REVIEW ARTICLE

Vitamin D Supplementation and Total Mortality

A Meta-analysis of Randomized Controlled Trials

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Background: Ecological and observational studies suggest that low vitamin D status could be associated with higher mortality from life-threatening conditions including cancer, cardiovascular disease, and diabetes mellitus that account for 60% to 70% of total mortality in high-income countries. We examined the risk of dying from any cause in subjects who participated in randomized trials testing the impact of vitamin D supplementation (ergocalciferol [vitamin D_2] or cholecalciferol [vitamin D_3]) on any health condition.

Methods: The literature up to November 2006 was searched without language restriction using the following databases: PubMed, ISI Web of Science (Science Citation Index Expanded), EMBASE, and the Cochrane Library.

Results: We identified 18 independent randomized controlled trials, including 57 311 participants. A total of 4777 deaths from any cause occurred during a trial size–adjusted mean of 5.7 years. Daily doses of vitamin D supplements varied from 300 to 2000 IU. The trial size–adjusted mean daily vitamin D dose was 528 IU. In 9 trials, there was a 1.4- to 5.2-fold difference in serum 25-hydroxyvitamin D between the intervention and control groups. The summary relative risk for mortality from any cause was 0.93 (95% confidence interval, 0.87-0.99). There was neither indication for heterogeneity nor indication for publication biases. The summary relative risk did not change according to the addition of calcium supplements in the intervention.

Conclusions: Intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates. The relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates remains to be investigated. Population-based, placebo-controlled randomized trials with total mortality as the main end point should be organized for confirming these findings.

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ECOLOGICAL STUDIES IN NORTH America have suggested that mortality from several potentially life-threatening chronic health conditions such as cancer, cardiovascular diseases, and diabetes mellitus would increase with increasing latitude, that is, with residence increasingly distant from the equator.[1,2] Other studies have shown that the survival of patients with cardiovascular disease or with some cancer (eg, lung, colorectal, and breast cancer) was greater if the diagnosis was made during summer as compared with the winter.[3,4] Increasing distance from the equator and winter period were equated to decreasing exposure to sunlight, especially to UV-B radiation (280-315 nm) because with increasing latitude, amounts of UV-B radiation reaching the earth surface decrease faster than amounts of UV-A radiation (315-400 nm).[5] Also, seasonal variations are more pronounced for UV-B radiation than for the UV-A radiation.[5] Because UV-B radiation is necessary for the synthesis of vitamin D in the skin, it has been hypothesized that associations found between latitude or seasonality and mortality from several chronic conditions could be owing to variations in vitamin D status.[6-10] Some food products may also represent a source of vitamin D, although of highly variable content (eg, fortified foods, oily fish, eggs, and butter). Hence, low vitamin D status could proceed from the conjunction of insufficient intakes (exogenous source) and of insufficient skin synthesis (endogenous source) of vitamin D. Biological findings have reinforced the likelihood of the vitamin D hypothesis. First, vitamin D receptors have been found in various organs, and activation of these receptors by 1α,25 dihydroxyvitamin D_3 (calcitriol), the physiologically active form of vitamin D, induces cell differentiation and inhibits proliferation, invasiveness, angiogenesis, and metastatic potential.[11,12] These biological phenomena are typical of cancer genesis and some of them (eg, differentiation and proliferation) are also involved in cardiovascular ischemic diseases. Second, many tissues express the 1α-hydroxylase enzyme.[11] So, after 25-hydroxylation of vitamin D in

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the liver, many cell types are able to convert the circulating 25-hydroxyvitamin D into 1α,25-dihydroxyvitamin D, and autocrine or paracrine production of 1α,25-dihydroxyvitamin D would depend on serum concentration of 25-hydroxyvitamin D.

In industrialized countries, cancer, cardiovascular diseases, and metabolic disorders such as diabetes mellitus account for 60% to 70% of deaths among subjects 50 years or older.[13,14] If the associations made between vitamin D and these conditions were consistent, then interventions effectively strengthening vitamin D status should result in reduced total mortality. In this meta-analysis, we examined the risk of dying from any cause in subjects who participated in randomized trials testing the impact of vitamin D supplementation (ergocalciferol [vitamin D_2] or cholecalciferol [vitamin D_3]) on any health condition.

METHODS

The study design was the quantitative synthesis of randomized controlled trials that could contribute to evaluating the impact of vitamin D supplementation on death from any cause.

INTERVENTION AND OUTCOME

The outcome of this analysis was total mortality; the supplementation evaluated was vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol). Calcitriol and other vitamin D analogues have seldom been tested for prevention purposes. The few small trials that used these compounds for fracture prevention reported a total of 20 deaths from all causes and demonstrated their toxic effects, mainly hypercalcemia.[15] We did not include trials that evaluated treatment with 1α-hydroxyvitamin D_3 (alfacalcidol), the physiologically active form of vitamin D (1α,25-dihydroxyvitamin D_3 [calcitriol]), or other vitamin D analogues in patients with advanced prostate cancer, chronic renal disease, or end-stage renal disease or in patients undergoing renal dialysis.

LITERATURE SEARCH

The search was carried out for clinical trials, and no language or time restrictions were applied. The literature up to November 2006 was searched using the following databases: PubMed, ISI Web of Science (Science Citation Index Expanded), EMBASE, and the Cochrane Library. For intervention, the following keywords or corresponding MeSH terms were used: *vitamin D*, *cholecalciferol*, and *ergocalciferol*. For methods, the following keywords and or corresponding MeSH terms used were *randomized controlled trial* and *placebo*. A first general search was done using combinations of keywords for intervention and for method. After that, we made searches using combinations of intervention keywords with the following outcome keywords (and their corresponding MeSH terms): *congestive heart failure*, *coronary heart disease*, *cardiovascular disease*, *fracture*, *bone mineral density*, and *bone turnover*. *Mortality* was not a helpful keyword because none of the trials with vitamin D supplements, except for 1 trial in the United Kingdom,[16] had mortality as an end point.

The search for keywords in the title and in the abstract was done systematically. A manual search was done of references cited in the selected articles and in selected reviews or books. Any abstract or article whose title or summary contained at least 1 intervention keyword and 1 method keyword or 1 intervention keyword and 1 outcome keyword was retrieved and read.

SELECTION OF ARTICLES

For an article to be included in our analysis, it must have met the following criteria:

1. To represent the principal published report on a randomized controlled trial evaluating an intervention with vitamin D. The addition of calcium supplements in the intervention group and the absence of a placebo for vitamin D in the control group (ie, an open-label trial) were not exclusion criteria.
2. To be independent from other studies to avoid giving double weight to estimates derived from the same trial.
3. To have deaths from any cause reported separately for the intervention and the control groups. If in an article the number of all-cause deaths was not reported by treatment group, we tried to contact corresponding authors to obtain the missing information.
4. To have subjects randomized to the intervention and control groups on an individual basis. Cluster randomization (eg, a nursing home taken as a randomization unit) was not valid because mortality in a specific cluster could be increased by a health event (eg, an influenza epidemic) affecting this cluster and not the others.
5. To have sufficient information to allow adequate estimation of the relative risks (RRs) and 95% confidence intervals (CIs) (ie, crude data or adjusted RRs and standard errors, 95% CIs, or *P* values) to estimate mortality risk after vitamin D intake vs placebo or control.

DESCRIPTION OF STUDIES RETRIEVED

A total of 992 articles or abstracts were retrieved and checked for relevance in terms of intervention, design, and reporting of mortality data. This process resulted in retrieving a total of 27 articles or abstracts that published information on randomized clinical trials evaluating effects of vitamin D supplementation on any end point and reporting data on deaths. Of these 27 articles, 9 were not included in the meta-analysis for the following reasons: (1) Two articles referred to the same trial.[17,18] (2) Three did not report deaths by treatment arm (16 deaths overall) and this information could not be retrieved.[19-21] (3) In 2 trials, the intervention consisted of a set of drugs including vitamin D.[22,23] (4) Two trials were based on cluster randomization,[24,25] and 1 of them did not report deaths by trial groups.[25] A trial in England[24] randomized 118 homes for elderly people, including 3717 participants with a mean age of 85 years. The intervention was equivalent to a daily dose of 1100 IU of ergocalciferol. (5) A placebo-controlled randomized trial was excluded because it was impossible to relate numbers of reported deaths (about 17 deaths) with numbers of subjects in randomization groups.[26]

One article[27] compared an open-label trial with a subgroup of the placebo-controlled RECORD (Randomised Evaluation of Calcium Or vitamin D) trial.[28] We used the data from the open-label trial and not from the subgroup of the RECORD trial to have independent studies. For the open-label trial, we took the numbers of deaths at the end of the follow-up that were mentioned in another report.[15] **Table 1** summarizes the 18 studies that were used for the meta-analysis.

STATISTICAL ANALYSIS

Denominators used for calculating death rates in each randomization group were all participants randomized to that group (intent-to-treat analysis). Some trials, such as the RECORD trial,[28] had a factorial design (eg, calcium and vitamin D supplementation and vitamin D supplementation alone compared with calcium supplementation alone or with placebo). In such cases,

Table 1. Vitamin D Supplements and All-Cause Mortality: Overview of Trials Selected for Meta-analysis

Source	Country	Main End Point(s)	Study Population	Age at Baseline, y	Intervention	Placebo in Control Group	Mean Follow-up, mo
Chapuy et al,[29] 1992	France	Clinical fractures	N=3270 (F, institutionalized)	69-106 (Range)	Daily oral cholecalciferol (800 IU) + calcium (1.2 g)	Yes	18
Lips et al,[30] 1996	The Netherlands	Clinical fractures	N=2578 (M and F, community dwelling and institutionalized)	≥70	Daily oral cholecalciferol (400 IU)	Yes	42
Baeksgaard et al,[31] 1998	Denmark	Bone mineral density	N=160 (F, community dwelling)[a]	58-67 (Range)	Daily oral cholecalciferol (560 IU) + calcium (1 g)	Yes	24
Komulainen et al,[18] 1999	Finland	Bone mineral density	N=232 (F, community dwelling)[b]	47-56 (Range)	Daily oral cholecalciferol (300 IU + calcium [0.5 g] during 3 first years and 100 IU + calcium [0.5 g] in the last year)	No	60
Krieg et al,[32] 1999	Switzerland	Bone mineral density	N=248 (F, institutionalized)	62-98 (Range)	Daily oral cholecalciferol (880 IU) + calcium (1 g)	No	24
Chapuy et al,[33] 2002	France	Bone mineral density, hip fractures	N=583 (F, institutionalized)	64-99	Daily oral cholecalciferol (800 IU) + calcium (1.2 g)	Yes	24
Meyer et al,[34] 2002	Norway	Clinical fractures	N=1144 (M and F, institutionalized)	85 (Mean)	Daily oral cod liver oil, more or less cholecalciferol (400 IU)	Yes[c]	24
Trivedi et al,[16] 2003	United Kingdom	Clinical fractures and all-cause mortality	N=2686 (M and F, community dwelling)	65-84 (Range)	Oral cholecalciferol (100 000 IU every 4 mo)	Yes	60
Latham et al,[35] 2003	New Zealand and Australia	Physical health and falls	N=243 (M and F, frail elderly subjects)	79 (Mean)	Single-injection cholecalciferol (300 000 IU)	Yes	6
Harwood et al,[36] 2004	United Kingdom	Falls and bone turnover	N=150 (M and F with operated hip fracture)	67-92 (Range)	1 Group with single-injection ergocalciferol (300 000 IU), 1 group with single-injection ergocalciferol (300 000 IU) + oral calcium (1 g), 1 group with daily oral cholecalciferol (800 IU + calcium [1 g])	No	12
Avenell et al,[27] 2004[d]	United Kingdom	Compliance to vitamin D and calcium supplements	N=134 (M and F with past low-energy fracture)	≥70	Daily oral cholecalciferol (800 IU only) or daily oral cholecalciferol (800 IU) + calcium (1 g)[e]	Yes and no	12
Meier et al,[37] 2004	Germany	Bone turnover	N=55 (M and F, community dwelling)	33-78 (Range)	Daily oral cholecalciferol (500 IU) + calcium (0.5 g)	No	24
Brazier et al,[38] 2005	France	Safety of supplementation with vitamin D and calcium	N=192 (F with vitamin D insufficiency)	>65	Daily oral cholecalciferol (800 IU) + calcium (1 g)	Yes	12
Porthouse et al,[39] 2005	United Kingdom	Clinical fractures	N=3314 (F, community dwelling, at risk of hip fracture)	≥70	Daily oral cholecalciferol (800 IU) + calcium (1 g)	No	36
RECORD Trial,[28] 2005	United Kingdom	Clinical fractures	N=5292 (M and F, community dwelling, with past low-energy fracture)	≥70	Daily oral cholecalciferol (800 IU only) or daily oral cholecalciferol (800 IU) + calcium (1 g)[f]	Yes	60
Flicker et al,[40] 2004	Australia	Falls and clinical fractures	N=625 (M and F, institutionalized)	83.5 (Mean)	Weekly oral ergocalciferol (10 000 IU), followed by daily oral ergocalciferol (1000 IU)	Yes	24
Schleithoff et al,[41] 2006	Germany	Survival of patients with congestive heart failure	N=123 (M and F with congestive heart failure)	56 (Mean)	Daily oral cholecalciferol (2000 IU only) or daily oral cholecalciferol (800 IU) + calcium (0.5 g)	Yes	15
Jackson et al,[42] 2006 and Wactawski-Wende et al,[43] 2006	United States	Clinical fractures and colorectal cancer incidence	N=36 282 (F, community dwelling)	50-79 (Range)	Daily oral cholecalciferol (400 IU) + calcium (1 g)	Yes	84

Abbreviations: F, female; M, male.

[a] Women randomized to multivitamin supplement containing vitamin D were not included in the meta-analysis.

[b] Women randomized to hormone therapy or to hormone therapy and vitamin D groups were not included in the meta-analysis.

[c] Cod liver oil without cholecalciferol.

[d] The same article reported 2 randomized controlled trials. We took into account only the open label trial because the placebo-controlled trial was a part of the RECORD trial.[28] Mortality data of the open label trial we used were those reported by Avenell et al[15] in 2005.

[e] Intervention assumed to be the same as in the RECORD Trial.[28]

[f] Factorial design.

Table 2. Serum Levels of 25-Hydroxyvitamin D in Randomized Trials With Vitamin D Supplements[a]

Source	Mean Follow-up, mo	Daily Dose of Vitamin D in Intervention Group, IU	Mean Serum 25-Hydroxyvitamin D_3 (ng/mL)[b]				Ratio for In-Study Level, Intervention vs Control Group
			Intervention Group		Control Group		
			Baseline	In Study	Baseline	In Study	
Chapuy et al,[29] 1992	18	800	14.5	42.0	14.5	11.0	3.8
Lips et al,[30] 1996	42	400	10.4	24.8	10.8	9.2	2.7
Krieg et al,[32] 1999	24	880	11.9	26.5	11.7	5.7	4.6
Chapuy et al,[33] 2002[c]	24	800	8.8	31.0	9.1	6.0	5.2
Meyer et al,[34] 2002	24	400	18.8	25.6	20.4	18.4	1.4
Trivedi et al,[16] 2003	60	830[d]	NA	29.7	NA	21.4	1.4
Meier et al,[37] 2004	24	500	30.1	35.1	30.8	20.5	1.7
RECORD Trial,[28] 2005	60	800	15.2	24.8	15.2	17.4	1.4
Schleithoff et al,[41] 2006	15	2000	14.4	41.2	15.3	18.9	2.2

Abbreviation: NA, not applicable.
[a] Trials in Table 1 not included in Table 2 did not report serum 25-hydroxyvitamin D levels.
[b] Measurements of serum levels were always performed in subsamples of subjects in intervention and control groups.
[c] In-study serum 25-hydroxyvitamin D levels were derived from Figure 1 in the original publication.[33]
[d] Estimated from oral cholecalciferol, 100 000 IU every 4 mo.

in the meta-analyses, data related to groups receiving vitamin D were considered as coming from the "intervention group" and data related to groups not receiving vitamin D were considered as coming from the "control group."

In most of the selected studies, mortality was a relatively rare event, and we therefore ignored the distinction between the various measures of relative risk (ie, odds ratio, rate ratio, and risk ratio). We transformed the RR estimates and their CIs into log RR, and we calculated the corresponding variance using the formula proposed by Greenland[44] in 1987. When estimates were not given, we calculated them from tabular data, and we used the Woolf formula to evaluate the standard error of the log odds ratio.[44] Logit estimators were used for a correction of 0.5 in every cell of those tables that contained a zero (Proc Freq with SAS [SAS Windows version 8.02; SAS Institute Inc, Cary, North Carolina; 1999]).

The association between intake of vitamin D supplements and all-cause mortality across selected trials was computed as a summary RR (SRR) with 95% CIs. The SRR was considered statistically significant if the 95% CI did not include 1.0.

We assessed the homogeneity of the effect across studies using the large sample test based on the χ^2 statistic. Since the χ^2 test has limited power, we considered that statistically significant heterogeneity existed when the P value was $\leq .10$.[45] Subgroup analyses and meta-regressions were carried out to investigate between-study heterogeneity focusing on type of study, type of control, length of follow-up, vitamin D dose, use of calcium, year of publication, and country. Heterogeneity was compared among subgroup analyses by using the I^2 parameter, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance.[46] The SRR was estimated pooling the study-specific estimates by random effects models fitted using SAS (Proc Mixed) with maximum likelihood estimate. Two funnel plot–based approaches were used for assessing publication bias: the sensitivity analysis of Copas and Shi[47] and the funnel plot regression of ln(RR) on the sample size, weighted by the inverse of the pooled variance.[48]

RESULTS

The main meta-analysis was carried out on 18 independent randomized controlled trials with individual randomization (Table 1): 12 placebo-controlled and 6 open-label trials. The numbers of trial participants varied from 55 to 36 282. Mean follow-up varied between 6 months to 7 years, with a mean of 5.7 years after adjustment for trial sizes.

The mean daily dose of vitamin D supplements varied from 300 IU[18] to 2000 IU,[41] but most of the daily doses were between 400 IU and 833 IU. When taking trial sizes into account, the mean daily vitamin D dose was 528 IU. **Table 2** indicates a substantial increase from baseline levels of serum 25-hydroxyvitamin D levels in intervention groups, while levels tended to decrease in control groups, translating to a 1.4- to 5.2-fold difference in serum 25-hydroxyvitamin D level between intervention and control groups. However, increases from baseline levels and in-study differences between intervention and control groups seemed unrelated to daily dose taken. Compliance with taking vitamin D supplements in the largest trials (see "Trials With Decent Statistical Power" in the **Figure**) was 48% in the RECORD Trial,[28] 59% in the Women's Health Initiative trial,[42,43] 63% in the trial by Porthouse et al,[39] 68% in the trial by Ficker et al,[40] 79% in the trial by Meyer et al,[34] 80% in the trial by Trivedi et al,[16] 83% in the trial by Chapuy et al[33] in 2002, 85% in the trial by Lips et al,[30] and 95% in the trial by Chapuy et al[29] in 1992.

The 18 trials included 57 311 participants, and 4777 deaths for any cause occurred during follow-up. The Figure shows for each selected trial the RRs of dying from any cause associated with taking vitamin D supplements. The SRR synthesizing results of the 18 trials indicated a significant decrease in the risk of all-cause mortality with using vitamin D supplements (SRR, 0.93; 95% CI, 0.87-0.99). There was no indication for heterogeneity ($P = .52$) or of publication bias ($P = .37$ with the method of Copas and Shi[47] and $P = .77$ with the method of Macaskill et al[48]).

A subgroup analysis (**Table 3**) shows no appreciable change in SRR according to trial duration and dose of vitamin D supplements. Calcium supplements seemed not to be involved in the total mortality decrease, as the SRRs remained similar in trials with or

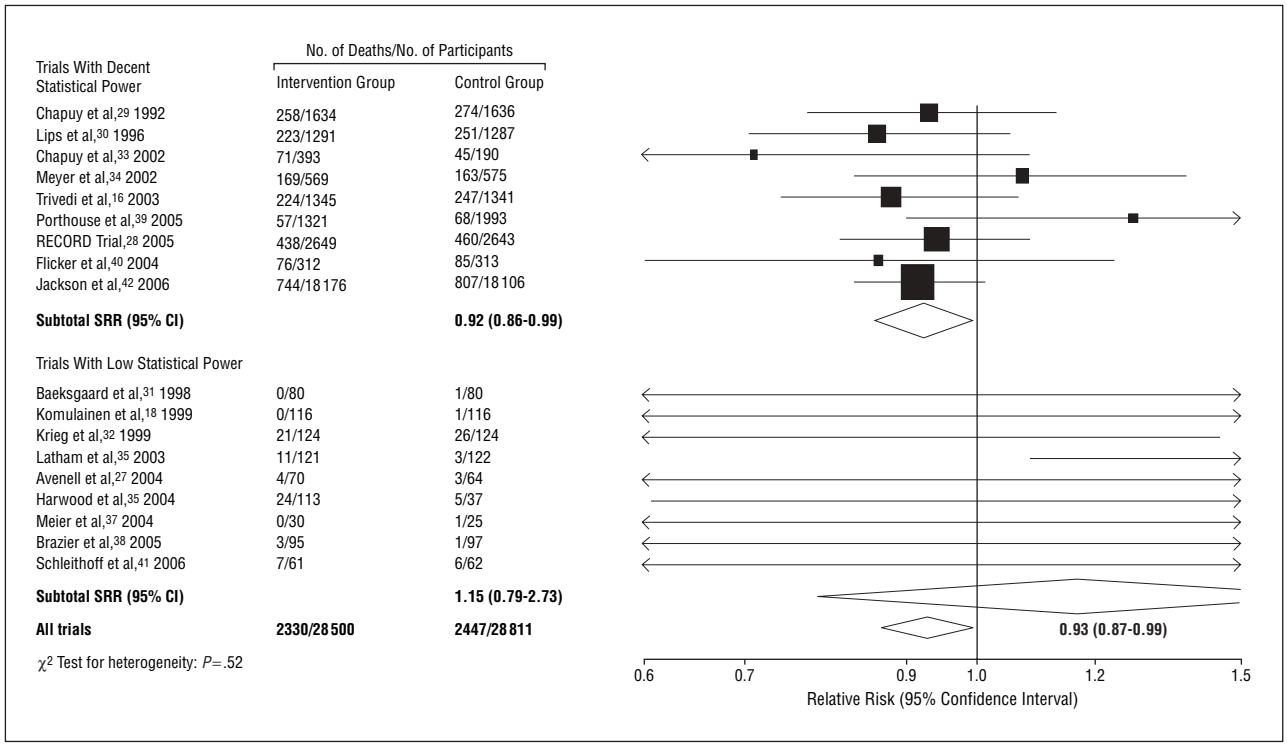

Figure. Meta-analysis of data on all-cause mortality in 18 randomized controlled trials with vitamin D. SRR indicates summary relative risk.

Table 3. Vitamin D Supplements and All-Cause Mortality: Subgroup and Sensitivity Analysis

Variable	No. of Trials in the Meta-Analysis	SRR (95% CI)	I^2 Parameter, %[a]	χ^2 for Heterogeneity, *P* Value
Subgroup analysis				
Follow-up ≥3 y	6	0.92 (0.83-1.01)	0	.50
Follow-up <3 y	12	0.95 (0.83-1.10)	5	.40
Vitamin D, ≥800 IU/d	12	0.93 (0.85-1.03)	15	.30
Vitamin D, 300 to 799 IU/d	6	0.92 (0.82-1.03)	0	.70
Placebo-controlled trials only	12	0.92 (0.86-0.98)	0	.51
Open-label trials only[b]	6	1.10 (0.84-1.45)	0	.67
Intervention was vitamin D and calcium supplements	13	0.93 (0.86-1.01)	0	.69
Intervention was vitamin D supplements only	5	0.91 (0.78-1.06)	42	.14
Cholecalciferol (vitamin D_3) and not ergocalciferol (vitamin D_2)	16	0.93 (0.87-0.98)	0	.43
Sensitivity analysis				
Exclusion of Meyer et al,[34] 2002	17	0.92 (0.86-0.98)	0	.54
Inclusion of Law et al,[24] 2006	19	0.97 (0.89-1.06)	32	.09

Abbreviation: CI, confidence interval; SRR, summary relative risk.
[a] The I^2 parameter represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.[46]
[b] No placebo for vitamin D in the control group.

without calcium supplements as part of the intervention. Exclusion of the quasirandomized trial[34] did not affect results. Inclusion of 1 cluster-randomized trial[25] increased the SRR but also brought substantial heterogeneity. In this respect, exclusion of this trial was justified.

COMMENT

Results of this meta-analysis of randomized controlled trials suggest that intake of vitamin D supplements may decrease total mortality during trial duration. Publication bias toward concealment of trial results showing no impact of vitamin D supplements on all-cause mortality is not likely because total mortality did not constitute a main end point for any of the 18 trials included in the meta-analysis except 1.[16] Timing of deaths during trials was never reported, and we thus could not assess whether exclusion of deaths occurring during the first year of follow-up would have modified the SRRs.

The effect on mortality was not likely to be due to calcium supplements, since the 5 trials that did not include calcium supplements in the intervention group[16,29,34,35,40] had an SRR similar to those found with trials that included both vitamin D and calcium supplements. No relationship was found with dose of vitamin D supplements, but in most trials, the daily dose range was relatively narrow (ie, 400-830 IU), and large variations in size of trials and in compliance to interventions preclude any conclusion on optimal vitamin D daily dose associated with mortality reduction.

Most trials included in the meta-analysis were conducted in frail elderly people who are at high risk of fall or of low-energy fracture, who often have low serum 25-hydroxyvi-

tamin D levels. Vitamin D is known to increase postural stability and to reduce fall incidence by 22% in elderly subjects, but about 15 elderly people must take vitamin D supplements for avoiding 1 person from falling.[49] Such an effect cannot translate to a 7% decrease in total mortality. Also, the Women's Health Initiative,[42,43] which accounted for nearly half of the participants considered in this meta-analysis, included younger women with a low probability to die because of falls.

Vitamin D regimens used in trials ranged from 300 to 833 IU, and most vitamin D supplements publicly available include a daily dose of 400 IU to 600 IU that entailed no toxic effects. Serum concentration of 25-hydroxyvitamin D is considered as a good reflection of skin synthesis and food intakes of vitamin D.[50] Data from 9 trials showed that the intake of vitamin D supplements resulted in increases in serum 25-hydoxyvitamin D levels. Such data were not available for the other trials, including the Women's Health Initiative.[42,43] It was thus not possible to assess from this meta-analysis whether a correlation exists between the magnitude of mortality reduction and the difference in circulating 25-hydroxyvitamin D.

Of the 18 randomized trials, 2 included in this meta-analysis (a trial in the United Kingdom[16] and the Women's Health Initiative[43]) reported the association of vitamin D supplements with incidence and mortality of some cancers and of cardiovascular diseases. In the United Kingdom trial, the rate ratios (95% CIs) between the intervention and control groups for the incidence of cardiovascular diseases, cancers, and colorectal cancer were 0.90 (0.77-1.06), 1.11 (0.86-1.42), and 1.02 (0.60-1.74), respectively.[16] For mortality, these ratios were 0.84 (0.65-1.10), 0.86 (0.61-1.20), and 0.62 (0.24-1.60), respectively. In the Women's Health Initiative trial, rate ratios (95% CIs) for incidence of cancer and of colorectal cancer were 0.98 (0.91-1.05) and 1.08 (0.86-1.34), respectively, and rate ratios (95% CIs) for mortality were 0.89 (0.77-1.03) and 0.82 (0.52-1.29), respectively.[43] Hence, although none of these results reached statistical significance, incidence rate ratios were always close to 1.0, while mortality rate ratios were always lower, suggesting that vitamin D supplementation would affect mortality associated with cancers and cardiovascular diseases, but would probably have less of an effect (or not at all) on their incidence. This hypothesis is reinforced by recent observations: one prospective cohort study among adult Finish male smokers showed an increasing incidence of pancreas cancer with increasing serum 25-hydroxyvitamin D level.[51] In contrast, another prospective study showed that women diagnosed as having advanced breast cancer had lower serum 25-hydroxyvitamin D concentrations than women diagnosed as having less advanced breast cancer.[52] In a prospective study in which serum 25-hydoxyvitamin D concentration was estimated using an indirect method based on questions, the influence of decreasing concentrations was more manifest for cancer mortality than for cancer incidence.[53]

A meta-analysis of randomized trials on supplementation with beta carotene, vitamins A and E, ascorbic acid, and selenium found an increased RR for all-cause mortality of 1.06 (95% CI, 1.02-1.10) associated with the taking of these supplements.[54] A randomized controlled trial of the Women's Health Study found no effect of supplementation with 600 IU/d of vitamin E on total mortality.[55] These results are contrasting with the results from our meta-analysis on vitamin D supplements. Our results also provide reassurance that at ordinary doses, long-term vitamin D supplementation does not seem to be associated with an overall adverse effect.

Mechanisms by which vitamin D supplementation would decrease all-cause mortality are not clear. The physiologically active form of vitamin D (1α,25 dihydroxyvitamin D [calcitriol]) acts as a hormone that has pleiotropic skeletal and extra skeletal effects on, among other things, calcium homeostasis, bone formation, cellular proliferation and differentiation, immune system, bile acid transport, rennin production, the endothelium and vascular walls, and the endocrine system.[11,56] Some effects mediated through the activation of the vitamin D receptor, such as inhibition of cellular proliferation and activation of cellular differentiation,[12,57] could reduce aggressiveness of cancerous processes and expansion of atheromatous lesions. Interestingly, the ability of strong cholesterol reducers, the statins, to decrease all-cause mortality could partly be due to increases in vitamin D levels they would provoke or though acting as vitamin D analogues on vitamin D receptors.[10,58] The biological mechanism by which vitamin D would prevent and possibly reduce the severity of type 2 diabetes mellitus[59] remains unknown.[60]

In conclusion, the intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates. The relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates remains to be investigated. Population-based, placebo-controlled randomized trials in people 50 years or older for at least 6 years with total mortality as the main end point should be organized to confirm these findings.

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Correction

Error in Figure. In the Original Investigation by Fitó et al titled "Effect of a Traditional Mediterranean Diet on Lipoprotein Oxidation: A Randomized Controlled Trial" published in the June 11, 2007, issue of the ARCHIVES (2007;167[11]:1195-1203), an error occurred in **Figure 2** wherein the y-axis labels in parts A and C were mistakenly transposed. A corrected figure and legend appears below.

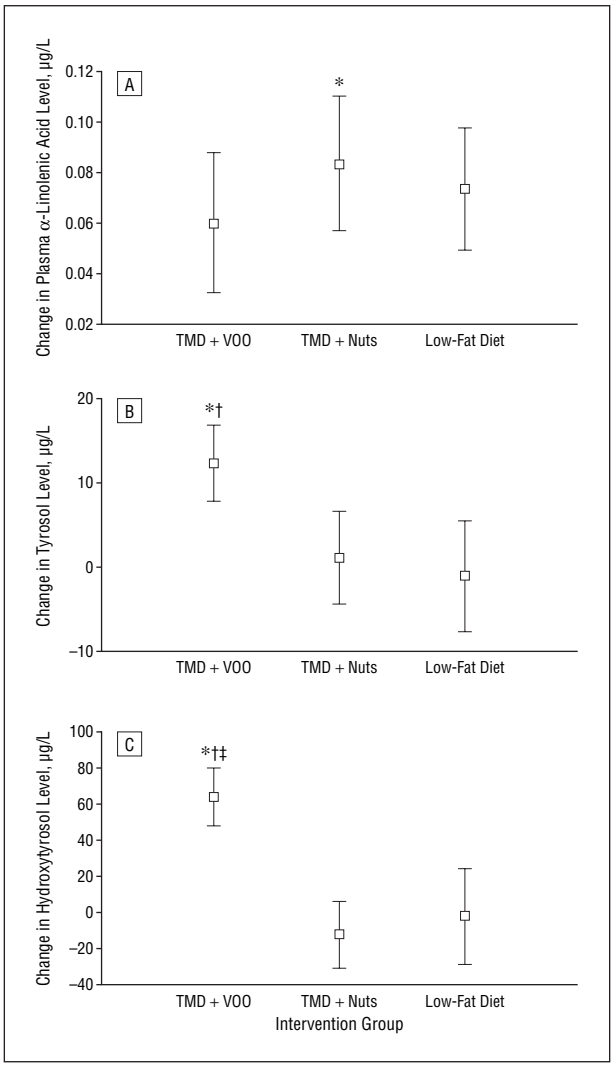

Figure 2. Mean±SD changes in plasma α-linolenic acid (A), urinary tyrosol (B), and hydroxytyrosol (C) after 3-month interventions. *$P<.05$ vs the corresponding baseline. †$P<.05$ vs low-fat diet group. ‡$P<.05$ vs TMD + nuts group. TMD indicates traditional Mediterranean diet; VOO, virgin olive oil.