Vitamin D and respiratory infection in adults

Ilkka Laaksi
Department of Cell Biology and Anatomy, Medical School, University of Tampere, Mediisinirinkatu 3, 33014
Tampere, Finland

Vitamin D insufficiency is a global issue that has significant implications for health. The classical role of vitamin D in bone mineralisation is well known; vitamin D deficiency leads to rickets, osteomalacia or osteoporosis. The role of vitamin D in an immune system is less known. Vitamin D is not an actual vitamin but a secosteroid hormone produced in the skin from 7-dehydrocholesterol after exposure to sunlight UVB radiation. Nutrition and supplements are main sources of vitamin D in wintertime in northern countries as sunlight exposure is inadequate for the production. For activation vitamin D needs to be hydroxylated in liver to form 25-hydroxyvitamin D and in kidney to 1,25-dihydroxyvitamin D, the most active hormone in Ca absorption in the gut. For determination of vitamin D status serum 25-hydroxyvitamin D level, the major circulating form of the hormone is to be measured. Vitamin D regulates gene expression through binding with vitamin D receptors, which dimerises with retinoid X receptor. This complex binds to vitamin D-responsive elements inside the promoter regions of vitamin D-responsive genes. Vitamin D has a key role in innate immunity activation; the production of antimicrobial peptides (cathelicidin and defensins) following Toll-like receptor stimulation by pathogen lipopeptides is dependent on sufficient level of 25-hydroxyvitamin D. Clinically, there is evidence of the association of vitamin D insufficiency and respiratory tract infections. There is also some evidence of the prevention of infections by vitamin D supplementation. Randomised controlled trials are warranted to explore this preventive effect.

Hippocrates in ancient Greece recognised the importance of sunlight to benefit human health as he expressed the belief that the southern side of the hill receiving the most daily sunlight in the northern hemisphere, was the healthiest place to live. Later in 1650 Glisson, DeBoot and Whistler discovered rickets, a bone disease in children who lived in the cities of Great Britain and northern Europe characterised by bone pain, skeletal deformity, impaired growth and weakness. In 1822, Polish Sniadecki noticed that children living in the city of Warsaw had high incidence of rickets while children living in rural regions did not develop rickets. He hypothesised that increased exposure to sunlight in the countryside prevented these children from developing rickets. The findings of Sniadecki and Palm remained broadly unrecognised until 1919 when British lecturer Edward Mellanby reported that restrictive diet led to rickets in dogs. Specifically, he found that adding cod liver

Abbreviations: DBP, vitamin D-binding protein; 7-DHC, 7-dehydrocholesterol; 25(OH)D, 25-hydroxyvitamin D; 25(OH)D₃, 25-hydroxycholecalciferol; 1,25(OH)₂D₃, 1,25-dihydroxycholecalciferol; PTH, parathyroid hormone; VDR, vitamin D receptor.

Corresponding author: Ilkka Laaksi, fax + 358 3 3551 6170, email ilkka.laaksi@uta.fi
oil to the diet cured the rachitic dogs within a few months and concluded that a component of cod liver oil was essential in preventing rickets. He proposed that rickets is caused by the absence of a dietary factor(2).

A chemist named Elmer V. McCollum discovered the compound vitamin D by investigating the chemical composition of cod liver oil that was already known to prevent night blindness and fractures. He heated and oxygenated cod liver oil and discovered it still prevented fractures, but no longer night blindness meaning it consisted of two different active compounds; the compound destroyed this way was named vitamin A and the heat-stable component became known as vitamin D(3). Vitamin D became classified as a vitamin and not as a hormone; a compound that is synthesised in the body and acts as a chemical messenger from one cell, or group of cells, to another. It is now widely accepted that vitamin D is a secosteroid hormone.

Later in 1924, Steenbock and Black demonstrated that irradiation by UV light increased the vitamin D content of foods. They discovered that rats were cured of rickets when fed with irradiated food. They then suggested that UV light was essential in protection against rickets. Finally, Steenbock concluded that irradiation of food substances is beneficial for the protection against rickets in children(4). Soon after the findings of anti-rachitic activity of foods containing cholesterol could cure rickets after being UV irradiation by UV light increased the vitamin D content of foods. They discovered that rats were cured of rickets when fed with irradiated food. They then suggested that UV light was essential in protection against rickets. Finally, Steenbock concluded that irradiation of food substances is beneficial for the protection against rickets in children(4). Soon after the findings of anti-rachitic activity of foods containing cholesterol could cure rickets after being irradiated with UV light, the discovery of the precursor of cholecalciferol (7-dehydrocholesterol (7-DHC)) was determined by A. Windaus in 1937. Further, he was able to show that when exposed to the same amount of sunlight a person 70 years of age makes only one-quarter of the cholecalciferol that the 20-year-old person can make(11,12).

Pre-cholecalciferol is isomerised to form cholecalciferol by a non-enzymatic and highly temperature-dependent process. The formation of cholecalciferol is relatively rapid, reaching a maximum within 12–24 h after UVB exposure. In experimental studies, about half of the pre-cholecalciferol can isomerise to cholecalciferol within 2.5 h in the skin(7).

Both intensity of UV radiation and level of pigmentation in the skin regulate the rate of pre-cholecalciferol formation but not the maximal level achieved. The intensity of UV radiation from sunlight varies according to season and latitude and the farther from the equator, the less time of solar exposure to produce cholecalciferol during the year. Both clothing and sunscreen use prevent effective cholecalciferol production(13,14). In the case of excessive UVB radiation pre-cholecalciferol will be degraded into inactive lumisterol, tachysterol, toxisterols or it will be re-transformed to 7-DHC. In addition, cholecalciferol will be converted to suprasterols I, II and 5,6 transcholecalciferol avoiding vitamin D intoxication(15–17). Finally, vitamin D moves to the extracellular space and binds to vitamin D-binding protein (DBP) and enters the circulation. Nutritional vitamin D either from diet or dietary supplements is transported from the intestine in chylomicrons via lymph veins and is released into liver(18).

Vitamin D synthesised in epidermis or from diet and dietary supplements is biologically inert and requires further hydroxylations by mitochondrial P450. First, vitamin D is hydroxylated by 25-hydroxylase (CYP27A1) present in the liver to form 25-hydroxycholecalciferol (25(OH)D3). There is evidence that CYP27A1 is present not only in the human adult liver but also in the adult kidney and it is up-regulated in certain pathological situations such as in the hepatic carcinoma(19). The production of
of 25(OH)D$_3$ is not substantially regulated but is mainly dependent on substrate concentration and approximately 40% of cholecalciferol is converted to 25(OH)D$_3$ (20). After hydroxylation 25(OH)D$_3$ enters circulation and it has a half-life of about 15 d (21).

25(OH)D$_3$ is transported by DBP to the kidney for successive hydroxylation by 1α-hydroxylase (CYP27B1) to form the biologically most active form of vitamin D, 1,25-dihydroxycholecalciferol (1,25(OH)$_2$D$_3$).

DBP then transports the secosteroid to target tissues for biological response (6,22). The expression of CYP27B1 has also been documented in extrarenal tissues; skin (stratum basale), macrophages, lymph nodes (23), normal and malignant colon tissue (24), normal and malignant breast tissue (25). The hydroxylation is localised at the C$_1$ (CYP27B1) position of cholecalciferol and is tightly regulated by parathyroid hormone (PTH), Ca, phosphate, calcitonin, fibroblast growth factor 23 and 1,25(OH)$_2$D$_3$ itself (26). CYP27B1 is capable of catalysing only the hydroxylation of 25(OH)D$_3$ and 24,25(OH)$_2$D$_3$ in contrast to human CYP27A that is capable of catalysing multiple reactions involved in the cholecalciferol metabolism including the production of 1,25(OH)$_2$D$_3$ in addition to its major metabolite 25(OH)D$_3$ (27). The serum levels of 1,25(OH)$_2$D$_3$ are usually 75–200 pmol/l being 0–1% of that of 25(OH)D$_3$ (25–200 nmol/l) and have a serum half-life of 10–24 h (28).

In addition, epidermal keratinocytes (29,30), macrophages (31), prostate epithelial cells (32) and osteoblasts (33) are capable of producing 1,25(OH)$_2$D$_3$ from cholecalciferol due to their expression of both 25- and 1-hydroxylases. However, the amount of 25(OH)D$_3$ in epidermis is too small and serum 25(OH)D$_3$ is very tightly bound to DBP and nearly all of it is present as a complex with DBP limiting the passage from blood vessels to epidermal keratinocytes. It is thought that cutaneous metabolism of 1,25(OH)$_2$D$_3$ is not playing a significant role but fibroblasts in dermis expressing CYP27A1 (not CYP27B1) might provide cholecalciferol and 25(OH)D$_3$ for keratinocytes and serum (34).

The inactivation of 25(OH)D$_3$ and/or 1,25(OH)$_2$D$_3$ is catalysed by a mitochondrial P450 (CYP24A) that 24-hydroxylates these to form 24,25(OH)$_2$D$_3$, or 1α,24,25(OH)$_3$D$_3$ principally in the proximal tubules of the kidney (35).

Most biological actions of vitamin D are mediated through vitamin D receptor (VDR) that belongs to the nuclear hormone receptor family. As both calcium (or calcidiol) VDR will be phosphorylated and forms a heterodimer with 9-cis-retinoid X receptor. This complex acts as a transcription factor depending on steroid receptor co-activators that are attached to the complex (36). Finally, these complexes will be bound to vitamin D response elements that are specific genomic sequences inside the promoter region (20).

For the past six decades there has been the assumption of equivalency of ergocalciferol and cholecalciferol as these forms differ only by the side chain to the sterol skeleton. However, there is evidence that when administered orally cholecalciferol increases serum 25-hydroxyvitamin D (25(OH)D) up to 1.7 times more efficiently than ergocalciferol does when given equal molar amounts for 2 weeks. When given single doses of cholecalciferol or ergocalciferol it was noted that they led to equal increase in serum 25(OH)D levels and in the cholecalciferol group remained or even continued to rise after 3 d but declined and reached the baseline value in 2 weeks in the ergocalciferol group (37). In another study with twenty healthy volunteers ergocalciferol’s potency was less than one-third that of cholecalciferol on the basis of ability to elevate serum 25(OH)D concentrations (38). Due to the differences in the chemistry of the side chains their binding to the major transport proteins in blood, DBP and in the metabolism a single dose of ergocalciferol leads to lower levels of circulating 25(OH)D than a single dose of cholecalciferol (39). It has been noted that ergocalciferol has diminished binding ability to DBP in blood and shorter shelf life as supplement (40). As a result, there is a trend to replace ergocalciferol with cholecalciferol in fortified milk, margarine or butter and supplementation.

Vitamin D is produced very effectively in skin cells; a whole body exposure to UVB radiation of 15–20 min is able to produce up to 250 μg (10,000 IU) vitamin D (41). Of note, orally administered 1μg vitamin D daily increases circulating serum 25(OH)D levels from 0.6 to 1.2 nmol/l (42).

Due to its longer distance through the atmosphere the amount of UVB in sunshine is insufficient for vitamin D production during wintertime at northern latitudes.

**Vitamin D insufficiency**

Serum 25(OH)D$_3$ is the best marker for the vitamin D status since both high serum concentrations in the summer and low concentrations in the winter have been observed in northern latitudes, reflecting the amount of exposure to the sun (43). The presence of two forms of vitamin D and the hydrophobic nature of vitamin D makes the measurement challenging. The differences between methodologies confound the definition of a single cut point for the diagnosis of low vitamin D status (44). Vitamin D sufficiency can be detected from the increase in serum parathyroid hormone secretion that starts rising at 25(OH)D$_3$ cut-off levels of 78–90 nmol/l (43,45,46). There is evidence that the serum 25(OH)D threshold for PTH increase is lower in black people compared with white. In a study with 500 both pre- and post-menopausal healthy women, aged 20–80 years, the threshold was substantially lower for black than for white women, 37 and 59 nmol/l, respectively (47). Due to the relationship of skin pigmentation to vitamin D synthesis, serum 25(OH)D levels are highest in Caucasians and lowest in black women and intermediate in Hispanics (48).

On the other hand, PTH is related to skin pigmentation inversely as black women have the highest and Caucasians the lowest plasma levels of PTH (47). There is a growing consensus for different stages of vitamin D inadequacy: <25 nmol/l for deficiency, 25–49.9 nmol/l for insufficiency, 50–75 nmol/l for hypovitaminosis.

In the United States, the statistics demonstrate that more than 90% Blacks, Hispanics and Asians now suffer from vitamin D insufficiency, and with almost 75% of the white population also being vitamin D insufficient this suggests a
near doubling of the prevalence of vitamin D insufficiency in 10 years in the same population(23).

In Europe, vitamin D insufficiency is common in children during wintertime. In elderly people, it might last throughout the year and in institutionalised people serum 25(OH)D3 concentrations are even lower(49-51). Furthermore, vitamin D insufficiency can be regarded as epidemic among adults without sufficient sunlight exposure(32).

In Finland, vitamin D insufficiency is very common among young men, young girls and healthy adults in wintertime(23,26). After the recommendation by the Ministry of Social Affairs and Health, vitamin D has been added to liquid milk products (0.5 µg/dl), as well as margarines and butter (10 µg/100 g) from February 2003 in Finland. This fortification has substantially improved vitamin D status in Finland. Still, one-third of young Finnish men were vitamin D insufficient in our earlier study(55).

**Effect on bone and Ca metabolism**

A major physiological function of 1,25(OH)2D3 is to regulate the absorption of Ca and P from the intestine and maintain plasma concentrations of these ions by increasing their absorption from the intestine and enhancing their renal re-absorption(52). When intestinal absorption is unable to maintain normal serum Ca concentration, increased PTH secretion mobilises bone Ca and induces the synthesis of 1,25(OH)2D3(56). Rickets in childhood, mild osteomalacia, osteoporosis and an increased risk of hip and other fractures in adults are all known consequences of vitamin D deficiency(57,58).

Vitamin D is a hormone that is known for its effects on bone mineralisation. However, it also has rather interesting and important non-classical actions. The active form of vitamin D, 1,25(OH)2D3 has been shown to promote insulin secretion and inhibit adaptive immunity, but stimulate innate immunity. In addition, it inhibits cell proliferation and stimulates cell differentiation(29). Vitamin D also has apoptotic effects, e.g. on prostate cancer cells in vitro(59). It has effects on cancer invasion and angiogenesis(59-61). In epidemiological studies, vitamin D has been negatively associated with breast(62) and colon cancers(63). Vitamin D deficiency in infancy has also been associated with diabetes(64), hypertension, multiple sclerosis(65,66) and some other cancers(67). Vitamin D metabolites have clinical utility in that 1,25(OH)2D3 and analogues are successfully used for the treatment of hyper-proliferative skin disease and psoriasis(35).

**Vitamin D has a key role in immunity**

Innate immunity is part of the first-line barriers of host defence and responds rapidly to microbes that work as an activator of the system. Specific genetically encoded effectors are available for activation even before the body has recognised an antigen. The antimicrobial peptides are evolutionarily ancient weapons that have remained effective defensive weapons in the battle against bacteria, viruses and fungi(68).

Antimicrobial peptides have been found both in epithelial tissues and phagocytic blood cells in which they exhibit rapid and broad-spectrum antimicrobial activity by damaging the lipoprotein membranes of microbes(69). In the moist airways, these proteins are secreted into the biofilm covering the epithelial surface, thereby creating a barrier that is chemically lethal to microbes(68,70). Some antimicrobial peptides are secreted constitutively but others are secreted as a response to stimuli from microbial components (mainly lipopolysaccharides). The inducible antimicrobial peptides such as human β-defensin 2, 3 and cathelicidin also act as attractants for macrophages and neutrophils(69). Cathelicidin has also been shown to have a role in epithelial repair as it triggers epithelial growth and angiogenesis(71). Antimicrobial peptides are secreted as a thin layer of fluid lying above the apical surface of the epithelium and below the mucous layer. Binding of microbes to the epithelium provokes the expression of antimicrobial peptides creating a chemically lethal barrier to microbes(68,70).

In the late nineteenth century, scientists were trying to find a cure for tuberculosis and Dane N. Finsen was successful in that he exposed subjects with skin tuberculosis to artificial sunlight. He found that exposing a small area of affected skin to intense light produced moderate sunburn causing the superficial skin layer to peel away but exposed normal and healthy skin underneath. It has been estimated that the phototherapy improved the skin in almost all cases. Later it was used routinely as a treatment for pulmonary tuberculosis and for which Finsen was awarded the Nobel prize(72). Based on recent studies we now better understand the effect of sunlight exposure on infections. Liu et al.(23) were able to show that the synthesis of vitamin D by sunlight exposure up-regulates the expression of antimicrobial peptides. They examined Toll-like receptors that monitor the host for the presence of microbe antigens and found the stimulation by pathogen lipopeptides to lead to the production of antimicrobial peptides. They observed that Toll-like receptor activation of human macrophages up-regulates the expression of two genes in monocytes; VDR and CYP 27B1, converting 25(OH)D3 to active 1,25(OH)2D3 form. They then showed the incubation of these activated monocytes with 1,25(OH)2D3 to produce cathelicidin in a dose-dependent manner. Further, the gene encoding cathelicidin has vitamin D response elements within the promoter region and is positively regulated by vitamin D(73). This gene was recently found also in respiratory epithelial cells as Hansdottir et al.(74) demonstrated that primary airway epithelial cells convert 25(OH)D to the active 1,25(OH)2D form, leading to the production of cathelicidin. Cathelicidin concentrated in phagocytic vacuoles destroys Mycobacterium tuberculosis in vitro. The effect was more pronounced after macrophages were exposed to 1,25(OH)2D3. This pathogen stimulation of Toll-like receptor on human monocytes triggers a circuit that enhances the induction of the cathelicidin and is vitamin D dependent(23). Liu et al.(23) also reported that the induction of cathelicidin mRNA was substantially lower in the presence of serum.
from African Americans, known to contain less 25(OH)D than does the serum from Caucasian individuals. The study shows that raised serum levels of vitamin D by sunlight exposure stimulates the synthesis of potent antimicrobial peptides and increase the effectiveness of circulating monocytes and macrophages in killing microbes\(^{(22)}\). In respiratory infection epithelial cells activate vitamin D and create a microenvironment with high levels of the active form of the vitamin leading to increased levels of cathelicidin mRNA. This local vitamin D activation might be an important component of innate immunity in the lungs\(^{(74)}\).

Vitamin D appears to limit excessive production of the pro-inflammatory cytokines; interferon, TNF and IL-12 thus preventing an over reaction inflammatory response in the adaptive immune system preventing further cell or tissue damage by inflammation\(^{(65)}\).

In a recent study, vitamin D was shown to be essential in activating and controlling the T-cell antigen receptor and thus enhancing the recognition of antigens by T-lymphocytes\(^{(75)}\). 1,25(OH)\(_2\)D\(_3\) has been shown to activate H\(_2\)O\(_2\) secretion in human monocytes resulting in increased oxidative burst potential\(^{(79)}\).

**Clinical studies of vitamin D for the prevention of respiratory tract infections**

Clinically, antimicrobial peptides have been shown to inhibit invasive pneumococcal disease, meningococcal disease and group A streptococcal disease. Lee et al.\(^{(77)}\) were able to show that β-defensins inhibit the growth of otitis media pathogens; *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* consistent with the concept that secreted antimicrobial peptides as a part of innate immunity constitute the first line of defence protecting host mucosal surfaces mucosa against microbes\(^{(78)}\).

In a recent study, an association between SNP in the VDR gene with respiratory syncytial virus-related disease was found in South African children. Kresfelder et al. studied 409 African children (aged 12–15 weeks) and found that the carriers of the VDR SNP were more prone to respiratory syncytial virus disease than controls confirming earlier findings in the Netherlands\(^{(79)}\).

Higher vitamin D status has been proposed to protect against influenza. In a cohort study with nearly 7000 participants (aged >45 years) the prevalence of respiratory infections had a strong seasonal pattern inversely related to 25(OH)\(_3\) concentrations. After adjusting for adiposity, lifestyle and socio-economic factors each 10 nmol/l rise in serum 25(OH)\(_3\) concentration was associated with a 7% lower risk of infection in the study\(^{(80)}\). Berry et al.\(^{(80)}\) conclude that vitamin D status seems to have a linear relationship with respiratory infections shown also in other studies.

In a secondary analysis of the Third National Health and Nutrition Examination Survey (1988–1994) with almost 19,000 participants (>12 years) serum 25(OH)\(_3\) concentrations were inversely associated with recent upper respiratory tract infection. The analysis was adjusted for season, BMI, smoking, asthma and chronic obstructive pulmonary disease. Recent upper respiratory tract infection was reported by 24% of subjects with 25(OH)\(_3\) <25 nmol/l, by 20 % with 25(OH)\(_3\) 25–75 nmol/l and by 17% with serum 25(OH)\(_3\) >75 nmol/l revealing an independent association between lower serum 25(OH)\(_3\) and upper respiratory tract infection\(^{(81)}\). In our cohort study with 800 young Finnish men, the subjects with serum 25(OH)\(_3\) <40 nmol/l had substantially more days absent from duty due to respiratory tract infection than controls. The study was adjusted for smoking\(^{(82)}\).

There are some randomised placebo-controlled and double-blind trials of vitamin D for the treatment and prevention of viral upper respiratory tract infections in adult populations. Avennel et al.\(^{(83)}\) failed to show a significant difference between the vitamin D and placebo groups in either the primary end point of fracture prevention or the secondary end point of self-reported infection rate in the week before assessment in the study with almost 3500 community-dwelling elderly subjects who were given 20 μg (800 IU) vitamin D or placebo for longer than 2 years, as part of the Randomised Evaluation of Ca or Vitamin D trial. However, the results are complicated because of poor observed compliance with supplements in the study population as only half of the study subjects remained compliant with study medication at 2 years of follow-up. Moreover, the study demonstrated relatively inadequate increase from 38 to 63 nmol/l in serum 25(OH)\(_3\) levels of the intervention group after vitamin D therapy\(^{(83)}\). In another trial, by Li-Ng et al.\(^{(84)}\) with 208 healthy post-menopausal African American women who were given 20 μg (800 IU) vitamin D daily or placebo for 2 years, followed by 50 μg (2000 IU) vitamin D daily or placebo for 12 months the primary outcome of bone mineral density in the original study demonstrated no significant difference between the two groups, a lower rate of self-reported upper respiratory infection or influenza was observed in the intervention arm compared to the placebo group. After the increase in vitamin D dosage from 20 μg (800 IU) to 50 μg (2000 IU) daily the effect was even magnified\(^{(47)}\). Further, a follow-up study with 162 healthy adults given 50 μg (2000 IU) vitamin D or placebo daily for 12 weeks during the winter and spring months showed no benefit in the incidence and the severity of upper respiratory infection symptoms for the vitamin D group \(v\). the placebo group. In the study appropriate increase in serum 25(OH)\(_3\) levels in the intervention group from 62 to 89 nmol/l at 12 weeks was noted. However, there was a statistical trend to favour the vitamin D group suggesting that a larger sample size, adequate vitamin D repletion and a longer period may be beneficial in the design of future studies to maximise immunomodulatory effects\(^{(84)}\). Our recent placebo-controlled double-blinded study involving 164 young Finnish men who received 10 μg (400 IU) vitamin D or placebo daily provides some evidence for a preventive effect of vitamin D supplementation against respiratory tract infection. The Cox regression analysis of the study indicated that the hazard ratio for absence from duty due to respiratory tract infection was lower, the number of days absent was slightly lower and the proportion of subjects without any days absent was slightly higher in the vitamin D supplementation group compared to the control group. Due to a higher compliance in the beginning of the study the effect was even more...
pronounced during the first 6 weeks. Further, the number needed to treat, calculated from the proportion of men without any days absent from duty, was as low as 6.4, but a very wide CI. All Finnish men must complete 6, 9 or 12 months of compulsory military service from 18 to 29 years of age. That makes our study population exceptionally homogeneous with respect to age, physical activity, nutrition, clothing, living areas and exposure to sunlight in the military environment. As conscripts live in close quarters, respiratory infections are common in garrisons, which thereby offers an optimal setting for this kind of study.

### Conclusion

Several studies have revealed the high prevalence of vitamin D insufficiency worldwide. As we better understand the immunomodulatory and antimicrobial effects of vitamin D, the clinical significance of maintaining vitamin D sufficiency becomes even more apparent. The 2011 Report on Dietary Reference Intakes for Ca and Vitamin D from the Institute of Medicine in the USA\(^{(86)}\) concludes that scientific evidence supports a key role of vitamin D in skeletal health. However, for extraskeletal outcomes, including immune disorders, the evidence is still inconsistent and randomised clinical trial evidence is limited, inconclusive as to causality and insufficient to inform nutritional requirements. They conclude that based on bone health, the RDA for vitamin D is 15\(\mu\)g/d (600 IU/d) for ages 1–70 years and 20\(\mu\)g/d (800 IU/d) for ages 71 years and older corresponding to a serum 25(OH)D level of at least 50 nmol/L. Further, it seems that very high values are not associated with greater benefit, and for some outcomes U-shaped associations can be observed showing risks at both low and high levels\(^{(86)}\). Randomised controlled dose-ranging trials with larger populations are still warranted to explore the preventive effect of vitamin D supplementation on respiratory tract infections.

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