Agrawal, Sutapa; Fledderjohann, Jasmine; Vellakkal, Sukumar; Stuckler, David; (2015) Adequately diversified dietary intake and iron and folic acid supplementation during pregnancy is associated with reduced occurrence of symptoms suggestive of pre-eclampsia or eclampsia in Indian women. PloS one, 10 (3). e0119120-. ISSN 1932-6203 DOI: https://doi.org/10.1371/journal.pone.0119120

Downloaded from: http://researchonline.lshtm.ac.uk/id/eprint/2293284/

DOI: https://doi.org/10.1371/journal.pone.0119120

Usage Guidelines:

Please refer to usage guidelines at https://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: http://creativecommons.org/licenses/by/2.5/
Adequately Diversified Dietary Intake and Iron and Folic Acid Supplementation during Pregnancy Is Associated with Reduced Occurrence of Symptoms Suggestive of Pre-Eclampsia or Eclampsia in Indian Women

Sutapa Agrawal1*, Jasmine Fledderjohann2, Sukumar Vellakkal1,2, David Stuckler1,2

1 South Asia Network for Chronic Disease, Public Health Foundation of India, Gurgaon, Haryana, 122022, India, 2 Department of Sociology, Oxford University, Oxford, United Kingdom

* sutapa.agrawal@phfi.org

Abstract

Background/Objective

Pre-eclampsia or Eclampsia (PE or E) accounts for 25% of cases of maternal mortality worldwide. There is some evidence of a link to dietary factors, but few studies have explored this association in developing countries, where the majority of the burden falls. We examined the association between adequately diversified dietary intake, iron and folic acid supplementation during pregnancy and symptoms suggestive of PE or E in Indian women.

Methods

Cross-sectional data from India’s third National Family Health Survey (NFHS-3, 2005-06) was used for this study. Self-reported symptoms suggestive of PE or E during pregnancy were obtained from 39,657 women aged 15-49 years who had had a live birth in the five years preceding the survey. Multivariable logistic regression analysis was used to estimate the association between adequately diversified dietary intake, iron and folic acid supplementation during pregnancy and symptoms suggestive of PE or E after adjusting for maternal, health and lifestyle factors, and socio-demographic characteristics of the mother.

Results

In their most recent pregnancy, 1.2% (n=456) of the study sample experienced symptoms suggestive of PE or E. Mothers who consumed an adequately diversified diet were 34% less likely (OR: 0.66; 95% CI: 0.51-0.87) to report PE or E symptoms than mothers with inadequately diversified dietary intake. The likelihood of reporting PE or E symptoms was also 36% lower (OR: 0.64; 95% CI: 0.47-0.88) among those mothers who consumed iron and folic acid supplementation for at least 90 days during their last pregnancy. As a sensitivity analysis, we stratified our models sequentially by education, wealth, antenatal care visits, birth interval, and parity. Our results remained largely unchanged: both adequately
diversified dietary intake and iron and folic acid supplementation during pregnancy were associated with a reduced occurrence of PE or E symptoms.

**Conclusion**

Having a adequately diversified dietary intake and iron and folic acid supplementation in pregnancy was associated with a reduced occurrence of symptoms suggestive of PE or E in Indian women.

**Introduction**

Pre-eclampsia is a pregnancy-induced hypertensive disorder characterized by high blood pressure and proteinuria, i.e. elevated levels of protein in the urine (used to distinguish pre-eclampsia from gestational hypertension), after the 20th week of pregnancy [1]. Eclampsia is defined as the occurrence of generalized seizures/convulsions and/or unexplained coma during pregnancy or the postpartum period in the absence of other neurologic conditions such as epilepsy [2–3]. Pre-eclampsia or eclampsia (PE or E) is one of the leading causes of maternal and fetal mortality and morbidity worldwide [4], and is associated with adverse pregnancy outcomes including perinatal death, preterm birth, and intrauterine growth retardation [1,5]. Based largely on clinical data, the incidence of pre-eclampsia is between 2 and 10%, depending on the population studied and definition of pre-eclampsia used [6]; clinical studies suggest that the proportion of deliveries impacted by PE or E in Indian women ranges from as low as 0.9% to as high as 7.7% of all deliveries [7–9]. However, these clinical studies are likely to suffer from selection bias on the basis of severity of the condition, especially among populations with limited access to prenatal care, and therefore may underestimate the prevalence of the condition. Precise country-specific population level estimates of PE or E prevalence are largely unavailable.

Although the etiology of PE or E remains unclear, the role of maternal diet in the development of PE or E has recently received increased attention [10–11]. Several studies indicate that micronutrient deficiencies, such as magnesium, vitamins A and C, folic acid [12], and calcium [13–15] may contribute to PE or E risk. The evidence of a beneficial effect of maternal iron supplementation during pregnancy is particularly compelling [16]. As well, three large-scale cohort studies of the association between folic acid supplements containing multivitamins and gestational hypertension, including PE [12, 15,17–18], all show a protective effect of folic acid supplementation on pre-eclampsia. A recent large cohort study from Denmark [19] shows that regular use of folic acid in pregnancy is related to a reduced risk of pre-eclampsia among normal-weight women. However, two recent studies in China [20] and Holland [21] fail to find an effect of folic acid supplementation on pre-eclampsia or gestational hypertension. The links between micronutrient supplementation and PE or E have largely been assessed in clinical trials, but there is an urgent need for research examining links between PE or E and adequately diversified dietary intake during pregnancy more broadly, especially in light of research suggesting that nutrients may be better-absorbed from food sources than from supplements [22].

Several epidemiologic studies indicate that consumption of fruits, vegetables, and dietary fibre is associated with lower pre-eclampsia risk [23–26], possibly influencing pre-eclampsia through intestinal anti-inflammatory mechanisms [27]. It is hypothesized that inadequate antioxidant and folate intake may contribute to oxidative stress, thereby increasing the risk of pre-eclampsia [28]. Dietary intake, then, may shape PE or E risk by influencing micronutrient and...
antioxidant levels. For example, lycopene, an antioxidant found in many red fruits and vegetables, has been associated with a reduced risk of PE or E [29]. Dietary diversity—i.e. regular consumption of food items across a broad range of food groups—is widely recognized as a key dimension of diet quality, reflecting access to a variety of foods and serving as a proxy for individual nutrient adequacy [30]. There is ample evidence from developed countries showing that dietary diversity is indeed strongly associated with nutrient adequacy. Unfortunately there is a dearth of studies from developing countries, but the few available studies support an association between dietary diversity and nutrient adequacy [31–33].

Associations between diversified dietary intake, micronutrients, and hypertensive disorders are particularly relevant in India, where rates of malnutrition and micronutrient deficiencies are high among pregnant women [34]. To our knowledge, there has not been any previous large-scale population based study of the dietary risk factors for PE or E in Indian women. Studies which have examined the links between diet and PE or E empirically have not been conducted in high burden countries; nor have they employed appropriate multivariable models. Similarly, much research has focused on treatment of PE or E, but less is known about potential preventive factors, particularly those associated with maternal behaviours during pregnancy [35–36].

Identifying the link between an adequately diversified dietary intake and the risk of PE or E may suggest an important point of intervention at both the peri-conceptional and gestational stages particularly in a developing country such as India. In this study, as dietary diversity is a key factor in ensuring an adequate micronutrient balance, we use the large-scale, cross-sectional and nationally representative third National Family and Health Survey (NFHS-3) data [37–38] to test the hypothesis that adequately diversified dietary intake and iron and folic acid supplementation during pregnancy are inversely related to the risk of PE or E among Indian women.

Methodology

Cross-sectional data from the most recent wave of the National Family Health Survey (NFHS-3, 2005–2006), India’s Demographic and Health Survey (DHS), was used for this study. These data are publicly available by request from DHS [37]. The survey was approved by the ethics boards of the implementing agencies in the respective states of India and by the Indian government [38]. Our analysis used secondary survey data which was completely anonymised prior to access. As the data were anonymised by the DHS [37], no ethics board review was required. Using a multistage randomised cluster design (response rate = 98%), NFHS-3 employed an interviewer-administered questionnaire in the native language of the respondent to collect socio-demographic and health information, resulting in a nationally representative probability sample of 124,385 women aged 15–49 years. All states of India are represented in the sample (except the Union Territories covering less than 1% of India’s population). Full details of the survey have been published elsewhere [38].

To assess symptoms of PE or E, we restricted the sample to those women who had a live birth in the five years preceding the survey. We further restricted our analyses to data pertaining to the most recent birth, both to minimize recall bias and in order to draw on iron and folic acid supplementation and antenatal care (ANC) measures, which were only available for only the most recent pregnancy. This resulted in a final sample size of 39,657 participants.

Outcome Measure

To assess the occurrence of PE or E, we constructed a measure based on women’s self-reports of symptoms during pregnancy. Specifically, mothers were asked: “During this pregnancy, did
you have difficulty with your vision during daylight?”, “During this pregnancy, did you have swelling of the legs, body or face?” and “During this pregnancy, did you have convulsions not from fever?” The response options were “Yes”, “No”, and “Don’t know”. Following the World Health Organisations [39] and National Institute for Health and Care Excellence guidelines [40], we created a dichotomous indicator of PE or E: Women who reported both difficulty with vision during daylight and swelling of the legs, body, or face, were coded as having symptoms suggestive of pre-eclampsia, whereas those who additionally reported experiencing convulsions (not from fever) were coded as eclamptic. However, it was not possible to confirm clinical diagnosis of these symptoms. Data on blood pressure and proteinuria during pregnancy, which are typical clinical diagnostic markers of pre-eclampsia [41], were not available in the NFHS-3. Data on physician reported diagnosis of convulsions/seizures were also not available in the NFHS-3 to verify a self-reported diagnosis.

**Key Predictors**

Dietary diversity is often used as a proxy for dietary intake, both because it is a straightforward measure of nutrition, and also because the burden on respondents is relatively low [30]. The WHO [42] has identified 8 broadly defined food groups (grains, roots and tubers; legumes and nuts; dairy products; flesh foods; eggs; vitamin A-rich fruits and vegetables; and other fruits and vegetables), and suggests that individuals should eat from at least four food groups daily in order to achieve an adequately diversified dietary intake. Based on WHO criteria [42], we created a dietary diversity score from women’s self-reported frequency (daily, weekly, occasionally, or never) of their consumption of milk or curd, green leafy vegetables, other vegetables, fruits, pulses and beans, eggs, fish, and chicken or meat. For each food category, consumption of at least one food item from the category is worth 1 point; however, consumption of foods that fall into multiple categories (such as eggs, which are categorized both as flesh foods and eggs) is worth 2 points. A minimum of 4 points is necessary for an adequately diversified dietary intake [42]. However, as the NFHS-3 data do not contain consumption data for some of the WHO-defined categories (e.g. grains, roots and tubers), we have modified the score so that a dietary diversity score greater than or equal to three was considered to be an adequately diversified dietary intake, and less than three was considered inadequate. Dietary diversity at the time of the survey was taken as a proxy measure for dietary diversity during pregnancy.

The other main exposure variable used in our study was self-reported consumption of iron and folic acid supplementation during pregnancy. For the most recent birth, NFHS-3 asked to mothers “Were you given or did you buy any iron and folic acid tablets or syrup?” In addition, the duration (in days) of iron and folic acid supplementation was recorded, and was categorized based on proposed national guidelines and WHO guidelines [43]. As iron and folic acid supplementation were included in the same question rather than as separate survey items, we were not able to include them as independent predictors in our models. We created a dichotomous indicator of iron and folic acid supplementation.

**Control Variables**

Given the unknown etiology of PE or E, it is possible that its onset is influenced by sociodemographic and health-related factors. In order to adjust for this, we controlled for three groups of potential confounders.

**Maternal Factors.** Categorical measures of age (15–29, 30–39, and 40–49 years) and birth interval (first child, <2 years, 2–3 years, 3 years or more) and a dichotomous indicator of pregnancy type (single, multiple) were included to control for the positive association between maternal age [44–45], short birth intervals, multiple births, and health risks during pregnancy. As
pre-eclampsia and eclampsia risk has been found to be higher in nulliparous women [28, 46], we included a categorical measure of parity (1, 2, 3, or 4 or more). To control for the possibility that progression from gestational hypertension to pre-eclampsia may be increased by a prior miscarriage [47], we created a dichotomous indicator of whether the respondent ever had an induced or spontaneous abortion. As anemia during pregnancy has been linked to pre-eclampsia [48], we followed CDC recommendations [49] to construct a categorical measure of anemia level (not anemic, mildly anemic, moderately anemic, and severely anemic) adjusted for current pregnancy status, living at high altitudes, and smoking behaviour. In India, more than 80% of the pregnant women received iron and folic acid supplementation through antenatal care (ANC), and women were provided with information on proper nutrition and the signs and symptoms of pre-eclampsia and eclampsia during their ANC visit (38). Given the importance of appropriate ANC for maternal and child health, we thus included two controls for self-reported utilization of ANC: a categorical measure of the number of visits (none, 1–3, and 4 or more) and access to healthcare, measured by a categorical indicator of type of healthcare facility used (public medical sector, NGO trust hospital or clinic, private medical sector, and other sources).

Health and Lifestyle Factors. As dietary patterns are likely to be part of a broader health lifestyle, which may itself have implications for PE or E risk, we included a group of covariates to adjust for health and lifestyle factors. Studies have demonstrated that women with pre-eclampsia have a higher rate of pre-gestational hypertension and overweight or obese body mass index (BMI) [50]. Following this, we included a Asian Population standard [51–53] BMI (kg/m²) measure, categorized as underweight (≤18.5 kg/m²), normal (18.5 to 22.9 kg/m²), overweight (23.0 to 24.9 kg/m²), and obese (≥25.0 kg/m²). As change in BMI between pregnancies has been estimated to be over one-half a unit (median 0.7; IQR −0.3–1.7) [54], we assumed that there is unlikely to be a marked change in category of BMI between the birth and the time of the survey. We therefore used BMI at the time of the survey as a proxy for pre-pregnancy BMI. While maternal cigarette smoking increases the risk of a number of pregnancy complications, smoking has consistently been shown to reduce the risk of pre-eclampsia by approximately 30% in western studies [55–59]. In NFHS-3, participants were asked four yes/no questions on current use of cigarettes, pipes, other local tobacco smoking products, and snuff, chew, or other smokeless tobacco products. As a dichotomous measure of current tobacco use, we classified women as smokers if the response was ‘yes’ to smoking cigarettes, pipes, or other local smoking products. Women were classified as ‘smokeless tobacco users’ if the response was ‘yes’ to the use of chew, snuff, or other local smokeless tobacco products currently. As several studies have found a negative association between prenatal alcohol consumption and pre-eclampsia [60–62], we constructed a dichotomous indicator of current alcohol use. Due to the association between diabetes and maternal health, we also included dichotomous indicators of self-reported diabetes. Several studies have shown that women with gestational diabetes mellitus have an increased risk of pre-eclampsia or gestational hypertension [63–64] and that insulin resistance predates the development of pre-eclampsia, implying that insulin resistance may play a role in its etiology [65–66]. The risk of pre-eclampsia also increases with increasing glucose intolerance [64,67–68]. Some studies also suggest that asthmatics, particularly those who are symptomatic during pregnancy, may be at a higher risk of developing pre-eclampsia [69]. We thus included a dichotomous indicator of self-reported asthma in the current analysis.

Sociodemographic Characteristics. In order to reduce the risk of unobserved homogeneity in our models, we included a variety of socio-demographic controls. Religion was categorized into Hindu, Muslim, Christian, Sikhs or other/missing (Buddhist, Jain, Jewish, Zoroastrian etc.). Caste was categorized as scheduled caste, scheduled tribe, other backward class (NFHS-3 classification; hereafter referred to as disadvantaged class), general, and other/
missing [38]. We also included categorical indicators of maternal education (no education, primary, secondary, and higher) and occupation (professional/technical/managerial, clerical/sales, agricultural work, services, skilled and unskilled manual labour, and not working). Household wealth was categorized into quintiles based on the standard DHS index of household assets [37–38]. Place of residence was defined as either urban or rural. To account for differences in dietary preferences, food security subsidies, and other factors which may vary regionally, geographic regions was classified into six zones: north, northeast, central, east, west and south.

Statistical Analysis

All analyses were conducted using the SPSS statistical software package Version 19 (IBM SPSS Statistics, Chicago, Illinois, USA). Standard descriptive statistics were calculated for all variables, including means and standard deviations. Differences in categorical variables were tested using $\chi^2$ tests. We assessed the possibility of multicollinearity between the covariates by using a correlation matrix of covariates. All pairwise Pearson correlation coefficients were less than 0.5, suggesting that multicollinearity is not a concern. We included NFHS-3 sampling weights to account for the sample design and ensure the representativeness of the sample [38]. Fixed effects multivariable logistic regression models [70–71] were then used to estimate the association between dietary diversity, iron and folic acid supplementation during pregnancy, and PE or E.

Multivariable models were adjusted for the above described maternal factors, health and lifestyle factors and socio-demographic characteristics of the mother. In the first logistic regression model, we examined the unadjusted association between dietary diversity, iron and folic acid supplementation and PE or E symptoms independent of each other. In the second model, we adjusted for maternal factors in order to assess how much of the variance in this association was explained by maternal characteristics. In the third model, we added health lifestyle factors to our model. In the fourth and final model, we added socio-demographic characteristics in order to examine the association between dietary diversity, iron and folic acid supplementation and PE or E symptoms controlling for all the confounders discussed above. Maternal marital status was not included as part of the socio-demographic characteristics because the majority (i.e., 98%) were married. We also tested for a variety of potential interactive effects, for any possible significant interactions. In particular, given that ANC visits may improve maternal health outcomes both by direct treatment of health conditions and by providing women with dietary advice and supplementation, we tested for an interaction between ANC visits with each of our two key predictors. State fixed effects were included in all models, and standard errors were clustered at the primary sampling unit.

It has been argued that logistic regression models should be used with a minimum of 10 events per predictor variable (EPV) [72–74]. In this etiological observational study, we are interested in adjusting for a number of covariates. Simulation studies show that 16–24 events per variable also produce stable effect estimates [75]. Given that our sample size is 39,657 participants, a conservative event rate of 50% is an acceptable ratio of events to non-events to adjust for the large number of covariates [75].

Sensitivity analyses

Women with better socioeconomic resources may a) have a better understanding of their symptoms, b) report their experiences differently when compared to women in lower wealth and education groups, and c) have access to a better diet during pregnancy. To overcome potential sources of information bias, particularly with regard to self-reported diet and health
problems during pregnancy, we ran sensitivity analyses for level of education (higher than secondary) and household wealth (richest quintile). Given that the population of women attending ANC might be inherently different than those who do not, we also conducted a sensitivity analysis on ANC visits, restricting the sample to only those women who attended ANC.

Women who were currently pregnant or who had given birth within 2 months of the survey were not weighed, resulting in missing values on the BMI measure for currently or recently pregnant women. Due to list wise deletion, these women were excluded from our full regression models. Given that pregnancy should in theory be randomly distributed in the sample, it is unlikely that this sample restriction would bias our sample. However, to test for potential bias, we created a variable to flag cases that were missing on BMI, and ran our fully adjusted model including the flag variable, but without BMI as a covariate in order to retain these cases. However, since BMI is an important covariate that could influence the effect estimate, we have again re-estimated the models by adding an additional category to the existing BMI variable to signify those who were missing on the measure.

We also repeated the analysis, restricting it to those women who had given birth up to 3 years prior to the survey and reported PE or E symptoms to examine the potential effects of recall bias. Short birth intervals are associated with adverse perinatal outcomes [76], but long intervals, especially those longer than 5 years, are also independently associated with an increased risk of pre-eclampsia [77]. In a final set of sensitivity analyses, we restricted the models to multiparous women (74% of the sample) who were not currently pregnant, and examined the effect of the length of the birth interval and PE or E risk.

Results

Table 1 presents the characteristics of the study sample. Overall, 1.2% (n = 456) of mothers reported symptoms suggestive of PE or E. One-third of the mothers (31.1%) consumed an adequately diversified diet and one-fourth reported of taking iron and folic acid supplementation for at least 90 days during their last pregnancy, though almost two-thirds (65%) reported taking an iron and folic acid supplement at some point during their pregnancy. One-fourth of the mothers were at first parity, and 31% of the births were preceded by an interval of more than 3 years and 1% of the pregnancies were multiple births.

Approximately one-fifth (18.5%) of the mothers reported a spontaneous or induced abortion. Malnutrition rates were high: almost one-fifth of the mothers were moderately or severely anaemic, 31% were underweight while 22% were either overweight or obese. More than half the mothers had four or more ANC visits during their last pregnancy and almost 70% had access to the private medical sector to obtain their health care. Very few were current smokers (1.5%) or alcohol drinkers (2.3%), while almost one in ten were smokeless tobacco users (8.3%). Prevalence of diabetes (1.3%) and asthma (1.2%) were low. Most mothers (almost three-fourth) were aged 15–29 years, and almost half (47.4%) had no education. A majority of the mothers (four out of five) were identified as Hindu, and two-fifths belonged to a disadvantaged class. One in four mothers were agricultural worker while a very few (1.8%) worked in the service sector. One fourth belonged to the household with poorest wealth. More than 70% of the mothers were residing in rural areas and 28% were residents of Central India.

Table 2 provides the percentage distribution of PE or E cases and prevalence of symptoms of PE or E according to selected characteristics. Of women reporting PE or E symptoms, more than four-fifths reported of inadequately diversified dietary intake; half had consumed iron and folic acid supplementation and 13% adhered to the recommended duration (≥90 days) of IFA intake; two-fifths (41%) were four and higher order births; 39% had a birth interval of 3 years or more; 2.4% were multiple pregnancies; one-fourth had terminated pregnancies; almost
### Table 1. Characteristics of the study participants (n = 39,657), India 2005–06.

| Selected characteristics | Women age 15–49 years |
|--------------------------|-----------------------|
|                          | Number | %      |
| **Maternal factors**     |         |        |
| Pre-eclampsia or Eclampsia symptoms |         |        |
| No                       | 39155  | 98.8   |
| Yes                      | 456    | 1.2    |
| **Dietary diversity**    |         |        |
| Inadequate               | 27275  | 68.9   |
| Adequate                 | 12337  | 31.1   |
| **Iron and folic acid supplementation** |         |        |
| No                       | 13646  | 34.6   |
| Yes                      | 25809  | 65.4   |
| Missing cases            | 157    | 0.4    |
| **Duration of iron and folic acid supplementation** |         |        |
| <90 days                 | 29588  | 74.7   |
| ≥90 days                 | 10024  | 25.3   |
| **Parity**               |         |        |
| 1                        | 10453  | 26.4   |
| 2                        | 11370  | 28.7   |
| 3                        | 6810   | 17.2   |
| 4 and above              | 11005  | 27.8   |
| **Preceding birth interval** |         |        |
| First order birth        | 10546  | 26.6   |
| Interval <2 years        | 7124   | 18.0   |
| Interval 2-3 years       | 9538   | 24.1   |
| Interval 3 years or more | 12448  | 31.4   |
| **Type of pregnancy**    |         |        |
| Singleton                | 39298  | 99.1   |
| Multiple                 | 359    | 0.9    |
| Terminated pregnancy     |         |        |
| Never                    | 32319  | 81.5   |
| Ever                     | 7338   | 18.5   |
| **Anaemia level**        |         |        |
| Not anaemic              | 14939  | 40.1   |
| Mild                     | 15082  | 40.4   |
| Moderate                 | 6616   | 17.7   |
| Severe                   | 652    | 1.7    |
| Missing cases            | 2362   | 6.0    |
| **Number of ANC visits** |         |        |
| No visit                 | 9020   | 22.8   |
| 1-3                      | 9696   | 24.5   |
| 4 or more                | 20895  | 52.8   |
| **Healthcare access**    |         |        |
| Public medical sector    | 11303  | 31.3   |
| NGO Trust Hospital/Clinic| 113    | 0.3    |
| Private Medical Sector   | 24591  | 68.1   |
| Other sources            | 119    | 0.3    |

(Continued)
Table 1. (Continued)

| Selected characteristics | Women age 15–49 years |
|---------------------------|-----------------------|
|                           | Number | %      |
| Missing cases             | 3486   | 8.8    |
| Health and Lifestyle factors |       |        |
| Body Mass Index           |         |        |
| Underweight (<18.5 kg/m²) | 11592  | 30.5   |
| Normal (18.5-22.9 kg/m²) | 20714  | 54.4   |
| Overweight (23.0-24.9 kg/m²) | 2770  | 7.3    |
| Obese (≥25.0 kg/m²)      | 3226   | 14.7   |
| Missing cases             | 1609   | 4.1    |
| Smoking tobacco           |         |        |
| No                        | 39049  | 98.5   |
| Yes                       | 608    | 1.5    |
| Smokeless tobacco use     |         |        |
| No                        | 36333  | 91.7   |
| Yes                       | 3278   | 8.3    |
| Drinks alcohol            |         |        |
| No                        | 38735  | 97.7   |
| Yes                       | 911    | 2.3    |
| Missing cases             | 11     | 0.0    |
| Current medical conditions |         |        |
| Diabetes                  |         |        |
| No                        | 39123  | 98.7   |
| Yes                       | 160    | 1.3    |
| Missing cases             | 20     | 0.1    |
| Asthma                    |         |        |
| No                        | 39163  | 98.8   |
| Yes                       | 470    | 1.2    |
| Missing cases             | 24     | 0.1    |
| Socioeconomic and demographic factors |         |        |
| Age                       |         |        |
| 15-29 y                   | 29190  | 73.6   |
| 30-39 y                   | 9421   | 23.8   |
| 40-49 y                   | 1047   | 2.6    |
| Education                 |         |        |
| No education              | 18783  | 47.4   |
| Primary                   | 5550   | 14.0   |
| Secondary                 | 12959  | 32.7   |
| Higher                    | 2365   | 6.0    |
| Missing cases             | 1      | 0.0    |
| Religion                  |         |        |
| Hindu                     | 31280  | 78.9   |
| Muslim                    | 6482   | 16.3   |
| Christian                 | 814    | 2.1    |
| Sikhs                     | 514    | 1.3    |
| Others                    | 568    | 1.4    |
| Caste/tribe               |         |        |

(Continued)
half (46%) were mildly anemic; more than two-thirds (71%) had access to public medical sector for healthcare needs; 3% were obese; 2% was smoking tobacco; 13% were smokeless tobacco users; 5% drinks alcohol; 1.8% and 5% reported having diabetes or asthma respectively; two-thirds were in the age group 15–29 years; two-thirds had no education; 80% were Hindus; 38% belonged to disadvantaged class; half were not working; two-fifths belong to poorest wealth quintile; a majority resides in rural area whereas two-fifths resides in central India.

Considering prevalence of PE or E, a higher proportion of women with inadequate dietary diversity reported of PE or E symptoms (1.4%) than those women with adequately diversified dietary intake (0.6%). A higher proportion of those who did not consume iron and folic acid supplementation for at least 90 days also reported of high PE or E (1.3%) symptoms as compared to those who took iron and folic acid supplements for 90 or more days (0.6%).

Table 1. (Continued)

| Selected characteristics     | Women age 15–49 years |
|------------------------------|-----------------------|
|                              | Number | %   |
| Scheduled caste              | 7945   | 20.1 |
| Scheduled tribes             | 3742   | 9.5  |
| Disadvantaged class          | 15878  | 40.2 |
| General                      | 10845  | 27.5 |
| Missing caste                | 1089   | 2.8  |
| Missing cases                | 158    | 0.4  |
| Occupation                   |         |      |
| Not working                  | 24710  | 62.4 |
| Professional/technical/managerial | 670   | 1.7  |
| Clerical/Sales               | 566    | 1.4  |
| Agricultural work            | 9950   | 25.1 |
| Services                     | 715    | 1.8  |
| Skilled and unskilled-Mannual| 2991   | 7.6  |
| Missing cases                | 9      | 0.0  |
| Wealth index                 |         |      |
| Poorest                      | 9566   | 24.1 |
| Poorer                       | 8600   | 21.7 |
| Middle                       | 7769   | 19.6 |
| Richer                       | 7256   | 18.3 |
| Richest                      | 6466   | 16.3 |
| Place of residence           |         |      |
| Urban                        | 10622  | 26.8 |
| Rural                        | 29035  | 73.2 |
| Geographic Regions           |         |      |
| North                        | 5678   | 12.8 |
| Northeast                    | 1613   | 4.1  |
| Central                      | 11111  | 28.0 |
| East                         | 10042  | 25.3 |
| West                         | 5117   | 12.9 |
| South                        | 6696   | 16.9 |
| Total                        | 39657  | 100.0 |

Note: Number of women varies slightly for individual variables depending on the number of missing values

doi:10.1371/journal.pone.0119120.t001
Table 2. Percentage distribution of Pre-eclampsia or eclampsia cases and self-reported prevalence of symptoms suggestive of Pre-eclampsia or eclampsia according to selected characteristics, India 2005–06.

| Variables                                      | Total Number of Pre-eclampsia or Eclampsia cases | % Distribution of Pre-eclampsia or Eclampsia cases | % Prevalence of Pre-eclampsia or Eclampsia | X² p value |
|------------------------------------------------|-------------------------------------------------|-----------------------------------------------------|------------------------------------------|-----------|
| Diet and iron and folic acid intake            |                                                 |                                                    |                                          | <0.0001   |
| Dietary diversity                              |                                                 |                                                    |                                          | <0.0001   |
| In adequate                                    | 377                                             | 82.5                                               | 1.4                                      |           |
| Adequate                                       | 80                                              | 17.5                                               | 0.6                                      |           |
| Iron and folic acid supplementation            |                                                 |                                                    |                                          | <0.0001   |
| No                                             | 217                                             | 47.7                                               | 1.6                                      |           |
| Yes                                            | 238                                             | 52.3                                               | 0.9                                      |           |
| Duration of iron and folic acid supplementation|                                                 |                                                    |                                          | <0.0001   |
| <90 days                                       | 398                                             | 87.3                                               | 1.3                                      |           |
| >90 days                                       | 58                                              | 12.7                                               | 0.6                                      |           |
| Maternal factors                               |                                                 |                                                    |                                          |           |
| Parity                                         |                                                 |                                                    |                                          | <0.0001   |
| 1                                              | 85                                              | 18.6                                               | 0.8                                      |           |
| 2                                              | 103                                             | 22.6                                               | 0.9                                      |           |
| 3                                              | 81                                              | 17.8                                               | 1.2                                      |           |
| 4 and above                                    | 187                                             | 41.0                                               | 1.7                                      |           |
| Preceding birth interval                       |                                                 |                                                    |                                          | <0.0001   |
| First order birth                              | 85                                              | 18.6                                               | 0.8                                      |           |
| Interval <2 years                              | 88                                              | 19.3                                               | 1.2                                      |           |
| Interval 2-3 years                             | 104                                             | 22.8                                               | 1.1                                      |           |
| Interval 3 years or more                       | 179                                             | 39.3                                               | 1.4                                      |           |
| Type of pregnancy                              |                                                 |                                                    |                                          | 0.003     |
| Singleton                                      | 446                                             | 97.6                                               | 1.1                                      |           |
| Multiple                                       | 11                                              | 2.4                                                | 3.1                                      |           |
| Terminated pregnancy                           |                                                 |                                                    |                                          | 0.005     |
| Never                                          | 350                                             | 76.8                                               | 1.1                                      |           |
| Ever                                           | 106                                             | 23.2                                               | 1.4                                      |           |
| Anemia level                                   |                                                 |                                                    |                                          | <0.0001   |
| Not anaemic                                    | 129                                             | 29.6                                               | 0.9                                      |           |
| Mild                                           | 200                                             | 45.9                                               | 1.3                                      |           |
| Moderate                                       | 101                                             | 23.2                                               | 1.5                                      |           |
| Severe                                         | 6                                               | 1.4                                                | 0.9                                      |           |
| Number of ANC visits                           |                                                 |                                                    |                                          | <0.0001   |
| No visit                                       | 149                                             | 32.6                                               | 1.7                                      |           |
| 1-3                                            | 148                                             | 32.4                                               | 1.5                                      |           |
| 4 or more                                      | 160                                             | 35.0                                               | 0.8                                      |           |
| Healthcare access                              |                                                 |                                                    |                                          | 0.190     |
| Public medical sector                          | 124                                             | 28.8                                               | 1.1                                      |           |
| NGO Trust Hospital/Clinic                      | 3                                               | 0.7                                                | 2.7                                      |           |
| Private Medical Sector                         | 304                                             | 70.5                                               | 1.2                                      |           |
| Other sources                                  | 0                                               | 0.0                                                | 0.0                                      |           |
| Health and Lifestyle factors                   |                                                 |                                                    |                                          |           |
| Body Mass Index                                |                                                 |                                                    |                                          | 0.001     |

(Continued)
Table 2. (Continued)

| Variables                        | Total Number of Pre-eclampsia or Eclampsia cases | % Distribution of Pre-eclampsia or Eclampsia cases | % Prevalence of Pre-eclampsia or Eclampsia | $X^2$ | $p$ value |
|----------------------------------|--------------------------------------------------|---------------------------------------------------|-------------------------------------------|-------|-----------|
| Underweight ($\leq 18.5$ kg/m²) | 183                                              | 50.3                                              | 1.3                                       |       |           |
| Normal (18.5-22.9 kg/m²)         | 224                                              | 41.1                                              | 1.3                                       |       |           |
| Overweight (23.0-24.9 kg/m²)     | 23                                               | 5.2                                               | 0.8                                       |       |           |
| Obese ($\geq 25.0$ kg/m²)        | 15                                               | 3.4                                               | 0.5                                       |       |           |
| Smoking Tobacco                  |                                                  |                                                   |                                           | 0.164 |           |
| No                               | 446                                              | 97.8                                              | 1.1                                       |       |           |
| Yes                              | 10                                               | 2.2                                               | 1.7                                       |       |           |
| Smokeless tobacco use            |                                                  |                                                   |                                           | $<0.0001$ |           |
| No                               | 397                                              | 87.1                                              | 1.1                                       |       |           |
| Yes                              | 59                                               | 12.9                                              | 1.8                                       |       |           |
| Drinks Alcohol                   |                                                  |                                                   |                                           | $<0.0001$ |           |
| No                               | 433                                              | 94.7                                              | 1.1                                       |       |           |
| Yes                              | 24                                               | 5.3                                               | 2.6                                       |       |           |
| Current medical conditions       |                                                  |                                                   |                                           |       |           |
| Diabetes                         |                                                  |                                                   |                                           | 0.240 |           |
| No                               | 448                                              | 98.2                                              | 1.1                                       |       |           |
| Yes                              | 8                                                | 1.8                                               | 1.6                                       |       |           |
| Asthma                           |                                                  |                                                   |                                           | $<0.0001$ |           |
| No                               | 434                                              | 95.2                                              | 1.1                                       |       |           |
| Yes                              | 22                                               | 4.8                                               | 4.7                                       |       |           |
| Socioeconomic and demographic factors |                                              |                                                   |                                           |       |           |
| Age                              |                                                  |                                                   |                                           | 0.013 |           |
| 15-29 y                          | 309                                              | 67.6                                              | 1.1                                       |       |           |
| 30-39 y                          | 134                                              | 29.3                                              | 1.4                                       |       |           |
| 40-49 y                          | 14                                               | 3.1                                               | 1.3                                       |       |           |
| Education                        |                                                  |                                                   |                                           | $<0.0001$ |           |
| No education                     | 294                                              | 64.5                                              | 1.6                                       |       |           |
| Primary                          | 66                                               | 14.5                                              | 1.2                                       |       |           |
| Secondary                        | 91                                               | 20.0                                              | 0.7                                       |       |           |
| Higher                           | 5                                                | 1.1                                               | 0.2                                       |       |           |
| Religion                         |                                                  |                                                   |                                           | 0.027 |           |
| Hindu                            | 362                                              | 79.6                                              | 1.2                                       |       |           |
| Muslim                           | 69                                               | 15.2                                              | 1.1                                       |       |           |
| Christian                        | 6                                                | 1.3                                               | 0.7                                       |       |           |
| Sikhs                            | 4                                                | 0.9                                               | 0.8                                       |       |           |
| Others                           | 14                                               | 3.1                                               | 2.5                                       |       |           |
| Caste/tribe                      |                                                  |                                                   |                                           | $<0.0001$ |           |
| Scheduled caste                  | 99                                               | 21.8                                              | 1.2                                       |       |           |
| Scheduled tribes                 | 84                                               | 18.5                                              | 2.2                                       |       |           |
| Disadvantaged class              | 173                                              | 38.0                                              | 1.1                                       |       |           |
| General                          | 88                                               | 19.3                                              | 0.8                                       |       |           |
| Missing caste                    | 11                                               | 2.4                                               | 1.0                                       |       |           |
| Occupation                       |                                                  |                                                   |                                           | $<0.0001$ |           |
| Not working                      | 228                                              | 50.0                                              | 0.9                                       |       |           |

(Continued)
with mild (1.3%) and moderate anaemia (1.5%) also reported higher symptoms of PE or E as compared to those with no (0.9%) or severe (0.9%) anaemia. Compared to overweight (0.8%) or obese (0.5%) women, those who were underweight (1.3%) and normal weight (1.3%) reported higher proportion of PE or E symptoms.

Pregnancy and health risk factors were also significantly associated with PE or E symptoms, with a higher proportion of women of parity 4 or higher (1.7%) reported higher PE or E symptoms than women of lower parity. First order births had the lowest proportion of PE or E symptoms (0.8%), while women with a birth interval of 3 or more years experienced significantly higher symptoms of PE or E (1.4%). Multiple births were also associated with higher odds of PE or E symptoms (3.1%) compared to singleton births (1.1%), as were previously aborted pregnancies (1.4%) compared to those with no previous spontaneous or induced abortions (1.1%). A higher proportion of current smokeless tobacco users (1.8%), current alcohol drinkers (2.6%), and current tobacco smokers (1.7%) also reported PE or E symptoms compared to those who, respectively, do not currently use tobacco, drink, or smoke. Additionally, asthmatics (4.7%) reported higher PE or E symptoms than non-asthmatics (1.1%).

Significant associations were also found between socio-demographic characteristics and PE or E symptoms. A lower proportion of women aged 15–29 reported PE or E symptoms (1.1%) compared to women aged 30–39 (1.4%) and 40–49 years (1.3%). However, a higher proportion of women with no education (1.6%) reported PE or E symptoms compared to those with primary, secondary, or higher levels of education. Caste was also a significant correlate, with a higher proportion of women reporting PE or E symptoms belonging to a scheduled tribe.

Table 2. (Continued)

| Variables                | Total Number of Pre-eclampsia or Eclampsia cases | % Distribution of Pre-eclampsia or Eclampsia cases | % Prevalence of Pre-eclampsia or Eclampsia | \( \chi^2 \) p value |
|--------------------------|--------------------------------------------------|-----------------------------------------------|------------------------------------------|---------------------|
| Professional/technical/managerial | 8                                           | 1.8                                           | 1.2                                      | <0.0001 |
| Clerical/Sales           | 3                                           | 0.7                                           | 0.5                                      |         |
| Agricultural work        | 173                                         | 37.9                                          | 1.7                                      |         |
| Services                 | 71                                          | 1.5                                           | 1.0                                      |         |
| Skilled and unskilled-Manual | 37                                        | 8.1                                           | 1.2                                      |         |
| Wealth index             |                                               |                                               |                                          |         |
| Poorest                  | 187                                         | 41.1                                          | 2.0                                      |         |
| Poorer                   | 109                                         | 24.0                                          | 1.3                                      |         |
| Middle                   | 76                                          | 16.7                                          | 1.0                                      |         |
| Richer                   | 47                                          | 10.3                                          | 0.6                                      |         |
| Richest                  | 36                                          | 7.9                                           | 0.6                                      |         |
| Place of residence       |                                               |                                               |                                          | <0.0001 |
| Urban                    | 65                                          | 14.2                                          | 0.6                                      |         |
| Rural                    | 392                                         | 85.8                                          | 1.4                                      |         |
| Geographic Regions       |                                               |                                               |                                          | <0.0001 |
| North                    | 52                                          | 11.4                                          | 1.0                                      |         |
| Northeast                | 22                                          | 4.8                                           | 1.4                                      |         |
| Central                  | 188                                         | 41.2                                          | 1.7                                      |         |
| East                     | 137                                         | 30.0                                          | 1.4                                      |         |
| West                     | 36                                          | 7.9                                           | 0.7                                      |         |
| South                    | 21                                          | 4.6                                           | 0.3                                      |         |
| Total                    | 456                                         | 100.0                                         | 1.2                                      |         |

doi:10.1371/journal.pone.0119120.t002
than those in a scheduled caste (1.2%), disadvantaged class (1.1%) or general caste (0.8%). Those in the poorest wealth quintile reported the highest PE or E symptoms (2.0%) compared to those in the other four wealth quintiles, as did those in professional (1.2%) and agricultural (1.7%) occupations. Rural residence was also associated with increased proportion of women reporting a PE or E symptoms (1.4%) compared to urban residence (0.6%), and women living in central (1.7%), northeast (1.4%) and eastern (1.4%) India reported higher PE or E symptoms than those in other regions.

Table 3 shows results of multivariable logistic regression analyses of the association between dietary diversity, iron and folic acid supplementation and symptoms of pre-eclampsia or eclampsia, India, 2005–06.

| Key predictors | Model 1 Unadjusted OR [95%CI] | Model 2 Adjusted OR [95%CI] | Model 3 Adjusted OR [95%CI] | Model 4 Adjusted OR [95%CI] |
|----------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Dietary diversity |                               |                               |                               |                               |
| Adequate        | 0.52 [0.41–0.66]              | 0.57 [0.44–0.73]              | 0.56 [0.43–0.72]              | 0.66 [0.51–0.87]              |
| Inadequate R    | 1.00                          | 1.00                          | 1.00                          | 1.00                          |
| P value         | <0.0001                       | <0.0001                       | <0.0001                       | 0.003                        |
| Duration of iron and folic acid supplementation |                               |                               |                               |                               |
| ≥90 days        | 0.48 [0.36–0.64]              | 0.61 [0.45–0.82]              | 0.56 [0.42–0.75]              | 0.64 [0.47–0.88]              |
| <90 days R      | 1.00                          | 1.00                          | 1.00                          | 1.00                          |
| P value         | <0.0001                       | 0.001                         | <0.0001                       | 0.006                        |

R Indicates reference category; Sample size is 39,657

Model 1 unadjusted
Model 2 adjusted for maternal factors only
Model 3 adjusted for maternal factors, health and lifestyle factors and current medical conditions
Model 4 adjusted for maternal, health and lifestyle factors, current medical conditions and socio-demographic characteristics

Table 3 shows results of multivariable logistic regression analyses of the association between dietary diversity, iron and folic acid supplementation during pregnancy, and symptoms suggestive of PE or E, in unadjusted, partially adjusted and fully adjusted models. In the unadjusted analysis (Model 1), the likelihood of reporting PE or E symptoms was significantly lower among women who had an adequately diversified dietary intake (OR: 0.52; 95% CI: 0.41–0.66) than among those who did not have a diversified dietary intake. Similarly, women who took iron and folic acid supplements for 90 or more days during pregnancy had a lower likelihood of reporting PE or E symptoms (OR: 0.48; 95% CI: 0.36–0.64) than those who did not take iron or folic acid supplements for the recommended 90 days. Controlling for the maternal factors (in Model 2) slightly attenuated the inverse relationship between diversified dietary intake (OR: 0.57; 95% CI: 0.44–0.73) and PE or E, as well as between intake of iron and folic acid supplementation (OR: 0.61; 95% CI: 0.45–0.8) and PE or E symptoms. The inverse association between the effect of diversified dietary intake (OR: 0.56; 95% CI: 0.43–0.72), intake of iron and folic acid supplementation (OR: 0.56; 95% CI: 0.42–0.75) and PE or E symptoms remained virtually unchanged when health and lifestyle factors were additionally controlled for in Model 3. The final model (Model 4) in Table 3 provides the fully adjusted model with maternal factors, health and lifestyle factors, and socio-demographic characteristics included. Of the significant predictors from the bi-variable associations, twin pregnancy, ever having an abortion, mild or moderate anaemia, being asthmatic, occupation, wealth quintile, and caste remained significant predictors of PE or E symptoms in the fully adjusted model (Model 4), while parity, birth interval, BMI, alcohol and tobacco use, age, education, place of residence, and geographic
region were no longer significant. Jointly controlling for all of these factors, the inverse association between an adequately diversified dietary intake (OR: 0.66; 95% CI: 0.51–0.87), recommended intake of iron and folic acid supplementation (OR: 0.64; 95% CI: 0.47–0.88) and PE or E symptoms during pregnancy remains strong and statistically significant. We found no evidence of an interaction effect between dietary diversity, iron and folic acid supplementation and ANC utilization in the fully adjusted model.

**Results of the sensitivity analysis**

As a robustness check, we ran Models 1 through 4 restricting only to those cases with valid data on the BMI measure. Results remained largely unchanged: diversified dietary intake (OR: 0.67; 95% CI: 0.54–0.85; p = 0.004) and intake of iron and folic acid supplementation (OR: 0.65; 95% CI: 0.48–0.89; p = 0.006) continued to be significant predictors of lower occurrence of PE or E symptoms in Indian women (not shown on the table). We again re-estimated the models with BMI split into 5 categories (underweight, normal, overweight, obese, and missing) and could find no demonstrable change in the association. Among women in the highest education group, the likelihood of reporting symptoms of PE or E was lower among those with a adequately diversified dietary intake (OR: 0.60; 95% CI: 0.39–0.78) and recommended intake of iron and folic acid supplementation (OR: 0.68; 95% CI: 0.45–0.98) during pregnancy (not shown on the table). Even after additional adjustment for ANC visits, intake of an adequately diversified diet was associated with a 43% (OR: 0.57; 95% CI: 0.44–0.73) and iron and folic acid supplementation was associated with a 41% reduction in the likelihood of PE or E (OR: 0.59; 95% CI: 0.49–0.80) symptoms. Restricting our analysis to those women who had given birth up to 3 years prior to the survey and reported PE or E symptoms (1.4%), we found that the association of adequately diversified dietary intake, iron and folic acid supplementation, and PE or E symptoms was non-significant. However, the number of women in this restricted sample was very small (n = 46), and as a result the models had limited statistical power. In a final set of sensitivity analyses restricting the models to multiparous women we found that the significant inverse association between diversified dietary intake, intake of iron and folic acid supplementation during pregnancy and symptoms of PE or E still remained.

**Discussion**

In this study, we examined the association between adequately diversified dietary intake, iron and folic acid supplementation during pregnancy, and symptoms suggestive of PE or E in a large, nationally representative sample of Indian women. Our main analyses provide empirical evidence of an inverse association between an adequately diversified dietary intake, iron and folic acid supplementation during pregnancy and occurrence of symptoms suggestive of PE or E. This association remained significant after controlling for a wide range of socio-demographic, maternal, and health and lifestyle factors. Overall 1.2% of the study sample experienced symptoms suggestive of PE or E in their most recent pregnancy. Mothers who had a adequately diversified dietary intake during pregnancy were 34% less likely to report PE or E symptoms than mothers with inadequately diversified dietary intake. The likelihood of reporting PE or E symptoms was also 36% lower among those mothers who consumed iron and folic acid supplementation for at least 90 days during their last pregnancy. Results from the sensitivity analyses suggests that among highly educated mothers, the likelihood of reporting symptoms of PE or E was 40% lower among those with an adequately diversified dietary intake and recommended intake of iron and folic acid supplementation during pregnancy. Even after additional adjustment for ANC visits, intake of an adequately diversified diet and recommended intake of iron and folic acid supplementation were associated with a significantly lower likelihood of
reporting PE or E symptoms. Restricting our analysis to only multiparous women we found that the significant, inverse association between diversified dietary intake, recommended intake of iron and folic acid supplementation during pregnancy and symptoms of PE or E remained significant.

There is a mounting evidence that nutrition plays an important role in preventing hypertensive disorders [14–15, 78–81], and maternal nutritional status has long been hypothesized to have a role in the pathophysiology of PE or E [10, 29, 80, 82–90], especially in developed countries. There is also a strong evidence from both animal and human studies to support the hypothesized protective effect of micronutrients such as iron and folic acid on low PE or E risk [12, 15, 17–19]. Our study supports previous research [91–97] by providing population-level evidence from a developing country that iron and folic acid supplementation may reduce the symptoms of PE or E in pregnancy. Use of the National Family Health Survey data also provided adequate sample size to study the dietary correlates of PE or E in a population-level study, thus providing a unique opportunity for descriptive inferences about the social distribution and patterning of PE or E risk among Indian women.

Limitations of the study

There are several limitations to our study. First, most variables in the analyses (with the exception of anthropometrics) were self-reported, including a symptomatic rather than clinical measure of PE or E; it is possible that self-reported data may suffer from recall bias. Although we cannot rule out the possibility of misclassification within this context, it is unlikely that we have missed severe PE or E cases due to the generally clear manifestation of symptoms in severe cases. Second, due to the nature of the data, we could not identify the gestational onset of PE or E; it is possible that nutritional factors may be particularly important during critical periods of foetal development, which we are not able to assess in this study. Third, the role of folic acid independent of iron supplementation may be of interest. However, because iron and folic acid were measured jointly rather than as separate supplements in NFHS-3, we were unable to disentangle the effects of these two supplements. Similarly, information about other micronutrient supplementation is unavailable in the NFHS-3; while our models control for a wide range of health and sociodemographic factors, it is possible that other micronutrients, such as B12, may also shape PE or E risk. Further research is needed at the population level to understand the independent effects of micronutrient supplementation. An additional concern regarding the self-reported data is potential misreporting of dietary intake; this misreporting would most likely be non-differential, and may attenuate the association between dietary diversity and PE or E symptoms. Moreover, the broad categories of food intake in the NFHS-3 limits our ability to assess the impact of particular food items, especially those associated with diabetes (such as sugar) and other health conditions. An adequately diversified dietary intake was associated with higher socioeconomic status in our study; higher socioeconomic status may be associated with both better diets and regular health check-ups. However, the results of our sensitivity analyses of models stratified by wealth, education, and ANC visits suggest that this bias is limited.

In our sample, the prevalence of PE or E symptoms was quite low (1.2%) as compared to other studies in India. In part, this low prevalence is likely reflects the fact that survey participants were selected from the general population rather than from the higher-risk populations used in many clinical and epidemiological studies. Additionally, because we were unable to confirm PE or E with a clinical diagnosis, we have used a particularly stringent measure, requiring women to have experienced both difficulties with daytime vision and swelling of the face and extremities during pregnancy. This more stringent definition may result in a conservative
bias in our results, as some women who reported experiencing only one symptom (and thus were coded as not experiencing PE or E here) may have been identified as pre-eclamptic via clinical diagnosis.

Our study also showed the prevalence of PE or E was higher among women of higher parity, lean women, current smokers, and the less-educated. While these findings are in contrast to some of the existing literature conducted in developed countries, they are in keeping with other work among Asian women [46,98–99]. Our fully adjusted multivariable analyses results also fit with previous literature pointing to increased risk of PE or E symptoms for: multiple (rather than in singleton) pregnancies [100–102]; current smokers [55–56,103]; mothers with a history of spontaneous or induced abortion [104–105]; women with asthma [106–107] and diabetes [63,108]; and those from disadvantaged socio-demographic groups [47,109]. Lower age and parity were not found to be associated with pre-eclampsia in contrast to other studies [110–111]. The disparity between our study and other studies could be due to the differences in the population-based sample here compared to hospital-based samples elsewhere. Our finding that current tobacco smoking is associated with significantly increased risk of pre-eclampsia is also consistent with previous research [55,112] though an earlier systematic review analyzing the pooled data from cohort and case-control studies showed a lower risk of pre-eclampsia associated with cigarette smoking during pregnancy [56,103]. However, information on smoking and alcohol here referred to the current lifestyle of the respondent rather than behaviour during pregnancy, which may explain why our study departs from previous findings. Our findings concur with previous studies regarding risks of PE or E arising from medical conditions such as asthma, ethnicity [113], socio-economic position [109], and history of miscarriage or terminated pregnancy [104–105]. However, a minor limitation of the present study is the inability to differentiate between spontaneous and induced abortion because of the lack of information on this variable.

Adverse maternal and infant health outcomes often can be prevented by modifying maternal behaviours [35]. Monitoring behavioural risk factors can provide direction for interventions to improve the health of mothers and infants. The current study extends previous research by assessing the role of dietary factors and intake of iron and folic acid supplementation in pregnancy in shaping the PE or E risk. Low or inadequate diversified diet is particular problematic in low- and middle-income countries (LMICs) [114–115], where the diets contain a disproportionate share of starchy staples (e.g. rice, maize, potatoes) and wheat, while intake of animal-source foods (meat, fish, eggs and dairy) and fresh fruit and vegetables is often insufficient. In addition, certain staple foods, such as wheat, maize, and millet, can contain high levels of anti-nutrients (e.g. phytates), which reduce the absorption of available micronutrients [115]. Many of the important vitamins and minerals essential for a healthy diet are found in greatest abundance in fruits and vegetables, legumes, and flesh foods. The recent dietary transition in developing countries [116] towards low-cost processed grains, oils, and sugar has led to a reduced intake of micronutrients and a progressive loss of dietary diversity. As a large proportion of Indian women subsist on iron-poor vegetarian diets [117], large-scale iron supplementation and fortification of commonly consumed vegetarian foodstuffs constitutes a feasible, culturally appropriate, and cost-effective strategy for reducing pregnancy induced PE or E symptoms. However, iron and folic acid supplementation needs to be placed in the broader context of maternal nutritional status in India.

With the target of the Millennium Development Goals and adherence to India’s Five Year Plan for reproductive health in sight, PE or E should be identified as a priority area in reducing maternal morbidity in India. Dietary diversity and nutritional adequacy in pregnancy represent modifiable risk factors for PE or E, and should be considered as targets for prevention. Efforts which exclusively target micronutrient supplementation may not be sufficient for reducing PE
or E symptoms. Policies aiming to reduce the risk of hypertension in pregnancy should target improving access to, and compliance with, the simple recommended therapy of iron and folic acid supplementation and an adequately diversified dietary intake in tandem. However, as this analysis has demonstrated, there may be a substantial socioeconomic gradient in health risk behaviour and access to preventive care. Programmatic interventions should focus particularly on women with limited socioeconomic resources. For example, programs targeting food security among low income groups in India, such as the Public Distribution System (PDS), could improve maternal and child health and reduce the risk of PE or E by offering a more diversified basket of subsidized food items.

Conclusions

Using nationally representative data on reproductive health among Indian women, our study shows that having an adequately diversified dietary intake and iron and folic acid supplementation in pregnancy is associated with a reduced occurrence of symptoms suggestive of PE or E in Indian women. This relationship persists when sociodemographic, health lifestyle, and maternal factors are taken into consideration. Because ANC is the main source of iron and folic acid supplements and nutrition education during pregnancy, ensuring universal provision of comprehensive ANC, emphasized in India’s Eleventh Five Year Plan (2007–2012) [118], is vital for improving maternal nutrition and health in India. Further epidemiological research in India with large-scale cohorts should focus on uncovering preventable causes of PE or E such as diet and micronutrient supplementation during pregnancy, while public health practice and policy should promote improved access to better food and nutrition and mandatory intake of iron and folic acid supplementation during pregnancy among Indian mothers.

Acknowledgments

We would like to acknowledge the helpful comments from Shah Ebrahim on an earlier draft. SA and SV is supported by the Wellcome Trust Strategic Award Grant Number WT084674. DS is supported by a Wellcome Trust Investigator Award. The data for this research were collected by The Demographic and Health Surveys Program (www.dhsprogram.com), under a contract from the U.S. Agency for International Development. The support of Macro International (Calverton, MD, USA) and International Institute for Population Sciences (Mumbai, India) for providing access to the 2005–2006 Indian National Family Health Survey 3 data is greatly acknowledged. An earlier version of the manuscript was accepted for poster presentation at the Geneva Health Forum 15–17 April 2014.

Author Contributions

Conceived and designed the experiments: SA. Performed the experiments: SA. Analyzed the data: SA. Contributed reagents/materials/analysis tools: SA JF SV DS. Wrote the paper: SA JF.

References

1. Sibai B, Dekker G, Kupferminc M (2005) Pre-eclampsia. The Lancet 365(9461): 785–799. PMID: 15733721
2. Aagaard-Tillery KM, Belfort MA (2005) Eclampsia: morbidity, mortality, and management. Clin Obstet Gynecol 48: 12–23. PMID: 15725853
3. Sibai BM (2005) Diagnosis, prevention, and management of eclampsia. Obstet Gynecol 105: 402–10. PMID: 15684172
4. Confidential Enquiries into Maternal Deaths. Why mothers die 1997–1999. The fifth report of the confidential enquires into maternal deaths in the United Kingdom. London: Royal College of Obstetricians and Gynaecologists Press, 2001.
5. Duley L, Meher S, Abalos E (2006) Management of pre-eclampsia. BMJ; 332: 463–8. PMID: 16497761

6. World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. (1988) Geographic variation in the incidence of hypertension in pregnancy Am J Obst Gynecol; 158: 80–3. PMID: 2962500

7. Singh S, Behera A (2010) Eclampsia in Eastern India: Incidence, Demographic Profile and Response to Three Different Anticonvulsant Regimes of Magnesium Sulphate. The Internet Journal of Gynecology and Obstetrics 2010; 15(2).

8. Arora R, Ganguli RP, Swain S, Oumachigui A, Rajaram P (1994) Determinants of maternal mortality in eclampsia in India. Australian and New Zealand Journal of Obstetrics and Gynaecology 34(5): 537–539.

9. Swain S, Ojha KN, Prakash A, Bhatia BD (1993) Maternal and perinatal mortality due to eclampsia. Indian Pediatrics 30: 771–771. PMID: 8132257

10. Xu H, Shatenstein B, Luo Z-C, Wei S, Fraser W (2009) Role of nutrition in the risk of preeclampsia. Nutrition reviews 67(11): 639–657. doi: 10.1111/j.1753-4887.2009.00249.x PMID: 19906251

11. Lindheimer MD, Roberts JM, Cunningham GC, Chesley L. in Chesley's Hypertensive Disorders in Pregnancy (eds Lindheimer MD, Roberts JM, Cunningham GC), 1–24 ( Elsevier, 2009).

12. Xu H, Shatenstein B, Luo Z-C, Wei S, Fraser W (2009) Role of nutrition in the risk of preeclampsia. Nutrition reviews 67(11): 639–657. doi: 10.1111/j.1753-4887.2009.00249.x PMID: 19906251

13. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L, Torloni MR (2014) Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 6: CD001059. doi: 10.1002/14651858.CD001059.pub4 PMID: 24960615

14. Jain S, Sharma P, Kulsreshthra S, Mohan G, Singh S (2010) The role of calcium, magnesium, and zinc in pre-eclampsia. Biological trace element research 133(2): 162–170. doi: 10.1007/s12011-009-8423-9 PMID: 19547932

15. Bodnar LM, Tang G, Ness RB, Harger G, Roberts JM (2006) Periconceptional multivitamin use reduces the risk of preeclampsia. American journal of epidemiology 164(5): 470–477. PMID: 16772374

16. Christian P (2010) Micronutrients, birth weight, and survival. Annu Rev Nutr 30: 83–104. doi: 10.1146/annurev.nutr.012809.104813 PMID: 20415580

17. Wen SW, Zhou J, Yang Q, Fraser W, Olatunbosun O, Walker M (2008) Maternal exposure to folic acid antagonists and placenta-mediated adverse pregnancy outcomes. Canadian Medical Association Journal 179(12): 1263–1268. doi: 10.1503/cmaj.080859 PMID: 19047607

18. Hernández-Díaz S, Werler MM, Louik C, Mitchell AA (2002) Risk of gestational hypertension in relation to folic acid supplementation during pregnancy. American Journal of Epidemiology 156(8): 806–812. PMID: 12396998

19. Catov JM, Nohr EA, Bodnar LM, Knudson VK, Olsen SF, Olsen J (2009) Association of Periconceptional Multivitamin Use With Reduced Risk of Preeclampsia Among Normal-Weight Women in the Danish National Birth Cohort. Am J Epidemiol 169(11): 1304–1311. doi: 10.1093/aje/kwp052 PMID: 19372217

20. Li Z, Ye R, Zhang L, Li H, Liu J, Ren A (2013) Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. Hypertension 61(4): 873–879.

21. Timmermans S, Jaddoo VW, Silva LM, Hofman A, Raat H, et al (2011) Folic acid is positively associated with uteroplacental vascular resistance: The Generation R Study. Nutrition, Metabolism and Cardiovascular Diseases 21(1): 54–61. doi: 10.1016/j.numecd.2009.07.002 PMID: 19819678

22. Lichtenstein AH, Russell RM (2005) Essential nutrients: food or supplements? JAMA 294(3): 351–358. PMID: 16030260

23. Torjusen H, Brantsaeter AL, Haugen M, Alexander J, Bakketeig LS, et al (2014) Reduced risk of preeclampsia with organic vegetable consumption: results from the prospective Norwegian Mother and Child Cohort Study. BMJ Open 4:e006143. doi: 10.1136/bmjopen-2014-006143 PMID: 25208890

24. Brantsaeter AL, Haugen M, Samuelsen SO, Torjusen H, Trosgstad L et al (2009) A dietary pattern characterized by high intake of vegetables, fruits, and vegetable oils is associated with reduced risk of preeclampsia in nulliparous pregnant Norwegian women. J Nutr 139(6): 1162–1168. doi: 10.3945/jn.109.104968 PMID: 19369368

25. Qiu C, Coughlin KB, Frederick IO, Sorensen TK, Williams MA (2008). Dietary fiber intake in early pregnancy and risk of subsequent preeclampsia. Am J Hypertens 21(8): 903–909. doi: 10.1038/ajh.2008.209 PMID: 18636070
26. Longo-Mbenza B, Kadima-Tshimanga B, Buassa-bu-Tsumbu B, M'buyamba K Jr (2008) Diets rich in vegetables and physical activity are associated with a decreased risk of pregnancy induced hypertension among rural women from Kimpese, DR Congo. Niger J Med 17(3): 265–269. PMID: 18788250

27. North CJ, Venter CS, Jerling JC (2009) The effects of dietary fibre on C-reactive protein, an inflammation marker predicting cardiovascular disease. Eur J Clin Nutr 63(8): 921–933. doi: 10.1038/ejcn.2009.8 PMID: 19223918

28. Roberts JM, Lain KY (2002) Recent Insights into the Pathogenesis of Pre-eclampsia. Placenta 23(5): 359–372. PMID: 12061851

29. Sharma JB, Sharma A, Bahadur A, Vimala N, Satyam A, Mittal S (2006) Oxidative stress markers and antioxidant levels in normal pregnancy and pre-eclampsia. International Journal of Gynecology & Obstetrics 94(1): 23–27.

30. Ruel MT (2003) Is Dietary Diversity an Indicator of Food Security or Dietary Quality? A Review of Measurement Issues and Research Needs. Discussion paper 140. Washington D.C.

31. Torheim LE, Ouattara F, Diaira M, Thiam F, Barikmo I, et al (2004) Nutrient adequacy and dietary diversity in rural Mali: association and determinants. Eur J Clin Nutr 58(4): 594–604. PMID: 15042127

32. Torheim LE, Barikmo I, Parr CL, Hatloy A, Ouattara F, Oshaug A (2003) Validation of food variety as an indicator of diet quality assessed with a food frequency questionnaire for Western Mali. Eur. J. Clin. Nutr 57: 1283–1291. PMID: 14506490

33. Ogle B, Hung P, Tuyet H (2001) Significance of wild vegetables in micronutrient intakes of women in Vietnam: an analysis of food variety. Asia Pac J Clin Nutr 10(1): 21–30. PMID: 11708605

34. Pathak P, Kapil U, Kapoor SK, Saxena R, Kumar A, Gupta N, Singh P (2004) Prevalence of multiple micronutrient deficiencies amongst pregnant women in a rural area of Haryana. The Indian Journal of Pediatrics 71(11): 1007–1014. PMID: 15572822

35. Phares TM, Morrow B, Lansky A, Barfield WD, Prince CB, et al (2004). Surveillance for Disparities in Maternal Health-Related Behaviors—Selected States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2000–2001. MMWR Surveill Summ 53(4):1–13. PMID: 15229409

36. Beck LF, Morrow B, Lipscumb LE, Johnson CH, Gaffield ME, et al (2002) Prevalence of Selected Maternal Behaviors and Experiences, Pregnancy Risk Assessment Monitoring System (PRAMS), 1999. MMWR Surveill Summ 51(2):1–27. PMID: 12004983

37. Available: http://www.dhsprogram.com/data/available-datasets.cfm.

38. International Institute for Population Sciences (IIPS) and Macro International (2007) National Family Health Survey (NFHS-3), 2005–06. India. International Institute for Population Sciences: Mumbai.

39. World Health Organisation (WHO) (2007) Integrated Management of Pregnancy and Childbirth: Managing complications in pregnancy and childbirth: A guide for midwives and doctors. Department of Reproductive Health and Research. Geneva.

40. NICE guidelines [CG107] (2010) Available: http://www.nice.org.uk/guidance/CG107/chapter/1-Guidance. Accessed 2014 June 6.

41. Roberts JM, Balk JL, Bodnar LM, Belizán JM, Bergel E, Martinez A (2003) Nutrient involvement in pre-eclampsia. J Nutr 133(5 Suppl 2): 1684S–92S. PMID: 12730485

42. World Health Organization (2008) Indicators for assessing infant and young child feeding practices. Part 1. Definitions. Conclusions of a consensus meeting held 6–8 November 2007 in Washington, DC, USA.

43. WHO (2012). Guideline: Daily iron and folic acid supplementation in pregnant women. Geneva, World Health Organization. PMID: 23586119

44. Bianco A, Stone J, Lynch L, Lapinski R, Berkowitz G, Berkowitz RL (1996) Pregnancy outcome at age 40 and older. Obstet Gynecol 87: 917–22. PMID: 8649698

45. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R (1990) Epidemiology of preeclampsia and eclampsia in the United states, 1979–1986. Am J Obstet Gynecol 163: 460–5. PMID: 2386132

46. Lee CJ, Hsieh TT, Chiu TH, Chen KC, Lo LM, Hung TH (2000) Risk factors for pre-eclampsia in an Asian population. International Journal of Gynecology & Obstetrics 70: 327–333.

47. Conde-Agudelo A, Beliza JM (2000) Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women, BJOG 107:75–83. PMID: 10645865

48. Ali AA, Rayis DA, Abdallah TM, El-bashir MI, Adam I (2011) Severe anaemia is associated with a higher risk for preeclampsia and poor perinatal outcomes in Kassala Hospital, Eastern Sudan. BMC Res Notes 26: 311.

49. Centers for Disease Control and Prevention (CDC) (1998) Recommendations to prevent and control iron deficiency in the United States, Morbidity and Mortality Weekly Report 47(RR-3): 1–29.
50. Kaaja R, Kinnunen T, Luoto R (2005) Regional differences in the prevalence of pre-eclampsia in relation to the risk factors for coronary artery disease in women in Finland. Eur Heart J 26: 44–50. PMID: 15615798

51. Indian Consensus Group (1996) Indian consensus for prevention of hypertension and coronary heart disease. A joint scientific statement of Indian Society of Hypertension and International College of Nutrition. J Nutr Environ Med 6: 309–318.

52. WHO expert consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. The Lancet 157–163.

53. Misra A, Chowbey PK, Makkar BM, Vikram NK, Wasir JS, et al (2009) Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. J Assoc Physicians India 57: 163–70. PMID: 19582986

54. Villamor E, Cnattingius S (2006) Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet 368: 1164–70. PMID: 17011943

55. England L, Zhang J (2007) Smoking and risk of preeclampsia: a systematic review. Front Biosci 12: 2471–2483. PMID: 17127256

56. Conde-Agudelo A, Althabe F, Belizan JM, Kafury-Goeta AC (1999) Cigarette smoking during pregnancy and risk of preeclampsia: A systematic review. Am J Obstet Gynecol 181:1026–1035. PMID: 10521771

57. Sibai BM, Hauth J, Caritis S, Lindheimer MD, MacPherson C, et al Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol 182(4):938–42. PMID: 10764477

58. Salihu HM, Wilson RE (2007) Epidemiology of prenatal smoking and perinatal outcomes. Early Hum Dev 83(11): 713–20. PMID: 1784310

59. Kahn SR, Almeida ND, McNamara H, Koren G, Genest J, Dahou M, Platt RW, Kramer MS (2011) Smoking in preeclamptic women is associated with higher birthweight for gestational age and lower soluble fms-like tyrosine kinase-1 levels: a nested case control study. BMC Pregnancy and Childbirth 11: 91 doi: 10.1186/1471-2393-11-91 PMID: 22074109

60. Sibai BM, Hauth J, Caritis S, Lindheimer MD, MacPherson C, et al Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol 182(4):938–42. PMID: 10764477

61. Salihu HM, Wilson RE (2007) Epidemiology of prenatal smoking and perinatal outcomes. Early Hum Dev 83(11): 713–20. PMID: 1784310

62. McCarthy FP, O’Keeffe LM, Khaskan AS, North RA, Poston L, et al (2013) Association between maternal alcohol consumption in early pregnancy and pregnancy outcomes. Obstet Gynecol 122: 830–837. doi: 10.1097/AOG.0b013e3182a6b226 PMID: 24084541

63. Bryson CL, Ioannou GN, Rulyak SJ, Critchlow C (2003) Association between gestational diabetes and gestational hypertension. Am J Epidemiol 158: 1148–1153. PMID: 14652299

64. Vambergue A, Nuttens MC, Goeusse P, Biausque S, Lepeut M, et al (2002) Pregnancy induced hypertension in women with gestational carbohydrate intolerance: the diagest study. European J Obstet Gynec Repro Bio 102: 31–35.

65. Parretti E, Iapolla A, Dalfra MG, Pacini G, Mani A, et al (2006) Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. Hypertension 47: 449–453. PMID: 16446386

66. Sierra-Lagudo J, Garcia RG, Celedon J, Arenas-Martilla M, Pradilla LP, et al (2017) Determination of insulin resistance using the homeostatic model assessment (HOMA) and its relation with the risk of developing pregnancy—induced hypertension. Am J Hypertens 20: 437–442. PMID: 17386353

67. Joffe GM, Esterlitz JR, Levine RJ, Clemens JD, Ewell MG, et al (1998) The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. Calcium for Preeclampsia Prevention (CPEP) Study Group. Am J Obstet Gynecol 179: 1032–1037. PMID: 9790393

68. Sermer M, Naylor CD, Gare DJ (1995) Impact of increasing carbohydrate intolerance on maternal—fetal outcomes in 3637 women without gestational diabetes. Am J Obstet Gynecol 173: 146–156. PMID: 7631672

69. Rudra CB, Williams MA, Frederick IO, Luthy DA (2006) Maternal asthma and risk of preeclampsia: a case-control study. J Reprod Med 51: 94–100. PMID: 16572909

70. Goodman M (2013) Multivariate or multivariable regression? Am J Public Health 103(1): 39–40. doi: 10.2105/AJPH.2012.300897 PMID: 23153131
71. Tsai AC (2013) Achieving consensus on terminology describing multivariable analyses. Am J Public Health 103(6): e1. doi: 10.2105/AJPH.2013.301245 PMID: 23597386

72. Concato J, Peduzzi P, Holford TR, Feinstein AR (1995). Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. J Clin Epidemiol 48: 1495–501. PMID: 8543963

73. Peduzzi P, Concato J, Feinstein AR, Holford TR (1995). Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 48: 1503–10. PMID: 8543964

74. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR (1996) A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 49: 1373–9. PMID: 8970487

75. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE (2012) Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models; Series: Statistics for Biology and Health; 2nd ed. 2012, XX, 512 p.

76. Bhutta ZA, Lassi ZS, Blanc A, Donnay F (2010) Linkages among reproductive health, maternal health, and perinatal outcomes. Semin Perinatol 34: 434–45. doi: 10.1053/j.semperi.2010.09.002 PMID: 21094418

77. Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC (2007) Effects of birth spacing on maternal health: a systematic review. Am J Obstet Gynecol 196(4): 297–308. PMID: 17403398

78. Radhika G, Sudha V, Mohan Sathyar I, Ganesan A, Mohan V (2008) Association of fruit and vegetable intake with cardiovascular risk factors in urban south Indians. British Journal of Nutrition 99(02): 398–405.

79. Reddy KS, Katan MB (2004) Diet, nutrition and the prevention of hypertension and cardiovascular diseases. Public health nutrition 7(1A; SPI): 167–186.

80. Sacks FM, Moore TJ, Appel LJ, Obarzanek E, Cutler JA, Vollmer WM, Lin P-H (1999) A dietary approach to prevent hypertension: a review of the Dietary Approaches to Stop Hypertension (DASH) Study. Clinical cardiology 22(S3): 6–10.

81. Morris CD, Jacobson S- L, Anand R, Ewell MG, Hauth JC, et al (2001) Nutrient intake and hypertensive disorders of pregnancy: Evidence from a large prospective cohort. American Journal of Obstetrics and Gynecology 184(4): 643–651. PMID: 11262466

82. Brewer T (1969) Nutrition and preeclampsia. Obstet Gynecol 33(3): 448–9. PMID: 5776097

83. Chesley LC (1978) Hypertensive disorders of pregnancy. New York: Appleton-Century-Crofts.

84. Mardones-Santander F, Rosso P, Stekel A, Ahumada E, Llaguno S, et al (1988) Effect of a milk-based food supplement on maternal nutritional status and fetal growth in underweight Chilean women. Am J Clin Nutr 47(3): 413–9. PMID: 3279745

85. Herrera JA, Arevalo-Herrera M, Herrera S (1998) Prevention of preeclampsia by linoleic acid and calcium supplementation: a randomized controlled trial. Obstet Gynecol 91(4): 585–90. PMID: 9540946

86. Roberts JM (2000) Recent advances in obstetrics. BMJ 321: 33–35. PMID: 10875834

87. Bilodeau JF, Hubel CA (2003) Current concepts in the use of antioxidants for the treatment of preeclampsia. Journal of obstetrics and gynaecology Canada 25(9): 742. PMID: 12970809

88. Scholl TO, Leskiv M, Chen X, Sims M, Stein TP (2005) Oxidative stress, diet, and the etiology of preeclampsia. The American journal of clinical nutrition 81(6): 1390–1396. PMID: 15941892

89. Roberts JM, Bodnar LM (2007) Report on the WIC Nutrition Risk Criterion For Hypertension In Pregnancy Prepared for the US Department of Agriculture, Food and Nutrition Service.

90. Mehendale S, Kilari A, Dangal K, Taralekar V, Mahadik S, Joshi S (2008) Fatty acids, antioxidants, and oxidative stress in pre-eclampsia. International Journal of Gynecology & Obstetrics 100(3): 234–238.

91. Antony AC (2007) In utero physiology: role of folic acid in nutrient delivery and fetal development. Am J Clin Nutr 85: 598S–603S. PMID: 17294762

92. Wen SW, Champagne J, Rennicks R, Coyle WD, Fraser W, et al (2013) Effect of Folic Acid Supplementation in Pregnancy on Folic Acid Containing Pre-eclampsia: The Folic Acid Clinical Trial Study. Journal of Pregnancy Article ID 294312, 9 pages doi: 10.1155/2013/294312 PMID: 24349782

93. Ray JG, Mamdani MM (2002) Association between folic acid food fortification and hypertension or pre-eclampsia in pregnancy. Arch Intern Med 162(15): 1776–7. PMID: 12153382

94. Charles DH, Ness AR, Campbell D, Smith GD, Whiteley E, Hall MH (2005) Folic acid supplements in pregnancy and birth outcome: re-analysis of a large randomized controlled trial and update of Cochrane review. Paediatr Perinat Epidemiol 19(2): 112–24. PMID: 15767886

95. Taylor DJ, Mallen C, McDougal N, Lind T (1982) Effect of iron supplementation on serum ferritin levels during and after pregnancy. Br J Obstet Gynaecol 89(12): 1011–7. PMID: 7171510
96. US Congress, Office of Technology Assessment (1988) Healthy children: investing in the future. Washington, DC: US Government Printing Office, Publication no. OTA-H-345.

97. National Center for Health Statistics. Report of final natality statistics1995 (1997) Hyattsville, MD: US Department of Health and Human Services, Public Health Service, CDC1–3. (Monthly vital statistics report; 45(11).

98. Begum MR, Begum A, Quadir E, Akhter S, Shamsuddin L (2004) Eclampsia: Still a Problem in Bangladesh Med Gen Med 6(4): 52. PMID: 15775879

99. Pal A, Bhattacharyya R, Adhikari S, Roy A, Chakrabarty D, Ghosh P, Banerjee C (2011) Eclampsia-scenario in a hospital—a ten years study. Bangladesh Med Res Counc Bull 37: 66–70. PMID: 21877608

100. Sibai BM (2000) Risk factors, pregnancy complications, and prevention of hypertensive disorders in women with pregravid diabetes mellitus. J Matern Fetal Med 9:62–65. PMID: 10757438

101. Prasannan-Nair C, Reynolds SF, Budden G (2006) Partial molar pregnancy with severe preeclampsia at 19 weeks’ gestation. J Obstet Gyneco 8: 817. PMID: 17130046

102. Bdolah Y, Lam C, Rajakumar A, Shivalingappa V, Mutter W, et al (2008) Twin pregnancy and the risk of preeclampsia: bigger placenta or relative ischemia? American Journal of Obstetrics & Gynecology 198: 428.e1–6.

103. England LJ, Levine RJ, Qian C, Morris CD, Sibai BM, et al (2002) Smoking before pregnancy and risk of gestational hypertension and preeclampsia. Am J Obstet Gyneco 186(5): 1035–40. PMID: 12015533

104. Trogstad L, Magnus P, Moffett A, Stoltenberg C et al (2009) The effect of recurrent miscarriage and infertility on the risk of preeclampsia. B J Obstet Gynecol 116:108–113.

105. Hilby SE, Regan L, Lo W, Farrell L, Carrington M, Moffett A et al (2008) Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage. Hum Reprod 23: 972–976. doi: 10.1093/humrep/den011 PMID: 18263639

106. Rudra CB, Williams MA, Sheppard L, Koenig JQ, Schiff MA et al (2008) Twin pregnancy and the risk of preeclampsia: bigger placenta or relative ischemia? American Journal of Obstetrics & Gynecology 198: 428.e1–6.

107. Silva LM, Coolman M, Steegers EA, Jaddoe VW, Moll HA, et al (2008) Low socioeconomic status is a risk factor for preeclampsia: the Generation R Study. J Hypertens 26: 1200–1208. doi: 10.1097/HJH.0b013e3282fcc36e PMID: 18475158

108. Duckitt K, Harrington D (2005) Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 330:565. PMID: 15743856

109. Lamminpää R, Vehviläinen-Julkunen K, Gissler M, Heinonen S (2012) Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997–2008. BMC Pregnancy Childbirth 12: 47. doi: 10.1186/1471-2393-12-47 PMID: 22867260

110. Pipkin FB, on behalf of The Genetics of Preeclampsia Consortium (2008) Smoking in moderate/severe preeclampsia worsens pregnancy outcome, but smoking cessation limits the damage. Hypertension 51: 1042–1046. doi: 10.1161/HYPERTENSIONAHA.107.106559 PMID: 18259022

111. Rosenberg TJ, Garbers S, Chavkin W, Chiasson MA (2003) Prepregnancy weight and adverse perinatal outcomes in an ethnically diverse population. Obstet Gyneco 102: 1022–1027. PMID: 14672490

112. World Health Organization (2009) Global Health Risks. WHO, Geneva.

113. Burchi F, Fanzo J, Frison E (2011) The Role of Food and Nutrition System Approaches in Tackling Hidden Hunger. Int J Environ Res Public Health 8(2): 358–373. doi: 10.3390/ijerph8020358 PMID: 21556191

114. Shetty PS (2002) Nutrition transition in India. Public Health Nutr 5:175–182. PMID: 12027282

115. Agrawal S, Millett CJ, Dhillon PK, Subramanian S, Ebrahim S (2014) Type of vegetarian diet, obesity and diabetes in adult Indian population. Nutr J 13(1): 89.

116. Government of India. Eleventh Five Year Plan 2007–2012 (2007) Planning Commission. New Delhi: Government of India.