MICRONUTRIENT CONTROVERSY SYMPOSIUM

VITAMIN D:

IS THE RDA ENOUGH?

Presented by:

Allen Tran & Jessica Shields

March 21, 2012

INTRODUCTION: VITAMIN D

- Found naturally in few foods
- Produced endogenously when ultraviolet rays strike the skin
- Promotes calcium absorption in the gut
  - bone growth and bone remodeling by osteoblasts and osteoclasts[1,2]
- Other roles in the body
  - modulation of cell growth
  - neuromuscular and immune function
  - reduction of inflammation[1,3,4]
  - genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D [1].

Recommended Dietary Allowances (RDAs) for Vitamin D [1]

Age	Male	Female	Preg.	Lact.
0–12 months*	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

Tolerable Upper Intake Levels (ULs) for Vitamin D [1]

Age	Male	Female	Preg.	Lact.
0–6 months	1,000 IU (25 mcg)	1,000 IU (25 mcg)		
7–12 months	1,500 IU (38 mcg)	1,500 IU (38 mcg)		
1–3 years	2,500 IU (63 mcg)	2,500 IU (63 mcg)		
4–8 years	3,000 IU (75 mcg)	3,000 IU (75 mcg)		
≥9 years	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)	4,000 IU (100 mcg)

* Adequate Intake (AI)

SERUM 25-HYDROXYVITAMIN D [25(OH)D] CONCENTRATIONS AND HEALTH [1]

nmol/L**	ng/ml*	Health Status
<30	<12	Associated with vitamin D deficiency leading to rickets in infants and children and osteomalacia in adults
30-50	12-20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall heath in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

* Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL).
** 1 nmol/L = 0.4 ng/mL

THE CONTROVERSY

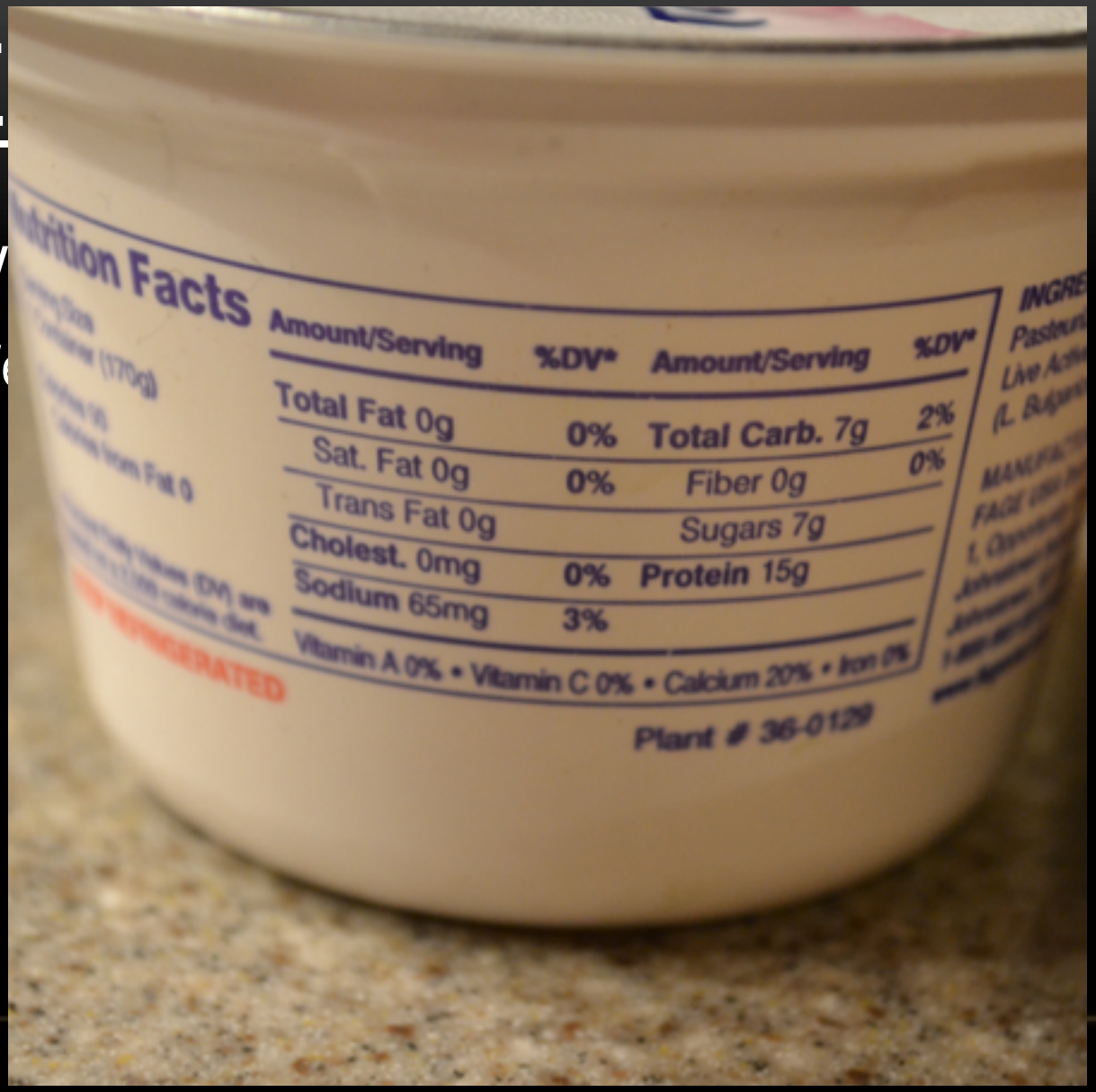
- Some argue that doses of vitamin D higher than the current RDA provide added health benefits
- Some counter that long-term supplementation above RDA may have negative effects.

WHY HIGHER DOSES OF VITAMIN D MAY BE WARRANTED

- Endogenous production is probably not enough
  - Indoor-bound, sedentary jobs
  - Seasonality
  - Increased use of sunscreen
  - Age
  - Latitude

THE

- Why
  - We


Nutrition Facts
Amount/Serving %DV* Amount/Serving %DV*
Total Fat 0g 0% Total Carb. 7g 2%
Sat. Fat 0g 0% Fiber 0g 0%
Trans Fat 0g Sugars 7g
Cholest. 0mg 0% Protein 15g
Sodium 65mg 3%
Vitamin A 0% • Vitamin C 0% • Calcium 20% • Iron 0%
Plant # 36-0129

- Unless you live in the South AND spend a fair amount of time outdoors

OR

- Like to eating fatty fish and vitamin D fortified foods

(subclinical)

You may be at risk for Vitamin D Deficiency

NOT JUST BONES…

- Nuclear receptors for the vitamin have been found in over 30 organs, including bone, intestine, kidney, lung, muscle, and skin.

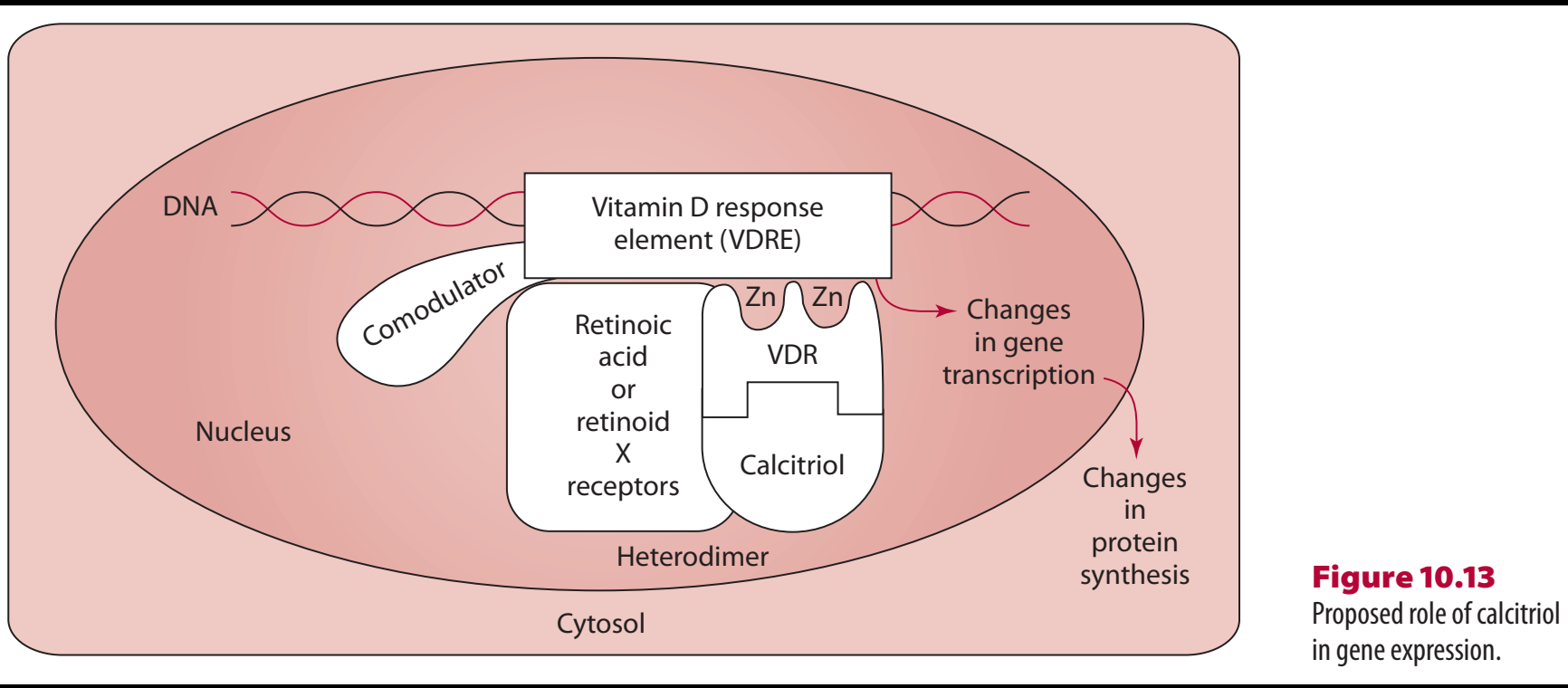


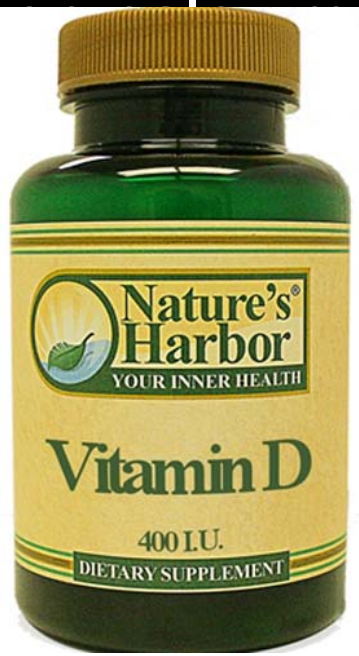
Figure 10.13
Proposed role of calcitriol in gene expression.

THE CONTROVERSY: CON

- Long-term intakes above the UL increase the risk of adverse health effects[1] Most reports suggest a toxicity threshold for vitamin D of 10,000 to 40,000 IU/ day and serum 25(OH)D levels of 500–600 nmol/L (200–240 ng/mL).
- FNB pointed to emerging science from national survey data, observational studies, and clinical trials suggesting that even lower vitamin D intakes and serum 25(OH)D levels might have adverse health effects over time.
- The FNB concluded that serum 25(OH)D levels above approximately 125–150 nmol/L (50–60 ng/mL) should be avoided, as even lower serum levels (approximately 75–120 nmol/L or 30–48 ng/mL) are associated with increases in all-cause mortality, greater risk of cancer at some sites like the pancreas, greater risk of cardiovascular events, and more falls and fractures among the elderly.

THE IOM

- Investigated the notion that, when it comes to dietary nutrients, “more is better” — a belief that has inspired a multibillion-dollar market for dietary supplements in the United States. Americans spent $1.2 billion last [illegible] supplements and $430 million on [illegible] vitamin D, according to the Nutriti[illegible] Journal.



SO HOW MUCH VITAMIN D IS ACTUALLY ENOUGH?

ESTIMATION OF THE DIETARY REQUIREMENT FOR VITAMIN D IN HEALTHY ADULTS

The American Journal of Clinical Nutrition

2008

Kevin D Cashman, Tom R Hill, Alice J Lucey, Nicola Taylor, Kelly M Seamans et al.

BACKGROUND

- It is well established that prolonged and severe clinical vitamin D deficiency, represented as serum or plasma 25-hydroxyvitamin D [25(OH)D] concentrations of <10–25 nmol/L, leads to rickets in children and osteomalacia in adults [1].
- Less severe vitamin D deficiency causes secondary hyperparathyroidism and increases bone turnover and bone loss [2-4].

OBJECTIVE

- Establish the distribution of dietary vitamin D required to maintain serum 25-hydroxyvitamin D [25(OH)D] concentrations above several proposed cutoffs (ie, 25, 37.5, 50, and 80 nmol/L) during wintertime after adjustment for the effect of summer sunshine exposure and diet.

SUBJECTS

- 245 healthy adults recruited
- Exclusion criteria:
  - consumed vitamin D–containing supplements for 12 wk before initiation of the study
  - planned to take a winter vacation to a location at which either the altitude or the latitude would be predicted to result in significant cutaneous vitamin D synthesis from solar radiation
  - medical illness, hypercalcemia, known intestinal malabsorption syndrome, excessive alcohol use, current medications known to interfere with vitamin D metabolism
  - pregnancy or plans to become pregnant

METHODS

- Double-blind, placebo-controlled
- Participants at 2 centers received:
  - D3
  - 22 weeks
  - 0 (placebo), 5, 10, 15 mcg/day
- Began intervention October 2- November 2
- Completed intervention February 27 – April 7
- Timespan which vitamin D status would be expected to decline

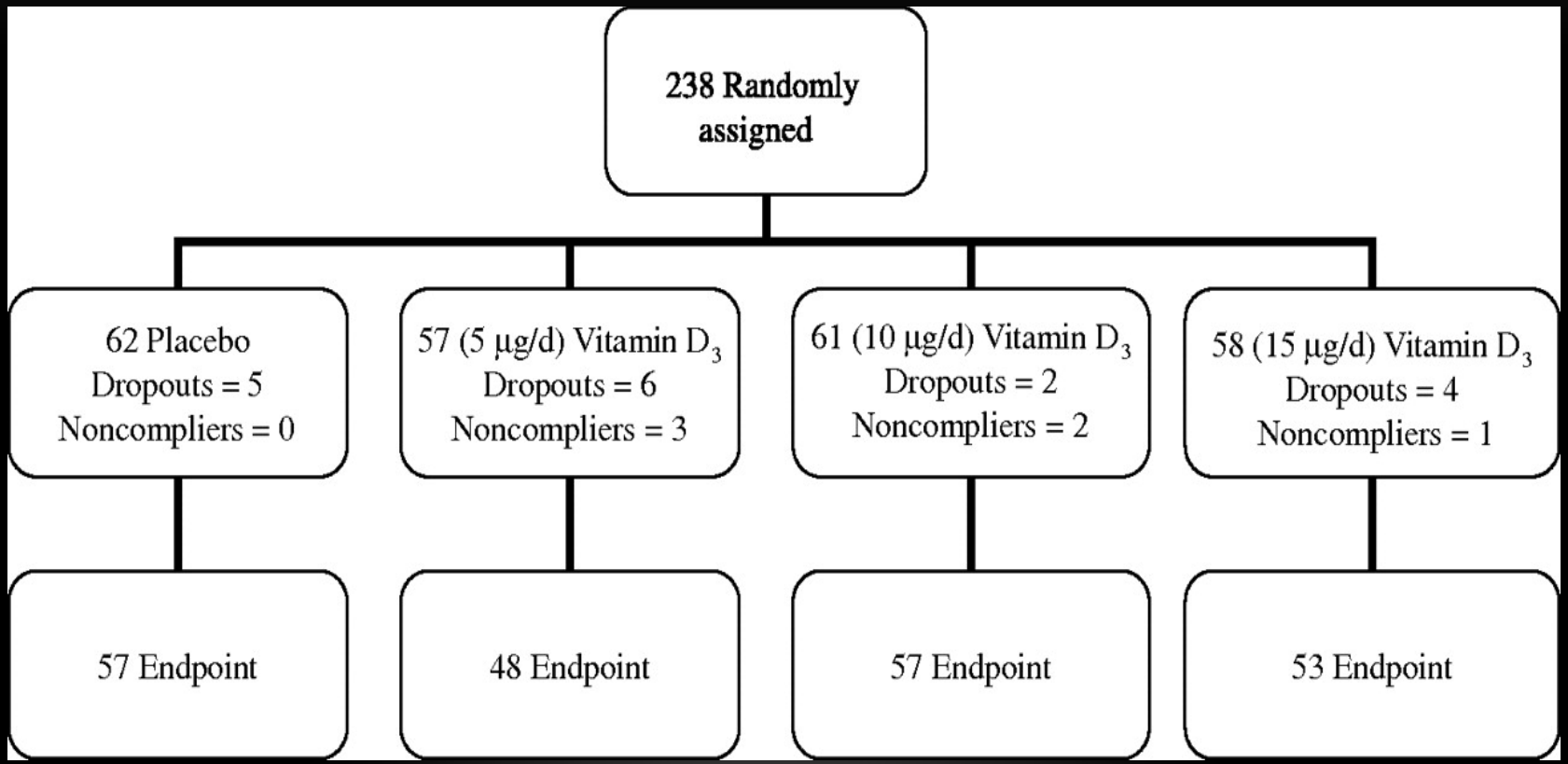
METHODS

- Measurements at baseline (wk. 0) and endpoint (wk. 22)
  - Overnight fasting blood sample
  - Anthropometric measurements
  - Habitual intakes of calcium and vitamin D were estimated by using a validated food-frequency questionnaire (FFQ) , administered by a research nutritionist;
  - Health and lifestyle questionnaire, which assessed physical activity, general health, smoking status, and alcohol consumption, also was completed.
- Participants contacted monthly to promote compliance and encourage completion of the study protocol.

LABORATORY ANALYSIS

- **Serum 25-hydroxyvitamin D**
- **Serum intact parathyroid hormone**
- **Serum total calcium**

FLOW OF SUBJECTS THROUGH STUDY



BASELINE CHARACTERISTICS

	All Subjects	Cork	Coleraine
Male:female (*n*)	111:111	54:54	57:56
Age (y)	29.9 ± 6.2[2]	28.7 ± 6.0	31.1 ± 6.3[3]
Weight (kg)	77.0 ± 15.8	76.6 ± 15.9	77.3 ± 15.7
Height (m)	1.71 ± 0.09	1.72 ± 0.10	1.71 ± 0.08
BMI (kg/m^2)	26.1 ± 4.3	25.8 ± 4.0	26.3 ± 4.5
Dietary calcium (mg/d)	976 (682–1301)[4]	955 (676–1301)	990 (718–1307)
Dietary vitamin D (µg/d)	3.6 (2.1–5.4)	3.4 (2.1–5.1)	3.6 (2.3–5.7)
Serum 25(OH)D (nmol/L)	70.3 (53.4–90.3)	76.2 (57.4–104.1)	64.9 (48.5–84.9)[4]
Serum PTH (ng/mL)	43.8 (32.3–59.3)	43.6 (31.5–57.6)	44.1 (34.4–60.1)
Serum calcium (mmol/L)[5]	8.8 ± 0.3	8.7 ± 0.3	8.9 ± 0.3[4]
Summer sun exposure preferences (%)			
Sun avoiders	12.7	13.0	12.4
Some exposure	48.8	54.0	44.2
Frequent exposure	38.5	33.0	43.4

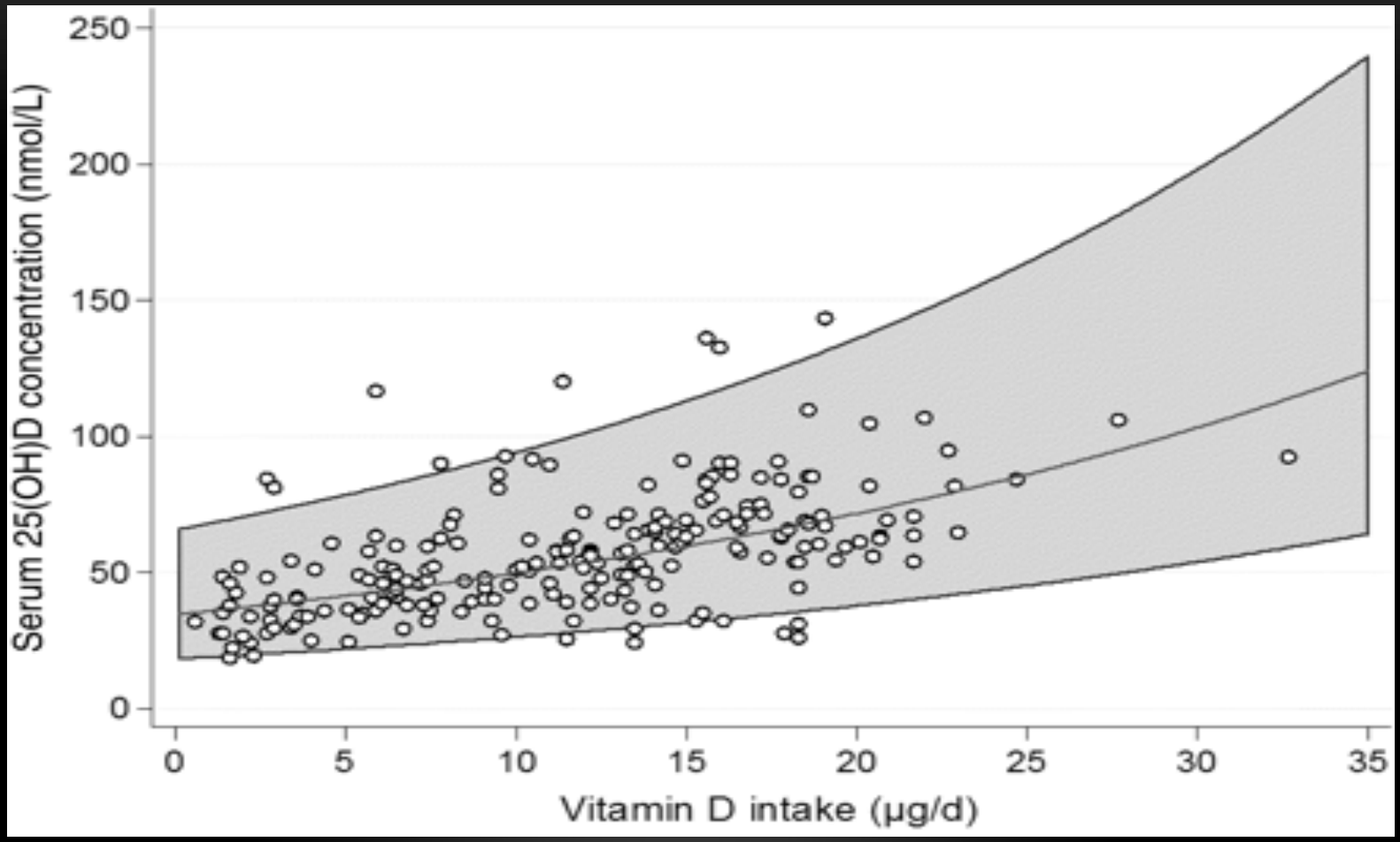
BASELINE CHARACTERISTIC SUMMARY

- baseline serum 25(OH)D concentrations did not differ by sex ($P = 0.5$)
  - they differed significantly ($P = 0.001$) by center
- no significant between-center difference in habitual vitamin D or calcium intake in subjects at baseline
  - men had significantly ($P < 0.006$) higher intakes of vitamin D and calcium than did women
  - men typically have higher food and nutrient intakes than do women
- Baseline serum 25(OH)D concentrations in subjects:
  - “often having exposure to summer sunshine” >> “avoiding” or “sometimes” having exposure to summer sunshine
  - ($P < 0.01$)

EFFECTS OF VITAMIN D INTERVENTION

- Compliance did not differ significantly among the 4 treatment groups ($P = 0.7$)
- There was a significant ($P < 0.0001$) effect of treatment on mean postintervention serum 25(OH)D concentrations, with clear dose-related increments with increasing supplemental vitamin D_3
- No significant difference in mean postintervention serum albumin–corrected calcium concentrations among the treatment groups

THE RELATION BETWEEN SERUM 25-HYDROXYVITAMIN D [25(OH)D] CONCENTRATIONS AND TOTAL VITAMIN D INTAKE (DIET AND SUPPLEMENTAL)



- The slope of the relation between total vitamin D intake and serum 25(OH)D concentrations in the entire group was 1.96 nmol/L·µg intake.

ESTIMATED DIETARY REQUIREMENTS FOR VITAMIN D AT SELECTED PERCENTILES IN 215 MEN AND WOMEN AGED 20–40 Y TO MAINTAIN SERUM 25-HYDROXYVITAMIN D [25(OH)D] CONCENTRATIONS ABOVE SELECTED BIOCHEMICAL CUTOFFS DURING WINTER

Cutoff	50th percentile	90th percentile	95th percentile	97.5th percentile
	μg/d			
Serum 25(OH)D >25 nmol/L	—	2.7 (0.0, 4.7)	5.9 (3.6, 8.0)	8.7 (6.5, 11.1)
Serum 25(OH)D >37.5 nmol/L	2.3 (0.0, 4.2)	13.8 (12.1, 15.9)	17.0 (14.8, 19.9)	19.9 (17.2, 23.5)
Serum 25(OH)D >50 nmol/L	10.2 (8.9, 11.4)	21.7 (19.3, 25.0)	25.0 (21.9, 29.1)	28.0 (24.2, 32.8)
Serum 25(OH)D >80 nmol/L	23.1 (21.0, 26.0)	34.8 (30.4, 40.6)	38.3 (33.0, 44.8)	41.1 (35.4, 48.7)

CONCLUSIONS

- Daily intake of 8.7 µg vitamin D/d maintained serum 25(OH)D concentrations >25 nmol/L in 97.5% of the sample.
- Vitamin D intakes required to ensure maintenance of wintertime vitamin D status [as defined by incremental cutoffs of serum 25(OH)D] >97.5% adults, considering a variety of sun exposure preferences, is between 7.2 and 41.1 microg/d.

DISCUSSION & CLINICAL IMPLICATIONS

- Available data about the relative contribution of sunshine and diet to vitamin D status and vitamin D requirements for health maintenance have presented international authorities with considerable difficulty in setting dietary requirements for vitamin D.
- RDA is in range estimated to keep serum levels adequate.

EFFECT OF FOUR MONTHLY ORAL VITAMIN D3 (CHOLECALCIFEROL) SUPPLEMENTATION ON FRACTURES AND MORTALITY IN MEN AND WOMEN LIVING IN THE COMMUNITY: RANDOMISED DOUBLE BLIND CONTROLLED TRIAL

The British Medical Journal

March 2003

Daksha P Trivedi, Richard Doll, Kay Tee Khaw

OBJECTIVE

- To determine the effect of four monthly vitamin D supplementation on the rate of fractures in men and women aged 65 years and over living in the Suffolk, UK community

SUBJECTS

- Invitations sent through mail to 11,120 people from a Hospital general practice register
- 3504 responded
- Exclusion criteria:
  - People already taking Vitamin D supplements
  - People with contraindications to vitamin D supplementation
    - Renal Stones
    - Sarcoidosis
  - Existing Cancer
- 2686 people (2037 men, 649 women) qualified

INTERVENTION

- Randomized double blind protocol
- One capsule 100,000 IU Vitamin D or matching placebo
- Mailed to subjects
- Required to complete & mail back a form that indicated that took the capsule

- Subjects continued any usual drug treatment
  - If advised to take vitamin D supplements duringthe study (>200IU), discontinued from trial

ASSESSMENT

- During study:

- Questionnaire of “major events”
  - Fracture
  - Major Illness
  - Death (by death certificate)

ASSESSMENT

- After 4 years:
- Measurement of serum vitamin D
- Parathyroid hormone
- Heel bone sonometry

RESULTS

- Compliance was not sig. diff. between groups
- Withdrawal rate was not sig. diff. between groups
- Parathyroid hormone levels were not sig. diff. between groups
- Heel ultrasound measures did not differ by treatment.

RESULTS: VITAMIN D LEVELS

Table 5 Bone heel ultrasound attenuation, velocity of sound, and concentrations of serum vitamin D and parathyroid hormone in subgroup of participants from general practice. Values are means (standard deviations) unless stated otherwise

	All			Men			Women		
Measurement	**Vitamin D (n=124)**	**Placebo (n=114)**	**P value**	**Vitamin D (n=65)**	**Placebo (n=57)**	**P value**	**Vitamin D (n=59)**	**Placebo (n=57)**	**P value**
Age (years)	76.1 (5.1)	75.4 (4.1)	0.20	75.7 (5.1)	75.0 (3.6)	0.37	76.6 (5.1)	75.7 (4.5)	0.33
Body mass index (kg/m^2)	27.4 (4.2)	26.8 (4.2)	0.15	26.9 (4.0)	26.2 (3.0)	0.30	28.0 (4.5)	27.1 (5.1)	0.28
Vitamin D (nmol/l)	74.3 (20.7)	53.4 (21.1)	<0.001	75.6 (19.0)	61.0 (21.5)	<0.001	72.0 (22.5)	45.37 (17.6)	<0.001
Parathyroid hormone (pmol/l)	5.2 (2.3)	5.5 (2.4)	0.25	4.8 (2.0)	5.0 (2.0)	0.68	5.6 (1.9)	6.13 (2.6)	0.25
Bone heel ultrasound attenuation (dB/MHz)	74.4 (21.9)	72.3 (19.7)	0.45	89.1 (15.4)	83.5 (16.2)	0.05	57.9 (15.4)	60.95 (16.3)	0.30
Velocity of sound (m/s)	1618.1 (41.2)	1613.6 (38.6)	0.39	1641.1 (32.2)	1629.2 (34.5)	0.05	1592.4 (34.5)	1597.7 (36.2)	0.42

Placebo had the adequate Vit D levels (>50 nmol/L), but the supplement group had significantly greater levels (~75 nmol/L)

SERUM 25-HYDROXYVITAMIN D [25(OH)D] CONCENTRATIONS AND HEALTH [1]

nmol/L**	ng/ml*	Health Status
<30	<12	Associated with vitamin D deficiency leading to rickets in infants and children and osteomalacia in adults
30-50	12-20	Generally considered inadequate for bone and overall health in healthy individuals
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>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

* Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL).
** 1 nmol/L = 0.4 ng/mL

RESULTS

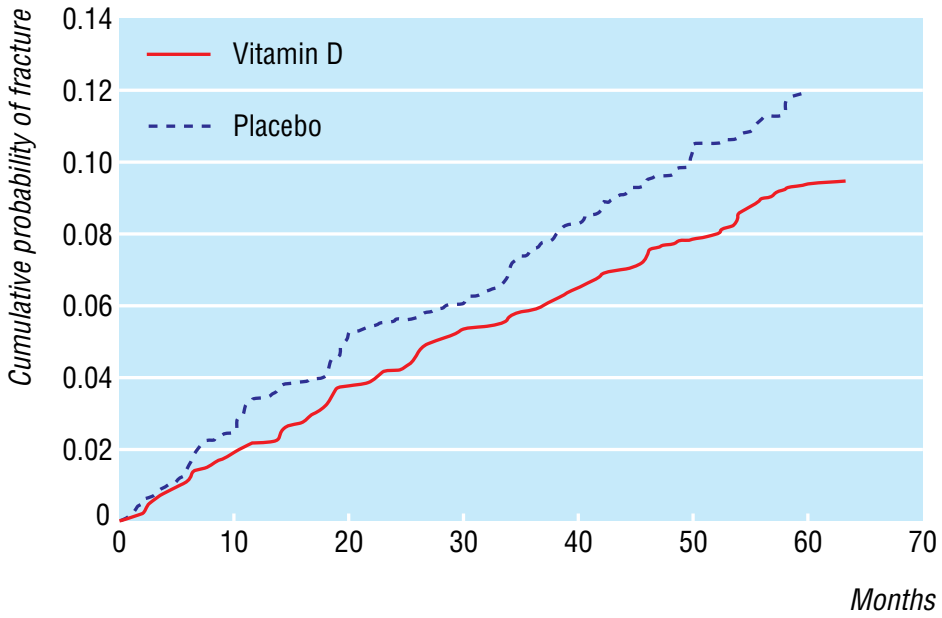

Fig 1 Cumulative probability of any first fracture according to treatment with vitamin D (n=1345) or placebo (n=1341), based on Cox regression; difference between two groups, P=0.04

Table 2 Incidence of fractures based on self report or mortality certification 1996-2002 and age adjusted relative risks (Cox regression), according to treatment allocation at randomisation (intention to treat) in 2686 men and women aged 65-85 years. Values are numbers (percentages) unless stated otherwise

Fractures	Vitamin D	Placebo	Age adjusted relative risk (95% CI)	P value*
All	(n=1345)	(n=1341)		
Any site	119 (8.8)	149 (11.1)	0.78 (0.61 to 0.99)	0.04
Hip, wrist or forearm, or vertebrae	60 (4.5)	87 (6.5)	0.67 (0.48 to 0.93)	0.02
Hip or wrist or forearm	43 (3.2)	62 (4.6)	0.67 (0.46 to 0.99)	0.04
Hip	21 (1.6)	24 (1.8)	0.85 (0.47 to 1.53)	0.59
Vertebrae	18 (1.3)	28 (2.1)	0.63 (0.35 to 1.14)	0.12
Men	(n=1019)	(n=1018)		
Any site	77 (7.6)	91 (8.9)	0.83 (0.61 to 1.13)	0.24
Hip, wrist or forearm, or vertebrae	36 (3.5)	50 (4.9)	0.70 (0.46 to 1.08)	0.11
Hip or wrist or forearm	22 (2.2)	31 (3.0)	0.70 (0.40 to 1.20)	0.19
Hip	11 (1.1)	14 (1.4)	0.76 (0.35 to 1.67)	0.49
Vertebrae	14 (1.4)	22 (2.2)	0.62 (0.32 to 1.22)	0.17
Women	(n=326)	(n=323)		
Any site	42 (12.9)	58 (18.0)	0.68 (0.46 to 1.01)	0.05
Hip, wrist or forearm, or vertebrae	24 (7.4)	37 (11.5)	0.61 (0.37 to 1.02)	0.06
Hip or wrist or forearm	21 (6.4)	31 (96)	0.64 (0.37 to 1.11)	0.11
Hip	10 (3.1)	10 (3.1)	0.98 (0.41 to 2.36)	0.97
Vertebrae	4 (1.2)	6 (1.9)	0.65 (0.18 to 2.30)	0.50

*P value (two sided) refers to difference between treatment groups.

RESULTS

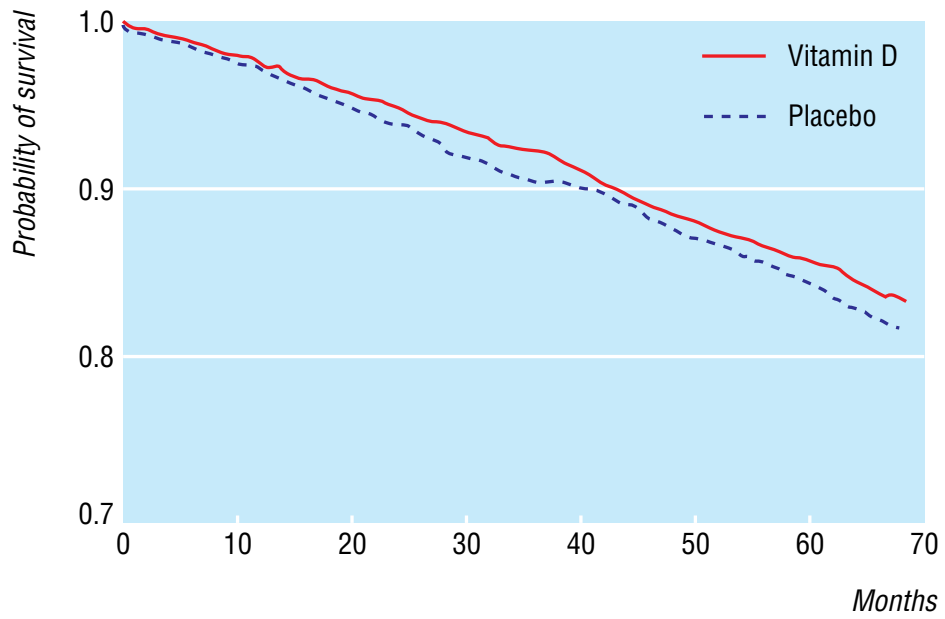

Fig 2 Cumulative survival according to treatment with vitamin D (n=1345) or placebo (n=1341), based on Cox regression; no significant difference between groups

No significant differences in:

- all-cause mortality
- cardiovascular disease
- cancer

than the placebo group.

DISCUSSION

- Participants in the vitamin D treatment group had a 22% lower rate for first fracture at any site and a 33% lower rate for a fracture occurring in the hip, wrist or forearm, or vertebrae
- No difference if mortality between groups

ORIGINAL CONTRIBUTION

Annual High-Dose Oral Vitamin D and Falls and Fractures in Older Women

A Randomized Controlled Trial

Kerrie M. Sanders, PhD
Amanda L. Stuart, BappSc
Elizabeth J. Williamson, MA, PhD
Julie A. Simpson, PhD
Mark A. Kotowicz, MBBS, FRACP
Doris Young, MD, MBBS, FRACGP
Geoffrey C. Nicholson, PhD, FRACP

Context Improving vitamin D status may be an important modifiable risk factor to reduce falls and fractures; however, adherence to daily supplementation is typically poor.

Objective To determine whether a single annual dose of 500 000 IU of cholecalciferol administered orally to older women in autumn or winter would improve adherence and reduce the risk of falls and fracture.

Design, Setting, and Participants A double-blind, placebo-controlled trial of 2256 community-dwelling women, aged 70 years or older, considered to be at high risk of fracture were recruited from June 2003 to June 2005 and were randomly assigned to receive cholecalciferol or placebo each autumn to winter for 3 to 5 years. The study concluded in 2008.

Intervention 500 000 IU of cholecalciferol or placebo.

THE RESULTS OF RANDOMIZED controlled trials investigating the effects of cholecalciferol

Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010 May 12;303(18):1815-22.

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* Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL).
** 1 nmol/L = 0.4 ng/mL

WHAT THE IOM SAYS

- "Practically all persons are sufficient at levels of 50 nmol/L (20 ng/ml) and above"
- Serum concentrations of 25OHD above 75nmol/L (30 ng/ml) are not associated with increased benefit

Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

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THE UNIVERSITY OF UTAH

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The new vitamin D recommendations; why the controversy?

BY THUNDER JALILI · DECEMBER 2, 2010 · 1 COMMENT

HEALTH & WELLNESS, POST HASTE RESPONSE · TAGGED: BONE HEALTH, CALCIUM RDA, VITAMIN D INTAKE

0
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Those who follow nutrition may have noticed that the Institute of Medicine has released new recommendations for calcium and vitamin D intake. What makes these newer recommendations interesting is that they reflect the growing interest among nutritionists to make recommendations that are based on preventing disease and optimizing health, rather than the old objective of just preventing nutrient deficiency.

In these new updates we see that calcium now has an "Recommended Dietary Allowance" value for specific ages, genders and life stages, as opposed to the old recommendations that stated an "adequate intake" recommendation. While this may be a notable development for scientists in the field, it's not an attention getter for the public since the actual target intakes of calcium haven't really changed very much.

recommendations were made based on optimizing bone health, however, vitamin D does other things in the body beyond the well-known role it plays in bone health.

vitamin D researchers who think it hasn't been increased nearly enough and are pushing for a much higher jump in recommendations. Why the controversy? Well, the currently recommendations were made based on optimizing bone health, however, vitamin D does other things in the body beyond the well-known role it plays in bone health.

In the last few years research studies have reported a protective role for vitamin D against various cancers, metabolic syndrome, and heart disease to name a few. These studies led some scientists to recommend a higher RDA for vitamin D. If this is true then why aren't we raising the vitamin D recommendation even more?

NOT THAT SIMPLE

- "Extraskeletal benefits"
  - Inconclusive studies
  - **Increased** risk of prostate cancer with supplementation

RDA?

- Challenge with establishing generalized recommendation vs individual differences

THE BIG QUESTION

- What is the most appropriate
  - General recommendation vs assessing status (and dosing accordingly)?

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