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Review

Efficacy of vitamin D_3 supplementation on cancer mortality: Systematic review and individual patient data meta-analysis of randomised controlled trials

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ABSTRACT

To evaluate the effect of vitamin D_3 supplementation on cancer mortality in the general population and on prognosis in cancer patients, a systematic review and meta-analysis of randomised, placebo-controlled trials (RCTs) and individual patient data (IPD) was conducted. Overall, 14 RCTs with a total of 104,727 participants (2015 cancer deaths) were identified and 7 RCTs, including 90 % of all study participants (n = 94,068), could be included in the IPD meta-analyses. The main meta-analysis of the 14 RCTs yielded a statistically non-significant reduction in cancer mortality by 6 % (risk ratio (RR) [95%-confidence interval (95%CI)]: 0.94 [0.86–1.02]). Subgroup analyses revealed a 12 % lower cancer mortality in the vitamin D_3 group compared with the placebo group in 10 trials with a daily dosing regimen (RR [95%CI]: 0.88 [0.78–0.98]), whereas no mortality reduction was seen in 4 trials using a bolus regimen (RR [95%CI]: 1.07 [0.91–1.24]; p-value for interaction: 0.042). The IPD meta-analysis (RR [95%CI]: 0.93 [0.84; 1.02]) confirmed the finding of all trials. The IPD were used to test effect modification by age, sex, body mass index, ethnicity, baseline serum 25-hydroxyvitamin D concentration, adherence and cancer-related factors but no statistically significant findings were obtained in meta-analyses of all trials. When restricted to trials with daily dosing in a post-hoc analysis, adults aged ≥ 70 years (RR [95%CI]: 0.83 [0.77; 0.98]) and subjects with vitamin D_3 therapy initiation before cancer diagnosis (RR [95%CI]: 0.87 [0.69; 0.99]) appeared to benefit most from daily vitamin D_3 supplementation. Measurements of baseline 25-

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hydroxyvitamin D levels and inclusion of other than non-Hispanic White adults were too sparse in the trials to draw conclusions. Results for all-cause and cancer-specific survival of participants with cancer were comparable to those obtained in the general population for cancer mortality. In conclusion, vitamin D_3 did not reduce cancer mortality in the main meta-analysis of all RCTs because the observed risk reduction by 6 % was not statistically significant. However, a subgroup analysis revealed that vitamin D_3 administered daily, in contrast to bolus supplementation, reduced cancer mortality by 12 %.

1. Introduction

1.1. Rationale

Despite enormous efforts in prevention and therapy, cancer remains a major burden; in 2020, there were 19.3 million new cancer cases and approximately 10 million cancer deaths worldwide (International Agency for Research on Cancer, 2020). The number of new cancer diagnoses is growing due to the aging population as well as changing risk factors and is projected to reach 30.2 million new cases by 2040 (International Agency for Research on Cancer, 2022).

Vitamin D deficiency is prevalent worldwide and more common in cancer patients during cancer therapy than in the general population. The prevalence of vitamin D deficiency (defined as 25-hydroxyvitamin D (25(OH)D) levels $<$ 30 nmol/L) in representative population samples from the United States and Europe has been reported recently as 6 % and 13 %, respectively (Cashman et al., 2016; Schleicher et al., 2016). For example, in a study with 2912 colorectal cancer patients, a much higher vitamin D deficiency prevalence of 59 % was found during or shortly after first-line treatment and, in agreement with previous observational studies, low 25(OH)D levels were strongly associated with poorer survival (Maalmi et al., 2018; Maalmi et al., 2017; Markotic et al., 2019).

From a biological perspective, it is plausible that a sufficient vitamin D status has an impact on cancer prognosis: by binding to the vitamin D receptor (VDR), the active hormone 1,25-dihydroxyvitamin D (1,25 $(OH)_2D$) influences signaling pathways that regulate cell proliferation, differentiation, and cell survival, and thus acts as an anti-proliferative agent in many tissues and can slow the growth of malignant cells (Fleet et al., 2012). For example, animal experiments showed that 1,25 $(OH)_2D$ delays age-related changes via VDR-mediated activation of Nrf2, inhibiting oxidative stress and DNA damage, which are relevant aspects of tumorigenesis (Calabrese et al., 2010; Chen et al., 2019).

Meta-analyses of observational studies reported elevated risks of lung cancer, colorectal cancer, breast cancer, bladder carcinoma, and lymphoma in people with low serum 25(OH)D concentration (Garland and Gorham, 2017; Li et al., 2014; Zhang et al., 2015a,b). Systematic reviews further concluded that sufficient 25(OH)D levels ($\geq$50 nmol/L) are associated with better prognosis in patients with breast and colorectal cancers, whereas there have been too few studies for other cancer sites to draw conclusions (Maalmi et al., 2018; Toriola et al., 2014; Vaughan-Shaw et al., 2017; Yao et al., 2017). Moreover, low 25(OH)D levels were substantially related to increased cancer mortality in the general population (Heath et al., 2019). Mendelian randomisation studies conducted by consortia of large cohorts from Denmark, the UK Biobank, and the CVD-EPIC study supported a causal relationship between low 25(OH)D levels and cancer mortality whereas this was not observed when also subjects with adequate 25(OH)D levels were included in the analysis, like done in an earlier Mendelian randomisation study using only the UK Biobank data (Afzal et al., 2014; Ong et al., 2018; Sofianopoulou et al., 2021).

Evidence regarding vitamin D_3 and cancer mortality from randomised controlled trials (RCTs) is conflicting. Despite strong heterogeneity in study populations, intervention schemes, and other important design aspects, four out of seven previous systematic reviews and meta-analyses reported a statistically significant reduction in cancer mortality in those randomised to vitamin D_3 (Bjelakovic et al., 2014; Goulão et al., 2018; Goulão et al., 2020; Guo et al., 2022; Keum et al., 2022; Keum et al., 2019; Zhang et al., 2022; Zhang et al., 2020; Zhang et al., 2019). However, none of the previous systematic reviews collected unpublished results on cancer mortality from eligible studies and individual patient data (IPD).

1.2. Objectives

We aimed to evaluate the effect of vitamin D_3 supplementation on cancer mortality in the general population and on prognosis in cancer patients. Potential heterogeneity among trial results according to region, health status of the included population, vitamin D_3 dose, regimen (daily or bolus), and duration of treatment was investigated. We also performed IPD subgroup analyses to shed light on potential effect modifiers, including patient characteristics (such as age, sex, body mass index (BMI), ethnicity, baseline serum 25(OH)D concentration, and adherence) and cancer-related factors.

2. Methods

2.1. Protocol and reporting checklist

This systematic review was registered in PROSPERO before data collection to preclude data-driven analyses and selective reporting (CRD42020185566). In addition, the methods, including the selection criteria, the statistical analysis, outcomes, and subgroup and sensitivity analyses, were published in advance in a study protocol (Schöttker et al., 2021). This was developed in line with the "Preferred reporting items for systematic review and meta-analysis protocols" (PRISMA-P), the Cochrane Handbook for Systematic Reviews of Interventions, and the Institute of Medicine guideline (Institute of Medicine, 2011b; Higgins et al., 2022; Moher et al., 2015; Shamseer et al., 2015). Any deviations were recorded in an amendment log, describing the exact change and rationale (supplementary table 1). Reporting is in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis of Individual Participant Data (PRISMA-IPD (Stewart et al., 2015); see Supplementary table 2 for completed checklist).

2.2. Search strategy

One researcher (SK) searched for eligible RCTs in MEDLINE, ISI Web of Science (WoS) and Cochrane Central Register of Controlled Trials (CENTRAL) plus appropriate systematic reviews and meta-analyses in the Cochrane Database of Systematic Reviews (CDSR) and Kleijnen Systematic Reviews (KSR) Evidence from inception to January 18, 2022. The search strings shown in Supplementary table 3 were conceived by two researchers (SK and BS) and reviewed by a specialist for systematic bibliographic searches at the Central Library of the German Cancer Research Center (Andrea Heppert). SK searched for ongoing or completed RCTs with unpublished data in the WHO's International Clinical Trials Research Portal (ICTRP) and clinicaltrials.gov via CENTRAL. Reference lists of eligible studies were scanned to yield relevant articles via cross-referencing. No restrictions regarding time of publication, language, settings, or geographical locations were applied.

2.3. Inclusion and exclusion criteria for meta-analysis

2.3.1. Study type

Double-blind RCTs with parallel-group designs were included. Single-arm studies, observational studies (e.g., cohort and case-control studies) and other records (e.g., narrative reviews, dissertations, editorials, study protocols, clinical guidelines, commentaries, correspondences, and letters) were excluded.

2.3.2. Participants

Studies were included if they were conducted in the general population or in a population suffering from any specific chronic disease (e.g., HIV patients). Special populations such as pregnant or lactating women, infants, and COVID-19 patients were excluded. No other age restrictions were applied.

2.3.3. Interventions

Trials that used vitamin D_3 and bioequivalent substances (e.g., calcitriol (i.e., $1,25(OH)_2D$), alfacalcidol, calcifediol (i.e., 25(OH)D) in any dose and any regimen (e.g., daily/weekly/monthly intake) for at least six months were included. Co-administration with other medications or dietary supplements (e.g., calcium or chemotherapy) was allowed if all arms received the same therapy. Studies not permitting personal/private use of vitamin D_3 supplements were included as well. Trials were excluded if vitamin D_3 was supplied via fortified foods, or if vitamin D_2 or bioequivalent substances were used because it was already found not to affect mortality in a previous meta-analysis (Bjelakovic et al., 2014).

2.3.4. Comparators

Studies that used placebo as the comparator were included. Studies were excluded if they were designed as open-label trials, used no treatment as control or administered an active control (e.g., standard of care or lower vitamin D_3 doses than the intervention dose) instead of a placebo.

2.3.5. Outcomes

Studies required at least one cancer death per arm to be eligible and were included if risk ratios for cancer mortality or cancer survival were published. Results of the intention-to-treat approach were used, including all participants randomised, when both intention-to-treat and per-protocol results were given. We prioritized unadjusted summary estimates over adjusted estimates since studies adjusted for different covariates. Published results including a subsequent follow-up were used in the meta-analyses only when results covering solely the intervention period were not available. If studies reported cancer incidence or all-cause mortality as a primary outcome or in the framework of serious adverse events, the authors were contacted to obtain unpublished data on cancer outcomes. Studies were excluded if no data on at least one of the outcomes of interest were obtainable.

2.4. Data extraction for meta-analysis

We used EndNote and Rayyan QCRI (web application) to manage citations, title/abstract screening and full-text selection (Ouzzani et al., 2016). We removed duplicates using an Excel sheet and the Bramer methods (Bramer et al., 2016). SK screened all titles and abstracts for potentially relevant RCTs and systematic reviews. SK excluded studies/reviews that did not meet the broad inclusion criteria regarding the population, intervention, comparator, and study type. In a second step, the screening for study eligibility was defined by the outcomes “cancer mortality”, “cancer survival”, “all-cause mortality” and “cancer incidence”.

To gather unpublished cancer mortality data, SK contacted authors of trials that met the inclusion criteria but reported only all-cause mortality and/or cancer incidence, had a completed, prematurely ended, unknown or ongoing status but no publication, or had unclear descriptions of the study design or intervention to determine final inclusion.

The full-text screening was conducted in duplicate by a second researcher (AZ). Furthermore, two investigators (SK and AZ) independently extracted data from included studies using standard and predefined data extraction forms. Any disagreements were resolved by consensus and third-party adjudication (BS).

2.5. Eligibility for IPD meta-analyses

If more than 20 cancer deaths were reported, studies included in the meta-analysis of all trials were additionally eligible for the IPD meta-analysis. To collect IPD, SK and BS approached the authors of eligible trials, defined conditions to use their IPD, and entered into data use agreements. To ensure the integrity of the IPD, datasets were checked for plausibility, consistency, and completeness of relevant categorical and continuous variables and compared with published results. All mortality- and survival- related outcomes were restricted to the intervention period.

2.6. Statistical analyses

The computation of the summary risk ratios (RR), 95 % confidence intervals (95 % CI), the tests for heterogeneity, and publication bias were performed independently by two researchers: BS used Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ) and SK used the meta and metafor packages in R 4.1.3 (Balduzzi et al., 2019; Viechtbauer, 2010). The results were compared and, if there were discrepancies, the computations were checked and corrected by each analyst separately until the reasons for the inconsistencies were found and both researchers obtained the same results.

We used the DerSimonian and Laird method to fit random effects models (primary analysis) and the Mantel-Haenzel method to calculate fixed effects summary estimates (secondary analysis). Generally, results of the random effects model are shown and for the main meta-analyses, results of the fixed effects model are shown in addition (Deeks et al., 2022). Heterogeneity between studies was assessed by Cochran’s Q test, the I^2 index, and tau^2. Small-study effects and publication bias were evaluated via funnel plots and Egger’s test (Egger et al., 1997).

2.6.1. Meta-analyses of all trials

A meta-analysis of all trials was conducted for the outcome “cancer mortality”. To explore sources of heterogeneity, subgroup analyses regarding methodological trial differences were performed including trial duration, study population, region, dose, and treatment regimen. Pre-specified sensitivity analyses were also conducted by excluding studies with: (1) a high risk of bias; (2) not reporting intention-to-treat (ITT) results; and (3) with co-supplementation of calcium.

2.6.2. IPD meta-analyses

Unadjusted and adjusted Cox proportional hazards regression models were run with harmonized variable definitions for the obtained IPD. Analyses were not conducted in one pooled data set. Instead, a two-step approach was used for the meta-analyses, whereby the analyses were carried out on a study-specific basis, and subsequently the effect estimates were pooled using the random effects model. Five studies sent data to the German Cancer Research Center (Heidelberg, Germany) and were analysed there with the same analysis protocol independently by SK and BS using SAS 9.4 (Avenell et al., 2012; Manson et al., 2019; Scragg et al., 2018; Urashima et al., 2019; Wactawski-Wende et al., 2006). Co-authors from the FIND and D-Health studies undertook the analyses in-house using SAS code provided by BS (Neale et al., 2022; Virtanen et al., 2022).

Three main IPD meta-analyses were conducted using adjusted and unadjusted models:

1) Efficacy of vitamin D_3 supplementation for cancer mortality reduction in the general population.
2) Efficacy of vitamin D_3 supplementation for cancer-specific survival of cancer patients.
3) Efficacy of vitamin D_3 supplementation for overall survival of cancer patients.

To assess cancer survival endpoints from general population cohorts, the studies were restricted to patients with a history of cancer in the five years preceding the baseline, a cancer diagnosis during the trial, or cancer death during the trial. For patients with a history of cancer in the five years preceding baseline and who died of cancer during the intervention period, the survival time was calculated from baseline to death or end of the intervention. For participants with a cancer diagnosis during the trial, the survival time was counted from the date of cancer diagnosis until death or end of the trial.

To explore sources of heterogeneity, we conducted subgroup analyses according to participant characteristics: (1) in the general population data by participant age, sex, BMI, ethnicity, baseline 25(OH)D level, cancer diagnosis before baseline, and adherence (defined as "low" if < 80 % or "high" if ≥ 80 %); and (2) in cancer patients additionally by cancer stage, cancer site, and time of cancer diagnosis.

With the exception of adherence, the factors used for the subgroup analyses were also used as covariates for the adjusted models. We further tested interactions between the treatment variable (vitamin D_3 vs. placebo) and these covariates to identify potential effect modifiers. Variables with ≥ 5 % of missing data were not used in the multivariable model of the respective study but were used in subgroup analyses. No

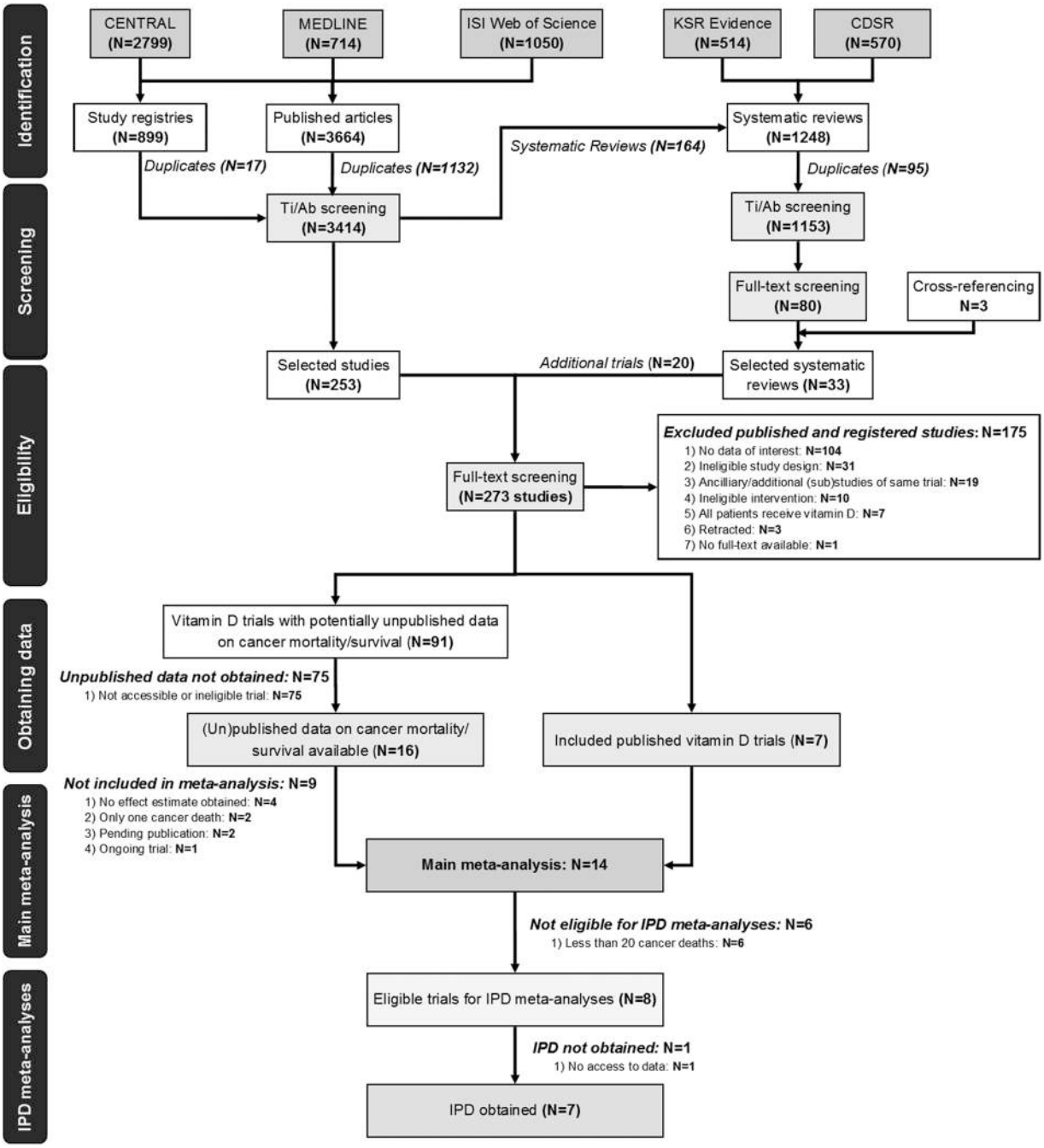

Fig. 1. Flow diagram of study selection. Abbreviations: CENTRAL Cochrane Central Register of Controlled Trials; CDSR Cochrane Database of Systematic Reviews; IPD individual patient data; KSR Kleijnen Systematic Reviews Ltd; Ti/Ab title/abstract.

imputation of missing covariate values was done and a complete case analysis approach was applied.

2.7. Risk of bias assessment

The risk of bias assessment of included studies was conducted for the outcome "cancer mortality" by two independent reviewers (SK, AZ) using the Cochrane risk-of-bias tool for randomised trials (RoB 2) (Sterne et al., 2019). They evaluated various domains of bias including aspects of trial design, conduct, and reporting. Cases of disagreement and critical points were discussed until a consensus was reached and documented accordingly.

2.8. Strength of body of evidence

The quality of evidence for the outcomes "cancer mortality", "overall cancer survival", "cancer-specific survival" was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2008).

3. Results

3.1. Study search and selection

The study search and selection process is summarised in Fig. 1. In our search for RCTs, we identified 3664 published articles and 899 registry records. Searches for systematic reviews and/or meta-analyses yielded 1248 potentially relevant records. After removal of duplicates and title/abstract screening, the full-text articles of 253 potentially eligible studies were identified. We identified a further 20 potentially eligible studies included in 33 previous systematic reviews. Overall, we reviewed the full-text articles of 273 studies, of which 175 studies met exclusion criteria as shown in Fig. 1 (Supplementary table 4 lists all excluded studies and reasons for exclusion).

From these articles, seven trials could be included directly in the meta-analysis. We also attempted contact with authors of 91 studies with potentially unpublished data on cancer mortality/survival or to clarify uncertainties (Supplementary table 5 for authors' (non-) responses). The authors of 16 studies responded but only seven trials met the inclusion criteria and could be included in the main meta-analysis. Based on published and acquired data, 14 RCTs were included in the main meta-analysis comparing vitamin D_3 and placebo for the endpoint "cancer mortality".

Eight trials with $\geq$ 20 cancer deaths were eligible for the IPD meta-analyses and seven provided data (Avenell et al., 2012; Manson et al., 2019; Neale et al., 2022; Scragg et al., 2018; Urashima et al., 2019; Virtanen et al., 2022; Wactawski-Wende et al., 2006). One trial's data (N = 2686) have been archived and are no longer accessible (Trivedi et al., 2003). No IPD data integrity issues were identified during our analysis.

3.2. Characteristics of included studies

The complete study characteristics of the included 14 RCTs are summarized in Table 1 and Supplementary table 6. The trials comprised a total of 104,727 participants; 1928 cancer deaths occurred within the intervention period and 87 additional cancer deaths occurred up to three years after the intervention. Two studies investigated cancer survival as the primary outcome, and seven trials examined cancer mortality as a secondary outcome. Five studies were conducted in Europe, four in North America (all in the United States), two in Australia/New Zealand, two in Asia (both in Japan), and one in Africa (Tanzania). Ten trials used a daily vitamin D_3 regimen ranging from 400 IU to 4000 IU daily. Four trials provided a large bolus dose of vitamin D_3 intermittently (60,000 IU monthly to 100,000 IU every four months). Two trials additionally featured a high initial dose at the beginning of the intervention followed by daily dosing. The duration of vitamin D_3 supplementation varied between one and seven years. Eleven studies measured the baseline 25 (OH)D in a subset or the entire population and the mean or median levels ranged from 37 to 77 nmol/L. Ten studies allowed personal vitamin D_3 supplementation in the control group, ranging from 200 IU to 2000 IU daily, and one study did not provide such information.

3.3. Main meta-analysis of all trials

3.3.1. Main pooled effect estimate

The pooled RR for vitamin D_3 supplementation and cancer mortality was 0.94 (95 % CI: 0.86; 1.02, p = 0.153) in both, fixed and random-effects models (Fig. 2), with no indication of heterogeneity (Cochran's Q = 10.96 (p = 0.614), I^2 = 0 %, tau^2 = 0 %). The lack of asymmetry in the funnel plot and the non-significant p-value of the Egger's test (p = 0.600) suggested no small-study effects or publication bias (Supplementary fig. 1).

3.3.2. Subgroup analyses

Fig. 3 presents the results of subgroup analyses pertinent to methodological parameters. In the ten studies using daily dosing, cancer mortality was 12% lower in the vitamin D_3 group compared with the placebo group (RR [95 % CI]: 0.88 [0.78; 0.98], p = 0.019), whereas no reduction in mortality was detected in the four studies that used bolus dosing (RR [95 % CI]: 1.07 [0.91; 1.24], p = 0.411). There was a statistically significant 13 % reduction in cancer mortality among the nine RCTs conducted in the United States or Europe (RR [95% CI]: 0.87 [0.78; 0.97], p = 0.009) and no effect in studies from other regions (RR [95 % CI]: 1.12 [0.95; 1.33], p = 0.165). The tests for interaction of the treatment effect with regimen (p = 0.042) and region (p = 0.010) were statistically significant. Of note, the results of regimen and region were closely linked, since seven of the nine trials conducted in the United States or Europe used daily dosing while the two largest of the four studies from "other regions" used bolus doses. No effect modification was observed by trial duration (p = 0.584), dose (p = 0.994 for 1000–2000 IU/d; p = 0.392 for >2000 IU/d), or health status of study participants (p = 0.854).

3.3.3. Risk of bias assessment

Of the 14 RCTs, eight studies had a low risk of bias and one study a high risk of bias (due to the ascertainment of cancer data, see footnote "k" in Table 1). Five studies were rated as having "some concerns" exclusively in the "Selection of the Reported Results" category, which was due to the outcome data used for the meta-analysis being obtained from the authors and not reported in the publication (Supplementary fig. 2).

3.3.4. Sensitivity analyses

The sensitivity analyses are summarized in Supplementary fig. 3. When only trials with a low risk of bias (n = 8) were considered, the effect estimate remained similar (RR [95% CI]: 0.94 [0.85; 1.03], p = 0.183). This was also the case when only trials reporting the intention-to-treat results were pooled (RR [95% CI]: 0.94 [0.86; 1.03], p = 0.161). When the large Women's Health Initiative (WHI) trial (Wactawski-Wende et al., 2006), the only study that used vitamin D_3 along with calcium, was removed, the summary RR increased from 0.94 to 0.97 (95% CI: 0.86; 1.08; p = 0.559).

3.4. Main IPD meta-analyses

3.4.1. Cancer mortality in the general population

Six of the seven studies included in the IPD meta-analyses were performed in the general population and could be included in the analysis on cancer mortality (N_{total}= 93,651, including 1683 cancer deaths during the intervention period (Avenell et al., 2012; Manson et al., 2019; Neale et al., 2022; Scragg et al., 2018; Virtanen et al., 2022;

Table 1
Characteristics of included studies.

First author, year, Study ID, country	Sample size (Randomised (R), analysed (A))	Vitamin D_3 dosing regimen, galenics	Vitamin D_3 daily or non-daily bolus	Intervention period [years]	No of cancer deaths in treatment period	Risk ratio for cancer mortality (95% CI) in treatment period
Trivedi et al. (2003) UK	R = A = 2686	100,000 IU Q4M (15 doses total), capsule	Bolus	5	135	0.86 (0.61–1.20)
Wactawski-Wende et al. (2006), Jackson et al., (2003, 2006),Chlebowski et al. (2008),Chacko et al. (2011), *WHI* (NCT00000611), US	R = A = 36,282[a]	400 IU/d + 1000 mg Ca/d, chewable tablet	Daily	7	726	0.89 (0.77–1.03)
Avenell et al. (2012) Grant et al. (2005) *RECORD* (ISRCTN51647438), UK	R = A = 2675[b]	800 IU/d, 1000 mg Ca/d, both/d, tablet	Daily	2–5.2	88[c]	0.83 (0.55–1.26)[c]
Baron et al. (2015) *VitDCa Polyp Prevention Study* (NCT00153816), US	R = 835[d]	1000 IU/d, 1200 mg Ca/d, both/d, tablet	Daily	3–5	5[e]	1.44 (0.24–8.63)[e]
Martineau et al. (2015) *ViDiCO* (NCT00977873), UK	R = A = 240	120,000 IU Q2M, Vigantol oil	Bolus	1	2	0.97 (0.06–15.29)[f]
Witte et al. (2016) *VINDICATE* (NCT01619891), UK	R = 223; A = 163	4000 IU/d, tablet	Daily	1	5 [g]	0.25 (0.03–2.44)[g]
Akiba et al. (2018) AMATERASU 4 (UMIN000001869), Japan	R = 155 [h]; A = 144	1200 IU/d, capsule	Daily	1	2[i]	1.01 (0.06–15.10)[i]
Manson et al. (2019) *VITAL* (NCT01169259), US	R = A = 25,871	2000 IU/d, n − 3 fatty acids 1 g/d, both/d, capsule	Daily	5	341	0.83 (0.67–1.02)
Scragg et al. (2018) *ViDA* (ACTRN12611000402943) New Zealand	R = 5110; A = 5108	Initial dose of 200,000 IU, then 100,000 IU/m, soft-gel capsule	Bolus	3.3[j]	60[k]	0.99 (0.60–1.64)[k]
Urashima et al. (2019) AMATERASU 5 (UMIN000001977) Japan	R = A = 417	2000 IU/d, capsule	Daily	5	62	1.09 (0.58–2.01)
Sudfeld et al. (2020) *ToV4* (NCT01798680), Tanzania	R = A = 4000	50,000 IU/wk for first month of ART, then 2000 IU/d, "supplements"	Daily	1	8 [l]	1.01 (0.25–4.02)[l]
Chatterjee et al. (2021) *D2dCA* (NCT01942694), US	R = A = 2385	4000 IU/d, soft-gel	Daily	3	6 [m]	0.23 (0.03–1.96)[m]
Neale et al. (2022)*D -Health* (ACTRN12613000743763), Australia	R = 21,315; A = 21,310	60,000 IU/m, gel capsule	Bolus	5	452 [n]	1.15 (0.96–1.39)[n]
Virtanen et al. (2022) *FIND* (NCT01463813), Finland	R = A = 2495	3200 IU/d, pills 1600 IU/d, pills Both intervention arms combined	Daily	5 5 5	36 [m, o] 36 [m, o] 36 [m, o]	0.90 (0.38–2.13)[m, o] 1.36 (0.63–2.97)[m, o] 1.13 (0.56–2.30)[m, o]

Abbreviations: /d, /wk, /m per day/week/month; ART antiretroviral therapy; Ca calcium; COD cause of death; FU follow-up; m month; OS overall survival; P placebo; Q2M / Q4M every 2 / 4 months; RR relative risk; VD vitamin D_3; VDS Vitamin D_3 supplementation; y year

Footnotes:

a Vitamin D_3 was inseparably combined with calcium.

b 5292 participants were randomised to vitamin D_3 and calcium combined.

c Derived from IPD analysis to restrict FU to intervention period. During the long-term FU, a total of 156 cancer deaths were recorded (HR (95 % CI): 0.85 (0.68–1.06)).

d Regarding the two-group randomisation (2GR), women could elect to be randomly assigned to receive either calcium or calcium plus vitamin D_3 (584 randomised, 540 analysed). Regarding the full factorial randomisation (FFR), all other patients were randomly assigned to receive one of the four regimens (1675 randomised, 1548 analysed). 835 refers to FFR.

e Unpublished data. During the entire trial duration, 17 cancer deaths were recorded (HR (95 % CI): 0.40 (0.14–1.14)). Vitamin D_3 combined with calcium yielded in 10 cancer deaths during the intervention period (HR (95% CI): 2.29 (0.59–8.86)) and a total of 30 cancer deaths during the entire trial duration (HR (95 % CI): 0.87 (0.43–1.79)).

f HR extracted from "Zhangyou Guo et al. (2022) Association between vitamin D supplementation and cancer incidence and mortality: A trial sequential meta-analysis of randomised controlled trials, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2022.2056574".

g Unpublished data. 5 cancer deaths were among cause of death I, one cancer death among cause of death II. Only cause of death I was included in the analysis. Risk ratio was self-calculated based on provided data.

h Eight patients from placebo arm did not receive allocated intervention.

i Self-calculated based on provided clinical data.

j Median

k Excluded those who died of cancer diagnosed before randomisation.

l Unpublished data. Note of author: Nearly all deaths were HIV related. We had eight deaths coded as attributable to cancers. However, these are based on verbal autopsy and rather incomplete medical records.

m Unpublished data.

n Underlying cause of death available for 889/1100. 452/889 died of cancer. **o** During the entire trial duration, 43 cancer deaths were recorded (HR (95% CI): 1.23 (0.59–2.56) for 1600 IU/d, 1.07 (0.50–2.28) for 3200 IU/d, 1.15 (0.60–2.21) for both dosages combined)

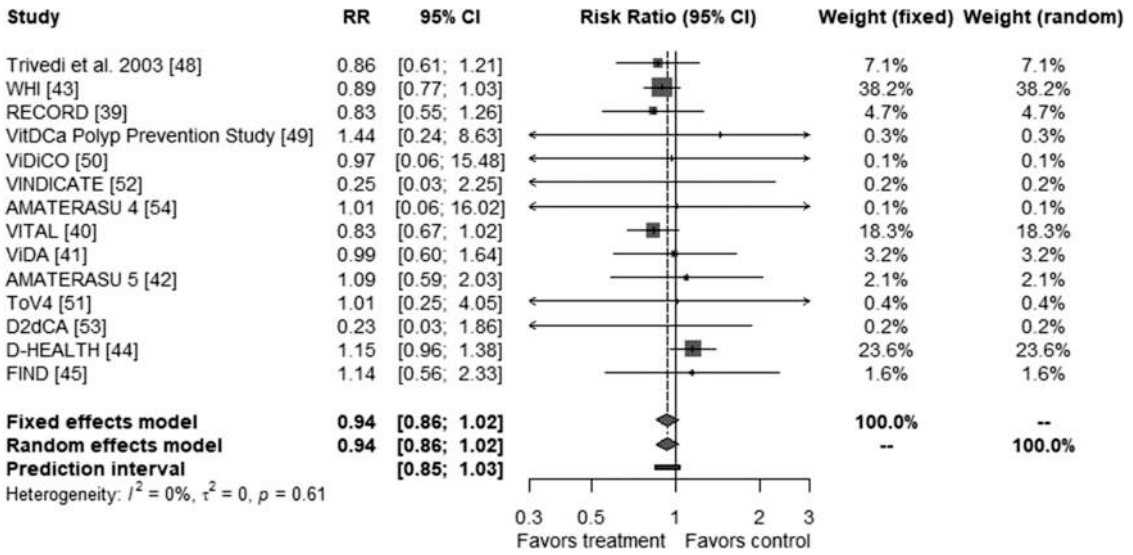

Fig. 2. Meta-analysis of all included RCTs comparing vitamin D_3 and placebo for the outcome "cancer mortality".

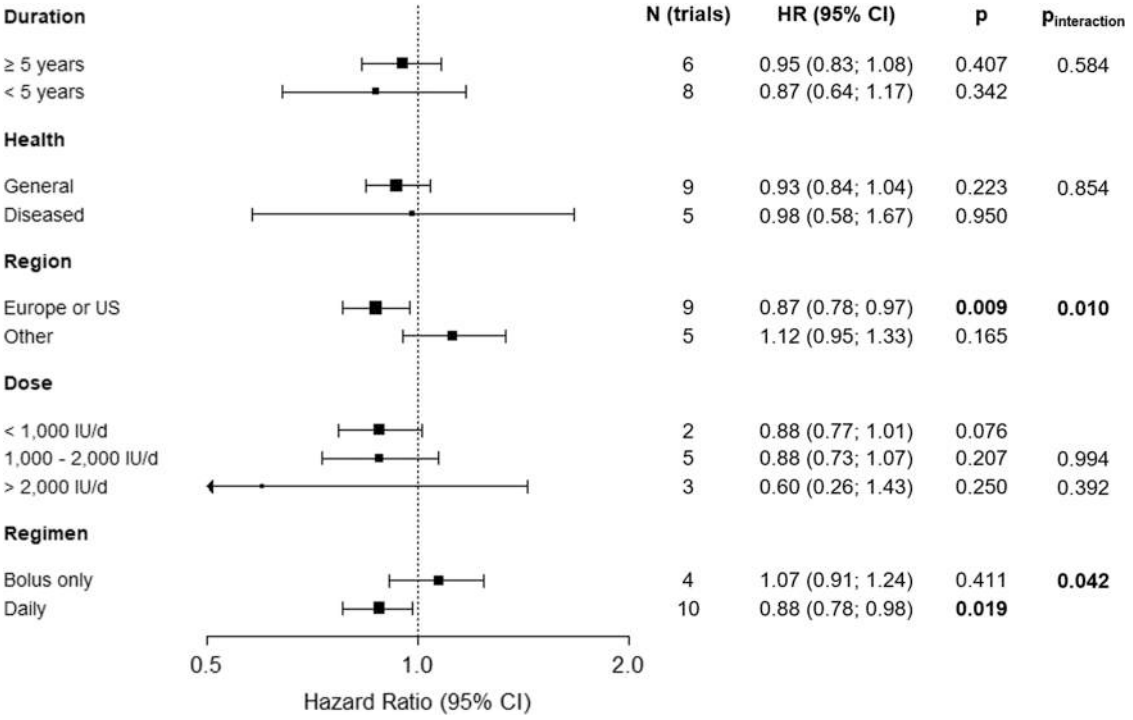

Fig. 3. Subgroup analyses of vitamin D_3 supplementation and cancer mortality by duration of intervention, health status, region, dose and regimen in all trials. Note: The FIND study appears twice in the subgroup analysis towards dose. The treatment arm with 1600 IU counted towards moderate dose and the one with 3200 IU counted towards high dose.

Wactawski-Wende et al., 2006)) The study participants' characteristics are shown in Supplementary table 7. These six trials contributed 89.6 % to the weight of the meta-analysis of all 14 trials on the association of vitamin D_3 supplementation with cancer mortality, and thus it was not surprising that the hazard ratio (HR) point estimate in the IPD meta-analysis (HR [95%CI]: 0.93 [0.84; 1.02], p = 0.125) was almost identical to that for all trials (RR [95%CI]: 0.94 [0.86; 1.02], p = 0.153). Fig. 4 panel A shows the forest plot of this IPD meta-analysis with unadjusted effect estimates. Details about the individual study results and the meta-analysis with the multivariable model, which yielded almost the same pooled effect estimate, can be found in Supplementary table 8.

3.4.2. *Cancer survival*

All seven studies included in the IPD analyses contributed to the meta-analysis of overall survival (N_{total}=7528, including 1932 cancer deaths during the intervention period) and cancer-specific survival (N_{total}=7513, including 1726 cancer deaths during the intervention period) among patients with cancer (of which most were diagnosed after randomisation and only a few up to 5 years prior to study enrolment). The patient characteristics of the study populations are provided in Supplementary table 9. In unadjusted models, vitamin D_3 supplementation was associated with a statistically non-significant 5% improved overall survival (HR [95 % CI]: 0.95 [0.87; 1.04], p = 0.270) and 7 % improved cancer-specific survival (HR [95% CI]: 0.93 [0.85; 1.03],

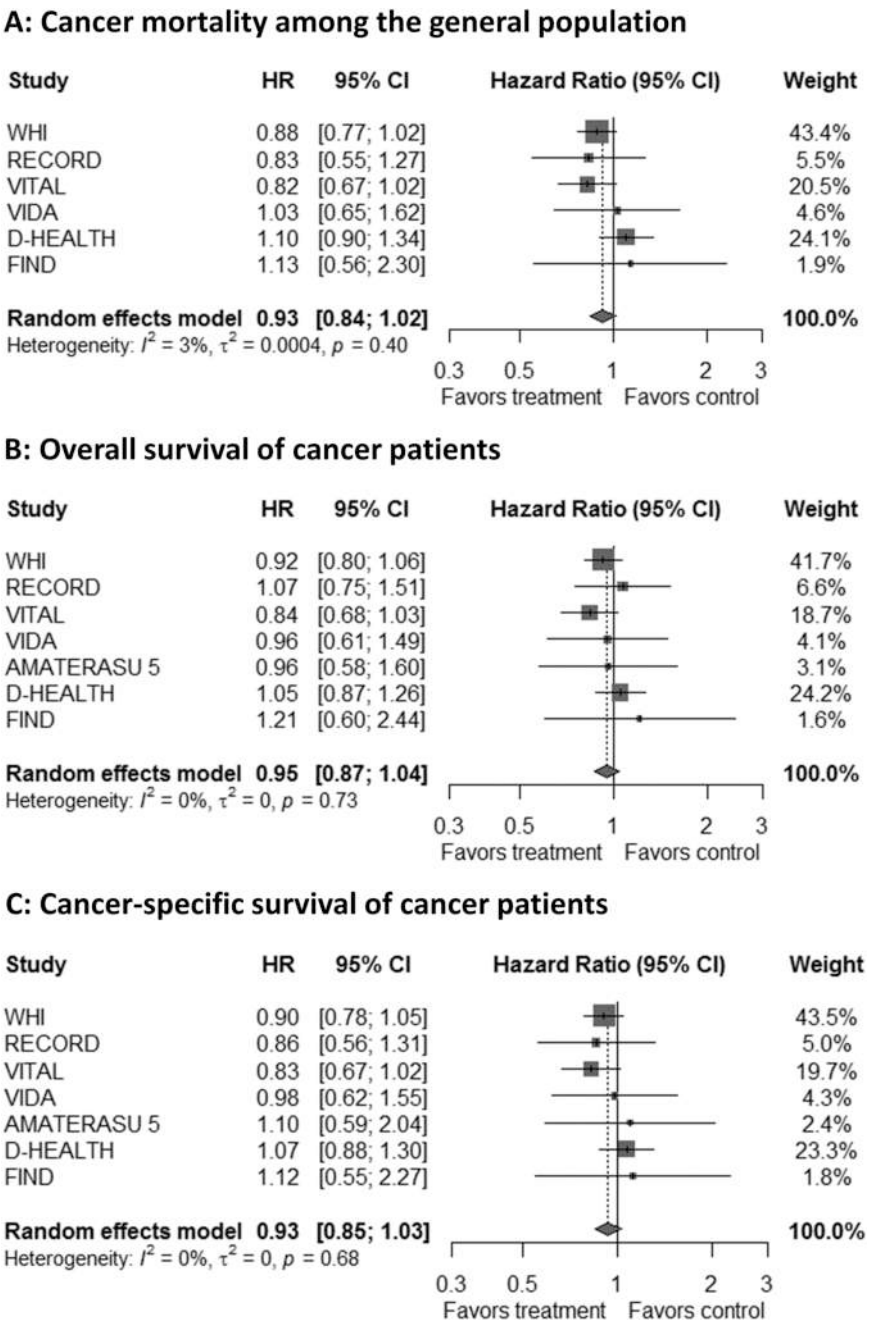

Fig. 4. IPD meta-analyses of RCTs comparing vitamin D_3 and placebo for the outcome "cancer mortality" in the general population (panel A) and for the outcomes "overall and cancer-specific survival" in cancer patients (panel B and C). Note: Unadjusted results are shown. The adjusted results are almost identical (Supplementary tables 8, 10 and 11).

p = 0.151). Fig. 4 panels B and C show the corresponding forest plots; additional details, including adjusted effect estimates, are presented in Supplementary tables 10 and 11.

3.5. IPD subgroup analyses

3.5.1. Cancer mortality in the general population

Fig. 5 illustrates the main results of the IPD subgroup analyses; details of the individual trial results and interaction tests are shown in Supplementary tables 12A and B and 13 A and B, respectively. None of the subgroup analyses showed a statistically significant effect of vitamin D_3 supplementation on cancer mortality (Fig. 5, panel A). However, statistically significant findings were observed in a post-hoc analysis when trials were restricted to those with a daily vitamin D_3 dosing regimen (Fig. 5, panel B). Statistically significant cancer mortality reductions by vitamin D_3 supplementation were observed among adults aged ≥ 70 years (HR [95 % CI]: 0.83 [0.69; 0.99], p = 0.043), men (HR [95 % CI]: 0.73 (0.56; 0.96), p = 0.024), non-Hispanic Whites (HR [95 % CI]: 0.84 [0.74; 0.95], p = 0.007), and individuals with no history of cancer prior to the trial (HR [95 % CI]: 0.87 [0.77; 0.98], p = 0.022). However, the interaction terms of these factors with the treatment group were not statistically significant. BMI, baseline 25(OH)D level, and adherence had no impact on the results. It should be mentioned that the number of 25(OH)D measurements at baseline was small and could only be used for our analysis from two trials. Moreover, only n = 3535 (17 %) of the participants with 25(OH)D measurements had vitamin D insufficiency (25(OH)D < 50 nmol/L).

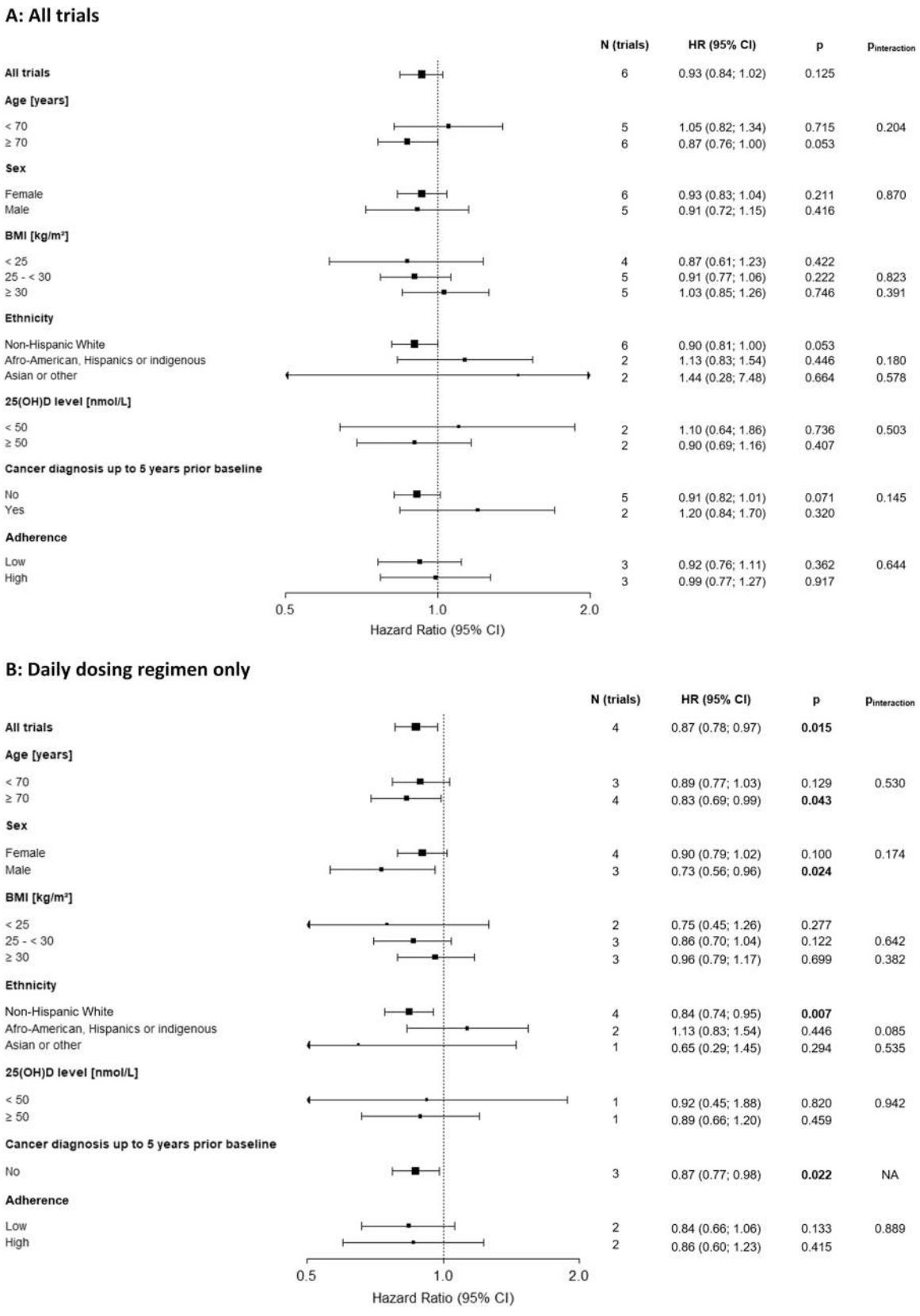

Fig. 5. IPD subgroup analyses of vitamin D_3 supplementation and cancer mortality in the general population by age, sex, BMI, ethnicity, vitamin D baseline level, cancer diagnosis in five years prior baseline, and adherence in all trials (panel A, main analysis) and restricted to trials with a daily dosing regimen (panel B, post-hoc analysis). **Note:** No studies available for "Cancer diagnosis up to 5 years prior baseline" = yes.

3.5.2. Cancer survival

Fig. 6 shows the pooled effect estimates of the IPD subgroup analyses for cancer-specific survival of cancer patients. Supplementary table 14A and B shows the individual study results and Supplementary table 15A and B presents the tests for interaction with vitamin D_3. Results were similar to those observed for cancer mortality in the general population. In the main analysis, none of the meta-analyses of all trials showed statistically significant vitamin D_3 effects on cancer survival except the subgroup conducted with patients free of cancer at baseline: HR [95 % CI]: 0.88 [0.79; 0.99], p = 0.030 (Fig. 6, panel A). Yet, when the trials were restricted to those with a daily dosing regimen in a post-hoc analysis, the effect estimates among all trials (HR [95 % CI]: 0.89 [0.80; 0.99], p = 0.040) and among non-Hispanic Whites were statistically significant while the results for patients free of cancer at baseline remained the same (HR [95 % CI]: 0.88 [0.79; 0.99], p = 0.032, Fig. 6, panel B). In contrast to the results for cancer mortality in the general population, there was some evidence of effect for cancer survival among adults aged ≥ 70 years (HR [95 % CI]: 0.85 [0.71; 1.01], p = 0.065) and men (HR [95 % CI]: 0.79 [0.61; 1.02], p = 0.069). Similarly, there was a suggestion of effect among prostate (HR [95 % CI]: 0.30 [0.08; 1.07], p = 0.064) and colorectal cancer patients (HR [95% CI]: 0.72 [0.51; 1.02], 0.061), whereas no vitamin D_3 effects were observed for cancer survival among breast and lung cancer patients. Only two trials had data on cancer stage, which provided too few patients to draw conclusions from this subgroup analysis. All interaction terms of population characteristics with the treatment group were not statistically significant (but were also underpowered).

3.6. Strength of evidence (GRADE)

Based on the GRADE approach, the quality of evidence was assessed as high for all outcomes (supplementary table 16). The "inconsistency" domain was not downgraded, although recent trials published since 2018 have suggested a trend toward lack of efficacy of vitamin D_3 supplementation on cancer mortality compared to older studies for the following reasons: (I) the studies using bolus vitamin D_3 treatment are among the new studies; (II) some new studies allowed personal use of vitamin D_3 up to 2000 IU/d (Neale et al., 2022; Virtanen et al., 2022) and, even if prohibited, the increased awareness of health effects by vitamin D_3 in the last decade might have led to increased self-medication with vitamin D_3 over time, which could align effects in the placebo group with those in the intervention group. The domain "imprecision" was not downgraded because wide confidence intervals were found primarily in studies with unpublished data and small case numbers.

4. Discussion

4.1. Summary of main findings

This systematic review and IPD meta-analysis observed that, overall, vitamin D_3 supplementation resulted in a statistically non-significant 6% reduction of cancer mortality in the general population, 5% improved overall survival of cancer patients and 7% improved cancer-specific survival of cancer patients. The relationship with cancer mortality was stronger and statistically significant when the analysis was restricted to trials with a daily vitamin D_3 dosing regimen (reduction by 12%). Subgroup analysis with IPD of trials with daily vitamin D_3 treatment revealed statistically significant efficacy for cancer mortality among adults aged ≥ 70 years, males, non-Hispanic Whites, and participants free of cancer at initiation of treatment. However, tests for interaction by these factors were not significant and these results must be interpreted with caution because they were post-hoc analyses and confidence intervals overlapped (see below).

4.2. Comparison with other systematic reviews

Previous meta-analyses reporting statistically significant effects of vitamin D_3 supplementation on cancer mortality did not include the recently published D-Health trial (Neale et al., 2022), which applied a bolus dosing regime, had a negative finding and contributed 23.6% of the weight to our meta-analysis of all trials (Bjelakovic et al., 2014; Guo et al., 2022; Keum et al., 2019; Zhang et al., 2019; Zhang et al., 2020). Our non-significant pooled effect estimate of all trials (RR [95% CI]: 0.94 [0.86; 1.02]) is comparable to the most recent systematic review by Zhang et al. (RR [95% CI]: 0.96 [0.80–1.16]), which also included the D-Health trial but not the WHI trial because of co-administration of calcium (Zhang et al., 2022). Thus, their result is similar to our sensitivity analysis excluding trials with co-administration of calcium (HR [95% CI]: 0.97 [0.86; 1.08]). However, it is debatable whether it is necessary to exclude the WHI trial because it is unclear whether calcium supplementation has an impact on cancer mortality. A meta-analysis of RCTs found no effect of calcium on cancer mortality at trial-level (HR [95%CI]: 0.96 [0.74; 1.24]) or patient-level (HR [95%CI]: 0.98 [0.74; 1.29]) and, moreover, no biologically plausible explanation is currently available for an effect of calcium supplementation on cancer mortality (Bristow et al., 2013; Yang et al., 2016).

4.3. Effect modification by vitamin D_3 dosing regimen

Our results showing efficacy of daily, but not bolus, vitamin D_3 supplementation in reducing cancer mortality are consistent with previous meta-analyses on cancer mortality or all-cause mortality (Guo et al., 2022; Keum et al., 2022; Keum et al., 2019; Zhang et al., 2022; Zhang et al., 2019). However, by including more trials than these previous meta-analyses, we were able to detect statistically significant effect modification by treatment regimen for the first time with statistical significance ($p_{interaction}$=0.042). The pattern of intake could be important for a favourable steady state of the bioavailability of the active 1,25 $(OH)_2D$ hormone. Daily administration counteracts the fast excretion of vitamin D from the circulation (Hollis and Wagner, 2013; Keum et al., 2022). Moreover, the enzymes CYP27B1 (converts 25(OH)D to 1,25 $(OH)_2D$) and CYP24A1 (inactivates 25(OH)D and 1,25$(OH)_2D$) follow first-order reaction kinetics (Vieth, 2009). This means that doubling the concentration of the precursor doubles the yield of the product, unlike other steroid hormones (e.g., cortisol, oestrogen, testosterone) that follow zero-order kinetics (Vieth, 2020). Intermittent, non-physiologically large vitamin D_3 bolus doses may lead to unstable cycling of 25(OH)D and 1,25$(OH)_2D$ levels in blood because the system needs time to adapt to the large doses (Hollis and Wagner, 2013; Keum et al., 2019; Vieth, 2020). In the long run, intermittent bolus regimens at weekly or larger intervals can lead to an up-regulation of countervailing factors (e.g., 24-hydroxylase (CYP24A1), 24,25$(OH)_2D$ and fibroblast growth factor 23), all of which ultimately leads to lower synthesis or higher degradation of 1,25$(OH)_2D$ levels (Mazess et al., 2021). Bolus doses, unlike daily doses, failed to reduce C-reactive protein response and actually elevated anti-inflammatory cytokines and doubled the risk of hypercalcemia in previous studies (Krishnan et al., 2012; Martineau et al., 2017; Mazess et al., 2021).

4.4. Effect modification by study region

The absence of an effect of vitamin D_3 supplementation on cancer mortality in the meta-analysis of trials not conducted in the United States or Europe was mainly driven by the D-Health and ViDA studies, which were conducted in Australia and New Zealand, respectively. According to nationally representative surveys with standardised 25(OH)D assays, the prevalence of vitamin D deficiency (defined as 25(OH)D < 30 nmol/L) is lower in Australia (4.7%) and New Zealand (4.9%) than in Europe (e.g., 15.0% in Germany) but not much lower than in the United States (5.0%) (Cashman, 2022). The latter can be explained by higher

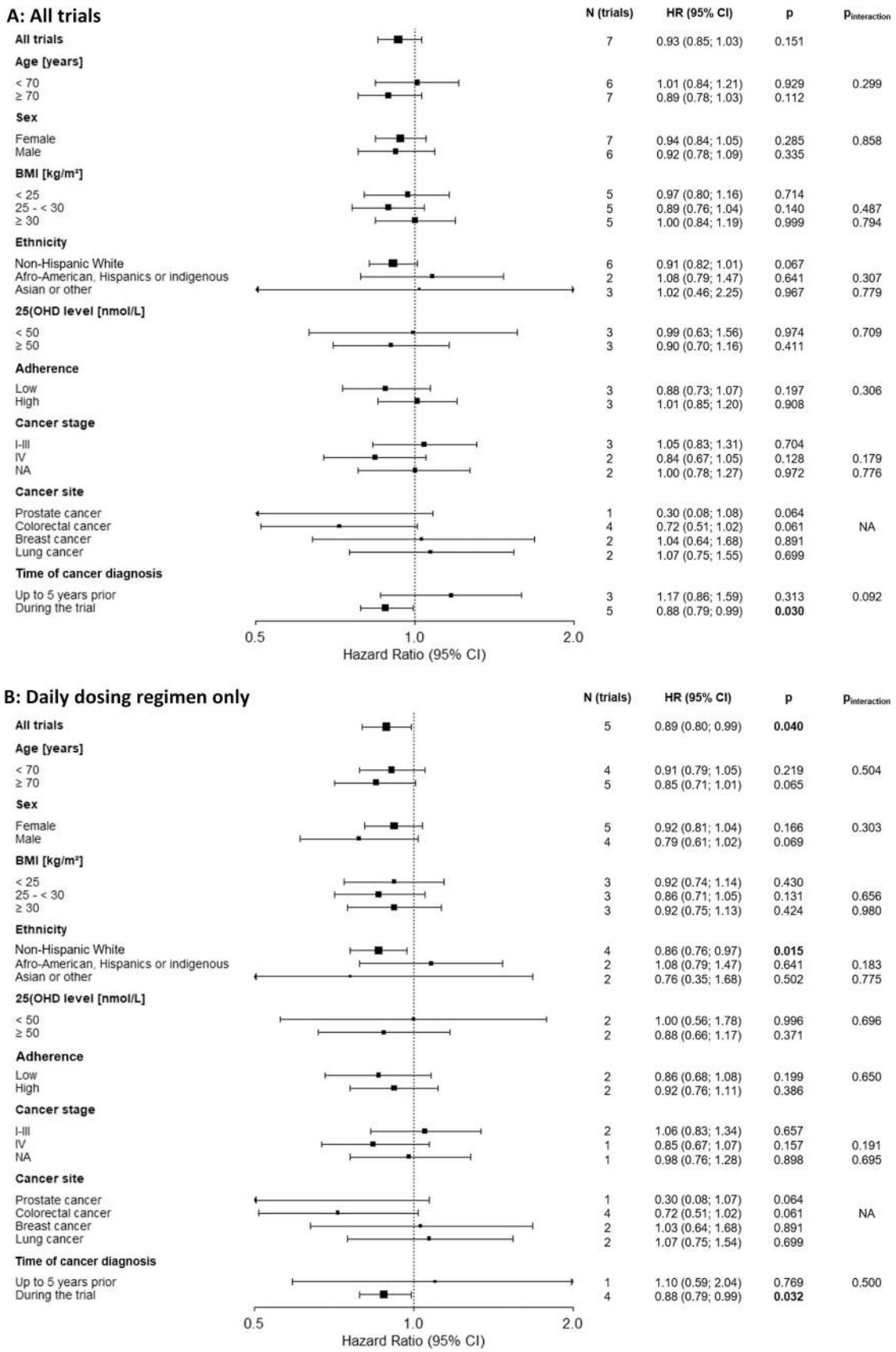

Fig. 6. IPD subgroup analyses of vitamin D_3 supplementation and cancer-specific survival in the cancer population by age, sex, BMI, ethnicity, vitamin D baseline level, adherence, cancer stage, cancer site, time of cancer diagnosis in all trials (panel A, main analysis) and restricted to trials with a daily dosing regimen (panel B, post-hoc analysis).

food fortification with vitamin D in the United States outweighing the lower UV-B radiation compared to Oceania (Cashman, 2021). Thus, the high UV-B radiation and low prevalence of vitamin D deficiency in Oceania, could explain a lower efficacy of vitamin D_3 supplementation in Oceania compared to Europe but not to the US. However, as the efficacy of vitamin D_3 supplementation on cancer mortality was the same in European (RR [95%CI]: 0.87 [0.68–1.10]) and US studies (RR [95% CI]: 0.87 [0.77–0.98]), it is more likely that it was not the study region that led to the null findings in the two studies from Oceania but rather the fact that both used a bolus vitamin D_3 regimen.

4.5. Discussion of IPD subgroup analyses

4.5.1. Ethnicity

The subgroup analyses for ethnicity need to be interpreted with caution due to small sample sizes for non-White ethnicities. Overall, 1437 cancer deaths were included in the subgroup analysis for non-Hispanic Whites, 161 for African Americans, Hispanics, or indigenous people, and 42 for Asians and other ethnicities (supplementary table 12B). As skin pigmentation has an influence on vitamin D synthesis and genetic variations with relevance for the biosynthesis of the vitamin D binding protein have been observed, which could have an influence on the 25(OH)D bioavailability (Jarrett and Scragg, 2020), results from non-Hispanic Whites should not be generalized to other ethnicities. Instead, further trials should be conducted with study participants from other ethnic backgrounds.

4.5.2. Age

Our IPD subgroup analysis restricted to studies applying a daily regimen in a post-hoc analysis is the first to show a statistically significant vitamin D_3 effect distinctly for those aged 70 years or older for cancer mortality (HR [95% CI]: 0.83 [0.69; 0.99], p = 0.043). However, the vitamin D_3 effect in people aged younger than 70 years was not much different from the one in the older age group and the confidence intervals widely overlapped (HR [95% CI]: 0.89 [0.77; 1.03], p = 0.129). Nevertheless, a somewhat higher vitamin D_3 efficacy in the older age group is plausible because the efficiency to synthesize vitamin D in the skin declines with ageing (Chalcraft et al., 2020). Furthermore, the older population is often found to be more homebound due to lower mobility and/or disabilities, further limiting sun exposure (Institute of Medicine, 2011a, 2011b). In addition, statins belong to typically prescribed co-medications due to cardiovascular co-morbidities and may reduce vitamin D synthesis (Robien et al., 2013).

4.5.3. Sex

Among males, we observed a statistically significant efficacy of vitamin D supplementation on cancer mortality in the post-hoc IPD meta-analysis of trials with daily vitamin D dosing regimen (HR [95% CI]: 0.73 [0.56; 0.96], p = 0.024). However, the effect in women was not suggestive, with clear overlap of the confidence intervals (HR [95% CI]: 0.90 [0.79; 1.02], p = 0.100). Thus, we believe there is insufficient evidence of sex differences in the results.

4.5.4. BMI

Body weight could have a role in the efficacy of vitamin D_3 supplementation because vitamin D metabolites are stored in adipose tissue. As a consequence, obese individuals usually have lower serum 25(OH)D levels than non-obese people and require higher vitamin D_3 doses to achieve adequate 25(OH)D levels (Jansen and Svendsen, 2014). Interestingly, the recent meta-analysis of Keum et al. observed a significant reduction of cancer incidence and cancer mortality by daily vitamin D supplementation in participants with BMI < 25 kg/m^2 but not in those with higher BMI (Keum et al., 2022). Furthermore, a secondary analysis of the VITAL trial observed a strong and statistically significant effect of vitamin D_3 in the reduction of the incidence of advanced (metastatic or fatal) cancer (HR [95%CI]: 0.62 [0.45–0.86]) in individuals with BMI < 25 kg/m^2, whereas no effects were observed among those with BMI 25 - < 30 (HR [95%CI]: 0.89 [0.68–1.17]) or BMI ≥ 30 (HR [95%CI]: 1.05 [0.74–1.49]) (Chandler et al., 2020). We observed the same trend among trials with daily dosing regimen in a post-hoc analysis: point estimates were also lower for the BMI < 25 kg/m^2 group (HR: 0.75) than in the groups with a BMI between 25 and 30 kg/m^2 (HR: 0.86) and a BMI ≥ 30 kg/m^2 (HR: 0.96). However, our results were not statistically significant although we included more trials than Keum et al. Future studies with more statistical power would be needed to elucidate whether daily vitamin D supplementation is more effective for cancer mortality in non-obese individuals.

4.5.5. Timing of cancer diagnosis and initiation of vitamin D_3 supplementation

For cancer survival, a statistically significant effect was observed if the cancer was diagnosed during the trial (HR [95% CI]: 0.88 [0.79; 0.99], p = 0.030), but not if it was diagnosed up to five years prior to the trial (HR [95% CI]: 1.17 [0.86; 1.59], p = 0.313). Thus, it could be important that vitamin D_3 treatment is initiated early, ideally before cancer diagnosis. The most relevant times for cancer survival are before diagnosis (because this is relevant for the stage at cancer detection) and during cancer therapy (since this time decides on the efficacy and tolerance of the cancer therapy). It is plausible that taking vitamin D_3 in these times is most relevant because vitamin D_3 has been ascribed anti-proliferative and anti-inflammatory effects in cancer patients (Krishnan et al., 2012). The former mechanism could reduce tumor size before diagnosis and the latter improve cancer treatment tolerance.

4.5.6. Cancer stage

The overall association between vitamin D_3 supplementation and cancer stage is biologically plausible as the vitamin D receptor is also present in malignant cells, enabling vitamin D_3 to slow tumor progression by promoting cell differentiation and inhibiting metastasis (Kim and Giovannucci, 2020). We observed a HR < 1.0 for stage IV cancer based on two studies but the results were not statistically significant (HR [95% CI]: 0.84 [0.67; 1.05], p = 0.13). There is epidemiological evidence that late stages of colorectal cancer are associated with vitamin D deficiency, which is consistent with the previously reported finding and again encourages vitamin D_3 supplementation (Negri et al., 2020). In contrast, the stage-specific data are conflicting for breast and prostate cancer (Negri et al., 2020).

4.5.7. Cancer site

None of the meta-analyses for overall survival of prostate, colorectal, breast, and lung cancer patients were statistically significant in the IPD analysis. However, it should be noted that overall prostate cancer and colorectal cancer survival narrowly missed statistical significance, whereas overall breast and lung cancer survival were unrelated to vitamin D supplementation. Future studies restricted to specific cancer sites are clearly needed and they might find differences in vitamin D_3 efficacy for cancer survival according to cancer sites (Sluyter et al., 2021). While the IPD meta-analysis on prostate cancer survival is based on only one study, the data availability is currently best for colorectal cancer with data from four RCTs. Taken together with evidence from observational studies, which have shown a statistically significant association of higher circulating 25(OH)D concentration as well as sun exposure with lower colorectal cancer risk (Grant, 2014; Grant and Garland, 2006; McCullough et al., 2019), a beneficial role of vitamin D_3 supplementation for colorectal cancer patients seems likely.

4.5.8. Baseline 25(OH)D level

Our IPD analyses did not show stronger effects in participants with vitamin D insufficiency (25(OH)D < 50 nmol/L) at baseline although this would be expected given the L-shaped association of 25(OH)D levels with cancer mortality reported from cohort studies (Brenner et al., 2017; Heath et al., 2019). The very low number of people with 25(OH)D levels

< 50 nmol/L that could be used for the meta-analysis on cancer mortality may best explain this finding (n_{total} = 3535, n_{cases} =55).

None of the trials included in this systematic review restricted recruitment to people with vitamin D insufficiency. In the three studies, in which 25(OH)D levels were measured in subgroups, most participants had adequate 25(OH)D levels at baseline > 50 nmol/L (Manson et al., 2019; Scragg et al., 2018; Urashima et al., 2019). It is highly likely that more than half of the study population included in this systematic review had no chance to benefit from a vitamin D_3 intervention because they already had a sufficient vitamin D status at baseline. This is the major limitation of the current evidence base, as treatment of people without low vitamin D status may have led to a substantial underestimation of the potential efficacy of vitamin D_3 supplementation (Brenner et al., 2017). A much higher vitamin D_3 efficacy could be expected from trials with initial restriction to people with vitamin D insufficiency (Pilz et al., 2022; Rejnmark et al., 2017; Sluyter et al., 2021; Wyse et al., 2021; Zgaga et al., 2022).

4.6. Strength of the vitamin D_3 dose

For daily dosing regimens and cancer mortality, we observed no efficacy differences between low doses of < 1000 IU/d and average doses of 1000 – 2000 IU/d. The point estimate of the HR was lower at high doses > 2000 IU/d but the confidence interval was wide and we cannot conclude that a higher dose has greater efficacy. It would be of interest to see future studies using a dose of 2000 IU/d or higher targeted to participants with initial vitamin D deficiency (see protocol of the VICTORIA trial for example (Schöttker et al., 2020)). The lack of an observation of a dose-response relationship in the currently available trials is in agreement with former systematic reviews and meta-analyses (Guo et al., 2022; Keum et al., 2019).

As an efficacy of low-dose vitamin D supplements for cancer mortality cannot be excluded, self-medication with vitamin D in the placebo group should be excluded as much as tolerated by study participants and ethically feasible in all future trials. However, this is challenging or even impossible for trials, which run for several years. In 10 of the 14 trials in the main meta-analysis, self-medication was allowed, which may have reduced the relative risk estimate between the vitamin D_3 and placebo group.

4.7. Strengths and limitations

This is the first systematic review and meta-analysis on the efficacy of vitamin D_3 supplementation for cancer mortality and survival using IPD. All major trials contributed IPD except a single older one (Trivedi et al., 2003), making the IPD analyses representative for the overall available evidence in this field. Furthermore, the acquisition of previously unpublished data is a strength of this systematic review, as it reduced selective reporting biases that were listed as limitations in previous systematic reviews. The final number of 14 RCTs included in meta-analyses for the endpoint “cancer mortality” involved 104,727 randomised participants including 1928 cancer deaths, which led to a high statistical power and precision of the pooled effect estimates, and allowed the conduction of subgroup analyses, which were nonetheless underpowered. No signs of heterogeneity or publication bias were detected.

A further strength of our systematic review is that we included exclusively double-blind and placebo-controlled randomised trials. We meticulously followed guidelines such as the PRISMA-IPD statement (supplementary table 2), registered the systematic review before any data collection occurred, published a protocol (Schöttker et al., 2021), recorded all deviations to ensure transparency (supplementary table 1), and evaluated the strength of evidence according to the GRADE approach. Moreover, data extraction, risk assessment and all statistical analyses were performed by two independent researchers.

However, our systematic review and IPD meta-analysis also has limitations. As anticipated in the protocol, the sample size was limited for certain subgroup analyses, such as non-White ethnicities, baseline 25(OH)D levels, cancer stage and cancer sites, and sometimes the studies contributed not to all subgroup meta-analyses for the same factor (e.g. if only women were included in the trial, the study could not contribute to the subgroup analysis on males), making it challenging to draw firm conclusions. The IPD subgroup analyses have the further limitation that the additional meta-analyses restricted to trials with daily vitamin D_3 dosing regimen were not specified in the review protocol and have to be reported as post-hoc analyses, which have been influenced by the knowledge of the review authors that statistically significant findings could only be observed in this subgroup of trials.

Despite the high response rate and excellent collaboration with authors from around the globe, we lacked replies from 30 studies and did not find an appropriate contact for ten studies. In most cases, these were studies that dated back more than 15 years and whose authors had moved on or retired, or whose data were stored in inaccessible archives. Thus, selective reporting bias cannot be completely excluded, but it is likely negligible because the results of the additional trial data obtained were equally distributed and did not all point into either a favourable or unfavourable direction for vitamin D.

5. Conclusions

The conclusion of the main meta-analysis of all RCTs is that vitamin D_3 supplementation did not reduce cancer mortality because the 6% reduction of cancer mortality was not statistically significant: HR 0.94 (95% CI: 0.86; 1.02). However, we believe that the arguments for an efficacy of daily (as compared to bolus) vitamin D treatment regimens are convincing. Indeed, restricting the IPD meta-analysis to trials with daily dosing regimen yielded a statistically significant 13% cancer mortality reduction and 11% increased cancer-specific survival. As these effect estimates are based on untargeted vitamin D_3 supplementation of individuals with and without vitamin D insufficiency, the potential in a situation where only patients with low vitamin D status are treated is likely to be substantially underestimated. Furthermore, our findings suggest that, for the health outcome “cancer survival”, starting vitamin D_3 treatment before or at least shortly after a cancer diagnosis could be beneficial, which was not done for all cancer patients in the large trials, which recruited from the general population. Considering the very likely underestimation of vitamin D_3 effects in the currently available trials by not focussing on subjects with low 25(OH)D levels and allowing vitamin D self-medication to the control group, the almost negligible risk of adverse events from vitamin D_3 supplementation at reasonable doses and the very low treatment costs, we believe that vitamin D is an underutilised medication for cancer patients and should be considered for use in addition to the primary cancer therapy when low serum 25(OH)D levels justify its use.

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Neither the project funder nor the study sponsors had a role in the study design in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. We hereby confirm the independence of researchers from funders and that all authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' contribution

All authors meet the ICMJE criteria for authorship as follows: BS and SK are the guarantors of the systematic review, therefore, are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. BS conceived and designed the base of the systematic review and all analyses. SK searched the literature, collected data and was responsible for data management as well as author contact. SK and BS conducted all the meta-analyses. SK drafted the manuscript, which BS revised critically for important intellectual content. All authors made substantial contributions to the interpretation of the findings, the discussion and approved the final version to be published. However, we would like to note that Rachel Neale and Mary Waterhouse agree with results and interpretation of the main cancer mortality findings. However, they have concerns about the interpretation of the subgroup analyses relating to studies using a daily dosing regimen, in light of the lack of significant interaction and the small sample size in some subgroups. Further, they would not have included analyses of cancer survival as they do not believe the design of the trials included is appropriate for this outcome; thus they would like to dissociate themselves from these aspects.

Declaration of Competing Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years except for Julie E. Buring who declares an association to Pharmavite. All authors further declare no other relationships or activities that could appear to have influenced the submitted work.

Data Availability

The authors do not have permission to share data.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2023.101923.

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