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.

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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 diabe-
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 conditions were consistent, then inter-
ventions effectively strengthening vitamin D status should result in
reduced total mortality. In this meta-
analyses, we examined the risk of dying
from any cause in subjects who
participated in randomized trials
testing the impact of vitamin D
supplementation (ergocalciferol [vi-
tamin D₃] or cholecalciferol [vi-
tamin D₂]) 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 D₃ (ergocalciferol) or vitamin D₂ (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 prevent-
ion reported a total of 20 deaths from
all causes and demonstrated their toxic
effects, mainly hypercalcemia.15 We did
not include trials that evaluated treat-
ment with 1α-hydroxyvitamin D₃ (alfa-
calcidol), the physiologically active form
of vitamin D (1α,25-dihydroxyvitamin
D₃ [calcitriol]), or other vitamin D anal-
ogues in patients with advanced pros-
tate cancer, chronic renal disease, or
end-stage renal disease or in patients un-
dergoing renal dialysis.

LITERATURE SEARCH

The search was carried out for clinical
trials, and no language or time restric-
tions were applied. The literature up to
November 2006 was searched using the
following databases: PubMed, ISI Web
of Science (Science Citation Index Ex-
panded), EMBASE, and the Cochrane Li-
brary. For intervention, the following
keywords or corresponding MeSH terms were used: vitamin D, cholecalciferol, and
ergocalciferol. For methods, the follow-
ing keywords and or corresponding
MeSH terms used were randomised con-
trolled 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 key-
words with the following outcome key-
words (and their corresponding MeSH
terms): congestive heart failure, coro-
nary heart disease, cardiovascular dis-
ease, fracture, bone mineral density, and
bone turnover. Mortality was not a help-
ful keyword because none of the trials
with vitamin D supplements, except for
1 trial in the United Kingdom,16 had mor-
tality as an end point.

The search for keywords in the title
and in the abstract was done systemati-
cally. A manual search was done of ref-
erences cited in the selected articles and
in selected reviews or books. Any ab-
tract or article whose title or summary
contained at least 1 intervention key-
word and 1 method keyword or 1 inter-
vention keyword and 1 outcome key-
word 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 pub-
lished report on a randomized con-
trolled trial evaluating an intervention
with vitamin D. The addition of cal-
cium supplements in the intervention
group and the absence of a placebo
for vitamin D in the control group (ie, a
open-label trial) were not exclusion
criteria.

2. To be independent from other studies
testing double weight to estimates derived from the same trial.

3. 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.

4. To have subjects randomized to
the intervention and control groups
on an individual basis. Cluster randomiza-
tion (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 screened 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-
cized 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
trial.17,18 (2) Three did not report deaths
by treatment arm (16 deaths overall) and
this information could not be re-
trieved.19-21 (3) In 2 trials, the interven-
tion 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 England24 ran-
monized 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 Evalu-
atin 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 supplementa-
tion alone or with placebo). In such cases,
RECORD trial. Mortality data of the open label trial we used were those reported by Avenell et al15 in 2005.

f Factorial design.

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

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

c Cod liver oil without cholecalciferol.

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

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

Abbreviations: F, female; M, male.

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,28 1992</td>
<td>France</td>
<td>Clinical fractures</td>
<td>N=3270 (F, institutionalized)</td>
<td>69-106 (Range)</td>
<td>Daily oral cholecalciferol (800 IU) + calcium (1.2 g)</td>
<td>Yes</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=2578 (M and F, community dwelling and institutionalized)</td>
<td>≥70</td>
<td>Daily oral cholecalciferol (400 IU)</td>
<td>Yes</td>
<td>42</td>
</tr>
<tr>
<td>Baeksgaard et al,31 1998</td>
<td>Denmark</td>
<td>Bone mineral density</td>
<td>N=160 (F, community dwelling)A</td>
<td>58-67 (Range)</td>
<td>Daily oral cholecalciferol (560 IU) + calcium (1 g)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Kormulainen et al,32 1999</td>
<td>. Finland</td>
<td>Bone mineral density</td>
<td>N=232 (F, community dwelling)B</td>
<td>47-56 (Range)</td>
<td>Daily oral cholecalciferol (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,33 1999</td>
<td>Switzerland</td>
<td>Bone mineral density</td>
<td>N=248 (F, institutionalized)</td>
<td>62-98 (Range)</td>
<td>Daily oral cholecalciferol (880 IU) + calcium (1 g)</td>
<td>No</td>
<td>24</td>
</tr>
<tr>
<td>Chapuy et al,34 2002</td>
<td>France</td>
<td>Bone mineral density, hip fractures</td>
<td>N=583 (F, institutionalized)</td>
<td>64-99 (Range)</td>
<td>Daily oral cholecalciferol (800 IU) + calcium (1.2 g)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Meyer et al,35 2002</td>
<td>Norway</td>
<td>Clinical fractures</td>
<td>N=1144 (M and F, institutionalized)</td>
<td>(Mean)</td>
<td>Daily oral cod liver oil, more or less cholecalciferol (400 IU)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Trivedi et al,36 2003</td>
<td>United Kingdom</td>
<td>Clinical fractures and all-cause mortality</td>
<td>N=2886 (M and F, community dwelling)</td>
<td>65-84 (Range)</td>
<td>Oral cholecalciferol (100 000 IU every 4 mo)</td>
<td>Yes</td>
<td>60</td>
</tr>
<tr>
<td>Latham et al,37 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>(Mean)</td>
<td>Single-injection cholecalciferol (300 000 IU)</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Harwood et al,38 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 (Range)</td>
<td>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])</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>Avenell et al,39 2004d</td>
<td>United Kingdom</td>
<td>Compliance to vitamin D and calcium supplements mortality</td>
<td>N=134 (M and F with past low-energy fracture)</td>
<td>≥70</td>
<td>Daily oral cholecalciferol (800 IU only) or daily oral cholecalciferol (800 IU + calcium [1 g])</td>
<td>Yes and no</td>
<td>12</td>
</tr>
<tr>
<td>Meier et al,30 2004</td>
<td>Germany</td>
<td>Bone turnover</td>
<td>N=55 (M and F, community dwelling)</td>
<td>23-78 (Range)</td>
<td>Daily oral cholecalciferol (500 IU) + calcium (0.5 g)</td>
<td>No</td>
<td>24</td>
</tr>
<tr>
<td>Brazier et al,41 2005</td>
<td>France</td>
<td>Safety of supplementation with vitamin D and calcium</td>
<td>N=192 (F with vitamin D insufficiency)</td>
<td>&gt;65</td>
<td>Daily oral cholecalciferol (800 IU) + calcium (1 g)</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>Porthouse et al,42 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 cholecalciferol (800 IU) + calcium (1 g)</td>
<td>No</td>
<td>36</td>
</tr>
<tr>
<td>RECORD Trial,43 2005</td>
<td>United Kingdom</td>
<td>Clinical fractures</td>
<td>N=5292 (M and F, institutionalized)</td>
<td>≥70</td>
<td>Daily oral cholecalciferol (800 IU only) or daily oral cholecalciferol (800 IU + calcium [1 g])</td>
<td>Yes</td>
<td>60</td>
</tr>
<tr>
<td>Flicker et al,44 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 ergocalciferol (10 000 IU), followed by daily oral ergocalciferol (1000 IU)</td>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>Schleithoff et al,45 2006</td>
<td>Germany</td>
<td>Survival of patients with congestive heart failure</td>
<td>N=123 (M and F with congestive heart failure)</td>
<td>(Mean)</td>
<td>Daily oral cholecalciferol (2000 IU only) or daily oral cholecalciferol (800 IU + calcium [0.5 g])</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>Jackson et al,46 2006 and Wactawski-Wende et al,47 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 cholecalciferol (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 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. 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.
Table 2. Serum Levels of 25-Hydroxyvitamin D in Randomized Trials With Vitamin D Supplements

<table>
<thead>
<tr>
<th>Source</th>
<th>Mean Follow-up, mo</th>
<th>Mean Serum 25-Hydroxyvitamin D$_3$ (ng/mL)$^b$</th>
<th>Ratio for In-Study Level, Intervention vs Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention Group</td>
<td>Control Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>In Study</td>
</tr>
<tr>
<td>Chapuy et al,$^2$</td>
<td>18</td>
<td>14.5</td>
<td>42.0</td>
</tr>
<tr>
<td>Lips et al,$^b$</td>
<td>42</td>
<td>10.4</td>
<td>24.8</td>
</tr>
<tr>
<td>Krieg et al,$^{a2}$</td>
<td>24</td>
<td>11.9</td>
<td>26.5</td>
</tr>
<tr>
<td>Schleithoff et al,$^{a1}$</td>
<td>24</td>
<td>8.8</td>
<td>31.0</td>
</tr>
<tr>
<td>Trivedi et al,$^a$</td>
<td>24</td>
<td>18.6</td>
<td>25.6</td>
</tr>
<tr>
<td>Trivedi et al,$^a$</td>
<td>60</td>
<td>30.1</td>
<td>35.1</td>
</tr>
<tr>
<td>Trivedi et al,$^a$</td>
<td>24</td>
<td>15.2</td>
<td>24.8</td>
</tr>
<tr>
<td>Schleithoff et al,$^a$</td>
<td>15</td>
<td>14.4</td>
<td>41.2</td>
</tr>
</tbody>
</table>

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.$^{31}$

$^d$Estimated from oral cholecalciferol, 100 000 IU every 4 mo.

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, 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, 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$^{48}$ 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 8.2; 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 $I^2$ statistic. Since the $I^2$ test has limited power, we considered that statistically significant heterogeneity existed when the $P$ value was $<.10$. 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. 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.$^{43}$

The percentage of total variation across studies that is attributable to heterogeneity rather than to chance. 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.$^{43}$
without calcium supplements as part of the intervention. Exclusion of the quasirandomized trial\textsuperscript{34} did not affect results. Inclusion of 1 cluster-randomized trial\textsuperscript{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.\textsuperscript{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\textsuperscript{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-
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.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-hydroxyvitamin D levels. Such data were not available for the other trials, including the Women’s Health Initiative.51 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 Kingdom49 and the Women’s Health Initiative52) 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.53 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 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.11,36 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.

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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.

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REFERENCES


**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.