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Association between vitamin D and human health: evidence from Mendelian randomization studies

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Abstract:	Objective To summarize the current evidence on the association between vitamin D and major health outcomes from Mendelian randomization (MR) studies. Methods PubMed and Embase were searched for original MR studies on vitamin D in relation to any health outcome from inception to September 1, 2022. Meta-analysis was preformed to synthesize study-specific estimates after excluding overlapping samples, where applicable. Methodological quality of the included studies was evaluated according to essential elements of the MR design. Results A total of 133 MR publications were eligible for inclusion for qualitative analyses. After excluding overlapping populations, 93 MR publications were left for quantitative analyses. The causal association between vitamin D status and 275 individual outcomes was examined. Linear MR analyses showed genetically high 25-

	hydroxyvitamin D (25(OH)D) concentrations were associated with reduced risk of multiple sclerosis incidence and relapse, non-infectious uveitis and scleritis, psoriasis, femur fracture, leg fracture, amyotrophic lateral sclerosis, anorexia nervosa, delirium, heart failure, ovarian cancer, non-alcoholic fatty liver disease, dyslipidemia, and bacterial pneumonia, but increased risk of Behçet's disease, Graves' disease, kidney stone disease, fracture of radium/ulna, basal cell carcinoma, and overall cataracts. Nonlinear MR analyses demonstrated that the inverse association of genetically predisposed 25(OH)D concentrations with the risk of cardiovascular diseases, dementia, and death from any cause, cancer, cardiovascular, and other causes was only pronounced in vitamin D-deficient individuals (especially 25(OH)D <25 nmol/L). The methodological quality of the included MR studies was substantially heterogeneous. Conclusions Current evidence from MR studies supports a causal role of vitamin D in human health.

Title: Association between vitamin D and human health: evidence from Mendelian randomization studies

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Abbreviations:
25(OH)D: 25-hydroxyvitamin D; 1,25(OH)2D: 1,25-dihydroxyvitamin D; ALS: amyotrophic lateral sclerosis; BCC: basal cell carcinoma; CAD: coronary artery disease; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; FIND: Finnish Vitamin D Trial; GI: genetic instrument; GWAS: genome-wide association study; HF: heart failure; HR: hazard ratio; IV: instrumental variable; KSD: kidney stone disease; MI: myocardial infarction; MR: Mendelian randomization; MS; multiple sclerosis; NAFLD: nonalcoholic fatty liver disease; OR: odds ratio; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SNP: single nucleotide polymorphisms; T2D: type 2 diabetes; UKB: UK Biobank; VDR: vitamin D receptor; ViDA: Vitamin D Assessment Study; VITAL: Vitamin D and Omega-3 Trial.

ABSTRACT

Objective

To summarize the current evidence on the association between vitamin D and major health outcomes from Mendelian randomization (MR) studies.

Methods

PubMed and Embase were searched for original MR studies on vitamin D in relation to any health outcome from inception to September 1, 2022. Meta-analysis was preformed to synthesize study-specific estimates after excluding overlapping samples, where applicable. Methodological quality of the included studies was evaluated according to essential elements of the MR design.

Results

A total of 133 MR publications were eligible for inclusion for qualitative analyses. After excluding overlapping populations, 93 MR publications were left for quantitative analyses. The causal association between vitamin D status and 275 individual outcomes was examined. Linear MR analyses showed genetically high 25-hydroxyvitamin D (25(OH)D) concentrations were associated with reduced risk of multiple sclerosis incidence and relapse, non-infectious uveitis and scleritis, psoriasis, femur fracture, leg fracture, amyotrophic lateral sclerosis, anorexia nervosa, delirium, heart failure, ovarian cancer, non-alcoholic fatty liver disease, dyslipidemia, and bacterial pneumonia, but increased risk of Behçet's disease, Graves' disease, kidney stone disease, fracture of radium/ulna, basal cell carcinoma, and overall cataracts. Nonlinear MR analyses demonstrated that the inverse association of genetically predisposed 25(OH)D concentrations with the risk of cardiovascular diseases, dementia, and death from any cause, cancer, cardiovascular, and other causes was only pronounced in vitamin D-deficient individuals (especially 25(OH)D <25 nmol/L). The methodological quality of the included MR studies was substantially heterogeneous.

Conclusions

Current evidence from MR studies supports a causal role of vitamin D in human health.

Keywords

Vitamin D, 25-hydroxyvitamin D, Mendelian randomization, systematic review, meta-analysis

INTRODUCTION

Vitamin D is the precursor of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$ or calcitriol), a potent steroid hormone involved in regulating calcium and phosphate homeostasis(1). $1,25(OH)_2D$ directly or indirectly controls 3%-5% of the human genome at the transcriptional level through binding to the nuclear vitamin D receptor (VDR), exerting a broad spectrum of classical and nonclassical actions such as regulation of cell proliferation, cell apoptosis, cell differentiation, and immune function(2-4). VDR is widely expressed throughout the human body(5). Additionally, CYP27B1 (1α-hydroxylase), the enzyme responsible for the synthesis of $1,25(OH)_2D$ from 25-hydroxyvitamin D (25(OH)D), is present in multiple extrarenal sites, suggesting vitamin D can function in an autocrine, intracrine or paracrine manner(6). Therefore, it is physiologically plausible that vitamin D may play a potential role in the prevention and treatment of a wide range of human diseases. However, to date, no consensus has been reached on whether vitamin D causally affects skeletal and extraskeletal diseases(7-10), except for nutritional rickets in infants and children(11).

Mendelian randomization (MR) studies provide an alternative approach to facilitate causal inference on exposure-outcome associations in a cost-effective and timely manner(12). MR analyses are performed in an observational setting while minimizing biases due to residual confounding, reverse causality, and exposure misclassification by using genetic variants as proxies for exposure(13). Vitamin D is primarily synthesized by the human body through the action of ultraviolet radiation in sunlight and most unfortified foods contain little vitamin D(2). Several large-scale genome-wide association studies (GWASs) have discovered a number of single nucleotide polymorphisms (SNPs) that are strongly and robustly associated with vitamin D status, measured by circulating 25(OH)D concentrations, including those around the genes involved in vitamin D synthesis, metabolism, and transport.(14-19) Using such genetic instruments (GI), a wealth of MR studies has investigated the association of genetically predisposed 25(OH)D concentrations with various health outcomes. Summarizing these available evidence will provide an overarching view of promising areas for vitamin D intervention in public health nutrition. Although a few researchers have qualitatively reviewed the findings of vitamin D and different diseases from MR studies(8-10, 20, 21), the number of eligible studies has doubled since their studies were published, which provides an opportunity to elucidate the causal relation of vitamin D for a broader range of health outcomes. Furthermore, individual MR studies have yielded conflicting results for some outcomes. Additionally, a systematic evaluation of the methodological quality of these studies is still lacking.

In this paper, we aimed to 1) provide an overview of the current evidence on the association between vitamin D and multiple health outcomes in an MR framework, 2) if possible, perform meta-analyses to synthesize relevant evidence after excluding overlapping study populations, and 3) assess the methodological quality of the available MR studies.

METHODS

The present review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement(22) and the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) statement(23). The protocol was registered on the protocol.io(24).

Literature search

We systematically searched PubMed and Embase from inception to September 1, 2022, for published, peer-reviewed MR studies using GIs as proxies for vitamin D status in relation to any health outcome. The key search terms are ('vitamin D' OR '25-hydroxyvitmain D') AND ('Mendelian randomization' OR 'Mendelian randomisation'); see Table S1. We also manually screened the reference lists of relevant reviews and the included studies to identify additional studies. Two investigators (AF, YZ) independently screened the titles and abstracts of all retrieved studies and subsequently reviewed the full text of potentially eligible studies in Covidence software. Any discrepancy was resolved by discussion.

Eligibility criteria

This study focused on the associations of vitamin D with major health outcomes from MR design. We excluded: 1) duplicate publications; 2) non-original articles, e.g., reviews, conference abstracts, editorials, commentaries, correspondences, opinions, corrections, and study proposals; 3) methodological studies that used vitamin D as an example of the application of MR; 4) studies that used vitamin D status as an outcome; 5) studies that did not provide sufficient original data, i.e., effect size and 95% confidence intervals (CIs) or standard error (SE) for the studied association; 6) studies that only reported single variant–outcome associations; 7) studies only using variants in the vitamin D-binding protein gene as instrumental variables (e.g., rs2282679, rs7041 in the *GC* gene); and 8) studies that only employed biomarkers or surrogate endpoints (e.g., serum lipids, bone mineral density) as outcomes.

Data extraction

We extracted the following information from the eligible MR studies using a predefined Excel template: first author's name, year of publication, MR design (one-sample or two-sample); exposure and outcome of interest, sample size, data source and ancestry of exposure and outcome populations, adjustments for exposure and outcome analysis; GI used (gene name, number of SNPs, specific SNPs), GI type (single SNP/allele, multiple SNPs in a single analysis, multiple SNPs in separate analyses, combination of SNPs, genetic risk score/allele score)(25), selection criteria for the GIs (percentage of variance explained by the GI, F-statistic, *P*-value threshold for genetic variant selection, threshold for linkage disequilibrium, biological relevance), statistical power of the GI and the corresponding effect estimate; type of instrumental variable (IV) analysis (formal or reduced IV analysis), unit of estimated effect, analytical method, effect metric [odds ratio (OR), hazard ratio (HR), beta, etc.],

effect size and the corresponding 95% CIs (if only SEs were presented, the values were converted to 95% CIs by the investigators), *P*-value, and Cochran's Q-statistic and I-square statistic (I^2) for heterogeneity of the GI (meta-analysis of individual SNPs) for the main analysis as defined by the authors. We also extracted sensitivity analyses results derived from different statistical approaches (e.g., MR-Egger, weighted median, weighted mode, MR-PRESSO, multivariable MR) or different sets of genetic variants and subgroups. We extracted *P*-values for the intercept of MR-Egger and for the MR-PRESSO global, outlier, and distortion tests to assess horizontal pleiotropy. For studies that performed nonlinear MR, we further extracted information on the analytical approach of nonlinear MR, curve shape, reference and threshold levels of 25(OH)D, and *P*-value for the nonlinearity. All data in each study were retrieved by one investigator (AF, YZ) and then double-checked by another investigator (AF, YZ, PY).

Quantitative analysis

When more than one GI was used for an identical outcome based on the same participants in one study, we only kept the record for the primary analysis. When one study reported MR estimates for an identical outcome from different outcome population sources, we kept all the records. If two or more studies were published on an identical outcome using GWAS data from the same study population, we gave priority to the study that conducted formal IV analysis. Otherwise, we included the publication with the largest sample size or with the greatest proportion of variance explained by the GI (if the sample size was the same). We further performed meta-analyses to combine estimates from a minimum of two non-overlapping samples for an identical outcome on the same scale. Since different units of estimated effect were used in different studies, we first converted MR estimates to the same scale (e.g., per 25 nmol/L increase in serum 25(OH)D levels, per SD increase in natural log-transformed serum 25(OH)D levels (log(25(OH)D)) before conducting meta-analysis. The heterogeneity among studies was quantified with the I^2 statistic. $I^2 \geq 50\%$ was considered high heterogeneity, in which case random-effects models were used; if not, fixed-effect models were adopted. Meta-analyses were performed using the 'meta' package, and forest plots were generated using the 'forestplot' package (R software version 4.1.3). A two-tailed *P* value < 0.05 was considered statistically significant.

Evaluation of methodological quality

Currently, no widely-accepted tools are available for systematic reviews of MR studies.(26) Thus, we developed a scoring system targeted to MR studies to assess the methodological quality of the included studies according to the published guidelines(23, 26-28). The scoring system has 11 items, including type of IV analysis, three core IV assumptions, population heterogeneity, GI selection, results reporting, sensitivity analysis, and dose-response relationship (Supplementary Methods). The standards for scoring each item are described in detail in Table S2.

RESULTS

Literature search and study selection

The search yielded a total of 627 publications, including 617 from electronic databases and 10 through manual search. After removing duplicates (n=242) and irrelevant articles (n=211), 174 MR publications reporting results of vitamin D with one or more health outcomes were identified. Of them, 41 reports were further excluded because of not providing original data, only presenting single SNP-outcome associations, merely using SNPs in GC gene as GI, or using surrogate endpoints as the outcome, leading to 133 eligible MR articles(17, 18, 20, 29-158) in qualitative analysis. In quantitative analysis, an additional 40 publications were removed because of overlapping or same outcome populations, leaving 93 publications(17, 18, 20, 29, 33, 35, 37, 40, 43-46, 48, 49, 52-54, 56, 57, 59-61, 63-66, 68, 69, 71-73, 75, 76, 78-85, 87, 89, 90, 92, 94, 96, 97, 99, 101, 103, 104, 108, 109, 113-119, 122-143, 145, 147, 149, 150, 152, 153, 155-158). An overview of the search and selection process is presented in Fig. S3.

Study description

The included MR articles were published between 2012 and 2022, with 76 (57.1%) published after 2020. A total of 92 (69.2%) publications adopted two-sample MR design, 34 (25.6%) publications used one-sample MR approach, and the remaining 7 (5.3%) publications performed both one-sample and two-sample MR analyses. There was a growing trend of applying the two-sample MR design (Fig. S4). All the publications employed circulating total 25(OH)D concentrations as exposure, 2 (1.5%) publications further used serum 25(OH)D_3 concentrations as exposure, 1 (0.8%) publication used C3-epi-25(OH)D_3 (above vs below lower limit of quantification) as exposure, 1 (0.8%) publication additionally used vitamin D deficiency [serum 25(OH)D < 25 nmol/L] as exposure, and another 2 (1.5%) publications used vitamin D deficiency [serum 25(OH)D < 50 nmol/L] and vitamin D insufficiency [serum 25(OH)D < 75 nmol/L] as exposures. The number of genetic variants selected as GIs ranged from 2 to 288, explaining up to 17.5% of the phenotypic variance. Most studies obtained GIs for vitamin D status from the SUNLIGHT consortium(14, 15) or UK Biobank (UKB)(16, 17). In total, 275 individual health outcomes were reported, including 16 all-cause and cause-specific mortality outcomes, 8 allergic disease outcomes, 24 autoimmune disease outcomes, 45 cardiovascular disease (CVD) outcomes, 30 musculoskeletal disease outcomes, 9 neurological disease outcomes, 19 psychiatric disease outcomes, 61 cancer incidence outcomes, 4 cancer survival outcomes, 9 metabolic disease outcomes, 15 infectious disease outcomes, 8 digestive disease outcomes, 4 respiratory disease outcomes, 6 genitourinary disease outcomes, 5 ophthalmic disease outcomes, 7 dental disease outcomes, 2 dermatologic disease outcomes, and 3 geriatric disease outcomes. The characteristics of each included study are shown in Table S3.

All-cause and cause-specific mortality

Ten publications(20, 30, 32, 37, 46, 56, 72, 80, 110, 136) reported MR estimates for

total 25(OH)D and all-cause mortality, with 1 inverse finding, 1 positive finding, and 8 null findings (Table S4). After excluding overlapping outcome populations, a meta-analysis of data from 51,013 deaths in 572,720 total participants showed a 25 nmol/L higher genetically predisposed 25(OH)D concentration was not associated with the risk of all-cause mortality (combined OR=0.98, 95% CI: 0.96-1.00; P=0.059; I^2=0%). However, in another smaller non-overlapping population (1,338 deaths and 7,079 controls)(46), that participants with higher 25(OH)D-increasing allele score had an increased risk of all-cause mortality (OR=1.08, 95% CI: 1.01-1.14) (Fig. 1, Table S5). Although one publication(37) found an inverse association of genetically predicted total 25(OH)D concentrations with cancer mortality and non-cardiovascular non-cancer mortality (Table S4), meta-analysis results were null (Fig. 1, Table S5). Null associations were also observed for cardiovascular mortality and other cause-specific mortality based on linear assumptions (Fig. 1, Table S4, Table S5). Nevertheless, a nonlinear MR analysis(136) using a stratification of residual 25(OH)D concentrations at 5 nmol/L interval suggested a threshold association of 25(OH)D with the risk of all-cause mortality (~40 nmol/L), cancer mortality (~35 nmol/L), cardiovascular mortality (~25 nmol/L), and non-cardiovascular non-cancer mortality (~40 nmol/L), in which an inverse association was only pronounced at lower levels of 25(OH)D (Table S6).

Allergic and autoimmune diseases

All nine publications(39, 45, 88, 93, 94, 96, 98, 107, 108) reported an inverse association between total 25(OH)D and multiple sclerosis (MS) risk (Table S7), with an 18% lower risk per standard deviation (SD) increase in generically determined log(25(OH)D) (OR=0.82, 95% CI: 0.69-0.99; P=0.035) or a 15% lower risk per 25(OH)D-increasing allele score (OR=0.85, 95% CI: 0.76-0.94; P=0.003) using non-overlapping outcome data (Fig. 2, Table S8). Additionally, genetically high 25(OH)D concentrations were associated with reduced risk of pediatric-onset MS (P=0.020)(48), MS relapse (P=0.025)(108), non-infectious uveitis and scleritis (P=0.049)(156), and psoriasis (P=0.020)(157), while increased risk of Behçet's disease (P=0.001)(114) and Graves' disease (P<0.001)(158) (Fig. 2, Table S8). No associations were found between total 25(OH)D concentrations and the risk of other allergic and autoimmune diseases or between serum 25(OH)D_3 concentrations and vitiligo risk (Fig. 2, Table S7, Table S8).

Cardiovascular diseases

One publication(35) showed that a 10% increase in genetically determined total 25(OH)D concentration was related to an 8% lower risk of hypertension (OR=0.92, 95% CI: 0.87-0.97; P=0.002), while the other four publications(17, 20, 87, 94) found null associations (Fig. 3, Table S9, Table S10). Genetically high 25(OH)D concentrations were associated with a reduced risk of heart failure (HF) (1/2 publications)(94, 150), overall intracerebral hemorrhage (1/2 publications)(80, 153), nonlobar intracerebral hemorrhage (1 publication)(153), recurrent or de novo ischemic stroke/myocardial infarction (MI) (1 publication)(131), recurrent stroke/MI

(1 publication)(131), recurrent MI (1 publication)(131), and combined cardiovascular endpoints and MI in hypertensive-diabetic subjects (1 publication)(142) (Table S9). After removing overlapping samples, genetically predisposed total 25(OH)D concentrations were not associated with the risk of other CVD endpoints, including overall CVDs, coronary artery disease (CAD), coronary heart disease (CHD), MI, overall stroke, hemorrhagic stroke, and ischemic stroke (Fig. 3, Table S10). Nonlinear MR analyses from the Emerging Risk Factors Collaboration/EPIC-CVD/Vitamin D Studies Collaboration(136) also did not observe any association of 25(OH)D concentrations with the risk of CHD, overall stroke, ischemic stroke, and hemorrhagic stroke. However, another nonlinear MR study using data from UKB(139) indicated an L-shaped association between residual 25(OH)D concentrations and overall CVD risk, leveling off at ~50 nmol/L (Table S11).

Musculoskeletal diseases

Three publications(66, 94, 113) examined the association between total 25(OH)D concentrations and any fracture risk, of which one(113) showed a positive association (P=0.040), and the others found null associations (Fig. 4, Table S12, Table S13). One publication(113) showed the risk of fracture of radium/ulna increased with the number of 25(OH)D-increasing alleles (P=0.020). In contrast, genetically high 25(OH)D concentrations were inversely associated with lower risks of femur fracture (P=0.013)(94) and leg fracture (P<0.001)(94). Total 25(OH)D concentrations were not linked to the risk of fractures at other skeletal sites (including the hip), osteoporosis, osteoarthritis, sarcopenia, and sciatica (Fig. 4, Table S12, Table S13).

Neuropsychological disorders

Nine publications(17, 47, 55, 67, 94, 96, 109, 112, 151) reported MR estimates for total 25(OH)D concentrations and Alzheimer's disease risk, and four articles using GWAS data from the International Genomics of Alzheimer’s Project (IGAP)(47, 55, 67, 151) all showed an inverse association; however, the association attenuated and became nonsignificant when merging with UKB GWAS data (Fig. 5, Table S14, Table S15). Higher genetically predisposed total 25(OH)D concentrations were associated with a lower risk of amyotrophic lateral sclerosis (ALS) (1/4 publications)(94, 96, 111, 145), anorexia nervosa (2/2 publications)(94, 96), delirium (2/2 publications)(74, 116), and depression (1/3 publications)(20, 94, 95) (Table S14). After excluding overlapping outcome data, the inverse association remained significant for ALS (P=0.025), anorexia nervosa (P=0.015), and delirium (P<0.001) (Fig. 5, Table S15). No significant associations were found between total 25(OH)D and other neuropsychological disorders based on linear MR analyses. However, a nonlinear MR analysis from UKB(147) suggested a threshold shape for all-causal dementia with evidence of an inverse association at 25(OH)D concentrations below ~50 nmol/L and null association above 50 nmol/L (Table S16).

Cancer incidence and survival

Higher genetically predisposed total 25(OH)D concentrations were associated with a decreased risk of overall ovarian cancer (3/7 publications)(44, 53, 69, 79, 94, 97, 158), high-grade serous ovarian cancer (1/3 publications)(44, 79, 97), and overall esophageal cancer (1/2 publications)(97, 158), but increased risk of basal cell carcinoma (BCC) (1/1 publication)(97) (Table S17). There were no associations between total 25(OH)D concentrations and the risk of any cancer (5 publications)(30, 56, 69, 94, 133) or site-specific cancers, including breast cancer (11 publications)(30, 52, 53, 56, 69, 71, 92, 94, 96, 97, 158), lung cancer (9 publications)(30, 53, 56, 61, 69, 94, 96, 97, 158), colorectal cancer (11 publications)(30, 31, 53, 56, 65, 69, 85, 92, 94, 129, 158), pancreatic cancer (5 publications)(53, 69, 89, 94, 97, 158), and prostate cancer (11 publications)(30, 53, 69, 71, 86, 92, 94, 96, 97, 148, 158), as well as breast cancer survival (1 publication)(96) and hepatocellular carcinoma survival (1 publication)(119) (Table S17). However, the MR estimates based on non-overlapping participants showed an inverse association between genetically predisposed 25(OH)D and the risk of overall ovarian cancer (P=0.02) and overall esophageal cancer (P=0.041), but a positive association with BCC risk (P=0.01) (Fig. 6, Table S18).

Other diseases

Seventeen publications(17, 18, 20, 29, 30, 34, 36, 60, 76, 82, 94, 96, 118, 121, 126, 127, 158) investigated the association between total 25(OH)D concentrations and the risk of type 2 diabetes (T2D), and three(82, 121, 127) suggested an inverse association (Table S19). After excluding overlapping outcome samples, a meta-analysis of data from 130,332 cases in total 1,448,251 participants showed a 5% lower risk of T2D with a SD increase in genetically predicted log(25(OH)D) (combined OR=0.95, 95% CI:0.90-0.99; P=0.027, I^2=0%). Nevertheless, no significant associations were found on other exposure scales (>114,535 patients in total 1,247,424 participants) (Fig. 7, Table S20). Similarly, one publication(18) showed a null association of genetically determined serum 25(OH)D_3 concentrations and higher C3-epi-25(OH)D3 concentrations with T2D risk (Table S19). There was evidence that genetically predisposed total 25(OH)D concentrations were inversely associated with the risk of dyslipidemia (1/1 publication)(17), nonalcoholic fatty liver disease (NAFLD) (1/2 publications)(57, 143), bacterial pneumonia (1/1 publication)(117), and other cataracts (1/1 publication)(158), but were positively associated with the risk of gout (1/2 publications)(94, 96), kidney stone disease (KSD) (1/1 publication)(135), COVID-19 hospitalization (B2) (1/2 publications)(101, 104), and cataract (1/2 publications)(94, 158) (Table S19). The combined MR estimates for NAFLD were 0.85 (95% CI: 0.73-0.99; P=0.035, I^2=71.7%) per SD increase in genetically predicted total 25(OH)D concentrations (Fig. 7, Table S20). No significant associations were reported between total 25(OH)D concentrations and risk of other diseases (Fig. 7, Table S19, Table S20). Vitamin D deficiency and insufficiency were also not linked to COVID-19 susceptibility, hospitalization, and severity (Table S19).

Methodological quality assessment

The assessment of methodological quality of the included studies is presented in Table

S21. Most publications (n=125, 94.0%) conducted formal IV analyses, and 8 (6.0%) publications only reported genetic associations (i.e., reduced IV analyses). 88 (66.2%) publications verified all the three core IV assumptions, with 131 (98.5%) meeting the first assumption, 109 (82.0%) meeting the second assumption, and 110 (82.7%) meeting the third assumption. 116 (87.2%) publications selected exposure and outcome samples from populations with the same ancestry. 129 (97.0%) publications reported the genetic variants used as GIs. 117 (88.0%) publications presented the MR estimates on an interpretable scale. 129 (95.5%) publications performed sensitivity analyses, and 127 (95.5%) produced consistent findings with the main analyses. Almost all publications (n=131, 98.5%) conducted linear MR analyses, but only 3 (2.3%) publications further applied nonlinear MR analytical approaches. Overall, 3 (2.3%), 64 (48.1%), 21 (15.8%), and 45 (33.8%) publications were rated as excellent, good, fair, and poor quality, respectively.

DISCUSSION

Main findings

Over the past decade, the causality between vitamin D and a broad spectrum of major health outcomes has been examined by more than 130 MR publications. The present systematic review and meta-analysis provide a comprehensive overview of the up-to-date evidence from these MR analyses. Taken together, MR analyses support that higher genetically predisposed total 25(OH)D concentrations were associated with reduced risk of MS incidence and relapse, non-infectious uveitis and scleritis, psoriasis, femur fracture, leg fracture, ALS, anorexia nervosa, delirium, HF, ovarian cancer, NAFLD, dyslipidemia, and bacterial pneumonia, but increased risk of Behçet's disease, Graves' disease, KSD, fracture of radium/ulna, BCC, and overall cataracts. Evidence from nonlinear MR studies further suggests a threshold association between genetically predicted 25(OH)D and the risk of CVDs, dementia, and death from any cause, cancer, CVDs, and other causes, with evidence of the benefit of higher 25(OH)D only in vitamin D-deficient individuals, especially below 25 nmol/L. In addition, there is conflicting MR evidence on the causal association of vitamin D with the risk of any fracture, hypertension, T2D, gout, intracerebral hemorrhage, and esophageal cancer.

Comparison with results from other study designs

Although vitamin D is essential for regulating bone metabolism, its role in maintaining skeletal health across adulthood is still a matter of controversy. Evidence from MR studies do not support a causal role of vitamin D in total and most site-specific fractures in community-dwelling individuals(20, 66, 94, 113). Other efforts to explore the causality between vitamin D and bone mineral mass also failed to provide supporting evidence for bone health(66, 96, 159-162). Similarly, meta-analyses of randomized controlled trials (RCTs) indicate that vitamin D supplementation alone does not reduce fracture risk in older adults(163-165). The conclusions are supported by several large-scale RCTs, including the Vitamin D Assessment Study (ViDA)(166), the DO-HEALTH study(167), and the Vitamin D and Omega-3 Trial (VITAL)(168). However, in these trials, most participants recruited were vitamin D replete with a fairly low risk of fracture.

Vitamin D regulates the activities of many cells in the innate and adaptive immune system and exerts immunomodulatory, anti-inflammatory, antioxidant, and anti-fibrotic functions(169). Consistent and robust MR evidence exists supporting a protective effect of vitamin D on MS incidence and relapse, regardless of GIs used and data sources(39, 45, 48, 88, 93, 94, 96, 98, 107, 108), in accordance with results from observational studies(170, 171). Additionally, MR studies reported that genetically high 25(OH)D concentrations were linked to decreased risk of non-infectious uveitis and scleritis(156) and psoriasis(157), but increased risk of Behçet's disease(114) and Grave’s disease(158). In the VITAL study, daily supplementation of 2,000 IU of vitamin D_3 for five years significantly decreased total autoimmune disease incidence by 22% compared with placebo(172); however, the study was

underpowered for individual endpoints(172). The Copenhagen studies suggest a potential role of vitamin D in preventing bacterial pneumonia(117). This finding is partly supported by the most recent meta-analysis of 46 RCTs including 75,541 participants, in which, vitamin D supplementation decreased the risk of acute respiratory infections by 8% compared with placebo, especially in deficient individuals(173). In contrast, MR analyses indicate that the association between vitamin D and the risk of allergic diseases(17, 43, 49, 51, 96, 115, 158) is unlikely to be causal. Consistently, evidence from RCTs also does not support the use of vitamin D supplements to protect against asthma and atopic dermatitis(174, 175).

Linear MR analyses failed to provide supporting evidence for vitamin D in preventing overall CVD(80, 94, 133, 139), as well as cause-specific CVD, such as CAD(17, 42, 94, 96, 118, 136, 158), MI(30, 38, 80, 96), and stroke(68, 80, 94, 96, 118, 136, 147, 158). These findings are in line with meta-analyses of RCTs(176) and several large-scale RCTs of vitamin D supplementation conducted in the United States(177), New Zealand(178), and Finland(179), designed with CVD as one of the primary outcomes. However, when applying nonlinear MR analytical approaches to data from UKB, an L-shaped association was observed between 25(OH)D concentrations and overall CVD risk, where an inverse association was only observed at concentrations below 50 nmol/L(139). The HERMES consortium reported an inverse association of genetically predisposed 25(OH)D concentrations with HF risk(150), which were not replicated by the FinnGen and Biobank Japan studies(94, 158). The VITAL Heart Failure study also reported no beneficial effect of vitamin D supplementation on reducing the first or recurrent hospitalization rates for HF(180). Linear MR results regarding vitamin D and hypertension risk remain contradictory(17, 20, 35, 36, 87). Given that a recent nonlinear MR analysis suggests a potential effect of higher 25(OH)D on lowing systolic and diastolic blood pressure up to a threshold of 50 nmol/L(139), further RCTs should target vitamin D-deficient participants.

Albeit many observational studies have linked vitamin D deficiency with increased risk of total and site-specific cancer(9, 181), evidence from MR analyses does not support a causal role of vitamin D in preventing most cancers. In accordance with the findings from MR studies, recently published large-scale RCTs, i.e., VITAL(177, 182), ViDA(183), and Finnish Vitamin D Trial (FIND)(179), failed to provide any supporting evidence for vitamin D in the primary prevention of total and site-specific cancers (breast, colorectal, prostate). Combining the existing RCTs also generated null results for the risk of total cancer(184, 185) and colorectal cancers and polyps(186), irrespective of baseline serum 25(OH)D concentrations. Nevertheless, MR studies, although not all, suggest a causal association of genetically high 25(OH)D with lower risk of epithelial ovarian cancer(44, 94, 97) and esophageal cancer(158), but higher risk of BCC(97). However, the positive association between genetically predicted 25(OH)D and BCC risk is likely attributed to pleiotropy, because the association was attenuated and became nonsignificant after adjustment for pigmentation and sun exposure(97). Consistently, RCTs also did not observe

deleterious effects of vitamin D supplementation on keratinocyte cancer(187, 188).

Our meta-analyses of MR studies demonstrated no association between vitamin D and all-cause and cause-specific mortality based on linear assumptions. However, recent nonlinear MR analyses uncovered an L-shaped association of genetically determined 25(OH)D concentrations with the risk of death from any cause, cancer, CVD, and non-cancer, non-cardiovascular causes, where the inverse association was only pronounced in vitamin D-deficient individuals (especially <25 nom/L)(136, 189). In contrast, vitamin D supplementation was not related to any death outcomes in several large-scale RCTs, including VITAL(177), ViDA(178, 183), FIND(179), and D-Health Trial(190). The discrepancy may partly be owing to the relatively short follow-up and recruitment of few participants with vitamin D deficiency in the RCTs. Meta-analyses of RCTs concluded that vitamin D supplementation reduced cancer mortality compared with no supplementation(184, 185, 191). Considering that vitamin D supplementation has little influence on cancer incidence(184, 185), the benefit on cancer mortality may reflect improved survival after cancer diagnosis by optimizing vitamin D status. Indeed, observational studies and RCTs have linked vitamin D supplementation with superior survival in cancer patients(192, 193).

Accumulating evidence suggests that vitamin D has potential neuroprotective properties through regulating neuronal differentiation, neurotrophin expression, neuromodulator synthesis, intracellular calcium signaling, stress responsivity, inflammation, and oxidative stress(194). Many observational studies have associated vitamin D deficiency with a broad range of neurological and psychiatric conditions(74, 116, 195-200), but only some links may be causal, e.g., delirium, ALS, and anorexia nervosa, as supposed by linear MR analyses. In addition, genetically predicted 25(OH)D concentrations, instrumented by the SNPs selected from the SUNLIGHT consortium(14, 15), were inversely associated with the risk of Alzheimer's disease in the IGAP consortium(47, 55, 67, 112, 151). However, the finding was not corroborated in other populations(17, 109, 112) or by using SNPs selected from UKB GWAS data(94, 96). A nonlinear MR study using data from UKB supports a beneficial effect of higher 25(OH)D on all-cause dementia in vitamin D-deficient individuals up to a threshold of ~50 nmol/L(147). Discordantly, post-hoc analyses of two RCTs demonstrated no cognitive benefit of 2000 IU/day vitamin D supplementation for 2-3 years in healthy older adults over 60 years(201, 202). Of note, in both trials, the proportion of participants with vitamin D deficiency was relatively low.

Since 2014, seventeen MR studies have been published for T2D risk, but most studies generated disappointing findings(17, 18, 20, 29, 30, 34, 36, 60, 76, 82, 94, 96, 118, 121, 126, 127, 158). Consistent with the findings from MR studies, three large RCTs reported no benefit of supplementation with vitamin D_3 or active vitamin D on preventing the progression of prediabetes into T2D(203-205). However, combining these three trials with 5 other smaller trials showed that vitamin D supplementation

resulted in a reduction in T2D incidence and an increase in the rate of regression to normoglycemia, especially in nonobese participants with prediabetes(206). In our review, evidence from MR studies also suggests a beneficial effect of vitamin D on preventing NAFLD and dyslipidemia. These findings are supported by several, although not all, MR studies investigating the causal role of vitamin D on serum lipids, in which genetically high 25(OH)D concentrations were associated with higher HDL cholesterol levels, and lower triglycerides and total cholesterol levels(33, 80, 207). However, a meta-analysis of 41 RCTs, including 3,434 participants, concluded that vitamin D supplementation reduced total cholesterol, LDL cholesterol, and triglyceride concentrations but did not affect HDL cholesterol(208). Additionally, MR studies reported positive associations between genetically predicted 25(OH)D concentrations and the risk of gout(96) and overall cataract(158), while these findings were not confirmed by using different GIs(94) or in different populations(94, 158). The D-Health Trial showed no effect of monthly 60,000 IU of vitamin D_3 supplementation for 5 years on the incidence of cataract surgery(209).

A newly published MR study using data from UKB, in which genetically high 25(OH)D concentrations were linked to increased risk of KSD, probably through elevating serum calcium levels, has raised concern about the safety of vitamin D supplement use(135). However, most intervention studies did not show that long-term, even large doses, vitamin D supplementation, which elevated serum 25(OH)D concentrations, increased KSD risk (210, 211). Similar conclusions were drawn in recent large-scale, long-term RCTs of vitamin D_3 supplementation, such as VITAL(177), ViDA(212), FIND(179), D-Health Trial(190), and Vitamin D and Type 2 Diabetes (D2d) trial(203). A nested case-control study in the Health Professional Follow-up Study suggests that higher concentrations of plasma $1,25(OH)_2D$, rather than 25(OH)D, increase KSD risk, even in normal ranges(213). Indeed, $1,25(OH)_2D$ is the active form of vitamin D responsible for stimulating intestinal calcium absorption. The renal activation of $1,25(OH)_2D$ is tightly regulated and is only slightly affected by circulating 25(OH)D concentrations(214). Some genetic variants that affect 25(OH)D concentration may also affect $1,25(OH)_2D$ levels(2); thus, it might be problematic to use SNPs related to serum 25(OH)D concentrations as instruments(135). In contrast, MR estimates from Biobank Japan suggest no association between genetic predisposed 25(OH)D concentrations and urolithiasis risk(158). However, given that both animal studies and human data observed increased incidence of hypercalcemia and/or hypercalciuria with high doses of vitamin D treatment(210, 211, 215, 216), the causal role of vitamin D in KSD cannot be excluded entirely, especially when exposure to both vitamin D and calcium supplementation(217).

Possible reasons for the discordance between different study designs

MR studies and RCTs draw concordant conclusions in most cases, but there are some exceptions. MR studies depend on valid IV assumptions. However, there are substantial differences in the methodological quality of the included MR studies. It is

hard to know whether the MR estimates from some studies are valid due to inadequate reporting of the methods and results. MR studies are also limited by the low variance of circulating 25(OH)D concentrations explained by most GIs (usually <5%), which may result in insufficient statistical power. Also, the associations varied by instruments, study populations, and analytical approaches. Additionally, most MR studies only applied standard MR analytical methods based on linear assumptions, which might mask the true cause and effect, as suggested by observational studies and recent nonlinear MR analyses. However, MR analyses have advantages over RCTs in predicting lifelong 25(OH)D concentrations. The duration of RCTs is usually no longer than 5 years, and such short-term scenarios may not be enough to evaluate the effectiveness and safety of vitamin D supplementation in the context of chronic diseases. Moreover, even large-scale RCTs, like VITAL with sufficient power to detect the effect of vitamin D supplementation on overall CVD and cancer, might be underpowered to examine the impact on individual outcomes. In addition, evidence from observational studies and nonlinear MR analyses suggests that the health effects of vitamin D might only be pronounced among vitamin D-deficient individuals. However, most RCTs have been undertaken in populations with good vitamin D status.

Strengths and limitations

In this systematic review and meta-analysis, we comprehensively summarized the evidence on vitamin D and a variety of major health outcomes from MR approaches. Furthermore, we performed meta-analyses, when appropriate, to synthesize the results from different study populations. In addition, unlike previous reviews, we systematically evaluated the methodological quality of the available MR studies. Nevertheless, several limitations are needed to be acknowledged in the review. First, the magnitude of the MR estimates cannot be comparable across outcomes because of diverse GIs and units of estimated effect used in the included MR studies, such as per allele change, per SD change in 25(OH)D, per unit change in log(25(OH)D)). Second, meta-analysis of studies was technically impossible for some endpoints on account of the large methodological heterogeneity. Third, the included MR studies are predominantly conducted among populations of European ancestry. As a result, caution should be taken when generalizing the findings to ethnically diverse populations. Fourth, quality assessment tool always involves some subjectivity, but we developed the tool according to well-accepted MR guidelines and tried to capture the critical elements of the MR design.

Conclusions

Although current evidence from MR studies does not support a causal role of vitamin D in most health outcomes, vitamin D is promising to protect against MS, non-infectious uveitis and scleritis, psoriasis, anorexia nervosa, delirium, ovarian cancer, bacterial pneumonia, CVDs, dementia, and death from any cause, CVDs, and cancer, especially in vitamin D-deficient individuals. Meanwhile, vitamin D potentially increases the risk of Behçet's disease, Graves' disease, and KSD. The heterogeneity in

methodological quality and contradictory findings across studies preclude drawing firm conclusions. High-quality MR studies with the ability to explore nonlinearity are needed to re-evaluate these associations, particularly in non-European populations. Additionally, well-designed, long-term, large-scale RCTs are warranted to confirm the results.

Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions

Edward L. Giovannucci and Aiping Fang conceptualized the review; Aiping Fang designed the search strategy and performed the literature search; Aiping Fang and Yue Zhao screened abstracts and full-texts; Aiping Fang and Yue Zhao extracted the data; Aiping Fang, Yue Zhao and Ping Yang checked the data; Yue Zhao, Ping Yang and Aiping Fang assessed the methodological quality of the included studies; Aiping Fang and Yue Zhao analyzed the data; Aiping Fang wrote the original draft of the manuscript; Edward L. Giovannucci and Xuehong Zhang edited and critically reviewed the original draft of the manuscript; Edward L. Giovannucci had primary responsibility for the final content; and all authors read and approved the final manuscript.

Ethics approval

Not available.

Consent to participate

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Data transparency

Data collection forms, data extracted from included studies, and data used for all analyses are available upon request to the corresponding author.

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Figure Captions

Fig. 1 Mendelian randomization results of the association between genetically determined 25(OH)D and risk of all-cause and cause-specific mortality.

Fig. 2 Mendelian randomization results of the association between genetically determined 25(OH)D and risk of allergic and autoimmune diseases.

Fig. 3 Mendelian randomization results of the association between genetically determined 25(OH)D and risk of cardiovascular diseases.

Fig. 4 Mendelian randomization results of the association between genetically determined 25(OH)D and risk of musculoskeletal diseases.

Fig. 5 Mendelian randomization results of the association between genetically determined 25(OH)D and risk of neurophysiologic diseases.

Fig. 6 Mendelian randomization results of the association between genetically determined 25(OH)D and cancer incidence and survival.

Fig. 7 Mendelian randomization results of the association between genetically determined 25(OH)D and risk of other diseases.

Figure 1

Outcome	N of papers	Total participants	Cases	Controls	HR/OR (95% CI)	P value
Per 25 nmol/L increase in 25(OH)D						
All-cause mortality	4	572,720	51,013	521,707	0.98 (0.96, 1.00)	0.059
Cancer mortality	3	562,219	<19,443	>542,776	0.97 (0.94, 1.00)	0.088
Cardiovascular mortality	2	533,052	<13,657	>519,395	1.00 (0.98, 1.03)	0.727
Major coronary event mortality	1	96,972	2,040	94,932	1.00 (0.96, 1.05)	0.91
Ischemic heart disease mortality	1	203,883	2,543	201,340	1.00 (0.96, 1.04)	0.924
Myocardial infraction mortality	1	204,873	1,265	203,608	0.99 (0.93, 1.05)	0.666
Stroke mortality	1	202,495	3,860	198,635	1.01 (0.98, 1.05)	0.453
Ischemic stroke mortality	1	205,923	596	205,327	0.98 (0.87, 1.10)	0.686
Subarachnoid hemorrhage mortality	1	98,955	57	98,898	0.98 (0.75, 1.28)	0.89
Intracerebral hemorrhage mortality	1	203,257	2,808	200,449	1.03 (0.99, 1.07)	0.121
Non-cardiovascular non-cancer mortality	2	428,768	<6,216	>422,552	0.85 (0.52, 1.39)	0.51
Nervous system mortality	1	333,002	1,043	331,959	1.03 (0.72, 1.47)	0.92
Digestive system mortality	1	333,002	798	332,204	1.10 (0.73, 1.68)	0.63
Respiratory disease mortality	2	538,925	4,007	534,918	1.00 (0.93, 1.06)	0.896
Infection mortality	1	205,923	433	205,490	1.08 (0.96, 1.21)	0.23
Per unit increase in log(25(OH)D)						
Cardiovascular mortality in hypertensive-diabetic subjects	1	3,746	35	3,711	0.87 (0.58, 1.19)	-
Per 25(OH)D-increasing allele score						
All-cause mortality	1	8,417	1,338	7,079	1.08 (1.01, 1.14)	-
Cancer mortality	1	8,417	500	7,917	1.03 (0.93, 1.14)	-
Cardiovascular mortality	1	8,417	449	7,968	1.10 (0.99, 1.22)	-

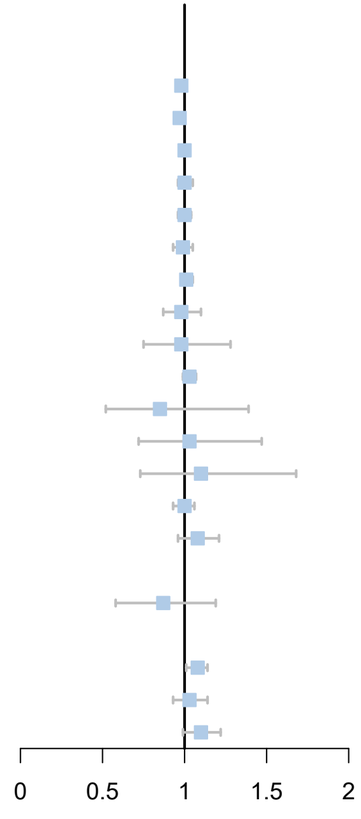

Figure 2

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Outcome	N of papers	Total participants	Cases	Controls	HR/OR (95% CI)	P value
Per 25 nmol/L increase in 25(OH)D						
Crohn's disease	1	115,110	653	114,457	0.73 (0.33, 1.61)	0.43
Ulcerative colitis	1	115,110	1,265	113,845	1.10 (0.61, 2.00)	0.73
Per SD increase in 25(OH)D						
Allergic rhinitis	1	297,526	29,856	267,670	0.96 (0.78, 1.18)	0.703
Allergic sensitization	1	24,481	8,040	16,441	1.06 (0.69, 1.63)	0.797
Ankylosing spondylitis	1	25,764	10,619	15,145	1.00 (1.00, 1.00)	0.724
Celiac disease	1	15,283	4,533	10,750	0.91 (0.76, 1.09)	0.308
Hyperthyroidism	1	85,465	947	84,518	1.00 (0.98, 1.02)	0.967
Hypothyroidism	1	94,710	10,192	84,518	1.00 (0.98, 1.03)	0.848
Idiopathic pulmonary fibrosis	1	11,259	2,668	8,591	0.97 (0.94, 1.01)	0.168
Inflammatory bowel disease	1	59,957	25,042	34,915	1.01 (0.97, 1.06)	0.521
Crohn's disease	1	40,266	12,194	28,072	1.02 (0.97, 1.08)	0.397
Ulcerative colitis	1	45,975	12,366	33,609	1.00 (0.96, 1.04)	0.972
Primary biliary cirrhosis	1	13,239	2,764	10,475	0.88 (0.73, 1.05)	0.142
Primary sclerosing cholangitis	1	14,890	2,871	12,019	0.99 (0.95, 1.02)	0.471
Type 1 diabetes	1	83,674	1,293	82,381	1.01 (0.99, 1.02)	0.259
Vasculitis	1	79,328	253	79,075	1.00 (0.98, 1.02)	0.846
Per SD increase in log(25(OH)D)						
Allergic disease (asthma, hay fever, or eczema)	1	360,838	180,129	180,709	1.04 (0.99, 1.09)	0.155
Asthma	3	484,238	53,279	430,959	1.05 (0.96, 1.15)	0.303
Paediatric asthma	1	15,008	7,047	7,961	1.05 (0.76, 1.45)	0.76
Pollinosis	1	212,453	5,746	206,707	1.01 (0.85, 1.21)	0.876
Atopic dermatitis	2	252,871	13,173	239,698	0.86 (0.72, 1.03)	0.095
Eczema	1	40,835	10,788	30,047	1.06 (0.94, 1.20)	0.33
Graves' disease	1	533,755	2,408	531,347	1.55 (1.22, 1.98)	<0.001
Non-infectious uveitis and scleritis	1	4,542	375	4,167	0.46 (0.22, 0.99)	0.049
Behcet's disease	1	7,909	2,214	5,695	3.96 (1.72, 9.13)	0.001
Juvenile idiopathic arthritis	1	12,501	3,305	9,196	0.99 (0.72, 1.35)	0.942
Multiple sclerosis	1	115,803	47,429	68,374	0.82 (0.69, 0.99)	0.035
Multiple sclerosis relapse	1	506	-	-	0.59 (0.38, 0.94)	0.025
Primary biliary cholangitis	1	13,239	2,764	10,475	0.92 (0.65, 1.30)	0.633
Psoriasis	1	462,933	5,314	457,619	0.76 (0.60, 0.96)	0.02
Vitiligo	1	44,266	4,680	39,586	0.93 (0.66, 1.31)	0.667
Rheumatoid arthritis	1	212,453	4,199	208,254	1.00 (0.77, 1.29)	0.988
Systemic lupus erythematosus	1	14,267	5,201	9,066	0.96 (0.74, 1.23)	0.729
Type 1 diabetes	1	25,063	9,358	15,705	0.91 (0.72, 1.17)	0.478
Per unit increase in RINT(25(OH)D)						
Rheumatoid arthritis	1	58,284	14,361	43,923	1.03 (0.82, 1.29)	0.82
Per 25(OH)D-increasing allele score						
Paediatric asthma	1	5,080	1,203	3,877	1.00 (1.00, 1.00)	0.85
Multiple sclerosis	1	22,168	7,391	14,777	0.85 (0.76, 0.94)	0.003
Multiple sclerosis (Paediatric-onset)	1	16,820	569	16,251	0.72 (0.55, 0.94)	0.02

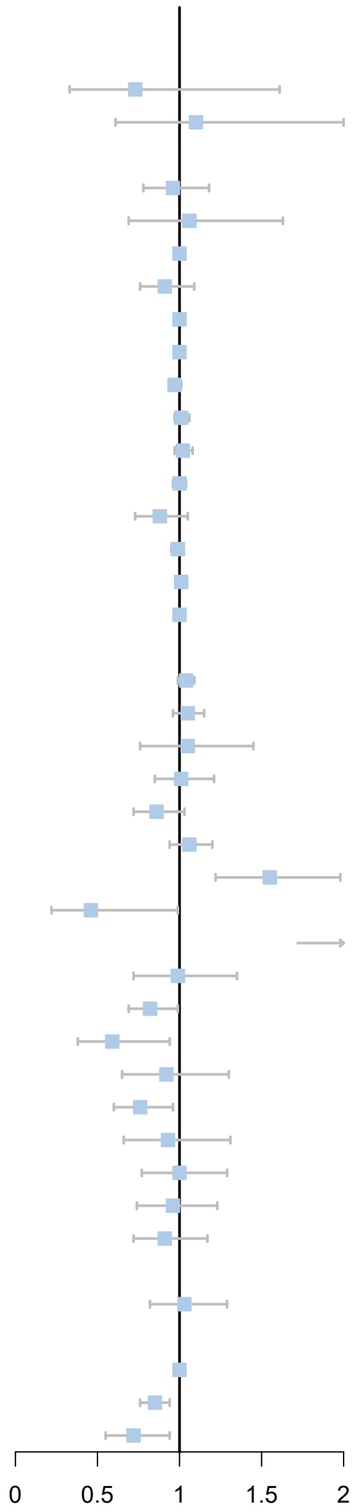

Figure 3

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Outcome	N of papers	Total participants	Cases	Controls	HR/OR (95% CI)	P value
Per 10% increase in 25(OH)D						
Hypertension	1	142,255	44,025	98,230	0.92 (0.87, 0.97)	0.002
Gestational hypertension	1	7,389	751	6,638	1.11 (0.93, 1.33)	0.14
Preeclampsia	1	16,836	3,523	13,313	1.01 (0.94, 1.09)	0.761
Per 25 nmol/L increase in 25(OH)D						
Cardiovascular disease	2	476,264	69,954	406,310	1.01 (0.99, 1.02)	0.387
Major coronary event	1	96,103	2,909	93,194	1.01 (0.98, 1.05)	0.59
Coronary heart disease	1	386,406	33,546	352,860	0.95 (0.88, 1.03)	0.18
Coronary heart disease (Incident only)	1	333,002	5,447	327,555	1.00 (0.85, 1.18)	0.98
Ischemic heart disease	1	189,748	15,503	174,245	1.00 (0.98, 1.01)	0.54
Myocardial infarction	1	201,860	3,991	197,869	1.00 (0.97, 1.03)	0.54
Stroke (Overall)	2	545,222	32,976	512,246	1.00 (0.99, 1.01)	0.956
Stroke (Incident only)	1	333,002	5,044	327,958	0.95 (0.80, 1.12)	0.49
Ischemic stroke (Overall)	2	528,379	15,657	512,722	1.00 (0.98, 1.02)	0.885
Haemorrhagic stroke	1	333,002	1,194	331,808	0.79 (0.57, 1.10)	0.19
Intracerebral hemorrhage (Overall)	1	200,318	5,837	194,481	1.01 (0.98, 1.04)	0.86
Subarachnoid hemorrhage	1	98,492	520	97,972	1.08 (0.99, 1.19)	0.14
Per SD increase in 25(OH)D						
Hypertension	1	91,302	22,142	69,160	1.00 (0.98, 1.03)	0.659
Aortic Valve Stenosis (Incident only)	1	361,930	1,602	360,328	1.06 (1.00, 1.13)	-
Atrial fibrillation	1	63,622	7,244	56,378	1.00 (0.98, 1.02)	0.933
Cardiovascular disease	1	217,892	111,108	106,784	1.03 (0.99, 1.07)	0.14
Coronary artery disease	1	184,305	60,801	123,504	0.92 (0.80, 1.04)	0.174
Coronary artery disease in patients with diabetes	1	15,666	3,968	11,698	1.04 (0.58, 1.87)	0.888
Stroke (Cardioembolic)	1	19,567	1,859	17,708	1.00 (0.97, 1.03)	0.948
Stroke (Large vessel)	1	19,525	1,817	17,708	0.99 (0.96, 1.02)	0.433
Stroke (Small vessel)	1	19,057	1,349	17,708	0.99 (0.96, 1.01)	0.341
Intracerebral hemorrhage (Overall)	1	3,026	1,545	1,481	0.63 (0.41, 0.95)	0.029
Intracerebral hemorrhage (Lobar)	1	2,145	664	1,481	0.70 (0.42, 1.16)	0.17
Intracerebral hemorrhage (Nonlobar)	1	2,362	881	1,481	0.53 (0.34, 0.85)	0.007
Heart failure	1	83,153	8,016	75,137	1.01 (0.99, 1.02)	0.432
Peripheral vascular disease	1	92,741	392	92,349	1.00 (0.99, 1.02)	0.662
Varicose veins	1	529,073	22,691	506,382	1.06 (0.98, 1.14)	0.173
Venous thromboembolism	1	96,499	3,303	93,196	1.00 (0.98, 1.03)	0.683
Per SD increase in log(25(OH)D)						
Hypertension	1	339,256	106,405	232,851	0.98 (0.93, 1.03)	0.343
Arrhythmia	1	212,453	17,861	194,592	1.10 (0.97, 1.25)	0.147
Atrial fibrillation	1	1,030,836	60,620	970,216	1.00 (0.95, 1.06)	0.959
Cerebral aneurysm	1	195,203	2,820	192,383	1.05 (0.80, 1.38)	0.732
Coronary heart disease	1	86,995	22,233	64,762	0.94 (0.79, 1.13)	0.515
Coronary artery disease	1	212,453	29,319	183,134	0.96 (0.80, 1.16)	0.705
Coronary artery disease (SOFT phenotype)	1	332,477	71,602	260,875	1.00 (0.92, 1.09)	0.954
Ischemic heart disease	1	339,256	28,337	310,919	1.02 (0.94, 1.11)	0.611
Myocardial infarction	1	171,875	43,676	128,199	0.97 (0.88, 1.06)	0.465
Stroke (Overall)	1	446,696	40,585	406,111	0.99 (0.92, 1.06)	0.735
Ischemic stroke (Overall)	2	648,901	51,888	597,013	1.00 (0.94, 1.07)	0.913
Ischemic stroke (Cardioembolic)	1	411,823	7,193	404,630	1.02 (0.90, 1.16)	0.74
Ischemic stroke (Large vessel)	1	409,003	4,373	404,630	0.94 (0.80, 1.11)	0.49
Ischemic stroke (Small vessel)	1	410,016	5,386	404,630	0.95 (0.82, 1.11)	0.55
Congestive heart failure	1	212,453	9,413	203,040	0.95 (0.78, 1.14)	0.57
Heart failure	1	977,323	47,309	930,014	0.81 (0.70, 0.94)	0.006
Peripheral artery disease	1	212,453	3,593	208,860	0.93 (0.68, 1.27)	0.655
Recurrent or de novo ischemic stroke/myocardial infarction	1	441	58	383	0.64 (0.42, 0.91)	-
Recurrent stroke/myocardial infarction	1	441	49	392	0.55 (0.35, 0.81)	-
Recurrent myocardial infarction	1	441	37	404	0.52 (0.30, 0.81)	-
Recurrent stroke	1	441	12	429	0.72 (0.30, 1.51)	-
Per unit increase in log(25(OH)D)						
Combined cardiovascular endpoints in hypertensive-diabetic subjects	1	3,746	561	3,185	0.86 (0.75, 0.95)	-
Congestive heart failure in hypertensive-diabetic subjects	1	3,746	372	3,374	0.93 (0.82, 1.04)	-
Myocardial infarction in hypertensive-diabetic subjects	1	3,746	162	3,584	0.76 (0.60, 0.90)	-
Ischemic stroke in hypertensive-diabetic subjects	1	3,746	79	3,667	0.90 (0.67, 1.09)	-
Peripheral vascular disease in hypertensive-diabetic subjects	1	3,746	22	3,724	0.85 (0.52, 1.30)	-
Per unit increase in RINT(25(OH)D)						
Coronary artery disease	1	296,525	34,541	261,984	0.98 (0.94, 1.02)	0.265
Per 25(OH)D-increasing allele score						
Hypertension	1	2,591	-	-	1.04 (0.90, 1.20)	0.62

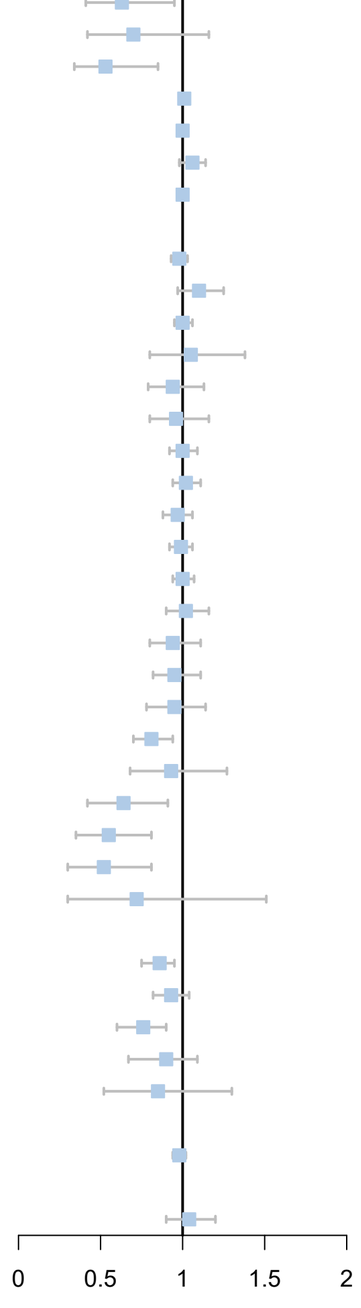

Figure 4

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Outcome	N of papers	Total participants	Cases	Controls	HR/OR (95% CI)	P value
Per SD increase in 25(OH)D						
Any fracture	1	562,258	185,057	377,201	1.19 (0.99, 1.44)	0.07
Fracture of face	1	361,194	1,351	359,843	1.11 (0.71, 1.74)	0.656
Fracture of femur	1	361,194	1,803	359,391	0.53 (0.32, 0.87)	0.013
Fracture of foot	1	361,194	681	360,513	1.00 (0.55, 1.80)	0.988
Fracture of forearm	1	361,194	5,080	356,114	1.42 (0.95, 2.11)	0.086
Fracture of hip	1	84,531	1,619	82,912	1.01 (1.00, 1.02)	0.193
Fracture of leg	1	361,194	4,557	356,637	0.60 (0.44, 0.80)	<0.001
Fracture of lumbar	1	361,194	874	360,320	1.41 (0.74, 2.68)	0.294
Fracture of neck	1	361,194	209	360,985	0.35 (0.07, 1.65)	0.185
Fracture of rib	1	361,194	947	360,247	1.91 (0.82, 3.25)	0.117
Fracture of shoulder	1	361,194	1,791	359,403	1.47 (0.99, 2.19)	0.059
Fracture of wrist	1	361,194	1,763	359,431	0.68 (0.46, 1.01)	0.053
Osteoarthritis (Overall)	1	455,221	77,052	378,169	1.02 (0.91, 1.15)	0.676
Sarcopenia	1	378,635	577	378,058	0.69 (0.16, 2.95)	0.625
Sciatica	1	78,053	3,464	74,589	1.00 (0.99, 1.02)	0.581
Per SD increase in log(25(OH)D)						
Osteoporosis	1	212,453	7,788	204,665	1.06 (0.89, 1.28)	0.499
Non-vertebral fracture	1	339,256	23,603	315,653	0.97 (0.89, 1.06)	0.497
Osteoarthritis (hospital diagnosed)	1	50,508	10,083	40,425	1.02 (0.94, 1.11)	0.601
Osteoarthritis (self-reported)	1	63,556	12,658	50,898	1.03 (0.95, 1.11)	0.5
Osteoarthritis of hip/knee (hospital diagnosed)	1	32,970	6,586	26,384	0.98 (0.88, 1.11)	0.787
Osteoarthritis of hip (hospital diagnosed)	1	11,989	2,396	9,593	1.03 (0.86, 1.23)	0.746
Osteoarthritis of knee (hospital diagnosed)	1	22,347	4,462	17,885	0.96 (0.84, 1.09)	0.522
Per unit increase in log(25(OH)D)						
Osteoarthritis of hip	1	613,790	17,151	596,639	1.03 (0.84, 1.26)	0.76
Osteoarthritis of knee	1	586,030	23,877	562,153	1.06 (0.83, 1.35)	0.63
Per 25(OH)D-increasing allele score						
Any fracture	1	116,334	15,556	100,778	1.01 (1.00, 1.02)	0.04
Fracture of hip/femur	1	116,334	2,726	113,608	1.02 (0.99, 1.05)	0.08
Fracture of humerus/scapula/clavicle	1	116,334	2,178	114,156	1.00 (0.98, 1.03)	0.74
Fracture of radius/ulna	1	116,334	3,582	112,752	1.03 (1.00, 1.06)	0.02
Fracture of spine/rib/pelvis	1	116,334	1,335	114,999	1.00 (0.97, 1.04)	0.87
Fracture of tibia/fibula	1	116,334	2,110	114,224	1.02 (0.99, 1.05)	0.17
Osteoporotic fracture	1	116,334	9,334	107,000	1.01 (0.99, 1.03)	0.08

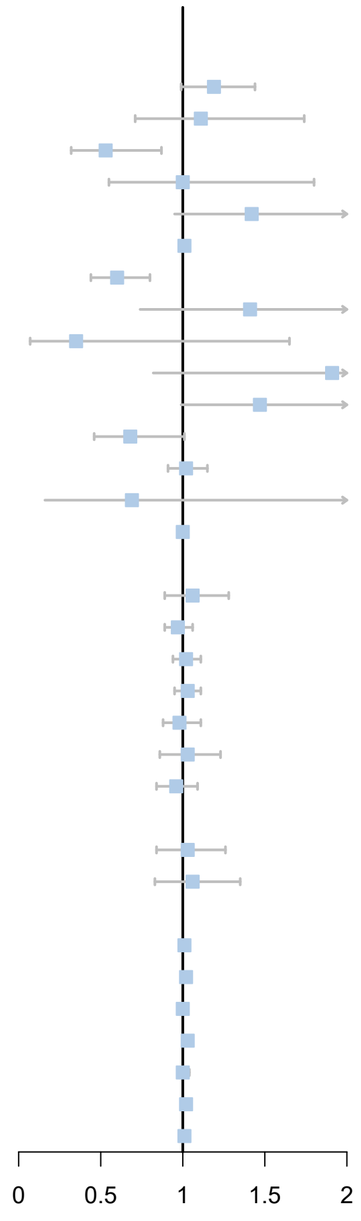

Figure 5

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Outcome	N of papers	Total participants	Cases	Controls	HR/OR (95% CI)	P value
Per SD increase in 25(OH)D						
Amyotrophic lateral sclerosis	1	138,086	27,205	110,881	0.90 (0.82, 0.99)	0.025
Epilepsy	1	34,853	8,696	26,157	0.98 (0.94, 1.02)	0.277
Tourette syndrome	1	14,307	4,819	9,488	1.00 (0.96, 1.04)	0.879
Antisocial behavior	1	16,400	-	-	1.02 (0.97, 1.07)	0.372
Bipolar disorder	1	51,710	20,352	31,358	1.00 (0.97, 1.03)	0.927
Depression	1	500,199	170,756	329,443	1.00 (0.99, 1.01)	0.625
Major depressive disorder	1	2,047	1,700	347	0.94 (0.84, 1.06)	0.34
Atypical depression	1	126,126	2,101	124,025	1.12 (0.88, 1.43)	0.356
Treatment-resistant depression	1	178,584	1,891	176,693	1.13 (0.87, 1.45)	0.355
Cannabis dependence	1	51,372	2,387	48,985	1.00 (0.99, 1.02)	0.619
Obsessive compulsive disorder	1	9,725	2,688	7,037	1.05 (0.97, 1.13)	0.225
Post-traumatic stress disorder	1	9,537	2,424	7,113	1.00 (0.98, 1.03)	0.894
Schizophrenia	1	105,318	40,675	64,643	1.00 (0.97, 1.03)	0.923
Suicide attempt	1	50,264	6,024	44,240	1.00 (0.97, 1.03)	0.966
Per SD increase in log(25(OH)D)						
Anorexia nervosa	1	14,477	3,495	10,982	0.74 (0.58, 0.94)	0.015
Epilepsy	2	361,821	6,731	355,090	0.96 (0.82, 1.12)	0.602
Insomnia complaints	1	113,006	32,384	80,622	1.04 (0.98, 1.10)	0.22
Parkinson's disease	1	482,730	33,674	449,056	0.92 (0.81, 1.03)	0.155
Attention deficit/hyperactivity disorder	1	55,374	20,183	35,191	1.00 (0.90, 1.11)	0.977
Autism spectrum disorder	1	46,351	18,382	27,969	1.01 (0.90, 1.13)	0.924
Generalized anxiety disorder	1	17,310	5,712	11,598	0.90 (0.67, 1.22)	0.491
Delirium	1	326,558	3,405	323,153	0.80 (0.74, 0.87)	<0.001
Broad depression	1	322,580	113,769	208,811	0.99 (0.98, 1.00)	0.07
Major depressive disorder (ICD-10 coded)	1	217,584	8,276	209,308	1.00 (1.00, 1.00)	0.664
Major depressive disorder (probable)	1	174,519	30,603	143,916	1.00 (0.99, 1.00)	0.205
Per unit increase in log(25(OH)D)						
All-cause dementia	1	294,514	2,339	292,175	0.87 (0.70, 1.08)	0.21
Per unit increase in RINT(25(OH)D)						
Alzheimer's disease	1	455,258	71,880	383,378	1.00 (0.98, 1.03)	0.848
Parkinson's disease	1	308,518	6,476	302,042	1.12 (1.00, 1.25)	0.073
Major depressive disorder	1	807,553	246,363	561,190	0.98 (0.96, 1.00)	0.082
Per 25(OH)D-increasing allele score						
All-cause dementia	1	1,087	234	853	1.04 (0.91, 1.19)	-
Alzheimer's disease	1	1,087	108	979	0.96 (0.79, 1.18)	-
Vascular dementia	1	1,087	58	1,029	1.08 (0.82, 1.42)	-
Cognitive impairment	1	471	77	394	1.03 (0.80, 1.34)	-

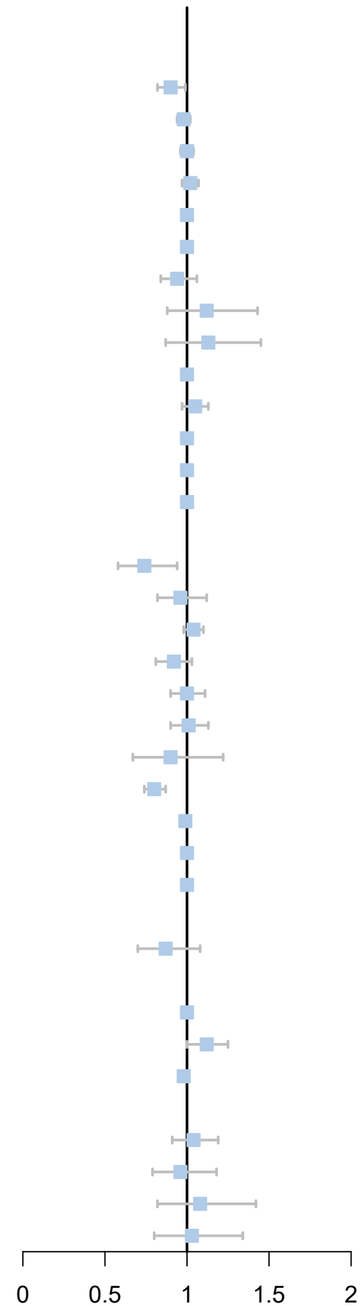

Figure 6

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A. Cancer incidence Outcome Per 25 nmol/L increase in 25(OH)D	N of papers	Total participants	Cases	Controls	HR/OR (95% CI)	P value
Any cancer	2	334,087	50,140	283,947	1.03 (0.88, 1.20)	0.748
Breast cancer (Overall)	3	528,586	136,240	392,346	1.01 (0.96, 1.06)	0.704
Breast cancer (ER-negative)	1	127,442	21,468	105,974	1.02 (0.90, 1.16)	0.75
Breast cancer (ER-positive)	1	175,475	69,501	105,974	1.00 (0.94, 1.07)	0.99
Lung cancer (Overall)	4	374,197	15,406	358,791	1.03 (0.90, 1.18)	0.702
Lung cancer (Adenocarcinoma)	2	74,673	3,993	70,680	0.99 (0.77, 1.29)	0.956
Lung cancer (Squamous cell)	2	74,560	3,687	70,873	0.93 (0.71, 1.22)	0.607
Lung cancer (Small cell)	1	54,580	90	54,490	0.58 (0.12, 2.69)	0.48
Lung cancer (Others/Unknown subtypes)	1	54,580	256	54,324	2.22 (0.86, 5.75)	0.1
Colorectal cancer (Overall)	3	325,472	21,359	304,113	0.97 (0.86, 1.10)	0.671
Colorectal cancer (Colon)	1	19,357	7,678	11,679	0.90 (0.73, 1.11)	0.33
Colorectal cancer (Distal colon)	1	15,033	3,354	11,679	0.97 (0.73, 1.28)	0.83
Colorectal cancer (Proximal colon)	1	15,864	4,185	11,679	0.83 (0.64, 1.07)	0.14
Colorectal cancer (Rectal)	1	14,462	2,783	11,679	0.93 (0.68, 1.26)	0.64
Gastric and oesophageal Cancer	1	265,597	959	264,638	0.72 (0.50, 1.05)	0.09
Oesophageal cancer (Adenocarcinoma)	1	21,271	4,112	17,159	0.62 (0.31, 1.24)	-
Pancreatic cancer	2	268,973	2,396	266,577	1.26 (0.84, 1.91)	0.267
Prostate cancer (Overall)	3	439,295	100,839	338,456	0.99 (0.93, 1.05)	0.78
Prostate cancer (Advanced)	2	90,644	19,612	71,032	1.04 (0.92, 1.17)	0.531
Ovarian cancer (Overall)	1	265,669	1,031	264,638	1.13 (0.76, 1.68)	0.57
Ovarian cancer (Serous)	1	27,482	5,828	21,654	0.79 (0.50, 1.25)	-
Ovarian cancer (Others)	1	23,258	1,604	21,654	0.89 (0.56, 1.41)	-
Endometrial cancer (Overall)	1	266,576	1,938	264,638	0.88 (0.66, 1.16)	0.38
Kidney cancer	1	265,650	1,012	264,638	1.27 (0.80, 2.01)	0.31
Lymphoid cancer	1	268,214	3,576	264,638	1.13 (0.90, 1.40)	0.29
Neuroblastoma	1	4,881	1,627	3,254	0.76 (0.47, 1.21)	0.24
Skin cancer (Melanoma)	2	303,473	15,632	287,841	0.91 (0.81, 1.03)	0.149
Skin cancer (Non-melanoma)	1	97,849	8,643	89,206	1.11 (0.91, 1.35)	-
Per SD increase in 25(OH)D						
Any cancer	1	218,792	38,036	180,756	1.01 (0.97, 1.05)	0.68
Barrett's oesophagus and oesophageal cancer	1	27,438	10,279	17,159	0.98 (0.85, 1.14)	0.98
Barrett's oesophagus	1	23,326	6,167	17,159	1.00 (0.84, 1.18)	0.97
Oesophageal cancer	1	21,271	4,112	17,159	0.97 (0.78, 1.20)	0.76
Lung cancer (Overall)	1	85,716	29,266	56,450	1.00 (0.97, 1.03)	0.844
Colorectal cancer (Overall)	2	164,377	27,240	137,137	1.00 (0.99, 1.01)	0.975
Ovarian cancer (Overall)	1	66,450	25,509	40,941	0.89 (0.82, 0.96)	0.02
Ovarian cancer (Clear cell)	1	42,307	1,366	40,941	0.87 (0.64, 1.18)	0.36
Ovarian cancer (Endometrioid)	1	43,751	2,810	40,941	0.94 (0.77, 1.15)	0.55
Ovarian cancer (High-grade serous)	1	53,978	13,037	40,941	0.92 (0.82, 1.03)	0.15
Ovarian cancer (Low-grade serous)	1	41,953	1,012	40,941	0.99 (0.71, 1.37)	0.94
Ovarian cancer (Mucinous)	1	42,358	1,417	40,941	0.94 (0.74, 1.18)	0.59
Uterus cancer	1	87,427	366	87,061	1.01 (0.99, 1.03)	0.299
Endometrial cancer (Overall)	1	121,885	12,906	108,979	0.95 (0.83, 1.09)	0.46
Endometrial cancer (Endometrioid)	1	54,884	8,758	46,126	0.93 (0.81, 1.08)	0.36
Endometrial cancer (Non-endometrioid)	1	36,677	1,230	35,447	1.02 (0.76, 1.36)	0.91
Thyroid cancer	1	87,382	321	87,061	0.99 (0.96, 1.02)	0.562
Glioma (Overall)	1	30,657	12,488	18,169	0.99 (0.86, 1.15)	0.933
Glioma (Glioblastoma)	1	24,352	6,183	18,169	0.88 (0.71, 1.05)	0.17
Glioma (Non-glioblastoma)	1	23,989	5,820	18,169	1.11 (0.92, 1.34)	0.264
Kidney cancer	1	96,499	301	96,198	1.00 (0.99, 1.01)	0.964
Bladder cancer	1	96,499	366	96,133	1.00 (0.99, 1.02)	0.576
Skin cancer (Overall)	1	87,956	895	87,061	1.02 (0.99, 1.04)	0.147
Skin cancer (Basal cell carcinoma)	1	293,989	14,940	279,049	1.16 (1.04, 1.28)	0.01
Skin cancer (Squamous cell carcinoma)	2	629,914	7,804	622,110	1.00 (1.00, 1.00)	1
Skin cancer (In situ)	1	87,181	342	86,839	1.01 (0.99, 1.03)	0.458
Leukemia	1	87,259	198	87,061	1.01 (1.00, 1.03)	0.098
Multiple myeloma	1	37,021	7,717	29,304	1.08 (0.84, 1.40)	0.54
Non-Hodgkin lymphoma	1	87,216	155	87,061	1.00 (0.98, 1.03)	0.873
Per SD increase in log(25(OH)D)						
Breast cancer (Overall)	2	98,969	7,209	91,760	0.98 (0.92, 1.05)	0.593
Lung cancer (Overall)	1	212,453	4,050	208,403	1.03 (0.78, 1.36)	0.84
Oral and oropharyngeal cancer	1	348,225	5,718	342,507	0.95 (0.74, 1.22)	0.68
Oral cancer	1	345,501	2,994	342,507	0.86 (0.70, 1.07)	0.18
Oropharyngeal cancer	1	345,231	2,724	342,507	1.03 (0.69, 1.53)	0.87
Oesophageal cancer (Overall)	1	518,347	1,866	516,481	0.71 (0.52, 0.99)	0.041
Gastric cancer	1	202,308	6,563	195,745	0.90 (0.68, 1.20)	0.477
Colorectal cancer (Overall)	1	202,807	7,062	195,745	1.14 (0.97, 1.35)	0.112
Hepatocellular carcinoma	1	197,611	1,866	195,745	0.90 (0.57, 1.41)	0.64
Biliary tract cancer	1	196,084	339	195,745	0.74 (0.39, 1.38)	0.344
Pancreatic cancer	1	196,187	442	195,745	1.15 (0.56, 2.36)	0.696
Ovarian cancer (Overall)	1	90,451	720	89,731	0.65 (0.38, 1.12)	0.123
Endometrial cancer (Overall)	1	90,730	999	89,731	0.91 (0.57, 1.44)	0.685
Cervical cancer	1	90,336	605	89,731	0.69 (0.41, 1.15)	0.157
Prostate cancer (Overall)	1	109,347	5,408	103,939	0.85 (0.67, 1.07)	0.163
Hematological malignancy	1	212,453	1,236	211,217	1.11 (0.74, 1.65)	0.612
Per unit increase in log(25(OH)D)						
Colorectal cancer (Distal colon)	1	-	-	22,848	0.74 (0.37, 1.50)	0.41
Colorectal cancer (Proximal colon)	1	-	-	22,848	1.16 (0.35, 3.84)	0.805
Colorectal cancer (Rectal)	1	-	-	22,848	1.21 (0.34, 4.29)	0.765
Pancreatic ductal adenocarcinoma	1	15,824	8,769	7,055	1.13 (0.71, 1.80)	0.6
Overian cancer (Low malignant potential)	1	44,044	3,103	40,941	1.02 (0.43, 2.42)	0.96
Per unit increase in RINT(25(OH)D)						
Colorectal cancer (Colon)	1	28,880	4,281	24,599	0.91 (0.76, 1.09)	0.289
Colorectal cancer (Rectal)	1	27,782	3,183	24,599	0.80 (0.55, 1.15)	0.229

B. Cancer survival Outcome Per SD increase in log(25(OH)D)	N of papers	Total participants	Cases	Controls	HR/OR (95% CI)	P value
Overall survival in patients with breast cancer	1	37,954	2,900	35,054	1.00 (0.81, 1.23)	0.985
Overall survival in patients with breast cancer (ER-positive)	1	23,059	1,333	21,726	1.09 (0.82, 1.45)	0.542
Per 25(OH)D-increasing allele score						
Disease-free survival in patients with hepatocellular carcinoma	1	98	46	52	1.78 (0.24, 13.31)	-
Overall survival in patients with hepatocellular carcinoma	1	100	30	70	0.36 (0.02, 5.41)	-

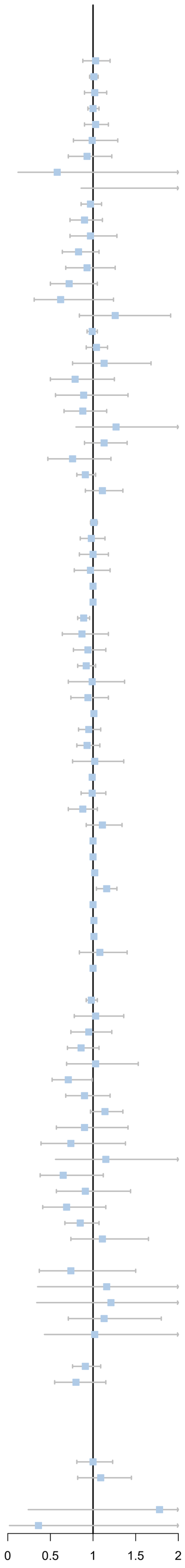

Figure 7

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Outcome	N of papers	Total participants	Cases	Controls	HR/OR (95% CI)	P value
Per 25 nmol/L increase in 25(OH)D						
Metabolic syndrome	2	13,048	3,469	9,579	0.98 (0.69, 1.39)	0.92
Any diabetes	1	96,423	5,705	90,718	0.78 (0.46, 1.32)	0.353
Type 2 diabetes	3	267,950	31,987	235,963	0.95 (0.87, 1.04)	0.284
Bacterial pneumonias	1	116,681	10,223	106,458	0.75 (0.63, 0.90)	0.003
Caries experience	1	5,545	1,933	3,612	0.83 (0.62, 1.12)	0.26
Dental general anesthetic	1	4,072	332	3,740	0.90 (0.49, 1.66)	0.72
Early caries onset	1	1,933	614	1,319	1.24 (0.74, 2.07)	0.37
Per doubling of 25(OH)D						
Metabolic syndrome	1	10,931	<3,275	>7,656	0.26 (0.06, 1.17)	0.08
Per SD increase in 25(OH)D						
Type 2 diabetes	1	923,892	80,983	842,909	0.96 (0.89, 1.03)	0.23
Nonalcoholic fatty liver disease	2	608,432	7,266	601,166	0.85 (0.73, 0.99)	0.035
Appendicitis	1	95,947	6,748	89,199	1.02 (1.00, 1.04)	0.074
Gastroesophageal reflux disease	1	90,043	4,883	85,160	1.01 (0.99, 1.02)	0.347
Diaphragmatic hernia	1	87,357	2,007	85,350	0.99 (0.97, 1.01)	0.247
Inguinal hernia	1	92,456	7,106	85,350	1.00 (0.97, 1.03)	0.987
Irritable bowel syndrome	1	84,575	1,806	82,769	1.01 (0.99, 1.02)	0.284
Liver cirrhosis	1	94,918	233	94,685	0.99 (0.97, 1.01)	0.55
Peptic ulcer	1	86,316	1,156	85,160	1.00 (0.98, 1.02)	0.933
Chronic kidney disease	1	117,165	12,385	104,780	1.03 (0.98, 1.08)	0.217
Longevity	1	123,694	18,444	105,250	0.92 (0.82, 1.02)	0.123
Cataract	1	95,576	9,880	85,696	1.01 (1.00, 1.02)	0.104
Glaucoma	1	96,499	3,463	93,036	1.01 (1.00, 1.03)	0.063
Chronic obstructive pulmonary disease	1	86,358	2,372	83,986	1.01 (1.00, 1.02)	0.169
Non-allergic rhinitis	1	11,634	2,028	9,606	0.94 (0.59, 1.49)	0.782
COVID-19 susceptibility (C1_EUR)	1	127,637	11,181	116,456	1.43 (0.41, 5.00)	0.57
COVID-19 susceptibility (C2_EUR)	1	2,298,674	87,870	2,210,804	1.01 (0.97, 1.05)	0.414
Per SD increase in log(25(OH)D)						
Type 2 diabetes	3	1,448,251	130,332	1,317,919	0.95 (0.90, 0.99)	0.027
Obesity class 1 (BMI ?30 kg/m2)	1	98,697	32,858	65,839	1.13 (1.00, 1.28)	0.059
Obesity class 2 (BMI ?35 kg/m2)	1	72,546	9,889	62,657	1.10 (0.89, 1.35)	0.361
Obesity class 3 (BMI ?40 kg/m2)	1	50,364	2,896	47,468	0.96 (0.65, 1.41)	0.831
Gout	1	69,374	2,115	67,259	1.45 (1.03, 2.04)	0.031
Benign oesophageal neoplasm	1	321,302	195	321,107	0.90 (0.42, 1.95)	0.793
Liver cirrhosis	1	212,453	2,184	210,269	1.14 (0.78, 1.66)	0.49
Endometriosis	1	103,106	734	102,372	1.15 (0.73, 1.83)	0.539
Kidney stone disease	1	395,043	6,535	388,508	1.47 (1.22, 1.77)	<0.001
Nephrotic syndrome	1	212,453	957	211,496	1.19 (0.76, 1.86)	0.442
Urolithiasis	1	212,453	6,638	205,815	1.01 (0.83, 1.23)	0.942
Uterine fibroids	1	100,964	5,954	95,010	0.86 (0.69, 1.07)	0.174
Chronic obstructive pulmonary disease	1	204,907	3,315	201,592	1.14 (0.86, 1.51)	0.359
Interstitial lung disease	1	212,453	806	211,647	1.08 (0.62, 1.86)	0.791
Acute respiratory distress syndrome	1	2,833	1,250	1,583	0.99 (0.67, 1.45)	0.938
Chronic hepatitis B	1	212,453	1,394	211,059	0.92 (0.61, 1.41)	0.714
Chronic hepatitis C	1	212,453	5,794	206,659	0.98 (0.81, 1.20)	0.855
COVID-19 hospitalization (B1)	1	10,908	2,430	8,478	1.23 (0.85, 1.77)	-
COVID-19 hospitalization (B2)	1	2,084,350	13,641	2,070,709	1.20 (1.00, 1.40)	0.032
COVID-19-positive cases versus COVID-19-negative controls (D1)	1	127,879	11,085	116,794	1.05 (0.92, 1.20)	-
COVID-19 severity (A2)	1	1,489,959	6,179	1,483,780	1.20 (0.94, 1.50)	0.16
Pulmonary tuberculosis	1	212,453	549	211,904	1.02 (0.54, 1.92)	0.959
Cataract	1	212,453	24,622	187,831	1.14 (1.03, 1.28)	0.016
Senile cataract	1	321,302	59,522	261,780	0.99 (0.90, 1.10)	0.911
Other cataract	1	321,302	17,699	303,603	0.84 (0.72, 0.97)	0.021
Glaucoma	1	212,453	5,761	206,692	1.09 (0.89, 1.34)	0.408
Caries in permanent teeth	1	12,935	<5,875	>7060	1.00 (0.76, 1.23)	0.97
Caries in primary teeth	1	16,572	<6,922	>9650	1.06 (0.81, 1.31)	0.66
Periodontal disease	1	212,453	3,219	209,234	1.17 (0.88, 1.55)	0.276
Periodontitis	1	45,563	17,353	28,210	1.04 (0.97, 1.12)	0.297
Drug eruption	1	210,081	430	209,651	0.68 (0.29, 1.61)	0.382
Keloid	1	212,453	812	211,641	1.63 (0.85, 3.12)	0.14
Fatigue (self-reported tiredness)	1	327,478	19,526	307,952	0.95 (0.79, 1.15)	0.62
Hearing impairment	1	52,409	6,527	45,882	0.95 (0.79, 1.15)	0.601
Per unit increase in log(25(OH)D)						
Prediabetes	1	10,655	3,915	6,740	0.99 (0.96, 1.01)	-
Type 2 diabetes	1	10,655	1,565	9,090	0.98 (0.95, 1.02)	-
Per unit increase in RINT(25(OH)D)						
Dyslipidemia	1	-	-	-	0.95 (0.92, 0.99)	0.007
Macular degeneration	1	117,890	2,726	115,164	0.96 (0.86, 1.08)	0.489
Per 25(OH)D-increasing allele score						
Type 2 diabetes	1	44,927	-	-	1.00 (1.00, 1.01)	0.12