PUBLIC HEALTH GRAND ROUNDS

Office of the Director

August 19, 2010

MONITORING THE NATION'S VITAMIN D STATUS: THE NHANES EXPERIENCE




Clifford L. Johnson, MSPH

Director

Division of Health and Nutrition Examination Surveys

National Center for Health Statistics

Centers for Disease Control and Prevention

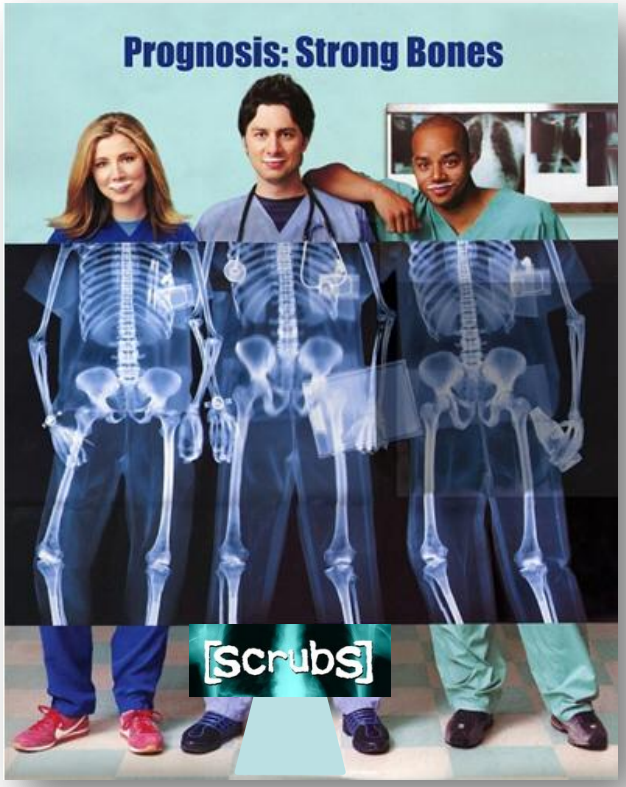
Overview

- **What is vitamin D and why do we need it?**
- **Which scientific and public health issues make vitamin D one of the most talked about nutritional issues today?**
- **How is vitamin D status in the U.S. population evaluated through the NHANES survey?**
  - Challenges and ways to address them

National Health and Nutrition Examination Survey

What is Vitamin D?

- **Fat-soluble vitamin that helps the body absorb calcium**
- **Primarily needed for bone growth and bone remodeling**
- **Other roles in human heath**
  - Modulates neuromuscular and immune function
  - Reduces inflammation



Main Sources of Vitamin D

Sunlight: UVB exposure

Vitamin D3 – cholecalciferol

Food

Vitamin D3 – cholecalciferol, animal sources

Vitamin D2 – ergocalciferol, plants (mushrooms)

Supplements

Vitamin D2 and vitamin D3

CDC. MMWR Recomm Rep 1992 Sep 11;41(RR-14):1-7

Main Dietary Sources of Vitamin D

Fortified milk	**400 IU/quart**
Some yogurts	**80 IU/8 oz**
Some fortified cereals	**40–100 IU/serving**
Some fortified juices	**100 IU/8 oz**
Fatty fish *(salmon, mackerel, herring, tuna)*	**200–400 IU/3 oz**
Some calcium and vitamin/mineral supplements	**Most often 400 IU**

Vitamin D Metabolism

- **Vitamin D is rapidly taken up and transported to the liver**
- **Vitamin D2 and vitamin D3 are metabolized**
  - First, in the liver to the circulating form: 25-hydroxyvitamin D or 25(OH)D
  - Then, to the active form:1,25-dihydroxyvitamin D in the kidney
- **The production of 1,25-dihydroxyvitamin D is tightly regulated by parathyroid hormone (PTH)**

CDC. MMWR Recomm Rep 1992 Sep 11;41(RR-14):1-7

Groups at Risk of Vitamin D Deficiency

- Breastfed infants
- Older adults
- People with limited sun exposure
- People with dark skin
- People with fat malabsorption
- People who are obese or who have undergone gastric bypass surgery

Vitamin D Deficiency Diseases

In children

- Low levels of vitamin D (<27.5 nmol/L) have been shown to be associated with a high risk for rickets in children (softening and weakening of the bone)
- Today, with fortification of milk with vitamin D, cases are extremely rare

In adults

- Inadequate levels of vitamin D leads to osteomalacia, causing bone pain and muscle weakness and possible fractures (especially in the elderly population)

Vitamin D and Health

- **Low vitamin D levels have been associated with increased risk for numerous other health outcomes**
  - Various cancers
  - Cardiovascular disease
  - Autoimmune disease (e.g., multiple sclerosis)
  - Dementia
  - Diabetes
  - Glucose intolerance
- **These associations are primarily based on ecologic/observational studies**
- **The cause and effect has not been proven for most of the associations**

Vitamin D: Nutrient of the Day

Vitamin D: The Silver Bullet Against Chronic Disease for African Americans
Wednesday, April 16, 2008 by: Paco Tabachinski. NaturalNews.com

Vitamin D deficiency linked to tuberculosis
Nächste Meldung 09.04.2008

Vitamin D found to guard against artery disease
Thu Apr 17, 2008 1:54am IST

Low Vitamin D Levels Linked to Leg Artery Blockages
But doctors are divided on whether supplements are a good option
By Ed Edelson, Posted 4/16/08, US News World Report

Vitamin D Proven to Lower the Risk of Breast Cancer
FeelGoodforLife.com Examines Women's Health Breakthrough

Science News
High Blood Levels Of Vitamin D Protect Women From Breast Cancer, Study Suggests
Science Daily (Apr. 22, 2008)

Vitamin D: Nutrient of the Day ???

Vitamin D -- Let's Get Back to the Evidence Base
Ian R. Reid, Intl Bone and Mineral Society, July, 2010

Vitamin D: A Place in the Sun?
Andrew Grey, Arch Intern Med, July 12, 2010

Anticancer Vitamins du Jour - The ABCED's So Far
Tim Byers, Am J of Epidemiol, 2010;172:1-3

Vitamin D Supplementation in the Age of Lost Innocence
Eliseo Guallar et al, Annals Intern Med, March 2, 2010

Issues Under Discussion

- **Vitamin D status of the U.S. population**
  - What is it and has it has changed over time?
- **Dietary sources**
  - What foods provide vitamin D?
  - Are dietary supplements a significant source of vitamin D?
- **Vitamin D requirements**
  - How much vitamin D do we need?
  - How much is too much?

Sources of Information on Vitamin D

- Clinical research studies
- Randomized clinical trials
- Population-based surveys or surveillance systems

National Health and Nutrition Examination Survey (NHANES)

Assessing the health and nutritional status of adults and children in the United States

www.cdc.gov/nchs/nhanes.htm

National Health and Nutrition Examination Surveys

Survey	Dates	Ages
NHES I	1959–62	18–79 years
NHES II	1963–65	6–11 years
NHES III	1966–70	12–17 years
NHANES I	1971–75	1–74 years
NHANES II	1976–80	6 months–74 years
Hispanic HANES	1982–84	6 months–74 years
NHANES III	1988–94	> 2 months
NHANES	1999+	All ages

NHES, National Health Examination Survey

NHANES Provides Data for Many Essential Public Health Functions

Reference data	Weight and height charts
Nutrition monitoring	Dietary intake
Disease control	Diabetes
Prevention initiatives	Folate
Monitor environmental exposure	Lead
Track health behaviors	Second-hand smoke

Assessment of Vitamin D Status in the U.S. Population

- Vitamin D intake from foods and dietary supplements
- Levels of vitamin D in serum
- Collecting risk factor data previously shown to be associated with vitamin D status

Vitamin D Intake from Foods and Dietary Supplements

Is intake adequate?
What are the groups of concern?

Current Guidelines for Adequate Intake for Vitamin D, Institute of Medicine (IOM) 1997

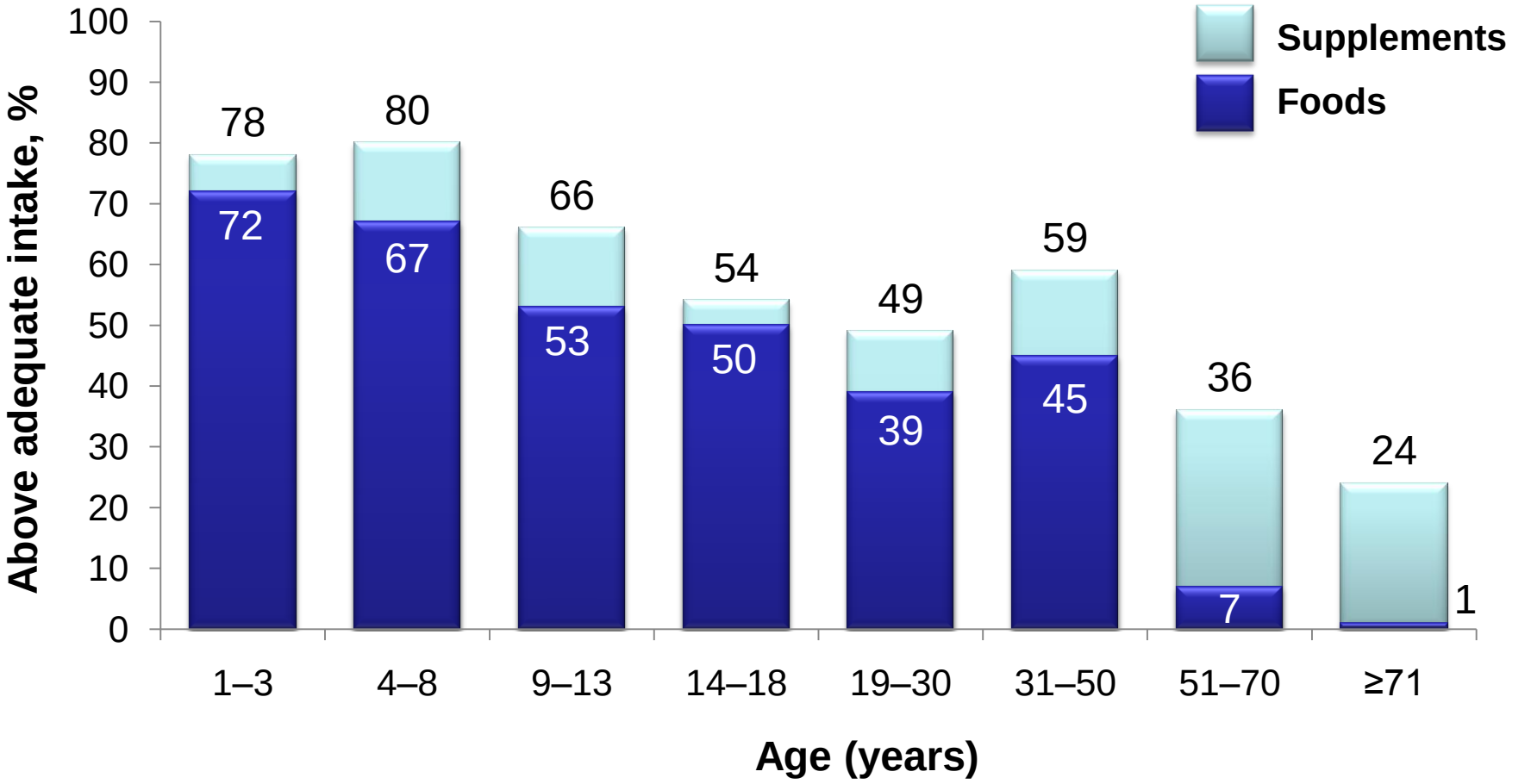
Age	Males and Females
0–50 years	200 IU/day
51–70 years	400 IU/day
≥71 years	600 IU/day
Pregnant and lactating females	200 IU/day

Tolerable Upper Intake Level (UL) for all population groups is 2000 IU/day

http://ods.od.nih.gov/factsheets/vitamind.asp

Vitamin D Intake from Foods and Dietary Supplements

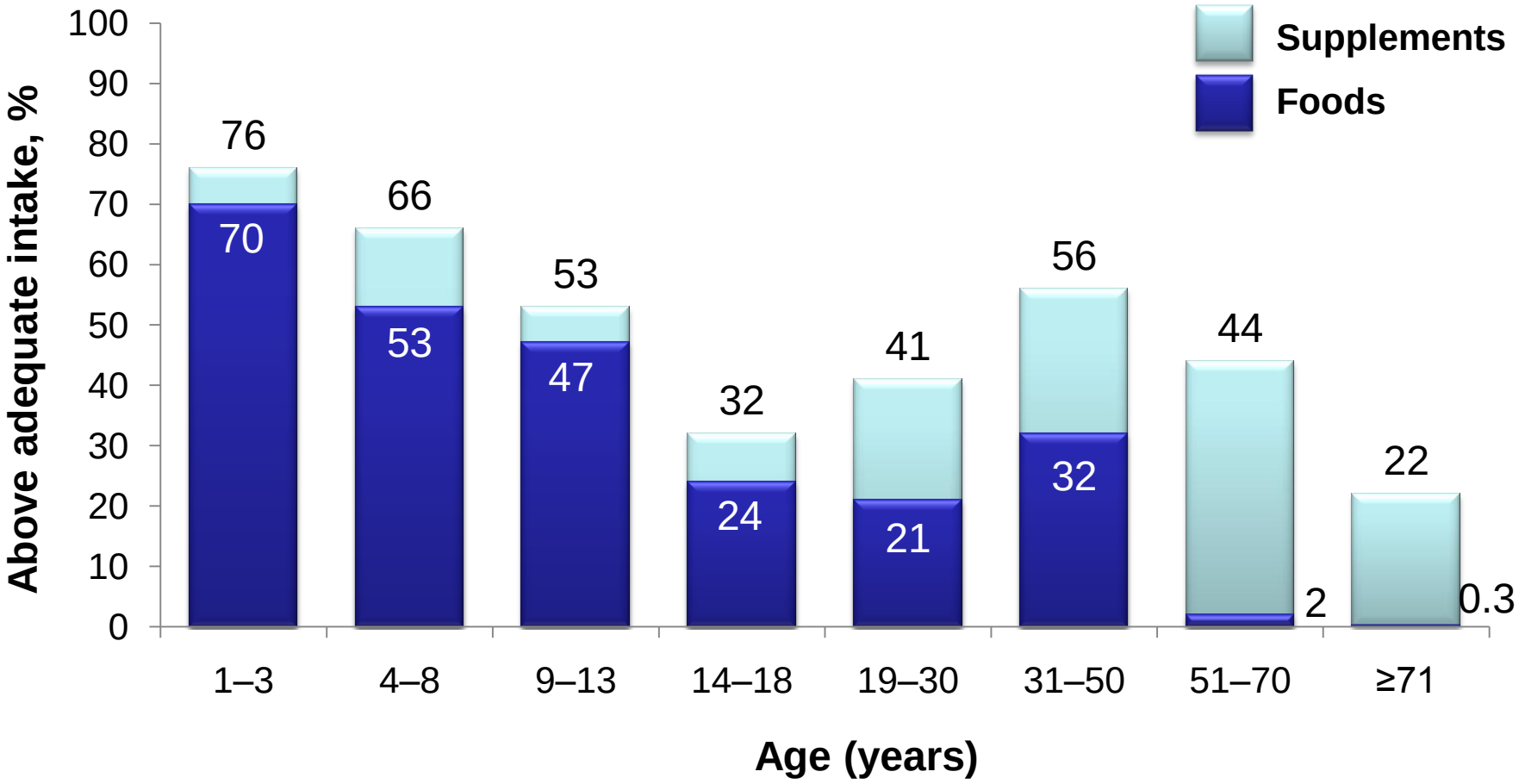
NHANES 2003–2006, Males



Bailey RL et al. J Nutr 2010;140:817-822

Vitamin D Intake from Foods and Dietary Supplements

NHANES 2003–2006, Females



Bailey RL et al. J Nutr 2010;140:817-822

Assessment of Vitamin D Status in the U.S. Population

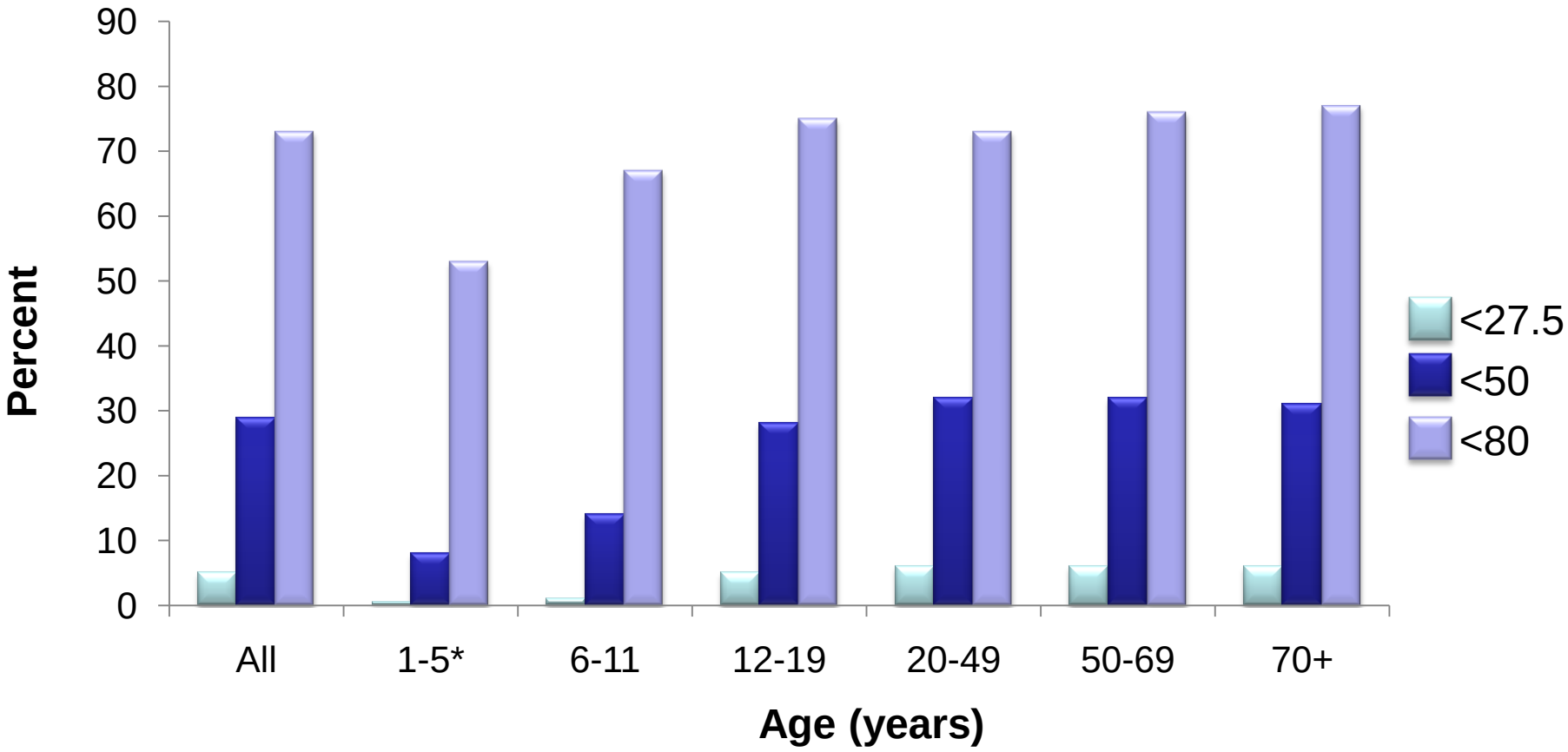
- Vitamin D intake from foods and dietary supplements
- Levels of vitamin D in serum
- Collecting risk factor data previously shown to be associated with vitamin D status

Levels of Vitamin D in Serum

- **Biomarker: Serum 25(OH)D**
- **Methodology: Radioimmunoassay (RIA)**
  - Issue: Reformulation of RIA
  - Consequence: Need to bridge the gap between data obtained by different RIA methodologies
- **Serum 25(OH)D cutoff values**

< 27.5 nmol/L	**Level defined by the 1997 IOM report**
< 50 nmol/L	**Levels defined by others in research community**
< 80 nmol/L	

Prevalence of Low Levels of Serum 25(OH)D (nmol/L) NHANES 2000–04



*Data for age 1-5 available from NHANES 2003–04 only

Yetley EA. Am J Clin Nutr 2008;88:558S-64S.

Current Status

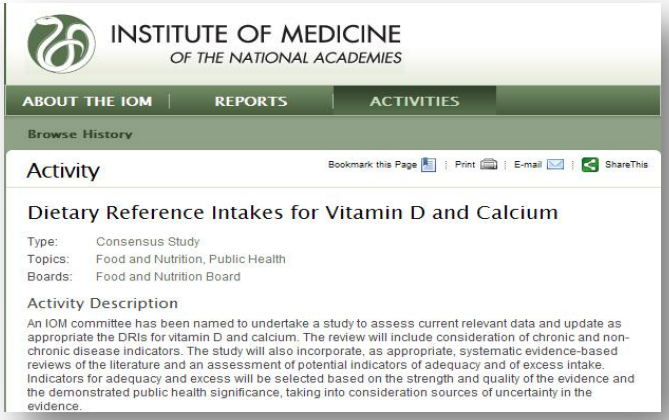
- **NHANES is valuable source of information on vitamin D**
- **Based on the current IOM criteria**
  - **Intake**: Fewer than 1/3 of older people meet the recommended adequate intake for vitamin D based on total intake (supplements included)
  - **Serum levels**: Fewer than 6% of the U.S. population has 25(OH)D levels generally considered inadequate
- **Biomarker serum levels decreased slightly from the late ‘80s/early ’90s, most likely as a response to altered behavior**
  - Increase in body mass index (BMI)
  - Decrease in sun exposure; decrease in milk consumption

Challenges and Opportunities

- **Interpretation and methodological issues**
  - There are 2 ways to assess vitamin D status in the U.S. population (intake and blood levels)
  - Measuring each has methodological challenges
  - Correlation of serum levels with adequacy established only at 27.5 nmol/L for children
  - Reformulations or changes in laboratory methods complicate the interpretation of trends in status over time
  - No agreed-on ”cutpoint” for vitamin D deficiency/adequacy
  - All issues that may lead to misinterpretation of population levels have to be examined carefully and communicated promptly

Current IOM Review

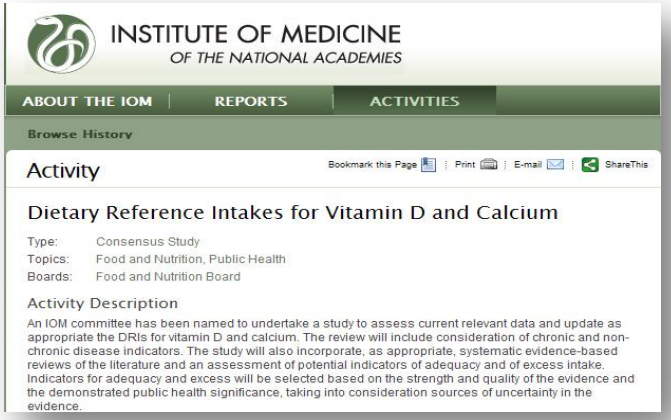
- **Assess current relevant data and update as appropriate the dietary reference intakes for vitamin D and calcium**
  - Review evidence on indicators of adequacy and indicators of adverse effects from excess
  - Give priority to indicators of adequacy for the various age, gender, and life-stage groups to define an Estimated Average Requirement
  - Give priority to selecting a critical adverse effect to define a so-called benchmark intake
  - Identify research gaps to address the uncertainties identified in the process of deriving the reference values and evaluating their public health implications



www.iom.edu/Activities/Nutrition/DRIVitDCalcium.aspx

Imminent and Next Steps

- **The IOM Report on Dietary Reference Intakes for Vitamin D and Calcium expected in late fall of 2010**
- **Depending on the recommendations (and possible new cutpoints)**
  - Further analyses of the NHANES data on vitamin D will likely occur
  - Future programmatic directions and public health guidance for vitamin D will likely be determined



TESTING FOR VITAMIN D BLOOD LEVELS: CHALLENGES AND OPPORTUNITIES




Christine M. Pfeiffer, PhD

Chief

Nutritional Biomarkers Branch

Division of Laboratory Sciences

National Center for Environmental Health

Centers for Disease Control and Prevention

Methodology to Monitor Vitamin D Status

- **Measuring total 25-hydroxyvitamin D, 25(OH)D**
  - In serum
  - Radioimmunoassay (RIA) developed in the mid-1980s
  - NHANES III (1988–1994): Original DiaSorin RIA
  - NHANES 2000–2006: Reformulated DiaSorin RIA
- **Measuring individual 25(OH)D forms**
  - In serum
  - Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS)
  - NHANES 2007 and forward

Issues with Classical Immunoassay Methodology

Performance characteristic	Definition	Impact on population monitoring
Lower precision	Greater variation in laboratory measurements	Difficult to identify small changes in the population over time
Lower specificity	Compounds other than 25(OH)D may alter results	Difficult to obtain accurate testing results
Lower robustness	Fluctuations in assay performance over time	Difficult to interpret changes in the population over time

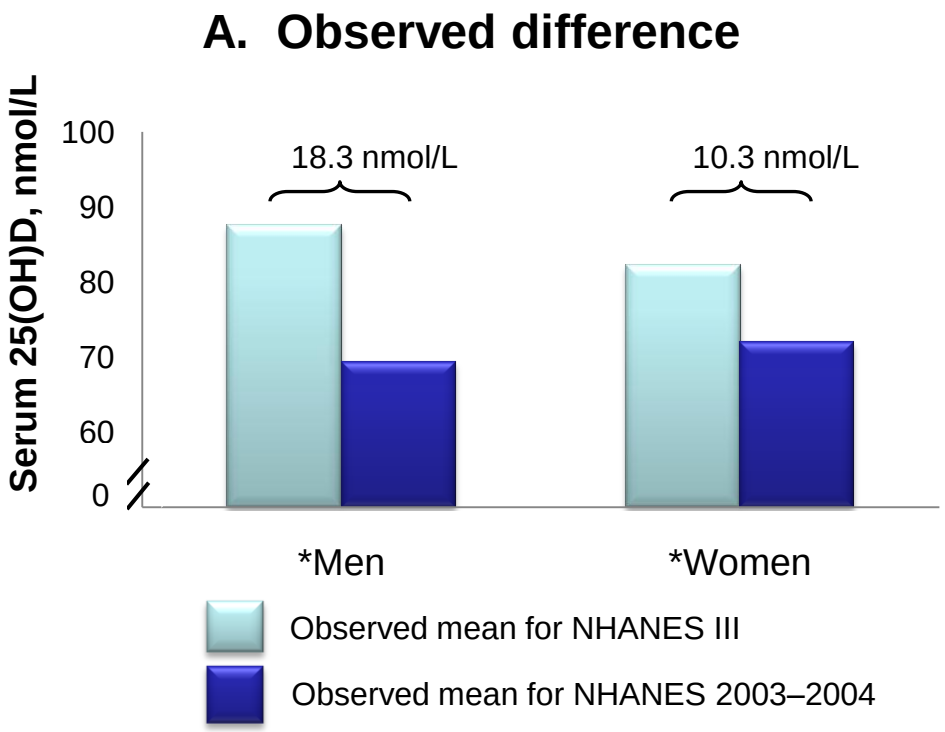
Changes in the DiaSorin RIA Over Time

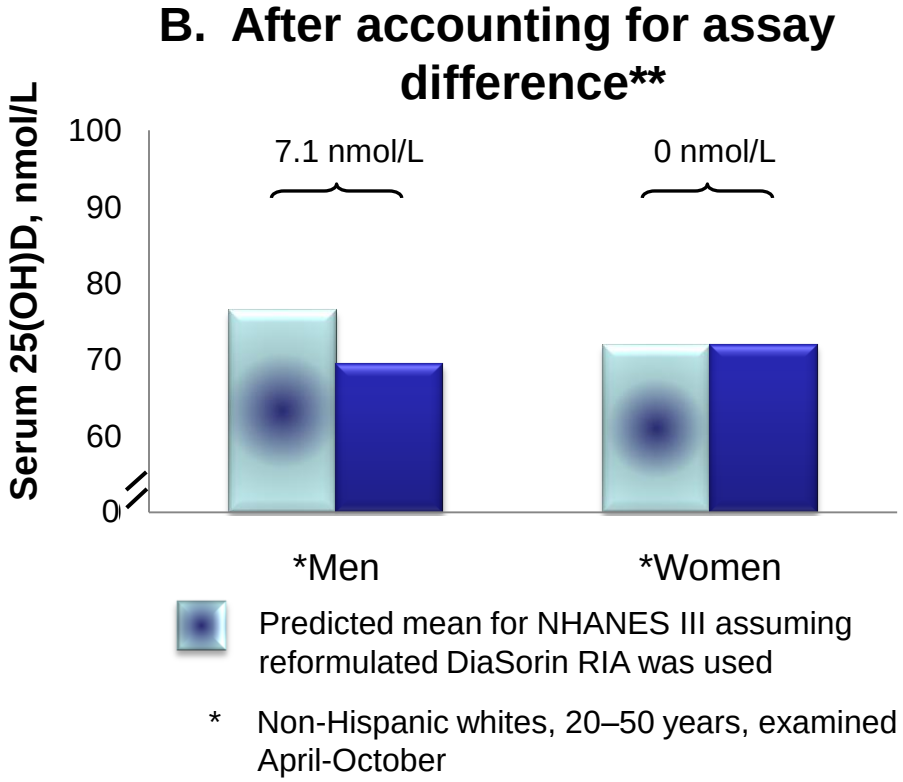
- **The change from the original RIA to the reformulated RIA**
  - Resulted in 12% lower biomarker levels
- **The reformulated RIA fluctuated over time**
  - Between 2000 and 2006, the assay performed for some extended periods 5–10% higher or lower than expected
- **Impact of assay changes on population levels**

NHANES 1988-1994
Original RIA

NHANES 2000-2006
Reformulated RIA

Impact of Assay Changes on Population Levels

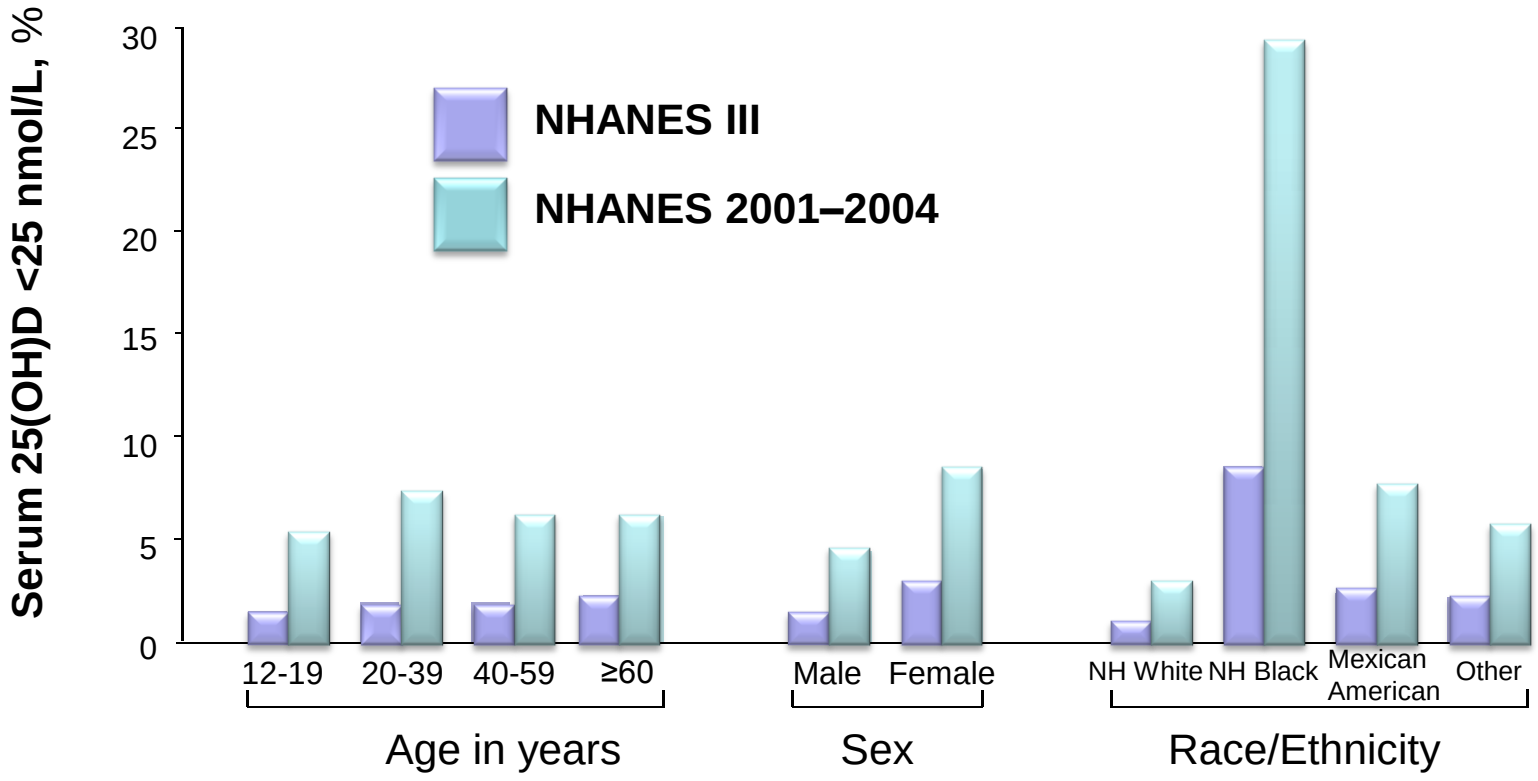




****The difference in age-standardized 25(OH)D means was reduced by 10–11 nmol/L after correcting for assay changes**

Looker AC et al. Am J Clin Nutr 2008;88:1519-27

Potential for Misinterpreting Population Levels



The prevalence of serum 25(OH)D levels of lower than 25 nmol/L (deficient) more than doubled from NHANES III to NHANES 2001–2004

Ginde AA et al. Arch Intern Med 2009;169:626-632

Potential for Misinterpreting Population Levels

- Rather small changes in the 25(OD)D levels (~10%), as a result of assay changes, can lead to big changes in population levels
- Lack of data adjustment for assay differences can lead to very different conclusions
- Timely and appropriate communication to the scientific community is critical to avoid publication of incorrect information

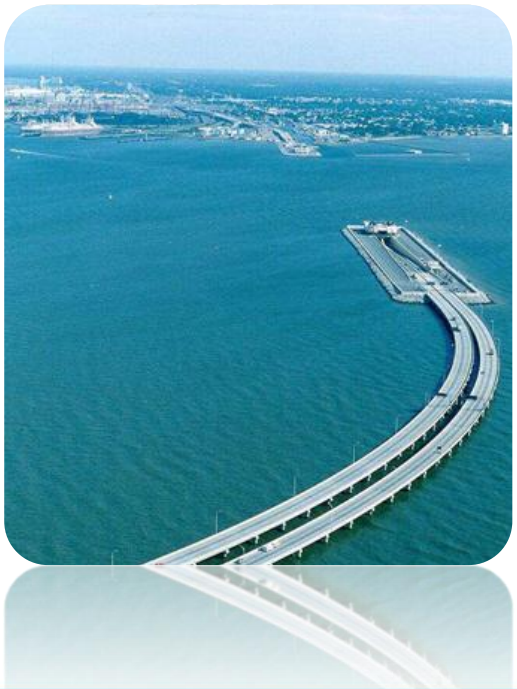
Outlook to a New Analytical Methodology
Isotope Dilution Tandem Mass Spectrometry Coupled to Liquid Chromatography (LC-MS/MS)

Precision	**<8% day-to-day variation**
Specificity	**Less possibility for compounds other than 25(OH)D to alter results**
Robustness	**In-house calibration with $25(OH)D_2$ and $25(OH)D_3$, and calibration verification with NIST reference material**

NIST, National Institute of Standards and Technology

Bridging the Gap by Making the Past and Future Data Comparable

- **In 2009, the NIH Office of Dietary Supplements and the CDC National Center for Health Statistics sponsored a roundtable on vitamin D issues in NHANES**
  - Future methodology should be LC-MS/MS
  - A subset of the samples analyzed with the DiaSorin RIA will be re-analyzed by LC-MS/MS to bridge the past and the future
  - Data generated previously with the DiaSorin RIA need to be adjusted for the assay changes to avoid incorrect interpretation of trends



Yetley EA et al. J Nutr 2010 (in press)

Importance of Standard Reference Materials in Providing Traceability

- **National Institute of Standards and Technology (NIST) and CDC National Center for Environmental Health (NCEH) collaborated in developing the first standard reference materials for 25(OH)D**
  - NIST standard reference materials SRM 972 and 2972
  - Improve accuracy of measurements
  - Improve comparability of data across methods and laboratories
- **NIST will conduct a commutability study to assess which SRM materials may be used to calibrate immunoassays**

Lessons Learned and Way Forward

- **Relatively small assay fluctuations can have a large impact on population levels and make interpretation of population data difficult**
- **NHANES**
  - Needs best possible analytical methodologies
  - Standardization, harmonization, and accuracy of analytical methodologies must be supported and strengthened
- **Validation of the new LC-MS/MS method and bridging the gap between samples analyzed by different methods is underway**

VITAMIN D: HOW RESEARCH INFORMS PUBLIC HEALTH POLICY




Paul M. Coates, PhD
Director
Office of Dietary Supplements
National Institutes of Health

Office of Dietary Supplements (ODS)

- **The Dietary Supplement Health and Education Act of 1994 authorized the establishment of the ODS at the NIH (created in 1995)**
- **Mission: Strengthen knowledge and understanding of dietary supplements to foster an enhanced quality of life and health for the U.S. population by**
  - Evaluating scientific information
  - Stimulating and supporting research
  - Disseminating research results
  - Educating the public

Public Law 103-417, DSHEA

Overview

- **What is the science telling us?**
  - Evidence for the importance of vitamin D in health
  - Scientific gaps: What are the key issues?
  - Who is doing what to fill the gaps?
- **Challenges and strategies to address the challenges**
  - Key partners/stakeholders and their roles

Vitamin D Initiative

- **Coordinated by the NIH Office of Dietary Supplements**
  - Involves partners from DHHS (NIH, CDC, FDA, AHRQ), NIST, DoD, USDA, and Health Canada
- **Goals**
  - Improve measurement of vitamin D in foods and supplements
  - Improve measurement of vitamin D status in NHANES
  - Identify research gaps
- **Outcomes**
  - Systematic reviews
  - Publications to inform public policy

AHRQ, Agency for Healthcare Research and Quality
NIST, National Institute of Standards and Technology

Systematic Reviews of Vitamin D Status and Health Outcomes

- **Agency for Healthcare Research and Quality (AHRQ)**
  - Evidence-Based Practice Center Network
  - Systematic reviews inform policy, research, and guidelines
- **2 Reviews of vitamin D**
  - Cranney A et al. Am J Clin Nutr 2008;88:513S-519S
    - Sponsored by NIH/ODS to inform a public meeting, 2007
  - Chung M et al. Am J Clin Nutr 2010;92:273-276
    - Sponsored by U.S. and Canadian governments to inform Dietary Reference Intakes Panel

      (Institute of Medicine, 2009)

Findings from the First Systematic Review

- **Evidence that vitamin D supplementation reduces falls, fractures, and bone loss in men and women >60 years**
- **Sparse data on other age and gender groups**
- **Not possible to separate the effect of vitamin D from calcium (Ca) supplementation**
  - Typical amounts used were 700-800 IU vitamin D/day and 500-1,200 mg Ca/day
- **Difficult to identify a specific blood level of 25(OH)D indicative of optimal bone health in all population subgroups: Lack of data**

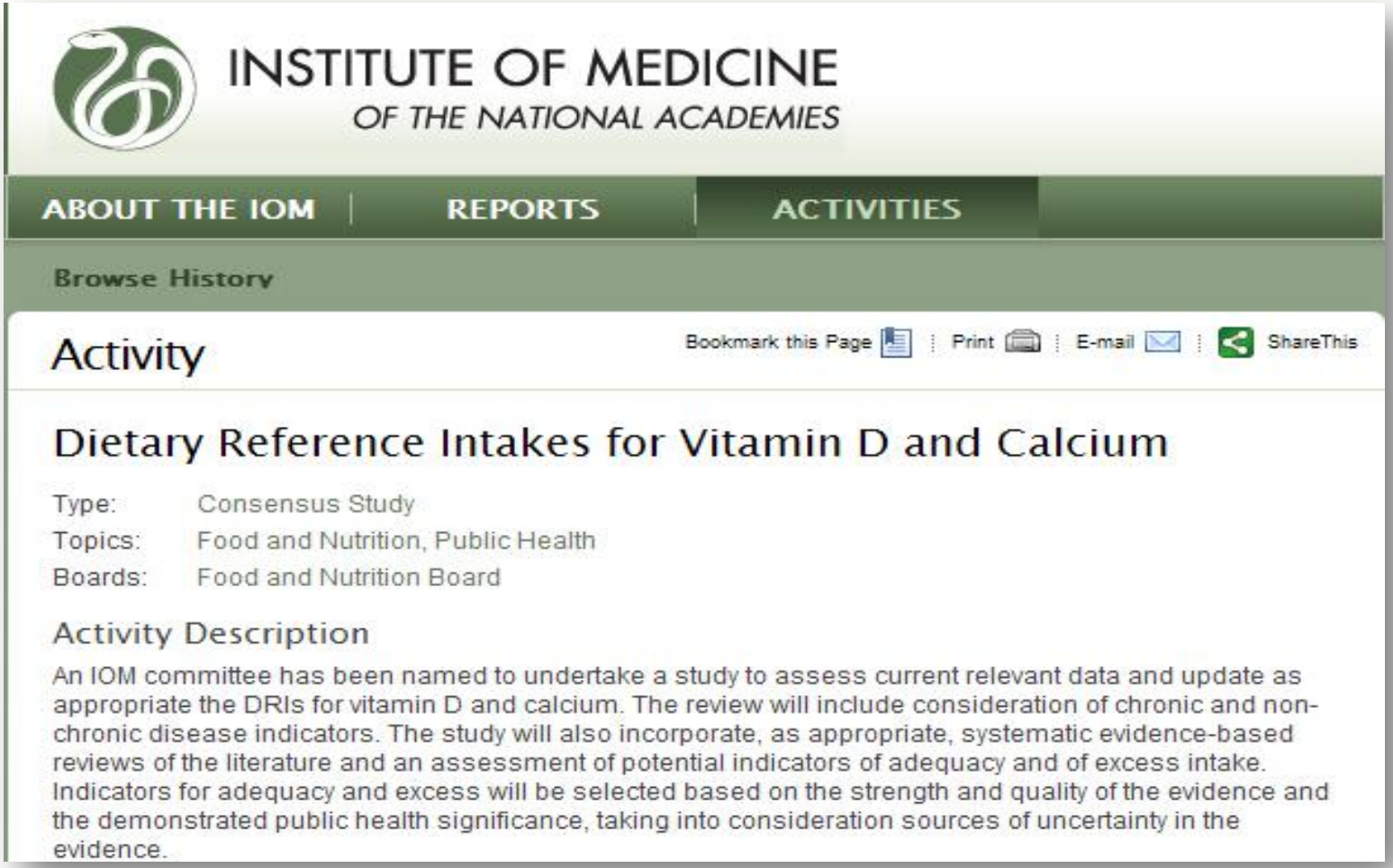
Cranney A et al: Am J Clin Nutr 2008;88:513S-519S8

Findings from the Second Systematic Review

- **Infant growth: Most studies found no effect**
- **Cardiovascular disease**
  - Randomized controlled trials: No effect
  - Cohort studies: Variable association
- **Body weight: No effect**
- **Cancer: No effect**
- **Infectious diseases: No effect**
- **Pregnancy outcomes: Inadequate data**
- **All-cause mortality: Inconsistent data**
- **Hypertension: Inconsistent data**

Chung M et al: Am J Clin Nutr 2010;92:273-276

IOM Review



INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

ABOUT THE IOM | REPORTS | ACTIVITIES

Browse History

Activity

Bookmark this Page | Print | E-mail | ShareThis

Dietary Reference Intakes for Vitamin D and Calcium

Type: Consensus Study
Topics: Food and Nutrition, Public Health
Boards: Food and Nutrition Board

Activity Description

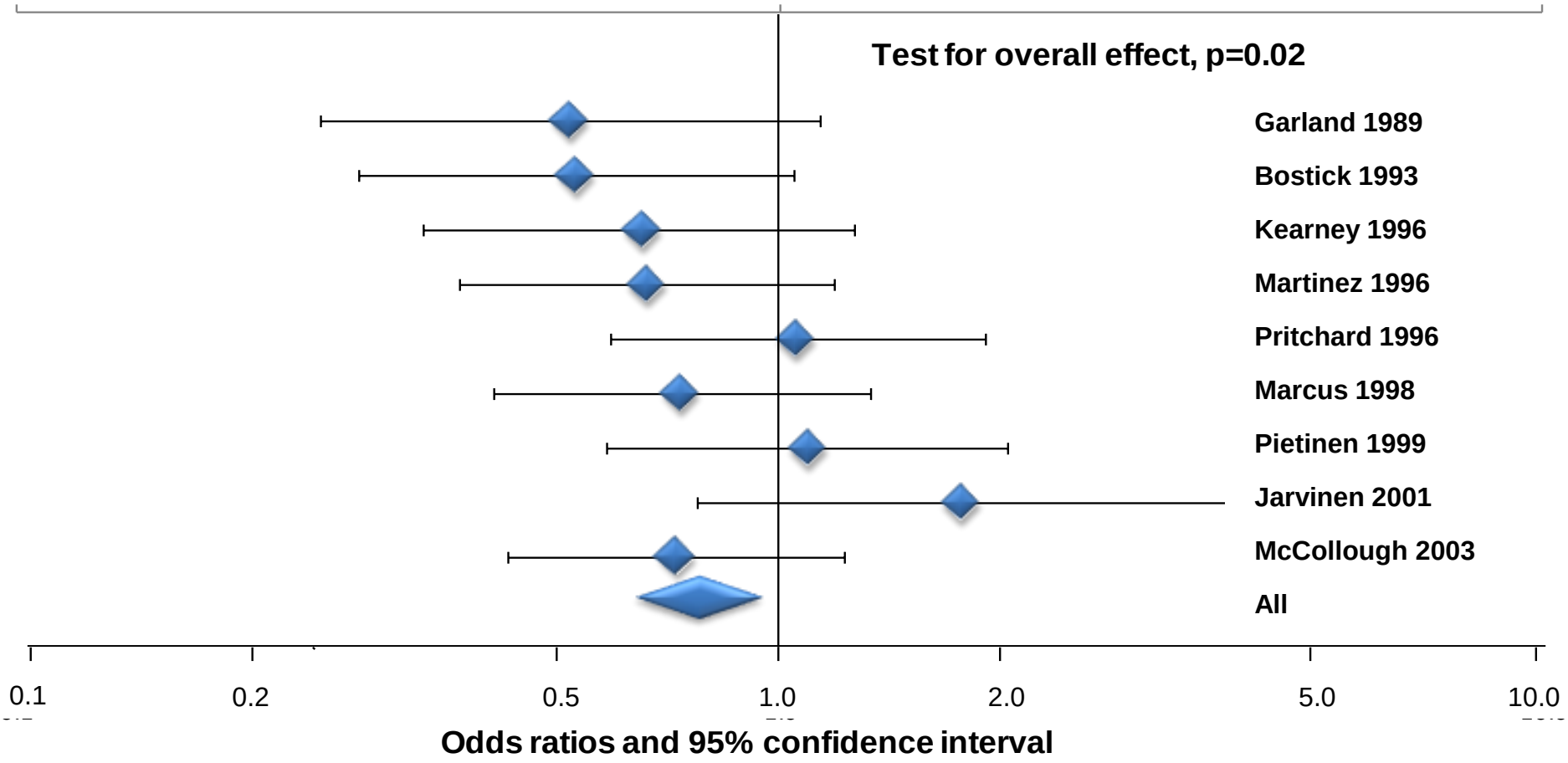
An IOM committee has been named to undertake a study to assess current relevant data and update as appropriate the DRIs for vitamin D and calcium. The review will include consideration of chronic and non-chronic disease indicators. The study will also incorporate, as appropriate, systematic evidence-based reviews of the literature and an assessment of potential indicators of adequacy and of excess intake. Indicators for adequacy and excess will be selected based on the strength and quality of the evidence and the demonstrated public health significance, taking into consideration sources of uncertainty in the evidence.

www.iom.edu/Activities/Nutrition/DRIVitDCalcium.aspx

Vitamin D Challenges

- **Exposure**
  - UVB exposure
  - Foods, including fortified foods
  - Dietary supplements
- **Health outcomes**
  - Enormous interest based on case reports, observational studies
  - Inconsistent findings from controlled studies
  - Safety must be addressed
- **Measurement of status**
  - Incorrect interpretation of status measurement, especially when assessing trends over time

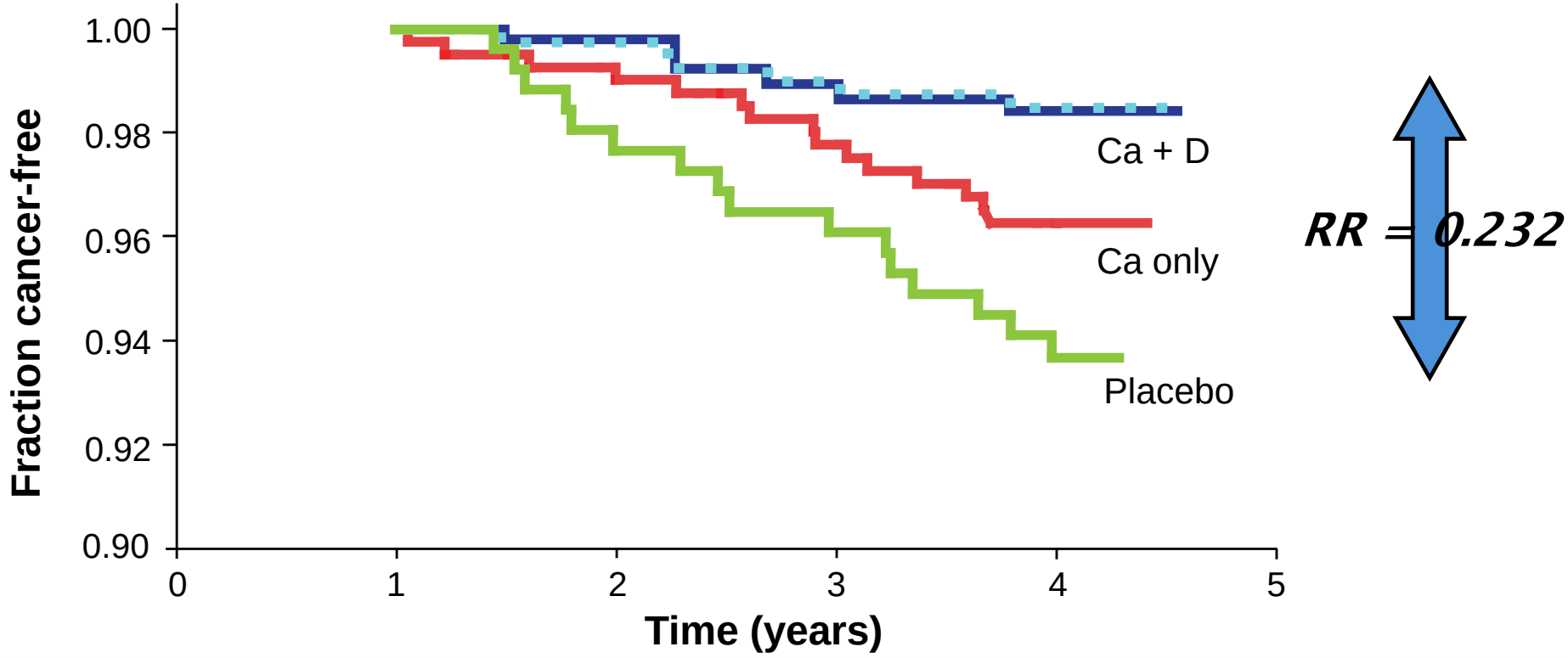
Vitamin D and Colorectal Cancer



Wei MY et al,.Cancer Epidemiol Biomarkers Prev 2008;17:2958-2969

Vitamin D and Cancer Incidence

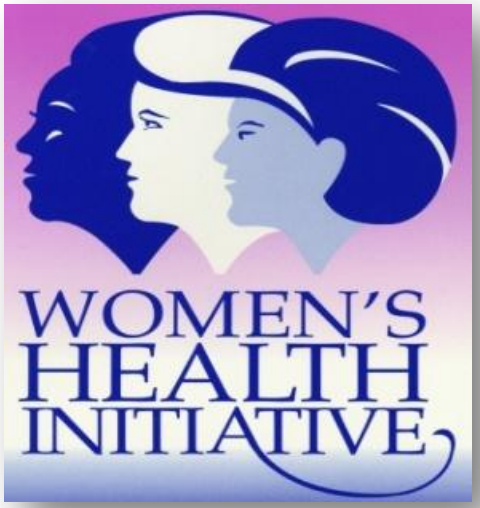
1179 healthy women, 66±7 years, 4-year study,
Ca (1400 mg/d), vitamin D3 (1100 IU/d)



Lappe J et al. Am J Clin Nutr 2007;85:1586-1591

Women's Health Initiative

- NIH-sponsored: http://www.nhlbi.nih.gov/whi
- Largest intervention trial in history: >160,000 women
- One of the substudies randomized women to vitamin D and calcium for a 7-year period to examine potential effects on hip fractures

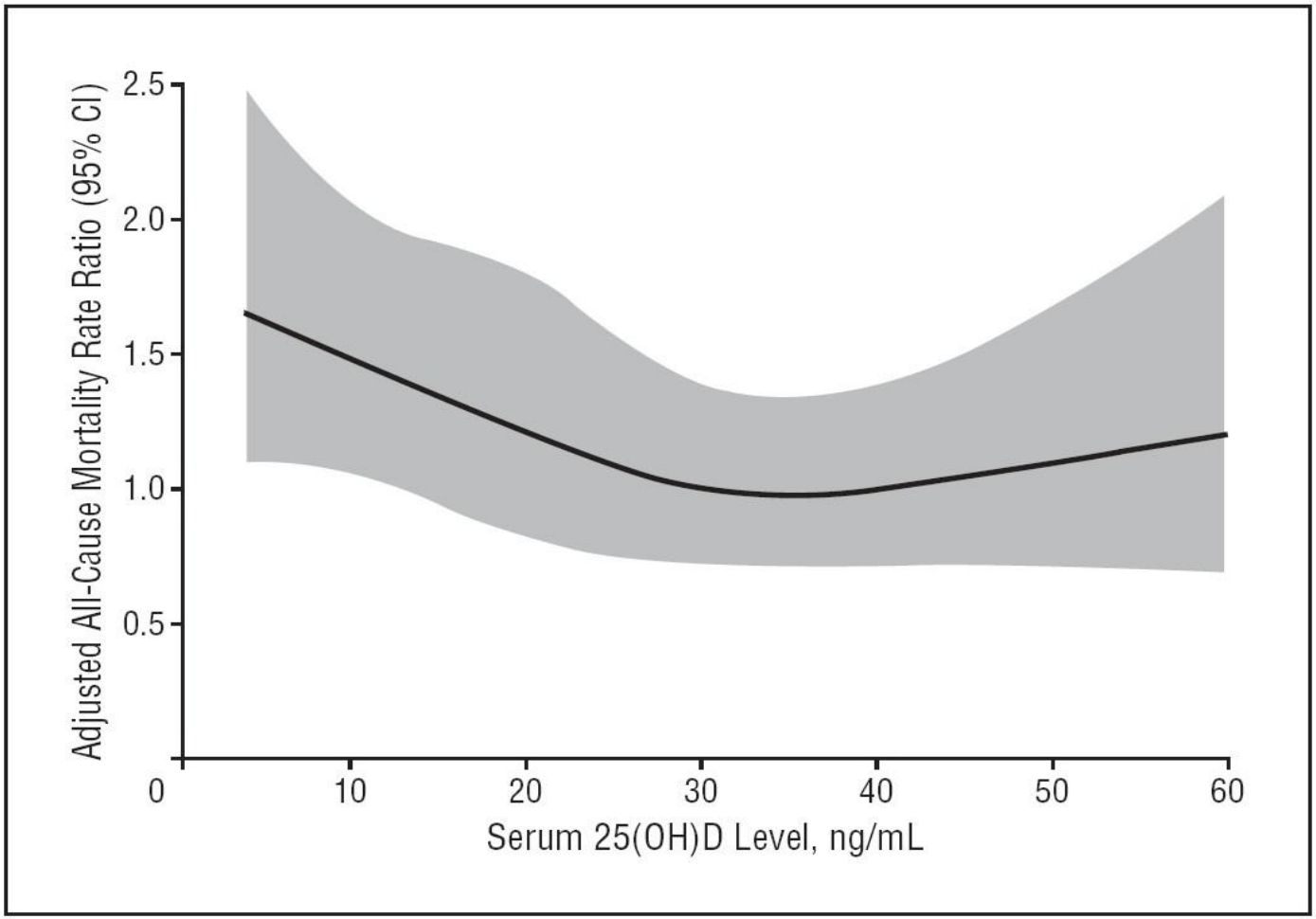


Trial Results after 7 Years

- **Hip fractures: 12% decrease, not significant**
  - 21% decrease for women aged 60–80 years at baseline
  - 29% decrease among women who took ≥80% of pills
  - Improved hip bone density
- **Other fractures: No differences (self-reported vertebral, lower arm/wrist, total)**
- **Kidney stones**
  - Significantly increased 17% (5 per 10,000/year)

Jackson RD et al. NEJM 2006;354:669-683

Serum 25(OH)D and All-Cause Mortality



Melamed et al. Arch Intern Med 2008;88:1629-1637

Examples of Ongoing NIH-supported Research

- **NCI and others: Vitamin D and Omega-3 Trial (VITAL) to examine the role of vitamin D and omega-3 fatty acids in primary prevention of cancer and CVD**
- **NIA and others: Dose response for vitamin D in elderly**
- **NCI: Replication of cancer incidence study**
- **Many NIH Institutes and Centers: Intermediary metabolism**
- **ODS and others: Incorporation of analytical tools into measurement of vitamin D status**
  - Standard reference material for 25(OH)D in serum
  - Reference methods developed by NIST and NCEH

NCI, National Cancer Institute
CVD, Cardiovascular disease
NIA, National Institute on Aging
ODS, Office of Dietary Supplements

Current Public Health Recommendations

- **Most recent Dietary Reference Intakes (IOM, 1997)**
  - Adequate Intake (AI): 200/400/600 IU/day
  - Upper Limit: 2000 IU/day
  - Summarized at: http://ods.od.nih.gov/factsheets/vitamind.asp
- **How can people meet these recommendations?**
  - Most organizations recommend brief sun exposure, although there is no agreement on how much
  - Foods, especially those fortified with vitamin D (e.g., milk)
  - Supplements, especially among the elderly
- **Ongoing IOM review of recommended intakes**
  - Expected release late fall of 2010

Recommendations Made by Professional Groups

- **American Academy of Pediatrics**
  - 400 IU for children
- **Canadian Paediatric Society**
  - Weight-based intake for children
  - Up to 2000 IU for pregnant and lactating women
- **American Academy of Dermatology**
  - More from supplements, not more sun exposure
- **National Osteoporosis Foundation, International Osteoporosis Foundation**
  - 400-800 IU for adults <50 years; 800-1000 IU >50 years

American Academy of Pediatrics: www.aap.org/healthychildren/09s_bts/Vitamin%20D.pdf
Canadian Paediatric Society: www.cps.ca/english/statements/ii/fnim07-01.htm
American Academy of Dermatology: www.aad.org/forms/policies/uploads/ps/ps-vitamin%20d.pdf
National Osteoporosis Foundation: www.nof.org/prevention/vitaminD.htm

- Continued monitoring of status to assess impact of public health recommendations for vitamin D intake
- Dose-response relationships
- Research into basic mechanisms
- Ongoing partnerships among agencies in the United States and Canada: CDC, NIH, NIST, USDA, and Health Canada

WAY FORWARD

PUBLIC HEALTH GRAND ROUNDS

Office of the Director

August 19, 2010