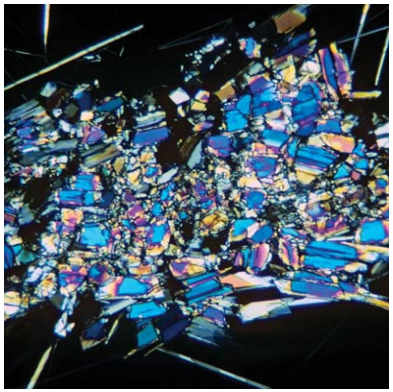
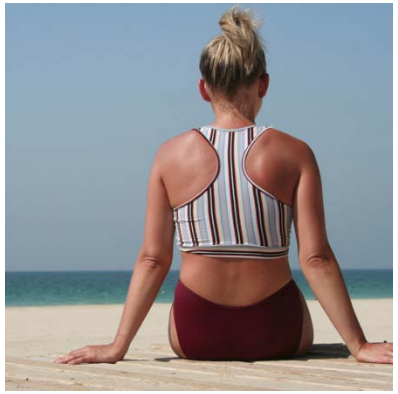




VITAMIN D: How Research Informs Public Health Policy



Paul M. Coates, Ph.D.
Director

Office of Dietary Supplements
National Institutes of Health

Overview

- **What is the science telling us about vitamin D?**
  - 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 them**
  - Key partners /stakeholders and their roles

Vitamin D: Nutrient of the 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
Reid IR, Intl Bone and Mineral Society, July, 2010

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

Anticancer Vitamins de Jour ---The ABCED's So Far
Byers T, Am J Epidemiol, 2010;172:1-3

Vitamin D Supplementation in the Age of Lost Innocence
Guallar E, Ann Intern Med, March 2, 2010

Vitamin D and Health

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

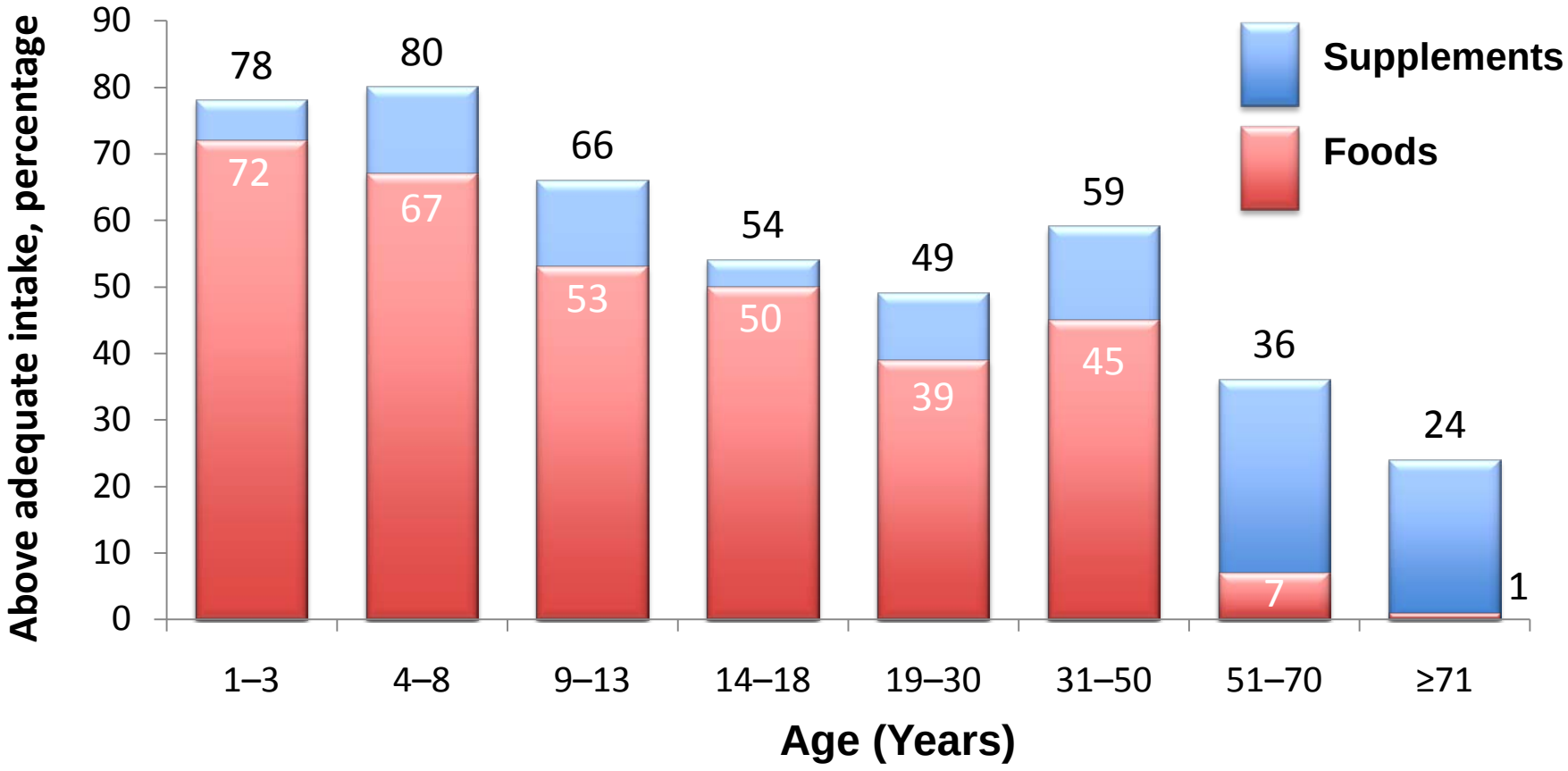
Current Guidelines for Adequate Intake for Vitamin D, IOM 1997

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 groups >1 year is 2000 IU/day

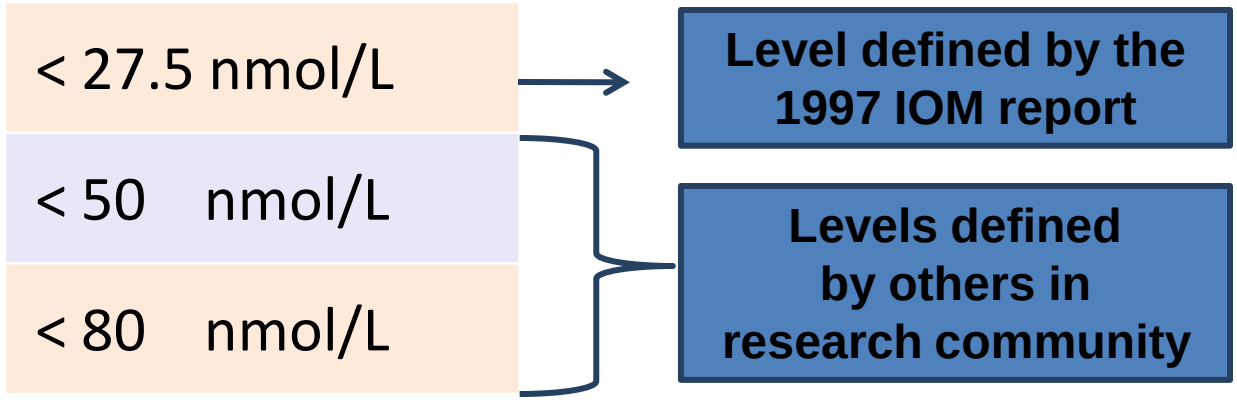
Vitamin D Intake from Foods and Dietary Supplements

NHANES 2003–2006, Males

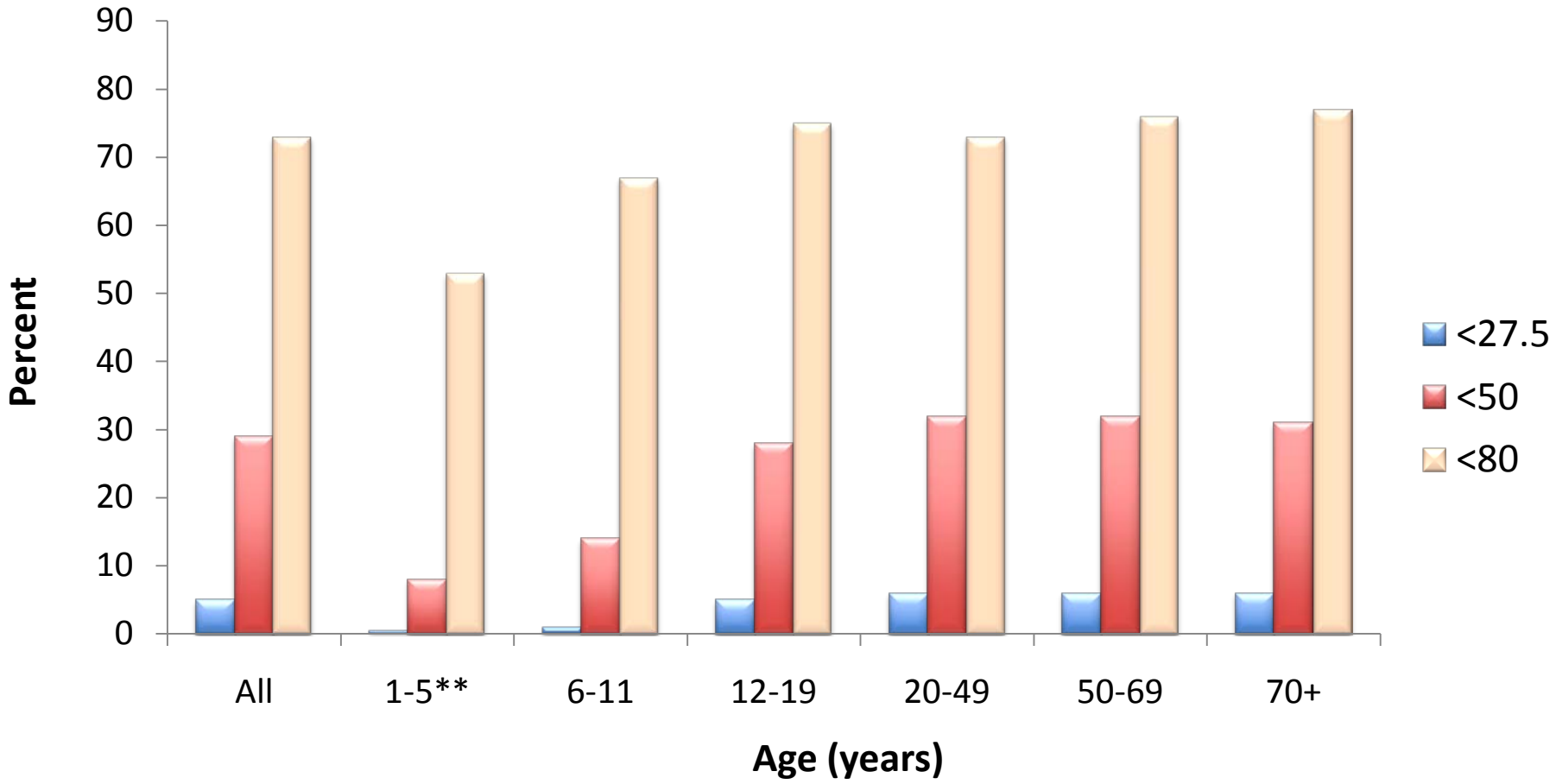


Measuring Vitamin D Status

- **Biomarker: Serum 25(OH)D**
- **Methodology: Radioimmunoassay (RIA)**
- **Serum 25(OH)D Cutoff Values**



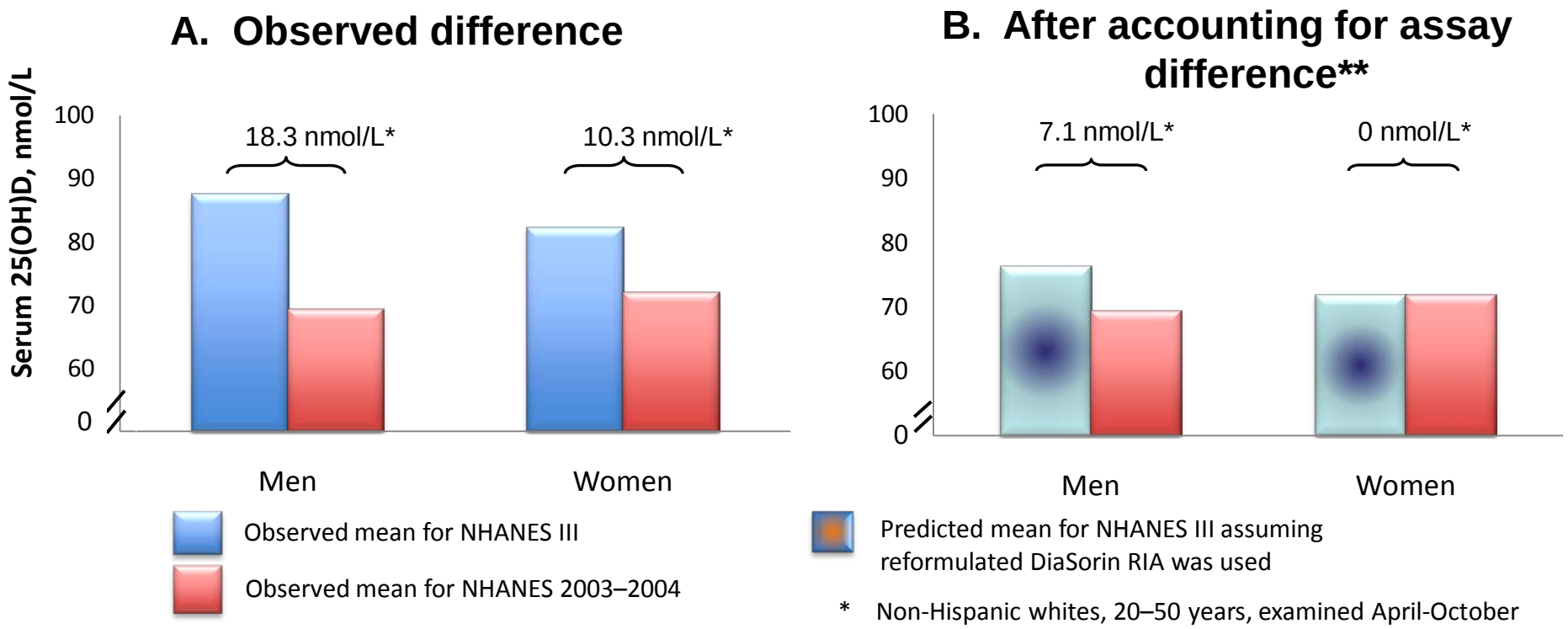
Prevalence of Low Levels of Serum 25(OH)D (nmol/L), NHANES 2000-2004



Changes in the DiaSorin RIA Over Time

- **Change from the original RIA to the reformulated RIA**
  - Resulted in 12% lower biomarker levels
- **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**

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**

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 have 25(OH)D levels generally considered inadequate
    - A subject of current and intense discussion
- **Serum levels decreased slightly from the late ‘80s/early ’90s to NHANES 2003-2004, most likely in response to altered behavior**
  - Increase in body mass index (BMI)
  - Decrease in sun exposure; decrease in milk consumption

Vitamin D Initiative

- **Coordinated by the NIH Office of Dietary Supplements**
  - Involves partners from DHHS (CDC, NIH, 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 and fill research gaps
- **Outcomes**
  - Systematic reviews, publications, conferences
  - Inform public policy

Systematic Reviews of Vitamin D Status and Health Outcomes

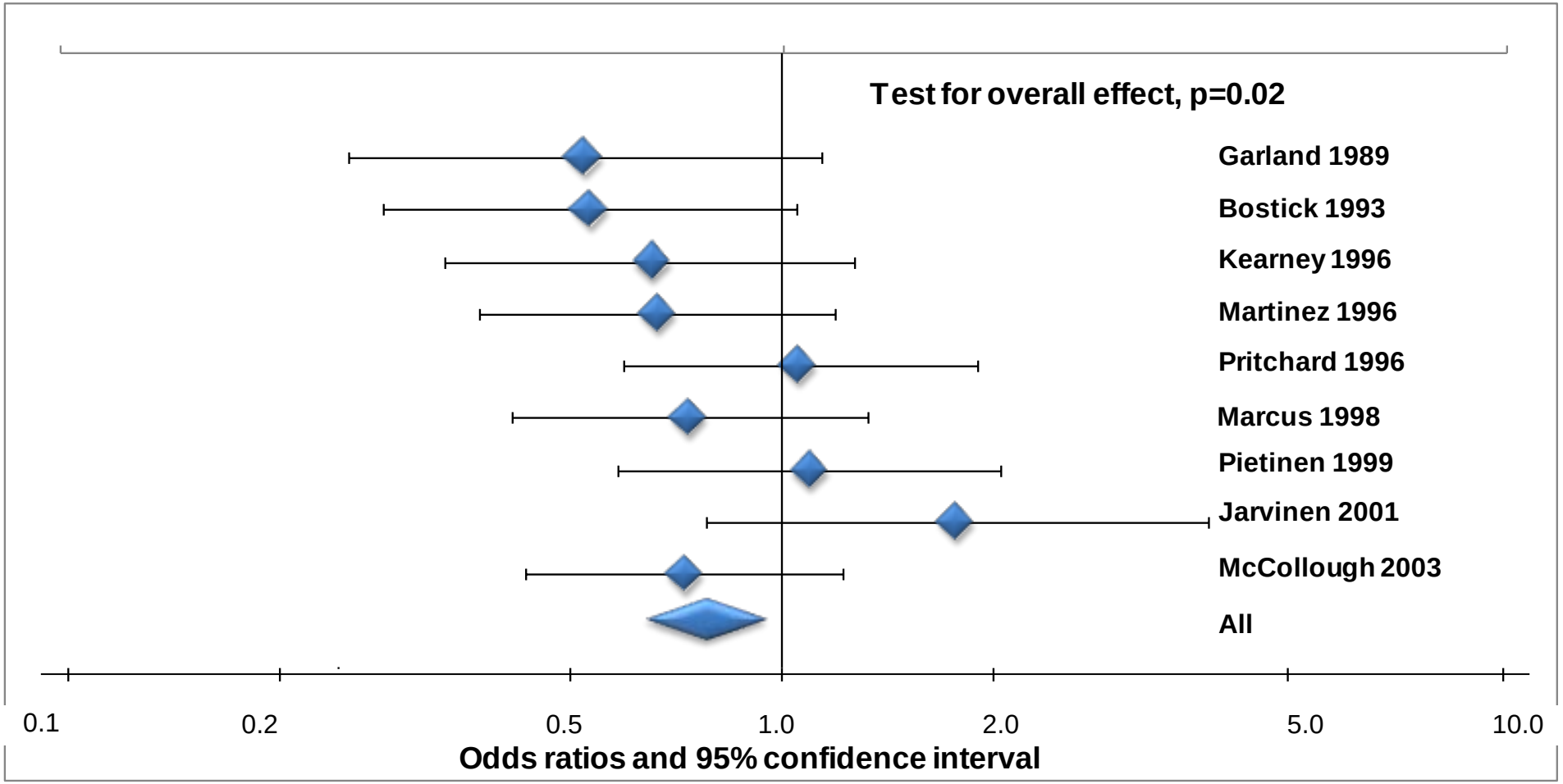
- **Agency for Healthcare Research and Quality (AHRQ)**
  - Evidence-Based Practice Center Network (www.ahrq.gov/clinic/epc)
  - Systematic reviews inform policy, research, guidelines
- **Two Reviews of Vitamin D**
  - Cranney A et al: Am J Clin Nutr 88:513S-519S, 2008
    - Sponsored by NIH/ODS to inform a public meeting, 2007
  - Chung M et al: Am J Clin Nutr 92:273-276, 2010
    - Sponsored by U.S. and Canadian governments to inform Dietary Reference Intakes Panel of the 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 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-hydroxyvitamin D indicative of optimal bone health in all population subgroups: Lack of data**

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

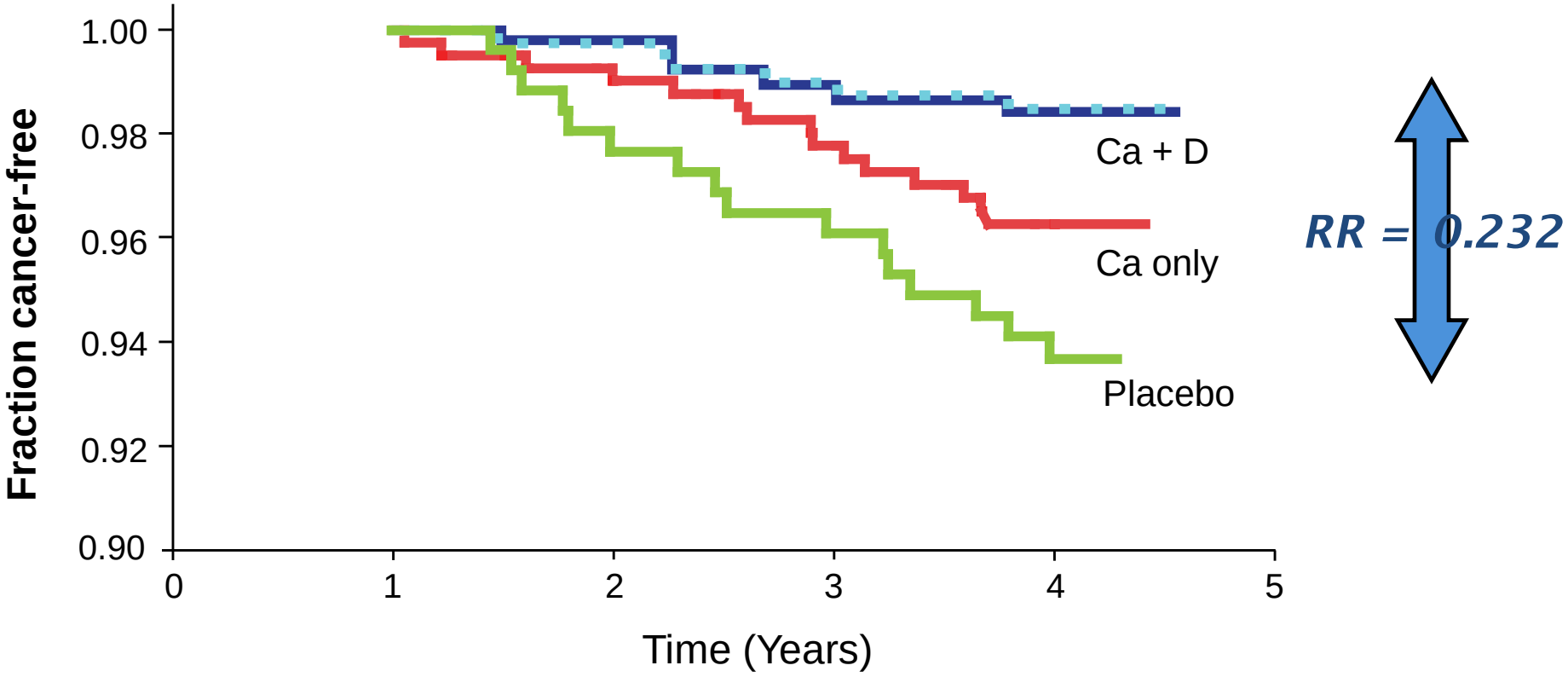
Vitamin D and Colorectal Cancer: Observation



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

Vitamin D and Cancer Incidence: Intervention

1179 Healthy women, 66±7 yrs, 4-year study, Ca (1400 mg/d), Vitamin D_3 (1100 IU/d)



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

Findings from the Second Systematic Review

- Infant growth: Most studies find 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 92:273-276, 2010

Women's Health Initiative

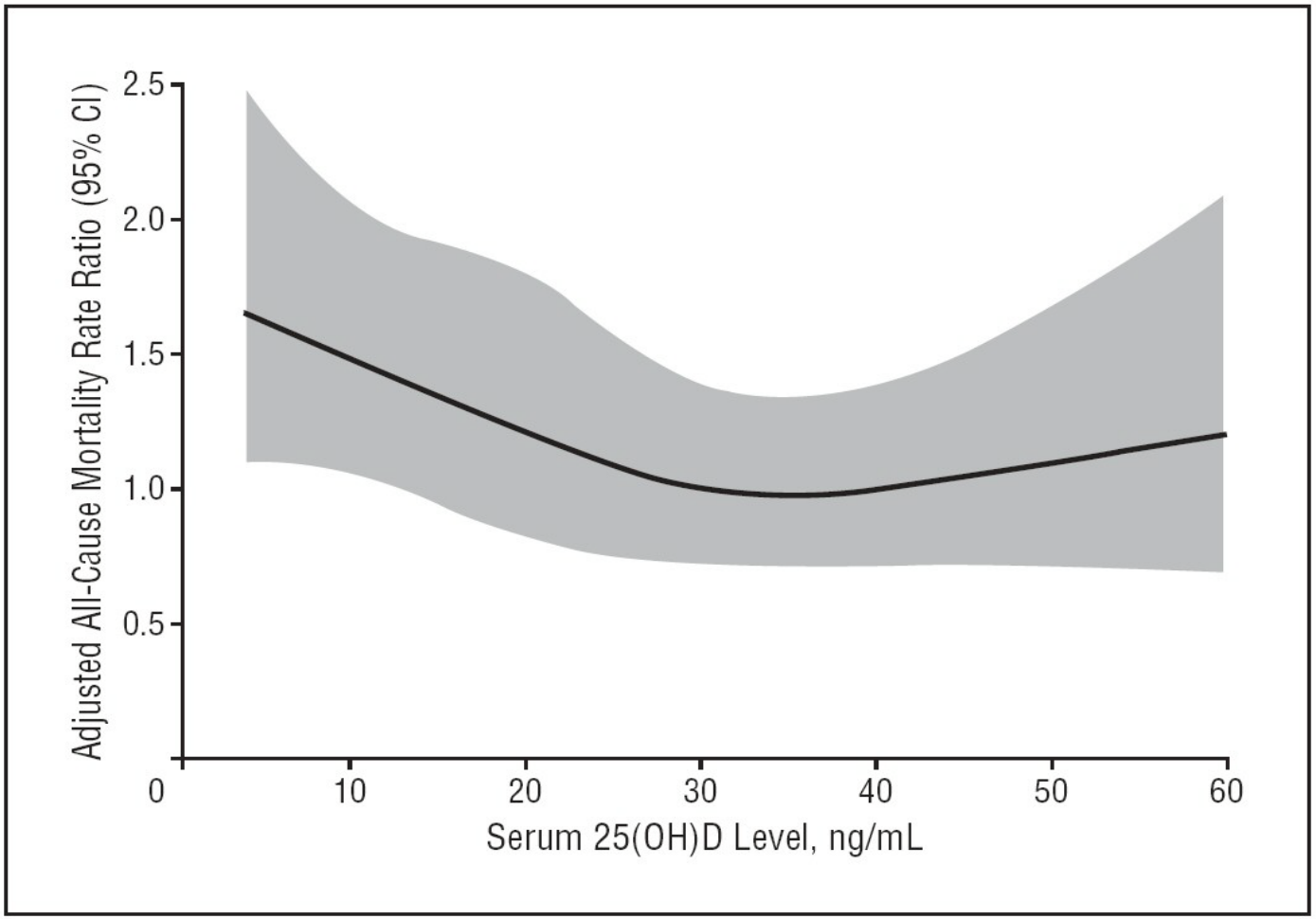
- **NIH-sponsored: http://www.nhlbi.nih.gov/whi/**
- **Largest intervention trial in history: >160,000 women**
- **One of the sub-studies randomized women to vitamin D and calcium for a 7-year period to examine potential effects on hip fractures**

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 (self-reported vertebral, lower arm/wrist, total): No differences**
- **Kidney stones: Significantly increased 17% (5 per 10,000/year)**

NEJM 354:669-683, 2006.

Serum 25(OH)D and All-Cause Mortality



Melamed et al. Arch Intern Med 2008;168:1629-1637

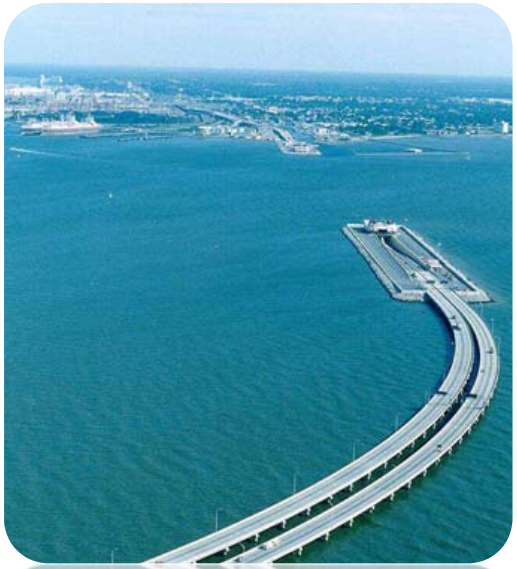
Examples of Ongoing NIH-supported Research

- **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 plasma
  - Reference methods developed by NIST and NCEH

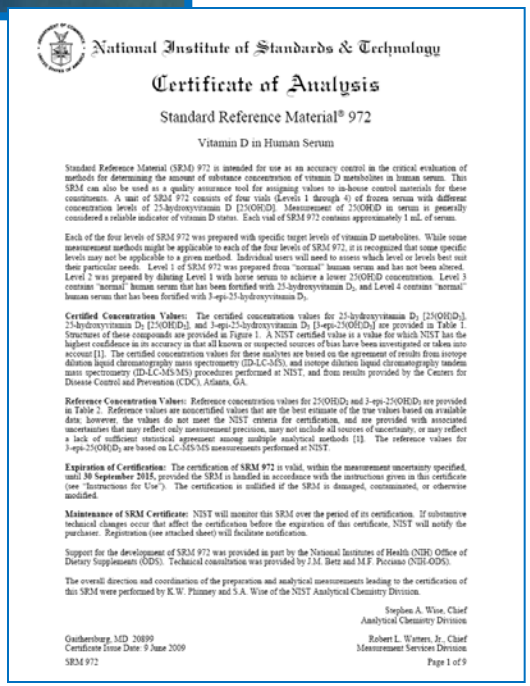
Vitamin D Status Measurement: Bridging the Gap

- **In 2009, ODS and NCHS sponsored a roundtable on vitamin D issues in NHANES and recommended:**

  - 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



NIST SRM 972 Vitamin D in Human Serum



National Institute of Standards & Technology

Certificate of Analysis

Standard Reference Material® 972

Vitamin D in Human Serum

Standard Reference Material (SRM) 972 is intended for use as an accuracy control in the critical evaluation of methods for determining the amount of substance concentration of vitamin D metabolites in human serum. This SRM can also be used as a quality assurance tool for assigning values to in-house control materials for these constituents. A unit of SRM 972 consists of four vials (Levels 1 through 4) of frozen serum with different concentration levels of 25-hydroxyvitamin D [25(OH)D]. Measurement of 25(OH)D in serum is generally considered a reliable indicator of vitamin D status. Each vial of SRM 972 contains approximately 1 mL of serum.

Each of the four levels of SRM 972 was prepared with specific target levels of vitamin D metabolites. While some measurement methods might be applicable to each of the four levels of SRM 972, it is recognized that some specific levels may not be applicable to a given method. Individual users will need to assess which level or levels best suit their particular needs. Level 1 of SRM 972 was prepared from "normal" human serum and has not been altered. Level 2 was prepared by diluting Level 1 with horse serum to achieve a lower 25(OH)D concentration. Level 3 contains "normal" human serum that has been fortified with 25-hydroxyvitamin D_2 and Level 4 contains "normal" human serum that has been fortified with 3-epi-25-hydroxyvitamin D_3.

Certified Concentration Values: The certified concentration values for 25-hydroxyvitamin D_2 [25(OH)D_2], 25-hydroxyvitamin D_3 [25(OH)D_3], and 3-epi-25-hydroxyvitamin D_3 [3-epi-25(OH)D_3] are provided in Table 1. Structures of these compounds are provided in Figure 1. A NIST certified value is a value for which NIST has the highest confidence in its accuracy in that all known or suspected sources of bias have been investigated or taken into account [1]. The certified concentration values for these analytes are based on the agreement of results from isotope dilution liquid chromatography mass spectrometry (ID-LC-MS), and isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) procedures performed at NIST, and from results provided by the Centers for Disease Control and Prevention (CDC), Atlanta, GA.

Reference Concentration Values: Reference concentration values for 25(OH)D_2 and 3-epi-25(OH)D_3 are provided in Table 2. Reference values are noncertified values that are the best estimate of the true values based on available data; however, the values do not meet the NIST criteria for certification, and are provided with associated uncertainties that may reflect only measurement precision, may not include all sources of uncertainty, or may reflect a lack of sufficient statistical agreement among multiple analytical methods [1]. The reference values for 3-epi-25(OH)D_3 are based on LC-MS/MS measurements performed at NIST.

Expiration of Certification: The certification of **SRM 972** is valid, within the measurement uncertainty specified, until **30 September 2015**, provided the SRM is handled in accordance with the instructions given in this certificate (see "Instructions for Use"). The certification is nullified if the SRM is damaged, contaminated, or otherwise modified.

Maintenance of SRM Certificate: NIST will monitor this SRM over the period of its certification. If substantive technical changes occur that affect the certification before the expiration of this certificate, NIST will notify the purchaser. Registration (see attached sheet) will facilitate notification.

Support for the development of SRM 972 was provided in part by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS). Technical consultation was provided by J.M. Betz and M.F. Picciano (NIH-ODS).

The overall direction and coordination of the preparation and analytical measurements leading to the certification of this SRM were performed by K.W. Phinney and S.A. Wise of the NIST Analytical Chemistry Division.

Stephen A. Wise, Chief
Analytical Chemistry Division

Robert L. Watters, Jr., Chief
Measurement Services Division

Gaithersburg, MD 20899
Certificate Issue Date: 9 June 2009

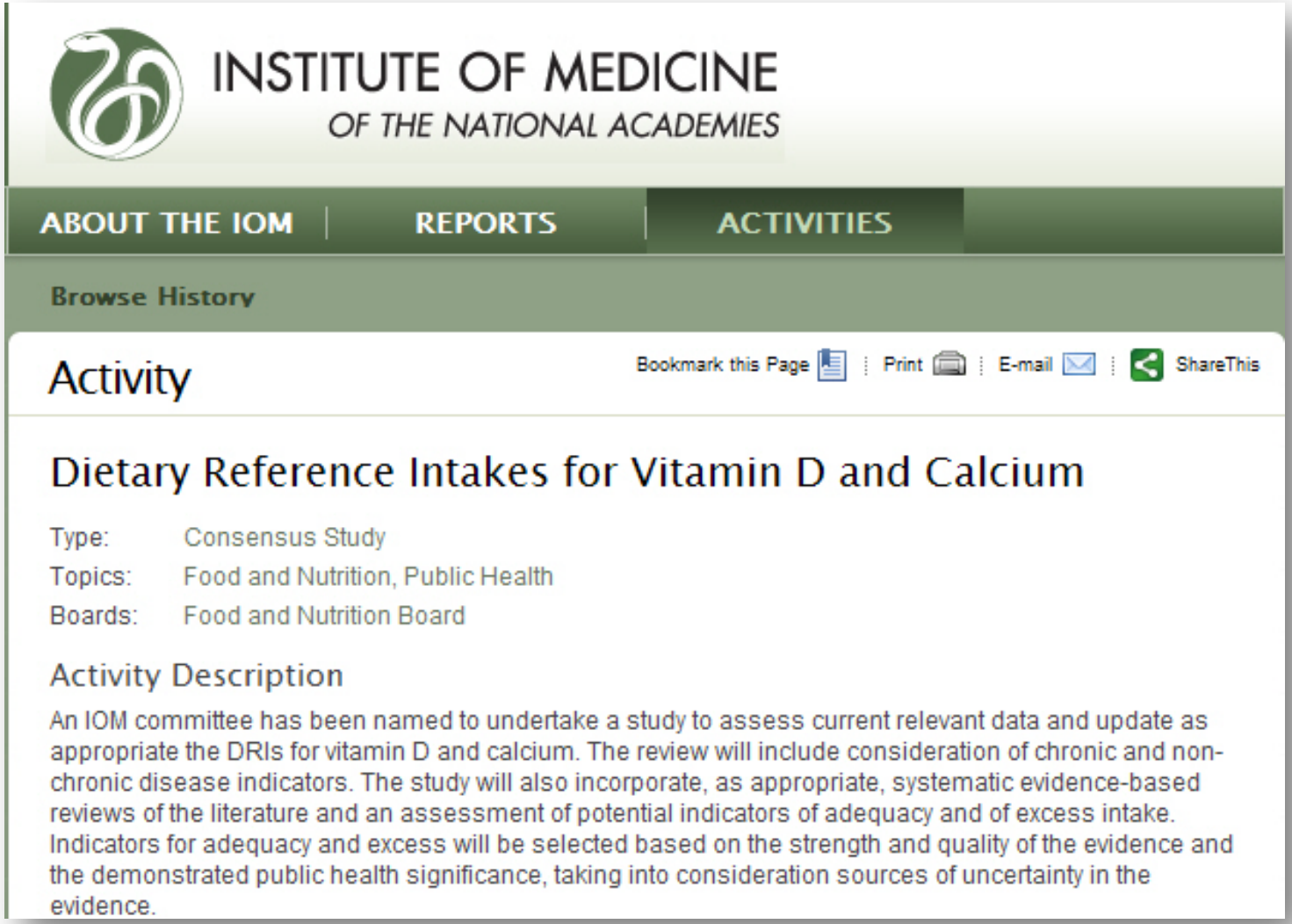
SRM 972

Page 1 of 9

- Four levels, each containing 1.0 mL serum
- Certified and reference values for 25(OH)D_2, 25(OH)D_3, and 3-epi-25(OH)D_3
- Value assignment by isotope-dilution LC-MS and LC-MS/MS using data from NIST and CDC

- Metabolite concentrations reported in ng/mL and nmol/L
- COA does not provide data from other analytical techniques

IOM Review of Dietary Reference Intakes



INSTITUTE OF MEDICINE
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Activity

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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

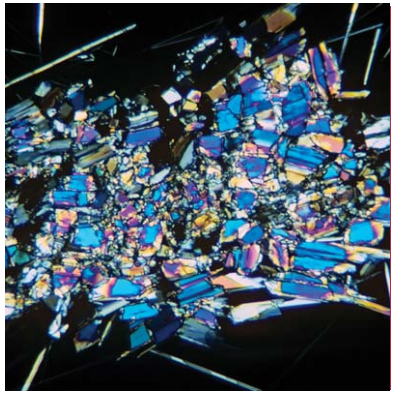
Current Public Health Recommendations

- **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
- **Ongoing IOM Review of Recommended Intakes**
  - Expected release: Fall 2010
- **Dietary Guidelines Advisory Committee Report (USDA-DHHS, 2010)**
  - Meet AI via food; some may require supplements
  - http://www.cnpp.usda.gov/dietaryguidelines.htm

Recommendations Made by Professional Groups

- **American Academy of Pediatrics** www.aap.org/healthychildren/09s_bts/Vitamin%20D.pdf
  - 400 IU for children
- **Canadian Paediatric Society** www.cps.ca/english/statements/ii/fnim07-01.htm
  - Weight-based intake for children
  - Up to 2000 IU for pregnant and lactating women
- **American Academy of Dermatology** www.aad.org/forms/policies/uploads/ps/ps-vitamin%20d.pdf
  - More from supplements, not more sun exposure
- **National Osteoporosis Foundation** www.nof.org/prevention/vitaminD.htm
  - 400-800 IU for adults <50 yrs; 800-1000 IU >50 yrs

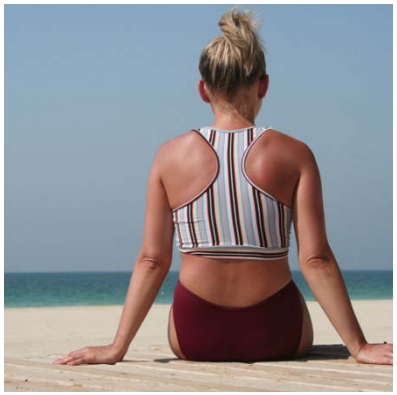
Vitamin D Challenges



- **Exposure**
  - UV 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**
  - Potential for incorrect interpretation of status measurement, especially when assessing trends over time

FUTURE NEEDS

- **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 US and Canada: CDC, NIH, NIST, USDA and Health Canada**



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