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The Effect of Vitamin D Supplementation on Insulin-Like Growth Factor-1: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Purpose

There is equivocality regarding the interaction between vitamin D and insulin-like growth factor-1 (IGF-1). Thus, the aim of this study was to elucidate the effect of vitamin D supplementation on serum levels of IGF-1 by conducting a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods

PubMed, Scopus, and ISI Web of Science databases were searched up to May 2019 for RCTs that evaluated the effect of vitamin D supplementation on IGF-1 levels. Mean and standard deviation changes of IGF-1 in each treatment group were considered for analysis and pooled using random-effect model. Risk of bias for included studies was assessed by the Cochrane scale and the NutriGrade approach was applied to evaluate the quality of evidence.

Results

Six trials (n= 773 participants) were included in the meta-analysis. Compared with control group, vitamin D supplementation yielded no significant effect on serum level of IGF-1 (weighted mean difference [WMD] = 4.66 ng/ml, 95% CIs: -6.72 to 16.03, P=0.42, I^2= 74.8, $P_{heterogeneity}$= 0.001). Additionally, no meaningful changes were observed in subgroup analyses.

Conclusion

The evidence from the limited number of published trials does not convincingly show that vitamin D supplementation elicits any clinically relevant effects on IGF-1 levels. More high-

quality studies are needed to reach a consensual conclusion in this area.

Keywords

Growth factor; Insulin-Like Growth Factor-1; Meta-analysis; Vitamin D

INTRODUCTION

Insulin-like growth factor-1 (IGF-1) is produced by the liver and is considered as a growth promoting peptide mediating growth hormone (GH) effects in the body (1, 2). Almost all (around 99%) circulating IGF-1 is bound to the IGF binding protein (IGFBP), and potentially inactive; while less than one percent of IGF-1 circulates unbound, which possesses an important role in the promotion of cell proliferation, differentiation, migration, and inhibition of cell apoptosis with a recognized effect on tumor development (3-5). Previous epidemiological studies have provided some evidence for the associations of circulating IGF-1 and progression of some tumors, including lung, esophageal, colorectal, prostate, ovarian and breast cancers (4, 6-8). These cancers account for a significant proportion of cancer occurrence worldwide; thus, investigating the factors affecting IGF-1 levels may help in the prevention or treatment of cancers (9).

Recently, a positive correlation has been reported between serum concentrations of IGF-1 and vitamin D status in healthy subjects (10-12). Although no mechanistic study has yet addressed the effect of vitamin D on circulating IGF-1 (10), it seems that vitamin D promotes liver production of IGF-1, IGF-1 receptors, and, likely, IGFBP3. Such effects are purported to occur directly through binding to, and activating, the nuclear vitamin D receptor, thereby inducing transcription of relevant genes (10, 13), and through enhancing GH stimulation (10, 14, 15). According to in vitro experiments, hepatic non-parenchymal cells, such as stellate, Kupffer, and sinusoidal endothelial cells, because of their high expression of vitamin D receptor, are target cells for vitamin D (16). Moreover, given intake of calcium is positively associated with circulating IGF-1 in humans (9, 17), vitamin D conceivably increases IGF-1 concentrations via

increases in intestinal calcium absorption. Recent reviews have reported a relationship between total vitamin D intake and inhibition of apoptosis (18), which is believed to play a part in preventing some cancers (19, 20). However, numerous studies have failed to replicate such results (21, 22). Therefore, the controversial role of vitamin D in cancer development may be partly explained by the focus of the efficacy of vitamin D supplementation on IGF-1 as an important mediator in the pathology of cancer.

A number of randomized controlled trials (RCTs) have been conducted to infer the possible effects of vitamin D supplementation on IGF-1 levels, yet results are bereft of uniformity. (10, 23). Therefore, the aim of this study was to investigate whether vitamin D supplementation can affect IGF-1 levels in adults, conducting a systematic review and meta-analysis of RCTs.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (24) and was registered in the international prospective register of systematic reviews (PROSPERO; registration code CRD42018107089).

Search strategy

A comprehensive search was undertaken through PubMed, Scopus, and ISI Web of Science databases, up to May 2019 and without any language restriction. In order to find relevant articles, a combination of MESH and non-MESH terms related to "insulin-like growth factor-1", "vitamin D" and "study design" were used. Further details regarding the search strategy are shown in **Table S1**. In addition, review articles and bibliographies were hand-searched to find additional eligible studies.

Eligibility criteria

Two authors (FM and SH A) independently conducted the study selection based on the inclusion and exclusion criteria. Original RCTs (either parallel or cross-over design) that were investigated the effect of vitamin D supplementation (oral or injectable supplement) on serum levels of IGF-1 (as primary or secondary outcome) on adult human subjects, were considered eligible for inclusion in the present meta-analysis.

Trials were excluded if they; (i) were conducted using children or adolescent subjects, or on pregnant or lactating women, (ii) did not include a placebo group or non-exposed control, (iii) used supplements as a placebo; and (iv) examined multiple interventions only.

Data extraction

The following information was extracted from each article: first author's name, year of publication, study location, age, gender, study design (e.g. parallel or crossover design), health

status of the participants, number of participants in intervention and control groups, baseline serum levels of 25(OH)D, the length of the intervention, type and dose of vitamin D supplement, measurement method of IGF-1 and mean and standard deviation (SD) of IGF-1 before and after intervention or mean and SD of IGF-1 change during the follow-up period. If data were insufficient for meta-analysis, relevant information was requested by contacting the corresponding author (25, 26). Vitamin D supplementation homogenized as weekly dose (15, 23, 27) and when multi-doses of vitamin D were administered in the trial, the highest dose was included in the analysis (15, 27). Serum levels of IGF-1 in all trials were also converted into ng/ml. Any disagreements were discussed and resolved via cooperative triangulation with the corresponding author (SS).

Quality assessment

Quality of eligible trials was assessed using the Cochrane risk of bias tool for RCTs (28). This scale covers six domains of bias including selection bias, performance bias, detection bias, attrition bias, reporting bias, and bias due to problems not covered elsewhere. These factors were classified as low risk of bias, high risk of bias, or unclear. Studies with a low risk of bias for all criteria were regarded as good quality; if one criterion not met or two criteria unclear, the study was regarded as fair; and studies which two or more criteria listed as high risk of bias were regarded as poor quality.

Quality of meta-evidence

The NutriGrade scoring system was used to assess the quality of evidence for each outcome

based on the major domain of study limitations including the risk of bias, precision, heterogeneity, directness, publication bias, funding bias and study design (29). The quality of evidence was categorized to high (≥ 8 points), moderate (6 to <8 points), low (4 to <6 points) and very low (0 to <4 points) based on this scoring system.

Statistical analyses

This meta-analysis was performed using Stata software version 14 (Stata Corp. College Station, Texas, USA). We used the mean difference (95% confidence intervals [CIs]) in IGF-1 levels between the intervention (vitamin D supplementation) and placebo groups as the effect size for the meta-analysis. When the SD of changes from baseline was missing, it was calculated using standard errors and the formula provided in the Cochrane Handbook of Systematic Reviews (30) (correlation R = 0.811) (15, 27). To evaluate whether the results of the studies were homogeneous, we used Cochran's Q test (31) and the I-square statistic (I^2) (32). In order to determine the potential sources of heterogeneity, sensitivity, and subgroups analyses were performed. Data were stratified into ten subgroups on the basis of study design, age of participants (less than or equal to 65 and greater than 65 years old of age), duration of the intervention (less than or equal to 12 weeks and more than 12 weeks), type of vitamin D supplement (vitamin D_3 and vitamin D_3+ D_2), dose of vitamin D supplement (7000 IU/week or less, and more than 7000 IU/week), baseline values of vitamin D (10-30 ng/ml and less than 10 ng/ml), method used for IGF-1 assessment (radioimmunoassay or chemiluminescence), quality of the studies (poor or fair), baseline values of body mass index (BMI) (< 25 kg/m^2, 25 to < 30 kg/m^2, and ≥30 kg/m^2), latitude (< 50 magnetic latitude, 50 to <60 , and ≥60 magnetic latitude) and health status of participants (endocrine disease, metabolic disease, bedridden

elderly or hypertensive disorder). Sensitivity analysis was conducted by excluding one study or a group of studies at a time, to explore which study might influence the overall effect size. Publication bias was evaluated using the visual inception of funnel plots and confirmed statistically by the Begg's adjusted-rank correlation (33) and the Egger's regression asymmetry tests (34). Two-sided P values <0.05 were considered significant.

RESULTS

Study selection and characteristics

The primary search yielded 2349 references, of which, 30 full-texts were assessed for inclusion in the present meta-analysis. The reason for exclusion of studies is presented in **Figure 1.** Eight trials were initially considered suitable for inclusion in the systematic review (15, 23, 25-27, 35-37). However, two trials were excluded because baseline values of IGF-1 levels in intervention and control groups were not presented separately (25). or, only the serum levels of IGF-1 as μg/10E06 platelets were reported (26). Finally, six trials were included in the meta-analysis (15, 23, 27, 35-37).

The general characteristics of the six studies are outlined in **Table 1**. Studies were published from 1994-2017 and were carried out in Italy (15), United States (36), Sweden (35), Finland (37), Norway (27) and Australia (23), respectively. Participants included both men and women in all trials (15, 23, 27, 35-37), and total sample size in the studies ranged from 39 to 318. Vitamin D regimens used in the trials ranged from 5000 to 85300 IU/week, whilst the duration of vitamin D administration varied from 8 to 52 weeks and all patients had oral treatment. All trials employed a parallel design. Only two trials were conducted in vitamin D deficient

subjects (≤30 ng/ml of serum 25(OH)vitamin D (23, 36). Trials enrolled participants with GH deficiency (15), hyperparathyroidism (35), pre-diabetes (36), hypertension (23), overweight and obesity (27) and one trial was also conducted on bedridden elderly (37). Vitamin D was used as cholecalciferol in five studies (15, 23, 27, 35, 36) and one trial used both cholecalciferol and ergocalciferol (37).

Risk of bias and quality of evidence

The overall quality of included trials was assessed and rated as "fair" (23, 35, 36) for three trials, and "poor" (high risk of bias) for the remaining studies (15, 27, 37) (**Table S2**). All trials were randomized (15, 23, 27, 35-37), although four of them did not explain the randomization process (15, 27, 36, 37). Masking of treatment allocation was not considered in any trials, and two trials were not blind in design (15, 37). All studies described details about withdrawal, and all expected outcomes were presented in all but two trials (27, 37).

The NutriGrade score demonstrated moderate confidence in the effect estimate of the vitamin D supplementation on IGF-1 (NutriGrade score= 7.05). (**Table S3**).

Meta-analysis

In total, six trials (n= 773 participants) were included in the final analysis (15, 23, 27, 35-37). Overall analysis revealed no significant effect of vitamin D supplementation on IGF-1 levels (weighted mean difference [WMD] = 4.66 ng/ml, 95% CIs: -6.72 to 16.03, P= 0.42) (**Figure 2**);

however, between-study heterogeneity was high (Q statistic= 19.81, P= 0.001, I^2= 74.8%). Subgroup analysis found the health status of participants, duration of vitamin D supplementation and dose of vitamin D were potential sources of heterogeneity; however, no meaningful changes were observed in any of the subgroups for IGF-1 levels **(Table 2)**.

Sensitivity analysis and publication bias

The sensitivity analysis was performed using step by step exclusion of each study from the analysis. Results from sensitivity analysis showed that omission of any one study from the analysis did not alter the overall effect of vitamin D supplementation on serum levels of IGF-1. There was no evidence of asymmetry in the Funnel plot, and Begg's and Egger's tests confirmed this finding (Begg's P= 0.85; Egger's P= 0.49).

DISCUSSION

The present meta-analysis of six randomized controlled trials showed that vitamin D supplementation did not significant effect on serum levels of IGF-1. Moreover, no significant changes were observed for IGF-1 levels in any of the subgroups.

Increased levels of IGF-1 have been suggested to contribute to the development of several types of tumor, which raises the possibility that the increase in serum IGF-1 following vitamin D treatment may be detrimental in some cases (3, 5, 38). There is some putative hypotheses that the active vitamin D metabolite can regulate the actions of IGF-1 (39), however, a plausible pathophysiological relationship between vitamin D and IGF-1 remains unclear (10). Vitamin

D is most likely able to regulate IGF-1 concentrations by acting in the liver, because hepatic cells are the main source of circulating IGF-1 (2).

Although the results in several antecedent trials suggest that vitamin D treatment significantly increases the serum levels of IGF-1 (10, 35), our meta-analysis did not support these findings, which are in line with some prior reports (23, 26, 36). There is some explanation that may influence our results. IGF-1 is mostly bound by one of the IGFBP members (40), therefore, the concentrations of free IGF-1 are negatively correlated with IGFBP-1 and IGFBP-3 (41). Vitamin D has been shown to mediate an increase in the production of IGFBP-3 and consequently decrease the IGF-1/IGFBP-3 ratio in some studies (42). So, the IGF-1/IGFBP-3 ratio may be a more sensitive marker of metabolic efficacy of IGF-1, which corresponds with previous observations (27). However, we were unable to analyze this ratio because only two trials assessed IGFBP-1 (35) and IGF-1/IGFBP-3 ratio (27), therefore, this represents a sensible avenue for future research.

Body weight is another factor that may affect IGF-1 levels. IGF-1 is originally synthesized in the liver, but is also found in other tissues like fat mass, where it's expression is stimulated by $1,25(OH)_2D$ (43). Studies have shown that IGF-1 is linked with BMI in a non-linear manner, where individuals with extremely low and/or high BMI had lower levels of IGF-1 (44). Also, people with obesity are more likely to experience vitamin D deficiency, as compared to normal-weight counterparts. It may be suggested that the lack of a notable increase in supplemental vitamin D in obese people may conceivably be attributed to their higher BMI, since excess adiposity dilutes supplemental vitamin D (45). Notwithstanding, however, we did not find any significant result in this regard.

Latitude is known as one of the main eco-environmental determinants of dermal photosynthesis of vitamin D (46). It is believed that insufficient intensity of sunlight at higher latitudes is the cause of decreasing circulating 25(OH)D concentrations (47). In the same way, we found that vitamin D supplementation was marginally, yet significantly, associated with lower levels of IGF-1 when analysis was restricted to studies conducted in higher latitudes. It seems the small number of studies may explain the non-significant results; nevertheless, detailed examination of eco-environmental determinants warrants further investigation.

Our analysis also showed a marginal significant reduction in IGF-1 levels when vitamin D was administered in periods longer than 12 weeks. It has been suggested that vitamin D supplementation has a time-dependent effect on IGF-1 levels (48); however, there were no studies that monitored the effect of vitamin D supplementation on IGF-1 concentrations across several time points.

Calcium, phosphate, and PTH are classical regulators of renal 1α -hydroxylase and, by extension, the endocrine actions of vitamin D (10). In the present meta-analysis, regarding controlling for these regulators, four RCTs excluded patients with hypercalcemia (defined as a plasma calcium concentration >2.65 mmol/L) (23, 27, 35, 37) and two adjusted for the outcome measurement (23, 35). However, several studies have not considered the regulatory effect of calcium, phosphate, and PTH on vitamin D action, respectively.

To the best of our knowledge, this is the first meta-analysis of randomized controlled clinical trials to evaluate the effect of vitamin D supplementation on serum levels of IGF-1 across different subgroups. This study has some strengths; first, all included studies were

randomized controlled trials, providing gold standard results. Second, a comprehensive search strategy was used to identify all relevant articles. Third, several subgroup analyses were performed to explore sources of heterogeneity. Fourth, the NutriGrade scoring system was used for quality assessment of included trials. Finally, the lack of significant asymmetry in the funnel plots of studies suggested that our results are unlikely to be affected by publication bias.

Whilst there were a number of strengths, there are some limitations that may affect the results, and must, therefore, be considered. The most important limitation of the present meta-analysis is the small number of included studies that made the reliability of our conclusions unclear, this was, however, out of the operational control of the study. Furthermore, the IGFBPs were not measured consistently across RCTs, which, consequently, limited our ability to conduct analysis based on IGF/IGBP ratio. In addition, IGF-1 was measured as a secondary outcome in most of the included studies which may reduce the statistical power to detect significant effects. In addition, the regulatory effect of calcium and phosphate intake on the endocrine actions of vitamin D was not well controlled across all of RCTs, which may conceivably have impacted our findings.

Based on the limited evidence, it is not possible to draw any firm conclusions regarding the effect of vitamin D supplementation on serum level of IGF-1. Therefore, it is pragmatic to assert that further studies to test the efficacy of vitamin D supplementation are urgently warranted.

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Legends of Tables

Table 1: Characteristics of trials that investigated the effect of vitamin D supplementation on IGF-1 levels in adults and were eligible for inclusion in the meta-analysis

Table 2: Meta-analysis showing the effect of vitamin D supplementation on serum levels of IGF-1 (ng/ml) based on several subgroups (all analyses were conducted using random effects model)

Table1. Characteristic of trials that investigated the effect of vitamin D supplementation on IGF-1 levels in adults and were eligible for inclusion in the meta-analysis

Author, year	Participants, gender	Mean age	country	Participants health status	Inclusion criteria for serum 25(OH)D	Vitamin D type	Dosage (IU/week)	Duration (weeks)	Results
Ameri, 2013 (15)	39, M & F	61.9	Italy	GH deficiency	No	Vitamin D3	5000 7000	12	Significant increase in the 7000 IU group
Kamycheva, 2013 (27)	318, M & F	49.2	Norway	Overweight and obese	No	Cholecalciferol	40 000 20 000	52	Significant increase in IGF-1/IGFBP-3 ratio in subjects with sever obesity in vitamin D group
Norenstedt, 2013 (35)	150, M & F	58 (int) 59.7 (cont)	Sweden	Hyperparathyroidism	No	Cholecalciferol	1600[1]	52	Significant increase in vitamin D group
Sinha-Hikim, 2015 (36)	80, M & F	51.6 (int) 52.4(cont)	United States	Pre-diabetes	Yes (<30ng/ml)	Vitamin D3	85 300 ± 16 000 IU[1]	52	No significant change
Sorva, 1994 (37)	55, M & F	84	Finland	Bedridden elderly	No	Vitamin D3 and D2	1000[2]	40	No significant change
Trummer, 2017 (23)	200, M & F	61 (int) 60 (cont)	Australia	Hypertension	Yes (<30 ng/ml)	Vitamin D3	2800[1]	8	No significant change

Cont, control; F, Female; GH, Growth hormone, IGF, Insulin-like growth factor; IGFBP, Insulin-like growth factor binding protein; Int, intervention, M, Male

[1]The formula for vitamin D supplementation was (100-baseline vitamin D) × kg weight × 15.7 = IU per week

[2]Daily administration

Table 2. Meta-analysis showing the effect of vitamin D supplementation on serum levels of IGF-1 (ng/ml) based on several subgroups (all analyses were conducted using random effects model)

		Meta-analysis			Heterogeneity		
Study group	**Studies (n)**	**Participants (n)**	**WMD (95%CI)**	**P effect**	**Q statistic**	**P within group**	**I^2 (%)**	**P between group**
Overall	6	773	4.66 (-6.72, 16.03)	0.42	19.81	0.001	74.8	
Age of participants (years)								0.721
<65	5	630	5.42 (-6.57, 17.42)	0.37	19.69	0.001	79.7	
≥65	1	17	-7.64 (-54.95, 39.67)	0.75	0.00	-	-	
Health status								0.432
Endocrine disease[1]	2	160	15.83 (-33.01, 64.89)	0.52	16.79	<0.001	94	
Metabolic disease[2]	2	295	-2.28 (-11.31, 6.75)	0.62	0.27	0.602	0.00	
Bedridden elderly	1	17	-7.64 (-54.95, 39.67)	0.75	0.00	-	-	
Hypertension	1	175	6.00 (-1.64, 13.64)	0.12	0.00	-	-	
Assessment method of IGF-1								0.004
Radioimmunoassay	3	122	17.90 (-13.00, 48.80)	0.25	5.35	0.069	62.6	
Chemiluminescence	3	525	-1.46 (-9.96, 7.03)	0.73	6.04	0.049	66.9	
Quality of studies								0.497
Poor	3	257	11.99 (-22.04, 46.02)	0.49	13.40	0.001	85.1	
Fair	3	390	-0.13 (-11.71, 11.45)	0.98	5.95	0.051	66.4	

Length of the intervention (week)								0.002
≤12	2	33	22.35 (-12.69, 57.40)	0.21	8.89	0.003	88.8	
>12	4	614	-5.37 (-11.49, 0.74)	0.08	1.10	0.776	0.00	
Baseline values of vitamin D (ng/ml)								0.721
10-30	5	630	5.43 (-6.57, 17.42)	0.37	19.69	0.001	79.7	
<10	1	17	-7.64 (-54.95, 39.67)	0.75	0.00	-	-	
Baseline BMI (kg/m^2)								
<25	1	26	-7.64 (-54.95, 39.67)	0.75	0.0	-		0.64
25- 29.9	2	174	15.83 (-33.01, 64.68)	0.52	16.79	<0.001	94.0	
≥30	3	573	2.45 (-3.79, 8.7)	0.44	2.16	0.34	7.2	
Latitude (degrees)								0.001
<50	3	294	17.63 (-6.67, 41.94)	0.15	8.94	0.01	77.6	
50-60	3	479	-5.79 (-12.02, 0.43)	0.06	0.61	0.73	0.0	
Type of vitamin D								0.752
Cholecalciferol, Vitamin D3	6	639	4.66 (-6.72, 16.03)	0.42	19.81	0.001	74.8	
Vitamin D3+ D2	1	17	-2.29 (-21.83, 17.25)	0.81	0.00	-	-	
Dose of vitamin D (IU/week)								0.006
7000<	5	78	-1.88 (-7.82, 4.06)	0.53	6.75	0.150	40.7	
≤7000	4	815	14.22 (-6.59, 35.03)	0.18	9.46	0.024	68.3	

BMI, Body mass index; IGF, Insulin-like growth factor; IU, International unit; WMD, Weighted mean difference.

[1]Including growth hormone deficiency and hyperparathyroidism

[2]Including obesity and pre-diabetes

Legend of Figures

Figure 1: Flow diagram for study selection process.

Figure 2: Forest plot of randomized controlled clinical trials (RCTs) illustrating weighted mean difference in serum levels of IGF-1 change (ng/ml) between the vitamin D supplementation and control groups for all eligible studies. Analysis was conducted using random effects model.

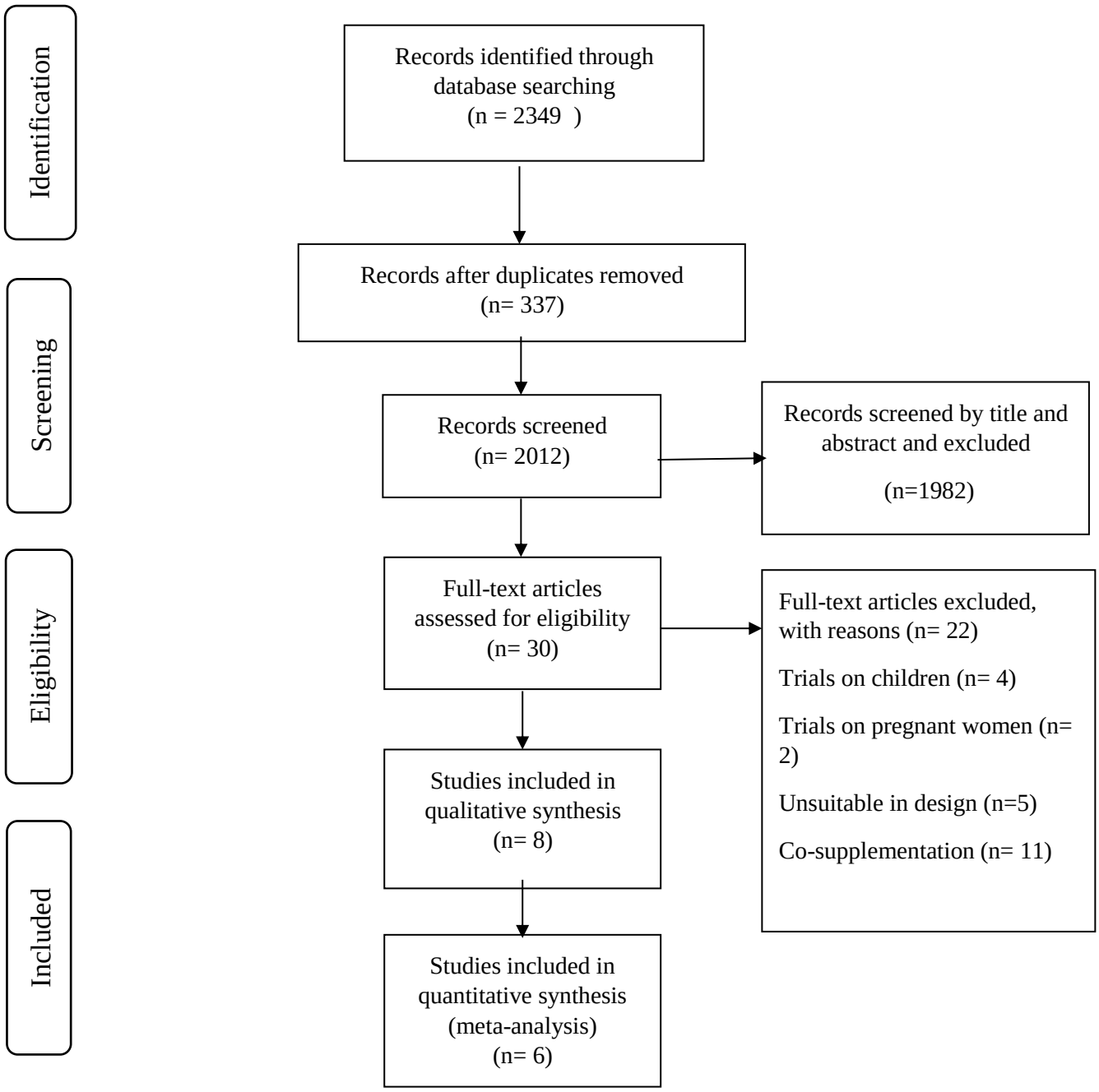

Figure 1. Flowchart which describes the methodology of selection of the articles.

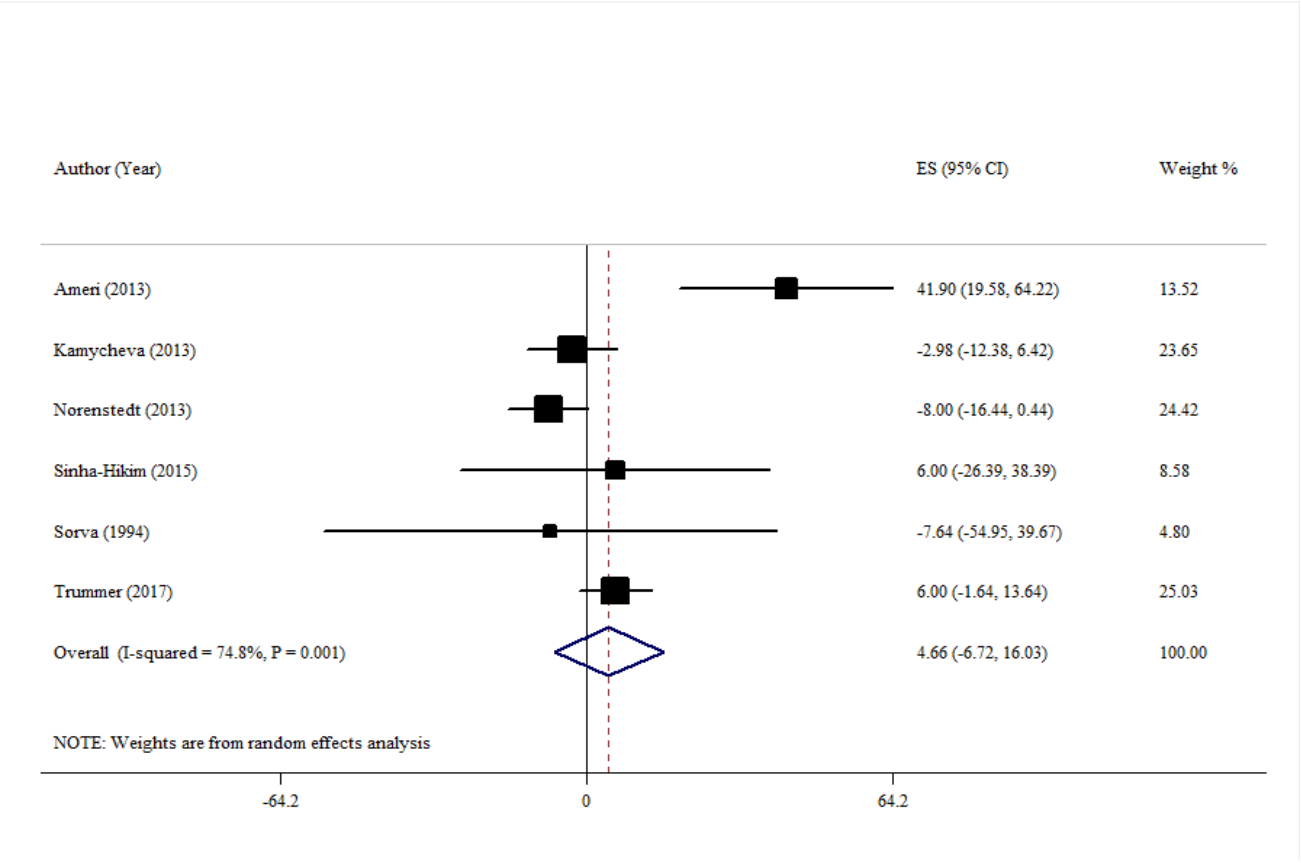

Figure 2: Forest plot of randomized controlled clinical trials (RCTs) illustrating weighted mean difference in serum levels of IGF-1 change (ng/ml) between the vitamin D supplementation and control groups for all eligible studies. Analysis was conducted using random model effect.