ΒΙΤΑΜΙΝΗ D

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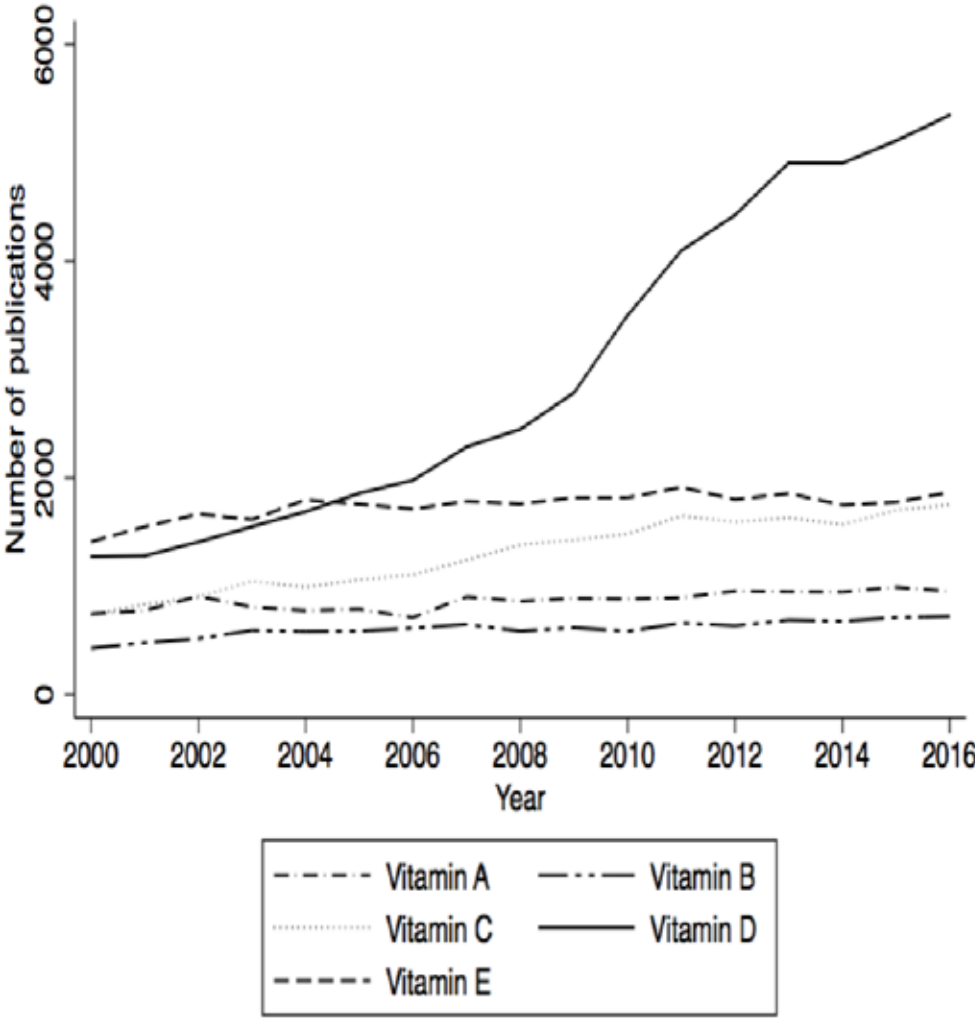
ΣΥΓΚΡΟΥΣΗ ΣΥΜΦΕΡΟΝΤΩΝ

- Αμοιβή για διαλέξεις: Φαρμασερβ –Λιλλυ, Amgen Hellas, Servier, Vianex,Galenica, ITF Hellas, Merck Hellas, AstraZeneca,Libytec.

D OR NOT TO D?



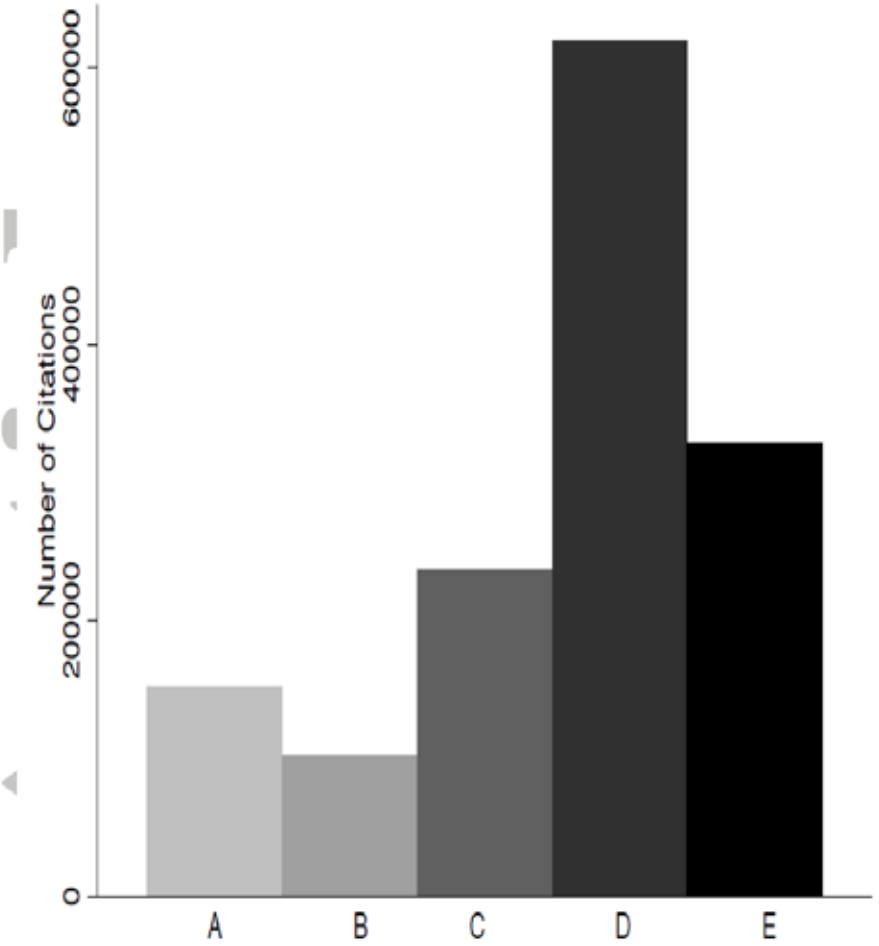


Figure 2 Number of Citations for Vitamins A-E between 2000-2016

Serum 25-hydroxyvitamin D status, quantitative ultrasound parameters, and their determinants in Greek population

Effimia V. Grigoriou[1] · George Trovas[2] · Nikolaos Papaioannou[2] · Polyzois Makras[3,4] · Panagiotis Kokkoris[3,4] · Ismene Dontas[2] · Konstantinos Makris[5] · Symeon Tournis[2] · George V. Dedoussis[1]

- 970 άτομα ,18-86 ετών , γυναίκες (830) και άνδρες (133) από όλη την Ελλάδα :
- Αττική, Πελοπόννησος, Βοιωτία, Φωκίδα, Εύβοια, Χαλκίδα, Γαλαξίδι, Κάρυστος, Κύμη, Άμφισσα, Φθιώτιδα, Θεσσαλία, Μαγνησία, Μακεδονία, Σαλαμίνα, Λήμνος ,Πάτμος.
- Από αστικές και αγροτικές περιοχές.

- 50% των ατόμων **είχαν επίπεδα** βιταμίνης D κάτω από 20 ng/ml (Έλλειψη)
- 8% είχαν **πολύ χαμηλά** κάτω από 10ng/ml(Σοβαρή έλλειψη).

Archives of Osteoporosis (2018) 13:111

ΕΠΙΠΕΔΑ ΒΙΤΑΜΙΝΗΣ D
>75nmol/l-30ng/ml Επάρκεια
50-75nmol/l-20-30ng/ml Ανεπάρκεια
25-50nmol/l-10-20ng/ml Έλλειψη
<25nmol/l-10ng/ml Σοβαρή έλλειψη

Table 1 Definitions of vitamin D deficiency and sufficiency according to different advisory bodies.

Serum 25(OH)D concentration (nmol/L)	**Institute of Medicine** (2)	**Endocrine Society** (1)	**EFSA** (29)	**SACN** (27)	**ECTS** (this paper)
<25/30 10-12ng/ml	Deficient	Deficient	Deficient	Deficient	Severely deficient
25–50 10-20ng/ml	Uncertain*	Deficient	Deficient		Deficient
50–75 20-30ng/ml	Sufficient	Insufficient	Sufficient		Sufficient
>75 >30ng/ml		Sufficient			

*According to the IOM serum 25(OH)D 30–50 nmol/L can be adequate or inadequate.

Scientific Advisory Committee on Nutrition [SACN] UK
European Food Safety Authority [EFSA] Europe

a position statement of the European Calcified Tissue Society 2019

Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis

Mark J Bolland, Andrew Grey, Alison Avenell

Lancet Diabetes Endocrinol 2018

Published Online October 4, 2018

- Since the last major systematic reviews of vitamin D and musculoskeletal health were published in 2012–17, 45 randomised controlled trials of vitamin D monotherapy (n=20131) have reported on bone mineral density, falls, and fractures, increasing the number of trial participants with these outcomes by 40–85%.
- Most new trials have also used substantially higher doses of vitamin D than earlier trials.
- Consequently, the currently available set of randomised controlled trials has much greater power for meta-analysis and trial sequential analysis, and allows a detailed exploration of potentially important clinical factors in subgroup analyses, including comparisons of high and low doses of vitamin D.

n=53 537 participants

	All trials (n=81)
Population unselected for underlying illness	61 (75%)
Treatment studied	
Vitamin D *vs* controls	39 (48%)
Vitamin D with agent *vs* agent	26 (32%)
Calcium	20 (25%)
Exercise	2 (2%)
Calcium and exercise	1 (1%)
Other	3 (4%)
High-dose *vs* low-dose vitamin D	16 (20%)
Vitamin D dose >800 IU per day	55 (68%)
Frequency of vitamin D dose	
Daily	44 (54%)
Intermittent	36 (44%)
Mixed	1 (1%)
Trial duration ≤1 year	55 (68%)
>200 participants	39 (48%)
Community-dwelling participants	69 (85%)
Majority of participants female	62 (77%)
Baseline mean age <65 years	33 (41%)
Baseline mean BMI <30 kg/m²	58 (72%)
Baseline 25-hydroxyvitamin D concentration	
<25 nmol/L	4/72 (6%)
<50 nmol/L	41/72 (57%)
<75 nmol/L	71/72 (99%)
Achieved 25-hydroxyvitamin D concentration	
≥50 nmol/L	69/76 (91%)
≥75 nmol/L	44/76 (58%)
Outcome data	
Fracture	42 (52%)
Falls	37 (46%)
Bone mineral density	41 (51%)

Data are n (%) or n/N (%), since some characteristics were not reported in all trials. See appendix (pp 4–9) for full details of trial characteristics.

Table 1: **Selected trial characteristics**

RESULTS

- The results for the primary outcome showed no effect of vitamin D on total fracture (relative risk 1·00, 95% CI 0·93–1·07),
- no effect on hip fracture (1·11,0·97–1·26),
- and no effect on falls (0·97, 0·93–1·02).
- For the secondary outcome of bone mineral density, the between-group differences were
- 0·25% (95% CI 0·00 to 0·49) for lumbar spine,
- 0·76% (0·42 to 1·09) for femoral neck, and
- 0·13% (–0·16 to 0·42) for total body, which are not clinically relevant.

- In summary, vitamin D supplementation did not have meaningful effects on fracture, falls, or bone mineral density, and future trials are unlikely to alter these conclusions.
- Therefore, there is little justification for the use of vitamin D supplements to maintain or improve musculoskeletal health, and clinical guidelines should reflect these findings
- The clear exception to this is for the prevention or treatment of the rare conditions of rickets and osteomalacia, which can occur after a prolonged lack of exposure to sunshine that leads to 25OHD concentrations lower than 25 nmol/L(**10ng/m**l).

Vitamin D and bone density, fractures, and falls: the end of the story? Comment

- There are still unanswered questions because 70% of daily treatment groups were of doses of 1000 IU per day or less, and serum 25OHD concentrations possibly did not reach the range of interest.
- for studies more than 10 years old, interlaboratory serum 25OHD measurements were not standardised.
- Another issue with fixed doses is the large variance in the change in serum 25OHD concentrations.
- Patients taking 800 IU daily had increased serum 25OHD concentrations, from 38 nmol/L (SD 9·4)(15,2ng/ml) to final values ranging from 50–125 nmol/L(20-50ng/ml).

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Lancet Diabetes Endocrinol 2018

- In a secondary analysis of a falls study with daily vitamin D, there was a U-shaped response;
- the minimum effective dose was 1600 IU per day and serum 25OHD concentrations ranged from 87 nmol/L(34,8 ng/ml) to 102 nmol/L(40,8ng/ml).
- However, patients receiving doses greater than 4000 IU daily had serum 250HD concentrations ranging from 103 nmol/L(41,2ng/ml) to 122 nmol/L(48,8), and there was an increase in falls.
- This variation in response suggests that analysis by quartiles of standardised serum 25OHD measurements might be more useful than dose.

Correspondence

Roger Bouillon, Paul Lips,John P Bilezikian(Lancet)

- Bolland and colleagues are experts in meta-analysis, but their analysis falls into a common trap of misleading selection of primary data.
- Several meta-analyses clearly showed that a supplement of vitamin D combined with calcium, given to older participants with a calcium intake well below the recommended intake for their age and with mild or severe vitamin D deficiency, results in a 15–20% reduction of hip or non-vertebral fractures.
- Bolland and colleagues recently also corroborated the beneficial effects of combined supplementation, in line with most guidelines.
- However, Bolland and colleagues excluded all studies using combined vitamin D and calcium supplementation (compared with double placebo), and only assessed the results of vitamin-D-only supplementation (with or without another agent in both arms of the study).

- Another major problem is that most of the studies included were done in vitamin D-sufficient participants.
- Since vitamin D is a threshold nutrient, it would be surprising if a therapeutic benefit was observed in the context of already normal concentrations. However, a third of the world's population have serum concentrations of 25-hydroxyvitamin D (25OHD) that are less than 50 nmol/L, and more than 7% that are less than 30nmol/L. Such low concentrations (ie, <30 nmol/L) are uniformly considered in all guidelines to be a risk factor for rickets and osteomalacia.
- Additionally, several studies have showed that supplementation in participants with such low 25OHD concentrations results in substantial improvements of multiple outcomes, including fewer respiratory infections, reduced loss of bone mass over time, improved lung function of patients with asthma or chronic obstructive pulmonary disease, and reduced mortality.

In response to Bouillon and colleagues

- Their assertion that the majority of trials were in vitamin D replete participants (25OHD≥50 nmol/L) is wrong: 57% of all trials (and 64% of trials reporting falls or fracture as an outcome) had mean baseline 25OHD concentrations of less than 50 nmol/L(20ng/ml).
- Finally, their description of vitamin D as a ‘threshold nutrient’ is misleading and simplistic:
- vitamin D is a hormone and thresholds of 25OHD for deficiency and insufficiency remain contentious.

Adrian R Martineau(Lancet)

- The authors did prespecified subgroup analyses to test for interactions between the effects of vitamin D supplementation on fractures, falls, and bone mineral density for, among others, baseline 25OHD concentrations less than 25 nmol/L versus 25 nmol/L or more.
- However, participants were not assigned to subgroups according to their individual baseline 25OHD concentration; instead, classification was apparently done according to the mean (or sometimes the median) baseline 25OHD concentration in a given study population as a whole, or a subset there of.
- This approach introduces the potential for misclassification bias in the meta analysis
- Contamination of the sub-25 nmol/L subgroup with participants having higher baseline 25OHD concentrations could obscure protective effects of the intervention in the profoundly deficient subgroup.
- Conversely, for studies in which the mean or median 25OHD concentration at baseline was just above the 25 nmol/L threshold, a large proportion of deficient participants will have been misclassified as having 25OHD levels greater than or equal to 25 nmol/L for the purposes of the subgroup analysis

Don’t confuse vitamin D supplements with calcium AND vitamin D supplements

OCTOBER 19, 2018

IOF STATEMENT

In this response to the recent findings of the paper by Bolland et al., the International Osteoporosis Foundation urges patients not to stop taking prescribed supplements without discussing the implications with their doctors first.

- The widely reported message that vitamin D supplements are not needed, stemming from the recent publication by Bolland et al. in the Lancet Diabetes and Endocrinology, has caused much confusion and concern, particularly amongst older patients with osteoporosis. This statement sets out the response from the International Osteoporosis Foundation.
- In their systematic review, meta-analysis and trial sequential analysis, Bolland et al.(1) conclude that there the current evidence base indicates no benefits of vitamin D supplements for outcomes such as fracture and fall reduction, or improving bone mineral density.
- In fact this finding is not new, certainly for fractures and bone mineral density, and the majority of guidelines for the assessment and treatment of osteoporosis worldwide do not advocate the use of vitamin D supplements as sole agents for fracture prevention.(2-4) Indeed Bolland et al. published very similar results a few years earlier,(5-7) with the most recent publication a more comprehensive and up to date account of the evidential landscape.
- **Professor Cyrus Cooper, President of the International Osteoporosis Foundation** comments,
- Critically, this study relates to supplementation with vitamin D alone, and not with the combination of calcium and vitamin D, for which there is convincing evidence of modest benefits for fracture reduction, albeit not of great enough magnitude to warrant their use as sole treatments for osteoporosis. Calcium and vitamin D supplements are usually recommended for people who are being treated with bone active drugs such as bisphosphonates or denosumab, since in the majority of trials of these medications participants were supplemented in this way.”
- **Professor Serge Ferrari, Chair of the IOF Committee of Scientific Advisors said**,
- Dietary intakes of calcium and vitamin D vary greatly between individuals and between populations, as does the ability to make new vitamin D through the action of sunshine on the skin. Where individuals have insufficient calcium intake, or are deficient in vitamin D, particularly when these low intakes are associated with symptoms or the presence of osteoporosis, supplementation with vitamin D and/or calcium is usually the required therapeutic approach.”
- **Professor Nicholas Harvey, Vice-Chair of the IOF Committee of Scientific Advisors added**,
- Although this recent study is consistent with many previous studies demonstrating the limited benefits of pure vitamin D supplementation, it does not address the use of calcium with vitamin D supplements, or of their use with treatments for osteoporosis - it is important for patients not to stop any prescribed supplements without discussing the implications with their doctor first.”
- References

- 1. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. The lancet Diabetes & endocrinology. 2018.
- 2. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Archives of osteoporosis. 2017;12(1):43.
- 3. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24(1):23-57.
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Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis

Patricia Barrionuevo,[1,2] Ekta Kapoor,[1,3] Noor Asi,[1] Fares Alahdab,[1] Khaled Mohammed,[1] Khalid Benkhadra,[4] Jehad Almasri,[1] Wigdan Farah,[1] Maria Sarigianni,[1] Kalpana Muthusamy,[1] Alaa Al Nofal,[5] Qusay Haydour,[1] Zhen Wang,[1] and Mohammad Hassan Murad[1]

J Clin Endocrinol Metab, May 2019, 104(5):1623–1630

Table 1. Network Meta-Analysis of Hip Fractures

Calcium	Vitamin D + Calcium	Vitamin D
1.39 (0.90–2.15)	0.81 (0.71–0.93)[a]	0.69 (0.43–1.09)

Table 2. Network Meta-Analysis of Nonvertebral Fractures

Calcium	Vitamin D	Vitamin D + Calcium
0.77 (0.56–1.05)	0.44 (0.23–0.85)[a]	0.93 (0.85–1.01)

calcium comparing with placebo showed no significant effect on reduction in the risk of vertebral or hip fractures, but a 37% reduction in the risk of nonvertebral fractures (HR, 0.63; 95% CI,0.45 to 0.90).

The meta-analysis that compared the combination of calcium and vitamin D with placebo showed no significant effect on reduction in the risk of vertebral fractures,
but a 19% reduction in the risk of hip fractures (HR, 0.81; 95% CI,0.71 to 0.93),
and a 5% reduction in the risk of nonvertebral fractures (HR, 0.95; 95% CI, 0.90 to1.00).

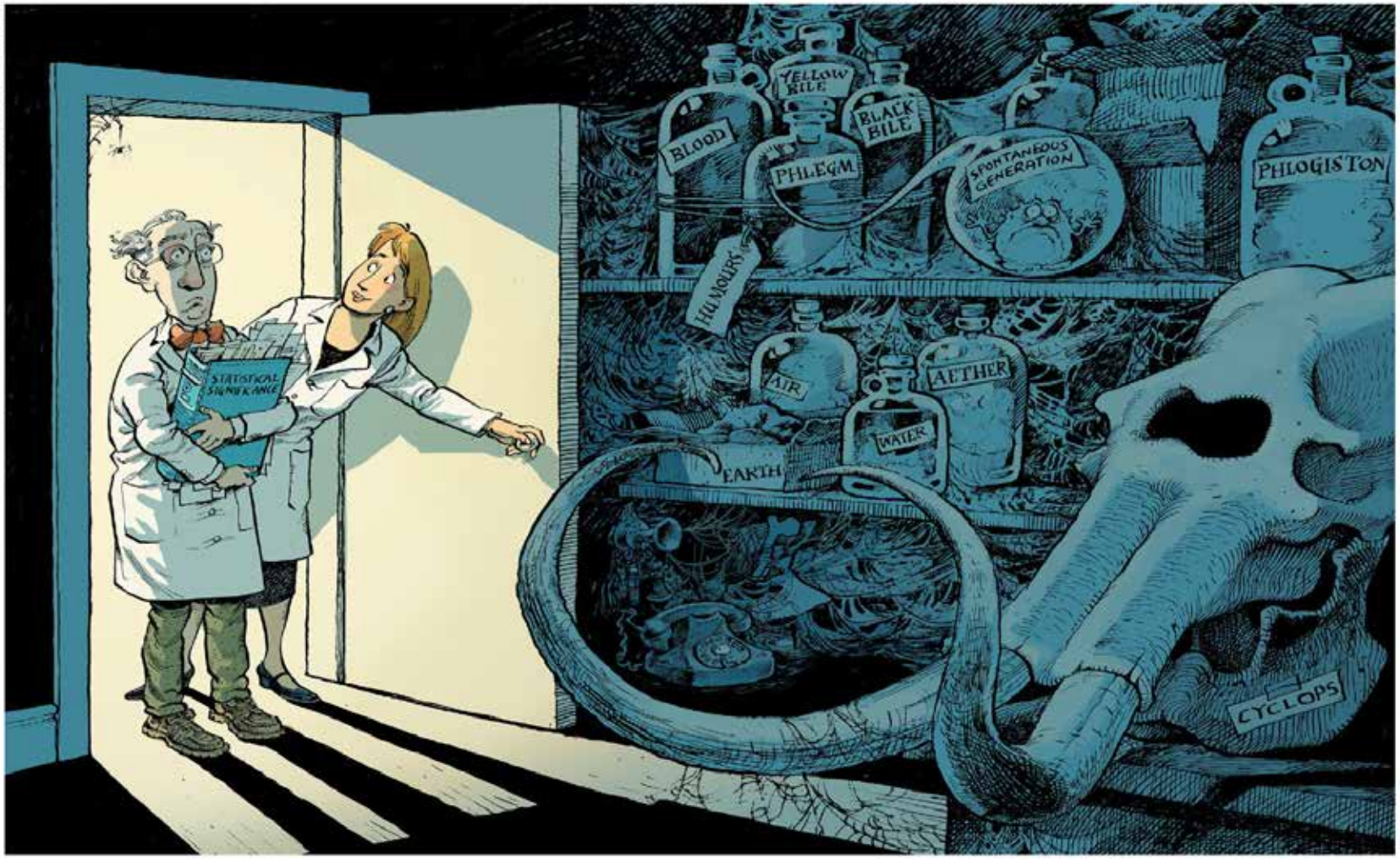


ILLUSTRATION BY DAVID PARKINS

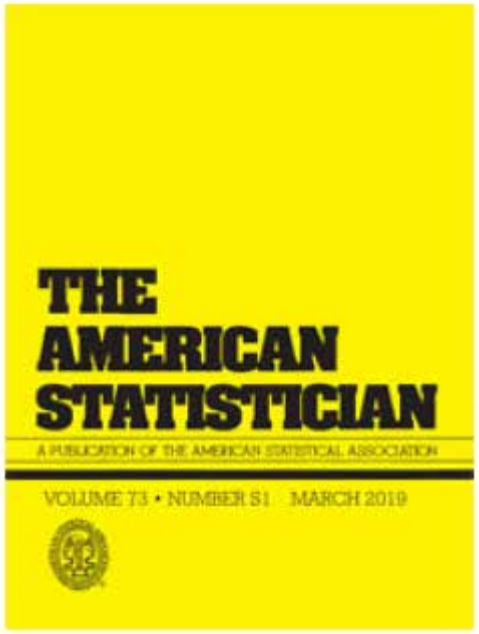
Retire statistical significance

Valentin Amrhein, Sander Greenland, Blake McShane and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.

VIEWPOINT

John P. A. Ioannidis, MD, DSc
Stanford Prevention Research Center, Meta-Research Innovation Center at Stanford, Departments of Medicine, Health Research and Policy, Biomedical Data Science, and Statistics, Stanford University, Stanford, California.

The Proposal to Lower *P* Value Thresholds to .005



Moving to a World Beyond "$p < 0.05$"

Ronald L. Wasserstein, Allen L. Schirm & Nicole A. Lazar

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

This article was published on November 10, 2018, at NEJM.org.

We conducted a nationwide, randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D3 (cholecalciferol) at a dose of 2000 IU per day and marine n−3 (also called omega-3) fatty acids at a dose of 1 g per day for the prevention of cancer and cardiovascular disease among men 50 years of age or older and women 55 years of age or older in the United States.

Primary end points were invasive cancer of any type and major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes).

Secondary end points included site-specific cancers, death from cancer, and additional cardiovascular events.

This article reports the results of the comparison of vitamin D with placebo.

CONCLUSIONS

Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo.

COMMENTS(1)

- This study had numerous strengths: it was placebo controlled,
- It included an impressive 25 871 participants,
- follow-up was 5·3 years,
- the dose (2000 IU per day) was sufficient to increase circulating 25-hydroxyvitamin D (25[OH]D) by about 30 nmol/L, and
- Conclusions were based on hard clinical outcomes.
- Notably, the average baseline 25(OH)D level of 77 nmol/L(30,8ng/ml) was comfortably within what is considered to be normal, and only 13% of participants had levels below 50 nmol/L, although there was no clear pattern to suggest benefits might have occurred in such participants. Showing any convincing effect on cancer might require longer follow-up than 5 years—as such, the VITAL investigators are continuing follow-up for a few more years.
- Results related to fracture are awaited.
- Whether these results might have been different in a trial limited to participants with low vitamin D levels is hard to say, but that approach would have rendered the trial hugely more expensive and very challenging to recruit.

COMMENTS(2)

- The Vitamin D Assessment Study (VIDA) was a 3-year, randomized, placebo controlled trial in New Zealand that involved 5110 persons who receive supplementation with high dose (100,000 IU) vitamin D monthly.
- In that trial, there was no effect of vitamin D supplementation on the incidence of major cardiovascular events. Similarly in a post hoc analysis from VIDA, the supplemental use of vitamin D had no effect on cancer outcomes.
- VITAL enrolled 25,871 men and women and followed them for a median of 5.3 years. Adherence rates in the trial averaged 80% for both supplements and placebos. Manson et al. found no effect of vitamin D supplementation on a primary end point of invasive cancer of any type or on the secondary end points of site-specific cancers or death from cancer. Other aspects of this trial are noteworthy.
- First, the number of participants and the substantial proportion of black participants make this cohort a nationally representative sample. In that vein, the results of this trial should be directly generalizable to most patients.
- Second, although the median serum 25-hydroxyvitamin D level at baseline was 30.8 ng per milliliter, approximately 1 in 13 participants had a serum 25-hydroxyvitamin D level of less than 20 ng per milliliter at baseline. Even in that subgroup, vitamin D supplementation had no effect on the number of cases of invasive cancer of any type.

COMMENTS(3)

- A post hoc analysis of the rate of death from cancer suggested a possible benefit with respect to the rate of total deaths from cancer after exclusion of early follow- up data, based on an unadjusted 95% confidence interval that does not include 1.
- the medical literature is replete with exciting secondary end points that have failed when they were subsequently formally tested as primary end points in adequately powered randomized trials.
- **Adverse Events** There were no significant differences between the two groups with respect to incident diagnoses of hypercalcemia, kidney stones, or gastrointestinal symptoms.

Clinical Trial

25-Hydroxyvitamin D Threshold for the Effects of Vitamin D Supplements on Bone Density Secondary Analysis of a Randomized Controlled Trial†

Helen M Macdonald, Ian R Reid, Gregory D Gamble, William D Fraser, Jonathan C Tang, Adrian D Wood

JBMR April 2018

- Significant treatment effects (1000UI/d) were apparent at both **the spine and hip** in those with baseline 25-hydroxyvitamin D ≤30 nmol/L,(12ng/ml) but no significant effects were apparent in those with baseline 25-hydroxyvitamin D above this level.
- There was evidence of a similar threshold for effects on parathyroid hormone, but no groups showed changes in bone turnover markers during the study.

Vitamin D Toxicity–A Clinical Perspective

Ewa Marcinowska-Suchowierska[1], Małgorzata Kupisz-Urbańska[1], Jacek Łukaszkiewicz[2], Paweł Płudowski[3] and Glenville Jones[4]*

- **Acute toxicity** would be caused by doses of vitamin D probably in excess of 10,000 IU/day, which result in serum 25(OH)D concentrations >150 ng/ml (>375nmol/l). That level is clearly more than the IOM-recommended UL of 4,000 IU/day,is characterized by hypercalciuria, hypercalcemia, elevated 25(OH)D >150 ng/ml (>375 nmol/l), and usually normal or slightly increased 1,25(OH)2D concentration.
- **Potential chronic toxicity** would result from administration of doses above 4,000 IU/day for extended periods, possibly for years, that cause serum 25(OH)D concentrations in the 50–150 ng/ml (125–375 nmol/l) range

Review

A review of the growing risk of vitamin D toxicity from inappropriate practice

PN Taylor[1] and JS Davies[2]

Br J Clin Pharmacol. 2018 Jun;84(6):1121-1127

Table 2: Reports of vitamin D toxicity due to errors in formulation of vitamin D

Author, year (reference)	Country	Stated dose	Actual dose received	Number of patients affected
Koutkia et al, 2001 (27)	US	2000iu	156,000-2.6M IU/d	1 adult
Klontz et al, 2007 (28)	US	400IU	188,000	1 adult + 3 children
Kaptein et al, 2010 (34)	Netherlands	150IU	15,000-150,000 IU	2 adults
Lowe et al, 2011 (35)	Dominican Republic	600,000IU/5ml	900k-1M IU	9 adults
Araki et al, 2011 (21)	US	1600IU	186,000IU	2 adults
Granado-Lorenzio et al, 2012 (41)	Ecuador	Unstated Vial/d – 4 wks	600,000IU/vial	1 adult
Kara et al, 2013 (31)	Turkey	2000IU/5ml	800,000IU	7 children
Bell et al, 2013 (42)	Australia	300IU/d	300,000IU	1 adult
Anik et al, 2013 (32)	Turkey	10IU/ml	Unknown	3 children
Benemei et al, 2013 (29)	Italy	600IU	52,800IU	3 adults
Marins et al, 2014 (43)	Brazil	2000/d	4M IU/d	1 adult
Ketha et al, 2015 (30)	US	2000IU/drop	6000IU/drop	1 child
Zigenhorn et al, 2016 (37)	Netherlands		78x stated dose	1 adult
Guerra et al, 2016 (36)	Brazil	2000IU	unknown	1 adult

- An exclusively breastfed infant required emergency admission. The mother was on a vitamin D prescription of 1 ml (400 IU per 1ml daily), however the vitamin D supplement purchased online was 400 IU per drop resulting in a 30 fold higher dose than intended (12,000 IU a day), with excess vitamin D being present in her breast milk.
- Toxic vitamin D levels can also arise from misuse and inappropriate administration. A 19 year old male was admitted with acute kidney injury and hypercalcemia with a vitamin D level of 150ng/ml. He was using a parenteral formulation of vitamins A, D and E restricted for veterinary use containing 20,000,000 IU of vitamin A; 5,000,000 IU of vitamin D3; and 6,800 IU of vitamin E per 100 mL. He was using the preparation as a “filler” to enhance his muscle definition rather than for any nutritional benefit.

Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society

(Dedicated to the memory of Prof. Steven Boonen and Prof. Silvano Adami)

Paul Lips[1], Kevin D Cashman[2], Christel Lamberg-Allardt[3], Heike Annette Bischoff-Ferrari[4], Barbara Obermayer-Pietsch[5], Maria Luisa Bianchi[6], Jan Stepan[7], Ghada El-Hajj Fuleihan[8] and Roger Bouillon[9] on behalf of the Working Group on Vitamin D of the European Calcified Tissue Society

Conclusion

In order to compare vitamin D status between different countries and to get a reliable estimate of the prevalence of vitamin D deficiency, standardized 25(OH)D assays should be used in population-based surveys. This should include all ongoing studies and whenever possible, also representative samples of older major published surveys and trials.

The prevalence of a low serum 25(OH)D concentration (<50 nmol/L) is high, that is more than 50% during winter, in many European and Middle East countries. Even more worrying is the presence of severe vitamin D deficiency (below 25/30 nmol/L) in specific risk groups. The spectrum ranges from adequate vitamin D status in the Nordic countries to severe deficiency in the Middle East. Vitamin D status usually is poor in non-Western immigrants.

According to current evidence, the desirable serum 25(OH)D concentration is set at 50 nmol/L or higher. While most experts agree on this concentration, it is uncertain whether higher concentrations provide additional benefit. When the results of ongoing randomized clinical trials are available, the required serum 25(OH)D concentration may have to be modified, depending on the outcome. It will require a tremendous effort to improve vitamin D status in Europe and the Middle East and reduce the percentage of the population with a serum 25(OH)D concentration below 50 nmol/L. This may translate into targeted approaches such as prudent sun exposure, adequate nutrition, food fortification policy and vitamin D supplementation for high-risk groups. Elimination of nutritional rickets should receive the highest priority. As there is near universal agreement that serum 25(OH)D concentrations should exceed 25/30 nmol/L; at whatever age, strategies to eliminate this deficiency, particularly in children, pregnant women, older persons and immigrants, should receive the highest priority by public health authorities and health care providers

European Journal of Endocrinology(2019) 180, P23–P54

Vitamin D Assays and the Definition of Hypovitaminosis D: Results from the 1st International Conference on Controversies in Vitamin D

Running Title: Vitamin D Assays and Defining Hypovitaminosis D

Christopher T. Sempos[1,13], Annemieke C. Heijboer[2], Daniel D. Bikle[3], Jens Bollerslev[4]; Roger Bouillon[5], Patsy M. Brannon[6], Hector F. DeLuca[7], Glenville Jones[8], Craig F. Munns[9], John P. Bilezikian[10], Andrea Giustina[11], Neil Binkley[12].

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- Serum 25-hydroxyvitamin D (25(OH)D) concentration, i.e., the sum of 25(OH)D3 and 25(OH)D2, remains the critical measurement for defining vitamin D status. Assay variation for 25(OH)D has contributed to the current chaos surrounding efforts to define hypovitaminosis D.
- An essential requirement to develop consensus on vitamin D status is that measurement of 25(OH)D and, in the future, other potential vitamin D biomarkers, e.g., 1α,25(OH)2D3, 3-epi-25(OH)D, 24,25(OH)2D3, vitamin D binding protein (DBP), free/bioavailable 25(OH)D and parathyroid hormone be standardized/harmonized, to allow pooling of research data.
- Vitamin D Standardization Program (VDSP) tools are described and recommended for standardizing 25(OH)D measurement in research. In the future, similar methodology, based on National Institute for Standards and Technology (NIST) Standard Reference Materials, must be developed for other candidate markers of vitamin D status. Failure to standardize/harmonize vitamin D metabolite measurements is destined to promulgate continued chaos.
- At this time, 25(OH)D values below 12 ng/mL (30 nmol/L) should be considered to be associated with an increased risk of rickets/osteomalacia while 25(OH)D concentrations between 20-50 ng/mL (50-125 nmol/L) appear to be safe and sufficient in the general population for skeletal health. In an effort to bridge knowledge gaps in defining hypovitaminosis D, an international study on rickets as a multifactorial disease is proposed.

Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults

US Preventive Services Task Force Recommendation Statement

JAMA. 2018;319(15):1592-1599. doi:10.1001/jama.2018.3185

Figure 2. Clinical Summary: Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults

Population	Men and premenopausal women	>400 IU of vitamin D and >1000 mg of calcium in postmenopausal women	≤400 IU of vitamin D and ≤1000 mg of calcium in postmenopausal women
Recommendation	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)	Do not recommend. Grade: D

D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Skeletal and extra-skeletal actions of vitamin D: Current evidence and outstanding questions

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- Vitamin D deficiency increases serum PTH but the majority of vitamin D deficient subjects do not have PTH concentrations above the normal range. This results in progressive bone loss, and when severe, also mineralization defects.
- Epidemiologic studies show that vitamin D deficiency is associated with lower BMD and fractures.
- These consequences can be avoided by modest doses of vitamin D and calcium supplements . RCTs have shown that vitamin D decreases the incidence of hip fractures and other non-vertebral fractures of about 15 %,
- The effect being greater in the 80+ and 70-80 years persons than in persons of 60-70 years,
- in the institutionalized than in community living elderly,
- when combined with calcium and
- When compliance is > 80 %.
- Vitamin D supplementation should be advised in all institutionalized and frail older persons.
- There is great unanimity that serum 25OHD concentrations below 30 nmol/l should be corrected.
- Serum 25OHD levels lower than 50 nmol/l should be avoided.
- This conclusion is also not contradicting the conclusion of United States Preventive Services Task Force dealing with a younger community dwelling population (mostly postmenopausal women) with a much better vitamin D status than the elderly or institutionalized subjects.

ΠΑΘΟΦΥΣΙΟΛΟΓΙΑ

- The skeletal effects of moderate vitamin D deficiency in adults or elderly subjects are mainly caused by an increase of the serum parathyroid hormone (PTH) concentration, leading to high bone turnover and associated cortical bone loss .
- In the MORE study, the groups with vitamin D deficiency (serum 25OHD<10ng/ml <25 nmol/l, n=297 and 25OHD 10-20ng/ml 25-50 nmol/l, n=1721) both show significantly higher serum PTH (4.8±2.2 and 4.1±1.8 pmol/l, respectively) compared to people with 25OHD>20ng/ml >50 nmol/l (n= 4,982, serum PTH 3.5 pmol/l).
- Both groups show a significant decrease of serum PTH after treatment with vitamin D (17% and 12% lower serum PTH, P<0.001), implicating that serum PTH was elevated on an individual level in most patients.
- Very similar observations were made in the bazedoxifene trial in more than 7000 participants .

VITAMIN D AND EXTRA-SKELETAL HEALTH: SUMMARY

- The vitamin D endocrine system regulates a very large number of genes in many cells and tissuesnot related to calcium homeostasis.
- This effect is seen early in the evolution of vertebrates and in mammals and humans. Thus, it is plausible that vitamin D has non-skeletal effects.
- A large set of observational data and some MR studies support this hypothesis.
- Intervention studies, however, have so far been inconsistent or generated “null effects”.
- The strongest data for possible extraskeletal effects of vitamin D so far deal with modest effects on muscle strength and falls, acute respiratory infections, and on mortality risks.
- Hopefully, a large number of ongoing (large scale) trials will generate clearer answers.

Table 5 Megatrials with multiple outcomes with expected results in the coming 5 years.

Consortium	Number of subjects	Study design	Dose	Outcome	Results	References
VIDA	5110	DB, two groups	100 000 IU/month	Fract, CVD, ARI	No effect on falls and fractures, CVD	Khaw *et al*. 2017 (298) Scragg *et al*. 2017 (242)
VITAL	28 875	Factorial design 2/2	2000 IU/day/fish oil/placebo	Cancer, CVD	No effect on CVD and cancer	Bassuk *et al*. 2016 (299) Manson *et al*. 2018 (243)
TIPS-3	5500	Factorial design 2/2/2	60 000 IU/month/polycaps/aspirin	CVD, fract, cancer	Jan 2019	NCT01646437*
FIND	18 000		3200 vs 1600 IU/day vs placebo	CVD, cancer	Dec 2019	NCT01463813*
DO-HEALTH	2152	Factorial design 2/2/2	2000 IU/omega-3/physical exercise	Fract, functional decline, blood pressure, cognitive decline, infection		NCT01745263*
D-HEALTH	25 000		60 000 IU/month	CVD, DM, cancer		Neale *et al*. 2016 (300)
VIDIKids	5400 children	DB, two groups	10 000 IU/week	Tuberculosis, astma, acute resp infection	2022	NCT02880982*

Results are expected between 2015 and 2020. Investigators: R Scragg, JE Manson, S Yusuf, TP Tuomainen, H Bischoff-Ferrari, R Neale, A Martineau.
*Clinical Trials Registry at clinicaltrials.gov. DB, double blind; ARi, acute respiratory infection.

According to the NIH ClinTrial register, about 3000 RCTs dealing with vitamin D are still ongoing so that we may hope that within the next decade the results of these studies will further clarify the possible beneficial effects of vitamin D

ΕΥΧΑΡΙΣΤΩ