Hypercalcemia, hypercalciuria, and kidney stones in long-term studies of vitamin D supplementation: a systematic review and meta-analysis[1,2]

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ABSTRACT

Background: Vitamin D supplementation is increasingly being used in higher doses in randomized controlled trials (RCTs). However, adverse events from very large annual doses of vitamin D have been shown in 2 RCTs, whereas in a third RCT, low-dose vitamin D, with calcium supplements, was shown to increase kidney stone risk.

Objective: We analyzed the side effects related to calcium metabolism in RCTs, specifically hypercalcemia, hypercalciuria, and kidney stones, in participants who were given vitamin D supplements for ≥24 wk compared with in subjects in the placebo arm.

Design: The following 3 main online databases were searched: Ovid Medline (PubMed), EMBASE, and the Cochrane Library. Software was used for the meta-analysis.

Results: A total of 48 studies with 19,833 participants were identified, which reported ≥1 of the following side effects: hypercalcemia, hypercalciuria, or kidney stones. Of these studies, kidney stones were reported in only 9 trials with a tendency for fewer subjects reporting stones in the vitamin D arm than in the placebo arm (RR: 0.66, 95% CI: 0.41, 1.09; $P = 0.10$). In 37 studies, hypercalcemia was shown with increased risk shown for the vitamin D group (RR: 1.54; 95% CI: 1.09, 2.18; $P = 0.01$). Similar increased risk of hypercalciuria was shown in 14 studies for the vitamin D group (RR: 1.64; 95% CI: 1.06, 2.53; $P = 0.03$). In subgroup analyses, it was shown that the effect of vitamin D supplementation on risk of hypercalcemia, hypercalciuria, or kidney stones was not modified by baseline 25-hydroxyvitamin D, vitamin D dose and duration, or calcium co-supplementation.

Conclusions: Long-term vitamin D supplementation resulted in increased risks of hypercalcemia and hypercalciuria, which were not dose related. However, vitamin D supplementation did not increase risk of kidney stones. Additional large RCTs of long-term vitamin D supplementation are required to confirm these findings. *Am J Clin Nutr* 2016;104:1039–51.

Keywords: hypercalcemia, hypercalciuria, kidney stones, randomized controlled trials, vitamin D supplements

INTRODUCTION

The 2 sources of vitamin D are from the diet (either from food or supplements) or sun exposure (1). Humans have developed a homeostatic mechanism that prevents vitamin D intoxication from sun exposure through the conversion of pre–vitamin D to non–vitamin D photoproducts such as lumisterol or tachysterol (2). However, this protective mechanism does not apply to dietary vitamin D as has been evidenced by side effects that result from the ingestion of very large pharmacologic doses (3). Thus, safety is an issue that is related to vitamin D supplementation, which has been made more relevant by several recent, large randomized controlled trials (RCTs) of vitamin D supplementation (4, 5).

The safety of vitamin D supplements has been examined in a number of reviews and meta-analyses (6–9). The safety of a large single dose of vitamin D_2 and D_3 supplementation was assessed in a recent systematic review that reviewed 30 studies and concluded that large doses ≤300,000 IU/d do not result in any side effects in healthy elderly populations and can improve the serum vitamin D status in the short term (10). In contrast, 2 recent Cochrane meta-analyses of RCTs of vitamin D supplementation (including active analogs) showed that vitamin D supplementation increased risk of hypercalcemia and, when combined with calcium supplements, also increased risk of nephrolithiasis or renal insufficiency (7, 8). An additional Cochrane review of RCTs of vitamin D supplementation in relation to cancer prevention did not find increased risk for hypercalcemia, but there was increased risk for kidney stones (9).

These meta-analyses were restricted to studies that reported outcomes either of mortality (8), fractures (7), or cancer (9) and did not select studies on the basis of the outcomes that are related to calcium metabolism such as hypercalcemia, hypercalciuria, and kidney stones. Moreover, these meta-analyses of RCTs included short-term studies, which could have masked possible long-term side effects from vitamin D, or included studies that compared vitamin D given in combination with calcium supplements with a placebo, which could have produced joint adverse effects from both supplements. There is evidence that calcium by itself causes side effects (11, 12).

[1] Supported the University of Auckland (doctoral scholarship; to ZM) and by the China Scholarship Council (state scholarship fund; to ZW).

[2] Supplemental Table 1 and Supplemental Figures 1–5 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Because of these concerns and because these meta-analyses have only included RCTs that were published up to January 2013, we carried out a meta-analysis of RCTs of vitamin D supplementation in adults (inpatients, outpatients, and healthy adults). This study aimed to update the finding of previous studies and to determine whether long-term vitamin D supplementation (≥24 wk), given by itself against a placebo or with calcium in both arms, increased risk of side effects related to calcium metabolism, specifically hypercalcemia, hypercalciuria, and kidney stones.

METHODS

Online databases

Ovid Medline (PubMed), EMBASE (http://ovidsp.tx.ovid.com.ezproxy.auckland.ac.nz/sp-3.21.0a/ovidweb.cgi), and the Cochrane Library (http://www.cochranelibrary.com.ezproxy.auckland.ac.nz/) were searched up to 28 October 2015 with the use of the following key words and terms: vitamin D, vitamin D_2, vitamin D_3, ergocalciferol, cholecalciferol AND supplementation, AND "randomized controlled trials." The search was further limited to publications in English and to studies with adults ≥18 y old. A total of 1785 publications were identified for screening after duplicates were removed. As shown in **Figure 1**, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram details the search process that resulted in the exclusion and inclusion of studies.

Data-extraction strategy

Two researchers (ZM and RS) independently scanned the search results for the inclusion criteria, and any inconsistencies were discussed and resolved. We retrieved the full texts of potential studies that met the inclusion criteria for a closer assessment. ZM did all data extraction with further confirmation from RS. We initially started a process of contacting the main author of each publication that did not report side effects. However, because of a poor response, we decided to use published data only.

Inclusion criteria

All RCTs were included in the review if they included *1*) adults aged ≥18 y, *2*) provided vitamin D_2 or D_3 supplements in the vitamin D arm, and *3*) had ≥24 wk of supplementation or ≥24 wk of follow-up if large bolus doses (100,000 IU) were given and participants were followed for ≥24 wk. Studies that used ≤600 IU vitamin D_2 or D_3/d in the control arm were also included because many studies allowed vitamin D supplementation of 400

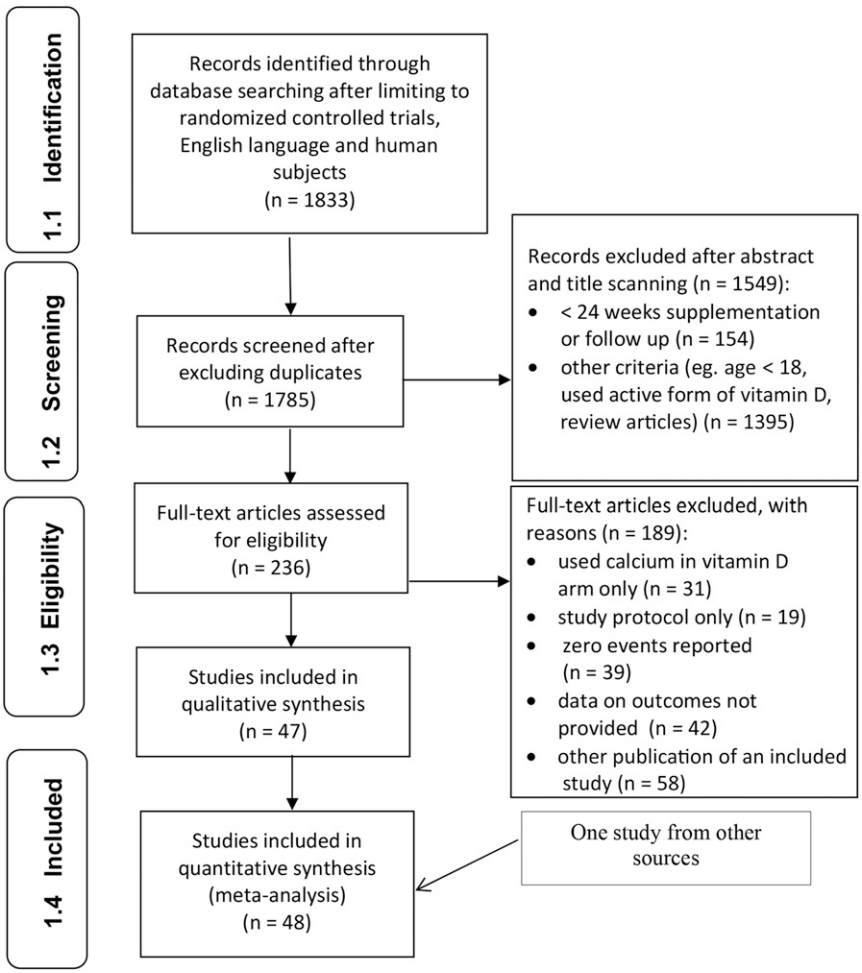

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of number of included and excluded studies.

or 600 IU/d vitamin D supplementation in all participants. In addition, studies with the co-supplementation of calcium with vitamin D were included provided that the control or placebo arm also received calcium. For some studies with a 2 × 2-factorial design, only studies with 2 arms that met the inclusion criteria were included (13).

Exclusion criteria

Studies were excluded if they *1*) gave a supplement of vitamin D plus calcium compared with a no-calcium supplement in the placebo arm, *2*) were conducted in pregnant women, *3*) gave >600 IU vitamin D_2 or D_3/d in the control arm, *4*) had vitamin D in fortified foods rather than as a supplement, *5*) had a duration of supplementation or follow-up <24 wk, and *6*) gave analogs of vitamin D.

Definition of outcomes

The 3 primary outcomes were hypercalcemia, hypercalciuria, or kidney stones. The definitions of hypercalcemia and hypercalciuria varied between studies. Some studies defined hypercalcemia as a serum calcium concentration from >10.2 to 11 mg/dL (2.55–2.75 mmol/L) depending on the target population. In studies that reported cases with the use of different definitions, the definition that was closest to the Institute of Medicine definition [i.e., serum calcium concentration >10.5 mg/dL (equivalent to 2.63 mmol/L)] was used (14). For studies that did not mention a cutoff, the reported number of cases was used for this meta-analysis. Cases that were reported as transient hypercalcemia (on the basis of the previously stated definitions) were also entered into the meta-analysis. For hypercalciuria, the Institute of Medicine defined this as a urinary calcium-to-creatinine ratio >0.3 mg/mg (equivalent to >1 mmol/mmol) or as a 24-h urinary calcium excretion >250 mg/d for women and >275–300 mg/d for men (14). For kidney stones, adverse events were generally verified by clinical evidence in studies that reported them.

Data analysis

Data analyses were conducted with the use of a random-effect meta-analysis with the use of Review Manager Software (RevMan version 5.3; The Cochrane Collaboration). RRs with 95% CIs were the main summary measures in this study of dichotomous outcomes. The Review Manager Software does not calculate a summary estimate if both study arms reported no events because there is no change in the ratio measures of effects (ORs and RRs) if zero-event studies were included (15, 16). We used the Mantel-Haenszel method for combining data from included studies. Predefined subgroup analyses were carried out to determine whether the primary outcomes in the vitamin D and placebo arms varied by baseline 25-hydroxyvitamin D [25(OH)D] concentration (≤50 or >50 nmol/L), use of calcium in both arms or in vitamin D–only compared with placebo arms, length of vitamin D supplementation (24–52 wk or >1 y), and vitamin D dose (≤800 or >800 IU/d). Interactions for subgroups were tested with the use of standard methods (difference between log RRs) for calculating a difference between 2 estimates (17).

For studies that did not report side effects in individual arms but combined 2 arms with vitamin D and 2 placebo arms (18, 19), their data were entered into the meta-analysis in the same way as reported (calcium plus vitamin D and vitamin D arms compared with placebo and calcium-only arms).

A quality assessment of all included studies was conducted independently by 2 researchers (ZM and ZW) on the basis of Cochrane Review risk-of-bias assessment criteria (20). **Supplemental Figures 1–5** show the results of the risk-of-bias assessment and funnel plots for the included studies. STATA software (version 13.1; StataCorp LP) was used to assess risk of publication bias (with the use of Egger's test) and to carry out the meta-regression (metareg command in STATA).

RESULTS

From the 1785 articles screened, 1549 articles were excluded as being ineligible, which left 236 articles for the assessment (Figure 1). Of these 236 articles, an additional 189 articles were excluded (references to studies with zero events or no data of interest are presented in the **Supplemental Table 1**). A total of 48 studies with 19,833 participants (n = 10,279 in the vitamin D arm, and n = 9554 in the placebo arm) reported ≥1 of the 3 side effects and were included for the analyses; 37 studies reported on hypercalcemia (18, 19, 21–55), 14 studies reported on hypercalciuria (21–23, 27, 28, 31, 32, 44, 56–61), and 9 studies reported on kidney stones (18, 19, 45, 59, 62–66). **Table 1** shows the characteristics of included studies. The mean ± SD age of participants was 58.7 ±16.9 y, and 67% of participants were women.

Of 48 included studies, 3 studies were open labeled (38, 40, 51), whereas the remaining studies were double-blind controlled trials. Five of the double-blind studies gave low-dose vitamin D_3 instead of a placebo in the control group (25, 37, 44, 57, 60) with the highest dose in the control arm being 500 IU/d (60). Seven studies used vitamin D_2 supplements (28, 29, 38, 43, 44, 46, 55) with a median vitamin D_2 dose of 3295 IU/d in studies that used this supplement, which included the study of Brohult and Jonson (28) that administered 100,000 IU/d for 1 y. In all other studies, vitamin D_3,was given with a mean dose of 2354 IU/d.

Hypercalcemia

In 37 studies (with 17,473 participants) that reported on hypercalcemia in one or both arms, there was increased risk of hypercalcemia from vitamin D than from the placebo (RR: 1.54, 95% CI: 1.09, 2.18; P = 0.01) (**Figure 2**). As shown in **Table 2**, the effect of vitamin D on hypercalcemia was not modified by the co-intervention of calcium (in both arms or in neither arm), the dose of vitamin D (≤800 or >800 IU), baseline vitamin D status (≤50 or >50 nmol/L), or the duration of supplementation (≤1 or >1 y). The meta-regression showed no association between vitamin D dose and risk of hypercalcemia (P = 0.52).

Hypercalciuria

Overall, 14 studies (with 1987 participants) reported on hypercalciuria with increased risk in the vitamin D arm compared with in the placebo arm (RR: 1.64; 95% CI: 1.06, 2.53; P = 0.03) (**Figure 3**). Subgroup analyses did not show any interactions (P > 0.05) with regard to the dose, duration, baseline D status, or combination with calcium on the effect of vitamin D on risk of hypercalciuria (Table 2). The removal of the study with the

TABLE 1
Characteristics of the included RCTs with vitamin D supplementation[1]

Study	Sample	Women, %	Age[2]	Vitamin D analog and dosage	Duration of supplementation (of follow-up)[3]	Serum 25-hydroxy vitamin D nmol/L	
						Vitamin D	Placebo
Brohult and Jonson, 1973 (28)	49 RA patients	68	52	*1*) 100,000 IU vitamin D_3/d *2*) Placebo	1 y	NR	NR
Johnson et al., 1980 (34)	120 elderly patients from general practitioner list	NR	NR	*1*) 2000 IU vitamin D/d *2*) Placebo	6 mo	NR	NR
Corless et al., 1985 (29)	82 patients from geriatric ward and outpatients; 25(OH)D concentrations <40 nmol/L	78.4	82.4	*1*) 9000 IU vitamin D_2/d *2*) Placebo	9 mo	16.6	17.6
Dawson-Hughes, 1991 (61)	276 healthy postmenopausal women	100	61.5	*1*) 400 IU vitamin D/d + 377 g Ca/d *2*) 377 g Ca/d	1 y	NR	NR
Dawson-Hughes et al., 1995 (57)	247 healthy postmenopausal women	100	63.5	*1*) 100 IU vitamin D_3/d + 500 mg Ca/d *2*) 700 IU vitamin D_3/d + 500 mg Ca/d	2 y	NR	NR
Ooms et al., 1995 (42)	348 ambulatory women from homes and apartments for the elderly	100	70.3	*1*) 400 IU vitamin D_3/d *2*) Placebo	2 y	Median: 27	Median: 25
Aloia et al., 2005 (22); Talwar et al., 2007 (67)	208 postmenopausal black women from the Long Island community	100	60	*1*) 800 IU vitamin D_3/d for 2 y and then 2000 IU vitamin D_3/d for 1 y + 1200–1500 mg Ca/d *2*) Placebo + 1200–1500 mg Ca/d	3 y	46.9	43.2
Grant et al., 2005 (18); Avenell et al., 2012 (68)	5292 subjects ≥70 y old with a recent osteoporotic fracture from outpatients, inpatients or community via phone call	85	77	*1*) 800 IU vitamin D_3/d *2*) 1000 mg Ca/d *3*) 800 IU D_3/d + 1000 mg Ca/d *4*) Placebo tablets	3 y (6.2 y)	38	38
Wissing et al., 2005 (51)	90 post–kidney transplantation patients	43	42.8	*1*) 1000 mg Ca/d *2*) 1000 mg Ca/d + 25,000 IU vitamin D_3/mo	1 y	61.1	48.7
Law et al., 2006 (38)	3717 residents of 118 nursing homes in Britain; ≥60 y old	76	85	*1*) 100,000 IU vitamin D_3/mo *2*) Controls	7–14 mo (median: 10 mo)	Median: 47	Median: 47
Schleithoff et al., 2006 (63)	123 CHF patients (mean age: 57 and 54 y in vitamin D and placebo arms, respectively)	20	55.5	*1*) 2000 IU D_3/d + 500 mg Ca/d *2*) Placebo + 500 mg Ca/d	9 mo	Median: 41	NR
Lappe et al., 2007 (62)	1179 healthy postmenopausal women	100	66.7	*1*) 1400–1500 mg Ca/d + 1100 IU vitamin D_3/d *2*) 1400–1500 mg Ca/d *3*) Placebo	4 y	71.8	71.6
Aloia et al., 2008 (56)	138 healthy Americans from community (residents of Long Island, New York) aged 18–65 y	81	NR	*1*) Increasing dose that was based on the subject's serum 25(OH)D concentration to reach a target of >80 nmol/L; mean: 3440 IU vitamin D_3/d *2*) Placebo	6 mo	NR	NR
Björkman et al., 2008 (26)	218 bed-ridden inpatients aged >65 y	81	84.5	*1*) 400 IU vitamin D_3/d *2*) 1200 IU vitamin D_3/d *3*) Placebo	6 mo	*1*) 21.1 *2*) 23.5	*3*) 23.8
Sneve et al., 2008 (45); Jorde et al., 2008 (69); Jorde et al., 2010 (70)	445 healthy subjects from outpatient clinics, 21–75 y old; BMI (in kg/m^2): 28–47	64	50	*1*) 40,000 IU vitamin D_3/wk + 500 mg Ca/d *2*) 20,000 IU vitamin D_3/wk + 500 mg Ca/d *3*) 2 placebos/wk + 500 mg Ca/d	1 y	*1*) 54.5 *2*) 51.4	*3*) 53.2
Prince et al., 2008 (43); Zhu et al., 2008b (71)	302 community-dwelling women; 25(OH)D concentrations <60 nmol/L	100	77.2	*1*) 1000 IU vitamin D_2/d + 1000 mg Ca/d *2*) Placebo + 1000 mg Ca/d	1 y	44.8	43.7

(Continued)

TABLE 1 (*Continued*)

Study	Sample	Women, %	Age[2]	Vitamin D analog and dosage	Duration of supplementation (of follow-up)[3]	Serum 25-hydroxy vitamin D nmol/L	
						Vitamin D	Placebo
Zhu et al., 2008a (55)	120 healthy women from the community aged 70–80 y	100	74.8	*1*) 1000 IU vitamin D_2/d + 1200 mg Ca/d *2*) 1200 mg Ca/d + placebo *3*) Placebo	5 y	70.2	66.6
Jorde and Figenschau, 2009 (35)	36 patients with type 2 diabetes, 21–70 y old	44	56.2	*1*) 40,000 IU vitamin D_3/wk *2*) Placebo/wk	6 mo	60	58.5
Rastelli et al., 2011 (44)	58 women with nonmetastatic breast cancer after 8 wk of adjuvant or anastrozole therapy	100	61.5	*1*) Baseline 25(OH)D concentration: 50–72 nmol/L = 50,000 IU vitamin D_2/wk for 8 wk and then monthly for 4 mo *2*) 25(OH)D concentration 25–50 nmol/L = 50,000 IU vitamin D_2/wk for 16 wk and then monthly for 2 mo *3*) Placebo for each regimen All received 400 mg Ca/d + 400 IU vitamin D_3/d	6 mo	*1*) and *2*) 57.4	*3*) 55
Steffensen et al., 2011 (64) and 2013 (72)	71 patients with multiple sclerosis aged 18–50 y	71	40	*1*) 20,000 IU vitamin D_3/wk + 500 mg Ca/d *2*) Placebo + 500 mg Ca/d	96 wk	56	57
Gallagher et al., 2012 (VIDOS; 30)	163 postmenopausal white women, aged 50–90 y, with vitamin D insufficiency (≤50 nmol/L)	100	67	8 groups of treatment: *1*) placebo, *2*) 400 IU vitamin D_3/d, *3*) 800 IU vitamin D_3/d, *4*) 1600 IU vitamin D_3/d, *5*) 2400 IU vitamin D_3/d, *6*) 3200 IU D_3/d, *7*) 4000 IU vitamin D_3/d, *8*) 4800 IU vitamin D_3/d or matched placebo, plus calcium supplements to reach total intake of 1200–1400 mg/d	1 y	38.2	37.7
Goswami et al., 2012 (32); Das et al., 2014 (73)	173 healthy women	100	21.7	*1*) 60,000 IU vitamin D_3/wk for 8 wk and then 60,000 IU D_3 2 times/mo for 4 mo + 1000 mg Ca/d 60,000 IU vitamin D_3/wk for 8 wk and then 60,000 IU 2 times/mo for 4 mo *2*) 60,000 IU vitamin D_3/wk for 8 wk, then 60,000 IU vitamin D_3 2 times/mo for 4 mo *3*) 1000 mg Ca/d *4*) Double placebo	6 mo	*1*) 23.7 *2*) 22.9	*3*) 24.7 *4*) 21.4
Kjærgaard et al., 2012 (36)	237 healthy adults with 25(OH)D concentrations <55 or >70 nmol/L	50	53.6	*1*) 40,000 IU vitamin D_3/wk *2*) Placebo	6 mo	47.7	47.7
Lagari et al., 2012 (37)	105 ambulatory elderly subjects with 25(OH)D concentrations <75 or ≥75 nmol/L; 65–95 y old	83	73.5	*1*) 25(OH)D concentration ≥75 nmol/L:2000 IU vitamin D_3/d *2*) 25(OH)D concentration <75 nmol/L: 2000 IU vitamin D_3/d *3*) 25(OH)D concentration ≥75nmol/L:400 IU vitamin D_3/d *4*) 25(OH)D concentration <75 nmol/L:400 IU vitamin D_3/d	6 mo	*1*) 97.3 *2*) 54.9	*3*) 92.3 *4*) 57.4
Lehouck et al., 2012 (39)	182 patients with chronic obstructive pulmonary disease	7.6	73	*1*) 100,000 IU vitamin D_3/mo *2*) Placebo/mo	1 y	49.9	49.9

(Continued)

TABLE 1 (*Continued*)

Study	Sample	Women, %	Age[2]	Vitamin D analog and dosage	Duration of supplementation (of follow-up)[3]	Serum 25-hydroxy vitamin D nmol/L	
						Vitamin D	Placebo
Tran et al., 2012 (48); Waterhouse et al., 2014 (74)	644 adults aged 60–84 y from the community in Australia	47	72	*1*) 60,000 IU vitamin D_3/mo (n = 215) *2*) 30,000 IU vitamin D_3/mo (n = 215) *3*) Placebo (n = 214)	12 mo	*1*) 41.7; *2*) 41.6	*3*) 41.9
Abou-Raya et al., 2013 (21)	228 premenopausal women and 39 men with systemic lupus erythematous	85	38.8	*1*) 2000 IU vitamin D_3/d *2*) Placebo	12 mo	49.4	49.4
Aloia et al., 2013 (23)	159 healthy postmenopausal women from the community	100	59	*1*) 4000 IU vitamin D_3/d + 1200 mg Ca *2*) 4000 IU vitamin D_3/d *3*) 1200 mg Ca/d *4*) Double placebo	6 mo (28 wk)	*1*) 69 *2*) 64	*3*) 66 *4*) 67
Bolland et al., 2013 (27)	27 sarcodiasis patients with 25(OH)D concentrations <50 nmol/L and normal serum calcium	70	57	*1*) 50,000 IU vitamin D_3/wk for 1 mo and then 50,000 IU vitamin D_3/mo for 11 mo *2*) Placebo	1 y	35	38
Hewitt et al., 2013 (33)	60 hemodialysis patients (3 times/wk) with 25(OH)D concentrations <65 nmol/L and aged 20–76 y	0	63.5	*1*) 50,000 IU vitamin D_3/wk for 8 wk and then monthly for 4 mo *2*) Placebo	6 mo	44.9	39.9
McAlindon et al., 2013 (59)	146 patients with knee osteoarthritis	61	62.4	*1*) 2000 IU vitamin D_3/d *2*) Placebo	2 y	56.6	54.6
Reddy et al., 2013 (60)	40 pancreatitis patients (tropical calcific type) with 25(OH)D concentrations <75 nmol/L	35	33	*1*) 600,000 IU vitamin D_3 *2*) 300,000 IU vitamin D_3 *3*) Placebo + 500 IU vitamin D_3/d and 1 g Ca/d in all arms	9 mo	*1*) 30.8 *2*) 23.5	*3*) 26.9
Suzuki et al., 2013 (47)	114 Parkinson patients aged 45–85	48	72	*1*) 1200 IU vitamin D_3/d *2*) Placebo	1 y	56.2	52.6
Wamberg et al., 2013 (49)	52 healthy and obese people aged 18–50 y with 25(OH)D concentrations <50 nmol/L and BMI >30 kg/m^2	71	40.5	*1*) 7000 IU vitamin D_3/d *2*) Placebo	26 wk	34.5	34.6
Witham et al., 2013a (53)	159 patients with "isolated systolic hypertension" aged ≥70	49	76.8	*1*) 100,000 IU vitamin D_3 every 3 mo *2*) Placebo every 3 mo	1 y	44.92	44.92
Witham et al., 2013b (52)	75 postmyocardial infarction patients (in ≤6 wk)	31	66	*1*) 100,000 IU vitamin D_3 at 3 times: baseline, 2 and 4 mo *2*) Placebo	4 mo (6 mo)	49	45
Amrein et al., 2014 (75)	492 ICU patients with 25(OH)D concentrations <50 nmol/L; hypercalcemia was reported for 80 subjects	35	64.6	*1*) Day 1: 540,000 IU vitamin D_3, then 90,000 IU vitamin D_3/mo for 5 mo starting from day 28 *2*) Placebo	6 mo	32.7	32.5
Gallagher et al., 2014 (31)	198 white and black women aged 25–45 y	100	36.7	*1*) 400 IU vitamin D_3/d + 200 mg Ca/d *1*) 800 IU vitamin D_3/d + 200 mg Ca/d *3*) 1600 IU vitamin D_3/d + 200 mg Ca/d *4*) 2800 IU vitamin D_3/d + 200 mg Ca/d *5*) Placebo + 200 mg Ca/d	1 y	*1*) 32.7 *2*) 34.4 *3*) 33.2 *4*) 33.2	*5*) 35.2

(Continued)

TABLE 1 (*Continued*)

Study	Sample	Women, %	Age[2]	Vitamin D analog and dosage	Duration of supplementation (of follow-up)[3]	Serum 25-hydroxy vitamin D nmol/L	
						Vitamin D	Placebo
Li et al., 2014 (40)	96 hemodialysis patients aged ≤18 y with 25(OH)D concentrations <62 nmol/L	42	59	*1*) 50,000 IU vitamin D_3/wk for 6 wk and then 10,000 IU vitamin D_3/wk in subjects with 25(OH)D concentrations >87.4 nmol/L and 500,000 IU vitamin D_3/wk in subjects with 25(OH)D concentrations ≤87.4 nmol/L *2*) Controls	12 mo	33.7	32.7
Mose et al., 2014 (41)	64 chronic dialysis patients >18 y old with 3 mo of treatment history.	58	67.5	*1*) 3000 IU vitamin D_3/d *2*) Placebo/d	6 mo	Median: 28	Median: 28
Sollid et al., 2014 (46)	511 subjects with IFG or IGT aged 21–70 y; IFG concentrations >7.0 mmol/L and IGT concentrations >7.7 and <11.1 mmol/L	39	62.1	*1*) 20,000 IU vitamin D_2/wk *2*) Placebo	1 y	59.9	61.1
Turner et al., 2014 (65)	118 women with symptomatic bacterial vaginosis (median age = 26 y)	100	26	*1*) 50,000 IU vitamin D_3 (9 capsules)/wk for first month and monthly afterward *2*) Placebo/d (9 capsules) Both received an additional 500 mg metronidazole for 7 d	24 wk	41.4	39.4
Wepner et al., 2014 (50)	30 orthopedic inpatients and outpatients with fibromyalgia syndrome and 25(OH)D concentrations <80 nmol/L	90	47.3	*1*) 1200 IU vitamin D_3/d if 25(OH)D concentrations were 60–80 nmol/L *2*) 2400 IU vitamin D_3/d if 25(OH)D concentrations were <60 nmol/L *3*) Placebo	24 wk (48 wk)	47.4	52.1
Wood et al., 2012 (76) and 2014 (54); Murdoch et al., 2012 (77)	305 postmenopausal women	100	63.3	*1*) 400 IU vitamin D_3/d *2*) 1000 IU vitamin D_3/d *3*) Placebo/d	1 y	*1*) 32.7 *2*) 32.4	*3*) 36.2
Arora et al., 2015 (25)	Patients with systolic BP from 120 to 159 mm Hg and diastolic BP <99 mm Hg; 25(OH)D concentrations <62.4 nmol/L	38	36.5	*1*) 4000 IU vitamin D_3/d *2*) 400 IU vitamin D_3/d	6 mo	Median: 38.9	Median: 39.4
Baron et al., 2015 (19)	2259 patients with recently diagnosed adenomas and no known colorectal polyps remaining after colonoscopy	15	57	*1*) 1000 IU vitamin D_3/d *2*) 1000 vitamin D_3/d + 1200 mg Ca/d *3*) 1200 mg Ca/d *4*) Double placebo	3–5 y	61.6	60.8
Garg et al., 2015 (58)	Women with PCOS (aged 18–35 y) who received metformin (1500 mg/d)	100	22.4	*1*) 120,000 IU vitamin D_3/mo *2*) Placebo/mo	24 wk	19.2	16.9
Krul-Poel et al., 2014 (66)	274 outpatients with type 2 diabetes from 5 general practices	35	67	*1*) 50,000 IU vitamin D_3/mo *2*) Placebo/mo	6 mo	60.6	59.1

[1]BP, blood pressure; CHF, chronic heart failure; ICU, intensive care unit; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IM, intramuscular injection; NR, not reported; PCOS, polycystic ovary syndrome; RA, rheumatoid arthritis; VIDOS, Vitamin D Osteoporosis Study; 25(OH)D, 25-hydroxyvitamin D.

[2]All values are means.

[3]Duration of follow-up is mentioned in parentheses if different from that in the supplementation period.

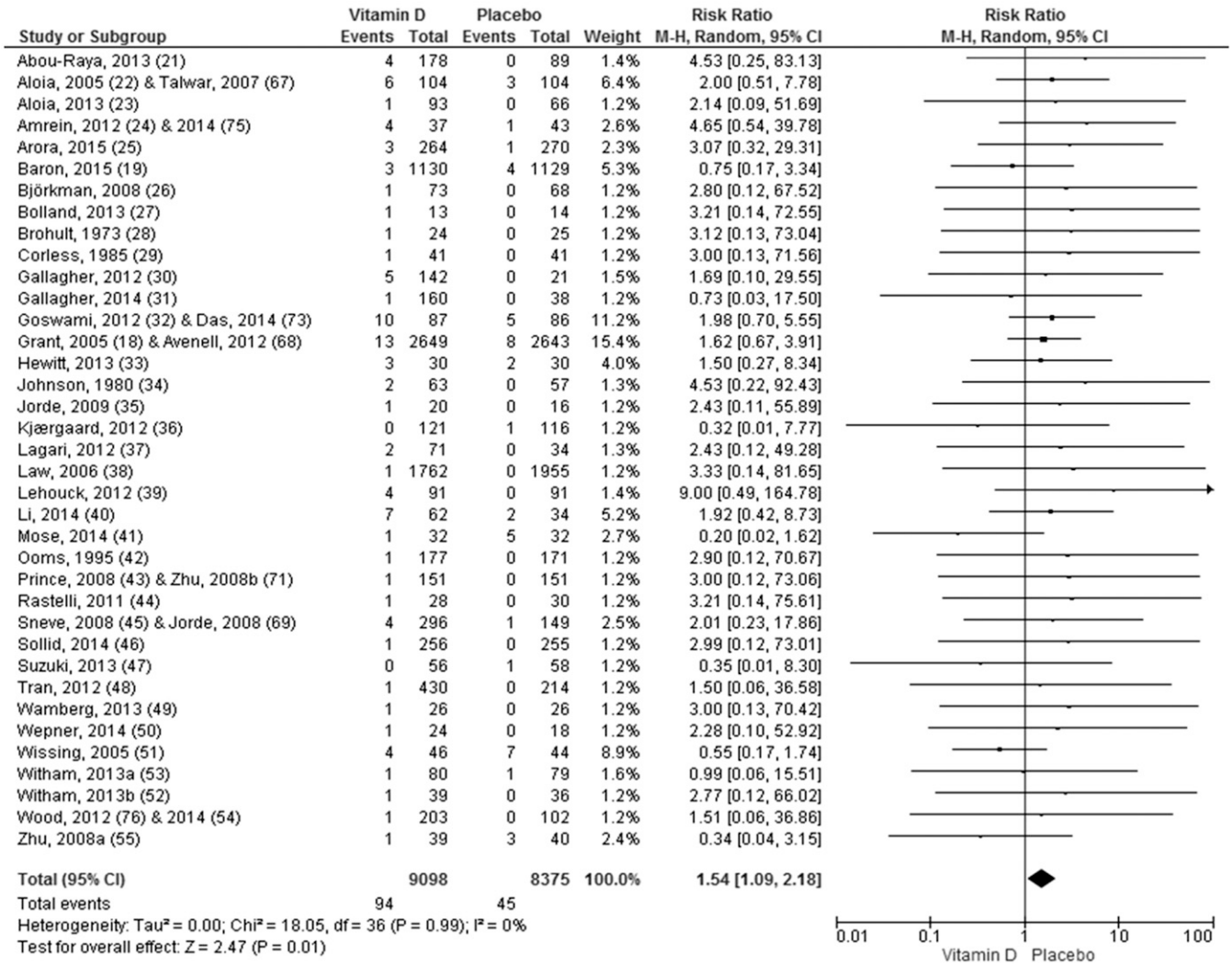

FIGURE 2 Forest plots of studies with hypercalcemia side effects (for each study the dot is the RR and the line is the 95% CI). M-H, Mantel-Haenszel method.

greatest number of events (30) did not change the effect size (RR: 1.62; 95% CI: 0.99, 2.06; $P = 0.06$).

Kidney stones

There were 9 studies (with 9619 participants) that reported on kidney stones (**Figure 4**). Overall results showed no increase in risk of kidney stones from vitamin D supplementation (RR: 0.66; 95% CI: 0.41, 1.09; $P = 0.10$). The effect of vitamin D on risk of kidney stones did not vary between subgroups (Table 2). The study of Baron et al. (19) had the greatest number of events, and the removal of the study changed the effect size to 0.63 (95% CI: 0.24, 1.62; $P = 0.34$).

Bias and heterogeneity

Approximately 75% of studies had low risk of bias in terms of allocation concealment, blinding, selective reporting, and incomplete outcome data (Supplemental Figure 1). There was low heterogeneity between studies for each outcome ($I^2 = 0\%$). The funnel plots showed no apparent publication bias (Supplemental Figures 3–5), which was confirmed with the use of Egger's test for each outcome (hypercalcemia: $t = 1.58$, $P = 0.12$; hypercalciuria: $t = 1.61$, $P = 0.13$; kidney stones: $t = -0.33$, $P = 0.75$).

DISCUSSION

We have shown, in a large meta-analysis that included studies published up to October 2015, that vitamin D supplementation resulted in changes in calcium metabolism with increased risks of hypercalcemia and hypercalciuria but no increase in risk of reported kidney stones. The duration of supplementation, co-supplementation of calcium, dosage, and baseline 25(OH)D in substudy analyses did not change the calculated effects.

Our results show, for the first time to our knowledge, that vitamin D_3 or D_2, when given alone or in studies with calcium in both arms, significantly increased risk of hypercalcemia (Figure 2, $P = 0.01$). In our hypercalcemia analyses, we included 17,801 participants from 38 studies. These numbers were more than the amounts reported in previous meta-analyses of natural vitamin D. For example, Bjelakovic et al. (8) showed a nonsignificant

TABLE 2
Summary table of RRs for each outcome and its subgroups for randomized controlled trials of vitamin D supplementation compared with a placebo or control

Outcome or subgroup	Studies, *n*	Participants, *n*	Effects size[1]	*Z*	*P*	Interaction tests[2] *Z*	*P*
1) Hypercalcemia	37	17,473	1.54 (1.09, 2.18)	2.47	0.01	—	—
1.1.a) Hypercalcemia in studies with calcium in both arms	12	1916	1.02 (0.58, 1.78)	0.06	0.95	−1.77	0.07
1.1.b) Hypercalcemia in studies with vitamin D only compared with placebo or control	25	7993	2.04 (1.21, 3.45)	2.66	0.008		
1.2.a) Hypercalcemia in studies using ≤800 IU/d	3	5715	1.76 (0.78, 3.99)	1.35	0.18	0.66	0.51
1.2.b) Hypercalcemia in studies using >800 IU/d	33	11,362	1.31 (0.95, 1.80)	1.67	0.1		
1.3.a) Hypercalcemia in studies with mean baseline 25(OH)D[3] concentrations ≤50 nmol/L	24	13,406	1.85 (1.23, 2.78)	2.96	0.003	1.96	0.05
1.3.b) Hypercalcemia in studies with mean baseline 25(OH)D concentrations >50 nmol/L	9	3766	1.00 (0.63, 1.57)	0.01	0.99		
1.4.a) Hypercalcemia in studies with ≤1 y of supplementation or follow-up	31	9226	1.62 (1.07, 2.47)	2.27	0.02	1.25	0.20
1.4.b) Hypercalcemia in studies with >1 y supplementation or follow-up	6	8238	1.11 (0.73, 1.68)	0.49	0.63		
2) Hypercalciuria	14	1987	1.64 (1.06, 2.53)	2.24	0.03	—	—
2.1.a) Hypercalciuria in studies using ≤800 IU/d	3	585	1.02 (0.46, 2.28)	−0.06	0.95	−1.13	0.25
2.1.b) Hypercalciuria in studies using >800 IU/d	11	1215	1.82 (1.0, 3.33)	1.95	0.05		
2.2.a) Hypercalciuria in studies with calcium in both arms[4]	7	884	1.62 (0.87, 3.02)	1. 53	0.13	0.014	1.00
2.2.b) Hypercalciuria in studies with vitamin D only compared with placebo or control[4]	9	1103	1.61 (0.88, 2.96)	1.54	0.12		
2.3.a) Hypercalciuria in studies with baseline 25(OH)D concentrations ≤50 nmol/L	7	914	1.94 (1.07, 3.52)	2.17	0.03	0.41	0.68
2.3.b) Hypercalciuria in studies with baseline 25(OH)D concentrations >50 nmol/L	3	363	1.54 (0.61, 3.91)	0.91	0.36		
2.4.a) Hypercalciuria in studies with ≤1 y supplementation or follow-up	11	1387	1.66 (1.02, 2.71)	2.04	0.04	0.22	0.82
2.4.b) Hypercalciuria in studies with >1 y supplementation or follow-up	3	601	1.54 (0.60, 3.95)	2.23	0.03		
3) Kidney stones	9	9619	0.66 (0.41, 1.09)	1.63	0.10	—	—
3.1.a) Kidney stones in studies with calcium in both arms[4]	6	6311	0.66 (0.39, 1.10)	1.60	0.11	−0.08	0.38
3.1.b) Kidney stones in studies with vitamin D only compared with placebo or control[4]	4	3155	1.00 (0.18, 5.73)	0.00	0.10		
3.2.a) Kidney stones in studies with ≤800 IU/d	1	5292	1.00 (0.14, 7.08)	0.00	1.00	0.41	0.67
3.2.b) Kidney stones in studies with >800 IU/d	8	4327	0.65 (0.39, 1.07)	1.68	0.09		
3.3.a) Kidney stones in studies ≤1 y supplementation or follow-up	3	515	0.70 (0.11, 4.39)	0.38	0.70	0.06	0.95
3.3.b) Kidney stones in studies with >1 y supplementation or follow-up	6	9104	0.66 (0.40, 1.10)	1.58	0.11		
3.4.a) Kidney stones in studies with baseline 25(OH)D concentrations ≤50 nmol/L	3	5533	0.62 (0.14, 2.73)	0.63	0.53	−0.09	0.92
3.4.b) Kidney stones in studies with baseline 25(OH)D concentrations >50 nmol/L	6	4106	0.67 (0.40, 1.13)	1.52	0.13		

[1]All values are RRs (95% CIs). The Mantel-Haenszel test was used to measure RRs in a random-effects model.
[2]Test of interaction for the difference between 2 estimates was used (17).
[3]25(OH)D, 25-hydroxyvitamin D.
[4]For studies with 4 arms, we combined 2 arms into appropriate subgroups (calcium and calcium plus vitamin D in one subgroup compared with vitamin D and placebo in the other subgroup). Therefore, the total number of studies in subgroups may not match the total number of included studies for the outcome of interest.

RR of 1.36 (95% CI: 0.85, 2.18) in 11,323 participants from 15 studies and concluded that vitamin D_3 or D_2 did not cause hypercalcemia. Avenell et al. (7) also reported a nonsignificant RR of 1.57 (95% CI: 0.80, 3.05) in 11,355 participants from 8 studies for vitamin D_3, vitamin D_2, and 25(OH)D (7). The effect size of this study was similar to that of the aforementioned studies. Our larger sample size provided greater power with which we could be more confident about the observed effects. The study results showed that natural vitamin D has hypercalcemic effects and increases risk ~50%, when calcium is balanced in both vitamin D and placebo arms. This finding complements the stronger 3–4-fold higher risk from active vitamin D that was reported by both previous meta-analyses (7, 8).

Although the presence of calcium did not modify the effect of vitamin D (Table 2), results from the studies in our meta-analysis also showed that the cumulative incidence of hypercalcemia was much higher in studies that provided calcium supplements in both arms (3.9% and 3.0% in vitamin D plus calcium and calcium-only arms, respectively) than in studies that did not (1.2% and 0.4% in vitamin D and placebo arms, respectively). Thus, calcium seems to increase risk of hypercalcemia much more than vitamin D does, which indicated that studies that compared both vitamin D and calcium in combination with a placebo (plus calcium) had overestimated the effect of vitamin D. In studies that gave both calcium and vitamin D, the additional intake of calcium supplements may have hidden any increase in risk of hypercalcemia from vitamin D, which was more apparent in studies that gave only vitamin D (Table 2).

Our results show, for the first time to our knowledge, that natural vitamin D, when calcium supplementation is balanced in

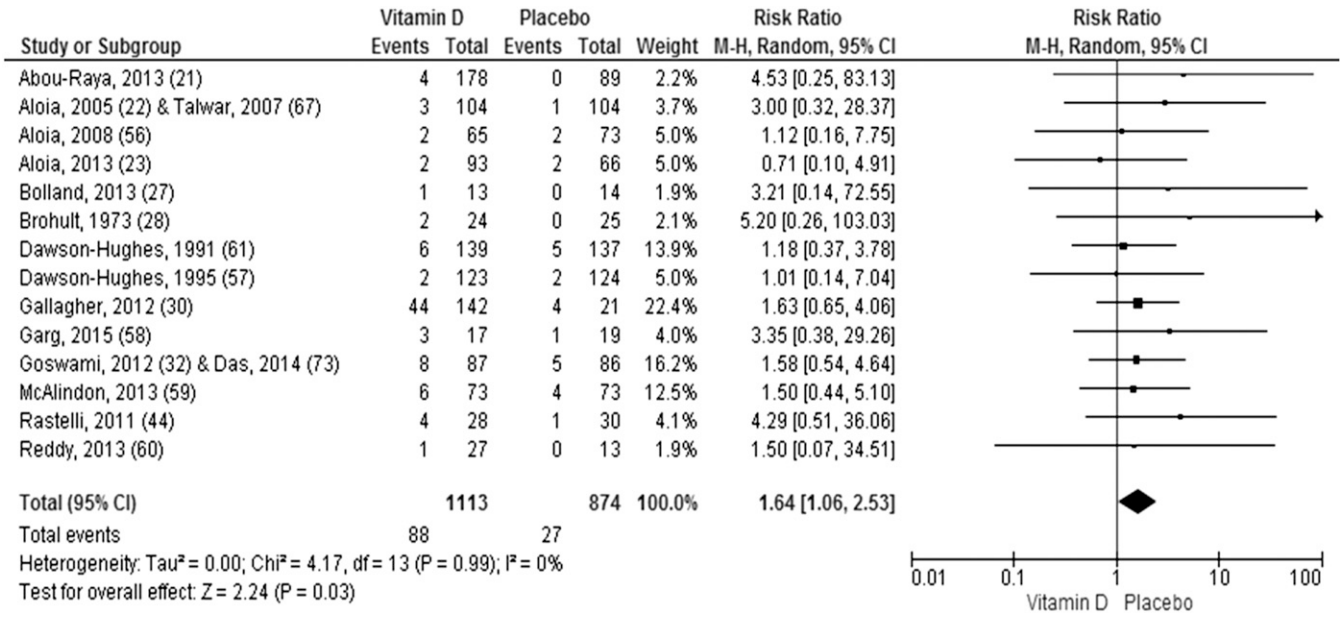

FIGURE 3 Forest plots for studies with hypercalciuria side effects (for each study the dot is the RR and line is the 95% CI). M-H, Mantel-Haenszel method.

both arms, also significantly increases risk of hypercalciuria (by 64%) (Figure 3). In our hypercalciuria analyses, we included 1987 participants from 14 studies, which was more than in the only previous meta-analysis with 695 participants from 3 studies that reported an RR of 4.64 (95% CI: 0.99, 21.8) (8). Because the *P* value for the latter result was 0.051, the authors concluded that vitamin D did not cause hypercalciuria. However, our larger sample size indicated that there is an effect from vitamin D, but the effect size is much smaller. Hypercalciuria may be a more sensitive criterion for excessively increased vitamin D status because more cases of it were reported than of hypercalcemia in those studies that investigated both variables in all patients (31, 78), although this finding has not been completely consistent (32). The mechanism by which vitamin D supplements increases risk of hypercalciuria is unclear. Although there is evidence that vitamin D supplements increase risk of hypercalcemia by increasing calcium absorption from the gut and increasing resorption from bone (79), episodes of hypercalciuria do not appear to be related to hypercalcemia (78).

Contrary to previous meta-analyses, we did not find increased risk of renal stones from natural vitamin D in 9619 participants in 9 studies (RR: 0.66; 95% CI: 0.41, 1.09) (Figure 4). Both Cochrane meta-analyses reported significant 17% increased risk of kidney stones from vitamin D (7, 8). However, the analyses were dominated by the Women's Health Initiative (80), which compared vitamin D and calcium combined with neither and reported an HR of 1.17 (95% CI: 1.02, 1.34). The study had a weight of 99% in the Cochrane analysis (8). When natural vitamin D or 25(OH)D was given (without any calcium), the RR of stones or renal insufficiency from 5844 participants in 3 studies was 0.59 (95% CI: 0.24, 1.42) in one of the previous meta-analyses (7), which was a result that was very similar to our value. Our results suggest that controlling for the effect of calcium supplementation removes any adverse effect of vitamin D supplementation on risk of kidney stones. The lack of an effect of vitamin D supplementation on risk of kidney stones, in contrast with increased risks of hypercalcemia and hypercalciuria, may have been be due to the transient and asymptomatic nature of the latter 2 conditions (21, 33, 44, 78) and the relatively short period of follow-up (6–12 mo in most studies), which may not have been long enough for kidney stones to form (25, 33, 75). Our kidney stone results were consistent with

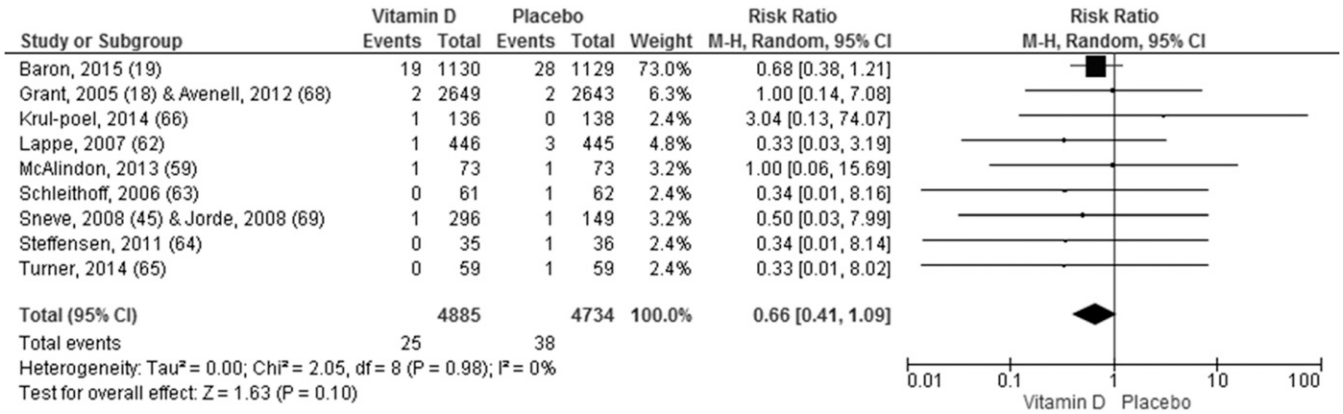

FIGURE 4 Forest plots of studies with kidney stone side effect (for each study the dot is the RR and line is the 95% CI). M-H, Mantel-Haenszel method.

observational studies that reported no association between vitamin D status and risk of kidney stones, and there is no known mechanism for any such association (81).

To the best of our knowledge, there has been no previous meta-analysis that targeted long-term vitamin D supplementation with a focus on vitamin D_2 and D_3. Previous meta-analyses were limited to studies that reported other specific outcomes (mortality or fractures), included studies with short-term durations of supplementation with any type of vitamin D analog, and included studies in their analyses with vitamin D plus calcium as a combination therapy although there was not a calcium supplement in the placebo arm (7, 8). However, our study has some limitations. The outcomes we analyzed were not systematically searched for in all participants of the RCTs in our meta-analysis. Thus, we may have underestimated the effect of vitamin D although this measurement error should have been similar in both vitamin D and placebo arms. In addition, by only including studies that provided supplementation ≥24 wk, we may not have detected short-term calcium-related effects from vitamin D supplements, although we considered these effects to have been less likely to have occurred than those that arise from longer-term supplementation. In addition, the fewer studies and participants in studies with hypercalciuria and renal stone outcomes than with hypercalcemia outcomes decreased the power to detect any effect modification in the subgroup analyses, and thus, the presence of and effect modification could not be ruled out for the former 2 outcomes.

In conclusion, our results show that vitamin D supplementation results in changes in calcium metabolism with increased risks of hypercalcemia and hypercalciuria, which are not related to the vitamin D dose, but no increase in risk of reported kidney stones. The clinical significance of our results is unclear because of the asymptomatic side effects that are linked to vitamin D. Additional large RCTs of long-term vitamin D supplementation are required to confirm these findings.

The authors' responsibilities were as follows—ZM: analyzed the data; ZM, ZW, and RS: conducted the research; ZM and RS: designed the research and wrote the first draft of manuscript; AWS: provided advice regarding the analysis of the data; CMML: provided support in the design of the research; RS: had primary responsibility for the final content of the manuscript; and all authors: edited and contributed to the preparation of all sections of the manuscript and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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