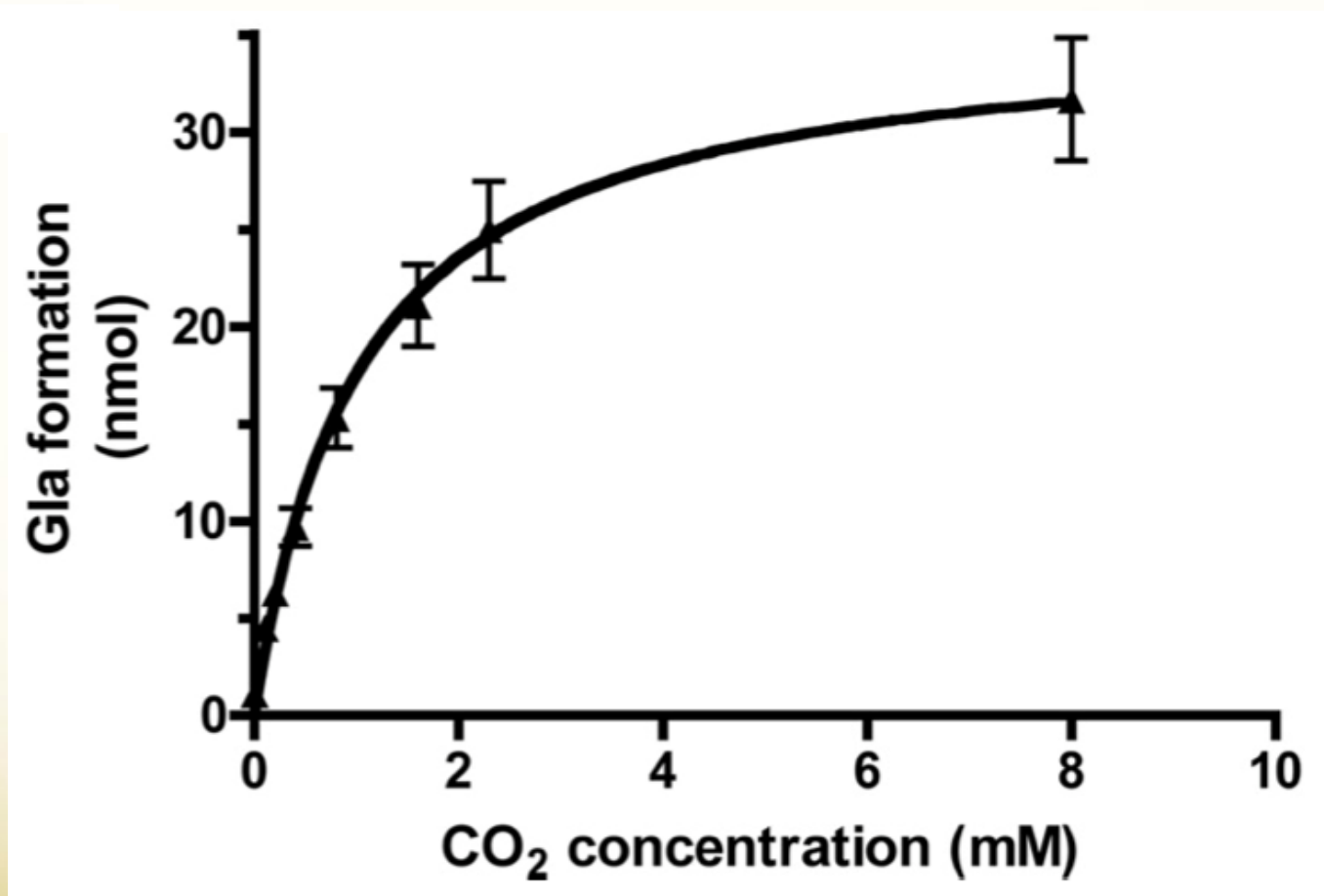
Percent Absorption  
of Beta-Carotene  
From a Liquid 28% Fat Test Meal



# Vitamin K Activates Proteins With Carbon Dioxide, Giving Them the Ability to Bind Calcium



# Activation of Vitamin K-Dependent Proteins Depends on the Concentration of CO<sub>2</sub>



Rishavy et al. The Vitamin K-dependent Carboxylase Generates [gamma]-Carboxylated Glutamates by Using CO<sub>2</sub> to Facilitate Glutamate Deprotonation in a Concerted Mechanism That Drives Catalysis. *J Biol Chem.* 2011;286(52):44821-32.

# Blood Results for Gary Taubes

03/30/2011 07:16AM

QUEST DIAGNOSTICS FAX REPORT

PAGE 2 01

QUEST DIAGNOSTICS INCORPORATED

SPECIMEN INFORMATION

SPECIMEN: BA3869843  
REQUISITION: SCRIPT,

COLLECTED: 03/22/11 16:16  
RECEIVED: 03/22/11 16:18  
REPORTED: 03/30/11 07:15

PATIENT INFORMATION

TAUBES, GARY

DOB: 04/30/1956 AGE: 54  
GENDER: M FASTING: U

ID:  
PHONE: ~~XXXXXXXXXX~~

REPORT STATUS **FINAL** R

ORDERING PHYSICIAN  
**NAGLER, BILL**

CLIENT INFORMATION  
4207630  
NAGLER, BILL  
16311 MIDDLEBELT  
LIVDNIA, MI 48154

COMMENTS: The original copy of this report was printed on: 03/25/11 at 04:35

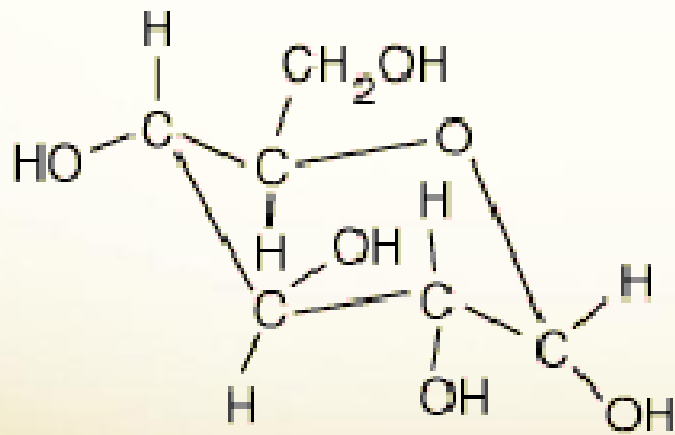
Test Name	In Range	Out of Range	Reference Range
COMPREHENSIVE METABOLIC PANEL			
COMPREHENSIVE METABOLIC PANEL			
SODIUM, SERUM	143		135-146 mmol/L
POTASSIUM, SERUM	4.3		3.5-5.3 mmol/L
CHLORIDE, SERUM	107		98-110 mmol/L
<b>CARBON DIOXIDE (CO2)</b>		<b>19 L</b>	<b>21-33 mmol/L</b>
UREA NITROGEN, BLOOD (BUN)	24		7-25 mg/dL
CREATININE, SERUM	1.08		0.76-1.46 mg/dL
eGFR	>60		SEE BELOW



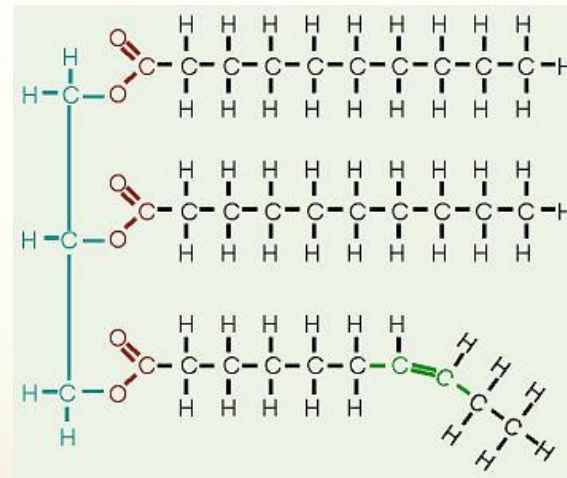
# Carbon Dioxide – What's the Limiting Atom?



Carbon Dioxide

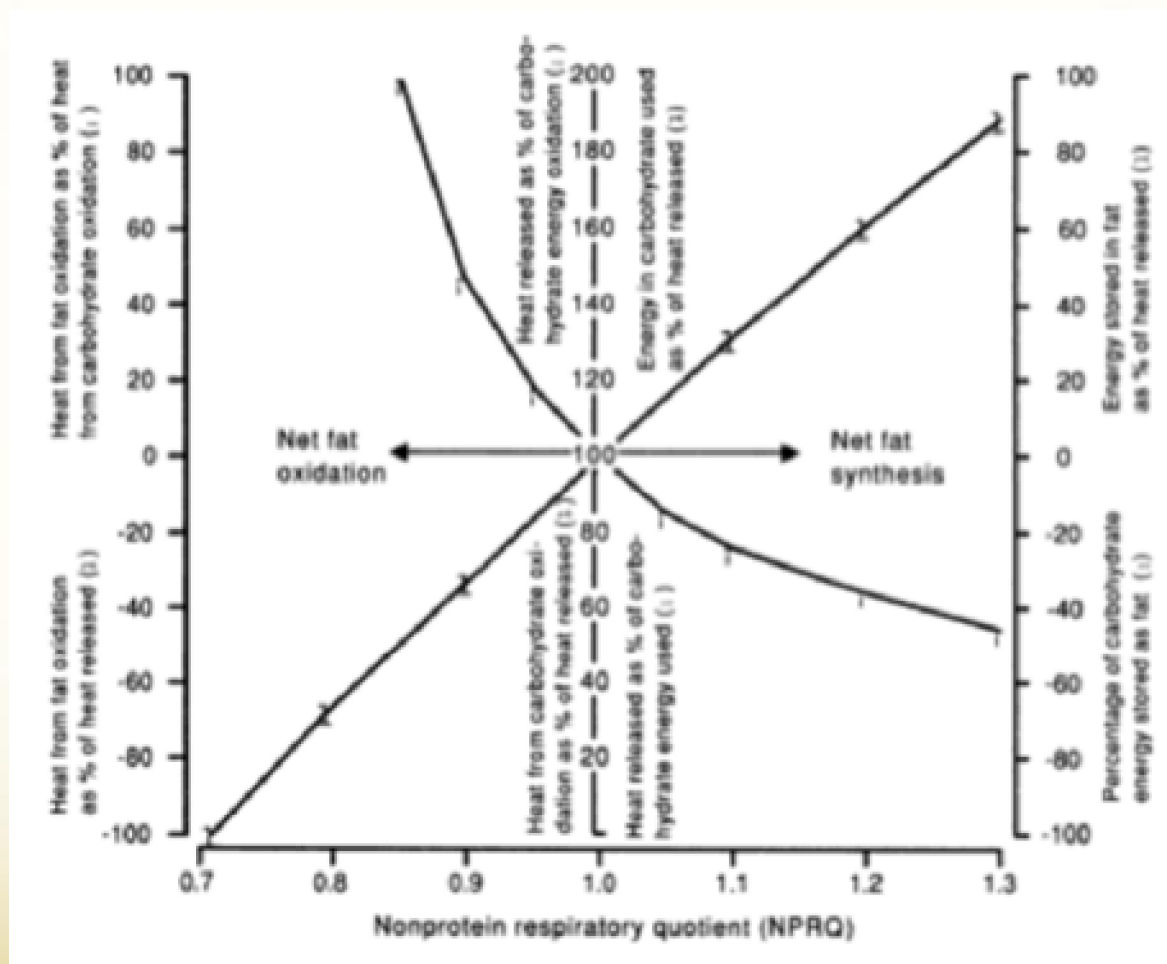


Glucose

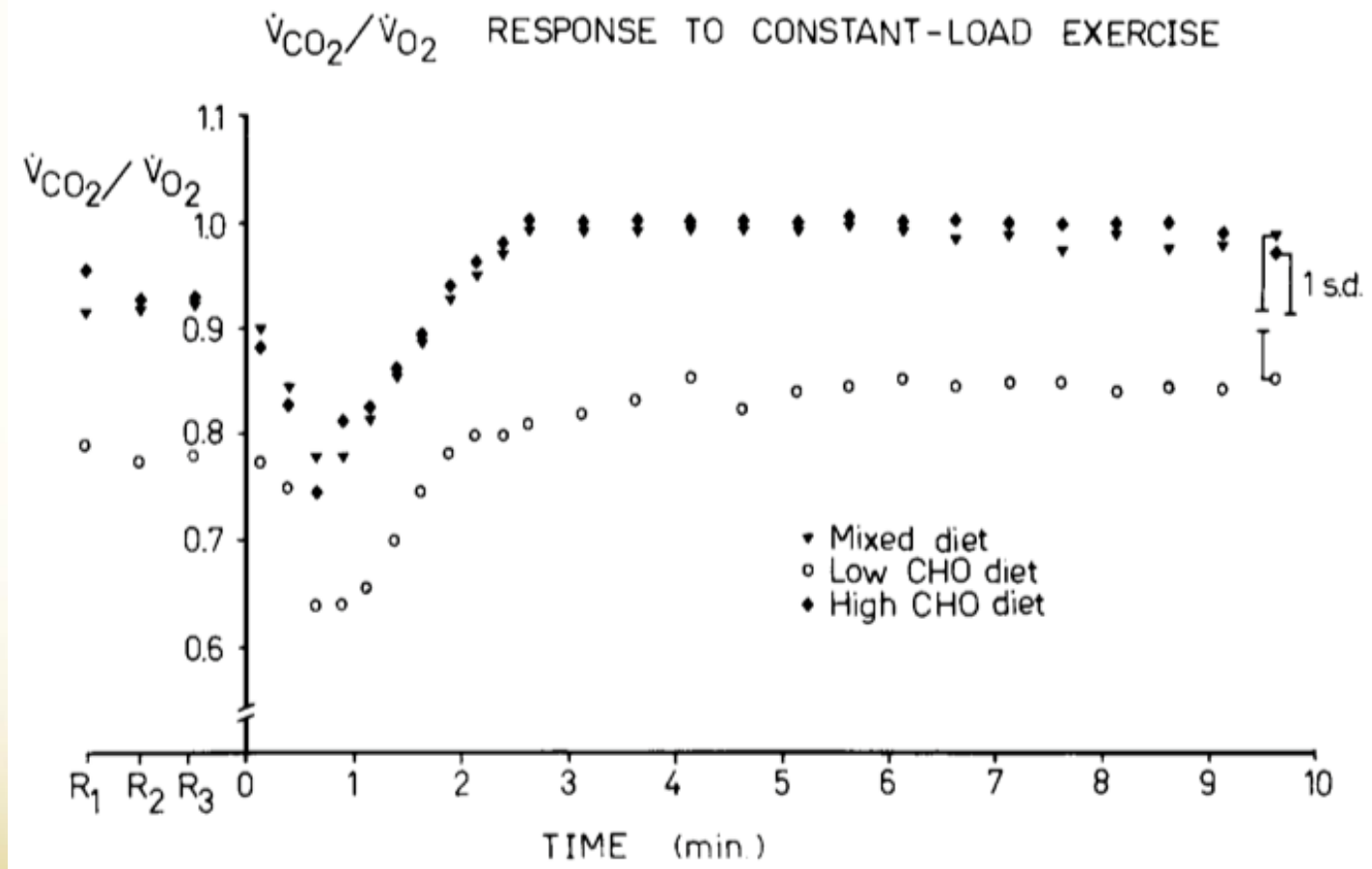


Fat

# The Respiratory Quotient ( $\text{CO}_2/\text{O}_2$ ) Increases Proportionally With Carbohydrate Utilization

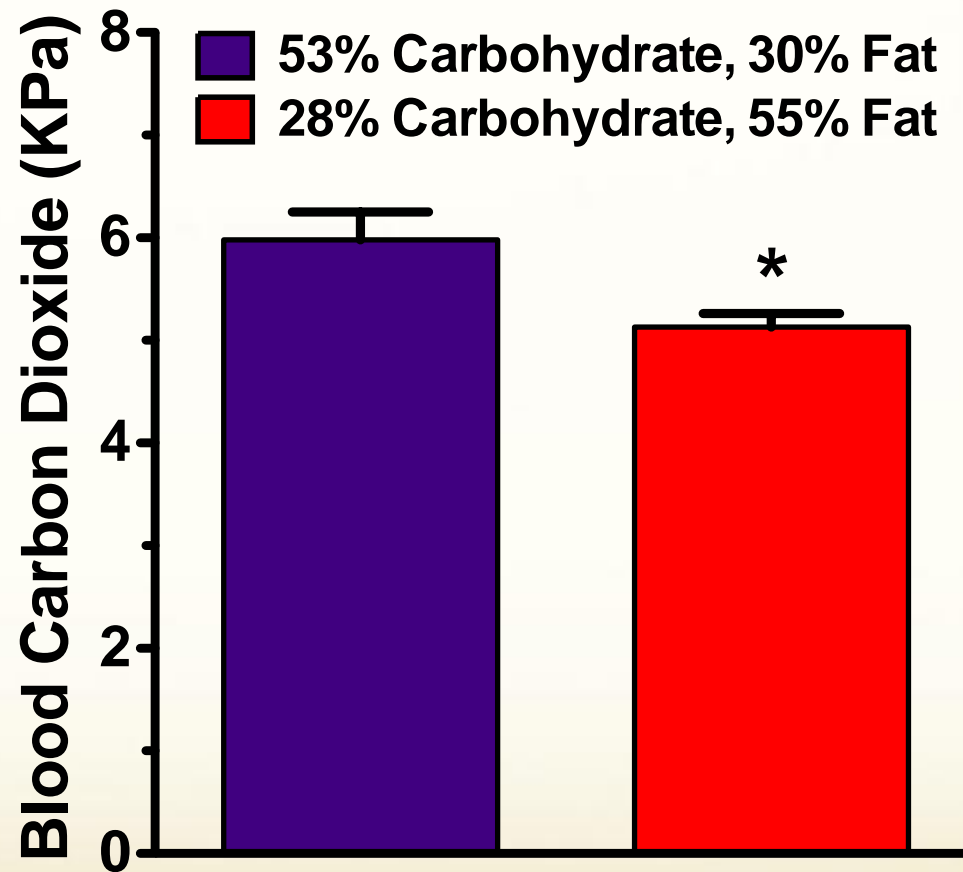


# Production of CO<sub>2</sub> Declines on a Low-Carbohydrate Diet



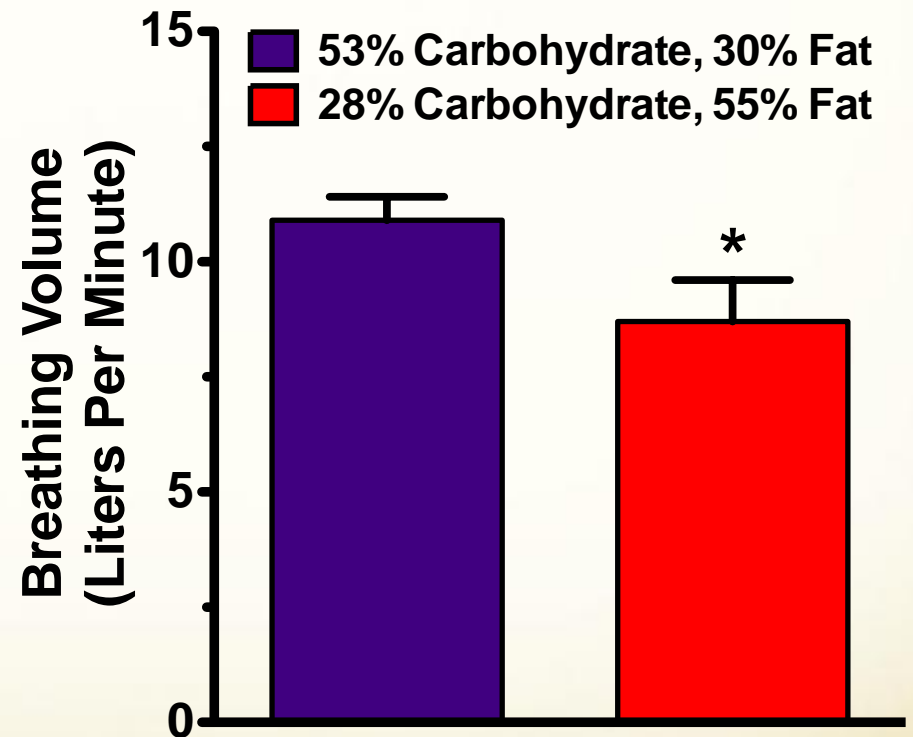
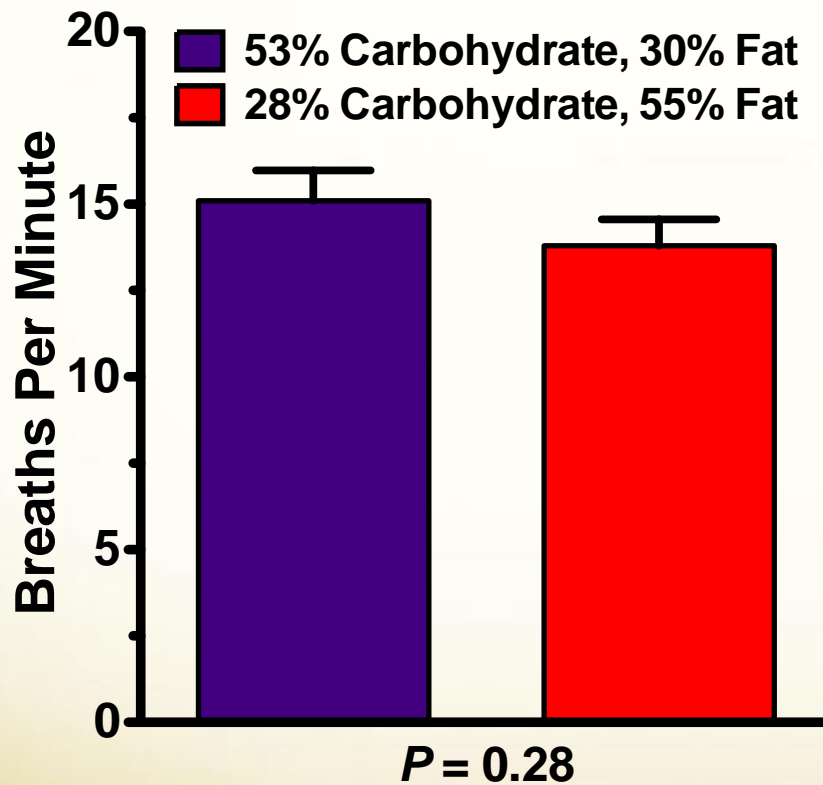
Hughson and Kowalchuk. Influence of Diet on CO<sub>2</sub> Production and Ventilation in Constant-Load Exercise. *Respiration Physiology*. 1981;46:149-160.

# Low-Carbohydrate Diets Lower Blood Levels of Carbon Dioxide



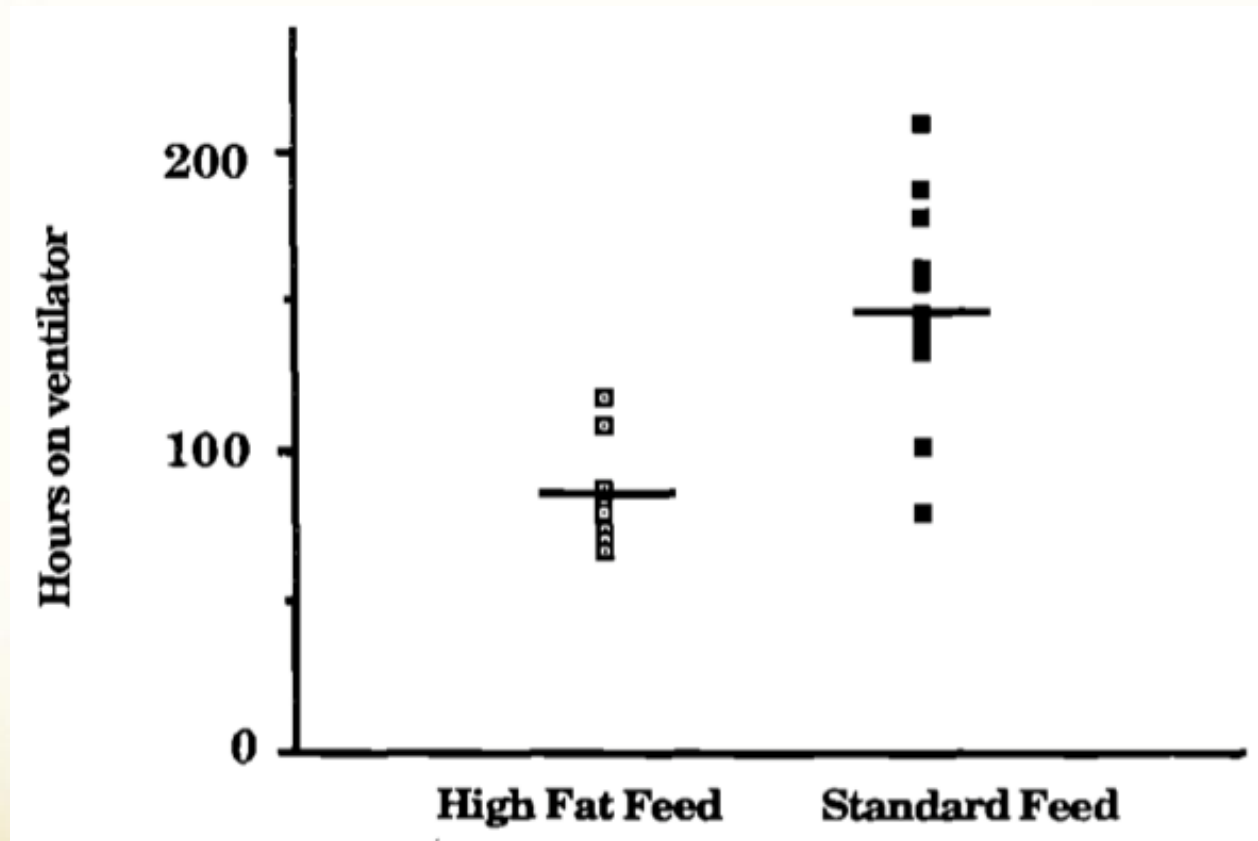
20 adult patients requiring artificial ventilation fed a standard or low-carb, high-fat diet through a feeding pump

# Low-Carbohydrate Diets Lower the Breathing Rate



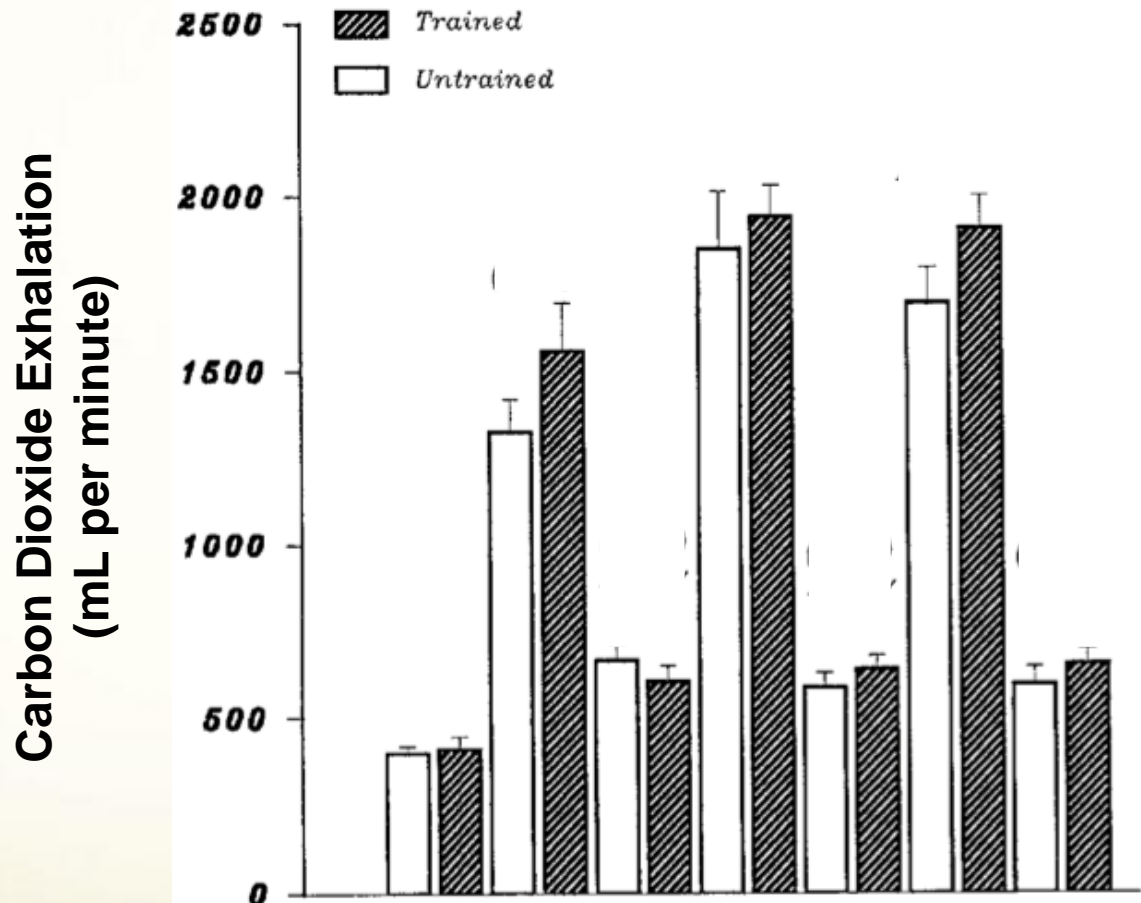
20 adult patients requiring artificial ventilation fed a standard or low-carb, high-fat diet through a feeding pump

# Low-Carbohydrate Diets Reducing Breathing Rate and Time on Ventilator



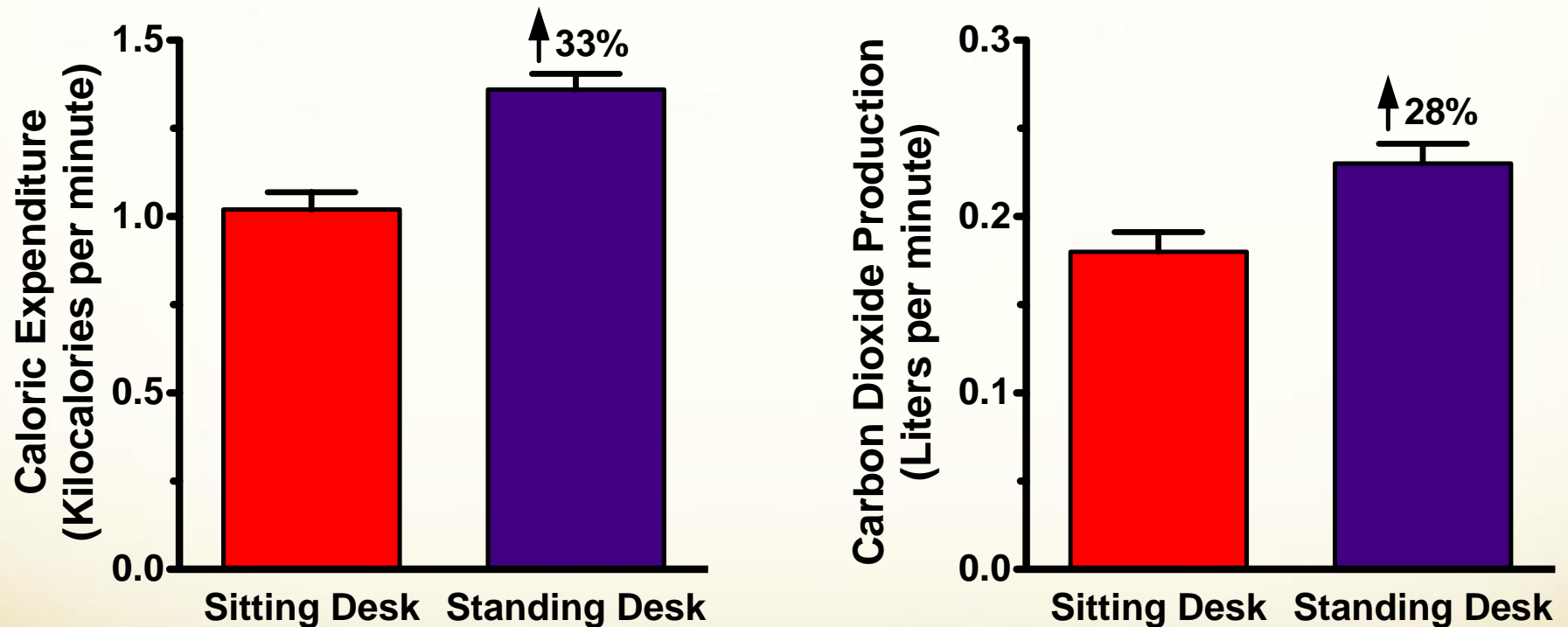
20 adult patients requiring artificial ventilation fed a standard or low-carb, high-fat diet through a feeding pump

# Intense Exercise Increases Carbon Dioxide



**Pre-exercise, followed by three six-second periods of intense cycling interspersed by five-minute periods of rest, among 18 trained or untrained healthy men ages 18-33.**

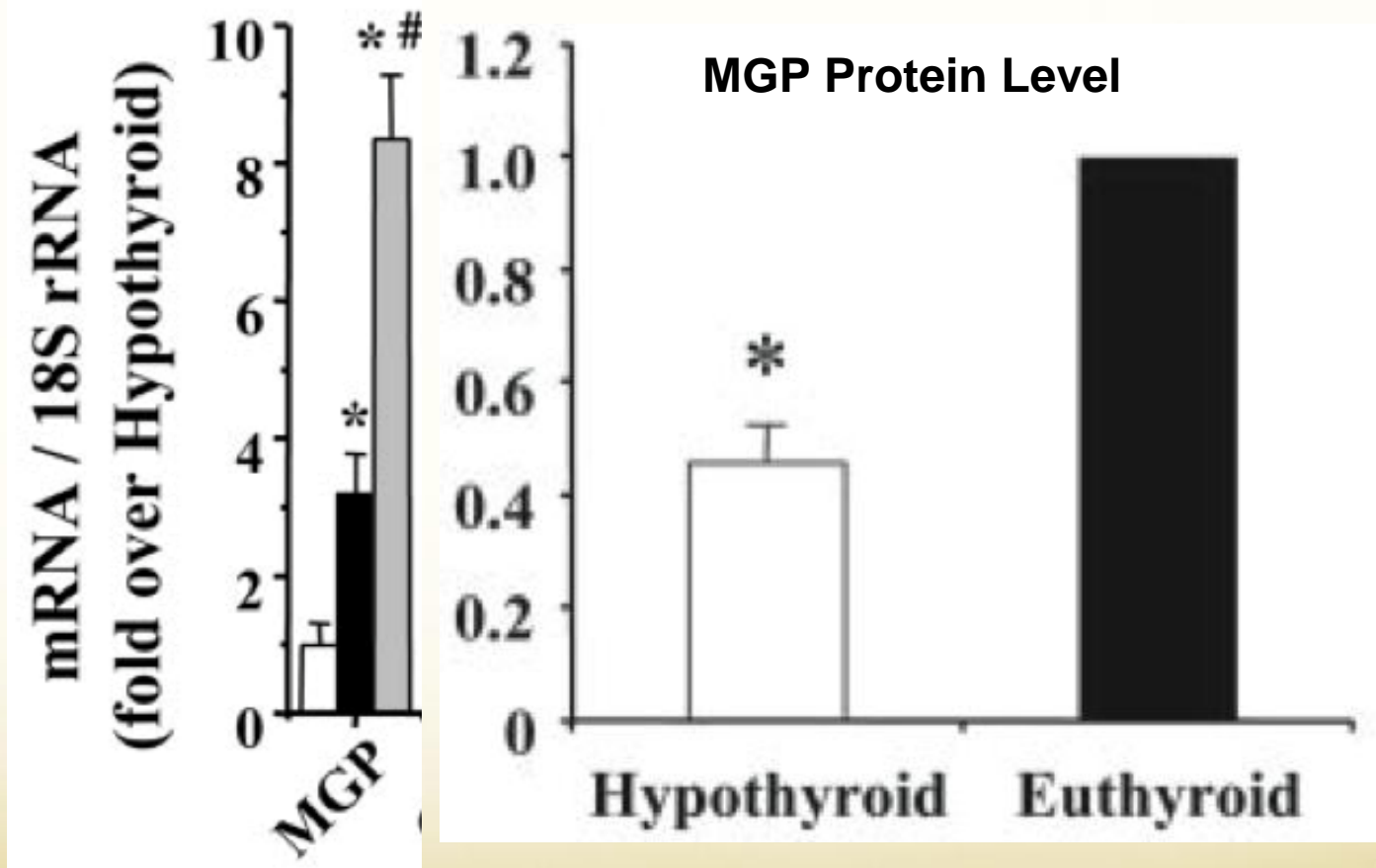
# Working at a Standing Desk Increases Carbon Dioxide Production



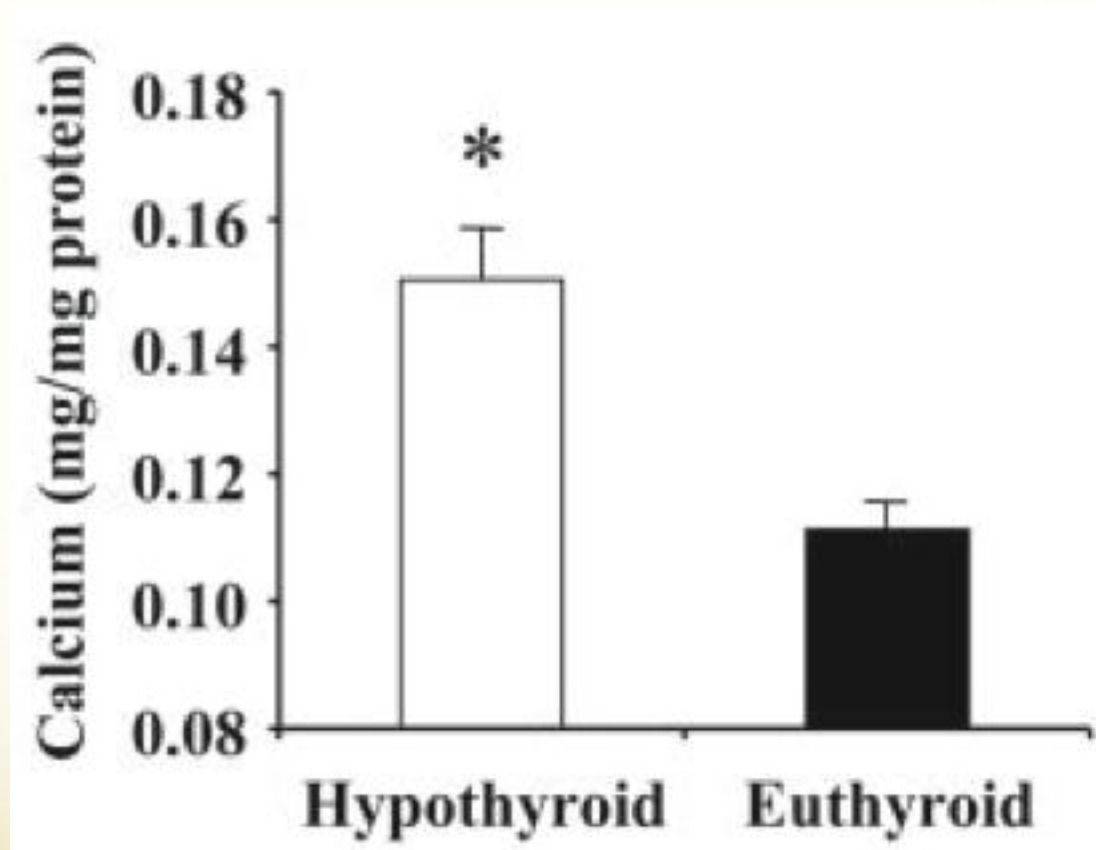
20 healthy young adult men and women performed crossword puzzles and wordfinds for 45 minutes.



# Thyroid Hormone Increases the Production of Vitamin K-Dependent Proteins in Rats



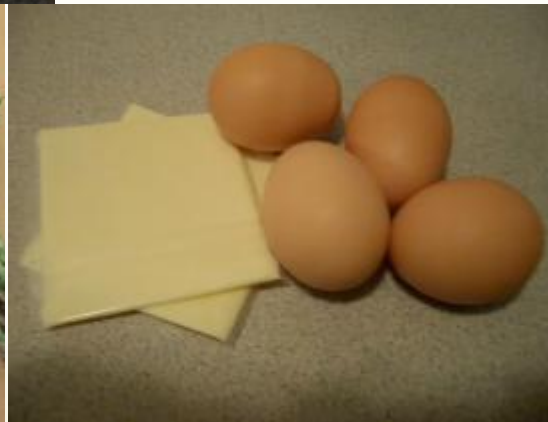
# Thyroid Hormone Prevents Blood Vessel Calcification



# Conclusions

- Vitamins A, D, and K<sub>2</sub> cooperate together to protect soft tissues from calcification, provide for adequate growth, and nourish strong bones and teeth.
- Vitamin A is found primarily in liver and cod liver oil, while carotene-rich plant foods can also support vitamin A status.
- Vitamin D is found primarily in cod liver oil and fatty fish, and obtained from sunshine.
- Vitamin K<sub>2</sub> is found primarily in animal fats and fermented foods, especially egg yolks and hard cheeses.
- Zinc and magnesium are needed to support the fat-soluble vitamins. The best way to obtain these minerals is to eat a diet inclusive of both animal foods and plant foods but devoid of refined carbohydrates.
- Fat is necessary to absorb fat-soluble vitamins, while carbohydrate, thyroid hormone, and exercise may help optimize carbon dioxide production for the activation of vitamin K-dependent proteins.

# Thank You!



Chris Masterjohn, PhD  
Blog: *The Daily Lipid*  
<http://blog.cholesterol-and-health.com>