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The effect of vitamin D supplementation on glycaemic control in patients with Type 2 Diabetes Mellitus: a systematic review and meta-analysis

Running title: 'Vitamin D & type 2 diabetes, a systematic review'

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Abstract

Objective Epidemiologic studies suggest that vitamin D status plays a role in glycaemic control in patients with type 2 diabetes. However, intervention studies yielded inconsistent results. The aim of this study is to systematically review the effect of vitamin D supplementation on glycaemic control in patients with type 2 diabetes

Methods Systematic review and meta-analysis. We searched Medline, Embase and the Cochrane Library for RCTs examining the effect of vitamin D supplementation on glycaemic control in patients with type 2 diabetes. A random-effect model meta-analysis was performed to obtain a summarized outcome of vitamin D supplementation on HbA_{1c}, fasting glucose and homeostatic model assessment – insulin resistance (HOMA-IR).

Results Twenty-three RCTs were included in this systematic review representing a total of 1797 patients with type 2 diabetes. Mean change in serum 25-hydroxyvitamin D varied from 1.8 ± 10.2 nmol/l to 80.1 ± 54.0 nmol/l. Nineteen studies included HbA_{1c} as outcome variable. Combining these studies no significant effect in change of HbA_{1c} was seen after vitamin D intervention compared to placebo. A significant effect of vitamin D supplementation was seen on fasting glucose in a subgroup of studies (n=4) with a mean baseline $HbA_{1c} \geq 8\%$ (64 mmol/mol) (standardized difference in means: 0.36; 95% CI: 0.12 to 0.61, p = 0.003)

Conclusions Current evidence of RCTs shows no evidence to support short-term vitamin D supplementation in a heterogeneous population with type 2 diabetes. However, in patients with poorly controlled diabetes a favourable effect of vitamin D is seen on fasting glucose.

Introduction

Vitamin D is a key factor for the maintenance of calcium and bone homeostasis. Over the past decade, vitamin D has attracted substantial interest towards extra-skeletal roles in various disease conditions, including diabetes mellitus (1). This interest has arisen due to the identification that most cells, including the pancreatic beta-cells, contain the vitamin D receptor (VDR). Most of these cells also have the capability to produce the biologically active form of vitamin D: 1,25-dihydroxyvitamin D for paracrine functions (1-3). Furthermore, vitamin D is known to have immuno-modulatory and anti-inflammatory effects, which could improve peripheral insulin resistance by altering low-grade chronic inflammation that has been implicated in insulin resistance in type 2 diabetes mellitus (3-5).

Observational studies have demonstrated a link between vitamin D deficiency and the onset of and progression of type 2 diabetes (6-9). Furthermore low vitamin D status is associated with future macrovascular events in patients with type 2 diabetes mellitus (10). This association may be the result of the link between vitamin D status and renin-angiotensin system (11), endothelial function (12), blood pressure (13), or chronic inflammation (4).

A recent meta-analysis performed in 2012 by George et al. (14) demonstrated a weak positive effect of vitamin D supplementation on fasting glucose and insulin resistance in patients with type 2 diabetes mellitus. However, overall the authors concluded that there was insufficient evidence of a beneficial effect to recommend vitamin D supplementation as a means of improving glycaemic control in patients with type 2 diabetes, impaired fasting glucose or normal glucose tolerance. Inconsistency in these results may be due to the different study populations (normal glucose tolerance, impaired glucose tolerance and type 2 diabetes), small sample sizes, and different dosage regimes of vitamin D supplementation. Additionally, in 2014 a meta-analysis published by Seida et al. which included RCTs among adults with normal glucose tolerance, prediabetes and/or type 2 diabetes, demonstrated no effect of

vitamin D supplementation on improving glucose homeostasis and preventing diabetes including only RCTs. Definitive conclusion could not be drawn in the context of heterogeneity, short-term follow-up duration and variable risk of bias (15).

Due to the ongoing increased interest in the effect of vitamin D on glycaemic control in type 2 diabetes, many more studies have been published since these meta-analyses were performed. Taken together, it is still unclear whether vitamin D supplementation has a beneficial effect on glycaemic control in patients with type 2 diabetes mellitus. We present an up to date analysis of the effect of vitamin D supplementation on glycaemic indices (HbA_{1c}, insulin resistance and fasting glucose) in patients with type 2 diabetes mellitus.

Methods

Search strategy and selection criteria

A systematic literature search (MEDLINE, Embase and The Cochrane Library) was performed to identify articles from January, 1976, to 15 October 2015 that assessed the effect of vitamin D supplementation on glycaemic indices in patients with type 2 diabetes. The search terms included type 2 diabetes mellitus AND [vitamin D OR vitamin D deficiency OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol]. References of the retrieved articles were scanned for additional studies. The objective was to systematically review the evidence that vitamin D can improve glycaemic indices (HbA_{1c}, insulin resistance and fasting glucose) in patients with type 2 diabetes. One author (YK-P) performed an initial screening of titles and abstracts. Full-text articles of the selected titles were screened using the inclusion criteria described below. If there was a doubt to whether a particular article should be included, the author discussed the article with the last author (SS) until consensus was reached.

We included randomized controlled trials (RCT) in the following groups: vitamin D supplementation versus placebo, vitamin D supplementation and calcium supplementation

versus calcium alone and / or placebo. Additional inclusion criteria were: 1) the study population consisted of patients with type 2 diabetes; 2) supplementation of vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) for intervention; 3) HbA_{1c} or parameters of glycaemic control (fasting glucose, fasting insulin or homeostatic model assessment - insulin resistance [HOMA-IR]) had to be a primary or secondary outcome; 4) the authors report data of an original clinical study (i.e. no review, commentary, case reports, or editorial); 5) study performed in adults ≥ 18 years; 6) published in English. We excluded studies using 1,25 dihydroxyvitamin D and studies performed in patients other than type 2 diabetes mellitus, or patients on dialysis.

Quality assessment and data extraction

The quality of selected articles was assessed by two reviewers using a checklist from the Dutch Cochrane Collaboration (Fig 1) (16). The checklist consists of 11 criteria which has three answer options: yes (adequate information/approach); no (no adequate information/approach); or little information. Each criteria answered with yes scored one point, we considered a total score ≥ 9 points as a good quality study.

Data were extracted by one author (YK-P) and controlled by the last author (SS) using a self composed form including the following items of studies included: country, design, publication year, participants, therapy duration, type and dose of vitamin D supplementation, primary outcome, baseline and change in serum 25-hydroxy vitamin D (25(OH)D) and parameters of glycaemic control ($HbA_{1c,}$ fasting glucose, fasting insulin and homeostasis model of assessment – insulin resistance (HOMA-IR)). For studies lacking a reported standard deviation of change in outcome between baseline and follow-up, we derived standard deviation of change as the mean of the baseline and follow-up standard deviations for each treatment group. This method was used successfully in the meta-analysis from George et al. performed on this subject (14).

Statistical analysis

To obtain a summarized outcome of the effect of vitamin D supplementation on glycaemic control, we compared the mean change between baseline and follow-up of each variable of the intervention and control group. Studies in which the mean change and/or standard deviation was not reported or could not be derived, were excluded in the meta-analysis. If a study included more than two groups, we used the data of the group in which the highest dose of vitamin D supplementation was given for the meta-analysis compared to placebo. If studies compared both vitamin D and/or calcium supplementation versus placebo, the data of the group with solely vitamin D supplementation was used for the meta-analysis.

The results of the included studies were pooled and meta-analyses were carried out using random-effects models as some heterogeneity of outcome was expected. To compare the intervention and placebo group, the results are presented as between group standardized mean differences with 95% CI. Subgroup analyses were performed for studies with a baseline mean serum 25(OH)D < 50 nmol/l and < 30 nmol/l, and for studies having a mean baseline $HbA_{1c} \geq$ 8% (64 mmol/l) in the intervention group. We assessed statistical heterogeneity between studies with I^2 statistic (with 95% CIs). The I^2 is the proportion of total variation contributed by between-study variation. In general, I^2values greater than 60-70% indicate the presence of substantial heterogeneity (17). In the presence of heterogeneity between studies, we assessed potential publication bias using formal tests, being the funnel plot and Egger test (18). Meta-analyses were performed using comprehensive meta-analysis version 3.0 (http://www.meta-analysis.com). A p-value < 0.05 was considered statistically significant.

Results

Selected articles

The initial systematic search yielded 1489 articles. Of those, 328 were duplicates and 1074 articles were excluded based on abstract and title. The most common reasons for exclusion of these articles were no inclusion of patients with type 2 diabetes or no intervention with vitamin D. Eighty-seven articles were selected for full text review as shown in Fig. 2. Finally, 23 trials were selected for quality assessment and included in this systematic review.

Description of the studies

Twenty-three RCTs representing a total of 1797 patients with type 2 diabetes were included in this systematic review. The quality assessment of the studies resulted in 14 out of 23 studies having a good quality (appendix 1) (12,19-31). Table 1 represents the main characteristics and main outcomes of the included studies. All studies had a randomized controlled trial design of which 18 studies used a placebo for control (12,19,20,22-25,27,29-38), three studies compared vitamin D fortified yoghurt versus plain yoghurt (21,28,39), one study used oral calcium supplementation for control (26), and one study used vitamin C supplementation for control (40). Besides from two studies, which solely included post-menopausal women (21,33), all studies included both men and women. Mean age varied from 44 to 67 years (24,25). Mean HbA_{1c} varied from 6.2% (44 mmol/mol) (20) to 8.7% (71 mmol/mol) (28) in the intervention group. Six studies had a mean baseline $HbA_{1c} \geq 8\%$ (64 mmol/mol) in the intervention group (27,28,32,33,36,40). Different assays were used for measurement of serum 25(OH)D with most studies using an enzyme-immunoassay (12,20,21,23,24,26,27,29-37), three studies measures serum 25(OH)D using high-performance liquid chromatography (22,28,39), two studies used a radio-immunoassay method (25,38), one study used a competitive protein-binding assay (19), and one study did not report the method of measurement (40).

A wide variety was seen in mean baseline serum 25(OH)D in the intervention group, with the lowest value of 21.5 ± 23.7 nmol/l (34) and a highest value of 117.3 ± 86.7 nmol/l (35). Four

studies included only vitamin D deficient (serum 25(OH)D < 50 nmol/l) patients (12,23,26,27). Many different intervention regimes were used. The mean change in serum 25(OH)D between the intervention and control group is summarized for each study in Fig. 3. Except for two studies performed by Breslavsky (19) and Cavalcante (33), all studies observed a significant increase in serum 25(OH)D in the intervention group compared with the placebo group with an overall mean difference: 30.2 nmol/l; 95% CI: 23.1 to 37.3, p < 0.01). Five studies could not be included in this analysis due to missing data (20,29,31,38,40).

The effect on HbA_{1c}

Nineteen studies reported sufficient data for inclusion in the meta-analysis to measure the overall effect of vitamin D on HbA_{1c} (12,19-22,24-30,32,34-37,39,40). Four studies were excluded from this analysis by the following reasons: 1. no post-intervention HbA_{1c} of the control group (33); 2. glycaemic control was measured by hyperinsulinemic euglycemic clamp method (23); 3. no baseline HbA_{1c} was available in the intervention group (38), and 4. no standard deviations were reported (31). The total number of included patients was 1475 of whom 755 were included in the treatment group and 720 in the placebo group. One out of these 19 studies reported a significant reduction in HbA_{1c} after vitamin D intervention compared to placebo (39). In a study among 118 patients who were randomized to either vitamin D with or without calcium, or placebo, a significant decrease in HbA_{1c} was seen in the vitamin D plus calcium group versus placebo. However, this study failed to reach a significant reduction in HbA_{1c} in the group with solely vitamin D supplementation (29). A pilot RCT performed by Soric et al. (40) showed a trend towards a greater reduction in mean change of HbA_{1c} in the vitamin D group compared to the control group, however, this difference was not statistically significant. In a subgroup analysis among patients with an HbA_{1c} > 9.0%, a significantly greater reduction in HbA_{1c} was observed in the intervention group (mean change: - 1.4%; 95% CI: -2.4 to -0.4, p = 0.01) compared to placebo (40). In our

own study population, a significant effect of vitamin D supplementation on HbA_{1c} was seen in patients with a serum 25(OH)D level ≤ 30 nmol/l (n = 19, mean change: -0.34%; 95% CI: -0.65 to -0.04, p = 0.02) (24). Furthermore, Nasri et al. (37) reported a significant difference in HbA_{1c} between the intervention and control group only in male patients.

Based on a random-effect meta-analysis, comparing the mean change in HbA_{1c} from baseline between the intervention and placebo group, no overall effect was seen on HbA_{1c} after vitamin D intervention (standardized difference in means: 0.12; 95% CI: -0.03 to 0.26, p = 0.11) (Fig. 4a). Heterogeneity was present (I^2 = 42%, p = 0.03) However, there was no evidence for publication bias (Egger's test: p = 0.38).

Including only the studies with a mean baseline 25(OH)D < 50 nmol/l did not change the effect of vitamin D intervention on HbA_{1c} (standardized difference in means: 0.14; 95% CI: -0.07 to 0.35, p = 0.20) (Fig 4b) (12,19,22,23,25,27-30,32,34,38,39). In addition no difference was seen including only the studies with a mean baseline serum 25(OH)D < 30 nmol/l (standardized difference in means: 0.02; 95% CI: -0.18 to 0.23, p = 0.82) (Fig 4c). Including the studies with a baseline mean HbA_{1c} ≥ 8% (64 mmol/mol) a trend towards a positive effect of vitamin D supplementation was seen, but this was not significant (standardized difference in means: 0.14; 95% CI -0.05 to 0.33, p = 0.14) (Fig 4d). Furthermore, inclusion of the studies which were labelled as good quality did not alter the results (standardized difference in means: 0.01; 95% CI -0.12 to 0.14, p = 0.90) (Fig 5). Heterogeneity was not present (I^2 = 1%).

The effect on fasting glucose

Of the 23 studies that were included in the systematic review, 13 reported fasting glucose as primary or secondary outcome measure (19-24,26-28,32,35,36,39). Three studies reported a significant reduction of fasting glucose after vitamin D supplementation (21,28,39).

A pooled meta-analysis including 1180 patients (vitamin D: n = 608; controls: n = 572) comparing the mean change in fasting glucose between baseline and follow-up for both groups did not reveal an overall effect of vitamin D supplementation on fasting glucose (between group standardized mean difference: 0.09; 95% CI: -0.11 to 0.28, p = 0.39, I^2 = 60%) (Fig. 6a). No evidence for publication bias was found using a funnel plot and Egger's test (p = 0.97). Including only the good quality studies did not alter the effect on fasting glucose. A pooled meta-analysis with the inclusion of the studies with a mean baseline HbA_{1c} ≥ 8% (64 mmol/mol) shows a significant effect of vitamin D on fasting glucose (standardized difference in means: 0.36; 95% CI: 0.12 to 0.61, p = 0.003, I^2 = 0%) (Fig 6b).

The effect on insulin resistance

Thirteen studies reported data on insulin resistance of which twelve studies used the HOMA-IR to quantify insulin resistance (19-22,24-26,29,30,35,36,39), and one study measured insulin resistance through hyperinsulinemic euglycaemic clamp method (23). Two studies observed a significant reduction of insulin resistance after vitamin D supplementation (21,39), and one study found a negative effect of vitamin D supplementation on insulin resistance compared to placebo (35).

Twelve studies were compared in a random effects meta-analysis model, demonstrating no significant effect of vitamin D supplementation on insulin resistance compared to controls (between group standardized difference in means: 0.23; 95% CI: -0.06 to 0.53, p = 0.12; I^2 77%, p = 0.04) (Fig 7). No evidence for publication bias was found using a funnel plot and Egger's test (p = 0.26). Inclusion of the studies which were qualified as good did not alter the results. Only one study reported data of HOMA-IR with a baseline HbA_{1c} ≥ 8%. The study performed by Kampmann et al. (23) which measured insulin resistance by using the hyperinsulinemic euglycemic clamp method, which is the golden standard, did not find a positive effect of vitamin D on glycaemic control in 16 patients with type 2 diabetes.

241

242 **Discussion**

243 Our systematic review and meta-analysis examined the effect of vitamin D supplementation
244 on glycaemic indices in patients with type 2 diabetes mellitus. Combining all studies no effect
245 was seen of vitamin D supplementation on parameters of glycaemic control (i.e. HbA_{1c},
246 fasting glucose and HOMA-IR) in patients with type 2 diabetes. Including only studies with a
247 mean baseline serum 25(OH)D < 50 nmol/l or < 30 nmol/l did not change these results.
248 Including only the studies with a mean baseline $HbA_{1c} \geq 8\%$ (64 mmol/mol) revealed a
249 significant effect of vitamin D supplementation on fasting glucose.
250 The main challenge of this systematic review was the heterogeneity between the studies. To
251 level for this challenge we only included RCTs. However, still heterogeneity was present with
252 a wide variety of intervention schemes and follow-up duration used in the included studies,
253 which resulted in a varying increase in serum 25(OH)D as was shown in Figure 2. To resolve
254 the problem of heterogeneity we applied a quality assessment of all included studies.
255 Including only good quality studies did not alter the effect of vitamin D supplementation on
256 glycaemic indices.
257 Still no consensus has been reached in the optimal value of serum 25(OH)D and the best
258 supplementation regime. Nowadays vitamin D deficiency is commonly defined by a serum
259 25(OH)D less than 30 nmol/l. This threshold level has been confirmed by the Institute of
260 Medicine at the end of 2010 and the Endocrine Society Guideline (41,42). Optimal serum
261 25(OH)D is defined as a level above 50 nmol/l according to the Institute of Medicine and
262 above 75 nmol/l according to the Endocrine Society.
263 A possible explanation for the lack of effect found in most studies could be an
264 underrepresentation of vitamin D deficient patients. It is possible that vitamin D could only be
265 effective in vitamin D deficient patients, and especially in those with poor glycaemic control

(43,44). This hypothesis was confirmed in the study performed by Soric et al. (40) who showed a 1.4% decrease in HbA_{1c} in patients with a baseline HbA_{1c} level ≥ 9.0% after 12 weeks with a daily consumption of 2.000 IU vitamin D in contrast to patients with a HbA_{1c} < 9.0% where no effect on glycaemic control was seen after vitamin D treatment. Additionally, in our previous RCT among 275 patients with type 2 diabetes, in 19 patients with a serum 25(OH)D below 30 nmol/l a significant decrease in HbA_{1c} was seen after six months of vitamin D supplementation compared to placebo (24). Another important note is the wide range in follow-up duration between the studies. As HbA_{1c} is representing the glycosylated haemoglobin which has a life time around 100 days, a follow-up duration of more than three months is favourable.

Of interest is the possibility that vitamin D could only be beneficial in patients with normal glucose tolerance or impaired glucose tolerance. The pathogenesis of type 2 diabetes consists of a progressive insulin resistance, which is initially compensated by enhanced insulin secretion by the pancreatic beta-cells. At the time of onset of type 2 diabetes the beta-cell mass is reduced by 25-50% (45). The direct effect of vitamin D on the pancreatic beta-cell might be negligible at this time. In this line, our systematic review including only studies examining patients with type 2 diabetes is a limitation of this study.

Individual variability explained by vitamin D receptor polymorphisms may also play a role in the study results. Earlier research demonstrated an association between vitamin D receptor polymorphisms and the risk for type 2 diabetes, suggesting that timing of vitamin D supplementation is critical (46,47). In addition, a study performed by Wang et al. demonstrated that the vitamin D binding protein polymorphism, and thus vitamin D bioavailability, was moderately associated with increased susceptibility to type 2 diabetes in Asians, but not in Caucasians, suggesting that ethnicity might be a potential factor associated with heterogeneity (48) .

Another relevant note is the different vitamin D assays which were used in the included studies. Much discussion is going on about the comparability and accuracy of the different assays, which raises concerns (49). Most of the studies included in this review used an enzyme-immunoassay method for measurement of serum 25(OH)D, where the liquid chromatography-mass spectrometry (LC-MS) method is the golden standard.

The strength and limitations of our study needs to be mentioned. First, our initial search was performed by only one author, which may cause that eligible studies have not been included. However, our negative findings suggest that unpublished studies (which also tend to be negative) would be very unlikely to alter our conclusions. We found no evidence for publication bias from the funnel plots. For the meta-analysis we performed a quality assessment according to the checklist of the Dutch Cochrane Collaboration which has some limitations, especially when trying to decide on the relative importance of the different criteria (16). Another note is that we did not have access to all original data, which is the best method to perform a meta-analysis. A strength of our study is that we included only RCT's to assess the strength of evidence and limit the role of bias.

In conclusion, current evidence of RCTs shows no evidence to support short-term vitamin D supplementation in a heterogeneous population with type 2 diabetes. However, in patients with poorly controlled diabetes a favourable effect of vitamin D is seen on fasting glucose. Future research in this subgroup is highly of interest.

Declaration of interest

The authors declare that they have no competing interests

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316 **Author's contributions**

317 Each author contributed in a substantial way to the work described in the manuscript and its
318 preparation. S. Simsek initiated the systematic review. Y. Krul-Poel performed the systematic
319 search and data extraction, S. Simsek checked the search. Y. Krul-Poel and M. ter Wee
320 performed the statistical analyses. Y. Krul-Poel wrote the first version of the manuscript and
321 all authors revised the paper critically. Y. Krul-Poel was responsible for the figures. All the
322 authors were involved in the final approval of the version to be published.

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Fig. 1 Quality checklists randomized controlled trials (RCTs)

Fig. 2 Flow chart of literature search

Fig. 3 Mean change from baseline in serum 25(OH)D (nmol/l) between intervention and control

Fig. 4 Meta-analysis of effects on HbA_{1c} in all studies (a) and in studies with a baseline mean serum 25(OH)D < 50 nmol/l (b) or < 30 nmol/l (c), and mean baseline $HbA_{1c} \geq 8\%$ (d).

Fig. 5 Meta-analysis of effects on HbA_{1c} in studies labelled as good quality

Fig. 6 Meta-analysis of effects on fasting glucose in all studies (a) and in studies with a baseline mean $HbA_{1c} \geq 8\%$ (b)

Fig. 7 Meta-analysis of effects on HOMA-IR

Table 1. Summary of the intervention studies included in this systematic review

Name (year), ref	Location	Cohort T2DM (n)	Intervention	Control	Duration	Primary outcome	25(OH)D nmol/l before & after treatment*	Baseline Hba1c (%)*	Main results
Al-Zahrani (2014), (32)	Saudi Arabia	183, 25(OH)D < 75 nmol/l	Vitamin D_3 45000 IU/week	Placebo	3 m	Metabolic parameters	25.3 ± 15.8 to 82.8 ± 31.7	8.5 ± 1.6	↓ diastolic blood pressure = $HbA_{1c,}$ fasting glucose, lipid profile
Breslavsky (2013), (19)	Israël	47	Vitamin D_3 1000 IU/day	Placebo	12 m	Metabolic parameters	29.5 ± 27.2 to 43.9 ± 28.7	7.3 ± 1.1	= $HbA_{1c,}$ fasting glucose, insulin, HOMA-IR, lipid profile
Cavalcante (2015), (33)	Brazil	38 post-menopausal women, 25(OH)D < 75 nmol/l,	Vitamin D_3 6600 IU/week	Placebo	3 m	Metabolic parameters and muscle strength	55.5 ± 9.9 to 57.4 ± 10.5	8.2 ± 2.1	↑ handgrip strength = $HbA_{1c,}$ fasting glucose, insulin, lipid profile
Elkassaby (2014), (20)	Australia	50 T2DM duration < 1 year	Vitamin D_3 10000 IU/day for 2 weeks followed by 6000 IU/day for 6 months	Placebo	6 m	Change in C-peptide	59 (42 – 75) to 128 (111 – 146)	6.2 (6.0 – 6.6)	= C-peptide = $HbA_{1c,}$ fasting glucose, insulin, HOMA-IR
Ghavamzadeh (2013), (34)	Iran	51, non insulin	Vitamin D_3 400 IU/day	Placebo	14 w	HbA_{1c}, TNF-α, leptin	21.5 ± 23.7 to 46.4 ± 35.1	6.8 ± 0.4	= HbA_{1c} ↑ serum leptin ↓ TNF-α
Heshmat (2012), (35)	Iran	42, non insulin	Vitamin D_3 300.000 IU single dose	Placebo	3 m	Glycaemic parameters	117.3 ± 86.7 to 173.2 ± nr	6.5 ± 0.9	= HbA_{1c} ↑ HOMA-IR, fasting glucose
Jafari (2015), (21)	Iran	59 post-menopausal women, non insulin	Vitamin D_3 fortified yoghurt (2000 IU/day)	Plain yoghurt	12 w	Metabolic parameters	62.2 ± 24.6 to 86.8 ± 26.7	7.2 ± 1.3	= HbA_{1c} ↓ fasting glucose, insulin, HOMA-IR, lipid profile
Jehle (2014), (22)	Switzerland	55 T2DM duration > 10 years	Vitamin D_3 300000 IU single dose i.m.	Placebo	6 m	Change in HbA_{1c}	36.0 ± 18.1 to 84.9 ± 16.0	7.0 ± 1.1	↓ HOMA-IR = fasting insulin and glucose Significantly less increase in HbA_{1c} in the intervention group
Jorde (2009), (36)	Norwegian	36, insulin treatment	Vitamin D_3 40000 IU/week	Placebo	6 m	Glycaemic parameters	60.0 ± 14.0 to 118.3 ± nr	8.0 ± 1.3	= $HbA_{1c,}$ HOMA-IR, lipid levels
Kampmann (2014), (23)	Denmark	16, 25(OH)D < 50 nmol/l	Vitamin D_3 11200 IU/day for 2 weeks followed by 5600 IU/day for 10 weeks	Placebo	12 w	Glycaemic parameters†	31.0 ± 13.6 to 104.9 ± 53.7	nr	= insulin sensitivity, $HbA_{1c,}$ lipid profile, 24h blood pressure
Krul-Poel (2015), (24)	Netherlands	261, non insulin	Vitamin D_3 50000 IU/month	Placebo	6 m	HbA_{1c}	60.6 ± 23.3 to 101.4 ± 27.6	6.8 ± 0.5	= HbA_{1c}, HOMA-IR, lipid levels ↓ HbA_{1c} (subgroup: 25(OH)D ≤ 30 nmol/l)
Nasri (2013), (37)	Iran	60	Vitamin D_3 50000 IU/week	Placebo	12 w	Glycaemic parameters	83.9 ± 52.0 to 164.0 ± 57.0	7.7 ± 0.4	↓ HbA_{1c} in male subjects
Nikooyeh	Iran	90	1. Vitamin D_3 fortified	Plain	12 w	Metabolic	44.4 ± 28.7 to	7.4 ± 1.8	↓ $HbA_{1c,}$ HOMA-IR, fasting

(2011), (39)			yoghurt (1000 IU/day) 2. Vitamin D_3 + Ca fortified yoghurt (1000 IU / 500 mg/day)	yoghurt		parameters	77.7 ± 28.6		glucose and insulin, BMI = lipid levels
Parekh (2010), (25)	India	28, non insulin	Vitamin D_3 300000 IU single dose i.m.	Placebo	4 w	Glycaemic parameters; OGTT	37.2 ± 16.9 to 103.8 ± 30.5	7.6 ± 0.6	= $HbA_{1c,}$ HOMA-IR, fasting glucose, insulin
Ryu (2013), (26)	Korea	158, non insulin, 5(OH)D < 50 nmol/l	Vitamin D_3 1000 IU/day + Ca 100mg bid	Ca 100mg bid	24 w	Glycaemic parameters	27.0 ± 12.7 to 75.4 ± 27.0	7.3 ± 0.6	= $HbA_{1c,}$ HOMA-IR
Sadiya (2014), (27)	United Arab Emirates	8,7 25(OH)D < 50 nmol/l, BMI > 30	Vitamin D_3 6000 IU/day for 3 months followed by 3000 IU/day for 3 months	Placebo	6 m	Metabolic parameters	28.5 ± 9.5 to 62.3 ± 20.8	8.3 ± 1.3	= $HbA_{1c,}$ fasting glucose, lipid levels Subgroup 25(OH)D < 30nmol/l: no difference
Shab-Bidar (2011), (28)	Iran	100, non insulin	Vitamin D_3 fortified doogh (1000 IU/day + 340 mg Ca/day)	Plain doogh (340 mg Ca)	12 w	Metabolic parameters, endothelial biomarkers	38.5 ± 20.2 to 72.0 ± 23.5	8.7 ± 1.8	↓ fasting glucose, insulin, lipid profile, endothelial biomarkers = HbA_{1c}
Soric (2012), (40)	US	37	Vitamin D_3 1200 IU/day	Vitamin C 500mg /day	12 w	HbA_{1c}	nr	8.6 ± 1.2	= HbA_{1c} (total group) ↓ HbA_{1c} (subgroup: $HbA_{1c} \geq 9.0$ %)
Strobel (2013), (38)	Germany	86, non insulin	Vigantol oil (vitamin D_3 1904 IU/day)	Placebo	6 m / 12m	Glycaemic parameters	30.2 ± nr to 87.4 ± nr	nr	= $HbA_{1c,}$ HOMA-IR, fasting insulin and glucose
Sugden (2008), (12)	UK	34, 25(OH)D < 50 nmol/l	Vitamin D_3 100000 IU single dose	Placebo	8 w	Endothelial function	40.2 ± 10.3 to 63.1 ± nr	7.5 ± 1.6	↑ FMD brachial artery = HbA_{1c}
Tabesh (2014), (29)	Iran	118, 25(OH)D < 75 nmol/l	1. Vitamin D_3 50000 IU /week 2. Ca 1000mg/day 3. Vitamin D_3 50000 IU /week + Ca 1000 mg/day	Placebo	8 w	Metabolic parameters	28.0 ± 13.9 to nr	6.6 ± 0.8	↓ $HbA_{1c,}$ HOMA-IR, fasting glucose and insulin, LDL-cholesterol in Calcium + Vitamin D group. No change in the vitamin D group
Witham (2010), (30)	UK	61	Vitamin D_3 single dose: 1. 100.000 IU 2. 200.000 IU	Placebo	16 w	Metabolic parameters	48.0 ± 21.0 to 76.0 ± 30.0	6.9 ± 0.8	= HbA_{1c}, HOMA-IR, lipid levels
Yiu (2013), (31)	China	100, 25(OH)D < 75 nmol/l	Vitamin D_3 5000 IU/day	Placebo	12 w	Endothelial function	52.7 ± 11.0 to 146.3 ± nr	7.4 (6.8 – 8.5)	= FMD, HbA_{1c}, lipid levels

25(OH)D, 25-hydroxy vitamin D; BMI, body mass index; Ca, calcium; FMD, flow-mediated dilatation; HOMA-IR, homeostatic model assessment – insulin resistance; nr, not reported; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

*Baseline values of the intervention groups.

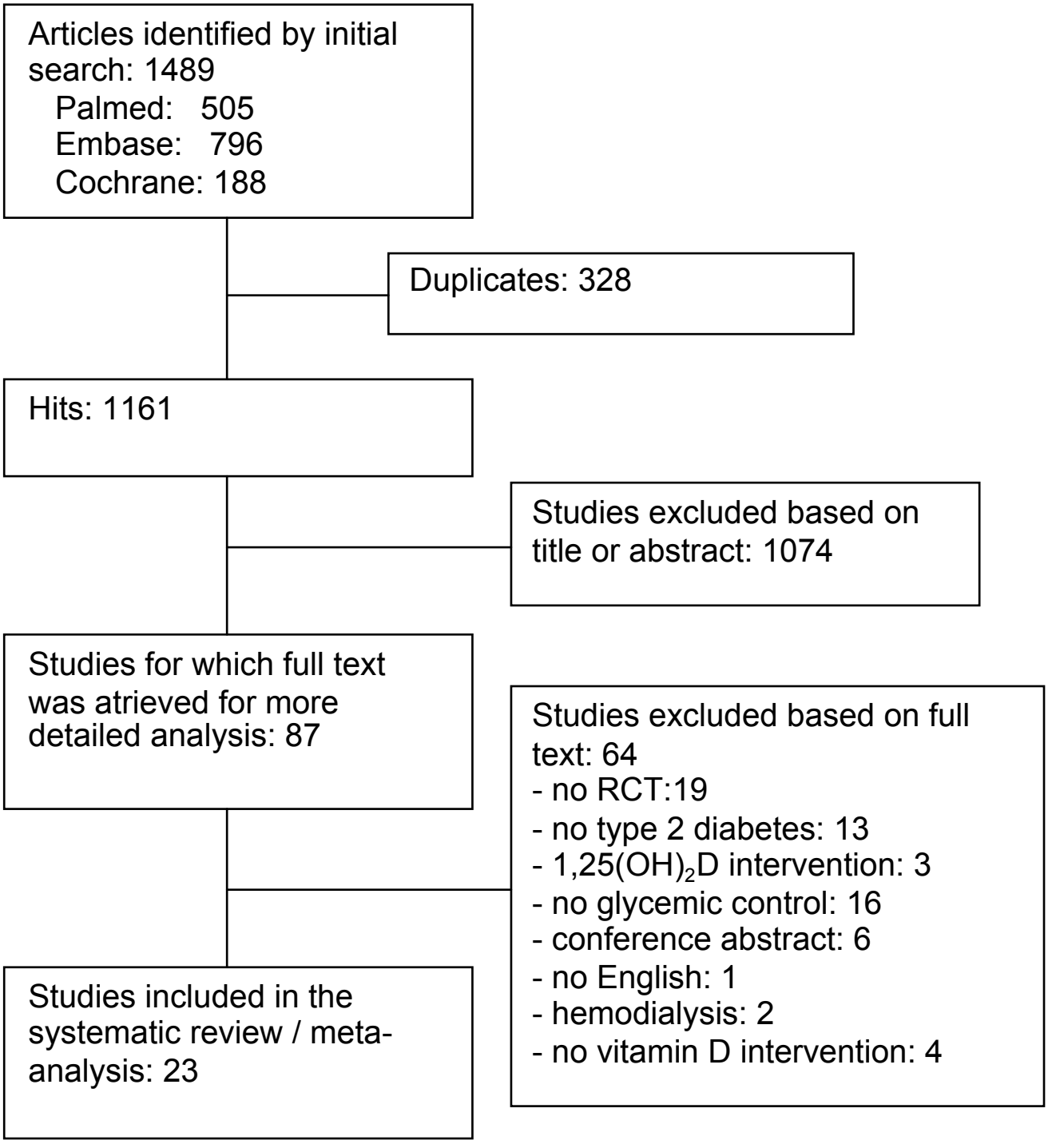
↑ = increasement

↓ = decreasement

† hyperinsulinemic euglycaemic clamp method

Quality assessment RCTs studies

a. Was assigning of the intervention done by randomisation?
b. The person who includes patients should not know the randomisation sequence? Was that the case?
c. Were patients blinded for the treatment?
d. Were treating physicians blinded for the treatment?
e. Were effect assessors blinded for the treatment?
f. Were the groups similar at baseline? Extra answer option: a) no, but corrected for or b) no and not corrected for.
g. Is a complete follow-up period available for a sufficient proportion of the included patients? If the answer is no: is selective loss to follow-up appropriately accounted for?
h. Were al included patients analysed in the group were they were randomised in (intention to treat population)?
i. Were the groups equally treated, apart from the intervention?
j. Is selective publication of results sufficiently ruled out?
k. Is adverse influence of sponsors sufficiently ruled out?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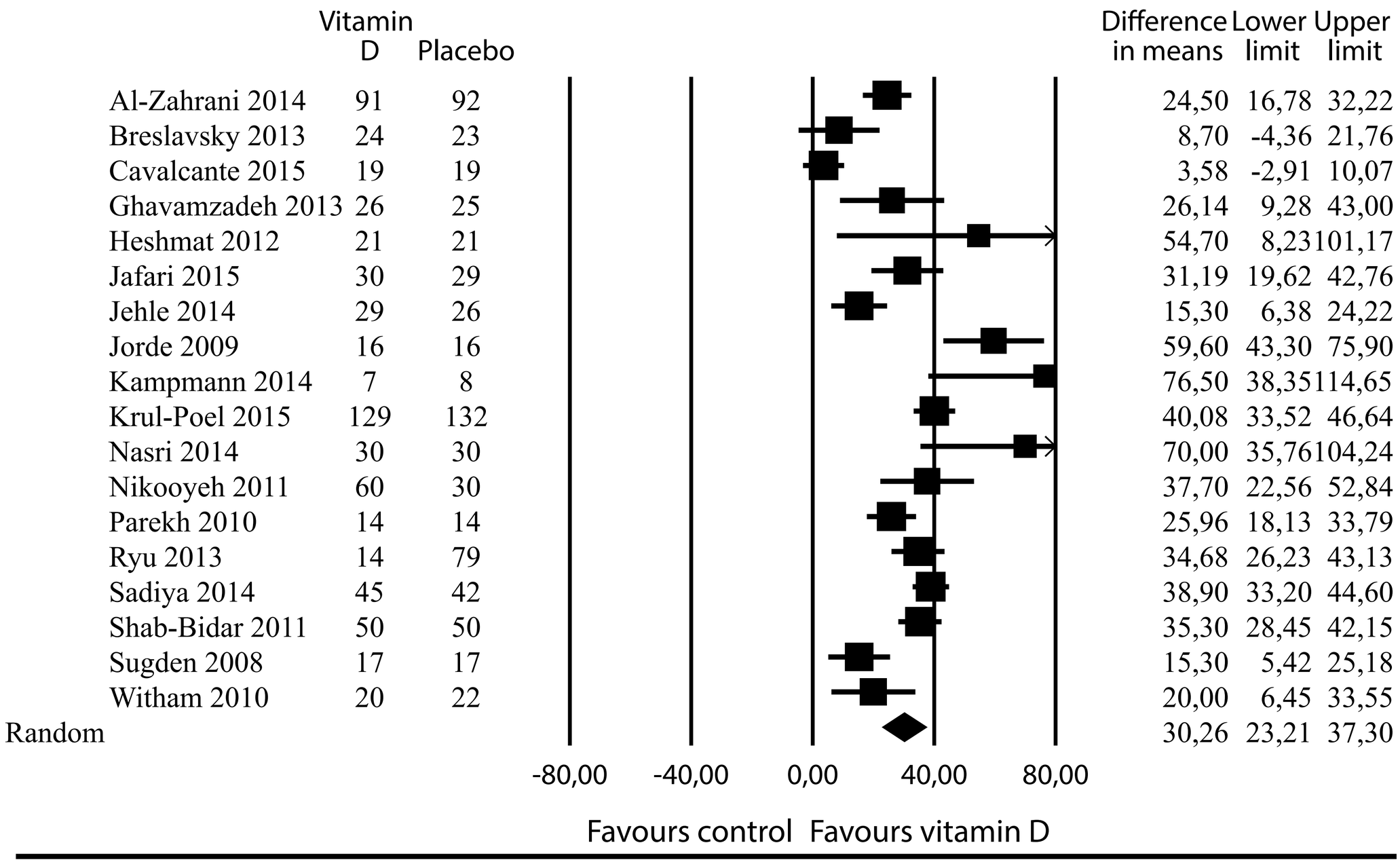
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Cavalcante 2015 19 19 3,58 -2,91 10,07
Ghavamzadeh 2013 26 25 26,14 9,28 43,00
Heshmat 2012 21 21 54,70 8,23 101,17
Jafari 2015 30 29 31,19 19,62 42,76
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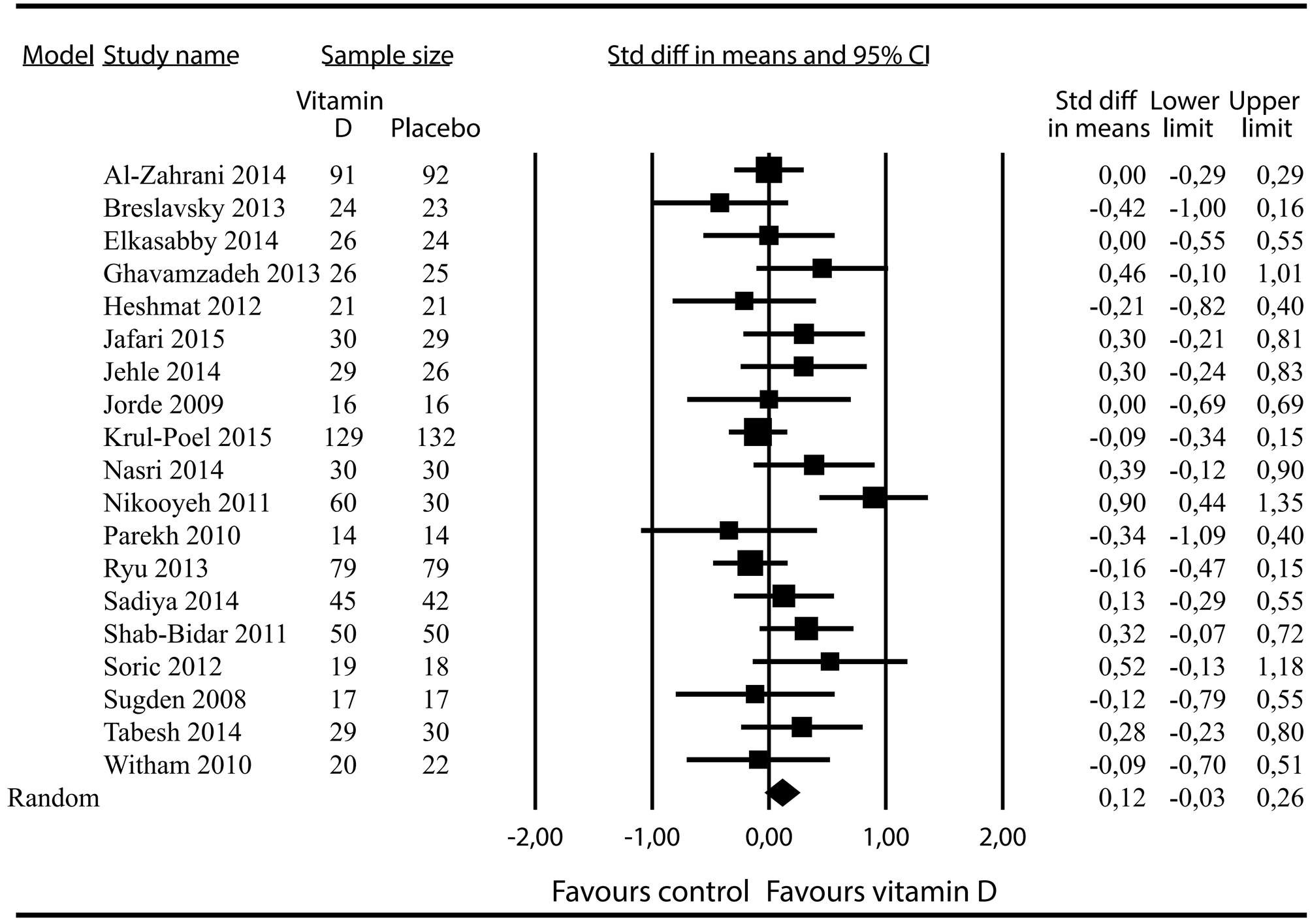
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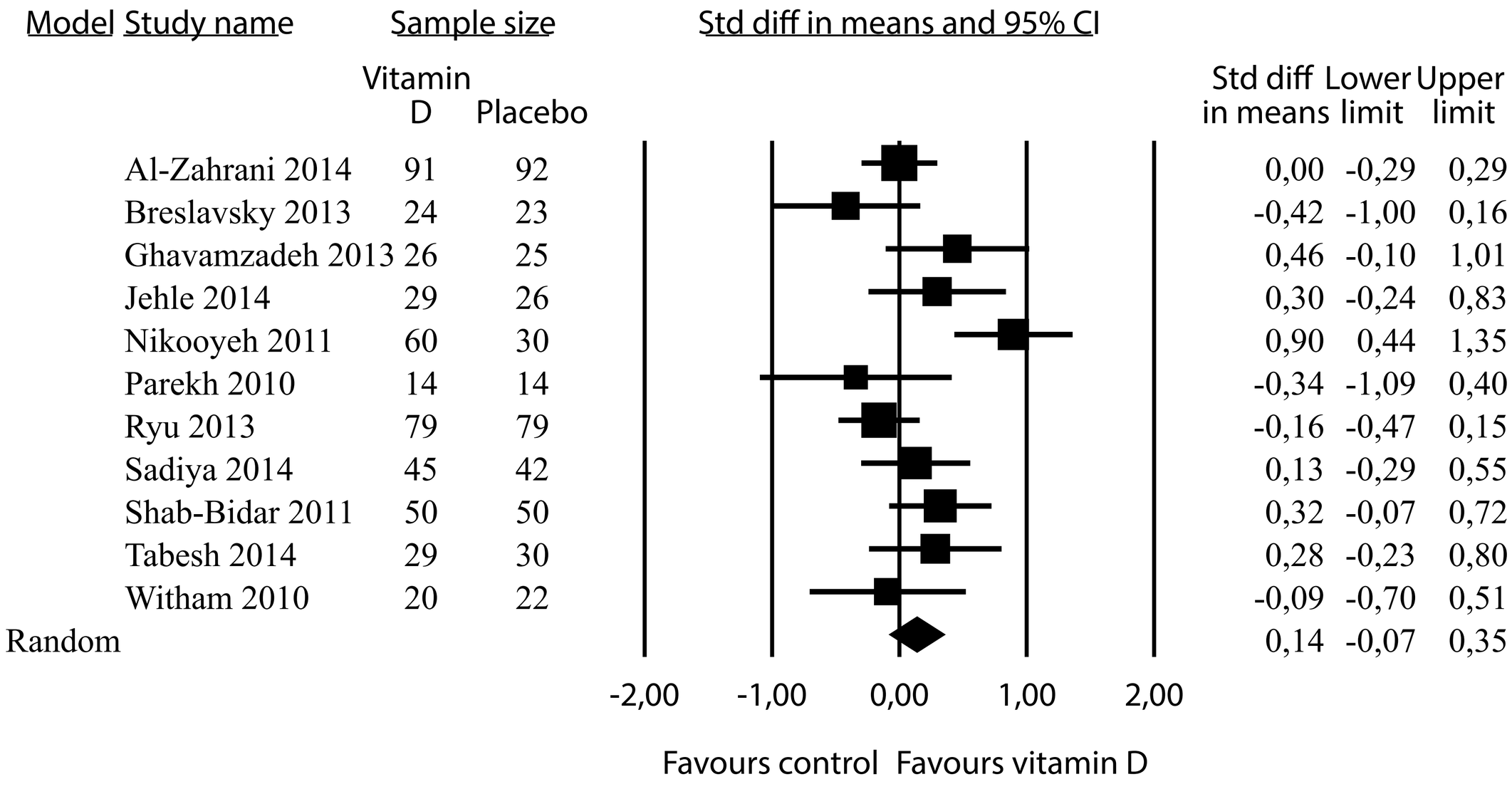
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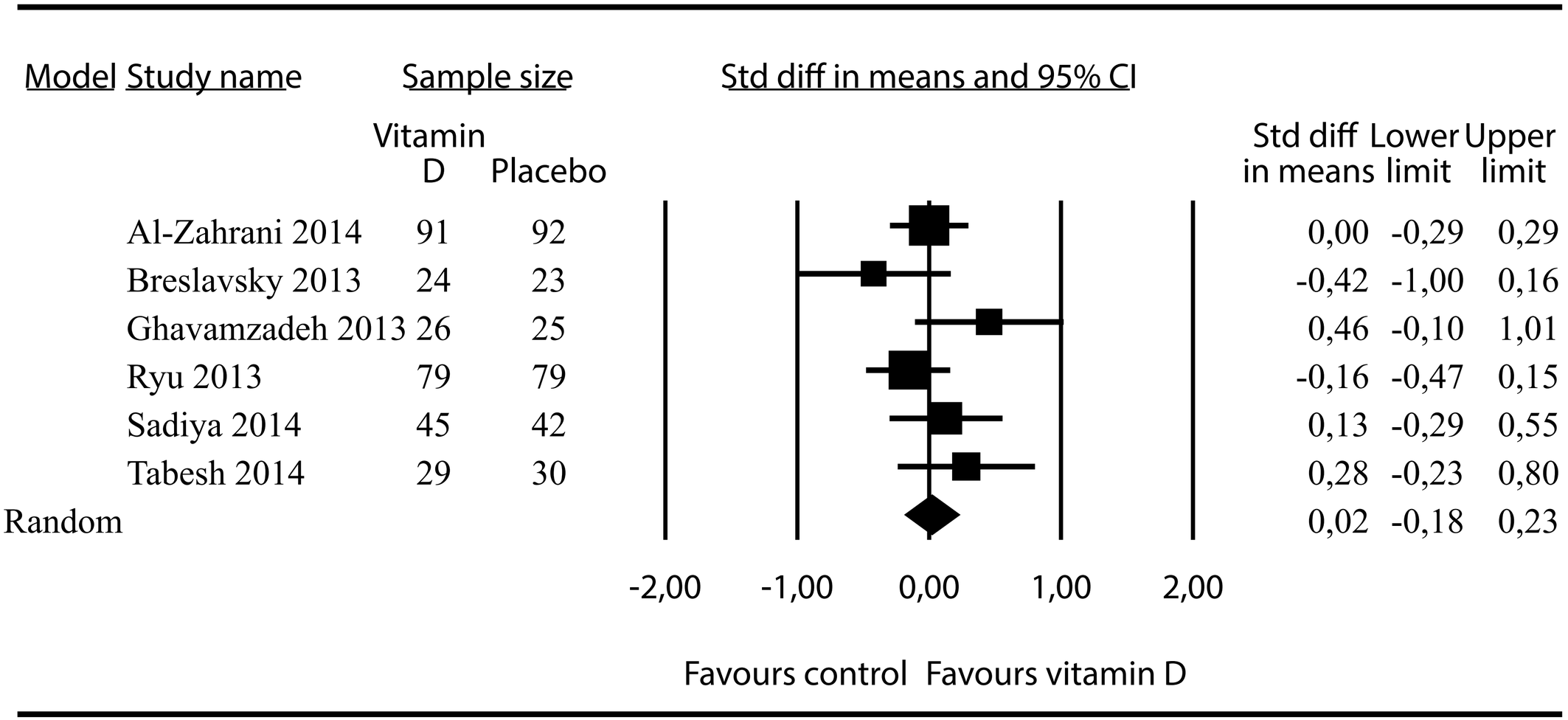
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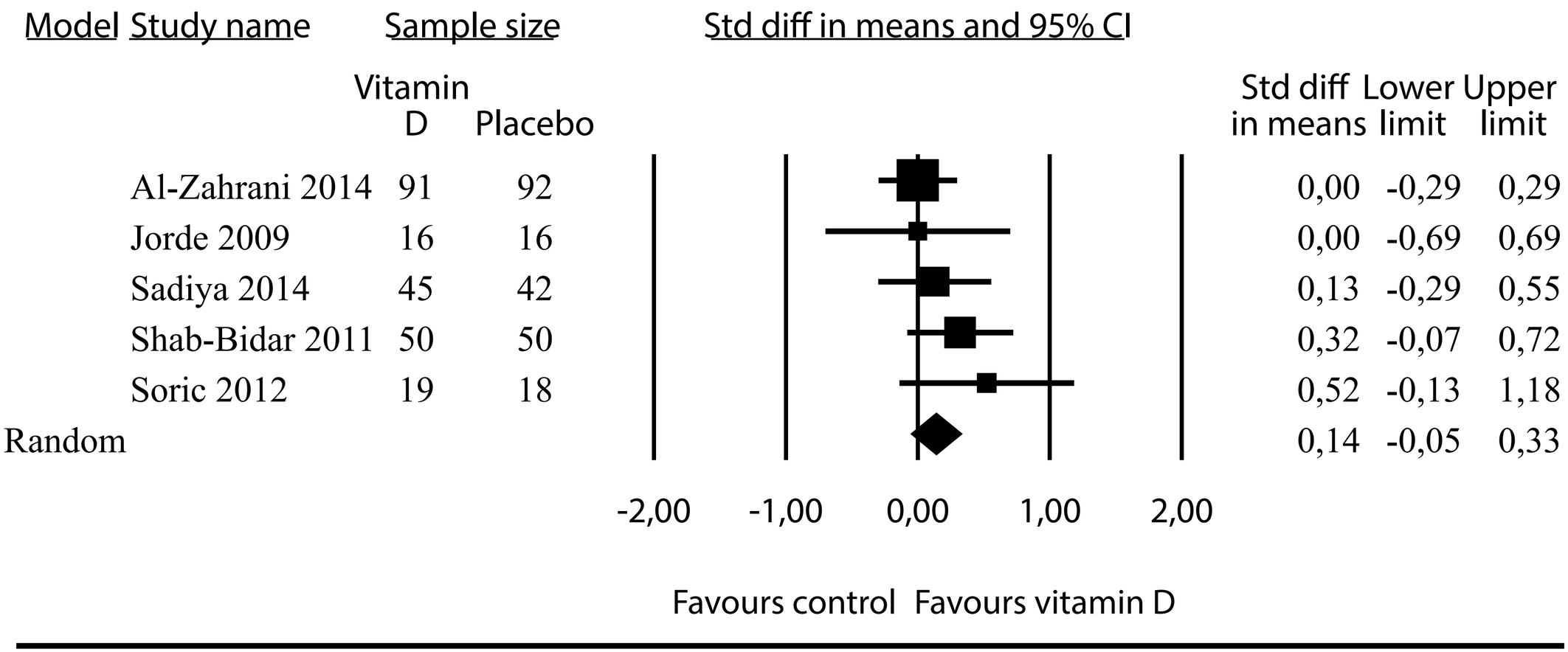
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Favours control
Favours vitamin D

Model	Study name	Sample size: Vitamin D	Sample size: Placebo	Std diff in means	Lower limit	Upper limit
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	Elkasabby 2014	26	24	0,00	-0,55	0,55
	Jafari 2015	30	29	0,30	-0,21	0,81
	Jehle 2014	29	26	0,30	-0,24	0,83
	Krul-Poel 2015	129	132	-0,09	-0,34	0,15
	Parekh 2010	14	14	-0,34	-1,09	0,40
	Ryu 2013	79	79	-0,16	-0,47	0,15
	Sadiya 2014	45	42	0,13	-0,29	0,55
	Shab-Bidar 2011	50	50	0,32	-0,07	0,72
	Sugden 2008	17	17	-0,12	-0,79	0,55
	Tabesh 2014	29	30	0,28	-0,23	0,80
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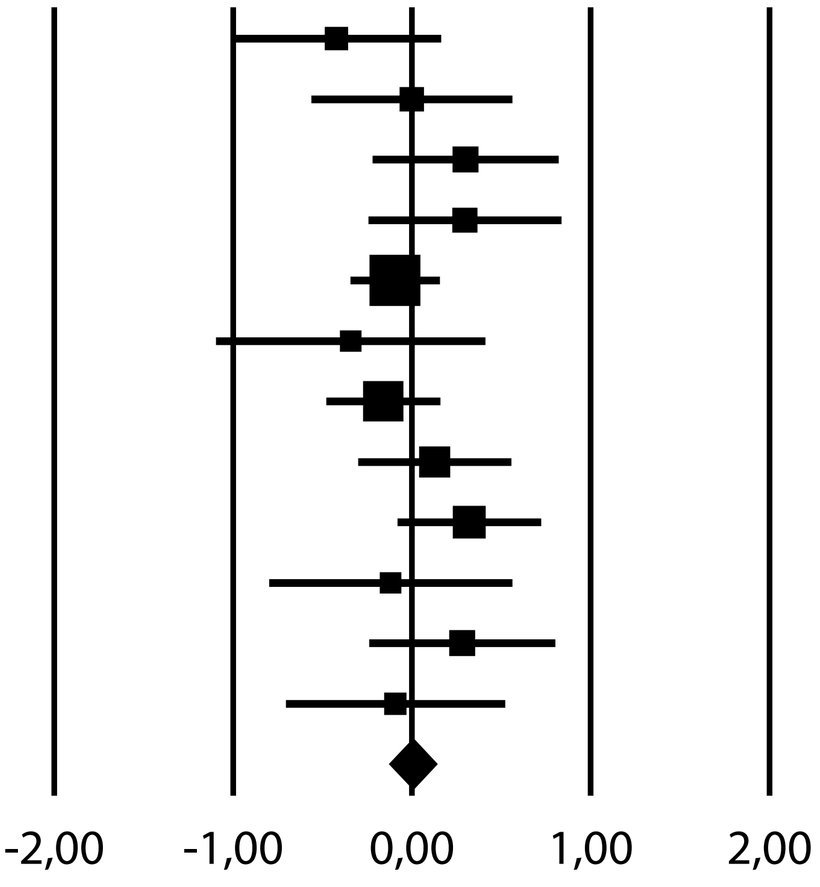

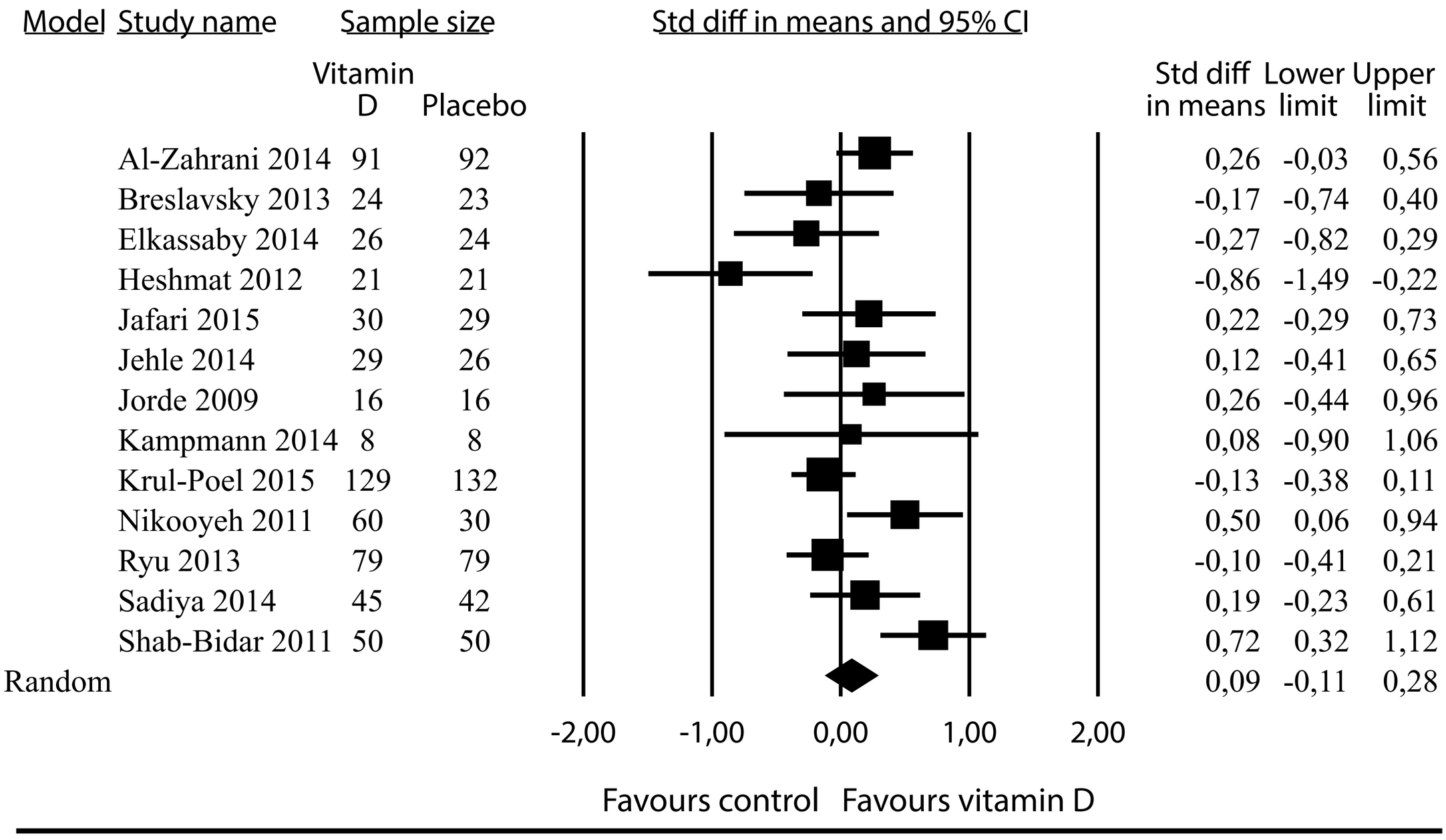
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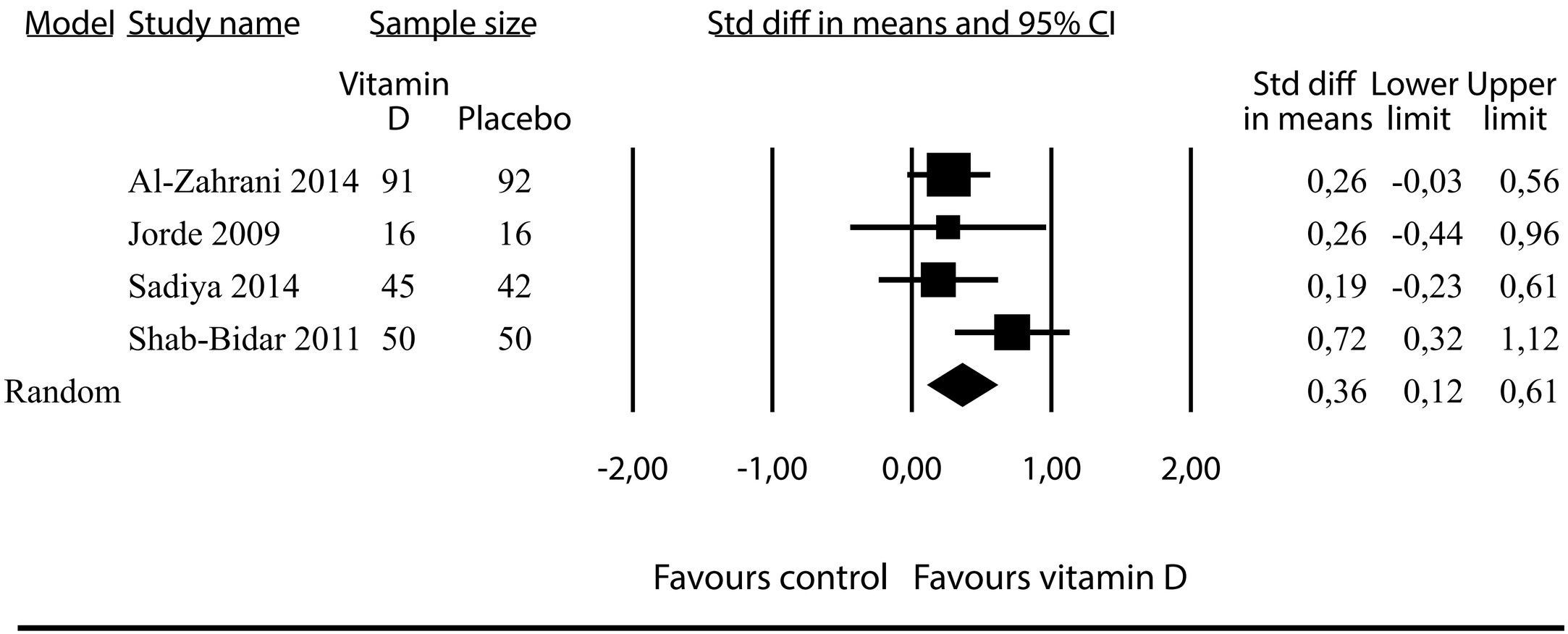
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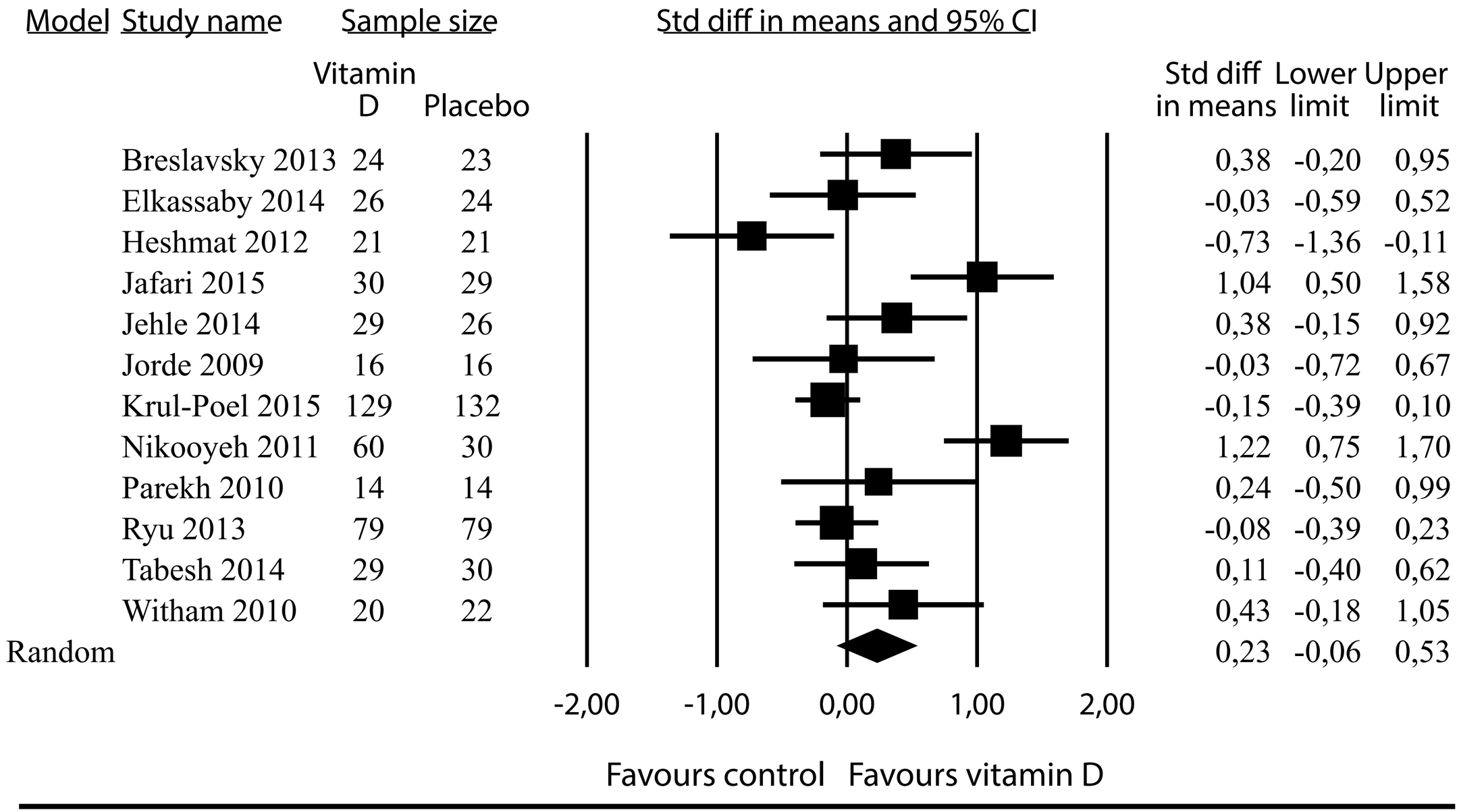
Favours control
Favours vitamin D


Model
Study name
Sample size
Vitamin D
Placebo
Std diff in means and 95% CI
Std diff in means
Lower limit
Upper limit
Breslavsky 2013 24 23 0,38 -0,20 0,95
Elkassaby 2014 26 24 -0,03 -0,59 0,52
Heshmat 2012 21 21 -0,73 -1,36 -0,11
Jafari 2015 30 29 1,04 0,50 1,58
Jehle 2014 29 26 0,38 -0,15 0,92
Jorde 2009 16 16 -0,03 -0,72 0,67
Krul-Poel 2015 129 132 -0,15 -0,39 0,10
Nikooyeh 2011 60 30 1,22 0,75 1,70
Parekh 2010 14 14 0,24 -0,50 0,99
Ryu 2013 79 79 -0,08 -0,39 0,23
Tabesh 2014 29 30 0,11 -0,40 0,62
Witham 2010 20 22 0,43 -0,18 1,05
Random 0,23 -0,06 0,53
-2,00
-1,00
0,00
1,00
2,00
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