

REVIEW

Why do so many trials of vitamin D supplementation fail?

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Abstract

Our knowledge of vitamin D has come a long way since the 100 years it took for doctors to accept, between 1860 and 1890, that both sunlight and cod liver oil (a well-known folk remedy) cured and prevented rickets. Vitamins D₂/D₃ were discovered exactly a hundred years ago, and over the last 50 years vitamin D has been found to have many effects on virtually all human tissues and not just on bone health, while mechanisms affecting the actions of vitamin D at the cellular level are increasingly understood, but deficiency persists globally. Observational studies in humans have shown that better provision of vitamin D is strongly associated, dose-wise, with reductions in current and future health risks in line with the known actions of vitamin D. Randomised controlled trials, commonly accepted as providing a 'gold standard' for assessing the efficacy of new forms of treatment, have frequently failed to provide supportive evidence for the expected health benefits of supplementation. Such RCTs, however, have used designs evolved for testing drugs while vitamin D is a nutrient; the appreciation of this difference is critical to identifying health benefits from existing RCT data and for improving future RCT design. This report aims, therefore, to provide a brief overview of the evidence for a range of non-bony health benefits of vitamin D repletion; to discuss specific aspects of vitamin D biology that can confound RCT design and how to allow for them.

Key Words

- ▶ vitamin D
- ▶ trials
- ▶ confounding
- ▶ nutrition
- ▶ health outcomes
- ▶ non-bony

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Associations of vitamin D status with health outcomes

Cross-sectionally, vitamin D cures/prevents rickets but populations remain deficient (1, 2) as assessed by serum 25-hydroxyvitamin D concentration (25(OH)D), which is inversely associated with obesity, immunity, the rates of many infections, cancers (e.g. breast and colorectal), and cancer mortality, with chronic disorders such as insulin resistance, metabolic syndrome (Syndrome X), type 2 diabetes (T2DM), acute cardiovascular events (e.g. myocardial infarction) and with disorders of pregnancy (stillbirth, small for date babies, pre-term births and gestational diabetes) (3, 4, 5, 6, 7, 8, 9, 10).

Prospectively, higher vitamin D status (serum 25(OH)D concentration) predicts later reductions in

the risks of many disorders, dose-wise. For example, of metabolic syndrome after ~10 years, of T2DM after ~10 years, of T1DM after 3–5 years (in early life), of CVD events and in overall CVD mortality. Lower incidence and mortality rates are also reported for some cancers (e.g. breast and colorectal). Such predictive associations may seem surprising when serum 25(OH)D is well-known to vary with season but between 30 and 50% of an individual's 25(OH)D is heritable, based on genome-wide association study data, while baseline 25(OH)D predicted ~50% of 25(OH)D remeasured after 14 years (11, 12, 13, 14, 15, 16, 17).

Vitamin D in evolution

Ergocalciferol and cholecalciferol (vitamins D₂ and D₃) first appeared in early unicellular ocean dwelling organisms and are thought to have allowed their survival by providing protection from the intensive UVB reaching the earth's surface, its energy being dissipated as it destroyed these compounds. Synthesis of ergocalciferol persists in plants and fungi and of cholecalciferol in most animals, though some acquire it solely through the food chain (18). Both forms of vitamin D are fat soluble and biologically inert. Further references to vitamin D in this report are limited to cholecalciferol (D₃) unless otherwise stated.

Production of vitamin D

Cholecalciferol is synthesised in the skin under the influence of UVB (wavelength 270–300 nm) in sunlight that reaches the earth's surface in the greatest amounts in equatorial regions and in the lowest amounts near the poles. Skin synthesis is reduced by skin pigmentation, melanin acting as a sunscreen in those evolving in equatorial Africa. The evolution of fairer skin as humans migrated towards the polar regions, allowing increased skin synthesis despite less available UVB, was important in human survival following those migrations since little vitamin D is provided in foods, for example, in egg yolk, oily sea and fresh-water (but not farmed) fish and fortified foods, but in much smaller amounts than is induced *in vivo* by moderate skin exposure to UVB from summer sunshine (19, 20).

The common problem of vitamin D inadequacy

Modern lifestyles reduce our exposure to sunshine due to working, exercising and travelling behind glass, which blocks UVB transmission, aggravated by widespread sun-avoidance aimed at reducing skin ageing and skin cancer risks, by the increasing use of sunscreens and cosmetics containing sun-blockers and by the continuing migration of dark skinned peoples to temperate zones. Skin synthesis also falls with age, increasing the risks of deficiency in the elderly (20, 21, 22). It is no surprise, therefore, that there is currently a global problem of vitamin D inadequacy with the reappearance of rickets and osteomalacia, the classic bone diseases seen in vitamin D deficiency (23). Though most countries provide guidance on recommended daily intakes of vitamin D, especially in infants and children,

actual intakes are often inadequate for bone health, especially in dark skinned migrant communities, while the intakes needed to reduce non-skeletal health risks of deficiency are increasingly recognised as being higher than those for bone health (24).

Route from inert vitamin D to hormonal activity

Both vitamins D₂ and D₃ are inert and fat soluble, best absorbed when eaten with fatty foods, and stored in fatty tissues, though absorption falls with ageing. Two-stage hydroxylation of the inert vitamin leads to its activation; first, a specific 25-hydroxylase (CYP2R1, found mainly in the liver, adds an –OH group at the 25-position forming 25-hydroxyvitamin D (25(OH)D). This metabolite binds to specific binding proteins (and albumen) in the blood stream and leaves the circulation with a half-life of 2–17 weeks, the half-life increasing mainly with baseline vitamin D status but also varying with genetics (25). Vitamin D provision from skin synthesis raises serum 25(OH)D concentrations faster and to higher levels than oral intakes, reflecting the 25-hydroxylation of vitamin D in the skin (26), while absorption of D₃ from skin may be faster than from the gut.

Circulating concentrations of 25(OH)D are generally accepted as reflecting body stores of vitamin D (vitamin D status), mainly because they relate closely to health outcomes cross-sectionally and prospectively, as mentioned earlier. 25(OH)D is the substrate taken up by cells where a second hydroxylation by a specific 1 α -hydroxylase (CYP-27B1) forms calcitriol (1 α ,25(OH)₂ vitamin D), first identified in the kidney, with hormonal effects modulating processes relevant to bone health. This activation is now known to occur in all target tissues, where locally produced calcitriol has autocrine and paracrine functions. Renal calcitriol production is regulated by factors including parathyroid hormone, FGF23 (fibroblast growth factor 23), serum phosphate and prolactin. In other target tissues, all of which express both the activating hydroxylase and the vitamin D receptor, calcitriol production is mainly up-regulated by serum 25(OH)D concentration and down-regulated by the specific catabolic 24-OHase, explaining the value of serum 25(OH)D data for evaluating vitamin D 'status' and for assessing the effects of changes in vitamin D status on health risks and health outcomes *in vivo*. Circulating calcitriol concentrations, in contrast, are tightly regulated, do not reflect vitamin D status, are unhelpful in diagnosing

vitamin D deficiency and rarely relate closely to human disease risks, though it is calcitriol that effects the actions of vitamin D in the tissues (27, 28). Both skin synthesis of vitamin D and its activation are self-regulated, avoiding excessive production of vitamin D₃ or of calcitriol. Thus, vitamin D toxicity cannot be induced by sunshine in health, though hugely excessive intakes can overwhelm the regulatory system causing hypercalcaemic toxicity. Rare lymphoid disorders (e.g. sarcoidosis), with loss of local tissue regulation, especially in macrophages, allow unregulated calcitriol overproduction ('vitamin D hypersensitivity') (29).

Induction of biological effects of vitamin D in target tissues

There are three major mechanisms by which calcitriol induces its effects on the tissues. In brief, the first mechanism follows non-genomic binding of calcitriol to vitamin D receptors (VDRs) in cell wall caveolae causing rapid rises in intracellular calcium concentrations which, in turn, activate rapid effects (30). For example, this mechanism triggers early insulin release in response to rise in blood glucose through activation of certain beta cell endopeptidases that release insulin from pancreatic islet beta cell storage granules by splitting insulin from proinsulin and raising circulating insulin within minutes (31). The second and slower mechanism is induction of changes in the rates of synthesis of gene products following the binding of ligand (calcitriol)-bound VDRs (commonly complexed with retinol-X receptors), to vitamin D response elements (VDREs) in the promoter regions of many hundreds of target genes; multiple genes show seasonal variation in expression, many relating to varying vitamin D status (32, 33). One example is the slower increase in islet beta cell insulin synthesis, during phase 2 of the insulin response to glucose, peaking ~20–30 min after glycaemia begins to rise. The third mechanism is through epigenetic effects of vitamin D at different stages in development which silence various metabolic and developmental processes temporarily where appropriate (28), and that appear to be especially important in early life. Epigenetic effects are induced through three main mechanisms (many being reversible), either by altering gene methylation, by changing the configuration of histone cores around which chromatid chains are wound within the chromosomes, or by inducing changes in non-coding genetic RNA (34).

Many mechanistic effects improve function or reduce damage in non-skeletal tissues

Though beyond the scope of this discussion, there are many well-understood actions due to the rapid non-genomic or slow genomic effects of calcitriol mentioned above, that are protective. For obesity, T2DM and hypertension these include effects on the pancreas, liver, and muscle that reduce abnormal insulin resistance, protect beta cell function and protect against arterial wall damage (35, 36, 37, 38, 39, 40, 41). In the immune system they protect against bacterial and viral infections, excessive acquired immune responses and more generally against inflammatory tissue damage (42, 43, 44, 45, 46, 47, 48, 49, 50, 51). Other beneficial effects include inhibition of cancer development and progression (52, 53, 54, 55), promotion of normal foetal development (notably of the brain) and of healthy pregnancy through direct effects of maternal vitamin D status and epigenetic effects of maternal vitamin D status on the developing foetus (56, 57, 58, 59).

In view of these well-understood effects of vitamin D and of the consistent associations of poor vitamin D status with increase in health risks in the areas mentioned, one has to wonder whether the failures of RCTs to show the expected health benefits with supplementation might reflect a degree of confounding of those RCTs, rather than that all of the mechanisms identified as being active in human tissues are irrelevant to human health. This concern is strengthened by the fact that provision of vitamin D in pet foods, especially for domestic pets and carnivores unable to synthesise the vitamin efficiently, is now a standard practice, as it is in zoos and for animals farmed under partly indoor conditions, including ruminants and poultry, because of the evident health benefits (https://www.dsm.com/markets/anh/en_US/Compendium/companion_animals/vitamin_D.html).

Potential confounders of vitamin D RCTs

Design defects

First, vitamin D is a nutrient, not a drug, and the graphs for changes in biological effects as vitamin D provision increases from nil to adequacy are not linear but S-shaped, both for rise in serum 25(OH)D with better vitamin D provision and for increase in the effects of increase in serum 25(OH)D (60). These S-shaped response curves mean that, in deficiency, no changes in function/benefits will be seen

unless 25(OH)D values are raised from deficiency onto the steep part of the S curve for the effect(s) of interest and that when baseline 25(OH)Ds are already on the upper plateau of the S curve, extra provision will not induce benefits. Thus, in RCTs, where identical doses are given to everyone in the treatment arm, the doses will be too small to normalise serum 25(OH)D in many deficient subjects and unable to induce significant changes in effects/outcomes in 'replete' subjects. Thus, the chances of seeing measurable health benefits will be lost in significant proportions of study subjects in the treatment arm unless results can be picked out for those who were deficient at baseline, and, ideally, made replete during the RCT. Most workers, however, have simply aimed to seek health benefits in the general population. The need to allow for this confounder is well-illustrated by a study of individual participant data retrieved from 25 previous RCTs for reduction of upper respiratory tract infection rates by supplementation where re-examination by meta-analysis used baseline 25(OH)D data available for ~11,000 participants stratified by 'status'. The overall hazard ratio (HR) for that cohort was 0.88 (95% CI; 0.81–0.96), but for subjects with a baseline 25(OH)D <25 nmol/L it was 0.30 (95% CI; 0.17–0.53) for those on daily/weekly dosing (but not in those on interval doses using large boluses (which have previously been reported to induce adverse effects on bone health)) (61, 62). Other analyses using stratified 25(OH)D data have shown improvements in insulin resistance and diabetic control, and in a meta-analysis of RCT data on supplementation in T2DM (63). In pre-diabetes fasting plasma glucose fell with supplementation in subjects with baseline BMIs <25 or 25(OH)Ds of 50–75 nmol/L, insulin resistance was reduced with baseline 25(OH)Ds >75 nmol/L and reductions in T2DM risk were found for subjects with BMIs <25 or 25(OH)Ds of 50–75 nmol/L. These benefits were largest with higher dosages (2000 IU/day) and when supplementation did not include calcium (63, 64).

Variations in 25(OH)D effect thresholds

This phenomenon is another potential confounder of RCT analyses (65). Bone health, for example, is generally accepted as being protected when serum 25(OH)D values are at least 50 nmol/L, as assessed from the available evidence in 2011 by the North American Institute of Medicine in 2011 (66).

While this threshold for bone health continues to be used, higher thresholds of serum 25(OH)D concentration

are emerging for non-skeletal health benefits. For example, abnormal insulin resistance in deficient subjects with normoglycaemia was not reduced unless 25(OH)D values reached at least 80 nmol/L (67). Other suggested thresholds lie between 50 and 100 nmol/L. Thus, failure to ensure that the necessary thresholds are reached, and maintained, for the health outcome(s) of interest during RCTs is a likely confounder. Avoidance of this problem would require checking 25(OH)D values during RCTs so that individual dosages could be adjusted for maintenance of 25(OH)Ds at or above the appropriate thresholds. Furthermore, if binary analyses of outcomes are made for 25(OH)D values, for example, for outcomes in subjects reaching 25(OH)D values more or less than 50 nmol/L, when the actual effect threshold is considerably higher, the findings would be confounded by including many inadequately supplemented subjects in the stratum of data hypothesised, *a priori*, as likely to benefit from supplementation. However, specific thresholds could be detected by using various potential cut-offs in such comparisons.

Non-supplemental vitamin D intakes during RCTs and varying absorption

Vitamin D is normally acquired through skin synthesis and from food, but these sources are rarely controlled for. Continued self-supplementation during RCTs can contribute to confounding of RCT data analyses, but is often allowed (e.g. in the VITAL study) (68). Higher socio-economic status is clearly associated with healthier lifestyles, including increases in physical activity, access to healthier foods and more sunshine holidays. These factors are associated with higher vitamin D status and usually allowed for in RCT data analyses, even though increased supplement usage is not.

Absorption of supplemental vitamin D varies with how much fat it is taken with, but RCT subjects are not normally asked to take supplements in any specific way. Absorption of vitamin D becomes less efficient with age, but compensatory dose increases are not provided (69). Importantly also, $\times 1.5$ - and $\times 2$ – 3 -fold increases in vitamin D dose are needed in overweight and obese people respectively, to achieve adequate 25(OH)D rises matching those in the non-obese, but are not normally provided in RCTs (70). None of these problems, common in vitamin D RCTs, would matter if RCTs were organised by baseline and achieved 25(OH)D values, monitoring status and adjusting doses to ensure planned target vitamin D status

is maintained throughout (71). Additionally, since it is not ethically acceptable to leave controls deficient during longer RCTs, they are often given locally advised daily recommended supplements, possibly affecting repletion in some control subjects.

Other dietary factors modulating vitamin D efficacy

These include calcium intake, sometimes allowed for or given as additional supplementation (69). Calcium is an important nutrient since childhood rickets can be healed by adequate calcium intake; however, for non-bony effects, on the cardiovascular system for example, where higher dietary calcium intakes have been reported to have beneficial effects on CVD outcomes, supplemental calcium may have adverse effects (72, 73). Other dietary factors rarely assessed include magnesium, commonly deficient, which is essential for optimal enzyme function, including those in the vitamin D axis and signalling pathways (74). Vitamin A is necessary for vitamin D signalling but excessive intakes, common in developed countries, can antagonise vitamin D's effects, perhaps through annexation of the retinoid X receptor (RXR) to form RXR:RAR complexes (75). Experimentally, vitamin D toxicity is mitigated by large doses of vitamin A and in humans supplemental vitamin A can abolish health benefits of vitamin D supplementation (76, 77). Other interactions are reported for vitamin K (and possibly other vitamins) (78). Intakes of these nutritional factors should, therefore, be allowed in RCT analyses, ideally through dietary data collection for automated *in silico* analyses of those intakes in both arms of vitamin D RCTs.

Stratification by vitamin D 'status' or by effect thresholds?

Most RCT analyses have used baseline (+/- achieved) vitamin D status to stratify their analyses using existing definitions of deficiency, for example, <25 nmol/L in the United Kingdom (where 25–75 nmol/L = insufficiency), <50 nmol/L in North America's Institute of Medicine guidelines and <75 nmol/L in the US Endocrine Society guidelines (66, 79, 80). Other thresholds have been suggested and 25(OH)D thresholds for plateaus in serum parathyroid hormone concentrations also vary, an observation of as yet unknown significance (81). Thresholds for outcomes suggested from RCT data rarely match such definitions, which will perturb outcome

analyses, as discussed above. Additionally, different definitions of 'status' make it difficult to compare findings or to gather RCT data for meta-analysis unless individual participant data (IPD) is available. The use of tertiles, quintiles may sound a reasonable way to avoid these problems but for health benefits with specific 25(OH)D thresholds this methodology is unlikely to produce stratification matching specific thresholds, so that this methodology could obscure health benefits. Many of these aspects of RCT data analysis could be better allowed for once assay data harmonisation becomes routine and effect thresholds are identified and agreed internationally.

Factors affecting the consistency of 25(OH)D assay measurements

25(OH)D data has been widely used in observational studies and RCTs, but there has been little allowance for the many problems inherent to these measurements. First, the variability of the widely used immunoassay methodology is considerable, with cumulative variances of 7–19% in one study (82). This problem has been reduced by increasing compliance of laboratories world-wide with the international quality control scheme, DEQAS (83). The increasing use of the current 'gold standard' HPLC-TMS assay methodology (high pressure liquid chromatography-tandem mass spectroscopy) produces 25(OH)D concentrations higher than immunoassay results by +3 to +6%, and occasionally by up to +33% (84, 85). This problem means that data from various studies, including RCTs, cannot always be compared or used in meta-analyses unless stored samples from older studies are available for re-assay with HPLC-TMS methodology, allowing assay 'Harmonisation' (86). These differences in 25(OH)D assay values also mean that 25(OH)D cut-off levels used to define 'status' need to be updated, and agreed internationally, if future study data is to be used in comparisons, for meta-analyses, or for international agreement on effect thresholds – a matter likely to increase in importance once effect thresholds can be used to define degrees of vitamin D adequacy for different disorders.

Serum 25(OH)D values vary with genetic polymorphisms

Variants are common in genes relating to D binding proteins and in genes regulating vitamin D activation. Importantly, many of these variants affect the size of the

increase in 25(OH)D with supplementation and these variations can be as large or larger than 25(OH)D assay variability. Some gene effects are only seen in the winter, being swamped by summertime increase in 25(OH)D (87, 88). Few studies allow for these genetic variations as yet but, since they contribute to the provision of circulating 25(OH)D substrate to local target tissues for activation, they must modulate vitamin D efficacy. Adjustment for these gene variants, therefore, may well become routine in future RCT analyses.

Free vs bound 25-hydroxyvitamin D

Most 25(OH)D in the circulation is bound to the binding proteins already mentioned but small amounts remain unbound or 'free'. The relative importance of unbound versus bound 25(OH)D uptake by different target tissues remains unclear but may become more important as this factor becomes better understood (89).

Newer findings on disorders directly affecting serum 25(OH)D concentrations

In addition to the factors discussed above, it has been reported that the specific hepatic 25-hydroxylase enzyme, previously assumed to be constitutively expressed, is down-regulated in obesity (and diabetes). Additionally, expression of the 24(OH)ase specifically catabolic for calcitriol and its precursor is increased in obesity, supporting Mendelian randomisation reports that obesity reduces serum 25(OH)D rather than that deficiency increases obesity (90, 91, 92). This could be taken to mean that low 25(OH)D values in obesity have no importance, being due to reverse confounding; however, this effect reduces 25(OH)D availability to target tissues, which is likely to worsen the severity of disorders associated with both obesity and T2DM. Interestingly, this additional problem in obesity can also be countered by increased glutathione provision (93, 94). Obesity-related disorders include inflammation, which extends to tissues remote from adipose tissue (e.g. atheromatous plaque) (95). Thus, the reduced insulin secretory capacity and increased insulin resistance that follow as a result of adverse mechanistic effects of vitamin D inadequacy on liver, muscle and pancreatic islet function will increase the risks of overt T2DM, of atheromatous disease and of acute CVD events and death in obesity and T2DM. In view of these problems, patients with obesity, T2DM, or both, need higher than usual supplemental vitamin D

intake to achieve adequate vitamin D status (e.g. 25(OH)D values >75 nmol/L) which should reduce the risks of the disorders associated with obesity and diabetes that are modulated by vitamin D (96). However, this consideration is not regularly allowed for in the routine management of patients with overweight, obesity or diabetes or in RCTs designed for assessing the potential of vitamin D supplementation for prevention or amelioration of these disorders or their sequelae.

Lack of long-term RCTs

No sufficiently long-term RCTs exist to test whether achieving long-term repletion may reduce the risks of the very chronic disorders they may aggravate, such as CVD, nor will they be, since leaving controls deficient long-term is unethical. Fortunately, on-going Finnish public health data collection following the introduction of food fortification in 2003 and the virtual abolition of deficiency from 2010 onwards may reveal reductions in the risks of these chronic disorders, for example, of T2DM since 10–20 years is the average time for increased insulin resistance to lead to overt T2DM (39, 97). Since overt CVD is well-known to result from progressive atherosclerosis, from adolescence or early adulthood onwards (98), any vitamin D supplementation-related benefits for CVD risks could take much longer to appear, even in Finland.

Mendelian randomisation data

A recent Mendelian randomisation (MR) study found no evidence that higher D status as judged from genetic variant associations reduces inflammation in obesity, though greater T2DM risks (+14%) were found for genetic variants associated with lower 25(OH)D values than were found with the actual 25(OH)D assay data (+9%) (99). Since the 25(OH)D assays had been carried out in a single laboratory, these data support the view that 25(OH)D assay variability can confound epidemiological data analyses. A further MR study supports the suggestion that reduction in vitamin D status is a causal determinant of T2DM risk (100). Various factors perturbing RCT outcome analyses also apply to MR analyses for 25(OH)D as an outcome, necessarily reducing MR ability to detect health benefits with specific genetic variants, especially where many subjects have 25(OH)D values on the upper or lower plateaus of observational S-shaped association curves. Re-analyses using 25(OH)D data stratified around

specific thresholds of interest or along steep parts of the curves for observational associations of health outcome of interest with 25(OH)D might reveal genetic variant effects that are not detected using standard MR methodology (B J Boucher, unpublished observations).

Future RCT design

Allowing for the various factors reducing RCT specificity discussed above should improve our ability to get definite answers to the many persisting queries about whether known mechanistic effects of vitamin D translate into non-skeletal health benefits. The costly and labour-intensive VITAL study was designed before most of these problems in vitamin D RCTs had become apparent, for example, 25(OH)D values were <75 nmol/L in only 12.7% of those assessed. However, cancer mortality was reduced by supplementation, and further outcome analyses in initially deficient subjects will be of interest (68). Ensuring that 25(OH)D threshold values for different disorders are identified from future RCTs could encourage efforts to ensure vitamin D adequacy is achieved globally especially since the intakes, planned to achieve 50 nmol/L in 97.5% of the population by the North American Institute of Medicine (IOM), are thought to have been calculated to achieve that target in only 50% of the population (reported as ten-fold underestimates of the intakes necessary) (101, 102). However, the original IOM (now the National Academy of Medicine) advice remains unchanged. The guidelines on recommended daily intakes for different adult population groups continue to differ widely, even when directed solely at maintaining skeletal health and used different 25(OH)D cut-offs for protecting bone health. The IOM, for example, defines deficiency as serum 25(OH)D values <50 nmol/L and insufficiency as 50–75 nmol/L; the American Endocrine Society defines deficiency as 25(OH)D values <75 nmol/L. The UK Specialist Advisory Committee on Nutrition (SACN) defines deficiency as 25(OH)D values <25 nmol/L and insufficiency as 25–50 nmol/L. In Europe, deficiency is defined by 25(OH)D values <50 nmol/L (80, 103, 104). However, all of these guidelines are either inadequate, or ineffective, since deficiency and insufficiency for bone health continue to be present globally at levels that have been described as ‘pandemic’ (2). Currently, vitamin D inadequacy is also postulated to increase the risks of severe COVID-19 in the current SARS-2 outbreak through various mechanisms including reduced production of antibacterial and antiviral defensins and cathelicidin,

inadequate secretion of anti-inflammatory cytokines, reduced suppression of pro-inflammatory cytokine, secretion and inadequate pulmonary secretion of ACE2, a known protective factor for other acute respiratory distress syndromes (4, 105).

Overview

Vitamin D deficiency has no health benefits and continues to cause overt, painful and disabling bone disease while, concurrently, correction of deficiency by supplementation is reported to reduce T2DM risks and cancer mortality (39, 68). The problem of deficiency persists because of the poor provision of vitamin D by foodstuffs and because current lifestyles reduce exposure to sunlight. In addition, policy makers advising on minimal vitamin D intakes at the population level have relied heavily on data for health benefits from RCTs inappropriate for studying nutrients, since they can miss or obscure such benefits. Fortunately, current improvements in RCT data handling are now revealing some mechanistically predicted non-skeletal health benefits. However, while future RCTs of vitamin D must allow adequately for its biology when seeking further evidence in this area, the difficulties in ensuring that RCT design is fit for purpose does not justify the continuing acceptance of deficiency at current levels, globally, when it has been formally recognised as requiring correction for protection of skeletal health since 2011 (66).

Vitamin D deficiency severe enough to cause bone disease is avoidable through simple measures, as humankind has known for well over 100 years – these are used routinely in animal husbandry, commercial pet foods and zoos but are provided in few human populations (106, 107).

Vitamin D inadequacy has been well-known for ~60 years to be more common in people of south Asian than of indigenous origin in the United Kingdom and is currently suspected of being a factor that increases COVID-19 risks (108, 109). The UK Biobank data from 2003–2010 confirms the persistence of this problem in a reasonably large cohort of healthy volunteers and recent analyses suggest that lifestyle factors and deprivation do not fully explain these increased risks. Better lifestyle is associated with higher vitamin D status and is an obvious confounder of RCT findings of benefit with vitamin D. Obesity and diabetes, both of which specifically lower D status, are considered significant risk factors for COVID-19 severity. The adjustment of data in analyses such as those using the UK Biobank data is therefore

complex, with many interactive confounders. This is an example of an acute disorder where cross-sectional and prospective risks with vitamin D status may be less helpful than the results of trials of supplementation of deficiency in at risk communities and in early covid-19 illness for the determination of the relative roles of these risk factors for this acute illness (110).

Overall, it would be helpful if vitamin D deficiency, as currently defined for skeletal health, could be abolished in humans at the population level by measures independent of individual effort, such as the highly effective food fortification + self-supplementation programme in Finland (111). Fortification of flour plus free supplementation of high-risk groups, for example, has been proposed as a cost-effective way to abolish deficiency in the United Kingdom (112). With effective programmes to reduce skeletal health risks in place, future research could focus on other aspects of vitamin D's role in human health such as establishing what further contributions improved vitamin D status may make to non-skeletal health, the correction of undesirable epigenetic effects of deficiency (especially in pregnancy where it may increase later health risks in offspring), the identification and correction of disadvantageous nutrient interactions and dealing with new problems that emerge as our understanding of the complexities of the vitamin D system increases.

Declaration of interest

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