0163-769X/02/$20.00/0
Printed in U.S.A.

Endocrine Reviews 23(4):560–569

doi: 10.1210/er.2001-8002

VIII: Meta-Analysis of the Efficacy of Vitamin D Treatment in Preventing Osteoporosis in Postmenopausal Women

EMMANUEL PAPADIMITROPOULOS, GEORGE WELLS, BEVERLEY SHEA, WILLIAM GILLESPIE, BRUCE WEAVER, NICOLE ZYTARUK, ANN CRANNEY, JONATHAN ADACHI, PETER TUGWELL, ROBERT JOSSE, CAROL GREENWOOD, GORDON GUYATT, THE OSTEOPOROSIS METHODOLOGY GROUP, AND THE OSTEOPOROSIS RESEARCH ADVISORY GROUP

A. Abstract

Objective: To review the effect of vitamin D on bone density and fractures in postmenopausal women.

Data Source: We searched MEDLINE and EMBASE from 1966 to 1999 and examined citations of relevant articles and proceedings of international meetings. We contacted osteoporosis investigators and primary authors to identify additional studies and to obtain unpublished data.

Study Selection: We included 25 trials that randomized women to standard or hydroxylated vitamin D with or without calcium supplementation or a control and measured bone density or fracture incidence for at least 1 yr.

Data Extraction: For each trial, three independent reviewers assessed the methodological quality and abstracted data.

Data Synthesis: Vitamin D reduced the incidence of vertebral fractures [relative risk (RR) 0.63, 95% confidence interval (CI) 0.45–0.88, $P < 0.01$) and showed a trend toward reduced incidence of nonvertebral fractures (RR 0.77, 95% CI 0.57–1.04, $P = 0.09$). Most patients in the trials that evaluated vertebral fractures received hydroxylated vitamin D, and most patients in the trials that evaluated nonvertebral fractures received standard vitamin D.

Hydroxylated vitamin D had a consistently larger impact on bone density than did standard vitamin D. For instance, total body differences in percentage change between hydroxylated vitamin D and control were 2.06 (0.72, 3.40) and 0.40 (−0.25, 1.06) for standard vitamin D. At the lumbar spine and forearm sites, hydroxylated vitamin D doses above 50 μg yield larger effects than lower doses.

Vitamin D resulted in an increased risk of discontinuing medication in comparison to control as a result of either symptomatic adverse effects or abnormal laboratory results (RR 1.37, 95% CI 1.01–1.88), an effect that was similar in trials of standard and hydroxylated vitamin D.

Conclusions: Vitamin D decreases vertebral fractures and may decrease nonvertebral fractures. The available data are uninformative regarding the relative effects of standard and hydroxylated vitamin D.

B. Introduction

A NUMBER OF groups have developed guidelines for the prevention and treatment of osteoporosis (1–3). Guidelines are only as strong as the evidence on which they are based. The evidence supporting the current guidelines, particularly with respect to the administration of vitamin D, is limited. Gillespie *et al.* (4) have conducted a meta-analysis addressing the effect of vitamin D on vertebral and nonvertebral fractures. This meta-analysis met major methodological criteria: the question was clear and sensible, inclusion and exclusion criteria were explicit, and the search for studies comprehensive.

The Gillespie *et al.* meta-analysis is, however, limited in that it did not address the effect of vitamin D on bone density. Furthermore, Gillespie *et al.* took a relatively conservative approach to pooling, and made little use of regression methods to explore the appropriateness of combining data across different forms of vitamin D and variations in study design. As a result, the Gillespie study was largely descriptive and permitted few definitive conclusions (4). As part of our series of systematic reviews of osteoporosis treatment, we therefore conducted another systematic review to address these limitations using the Cochrane methodology. We describe the methods of our review in detail in *Section I*.

C. Methods

1. Inclusion criteria. Studies satisfied the following inclusion criteria; 1) participants were women older than 45 yr with absence of menses for a minimum of 6 months; 2) the treatment group received some form of vitamin D greater than 400 IU daily, or some form of dihydroxyvitamin D; 3) a follow-up of at least 1 yr; 4) results reported on x-ray evidence of fractures of hip, vertebrae, or wrist, or bone mineral density measured in grams per centimeter or grams per centimeter squared, by single-photon absorptiometry, dual-photon absorptiometry, or dual x-ray absorptiometry in at least one of the following sites: femoral neck, total hip, trochanter, lumbar spine, total body, and the combined forearm, and reporting results on individual patients (as opposed to number of fractures); 5) the study was designed as a randomized control trial (RCT).

We included studies irrespective of whether calcium was added to vitamin D in the treatment or provided to the control group. We considered doses of vitamin D of no more than 100 IU daily to be negligible, and thus included studies in which control patients received vitamin D in these low doses. We excluded studies that compared different types or doses of vitamin D.

Abbreviations: CI, Confidence interval; RCT, randomized control trial; RR, relative risk.

2. Study search and selection. The structured and tested Cochrane Collaborative approach for identifying RCTs, as described by Dickersin *et al.* (5) and modified for the Cochrane Muscular Skeletal Group, guided our MEDLINE and EMBASE searches. We also conducted hand searches of bibliographic references and the Cochrane Controlled Trials Register and included all references in the Cochrane reviews update to September 2000 (5). We asked content experts to identify published or unpublished relevant RCTs we had overlooked. Two reviewers (E.P., B.S.) examined each title generated from the search and identified potentially eligible articles for which we obtained the abstracts. For abstracts consistent with study eligibility, we obtained the full article text.

3. Methodological quality. We rated the methodological quality of each eligible study with respect to concealment of randomization; whether patients, caregivers, and those measuring outcome were blind to allocation; the extent of loss to follow-up; and whether the analysis was intention to treat. We used more than one reviewer in the selection of studies, the assessment of methodological quality, and the extraction of data. For all aspects of the review in which raters made duplicate judgements, they resolved disagreements by consensus.

4. Data collection. Reviewers abstracted data regarding study design, patient characteristics, treatment duration, dosage, mean change, and SD values for bone density, and number of vertebral and nonvertebral fractures. For toxicity, we examined the rate of withdrawal due to side effects and the rate of withdrawal due to investigator-labeled adverse laboratory results. On most occasions, the adverse laboratory result was hypercalciuria. We sought key data that were missing from the original reports through correspondence with the investigators.

5. A priori hypotheses regarding heterogeneity. To explore reasons for differences in results between studies (heterogeneity), we developed *a priori* hypotheses relating to the study design, the methodological quality of the study, and the study population. We describe these hypotheses below:

1) We identified four study designs; given that calcium itself increases bone density relative to ordinary diet, we anticipated that we would see the largest effects with trial design A, intermediate effects with trial designs B and C, and the smallest effect with trial design D.

A) vitamin D and calcium supplementation *vs.* normal diet

B) vitamin D alone *vs.* normal diet

C) vitamin D combined with calcium supplementation *vs.* calcium supplementation

D) vitamin D alone *vs.* calcium supplementation

2) whether the experimental intervention was standard vitamin D or 25-OH vitamin D on the one hand, or hydroxylated vitamin D (1,25-OH vitamin D or calcitriol) on the other hand;

3) different methodological quality (randomization concealed or unconcealed; blinded or unblinded; extent of loss to follow-up; intention-to-treat analysis);

4) primary prevention *vs.* secondary treatment, hypothesizing that the magnitude of the treatment effect may vary in early postmenopausal women with bone density in the normal or near normal range (prevention) *vs.* women with established osteoporosis (treatment).

5) study duration

6) dose of vitamin D

7) level of calcium supplementation ($<$500 mg or $>$500 mg)

6. Statistical analysis. For fractures, we calculated a RR using methods described by Fleiss (6). We constructed two-by-two tables for both vertebral and nonvertebral fractures in each study for which the data were available, and calculated the associated risk ratios. We tested for heterogeneity using a χ^2 procedure (6). We tested whether our *a priori* hypotheses could explain variability in the magnitude of treatment effects across studies using a procedure described by Hedges and Olkin (7). For study design, which had the four levels described above (A, B, C, and D), we used the following planned orthogonal contrasts: A *vs.* [B, C, D]; [B, C] *vs.* D; B *vs.* C.

We used analytic strategies similar to those for fracture rates in examining the incidence of side effects and toxicity.

For each bone density site (lumbar spine, total body, combined hip, and combined forearm), we calculated the weighted mean difference in bone density between treatment and control groups using the percentage change from baseline in the treatment and placebo groups and the associated SD values. We constructed regression models in which the independent variables were year and dose and the dependent variable the effect size, and we used this regression to determine the years across which pooling was appropriate. To assess whether the magnitude of heterogeneity (differences in apparent treatment effect across studies) was greater than one might expect by chance, we conducted a test based on the χ^2 distribution with N-1 degrees of freedom, where N is the number of studies (6).

D. Results

1. Search results. Electronic and hand searching resulted in the retrieval of a total of 83 published papers that addressed the relationship between vitamin D and bone mineral density or fracture incidence (Fig. 1). Forty described RCTs (8–47). Reasons for excluding 15 of these trials (33–47) were: 10 trials compared different types or doses of vitamin D, or studied combinations of vitamin D with other agents, without including a control group that did not receive vitamin D (33–37, 39–43); 4 trials because trial duration was less than 1 yr (38, 44–46); and 1 trial because bone mineral density was measured at the metacarpal site only (47). Thus, 25 RCTs fulfilled our eligibility criteria (Table 1) (8–32).

Of the 25 trials included in this analysis, we had to contact 10 authors for additional information (9–11, 14, 16, 18, 19, 21, 27, 31). Six investigators supplied the information we needed (9, 11, 14, 16, 19, 21).

Table 1 describes these 25 studies in which a total of 4017 patients received some form of vitamin D and 4107 a controlled intervention. Seventeen trials enrolled patients with decreased bone density; 10 used some form of standard vitamin D, 14 hydroxylated vitamin D, and 1 trial had both a standard and a hydroxylated vitamin D group in comparison to a control group (24). Follow-up ranged from 1 to 5 yr; loss

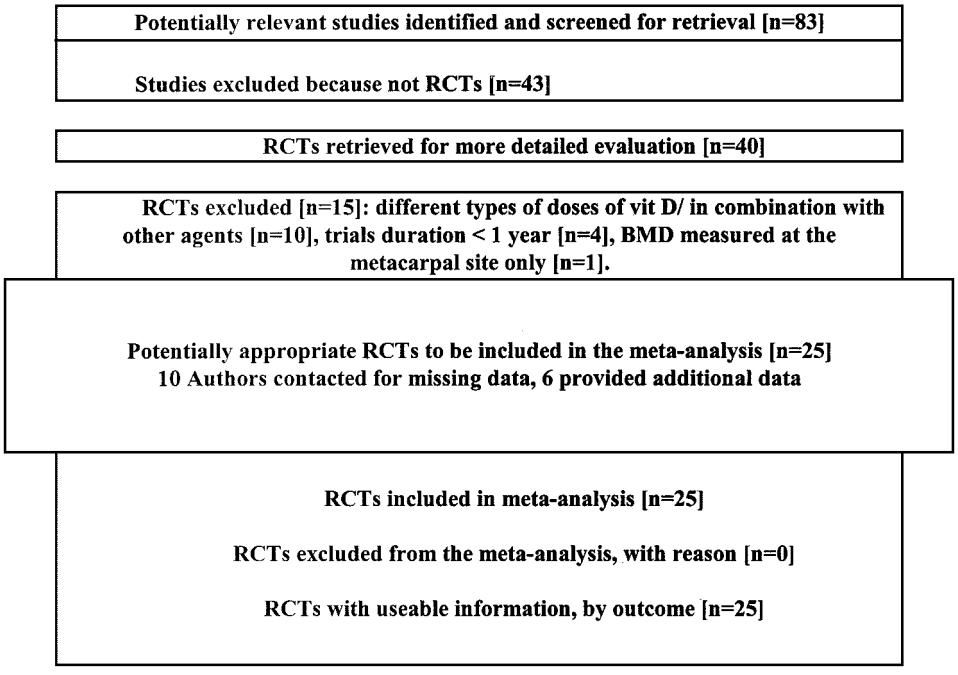

FIG. 1. Search results for calcium/vitamin D review.

to follow-up was less than 10% in two studies, between 10 and 20% in 8 studies, 20% or greater in 13, and unknown in 2 trials (10, 27). Eighteen trials were blinded (8, 9, 11–21, 23–25, 30, 31), 5 trials were not (22, 26, 28, 29, 32), and the blinding status was not clear in 2 of the trials (10, 27).

2. Fractures. Of the 25 eligible studies, 8 (total 1130 patients) measured the effect of vitamin D on morphometric vertebral fractures; all but 1 tested hydroxylated vitamin D. Rates of vertebral fractures in the control groups varied from 1% to 58%. Figure 2 depicts the results of the individual studies and the pooled estimates of the effect of vitamin D on vertebral fractures, and Table 2 summarizes the pooled estimates. The pooled estimate indicates a 37% reduction in RR (95% CI 0.45–0.88) (Table 2). The point estimates from the individual trials are somewhat disparate, although the formal test of heterogeneity did not reach conventional levels of statistical significance. None of the factors we identified in advance explained the heterogeneity that does exist.

Six studies (a total of 6187 patients) measured the effect of vitamin D on nonvertebral fractures. Fracture rates in the control group varied from 0% to 21%. Studies with standard vitamin D enrolled far more patients then studies of hydroxylated vitamin D (Table 2). The pooled estimate suggests a RR reduction of 23%, but the CI includes a RR increase of 4%. The studies show quite disparate results (Fig. 3), although the CIs are widely overlapping. The test of heterogeneity reaches our threshold for statistical significance for standard vitamin D and the combined results. None of the factors we identified in advance, however, explained the heterogeneity.

For both fracture analyses, funnel plots showed no suggestion of publication bias.

3. Bone density. Table 3 summarizes the impact of vitamin D on bone mineral density at the four sites we examined. The pooling of years and doses was determined by the regression analyses described in detail in *Section I*.

When sample size was adequate, the data showed large, consistent, statistically significant effects of hydroxylated vitamin D in all sites for all doses above 0.43 μg. The effect of standard vitamin D on bone density was consistently much smaller, and reached statistical significance only for lumbar spine at 1 yr and the femoral neck at final year. The difference between standard and hydroxylated vitamin D was statistically significant for total body ($P = 0.03$) and for combined forearm ($P = 0.01$) after the final year of treatment. Figure 4 depicts the results for combined forearm.

For three of the analyses, there were large differences in results between trials reflected in small P values associated with the formal test of heterogeneity. We found a number of apparent contributing factors (Table 4). We have already noted the differential impact by type of vitamin D. Contrary to our prediction of little difference between trial designs B (vitamin D supplementation *vs.* normal diet) and C (vitamin D and calcium supplementation *vs.* calcium supplementation), the lumbar spine site did show significance. The result was anomalous: standard vitamin D when compared with regular diet showed a substantial negative effect on bone density, whereas when vitamin D and calcium were compared with calcium alone there was no effect. However, this result was based upon the comparison of only two trials. High *vs.* low levels of calcium supplementation yielded significantly different effects for all three analyses presented in Table 4. For hydroxylated doses (0.50–1.00 μg) at the combined forearm sites at yr 1–3, the effect of vitamin D was greater for patients receiving lower levels of calcium; but for lumbar spine and total body with standard doses at final year, the effect was greater for those receiving higher levels of calcium. Intention-to-treat analysis and loss-to-follow-up results were also statistically significant for total body and

TABLE 1. Trial characteristics

Trial (first author/ year/Ref.) (treatment/ prevention)	No. of patients (treatment/ control)	Mean age (SD) Year since menopause (YSM) [Baseline Ca^{2+} (SD)] Baseline 25OH D level Lumbar BMD (SE) g/cm^2 T-score	Intervention (trial type)[a] [Supplementation]	Duration (years)	Outcomes measured	Overall lost to follow-up (%) Treatment control
Komulainen, 1999 (28) (prevention)	112/115 (HRT groups not included)	52.8 (1.0) 1.1 (1.0) [835 (416) mg/d] —[b] 1.15 (0.09)g/cm^2 0.9	300 IU Cholecalciferol *vs.* placebo (C) [500 mg calcium to both groups]	5	BMD: Lumbar spine and femoral neck	3/227 (1.3%) 2/1
Baeksgaard, 1998 (8) (treatment)	80/80 (Multivitamin arm excluded)	62.5 (4.5) — [876 (512) mg/d] — — —	560 IU Cholecalciferol and 1 g calcium *vs.* placebo (A) [1 g calcium/d for treatment group only]	2	BMD: Lumbar spine, femoral neck, and 1/3 distal forearm	31/160 (19.4%) 15/16
Dawson-Hughes, 1997 (23) (prevention)	123/123	71.5 (4.5) — [746 (312) mg/d] 5.1 (0.2) mg/ml 1.04 (0.19) g/cm^2 −0.1	700 IU Cholecalciferol *vs.* placebo (C) [500 mg calcium/d each group]	3	BMD: Lumbar spine, femoral neck, and total body Fractures: Nonvertebral	33/246 (13.4%) 22/11
Chen, 1997 (32) (prevention)	25/25	52.6 (5.2) 3.7 (5.8) [600 mg/d] 17.8 (1.51) mg/ml 0.90 (0.008) g/cm^2 −1.3	0.75 μg α-Hydroxyvitamin D_3 *vs.* control (C) [150 mg calcium/d each group]	1	BMD: Lumbar spine	5/50 (10%) 2/3
Lips, 1996 (14) (treatment)	958/958 (662 men excluded from analysis)	80.0 (6.0) 32.4 (7.0) [868 (344) mg/d] 27 (13.1) mg/ml 26 (13.1) mg/ml —	400 IU Cholecalciferol *vs.* placebo (B)	3.5	Fractures: nonvertebral	278/1916 (24.9)%
Ooms, 1995 (16) (treatment)	177/171	80.3 (5.6) 32.5 (7.0) [868 (344) mg/d] — −2.0	400 IU Cholecalciferol *vs.* placebo (B)	2	BMD: Femoral neck, trochanter, and distal radius	104/348 (29.9%) 51/53
Ushiroyama, 1995 (22) (prevention)	15/35 (ipriflavone groups excluded from analysis)	51.9 (6.2) 4.4 (4.2) [—] — 0.88 (0.13) g/cm^2	1 μg α-Calcidiol *vs.* control (B)	1.5	BMD: Lumbar spine	13/50 (26%) 1/12
Menczel, 1994 (15) (treatment)	24/42	66.7 (7.6) 19.6 (9.9) [—] — — —	0.5 μg α-Cacidiol *vs.* placebo (C) [1000 mg calcium/d each group]	3	BMC: 1/3 distal radius	20/66 (30.3%) 7/13
Orimo, 1994 (17) (treatment)	38/42	71.9 (7.3) 23.3 (9.1) [—] 21.7 (7.8) mg/ml 0.80 (0.12) g/cm^2 −2.5	1 μg Alfarol *vs.* placebo (C) [300 mg calcium/d each groups]	1	BMD: Lumbar spine, femoral neck, trochanter, and ward's triangle Fractures: Vertebral and nonvertebral	6/80 (7.5%) 4/2
Chapuy, 1992 (9) (treatment)	1634/1636 (27/29 with BMD assessments)	84.0 (6.0) — [513 (165) mg/d] 14.0 (10.0) mg/ml — —	800 IU Cholecalciferol *vs.* placebo (A) [1200 mg calcium + 600 mg phosphate to treatment group only]	1.5	BMD: Femoral neck, trochanter, interotrochanteric, and total proximal femur Nonvertebral fractures	1505/3270 (46.0%) 757/748
Tilyard, 1992 (21) (treatment)	314/308	63.7 (7.2) 14.9 (8.3) [892 (367) mg/d] — — —	0.5 μg Calcitriol *vs.* 1 g calcium	3	Fractures: Vertebral and nonvertebral	190/622 (30.5%) 101/89
Dawson-Hughes, 1991 (11) (prevention)	139/137	61.7 (0.5) 13.5 (0.6) [—] — 1.04 (0.02) g/cm^2 −0.1	400 IU Cholecaliferol *vs.* placebo (C) [377 mg calcium/d each group]	1	BMD: Lumbar spine and total body	27/276 (9.8%) 15/12

[a], Trial design: A = Vitamin D (VD)+ Calcium (Ca) *vs.* Normal Diet (ND); B = VD *vs.* ND; C = VD+ Ca *vs.* Ca; D = VD *vs.* Ca.
[b], Data not available/collected.

TABLE 1. Continued

Trial (first author/ year/Ref.) (treatment/ prevention)	No. of patients (treatment/ control)	Mean age (SD) Years Since Menopause (YSM) [Baseline Ca^{++} (SD)] Baseline 25OH D Level Lumbar BMS (SE) g/cm^2 T-score	Intervention (trial type)[a] [Supplementation]	Duration (years)	Outcomes measured	Overall lost to follow-up (%) Treatment/ Control
Shiraki, 1991 (29) (treatment)	16/30 (HRT groups not included)	73.9 (1.4) — [—] — —	0.5 α-Calcidiol *vs.* control (B)	2	BMD: 1/3 distal radius	4/46 (8.6%) 2/2
Gallagher, 1990 (12) (treatment)	25/25	69.7 (6.5) 23.5 (7.5) [699 (326) mg/d] — 0.73 (0.12)g/cm^2 −2.9	0.62 μg Calcitriol *vs.* placebo (C) [240 mg calcium and 400 IU cholecaliferol each group]	2	BMD: Lumbar spine and total body Fractures: Vertebral	10/50 (20%) 7/3
Orwoll, 1989 (18) (treatment)	19/20	69.0 (7.0) 23.0 (9.0) [854 (415) mg/d] 16.0 (7.0) mg/ml — —	1600 IU α-Calcidial *vs.* control (C) [1200 mg calcium/d each group]	2	BMD: Distal and proximal radius Vertebral Fractures	8/39 (20.5%) 5/3
Ott, 1989 (19) (treatment)	43/43	67.5 (7.2) — [823 (356) mg/d] 26.5 (2.2) mg/ml — —	0.43 μg Calcitriol *vs.* placebo (C) [1 g calcium/d each group]	2	BMD: Lumbar spine, total body, and distal radius Fractures: Vertebral and nonvertebral	14/86 (16.3%) 8/6
Orimo, 1987 (27) (treatment)	38/48	71.7 (7.1) — [—] — — —	1.0 μg Calcitriol with or without calcium *vs.* control or calcium group (A, B, C, D)	2	Fractures: Vertebral	–/86
Riis, 1986 (20) (prevention)	29/29	50.1 (0.5) 1.5 (2.3) [—] 31.5 (4.4) mg/ml 0.93 (0.03) g/cm^2 −1.1	400 IU Cholecaliferol *vs.* placebo (B)	2	BMD: Lumbar spine, total body, distal and proximal ulna and radius	7/58 (12.1%) 3/4
Guesens, 1986 (25) (treatment)	16/16 (Nandrolone arm and men excluded from analysis)	70.0 (8.5) — [594 (465) mg/d] — — —	1.0 μg α-Calcidiol *vs.* control (D) [900 mg calcium to control group]	2	BMD: 1/3 distal radius Fractures: Vertebral	13/32 (40.6%) 6/7
Thomsen, 1986 (31) (prevention)	29/29 (HRT arms excluded from analysis)	50.0 (2.2) 1.4 (0.7) [—] — — —	400 IU Cholecaliferol *vs.* placebo (B)	2	BMC: Distal ulna and radius	13/58 (22.4%) 5/8
Shiraki, 1985 (26) (treatment)	55/23	72.4 (1.2) — [—] 16.9 (7.2) mg/ml — —	0.5 μg or 1.0 μg α-Calcidiol *vs.* control (B)	2	BMC: Distal radius	24/78 (30%) 21/3
Caniggia, 1984 (30) (treatment)	7/7 (HRT arms excluded from analysis)	64.0 (10.0) — [—] — — —	0.5 μg α-Calcidiol *vs.* placebo (B)	1	BMC: Distal radius Fractures: Vertebral	4/14 (28.6%) 2/2
Jensen, 1982 (13) (secondary)	29/29	70.0 — [—] — — —	0.5 μg Dihydroxycholecalciferol *vs.* control (C) [500 mg calcium/d each group]	1	BMC: Distal ulna and radius	15/58 (25.9%) 10/5
Christiansen, 1981 (10) (primary)	21/23	49.9 3.68 [—] — — —	0.25 μg Dihydroxycholecalciferol *vs.* placebo (C) [500 mg calcium/d each group]	1	BMC: Distal ulna and radius (mean of 12 scans on the forearm)	–/44
Christiansen, 1980 (24) (primary)	56/121 (HRT and Fluoride arms excluded)	50.1 1.7 [—] — —	2000 IU Cholecaliferol or 0.25 μg α-calcidiol *vs.* placebo [500 mg calcium/d each group]	2	BMC: Distal ulna and radius	26/177 (14.6%) 8/18

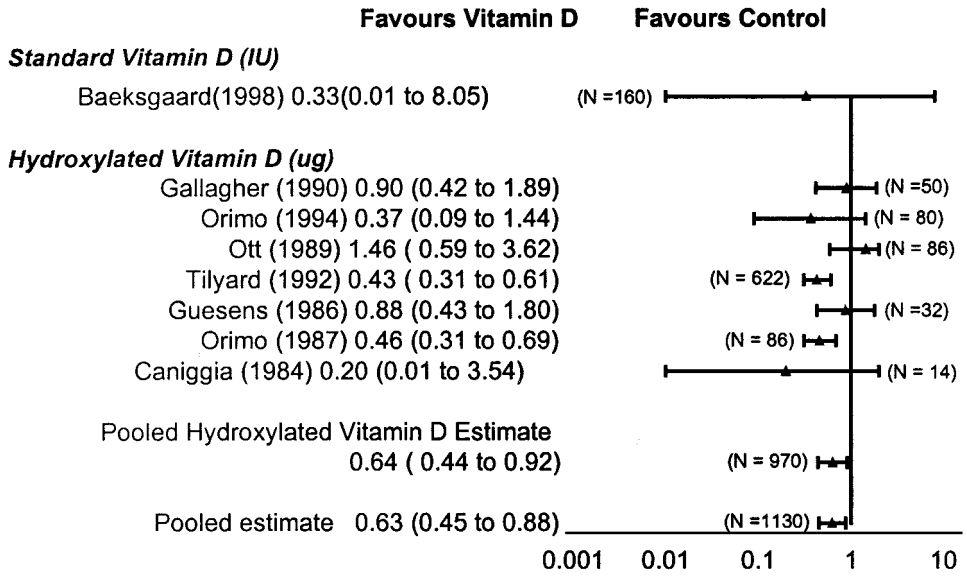

FIG. 2. RR with 95% CI for vertebral fractures after treatment with vitamin D.

TABLE 2. Weighted RR with 95% CI after treatment with vitamin D

Fracture sites	Type standard/ hydroxylated	No. of trials	No. of patients	RR (95% CI)	RR *P* value	Heterogeneity *P* value
Vertebral	Combined	8	1130	0.63 (0.45, 0.88)	<0.01	0.16
	Standard	1	160	0.33 (0.01, 8.05)	0.49	–
	Hydroxylated	7	970	0.64 (0.44, 0.92)	0.02	0.11
All nonvertebral	Combined	6	6187	0.77 (0.57, 1.04)	0.09	0.09
	Standard	3	5399	0.78 (0.55, 1.09)	0.15	0.05
	Hydroxylated	3	788	0.87 (0.29, 2.59)	0.80	0.19

We interpreted $P \leq 0.05$ as indicating important between-study differences in results.

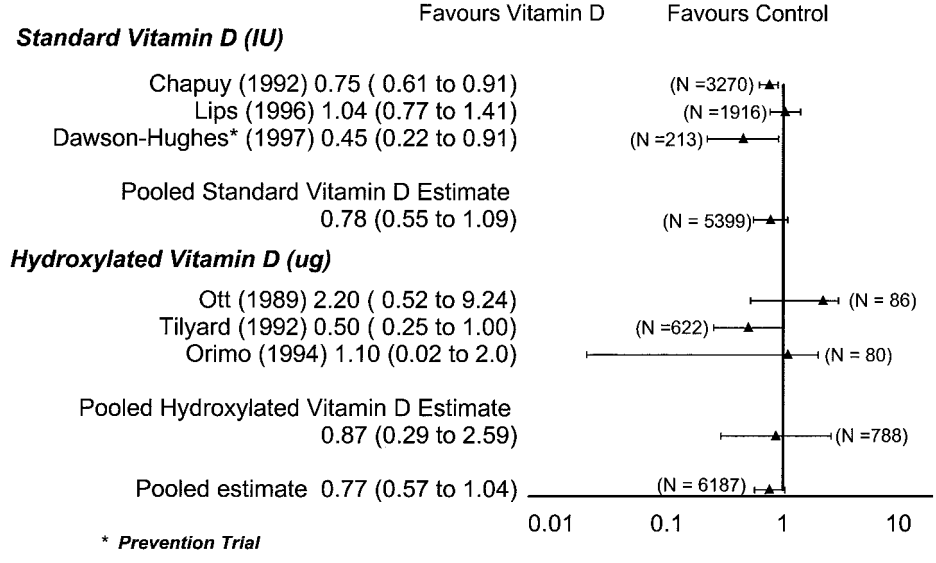

FIG. 3. RR with 95% CI for nonvertebral fractures after treatment with vitamin D.

combined forearm bone density. Larger effects were seen in studies that did conduct an intention-to-treat analysis. The small number of studies makes inferences from these analyses insecure.

For all bone density analyses, we found only one instance suggesting publication bias, the investigation of the effect of hydroxylated vitamin D on forearm bone density. One trial, appreciably larger than the rest, showed a negligible effect of hydroxylated vitamin D on forearm bone density. A number of small trials showed a substantial effect (Fig. 5). Although by no means definitively demonstrating publication bias, these results do raise the possibility.

TABLE 3. Weighted mean difference of bone density after treatment with vitamin D

Bone density site	Type standard/ hydroxylated	Trial year	Dose	No. of Trials	Sample size (n)	Weighted mean difference (95% CI)	*P* value	Test of heterogeneity *P* value
Total body	Standard	Final [yr 1–3]	All	3	508	0.40 (−0.25, 1.05)	0.23	<0.01
	Hydroxylated	Final [yr 1–3]	All	1	39	2.06 (0.72, 3.40)	<0.01	–
Lumbar spine	Standard	1	All	4	563	0.86 (0.17, 1.54)	0.01	0.10
	Standard	2–5	All	4	608	−0.40 (−2.06, 1.25)	0.63	<0.00
	Hydroxylated	1–2	0.43 μg	1	56	−1.00 (−6.45, 4.45)	0.72	–
	Hydroxylated	1–2	0.60–0.75 μg	2	89	4.60 (3.19, 6.01)	<0.01	0.35
	Hydroxylated	1–2	1.0 μg	2	97	2.45 (1.47, 3.42)	<0.01	0.60
Combined forearm	Standard	1–2	All	5	597	−0.48 (−1.18, 0.22)	0.18	0.42
	Hydroxylated	Final [1–3]	0.25–0.43 μg	3	240	−0.47 (−1.17, 0.33)	0.77	0.31
	Hydroxylated	Final [1–3]	0.50–1.00 μg	6	206	9.79 (3.39, 16.18)	<0.01	<0.01
Femoral neck	Standard	Final [yr 1–5]	All	5	862	0.98 (0.10, 1.85)	0.03	0.22
	Hydroxylated	Final [yr 1–5]	All	1	34	2.46 (−7.80, 12.72)	0.64	–

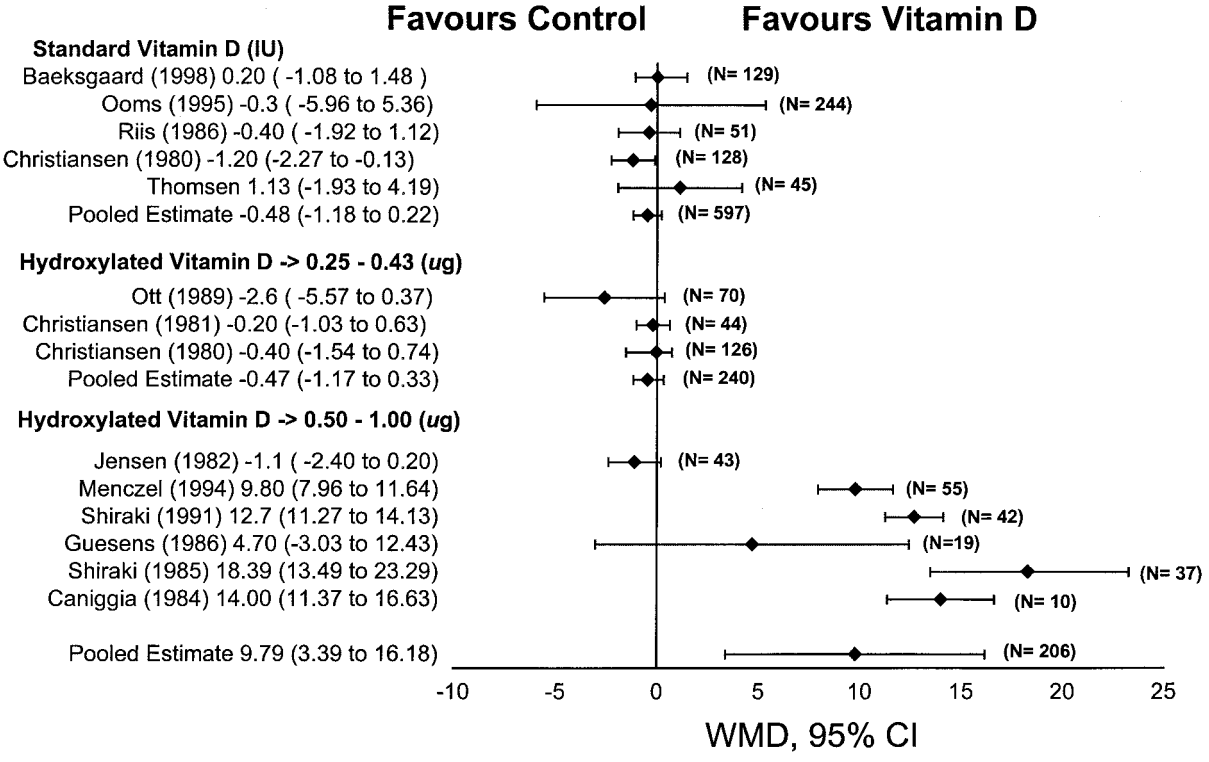

FIG. 4. Weighted mean difference of distal forearm after treatment with vitamin D.

4. Side effects and toxicity. Our pooled estimate of the RR of discontinuing medication as a result of either symptomatic adverse effects or abnormal laboratory results from the 12 trials that reported such events was 1.37 (95% CI 1.01–1.88, *P* value 0.05, heterogeneity *P* value 0.99). The RR of withdrawal was similar in the trials of standard Vitamin D (RR 1.40, 95% CI, 0.94 to 2.06, p values 0.10) and hydroxylated vitamin D (RR 1.34, 95% CI 0.80–2.24, *P* value 0.27), respectively (*P* value on the difference between the two estimates of RR = 0.90).

E. Discussion

Inferences from the results of these analyses are limited by the variability in study designs, methodological weaknesses in the primary studies (including lack of blinding in many studies), the paucity of data, and the inconsistency of results. Two issues of study design are particularly problematic. First, the methods of supplementation, and the use of calcium in addition to vitamin D, vary from study to study. In the prior section in this series, we presented a meta-analysis suggesting that calcium alone increases bone density from 1.5% to 2%. We therefore anticipated that we might see largest effects when the intervention, but not the control group, received calcium in addition to vitamin D. We expected intermediate effects when calcium was withheld from, or offered to, both treatment and control groups, and smallest effects when calcium was given to only the control arm.

The fracture data revealed quite a different pattern: the largest effect and most precise estimate of vitamin D effect on fracture came from a study in which only the control group received calcium (21). Similarly, we failed to see the

TABLE 4. Heterogeneity of difference of bone mineral density after treatment with vitamin D

BMD site Vit D type Study year	Study population Prevention *vs.* treatment Difference (95% CI) *P* value	Trial design[a] A *vs.* B, C, and D Difference (95% CI) *P* value	Trial design[a] B and C *vs.* D Difference (95% CI) *P* value	Trial design[a] B *vs.* C Difference (95% CI) *P* value	Ca^{2+} supplementation <500 mg *vs.* >500 mg Difference (95% CI) *P* value	ITT analysis Yes *vs.* no Difference (95% CI) *P* value	Lost to follow-up <20% *vs.* >20% Difference (95% CI) *P* value
Total body	0.56; 0.11	1.12; 0.08	Not applicable	0.00; 0.11	0.08; 1.12	1.12; 0.08	Not applicable
Standard	0.45 (−0.69, 1.59)	1.04 (0.44, 1.64)		0.11 (−0.53, 0.75)	1.04 (0.44, 1.64)	1.04 (0.43, 1.65)	
Final year	$P = 0.44$	$P < 0.01$		$P = 0.74$	$P < 0.01$	$P < 0.01$	
Lumbar spine	−0.75; 0.60	0.61; 1.44	Not applicable	−2.70; −0.10	−2.70; 0.44	0.32; −1.05	Not applicable
Standard	1.35 (−1.03, 3.72)	2.06 (−0.62, 4.73)		2.60 (0.78, 4.42)	3.14 (1.83, 4.46)	1.37 (−2.00, 4.73)	
2–5 yr	$P = 0.27$	$P = 0.13$		$P = 0.01$	$P < 0.01$	$P = 0.43$	
Combined forearm	Not applicable	Not applicable	10.62; 4.70	14.22; 4.33	14.22; 4.43	14.00; 8.69	12.70; 9.17
Hydroxylated			5.92 (−4.49, 16.33)	9.89 (−1.09, 20.87)	979 (0.69, 18.89)	5.31 (0.42, 10.20)	3.53 (−4.19, 11.26)
0.50–1.00 μg Final year			$P = 0.26$	$P = 0.08$	$P = 0.03$	$P = 0.03$	$P = 0.37$

We interpreted the heterogeneity $P \leq 0.05$ as indicating important between-study differences in results.
[a]Trial design: A = Vitamin D (VD)+ Calcium (Ca) *vs.* Normal Diet (ND); B = VD *vs.* ND; C = VD+ Ca *vs.* Ca; D = VD *vs.* Ca.

FIG. 5.

expected pattern in our examination of heterogeneity of findings in studies of bone density (Table 4). These puzzling results highlight the uncertainties regarding the effects of vitamin D that the studies to date have not resolved.

The second major issue in the possibility that vitamin D will have a different impact in different populations. We could not explore this issue adequately because studies typically did not record baseline levels of vitamin D, the most likely explanation of heterogeneity of treatment effect across studies.

The variability in study results further limits any inferences one can make on the basis of the studies to date. We found statistically significant heterogeneity not only in a number of our bone density analyses, but also in the analysis of the effect of standard vitamin D, and the pooled analysis of all formulations, on nonvertebral fractures. Our *a priori* hypotheses failed to adequately explain this variability.

Nevertheless, combining across all trials, we found a significant effect of vitamin D in reducing vertebral fractures and a trend toward reduction in nonvertebral fractures (Table 2 and Figs. 2 and 3). The case for a biological mechanism for the vitamin D effect gains some strength from our analysis of bone density, which suggested a positive impact on bone density at every site, particularly with hydroxylated vitamin D.

The biology of standard and hydroxylated vitamin D is sufficiently different that one might be reluctant to pool in the first place (48). Both forms showed a similar effect on fractures. However, the confidence intervals around these effects are extremely wide, and it is quite possible that true effects differ greatly. Thus, the available data provide little guidance on the choice of vitamin D formulation.

In summary, secure inferences from the available randomized trials of vitamin D are very limited. Vitamin D formulations probably reduce vertebral fractures. Their impact on nonvertebral fractures is uncertain. Moreover, the relative impact of different formulations on fracture rates, and the extent to which vitamin D effects vary in different populations, is extremely uncertain. These issues offer potentially fruitful questions for subsequent investigation.

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