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 D2] or cholecalciferol [vitamin D3]) 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 4,777 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.

Arch Intern Med. 2007;167(16):1730-1737

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. 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. 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). Also, seasonal variations are more pronounced for UV-B radiation than for the UV-A radiation. 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. 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 D3 (calcitriol), the physiologically active form of vitamin D, induces cell differentiation and inhibits proliferation, invasiveness, angiogenesis, and metastatic potential. 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. So, after 25-hydroxylation of vitamin D in

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

In industrialized countries, cancer,
cardiovascular diseases, and metabolic disorders such as dia-
etes 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 condi-
tions were consistent, then inter-
ventions effectively strengthening
vitamin D status should result in
reduced total mortality. In this meta-
analysis, we examined the risk of dy-
ing from any cause in subjects who
participated in randomized trials
testing the impact of vitamin D
supplementation (ergocalciferol [vi-
tamin D₂] or cholecalciferol [vita-
m in D₃]) 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 evalu-
ated was vitamin D₂ (ergocalciferol) or
vitamin D₃ (cholecalciferol). Calcitriol
and other vitamin D analogues have sel-
dom been tested for prevention pur-
poses. The few small trials that used
these compounds for fracture preven-
tion reported a total of 20 deaths from
causes and demonstrated their toxic
effects, mainly hypercalcemia.15 We
did not include trials that evaluated
or calcium supplements in the interven-
tion group and the absence of a placebo for
vitamin D in the control group (ie, an
open-label trial) were not exclusion
criteria.

To be independent from other
studies without giving double weight to
estimates derived from the same trial.

To have deaths from any cause re-
ported 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 ob-
tain the missing information.

To have subjects randomized to
the intervention and control groups on
an individual basis. Cluster randomi-
ation (eg, a nursing home taken as a ran-
domization unit) was not valid because
mortality in a specific cluster could be
increased by a health event (eg, an in-
fluenza epidemic) affecting this cluster
and not the others.

5. To have sufficient information to
allow adequate estimation of the rela-
tive risks (RRs) and 95% confidence in-
tervals (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 random-
ized clinical trials evaluating effects of vi-
tamin 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 rea-
sons: (1) Two articles referred to the same
trial17,18 (2) Three did not report deaths by
treatment arm (16 deaths overall) and
this information could not be re-
trieved19,20 (3) In 2 trials, the interven-
tion consisted of a set of drugs including
vitamin D.21,22 (4) Two trials were based
on cluster randomization,23,24 and 1 of
them did not report deaths by trial
groups.25 A trial in England24 random-
ized 118 homes for elderly people, in-
cluding 3717 participants with a mean age
of 85 years. The intervention was equiva-
 lent to a daily dose of 1100 IU of ergocal-
ciferol. (5) A placebo-controlled random-
ized 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 article27 compared an open-
label trial with a subgroup of the placebo-
controlled RECORD (Randomised Evalua-
tion 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.13

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 de-
sign (eg, calcium and vitamin D supple-
mentation and vitamin D supplementation
alone compared with calcium supplemen-
tation alone or with placebo). In such cases,
### Table 1. Vitamin D Supplements and All-Cause Mortality: Overview of Trials Selected for Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Main End Point(s)</th>
<th>Study Population</th>
<th>Age at Baseline, y</th>
<th>Intervention</th>
<th>Placebo in Control Group</th>
<th>Mean Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy et al., 1992</td>
<td>France</td>
<td>Clinical fractures</td>
<td>N=2488 (M and F, institutionalized)</td>
<td>≥70</td>
<td>Daily oral cholecalcifer         (800 IU) + calcium (1.2 g)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Lips et al., 1996</td>
<td>The Netherlands</td>
<td>Clinical fractures</td>
<td>N=1144 (M and F, institutionalized)</td>
<td></td>
<td>Daily oral cholecalcifer         (800 IU) + calcium (1.2 g)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Baeksgaard et al., 1998</td>
<td>Denmark</td>
<td>Bone mineral density</td>
<td>N=160 (F, community dwelling)</td>
<td>58-67</td>
<td>Daily oral cholecalcifer         (500 IU) + calcium (1 g)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Komulainen et al., 1999</td>
<td>Finland</td>
<td>Bone mineral density</td>
<td>N=232 (F, community dwelling)</td>
<td>47-56</td>
<td>Daily oral cholecalcifer         (300 IU + calcium [0.5 g] during 3 first years and 100 IU + calcium [0.5 g] in the last year)</td>
<td>No</td>
<td>60</td>
</tr>
<tr>
<td>Krieg et al., 1999</td>
<td>Switzerland</td>
<td>Bone mineral density</td>
<td>N=248 (F, institutionalized)</td>
<td>62-98</td>
<td>Daily oral cholecalcifer         (800 IU) + calcium (1.2 g)</td>
<td>No</td>
<td>24</td>
</tr>
<tr>
<td>Chapuy et al., 2002</td>
<td>France</td>
<td>Bone mineral density, hip fractures</td>
<td>N=583 (F, institutionalized)</td>
<td>64-99</td>
<td>Daily oral cholecalcifer         (800 IU) + calcium (1.2 g)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Meyer et al., 2002</td>
<td>Norway</td>
<td>Clinical fractures</td>
<td>N=1144 (M and F, institutionalized)</td>
<td>85 (Mean)</td>
<td>Daily oral cod liver oil, more or less cholecalcifer (400 IU)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Trivedi et al., 2003</td>
<td>United Kingdom</td>
<td>Clinical fractures and all-cause mortality</td>
<td>N=2686 (M and F, community dwelling)</td>
<td>65-84</td>
<td>Oral cholecalcifer (100 000 IU every 4 mo)</td>
<td>Yes</td>
<td>60</td>
</tr>
<tr>
<td>Latham et al., 2003</td>
<td>New Zealand and Australia</td>
<td>Physical health and falls</td>
<td>N=243 (M and F, frail elderly subjects)</td>
<td>79 (Mean)</td>
<td>Single-injection cholecalcifer (300 000 IU)</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Harwood et al., 2004</td>
<td>United Kingdom</td>
<td>Falls and bone turnover</td>
<td>N=150 (M and F with operated hip fracture)</td>
<td>67-92</td>
<td>1 Group with single-injection ergocalcifer (300 000 IU), 1 group with single-injection ergocalcifer (300 000 IU) + oral calcium (1 g), 1 group with daily oral cholecalcifer (800 IU + calcium [1 g])</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Avenell et al., 2004</td>
<td>United Kingdom</td>
<td>Compliance to vitamin D and calcium supplements</td>
<td>N=134 (M and F with past low-energy fracture)</td>
<td>≥70</td>
<td>Daily oral cholecalcifer         (800 IU only) or daily oral cholecalcifer (800 IU + calcium [1 g])</td>
<td>Yes and no</td>
<td>12</td>
</tr>
<tr>
<td>Meier et al., 2004</td>
<td>Germany</td>
<td>Bone turnover</td>
<td>N=55 (M and F, community dwelling)</td>
<td>23-78 (Mean)</td>
<td>Daily oral cholecalcifer         (500 IU) + calcium (1 g)</td>
<td>No</td>
<td>24</td>
</tr>
<tr>
<td>Brazier et al., 2004</td>
<td>France</td>
<td>Safety of supplementation with vitamin D and calcium</td>
<td>N=192 (F with vitamin D deficiency)</td>
<td>&gt;65</td>
<td>Daily oral cholecalcifer         (800 IU + calcium [1 g])</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>Porthouse et al., 2005</td>
<td>United Kingdom</td>
<td>Clinical fractures</td>
<td>N=3314 (F, community dwelling, at risk of hip fracture)</td>
<td>≥70</td>
<td>Daily oral cholecalcifer         (800 IU) + calcium (1 g)</td>
<td>No</td>
<td>36</td>
</tr>
<tr>
<td>RECORD Trial, 2005</td>
<td>United Kingdom</td>
<td>Clinical fractures</td>
<td>N=123 (M and F with congestive heart failure)</td>
<td>56 (Mean)</td>
<td>Daily oral cholecalcifer         (800 IU only) or daily oral cholecalcifer (800 IU + calcium [1 g])</td>
<td>Yes</td>
<td>60</td>
</tr>
<tr>
<td>Flicker et al., 2004</td>
<td>Australia</td>
<td>Falls and clinical fractures</td>
<td>N=625 (M and F, institutionalized)</td>
<td>83.5 (Mean)</td>
<td>Weekly oral ergocalcifer (10 000 IU), followed by daily oral ergocalcifer (1000 IU)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Schleithoff et al., 2006</td>
<td>Germany</td>
<td>Survival of patients with congestive heart failure</td>
<td>N=362 (F, community dwelling)</td>
<td>50-79 (Range)</td>
<td>Daily oral cholecalcifer (2000 IU only) or daily oral cholecalcifer (800 IU + calcium [0.5 g])</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>Jackson et al., 2006</td>
<td>United States</td>
<td>Clinical fractures and colorectal cancer incidence</td>
<td>N=36 282 (F, community dwelling)</td>
<td>50-79 (Range)</td>
<td>Daily oral cholecalcifer         (400 IU) + calcium (1 g)</td>
<td>Yes</td>
<td>84</td>
</tr>
</tbody>
</table>

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 cholecalcifer.

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. Mortality data of the open label trial we used were those reported by Avenell et al. in 2005.

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

f Factorial design.
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 calculated them from tabular data, and we estimated when the 95% CI did not include 1.0. The SRR was considered statistically significant if the 95% CI did not include 1.0.

### 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 to 2000 IU, 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,59 59% in the Women's Health Initiative trial,12,63 63% in the trial by Porthouse et al,60 68% in the trial by Ficker et al,60 79% in the trial by Meyer et al,64 80% in the trial by Trivedi et al,61 83% in the trial by Chapuy et al62 in 2002, 85% in the trial by Lips et al,63 and 95% in the trial by Chapuy et al64 in 1992.

The 18 trials included 57,311 participants, and 4,777 deaths for any cause occurred during follow-up. The Figure shows for each selected trial the RR 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 Shi65 and P = .77 with the method of Macaskill et al66).

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 without calcium. The heterogeneity focusing on type of study, trial duration, and country. Heterogeneity was assessed among subgroup analyses by using the I² statistic. Since the I² statistic has limited power, we considered that heterogeneity focusing on type of study, trial duration, and country. Heterogeneity was assessed among subgroup analyses by using the I² statistic.
without calcium supplements as part of the intervention. Exclusion of the quasirandomized trial34 did not affect results. Inclusion of 1 cluster-randomized trial25 increased the SRR but also brought substantial heterogeneity. In this respect, exclusion of this trial was justified.

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 group16,29,34,35,40 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-

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**COMMENT**

**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**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Trials in the Meta-Analysis</th>
<th>SRR (95% CI)</th>
<th>$I^2$ Parameter, %</th>
<th>$\chi^2$ for Heterogeneity, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up $\geq$3 y</td>
<td>6</td>
<td>0.92 (0.83-1.01)</td>
<td>0</td>
<td>.50</td>
</tr>
<tr>
<td>Follow-up $&lt;$3 y</td>
<td>12</td>
<td>0.95 (0.83-1.10)</td>
<td>5</td>
<td>.40</td>
</tr>
<tr>
<td>Vitamin D, $\geq$800 IU/d</td>
<td>12</td>
<td>0.93 (0.85-1.03)</td>
<td>15</td>
<td>.30</td>
</tr>
<tr>
<td>Vitamin D, 300 to 799 IU/d</td>
<td>6</td>
<td>0.92 (0.82-1.03)</td>
<td>0</td>
<td>.70</td>
</tr>
<tr>
<td>Placebo-controlled trials only</td>
<td>12</td>
<td>0.92 (0.86-0.98)</td>
<td>0</td>
<td>.51</td>
</tr>
<tr>
<td>Open-label trials onlyb</td>
<td>6</td>
<td>1.10 (0.84-1.45)</td>
<td>0</td>
<td>.67</td>
</tr>
<tr>
<td>Intervention was vitamin D and calcium supplements</td>
<td>13</td>
<td>0.93 (0.86-1.01)</td>
<td>0</td>
<td>.69</td>
</tr>
<tr>
<td>Intervention was vitamin D supplements only</td>
<td>5</td>
<td>0.91 (0.78-1.06)</td>
<td>42</td>
<td>.14</td>
</tr>
<tr>
<td>Cholecalciferol (vitamin D$_3$) and not ergocalciferol (vitamin D$_2$)</td>
<td>16</td>
<td>0.93 (0.87-0.98)</td>
<td>0</td>
<td>.43</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion of Meyer et al,34 2002</td>
<td>17</td>
<td>0.92 (0.86-0.98)</td>
<td>0</td>
<td>.54</td>
</tr>
<tr>
<td>Inclusion of Law et al,39 2006</td>
<td>19</td>
<td>0.97 (0.89-1.06)</td>
<td>32</td>
<td>.09</td>
</tr>
</tbody>
</table>

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.
Vitamin 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.29 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-hydroxyvitamin 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 Kingdom16 and the Women’s Health Initiative47) reported the association of vitamin D supplements with incidence and mortality of some cancers and 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 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.47 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-hydroxyvitamin 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 contrasted 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.11,36 Some effects mediated through the activation of the vitamin D receptor, such as inhibition of cellular proliferation and activation of cellular differentiation,12,37 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.10,38 The biological mechanism by which vitamin D would prevent and possibly reduce the severity of type 2 diabetes mellitus59 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.

Accepted for Publication: April 18, 2007.
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Author Contributions: Drs Autier and Gandini had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Autier. Acquisition of data: Autier and Gandini. Analysis and interpretation of data: Autier and Gandini. Drafting of the manuscript: Autier. Statistical analysis: Gandini. Administrative, technical, and material support: Autier. Study supervision: Autier.
Financial Disclosure: None reported.

Additional Contributions: The librarians William Russel-Edu of the European Institute of Oncology and Sharon Grant from the International Agency for Research on Cancer retrieved the literature. John Daniels of the International Agency for Research on Cancer provided editorial help.

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Correction

Error in Figure. In the Original Investigation by Fito 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.