Vitamin D status and ill health: a systematic review

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Low serum concentrations of 25-hydroxyvitamin D (25[OH]D) have been associated with many non-skeletal disorders. However, whether low 25(OH)D is the cause or result of ill health is not known. We did a systematic search of prospective and intervention studies that assessed the effect of 25(OH)D concentrations on non-skeletal health outcomes in individuals aged 18 years or older. We identified 290 prospective cohort studies (279 on disease occurrence or mortality, and 11 on cancer characteristics or survival), and 172 randomised trials of major health outcomes and of physiological parameters related to disease risk or inflammatory status. Investigators of most prospective studies reported moderate to strong inverse associations between 25(OH)D concentrations and cardiovascular diseases, serum lipid concentrations, inflammation, glucose metabolism disorders, weight gain, infectious diseases, multiple sclerosis, mood disorders, declining cognitive function, impaired physical functioning, and all-cause mortality. High 25(OH)D concentrations were not associated with a lower risk of cancer, except colorectal cancer. Results from intervention studies did not show an effect of vitamin D supplementation on disease occurrence, including colorectal cancer. In 34 intervention studies including 2805 individuals with mean 25(OH)D concentration lower than 50 nmol/L at baseline supplementation with 50 µg per day or more did not show better results. Supplementation in elderly people (mainly women) with 20 µg vitamin D per day seemed to slightly reduce all-cause mortality. The discrepancy between observational and intervention studies suggests that low 25(OH)D is a marker of ill health. Inflammatory processes involved in disease occurrence and clinical course would reduce 25(OH)D, which would explain why low vitamin D status is reported in a wide range of disorders. In elderly people, restoration of vitamin D deficits due to ageing and lifestyle changes induced by ill health could explain why low-dose supplementation leads to slight gains in survival.

Introduction

Vitamin D is a prohormone that has a key role in calcium and phosphate balance and bone structure. In the past decade, vitamin D has been the focus of keen interest because, beyond these known effects, data from ecological and observational studies have shown associations between low concentration of serum 25-hydroxyvitamin D (25[OH]D; usually used as a proxy for an individual's vitamin D status) and increased risk of cancer, cardiovascular diseases, disorders of glucose metabolism, neurodegenerative diseases, and death.[1]

Many factors, such as season, ageing, latitude, adiposity, physical activity, smoking, and diet (appendix p 2), can affect the link between 25(OH)D and health outcomes, but because of the number of factors and inaccuracies in their measurement, observational studies might not be able to control fully for their confounding effects. Furthermore, the list of disorders associated with low 25(OH)D has continuously increased. These issues have raised the question of whether low 25(OH)D might be the result, rather than the cause, of physiological disturbances involved in some diseases.[2]

See Online for appendix

Observational research is not sufficient to support the notion that a person's health would benefit from increases in 25(OH)D concentration—eg, through supplementation. Such claims must be supported by evidence from randomised controlled trials. If the health benefits of high 25(OH)D concentrations shown by data from observational studies are not reproduced in randomised trials, then the relation between 25(OH)D and disorders is probably the result of confounding or physiological events involved in these disorders.

Reports from the International Agency for Research on Cancer (IARC)[3] and the US Institute of Medicine[4] concluded that insufficient evidence linked 25(OH)D and most non-skeletal health disorders. However, the two reports did not provide hypotheses for why so many disorders were associated with low 25(OH)D concentrations. In this systematic review, we compare the observational and experimental data relating 25(OH)D concentrations to non-skeletal disorders in adults, aiming to formulate hypotheses that can integrate findings.

Methods

Search strategy and selection criteria

We searched PubMed and Embase for articles published in English from inception to Dec 31, 2012, including articles published online ahead of publication. We focused on individuals aged 18 years or older. To define the exposure, we used the following key words: "vitamin", "vitamin D", "25-hydroxyvitamin D", "25(OH)D", "cholecalciferol", "ergocalciferol", "calcidiol", "calcitriol", and "vitamin D receptors". For disorders, we used keywords related to all-cause mortality, and to the incidence, survival, or mortality of cancers, cardiovascular diseases, glucose metabolism disorders, obesity, metabolic syndrome, and acute and chronic infectious diseases, including tuberculosis. We also searched for physical functioning, psychiatric (eg, mood disorders), neurological (eg, multiple sclerosis), and cognitive disorders (eg, Alzheimer's disease). We did a separate search for blood lipids and inflammation biomarkers (C-reactive protein, interleukin 6, tumour necrosis factor-α [TNFα]), and a separate search for

cancer characteristics and survival. We manually searched references cited in the chosen articles and in published reviews. We did not include study design (case-control, prospective cohort, randomised trial, etc) in our search algorithms. We searched for our chosen keywords in the header and abstract of articles, and chose prospective cohort and randomised trials, and their meta-analyses, on the basis of titles and abstracts. After the release of the IARC report on vitamin D and cancer,[3] we updated the report's literature search by extending searches to non-cancerous conditions, and included studies as per our criteria. We also identified meta-analyses (ie, summary analyses based on published results) and pooled analyses (ie, summary analyses based on individual data) of prospective or randomised studies.

We excluded cross-sectional and case-control studies that were based on measurements of 25(OH)D in individuals already diagnosed with the health disorder under study. This exclusion avoids the bias of reverse causation—ie, low 25(OH)D concentration being a result of the physiological disturbances associated with the disease, rather than a cause of the disease. Furthermore, a disease and its treatment might lead to reduced exposure to sunlight, and modifications in dietary habits due to hospital admissions, treatments, reduced mobility, and other changes in lifestyle, which all contribute to lowering of 25(OH)D.

Prospective studies

We included prospective studies and case-control studies nested in a cohort in which 25(OH)D concentration was measured in blood serum obtained many years before occurrence of the outcome of interest. We did not include studies that used 25(OH)D concentrations predicted by models constructed with factors known to be associated with vitamin D status.[5] The main limitation of these studies is that, because the factors are used for prediction of 25(OH)D concentrations, the statistical association between the predicted 25(OH)D concentration and an outcome cannot be adjusted for these factors.

We also included prospective studies of survival in patients with cancer, and cardiovascular and other chronic diseases, provided that statistical analyses were carefully adjusted for major prognostic factors such as age, sex, and disease stage at diagnosis. For patients with cancer, we also included studies of 25(OH)D concentration and cancer characteristics at diagnosis because 25(OH)D concentration was compared between patients with cancer of the same organ, and not with a control group of individuals without cancer. However, we chose only studies that adjusted results for main confounders (eg, age and month that blood was drawn).

Randomised trials

We included randomised trials that used cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). We excluded trials that used other vitamin D compounds and trials in which other drugs or supplements were given concomitantly with vitamin D, except calcium supplements. We excluded trials that tested vitamin D given in enriched food. We made no exclusion on the basis of trial or follow-up duration, or type of population studied.

Meta-analyses and pooled analyses

Whenever available, we first reported summary relative risks from meta-analyses or pooled analyses of observational or randomised studies. When several meta-analyses existed for an outcome, we used the most recent meta-analysis if it included more studies than did previous meta-analyses. If recent meta-analyses had a different study selection, we chose to display the two or more recent meta-analyses so that results could be compared.

One meta-analysis of randomised trials of glucose metabolism did not include several trials published at the time the meta-analysis was done,[6] and in another meta-analysis,[7] investigators did not report from which trials data were extracted to compute the summary effect sizes. Therefore, we chose to report on all trials of vitamin D supplementation and glucose-metabolism-related end-points. We then did our own meta-analysis of results for trials of HbA_{1C}, which is the most accepted measure of overall, long-term, blood glucose control in people with diabetes (appendix pp 4–7).[8]

Data synthesis and statistical considerations

Two authors (PM and PA) independently extracted data from studies and entered them into predefined databases specific to prospective and randomised studies. Conflicts were solved by consensus between the authors. Because we considered all main outcomes reported in studies, studies that addressed more than one outcome can appear several times in a table. We did a random-effect meta-analysis for trials that used HbA_{1C} concentration as an endpoint (appendix pp 4–7). For one randomised trial,[9] we did an intention-to-treat calculation of the cancer risk associated with intake of vitamin D supplements, which was not done in the original article (appendix p 3). Because of the common perception that so-called vitamin D sufficiency is achieved when 25(OH)D is higher than 75 nmol/L,[10] we systematically identified trials in which mean in-trial concentration of 25(OH)D in the intervention group exceeded 72 nmol/L.

Randomised trials that included patients with low 25(OH)D concentrations at baseline and tested high doses of vitamin D might be the most informative studies for the effect of 25(OH)D on health outcomes. Therefore, we focused on trials with a main endpoint that could be objectively assessed—ie, trials of vascular endothelial function, blood pressure, glucose metabolism, markers of inflammation, and infectious

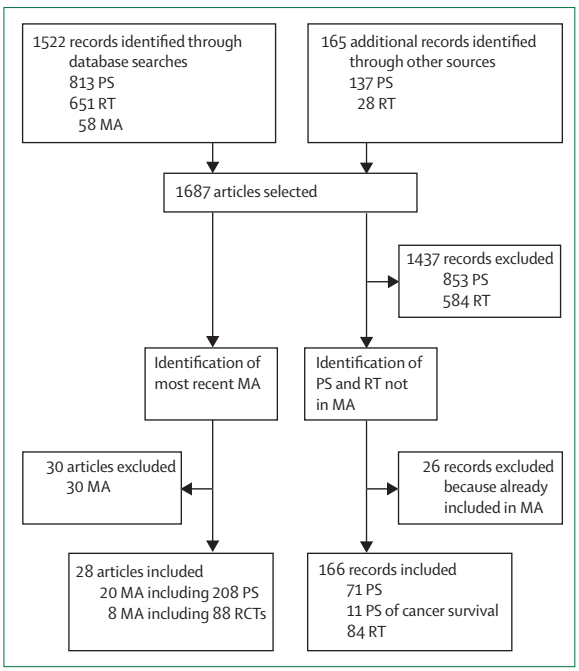

Figure 1: **Study selection**
MA=meta-analyses or pooled analyses. PS=prospective study. RT=randomised intervention trial. 25(OH)D=25-hydroxyvitamin D.

diseases. We then identified trials that included patients with mean baseline concentration of 25(OH)D lower than 50 nmol/L, and tested supplementation of 50 μg per day or more.

Results

Study inclusion

Our systematic review included about 290 prospective cohort studies (279 on disease occurrence and 11 on cancer characteristics or survival), and 172 randomised trials of major health outcomes and of physiological parameters related to disease risk or inflammatory status (figure 1).

Observational prospective studies

The 20 most recent meta-analyses and pooled analyses provided summary relative risks for 208 prospective studies, some of which might have been included in different meta-analyses because they addressed several outcomes (table 1). We identified 71 prospective studies that were not part of meta-analyses or pooled analyses (table 2).

Findings from meta-analyses or pooled analyses that compared patients in the highest versus lowest quantile of 25(OH)D concentration showed decreases of 14–58% in risk of cardiovascular events, diabetes, and metabolic syndrome (table 1). Results of 14 cohort studies of these disorders not included in meta-analyses or pooled analyses had overall similar findings for these disorders (table 2). For eight cancers—breast, prostate, oesophageal, ovarian, endometrial, bladder, and kidney cancer, and non-Hodgkin lymphoma—data from meta-analyses and pooled analyses suggest that there was no association between disease incidence and 25(OH)D concentrations (table 1). We noted decreasing cancer risk associated with increasing 25(OH)D concentrations for colorectal cancer only. One pooled analysis showed increased risk of pancreatic cancer associated with high 25(OH)D concentration. Taken together, the mixed results of the five studies of breast cancer not included in meta-analyses or pooled analyses were similar to results of meta-analyses (table 2). Data for the three most recent studies of prostate cancer not included in meta-analyses or pooled analyses showed increased risk with high 25(OH)D concentrations. We noted mixed results for the link between 25(OH)D concentration and skin cancer incidence and for all-cancer incidence or mortality (table 2).

Six studies had results suggesting an inverse relation between 25(OH)D concentration and frequency or severity of infectious diseases (table 2). Five studies had findings that showed an increased frequency of mood disorders associated with low 25(OH)D concentrations. Studies of Parkinson's disease, decreases in cognitive function, and non-Alzheimer dementia had similar results (table 2). Data from two studies of patients with multiple sclerosis showed decreases in risk of relapse and disability with high 25(OH)D concentrations, but investigators of another study reported no association. Findings from two of four studies showed improved physical performance (measured by the ability to do specific movements) of elderly people with high 25(OH)D concentrations. A meta-analysis of 14 studies showed a 29% decrease in all-cause mortality between the highest and the lowest 25(OH)D quantiles (table 1). Of 17 studies of all-cause mortality not included in meta-analyses, 15 obtained results showing a substantial and significant decrease in risk of death from any cause associated with high 25(OH)D concentrations (table 2). Five studies using composite endpoints including all-cause mortality, disease incidence, or frailty status had results similar to those using all-cause mortality only (table 2).

Cancer characteristics and survival

11 studies that examined links between 25(OH)D concentrations at diagnosis and tumour characteristics or patient survival were adjusted for major personal, clinical, and histological predictors of disease extent or outcome (table 3). Some studies showed that survival of patients with breast (one of two studies), colorectal (two of three studies), and prostate cancer (one study; lower risk of prostate cancer death, not overall survival), and cutaneous melanoma (one study) increased with high 25(OH)D concentrations. We noted no significant link between 25(OH)D concentrations and overall survival from lung cancer or head and neck cancer. For breast

cancer, prostate cancer, and cutaneous melanoma, disease aggressiveness and extent were inversely correlated with 25(OH)D concentrations.

Randomised controlled trials

The seven most recent meta-analyses summarised results of 88 randomised trials, some of which were included in several meta-analyses (table 4). We identified an additional 84 articles of randomised trials not included in published meta-analyses (table 5).

With 36 282 postmenopausal women, the Women's Health Initiative (WHI) study was the largest trial done of vitamin D supplementation.[11] This trial tested a daily dose of 10 µg vitamin D3 (cholecalciferol), and 1 g of elementary calcium for 84 months. 11 articles based on WHI data, but not included in meta-analyses, reported on various non-skeletal outcomes (table 5). Trials included in meta-analyses enrolled about 100 000 patients, a figure counting the WHI trial only once. Doses of vitamin D supplements were highly variable, but most trials started after 2000 tended to use daily doses higher than 20 µg of vitamin D2 and D3 (data not shown). In 110 (72%) of 153 non-WHI trials cited in table 5, mean 25(OH)D concentration in intervention groups exceeded 72 nmol/L.

Meta-analyses of trials of vitamin D supplementation for the prevention of cardiovascular disease occurrence or death had null results (table 4). Seven trials not included in published meta-analyses that examined 15 outcomes related to endothelial function had results indicating a favourable effect of supplementation for three outcomes (table 5). In nearly all trials, supplementation did not

	Year of publication (appendix reference)*	Studies (n)	Individuals (n)	Cases (n)	SRR for highest *vs* lowest quantile of 25(OH)D concentration (95% CI)
Cardiovascular disease incidence and risk factors					
Myocardial infarction	2010 (1)	4	5253	756	0·65 (0·51–0·82)
Stroke	2012 (2)	6	70 993	1214	0·66 (0·54–0·83)
Hypertension	2010 (3)	3	95 243	1149	0·57 (0·41–0·79)
Cardiovascular disease incidence and mortality					
Cardiovascular disease	2010 (4)†	5	19 376	2417	0·42 (0·28–0·65)
Cardiovascular disease	2011 (5)†	7	27 620	2530	0·60 (0·44–0·81)
Cardiovascular disease	2012 (6)†	17	65 994	6123	0·66 (0·56–0·77)
Coronary heart disease	2012 (6)	8	33 249	1973	0·72 (0·64–0·83)
Stroke	2012 (6)‡	7	39 264	726	0·72 (0·64–0·83)
Stroke	2012 (7)‡	7	47 809	926	0·60 (0·48–0·72)
Cardiovascular disease mortality					
Cardiovascular disease mortality	2012 (6)	13	61 710	3715	0·70 (0·58–0·84)
Diabetes incidence					
Diabetes incidence	2013 (8)§	14	76 220	4996	0·62 (0·54–0·70)
Diabetes incidence	2013 (9)§	16	72 204	4877	0·67 (0·60–0·75)
Overweight, obesity, and metabolic syndrome					
Overweight, obesity, and metabolic syndrome	2012 (10)	4	19 481	6554	0·86 (0·80–0·92)
Cancer incidence					
Breast cancer incidence	2010 (11)	5	23 595	4393	0·97¶ (0·92–1·03)
Colorectal cancer incidence	2011 (12)	9	3938	2690	0·66 (0·54–0·81)
Prostate cancer incidence	2010 (11)	11	62 855	3145	0·99¶ (0·95–1·03)
Oesophageal and gastric incidence	2010 (13)‖	8	1066	1065	0·81 (0·39–1·69)
Ovarian cancer incidence	2010 (14)‖	7	770	516	1·11 (0·61–2·05)
Endometrial cancer incidence	2010 (15)‖	7	992	830	0·85 (0·47–1·53)
Non-Hodgkin lymphoma incidence	2010 (16)‖	10	1778	1353	0·86 (0·57–1·27)
Bladder and kidney cancer incidence	2010 (17)‖	8	775	775	0·92 (0·44–1·92)
Pancreatic cancer incidence	2010 (18)‖	8	1333	952	2·24 (1·22–4·12)
All-cause mortality					
All-cause mortality	2011 (19)	14	62 548	5562	0·71 (0·50–0·91)
All-cause mortality in patients with chronic kidney disease	2011 (20)	10	6853	2110	0·86 (0·82–0·91)¶

SRR=summary relative risk. 25(OH)D=25-hydroxyvitamin D. *References are listed in appendix pp 8–9. †(5) and (6) do not include one study included in (4); two studies in (5) are not included in (6). ‡Four studies not in common. §(8) does not include four studies in (9); (9) does not include three studies in (8). ¶SRR per 25 nmol/L increase in 25(OH)D D concentration. ‖Pooled analyses.

***Table 1*: Meta-analyses of prospective cohort studies of 25(OH)D and non-skeletal disorders**

	Study (appendix reference)*	RR of highest *vs* lowest quintile†				Outcome as a continuous variable‡	Individuals (n)	Cases (n)
		<0·50	0·50 to 0·95	0·95 to 1·05	>1·05			
Cardiovascular disease incidence and risk factors								
Myocardial infarction	(1), (2)	1 [1†]	..	..	1	..	9914	776
Cardiovascular disease	(3), (4)	..	1	..	1	..	2634	645
Stroke	(2), (5), (6)	..	2 [2†]	..	1	..	18765	2200
Hypertension	(7)	..	..	1	..	..	2571	403
Coronary artery calcification	(8)	1	..	..	..	..	1370	723
Hypercholesterolaemia	(7)	..	1 [1†]	..	..	..	2363	431
Cardiovascular disease incidence and mortality								
Cardiovascular disease	(9)	..	..	1	..	..	2081	416
Coronary heart disease	..	..	..	..	..	..	..	..
Stroke	..	..	..	..	..	..	..	..
Cardiovascular disease mortality								
Cardiovascular disease mortality	(4), (10), (11), (12), (13), (71)	4 [4†]	1	1	..	..	7980	1061
Overweight, obesity, and metabolic syndrome								
Overweight, obesity and metabolic syndrome	(7)			1	..	..	2623	323
Cancer incidence								
Breast cancer incidence	(14), (15), (16), (17), (18)	..	2 [1†]	1	2	..	6554	2344
Colorectal cancer incidence	(19)	..	..	1	..	..	859	431
Prostate cancer incidence	(20), (21), (65)	..	..	..	3 [2†]	..	7197	3435
Oesophageal and gastric incidence	(22)	..	..	..	1	..	1650	979
Bladder and kidney cancer incidence	(23)	..	1 [1†]	..	..	..	250	250
Oropharynx and larynx cancer incidence	(24)	..	..	..	1	..	340	340
Skin cancer incidence§	(25), (26), (27)	..	2 [1†]	..	4 [2†]	..	14247	1339
All-cancer incidence	(28¶), (29)	..	..	1	1	..	2665	378
All-cancer mortality								
All-cancer mortality	(11), (13), (28¶),(30), (64)	..	2 [1†]	2	1	..	23366	1482
Infectious disease incidence and severity								
Bacterial vaginosis	(31)	..	1 [1†]	..	..	..	469	192
Days of absence due to respiratory infections	(32)	..	1 [1†]	..	..	..	800	24
Respiratory infections	(33), (34)	..	..	..	..	2 inverse [2‡]	6987	..
Chronic obstructive pulmonary disease exacerbation	(35), (36)	..	..	..	..	2 inverse [2‡]	1070	..
Neurological and psychiatric disorders (change in disease)								
Mood disorders (depression)	(37), (38), (39), (40), (41)	4 [4†]	..	..	..	1 inverse [1‡]	6016	514
Parkinson's disease	(42)	1 [1†]	..	..	..	..	3173	50
Cognitive function	(43), (44), (45), (46)	..	3 [2†]	..	..	1 inverse [1‡]	10358	260
Non-Alzheimer dementia	(47)	1 [1†]	..	..	..	..	40	6
Multiple sclerosis	(48), (49), (50)	1 [1†]	..	1	..	1 inverse [1‡]	917	257
Physical performance of elderly people								
Physical performance of elderly people	(66), (67), (68), (69)	..	..	2	..	2 inverse [2‡]	3078	..
All-cause mortality								
All-cause mortality	(3), (4), (7), (9), (10), (11), (12), (13), (51), (52), (53), (54), (55), (56), (57), (58),(59)	5 [4†]	10 [8†]	..	..	..	208692	18912
Composite score for incidence and all-cause mortality	(60), (61), (70)	1 [1†]	2 [2†]	..	..	..	23706	1261
Frailty status incidence and all-cause mortality	(62), (63)	..	1	..	..	..	7578	1305

RR=relative risk.*References are listed in the appendix pp 8–9. †Numbers of endpoints that were within specified RR. Number of endpoints with significance (p<0·05) shown in square brackets. ‡Number of studies with direct or inverse relation between serum 25-hydroxyvitamin D concentrations and the outcome. Number of endpoints with significance (p<0·05) shown in square brackets. §Six endpoints: non-melanoma skin cancer for (2`5); basal-cell carcinoma, squamous-cell carcinoma, and melanoma for (26); non-melanoma skin cancer and melanoma for (27). ¶For (28), we computed RR and 95% CI through the comparison of patients with 25-hydroxyvitamin D concentration higher than cutoff for the 90th percentile, with patients with 25-hydroxyvitamin D in the lowest 10th percentile.

Table 2: **Prospective cohort studies of serum 25-hydroxyvitamin D concentration and non-skeletal disorders that were not included in published meta-analyses**

	Main outcome	Disease and patient characteristics	Cases (n)	Follow-up (years)	RR highest *vs* lowest 25-hydroxyvitamin D concentrations, most adjusted (95% CI)
Breast cancer					
Goodwin et al, 2009 (1)	Overall survival	Breast cancer, all ages	512	11·6	0·63 (0·38–1·04)
Yao et al, 2011 (2)	Triple negative *vs* luminal A cancer	Breast cancer, premenopausal; breast cancer, postmenopausal	216; 290	..	0·26 (0·09–0·71); 1·13 (0·52–2·43)
Kim et al, 2011 (3)	Overall survival	Breast cancer, all ages	310	2	0·25 (0·11–0·56)
Peppone et al, 2012 (4)	Triple negative and ER status	Breast cancer, all ages	149	..	Lower proportion of triple-negative and ER-negative breast cancer
Colorectal cancer					
Ng et al, 2008 (5)	Overall survival; colorectal cancer-specific survival	Colorectal cancer, all ages	304	6·5	0·52 (0·29–0·94); 0·61 (0·31–1·10)
Ng et al, 2011 (6)	Overall survival	Stage IV colorectal cancer	515	5·1	0·94 (0·72–1·23)
Fedirko et al, 2012 (7)	Overall survival; colorectal cancer-specific mortality	Colorectal cancer, all ages	1202	6·1	0·67 (0·50–0·88); 0·69 (0·50–0·93)
Prostate cancer					
Fang et al, 2011 (8)	Overall survival; prostate cancer death; Gleason's score at diagnosis	Prostate cancer, all ages	1822	9·9	0·82 (0·65–1·03); 0·63 (0·42–0·94); lower proportion of high score cancer
Head and neck cancer					
Meyer et al, 2011 (9)	Overall survival	Stage I and II head and neck cancer	540	4·4	0·85 (0·57–1·28)
Lung cancer					
Zhou et al, 2007 (10)	Overall survival	Early stage non-small-cell lung cancer	447	6	0·74 (0·50–1·10)
Cutaneous melanoma					
Newton-Bishop et al, 2009 (11)	Overall survival; Breslow's thickness	Melanoma, all ages	271	4·7	0·72 (0·54–0·96); decreases in Breslow's thickness

ER=oestrogen receptor. *References are listed in the appendix pp 12–13.

***Table 3*: Prospective studies (appendix reference)* of 25-hydroyvitamin D and cancer characteristics and outcome**

affect concentrations of blood lipids involved in atherosclerosis. In most trials, supplementation did not affect serum concentrations of C-reactive protein or of inflammatory cytokines.

31 trials assessed the effect of supplementation on glucose metabolism in patients with and without diabetes (table 5; appendix p 4–5). These trials included 41 916 patients; 2673 of participants were not part of the WHI trial or of the RECORD trial. 14 trials tested vitamin D2 or D3 doses of 100 µg per day or greater, two trials had baseline values higher than 72 mmol/L, and 16 trials obtained in-trial 25(OH)D concentrations higher than 72 nmol/L. Overall, results for four (4%) of the 91 total endpoints obtained (encompassing 8 different outcomes) examined were consistent with a beneficial effect of vitamin D supplementation: three for HOMA-IR (insulin resistance, derived from the homoeostasis model assessment) and one for fasting plasma glucose (appendix p 4). The four trials that included 100 individuals or more, had 12 months or more of follow-up, and obtained mean in-trial 25(OH)D concentrations higher than 72 nmol/L had null results.

To accompany our systematic review, we did a meta-analysis of 16 trials that used HbA_{1c} as an endpoint, including 1491 individuals who showed no reduction in proportions of HbA_{1C} (table 4, figure 2). Sensitivity analyses did not suggest different results for patients with or without diabetes, or when analyses were restricted to longer-duration trials, or to trials that used vitamin D doses of 92·5 µg per day or higher (appendix pp 4–7). In three trials, vitamin D supplementation did not decrease risk of cancer, including colorectal cancer (table 5).

Before antibiotics, high doses of vitamin D were commonly given to patients with tuberculosis.[12] In trials that tested the effectiveness of high doses of vitamin D to speed up sputum conversion, two had negative findings and one had positive results (table 5). Two trials testing whether supplementation could improve clinically defined tuberculosis scores obtained null results. Most trials that tested whether supplementation of vitamin D could prevent or accelerate healing of infectious episodes obtained null results.

Two trials obtained results suggesting that supplementation could help to improve mood or cognitive disorders, and five had null results (table 5). For physical functioning, one meta-analysis including three trials had results favourable to vitamin D supplementation for two physical tests (table 4). Another meta-analysis of 11 trials of proximal leg strength and seven trials of grip

	Year (appendix ref)*	RCTs (n)	Individuals (n)	Cases (n)	Trial duration (months)	Dose of vitamin D3 (μg per day)	Measure of outcome	Difference intervention *vs* control (95% CI)	Trials with significant change in favour of vitamin D supplementation (n)
Cardiovascular diseases									
Cardiovascular diseases	2010 (1)	4	41 346	1976	12–60	10–25	Incidence	RR 0·99† (0·89–1·09)	0
Myocardial infarction	2011 (2)	6	39 879	1353	1–84	8–25	Incidence	RR 1·02 (0·93–1·13)	0
Stroke	2011 (2)	6	39 879	1006	1–84	10–25	Incidence	RR 1·05 (0·88–1·25)	0
Systolic blood pressure	2011 (2)	14	NR	CO	1–84	NR	Change (mm Hg)	ES −0·06 (−1·98 to 1·87)	2‡
Diastolic blood pressure	2011 (2)	14	NR	CO	1–84	NR	Change (mm Hg)	ES −0·34 (−1·03 to 0·35)	1, and 1 in favour of control‡
Cardiovascular mortality	2011 (3)	7	41 879	1229	1–84	8–35	Deaths	RR 1·02 (0·91–1·13)	0
Blood lipids§									
Total cholesterol	2011 (2)	11	2267	CO	1–84	NR	Change (mmol/L)	ES 0·00 (−0·06 to 0·07)	NR
Total cholesterol	2012 (4)	12	1346	CO	2–36	8–214	Change (mg/dL)	ES 3·23 (0·55–5·90)	0
LDL	2011 (2)	11	2210	CO	1–84	NR	Change (mmol/L)	ES −0·09 (−0·24 to 0·07)	NR
LDL	2012 (4)	12	1346	CO	2–36	8–214	Change (mg/dL)	ES 1·52 (−1·42 to 4·46)	0
HDL	2011 (2)	12	2285	CO	1–84	NR	Change (mmol/L)	ES 0·06 (−0·11 to 0·24)	NR
HDL	2012 (4)	12	1346	CO	2–36	8–214	Change (mg/dL)	ES −0·14 (−0·99 to 0·71)	1 inverse
Triglycerides	2011 (2)	11	2098	CO	1–84	NR	Change (mmol/L)	ES −0·04 (−0·11 to 0·03)	NR
Triglycerides	2012 (4)	12	1346	CO	2–36	8–214	Change (mg/dL)	ES −1·92 (−7·72 to 3·88)	1 inverse
Glucose metabolism									
HbA_{1c}	2013¶ (appendix pp 6–7)	16	1491	CO	1–12	20–317	% of total Hb	ES −0·01 (−0·25 to 0·23)	..
Physical function‖									
Balance sway	2011 (5)	3	413	CO	9–20	10–25	Score	ES −0·20 (−0·39 to 0·01)	0
Timed up and go test	2011 (5)	3	551	CO	9–20	10–25	Score	ES −0·19 (−0·35 to 0·02)	0
Proximal leg strength	2012 (6)	11	1255	CO	3–60	10–40	Score	ES 0·11 (−0·01 to 0·22)	0
Grip strength	2012 (6)	7	3648	CO	4–60	10–25	Score	ES −0·02 (−0·15 to 0·11)	None, and 1 in favour of control
Mortality									
All-cause mortality	2011 (2)	30	62 231	6493	1–84	5–50	Death	RR 0·96 (0·93–1·00)	0
All-cause mortality	2011 (3)	50	94 148	10 685	1–84 (median 24)	7·5–50	Death	RR 0·95 (0·91–0·99)	0
All-cause mortality	2012 (7); 2012 (7)	8**; 24	70 528; 88 097	3832; NR	36; 36	≥10; ≥10	Death; death	RR 0·93 (0·88–0·99); RR 0·94 (0·88–0·99)	0; 0
Cancer mortality	2011 (3)	3	39 200	863	1–84	8–20	Death	RR 0·89 (0·78–1·02)	0

RCT=randomised controlled trials. RR=relative risk. ES=effect size. NR=not reported. CO=the endpoint was a change in continuous variable measured in all individuals. Hb=haemoglobin. *References are listed in the appendix pp 13. †Our calculation. ‡From (8). §(4) and (2) have seven studies in common. ¶Meta-analysis done by authors, details in appendix p 4. ‖(5) and (6) have six trials in common. **Pooled analysis of trials of 1000 individuals or more.

Table 4: **Meta-analyses of randomised trials of vitamin D supplementation and non-skeletal endpoints**

strength did not show benefit for supplementation. Three trials of physical functioning not included in meta-analyses had positive results for two of 13 outcomes (table 5). None of the six trials that tested high doses of vitamin D in patients with multiple sclerosis had results suggesting an effect on any clinical endpoint (table 5). Of 12 trials, only results of the WHI trial showed significant, but small, weight loss associated with supplementation (mean loss of 0·13 kg, 95% CI 0·05–0·21).

Results of meta-analyses and pooled analyses consistently showed that supplementation could significantly reduce the risk of all-cause mortality, with relative risks ranging from 0·93 to 0·96 (table 4). Most trials included elderly women and a sizeable proportion

of individuals were living in institutions. Decreases in risks of death were not associated with trial duration and baseline 25(OH)D concentration.[13] Mortality reductions in trials that used doses of 10–20 μg per day of vitamin D seemed greater than were reductions noted with higher doses.[13,14] Investigators of the WHI trial reported a 9% reduction in all-cause mortality (95% CI –1% to 17%).[11]

	RCTs (n)	Appendix reference*	RCT duration (months)	Individuals included in trials (n)	Range of vitamin D dose (μg per day)	Baseline 25(OH)D in intervention groups (nmol/L)†	25(OH)D during the intervention (nmol/L)†	Intervention groups with mean 25(OH) D higher than 72 nmol/L in the trial (n)†	Number of outcomes assessed by trials (n)	Number of outcomes with significant improvement‡ (n [appendix reference])
Cardiovascular diseases or physiological measures										
Coronary artery calcification	1	(1§)	84	754	10	NR	NR	NR	1	0
Multiple outcomes related to arterial and endothelial function	7	(2), (3), (4), (5), (6), (7), (8)	1–4	425	46–179	22·4–52·6	34·9–110·8	4	15	3 ([2], [3], [5])
Systolic or diastolic blood pressure	9	(4), (7), (8), (9), (10§), (11), (12), (13), (14)	1–84	37 163	10–125	22·4–75·6	34·9– 146·2	5	18	0
Blood lipids and cytokines										
Total cholesterol, LDL-cholesterol , HDL-cholesterol, triglycerides, ratio between total cholesterol and HDL-cholesterol	8	(4), (8), (13), (14), (15), (16), (17), (26)	2–12	1003	10–180	22·4–75·6	34·9–146·2	6	40	2 ([26])
C-reactive protein	14	(4), (6), (7), (8), (13), (14), (16), (17), (18), (19), (20), (21), (26), (46)	1–36	3245	10–179	22·4–79·9	34·9–147·3	11	14	0
Inflammation serum cytokines (interleukin 6 or TNFα)	8	(4), (6), (14), (19), (22), (26), (46), (82)	2·7–36	1238	10–179	22·4–79·9	35·0–109·8	5	12	3 ([4], [26], [83])
Diabetes mellitus and glucose metabolism disorders										
Incidence	2	(23¶), (24)	24–84	39 243	10–20	42·2‖	54·2‖	0	2	0
Glycated haemoglobin (HbA_{1c})	14	(2), (8), (15), (16), (25), (26), (27), (28), (29), (30), (31), (32), (33), (78)	2–12	1491	20–317	24·2–74·9	61·9–174·7	11	16	0
Plasma glucose	23	(4), (8), (14),(15), (16), (19), (23§), (25), (26), (27), (29), (30), (31), (32), (33), (34), (35), (36), (37), (38), (78), (79), (80)	2–36	36 400	10–317	17·2–117·1	34·9–174·7	16	22	1 ([35])
Oral glucose tolerance test	5	(29), (27), (33), (38), (78)	3–12	794	50–317	51·9–60·4	81·9–174·7	6	6	0
Insulin sensitivity	6	(15), (16), (29), (33), (81)	4–6	286	20–317	38·9–64·9	68·4–174·7	3	5	0
Serum insulin	12	(4), (15), (14), (16), (25), (27), (29), (32), (35), (36), (37), (38)	2–12	929	10–268	17·2–66·4	34·9–142·5	9	12	0
C-peptide	4	(25), (32), (35), (36)	3–62	261	100–120	21·0–63.7	79·9–137·3	4	4	0
HOMA-IR or HOMA-IS	16	(2), (4), (14), (16), (19), (27), (28), (31), (33), (35), (37), (38), (39), (77), (78), (73)	2–36	1987	17–317	17·2–117·0	34·9–174·7	12	19	3 ([19], [31], [35])
Cancer incidence										
Breast cancer incidence	1	(40¶)	84	36 282	10	42·8	54·2	0	1	0
Colorectal cancer incidence	2	(41), (42¶)	60 and 84	38 968	10 and 20	42·8 and 53·4	54·2 and 74·1	1	2	0
Non-melanoma skin cancer incidence	1	(43¶)	84	36 282	10	42·8	54·2	0	1	0
All-cancers incidence	3	(41), (44**), (45¶)	48–260	40 187	10–20	42·8–71·64	54·2–95·0	2	3	0
Proliferative benign breast diseases										
Proliferative benign breast diseases	1	(47¶)	84	36 282	10	42·8	54·2	0	1	0

(Continues on next page)

	RCTs (n)	Appendix reference*	RCT duration (months)	Individuals included in trials (n)	Range of vitamin D dose (µg per day)	Baseline 25(OH)D in intervention groups (nmol/L)†	25(OH)D during the intervention (nmol/L)†	Intervention groups with mean 25(OH)D higher than 72 nmol/L in the trial (n)†	Number of outcomes assessed by trials (n)	Number of outcomes with significant improvement‡ (n [appendix reference])
(Continued from previous page)										
Infectious diseases										
Sputum conversion in tuberculosis patients	3	(30), (48), (49)	1–3	283	220–250	22·4–32·0	63·4–109·8	1	3	1 (48)
Restriction of mycobacteria growth	1	(50)	1·5	131	60	35·0	67·4	1	1	1 (50)
Tuberculosis score in tuberculosis patients	2	(51), (52)	1–12	485	17–20	17·5–77·4	50·0–97·8	1	2	0
Viral response in hepatitis C patients	1	(53)	6	72	50	22·4	92·4	1	1	1 (53)
Upper respiratory tract infections	5	(54), (55), (56), (57), (58)	3–62	6057	20–100	64·1–78·6	71·4–124·8	2	11	2 ([54], [57])
CD4 count and skin regulatory cells in patients with HIV	2	(59), (83)	2 and 12	76	20–89	25·0–60·2	80·9–179·7	2	7	0
Chronic obstructive pulmonary disease										
Chronic obstructive pulmonary disease	1	(60)	12	182	90	50·0	129·8	1	1	0
Mood and cognitive disorders										
Mood disorders	6	(61), (62), (63), (64), (65), (66††), (84)	0·2–60	7191	10–143	52·7–76·7	93·9–147·5	4	11	3 ([61], [65])
General dementia	1	(67¶)	84	4143	10	50·0	NR	NR	1	0
Physical functioning										
Physical functioning	3	(28), (38), (68)	3–5	354	10–100	20·1–51·92	39·9–83·4	1	13	2 ([28], [38])
Multiple sclerosis										
Multiple sclerosis, clinical endpoints (eg, relapse, disability)	6	(69), (70), (71), (72), (73), (78)	6–24	241	71–800	20·0–77·0	110·8 to about 119·7	6	15	0
Rheumatoid arthritis										
Rheumatoid arthritis	1	(81)	3	117	179	106·8	124·8	1	4	0
Weight loss										
Weight loss	12	(8), (11), (15), (16), (19), (31), (34), (37), (39), (74), (75¶), (76)	2–36	37791	7–214	18·5–81·2	54·2–146·3	5	12	1 ([76])

RCT=randomised controlled trial. HOMA-IR=insulin resistance, derived from the homoeostasis model assessment. HOMA-IS=insulin sensitivity, derived from the homoeostasis model assessment. *References are listed in appendix pp 14–18. Some RCTs that were excluded, with reason, are referenced in appendix p 19. †If reported by RCTs. ‡Based on statistical test result for the difference between intervention and control group had an associated p value <0·05. Appendix reference number given in parentheses. §Trial result from an ancillary substudy of the Women's Health Initiative trial that included 754 women. ¶Women's Health Initiative trial. ||Only for the Women's Health Initiative trial; the RECORD trial (24) did not report on this item. **Results of (44) were recalculated according to intention-to-treat (appendix p 3). ††Trial result from an ancillary substudy of the Women's Health Initiative trial that included 2252 women.

Table 5: **Randomised trials of vitamin D supplementation and non-skeletal disorders that were not included in published meta-analyses**

Overall, three of 88 trials included in meta-analyses obtained results in favour of supplementation and two had results suggesting negative effect of supplementation. 84 trials not included in meta-analyses had findings in favour of supplementation for 23 of 276 (8%) outcomes assessed.

We identified 34 trials of some outcomes that included patients with mean 25(OH)D concentrations less than 50 nmol/L at baseline and that used supplementation of 50 µg per day or higher (table 6). Results were not in favour of supplementation for any disorder. After consideration of all trials, results for seven of 68 outcomes (10%) were in favour of supplementation, a proportion close to the 8% shown for all trials not included in meta-analyses.

Discussion

Prospective studies generally documented moderate to strong decreases in: cardiovascular disease, serum lipid concentrations, serum markers of inflammation, glucose metabolism disorders, weight gain, infectious diseases, mood disorders, declining cognitive function, and impaired physical functioning associated with increasing 25(OH)D. By contrast, intervention studies with vitamin D supplementation had little to no effect on these disorders.

Results of prospective studies did not suggest a protective effect of high 25(OH)D on cancer, except colorectal cancer. However, two large trials did not show any evidence that vitamin D supplementation could decrease the incidence of colorectal cancer. Risk of

pancreatic and prostate cancers might be higher in patients with high 25(OH)D than in patients with lower concentrations. Individuals with higher 25(OH)D concentrations at cancer diagnosis usually had longer overall and cancer-specific survival than did those with lower 25(OH)D concentrations. Exceptions were survival for patients with head and neck and lung cancers, which are much more related to tobacco smoking than to other factors. Cancer characteristics predicting disease aggressiveness were inversely associated with 25(OH)D concentrations at diagnosis.

For multiple sclerosis, results of trials showed no relation between 25(OH)D concentrations and disease course. We noted agreement between prospective and intervention studies associated with increasing 25(OH)D concentrations for all-cause mortality. Intervention studies indicated much less impressive gains than were suggested by prospective studies, in part because of smaller differences in 25(OH)D concentrations achieved in trials than present in general populations.

Our systematic review has some limitations. Intervention studies were of variable quality, and assessment of the quality of randomised trials was beyond the scope of this article. Therefore, for some diseases, additional valuable information might come from non-randomised studies—eg, most of the knowledge about an association between vitamin D and cancer is from prospective studies. The effect of the WHI trial should be examined because of its size and the multiple outcomes that it addressed. In this trial, the mean 25(OH)D concentration increased from 42·1 nmol/L at baseline to 53·9 nmol/L after 2 years.[15] However, in many other trials, patients in intervention groups had mean 25(OH)D concentrations higher than 72 nmol/L. Moreover, outcome rates were generally higher in individuals from trials other than the WHI, and therefore the statistical weight of the WHI trial is less than is suggested by its size. For instance, in the meta-analysis of cardiovascular diseases by Wang and colleagues (table 4, appendix reference [1]), the WHI trial contributed to 92% of all patients, but to 49% of the cardiovascular events. For many outcomes not explored by the WHI trial (eg, most glucose metabolism disorders, or multiple sclerosis), trials were essentially null and were not in favour of vitamin D supplementation. Hence, results of intervention studies cannot be explained by the effect of the WHI trial.

The randomised controlled trial is considered the gold-standard design to establish a causal relation between an exposure and an outcome.[16] Nonetheless, randomised trials of vitamin D supplementation might have obtained null results for different reasons, such as inclusion of patients without hypovitaminosis D, too low a dose of vitamin D, or too short a duration of supplementation. However, several of the most recent trials that obtained null results were purposely done in patients with low 25(OH)D concentrations at randomisation, and with use of high doses to achieve high 25(OH)D concentrations.[17] The 25(OH)D concentration induced by supplementation exceeded 72 nmol/L in many trials. Trials in patients with low 25(OH)D concentrations at baseline that used doses of at least 50 µg per day did not have more convincing results.

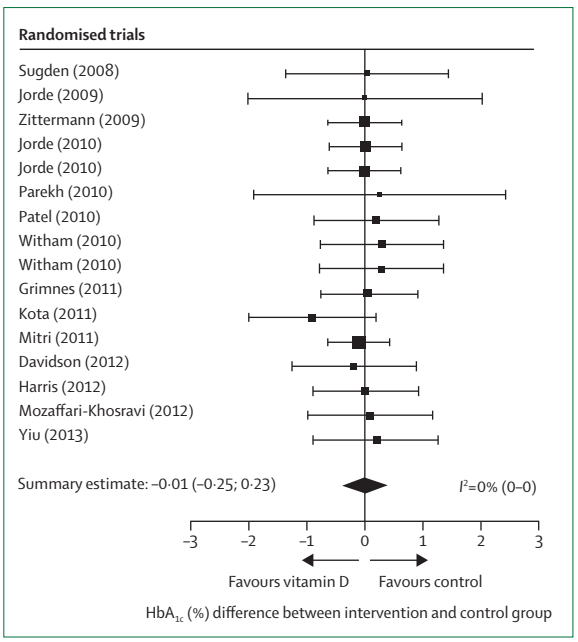

Figure 2: **Forrest plot of changes in percentages of HbA_{1c} and strength of association with vitamin D supplementation.**

Vitamin D supplementation dose of less than 20 µg per day had an effect on all-cause mortality that was equivalent to higher doses,[13,14] which suggests that vitamin D dose is perhaps not very crucial to achieve a biological effect in patients likely to benefit from such supplementation. Vitamin D supplementation is usually believed to be an innocuous healthy option, and therefore, patients included in most trials are likely to be representative populations in which prospective observational studies were done.

Calcium supplements were often given concomitantly to vitamin D supplements. Calcium supplements were not part of many null trials—eg, those of glucose metabolism, infectious diseases, or mood disorders. Two systematic reviews of all-cause mortality, which used appropriate statistical methods, reported no significant difference in results (ie, no interaction) when vitamin D was used alone or concomitantly with calcium.[13,18] We propose hypotheses attempting to shed light on the reasons for the contrast in results from observational and randomised studies.

Postulations for the link between vitamin D and ill health

25(OH)D concentrations as a result of ill health

The absence of an effect of vitamin D supplementation on disease occurrence, severity, and clinical course leads

	RCTs (n)	Appendix references*	Individuals (n)	Outcomes (n)	Outcomes with significant (p<0·05) result in favour of vitamin D supplementation
Vascular endothelial function	5	(3), (4), (5), (6), (7)	291	9	2
Systolic and diastolic blood pressure	5	(4), (7), (8), (26), (86)	619	10	0
Serum CRP	6	(4), (6), (7), (16), (17), (26)	642	6	0
Interleukin 6 or TNFα	3	(4), (6), (26)	335	4	2
Glucose metabolism markers	13	(2), (4), (16), (26), (27), (28), (30), (31), (32), (35), (37), (39), (80)	590	37	3
Infectious diseases	2	(49), (60)	328	2	0
All disorders	34		2805	68	7

RCT=randomised controlled trial. CRP=C-reactive protein. TNF=tumour necrosis factor. *See appendix pp 20–24 for references and description of trials.

Table 6: **Results of trials that included individuals with baseline 25-hydroxyvitamin D concentrations less than 50 nmol/L and that tested vitamin D supplementation of 50 μg per day or greater***

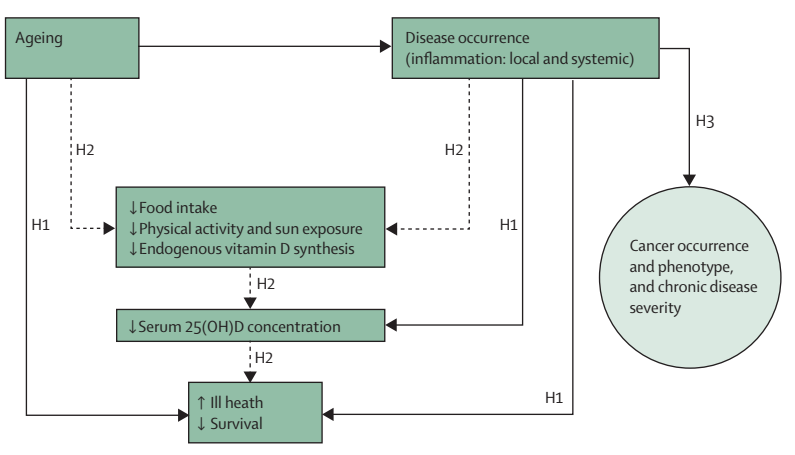

Figure 3: **Vitamin D status estimated through measurement of 25[OH]D, ill health and survival**
Solid line represents direct effects of ageing, diseases, and inflammation; dotted line represents indirect effects of ageing, diseases, and inflammation. Hypothesis one (H1): ageing is directly associated with disease occurrence, inflammation, and mortality. Diseases are often associated with local or systemic inflammation or both. Ageing and inflammatory processes have a negative effect on disease course and survival, and on 25(OH)D. Low 25(OH)D concentration is a result of ageing and inflammatory processes, and is not a cause of ill health. Hypothesis two (H2): ageing and ill health lead to a decrease in capacity to synthesise vitamin D in the skin and to changes in nutrition and lifestyle, all factors that might contribute to create a deficit in vitamin D that could have a negative effect on disease course and survival. Hypothesis three (H3): systemic or local inflammation, or both, increases the risk of occurrence and severity of chronic diseases. Because of the simultaneous effect of inflammation on vitamin D status, a statistical association might exist between 25(OH)D and cancer risk or phenotype. 25[OH]D=25-hydroxyvitamin D.

to the hypothesis that variations in 25(OH)D concentrations would essentially be a result, and not a cause, of ill health. Decreases in vitamin D status would be a biological marker of deteriorating health—characterised by accumulation and severity of disorders driving 25(OH)D to low concentrations (figure 3). Results of observational studies support this hypothesis. For instance, in a large Dutch cohort of elderly people, overall survival gradually decreased with decreases in 25(OH)D concentrations.[19] However, successive adjustments for concomitant health disorders, lifestyle, and frailty (known to be associated with low 25[OH]D) led to a non-significant association between 25(OH)D and survival. Similar sensitivity to adjustment was noted in other large prospective studies.[20–22]

Possible non-skeletal health benefits of vitamin D supplementation

The slight reduction in all-cause mortality in trials with moderate doses of vitamin D seems to be a robust finding. But gains in survival are mainly in elderly women living independently or in institutional care, who are likely to initially have a very low concentration of 25(OH)D with a substantial risk of falls and fractures.[13,23] Ageing is associated with decreases in capacity to synthesise vitamin D in the skin, reductions in sun exposure and in physical activity, loss of appetite, and changes in dietary habits. Our second hypothesis is therefore that the results of ageing and ill health on physiological functioning and lifestyle would reduce 25(OH)D, which would further affect health and, probably, the calcium balance (figure 3). Use of standard doses of vitamin D would improve yet unknown physiological functions, which would result in slight gains in survival.

Ill health, inflammation, and vitamin D

Do disorders and lifestyle exert their effect on 25(OH)D through a similar mechanism? Inflammatory processes—as measured by concentrations of serum TNFα, interleukin 6, and C-reactive protein—are usually active in individuals who smoke, are frail, or have a sedentary lifestyle, and in people with obesity, diabetes, cardiovascular diseases, or acute or chronic infections; high levels of systemic inflammation correlate with disease severity and low survival.[24–40] 25(OH)D concentrations drop substantially during acute health episodes—characterised by severe inflammation and multiorgan failure, such as in patients admitted to intensive care units.[41,42] Similar substantial reductions have been reported in disorders characterised by large amounts of inflammation, such as knee replacements,[43,44] acute pancreatitis,[45] or congestive heart failure.[30] Furthermore, serum concentrations of TNFα or C-reactive protein are inversely correlated with 25(OH)D concentrations.[24,46,47] Therefore, we postulate that inflammation is the common factor between most non-skeletal health disorders and low 25(OH)D concentrations. However, increases in 25(OH)D have no

effect on inflammatory processes or on disorders at the origin of these processes. Only the healing of these disorders could be followed by a restoration of 25(OH)D concentrations, but few studies have documented this possibility.[48]

For mood disorders, low 25(OH)D could be a result of poor lifestyle habits (eg, smoking, or sedentary living) and obesity, which are more prevalent in individuals with depressive symptoms. However, investigators of prospective studies have documented associations between inflammatory states and mood disorders, which could contribute to the low 25(OH)D noted in people with depressive symptoms.[49,50]

Inflammation, vitamin D, cancer, and other chronic diseases

Cancer occurrence is favoured by pre-existing local inflammatory lesions, and cancer progression often occurs in the context of inflammation involving tumours and surrounding tissues.[51] Long-term intake of non-steroidal anti-inflammatory drugs reduces the risk of breast and colorectal cancer, and of melanoma.[52–55] Failure of the study by Trivedi and colleagues[56] and the WHI trials[57] to decrease the incidence of colorectal cancer through vitamin D supplementation has been attributed to insufficient statistical power or too low a dose of vitamin D.[15] However, colorectal cancer occurrence and growth are associated with strong inflammatory processes.[58,59] Hence low 25(OH)D concentrations could indicate inflammatory disorders favouring colorectal cancer occurrence (eg, chronic colitis), or inflammation associated with progression of precursor lesions (eg, adenomatous polyps) to localised invasive cancer, and then to distant metastases.

For the associations between low 25(OH)D concentrations and more aggressive phenotypes of breast cancer, prostate cancer, and cutaneous melanoma, would the inflammation in the tumour micro-environment be sufficient to induce reductions in 25(OH)D that would be proportional to tumour growth and aggressiveness? An alternative explanation could stem from two observations. First, in several types of solid cancer, increased systemic inflammation (indicated by serum C-reactive protein concentrations), is associated with rapid progression and poor prognosis.[35,36] Second, women who are obese and have diabetes who have lower 25(OH)D concentrations and more inflammation than have lean healthy women are also more likely to be diagnosed with aggressive breast cancers, such as triple-negative breast cancer.[60–62] Hence, low 25(OH)D concentrations and the aggressive cancer phenotype could be the result of systemic inflammation (figure 3). Additionally, low 25(OH)D concentrations and severity of non-cancerous chronic disease could be affected by systemic inflammation. Future research should examine the likelihood of these hypotheses.

Conclusions

Many prospective studies have shown associations between low 25(OH)D concentrations and a wide range of acute and chronic health disorders. However, an equally similar number of randomised trials have not confirmed that raising of 25(OH)D concentrations can modify the occurrence or clinical course of these disorders. Hence, associations between 25(OH)D and health disorders reported by investigators of observational studies are not causal. Low 25(OH)D could be the result of inflammatory processes involved in the occurrence and progression of disease. An exception would be slight gains in survival after the restoration of vitamin D deficits due to lifestyle changes induced by ageing and ill health. Five trials including 2150–20 000 patients aged 50 years or older are in progress, testing whether vitamin D supplementation at 40–80 µg per day can reduce the risk of cancer, cardiovascular diseases, diabetes, infections, declining cognitive functions, and fractures.[63] The first results are not expected before 2017, but these studies have the potential to test our hypotheses.

Contributors

PA and PM worked on the original idea for the Review, searched the published work, extracted data, and summarised data in tables. CP and MB did the meta-analysis for studies of diabetes. MB critically reviewed the statistics reported in selected articles. PA drafted the first draft of the Review. PA wrote the hypotheses for the link between vitamin D status and inflammation. All authors read the final version of the Review.

Conflicts of interest

We declare that we have no conflicts of interest.

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