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Meta-analyses

Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials

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SUMMARY

Background: Maternal vitamin D deficiency has been associated with an increased risk for preeclampsia. Despite this, the current evidence regarding the efficacy of vitamin D supplementation in preventing preeclampsia is controversial. To assess the impact of vitamin D supplementation on the risk of preeclampsia, we performed a systematic review of the literature and a meta-analysis of the available randomized clinical trials (RCTs).

Methods: The primary outcome was preeclampsia. Subgroup analyses were carried out considering the timing of the supplementation, type of intervention and the study design. Meta-regression analysis, including the amount of vitamin D and maternal age, were planned to explore heterogeneity (PROSPERO database registration number: CRD42019119207).

Results: Data were pooled from 27 RCTs comprising 59 arms, which included overall 4777 participants, of whom 2487 were in the vitamin D-treated arm and 2290 in the control arm. Vitamin D administration in pregnancy was associated with a reduced risk of preeclampsia (odd ratio [OR] 0.37, 95% confidence interval [CI]: 0.26, 0.52; $I^2 = 0\%$). If the vitamin D supplementation was started up to 20 weeks' gestation, the odds was a little lower (OR 0.35, 95% CI: 0.24, 0.50, $p < 0.001$). The effect was largely independent of the supplementation cessation (until delivery or not), type of intervention (vitamin D alone or in association with calcium), and study design. Increasing dose of vitamin D was associated with reduced incidence of preeclampsia (slope of *log* OR: −1.1, 95% CI: −1.73, −0.46; $p < 0.001$).

Conclusions: Results suggest that vitamin D supplementation may be useful in preventing preeclampsia. These data are especially useful for health-care providers who engage in the management of pregnant women at risk for preeclampsia. Our findings are a call for action to definitively address vitamin D supplementation as a possible intervention strategy in preventing preeclampsia in pregnancy.

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1. Introduction

Vitamin D deficiency, as measured by circulating 25(OH)-vitamin D concentrations, is reported to be as high as 40% among pregnant women and is also very common and profound during lactation [1]. In Mediterranean countries, where vitamin D deficiency is even more prevalent (up to 60–80%), neither vitamin D supplementation nor policies of food fortification are currently recommended during pregnancy, and they remain entirely absent from clinical practise [2]. As pregnancy progresses, the requirements of vitamin D increase and consequently, any preexisting vitamin D deficiency can worsen [3]. In particular, a compromised maternal vitamin D status has been associated with an approximately two-fold increased prevalence of congenital heart defects in offsprings and a higher incidence of fetal miscarriage, gestational diabetes, bacterial vaginosis and perinatal depression in mothers, other than impaired fetal and childhood growth [3–5]. Furthermore, inadequate plasma 25(OH)-vitamin D concentration during early pregnancy seems to be associated with more pronounced changes in total cholesterol and low-density lipoprotein cholesterol throughout gestation [6], and with an increased risk of developing hypertensive disorders [7].

In a cohort study performed on 13 806 pregnant women, maternal vitamin D deficiency at 23–28 weeks of gestation was strongly associated with an increased risk for severe preeclampsia after adjustment for relevant confounders (odd ratio [OR] 3.16, 95% confidence interval [CI]: 1.77–5.65) [8]. To date, vitamin D supplementation has been demonstrated to potentiate nifedipine treatment for preeclampsia, shortening the time to control blood pressure and prolonging time before subsequent hypertensive crisis, probably *via* an immunomodulatory mechanism [9], though data on the effect of vitamin D supplementation in preventing the onset of preeclampsia in pregnancy are still inconclusive [10].

For this reason, we aimed to assess the impact of vitamin D supplementation on the risk of preeclampsia through a systematic review of the literature and a meta-analysis of the available randomized controlled clinical trials [RCTs].

2. Methods

The study was designed according to guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [11], and was registered in the PROSPERO database (ID: CRD42019119207). Due to the study design (meta-analysis), neither Institutional Review Board (IRB) approval, nor patient informed consents were required.

2.1. Search strategy

PubMed, SCOPUS, Google Scholar and ISI Web of Science by Clarivate databases were searched, with no language restriction, using the following search terms: ("Vitamin D" OR "Hydroxyvitamin D (25(OH)D)" OR "25(OH)D" OR "25-hydroxycholecalciferol") AND ("Pregnancy" OR "Pregnant women" OR "Gestation") AND ("Clinical trial" OR "Clinical study" OR "study" OR "prospective study" OR "Randomized controlled trial" OR "RCT"). The wild-card term "*" was used to increase the sensitivity of the search strategy, which was limited to studies in humans. The reference list of identified papers was manually checked for additional relevant articles. In particular, additional searches for potential trials included the references of review articles on that issue, and the abstracts from selected congresses on the subject of the meta-analysis. Literature was searched from inception to January 21st, 2019.

All abstracts were screened by two reviewers (SF and FF) in order to remove ineligible articles. The remaining articles were obtained in full-text and assessed again by the same two researchers who evaluated each article independently and carried out data extraction and quality assessment. Disagreements were resolved by discussion with a third party (AFGC).

2.2. Study selection criteria

Original studies were included if they met the following criteria: (i) being a prospective randomized controlled trial with either multicentre or single-centre design, (ii) having at least a single dose of vitamin D prescribed in the active group, (iii) having a control group for vitamin D supplementation, (iv) involving pregnant women not treated with vitamin D before gestation, (v) testing the safety of vitamin D administration, (vi) reporting all the adverse events occurred during the treatment.

Studies were also excluded according to the following criteria: (i) lacking an appropriate controlled design for vitamin D supplementation or testing multivitamin or multimineral supplements with vitamin D; (ii) studies with the overlapping participants with other studies; (iii) reviews, letters or comments; (iv) population-based cohort studies. Narrative reviews, comments, opinion papers, editorials, letters or any other publication lacking primary data and/or explicit method descriptions, were also excluded.

2.3. Data extraction

Data abstracted from the eligible studies were: i) first author's name; ii) year of publication; iii) study location; iv) study design; v) main inclusion criteria and underlying disease; vi) type of intervention; vii) study groups; vii) number of participants in the active and control groups; viii) maternal and ix) gestational age at baseline. Missing or unpublished data were sought by trying to contact authors or sponsors *via* e-mail and repeated messages were sent in case of no response. All data extraction and database typing were reviewed by the principal investigator (AFGC) before the final analysis, and doubts were resolved by mutual agreement among the authors.

2.4. Quality assessment

A systematic assessment of risk of bias in the included studies was performed using the Cochrane criteria risk of bias tool [12]. The following items were used: adequacy of sequence generation, allocation concealment, blinding addressing of dropouts (incomplete outcome data), selective outcome reporting, and other probable sources of bias [13]. Risk-of-bias assessment was independently performed by 2 authors (FF and AFGC); disagreements were resolved by a consensus-based discussion.

2.5. Data synthesis

Meta-analysis was entirely conducted using Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ) [14]. Effect size was expressed as odd ratio (OR) and 95% CI [15]. Studies' findings were combined using a fixed-effect model since the low level of heterogeneity, which was quantitatively assessed using the Higgins index (I^2) [16]. When results were presented in multiple time points, only data relating to the longest duration of treatment were considered. Furthermore, in order to avoid a double-counting problem, in trials comparing multiple treatment arms versus a single control group, the number of subjects in the control group was divided by the required comparisons. Studies with zero events in both arms were excluded.

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In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method (i.e. removing one study at a time and repeating the analysis) [17].

Subgroup analyses were performed to explore the impact on the effect size of the beginning of the supplementation related to the gestational age (≤20 weeks or >20 weeks), whether the supplementation lasted up to the delivery and the impact of calcium intake and study blindness. Finally, as potential confounders of the treatment response, vitamin D biweekly supplemented dose and maternal age were entered into a fixed-effect meta-regression model to explore their association with the estimated effect size on the risk of preeclampsia. Two-sided *p*-values ≤0.05 were considered statistically significant for all tests.

2.6. Publication bias

Potential publication biases were explored using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation test and Egger's weighted regression test [18,19]. The Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication biases [20]. Two-sided *p* values ≤0.05 were always considered as statistically significant and, in case of a significant result, Rosenthal fail-safe N test was applied in order to calculate the number of additional negative studies that would be needed to increase the *p* value for the meta-analysis to above 0.05 [21].

3. Results

3.1. Flow and characteristics of the included studies

After database searches performed strictly according to inclusion and exclusion criteria, 257 published articles were identified, and the abstracts were reviewed. Of these, 151 were excluded because they were non-original articles. Another 59 were eliminated because they did not finally meet the inclusion criteria. Thus, 47 articles were carefully assessed and reviewed. An additional 20 studies were excluded because of substantial sample overlap ($n = 6$), studies testing multivitamin or multimineral supplements with vitamin D ($n = 3$), or lack of a control group for vitamin D supplementation ($n = 11$) (Appendix 1).

Finally, 27 RCTs were eligible and included in the meta-analysis [22–48]. The study selection process is shown in Fig. 1. Data were pooled from 27 RCTs comprising 59 arms, which included 4777 participants, with 2487 in the vitamin D-treated arm and 2290 in the control one.

Eligible studies were published between 1980 and 2018 and enrolled pregnant women at low-to-high risk for preeclampsia according to the most recent guidelines of the European Society of Cardiology (ESC), the American Heart Association (AHA), and the American College of Obstetricians and Gynecologists (ACOG) [49–51]. They were conducted in Iran ($n = 15$), India ($n = 3$), Bangladesh ($n = 2$), France ($n = 2$), Brazil ($n = 1$), China ($n = 1$),

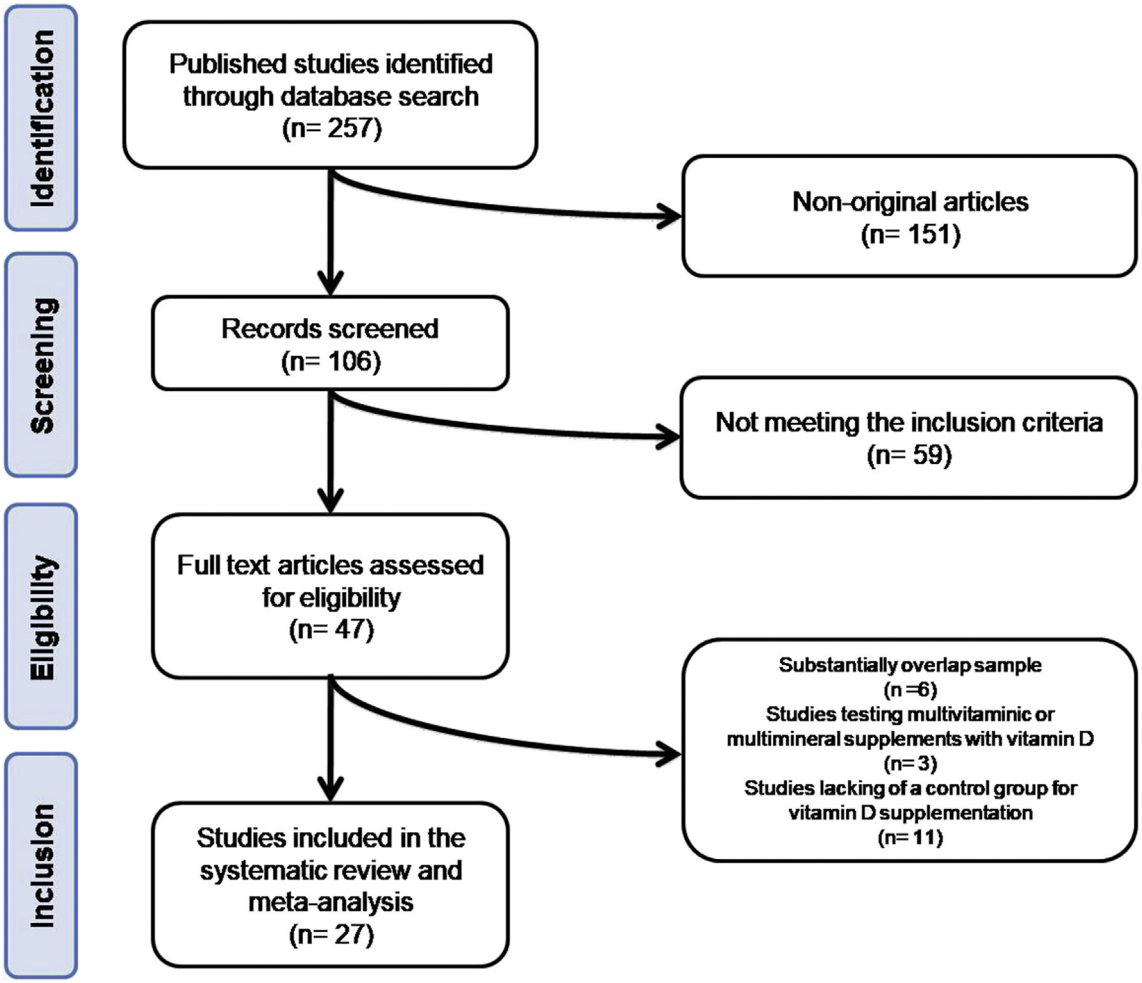

Fig. 1. Flow chart of the number of studies identified and included into the meta-analysis.

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Table 1
Baseline characteristics of the studies included in the meta-analysis. Numerical data are reported as absolute number or mean ± standard deviation, unless otherwise specified.

First author (year)	Study location	Design	Main inclusion criteria for the studies	Intervention	Study group	Participants (n)	Maternal age (years)	Gestational age (weeks)
Jamilian, M (2018) [22]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Aged 18–40 years -primigravida women - 24–28 weeks of gestation - diagnosis of gestational diabetes mellitus	Vitamin D	Vitamin D_3 50 000 IU and probiotics once every two weeks	30	28.9 ± 6.1	NA
					Probiotics	30	31.2 ± 5.9	NA
Sasan, SB (2017) [23]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical study	- History of preeclampsia in previous pregnancies - serum 25-OH vitamin D ≥ 25 ng/ml	Vitamin D	Vitamin D_3 50 000 IU once every two weeks	70	32 ± 5.9	14.4 ± 3.1
					Placebo	72	29.8 ± 5.2	14.4 ± 2.7
Asemi, Z (2016) [24]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical study	- Aged 18–40 years - singleton pregnancy - 25 weeks of gestation	Vitamin D + Calcium	Vitamin D_3 200 IU/ day + Calcium 500 mg/day	23	25.7 ± 4.2	NA
					Placebo	23	24.3 ± 3.4	NA
Cooper, C (2016) [25]	United Kingdom	Multicentre, randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Age > 18 years - singleton pregnancy - <17 weeks of gestation	Vitamin D	Vitamin D_3 1000 IU/day	565	30.5 ± 5.2	NA
					Placebo	569	30.5 ± 5.2	NA
					Vitamin D_3 2000 IU/day	86	26 (22–33)[a]	27 (26–29)[a]
					Placebo	87	28 (23–33)[a]	27 (26–29)[a]
Vaziri, F (2016) [26]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Age ≥ 18 years - singleton pregnancy - 26–28 weeks of gestation - no previous cesarean sections	Vitamin D	Vitamin D_3 2000 IU/day	78	26.4 ± 4.88	NA
					Placebo	75	26.2 ± 4.3	NA
					Vitamin D_3 2000 IU/day	86	29 ± 6	27 (26–30)[a]
					Placebo	87	30 ± 6	27 (26–29)[a]
Yazdchi, R (2016) [27]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Age 15–45 years - 24–28 weeks of gestation - diagnosis of gestational diabetes mellitus	Vitamin D	Vitamin D_3 50 000 IU once every two weeks	38	31.6 ± 4.4	NA
					Placebo	38	32.1 ± 3.6	NA
Karamali, M (2015) [28]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Age 18–40 years - primigravida women - women at risk for preeclampsia	Vitamin D	Vitamin D_3 50 000 IU once every two weeks	30	27.4 ± 5.2	NA
					Placebo	30	27.4 ± 5.2	NA
Lei, Q (2015) [29]	China	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Age 20–32 years - nulliparous woman - singleton pregnancy - 18–20 weeks of gestation	Vitamin D	Vitamin D_3 2000 IU/day	30	NA	NA
					Placebo	30	NA	NA
Mohammad-Alizadeh-Charandabi, S (2015) [30]	Iran	Randomized, triple-blind, placebo-controlled, parallel-group, clinical trial	- Age 18–39 years - 25–30 weeks of gestation	Vitamin D and Vitamin D + Calcium	Vitamin D_3 1000 IU/day	42	27.7 ± 5.6	NA
					Vitamin D_3 1000 IU/ day + Calcium 300 mg/day	42	27.5 ± 5.3	NA
					Placebo	42	26.4 ± 4.9	NA
Sablok, A (2015) [31]	India	Randomized controlled trial	- Primigravida woman - singleton pregnancy - 14–20 weeks of gestation	Vitamin D	Vitamin D_3 60 000 IU once at 20 weeks of gestation	120	NA	NA
					Vitamin D_3 120 000 IU at 20 and 24 weeks of gestation			
					Vitamin D_3 120 000 IU at 20, 24, 28 and 32 weeks of gestation			
					No intervention	60	NA	NA
Samimi, M (2015) [32]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Age 18–40 years - primigravida women - women at risk for preeclampsia	Vitamin D + Calcium	Vitamin D_3 50 000 IU every two weeks + Calcium 1000 mg/day	30	27.3 ± 3.7	NA
					Placebo	30	27.1 ± 5.2	NA
Shahgheibi, S (2015) [33]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- At least one risk factor for gestational diabetes mellitus	Vitamin D_3	Vitamin D_3 5000 IU/day	50	NA	NA
					Placebo	50	NA	NA
Asemi, Z (2014) [34]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Age 18–40 years - diagnosis of gestational diabetes mellitus at 24–28 weeks of gestation - no insulin therapy	Vitamin D + Calcium	Vitamin D_3 50 000 IU at study baseline and on day 21 + Calcium 1000 mg/day	28	28.7 ± 6.0	NA
					Placebo	28	30.8 ± 6.6	NA
Grant, CC (2014) [35]	New Zealand	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- >27-weeks of gestation - singleton pregnancy	Vitamin D	Vitamin D_3 1000 IU/day	87	27 ± 6	28 (26–29)[a]
					Vitamin D_3 2000 IU/day	86	26 ± 6	27 (26–29)[a]
					Placebo	87	28 ± 6	27 (26–29)[a]

Table 1 (*continued*)

First author (year)	Study location	Design	Main inclusion criteria for the studies	Intervention	Study group	Participants (n)	Maternal age (years)	Gestational age (weeks)
Harrington, J (2014) [36]	Bangladesh	Randomized, double-blind, placebo-controlled, parallel-group clinical study	- Third trimester of gestation	Vitamin D	Vitamin D_3 35 000 IU once every week	80	NA	NA
					Placebo	80	NA	NA
Asemi, Z (2013) [37]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Aged 18–40 years - 25 weeks of gestation	Vitamin D	Vitamin D_3 400 IU/day	27	25.3 ± 4.2	NA
					Placebo	27	24.8 ± 3.6	NA
Asemi, Z (2013) [38]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Aged 18–40 years - diagnosis of gestational diabetes mellitus at 24–28 weeks of gestation	Vitamin D + Calcium	Vitamin D_3 IU 50 000 IU at study baseline and on day 21 + Calcium 1000 mg/day	27	31.7 ± 5.6	NA
					Placebo	27	31.8 ± 6.6	NA
Diogenes, ME (2013) [39]	Brazil	Randomized, single-blind, placebo-controlled, parallel-group, clinical trial	- Age 13–19 years - primigravida women - singleton pregnancy - 23–29 weeks of gestation	Vitamin D + Calcium	Vitamin D_3 200 IU/ day + Calcium 600 mg/day	43	NA	NA
					Placebo	41	NA	NA
Jelsma, JG (2013) [40]	Europe	Multicentre Europe-wide, randomized, single-blind, placebo-controlled, clinical trial	- Age ≥ 18 years - BMI ≥ 29 kg/m^2 - singleton pregnancy - ≤19 weeks and 6 days of gestation	Vitamin D	Vitamin D_3 1600 IU/day	110	NA	NA
					Placebo	110	NA	NA
Naghshineh, E (2013) [41]	Iran	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Nulliparous women - <16 weeks of gestation	Vitamin D	Vitamin D_3 600 IU/day	70	25 ± 4.1	NA
					Placebo	70	25 ± 4.1	NA
Roth, DE (2013) [42]	Bangladesh	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Age 18–35 years - 26–30 weeks of gestation	Vitamin D	Vitamin D_3 35 000 IU once every week	80	22.4 ± 3.5	27.6 ± 1.1
					Placebo	80	22.4 ± 3.4	27.9 ± 1.0
Asemi, Z (2012) [43]	Iran	Randomized, single-blind, placebo-controlled, parallel-group, clinical trial	- Age 18–35 years - primigravida women - singleton pregnancy - women at risk for preeclampsia - third trimester of gestation	Vitamin D + Calcium	Vitamin D_3 200 IU/ day + Calcium 500 mg/day	24	24.9 ± 4.2	NA
					Placebo	25	24.9 ± 3.7	NA
Taherian AA (2002) [44]	Iran	Randomized controlled trial	- Nulliparous woman - singleton pregnancy - <20 weeks of gestation - SBP/DBP ≤ 130/ 80 mmHg and no proteinuria detectable by a dipstick	Vitamin D + Calcium	Vitamin D_3 200 IU/ day + Calcium 500 mg/day	330	21.9 (21.6 –22.4)[a]	NA
					No treatment	330	21.2 (20.8 –21.6)[a]	NA
Marya, RK (1987) [45]	India	Randomized controlled trial	- Age 20–35 years	Vitamin D + Calcium	Vitamin D_3 1200 IU/ day + Calcium 375 mg/day	200	NA	NA
					No treatment	200	NA	NA
Delvin, EE (1986) [46]	France	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Singleton pregnancy - third trimester of pregnancy	Vitamin D	Vitamin D_3 1000 IU/day	40	NA	NA
					Placebo	40	NA	NA
Mallet, E (1986) [47]	France	Randomized controlled trial	- Third trimester of pregnancy in winter	Vitamin D	Vitamin D_2 1000 IU/day	21	26 (18 –35)[b]	NA
					Vitamin D_2 200 000 IU	27	25 (19 –36)[b]	NA
					No treatment	29	25 (18 –35)[b]	NA
Brooke, OG (1980) [48]	India	Randomized, double-blind, placebo-controlled, parallel-group, clinical trial	- Asian ethnicity	Vitamin D	Vitamin D_3 1000 IU/day	59	23.9 ± 4.8	NA
					Placebo	67	23.7 ± 3.1	NA

DBP = Diastolic blood pressure; NA = Not available; SBP = Systolic blood pressure.
[a] Expressed as median and (95% confidence interval).
[b] Expressed as mean and variation range.

Europe (multicentre Europe-wide study) ($n = 1$), New Zealand ($n = 1$), and United Kingdom ($n = 1$). Several pharmaceutical forms of vitamin D and different timings of administration were tested across the studies. Detailed baseline characteristics of the evaluated studies are summarized in Table 1.

3.2. Risk of bias assessment

Almost every included study was characterized by sufficient information regarding random sequence generation, allocation concealment and personnel blinding, and outcome assessments, and showed low risk of bias because of incomplete outcome data and selective outcome reporting. Details of the quality of bias assessment are reported in Table 2.

3.3. Risk of preeclampsia

No cases of preeclampsia were experienced by pregnant women enrolled in 17 studies among those selected. In pooled analyses for the remaining 12 studies, vitamin D supplementation was inversely associated with an increased risk of preeclampsia (OR 0.37, 95% CI: 0.26, 0.52, $p < 0.001$; $I^2 = 0\%$) (Fig. 2) and the results remained

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Table 2
Quality of bias assessment of the included studies according to Cochrane guidelines.

First author (year)	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Jamilian, M (2018) [22]	L	L	L	L	L	L
Sasan, SB (2017) [23]	L	L	L	L	L	L
Asemi, Z (2016) [24]	L	L	L	L	L	L
Cooper, C (2016) [25]	L	L	L	L	L	L
Vaziri, F (2016) [26]	L	L	L	L	L	L
Yazdchi, R (2016) [27]	L	L	L	L	L	L
Karamali, M (2015) [28]	L	L	L	L	L	L
Lei, Q (2015) [29]	L	L	L	L	L	L
Mohammad-Alizadeh-Charandabi, S (2015) [30]	L	L	L	L	L	L
Sablok, A (2015) [31]	H	H	H	L	L	U
Samimi, M (2015) [32]	L	L	L	L	L	L
Shahgheibi, S (2015) [33]	L	L	L	L	L	L
Asemi, Z (2014) [34]	L	L	L	L	L	L
Grant, CC (2014) [35]	L	L	L	L	L	L
Harrington, J (2014) [36]	L	L	L	L	L	L
Asemi, Z (2013 a) [37]	L	L	L	L	L	L
Asemi, Z (2013 b) [38]	L	L	L	L	L	L
Diogenes, ME (2013) [39]	H	H	U	L	L	L
Jelsma, JG (2013) [40]	U	U	U	L	L	L
Naghshineh, E (2013) [41]	L	L	L	L	L	L
Roth, DE (2013) [42]	L	L	L	L	L	L
Asemi, Z (2012) [43]	H	H	U	L	L	L
Taherian AA (2002) [44]	H	H	H	L	L	U
Marya, RK (1987) [45]	H	H	H	L	L	U
Delvin, EE (1986) [46]	L	L	L	H	U	L
Mallet, E (1986) [47]	H	H	H	L	L	U
Brooke, OG (1980) [48]	L	L	L	H	U	L

L = Low risk of bias; H = High risk of bias; U = Unclear risk of bias.

strong in the leave-one-out sensitivity analysis (Fig. S1). When the supplementation began up to 20 weeks of gestation, the risk was even a little lower (OR 0.35, 95% CI: 0.24, 0.50, $p < 0.001$; $I^2 = 0\%$). When the supplementation of vitamin D was started after the 20th week, the statistical significance was lost, though the trend was maintained (OR 0.60, 95% CI: 0.18, 2.03, $p = 0.411$; $I^2 = 0\%$). The test to compare the two effect sizes (0.35 *vs* 0.60) yielded a Q-value of 0.69 with a corresponding p value of 0.408, so that there were no significant differences between groups.

The effect was largely independent from the continuity of the supplementation before (OR 0.36, 95% CI: 0.23, 0.55, $p < 0.001$; $I^2 = 0\%$) or up to delivery (OR 0.38, 95% CI: 0.21, 0.69, $p = 0.002$; $I^2 = 0\%$) (p between groups 0.877), from the type of intervention considering vitamin D alone (OR 0.37, 95% CI: 0.24, 0.56, $p < 0.001$; $I^2 = 0\%$) or in association with calcium (OR 0.36, 95% CI: 0.20, 0.67, $p = 0.001$; $I^2 = 0\%$) (p between groups 0.966) and whether open-label (OR 0.34, 95% CI: 0.21, 0.55, $p < 0.001$; $I^2 = 0\%$) or blinded (OR 0.40, 95% CI: 0.23, 0.56, $p < 0.001$; $I^2 = 0\%$) (p between groups

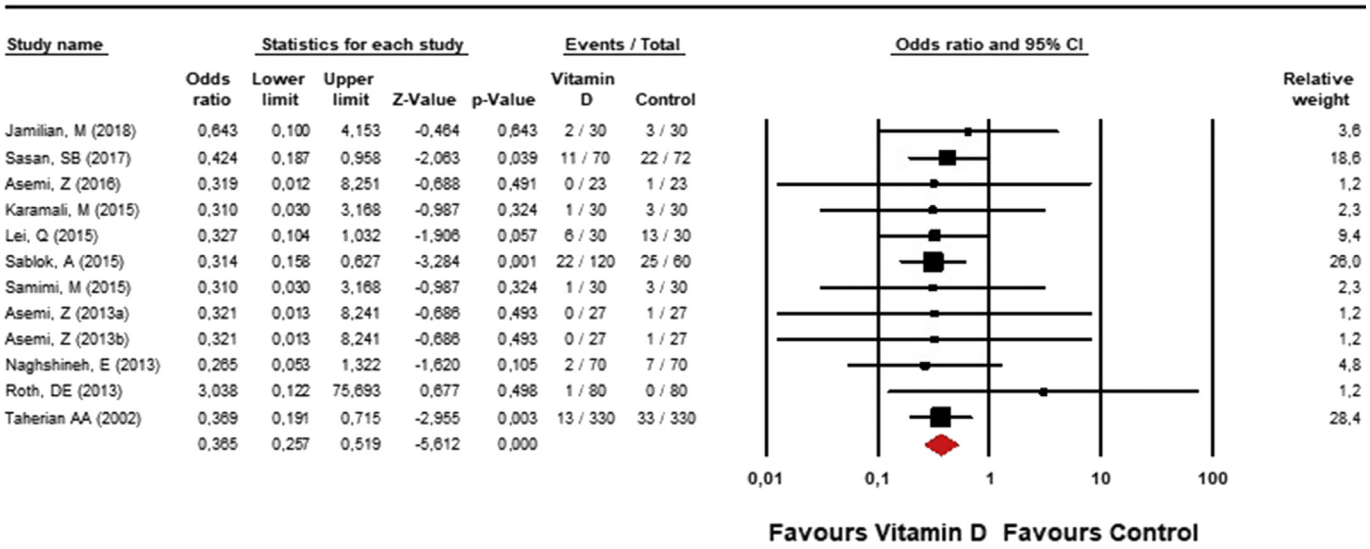

Fig. 2. Forest plot comparing the risk of preeclampsia in the studied groups.

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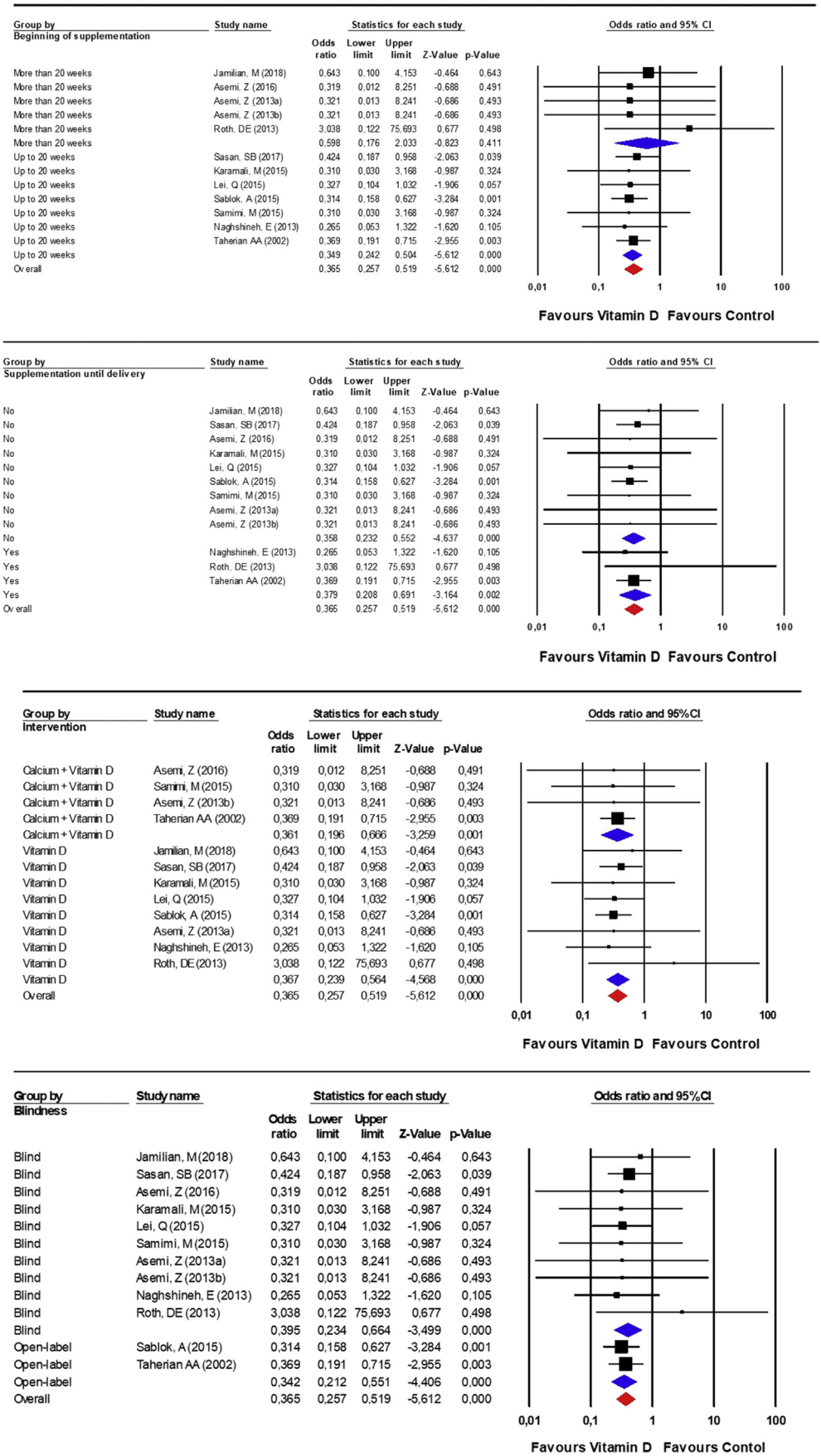

Fig. 3. Forest plot displaying the risk of preeclampsia in the studied groups. Subgroup analyses stratified by timing for the supplementation, the type of intervention and the study design.

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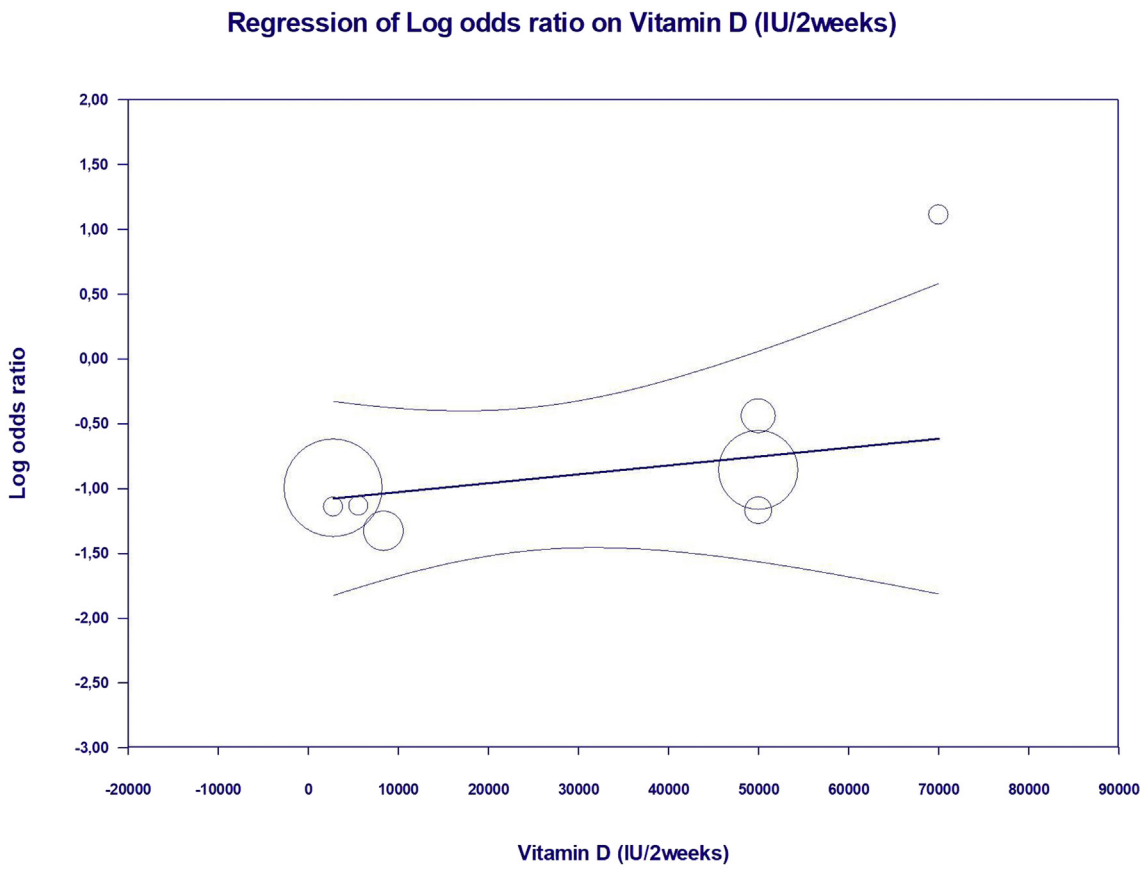

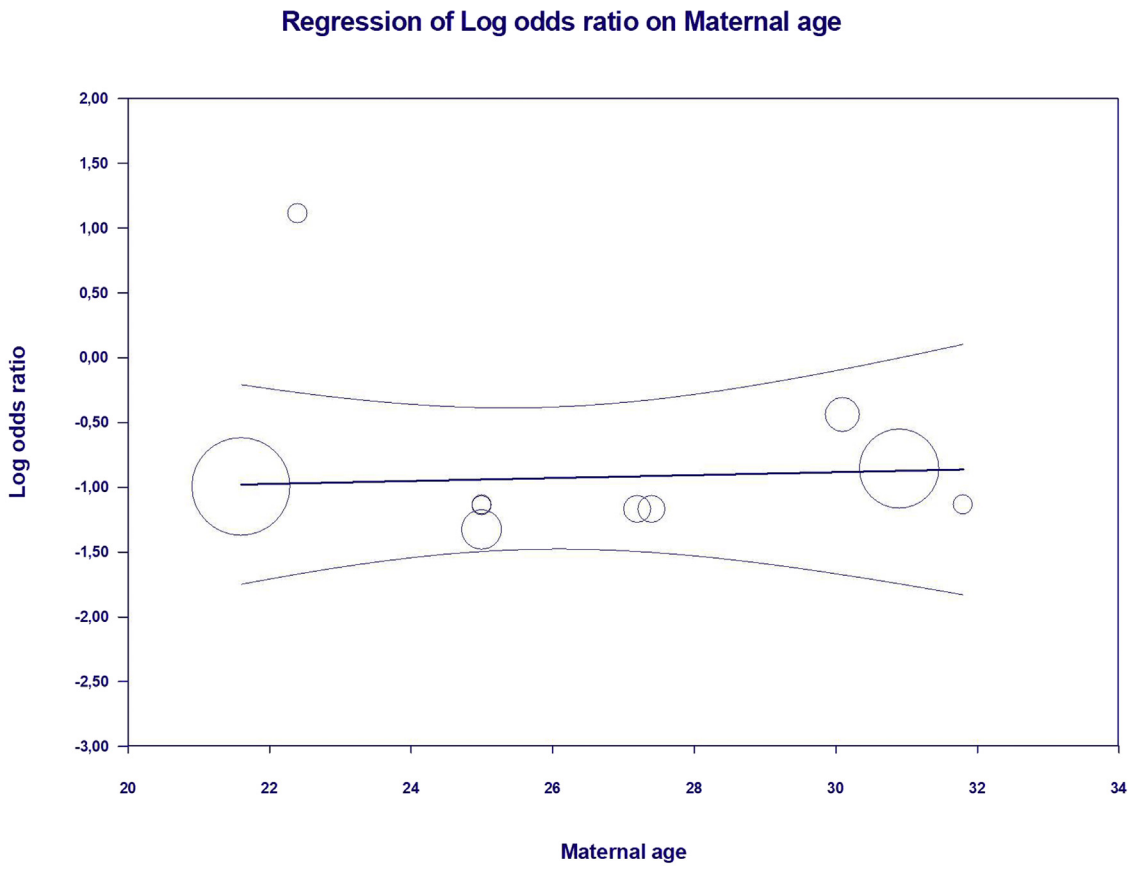

Fig. 4. Meta-regression bubble plots of the association between log odds ratio and vitamin D dosage (above) and maternal age (below). The size of each circle is inversely proportional to the variance of change.

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0.690) (Fig. 3). Increasing the dosage of vitamin D was inversely associated with the increasing risk of preeclampsia (slope of *log* OR: −1.1, 95% CI: −1.73, −0.46, corresponding to OR 0.33, 95% CI: 0.18, 0.63; two-tailed $p < 0.001$) (Fig. 4). This risk of preeclampsia was not associated with maternal age ($p > 0.05$) (Fig. 4).

Visually, the funnel plot of standard error by log odds ratio was slightly asymmetric (Fig. S2). This asymmetry was imputed to two potentially missing studies on the right side of the funnel plot, which altered the estimated risk of preeclampsia from 0.365 to 0.373 (95% CI: 0.265, 0.524). However, Egger's linear regression and Begg's rank correlation did not confirm the presence of any publication bias ($p > 0.05$ for all comparisons). Finally, the classic fail-safe N test suggested that 52 studies with negative results would be needed to bring the estimated risk of preeclampsia to a non-significant level ($p > 0.05$).

4. Discussion

Preeclampsia is associated with adverse maternal and fetal outcomes [52,53], hence there is an increasing urgency in identifying clinical and laboratory predictors of preeclampsia, though it is even more important to identify safe and effective ways to prevent its development. To the best of our knowledge, the current systematic review and meta-analysis is the first to comprehensively analyze evidence from randomized controlled clinical studies on the efficacy of supplementation with vitamin D on the prevention of preeclampsia.

A previous meta-analysis by Khaing et al. mainly focused on calcium supplementation, concluded that vitamin D supplementation might also have been beneficial for the prevention of hypertensive disorders in pregnancy, though more evidence was needed [54]. However, our meta-analysis would be large enough to dispel any doubt. On the basis of the present findings, vitamin D supplementation was very beneficial in prevention of preeclampsia and largely independent of the timing of the supplementation (until delivery or not), maternal age and vitamin D dosage. When the supplementation is started up to 20 weeks of gestation, the benefit for pregnant women seems to be much higher.

Furthermore, co-administration of vitamin D combined with calcium does not seem to bring an additional benefit. On the other hand, calcium requires daily administration and a high dosage, that could increase the general cardiovascular risk of the pregnant women [55,56]. Indeed, the most recent ESC, World Health Organization (WHO) and ACOG Guidelines [49,51,57] recommend calcium supplementation to be prescribed in deficiency in the pregestational age without referring to vitamin D, although the latter might be preferred for preventing preeclampsia. Indeed, vitamin D deficiency is associated with a relatively large number of risk factors for endothelial dysfunction and vascular health impairment [58]. On the other side, adequate vitamin D intake might help with the maintenance of the calcium homeostasis − which is inversely related to blood pressure levels − [32] or may directly suppress the proliferation of the vascular smooth muscle cells [59]. Furthermore, vitamin D might be a powerful endocrine suppressor of renin biosynthesis and could regulate the renin−angiotensin system, which plays a critical role in blood pressure control [59]. Finally, vitamin D could also modulate the synthesis of adipokines related to endothelial and vascular health [60].

There are some limitations of the current analysis. The main one is related to the different administration timing and pharmaceutical forms of vitamin D supplemented to the pregnant women. At a high dosage, even in a single administration, vitamin D may therefore be sufficient to prevent preeclampsia, considering that vitamin D accumulates in body fat [61]. Further research should be focused on the recommended regimen in pregnancy (i.e. daily, weekly or a single dose). Based on our data we might recommend beginning of a supplementation up to 20 week of a pregnancy, irrespective it is going to be continued up to delivery or not, with the dose around 25.000 UI/week, where the weekly administration could require the monitoring of calcemia and calciuria as potentially markers of potential vitamin D overdose. Thought it seems to be no interaction between vitamin D and preeclampsia by maternal age, the explored range of age in our meta-analysis is narrow since the included studies do not enroll women younger than 20 or older than 34 years. Then, in the included RCTs, no information on achieved vitamin D serum level is reported. As a result, it is still unknown if the benefit of vitamin D supplementation is greater among women still with vitamin D deficiency and/or in the ones reaching the optimal serum vitamin D levels. However, the aim of our study was to evaluate if clinical vitamin D supplementation *per se* could prevent a clinically relevant outcome such as preeclampsia incidence and our results confirm this hypothesis. Moreover, our positive results could also underestimate the potential preventive effect of vitamin D supplementation, since the most part of enrolled patients were not strictly selected based on their baseline circulating vitamin D nor their achievement of optimal vitamin D after supplementation. Studies from North America and Africa are also not available and this is of particular importance since prevalence of 25(OH)-vitamin D deficiency differs in various parts of the world based on latitude and sociocultural practices such as covered manner of dress for women [62,63]. Thus, our data could not automatically inferred to North-American and African women, even if we could suppose that the mechanisms potentially involved in the protective effect of vitamin D towards preeclampsia incidence are similar in all ethnicities [63−65].

The main strength of this meta-analysis is the number of the studies included and the low degree of heterogeneity observed. Our meta-analysis might have also important clinical relevance as it indicates that vitamin D supplementation may prevent preeclampsia. For that reason, it should be especially considered in pregnant women at increased risk of developing hypertensive disorders, mostly in countries with a high risk for vitamin D deficiency, including most of the European and some Asian countries [62−65]. This is relevant since in the most recent guidelines, vitamin D supplementation is not taken into consideration for preeclampsia prevention [49,50,57].

5. Conclusions

In conclusion, vitamin D supplementation may be useful in preventing preeclampsia. Large, well-designed prospective randomized clinical trials are needed to definitively address vitamin D supplementation as a possible intervention strategy and in order to identify the most effective dose regimen.

Authors' contribution

Silvia Fogacci and *Federica Fogacci* conceived, designed and performed the analysis; *Maciej Banach* and *Arrigo F.G. Cicero* verified the analytical methods; *Silvia Fogacci*, *Federica Fogacci*, *Maciej Banach* and *Arrigo F.G. Cicero* wrote the paper; *Michael J. Blaha*, *Silvia Fogacci*, *Adrian V. Hernandez*, *Gregory Y.H. Lip, Erin D. Michos* and *Peter P. Toth* provided critical revision of the manuscript; all Authors discussed the results and contributed to the final manuscript.

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Conflict of interest

Maciej Banach has served on the speakers bureau of Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Servier and Valeant, has served as a consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis, and has received grants from Sanofi and Valeant; *Claudio Borghi* has served as a consultant to Menarini and Servier; *Arrigo F.G. Cicero* has given talks, furnished scientific consultancies and/or participated in trials sponsored by Amgen, Angelini, Menarini and Mylan; *Federica Fogacci* has served as a consultant to Mylan; *Peter P. Toth* is a speaker and/or consultant for Amarin, Amgen, AstraZeneca, Kowa, Novo-Nordisk, Regeneron, Resverlogix, and Sanofi; *Michael J. Blaha*, *Silvia Fogacci*, *Adrian V. Hernandez*, *Gregory Y.H. Lip* and *Erin D. Michos* have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.08.015.

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