

# Vitamin D and public health: an overview of recent research on common diseases and mortality in adulthood

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## Abstract

**Objective:** There is increasing interest in vitamin D and its possible health effects. The aims of the present overview are to summarise the research on common diseases for which there is substantial evidence on vitamin D, identify diseases where vitamin D may be beneficial and discuss the public health implications of these findings.

**Design:** Literature search of PubMed for the years 2000 to 2010 to identify cohort studies with baseline measures of 25-hydroxyvitamin D (25(OH)D) and randomised controlled trials (RCT) of vitamin D supplementation in relation to fractures, colorectal cancer, CVD and all-cause mortality. Risk ratios of disease from comparisons between 25(OH)D quantiles in these studies were summarised using RevMan software version 5.1 (The Nordic Cochrane Centre, Copenhagen).

**Setting:** Community-based samples recruited into cohort studies from many countries.

**Subjects:** Older men and women, mostly above 50 years of age.

**Results:** When comparing the lowest 25(OH)D category with the highest (or reference), the pooled risk ratio (95% CI) was: 1.34 (1.13, 1.59) for fractures from nine studies; 1.59 (1.30, 1.95) for colorectal cancer from nine studies; 1.35 (1.17, 1.56) for CVD from twelve studies; and 1.42 (1.23, 1.63) for all-cause mortality from twelve studies.

**Conclusions:** Cohort studies show that baseline 25(OH)D levels predict increased risk of fractures, colorectal cancer, CVD and all-cause mortality. These associations are weak and could be explained by confounding variables such as obesity and physical activity. Because of their potential public health significance, RCT using vitamin D doses  $\geq 50 \mu\text{g/d}$  are required to determine whether vitamin D protects against these diseases.

**Keywords**  
All-cause mortality  
CVD  
Colorectal cancer  
Fractures  
Vitamin D

During the last decade vitamin D has emerged from the shadow of other nutrients to centre stage. This trend has been driven by a combination of factors including recent disappointing negative findings from supplementation trials of other vitamins<sup>(1)</sup>, some of which have shown harm<sup>(2)</sup>, and the evidence of pleiotropic effects of vitamin D on many body tissues<sup>(3)</sup>. A further development has been the report from the US Institute of Medicine (IOM) revising slightly higher the recommended daily intake of vitamin D<sup>(4)</sup>, which has received a mixed response from researchers and clinicians<sup>(5,6)</sup>. The accumulating evidence, much of which was ignored by the IOM because of its observational nature, has reached tipping point for a number of disease outcomes, such that randomised controlled trials (RCT) are required urgently to provide certainty about the possible health benefits from vitamin D.

The aims of the present overview are to summarise the research on common diseases for which there is substantial evidence on vitamin D and identify diseases where vitamin D may be beneficial. The focus is on community-based studies of free-living people, rather than studies of

clinic-based patients or laboratory-based animals, which are cited only to understand possible biological mechanisms; and on vitamin D itself, rather than the active metabolite calcitriol and other analogues of active vitamin D. Such evidence is required to support the introduction of public health programmes to increase the vitamin D status of the general population, which, surely, should be our ultimate aim, should vitamin D be shown by RCT to be beneficial.

## Study design and causation

The quality of the evidence used to decide whether vitamin D is beneficial depends on study design. At the lowest rung sit ecological studies, which examine associations between exposure (e.g. vitamin D status) and disease at the group level. Typically, comparisons of these measures are made for populations living in towns, cities, counties or countries. These studies are typically used to generate rather than test hypotheses, since the association between exposure and disease is not made at the individual level. The latter studies, where exposure and disease status are measured in individuals, are termed

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analytic and are categorised into two main groups: (i) experimental studies, such as RCT, where the exposure is actively changed by the researchers; and (ii) observational studies, where the researchers only observe and measure exposure.

Epidemiologists typically use the following hierarchy, in descending order of importance, to decide on causation when comparing results from different analytical study designs: (i) experimental studies (i.e. RCT) provide the strongest evidence, since the exposure is actively modified by researchers; (ii) cohort studies (including nested case–control studies) are next, since measurement of exposure precedes disease onset; and (iii) case–control and cross-sectional studies are lowest, since measurement of exposure may be affected by the disease process or biased after disease onset.

### Vitamin D status

Vitamin D occurs in the human body in two forms, either as: (i) cholecalciferol (vitamin D<sub>3</sub>) from sun exposure or eating animal foods; or (ii) ergocalciferol (vitamin D<sub>2</sub>) from mushrooms and yeast irradiated with UV light<sup>(7)</sup>. The sun is the major source of vitamin D in most land animals including man, and vitamin D<sub>3</sub> is synthesised in the skin by UV-B radiation activating its precursor 7-dehydrocholesterol<sup>(7)</sup>; although dietary sources of vitamin D can also be important, particularly in people who take vitamin D supplements<sup>(8)</sup>. Vitamin D from both sources then circulates in the blood to the liver where it is converted to its main metabolite, 25-hydroxyvitamin D (25(OH)D), which has blood levels about 1000 times higher than the active metabolite, 1,25-dihydroxyvitamin D (1,25-(OH)<sub>2</sub>D). Until recently, it was thought that the conversion to 1,25-(OH)<sub>2</sub>D occurred only in the kidneys, but there is now overwhelming evidence, originally from laboratory cancer research<sup>(9)</sup>, that the cells of most organs

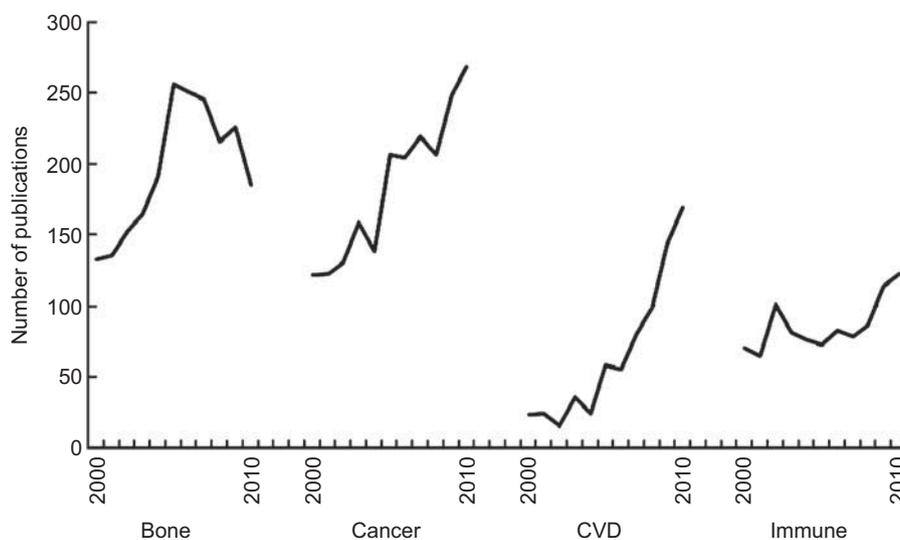
have the vitamin D receptor and, along with this, the capacity to synthesise 1,25-(OH)<sub>2</sub>D locally – the so-called autocrine or paracrine synthesis of the active metabolite<sup>(3,10)</sup>. The autocrine synthesis of 1,25-(OH)<sub>2</sub>D is dependent on circulating levels of 25(OH)D. The main marker of vitamin D status is 25(OH)D, which provides a better assessment of vitamin D status than dietary methods since most vitamin D comes from sun exposure<sup>(11,12)</sup>. Objective laboratory measurements of blood vitamin D levels are likely to be less biased than measurement of dietary vitamin D intake using subjective questionnaire methods. Thus, cohort studies which associate 25(OH)D levels at baseline with subsequent disease risk provide the strongest evidence of causation next to that from RCT of vitamin D supplementation.

### Vitamin D and disease

Vitamin D has been linked to a very wide range of diseases, but sufficient evidence from epidemiological studies has now emerged for the following diseases: fractures, cancer, CVD (including hypertension and type 2 diabetes), and diseases from altered immune function. The evidence for each is discussed in turn, with the focus on cohort studies of non-clinic selected samples with baseline blood measures of 25(OH)D and RCT of vitamin D supplementation.

### Methods

To identify relevant articles for each of these disease groups, PubMed was searched for the years 2000 to 2010 (19 March 2011) using the term ‘vitamin D’ with the following keywords: ‘fractures’ or ‘osteoporosis’ (number of publications=2161); ‘cancer’ (=2031); ‘infection’ or ‘cytokines’ for immune function (=955); and ‘cardiovascular disease’ (=736). The annual number of publications in each of these four disease categories during 2000–2010 is shown in Fig. 1. Cohort studies and RCT were identified



**Fig. 1** Trends in vitamin D publications, by disease group, 2000 to 2010

by searching the abstracts of these publications, and recent reviews and meta-analyses were searched to identify studies published before 2000. The inclusion criteria for cohort studies (including nested case-control studies) were: (i) study samples recruited from community or occupational groups (patient samples were excluded); and (ii) baseline vitamin D status assessed using blood measures of 25(OH)D (studies of dietary vitamin D status were excluded). Many of the cohort studies of CVD also reported on all-cause mortality, so this has been added as an additional outcome in the overview. Eligible cohort studies are summarised in Tables 1–3 for fractures ( $n$  9), colorectal cancer ( $n$  10), CVD ( $n$  13) and all-cause mortality ( $n$  12).

Measures of effect (relative risks, odds ratios and hazard ratios) associated with quantiles of 25(OH)D were extracted from identified cohort studies and summarised with RevMan software version 5.1 (The Nordic Cochrane Centre, Copenhagen), using a random effects model with weighting by the inverse variance method and the  $I^2$  test to assess heterogeneity<sup>(13)</sup>. This approach of summarising effect measures from 25(OH)D quantiles has been used in previous meta-analyses<sup>(14,15)</sup>. The main advantages of this approach are that: (i) non-linear associations can be evaluated (this issue is discussed later with regard to the IOM report and the public health implications of current research); and (ii) any effect from variation between different methods for measuring 25(OH)D is minimised as the relative risks come from comparisons of participants tested with the same assay within each study. However, the main disadvantage is that the cut-off points used to define 25(OH)D categories vary between studies, which may have resulted in attenuation of effect because of measurement error. Further, the cut-off points in many studies have been below the range of 80–100 nmol/l associated with optimum health outcomes<sup>(16)</sup>, which also will have resulted in underestimation of the maximum effect measure. Thus, the summary measures of effect in the present report probably underestimate the full effects associated with variations in 25(OH)D across the normal population range.

### Fractures

Recognition of the role of vitamin D deficiency in causing bone disease extends back to the 1920s, from the classic studies showing that vitamin D supplementation cured rickets<sup>(17)</sup>. Evidence that vitamin D deficiency might have a causal role in fractures first came from UK studies carried out in the 1970s which showed that osteomalacia ('adult rickets') was common in patients with hip fracture<sup>(18)</sup> and more common after winter (February–April) than in other months of the year<sup>(19)</sup>. Following this, numerous (at least thirty) case-control studies were carried out which collectively showed that hip-fracture cases had lower 25(OH)D levels than controls<sup>(20)</sup>.

The usual sequence is for cohort studies to be carried out after case-control studies, before progressing to RCT. However, for fractures, the RCT were started first, partly

driven by pharmaceutical companies with a commercial interest, seeking to show that the active metabolite (calcitriol) and its analogues (alphacalcidol) might reduce the risk of fractures. At least twenty-five studies of active vitamin D have been carried out, extending back to the 1980s; with meta-analyses of these showing that active vitamin D reduces the incidence of fractures, but increases the incidence of hypercalcaemia<sup>(21–23)</sup>. This latter finding, combined with the high cost of active vitamin D, which needs to be taken daily because of its short half-life, make these medications unsuitable for population-based fracture prevention programmes.

At least twenty-four RCT have been carried out using vitamin D (alone or with Ca)<sup>(23)</sup>, beginning with the first one from France published in 1992<sup>(24)</sup> and continuing to the most recent in 2010 from Australia and Finland<sup>(25,26)</sup>. These RCT have two widely accepted limitations. First, the daily dose in many of these studies (average about 12.5 µg/d) is now considered too low as it would raise 25(OH)D levels only by 10–15 nmol/l<sup>(27)</sup>. Current recommendations are that at least 42.5 µg/d is required to increase 25(OH)D levels up to those associated with optimum health (80 nmol/l)<sup>(28)</sup>. Second, many of these RCT gave Ca in combination with vitamin D, and usually with higher doses of vitamin D (17.5–20 µg/d) compared with studies that gave vitamin D by itself (10 µg/d). Thus, it is not possible to conclude whether any beneficial effect on fracture incidence is from vitamin D by itself. Hence the inconsistent findings from recent meta-analyses, with some concluding that vitamin D is beneficial against fractures only when combined with Ca<sup>(23,29,30)</sup> and others concluding that vitamin D taken in higher doses (>17.5 µg/d) is effective by itself<sup>(31–34)</sup>, while yet another concluded that Ca supplementation by itself had no effect on fracture incidence<sup>(35)</sup>. The eventual outcome of this debate has important implications for any future public health prevention strategies, should future research show that vitamin D (with or without Ca) is beneficial (see public health implications below).

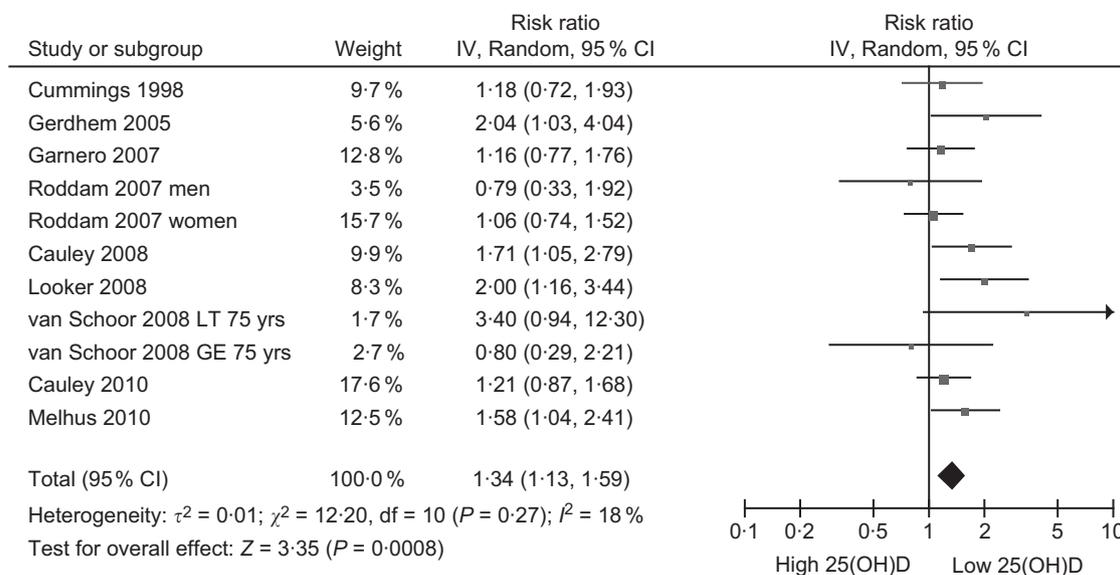
The inconclusive results from RCT of vitamin D supplementation increase the importance of evidence from cohort studies comparing baseline 25(OH)D levels with subsequent risk of fracture. At least ten of these cohort studies have been published, beginning with a very small study in 1990 (in which nine participants had fractures during 30-month follow-up) which is not included in the summary analysis since its sample of older adults was recruited from sheltered housing and not the general community<sup>(36)</sup>. The first community-based study was published in 1998<sup>(37)</sup>, and the rest since 2005<sup>(38–45)</sup>. The main outcomes examined have been hip and non-vertebral fractures (Table 1). The pooled relative risk is 1.34 (95% CI 1.13, 1.59) comparing the lowest 25(OH)D quantile with the higher reference category in each study (Fig. 2), indicating a weak effect associated with low vitamin D status. The possibility of residual confounding remains as

**Table 1** Relative risk of having a fracture associated with low baseline level of 25-hydroxyvitamin D (25(OH)D) in cohort studies

Publication (source in cited publication)	Sample	Type of fracture (no. with fracture)	25(OH)D in nmol/l (quantile)	RR (95% CI)	Adjusted confounders
Cummings <i>et al.</i> (1998) <sup>(37)</sup> (Table 2)	Community-living women $\geq 65$ years age, followed for 5.9 years	Hip (133)	$\leq 47$ (Q1) $> 47$ (Q2)	1.2 (0.7, 1.9) 1.0	Age, weight
Gerdhem <i>et al.</i> (2005) <sup>(38)</sup>	Population-sampled women aged 75 years, followed for 3 years	All (119)	$< 50$ (Q1) $\geq 50$ (Q2)	2.04 (1.04, 4.04) 1.00	None stated
Garnero <i>et al.</i> (2007) <sup>(39)</sup>	Employed postmenopausal women, followed for median 11.2 years	All (134)	Per SD decrease	1.16 (0.77, 1.76)	Age, prevalent fracture, physical activity
Roddam <i>et al.</i> (2007) <sup>(40)</sup> (Table 4)	Community-living men and women $\geq 20$ years age, followed for 5 years	Non-vertebral (730)	Women: $< 50$ (Q1) $\geq 100$ (Q4) Men: $< 50$ (Q1) $\geq 100$ (Q4)	Women: 1.06 (0.74, 1.52)* 1.00 Men: 0.79 (0.33, 1.92)* 1.00	Age, month of blood draw, BMI, smoking, Ca intake, energy intake, alcohol, physical activity, marital status, and (for women) parity, hormone therapy
Cauley <i>et al.</i> (2008) <sup>(41)</sup> (Table 2)	Community-living women 50–79 years age, followed for median 7.1 years	Hip (400)	$\leq 47.5$ (Q1) $\geq 70.7$ (Q4)	1.71 (1.05, 2.79) 1.00	Age, BMI, history of fracture, smoking, alcohol, Ca intake, steroid use, region
Looker & Mussolino (2008) <sup>(42)</sup> (Table 3)	Population-sampled men and women $\geq 65$ years age, followed from 1988–94 to 2000	Hip (156)	$\leq 42.9$ (Q1) $\geq 82.5$ (Q4)	2.00 (1.16, 3.44)* 1.00	Age, sex, bone density, BMI, Ca intake, energy intake, weight loss
van Schoor <i>et al.</i> (2008) <sup>(43)</sup> (Table 3)	Population-sampled men and women $\geq 55$ years age, followed for 6 years	Non-vertebral (115)	$< 75$ years: $< 25$ (Q1) $\geq 75$ (Q4) $\geq 75$ years: $< 25$ (Q1) $\geq 75$ (Q4)	$< 75$ years: 3.4 (0.9, 12.1) 1.0 $\geq 75$ years: 0.8 (0.3, 2.2) 1.0	Age, sex, season
Cauley <i>et al.</i> (2010) <sup>(44)</sup> (Table 4)	Community-living men $\geq 65$ years age, followed for mean of 5.3 years	Non-vertebral (436)	$< 47$ (Q1) $\geq 70$ (Q4)	1.21 (0.96, 1.65) 1.00	Age, race, clinic, season, physical activity, height, weight
Melhus <i>et al.</i> (2010) <sup>(45)</sup> (Table 2)	Population-sampled men, mean age 71 years, followed for median 11 years	All fractures (309)	$< 40$ (Q1) $> 40$ (Q2)	1.58 (1.04, 2.41) 1.00	Age, weight, height, season, Ca intake, activity, smoking, diabetes and other chronic diseases

RR, relative risk.

\*Inverse of published relative risk to make highest 25(OH)D group the reference.



**Fig. 2** Forest plot of relative risks of fracture associated with the lowest 25-hydroxyvitamin D (25(OH)D) category compared with the highest (or reference) in cohort studies

some studies did not control for BMI and physical activity, the two most important confounders (Table 1).

In summary, research on vitamin D and fractures appears to have lost momentum over the last 5 years, as indicated by the decline in publications during this period (Fig. 1). Conclusions from meta-analyses are inconsistent, because of low doses of vitamin D, often used in combination with Ca. However, the cohort studies indicate that people with low vitamin D levels are at increased risk of suffering fractures (Table 1), but these findings could be explained by other possible confounding factors. RCT giving higher doses of vitamin D than used previously are required to resolve the current uncertainty.

**Cancer**

A possible link between vitamin D and cancer first came from US ecological studies published around 1940 showing that a range of cancers were associated with sunlight exposure and latitude<sup>(46,47)</sup>.

However, the modern body of research on this topic is generally considered to have been stimulated by a later ecological study from US researchers who, unaware of the earlier studies, published a paper in 1980 showing an inverse association between latitude and colorectal cancer mortality in the USA<sup>(48)</sup>. Since then, further ecological studies have shown inverse associations between solar radiation and cancers of the breast<sup>(49)</sup>, prostate<sup>(50)</sup>, ovary<sup>(51)</sup> and lymphoma<sup>(52)</sup>, suggesting that vitamin D may protect against a wide range of cancers.

A substantial number of cohort studies, with baseline measures of 25(OH)D, have been carried out to test the hypotheses generated by the above ecological studies. These studies have been reviewed in a recent report by the International Agency for Research on Cancer (IARC)<sup>(53)</sup>,

since updated by the same authors<sup>(54)</sup>. Despite the extensive laboratory research showing the anticancer properties of vitamin D in prostate cells<sup>(55)</sup>, the current evidence does not support an association between vitamin D and prostate cancer risk. Eleven cohort studies of 25(OH)D and prostate cancer were published up until December 2009, with enough cases ( $n$  3956) to detect a very small effect<sup>(54)</sup>. However, meta-analyses of these studies show no association between 25(OH)D and prostate cancer risk<sup>(53,54,56)</sup>. A further recent nested case-control study from Hawaii also found no association between baseline plasma 25(OH)D and prostate cancer risk<sup>(57)</sup>, confirming the conclusions of the meta-analyses.

The evidence is stronger for breast cancer, with five cohort studies published up until December 2009 and the pooled relative risk being inverse but not statistically significant<sup>(54,58)</sup>. For example, one meta-analysis calculated that a 50 nmol/l increase in 25(OH)D was associated with a relative risk of 0.92 (95% CI 0.82, 1.04;  $P = 0.016$ )<sup>(58)</sup>, which suggests that if vitamin D is eventually confirmed to protect against breast cancer, the reduction in individual risk could be small. Since these meta-analyses, three further cohort studies of serum 25(OH)D and breast cancer have been published. One study from France reported a significant inverse association between baseline 25(OH)D and subsequent breast cancer risk<sup>(59)</sup>, a Swedish study reported a non-significant inverse association<sup>(60)</sup>, while further follow-up of mortality from the Third National Health and Nutrition Examination Survey (NHANES) cohort also has reported a non-significant inverse association<sup>(61)</sup>. Thus, the overall evidence from cohort studies suggests there may be an inverse association between vitamin D status and subsequent risk of breast cancer, but further cohort studies are required to confirm this.

The cancer most strongly linked to vitamin D deficiency is colorectal cancer. To date, there are ten published cohort studies which have examined the association between baseline blood levels of 25(OH)D and incidence of colorectal cancer, beginning with the first report in 1989<sup>(62)</sup> and the rest since the mid-1990s<sup>(61,63–70)</sup> (Table 2). Nine of these studies have been summarised in a meta-analysis, which found a significantly reduced risk of colorectal cancer with increasing 25(OH)D levels<sup>(54)</sup>. For a 25 nmol/l increase in 25(OH)D, colorectal cancer risk was decreased by 15% (95% CI 8, 21%). An indication of the possible change in risk across the population range of 25(OH)D is shown in Fig. 3, with the pooled relative risk for people in the lowest 25(OH)D category being 1.59 compared with the lowest category. This suggests that the strength of the association between vitamin D and colorectal cancer is weak to moderate. The IARC report concluded that there was a significant inverse association between vitamin D status and colorectal cancer, but considered this to be 'only limited evidence of a causal link due to confounding by other dietary or lifestyle factors' (p. 305)<sup>(53)</sup>. The main possible confounder is physical activity, since this is associated with both colorectal cancer<sup>(71)</sup> and 25(OH)D levels<sup>(72)</sup>. Although physical activity was controlled for in several of the studies (Table 3), it is possible that errors in accurately measuring physical activity with questionnaires may have resulted in residual confounding and failure to control fully for its effects in multivariate analyses. Alternatively, it is also possible that any beneficial effect from physical activity could be from increased 25(OH)D levels resulting from activity. Only clinical trials of vitamin D supplementation will resolve this uncertainty.

The main RCT carried out to date to see if vitamin D supplementation reduces incidence of colorectal cancer is the Women's Health Initiative. This study recruited 36 282 women aged 50–79 years into the vitamin D/calcium part of the wider study<sup>(66)</sup>. Women in the intervention arm of the study were given 10 µg of vitamin D and 1000 mg of Ca to take daily. At the end of the follow-up period (average of 7 years), there was no difference in the incidence of colorectal cancer between treatment and placebo arms. This negative finding could be due to some well-recognised limitations in the study design. These include: (i) too low a dose of vitamin D, which has been estimated to increase 25(OH)D levels only by about 7 nmol/l<sup>(73)</sup>; (ii) low compliance with only 70% of participants taking the study capsules 50% or more of the time; and (iii) contamination in the control group with many of them continuing to take vitamin D supplements during the follow-up period<sup>(74)</sup>. One other RCT of vitamin D supplementation and cancer has been conducted<sup>(75)</sup>. In that study, 1179 women from Nebraska were given both vitamin D (27.5 µg/d) and Ca (1400–1500 mg/d) together, Ca only or placebo. After 4 years' follow-up, women in both treatment arms had about half the risk of any type of cancer compared with those taking placebo, indicating a consistent beneficial effect for Ca. Thus, the role of

vitamin D by itself is still unclear after this study and needs confirmation by other RCT.

The relationship between 25(OH)D levels and other rarer cancers has also been examined. In analyses pooling data from ten cohort studies, serum 25(OH)D was not associated with any of the following cancers: endometrial, oesophageal, gastric, kidney, non-Hodgkin lymphoma or ovarian; although risk of pancreatic cancer was found to be increased in people with 25(OH)D levels above 100 nmol/l<sup>(76)</sup>. However, the latter finding was not confirmed in another US cohort study which reported a significant inverse association between predicted 25(OH)D level and risk of pancreatic cancer<sup>(77)</sup>. Thus, the evidence on the association between vitamin D status and pancreatic cancer is inconsistent.

In summary, research on vitamin D and cancer has strong momentum, as indicated by the continuing increase in the annual number of publications during the last decade (Fig. 1). There is now a large body of laboratory work showing that active vitamin D (including calcitriol and its analogues) has anticancer properties by encouraging cell differentiation and proliferation of cancer cells from a range of tissues<sup>(78)</sup>. The cancer most strongly linked with low vitamin D status is colorectal cancer. However, this research has reached a tipping point, and RCT of vitamin D supplementation are now required to determine whether or not vitamin D protects against this cancer.

### CVD

Research on vitamin D and CVD has increased more rapidly during the last decade than on other diseases (Fig. 1). This increase belies the major changes in scientific opinion about the role of vitamin D in CVD that has taken place over the last 40 years<sup>(79)</sup>. Until the 1970s, it was generally believed by researchers and clinicians that vitamin D was a cause of atherosclerosis and CHD<sup>(80–84)</sup>. These conclusions were based on animal studies which used pharmacological doses of vitamin D (125–250 µg/kg per d) in a cholesterol model to produce arteriosclerosis and on case reports of patients with arterial calcification and hypertension without controls to provide a reference point for vitamin D intake<sup>(79)</sup>. A major step was the development of the assays for measuring blood levels of 25(OH)D<sup>(85)</sup>, which showed that most vitamin D (>80%) came from dermal production following sun exposure, not diet<sup>(11,12)</sup>.

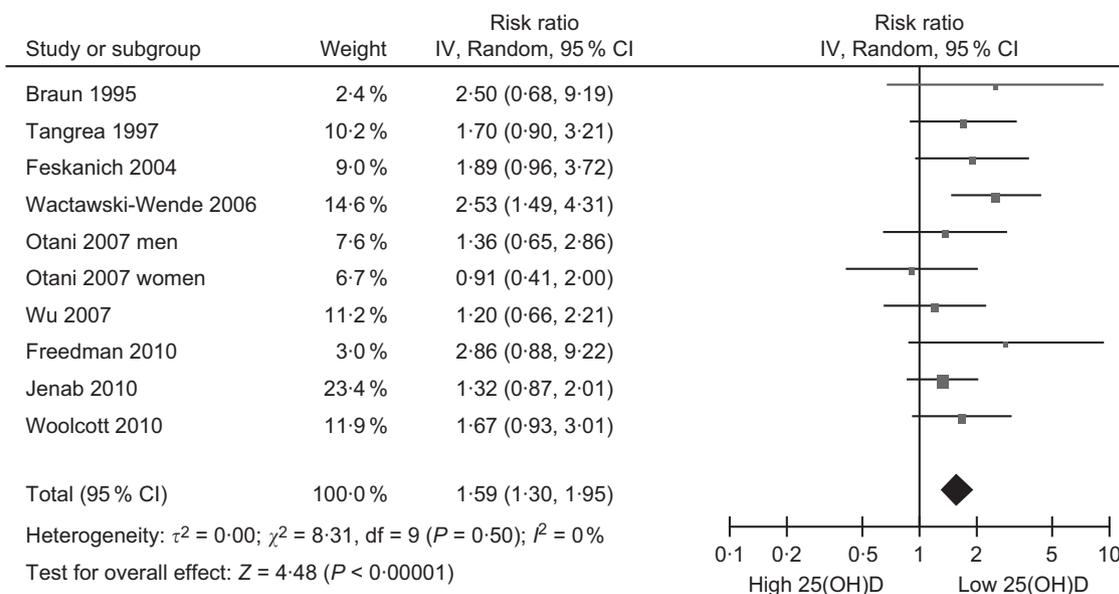
Opinions about the role of vitamin D in CVD started to change (by 1980) with the publication of the hypothesis that UV radiation, through vitamin D formation, may protect against CVD<sup>(86)</sup>, which was subsequently expanded<sup>(87)</sup>; and the identification of a vitamin D receptor in rat heart<sup>(88)</sup>, along with animal studies showing that vitamin D affected cardiovascular function<sup>(89)</sup>. The first case-control studies to use the newly developed assay for 25(OH)D found, unexpectedly at the time, that myocardial infarction cases had similar or lower 25(OH)D levels than controls<sup>(90–92)</sup>. The initial test of the hypothesis

**Table 2** Relative risk of having colorectal cancer associated with low baseline level of 25-hydroxyvitamin D (25(OH)D) in cohort studies

Publication (source in cited publication)	Sample	No. of cases	25(OH)D in nmol/l (quantile)	RR (95% CI)	Adjusted confounders
Garland <i>et al.</i> (1989) <sup>(62)</sup> (Fig. 2)	Community volunteers aged $\geq 35$ years, surveyed in 1974, followed up to 1983	34	<50 (Q1) $\geq 50$ (Q2)	3.3 ( $P < 0.05$ )* 1.0	Controls matched for age, sex, race and month of blood draw
Braun <i>et al.</i> (1995) <sup>(63)</sup> (Table 1)	Community volunteers aged $\geq 35$ years, surveyed in 1974, followed from 1983 to 1991	57	<43 (Q1) >75 (Q5)	2.5 (0.71, 10.00)* 1.0	Controls matched for age, sex, race and month of blood draw
Tangrea <i>et al.</i> (1997) <sup>(64)</sup> (Table 4)	Cancer-free male smokers aged 50–69 years, followed up to 8 years	146	<24 (Q1) >48 (Q4)	2.7 (0.9, 3.0)* 1.0	Controls matched for age, clinic and month of blood collection
Feskanich <i>et al.</i> (2004) <sup>(65)</sup> (Table 2)	Female nurses aged 43–70 years, followed up to 11 years	193	Low (Q1) High (Q5)	1.89 (0.96, 3.70)* 1.00	Age, month of blood collection, BMI, activity, smoking, alcohol, menopause, hormone therapy, aspirin, family history of colorectal cancer, intakes of Ca and red meat
Wactawski-Wende <i>et al.</i> (2006) <sup>(66)</sup> (Table 2)	Volunteer women in clinical trial, aged 50–79 years, followed for mean of 7 years	317	<31.0 (Q1) $\geq 58.4$ (Q4)	2.53 (1.49, 4.32) 1.00	None
Otani <i>et al.</i> (2007) <sup>(67)</sup> (Table 4)	Population-sampled men and women 40–69 years age, followed for mean of 11.5 years	375	Men: <57 (Q1) $\geq 80$ (Q4) Women: <57 (Q1) $\geq 80$ (Q4)	Men: 1.36 (0.70, 2.86)* 1.00 Women: 0.90 (0.40, 2.00)* 1.00	Age, sex, date of blood draw, region, smoking, alcohol, BMI, physical activity, supplement use, family history of colorectal cancer
Wu <i>et al.</i> (2007) <sup>(68)</sup> (Table 2)	Male health professionals mean age 66 years, followed up to 8 years	179	Low (Q1) High (Q5)	1.20 (0.66, 2.22)* 1.00	Age, month of blood collection, family history, aspirin, smoking, alcohol, physical activity, Ca and meat intakes
Freedman <i>et al.</i> (2010) <sup>(61)</sup> (Table 4)	Population-sampled men and women $\geq 17$ years age, followed from 1988–94 to 2006	95	<50 (Q1) $\geq 100$ (Q4)	2.86 (0.88, 9.09)* 1.00	Age, sex, race/ethnicity, smoking, BMI
Jenab <i>et al.</i> (2010) <sup>(69)</sup> (Table 2)	Men and women, mean age 58 years, recruited from community, followed for mean of 4 years	1248	<25 (Q1) $\geq 50$ to <75 (Q3 of 5)	1.32 (0.87, 2.01) 1.00	Age, sex, study centre, education, BMI, physical activity, smoking, alcohol, diet (including meat), and (for women) menopause, hormone therapy use
Woolcott <i>et al.</i> (2010) <sup>(70)</sup> (Table 2)	Men and women, 45–75 years age, recruited from community, followed for mean of 1.7 years	229	<42 (Q1) $\geq 82$ (Q5)	1.67 (0.93, 3.03)* 1.00	Age, sex, ethnicity, area, date of blood draw, family history, BMI, meat intake

RR, relative risk.

\*Inverse of published relative risk to make highest 25(OH)D group the reference.



**Fig. 3** Forest plot of relative risks of colorectal cancer associated with the lowest 25-hydroxyvitamin D (25(OH)D) category compared with the highest (or reference) in cohort studies (the study by Garland *et al.*<sup>(62)</sup> is excluded because it did not report 95 % CI)

that vitamin D may protect against CVD was a population-based case-control study from New Zealand, published in 1990, which found a significant inverse association between 25(OH)D levels and risk of myocardial infarction<sup>(93)</sup>. However, because of the case-control design with collection of blood samples after the onset of disease, uncertainty remained as to whether or not 25(OH)D levels in cases had been affected by the disease process.

The first cohort study comparing baseline 25(OH)D levels and risk of subsequent CVD was not published until 2005. That study of elderly people in Finland showed a significant inverse association between baseline 25(OH)D levels and subsequent risk of acute myocardial infarction, but not of stroke (Table 3)<sup>(94)</sup>. The study was initially unnoticed, possibly because vitamin D was one of many nutrients examined. The publication that drew the notice of researchers was from the Framingham Offspring Study which found that participants with 25(OH)D levels  $<10 \mu\text{g/ml}$  (25 nmol/l) had nearly double the risk of CVD during follow-up compared with those  $\geq 15 \mu\text{g/ml}$  (37.5 nmol/l)<sup>(95)</sup>. Since then, there has been a rush of publications from cohort studies of community-based samples, with eleven other studies reporting on the association between 25(OH)D levels and risk of CVD (Table 3)<sup>(96–106)</sup>. Although not all of these studies have reported significant inverse associations, when combined, overall they show that participants in the lowest 25(OH)D category have a 35% increased risk of CVD compared with the reference category, after adjusting for covariates including (in most studies) obesity and physical activity (Fig. 4). Still, this small increase in risk indicates that the association is a weak one, and residual confounding remains a possible explanation for it.

Only one RCT with sufficient power to detect any beneficial effect on CVD incidence has been carried out. This is the Women's Health Initiative RCT, which randomised over 36 000 women aged 50–79 years to taking daily doses of vitamin D (10  $\mu\text{g}$ ) and Ca (1000 mg) or placebo (as reported above for colorectal cancer). There was no difference between treatment and placebo groups in the risk of CVD during the 7-year follow-up period<sup>(107)</sup>. The lack of a treatment effect is attributed to the limitations of this trial<sup>(108)</sup>, as outlined above for colorectal cancer.

Research has also examined the association that vitamin D status has with cardiovascular risk factors, particularly blood pressure and type 2 diabetes. For blood pressure, there have been numerous cross-sectional studies and at least four cohort studies which have compared baseline 25(OH)D levels with subsequent risk of hypertension<sup>(109,110)</sup>, with a 27% reduction in risk of hypertension for participants in the highest vitamin D category compared with the lowest<sup>(110)</sup>. However, RCT of vitamin D supplementation and blood pressure have produced conflicting results, with most long-term studies showing no beneficial effect<sup>(109)</sup>. It is possible that vitamin D may affect arterial function through different mechanisms than blood pressure, since intimal medial thickening of carotid arteries is inversely associated with 25(OH)D<sup>(111)</sup>, although vitamin D supplementation has been found to have inconsistent effects on endothelial function<sup>(112,113)</sup>.

With regard to type 2 diabetes, there have also been numerous cross-sectional studies showing inverse associations between blood 25(OH)D levels and risk of diabetes<sup>(114)</sup>, and at least five cohort studies showing that baseline 25(OH)D levels predict diabetes or other

**Table 3** Relative risk of CVD and all-cause mortality associated with low baseline level of 25-hydroxyvitamin D (25(OH)D) in cohort studies

Publication (source in cited publication)	Sample	25(OH)D in nmol/l (quantile)	RR (95% CI) no. of cases		Adjusted confounders
			CVD	All-cause mortality	
Marniemi <i>et al.</i> (2005) <sup>(94)</sup> (Table 5)	Population-sampled men and women, aged 65–99 years, followed up to 10 years	MI: Low (Q1) High (Q3)  Stroke: Low (Q1) High (Q3)	MI: 1.30 (0.79, 2.13)* 1.00 n 130†  Stroke: 1.00 (0.52, 1.96)* 1.00 n 70†		Age, sex, smoking, functional capacity
Visser <i>et al.</i> (2006) <sup>(126)</sup> (Table 3)	Population-sampled men and women ≥55 years age, followed for 6 years	<25 (Q1) ≥75 (Q4)		1.47 (0.99, 2.19) 1.00 n 380	Age, sex, education, chronic diseases, cognitive status, depression, BMI, smoking, alcohol, activity
Jia <i>et al.</i> (2007) <sup>(127)</sup> (Table 2)	Men and women registered with the UK National Health Service, aged ≥75 years, followed for median 69 months	≤23 (Q1) ≥47 (Q5)		2.22 (1.22, 4.08) 1.00 n 129	Age, sex, medication, health status, heart disease, diabetes
Giovanucci <i>et al.</i> (2008) <sup>(96)</sup> (Table 3)	Male health professionals aged 40–75 years, followed up to 10 years	≤37 (Q1) ≥75 (Q4)	2.09 (1.24, 3.54) 1.00 n 454† (MI)		Age, race, region, blood draw date, smoking, alcohol, activity, BMI, family history, diabetes, hypertension, vitamins, lipids
Melamed <i>et al.</i> (2008) <sup>(97)</sup> (Table 4)	Population-sampled men and women ≥20 years age, followed from 1988–94 to 2000	<44 (Q1) >80 (Q4)	1.22 (0.90, 1.65) 1.00 n 777‡	1.28 (1.11, 1.48) 1.00 n 1806	Age, sex, race, SES, season, smoking, activity, BMI, CVD history, lipids, lipid-lowering drugs, C-reactive protein, renal function, use of vitamin D supplements
Wang <i>et al.</i> (2008) <sup>(95)</sup> (Table 3)	Community sample of men and women, mean age 59 years, followed for mean 5.4 years	<25 (Q1) ≥37 (Q3)	1.80 (1.05, 3.08) 1.00 n 120†		Age, sex, BMI, smoking, blood pressure, diabetes, blood pressure medication, lipids, serum creatinine
Kilkinen <i>et al.</i> (2009) <sup>(98)</sup> (Table 2)	Population-sampled men and women ≥30 years age, followed from 1978–80 to 2006	Low (Q1) High (Q5)	1.32 (1.05, 1.64)* 1.00 n 933‡		Age, sex, marital status, education, season of blood collection, BMI, activity, smoking, alcohol
Piiz <i>et al.</i> (2009) <sup>(99)</sup> (Table 2)	Population-sampled men and women, mean age 70 years, followed for mean 6.2 years	Low (Q1) High (Q2–4)	5.02 (1.88, 13.42) 1.00 n 20‡	1.93 (1.06, 3.51) 1.00 n 51	Age, sex, diabetes, smoking, hypertension, lipids, renal function, waist-to-hip ratio, activity

Table 3 Continued

Publication (source in cited publication)	Sample	25(OH)D in nmol/l (quantile)	RR (95% CI) no. of cases		
			CVD	All-cause mortality	Adjusted confounders
Semba <i>et al.</i> (2009) <sup>(128)</sup> (Table 2)	Community-dwelling women aged 70–79 years, followed for median 6 years	<38 (Q1) >67 (Q4)		2.45 (1.12, 5.36) 1.00 <i>n</i> 100	Age, race, education, season, BMI, smoking, supplement use, physical activity, lipids, history of CVD and renal disease
Szulc <i>et al.</i> (2009) <sup>(129)</sup> (Table 4)	Men recruited from insurance rolls, aged ≥50 years, followed for 3 to 10 years	Low (Q1) High (Q4)		1.70 (0.95, 3.05) 1.00 <i>n</i> 182	Age, BMI, smoking, physical performance, physical activity, heart disease, diabetes, Parkinson's disease, vitamin D supplementation
Anderson <i>et al.</i> (2010) <sup>(100)</sup> (Table 6)	Men and women in a community health-care plan with a vitamin D blood test during 2000–09, mean age 55 years, followed for mean of 1.3 years	≤37 (Q1) >75 (Q3)	1.45 (1.18, 1.67)§ 1.00 <i>n</i> 763   (MI)	1.77 (1.49, 2.10)§ 1.00 <i>n</i> 1193	Age, sex, hypertension, lipids, diabetes, peripheral vascular disease
Bolland <i>et al.</i> (2010) <sup>(101)</sup> (Table 2)	Women volunteers in a clinical trial, aged >55 years, followed for 5 years	<50 (Q1) ≥50 (Q2)	1.2 (0.8, 1.8) 1.0 <i>n</i> 110†	0.9 (0.5, 1.6) 1.0 <i>n</i> 63	Treatment allocation, age, weight, smoking, blood pressure, CVD history, lipids, diabetes
Cawthon <i>et al.</i> (2010) <sup>(102)</sup> (Table 3)	Community sample of men, aged ≥65 years, followed for mean 7.3 years	<50 (Q1) ≥75 (Q4)	1.52 (0.83, 2.80) 1.00 <i>n</i> 110‡	0.95 (0.68, 1.34) 1.00 <i>n</i> 330	Age, race, education, clinic, season of blood draw, body fat, weight, health status, activity, medical history, serum Ca & P, renal function
Hutchinson <i>et al.</i> (2010) <sup>(103)</sup> (Tables 2 & 3)	Population-sampled men and women, mean age 59 years, followed for mean 11.7 years	Non-smokers: Low (Q1) High (Q4)	Non-smokers: 1.08 (0.79, 1.48) 1.00 <i>n</i> 325‡	Non-smokers: 1.32 (1.07, 1.62) 1.00 <i>n</i> 798	Age, sex, BMI, activity, diabetes, hypertension, creatinine, history of CVD and cancer
		Smokers: Low (Q1) High (Q4)	Smokers: 0.93 (0.61, 1.44) 1.00 <i>n</i> 188‡	Smokers: 1.06 (0.83, 1.35) 1.00 <i>n</i> 561	
Jassal <i>et al.</i> (2010) <sup>(104)</sup> (Table 2)	Community sample of men and women, mean age 74 years, followed for mean 6.4 years	Per SD increase	1.07 (0.86, 1.33) <i>n</i> 111‡		Age, sex, BMI, season of blood draw, blood pressure, lipids, glucose, exercise, CVD, renal function, medication

Table 3 Continued

Publication (source in cited publication)	Sample	25(OH)D in nmol/l (quantile)	RR (95% CI) no. of cases		Adjusted confounders
			CVD	All-cause mortality	
Michaelsson <i>et al.</i> (2010) <sup>(105)</sup> (Table 2)	Population-sampled men, mean age 71 years, followed for median 12.7 years	<10% 10–90%	1.53 (0.97, 2.41) 1.00 n 177‡	1.43 (1.11, 1.84) 1.00 n 584	Age, weight, height, season of blood draw, SES, weight, height, smoking, alcohol, activity, cardiovascular risk factors, other diseases
Semba <i>et al.</i> (2010) <sup>(106)</sup> (Tables 2 & 3)	Population-sampled men and women, aged ≥65 years, followed for mean 6.5 years	<46 (Q1) >64 (Q4)	2.57 (1.12, 5.91) 1.00 n 107‡	2.20 (1.28, 3.77) 1.00 n 228	Age, sex, education, season, BMI, smoking, activity, lipids, aspirin use, cognitive function

RR, relative risk; MI, myocardial infarction; SES, socio-economic status.  
 \*Inverse of published relative risk to make highest 25(OH)D group the reference.  
 †Fatal and non-fatal disease.  
 ‡Fatal disease only.  
 §Confidence intervals estimated from Fig. 3.  
 ||Non-fatal disease only.

glycaemic measures<sup>(115–119)</sup>. Another cohort study has reported that people with increased sun exposure have a reduced risk of diabetes<sup>(120)</sup>. However, the few RCT to date have shown inconsistent results<sup>(121–123)</sup>.

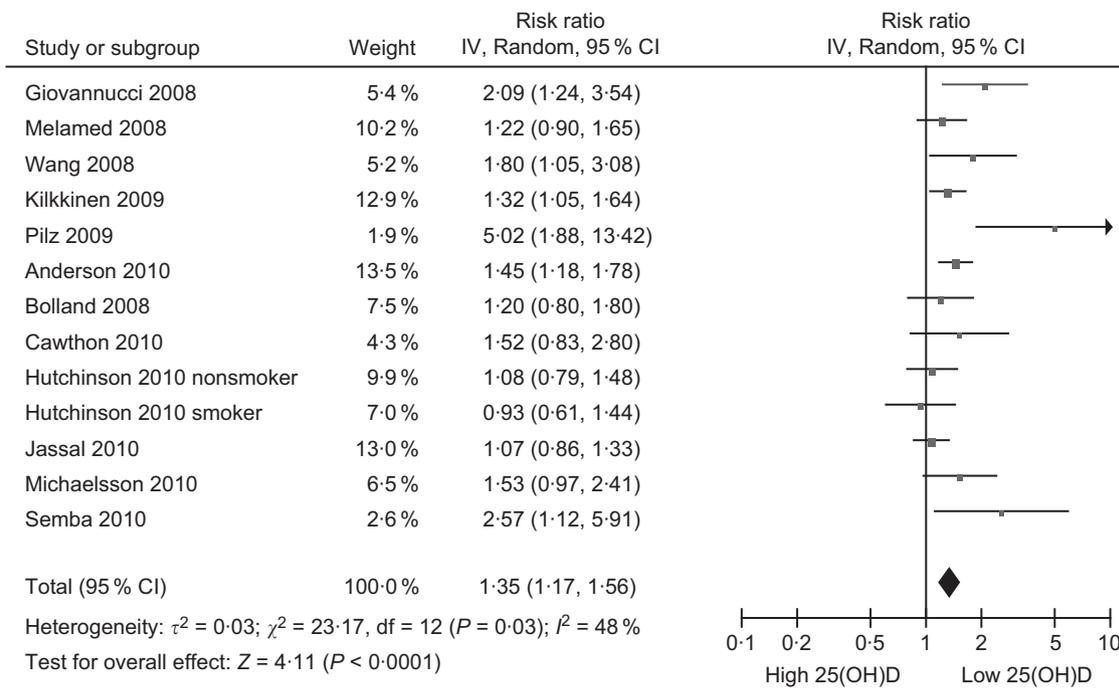
In summary, vitamin D research over the last 10 years has increased more rapidly for CVD than any other disease group (Fig. 1). A substantial number of community-sampled cohort studies have been carried out which collectively show that low baseline blood 25(OH)D levels predict increased risk of CVD (Fig. 4). Substantial clinical and laboratory research has identified a range of mechanisms by which vitamin D may affect risk of CVD, including alterations in immune function, cardiac size and function, insulin resistance and arterial function<sup>(124)</sup>. However, the association between vitamin D and CVD is weak and, as for colorectal cancer, large RCT are required to confirm the findings from the observational studies.

**All-cause mortality**

The accumulating research on vitamin D and CVD inevitably led to an interest in the possible association between vitamin D and all-cause mortality, given that CVD is the leading cause of mortality in developed countries. Research on this topic has been stimulated greatly by a recent meta-analysis of RCT originally undertaken to determine the effect of vitamin D supplementation on risk of fractures (summarised above). This meta-analysis found that participants in these trials given vitamin D had a 7% decrease in all-cause mortality compared with those receiving placebos<sup>(125)</sup>. The weighted dose of vitamin D in these trials was only 528 IU/d, suggesting that vitamin D may decrease mortality by much greater amounts if given in higher doses. This analysis has stimulated other researchers of cohort studies to include all-cause mortality as an outcome, along with CVD (Table 3). Surprisingly, the first cohort study to report on the association between baseline 25(OH)D levels and subsequent risk of death, which was from the Netherlands, was missed in the subsequent rush of papers on this topic, perhaps because its focus was on predicting admission to nursing homes rather than death<sup>(126)</sup>. However, since then, eleven other cohort studies have reported on this association (Table 3)<sup>(97,99–103,105,106,127–129)</sup>. The summary relative risk from these studies is 1.42, when comparing the lowest 25(OH)D category with the reference (Fig. 5), which indicates a weak association across the range of 25(OH)D concentrations in the general population. Although a small effect, a reduction of this amount in all-cause mortality would be substantial, so it is potentially of great health significance. However, large RCT are required to confirm if vitamin D supplementation by itself reduces all-cause mortality since another meta-analysis has concluded that vitamin D is beneficial only when combined with Ca<sup>(23)</sup>.

**Infection and immune function**

The final disease group considered in the present overview is infection and the effects of vitamin D on immune



**Fig. 4** Forest plot of relative risks of CVD associated with the lowest 25-hydroxyvitamin D (25(OH)D) category compared with the highest (or reference) in cohort studies (the study by Marniemi *et al.*<sup>(94)</sup> is excluded because it reported relative risks separately for myocardial infarction and stroke)

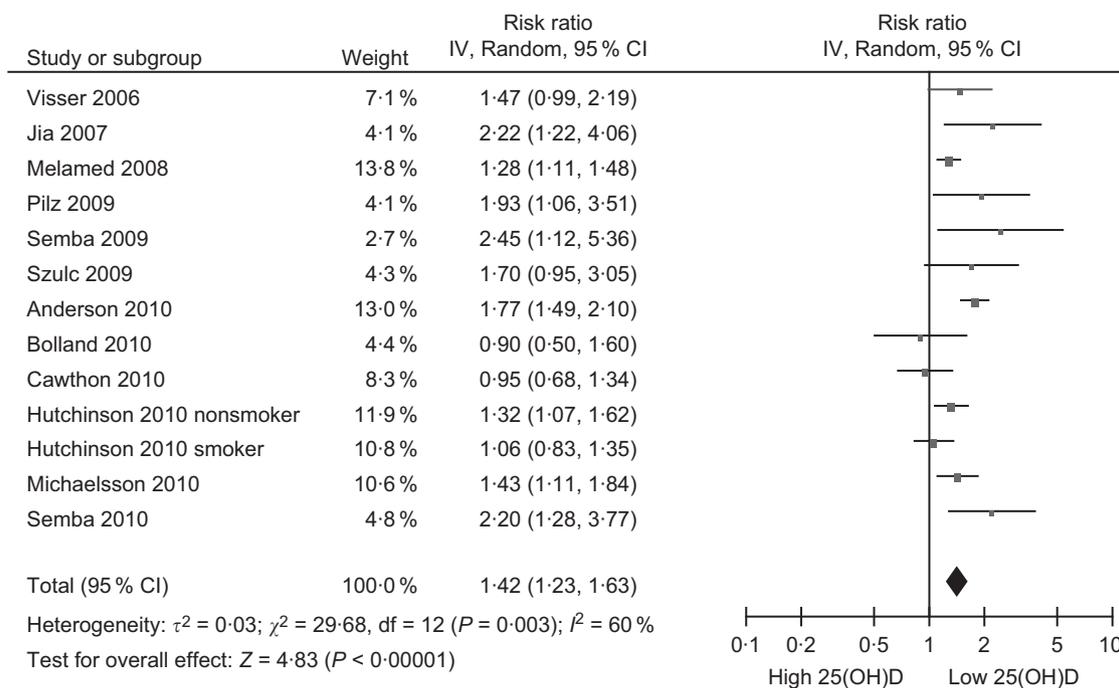
function. Research on the beneficial effects of vitamin D against infection extends back to the beginning of the 20th century when Nils Finsen, a physician from Copenhagen, was awarded the Nobel Prize for the heliotherapy he developed using the eponymous lamp to cure lupus vulgaris, a disfiguring skin disease caused by tuberculosis (TB) which typically affects the face<sup>(130)</sup>. The success of his treatment eventually led to the establishment of sanatoria for TB patients where a key part of the treatment was exposure to sunlight<sup>(131)</sup>. Up until the early 1950s, patients with TB were being increasingly treated with vitamin D<sup>(132)</sup>. However, the introduction of antibiotics in the 1950s, with their greater effectiveness, soon resulted in the abandonment of vitamin D as a therapeutic agent against TB.

Immune function can be split broadly into two components: innate and acquired. The key agents of the innate immune system are antimicrobial peptides, which are the immediate, non-specific, first line of defence for plants and animals against infectious organisms<sup>(133)</sup>. The main antimicrobial peptide in man is cathelicidin. An influential paper published in 2006 showed that vitamin D increases synthesis of cathelicidin<sup>(134)</sup>, and it is through this mechanism that vitamin D is thought to protect against TB and other infectious diseases<sup>(135,136)</sup>. Low plasma levels of cathelicidin have recently been shown to predict increased mortality from infectious disease in renal dialysis patients<sup>(137)</sup>. A meta-analysis has shown that TB cases have lower 25(OH)D levels than controls<sup>(138)</sup>,

and vitamin D has been used in recent RCT with mixed results<sup>(139,140)</sup>. There is also increasing evidence of a link between vitamin D status and viral respiratory tract infections. Observational studies mostly show lower 25(OH)D levels in cases compared with controls, and four out of five RCT have shown that vitamin D supplementation reduces incidence of respiratory tract infection or influenza<sup>(141)</sup>.

Vitamin D also affects acquired immune function and risk of related autoimmune diseases, such as multiple sclerosis and type 1 diabetes. The occurrence of multiple sclerosis increases with latitude<sup>(142)</sup> and evidence from observational studies shows that decreased sun exposure and 25(OH)D levels are risk factors for this disease<sup>(143–145)</sup>. For type 1 diabetes, animal studies over 30 years ago identified a pancreatic receptor to vitamin D<sup>(146)</sup> and showed that vitamin D deficiency decreased insulin secretion by the pancreas<sup>(147)</sup>. A meta-analysis of observational studies in man has confirmed these findings, with a history of taking vitamin D supplements during childhood being associated with a 29% decreased risk of type 1 diabetes compared with children who did not take vitamin D<sup>(148)</sup>.

In summary, research on vitamin D and immune function is increasing (Fig. 1). The evidence indicates that vitamin D may protect against a wide range of infections including TB and respiratory infections. RCT that are currently underway should provide a clear picture within the next 5–10 years as to whether vitamin D is effective against these diseases.



**Fig. 5** Forest plot of relative risks of all-cause mortality associated with the lowest 25-hydroxyvitamin D (25(OH)D) category compared with the highest (or reference) in cohort studies

**Institute of Medicine report**

The IOM in the USA released its report on the recommended dietary intakes of Ca and vitamin D at the end of November 2010<sup>(4)</sup>. It is a substantial document, based largely on two commissioned systematic reviews. The first review, by researchers in Ottawa, summarised the literature on vitamin D and bone health published up to mid-2006, with a focus on RCT<sup>(149)</sup>. The second review, by researchers in Boston, was of publications up to April 2009<sup>(150)</sup>. It updated the bone data published since the Ottawa review, but also reviewed many other health outcomes. It focused on RCT and cohort studies, and excluded cross-sectional and case-control studies. The IOM report mainly relied on these two reviews, but also considered data from other study designs including observational studies (e.g. case-control and cross-sectional) in man and animal studies of biological mechanisms. It assessed the evidence on vitamin D for a wide range of outcomes (Table 4.1 of the IOM report), which surprisingly did not include all-cause mortality. Its main conclusions with regard to vitamin D were that: (i) vitamin D status was related only to bone health; and (ii) 25(OH)D levels of 50 nmol/l represent vitamin D sufficiency because above this level there was no consistent evidence of increased health benefit. On this basis, the IOM decided to marginally increase the dietary reference intake (from the previous recommendations in their 1997 report) to 15 µg/d for adults up to 70 years of age and 20 µg/d above this age. The smallness of this increase has

surprised many vitamin D researchers and clinicians, since these daily intakes will increase 25(OH)D levels by only 5–20 nmol/l depending on a person’s starting 25(OH)D level<sup>(8)</sup>.

As with any report of this magnitude, the evidence on which its conclusions are based will rapidly become out of date; this is already happening with the IOM report. For example, seven of the nine cohort studies of fractures in Table 1, all published from 2007<sup>(39–45)</sup>, are not mentioned in the IOM report or the systematic reviews on which it is based; while for colorectal cancer, two out of the ten cohort studies in Table 2 were not included<sup>(61,70)</sup>, one of which<sup>(151)</sup> was an update of the third NHANES included in the report.

However, it is in the areas of CVD and all-cause mortality, where publications are more recent, that the omissions are greatest. In the section on CVD, there is no mention in the IOM report about nine of the cohort studies of CVD in Table 3<sup>(98–106)</sup>, all published from 2009, although the study by Bolland *et al.*<sup>(101)</sup> is described elsewhere in the report. Instead, the IOM report focuses on the papers from the Framingham Offspring Study, which it describes as having a U-shaped association between CVD risk and 25(OH)D above 75 nmol/l<sup>(95)</sup>, and the initial mortality report from NHANES which it also described as having a U-shaped dose-response relationship<sup>(97)</sup>; but made no mention in the discussion of chapter 4 on health outcomes of a further analysis of the NHANES data of people aged ≥65 years which found an inverse linear association across the population distribution of

25(OH)D rather than a U-shaped relationship<sup>(152)</sup>. The possible U-shaped dose–response relationship is one of the rationales used by the IOM for keeping the cut-off point for vitamin D sufficiency at a 25(OH)D concentration of 50 nmol/l. Of the cohort studies on CVD not cited in the IOM report which had more than two 25(OH)D comparison groups, two described a U-shaped association in all<sup>(105)</sup> or some (i.e. non-smokers)<sup>(103)</sup> of their participants and four showed evidence of an inverse linear association<sup>(98,100,102,106)</sup>. If the latter are combined with the other publication mentioned by the IOM from the study of US male health professionals which showed a significant dose–response association<sup>(96)</sup>, then the emphasis by the IOM about a likely U-shaped dose–response relationship between 25(OH)D and CVD, and their conclusion that the 25(OH)D evidence does not show a relationship with risk for developing CVD, do not look convincing.

Death trumps all other outcomes, so even more surprising is the absence of all-cause mortality from the list of health outcomes in Table 4.1 of the IOM report, even though this outcome was examined in one of the systematic reviews used by the report<sup>(150)</sup>. The meta-analysis of RCT of vitamin D supplementation (with or without Ca) is not even listed in the references of the IOM report, despite being published in 2007<sup>(125)</sup>. Seven of the twelve cohort studies in Table 3 which have published data on the association between 25(OH)D and all-cause mortality are not referenced in the IOM report<sup>(99,100,102,103,105,106,129)</sup>. This omission is all the more surprising when the IOM report includes many references from 2010, which suggests that there was selective reporting of publications from the two years (2009 and 2010) preceding the release of the report.

Despite the above limitations, the additional publications from cohort studies since 2009, which have added greatly to the body of evidence, have not diminished but increased the need for evidence from large RCT to determine with greater certainty whether vitamin D protects against the diseases covered in the present overview. By increasing the dietary reference intake only up to 20 µg/d (for the oldest age groups) the IOM has provided a window of opportunity for researchers to undertake RCT for disease outcomes. If the daily dietary reference intake had been increased up to 50 µg or higher, it would have been ethically difficult for researchers to do RCT as they would have been obligated to give participants in the control arm this high dose. The resulting contamination in the control arm would have made it difficult to detect any beneficial effect from vitamin D. At least two large RCT using higher doses of vitamin D have started. These are: (i) the US VITAL study ([www.vitalstudy.org](http://www.vitalstudy.org)), which is recruiting 20 000 older adults to determine if 50 µg vitamin D<sub>3</sub>/d prevents cancer and CVD (ClinicalTrials.gov identifier: NCT01169259); and (ii) the ViDA study from New Zealand, which is recruiting 5100 older adults to determine if 2.5 mg vitamin D<sub>3</sub>/month prevents CVD, respiratory disease (including infections)

and non-vertebral fractures ([www.ANZCTR.org.au](http://www.ANZCTR.org.au) registration number: ACTRN12611000402943).

## Public health implications

Why do we need RCT to prove the benefit of vitamin D if the cohort data look so convincing? First, the recent evidence for other micronutrients, such as vitamins A, B, C and E, has shown that results from observational studies, which generally reported inverse associations between nutrient status and risk of cancer and CVD disease, have not been confirmed by RCT; in fact, supplementation increases mortality<sup>(1,2)</sup>. Hence the need for caution with vitamin D and the need to show that it is both safe and effective; although vitamin D may be different from other micronutrients because it is a hormone<sup>(153)</sup>. Second, the ultimate goal of vitamin D research, if vitamin D is truly beneficial, must be for state-funded programmes to increase vitamin D levels in the general population through the available strategies, such as increased (but safe) sun exposure, fortification and supplementation. If the state is to invest in such programmes, there will be an opportunity cost (from less money to spend on other programmes) and it needs evidence from RCT and cost-effectiveness analyses to show that any benefit from investment in vitamin D programmes is equivalent to or higher than that for other publicly funded interventions. In the absence of state-funded programmes, health inequalities will increase if vitamin D is beneficial, since poorer sections of the community, which typically have the lowest vitamin D levels, are likely to have the least capacity to increase their vitamin D levels.

Assuming that RCT show benefit, the strategies used in future public health programmes will be influenced by some of the disputed evidence described above. For example, the uncertainty about whether vitamin D is associated linearly or in a U-shaped pattern with disease risk will determine whether population or high-risk approaches to prevention are used<sup>(154)</sup>. If the association between vitamin D status and risk of disease were inversely linear, then programmes targeting the general population would be required. However, if the association is U-shaped, then high-risk strategies which identify and target people with low vitamin D levels would be preferred, since people with high levels would not gain from having even higher vitamin D levels.

Another point of contention, which will shape the type of interventions, is whether vitamin D is beneficial by itself, or whether it needs to be combined with Ca. Ca is a much more expensive supplement than vitamin D to use in public health campaigns since it needs to be taken on a daily basis because of its water solubility. As well, there are safety issues with Ca<sup>(155)</sup> that were downplayed in the IOM report. In contrast, vitamin D is fat soluble and can be taken less often (e.g. monthly)<sup>(156)</sup>. This greatly decreases the cost, and respondent burden, for running population-wide supplementation programmes.

## Conclusions

Cohort studies show that baseline 25(OH)D levels predict increased risk of fractures, colorectal cancer, CVD and all-cause mortality. However, these associations are weak, with relative risks comparing the lowest 25(OH)D category with the highest (or reference) being in the range of 1.3 to 1.6. While these could be underestimates of the true effect (for reasons discussed in the Methods), it is also possible they are caused by confounding from other variables such as obesity and physical activity. RCT using vitamin D doses  $\geq 50 \mu\text{g/d}$  are required to determine whether vitamin D protects against these diseases. The evidence in the IOM report is now out of date for the above outcomes. However, its recommendation for daily vitamin D intakes up to  $20 \mu\text{g}$  provides a window for researchers to undertake higher-dose RCT. These are now starting and should provide definitive answers about the health benefits of vitamin D during the coming decade.

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