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REVIEW

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Do studies reporting 'U'-shaped serum 25-hydroxyvitamin D–health outcome relationships reflect adverse effects?

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ABSTRACT

Several reports describe U-shaped 25-hydroxyvitamin D [25(OH)D] concentration–health outcomes, including musculo-skeletal disorders such as falls and fractures, several cancers, cardiovascular disease (CVD), cognitive function, all-cause mortality rates, birth outcomes, allergic reactions, frailty, and some other disorders. This paper reviews reports of U-shaped outcome associations with vitamin D status for evidence of underlying pathophysiological processes, or of confounding, finding that some U-shaped associations appear to be biologically meaningful, but that many could well reflect confounding by factors such as lifestyle, or hypovitaminosis D-related disease onset being masked by self-supplementation that was begun too late to correct developing health problems but before baseline vitamin D status assessment. However, the various U-shaped associations for allergic reactions may be due to vitamin D modulation of the phenotype of the immune response, shifting the Th1-Th2 balance toward Th2 formation. For prostate cancer, there seems to be little effect of 25(OH)D concentration on incidence; however, there is an inverse correlation between 25(OH)D concentration and mortality rates. Future observational studies, and randomized controlled trial data analyses, should include adjustment for data collected on prior long-term vitamin D supplementation and solar UVB exposure, as well as other potential confounders.

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Introduction

The study of the health benefits of vitamin D has expanded in scope during the past 15 y to encompass many conditions and diseases to include musculo-skeletal disorders,[1,2] chronic disorders such as metabolic syndrome, types 1 and 2 diabetes[3] and cardiovascular disease (CVD),[4] various cancers,[5,6] allergic reactions,[7] neuro-psychiatric disorders, including Alzheimer disease[8] and autism,[9] autoimmune disease,[10] pregnancy and birth outcomes,[11] respiratory, including tuberculosis,[12] and other infections, including dental caries.[13] Most observational studies have reported inverse correlations of serum 25-hydroxyvitamin D [25(OH)D] with health outcomes. However, a few studies also reported adverse outcomes with higher 25 (OH)D concentrations, suggesting caution is needed in considering vitamin D supplementation >10,000 IU/d (>250 μg/d) until this phenomenon is understood,[14] and existing clinical trials have been examined for the safety of higher vitamin D_3 doses.[15]

Methods

In an attempt to resolve those discrepancies we reviewed the literature on vitamin D and health outcomes to determine how to consider upturns in adverse outcomes with

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higher vitamin D status. Using the National Library of Medicine's PubMed database and Google Scholar, we focused on health outcomes for which studies found U, or similarly shaped, associations between 25(OH)D concentration and health outcomes. We also searched related articles and links and, by manually searching references cited in key reports, identified some additional articles. We evaluated the magnitude and relevance of the evidence for U-, or similarly shaped, associations. In each case, we considered whether explanations can be offered, either to account for the observed relationship, or to suggest that the observed relationships were not necessarily causal, but could be explained by covariates not normally considered in studies on vitamin D status and health outcomes.

Results

Cancer

Only a few studies report either a direct (positive) or a U-shaped relation between serum 25(OH)D concentrations and later cancer incidence. This section reviews these studies, pointing out strengths and weaknesses.

Pancreatic cancer

Two prospective observational studies reported increased risk of pancreatic cancer incidence with higher 25(OH)D concentrations: one in Finland[16] and one in the United States.[17] However, when the US cohort was examined by regions of low and high residential sun exposure, people with low sun exposure had a significantly higher incidence rate, with baseline 25(OH)D concentrations of >78 nmol/L and <49 nmol/L, respectively, while those living in regions with high sun exposure had insignificantly increased risk: the authors noted that 25(OH)D concentrations were a total of vitamin D_2 and D_3 metabolites. In comparison, 2 prospective observational studies of participants enrolled from the entire United States (one based on "predicted vitamin D levels;"[18] the other, a pooled analysis of 5 nested case–control studies),[19] found inverse correlations between 25(OH)D concentrations and pancreatic cancer risk. One feasible explanation for the discrepancy between these 2 studies, is that people living in regions of low sun exposure were taking vitamin D supplements, possibly begun shortly before enrollment and blood sampling. A recent paper reported that 25(OH)D_2 was detected in 57% of blood samples that had a total 25(OH)D >125 nmol/L in blood samples collected from adults in the United States throughout the year. Since vitamin D_2 is the main form of vitamin D that is available in United States on prescription, these data suggested that a majority of patients were being treated with vitamin D, and probably for deficiency.[20] Geographical ecological studies support a role of solar ultraviolet-B (UVB) radiation in reducing risk of pancreatic cancer through vitamin D production and possibly other mechanisms.[6]

Prostate cancer

Observational studies associate both the lowest and highest 25(OH)D concentrations with increased risk of prostate cancer (PC). The first study from Scandinavian countries reported a U-shape association of 25(OH)D with PC risk in 2004.[21] The findings for this and similar studies reporting U-shaped 25(OH)D concentration-PC incidence relations are given in Table 1. The 25(OH)D concentration associated with minimum risk of PC incidence in these studies varies from <16.3 nmol/L to 72.9 nmol/L. One possible problem with these studies is that long follow-up times were used. However, in an analysis of the effect of follow-up time on 25(OH)D concentration and cancer incidence associations for colorectal cancer, after up to 14 years, still showed significant inverse correlations for risk with both high and low 25(OH)D concentration, while

Table 1. Reports of U-shaped 25(OH)D concentration-PC incidence relations.

Location	Follow-up period (yrs)	Optimal 25(OH)D concentration (nmol/L)	Adverse higher 25(OH)D concentration (nmol/L)	Reference
Finland, Norway and Sweden	Up to 11, 16, or 24, depending on country	40–59	80	21
Finland	Up to 20	<16.3	23.8–33.3 and >45	23
Sweden	Up to 14	<68	85–102	24
Norway	Up to 25	30–69	>69	25
USA	Up to 8	58.2–72.9	>72.9	26
France	13	>62	Not given	27

for breast cancer, significant inverse correlations were found only for follow-up times less than 3 y.[22] For PC, the results were generally not significant for follow-up times between 4 and 28 y.

A recent meta-analysis of 21 observational studies found an odds ratio (OR) for PC, for highest versus lowest 25(OH)D quartiles, of 1.17 (95% confidence interval [CI], 1.08–1.27).[28] Twelve of the studies were from the US.

One possible confounding factor that might help explain the slight increased detection of PC for those with higher 25(OH)D concentrations is the widespread use of the PSA test for screening. By the early 1980s, PC incidence rates in the US started to climb, peaking at a 120% increase by 1992 before declining to a 50% increase through the early 2000s.[29] At the same time, mortality rates rose by 30% by 1992 before declining to pre-PSA era rates by 2002. PSA screening has been widespread, but with different effects on mortality rates in different countries.[30] It could be the case that men who are more health conscious have both higher 25(OH)D concentrations and are more likely to use PSA screening for PC detection.

There is, however, good evidence that higher 25(OH) D concentrations are associated with reduced risk of lethal PC. A prospective nested case-control study from the Health Professionals Follow-up Study involving 1260 men who were diagnosed with PC between 1993 and 2004 found that those in the highest 2 25(OH)D quartiles had significantly lower risk of fatal PC compared to those in the lowest quartile; however, there were no significant differences in risk of PC with respect to 25(OH)D concentration.[31] Analysis of deaths for 1000 PC cases from the Alpha-Tocopherol, Beta-Carotene Prevention Study in the US found that for those who survived >3.3 years, the hazard ratio for death for high vs. low quintile of 25(OH)D concentration from time of enrollment was 0.53 (95% CI, 0.34–0.85, $P_{trend} = 0.0002$).[32] The effect for shorter times was insignificant.

In a clinical trial in which 48 men with low-grade PC and mean baseline 25(OH)D concentration of 82 nmol/L took 4000 IU/day vitamin D_3 for a year,[33] they reached a mean 25(OH)D concentration of 166 nmol/L. PC progression in comparisons of repeat biopsy outcome was observed in 34% of the participants compared to 63% of historical controls while 55% had improvement on repeat biopsy compared with 21% of historical controls,[33] suggesting that vitamin D may reduce progression of PC.

PC grade may play an important role in explaining the possible U-shaped pattern. Analysis of serum 25 (OH)D with advanced vs. localized PC, and by Gleason grade (high vs. low) demonstrated an increased risk of more aggressive PC in men with 25(OH)D concentrations <30 nmol/L.[34,35] Two single-nucleotide polymorphisms (rs4588-A and rs7041-T) in the gene for vitamin D–binding protein, associated with low 25 (OH)D concentration, are also associated with increases in both PC risk and grade.[36] However, higher serum 25(OH)D concentrations may modestly increase PC risks at Gleason scores of 2–6 but reduce the risks of more aggressive PC at Gleason 8–10.[26,37]

Confounding of incidence rates of disorders in relation to risk factors that affect survival, independent of the disorder itself, is well recognized (Neyman's survival bias[38]). However, increasing age is recognized to be associated with lower values of serum 25(OH)D; thus, the association of increased PC rates with higher serum 25(OH)D values, producing U-shaped associations, is unlikely to reflect the Neyman effect, a view supported by the age-matched (within 6 months at enrolment) data for 652 cases and 752 controls that shows no significant correlation of PC incidence with respect to 25(OH)D concentration.[39]

All-cancer mortality rate

The Uppsala Longitudinal Study of Adult Men used blood samples from 1991–1995 and monitored participants through 2007.[40] It found higher cancer incidence and mortality rates for the top 95th percentile of 25(OH)D concentrations for cancer, but not for CVD. The mean age of the men at baseline blood draw was 71 y in 1991–1995, and the lower end of the 95th percentile was 100 nmol/L (40 ng/ml). The authors suggested several mechanisms whereby higher 25(OH)D concentrations could be associated with cancer risk, including well-known effects such as stimulation of the vitamin D catabolic enzyme, (CYP24A1), increased production of insulin-like growth factor; and suppression of the farnesoid X receptor that detoxifies carcinogenic bile acids, reducing risk of cancer of the enterohepatic system. The follow-up period for the Uppsala study was about 14 y. In a study in Norway, the correlation coefficient for 25 (OH) D concentrations at baseline and 14 y follow up was between 0.39 and 0.52,[41] a factor likely to affect the strength of long-term prospective associations.[42]

Cardiovascular disease

Two of 24 prospective studies of this association identified in 2012[4] found U-shaped relationships between 25(OH)D concentration and CVD events, or deaths [in Israel[43] and in Denmark[44]]; their findings are shown in Table 2, but present obvious anomalies. The Israeli study did not distinguish acute coronary events from all-cause deaths - the authors noting that only 29% of deaths in the study group (aged >45 y old), were due to CVD., while the German study dealt with a small population subgroup, subjects undergoing cardiac surgery. Furthermore, those with the highest 25 (OH) D concentrations were very small fractions of the study groups (1.5%–5.0%).

In contrast to those findings, a meta-analysis of CVD incidence or mortality rate, based on 19 independent studies with 6,123 CVD events, including deaths, in 65,994 participants, found a relative risk (RR) of 1.0 for 25(OH) D concentrations >75 nmol/L, although there were only 2 data points for higher concentrations, (93 or 110 nmol/L).[4] A more recent meta-analysis considered values >90 nmol/L, the highest 25(OH)D concentration decile, and found no U-shaped relationship.[46]

Despite the confusion in the findings for U-shaped relationships of outcomes with vitamin D status, the possible confounding factors, explaining such associations, are of interest. Zittermann found that those with the highest 25(OH)D concentration had low 1,25-dihydroxyvitamin D concentrations, and hypothesized that reduced activation of 25(OH)D might account for the U-shaped associations in some disorders.[47,48] Another feasible explanation is that subjects started taking vitamin D after disease development, but before vitamin D status assessment, in various types of association studies. This factor is increasingly likely, with the increasing media coverage on the need to take more vitamin D, as a result of sun avoidance for avoidance of skin cancers. Two cross-sectional studies of frailty status in the elderly with respect to 25(OH) D concentrations in the United States provide some support for this view; in men, an inverse linear relationship[49] was found, but in women, a U-shaped relationship was found,[50] and it is common practice to supplement older women, but not men, with vitamin D in the USA, as in many Western populations.

Thus, though some evidence exists for a U-shaped CVD risk relationship with vitamin D status, it could be due to confounding by taking vitamin D supplements pre-study, but too late to have prevented disease development, or due to D_2 supplementation which may or may not have effects on CVD risks.

Clarification on whether or not increases in serum 25(OH)D can have adverse effects on the cardiovascular system if they rise above some specific concentration requires further studies that can assess intakes from diet of D_3, D_2, and their 25-(OH)D metabolites, as well as of other nutrients known to affect the CVS (including calcium, magnesium, lipids), and also levels of supplementation and when it began.

Falls, fractures, and frailty

As well as having established benefits on calcium metabolism and musculoskeletal health, several lines of evidence link adequate vitamin D status to muscle strength and lower risks of falls.[51] Proximal muscle weakness is a feature of clinical vitamin D deficiency;[52]vitamin D receptor (VDR) is expressed in human muscle[53-56] and vitamin D activation promotes de novo protein synthesis, preferentially, in type II fast twitch muscle fibers, (relevant in fall prevention.[51,53,56] Though several meta-analyses of clinical trials of vitamin D supplementation suggest reductions in falls[57-60] and fractures,[61-63] these outcomes have varied with variations in trial design, and trials selected for meta-analysis.[57,62,64] Furthermore, these outcomes may also vary with vitamin D dosage, dosing interval, and achieved 25(OH)D concentrations. For example, 2 meta-analyses show daily low-dose vitamin D was ineffective when compared with daily doses of 800 IU/

Table 2. Results of the 2 observational studies with U-shaped 25(OH)D concentration-CVD risk associations.

Study Location	Outcome examined	Type of Study	25(OH)D (nmol/L)	Fraction of Cases	HR (95% CIs)	Reference
Israel	MACS	Historical prospective	>90–100	0.05?	HR = 1.08 (1.00–1.11)	43
	MACS	Historical prospective	>100	0.03	HR = 1.13 (1.01–1.21)	43
Germany	MACCE	Prospective	>100	0.03	OR = 2.34 (1.12–4.89)	45
Denmark	CVD mortality	Prospective	<75–100	0.12	MR = 1.10	44
	CVD mortality	Prospective	>100–125	0.04	MR = 1.44	44
	CVD mortality	Prospective	<125	0.02	MR = 1.51	44

95% CI, 95% confidence interval; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events during of cardiac surgery or while still at the hospital; MACS, mortality or acute coronary syndrome; MR, mortality rate; OR, odds ratio.

day.[57,59,65] Trials of higher doses of vitamin D for fall prevention are limited, but one showed no fall reduction in 173 frail seniors post- acute hip fracture with 2000 IU vitamin D/day vs. 800 IU/day over 12 months (HR 1.28; 95% CI: 96%, 168%),[66] with an achieved mean 25(OH)D concentration at 12 months of 111.5 nmol/L in the 2000 IU/day group vs. 88.5 nmol/L in the 800 IU/day group. A further trial in 2256 senior women at high risk of hip fracture using an annual bolus of 500,000 IU of vitamin D vs. placebo, increased fall rates (RR=1.15; 95% CI:1.02–1.30),[67] with an achieved mean 25(OH)D concentration of 120 nmol/L at 1 month and 90 nmol/L at 3 months post dose, by which time most additional falls had happened. A more recent trial tested 3 monthly doses of vitamin D among 200 community-dwelling seniors who all had fallen in the prior year.[68] Of the 200 participants, 60.5 percent (121 of 200) fell during the 12-month treatment period. The two monthly high dose groups, 60,000 IU and 24,000 IU plus calcifediol, had no benefit in lower extremity function and had significantly higher percentages of participants who fell (66.9 percent and 66.1 percent, respectively) compared with the 24,000 IU group (47.9 percent). Participants in the 24,000 IU vitamin D group (equivalent to 800 IU/day) also experienced the most improved lower extremity function as well as the fewest number of falls. A consistent pattern was seen by achieved 25(OH)D blood concentrations. The best functional improvement and fewest falls were observed at the lower replete 25(OH)D range of 53.3 to 75.8 nmol/L, while no functional benefit, plus most falls, were observed between 111.8–247.3 nmol/L[68]. These trials both suggest that the risks of falls and fractures may be increased in seniors if achieved serum 25(OH)D concentrations reach >112 nmol/L, a finding requiring further investigation. One explanation may be that there is a therapeutic range for vitamin D with respect to fall prevention among seniors who had a prior fall. In fact, the most recent study points to the range between 53 to 76 nmol/L as optimal because both 25(OH)D concentrations below 53 nmol/L (vitamin D deficiency) and above 112 nmol/L were associated with increased risk of falling. An alternative explanation may be that higher bolus doses of vitamin D are not advantageous. Also, if higher serum 25(OH)D is associated with a tendency to walk more, which is likely, an individual may be at higher risk of the type of trips and falls that occur while walking. Patients who are bedbound or very sedentary will be less exposed to walking and to risk of tripping and falling while walking. So this finding does not directly implicate vitamin D as an etiological factor."

For fracture prevention, similar findings have emerged,[61,69]. Two meta-analyses of double-blind RCTs support minimal daily doses of 800 IU of vitamin D for fracture prevention at any non-vertebral site [14%to 20%[57]] and at the hip [18% to 30%[70]], vs. lower doses, and fracture prevention was found in RCTs that achieved mean 25(OH)D concentrations of 75 to 112 nmol/L.[57,71] Higher doses of vitamin D were explored in 3 large trials for fracture prevention, one used 100,000 IU vitamin D_3 [71] given orally, 4 monthly, one gave 300,000 IU vitamin D_2 [72] intra-muscularly 4 monthly, and another gave oral boluses, yearly, of 500,000 IU vitamin D_3. [67] While the fracture risk was reduced with treatment in the lowest dose trial, (RR = 0.78 (95% CI 0.61 to 0.99) for any first fracture[71]), both of the higher annual bolus dose trials increased fracture risks (RR = 1.09 (95% CI 0.93–1.28); [72] RR = 1.26 (95% CI 1.00–1.59; P = 0.047[67] for any first fracture), with mean achieved 25(OH)D concentrations of 75 nmol/L in the lowest dose RCT,[71] and most markedly raised with the annual 500,000 IU dose with mean achieved concentrations of 120 nmol/L.[67] Notably, the physiology behind a possible detrimental effect of a high dose of vitamin D monthly or less frequently on muscle function, falls and fractures, may well include increased catabolism of activated vitamin D, but remains unclear and needs further investigation.

One recent observational study, from Australia, found a decrease in fracture rates in older men from 36 fractures/323 persons with baseline 25(OH)D concentrations <36 nmol/L and 13 fractures/355 persons with baseline 25(OH)D concentrations of 36 to 73 nmol/L, and 35 fractures/340 persons with 25(OH)D concentrations >73 nmol/L.[73] While vitamin D supplement use was ~8% for both men who suffered fractures and those who did not, these data reflect either adverse effects of higher vitamin D status, or unidentified confounding, possibly by vitamin D supplementation, (or UVB exposure) being more common in those with the highest status, or by concomitant vitamin A supplementation, but the report was unable to report supplementation rates in the various subgroups.

Two ongoing trials (VITAL[74] and DO-HEALTH (http://do-health.eu/wordpress/)) test 2000 IU vitamin

D_3/day for fall and fracture reduction, but patient characteristics differ from many others in targeting relatively healthy older adults and seniors, and by supplementing with additional Omega-3 FFAs in the VITAL study. These trials should, however, provide important opportunities to determine whether there is an optimal range of serum 25(OH)D concentration for fall and fracture prevention and whether supplementation reduces these risks or not. Another randomized placebo-controlled clinical trial using 2,000 IU/day of vitamin D_3 and 1,500 mg/day of calcium in 2,300 participants studied for 4 y just ended at Creighton University in Omaha NE. Analysis of the effect of this intervention on disease incidence has begun, and the results will be submitted for publication soon.

Frailty

Serum 25(OH)D concentrations and frailty status were assessed in a cohort of 6307 community-dwelling women aged ≥69 years enrolled in the US. Study of Osteoporotic Fractures, and both lower (<50 nmol/L) and higher (≥75 nmol/L) values of 25(OH)D were moderately, but significantly, associated with a higher risk of baseline frailty.[50] In men however, a similar study found a monotonic inverse relation between 25 (OH)D values and frailty status.[49] Thus, while a U-shaped association cannot be excluded for vitamin D status and concomitant frailty in women, such an association was not seen in men; also, since elderly women are much more likely to be given vitamin D, especially when frail, confounding by indication (i.e. placement in the wrong long-term 25(OH)D category) in the Study of Osteoporotic Fractures, in women, could explain the U-shaped curve.

Overall, there is no RCT data, to date, to determine whether there is an optimal vitamin D status for frailty, or a simple threshold serum 25(OH)D for reduction in the risks of frailty.

Cognitive function

Vitamin D has emerged as a neurosteroid hormone involved in brain health and function.[75,76] Neuroepidemiology has consistently shown positive linear associations between serum 25(OH)D concentration and cognitive performance,[77-79] and 3 studies have reported U-shaped relationships, with worse cognitive scores with both lower and higher 25(OH) D concentrations.[80-82] The first, using data from NHANES III,[80] reported cognitive differences between 25(OH)D quintiles - participants in the highest quintile (25(OH)D >85.4 nmol/L) being most memory impaired, though this significant finding (p =0.02) was not clinically meaningful, and, as no adjustment for multiple comparisons was made, the authors interpreted this finding as a false positive.[80] The second paper found a U-shaped association for 45 y olds, prospectively, between 25(OH)D concentrations and word recall aged 50 y ($p_{curvature}$=0.01),[81] but had more postmenopausal subjects in both the groups with concentrations < 25nmol/L and ≥100 nmol/L, suggesting that provision of vitamin D to menopausal women might have driven the U-shaped findings. The third paper, on data from the Newcastle 85+ study,[82] found participants in the lowest and highest 25(OH)D quartiles to have increased risks of cognitive disorders (RR=1.62, p =0.04) vs. those in the middle quartiles, and at baseline, but not at 3-year follow-up; this U shaped association was observed solely in participants using vitamin D supplements, suggesting that it could have been driven by supplementation of those with hypovitaminosis D that had begun after the onset of cognitive disorders.

Compared with the growing body of evidence for a positive linear relationship between 25(OH)D and cognitive ability in adults,[78,79,83] with a possible threshold effect,[8,79,83] data in favor of a U-shaped relationship are scarce,[80-82] and might be due to chance, or to late-onset supplementation, a possibility requiring investigation.

All-cause mortality

A meta-analysis of 32 studies[84] revealed no U- or J-shaped relationship of serum 25(OH)D, [or of tertiles, quartiles or quintiles of serum 25(OH)D] with all-cause mortality, which was inversely associated with lower all-cause mortality rates ($p < 0.01$), with no evidence of publication bias according to a funnel-plot analysis (see Figure 3 of that paper) for serum 25 (OH)D values up to ~175 nmol/L (70 ng/ml) and showing no adverse association of these serum 25 (OH)D values with all-cause mortality. These data do not rule out that extremely high serum 25(OH)D concentrations [e.g. 400 nmol/L (160 ng/ml)] may be associated with increased all-cause mortality though not all studies have been in agreement. This meta-analysis, with 32 cohort and 2 nested cased-control studies included several studies in which participants were patients rather than healthy people. The

age-adjusted hazard ratio for all-cause mortality showed a linear decrease up to 90 nmol/L (36 ng/mL), above which no further change occurred. Another meta-analysis in 2012 included 14 prospective cohort studies for generally healthy community-dwelling individuals, with 5,562 deaths in 62,548 individuals.[85] The minimum relative risk was found with values near 80 nmol/L, with nonsignificant increases at concentrations up to 115 nmol/L.

Two papers from Denmark reported reverse-J shaped associations, one for all-cause mortality and 25 (OH)D concentration,[86] and one for CVD mortality,[44] though the authors did not claim causality in the absence of data on vitamin D supplementation.[87]

A prospective study of all-cause mortality rates in very old men and women (>85 years) in Newcastle[82] offers some support for the suggestion of 'recent vitamin D supplementation' since for men, neither low nor high 25(OH)D concentration was associated with increased mortality rate. However, for women in the upper quartile (≥47 nmol/L in spring and ≥69 nmol/L in summer), significantly increased hazard ratios for mortality emerged in all 4 models, but when the analysis was restricted to women not taking vitamin D supplements, the hazard ratio for mortality was not significantly increased.

An American study found that patients admitted to 2 hospitals in Boston had significantly higher 90-day mortality rates for 25(OH)D concentrations <75 nmol/L and >150 nmol/L[88] and one clinical trial reports that patients in intensive care in a hospital in Austria, where the study group received 540,000 IU of vitamin D_3 shortly after admission and 90,000 IU of vitamin D_3 per month thereafter had a nonsignificantly reduced 6-month mortality rate, but no indication of increased mortality.[89]

Pregnancy

We have found 2 birth outcome studies that have reported a U-shaped relation of outcomes to 25(OH) D concentration. One from the Pittsburgh in 1997–2001, with blood-sampled between the 16th and 22nd week of pregnancy where white women with 25(OH) D concentration >75 nmol/L had an odds ratio of 2.1 (95% CI, 1.2–3.8) for having small-for-gestational-age neonates.[90] The authors could not explain their findings but did mention confounders such as consumption of oily fish (which contains pollutants, including mercury, which reduces birth weight).[91] Similar findings were reported in a recent study from Hefei, China, which examined the association of cord blood concentrations of 25(OH) D in 1491 neonates and birth weight. Birth weight increased by 61.0 g (95% CI, 31.9–89.9 g) at concentrations less than 40 nmol/L and then decreased by 68.5 g (95% CI, −110.5 to −26.6 g) at concentrations from 40 to 70 nmol/L.[92] The 95% CIs at the extremes of low and higher 25 (OH)D concentrations were for birth weights below their 95% CIs, at 25(OH)D values<40 nmol/L for both male and female offspring. However, the lack of data to allow adjustment of the findings for relevant factors such as outdoor activity, dietary intake, environmental factors, or genetic variation, means that residual confounding was not excluded.

Allergies

A Finnish birth cohort study suggested a different relationship between vitamin D status and allergic diseases. Infants (n=5007 out of 7648 studied) were supplemented with vitamin D during the first year of life.[93] The prevalence of atopy, allergic rhinitis, and asthma at age 31 y was higher in people who, as infants, had been supplemented regularly with approximately 2000 IU of vitamin D per day—a dose significantly higher than that usually recommended for infants.[94] Those associations (other than for asthma) remained significant after adjustment for potential confounders, but data for serum 25(OH)D concentrations were unavailable. Another study, reported an almost twofold increase in susceptibility to asthma and food hypersensitivity after supplementation with vitamin D (400 IU/d) and vitamin A (1000 IU) for the first year of life.[95] The increase in allergic disease in that study could not be attributed to vitamin D supplementation per se, since infants were also supplemented with vitamin A, which appears to be an independent risk factor for asthma.[96] A Swedish birth cohort study reported similar findings prospectively when 123 children were studied, in conjunction with vitamin D and vitamin A supplemental intake data, during the first 24 months of life.[97] A large birth prospective cohort study associated maternal 25(OH)D concentrations >75 nmol/L during late pregnancy with increased offspring eczema risks aged 9 months, and asthma risks aged 9 years;[98] however, limitations of that study included the small number of incident allergic conditions (n=15 for atopic eczema at

9 months and n=9 for asthma at 9 years), a high drop-out rate by age 9 years, and the absence of data on vitamin D or A supplementation. Randomized, double-blind, placebo-controlled trial data from Japanese children showed that those receiving 1200 IUs of vitamin D daily for 4 months during the winter, reduced both their influenza infection risk by 42%, and their asthmatic attack rates by >90%.[99]

A large cross-sectional study of participants in the fourth decade of life ($n = 7288$) with serum 25(OH) D concentrations >135 nmol/L found a significant increase in immunoglobulin E concentrations (29% higher) vs. the reference group.[100] Cord blood 25(OH) D concentrations ≥100 nmol/L were associated with significantly higher total, and allergy-specific inhalant immunoglobulin E concentrations in a birth cohort from Arizona,[101] and with rates of skin-prick test positivity (adjusted OR, 3.4; 95% CI, 1.0–11.14; $p = 0.046$), using 25(OH) D concentrations at birth, without data on supplementation, dietary habits, or sunshine exposure.[101] However, another prospective study associating increased risk of wheezing with higher 25(OH) D concentrations,[102] found no association of lower vitamin D status with upper respiratory disease risks. Similar results were seen in a cross-sectional study in children aged 6–12 years, where 25(OH)D concentrations ≥75 nmol/L were associated with increased risk of wheezing (OR, 2.14; 95% CI, 1.07–4.28) vs. children with 25(OH)D concentrations of 50-<75nmol/L.[103] Significant numbers of that cohort (46.9%) were in the highest 25(OH)D concentration category; however, as the authors report, the study was conducted in the north, (43°N latitude), with children receiving sunlight for short durations, even in the summer. These authors later associated high 25 (OH)D concentrations with lower mean FEV_1/FVC ratios.[104] Mid-pregnancy and dietary lifestyle characteristics and maternal mid-pregnancy 25(OH)D concentrations ≥100 nmol/L were associated with increased risks of child asthma at 18 months (RR = 1.36). Measurements of offspring 25(OH)D concentrations at birth or during childhood were not available.[105] The same group later replicated those findings in the same birth cohort,[106] and also associated in utero exposure to higher maternal 25 (OH)D concentrations (≥125 nmol/L) with increased risks of asthma hospitalizations and self-reported asthma (HR, 1.81; 95% CI, 0.78–4.16 and OR, 1.82; 95% CI, 0.81–4.04) vs. the reference group (maternal values, 75–125 nmol/L).

Overall, data indicating associations between vitamin D status and allergy risks are derived mainly from studies using single time-point serum concentrations, and not monitoring vitamin D supplementation. Significant variables, such as prior exposure to vitamin D, +/− other supplements and potential confounders, with clearly defined allergy outcomes, will be essential in future supplementation studies, as in any search for evidence of a causal relationship.[11]

Other diseases

One study reports a U-shaped association between vitamin D status and hypogonadism in men, suggesting an unexplained optimal 25(OH)D concentration of 82–102 nmol/L in men.[107] Data on vitamin D intake and use of vitamin D supplements during or prior to the study were not reported, which may explain the higher vitamin D concentrations compared with what was previously described in healthy populations.[108] Overall, no conclusions indicating causality between vitamin D status and hypogonadism could be drawn because of the cross-sectional design of available studies.[107,109,110]

Discussion

There are several health outcomes for which a U, or similarly shaped, relationship with serum 25(OH)D concentrations has been suggested, most consistently for allergic reactions, PC, and cardiovascular disease. (Table 3).

There are several possible explanations for apparent or artifactual U-shape curvilinear relationships between serum 25(OH) D and health outcomes. Some are specific, depending on problem and the mechanisms affecting the health outcome; others are more general, or linked to vitamin D supplementation in response to early signs or symptoms of a disease. For instance, allergic worsening at high 25(OH)D concentration could be explained by vitamin D's role in shifting the Th1–Th2 balance in favor of pro-inflammatory factor secreting Th2 cells; [112] the occasional purported U-shaped 25(OH)D concentration–CVD mortality association may reflect lower $1,25(OH)_2D$ formation due to concomitant kidney dysfunction[113,114] or to enhanced calcitriol catabolism, or to various biases that can influence results.

Some U-shaped relationships, seen sporadically, may be due to chance, or explained by unidentified

Table 3. Summary of findings.

Outcome of interest	Studies (N) with 'U'-shaped findings, by topic	Type of study	Reference	Validity	Comments	Possible Non-causal confounders Identified
Allergies				Probable	Common findings	Shift of Th cell balance from Th1 to Th2 cells, increasing inflammatory cytokines
Cancer, of the prostate	6	NCCMeta-analysis	21,23,24,26,28	Probably not	Confounding by PSA testing possible	Unknown
Pancreatic Cancer	2	NCC	16,17	No	Not found at lower latitudes	Possible recent high-dose vitamin D supplementation (before blood draw)
CVD	3	Prospective	43-45,111	Probably not	U-shaped relationship found in 3studies; 1,25 $(OH)_2D$ measured in one study. Not found in most studies.	Recent vitamin D supplementation, meat consumption, low 1,25$(OH)_2D$ production
Cognition	3		80-82	No	Weak studies, not consistent in outcomes	Recent vitamin D supplementation
Falls, fractures, bolus doses	2		67,72	Maybe	Repeated	
Fractures	1	Prospective	73	No		Recent vitamin D supplementation
Frailty status	1	Cross-sectional	50	No	Observed for women but not men	Recent vitamin D supplementation
Mortality rate	3		40,86,88	Probably not	Observed in some studies; found for some outcomes	CVD, PC.
Pregnancy outcomes	2		90,92	No	Found in only 2 studies	Not known, but 25(OH) D was measured at <22 weeks' gestation or at term at a single time point Data on dietary intake (vitamins A, C, K; calcium; and magnesium) not available

NCC, nested case–control

confounding factors. One important confounding factor that may affect studies reporting adverse health outcomes at higher 25(OH)D concentrations is supplementation with vitamin D that starts too late to affect disease progression, but before blood draw for 25(OH)D measurement. For overall mortality rate, for example, some U-shaped findings may be related to late onset supplementation, or treatment of long standing deficiency, since with the current heightened awareness of the health benefits of vitamin D, many physicians are now recommending supplementation, especially for elderly subjects at risk of osteoporosis. In addition, many people now self-administer vitamin D supplements in response to increased media coverage on sunshine avoidance, on the lack of sunshine, and on the more widely recognized need to take vitamin D supplements. Further support for vitamin D supplementation accounting for associations of apparent adverse effects with 25(OH)D concentration was found in the >3.8 million values from the United States (January 2007-December 2009), where 2678 (57%) of participants with 25(OH)D concentrations >125 nmol/L had 25(OH)D_2 values >10 nmol/L,[20] again suggesting they were taking vitamin D_2 supplements.

Another concern about observational studies of health associations with serum 25(OH)D concentrations is that the assays themselves have analytical biases. Comparing values measured in 3 laboratories with values from a Vitamin D External Quality Assessment (DEQAS) compliant laboratory showed liquid chromatography-tandem mass spectrometry mean values from 2 centers were higher than certified laboratory results by 16.5 and 16.9 nmol/L, and these increases were greatest at higher values, but means from the center using DiaSorin Liaison were 11.1 nmol/L different from DEQAS findings.[115] This problem has been noted to affect the setting of dietary guidelines.[116] DEQAS,

established to help laboratories ensure the accuracy of their measurements,[117] can [117](117)[117](117)(115)(118)be used to standardize (harmonise) historical values,[118] a measure that can be expected to reduce the finding of U-shaped 25(OH)D concentration-health outcome relationships, since fewer high 25(OH)D concentration values would probably be found; however, though assay standardization would reduce bias as a confounder, whether it would abolish the markedly U-shaped findings reported for some diseases is unknown, and needs to be investigated.

The lack of data allowing assessment of the importance of nutritional confounding factors is concerning, and researchers conducting future observational studies and randomized controlled trials should obtain vitamin D supplementation histories from participants, and data for when supplementation began, so that analyses can allow for different durations of supplementation before outcome analysis. Furthermore, where early life intakes appear able to affect risk factors before disease becomes overt, as for cardiovascular disease,[113] reliance on data from supplemental studies in later life would be misleading, so that long term intake data, for individuals and/or populations, will be needed to allow adequate adjustments for such confounding. Similarly, assessment of intakes of nutrients interacting with vitamin D (including vitamins A, K, and C, calcium and magnesium) in future studies, and adjustment for those intakes, would allow better evaluation of vitamin D's independent health effects.[119]

Conclusion

Although there are occasional reports in the peer-reviewed journal literature of U-like serum 25(OH)D concentration–health outcome relationships, few are consistent, or reflect identifiable underlying pathophysiological processes, apart from allergic reactions, probably reflecting the shifting of the Th1–Th2 cell balance toward Th2, with increased production of pro-inflammatory cytokines. In some people with CVD, an adverse effect of higher 25(OH)D concentration might be possible. In other conditions a highly plausible reason for these findings is that people who had been vitamin D insufficient over many years had started taking vitamin D supplements too late in life to correct disorders aggravated by poor vitamin D status. Future observational studies, including RCTs, should, therefore, collect data on vitamin D supplementation, solar UVB exposure, and the intakes of potentially confounding nutrients (e.g., calcium, magnesium, vitamins A, K, C and E), and should use standardized 25(OH)D assays. Furthermore, the results of clinical trials of vitamin D supplementation, including the 5 or 6 major trials now underway, should be examined for evidence of increased risk at higher 25(OH)D concentrations, although substantial side effects are unlikely at the vitamin D3 doses that were used in these studies (< 10,000 IU/day).

Abbreviations

25(OH)D	25-hydroxyvitamin D
CI	confidence interval
CVD	cardiovascular disease
DEQAS	Vitamin D External Quality Assessment
FFA	free fatty acids
HR	hazard ratio
IU	international units
MACCE	major adverse cardiac and cerebrovascular events during of cardiac surgery or while still at the hospital
MACS	mortality or acute coronary syndrome
MR	mortality rate
nmol/L	nanomols/liter
NCC	nested case–control
OR	odds ratio
PC	prostate cancer
RR	relative risk
Th	T-helper

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