

# Effect of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D and Homeostatic Model of Insulin Resistance Levels in Healthy Pregnancy: A Systematic Review and Meta-Analysis

Seyedeh Maryam Sharafi<sup>1</sup>, PhD;  Maryam Yazdi<sup>2</sup>, PhD; Masoomeh Goodarzi-Khoigani<sup>2</sup>, PhD;  Roya Kelishadi<sup>3</sup>, PhD

<sup>1</sup>Environment Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran;

<sup>2</sup>Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran;

<sup>3</sup>Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

## Correspondence:

Masoomeh Goodarzi-Khoigani, PhD;  
Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Afarinesh Building, Hezar Jarib St., Postal code: 81746-73461, Isfahan, Iran  
Tel: +98 31 37925285

Fax: +98 31 37925282

Email: masoomeh\_goodarzi@nm.mui.ac.ir  
masoomeh.goodarzi.kh@gmail.com

Received: 06 May 2021

Revised: 16 August 2021

Accepted: 01 November 2021

## What's Known

- Vitamin D supplementation decreases fasting plasma glucose and insulin levels in prediabetes, but not in healthy pregnant women. It also reduces these levels in women with gestational diabetes mellitus and has a weak effect on attenuating insulin resistance in patients with type 2 diabetes or impaired glucose tolerance.

## What's New

- Vitamin D supplementation increased 25(OH)D and reduced the homeostatic model of insulin resistance (HOMA-IR) in non-diabetic pregnant women and had preventive effects.
- Vitamin D in high doses further reduced HOMA-IR, but did not affect 25(OH)D. Intervention duration was not significantly associated with the mean changes in HOMA-IR and 25(OH)D levels.

## Abstract

**Background:** Progressive insulin resistance is a physiological condition during pregnancy that can lead to gestational diabetes. Given the association between low blood vitamin D levels and insulin resistance, the present meta-analysis evaluated the effect of vitamin D supplementation on serum 25-hydroxyvitamin D (25[OH]D) and the homeostatic model of insulin resistance (HOMA-IR) levels in non-diabetic pregnant women.

**Methods:** A comprehensive literature search was conducted using electronic databases and gateways such as Cochrane Library, Medline, Google Scholar, Science Direct, Web of Sciences, Embase, and Scopus. Articles up to 2020 in both English and Persian were included in the study. The effect of vitamin D supplementation on 25(OH)D and HOMA-IR was determined based on the differences in mean changes from baseline to post-intervention. Weighted mean and 95% confidence intervals (CI) were pooled using a random-effects model. Data were analyzed using STATA software.

**Results:** Four studies, including six trials with 380 participants, reported that vitamin D supplementation increased 25(OH)D (mean change: 13.72, 95% CI: 7.28-20.17) and decreased HOMA-IR (mean change: 1.46, 95% CI: 0.56-2.37) levels compared with the placebo group. A high weekly dose of vitamin D further reduced HOMA-IR levels (adjusted  $R^2=77.99$ ,  $I^2$  residuals=80.49%,  $P=0.047$ ). There was no significant association between the dose of vitamin D and 25(OH)D ( $P=0.974$ ). Intervention duration was not associated with an increase in 25(OH)D ( $P=0.102$ ), nor with a decrease in HOMA-IR ( $P=0.623$ ).

**Conclusion:** Vitamin D supplementation increased 25(OH)D and decreased HOMA-IR levels in non-diabetic pregnant women. Vitamin D in high doses further reduced HOMA-IR, but did not affect 25(OH)D concentrations.

Please cite this article as: Sharafi SM, Yazdi M, Goodarzi-Khoigani M, Kelishadi R. Effect of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D and Homeostatic Model of Insulin Resistance Levels in Healthy Pregnancy: A Systematic Review and Meta-Analysis. *Iran J Med Sci.* 2023;48(1):4-12. doi: 10.30476/ijms.2021.90586.2166.

**Keywords** • Vitamin D • 25-hydroxyvitamin D • Insulin resistance • Pregnancy • Meta-analysis

## Introduction

Gestational insulin resistance during pregnancy is caused by the response of tissue cells to insulin reduction. This physiological

condition can lead to an increased response in B cells and hyperinsulinemia, both characteristics of gestational diabetes mellitus (GDM). The prevalence of GDM is on the rise due to an unhealthy lifestyle.<sup>1-3</sup> It has been shown that certain vitamin D receptors are expressed in B cells,<sup>4, 5</sup> and 1.25-dihydroxyvitamin D (1.25-[OH]<sub>2</sub>D) can regulate insulin secretion and activity.<sup>6, 7</sup> It is therefore recommended to adapt strategies to optimize vitamin D levels to improve glucose intolerance and impaired insulin secretion.<sup>8</sup> A previous study assessed the impact of different doses of vitamin D supplementation in non-diabetic pregnant women and showed that taking 50,000 IU of vitamin D every two weeks will significantly reduce insulin resistance.<sup>9</sup> Another study reported that the use of cholecalciferol as a dietary supplement improved insulin metabolism parameters in pregnant women.<sup>10</sup>

Several meta-analyses have been conducted to evaluate the effect of vitamin D supplementation on the homeostatic model of insulin resistance (HOMA-IR) index. These studies analyzed data from randomized controlled trials (RCTs) across different age groups and populations, excluding non-diabetic pregnant women. A meta-analysis reported no beneficial effect of vitamin D on insulin resistance and glycemic indices in prediabetes.<sup>11</sup> Another meta-analysis of RCTs in patients with type 2 diabetes showed that vitamin D supplementation improved HOMA-IR. While other systematic reviews and meta-analyses reported that vitamin D supplementation had no significant effect on fasting plasma glucose and insulin levels in GDM patients and did not improve HOMA-IR levels.<sup>12, 13</sup>

Overall, there are contradictory results on the effect of vitamin D supplementation on diabetes. To the best of our knowledge, no meta-analyses have been conducted in non-diabetic pregnant women, for whom it is important to prevent gestational diabetes due to insulin resistance. We, therefore, conducted a systematic review and meta-analysis of several RCTs to evaluate the effect of vitamin D supplementation, its average weekly dose, and intervention duration on 25-hydroxyvitamin D (25[OH]D) and HOMA-IR in non-diabetic pregnant women.

## Materials and Methods

### Search Strategy

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A comprehensive literature search was conducted using electronic databases and gateways such as Cochrane Library, Medline,

Google Scholar, Science Direct, Web of Sciences, Embase, and Scopus. Articles up to 2020 in both English and Persian were included in the study. The search was performed using keywords (“vitamin D supplementation” or “vitamin D\*”) AND (“insulin resistance” or “insulin”) AND (pregnan\* or gestat\*). The abstract and reference list of all articles from the initial search were reviewed for any additional articles. The present study was registered in PROSPERO (ID: CRD42021237175). EndNote software (version 8.0, Philadelphia, USA) was used to manage the search results.

### Inclusion and Exclusion Criteria

The PICOS (population, intervention, comparison, outcomes, study type) process was used for the RCTs. In total, 707 non-diabetic pregnant women in the first or second trimester using vitamin D supplements were compared to those using placebo or lower doses of vitamin D. The effects of vitamin D (D<sub>2</sub> or D<sub>3</sub>; in ng/mL or µg/L) on 25(OH)D and HOMA-IR were investigated without limitations in terms of dose and duration of intervention. Two separate analyses were performed, namely (i) comparing participants using vitamin D (n=191) with placebo (n=189), and (ii) comparing other participants using vitamin D (n=167) with those using lower doses of vitamin D (n=160). The exclusion criteria were articles with other study protocols, animal studies, overlapping articles, letters to editors, and trials evaluating vitamin D in combination with other supplements or medications.

### Data Extraction

Two researchers (M. G-KH and S.M. SH) independently extracted the following information from the selected articles: name of the first author, publication year, country, vitamin D type and dose, treatment duration, sample size, vitamin D concentration in the blood, and HOMA-IR (mean change from baseline to post-intervention levels). The results were then verified by the third author (M. Y) (table 1).

### Quality Assessment and Risk of Bias

The quality of the selected articles and the risk of bias in RCTs were evaluated according to the Cochrane criteria checklist (table 2). Initial evaluation was performed by one of the authors (M. G-KH) and verified by another (S.M. SH).

### Statistical Analysis

The data were analyzed using STATA software version 13.0 (Stata Corp LLC, College Station, TX, USA). The effect of interventions was determined based on the difference in mean

Table 1: Descriptive summary of included studies about the effect of vitamin D supplementation on serum 25-hydroxyvitamin D levels and homeostatic model of insulin resistance index

Study	Study characteristics					Intervention					Control				
	Country	Age (year)	Treatment duration (wk)	Control dose	Intervention dose	Number of participants	Post-intervention HOMA-IR	Change from baseline HOMA-IR	Post-intervention vit d	Change from baseline vit d	Number of participants	Change from baseline HOMA-IR	Post-intervention HOMA-IR	Post-intervention vit d	Change from baseline vit d
Soheilykhah et al. <sup>9</sup>	Iran	12-40	24	200 IU/day	50,000 IU/month	38	2.39±0.87	1.01±1.01	27.20±10.70	19.9±11.2	35	1.46±1.69	3.00±2.19	17.70±9.30	9.40±8.60
Asemi et al. <sup>14</sup>	Iran	18-40	9	200 IU/day	50,000 IU/2 wk	40	2.24±1.27	0.70±1.04	34.10±11.50	26.83±12.29	24	1.46±1.69	3.00±2.19	17.70±9.30	9.40±8.60
Corcoy et al. <sup>15</sup>	Seven European countries	>18	36	Placebo	400 IU/day	24	1.02±0.10	-0.34±0.19	13.30±1.10	3.70±1.60	59	0.60±0.46	1.84±0.44	3.70±1.60	-1.20±0.40
Karamali et al. <sup>10</sup>	Iran	18-40	12	Placebo	1,600 IU/day	67	3.37±1.70	-	122.90±38.80	-	65	-	3.60±1.56	84.50±39.80	-
Yap et al. <sup>16</sup>	Australia	>18	6	Placebo	1600 IU/day	75	3.07±1.26	-	-	-	30	-	3.07±1.63	-	-
Tamin et al. <sup>17</sup>	Jordan	29.39±3.9	20	Placebo	50,000 IU/2 wk	30	2.48±1.14	0.19±1.47	34.91±2.36	17.92±2.88	80	2.10±2.67	4.35±2.40	17.37±4.04	0.27±3.19
		29.77±4.01		Placebo	400 IU/day	78	1.00±0.96	-	36.00±11.00	-	12	-	0.80±1.19	24.00±9.00	-
		28.77±4.38		Placebo	10,000 IU/wk	11	2.72±2.22	-	39.95±8.90	-	22	-	4.89±4.95	29.00±5.62	-
				Placebo	20,000 IU/wk	21	2.04±1.15	-	34.67±4.89	-	26	-	6.78±9.99	25.81±5.07	-
				Placebo	50,000 IU/wk	26	2.05±1.35	-	23.20±3.95	-		-	6.72±6.87	18.06±3.82	-

-: No information available; vit d: Vitamin D; wk: Week; HOMA-IR: Homeostatic model of insulin resistance

change between the 25(OH)D and HOMA-IR levels. For those studies that did not report these scores, we estimated the mean change (with standard deviation) from baseline according to Cochrane guidelines. Data from the intention-to-treat (ITT) analysis were preferred over the data obtained from the modified-ITT or per-protocol analysis.<sup>18</sup> The inverse variance-weighted average method was used to determine the effect size of each study. The weighted mean and 95% confidence interval (CI) were pooled using a random-effects model. The I<sup>2</sup> test (percentage of the total variation across studies due to heterogeneity) was used to determine the heterogeneity between the studies. A subgroup analysis was performed for studies that included placebo and low-dose vitamin D supplements as the control group. A meta-regression analysis, using the “metareg” command in STATA software, was performed to assess the effect of the average-weekly dose of vitamin D and intervention duration on the mean change in 25(OH)D and HOMA-IR levels.<sup>19</sup> Publication bias was identified using the trim and filled method and Egger’s test. A two-tailed test was used to determine significance at the 5% level.

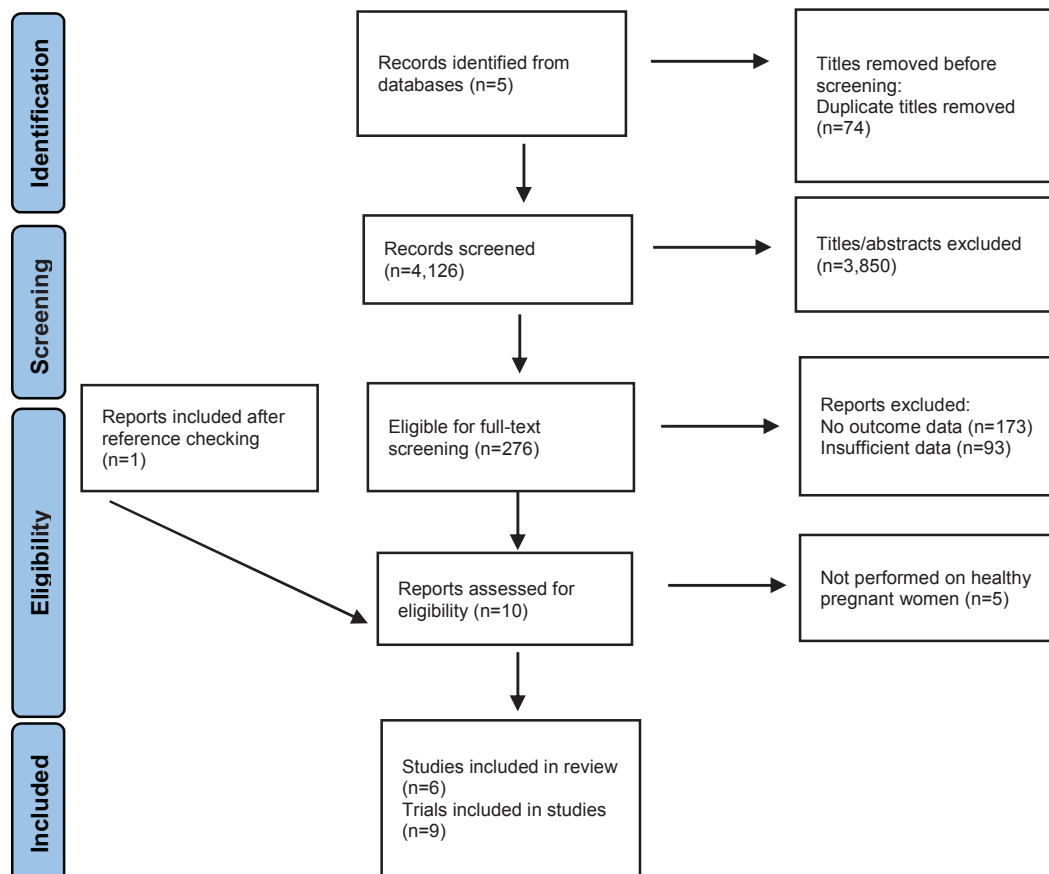
## Results

The PRISMA flow diagram of the study selection procedure is presented in figure 1. In total, six studies<sup>9, 10, 14-17</sup> comprising nine different trials examining the effect of vitamin D supplementation on 25(OH)D and HOMA-IR concentrations were included in our review (table 1). The selected RCTs included 707 non-diabetic pregnant women. Four of these studies<sup>10, 14, 15, 17</sup> compared participants using vitamin D (n=191) with those using placebo (n=189), of which one study included three trials.<sup>17</sup> The two other studies<sup>9, 16</sup> compared participants using vitamin D (n=167) with those using low-dose vitamin D (n=160), one of which included two trials in non-diabetic pregnant women in the first or second trimester.<sup>9</sup> In the included studies, trials were conducted in Iran,<sup>9, 10, 14</sup> seven European countries,<sup>15</sup> Australia,<sup>16</sup> and Jordan.<sup>17</sup> The sample size ranged from 48<sup>14</sup> to 179<sup>16</sup> pregnant women. Pre-pregnancy BMIs (Kg/m<sup>2</sup>) were ≤35,<sup>10, 16</sup> ≤30,<sup>9</sup> ≤29,<sup>14</sup> ≥29,<sup>15</sup> and ≥30.<sup>17</sup>

In a study by Soheilykhah and others, 120 pregnant women were enrolled and randomly assigned to three groups, namely group A (received 200 IU vitamin D daily), group B (50,000 IU monthly), and group C (50,000 IU every two weeks from <12 weeks of gestation until childbirth).<sup>9</sup> Two trials were conducted comparing groups B and C with control group A.

**Table 2:** The results of the risk bias assessment in included randomized controlled trials

Study	Sequence generation	Blinding of participants	Blinding of personnel	Blinding of outcomes	Similarity of baselines	Incomplete outcome data	Dropouts
Soheilykhah et al. <sup>9</sup>	Yes	No	No	No		Yes	No
Asemi et al. <sup>14</sup>	Yes	No	No	No	Yes	Yes	Yes
Corcoy et al. <sup>15</sup>	Yes	Unclear	Unclear	Unclear	Yes	Yes	Intention-to-treat
Karamali et al. <sup>10</sup>	Yes	Yes	Yes	No	Yes	Yes	No
Yap et al. <sup>16</sup>	Yes	Yes	Yes	No	Yes	Yes	Yes
Tamim et al. <sup>17</sup>	Yes	Yes	Yes	No	Yes	Yes	Yes



**Figure 1:** PRISMA flow diagram indicating the articles screening inclusion and exclusion process.

They reported that 50,000 IU of vitamin D every two weeks reduced insulin resistance. In a study by Asemi and others, pregnant women received 400 IU cholecalciferol per day (n=24) or placebo (n=24) for nine weeks. They reported a significant increase in vitamin D concentrations in the blood, while a descending trend in HOMA-IR levels was observed.<sup>14</sup> In another study, pregnant women with plasma concentrations  $\leq 20$  ng/mL received 50,000 IU vitamin D<sub>3</sub> daily (n=89) and compared with those receiving 400 IU daily (n=90) from 20 weeks of pregnancy until delivery.<sup>16</sup> It was reported that 25(OH)D increased significantly, however, 10% in the high-dose group and 34% in the low-dose group were still vitamin D deficient (25[OH]D  $\leq 20$  ng/mL,  $P < 0.001$ ). Moreover, HOMA-IR did not change after intervention.

A study by Karamali and others compared pregnant women who received 50,000 IU vitamin D every two weeks (n=30) or placebo (n=30) from 20 to 32 weeks of gestation and reported a significant increase in serum 25(OH)D and HOMA-IR levels.<sup>10</sup> Corcoy and others recruited women close to 15 weeks of pregnancy, and the participants received 1,600 IU of vitamin D<sub>3</sub> daily or placebo plus multivitamins. The results showed that serum 25(OH)D levels increased, and fasting plasma glucose decreased significantly in almost all participants with a pre-pregnancy BMI  $\geq 29$  Kg/m<sup>2</sup>, as well as vitamin D sufficiency at 35-37 weeks.<sup>15</sup> Tamim and others conducted three separate trials and investigated the effect of vitamin D on HOMA-IR reduction in three groups, namely mothers with normal serum 25(OH)D levels  $\geq 30$ -50 ng/mL (group 1), insufficient levels



21-29 ng/mL (group 2), and deficient levels  $\leq 20$  ng/mL (group 3).<sup>17</sup> They reported that serum 25(OH)D levels increased significantly in all groups, however, insulin resistance decreased significantly in groups 2 and 3.

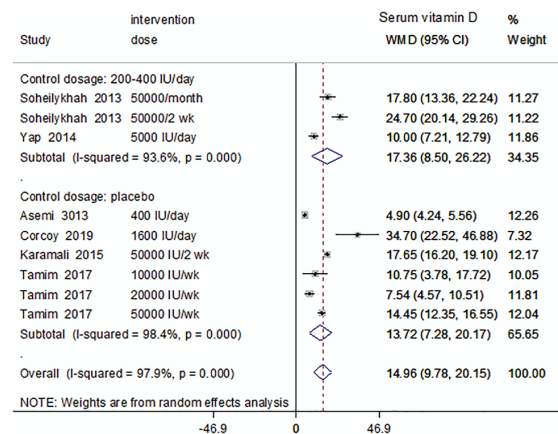
**Bias Assessment**

The risk of bias assessment in the included studies is shown in table 2. In all studies, the randomization method was used by a computer-generated random number list. In three trials, the allocation sequence was concealed from the researcher and participants until the completion of the main analysis (low risk of bias). However, one study did not provide any information about the allocation process and was thus classified as unclear risk of bias in our analysis.<sup>15</sup> The risk of bias was also assessed in terms of adequate blinding of participants and personnel, which criterion was met by all but one of the studies.<sup>15</sup> Blind outcome assessment was used in all included studies. In one study,<sup>14</sup> incomplete outcome data were reported stating that patients who did not complete the treatment regimen were included in the final analysis.

**The Outcome of Meta-analysis  
Vitamin D**

In a random-effects meta-analysis, the mean change of serum 25(OH)D concentrations in placebo and treatment groups was compared. The mean change from baseline was significantly higher in the vitamin D group than the placebo group (mean change: 13.72, 95% CI: 7.28-20.17). Analysis between the groups receiving vitamin D and low-dose vitamin D showed that the mean change from baseline in the group receiving vitamin D was higher (mean change: 17.36, 95% CI: 8.5-26.32).

There was evidence of heterogeneity between the included studies ( $I^2=98.4\%$ ,  $P<0001$ ) (figure 2). To investigate the source of heterogeneity, a meta-regression analysis was conducted between the average weekly dose of vitamin D and intervention duration (ranging from six to 28 weeks) in studies with placebo as the control group (table 3). The results showed no significant association between a high weekly dose of vitamin D ( $P=0.974$ ) and intervention duration ( $P=0.102$ )



**Figure 2:** Forest plot showing the effect of vitamin D supplementation on serum 25(OH)D levels. Effect sizes are expressed as the score of the mean change in the intervention and control groups.

with a stronger effect of vitamin D supplements (table 3).  $I^2$  residuals decreased to 96.0%.

**HOMA-IR Index**

In a random-effects meta-analysis, the mean change of HOMA-IR levels in the placebo and vitamin D groups were compared. The mean change from baseline was significantly higher in the vitamin D group than the placebo group (mean change: 1.46, 95% CI: 0.56-2.37). Analysis between the groups receiving vitamin D and low-dose vitamin D (200-400 IU/day) showed a reduction in HOMA-IR (mean change: 0.6, 95% CI: 15-1.06) in the vitamin D compared to the low-dose vitamin D group. This indicates that even a daily low-dose vitamin D supplementation can be as effective as a high dose once a month or every two weeks.

There was evidence of heterogeneity between the included studies ( $I^2=82.4\%$ ,  $P<0001$ ) (figure 3). To investigate the source of heterogeneity, a meta-regression analysis was conducted between the average weekly dose of vitamin D and intervention duration. The results showed a significant association between a high weekly dose of vitamin D and HOMA-IR reduction (adjusted  $R^2=77.99$ ,  $I^2$  residuals=80.49%,  $P=0.047$ ) (table 3 and figure 3). Intervention duration (ranging from six to 28 weeks) was not significantly associated with HOMA-IR reduction ( $P=0.623$ ).

**Table 3:** The results of meta-regression, using the restricted maximum likelihood method, on the association between the study-specific mean change of vitamin D supplementation dose and intervention duration

Outcome variable	Covariate variable	Coefficient	95% CI	SEM	T value	P value
Vitamin D	Average weekly dose	0.00001	-0.001, 0.001	0.0003	0.03	0.974
	Intervention duration (month)	0.81	-0.25, 1.87	0.38	2.11	0.102
HOMA-IR	Average weekly dose	-0.00009	-0.00017, -0.000002	0.00003	-2.85	0.047
	Intervention duration (month)	0.05	-0.19, 0.28	0.09	0.53	0.623

HOMA-IR: Homeostatic model of insulin resistance; SEM: Standard error of mean; CI: Confidence interval

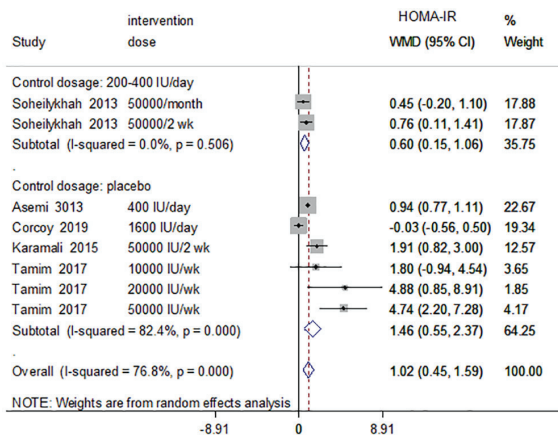


Figure 3: Forest plot showing the effect of vitamin D supplementation on HOMA-IR. Effect sizes are expressed as the score of the mean change in the intervention and control groups.

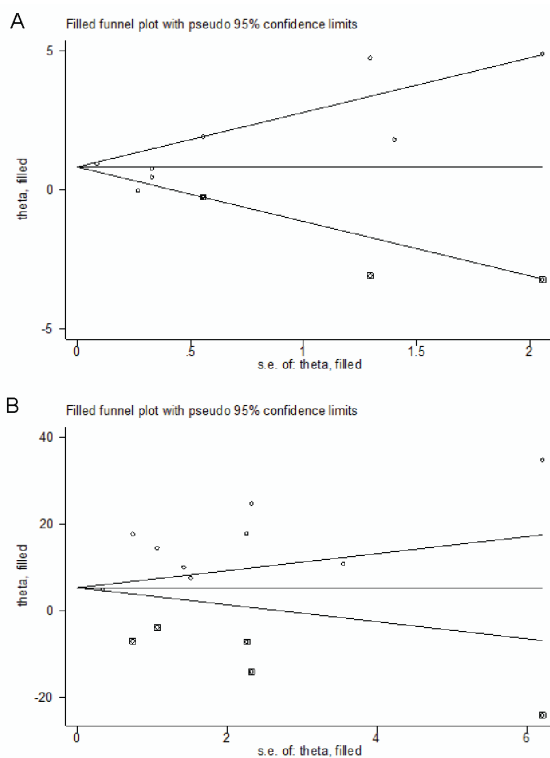


Figure 4: Funnel plot, using the trim and fill method, for publication bias assessment showing the mean change of (a) HOMA-IR and (b) 25(OH)D as the outcome variable.

**Publication Bias**

HOMA-IR: Trim and fill analysis imputed three more studies to adjust for funnel plot symmetry. However, the pooled mean change (including augmented studies) was not substantially different from that of the original studies (figure 4a). Moreover, Egger’s test did not reveal any evidence of publication bias (P=0.458).

25(OH)D: Egger’s test revealed no evidence of publication bias for the effect of vitamin D supplementation on 25(OH)D levels (P=0.057). However, trim and fill analysis imputed five

more studies to produce funnel plot symmetry and pooled mean change (including augmented studies) was different from that of the original studies (figure 4b).

**Discussion**

The results of the present systematic review and meta-analysis showed that vitamin D supplementation increased serum 25(OH)D level and reduced the HOMA-IR index in healthy pregnant women. In line with our results, a meta-analysis by Yin and others showed that vitamin D supplementation decreased fasting plasma glucose and insulin concentrations and can be used to prevent and treat GDM by improving HOMA-IR.<sup>20</sup> In a meta-analysis study, Mirhosseini and others also demonstrated that vitamin D supplementation improved serum 25(OH)D levels and increased insulin sensitivity (reduced HOMA-IR) in patients with prediabetes or individuals at high risk of developing diabetes.<sup>21</sup> Another meta-analysis showed that, compared to controls, vitamin D supplementation improved glycemic control in women with GDM, while it reduced fasting plasma glucose and serum insulin levels by a mean of 0.46 mmol/L and 4.10 μIU/mL, respectively.<sup>22</sup> A meta-analysis by George and others showed a small effect of vitamin D supplementation on attenuating insulin resistance in patients with type 2 diabetes or impaired glucose tolerance but had no effect in patients with normal glucose tolerance.<sup>23</sup> They stated that most of the included studies used doses of <2,000 IU vitamin D per day, but doses of 5,000 IU per day may be required to increase serum 25(OH)D levels above 75 nmol/L (the optimum level for good health). Another meta-analysis showed that vitamin D supplementation did not improve HOMA-IR in prediabetes, but HOMA-IR decreased significantly in a subgroup of participants with baseline 25(OH)D ≥50 nmol/L.<sup>11</sup> However, the results of baseline mean serum 25(OH)D was inconclusive. The mean baseline BMI was 25-29 Kg/m<sup>2</sup> in two studies, and ≥30 Kg/m<sup>2</sup> in seven trials. It was reported that the effect of vitamin D may be affected by overweight or obesity, since high levels of vitamin D binding protein in obese participants were correlated with the reduced unbound 15(OH)D levels.<sup>11</sup> Vitamin D directly increases insulin secretion.<sup>24</sup> According to *in vitro* studies, 1,25-(OH)<sub>2</sub>D increases insulin receptor gene transcription and up-regulates insulin-related glucose-transfer genes.<sup>25</sup> In addition, 1,25-(OH)<sub>2</sub>D promotes glucose oxidation.<sup>26</sup> Overall, there is sufficient justification for the assumption that vitamin D supplementation reduces insulin resistance.

We found that a high weekly dose of vitamin D further reduced HOMA-IR. Likewise, a meta-analysis by Li and others showed that vitamin D supplementation considerably decreased insulin resistance in patients with type 2 diabetes, especially in high doses (>2,000 IU/day).<sup>27</sup> Mirhosseini and others suggested that serum 25(OH)D levels >86 nmol/L can control glucose metabolism indices and response to insulin in prediabetes.<sup>21</sup> These levels can be achieved by using vitamin D supplementation of 88 µg/d (3500 IU/d) or higher. A clinical trial in GDM patients showed that high- or medium-dose vitamin D supplementation reduced HOMA-IR compared to those receiving placebo or low-dose.<sup>28</sup> Another clinical trial in patients with prediabetes revealed that high dose vitamin D decreased insulin resistance and subsequent progression to diabetes.<sup>29</sup> Therefore, it is plausible that higher doses can correct vitamin D deficiency, i.e., increase 25(OH)D levels.

All studies in our meta-analysis reported that vitamin D supplementation increased serum 25(OH)D levels. However, the dosage of vitamin D was not significantly correlated with the mean change in 25(OH)D. We noticed that only the meta-analysis by Li and others indicated a significant increase in the serum 25(OH)D level after vitamin D supplementation in all subgroups, except for participants with adequate levels of vitamin D prior to the intervention.<sup>27</sup> The reason behind our findings could be due to heterogeneity between the included studies in terms of the types of vitamin D supplements, baseline 25(OH)D level, nationality, and pre-gravid BMI. Other studies have also reported that the response to vitamin D is related to BMI,<sup>30</sup> bodyweight, genes, and baseline 25(OH)D level.<sup>30, 31</sup> In a subgroup analysis, Tamim and others concluded that higher doses of vitamin D increased serum 25(OH)D levels compared to lower doses. This association was insignificant in some subgroups due to the small sample size, obesity (BMI≥30 Kg/m<sup>2</sup>), and short duration of vitamin D supplementation.<sup>17</sup>

Our results showed that intervention duration (ranging from six to 28 weeks) was not significantly associated with the mean change in HOMA-IR and 25(OH)D levels. Likewise, Mirhosseini and others reported a further, but insignificant, reduction in HOMA-IR levels in prediabetes, overweight, and obese adults after >6 months of supplementation compared to a shorter period of supplementation.<sup>21</sup> Li and others showed that the effect of vitamin D supplements was observed within three months, however, they used the highest dose of vitamin D of all included studies.<sup>27</sup>

The main strength of the present study is the comprehensive review of RCTs assessing the effect of vitamin D supplementation in non-diabetic pregnant women. By doing so, we addressed the limitations of previous observational studies as well as clinical trials on prediabetes, insulin resistance, diabetes, and non-pregnant participants. Another strength is that we conducted a meta-analysis on the effect of an average weekly dose of vitamin D supplementation and intervention duration on HOMA-IR and 25(OH)D to provide a stronger portfolio of evidence that previous systematic reviews. The main limitation of the present study is related to the small number of studies, partly due to the exclusion of non-English articles. In addition, the dosages and pre-pregnancy BMI were heterogeneous in all included studies.

## Conclusion

Vitamin D supplementation increased 25(OH)D and decreased HOMA-IR levels in non-diabetic pregnant women. Vitamin D in high doses further reduced HOMA-IR, but did not affect 25(OH)D. We recommend further clinical trials to evaluate the preventive effect of vitamin D supplementation in GDM patients.

## Acknowledgment

We would like to thank the Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease (Isfahan, Iran) for their support in performing the meta-analysis.

## Authors' Contribution

S.M.Sh: Comprehensive literature search using electronic databases, interpretation of data for the work, drafting a part of the manuscript, revising the work critically for important intellectual; M.Y: Meta-analysis, Interpretation of data for the work, drafting a part of the manuscript, revising the work critically for important intellectual content; M.G.Kh: Conception and design of the work, comprehensive literature search using electronic databases, hand-searching abstracts of the included studies and reviewing references to inclusion of any possible trials, assessment the quality of included articles, drafting a large section of the manuscript; R.K: Interpretation of data for the work, revising the work critically for important intellectual content. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the

accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of Interest:** None declared.

## References

- Stanley K, Fraser R, Bruce C. Physiological changes in insulin resistance in human pregnancy: longitudinal study with the hyperinsulinaemic euglycaemic clamp technique. *Br J Obstet Gynaecol.* 1998;105:756-9. doi: 10.1111/j.1471-0528.1998.tb10207.x. PubMed PMID: 9692417.
- Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. *Diabet Med.* 2012;29:844-54. doi: 10.1111/j.1464-5491.2011.03541.x. PubMed PMID: 22150506.
- Egan AM, Vellinga A, Harreiter J, Simmons D, Desoye G, Corcoy R, et al. Epidemiology of gestational diabetes mellitus according to IADPSG/WHO 2013 criteria among obese pregnant women in Europe. *Diabetologia.* 2017;60:1913-21. doi: 10.1007/s00125-017-4353-9. PubMed PMID: 28702810; PubMed Central PMCID: PMC6448875.
- Roth J, Bonner-Weir S, Norman AW, Orci L. Immunocytochemistry of vitamin D-dependent calcium binding protein in chick pancreas: exclusive localization. *Endocrinology.* 1982;110:2216-8. doi: 10.1210/endo-110-6-2216. PubMed PMID: 7042327.
- Clark SA, Stumpf WE, Sar M, DeLuca HF, Tanaka Y. Target cells for 1,25 dihydroxyvitamin D3 in the pancreas. *Cell Tissue Res.* 1980;209:515-20. doi: 10.1007/BF00234764. PubMed PMID: 6996826.
- Zhang Y, Gong Y, Xue H, Xiong J, Cheng G. Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect. *BJOG.* 2018;125:784-93. doi: 10.1111/1471-0528.15060. PubMed PMID: 29244241.
- Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. *Diabetes Res Clin Pract.* 1995;27:181-8. doi: 10.1016/0168-8227(95)01040-k. PubMed PMID: 7555599.
- Inomata S, Kadowaki S, Yamatani T, Fukase M, Fujita T. Effect of 1 alpha (OH)-vitamin D3 on insulin secretion in diabetes mellitus. *Bone Miner.* 1986;1:187-92. PubMed PMID: 3334207.
- Soheilykhah S, Mojibian M, Moghadam MJ, Shojaoddiny-Ardekani A. The effect of different doses of vitamin D supplementation on insulin resistance during pregnancy. *Gynecol Endocrinol.* 2013;29:396-9. doi: 10.3109/09513590.2012.752456. PubMed PMID: 23350644.
- Karamali M, Beihaghi E, Mohammadi AA, Asemi Z. Effects of High-Dose Vitamin D Supplementation on Metabolic Status and Pregnancy Outcomes in Pregnant Women at Risk for Pre-Eclampsia. *Horm Metab Res.* 2015;47:867-72. doi: 10.1055/s-0035-1548835. PubMed PMID: 25938886.
- Poolsup N, Suksomboon N, Plordplong N. Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: a systematic review and meta-analysis. *Diabet Med.* 2016;33:290-9. doi: 10.1111/dme.12893. PubMed PMID: 26308752.
- Hu Z, Chen J, Sun X, Wang L, Wang A. Efficacy of vitamin D supplementation on glycaemic control in type 2 diabetes patients: A meta-analysis of interventional studies. *Medicine (Baltimore).* 2019;98:e14970. doi: 10.1097/MD.00000000000014970. PubMed PMID: 30946322; PubMed Central PMCID: PMC6456062.
- Akbari M, Moosazaheh M, Lankarani KB, Tabrizi R, Samimi M, Karamali M, et al. The Effects of Vitamin D Supplementation on Glucose Metabolism and Lipid Profiles in Patients with Gestational Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Horm Metab Res.* 2017;49:647-53. doi: 10.1055/s-0043-115225. PubMed PMID: 28759943.
- Asemi Z, Samimi M, Tabassi Z, Shakeri H, Esmailzadeh A. Vitamin D supplementation affects serum high-sensitivity C-reactive protein, insulin resistance, and biomarkers of oxidative stress in pregnant women. *J Nutr.* 2013;143:1432-8. doi: 10.3945/jn.113.177550. PubMed PMID: 23884390.
- Corcoy R, Mendoza LC, Simmons D, Desoye G, Adelantado JM, Chico A, et al. The DALI vitamin D randomized controlled trial for gestational diabetes mellitus prevention: No major benefit shown besides vitamin D sufficiency. *Clin Nutr.* 2020;39:976-84. doi: 10.1016/j.clnu.2019.04.006. PubMed PMID: 31053513.
- Yap C, Cheung NW, Gunton JE, Athayde N, Munns CF, Duke A, et al. Vitamin D supplementation and the effects on glucose metabolism during pregnancy: a randomized controlled trial. *Diabetes Care.* 2014;37:1837-44. doi: 10.2337/dc14-0155. PubMed PMID: 24760259.



- 17 Tamim F, Takruri H, Aframb K, Thikrallah F, Al-Khadrab M. Effect of vitamin D supplementation for obese pregnant women on gestational diabetes and diabetes biomarkers. *J Clin Nutr Metab.* 2017;1:1-7.
- 18 Ahmed A, Bourge RC, Fonarow GC, Patel K, Morgan CJ, Fleg JL, et al. Digoxin use and lower 30-day all-cause readmission for Medicare beneficiaries hospitalized for heart failure. *Am J Med.* 2014;127:61-70. doi: 10.1016/j.amjmed.2013.08.027. PubMed PMID: 24257326; PubMed Central PMCID: PMCPMC3929967.
- 19 StataCorp L. Stata statistical software: Release 13 [Computer software]. College Station: StataCorp LP. 2013.
- 20 Yin W, Jin D, Yao M, Yu W, Zhu P. [Effect of vitamin D supplementation on gestational diabetes mellitus:a Meta-analysis]. *Wei Sheng Yan Jiu.* 2019;48:811-21. PubMed PMID: 31601326.
- 21 Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM. Vitamin D Supplementation, Glycemic Control, and Insulin Resistance in Prediabetics: A Meta-Analysis. *J Endocr Soc.* 2018;2:687-709. doi: 10.1210/je.2017-00472. PubMed PMID: 29951596; PubMed Central PMCID: PMCPMC6016617.
- 22 Ojo O, Weldon SM, Thompson T, Vargo EJ. The Effect of Vitamin D Supplementation on Glycaemic Control in Women with Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Int J Environ Res Public Health.* 2019;16. doi: 10.3390/ijerph16101716. PubMed PMID: 31100793; PubMed Central PMCID: PMCPMC6572053.
- 23 George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabet Med.* 2012;29:e142-50. doi: 10.1111/j.1464-5491.2012.03672.x. PubMed PMID: 22486204.
- 24 Tai K, Need AG, Horowitz M, Chapman IM. Vitamin D, glucose, insulin, and insulin sensitivity. *Nutrition.* 2008;24:279-85. doi: 10.1016/j.nut.2007.11.006. PubMed PMID: 18187309.
- 25 Tai K, Need AG, Horowitz M, Chapman IM. Glucose tolerance and vitamin D: effects of treating vitamin D deficiency. *Nutrition.* 2008;24:950-6. doi: 10.1016/j.nut.2008.04.009. PubMed PMID: 18653316.
- 26 Maestro B, Molero S, Bajo S, Davila N, Calle C. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). *Cell Biochem Funct.* 2002;20:227-32. doi: 10.1002/cbf.951. PubMed PMID: 12125099.
- 27 Li X, Liu Y, Zheng Y, Wang P, Zhang Y. The Effect of Vitamin D Supplementation on Glycemic Control in Type 2 Diabetes Patients: A Systematic Review and Meta-Analysis. *Nutrients.* 2018;10. doi: 10.3390/nu10030375. PubMed PMID: 29562681; PubMed Central PMCID: PMCPMC5872793.
- 28 Zhang Q, Cheng Y, He M, Li T, Ma Z, Cheng H. Effect of various doses of vitamin D supplementation on pregnant women with gestational diabetes mellitus: A randomized controlled trial. *Exp Ther Med.* 2016;12:1889-95. doi: 10.3892/etm.2016.3515. PubMed PMID: 27588106; PubMed Central PMCID: PMCPMC4998009.
- 29 Niroomand M, Fotouhi A, Irannejad N, Hosseini F. Does high-dose vitamin D supplementation impact insulin resistance and risk of development of diabetes in patients with prediabetes? A double-blind randomized clinical trial. *Diabetes Res Clin Pract.* 2019;148:1-9. doi: 10.1016/j.diabres.2018.12.008. PubMed PMID: 30583032.
- 30 Saliba W, Barnett-Griness O, Rennert G. The relationship between obesity and the increase in serum 25(OH)D levels in response to vitamin D supplementation. *Osteoporos Int.* 2013;24:1447-54. doi: 10.1007/s00198-012-2129-0. PubMed PMID: 22955311.
- 31 Didriksen A, Grimnes G, Hutchinson MS, Kjaergaard M, Svartberg J, Joakimsen RM, et al. The serum 25-hydroxyvitamin D response to vitamin D supplementation is related to genetic factors, BMI, and baseline levels. *Eur J Endocrinol.* 2013;169:559-67. doi: 10.1530/EJE-13-0233. PubMed PMID: 23935129.