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Review Article EP13265.RA

LARGE, SINGLE-DOSE, ORAL VITAMIN D SUPPLEMENTATION IN ADULT POPULATIONS: A SYSTEMATIC REVIEW

Running Title: Large, Once-Yearly Vitamin D Dosing

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ABSTRACT

Objective: Daily supplementation is often inadequate in treating vitamin D deficiency due to poor compliance. A single, large dose of vitamin D given at timed intervals may be an alternative strategy.

Methods: We identified 2243 articles in PUBMED using the terms "high dose vitamin D," "single dose vitamin D," "bolus vitamin D," or "annual dose vitamin D." Review articles, cross-sectional studies, non-human studies, responses to other articles, and non-English articles were excluded. Manuscripts were also excluded if the study: (1) did not use oral cholecalciferol or ergocalciferol, (2) used vitamin D analogs, (3) enrolled participants under age 18, (4) administered doses <100,000 IU (2.5 mg), or (5) administered >1 dose per year. References of eligible manuscripts and the Cochrane databases were also searched. Two independent reviewers identified eligible manuscripts, and a third reviewer evaluated disagreements. Thirty manuscripts were selected using these criteria.

Results: Large, single doses of vitamin D consistently increased serum 25-hydroxyvitamin D (25(OH)D) concentrations in several vitamin D sufficient and deficient populations. Vitamin D_3 doses of 300,000 IU or greater provided optimal changes in serum 25(OH)D and parathyroid hormone (PTH) concentrations. Vitamin D supplementation also impacted bone health and extra-skeletal endpoints.

Conclusions: This review recommends vitamin D_3 be used for supplementation over vitamin D_2, and that single vitamin D_3 doses of 300,000 IU and greater are most effective at improving vitamin D status and suppressing PTH concentrations for up to 3 months. Lower doses, however, may be sufficient in certain populations. Vitamin D doses >500,000 IU should be used judiciously in order to minimize adverse events.

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Keywords: Vitamin D, high-dose, single-dose, annual dose, cholecalciferol, ergocalciferol

Abbreviations:

D 25(OH)D = 25-hydroxyvitamin; **CF =** cystic fibrosis; **DM =** diabetes; **PTH =** parathyroid hormone; **TB =** tuberculosis

INTRODUCTION

Vitamin D insufficiency is linked not only to bone disease (1, 2), but also to several non-skeletal conditions including type 2 diabetes mellitus (DM)(3), cardiovascular disease (4-7), chronic lung disease (8-11), tuberculosis (TB) (12-14) and upper respiratory infections (15, 16). Vitamin D status is determined by serum 25-hydroxyvitamin D (25(OH)D), the major circulating form of vitamin D (17). Controversy exists as to what serum concentration of 25(OH)D is sufficient; while The Endocrine Society Clinical Practice Guidelines on vitamin D have defined sufficiency as >30 ng/mL (18), the Institute of Medicine (IOM) suggests there is no consistent benefit associated with serum 25(OH)D concentrations >20 ng/mL (19, 20).

Correction of vitamin D insufficiency is commonly achieved using oral vitamin D supplements. The Endocrine Society guidelines suggest that daily intake of 1,500-2,000 IU of vitamin D is necessary to achieve serum 25(OH)D concentrations consistently >30 ng/mL in adults (18). However, adherence to daily doses has been reported to be low in several large clinical trials (1). Poor adherence has been associated with difficulty swallowing combined vitamin D/ calcium tablets, gastrointestinal (GI) side-effects (21), the number of concurrent treatments a patient is receiving, and the patient's attitude towards vitamin D supplementation (22). Vitamin D given as a large bolus dose has demonstrated higher adherence rates compared to daily and monthly dosing regimens, and has the potential to yield sustained improvements in serum 25(OH)D and PTH concentrations (23). The sustained effect of high-dose vitamin D may be attributed to its long half-life. Upon ingestion, vitamin D is either converted to 25(OH)D or redistributed into fat, from which it is slowly released over time. By this mechanism, Ish-Shalom *et al* (24) suggests that daily, weekly and monthly vitamin D dosing will result in the same circulating concentrations of 25(OH)D over an equivalent period of time. The purpose of this

systematic review was to investigate the effects of single, large, bolus doses of vitamin D on serum 25(OH)D concentrations, PTH suppression and other health outcomes in adults.

METHODS

We searched the terms "high dose vitamin D," "single dose vitamin D," "bolus vitamin D," or "annual dose vitamin D" in PUBMED through the present date (9/01/2012). Limits were pre-set to manuscripts published in the English language. Titles and abstracts were reviewed. Review articles, cross-sectional studies, non-human studies, and responses to other articles were excluded. Manuscripts were also excluded if: (1) they did not use oral cholecalciferol or ergocalciferol, (2) they used analog compounds of vitamin D (ie. calcitriol, doxercalciferol, paricalcitol), (3) study participants were under age 18, (4) the study administered doses <100,000 IU (2.5 mg), or (5) vitamin D was given more than once within a year. Manuscripts not excluded by information in the abstract and titles were examined in their entirety, and their references scanned for additional manuscripts. We also searched the Cochrane databases using the same criteria. Two independent reviewers (J.A., M.K.) identified manuscripts with these criteria, and a third reviewer (V.T.) determined manuscript eligibility when there were disagreements.

Outcomes of interest include: (1) serum/plasma 25(OH)D, (2) serum/plasma PTH, (3) differences between vitamin D_2 and D_3, and (4) adverse effects.

PUBMED search results

There were 2,243 manuscripts identified from the specified search terms (Fig. 1) and 42 were deemed potentially eligible after applying exclusion criteria to the title and abstract. Following review of these manuscripts, 12 studies were subsequently excluded by criteria not included in the title and abstract. No papers were added from the references of selected

manuscripts or the Cochrane databases. A total of 30 studies were included in this review. Of the 30 manuscripts evaluated, three (25-27) provided secondary analyses of data that was published in earlier studies that were also included in this paper (28-30).

RESULTS

Study design

The 30 studies that met eligibility criteria of this paper were published after 1990 and evaluated adult populations receiving single, oral vitamin D doses >100,000 IU. Elderly populations were sampled in 14 studies (26, 27, 29-40), and vitamin D deficient adults were observed in 2 studies (41, 42). Five studies evaluated cardiovascular risk factors (type 2 DM, insulin resistance, peripheral artery disease (PAD), and stroke history)(3, 43-46). Two studies evaluated populations with autoimmune and inflammatory conditions (primary dysmenorrhea and rheumatologic patients) (47, 48). Seven studies looked at populations with infectious or acquired conditions (alcoholic liver cirrhosis (49), cystic fibrosis (CF) (25, 28), tuberculosis (TB) (50, 51), intensive care unit (ICU) placement (52), and pregnancy (53)).

Table 1 represents the 21 studies that provided information on serum 25(OH)D or PTH before and after vitamin D dosing compared to a control group. Three studies (25-27) not included in Table 1 provided additional analysis of previously published studies that were already included in the table. The remaining six studies (32, 37, 42, 46, 47, 49) are discussed below when relevant to adverse events or secondary measures.

Vitamin D on serum/plasma 25(OH)D and PTH concentrations

Oral doses of vitamin D2 and D3 (100,000-600,000 IU) significantly increased serum 25(OH)D concentration from baseline in all reviewed studies. The greatest increases in serum 25(OH)D consistently occurred between days 1 and 30 (Fig. 2); peak levels were measured at 3

days (34) and 7 days (25, 40, 49) following dosing, though concentrations >30 ng/mL were noted as soon as 1 day following 600,000 IU D3 (34) and 540,000 IU D3(52).

Improvement in vitamin D status was associated with lowering of PTH concentration in a majority of the studies (30, 31, 34-36, 38, 39, 41, 52, 53); significant decreases ($p<0.001$) were noted as soon as day 3 in studies using 600,000 IU of vitamin D_3 (34), and remained significantly decreased for as long as 12 months (following 600,000 IU of vitamin D_3)(36). However, lower single doses of vitamin D in the range of 100,000- 500,000 IU did not significantly lower PTH concentrations in several studies (3, 25, 28, 29, 40, 43-45).

Data regarding PTH and 25(OH)D modulation is stratified below by: vitamin D formulation (D_2 vs. D_3), dose (100,000 IU, 200,000-300,000 IU, and >300,000 IU), and relative baseline 25(OH)D concentration (>20 ng/mL or <20 ng/mL).

Supplementation of 100,000 IU Vitamin D: Baseline serum 25(OH)D <20 ng/mL

A 100,000 IU dose of vitamin D_3 in subjects with serum 25(OH)D <20 ng/mL failed to increase serum 25(OH)D concentrations >30 ng/mL. However, serum 25(OH)D concentrations greater than 20 ng/ml were sustained at: 4 weeks in patients with PAD(45), 5 weeks in healthy adults (27, 30), and 8 (44) and 26 weeks (3) in populations with type 2 DM.

Two studies evaluated doses of 100,000 IU vitamin D_2 in patients with TB (50, 51). Martineau et al (51) demonstrated that subjects reached a mean serum 25(OH)D concentration >30 ng/mL at 1 week following the vitamin D dose, but were unable to maintain the serum 25(OH)D concentration above 30 ng/mL at 8 weeks. Both studies (50, 51) maintained serum 25(OH)D concentrations >20 ng/mL at 6 weeks (50) and 8 weeks (51).

The dose of 100,000 IU of vitamin D was only associated with a significant lowering of PTH concentration in the study by Khaw et al (30), which had a much larger sample size (n=189) than the other studies that evaluated PTH lowering at this dose (n=34 (44), n=61 (3), n=62 (45)).

Supplementation of 100,000 IU Vitamin D: Baseline serum 25(OH)D >20 ng/mL

Only Ilahi et al (40) dosed 100,000 IU of vitamin D_3 in a relatively vitamin D sufficient population, observing an increase in 25(OH)D concentration that peaked at one week and remained >30 ng/mL at week 12. This study observed no significant decrease in PTH concentration.

Supplementation of 200,000-300,000 IU of Vitamin D: Baseline serum 25(OH)D <20 ng/mL

A dose of 200,000 IU of vitamin D_3 increased mean 25(OH)D concentrations to >30 ng/mL for up to 16 weeks in adults with type 2 DM(3), while 300,000 IU of vitamin D_3 increased serum 25(OH)D concentrations to >30 ng/mL after 4 weeks (not significant at 12 weeks)(35), 8 weeks(31), and 12 weeks (not significant at 24 weeks)(41) in elderly adults.

In contrast, vitamin D2 (ergocalciferol) in the dose range of 200,000 IU -300,000 IU consistently failed to achieve 30 ng/mL concentrations of serum 25(OH)D (31, 33, 43, 53), though concentrations >20 ng/ml occurred at: 8 weeks in vitamin D deficient adults (31), 12 weeks in frail elderly (33), and 16 weeks in stroke patients (43). Yu et al 2009 (53) failed to achieve average 25(OH)D concentrations >20 ng/mL in a group of pregnant participants.

Vitamin D doses in the range of 200,000-300,000 IU were associated with significantly lower plasma PTH concentrations in at 8 weeks in elderly adults (31, 35) and 24 weeks in vitamin D deficient adults (41). Only Witham et al (3), which used a dose of 200,000 IU of vitamin D_3, failed to observe a significant decrease in PTH over a 16-week study. Baseline

25(OH)D was relatively high (19.2± 8.4 ng/mL) in this population relative to other groups (range of 10.8 and 13.3± 9.9) (31, 35, 41).

Three of four studies failed to show PTH lowering using 200,000-300,000 IU vitamin D_2 (31, 33, 43); only Yu et al (53) showed a significant decrease in PTH in pregnant women at delivery, following administration of 200,000 IU of vitamin D in the 27^{th} week of pregnancy. This population exhibited a high prevalence (27%) of secondary hyperparathyroidism (53).

Supplementation of 200,000-300,000 IU Vitamin D: Baseline serum 25(OH)D >20 ng/mL

Two studies (28, 48)achieved 25(OH)D concentrations >30 ng/mL at: 12 weeks following a dose of 300,000 IU vitamin D_3 in patients with rheumatologic conditions (48) and one week (not significant at 12 weeks) following a dose of 250,000 IU vitamin D_3 in patients with CF (28). Sakalli et al (38) did not show serum concentrations of 25(OH)D >30 ng/mL at 6 weeks in an elderly population; this study population only reached 27± 12 ng/mL.

PTH suppression was inconsistent between studies; Grossman et al (28) showed no suppression in PTH concentration following a 250,000 IU dose of vitamin D_3 in patients with CF while Sakalli et al (38) observed a significant decrease in PTH concentration in elderly patients at 6 weeks (82.7 ± 32.5 pg/ml to 50.8± 23.4 pg/ml). This study population had the highest PTH concentration at baseline of all studies evaluated and did not have a malabsorptive disorder.

Supplementation of >300,000 IU vitamin D: Baseline serum 25(OH)D <20 ng/mL

Following a dose of 540,000 IU of vitamin D_3 , mean serum 25(OH)D concentrations were >20 ng/mL by 1 day and peaked at 38.2 ± 16.5 ng/mL by 1 week in a population of ICU patients (52). Similarly, a dose of 600,000 IU of vitamin D_3 raised serum 25(OH)D >30 ng/mL by 12 weeks in elderly subjects (36). PTH concentrations were significantly lowered in both of the studies that evaluated PTH lowering in this subset of studies(36, 52).

Supplementation of >300,000 IU vitamin D: Baseline serum 25(OH)D >20 ng/mL

Vitamin D_3 doses >300,000 IU were similarly effective in patients with 25(OH)D concentrations >20 ng/mL; all three studies (29, 34, 39) observed mean concentrations >30 ng/mL at 4 weeks, though the results peaked at day 3 (reaching 67.1 ± 17.1 ng/mL from 21.7 ± 5.6 at baseline) in Rossini et al (34). Sanders et al (29) showed long term efficacy of a 500,000 IU dose; 25(OH)D concentration remained >30 ng/mL at 12 weeks, and was significantly increased at 1 year in a cohort of women with osteoporosis. Bacon et al (39) did not sustain a mean 25(OH)D concentration >30 ng/mL at 12 weeks in a frail elderly population.

PTH concentrations were found to be significantly decreased in both studies by Rossini et al (34) and Bacon et al (39) which demonstrated significant suppression of PTH by 3 days (34) and 4 weeks (34, 39) following the dose of vitamin D. Sanders et al (29)did not show a significant decrease in PTH.

D_2 vs. D_3

Two studies compared single, large doses of vitamin D_2 and D_3. Romagnoli et al (31) found serum 25(OH)D concentrations >30 ng/mL to be achieved consistently only by those taking oral vitamin D_3. Similarly, Leventis and Kiely (41) found 100% of participants receiving 300,000 IU of vitamin D_3 to have sustained serum 25(OH)D >20 ng/mL by 6 weeks, compared to 0% of those receiving vitamin D_2. Vitamin D_3 also enabled greater PTH suppression than vitamin D_2 (31, 41); Leventis and Kiely (41) found 300,000 IU of vitamin D_3 to suppress secondary hyperparathyroidism in 100% of participants by 12 weeks compared to 42% of participants receiving vitamin D_2. The superiority of vitamin D_3 in suppressing PTH compared to D_2 was evident within 3 days ($p<0.01$), and persisted for >60 days ($p<0.01$)(31). Taken together, single large doses of vitamin D_3, rather than vitamin D_2, appear to be superior in achieving

higher and more sustained serum 25(OH)D concentrations. However, vitamin D_2, as illustrated by its positive effects in several studies, including Rossini et al (32) on reducing fracture risk, may have disease-specific indications.

Adverse effects

Very few studies reported complications following high-dose vitamin D supplementation. Three studies reported subjects with GI complaints, including: an episode of vomiting following administration of 300,000 IU of vitamin D_3 in a vegetable-oil solution (41), and various GI complaints following ingestion of 300,000 IU of vitamin D_3 and 200,000 IU of vitamin D_2 in tablet form (n=2 and n=3, respectively)(35, 53). Rossini et al (34) showed an increase in several bone turnover markers (collagen type 1 cross-linked N-telopeptide (sNTX) and collagen type 1 cross-linked C-telopeptide (sCTX)) following 600,000 IU of vitamin D_3. von Restorff (37) documented two participants with mild hypercalcemia (>10.76 mg/dl) that normalized by 6 months following a 300,000 IU dose of vitamin D_3. Hypercalciuria immediately following ingestion of 300,000 IU vitamin D_3 (38) and within twelve weeks of ingesting 600,000 IU vitamin D_3 (36), in addition to increased urine magnesium 3 days after 600,000 IU vitamin D_3 (42), has also been reported. The reports of hypercalciuria were linked to no significant clinical complications (36, 38). The clinical significance of increased urine magnesium was also unclear, since serum calcium and magnesium remained normal in these subjects (42).

DISCUSSION

This systematic review demonstrated the consistent efficacy and safety of single, large, oral doses of vitamin D in adults. All studies evaluated report a significant increase in serum 25(OH)D concentration relative to baseline, which tended to peak between days 7 and 30 (Fig. 2). Mean serum 25(OH)D concentration surpassed IOM guidelines for vitamin D sufficiency

(25(OH)D concentration >20 ng/ml) in all but one study (53). However, the formulation and dose of vitamin D appeared to impact the ability for certain doses to meet The Endocrine Society Guidelines' target for serum 25(OH)D (>30 ng/ml).

While many groups receiving vitamin D_3 (cholecalciferol) formulations achieved mean serum 25(OH)D concentrations >30 ng/mL, only one study using vitamin D_2 (ergocalciferol) surpassed that benchmark (51). Thus, vitamin D_2 was consistently less effective than vitamin D_3 in achieving optimal serum 25(OH)D concentrations. In head-to-head studies, vitamin D_3 was almost twice as potent as equimolar vitamin D_2 (31) and elicited a greater, more sustained, and more rapid serum 25(OH)D response D_2 (31, 41, 52). Thus, vitamin D_3 should be the formulation of choice for high doses of vitamin D.

The dose of vitamin D also affected the increase of 25(OH)D concentration observed. Doses 100,000 IU of vitamin D_3 were insufficient to meet The Endocrine Society Guidelines for sufficiency in populations with baseline 25(OH)D concentrations <20 ng/mL; Ilahi et al (40), which had a mean baseline 25(OH)D concentration of 27.1± 7. 7 ng/mL was the only study in which 100,000 IU vitamin D_3 was sufficient to achieve 25(OH)D concentrations >30 ng/mL. Generally, doses of 200,000 IU of vitamin D_3 and greater were required to sustain mean 25(OH)D concentrations >30 ng/mL (3, 28, 29, 31, 34-36, 39, 41, 48, 52). Only Sakalli et al (38) narrowly failed to reach this benchmark, reaching 25(OH)D concentrations of 27 ± 12 ng/mL at 6 weeks.

The increases in serum 25(OH)D concentration observed occurred safely in a majority of individuals; no adverse effects were noted at doses <200,000 IU vitamin D, and many studies found no adverse events at up to 500,000 IU D_3 (26, 29, 31) and 540,000 IU D_3(52). However, potentially detrimental changes in biochemical markers occurred in all studies evaluating a single

dose of 600,000 IU of vitamin D_3, indicating the need for greater discretion when administering doses of >500,000 IU as a single dose. Overall, while vitamin D_3 doses of 200,000 IU or greater appear to be most effective in promoting vitamin D sufficiency, certain healthy, relatively vitamin D sufficient populations, as in Ilahi et al (40), may benefit from smaller doses, and may thus avoid the risk of adverse events with higher doses.

Vitamin D classically influences bone metabolism through its increase in GI tract absorption of calcium and subsequent lowering of PTH. Significant decreases in plasma PTH concentrations were observed in a majority of studies evaluated, occurring as soon as day 3 in studies using 600,000 IU of vitamin D_3 (34), and remaining significantly decreased for as long as 12 months (following 600,000 IU of vitamin D_3)(36). However, variability between results was evident. This inconsistency was likely due primarily to the dose of vitamin D administered and the populations under study. Vitamin D_3 doses <300,000 IU appeared generally insufficient at decreasing PTH concentrations regardless of baseline serum 25(OH)D concentration(3, 28, 40, 44, 45); only one study (30) showed a significantly decreased PTH concentration using a 100,000 IU dose of vitamin D_3. Doses of 300,000 IU of vitamin D_3 and greater showed more consistent PTH lowering; of studies evaluating PTH concentration, only Sanders et al (29) did not to elicit a significant decrease of PTH concentration following a dose of 500,000 IU vitamin D_3 in osteoporotic women. Overall, it appears that doses <300,000 IU may not provide an adequate amount of vitamin D to restore vitamin D status and to lower plasma PTH concentrations in most populations. In addition, baseline serum 25(OH)D concentration does not appear to have an impact decreasing PTH concentrations following a single, large dose of vitamin D in doses >100,000 IU.

Lowered PTH concentrations in response to vitamin D supplementation have been associated with lower fracture risk (54, 55). However, higher doses of vitamin D in the range of 300,000-600,000 IU may actually increase fracture risk (29, 34), as seen in Rossini et al (34), which showed elevated bone turnover markers following a dose of 600,000 IU vitamin D_3 . Rapidly increased calcitriol concentrations may have some osteoclastic activity (56), and may also inhibit osteoblast function in bone mineralization (57). Additional studies are needed to determine the potential fracture risk posed by high-dose vitamin D, particularly in patients at risk for fractures and osteoporotic changes. An optimal therapeutic dose of vitamin D must balance these potential negative impacts on bone mineralization.

In addition to the classical effects on bone outcomes, improving vitamin D status provides extra-skeletal benefits for several populations at risk for vitamin D insufficiency. In patients with CF who were hospitalized for pulmonary exacerbation, a single dose of 250,000 IU of vitamin D_3 increased one-year survival and hospital-free days, and decreased inflammatory cytokines (25, 28). A 100,000 IU dose of vitamin D_2 decreased *in vitro* bacterial growth in a population with active TB, and may prevent reactivation of latent TB infection (50). Lasco et al (47) suggested that a single 300,000 IU dose of vitamin D_3 resulted in reduced in pain in women with dysmenorrhea. Vitamin D may also play some role in affecting cardiovascular system factors, though positive results were seen in some (3, 43, 44, 46), but not all (3, 27, 45), studies reviewed.

The limitations of this review are based largely on the inconsistencies between study populations and vitamin doses, which prevent reliable inter-study comparisons, in addition to the lack of data from healthy, non-elderly, adult populations, which would allow the impact of vitamin D supplementation to be observed without concurrent disease processes. Furthermore,

once-yearly doses of vitamin D are non-physiologic; while large doses consistently show better efficacy than daily doses, there may be a more optimal intermittent dosing strategy not evaluated by this review. As discussed in Ilahi et al (40), 100,000 IU vitamin D_3 dosed every 2-3 months may provide optimal benefit in people with baseline 25(OH)D concentrations >20 ng/mL. Bacon et al (39) showed similar improvements to the sustainability of 25(OH)D concentrations in the long-term by adding monthly 50,000 IU vitamin D_3 doses following an initial 500,000 IU vitamin D_3 bolus. Such sub-annual dosing strategies may strike a balance between the convenience of once-yearly dosing and the poor compliance of daily dosing, and thus serve to better maintain 25(OH)D concentrations in deficient populations.

In conclusion, a single dose of vitamin D_3 in the amount of 100,000 IU and greater offers a consistently efficient means of improving short-term vitamin D status >20 ng/mL, though doses of vitamin D_3 of 300,000 IU or greater are necessary for 25(OH)D concentrations >30 ng/mL and lowering of plasma PTH concentrations. Though generally safe, bolus doses >500,000 IU vitamin D_3 must be used with caution due to the potential for increased fracture risks, altered biochemical markers, and issues with tolerability, such as GI upset. Future considerations not addressed specifically by studies in this review include: (1) vitamin D doses to prevent the winter decline of serum 25(OH)D; (2) vitamin D supplementation in healthy, non-elderly adult populations; and (3) the duration of the serum 25(OH)D increase following supplementation.

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Figure Legends

Figure 1. Flow diagram of studies identified for review.

Figure 2. Relationship between single, high-dose, vitamin D_3 and serum 25(OH)D concentration within the 90 days following the dose. Serum 25(OH)D increased significantly from baseline in all studies that administered vitamin D ($p<0.05$). A majority of data points were confined to the first 90 days following the dose of vitamin D.

Table 1. Summary of studies investigating single, high-dose vitamin D

Author/ year	Dose (IU)	Population	Baseline/ Post-treatment 25D (ng/ml) [†1]	Baseline/ Post-treatment PTH (pg/ml) [†1]	Other Outcomes
D_2 and D_3: 300,000 IU					
Romagnoli at al 2008 (31)	300,000 D_2 vs. 300,000 D_3	32 vitamin D deficient elderly females n= 8; mean age 78.5 (7.5) yr	Baseline: 12.6 (9.1) Day 30: +17.3(4.7)* Day 60: +10.19 (6.75)*	Baseline: 32.5 (20.3) Day 60: +0.96 (7.51)	↑ 25D most rapid in PO groups. ↑ 25D from baseline at 30 days only in D_3 groups. D_3 is 2x as potent as D_2. ↓ PTH in D_3 group only at 60 days.
	300,000 D_3 vs. 300,000 D_2	n=8; mean age 80.6 (5.0) yr	Baseline: 13.3 (9.9) Day 30: +47.8 (7.3)*[b]	Baseline: 43.8 (24.5) Day 60: -22.8 (16)*[b]	

			Day 60: +28.06 (8.33)*[b]		
Leventis and Kiely 2009 (41)	300,000 D_3 PO vs. 300,000 D_2 IM vs	69 vitamin D deficient adults; mean age 43 yr	Baseline: 10.8 Week 6: 53.84 (26-85.6)*[be] Week 12: 32.72 (18.8-47.6)*[be] Week 24: 17.12 (9.2-31.2)*[be]	Baseline: 52.45 (24.44-83.66)[e] Week 12: 40.51 (16.92-54.52)*[e] Week 24: 41.08 (26.32-55.46)[e]	↑ 25D in D_3> D_2. ↓ PTH at 12 weeks in 42%(D_2) and 89% (D_3) of subjects with elevated PTH . Vomiting after dose (n=1).
D_2: 100,000 IU					
Martineau et al	100,000 D_2 vs.	192 patients with	Baseline: 14.08	unlisted	↓ *in vitro*

2007 (50)	placebo	Tuberculosis; mean age 30.1 yr	Week 6: 26.96 (10.52-35.48)*[c]		bacterial growth. ↔ IFN-y response.
Martineau et al 2009 (51)	100,000 D_2 vs. placebo 100,000 D_2	81 patients with Tuberculosis; mean age 38.7(12.4) yr 81 healthy controls; mean age 33.5 (12.7) yr	Baseline: 9.28 (7.4) Week 1: +43.8 (28.84-58.72)*[bc] Week 8: +8.72 (0.56-12.96)*[bc] Baseline: 13.76 (11.12) Week 1: +27.05 (23.96-30.12)*[c] Week 8: unlisted	unlisted	↑25D in TB patients>healthy controls after 1 week. Difference attributed to larger BMI in healthy group.
Witham et al 2012 (43)	100,000 D_2 vs. placebo	58 patients with stroke; mean age 66.2 (13.0)	Baseline: 15.48 (7.04) Week 8: 21.6 (6)* Week16: 20.4 (8.8)	Baseline: 58.19 (26.88) Week 8: 49.82 (17.86) Week 16: 49.82 (16.92)	↑endothelial function at 8 but not 16 weeks. ↔

					BP.
D_2: 200,000 IU-300,000 IU					
Yu et al 2009 (53)	200,000 D_2 vs. 800 D_2 daily	180 pregnant women; ages 18-45 yrs	Week 27 of pregnancy: 10.4 (8.4-16.4)[f] Delivery: 13.6 (12-18.4)*[f]	Week 27 of pregnancy: 41.36 (24.44-63.92)[f] delivery: 31.02 (13.16-156.04)*[f]	↑ cord 25D. Only 9% of infants sufficient post-supplement. GI upset (n=3).
Lantham et al 2003 (33)	300,000 D_2 vs. placebo, w/ or w/out high-intensity exercises	243 frail elderly; mean age 79 (77–80) yr	Baseline: 15 (14–18) Month 3: +9 (7–11)*[d]	unlisted	↔ frailty, physical health or falls. ↑ risk of injury w/ exercises.
D_3: 100,000 IU					
Khaw et al 1994	100,000 D_3 vs.	189 healthy elderly	Baseline: 14.6 (6.2)	Baseline: 29.89	

(30)	placebo	adults; mean age 69.4 (2.9) yr	Week 5: +7.76 (4.64)*	Week 5: -2.54 (7.33)*	
Ilahi et al 2008 (40)	100,000 D_3 vs. placebo	40 healthy elderly; ages 61–84 yr	Baseline: 27.1 (7.7) Day 7: 42.0 (9.1)* Day 84: 32.1	Baseline: 22.1 (7.41) Day 60: 23.6 (9.22)	Better ↑ 25D with younger age.
Sugden et al 2008 (44)	100,000 D_3 vs. placebo	34 patients with type 2 DM; mean age 64 yr	Baseline: 16.08 (4.12) Week 8: +9.16 (6.64)*	Baseline: 40.33 (16.83) Week 8: −1.32 (9.31)	↑ endothelial function in those with low 25D. ↓ systolic BP. ↔ IR
Witham et al 2010 (3)	100,000 D_3 vs. placebo	61 adults with Type 2 DM; mean age 65.3(11) yr	Baseline: 16.4 (5.6) Week 8: 25.2 (8)* Week16: 23.6 (7.2)	Baseline: 42.3 (16.92) Week 8: 37.6 (14.1) Week 16: 38.94 (18.8)	↓ BP at 8 weeks. ↔ endothelial function, glycosylated hemoglobin, IR .
Stricker et al 2012 (45)	100,000 D_3 vs. placebo	62 patients with peripheral artery	Baseline: 16.3 (6.7) Day 30: 24.3 (6.2)*	Baseline: 50.76 (30.08) Day 30: unlisted (NS)	8ng/ml ↓ 25D in winter vs.

		disease; mean age 72.9(8.7) yr			summer. ↔ endothelial function, coagulation, inflammation.
D_3: 200,000 IU-300,000IU					
Witham et al 2010 (3)	200,000 D_3 vs. placebo	61 adults with Type 2 DM; mean age 63.3(9.6) yr	Baseline: 19.2 (8.4) Week 8: 31.6 (12.4)* Week16: 30.4 (12)*	Baseline: 41.36 (17.86) Week 8: 43.24 (22.56) Week 16: 36.66 (15.98)	↓ BP at 8 weeks. ↓ BNP. ↔ endothelial function, glycosylated hemoglobin, IR
Grossman et al 2012 (25, 28)	250,000 D_3 vs. placebo	30 patients with cystic fibrosis; age >18 yr	Baseline: 30.6 (3.2) Week 1: 58.1 (3.5)* Week12: 36.7 (2.6)	Baseline: 44.6 (9.2) Week 1: 39.8 (12.8) Week 12: 32.4 (6.0)	↑ 1-year survival and hospital-free days. ↓ TNF- α

					concentration at 12 weeks. Trend towards ↑ IV antibiotic-free days.
Premaor et al 2008 (35)	300,000 D_3 vs. 800 IU daily	28 low-income elderly with hyperparathyroidism; mean age 80.8 (8.7) yr	Baseline: 12.4 (6.7) Month 1: 35*[b(E)] Month 2: 28*[b(E)] Month 3: 24[(E)] Month 6: 14[(E)] Month 9: 18[(E)]	Baseline: 74.5 (26.2) Month1: 50[(E)] Month 2: 46*[(E)] Month 3: 60[(E)] Month 6: 58[(E)] Month 9: 55[(E)]	Single dose vitamin D improved 25D better than daily 800 IU vitamin D. GI upset (N=2).
Sakalli et al 2012 (38)	300,000 D_3 oral vs. 300,000 D_3 IM vs. placebo	120 vitamin D deficient elderly; mean age 70.1 (4.3) yr	Baseline: 20.9 (9.5) Week 6: 27.0 (12.0)*	Baseline: 82.7 (32.5) Week 6: 50.8 (23.4)*	Improved Timed Up and Go, visual analog scale tests, physical

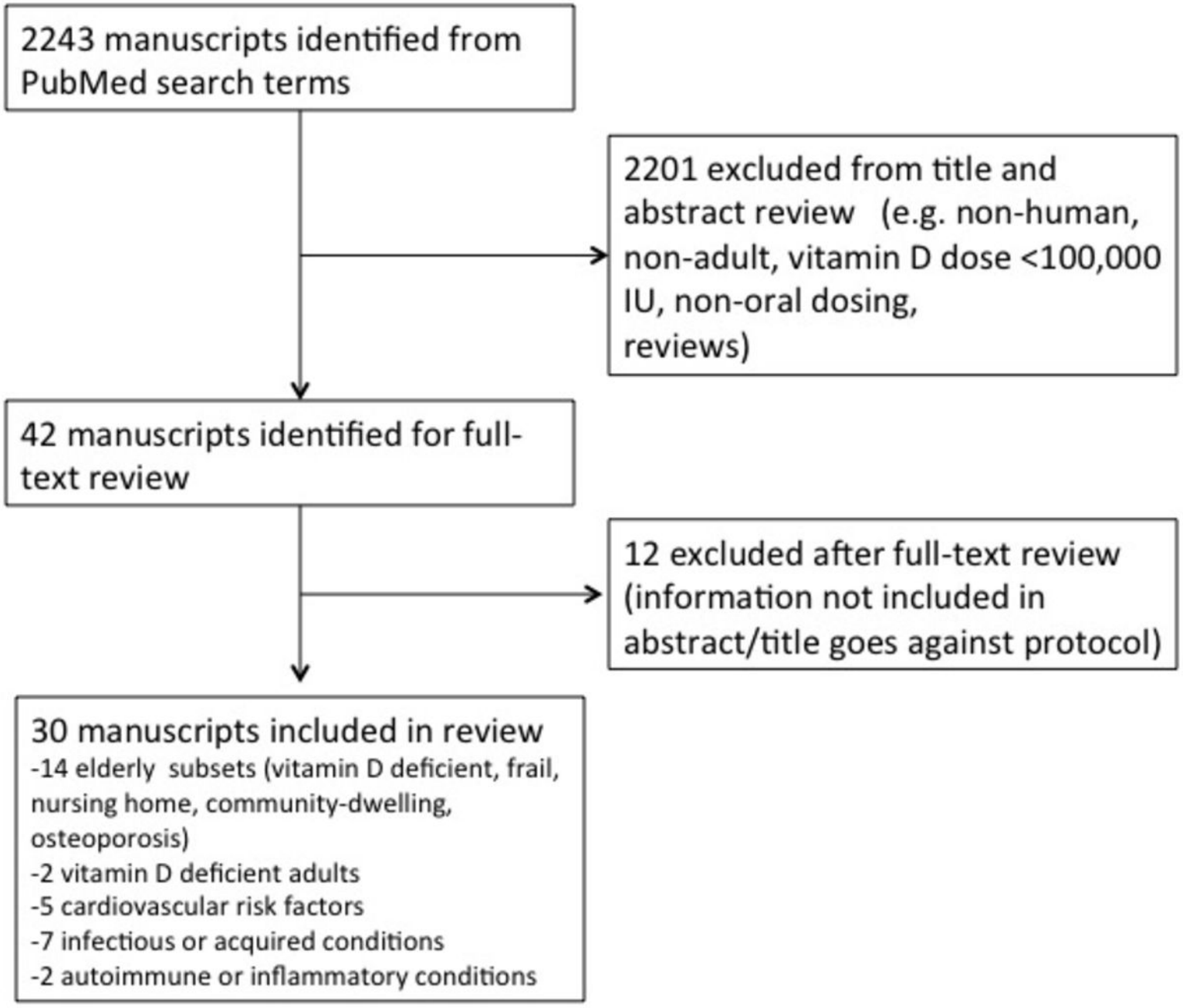
					functioning, and fulfillment of physical roles. ↑ urine calcium.
Stoll et al 2012 (49)	300,000 D_3 vs. placebo	124 Rheumatologic patients; mean age 49.2 (13.1) yr	Baseline: 21 (1.5–45.9)[e] Month 3: 28.6 (7.5–56.5)*[e]	unlisted	1 or 2 oral doses ↑ 25D in 50% of participants.
D_3: >300,000 IU					
Bacon et al 2009 (39)	500,000 D_3 vs. 500,000 D_3 + 50,000 D_3/month vs. 50,000 D_3/month	63 frail elderly; mean age 82(7) yr	Baseline: 23.2 (12.8) Month 1: +23.2 (11.2)* Month 3: +4.4 (0.8)	Baseline: 47.94 (22.56) Month 1: -9.4*	Plateau in 25D at 3-5 month with 50,000 IU/month following 500,000 IU stat dose.
Sanders et al	500,000 IU D_3	137 elderly females	Baseline: 21.2 (16-26)[e]	Baseline: 40.42 (27.26-	Fall rate ↑in

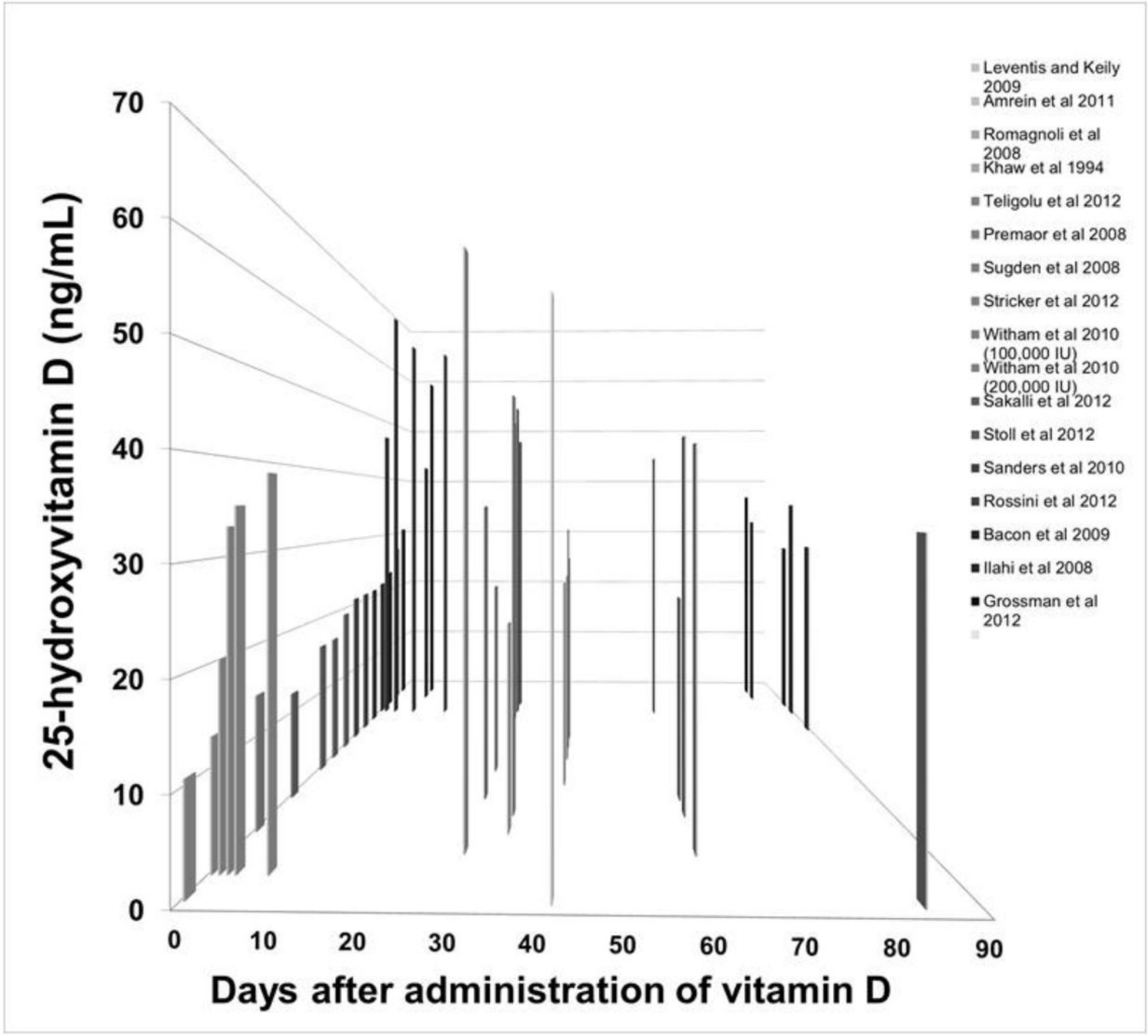
2010 (29)	vs. placebo	at risk for hip fracture; mean age 76 yr	Month 1: 48*[a(E)] Month 3: 36*[(E)] Month 12: 29.6 (22-29.6)*[e]	65.8) Month 1: unlisted (NS) Month 12: unlisted (NS)	vitamin D group. Trend towards ↑ fracture risk. 41% ↑ 25D 12-months after dose (received in 2-5 consecutive years).
Amrein et al 2011 (52)	540,000 D_3 vs. 200 IU/day	25 ICU patients; mean age 62(16) yr	Baseline: 13.1(2.0) Day1: 20.5* Day 2: 33.1* Day 3: 35.1(15.2)* Day 7: 38.2(16.5)*	Baseline: 73.7 Day 1: 65.1 Day 2: 77.3 Day 3: 100.4 Day 7: 52.0*	↑ 25D >30 ng/mL 2 days after dose (range 1-47 ng/mL).
Rossini et al 2012 (34)	600,000 D_3 vs. placebo	36 elderly women with osteoporosis; mean age 76(3) yr	Baseline: 21.7 (5.6) Day1: 46.8 (7.5)* Day 3: 67.1 (17.1)*	Baseline: 35.0 (8.7) Day 1: 32.0 (9.5) Day 3: 25.5 (7.4)*	↑ sCTX and sNTX. ↔ ALP (markers

			Day 7: 62.2 (12.5)* Day 14: 60.9 (13.3)* Day 30: 51.6 (11.9)* Day 60: 43.1 (10.3)* Day 90: 35.2 (5.8)*	Day7: 23.4 (6.4)* Day 14: 15.8 (7.8)* Day 30: 27.0 (9.8)* Day 60: 29.3 (6)* Day 90: 28.3 (6.1)*	of bone metabolism). ↑ $1,25(OH)_2D$ (25-50% from baseline).
Telligolu et al 2012 (36)	600,000 D_3 oral vs. 600,000 D_3 IM	66 vitamin D deficient, elderly, nursing home residents; mean age 75.3 (7.5) yr	Baseline: 14.87 (6.9) Week 6: 47.57 (12.7)*[b] Week12: 42.94 (13.4)*	Baseline: 52.03 (22.5) Week 12: 40.58*	↑ 25D IM > oral at 12 weeks. 25D>30 ng/ml in 100% IM vs 83.3% oral. ↑ balance and quadriceps strength with supplements. Hypercalcuria (n=6).

Abbreviations: 25D, 25-hydoxyvitamin D; IR, insulin resistance; PTH, parathyroid hormone; QOL, quality of life; IM, intramuscular; BNP, B-type natriuritic peptide; sNTX, collagen type 1 cross-linked N-telopeptide; sCTX, collagen type 1 cross-linked C-telopeptide; ALP, alkaline phosphatase; TNF-α, tumor necrosis factor-α.

[†]mean(± SD) (unless otherwise noted); [1]data provided for single, oral doses of vitamin D_2 or D_3 only; *$p < 0.05$ (change from baseline); [a]median (range); [b]$p < 0.05$ (difference from other group); [c]mean (95% CI); [d]median (95% CI); [e]mean (range); [f]median (IQR); ↑, increase; ↓, decrease; ↔, no change; (NS), not significant;[(E)]value is estimated from tables in paper.


2243 manuscripts identified from PubMed search terms
2201 excluded from title and abstract review (e.g. non-human, non-adult, vitamin D dose <100,000 IU, non-oral dosing, reviews)
42 manuscripts identified for full-text review
12 excluded after full-text review (information not included in abstract/title goes against protocol)
30 manuscripts included in review
-14 elderly subsets (vitamin D deficient, frail, nursing home, community-dwelling, osteoporosis)
-2 vitamin D deficient adults
-5 cardiovascular risk factors
-7 infectious or acquired conditions
-2 autoimmune or inflammatory conditions


25-hydroxyvitamin D (ng/mL)
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
Days after administration of vitamin D
Leventis and Keily 2009
Amrein et al 2011
Romagnoli et al 2008
Khaw et al 1994
Teligolu et al 2012
Premaor et al 2008
Sugden et al 2008
Stricker et al 2012
Witham et al 2010 (100,000 IU)
Witham et al 2010 (200,000 IU)
Sakalli et al 2012
Stoll et al 2012
Sanders et al 2010
Rossini et al 2012
Bacon et al 2009
Ilahi et al 2008
Grossman et al 2012