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Test of efficacy of a personalized vitamin D supplementation to treat vitamin D deficiency in colorectal cancer patients and the potential implications on cancer prognosis

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If you want to go fast, go alone.

If you want to go far, go together.

African Proverb

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LIST OF ABBREVIATIONS

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
95% CI	95% confidence interval
AMATERASU 4	A randomized, double blind, comparative study of STATUS D_3 (vitamin D_3) versus placebo in patients with lung cancer to prevent relapse after operation
AMATERASU 5	A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation
BMI	body mass index
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRC	colorectal cancer
D2dCA	D2dCA, Vitamin D and type 2 diabetes cancer outcomes study
D-Health	A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EORTC QLQ-FA12	European Organization for Research and Treatment of Cancer – Cancer related Fatigue
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer – Core Quality of life questionnaire with 30 items
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FIND	Finnish Vitamin D Trial
FWB	Functional Well-Being
GDS-15	Geriatric depression scale
GP	general practitioner
HR	hazard ratio
IPD	individual patient data
ITT	intention-to-treat
IU	international units
KSR	Kleijnen Systematic Reviews
PP	per protocol
RCT	randomized controlled trial
RECORD	Randomized Evaluation of Calcium Or vitamin D

List of abbreviations

RoB 2	Cochrane risk-of-bias tool for randomized trials
RR, risk ratio	risk ratio
ToV4	Trial of Vitamin D in HIV Progression
US	United States
VICTORIA	Personalized vitamin D supplementation for reducing or preventing fatigue and enhancing quality of life of patients with colorectal tumor – randomized intervention trial
ViDA	Vitamin D Assessment Study
ViDiCO	Vitamin D Supplementation in Chronic Obstructive Pulmonary Disease
VINDICATE	Vitamin D treating patients with chronic heart failure
VITAL	Vitamin D and Omega-3 Trial
WCRF	World Cancer Research Fund International
WHI	Women's Health Initiative
WHO	World Health Organization
WKOF	Wereld Kanker Onderzoek Fonds
WoS	Web of Science

1. INTRODUCTION

1.1 Efficacy of vitamin D_3 supplementation on cancer mortality

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 2020b). 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 2020a).

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 (US) 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 2,912 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).

From a biological perspective, it is plausible that a sufficient vitamin D status has an impact on cancer prognosis: 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).

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; Zhang et al. 2015b). Systematic reviews further concluded that sufficient 25(OH)D levels (25(OH)D ≥ 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; 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 randomization 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 randomization 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 randomized 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 randomized to vitamin D_3 (Bjelakovic et al. 2014; Goulao et al. 2020; Goulão et al. 2018; Guo et al. 2022; Keum et al. 2022; Keum et al. 2019; Zhang et al. 2022; Zhang et al. 2019; Zhang et al. 2020). However, none of the previous systematic reviews collected unpublished results on cancer mortality from eligible studies and individual patient data (IPD).

1.2 Personalized vitamin D_3 loading doses in colorectal cancer patients with vitamin D insufficiency

Colorectal cancer (CRC) remains a major public health challenge and accounts for more than 60,000 new cases and more than 24,000 deaths per year in Germany (Robert Koch Institut 2017).

The 25(OH)D level is considered the best-established biomarker to determine vitamin D deficiency and insufficiency, which are defined by the US American Institute of Medicine as 25(OH)D levels below 30 nmol/L and below 50 nmol/L, respectively (Institute of Medicine (US) 2011b). Vitamin D insufficiency is very common among CRC patients at all stages, not only shortly after cancer treatment but also at least in the first 2 years after surgery (Maalmi et al. 2017; Skender et al. 2017). Low 25(OH)D levels were found to be strongly associated with poorer overall survival of CRC patients in a systematic review of cohort studies from the year 2018 and in more recently published cohort studies (Maalmi et

al. 2018; Wesselink et al. 2021; Zhou et al. 2021). Furthermore, a recently published systematic review and meta-analysis of RCTs showed that vitamin D supplementation significantly improved the progression-free survival of CRC patients (hazard ratio (HR), 95% confidence interval (95% CI): 0.65 (0.36; 0.94) (Vaughan-Shaw et al. 2020). In addition, there are preliminary data suggesting that vitamin D supplementation might increase the efficacy of chemotherapy and alleviate its adverse reactions (Peng et al. 2020). Vitamin D insufficiency is usually neither diagnosed nor treated in CRC patients. There is preliminary evidence that it should be treated (Maalmi et al. 2018; Vaughan-Shaw et al. 2020; Wesselink et al. 2021; Zhou et al. 2021) but the optimal dosing regimen is unknown.

A pragmatic approach is to quickly increase the 25(OH)D levels using a loading dose followed by a maintenance dose. Several clinical trials highlighted that 25(OH)D levels achieved by vitamin D_3 loading doses strongly depend on the baseline 25(OH)D level and the person's body weight (Hoffer et al. 2016; Jansen and Svendsen 2014; van Groningen et al. 2010). To consider the patient's body weight is important, because 25(OH)D is stored in adipocyte fat globules to a large extent (100–300 nmol/kg body weight) and, therefore, is of limited availability in the circulatory system of obese patients (Heaney and Armas 2015). However, the literature on trials testing personalized vitamin D_3 loading doses is sparse, and none has previously been conducted with CRC patients.

A personalized vitamin D_3 loading dose followed by a maintenance dose of 2,000 international units (IU) per day for 12 weeks is used in an ongoing placebo-controlled RCT enrolling CRC patients with initial vitamin D insufficiency (25(OH)D < 50 nmol/L). I performed an analysis including results on how effectively the 25(OH)D levels were raised and on predefined safety outcomes related to serum 25(OH)D levels, serum and urinary calcium levels, and renal function.

1.3 Aims

The aims of this dissertation were first, to elucidate the potential effects of vitamin D_3 supplementation on cancer prognosis (I) and second, to use data from a self-conducted clinical trial to contribute initial insights into a personalized vitamin D regimen to treat vitamin D deficiency in colorectal cancer patients (II).

In order to achieve aim (I), the following milestones were defined.

- To systematically investigate the efficacy of vitamin D_3 supplementation on cancer mortality in the general population and on survival in patients with cancer by conducting a systematic review, updating former meta-analyses with recently published or unpublished RCTs, and to re-analyze IPD from clinical trials.
- To examine potential effect modifiers of vitamin D_3 supplementation based on patient characteristics and cancer-related factors using IPD subgroup analyses.

In order to achieve aim (II), the following milestones were defined.

- To assess to what extent a personalized vitamin D_3 regimen was able to raise 25(OH)D levels to an optimal level in a clinical trial setting.
- To evaluate the safety of a vitamin D_3 regimen based on high individualized loading doses and maintenance doses in a clinical trial setting.

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2. MATERIAL AND METHODS

2.1 Systematic review and individual patient data meta-analysis of randomized controlled trials

2.1.1 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 (Higgins et al. 2022; Institute of Medicine (US) 2011a; Moher et al. 2015; Shamseer et al. 2015). Any deviations were recorded in an amendment log, describing the exact change and rationale (**Supplemental Table 1**). Reporting is following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis of Individual Participant Data (PRISMA-IPD; see **Supplemental Table 2** for the completed checklist) (Stewart et al. 2015).

2.1.2 Information sources and search strategy

I searched for eligible RCTs in MEDLINE, 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 **Supplemental Table 3** were conceived by two researchers (me and PD Dr. Ben Schöttker) and reviewed by a specialist for systematic bibliographic searches at the Central Library of the German Cancer Research Center (Andrea Heppert). I searched for ongoing or completed RCTs with unpublished data in the World Health Organization's (WHO) International Clinical Trials Research Portal and clinicaltrials.gov via CENTRAL. Reference

lists of eligible studies were scanned to yield relevant articles via cross-referencing. No restrictions regarding the time of publication, language, settings, or geographical locations were applied.

2.1.3 Study selection criteria for meta-analysis

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.

Participants: Studies conducted in the general population or in a population suffering from a chronic disease were included. Special populations such as pregnant or lactating women, infants, and COVID-19 patients were excluded. No other age restrictions were applied.

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).

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).

Outcomes: Studies required at least one cancer death per arm to be eligible and were included if risk ratios (RR) for cancer mortality or cancer survival were published. Results of the intention-to-treat (ITT) approach were used, including all participants randomized, when both ITT and per-protocol (PP) results were given. Unadjusted summary estimates were prioritized over adjusted estimates since the 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.

2.1.4 Data collection and management for meta-analysis

I used EndNote and Rayyan QCRI (web application) to manage citations, title/abstract screening, and full-text selection (Ouzzani et al. 2016). I removed duplicates using an Excel sheet and the Bramer methods (Bramer et al. 2016). I screened all titles and abstracts for potentially relevant RCTs and systematic reviews. I 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 relevant outcomes “cancer mortality” and “cancer survival” and intermediately “all-cause mortality” and “cancer incidence”.

To gather unpublished cancer mortality data, I 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.

All pre-selected studies and those with uncertain eligibility criteria were screened independently by a second researcher (Anna Zhu). Two investigators (me and Anna Zhu) independently extracted data from included studies using standard and predefined data extraction forms. Any disagreements were resolved by consensus and third-party adjudication (PD Dr. Ben Schöttker).

2.1.5 Eligibility for IPD meta-analysis

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, I and PD Dr. Ben Schöttker 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.

2.1.6 Statistical analyses

The computation of the summary RR, 95% CI, the tests for heterogeneity, and publication bias were performed independently by two researchers: PD Dr. Ben Schöttker used Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ) and I 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.

The DerSimonian and Laird method was used to fit random effects models (primary analysis) and the Mantel-Haenzel method to calculate fixed effects summary estimates (secondary analysis). Generally, the results of the random effects model are reported, and for the main meta-analyses, the results of the fixed effects model are shown as well (Deeks et al. 2020). Heterogeneity between studies was assessed by Cochran's Q test, the I^2 index, and tau2. Small-study effects and publication bias were evaluated via funnel plots and Egger's test (Egger et al. 1997).

2.1.6.1 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 ITT results; and 3) co-supplementation of calcium.

2.1.6.2 IPD meta-analyses

Unadjusted and adjusted Cox proportional hazards regression models were run with harmonized variable definitions for the obtained IPD. Five studies sent data to the German Cancer Research Center

(Heidelberg, Germany) and were analyzed there with the same analysis protocol independently by me and PD Dr. Ben Schöttker 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 (Finnish Vitamin D Trial) and D-Health (A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79) studies undertook the analyses in-house using the SAS code provided by BS (Neale et al. 2022; Virtanen et al. 2022). 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.

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 the end of the trial.

To explore sources of heterogeneity, I conducted subgroup analyses according to participant characteristics: (1) in the general population data by participant age, sex, body mass index (BMI), ethnicity, baseline 25(OH)D level, cancer diagnosis before baseline, and adherence; and (2) in cancer patients additionally by cancer stage, cancer site, and time of cancer diagnosis.

Apart from adherence, the factors used for the subgroup analyses were also used as covariates for the adjusted models. I further tested for 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 imputation of missing covariate values was done, and a complete case analysis approach was applied.

2.1.7 Risk of bias assessment

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

2.1.8 Strength of body of evidence

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

2.1.9 Ethics

Ethical approval was not required as only previously published trial data was used. All included studies have their own ethical approvals that can be found in the original publications.

2.1.10 Funding

This project was supported by a grant from the non-profit organization "Deutsche Krebshilfe" (grant number 70114605).

2.2 VICTORIA: a randomized controlled trial

2.2.1 Study design and participants

This dissertation used data from the ongoing VICTORIA study ("*Personalized vitamin D supplementation for reducing or preventing fatigue and enhancing quality of life of patients with colorectal tumor – randomized intervention trial*"; EudraCT number: 2019-000502-30; DRKS00019907) covering selected secondary trial outcomes related to the efficacy and safety of a personalized vitamin D_3 intervention. The primary outcome of the VICTORIA trial "cancer-related fatigue" or secondary outcomes related to the quality of life, diseases, or symptoms are not addressed within the interim analysis.

Details of the study design, including the main and interim analyses, have been reported in the trial protocol (Schöttker et al. 2020). VICTORIA is an ongoing parallel-group, randomized, double-blind, placebo-controlled clinical trial. Overall, 456 colorectal cancer patients aged 18 years and older were recruited from 7 German rehabilitation clinics. The interim analysis included the first 74 enrolled study participants who were recruited between September 2020 and December 2021 in the first three initiated rehabilitation clinics, which are located in the towns Bad Neuenahr-Ahrweiler, Bad Driburg, and Thyrnau (Germany).

Eligible patients had a diagnosis of non-metastatic colorectal cancer (not stage IV), a tumor surgery within the past year (type of surgery not specified), and vitamin D insufficiency (25(OH)D) levels < 50 nmol/L) at the time of screening. Most of the patients in the interim analysis were recruited before a protocol amendment was made for the 25(OH)D level inclusion cut-off and needed even lower, season-standardized 25(OH)D levels < 50 nmol/L (see study protocol for details (Schöttker et al. 2020)). Exclusion criteria comprised mainly an already existing supplementation with high-dose vitamin D, high-dose calcium therapy, and medical conditions/concurrent medication contraindicated for vitamin D_3 therapy according to the Summary of Product Characteristics (see **Supplemental Table 4**).

2.2.2 Intervention

Participants were randomly assigned in a 1:1 ratio to the vitamin D or placebo group. The placebo capsules had the same appearance and approximately the same weight. During the first 11 days, a personalized loading dose based on the 25(OH)D level and BMI at screening was administered, followed by a daily maintenance dose of 2,000 IU (2 tablets of Dekristol® 1,000 IU merged in 1 capsule) until the end of the trial after 12 weeks.

The personalized loading dose was calculated with the equation of Jansen et al. (Jansen and Svendsen 2014), which targets a 25(OH)D level of 80 nmol/L, which is consistent with the Endocrine Society's consensus for the optimal 25(OH)D levels of 75–100 nmol/L (Holick et al. 2011).

$$\text{Loading dose} = 165 * \text{BMI [kg/m}^2\text{]} * (70 - \text{baseline 25(OH)D level [nmol/L]})$$

To avoid nonphysiologically high doses of vitamin D_3 supplements, the loading dose was administered over 11 days in units of 20,000 or 40,000 IU per day (i.e., 1 or 2 capsules of Dekristol® 20,000 IU or placebo) instead of one large bolus. This was primarily justified by emerging findings on vitamin D metabolism and only secondarily by safety concerns (Heaney and Armas 2015).

The randomization list was computer-generated and managed by the pharmacy of the Heidelberg University Hospital. Patients and study staff were masked to the group assignment (double-blind trial).

2.2.3 Study procedures

Blood and urine samples were collected at screening (to determine the laboratory test-based in- and exclusion criteria), visit 1 (trial days 12–21, i.e., end of loading dose and end of rehabilitation clinic stay), and visit 2 (trial weeks 13–16, i.e., end of maintenance dose and end of trial).

2.2.4 Data management

2.2.4.1 Data collection and documentation by trial sites

Written informed consent was obtained for each participant before enrolment in the trial and was kept in the investigator site file at the respective study centers. The investigators entered the date and

quantities of distributed and returned study medication as well as all participant data collected during rehabilitation into the electronic case report form (eCRF), except biomarker results from the second blood and urine sample collection to avoid unblinding. All data entries in the eCRF underwent an automatic online check for plausibility and consistency as defined in the data validation plan. In case of implausibility, a warning message was produced during data entry. A responsible investigator or a designated representative was obliged either to correct the implausible data or to confirm its authenticity and to give an appropriate explanation. The responsible data manager checked all explanations and resolved the warning if the explanation is appropriate.

The responsible investigator confirmed the correctness of all entries in the eCRF with a dated electronic signature. The time points and frequency were pre-defined in the eCRF specification.

All missing data or inconsistencies were reported back to the study centers and had to be clarified by the responsible investigator before the database lock. After applying all applicable corrections in the database, it was declared locked and was used for statistical analyses.

2.2.4.2 Data collection and documentation by the coordinating center

The coordinating center entered the pseudonymized laboratory results of the second and the final sample collection as well as study data from questionnaires and patient diaries in the eCRF. To ensure the integrity of the data, staff members of the coordinating center had clearly defined roles and tasks which were assigned via a delegation log. For example, coordinating center staff members who contact the study participants did not have access to the eCRF, the laboratory results, or the sealed envelopes containing the information on the allocation of treatment. Staff members who open these envelopes or check the pseudonymized laboratory results of the study participants, in turn, did not have access to any patient-identifying data or other study data.

The data management department checked the completeness, the validity, and the plausibility of the entered data using validation programs generating queries where applicable. The head of the

coordinating center or a designated representative confirmed the correctness of all entries in the eCRF by a dated signature as defined in the eCRF specification.

2.2.4.3 Questionnaires

Each patient completed a questionnaire in the rehabilitation clinic at baseline and in study weeks 13 to 16. The questionnaires addressed lifestyle factors (smoking, alcohol consumption, diet, physical activity), CRC therapy (chemotherapy, radiotherapy, operation), and medical history (common diseases, family history of diseases) as well as the (validated) tools for assessment of the outcomes.

2.2.4.4 Laboratory measurements (blood and urine sampling)

Patients were asked to provide a blood and a spontaneous urine sample upon screening (baseline), at the end of rehabilitation (days 12–21), and once again in the study weeks 13 to 16. The first two samples were collected in the rehabilitation clinic (inpatient) while the final sample was collected by the patient's general practitioner (GP, outpatient). For the sampling at the GP's office, the coordinating center sent pseudonymized sampling kits to the participants after trial week 12. One part of the samples was used to determine biomarkers immediately (as efficacy or safety outcomes). Another part was stored at the coordinating center for potential future post-hoc analyses with novel biomarkers.

All blood samples drawn during the trial were either collected in tubes containing clotting activator for analysis of serum or in EDTA tubes for analysis of whole blood. The urine samples were donated in a collection cup of 40 ml from which a volume of 10 ml is extracted using Urin-Monovette®, Luer, Germany. Any residual volume was discarded. The quantity of collected blood and urine samples is shown in **Table 1**.

Table 1. *Time and volume of sampling*

Setting	**No. of sample**	**Phase of clinical trial**	**Blood Sampling**		**Urine Sampling**
			EDTA tube	Serum tube	
Inpatient	1	Screening	1 x 2.7 ml	1 x 9 ml	1 x 10 ml
	2	Day 12 to 21	1 x 2.7 ml	4 x 9 ml	2 x 10 ml
Outpatient	3	Week 13 to 16	1 x 2.7 ml	4 x 9 ml	2 x 10 ml

1st and 2nd samples: The EDTA tube, one serum tube, and 10 ml urine were prepared for transportation by the laboratories with which the rehabilitation clinics normally cooperate. This procedure ensures rapid transport and analysis of biomarkers within 48 hours. The remaining samples (if any) were sent via express mail to the coordinating center for aliquoting and storage at -80°C.

3rd sample: The GP sent all samples to the laboratory of the coordinating center via express mail. The latter immediately sent the EDTA tube, one serum tube, and 10 ml urine via express mail to the same cooperating laboratories that had also processed the first two specimens. The remaining samples were stored at the laboratory of the coordinating center at -80°C. Using the same laboratories for the sample analysis avoided bias due to different measurement methods.

To comply with the pre-analytical requirements, it was ensured that the transport time from sampling to analysis was less than 48 hours and that the temperature of the samples during transport was between 2 and 25°C (2022). Serum tubes were inverted 3–5 times immediately after collection and then stored at room temperature for 30 to 60 minutes to allow blood clotting. Tubes were subsequently centrifuged at 2500–3500 revolutions per minute for 10 minutes. EDTA tubes were inverted eight to 10 times to ensure an even mixture of EDTA and blood.

The laboratories cooperating with the rehabilitation clinics measured all parameters with standard state-of-the-art lab methods.

2.2.5 Outcomes and endpoints

The trial outcomes have been chosen in order to determine the efficacy and safety of the intervention. The following efficacy outcomes are addressed in the interim and main analysis:

- Mean difference in the serum 25(OH)D levels between the intervention and placebo groups at visits 1 and 2.
- Mean difference in the change of the serum 25(OH)D levels from screening to visits 1 and 2.

- Difference in prevalence of subjects with adequate serum 25(OH)D levels ≥ 50 nmol/L (Institute of Medicine (US) 2011b) in the intervention group and placebo group at visits 1 and 2.

The following safety outcomes are addressed in the interim and main analysis:

- Difference in the frequency of hypervitaminosis D (25(OH)D levels > 150 nmol/L (Institute of Medicine (US) 2011b)), hypercalcemia (albumin-corrected serum calcium > 2.65 mmol/L (Meng and Wagar 2015)), hypercalciuria (random urine calcium ≥ 0.79 mmol/mmol creatinine (Tellioglu et al. 2012)), and renal dysfunction (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al. 2009)) between the intervention and placebo group at visits 1 and 2.
- Mean differences in the levels of albumin-corrected serum calcium, urine calcium/creatinine ratio, and eGFR between the intervention and placebo groups at visits 1 and 2.

The following outcomes are only addressed in the main analysis:

The primary outcome fatigue will be evaluated by using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) fatigue subscale, version 4.0, a commonly used and well-validated measure of fatigue in people with cancer and other chronic health conditions (Cella et al. 1993). The tool assesses self-reported tiredness, weakness, and difficulty conducting common activities due to fatigue. Higher scores represent less fatigue. The primary endpoint will be measured as the mean difference in the FACIT-F fatigue subscale between the intervention and placebo group at trial weeks 13–16. A mean difference of ≥ 3 FACIT-F fatigue subscale points will be considered a clinically relevant difference (Cella et al. 2002). Additionally, the mean difference in change of FACIT-F fatigue subscale from baseline to trial weeks 13–16 between the intervention and placebo group will be determined as a secondary endpoint.

Subdomains of fatigue will be evaluated using the European Organization for Research and Treatment of Cancer – Cancer related Fatigue (EORTC QLQ-FA12) questionnaire. This is an alternative to the FACIT-F fatigue subscale without being a global fatigue assessment tool (Weis et al. 2017; Weis et al. 2019), with higher scores representing more severe fatigue. Physical, emotional, and cognitive fatigue domains are relevant for the VICTORIA study. They will be assessed as the mean differences in EORTC QLQ-FA12 physical, emotional and cognitive fatigue scores between the intervention and placebo group at trial weeks 13–16 as well as mean differences in changes in these scores from baseline to trial weeks 13–16 between the intervention and placebo group.

Quality of life will be determined with the European Organization for Research and Treatment of Cancer – Core Quality of life questionnaire with 30 items (EORTC-QLQ-C30), version 3.0. The questionnaire is used to gauge the overall and domain-specific QoL in cancer patients (Aaronson et al. 1993). Higher scores represent better functioning. Items relevant to the VICTORIA study include the five functional scales (assessing physical, role, emotional, cognitive, and social functioning) and one global health status/QoL scale. Endpoints are the mean differences in overall and domain-specific quality of life scores of the EORTC QLQ-C30 questionnaire between the intervention and placebo group at trial weeks 13–16 as well as mean differences in changes in these scores from baseline to trial weeks 13–16 between the intervention and placebo group. Mean differences ≥ 5 points in the overall and domain-specific scores of the EORTC QLQ-C30 will be considered clinically relevant differences (Osoba et al. 1998).

Probable depression will be ascertained with the Geriatric Depression Scale (GDS-15) which has been developed for use among older adults (Dias et al. 2017; Stiles and McGarrahan 1998). The focus on the elderly is crucial for this trial as the mean age of the CRC patients to be included is expected to be approximately 65 years. An overall score ≥ 5 points is considered probable depression (Dias et al. 2017). The endpoint will be the mean difference in the GDS-15 scale between the intervention and placebo group at trial weeks 13–16 as well as the mean difference in changes in this scale from baseline to trial weeks 13–16 between the intervention and placebo group.

The FACIT-F Functional Well-Being (FWB) subscale will be used to assess the FWB by querying about limitations in the ability to work, coping with the disease, and general life satisfaction (Cella et al. 1993). Higher scores represent better well-being. The endpoint will be the mean difference in the FACIT-F FWB score between the intervention and placebo group at trial weeks 13–16 as well as the mean difference in changes in this score from baseline to trial weeks 13–16 between the intervention and placebo group.

Infection frequency will be assessed by a self-developed questionnaire. Participants will be asked to state the number of infection episodes for the following infections during the last 12 weeks: Infections of the upper and lower respiratory tract, gastrointestinal infection with diarrhea, cystitis, and fever higher than 38 °C. The total infection frequency will be the sum of all reported infection episodes. If this sum is lower than the number of stated fever episodes with ≥ 38°C, the latter will be used as the total infection frequency. Endpoints will be the mean differences in infection frequencies (total, upper respiratory, and lower respiratory tract infections between the intervention and placebo group at trial weeks 13–16.

Finally, the following laboratory parameters complete the secondary endpoints:

- Mean differences in levels of biomarkers (white blood cell count, leukocyte subtype counts (band neutrophils, segmented neutrophils, eosinophils, basophils, lymphocytes, and monocytes), serum C-reactive protein, serum uric acid, serum creatinine, serum total cholesterol, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, and serum triglycerides between intervention and placebo group at trial days 12–21 and in trial weeks 13–16 as well as the mean difference in change of levels of these biomarkers from baseline to trial days 12–21 and from baseline to trial weeks 13–16.
- Mean difference in HbA_{1c} levels between intervention and placebo group at trial weeks 13–16 as well as the mean difference in change of HbA_{1c} levels from baseline to trial weeks 13–16.

2.2.6 Laboratory methods for 25(OH)D measurements

The biomarker measurements took place in the laboratories with which the recruiting rehabilitation clinics collaborate in clinical practice (MVZ Labor Dr. Quade & Kollegen GmbH, Cologne; MVZ Labor Passau, Passau; LADR GmbH MVZ, Paderborn). All three labs used the LIAISON® 25 OH VITAMIN D TOTAL chemiluminescent immunoassay of DiaSorin, Saluggia, Italy. According to the manufacturer, the intraassay and interassay coefficients of variation were 5.4% and 10.6%, respectively, and the detection range was 10–375 nmol/L. Regarding the comparability of results between collaborating laboratories, all part of them participated in the quality assurance of the laboratory medical examinations of the Federal Medical Association ("Bundesärztekammer") and conduct regular ring tests.

2.2.7 Safety assessment

Participants were asked about concomitant medication and diseases before inclusion. To minimize the risk of AEs and exacerbation of existing conditions, only patients without conditions listed as contraindications in the Summary of Product Characteristics (SmPC) of Dekristol® 20,000 IU or requiring special safety monitoring were enrolled (see exclusion criteria **Supplemental Table 4**). In the patient information document, patients were informed about potential risks associated with trial participation and were instructed to contact the trial physician in case of serious medical problems. The observation period of AEs begun with the first administration of the trial medication and ended with its last administration. Events happening before the first administration were defined as medical history. AEs were queried during every visit with the responsible investigator and additionally within the patient diary during the entire intervention phase. All AEs were documented in the eCRF stating the participant's randomization number, the start and end date, a description, the intensity, the seriousness, the relationship with the study medication, the measures taken, and the outcome.

All serious adverse events (SAEs) were reported by the investigator to the pharmacovigilance department of KKS using a standardized form within 24 hours after initial observation or awareness of the event. Every SAE was subject to a second assessment by a designated person, independent of the

reporting investigator. All SAEs and their relevance for the risk-benefit assessment of the trial as well as the final report were evaluated continuously during the trial.

A steering committee was convened to ensure the ethical conduct of the trial and to protect the rights as well as the welfare of the patients. The board consists of the coordinating investigator, the head of the coordinating center, the deputy head of the coordinating center, and the clinical pharmacology consultant. By periodically assessing the safety of the intervention and reviewing potential safety issues, amendments to the further trial conduct (modification, continuation, closure) were decided and documented.

2.2.8 Quality control and assurance

Internal standard operating procedures and all applicable regulations were followed for the preparation, implementation, documentation, and analyses of the clinical trial. The pharmacy of the University Hospital Heidelberg is holding a manufacturing license and was therefore authorized to produce the required study medication. Packing, labeling, and blinding took place according to the applicable GCP and GMP regulations and standards.

As required by the German Drug Law (AMG) for multicenter trials, the sponsor has appointed a coordinating investigator (German: Leiter der klinischen Prüfung). Moreover, every trial site has selected one principal investigator and at least one deputy investigator. All trial physicians and trial centers comply with the qualification requirements of the responsible Ethics Committee in terms of professional education, experience in clinical trials, and equipment. Since the trial medication is well characterized, has low risk, and was tested in a non-critical indication (fatigue), a Data Monitoring Committee has not been set up (EMEA 2005).

All data obtained over the course of the trial were treated pursuant to the German Federal Data Protection Act (BDSG) and the European ordinance (EU) 2016/679. The individual participants were exclusively identified by their patient identification and randomization numbers. The investigators provide direct access to source data/documents for trial-related monitoring, audits, and regulatory

inspection. Each participant had to agree to a written informed consent form to have direct access to their original medical records for purposes of study monitoring, audit, and regulatory inspection.

Qualified staff regularly monitored every study site by reviewing source documents, entries into the eCRFs, and essential documents to ensure that the trial met the protocol and regulatory requirements. Monitoring included an on-site initiation visit, regular on- and off-site visits during the recruitment phase, and a close-out visit. Before the study started, the participating sites were personally trained and introduced to all study specific procedures during the on-site initiation visits. After each visit, the monitor prepared a report for the sponsor and a follow-up letter with findings and eventual necessary measures for the sites. All procedures were pre-defined in the monitoring manual.

All planned substantial changes to the clinical study need to be signed by the sponsor, the coordinating investigator, the biometrician, and the clinical pharmacology consultant. According to §10 of the GCP-V, protocol amendments are submitted in writing to the responsible Ethics Committee and the national competent authority.

2.2.9 Statistical analysis

2.2.9.1 Sample size estimation for VICTORIA trial

The sample size calculation was based on the primary endpoint FACIT-F fatigue subscale and the assumption of its normal distribution. An increase in the FACIT-F fatigue subscale by three points was found to be a clinically relevant reduction of fatigue (Cella et al. 2002). The assumed mean and standard deviation of the FACIT-F fatigue subscale were extracted from the representative study of Jones et al. (Jones et al. 2016), which were 38.5 and 10.8, respectively. With a significance level of 0.05 and 80% power, 205 patients were needed in each group to detect a score difference of three or more points using a two-sample t-test for the mean difference, i.e., 410 patients were required in total. The number of patients to be randomized was calculated assuming a 10% drop-out rate. Under these assumptions, 500 CRC patients need to be screened, and from these, 456 eligible patients randomized to reach the analyzable sample size of $n = 410$.

Given the annual number of overall 1,400 eligible CRC patients reported by the participating three rehabilitation clinics in 2016, recruitment of 456 eligible stage I–III CRC patients was expected to be feasible within 24 months.

2.2.9.2 Statistical methods for the interims analysis

The ITT analysis included all randomized patients who provided a blood sample either on trial days 12–21 or trial weeks 13–16. The PP analysis excluded study participants who failed to comply with the trial medication (<80% of capsules), who were falsely included, who discontinued treatment after visit 1 due to safety concerns prespecified in the protocol, who were nonadherent, and who were taking any vitamin D product in addition to the trial medication. Due to the importance of protocol adherence for the relationship between vitamin D supplementation and 25(OH)D level changes, the PP results are shown in the main text and the ITT results are presented in the Supplemental Material.

Assuming a normal distribution for the total serum 25(OH)D level, a two-sample, two-tailed *t*-test was performed for continuous outcomes, including the computation of means with a 95% CI. The *p*-value was derived by using the Satterthwaite method. If at least one event occurred during the trial in both trial arms, Fisher's exact test was utilized for dichotomous outcomes to test for differences between the verum and placebo groups. A two-sided significance level of 0.04 was used for all tests in this interim analysis to leave a significance level of 0.01 for the main analysis when recruitment is completed. No multivariate models were used in the interim analysis.

All analyses were conducted using SAS software version 9.4.

2.2.9.3 Statistical methods for the main analysis

The homogeneity of the treatment groups will be described by comparison of the demographic data and the baseline values of key variables. All statistical tests will have a two-sided significance level of 0.05. Besides, 95% CI will be estimated for all outcomes in the placebo and verum groups.

The primary analysis will test the null hypothesis

H_0: The FACIT-F fatigue subscale at weeks 13–16 is the same in the two groups

versus the alternative hypothesis

H_1: The FACIT-F fatigue subscale at weeks 13–16 is different in the two groups.

The primary endpoint FACIT-F fatigue subscale will be analyzed with an ITT approach. The ITT population will include all randomized study participants with data for the primary endpoint and who did not withdraw consent during the trial. A PP analysis will be done additionally as a sensitivity analysis. The PP population will exclude study participants who meet the following criteria:

- Fatigue questionnaire missing at trial weeks 13–16
- Error in the timing of collection of fatigue questionnaire at trial weeks 13–16
- After enrollment, it becomes evident that the patient met exclusion criteria at the time of recruitment or did not meet inclusion criteria.
- Non-adherence to trial medication (defined as intake of less than 80% of capsules) unless treatment was terminated due to safety reasons
- Self-reported intake of vitamin D or vitamin D analogs in addition to the trial medication.
- Criteria for discontinuation of study medication were met but study medication intake was continued.

Normal distribution for the outcome FACIT-F fatigue subscale will be tested using the Shapiro-Wilks test. If a normal distribution can be assumed, the primary test statistic will be the two-sample t-test for the mean difference. If a normal distribution cannot be assumed, the FACIT-F fatigue subscale will be log-transformed and retested for normal distribution using the Shapiro-Wilks test. If a normal distribution cannot be assumed for either the FACIT-F fatigue subscale or the log-transformed FACIT-F fatigue subscale, a Wilcoxon Rank-Sum test will be performed. In addition, an appropriate 95% CI will be estimated for the FACIT-F fatigue subscale in the two groups and the difference in the FACIT-F fatigue subscale between the two groups.

A priori defined subgroup analyses will be conducted for groups defined by age (< 65 / ≥ 65 years), sex (male / female), CRC stage (I or II / III), 25(OH)D levels at screening (< 30 / ≥ 30 nmol/L), season at

screening (Dec-Feb/Mar-Mai/Jun-Aug/Sept-Nov), BMI at screening (< 30 / ≥ 30 kg/m²), FACIT-F fatigue subscale at screening (≤ 34 / > 34 points), mild to moderate anemia at screening (hemoglobin 8–10 mg/dl / > 10 mg/dl), chemotherapy and/or radiotherapy in nine months before screening (yes / no), chemotherapy and/or radiotherapy during trial (yes / no), geriatric depression scale (GDS-15) score at follow-up (< 5 / ≥ 5 points), insomnia at follow-up (EORTC QLQ-C30 insomnia item < 3 / ≥ 3 points), pain at follow-up (EORTC QLQ-C30 pain scale < 6 / ≥ 6 points), use of strong opioids (ATC codes N02AB03, N02AA01, N02AG01, N02AA51, N02AA03, N02AG04, N02AA53, N02AA05, N02AJ18, N02AJ19, N02AA55, N02AA56, N02AJ17, N02AX06, N02AE01, and N02AA25) at follow-up (yes / no), use of psycholeptics (ATC code N05) at follow-up (yes / no), and use of corticosteroids for systemic use (ATC code H02) at follow-up (yes / no).

In addition, a subgroup analysis will be conducted for study participants, who most likely profit from the vitamin D_3 intervention because of the following conditions (yes / no): No protocol deviations (patients did not withdraw consent during the trial, were adherent to the trial medication (defined as taking at least 80% of all capsules), and did not take vitamin D_3 or vitamin D analogs in addition to the trial medication), FACIT-F fatigue subscale ≤ 34 at screening, and no use of strong opioids or psycholeptics at follow-up.

A mean difference ≥ 3 FACIT-F fatigue subscale points will be considered a clinically relevant difference (Cella et al. 2002).

Depending on the availability of future funding for genotyping of all randomized participants, further subgroup analyses are planned that stratify participants by genetic susceptibility for low 25(OH)D levels or cancer-related fatigue (Manousaki et al. 2020; Yang et al. 2019).

As a sensitivity analysis, a linear regression model will be conducted using the FACIT-F fatigue subscale as the dependent variable and the treatment group as the independent variable. The linear regression model will be adjusted for all variables designated in the subgroup analysis while using some variables continuously instead of categorically (age, hemoglobin levels at screening, 25(OH)D levels at screening, BMI at screening, FACIT-F fatigue subscale at screening, insomnia scale at follow-up and

pain scale at follow-up). If appropriate, missing covariate values will be imputed with multiple imputations.

All secondary endpoints with a continuous scale will be analyzed using the same statistical methods as described for the primary endpoint. All dichotomous secondary endpoints will be tested with a Chi^2 test. AEs will be analyzed with descriptive statistics including frequencies of SAEs.

Lastly, the success of the personalized vitamin D_3 intervention in raising the serum 25(OH)D level will be evaluated in the intervention group on trial days 12–21. Furthermore, the ability of the maintenance dose to maintain sufficient vitamin D status in the intervention group will be evaluated in trial weeks 13–16. To be successful, the mean 25(OH)D levels in the group with personalized vitamin D_3 intervention should be higher than 50 nmol/L. This translates into the following test hypotheses:

H_0: Mean $25(OH)D_{\text{personalized intervention}} \leq 50$ nmol/L

H_1: Mean $25(OH)D_{\text{personalized intervention}} > 50$ nmol/L

To test these hypotheses, a one-sample t-test on the mean 25(OH)D levels will be conducted at a one-sided significance level of 0.025. 25(OH)D levels may be log-transformed if this improves the approximation to a normal distribution (tested with a Shapiro-Wilks test).

2.2.9.4 Exploratory sub-project: "Determinants of the achieved 25(OH)D levels by the personalized vitamin D_3 intervention"

In the following, the statistical methods of an observational sub-project for the secondary outcome "25(OH)D level" are described. This solely observational research project will be addressed in those 228 VICTORIA trial participants who received the personalized vitamin D_3 intervention and adhered to the trial medication (defined by taking at least 80% of the trial medication capsules), which will result in a final sample size $n < 228$. If 25(OH)D levels or log-transformed 25(OH)D levels are normally distributed (tested with a Shapiro-Wilks test), a linear regression model will be carried out with a continuous 25(OH)D level variable. In addition, a logistic regression model will be used with a dichotomized 25(OH)D level variable (< 50 nmol/L / ≥ 50 nmol/L) as the dependent variable.

Covariates for the linear and logistic regression model will be study center, age, sex, baseline 25(OH)D, compliance up to time of blood sampling, difference between exactly calculated and rounded supplied loading dose, number of days between last intake of trial medication and blood sampling, season at recruitment, baseline BMI, baseline waist circumference, baseline smoking, baseline physical activity, baseline physical functioning (EORTC QLQ-C30 subscale), baseline Charlson Comorbidity Index, baseline frailty, baseline FACIT-F fatigue subscale, GDS-15 total score ≥ 5 points (at baseline), baseline anxiety (GAD-7 score), baseline pain (EORTC QLQ-C30 pain scale), CRC stage, time since CRC tumor surgery, stoma, concomitant use of vitamin D products (at follow-up), chemotherapy and/or radiotherapy in nine months before trial (yes / no), chemotherapy and/or radiotherapy during trial (yes / no), concomitant use of laxatives (at baseline and/or follow-up), concomitant use of other drugs limiting vitamin D_3 bioavailability at baseline and/or follow-up (phenytoin, barbiturates, systemic glucocorticoids, rifampicin, isoniazid, cholestyramine, orlistat, dactinomycin or systemic azole-antimycotics), nutritional vitamin D intake (at follow-up), appetite loss (at baseline and/or follow-up), sun exposure in last summer before baseline, skin type, solarium use in last two months before baseline, frequency of diarrhea (at baseline and/or follow-up), vitamin D binding protein levels and single nucleotide polymorphisms previously shown to be associated with low 25(OH)D levels. If appropriate, missing covariate values will be imputed with multiple imputations.

Mean 25(OH)D levels and proportions of study participants with 25(OH)D levels < 50 nmol/L will be presented distinctly for factors that were statistically significant ($p<0.05$) determinants of achieved 25(OH)D levels.

The analyses will be carried out both for the 25(OH)D measurement from day 12–21 (end of loading dose consumption) and for the 25(OH)D measurement from week 13–16 (end of maintenance dose consumption).

2.2.10 Ethics approval

Ethical approval for the study was granted by the responsible Ethics Committee of the State Chamber of Medicine in Rheinland-Pfalz and the local Ethics Committee of the Chamber of Medicine Westfalen-

Lippe responsible for the participating study center (approval number: 2020-14854_3-AMG). The study was further approved by the national competent authority, the Federal Institute for Drugs and Medical Devices (BfArM; approval number: 61-3910-4044014). The trial was planned and conducted in line with the principles of the Declaration of Helsinki (latest amendment), the standards of ICH-GCP (topic E6), the GCP-V, the AMG, and the BDSG. In addition, the clinical trial office, the division of data protection, quality management, and the legal department of the German Cancer Research Center reviewed the entire planning phase of the study. The trial was registered in the German Clinical Trials Register "DRKS" (DRKS00019907) before the first patient was recruited.

2.2.11 Funding

The clinical trial is funded by the Wereld Kanker Onderzoek Fonds (WKOF) as part of the World Cancer Research Fund International (WCRF), grant number 2018/1696, and supported by own resources of the sponsor (German Cancer Research Center). The funding source was not involved in the study design and has no role in data collection, data analysis, and interpretation, or decision to submit results for presentation or publication.

3. RESULTS

3.1 Systematic review and individual patient data meta-analysis on the efficacy of vitamin D_3 supplementation on cancer mortality

3.1.1 Study search and selection

The study search and selection process are summarized in **Figure 1**. In my search for RCTs, I identified 3,664 published articles and 899 registry records. Searches for systematic reviews and/or meta-analyses yielded 1,248 potentially relevant records. After the removal of duplicates and title/abstract screening, the full-text articles of 253 potentially eligible studies were identified. I identified a further 20 potentially eligible studies included in 33 previous systematic reviews. Overall, I reviewed the full-text articles of 273 studies, of which 175 studies met exclusion criteria as shown in **Figure 1** (**Supplemental Table 5** lists all excluded studies and reasons for exclusion).

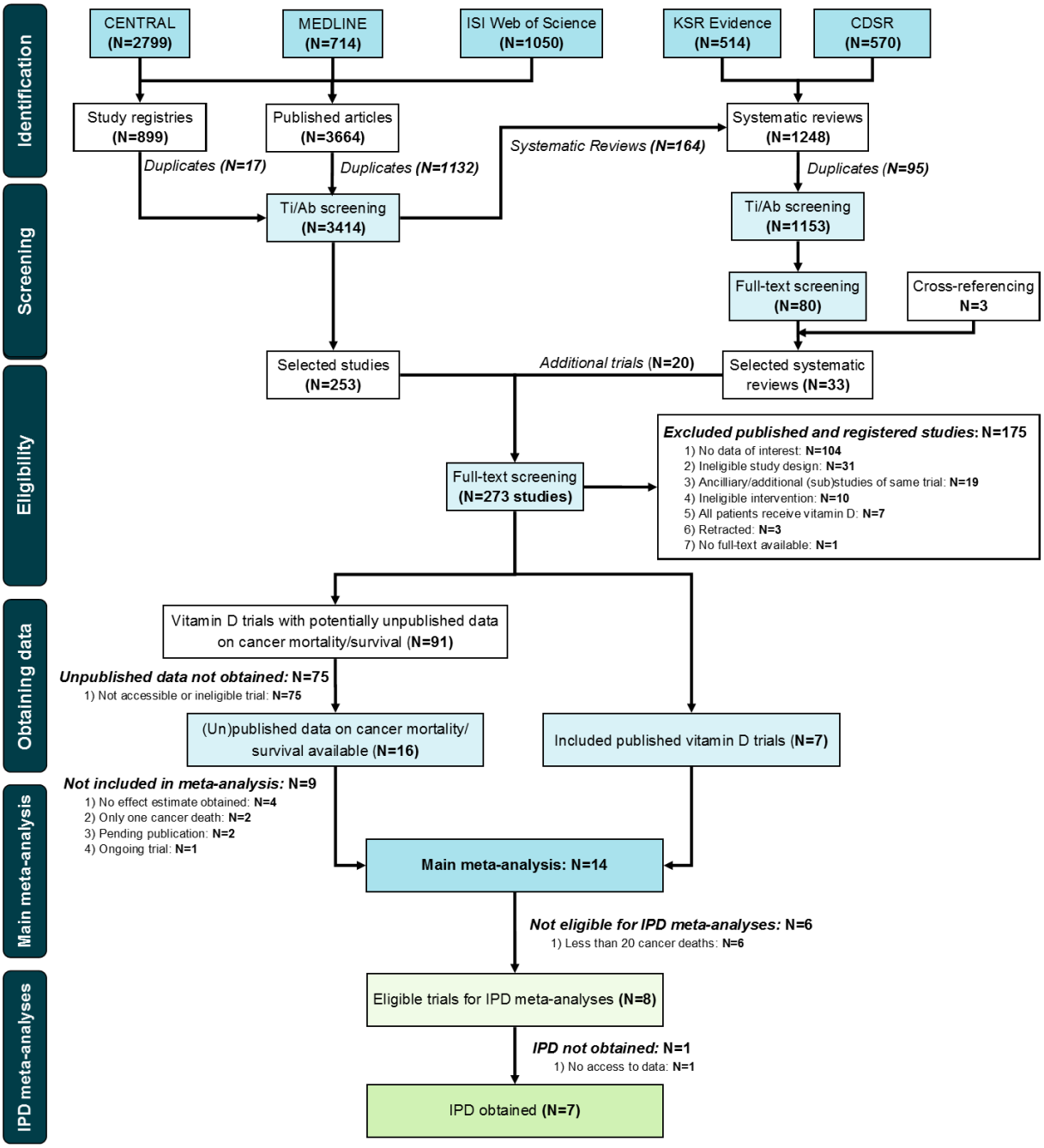

Figure 1. *Flow diagram of study selection*

Note: N represents the count.
Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; CDSR, Cochrane Database of Systematic Reviews; KSR, Kleijnen Systematic Reviews

From these articles, seven trials could be included in the meta-analysis. I also attempted contact with authors of 91 studies with potentially unpublished data on cancer mortality/survival or to clarify uncertainties (**Supplemental Table 6** 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 ≥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 = 2,686) have been archived and are no longer accessible (Trivedi et al. 2003). No IPD data integrity issues were identified during my analysis.

3.1.2 Characteristics of included studies

The complete study characteristics of the included 14 RCTs are summarized in Table 2 and **Supplemental Table 7**. 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 (Avenell et al. 2012; Baron et al. 2015; Chatterjee et al. 2021; Manson et al. 2019; Martineau et al. 2015; Neale et al. 2022; Scragg et al. 2018; Sudfeld et al. 2020; Trivedi et al. 2003; Virtanen et al. 2022; Wactawski-Wende et al. 2006; Witte et al. 2016). Two studies investigated cancer survival as the primary outcome (Akiba et al. 2018; Urashima et al. 2019), and seven trials examined cancer mortality as a secondary outcome (Avenell et al. 2012; Chatterjee et al. 2021; Manson et al. 2019; Neale et al. 2022; Scragg et al. 2018; Trivedi et al. 2003; Virtanen et al. 2022). Five studies were conducted in Europe (Avenell et al. 2012; Martineau et al. 2015; Trivedi et al. 2003; Virtanen et al. 2022; Witte et al. 2016), four in North America (all in the US) (Baron et al. 2015; Chatterjee et al. 2021; Manson et al. 2019; Wactawski-Wende et al. 2006), two in Australia/New Zealand (Neale et al. 2022; Scragg et al. 2018), two in Asia (both in Japan) (Akiba et al. 2018; Urashima et al. 2019), and one in Africa (Tanzania) (Sudfeld et al. 2020). Ten trials used a daily vitamin D_3 regimen ranging from 400

IU to 4000 IU daily (Akiba et al. 2018; Avenell et al. 2012; Baron et al. 2015; Chatterjee et al. 2021; Manson et al. 2019; Sudfeld et al. 2020; Urashima et al. 2019; Virtanen et al. 2022; Wactawski-Wende et al. 2006; Witte et al. 2016). Four trials provided a large bolus dose of vitamin D_3 intermittently (60,000 IU monthly to 100,000 IU every four months) (Martineau et al. 2015; Neale et al. 2022; Scragg et al. 2018; Trivedi et al. 2003). Two trials additionally featured a high initial dose at the beginning of the intervention followed by daily dosing (Scragg et al. 2018; Sudfeld et al. 2020). 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 (Akiba et al. 2018; Avenell et al. 2012; Baron et al. 2015; Chatterjee et al. 2021; Manson et al. 2019; Martineau et al. 2015; Scragg et al. 2018; Sudfeld et al. 2020; Urashima et al. 2019; Virtanen et al. 2022; Wactawski-Wende et al. 2006; Witte et al. 2016). Ten studies allowed personal vitamin D_3 supplementation in the control group, ranging from 200 IU to 2,000 IU daily, and one study did not provide such information (Akiba et al. 2018; Sudfeld et al. 2020; Urashima et al. 2019; Witte et al. 2016).

Table 2. *Characteristics of included studies*

FIRST AUTHOR, YEAR, STUDY ID, COUNTRY	**SAMPLE SIZE (RANDOMIZED, ANALYZED)**	**VITAMIN D_3 DOSING REGIMEN, GALENICS**	**INTERVENTION PERIOD [YEARS]**	**NO OF CANCER DEATHS IN TREATMENT PERIOD**	**RISK RATIO FOR CANCER MORTALITY (95% CI) IN TREATMENT PERIOD**
TRIVEDI, 2003 UK	R = A = 2,686	100,000 IU Q4M (15 doses total), capsule	5	135	0.86 (0.61; 1.20)
WACTAWSKI-WENDE, 2006; JACKSON, 2003; JACKSON, 2006; CHLEBOWSKI, 2008; CHACKO, 2011 ***WHI*** **(NCT00000611), US[A]**	R = A = 36,282[a]	400 IU/d + 1,000 mg Ca/d, chewable tablet	7	726	0.89 (0.77; 1.03)
AVENELL, 2012; GRANT, 2005 ***RECORD*** **(ISRCTN51647438), UK**	R = A = 2,675[b]	800 IU/d, 1,000 mg Ca/d, both/d, tablet	2–5.2	88[c]	0.83 (0.55; 1.26)[c]
BARON, 2015 ***VITAMIN D/CALCIUM POLYP PREVENTION STUDY*** **(NCT00153816), US**	R = 835[d]	1,000 IU/d, 1,200 mg Ca/d, both/d, tablet	3–5	5[e]	1.44 (0.24; 8.63)[e]
MARTINEAU, 2015 ***VIDICO*** **(NCT00977873), UK**	R = A = 240	120,000 IU Q2M, Vigantol oil	1	2	0.97 (0.06; 15.29)[f]
WITTE, 2016 ***VINDICATE*** **(NCT01619891), UK**	R = 223; A = 163	4,000 IU/d, tablet	1	5[g]	0.25 (0.03; 2.44)[g]
AKIBA, 2018 AMATERASU 4 (UMIN000001869), JAPAN	R = 155[h]; A = 144	1,200 IU/d, capsule	1	2[i]	1.01 (0.06; 15.10)[i]
MANSON, 2018, ***VITAL*** **(NCT01169259), US**	R = A = 25,871	2,000 IU/d, n-3 fatty acids 1g/d, both/d, capsule	5	341	0.83 (0.67; 1.02)
SCRAGG, 2018 ***VIDA*** **(ACTRN12611000402943), NEW ZEALAND**	R = 5,110; A = 5,108	Initial dose of 200,000 IU, then 100,000 IU/m, soft-gel capsule	3.3[j]	60[k]	0.99 (0.60; 1.64)[k]
URASHIMA, 2019 AMATERASU 5 (UMIN000001977), JAPAN	R = A = 417	2,000 IU/d, capsule	5	62	1.09 (0.58; 2.01)

FIRST AUTHOR, YEAR, STUDY ID, COUNTRY	SAMPLE SIZE (RANDOMIZED, ANALYZED)	VITAMIN D_3 DOSING REGIMEN, GALENICS	INTERVENTION PERIOD [YEARS]	NO OF CANCER DEATHS IN TREATMENT PERIOD	RISK RATIO FOR CANCER MORTALITY (95% CI) IN TREATMENT PERIOD
SUDFELD, 2020 ***TOV4*** **(NCT01798680), TANZANIA**	R = A = 4,000	50,000 IU/wk for first month of ART, then 2,000 IU/d, "supplements"	1	8[l]	1.01 (0.25; 4.02)[l]
CHATTERJEE 2021 ***D2DCA*** **(NCT01942694), US**	R = A = 2,385	4,000 IU/d, soft-gel	3	6[m]	0.23 (0.03; 1.96)[m]
NEALE, 2022 ***D-HEALTH*** **(ACTRN12613000743763), AUSTRALIA**	R = 21,315; A = 21,310	60,000 IU/m, gel capsule	5	452[n]	1.15 (0.96; 1.39)[n]
VIRTANEN, 2022, ***FIND*** **(NCT01463813), FINLAND**	R = A = 2,495	3,200 IU/d, pills	5	36[m, o]	0.90 (0.38; 2.13)[m, o]
		1,600 IU/d, pills	5	36[m, o]	1.36 (0.63; 2.97)[m, o]
		Both intervention arms combined	5	36[m, o]	1.13 (0.56; 2.30)[m, o]

Abbreviations: /d, /wk, /m, per day/week/month; AMATERASU 4, A randomized, double blind, comparative study of STATUS D_3 (vitamin D_3) versus placebo in patients with lung cancer to prevent relapse after operation; AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; ART, antiretroviral therapy; Ca, calcium; COD, cause of death; D2dCA, Vitamin D and type 2 diabetes cancer outcomes study; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; FU, follow-up; m month; OS, overall survival; P, placebo; Q2M / Q4M, every 2 / 4 months; RECORD, Randomized Evaluation of Calcium Or vitamin D; RR, relative risk; ToV4, Trial of Vitamin D in HIV Progression; VD, vitamin D_3; VDS, Vitamin D_3 supplementation; ViDA, Vitamin D Assessment Study; ViDiCO, Vitamin D Supplementation in Chronic Obstructive Pulmonary Disease; VINDICATE, Vitamin D treating patients with chronic heart failure; VITAL, Vitamin D and Omega-3 Trial; WHI, Women's Health Initiative; y, year

Footnotes:

[a] Vitamin D_3 was inseparably combined with calcium.

[b] 5,292 participants were randomized 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 randomization (2GR), women could elect to be randomly assigned to receive either calcium or calcium plus vitamin D_3 (584 randomized, 540 analyzed). Regarding the full factorial randomization (FFR), all other patients were randomly assigned to receive one of the four regimens (1,675 randomized, 1,548 analyzed). 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 randomized 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 randomization.

[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)

3.1.3 Meta-analysis of all trials

3.1.3.1 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, with no indication of heterogeneity (Cochran's Q = 10.96 (p = 0.614), I^2 = 0%, tau^2 = 0%; **Figure 2**). 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 (**Supplemental Figure 1**).

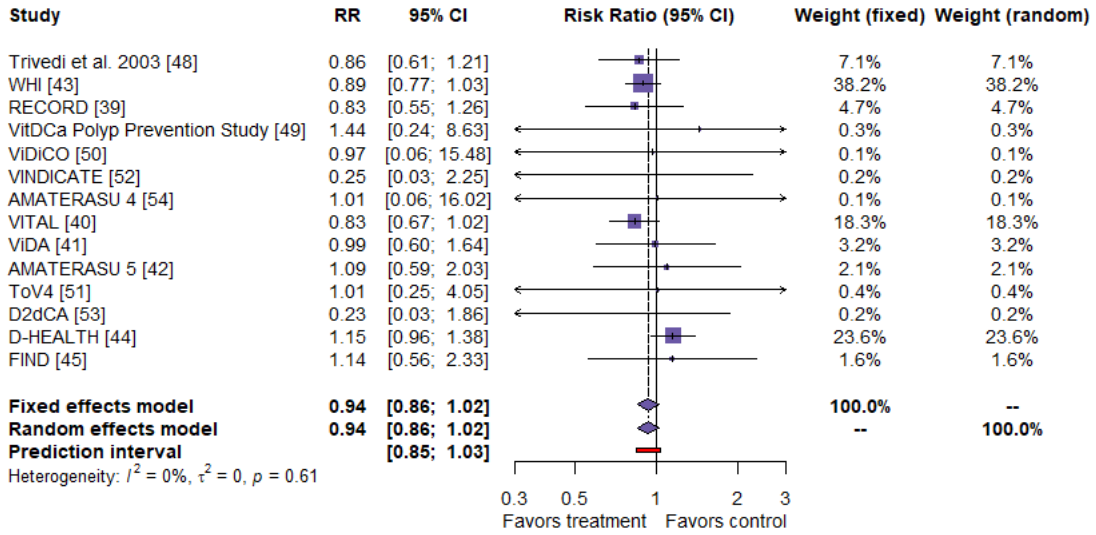

Figure 2. *Meta-analysis of all included RCTs comparing vitamin D_3 and placebo for the outcome "cancer mortality"*

Abbreviations: 95% CI, 95% confidence interval; AMATERASU 4, A randomized, double blind, comparative study of STATUS D_3 (vitamin D_3) versus placebo in patients with lung cancer to prevent relapse after operation; AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; D2dCA, Vitamin D and type 2 diabetes cancer outcomes study; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; RECORD, Randomized Evaluation of Calcium Or vitamin D; RR, risk ratio; ToV4, Trial of Vitamin D in HIV Progression; ViDA, Vitamin D Assessment Study; ViDiCo, Vitamin D Supplementation in Chronic Obstructive Pulmonary Disease; VINDICATE, Vitamin D treating patients with chronic heart failure; VITAL, Vitamin D and Omega-3 Trial; VitDCa, Vitamin D/Calcium; WHI, Women's Health Initiative

3.1.3.2 Subgroup analyses

Figure 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 US 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 the 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 US or Europe used daily

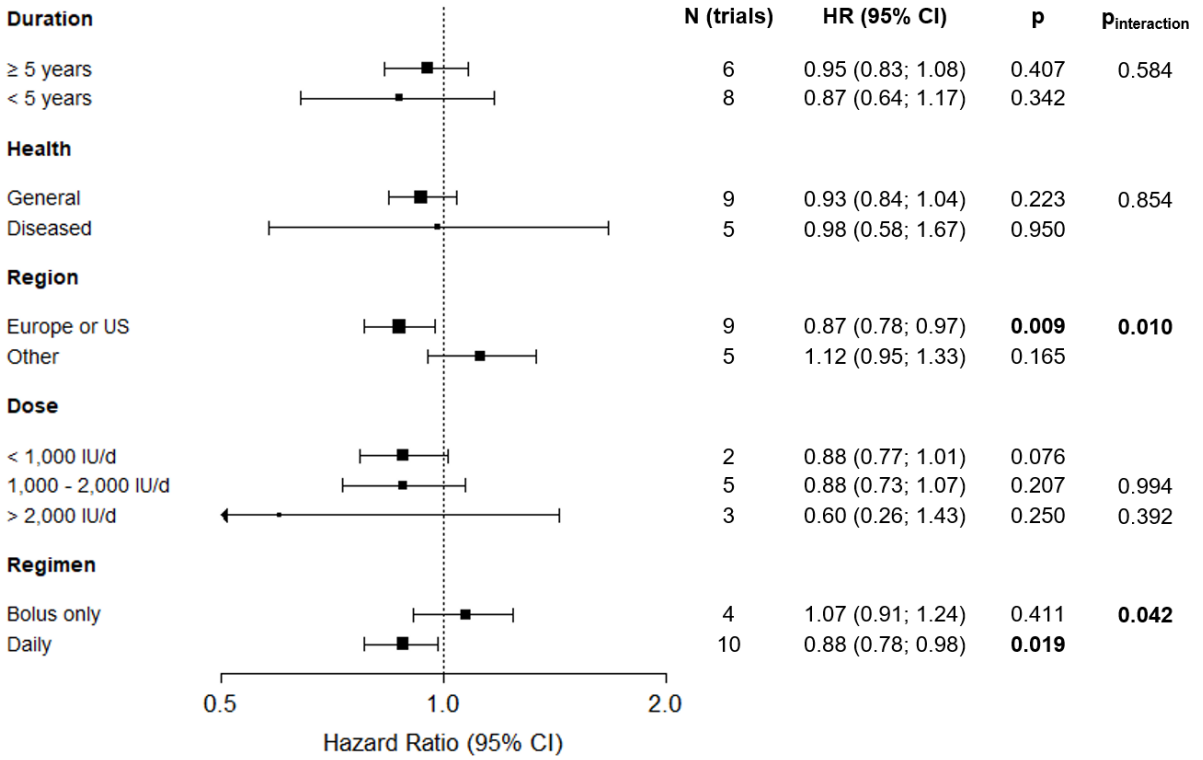

Figure 3. *Subgroup analyses of vitamin D_3 supplementation and cancer mortality by duration of intervention, health status, region, dose and regimen in all trials*

Note: N represents the count.
Abbreviations: 95% CI, 95% confidence interval; /d, per day; HR, hazard ratio; IU, International Units; US, United States

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 1,000–2,000 IU/d; p = 0.392 for > 2,000 IU/d), or health status of study participants (p = 0.854).

3.1.3.3 Risk of bias assessment

Of the 14 RCTs, eight studies had a low risk of bias, and one study had a high risk of bias (due to the ascertainment of cancer data, see footnote "l" in Table 2 (Sudfeld et al. 2020)). 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 (**Supplemental Figure 2**).

3.1.3.4 Sensitivity analyses

The sensitivity analyses are summarized in **Supplemental Figure 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 ITT 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).

3.1.4 IPD meta-analyses

3.1.4.1 Cancer mortality in the general population – Main analyses

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 1,683 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; Wactawski-Wende et al. 2006). The study participants' characteristics are shown in **Supplemental Table 8**. 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 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). **Figure 4** 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 **Supplemental Table 9**.

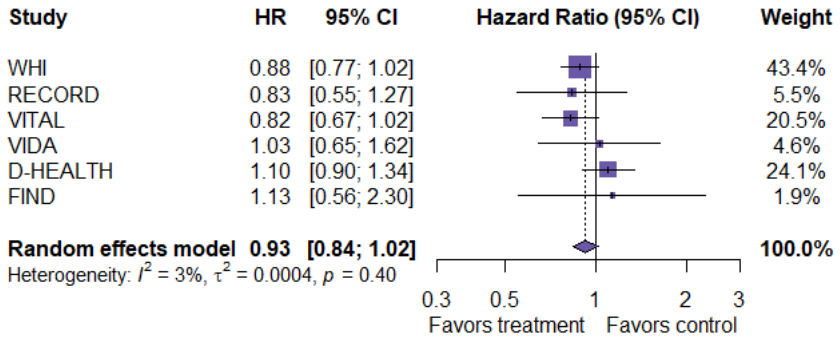

Figure 4. *IPD meta-analyses of RCTs comparing vitamin D_3 and placebo for the outcome "cancer mortality" in the general population*

Abbreviations: 95% CI, 95% confidence interval; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; HR, hazard ratio; RECORD, Randomized Evaluation of Calcium Or vitamin D; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial; WHI, Women's Health Initiative

3.1.4.2 Cancer mortality in the general population – Subgroup analyses

Figure 5 and **Figure 6** illustrate the main results of the IPD subgroup analyses; details of the individual trial results and interaction tests are shown in **Supplemental Table 10 A** and **B** and in **Supplemental Table 11 A** and **B**, respectively. None of the subgroup analyses showed a statistically significant effect of vitamin D_3 supplementation on cancer mortality (**Figure 5**). However, statistically significant findings were observed when trials were restricted to those with a daily vitamin D_3 dosing regimen (**Figure 6**). 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 the 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).

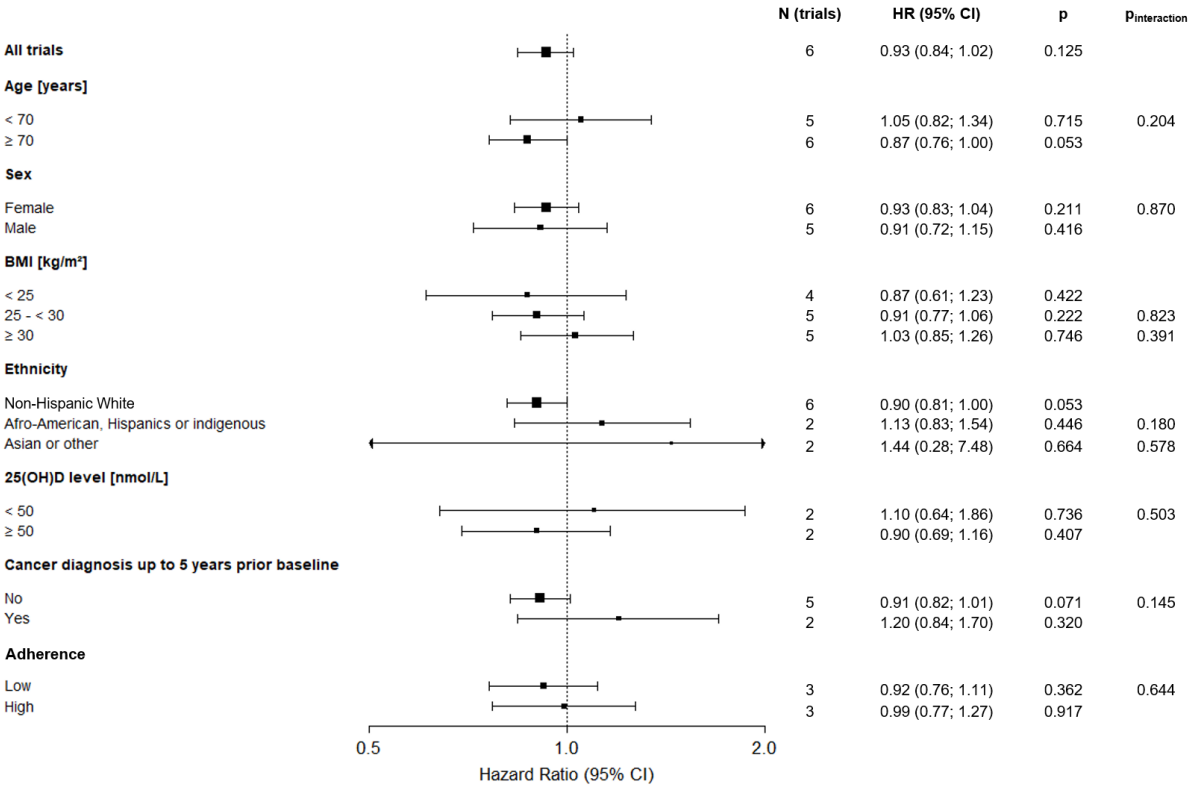

Figure 5. *IPD subgroup analyses of vitamin D_3 supplementation and cancer mortality in the general population by age, sex, BMI, ethnicity, vitamin D baseline level, cancer diagnosis in five years prior baseline, and adherence in all trials*

Note: N represents the count.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 95% CI, 95% confidence interval; BMI, body mass index; HR, hazard ratio

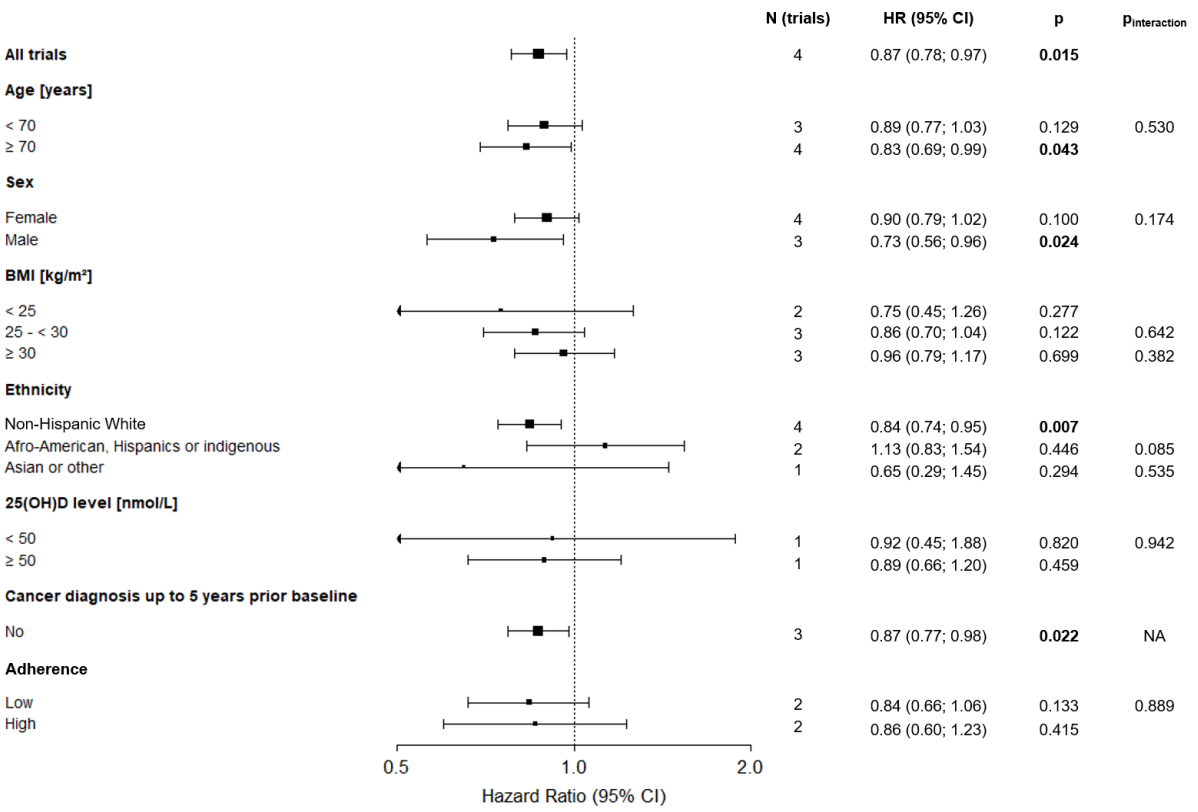

Figure 6. *IPD subgroup analyses of vitamin D_3 supplementation and cancer mortality in the general population by age, sex, BMI, ethnicity, vitamin D baseline level, cancer diagnosis in five years prior baseline, and adherence restricted to trials with a daily dosing regimen*

Note: N represents the count.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 95% CI, 95% confidence interval; BMI, body mass index; HR, hazard ratio; NA, not applicable

3.1.4.3 Cancer survival – Main analyses

All seven studies included in the IPD analyses contributed to the meta-analysis of overall survival (N_{total}=7,528, including 1,932 cancer deaths during the intervention period) and cancer-specific survival (N_{total}=7,513, including 1,726 cancer deaths during the intervention period) among patients with cancer (of which most were diagnosed after randomization and only a few up to 5 years prior to study enrolment). The patient characteristics of the study populations are provided in **Supplemental Table 12**. 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), p = 0.151). **Figure 7** and **Figure 8** show the

corresponding forest plots; additional details, including adjusted effect estimates, are presented in **Supplemental Table 13** and **Supplemental Table 14**.

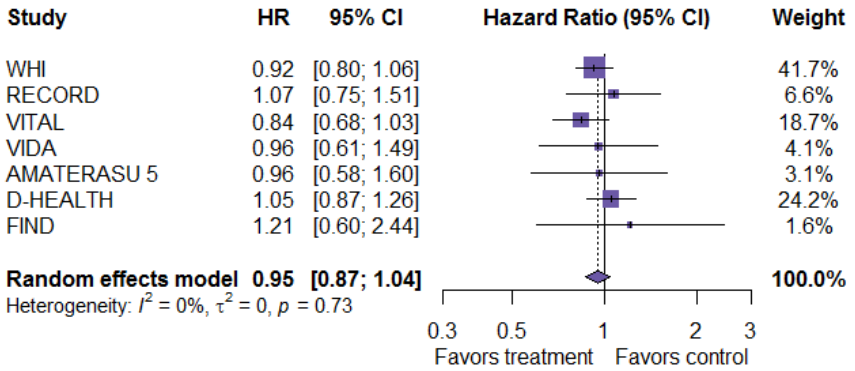

Figure 7. *IPD meta-analyses of RCTs comparing vitamin D_3 and placebo for the outcome "overall survival" in cancer patients*

Abbreviations: 95% CI, 95% confidence interval; AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; HR, hazard ratio; RECORD, Randomized Evaluation of Calcium Or vitamin D; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial; WHI, Women's Health Initiative

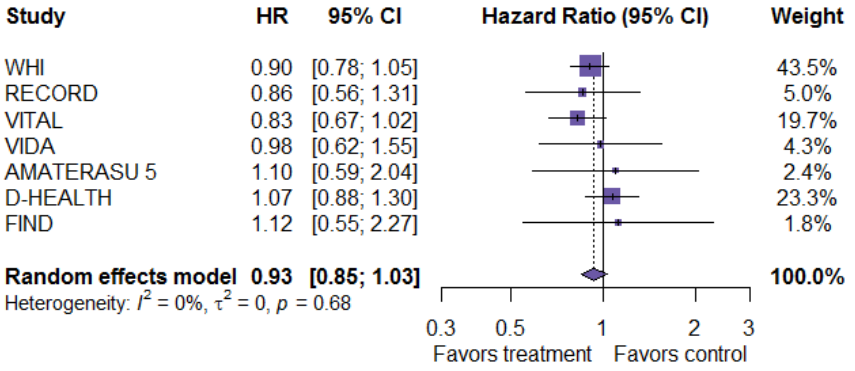

Figure 8. *IPD meta-analyses of RCTs comparing vitamin D_3 and placebo for the outcome "cancer-specific survival" in cancer patients.*

Abbreviations: 95% CI, 95% confidence interval; AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; HR, hazard ratio; RECORD, Randomized Evaluation of Calcium Or vitamin D; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial; WHI, Women's Health Initiative

3.1.4.4 Cancer survival – Subgroup analyses

Figure 9 and **Figure 10** shows the pooled effect estimates of the IPD subgroup analyses for cancer-specific survival of cancer patients. **Supplemental Table 15 A** and **B** shows the individual study results and **Supplemental Table 16 A** and **B** presents the tests for interaction with vitamin D_3. Results were like those observed for cancer mortality in the general population. 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), $p = 0.030$ (**Figure 9**). Yet, when the trials were restricted to those with a daily dosing regimen, the effect estimates were statistically significant in all trials (HR (95% CI): 0.89 (0.80; 0.99), $p = 0.040$) and in Non-Hispanic Whites, while the results remained unchanged for patients without cancer at baseline (HR (95% CI): 0.88 (0.79; 0.99), $p = 0.032$, **Figure 10**). 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), $p = 0.061$), 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).

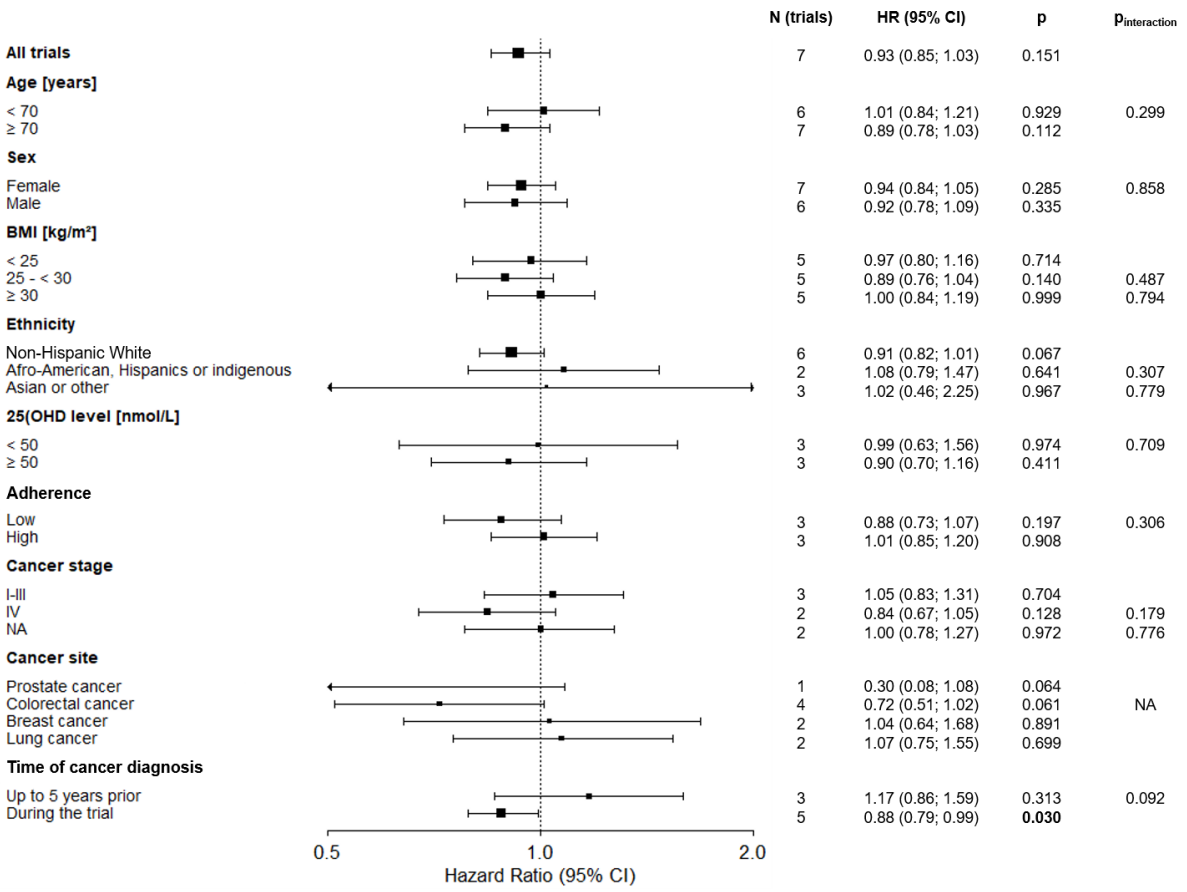

Figure 9. *IPD subgroup analyses of vitamin D_3 supplementation and cancer-specific survival in the cancer population by age, sex, BMI, ethnicity, vitamin D baseline level, adherence, cancer stage, cancer site, time of cancer diagnosis in all trials*

Note: N represents the count.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 95% CI, 95% confidence interval; BMI, body mass index; HR, hazard ratio

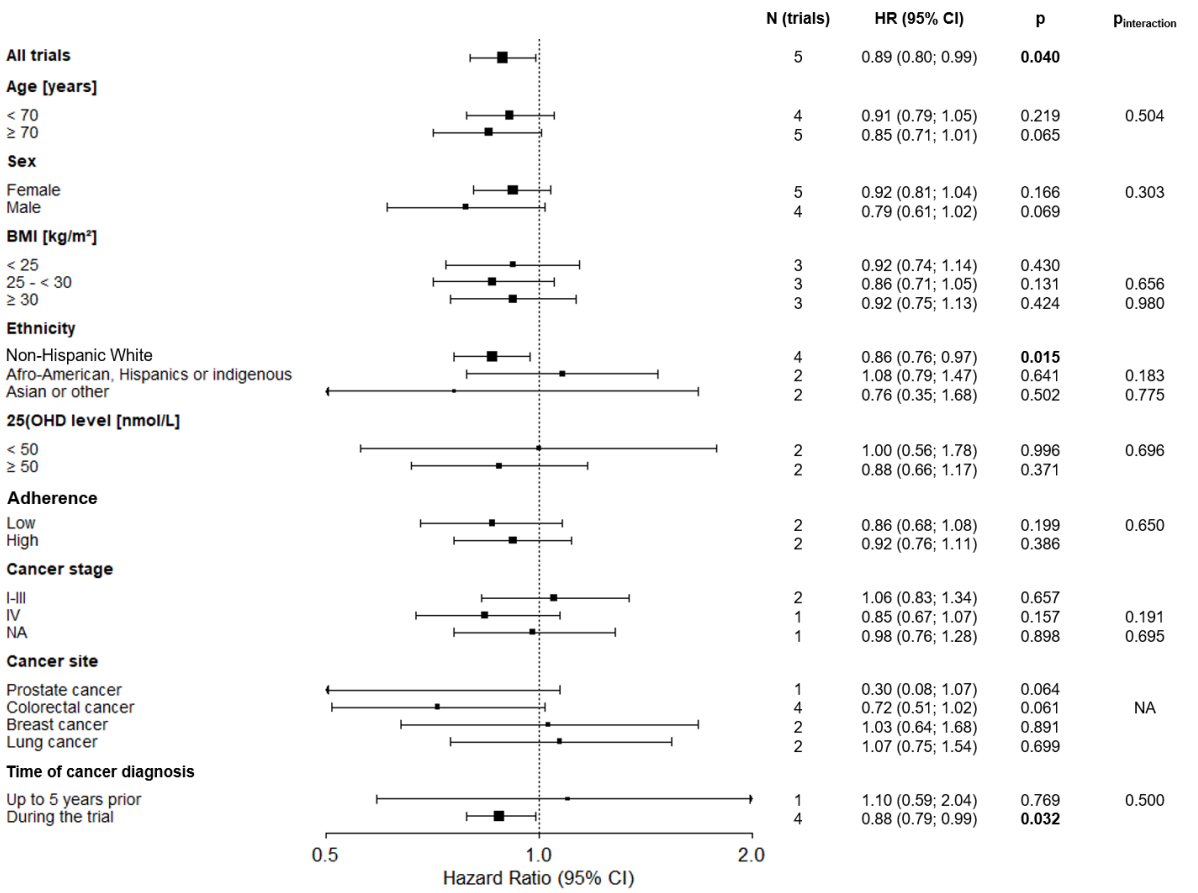

Figure 10. *IPD subgroup analyses of vitamin D_3 supplementation and cancer-specific survival in the cancer population by age, sex, BMI, ethnicity, vitamin D baseline level, adherence, cancer stage, cancer site, time of cancer diagnosis restricted to trials with a daily dosing regimen*

Note: N represents the count.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 95% CI, 95% confidence interval; BMI, body mass index; HR, hazard ratio; NA, not applicable

3.1.5 Strength of evidence (GRADE)

Based on the GRADE approach, the quality of evidence was assessed as high for all outcomes (**Supplemental Table 17**). 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 2,000 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.

3.2 Efficacy and safety analysis of a personalized vitamin D_3 loading dose followed by 2,000 IU daily in vitamin D-insufficient colorectal cancer patients

3.2.1 Study population

In the analysis, I included the first enrolled 74 study participants who completed the VICTORIA trial until 10 April 2022. Overall, 36 participants were randomly allocated to the placebo arm and 38 to the vitamin D_3 arm. Due to missing blood samples, only 68 and 52 study participants could be included in the ITT analysis for laboratory measurement-based outcomes assessed at visits 1 and 2, respectively (**Figure 11**). Due to further exclusions, these numbers dropped to n = 64 and n = 41 for the PP analysis for visits 1 and 2, respectively.

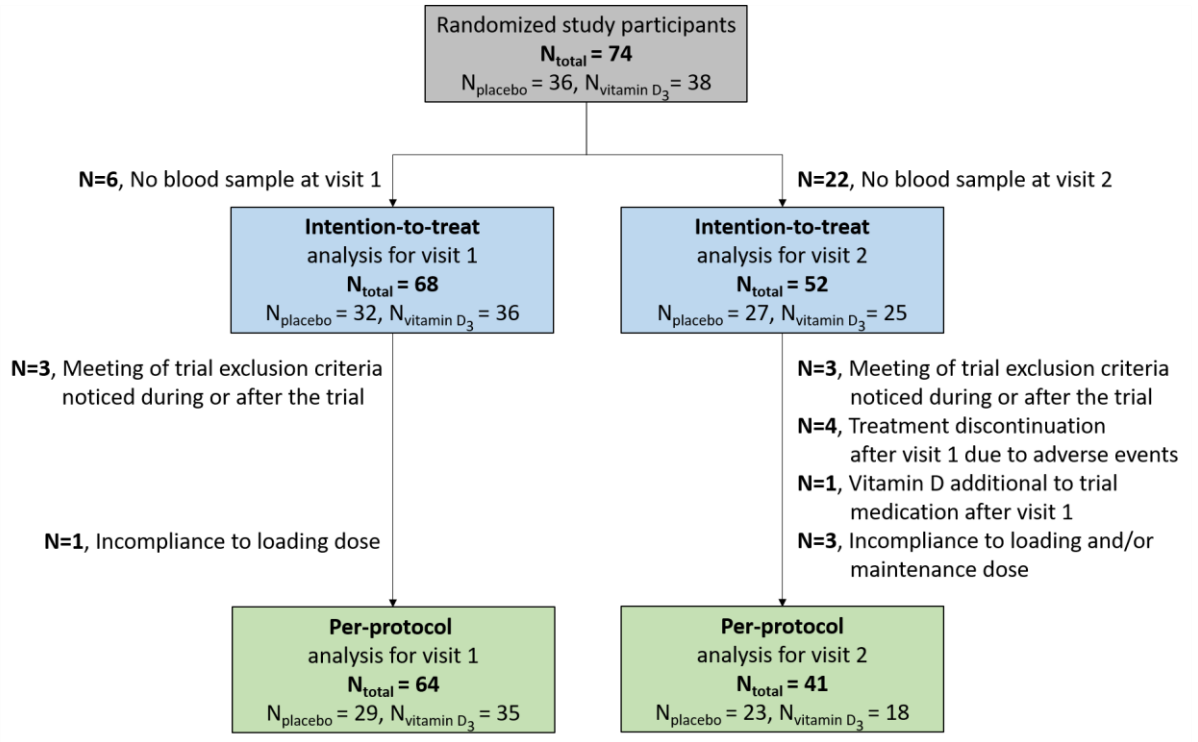

Figure 11. *Flowchart of the study population*

Note: N represents the total number.

Table 3 shows the baseline characteristics of the included participants. The mean age of all randomized participants was 61.8 years; 32.4% were female; and CRC stages I–III were approximately equally distributed (33.8% stage I, 29.7% stage II, and 29.7% stage III), while the stage of cancer was not determined in 6.8% of patients. However, it was known that these study participants were free of metastases, which was defined as an exclusion criterion. With 28.2 kg/m^2, the mean BMI was within the WHO's definition of overweight (25– < 30 kg/m^2). With 27.3 nmol/L, the mean 25(OH)D level was below the Institute of Medicines' deficiency threshold of 30 nmol/L. With 87.8 mL/min/1.73 m^2, the mean eGFR was close to the optimal levels > 90 mL/min/1.73 m^2. The mean albumin-corrected serum calcium and urinary calcium-to-creatinine ratio were far below the cut-offs for hypercalcemia and hypercalciuria stated in the section "Materials and Methods". Of note, sufficient vitamin D status (25(OH)D levels ≥ 50 nmol/L) and severe renal dysfunction (eGRF < 30 mL/min/1.73 m^2), as well as hypercalcemia and hypercalciuria, were exclusion criteria.

Table 3. *Baseline characteristics of the first 74 participants in the VICTORIA study*

	All randomized (*N* = 74)	**Vitamin D_3 (*N* = 38)**	**Placebo (*N* = 36)**
Age [years], mean (SD)	61.8 (9.8)	62.1 (9.9)	61.6 (9.7)
Sex			
Female, *n*, %	24 (32.4)	14 (36.8)	10 (27.8)
Male, *n*, %	50 (67.6)	24 (63.2)	26 (72.2)
Cancer stage			
I, *n*, %	25 (33.8)	8 (21.1)	17 (47.2)
II, *n*, %	22 (29.7)	17 (44.7)	5 (13.9)
III, *n*, %	22 (29.7)	11 (28.9)	11 (30.6)
Unknown, *n*, %	5 (6.8)	2 (5.3)	3 (8.3)
BMI [kg/m²], mean (SD)	28.2 (5.8)	28.5 (6.1)	28.0 (5.5)
25(OH)D level [nmol/L], mean (SD)	27.3 (10.7)	26.5 (9.9)	28.2 (11.6)
Albumin-corrected serum calcium [mmol/L], mean (SD)	2.29 (0.10)	2.29 (0.09)	2.29 (0.11)
Urinary calcium-to-creatinine ratio [mmol/mmol], mean (SD)	0.28 (0.19)	0.28 (0.20)	0.28 (0.17)
Estimated glomerular filtration rate [ml/min/1.73 m^2], mean (SD)	87.8 (15.0)	89.0 (15.4)	86.5 (14.6)

Note: n represents the total sample number, N represents the total number.
Abbreviations: BMI, body mass index; SD, standard deviation.

No relevant differences between the vitamin D_3 and placebo arms were observed with respect to age, BMI, and laboratory-based factors. By chance, more females were included in the vitamin D (36.8%) than in the placebo arm (27.8%). Furthermore, the CRC stage distribution differed, wherein patients with stage II cancers formed the largest group in the vitamin D arm (44.7%) and patients with stage I cancers constituted the largest group in the placebo arm (47.2%).

The median calculated loading dose for all analyzed trial participants (regardless of whether vitamin D_3 or placebo was given) was 200,000 IU vitamin D_3 (Interquartile range: 160,000–240,000), with large individual variations from 80,000 to 420,000 IU (**Figure 12**, all values were rounded up to the next 20,000 IU unit). To illustrate the range of a personalized loading dose, the extremes of the distribution are exemplarily described as follows: The person who received a loading dose of 80,000 IU had a baseline 25(OH)D level of 48.7 nmol/L and a BMI of 24.5 kg/m^2. In contrast, the person who received a loading dose of 420,000 IU had a baseline 25(OH)D level of 4.8 nmol/L and a BMI of 46.5 kg/m^2.

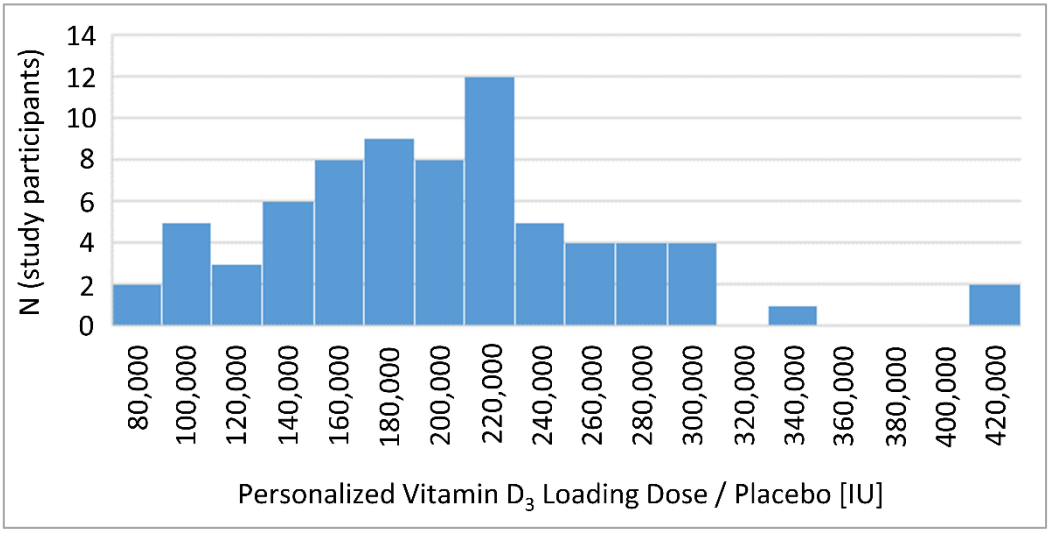

Figure 12. *Distribution of the personalized loading dose*

Note: Doses were rounded up to the next 20,000 unit. The histogram shows the loading doses of all randomized study participants, except one. The single study participant not shown is an outlier, because he/she was falsely included in the study (no vitamin D insufficiency at screening). Due to the study participants' high 25(OH)D level of 61 nmol/L at screening, he/she received a vitamin D_3/placebo loading dose of 40.000 IU. N represents the total number.
Abbreviations: IU, International Units

3.2.2 Efficacy endpoints

3.2.2.1 Serum 25(OH)D levels in the total trial population

In the placebo group, the mean 25(OH)D levels (95% CI) at screening (27.6 (23.6; 31.6) nmol/L) did not change much until visit 1 (31.0 (27.2; 34.7) nmol/L) and visit 2 (34.1 (27.1; 41.1) nmol/L, (**Figure 13** and **Supplemental Table 18**). In the verum group, the mean 25(OH)D levels (95% CI) at screening (25.9 (22.5; 29.3) nmol/L) more than doubled until visit 1 (63.1 (58.1; 68.0) nmol/L) and increased further until visit 2 (75.5 (69.2; 81.9) nmol/L). The statistical tests for the 25(OH)D level comparisons between the two study arms were statistically significant at visits 1 and 2 (both $p < 0.001$) but not at the baseline ($p = 0.501$).

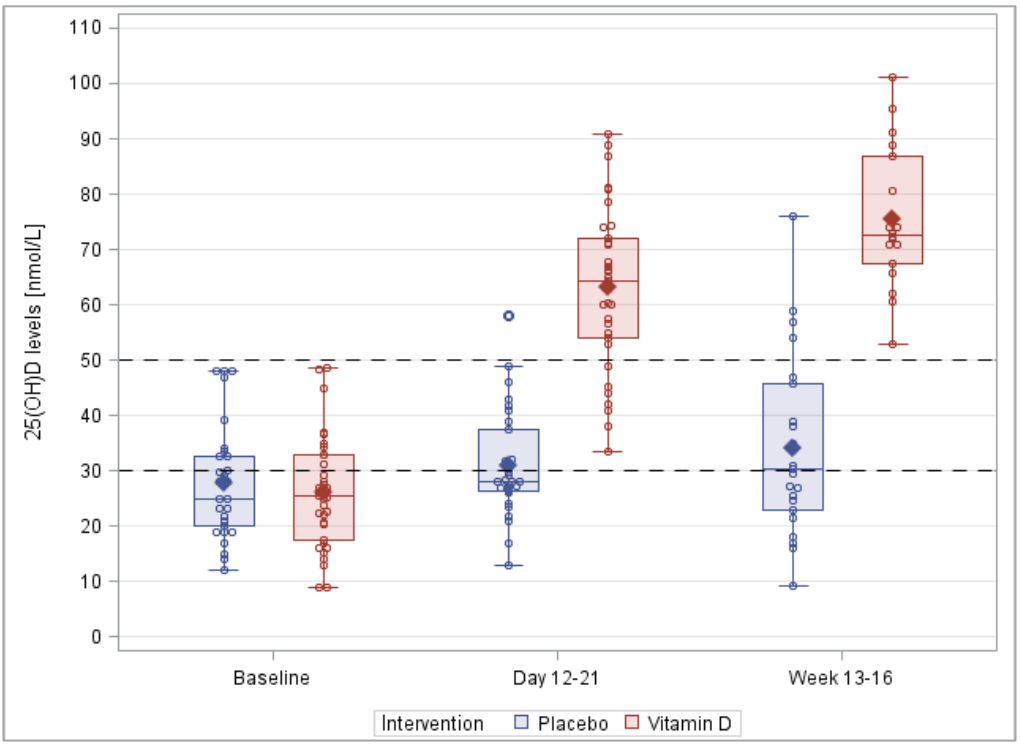

Figure 13. *Boxplots of the 25(OH)D levels over the course of the trial*

Note: This figure is based on the detailed results of the PP analysis shown in **Supplemental Table 18**, which also shows the corresponding results of the ITT analysis.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D.

For subjects with repeated blood samples, the mean differences (95% CI) in the 25(OH)D levels from screening to visit 1 (3.3 (1.4; 5.2) nmol/L) and from screening to visit 2 (5.5 (−2.1; 13.1) nmol/L) were

small in the placebo group (**Figure 14** and **Supplemental Table 19**). The mean differences (95% CI) in the vitamin D_3 group, however, were large, with an increase by 37.2 (31.8; 42.5) nmol/L until visit 1 and by 45.0 (36.2; 53.8) nmol/L until visit 2. The tests for comparisons between the two study arms were statistically significant at visits 1 and 2 (both $p < 0.001$).

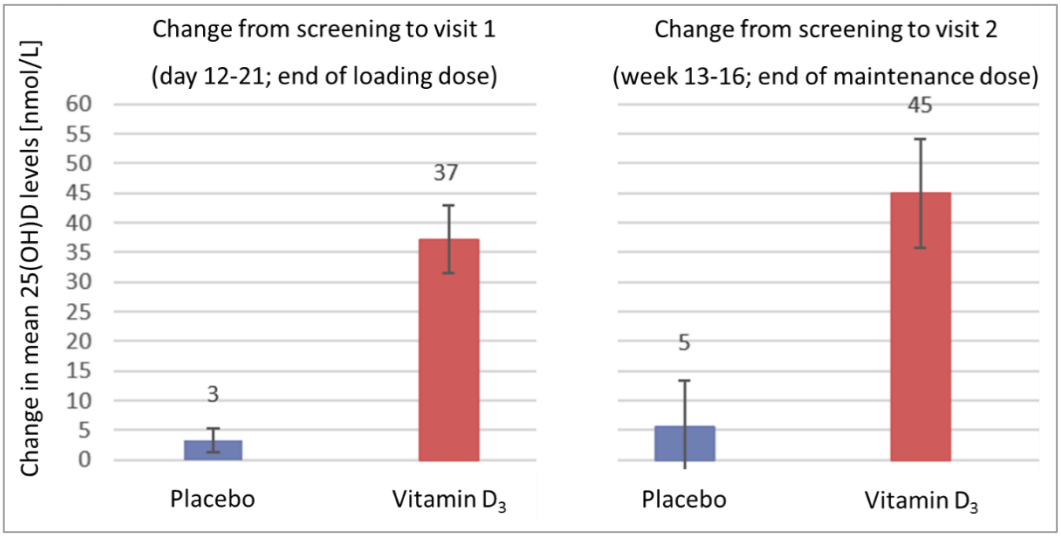

Figure 14. *Change in the mean 25(OH)D levels with 95% confidence interval bars from screening to the end of rehabilitation (visit 1, end of loading dose, days 12–21) and from screening to end of the study (visit 2, end of maintenance dose, weeks 13–16).*

Note: This figure is based on the detailed results of the PP analysis shown in **Supplemental Table 19**, which also shows the corresponding results of the ITT analysis. A more detailed display of the changes in the 25(OH)D levels in the boxplots is shown in **Supplemental Figure 4**.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D.

The prevalence of vitamin D insufficiency (25(OH)D levels < 50 nmol/L) in the placebo group remained high at visit 1 (96.6%) and visit 2 (82.6%) (**Table 4** and **Supplemental Table 20**). In contrast, only 20.0% of the study participants of the vitamin D_3 group remained at the 25(OH)D levels < 50 nmol/L, and all of them had a sufficient vitamin D status at visit 2. The prevalence differences were highly statistically significant at both visits 1 and 2 (both $p < 0.001$).

***Table 4**. Prevalence of vitamin insufficiency over the course of the trial*

Trial arm	N	Vitamin D insufficiency (25(OH)D < 50 nmoL/L)		*p*[a]
		No n (%)	Yes n (%)	
Visit 1 (Days 12–21; end of loading dose)				
Placebo	29	1 (3.5)	28 (96.6)	< 0.001
Vitamin D_3	35	28 (80.0)	7 (20.0)	
Visit 2 (Weeks 13–16; end of maintenance dose)				
Placebo	23	4 (17.4)	19 (82.6)	< 0.001
Vitamin D_3	18	18 (100.0)	0 (0.0)	

Note: This table is based on the detailed results of the per-protocol analysis shown in **Supplemental Table 20**, which also shows the corresponding results of the intention-to-treat analysis. n represents the total sample number, N represents the total number.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; NA, not applicable.
Footnotes: [a]Fisher's exact test. Statistically significant in the analysis if p < 0.04.

3.2.2.2 Serum 25(OH)D levels in patients with vitamin D deficiency at enrolment

The boxplots of 25(OH)D levels over the course of the trial, restricted to subjects with vitamin D deficiency at screening (i.e., 25(OH)D < 30 nmol/L), are shown in **Supplemental Figure 5**. The boxplots at visits 1 and 2 were comparable to those obtained from the total population, but the mean changes (95% CI) in the 25(OH)D levels from screening to visit 1 (41.2 (35.1; 47.3) nmol/L) and from screening to visit 2 (55.4 (41.5; 69.2) nmol/L) were higher compared to the total trial population with vitamin D insufficiency (i.e., 25(OH)D < 50 nmol/L).

3.2.3 Safety endpoints

A tabulation of the safety events is shown in **Table 5**. No cases of hypervitaminosis D, hypercalcemia, or renal dysfunction were observed. Numerically, more cases of hypercalciuria were observed in the vitamin D_3 than in the placebo group but the difference was not statistically significant ($p = 0.209$). In six patients with hypercalciuria, treatment was discontinued after visit 1 according to the protocol, and four of them provided blood and urine samples again at visit 2, which showed a reduction of the urinary calcium-to-creatinine ratio to the levels at screening or even below them (**Supplemental Table 21**). Importantly, the albumin-corrected serum calcium was not similarly increased in these six patients at

visit 1, and the eGFR remained stable at high levels > 80 mL/min/1.73 m2 throughout the study (**Supplemental Table 21**).

Table 5. *Safety events over the course of the trial*

Trial arm	N	Hypervitaminosis D[1]	Hypercalcemia[2]	Hypercalciuria[3]	Renal dysfunction[4]
		n (%)	*n* (%)	*n* (%)	*n* (%)
Visit 1; end of loading dose; days 12 to 21					
Placebo	29	0 (0)	0 (0)	1 (3.4)	0 (0)
Vitamin D_3	35	0 (0)	0 (0)	5 (14.3)	0 (0)
Visit 2; end of maintenance dose; weeks 13 to 16					
Placebo	23	0 (0)	0 (0)	0 (0)	0 (0)
Vitamin D_3	18	0 (0)	0 (0)	0 (0)	0 (0)

Note: This table shows the results of the PP analysis. The ITT analysis had the same number of adverse events. Due to different sample sizes in the ITT analysis, the prevalence of hypercalciuria at visit 1 was 13.9% in the vitamin D_3 group vs. 3.1% in the placebo group ($p = 0.203$). n represents the total sample number, N represents the total number.

Footnotes:

[1] 25(OH)D levels > 150 nmol/L (Institute of Medicine (US) 2011b)

[2] Albumin-corrected serum calcium > 2.65 mmol/L (Meng and Wagar 2015)

[3] Random urine calcium ≥ 0.79 mmol/mmol creatinine (Tellioglu et al. 2012)

[4] eGFR < 30 ml/min/1.73 m^2 (Levey et al. 2009)

Figure 15 shows the distribution of the urinary calcium-to-creatinine ratio over the course of the trial. While no change was observed in the placebo group from screening to visit 1, the mean and standard deviation increased for the intervention group (**Supplemental Table 22**). However, the urinary calcium-to-creatinine ratio decreased from screening to visit 2 in both the vitamin D_3 and placebo arm, and the mean ratio was comparable for the two groups at visit 2 (**Supplemental Table 22**). This might be partly explained by the treatment discontinuation of the six patients with hypercalciuria at visit 1. The mean urinary calcium-to-creatinine ratio difference between the vitamin D_3 and placebo group at visits 1 and 2 was not statistically significant ($p = 0.152$ and $p = 0.618$, respectively).

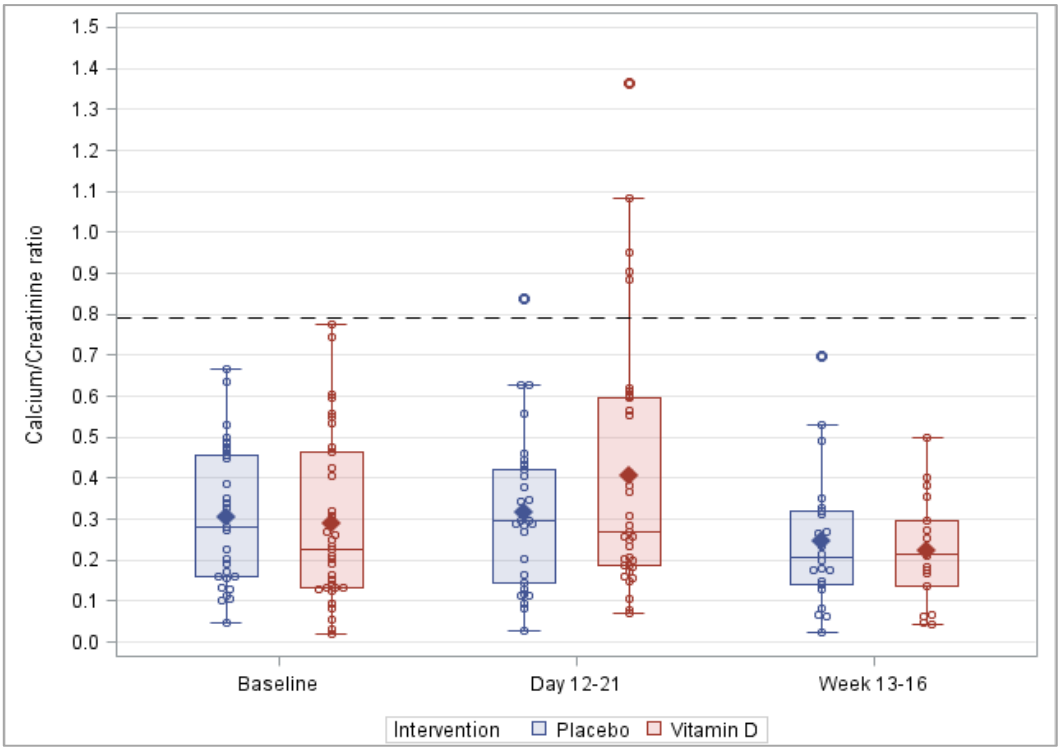

Figure 15. *Boxplots of the urinary calcium-to-creatinine ratio over the course of the trial*

Note: This figure is based on the detailed results of the per-protocol analysis shown in **Supplemental Table 22**, which also shows the corresponding results of the intention-to-treat analysis.

The means and distributions of the albumin-corrected serum calcium levels were very similar in the vitamin D_3 and placebo groups during all study visits (**Figure 16**), and none of the statistical tests indicated a difference between the two groups at any time point (**Supplemental Table 23**).

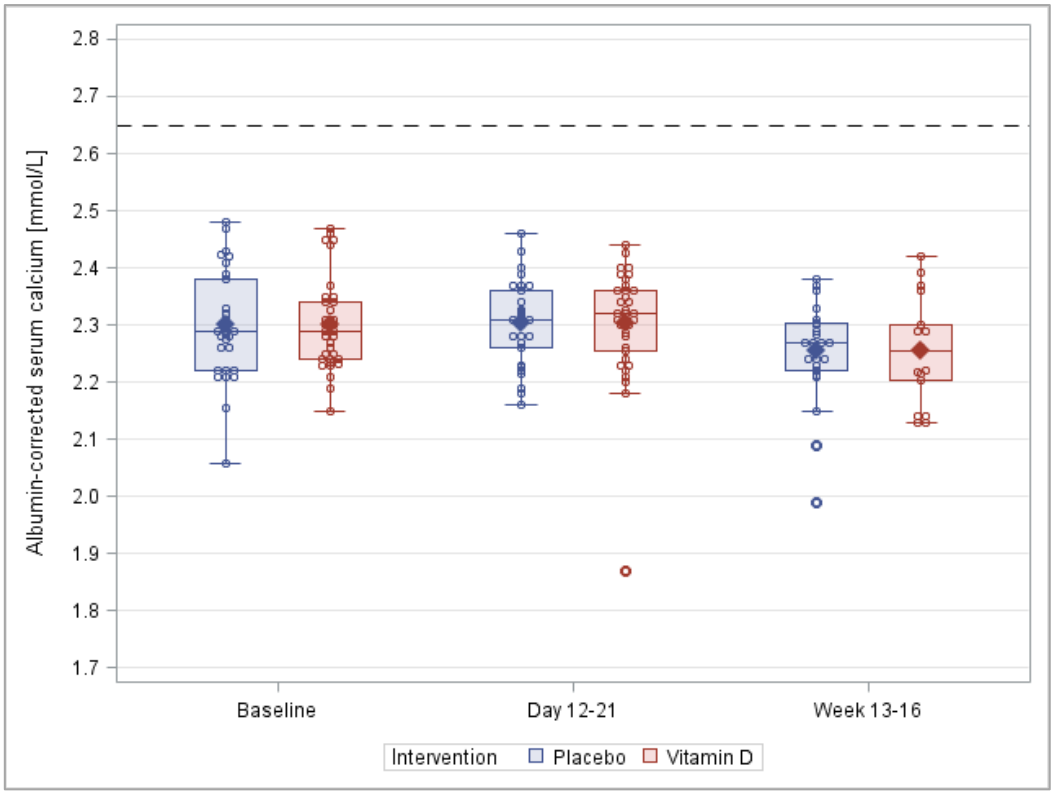

Figure 16. *Boxplots of the albumin-corrected serum calcium over the course of the trial*

Note: This figure is based on the detailed results of the per-protocol analysis shown in **Supplemental Table 23**, which also shows the corresponding results of the intention-to-treat analysis and the statistical test results.

In addition, the means and distributions of the eGFR were very similar in the two groups (**Figure 17**), and no statistically significant differences were observed at any time point (**Supplemental Table 24**).

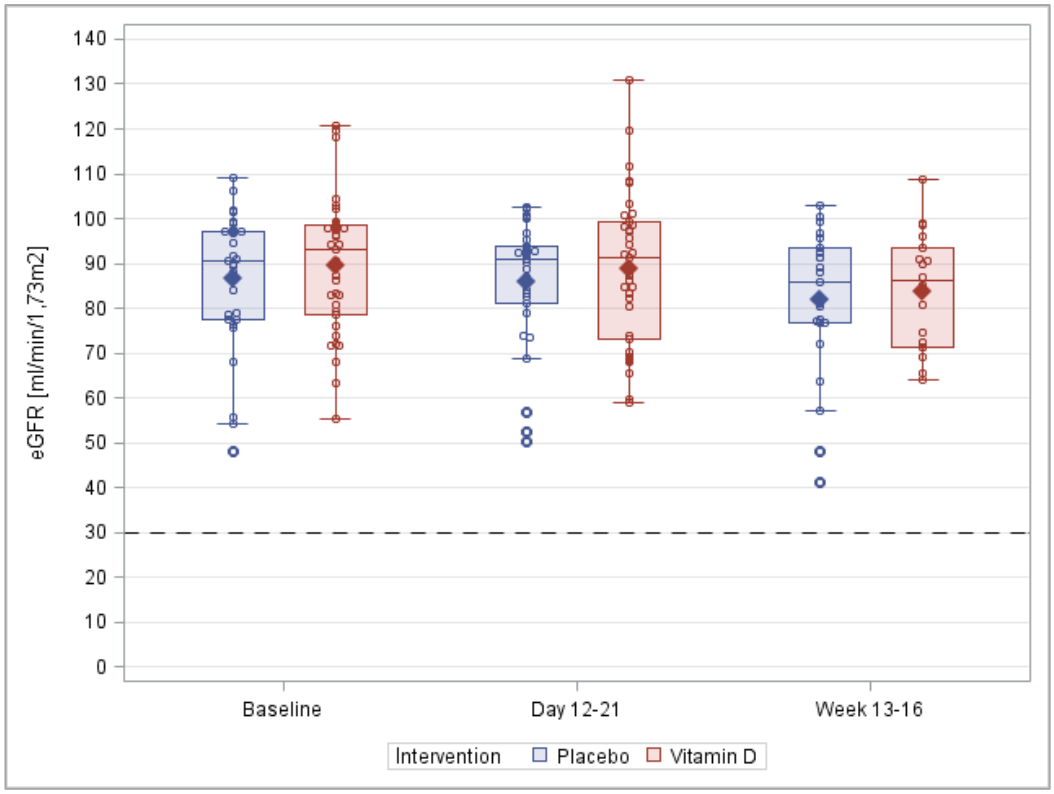

Figure 17. *Boxplots of the eGFR during the trial*

Note: This figure is based on the detailed results of the per-protocol analysis shown in **Supplemental Table 24**, which also shows the corresponding results of the intention-to-treat analysis and the statistical test results.
Abbreviations: eGFR, estimated glomerular filtration rate.

4. DISCUSSION

4.1 Systematic review and individual patient data meta-analysis of randomized controlled trials on the efficacy of vitamin D_3 supplementation on cancer mortality

4.1.1 Summary of main findings

The 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 due to overlapping confidence intervals (see below).

4.1.2 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 had a negative finding and contributed 23.6% of the weight to my 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). My 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)) (Zhang et al. 2022) which also included the D-Health trial but not the WHI (Women's Health Initiative) trial because of co-administration of calcium. Thus, their result is similar to my 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)) (Bristow et al. 2013) and no biologically plausible explanation is currently available for an effect of calcium supplementation on cancer mortality (Yang et al. 2016).

4.1.3 Effect modification by defined variables

4.1.3.1 Vitamin D_3 dosing regimen

My results showing the 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, I was able to detect statistically significant effect modification by treatment regimen for the first time with statistical significance ($p_{interaction} = 0.042$). The timing of intake could be important for a favorable 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, estrogen, 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 the 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, 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).

4.1.3.2 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 US or Europe was mainly driven by the D-Health and ViDA (Vitamin D Assessment Study) studies, which were conducted in Australia and New Zealand, respectively. According to nationally representative surveys with standardized 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 US (5.0%) (Cashman 2022). The latter can be explained by higher food fortification with vitamin D in the US 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.

4.1.3.3 Ethnicity

The subgroup analyses for ethnicity should be interpreted with caution due to the small sample sizes for Non-White ethnicities. Overall, 1,437 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 (**Supplemental Table 10 B**). 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.

4.1.3.4 Age

My IPD subgroup analysis restricted to studies applying a daily regimen 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 aging (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 (US) 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).

4.1.3.5 Sex

Among males, I observed a statistically significant efficacy of vitamin D supplementation on cancer mortality in the IPD meta-analysis of trials with a 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 a clear overlap of the confidence intervals (HR (95% CI): 0.90 (0.79; 1.02), $p = 0.100$). Thus, I believe there is insufficient evidence of sex differences in the results.

4.1.3.6 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/m² but not in those with higher BMI (Keum et al. 2022). I observed the same trend among trials with daily dosing regimen: point estimates were also

lower for the BMI < 25 kg/m² group (HR: 0.75) than in the groups with a BMI between 25 and 30 kg/m² (HR: 0.86) and a BMI ≥ 30 kg/m² (HR: 0.96). However, my results were not statistically significant although I 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.

4.1.3.7 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 to the stage at which the cancer is detected) 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 at this time is particularly relevant, as vitamin D_3 has been attributed with 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.

4.1.3.8 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). I observed an 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).

4.1.3.9 Cancer site

None of the meta-analyses for the 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 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 that have shown a statistically significant association between both higher circulating 25(OH)D levels and sun exposure, and a reduced risk of colorectal cancer (Grant 2014; Grant and Garland 2006; McCullough et al. 2019), a beneficial role of vitamin D_3 supplementation for colorectal cancer patients seems likely.

4.1.3.10 Baseline 25(OH)D level

My 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} = 3,535, 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 vitamin D status at baseline (25(OH)D levels > 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 of benefiting from a vitamin D_3 intervention because they already had 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).

4.1.3.11 Strength of the vitamin D_3 dose

For daily dosing regimens and cancer mortality, I observed no efficacy differences between low doses of < 1,000 IU/d and average doses of 1,000–2,000 IU/d. The point estimate of the HR was lower at high doses > 2,000 IU/d but the confidence interval was wide, and I cannot conclude that a higher dose has greater efficacy. It would be of interest to see future studies using a dose of 2,000 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 agrees with former systematic reviews and meta-analyses (Guo et al. 2022; Keum et al. 2019).

As the 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 several of the previous trials, self-medication was allowed (Avenell et al. 2012; Baron et al. 2015; Chatterjee et al. 2021; Manson et al. 2019; Martineau et al. 2015; Neale et al. 2022; Scragg et al. 2018; Trivedi et al. 2003; Virtanen et al. 2022; Wactawski-Wende et al. 2006), which may have reduced the relative risk estimate between the vitamin D_3 and placebo group.

4.1.4 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 of 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 randomized participants including 1,928 cancer deaths, which led to 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 my systematic review is that I included exclusively double-blind and placebo-controlled randomized trials. I meticulously followed guidelines such as the PRISMA-IPD statement (**Supplemental Table 2**), registered the systematic review before any data collection occurred, published a protocol (Schöttker et al. 2021), recorded all deviations to ensure transparency (**Supplemental Table 1**), and evaluated the strength of evidence according to the GRADE approach (**Supplemental Table 17**). Moreover, data extraction, risk assessment, and all statistical analyses were performed by me and another independent researcher.

However, my systematic review and IPD meta-analysis also have 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.

Despite the high response rate and excellent collaboration with authors from around the globe, I 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 to be negligible, because the results of the additional trial data obtained were evenly distributed and did not all point in a favorable or unfavorable direction for vitamin D.

4.2 Analysis of a randomized controlled trial of the efficacy and safety of an individualized vitamin D_3 loading dose followed by 2,000 IU daily in vitamin D-insufficient colorectal cancer patients

The analysis revealed that the combination of a personalized vitamin D_3 loading dose, calculated with the equation of Jansen et al. (Jansen and Svendsen 2014), and a maintenance dose of 2,000 IU for 12 weeks successfully treated vitamin D insufficiency in all included CRC patients. The personalized loading dose elevated the 25(OH)D level's substantially by, on average, 37 nmol/L during the first 11 days of the study, and 80% of patients already reached sufficient 25(OH)D levels ≥ 50 nmol/L at this early time point in the trial. All study participants reached sufficient vitamin D status after using the maintenance dose for 12 weeks. Among the safety parameters, only hypercalciuria occurred more frequently without statistical significance in the vitamin D_3 group. Notably, the kidney function, which is needed to excrete high serum calcium, and the serum calcium levels were not affected by the intervention. The maximum 25(OH)D level observed in the trial population was 101 nmol/L, which is far from potentially harmful 25(OH)D levels > 150 nmol/L (Institute of Medicine (US) 2011b).

Regarding safety issues, previous clinical trials that administered very high bolus doses observed no single case of a clinically manifested overdose (Jansen and Svendsen 2014; Leventis and Kiely 2009; Romagnoli et al. 2008). Overdoses have only been described in the literature for much higher cumulative vitamin D doses, typically between 2,220,000 and 6,360,000 IU (Kaur et al. 2015). The vitamin D intoxication dose reported in the SmPC of Dekristol® 20,000 IU is stated to range between 40,000 and 100,000 IU per day administered over 1 to 2 months, resulting in a cumulative dose between 2,440,000 and 6,100,000 IU. This is consistent with cited reports from the scientific literature. Thus, even more than five times the maximum vitamin D_3 loading dose (420,000 IU) in the VICTORIA trial could be considered safe when administered to patients without contraindications to vitamin D use.

I assume that the increase in urinary calcium levels after absorbing a high vitamin D_3 loading dose is a normal physiological response of the body and disappears shortly after the dose is reduced to 2,000 IU

per day. Since the blood calcium levels did not rise concomitantly, short-term hypercalciuria is not a recognizable safety risk as long as the kidney function is not impaired and the kidney can still eliminate the excess calcium. When the first six cases of hypercalciuria were reported to the competent authority for drug safety (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany), an amendment of the study protocol with respect to the treatment discontinuation rules for hypercalciuria was granted. Treatment of individuals with hypercalciuria after visit 1 is only discontinued if, additionally, either eGFR is less than 60 mL/min/1.73 m^2 or renal function has significantly deteriorated (i.e., eGFR $\geq$ 20% compared to eGFR at screening). In none of the six cases in the analysis dataset would treatment have had to be discontinued under these new rules. It will be of interest to observe in the further course of the study whether the assumption that the urinary calcium excretion of subjects with hypercalciuria normalizes within a few weeks after the intake of the loading dose despite taking the maintenance dose of 2,000 IU vitamin D_3, proves true.

Regarding efficacy, the mean 25(OH)D level achieved by the personalized loading dose in the VICTORIA trial was lower (63.1 nmol/L) than the target of 80 nmol/L, which was reached in the validation study of Jansen et al. 7 days after intake of the loading dose (82 nmol/L). There are two potential explanations: First, since the blood samples for the measurement of the 25(OH)D levels were mostly taken in the morning of day 12 and sometimes in the morning of day 13, patients who took their last loading dose capsule on day 11 may not have fully absorbed and metabolized it. Although a vitamin D_3 bolus is rapidly absorbed and most of the 25(OH)D increase is measurable in blood samples withdrawn on the next day, about 18% of the total increase in 25(OH)D levels is not quantifiable one day later and about 8% is measurable as late as two days later because the 25(OH)D level peaks on the third day after taking the supplement (Chen et al. 2016). Study participants who took vitamin D_3 loading dose capsules until day 11 had, on average, 2.6 nmol/L lower 25(OH)D levels at visit 2 than patients who took loading dose capsules up to day 10. Thus, the timing of the blood sampling played a minor role. Second, differences in study populations may be more relevant. The study population of Jansen et al. was recruited at the endocrinological outpatient clinic at Bispebjerg Hospital, University of

Copenhagen, Denmark (Jansen and Svendsen 2014). The patients attended the clinic because of vitamin D insufficiency or endocrinological diseases (primarily diabetes mellitus). There might be special patient characteristics among CRC patients that require higher vitamin D_3 loading doses.

However, taken together with the maintenance dose of 2,000 IU per day for 12 weeks, the applied loading dose equation of Jansen et al. (Jansen and Svendsen 2014) was perfectly suitable for CRC patients, because all CRC patients included in the VICTORIA study reached sufficient 25(OH)D levels > 50 nmol/L in the end if they were randomized to the vitamin D_3 group. It should be mentioned that there is no consensus among medical societies on the cut-off for sufficient 25(OH)D levels and, e.g., the Endocrine Society suggests using 75 nmol/L instead of the 50 nmol/L suggested by the IOM to define the sufficient 25(OH)D level (Pludowski et al. 2018). This higher cut-off value would have led to a lower success rate in the VICTORIA study. However, as the association between 25(OH)D levels and adverse health outcomes, such as all-cause mortality, is not linear, and the excess risk is much higher in subjects with 25(OH)D levels < 50 nmol/L (especially in those with 25(OH)D < 30 nmol/L) than among subjects with 50– < 75 nmol/L, treating people with 25(OH)D levels < 50 nmol/L is of greater clinical relevance (Fan et al. 2020; Zhu et al. 2022). Once the decision has been made for long-term treatment with vitamin D supplements, nothing speaks against aiming for 25(OH)D levels > 75 nmol/L.

I am aware of only one alternative equation for the personalization of a vitamin D_3 loading dose, which has some similarities with the one of Jansen et al. (Jansen and Svendsen 2014). Van Groningen et al. derived an equation based on the baseline 25(OH)D and body weight to target a 25(OH)D level of 75 nmol/L (van Groningen et al. 2010):

Loading dose = 40 * (target 25(OH)D level – baseline 25(OH)D level [nmol/L])* body weight

The equation was derived from the general population without cancer and suboptimal vitamin D status (van Groningen et al. 2010). A small validation study with nursing home inhabitants with vitamin D insufficiencies (25(OH)D < 50 nmol/L) applied a modified version of the equation of van Groningen by inserting 100 nmol/L instead of 75 nmol/L into the equation. Overall, 11 out of 14 (79%) study participants reached 25(OH)D levels > 75 nmol/L after 5 weeks (Wijnen et al. 2015). Interestingly,

although high personalized loading doses were applied (rounded median of calculated doses: 236,000 IU (IQR 185,000–251,000)), such as in the VICTORIA study, no changes in the albumin-corrected serum calcium and no differences in monitored adverse events rates compared with the control group were observed, and the maximum reached 25(OH)D levels were not much above 100 nmol/L. However, urinary calcium levels were not assessed.

For a fair comparison of the equations of Jansen et al. and van Groningen et al., the equation of van Groningen et al. was applied and the target 25(OH)D level of Jansen et al.'s equation (80 nmol/L) was used. Thus, the following version of the equation by van Groningen et al. was employed:

Loading dose = 40 * (80 – baseline 25(OH)D level [nmol/L])* body weight

The comparison of the distribution of the personalized loading dose of the two equations in the total study population and stratified by obesity and vitamin D deficiency is shown in **Supplemental Table 25**. In the total trial population, the equation of van Groningen et al. would have yielded a 13% lower median loading dose than the equation of Jansen et al., and also, subjects requiring either low or high loading doses would have received less vitamin D_3 if the van Groningen equation had been used. The gap between the two equations was similar for subjects with and without obesity. However, the von Groningen equation leads especially to lower loading doses than the Jansen equation for subjects with vitamin D deficiency, whereas the results were closer together for subjects with 25(OH)D levels between 30 and 50 nmol/L. Taking into consideration the importance of quickly raising the 25(OH)D levels of subjects with vitamin D deficiencies, the van Groningen equation is not preferred for CRC patients.

Typically, vitamin D_3 loading doses are administered as a large bolus at once, followed by a much lower maintenance dose. Such non-physiological high doses can lead to an upregulation of countervailing factors, which can ultimately lead to a lower synthesis or higher degradation of the biologically active hormone 1,25-dihdroxyvitamin D (Mazess et al. 2021). A recent systematic review and meta-analysis observed that vitamin D supplementation did not reduce cancer mortality in studies using large, intermittently administered bolus doses but in studies that used daily vitamin D dosing regimens (Keum

et al. 2022). I assume that two aspects are important for a vitamin D_3 dosing regimen: a daily dosing regimen and the avoidance of non-physiological high doses. First, it should be noted that high initial bolus doses as loading doses are acceptable as long as they are administered daily and not with long breaks without treatment in between (Wimalawansa and Whittle 2022). Second, the term "physiological dose" requires a more specific definition. I used the vitamin D_3 equivalent to the amount of vitamin D_3 the human body can naturally produce in the skin by sunbathing in a swimsuit for a whole day in the summer, which is 20,000 IU (Holick 2011). Thus, I would recommend consuming a loading dose with one capsule of 20,000 IU per day (e.g., 200,000 IU over 10 days and 400,000 IU over 20 days). Up to 3 weeks for most patients is still a relatively short time to overcome vitamin D insufficiency. In the VICTORIA trial, 40,000 IU per day was allowed because only 11 days could be considered for taking the total loading dose during the three-week clinic stay. Visit 1 had to occur at the end of the rehabilitation so that blood and urine samples could be collected to check safety parameters.

The maintenance dose of 2,000 IU proved to be ideal for all patients in this 12-week trial. The data did not allow conclusions to be drawn as to whether this dosage is also optimal in the long run and it stands to reason that it should be also personalized to the BMI of the patients. Physicians who would like to use the treatment regimen from the VICTORIA study during their clinical routine can measure the 25(OH)D serum status every three months and adapt the daily vitamin D_3 dose until a stable 25(OH)D level is reached in the target range of the IOM, which is between 50 and 150 nmol/L. The Endocrine Society Clinical Practice Guideline considers a 25(OH)D level $\geq$ 75 nmol/L as optimal (Holick et al. 2011). It should be additionally mentioned that vitamin D_2 could be also potentially used instead of vitamin D_3 because both are equally effective in increasing the serum 25(OH)D levels in healthy adults aged 18–84 years at doses of 1000 IU daily (Holick et al. 2008). However, higher doses of vitamin D_3 were used in diseased patients (CRC patients) in the VICTORIA study, and it cannot be taken for granted that vitamin D_2 would have been as effective as vitamin D_3 in the VICTORIA study.

The major strength of this study was the placebo-controlled randomized design allowing direct comparisons to an untreated group, which was also not allowed to co-supplement vitamin D using over-

the-counter (OTC) preparations. The small 25(OH)D level increase in the placebo group could rather be explained by more sun exposure after rehabilitation due to improved health status and a more active lifestyle than by undisclosed OTC vitamin D_3 use, which would likely have manifested in more pronounced changes. The main limitation of this analysis was the low sample size, which led to less precise effect estimates as desired and not enough statistical power to detect a statistically significant difference for hypercalciuria in the two groups. Furthermore, other adverse events than those shown were recorded but are not evaluated before recruitment of the total trial population is completed.

4.3 Conclusion

Drawing a conclusion from the systematic review and meta-analysis may be controversial because the 6% reduction of cancer mortality observed in the main meta-analysis with vitamin D_3 supplementation was not statistically significant: HR 0.94 (95% CI: 0.86; 1.02). However, I believe that the arguments for the efficacy of daily (as compared to bolus) vitamin D treatment regimens are convincing. Indeed, restricting the IPD meta-analysis to trials with a 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, my findings suggest that starting vitamin D_3 treatment before or at least shortly after a cancer diagnosis may be beneficial for the health outcome "cancer survival", which has not been done for all cancer patients in the large trials recruited from the general population. The effect of vitamin D_3 was most likely underestimated in the currently available trials because they did not focus on subjects with low 25(OH)D levels and allowed the control group to self-medicate with vitamin D. Vitamin D_3 supplementation is also associated with very low treatment costs and, at reasonable doses, with almost negligible risks of adverse events.

Therefore, I believe that vitamin D is an underutilized medication for cancer patients and should be considered as an adjunct to primary cancer therapy when low serum 25(OH)D levels warrant its use.

Moreover, the results of the analysis of the clinical trial VICTORIA provided the first evidence that the applied personalized vitamin D_3 loading dose followed by a maintenance dose of 2,000 IU, was safe and effectively treated vitamin D insufficiency in subjects with CRC.

5. SUMMARY

Vitamin D deficiency is prevalent worldwide and more common among cancer patients. In clinical practice, vitamin D insufficiency is usually not diagnosed or treated and the optimal dosing regimen is also unknown. To rapidly raise the 25-hydroxyvitamin D levels to ideal levels, it is reasonable to individualize the loading dose and consider factors that influence the efficiency of supplementation. Yet, a personalized vitamin D_3 loading dose has not been tested in cancer patients to date. In my own analysis, I evaluated the efficiency and safety of a personalized vitamin D_3 regimen to raise 25-hydroxyvitamin D levels to optimal levels as part of a clinical trial.

Evidence from clinical trials on the efficacy of vitamin D_3 supplementation on cancer mortality was conflicting during the time of this thesis. Thus, another aim of this dissertation was to conduct a systematic review, to update former meta-analyses with recently published or unpublished randomized controlled trials and to re-analyze individual patient data with the ultimate goal to estimate the efficacy of vitamin D_3 supplementation on cancer mortality in the general population and on survival in patients with cancer.

Relevant literature for the systematic review was retrieved from the databases MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Kleijnen Systematic Reviews Evidence. Included trials compared vitamin D_3 supplementation with placebo in any population and prospectively assessed the endpoints of cancer mortality, cancer survival, and/or cancer-specific survival. The meta-analysis of 14 studies (104,727 participants and 2,015 cancer deaths) yielded a statistically non-significant reduction in cancer mortality by 6% with no indication of heterogeneity or publication bias. Similar results were obtained from meta-analyses of individual patient data on cancer mortality in the general population, all-cause survival and cancer-specific survival of cancer patients (most of whom were diagnosed after randomization). Subgroup analyses revealed a statistically significant 12% reduction in cancer mortality in the vitamin D_3 group compared with the placebo group in those ten trials using daily dosing and not in the four trials using a bolus regimen. Restricting subgroup analyses of individual patient data to daily dosing trials yielded

biologically plausible findings: adults aged 70 years or older and individuals in whom vitamin D_3 therapy was initiated before or at least shortly after the cancer diagnosis appeared to benefit most from daily vitamin D_3 supplementation – however, the confidence intervals overlapped for each subgroup effect estimate. Of note, these effect estimates are based on untargeted vitamin D_3 supplementation of individuals with and without vitamin D insufficiency. The potential for patients with low vitamin D status is likely to be substantially underestimated.

From the randomized, placebo-controlled VICTORIA trial, I analyzed the first 74 recruited German adults with non-metastatic colorectal cancer who had undergone tumor surgery within the past year and had 25-hydroxyvitamin D levels below 50 nmol/L. Study participants received a loading dose tailored to their baseline 25-hydroxyvitamin D levels and body mass index for the first 11 days, followed by a daily maintenance dose of 2,000 International Units vitamin D_3 until the end of trial week 12. The mean 25-hydroxyvitamin D levels were 27.6, 31.0, and 34.1 nmol/L in the placebo group and 25.9, 63.1, and 75.5 nmol/L in the verum group during screening, visit 1 (end of loading dose), and visit 2 (end of maintenance dose), respectively. The prevalence of adequate 25-hydroxyvitamin D levels (equivalent to 50 nmol/L or greater) at visits 1 and 2 was 3.5% and 17.4% in the placebo group and 80.0% and 100% in the verum group. No events of 25-hydroxyvitamin D greater than 150 nmol/L or hypercalcemia were observed. Hypercalciuria events at visit 1 ($n = 5$ in verum and $n = 1$ in the placebo group; $p = 0.209$) receded after discontinuation of the study medication. In conclusion, the personalized loading dose effectively and safely increased the 25-hydroxyvitamin D levels, and 2,000 International Units of vitamin D_3 daily sustained the achieved levels.

My findings highlight the invaluable public health potential of the investigated personalized vitamin D_3 supplementation in cancer care, as it effectively raises 25-hydroxyvitamin D levels to optimal levels with an almost negligible risk of adverse events and very low treatment costs. According to my meta-analysis, daily vitamin D_3 supplementation leads to a 12% reduction in cancer mortality.

6. ZUSAMMENFASSUNG

Vitamin-D-Mangel ist weltweit verbreitet und kommt besonders bei Krebspatienten häufig vor. In der klinischen Praxis wird eine Vitamin-D-Insuffizienz meist weder diagnostiziert noch behandelt und das optimale Dosierungsschema ist ebenfalls unbekannt. Für eine rasche Anhebung des 25-Hydroxyvitamin-D-Spiegels auf ein ideales Niveau ist eine Individualisierung der Initialdosis und die Berücksichtigung von Faktoren, die die Wirksamkeit der Supplementierung beeinflussen, sinnvoll. Solch eine personalisierte Vitamin-D_3-Initialdosis wurde noch nicht bei Krebspatienten untersucht. In einer eigenen Analyse untersuchte ich im Rahmen einer klinischen Prüfung die Wirksamkeit und Sicherheit einer individuellen Vitamin-D_3-Gabe um den 25-Hydroxyvitamin-D-Spiegel auf ein optimales Niveau anzuheben.

Die Erkenntnisse aus klinischen Studien über den Effekt von Vitamin D_3 auf die Krebsmortalität waren zum Zeitpunkt der Erstellung dieser Arbeit widersprüchlich. Daher war ein weiteres Ziel dieser Dissertation, die Durchführung eines systematischen Reviews, die Aktualisierung früherer Meta-Analysen mit kürzlich veröffentlichten oder unveröffentlichten randomisierten kontrollierten Studien und die Neuanalyse individueller Patientendaten um die Wirksamkeit von Vitamin D_3 auf die Krebsmortalität in der Allgemeinbevölkerung und auf das Überleben von Krebspatienten abzuschätzen.

Relevante Literatur für den systematischen Review wurde in den Datenbanken MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews und Kleijnen Systematic Reviews Evidence identifiziert. Die eingeschlossenen Studien verglichen Vitamin D_3 mit Placebo in einer beliebigen Population und untersuchten prospektiv Krebsmortalität, Krebsüberleben und/oder krebsspezifisches Überleben. Die Meta-Analyse von 14 Studien (104.727 Teilnehmer und 2.015 Krebstodesfälle) ergab eine statistisch nicht signifikante Verringerung der Krebssterblichkeit um 6%, ohne Hinweis auf Heterogenität oder Publikationsbias. Ähnliche Ergebnisse erzielten die Meta-Analysen der individuellen Patientendaten zur Krebsmortalität in der Allgemeinbevölkerung, zum Gesamtüberleben und zum krebsspezifischen Überleben von Krebspatienten (Krebsdiagnose erfolgte meist nach Randomisierung). Die Subgruppenanalyse zeigte eine statistisch signifikante Verringerung der Krebsmortalität um 12% in der Vitamin-D_3-Gruppe im Vergleich zur Placebogruppe in den zehn Studien mit täglicher Gabe, nicht aber in den vier Studien mit einer Bolus-Gabe. Beschränkte man die Subgruppenanalysen der individuellen Patientendaten auf

Studien mit täglicher Dosierung, ergaben sich biologisch plausible Ergebnisse: Erwachsene im Alter von 70 Jahren oder älter und bei denen die Vitamin-D_3-Therapie vor oder zumindest kurz nach der Krebsdiagnose begonnen wurde, schienen am meisten von einer täglichen Gabe zu profitieren – die Konfidenzintervalle der Effektschätzer überlappten sich jedoch in jeder Subgruppe. Die Ergebnisse beruhen auf einer ungezielten Vitamin-D_3-Gabe von Personen mit und ohne Vitamin-D-Insuffizienz, sodass das Potenzial für diejenigen mit niedrigem Vitamin-D-Status vermutlich erheblich unterschätzt wird.

Aus der randomisierten, placebo-kontrollierten VICTORIA-Studie, analysierte ich die ersten 74 rekrutierten deutschen Erwachsenen mit nicht-metastasiertem Darmkrebs, die sich innerhalb des letzten Jahres einer Tumoroperation unterzogen hatten und einen 25-Hydroxyvitamin-D-Spiegel kleiner als 50 nmol/L aufwiesen. Die Studienteilnehmer erhielten in den ersten 11 Tagen eine auf den 25-Hydroxyvitamin-D-Grundwert und den Body Mass Index abgestimmte Initialdosis, gefolgt von einer täglichen Erhaltungsdosis mit 2,000 Internationale Einheiten Vitamin D_3 bis zum Ende der 12 Woche. Die mittleren 25-Hydroxyvitamin-D-Werte betrugen für Screening, Besuch 1 (Ende der Initialdosis) und Besuch 2 (Ende der Erhaltungsdosis) 27.6, 31.0 und 34.1 nmol/L in der Placebogruppe bzw. 25.9, 63.1 und 75.5 nmol/L in der Verumgruppe. Die Prävalenz eines als ausreichend erachteten 25-Hydroxyvitamin-D-Spiegel (entspricht 50 nmol/L oder mehr) bei Besuch 1 und 2 betrug 3,5 % und 17,4 % in der Placebogruppe und 80,0 % und 100 % in der Verumgruppe. 25-Hydroxyvitamin-D-Spiegel über 150 nmol/L oder eine Hyperkalzämie wurden nicht beobachtet. Eine bei Besuch 1 auftretende Hyperkalziurie (n = 5 in der Verum- und n = 1 in der Placebogruppe; p = 0,209) bildete sich nach Absetzen der Studienmedikation wieder zurück. Folglich konnte mit der individualisierten Initialdosis der 25-Hydroxyvitamin-D-Spiegel wirksam und sicher erhöht und die erreichten Werte mit täglich 2,000 Internationale Einheiten Vitamin D_3 aufrechterhalten werden.

Meine Ergebnisse unterstreichen das unschätzbare gesundheitspolitische Potential der getesteten personalisierten Vitamin-D_3-Gabe in der onkologischen Versorgung, da sie eine optimale Anhebung des 25-Hydroxyvitamin-D-Spiegels bei nahezu vernachlässigbaren Risiko unerwünschter Ereignisse und sehr geringen Behandlungskosten ermöglicht. Gemäß meiner Meta-Analyse, führt eine tägliche Vitamin-D_3-Gabe zu einer um 12% verringerten Krebsmortalität.

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8. OWN PUBLICATIONS AND CONTRIBUTIONS

Parts of this dissertation are based on data from the VICTORIA study which is a randomized controlled trial designed and led by Professor Brenner and PD Dr. Ben Schöttker. I was involved in the project administration of the VICTORIA study including study coordination and clinical monitoring. Thereby, my main tasks included the establishment of a quality management system for clinical trials including the creation of standard operating procedure documents (so-called SOPs), initial submission of the clinical trial as well as submission of amendments to authorities and ethics committees, supervision, and GCP-/study-specific training of trial sites and various other operational activities according to ICH-GCP, GCP guideline, and the German Medicines Act. I supervised the study as a clinical research associate, independently initiating new study sites and ensuring compliance with the study protocol and regulatory requirements.

The medical documentarist, Dr. Utz Benscheid, created the raw datasets from the VICTORIA trial, and based thereon I have created the final analysis datasets by coding and documenting the variables. I composed the statistical analysis plan which was then reviewed and approved by PD Dr. Ben Schöttker, Professor Brenner, Professor Kopp-Schneider, and Dr. Caspari. The statistical analysis of the data using R and SAS as well as the interpretation of the results were completely performed by myself. My results were cross-checked by Professor Kopp-Schneider and PD Dr. Ben Schöttker for integrity and completeness.

PD Dr. Ben Schöttker designed the systematic review, wrote its protocol, and obtained funding for its realization. I was hired to conduct this project and refined the initial search strategy, the selection criteria, the data extraction criteria, the risk of bias assessment, and the statistical methods. I conducted the literature search, title/abstract and full-text screening, data extraction and management myself. Furthermore, I conducted all meta-analyses using R. Regarding the IPD, I created the final datasets from raw data of the WHI and the VITAL (Vitamin D and Omega-3 Trial) study and coded the required variables. The preparation and conduct of all meta-analyses, subgroup and sensitivity analyses as well as the and the subsequent interpretation of the results were completely performed by myself using R. PD Dr. Ben Schöttker repeated the meta-analyses independently using Comprehensive Meta-Analysis 2.0 in the

framework of the four-eyes principle. The data extraction and the risk of bias assessment were also repeated by a second person (Anna Zhu) in the framework of the four-eye principle.

Parts of this dissertation have already been published in peer-reviewed and internationally recognized scientific journals or are currently submitted for publication. The following lists provide an overview of pertaining publications.

8.1 Published articles directly related to this dissertation:

1. Kuznia, S., Czock, D., Kopp-Schneider, A., Caspari, R., Fischer, H., Laetsch, D.C., Slavic, M., Brenner, H. and Schöttker, B. (2022). **Efficacy and Safety of a Personalized Vitamin D_3 Loading Dose Followed by Daily 2000 IU in Colorectal Cancer Patients with Vitamin D Insufficiency: Interim Analysis of a Randomized Controlled Trial.** Nutrients 14, 4546.
2. Schöttker, B.[1], Kuznia, S.[1] and Brenner, H. (2021). **Efficacy of vitamin D_3 supplementation on cancer mortality in the general population and the prognosis of patients with cancer: protocol of a systematic review and individual patient data meta-analysis of randomised controlled trials.** BMJ Open 11, e041607.
3. Schöttker, B.[1], Kuznia, S.[1], Laetsch, D.C.[1], Czock, D., Kopp-Schneider, A., Caspari, R. and Brenner, H. (2020). **Protocol of the VICTORIA study: personalized vitamin D supplementation for reducing or preventing fatigue and enhancing quality of life of patients with colorectal tumor – randomized intervention trial.** BMC Cancer 20, 739.

8.2 Paper submitted for publication:

4. Kuznia, S., Zhu, A., Akutsu, T., Buring, J., Camargo, Jr. C., Cook, N., Chen, L.J., Cheng, T.Y.D., Hantunen, S., Lee, I.M., Manson, J.A., Neale, R., Scragg, R., Shadyab, A., Sha, S., Sluyter, J., Tuomainen, T.P., Urashima, M., Virtanen, J., Voutilainen, A., Wactawski-Wende, J., Waterhouse,

[1] Joint first authors with equal contributions

M., Brenner, H. and Schöttker, S. **Efficacy of vitamin D_3 supplementation on cancer mortality: systematic review and individual patient data meta-analysis of randomized controlled trials.**

Chapters 1.2, 1.3, 2.2, 3.2 (including 3.2.1 to 3.2.3), 4.2, 4.3, 5, and 6 of this dissertation are based on publication #1, and #3, respectively. Chapters 1.1, 1.3, and 2.1 (including 2.1.1 to 2.1.10) of this dissertation are based on publication #2. Chapters 1.1, 1.3, 2.1 (including 2.1.1 to 2.1.10), 3.1 (including 3.1.1 to 3.1.5), 4.1 (including 4.1.1 to 4.1.4), 4.3, 5, and 6 of this dissertation are based on publication #4.

My personal contribution to publication #1 extends to the methodology, data curation, formal analysis, visualization, and manuscript composition. PD Dr. Ben Schöttker revised the manuscript and contributed important intellectual content to the interpretation and discussion of results.

My personal contribution to publication #2 extends to the research of the background literature concerning the conduct of systematic reviews and meta-analyses, particularly in the framework of individual patient data following the PRISMA-P guidelines. I composed the manuscript which PD Dr. Ben Schöttker and Professor Brenner revised critically for important intellectual content.

My personal contribution to publication #3 consisted of the research of the background literature concerning the correct publication of clinical trials according to the SPIRIT guidelines. Moreover, I revised the study protocol and transformed it into a publishable manuscript.

My personal contribution to publication #4 consisted of the research of the background literature concerning the correct publication of meta-analyses with IPD according to the PRISMA-IPD guidelines and the manuscript composition. PD Dr. Ben Schöttker critically revised the manuscript for important intellectual content.

All co-authors made substantial contributions to the interpretation and discussion of results and approved the respective final manuscripts.

8.3 Articles unrelated to this dissertation:

5. Niedermaier, T., Gredner, T., Kuznia, S., Schöttker, B., Mons, U., Lakerveld, J., Ahrens, W., Brenner, H. and PEN-Consortium (2022). **Vitamin D food fortification in European countries: the underused potential to prevent cancer deaths.** Eur J Epidemiol 37, 309-320.
6. Sha, S., Nguyen, T.M.N., Kuznia, S., Niedermaier, T., Zhu, A., Brenner, H. and Schöttker, B. (2022). **Real-world evidence for the effectiveness of vitamin D supplementation in reduction of total and cause-specific mortality.** J Intern Med, 10.1111.
7. Zhu, A., Kuznia, S., Boakye, D., Schöttker, B., and Brenner, H. (2022). **Vitamin D-binding Protein, Bioavailable, and Free 25(OH)D, and Mortality: A Systematic Review and Meta-Analysis.** Nutrients 14, 3894.
8. Zhu, A., Kuznia, S., Niedermaier, T., Holleczek, B., Schöttker, B. and Brenner, H. (2022). **Consistent Inverse Associations of Total, Bioavailable, Free and "Non-bioavailable" Vitamin D with Incidence of Diabetes among Older Adults with Lower Baseline HbA_{1c} (≤6%) Levels.** Nutrients 14, 3282.
9. Zhu, A., Kuznia, S., Niedermaier, T., Holleczek, B., Schöttker, B. and Brenner, H. (2022). **Vitamin D-binding protein, Total, "Non-bioavailable," Bioavailable, and Free 25-hydroxyvitamin D, and Mortality in A Large Population-based Cohort of Older Adults.** J Intern Med 292, 463-476.
10. Brenner, H., Kuznia, S., Laetsch, C., Niedermaier, T. and Schöttker, B. (2021). **Prevention of Advanced Cancer by Vitamin D_3 Supplementation: Interaction by Body Mass Index Revisited.** Nutrients 13, 1408.
11. Niedermaier, T., Gredner, T., Kuznia, S., Schöttker, B., Mons, U. and Brenner, H. (2021). **Vitamin D supplementation to the older adult population in Germany has the cost-saving potential of preventing almost 30 000 cancer deaths per year.** Mol Oncol. 15, 1986-1994.
12. Niedermaier, T., Gredner, T., Kuznia, S., Schöttker, B., Mons, U. and Brenner, H. (2021). **Potential of Vitamin D Food Fortification in Prevention of Cancer Deaths-A Modeling Study.** Nutrients 13, 3986.

13. Zhu, A., Kuznia, S., Niedermaier, T., Holleczek, B., Schöttker, B. and Brenner, H. (2021). **Distribution and Determinants of Vitamin D-Binding Protein, Total, "Non-Bioavailable", Bioavailable, and Free 25-Hydroxyvitamin D Concentrations among Older Adults.** Nutrients 13, 3982.

8.4 Poster and oral presentations at scientific conferences:

Published conference abstract from 38th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE, August 26-28, 2022, Copenhagen, Denmark)

14. Schöttker, B., Brenner, H. and Kuznia, S. (2022). **Efficacy and safety of a personalized vitamin D_3 loading dose followed by 2000 IU per day to raise serum 25-hydroxyvitamin D levels in colorectal cancer patients with vitamin D insufficiency. Interim analysis of a RCT.** Pharmacoepidemiol Drug Saf 31, 331-331.

Published conference abstract from International Symposium "Vitamin D in Prevention and Therapy" (May 4-5, 2022, Homburg, Germany)

15. Oral presentation: Kuznia, S., Zhu, A., Schöttker, B. and Brenner, H. (2022). **Efficacy Of Vitamin D_3 Supplementation On Cancer Mortality In The General Population And The Prognosis Of Patients With Cancer: A Systematic Review And Individual Patient Data Meta-Analysis Of Randomized Controlled Trials.** Anticancer Res 42, 2193-2222.

DKFZ PhD Poster Presentation (November 16, 2021, Heidelberg, Germany)

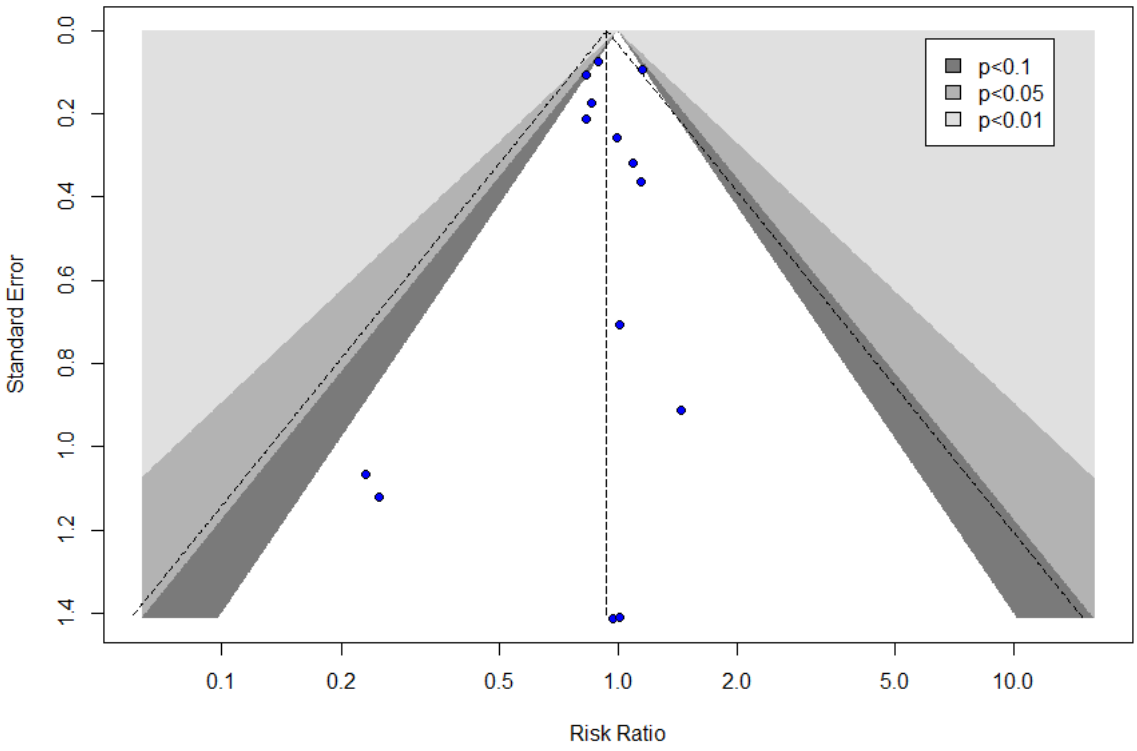
16. Poster presentation: Kuznia, S., Schöttker, B. and Brenner, H. (2021). **Efficacy of vitamin D_3 supplementation on cancer mortality in the general population and cancer prognosis: a systematic review and individual patient-data meta-analysis.**

APPENDICES

List of supplemental figures

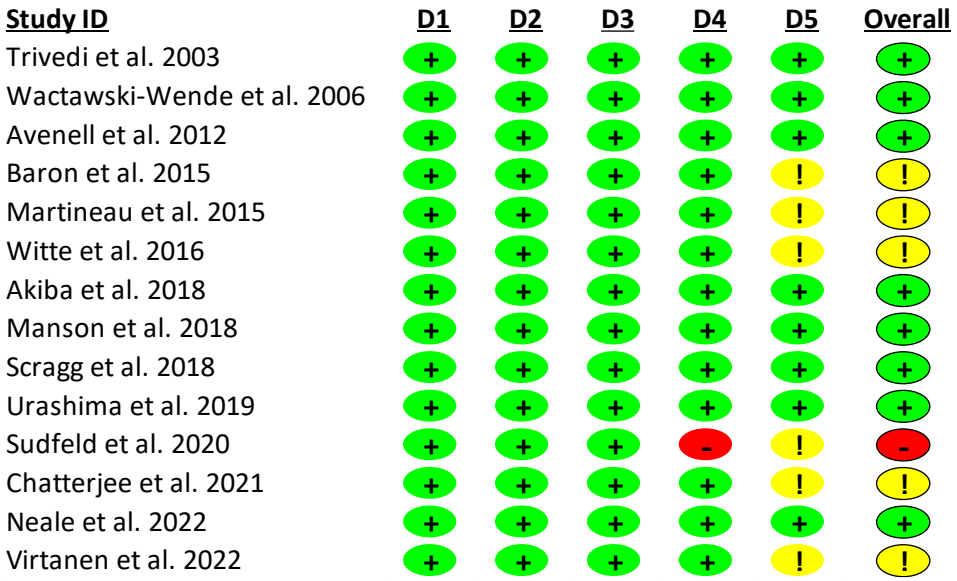
List of supplemental tables

Supplemental Figure 1. *Funnel plot of included studies*



Note: Egger's test result: Intercept (95% CI): -0.20 (-0.92; 0.52), *p*-value: 0.600

Supplemental Figure 2. *Quality appraisal via the Cochrane risk-of-bias tool for randomized trials (RoB) 2*



Legend to supplemental figure 2:

Explanation of symbols

+ Low risk

! Some concerns

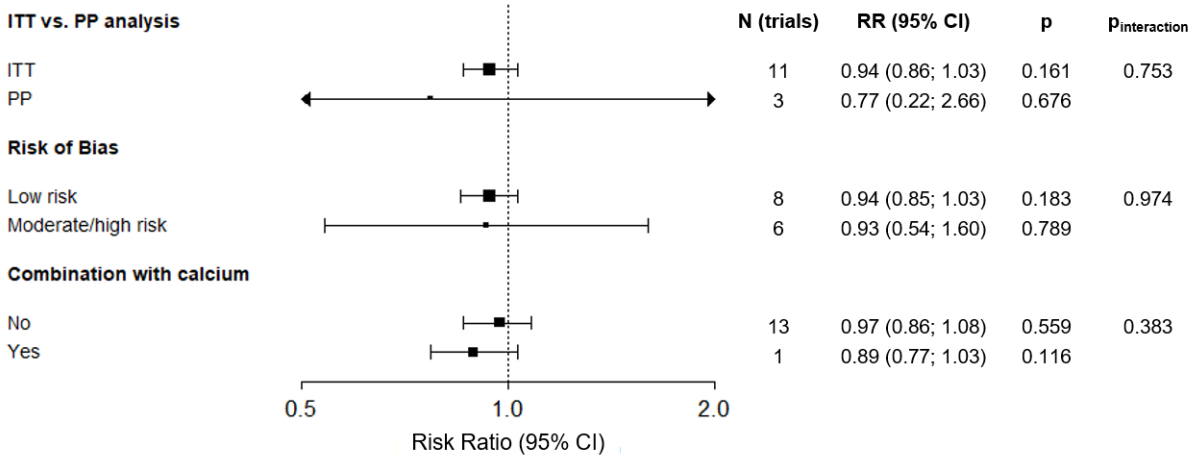
- High risk

Explanation of domains

D1 Randomization process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

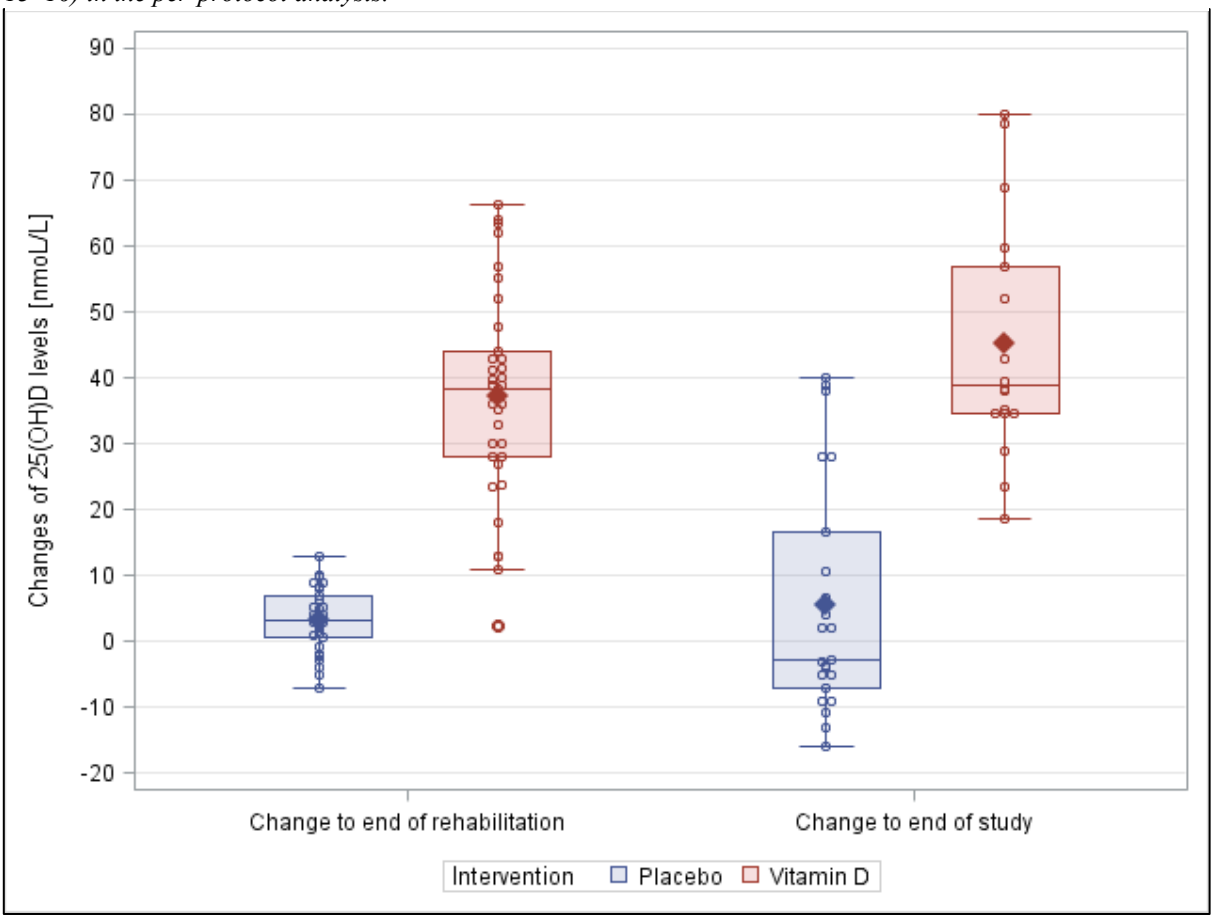
Note: The risk appraisal was applied specifically for the outcomes "cancer mortality" or "cancer survival". To account for a consistent evaluation of studies with unpublished data, domains 4.1, 4.2, 5.1 and 5.2 were scored as "no information (NI)" because the relevant outcomes were counted as adverse events, if at all, and thus, no defined measurement or pre-specified analysis was available. If unpublished data were received, domain 3.1 was rated with "probably yes" and domain 5.3 with "no" because I asked for an unadjusted Cox regression analysis and therefore, the authors did not have a choice of methods. Likewise, if unpublished data were not received, domains 3.1 and 5.3 were assigned a "NI".

Supplemental Figure 3. *Sensitivity analysis*



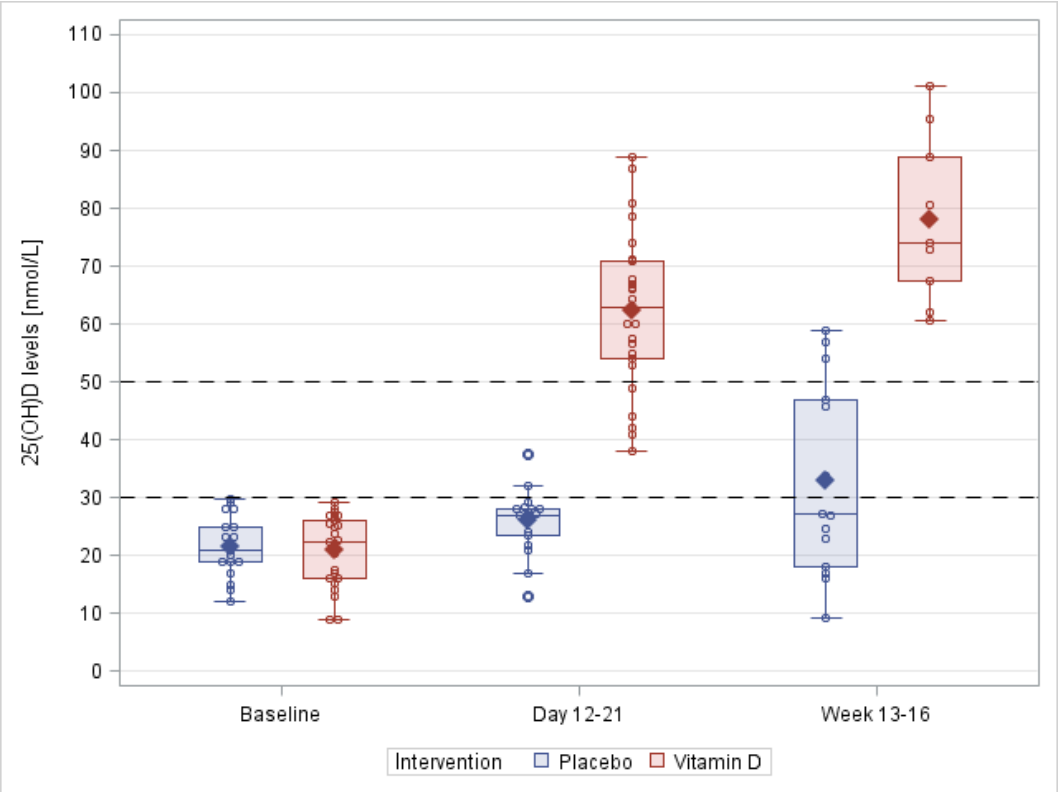
Note: N represents the count.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; PP, per-protocol; RR, risk ratio

Supplemental Figure 4. *Boxplots of changes in 25(OH)D levels from screening to end of rehabilitation (visit 1, end of loading dose, days 12–21) and from screening to end of the study (visit 2, end of maintenance dose, weeks 13–16) in the per-protocol analysis.*



Abbreviations: 25(OH)D, 25-hydroxyvitamin D

Supplemental Figure 5. *Boxplots of 25(OH)D levels during the trial restricted to subjects with vitamin D deficiency (25(OH)D < 30 nmol/L) at screening (per-protocol analysis)*



Abbreviations: 25(OH)D, 25-hydroxyvitamin D

Supplemental Table 1. *List of deviations from systematic review protocol*

Date (DD/MM/YYYY)	**Description of the change**	**Rationale**	**Made by**
26.01.2021	"Inclusion criteria for study design": include double-blinded trials, exclude open-label	Details were not specified before	SK
26.01.2021	"Inclusion criteria for intervention": include studies with combination with other drugs than vitamin D_3 as long as both vitamin D_3 and placebo arms get the same other drugs in the same dosing regimen	Details were not specified before	SK
09.02.2021	"Inclusion criteria for study population": no age restriction, pregnancy excluded	Details were not specified before	SK
09.09.2021	"Data synthesis": if no cancer diagnosis prior the day of death is available for study participants who died of cancer during the trial, the survival time will be counted from baseline to date of death.	Needed for statistical analysis. This was not specified in the protocol before but is no change of plan.	BS
24.08.2021	"Data synthesis": studies who have not assessed a variable or for which all study participants are in the same category will not be adjusted for the affected variable(s).	Needed for statistical analysis. This was not specified in the protocol before but is no change of plan.	BS
25.08.2021	"Data synthesis": age, baseline 25(OH)D level and BMI used as continuous instead of categorical model variables.	Change needed because not all studies had study participants in all categories.	BS
24.02.2022	"Data synthesis": Variable skin color was replaced by ethnicity.	Studies assessed ethnicity but not skin color.	BS
09.09.2021	"Data synthesis": for subgroup analyses on baseline 25(OH)D level cut-off of 50 instead of 30 nmol/L chosen	Too few study participants with 25(OH)D levels < 30 nmol/L.	BS
09.09.2021	"Data synthesis": change in categories for variable "time since cancer diagnosis" from "< 1 year vs. 1–5 years" to "up to 5 years prior vs. during the trial".	Too few study participants with cancer diagnosis in first year prior baseline. Furthermore, cancer deaths during the study should be included.	BS
07.09.2021	"Data synthesis": subgroup analyses in samples with less than 10 cases will not be performed.	Added to ensure model stability.	BS
26.08.2021	"Data synthesis": sensitivity analysis about excluding events in the first year of follow-up was not conducted.	Case numbers too low.	BS
26.08.2021	"Data synthesis": Dealing with missing data was changed as follows: Instead of using "unknown" categories for missing values, variables with < 5% of missing data will lead to exclusions of the respective study participants from the multivariate model. Variables with ≥ 5% of missing data will not be used in the multivariate model of the respective study.	Change made to ensure that the majority of study participants of all trials can still be used in the meta-analyses despite missing data. "Unknown" categories could lead to bias.	BS

12.05.2022	"Data synthesis": change in model variable cancer stage to the three categories stage I–III, stage 4 and unknown.	Cancer stage I, II and III were not distinguishable in all trials and were therefore grouped together.	BS
12.05.2022	"Data synthesis": change in model variable cancer site from one categorical variable to four single variables for each cancer site (i.e., prostate, colorectal, breast and lung cancer).	The categorical variable did not work because some study participants had more than one cancer.	BS
19.05.2022	"Data synthesis": Subgroup analysis "Region" adjusted: Europe and North America summarized into one category "Europe or USA"	For "North America", only studies from the US were found and thus the name was changed. Point estimates for Europe (RR (95% CI): 0.87 (0.68; 1.10) and USA (RR (95% CI): 0.87 (0.77; 0.98)) were the same and allowed merging of the two categories. This shall avoid reporting a non-statistical finding for Europe that could be misinterpret as an absence of an effect of the intervention in Europe.	BS
30.06.2022	"Data synthesis": In the subgroup analysis for "Dosing" the categories "bolus dose at the beginning of the trial followed by a daily dose" was merged with the category "daily dose".	For the subgroup "bolus dose at the beginning of the trial followed by a daily dose" only one trial was found.	SK
08.06.2022	"Data synthesis": Instead of conducting two meta-analyses for "general population" and "cancer population" with all published trials, all trials were put in one meta-analysis.	The term "general population" did not fit anymore because studies with diabetes and HIV patients were found. For the meta-analysis on cancer population, only two trials were found of which one was very small, which was not enough studies for a stand-alone meta-analysis. However, the two distinct meta-analyses were carried out in the IPD analyses in which more studies with cancer patients were available.	BS
22.7.2022	Subgroup analyses with IPD data also carried out with inclusion of only studies with daily vitamin D_3 dosing regimen.	It became apparent in the data analysis that only studies with daily vitamin D_3 dosing regimen showed an efficacy for the outcomes. Thus, it is reasonable to conduct subgroup analyses restricted to these studies, too.	BS

Supplemental Table 2. *PRISMA IPD checklist*

PRISMA-IPD Section/topic	Item No	Checklist item	Reported in chapter
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	2.1.1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	1.1, 2.1, 3.1, 4.1
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations* of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1.1
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	1.3, 2.1.3
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	2.1.1
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g., years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e., whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	2.1.2, 2.1.3
Identifying studies – information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and	2.1.2

		agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	
Identifying studies – search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Supplemental Table 3**
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	2.1.2, 2.1.3, 2.1.4
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	2.1.4, 2.1.5, 3.1.1
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardizing or translating variables within the IPD datasets to ensure common scales or measurements across studies.	2.1.4, 2.1.5, **Table 2**, **Supplemental Table 7**, **Figure 3**, **Figure 5**, **Figure 9**, **Figure 10**
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	2.1.5, 3.1.1
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	2.1.7
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	2.1.6
Synthesis methods	14	Describe the meta-analysis methods used to synthesize IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analyzed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	2.1.6
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analyzed as potential effect modifiers, and whether these were pre-specified.	2.1.6
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	2.1.7, 2.1.8
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	2.1.6

Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	3.1.1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	3.1.2, **Table 2**, **Supplemental Table 7**
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	3.1.1
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	3.1.3, **Supplemental Figure 2**
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	3.1.2
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	3.1.3, 3.1.4, **Figure 2**, **Figure 4**, **Figure 7**, **Figure 8**
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	3.1.5, **Supplemental Table 17**
Additional analyses	23	Give results of any additional analyses (e.g., sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarize the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	3.1.3, **Supplemental Figure 3**
Discussion			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome.	4.1.1, 4.1.2, 4.1.3
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	4.1.4
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	4.3
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	4.3
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	2.1.10

Supplemental Table 3. *Search Strings*

Step	Search string
MEDLINE	
1	"vitamin d"[tw] OR "vitamin D"[MeSH] OR cholecalciferol[MeSH] OR cholecalciferol*[tw] OR calciol[tw] OR hydroxycholecalciferols[MeSH] OR hydroxycholecalciferol*[tw] OR dihydroxycholecalciferol*[tw] OR “vitamin d3"[tw] OR “vitamin d 3”[tw] OR calcitriol[MeSH] OR calcitriol[tw] OR "1-hydroxycholecalciferol"[tw] OR calcifediol[MeSH] OR calcifediol[tw] OR calcidiol[tw] OR alfacalcidol[Supplementary Concept] OR alphacalcidol[tw] OR alfacalcidol[tw]
2	mortality[tw] OR mortality[MeSH] OR death[MeSH] OR death[tw] OR died[tw] OR dead[tw] OR survival[tw] OR surviv*[tw] OR survival[MeSH]
3	neoplasms[MeSH] OR neoplas*[tw] OR malignanc*[tw] OR cancer*[tw] OR tumor*[tw] OR tumour*[tw] OR carcinoma*[tw]
4	(((((((((“randomised controlled trial”[pt]) OR “controlled clinical trial”[pt]) OR randomised[tiab]) OR placebo[tiab]) OR “drug therapy”[sh]) OR randomly[tiab]) OR trial[tiab]) OR groups[tiab])) NOT ((animals[mh] NOT humans[mh]))
5	placebos[MeSH] OR placebo[tw]
6	2 OR 3
7	1 AND 4 AND 5 AND 6
CENTRAL and CDSR	
1	#1 MeSH descriptor: [Vitamin D] explode all trees #2 MeSH descriptor: [Cholecalciferol] explode all trees #3 MeSH descriptor: [Calcifediol] explode all trees #4 MeSH descriptor: [Calcitriol] explode all trees #5 MeSH descriptor: [Hydroxycholecalciferols] explode all trees #6 (("alfacalcidol") OR ("alphacalcidol") OR ("hydroxycholecalciferol*") OR ("1- hydroxycholecalciferol") OR ("hydroxyvitamin* D") OR ("calcifediol") OR (“calcidiol”) OR ("calcitriol") OR ("dihydroxycholecalciferol*") OR (“dihydroxyvitamin d*”) OR ("vitamin D") OR (cholecalciferol*) OR ("vitamin D3") OR ("vitamin D 3") OR (“calciol”)) (Word variations have been searched) #7 ("vitamin d*"):ti,ab,kw (Word variations have been searched) #8 1-#7
2	#9 MeSH descriptor: [Mortality] explode all trees #10 MeSH descriptor: [Death] explode all trees #11 MeSH descriptor: [Survival] explode all trees #12 ("mortality" OR "dea*" OR “died” OR "survival" OR “surviv*”) (Word variations have been searched) #13 1-#12
3	#14 MeSH descriptor: [Neoplasms] explode all trees #15 (carcinoma* OR tumour* OR tumor* OR cancer* OR malignanc* OR neoplas*) (Word variations have been searched) #16 #14 OR #15
4	#17 #13 OR #16
5	**#18 #8 AND #17 in Cochrane Reviews (Word variations have been searched)**

6	**#19 #8 AND #17 in Trials (Word variations have been searched)**
WEB OF SCIENCE (WoS Core Collection, all years)	
1	TS=(al*acalcidol OR calcidiol OR calcifediol OR calcitriol OR dihydroxycholecalciferol* OR (1-hydroxycholecalciferol) OR (25(OH)D) OR (25OHD) OR hydroxycholecalciferol* OR calciol OR cholecalciferol* OR (vitamin D) OR (vitamin d3))
2	TS=(mortality OR dea* OR died OR surviv*)
3	TS=(carcinoma* OR tumour* OR tumor* OR *cancer* OR malignanc* OR neoplas*)
4	TS=((blind AND (single OR double OR treble OR triple)) OR (*clinical trial*) OR (controlled clinical trial) OR (random* AND (allocat* OR assign*)) OR (randomised OR randomisation) OR randomised controlled trial)
5	TS=placebo*
6	2 OR 3
7	1 AND 4 AND 5 AND 6
KSR Evidence	
1	"vitamin d" or "vitamin d3" or "vitamin d 3" or cholecalciferol* or calci* or hydroxycholecalciferol* or dihydroxycholecalciferol* or alfacalcidol* or alphacalcidol* in All text
2	mortality or dea* or died or surviv* in All text
3	neoplas* or malignanc* or cancer* or tumor* or tumour* or carcinom* in All text
4	"randomised controlled trial*" or "randomised controlled trial*" or RCT* or "randomised trial*" or "randomised trial*" or "controlled clinical trial*" or CCT* or "controlled trial*" or "clinical trial*" or random* in All text
5	#2 or #3 in All text
6	#1 and #4 and #5 in All text
	Sorted by risk of bias

Supplemental Table 4. *Exclusion criteria of the VICTORIA trial*

Exclusion criterion	**Ascertainment/ Operationalization**	**Justification**
No vitamin D insufficiency or deficiency	Measurement	An efficacy of a vitamin D_3 intervention for patients without vitamin D insufficiency or deficiency is not expected. The threshold for vitamin D insufficiency of the US American Institute of Medicine is 50 nmol/L (2011b).
Severe renal impairment	eGFR < 30 ml/min/1.73 m^2 calculated with CKD-EPI equation	Limited calcium and phosphate excretion; Special precautions for use of vitamin D_3 high-dose therapy according to Dekristol® 20,000 I.E. (SmPC)
Hypercalciuria	Random urine calcium ≥ 0.28 mg/mg creatinine (equals 0.79 mmol/mmol creatinine) (Tellioglu et al. 2012)	Contraindication for vitamin D_3 high-dose therapy according to Dekristol® 20,000 I.E. (SmPC)
Hypercalcemia	Albumin-corrected serum calcium > 2.65 mmol/L (Meng and Wagar 2015)	Contraindication for vitamin D_3 high-dose therapy according to Dekristol® 20,000 I.E. (SmPC)
High-dose vitamin D_3 therapy	Vitamin D_3 daily ≥ 2,000 IU, vitamin D_3 weekly ≥ 14,000 IU or similar dosing regimen leading to average exposure to vitamin D_3 of ≥ 2,000 IU per day Interview with the patient; Medical records;	Therapy would need to be stopped for trial participation.
Therapy with vitamin D analogs	Vitamin D_2 (Ergocalciferol), Dihydrotachysterol, Alfacalcidol, Calcitriol, or Calcifediol)	Therapy would need to be stopped for trial participation.
Topical therapy with vitamin D_3 or vitamin D analogs	Topical vitamin D_3 (e.g., Silikis®) or topical vitamin D analogs	Therapy would need to be stopped for trial participation.
Hypersensitivity to peanuts, soy, gelatin, lactose, maize starch or sucrose (ingredients in Dekristol® 20,000/1,000 I.E.)	Interview with the patient	Contraindication for Dekristol® 20,000 I.E. or Dekristol® 1,000 I.E. according to SmPC
Nephrolithiasis with symptoms in the last 12 months	Medical records	Condition can worsen because of increased serum calcium under vitamin D_3 therapy. Contraindication for Dekristol® 1 000 I.E. according to SmPC
Pseudohypoparathyreodism	Medical records	Contraindication for vitamin D_3 high-dose therapy according to Dekristol® 20,000 I.E. (SmPC); Risk of vitamin D_3 overdose

Exclusion criterion	Ascertainment/ Operationalization	Justification
Sarcoidosis	Medical records	Increased production of the active form of vitamin D ($1,25(OH)_2$-vitamin D). Special precautions for use of vitamin D_3 high-dose therapy according to Dekristol® 20,000 I.E. (SmPC)
Therapy with cardiac glycosides	Medical records	Increased susceptibility to high calcium levels leads to enhanced risk of adverse effects from cardiac glycosides according to Dekristol® 20,000 I.E. (SmPC)
Therapy with high-dose calcium supplements	> 1,000 mg calcium daily Interview with the patient; Medical records	Simultaneous therapy with vitamin D_3 and high-dose calcium might increase the risk of stroke (Jenkins et al. 2018; Khan et al. 2019)
Participation in another intervention trial	Interview with the patient	To avoid potential conflicts in trial protocols and to ensure the safety of the participants by avoiding potential drug-drug interactions.
Pregnancy, planned pregnancy in next 12 weeks, or lactation	Urine pregnancy test during the screening phase	To ensure the safety of the unborn/newborn child.
No use of adequate contraceptive measures in women of childbearing potential	Interview with the patient	To ensure the safety of the unborn/newborn child.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate, I.E., Internationale Einheiten; IU, international units; SmPC, Summary of Product Characteristics.

Supplemental Table 5. *Excluded Studies*

AUTHOR (YEAR), ACRONYM, STUDY-ID	STATUS	EXCLUSION CATEGORY	REASON FOR EXCLUSION
2016-002913-23	Prematurely ended	Ineligible study design	open label, no placebo (other arm is no treatment)
2020-001960-28	Ongoing	No data of interest	study on Corona
ChiCTR1800018154	Recruitment complete	Ineligible intervention	single dose
ChiCTR-INR-16009235	Recruiting pending	Ineligible study design	no placebo, open label
CTRI/2013/04/003566	Open to recruitment	Ineligible study design	study on infants and pregnant women
IRCT2013030912762N1, NCT01863641	Unknown (Recruiting)	No data of interest	wrong outcome
IRCT2013050413223N1	Recruitment complete	No data of interest	wrong outcome
IRCT2013061610326N1	Recruitment complete	No data of interest	wrong outcome
IRCT2013123116020N1	Recruitment complete	Ineligible intervention	single dose
IRCT201609026026N4	Recruitment complete	No data of interest	wrong outcome
IRCT2017021030705N1	Recruitment complete	No data of interest	wrong outcome
IRCT20200324046850N1	Recruitment complete	Ineligible intervention	arms not comparable
JPRN-jRCTs031200376	Recruiting	Ineligible study design	wrong study population
KCT0000152	Not yet recruiting	Ineligible study design	open label design, standard treatment as control
Matsumoto, 2005		All patients receive vitamin D	all pt. receive 200 or 400 IU; no death published, acc to Goulao 4 CI
NCT00482157	Withdrawn 03/22	Retracted	withdrawn, no participants recruited
NCT00749736	Completed	No data of interest	wrong outcome
NCT00887432	Completed	No data of interest	no deaths/CI
NCT01323712	Unknown ((Active, not recruiting)	No data of interest	wrong outcome
NCT01419730	Completed	All patients receive vitamin D	all pt. receive 600 IU
NCT01521936	Terminated (Lack of funding)	Ineligible study design	open label, 4 participants
NCT01574027	Completed	No data of interest	wrong outcome
NCT01600430	Completed	Ineligible study design	less 6 months
NCT01651000 (CTAP101-CL-3001)	Completed	Ineligible study design	3 CI in 1 arm but not deaths (AE), safety efficacy of CTAP101, CTAP101-CL-3001 (3002 (NCT02282813) no outcomes + open label)
NCT01724190	Completed	No data of interest	wrong outcome
NCT01809171, 2013-001064-27	Terminated (Inclusion problems)	All patients receive vitamin D	only 15 participants, breast cancer population, all pt. receive 800 IU
NCT02064946	Completed	All patients receive vitamin D	both arms receive 600 IU
NCT02704624	Enrolling by invitation	No data of interest	wrong outcome

NCT03483441	Recruiting	Ineligible study design	intervention only given for few days (less 6 months)
NCT03779776	Completed	Ineligible study design	less 6 months, both arms VD
NCT04244474	Active, not recruiting	Ineligible intervention	single injection
NCT04355572	Not yet recruiting	No data of interest	wrong outcome
NCT04536831	Completed	Ineligible study design	less 6 months, single blinded
SLCTR/2018/019	Recruiting	No data of interest	wrong outcome
TCTR20161101004	Enrolling by invitation	Ineligible study design	less 6 months
UMIN000004854	Enrolling by invitation	No data of interest	answer author: "The target was patients who received polypectomy (free of cancer); The follow-up period was short; and the endpoint of this study was recurrence of adenoma (mainly). Actually, we observed no case of death. So, it would be better to exclude our study from your analysis."
DEDiCa, NCT02786875, 2015-005147-14	Recruiting	Ineligible study design	open label, recruiting
D-Light, NCT02495584	Completed	No data of interest	fortified milk combined with supplements, wrong outcome
D-SAF, NCT03963128	Recruiting	No data of interest	wrong outcome
D-Wheeze, NCT01601847	Completed	No data of interest	only 1 AM
FLASH, NCT01141972	Completed	No data of interest	wrong outcome
LungVITAL, NCT01728571	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL
Pittsburgh VD Study, NCT02532062	Terminated	All patients receive vitamin D	both arms receive 400 IU, terminated, only 10 participants
PROVENT, NCT03103152, 2014-001784-13, ISRCTN91422391	Active not recruiting	No data of interest	only 1 AM
Safe-D Study Part B, ACTRN12613000972729	Not yet recruiting	Ineligible study design	less 6 months, open label, wrong outcome Part A: cross-sectional
SIMPLIFIED, ISRCTN15087616, 2015-005003-88	Ongoing, no longer recruiting	Ineligible study design	open label design, standard treatment as control
STURDY, NCT02166333	Terminated	Ineligible study design	no placebo
VD3PCa, NCT01759771	Completed	No data of interest	wrong outcome
Vit D & Pca, NCT00953225	Completed	No data of interest	no AM and CI
VITAL Anemia, NCT01632761	Unknown (Enrolling by invitation)	Ancilliary (sub)study	ancilliary study to VITAL
VITAL Cerebrovascular disease, NCT04070833	Completed	Ancilliary (sub)study	ancilliary study to VITAL
VITAL Rhythm, NCT02178410	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Adipositas, NCT01785004	Unknown (Enrolling by invitation)	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-AMD, NCT01782352	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Biomarkers of systemic inflammation,	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL

NCT01351805			
VITAL-Bone Structure and Architecture, NCT01747447	Completed	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-COG, NCT01669915	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-DEP, NCT01696435	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Diabetes, NCT01633177	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Diabetic kidney disease, NCT01684722	Completed	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Fractures, Vitamin D and Genetic Markers, NCT01704859	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Heart failure, NCT02271230	Completed	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Infections, NCT01758081	Active, not recruiting	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Kidney in Hypertensives, NCT02757872	Completed	Ancilliary (sub)study	ancilliary study to VITAL
VITAL-Mammographic Density and Breast, Tissue NCT02239874	Unknown (Enrolling by invitation)	Ancilliary (sub)study	ancilliary study to VITAL
VITdALIZE-KIDS, NCT03742505	Recruiting	Ineligible intervention	single dose
VITdAL-PICU, NCT02452762	Completed	Ineligible intervention	single dose
VIVA (VIVA-VA), NCT01170273	Completed	No data of interest	3 CI only in 1 arm
Al-Beltagi, 2019		Ineligible study design	open label
Aloia, 2013 (NCT00762775)	Completed	No data of interest	no deaths/CI
Aloia, 2018 (PODA, NCT01153568)	Completed	No data of interest	18 CI, 1 AM (cardiorespiratory failure) Outcome only found here: Vitamin D Supplementation in Elderly Black Women Does Not Prevent Bone Loss: A Randomised Controlled Trial
Alvarez, 2012 (POSH-D, NCT00781417)	Completed	No data of interest	no deaths/CI
Arihiro, 2019 (UMIN000014743)	Completed	No data of interest	no deaths/CI
Banerjee, 2021		No data of interest	1 CI, no deaths,
Barchetta, 2016 (2011-003010-17)	Ongoing	No data of interest	no deaths/CI
Belenchia, 2013 (NCT00994396)	Completed	No data of interest	no deaths/CI
Bellantone, 2002		No data of interest	only 3 patients at 6 months, wrong outcome
Bhutta, 2011 (NCT01229189)	Completed	Ineligible study design	pregnant women AND their newborn get VD, outcome pregnancy related
Bizzarri, 2010 (IMDIAB XIII, NCT01120119)	Completed	No data of interest	no deaths/CI
Briffa, 2003		Ineligible study design	no placebo
Brisson, 2017 (EVIDENSE, NCT01747720)	Completed	No data of interest	1 CI, no deaths
Bucharles, 2019		No data of interest	no deaths/CI
Bueloni-Dias, 2018 (RBR-4MHS32)	Data analysis completed	No data of interest	no deaths/CI

Buettner, 2015 (NCT01225263)	Completed	No data of interest	no deaths/CI
Calarge, 2018 (NCT00799383)	Completed	No data of interest	wrong outcome
Camu, 2019 (CHOLINE, NCT01198132)	Completed	No data of interest	3 CI, no deaths
Chen, 1997		Ineligible study design	open label design
Cohen, 1983		Ineligible intervention	combo inadequat/arms not comparable: VD with 3 agents vs 4 P
Cooper, 2021 (NCT00887432)	Completed	No data of interest	no deaths
Crew, 2019 (SWOG S0812, NCT01097278)	Completed	All patients receive vitamin D	all pt. receive 600 IU
Crom, 2006		No data of interest	wrong outcome
Dalbeni, 2014		No data of interest	no deaths/CI
de Bruyn, 2021 (DETECT, NCT02010762)	Completed	No data of interest	1 CI, no deaths
de Nijs, 2007 (STOP-study, NCT00138983)	Completed	Ineligible intervention	alendronate + placebo vs. alfacalcidol + placebo
Diaz, 2008		Ineligible study design	no blinding of caregivers/investigators (open label, no placebo)
Doi, 2021 (UMIN000020597)	No longer recruiting	No data of interest	2 AM only in 1 arm, 1 multiple myeloma (but did not start treatment) Hospitalization-requiring infection-free survival?
Farrokhian, 2017 (IRCT201510315623N56)	Recruitment complete	Retracted	retracted
Firouzabadi, 2012		No data of interest	wrong outcome
Gabbay, 2012		No data of interest	no deaths/CI
Gagnon, 2014 (ACTRN12609000043235)	Recruiting	No data of interest	no deaths/CI
Gallagher, 2014 (VIDOS, NCT00472823)	Completed	No data of interest	no deaths/CI
Genser, 2014		Ineligible study design	no treatment as control
Glendenning, 2012 (ACTRN12609000748213)	Active, not recruiting	No data of interest	34 CI as AE but only 2 deaths in VD arm
Golubic, 2018		Ineligible study design	open label, standard treatment as control
Grove-Laugesen, 2019 (DAGMAR, NCT02384668)	Active, not recruiting	No data of interest	no deaths/CI
Gupta, 2016 (CTRI/2013/02/003440)	Completed	Ineligible study design	open label design, usual care as control
Hansen, 2015 (NCT00933244)	Completed	No data of interest	8 CI but and no deaths (S-table 6+9) but "We reported serious adverse events"
Hansen, 2015 (NCT00933244)	Completed	No data of interest	8 CI but no deaths (S-table 6+9)
Hewitt, 2013 (ACTRN12611000199910)	Recruitment complete	No data of interest	2 deaths but not cancer related
Hin, 2017 (BEST-D, 2011-005763-24)	Completed	No data of interest	16 CI, but deaths only in placebo arm (total 3, 2 neoplastic) dose finding for future large trial
Hollis, 2015 (NCT00412074)	Completed	Ineligible study design	sudden unexpected infant death (3x), no placebo, all pt. receive VD
Hupperts, 2019 (SOLAR, NCT01285401)	Completed	No data of interest	no AM, 2 CI in 1 arm
Inanir, 2004		No data of interest	wrong outcome
Ivarsen, 2011 (NCT00175149)	Terminated	Ineligible study design	open label

Jin, 2016; Zheng, 2018 (VIDEO, NCT01176344, ACTRN12610000495022)	Completed	Nodataofinterest	1 death + 6 malignancies (AE)
Johansson, 2021		No data of interest	no deaths
Jorde, 2010 (NCT00243256)	Completed	No data of interest	no deaths/CI
Jorgensen, 2010 (NCT00122184)	NCT# not listed in clinicaltrials.gov	No data of interest	outcome not found (no death, CI)
Karefylakis, 2018 (2015-000223-85)	Ongoing	No data of interest	no deaths/CI
Rai, 2008; Kaste, 2014 (BONEII, NCT00186901)	Completed	No data of interest	no deaths/CI
Khan, 2017 (VITAL trial, NCT00867217)	Completed	All patients receive vitamin D	All patients receive 600 IU
Kharlamov, 2012		No data of interest	deaths non-cancer related
Kyle, 1980		No data of interest	no deaths in extended VD study
Lehouck, 2012 (NCT00666367, 2007-004755-11)	Completed	No data of interest	15 deaths only 1 CM (lung cancer (AE))
Lerchbaum, 2021		No data of interest	no deaths
Lewis, 2013		No data of interest	no deaths/CI
Luger, 2015 (LOAD, NCT02092376, 2013-003546-16)	Completed	No data of interest	no deaths/CI
Mak, 2014 REVITAHIP (ACTRN12610000392066)	Recruiting	Ineligible study design	only loading dose placebo-controlled, given for 7 days
Manaseki-Holland 2012, Aluisio 2013 (NCT00548379)	Unknown (active, not recruiting)	No data of interest	...there were 534 (18%) children lost to follow-up, of which 17 (3%) died (Fig. 1). Ten deaths were attributed to pneumonia/septicemia and seven were due to congenital or accidental causes.
Martineau, 2015 (ViDiFlu, NCT01069874)	Completed	No data of interest	3 CI, no deaths
Marton, 2003		No full-text available	no full text available
Mason, 2014 (ViDA study (Vitamin D, Diet and Activity study), NCT01240213)	Completed	No data of interest	no deaths/CI
Mazzanti, 2015; Vignini, 2017		Ineligible intervention	arms not comparable, D_3, K1, B6 vs placebo
Moretti, 2017 (NCT01636570)	Completed	No data of interest	no deaths/CI
Munoz-Aguirre, 2015 (NCT01019642)	Completed	No data of interest	no deaths/CI
Obi, 2020 (CHAMBER, UMIN000014819, NCT02214563)	Completed	No data of interest	only 1 AM in placebo arm 1 cancer incidence in VD arm
Ooms, 1995		Ancilliary (sub)study	substudy to Lips 1996
Overton, 2015 (NCT01403051)	Completed	No data of interest	only 1 death in VD arm (renal failure)
Petchey, 2009 (ACTRN12609000246280)	Recruitment complete	No data of interest	wrong outcome
Pfeifer, 2005		No data of interest	no deaths/CI

Pommergaard, 2015 (NCT00486512, 2004-000693-31)	Terminated	No data of interest	only 3 CI in verum arm (table 3), arms not comparable (aspirin, calcitriol, Ca vs. P)
Porto, 2019 (U1111-1217-9237, RBR-6yj8sj)	Not yet recruiting	No data of interest	wrong outcome
Punthakee, 2012 (TIDE, NCT00879970, 2008-005030-73)	Terminated	No data of interest	2 AM in placebo arm, 3 CI in both arms
Rafiq, 2017 (NTR2827, NCT02122627)	Planned	No data of interest	no deaths/CI
Rashid, 2020 (Conf. abstract)		Ineligible study design	no placebo
Reid, 2017		Ancilliary (sub)study	substudy to ViDA
Rejnmark, 2011 (Randers City study)		Ineligible study design	no treatment as comparator
Saad, 2018 (UMIN000020281)	Main results already published	Retracted	less 6 months + retracted
Saleem, 2018 (NCT03170479)	Completed	Ineligible intervention	only 2 doses
Samaan, 2019 (RBR-95j5pm)	Recruitment completed	No data of interest	death occured outside clinical study
Scher, 2011 (ASCENT-2, NCT00273338, 2006-001702-88)	Terminated (DSMB)	Ineligible study design	open label
Shedeed, 2012		Ineligible study design	less 6 months
Singer, 2018 (ACTRN12611001260910)	Recruitment complete	No data of interest	1 death in VD arm, 1 death in unknown arm but was already withdrawn from all active treatment
Sinha-Hikim, 2015 (NCT00876928)	Completed	No data of interest	no deaths/CI
Soilu Hänninen, 2012 (NCT01339676, 2007-001958-99)	Unknown (Active, not recruiting)	No data of interest	no deaths/CI
Sprague, 2016		No data of interest	no deaths/CI
Stallings, 2015 (NCT01475890)	Completed	No data of interest	no deaths/CI
Strobel, 2014 (2006-006180-23)	Ongoing (since 2007)	No data of interest	no deaths/CI
Treiber, 2015 (NCT01390480)	Completed	No data of interest	wrong outcome
Trummer, 2018 (NCT01721915, 2011-000994-30)	Completed	No data of interest	no deaths/CI
Tsujita, 2022 (UMIN000020597)	No longer recruiting	No data of interest	2 deaths and 1 CI in VD arm
Tu, 2013; Fedirko, 2009 (CaDvMAP, NCT00208793)	Completed	No data of interest	only 1 death due to CV
Uusi-Rasi, 2012/2015 (DEX, NCT00986466)	Completed	No data of interest	4 deaths, but 2 CM only in 1 arm
Vahedpoor, 2017 (IRCT201412065623N30)	Recruitment complete	No data of interest	related to IRCT201601045623N65; no CI, no deaths
Vahedpoor, 2018 (IRCT201601045623N65)	Recruitment complete	No data of interest	no deaths
Vos, 2017 (VIT001, NCT01212406)	Completed	No data of interest	only 1 cancer death in VD arm
Wamberg, 2013		No data of interest	wrong outcome
Witham, 2012 (DAMI, ISRCTN32927244)	Completed	No data of interest	only 1 death in VD arm

Witham, 2015 (ISRCTN59927814)	Completed	No data of interest	2 CI only in VD arm, no deaths
Yarparvar, 2020		No data of interest	wrong outcome
Yarparvar, 2020		No data of interest	no deaths
Yokoyama, 2013		No data of interest	only 1 lung cancer death in control
Zendehdel, 2021 (IRCT20180922041089N3)	Completed	No data of interest	no deaths
Zittermann, 2009 (SMART, NCT00493012)	Completed	No data of interest	only 1 CI

Abbreviations: CI, cancer incidence; CM, cancer mortality: VD, vitamin D.

Supplemental Table 6. *Author contact overview with response outcomes*

AUTHOR (YEAR), ACRONYM, STUDY ID	SAMPLE SIZE	RESPONSE[A]									
		1	2	3	4	5	6	7	8	9	10
2011-000868-95	115 (T)						x				
2018-001488-21	102 (T)						x				
CHICTR2000035574	111 (T)									x	
IRCT2013072114085N2	50 (T)									x	
ISRCTN23173889	80 (T)										x
NCT00051532	700 (T)					x					
NCT00051545	608 (T)					x					
NCT00536770	132 (T)									x	
NCT00870961	22 (A)									x	
NCT01512862	240 (T)									x	
NCT01535196	8 (A)									x	
NCT02066688	2400 (T)									x	
NCT02143505	900 (T)									x	
NCT02802267	110 (T)										x
NCT02877641	4 (A)						x				
NCT03602261	256 (A)									x	
RBR-10R7D6F3	120 (T)									x	
AKIBA, 2018 (AMATERASU 4, UMIN000001869)	155 (A)	x									
ALOIA, 2005	208 (A)										x
AMATERAS VII UMIN000002637	250 (T)						x				
AMATERAS VIII UMIN000002638	250 (T)						x				
AMROUSY, 2020 PACTR 201712002835247	120 (A)							x			
ARDEN, 2016 VIDEO, ISRCTN94818153	474 (A)							x			
ARINGAZINA, 2021	336 (A)									x	
BARON 2015 (VITAMIN D/CALCIUM POLYP PREVENTION STUDY, NCT00153816)	2259 (A)	x									
BEER, 2007 (ASCENT, NCT00043576)	250 (A)							x			

AUTHOR (YEAR), ACRONYM, STUDY ID	SAMPLE SIZE	RESPONSE[A]									
		1	2	3	4	5	6	7	8	9	10
BISCHOFF-FERRARI, 2020 (DO-HEALTH, NCT01745263, 2012-001249-41)	2157 (A)		x								
BJORKMAN, 2008	218 (A)										x
BOLTON-SMITH, 2007	244 (A)							x			
BOXER, 2014	64 (A)					x					
BURLEIGH, 2007	205 (A)									x	
CECRLE, 2020 (REINFORCE-D, 2016-002606-39)	600 (T)									x	
CHAPUY, 1992; MEUNIER, 1996 (DECALYOS I)	3270 (A)										x
CHAPUY, 2002 (DECALYOS II)	610 (A)										x
CHATTERJEE, 2021 (D2DCA, NCT01942694)	2385 (A)	x									
DAWSON -HUGHES, 1997; BLUM, 2008	445 (A)							x			
DELANAYE, 2013 (B70720084117)	43 (A)							x			
D-HEM, NCT01518959	31 (A)									x	
GALLAGHER, 2001 (STOP IT)	489 (A)							x			
GANMAA, 2020	8851 (A)		x								
GREGORIO, 2021	32 (A)									x	
GROVER, 2022 (VITHOD, CTRI/2015/04/005674)	164 (A)									x	
HAMDY, 1995	176 (A)										x
HARTLEY, 2015 (SEDS, ACTRN12613000290796)	500 (T)							x			
HIDALGO, 2011 (ANVITAD, NCT01452243, 2006-001643-63)	704 (T)									x	
INKOVAARA, 1983	327 (A)					x					
JORDE, 2016; SOLLID, 2014 (TROMSØ VITAMIN D AND T2DM TRIAL, NCT00685594)	511 (A)							x			
KUMAR, 2011 (DIVIDS, NCT00415402)	2079 (A)							x			
LAIZ, 2017	675 (A)									x	
LAPPE, 2007 (NCT00352170)	1179 (A)		x								
LAPPE, 2017 (CAPS, NCT01052051)	2303 (A)		x								
LEVIN, 2017 (NCT01247311)	119 (A)							x			
LIPS, 1996	2578 (A)					x					
MAHJABEEN, 2021	110 (A)									x	
MARTINEAU, 2015 (VIDICO, NCT00977873)	240 (A)	x[#]									
MELAVID, NCT01264874, 2009-012049-46	150 (A)									x	

AUTHOR (YEAR), ACRONYM, STUDY ID	SAMPLE SIZE	RESPONSE[A]									
		1	2	3	4	5	6	7	8	9	10
MEYER, 2002	1144 (A)					x					
MURDOCH, 2012 (VIDARIS, ACTRN12609000486224)	322 (A)							x			
NAIR-SHALLIKER, 2021 (PROSD, ACTRN12616001707459)	120 (T)								x		
O'SULLIVAN, 2019 (VITD-CD, NCT01369667)	92 (A)							x			
RAKE, 2020 (VIDAL, ISRCTN46328341, 2011-003699-34)	1615 (787 blinded)		x								
SANDERS, 2010 (VITAL D STUDY, ACTRN12605000658617, ISRCTN83409867)	2256 (A)										x
SAW, 2014 (MEL-D, ACTRN12609000351213)	75 (T)									x	
SCHLEITHOFF, 2006/2007	123 (A)							x			
SU, 2011 (FLUID, NCT01045980)	70 (T)							x			
SUDFELD, 2017, 2020 (TOV4, NCT01798680)	4000 (A)	x									
TABRA, 2020	100 (A)									x	
TANGPRICHA 2016 (DISC, NCT01426256)	91 (A)							x			
THIEM, 2009 (VITA-D, NCT00752401)	200 (T)							x			
TIPS 3, NCT01646437, CTRI/2012/11/003108	5713 (A)		x								
TRAN, 2012 (PILOT D-HEALTH, ACTRN12609001063202)	644 (A)							x			
TURRINI, 2017	33 (A)									x	
VIRTANEN, 2022 (FIND, NCT01463813)	2495 (A)	x									
VITADEM, 2012-004602-97	100 (T)										x
VITDAL-ICU, NCT01130181, 2010-018798-39, DRKS00000750	480 (A)							x			
VITD-HI, NCT01292720, 2010-022763-35	29 (A)							x			
WEJSE, 2009 (ISRCTN35212132)	365 (A)							x			
WITTE, 2016 (VINDICATE, NCT01619891)	223 (A)	x									
WOOD ADRIAN, 2012 (VICTORY, ISRCTN20328039)	305 (A)							x			
WOOD M., 2011 (CALGB 70806 / ALLIANCE NCT01224678)	300 (A)				x						
ZITTERMANN, 2017 (EVITA, NCT01326650, 2010-020793-42)	400 (A)				x						
2009-017137-22*	400 (T)									x	
ACTRN12611000950965*	250 (T)									x	
CTRI/2019/05/019211*	125 (T)								x		
NCT03389659*	750 (T)									x	
DE SMEDT, 2017* (VIDME, NCT01748448, 2012-002125-30)	500 (T)			x							
ILYAD NCT03078855*	211 (A)								x		

AUTHOR (YEAR), ACRONYM, STUDY ID	SAMPLE SIZE	RESPONSE[A]									
		1	2	3	4	5	6	7	8	9	10
TUNON, 2016* (VITDAMI, NCT02548364)	144 (T)								x		
VIDIFATIMA, 2009-012300-69*	146 (T)									x	
VINDICATE2, NCT03416361*	1253 (T)								x		
VITDCAOV, NCT04864431*	54 (T)								x		

Note: Two trials only recorded one cancer death and were, therefore, ineligible for inclusion (Apoe et al. 2016; Zittermann et al. 2017). Authors from two studies refused to disclose information because of a pending publication (Bischoff-Ferrari et al. 2022; Yusuf et al. 2021). Four trials were unable/unwilling to share the effect estimate (Ganmaa et al. 2020; Lappe et al. 2017; Lappe et al. 2007; Rake et al. 2020). One trial recorded cancer deaths but is still ongoing (De Smedt et al. 2017). The number of cancer deaths and the corresponding effect estimate could be obtained from six trials (Akiba et al. 2018; Baron et al. 2015; Chatterjee et al. 2021; Guo et al. 2022; Martineau et al. 2015; Sudfeld et al. 2020; Witte et al. 2016).

Abbreviations: A, actual; T, target

Footnotes:*ongoing studies

#effect estimated derived from another systematic review1

[A] Outcome of author contact:

1 Cancer Deaths – Data receipt
2 Cancer Deaths – no/partial data receipt
3 Cancer deaths but ongoing study
4 Only one (cancer) death
5 No access to data
6 No (sufficient) recruitment
7 No (cancer) deaths / data not collected
8 Ongoing (blinded, no results yet)
9 Pending reply
10 Undeliverable / No contact available

Supplemental Table 7. *Characteristics of included studies – additional information*

STUDY	AGE-RANGE, DEFINED CONDITION I.A.	AGE (MEAN OR MEDIAN[§])	SEX (FEMALE %)	ETHNICITY (WHITE %)	BMI [KG/M²] (MEAN OR MEDIAN[§])	25(OH)D AT BASELINE (MEAN OR MEDIAN[§]) [NMOL/L]	PERSONAL USE OF VD: EXCLUDED IF […]	ADHERENCE (%)	FU-TIME: (I) MAXIMUM (II) MEAN OR MEDIAN[§] [YEARS]	COVARIATES ADJUSTED FOR
TRIVEDI, 2003 UK	65–85 YO	74.8	24.2	n.a.	24.3	post-treatment: 64.3 nmol/L	> 200 IU	12/15 doses (80%): 76%; final dose: 66%, excluding deaths: 80%	(I) 5 (II) n.a.	age
WACTAWSKI-WENDE, 2006; JACKSON, 2003; JACKSON, 2006; CHLEBOWSKI, 2008; CHACKO, 2011 *WHI* (NCT00000611), US[A]	50–79 YO, post-menopausal	62.4	100	83.1	29.0	47[§] (nested case-control: 46.0 (hip fracture), 48.4 (controls))	(I) ≥ 600 IU, later > 1,000 IU; (II) use of calcitriol	≥ 80% (1–6y): ~ 60%; ≥ 50% (1–6y): ≥ 70%	(I) 9.7 (II) 7.0	stratified by age, randomized assignment in HT and DT trials, presence or absence of corresponding prevalent condition
AVENELL, 2012; GRANT, 2005 *RECORD* (ISRCTN51647438), UK	≥70 YO, previous low-trauma fracture	77.0	84.7	99.2	n.a.	38 (*n* = 60)	(I) VD use > 200 IU/d, (II) use of VD metabolites in past 5y or VD injection in last year	67% at 12 mo; 63% at 24 mo[b]	(I) 8[c] (II) 6.2[§]	treatment group, variables used for minimization at randomization (age, gender, time since fracture, and type of fracture)
BARON 2015 *VITAMIN D/CALCIUM POLYP PREVENTION STUDY* (NCT00153816), US	45–75 YO, hx of removed colorectal adenomas	58.1	37.0	88.0[d]	29.0	61.5	> 400 IU VD, therapeutic VD in past 5 years, later ≤ 1,000 IU allowed	During treatment period: ≥ 80% 76.1%, ≥ 50% 86.3% 1st y: ≥ 80% 87.4% final y: ≥ 80% 73.6%	(I) 5 (II) n.a.	n.a.
MARTINEAU, 2015 *VIDICO* (NCT00977873), UK	< 40 YO, COPD	64.7	40.0	94.6	27.6	46.0	> 400 IU/d	Administration of dose 1–3 directly observed, dose 4–6 during telephone call[e]	(I) 1 (II) n.a.	n.a.
WITTE, 2016 *VINDICATE* (NCT01619891), UK	≥ 18 YO, chronic HF due to LVSD & 25(OH)D ≤ 50 nmol/L	68.7	20.9	90	30.0	37.3	any VDS in last 3 mo	"indicating excellent adherence to treatment (Figure 2)"	(I) 1 (II) n.a.	n.a.
AKIBA, 2018 AMATERASU 4 (UMIN000001869) JAPAN	20–75 YO, NSCLC[f]	68.0	24.5	n.a.	22.6	51.8 47.5[§]	any VDS or active VD	n.a.	(I) 8 (II) 3.3[§]	adjusted for early stage, adenocarcinoma, and VDS

Appendices

STUDY	AGE-RANGE, DEFINED CONDITION I.A.	AGE (MEAN OR MEDIAN[§])	SEX (FEMALE %)	ETHNICITY (WHITE %)	BMI [KG/M²] (MEAN OR MEDIAN[§])	25(OH)D AT BASELINE (MEAN OR MEDIAN[§]) [NMOL/L]	PERSONAL USE OF VD: EXCLUDED IF […]	ADHERENCE (%)	FU-TIME: (I) MAXIMUM (II) MEAN OR MEDIAN[§] [YEARS]	COVARIATES ADJUSTED FOR
MANSON, 2018 ***VITAL*** **(NCT01169259),US**	men ≥ 50 YO, women ≥ 55 YO	67.1	50.6	71.3	28.1	77 (*n* = 15,787); **< 50:** 12.7% **50– < 75**: 32.2% 77.5[§]	> 800 IU/d	**2/3 of trial regimen:** VD 82.0%, P 80.3%	(I) 6[g] (II) 5.3[§]	age, sex, and n−3 fatty acid randomization group; not adjusted for multiple comparisons, no formal adjustments to p-values or confidence intervals
SCRAGG, 2018 ***VIDA*** **(ACTRN12611000402943) NEW ZEALAND**	50–84 YO	65.9	41.9	83.3 (European or another race/ethnicity)	28.4	63.3 deseasonalized: 66.3	> 600 IU/d (aged 50–70y); > 800 IU/d (71–84y); use of cod liver oil	VD 84.8%[h] P 83.1%[h]	(I) n.a. (II) 3.3[§]	age, sex, race/ethnicity
URASHIMA, 2019 AMATERASU 5 (UMIN000001977) JAPAN	30–90 YO, Digestive tract cancer[i]	66.0[§]	33.8	n.a.	22.0[§]	**< 50:** 41.5% **50–100:** 55.6% **> 100:** 1.2%	use of VD or active VD	"approximately 10% of the participants stopped taking study medication during the trial, adherence was based only on patient self-report"	(I) 7.6 (II) 3.5[§]	age quartiles, stage I disease status
SUDFELD, 2020 ***TOV4*** **(NCT01798680), TANZANIA**	≥ 18 YO, HIV + initiated ART, 25(OH)D < 75nmol/L	38.7	68.4	0 (100% Tanzanian)	n.a.[h]	**< 24.8:** 7.2% **25–49.8:** 44.6% **50–75:** 48.2%	n.a.	**initial dose:** **100%:** VD 81.6%, P 81.4% **100% or missed 1 dose:** VD 98.1%, P 96.0% **maintenance dose:** VD 89.6%[§], P 89.6%[§]	(I) 1 (II) n.a.	n.a.
CHATTERJEE 2021 ***D2DCA*** **(NCT01942694), US**	≥ 30 YO[j], prediabetes/ high risk for diabetes and overweight/ obesity	60.0	44.5	66.9	32.0	70.0	>1,000 IU/d	n.a.	(I) n.a. (II) 2.9[§]	n.a.
NEALE, 2022 ***D-HEALTH*** **(ACTRN12613000743763), AUSTRALIA**	60–84 YO	69.3	45.9	**Brit./Europ.:** 91.3% **Aust./N.Zeal.:** 3.4%	n.a.	n.a.	**trial entry:** > 500 IU/d **during trial:** > 2,000 IU/d	**≥ 80%:** VD 84.5%, P 82.5%	(I) 6[k] (II) 5.7	flexible parametric modelling: randomization group, age, sex, state of residence at baseline

STUDY	AGE-RANGE, DEFINED CONDITION I.A.	AGE (MEAN OR MEDIAN[§])	SEX (FEMALE %)	ETHNICITY (WHITE %)	BMI [KG/M²] (MEAN OR MEDIAN[§])	25(OH)D AT BASELINE (MEAN OR MEDIAN[§]) [NMOL/L]	PERSONAL USE OF VD: EXCLUDED IF […]	ADHERENCE (%)	FU-TIME: (I) MAXIMUM (II) MEAN OR MEDIAN[§] [YEARS]	COVARIATES ADJUSTED FOR
VIRTANEN, 2022 *FIND* (NCT01463813), FINLAND	men ≥ 60 YO; women ≥ 65 YO	68.2	42.8	100	27.1	74.8[l]; **< 50:** 9.1% **≥ 75:** 50.0%	> 800 IU from all supplemental sources combined	**100%:** 74.8% **≥ 80%:** 1,600 IU/day 95.7%, 3,200 IU/day 95.1%, P 95.0% P + VD combined: 95.3%[m]	(I) 5 (II) 4.3	n.a.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; /d, per day; AMATERASU 4, A randomized, double blind, comparative study of STATUS D_3 (vitamin D_3) versus placebo in patients with lung cancer to prevent relapse after operation; AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; ART, antiretroviral therapy; Aust, Australian; BMI, body mass index; Brit, Britain; Ca, calcium; D2dCA, Vitamin D and type 2 diabetes cancer outcomes study; Europ, European; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; FU, follow-up; mo, month; N. Zeal, New Zealander; P, placebo; RECORD, Randomized Evaluation of Calcium Or vitamin D; ToV4, Trial of Vitamin D in HIV Progression; VD, vitamin D_3; VDS, Vitamin D_3 supplementation; ViDA, Vitamin D Assessment Study; ViDiCo, Vitamin D Supplementation in Chronic Obstructive Pulmonary Disease; VINDICATE, Vitamin D treating patients with chronic heart failure; VITAL, Vitamin D and Omega-3 Trial; WHI, Women's Health Initiative; y, year.

Footnotes:

[a] Participants included from parent HT or DM trials thus partial concomitant estrogen/progestin administration

[b] Poorer adherence with tablets containing calcium (difference 9.4% for all participants randomized at 2 y)

[c] From Fig.1

[d] Missing data excluded

[e] Intermittent bolus dosing regimen, which allowed to achieve a high degree of adherence with the intervention

[f] Adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell lung carcinoma. Stage: IA 50%; IB 23%; IIA 10%; IIB 7%; IIIA 10%

[g] From Fig. 2

[h] Vitamin D: 85,280 capsules during 100,535 person-months; Placebo 83,387 capsules during 100,401 person-months

[i] Esophagus 9.6%; stomach 41.7%; small bowel 0.5%; colorectal 48.2%; I 43.6%; II 26.6%; III 29.7%

[j] ≥ 25 YO for American Indians, Alaska Natives, Native Hawaiians, and other Pacific Islanders

[k] "… departure from the protocol, … with only 6 years of follow-up rather than waiting for the 10 years specified…"

[l] Referring to subcohort of 551 participants

[m] Among 1609 participants who completed last questionnaire

Supplemental Table 8. *Description of participant's characteristics of general population studies included in IPD analyses*

Variables	VIDA *n* = 5,108 (Scragg et al. 2018)			RECORD *n* = 2,675 (Avenell et al. 2012)			FIND *n* = 2,495 (Virtanen et al. 2022)			VITAL *n* = 25,871 (Manson et al. 2019)			WHI *n* = 36,282 (Wactawski-Wende et al. 2006)			D-Health *n* = 21,310 (Neale et al. 2022)		
	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%
Age (years)	5106	65.8 (8.3)		2675	77.5 (5.6)		2495	68.2 (4.5)		25871	66.6 (7.1)		36282	62.4 (6.9)		21310	69.3 (5.5)	
< 70	3380		66.2	0		0	1709		68.5	18022		69.7	29941		82.5	10792		50.6
≥ 70	1726		33.8	2675		100	786		31.5	7849		30.3	6341		17.5	10518		49.4
Sex	5106			2675			2495			25871			36282			21310		
Female	2138		41.9	2264		84.6	1069		42.9	13085		50.6	36282		100	9780		45.9
Male	2968		58.1	411		15.4	1426		57.2	12786		49.4	0		0	11530		54.1
BMI (kg/m²)	5084	28.4 (5.1)		NA	NA		2491	27.1 (4.3)		25254	28.1 (5.7)		36104	29.0 (5.9)		21191	27.8 (5.1)	
< 25	1207		23.8	NA		NA	850		34.1	7843		31.1	9579		26.5	6417		30.3
25– < 30	2294		45.1	NA		NA	1132		45.4	10122		40.1	12963		35.9	9029		42.6
≥ 30	1583		31.1	NA		NA	509		20.4	7289		28.9	13562		37.6	5745		27.1
Ethnicity	5108			2665			2495			25304			36271			20934		
Non-Hispanic White	4253		83.3	2652		99.5	2495		100.0	18046		71.3	31257		86.2	20177		96.4
Afro-American, Hispanics or indigenous [a]	606		11.9	11		0.4	0		0	6347		25.1	3793		10.5	151		0.7
Asian or other	249		4.9	2		0.1	0		0	911		3.6	1221		3.4	606		2.9
25(OH)D level (nmol/L)	5106	63.2 (23.6)		NA	NA		550	74.8 (18.2)		15787	NA[b]		115[c]	45.4 (18.7)		NA	NA	NA
< 50	1534		30.0	NA		NA	50		9.1	2001		12.7	78[c]		67.5	NA		NA
≥ 50	3572		70.0	NA		NA	500		90.9	13786		87.3	37[c]		32.2	NA		NA
Cancer diagnosis up to 5 years prior baseline	5108			NA			2495			25871			36282			21310		
No	4966		97.2	NA[e]		NA[e]	2495		100.0	25871		100	36282		100	19734[i]		92.6[i]
Yes	142		2.8	NA[e]		NA[e]	0[f]		0	0[g]		0	0[h]		0	1576[i]		7.4[i]
Randomization	5108			2675			2495			25871			36282			21310		
Placebo	2550		49.9	1332		49.8	830		33.3	12944		50.0	18106		49.9	10649		50.0
Vitamin D_3	2558		50.1	1343		50.2	1665		66.7	12927		50.0	0		0	10661		50.0
Vitamin D_3 + Ca	0		0	0		0	0		0	0		0	18176		50.1	0		0
Adherence	NA			2463[j]			1609[k]			NA[b]			34848[l]			21307[m]		
Low	NA		NA	1201[j]		48.8	76[k]		4.7	NA[b]		NA[b]	13800[l]		39.6	3518[m]		16.5
High	NA		NA	1262[j]		51.2	1533[k]		95.3	NA[b]		NA[b]	21048[l]		60.4	17789[m]		83.5
Events during trial																		
Trial duration (years)	5108	3.3 (0.5)		2675	3.3 (1.0)		2495	4.9 (0.4)		25871	5.3 (0.7)		36282	7.1 (1.4)		21310	4.8 (0.7)	
Deaths	123		2.4	442		16.5	71		2.9	978		3.8	1584		4.4	866		4.1

Variables	VIDA *n* = 5,108 (Scragg et al. 2018)			RECORD *n* = 2,675 (Avenell et al. 2012)			FIND *n* = 2,495 (Virtanen et al. 2022)			VITAL *n* = 25,871 (Manson et al. 2019)			WHI *n* = 36,282 (Wactawski-Wende et al. 2006)			D-Health *n* = 21,310 (Neale et al. 2022)		
	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%
Cancer deaths	73		1.4	88		3.3	36		1.4	341		1.3	747		2.1	398		1.9
Incident cancer cases	254		5.0	184		6.9	160		6.4	1617		6.3	2882		7.9	NA		NA

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79*;* FIND*,* Finnish Vitamin D Trial; RECORD*,* Randomized Evaluation of Calcium Or vitamin D; SD, standard deviation; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial*;* WHI, Women's Health Initiative

Footnotes:

[a] Includes native American, Australian, New Zealander or Hawaiian inhabitants.

[b] Has been assessed by the VITAL study but was not shared as part of the public use data file.

[c] In the WHI trial, 25(OH)D levels were measured in case-control samples. Only the measurements from the controls were used.

[d] In the trials, the WHI trial was recruiting patients from, cancer was an exclusion criterion. The time between the preceding trials and the WHI trial was rather short (approx. up to 1 year) and from the WHI study participants, only n = 2 reported to have been diagnosed with cancer in the last 10 years. Unfortunately, the cancer diagnosed in the last 5 years prior baseline were not assessed. Due to this extremely low number of reported cancers diagnosed the last 10 years (n = 2 out of n = 36,282 study participants), I assumed that no cancer diagnoses were made up to 5 years prior to the WHI trial.

[e] In RECORD, cancer likely to metastasize to bone within the previous 10 year cancer was an exclusion criterion at baseline recruitment. Information about other cancers not fulfilling this exclusion criterion were not available.

[f] In FIND, diagnosis dates of cancers prior baseline were not assessed and thus, cancers prior baseline were not included in this analysis.

[g] In VITAL, cancer (except non-melanoma skin cancer) was an exclusion criterion.

[h] In the trials, the WHI trial was recruiting patients from, cancer was an exclusion criterion. The time between the preceding trials and the WHI trial was rather short (approx. up to 1 year) and from the WHI study participants, only n = 2 reported to have been diagnosed with cancer in the last 10 years. Unfortunately, the cancer diagnosed in the last 5 years prior baseline were not assessed. Due to this extremely low number of reported cancers diagnosed the last 10 years (n = 2 out of n = 36,282 study participants), I assumed that no cancer diagnoses were made up to 5 years prior to the WHI trial

[i] Of the six Australian states, New South Wales (NSW) refused to provide a cancer diagnosis date. Thus, in NSW, cancers reported from the cancer registry were only counted if the self-reported cancer diagnosis date was up to 5 years prior baseline. For all other states, cancer diagnoses up to five years prior to randomization could be based on cancer registry data.

[j] In RECORD, high adherence is defined as > 80% of days of capsule intake up to the 2-year follow-up. Deaths in the first 2 years have been assigned missing values because they could not attend the 2-year follow-up.

[k] In FIND, adherence was assessed at the end of the study via a questionnaire; 74.8% reported using all study pills during the study and 95.3% reported using ≥80% of the pills.

[l] In WHI, adherence was defined as an adherence rate ≥ 0.80 in the period between the 1st and 2nd annual visit. Subjects who did not take part in the 2nd annual visit or deceased in the first 2 years of the trial were assigned missing values.

[m] In D-Health, adherence was defined as taking ≥ 80% of the intended capsules until end of study or until death.

Supplemental Table 9. *Efficacy of vitamin D_3 supplementation for the endpoint "cancer mortality" in general population studies included in the IPD analysis*

Study	Unadjusted				Adjusted [a]			
	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	*p*	N_{total}[c]	$N_{cancer\ deaths}$	HR (95% CI)	*p*
WHI	36282	747	0.884 (0.766; 1.021)	0.093	36093	742	0.875 (0.758; 1.011)	0.070
RECORD	2675	88	0.832 (0.547; 1.266)	0.390	2675	88	0.830 (0.545; 1.262)	0.383
VITAL	25871	341	0.825 (0.666; 1.021)	0.077	24702	326	0.823 (0.662; 1.024)	0.081
VIDA[b]	5108	73	1.026 (0.649; 1.624)	0.912	5080	73	1.025 (0.647; 1.622)	0.917
D-HEALTH[c]	21220	398	1.097 (0.901; 1.335)	0.358	20749	382	1.131 (0.925; 1.383)	0.229
FIND	2495	36	1.133 (0.557; 2.302)	0.731	2491	36	1.144 (0.562; 2.326)	0.711
Meta-analysis	93651	1683	0.926 (0.839; 1.022)	0.125	91790	1647	0.932 (0.827; 1.050)	0.247

Abbreviations: CI, confidence interval; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; HR, hazard ratio*;* RECORD, Randomized Evaluation of Calcium Or vitamin D; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial; WHI, Women's Health Initiative

Footnotes:

[a] WHI is adjusted for age, BMI and ethnicity. Not adjusted for sex because all study participants were women. Not adjusted for 25(OH)D levels because they were measured only in a small subsample. Not adjusted for cancer diagnosis in 5 years prior baseline because study participants participated in other trials too, which started shortly before the WHI trial and had cancer as an exclusion criterion.

RECORD is adjusted for age and sex. Not adjusted for BMI, 25(OH)D level at baseline and cancer diagnosis in 5 years prior baseline because these data were not assessed (or not assessed for all study participants). Not adjusted for ethnicity because all cancer deaths were among the white study participants who contributed 99.5% of the study population.

VITAL is adjusted for age, sex, BMI and ethnicity. Not adjusted for cancer diagnosis in 5 years prior baseline because cancer was an exclusion criterion. Not adjusted for 25(OH)D level because blood sample donation was voluntary and only 65.5% of randomized study participants donated a blood sample.

VIDA is adjusted for age, sex, BMI, ethnicity, 25(OH)D level at baseline and cancer diagnosis in 5 years prior baseline.

In D-Health, adjusted for age, sex, BMI, ethnicity and history of cancer. Not adjusted for baseline 25(OH)D because it was not measured.

FIND is adjusted for age, sex and BMI. Not adjusted for ethnicity and cancer because all study participants were Whites and subjects with cancer were excluded from the trial. Not adjusted for 25(OH)D level because only a minority of the trial participants (22.2%) had 25(OH)D measurements.

[b] One study participant could not be included in the unadjusted analysis, because the date of death was very close to the date of the start of the trial and in the data set this led to no positive follow-up time.

[c] n = 90 participants not used due to unknown cause of death and resulting missing value in the cancer mortality variable.

[d] If not identical with N_{total} in unadjusted analysis, this is due to missing covariate values.

***Supplemental Table 10 A+B**. Subgroup analyses for the efficacy of vitamin D_3 supplementation on cancer mortality in the general population*

A.

Subgroup	VIDA (*n* = 5,108)			RECORD (*n* = 2,675)			FIND (*n* = 2,495)			VITAL (*n* = 25,871)		
	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)
Age (years)												
< 70	3380	28	2.113 (0.956; 4.669)	0	0	NA	1709	15	0.760 (0.271; 2.135)	18022	187	0.890 (0.668; 1.185)
≥ 70	1726	45	0.661 (0.364; 1.200)	2675	88	0.832 (0.547; 1.266)	786	21	1.535 (0.562; 4.190)	7849	154	0.751 (0.546; 1.033)
Sex												
Female	2138	21	1.147 (0.487; 2.700)	2264	75	0.785 (0.498; 1.239)	1069	15	1.469 (0.468; 4.613)	13085	155	1.013 (0.739; 1.388)
Male	2968	52	0.971 (0.564; 1.672)	411	13	1.134 (0.381; 3.375)	1426	21	0.944 (0.381; 2.340)	12786	186	**0.692 (0.517; 0.927)**
BMI (kg/m²)												
< 25	1207	16	0.738 (0.275; 1.983)	NA	NA	NA	850	7	NA[a]	7843	106	**0.566 (0.381; 0.842)**
25– < 30	2294	33	1.544 (0.768; 3.103)	NA	NA	NA	1132	16	1.149 (0.399; 3.306)	10122	140	0.894 (0.642; 1.246)
≥ 30	1583	24	0.731 (0.325; 1.645)	NA	NA	NA	509	13	1.769 (0.487; 6.427)	7289	85	1.158 (0.756; 1.775)
Ethnicity												
Non-Hispanic White	4253	63	0.970 (0.592; 1.590)	2652	88	0.832 (0.547; 1.265)	2495	36	1.133 (0.557; 2.302)	18046	241	0.786 (0.609; 1.013)
Afro-American, Hispanics or indigenous	606	9	NA[a]	11	0	NA[a]	0	0	NA[a]	6347	85	1.064 (0.695; 1.628)
Asian or other	249	1	NA[a]	2	0	NA[a]	0	0	NA[a]	911	9	NA[a]
25(OH)D level (nmol/L)												
< 50	1534	25	1.354 (0.615; 2.982)	NA	NA	NA	57	0	NA[a]	2001	30	0.920 (0.449; 1.884)
≥ 50	3572	48	0.898 (0.510; 1.582)	NA	NA	NA	493	5	NA[a]	13786	175	0.894 (0.665; 1.203)
Cancer diagnosis up to 5 years prior baseline												
No	4966	51	0.961 (0.555; 1.664)	NA	NA	NA	2495	36	1.133 (0.557; 2.302)	25871	341	0.825 (0.666; 1.021)
Yes	142	22	1.177 (0.508; 2.724)	NA	NA	NA	0	0	NA[a]	0	0	NA
Adherence												
Low	NA	NA	NA	1201	20	0.736 (0.301; 1.801)	76	0[b]	NA[a]	NA	NA	NA
High	NA	NA	NA	1262	19	0.538 (0.212; 1.367)	1533	0[b]	NA[a]	NA	NA	NA

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; FIND, Finnish Vitamin D Trial; HR, hazard ratio; NA, not applicable; RECORD, Randomized Evaluation of Calcium Or vitamin D; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial

Footnotes:

[a] Not calculated due to low case number (< 10 cases) and potential model instability.

[b] In FIND, adherence was assessed only once at the end of the study via a questionnaire. Study participants who died during the trial could not respond.

Note: The models are unadjusted. Bold print: Statistically significant ($p < 0.05$).

B.

Subgroup	WHI (*n* = 36,282)			D-Health (*n* = 21,220)			Meta-analysis				
	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	$N_{studies}$	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	*p*
Age (years)											
< 70	29941	528	0.899 (0.758; 1.066)	10767	127	1.359 (0.956; 1.932)	5	63819	885	1.047 (0.818; 1.341)	0.715
≥ 70	6341	219	0.851 (0.653; 1.110)	10453	271	0.991 (0.781; 1.258)	6	29830	798	0.871 (0.758; 1.002)	0.053
Sex											
Female	36282	747	0.884 (0.766; 1.021)	9758	128	1.135 (0.802; 1.607)	6	64596	1141	0.928 (0.826; 1.043)	0.211
Male	0	0	NA	11462	270	1.079 (0.850; 1.370)	5	29053	542	0.909 (0.721; 1.145)	0.416
BMI (kg/m²)											
< 25	9579	208	0.958 (0.730; 1.258)	6388	102	1.233 (0.834; 1.823)	4	18024	333	0.866 (0.609; 1.231)	0.422
25– < 30	12963	248	0.822 (0.640; 1.056)	9000	168	0.933 (0.689; 1.263)	5	35511	605	0.905 (0.771; 1.062)	0.222
≥ 30	13562	290	0.893 (0.709; 1.124)	5714	122	1.292 (0.903; 1.849)	5	28657	534	1.034 (0.847; 1.262)	0.746
Ethnicity											
White	31257	642	**0.852 (0.729; 0.995)**	20093	367	1.073 (0.875; 1.317)	6	78796	1437	0.902 (0.812; 1.001)	0.053
Afro-American, Hispanics or indigenous	3793	76	1.205 (0.767; 1.894)	150	2	NA[a]	2	10140	161	1.128 (0.828; 1.538)	0.446
Asian or other	1221	25	0.651 (0.292; 1.449)	604	17	3.504 (1.142; 10.745)	2	1825	42	1.440 (0.277; 7.475)	0.664
25(OH)D level (nmol/L)											
< 50	78	1	NA[a]	NA	NA	NA	2	3535	55	1.096 (0.644; 1.863)	0.736
≥ 50	37	0	NA[a]	NA	NA	NA	2	17358	223	0.895 (0.688; 1.164)	0.407
Cancer diagnosis up to 5 years prior baseline											
No	36282	747	0.884 (0.766; 1.021)	19659	296	1.058 (0.843; 1.329)	5	89273	1471	0.910 (0.821; 1.008)	0.071
Yes	0	0	NA	1561	102	1.201 (0.813; 1.774)	2	1703	124	1.197 (0.840; 1.704)	0.320
Adherence											
Low	13800	259	0.843 (0.660; 1.075)	3487	156	1.080 (0.789; 1.478)	3	18488	435	0.916 (0.759; 1.106)	0.362
High	21048	406	0.925 (0.761; 1.124)	17730	242	1.174 (0.911; 1.512)	3	40040	667	0.987 (0.766; 1.270)	0.917

Note: The models are unadjusted. Bold print: Statistically significant ($p < 0.05$).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; HR, hazard ratio; NA, not applicable; WHI, Women's Health Initiative

Footnote:

[a] Not calculated due to low case number (< 10 cases) and potential model instability.

Supplemental Table 11 A+B. *Test for effect modification by other factors with respect to the association of vitamin D_3 supplementation with cancer mortality in general population studies included in the IPD analysis*

A.

Factors	VIDA (*n* = 5,108)				RECORD (*n* = 2,675)				FIND (*n* = 2,495)				VITAL (*n* = 25,871)			
	N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term	
			ß (SE)	*p*			ß (SE)	*p*			ß (SE)	*p*			ß (SE)	*p*
Age (years)	5106	73	-0.064 (0.030)	0.036	2675	88	0.044 (0.035)	0.205	2495	36	0.059 (0.074)	0.429	25871	341	0.007 (0.015)	0.619
< 70	3380	28	Ref		0	0	Ref		1709	15	Ref		18022	187	Ref	
≥ 70	1726	45	**-1.160 (0.506)**	**0.022**	2675	88	NA	NA	786	21	0.702 (0.735)	0.340	7849	154	-0.169 (0.219)	0.440
Sex	5106	73			2675	88			2495	36			25871	341		
Female	2138	21	Ref		2264	75	Ref		1069	15	Ref		13085	155	Ref	
Male	2968	52	-0.164 (0.518)	0.752	411	13	0.384 (0.603)	0.524	1426	21	-0.441 (0.745)	0.554	12786	186	-0.381 (0.219)	0.082
BMI (kg/m²)	5084	73	0.002 (0.044)	0.970	NA	NA	NA	NA	2491	36	0.016 (0.072)	0.820	25254	331	0.027 (0.019)	0.158
< 25	1207	16	-0.731 (0.617)	0.237	NA	NA	NA	NA	850	7	NA[a]	NA[a]	7843	106	-0.456 (0.264)	0.084
25– < 30	2294	33	Ref		NA	NA	Ref		1132	16	Ref		10122	140	Ref	
≥ 30	1583	24	-0.748 (0.546)	0.171	NA	NA	NA	NA	509	13	0.432 (0.851)	0.612	7289	85	0.260 (0.276)	0.345
Ethnicity	5108	73			2665	88			2495	36			25304	335		
White	4253	63	Ref		2652	88	Ref		2495	36	Ref		18046	241	Ref	
Afro-American, Hispanics or indigenous	606	9	NA[a]	NA[a]	11	0	NA[a]	NA[a]	0	0	NA[a]	NA[a]	6347	85	0.304 (0.253)	0.229
Asian or other	249	1	NA[a]	NA[a]	2	0	NA[a]	NA[a]	0	0	NA[a]	NA[a]	911	9	NA[a]	NA[a]
25(OH)D level (nmol/L)	5106	73	-0.014 (0.010)	0.150	NA	NA	NA	NA	550	5	NA[a]	NA[a]	15787	205	NA	NA
< 50	1534	25	-0.407 (0.496)	0.411	NA	NA	NA	NA	57	0	NA[a]	NA[a]	2001	30	0.033 (0.396)	0.934
≥ 50	3572	48	Ref		NA	NA	Ref		493	5	Ref		13786	175	Ref	
Cancer diagnosis up to 5 years prior baseline	5108	73			NA	NA			2495	36			NA	NA		
No	4966	51	Ref		NA	NA	Ref		2495	36	Ref		NA	NA	Ref	
Yes	142	22	0.204 (0.512)	0.690	NA	NA	NA	NA	0	0	NA[a]	NA[a]	NA	NA	NA	NA
Adherence	NA	NA			2463	88			1609	0			NA	NA		
Low	NA	NA	Ref		1201	20	Ref		76	0[b]	Ref	NA[a]	NA	NA	Ref	
High	NA	NA	NA	NA	1262	19	-0.309 (0.659)	0.639	1533	0[b]	NA[a]	NA[a]	NA	NA	NA	NA

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; FIND, Finnish Vitamin D Trial; HR, hazard ratio; NA, not applicable; RECORD, Randomized Evaluation of Calcium Or vitamin D; SE, standard error; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial

Footnotes:

[a] Not calculated due to low case number (< 10 cases) and potential model instability.

[b] In FIND, adherence was assessed only once at the end of the study via a questionnaire. Study participants who died during the trial could not respond.

Note: The models contain only the single terms and the interaction term of the two variables of interest. Bold print: Statistically significant ($p < 0.05$).

B.

Factors	WHI (*n* = 36,282)				D-Health (*n* = 21,220)				Meta-analysis				
	N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term		$N_{studies}$	N_{total}	$N_{cancer\ deaths}$	Interaction term	
			ß (SE)	*p*			ß (SE)	*p*				ß (95% CI)	*p*
Age (years)	36282	747	0.001 (0.010)	0.920	21220	398	-0.009 (0.019)	0.629	6	93649	1683	-0.001 (-0.021; 0.018)	0.893
< 70	29941	528	Ref		10767	127	Ref		5	63819	885	Ref	
≥ 70	6341	219	-0.055 (0.161)	0.732	10453	271	-0.316 (0.217)	0.145	5	29830	798	-0.210 (-0.150; -0.022)	0.162
Sex	36282	747			21220	398							
Female	36282	747	Ref		9758	128	Ref		5	28314	394	Ref	
Male	0	0	NA	NA	11462	270	-0.051 (0.215)	0.814	5	29053	542	-0.815 (-0.460; 0.090)	0.187
BMI (kg/m²)	36104	746	0.0004 (0.001)	0.977	21102	392	0.002 (0.018)	0.917	5	90035	1578	0.0005 (-0.001; 0.002)	0.629
< 25	9579	208	0.155 (0.188)	0.412	6388	102	0.279 (0.253)	0.268	5	25867	439	-0.072 (-0.441; 0.298)	0.704
25– < 30	12963	248	Ref		9000	168	Ref		5	35511	605	Ref	
≥ 30	13562	290	0.084 (0.173)	0.627	5714	122	0.326 (0.239)	0.173	5	28657	534	0.146 (-0.091; 0.382)	0.227
Ethnicity	36271	743			20847	386							
Non-Hispanic White	31257	642	Ref		20093	367	Ref		3	69396	1250	Ref	
Afro-American, Hispanics or indigenous	3793	76	0.345 (0.244)	0.157	150	2	NA[a]	NA[a]	2	10140	161	0.325 (-0.019; 0.670)	0.064
Asian or other	1221	25	-0.272 (0.416)	0.514	604	17	**1.186 (0.581)**	**0.041**	2	1825	42	0.401 (-1.024; 1.825)	0.582
25(OH)D level (nmol/L)	115	1	NA[a]	NA[a]	NA	NA	NA	NA	1	5106	73	-0.014 (-0.034; 0.006)	0.150
< 50	78	1	NA[a]	NA[a]	NA	NA	NA	NA	2	3535	55	-0.138 (-0.745; 0.468)	0.655
≥ 50	37	0	Ref		NA	NA	Ref		2	17358	223	Ref	
Cancer diagnosis up to 5 years prior baseline	NA	747			21220								
No	36282	747	Ref		19659	296	Ref		2	24625	347	Ref	
Yes	0	0	NA	NA	1561	102	0.129 (0.230)	0.574	2	1703	124	0.142 (-0.270; 0.553)	0.500
Adherence	34848	665			21217	398							
Low	13800	259	Ref		3487	156	Ref		3	18488	435	Ref	
High	21048	406	0.093 (0.159)	0.560	17730	242	0.083 (0.206)	0.685	3	40040	667	0.075 (-0.167; 0.318)	0.543

Note: The models contain only the single terms and the interaction term of the two variables of interest. Bold print: Statistically significant ($p < 0.05$).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; HR, hazard ratio; NA, not applicable; SE, standard error; WHI, Women's Health Initiative

Footnotes:

[a] Not calculated due to low case number (< 10 cases) and potential model instability.

Supplemental Table 12. *Description of study participants with cancer included in IPD analyses*

Variables	VIDA *n* = 396 (Scragg et al. 2018)			RECORD *n* = 184 (Avenell et al. 2012)			FIND *n* = 160 (Virtanen et al. 2022)			VITAL *n* = 1617 (Manson et al. 2019)			WHI *n* = 2882 (Wactawski-Wende et al. 2006)			AMATERASU 5 *n* = 417 (Urashima et al. 2019)			D-HEALTH *n* = 1872 (Neale et al. 2022)		
	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%
Age (years)	396	69.1 (8.1)		184	78.8 (5.8)		160	69.0 (4.6)		1617	68.5 (6.6)		2882	63.8 (6.9)		417	66.2 (10.6)		1872	70.8 (5.3)	
< 70	200		50.5	0		0	97		60.6	978		60.4	2228		77.3	252		60.4	746		39.9
≥ 70	196		49.5	184		100	63		39.4	639		39.5	654		22.7	165		39.6	1126		60.2
Sex	396			184			160			1617			2882			417					
Female	126		31.8	143		77.7	59		36.9	677		41.9	2882		100	141		33.8	558		29.8
Male	270		68.2	41		22.3	101		63.1	940		58.1	0		0	276		66.2	1314		70.2
BMI (kg/m²)	395	28.7 (5.0)		NA	NA		160	27.1 (4.2)		1572	27.8 (5.2)		2875	29.3 (5.9)		414	22.0 (3.2)		1859	27.8 (5.3)	
< 25	84		21.3	NA		NA	51		31.9	484		30.8	715	24.9		352		85.0	561		30.2
25– < 30	180		45.6	NA		NA	77		48.1	661		42.1	994	34.6		54		13.0	805		43.3
≥ 30	131		33.2	NA		NA	32		20.0	427		27.2	1166	40.6		8		1.9	493		26.5
Ethnicity	396			184			160			1587			2878			417			1845		
Non-Hispanic White	351		88.6	183		99.5	160		100	1258		79.3	2577	89.5		0		0	1789		97.0
Afro-American, Hispanics or indigenous[a]	37		9.3	1		0.5	0		0	281		17.7	224	7.8		0		0	11		0.6
Asian or other	8		2.0	0		0	0		0	48		3.0	77	2.7		417		100	45		2.4
25(OH)D level (nmol/L)	396	62.4 (23.9)		NA	NA		28	77.0 (17.0)		1044	NA[b]		8[c]	40.7 (15.9)		410	54.2 (19.7)		NA	NA	
< 50	136		34.3	NA		NA	1		3.6	121		11.6	6[c]	75.0		193		47.1	NA		NA
≥ 50	260		66.2	NA		NA	27		96.4	923		88.4	2[c]	25.0		217		52.9	NA		NA
Randomization	396			184			160			1617			2882			417			1872		
Placebo	197		49.8	94		51.1	50		31.3	824		51.0	1453	50.4		166		39.8	919		49.1
Intervention	199		50.3	90		48.9	110		68.8	793		49.0	1429	49.6		251		60.2	953		50.9
Adherence[d]	NA			116			65			NA[b]			2726			NA			1872		
Low	NA		NA	65		72.3	2		3.1	NA[b]		NA[b]	1086	39.8		NA		NA	422		22.5
High	NA		NA	51		27.7	63		96.9	NA[b]		NA[b]	1640	60.2		NA		NA	1450		77.5
Cancer stage	396			NA			NA			NA[b]			2882			417			NA		
I–III	216		54.6	NA		NA	NA		NA	NA[b]			2053	71.2		417		100	NA		NA
IV	28		7.1	NA		NA	NA		NA	NA[b]		NA[b]	518	18.0		0		0	NA		NA
Unknown	152		38.4	NA		NA	NA		NA	NA[b]		NA[b]	311	10.8		0		0	NA		NA
Cancer site	396			184			160			1617						417			NA		
Prostate cancer	92		23.2	15		8.2	50		31.3	411		25.4	0	0		0			NA		NA
Colorectal cancer	56		14.4	19		10.3	14		8.8	98		6.1	327	11.4		201		48.2	NA		NA
Breast cancer	45		11.4	20		10.9	17		10.6	246		15.2	1090	37.8		0			NA		NA
Lung cancer	24		6.0	17		9.2	11		6.9	NA[b]		NA[b]	297	10.3		0			NA		NA

Variables	VIDA *n* = 396 (Scragg et al. 2018)			RECORD *n* = 184 (Avenell et al. 2012)			FIND *n* = 160 (Virtanen et al. 2022)			VITAL *n* = 1617 (Manson et al. 2019)			WHI *n* = 2882 (Wactawski-Wende et al. 2006)			AMATERASU 5 *n* = 417 (Urashima et al. 2019)			D-HEALTH *n* = 1872 (Neale et al. 2022)		
	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%	N_{total}	Mean (SD)	%
Time of cancer diagnosis	396			184			160			1617			2882			417			1872		
Up to 5 years prior baseline	142		35.9	0[e]		0	0[f]		0	0[g]		0	0[h]		0	417		100	1576		84.2
During the trial	254		64.1	184		100	160		100	1617		100	2882		100	0		0	NA[i]		NA
Events during trial																					
Trial duration (years)	396	2.0 (1.2)		184	1.3 (1.1)		160	1.9 (1.4)		1617	2.6 (1.6)		2882	3.1 (2.3)		417	3.7 (1.8)		1872	4.3 (1.3)	
Deaths	78		19.7	128		69.6	38		23.8	363		22.5	798		27.7	62		14.9	465		24.8
Cancer deaths	73		18.4	88		47.8	36		22.5	341		21.1	747		25.9	43		10.3	398		21.4

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; BMI, body mass index; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; RECORD, Randomized Evaluation of Calcium Or vitamin D; SD, standard deviation; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial; WHI, Women's Health Initiative;

Footnotes:

[a] Includes native American, Australian, New Zealander or Hawaiian inhabitants.

[b] Has been assessed by the VITAL study but was not shared as part of the public use data file.

[c] In the WHI trial, 25(OH)D levels were measured in case-control samples. Only the measurements from the controls were used.

[d] In RECORD, high adherence is defined as > 80% of days of capsule intake up to the 2-year follow-up. Deaths in the first 2 years have been assigned missing values because they could not attend the 2-year follow-up. In FIND, adherence was assessed at the end of the study via a questionnaire; 74.8% reported using all study pills during the study and 95.3% reported using ≥80% of the pills. In WHI, adherence was defined as an adherence rate ≥ 0.80 in the period between the 1st and 2nd annual visit. Subjects who did not take part in the 2nd annual visit or deceased in the first 2 years of the trial were assigned missing values.

[e] In RECORD, cancer likely to metastasize to bone within the previous 10 yr cancer was an exclusion criterion at baseline recruitment. Information about other cancers not fulfilling this exclusion criterion were not available.

[f] In FIND, diagnosis dates of cancers prior baseline were not assessed and thus, cancers prior baseline were not included in this analysis.

[g] In VITAL, cancer (except non-melanoma skin cancer) was an exclusion criterion.

[h] In the trials, the WHI trial was recruiting patients from, cancer was an exclusion criterion. The time between the preceding trials and the WHI trial was rather short (approx. up to 1 year) and from the WHI study participants, only 2 reported to have been diagnosed with cancer in the last 10 years. Unfortunately, the cancer diagnosed in the last 5 years prior baseline were not assessed. Due to this extremely low number of reported cancers diagnosed the last 10 years (n = 2 out of n = 36,282 study participants), I assumed that no cancer diagnoses were made up to 5 years prior to the WHI trial.

[i] Cancer diagnoses were not assessed during the D-Health trial.

Supplemental Table 13. *Efficacy of vitamin D_3 supplementation for overall survival of cancer patients*

Study	Unadjusted				Adjusted[a]			
	N_{total}	N_{deaths}	HR (95% CI)	*p*	N_{total}	N_{deaths}	HR (95% CI)	*p*
WHI	2882	798	0.924 (0.804; 1.061)	0.264	2871	793	0.988 (0.859; 1.136)	0.865
RECORD	184	128	1.068 (0.754; 1.513)	0.712	184	128	0.925 (0.651; 1.313)	0.662
VITAL	1617	363	0.838 (0.681; 1.030)	0.093	1544	347	0.825 (0.666; 1.022)	0.078
VIDA	396	78	0.955 (0.613; 1.489)	0.839	395	78	1.348 (0.846; 2.150)	0.209
AMATERASU 5	417	62	0.960 (0.578; 1.596)	0.876	407	60	0.787 (0.458; 1.349)	0.383
D-HEALTH	1872	465	1.048 (0.874; 1.258)	0.610	1834	447	1.069 (0.888; 1.287)	0.482
FIND	160	38	1.209 (0.599; 2.439)	0.560	160	38	1.010 (0.480; 2.122)	0.980
Meta-analysis	7528	1932	0.951 (0.870; 1.040)	0.270	7395	1891	0.976 (0.891; 1.069)	0.599

Abbreviations: AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; CI, confidence interval; D2dCA, Vitamin D and type 2 diabetes cancer outcomes study; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; FIND, Finnish Vitamin D Trial; HR, hazard ratio; RECORD, Randomized Evaluation of Calcium Or vitamin D; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial; WHI, Women's Health Initiative

Footnote:

[a] WHI is adjusted for age, BMI, ethnicity, cancer stage and cancer site. Not adjusted for sex because all study participants were women. Not adjusted for 25(OH)D levels because they were measured only in a small subsample. Not adjusted for time of cancer diagnosis because study participants participated in other trials too, which started shortly before the WHI trial and had cancer as an exclusion criterion.

RECORD is adjusted for age, sex, and cancer site. Not adjusted for BMI, 25(OH)D level at baseline, cancer stage and time of cancer diagnosis because patients with a history of cancer were not included in the trial. Not adjusted for ethnicity because all cancer deaths were among the white study participants who contributed 100% of the study population with cancer.

VITAL is adjusted for age, sex, BMI, ethnicity and cancer site (prostate, breast and colorectal cancer). Not adjusted for lung cancer and cancer stage because these variables are not included in the public use data file. Not adjusted for cancer diagnosis in 5 years prior baseline because cancer was an exclusion criterion. Not adjusted for 25(OH)D level because blood sample donation was voluntary and only 65.5% of randomized study participants donated a blood sample.

VIDA is adjusted for age, sex, BMI, ethnicity, 25(OH)D level at baseline, time of cancer diagnosis, cancer stage, and cancer site (prostate, colorectal, breast and lung cancer).

AMATERASU 5 is adjusted for age, sex, BMI, 25(OH)D level at baseline, and colorectal cancer. Not adjusted for prostate, colorectal and lung cancer because these cancer sites were not included in the trial. Not adjusted for cancer stage because all subjects were diagnosed with stage I–III cancers. Not adjusted for ethnicity because all study participants were Asian. Not adjusted for time of cancer diagnosis because cancer was an inclusion criterion.

D-Health is adjusted for age, sex, BMI and ethnicity. Not adjusted for cancer site and stage as these variables were not available. Not adjusted for time of cancer diagnosis because cancer diagnoses were not assessed during the trial. All of those who were cancer-free at baseline in this variable died of cancer during follow-up.

FIND is adjusted for age, sex, BMI and cancer site. Not adjusted for ethnicity and time of cancer diagnosis because all study participants were Whites and subjects with cancer were excluded from the trial. Not adjusted for 25(OH)D level because only a minority of the trial participants (22.2%) had 25(OH)D measurements.

Supplemental Table 14. *Efficacy of vitamin D_3 supplementation for cancer specific survival of cancer patients*

Study	Unadjusted				Adjusted[a]			
	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	*p*	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	*p*
WHI	2882	747	0.905 (0.783; 1.044)	0.171	2871	742	0.970 (0.840; 1.122)	0.685
RECORD	184	88	0.857 (0.561; 1.308)	0.475	184	88	0.772 (0.505; 1.181)	0.234
VITAL	1617	341	0.827 (0.668; 1.024)	0.082	1544	326	0.823 (0.660; 1.026)	0.084
VIDA	396	73	0.980 (0.620; 1.551)	0.932	395	73	1.378 (0.852; 2.231)	0.191
AMATERASU 5	417	43	1.097 (0.591; 2.035)	0.770	407	41	0.954 (0.491; 1.854)	0.889
D-HEALTH	1857	398	1.071 (0.879; 1.303)	0.497	1820	382	1.104 (0.903; 1.350)	0.336
FIND	160	36	1.118 (0.550; 2.274)	0.758	160	36	0.926 (0.434; 1.975)	0.842
Meta-analysis	7513	1726	0.933 (0.848; 1.026)	0.151	7381	1688	0.969 (0.866; 1.084)	0.579

Abbreviations: AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation*;* CI, confidence interval; D2dCA*,* Vitamin D and type 2 diabetes cancer outcomes study*;* D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79*;* FIND*,* Finnish Vitamin D Trial; HR, hazard ratio*;* RECORD*,* Randomized Evaluation of Calcium Or vitamin D; ViDA, Vitamin D Assessment Study*;* VITAL, Vitamin D and Omega-3 Trial*;* WHI, Women's Health Initiative

Footnote:

[a] For adjustment factors of the specific studies, see legend of **Supplemental Table 10**.

Supplemental Table 15 A+B. *Subgroup analyses for the efficacy of vitamin D_3 supplementation for cancer specific survival of cancer patients*
A.

Subgroup	VIDA (*n* = 396)			RECORD (*n* = 184)			FIND (*n* = 160)			VITAL (*n* = 1617)		
	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)
Age (years)												
< 70	200	28	1.910 (0.864; 4.222)	0	0	NA[a]	97	15	0.827 (0.294; 2.325)	978	187	0.875 (0.656; 1.167)
≥ 70	196	45	0.678 (0.373; 1.230)	184	88	0.857 (0.561; 1.308)	63	21	1.346 (0.493; 3.680)	639	154	0.761 (0.552; 1.049)
Sex												
Female	126	21	1.070 (0.454; 2.520)	143	75	0.798 (0.503; 1.264)	59	15	1.331 (0.424; 4.190)	677	155	0.968 (0.706; 1.327)
Male	270	52	0.940 (0.546; 1.620)	41	13	1.326 (0.442; 3.976)	101	21	0.978 (0.394; 2.425)	940	186	**0.719 (0.536; 0.965)**
BMI (kg/m²)												
< 25	84	16	0.789 (0.293; 2.121)	NA	NA	NA	51	7	NA[a]	484	106	0.758 (0.510; 1.128)
25– < 30	180	33	1.183 (0.588; 2.381)	NA	NA	NA	77	16	0.801 (0.273; 2.350)	661	140	0.815 (0.584; 1.136)
≥ 30	131	24	0.878 (0.390; 1.976)	NA	NA	NA	32	13	1.775 (0.488; 6.460)	427	85	0.998 (0.650; 1.532)
Ethnicity												
Non-Hispanic White	351	63	0.956 (0.583; 1.567)	183	88	0.845 (0.554; 1.290)	160	36	1.118 (0.550; 2.274)	1258	241	**0.766 (0.594; 0.988)**
Afro-American, Hispanics or indigenous	37	9	NA[a]	1	0	NA[a]	0	0	NA[a]	281	85	1.024 (0.665; 1.576)
Asian or other	8	1	NA[a]	0	0	NA[a]	0	0	NA[a]	48	9	NA[a]
25(OH)D level (nmol/L)												
< 50	136	25	0.987 (0.447; 2.176)	NA	NA	NA	1	0	NA[a]	121	30	0.771 (0.371; 1.605)
≥ 50	260	48	0.986 (0.559; 1.737)	NA	NA	NA	27	5	NA[a]	923	175	0.877 (0.652; 1.180)
Adherence												
Low	NA	NA	NA	65	20	0.609 (0.239; 1.548)	2	0[b]	NA[a]	NA	NA	NA
High	NA	NA	NA	51	19	0.875 (0.339; 2.262)	63	0[b]	NA[a]	NA	NA	NA
Cancer stage												
I–III	216	21	0.924 (0.392; 2.175)	NA	NA	NA	NA	NA	NA	NA	NA	NA
IV	28	18	0.743 (0.293; 1.887)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Unknown	152	34	1.084 (0.551; 2.135)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cancer site												
Prostate cancer	92	5	NA[a]	15	1	NA[a]	50	2	NA[a]	411	14	0.300 (0.084; 1.077)
Colorectal cancer	56	9	NA[a]	19	10	0.700 (0.200; 2.451)	14	3	NA[a]	98	24	0.519 (0.224; 1.201)
Breast cancer	45	1	NA[a]	20	3	NA[a]	17	2	NA[a]	246	11	1.418 (0.400; 5.028)
Lung cancer	24	8	NA[a]	17	12	0.569 (0.159; 2.034)	11	4	NA[a]	NA	NA	NA
Time of cancer diagnosis												
Up to 5 years prior BL	142	22	1.177 (0.508; 2.724)	0	0	NA[a]	0	0	NA[a]	0	0	NA[a]
During the trial	254	51	0.904 (0.522; 1.566)	184	88	0.857 (0.561; 1.308)	160	36	1.118 (0.550; 2.274)	1617	341	0.827 (0.668; 1.024)

Note: The models are unadjusted.
Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BL, baseline; BMI, body mass index; CI, confidence interval; FIND, Finnish Vitamin D Trial; HR, hazard ratio; NA, not applicable; RECORD, Randomized Evaluation of Calcium Or vitamin D; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial
Footnotes:
[a] Not calculated due to low case number (< 10 cases) and potential model instability.
[b] In FIND, adherence was assessed only once at the end of the study via a questionnaire. Study participants who died during the trial could not respond.

B.

Subgroup	WHI (*n* = 2,882)			AMATERASU 5 (*n* = 417)			D-HEALTH (*n* = 1,872)			Meta-analysis				
	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	$N_{studies}$	N_{total}	$N_{cancer\ deaths}$	HR (95% CI)	*p*
Age (years)														
< 70	2228	528	0.911 (0.768; 1.081)	252	25	1.497 (0.661; 3.389)	744	127	1.219 (0.857; 1.732)	6	5243	1037	1.008 (0.842; 1.208)	0.929
≥ 70	654	219	0.892 (0.684; 1.164)	165	18	0.663 (0.257; 1.712)	1113	271	1.031 (0.812; 1.308)	7	4127	1087	0.894 (0.778; 1.027)	0.112
Sex														
Female	2882	747	0.905 (0.783; 1.044)	141	15	1.383 (0.491; 3.890)	558	128	1.114 (0.787; 1.576)	7	5144	1284	0.939 (0.836; 1.054)	0.285
Male	0	0	NA	276	28	0.990 (0.457; 2.146)	1299	270	1.051 (0.828; 1.334)	6	4226	840	0.922 (0.781; 1.088)	0.335
BMI (kg/m²)														
< 25	715	208	0.957 (0.729; 1.256)	352	38	1.219 (0.630; 2.356)	557	102	1.187 (0.803; 1.755)	5	2749	572	0.966 (0.804; 1.161)	0.714
25– < 30	994	248	0.889 (0.692; 1.142)	54	3	NA[a]	801	168	0.903 (0.667; 1.222)	5	3514	773	0.886 (0.755; 1.041)	0.140
≥ 30	1166	290	0.882 (0.701; 1.111)	8	1	NA[a]	486	122	1.305 (0.913; 1.867)	5	2728	656	1.000 (0.837; 1.194)	0.999
Ethnicity														
Non-Hispanic White	2577	642	0.884 (0.757; 1.033)	0	0	NA	1775	367	1.049 (0.855; 1.288)	6	8079	1804	0.907 (0.818; 1.007)	0.067
Afro-American, Hispanics or indigenous	224	76	1.139 (0.724; 1.792)	0	0	NA	11	2	NA[a]	2	505	161	1.077 (0.788; 1.472)	0.641
Asian or other	77	25	0.487 (0.218; 1.088)	417	43	1.097 (0.591; 2.035)	45	17	2.415 (0.787; 7.415)	3	584	102	1.017 (0.461; 2.246)	0.967
25(OH)D level (nmol/L)														
< 50	6	1	NA[a]	193	25	1.394 (0.601; 3.232)	NA	NA	NA	3	450	80	0.993 (0.631; 1.561)	0.974
≥ 50	2	0	NA[a]	217	17	0.895 (0.340; 2.352)	NA	NA	NA	3	1400	240	0.899 (0.698; 1.159)	0.411
Adherence														
Low	1086	259	0.877 (0.687; 1.119)	NA	NA	NA	417	156	0.932 (0.681; 1.276)	3	1985	591	0.883 (0.731; 1.067)	0.197
High	1640	406	0.921 (0.758; 1.119)	NA	NA	NA	1440	242	1.175 (0.912; 1.513)	3	4571	909	1.010 (0.848; 1.204)	0.908
Cancer stage														
I–III	2053	235	1.048 (0.811; 1.354)	417	43	1.097 (0.591; 2.035)	NA	NA	NA	3	2686	299	1.045 (0.832; 1.313)	0.704
IV	518	287	0.845 (0.669; 1.067)	0	0	NA	NA	NA	NA	2	546	305	0.839 (0.669; 1.052)	0.128
Unknown	311	225	0.983 (0.756; 1.277)	0	0	NA	NA	NA	NA	2	463	259	0.996 (0.780; 1.270)	0.972
Cancer site														
Prostate cancer	0	0	NA	0	0	NA	NA	NA	NA	1	411	14	0.300 (0.084; 1.077)	0.064
Colorectal cancer	327	84	0.708 (0.460; 1.091)	201	17	1.263 (0.467; 3.418)	NA	NA	NA	4	645	135	0.720 (0.510; 1.015)	0.061
Breast cancer	1090	56	0.980 (0.580; 1.655)	0	0	NA	NA	NA	NA	2	1336	67	1.035 (0.637; 1.679)	0.891
Lung cancer	297	188	1.134 (0.850; 1.514)	0	0	NA	NA	NA	NA	2	314	200	1.074 (0.747; 1.545)	0.699
Time of cancer diagnosis														
Up to 5 years prior baseline	0	0	NA	417	43	1.097 (0.591; 2.035)	1576	102	1.201 (0.813; 1.774)	3	3711	269	1.171 (0.862; 1.592)	0.313
During the trial	2882	747	0.905 (0.783; 1.044)	0	0	NA	NA[b]	NA[b]	NA[b]	5	5097	1263	**0.884 (0.792; 0.988)**	**0.030**

Note: The models contain only the single terms and the interaction term of the two variables of interest.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; BMI, body mass index; CI, confidence interval; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; HR, hazard ratio; NA, not applicable; WHI, Women's Health Initiative

Footnotes:

[a] Not calculated due to low case number (< 10 cases) and potential model instability.

[b] Not calculated because cancer diagnoses were not assessed during the D-Health trial.

Supplemental Table 16 A+B. *Test for effect modification of the efficacy of vitamin D_3 supplementation for cancer specific survival of cancer patients by other factors*

A.

Factors	VIDA (*n* = 396)				RECORD (*n* = 184)				FIND (*n* = 160)				VITAL (*n* = 1,617)			
	N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term	
			ß (SE)	*p*			ß (SE)	*p*			ß (SE)	*p*			ß (SE)	*p*
Age (years)	396	73	-0.052 (0.031)	0.101	184	88	0.024 (0.038)	0.531	160	36	0.049 (0.076)	0.519	1617	341	0.002 (0.024)	0.877
< 70	200	28	Ref		0	0	Ref		97	15	Ref		978	187	Ref	
≥ 70	196	45	-1.031 (0.506)	**0.042**	184	88	NA	NA	63	21	0.498 (0.736)	0.499	639	154	-0.141 (0.219)	0.520
Sex	396	73			184	88			160	36			1617	341		
Female	126	21	Ref		143	75	Ref		59	15	Ref		677	155	Ref	
Male	270	52	-0.127 (0.518)	0.806	41	13	0.473 (0.604)	0.434	101	21	-0.307 (0.746)	0.681	940	186	-0.289 (0.219)	0.188
BMI (kg/m²)	395	73	0.024 (0.047)	0.617	NA	NA	NA	NA	160	36	0.084 (0.075)	0.264	1572	331	0.016 (0.021)	0.430
< 25	84	16	-0.464 (0.618)	0.452	NA	NA	NA	NA	51	7	NA[a]	NA[a]	484	106	-0.086 (0.264)	0.106
25– < 30	180	33	Ref		NA	NA	Ref		77	16	Ref		661	140	Ref	
≥ 30	131	24	-0.309 (0.547)	0.572	NA	NA	NA	NA	32	13	0.936 (0.866)	0.280	427	85	0.193 (0.276)	0.484
Ethnicity	396	73			184	88			160	36			1587	335		
Non-Hispanic White	351	63	Ref		183	88	Ref		160	36	Ref		1258	241	Ref	
Afro-American, Hispanics or indigenous	37	9	NA[a]	NA[a]	1	0	NA[a]	NA[a]	0	0	NA	NA	281	85	0.382 (0.253)	0.132
Asian or other	8	1	NA[a]	NA[a]	0	0	NA[a]	NA[a]	0	0	NA	NA	48	9	NA[a]	
25(OH)D level (nmol/L)	396	73	-0.001 (0.010)	0.888	NA	NA	NA	NA	28	5	NA[a]	NA[a]	NA	NA	NA	NA
< 50	136	25	0.004 (0.496)	0.993	NA	NA	NA	NA	1	0	NA[a]	NA[a]	121	30	-0.074 (0.397)	0.853
≥ 50	260	48	Ref		NA	NA	Ref		27	5	Ref		923	175	Ref	
Adherence	NA	NA			116	39			65	0[b]			NA	NA		
Low	NA	NA	Ref		65	20	Ref		2	0[b]	Ref		NA	NA	Ref	
High	NA	NA	NA	NA	51	19	0.291 (0.676)	0.666	63	0[b]	NA[a]	NA[a]	NA	NA	NA	NA
Cancer stage	396	73			NA	NA			NA	NA			NA	NA		
I–III	216	21	Ref		NA	NA	Ref		NA	NA	Ref		NA	NA	Ref	
IV	28	18	-0.324 (0.646)	0.615	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Unknown	152	34	0.152 (0.557)	0.785	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cancer site	396	73			184	88			160	36			1617	341		
Prostate cancer	92	5	NA[a]	NA[a]	15	1	NA[a]	NA[a]	50	2	NA[a]	NA[a]	411	14	-1.038 (0.661)	0.116
Colorectal cancer	56	9	NA[a]	NA[a]	19	10	-0.293 (0.678)	0.666	14	3	NA[a]	NA[a]	98	24	-0.485 (0.437)	0.267
Breast cancer	45	1	NA[a]	NA[a]	20	3	NA[a]	NA[a]	17	2	NA[a]	NA[a]	246	11	0.674 (0.636)	0.290
Lung cancer	24	8	NA[a]	NA[a]	17	12	-0.524 (0.657)	0.425	11	4	NA[a]	NA[a]	NA	NA	NA	NA
Time of cancer diagnosis	396	73			184	88			160	36			1617	341		
Up to 5 years prior baseline	142	22	Ref		0	0	Ref		0	0	Ref		0	0	Ref	
During the trial	254	51	-0.279 (0.512)	0.586	184	88	NA	NA	160	36	NA	NA	1617	341	NA	NA

Note: The models contain only the single terms and the interaction term of the two variables of interest

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; FIND, Finnish Vitamin D Trial; NA, not applicable; RECORD, Randomized Evaluation of Calcium Or vitamin D; SE, standard error; ViDA, Vitamin D Assessment Study; VITAL, Vitamin D and Omega-3 Trial

Footnotes:

[a] Not calculated due to low case number (< 10 cases) and potential model instability.

[b] In FIND, adherence was assessed only once at the end of the study via a questionnaire. Study participants who died during the trial could not respond.

B.

Factors	WHI (*n* = 2,882)				AMATERSU 5 (*n* = 417)				D-HEALTH (*n* = 1,872)				Meta-analysis				
	N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term		N_{total}	$N_{cancer\ deaths}$	Interaction term		$N_{studies}$	N_{total}	$N_{cancer\ deaths}$	Interaction term	
			ß (SE)	*p*			ß (SE)	*p*			ß (SE)	*p*				ß (95% CI)	*p*
Age (years)	2882	747	0.028 (0.028)	0.868	417	43	-0.031 (0.031)	0.322	1857	398	-0.001 (0.020)	0.970	7	7513	1726	-0.003 (-0.024; 0.018)	0.789
< 70	2228	528	Ref		252	25	Ref		744	127	Ref		6	4499	910	Ref	
≥ 70	654	219	-0.017 (0.161)	0.919	165	18	-0.829 (0.638)	0.194	1113	271	-0.168 (0.217)	0.439	6	2830	728	-0.153 (-0.386; 0.080)	0.198
Sex	2882	747			417	43			1857	398							
Female	2882	747	Ref		141	15	Ref		558	128	Ref		6	1704	409	Ref	
Male	0	0	NA	NA	276	28	-0.330 (0.659)	0.617	1299	270	-0.058 (0.215)	0.786	6	2927	570	-0.146 (-0.416; 0.123)	0.286
BMI (kg/m²)	2875	746	-0.002 (0.013)	0.901	414	42	0.015 (0.116)	0.897	1844	392	-0.006 (0.018)	0.712	6	7260	1620	0.003 (-0.015; 0.021)	0.764
< 25	715	208	0.072 (0.189)	0.702	352	38	1.646 (1.679)	0.195	557	102	0.279 (0.252)	0.269	5	2192	470	0.074 (-0.176; 0.325)	0.561
25– < 30	994	248	Ref		54	3	Ref		801	168	Ref		6	2767	608	Ref	
≥ 30	1166	290	-0.005 (0.174)	0.975	8	1	NA[a]	NA[a]	486	122	0.367 (0.239)	0.125	5	2242	534	0.132 (-0.105; 0.369)	0.276
Ethnicity	2878	743			417	43			1831	386							
Non-Hispanic White	2577	642	Ref		0	0	Ref		1775	367	Ref		3	5610	1250	Ref	
Afro-American, Hispanics or indigenous	224	76	0.271 (0.244)	0.267	0	0	NA	NA	11	2	NA[a]	NA[a]	2	505	161	0.324 (-0.020; 0.669)	0.065
Asian or other	77	25	-0.622 (0.416)	0.134	417	43	NA	NA	45	17	0.877 (0.581)	0.131	2	122	42	0.073 (-1.392; 1.538)	0.923
25(OH)D level (nmol/L)	8	1	NA[a]	NA[a]	410	42	-0.003 (0.018)	0.872	NA	NA			2	806	115	-0.002 (-0.019; 0.016)	0.866
< 50	6	1	NA[a]	NA[a]	193	25	0.449 (0.653)	0.492	NA	NA	Ref	NA	3	450	80	0.047 (-0.502; 0.596)	0.867
≥ 50	2	0	Ref		217	17	Ref		NA	NA	NA	NA	3	1400	240	Ref	
Adherence	2726	665			NA				1857	398							
Low	1086	259	Ref		NA	NA	Ref		417	156	Ref		3	1568	435	Ref	
High	1640	406	0.054 (0.159)	0.735	NA	NA	NA	NA	1440	242	0.234 (0.206)	0.256	3	3131	667	0.127 (-0.116; 0.369)	0.305
Cancer stage	2882	747			417	43			NA	NA							
I–III	2053	235	Ref		417	43	Ref		NA	NA	Ref	NA	2	2269	256	Ref	
IV	518	287	-0.219 (0.177)	0.220	0	0	NA	NA	NA	NA	NA	NA	2	546	305	-0.226 (-0.561; 0.108)	0.185
Unknown	311	225	-0.056 (0.187)	0.763	0	0	NA	NA	NA	NA	NA	NA	2	463	259	-0.035 (-0.382; 0.313)	0.845
Cancer site					417				NA								
Prostate cancer	0	0	NA	NA	0	0	NA	NA	NA	NA	NA	NA	1	411	14	-1.038 (-2.334; 0.258)	0.116
Colorectal cancer	327	84	-0.276 (0.233)	0.236	201	17	0.225 (0.648)	0.728	NA	NA	NA	NA	4	645	135	-0.274 (-0.643; 0.095)	0.146
Breast cancer	1090	56	0.088 (0.278)	0.751	0	0	NA	NA	NA	NA	NA	NA	2	1336	67	0.182 (-0.317; 0.681)	0.475
Lung cancer	297	188	0.243 (0.169)	0.151	0	0	NA	NA	NA	NA	NA	NA	2	314	200	0.122 (-0.425; 0.670)	0.662
Time of cancer diagnosis	2882	747			417				1857	398							
Up to 5 years prior BL	0	0	Ref		417	43	Ref		1576	102	NA	NA	1	142	22	Ref	
During the trial	2882	747	NA	NA	0	0	NA	NA	NA[b]	NA[b]	NA[b]	NA[b]	1	254	51	0.279 (-1.283; 0.725)	0.586

Note: The models contain only the single terms and the interaction term of the two variables of interest.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AMATERASU 5, A randomized, double blind, comparative study of vitamin D_3 versus placebo in patients with cancer in gastrointestinal tract to prevent relapse after operation; BL baseline; BMI, body mass index; D-Health, A randomized placebo-controlled trial of high-dose vitamin D supplementation for prevention of mortality and cancer in Australian adults aged 60–79; SE, standard error; NA, not applicable; WHI, Women's Health Initiative

Footnotes:

[a] Not calculated due to low case number (< 10 cases) and potential model instability.

[b] Not calculated because cancer diagnoses were not assessed during the D-Health trial.

Supplemental Table 17. *Strength of evidence (GRADE)*

Certainty assessment								Summary of Findings
Outcome	**Participants (studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Relative effect (95% CI)**
Cancer mortality (main analysis)	104,727 (14 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	**RR 0.94** (0.86; 1.02)
Cancer mortality (IPD analysis)	93,651 (6 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	**HR 0.93** (0.84; 1.02)
Cancer-specific survival (IPD analysis)	7,513 (7 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	**HR 0.93** (0.85; 1.03)
Overall survival (IPD analysis)	7,528 (7 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	**HR 0.95** (0.87; 1.04)

Abbreviations: CI, confidence interval; HR, hazard Ratio; RR, risk ratio.

Supplemental Table 18. *Serum 25(OH)D levels at screening, visit 1 and visit 2*

Intervention	ITT/ PP	N	25(OH)D (nmoL/L)							*p*[a]
			Median	Mean (95% CI)	SD	Min	P25	P75	Max	
Screening; day -8 to 0										
No	ITT	33	28.0	28.4 (24.3; 32.5)	11.6	12.0	20.0	32.5	61.0 [b]	0.360
Yes	ITT	37	26.0	26.0 (22.8; 29.3)	9.7	9.0	20.4	31.3	48.5	
No	PP	29	25.0	27.6 (23.6; 31.6)	10.5	12.0	20.0	32.5	48.0	0.501
Yes	PP	35	25.5	25.9 (22.5; 29.3)	9.9	9.0	17.4	32.8	48.5	
Visit 1; end of loading dose; day 12 to 21										
No	ITT	32	28.0	31.6 (27.3; 35.8)	11.8	13.0	26.1	38.3	68.0	< 0.0001
Yes	ITT	36	64.6	63.1 (58.3; 67.9)	14.3	33.5	54.5	71.6	91.0	
No	PP	29	28.0	31.0 (27.2; 34.7)	9.9	13.0	26.3	37.5	58.0	< 0.0001
Yes	PP	35	64.2	63.1 (58.1; 68.0)	14.5	33.5	54.0	72.0	91.0	
Visit 2; end of maintenance dose; week 13 to 16										
No	ITT	27	30.2	35.1 (28.5; 41.8)	16.8	9.2	23.0	45.8	76.0	< 0.0001
Yes	ITT	25	71.9	72.5 (66.3; 78.5)	14.9	30.8	65.8	80.5	101.0	
No	PP	23	30.2	34.1 (27.1; 41.1)	16.1	9.3	23.0	45.8	76.0	< 0.0001
Yes	PP	18	72.4	75.5 (69.2; 81.9)	12.8	52.8	67.4	87.0	101.0	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ITT, intention-to-treat analysis; Max, maximum; Min, minimum; P25, 25th Percentile; P75, 75th Percentile; PP, per-protocol analysis; SD, standard deviation.
Footnotes:
[a] Two-sample two-tailed t-test used to test on difference of the means of two groups. Statistically significant in analysis if $p < 0.04$. The p-value of the test was derived by the Satterthwaite method.
[b] One patient without vitamin D insufficiency and a 25(OH)D level of 61.0 nmol/L was falsely included. Without this falsely included study participant, the maximum 25(OH)D level would have been 48.0 nmol/L.

Supplemental Table 19. *Changes of 25(OH)D levels from screening to visit 1 and from screening to visit 2*

Intervention	ITT/ PP	N	25(OH)D (nmoL/L)							*p*[a]
			Median	Mean (95% CI)	SD	Min	P25	P75	Max	
Change from screening to visit 1										
No	ITT	32	3.1	3.3 (1.5; 5.0)	4.8	-7.3	0.5	7.0	13.0	< 0.0001
Yes	ITT	36	38.5	37.2 (32.0; 42.5)	15.4	2.3	28.0	43.5	66.4	
No	PP	29	3.3	3.3 (1.4; 5.2)	5.0	-7.3	0.5	7.0	13.0	< 0.0001
Yes	PP	35	38.3	37.2 (31.8; 42.5)	15.6	2.3	28.0	44.0	66.4	
Change from screening to visit 2										
No	ITT	27	-1.3	5.6 (-1.0; 12.3)	16.7	-16.0	-6.4	16.5	40.0	< 0.0001
Yes	ITT	25	38.3	43.3 (36.0; 50.6)	17.8	10.3	34.0	57.0	80.0	
No	PP	23	-2.8	5.5 (-2.1; 13.1)	17.5	-16.0	-7.0	16.5	40.0	< 0.0001
Yes	PP	18	38.9	45.0 (36.2; 53.8)	17.7	18.5	34.5	57.0	80.0	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ITT, intention-to-treat analysis; Max, maximum; Min, minimum; P25, 25th Percentile; P75, 75th Percentile; PP, per-protocol analysis; SD, standard deviation.
Footnotes:
[a] Two-sample two-tailed t-test used to test on difference of the means of two groups. Statistically significant in analysis if $p < 0.04$. The p-value of the test was derived by the Satterthwaite method.

Appendices

Supplemental Table 20. *Prevalence of vitamin insufficiency during the course of the trial*

Intervention	ITT/ PP	N	Vitamin D insufficiency (25(OH)D ≤ 50 nmoL/L)		*p*[a]
			No N (%)	Yes N (%)	
Screening; day -8 to 0					
No	ITT	33	1[b] (3.2)	32 (97.0)	NA
Yes	ITT	37	0 (0.0)	37 (100.0)	
No	PP	29	0 (0.0)	29 (100.0)	NA
Yes	PP	35	0 (0.0)	35 (100.0)	
Visit 1; end of loading dose; day 12 to 21					
No	ITT	32	2 (6.3)	30 (93.8)	< 0.0001
Yes	ITT	36	29 (80.6)	7 (19.4)	
No	PP	29	1 (3.5)	28 (96.6)	< 0.0001
Yes	PP	35	28 (80.0)	7 (20.0)	
Visit 2; end of maintenance dose; week 13 to 16					
No	ITT	27	5 (18.5)	22 (81.5)	< 0.0001
Yes	ITT	25	24 (96.0)	1 [c] (4.0)	
No	PP	23	4 (17.4)	19 (82.6)	< 0.0001
Yes	PP	18	18 (100.0)	0 (0.0)	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ITT, intention-to-treat analysis; NA, not applicable; PP, per-protocol analysis.
Footnotes:
[a] Fisher's exact test. Statistically significant in analysis if p < 0.04.
[b] One patient without vitamin D insufficiency was falsely included.
[c] Treatment discontinuation after visit 1 due to hypercalciuria.

Supplemental Table 21. *Safety parameters of six patients who experienced hypercalciuria*

Arbitrary patient no.	Treatment arm	25(OH)D [nmol/L]	Albumin-corrected serum calcium [mmol/L]	Urinary calcium-to-creatinine ratio [mmol/mmol]	eGFR [ml/min/1.73 m^2]
Screening visit; day -8 to 0					
1	Placebo	17.0	2.5	0.6	88.1
2	Vitamin D	20.4	2.3	0.6	98.5
3	Vitamin D	13.0	2.2	0.4	102.9
4	Vitamin D	16.0	2.5	0.7	82.9
5	Vitamin D	25.0	2.5	0.8	94.3
6	Vitamin D	27.0	2.3	0.1	97.7
Visit 1; end of loading dose; day 12 to 21					
1	Placebo	13.0	2.4	0.8	96.7
2	Vitamin D	56.5	2.2	0.9	111.6
3	Vitamin D	49.0	2.3	0.9	101.1
4	Vitamin D	60.0	2.4	1.1	82.1
5	Vitamin D	89.0	2.4	1.4	95.8
6	Vitamin D	54.0	2.3	0.9	97.2
Visit 2; end of maintenance dose; week 13 to 16					
1	Placebo	40.0	2.4	0.6	88.1
2	Vitamin D	30.8	2.3	0.4	105.3
3	Vitamin D	-	-	-	-
4	Vitamin D	76.0	2.3	0.3	85.4
5	Vitamin D	-	-	-	-
6	Vitamin D	57.0	2.3	0.4	96.7

Abbreviations: 25(OH)D, 25-hydroxyvitamin D. **Note:** Hyphen instead of a numeric value means that value is missing.

Supplemental Table 22. *Urinary calcium-to-creatinine ratio at screening, visit 1 and visit 2*

Intervention	ITT/ PP	N	Urinary calcium-to-creatinine ratio [mmol/mmol]							*p*[a]
			Median	Mean (95% CI)	SD	Min	P25	P75	Max	
Screening; day -8 to 0										
Placebo	ITT	33	0.3	0.3 (0.2; 0.4)	0.2	0.05	0.2	0.5	0.7	0.814
Vitamin D	ITT	37	0.2	0.3 (0.2; 0.4)	0.2	0.02	0.1	0.4	0.8	
Placebo	PP	29	0.3	0.3 (0.2; 0.4)	0.2	0.05	0.2	0.5	0.7	0.737
Vitamin D	PP	35	0.2	0.3 (0.2; 0.4)	0.2	0.02	0.1	0.5	0.8	
Visit 1; end of loading dose; day 12 to 21										
Placebo	ITT	32	0.3	0.3 (0.2; 0.4)	0.2	0.03	0.1	0.4	0.8	0.112
Vitamin D	ITT	36	0.3	0.4 (0.3; 0.5)	0.3	0.07	0.2	0.6	1.4	
Placebo	PP	29	0.3	0.3 (0.2; 0.4)	0.2	0.03	0.1	0.4	0.8	0.152
Vitamin D	PP	35	0.3	0.4 (0.3; 0.5)	0.3	0.07	0.2	0.6	1.4	
Visit 2; end of maintenance dose; week 13 to 16										
Placebo	ITT	26	0.2	0.2 (0.2; 0.3)	0.2	0.02	0.1	0.3	0.7	0.946
Vitamin D	ITT	25	0.2	0.2 (0.2; 0.3)	0.1	0.04	0.2	0.4	0.5	
Placebo	PP	22	0.2	0.2 (0.2; 0.3)	0.2	0.02	0.1	0.3	0.7	0.618
Vitamin D	PP	18	0.2	0.2 (0.2; 0.3)	0.1	0.04	0.1	0.3	0.5	

Abbreviations: ITT, intention-to-treat analysis; Max, maximum; Min, minimum; P25, 25th Percentile; P75, 75th Percentile; PP, per-protocol analysis; SD, standard deviation.
Footnotes:
[a] Two-sample two-tailed t-test used to test on difference of the means of two groups. Statistically significant in analysis if $p < 0.04$. The p-value of the test was derived by the Satterthwaite method.

Supplemental Table 23. *Albumin-corrected serum calcium at screening, visit 1 and visit 2*

Intervention	ITT/ PP	N	Albumin-corrected serum calcium [mmol/L]							p^a
			Median	Mean (95% CI)	SD	Min	P25	P75	Max	
Screening; day -8 to 0										
Placebo	ITT	33	2.3	2.3 (2.3; 2.3)	0.1	2.1	2.2	2.4	2.5	0.939
Vitamin D	ITT	37	2.3	2.3 (2.3; 2.3)	0.1	2.1	2.2	2.3	2.5	
Placebo	PP	29	2.3	2.3 (2.3; 2.3)	0.1	2.1	2.2	2.4	2.5	0.934
Vitamin D	PP	35	2.3	2.3 (2.3; 2.3)	0.1	2.2	2.2	2.3	2.5	
Visit 1; end of loading dose; day 12 to 21										
Placebo	ITT	32	2.3	2.3 (2.3; 2.3)	0.1	2.2	2.2	2.4	2.5	0.940
Vitamin D	ITT	36	2.3	2.3 (2.3; 2.3)	0.1	1.9	2.2	2.4	2.4	
Placebo	PP	29	2.3	2.3 (2.3; 2.3)	0.1	2.2	2.3	2.4	2.5	0.965
Vitamin D	PP	35	2.3	2.3 (2.3; 2.3)	0.1	1.9	2.3	2.4	2.4	
Visit 2; end of maintenance dose; week 13 to 16										
Placebo	ITT	27	2.3	2.3 (2.2; 2.3)	0.1	2.0	2.2	2.3	2.4	0.829
Vitamin D	ITT	25	2.3	2.3 (2.2; 2.3)	0.1	2.1	2.2	2.3	2.4	
Placebo	PP	23	2.3	2.3 (2.2; 2.3)	0.1	2.0	2.2	2.3	2.4	0.960
Vitamin D	PP	18	2.3	2.3 (2.2; 2.3)	0.1	2.1	2.2	2.3	2.4	

Abbreviations: ITT, intention-to-treat analysis; Max, maximum; Min, minimum; P25, 25th Percentile; P75, 75th Percentile; PP, per-protocol analysis; SD, standard deviation.
Footnotes:
[a] Two-sample two-tailed t-test used to test on difference of the means of two groups. Statistically significant in analysis if $p < 0.04$. The p-value of the test was derived by the Satterthwaite method.

Supplemental Table 24. *eGFR at screening, visit 1 and visit 2*

Intervention	ITT/ PP	N	eGFR [ml/min/1.73 m^2]							p^a
			Median	Mean (95% CI)	SD	Min	P25	P75	Max	
Screening; day -8 to 0										
Placebo	ITT	33	90.0	86.9 (81.7; 92.1)	14.6	48.0	78.5	97.2	109.0	0.479
Vitamin D	ITT	37	93.0	89.5 (84.3; 94.6)	15.4	55.5	78.5	98.5	120.6	
Placebo	PP	29	90.7	86.6 (80.7; 92.5)	15.5	48.0	77.6	97.2	109.0	0.458
Vitamin D	PP	35	93.1	89.5 (84.2; 94.8)	15.4	55.5	78.5	98.5	120.6	
Visit 1; end of loading dose; day 12 to 21										
Placebo	ITT	32	91.2	86.3 (81.3; 91.3)	13.8	50.1	81.8	95.0	102.5	0.466
Vitamin D	ITT	36	91.6	89.0 (83.3; 94.8)	17.0	59.1	73.4	100.2	130.9	
Placebo	PP	29	90.8	85.8 (80.4; 91.2)	14.3	50.1	81.2	93.9	102.5	0.468
Vitamin D	PP	35	91.1	88.7 (82.8; 94.6)	17.1	59.1	73.0	99.4	130.9	
Visit 2; end of maintenance dose; week 13 to 16										
Placebo	ITT	27	87.5	82.7 (76.5; 88.9)	15.6	41.2	76.8	93.6	102.8	0.962
Vitamin D	ITT	25	85.3	82.9 (77.3; 88.5)	13.6	64.0	71.2	93.4	108.7	
Placebo	PP	23	85.7	81.7 (74.5; 88.8)	16.5	41.2	76.6	93.6	102.8	0.651
Vitamin D	PP	18	86.1	83.8 (77.2; 90.3)	13.1	64.0	71.4	93.4	108.7	

Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intention-to-treat analysis; Max, maximum; Min, minimum; P25, 25th Percentile; P75, 75th Percentile; PP, per-protocol analysis; SD, standard deviation.

Footnotes:

[a] Two-sample two-tailed t-test used to test on difference of the means of two groups. Statistically significant in analysis if $p < 0.04$. The p-value of the test was derived by the Satterthwaite method.

Supplemental Table 25. *Comparison of the distribution of loading doses hypothetically calculated with the equations of Jansen et al. and von Groningen et al. for the study participants of the VICTORIA trial*

Population	Equation	Distribution of loading dose				
		Minimum	**25th pct.**	**Median**	**75 th pct.**	**Maximum**
Total	Jansen	86,302	153,574	199,287	235,521	480,805
population	v. Groningen	71,280	133,163	159,310	200,000	388,080
(*n* = 73)[a]	Δ v. Groningen-Jansen	-4,222	-8,211	-25,207	-15,521	-61,925
	(Δ v. Groningen-Jansen)/Jansen	-5%	-5%	-13%	-7%	-13%
BMI < 30	Jansen	86,302	142,822	177,725	212,129	269,981
kg/m²	v. Groningen	71,280	120,600	141,100	166,160	230,400
(*n* = 51)	Δ v. Groningen-Jansen	-4,222	-11,062	-20,025	-31,535	-20,381
	(Δ v. Groningen-Jansen)/Jansen	-5%	-8%	-11%	-15%	-8%
BMI ≥ 30	Jansen	134,681	215,201	268,210	302,240	480,805
kg/m²	v. Groningen	120,000	179,200	210,100	249,600	388,080
(*n* = 22)	Δ v. Groningen-Jansen	5,319	-15,381	-37,110	-26,640	-61,925
	(Δ v. Groningen-Jansen)/Jansen	4%	-7%	-14%	-9%	-13%
25(OH)D <	Jansen	131,274	192,594	218,503	261,064	480,805
30 nmol/L	v. Groningen	110,200	144,624	173,326	211,200	388,080
(*n* = 49)	Δ v. Groningen-Jansen	-9,474	-34,170	-28,183	-29,264	-61,925
	(Δ v. Groningen-Jansen)/Jansen	-7%	-18%	-13%	-11%	-13%
25(OH)D ≥	Jansen	86,302	103,074	140,753	180,252	235,521
30 nmol/L	v. Groningen	71,280	96,590	120,300	153,575	225,280
(*n* = 24)	Δ v. Groningen-Jansen	-4,222	9,261	-3,753	-8,977	15,359
	(Δ v. Groningen-Jansen)/Jansen	-5%	9%	-3%	-5%	7%

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; pct., percentile.
Footnotes:
[a] One study participant was excluded because he/she had no vitamin D insufficiency at screening and should not have been included in the VICTORIA trial.

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EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zu dem Thema

"Test of efficacy of a personalized vitamin D supplementation to treat vitamin D deficiency in colorectal cancer patients and the potential implications on cancer prognosis"

handelt es sich um meine eigenständig erbrachte Leistung.

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