



Πόσο ευρεία πρέπει να είναι η χορήγηση της βιταμίνης D Αντίλογος

Σπύρος Ν Νίκας

Ρευματολόγος

Ιωάννινα

Σύγκρουση συμφερόντων

ΚΑΜΙΑ, για τη σημερινή ομιλία

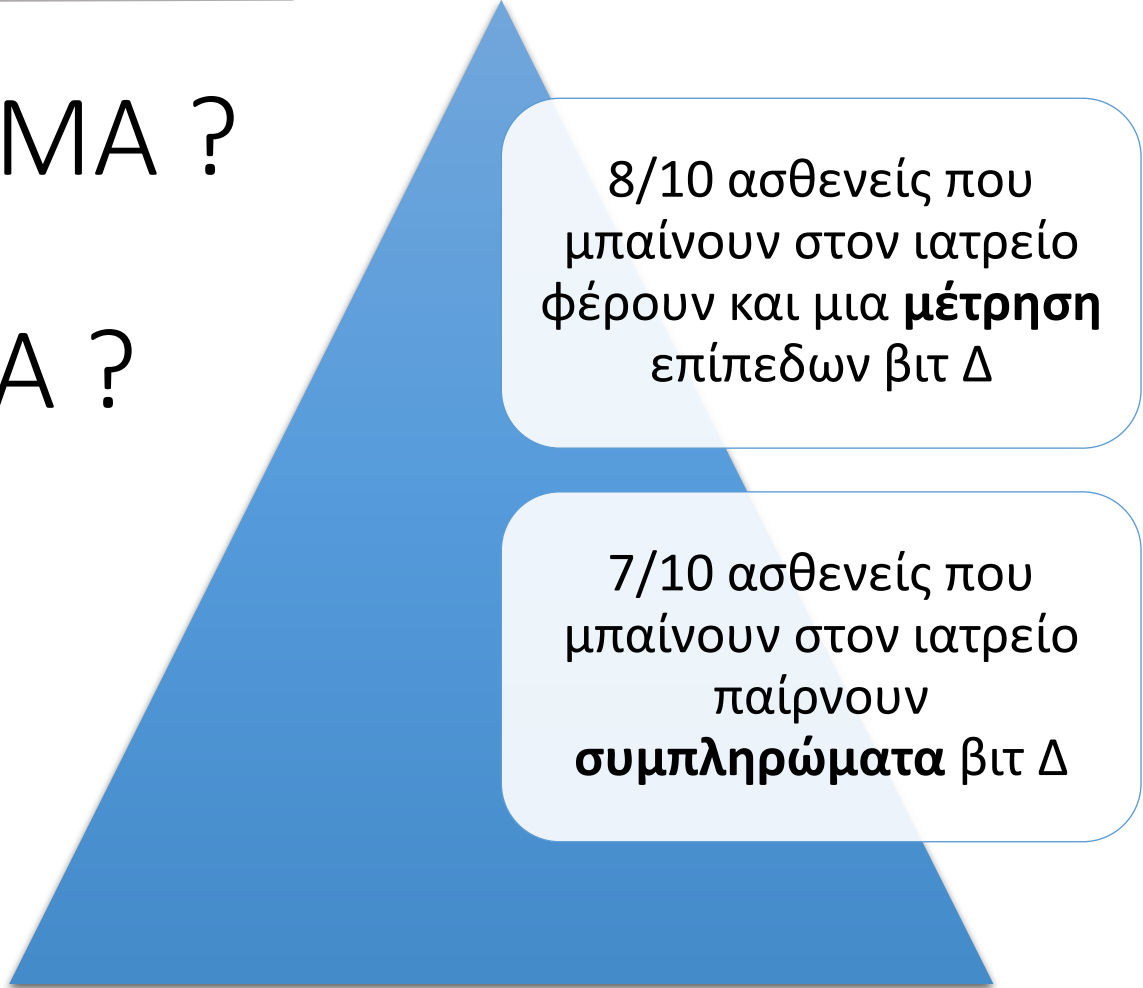
Θεματολογία

- Σε **ποιους** πρέπει να μετράμε
- Αξιοπιστία της **μεθόδου** προσδιορισμού
- **Όρια** της υποβιταμίνωσης και της αβιταμίνωσης
- Συμμετοχή της βιταμίνης D στην παθογένεια **εξωσκελετικών** νοσημάτων
- Σκοπιμότητα της εξωγενούς **χορήγησης**
- **Δόσεις** χορήγησης

ΤΟ ΠΡΟΒΛΗΜΑ

ΤΟ ΕΡΩΤΗΜΑ ?

ΠΑΝΔΗΜΙΑ ?



8/10 ασθενείς που
μπαίνουν στον ιατρείο
φέρουν και μια **μέτρηση**
επίπεδων βιτ Δ

7/10 ασθενείς που
μπαίνουν στον ιατρείο
παίρνουν
συμπληρώματα βιτ Δ

Τι θα συζητήσουμε ?

ΘΕΜΑΤΑ ΚΟΙΝΟΤΗΤΑΣ

ΔΕΝ ΘΑ ΑΣΧΟΛΗΘΟΥΜΕ :

(ειδικές καταστάσεις)

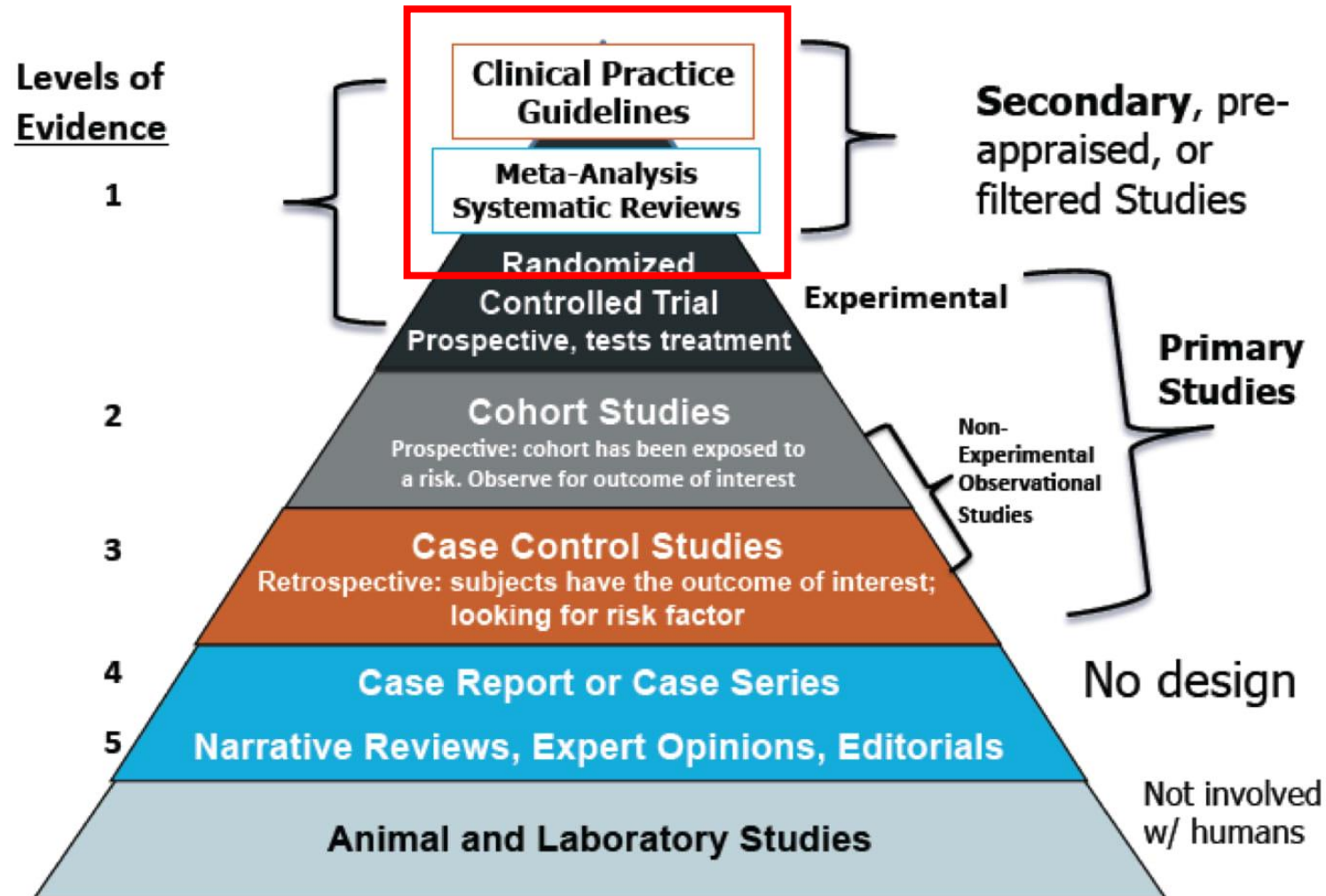
- Οστεοπόρωση
- Οστεομαλάκυνση
- Υπερ-παραθυροειδισμός κα
- Πειραματικά μοντέλα

Παραδοχές
“που πάω” ?



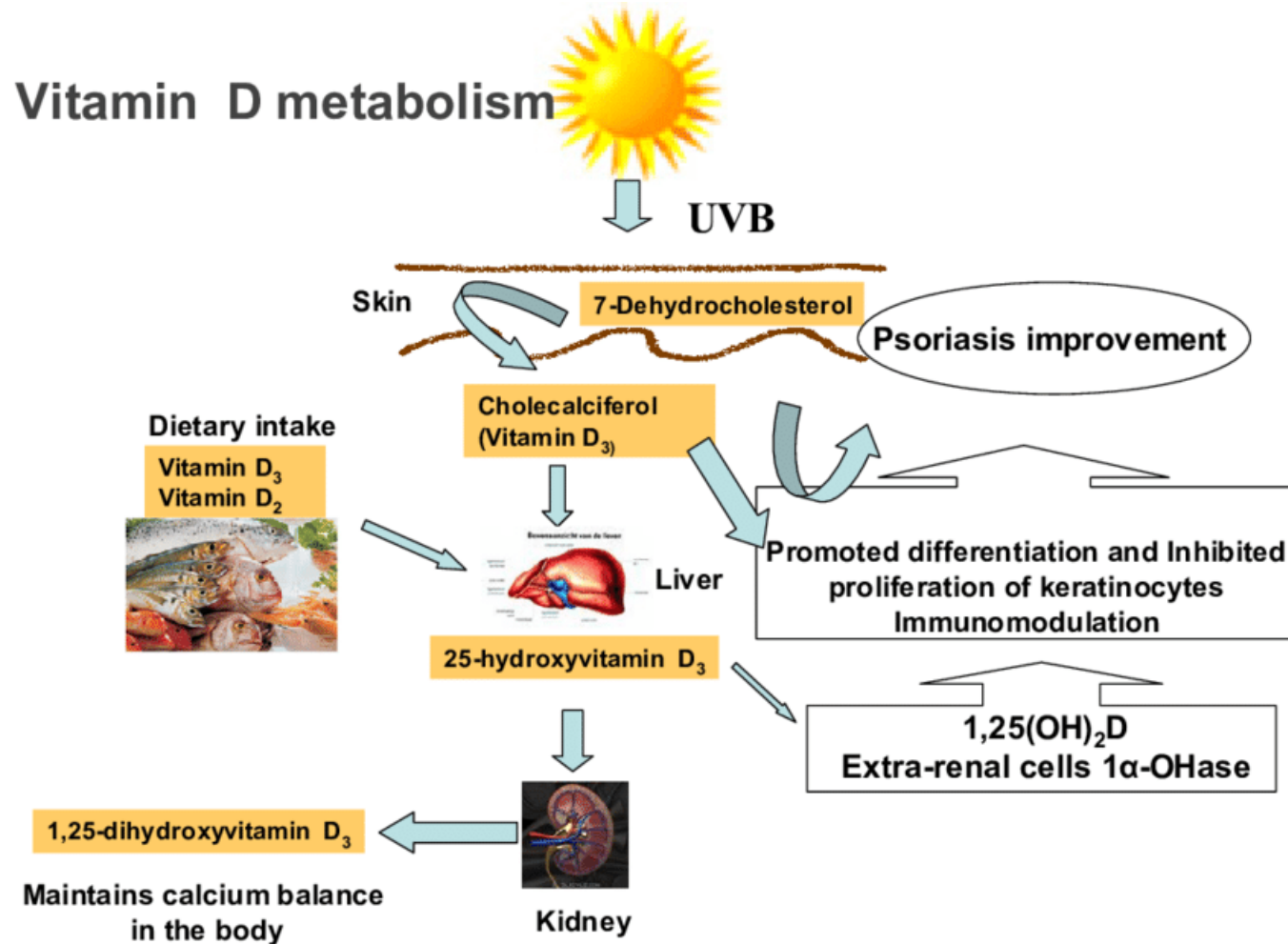
Παραδοχές

Evidence based medicine



Παραδοχές

Δεν έχω ιδέα τι είναι η βιτ Δ



Γιατί είμαι εδώ ? μια ιστορία “common sense”

2011: όλοι ζητούσαν σε
ΟΛΟΥΣ έλεγχο για βιτ Δ

D R I DIETARY REFERENCE INTAKES **Calcium Vitamin D**

Committee to Review Dietary Reference Intakes for Vitamin D and Calcium
Food and Nutrition Board
A. Catharine Ross, Christine L. Taylor, Ann L. Yaktine, and
Heather B. Del Valle, Editors

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

2012: Η Βιτ D
σχετίζεται με τα
ΠΑΝΤΑ (Ca, CVD,
αυτοανοσία κ)

2013: ΟΛΟΙ έδιναν σε
ΟΛΟΥΣ βιτ Δ

BMJ

BMJ 2014;348:g2035 doi: 10.1136/bmj.g2035 (Published 1 April 2014)

Vitamin D and multiple health outcomes: a review of systematic reviews and observational studies and randomised controlled trials

OPEN ACCESS

Evropi Theodoratou research fellow¹, Ioanna Tzoulaki lecturer²,
John P A Ioannidis professor^{3,4}

Vitamin D Deficiency — Is There Really a Pandemic?

JoAnn E. Manson, M.D., Dr.P.H., Patsy M. Brannon, Ph.D., R.D., Clifford J. Rosen, M.D., and Christine L. Taylor, Ph.D.

In recent years, numerous clinical research articles have concluded that large proportions of North American and global populations are “deficient” in vitamin D.¹⁻³ Most of the evidence cited focuses on one of two observations: that many people have serum concentrations of vitamin D (i.e., 25-hydroxyvitamin D

[25(OH)D]) below 20 ng per milliliter (50 nmol per liter), which the Institute of Medicine (IOM) estimated in 2011 was the appropriate level⁴; or that supplementation with 600 to 800 IU per day — the IOM Recommended Dietary Allowance (RDA) for adults — or more fails to achieve serum concentrations above 20 ng per milliliter in some study participants. Such conclusions, however, are based on misinterpretation and misapplication of the IOM reference values for vitamin D. Because such misunderstandings can have adverse implications for patient care, including unnecessary vitamin D screening and supplementation as well as escalating health care costs

N ENGL J MED 375:19 NEJM.ORG NOVEMBER 10, 2016

1817

Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials



OPEN ACCESS

Evropi Theodoratou *research fellow*¹, Ioanna Tzoulaki *lecturer*^{2,3}, Lina Zgaga *associate professor*⁴, John P A Ioannidis *professor*^{5,6}

- **107** systematic literature reviews
- **74** meta-analyses of **observational** studies of plasma vitamin D concentrations
- **87** meta-analyses of **RCTs** of vitamin D

Στατ. σημαντικότητα φάνηκε μόνο για το βάρος γέννησης νεογνού (επίπεδα βιτ Δ μητέρας)

Κάποια σχέση με

- δόντια νεογνού
- PTH στη ΧΝΑ

Conclusions Despite a few meta-analyses, highly consistent evidence does not exist for any outcomes, and other outcomes are probable.

Νεοπλασία, CVD, αυτοανοσία, λοιμώξεις, κα

Vitamin D Deficiency — Is There Really a Pandemic?

JoAnn E. Manson, M.D., Dr.P.H., Patsy M. Brannon, Ph.D., R.D., Clifford J. Rosen, M.D., and Christine L. Taylor, Ph.D.

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THE TOC

ΥΓΕΙΑ

Έλλειψη βιταμίνης D: Τα συμπτώματα που όλοι πρέπει να γνωρίζουν

Περίπου το ένα τρίτο του πληθυσμού έχει ανεπάρκεια στη βιταμίνη D ή αλλιώς στη "βιταμίνη της ηλιοφάνειας".

THE TOC

ΓΡΑΦΕΙ: ΕΛΕΝΗ ΔΑΣΚΑΛΑΚΗ
PUBLISHED 30 ΙΟΥΝ. 21 (08:42)



Intake of Vitamin D

: the **RDA*** functions (20ng) as a “cut point” (*appropriate level*)=> must have a serum 25(OH)D level above 20 ng /milliliter to

RDA, reflects the estimated requirement for people at the **highest** end of the distribution (2,5%)

The **reality** is that the **majority** (about 97.5%) of the population has a requirement of 20 ng per milliliter **or less**

the goal of achieving population levels above the **EAR** (16ng), **not the RDA**

The EAR reflects the **most likely requirement** for the population

=> < **6%** are **deficient** in vitamin D[serum 25(OH)D levels (<12.5 ng /ml)

Many studies establish “inadequacy” using the **RDA**, though it **is actually at the upper** end of the spectrum of human need

*Institute of Medicine (IOM) Dietary reference intakes: calcium and vitamin D.

Υπάρχει και ένα 3^ο paper

US Preventive Services Task Force | Recommendation Statement

FREE

April 13, 2021

Screening for Vitamin D Deficiency in Adults

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

Article Information

JAMA. 2021;325(14):1436-1442. doi:10.1001/jama.2021.3069

Table. Summary of USPSTF Rationale

Rationale	Assessment
Detection	<ul style="list-style-type: none">• Vitamin D requirements may vary by individual, and there is no one 25(OH)D level that defines deficiency for all individuals.• Total 25(OH)D levels are currently considered the best marker of vitamin D status; however, levels are difficult to measure accurately.• Evidence suggests that <u>results vary by testing method and between laboratories using the same testing methods.</u>
Benefits of early detection and intervention and treatment	<ul style="list-style-type: none">• No direct evidence on the benefits of <u>screening for vitamin D deficiency.</u>• <u>Adequate evidence that treatment of asymptomatic vitamin D deficiency has no benefit on mortality, risk for fractures in persons selected solely on the basis of low vitamin D levels (as opposed to clinical risks such as low bone density), or incidence of type 2 diabetes mellitus.</u>• <u>Inadequate evidence on the benefit of treatment of asymptomatic vitamin D deficiency on other outcomes, including falls, cancer, cardiovascular events, depression, infection, or physical functioning.</u>• Despite adequate evidence to conclude no benefit for a few health outcomes, evidence on the benefits of treatment of asymptomatic vitamin D deficiency in adults for other health outcomes remains inadequate. The overall evidence on the benefits of treatment of asymptomatic vitamin D deficiency in adults is inadequate.
Harms of early detection and intervention and treatment	<ul style="list-style-type: none">• No direct evidence on the harms of screening for vitamin D deficiency.• Adequate evidence that the harms of treatment of vitamin D deficiency are small to none.
USPSTF assessment	The overall evidence on the benefits of screening for vitamin D deficiency is lacking. Therefore, the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults cannot be determined.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; USPSTF, US Preventive Services Task Force.

Ειδικά για βιταμίνη



JAMA

16 Απριλίου · 🌐



Among asymptomatic, community-dwelling populations with low vitamin D levels, evidence suggests that treatment with vitamin D has no effect on mortality or the incidence of fractures, falls, depression, diabetes, CVD, cancer, or adverse events. Evidence is inconclusive about the effect of treatment on physical functioning and infection.
<https://ja.ma/3uQkv4T>

Key questions








- 1
 - a. Does screening for vitamin D deficiency improve health outcomes?
 - b. Does screening efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?
- 2 What are the harms of screening for vitamin D deficiency?
- 3
 - a. Does treatment of vitamin D deficiency with vitamin D improve health outcomes?
 - b. Does treatment efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?
- 4
 - a. What are the harms of treatment of vitamin D deficiency with vitamin D?
 - b. Do harms vary among patient subpopulations at higher risk for vitamin D deficiency (eg, persons residing in institutions, persons with obesity, persons with low levels of sun exposure, or older adults) or vary by race/ethnicity?



JAMANETWORK.COM

USPSTF Review: Screening for Vitamin D Deficiency in Adults

Μα και η ΕΕΜΜΟ συμφωνεί ...!




Θεραπευτικοί στόχοι 25(OH)D


- Γενικός Πληθυσμός: -ΔΕΝ απαιτείται μέτρηση στους υγιείς (υγιείς)
 - βέλτιστα ≥ 20 ng/ml
 - δυνητικά επιτρεπτό χωρίς θεραπεία με συμπληρώματα αλλά μόνο με οδηγίες >12 ng/ml*
- Ασθενείς με οστεοπόρωση: > 20 ng/ml - κατά περίπτωση >30 ng/ml
- Εύρος επιθυμητών τιμών: 20-50 ng/ml

ΧΡΕΙΑΖΕΤΑΙ ΛΟΙΠΟΝ ΘΕΡΑΠΕΙΑ ΜΕ ΣΥΜΠΛΗΡΩΜΑΤΑ ΤΟ 13 ng /ml ?


*Shah et al. JCEM 2017



Π. Μάκρας

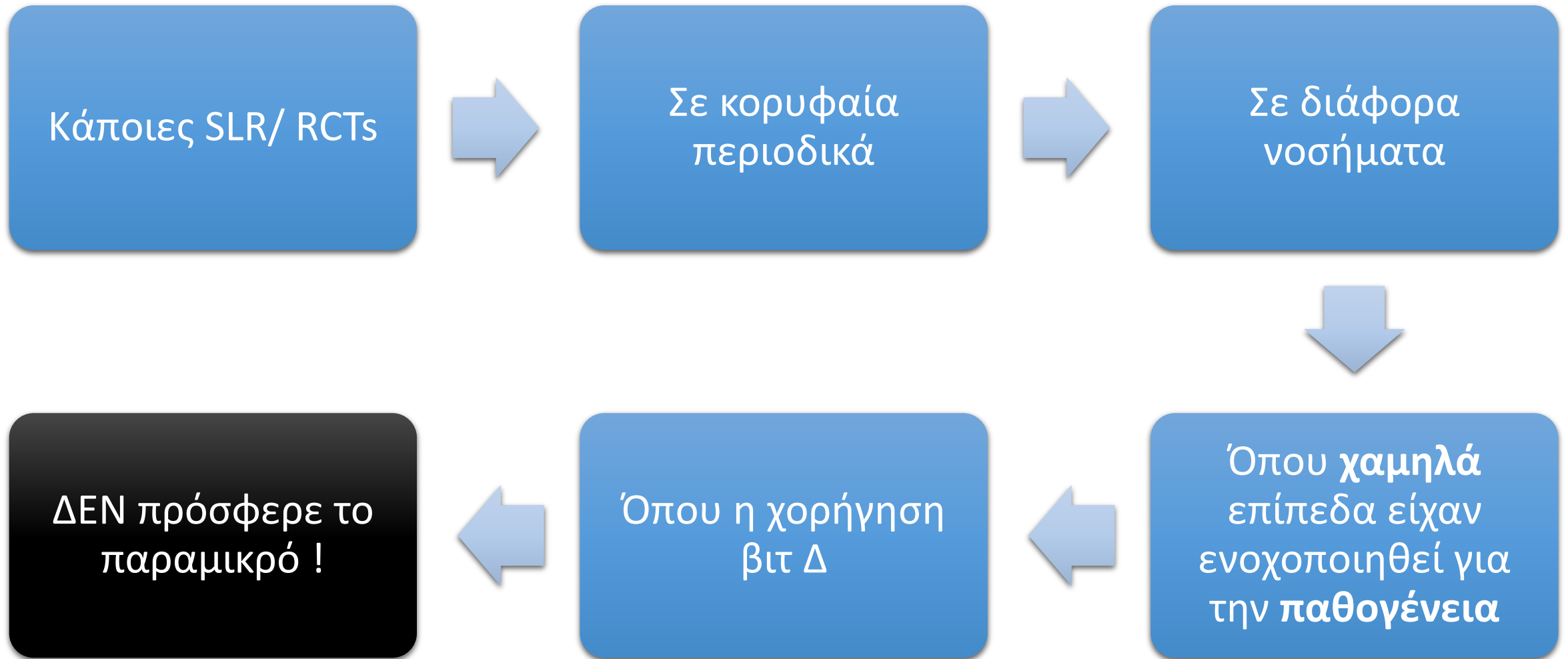


Σ. Τουρνης



Χ. Κοσμιδης

Η παρουσίαση θα μπορούσε να τελειώσει εδώ



THE LANCET

Diabetes & Endocrinology

ARTICLES | VOLUME 6, ISSUE 11, P847-858, NOVEMBER 01, 2018

Effects of systematic

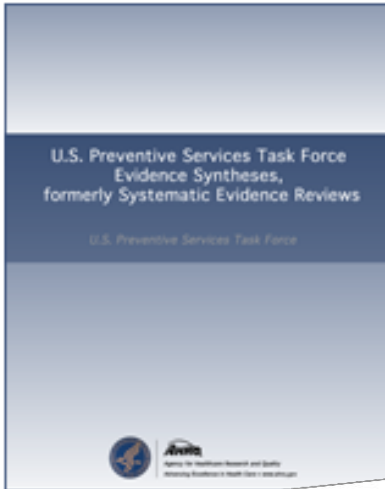
Mark J Bolland

Published: Octo

Interpretation

Our findings suggest that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. There were no differences between the effects of higher and lower doses of vitamin D. There is little justification to use vitamin D supplements to maintain or improve musculoskeletal health. This conclusion should be reflected in clinical guidelines.

- bone mineral density (n=41)



Screening for Vitamin D Deficiency in Adults: An Evidence Review for the U.S. Preventive Services Task Force

Evidence Synthesis, No. 201

Investigators: Leila C. Kahwati, MD, MPH, Erin LeBlanc, MD, MPH, Rachel Palmieri Weber, PhD, Kayla Giger, BS, Rachel Clark, BA, Kara Suvada, BS, Amy Guisinger, BS, and Meera Viswanathan, PhD.

Rockville, MD

Conclusions: No studies have evaluated the direct benefit or harms of screening for vitamin D deficiency. Among asymptomatic, community-dwelling populations with low vitamin D levels, the evidence suggests that treatment with vitamin D (with or without calcium) has no effect on mortality or the incidence of fractures, falls, depression, diabetes, cardiovascular disease, cancer, or adverse events. The evidence is inconclusive about the impact of treatment on physical functioning and infection.

Review

➤ Clin Rheumatol. 2017 May;36(5):1201-1208. doi: 10.1007/s10067-016-3205-1.

Epub 2016 Feb 9.

Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis

selection criteria. Three studies were included in the meta-analysis. We found **no effect** of vitamin D supplementation (standardised mean difference (SMD) 0.004; 95 % confidence interval (CI) -0.248 to 0.256) on pain in CNMP patients. Forest plot is used to present the results from meta-analysis. Contrary to a widespread clinical view, there is a moderate level of evidence that vitamin D supplementation is not helpful for treating CNMP patients.

ORIGINAL ARTICLE

Vitamin D Supplementation and Prevention of Type 2 Diabetes

Anastassios G. Pittas, M.D., Bess Dawson-Hughes, M.D., Patricia Sheehan, R.N., M.P.H., M.S., James H. Ware, Ph.D., William C. Knowler, M.D., Dr.P.H., Vanita R. Aroda, M.D., Irwin Brodsky, M.D., Lisa Ceglia, M.D., Chhavi Chadha, M.D., Ranee Chatterjee, M.D., M.P.H., Cyrus Desouza, M.B., B.S., et al., for the D2d Research Group*

CONCLUSIONS

Among persons at high risk for type 2 diabetes not selected for vitamin D insufficiency, vitamin D₃ supplementation at a dose of 4000 IU per day **did not result in a significantly lower risk of diabetes** than placebo. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; D2d ClinicalTrials.gov number, **NCT01942694**.)

August 25, 2020

Effect of Vitamin D₃ Supplementation on Severe Asthma Exacerbations in Children With Asthma and Low Vitamin D Levels

The VDKA Randomized Trial

Conclusions and Relevance Among children with persistent asthma and low vitamin D levels, vitamin D₃ supplementation, compared with placebo, did not significantly improve the time to a severe asthma exacerbation. The findings do not support the use of vitamin D₃ supplementation to prevent severe asthma exacerbations in this group of patients.

ORIGINAL ARTICLE

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.,
Heike Gibson, Ph.D., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedman, M.D.,
the VITAL Research Group

CONCLUSIONS

Supplementation with vitamin D **did not result** in a lower incidence of invasive cancer or cardiovascular events than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, [NCT01169259](#).)

June 19, 2019

Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83 000 Individuals in 21 Randomized Clinical Trials

A Meta-analysis

Conclusions and Relevance In this updated meta-analysis, vitamin D supplementation was not associated with reduced major adverse cardiovascular events, individual CVD end points (myocardial infarction, stroke, CVD mortality), or all-cause mortality. The findings suggest that vitamin D supplementation does not confer cardiovascular protection and is not indicated for this purpose.

ACR Open Rheumatology

Vol. 1, No. 5, July 2019, pp 318–326

DOI 10.1002/acr2.1042

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REVIEW

Therapeutic and Preventive Potential of Vitamin D Supplementation in Knee Osteoarthritis

Behzad Heidari 

Results. The results of a few studies showed a preventive potential for vitamin D in KOA, but most of the randomized clinical trials that assessed the therapeutic efficacy of vitamin D supplementation in KOA found no clear therapeutic effect, with the exception of one study that found a small but significant effect of vitamin D on pain and knee function. Nonetheless, the results of a few longitudinal studies as well as systematic reviews are promising and thus encourage further studies. Inconsistent results on the effect of vitamin D on KOA may be attributed to factors such as severity of KOA, baseline level of serum vitamin D, duration of treatment, and vitamin D dosages.

August 4, 2020

Effect of Long-term Vitamin D₃ Supplementation vs Placebo on Risk of Depression or Clinically Relevant Depressive Symptoms and on Change in Mood Scores

A Randomized Clinical Trial

Olivia I. Okereke, MD, SM^{1,2,3}; Charles F. Reynolds III, MD⁴

Conclusions and Relevance Among adults aged 50 years or older without clinically relevant depressive symptoms at baseline, treatment with vitamin D₃ compared with placebo **did not result** in a statistically significant difference in the incidence and recurrence of depression or clinically relevant depressive symptoms or for change in mood scores over a median follow-up of 5.3 years. These findings do not support the use of vitamin D₃ in adults to prevent depression.

News

February 17, 2021

Effect of a Single High Dose of Vitamin D₃ on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial

Igor H. Murai, PhD¹; Alan L. Fernandes, PhD¹; Lucas P. Sales, MSc¹; et al

» Author Affiliations | Article information

JAMA. 2021;325(11):1053-1060. doi:10.1001/jama.2020.26848

Respiratory infections, reviews

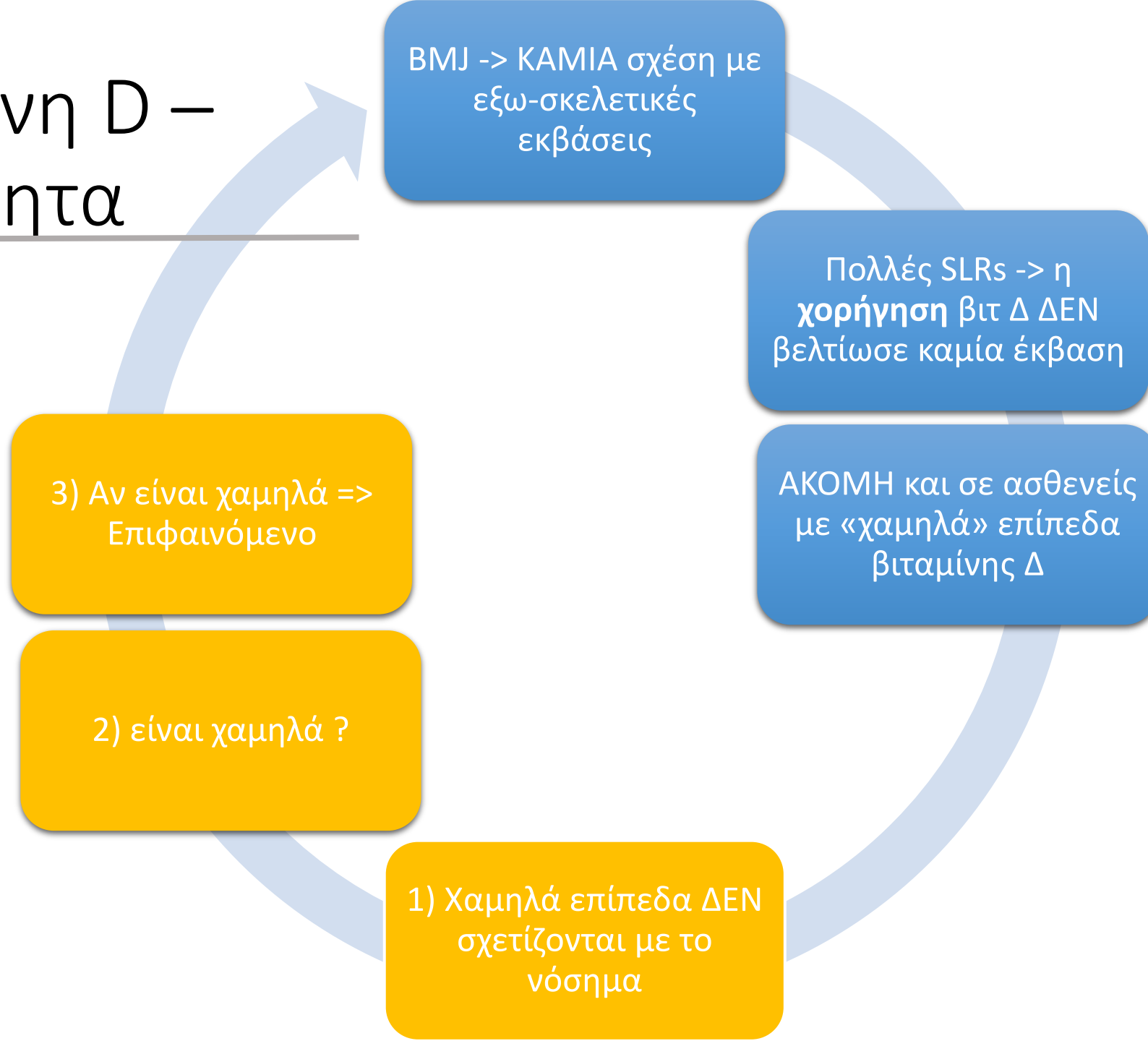
(2020)

Σύμφων
ΥΠΑΡΧΟ
μπορού

Μια τρίτη, ανεξάρτητη ανασκόπηση (από το Royal Society) έδειξε ότι η **ανεπάρκεια** βιτ D σχετίζεται με αυξημένο κίνδυνο **ιογενών** λοιμώξεων αναπνευστικού και **ΙΣΩΣ** με ευπάθεια στην COVID19

s in England) φαίνεται ότι **ΔΕΝ**
ή χορήγηση βιταμίνης D θα
των οποίων και της COVID19

Βιταμίνη D – κοινότητα



Το ερώτημα Γιατί για μια “κατάσταση” που:



Δεν έχει αξιόπιστη
μέθοδο **μέτρησης**

Δεν έχει ξεκάθαρα
όρια (φυσιολογικές
τιμές)

Δεν σχετίζεται με
εξω-σκελετικές
εκβάσεις

Δεν έχει **καμία**
δράση όταν δίνεις
συμπληρώματα σε
ΟΛΕΣ τις πιθανές
εκβάσεις

ΕΧΟΥΜΕ ΓΕΜΙΣΕΙ
ΤΟΝ **ΟΛΟ** ΤΟΝ
ΚΟΣΜΟ ΜΕ
ΕΞΕΤΑΣΕΙΣ -> ΑΣΘΕΝΗ
-> ΘΕΡΑΠΕΙΑ



no one serum vitamin D level cutpoint defines deficiency, and no consensus exists regarding the precise serum levels of vitamin D that represent optimal health or sufficiency.

According to the **National Academy of Medicine**, an estimated 97.5% of the population will have their vitamin D needs met at a serum level of 20 ng/mL (49.9 nmol/L) and risk for **deficiency**, relative to bone health, begins to occur at levels **less than 12 to 20 ng/mL (29.9-49.9 nmol/L)**

Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53-58. doi:10.1210/jc.2010-2704

Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press; 2011.

Low **dietary** vitamin D intake may be associated with lower 25(OH)D levels.⁷ Little or no UV B **exposure** (eg, because of winter season, *high latitude, or sun avoidance*) and **older age** are also associated with an increased risk for low vitamin D levels. **Obesity** is associated with lower 25(OH)D levels

The prevalence of vitamin D deficiency varies based on how deficiency is defined. According to data from the 2011 to 2014 National Health and Nutrition Examination Survey, which used the **liquid chromatography–tandem** mass spectrometry (LC-MS/MS) assay to measure 25(OH)D levels,

- **5% of the population 1 year or older had very low 25(OH)D levels (<12 ng/mL) and**
- **18% had levels between 12 and 19 ng/mL**

LC-MS/MS is considered the reference assay. However, LC-MS/MS is a complicated process and is subject to **variation and error**, including interference from other chemical compounds

Herrick KA, Storandt RJ, Afful J, et al. Vitamin D status in the United States, 2011-2014. Am J Clin Nutr. 2019;110(1):150-157. doi:10.1093/ajcn/nqz037

Screening may misclassify persons with a vitamin D deficiency because of the uncertainty about the cutoff for defining deficiency and the variability of available testing assays. Misclassification may result in overdiagnosis

A rare but potential harm of treatment with **vitamin D is toxicity**, which is characterized by marked hypercalcemia as well as hyperphosphatemia and hypercalciuria. However, the 25(OH)D level associated with toxicity (**typically >150** ng/mL)²⁰

a more than 80-fold increase in Medicare reimbursement volumes for vitamin D testing from 2000 to 2010

Shahangian S, Alspach TD, Astles JR, Yesupriya A, Dettwyler WK. Trends in laboratory test volumes for Medicare Part B reimbursements, 2000-2010. Arch Pathol Lab Med. 2014;138(2):189-203.
doi:10.5858/arpa.2013-0149-OA

Eight RCTs and 1 nested case-control study reported **on all-cause mortality** in community-dwelling adults. Study duration ranged from 16 weeks to 7 years. In a pooled analysis of the 8 trials (n = 2006), there was **no difference** in all-cause mortality in persons randomized to vitamin D treatment compared with controls (relative risk [RR], 1.13 [95% CI, 0.39-3.28])

Kahwati LC, LeBlanc E, Palmieri Weber R, et al. Screening for vitamin D deficiency in adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. Published April 13, 2021. doi:10.1001/jama.2020.26498

Six RCTs reported on fracture outcomes in community-dwelling adults. Study duration ranged from 12 weeks to 7 years. A pooled analysis of the **6 trials** (n = 2186) found no difference in the **incidence of fractures among** those randomized to vitamin D treatment compared with placebo (RR, 0.84 [95% CI, 0.58-1.21])

Kahwati LC, LeBlanc E, Weber RP, et al. Screening for Vitamin D Deficiency in Adults: An Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 201. Agency for Healthcare Research and Quality; 2021. AHRQ publication 20-05270-EF-1.

No organization recommends population-based screening

- for vitamin D deficiency, and the American Society for Clinical Pathology recommends against it.⁴⁷ The American Academy of Family Physicians supports the USPSTF 2014 recommendation, which states that there is insufficient evidence to recommend screening the general population for vitamin D deficiency.⁴⁸ The Endocrine Society⁴⁹ and the American Association of Clinical Endocrinologists⁵⁰ recommend screening for vitamin D deficiency in individuals **at risk**. The Endocrine Society does not recommend population screening for vitamin D deficiency in individuals not at risk.
- that many people have serum concentrations of vitamin D (i.e., 25-hydroxyvitamin D) below 20 ng per milliliter (50 nmol per liter), which the Institute of Medicine (IOM) estimated in 2011 was the appropriate level. Such conclusions, however, are based on misinterpretation and misapplication of the IOM reference values
- Institute of Medicine. Dietary reference intakes: calcium and vitamin D. Washington, DC: National Academies Press, 2011.

No organization recommends population-based screening

- There is a high prevalence of vitamin D **insufficiency** ($25(\text{OH})\text{D} < 50 \text{ nmol/l}$ (i.e., **20 ng/mL**)) or **deficiency** ($25(\text{OH})\text{D} < 25 \text{ nmol/l}$ (i.e., **10 ng/mL**)) in patients with fragility fractures and especially in those with a hip fracture.