Dietary Reference Intakes for Calcium and Vitamin D: Challenges of the Evidence Base

IOM Committee to Review Dietary Reference Intakes for Vitamin D & Calcium

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APHA Significant Advances in Evidence-Based Public Health and Policy Recommendations from the Institute of Medicine
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Presenter Disclosure

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Member of IOM Committee to Review DRI's for Calcium and Vitamin D

Employee of Cornell University

No relationships, conflict of interest or funding sources to disclose

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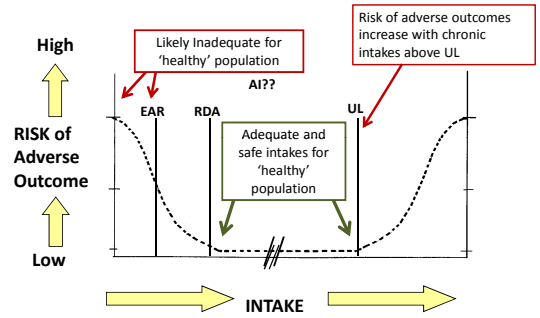
Objectives

- Describe the risk assessment framework & scientific evidence base for the **2011** DRI's for Vitamin D.
- Relate the challenges, uncertainties and limitations in the scientific evidence base.
- Explain the evidence-based judgments and decisions made by the committee.

Institute of Medicine Dietary Reference Intakes



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What Was Done: Scope of Work

- Review evidence regarding health outcomes relevant to developing DRIs for vitamin D and Ca
- Update DRIs for vitamin D and Ca, as appropriate
  - Specify the requirement -> Distribution of requirements
  - Indicate how much is too much
- Incorporate risk assessment approach
- Incorporate systematic evidence-based reviews (SEBR's)
  - Consider SEBR conducted by Agency for Health Quality Research Evidence Based Practice Centers at Tufts 2008-2009 and by Ottawa 2006-2007
- Enhance transparency of decision-making
- Identify research needs

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Committee Membership

A. CATHARINE ROSS (*Chair*), The Pennsylvania State University
STEVEN A. ABRAMS, Baylor College of Medicine
JOHN F. ALOIA, Winthrop-University Hospital
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STEVEN K. CLINTON, The Ohio State University
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CHRISTOPHER S. KOVACS, Memorial University of Newfoundland
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CLIFFORD J. ROSEN, Maine Medical Center Research Institute
SUE A. SHAPSES, Rutgers University

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Decision-Making Steps*: A Systematic Approach

1. Hazard (Outcome) Identification (Literature Review)
2. Hazard Characterization (Dose-Response Assessment → Ref. Value)
3. Intake Assessment (Prevalence of Intakes Outside Ref. Value)
4. Risk Characterization (Public Health Implications)

Risk Analysis Foundation		
Based on probability, prevalence, risk & distribution	Supports: transparency, objective independent review & scientific judgment re: limited data	Specified roles & tasks Specifies Problem Formulation

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*Based on nutrient risk assessment models (WHO, 2006)

1. Hazard (Outcome) Identification (Literature Review)

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Vitamin D: Challenges

Vitamin D → Hormone

Sun exposure

- Known factor based on seasonal changes in serum
- Cannot incorporate readily in DRI considerations
  - Not well quantified
  - Risk of skin cancer

Serum 25OHD: Biomarker of exposure

- Most data relate to serum values, not to intake
- Measurement issues regarding standardization and harmonization
- Not validated as biomarker of effect

Studies that combined vitamin D and calcium and administered only relatively high doses

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Health Outcomes Evaluated

Cancer/Neoplasms
- All Cancers, Breast Cancer, Colorectal Cancer, Colon Polyps, Prostate Cancer

Cardiovascular Diseases and Hypertension

Diabetes (Type 2) and Metabolic Syndrome (Obesity)

Falls

Immune Functioning

Asthma

Autoimmune Disease
- Type 1 Diabetes, Inflammatory Bowel and Crohn's Disease, Multiple Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus

Infectious Diseases
- **Tuberculosis, Influenza/Upper Respiratory Infections**

Neuropsychological Functioning
- Autism, Cognitive Function, Depression

Physical Performance

Preeclampsia of Pregnancy

Skeletal Health (commonly Bone Health)
- **Calcium Absorption, Calcium Balance, BMC/BMD, Fracture Risk, Rickets/Osteomalacia, 24OHD (intermediate), PTH (intermediate)**

Insufficient to establish DRI: lack causality and inconsistent

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CANCER - RCT (placebo-conrolled) –secondary analysis

Lappe : women, age 67yrs, 4 years
- vitamin D 1,000 IU
- vitamin D + calcium1gm
- placebo
- n 1179

2.9%
3.8%
6.9%
← no difference 2 treatments
significantly higher p<0.03

cancer incidence

Trivedi : men + women , age 75 yrs, 5 years
- quarterly 100,000IU tabs
- Vitamin D 833IU/d
- placebo
- n 2686

13.90%
12.86%
no significant difference

cancer incidence

WHI women, age 50-62 yrsv,6 years
- vitamin D 400 IU+ Ca1gm
- placebo
- n 36,282

0.27%
0.30%
OR 0.89 [0.77-1.03]

annualized cancer mortality

Conflicting Results: Inconsistent!

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Cancer and serum 25OHD - Observational studies

Study	Serum 25OHD ng/ml	Cancer mortality	Cancer incidence
Freedman 2007 NHANES 12 years		No interaction with cancer	
Giovannuci 2006 HPS 14 years	Each 10 ng/ml increase	Decrease 13%	Decrease of 17%
Pilz 2008 7.8 years	< 10	Increased mortality	
Jenab 2010 (EPIC)	<10 10-20 20-30 30-36 >36		1.32 (0.87-1.32) 1.28 (1.05-1.56) 1.0 ref 0.88 (0.68 – 1.33) 0.77 (0.56 – 1.06)
Nested case control			

Inconsistent Results

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2. Hazard Characterization (Dose-Response Assessment → Ref. Value)

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Vitamin D and BMD

Relationship serum 25OHD with BMD *discordant across* **6 RCT's, 7 prospective cohort studies, and 6 case-control studies,**

Evidence is fair that support an association between serum 25OHD and BMD or change in BMD .

21 RCT - vitamin D usually combined with calcium 500-1000mg/day.

Meta analysis (AHRQ Ottawa/Tufts) -small positive effect on BMD at spine, femoral neck and total body sites on Vitamin D3 800 IU + calcium ~500mg/d

***None of the 21 studies had a dose response design**

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Evidence Summary: Vitamin D & Bone Health

Serum 25OHD

Ca absorption ↓ < 12.5 nmol/L (totality of evidence)
Supportive for ↑ BMC in children
Only fair for ↑ BMD in adults
Good for low 25OHD (< 50 nmol/L) and fractures
< 1% osteomalacia with serum 25OHD > 50/nmol/L
No threshold for rickets, but ↑ risk <30 nmol/L

BMD -. small ↑ with Vitamin D 800IU (& 500mg Ca) in older ♀

Fractures - ↓ with vitamin D (300-1200IU/d) & Ca ~1000mg

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What level of serum 25OHD affects bone health?

- **Calcium absorption**
- **Rickets**
- **Osteomalacia**
- **BMD**
- **Fracture risk: RCTs & Observational**

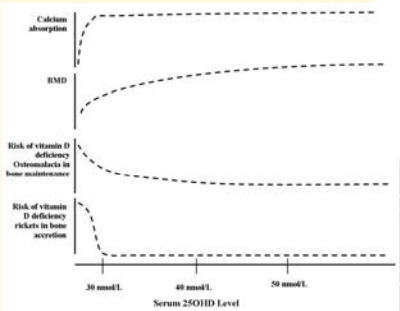

FIGURE 5-1 Conceptualization of integrated bone health outcomes and vitamin D exposure

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Evidence for a threshold of serum 25OHD between 40-50 nmol/L related to prevention of fractures

Study	Serum 25OHD(nmol/L)	OR/HR 95% CL)	Outcome	N	Age (yrs)	Gender
Melhus 2010	<40	1.71 (1.13-2.57)	Hip fracture	1194	71	men
Cauley 2008 (WHI)	<25	1.71 (1.05-2.79)	Hip fracture	800	71	women
Cauley 2010 (Mr. OS)	<47.5	2.36 (1.08-5.16)	Hip fracture	1665	73	men
Looker 2008 (NHANES 3)	<40	2.0	Hip fracture	1917	≥ 65	both
Gerdhem 2005	<50	2.04 (1.04-4.04)	Hip fracture	986	75	women

Gallagher JC , Sai AJ. 2010 Vitamin D Insufficiency, Deficiency and Bone Health 2010 JCEM :95,2630

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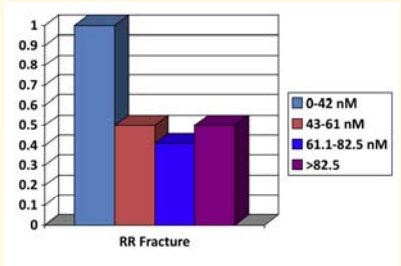
Association between Serum 25(OH)D and Hip Fracture (NHANES III)



Looker AC, Mussolino ME . JBMR 2008; 23:143-150.

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Association between Serum 25OHD and Osteomalacia

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Priemel et al. BMR 2010; 25:305-12.

Vitamin D: Development of Requirement Distribution

Step 1 – Link serum levels to distribution requirement

- **40 nmol/L (16 ng/mL) roughly equivalent to EAR**
- **50 nmol/L (20 ng/mL) roughly equivalent to RDA**
- **Note:**
  - **Some studies (bone) suggest 50 nmol/L TOO HIGH for RDA;**
  - **others suggest 50 nmol/L TOO LOW for RDA;**
  - **Decision was made by the COMMITTEE based on the totality of the evidence.**
  - **Many new studies available that were not available at the time of the 1997 DRI report (that set an AI)**
- **Why not 75 nmol/L (30 ng/mL)?**
  → Other lines of evidence also did not support:
  - **Calcium Absorption**
  - **PTH Suppression**
  - **Falls**

Process of Evaluation: Reanalyzing the Relationship of Serum 25OHD Levels & Calcium Absorption

Heaney, R.P. J Steroid Biochem Mol Biol 2005;97(1-2): 13-9.

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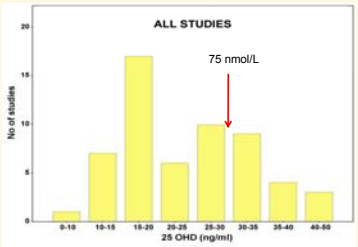
Need et alJBMR,2008

Need AG et al. Bone. 2008 Jun;42(6):1021-4.

Process of Evaluation: Relationship of Serum 25OHD Levels & Parathyroid hormone (PTH)

- **Inverse correlation serum PTH and 25OHD**
- **No consistent threshold serum 25OHD and suppression of serum PTH***



(Sai AJ et al. JCEM 2010 December - online)

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Effect of vitamin D Dose on Falls: Relation to serum 25OHD

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Conclusions

Vitamin D 700-1000IU daily significantly reduced falls by 19%

To prevent falls serum 25OHD should exceed 60 nmol/L

Bischoff –Ferrari et al. BMJ 2009

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Process of Evaluation : Reanalysis Falls

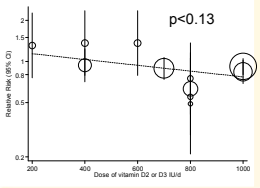

FIGURE 4-2 Relative risk of falls and vitamin D supplementation doses: correct meta-regressions with continuous predictors showing nonsignificance. NOTE: Relative risk reduction is 0.95 (95% confidence interval [CI] 0.89 to 1.02; $p = 0.13$) per 100 IU/day difference (increase) in dose.

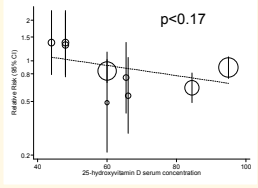

FIGURE 4-3 Relative risk of falls and mean achieved serum 25OHD concentrations: correct meta-regressions with continuous predictors showing nonsignificance. NOTE: Relative risk reduction is 0.92 (95% confidence interval [CI] 0.80 to 1.05; $p = 0.17$) per 10 nmol/L difference (increase) in mean achieved 25OHD concentration.

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Vitamin D Potential Indicators for Excess Intake

- Hypercalcemia; hypercalciuria
  - ≥ 10,000 IU/d
- (Infants) retarded growth
- Emerging evidence for all-cause mortality, cancer, CVD, falls and fractures at high exposures
  - Committee determined that serum 25(OH)D levels >125-150 nmol/L associated with ↑ risk
  - Confounding possible:
    - Risk at low status- lack of physical activity, obesity, race, and SES (poorer diet/no supplement use)
    - Risk at high status - recent weight loss, supplement-taking in individuals with chronic illness

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Vitamin D: Development of Requirement Distribution

Step 2 – Determine how much intake to achieve designated serum level

- Assumption of minimal sun exposure
- Assumption of adequate calcium intakes
- Integration of studies conducted in winter in northern latitudes & Antarctica (many recent studies)
- ***Simulation of dose-response***

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Figure 5-3. Age Does Not Affect Response of 25OHD Levels to Total Dietary Vitamin D Intake at Latitudes >50^0 During Winter

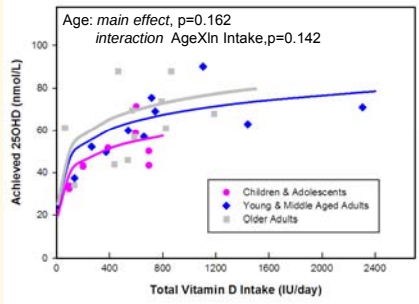

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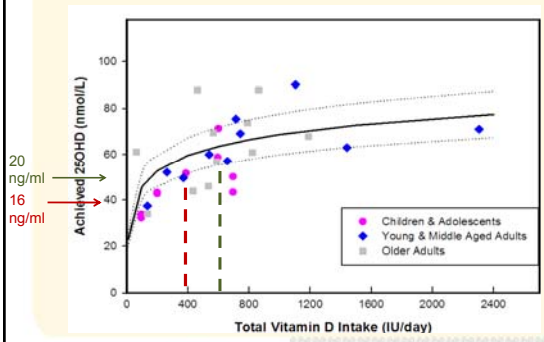
Figure 5-4. Response of 25OHD Level to Total Dietary Vitamin D Intake in All Age Groups at Latitudes >50^0 During Winter



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  - Committee determined serum 25(OH)D levels >125-150 nmol/L associated with ↑ risk
  - Confounding possible:
    - Risk at low status- lack physical activity, obesity, race, and SES (poorer diet/no supplement use)
    - Risk at high status - recent weight loss, supplement-taking in individuals with chronic illness
- UL set at 4000IU/d [Adjusted dose of 5000 IU/d (<150 nmol/L for 160 d; Heaney et al. AJCN 2003) for uncertainty

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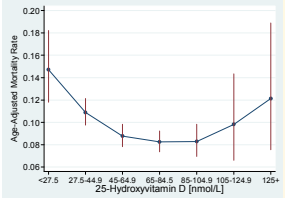
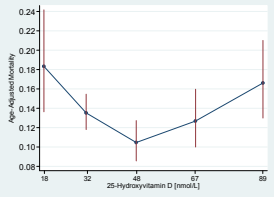
Committee analysis of NHANES data: Confirmed published U-Shaped Relationship

(Melamed, Arch Int Med 2008)



NHANES African Americans, IOM Analysis, unpublished data



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Vitamin D DRI

	EAR (IU/day	RDA (IU/day)	UL(IU/day)
1-70 years	400	600	
>70 years	400	800	
9-70+ years			4000
Preg/lac 14-50 years	400	600	4000

Infants 0 to 12 mos: AI = 400

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Calcium DRI

Key Bone Health Indicator	Years	EAR	RDA (mg/day)	UL
Average Ca Accretion	1-3	500	700	2500
	4-8	800	1000	2500
	9-18	1100	1300	3000
Ca balance	19-50	800	1000	2500
	51-70 M	800	1000	2000
BMD	51-70 F	1000	1200	2000
Fracture risk	>70	1000	1200	2000
	Preg/lac 14-18 years	1100	1300	3000
	Preg/lac 19-50 years	800	1000	2500

Infants 0 to 6 mos: AI = 200
Infants 6 to 12 mos: AI= 260

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Need for Evidence-Based Consensus Guidelines for Interpreting Serum 25OHD Levels

- **Controversial – many 'cut-points' suggested in literature**
  - **Deficiency - < 30, <50, or < 75-80 nmol/L**
  - **Sufficiency - ≥ 50 or > 75-80 nmol/L**
  - **Optimal - > 75-80 nmol/L**
- **Implications of 2011 DRI's**
  - **< 30 nmol/L – increased risk deficiency**
  - **< 40 nmol/L – increased risk of inadequacy**
  - **≥ 50 nmol/L – adequate intake (or 'exposure')**
  - **> 125/nmol/L – sustained high level associated with increased risk of adverse outcomes**

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