

LETTER TO THE EDITOR

Multivitamin use may lower risk of preeclampsia: A meta-analysis

Sir,
There is increasing interest in the use of vitamins and minerals for preeclampsia prophylaxis. On current evidence, however, the systematic review by Christiansen et al.¹ was unable to draw “any final conclusions...regarding a preventive effect of multivitamin use in relation to preeclampsia”.

Nevertheless, we believe the existing literature indicates that multivitamins may reduce the risk of preeclampsia. To start with, considering the limited evidence base identified by Christiansen et al.,¹ we see no reason to exclude studies investigating foods fortified with multiple vitamins/minerals, provided the control group

is given placebo food without fortification.^{2,3} We also believe that Chen et al.,⁴ despite being excluded for having “wrong outcomes”, can be included since their “severe PIH” outcome is consistent with the diagnostic criteria for preeclampsia with severe features.⁵ Lastly, we are not convinced that it is inappropriate to pool results from trials with differences in population or timing of intervention, though this may require exploration with stratification/sensitivity analyses and/or downgrading of GRADE based on indirectness.

Accordingly, we performed a random effects meta-analysis including the aforementioned randomized controlled trials (RCTs).²⁻⁴ The statistics of Christiansen et al.¹ (REVMAN) were replicated using

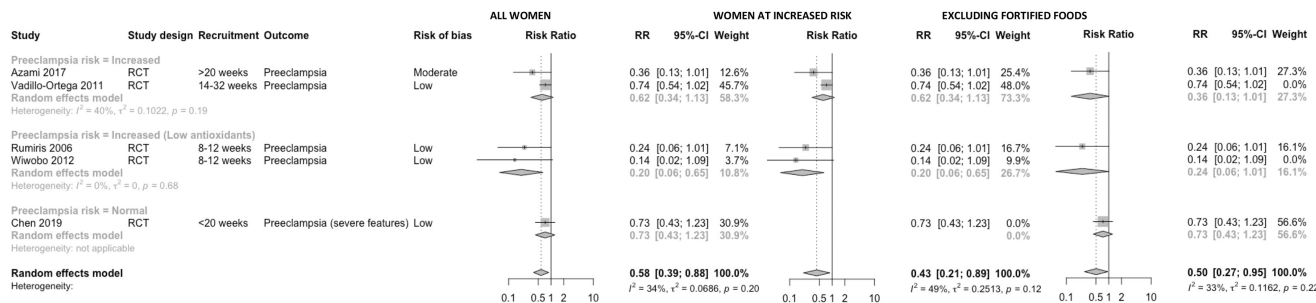


FIGURE 1 Meta-analysis of interventional data examining the effect of multivitamin use on risk of preeclampsia irrespective of baseline preeclampsia risk (left), examining only women with increased risk of preeclampsia (middle), and excluding studies with supplementation from fortified foods (right), with stratification for risk of preeclampsia.

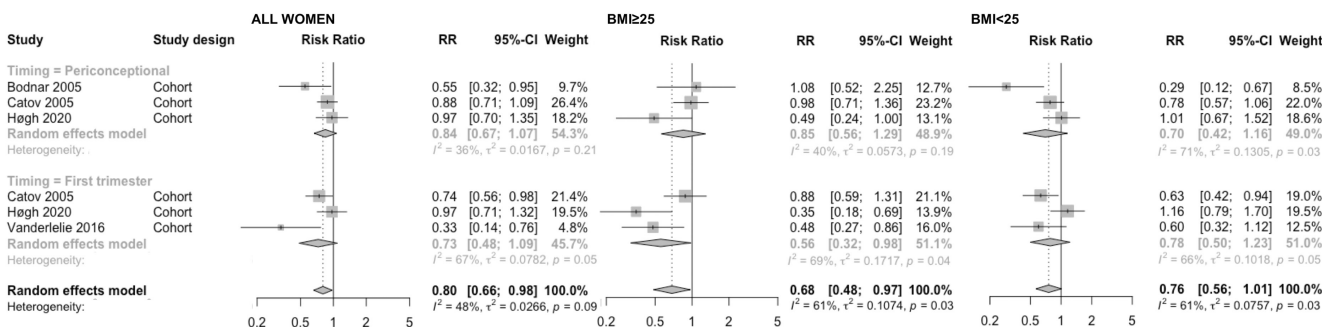


FIGURE 2 Meta-analysis of adjusted observational data examining the effect of multivitamin use on risk of preeclampsia for all women (left), for women with BMI ≥ 25 (middle), and for women with BMI < 25 (right), with stratification for timing of multivitamin use.

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the meta package in R (Version 4.0.5) and the DerSimonian–Laird estimator for between-study variance. Our meta-analysis of RCTs indicate that multivitamins reduce the risk of preeclampsia, though most trials were conducted in women with increased risk of the condition (Figure 1). Sensitivity analyses including only women with increased risk of preeclampsia or excluding studies investigating fortified foods remained significant and reported lowered risk estimates.

Turning to the non-significant meta-analysis of adjusted observational data by Christiansen et al.,¹ we believe Catov et al. can be included, as HR/RRs approximate ORs under the rare disease assumption. Hence, periconceptual/first trimester multivitamin use is associated with significantly reduced preeclampsia incidence (Figure 2). Although there was evidence of moderate between-study heterogeneity, this is likely explained in part by different study methodologies. For example, although Catov et al. and Høgh et al. both examined Danish populations, the former excluded single supplement and irregular multivitamin use, whereas the latter's control group included any individual who answered “no” to daily multivitamin use, which could explain the latter's elevated odds ratios. A sensitivity analysis including Chen et al.⁴ in this meta-analysis (since they also examined a non-high-risk population) did not materially change the risk estimate but reduced heterogeneity (RR = 0.80, 95% CI = 0.67–0.95; $I^2 = 39%$, $P = 0.13$). Meanwhile, subgroup analyses found a reduced risk of preeclampsia with multivitamin use in women with a body mass index (BMI) ≥ 25 but not in women with BMI < 25 .

In conclusion, there is evidence of moderate certainty that multivitamin use may be beneficial for women at increased risk of preeclampsia (including having low antioxidant levels), with downgrading of evidence due to differences in population and intervention. However, the certainty of evidence for multivitamin use in healthy women is low, being based largely on observational data. Nevertheless, it is unclear whether the decreased risk is driven by certain multivitamin components (e.g. calcium⁶) and what vitamin and mineral combinations may confer the most benefit (e.g. vitamin C and E combinations may not be effective⁷). Further clarification of these aspects is warranted.

AUTHOR CONTRIBUTIONS

ACQL and CCWL conceived the study, and wrote and reviewed the manuscript. ACQL performed the statistical analyses.

Andre C. Q. Lo¹ 
Charmaine Chu Wen Lo^{2,3,4}

¹University of Cambridge School of Clinical Medicine,
Addenbrooke's Hospital, Cambridge, UK

²Liverpool Hospital, Liverpool, New South Wales, Australia

³University of New South Wales Faculty of Medicine,
Kensington, New South Wales, Australia

⁴Western Sydney University School of Medicine, Penrith, New
South Wales, Australia

Correspondence

Andre C. Q. Lo
Email: acql2@cam.ac.uk

ORCID

Andre C. Q. Lo  <https://orcid.org/0000-0001-7339-6809>

REFERENCES

- Christiansen CH, Høgh S, Rode L, Schroll JB, Hegaard HK, Wolf HT. Multivitamin use and risk of preeclampsia: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2022. doi:10.1111/aogs.14356. Epub ahead of print.
- Vadillo-Ortega F, Perichart-Perera O, Espino S, et al. Effect of supplementation during pregnancy with L-arginine and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial. *BMJ*. 2011;342:d2901.
- Wibowo N, Purwosunu Y, Sekizawa A, Farina A, Idriansyah L, Fitriana I. Antioxidant supplementation in pregnant women with low antioxidant status. *J Obstet Gynaecol Res*. 2012;38:1152-1161.
- Chen S, Li N, Mei Z, et al. Micronutrient supplementation during pregnancy and the risk of pregnancy-induced hypertension: a randomized clinical trial. *Clin Nutr*. 2019;38:146-151.
- Gestational hypertension and preeclampsia: ACOG practice bulletin, Number 222. *Obstet Gynecol*. 2020;135:e237-e260.
- Sun X, Li H, He X, et al. The association between calcium supplement and preeclampsia and gestational hypertension: a systematic review and meta-analysis of randomized trials. *Hypertens Preg*. 2019;38:129-139.
- Conde-Agudelo A, Romero R, Kusanovic JP, Hassan SS. Supplementation with vitamins C and E during pregnancy for the prevention of preeclampsia and other adverse maternal and perinatal outcomes: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2011;204:503. e1-e12.