Association between vitamin D supplementation and mortality: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To investigate whether vitamin D supplementation is associated with lower mortality in adults.

DESIGN

Systematic review and meta-analysis of randomised controlled trials.

DATA SOURCES

Medline, Embase, and the Cochrane Central Register from their inception to 26 December 2018.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised controlled trials comparing vitamin D supplementation with a placebo or no treatment for mortality were included. Independent data extraction was conducted and study quality assessed. A meta-analysis was carried out by using fixed effects and random effects models to calculate risk ratio of death in the group receiving vitamin D supplementation and the control group.

MAIN OUTCOME MEASURES

All cause mortality.

RESULTS

52 trials with a total of 75 454 participants were identified. Vitamin D supplementation was not associated with all cause mortality (risk ratio 0.98, 95% confidence interval 0.95 to 1.02, I^2=0%), cardiovascular mortality (0.98, 0.88 to 1.08, 0%), or non-cancer, non-cardiovascular mortality (1.05, 0.93 to 1.18, 0%). Vitamin D supplementation statistically significantly reduced the risk of cancer death (0.84, 0.74 to 0.95, 0%). In subgroup analyses, all cause mortality was significantly lower in trials with vitamin D_3 supplementation than in trials with vitamin D_2 supplementation (P for interaction=0.04); neither vitamin D_3 nor vitamin D_2 was associated with a statistically significant reduction in all cause mortality.

CONCLUSIONS

Vitamin D supplementation alone was not associated with all cause mortality in adults compared with placebo or no treatment. Vitamin D supplementation reduced the risk of cancer death by 16%. Additional large clinical studies are needed to determine whether vitamin D_3 supplementation is associated with lower all cause mortality.

STUDY REGISTRATION

PROSPERO registration number CRD42018117823.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational studies showed that low vitamin D levels were associated with increased mortality from life threatening conditions such as cancer and cardiovascular disease

Clinical data examining the effect of vitamin D supplementation on mortality reduction are inconsistent

WHAT THIS STUDY ADDS

Vitamin D supplementation alone was not associated with all cause mortality in adults compared with placebo or no treatment

Vitamin D supplementation reduced the risk of cancer death

Introduction

Vitamin D supplementation has been advocated for maintaining or even improving musculoskeletal health. Evidence from observational studies indicates that low vitamin D status is associated with higher mortality from life threatening conditions such as cancer and cardiovascular disease.[1 2] Therefore, supplemental vitamin D has been viewed as a potential strategy for preventing non-skeletal chronic diseases.[3-5] If adequate vitamin D concentrations were to reduce risk of death from a wide variety of medical conditions, vitamin D supplementation would be a safe, economical, and widely available method to reduce mortality.

Clinical data examining the effect of vitamin D supplementation on mortality reduction are inconsistent. Observational studies have revealed an inverse association of vitamin D status and mortality.[6-9] Previous systemic reviews and meta-analyses of randomised controlled trials suggested that vitamin D supplementation has a small effect on total mortality.[5 10 11] Interpretation of these reviews is difficult because they include trials of vitamin D administered with calcium, which has been associated with uncommon but important side effects (eg, cardiovascular events).[12-15] Additionally, these reviews lack sufficient detail (eg, community versus institution settings), and trial sequential analysis showed that the pooled sample size failed to meet the optimum size.[10 11]

Recently, additional trials[16-33] assessing the effect of vitamin D supplementation on mortality have become available, which have approximately doubled the number of trial participants. Among these trials, the Vitamin D and Omega 3 Trial (VITAL) did not confirm the benefit of vitamin D supplementation on mortality.[32] Because of the conflicting evidence, limitations of previous reviews, and availability of new data, we aimed to conduct a systematic review and meta-analysis of randomised controlled trials to evaluate the effect of vitamin D supplementation on all cause mortality.

Methods

Protocol and guidance

This study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-

Analysis (PRISMA).[34] The protocol for this review was registered with PROSPERO (CRD42018117823).

Inclusion criteria

We considered trials to be eligible if they enrolled adults (age ≥18) with any health condition; if they compared vitamin D supplements at any dose with placebo or no treatment (when other agents were also given (eg, calcium), they had to be the same dosage in all groups); if they provided information on deaths from all causes (non-accidental) or any cause reported separately; and if they were randomised controlled trials (including quasi randomised and cluster randomised trials).

Exclusion criteria

We excluded studies if they were case reports, case series, or observational studies; if all the participants received vitamin D; if they included pregnant or lactating women, or critically ill patients; if they used hydroxylated vitamin D or vitamin D analogues (which could differ from native vitamin D in effect and safety, including lower risk of fall[35] and higher risk of hypercalcaemia[10 35]).

Outcomes

The primary outcome was all cause mortality. Secondary outcomes were cancer mortality, cardiovascular mortality, non-cancer or non-cardiovascular mortality, cerebrovascular disease mortality, and ischaemic heart disease mortality. Supplemental eTable 1 shows the definitions of these outcomes.

Search strategy

One of the authors (PX) conducted the search of several databases: Medline (Ovid), Embase (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), from inception to 26 December 2018. We also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform to identify ongoing or unpublished eligible trials. To maximise the search for relevant articles, we reviewed reference lists of identified trials and systematic reviews. We did not apply language restrictions. Supplemental eTable 2 presents the search strategy.

Study selection

After removal of duplicates, two independent researchers (YZ and LJ) screened all titles and abstracts. They obtained full texts and performed further screening when studies were deemed eligible. Disagreements were resolved by consensus.

Data collection process

Two independent researchers (YZ and LJ) used a standard data extraction form to extract data from the included trials. When randomised controlled trials had more than two arms, we pooled data from the separate treatment arms. When a study mentioned an outcome of interest without providing estimates, we contacted the author for the data. Disagreements were resolved by consensus.

Assessment of risk of bias and quality of evidence

Two researchers (YZ and LJ) independently assessed the quality of all included trials by using the Cochrane Collaboration risk of bias tool.[36] They also examined the quality of evidence for outcomes using the grading of recommendations assessment, development, and evaluation (GRADE) approach.[37]

Data synthesis

We performed statistical analyses using RevMan (version 5.3.3; The Cochrane Collaboration) and the meta package in R (version 3.4.3; R Project for Statistical Computing). Analyses for all outcomes were conducted on an intention to treat basis. We used risk ratios and their associated 95% confidence intervals to assess outcomes, and considered a P value less than 0.05 to be statistically significant. We assessed heterogeneity using the I^2 test.[38] If significant heterogeneity was not present (I^2<50%), we used fixed effects models to pool outcomes; we used random effects models when significant heterogeneity was present (I^2≥50%). The possibility of small study effects was assessed qualitatively by visual estimate of the funnel plot and quantitatively by calculation of the Egger test, the Begg test, and the Harbord test.[39]

Trial sequential analysis

We performed trial sequential analysis to explore whether cumulative data were adequately powered to evaluate outcomes. Trial sequential analysis (version 0.9.5.10)[40] was used to maintain an overall 5% risk of type I error and 80% power. We initially anticipated an intervention effect of a 10% relative risk reduction for all cause mortality. In additional analyses, we used progressively smaller thresholds (7.5% and 5%) until the optimum sample size exceeded the actual sample size.

Subgroup analyses

We performed several subgroup analyses to test interactions according to dose (≥2000 and <2000 IU/day); type of vitamin D (vitamin D_2 and vitamin D_3); timing of treatment (daily and intermittently); baseline 25 hydroxyvitamin D (≥50 and <50 nmol/L); and mean age (≥70 and <70 years). We conducted retrospective subgroup analyses based on length of follow-up (at least three years and less than three years); year of publication (before 2014 and in or after 2014); sex (female and both sexes); residential status (community and institution); bolus (yes and no); intervention (vitamin D and calcium with vitamin D); and latitude (≥40° and <40°).

Sensitivity analyses

We conducted sensitivity analyses by excluding trials with high or unknown risk of bias; excluding trials with high risk or unknown risk of bias of the different domains; excluding quasi randomised or

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cluster randomised trials; excluding the largest trial; excluding trials with a follow-up of less than one year; using random effect models; adding trials that had been excluded for using vitamin D administered with calcium; and adding trials that had been excluded for using hydroxylated vitamin D or vitamin D analogues.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing of results. The results will be disseminated to a wide audience, including members of the public, patients, health professionals, and experts in the specialty through social media and networks.

Results

Eligible studies and study characteristics

We initially identified 21 425 records, and included 52 eligible trials[16-33 41-74] in the final meta-analysis (fig 1). Table 1 shows a summary of included trials and supplemental eTables 3 and 4 give details of those trials. The trials comprised 75 454 participants, with 8033 all cause deaths, 1331 deaths from cardiovascular disease, 877 deaths from cancer, and 1045 deaths from non-cancer, non-cardiovascular disease. Supplemental eTable 5 summarises the details of three large ongoing randomised trials.

Supplemental eFigures 1 and 2 show risk of bias. Twenty one trials had a low risk of bias, 18 trials had an unclear risk, and 13 trials had a high risk of bias. Using the GRADE summary of evidence, the quality of evidence for the primary outcome was high (supplemental eTable 6).

Primary outcome: all cause mortality

All 52 trials reported all cause mortality. There was no statistically significant difference in all cause mortality between the vitamin D supplementation group and the control group (risk ratio 0.98, 95% confidence interval 0.95 to 1.02, I^2=0%; fig 2). In trial sequential analysis, the information size of all cause mortality met the required size of 10% and 7.5% relative risk reduction; however, futility was not reached in our additional trial sequential analysis with 5% relative risk reduction (supplemental eFigures 3-5). Funnel plot analysis showed no asymmetry (supplemental eFigure 6); additionally the Egger test (P=0.412), Begg test (P=0.282), and Harbord test (P=0.341) detected no significant small study effects. The meta-analysis results for all cause mortality were robust in sensitivity analyses (supplemental eTable 7).

Subgroup analyses found that all cause mortality was significantly lower among trials with vitamin D_3 supplementation than in trials with vitamin D_2 supplementation (P for interaction=0.04; table 2), although neither group was associated with all cause mortality. Meta-regressions found that all cause mortality was significantly lower in trials with longer follow-up (P for interaction=0.04; supplemental eFigures 9 and 10).

Secondary outcome: other mortality

Vitamin D supplementation was associated with significant reduction in cancer mortality (risk ratio 0.84, 95% confidence interval 0.74 to 0.95, I^2=0%; fig 3). However, benefit was only seen in participants receiving vitamin D_3 supplementation not vitamin D_2 supplementation (P for interaction=0.11; supplemental eTable 8). We found no statistically significant difference between groups in cardiovascular mortality (0.98, 0.88 to 1.08, I^2=0%) or non-cancer, non-cardiovascular mortality (1.05, 0.93 to 1.18, I^2=0%). Vitamin D supplementation did not reduce the risk of death from cerebrovascular disease (1.04, 0.84 to 1.29, I^2=0%; supplemental eTable7) or ischaemic heart disease (0.96, 0.81 to 1.15, I^2=0%; supplemental eTable 8).

Discussion

In this meta-analysis of 52 randomised controlled trials with a total of 75 454 participants, vitamin D supplementation was not significantly associated with total mortality (risk ratio 0.98, 95% confidence interval 0.95 to 1.02). The findings suggest that vitamin D supplementation reduced cancer mortality by 16% (95% confidence interval 0.74 to 0.95), but not mortality from cardiovascular disease, cerebrovascular disease, or ischaemic heart disease.

Principal findings and comparison with other studies

The results of this study on all cause mortality differ from two previous systematic reviews.[5 10 11] A Cochrane review in 2014 found that vitamin D supplementation decreased all cause mortality in analyses of 56 trials with a total of 95 286 participants (relative risk 0.97, 95% confidence interval 0.94 to 0.99, P=0.02).[10] In the same year, a systematic review by Bolland and colleagues that included 40 trials with a total of 81 173 participants also suggested a small effect on all cause mortality (0.96, 0.93 to 1.00, P=0.04).[11] The previous reviews probably reached more optimistic conclusions as a result of different selection criteria and newly published trials. Compared with these reviews,[10 11] we excluded more than 10 trials totalling approximately 50 000 participants of vitamin D administered with calcium, six trials[75-81] of hydroxylated vitamin D or vitamin D analogues, and one trial[82] retracted in 2017. To determine whether the null finding was driven by excluding trials which had been included in previous reviews, we performed two sensitivity analyses by adding trials that were originally excluded, and confirmed the results of the overall analysis. Moreover, this study additionally included 18 randomised controlled trials[16-33] published after 2014, so that the more recent trials accounted for 50.3% (38 019/75 454) of the total number of participants.

In contrast to the results for total mortality, this study found that vitamin D supplementation reduced

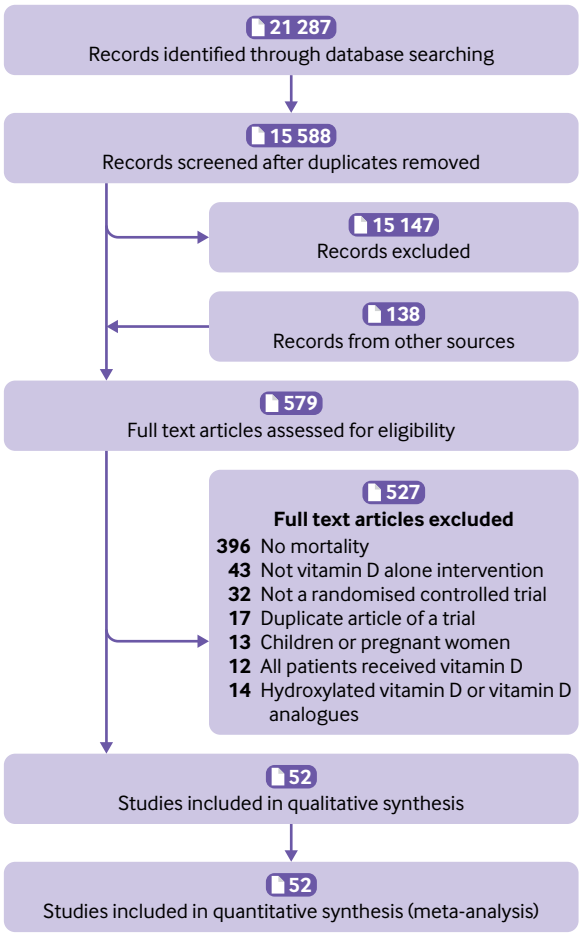

Fig 1 | Search strategy and final included and excluded studies

cancer mortality by 16%. The results of previous reviews on cancer mortality have been inconsistent. In 2014, a Cochrane review by Bjelakovic and colleagues presented low quality evidence that vitamin D supplementation resulted in a decrease in cancer mortality (relative risk 0.88, 95% confidence interval 0.78 to 0.98), but suggested that the required information size was not reached.[83] In parallel, two systematic reviews published similar results.[11 84] However, their meta-analyses were limited by the number of trials (n≤4), administration of a generally low dose of vitamin D (≤1100 IU/day), and mixed interventions (vitamin D plus calcium). In 2018, a meta-analysis by Goulão and colleagues did not find evidence to suggest that vitamin D supplementation alone reduced cancer mortality (1.03, 0.91 to 1.15).[85] After we submitted our current study for initial review by *The BMJ*, an additional meta-analysis by Keum and colleagues was published.[86] Their review found that vitamin D supplementation significantly reduced cancer mortality (0.87, 0.79 to 0.96).[86] Our findings on cancer mortality are consistent with those of Keum and colleagues, but some of the methods used in the two studies differ. The study by Keum and colleagues included trials of hydroxylated vitamin D, vitamin D analogues, and vitamin D administered with calcium, which were excluded in our study. Moreover, our study provided absolute and relative risks, evaluated the quality of the evidence by using the GRADE approach, and explored the optimum sample size with trial sequential analysis. More importantly, our study found that reduced cancer mortality was only seen with vitamin D_3 supplementation, not with vitamin D_2 supplementation.

An important finding from our subgroup analysis was that the effect of vitamin D differs for vitamin D_2 and D_3 supplementation. We found that all cause mortality was significantly lower among trials with vitamin D_3 supplementation than in trials with vitamin D_2 supplementation; however neither supplement was associated with statistically significant reduced risk. Similarly, vitamin D_3 supplementation reduced the risk of cancer mortality, but vitamin D_2 did not. The different effect on mortality of vitamin D_2 and D_3 might be explained by the diverse effect on raising 25 hydroxyvitamin D concentrations. Historically, vitamin D_2 and vitamin D_3 were considered to be equally effective at raising 25 hydroxyvitamin D concentrations. Currently, the comparative efficacy of vitamins D_2 and D_3 has been investigated in several intervention trials, with most indicating that vitamin D_3 increases 25 hydroxyvitamin D concentrations more efficiently than vitamin D_2.[87 88] A Cochrane review in 2014 found that vitamin D_3 seemed to reduce total mortality (risk ratio 0.94, 95% confidence interval 0.91 to 0.98), whereas vitamin D_2 had no statistically significant beneficial effects on total mortality (1.02, 0.96 to 1.08).[10] However, the Cochrane review did not reveal heterogeneity between vitamin D_2 and D_3. Therefore, we should be cautious about the strength of the evidence that vitamin D_3 reduced all cause mortality (0.95, 0.90 to1.00, P=0.06).

Vitamin D_3 is the most widely used type of vitamin D supplementation and has a clinically relevant effect of reducing all cause mortality by 5%, with the P value and 95% confidence interval close to the level of formal statistical significance. The current study is not a positive study, but it is also not an unambiguously negative study. In addition, subgroup

Table 1 | Summary characteristics of included studies

Characteristics	No of trials (No of participants)
Eligible studies:	
Total No of trials (No of participants)	52 (75 454)
Median (IQR) follow-up (years)	1.2 (0.8-3)
Follow-up at least three years	14 (56 429)
Median (IQR) No of participants	281 (129-737)
Total No of deaths	8033
Median (IQR) % female	71 (42-100)
Median (IQR) age (years)	74 (65-80)
Country:	
European	29 (32 954)
American	10 (31 230)
Asian-Pacific	11 (42 316)
International country	1 (518)
Baseline 25 hydroxyvitamin D (nmol/L):	
<25	5 (290)
25-50	49 (42 161)
50-75	30 (17 410)
>75	2 (165)

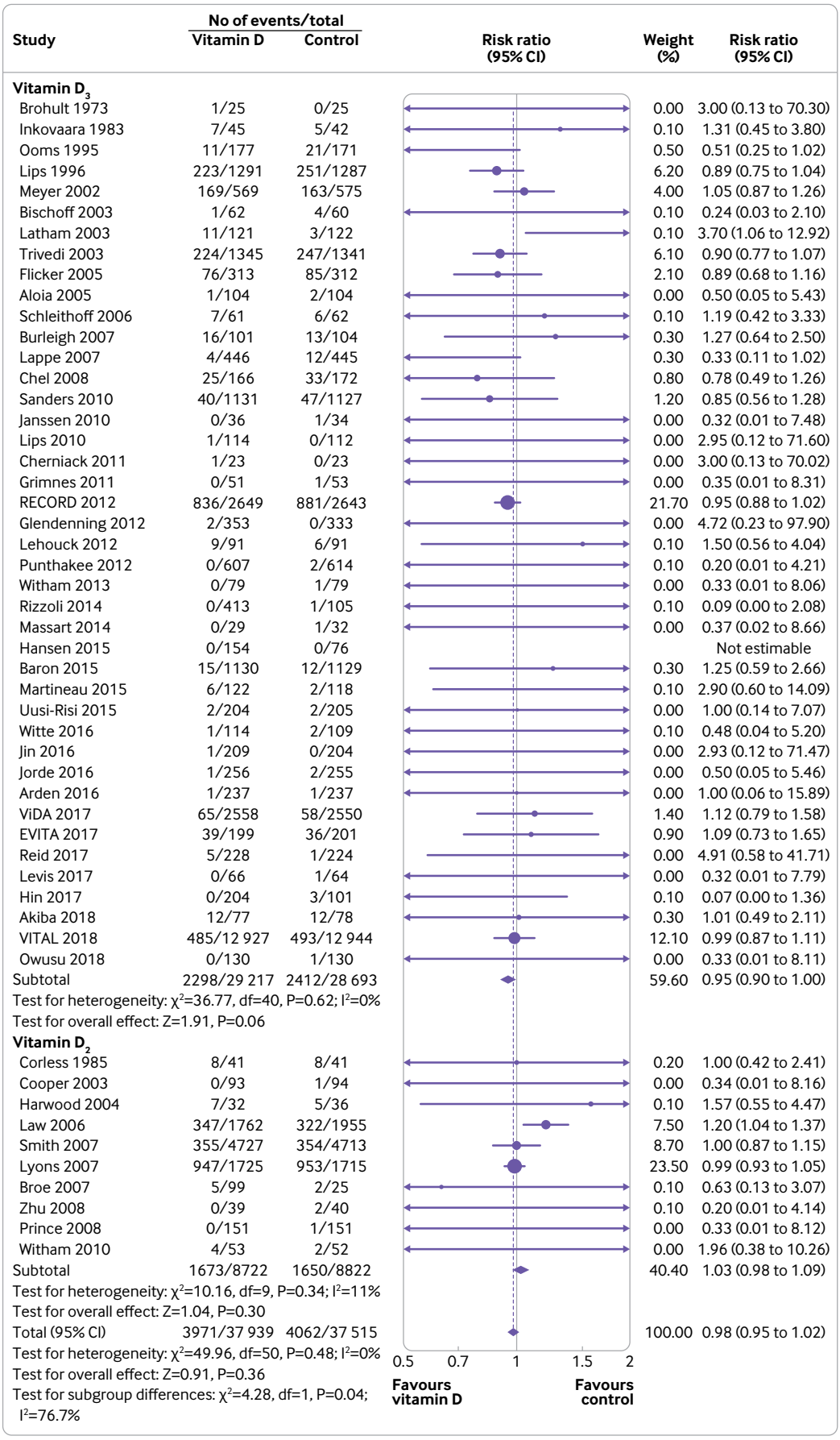

Fig 2 | Forest plot of all cause mortality of trials evaluating vitamin D_3 and vitamin D_2 supplementation

Table 2 | Subgroup analysis of the effect of vitamin D on all cause mortality

Subgroup title	No of trials	No of participants	I^2 (%)	Risk ratio (95% CI)	P for interaction
Overall	52	75 454	0	0.98 (0.95 to 1.02)	—
No of participants:					
≥2000	11	63 793	24	0.99 (0.95 to 1.03)	0.43
<2000	41	11 661	0	0.93 (0.80 to 1.08)	
No of events:					
≥200	8	54 168	0	0.99 (0.95 to 1.03)	0.63
<200	44	21 286	0	0.95 (0.84 to 1.09)	
Age (years):					
≥70	22	39 390	0	1.00 (0.90 to 1.11)	0.76
<70	30	36 064	0	0.98 (0.94 to 1.02)	
Sex:					
Female	15	18 019	0	0.94 (0.85 to 1.04)	0.28
Male and female	37	57 435	0	0.99 (0.95 to 1.03)	
Baseline mean 25 hydroxyvitamin D (nmol/L):					
≥50	13	40 664	0	0.99 (0.90 to 1.08)	0.92
<50	31	26 052	21	0.99 (0.94 to 1.05)	
Year of publication:					
Before 2014	34	37 435	0	0.98 (0.94 to 1.02)	0.65
In or after 2014	18	28 019	0	1.01 (0.90 to 1.12)	
Type of vitamin D:					
Vitamin D_3	42	57 910	0	0.95 (0.90 to 1.00)	0.04*
Vitamin D_2	10	17 544	11	1.03 (0.98 to 1.09)	
Daily dose equivalent (IU):					
<2000	31	40 133	0	0.97 (0.94 to 1.01)	0.45
≥2000	17	34 567	5	1.02 (0.91 to 1.13)	
Timing:					
Daily	32	48 279	0	0.98 (0.93 to 1.04)	0.47
Intermittently	16	26 266	0	0.98 (0.93 to 1.03)	
Bolus or not:					
Bolus	11	25 063	0	0.99 (0.93 to 1.04)	0.84
Non-bolus	37	49 482	0	0.98 (0.93 to 1.03)	
Residential status:					
Community	42	62 813	0	0.97 (0.92 to 1.02)	0.40
Institution	10	12 641	0	1.00 (0.95 to 1.05)	
Follow-up:					
At least three years	13	57 807	0	0.97 (0.93 to 1.01)	0.36
Less than three years	39	17 647	0	1.01 (0.94 to 1.10)	
Intervention:					
Vitamin D	35	63 114	0	1.00 (0.96 to 1.05)	0.10
Vitamin D plus calcium	17	12 340	0	0.93 (0.87 to 1.00)	
Latitude:					
≥40°	38	41 801	0	0.99 (0.95 to 1.03)	0.70
<40°	13	33 135	0	0.97 (0.87 to 1.07)	

*Statistically significant.

analyses are observational by nature and are not based on randomised comparisons.[8 9] Therefore, the effect of vitamin D_3 on all cause mortality requires additional evidence, preferably gathered by future large randomised controlled trials.

A further important finding from meta-regression was that all cause mortality was statistically significantly lower in trials with longer follow-up. Sensitivity analysis found a potential effect of vitamin D supplementation on all cause mortality after trials with a follow-up of less than one year were excluded (risk ratio 0.97, 95% confidence interval 0.93 to 1.00). However, subgroup analysis did not find a statistically significant difference in the effect of vitamin D supplementation on mortality in trials with a follow-up of less than three years and more than three years (P=0.37). Additionally, the previous meta-analysis did not find a subgroup difference according to the length of follow-up.[10 11]

The VITAL trial reported increasing benefit over time.[32] Although no significant differences relate to cancer mortality (risk ratio 0.83, 95% confidence interval 0.67 to 1.02) or all cause mortality (0.99, 0.87 to 1.12), after excluding the first one and two years of follow-up, the risk ratio was significantly reduced to 0.75 for cancer mortality (95% confidence interval 0.59 to 0.96) and was slightly reduced to 0.96 for all cause mortality (0.84 to 1.11). Therefore, the length of follow-up could modify the effect of vitamin D supplementation on all cause mortality.

Strengths and limitations

This systematic review and meta-analysis has several methodological strengths. We followed the recommendations of the Cochrane Collaboration and PRISMA statement, including a priori protocol. This study also included a rigorous assessment of the quality of evidence using the GRADE approach (the quality for the primary outcome was high) and of the minimum information size required in trial sequential analysis (the study met the optimum size).

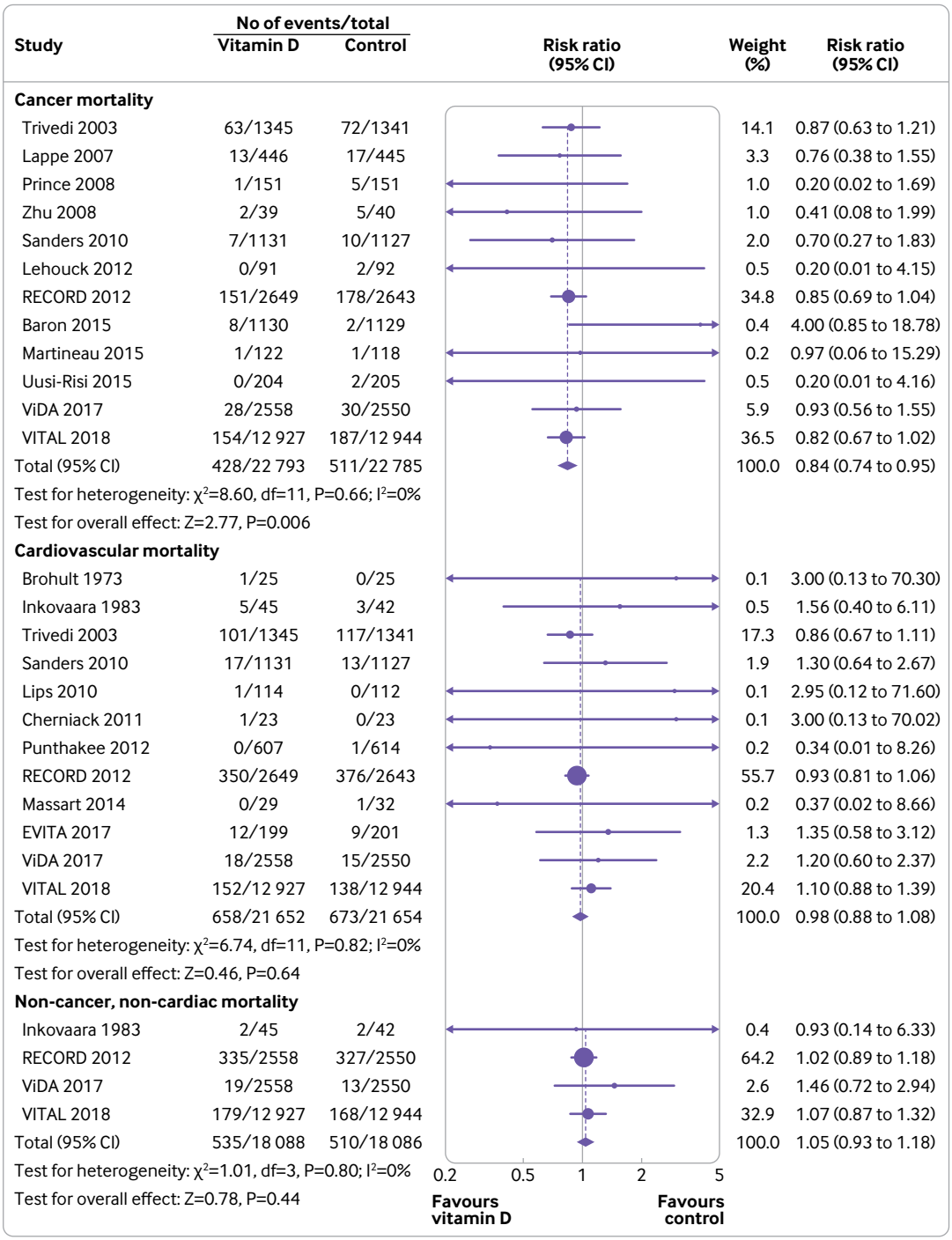

Fig 3 | Forest plot of cancer mortality, cardiovascular mortality, and non-cancer, non-cardiovascular mortality of trials evaluating vitamin D supplementation

Our study has important limitations. The study was based solely on published trials that reported mortality outcomes. However, most trials of vitamin D supplementation did not report mortality, which suggests that substantial selective reporting was likely. Also, all cause mortality reported among all included trials was the secondary outcome of the trials. Data for this secondary outcome might have been collected differently than data for the primary outcome in the trials.

Most included trials allowed personal supplementation with low dose vitamin D in the control group. In the VITAL trial,[32] for example, 42.5% of participants in the control group used vitamin D supplementation (≤800 IU/day). The high prevalence of vitamin D supplementation in the control group made it more difficult to distinguish between the treatment and control groups.

The dose of vitamin D used in included trials varied. Our study could not accurately compare equivalent daily vitamin D supplementation dose in the included trials because they all had different treatment regimens and dosing intervals (daily,

weekly, monthly, or bolus doses). This might be one of the reasons why this study did not determine an effective daily dose of vitamin D supplementation. Furthermore, the vitamin D status before, during, and after treatment is useful to determine the effectiveness of vitamin D supplementation in improving the actual vitamin D status. Long term vitamin D status is expected to be a much more accurate, reliable, and important clinical parameter compared with a daily dose of vitamin D supplementation. However, previous trials were limited in providing such data. These limitations and uncertainties associated with vitamin D supplementation dose and vitamin D status in treatment and control groups warrant further investigation.

The baseline 25 hydroxyvitamin D concentrations of trial participants have not been low enough, which could partly contribute to the null finding on the association of vitamin D supplementation and all cause mortality. Observational studies have indicated an increased mortality risk only at low 25 hydroxyvitamin D concentrations. An individual participant data meta-analysis of observational studies showed that the adjusted hazard ratio (95% confidence interval) for mortality in the 25 hydroxyvitamin D groups with concentrations less than 30, 30-40, and 40-50 nmol/L were 1.67 (1.44 to 1.89), 1.33 (1.16 to 1.51), and 1.15 (1.00 to 1.29), respectively, compared with participants with 25 hydroxyvitamin D concentrations of 75-100 nmol/L.[8] In this study, more than half of participants (40 664/66 716) from trials reported a baseline mean 25 hydroxyvitamin D concentration of more than 50 nmol/L.

Implications

Mortality is the most important clinical outcome. Our study size met the optimum sample size of 7.5% relative risk reduction and the pooled risk ratio was close to 1 with a narrow confidence interval. Our findings suggest that vitamin D supplementation did not have a clinically relevant effect on all cause mortality, and so there is little evidence that vitamin D supplementation reduces all cause mortality. However, vitamin D supplementation reduced cancer mortality by 16%. Therefore, this analysis supports the concept that the risk of cancer death could be reduced by vitamin D supplementation, and a more targeted intervention for this role might be appropriate.

The current study found that all cause mortality was significantly lower among trials with vitamin D_3 supplementation than in trials with vitamin D_2 supplementation, with a trend towards reduced all cause mortality in those taking vitamin D_3 (P=0.06). Similarly, vitamin D_3 supplementation reduced the risk of cancer death, but vitamin D_2 did not. Another finding from subgroup analysis suggested that all cause mortality was significantly lower in trials with longer follow-up, and that the benefit of reduced cancer mortality was seen in trials with longer follow-up (more than three years) but not in those with a shorter follow-up. According to these findings, supplementation with vitamin D_3 for at least three years should be considered. Additional large randomised controlled trials are needed to confirm the results from our subgroup analyses.

Several large ongoing trials have the potential to corroborate or refute our findings. In the D-Health trial (Australian New Zealand Clinical Trials Registry: ACTRN12613000743763), high dose vitamin D supplementation (60 000 IU/month) is being used to prevent mortality and cancer in Australian adults aged 60-79. The D-Health trial recently completed the recruitment of almost 21 315 participants, with a minimum of five years of follow-up. Using a similar study design, the VIDAL trial (Vitamin D and Longevity trial; ISRCTN46328341) is analysing the effect of intermittent high dose vitamin D supplementation (60 000 IU/month) on all cause mortality in adults aged 65-84 with a corrected serum calcium level of 2.65 mmol/L. The DO-HEALTH trial (Vitamin D3-Omega3-Home Exercise-Healthy Ageing and Longevity Trial; ClinicalTrials.gov identifier: NCT01745263) has recruited 2152 participants from five European countries aged 70 years and older. The specific aim is to establish whether vitamin D will prevent disease at an older age. The final results of the DO-HEALTH trial will be available in autumn 2019. Although none of these trials have screened for low baseline 25 hydroxyvitamin D for eligibility, all trials have used vitamin D_3 as the intervention.

Conclusions

Overall, vitamin D supplementation was not associated with all cause mortality, cardiovascular mortality, or non-cancer, non-cardiovascular mortality in adults. However, vitamin D supplementation was associated with a reduced risk of cancer mortality by 16%. There was a trend towards reduced all cause mortality with vitamin D_3 supplementation, which warrants further investigation.

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Contributors: FF and YZ conceived the study and designed the protocol. PX performed the literature search. YZ and LJ selected the studies and extracted the relevant information. JT, YF, and YZ synthesised the data. YZ wrote the first draft of the paper. All authors critically revised successive drafts of the paper and approved the final version. FF and YZ are the study guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required.

Data sharing: Additional data available from the corresponding author at fangfang1057@outlook.com.

The lead author (FF) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Web appendix: Supplemental e-material