Original Article

First trimester multivitamin/mineral use is associated with reduced risk of pre-eclampsia among overweight and obese women

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Abstract

The use of pregnancy-specific multivitamin supplements is widely recommended to support maternal homeostasis during pregnancy. Our objective was to investigate whether multivitamin use during pregnancy is associated with a reduced risk of pre-eclampsia. The effect of multivitamin use on incidence of pre-eclampsia in lean and overweight/obese women was analysed using data collected between 2006 and 2011 as part of the Environments for Healthy Living Project, Griffith University, Australia. A total of 2261 pregnancies were included in the analysis with pre-eclampsia reported in 1.95% of subjects. Body mass index (BMI) ≥ 25 was associated with a 1.97-fold [95% confidence interval (CI): 0.93, 4.16] increase in pre-eclampsia risk. First trimester multivitamin use was reported by 31.8% of women and after adjustment, was associated with a 67% reduction in pre-eclampsia risk (95%CI: 0.14, 0.75). Stratification by BMI demonstrated a 55% reduction in pre-eclampsia risk (95%CI: 0.30, 0.86) in overweight (BMI: 25–29.9) and 62% risk reduction (95%CI: 0.16, 0.92) in obese (BMI: ≥ 30) cohorts that supplemented with multivitamins in the first trimester of pregnancy. This finding may be particular to the Australian population and reflect inherent nutritional deficits. First trimester folate supplementation was found to reduce pre-eclampsia incidence [adjusted odds ratios (AOR) 0.42 95%CI: 0.13, 0.98] and demonstrated significance upon stratification by overweight status for women with BMI >25 (AOR 0.55 95%CI: 0.31, 0.96). These results support the hypothesis that multivitamin supplementation may be beneficial in reducing the incidence of pre-eclampsia during pregnancy and be of particular importance for those with a BMI ≥ 25 .

Keywords: multivitamin, micronutrient, pregnancy, pre-eclampsia, obesity, human

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Introduction

Adequate maternal health and nutrition have long been considered important to a healthy pregnancy (Abu-Saad & Fraser 2010; Ramakrishnan *et al.* 2012; Blumfield *et al.* 2013). Now, more than ever before, the use of pregnancy-specific multivitamin/mineral supplements is widely recommended to prevent disorders such as neural tube defects and support the mother to cope with the stresses of pregnancy. Recent

studies have suggested that the use of multivitamin/minerals during pregnancy may significantly reduce the risk of developing pre-eclampsia (Bodnar *et al.* 2006; Wen *et al.* 2008; Catov *et al.* 2009) and other complications of pregnancy (Scholl *et al.* 1997; Catov *et al.* 2011).

Pre-eclampsia is a multisystem, hypertensive disorder of pregnancy that complicates approximately 4% of pregnancies worldwide (Vanderlelie & Perkins 2011). Shallow trophoblast invasion, poor

placentation and transient placental perfusion are important early pathophysiological events (Redman & Sargent 2005). The resulting increase in reactive oxygen species in combination with antioxidant disequilibria is considered central to the feed-forward generation of oxidative stress, damage to the placental bed and resulting to increases in shedding of apoptotic, necrotic and autophagic debris into the maternal circulation. Increased circulating trophoblast debris stimulates a hyperimmune and inflammatory response in the mother, leading to endothelial cell dysfunction and the maternal symptom manifestation characteristic of the disease (Raijmakers *et al.* 2004; Siddiqui *et al.* 2010). A pre-pregnancy body mass index (BMI) ≥ 25 is a well-established risk factor for the development of pre-eclampsia (Bodnar *et al.* 2005b; Callaway *et al.* 2006). The increased inflammation and oxidative stress associated with obesity, overlaid with poor diet and lifestyle factors, may play a role in increasing the risk of pre-eclampsia in this group of women (Roberts *et al.* 2011).

Adequate micronutrition may play a critical role in determining pregnancy outcome, through the modulation of maternal and fetal metabolism, oxidative stress and placentation (Blumfield *et al.* 2013). Vitamins A, B6, B12, C, D, E, folate and the minerals Selenium and Zinc have been suggested to improve immune function, reduce placental oxidative stress and may be important in improving maternal capacity to deal with the increased physiological stress of pregnancy (Roberts *et al.* 2003; Ramakrishnan *et al.* 2012). This may be of particular importance in obese populations whose intake of antioxidants has been identified as reduced (Neuhouser *et al.* 2001; Wallstrom *et al.* 2001; Damms-Machado *et al.* 2012).

Considering evidence that the Australian population may be at risk of a number of micronutrient deficiencies including thiamin, vitamin A, folate, vitamin D, calcium, iron, magnesium and zinc (Blumfield *et al.* 2013) and increasing rates of obesity in this population (Callaway *et al.* 2006), the aim of the current study was to investigate the association between first trimester multivitamin/mineral supplementation and the risk of pre-eclampsia in a South East Queensland population.

Materials and methods

The Environments for Healthy Living (EFHL) cohort is a prospective, longitudinal birth cohort study conducted by Griffith University across the Logan, Beaudesert, Gold Coast and Tweed Heads Health Districts in South East Queensland (QLD) and northern New South Wales (NSW) Australia. The study is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12610000931077) and detailed methodology has been published elsewhere (Cameron *et al.* 2012b).

Data sources

Data for the current analysis were collected from the maternal baseline survey and hospital perinatal data records for the Logan, Gold Coast hospitals in QLD and Tweed hospital in NSW. The maternal baseline survey is a self-reported questionnaire consisting of 48 multi-item questions that assess a range of maternal and family characteristics. Specifically, this study analysed the questions on maternal age, maternal

Key messages

- Increasing body mass index is associated with an increased risk of pre-eclampsia.
- First trimester multivitamin/mineral supplementation may be beneficial in reducing the risk of pre-eclampsia particularly in women who are overweight and obese.
- Improvements in baseline micronutrient status particularly thiamin, vitamin A, folate, vitamin D, calcium, iron, magnesium and zinc that have been reported as reduced in the Australian population may be contributing to the beneficial effect of supplementation.
- Increased education of health care practitioners and pregnant women as to the benefits of multivitamin/mineral supplementation in reducing the incidence of pre-eclampsia and other pregnancy-specific conditions associated with oxidative stress is advocated.

weight and height, gross household income, maternal smoking and supplement usage. Data were obtained for multivitamin/mineral preparations, folate, zinc, calcium, vitamin C, vitamin E, iron and other supplements with individual questions for each supplement related to supplement use in the periconception period, first, second and third trimesters of pregnancy. For the other supplement use question, women also had the opportunity to name the preparation, which in a number of cases was a multivitamin/mineral supplement. For these cases, use of the 'other supplement' was considered a multivitamin/mineral and included in the analysis. Perinatal data records were obtained from participating hospitals after discharge for recruited patients and relevant data items utilized in this analysis included parity, plurality, pre-existing maternal health conditions (essential hypertension, diabetes Type I and II), diagnosis of pre-eclampsia and indigenous status.

Data were stratified by hospital; the data for the NSW participants were excluded from the study because of variation in the reporting of pre-eclampsia on the perinatal data sheets and failure to delineate between pregnancy-induced hypertension and pre-eclampsia.

Participants

From November 2006 to October 2011, a total of 2619 live births were recorded from mothers recruited to the study in QLD; this equated to 23.4% of total births in the target population hospitals during the recruitment periods (Cameron *et al.* 2012a). Pre-eclampsia ($n = 44$) was diagnosed in hospital as defined by the Council of the Australasian Society for the Study of Hypertension in Pregnancy (blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic; or a rise of >30 mm Hg or >15 mm Hg above initial systolic and diastolic pressures, respectively and proteinuria: defined as >0.3 g of protein secreted/24 h) (Brown *et al.* 2000). Validity of hospital collected perinatal data has been previously established, and any misclassification is expected to be minimal (Klemmensen *et al.* 2007).

Self-reported pre-pregnancy weight and height were used to calculate BMI using the formula weight

(kg)/height (m)². From this data, women were categorized according to World Health Organisation (WHO) guidelines (World Health Organization 2000) that state that a BMI below 18.5 is considered underweight, 18.5–24.9 represent a healthy weight, 25–29.9 are classified as overweight and a BMI 30 and above is considered obese. We subsequently dichotomized women as 'lean' and 'overweight' if BMI was less than 25 or greater than 25, respectively.

Women who were missing data on BMI ($n = 37$), supplement use or reported only single supplement usage were excluded ($n = 249$), as were women with multifetal gestations ($n = 27$), pre-existing diabetes ($n = 18$) or essential hypertension ($n = 27$). The final study sample was 2261 with 1066 women reporting no multivitamin use, 719 reporting multivitamin use in the first trimester and 476 reporting folate supplementation only.

Statistical analysis

Multivariate logistic regression was applied to estimate the independent effect of first trimester multivitamin supplementation on the risk of pre-eclampsia using SPSS STATISTICS VERSION 19.0 (IBM, Corporation: Armonk, NY, USA). Non-supplement users were the referent for all models. An interaction term was included in the model to assess the interaction between multivitamin use and BMI category as part of the stratification analyses. Hosmer–Lemeshow goodness-of-fit tests, residual and influence analyses were performed. Significance was accepted at the 5% level for all measures, and results are presented as adjusted odds ratios (AOR) and 95% confidence intervals (CI).

Covariates for analysis included maternal age at delivery (continuous), smoking status during pregnancy (yes, no), indigenous status (i.e. Aboriginal/Torres Strait Islander descent) (yes, no), socioeconomic status (income quintile), parity (nulliparous, multiparous) and gestational diabetes (yes, no) due to the association between these factors and pre-eclampsia risk and possible confounding by health-promoting behaviours that are likely associated with multivitamin use. Potential confounders were retained in the model if they altered multivitamin exposure by >10%. Maternal age, parity, maternal

smoking, gestational diabetes and indigenous status met our definition of confounding and were included in the final model.

Ethics approval

The EFHL study was approved by the Griffith University Human Ethics Committee (MED/16/06/HREC, MED/23/11/HREC). Additional ethical approval was obtained from each recruiting hospital (Logan HREC/06QPAH/96, Gold Coast Hospital HREC/06/GCH/52 and Tweed Hospital NCAHS HREC 358N).

Results

In total 719 women (31.8%) reported multivitamin/mineral use in the first trimester of pregnancy

(Table 1). Multivitamin/mineral users were more likely to be >25 years of age, with a pre-pregnancy BMI between 25 and 29.9 and of non-indigenous descent. For all other demographics, data were comparable between multivitamin/mineral users and non-supplement users. The individual components of the most common multivitamin/mineral preparation taken in by the EFHL cohort are provided in Table 2. This particular preparation was identified by 52% of those reporting a specific multivitamin in their response and is coherent with market trends in Australia.

The overall incidence of pre-eclampsia in the cohort was 1.95% ($n = 44$), with lower occurrence in women reporting multivitamin (0.97%) and folate-only (1.26%) supplementation when compared with non-supplement users (2.9%) (Table 3). After

Table 1. Maternal characteristics according to first trimester multivitamin or folate-only supplementation, Environments for Healthy Living cohort 2006–2011

	Non-supplement users ($n = 1066$)	Multivitamin users ($n = 719$)	Folate-only users ($n = 476$)
Maternal age (%)			
<18 years	1.5	0.8	0.6
18–21 years	11.2	6.4	11.8
22–24 years	16.3	15.2	12.1
25–29 years	26.9	32.1	31.5
30–34 years	25.1	27.0	24.5
≥35 years	18.9	18.4	19.5
Parity (%)			
Nulliparous	26.7	28.1	28.2
Multiparous	73.3	71.9	71.8
BMI (%)			
<18.5 kg/m ²	8.8	7.3	7.0
18.5–24.9 kg/m ²	49.0	49.2	52.4
25–29.9 kg/m ²	19.2	24.8	21.5
30–34.9 kg/m ²	13.0	9.7	10.9
≥35 kg/m ²	7.7	6.2	5.9
Household income quintile (%)			
1	17.5	17.2	17.7
2	16.5	18.1	17.3
3	18.4	15.4	17.9
4	14.6	17.5	17.3
5	13.6	16.5	16.8
Declined to answer	19.3	15.3	13.1
Smoking during pregnancy (%)			
Non-smoker	78.8	78.4	72.1
Smoker	21.2	21.6	27.9
Aboriginal and Torres Strait Islander descent (%)			
Yes	2.4	1.6	1.3
No	97.6	98.4	98.7

adjusting for maternal age, parity, gestational diabetes, maternal smoking and indigenous status, multivitamin/mineral use was associated with a 66% reduction in pre-eclampsia risk (AOR 0.33 95%CI: 0.14, 0.75). Folate-only supplementation was also associated with a reduction in pre-eclampsia risk (AOR 0.42, 95%CI: 0.13, 0.98) in this cohort.

After stratification by BMI, the incidence of pre-eclampsia in women with a BMI greater than 25 was 2.79%. Overweight/obese women ($n = 956$) displayed increased risk of pre-eclampsia with an AOR of 1.97 (95%CI: 0.93, 4.16) when compared with their lean counterparts. Multivitamin/mineral supplement use in

the first trimester of pregnancy was reported by 31.1% of lean women and 32.5% of overweight/obese women. Multivitamin/mineral use was found to reduce the risk of pre-eclampsia in both lean and overweight/obese women (Table 4); however, the AOR did not reach significance at the 5% level for lean users (AOR 0.60; 95%CI: 0.39, 1.36). In the obese/overweight cohort, first trimester multivitamin/mineral use reduced the odds of pre-eclampsia by 52% (AOR 0.48, 95%CI: 0.27, 0.86). This significant reduction in odds resulted in comparable incidence of pre-eclampsia for multivitamin/mineral users in both weight categories. Folate-only supplementation was reported in 21.97% of lean women and 20.7% of overweight/obese women, and upon stratification by BMI, it was associated with a 45% reduction in pre-eclampsia risk in overweight and obese users (AOR 0.55 95%CI: 0.31, 0.96).

Further adjustment of the overweight and obese category into distinct groups with BMI ranges 25–29.9 for overweight ($n = 515$) and >30 for obese ($n = 441$) revealed that the risk of pre-eclampsia increased in both the overweight (AOR 1.51, 95%CI: 0.66, 3.44) and obese (AOR 2.75, 95%CI: 1.33, 5.69) categories when compared with the lean group. Multivitamin/mineral use was comparable between BMI groups with 31.1% of lean women, 36.7% of overweight women and 27.7% of obese women reporting multivitamin/mineral supplementation in the first trimester. The protective effect of first trimester multivitamin/mineral use was seen to increase with increasing BMI with a 55% risk reduction (AOR 0.45, 95%CI: 0.30, 0.86) in the overweight cohort that saw the incidence of pre-eclampsia drop from 3.20% to 1.23%. A 62% reduction in odds (AOR 0.38, 95%CI:

Table 2. Components of the most commonly used multivitamin supplement in the Environments for Healthy Living Cohort, 2006–2011

Nutrient	Unit	
	µg	mg
Thiamin (B ₁)		1.55
Riboflavin (B ₂)		1.8
Niacin (B ₃)		19
Pantothenic acid (B ₅)		10
Vitamin (B ₆)		2.6
Vitamin (B ₁₂)	4.0	
Vitamin C		100
Vitamin D ₃	12.5	
Vitamin E		15
Biotin	200	
Folic Acid	800	
Calcium		125
Iron		60
Iodine	250	
Magnesium		100
Phosphorous		125
Copper		1
Manganese		1
Zinc		7.5

Table 3. Association between first trimester multivitamin use and the risk of pre-eclampsia in the South East Queensland subpopulation of the Environments for Healthy Living Study ($n = 2261$), 2006–2011

First trimester supplement use	Unadjusted Prevalence (%)	Unadjusted odds ratio	95% confidence interval	Adjusted odds ratio*	95% confidence interval
Nil	2.9	1	Referent		Referent
Multivitamin	0.97	0.55	0.36, 0.83	0.33	0.14, 0.75
Folate only	1.26	0.57	0.38, 0.85	0.42	0.13, 0.98

*Adjusted for maternal age, parity, gestational diabetes, indigenous status and maternal smoking.

Table 4. Association between first trimester multivitamin use and the risk of pre-eclampsia stratified by pre-pregnancy body mass index, pre-eclampsia in the South East Queensland sub population of the Environments for Healthy Living Study, 2006–2011

First trimester supplement use	Unadjusted PET prevalence (%)	Unadjusted odds ratio	95% confidence interval	Adjusted odds ratio*	95% confidence interval
Pre-pregnancy body mass index <25 kg/m ² (<i>n</i> = 1305)					
Nil	1.87	1	Referent	1	Referent
Multivitamin	1.08	0.74	0.39, 1.40	0.60	0.39, 1.36
Folate only	1.14	0.73	0.40, 1.34	0.72	0.39, 1.35
Pre-pregnancy body mass index ≥25 kg/m ² (<i>n</i> = 956)					
Nil	4.6	1	Referent	1	Referent
Multivitamin	1.1	0.49	0.28, 0.88	0.48	0.27, 0.86
Folate only	2.36	0.56	0.32, 0.98	0.55	0.31, 0.96

*Adjusted for maternal age, parity, gestational diabetes, indigenous status and smoking.

0.16, 0.92) was noted in the obese cohort with a pre-eclampsia incidence of 0.96% for multivitamin/mineral users compared with 6.29% in non-users. Significant interaction was also found between multivitamin use and BMI category ($P = 0.042$) and its inclusion into the model confirmed the increased beneficial effect of multivitamin supplementation with increasing body mass (AOR 0.127, 0.02, 0.93).

Discussion

The finding of this observational study of a South East Queensland birth cohort are consistent with that of others across the globe [for reviews see (O'Brien *et al.* 2003; Ramakrishnan *et al.* 2012)] and in Australia (Callaway *et al.* 2006; Campbell *et al.* 2013) that found increasing pre-pregnancy BMI is associated with an increased risk of pre-eclampsia. Multivitamin/mineral supplementation in the first trimester of pregnancy was associated with a 66% reduction in pre-eclampsia risk in the EFHL cohort. Interestingly, despite a 40% reduction in odds for lean women, the protective effect of first trimester multivitamin/mineral supplementation only reached significance in women with a BMI of ≥25. In this subset, there was a 55% reduction in pre-eclampsia risk in overweight women and a 62% risk reduction in those women whose BMI exceeded 30. These results offer an alternate perspective than those reported by Catov *et al.* (2009), which assessed both periconceptional and first trimester

multivitamin/mineral use in the Danish National Birth Cohort (DNBC) and found that significant reductions in pre-eclampsia risk were confined to lean women (Catov *et al.* 2009). Possible suggestions for this disparity may include a smaller sample size, generally lower rate of first trimester supplement use in the EFHL cohort (31.8% EFHL vs. 39% DNBC) and significantly lower rates of periconceptional multivitamin/mineral use in the EFHL cohort (13.5%) compared with the DNBC (65%), which may have altered the baseline status of the cohorts.

Additionally, the EFHL cohort consisted of a higher proportion of women aged 35 years and above and an increased rate of multiparous individuals. Considering previous evidence that BMI of female increases with reproductive age (Cameron *et al.* 2003; Callaway *et al.* 2006) and parity (Polley *et al.* 2002), these factors may have contributed to the increased pre-pregnancy BMI of this cohort (26% overweight, 17.6% obese) when compared with that of the DNBC (20.2% overweight, 9% obesity) (Catov *et al.* 2009). It is worth noting at this point that the increased rate of obesity in the EFHL cohort is consistent with both the wider South East Queensland (Callaway *et al.* 2006) and Australian (Daly *et al.* 2012) populations. Despite elevated BMI, the overall incidence of pre-eclampsia in the EFHL population was low at 1.95% when compared with both the DNBC (2.3%) (Catov *et al.* 2009) and the general South East Queensland population (4.3%) (Callaway *et al.* 2006).

The recruitment of individuals to a study called 'Environments for Healthy Living' may have naturally selected for participation women whose health status was generally good. Indeed, rates of other health determinants such as substance abuse, smoking, diabetes and essential hypertension were comparatively lower than would be expected of the general Australian population (Australian Institute of Health and Welfare 2012). For this reason, the rates of confounding were quite low in this study although these demographic considerations may have resulted in the reduced significance in our lean cohort.

Differences in the composition of multivitamin/mineral supplements between the EFHL study and the DNBC (Catov *et al.* 2009) (higher folate, iron and B-group vitamin, lower zinc and no selenium in EFHL) and variation in baseline nutritional status may also have contributed to altered efficacy of multivitamin supplementation in the first trimester. A large systematic review recently reported that the Australian population might be at risk of a number of micronutrient deficiencies (Blumfield *et al.* 2013). Nutrient intakes of thiamin, vitamin A, folate, vitamin D, calcium, iron, magnesium and zinc were found to be below the estimated average requirement in Australian women and significantly lower than that of the United States (Blumfield *et al.* 2013). In the context of this nutritional standpoint and significant evidence of deficiencies in important micronutrients such as folate, vitamin D, vitamin C, selenium, iron, β -carotene and zinc associated with obesity (Neuhouser *et al.* 2001; Wallstrom *et al.* 2001; Kimmons *et al.* 2006; Ernst *et al.* 2009; Madan *et al.* 2010; Damms-Machado *et al.* 2012), the positive effect of micronutrient supplementation across the spectra of BMI in the EFHL cohort may not be unexpected.

The most commonly reported single supplement used in the first trimester by women of the EFHL cohort was folate and the most commonly used multivitamin/mineral contained four times the amount of supplemental folate (800 μ g) than that of the DNBC (Catov *et al.* 2009). Such increased folate supplementation may be responsible for the increased reduction in pre-eclampsia risk (AOR 0.42, 95%CI: 0.13, 0.98) in the EFHL cohort that was not seen by others. The increased significance of folate

supplementation for overweight and obese women in this cohort (AOR 0.55, 95%CI: 0.31, 0.96) agrees with previous work in the field that suggests that folate may play a role in the protective effect associated with multivitamin/mineral use in pre-eclampsia (Wen *et al.* 2008). However, the increased benefit of comprehensive supplementation adds further weight to the hypothesis that pregnant Australian women may be exposed to a reduction in baseline nutritional status, which could be improved through multivitamin/mineral supplementation.

When considering the well-supported role of oxidative stress and inflammation in the pathogenesis of pre-eclampsia (Redman 2011), deficiency in micronutrients such as folate, selenium, vitamin C, vitamin E and β -carotene may perpetuate the inflammatory and oxidative state in pregnant individuals and contribute to endothelial dysfunction and clinical symptom manifestation in pre-eclampsia (Xu *et al.* 2009). For obese populations known to exhibit baseline elevations in oxidative stress, reductions in antioxidant status (Neuhouser *et al.* 2001; Wallstrom *et al.* 2001; Kimmons *et al.* 2006; Ernst *et al.* 2009; Madan *et al.* 2010; Damms-Machado *et al.* 2012), elevations in inflammatory mediators such as C-reactive protein (Wolf *et al.* 2001; Bodnar *et al.* 2005a) and Interleukin-6, increased circulating free fatty acids (Roberts *et al.* 2011) and the association between high carbohydrate and fat intakes and leukocyte radical production (Dandona *et al.* 2005), it is no surprise that the risk of pre-eclampsia associated with inadequate micronutrition is compounded. With this in mind, and in the context of wider maternal nutrition, it may be that a single micronutrient may not be the answer to the pre-eclampsia puzzle and that comprehensive supplementation with a multivitamin/mineral preparation may prepare women more completely for the stress of pregnancy by ensuring micronutrient sufficiency.

The results of this investigation should be viewed in light of its limitations. We were unable to specifically study the content of each multivitamin/mineral supplement used in the EFHL cohort and specific data on the duration of use within a particular trimester were not recorded, which may have biased our results. Although this study calculated BMI from

self-reported weight and height information that may have been subject to error, this was not considered significant in light of evidence that self-reported weight is generally well correlated with direct measurement (Willet 1998). Finally, although we adjusted for several obstetric, socioeconomic and lifestyle factors in our analysis, unmeasured residual confounding may have also been a factor in this analysis. The authors look forward to further analyses of the association between multinutrient supplementation and the risk of pre-eclampsia in a larger Australian setting.

The results of this study, which demonstrate a significant reduction in pre-eclampsia risk, are associated with first trimester multivitamin/mineral use that is specifically more pronounced in women with a BMI of ≥ 25 . The growing body of evidence in this area supports progression towards a randomised, controlled trial to provide definitive evidence of the effectiveness of multivitamin/mineral supplementation in the prevention of pre-eclampsia. These findings may be of particular importance to populations with reduced baseline micronutrient status like Australia. From this standpoint, increasing education of health care practitioners and pregnant women as to the benefits of multivitamin/mineral supplementation, particularly during the first trimester, in reducing the incidence of pre-eclampsia and other pregnancy-specific conditions associated with oxidative stress is advocated.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

PAS and RScott managed the EFHL cohort and are responsible for patient recruitment and data collection. RShibl was the data manager for the EFHL and involved in the data cleaning and sorting. JV, JL and AP were involved in project design, statistical analysis. JV drafted the manuscript and all authors contributed to revisions and have read and approved the final manuscript.

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