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SYSTEMATIC REVIEW

Multivitamin use and risk of preeclampsia: A systematic review and meta-analysis

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Abstract

Introduction: Preeclampsia is associated with adverse maternal and neonatal outcomes. It is unclear whether multivitamin use reduces the risk of preeclampsia. This systematic review and meta-analysis aimed to evaluate the association between multivitamin use and the risk of preeclampsia.

Material and methods: We searched PubMed, Embase and the Cochrane Library from database inception to July 2021. Randomized controlled trials (RCTs), case–control and cohort studies assessing the association between multivitamin use and risk of preeclampsia were eligible. Studies of treatment with a single micronutrient were excluded. Relative risks and 95% confidence intervals (95% CI) were calculated using random-effects models. RoB2, the Newcastle Ottawa Scale and GRADE were used to assess risk of bias and quality of evidence. The protocol was registered in PROSPERO (no. CRD42021214153).

Results: Six studies were included (33 356 women). Only two RCTs were found, both showing a significantly decreased risk of preeclampsia in multivitamin users. These studies were not compatible for meta-analysis due to clinical heterogeneity. A meta-analysis of observational studies using a random-effects model showed an unchanged risk of preeclampsia following multivitamin use (relative risk 0.85, 95% CI 0.69–1.03). The quality of evidence according to GRADE was very low.

Conclusions: Very weak evidence suggests that multivitamin use might reduce the risk of preeclampsia; however, more research is needed. Large RCTs should be prioritized. The results of this review do not allow any final conclusions to be drawn regarding a preventive effect of multivitamin use in relation to preeclampsia.

KEYWORDS
eclampsia, HELLP, micronutrients, multivitamin, preeclampsia, pregnancy, pregnant women

Abbreviations: AOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; NOS, Newcastle Ottawa Scale; RCT, randomized controlled trial.

1 | INTRODUCTION

Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality, complicating approximately 5% of pregnancies.[1] Preeclampsia and eclampsia are responsible for up to 63 000 deaths each year worldwide.[2] Preeclampsia is a pregnancy-induced disorder characterized by de novo development of concurrent hypertension and proteinuria, sometimes progressing into multiorgan dysfunction,[3] and is associated with an increased risk of cardiovascular and metabolic disease later in life.[4–8]

Although widely examined, the pathogenesis of preeclampsia remains unclear. It has been established that preeclampsia requires a placenta, not a fetus; hence, in terms of pathogenesis, preeclampsia is primarily a placental disorder.[9] Emerging evidence indicates that preeclampsia appears in at least two subtypes: early-onset preeclampsia, acknowledged to have a primarily placental cause, and late-onset preeclampsia, assumed to be caused by senescence of the placenta and a maternal predisposition to cardiovascular and metabolic disease.[10] Preeclampsia is hypothesized to result from poor placentation due to impaired remodeling of the spiral arteries during trophoblast invasion of the myometrium, leading to vascular placental hypoxia and increased oxidative stress.[11,12] Increased oxidative stress refers to elevated levels of reactive oxygen species, which can cause cell damage[13] and potentially impair the function and expression of endothelial nitric oxide synthase.[14] Dysfunction of endothelial nitric oxide synthase has been suggested as a potential cause of preeclampsia.[15] Oxidative stress causes syncytiotrophoblast cells to release proinflammatory cytokines, exosomes, anti-angiogenic agents and cell-free fetal DNA into the maternal circulation, which disrupts the homeostasis of the maternal endothelium.[16–18] This disruption leads to a systemic inflammatory response and, thus, the clinical syndrome of preeclampsia.[9] Reactive oxygen species can be balanced by antioxidants,[19] which is the rationale behind antioxidant therapy for the prevention of preeclampsia.

Studies of preeclamptic women have shown evidence of increased oxidative stress in the placenta[20–22] and low serum levels of antioxidants.[22–24] Multivitamins contain various antioxidants; hence, it is speculated that supplementation can decrease the risk of preeclampsia.[9] Furthermore, multivitamins contain calcium and vitamin D, which could play a role in preventing preeclampsia.[25–31]

The objective of this systematic review and meta-analysis was to examine whether there is an association between multivitamin use and the risk of preeclampsia. We hypothesized that preeclampsia is less frequent in women who use multivitamins in relation to pregnancy.

Key message

It is unclear whether multivitamin use reduces the risk of preeclampsia. Very weak evidence suggests that multivitamin use might reduce the risk of preeclampsia; however, more research is needed. Large randomized controlled trials should be prioritized.

2 | MATERIAL AND METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[32] The review protocol was registered in PROSPERO (no. CRD42021214153). There was no direct patient or public involvement.

2.1 | Data sources

With assistance from a librarian, we conducted a systematic search of PubMed, Embase and the Cochrane Library from database inception to July 2021. The search strategy was developed for MEDLINE and converted for use in the Embase and Cochrane Library databases. The search strategy included terms used to describe interventions with multivitamin use and the event of preeclampsia. The detailed search strategy is presented in Appendix S1.

2.2 | Selection criteria

Studies investigating multivitamin use in relation to pregnancy were considered eligible. We defined multivitamin use as the intake of capsules or tablets containing three or more vitamins or minerals. Studies including women being treated with fortified food, folic acid, iron or other micronutrients alone were excluded. No restrictions were applied regarding the date, publication or language, although studies were limited to those with human participants. Review papers, conference proceedings and case reports were not included. Two authors, CHC and SH, performed the abstract screening, full-text screening and extraction of included articles using the web-based tool Covidence,[33] used by Cochrane.[34] Any disagreement was discussed and resolved by consensus among CHC, SH and HTW.

2.3 | Data extraction

Study characteristics, including the setting, study design and measures, were extracted by CHC and SH. Data for the meta-analysis were extracted as raw data. The primary outcome was preeclampsia as defined by the authors. Secondary outcomes included hypertension, eclampsia, HELLP and newborn weight.

2.4 | Assessment of study quality

Three authors (CHC, SH and HTW) individually assessed the risk of bias using the Cochrane Collaboration risk of bias tool for randomized controlled trials 2.0 (RoB2)[35] and the Newcastle Ottawa Scale (NOS) for observational studies.[36] SH and HTW authored one of the included studies.[37] Hence, that particular study was assessed

by two other authors (CHC and LR). The NOS scale grades the studies through a star system with a maximum of nine stars. The studies are evaluated in three domains: selection of study groups, comparability of study groups and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies.[36] Since no universal standard criteria have been established, we defined studies with full scores or one missing star to be at low risk of bias, studies that had one missing star in more than one domain to be at moderate risk of bias, and studies with more than one missing star in a domain to be at high risk of bias. Finally, the quality of evidence across the studies was rated by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) framework.[38] Confidence in the estimate of the primary outcome was based on five domains (risk of bias, inconsistency, indirectness, imprecision and other considerations) and was categorized into four levels, from very low (⊕⊖⊖⊖) to high (⊕⊕⊕⊕). We resolved any differences in bias assessment and in grading by discussion until a consensus was reached.

2.5 | Statistical analysis

The meta-analysis was conducted using raw data if there were two or more available trials related to the specific outcome. For comparison, an additional meta-analysis was conducted using adjusted data from studies providing adjusted odds ratios. The meta-analysis was conducted using REVMAN (version 5.3). The heterogeneity was assessed by I^2, with I^2 >50% considered to indicate substantial heterogeneity, as described in the Cochrane Handbook for Systematic Reviews of Interventions.[34] Data were pooled in meta-analyses using random effects models. Calculation of number needed to treat was not applicable due to insignificant results.

3 | RESULTS

We identified 3794 articles through our literature search. After screening the abstracts, we excluded 3753 articles (Figure 1). This left 41 articles eligible for full-text review, of which six could be included in the review (Table S1). Two were based on randomized controlled trials (RCTs)[39,40] and four on observational studies.[37,41–43] The six included studies were carried out from 2005 to 2020 in five high-income and upper middle-income countries. The exclusion criteria and content of multivitamins varied, and all studies, except one RCT,[39] had a low risk of bias (Tables 1 and 2). One study did not provide sufficient measures to extract its raw data. Instead, these data were estimated in the meta-analyses from the given hazard ratio and prevalence in the group of the population using multivitamins and the group of non-users. The group of users only taking a supplementation of folic acid was not included in the meta-analysis.[42] None of the included studies reported use of prophylactic acetylsalicylic acid. The articles addressed multivitamin use in different periods of pregnancy. Due to substantial clinical heterogeneity, we did not perform a meta-analysis on RCTs.

3.1 | Randomized controlled trials

We included two RCTs.[39,40] The RCTs evaluated the effect of multivitamin use on preeclampsia risk later in pregnancy compared with the observational studies. Rumiris et al. included women with low antioxidant status after 8–12 weeks of gestation,[40] whereas Azami et al. included women above 20 weeks of gestation who had at least one risk factor for preeclampsia, including chronic vascular disease, hydatidiform mole, multiparity, diabetes mellitus, thyroid disease, chronic hypertension, nulliparity, history of preeclampsia, maternal age >35 years, kidney disease, collagen vascular disease, antiphospholipid antibody syndrome, family history of preeclampsia, thrombophilia and body mass index (BMI) >25 kg/m^2.[39] Both studies found a decreased risk of preeclampsia due to multivitamin use. In Rumiris et al., the intervention group of 29 subjects receiving multivitamins had two cases of preeclampsia, whereas the control group of 31 subjects had nine cases.[40] Azami et al. had two intervention groups, groups A and B, receiving different multivitamins (Table 1).[39] Each group consisted of 30 women. In group A (treated with ferrous sulfate, 800 mg Ca, 200 mg Mg, 8 mg Zn, 400 IU vitamin D_3), the incidence of preeclampsia was 13.3% compared with 33.3% in group B (treated with ferrous sulfate, 250 mg vitamin C, 55 mg vitamin E). In the control group (treated with ferrous sulfate), the incidence was 36.7%. The study by Rumiris et al. had a low risk of bias,[40] whereas the risk of bias in the RCT by Azami et al. was moderate due to an uncertain randomization process and deviations from the intended intervention (Figure S1).[39] We did not find the studies comparable for a meta-analysis due to inconsistency in selection criteria of the populations and difference in timing of the supplementation.

3.2 | Observational studies

The four included observational studies addressed multivitamin use in the periconceptional period and early pregnancy.[37,41–43] Three of the studies provided adjusted odds ratios (AORs),[37,41,43] which were pooled in a meta-analysis using a random effects model (Figure 2). This meta-analysis showed no significant decreased risk of preeclampsia (relative risk 0.74, 95% confidence interval [CI] 0.50–1.08). The statistical heterogeneity was 65%. One study had divided its population based on the timing of the multivitamins. Both subpopulations used the multivitamins before completed placentation. Since the data of this study is presented as two separate AORs, they were included separately in the meta-analysis.[37] All the observational studies provided raw data for meta-analysis. When using a random effects model on raw data, an relative risk of 0.85 (95% CI 0.69–1.03) was found. This analysis was based on 33 206 women and 955 events (Figure 2). The statistical heterogeneity was 30%. All the observational studies had a low risk of bias; they had relevant populations and used adjustments for relevant confounders (Figure S1).

The observational studies all conducted subgroup analyses on women with a BMI ≥25 kg/m^2. One study found a statistically

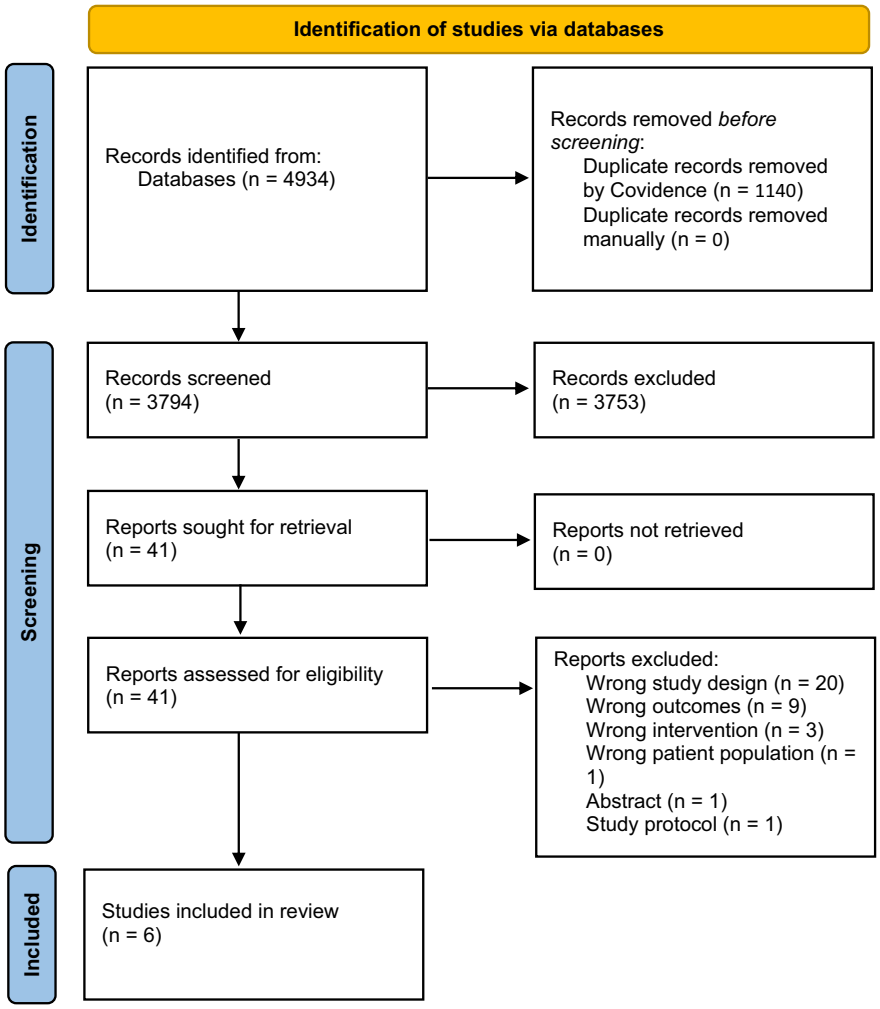

FIGURE 1 Flow chart of search results and process for selection and inclusion of references in systematic review

significant reduced risk of preeclampsia among women with a BMI ≥25 kg/m^2 (AOR 0.48, 95% CI 0.27–0.86).[43] Another study found a statistically significant reduced risk of preeclampsia among women with BMI between 25 kg/m^2 and 29.9 kg/m^2 in both the periconceptional period (AOR 0.49, 95% CI 0.24–0.99) and during early pregnancy (AOR 0.35, 95% CI 0.18–0.69).[37] The remaining observational studies found no significant reduction in the risk related to multivitamin use among women with a BMI ≥25 kg/m^2.[41,42]

The GRADE estimate for quality of evidence of both the observational studies and the RCTs was very low (⊕⊖⊖⊖) (Figure S2). The RCTs were downgraded to this measure due to inconsistency in populations and to concerns about risk of bias in one study,[39] and the evidence of the observational studies was downgraded from low to very low due to inconsistency in results. Since the RCTs were not comparable in a meta-analysis, the graded evidence contains no pooled relative effect measure.

3.3 | Secondary outcomes

We planned to assess hypertension, eclampsia, HELLP and newborn weight as secondary outcomes. Hypertension was measured in one of the included RCTs in which blood pressure at delivery was significantly lower in the intervention group than in the control group (systolic, 117.9 ± 10.7 vs 132.5 ± 23.8 mmHg, $P = 0.006$; diastolic, 77.5 ± 8.4 vs 86.0 ± 13.1 mmHg, $P = 0.009$).[40] This study also assessed newborn weight and found no significant difference in the median birthweight between the supplement group and the control group (3200 vs 3125 g, respectively). HELLP and eclampsia were assessed in one study including 15 154 women in which these outcomes were very rare (0.19% and 0.03%, respectively).[37]

4 | DISCUSSION

This review found no statistical significance when pooling the observational studies in meta-analyses. This applied to both adjusted and unadjusted data. (Figure 2). The observational studies all conducted subgroup analyses investigating the association between preeclampsia and multivitamin use in women with a BMI ≥25 kg/m^2, but the results were inconsistent. The observational studies were comparable due to similar populations (Table 2) and the timing of the multivitamin use, as there was an overlap between the periconceptional period and early pregnancy, with both periods occurring before completed placentation. This review also included two RCTs, but these were not found to be comparable for a meta-analysis.

TABLE 1 Included randomized controlled trials (RCTs)

Reference, year, country	Study design, study period, participants	Population, inclusion criteria	Exclusion criteria	Timing of multivitamin use	Content of multivitamin, control regimen used	Preeclampsia	Hypertension	Newborn weight	Adjustment	Risk of bias (RoB2)
Rumiris et al., 2006, Indonesia	RCT, 2003–2004, $n = 60$ (S: $n = 29$, control: $n = 31$)	Women with low antioxidant status, superoxide-dismutase level < 1102 U/g or 164 U/mL	Use of anti-hypertensive medication, diuretics, platelet active drugs, non-steroidal anti-inflammatory drugs or vitamins C > 150 mg and/or E > 75 IU per day, placental abnormalities, in vitro fertilization, fetal abnormalities, uterine bleeding/malformations, complications	8–12 weeks of gestation	S: 1000 IU vitamin A, 2.2 mg vitamin B12, 200 mg vitamin C, 400 IU vitamin E, 400 ug folic acid, 200 mg N-acetylcysteine, 2 mg Cu, 15 mg Zn, 0.5 mg Mn, 30 mg Fe, 800 mg Ca, 100 mg selenium Control: 30 mg Fe and 400 μg folic acid	OR 0.18 (95% CI 0.03–0.92)	Systolic blood pressure: 117.9 mmHg ± 10.7 vs 132.5 mmHg ± 23.8, $P = 0.006$. Diastolic blood pressure:77.5 mmHg ± 8.4 vs 86.0 mmHg ± 13.1, $P = 0.009$	3200 g vs 3125 g	NA	Low
Azami et al., 2017, Iran	RCT, 2014, $n = 90$ (S_A: $n = 30$, S_B: $n = 30$)	Women aged >35 years at increased risk of preeclampsia (chronic vascular disease, hydatidiform mole, multiparity, diabetes mellitus, thyroid disease, chronic hypertension, nulliparity, history of preeclampsia, kidney disease, collagen vascular disease, antiphospholipid antibody syndrome, family history of preeclampsia), thrombophilia, BMI >25 kg/m^2	Changes in diet during the trial	> 20 weeks of gestation	S_A: ferrous sulfate, 800 mg Ca, 200 mg Mg, 8 mg Zn, 400 IU vitamin D3 S_B: ferrous sulfate, 250 mg vitamin C, 55 mg vitamin E Control: ferrous sulfate	Prevalence of preeclampsia: S_A: 13.3% S_B: 33.3% Control: 36.7%	NA	NA	NA	Moderate

TABLE 2 Included observational studies

Reference, year, country	Study design, study period, participants	Population, inclusion criteria	Exclusion criteria	Timing of multivitamin use	Content of multivitamin	Preeclampsia (AOR/HR)	Hypertension	Adjustment	Risk of bias (NOS)
Bodnar et al., 2005, USA	Cohort study, 1997–2001, *n* = 1835	Pregnant women <16 weeks of gestation, aged 14–44 years carrying singletons	Pregnancy termination, delivery at another hospital, rescinded consent, adverse events, preexisting medical condition, toxicology screen positive, missing data	Periconceptional period	Unknown	AOR 0.55 (95% CI 0.32–0.95)	NA	Race, marital status, parity, physical activity, poverty index ratio	Low
Catov et al., 2008, Denmark	Cohort study, 1997–2003, *n* = 28 601	Pregnant women between 5 and 24 weeks of gestation carrying singletons	Single supplement use, no report duration of use, non-livebirths, preexisting diabetes	Periconceptional period	Unknown	HR 0.88 (95% CI 0.71–1.08)	NA	Body mass index, smoking, parity, gestational age at recruitment, and chronic hypertension	Low
Vanderlelie et al., 2016, Australia	Cohort study, 2006–2011, *n* = 2261	Pregnant women carrying singletons	Missing data, single supplement usage, pre-existing diabetes or essential hypertension	First trimester	Unknown	AOR 0.33 (95% CI 0.14–0.75)	NA	Maternal age, parity, gestational diabetes, indigenous status, maternal smoking	Low
Høgh et al., 2020, Denmark	Cohort study, 2012–2016, *n* = 15 154	Pregnant women without any risk factors of preeclampsia	Miscarriage, chronic disease, no information on multivitamin use, only preconception multivitamin use	Periconceptional period and early pregnancy	Unknown	Periconceptional period: AOR 0.97 (95% CI 0.70–1.36) Early pregnancy: AOR 0.97 (95% CI 0.71–1.32)	NA	Parity, age, smoking, education, exercise, ethnicity, BMI	Low

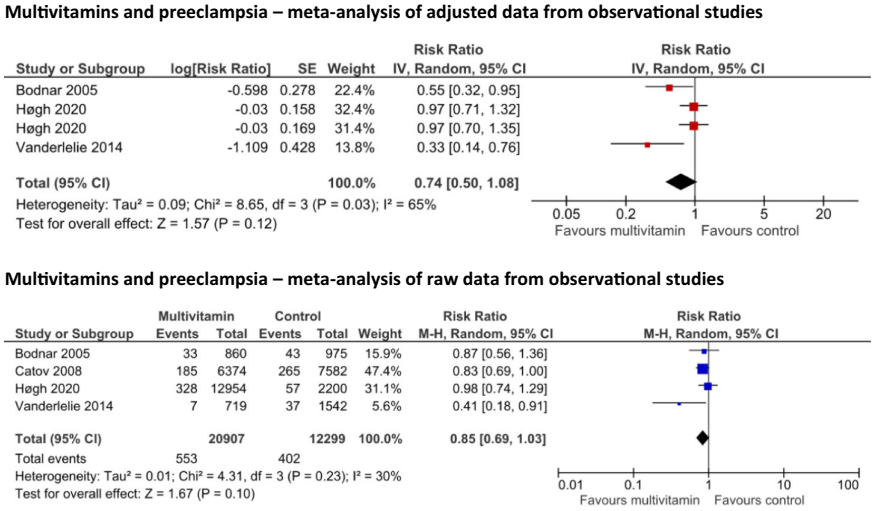

FIGURE 2 Meta-analyses. Forest plots of effect estimates for preeclampsia

However, the individual studies each showed a decreased risk of preeclampsia in relation to multivitamin use. Overall, the results of this review do not allow any final conclusions to be drawn regarding a preventive effect of multivitamin use in relation to preeclampsia.

Other reviews have studied the correlation between vitamins, antioxidants and pregnancy outcomes. One systematic review evaluating vitamin E and pregnancy outcomes found no reduction in the risk of preeclampsia due to supplementation with vitamin E,[44] whereas another systematic review found a reduced risk of preeclampsia due to vitamin D supplementation.[30] The effect of antioxidants, a prominent component of multivitamins, on the risk of preeclampsia was examined in a large Cochrane systematic review with uncertain results due to inconsistencies and high levels of statistical heterogeneity.[45] Multivitamins and adverse birth outcomes other than preeclampsia were evaluated in another systematic review,[46] which found that multivitamin use reduced the risk of children being born small-for-gestational age, a condition that can be related to preeclampsia.[47] The risk of preterm birth and low birthweight was unchanged.[46]

A strength of this review is the extensive systematic research of the literature covering a range of databases with no restrictions on language or date. The review provides a comprehensive assessment of evidence including both RCTs and observational studies with meta-analyses. The review was further strengthened by the use of bias assessment tools (RoB2 and NOS) and the GRADE approach to link evidence-quality evaluations to clinical recommendations.

We recognize that there are several limitations to this review. Most included studies were observational, with results based solely on data from maternal self-report. Although they had a low risk of bias, limitations apply due to the difficulty with inferences of causality and unknown factors introducing residual confounding, such as the consumption of micronutrients in the groups. In addition, confounding factors were not similar throughout all studies, and one study did not adjust for socioeconomic status,[43] a well-known risk factor for preeclampsia.[48] Furthermore, data in the meta-analyses were not adjusted for confounders. This leads to the risk of underestimating the effect shown in the two smallest observational studies, which showed a statistically significant lower risk of preeclampsia when adjusting for confounding factors.[41,43] This was not illustrated in our meta-analysis constructed from raw data; however, the meta-analysis seems robust, as the two larger studies adjusted for similar confounders without affecting the effect size or the confidence interval.[37,42] In addition, by using the random effects measure on the meta-analysis, we have taken the different population sizes into account. Our meta-analysis of adjusted data evaluates the effect of the confounding factors of three of our included studies (Figure 2)[37,41,43] but shows no significant decrease in risk of preeclampsia, and has a substantial statistical heterogeneity of 65%.

The content of the multivitamins in the observational studies was largely unknown and by using a wide definition of multivitamins, we might have introduced clinical heterogeneity due to slightly different intervention profiles. Additionally, one RCT has an intervention group receiving four minerals but only one vitamin.[39]

The decrease in the risk of preeclampsia in the included RCTs may have been influenced by the population being women at high risk of preeclampsia. This may also explain the high prevalence of preeclampsia in the studies.[39,40] One intervention started at 20 weeks,[39] after completion of placentation, and therefore does not support our rationale. Furthermore, this study had a moderate risk of bias arising from its randomization process, raising questions about the validity of the reasons for the reported incidences of preeclampsia, since socioeconomic status was unevenly distributed between the control and intervention groups. One should also note that the two RCTs comprised only 150 women in total, whereas the observational studies consisted of 33 206 women in total.

Two studies demonstrated a significantly lower risk of preeclampsia among women with a BMI ≥25 kg/m^2 who used multivitamin in early pregnancy.[37,43] Recent studies found an inverse correlation between total antioxidant capacity, oxygen radical absorbance capacity and BMI.[49–51] Furthermore, a study found that increasing BMI

was associated with increasing systemic oxidative stress.[52] High levels of oxidative stress may indicate a higher impact of multivitamin use on the risk of preeclampsia in overweight women. This may also explain the significant reduction in the risk of preeclampsia due to multivitamin use in women with low antioxidant status found in one of the included RCTs.[40]

The included studies were based on populations in high- and upper middle-income countries in which poor nutrition is less frequent than in low- and middle-income countries, where calcium intake is often below recommendations.[53] Daily calcium supplementation in populations with low dietary calcium intake is recommended by the World Health Organization to prevent preeclampsia.[31] A systematic review evaluating the dietary intake of women during pregnancy in low- and lower middle-income countries found that imbalanced macronutrients and inadequate micronutrient intake were common in the diet of pregnant women in developing countries.[54]

We estimated our evidence to be of very low quality, primarily due to the observational nature of the studies. This situation indicates the need for large, well-conducted RCTs. Dietary supplement use during pregnancy has been found to be positively correlated with higher income and higher socio-professional categories.[55] This makes RCTs difficult to conduct in high-income countries, since a large proportion of the population may already use the supplements, as seen in a Danish study including 15 629 women, of which 85.6% took pregnancy multivitamins.[56]

This review emphasizes the importance of a representative sample size, blinding of RCTs, and timing to conduct studies and meta-analyses with high levels of evidence. To produce a meta-analysis on future studies, the RCTs will especially need to be standardized to be comparable. Future RCTs could include pregnant women in low-income countries, providing folic acid and iron for both the control and intervention groups to avoid other adverse birth outcomes, while giving the intervention group extensive multivitamins. Another option is to examine multivitamin use and the risk of preeclampsia in high-risk groups, such as overweight women. Observational studies could be optimized by reporting the content of the multivitamins.

5 | CONCLUSION

It remains unclear whether multivitamin use during pregnancy reduces the risk of preeclampsia. Only two small RCTs and four observational studies were found. The results of the RCTs indicated that multivitamin use may lower the risk of preeclampsia. However, the results of the meta-analyses of the observational studies showed no statistically significant reduction in risk of preeclampsia in multivitamin users. Due to the very low quality of evidence, further research is needed to investigate this potential association. The results of this review do not allow any final conclusions to be drawn regarding a preventive effect of multivitamin use in relation to preeclampsia.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

HKH, HTW, SH, CHC, LR and JS were responsible for the conception and design of this study. Data collection and data management was done by CHC, SH, and HTW. CHC and HTW conducted the analyses. CHC drafted the initial manuscript, which was reviewed and revised by all authors. All authors approved the final draft.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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