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Determinants of parathyroid hormone response to vitamin D supplementation: a systematic review and meta-analysis of randomised controlled trials

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Abstract

This systematic review aimed to assess the determinants of the parathyroid hormone (PTH) level response to vitamin D supplementation. We searched Medline, Google Scholar and the reference lists of previous reviews. All randomised controlled trials (RCT) on vitamin D supplementation that involved apparently healthy human subjects with a report of PTH were selected. Potential studies were screened independently and in duplicate. Results are summarised as mean differences with 95 % confidence intervals. Quality assessment, subgroup analysis, meta-analysis and meta-regression analysis were carried out. Thirty-three vitamin D supplementation RCT were included. Vitamin D supplementation significantly raised circulating 25-hydroxyvitamin D (25(OH)D) with significant heterogeneity among studies with a pooled mean difference (PMD) of 15.5 ng/ml (test for heterogeneity: $P < 0{\cdot}001$ and $I^2 = 97{\cdot}3$ %). Vitamin D supplementation significantly reduced PTH level with PMD of −8·0 pg/ml, with significant heterogeneity ((test for heterogeneity: $P < 0{\cdot}001$) and the I^2 value was 97·3 %). In the subgroup analyses, the optimum treatment effect for PTH was observed with Ca doses of 600–1200 mg/d (−22·48 pg/ml), after the duration of a >12-month trial (−18·36 pg/ml), with low baseline 25(OH)D concentration of <20 ng/ml (−16·70 pg/ml) and in those who were overweight and obese (−18·11 pg/ml). Despite the present meta-analysis being hindered by some limitations, it provided some interesting evidence, suggesting that suppression of PTH level needs higher vitamin D intake (75 μg/d) than the current recommendations and longer durations (12 months), which should be taken into account for nutritional recommendations.

Key words: Cholecalciferol: Vitamin D: Parathyroid hormone: Meta-analyses: Randomised controlled trials

The central role of vitamin D in the maintenance of bone health is well documented. Recent evidence reports a link between lower serum 25-hydroxyvitamin D (25(OH)D) concentrations and a variety of chronic illnesses[1]. Low serum 25(OH)D is considered to be the best indicator of overall vitamin D deficiency. Severe vitamin D deficiency (serum 25(OH)D < 25 nmol/l)) is associated with increased bone resorption, accelerated cortical bone loss and increased fractures[2].

Health authorities around the world recommend widely variable supplementation strategies for adults[3]. The reference daily intake is 10 μg/d for children between 0 and 12 months of age, 15 μg/d for males and females aged between 1 and 70 years and 20 μg/d for people older than 70 years to prevent fracture[4]. According to our previous meta-analysis, to obtain an optimal vitamin D status of 50 nmol/l in adults, 20 μg is sufficient[5].

Serum parathyroid hormone (PTH) has been studied as a surrogate marker of vitamin D status. There are too many publications that show the inverse relationship between serum PTH and serum 25(OH)D. Moreover, many studies have tried to define a level of serum 25(OH)D at which serum PTH levels decreased and reached a plateau. However, the reported thresholds are highly variable, varying between 10 and 50 ng/ml. It is important to note that some other studies failed to

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; MD, mean difference; PTH, parathyroid hormone; PMD, pooled mean difference; RCT, randomised controlled trial.

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demonstrate definite thresholds[6]. Based on the results of some reports, there are certain possible factors affecting PTH response to vitamin D supplementation, including method of PTH measurement, BMI, age, renal function, Ca intake and baseline level of serum 25(OH)D and PTH[7]. To the best of our knowledge, except for one systemic review[8], there has been no systematic review and meta-analysis thus far thoroughly addressing the question 'at what level of serum 25(OH)D level does PTH reach the threshold and what are the determinants of PTH level?'

Therefore, in context of a systematic review and meta-analysis on randomised controlled trials (RCT), we conducted a meta-analysis and a meta-regression analysis on randomised clinical trials to explain existing heterogeneity regarding determinants of PTH level response to vitamin D supplementation in adults.

Methods

Search strategy and identification of the studies

The study was carried out using a detailed protocol developed in advance, including predefined research questions and objectives, search strategy, study eligibility criteria, the methods of data extraction and statistical analysis. All the variables for subgroup analysis were predefined. We used the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for reporting the present study[9].

We searched the English-language medical literature published between January 1980 and November 2013 using the Medline and Google scholar database. We used structured search strategy using various combinations of keywords for vitamin D (online Supplementary Table S1). We also checked the references of recent systematic reviews that investigated the effects of oral intake or intramuscular injection of vitamin D supplements to find additional relevant studies.

RCT on vitamin D (with or without Ca) supplementation that involved apparently healthy human subjects or patients whose disease has no effect on vitamin D metabolism were included in the analysis. RCT were selected because the greatest validity and causal interference can be found in such studies[10].

We included studies that fulfilled the following criteria: (1) vitamin $D_3 \geq 10$ μg/d administered orally *per se* or with Ca on a daily basis (inclusion of vitamin D_3 and D_2 was chosen, although the Institute of Medicine dietary recommended intakes (IOM) DRI committee has defined DRI based on studies with vitamin D_3[11] and there is evidence that vitamin D_3 increases serum 25(OH)D more efficiently than vitamin D_2[12,13]); (2) separately reported serum or plasma 25(OH)D levels in intervention and control groups; (3) separately reported serum or plasma PTH levels in intervention and control groups; (4) a minimum duration of 6 weeks, because serum 25(OH)D concentrations reach equilibrium after at least 6–8 weeks in adults[5,14,15].

The exclusion criteria included the following: (1) use of compounds such as vitamin D metabolites (25(OH)D and 1,25(OH)2D) and analogues (e.g. α-calcidol) co-administered; (2) studies carried out in infants, children, adolescents and pregnant or lactating women; (3) studies in which vitamin D was administered as fortified food; (4) interventions that included patients with chronic renal disease, chronic heart disease, cirrhosis and hyperparathyroidism; (5) RCT that used cluster randomisations and cross-over studies; (6) trials without control or placebo groups; (7) studies published in languages other than English, because effect sizes did not differ significantly in language-restricted meta-analyses compared with language-inclusive ones[16], as well as lower quality in the non-English medical literature[17]; (8) repeated studies, if the results of the trials had been published in more than one article, we used the reporting results on the largest sample of individuals, or the most recently published or the more detailed results; (9) abstracts, because of insufficient information; and (10) dissertations, because the full text was rarely available.

Variations between the extracted studies regarding supplement dosage, frequency of supplementation and use of either intramuscular or oral delivery methods were acceptable and were not excluded.

Data collection and synthesis

To identify and include eligible studies in the final analysis, two authors (S. S.-B. and N. M.), independently, reviewed the titles of the articles extracted by the search for relevance to our topic, and then we retrieved the full-text articles of those that were potentially relevant. Screening list was used to select eligible articles. Backward search was carried out through published reviews previously and those published after our search date.

Moreover, the quality control of the articles was carried out independently by two authors (S. S.-B. and N. M.). Discrepancies between authors were solved by consensus with the third author (F. H.). We included only data reported in the study, because recall bias in the information or data might be provided by authors[18].

All relevant information were abstracted on study characteristics including the following: first author, publication year, country of origin, study design, the number of participants in each arm of RCT, age, sex, the dose of supplement, frequency supplement use, duration of supplementation, type of supplement used in the RCT, mean values and standard deviations of the baseline and final values for 25(OH)D and PTH in the treatment and control arms at each time point and for each vitamin D dose. In studies with different doses, we included each dose as a separate study and used the dose subgroups *v.* controls separately. If a study had several intervals for follow-up measurements of 25(OH)D, we included each time interval as a separate study. If studies had subgroups such as sex, they were included in our study as a separate study.

For any other information pertinent to the review, such as potential confounders to the RCT (i.e. the season of implementing the intervention and BMI), the analysis technique chosen to assess serum 25(OH)D and the dropout rates were also noted when reported.

Quality of assessment

We assessed the quality of studies using Jadad scales[19], which include the following four items: reporting of randomisation method, allocation concealment, blinding of outcome assessment and completeness of follow-up (online Supplementary Table S2).

Statistical analysis

The mean difference (MD) of achieved levels of 25(OH)D and PTH between the intervention and control groups for each individual study was calculated. If the standard error was reported for variation of mean, we calculated SD by dividing SE/n^2. For the calculation of the standard deviation from the range and confidence intervals, we divided the range by 5·88 and CI by 3·92.

Cochran's Q statistic and the I^2 statistic were used to assess statistical heterogeneity in the meta-analysis[20]. Both the fixed-effects and random-effects models were used to calculate the pooled MD of PTH level in response to vitamin D. In this review, we present results from the random-effects model because significant heterogeneity was identified among studies[21].

Potential sources of heterogeneity were also investigated in predefined subgroups. We assessed treatment effects in preset subgroups: (1) dose (≤20 and >20 μg); (2) vitamin supplementation with or without Ca; (3) Ca dose (no Ca, 400–600 and 600–1200); (4) duration (<3, 3–6, 6–12 and >12 months); (5) baseline 25(OH)D (<20 or ≥20 ng/ml); (6) baseline PTH (≤6·0, 6·1–38·0, 38·1–49·0 and ≥49·0); (7) BMI (>25, 25–30 and ≥30 kg/m^2); (8) sex (men, women, both); (9) age (<50 and ≥50 years); and (10) study quality (low quality *v.* high quality).

The meta-regression was used to analyse factors within a trial that best explained the variance in MD of PTH. Using meta-regression, we analysed the effects of daily doses of vitamin D, duration of the trial, baseline 25(OH)D, baseline PTH, BMI and age on MD.

We performed ancillary analyses including curve estimation models for weighted mean difference (WMD) of serum levels of PTH according to dose and duration and baseline 25(OH)D and PTH as continuous variables.

A cumulative meta-analysis[22] was also performed to determine that the evidence was consistent over time. Influence analysis was carried out to show that no particular trial affected the pooled effect size.

A formal statistical test on publication bias was not meaningful because we excluded studies with sample sizes <30. However, publication bias was analysed by funnel plot analysis (online Supplementary Fig. S1) and Egger's regression asymmetry test for the included studies[23,24]. In our analysis, the summary estimate for PTH was statistically significant when we included Suzuki *et al.*'s study[25] that reported a large WMD. We then considered this study to be a possible outlier, and thus excluded the study from our analysis. All tests were two-tailed, and a probability level <0·05 was considered to be statistically significant. Statistics were performed using Stata version 12.0 (Stata Corporation) and SPSS version 18.

Results

Study characteristics

Of the 2360 studies identified, thirty-three studies[26–58] including fifty intervention groups with 7574 participants (n 3851 in intervention group and n 3663 in placebo group) were selected for the present meta-analysis (Fig. 1). All of them were RCT;

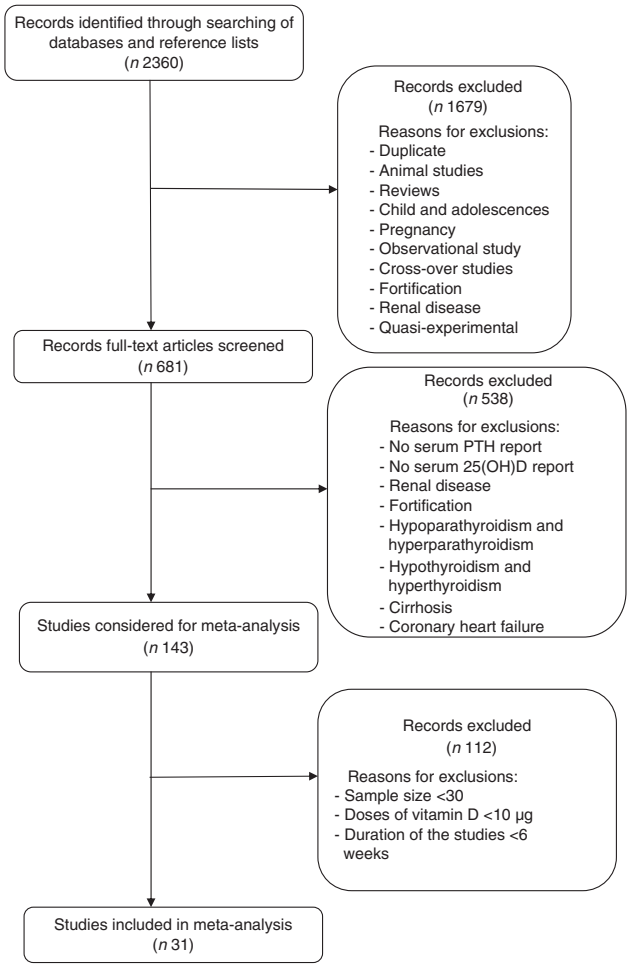

Fig. 1. Flow chart of study selection for inclusion in the systematic review. 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

however, sixteen studies did not clarify the method of randomisation[26–31,33,35,36,41–44,47,50,53]. The mean age of the participants ranged from twenty-one to 85 years. The daily doses of vitamin D supplementation varied from 10 to 250 μg/d; only two studies supplemented vitamin D in the form of ergocaciferol[26,51], and two studies did not report the form of vitamin D supplement used[27,34]. The duration of supplementation ranged from 2 to 36 months. The majority of studies were conducted on women or on women and men together; only two studies were conducted only on men[30,34]. Using the Jadad scale, 81·8 % of the studies were of high quality (scores ≥3), with an average score of 3·6. Six studies were considered to be of low quality (scores ≤2)[26,28,31,41,47,53] (online Supplementary Table S2). Study characteristics are summarised in Table 1.

Meta-analysis for serum vitamin D responses

The pooled mean difference (PMD) of 25(OH)D from the pre-trial was +15·5 ng/ml (−5 to +40 ng/ml) in the intervention group. The forest plot with MD in post-trial 25(OH)D concentrations between intervention and placebo groups and their 95 % confidence intervals are illustrated in Fig. 2. As there

Table 1. Study and participant characteristics

Author	Year	Country	Total number	Mean age (years)	Participants	Sex	Treatment	Trial duration (months)	Daily dose (Ca (mg)/ vitamin D (μg))	Final MD of serum 25(OH)D* (ng/ml)	Final MD of serum PTH† (pg/ml)
Chapuy[26]	1987	France	38	74	Elderly people	3	Ca + vitamin D_2	6	1000/20	14·60	−37·90
Dawson-Hughes[27]	1991	USA	124	61	Elderly women	2	Ca + vitamin D	12	400/12·5	12·60	−2·90
Chapuy[28]	1992	France	73	84	Elderly people	2	Ca + vitamin D_3	6	1200/20	27·00	−15·0
Chapuy[28]	1992	France	73	84	Elderly people	2	Ca + vitamin D_3	12	1200/20	32·00	−27·0
Chapuy[28]	1992	France	73	84	Elderly people	2	Ca + vitamin D_3	18	1200/20	31·00	−26·0
Ooms[29]	1995	Holland	177	80	Elderly women	2	Vitamin D_3	12	10	15·60	−5·45
Dawson-Hughes[30]	1997	USA	167	71	Elderly people	2	Ca + vitamin D_3	36	500/17·5	34·72	−16·4
Dawson-Hughes[30]	1997	USA	146	70	Elderly people	1	Ca + vitamin D_3	36	500/17·5	32·43	−10·0
Krieg[31]	1999	Switzerland	34	84	Elderly institutionalised women	2	Ca + vitamin D_3	12	1000/22	21·50	−23·30
Krieg[31]	1999	Switzerland	34	84	Elderly institutionalised women	2	Ca + vitamin D_3	24	1000/22	20·82	−31·70
Hunter[32]	2000	London	64	59	Women	2	Vitamin D_3	3	20	3·00	−2·30
Hunter[32]	2000	London	64	59	Women	2	Vitamin D_3	6	20	11·70	−1·60
Pfeifer[33]	2001	Germany	74	75	Elderly women	2	Ca + vitamin D_3	2	1200/20	8·19	−6·45
Kenny[34]	2003	Farmington, CT	33	76	Men	1	Ca + vitamin D	6	500/25	12·00	−19·00
Grados[35]	2003	France	95	74	Ambulatory elderly women	2	Ca + vitamin D_3	12	1000/20	27·34	−38·70
Brazier[37]	2005	France	95	74	Elderly women	2	Ca + vitamin D_3	12	1000/20	18·04	−7·50
Talwar[38]	2007	Mineola, NY	104	60	Healthy black postmenopausal women	2	Vitamin D_3	3	20	12·92	−1·40
Talwar[38]	2007	Mineola, NY	104	60	Healthy black postmenopausal women	2	Vitamin D_3	24	50	9·72	1·10
Talwar[38]	2007	Mineola, NY	104	60	Healthy black postmenopausal women	2	Vitamin D_3	27	50	16·80	0·80
Pittas[39]	2007	Boston	45	71	Adults with IFG	3	Ca + vitamin D_3	36	500/17·5	11·60	−7·45
Pittas[39]	2007	Boston	108	71	Adults without IFG	3	Ca + vitamin D_3	36	500/17·5	16·52	−13·91
Sneve[40]	2008	Norway	116	46	Obese or overweight adults	3	Ca + vitamin D_3	12	500/142·9	25·36	−13·73
Sneve[40]	2008	Norway	106	48	Obese or overweight adults	3	Ca + vitamin D_3	12	500/71·4	15·32	−13·55
Chel[41]	2008	Holland	45	84	Elderly subjects	3	Vitamin D_3	4	15	8·20	−8·18
Chel[41]	2008	Holland	48	84	Elderly subjects	3	Vitamin D_3	4	15	13·80	−9·09
Chel[41]	2008	Holland	46	84	Elderly subjects	3	Vitamin D_3	4	15	14·24	−19·09
Björkman[42]	2008	Finland	77	84	Bedridden older patients	2	Ca + vitamin D_3	6	500/10	9·08	−14·40
Björkman[42]	2008	Finland	73	84	Bedridden older patients	2	Ca + vitamin D_3	6	500/30	19·28	−19·90
Cashman[43]	2008	UK	57	30	Healthy young	3	Vitamin D_3	6	10	9·04	−5·70
Cashman[43]	2008	UK	53	30	Healthy young	3	Vitamin D_3	6	15	12·64	−13·20
Pfeifer[44]	2009	Germany	121	76	Community-dwelling seniors	3	Ca + vitamin D_3	12	1000/20	10·80	−4·00
Pfeifer[44]	2009	Germany	121	76	Community-dwelling seniors	3	Ca + vitamin D_3	20	1000/20	4·00	11·00
Zitterman[45]	2009	Germany	82	47	Healthy overweight subjects	3	Vitamin D_3	12	83·3	17·40	−5·00
Islam[46]	2010	Finland	40	22	Apparently healthy subjects	2	Ca + vitamin D_3	12	600/10	14·08	−5·50
Islam[46]	2010	Finland	40	22	Apparently healthy subjects	2	Vitamin D_3	12	10	13·68	−2·90
Jorde[47]	2010	Norway	62	46	Obese or overweight subjects	3	Ca + vitamin D_3	12	500/71·43	15·18	−5·27
Jorde[47]	2010	Norway	63	46	Obese or overweight subjects	3	Ca + vitamin D_3	12	500/142·85	30·58	6·55
Lips[48]	2010	Holland	113	79	Older subjects	3	Ca + vitamin D_3	4	500/30	12·50	−6·00
Grimnes[49]	2011	Norway	49	52	Participants with low serum vitamin D	3	Vitamin D_3	6	142·9	39·92	−5·64
Chung[50]	2011	Korea	82	65	Osteoporotic adults	3	Ca + vitamin D_3	4	500/20	14·32	−8·80
Sokol[51]	2012	USA	45	55	Coronary artery disease patients	2	Vitamin D_2	3	178.6	10·00	−6·50
Ponda[52]	2012	New York	76	48	Adults	3	Vitamin D_3	2	250	28·40	−14·00
Harris[53]	2012	Boston	43	57	Overweight or obese with pre- or early diabetes	3	Ca + vitamin D_3	3	600/100	17·48	−14·90
Larsen[54]	2012	Denmark	55	60	Hypertensive patients	3	Vitamin D_3	5	75	24·00	−7·80
Kjærgaard[55]	2012	Norway	120	53	Adults with depression	3	Vitamin D_3	6	142·9	38·08	−9·09
Salehpour[56]	2012	Iran	39	38	Adults	2	Vitamin D_3	3	25	9·40	−4·55
Goswami[57]	2012	India	43	21	Healthy women	2	Ca + vitamin D_3	6	1000/214·3	19·28	−23·90
Goswami[57]	2012	India	43	21	Healthy women	2	Vitamin D_3	6	214·3	22·20	−16·60
Suzuki[58]	2013	Japan	55	73	Parkinson disease	3	Vitamin D_3	12	30	31·92	−15·00

1, male; 2, female; 3, male and female; 25(OH)D, 25-hydroxyvitamin D; MD, mean difference; PTH, parathyroid hormone; IFG, impaired fasting glucose.
* Final serum 25(OH)D in the intervention group minus final serum 25(OH)D in the placebo group.
† Final serum PTH in the intervention group minus final serum PTH in the placebo group.

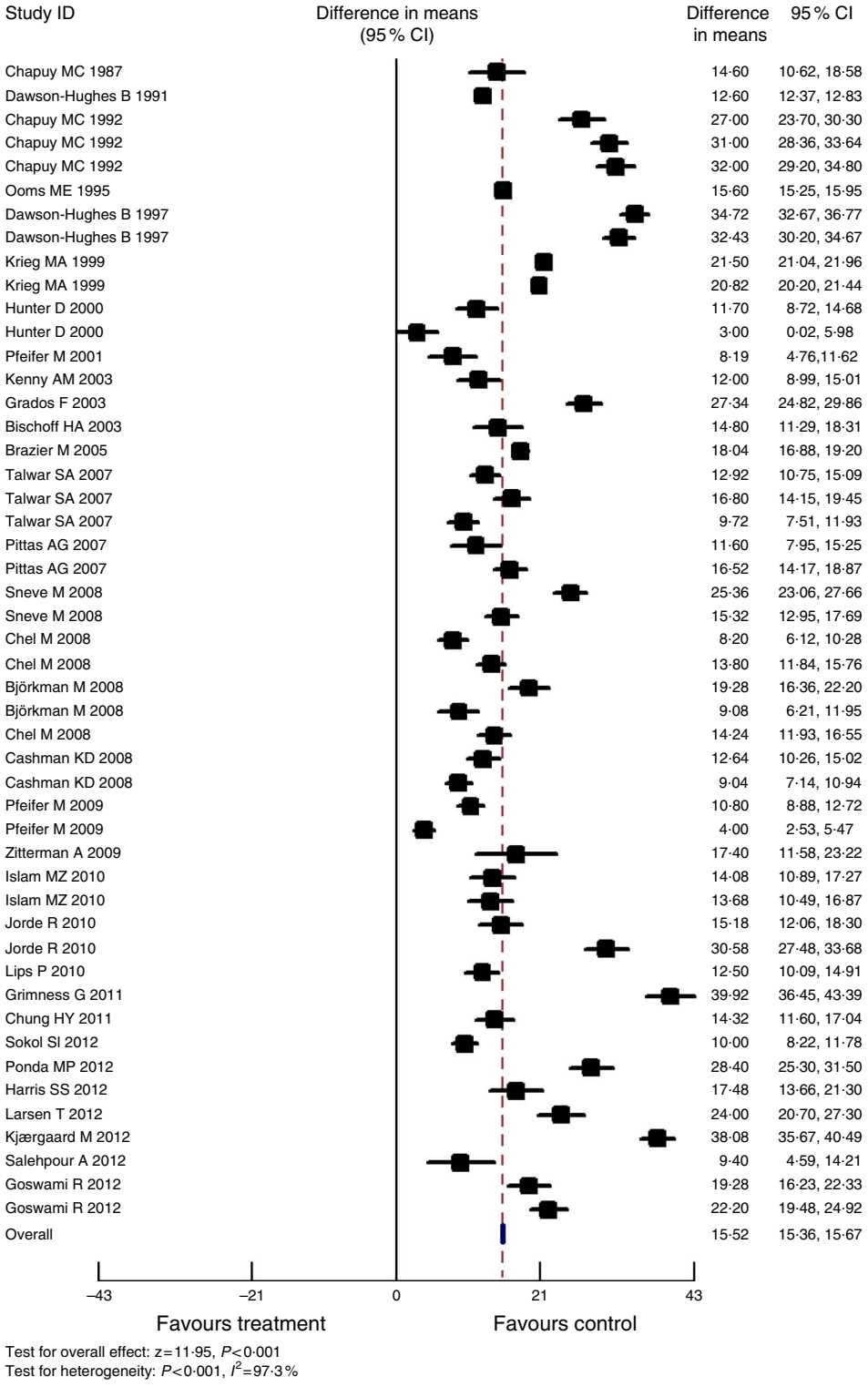

Fig. 2. Effect of vitamin D supplementation on serum 25-hydroxyvitamin D.

was significant heterogeneity between studies (test for heterogeneity: $P < 0{\cdot}001$ and $I^2 = 97{\cdot}3\,\%$), we used the random-effects model to estimate the PMD in serum vitamin D concentration. Vitamin D supplementation resulted in a PMD of 15·52 ng/ml in serum 25(OH)D concentration (95 % CI 15·38, 15·67).

Meta-analysis for serum parathyroid hormone response

The PMD of serum PTH from the pre-trial was −10·17 pg/ml (−11·83, −8·50 to +7·5 pg/ml) in the intervention group. Individual and pooled MD in serum PTH concentration and 95 % CI

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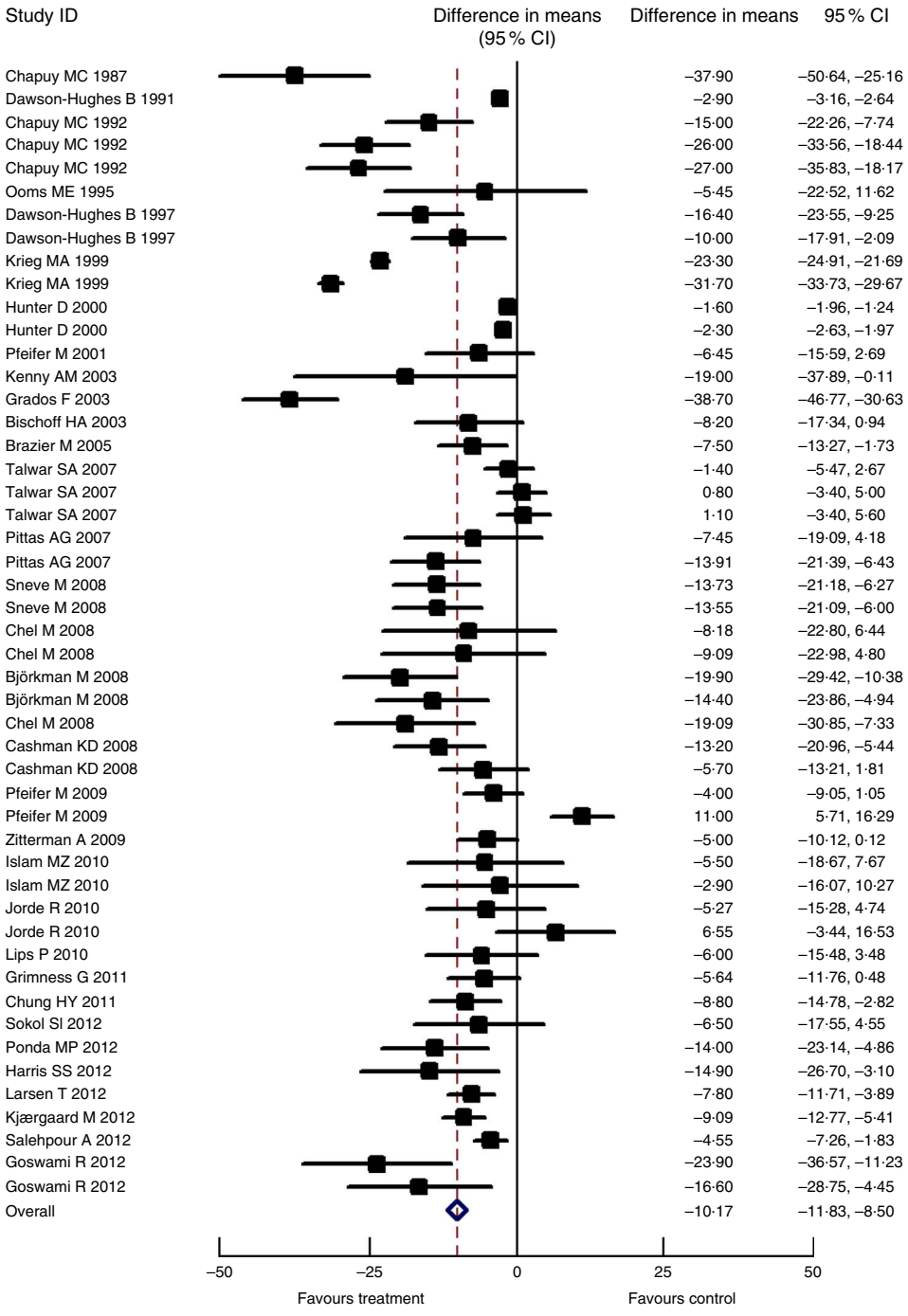

Test for overall effect: z=11·95, $P<0·001$
Test for heterogeneity: $P<0·001$, $I^2=97·3\,\%$

Fig. 3. Effect of vitamin D supplementation on serum parathyroid hormone (PTH).

after vitamin D supplementation that were derived from a random-effects model have been illustrated in Fig. 3. The meta-analysis demonstrated that the vitamin D supplementation decreased PTH levels significantly in the intervention group compared with the placebo (PMD: −10·17; 95 % CI −11·84, −8·50). There was significant heterogeneity between studies (test for heterogeneity: $P<0·001$), and the I^2 value was 97·3 %, which can be interpreted as the amount of variation across the studies being attributed to heterogeneity rather than chance.

Subgroup meta-analysis for serum parathyroid hormone response

Each subgroup analyses significantly affected the treatment effect except for the dose of vitamin D supplementation (Table 2).

Table 2. Subgroup analysis for effectiveness of vitamin D supplementation on serum parathyroid hormone (PTH) (Mean differences (MD) and 95 % confidence intervals)

Subgroups	Subtotal (*n*)	MD	95 % CI	*P*
Vitamin D dose (μg/d)				0·713
≤20	1173	−2·98	−3·24, −2·72	
>20	2559	−3·05	−3·28, −2·81	
Supplementation				<0·001
Vitamin D	1415	−2·09	−2·33, −1·85	
Vitamin D and Ca	2317	−4·08	−4·33, −3·82	
Ca dose (mg/d)				<0·001
0	1415	−2·09	−2·33, −1·85	
400–600	1315	−3·00	−3·26, −2·74	
600–1200	1002	−22·48	−23·57, −21·40	
Duration of trial (months)				<0·001
<3	490	−2·37	−2·69, −2·04	
3–6	1112	−1·96	−2·31, −1·61	
6–12	1228	−3·52	−3·78, −3·26	
>12	902	−18·26	−19·72, −16·79	
Baseline serum 25(OH)D (ng/ml)				<0·001
<20	2227	−16·70	−17·75, −15·84	
≥20	1505	−2·44	−2·62, −2·26	
Baseline serum PTH (pg/ml)				
≤6·0				<0·001
6·1–38·0	918	−6·85	−8·95, −5·11	
38·1–49·0	1077	−2·44	−2·61, −2·26	
≥49·1	882	−17·49	−18·49, −16·49	
	855	−20·67	−23·34, −18·00	
Age (years)				<0·001
≤50	820	−6·92	−8·74, −5·09	
>50	2912	−2·98	−3·16, −2·81	
Participants' BMI (kg/m^2)				<0·001
<25·0				
25·0–30·0	476	−2·01	−2·26, −1·77	
≥30·0	1312	−18·11	−19·07, −17·15	
	511	−5·86	−7·92, −3·80	
Sex				<0·001
Men-only studies	179	−11·34	−18·63, −4·05	
Women-only studies	1904	−2·95	−3·13, −2·77	
Men and women studies	1649	−7·20	−8·65, −5·75	
Study quality (Jadad score)				<0·001
Low	632	−25·17	−26·34, −23·99	
High	3100	−2·52	−2·69, −2·34	

25(OH)D, 25-hydroxyvitamin D.

There was a very small non-significant difference in PMD of serum PTH between vitamin D dosages of ≤20 and >20 μg/d (−2·98 (95 % CI −3·24, −2·72) *v.* −3·05(95 % CI −3·28, −2·81)) ($P=0·713$). The addition of Ca to vitamin D supplementation increased the treatment effect of vitamin D supplementation (−4·08 (95 % CI −4·33, −3·82) *v.* −2·09 (95 % CI −2·33, −1·85); $P<0·001$). The treatment effect was also the best with Ca doses of 600–1200 mg/d. Duration of vitamin D supplementation changed the treatment effect significantly, the best effect being observed when the trial duration was >12 months. Participants with low baseline 25(OH)D concentration (25(OH)D <20 ng/ml) had higher PMD of serum PTH than those whose serum 25(OH)D was ≥20 ng/ml (−16·70 (95 % CI −17·75, −15·84) *v.* −2·44 (95 % CI −2·62, −2·26); $P<0·001$). Baseline serum PTH also affected responses to vitamin D supplementation; participants with highest baseline serum PTH had the highest PMD. The treatment effect was lower in people aged >50 years than in those who were under 50 (−2·98 (95 % CI −3·16, −2·81) *v.* −6·92 (95 % CI −8·74, −5·09)); $P<0·001$). The treatment effect was the greatest in people with BMI ranging from 25 to 30 kg/m^2 compared with those with BMI <25 kg/m^2 (−18·11 (95 % CI −19·07, −17·15) *v.* −2·01 (95 % CI −2·26, −1·77)) and those with BMI ≥30 kg/m^2 (−18·11 (95 % CI −19·07, −17·15) *v.* −5·86 (95 % CI −7·92, −3·80); $P<0·001$). The treatment effect appeared to be greater in men-only studies compared with those conducted only in women (−11·34 (95 % CI −18·63, −4·05) *v.* −2·95 (95 % CI −3·13, −2·77); $P<0·001$).

Meta-regression and source of heterogeneity for serum parathyroid hormone responses

We used univariate meta-regression analysis to examine the variation in treatment effect attributed to some pre-specified covariates. The univariate meta-regression analysis showed that none of the covariates including the dose of vitamin D supplementation, dose of Ca supplementation, baseline serum PTH, age, duration of trial and baseline serum 25(OH)D concentrations have significant effects on between-study heterogeneity (Fig. 4 and Table 3).

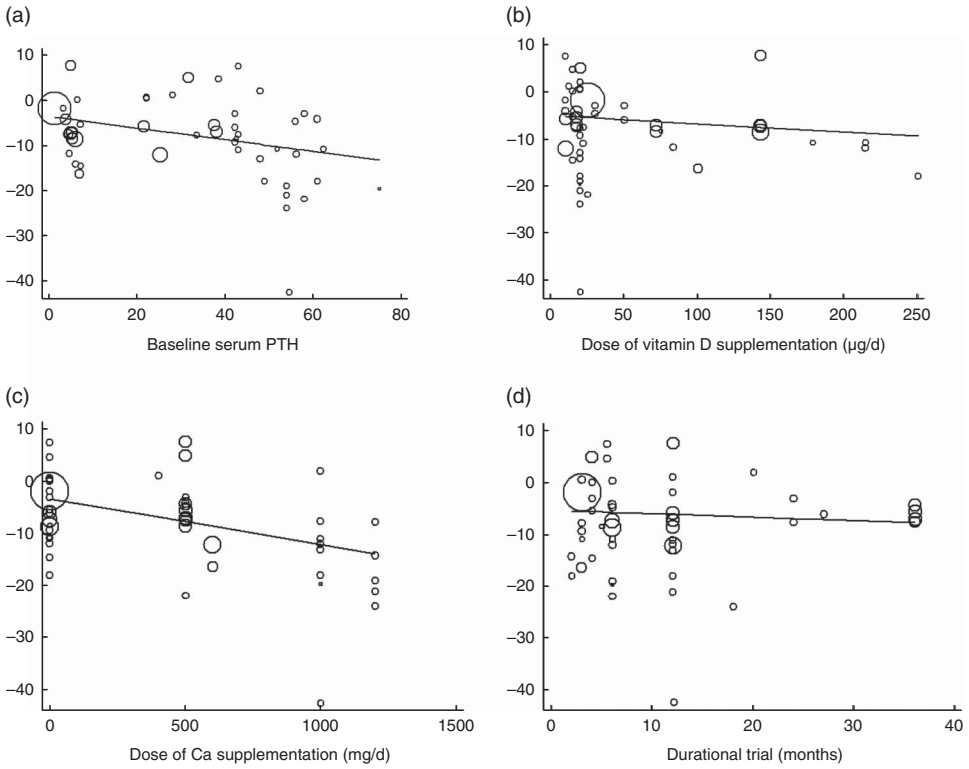

Fig. 4. Meta-regression analysis of baseline serum parathyroid hormone (PTH) (a), dose of vitamin D supplementation (b), dose of Ca supplementation (c) and trial duration (d).

Table 3. Summary of the meta-regression analysis (Slope and 95 % confidence intervals)

	Slope	95 % CI	*P*
Dose of vitamin D supplementation	−0·0004	−0·003, 0·002	0·686
Dose of Ca supplementation	−0·009	−0·021, 0·004	0·170
Baseline serum PTH concentrations	−0·129	−0·361, 0·104	0·272
Age	−0·088	−0·333, 0·158	0·475
Duration of trial	−0·067	−0·515, 0·381	0·765
Baseline serum 25(OH)D	0·229	−0·460, 0·918	0·507

25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

Ancillary analysis

Using curve estimation regression models, we found non-linear associations between dose of vitamin D supplementation and WMD in the post-trial serum PTH concentrations. WMD in the post-trial PTH was negatively and quadratically correlated with the dose of vitamin D supplementation (R^2 0·03, $P<0·001$; Fig. 5(a)), duration of the trial (R^2 0·01, $P<0·001$; Fig. 5(b)) and 25(OH)D concentration (R^2 0·01, $P<0·001$; Fig. 5(c)), reaching a plateau following a dosage of 75 μg/d after 12 months and at baseline 25(OH)D of 30 ng/ml.

Cumulative and influence analysis

No individual study was found to have excessive influence on the pooled effect when the influence analysis was carried out (Fig. 6). A cumulative random-effect meta-analysis showed consistency from the year 2000 (Fig. 7).

Publication bias

An asymmetric funnel plot suggested a possible publication bias (online Supplementary Fig. S1). Egger's linear regression also confirmed publication bias among studies ($P=0·003$), which is not unexpected because publication bias testing does not work when the meta-analysis has only selected RCT with a minimum of thirty participants. Publication bias, including funnel plot, assumes that all published studies are included and what is missing are the unpublished studies. However, the trim and fill method did not reveal any missing study, and thus the PMD estimate in post-trial PTH concentration remained unchanged.

Discussion

To our knowledge, this is the first meta-analysis of vitamin D supplementation on PTH response. In the present meta-analysis of forty-nine RCT arms, vitamin D supplementation significantly

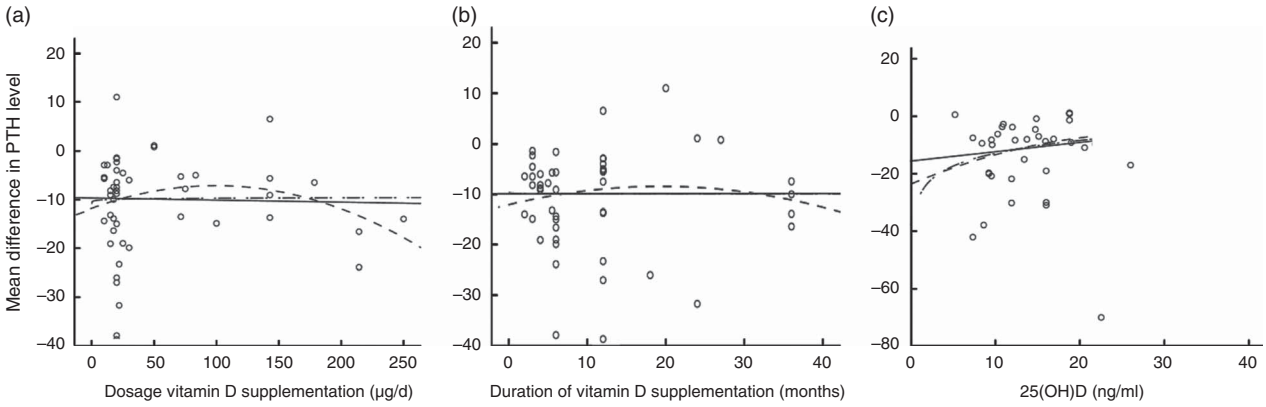

Fig. 5. Correlation of mean differences (MD) in parathyroid hormone (PTH) level with (a) dose of vitamin D, (b) duration of the trial and (c) baseline 25-hydroxyvitamin D (25(OH)D). ◯, Observed; ———, Linear; – — –, Logarithmic; — —, Quadratic.

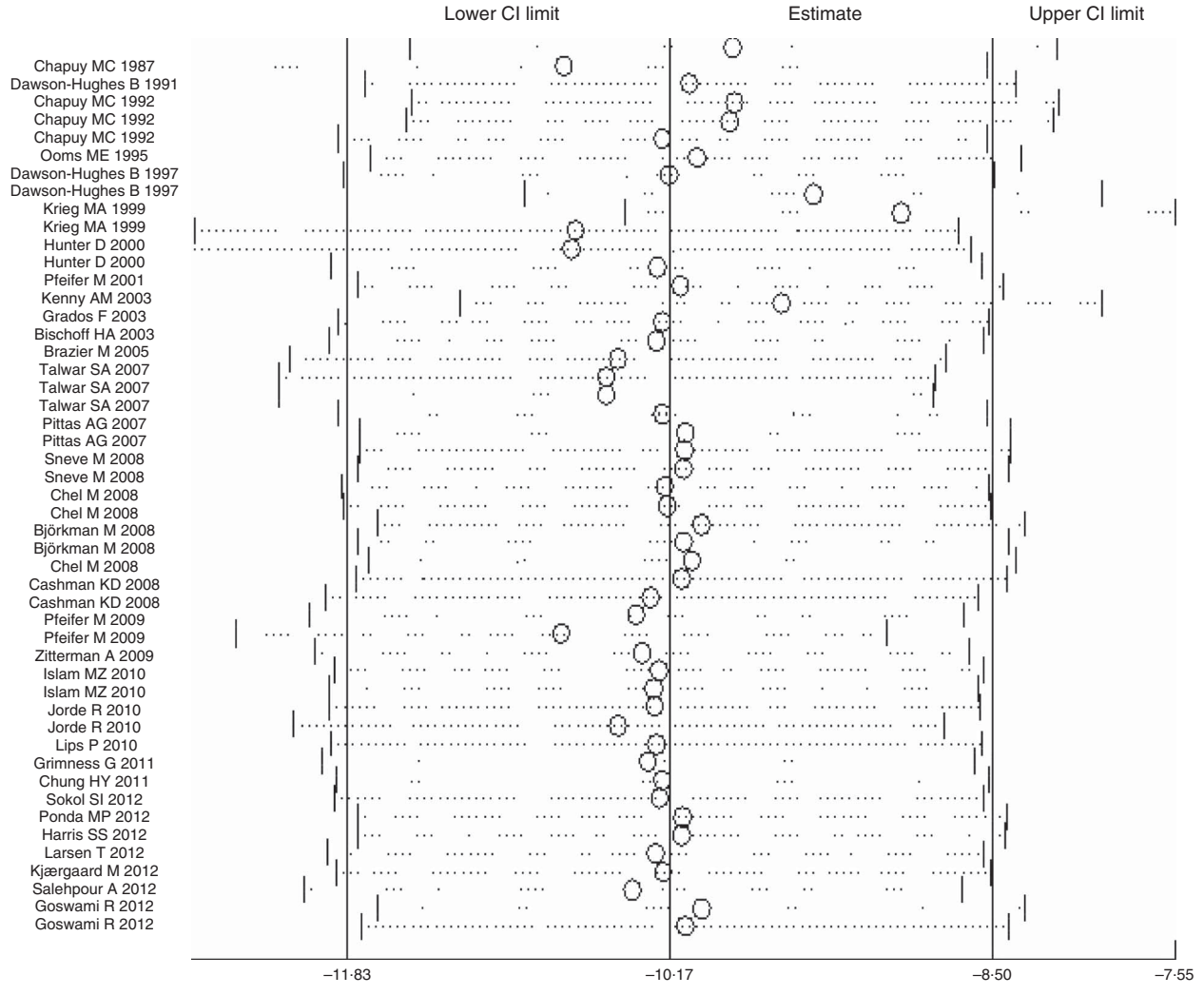

Fig. 6. Influence analysis.

increased serum 25(OH)D with a PMD of 15·5 ng/dl. Moreover, vitamin D supplementation significantly reduced PTH concentration with PMD of −10·17 pg/ml (95 % CI −11·83, −8·50 to +7·5 pg/ml), although a significant heterogeneity was observed between studies, and this reduction depended on Ca dose, trial duration, baseline levels of PTH/25(OH)D, BMI, sex and age. The serum PTH reached a plateau after 12 months with a dose of vitamin D >75 μg/d.

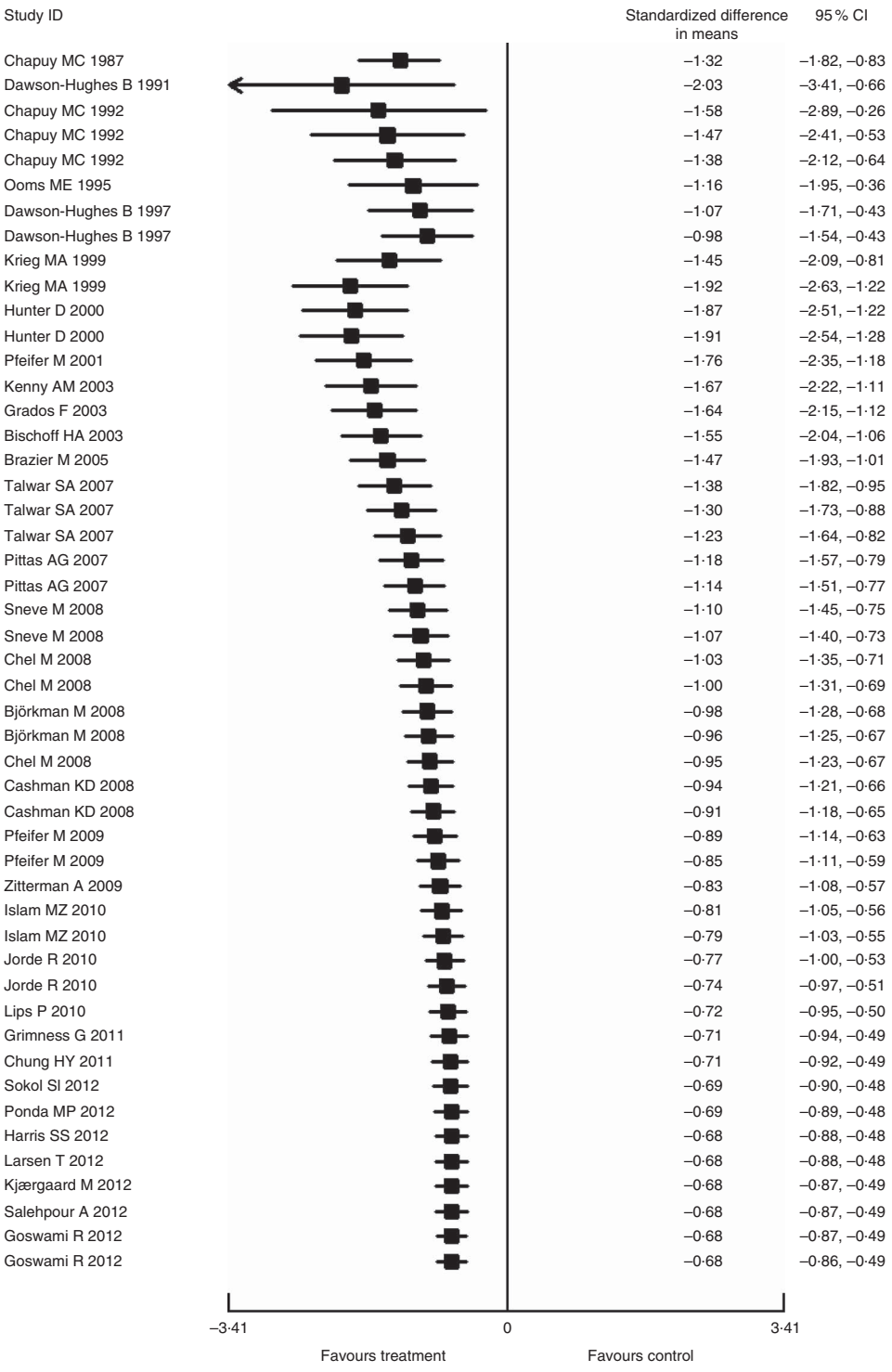

Fig. 7. Cumulative analysis.

Dose of vitamin D

In the present study, meta-regression analysis did not show the dose of vitamin D as a source of heterogeneity among studies. Vitamin D supplementation significantly decreased PTH concentrations in forty trials[31,38–41,44–46,48,49,51–55,57,59–70], thirty of which were in vitamin D-deficient populations[31,38,40–42,45,46,48,49,51–53,55,57,60,64–68,70,71]. It, however, increased PTH levels in eight trials[43,44,50,63,72,73] and caused no changes in one trial[68]. Thirty of those trials with decrease in serum PTH used a vitamin D dose ≥20 μg/d, and ten studies used vitamin D doses >75 μg/d. In those studies in which PTH

responded to vitamin D, the mean vitamin D supplementation was 57 μg/d and mean baseline 25(OH)D was 25·2 ng/dl, whereas in those studies where PTH did not respond to vitamin D supplementation the mean dosage of vitamin D was 30·5 μg/d with baseline 25(OH)D level of 16·6 ng/dl. Cranny *et al.*[74] have found that vitamin D_3 doses ≥17·5 μg daily, significantly and consistently decreased serum concentrations of PTH in vitamin D-deficient populations. As Cranny *et al.*[74] mentioned in their systematic review, reasons for lack of achievement of reduction in serum PTH in some studies may be due to a very low amount of the vitamin D dose for a population with low baseline 25(OH)D concentrations. In addition, changes in PTH level may not occur with baseline serum 25(OH)D above the threshold of PTH suppression[74].

PTH level plateaued in a quadratic model at a dose of vitamin D >75 μg/d, a finding in contrast with the first dose–response RCT in older white women by Gallagher *et al.*[75], who found a linear relationship between vitamin D_3 dose and PTH level. The quadratic dose term and interaction between quadratic dose and time were NS in the PTH model. Heaney *et al.*[76] reported that the 25(OH)D level that PTH will suppress is 75 nmol/l. Interestingly, Vieth *et al.* reported that a dose above 82·5 μg of ergocalciferol and 20 μg of cholecalciferol was needed to ensure post-trial 25(OH)D levels of at least 50 nmol/l, whereas to ensure mean post-trial 25(OH)D levels of at least 75 nmol/l doses of 12·5 μg/d and 71·25 μg/d are needed[8,77]. It was also reported that very high doses of vitamin D can certainly increase 25(OH)D to levels high enough to suppress PTH, but there are sparse data available on this. It is also interesting to note that it was estimated that intoxication may not occur with 25(OH)D levels up to 375 nmol/l[8,78].

An earlier meta-analysis by Shab-Bidar *et al.* concluded that the treatment effect of oral vitamin D_3 supplementation increases with increasing doses. Meta-regression results demonstrated a significant association between dose and serum 25(OH)D levels ($P = 0·04$)[5], and the results were confirmed by Cranny[74] who suggested that 2·5 μg of vitamin D_3 increases serum 25(OH)D concentrations by 1–2 nmol/l, and therefore vitamin D supplements at doses of 10–20 μg daily may be inadequate to prevent vitamin D deficiency in at-risk individuals[74].

Duration of trial

Based on the findings of the present study, the best effect of treatment with vitamin D on PTH response was observed when the duration of the trial was >12 months. An increase in PMD was found, which plateaued after 12 months. Previous trials reported no significant change in PTH levels after 3 months of vitamin D supplementation[5], an observation, however, supported by Gallagher *et al.*[75], who also observed significant decreases in serum PTH levels with increasing vitamin D doses at 12 months.

Calcium intake

Serum PTH response may be partially modulated by the amount of Ca intake through diet or combined supplementation of vitamin D with Ca[79]. We noted a higher treatment effect in individuals with Ca–vitamin D supplementation than in those who were supplemented only with vitamin D (−4·08 *v.* −2·09; $P < 0·001$). The treatment effect was also the best with Ca doses of 600–1200 mg/d, which is important because PTH suppression may not be ensured without sufficient Ca intakes, especially when there are several reports in which inadequate dietary Ca is prevalent throughout the world. In contrast, data from another study suggest that vitamin D sufficiency can ensure ideal serum PTH values even when the Ca intake level is <800 mg/d, whereas high Ca intake (>1200 mg/d) is not sufficient to maintain ideal serum PTH, as long as the vitamin D status is insufficient[80]. This is further reflected in ionised Ca levels that were dependent on serum 25(OH)D levels but not on Ca intake.

Another study concluded that vitamin D supplementation had a reducing effect on serum PTH only when the vitamin D *per se* was given[81]. Although sufficient intakes of vitamin D and Ca are definitely important, Ca intake may not necessarily be a contributing factor in maintaining Ca homoeostasis as long as vitamin D status would be benefitted with vitamin D supplementation and sun exposure[82]. Other investigators have suggested that the response of circulating 25(OH)D to supplemental vitamin D was similar whether Ca was co-administered or not[83]. Aloia *et al.*[84] reported that most of the studies examining optimal vitamin D status do not control for Ca intake, and they found that serum 25(OH)D and dietary Ca influence the PTH threshold independently and together account for about 67 % of the variance in reported thresholds among the studies. The contribution of dietary Ca to the prediction of the threshold remained significant even after controlling for serum 25(OH)D[84].

One study suggested that the response of serum PTH differs by Ca intake, only in those individuals with low vitamin D status, which can be explained by the less-active transport of Ca[80]. It has been suggested that in the absence of sufficient active Ca transport in the gut, as in vitamin D insufficiency, one must meet the requirements of the body with higher Ca intakes[85].

We explored the interaction between baseline 25(OH)D and Ca intake, and found that in studies with 25(OH)D >50 nmol/l Ca intake did not affect PTH response, whereas in those with a mean 25(OH)D <50 nmol/l dietary Ca was inversely related to PTH (data not shown). These results are in agreement with those of Aloia *et al.*[84] following a study of African-Americans.

Some studies have discussed the sparing effect of dietary Ca intake on serum 25(OH)D because PTH concentrations are suppressed, thus less serum 25(OH)D is converted to 1,25(OH)D[86].

Baseline 25-hydroxyvitamin D concentration

In this study, participants with low baseline 25(OH)D concentration (25(OH)D < 20 ng/ml) had more reduction in serum PTH than those in whom serum 25(OH)D was ≥20 ng/ml (−16·70 *v.* −2·44; $P < 0·001$). According to our previous study, baseline 25(OH)D was one of the important determinants of response to vitamin D supplementation[5]. In the present study,

we categorised both vitamin D deficiency and insufficiency together. Vitamin D deficiency is known to be associated with secondary hyperparathyroidism, increased bone turnover and bone loss[87]. A negative correlation between serum PTH and serum 25(OH)D levels has been reported by many investigators[79]. We expect that betterment of vitamin D deficiency would follow after significant improvements of PTH concentration.

Some have argued that serum PTH declines significantly after vitamin D and Ca intervention is initiated with low baseline serum 25(OH)D levels <20 ng/ml (<50 nmol/l)[74]. Interestingly, Lips *et al.*[79] demonstrated that the mean serum PTH level was 30 % higher in those with low serum 25(OH)D (<25 nmol/l) than in women with higher serum 25(OH)D (<50 nmol/l). Based on the findings of the Gallagher *et al.*[88] study, clinical importance was only observed in 25(OH)D-deficient status and elevated PTH level. However, the threshold of 25(OH)D to prevent a rise in PTH concentration varies widely, as many studies have found most estimates clustered between 40 and 50 nmol/l or between 70 and 80 nmol/l. The variability in the estimates may be due to different Ca intakes, different 25(OH)D assays, age of the participants and vitamin D insufficiency[84].

In the meta-regression analysis, we found a non-significant association between baseline 25(OH)D and response of PTH. Aloia *et al.*[84] in a review of twenty-five studies reported that the average correlation between PTH and vitamin D was −0·30 and serum 25(OH)D just contains 9 % of the variance in PTH.

Age

The treatment effect was lower in people aged >50 years than in those who were younger than 50 (−2·98 *v.* −6·92); $P < 0·001$). Previous observations have demonstrated that older participants had a better response to vitamin D_3 intake, although the response was independent of baseline 25(OH)D[5]. Bjorkman *et al.* also showed that age of the patients can have major effects on the elevation of PTH levels independently. The higher effect could be attributed to the high prevalence of vitamin D deficiency in the elderly[89,90]. We expected that following amelioration of vitamin D deficiency PTH level might be suppressed maximally. However, the better response to vitamin D intake was not enough to guarantee PTH suppression in the elderly, as the achieved 25(OH)D was not sufficient. Indeed, skin content of 7-dehydrocholesterol drops by 50 % between 20–80 years of age[91], and the same dose of UV-B radiation in older individuals produces a smaller rise in serum 25(OH)D compared with young individuals[92]. Ageing is associated with a decline in renal function, and higher concentrations of 25(OH)D are needed to prevent a rise in serum PTH in the elderly[93].

BMI

In the present study, the treatment effect was the highest in people who were overweight and obese. There is an altered vitamin D endocrine system in obese individuals[94]. Studies have shown that obesity, and specifically body fat content, is inversely associated with 25(OH)D and is positively associated with PTH concentrations[95,96]. In a recent study by Gallagher *et al.*[75], underweight to normal weight and the overweight groups tended to have lower PTH levels than the obese group ($P = 0·065$). It has been reported that, with a similar amount of 7-dehydrocholesterol in the epidermis, the increase in serum 25(OH)D after UV-B irradiation was 57 % less in obese compared with non-obese subjects[97]. It is suggested that lower serum 25(OH)D may be a factor partially contributing to the relationship of higher serum PTH with greater adiposity[95,96,98]. In a recent study, Shapses *et al.* showed that PTH is suppressed at a lower 25(OH)D concentration in the obese compared with the entire population. Therefore, the lower average 25(OH)D concentrations in the obese may not have the same physiological significance as in the general population. Evidence also shows that, in spite of physiological changes associated with the higher BMI, including higher PTH levels and higher bone resorption, bone mineral density may not be reduced in overweight women[99].

Limitations

This meta-analysis has some limitations. First, many analyses suffer from high levels of heterogeneity, but this is not unexpected because the included RCT had variable population groups, doses and supplementation forms (vitamin D_2 or D_3, with or without supplemental Ca). Second, our search was limited to the published studies. Third, not all studies reported data for seasonal influences, sun exposure, physical activity and dietary intake of vitamin D and Ca; therefore, we were unable to adjust for these variables in our analysis. Fourth, multiple comparisons in the subgroup analysis may increase the likelihood of type 1 error. Finally, the validity of the study results may be influenced by the use of different assay types.

Conclusion

In conclusion, although the present meta-analysis was hindered by some limitations, all of which contributed to the heterogeneity, it provides some interesting evidence, suggesting that suppression of PTH level needs higher vitamin D intake (75 μg/d) and longer duration (12 months) than those currently recommended, which should be taken into account for nutritional recommendations.

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S. S.-B. designed and supervised the study (project conception, development of overall research plan and study oversight). S. S.-B and N. M. conducted the research (hands-on conduct of the experiments and data collection), performed most of statistical analysis and wrote the preliminary manuscript. P. M., F. H. and F. A. helped intellectually in finalising the manuscript. All the authors read and approved the final version of the manuscript.

There are no conflicts of interest to declare.

Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S0007114515003189

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