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Highlights

- Vitamin D may be beneficial in preventing the occurrence of preeclampsia.
- Studies have yielded inconsistent results about the benefits of Vitamin D for preeclampsia.
- A new meta-analysis was needed to include recent studies.
- The meta-analysis assessed vitamin D's impact on preeclampsia risk during pregnancy.
- Vitamin D supplementation reduces the incidence of preeclampsia.

The effect of vitamin D supplementation in pregnancy on the incidence of preeclampsia: A systematic review and meta-analysis

Running title: vitamin D supplementation and preeclampsia

Zainab Alimoradi[1], Farideh Kazemi[2*], Azita Tiznobeik[3], Mark D. Griffiths[4], Seyyedeh Zahra Masoumi[5], Soodabeh Aghababaei[6]

[1] Associate Professor, Social Determinants of Health Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran.

Email: zainabalimoradi@yahoo.com

Tel: +989123594581

ORCID: 0000-0001-5327-2411

[*2]Assistant Professor, Mother & Child Care Research Center, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran.

Email: faridehkazemi21@yahoo.com

Tel: +989183127351

ORCID: 0000-0001-9525-1010

[3]Assistant Professor, Mother & Child Care Research Center, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran.

Email: azita.tizno@gmail.com

Tel: +989183152476

ORCID: 0000-0002-5220-9442

[4] International Gaming Research Unit, Psychology Department, Nottingham Trent University, Nottingham, UK.

Email: mark.griffiths@ntu.ac.uk

Tel: 0115-8482401

ORCID: 0000-0001-8880-6524

[5] Professor, Mother & Child Care Research Center, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran.

Email: zahramid2001@gmail.com

Tel: +989183129058

ORCID: 0000-0002-2045-3707

[6] Associate Professor, Mother & Child Care Research Center, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Hamadan, Iran.

Email: aghababaii@yahoo.com

Tel: +989183164291

ORCID: 0000-0003-2446-3037

PROSPRO registration code: CRD42022358736 (7 September 2022)

Corresponding author's contact information:

Farideh Kazemi

Email: faridehkazemi21@yahoo.com

Address: Hamadan University of Medical Sciences, In front of the Mardom's Park, Shahid Fahmideh Boulevard, Hamadan, Iran

Cell phone numbers: +98 09183127351

Fax number: +98 38380447

Abstract

Background: The results of previous studies on the effect of vitamin D on the incidence of preeclampsia are inconsistent. Therefore, the primary objective of the present review was to determine the effect of vitamin D supplementation during pregnancy on the risk of preeclampsia.

Methods: Five major scientific databases were searched from inception to June 10, 2023. Studies with randomized controlled trial designs were searched. To assess the methodological quality of the selected studies, the Cochrane Tool Checklist (CTC) was used. The random effect model was chosen as a combination model. Statistical heterogeneity was evaluated using the standard χ^2 test, and the intensity of heterogeneity was calculated using I^2. Effect size indicators including risk ratio (RR), risk difference (RD), and number needed to treat (NNT) were calculated with estimated 95% confidence intervals.

Results: Nineteen studies were included in a systematic review and meta-analysis. The pooled RR of preeclampsia in the intervention group compared to the control group was 0.61 (95% CI, 0.47 to 0.78; I^2=14.4%; χ^2=23.37; p=0.27; tau^2=0.05), and indicated a 39% reduction in the risk of preeclampsia. The pooled RD of preeclampsia in the intervention group compared to the control group was -0.03 (95% CI: -0.05 to -0.01; I^2=45.5%; χ^2=36.68; p=0.01; tau^2=0.0008) and the difference in the risk of preeclampsia among women who received vitamin D supplements was 3% less than the control group. The NNT was 29 (95% CI: 20 to 52).

Conclusion: Vitamin D supplementation significantly reduces preeclampsia during pregnancy.

Keywords: pregnancy; risk ratio; risk difference; supplementation; quality of evidence; hypertension

Abbreviations

BMI: body mass index CI: confidence interval

CTC: Cochrane Tool Checklist

GDM: gestational diabetes mellitus

GRADE: Grading of Recommendations Assessment, Development and Evaluation

MVM: multivitamin-mineral

NNT: number needed to treat

OR: odds ratio

PE: preeclampsia

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

RCTs: Randomized controlled trials

RR: risk ratio

RD**:** risk difference

25(OH)D: 25hydroxyvitamin D

1. Introduction

Preeclampsia is one of the most important challenges in midwifery. The disorder is defined based on increased blood pressure and newly started proteinuria after the 20th week of pregnancy. In the absence of proteinuria, high blood pressure with evidence of systemic disease (such as thrombocytopenia or elevated liver transaminases) is also suggestive of preeclampsia [1, 2]. In total, preeclampsia and its complications are responsible for 63,000 maternal deaths worldwide each year, accounting for 12% of all maternal deaths [2]. The disorder affects 3%-5% of pregnancies worldwide [1-3]. The incidence of the disorder in developed countries is approximately 3.4%, and in developing countries it ranges from 1.8% to 16.7% [4]. Differences in incidence among countries reflect, at least in part, differences in maternal age distribution and the proportion of primiparous pregnant mothers in that country's population [3].

Preeclampsia is a multisystem disease with adverse short-term and long-term consequences for both mother and fetus [3]. Pregnant women with pre-eclampsia are prone to pulmonary edema, coagulation defects, and kidney failure in the current pregnancy, as well as being at greater risk of increased blood pressure and cardiovascular diseases in the later stages of life [5]. Fetal consequences of preeclampsia include intrauterine growth restriction and oligohydramnios, as well as increasing the need to terminate the pregnancy in the form of premature birth, which increases perinatal complications and mortality (3). The greatest risk is in pregnancies with the onset of preeclampsia before the 34th week of pregnancy [3].

Various hypotheses have been proposed for the etiology of preeclampsia. Placental dysfunction is accepted as the main cause of preeclampsia because the definitive treatment for preeclampsia is delivery. Placental hypoxia, oxidative stress, vascular endothelial dysfunction, immunity, and genetic factors also contribute to placental dysfunction and vascular

abnormalities, which are thought to be the main cause of preeclampsia [6]. Among women at high risk of preeclampsia, an inverse relationship between maternal vitamin D levels in the second trimester and the risk of early preeclampsia has been observed [7, 8]. Taking cholecalciferol (vitamin D) supplements can increase glutathione levels and reduce the production of lipid peroxidation products, leading to a reduction in oxidative stress. Therefore, it is possible that early supplements with a high dose of cholecalciferol can be useful in reducing oxidative stress biomarkers as well as improving vascular endothelial function and preventing the occurrence of preeclampsia [9].

Regarding the relationship between the serum level of vitamin D and the occurrence of preeclampsia, a few systematic review and meta-analysis studies have summarized the available evidence from interventional studies on the effect of vitamin D supplementation on the chances of preeclampsia using the odds ratio (OR) [10, 11]. In Gallo et al.'s study, the chance of preeclampsia was reduced by 30% but was not statistically significant [11]. In 2020, Fogacci et al. (10) also found an OR equal to 0.37. Although this was statistically significant, some of the studies included in this meta-analysis were later retracted, Furthermore, in this meta-analysis, the appropriate effect size indices for interventional studies such as RR or RD were not calculated, and only the odds ratios (ORs) were reported. Given that ORs always exaggerate the size of the effect compared to relative risk [12], the results are not reliable. Lo and Lo updated Fogacci et al. study in 2022 and they excluded some studies that were retracted or whose data were not properly extracted, and one study that was found in the manual search added to the meta-analysis [13]. Therefore, the aim of the present review was to conduct the meta-analysis more accurately. The review included three studies published in 2021 [14-16] in the meta-analysis as well as correctly extracting the data of the Sablok et al. [17] study which was excluded from the meta-

analysis by Lo and Lo. The RD and NNT was also calculated, in addition to the risk ration (RR) so that readers can better interpret the results. In other studies, where the results were analyzed using the RR, two studies reported a reduction in the risk of preeclampsia by 9% [18] and 53% [4], and one study also reported a slight increase in the risk of preeclampsia [19].

According to the explanations given above, and the inconsistent results of previous studies, the need to re-conduct a meta-analysis study with a comprehensive and up-to-date search in academic databases, as well as performing analyses using appropriate effect size indicators, is necessary. Therefore, the present systematic review and meta-analysis were designed with the main goal of investigating the effect of vitamin D supplementation during pregnancy on the risk of preeclampsia.

2. Methods

The present review was designed based on the stages of systematic review studies using the guidelines for preferred reporting items for systematic review and meta-analysis (PRISMA) [20]. The review proposal (Research project number: 140110138821) was approved by the Research Council and Ethics Committee in Biological Research of Hamedan University of Medical Sciences (Ref: IR.UMSHA.REC.1401.712). The review protocol was registered in the PROSPRO system (code CRD42022358736).

2.1. Study Outcomes

2.1.1. Primary outcome: The incidence of preeclampsia after vitamin D intake in pregnancy

2.1.2. Secondary outcomes: (i) investigation of the impact of the following variables on the pooled effect size using subgroup analysis: woman's age, gestational age at the time of vitamin D administration, continuation of supplementation until delivery, quality of primary studies, type

of intervention group in terms of received supplements, type of comparison group (placebo, no intervention, routine treatment), the dose of vitamin D prescribed in the intervention group, the income status of the countries based on the World Bank classification, vitamin D deficiency at the beginning of the study, and BMI status and pregnancy status, (ii) investigation of potential sources of heterogeneity, and (iii) investigation of publication bias in retrieved studies.

2.2. Eligibility criteria

2.2.1. Characteristics of studies: Studies with randomized controlled trial designs published up to June 10, 2023, were searched for. Studies were eligible for inclusion if the study reported the incidence of preeclampsia (in the form of frequency and percentage) as an outcome after vitamin D administration in pregnancy and had a control group. Studies that prescribed vitamin D supplementation in combination with other minerals or vitamins were also included. Original empirical research studies were included in the analysis. Systematic review papers, case reports, and letters to the editor were not included in the analysis.

2.2.2. Participant characteristics: There was no limitation in terms of age, number of births, vitamin D dosage, time of vitamin D initiation in pregnancy, type of control group, or high-risk or low-risk pregnancy status in the selection of participants.

Type of intervention: Vitamin D administration during pregnancy was considered as the intervention.

2.3. Information sources

The search was performed using *Scopus, PubMed, Science Direct, ProQuest,* and *ISI Web of Knowledge* databases. In addition, *Google Scholar* as well as the reference list of previous review papers. Selected studies from the search in the present review were also checked

manually so that the search could be done comprehensively and all papers related to the topic could be retrieved.

2.4. Search strategy

For searching, the keywords found in the published primary and review papers and MeSH were used. The main keywords included ‘preeclampsia’, ‘Vitamin D’, and ‘trial’. There was no restriction on the initial search period, and papers published up to June 10, 2023, were searched. No filter was used in the search. The search terms were based on the specific characteristics of the investigated databases. The key components of the search were selected based on PICO components to answer the research question (in the case of the present review, the intervention of vitamin D administration and the outcome of preeclampsia incidence were selected). AND/OR operators were used to formulate the search syntax. Matching of search syntaxes was performed according to the advanced search features of each database. It should be noted that the search for studies was carried out internationally and studies published in local journals of countries including Iran were not searched for (in the table in Appendix A).

2.5. Study selection

After searching and saving the retrieved information separately from the databases, duplicate items were retrieved and removed from the list of studies using *Endnote* software. Then, the title and abstract of retrieved studies were checked based on inclusion and exclusion criteria. Following this, the full text of the selected papers was checked according to the inclusion and exclusion criteria. This process was designed and carried out independently by two of the research team.

2.6. Data extraction

After screening, selecting, and evaluating the quality of selected studies, data were extracted and recorded in pre-designed forms. Data extraction and recording were done by two of the research team independently. The following information was collected from each study: name of the first author, year of publication, country where the research was conducted, sample size, women's age, gestational age at the time of vitamin D administration, status of continuation of supplementation until delivery, quality of primary studies, type of intervention group in terms of supplements received, type of comparison group (placebo, no intervention, routine treatment), vitamin D dose prescribed in the intervention group, income status of countries based on World Bank classification, vitamin D deficiency at the beginning of the study, BMI, pregnancy status, and the raw data of 2*2 tables related to the incidence of preeclampsia in each group.

2.7. Assessment of risk of bias

To assess the methodological quality of the selected studies, the Cochrane Tool Checklist (CTC) was used. The CTC is a valid tool used to assess the quality of interventional studies through seven items (correct random sequence generation, allocation concealment, blind application of participants and investigators, blinded evaluation results, completeness of information, whether selective reporting was used, and any other risk of implementation bias), and the included studies are categorized into three categories: poor, fair, and good [21]. This step was designed and carried out independently by two of the research team. The agreement between the two evaluators was calculated using the Kappa coefficient.

Additionally, study quality was also assessed using Heaney's guidelines [22], which were specifically designed to optimize the design and analysis of clinical studies examining the effects of nutrients. More specifically, the quality of a study is evaluated using seven items. If the item meets the criteria, a score of 1 is given which means the maximum score is 7. The seven

guideline criteria are that (i) serum 25(OH)D concentrations be measured for all prospective participants, (ii) those with low concentrations be included in the trial, (iii) vitamin D doses be large enough to raise 25(OH)D concentrations high enough to significantly affect the health outcomes of interest, (iv) achieved 25(OH)D concentrations be measured, (v) the control group should not be given vitamin D, (vi) co-nutrient status must be optimized to ensure that the test nutrient is the only nutrition-related, limiting factor in the response, and (vii) the results should be based on serum 25(OH)D concentrations, not the presence or absence of vitamin D treatment [22].

2.8. Data synthesis

Combining the results of selected studies based on the items suggested in PRISMA was performed using *Stata-13*. Since the studies were from different communities and considering both within-group and between-group variance, the random effect model was chosen as a combination model and the Der-Simonian-Laird weighting method was used [23]. Effect size indicators including RR, RD, and NNT were calculated. The interpretation areas of RR are as follows: 1-0.69 = very small, 0.69-0.40 = small, 0.23-0.40 = medium, and 0.23 ≥ large [24]. The interpretation areas of RD are as follows: 0-11% = very small, 11%-28% = small, 28%-43% = medium, 43%-52% = large, and 52% ≤ very large [25]. In the case of NNT, if it is less than 10, it is considered clinically significant [26]. Prediction intervals were also calculated to describe the distribution of true effects concerning the summary effect [27].

Statistical heterogeneity was evaluated using the standard χ^2 test, and the intensity of heterogeneity was calculated using the I^2 index. If I^2 was <25%, it was considered mild heterogeneity, between 25% and 50% moderate heterogeneity, and between 50% and 75% severe heterogeneity [21]. Analysis of secondary objectives was performed using subgroup analysis on

the aforementioned variables. Evaluation of publication bias was performed using a funnel plot and Begg's test, and if the results indicated publication bias, the Fill and Trim method was used [28, 29]. Sensitivity analysis was performed using the jackknife (one-out removal) method. The quality of evidence of the main outcome of the review as well as the subgroups was evaluated with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool. All analyses were performed in both RR and RD indices.

2.9. Ethics approval and consent to participate

The review (Research project number: 140110138821) was approved by the Research Council and Ethics Committee in Biological Research of Hamedan University of Medical Sciences (Ref: IR.UMSHA.REC.1401.712). The review protocol was registered in the PROSPRO system (code CRD42022358736).

3. Results

3.1. Study selection

The search process led to the retrieval of 1464 potentially relevant papers. Among these papers, 209 papers were removed due to duplication. Then, the title and abstract were checked and 1232 irrelevant papers were removed (such as being non-intervention studies, animal studies, not containing empirical data, and/or not meeting the requirements of the inclusion criteria). Finally, the full text of the remaining 23 papers was studied, of which five were excluded from the analysis due to not meeting the inclusion criteria. One study was retrieved through a manual review of reference lists [30] and was incorporated into the analysis because it met all the study inclusion criteria. This meant that 19 studies were included in the final analysis. The Cohen's

kappa coefficient between the two evaluators was 0.78 in the abstract review stage and 0.89 in the full-text review stage. The search process based on the PRISMA flowchart is shown in Figure 1.

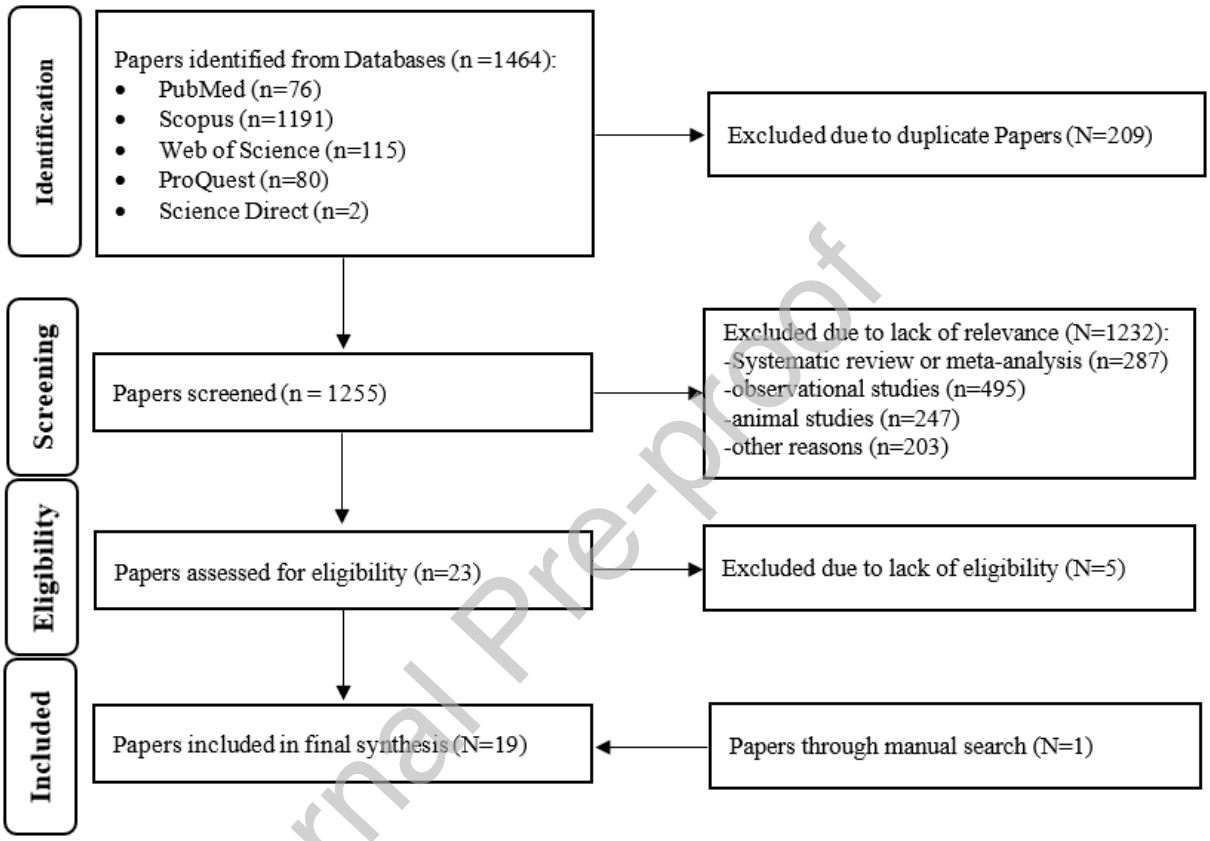

Figure 1. PRISMA flowchart of selected studies. PRISMA=Preferred Reporting Items for Systematic Review and Meta-Analysis

3.2. Study characteristics

In the present meta-analysis, 19 studies were included. Because two studies [14, 16] compared the results in three groups, the results of the two-by-two comparisons of the groups were analyzed separately, and the letters ‘a’ and ‘b’ were added to the cited reference in the table

in Appendix A to differentiate the within-study findings. The total participants of in the intervention group was 2440 and the comparison group was 2362. Among the 19 RCTs included in the review, 10 were double-blind studies and 11 studies were conducted in Iran. The largest sample size was 876 [31] and the smallest was 46 [32]. Information about the included studies is shown in Table 2.

Table 2. Summarized characteristics of selected primary studies

First author (year)	Country	Blinding status	Intervention group	Comparison group	Sample size	Pregnancy status	Maternal age (years)
Samimi (2015) [33]	Iran	Double-blind	Vitamin D 50000 IU every two weeks + Ca 1000 mg/daily + MVM/daily	Placebo+ MVM/daily	G1=30 G2=30	High risk of PE	27.2
Sablok (2015) [17]	India	Open-label	Vitamin D 60 000 IU once at 20 weeks of gestation Vitamin D 120 000 IU at 20 weeks and 24 weeks of gestation Vitamin D 120 000 IU at 20, 24, 28, and 32 weeks of gestation (based on deficiency level)	No intervention	G1=120 G2=60	Low risk	NA
Razavi (2017) [34]	Iran	Double-blind	Vitamin D 50,000 IU every two weeks	Placebo	G1=30 G2=30	GDM	29.6
Taherian (2002) [35]	Iran	Open-label	Vitamin D 200 IU/ daily + Ca 500mg/ daily	No intervention	G1=330 G2=330	Low risk	21.6
Naghshineh (2016) [36]	Iran	Double-blind	Vitamin D 600 IU/daily	Placebo	G1=70 G2=70	Low risk	24.9
Karamali (2016) [37]	Iran	Double-blind	Vitamin D 50 000 IU every three weeks for two doses + Ca 1000 mg/daily	Placebo	G1=30 G2=30	GDM	30.2
Hossain (2014) [38]	Pakistan	Open-label	Vitamin D 4000 IU/daily	No intervention	G1=100 G2=100	Low risk	25.6
Marya (1987) [30]	India	Open-label	Vitamin D 1200 IU/daily +Ca 375mg/daily	No intervention	G1=200 G2=200	Low risk	27.5

Sasan (2017) [39]	Iran	Double-blind	Vitamin D 50,000 IU every two weeks	Placebo	G1=70 G2=72	High risk of PE	30.9
Karamali (2015) [9]	Iran	Double-blind	Vitamin D 50,000 IU every two weeks + MVM/daily	Placebo+ MVM/daily	G1=30 G2=30	High risk of PE	27.4
Asemi (2015) [32]	Iran	Double-blind	MVM	Placebo	G1=23 G2=23	High risk of PE	24.7
Jamilian (2019) [40]	Iran	Double-blind	MVM (half dose) twice a day	Placebo+ Vitamin D 1000 IU	G1=30 G2=30	GDM	28.4
Azami (2017) [41]	Iran	Open-label	MVM/daily	No intervention	G1=30 G2=30	High risk of PE	31.6
Ali (2019) [42]	Saudi Arabia	Open-label	Vitamin D 4000 IU/daily	MVM	G1=93 G2=86	High risk of PE	29.4
Jiang (2021a) [14]	China	Open-label	Vitamin D 1500 IU/daily	Vitamin D 400 IU	G1=150 G2=150	Low risk	28.7
Jiang (2021b) [14]	China	Open-label	Vitamin D 4000 IU/daily	Vitamin D 400 IU	G1=150 G2=150	Low risk	28.9
Nausheen (2021a) [16]	Pakistan	Double-blind	Vitamin D 4000 IU/daily	Vitamin D 400 IU	G1=120 G2=115	Low risk	26.1
Nausheen (2021b) [16]	Pakistan	Double-blind	Vitamin D 2000 IU/daily	Vitamin D 400 IU	G1=115 G2=115	Low risk	26.3
Manasova (2021) [15]	Ukraine	Open-label	MVM until 16 weeks then, Vitamin D 2000 IU/daily	MVM	G1=29 G2=25	High risk of PE	27.8
Mojibian (2015) [43]	Iran	Open-label	Vitamin D 50,000 IU every two weeks	Vitamin D 400 IU	G1=250 G2=250	Low risk	27.6
Mirzakhani (2016) [31]	USA	Double-blind	Vitamin D 4000 IU/daily +MVM/daily	Placebo+ MVM	G1=440 G2=436	Low risk	27.4

MVM=multivitamin mineral; G1=intervention group; G2=comparison group; PE=preeclampsia

3.3. Risk of bias of included studies

The risk of bias in the primary studies was evaluated using the CTC. The Cohen's kappa coefficient between the two evaluators in the study quality review phase was 0.79. The results of the quality review of the studies are reported in the table in Appendix B. Investigations showed that all studies had low bias in terms of the two items (selective reporting and incomplete outcome data), but there was variation in the range of bias in the other five items (see the table in Appendix B and the figure in Appendix A). Using Heaney's study quality criteria, the range of

scores was 0-5, and none of the studies included in the meta-analysis met all the criteria (see the table in Appendix C).

3.4. Synthesis of results

The results are provided in two sections based on selected effect sizes of risk ratio and risk difference.

3.5. Overall risk ratio estimation

The pooled effect size in the RR of preeclampsia in the intervention group compared to the control group was 0.61 (95% CI, 0.47 to 0.78; I^2=14.4%; χ^2=23.37; p=0.27; tau^2=0.05) and the prediction interval ranged from 0.36 to 1.03. Therefore, the results showed that the risk ratio of preeclampsia among women who received vitamin D supplements was 39% lower than the control group (irrespective of the type of control group). The forest plot is shown in Figure 2.

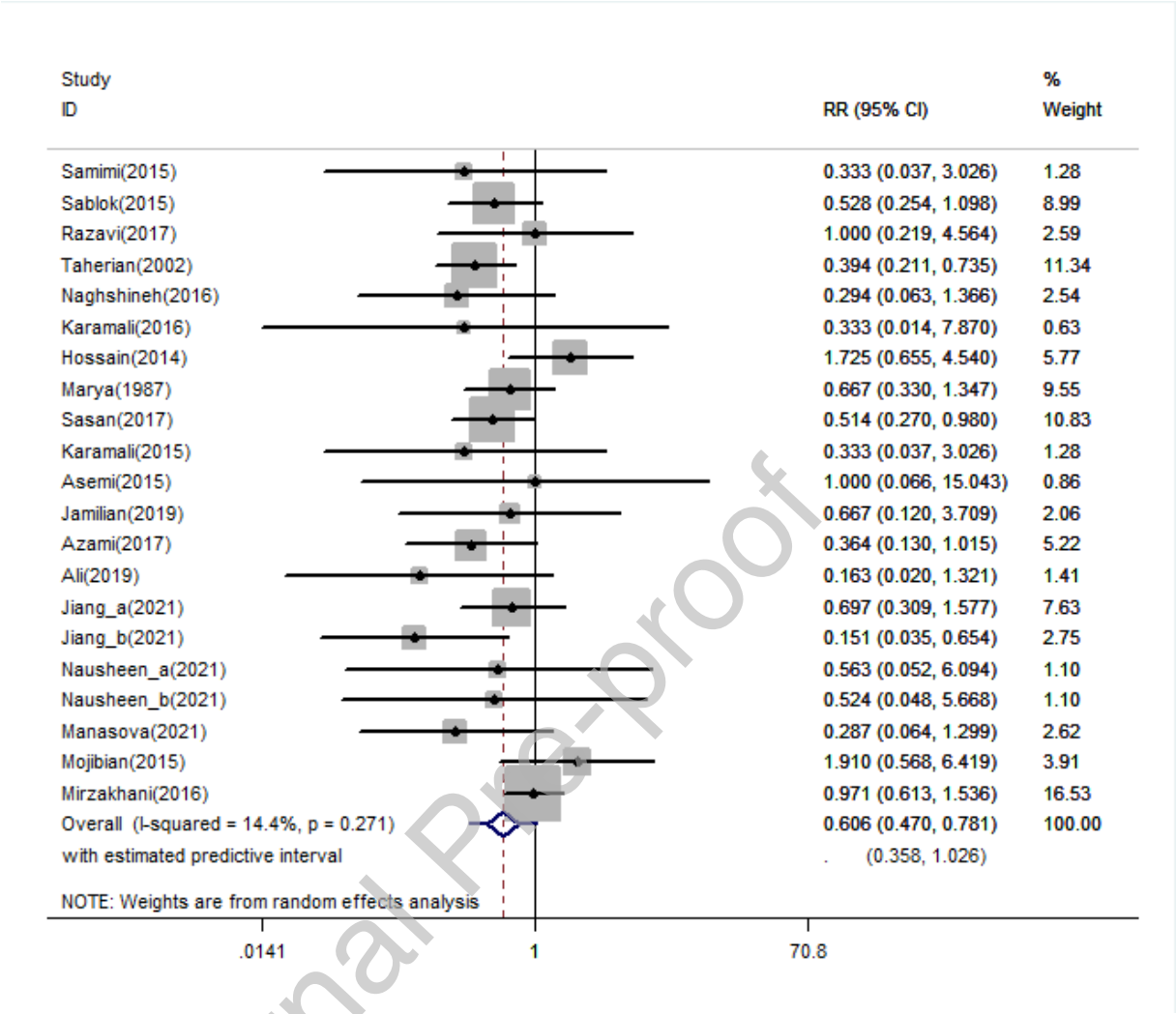

Figure 2. Forest plot of overall risk ratio (RR) for preeclampsia incidence

Subgroup analysis was performed to determine the variables affecting heterogeneity. The results showed that none of the studied variables had a significant effect on the relationship between vitamin D supplementation and preeclampsia. Some of these variables included women's age (p=0.11), the start time of supplementation in pregnancy (p=0.47), the type of

comparison group (p=0.47), and the quality of study evaluation (p=0.11). The rest of the results are shown in Table 3.

Table 3. Subgroup analysis using risk ratio

Potential factors		No of studies	Pooled risk ratio (95% CI)	Heterogeneity χ^2	p-value for Heterogeneity	I^2	Interaction p-value
Maternal age (in years)	≤26	6	0.62 (0.31, 1.22)	7.27	0.20	31.2%	0.11
	26-28	7	0.83 (0.59, 1.16)	5.91	0.43	0.0%	
	>28	7	0.48 (0.32, 0.72)	5.63	0.47	0.0%	
Time of beginning supplementation	< 20 weeks of gestation	10	0.58 (0.37, 0.91)	14.27	0.11	36.9%	0.47
	≥ 20 weeks of gestation	11	0.57 (0.42, 0.79)	8.64	0.57	0.0%	
Continuation of the intervention until delivery	Yes	8	0.73 (0.43, 1.24)	13.59	0.06	48.5%	0.24
	No	9	0.57 (0.40, 0.82)	1.62	0.99	0.0%	
World Bank country classifications by income	Lower-middle-income	17	0.57 (0.44, 0.75)	14.07	0.59	0.0%	0.25
	Upper-middle-income or high-income	4	0.51 (0.22, 1.16)	8.15	0.04	63.2%	
Pregnancy status	High risk of PE	7	042 (0.26, 0.67)	1.99	0.92	0.0%	0.16
	Low risk of PE	11	0.67 (0.46, 097)	17.37	0.07	42.4%	
	GDM	3	0.75 (0.26, 2.20)	0.41	0.81	0.0%	
Type of intervention group	Vitamin D	11	0.63 (0.41, 0.97)	14.70	0.14	0.0%	0.95
	Vitamin D + Ca or MVM or both	10	0.62 (0.46, 0.83)	8.68	0.47	32.0%	
Type of comparison group	Placebo	5	0.53 (0.31,	1.54	0.82	0.0%	0.47

			0.90)				
	No-intervention	5	0.59 (0.37, 0.95)	7.35	0.12	45.6%	
	MVM or Vitamin D or placebo+ MVM or Vitamin D	11	0.62 (0.39, 0.98)	13.10	0.22	23.7	
Vitamin D supplementation dosage	<4000 IU daily	9	0.49 (0.35, 0.70)	3.55	0.90	0.0%	0.10
	4000-5000 IU daily	5	0.61 (0.25, 1.48)	10.54	0.03	62.0%	
	≥50000 IU every 1 to 4 weeks	7	0.61 (0.40, 0.92)	4.96	0.55	0.0%	
Quality assessment	Good	10	0.71 (0.51, 0.99)	5.44	0.79	0.0%	0.11
	Poor	11	0.57 (0.38, 0.85)	16.96	0.08	41.0%	
Vitamin D deficiency	No	2	0.47 (0.26, 0.86)	0.44	0.51	0.0%	0.30
	Yes	7	0.58 (0.27, 1.25)	14.05	0.03	57.3%	
BMI	Normal	4	0.56 (0.25, 1.28)	9.86	0.02	69.6%	0.18
	Over-weight or obese	12	0.82 (0.57, 1.17)	8.56	0.66	0.0%	

CI=confidence interval; MVM=multivitamin mineral; PE=preeclampsia, GDM=gestational diabetes mellitus; BMI=body mass index

Investigation of diffusion bias was performed using a funnel plot (see the figure in Appendix B) and Begg's test. The result of Begg's test ($z<0.001$, p-value=1.00) indicated low publication bias. The jackknife (one-out removal) method was used to evaluate small study effects. The sensitivity analysis showed that the estimated pooled RR was not affected by the small number of studies and none of the studies had a significant effect on the overall results in the review (see the figure in Appendix C and the table in Appendix D).

3.6. Overall risk difference estimation

The pooled effect size in the risk difference of preeclampsia in the intervention group compared to the control group was -0.03 (95% CI: -0.05 to -0.01; I^2=45.5%; χ^2=36.68; p=0.01; tau^2=0.0008) and the prediction interval ranged from -0.10 to 0.03. The results showed that the difference in the risk of preeclampsia among women who received vitamin D supplements was 3% less than the control group (irrespective of the type of control group). The accumulation chart is shown in Figure 3.

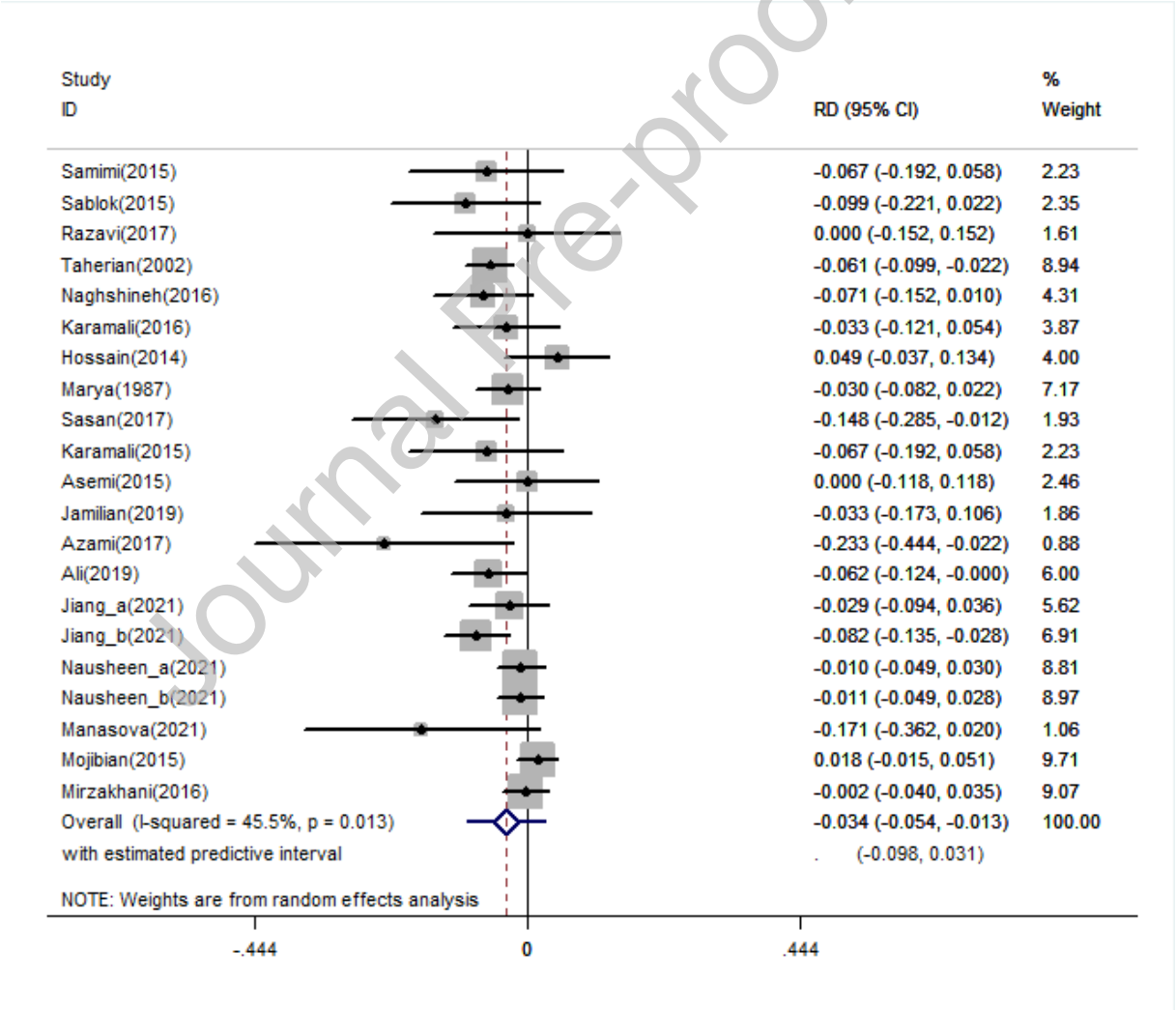

Figure 3. Forest plot of overall risk difference for preeclampsia incidence

The analysis of subgroups was performed to determine the variables affecting heterogeneity (Table 4). The results showed that women's age, pregnancy status, and BMI had a significant effect on the relationship between vitamin D supplementation and preeclampsia. More specifically, among women aged over 28 years, the pooled risk difference was -0.06 (95%CI: -0.10, -0.03), which compared to the other two age groups had a significant effect on reducing the incidence of preeclampsia following vitamin D supplementation (p=0.009). Also, high-risk women for preeclampsia showed a significant reduction in the incidence of preeclampsia following vitamin D supplementation compared to the other two groups (p=0.05, RD=-0.08, 95%CI: -0.14, -0.03) and women with normal BMI compared to individuals who were overweight or obese (p=0.01, RD= -0.04, 95%CI: -0.09, 0.005).

Table 4. Subgroup analysis using risk difference

Potential factors		No of studies	Pooled risk difference (95% CI)	Heterogeneity χ^2	*p*-value for Heterogeneity	I^2	Interaction *p*-value
Maternal age, year	≤26	6	-0.02 (-0.05, 0.008)	9.22	0.10	45.8%	0.009
	26-28	7	-0.01 (-0.04, 0.02)	8.32	0.22	27.8%	
	>28	7	-0.06 (-0.10, -0.03)	7.24	0.30	17.1%	
Time of beginning supplementation	< 20 weeks of gestation	10	-0.03 (-0.06, -0.004)	22.72	0.007	60.4%	0.11
	≥ 20 weeks of gestation	11	-0.04 (-0.07, -0.01)	10.75	0.38	6.9%	
Continuation of the intervention until delivery	Yes	8	-0.02 (-0.04, 0.01)	16.72	0.02	58.1%	0.09
	No	9	-0.04 (-0.08, -0.01)	5.20	0.74	0.0%	
World Bank country classifications by income	Lower-middle-income	17	-0.03 (-0.06, -0.007)	32.88	0.008	51.3%	0.42
	Upper-middle-income or	4	-0.04 (-0.08, -	6.82	0.07	56.0%	

Table 4. Subgroup analysis using risk difference

Potential factors		No of studies	Pooled risk difference (95% CI)	Heterogeneity χ^2	*p*-value for Heterogeneity	I^2	Interaction *p*-value
	high-income		0.001)				
Pregnancy status	High risk of PE	7	-0.08 (-0.14, -0.03)	8.11	0.23	26.1%	0.05
	Low risk of PE	11	-0.02 (-0.05, -0.001)	22.42	0.01	55.4%	
Type of intervention	GDM	3	-0.03 (-0.09, 0.04)	0.17	0.92	0.0%	0.23
	Vitamin D	11	-0.03 (-0.06, -0.001)	24.95	0.005	59.9%	
	Vitamin D + Ca or Vitamin D + MVM or Vitamin D + Ca+ MVM	10	-0.04 (-0.07, -0.01)	10.86	0.27	17.1%	
	Placebo	5	-0.05 (-0.10, -0.001)	4.37	0.36	8.5%	
Type of comparison group	No intervention	5	-0.05 (-0.10, 0.008)	9.55	0.05	51.1%	0.12
	MVM or Vitamin D or placebo+ MVM or Vitamin D	11	-0.03 (-0.05, -0.001)	17.28	0.07	42.1%	
Vitamin D supplementation dosage	<4000 IU daily	9	-0.04 (-0.07, -0.01)	11.14	0.19	28.2%	0.22
	4000-5000 IU daily	5	-0.02 (-0.06, 0.01)	10.62	0.03	62.3%	
	>=50000 IU every 1-4 weeks	7	-0.05 (-0.11, 0.01)	16.34	0.01	63.3%	
Quality assessment	Good	10	-0.02 (-0.04, 0.001)	8.27	0.51	0.0%	0.36
	Poor	11	-0.04 (-0.08, -0.007)	27.19	0.002	63.2%	
Vitamin D deficiency	No	2	-0.09 (-0.18, -0.01)	1.22	0.27	17.9%	0.06
	Yes	7	-0.03 (-0.08, 0.01)	17.88	0.007	66.4%	
BMI	Normal	4	-0.04	7.31	0.06	59.0%	0.01

Table 4. Subgroup analysis using risk difference

Potential factors	No of studies	Pooled risk difference (95% CI)	Heterogeneity χ^2	*p*-value for Heterogeneity	I^2	Interaction *p*-value
Overweight or obese	12	(-0.09, 0.005) -0.01 (-0.03, 0.007)	10.60	0.48	0.0%	

CI-confidence interval; MVM=multivitamin mineral; PE=preeclampsia; GDM=gestational diabetes mellitus; BMI=body mass index

Publication bias was performed using a funnel plot, Begg's test, and the Fill and Trim method. The result of Begg's test (z=1.93, *p*=0.05) indicated the presence of publication bias, but since no study was added with the Fill and Trim test (see the figures in Appendix D and Appendix E), the results showed that publication bias was low.

The jackknife (one-out removal) method was used to evaluate small study effects. The sensitivity analysis showed that the estimated pooled RD was not affected by the small number of studies and none of the studies had a significant impact on the overall results in the review (see the table in Appendix D and the figure in Appendix F). The quality of evidence was rated based on GRADE regarding both RR and RD indicators and also by sub-groups (the results of which are presented in the tables in Appendix E and Appendix F).

4. Discussion

4.1. Principal findings

The present review was conducted to investigate the effect of vitamin D supplementation during pregnancy on the incidence of preeclampsia. For this purpose, both risk ratio (RR) and risk difference (RD) indices were examined. Over half of the studies included in the present meta-analysis were conducted in Iran, and except for two studies that were conducted in Ukraine

and America, the rest of the studies were conducted in Asian countries. One of the reasons for more studies in Iran may be the lower level of serum Vitamin D among Iranian people. Because vitamin D levels are low among Iranian individuals, researchers in Iran have conducted more research in this field than elsewhere, hypothesizing that there may be a relationship between vitamin D deficiency among pregnant women and the incidence of preeclampsia. Although the majority of the studies included in the present review were conducted in Asian countries, especially Iran, the results of the sensitivity analysis showed that the effect of vitamin D on the incidence of preeclampsia was consistent in all studies. In other words, despite the lack of information from other countries in the world, their results were compatible with the results from Asian countries, and this compatibility strengthened the review's findings.

The findings of the review showed a 39% reduction in the risk of preeclampsia among women taking vitamin D during pregnancy compared to the comparison group (and the prediction interval ranged from benefits to harms). However, because the CI related to the RR included two very small to small interpretation areas (from 22% to 53%), the obtained result was not conclusive. In the present review, the effect size of RD was also analyzed. The results of the RD analysis showed that the risk difference between the two groups was approximately 0.03 which means the incidence of preeclampsia decreased by 3% (1%-5%) with vitamin D supplementation during pregnancy (and the prediction interval ranged from benefits to harms: -0.10, 0.03). Since the statistical heterogeneity was low, the result of the present review can be considered conclusive. The analysis of subgroups regarding the RR showed that none of the investigated variables had a significant effect on the relationship between vitamin D supplementation and the occurrence of preeclampsia, while this was different in the case of the RD.

4.2. Comparison with existing literature

The results of some studies are consistent with the present review. In the overview of systematic reviews conducted by Bialy et al. in 2019 [44], the effectiveness of vitamin D on the incidence of preeclampsia was included in the review. This overview of four systematic reviews showed a reduction in the risk of preeclampsia between 9%-53%. In one of the studies, the risk was increased by 9%. In these four, the quality of evidence for this outcome ranged from low to very low. The highest quality of evidence was low, which was related to the study by Pérez-López [18], and the results of the present review indicated the lack of effect of vitamin D consumption in reducing the incidence of preeclampsia (RR=0.91, 95% CI: 0.45 to 1.86).

Considering that in the present review, the result was not statistically significant and the CI range indicated benefits to harms, the result is not robust. Irwinda et al. searched for RCTs conducted up to 2022 to compare the effect of vitamin D intake above 2000 IU/day with a lower dose. They concluded that taking vitamin D at any dose during pregnancy reduced the risk of preeclampsia (RR=0.29, 95% CI: 0.09, 0.95) [45].

In the meta-analysis by Irwinda et al., two subgroup analyses were performed on the outcome of preeclampsia. In the first analysis, a meta-analysis was performed on three studies that compared the use of vitamin D supplements with the placebo group. The results showed that although the RR indicated a moderate effect of the treatment on the incidence of preeclampsia, the confidence intervals were very wide (from no effect to large effect), and therefore the result obtained was not conclusive. In the second analysis, the studies that compared the effect of high-dose vitamin D supplementation with low-dose vitamin D supplementation on the incidence of preeclampsia were included in the meta-analysis. The obtained confidence interval showed that the effect of vitamin D on the incidence of preeclampsia ranged from benefits to harms, and therefore the result was not definitive. The added advantage of the present meta-analytic review

as the comprehensive search for studies in numerous academic databases, which led to the retrieval of more studies included in the analysis (19 studies in the present review versus 11 studies in the previously published meta-analysis).

Some of the RCTs included in the present meta-analysis met some of the study quality criteria of Heaney's guidelines for vitamin D [22] in their study design. Six studies [9, 14, 15, 38, 42, 43] measured the serum level of vitamin D at the beginning of the study and included only pregnant women with vitamin D deficiency. In these studies, the serum level of vitamin D was also measured after the intervention, and the results showed that serum vitamin D deficiency was corrected by taking supplements in the intervention group. However, in three studies [9, 38, 43], the control group did not receive vitamin D. One of the limitations in four of the studies [14, 15, 42, 43], was that the control group was also prescribed low-dose vitamin D, which did not adhere to Heaney's guidelines. Moreover, none of the studies used the change in vitamin D serum level to evaluate the outcome. One of the studies that was not included in the meta-analysis was the quasi-experimental study by Rostami et al. [46]. Although it met most of Heaney's study quality guidelines it did not meet the present review's inclusion criteria. In Rostami et al' study, pregnant women with moderate and severe vitamin D deficiency received the intervention, and the desired outcomes were analyzed based on serum vitamin D status. The results of Rostami et al' study showed that the screening program used in women with vitamin D deficiency led to a reduction in outcomes such as preeclampsia. However, the control group was selected from pregnant women whose serum vitamin D status was not measured and was unclear [46].

In the present review, NNT was also calculated and the findings showed that out of every 29 pregnant women who received vitamin D supplements, one case of preeclampsia was prevented (95% CI: 20, 52). Considering that this represents a small effect, it was not clinically significant

[26]. In Khaing et al.'s study, the NNT related to the use of vitamin D supplements in the prevention of preeclampsia was reported to be 17 (95% CI: -89, 12), and the NNT related to the use of vitamin D supplements plus calcium in the prevention of preeclampsia was reported to be 23 (95% CI: -98, 14). Because their CIs ranged from benefits to harms [4], they were not consistent with the results of the present review. The reason for this contradiction could be that in Khaing et al.'s study, the search for studies was up until 2017, whereas in the present review, new studies were added, which had an impact on the overall result.

4.3. Strengths and limitations

The present review has some limitations. First, the majority of the studies included in the systematic review and meta-analysis were conducted in Asian countries, which could affect the results, considering that the incidence of preeclampsia can be influenced by race. It should also be noted that over half of the studies included were from Iran. This may limit the generalizability of the findings to other countries. Another limitation was the variation in the doses of vitamin D and the use of concomitant supplements such as MVM in both the intervention group and the comparison group. Moreover, only five studies with a comparison group received a placebo. The intervals of vitamin D administration were also varied in the studies and all these cases could affect the results. Finally, none of the studies included in the present meta-analysis followed Heaney's study quality guidelines in the design, implementation of the intervention, and analysis of their outcomes. More specifically, their design was based on guidelines for pharmaceutical drugs, not nutrients. Although an attempt was made to investigate the impact of these variables as much as possible by performing subgroup analysis based on the aforementioned variables, readers should take these limitations into account when interpreting and applying the findings.

5. Conclusions

The quality of evidence, based on GRADE ratings, was found to be high in the case of the pooled RR and moderate in the case of the pooled RD. Based on all the studies reviewed, Vitamin D supplementation significantly reduced preeclampsia during pregnancy. More specifically. the pooled RR and RD of preeclampsia in the intervention group compared to the control group were both significant. Moreover, due to the aforementioned limitations, it would be useful to design high-quality interventional studies based on Heaney's study quality guidelines to investigate the effect of vitamin D supplementation alone compared to placebo.

Declarations

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Data availability

The data used for all analyses is available to other researchers from the corresponding author upon reasonable request.

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Not applicable

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CRediT author statement

FK and ZA collected all data and performed the meta-analysis. SZM and SA checked the methodology and statistical analysis. AT and MG drafted the first paper. All authors contributed equally to the final article.

Declaration-of-competing-interests

None