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Efficacy of Vitamin D3 supplementation on cancer mortality in the general population and the prognosis of cancer patients: Protocol of a systematic review and individual patient data meta-analysis of randomized controlled trials

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3 1 **Efficacy of Vitamin D₃ supplementation on cancer mortality in the**
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5 2 **general population and the prognosis of cancer patients: Protocol of a**
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7 3 **systematic review and individual patient data meta-analysis of**
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9 4 **randomized controlled trials**

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37 **ABSTRACT**

38 **Introduction**

39 Vitamin D insufficiency is much more common among cancer patients than the general population.
40 Previous meta-analyses of controlled trials showed an approx. 15% reduction of cancer mortality
41 by vitamin D supplementation compared to placebo or no treatment in the general population.

42 On top of updating the latest systematic review on vitamin D supplementation and cancer mortality
43 in the general population, we aim to conduct the first meta-analyses of trials on vitamin D₃
44 supplementation and cancer-specific and overall survival of cancer patients. In addition, none of the
45 previous systematic reviews collected individual patient data. We will do this for the first time to be
46 able to conduct subgroup analyses.

47 **Methods and analysis**

48 A systematic review and individual patient data meta-analysis will be performed on randomized
49 placebo-controlled trials with a vitamin D₃ intervention. The addressed outcomes are cancer mortality
50 in the general population as well as cancer-specific and overall survival of cancer patients. The
51 quality appraisal of the studies will be evaluated by the Cochrane Collaboration's tool for assessing
52 risk of bias. Trial results will be re-analyzed using adjusted and unadjusted Cox proportional hazard
53 regression models and meta-analyses are planned. Cochran's Q-Test and the I² index will be used
54 to statistically assess the level of heterogeneity, while sensitivity and subgroup analyses serve to
55 identify potential causes of heterogeneity. Subgroup analyses will be conducted for vitamin D₃
56 dosing, follow-up time, co-supplementation of calcium, age, sex, obesity, vitamin D
57 deficiency/insufficiency, history of cancer, and compliance. Publication bias will be assessed by
58 funnel plots and Egger's test.

59 **Ethics and dissemination**

60 Ethical approval is not required since no human beings are involved in this systematic review.

61 Results will be published in a peer-reviewed journal with open access. They will be presented at
62 conferences and sent to patient advocacy groups and German oncologic rehabilitation centers.

63 **Trial registration number**

64 In accordance with the guidelines, our systematic review protocol was submitted to the International
65 Prospective Register of Systematic Reviews (PROSPERO) on May 15th, 2020 [registration ID
66 185566].

67 **Keywords**

68 Vitamin D, cancer, mortality, systematic review, meta-analysis

70 **Strengths and limitations of this study**

- 71 • First meta-analysis on vitamin D₃ supplementation and cancer survival as well as first individual
72 patient data meta-analysis on this research topic.
- 73 • Thorough assessment of study quality and sources of heterogeneity and bias in meta-analyses.
- 74 • Conduction of the systematic review according to this protocol minimizes the risk of bias and will
75 gather reproducible results.
- 76 • Number of studies with eligible data for subgroup analyses may be limited.

77 INTRODUCTION

78 Background

79 The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths
80 in 2018.(1) There is accumulating evidence from epidemiological studies that a low vitamin D status
81 goes along with increased risks of several types of cancer. Meta-analyses of observational studies
82 reported increased risks of lung cancer, colorectal cancer, breast cancer, bladder carcinoma, and
83 lymphoma in subjects with low 25(OH)D serum concentrations.(2-5) Furthermore, epidemiological
84 studies have shown that low serum levels of 25-hydroxyvitamin D (25(OH)D), the acknowledged
85 best biomarker to measure vitamin D status, were strongly associated with substantially increased
86 cancer mortality.(6) For example, in a German population-based cohort study of older adults, the
87 risk to die of cancer was increased by 42% in study participants with vitamin D deficiency (defined
88 as 25(OH)D < 30 nmol/L) compared to individuals with sufficient 25(OH)D levels > 50 nmol/L (hazard
89 ratio [HR] and 95% confidence interval (95%CI): 1.42 [1.08; 1.87]).(7)

90 The molecular links between vitamin D and carcinogenesis and progression have been described in
91 detail by Moukayed and Grant.(8) In brief, genomic mechanisms of the active hormone 1,25(OH)₂D
92 impact signaling pathways that regulate cell proliferation, differentiation, and cell survival.
93 1,25(OH)₂D may primarily act as an anti-proliferative agent in many tissues and may slow down
94 malignant cellular growth. Thus, there is biological plausibility that a sufficient vitamin D supply is
95 especially essential for good cancer prognosis. A causal relationship of low 25(OH)D levels and
96 cancer mortality was furthermore supported by a Mendelian randomization study conducted within
97 three large cohorts from Denmark.(9)

98 Several randomized trials with vitamin D supplementation have been conducted with mostly the aim
99 to improve skeletal outcomes at older ages. Cancer mortality was a secondary outcome in all trials
100 and therefore the trials were not specifically designed for this outcome.(10) Despite strong
101 heterogeneity in study populations, intervention schemes, and other important design aspects, three
102 out of four meta-analyses demonstrated a statistically significant reduction in cancer mortality.(11-
103 14)

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2 104 However, most trials have not been restricted to patients that were vitamin D deficient.(10) The latter
3
4 105 is important because the association of 25(OH)D levels and adverse health outcomes is not linear.(6)
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6 106 Neglecting this dose-response relationship by treating subjects with optimal 25(OH)D levels is
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8 107 expected to have led to a substantial underestimation of the potential efficacy of vitamin D
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10 108 supplementation in previous clinical trials.(15) Therefore, there is a need for a systematic review that
11
12 109 re-analyses individual patient data (IPD) from previous trials restricted to subjects with vitamin D
13
14 110 insufficiency (25(OH)D < 50 nmol/L) or deficiency (25(OH)D < 30 nmol/L).
15
16

17
18 111 Another important reason to re-analyze the previous trial data is that most studies were not restricted
19
20 112 to cancer patients. Vitamin D deficiency or insufficiency are much more common among cancer
21
22 113 patients than among the general population. In a study with 2,912 colorectal cancer patients, vitamin
23
24 114 D deficiency (25(OH)D levels < 30 nmol/L) was found among 59% of colorectal cancer patients
25
26 115 during or shortly after first-line treatment, and, in agreement with previous evidence, low 25(OH)D
27
28 116 levels were strongly associated with poorer survival.(16, 17) Systematic reviews of observational
29
30 117 studies on 25(OH)D levels and cancer prognosis concluded that sufficient 25(OH)D levels are
31
32 118 associated with a better prognosis of breast and colorectal cancer, whereas there are too few studies
33
34 119 for other cancer sites up to date to draw conclusions.(16, 18)
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38 120 Further important potential effect modifiers of vitamin D effects on cancer survival that deserve close
39
40 121 investigation are obesity and compliance. People with low compliance and/or obesity (who may need
41
42 122 higher vitamin D doses because vitamin D is being stored in adipocytes) might have led to an
43
44 123 attenuation of the overall treatment effect in the trials.(19)
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46

50 125 **Objective**

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53 126 The objective of our systematic review is to assess the efficacy of vitamin D₃ supplementation on
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55 127 cancer mortality in the general population and the prognosis of cancer patients with special attention
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57 128 to potential effect modifiers, including baseline 25(OH)D levels, cancer at baseline, BMI and
58
59 129 compliance.
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2 130 The main outcomes include “cancer mortality in the general population”, “cancer-specific survival of
3
4 131 cancer patients” and “overall survival of cancer patients”. These outcomes are universally used in
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6 132 cancer studies and do not need further refinement during the review.
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9 133 In a first step, we intend to update the previous systematic reviews on vitamin D supplementation
10
11 134 and cancer mortality in the general population by including newly published trials and unpublished
12
13 135 data from trials with outcome data on cancer incidence or all-cause mortality by asking the authors
14
15 136 for data on cancer mortality. Second, we will obtain data for an IPD meta-analysis. Third, we will
16
17
18 137 conduct IPD meta-analyses on vitamin D₃ supplementation and overall and cancer-specific survival
19
20 138 among cancer patients. Forth, we will conduct subgroup analyses to explore sources of
21
22 139 heterogeneity and to identify effect modifiers. The timetable for the review is shown in Table 1.
23
24

25 140 **Table 1:** Proposed timetable for conducting the review
26

Step	Timeframe for completion
Literature search, abstract and full-text selection	2.5 months
Data extraction & individual patient data acquisition	2.5 months
Quality appraisal	2 months
Data analysis & meta-analysis	3 months
Writing of manuscript	2 months
Total	12 months

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42 142 **METHODS AND ANALYSIS**

43 44 45 143 **Study selection criteria/ Eligibility criteria**

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49 144 We will follow a two-step approach for the study selection: First, all trials will be selected that could
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51 145 have potentially published or unpublished data on the research topic. All authors of trials with
52
53 146 potentially unpublished data on cancer mortality/survival will be contacted to provide data. In the
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55 147 second step, trials without eligible data for a meta-analysis will be excluded.
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1
2 148 Step 1: Inclusion criteria for trials

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5 149 Participants: We will include studies investigating the general adult population (18 years or older)
6
7 150 but exclude those limited to particular diseases or conditions (e.g. studies that recruited only patients
8
9 151 with type 2 diabetes). However, we will also include studies conducted with cancer populations (18
10
11 152 years or older). Apart from the exclusion of non-melanoma skin cancers and benign tumors (where
12
13 153 information is available), no restrictions will be made regarding cancer stage or tumor site, as the
14
15 154 anti-proliferative effects of vitamin D₃ are not assumed to be specific for cancer site or stage.
16
17
18 155 Therefore, we expect our results to be largely generalizable to the general population and cancer
19
20 156 patients, respectively.

21
22
23 157 Interventions: We will focus on trials that used vitamin D₃ in any dose and any regimen (e.g.
24
25 158 daily/weekly/monthly intake) as the intervention. However, the minimum time of the intervention shall
26
27 159 be six months to exclude studies with one-time bolus interventions or very short intervention periods.
28
29 160 The first reason is that cancer mortality is highly unlikely to be influenced by very brief intervention
30
31 161 periods. The second reason is that after initiating daily, weekly, or monthly supplementation
32
33 162 schedules, it takes three to six months for 25(OH)D levels to reach homeostasis.

34
35
36 163 Besides, we will also include studies using vitamin D₃ bioequivalent substances such as alfacalcidol,
37
38 164 calcifediol, and calcitriol, as all of them are metabolized equally to the active vitamin D hormone
39
40
41 165 1,25(OH)₂D.

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43
44 166 We will exclude studies with vitamin D₂ supplementation since the Cochrane review of Bjelakovic et
45
46 167 al. showed clearly no efficacy on mortality.⁽¹¹⁾ Co-supplementation with calcium or other dietary
47
48 168 supplements in the intervention arm will not be an exclusion criterion. A sensitivity analysis will
49
50 169 elucidate whether the inclusion of these studies had an impact on the overall effect estimate of the
51
52 170 meta-analysis.

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55 171 Comparators: We will include only studies, which used placebo as the comparator.

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57
58 172 Outcomes: To be eligible for inclusion in a meta-analysis trials need to have assessed the outcome
59
60 173 cancer mortality, cancer survival, or cancer-specific survival. In an intermediate step of the

1
 2 174 systematic review, we will also record studies with the outcomes cancer incidence or all-cause
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 4 175 mortality and will contact the authors if they have data for the outcomes needed for the planned
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 6 176 meta-analyses. The definitions of all outcomes are shown in Table 2.
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 8

9 177 **Table 2:** Definition of outcomes
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Outcome	Definition
All-cause mortality	Rate of deaths during a specific time period in population at risk
Cancer mortality	Rate of cancer deaths during a specific time period in population at risk
Cancer incidence	Rate of newly diagnosed cancer cases during a specific time period in population at risk
Overall cancer survival	Proportion of patients from a cancer population at risk alive at some point subsequent to the diagnosis of their cancer
Cancer-specific survival	Proportion of patients from a cancer population at risk who did not die of cancer at some point subsequent to the diagnosis of their cancer

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 28 179 Study design: We will include RCTs in which, analogous to the intervention period, the follow-up
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 30 180 period is at least six months. The follow-up time should not be longer than the time under treatment.
 31
 32 181 We will focus on parallel-group designs and exclude single-arm studies. We will further exclude all
 33
 34 182 types of cohort studies and case-control studies as well as the following types of records: reviews,
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 36 183 dissertations, theses, editorials, study protocol, clinical guidelines, commentaries, and letters.
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 40 184 Setting: There will be no restrictions by type of setting.
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 43 185 Minimum sample size: The studies need to have at least one cancer death in the verum and placebo
 44
 45 186 group.
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 48 187 Geographical location: No restrictions are defined regarding the geographical location.
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 51 188 Step 2: Exclusion criteria for pooling in meta-analysis:
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 54 189 Studies will be excluded for pooling in the meta-analysis, if
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- 56 190 - A risk ratio and 95% confidence interval for at least one outcome of interest (cancer mortality in
 57
 58 191 the general population, cancer-specific survival of cancer patients or overall survival of cancer
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2 192 patients) were not reported in publication and could not be obtained from authors or individual
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4 193 participant data
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6 194 - The trial is already included in the meta-analysis (in case of double publication from the same
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8 195 trial only the publication with the largest amount of information, e.g. the longest follow-up is
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10 196 included)

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15 198 **Information sources and search strategy**

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19 199 The search strategy will be elaborated by SK, BS, and A Heppert. Mrs. Heppert is a specialist for
20
21 200 systematic bibliographic searches at the Central Library of the German Cancer Research Center
22
23 201 and is not otherwise associated with the project. Finally, it will be peer-reviewed by HB and carried
24
25 202 out by SK.

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28 203 The bibliographic databases MEDLINE (Pubmed interface), ISI Web of Science (WoS; Clarivate
29
30 204 Analytics interface), and the Cochrane Central Register of Controlled Trials (CENTRAL; OVID
31
32 205 interface) will be searched systematically. In addition, we will also carry out a systematic search for
33
34 206 previous systematic reviews in the Cochrane Database of Systematic Reviews (CDRS, OVID
35
36 207 interface) and KRS Evidence (<https://ksevidence.com>), which are both specialized search engines
37
38 208 for systematic reviews. RCTs included in meta-analyses on the topics vitamin D supplementation
39
40 209 and cancer mortality, cancer incidence, all-cause mortality, or cancer survival will be extracted and
41
42 210 merged with the hits found in the bibliographic database search. The electronic database search will
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44 211 be complemented by searching the WHO's International Clinical Trials Research Portal (ICTRP) to
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46 212 capture results from ongoing or recently completed RCTs that have not been published in scientific
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48 213 journals, yet. We will also scan the reference lists of eligible studies to yield additional trial articles
49
50 214 via cross-referencing. A draft of the search strategy is presented in Figure 1.

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54 215 We will search in MEDLINE, ISI WoS, and CENTRAL for medical subject headings (MeSH), free text
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56 216 words, synonyms, and related search terms for the concepts "vitamin D", "mortality", "cancer",
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58 217 "randomized controlled trial" and "placebo". Besides, standard search terms for RCTs will be used
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60 218 additionally wherever available. No restrictions are planned in the search strategy to prevent

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2 219 overlooking important studies that have not been correctly classified in the respective bibliographic
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4 220 databases. All databases will be searched from inception dates. Moreover, we will not limit the
5
6 221 search to studies in English as relevant studies might also be published in other languages. The
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8 222 search string for MEDLINE is shown in Table 3.

11 223 **Table 3:** Search string for MEDLINE

Step	Search string
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 calciol[tw] OR alfalcidol[Supplementary Concept] OR alphacalcidol[tw] OR alfalcidol[tw]
2	mortality[tw] OR mortality[MeSH] OR death[MeSH] OR death[tw] OR survival[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	(((((("randomized controlled trial"[pt]) OR "controlled clinical trial"[pt]) OR randomized[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

34 224
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37 225 To search for systematic reviews in CDSR and KRS Evidence, a shortened version of the MEDLINE
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39 226 search string will be used. Only the first three search steps are needed because the study design is
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42 227 "systematic review" and not "placebo-controlled RCT". The search string for CDSR is shown in Table
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44 228 4. The literature search will be updated during the peer-review process of the publication in order to
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46 229 include the most up to date literature.

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Table 4: Search string for the Cochrane Database of Systematic Reviews

Step	Search string
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 {OR #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 "death" OR "survival") (Word variations have been searched) #13 {OR #9-#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)

Data collection and management

Study selection and data extraction will be performed in duplicate by two reviewers. Both are blinded to each other's decision but not to journal titles, study authors, or institutions. The screening will be conducted by entering data into blank Microsoft Word or Excel spreadsheets. The software EndNote will be used to store, organize, and manage all the references and allow a transparent and reproducible systematic search. To assure validity and high quality of the data, the data extraction will be performed by using standard and predefined data extraction forms. Both reviewers will scan independently the titles and abstracts of studies obtained by the aforementioned search strategy against the eligibility criteria. For those studies that meet the inclusion criteria or that cannot yet be fully excluded, full-text reports will be acquired and screened again towards the inclusion criteria. In

1
2 243 the next step, the results of both reviewers will be compared and in cases of disagreement, critical
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4 244 points will be discussed until a consensus is reached. If necessary, we will contact study authors to
5
6 245 resolve questions about eligibility. We will document the reasons for excluding trials.
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9 246 After completing the abstract and full-text selection with eligible studies, the two reviewers will extract
10
11 247 independently the pre-defined data. Extracted items will include first author, publication year,
12
13 248 country, number of participants, general population or medical condition (including cancer site and
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15 249 stage(s)), sex, mean/median age, race/ethnicity/skin color, mean/median BMI, mean/median
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17 250 25(OH)D levels at baseline, vitamin D₃ dosing regimen, duration of vitamin D₃ supplementation,
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20 251 compliance, mean/median and maximum follow-up time, number of cancer deaths and effect
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22 252 estimates (including confidence intervals) reported for cancer mortality/cancer survival. Individual
23
24 253 patient data for the aforementioned variables will be obtained from all trials with at least 20 cancer
25
26 254 deaths. If summary data are not published, they shall be calculated from the obtained data. All
27
28 255 authors will be contacted by e-mail with a maximum of three attempts sent with two weeks apart.
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31 256 For the meta-analyses on cancer survival and cancer-specific survival, we will ask all authors who
32
33 257 conducted trials in the general population to provide IPD for cancer diagnoses in the five years prior
34
35 258 to baseline and during the trial (including cancer site with ICD-code, stage and diagnosis date). The
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37 259 following IPD will be additionally collected: age, sex, BMI, race/ethnicity/skin color, baseline 25(OH)D
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40 260 levels, compliance, randomization group allocation, baseline date, deaths during follow-up with date,
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42 261 cancer deaths with date, censoring dates for survival outcomes, and censoring date for patients not
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44 262 dying of cancer. If IPD cannot be shared, the authors of the studies will be asked to conduct the
45
46 263 analyses in-house and to provide the summary estimates for the meta-analysis. If trial authors do
47
48 264 not collaborate, their study cannot be included in subgroup analyses for which no effect estimates
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50 265 were published but the result from the total trial population will remain included in the main meta-
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52 266 analysis.
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Quality assessment

The protocol of the systematic review with all planned statistical analyses has been registered in PROSPERO before data collection to preclude data-driven analyses and selective reporting of only statistically significant findings. The study protocol has been developed in line with the “Preferred reporting items for systematic review and meta-analysis protocols” (PRISMA-P) as well as the Institute of Medicine guideline.(20-22) We will ensure to fulfill all requirements recommended by the current PRISMA guideline when writing the publication of the systematic review.(23, 24)

The Cochrane Collaboration’s tool for assessing risk of bias (table 8.5.a in the Cochrane Handbook for Systematic Review of Interventions) will be used to assess selection, performance, detection, attrition, reporting and other bias at study level.(25, 26) The following domains will be covered during the evaluation: sequence generation, allocation concealment, blinding, incomplete outcome data (e.g. withdrawals and dropouts), and selective outcome reporting. A summary assessment will be made based on the extracted items, judging whether the risk of bias in the respective study is low or high. If only insufficient data is reported, the risk of bias is “unclear” and the original study authors will be contacted for further information. The assessment will be conducted by two independent reviewers based on the criteria for judging the risk of bias (table 8.5.d in the Cochrane Handbook for Systematic Review of Interventions V.6).(26) In cases of disagreement, critical points will be discussed until a consensus is reached. The risk of bias evaluation will be incorporated into the data synthesis by performing a sensitivity analysis by excluding studies of low or unclear quality.

Descriptive analysis and meta-analysis

Measures of treatment effect

The mortality/survival outcomes shall be addressed by estimating hazard ratios (HR) and 95% confidence intervals (95%CI). Results of the intention-to-treat (ITT) approach will be used, including all patients randomized, if both ITT and per-protocol results are given.

1
2 293 Data synthesis

3
4
5 294 As far as study quality and differences between studies allow, effect estimates of all eligible studies
6
7 295 with data for the following three main meta-analyses will be pooled deriving random effects results
8
9 296 with the DerSimonian and Laird method (primary analysis) and fixed effects summary estimates
10
11 297 using the Mantel-Haenzel method (secondary analysis).

- 12
13 298 1) Association of vitamin D₃ supplementation and cancer mortality in the general population
14
15 299 2) Association of vitamin D₃ supplementation and cancer-specific survival of cancer patients
16
17 300 3) Association of vitamin D₃ supplementation and overall survival of cancer patients

18
19
20 301 For all studies that provide IPD, unadjusted Cox proportional hazard regression models will be used
21
22 302 to estimate HRs and 95% CIs for the main meta-analyses in which we will pool effect size data from
23
24 303 studies who do and who do not provide IPD in a two-step approach. For studies that cannot send
25
26 304 IPD to the coordinating center (German Cancer Research Center, Heidelberg), authors are being
27
28 305 asked to estimate the HRs and 95% CIs themselves and send the summary data for the meta-
29
30 306 analyses. To assess cancer survival as time-to-event data from general population cohorts, the study
31
32 307 will be restricted to patients with a history of cancer in the five years preceding baseline or a cancer
33
34 308 diagnosis during the trial. For the former, the survival time will be calculated from baseline to
35
36 309 death/end of the trial, and for the latter, survival time will be counted from the date of cancer diagnosis
37
38
39 310 till death/end of the trial.

40
41
42 311 With all studies that agree to send IPD data to the coordinating center or to do additional analyses
43
44 312 in-house, we will also conduct an additional multivariate Cox proportional hazards regression model.
45
46 313 The model for the outcome cancer mortality among general population studies will contain the
47
48 314 variables vitamin D₃ intervention (vs. placebo), age (continuous; < 70 vs. ≥ 70 years), sex (male,
49
50 315 female, unknown), BMI (< 25 vs. 25 – 29.9 vs. ≥ 30 kg/m² vs. unknown), skin color (white vs.
51
52 316 black/brown vs. other), 25(OH)D baseline level (< 30 vs. 30 – 49.9 nmol/L vs. ≥ 50 nmol/L vs.
53
54 317 unknown), diagnosis of cancer (except non-melanoma skin cancer) in five years before baseline
55
56 318 (yes vs. no vs. unknown), and compliance (< 80% vs. ≥ 80% vs. unknown). The models for the
57
58
59 319 outcomes overall and cancer-specific survival of cancer patients will be adjusted for the same
60
320 variables but the cancer variable will be replaced by more specific variables for cancer stage (only

1
2 321 advanced stages III and/or IV vs. unknown), cancer site (prostate vs. colorectal vs. breast vs. lung
3
4 322 vs. other vs. unknown) and time since cancer diagnosis (<1 year vs. 1-5 years). We will test for
5
6 323 interactions of the treatment variable (vitamin D₃ vs. placebo) with these covariates to identify
7
8 324 potential effect modifiers. Again, a two-step approach will be used for the meta-analyses, whereby
9
10 325 the analyses are carried out on a study-specific basis, and then the effect estimates are pooled. To
11
12 326 further explore the variation of the treatment effect by methodological or patient characteristics
13
14 327 differences of the studies, the following subgroup analyses will be performed with IPD data and
15
16 328 studies that published eligible data:

17 329 Subgroup analyses according to trial design

- 22 330 - Daily dose vs. weekly/monthly bolus dose vs. bolus dose at the beginning of the trial followed
23
24 331 by a daily dose
- 26 332 - Low vs. moderate vs. high vitamin D₃ dosing (< 1000 IU vs. 1,000 – 2,000 IU vs. > 2,000 IU
27
28 333 per day or equivalent weekly or monthly taken dose)
- 30 334 - Vitamin D₃ supplementation duration (< 5 vs. ≥ 5 years)
- 32 335 - Region (North America vs. Europe vs. Other)

35 336 Subgroup analyses according to patient characteristics

- 38 337 - Age (< 70 vs. ≥ 70 years)
- 39
40 338 - Sex (Male vs. female)
- 42 339 - Skin color (white vs. black/brown vs. other)
- 43
44 340 - BMI (< 25 vs. 25 – 29.9 vs. ≥ 30 kg/m²)
- 45
46 341 - Baseline 25(OH)D levels (< 30 vs. 30 – 49.9 nmol/L vs. ≥ 50 nmol/L)
- 47
48 342 - Compliance rate (< 80% vs. ≥ 80%)

51 343 For meta-analyses conducted in cancer patients in addition:

- 53 344 - Cancer stage (mix of all stages vs. only advanced stages III and/or IV)
- 55
56 345 - Cancer site (Prostate vs. colorectal vs. breast vs. lung vs. other)
- 57
58 346 - Time since cancer diagnosis (<1 year vs. 1-5 years)

1
2 347 Analyses in the coordinating center will be done with the statistical software SAS 9.4. The meta-
3
4 348 analyses will be performed with Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ).

5
6
7 349 Assessment of heterogeneity

8
9
10 350 Heterogeneity will be presented visually by forest plots and assessed statistically by Cochran's Q
11
12 351 test (significance level = 0.05) as well as the I^2 index (< 25% low, 25-50% moderate, > 50% high
13
14 352 heterogeneity). Meta-Analyses will be conducted even if high heterogeneity is being detected and
15
16 353 the results will be discussed taking the heterogeneity into consideration. Sources of heterogeneity
17
18
19 354 will be explored by the subgroup analyses outlined in the previous section and the following
20
21 355 sensitivity analyses:

- 22
23 356 - Excluding studies with a high risk of bias according to assessment with the Cochrane
24
25 357 Collaboration's tool
26
27 358 - Excluding studies not reporting ITT results
28
29 359 - Excluding trials with co-supplementation of calcium
30
31

32 360 Assessment of publication bias

33
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35 361 Publication bias will be accessed visually in funnel plots and tested for with Egger's test.
36
37

38 362 Dealing with missing data

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41
42 363 In case of missing data, we will seek contact with the original investigators. If possible, we will
43
44 364 calculate missing numerical data from the given reported data.
45
46

47 365 Strength of the body of evidence

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49
50 366 The quality of the evidence for each outcome will be evaluated using the Grading of
51
52 367 Recommendations Assessment, Development and Evaluation (GRADE) approach. The four levels
53
54 368 of evidence comprise very low, low, moderate, and high. Evidence from RCTs starts as high quality
55
56 369 but can be decreased for reasons such as the risk of bias, imprecision, inconsistency, indirectness,
57
58 370 and publication bias.
59
60

371 **Amendments**

372 In the case of protocol amendments, we will document the date, the description of the change and
373 the rationale in a pre-defined log sheet in Microsoft Word or Excel.

375 **Patient and public involvement**

376 Patients and the public were not involved in the development of the study design. Since this is a
377 protocol for a systematic review and no participant recruitment will take place, the involvement of
378 patients in the recruitment, the conduct of the study and the dissemination of findings to study
379 participants are not applicable.

381 **Dissemination**

382 The systematic review will be published in an international journal for clinical oncology or general
383 medicine with open access option and presented in national and international meetings. If the meta-
384 analyses of the systematic review obtain statistically significant findings, we expect the result to be
385 reflected in national and international guidelines and to change the current practice of tertiary
386 prevention among cancer patients. Vitamin D₃ is already on the market in various doses and at low
387 costs because it is not patented.

388 Patients will be informed via a press release from the German Cancer Research Center. Moreover,
389 we will send a summary of the results in a language suitable for laypersons to all patient advocacy
390 groups recommended by the Cancer Information Service of the German Cancer Research Center
391 (up to data n = 30) for further dissemination among their members.(27) With respect to oncologists,
392 we will disseminate the results to all German rehabilitation centers with a ward for oncologic
393 rehabilitation, as listed in the register of the *Bundesarbeitsgemeinschaft für Rehabilitation e.V.*(28)
394 As the topic of the review is in the field of tertiary prevention, oncologists in the rehabilitation setting
395 are the target audience for information dissemination.

1
2 396 **DISCUSSION**

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5 397 One of the strengths of this systematic review comprises the first meta-analysis on vitamin D
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7 398 supplementation and cancer survival and additionally the first IPD meta-analysis on this research
8
9 399 topic. The IPD meta-analysis will allow the investigation of potential effect modifiers. Especially
10
11 400 25(OH)D levels at baseline, BMI, and compliance are candidates that could have had a great impact
12
13 401 on the overall trial results.

14
15
16 402 The creation of this research protocol prompted us to plan carefully all the details of the systematic
17
18 403 review and to anticipate and address potential problems before their actual occurrence. Arbitrary
19
20 404 decision making concerning any procedure of this systematic review is prevented, resulting again in
21
22
23 405 a decreased risk of publication bias and selective reporting bias. The protocol allows reproducible
24
25 406 and transparent research for future reviewers.

26
27
28 407 Possible limitations of our review include a potentially insufficient number of cancer deaths in the
29
30 408 studies and high heterogeneity, which could both negatively influence the statistical power of the
31
32 409 meta-analyses. However, it is too early now to judge if these limitations will really occur.

33
34
35 410 The quality of selected studies will be assessed and the quality of the evidence will be judged. The
36
37 411 ultimate goal is to ensure the reporting of highly meaningful findings for clinicians and patients.
38
39 412 Oncologists are well aware that vitamin D deficiency and insufficiency are very common in cancer
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41 413 patients but there is uncertainty about whether and how they should routinely perform preventive
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43
44 414 screening and treatments. In some clinics, all cancer patients receive low-dose vitamin D with a “one
45
46 415 dose fits all” approach, which does not take individual 25(OH)D levels of the patients into account.
47
48 416 Since vitamin D products are readily available in pharmacies or drug stores, many patients use low-
49
50 417 dose vitamin D supplementation as self-medication. Yet, it can be doubted whether this untargeted
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52 418 intervention has any effect on cancer prognosis. Consequently, evidence-based recommendations
53
54 419 for high-dose vitamin D supplementation are highly relevant for both, clinicians and patients.

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56
57 420 If the planned systematic review determines the efficacy of vitamin D supplementation on cancer
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59 421 prognosis in the expected magnitude of 10-15%, the review will be used to provide clear suggestions

1
2 422 on how vitamin D can be appropriately dosed to overcome vitamin D deficiency or insufficiency in
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4 423 cancer patients.(12) Furthermore, our systematic review would provide the evidence for statutory
5
6 424 health insurances to cover the costs for screening for vitamin D deficiency or insufficiency in cancer
7
8 425 patients and a subsequent vitamin D supplementation. With expected relatively large effects and
9
10 426 very low screening and treatment costs (a vitamin D blood test costs approx. € 20, and one year of
11
12 427 vitamin D therapy costs less than € 100), vitamin D supplementation will be highly cost-effective.
13
14 428 The costs would be close to negligible compared to other current cancer treatment costs.

16 17 429 18 19 430 **Status**

20
21 431 At the time of submission, the study selection for the systematic review has not started.
22
23 432

24 25 433 **Acknowledgements**

26
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28
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30
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32 33 437 34 35 438 **Authors' contribution**

36
37 439 BS and SK are the guarantors of the systematic review. BS designed the search strategy, the
38
39 440 selection criteria, the risk of bias assessment strategy, the data extraction criteria, and the statistical
40
41 441 methods. SK drafted the first version of the protocol publication, which BS and HB revised.
42
43 442

44 45 443 **Contributors**

46
47 444 The following researchers have agreed to contribute to this systematic review by sharing IPD and
48
49 445 giving intellectual input for the discussion of the results: Taisuke Akutsu (Jikei University School of
50
51 446 Medicine. Tokyo, Japan), professor Julie E. Buring (ScD. Brigham and Women's Hospital and
52
53 447 Harvard Medical School. Boston), Professor Carlos A. Camargo Jr (MD, DrPH. Massachusetts
54
55 448 General Hospital, Harvard Medical School. Boston), Professor Nancy R. Cook (ScD. Brigham and
56
57 449 Women's Hospital and Harvard Medical School. Boston), professor I-Min Lee (MB, BS, ScD.
58
59 450 Brigham and Women's Hospital and Harvard Medical School. Boston), Professor JoAnn E. Manson

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7
8 454 Zealand), professor Mitsuyoshi Urashima (MD. Jikei University School of Medicine. Tokyo, Japan),
9
10 455 professor Jean Wactawski-Wende (PhD. University at Buffalo. Buffalo, New York).

11
12 456

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20
21 460 a role in the design of the review protocol, data collection, data analyses, the interpretation of results,
22
23 461 or the decision about the publication of the results.

24
25 462

26 27 463 **Data availability statement**

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29 464 As no new data are obtained in this systematic review, no data will be made publicly available to
30
31 465 third parties. Decisions on data use by third parties can only be made by the principal investigators
32
33 466 of the original studies, taking into account the votes of the responsible ethics committees.

34
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37 467

38 468 **Disclaimer**

39
40 469 The views of the authors do not necessarily reflect those of the German Cancer Research Center.

41
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43 470

44 45 471 **Competing interests**

46
47 472 None declared.

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50 51 474 **Patient consent for publication**

52
53 475 Not required.

54
55 476

56 57 477 **Provenance and peer review**

58
59 478 Not commissioned; externally peer-reviewed

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2 563 **Appendix 1:**
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4 564 Supplementary material consisting of data extraction form, risk of bias assessment and list of
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7 565 individual patient data to be obtained from original researchers
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Figure

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Figure 1: Draft of the search strategy and study selection process

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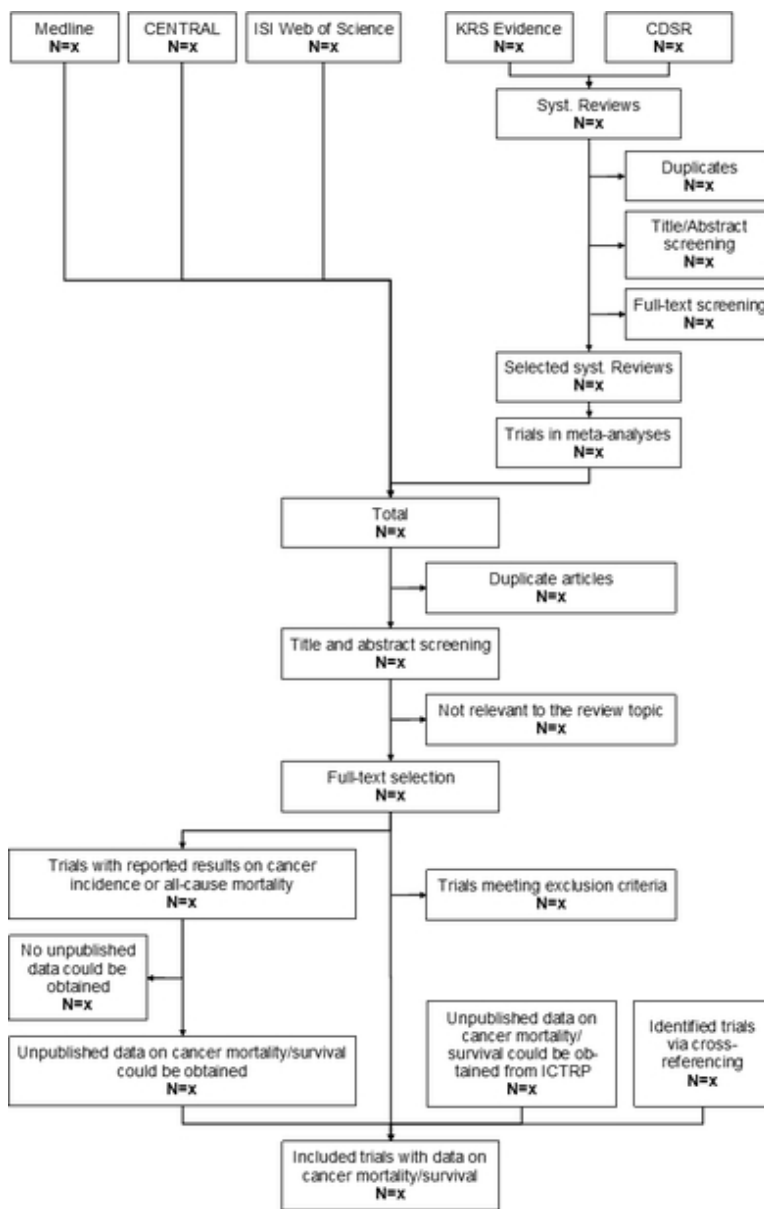


Figure 1: Draft of the search strategy and study selection process

16x25mm (600 x 600 DPI)

Appendix 1 -Data Extraction Form

Table A1 - Extraction of data from publications

Study			Population								Intervention		
First author (or study name), Year (REF)	Country	Sample size	General population (y/n)	Cancer population (y/n)	Cancer site + stage	Age (mean or median)	Sex (female %)	Race/ ethnicity/ skin color (white %)	BMI [kg/m ²] (n, mean or median)	25(OH)D (n, mean or median)	Vitamin D ₃ dosing regimen	Duration of vitamin D ₃ supplementation	Compliance in intervention group (%)

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Comparator		Outcomes							Comments
Placebo (y/other)	Compliance in comparator group (%)	Maximum follow-up time	Mean or median follow-up time	No of cancer deaths	Cancer mortality in general population HR (95% CI)	Cancer-specific survival of cancer patients HR (95% CI)	Overall survival of cancer patients HR (95%CI)	Covariates adjusted for	

Table A2 - Risk of Bias Assessment

First author (or study name), Year (REF)	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias

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Table A3 - Variables to be obtained for all trial participants in order to conduct the IPD meta-analysis

No.	Variables
1	Age
2	Sex
3	BMI
4	Race/ethnicity/skin color
5	Baseline 25(OH)D levels
6	Compliance
7	Randomisation group allocation
8	Baseline date
9	Death during follow-up (y/n)
10	Date of death
11	Censoring date for survivors
12	Cancer death during follow-up (y/n)
13	Date of cancer death
14	Censoring date for non-cancer deaths
15	Cancer* diagnosis during follow-up (y/n)
16	Cancer* site for each cancer during follow-up
17	Cancer* stage for each cancer during follow-up
18	Date of cancer* diagnosis for each cancer during follow-up
19	Cancer* diagnosis in first 5 years before baseline (y/n)
20	Cancer* site for each cancer in first 5 years before baseline
21	Cancer* stage for each cancer in first 5 years before baseline
22	Date of cancer* diagnosis for each cancer in first 5 years before baseline

* Excluding non-melanoma skin cancers

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n.a. (first submission)
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	63-66
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-34
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	438-441
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	371-373
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	457-461
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	457-461
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	459-461
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	77-123
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	125-141
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	148-188
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	198-231, 256-266
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	198-231, 223-224, 230-231, 566-569
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	233-266
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	234-245
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	246-255, 362-364, 563-565
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	289-292, 362-364
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	126-139, 172-178, table 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	268-286, 365-370
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	294-300
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	301-328, 347-348, 349-359
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	329-346, 353-359
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n.a. (quantitative)

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					synthesis will be performed)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	360-361, 402-406
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	365-370

For peer review only

BMJ Open

Efficacy of Vitamin D3 supplementation on cancer mortality in the general population and the prognosis of cancer patients: Protocol of a systematic review and individual patient data meta-analysis of randomized controlled trials

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Primary Subject Heading:	Patient-centred medicine
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Keywords:	Nutritional support < ONCOLOGY, ONCOLOGY, NUTRITION & DIETETICS, PUBLIC HEALTH, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < ONCOLOGY

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3 1 **Efficacy of Vitamin D₃ supplementation on cancer mortality in the**
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5 2 **general population and the prognosis of cancer patients: Protocol of a**
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7 3 **systematic review and individual patient data meta-analysis of**
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9 4 **randomized controlled trials**
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11 5

12 6 Ben Schöttker^{1,2*}, Sabine Kuznia^{1*}, Hermann Brenner¹⁻⁴
13 7

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32 20 preparation of the manuscript.
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37 **ABSTRACT**

38 **Introduction**

39 Vitamin D insufficiency is much more common among cancer patients than the general population.
40 Previous meta-analyses of controlled trials showed an approximately 15% reduction of cancer
41 mortality by vitamin D supplementation compared to placebo or no treatment in the general
42 population.

43 On top of updating the latest systematic review on vitamin D supplementation and cancer mortality
44 in the general population, we aim to conduct the first meta-analyses of trials on vitamin D₃
45 supplementation and cancer-specific and overall survival of cancer patients. Besides, we will conduct
46 for the first time subgroup analyses based on individual patient data collected from randomized
47 controlled trials.

48 **Methods and analysis**

49 A systematic review and individual patient data meta-analysis will be performed on randomized
50 placebo-controlled trials with a vitamin D₃ intervention. The addressed outcomes are cancer mortality
51 in the general population as well as cancer-specific and overall survival of cancer patients. The
52 quality appraisal of the studies will be evaluated by the Cochrane risk-of-bias tool for randomized
53 trials. Trial results will be re-analyzed using adjusted and unadjusted Cox proportional hazard
54 regression models and meta-analyses are planned. Cochran's Q-Test and the I² index will be used
55 to statistically assess the level of heterogeneity, while sensitivity and subgroup analyses serve to
56 identify potential causes of heterogeneity. Subgroup analyses will be conducted for vitamin D₃
57 dosing, follow-up time, age, sex, obesity, vitamin D deficiency/insufficiency, history of cancer, and
58 compliance. Publication bias will be assessed by funnel plots and Egger's test.

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2 **59 Ethics and dissemination**
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5 60 Ethical approval is not required since no human beings are involved in this systematic review.
6

7 61 Results will be published in a peer-reviewed journal with open access. They will be presented at
8
9 62 conferences and sent to patient advocacy groups and German oncologic rehabilitation centers.
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12 **63 PROSPERO registration number**
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15 64 CRD42020185566
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18 **65 Keywords**
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21 66 Vitamin D, cancer, mortality, systematic review, meta-analysis
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27 **68 Strengths and limitations of this study**
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30 69 • First meta-analysis on vitamin D₃ supplementation and cancer survival as well as first individual
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32 70 patient data meta-analysis on this research topic.
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35 71 • Results of subgroup analyses based on individual patient data allow fundamental insights for
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37 72 personalized medicine and may be used as guidance for future clinical trials targeting cancer
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39 73 patients that presumably profit most from vitamin D supplementation
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42 74 • Conduction of the systematic review according to this protocol and a thorough assessment of
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44 75 study quality, sources of heterogeneity, and bias in meta-analyses minimize the risk of bias and will
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46 76 gather reproducible results.
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50 77 • Number of studies with eligible data for subgroup analyses may be limited.
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78 INTRODUCTION

79 Background

80 The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths
81 in 2018.(1) There is accumulating evidence from epidemiological studies that a low vitamin D status
82 goes along with increased risks of several types of cancer. Meta-analyses of observational studies
83 reported increased risks of lung cancer, colorectal cancer, breast cancer, bladder carcinoma, and
84 lymphoma in subjects with low 25(OH)D serum concentrations.(2-5) Furthermore, epidemiological
85 studies have shown that low serum levels of 25-hydroxyvitamin D (25(OH)D), the acknowledged
86 best biomarker to measure vitamin D status, were strongly associated with substantially increased
87 cancer mortality.(6) For example, in a German population-based cohort study of older adults, the
88 risk to die of cancer was increased by 42% in study participants with vitamin D deficiency (defined
89 as 25(OH)D < 30 nmol/L) compared to individuals with sufficient 25(OH)D levels > 50 nmol/L (hazard
90 ratio [HR] and 95% confidence interval (95%CI): 1.42 [1.08; 1.87]).(7)

91 The molecular links between vitamin D and carcinogenesis and progression have been previously
92 described.(8) In brief, genomic mechanisms of the active hormone 1,25(OH)₂D impact signaling
93 pathways that regulate cell proliferation, differentiation, and cell survival. 1,25(OH)₂D may primarily
94 act as an anti-proliferative agent in many tissues and may slow down malignant cellular growth.
95 Thus, there is biological plausibility that a sufficient vitamin D supply is especially essential for a
96 good cancer prognosis. A causal relationship of low 25(OH)D levels and cancer mortality was
97 furthermore supported by a Mendelian randomization study conducted within three large cohorts
98 from Denmark.(9)

99 Several randomized trials with vitamin D supplementation have been conducted with mostly the aim
100 to improve skeletal outcomes at older ages. Cancer mortality was a secondary outcome in all trials
101 and therefore the trials were not specifically designed for this outcome.(10) Despite strong
102 heterogeneity in study populations, intervention schemes, and other important design aspects, three
103 out of four meta-analyses demonstrated a statistically significant reduction in cancer mortality.(11-
104 15)

1
2 105 However, most trials have not been restricted to patients that were vitamin D deficient.(10) The latter
3
4 106 is important because the association of 25(OH)D levels and adverse health outcomes is not linear.(6)
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6 107 Neglecting this dose-response relationship by treating subjects without hypovitaminosis D is
7
8 108 expected to have led to a substantial underestimation of the potential efficacy of vitamin D
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10 109 supplementation in previous clinical trials.(16) Therefore, there is a need for a systematic review that
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12 110 re-analyses individual patient data (IPD) from previous trials restricted to subjects with vitamin D
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14 111 insufficiency (25(OH)D < 50 nmol/L) or deficiency (25(OH)D < 30 nmol/L).
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18 112 Another important reason to re-analyze the previous trial data is that most studies were not restricted
19
20 113 to cancer patients. Vitamin D deficiency or insufficiency are much more common among cancer
21
22 114 patients than among the general population. In a study with 2,912 colorectal cancer patients, vitamin
23
24 115 D deficiency (25(OH)D levels < 30 nmol/L) was found among 59% of colorectal cancer patients
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26 116 during or shortly after first-line treatment, and, in agreement with previous evidence, low 25(OH)D
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28 117 levels were strongly associated with poorer survival.(17, 18) Systematic reviews of observational
29
30 118 studies on 25(OH)D levels and cancer prognosis concluded that sufficient 25(OH)D levels are
31
32 119 associated with a better prognosis of breast and colorectal cancer, whereas there are too few studies
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34 120 for other cancer sites up to date to draw conclusions.(17, 19)
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38 121 Further important potential effect modifiers that deserve close investigation are obesity and
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40 122 compliance. People with low compliance and/or obesity, who may need higher vitamin D doses
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42 123 because vitamin D is stored in adipocytes, might have attenuated the overall treatment effect in the
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44 124 trials.(20)
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50 126 **Objective**

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53 127 The objective of our systematic review is to assess the efficacy of vitamin D₃ supplementation on
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55 128 cancer mortality in the general population and the prognosis of cancer patients with special attention
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57 129 to potential effect modifiers, including baseline 25(OH)D levels, cancer at baseline, BMI and
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59 130 compliance.
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2 131 The main outcomes include “cancer mortality in the general population”, “cancer-specific survival of
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4 132 cancer patients” and “overall survival of cancer patients”. These outcomes are universally used in
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6 133 cancer studies and do not need further refinement during the review.
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9 134 In a first step, we intend to update the previous systematic reviews on vitamin D supplementation
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11 135 and cancer mortality in the general population by including newly published trials and unpublished
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13 136 data from trials with outcome data on cancer incidence or all-cause mortality by asking the authors
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15 137 for data on cancer mortality. Second, we will obtain data for an IPD meta-analysis. Third, we will
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18 138 conduct IPD meta-analyses on vitamin D₃ supplementation and overall and cancer-specific survival
19
20 139 among cancer patients. Forth, we will conduct subgroup analyses to explore sources of
21
22 140 heterogeneity and to identify effect modifiers. The timetable for the review is shown in Table 1.
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24

25 141 **Table 1:** Proposed timetable for conducting the review
26

Step	Timeframe for completion
Literature search, abstract and full-text selection	2.5 months
Data extraction & individual patient data acquisition	2.5 months
Quality appraisal	2 months
Data analysis & meta-analysis	3 months
Writing of manuscript	2 months
Total	12 months

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42 143 **METHODS AND ANALYSIS**

43 44 45 144 **Study selection criteria/ Eligibility criteria**

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49 145 We will follow a two-step approach for the study selection: First, all trials will be selected that could
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51 146 potentially have published or unpublished data on the research topic. All authors of trials with
52
53 147 potentially unpublished data on cancer mortality/survival will be contacted to provide data. In the
54
55 148 second step, only trials with eligible data for a meta-analysis will be included.
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Step 1: Inclusion criteria for trials

Participants: We will include studies investigating the adult population (18 years or older). We will also include studies conducted solely with cancer populations or patients with other conditions (e.g. studies that recruited only patients with type 2 diabetes).

Interventions: We will focus on trials that used vitamin D₃ in any dose and any regimen (e.g. daily/weekly/monthly intake) as the intervention. However, the minimum time of the intervention shall be six months to exclude studies with one-time bolus interventions or very short intervention periods. The first reason is that cancer mortality is highly unlikely to be influenced by very brief intervention periods. The second reason is that after initiating daily, weekly, or monthly supplementation schedules, it takes three to six months for 25(OH)D levels to reach homeostasis.

Besides, we will also include studies using vitamin D₃ bioequivalent substances such as calcitriol, being the active vitamin D hormone 1,25(OH)₂D, as well as alfacalcidol and calcifediol, which are both equally metabolized to 1,25(OH)₂D.

We will exclude studies with vitamin D₂ supplementation since the Cochrane review of Bjelakovic et al. and other recent data showed clearly no efficacy on mortality.(10, 11, 15, 21) Co-supplementation with calcium or other dietary supplements in the intervention arm will not be an exclusion criterion. A sensitivity analysis will elucidate whether the inclusion of these studies had an impact on the overall effect estimate of the meta-analysis.

Comparators: We will include only studies, which used placebo as the comparator.

Outcomes: To be eligible for inclusion in a meta-analysis trials need to have assessed the outcome of cancer mortality, cancer survival, or cancer-specific survival. In an intermediate step of the systematic review, we will also record studies with the outcomes of cancer incidence or all-cause mortality and contact the authors if they have data for the outcomes needed for the planned meta-analyses. The definitions of all outcomes are shown in Table 2.

Table 2: Definition of outcomes

Outcome	Definition
All-cause mortality	Rate of deaths during a specific time period in population at risk
Cancer mortality	Rate of cancer deaths during a specific time period in population at risk
Cancer incidence	Rate of newly diagnosed cancer cases during a specific time period in population at risk
Overall cancer survival	Proportion of patients from a cancer population at risk alive at some point subsequent to the diagnosis of their cancer
Cancer-specific survival	Proportion of patients from a cancer population at risk who did not die of cancer at some point subsequent to the diagnosis of their cancer

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Study design: We will include RCTs in which, analogous to the intervention period, the follow-up period is at least six months. The follow-up time should not be longer than the time under treatment. We will focus on parallel-group designs and exclude single-arm studies. We will further exclude all types of cohort studies and case-control studies as well as the following types of records: reviews, dissertations, theses, editorials, study protocol, clinical guidelines, commentaries, and letters.

Setting: There will be no restrictions by type of setting.

Minimum sample size: The studies need to have at least one cancer death in the verum and placebo group.

Geographical location: No restrictions are defined regarding the geographical location.

Step 2: Inclusion criteria for pooling in meta-analysis

Studies will be included for pooling in the meta-analysis, if the risk ratio and 95% confidence interval for at least one outcome of interest (cancer mortality in the general population, cancer-specific survival of cancer patients, or overall survival of cancer patients) were either reported in the publication or could be obtained from authors or individual participant data. In the case of double publication from the same trial, only the publication with the largest amount of information, e.g. the longest follow-up, will be included in the meta-analysis.

192 Information sources and search strategy

193 The search strategy will be elaborated by SK, BS, and A Heppert. Mrs. Heppert is a specialist for
194 systematic bibliographic searches at the Central Library of the German Cancer Research Center
195 and is not otherwise associated with the project. Finally, it will be peer-reviewed by HB and carried
196 out by SK.

197 The bibliographic databases MEDLINE (Pubmed interface), ISI Web of Science (WoS; Clarivate
198 Analytics interface), and the Cochrane Central Register of Controlled Trials (CENTRAL; OVID
199 interface) will be searched systematically. We will also carry out a systematic search for previous
200 systematic reviews in the Cochrane Database of Systematic Reviews (CDRS, OVID interface) and
201 KSR Evidence (<https://ksevidence.com>), which are both specialized search engines for systematic
202 reviews. RCTs included in meta-analyses on the topics vitamin D supplementation and cancer
203 mortality, cancer incidence, all-cause mortality, or cancer survival will be extracted and merged with
204 the hits found in the bibliographic database search. The electronic database search will be
205 complemented by searching the WHO's International Clinical Trials Research Portal (ICTRP) and
206 clinicaltrials.gov to capture results from ongoing or recently completed RCTs that have not been
207 published in scientific journals, yet. We will also scan the reference lists of eligible studies to yield
208 additional trial articles via cross-referencing. A draft of the search strategy is presented in Figure 1.

209 We will search in MEDLINE, ISI WoS, and CENTRAL for medical subject headings (MeSH), free text
210 words, synonyms, and related search terms for the concepts "vitamin D", "mortality", "cancer",
211 "randomized controlled trial" and "placebo". Besides, standard search terms for RCTs will be used
212 additionally wherever available. No restrictions are planned in the search strategy to prevent
213 overlooking important studies that have not been correctly classified in the respective bibliographic
214 databases. All databases will be searched from inception dates. Moreover, we will not limit the
215 search to studies in English as relevant studies might also be published in other languages. The
216 search string for MEDLINE is shown in Table 3.

1
2 217 **Table 3:** Search string for MEDLINE

Step	Search string
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	(((((("randomized controlled trial"[pt]) OR "controlled clinical trial"[pt]) OR randomized[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

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28 219 A shortened version of the MEDLINE search string will be used to search for systematic reviews in
29
30 220 CDSR and KSR Evidence. Only the first three search steps are needed because the study design is
31
32 221 "systematic review" and not "placebo-controlled RCT". The search string for CDSR is shown in Table
33
34 222 4. The literature search will be updated during the peer-review process of the publication in order to
35
36
37 223 include the most up to date literature.

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39
40 224 **Table 4:** Search string for the Cochrane Database of Systematic Reviews

Step	Search string
1	<p>#1 MeSH descriptor: [Vitamin D] explode all trees</p> <p>#2 MeSH descriptor: [Cholecalciferol] explode all trees</p> <p>#3 MeSH descriptor: [Calcifediol] explode all trees</p> <p>#4 MeSH descriptor: [Calcitriol] explode all trees</p> <p>#5 MeSH descriptor: [Hydroxycholecalciferols] explode all trees</p> <p>#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)</p> <p>#7 ("vitamin d*"):ti,ab,kw (Word variations have been searched)</p> <p>#8 {OR #1-#7}</p>
2	<p>#9 MeSH descriptor: [Mortality] explode all trees</p> <p>#10 MeSH descriptor: [Death] explode all trees</p> <p>#11 MeSH descriptor: [Survival] explode all trees</p>

60

	#12	("mortality" OR "dea*" OR "died" OR "survival" OR "surviv*") (Word variations have been searched)
	#13	{OR #9-#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)

Data collection and management

Study selection and data extraction will be performed in duplicate by two reviewers. Both are blinded to each other's decision but not to journal titles, study authors, or institutions. The screening will be conducted by entering data into blank Microsoft Word or Excel spreadsheets. The software EndNote will be used to store, organize, and manage all the references and allow a transparent and reproducible systematic search. To assure validity and high quality of the data, the data extraction will be performed by using standard and predefined data extraction forms (see Appendix 1). Both reviewers will scan independently the titles and abstracts of studies obtained by the aforementioned search strategy against the eligibility criteria. For those studies that meet the inclusion criteria or that cannot yet be fully excluded, full-text reports will be acquired and screened again towards the inclusion criteria. In the next step, the results of both reviewers will be compared and in cases of disagreement, critical points will be discussed until a consensus is reached. If necessary, we will contact study authors to resolve questions about eligibility. We will document the reasons for excluding trials.

After completing the abstract and full-text selection with eligible studies, the two reviewers will extract independently the pre-defined data (see Appendix 1). Extracted items will include first author, publication year, country, number of participants, general population or medical condition (including cancer site and stage(s)), sex, mean/median age, race/ethnicity/skin color, mean/median BMI, mean/median 25(OH)D levels at baseline, vitamin D₃ dosing regimen, duration of vitamin D₃

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2 246 supplementation, compliance, mean/median and maximum follow-up time, number of cancer deaths
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4 247 and effect estimates (including confidence intervals) reported for cancer mortality/cancer survival.
5
6 248 Individual patient data for the aforementioned variables will be obtained from all trials with at least
7
8 249 20 cancer deaths (see Appendix 1). If summary data are not published, they shall be calculated from
9
10 250 the obtained data. All authors will be contacted by e-mail with a maximum of three attempts sent with
11
12 251 two weeks apart.

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16 252 For the meta-analyses on cancer survival and cancer-specific survival, we will ask all authors who
17
18 253 conducted trials in the general population to provide IPD for cancer diagnoses in the five years prior
19
20 254 to baseline and during the trial (including cancer site with ICD-code, stage, and diagnosis date). The
21
22 255 following IPD will be additionally collected: age, sex, BMI, race/ethnicity/skin color, baseline 25(OH)D
23
24 256 levels, compliance, randomization group allocation, baseline date, deaths during follow-up with date,
25
26 257 cancer deaths with date, censoring dates for survival outcomes, and censoring date for patients not
27
28 258 dying of cancer (see Appendix 1). If IPD cannot be shared, the authors of the studies will be asked
29
30 259 to conduct the analyses in-house and to provide the summary estimates for the meta-analysis. If trial
31
32 260 authors do not collaborate, their study cannot be included in subgroup analyses for which no effect
33
34 261 estimates were published but the result from the total trial population will remain included in the main
35
36 262 meta-analysis.

38
39
40 263

41 42 43 264 **Quality assessment**

44
45
46 265 The protocol of the systematic review with all planned statistical analyses has been registered in
47
48 266 PROSPERO before data collection to preclude data-driven analyses and selective reporting of only
49
50 267 statistically significant findings. The study protocol has been developed in line with the “Preferred
51
52 268 reporting items for systematic review and meta-analysis protocols” (PRISMA-P, see Appendix 2),
53
54 269 the Cochrane Handbook for Systematic Reviews of Interventions as well as the Institute of Medicine
55
56 270 guideline.(22-25) We will ensure to fulfill all requirements recommended by the current PRISMA
57
58 271 guideline when writing the publication of the systematic review.(26, 27)
59
60

1
2 272 The Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used to assess various domains
3
4 273 of bias including aspects of trial design, conduct, and reporting (see Appendix 1).(28, 29) The
5
6 274 following domains will be covered during the evaluation: sequence generation, allocation
7
8 275 concealment, blinding, incomplete outcome data (e.g. withdrawals and dropouts), and selective
9
10 276 outcome reporting. A summary assessment will be made based on the extracted items, judging
11
12 277 whether the risk of bias in the respective study is low, high, or has some concerns. If only insufficient
13
14 278 data is reported, the risk of bias is “unclear” and the original study authors will be contacted for further
15
16 279 information. The assessment will be conducted by two independent reviewers using the RoB 2
17
18 280 tool.(28, 29) In cases of disagreement, critical points will be discussed until a consensus is reached.
19
20
21 281 The risk of bias evaluation will be incorporated into the data synthesis by performing a sensitivity
22
23 282 analysis that excludes studies with high or unknown risk of bias.
24

25 283 26 27 284 **Descriptive analysis and meta-analysis**

28 29 285 Measures of treatment effect

30
31 286 The mortality/survival outcomes shall be addressed by estimating hazard ratios (HR) and 95%
32
33 287 confidence intervals (95%CI). Results of the intention-to-treat (ITT) approach will be used, including
34
35 288 all patients randomized when both ITT and per-protocol results are given.
36
37

38 39 289 Data synthesis

40
41
42 290 As far as study quality and differences between studies allow, effect estimates of all eligible studies
43
44 291 with data for the following three main meta-analyses will be pooled deriving random effects results
45
46 292 with the DerSimonian and Laird method (primary analysis) and fixed effects summary estimates
47
48 293 using the Mantel-Haenzel method (secondary analysis).
49

- 50 294 1) Association of vitamin D₃ supplementation and cancer mortality in the general population
- 51
52 295 2) Association of vitamin D₃ supplementation and cancer-specific survival of cancer patients
- 53
54 296 3) Association of vitamin D₃ supplementation and overall survival of cancer patients
- 55

56
57 297 For all studies that provide IPD, unadjusted Cox proportional hazard regression models will be used
58
59 298 to estimate HRs and 95%CIs for the main meta-analyses in which we will pool effect size data from
60
299 studies who do and who do not provide IPD in a two-step approach. For studies that cannot send

1
2 300 IPD to the coordinating center (German Cancer Research Center, Heidelberg), authors are being
3
4 301 asked to estimate the HRs and 95% CIs themselves and send the summary data for the meta-
5
6 302 analyses. To assess cancer survival as time-to-event data from general population cohorts, the study
7
8 303 will be restricted to patients with a history of cancer in the five years preceding baseline or a cancer
9
10 304 diagnosis during the trial. For the former, the survival time will be calculated from baseline to
11
12 305 death/end of the trial, and for the latter, survival time will be counted from the date of cancer diagnosis
13
14 306 till death/end of the trial.
15
16

17
18 307 With all studies that agree to send IPD data to the coordinating center or to do additional analyses
19
20 308 in-house, we will also conduct an additional multivariate Cox proportional hazards regression model.
21
22 309 The model for the outcome cancer mortality among general population studies will contain the
23
24 310 variables vitamin D₃ intervention (vs. placebo), age (continuous; < 70 vs. ≥ 70 years), sex (male,
25
26 311 female, unknown), BMI (< 25 vs. 25 – 29.9 vs. ≥ 30 kg/m² vs. unknown), skin color (white vs.
27
28 312 black/brown vs. other), 25(OH)D baseline level (< 30 vs. 30 – 49.9 nmol/L vs. ≥ 50 nmol/L vs.
29
30 313 unknown), diagnosis of cancer (except non-melanoma skin cancer and benign tumors) in five years
31
32 314 before baseline (yes vs. no vs. unknown), health status (general healthy population vs. diseased
33
34 315 population), and compliance (< 80% vs. ≥ 80% vs. unknown). The models for the outcomes overall
35
36 316 and cancer-specific survival of cancer patients will be adjusted for the same variables but the variable
37
38 317 “diagnosis of cancer in five years before baseline” will be replaced by more specific variables for
39
40 318 cancer stage (only advanced stages III and/or IV vs. unknown), cancer site (prostate vs. colorectal
41
42 319 vs. breast vs. lung vs. other vs. unknown) and time since cancer diagnosis (<1 year vs. 1-5 years).
43
44 320 We will test for interactions of the treatment variable (vitamin D₃ vs. placebo) with these covariates
45
46 321 to identify potential effect modifiers. Again, a two-step approach will be used for the meta-analyses,
47
48 322 whereby the analyses are carried out on a study-specific basis, and then the effect estimates are
49
50 323 pooled. To further explore the variation of the treatment effect by methodological or patient
51
52 324 characteristics differences of the studies, the following subgroup analyses will be performed with IPD
53
54 325 data and studies that published eligible data:
55
56

57
58
59 326 Subgroup analyses according to trial design
60

- 1
2 327 - Daily dose vs. weekly/monthly bolus dose vs. bolus dose at the beginning of the trial followed
3
4 328 by a daily dose
5
6 329 - Low vs. moderate vs. high vitamin D₃ dosing (< 1,000 IU vs. 1,000 – 2,000 IU vs. > 2,000 IU
7
8 330 per day or equivalent weekly or monthly taken dose)
9
10 331 - Vitamin D₃ supplementation duration (< 5 vs. ≥ 5 years)
11
12 332 - Health status (general population vs. diseased population)
13
14 333 - Region (North America vs. Europe vs. Other)
15
16

17
18 334 Subgroup analyses according to patient characteristics

- 19
20 335 - Age (< 70 vs. ≥ 70 years)
21
22 336 - Sex (male vs. female)
23
24 337 - Skin color (white vs. black/brown vs. other)
25
26 338 - BMI (< 25 vs. 25 – 29.9 vs. ≥ 30 kg/m²)
27
28 339 - Baseline 25(OH)D levels (< 30 vs. 30 – 49.9 nmol/L vs. ≥ 50 nmol/L)
29
30 340 - Compliance rate (< 80% vs. ≥ 80%)
31
32

33
34 341 For meta-analyses conducted in cancer patients in addition:

- 35
36 342 - Cancer stage (only advanced stages III and/or IV vs. unknown)
37
38 343 - Cancer site (prostate vs. colorectal vs. breast vs. lung vs. other)
39
40 344 - Time since cancer diagnosis (<1 year vs. 1-5 years)
41

42
43 345 Analyses in the coordinating center will be done with the statistical software SAS 9.4. The meta-
44
45 346 analyses will be performed with Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ).
46

47
48 347 Assessment of heterogeneity

49
50
51 348 Heterogeneity will be presented visually by forest plots and assessed statistically by Cochran's Q
52
53 349 test (significance level = 0.05) as well as the I² index (< 25% low, 25-50% moderate, > 50% high
54
55 350 heterogeneity). Meta-Analyses will be conducted even if high heterogeneity is being detected and
56
57 351 the results will be discussed taking the heterogeneity into consideration. Sources of heterogeneity
58
59
60

1
2 352 will be explored by the subgroup analyses outlined in the previous section and the following
3
4 353 sensitivity analyses:

- 6 354 - Excluding studies with a high or unknown risk of bias according to assessment with the
7
8 355 Cochrane risk-of-bias tool for randomized trials
- 10 356 - Excluding studies not reporting ITT results
- 12 357 - Excluding trials with co-supplementation of calcium
- 14 358 - Excluding events in the first year of follow-up

17 18 359 Assessment of publication bias

20
21 360 Publication bias will be assessed visually in funnel plots and tested for with Egger's test.

23 24 361 Dealing with missing data

25
26
27 362 In case of missing data, we will seek contact with the original investigators. If possible, we will
28
29 363 calculate missing numerical data from the given reported data.

31 32 364 Strength of the body of evidence

33
34
35 365 The quality of the evidence for each outcome will be evaluated using the Grading of
36
37 366 Recommendations Assessment, Development and Evaluation (GRADE) approach. The four levels
38
39 367 of evidence comprise very low, low, moderate, and high. Evidence from RCTs starts as high quality
40
41 368 but can be decreased for reasons such as the risk of bias, imprecision, inconsistency, indirectness,
42
43
44 369 and publication bias.

45 46 47 370 **Amendments**

48
49
50 371 In the case of protocol amendments, we will document the date, the description of the change, and
51
52 372 the rationale in a pre-defined log sheet in Microsoft Word or Excel.

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374 Patient and public involvement

375 Patients and the public were not involved in the development of the study design. Since this is a
376 protocol for a systematic review and no participant recruitment will take place, the involvement of
377 patients in the recruitment, the conduct of the study and the dissemination of findings to study
378 participants are not applicable.

380 Ethics and dissemination

381 An ethics approval is not required for this systematic review because it is only a summary of already
382 published trial data. All studies to be included in the systematic review have their own ethics
383 approvals, which are named in the original publications. For the IPD meta-analysis, we will take care
384 that the additional analyses are in adherence with the ethics approvals of the trials.

385 The systematic review will be published in an international peer-reviewed journal for clinical oncology
386 or general medicine with open access option and presented in national and international meetings.
387 If the meta-analyses of the systematic review obtain statistically significant findings, we expect the
388 result to be reflected in national and international guidelines and to change the current practice of
389 tertiary prevention among cancer patients. Vitamin D₃ is already on the market in various doses and
390 at low costs because it is not patented.

391 Patients will be informed via a press release from the German Cancer Research Center. Moreover,
392 we will send a summary of the results in a language suitable for laypersons to all patient advocacy
393 groups recommended by the Cancer Information Service of the German Cancer Research Center
394 (up to data n = 30) for further dissemination among their members.(30) With respect to oncologists,
395 we will disseminate the results to all German rehabilitation centers having a ward for oncologic
396 rehabilitation, as listed in the register of the *Bundesarbeitsgemeinschaft für Rehabilitation e.V.*(31)
397 As the topic of the review is in the field of tertiary prevention, oncologists in the rehabilitation setting
398 are the target audience for information dissemination.

1
2 399 **DISCUSSION**

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5 400 One of the strengths of this systematic review comprises the first meta-analysis on vitamin D
6
7 401 supplementation and cancer survival and additionally the first IPD meta-analysis on this research
8
9 402 topic. The IPD meta-analysis will allow the investigation of potential effect modifiers. Especially
10
11 403 25(OH)D levels at baseline, BMI, and compliance are candidates that could have had a great impact
12
13 404 on the overall trial results.

15
16 405 The creation of this research protocol prompted us to plan carefully all the details of the systematic
17
18 406 review and to anticipate and address potential problems before their actual occurrence. Arbitrary
19
20 407 decision making concerning any procedure of this systematic review is prevented, resulting again in
21
22 408 a decreased risk of publication bias and selective reporting bias. The protocol allows reproducible
23
24 409 and transparent research for future reviewers.

26
27
28 410 Possible limitations of our review include a potentially insufficient number of cancer deaths in the
29
30 411 studies and high heterogeneity, which could both negatively influence the statistical power of the
31
32 412 meta-analyses. However, it is still too early to judge whether these limitations occur.

34
35 413 The quality of selected studies will be assessed and the quality of the evidence will be judged. The
36
37 414 ultimate goal is to ensure the reporting of highly meaningful findings for clinicians and patients.
38
39 415 Oncologists are well aware that vitamin D deficiency and insufficiency are very common in cancer
40
41 416 patients but there is uncertainty about whether and how they should routinely perform preventive
42
43 417 screening and treatments. In some clinics, cancer patients receive a uniform dose of vitamin D with
44
45 418 a “one-dose-fits-all” approach, which does not take individual 25(OH)D levels or other patient
46
47 419 characteristics into account. The optimal dose for one person may be utterly insufficient for another
48
49 420 one to achieve beneficial vitamin D levels. Since vitamin D products are readily available in
50
51 421 pharmacies or drug stores, many patients use low-dose vitamin D supplementation as self-
52
53 422 medication. Yet, it can be doubted whether this untargeted intervention has any effect on cancer
54
55 423 prognosis. Consequently, evidence-based recommendations for high-dose vitamin D
56
57 424 supplementation are highly relevant for both, clinicians and patients.

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1
2 425 If the planned systematic review determines the efficacy of vitamin D supplementation on cancer
3
4 426 prognosis in the expected magnitude of 10-15%, the review will be used to provide clear suggestions
5
6 427 on how vitamin D can be appropriately dosed to overcome vitamin D deficiency or insufficiency in
7
8 428 cancer patients.(12) Furthermore, our systematic review would provide the evidence for statutory
9
10 429 health insurances to cover the costs for screening for vitamin D deficiency or insufficiency in cancer
11
12 430 patients and a subsequent vitamin D supplementation. With expected relatively large effects and
13
14 431 very low screening and treatment costs (A vitamin D blood test costs approx. € 20, and one year of
15
16 432 vitamin D therapy costs less than € 100.), vitamin D supplementation will be highly cost-effective.
17
18
19 433 The costs would be close to negligible compared to other current cancer treatment costs.
20
21 434

22 23 435 **Status**

24
25 436 At the time of submission, the study selection for the systematic review has not started.
26
27 437

28 29 438 **Acknowledgements**

30
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32
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34
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36
37
38 442

39 40 443 **Authors' contribution**

41
42 444 All authors meet the ICMJE criteria for authorship as follows: BS and SK are the guarantors of the
43
44 445 systematic review, therefore, are accountable for all aspects of the work in ensuring that questions
45
46 446 related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
47
48 447 All authors made substantial contributions to the conception of the work. BS and SK designed the
49
50 448 search strategy and the risk of bias assessment strategy. BS developed the selection criteria, the
51
52 449 data extraction criteria, and the statistical methods. SK drafted the protocol publication, which BS
53
54 450 and HB revised critically for important intellectual content. All authors approved the final version to
55
56
57 451 be published.
58
59 452
60

1
2 453 **Contributors**

3
4 454 The following researchers have agreed to contribute to this systematic review by sharing IPD and
5
6 455 giving intellectual input for the discussion of the results: Taisuke Akutsu (Jikei University School of
7
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9
10 457 Harvard Medical School. Boston), Professor Carlos A. Camargo Jr (MD, DrPH. Massachusetts
11
12 458 General Hospital, Harvard Medical School. Boston), Professor Nancy R. Cook (ScD. Brigham and
13
14 459 Women's Hospital and Harvard Medical School. Boston), Professor I-Min Lee (MB, BS, ScD.
15
16
17 460 Brigham and Women's Hospital and Harvard Medical School. Boston), Professor JoAnn E. Manson
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24
25 464 Zealand), Professor Mitsuyoshi Urashima (MD. Jikei University School of Medicine. Tokyo, Japan),
26
27 465 Professor Jean Wactawski-Wende (PhD. University at Buffalo. Buffalo, New York).

28
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30
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36
37
38 470 a role in the design of the review protocol, data collection, data analyses, the interpretation of results,
39
40 471 or the decision about the publication of the results.

41
42 472
43
44 473 **Data availability statement**

45
46 474 As no new data are obtained in this systematic review, no data will be made publicly available to
47
48 475 third parties. Decisions on data use by third parties can only be made by the principal investigators
49
50 476 of the original studies, taking into account the votes of the responsible ethics committees.

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53 477
54
55 478 **Disclaimer**

56
57 479 The views of the authors do not necessarily reflect those of the German Cancer Research Center.
58
59 480

1
2 481 **Competing interests**

3
4 482 None declared.

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6 483
7
8 484 **Patient consent for publication**

9
10 485 Not required.

11 486
12
13
14 487 **Provenance and peer review**

15
16 488 Not commissioned; externally peer-reviewed

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2 586 **Appendix 1:**
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4 587 Supplementary material consisting of data extraction form, risk of bias assessment and list of
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7 588 individual patient data to be obtained from original researchers

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9 589 **Appendix 2:**
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11 590 Supplementary material consisting of PRISMA-P checklist
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2 591 **Figure**

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7 594 **Figure 1:** Draft of the study selection process

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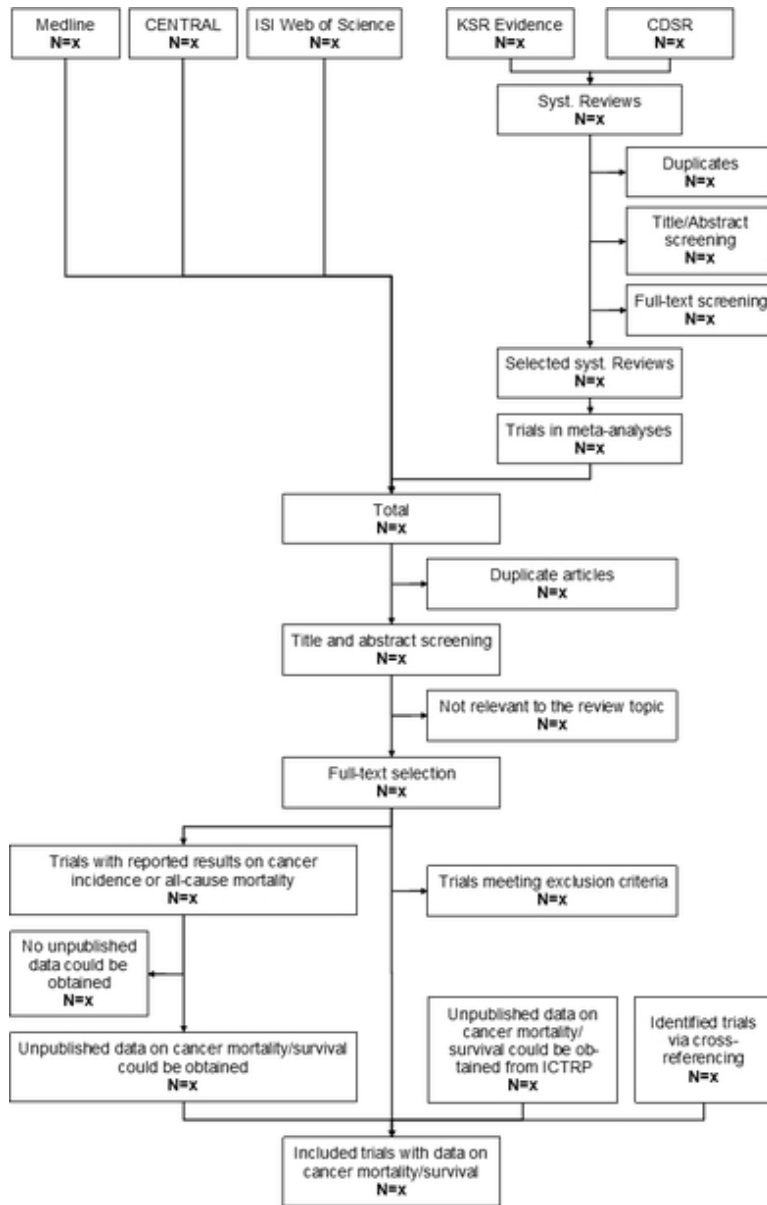


Figure 1: Draft of the study selection process

16x25mm (600 x 600 DPI)

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Study			Population				
First author (or study name), Year (REF)	Country	Sample size	General population (y/n)	Cancer population (y/n)	Cancer site + stage	Age (mean or median)	Sex (female %)

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			Intervention			Comp
Race/ ethnicity/ skin color (white %)	BMI [kg/m ²] (n, mean or median)	25(OH)D (n, mean or median)	Vitamin D ₃ dosing regimen	Duration of vitamin D3 supplementation	Compliance in intervention group (%)	Placebo (y/other)

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Comparator	Outcomes				
Compliance in comparator group (%)	Maximum follow-up time	Mean or median follow-up time	No of cancer deaths	Cancer mortality in general population HR (95% CI)	Cancer-specific survival of cancer patients HR (95% CI)

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		Comments
Overall survival of cancer patients HR (95%CI)	Covariates adjusted for	

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First author (or study name), Year (REF)	R	D	Mi	Me	S	O

Risk of bias legend

- R** Bias arising from the randomiation
- D** Bias due to deviations from
- Mi** Bias due to missing outcome data
- Me** Bias in measurement of the
- S** Bias in selection of the reported
- O** Overall risk of bias

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The following variables will be obtained for all trial participants in order to conduct the IPD meta-

No.	Variables
1	Age
2	Sex
3	BMI
4	Race/ethnicity/skin color
5	Baseline 25(OH)D levels
6	Compliance
7	Randomisation group allocation
8	Baseline date
9	Death during follow-up (y/n)
10	Date of death
11	Censoring date for survivors
12	Cancer death during follow-up (y/n)
13	Date of cancer death
14	Censoring date for non-cancer deaths
15	Cancer* diagnosis during follow-up (y/n)
16	Cancer* site for each cancer during follow-up
17	Cancer* stage for each cancer during follow-up
18	Date of cancer* diagnosis for each cancer during follow-up
19	Cancer* diagnosis in first 5 years before baseline (y/n)
20	Cancer* site for each cancer in first 5 years before baseline
21	Cancer* stage for each cancer in first 5 years before baseline
22	Date of cancer* diagnosis for each cancer in first 5 years before baseline

* Excluding non-melanoma skin cancers and benign tumors

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2 **analysis:**
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n.a. (first submission)
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	63-64
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-34
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	443-451
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	370-372
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	467-471
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	467-471
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	467-471
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	79-124
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	126-140
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	150-190
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	192-225
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	217-218, 224-225, figure 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-262
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-262
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-262, appendix 1
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	361-363, appendix 1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	131-133, 168-172, table 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	264-282, 347-360
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	290-297
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	297-325, 345-358
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	326-344, 351-358
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n.a. (quantitative)

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					synthesis will be performed)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	359-360
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	364-369

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BMJ Open

Efficacy of Vitamin D3 supplementation on cancer mortality in the general population and the prognosis of cancer patients: Protocol of a systematic review and individual patient data meta-analysis of randomized controlled trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041607.R2
Article Type:	Protocol
Date Submitted by the Author:	16-Nov-2020
Complete List of Authors:	Schöttker, Ben; German Cancer Research Centre, Division of Clinical Epidemiology and Aging Research; University of Heidelberg, Network Aging Research Kuznia, Sabine; German Cancer Research Centre, Division of Clinical Epidemiology and Aging Research Brenner, Hermann; German Cancer Research Centre, Division of Clinical Epidemiology and Aging Research; National Center of Tumor Diseases, Division of Preventive Oncology
Primary Subject Heading:	Patient-centred medicine
Secondary Subject Heading:	Public health
Keywords:	Nutritional support < ONCOLOGY, ONCOLOGY, NUTRITION & DIETETICS, PUBLIC HEALTH, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < ONCOLOGY

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3 1 **Efficacy of Vitamin D₃ supplementation on cancer mortality in the**
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5 2 **general population and the prognosis of cancer patients: Protocol of a**
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7 3 **systematic review and individual patient data meta-analysis of**
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9 4 **randomized controlled trials**

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11 5
12 6 Ben Schöttker^{1,2*}, Sabine Kuznia^{1*}, Hermann Brenner¹⁻⁴

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31 19 * Ben Schöttker and Sabine Kuznia share the first authorship and contributed equally to the
32 20 preparation of the manuscript.

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36 Word Count (excluding title page, abstract, references, figures, and tables): 4,351

37 **ABSTRACT**

38 **Introduction**

39 Vitamin D insufficiency is much more common among cancer patients than the general population.
40 Previous meta-analyses of controlled trials showed an approximately 15% reduction of cancer
41 mortality by vitamin D supplementation compared to placebo or no treatment in the general
42 population.

43 On top of updating the latest systematic review on vitamin D supplementation and cancer mortality
44 in the general population, we aim to conduct the first meta-analyses of trials on vitamin D₃
45 supplementation and cancer-specific and overall survival of cancer patients. Besides, we will conduct
46 for the first time subgroup analyses based on individual patient data collected from randomized
47 controlled trials.

48 **Methods and analysis**

49 A systematic review and individual patient data meta-analysis will be performed on randomized
50 placebo-controlled trials with a vitamin D₃ intervention. All databases are searched from inception
51 without time restriction. The addressed outcomes are cancer mortality in the general population as
52 well as cancer-specific and overall survival of cancer patients. The quality appraisal of the studies
53 will be evaluated by the Cochrane risk-of-bias tool for randomized trials. Trial results will be re-
54 analyzed using adjusted and unadjusted Cox proportional hazard regression models and meta-
55 analyses are planned. Cochran's Q-Test and the I² index will be used to statistically assess the level
56 of heterogeneity, while sensitivity and subgroup analyses serve to identify potential causes of
57 heterogeneity. Subgroup analyses will be conducted for vitamin D₃ dosing, follow-up time, age, sex,
58 obesity, vitamin D deficiency/insufficiency, history of cancer, and compliance. Publication bias will
59 be assessed by funnel plots and Egger's test.

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2 **60 Ethics and dissemination**
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5 61 Ethical approval is not required since no human beings are involved in this systematic review.
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7 62 Results will be published in a peer-reviewed journal with open access. They will be presented at
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9 63 conferences and sent to patient advocacy groups and German oncologic rehabilitation centers.
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12 **64 PROSPERO registration number**
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15 65 CRD42020185566
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18 **66 Keywords**
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21 67 Vitamin D, cancer, mortality, systematic review, meta-analysis
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27 **69 Strengths and limitations of this study**
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30 70 • First meta-analysis on vitamin D₃ supplementation and cancer survival as well as first individual
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32 71 patient data meta-analysis on this research topic.
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35 72 • Results of subgroup analyses based on individual patient data allow fundamental insights for
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37 73 personalized medicine and may be used as guidance for future clinical trials targeting cancer
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39 74 patients that presumably profit most from vitamin D supplementation
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42 75 • Conduction of the systematic review according to this protocol and a thorough assessment of
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44 76 study quality, sources of heterogeneity, and bias in meta-analyses minimize the risk of bias and will
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46 77 gather reproducible results.
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50 78 • Number of studies with eligible data for subgroup analyses may be limited.
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79 INTRODUCTION

80 Background

81 The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths
82 in 2018.(1) There is accumulating evidence from epidemiological studies that a low vitamin D status
83 goes along with increased risks of several types of cancer. Meta-analyses of observational studies
84 reported increased risks of lung cancer, colorectal cancer, breast cancer, bladder carcinoma, and
85 lymphoma in subjects with low 25(OH)D serum concentrations.(2-5) Furthermore, epidemiological
86 studies have shown that low serum levels of 25-hydroxyvitamin D (25(OH)D), the acknowledged
87 best biomarker to measure vitamin D status, were strongly associated with substantially increased
88 cancer mortality.(6) For example, in a German population-based cohort study of older adults, the
89 risk to die of cancer was increased by 42% in study participants with vitamin D deficiency (defined
90 as 25(OH)D < 30 nmol/L) compared to individuals with sufficient 25(OH)D levels > 50 nmol/L (hazard
91 ratio [HR] and 95% confidence interval (95%CI): 1.42 [1.08; 1.87]).(7)

92 The molecular links between vitamin D and carcinogenesis and progression have been previously
93 described.(8) In brief, genomic mechanisms of the active hormone 1,25(OH)₂D impact signaling
94 pathways that regulate cell proliferation, differentiation, and cell survival. 1,25(OH)₂D may primarily
95 act as an anti-proliferative agent in many tissues and may slow down malignant cellular growth.
96 Thus, there is biological plausibility that a sufficient vitamin D supply is especially essential for a
97 good cancer prognosis. A causal relationship of low 25(OH)D levels and cancer mortality was
98 furthermore supported by a Mendelian randomization study conducted within three large cohorts
99 from Denmark.(9)

100 Several randomized trials with vitamin D supplementation have been conducted with mostly the aim
101 to improve skeletal outcomes at older ages. Cancer mortality was a secondary outcome in all trials
102 and therefore the trials were not specifically designed for this outcome.(10) Despite strong
103 heterogeneity in study populations, intervention schemes, and other important design aspects, three
104 out of four meta-analyses demonstrated a statistically significant reduction in cancer mortality.(11-
105 15)

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2 106 However, most trials have not been restricted to patients that were vitamin D deficient.(10) The latter
3
4 107 is important because the association of 25(OH)D levels and adverse health outcomes is not linear.(6)
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6 108 Neglecting this dose-response relationship by treating subjects without hypovitaminosis D is
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8 109 expected to have led to a substantial underestimation of the potential efficacy of vitamin D
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10 110 supplementation in previous clinical trials.(16) Therefore, there is a need for a systematic review that
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12 111 re-analyses individual patient data (IPD) from previous trials restricted to subjects with vitamin D
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14 112 insufficiency (25(OH)D < 50 nmol/L) or deficiency (25(OH)D < 30 nmol/L).

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18 113 Another important reason to re-analyze the previous trial data is that most studies were not restricted
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20 114 to cancer patients. Vitamin D deficiency or insufficiency are much more common among cancer
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22 115 patients than among the general population. In a study with 2,912 colorectal cancer patients, vitamin
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24 116 D deficiency (25(OH)D levels < 30 nmol/L) was found among 59% of colorectal cancer patients
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26 117 during or shortly after first-line treatment, and, in agreement with previous evidence, low 25(OH)D
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28 118 levels were strongly associated with poorer survival.(17, 18) Systematic reviews of observational
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30 119 studies on 25(OH)D levels and cancer prognosis concluded that sufficient 25(OH)D levels are
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32 120 associated with a better prognosis of breast and colorectal cancer, whereas there are too few studies
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34 121 for other cancer sites up to date to draw conclusions.(17, 19)

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38 122 Further important potential effect modifiers that deserve close investigation are obesity and
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40 123 compliance. People with low compliance and/or obesity, who may need higher vitamin D doses
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42 124 because vitamin D is stored in adipocytes, might have attenuated the overall treatment effect in the
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44 125 trials.(20)

50 127 **Objective**

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53 128 The objective of our systematic review is to assess the efficacy of vitamin D₃ supplementation on
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55 129 cancer mortality in the general population and the prognosis of cancer patients with special attention
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57 130 to potential effect modifiers, including baseline 25(OH)D levels, cancer at baseline, BMI and
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59 131 compliance.

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2 132 The main outcomes include “cancer mortality in the general population”, “cancer-specific survival of
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4 133 cancer patients” and “overall survival of cancer patients”. These outcomes are universally used in
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6 134 cancer studies and do not need further refinement during the review.
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9 135 In a first step, we intend to update the previous systematic reviews on vitamin D supplementation
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11 136 and cancer mortality in the general population by including newly published trials and unpublished
12
13 137 data from trials with outcome data on cancer incidence or all-cause mortality by asking the authors
14
15 138 for data on cancer mortality. Second, we will obtain data for an IPD meta-analysis. Third, we will
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18 139 conduct IPD meta-analyses on vitamin D₃ supplementation and overall and cancer-specific survival
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20 140 among cancer patients. Forth, we will conduct subgroup analyses to explore sources of
21
22 141 heterogeneity and to identify effect modifiers. The timetable for the review is shown in Table 1.
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25 142 **Table 1:** Proposed timetable for conducting the review
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Step	Timeframe for completion
Literature search, abstract and full-text selection	2.5 months
Data extraction & individual patient data acquisition	2.5 months
Quality appraisal	2 months
Data analysis & meta-analysis	3 months
Writing of manuscript	2 months
Total	12 months

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42 144 **METHODS AND ANALYSIS**

43 44 45 145 **Study selection criteria/ Eligibility criteria**

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49 146 We will follow a two-step approach for the study selection: First, all trials will be selected that could
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51 147 potentially have published or unpublished data on the research topic. All authors of trials with
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53 148 potentially unpublished data on cancer mortality/survival will be contacted to provide data. In the
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55 149 second step, only trials with eligible data for a meta-analysis will be included.
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Step 1: Inclusion criteria for trials

Participants: We will include studies investigating the adult population (18 years or older). We will also include studies conducted solely with cancer populations or patients with other conditions (e.g. studies that recruited only patients with type 2 diabetes).

Interventions: We will focus on trials that used vitamin D₃ in any dose and any regimen (e.g. daily/weekly/monthly intake) as the intervention. However, the minimum time of the intervention shall be six months to exclude studies with one-time bolus interventions or very short intervention periods. The first reason is that cancer mortality is highly unlikely to be influenced by very brief intervention periods. The second reason is that after initiating daily, weekly, or monthly supplementation schedules, it takes three to six months for 25(OH)D levels to reach homeostasis.

Besides, we will also include studies using vitamin D₃ bioequivalent substances such as calcitriol, being the active vitamin D hormone 1,25(OH)₂D, as well as alfacalcidol and calcifediol, which are both equally metabolized to 1,25(OH)₂D.

We will exclude studies with vitamin D₂ supplementation since the Cochrane review of Bjelakovic et al. and other recent data showed clearly no efficacy on mortality.(10, 11, 15, 21) Co-supplementation with calcium or other dietary supplements in the intervention arm will not be an exclusion criterion. A sensitivity analysis will elucidate whether the inclusion of these studies had an impact on the overall effect estimate of the meta-analysis.

Comparators: We will include only studies, which used placebo as the comparator.

Outcomes: To be eligible for inclusion in a meta-analysis trials need to have assessed the outcome of cancer mortality, cancer survival, or cancer-specific survival. In an intermediate step of the systematic review, we will also record studies with the outcomes of cancer incidence or all-cause mortality and contact the authors if they have data for the outcomes needed for the planned meta-analyses. The definitions of all outcomes are shown in Table 2.

Table 2: Definition of outcomes

Outcome	Definition
All-cause mortality	Rate of deaths during a specific time period in a population at risk
Cancer mortality	Rate of cancer deaths during a specific time period in a population at risk
Cancer incidence	Rate of newly diagnosed cancer cases during a specific time period in a population at risk
Overall cancer survival	Proportion of patients from a cancer population at risk alive at some point subsequent to the diagnosis of their cancer
Cancer-specific survival	Proportion of patients from a cancer population at risk who did not die of cancer at some point subsequent to the diagnosis of their cancer

175

Study design: We will include RCTs in which, analogous to the intervention period, the follow-up period is at least six months. The follow-up time should not be longer than the time under treatment. We will focus on parallel-group designs and exclude single-arm studies. We will further exclude all types of cohort studies and case-control studies as well as the following types of records: reviews, dissertations, theses, editorials, study protocol, clinical guidelines, commentaries, and letters.

Setting: There will be no restrictions by type of setting.

Minimum sample size: The studies need to have at least one cancer death in the verum and placebo group.

Geographical location: No restrictions are defined regarding the geographical location.

Step 2: Inclusion criteria for pooling in meta-analysis

Studies will be included for pooling in the meta-analysis, if the risk ratio and 95% confidence interval for at least one outcome of interest (cancer mortality in the general population, cancer-specific survival of cancer patients, or overall survival of cancer patients) were either reported in the publication or could be obtained from authors or individual participant data. In the case of double publication from the same trial, only the publication with the largest amount of information, e.g. the longest follow-up, will be included in the meta-analysis.

193 Information sources and search strategy

194 The search strategy will be elaborated by SK, BS, and A. Heppert. Mrs. Heppert is a specialist for
195 systematic bibliographic searches at the Central Library of the German Cancer Research Center
196 and is not otherwise associated with the project. Finally, it will be peer-reviewed by HB and carried
197 out by SK.

198 The bibliographic databases MEDLINE (Pubmed interface), ISI Web of Science (WoS; Clarivate
199 Analytics interface), and the Cochrane Central Register of Controlled Trials (CENTRAL; OVID
200 interface) will be searched systematically. We will also carry out a systematic search for previous
201 systematic reviews in the Cochrane Database of Systematic Reviews (CDRS, OVID interface) and
202 KSR Evidence (<https://ksevidence.com>), which are both specialized search engines for systematic
203 reviews. RCTs included in meta-analyses on the topics vitamin D supplementation and cancer
204 mortality, cancer incidence, all-cause mortality, or cancer survival will be extracted and merged with
205 the hits found in the bibliographic database search. The electronic database search will be
206 complemented by searching the WHO's International Clinical Trials Research Portal (ICTRP) and
207 clinicaltrials.gov to capture results from ongoing or recently completed RCTs that have not been
208 published in scientific journals, yet. We will also scan the reference lists of eligible studies to yield
209 additional trial articles via cross-referencing. A draft of the search strategy is presented in Figure 1.

210 We will search in MEDLINE, ISI WoS, and CENTRAL for medical subject headings (MeSH), free text
211 words, synonyms, and related search terms for the concepts "vitamin D", "mortality", "cancer",
212 "randomized controlled trial" and "placebo". Besides, standard search terms for RCTs will be used
213 additionally wherever available. No restrictions are planned in the search strategy to prevent
214 overlooking important studies that have not been correctly classified in the respective bibliographic
215 databases. All databases will be searched from the inception of the databases without time
216 restriction. Moreover, we will not limit the search to studies in English as relevant studies might also
217 be published in other languages. The search string for MEDLINE is shown in Table 3.

1
2 218 **Table 3:** Search string for MEDLINE

Step	Search string
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 alfalcidol[Supplementary Concept] OR alphacalcidol[tw] OR alfalcidol[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	(((((("randomized controlled trial"[pt]) OR "controlled clinical trial"[pt]) OR randomized[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

25 219
26
27
28 220 A shortened version of the MEDLINE search string will be used to search for systematic reviews in
29
30 221 CDSR and KSR Evidence. Only the first three search steps are needed because the study design is
31
32 222 "systematic review" and not "placebo-controlled RCT". The search string for CDSR is shown in Table
33
34 223 4. The literature search will be updated during the peer-review process of the publication in order to
35
36 224 include the most up to date literature.

38
39
40 225 **Table 4:** Search string for the Cochrane Database of Systematic Reviews

Step	Search string
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 (("alfalcidol") 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 {OR #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	{OR #9-#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)

Data collection and management

Study selection and data extraction will be performed in duplicate by two reviewers. Both are blinded to each other's decision but not to journal titles, study authors, or institutions. The screening will be conducted by entering data into blank Microsoft Word or Excel spreadsheets. The software EndNote will be used to store, organize, and manage all the references and allow a transparent and reproducible systematic search. To assure validity and high quality of the data, the data extraction will be performed by using standard and predefined data extraction forms (see Appendix 1). Both reviewers will scan independently the titles and abstracts of studies obtained by the aforementioned search strategy against the eligibility criteria. For those studies that meet the inclusion criteria or that cannot yet be fully excluded, full-text reports will be acquired and screened again towards the inclusion criteria. In the next step, the results of both reviewers will be compared and in cases of disagreement, critical points will be discussed until a consensus is reached. If necessary, we will contact study authors to resolve questions about eligibility. We will document the reasons for excluding trials.

After completing the abstract and full-text selection with eligible studies, the two reviewers will extract independently the pre-defined data (see Appendix 1). Extracted items will include first author, publication year, country, number of participants, general population or medical condition (including cancer site and stage(s)), sex, mean/median age, race/ethnicity, mean/median BMI, mean/median 25(OH)D levels at baseline, vitamin D₃ dosing regimen, duration of vitamin D₃ supplementation,

1
2 247 compliance, mean/median and maximum follow-up time, number of cancer deaths and effect
3
4 248 estimates (including confidence intervals) reported for cancer mortality/cancer survival. Individual
5
6 249 patient data for the aforementioned variables will be obtained from all trials with at least 20 cancer
7
8 250 deaths (see Appendix 1). If summary data are not published, they shall be calculated from the
9
10 251 obtained data. All authors will be contacted by e-mail with a maximum of three attempts sent at two-
11
12 252 week intervals.

14
15
16 253 For the meta-analyses on cancer survival and cancer-specific survival, we will ask all authors who
17
18 254 conducted trials in the general population to provide IPD for cancer diagnoses in the five years prior
19
20 255 to baseline and during the trial (including cancer site with ICD-code, stage, and diagnosis date). The
21
22 256 following IPD will be additionally collected: age, sex, BMI, race/ethnicity, baseline 25(OH)D levels,
23
24 257 compliance, randomization group allocation, baseline date, deaths during follow-up with date, cancer
25
26 258 deaths with date, censoring dates for survival outcomes, and censoring date for patients not dying
27
28 259 of cancer (see Appendix 1). If IPD cannot be shared, the authors of the studies will be asked to
29
30 260 conduct the analyses in-house and to provide the summary estimates for the meta-analysis. If trial
31
32 261 authors do not collaborate, their study cannot be included in subgroup analyses for which no effect
33
34 262 estimates were published but the result from the total trial population will remain included in the main
35
36 263 meta-analysis.

38
39
40 264

41 42 43 265 **Quality assessment**

44
45
46 266 The protocol of the systematic review with all planned statistical analyses has been registered in
47
48 267 PROSPERO before data collection to preclude data-driven analyses and selective reporting of only
49
50 268 statistically significant findings. The study protocol has been developed in line with the “Preferred
51
52 269 reporting items for systematic review and meta-analysis protocols” (PRISMA-P, see Appendix 2),
53
54 270 the Cochrane Handbook for Systematic Reviews of Interventions as well as the Institute of Medicine
55
56 271 guideline.(22-25) We will ensure to fulfill all requirements recommended by the current PRISMA
57
58 272 guideline when writing the publication of the systematic review.(26, 27)

60

1
2 273 The Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used to assess various domains
3
4 274 of bias including aspects of trial design, conduct, and reporting (see Appendix 1).(28, 29) The
5
6 275 following domains will be covered during the evaluation: sequence generation, allocation
7
8 276 concealment, blinding, incomplete outcome data (e.g. withdrawals and dropouts), and selective
9
10 277 outcome reporting. A summary assessment will be made based on the extracted items, judging
11
12 278 whether the risk of bias in the respective study is low, high, or has some concerns. If only insufficient
13
14 279 data is reported, the risk of bias is “unclear” and the original study authors will be contacted for further
15
16 280 information. The assessment will be conducted by two independent reviewers using the RoB 2
17
18 281 tool.(28, 29) In cases of disagreement, critical points will be discussed until a consensus is reached.
19
20 282 The risk of bias evaluation will be incorporated into the data synthesis by performing a sensitivity
21
22 283 analysis that excludes studies with high or unknown risk of bias.
23
24
25 284

27 285 **Descriptive analysis and meta-analysis**

29 286 Measures of treatment effect

31 287 The mortality/survival outcomes shall be addressed by estimating hazard ratios (HR) and 95%
32
33 288 confidence intervals (95%CI). Results of the intention-to-treat (ITT) approach will be used, including
34
35 289 all patients randomized when both ITT and per-protocol results are given.
36
37

39 290 Data synthesis

42 291 As far as study quality and differences between studies allow, effect estimates of all eligible studies
43
44 292 with data for the following three main meta-analyses will be pooled deriving random effects results
45
46 293 with the DerSimonian and Laird method (primary analysis) and fixed effects summary estimates
47
48 294 using the Mantel-Haenzel method (secondary analysis).

- 50 295 1) Association of vitamin D₃ supplementation and cancer mortality in the general population
- 52 296 2) Association of vitamin D₃ supplementation and cancer-specific survival of cancer patients
- 54 297 3) Association of vitamin D₃ supplementation and overall survival of cancer patients

56 298 For all studies that provide IPD, unadjusted Cox proportional hazard regression models will be used
57
58 299 to estimate HRs and 95%CIs for the main meta-analyses in which we will pool effect size data from
59
60 300 studies who do and who do not provide IPD in a two-step approach. For studies that cannot send

1
2 301 IPD to the coordinating center (German Cancer Research Center, Heidelberg), authors are being
3
4 302 asked to estimate the HRs and 95% CIs themselves and send the summary data for the meta-
5
6 303 analyses. To assess cancer survival as time-to-event data from general population cohorts, the study
7
8 304 will be restricted to patients with a history of cancer in the five years preceding baseline or a cancer
9
10 305 diagnosis during the trial. For the former, the survival time will be calculated from baseline to
11
12 306 death/end of the trial, and for the latter, survival time will be counted from the date of cancer diagnosis
13
14 307 till death/end of the trial.
15
16

17
18 308 With all studies that agree to send IPD data to the coordinating center or to do additional analyses
19
20 309 in-house, we will also conduct an additional multivariate Cox proportional hazards regression model.
21
22 310 The model for the outcome cancer mortality among general population studies will contain the
23
24 311 variables vitamin D₃ intervention (vs. placebo), age (continuous; < 70 vs. ≥ 70 years), sex (male,
25
26 312 female, unknown), BMI (< 25 vs. 25 – 29.9 vs. ≥ 30 kg/m² vs. unknown), ethnicity (white vs.
27
28 313 black/brown vs. other), 25(OH)D baseline level (< 30 vs. 30 – 49.9 nmol/L vs. ≥ 50 nmol/L vs.
29
30 314 unknown), diagnosis of cancer (except non-melanoma skin cancer and benign tumors) in five years
31
32 315 before baseline (yes vs. no vs. unknown), health status (general healthy population vs. diseased
33
34 316 population), and compliance (< 80% vs. ≥ 80% vs. unknown). The models for the outcomes overall
35
36 317 and cancer-specific survival of cancer patients will be adjusted for the same variables but the variable
37
38 318 “diagnosis of cancer in five years before baseline” will be replaced by more specific variables for
39
40 319 cancer stage (only advanced stages III and/or IV vs. unknown), cancer site (prostate vs. colorectal
41
42 320 vs. breast vs. lung vs. other vs. unknown) and time since cancer diagnosis (<1 year vs. 1-5 years).
43
44 321 We will test for interactions of the treatment variable (vitamin D₃ vs. placebo) with these covariates
45
46 322 to identify potential effect modifiers. Again, a two-step approach will be used for the meta-analyses,
47
48 323 whereby the analyses are carried out on a study-specific basis, and then the effect estimates are
49
50 324 pooled. To further explore the variation of the treatment effect by methodological or patient
51
52 325 characteristics differences of the studies, the following subgroup analyses will be performed with IPD
53
54 326 data and studies that published eligible data:
55
56

57
58
59 327 Subgroup analyses according to trial design
60

- 1
2 328 - Daily dose vs. weekly/monthly bolus dose vs. bolus dose at the beginning of the trial followed
3
4 329 by a daily dose
5
6 330 - Low vs. moderate vs. high vitamin D₃ dosing (< 1,000 IU vs. 1,000 – 2,000 IU vs. > 2,000 IU
7
8 331 per day or equivalent weekly or monthly taken dose)
9
10 332 - Vitamin D₃ supplementation duration (< 5 vs. ≥ 5 years)
11
12 333 - Health status (general population vs. diseased population)
13
14 334 - Region (North America vs. Europe vs. Other)
15
16

17
18 335 Subgroup analyses according to patient characteristics

- 19
20 336 - Age (< 70 vs. ≥ 70 years)
21
22 337 - Sex (male vs. female)
23
24 338 - Ethnicity (white vs. black/brown vs. other)
25
26 339 - BMI (< 25 vs. 25 – 29.9 vs. ≥ 30 kg/m²)
27
28 340 - Baseline 25(OH)D levels (< 30 vs. 30 – 49.9 nmol/L vs. ≥ 50 nmol/L)
29
30 341 - Compliance rate (< 80% vs. ≥ 80%)
31
32

33
34 342 For meta-analyses conducted in cancer patients in addition:

- 35
36 343 - Cancer stage (only advanced stages III and/or IV vs. unknown)
37
38 344 - Cancer site (prostate vs. colorectal vs. breast vs. lung vs. other)
39
40 345 - Time since cancer diagnosis (<1 year vs. 1-5 years)
41

42
43 346 Analyses in the coordinating center will be done with the statistical software SAS 9.4. The meta-
44
45 347 analyses will be performed with Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ).
46

47
48 348 Assessment of heterogeneity

49
50
51 349 Heterogeneity will be presented visually by forest plots and assessed statistically by Cochran's Q
52
53 350 test (significance level = 0.05) as well as the I² index (< 25% low, 25-50% moderate, > 50% high
54
55 351 heterogeneity). Meta-Analyses will be conducted even if high heterogeneity is being detected and
56
57 352 the results will be discussed taking the heterogeneity into consideration. Sources of heterogeneity
58
59
60

1
2 353 will be explored by the subgroup analyses outlined in the previous section and the following
3
4 354 sensitivity analyses:

- 6 355 - Excluding studies with a high or unknown risk of bias according to assessment with the
7
8 356 Cochrane risk-of-bias tool for randomized trials
- 10 357 - Excluding studies not reporting ITT results
- 12 358 - Excluding trials with co-supplementation of calcium
- 14
15 359 - Excluding events in the first year of follow-up

17 18 360 Assessment of publication bias

19
20
21 361 Publication bias will be assessed visually in funnel plots and tested for with Egger's test.

22 23 24 362 Dealing with missing data

25
26
27 363 In case of missing data, we will seek contact with the original investigators. If possible, we will
28
29 364 calculate missing numerical data from the given reported data.

30 31 32 365 Strength of the body of evidence

33
34
35 366 The quality of the evidence for each outcome will be evaluated using the Grading of
36
37 367 Recommendations Assessment, Development and Evaluation (GRADE) approach. The four levels
38
39 368 of evidence comprise very low, low, moderate, and high. Evidence from RCTs starts as high quality
40
41 369 but can be decreased for reasons such as the risk of bias, imprecision, inconsistency, indirectness,
42
43
44 370 and publication bias.

45 46 47 371 **Amendments**

48
49
50 372 In the case of protocol amendments, we will document the date, the description of the change, and
51
52 373 the rationale in a pre-defined log sheet in Microsoft Word or Excel.

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375 Patient and public involvement

376 Patients and the public were not involved in the development of the study design. Since this is a
377 protocol for a systematic review and no participant recruitment will take place, the involvement of
378 patients in the recruitment, the conduct of the study and the dissemination of findings to study
379 participants are not applicable.

381 Ethics and dissemination

382 An ethics approval is not required for this systematic review because it is only a summary of already
383 published trial data. All studies to be included in the systematic review have their own ethics
384 approvals, which are named in the original publications. For the IPD meta-analysis, we will take care
385 that the additional analyses are in adherence with the ethics approvals of the trials.

386 The systematic review will be published in an international peer-reviewed journal for clinical oncology
387 or general medicine with open access option and presented in national and international meetings.
388 If the meta-analyses of the systematic review obtain statistically significant findings, we expect the
389 result to be reflected in national and international guidelines and to change the current practice of
390 tertiary prevention among cancer patients. Vitamin D₃ is already on the market in various doses and
391 at low costs because it is not patented.

392 Patients will be informed via a press release from the German Cancer Research Center. Moreover,
393 we will send a summary of the results in a language suitable for laypersons to all patient advocacy
394 groups recommended by the Cancer Information Service of the German Cancer Research Center
395 (up to data n = 30) for further dissemination among their members.(30) With respect to oncologists,
396 we will disseminate the results to all German rehabilitation centers having a ward for oncologic
397 rehabilitation, as listed in the register of the *Bundesarbeitsgemeinschaft für Rehabilitation e.V.*(31)
398 As the topic of the review is in the field of tertiary prevention, oncologists in the rehabilitation setting
399 are the target audience for information dissemination.

1
2 400 **DISCUSSION**

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4
5 401 One of the strengths of this systematic review comprises the first meta-analysis on vitamin D
6
7 402 supplementation and cancer survival and additionally the first IPD meta-analysis on this research
8
9 403 topic. The IPD meta-analysis will allow the investigation of potential effect modifiers. Especially
10
11 404 25(OH)D levels at baseline, BMI, and compliance are candidates that could have had a great impact
12
13 405 on the overall trial results.

14
15
16 406 The creation of this research protocol prompted us to plan carefully all the details of the systematic
17
18 407 review and to anticipate and address potential problems before their actual occurrence. Arbitrary
19
20 408 decision making concerning any procedure of this systematic review is prevented, resulting again in
21
22 409 a decreased risk of publication bias and selective reporting bias. The protocol allows reproducible
23
24 410 and transparent research for future reviewers.

25
26
27
28 411 Possible limitations of our review include a potentially insufficient number of cancer deaths in the
29
30 412 studies and high heterogeneity, which could both negatively influence the statistical power of the
31
32 413 meta-analyses. However, it is still too early to judge whether these limitations occur.

33
34
35 414 The quality of selected studies will be assessed and the quality of the evidence will be judged. The
36
37 415 ultimate goal is to ensure the reporting of highly meaningful findings for clinicians and patients.
38
39 416 Oncologists are well aware that vitamin D deficiency and insufficiency are very common in cancer
40
41 417 patients but there is uncertainty about whether and how they should routinely perform preventive
42
43 418 screening and treatments. In some clinics, cancer patients receive a uniform dose of vitamin D with
44
45 419 a “one-dose-fits-all” approach, which does not take individual 25(OH)D levels or other patient
46
47 420 characteristics into account. The optimal dose for one person may be utterly insufficient for another
48
49 421 one to achieve beneficial vitamin D levels. Since vitamin D products are readily available in
50
51 422 pharmacies or drug stores, many patients use low-dose vitamin D supplementation as self-
52
53 423 medication. Yet, it can be doubted whether this untargeted intervention has any effect on cancer
54
55 424 prognosis. Consequently, evidence-based recommendations for high-dose vitamin D
56
57 425 supplementation are highly relevant for both, clinicians and patients.

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1
2 426 If the planned systematic review determines the efficacy of vitamin D supplementation on cancer
3
4 427 prognosis in the expected magnitude of 10-15%, the review will be used to provide clear suggestions
5
6 428 on how vitamin D can be appropriately dosed to overcome vitamin D deficiency or insufficiency in
7
8 429 cancer patients.(12) Furthermore, our systematic review would provide the evidence for statutory
9
10 430 health insurances to cover the costs for screening for vitamin D deficiency or insufficiency in cancer
11
12 431 patients and a subsequent vitamin D supplementation. With expected relatively large effects and
13
14 432 very low screening and treatment costs (A vitamin D blood test costs approx. € 20, and one year of
15
16 433 vitamin D therapy costs less than € 100.), vitamin D supplementation will be highly cost-effective.
17
18
19 434 The costs would be close to negligible compared to other current cancer treatment costs.
20
21 435

22 23 436 **Status**

24
25 437 At the time of submission, the study selection for the systematic review has not started.
26
27 438

28 29 439 **Acknowledgements**

30
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32
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34
35 442 scholarship to Sabine Kuznia.
36
37
38 443

39 40 444 **Authors' contribution**

41
42 445 All authors meet the ICMJE criteria for authorship as follows: BS and SK are the guarantors of the
43
44 446 systematic review, therefore, are accountable for all aspects of the work in ensuring that questions
45
46 447 related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
47
48 448 All authors made substantial contributions to the conception of the work. BS and SK designed the
49
50 449 search strategy and the risk of bias assessment strategy. BS developed the selection criteria, the
51
52 450 data extraction criteria, and the statistical methods. SK drafted the protocol publication, which BS
53
54 451 and HB revised critically for important intellectual content. All authors approved the final version to
55
56
57 452 be published.
58
59 453
60

1
2 454 **Contributors**

3
4 455 The following researchers have agreed to contribute to this systematic review by sharing IPD and
5
6 456 giving intellectual input for the discussion of the results: Taisuke Akutsu (Jikei University School of
7
8 457 Medicine. Tokyo, Japan), Professor Julie E. Buring (ScD. Brigham and Women's Hospital and
9
10 458 Harvard Medical School. Boston), Professor Carlos A. Camargo Jr (MD, DrPH. Massachusetts
11
12 459 General Hospital, Harvard Medical School. Boston), Professor Nancy R. Cook (ScD. Brigham and
13
14 460 Women's Hospital and Harvard Medical School. Boston), Professor I-Min Lee (MB, BS, ScD.
15
16
17 461 Brigham and Women's Hospital and Harvard Medical School. Boston), Professor JoAnn E. Manson
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24
25 465 Zealand), Professor Mitsuyoshi Urashima (MD. Jikei University School of Medicine. Tokyo, Japan),
26
27 466 Professor Jean Wactawski-Wende (PhD. University at Buffalo. Buffalo, New York).

28
29 467
30
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32
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34
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36
37
38 471 a role in the design of the review protocol, data collection, data analyses, the interpretation of results,
39
40 472 or the decision about the publication of the results.

41
42 473
43
44 474 **Data availability statement**

45
46 475 As no new data are obtained in this systematic review, no data will be made publicly available to
47
48 476 third parties. Decisions on data use by third parties can only be made by the principal investigators
49
50 477 of the original studies, taking into account the votes of the responsible ethics committees.

51
52
53 478
54
55 479 **Disclaimer**

56
57 480 The views of the authors do not necessarily reflect those of the German Cancer Research Center.

58
59 481
60

1
2 482 **Competing interests**

3
4 483 None declared.
5

6 484
7
8 485 **Patient consent for publication**

9
10 486 Not required.
11

12 487
13
14 488 **Provenance and peer review**

15
16 489 Not commissioned; externally peer-reviewed
17
18
19

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2 587 **Appendix 1:**
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4 588 Supplementary material consisting of data extraction form, risk of bias assessment, and list of
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7 589 individual patient data to be obtained from original researchers

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9 590 **Appendix 2:**
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11 591 Supplementary material consisting of PRISMA-P checklist
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2 **Figure**

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7 **Figure 1:** Draft of the study selection process
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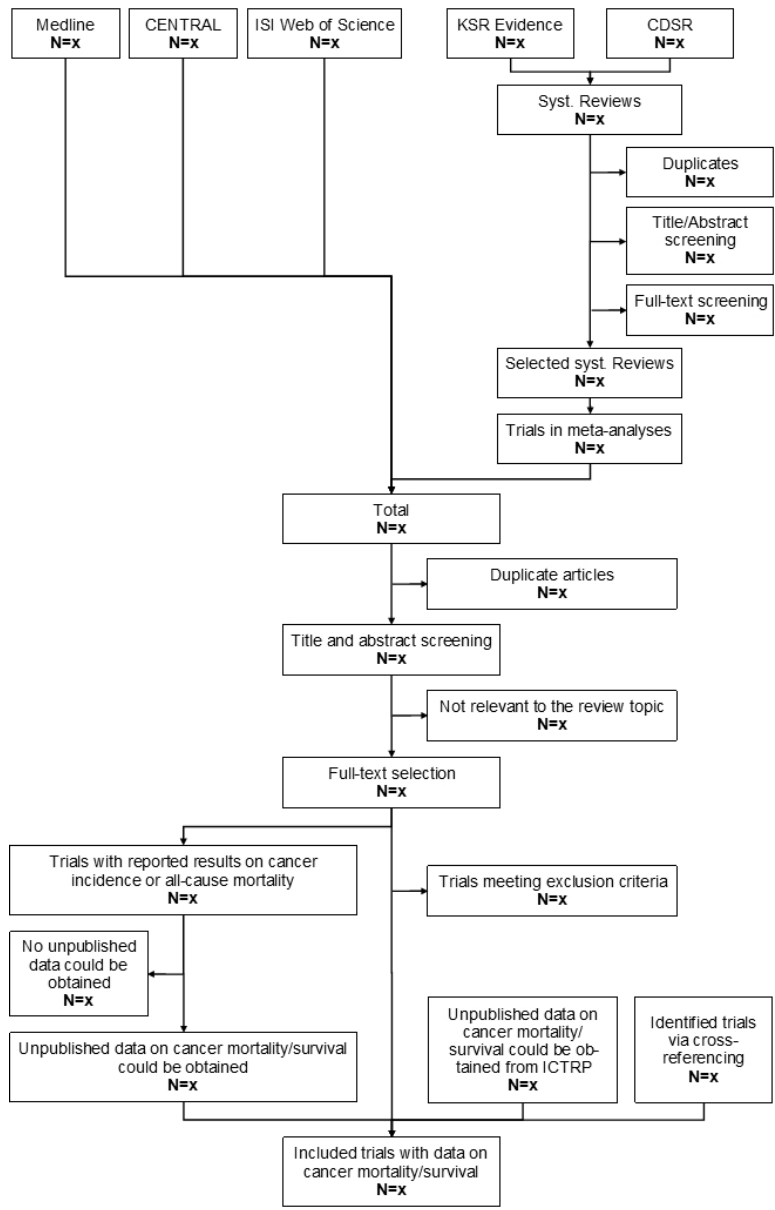


Figure 1: Draft of the study selection process

16x25mm (1000 x 1000 DPI)

Study			Population				
First author (or study name), Year (REF)	Country	Sample size	General population (y/n)	Cancer population (y/n)	Cancer site + stage	Age (mean or median)	Sex (female %)

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			Intervention			Comp
Race/ ethnicity/ skin color (white %)	BMI [kg/m ²] (n, mean or median)	25(OH)D (n, mean or median)	Vitamin D ₃ dosing regimen	Duration of vitamin D3 supplementation	Compliance in intervention group (%)	Placebo (y/other)

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Comparator	Outcomes				
Compliance in comparator group (%)	Maximum follow-up time	Mean or median follow-up time	No of cancer deaths	Cancer mortality in general population HR (95% CI)	Cancer-specific survival of cancer patients HR (95% CI)

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		Comments
Overall survival of cancer patients HR (95%CI)	Covariates adjusted for	

First author (or study name), Year (REF)	R	D	Mi	Me	S	O

Risk of bias legend

- R** Bias arising from the randomiation
- D** Bias due to deviations from
- Mi** Bias due to missing outcome data
- Me** Bias in measurement of the
- S** Bias in selection of the reported
- O** Overall risk of bias

The following variables will be obtained for all trial participants in order to conduct the IPD meta-

No.	Variables
1	Age
2	Sex
3	BMI
4	Race/ethnicity/skin color
5	Baseline 25(OH)D levels
6	Compliance
7	Randomisation group allocation
8	Baseline date
9	Death during follow-up (y/n)
10	Date of death
11	Censoring date for survivors
12	Cancer death during follow-up (y/n)
13	Date of cancer death
14	Censoring date for non-cancer deaths
15	Cancer* diagnosis during follow-up (y/n)
16	Cancer* site for each cancer during follow-up
17	Cancer* stage for each cancer during follow-up
18	Date of cancer* diagnosis for each cancer during follow-up
19	Cancer* diagnosis in first 5 years before baseline (y/n)
20	Cancer* site for each cancer in first 5 years before baseline
21	Cancer* stage for each cancer in first 5 years before baseline
22	Date of cancer* diagnosis for each cancer in first 5 years before baseline

* Excluding non-melanoma skin cancers and benign tumors

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2 **analysis:**
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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n.a. (first submission)
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	63-64
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-34
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	443-451
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input checked="" type="checkbox"/>	<input type="checkbox"/>	370-372
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	467-471
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	467-471
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	467-471
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	79-124
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	126-140
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	150-190
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	192-225
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	217-218, 224-225, figure 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-262
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-262
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	227-262, appendix 1
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	361-363, appendix 1
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	131-133, 168-172, table 2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	264-282, 347-360
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	290-297
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	297-325, 345-358
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	326-344, 351-358
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	n.a. (quantitative)

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					synthesis will be performed)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	359-360
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	364-369

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