German Federal Institute for Risk Assessment

Opinion 055/2023

https://doi.org/10.17590/20250827-113843-0

31 October 2023

Food supplements with vitamin D – useful or unnecessary?

Vitamin D plays an important role in calcium and phosphate metabolism and thus in the development and maintenance of healthy bones. It also strengthens muscles and supports a well-functioning immune system. It is therefore important to get an adequate supply of vitamin D.

Vitamin D can be produced in the skin following exposure to sunlight. With sufficient exposure to sunlight, endogenous production in the skin contributes 80–90% to the vitamin D supply. However, the amount of sunlight in Germany in autumn and winter is not sufficient to produce enough vitamin D through the skin. So do we need vitamin D supplements at least in the dark season?

There is no general answer to this question. The body stores vitamin D in fat and muscle tissue. Through physical activity, it can be released from these stores and contribute to the vitamin D supply in winter. Sufficient time outdoors with adequate sun exposure of the skin, physical exercise and activity as well as a balanced diet with oily fish (e.g. salmon or herring) at best twice a week generally ensure a good supply of vitamin D in the body. A good supply is achieved with serum levels of 50 nmol/l (20 ng/ml) or more.

However, depending on age and skin type as well as sun exposure, sufficient vitamin D levels are not always achieved through endogenous production. An additional intake of vitamin D may therefore be useful for certain groups at risk of a deficiency, especially in the winter months.

Risk groups for an inadequate vitamin D supply include people who spend little or no time outdoors or those who, for cultural or religious reasons, go outdoors only with their body completely covered. Furthermore, people with dark skin belong to these risk groups because, due to the high concentration of the skin pigment melanin, they produce less vitamin D than people with light skin. Another important risk group includes the elderly because vitamin D production declines considerably with age. In addition, the elderly population often includes people with limited mobility and chronic illnesses as well as those in need of care, who spend little, if any, time outdoors.

In contrast, according to large-scale clinical studies, people with adequate blood levels of vitamin D gain no additional benefit from vitamin D supplementation. In these studies,

people with adequate serum levels who took vitamin D supplements were not less likely to be affected by cancer, type 2 diabetes, cardiovascular disease, bone fractures, and falls than people who did not take vitamin D supplements. Therefore, based on the scientific data currently available, a general recommendation for vitamin D supplementation for disease prevention is not justifiable. However, vitamin D deficiency should be avoided at all costs.

Those who wish to supplement vitamin D should opt for food supplements with a maximum amount of 20 µg of vitamin D (800 IU) per day because this dose has not been associated with harmful health effects – even when taken over the long term and taking into account other sources of vitamin D (e.g. fortified foods). With this dose, an adequate vitamin D serum concentration of 50 nmol/l (20 ng/ml) can generally be achieved without exposing the skin to sunlight.

High-dose vitamin D supplements should be taken only under medical supervision. In some clinical studies, the daily administration of an additional 100 µg (4,000 IU) of vitamin D over a longer period of time was associated with a greater decrease in bone density in older women, an increase in the risk of falls, and a deterioration in heart function in people with heart disease compared with controls. After the intake of excessively high doses, case reports have described vitamin D poisoning in children and adults who required intensive medical treatment and, in one case, led to irreversible kidney damage requiring dialysis.

High-dose food supplements with a vitamin D dose of 4,000 international units (100 µg) or more per recommended daily intake could lead to total vitamin D intake levels that are harmful to health if taken additionally over a long period of time.

Vitamin D plays an important role in calcium and phosphate metabolism and thus in the development and maintenance of healthy bones. It also strengthens muscles and supports a well-functioning immune system. An adequate supply of vitamin D is therefore important[1-4].

The physiological requirements for vitamin D vary greatly from person to person. The former *Institute of Medicine (IOM)* (today: *National Academy of Medicine*) in the USA has derived an adequate vitamin D serum level based on studies that take this into account. Accordingly, a 25-hydroxyvitamin D serum level of 50 nmol/l (20 ng/ml) is sufficient to meet the requirements for healthy bones in almost all individuals in a population[5,6]. This means that even people with particularly high requirements are well supplied at this serum level. For most people, this level is already above the actual individual requirement for good bone health. Serum levels between 30 nmol/l (12 ng/ml) and 50 nmol/l (20 ng/ml) are considered sub-optimal. However, depending on individual requirements, people are not necessarily under-supplied at these serum levels. If the serum level is below 30 nmol/l (12 ng/ml), there is a risk of vitamin D deficiency. In the long term, this can also lead to an increased risk of osteomalacia (bone softening) and rickets.

In Germany, around 54% of children and adolescents and 44% of adults have adequate vitamin D serum levels of 50 nmol/l (20 ng/ml) or more; around 13% of children and adolescents and 15% of adults are at risk of vitamin D deficiency. About 33% of children and adolescents and 41% of adults are in the sub-optimal range[7].

In many observational studies, low vitamin D levels were associated with an increased risk of extraskeletal diseases (e.g. cancer, cardiovascular diseases, type 2 diabetes, depression, asthma, and respiratory infections)[4,8]. Based on these study results, there is a high expectation that taking vitamin D preparations, which are available as medicinal products as well as over-the-counter food supplements, could protect against these diseases or alleviate their progression. However, no causal relationships can be derived from observational studies. The question therefore remains as to whether low vitamin D levels are the cause or the consequence of these diseases.

Whether or not a causal relationship exists is best examined through controlled clinical trials. In these, the participants receive either the potential active ingredient, in this case a vitamin D preparation (intervention group), or a placebo without active ingredient (control group). A sufficiently long treatment period is also important in order be able to assess the long-term effects. Moreover, the larger the number of participants in a study, the more statistically significant the result.

In recent years, results from large placebo-controlled vitamin D studies with more than 2,000 participants and a study duration of 2.5–5.3 years have been published[9-42]. Vitamin D was administered either daily (with 1,600–4,000 IU or 40–100 µg of vitamin D per day) or as a weekly (14,000 IU or 350 µg of vitamin D per week) or monthly (60,000–100,000 IU or 1,500–2,500 µg of vitamin D per month) bolus dose. The most comprehensive study to date is the VITAL study from the US with over 25,000 adult participants (average age 67 years), who received 2,000 IU or 50 µg of vitamin D per day for more than five years[9]. In almost all of these studies, the participants already had adequate vitamin D serum levels of around 55–80 nmol/l (22–32 ng/ml) on average at the beginning of the study.[a] Whilst vitamin D levels remained almost constant in the placebo group, the administration of vitamin D led to a clear increase in serum levels. However, a further increase in vitamin D serum levels from an already adequate to supra-physiological range showed no additional benefit for the prevention of the following diseases or health impairments investigated:

- Cancer (daily administration)[9,14,17]
- Total mortality (daily administration or monthly bolus administration)[9,26]
- Cardiovascular diseases (daily administration or monthly bolus administration)[9-11,14]
- Fractures (daily administration or monthly bolus dose administration)[11,18,19,42]
- Falls (daily administration or monthly bolus dose administration)[19-22]
- Frailty (daily administration)[23,33]
- Type 2 diabetes (daily administration)[12]
- Renal dysfunction (daily administration)[25]
- Incontinence (daily administration)[36]
- Age-related macular degeneration (daily administration)[29]
- Respiratory infections (daily administration or monthly weekly bolus dose administration)[11,15,16,24]
- Depression (daily administration or monthly bolus dose administration)[28,39,41].

[a] Only in one study the participating children from Mongolia (N: 8,851; age: 9 ± 2) had insufficient 25-hydroxyvitamin D serum levels of around 30 nmol/l or 12 ng/ml at the beginning.[16]

Similarly, there was no positive effect of additional vitamin D on

- growth (weekly bolus administration in children)[34]
- bone density (daily administration)[35]
- heart structure and function (daily administration)[31]
- the perception of pain (bolus administration)[38]
- weight (daily administration)[30]
- body composition (daily or weekly administration)[30,34]
- physical and cognitive performance (daily administration)[11]
- the composition of the gut microbiome (monthly bolus dose administration)[37].

With regard to the risk of dying from an existing cancer, the results varied depending on the type of intervention: In a study in which participants received a long-term daily supplement of vitamin D (2,000 IU or 50 µg per day), a lower cancer mortality rate was observed[9], while in another study, involving long-term high-dose monthly bolus doses (60,000 IU or 1,500 µg of vitamin D per month), the risk was slightly increased[26]. In people taking cardiovascular medication, this bolus dose led to a reduced risk of cardiovascular effects[40]. In terms of the development and progression of autoimmune diseases, participants appeared to benefit from a daily administration of 50 µg (2,000 IU) of vitamin D[27,32].

In summary, these large clinical studies show that people with adequate vitamin D status generally do not gain any additional benefit from taking vitamin D.

With regard to the risk of falls and fractures, an additional evaluation of the VITAL study also showed no benefit from the sole administration of 50 µg (2,000 IU) of vitamin D per day (without calcium) in people with vitamin D levels below 50 nmol/l (20 ng/ml)[18,20]. However, the VITAL study was not primarily aimed at investigating the effect of vitamin D on bone health. Risk groups (e.g. osteoporosis patients) were therefore not specifically recruited for this study.

In contrast, in the case of a pronounced vitamin D deficiency (< 30 nmol/l or < 12 ng/ml), further studies have observed an improvement in bone density through vitamin D supplementation alone[43,44].

For respiratory tract infections associated with insufficient vitamin D status, meta-analyses (i.e. studies that summarise the results of clinical trials) revealed an inconsistent picture regarding the benefits of vitamin D preparations[16,45,46].

Clinical studies investigating whether taking vitamin D provides protection against SARS-CoV-2 infection have also yielded mixed results. However, these studies varied with respect to study design, number of participants, vitamin D levels at baseline, and dosage of the study preparations used[47-49].

Based on the scientific data currently available, a general recommendation to take preparations containing vitamin D to prevent illness is therefore not justifiable. However, a vitamin D deficiency should be avoided at all costs.

The best way to achieve an adequate supply of vitamin D is through endogenous synthesis in the skin. With sufficient exposure to sunlight, endogenous production in the skin contributes

80–90% to the vitamin D supply.[b] The intake via the usual diet is usually low because only a few foods (e.g. fatty fish such as salmon or herring[50]) contain appreciable amounts of vitamin D.

In contrast to the summer months, sunlight in Germany from October to March is not strong enough to produce sufficient amounts of endogenous vitamin D[51,52]. However, the body stores vitamin D in fat and muscle tissue. This can be released through physical activity and contribute to the vitamin D supply in winter[53-56].

A good supply of vitamin D can be achieved by spending sufficient time outdoors and exposing the skin to sufficient sunlight, by physical exercise and activity, and a balanced diet with oily fish, if possible, once or twice a week.

However, sufficient vitamin D levels are not always achieved through endogenous production[7], this depends not only on exposure to sunlight, but also on age and skin type. An additional intake of vitamin D can therefore be useful for certain groups of people, especially in the winter months. Risk groups for an inadequate vitamin D supply include people who spend little or no time outdoors or those who, for cultural or religious reasons, go outdoors only with their body completely covered. Furthermore, people with dark skin also belong to the risk groups because they produce less vitamin D than people with light skin due to the high concentration of the skin pigment melanin. Another important risk group includes the elderly because vitamin D production declines considerably with age. In the elderly population, there are often people with limited mobility, people who are chronically ill, and people in need of care, who spend little, if any, time outdoors[57]. A vitamin D deficiency can therefore be particularly widespread among nursing home residents[58]. For this risk group, general supplementation with up to 20 µg (800 IU) of vitamin D per day should therefore be considered.

With 20 µg (800 IU) of vitamin D per day, a 25-hydroxyvitamin D serum concentration of 50 nmol/l (20 ng/ml)[b] can generally be achieved without exposing the skin to any sunlight[50]. From a medical perspective, there may be an indication for higher doses in certain cases. But then serum levels should be monitored regularly in parallel with supplementation.

In the case of additional intake of vitamin D via food supplements, it should be taken into account that the European Food Safety Authority (EFSA) has derived a *Tolerable Upper Intake Level* (UL) for vitamin D of 100 µg (4,000 IU) per day for children and adolescents (11 to 17 years old) and adults[59]. For younger children from 1 to 10 years, a UL of 50 µg (2,000 IU) per day was derived. The ULs refer to an intake from all food sources, including food supplements containing vitamin D and fortified foods. However, the UL does not represent an intake recommendation. A regular daily vitamin D intake above the UL increases the risk of adverse effects. Given the typical dietary habits and the fact that most foods contain only small amounts of vitamin D, exceeding the UL is currently only possible by taking high-dose vitamin D preparations.

For medical reasons (i.e. as part of medical treatment), it may be necessary to supplement higher amounts of vitamin D. However, vitamin D preparations with dosages above the UL should be taken only under medical supervision, taking into consideration the individual

[b] Special conditions apply to infants and children under one year of age (medically controlled vitamin D prophylaxis with 10–12.5 µg per day) because they should not be exposed to direct sunlight (https://www.gesund-ins-leben.de/fuer-fachkreise/bestens-unterstuetzt-durchs-1-lebensjahr/nachgefragt/warum-brauchen-saeuglinge-zusaetzlich-vitamin-d/).

vitamin D status. Case reports have shown that taking excessively high doses on one's own can have serious health consequences.

In recent years, the Drug Commission of the German Medical Association (AkdÄ) has drawn attention to case reports[60,61]: Two elderly people (aged 78 and 60) had made their own purchase of high-dose vitamin D preparations on the Internet and were taken them daily in high doses (10,000 IU (250 µg) and 50,000 IU (1250 µg) per day, respectively). Both developed pronounced hypercalcaemia and acute renal failure. Whilst the condition of the patient who had taken 10,000 IU per day improved after therapy, the patient who had taken 50,000 IU per day developed renal insufficiency requiring dialysis.

Another case involved a seven-month-old infant, who was admitted to the intensive care unit because of weight loss, excessive fluid loss (dehydration), and loss of consciousness.[61] The child had initially received the medically prescribed vitamin D prophylaxis of 500 IU (12.5 µg) per day. On the advice of friends, the parents had switched to a highly concentrated preparation that was freely available on the Internet. The infant had received 40 drops of vitamin D3 (approx. 40,000 IU or 1,000 µg) daily for five months. A pronounced chronic vitamin D intoxication with a significantly increased serum calcium concentration and renal calcification was observed. Three weeks after discharge, the 25-hydroxyvitamin D value was still elevated because of its long half-life.

Another published case in Germany involved a three-year-old boy who had attracted the attention of a paediatrician during the U7 examination[62]. Because of the child's weight loss, dehydration, and apathy, he was immediately admitted to hospital. In addition, the parents reported that their boy had poor appetite, occasional vomiting, and acute constipation. In the detailed interview, the parents stated that they had given their child a vitamin D supplement purchased on the Internet several times a week, which contained 5,000 IU (125 µg) of vitamin D per drop. The boy had been given an almost completely filled pipette several times a week for about three months. Further diagnostics revealed calcification of the kidneys, abnormalities in the electrocardiogram, and elevated blood pressure. The boy was discharged only after 10 days in hospital.

In some of these case studies, excessive amounts of vitamin D were ingested and led to extremely high 25-hydroxyvitamin D levels. This is why the classic symptoms of acute vitamin D intoxication appeared after a relatively short period of time.

In observational studies, long-term effects such as increased risk of cardiovascular disease[63-67], fractures[68,69], frailty[70,71], and mortality[63,64,72-74] were associated with both low (< 30–40 nmol/l) and high vitamin D serum levels (> 75–100 nmol/l). Serum levels of over 100 nmol/l can easily be achieved with a daily long-term intake of 4,000 IU (100 µg) of vitamin D[75-79]. However, no causal relationships can be derived from observational studies. However, in some clinical studies, the daily administration of 4,000 IU (100 µg) of vitamin D over one to three years resulted in a greater reduction in bone density in older women[76,79], a greater impairment of heart function in heart patients[78], and an increased occurrence of hypercalcaemia[78,80], falls[81], and adverse gastrointestinal effects[82] compared with placebo or lower doses. In the case of persistent severe hypercalcaemia, this can lead to kidney stones, kidney calcifications, and ultimately to a decrease in renal function[60].

In addition, clinical trials with annual high-dose vitamin D bolus doses reported an increase in falls and fractures in the vitamin D group[83,84]. But also monthly high-dose bolus applications led to an increased risk of falls compared to lower doses[85].

High-dose vitamin D preparations of 4,000 IU or more per recommended daily dose have the potential to cause total vitamin D intake amounts that are harmful to health if taken over the long term.

People who want to take vitamin D via food supplements should use products with a maximum of 20 µg of vitamin D (800 IU) per day[c] because this dose has not been associated with harmful effects on health – even when taken over a long period of time and taking into consideration other sources of vitamin D (e.g. fortified foods)[86].

Food supplements are not intended to treat or alleviate a disease. Food supplements are not medicines but rather foods that are intended to supplement the normal diet. Food supplements must be safe and may not have any adverse health effects.

[c] Special conditions apply to infants and children under one year of age (i.e. medically supervised vitamin D prophylaxis with 10–12.5 µg per day; https://www.gesund-ins-leben.de/fuer-fachkreise/bestens-unterstuetzt-durchs-1-lebensjahr/nachgefragt/warum-brauchen-saeuglinge-zusaetzlich-vitamin-d/).

Further information on vitamin D is available on the BfR website

Questions and answers on vitamin D
https://www.bfr.bund.de/cm/349/selected-questions-and-answers-on-vitamin-d.pdf

BfR opinion: Vitamin D: consumption of high-dose food supplements is unnecessary
https://www.bfr.bund.de/cm/349/vitamin-d-consumption-of-high-dose-food-supplements-is-unnecessary.pdf

References

1. EFSA. Scientific Opinion on the substantiation of health claims related to vitamin D and normal function of the immune system and inflammatory response (ID 154, 159), maintenance of normal muscle function (ID 155) and maintenance of normal cardiovascular function (ID 159) pursuant to Article 13(1) of Regulation (EC) No 1924/20061. EFSA Journal 2010;8:1468.
2. EFSA. Scientific Opinion on the substantiation of health claims related to vitamin D and maintenance of bone and teeth (ID 150, 151, 158), absorption and utilisation of calcium and phosphorus and maintenance of normal blood calcium concentrations (ID 152, 157), cell division (ID 153), and thyroid function (ID 156) pursuant to Article 13(1) of Regulation (EC) No 1924/20061. EFSA Journal 2009;7.
3. EFSA. Scientific Opinion on the substantiation of health claims related to calcium and vitamin D and maintenance of bone (ID 350) pursuant to Article 13(1) of Regulation (EC) No 1924/20061. EFSA Journal 2009;7.
4. Holick MF. Vitamin D deficiency. The New England journal of medicine 2007;357:266-81.
5. Aloia JF. Clinical Review: The 2011 report on dietary reference intake for vitamin D: where do we go from here? J Clin Endocrinol Metab 2011;96:2987-96.
6. IOM. DRI - Dietary Reference Intakes for Calcium and Vitamin D. Committee to Review Dietary Intakes for Vitamin D and Calcium - Food and Nutrition Board. Washington, D.C.; Institute of Medicine. 2011:1-1115.
7. Rabenberg M, Scheidt-Nave C, Busch MA, et al. Implications of standardization of serum 25-hydroxyvitamin D data for the evaluation of vitamin D status in Germany, including a temporal analysis. BMC Public Health 2018;18:845.
8. Bouillon R, Marcocci C, Carmeliet G, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocrine reviews 2019;40:1109-51.
9. Manson JE, Cook NR, Lee IM, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. The New England journal of medicine 2019;380:33-44.
10. Scragg R, Stewart AW, Waayer D, et al. Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study : A Randomized Clinical Trial. JAMA cardiology 2017;2:608-16.
11. Bischoff-Ferrari HA, Vellas B, Rizzoli R, et al. Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial. Jama 2020;324:1855-68.
12. Pittas AG, Dawson-Hughes B, Sheehan P, et al. Vitamin D Supplementation and Prevention of Type 2 Diabetes. The New England journal of medicine 2019;381:520-30.
13. Lappe J, Watson P, Travers-Gustafson D, et al. Effect of Vitamin D and Calcium Supplementation on Cancer Incidence in Older Women: A Randomized Clinical Trial. Jama 2017;317:1234-43.
14. Virtanen JK, Nurmi T, Aro A, et al. Vitamin D supplementation and prevention of cardiovascular disease and cancer in the Finnish Vitamin D Trial: a randomized controlled trial. Am J Clin Nutr 2022;115:1300-10.
15. Pham H, Waterhouse M, Baxter C, et al. The effect of vitamin D supplementation on acute respiratory tract infection in older Australian adults: an analysis of data from the D-Health Trial. Lancet Diabetes Endocrinol 2021;9:69-81.
16. Ganmaa D, Uyanga B, Zhou X, et al. Vitamin D Supplements for Prevention of Tuberculosis Infection and Disease. The New England journal of medicine 2020;383:359-68.
17. Bischoff-Ferrari HA, Willett WC, Manson JE, et al. Combined Vitamin D, Omega-3 Fatty Acids, and a Simple Home Exercise Program May Reduce Cancer Risk Among Active Adults Aged 70 and Older: A Randomized Clinical Trial. Front Aging 2022;3:852643.

18. LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. The New England journal of medicine 2022;387:299-309.

19. Khaw KT, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol 2017;5:438-47.

20. LeBoff MS, Murata EM, Cook NR, et al. VITamin D and OmegA-3 TriaL (VITAL): Effects of Vitamin D Supplements on Risk of Falls in the US Population. J Clin Endocrinol Metab 2020;105:2929-38.

21. Bischoff-Ferrari HA, Freystätter G, Vellas B, et al. Effects of vitamin D, omega-3 fatty acids, and a simple home strength exercise program on fall prevention: the DO-HEALTH randomized clinical trial. Am J Clin Nutr 2022;115:1311-21.

22. Waterhouse M, Sanguineti E, Baxter C, et al. Vitamin D supplementation and risk of falling: outcomes from the randomized, placebo-controlled D-Health Trial. J Cachexia Sarcopenia Muscle 2021;12:1428-39.

23. Orkaby AR, Dushkes R, Ward R, et al. Effect of Vitamin D3 and Omega-3 Fatty Acid Supplementation on Risk of Frailty: An Ancillary Study of a Randomized Clinical Trial. JAMA Netw Open 2022;5:e2231206.

24. Camargo CA, Sluyter J, Stewart AW, et al. Effect of Monthly High-Dose Vitamin D Supplementation on Acute Respiratory Infections in Older Adults: A Randomized Controlled Trial. Clin Infect Dis 2020;71:311-7.

25. Kim SH, Brodsky IG, Chatterjee R, et al. Effect of Vitamin D Supplementation on Kidney Function in Adults with Prediabetes: A Secondary Analysis of a Randomized Trial. Clin J Am Soc Nephrol 2021;16:1201-9.

26. Neale RE, Baxter C, Romero BD, et al. The D-Health Trial: a randomised controlled trial of the effect of vitamin D on mortality. Lancet Diabetes Endocrinol 2022;10:120-8.

27. Hahn J, Cook NR, Alexander EK, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. BMJ 2022;376:e066452.

28. Okereke OI, Reynolds CF, 3rd, Mischoulon D, et al. 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. Jama 2020;324:471-80.

29. Christen WG, Cook NR, Manson JE, et al. Effect of Vitamin D and ω-3 Fatty Acid Supplementation on Risk of Age-Related Macular Degeneration: An Ancillary Study of the VITAL Randomized Clinical Trial. JAMA Ophthalmol 2020;138:1280-9.

30. Chou SH, Murata EM, Yu C, et al. Effects of Vitamin D3 Supplementation on Body Composition in the VITamin D and OmegA-3 TriaL (VITAL). J Clin Endocrinol Metab 2021;106:1377-88.

31. Chandra A, Picard MH, Huang S, et al. Impact of Vitamin D3 Versus Placebo on Cardiac Structure and Function: A Randomized Clinical Trial. J Am Heart Assoc 2022;11:e025008.

32. Dong Y, Zhu H, Chen L, et al. Effects of Vitamin D(3) and Marine Omega-3 Fatty Acids Supplementation on Biomarkers of Systemic Inflammation: 4-Year Findings from the VITAL Randomized Trial. Nutrients 2022;14.

33. Gagesch M, Wieczorek M, Vellas B, et al. Effects of Vitamin D, Omega-3 Fatty Acids and a Home Exercise Program on Prevention of Pre-Frailty in Older Adults: The DO-HEALTH Randomized Clinical Trial. J Frailty Aging 2023;12:71-7.

34. Ganmaa D, Bromage S, Khudyakov P, Erdenenbaatar S, Delgererekh B, Martineau AR. Influence of Vitamin D Supplementation on Growth, Body Composition, and Pubertal Development Among School-aged Children in an Area With a High Prevalence of Vitamin D Deficiency: A Randomized Clinical Trial. JAMA Pediatr 2023;177:32-41.

35. LeBoff MS, Chou SH, Murata EM, et al. Effects of Supplemental Vitamin D on Bone Health Outcomes in Women and Men in the VITamin D and OmegA-3 TriaL (VITAL). Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2020;35:883-93.

36. Markland AD, Vaughan CP, Huang AJ, et al. Effect of Vitamin D Supplementation on Overactive Bladder and Urinary Incontinence Symptoms in Older Men: Ancillary Findings From a Randomized Trial. J Urol 2023;209:243-52.

37. Pham H, Waterhouse M, Rahman S, et al. The effect of vitamin D supplementation on the gut microbiome in older Australians - Results from analyses of the D-Health Trial. Gut Microbes 2023;15:2221429.

38. Rahman A, Waterhouse M, Baxter C, et al. The effect of vitamin D supplementation on pain: an analysis of data from the D-Health randomised controlled trial. The British journal of nutrition 2023;130:633-40.

39. Rahman ST, Waterhouse M, Romero BD, et al. Effect of vitamin D supplementation on depression in older Australian adults. Int J Geriatr Psychiatry 2023;38:e5847.

40. Thompson B, Waterhouse M, English DR, et al. Vitamin D supplementation and major cardiovascular events: D-Health randomised controlled trial. BMJ 2023;381:e075230.

41. Vyas CM, Mischoulon D, Chang G, et al. Effects of Vitamin D(3) and Marine Omega-3 Fatty Acids Supplementation on Indicated and Selective Prevention of Depression in Older Adults: Results From the Clinical Center Sub-Cohort of the VITamin D and OmegA-3 TriaL (VITAL). J Clin Psychiatry 2023;84.

42. Waterhouse M, Ebeling PR, McLeod DSA, et al. The effect of monthly vitamin D supplementation on fractures: a tertiary outcome from the population-based, double-blind, randomised, placebo-controlled D-Health trial. Lancet Diabetes Endocrinol 2023;11:324-32.

43. Macdonald HM, Reid IR, Gamble GD, Fraser WD, Tang JC, Wood AD. 25-Hydroxyvitamin D Threshold for the Effects of Vitamin D Supplements on Bone Density: Secondary Analysis of a Randomized Controlled Trial. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2018;33:1464-9.

44. Reid IR, Horne AM, Mihov B, et al. Effect of monthly high-dose vitamin D on bone density in community-dwelling older adults substudy of a randomized controlled trial. Journal of internal medicine 2017;282:452-60.

45. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. Bmj 2017;356:i6583.

46. Jolliffe DA, Camargo CA, Jr., Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol 2021;9:276-92.

47. Villasis-Keever MA, López-Alarcón MG, Miranda-Novales G, et al. Efficacy and Safety of Vitamin D Supplementation to Prevent COVID-19 in Frontline Healthcare Workers. A Randomized Clinical Trial. Arch Med Res 2022;53:423-30.

48. Jolliffe DA, Holt H, Greenig M, et al. Effect of a test-and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19: phase 3 randomised controlled trial (CORONAVIT). BMJ 2022;378:e071230.

49. Brunvoll SH, Nygaard AB, Ellingjord-Dale M, et al. Prevention of covid-19 and other acute respiratory infections with cod liver oil supplementation, a low dose vitamin D supplement: quadruple blinded, randomised placebo controlled trial. BMJ 2022;378:e071245.

50. D-A-CH. Referenzwerte für die Nährstoffzufuhr - Vitamin D. 1. Auflage. 4. korrigierter Nachdruck. 2012.

51. Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull 2014;39:322-50.

52. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988;67:373-8.

53. Dzik KP, Grzywacz T, Łuszczyk M, Kujach S, Flis DJ, Kaczor JJ. Single bout of exercise triggers the increase of vitamin D blood concentration in adolescent trained boys: a pilot study. Sci Rep 2022;12:1825.

54. Sun X, Cao ZB, Taniguchi H, Tanisawa K, Higuchi M. Effect of an Acute Bout of Endurance Exercise on Serum 25(OH)D Concentrations in Young Adults. J Clin Endocrinol Metab 2017;102:3937-44.

55. Sun X, Cao ZB, Tanisawa K, Taniguchi H, Kubo T, Higuchi M. Effects of chronic endurance exercise training on serum 25(OH)D concentrations in elderly Japanese men. Endocrine 2018;59:330-7.

56. Zhang J, Cao ZB. Exercise: A Possibly Effective Way to Improve Vitamin D Nutritional Status. Nutrients 2022;14.

57. BfR, DGE, MRI. Selected Questions and Answers on Vitamin D. 2012. https://www.bfr.bund.de/cm/349/selected-questions-and-answers-on-vitamin-d.pdf

58. Schilling S. Epidemischer Vitamin-D-Mangel bei Patienten einer geriatrischen Rehabilitationsklinik. Deutsches Ärzteblatt 2012;Heft 3.

59. EFSA. Scientific opinion on the tolerable upper intake level for vitamin D, including the derivation of a conversion factor for calcidiol monohydrate. EFSA J 2023;21:e08145.

60. AkdÄ. Arzneimittelkommission der deutschen Ärzteschaft. Drug Safety Mail 2017-42. https://www.akdae.de/arzneimittelsicherheit/drug-safety-mail/newsdetail/drug-safety-mail-2017-42. 2017.

61. AkdÄ. Arzneimittelkommission der deutschen Ärzteschaft. Vitamin-D3-Überdosierung bei einem Säugling. https://www.akdae.de/arzneimittelsicherheit/bekanntgaben/newsdetail/vitamin-d3-ueberdosierung-bei-einem-saeugling-aus-der-uaw-datenbank. Deutsches Ärzteblatt 2022;Jg. 119.

62. Simon A. Drei Jahre alter Junge mit ausgeprägter Hyperkalzämie im Rahmen einer chronischen Vitamin-D-Intoxikation. https://link.springer.com/article/10.1007/s00112-022-01428-5. Monatsschr Kinderheilkunde 2022.

63. Aleksova A, Beltrami AP, Belfiore R, et al. U-shaped relationship between vitamin D levels and long-term outcome in large cohort of survivors of acute myocardial infarction. International journal of cardiology 2016;223:962-6.

64. Durup D, Jorgensen HL, Christensen J, et al. A Reverse J-Shaped Association Between Serum 25-Hydroxyvitamin D and Cardiovascular Disease Mortality: The CopD Study. J Clin Endocrinol Metab 2015;100:2339-46.

65. Wang T, Sun H, Ge H, et al. Association between vitamin D and risk of cardiovascular disease in Chinese rural population. PLoS One 2019;14:e0217311.

66. Zhang R, Li B, Gao X, et al. Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies. Am J Clin Nutr 2017;105:810-9.

67. Zittermann A, Kuhn J, Dreier J, Knabbe C, Gummert JF, Börgermann J. Vitamin D status and the risk of major adverse cardiac and cerebrovascular events in cardiac surgery. Eur Heart J 2013;34:1358-64.

68. Julian C, Lentjes MA, Huybrechts I, et al. Fracture Risk in Relation to Serum 25-Hydroxyvitamin D and Physical Activity: Results from the EPIC-Norfolk Cohort Study. PLoS One 2016;11:e0164160.

69. Bleicher K, Cumming RG, Naganathan V, et al. U-shaped association between serum 25-hydroxyvitamin D and fracture risk in older men: results from the prospective population-based CHAMP study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2014;29:2024-31.

70. Kojima G, Iliffe S, Tanabe M. Vitamin D supplementation as a potential cause of U-shaped associations between vitamin D levels and negative health outcomes: a decision tree analysis for risk of frailty. BMC geriatrics 2017;17:236.

71. Ensrud KE, Ewing SK, Fredman L, et al. Circulating 25-hydroxyvitamin D levels and frailty status in older women. J Clin Endocrinol Metab 2010;95:5266-73.

72. Durup D, Jorgensen HL, Christensen J, Schwarz P, Heegaard AM, Lind B. A reverse J-shaped association of all-cause mortality with serum 25-hydroxyvitamin D in general practice: the CopD study. J Clin Endocrinol Metab 2012;97:2644-52.

73. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Archives of internal medicine 2008;168:1629-37.

74. Sempos CT, Durazo-Arvizu RA, Dawson-Hughes B, et al. Is there a reverse J-shaped association between 25-hydroxyvitamin D and all-cause mortality? Results from the U.S. nationally representative NHANES. J Clin Endocrinol Metab 2013;98:3001-9.

75. Appel LJ, Michos ED, Mitchell CM, et al. The Effects of Four Doses of Vitamin D Supplements on Falls in Older Adults : A Response-Adaptive, Randomized Clinical Trial. Annals of internal medicine 2021;174:145-56.

76. Burt LA, Billington EO, Rose MS, Kremer R, Hanley DA, Boyd SK. Adverse Effects of High-Dose Vitamin D Supplementation on Volumetric Bone Density Are Greater in Females than Males. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2020;35:2404-14.

77. Gallagher JC, Sai A, Templin T, 2nd, Smith L. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. Annals of internal medicine 2012;156:425-37.

78. Zittermann A, Ernst JB, Prokop S, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. Eur Heart J 2017;38:2279-86.

79. Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. Jama 2019;322:736-45.

80. Billington EO, Burt LA, Rose MS, et al. Safety of High-Dose Vitamin D Supplementation: Secondary Analysis of a Randomized Controlled Trial. J Clin Endocrinol Metab 2020;105.

81. Smith LM, Gallagher JC, Suiter C. Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: A randomized clinical trial. The Journal of steroid biochemistry and molecular biology 2017;173:317-22.

82. Johnson KC, Pittas AG, Margolis KL, et al. Safety and tolerability of high-dose daily vitamin D(3) supplementation in the vitamin D and type 2 diabetes (D2d) study-a randomized trial in persons with prediabetes. Eur J Clin Nutr 2022;76:1117-24.

83. 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;303:1815-22.

84. Smith H, Anderson F, Raphael H, Maslin P, Crozier S, Cooper C. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford) 2007;46:1852-7.

85. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. JAMA Intern Med 2016;176:175-83.

86. BfR. Updated recommended maximum levels for the addition of vitamins and minerals to food supplements and conventional foods. BfR Opinion No 009/2021 issued 15 March 2021. https://www.bfr.bund.de/cm/349/proposed-maximum-levels-for-the-addition-of-vitamin-d-to-foods-including-food-supplements.pdf

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This text version is a translation of the original German text which is the only legally binding version.

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Publisher:
German Federal Institute for Risk Assessment
Max-Dohrn-Straße 8-10
10589 Berlin
T +49 30 18412-0
F +49 30 18412-99099
bfr@bfr.bund.de
bfr.bund.de/en

Institution under public law
Represented by the president Professor Dr Dr Andreas Hensel
Supervisory Authority: German Federal Ministry of Food and Agriculture
VAT ID No.: DE 165 893 448
Responsible according to the German Press Law: Dr Suzan Fiack