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PRACTICE

UNCERTAINTIES

Should adults take vitamin D supplements to prevent disease?

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There are > 200 meta-analyses which have found effectivenss /is.gd/MetaD

I believe the taks force did NOT recommend, rather than recommend against

The US Preventive Services Task Force recommends against vitamin D and calcium supplementation for fracture prevention in otherwise healthy postmenopausal women.[1] However, despite high quality systematic reviews reporting ineffectiveness, many guideline groups continue to recommend vitamin D supplementation (with or without calcium) for fall or fracture prevention. Recently Public Health England recommended that everyone needs vitamin D equivalent to an average daily intake of 10 µg (400 IU) to protect bone and muscle health,[2] and more than 30-50% of older people in some Western countries take vitamin D supplements.[3 4] The role of vitamin D supplementation in individuals not at high risk of osteomalacia (box 1) has been extensively investigated in recent years, but some uncertainties remain.

26 of the meta-analyses for just falls/fractures

Since severe vitamin D deficiency causes osteomalacia (box 1), it is reasonable to ask whether less marked reductions in 25-hydroxyvitamin D are associated with musculoskeletal outcomes such as falls and fractures, or surrogate markers such as bone density, muscle function, and parathyroid hormone. Numerous observational studies have shown that low vitamin D status is associated with these musculoskeletal outcomes. These studies must be treated cautiously because observational studies are subject to confounding, and low vitamin D status might be a marker of poor health or lifestyle rather than a causal factor.

Based on these associations, the next step is to ask whether prescribing vitamin D to increase 25-hydroxyvitamin D levels prevents or modifies these outcomes. Although clinical trials show that vitamin D supplementation can lower parathyroid hormone, it is unclear whether this is a valid surrogate for clinical outcomes. Therefore, the effects of vitamin D supplementation must be determined from randomised controlled trials (RCTs) with "hard" clinical outcomes. A large number of RCTs and meta-analyses with clinical outcomes have been done.

Observational and preclinical studies have also associated low vitamin D status with a wide variety of non-skeletal adverse clinical outcomes (box 2)[6 7] that are not recognised features of osteomalacia. Trial data and some meta-analyses are now available to understand whether prescribing vitamin D to increase 25-hydroxyvitamin D makes a difference for such non-musculoskeletal outcomes.

What is the evidence of uncertainty?

Musculoskeletal outcomes

Vitamin D alone

Failed to mention: >15 of the meta DID find a benefit

Over 50 meta-analyses of vitamin D supplementation and falls or fractures have been published; some report small beneficial effects but others none. These results might seem inconsistent, but the differences are largely explained by differences in methodology. When all available RCTs are included, and all participants from all the studies are analysed by intention-to-treat (rather than "per protocol" or "completers" analyses), there is no consistent evidence that vitamin D supplementation or raising 25-hydroxyvitamin D levels improves musculoskeletal outcomes.[8-10] In such systematic reviews, vitamin D supplementation (when used as monotherapy without additional calcium supplementation) had no important effects on bone density[11] nor any consistent effects on falls,[12] total fracture, or hip fracture (table 1⇓).[13] Some individual trials reported statistically significant, clinically relevant increased risks of falls (range of relative risks 1.15-1.40)[14 15] and fractures (range of relative risks 1.26-1.49)[14 16] from intermittent, high dose vitamin D.

Agreed: raising vitamin D levels a few nanograms does not help

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series advisers are Sera Tort, clinical editor, and David Tovey, editor in chief, the Cochrane Library. To suggest a topic for this series, please email us at uncertainties@bmj.com

What you need to know

- Meta-analyses of randomised controlled trials (RCTs) show that vitamin D supplementation alone does not improve musculoskeletal outcomes
- Meta-analyses of randomised controlled trials of vitamin D on non-musculoskeletal outcomes suggest ongoing uncertainty:
  - There is no high quality evidence to suggest that it is beneficial for these outcomes
  - There is insufficient evidence to conclude firmly against small benefits, but RCT results exclude beneficial effects of a size suggested by observational studies
  - The clinical trials currently under way are unlikely to answer these uncertainties

BOX 1: Vitamin D facts

- Vitamin D is a prohormone synthesised in the skin in response to ultraviolet-B radiation in sunlight
- Dietary sources are limited and include oily fish, egg yolk, red meat, liver, and fortified breakfast cereals, fat spreads, and milk in some countries
- Vitamin D is needed to ensure adequate intestinal absorption of calcium to maintain normal serum calcium levels
- The best current test for vitamin D status is serum 25-hydroxyvitamin D
- 25-hydroxyvitamin D level <25 nmol/L is classified as vitamin D deficiency. Classifications of vitamin D sufficiency vary, ranging from ≥50 nmol/L to ≥80 nmol/L
- Those at high risk of vitamin D deficiency include people who are housebound, have very limited sunlight exposure, or have severe malabsorption syndromes
- In adults, severe vitamin D deficiency can cause osteomalacia:
  - A syndrome of impaired bone mineralisation, bone fragility, and proximal myopathy
  - Most likely when serum 25-hydroxyvitamin D level <15 nmol/L[5]
  - Counsel individuals at high risk about sunlight exposure and diet, and consider use of low dose vitamin D supplements (400-800 IU/day)

Seficiency is < 10ng, IoM says < 20 ng, many experts say it is < 30 or < 40 ng

Rickets can be suspected if < 36 nanogram (90 nmol https://is.gd/Rickets36

Box 2: Examples of conditions associated with low vitamin D status in observational studies

Cancer—Breast cancer, colorectal cancer

Cardiovascular—Myocardial infarction, ischaemic heart disease, congestive heart failure, hypertension, venous thromboembolism

Gastrointestinal—Inflammatory bowel disease, chronic pancreatitis

Infection—Infections, sepsis, hepatitis C

Metabolic—Type 1 and type 2 diabetes, obesity, metabolic syndrome, dyslipidaemia

Mortality—All-cause mortality, cardiovascular mortality, cancer mortality

Musculoskeletal—All fractures, hip fractures, falls, osteoarthritis, rheumatoid arthritis, muscle strength, physical performance

Neurological—Multiple sclerosis, Alzheimer's disease, cognitive decline, Parkinson's disease, mood disorders and depression

Pregnancy related—Gestational diabetes, pre-eclampsia

Respiratory—Respiratory infections, tuberculosis, lung function, asthma, bronchiectasis

Other—Systemic lupus erythematosus, infertility, chronic pain, autism, hearing loss

Again this is true, but they fail to mention that most of those health problems have had intrvention trials which showed that vitamin D helped http://is.gd/GiveVitaminD

Vitamin D with calcium

Results for co-administered vitamin D and calcium supplements and fracture differ slightly from those for vitamin D monotherapy. Meta-analyses report that co-administered vitamin D and calcium prevented hip and non-vertebral fractures in two trials of severely vitamin D deficient (mean baseline 25-hydroxyvitamin D 20 nmol/L) frail, elderly women in residential care, but not in seven trials of community dwelling older people.[13] When considering use of calcium in combination with vitamin D, the benefits from preventing fracture should be weighed against mild but common gastrointestinal side effects and serious but uncommon side effects of kidney stones and cardiovascular events.[17]

Non-skeletal outcomes

See box 2 for the range of potential non-skeletal outcomes. Systematic reviews of RCTs show no consistent effect of vitamin D supplementation on non-skeletal outcomes (table 2⇓).[6-18] This evidence is less strong than for musculoskeletal outcomes because most of the RCTs were designed and powered to assess surrogate outcomes, but a wide range of clinical outcomes have also been reported, albeit as secondary outcomes. We can be reasonably certain that for the most common or important conditions, these results exclude beneficial effects of vitamin D supplementation of a size suggested by observational studies. Although some meta-analyses have reported positive effects of vitamin D supplementation for a few outcomes, authors' comments suggest that they do not consider the evidence to be reliable enough to make definitive conclusions (table 2⇓).

Is ongoing research likely to provide relevant evidence?

We searched for ongoing large RCTs because they are most likely to influence clinical practice. There are at least seven ongoing large (n ≥1000) RCTs of vitamin D supplementation with a variety of non-skeletal primary outcomes. These are unlikely to alter conclusions from the current systematic reviews for two reasons. Firstly, a technique that estimates the strength and reliability of evidence from cumulative meta-analyses (trial sequential analyses) suggest that existing trial evidence reliably excludes clinically relevant (10-15%) reductions in relative risk of falls, fractures, myocardial infarction, stroke, and cancer from vitamin D supplementation and that new trial results are unlikely

to alter these conclusions.[12 18] Relative risk reductions of <10% are unlikely to be attractive to individuals because the absolute benefit of treatment is small, and there is a high likelihood of no benefit from treatment.

Secondly, most of the participants in existing RCTs had baseline 25-hydroxyvitamin D levels of 25-50 nmol/L. If vitamin D supplementation does have benefits, they are most likely to be seen in populations with severe vitamin D deficiency. None of the ongoing trials are targeting these population groups and are therefore unlikely to recruit cohorts with baseline 25-hydroxyvitamin D levels <25 nmol/L.[5]

Some earlier trials have reported increased risk of falls or fractures with high vitamin D doses.[14-16] The ongoing large trials are all using high daily or intermittent dose regimens and should clarify whether such doses are harmful.

What should we do in the light of the uncertainty?

Osteomalacia is an uncommon but serious illness that can readily be prevented. People at high risk (box 1) should be counselled about sunlight exposure and diet, and low dose vitamin D supplements (400-800 IU/day) can be considered on an individual basis. Otherwise, we conclude that current evidence does not support the use of vitamin D supplementation to prevent disease. This advice is similar to the recommendation of the Scientific Advisory Committee on Nutrition that 25-hydroxyvitamin D of individuals in the UK should not fall below 25 nmol/L.[5] We believe this can be achieved pragmatically by offering high risk individuals or populations low dose vitamin D of 400-800 IU/day; measurement of 25-hydroxyvitamin D is seldom necessary.

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Search strategies and trial registries searched

Our article is based on repeated searches carried out independently by two authors (MJB and AA) to inform systematic reviews of vitamin D published over several years with outcomes of fracture, falls, mortality, cardiovascular disease, stroke, cancer, and adverse events. The full text of the searches are available in the primary references,[12-18] but we have repeatedly searched Medline, PubMed, Embase, and the Cochrane Library and hand searched reference lists and relevant conference abstracts for randomised controlled trials and systematic reviews of vitamin D in adults. Our most recent search was in December 2015 to identify all published randomised controlled trials of vitamin D supplementation. We also searched ClinicalTrials.gov (https://clinicaltrials.gov/), the International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/), and the Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au/) for completed and ongoing trials, using vitamin D as the search term.

Recommendations for future research

- Future randomised controlled trials of vitamin D supplementation should focus on populations with severe vitamin D deficiency by enrolling individuals with 25-hydroxyvitamin D concentrations <25 nmol/L
- Such individuals would need to be at low risk of osteomalacia at baseline, and the trial protocol would need specific provision for monitoring for osteomalacia. However, there will be costs from identifying sufficient numbers of participants with low 25-hydroxyvitamin D

Education into practice

- If a middle aged patient who is otherwise well asks you whether they should take vitamin D what would you discuss with them to come to a decision?
- If you saw a housebound older person, how would you consider and discuss the pros and cons of vitamin D with them?
- Based on reading this article is there anything that you would do differently in your practice?

How patients were involved in the production of this article

No patients were involved in the production of this article

Tables

Table 1| Recent meta-analyses of vitamin D monotherapy which show no statistically significant difference on musculoskeletal outcomes

Outcome	No of trials	No of participants	Relative risk (95% CI)
Falls[12]	16	22 291	0.95 (0.89 to 1.02)
Total fracture[13]	15	28 271	1.03 (0.96 to 1.11)
Hip fracture[13]	11	27 693	1.12 (0.98 to 1.29)

Vitamin D prevents falls – majority of meta-analyses conclude – meta-meta analysis Feb 2015
http://vitamindwiki.com/tiki-index.php?page_id=6222

They fail to mention the **Cochrane** review on Falls and Fractures
"Fractures reduced with any amount of vitamin D and some Calcium - Cochraine April 2014"
http://vitamindwiki.com/tiki-index.php?page_id=5260

Table 2| Recent wide-ranging systematic reviews and Cochrane reviews of randomised controlled trials (RCTs) of vitamin D supplementation with non-skeletal outcomes

Review	Outcome	Description	Findings
Comprehensive, large systematic reviews			
Autier 2014[6]	Clinical and surrogate outcomes (including cardiovascular disease, mortality, cancer incidence, lipids, glucose metabolism, physical function)	172 RCTs	• No effect on disease occurrence. • Small reduction in all-cause mortality (RR range 0.93-0.96). • Authors state that RCTs of disease reduction are needed to test whether associations between low vitamin D status and ill health are mediated by inflammation.
Bolland 2014[18]	Stroke, myocardial infarction, cancer, fractures, mortality	Trial sequential analysis of RCTs	• Does not reduce skeletal or non-skeletal outcomes by more than 15% in unselected, community dwelling individuals.
Theodoratou 2014[7]	Clinical and surrogate outcomes	87 meta-analyses of RCTs	• No consistent effects on health outcomes.
Recent Cochrane reviews			
Bjelakovic 2014, (CD007469)	Cancer	18 RCTs	• No effect on cancer incidence. • Reduced cancer mortality in 4 trials (RR 0.88 (95% CI 0.78 to 0.98)), but authors rated this low quality evidence
Bjelakovic 2014, (CD007470)	Mortality	56 RCTs	• Reduced mortality by small amount (RR 0.97 (95% CI 0.94 to 0.99)). • Benefit in trials of vitamin D3 (RR 0.94 (0.91 to 0.98)) but not vitamin D2 (RR 1.02 (0.96 to 1.08)). • Authors state that risks of attrition bias, outcome reporting bias, and other weaknesses warrant further placebo-controlled RCTs
Ferguson 2014, (CD007298)	Cystic fibrosis	3 RCTs	• Insufficient evidence to draw reliable conclusions
Straube 2015, (CD007771)	Chronic pain	10 RCTs	• Insufficient evidence to draw reliable conclusions but large effect unlikely
De-Regil 2016, (CD008873)	Pregnancy and newborn outcomes	15 RCTs	• Insufficient evidence to draw reliable conclusions
Martineau 2016, (CD011511)	Asthma	7 RCTs (2 in adults)	• In each trial, vitamin D had no effect on primary or secondary clinical outcomes. • Reduced rate of exacerbations requiring corticosteroids or hospital visit. These were not the primary or secondary outcomes. • Authors recommend caution in applying evidence to clinical practice because results come from few trials.

RCT = randomised controlled trial. RR = relative risk. CI = confidence interval.