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Hypertensive disorders of pregnancy and risk of diabetes in Indian Women

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Data sharing statement: The authors confirm that all data underlying the findings are fully available without restriction. Data are publicly available from the Demographic and Health Surveys website: http://dhsprogram.com/what-we-do/survey/survey-display-264.cfm.

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Competing Interest: None to declare

Article Summary

Strength and limitations of this study

- Epidemiological data from high income countries suggests that women with HDP are more likely to develop cardiovascular risk, including diabetes, later in life. There is no empirical evidence of an association in low-and middle- income countries which have the highest burden.
- Our study observed a strong evidence of an increased risk of diabetes among women reporting symptoms suggestive of preeclampsia or eclampsia during their last pregnancy. This positive relation is robust even after adjustment for a comprehensive range of established risk factors of diabetes and possible clustering of lifestyles and other factors that may accompany HDP (e.g., smoking, alcohol intake, access to healthcare) and dietary predictors of diabetes (i.e. food consumption), BMI, and education level.
- To our knowledge, this is the largest nationally representative cross-sectional study of the population based association between pregnancy induced preeclampsia or eclampsia symptoms and diabetes risk in an Asian population.
- A history of preeclampsia or eclampsia during pregnancy should alert clinicians to the need for preventative counselling and more vigilant screening for diabetes.
- These findings are important for a country such as India which is already tackling the burden of NCD along with the infectious communicable diseases among its women population.

Abstract

Background: Epidemiological data from high income countries suggests that women with hypertensive disorders during pregnancy (HDP) are more likely to develop diabetes, later in life.

Objective: We investigated the association between preeclampsia and eclampsia (PE&E) during pregnancy and the risk of diabetes in Indian women.

Design: Cross-sectional study

Setting: India

Methods: Data from India's third National Family Health Survey (NFHS-3, 2005-06), a cross-sectional survey of women aged 15-49 years are used. Self-reported symptoms suggestive of PE&E were obtained from 39,657 women who had a live birth in the five years preceding the survey. The association between PE&E on self-reported diabetes status was assessed using multivariable logistic regression models adjusting for dietary intake, BMI, tobacco smoking, alcohol drinking, frequency of TV watching, socio-demographic characteristics and geographic regions.

Results: The prevalence of symptoms suggestive of PE&E in women with diabetes was 1.8% (n=207) (95%CI:1.5-2.0;p<0.0001) and 2.1% (n=85) (95%CI:1.8-2.3;p<0.0001) respectively, compared with 1.1% (n=304) (95%CI:1.0-1.4) and 1.2% (n=426) (95%CI:1.1-1.5) in women who did not report any PE&E symptoms. In the multivariable analysis, PE&E was associated with 1.6 times (OR=1.59;95% CI:1.31–1.94;p<0.0001) and 1.4 times (OR=1.36;95% CI:1.05–1.77;p=0.001) higher risk for self-reported diabetes even after controlling for dietary intake, BMI, and socio-demographic characteristics.

Conclusion: HDP is strongly associated with the risk of diabetes in a large nationally representative sample of Indian women. These findings are important for a country which is already tackling the burden of young onset of diabetes in the population. However, longitudinal medical histories and a clinical measurement of diabetes are needed in this low resource setting.

Keywords: preeclampsia; eclampsia; diabetes; women; India; NFHS-3

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) represent a group of conditions marked by high blood pressure during pregnancy, proteinuria, and in some cases convulsions. Gestational hypertension, preeclampsia and eclampsia (PE&E) are most common HDP and the most serious consequences for the mother and the baby results from PE&E.[1] Preeclampsia is a syndrome of pregnancy defined by the onset of hypertension and proteinuria and characterised by widespread dysfunction of the endothelium in the mother.[2] Eclampsia is usually a consequence of preeclampsia consisting of central nervous system seizures, unrelated to conditions such as epilepsy, which often leave the patient unconscious; if untreated it may lead to death. Worldwide HDP are more common, may complicate 5%-10% of all pregnancies and are responsible for 12-25% of maternal mortality during pregnancy and the puerperium.[3,4] PE&E are leading threats to safe motherhood in developing countries where a woman is seven times more likely to develop these conditions and 10-25% of these cases (an estimated ~40,000 women) lead to maternal deaths annually.[5]

Increasing evidence indicate that PE&E are not just a pregnancy disease that resolves at the time of delivery, but represent a risk marker of cardiovascular diseases later in life.[6] Studies that looked at the risk of developing type 2 diabetes in women with a history of preeclampsia are all conducted in western population and found a positive association equalling the risk attributed to obesity and smoking.[7-11] The Danish National Patient Registry study found that preeclampsia is associated with 3.1-3.7 –fold risk of developing type 2 diabetes.[12] A recent population-based study of >1 million women has found that women with preeclampsia or gestational hypertension have a twofold increased risk of developing diabetes after pregnancy.[13]

Studies showing the association between HDP and diabetes are based on non-representative clinical data and/or are based on data from western settings. Investigation of the links between PE&E symptoms and diabetes in LMICs has been severely limited which have the highest burden. Randomized trials have shown that diabetes can be prevented or delayed in high-risk groups by a variety of lifestyle and therapeutic interventions.[14,15] However, identifying at risk populations to screen for diabetes in a low resource setting such as India is a critical step in translating these findings into clinical practice. HDP such as preeclampsia may heighten the propensity for women to develop diabetes in the years following pregnancy, and such women may also be suitable targets for diabetes prevention. We investigated the association between PE&E during pregnancy and diabetes risk in a large sample of Indian women.

MATERIALS AND METHODS

Data

Data from the Indian National Family Health Survey (NFHS-3) for the years 2005/2006, a large, well-established, nationally representative survey based on a multi-stage cluster sample design that provides high-quality information on the health and nutrition of women and children with an overall response rate of 98% has been analysed.[16] NFHS is the Indian equivalent of the Demographic and Health Surveys, a series of standardised surveys which are routinely conducted in more than 80 developing countries. All data are in the public domain and can be downloaded, after registration, from http://www.measuredhs.com. The NFHS has been conducted in India for three successive rounds, each at an interval of 5 years. The NFHS-3 collected demographic, socioeconomic, and health information from a nationally representative probability sample of 124,385 women aged 15–49 years residing in 109,041 households. All states of India are represented in the sample (except the small Union Territories), covering more than 99% of the country's population. The survey was conducted using an interviewer-administered questionnaire in the native language of the respondent using a local, commonly understood term for diseases. A total of 18 languages were used with back translation to English to ensure accuracy and comparability. Full details of the survey have been published.[11]

To examine the association between HDP and risk of diabetes, we restricted the sample to only 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 to minimize recall bias. Missing data were dropped using list wise deletion. This resulted in a final sample size of 39,657 participants.

Outcome evaluation

The survey includes self-report data relating to specific health problems of the mother, including whether the respondent currently has diabetes.[16] Specifically, respondents were asked: 'Do you currently have diabetes?' with the response options of 'yes', 'no' and 'don't know'. It is important to recognize that self-reported diabetes is not as accurate as clinical measures of diabetes; no physician diagnosis or fasting blood glucose measures were included in the NFHS-3.[16]

Predictor variables

The NFHS-3 contains several items related to health problems during pregnancy. As physical markers (e.g. blood pressure, proteinuria) used in the clinical diagnosis of PE&E was not measured in the NFHS-3, we used three self-reported health items to construct a measure of PE&E. Specifically, in relation to their current or most recent pregnancy, 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[17], National Institute for Health and Care Excellence[18] guidelines, and NFHS-3 coding by Agrawal et al[19], we created a dichotomous indicator for PE&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 preeclampsia, while those who additionally reported experiencing convulsions (not from fever) were coded as eclamptic.

Covariates

In order to reduce the possibility that the association between PE&E and diabetes was driven by confounders, we included several sociodemographic control variables. Height and weight data were collected by the NFHS-3 interview staff, and BMI was calculated based on these data.[16] We included an ordinal measure of BMI, with thresholds defined as ≤18.4 kg/m^2 (underweight), 18.5 to 22.9 kg/m^2 (normal), 23.0 to 24.9 kg/m^2 (overweight), and ≥25 kg/m^2 (obese). Women who were pregnant at the time of the survey or women who had given birth during the two months preceding the survey were excluded from these measurements. In addition, previous studies have found that smokers are insulin resistant, exhibit several aspects of the insulin resistance syndrome, and are at an increased risk for type 2 diabetes[20], while moderate alcohol consumption may reduce the risk of type 2 diabetes. On the other hand, binge drinking and high alcohol consumption may increase the risk of type 2 diabetes in women or men.[21] We included controls for smoking and drinking behaviour: 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. We constructed a dichotomous indicator of current alcohol use in the present analysis. Frequency of watching television (almost every day, at least once weekly, less than once weekly, not at all) was used as a measure of sedentary behaviour. We measured access to healthcare by a categorical indicator of type of healthcare facility used (public medical sector, NGO trust hospital or clinic, private

medical sector, and other sources). A previous work[19] has shown that iron intake and consuming a diversified diet is associated with a reduced risk of PE&E. Dietary intake as indicated by consumption of selected foods was assessed by asking, 'How often do you yourself consume the following items: daily, weekly, occasionally or never?' related to the consumption of milk or curd, pulses or beans, green leafy vegetables, other vegetables, fruits, eggs, and chicken, meat or fish.[16]

In order to reduce the risk of unobserved homogeneity in our models, we included a variety of socio-demographic controls. The socio-demographic factors considered in the present analysis included age categories (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49); education was classified as no education, primary (5–7 years completed), secondary (8–9 years) or higher (10+ years); employment status (currently not working, working); religion (Hindu, Muslim, Christian, Sikhs, Others); caste/tribe (Scheduled Castes, Scheduled Tribes, Other Backward Class, General); a standard wealth index compiled by the NFHS-3 (measured by an index based on household ownership of assets and graded as lowest, second, middle, fourth and highest); place of residence (urban, rural); and geographic regions of India (north, northeast, central, east, west, south).

Statistical Analysis

Descriptive statistics were calculated with the use of standard methods. Differences in categorical variables were tested using Pearson's χ^2 tests. Multivariable logistic regression analysis was used to estimate the effect of symptoms suggestive of PE&E on self-reported diabetes risk. In the first logistic regression model, we examined the unadjusted association between PE&E symptoms and diabetes risk independent of each other. In the second model, we adjusted for the BMI status tobacco smoking, alcohol drinking, frequency of TV watching and access to healthcare in order to assess how much of the variance in this association was explained by those factors. In the third model, we added specific food and micronutrient intake to our model. In the fourth and final model, we added socio-demographic characteristics in order to examine the association between PE&E symptoms and diabetes risk controlling for all the confounders discussed above.

To adjust for the NFHS-3 sampling design, a sample weight was also included in the models.[11] Results are presented as odds ratios with 95% confidence intervals (OR;95%CI). The estimation of confidence intervals takes into account design effects due to clustering at the level of the primary sampling unit.

Before carrying out the multivariate model, the possibility of multicollinearity between the covariates was assessed. In the correlation matrix of covariates, all pair wise Pearson correlation coefficients were found <0.5, suggesting that multicollinearity did not affect the findings. All analyses were conducted using the SPSS statistical software package Version 19 (IBM SPSS Statistics, Chicago, Illinois, USA).

Ethical considerations

The NFHS-3 survey received ethical approval from the International Institute for Population Science's Ethical Review Board and Indian Government. Prior informed written consent was obtained from each respondent. The analysis presented in this study is based on secondary analysis of existing survey data with all identifying information removed; no ethical approval was required.

RESULTS

Table 1 presents the descriptive statistics for the sample, and bivariate associations between diabetes and PE&E. Overall, 28.7% (n=11,361) women reported symptoms suggestive of preeclampsia during their last pregnancy, and one out of ten women (10.3%; n=4071) reported symptoms suggestive of eclampsia. Thirty-eight percent were underweight, while 15% were either overweight or obese. A very few were current smokers (1.5%) or alcohol drinkers (2.3%) while 68% had access to the private medical sector to obtain their health care. One third viewed TV almost every day. Most mothers (nearly 75%) were aged between 15-29 years, and almost half (47%) had no education; 70% were not employed at the time of survey. A majority of the mothers (four out of five) identified as Hindu, and two-fifths belonged to a scheduled caste category. One fourth belonged to a household in the poorest wealth quintile. More than 70% of the mothers were residing in rural areas, while 28% were residents of Central India. Half of the mothers reported of consuming milk/curd whereas a majority reported of consuming pulses/beans and vegetables on a daily or weekly basis. However, only one third reported of consuming fruit (34%) and eggs (30%), while only one fourth or less of the sample respondents consumed fish (27%) or chicken/meat (21%) on a daily or weekly basis.

Of the women reporting diabetes, two out of five (41%) also reported symptoms suggestive of preeclampsia and 17% reported symptoms of eclampsia (Table 1). Eighteen percent were either obese or overweight; 2% were currently smoking tobacco; 5% were alcohol drinkers; a half of them reported of not watching TV at all, one in three visits to public medical sector for healthcare needs, two-thirds

(66%) were in the age group 15-29 years; half of them had no education; 77% were Hindus; 31% belonged to general category; 68% were not working, two-fifths belong to household with poorest wealth quintile, a majority resides in rural area whereas half of them resides in eastern India. Among the women who reported diabetes, a majority of them reportedly consumed pulses/beans and vegetables on a daily/weekly basis, more than two-fifth also reported consuming milk/curd daily/weekly, while the consumption of fruits (28%), eggs (27%), fish (32%) or chicken meat (16%) among them was less.

The prevalence of symptoms suggestive of PE&E in women with diabetes was 1.8% (95%CI:1.5-2.0;p<0.0001) and 2.1% (95%CI:1.8-2.3;p<0.0001) respectively, compared with 1.1% (95%CI:1.0-1.4) and 1.2% (95%CI:1.1-1.5) in women who did not report any PE&E symptoms (Table 1). Overweight (1.7%) or obese (1.4%) women had higher prevalence of diabetes than those who were underweight (1.4 %) and normal weight (1.1%). A higher proportion of current tobacco smokers (1.7%) and current alcohol drinkers (2.6%) also reported diabetes compared to those who, respectively, do not currently smoke or drink. Women who had access only to other sources for health care (5.1%) and NGO or Trust or Clinic (3.5) had higher prevalence of diabetes. Women reporting viewing TV not at all or less than once a week reported higher diabetes (1.5%) than their counterparts. Women consuming milk/curd (1.1% vs 1.5%), pulses/beans (1.2% vs 1.9%), vegetables (1.3% vs 1.6%), fruits (1.1% vs 1.4%), eggs (1.2% vs 1.3%), or chicken/meat (1.0% vs 1.4%) except fish (1.6% vs 1.2%) on a daily/weekly basis had a lower prevalence of diabetes than those never /occasionally consume them. Diabetes prevalence is higher among women aged 40-49 (2.9%) and 35-39 (2.1%) compared to women aged 15-29 years (1.2%). The prevalence of diabetes was also found higher among women belonging to Christian religion (2.5%), among women belonging to a scheduled tribe (1.9%) than those in a scheduled caste (1.4%), women in the poorest wealth quintile (1.7%), women residing in rural area (1.4%) and women living in eastern India (3.5%).

<Table 1 here>

Table 2 shows results of multivariable logistic regression analyses in unadjusted, partially adjusted and fully adjusted models. In the unadjusted analysis (Model 1), the likelihood of having diabetes was significantly higher among women who reported preeclampsia (OR:1.71;95%CI:1.43-2.04;p<0.0001) and eclampsia (OR:1.76;95%CI:1.40-2.23;p<0.0001) symptoms than among those who did not report these symptoms. Controlling for BMI, tobacco smoking, alcohol intake, TV watching and healthcare access (in Model 2) slightly attenuated the positive relationship between preeclampsia (OR:1.62;95%CI:1.33-1.96;p<0.0001) and eclampsia (OR:1.48;95%CI:1.15-1.91;p=0.003) symptoms and diabetes, but the

association remained positive, strong, and significant. The positive association between preeclampsia (OR:1.59;95%CI:1.31-1.93;p<0.0001) and eclampsia (OR:1.50;95%CI:1.16-1.95;p=0.002) and diabetes remained virtually unchanged when specific food and micronutrient intakes were additionally controlled for in Model 3. The final model (Model 4) in Table 2 provides the fully adjusted model with all covariates included. Jointly controlling for all of these factors, the positive association between symptoms suggestive of preeclampsia (OR:1.59;95%CI:1.31-1.94;p<0.0001) and eclampsia (OR:1.36;95%CI:1.05-1.77;p=0.020) during pregnancy and likelihood of diabetes remained strong and statistically significant.

DISCUSSION

In this study, we examined the association between HDPs, focusing on PE&E and diabetes risk in a large, nationally representative sample of Indian women. We observed a strong evidence of an increased risk of diabetes among women reporting symptoms suggestive of PE&E during their last pregnancy. This association is robust as we have adjusted for a comprehensive range of established risk factors of diabetes and possible clustering of lifestyles and other factors that may accompany HDP (e.g., smoking, alcohol intake, access to healthcare) and dietary predictors of diabetes (i.e. food consumption), BMI, and education level. To our knowledge, this is the largest nationally representative cross-sectional study at the population level showing the association between PE&E and diabetes risk in an Asian population. Another strength of this study is our ability to adjust for obesity, which in itself is associated with insulin resistance, and is a well-known risk factor for the development of diabetes and preeclampsia. These findings highlight and support the need to counsel patients with hypertensive disorders during pregnancy regarding postpartum diabetes screening prevention in a developing country setting.

The long term sequelae of both PE&E are not well-evaluated in LMICs especially in India, where the rate of HDP-related maternal mortality is high[1] and PE&E are thought to underlie around 5-10% of pregnancy complications and about 8-9% of maternal deaths in India.[22] Some clinical studies suggest that the proportion of deliveries impacted by PE&E in Indian women ranges from as low as 0.9% to as high as 7.7% of all deliveries.[22] 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.[19]

The pathway

Common pathogenic pathways may underlie the association between women with a history of preeclampsia and an increased risk of diabetes as each of these conditions is associated with manifestations of the metabolic syndrome (including endothelial dysfunction, obesity, hypertension, hyperglycemia, insulin resistance, renal disease and dyslipidemia), a syndrome known for its association with insulin resistance during pregnancy[23-25] which may be independent of obesity and glucose intolerance.[23-24,26] These conditions may subsequently predisposed women to develop hypertension, atherosclerosis, and type 2 diabetes mellitus in later life, which eventually lead to cardiovascular disease.[10,11,27]Other possible explanations for this cardiovascular profile include the following : (a) as both cardiovascular disease and preeclampsia share common risk factors turning pregnancy into a "stress test" with the development of HDP identifying a woman destined to develop cardiovascular disease[28]; (b) pregnancy, and especially preeclampsia, may induce permanent arterial changes—the proatherogenic stress of pregnancy, excessive in many women with preeclampsia, could activate arterial wall inflammation that fails to resolve after delivery, increasing the risk for future cardiovascular disease.[11] Women with early onset/severe preeclampsia, recurrent preeclampsia, or preeclampsia with onset as a multipara appear to be at highest risk of cardiovascular disease later in life, including during the premenopausal period.[6]

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 preeclampsia and diabetes; 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&E or diabetes 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 preeclampsia, nor the precise onset of diabetes. Furthermore, family history, physical activity, glucose, and blood pressure measures are also known risk factors for diabetes, which were not collected in the survey. From our data sources we could not differentiate type 1 from type 2 diabetes; however, given the mean age of the women was 26.4 y (±5.6SD), it is most likely that the majority of the women developed type 2 diabetes. We were, however, able to adjust for several other important confounding variables including socio economic and demographic factors and some lifestyle indicators and access to health care.

Conclusions

In summary, this study provides some initial empirical evidence that HDP, specifically symptoms suggestive of PE&E during pregnancy, are strongly associated with diabetes in a large nationally representative sample of Indian women that need further evaluation. These findings have important implications for maternal and child health, especially given the increase in obesity-related diseases in this low resource settings. A history of PE&E during pregnancy should alert clinicians to the need for preventative counseling and more vigilant screening for diabetes and women should be encouraged to have a more rigorous follow-up and adopt a healthier lifestyle. Follow-up and counseling of women with a history of PE&E may offer a window of opportunity for prevention of future cardiovascular diseases including diabetes. Patient and healthcare provider education is also essential for the successful assessment and management of cardiovascular risk and prevention of the long term burden associated with PE&E. Awareness of a history of PE&E might allow the identification of cases not previously recognized as at-risk for diabetes, allowing the implementation of measures to prevent the occurrence of these events. Moreover, evaluation of women prior to pregnancy and follow-up during pregnancy is needed to determine the role of shared risk factors. Regular medical follow-up and earlier screening for CVD should be considered in this population. At least, current screening guidelines should be followed and these women should receive advice on established preventive lifestyle measures and on treatment strategies that should be implemented by all women regardless of a previous history of gestational hypertension/preeclampsia.[29] Further research to verify accuracy of reporting of the symptoms of PE&E, longitudinal medical histories and a clinical measurement of diabetes are needed in an Indian setting.

REFERENCES

1. Dolea C, AbouZahr C. Global Burden of obstructed labor in the year 2000: version 2. 2003. Geneva: WHO.

2. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001;20:IX-XIV.

3. World Health Organization Collaboration. The world health report: make every mother and child count. 2005. Department of Reproductive Health and Research, WHO. www.who.int/whr/2005/en/index.html (accessed Aug 2015).

4. Lo JO, Mission JF, Caughey AB. Hypertensive disease of pregnancy and maternal mortality. *Curr Opin Obstet Gynecol* 2013;25(2):124-32. doi: 10.1097/GCO.0b013e32835e0ef5.

5. Maternal mortality in 2005: estimates developed by WHO, UNICEF, UNIFPA and the World Bank, Geneva, World Health Organization, 2007.

6. Garovic VD, Hayman SR. Hypertension in pregnancy: an emerging risk factor for cardiovascular disease. *Nat Clin Pract Nephrol* 2007;3(11):613-22.

7. Callaway LK, Lawlor DA, O'Callaghan M, Williams GM, Najman JM, et al. Diabetes mellitus in the 21 years after a pregnancy that was complicated by hypertension: findings from a prospective cohort study. *Am J Obstet Gynecol* 2007;197: 492.e1–492.e7.

8. Harskamp RE, Zeeman GG. Preeclampsia: at risk for remote cardiovascular disease. *Am J Med Sci* 2007;334: 291–295.

9. Engeland A, Bjorge T, Kjersti Daltveit AK, Skurtveit S, Vangen S, et al. Risk of diabetes after gestational diabetes and preelampsia. A registry-based study of 230,000 women in Norway. *Eur J Epidemiol* 2011;26: 157–163.

10. Wang IK, Tsai IJ, Chen PC, Liang CC, Chou CY, Chang CT, Kuo HL, Ting IW, Lin CC, Chuang FR, Huang CC, Sung FC. Hypertensive disorders in pregnancy and subsequent diabetes mellitus: a retrospective cohort study. *Am J Med* 2012;125(3):251-7. doi: 10.1016/j.amjmed.2011.07.040.

11. Chen CW, Jaffe IZ, Karumanchi SA. Pre-eclampsia and cardiovascular disease. *Cardiovascular Research* 2014;101(4):579-586. doi:10.1093/cvr/cvu018.

12. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009;53: 944–951.

13. Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. *CMAJ* 2008;179: 229–234.

14. Diabetes Prevention Program Research Group. *N Eng J Med* 2002;346: 393–403.

15. Tuomilehto J, Lindstro¨m J, Eriksson JG, Valle TT, Ha¨ma¨ la¨ inen H, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Eng J Med* 2001;344: 1343–1350.

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

17. World Health Organisation (WHO) 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. 2007.

18. NICE guidelines (CG107). 2010. Available at http://www.nice.org.uk/guidance/CG107/chapter/1-Guidance; (accessed on June 6 2014)

19. Xie Xi-tao, Liu Q, Jie WU, Makoto W. Impact of cigarette smoking in type 2 diabetes development. *Acta Pharmacol Sin* 2009;30(6): 784–787.

20. Agrawal S, Fledderjohann J, Vellakkal S, Stuckler D. Adequately Diversified Dietary Intake and Iron and Folic Acid Supplementation during Pregnancy Is Associated with Reduced Occurrence of Symptoms Suggestive of PreEclampsia or Eclampsia in Indian Women. *PLoS ONE* 2015;10(3): e0119120. doi:10.1371/journal.pone.0119120

21. Carlsson S, Hammar N, Grill V, Kaprio J. Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. *Diabetes Care* 2003;26(10):2785-90.

22. Singh S, Behera A. 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).

23. Parretti E, lapolla A, Dalfra MG, Pacini G, Mari A, et al. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. *Hypertension* 2006; 47: 449–453.

24. Sierra–Laguado J, Garcia RG, Celedo´n J, Arenas-Mantilla M, Pradilla LP, et al. Determination of insulin resistance using the homeostatic model assessment (HOMA) and its relation with the risk of developing pregnancy–induced hypertension. *Am J Hypertens* 2007;20: 437–442.

25. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. *Am J Obstet Gynecol* 2009;200: 58.e1–58.e8.

26. Soonthornpun K, Soonthornpun S, Wannaro P, Setasuban W, Thamprasit A. Insulin resistance in women with a history of severe pre–eclampsia. *J Obstet Gynaecol Res* 2009;35: 55–59.

27. Martillotti G, Boulvain M, Landau R, Pechère-Bertschi A. [Is preeclampsia a new cardiovascular and end-stage renal diseases risk marker?]. [Article in French] *Rev Med Suisse* 2009 Sep 9;5(216):1752-4, 1756-7.

28. Pinto PV, Rei M, Machado AP, Montenegro N. Preeclampsia and Future Cardiovascular Risk: Are Women and General Practitioners Aware of This Relationship? The Experience from a Portuguese Centre. *Obstetrics and Gynecology International* 2014; Article ID 531539, 7 pages. http://dx.doi.org/10.1155/2014/531539

29. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation* 2011;123:1243–1262.

Table 1: Sample distribution, number and distribution of diabetes cases and prevalence of diabetes according to PE&E and other factors among Indian women, 2005-06

Characteristics	Sample size	Diabetes cases		Diabetes prevalence %	Chi sq p value
	%[N]	Reported %[N]	Not reported %[N]		
Total	39612	512		1.3	
Preeclampsia symptoms					<0.0001
No	71.3[28250]	59.5[304]	71.5[27933]	1.1	
Yes	28.7[11361]	40.5[207]	28.5[11147]	1.8	
Eclampsia symptoms					<0.0001
No	89.7[35541]	83.4[426]	89.8[35096]	1.2	
Yes	10.3[4071]	16.6[85]	10.2[3984]	2.1	
Body Mass Index					0.023
Underweight (≤18.5kg/m^2)	38.0[14440]	41.8[208]	38.0[14227]	1.4	
Normal (18.5-22.9kg/m^2)	46.9[17833]	40.6[202]	47.0[17622]	1.1	
Overweight (23.0-24.9kg/m^2)	7.3[2766]	9.4[47]	7.3[2720]	1.7	
Obese (≥25.0kg/m^2)	7.8[2964]	8.2[41]	7.8[2919]	1.4	
Current Tobacco smoking					0.259
No	98.5[39006]	98.0[501]	98.5[38484]	1.3	
Yes	1.5[606]	2.0[10]	1.5[596]	1.7	
Drinks Alcohol					0.001
No	97.7[38690]	98.3[488]	97.7[38184]	1.3	
Yes	2.3[911]	4.7[24]	2.3[886]	2.6	
Frequency of TV viewing					0.001
Not at all	43.8[17351]	50.9[260]	43.7[17076]	1.5	
Less than once a week	11.3[449]	13.3[68]	11.3[4423]	1.5	
At least once a week	10.3[4074]	9.0[46]	10.3[4027]	1.1	
Almost everyday	34.6[13689]	26.8[137]	34.7[13548]	1.0	
Access to healthcare					<0.0001
Public Medical sector	31.3[11313]	34.5[162]	31.3[11138]	1.4	
NGO or Trust or Clinic	0.3[113]	0.9[4]	0.3[109]	3.5	
Private Medical Sector	68.1[24591]	63.4[298]	68.1[24279]	1.2	
Other source	0.3[119]	1.3[6]	0.3[112]	5.1	
Food and micronutrient intake					
Diversified dietary intake					0.193
Inadequate	68.9[27275]	68.8[26895]	70.7[362]	1.3	
Adequate	31.1[12337]	31.2[12185]	29.3[150]	1.2	
Intake of Iron and folic acid supplementation					0.212
No	74.7[29588]	74.7[29183]	76.3[390]	1.3	
Yes	25.3[10024]	25.3[9897]	23.7[121]	1.2	
Milk or curd					<0.0001
Never/occasionally	48.1[19046]	56.8[290]	48.0[18745]	1.5	
Daily/weekly	51.9[20561]	43.2[221]	52.0[20331]	1.1	
Pulses or beans					<0.0001
Never/occasionally	10.1[4014]	10.1[3935]	10.1[3935]	1.9	
Daily/weekly	89.9[35588]	89.9[35137]	89.9[35137]	1.2	
Vegetables					0.075
Never/occasionally	7.1[2804]	7.1[2759]	7.1[2759]	1.6	
Daily/weekly	92.9[36795]	92.9[36310]	92.9[36310]	1.3	

Fruits					0.002
Never/occasionally	65.7[26043]	72.0[368]	65.7[25663]	1.4	
Daily/weekly	34.2[13541]	28.0[143]	34.3[13390]	1.1	
Eggs					0.084
Never/occasionally	69.7[27601]	72.6[371]	69.7[27216]	1.3	
Daily/weekly	30.3[11985]	27.4[140]	30.3[11841]	1.2	
Fish					0.003
Never/occasionally	73.3[29043]	67.9[347]	73.4[28679]	1.2	
Daily/weekly	26.7[10558]	32.1[164]	26.6[10392]	1.6	
Chicken/meat					0.004
Never/occasionally	78.7[31158]	83.6[428]	78.6[30714]	1.4	
Daily/weekly	21.3[8439]	16.4[84]	21.4[8352]	1.0	
Socio-demographic characteristics					
Age groups					0.001
15-19	7.5[2982]	10.2[52]	7.5[2928]	1.7	
20-24	33.5[13269]	29.0[148]	33.6[13113]	1.1	
25-29	32.6[12908]	27.2[139]	32.7[12767]	1.1	
30-34	16.9[6685]	18.8[96]	16.8[6584]	1.4	
35-39	6.9[2723]	11.0[56]	6.8[2667]	2.1	
40-44	2.1[835]	2.7[14]	2.1[818]	1.7	
45-49	0.5[210]	1.2[6]	0.5[204]	2.9	
Education					0.064
No education	18758[47.4]	51.4[263]	47.3[18480]	1.4	
Primary	5545[14.0]	14.6[75]	14.0[5470]	1.4	
Secondary	12947[32.7]	30.3[155]	32.7[12790]	1.2	
Higher	2361[6.0]	3.7[19]	6.0[2339]	0.8	
Employment status					0.143
Currently not working	27665[69.9]	67.7[346]	70.0[27309]	1.3	
Working	11886[30.1]	32.3[165]	30.0[11713]	1.4	
Religion					0.035
Hindu	31248[78.9]	76.8[393]	78.9[30836]	1.3	
Muslim	6472[16.3]	17.2[88]	16.3[6383]	1.4	
Christian	811[2.0]	3.9[20]	2.0[791]	2.5	
Sikhs	513[1.3]	0.8[4]	1.3[509]	0.8	
Others	568[1.4]	1.4[7]	1.4[561]	1.2	
Caste/tribe					<0.0001
Scheduled caste	7938[20.1]	21.3[109]	20.1[7825]	1.4	
Scheduled tribes	3740[9.4]	13.7[70]	9.4[3666]	1.9	
Other backward class	15861[40.2]	30.3[155]	40.3[15696]	1.0	
General	10830[27.4]	30.9[158]	27.4[10669]	1.5	
Missing caste	1085[2.8]	3.7[19]	2.7[1060]	1.8	
Wealth index					<0.0001
Lowest	9553[24.1]	32.4[166]	24.0[9381]	1.7	
Second	8588[21.7]	22.3[114]	21.7[8465]	1.3	
Middle	7762[19.6]	19.9[102]	19.6[7661]	1.3	
Fourth	7251[18.3]	15.6[80]	18.3[7168]	1.1	
Highest	6458[16.3]	9.8[50]	16.4[6405]	0.8	
Place of residence					0.001
Urban	10615[26.8]	20.3[104]	26.9[10506]	1.0	
Rural	28997[73.2]	79.7[408]	73.1[28574]	1.4	
Geographic Regions					<0.0001
North	5076[12.8]	9.4[48]	12.9[5028]	0.9	

Northeast	1607[4.1]	5.9[30]	4.0[1576]	1.9
Central	11099[28.0]	17.8[91]	28.4[11000]	0.8
East	10031[25.3]	48.3[247]	25.0[9777]	3.5
West	5114[12.9]	6.1[31]	13.0[5081]	0.6
South	6684[16.9]	12.5[64]	16.9[6618]	1.0

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

Table 2: Unadjusted and partially adjusted and fully adjusted odds ratios (ORs) and 95% confidence interval (95%CI) showing the association between PE&E and other factors and diabetes risk among Indian women, 2005-06

	Unadjusted Model 1	Adjusted Model 2	Adjusted Model 3	Adjusted Model 4
	OR[95%CI]	OR[95%CI]	OR[95%CI]	OR[95%CI]
Preeclampsia symptoms				
No [Ref]	1	1	1	1
Yes	1.71[1.43-2.04]	1.62[1.33-1.96]	1.59[1.31-1.93]	1.59[1.31-1.94]
Eclampsia symptoms				
No [Ref]	1	1	1	1
Yes	1.76[1.40-2.23]	1.48[1.15-1.91]	1.50[1.16-1.95]	1.36[1.05-1.77]
Body Mass Index				
Underweight (≤18.5 kg/m^2)		1.24[1.01-1.52]	1.21[0.99-1.49]	1.17[0.95-1.44]
Normal (18.5-22.9 kg/m^2) [Ref]		1	1	1
Overweight (23.0-24.9 kg/m^2)		1.74[1.25-2.42]	1.78[1.27-2.47]	2.01[1.43-2.81]
Obese (≥25.0 kg/m^2)		1.47[1.02-2.10]	1.52[1.06-2.19]	1.85[1.26-2.72]
Current tobacco smoking				
No [Ref]		1	1	1
Yes		1.13[0.60-2.11]	1.13[0.60-2.12]	0.88[0.46-1.68]
Current alcohol drinking				
No [Ref]		1	1	1
Yes		1.93[1.26-2.95]	1.81[1.17-2.79]	1.36[0.84-2.20]
Frequency of TV viewing				
Not at all [Ref]		1	1	1
Less than once a week		1.04[0.78-1.38]	1.03[0.77-1.38]	1.21[0.90-1.63]
At least once a week		0.81[0.58-1.13]	0.84[0.60-1.18]	1.02[0.72-1.46]
Almost everyday		0.72[0.57-0.90]	0.80[0.62-1.02]	1.18[0.87-1.61]
Access to healthcare				
Public Medical sector [Ref]		1	1	1
NGO or Trust or Clinic		2.03[0.71-5.76]	2.06[0.72-5.91]	1.76[0.60-5.18]
Private Medical Sector		0.84[0.69-1.02]	0.89[0.73-1.08]	0.89[0.72-1.10]
Other source		3.16[1.31-7.59]	3.08[1.27-7.44]	2.57[1.05-6.33]
Food and micronutrient intake				
Diversified dietary intake				
Inadequate [Ref]			1	1
Adequate			1.54[1.16-2.04]	1.46[1.10-1.94]
Intake of Iron and folic acid supplementation				
No [Ref]			1	1
Yes			1.20[0.81-1.29]	1.11[0.87-1.41]
Milk or curd				
Never/occasionally [Ref]			1	1
Daily/weekly			0.87[0.71-1.07]	1.06[0.85-1.31]
Pulses or beans				
Never/occasionally [Ref]			1	1
Daily/weekly			0.76[0.58-1.00]	0.80[0.60-1.07]
Vegetables				
Never/occasionally [Ref]			1	1
Daily/weekly			0.90[0.65-1.25]	0.81[0.58-1.13]
Fruits				
Never/occasionally [Ref]			1	1

Daily/weekly	0.92[0.73-1.15]	1.05[0.82-1.33]
Eggs		
Never/occasionally [Ref]	1	1
Daily/weekly	0.90[0.70-1.16]	0.80[0.62-1.03]
Fish		
Never/occasionally [Ref]	1	1
Daily/weekly	1.76[1.38-2.25]	1.12[0.87-1.46]
Chicken/meat		
Never/occasionally [Ref]	1	1
Daily/weekly	0.60[0.45-0.80]	0.75[0.56-1.02]
Socioeconomic and demographic characteristics		
Age		
15-19 [Ref]		1
20-24		0.83[0.58-1.18]
25-29		0.71[0.49-1.02]
30-34		0.86[0.58-1.27]
35-39		1.25[0.81-1.91]
40-44		0.99[0.53-1.86]
45-49		1.49[0.60-3.68]
Education		
No education [Ref]		1
Primary		0.92[0.68-1.25]
Secondary		1.15[0.87-1.52]
Higher		0.96[0.53-1.74]
Employment status		
Currently not working [Ref]		1
Working		1.21[0.91-1.38]
Religion		
Hindu [Ref]		1
Muslim		1.00[0.74-1.35]
Christian		1.53[0.90-2.60]
Sikhs		0.79[0.27-2.31]
Others		0.65[0.29-1.47]
Caste/tribe		
Scheduled caste [Ref]		1
Scheduled tribes		0.97[0.68-1.38]
Other backward class		0.65[0.50-0.85]
General		1.11[0.83-1.49]
Missing caste		0.48[0.24-0.95]
Wealth index		
Lowest [Ref]		1
Second		0.89[0.68-1.16]
Middle		0.80[0.58-1.09]
Fourth		0.76[0.52-1.11]
Highest		0.45[0.27-0.78]
Place of residence		
Urban [Ref]		1
Rural		1.01[0.77-1.34]
Geographic Regions		
North [Ref]		1
Northeast		1.82[1.06-3.13]
Central		0.93[0.62-1.39]

East	2.68[1.83-3.93]
West	0.69[0.42-1.15]
South	1.28[0.82-1.99]
Number of cases	34978

* Note: [Ref] denotes reference category; Model 1 unadjusted; Model 2 adjusted for BMI, tobacco smoking, alcohol drinking, TV watching and access to healthcare; Model 3 adjusted for Model 2+ specific dietary intakes; Model 4 adjusted for all

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Hypertensive disorders of pregnancy and risk of diabetes in Indian Women

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Data sharing statement: The authors confirm that all data underlying the findings are fully available without restriction. Data are publicly available from the Demographic and Health Surveys website: http://dhsprogram.com/what-we-do/survey/survey-display-264.cfm.

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Article Summary

Strength and limitations of this study

- Epidemiological data from high income countries suggests that women with HDP are more likely to develop cardiovascular risk, including diabetes, later in life. There is no empirical evidence of an association in low-and middle- income countries, which have the highest burden.
- Our study provided strong evidence of an increased risk of diabetes among women reporting symptoms suggestive of preeclampsia or eclampsia during their last pregnancy. This positive relation is robust even after adjustment for a comprehensive range of established risk factors for diabetes and possible clustering of lifestyles and other factors that may accompany HDP (e.g., smoking, alcohol intake, access to healthcare) and dietary predictors of diabetes (i.e. food consumption), BMI, and education level.
- To our knowledge, this is the largest nationally representative cross-sectional study of the population based association between pregnancy induced preeclampsia or eclampsia symptoms and diabetes risk in an Asian population.
- A history of preeclampsia or eclampsia during pregnancy should alert clinicians to the need for preventative counselling and more vigilant screening for diabetes.
- These findings are important for a country such as India, which is tackling the dual-burden of NCDs and infectious diseases among its female population.

Abstract

Background: Epidemiological data from high income countries suggests that women with hypertensive disorders during pregnancy (HDP) are more likely to develop diabetes later in life.

Objective: We investigated the association between preeclampsia and eclampsia (PE&E) during pregnancy and the risk of diabetes in Indian women.

Design: Cross-sectional study

Setting: India

Methods: Data from India's third National Family Health Survey (NFHS-3, 2005-06), a cross-sectional survey of women aged 15-49 years are used. Self-reported symptoms suggestive of PE&E were obtained from 39,657 women who had a live birth in the five years preceding the survey. The association between PE&E and self-reported diabetes status was assessed using multivariable logistic regression models adjusting for dietary intake, BMI, tobacco smoking, alcohol drinking, frequency of TV watching, socio-demographic characteristics and geographic region.

Results: The prevalence of symptoms suggestive of PE&E in women with diabetes was 1.8% (n=207;95%CI:1.5-2.0;p<0.0001) and 2.1% (n=85;95%CI:1.8-2.3;p<0.0001) respectively, compared with 1.1%(n=304;95%CI:1.0-1.4)and 1.2% (n=426;95%CI:1.1-1.5) in women who did not report any PE&E symptoms. In the multivariable analysis, PE&E was associated with 1.6 times (OR=1.59;95%CI:1.31–1.94;p<0.0001) and 1.4 times (OR=1.36;95%CI:1.05–1.77;p=0.001) higher risk for self-reported diabetes even after controlling for dietary intake, BMI, and socio-demographic characteristics.

Conclusion: HDP is strongly associated with the risk of diabetes in a large nationally representative sample of Indian women. These findings are important for a country which is already tackling the burden of young onset of diabetes in the population. However, longitudinal medical histories and a clinical measurement of diabetes are needed in this low resource setting.

Keywords: preeclampsia; eclampsia; diabetes; women; India; NFHS-3

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) represent a group of conditions marked by high blood pressure during pregnancy, proteinuria, and in some cases convulsions. Gestational hypertension, preeclampsia and eclampsia (PE&E), are most common HDP, and some of the most serious pregnancy complications for the mother and the baby results from PE&E.[1] Preeclampsia is a syndrome of pregnancy defined by the onset of hypertension and proteinuria and characterised by widespread dysfunction of the endothelium in the mother.[2] Eclampsia is usually a consequence of preeclampsia. It consists of central nervous system seizures, unrelated to conditions such as epilepsy, which often leave the patient unconscious; if untreated it may lead to death. Worldwide HDP are more common, estimated to complicate 5%-10% of all pregnancies and to be responsible for 12-25% of maternal mortality during pregnancy and the puerperium.[3,4] PE&E are leading threats to safe motherhood in developing countries, where a woman is seven times more likely to develop these conditions and 10-25% of these cases lead to maternal deaths annually (an estimated ~40,000 women).[5]

Increasing evidence indicates that PE&E is not just a pregnancy-related disease that resolves at the time of delivery, but represent a risk marker of cardiovascular diseases later in life.[6]Studies that looked at the risk of developing type 2 diabetes in women with a history of preeclampsia have all been conducted in western populations, and have found a positive association equalling the risk attributed to obesity and smoking.[7-11]The Danish National Patient Registry study found that preeclampsia is associated with 3.1-3.7 –fold risk of developing type 2 diabetes.[12] A recent population-based study of >1 million women has found that women with preeclampsia or gestational hypertension have a twofold increased risk of developing diabetes after pregnancy.[13]

Studies showing the association between HDP and diabetes are based on non-representative clinical data and/or are based on data from western settings. Investigation of the links between PE&E symptoms and diabetes in LMICs, which have the highest burden of these conditions, has been severely limited. Randomized trials have shown that diabetes can be prevented or delayed in high-risk groups by a variety of lifestyle and therapeutic interventions.[14,15] However, identifying at risk populations to screen for diabetes in a low resource setting such as India is a critical step in translating these findings into clinical practice. HDP such as preeclampsia may heighten the propensity for women to develop diabetes in the years following pregnancy, and such women may also be suitable targets for diabetes prevention.

We investigated the association between PE&E during pregnancy and diabetes risk in a large sample of Indian women.

MATERIALS AND METHODS

Data

We analyse data from the Indian National Family Health Survey (NFHS-3) for the years 2005/2006, a large, well-established, nationally representative survey based on a multi-stage cluster sample design that provides high-quality information on the health and nutrition of women and children with an overall response rate of 98%.[16] NFHS is the Indian equivalent of the Demographic and Health Surveys, a series of standardised surveys which are routinely conducted in more than 80 developing countries. All data are in the public domain and can be downloaded, after registration, from http://www.measuredhs.com. The NFHS has been conducted in India for three successive rounds, each at an interval of ~5 years. The NFHS-3 collected demographic, socioeconomic, and health information from a nationally representative probability sample of 124,385 women aged 15–49 years residing in 109,041 households. All states of India are represented in the sample (except the small Union Territories), covering more than 99% of the country's population. The survey was conducted using an interviewer-administered questionnaire in the native language of the respondent using a local, commonly understood term for diseases. A total of 18 languages were used with back translation to English to ensure accuracy and comparability. Full details of the survey have been published elsewhere.[11]

To examine the association between HDP and risk of diabetes, we restricted the sample to only 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 to minimize recall bias. Missing data were dropped using list wise deletion. This resulted in a final sample size of 39,657 participants.

Outcome evaluation

The survey includes self-report data relating to specific health problems of the mother, including whether the respondent currently has diabetes.[16] Specifically, respondents were asked: 'Do you currently have diabetes?' with the response options of 'yes', 'no' and 'don't know'. It is important to

recognize that self-reported diabetes is not as accurate as clinical measures of diabetes; no physician diagnosis or fasting blood glucose measures were included in the NFHS-3.[16]

Predictor variables

The NFHS-3 contains several items related to health problems during pregnancy. As physical markers (e.g. blood pressure, proteinuria) used in the clinical diagnosis of PE&E were not measured in the NFHS-3, we used three self-reported health items to construct a measure of PE&E. Specifically, in relation to their current or most recent pregnancy, 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 Organisation[17] and National Institute for Health and Care Excellence[18]guidelines, and NFHS-3 coding by Agrawal et al[19], we created two dichotomous indicators for PE&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 preeclampsia, while those who additionally reported experiencing convulsions (not from fever) were coded as eclamptic.

Covariates

In order to reduce the possibility that the association between PE&E and diabetes was driven by confounders, we included several sociodemographic control variables. Height and weight data were collected by the NFHS-3 interview staff, and BMI was calculated based on this data.[16] We included an Asian Population standard [51–53] BMI(kg/m^2) measure, with thresholds defined as ≤18.4 kg/m^2 (underweight), 18.5 to 22.9 kg/m^2 (normal), 23.0 to 24.9 kg/m^2 (overweight), and ≥25 kg/m^2 (obese). Women who were pregnant at the time of the survey or women who had given birth during the two months preceding the survey were excluded from these measurements. In addition, previous studies have found that smokers are insulin resistant, exhibit several aspects of the insulin resistance syndrome, and are at an increased risk for type 2 diabetes[20], while moderate alcohol consumption may reduce the risk of type 2 diabetes. On the other hand, binge drinking and high alcohol consumption may increase the risk of type 2 diabetes in women or men.[21] We included controls for smoking and drinking behaviour: 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. We constructed a dichotomous indicator of current alcohol use in the present analysis. Frequency of watching television (almost every day, at least once weekly, less than once weekly, not at all), a categorical variable in the NFHS data, was used as a measure of sedentary behaviour. We measured access to healthcare by a categorical indicator of type of healthcare facility used (public medical sector, NGO trust hospital or clinic, private medical sector, and other sources). Previous work[19] has shown that iron intake and consuming a diversified diet is associated with a reduced risk of PE&E. Dietary intake as indicated by consumption of selected foods was assessed by asking, 'How often do you yourself consume the following items: daily, weekly, occasionally or never?' related to the consumption of milk or curd, pulses or beans, green leafy vegetables, other vegetables, fruits, eggs, and chicken, meat or fish.[16]

In order to reduce the risk of unobserved homogeneity in our models, we included a variety of socio-demographic controls. The socio-demographic factors considered in the present analysis included age categories (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49); education was classified as no education, primary (5–7 years completed), secondary (8–9 years) or higher (10+ years); employment status (currently not working, working); religion (Hindu, Muslim, Christian, Sikhs, Others); caste/tribe (Scheduled Castes, Scheduled Tribes, Other Backward Class, General); a standard wealth index compiled by the NFHS-3 (measured by an index based on household ownership of assets and graded as lowest, second, middle, fourth and highest); place of residence (urban, rural); and geographic regions of India (north, northeast, central, east, west, south).

Statistical Analysis

Descriptive statistics were calculated with the use of standard methods. Differences in categorical variables were tested using Pearson's χ^2 tests. Multivariable logistic regression analysis was used to estimate the effect of symptoms suggestive of PE&E on self-reported diabetes risk. In the first logistic regression model, we examined the unadjusted association between PE&E symptoms and diabetes risk independent of each other. In the second model, we adjusted for BMI status, tobacco smoking, alcohol drinking, frequency of TV watching, and access to healthcare in order to assess how much of the variance in this association was explained by those factors. In the third model, we added specific food and micronutrient intake to our model. In the fourth and final model, we added socio-demographic characteristics in order to examine the association between PE&E symptoms and diabetes risk controlling for all the confounders discussed above.

To adjust for the NFHS-3 sampling design, a sample weight was also included in the models.[11] Results are presented as odds ratios with 95% confidence intervals (OR;95%CI). The estimation of confidence intervals takes into account design effects due to clustering at the level of the primary sampling unit. Before carrying out the multivariate model, the possibility of multicollinearity between the covariates was assessed. In the correlation matrix of covariates, all pair wise Pearson correlation coefficients were found <0.5, suggesting that multicollinearity did not affect the findings. All analyses were conducted using the SPSS statistical software package Version 19 (IBM SPSS Statistics, Chicago, Illinois, USA).

Ethical considerations

The NFHS-3 survey received ethical approval from the International Institute for Population Science's Ethical Review Board and Indian Government. Prior informed written consent was obtained from each respondent. The analysis presented in this study is based on secondary analysis of existing survey data with all identifying information removed; no ethical approval was required.

RESULTS

Table 1 presents the descriptive statistics for the sample, and bivariate associations between diabetes and PE&E. Overall, 28.7% (n=11,361) of women reported symptoms suggestive of preeclampsia during their last pregnancy, and one out of ten women (10.3%; n=4071) reported symptoms suggestive of eclampsia. Thirty-eight percent were underweight, while 15% were either overweight or obese. A very few were current smokers (1.5%) or alcohol drinkers (2.3%), while 68% had access to the private medical sector to obtain their health care. One third viewed TV almost every day. Most mothers (nearly 75%) were aged between 15-29 years, and almost half (47%) had no education; 70% were not employed at the time of survey. A majority of the mothers (four out of five) identified as Hindu, and two-fifths belonged to a scheduled caste category. One fourth belonged to a household in the poorest wealth quintile. More than 70% of the mothers were residing in rural areas, while 28% were residents of Central India. Half of the mothers reported of consuming milk/curd whereas a majority reported of consuming pulses/beans and vegetables on a daily or weekly basis. However, only one third reported of consuming fruit (34%) and eggs (30%), while only one fourth or less of the sample respondents consumed fish (27%) or chicken/meat (21%) on a daily or weekly basis.

Of the women reporting diabetes, two out of five (41%) also reported symptoms suggestive of preeclampsia and 17% reported symptoms of eclampsia (Table 1). Eighteen percent were either obese or overweight; 2% were currently smoking tobacco; 5% were alcohol drinkers; a half of them reported of not watching TV at all, one in three visits to public medical sector for healthcare needs, two-thirds (66%) were in the age group 15-29 years; half of them had no education; 77% were Hindus; 31% belonged to general category; 68% were not working, two-fifths belong to household with poorest wealth quintile, a majority resides in rural area whereas half of them resides in eastern India. Among the women who reported diabetes, a majority of them reportedly consumed pulses/beans and vegetables on a daily/weekly basis, more than two-fifth also reported consuming milk/curd daily/weekly, while the consumption of fruits (28%), eggs (27%), fish (32%) or chicken meat (16%) among them was less.

The prevalence of symptoms suggestive of PE&E in women with diabetes was 1.8% (95%CI:1.5-2.0;p<0.0001) and 2.1% (95%CI:1.8-2.3;p<0.0001) respectively, compared with 1.1% (95%CI:1.0-1.4) and 1.2% (95%CI:1.1-1.5) in women who did not report any PE&E symptoms (Table 1). Overweight (1.7%) or obese (1.4%) women had higher prevalence of diabetes than those who were underweight (1.4 %) and normal weight (1.1%). A higher proportion of current tobacco smokers (1.7%) and current alcohol drinkers (2.6%) also reported diabetes compared to those who, respectively, do not currently smoke or drink. Women who had access only to other sources for health care (5.1%) and NGO or Trust or Clinic (3.5) had higher prevalence of diabetes. Women reporting viewing TV not at all or less than once a week reported higher diabetes (1.5%) than their counterparts. Women consuming milk/curd (1.1% vs 1.5%), pulses/beans (1.2% vs 1.9%), vegetables (1.3% vs 1.6%), fruits (1.1% vs 1.4%), eggs (1.2% vs 1.3%), or chicken/meat (1.0% vs 1.4%) except fish (1.6% vs 1.2%) on a daily/weekly basis had a lower prevalence of diabetes than those never /occasionally consume them. Diabetes prevalence is higher among women aged 40-49(2.9%) and 35-39 (2.1%) compared to women aged 15-29 years (1.2%). The prevalence of diabetes was also found higher among women belonging to Christian religion (2.5%), among women belonging to a scheduled tribe (1.9%) than those in a scheduled caste (1.4%), women in the poorest wealth quintile (1.7%), women residing in rural area (1.4%) and women living in eastern India (3.5%).

<Table 1 here>

Table 2 shows results of multivariable logistic regression analyses in unadjusted, partially adjusted and fully adjusted models. In the unadjusted analysis (Model 1), the likelihood of having diabetes was significantly higher among women who reported preeclampsia(OR:1.71;95%CI:1.43-2.04;p<0.0001) and

eclampsia (OR:1.76;95%CI:1.40-2.23;p<0.0001) symptoms than among those who did not report these symptoms. Controlling for BMI, tobacco smoking, alcohol intake, TV watching and healthcare access (in Model 2) slightly attenuated the positive relationship between preeclampsia(OR:1.62;95%CI:1.33-1.96;p<0.0001) and eclampsia (OR:1.48;95%CI:1.15-1.91;p=0.003) symptoms and diabetes, but the association remained positive, strong, and significant. The positive association between preeclampsia (OR:1.59;95%CI:1.31-1.93;p<0.0001) and eclampsia (OR:1.50;95%CI:1.16-1.95;p=0.002) and diabetes remained virtually unchanged when specific food and micronutrient intakes were additionally controlled for in Model 3. The final model (Model 4) in Table 2 provides the fully adjusted analysis with all covariates included. Jointly controlling for all of these factors, the positive association between symptoms suggestive of preeclampsia(OR:1.59;95%CI:1.31-1.94;p<0.0001) and eclampsia (OR:1.36;95%CI:1.05-1.77;p=0.020) during pregnancy and likelihood of diabetes remained strong and statistically significant.

The discussion of the adjusted effects of the control variables focuses on the full model (Model 4) in Table2. With other variables controlled, being overweight (OR:2.01;95%CI:1.43-2.81;p=0.030) and obese(OR:1.85;95%CI:1.26-2.72;p=0.010) has a positive and statistically significant effect on risk of diabetes among women. Women seeking healthcare from other sources had 2.5 times higher likelihood of diabetes (OR:2.57;95%CI:1.05-6.33;p=0.015) than their counterparts. Women consuming a adequately diversified diet also had a higher likelihood of reporting diabetes (OR:1.46;95%CI:1.10-1.94;p=0.005) than women consuming a inadequately diversified diet. Women residing in northern(OR:1.82;95%CI:1.06-3.13;p=0.005) and eastern regions of India (OR:2.68;95%CI:1.83-3.93;p=0.001) also had a higher likelihood of reporting diabetes risk than women residing in other parts of India. Positive association of diabetes were also observed with current alcohol intake, frequency of TV viewing, intake of micronutrient (such as IFA) and certain diets, higher age, working status, and location of women in northern and southern states of India but the association is not statistically significant. The likelihood of reporting diabetes among women does not vary significantly by the remaining other characteristics.

DISCUSSION

In this study, we examined the association between HDPs, focusing on PE&E and diabetes risk in a large, nationally representative sample of Indian women. We observed strong evidence of an increased risk of

diabetes among women reporting symptoms suggestive of PE&E during their last pregnancy. This association is robust, as we have adjusted for a comprehensive range of established risk factors of diabetes and possible clustering of lifestyles and other factors that may accompany HDP (e.g., smoking, alcohol intake, access to healthcare) and dietary predictors of diabetes (i.e. food consumption), BMI, and education level. Interestingly, we found evidence of an association between diabetes and many lifestyle factors (e.g. watching television), as well as evidence of regional variation. However, many of these associations were attenuated or non-significant in the adjusted models, highlighting the importance of the sociodemographic patterning of lifestyle and health behaviours.

To our knowledge, this is the largest nationally representative cross-sectional study at the population level showing the association between PE&E and diabetes risk in an Asian population. Another strength of this study is our ability to adjust for obesity, which in itself is associated with insulin resistance, and is a well-known risk factor for the development of diabetes and preeclampsia. These findings highlight and support the need to counsel patients with hypertensive disorders during pregnancy regarding postpartum diabetes screening prevention in a developing country setting.

The long term sequelae of both PE&E are not well-evaluated in LMICs especially in India, where the rate of HDP-related maternal mortality is high[1]and PE&E are thought to underlie around 5-10% of pregnancy complications and 8-9% of maternal deaths in India.[22] Some clinical studies suggest that the proportion of deliveries impacted by PE&E in Indian women ranges from as low as 0.9% to as high as 7.7% of all deliveries.[22] 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.[19]

Common pathogenic pathways may underlie the association between women with a history of preeclampsia and an increased risk of diabetes, as each of these conditions is associated with manifestations of the metabolic syndrome (including endothelial dysfunction, obesity, hypertension, hyperglycemia, insulin resistance, renal disease and dyslipidemia), a syndrome known for its association with insulin resistance during pregnancy[23-25],which may be independent of obesity and glucose intolerance.[23-24,26] These conditions may subsequently predispose women to develop hypertension, atherosclerosis, and type 2 diabetes mellitus in later life, which may eventually lead to cardiovascular disease.[10,11,27] Other possible explanations for this cardiovascular profile include the following: (a) as

both cardiovascular disease and preeclampsia share common risk factors turning pregnancy into a "stress test" with the development of HDP identifying a woman destined to develop cardiovascular disease[28]; (b) pregnancy, and especially preeclampsia, may induce permanent arterial changes—the proatherogenic stress of pregnancy, excessive in many women with preeclampsia, could activate arterial wall inflammation that fails to resolve after delivery, increasing the risk for future cardiovascular disease.[11] Women with early onset/severe preeclampsia, recurrent preeclampsia, or preeclampsia with onset as a multipara appear to be at highest risk of cardiovascular disease later in life, including during the premenopausal period.[6]

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 preeclampsia and diabetes. It is possible that self-reported data may suffer from recall bias. Moreover, many pregnant women may experience oedema that is not symptomatic of preeclampsia, and vision difficulties may be indicative not only of preeclampsia, but also secondary to gestational diabetes. Although we cannot rule out the possibility of misclassification within this context, it is unlikely that we have missed severe PE&E or diabetes cases due to the generally clear manifestation of symptoms in severe cases. However, mild cases of preeclampsia may be asymptomatic, and would likely be missed by our measure here. This possibility limits the applicability of our findings, as the majority of patients in clinical practice have mild to moderate preeclampsia, and may comprise much of this asymptomatic group. The presence or absence of convulsions may have greater face validity as a measure of eclampsia (as compared to swelling and blurred vision for preeclampsia), and we thus have greater confidence in our findings for eclampsia. Notably, however, we included preeclampsia and eclampsia as separate measures in the models, but found the coefficients for these measures to be in the same direction and of similar magnitude, providing some confidence in the validity of our measure of preeclampsia as well.

Second, due to the nature of the data, we could not identify precise timing during the gestational period of preeclampsia symptoms, nor the precise onset of diabetes. However the majority of individuals with type 2 diabetes mellitus have no symptoms and can be misclassified as non-diabetics in self-reports. This error may in fact strengthen our findings. Furthermore, family history, physical activity, glucose, and blood pressure measures are also known risk factors for diabetes, but were not collected in the survey.

From our data source, we could not differentiate type 1 from type 2 diabetes; however, given the mean age of the women was 26.4 y (±5.6SD), it is most likely that the majority of the women developed type 2 diabetes. We were, however, able to adjust for several other important confounding variables including socioeconomic and demographic factors and some lifestyle indicators and access to health care.

Conclusions

In summary, this study provides some initial empirical evidence that HDP, specifically symptoms suggestive of PE&E during pregnancy, are strongly associated with diabetes in a large nationally representative sample of Indian women. This is a high-risk population in need of further evaluation. These findings have important implications for maternal and child health, especially given the increase in obesity-related diseases in this low resource setting. A history of PE&E during pregnancy should alert clinicians to the need for preventative counselling and more vigilant screening for diabetes, and women should be encouraged to have a more rigorous follow-up and adopt a healthier lifestyle. Indeed, lifestyle were significantly associated with diabetes in our study (e.g. television viewing, dietary factors). While these associations were attenuated by the inclusion of socio demographic controls, this attenuation likely points to the socioeconomic gradient in lifestyle and health behaviours. Follow-up and counselling of women with a history of PE&E may offer a window of opportunity for prevention of future diabetes mellitus and cardiovascular disease. Patient and healthcare provider education is also essential for the successful assessment and management of cardiovascular risk and prevention of the long term burden associated with PE&E. Awareness of a history of PE&E might allow the identification of cases not previously recognized as at-risk for diabetes, allowing the implementation of measures to prevent the occurrence of these events. Moreover, evaluation of women prior to pregnancy and follow-up during pregnancy is needed to determine the role of shared risk factors. Regular medical follow-up and earlier screening for CVD should be considered in this population. At the least, current screening guidelines should be followed and these women should receive advice on established preventive lifestyle measures and on treatment strategies that should be implemented by all women regardless of a previous history of gestational hypertension/preeclampsia.[29] Further research to verify accuracy of reporting of the symptoms of PE&E is needed, and would be facilitated by longitudinal medical histories and a clinical measurement of diabetes in an Indian setting. Additional work is needed to investigate the association between diabetes and mild preeclampsia, particularly asymptomatic cases in a clinical setting.

REFERENCES

1. Dolea C, AbouZahr C. Global Burden of obstructed labor in the year 2000: version 2. 2003. Geneva: WHO.

2. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001;20:IX-XIV.

3. World Health Organization Collaboration. The world health report: make every mother and child count. 2005. Department of Reproductive Health and Research, WHO. www.who.int/whr/2005/en/index.html (accessed Aug 2015).

4. Lo JO, Mission JF, Caughey AB. Hypertensive disease of pregnancy and maternal mortality. *Curr Opin Obstet Gynecol*2013;25(2):124-32. doi: 10.1097/GCO.0b013e32835e0ef5.

5. Maternal mortality in 2005: estimates developed by WHO, UNICEF, UNIFPA and the World Bank, Geneva, World Health Organization, 2007.

6. Garovic VD, Hayman SR. Hypertension in pregnancy: an emerging risk factor for cardiovascular disease. *Nat Clin Pract Nephrol* 2007;3(11):613-22.

7. Callaway LK, Lawlor DA, O'Callaghan M, Williams GM, Najman JM, et al. Diabetes mellitus in the 21 years after a pregnancy that was complicated by hypertension: findings from a prospective cohort study. *Am J Obstet Gynecol*2007;197: 492.e1–492.e7.

8. Harskamp RE, Zeeman GG. Preeclampsia: at risk for remote cardiovascular disease. *Am J Med Sci*2007;334: 291–295.

9. Engeland A, Bjorge T, Kjersti Daltveit AK, Skurtveit S, Vangen S, et al. Risk of diabetes after gestational diabetes and preelampsia. A registry-based study of 230,000 women in Norway. *Eur J Epidemiol*2011;26: 157–163.

10. Wang IK, Tsai IJ, Chen PC, Liang CC, Chou CY, Chang CT, Kuo HL, Ting IW, Lin CC, Chuang FR, Huang CC, Sung FC. Hypertensive disorders in pregnancy and subsequent diabetes mellitus: a retrospective cohort study. *Am J Med* 2012;125(3):251-7. doi: 10.1016/j.amjmed.2011.07.040.

11. Chen CW, Jaffe IZ, Karumanchi SA. Pre-eclampsia and cardiovascular disease. *Cardiovascular Research* 2014;101(4):579-586. doi:10.1093/cvr/cvu018.

12. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009;53: 944–951.

13. Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. *CMAJ*2008;179: 229–234.

14. Diabetes Prevention Program Research Group.*N Eng J Med*2002;346: 393–403.

15. Tuomilehto J, Lindstro¨m J, Eriksson JG, Valle TT, Ha¨ma¨ la¨ inen H, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Eng J Med* 2001;344: 1343–1350.

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

17. World Health Organisation (WHO) 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.2007.

18. NICE guidelines (CG107).2010.Available at http://www.nice.org.uk/guidance/CG107/chapter/1-Guidance; (accessed on June 6 2014)

19. XieXi-tao, LiuQ, Jie WU, Makoto W. Impact of cigarette smoking in type 2 diabetes development. *Acta Pharmacol Sin*2009;30(6): 784–787.

20. Agrawal S, Fledderjohann J, Vellakkal S, Stuckler D. Adequately Diversified Dietary Intake and Iron and Folic Acid Supplementation during Pregnancy Is Associated with Reduced Occurrence of Symptoms Suggestive of PreEclampsia or Eclampsia in Indian Women. *PLoS ONE*2015;10(3): e0119120. doi:10.1371/journal.pone.0119120

21. Carlsson S, Hammar N, Grill V, Kaprio J. Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. *Diabetes Care*2003;26(10):2785-90.

22. Singh S, Behera A. Eclampsia in Eastern India: Incidence, Demographic Profile and Responseto Three different Anticonvulsant Regimes of Magnesium Sulphate. *The Internet Journal of Gynecologyand Obstetrics* 2010; 15(2).

23. Parretti E, lapolla A, Dalfra MG, Pacini G, Mari A, et al. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. *Hypertension* 2006; 47: 449–453.

24. Sierra–Laguado J, Garcia RG, Celedo´n J, Arenas-Mantilla M, Pradilla LP, et al. Determination of insulin resistance using the homeostatic model assessment (HOMA) and its relation with the risk of developing pregnancy–induced hypertension. *Am J Hypertens*2007;20: 437–442.

25. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. *Am J Obstet Gynecol*2009;200: 58.e1–58.e8.

26. Soonthornpun K, Soonthornpun S, Wannaro P, Setasuban W, Thamprasit A. Insulin resistance in women with a history of severe pre–eclampsia. *J Obstet Gynaecol Res*2009;35: 55–59.

27. Martillotti G, Boulvain M, Landau R, Pechère-Bertschi A. [Is preeclampsia a new cardiovascular and end-stage renal diseases risk marker?]. [Article in French] *Rev Med Suisse* 2009 Sep 9;5(216):1752-4, 1756-7.

28. PintoPV, ReiM, MachadoAP, Montenegro N. Preeclampsia and Future Cardiovascular Risk: Are Women and General Practitioners Aware of This Relationship? The Experience from a Portuguese Centre. *Obstetrics and Gynecology International*2014; Article ID 531539, 7 pages. http://dx.doi.org/10.1155/2014/531539

29. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation* 2011;123:1243–1262.

Table 1: Sample distribution, number and distribution of diabetes cases and prevalence of diabetes according to PE&E and other factors among Indian women, 2005-06

Characteristics	Sample size	Diabetes cases		Diabetes prevalence %	Chi sq p value
	%[N]	Reported %[N]	Not reported %[N]		
Total	39612	512		1.3	
Preeclampsia symptoms					<0.0001
No	71.3[28250]	59.5[304]	71.5[27933]	1.1	
Yes	28.7[11361]	40.5[207]	28.5[11147]	1.8	
Eclampsia symptoms					<0.0001
No	89.7[35541]	83.4[426]	89.8[35096]	1.2	
Yes	10.3[4071]	16.6[85]	10.2[3984]	2.1	
Body Mass Index					0.023
Underweight (≤18.5kg/m^2)	38.0[14440]	41.8[208]	38.0[14227]	1.4	
Normal (18.5-22.9kg/m^2)	46.9[17833]	40.6[202]	47.0[17622]	1.1	
Overweight (23.0-24.9kg/m^2)	7.3[2766]	9.4[47]	7.3[2720]	1.7	
Obese (≥25.0kg/m^2)	7.8[2964]	8.2[41]	7.8[2919]	1.4	
Current Tobacco smoking					0.259
No	98.5[39006]	98.0[501]	98.5[38484]	1.3	
Yes	1.5[606]	2.0[10]	1.5[596]	1.7	
Drinks Alcohol					0.001
No	97.7[38690]	98.3[488]	97.7[38184]	1.3	
Yes	2.3[911]	4.7[24]	2.3[886]	2.6	
Frequency of TV viewing					0.001
Not at all	43.8[17351]	50.9[260]	43.7[17076]	1.5	
Less than once a week	11.3[449]	13.3[68]	11.3[4423]	1.5	
At least once a week	10.3[4074]	9.0[46]	10.3[4027]	1.1	
Almost everyday	34.6[13689]	26.8[137]	34.7[13548]	1.0	
Access to healthcare					<0.0001
Public Medical sector	31.3[11313]	34.5[162]	31.3[11138]	1.4	
NGO or Trust or Clinic	0.3[113]	0.9[4]	0.3[109]	3.5	
Private Medical Sector	68.1[24591]	63.4[298]	68.1[24279]	1.2	
Other source	0.3[119]	1.3[6]	0.3[112]	5.1	
Food and micronutrient intake					
Diversified dietary intake					0.193
Inadequate	68.9[27275]	68.8[26895]	70.7[362]	1.3	
Adequate	31.1[12337]	31.2[12185]	29.3[150]	1.2	
Intake of Iron and folic acid supplementation					0.212
No	74.7[29588]	74.7[29183]	76.3[390]	1.3	
Yes	25.3[10024]	25.3[9897]	23.7[121]	1.2	
Milk or curd					<0.0001
Never/occasionally	48.1[19046]	56.8[290]	48.0[18745]	1.5	
Daily/weekly	51.9[20561]	43.2[221]	52.0[20331]	1.1	
Pulses or beans					<0.0001
Never/occasionally	10.1[4014]	10.1[3935]	10.1[3935]	1.9	
Daily/weekly	89.9[35588]	89.9[35137]	89.9[35137]	1.2	
Vegetables					0.075
Never/occasionally	7.1[2804]	7.1[2759]	7.1[2759]	1.6	
Daily/weekly	92.9[36795]	92.9[36310]	92.9[36310]	1.3	

Fruits					0.002
Never/occasionally	65.7[26043]	72.0[368]	65.7[25663]	1.4	
Daily/weekly	34.2[13541]	28.0[143]	34.3[13390]	1.1	
Eggs					0.084
Never/occasionally	69.7[27601]	72.6[371]	69.7[27216]	1.3	
Daily/weekly	30.3[11985]	27.4[140]	30.3[11841]	1.2	
Fish					0.003
Never/occasionally	73.3[29043]	67.9[347]	73.4[28679]	1.2	
Daily/weekly	26.7[10558]	32.1[164]	26.6[10392]	1.6	
Chicken/meat					0.004
Never/occasionally	78.7[31158]	83.6[428]	78.6[30714]	1.4	
Daily/weekly	21.3[8439]	16.4[84]	21.4[8352]	1.0	
Socio-demographic characteristics					
Age groups					0.001
15-19	7.5[2982]	10.2[52]	7.5[2928]	1.7	
20-24	33.5[13269]	29.0[148]	33.6[13113]	1.1	
25-29	32.6[12908]	27.2[139]	32.7[12767]	1.1	
30-34	16.9[6685]	18.8[96]	16.8[6584]	1.4	
35-39	6.9[2723]	11.0[56]	6.8[2667]	2.1	
40-44	2.1[835]	2.7[14]	2.1[818]	1.7	
45-49	0.5[210]	1.2[6]	0.5[204]	2.9	
Education					0.064
No education	18758[47.4]	51.4[263]	47.3[18480]	1.4	
Primary	5545[14.0]	14.6[75]	14.0[5470]	1.4	
Secondary	12947[32.7]	30.3[155]	32.7[12790]	1.2	
Higher	2361[6.0]	3.7[19]	6.0[2339]	0.8	
Employment status					0.143
Currently not working	27665[69.9]	67.7[346]	70.0[27309]	1.3	
Working	11886[30.1]	32.3[165]	30.0[11713]	1.4	
Religion					0.035
Hindu	31248[78.9]	76.8[393]	78.9[30836]	1.3	
Muslim	6472[16.3]	17.2[88]	16.3[6383]	1.4	
Christian	811[2.0]	3.9[20]	2.0[791]	2.5	
Sikhs	513[1.3]	0.8[4]	1.3[509]	0.8	
Others	568[1.4]	1.4[7]	1.4[561]	1.2	
Caste/tribe					<0.0001
Scheduled caste	7938[20.1]	21.3[109]	20.1[7825]	1.4	
Scheduled tribes	3740[9.4]	13.7[70]	9.4[3666]	1.9	
Other backward class	15861[40.2]	30.3[155]	40.3[15696]	1.0	
General	10830[27.4]	30.9[158]	27.4[10669]	1.5	
Missing caste	1085[2.8]	3.7[19]	2.7[1060]	1.8	
Wealth index					<0.0001
Lowest	9553[24.1]	32.4[166]	24.0[9381]	1.7	
Second	8588[21.7]	22.3[114]	21.7[8465]	1.3	
Middle	7762[19.6]	19.9[102]	19.6[7661]	1.3	
Fourth	7251[18.3]	15.6[80]	18.3[7168]	1.1	
Highest	6458[16.3]	9.8[50]	16.4[6405]	0.8	
Place of residence					0.001
Urban	10615[26.8]	20.3[104]	26.9[10506]	1.0	
Rural	28997[73.2]	79.7[408]	73.1[28574]	1.4	
Geographic Regions					<0.0001
North	5076[12.8]	9.4[48]	12.9[5028]	0.9	

Northeast	1607[4.1]	5.9[30]	4.0[1576]	1.9
Central	11099[28.0]	17.8[91]	28.4[11000]	0.8
East	10031[25.3]	48.3[247]	25.0[9777]	3.5
West	5114[12.9]	6.1[31]	13.0[5081]	0.6
South	6684[16.9]	12.5[64]	16.9[6618]	1.0

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

Table 2: Unadjusted and partially adjusted and fully adjusted odds ratios (ORs) and 95% confidence interval (95%CI) showing the association between PE&E and other factors and diabetes risk among Indian women, 2005-06

	Unadjusted Model 1	Adjusted Model 2	Adjusted Model 3	Adjusted Model 4
	OR[95%CI]	OR[95%CI]	OR[95%CI]	OR[95%CI]
Preeclampsia symptoms				
No [Ref]	1	1	1	1
Yes	1.71[1.43-2.04]	1.62[1.33-1.96]	1.59[1.31-1.93]	1.59[1.31-1.94]
Eclampsia symptoms				
No [Ref]	1	1	1	1
Yes	1.76[1.40-2.23]	1.48[1.15-1.91]	1.50[1.16-1.95]	1.36[1.05-1.77]
Body Mass Index				
Underweight (≤18.5 kg/m^2)		1.24[1.01-1.52]	1.21[0.99-1.49]	1.17[0.95-1.44]
Normal (18.5-22.9 kg/m^2) [Ref]		1	1	1
Overweight (23.0-24.9 kg/m^2)		1.74[1.25-2.42]	1.78[1.27-2.47]	2.01[1.43-2.81]
Obese (≥25.0 kg/m^2)		1.47[1.02-2.10]	1.52[1.06-2.19]	1.85[1.26-2.72]
Current tobacco smoking				
No [Ref]		1	1	1
Yes		1.13[0.60-2.11]	1.13[0.60-2.12]	0.88[0.46-1.68]
Current alcohol drinking				
No [Ref]		1	1	1
Yes		1.93[1.26-2.95]	1.81[1.17-2.79]	1.36[0.84-2.20]
Frequency of TV viewing				
Not at all [Ref]		1	1	1
Less than once a week		1.04[0.78-1.38]	1.03[0.77-1.38]	1.21[0.90-1.63]
At least once a week		0.81[0.58-1.13]	0.84[0.60-1.18]	1.02[0.72-1.46]
Almost everyday		0.72[0.57-0.90]	0.80[0.62-1.02]	1.18[0.87-1.61]
Access to healthcare				
Public Medical sector [Ref]		1	1	1
NGO or Trust or Clinic		2.03[0.71-5.76]	2.06[0.72-5.91]	1.76[0.60-5.18]
Private Medical Sector		0.84[0.69-1.02]	0.89[0.73-1.08]	0.89[0.72-1.10]
Other source		3.16[1.31-7.59]	3.08[1.27-7.44]	2.57[1.05-6.33]
Food and micronutrient intake				
Diversified dietary intake				
Inadequate [Ref]			1	1
Adequate			1.54[1.16-2.04]	1.46[1.10-1.94]
Intake of Iron and folic acid supplementation				
No [Ref]			1	1
Yes			1.20[0.81-1.29]	1.11[0.87-1.41]
Milk or curd				
Never/occasionally [Ref]			1	1
Daily/weekly			0.87[0.71-1.07]	1.06[0.85-1.31]
Pulses or beans				
Never/occasionally [Ref]			1	1
Daily/weekly			0.76[0.58-1.00]	0.80[0.60-1.07]
Vegetables				
Never/occasionally [Ref]			1	1
Daily/weekly			0.90[0.65-1.25]	0.81[0.58-1.13]
Fruits				
Never/occasionally [Ref]			1	1

Daily/weekly	0.92[0.73-1.15]	1.05[0.82-1.33]
Eggs		
Never/occasionally [Ref]	1	1
Daily/weekly	0.90[0.70-1.16]	0.80[0.62-1.03]
Fish		
Never/occasionally [Ref]	1	1
Daily/weekly	1.76[1.38-2.25]	1.12[0.87-1.46]
Chicken/meat		
Never/occasionally [Ref]	1	1
Daily/weekly	0.60[0.45-0.80]	0.75[0.56-1.02]
Socioeconomic and demographic characteristics		
Age		
15-19 [Ref]		1
20-24		0.83[0.58-1.18]
25-29		0.71[0.49-1.02]
30-34		0.86[0.58-1.27]
35-39		1.25[0.81-1.91]
40-44		0.99[0.53-1.86]
45-49		1.49[0.60-3.68]
Education		
No education [Ref]		1
Primary		0.92[0.68-1.25]
Secondary		1.15[0.87-1.52]
Higher		0.96[0.53-1.74]
Employment status		
Currently not working [Ref]		1
Working		1.21[0.91-1.38]
Religion		
Hindu [Ref]		1
Muslim		1.00[0.74-1.35]
Christian		1.53[0.90-2.60]
Sikhs		0.79[0.27-2.31]
Others		0.65[0.29-1.47]
Caste/tribe		
Scheduled caste [Ref]		1
Scheduled tribes		0.97[0.68-1.38]
Other backward class		0.65[0.50-0.85]
General		1.11[0.83-1.49]
Missing caste		0.48[0.24-0.95]
Wealth index		
Lowest [Ref]		1
Second		0.89[0.68-1.16]
Middle		0.80[0.58-1.09]
Fourth		0.76[0.52-1.11]
Highest		0.45[0.27-0.78]
Place of residence		
Urban [Ref]		1
Rural		1.01[0.77-1.34]
Geographic Regions		
North [Ref]		1
Northeast		1.82[1.06-3.13]
Central		0.93[0.62-1.39]

East	2.68[1.83-3.93]
West	0.69[0.42-1.15]
South	1.28[0.82-1.99]
Number of cases	34978

*Note: [Ref] denotes reference category; Model 1 unadjusted; Model 2 adjusted for BMI, tobacco smoking, alcohol drinking, TV watching and access to healthcare; Model 3 adjusted for Model 2+ specific dietary intakes; Model 4 adjusted for all

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Hypertensive disorders of pregnancy and risk of diabetes in Indian Women: A Cross-sectional Study

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Data sharing statement: The authors confirm that all data underlying the findings are fully available without restriction. Data are publicly available from the Demographic and Health Surveys website: http://dhsprogram.com/what-we-do/survey/survey-display-264.cfm.

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Article Summary

Strength and limitations of this study

- Epidemiological data from high income countries suggests that women with HDP are more likely to develop cardiovascular risk, including diabetes, later in life. There is no empirical evidence of an association in low-and middle- income countries, which have the highest burden.
- Our study provided strong evidence of an increased risk of diabetes among women reporting symptoms suggestive of preeclampsia or eclampsia during their last pregnancy. This positive relationship is robust even after adjustment for a comprehensive range of established risk factors for diabetes, possible clustering of lifestyles, other factors that may accompany HDP (e.g., smoking, alcohol intake, and access to healthcare), dietary predictors of diabetes (i.e. food consumption), BMI, and education level.
- To our knowledge, this is the largest nationally representative cross-sectional study of the population-based association between pregnancy induced preeclampsia or eclampsia symptoms and diabetes risk in an Asian population.
- A history of preeclampsia or eclampsia during pregnancy should alert clinicians to the need for preventative counselling and more vigilant screening for diabetes.
- These findings are important for a country such as India, which is tackling the dual-burden of NCDs and infectious diseases among its female population.

Abstract

Background: Epidemiological data from high income countries suggests that women with hypertensive disorders during pregnancy (HDP) are more likely to develop diabetes later in life.

Objective: We investigated the association between preeclampsia and eclampsia (PE&E) during pregnancy and the risk of diabetes in Indian women.

Design: Cross-sectional study

Setting: India

Methods: Data from India's third National Family Health Survey (NFHS-3, 2005-06), a cross-sectional survey of women aged 15-49 years, are used. Self-reported symptoms suggestive of PE&E were obtained from 39,657 women who had a live birth in the five years preceding the survey. The association between PE&E and self-reported diabetes status was assessed using multivariable logistic regression models adjusting for dietary intake, BMI, tobacco smoking, alcohol drinking, frequency of TV watching, socio-demographic characteristics and geographic region.

Results: The prevalence of symptoms suggestive of PE&E in women with diabetes was 1.8% (n=207)(95%CI:1.5-2.0;p<0.0001) and 2.1% (n=85) (95%CI:1.8-2.3;p<0.0001) respectively, compared with 1.1%(n=304) (95%CI:1.0-1.4)and 1.2% (n=426) (95%CI:1.1-1.5) in women who did not report any PE&E symptoms. In the multivariable analysis, PE&E was associated with 1.6 times (OR=1.59;95% CI:1.31–1.94;p<0.0001) and 1.4 times (OR=1.36;95% CI:1.05–1.77;p=0.001) higher risk for self-reported diabetes even after controlling for dietary intake, BMI, and socio-demographic characteristics.

Conclusion: HDP is strongly associated with the risk of diabetes in a large nationally representative sample of Indian women. These findings are important for a country which is already tackling the burden of young onset of diabetes in the population. However, longitudinal medical histories and a clinical measurement of diabetes are needed in this low resource setting.

Keywords: preeclampsia; eclampsia; diabetes; women; India; NFHS-3

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) represent a group of conditions marked by high blood pressure during pregnancy, proteinuria, and in some cases convulsions. Gestational hypertension, preeclampsia and eclampsia (PE&E) are the most common HDP. The most serious consequences for the mother and the baby result from PE&E.[1] Preeclampsia is a syndrome of pregnancy, defined by the onset of hypertension and proteinuria and characterised by widespread dysfunction of the endothelium in the mother.[2] Eclampsia is usually a consequence of preeclampsia, and consists of central nervous system seizures unrelated to conditions such as epilepsy, which often leave the patient unconscious; if untreated it may lead to death. Worldwide HDP are more common, and may complicate 5%-10% of all pregnancies. HDP are responsible for 12-25% of cases of maternal mortality during pregnancy and the puerperium.[3,4] PE&E are leading threats to safe motherhood in developing countries, where a woman is seven times more likely to develop these conditions[5]. In such settings, it is estimated that 10-25% of these cases (an estimated ~40,000 women) lead to maternal deaths annually.[5]

Increasing evidence indicates that PE&E is not just a disease of pregnancy that resolves at the time of delivery, but rather it represents a risk marker of cardiovascular diseases later in life.[6] Studies in western populations examining the risk of developing type 2 diabetes in women with a history of preeclampsia have found a positive association equalling the risk attributed to obesity and smoking.[7-11] The Danish National Patient Registry study, for example, found that preeclampsia is associated with a 3.1 to 3.7 fold risk of developing type 2 diabetes.[12] Similarly, a recent population-based study of more than 1 million women found that women with preeclampsia or gestational hypertension have a twofold increased risk of developing diabetes after pregnancy.[13]

Studies showing the association between HDP and diabetes are generally based on non-representative clinical data and/or are based on data from western settings. Investigation of the links between PE&E symptoms and diabetes in low and middle income countries (LMICs), which have the highest burden of these conditions, has been severely limited. Randomized trials have shown that diabetes can be prevented or delayed in high-risk groups by a variety of lifestyle and therapeutic interventions.[14,15] However, identifying at-risk populations to screen for diabetes in a low resource setting such as India is a critical step in translating these findings into clinical practice. HDP such as preeclampsia may heighten the propensity for women to develop diabetes in the years following pregnancy; such women may also

be suitable targets for diabetes prevention. We investigated the association between PE&E during pregnancy and diabetes risk in a large nationally representative sample of Indian women.

MATERIALS AND METHODS

Data

Data from the Indian National Family Health Survey (NFHS-3) for the years 2005/2006 are used in the study. The NFHS-3 is a large, well-established, nationally representative survey based on a multi-stage cluster random sampling design that provides high-quality information on the health and nutrition of women and children in India with an overall response rate of 98%.[16] The NFHS is the Indian equivalent of the Demographic and Health Surveys, a standardised series of surveys routinely conducted in more than 80 developing countries. All data from these surveys are in the public domain and can be downloaded, after registration, from http://www.measuredhs.com. The NFHS has been conducted in India for three successive rounds, each at an interval of 5 years. The NFHS-3 collected demographic, socioeconomic, and health information from a nationally representative probability sample of 124,385 women aged 15–49 years residing in 109,041 households. All states of India are represented in the sample (except the small Union Territories), covering more than 99% of the country's population. The survey was conducted using an interviewer-administered questionnaire in the native language of the respondent using a local, commonly understood term for any diseases. A total of 18 languages were used with back-translation to English to ensure accuracy and comparability. Full details of the survey have been published elsewhere.[16]

To examine the association between HDP and risk of diabetes, we restricted the sample to only 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 to minimize recall bias. Missing data were dropped using list wise deletion. This resulted in a final sample size of 39,657 participants for the analysis.

Outcome evaluation

The survey includes self-report data relating to specific health problems of the mother, including whether the respondent currently has diabetes.[16] Specifically, respondents were asked: 'Do you currently have diabetes?' with the response options of 'yes', 'no' and 'don't know'. Notably, self-

reported diabetes is not as accurate as clinical measures of diabetes; however, no physician diagnosis or fasting blood glucose measures were included in the NFHS-3.[16]

Predictor variables

The NFHS-3 contains several items related to health problems during pregnancy. As physical markers such as blood pressure, proteinuri) used in the clinical diagnosis of PE&E were not measured in the NFHS-3, we used three self-reported health items to construct a measure of PE&E. Specifically, in relation to their current or most recent pregnancy, 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 Organisation[17] and National Institute for Health and Care Excellence[18] guidelines, and NFHS-3 coding by Agrawal et al[19], we created a dichotomous indicator for PE&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 preeclampsia, while those who additionally reported experiencing convulsions (not from fever) were coded as eclamptic.

Covariates

In order to reduce the possibility that the association between PE&E and diabetes was driven by confounders, we included several sociodemographic control variables. Height and weight data were collected by the NFHS-3 interview staff, and BMI (measured as kg/m^2) was calculated based on this data.[16] We used standard Asian Population cut-offs[20-22] for the BMI measure, with thresholds defined as ≤18.4 kg/m^2 (underweight), 18.5 to 22.9 kg/m^2 (normal), 23.0 to 24.9 kg/m^2 (overweight), and ≥25 kg/m^2 (obese). Women who were pregnant at the time of the survey or women who had given birth during the two months preceding the survey were excluded from these measurements. In addition, previous studies have found that smokers are insulin resistant, exhibit several aspects of the insulin resistance syndrome, and are at an increased risk for type 2 diabetes[23], while moderate alcohol consumption may reduce the risk of type 2 diabetes. On the other hand, binge drinking and high alcohol consumption may increase the risk of type 2 diabetes.[24] We included controls for smoking and drinking behaviour: 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. We constructed a dichotomous indicator of current alcohol use in the present analysis. Frequency of watching television (almost every day, at least once weekly, less than once weekly, not at all), a categorical variable in the NFHS data, was used as a measure of sedentary behaviour. We measured access to healthcare with a categorical indicator of type of healthcare facility used (public medical sector, NGO trust hospital or clinic, private medical sector, and other sources). Previous work[19] has shown that iron intake and consuming a diversified diet is associated with a reduced risk of PE&E. Dietary intake as indicated by consumption of selected foods was assessed by asking, 'How often do you yourself consume the following items: daily, weekly, occasionally or never?' related to the consumption of milk or curd, pulses or beans, green leafy vegetables, other vegetables, fruits, eggs, and chicken, meat or fish.[16]

In order to reduce the risk of unobserved homogeneity in our models, we included a variety of socio-demographic controls. The socio-demographic factors considered in the present analysis included age in 5 year intervals (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49); education, classified as no education, primary (5–7 years completed), secondary (8–9 years) or higher (10+ years); employment status (currently not working, working);religion (Hindu, Muslim, Christian, Sikhs, Others); caste/tribe (Scheduled Castes, Scheduled Tribes, Other Backward Class, General); a standard wealth index compiled by the NFHS-3 (measured by an index based on household ownership of assets and graded as lowest, second, middle, fourth and highest); place of residence (urban, rural); and geographic regions of India (north, northeast, central, east, west, south).

Statistical Analysis

Descriptive statistics were calculated for all variables using standard methods. Differences in categorical variables were tested using Pearson's χ^2 tests. Multivariable logistic regression analysis was used to estimate the effect of symptoms suggestive of PE&E on self-reported diabetes risk. In the first logistic regression model, we examined the unadjusted association between PE&E symptoms and diabetes risk independent of each other. In the second model, we adjusted for BMI status, tobacco smoking, alcohol drinking, frequency of TV watching, and access to healthcare in order to assess how much of the variance in this association was explained by those factors. In the third model, we added food and micronutrient intake to our model. In the fourth and final model, we added socio-demographic characteristics in order to examine the association between PE&E symptoms and diabetes risk controlling for the confounders discussed above.

To adjust for the NFHS-3 sampling design, a sample weight was also included in the models.[11] Results are presented as odds ratios with 95% confidence intervals (OR;95%CI). The estimation of confidence intervals takes into account design effects due to clustering at the level of the primary sampling unit. Before carrying out the multivariate model, the possibility of multicollinearity between the covariates was assessed. In the correlation matrix of covariates, all pairwise Pearson correlation coefficients were found to be <0.5, suggesting that multicollinearity did not affect the findings. All analyses were conducted using the SPSS statistical software package Version 19 (IBM SPSS Statistics, Chicago, Illinois, USA).

Ethical considerations

The NFHS-3 survey received ethical approval from the International Institute for Population Science's Ethical Review Board and Indian Government. Prior informed written consent was obtained from each respondent. The analysis presented in this study is based on secondary analysis of existing survey data with all identifying information removed; no ethical approval was required.

RESULTS

Table 1 presents the descriptive statistics for the sample, and bivariate associations between diabetes and PE&E. Overall, 28.7% (n=11,361) women reported symptoms suggestive of preeclampsia during their last pregnancy, and one out of ten women (10.3%; n=4071) reported symptoms suggestive of eclampsia. Thirty-eight percent were underweight, while 15% were either overweight or obese. A very small number were current smokers (1.5%) or alcohol drinkers (2.3%), while 68% had access to the private medical sector to obtain their health care. One third viewed TV almost every day. Most mothers (nearly 75%) were aged between 15-29 years, and almost half (47%) had no education. Seventy percent were not employed at the time of survey. A majority of the mothers (four out of five) identified as Hindu, and two-fifths belonged to a scheduled caste. One fourth belonged to a household in the poorest wealth quintile. More than 70% of the mothers were residing in rural areas, while 28% were residents of Central India. Half of the mothers reported of consuming milk/curd, and a majority reported of consuming pulses/beans and vegetables on a daily or weekly basis. However, only one third reported of consuming fruit (34%) and eggs (30%) and only one fourth or less consumed fish (27%) or chicken/meat (21%) on a daily or weekly basis.

Of the women reporting diabetes, two out of five (41%) also reported symptoms suggestive of preeclampsia, and 17% reported symptoms of eclampsia (Table 1). Eighteen percent were either obese or overweight; 2% were currently smoking tobacco; 5% were alcohol drinkers; half reported not watching TV at all; one in three reported visiting the public medical sector for healthcare needs; two-thirds (66%) were in the age group 15-29 years; half of them had no education; 77% were Hindus; 31% belonged to general category; 68% were not working; two-fifths belong to household with poorest wealth quintile; a majority resided in a rural area; and half resided in eastern India. Among the women who reported diabetes, a majority of them reportedly consumed pulses/beans and vegetables on a daily/weekly basis and more than two-fifth also reported consuming milk/curd daily/weekly, while consumption of fruits (28%), eggs (27%), fish (32%) or chicken meat (16%) was less frequent.

The prevalence of symptoms suggestive of PE&E in women with diabetes was 1.8% (95%CI:1.5-2.0;p<0.0001) and 2.1% (95%CI:1.8-2.3;p<0.0001) respectively, compared with 1.1% (95%CI:1.0-1.4) and 1.2% (95%CI:1.1-1.5) in women who did not report any PE&E symptoms (Table 1). Overweight (1.7%) or obese (1.4%) women had higher prevalence of diabetes than those who were underweight (1.4 %) and normal weight (1.1%). A higher proportion of current tobacco smokers (1.7%) and current alcohol drinkers (2.6%) also reported diabetes compared to those who did not engage in these risk behaviours. Compared to those using public sector facilities, women who had access only to other sources for health care (5.1%) and NGO or Trust or Clinic (3.5) had higher prevalence of diabetes. Women reporting viewing TV not at all or less than once a week reported higher diabetes (1.5%) than more frequent viewers. Women consuming milk/curd (1.1% vs 1.5%), pulses/beans (1.2% vs 1.9%), vegetables (1.3% vs 1.6%), fruits (1.1% vs 1.4%), eggs (1.2% vs 1.3%), or chicken/meat (1.0% vs 1.4%) except fish (1.6% vs 1.2%) on a daily/weekly basis had a lower prevalence of diabetes than those who never or occasionally consume them. Diabetes prevalence was higher among women aged 40-49 (2.9%) and 35-39 (2.1%) compared to women aged 15-29 years (1.2%). The prevalence of diabetes was also higher among women belonging to Christian religion (2.5%), among women belonging to a scheduled tribe (1.9%) compared to those in a scheduled caste (1.4%), women in the poorest wealth quintile (1.7%), women residing in rural areas (1.4%), and women living in eastern India (3.5%).

<Table 1 here>

Table 2 shows the results of multivariable logistic regression analyses in unadjusted, partially adjusted, and fully adjusted models. In the unadjusted analysis (Model 1), the likelihood of having diabetes was significantly higher among women who reported preeclampsia (OR:1.71;95%CI:1.43-2.04;p<0.0001) and eclampsia (OR:1.76;95%CI:1.40-2.23;p<0.0001) symptoms than among those who did not report these symptoms. Controlling for BMI, tobacco smoking, alcohol intake, TV watching, and healthcare access (in Model 2) slightly attenuated the positive relationship between preeclampsia (OR:1.62;95%CI:1.33-1.96;p<0.0001) and eclampsia (OR:1.48;95%CI:1.15-1.91;p=0.003) symptoms and diabetes, but the association remained positive, strong, and significant. The positive association between preeclampsia (OR:1.59;95%CI:1.31-1.93;p<0.0001) or eclampsia (OR:1.50;95%CI:1.16-1.95;p=0.002) and diabetes remained virtually unchanged when specific food and micronutrient intakes were additionally controlled for in Model 3. The final model (Model 4) in Table 2 provides the fully adjusted analysis with all covariates included. Jointly controlling for all of these factors, the positive association between symptoms suggestive of preeclampsia(OR:1.59;95%CI:1.31-1.94;p<0.0001) or eclampsia (OR:1.36;95%CI:1.05-1.77;p=0.020) during pregnancy and diabetes remained strong and statistically significant.

As shown in the full model (Model 4) in Table2, with all other variables controlled for, being overweight (OR:2.01;95%CI:1.43-2.81;p=0.030) or obese (OR:1.85;95%CI:1.26-2.72;p=0.010) had a positive and statistically significant effect on risk of diabetes among women. Women seeking healthcare from other sources had 2.5 times higher odds of diabetes (OR:2.57;95%CI:1.05-6.33;p=0.015) compared to those accessing healthcare through the public sector. Women consuming an adequately diversified diet also had a higher likelihood of reporting diabetes (OR:1.46;95%CI:1.10-1.94;p=0.005) than women consuming an inadequately diversified diet. Women residing in northern (OR:1.82;95%CI:1.06-3.13;p=0.005) and eastern regions of India (OR:2.68;95%CI:1.83-3.93;p=0.001) also had a higher likelihood of reporting diabetes risk than women residing in other parts of India. The remaining covariates were not significantly associated with odds of reporting diabetes.

DISCUSSION

In this study, we examined the association between HDP, focusing specifically on PE&E, and diabetes risk in a large, nationally representative sample of Indian women. We observed strong evidence of an increased risk of diabetes among women reporting symptoms suggestive of PE&E during their last

pregnancy. This association is robust, as we have adjusted for a comprehensive range of established risk factors of diabetes and possible clustering of lifestyles and other factors that may accompany HDP (e.g., smoking, alcohol intake, access to healthcare) and dietary predictors of diabetes (i.e. food consumption), BMI, and education level. Interestingly, we found evidence of an association between diabetes and lifestyle factors (e.g. watching television), as well as evidence of regional variation in the prevalence of diabetes. However, many of these associations were attenuated or non-significant in the adjusted models, highlighting the importance of the socio-demographic patterning of lifestyle and health behaviours.

To our knowledge, this is the largest nationally representative cross-sectional study at the population level showing the association between PE&E and diabetes risk in an Asian population. Another strength of this study is our ability to adjust for obesity, which in itself is associated with insulin resistance, and is a well-known risk factor for the development of diabetes and preeclampsia. These findings highlight and support the need to counsel patients with hypertensive disorders during pregnancy regarding postpartum diabetes screening and prevention in a developing country setting.

The long term sequelae of both PE&E are not well-evaluated in LMICs. This lack of evidence is particularly problematic in India, where the rate of HDP-related maternal mortality is high[1], and PE&E are thought to underlie around 5-10% of pregnancy complications and about 8-9% of maternal deaths in India.[25] Some clinical studies suggest that the proportion of deliveries impacted by PE&E in Indian women ranges from as low as 0.9% to as high as 7.7% of all deliveries.[25] 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.

Common pathogenic pathways may underlie the association between women with a history of preeclampsia and an increased risk of diabetes as each of these conditions is associated with manifestations of metabolic syndrome (including endothelial dysfunction, obesity, hypertension, hyperglycemia, insulin resistance, renal disease, and dyslipidemia). Metabolic syndrome is known for its association with insulin resistance during pregnancy[26-28], which may be independent of obesity and glucose intolerance.[26,27,29] These conditions may subsequently predispose women to develop hypertension, atherosclerosis, and type 2 diabetes mellitus in later life, which eventually lead to

cardiovascular disease.[10,11,30] Other possible explanations for this association include the following: (a) as both cardiovascular disease and preeclampsia share common risk factors, pregnancy serve as a "stress test", with the development of HDP identifying a woman at high risk of developing cardiovascular disease later in life[31]; (b) pregnancy, and especially PE&E, may induce permanent arterial changes; the proatherogenic stress of pregnancy, often excessive in women with preeclampsia, could activate arterial wall inflammation that fails to resolve after delivery, increasing the risk of future cardiovascular disease.[11] Women with early onset/severe preeclampsia, recurrent preeclampsia, or preeclampsia with onset as a multipara appear to face the highest risk of cardiovascular disease later in life, including during the premenopausal period.[6]

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 preeclampsia and diabetes. It is possible that self-reported data may suffer from recall bias. Moreover, many pregnant women may experience oedema that is not symptomatic of preeclampsia, and vision difficulties may be indicative not only of preeclampsia, but also secondary to gestational diabetes. Although we cannot rule out the possibility of misclassification within this context, it is unlikely that we have missed severe PE&E or diabetes cases due to the generally clear manifestation of symptoms in severe cases. However, mild cases of preeclampsia may be asymptomatic, and would likely be missed by our measure here. This possibility limits the applicability of our findings, as the majority of patients in clinical practice have mild to moderate preeclampsia, and may comprise much of this asymptomatic group. The presence or absence of convulsions may have greater face validity as a measure of eclampsia (as compared to swelling and blurred vision for preeclampsia), and we thus have greater confidence in our findings for eclampsia. Notably, however, we included preeclampsia and eclampsia as separate measures in the models, but found the coefficients for these measures to be in the same direction and of similar magnitude, providing some confidence in the validity of our measure of preeclampsia as well.

Second, due to the nature of the data, we could not identify precise timing during the gestational period of preeclampsia symptoms, nor the precise onset of diabetes. However, the majority of individuals with type 2 diabetes mellitus have no symptoms and can be misclassified as non-diabetics in the self-reports. This error may in fact strengthen our findings. Furthermore, family history, physical activity, glucose, and

blood pressure measures are also known risk factors for diabetes, which were not collected in the survey. From the data used here, we could not differentiate type 1 from type 2 diabetes; however, given that the mean age of the women was 26.4 y (±5.6SD), it is most likely that the majority of the women developed type 2 diabetes. We were, however, able to adjust for several other important confounding variables including socioeconomic and demographic factors, lifestyle indicators, and access to health care.

Conclusions

In summary, this study provides some initial empirical evidence that HDP, specifically symptoms suggestive of PE&E during pregnancy, are strongly associated with diabetes in a large nationally representative sample of Indian women. This initial evidence provides an impetus for further evaluation. These findings have important implications for maternal and child health, especially given the increase in obesity-related diseases in this low resource setting. A history of PE&E during pregnancy should alert clinicians to the need for preventative counselling and more vigilant screening for diabetes, and women should be encouraged to have a more rigorous follow-up and adopt a healthier lifestyle. Indeed, lifestyle factors were significantly associated with diabetes in our study (e.g. television viewing, dietary patterns). While these associations were attenuated by the inclusion of socio-demographic controls, this attenuation likely points to the socioeconomic gradient in lifestyle and health behaviours. Follow-up and counselling of women with a history of PE&E may offer a window of opportunity for prevention of future diabetes mellitus and cardiovascular disease. Patient and healthcare provider education is also essential for the successful assessment and management of cardiovascular disease risk and prevention in the context of the long term burden associated with PE&E. Clinical awareness of a history of PE&E might allow the identification of cases not previously recognized as at-risk for diabetes, facilitating the implementation of preventive measures. Moreover, evaluation of women prior to pregnancy and follow-up during pregnancy is needed to determine the role of shared risk factors. Regular medical follow-up and earlier screening for cardiovascular disease should be considered in this population. At the least, current screening guidelines should be followed, and women should receive advice on established preventive lifestyle measures and treatment strategies that should be implemented by all women, regardless of a previous history of gestational hypertension/preeclampsia.[32] Further research to verify accuracy of reporting of the symptoms of PE&E is needed, and would be facilitated by longitudinal medical histories and a clinical measurement of diabetes in an Indian setting. Additional work is needed

to investigate the association between diabetes and mild preeclampsia, particularly asymptomatic cases that may be picked up in a clinical setting.

REFERENCES

1. Dolea C, AbouZahr C. Global Burden of obstructed labor in the year 2000: version 2. 2003. Geneva: WHO.

2. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001;20:IX-XIV.

3. World Health Organization Collaboration. The world health report: make every mother and child count. 2005. Department of Reproductive Health and Research, WHO. www.who.int/whr/2005/en/index.html (accessed Aug 2015).

4. Lo JO, Mission JF, Caughey AB. Hypertensive disease of pregnancy and maternal mortality. *Curr Opin Obstet Gynecol*2013;25(2):124-32. doi: 10.1097/GCO.0b013e32835e0ef5.

5. Maternal mortality in 2005: estimates developed by WHO, UNICEF, UNIFPA and the World Bank, Geneva, World Health Organization, 2007.

6. Garovic VD, Hayman SR. Hypertension in pregnancy: an emerging risk factor for cardiovascular disease. *Nat Clin Pract Nephrol* 2007;3(11):613-22.

7. Callaway LK, Lawlor DA, O'Callaghan M, Williams GM, Najman JM, et al. Diabetes mellitus in the 21 years after a pregnancy that was complicated by hypertension: findings from a prospective cohort study. *Am J Obstet Gynecol*2007;197: 492.e1–492.e7.

8. Harskamp RE, Zeeman GG. Preeclampsia: at risk for remote cardiovascular disease. *Am J Med Sci*2007;334: 291–295.

9. Engeland A, Bjorge T, Kjersti Daltveit AK, Skurtveit S, Vangen S, et al. Risk of diabetes after gestational diabetes and preelampsia. A registry-based study of 230,000 women in Norway. *Eur J Epidemiol*2011;26: 157–163.

10. Wang IK, Tsai IJ, Chen PC, Liang CC, Chou CY, Chang CT, Kuo HL, Ting IW, Lin CC, Chuang FR, Huang CC, Sung FC. Hypertensive disorders in pregnancy and subsequent diabetes mellitus: a retrospective cohort study. *Am J Med* 2012;125(3):251-7. doi: 10.1016/j.amjmed.2011.07.040.

11. Chen CW, Jaffe IZ, Karumanchi SA. Pre-eclampsia and cardiovascular disease. *Cardiovascular Research* 2014;101(4):579-586. doi:10.1093/cvr/cvu018.

12. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009;53: 944–951.

13. Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. *CMAJ*2008;179: 229–234.

14. Diabetes Prevention Program Research Group.*N Eng J Med*2002;346: 393–403.

15. Tuomilehto J, Lindstro¨m J, Eriksson JG, Valle TT, Ha¨ma¨ la¨ inen H, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Eng J Med* 2001;344: 1343–1350.

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

17. World Health Organisation (WHO) 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.2007.

18. NICE guidelines (CG107).2010.Available at http://www.nice.org.uk/guidance/CG107/chapter/1-Guidance; (accessed on June 6 2014)

19. Agrawal S, Fledderjohann J, Vellakkal S, Stuckler D. Adequately Diversified Dietary Intake and Iron and Folic Acid Supplementation during Pregnancy Is Associated with Reduced Occurrence of Symptoms Suggestive of PreEclampsia or Eclampsia in Indian Women. *PLoS ONE*2015;10(3): e0119120. doi:10.1371/journal.pone.0119120

20. 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.

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

22. 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.

23. XieXi-tao, LiuQ, Jie WU, Makoto W. Impact of cigarette smoking in type 2 diabetes development. *Acta Pharmacol Sin*2009;30(6): 784–787.

24. Carlsson S, Hammar N, Grill V, Kaprio J. Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. *Diabetes Care*2003;26(10):2785-90.

25. Singh S, Behera A. Eclampsia in Eastern India: Incidence, Demographic Profile and Responseto Three different Anticonvulsant Regimes of Magnesium Sulphate. *The Internet Journal of Gynecologyand Obstetrics* 2010; 15(2).

26. Parretti E, lapolla A, Dalfra MG, Pacini G, Mari A, et al. Preeclampsia in lean normotensive normotolerant pregnant women can be predicted by simple insulin sensitivity indexes. *Hypertension* 2006; 47: 449–453.

27. Sierra–Laguado J, Garcia RG, Celedo´n J, Arenas-Mantilla M, Pradilla LP, et al. Determination of insulin resistance using the homeostatic model assessment (HOMA) and its relation with the risk of developing pregnancy–induced hypertension. *Am J Hypertens*2007;20: 437–442.

28. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. *Am J Obstet Gynecol*2009;200: 58.e1–58.e8.

29. Soonthornpun K, Soonthornpun S, Wannaro P, Setasuban W, Thamprasit A. Insulin resistance in women with a history of severe pre–eclampsia. *J Obstet Gynaecol Res*2009;35: 55–59.

30. Martillotti G, Boulvain M, Landau R, Pechère-Bertschi A. [Is preeclampsia a new cardiovascular and end-stage renal diseases risk marker?]. [Article in French] *Rev Med Suisse* 2009 Sep 9;5(216):1752-4, 1756-7.

31. PintoPV, ReiM, MachadoAP, Montenegro N. Preeclampsia and Future Cardiovascular Risk: Are Women and General Practitioners Aware of This Relationship? The Experience from a Portuguese Centre. *Obstetrics and Gynecology International*2014; Article ID 531539, 7 pages. http://dx.doi.org/10.1155/2014/531539

32. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation* 2011;123:1243–1262.

Table 1: Sample distribution, number and distribution of diabetes cases and prevalence of diabetes according to PE&E and other factors among Indian women, 2005-06

Characteristics	Sample size	Diabetes cases		Diabetes prevalence %	Chi sq p value
	%[N]	Reported %[N]	Not reported %[N]		
Total	39612	512		1.3	
Preeclampsia symptoms					<0.0001
No	71.3[28250]	59.5[304]	71.5[27933]	1.1	
Yes	28.7[11361]	40.5[207]	28.5[11147]	1.8	
Eclampsia symptoms					<0.0001
No	89.7[35541]	83.4[426]	89.8[35096]	1.2	
Yes	10.3[4071]	16.6[85]	10.2[3984]	2.1	
Body Mass Index					0.023
Underweight (≤18.5kg/m^2)	38.0[14440]	41.8[208]	38.0[14227]	1.4	
Normal (18.5-22.9kg/m^2)	46.9[17833]	40.6[202]	47.0[17622]	1.1	
Overweight (23.0-24.9kg/m^2)	7.3[2766]	9.4[47]	7.3[2720]	1.7	
Obese (≥25.0kg/m^2)	7.8[2964]	8.2[41]	7.8[2919]	1.4	
Current Tobacco smoking					0.259
No	98.5[39006]	98.0[501]	98.5[38484]	1.3	
Yes	1.5[606]	2.0[10]	1.5[596]	1.7	
Drinks Alcohol					0.001
No	97.7[38690]	98.3[488]	97.7[38184]	1.3	
Yes	2.3[911]	4.7[24]	2.3[886]	2.6	
Frequency of TV viewing					0.001
Not at all	43.8[17351]	50.9[260]	43.7[17076]	1.5	
Less than once a week	11.3[449]	13.3[68]	11.3[4423]	1.5	
At least once a week	10.3[4074]	9.0[46]	10.3[4027]	1.1	
Almost everyday	34.6[13689]	26.8[137]	34.7[13548]	1.0	
Access to healthcare					<0.0001
Public Medical sector	31.3[11313]	34.5[162]	31.3[11138]	1.4	
NGO or Trust or Clinic	0.3[113]	0.9[4]	0.3[109]	3.5	
Private Medical Sector	68.1[24591]	63.4[298]	68.1[24279]	1.2	
Other source	0.3[119]	1.3[6]	0.3[112]	5.1	
Food and micronutrient intake					
Diversified dietary intake					0.193
Inadequate	68.9[27275]	68.8[26895]	70.7[362]	1.3	
Adequate	31.1[12337]	31.2[12185]	29.3[150]	1.2	
Intake of Iron and folic acid supplementation					0.212
No	74.7[29588]	74.7[29183]	76.3[390]	1.3	
Yes	25.3[10024]	25.3[9897]	23.7[121]	1.2	
Milk or curd					<0.0001
Never/occasionally	48.1[19046]	56.8[290]	48.0[18745]	1.5	
Daily/weekly	51.9[20561]	43.2[221]	52.0[20331]	1.1	
Pulses or beans					<0.0001
Never/occasionally	10.1[4014]	10.1[3935]	10.1[3935]	1.9	
Daily/weekly	89.9[35588]	89.9[35137]	89.9[35137]	1.2	
Vegetables					0.075
Never/occasionally	7.1[2804]	7.1[2759]	7.1[2759]	1.6	
Daily/weekly	92.9[36795]	92.9[36310]	92.9[36310]	1.3	

Fruits					0.002
Never/occasionally	65.7[26043]	72.0[368]	65.7[25663]	1.4	
Daily/weekly	34.2[13541]	28.0[143]	34.3[13390]	1.1	
Eggs					0.084
Never/occasionally	69.7[27601]	72.6[371]	69.7[27216]	1.3	
Daily/weekly	30.3[11985]	27.4[140]	30.3[11841]	1.2	
Fish					0.003
Never/occasionally	73.3[29043]	67.9[347]	73.4[28679]	1.2	
Daily/weekly	26.7[10558]	32.1[164]	26.6[10392]	1.6	
Chicken/meat					0.004
Never/occasionally	78.7[31158]	83.6[428]	78.6[30714]	1.4	
Daily/weekly	21.3[8439]	16.4[84]	21.4[8352]	1.0	
Socio-demographic characteristics					
Age groups					0.001
15-19	7.5[2982]	10.2[52]	7.5[2928]	1.7	
20-24	33.5[13269]	29.0[148]	33.6[13113]	1.1	
25-29	32.6[12908]	27.2[139]	32.7[12767]	1.1	
30-34	16.9[6685]	18.8[96]	16.8[6584]	1.4	
35-39	6.9[2723]	11.0[56]	6.8[2667]	2.1	
40-44	2.1[835]	2.7[14]	2.1[818]	1.7	
45-49	0.5[210]	1.2[6]	0.5[204]	2.9	
Education					0.064
No education	18758[47.4]	51.4[263]	47.3[18480]	1.4	
Primary	5545[14.0]	14.6[75]	14.0[5470]	1.4	
Secondary	12947[32.7]	30.3[155]	32.7[12790]	1.2	
Higher	2361[6.0]	3.7[19]	6.0[2339]	0.8	
Employment status					0.143
Currently not working	27665[69.9]	67.7[346]	70.0[27309]	1.3	
Working	11886[30.1]	32.3[165]	30.0[11713]	1.4	
Religion					0.035
Hindu	31248[78.9]	76.8[393]	78.9[30836]	1.3	
Muslim	6472[16.3]	17.2[88]	16.3[6383]	1.4	
Christian	811[2.0]	3.9[20]	2.0[791]	2.5	
Sikhs	513[1.3]	0.8[4]	1.3[509]	0.8	
Others	568[1.4]	1.4[7]	1.4[561]	1.2	
Caste/tribe					<0.0001
Scheduled caste	7938[20.1]	21.3[109]	20.1[7825]	1.4	
Scheduled tribes	3740[9.4]	13.7[70]	9.4[3666]	1.9	
Other backward class	15861[40.2]	30.3[155]	40.3[15696]	1.0	
General	10830[27.4]	30.9[158]	27.4[10669]	1.5	
Missing caste	1085[2.8]	3.7[19]	2.7[1060]	1.8	
Wealth index					<0.0001
Lowest	9553[24.1]	32.4[166]	24.0[9381]	1.7	
Second	8588[21.7]	22.3[114]	21.7[8465]	1.3	
Middle	7762[19.6]	19.9[102]	19.6[7661]	1.3	
Fourth	7251[18.3]	15.6[80]	18.3[7168]	1.1	
Highest	6458[16.3]	9.8[50]	16.4[6405]	0.8	
Place of residence					0.001
Urban	10615[26.8]	20.3[104]	26.9[10506]	1.0	
Rural	28997[73.2]	79.7[408]	73.1[28574]	1.4	
Geographic Regions					<0.0001
North	5076[12.8]	9.4[48]	12.9[5028]	0.9	

Northeast	1607[4.1]	5.9[30]	4.0[1576]	1.9
Central	11099[28.0]	17.8[91]	28.4[11000]	0.8
East	10031[25.3]	48.3[247]	25.0[9777]	3.5
West	5114[12.9]	6.1[31]	13.0[5081]	0.6
South	6684[16.9]	12.5[64]	16.9[6618]	1.0

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

Table 2: Unadjusted and partially adjusted and fully adjusted odds ratios (ORs) and 95% confidence interval (95%CI) showing the association between PE&E and other factors and diabetes risk among Indian women, 2005-06

	Unadjusted Model 1	Adjusted Model 2	Adjusted Model 3	Adjusted Model 4
	OR[95%CI]	OR[95%CI]	OR[95%CI]	OR[95%CI]
Preeclampsia symptoms				
No [Ref]	1	1	1	1
Yes	1.71[1.43-2.04]	1.62[1.33-1.96]	1.59[1.31-1.93]	1.59[1.31-1.94]
Eclampsia symptoms				
No [Ref]	1	1	1	1
Yes	1.76[1.40-2.23]	1.48[1.15-1.91]	1.50[1.16-1.95]	1.36[1.05-1.77]
Body Mass Index				
Underweight (≤18.5 kg/m^2)		1.24[1.01-1.52]	1.21[0.99-1.49]	1.17[0.95-1.44]
Normal (18.5-22.9 kg/m^2) [Ref]		1	1	1
Overweight (23.0-24.9 kg/m^2)		1.74[1.25-2.42]	1.78[1.27-2.47]	2.01[1.43-2.81]
Obese (≥25.0 kg/m^2)		1.47[1.02-2.10]	1.52[1.06-2.19]	1.85[1.26-2.72]
Current tobacco smoking				
No [Ref]		1	1	1
Yes		1.13[0.60-2.11]	1.13[0.60-2.12]	0.88[0.46-1.68]
Current alcohol drinking				
No [Ref]		1	1	1
Yes		1.93[1.26-2.95]	1.81[1.17-2.79]	1.36[0.84-2.20]
Frequency of TV viewing				
Not at all [Ref]		1	1	1
Less than once a week		1.04[0.78-1.38]	1.03[0.77-1.38]	1.21[0.90-1.63]
At least once a week		0.81[0.58-1.13]	0.84[0.60-1.18]	1.02[0.72-1.46]
Almost everyday		0.72[0.57-0.90]	0.80[0.62-1.02]	1.18[0.87-1.61]
Access to healthcare				
Public Medical sector [Ref]		1	1	1
NGO or Trust or Clinic		2.03[0.71-5.76]	2.06[0.72-5.91]	1.76[0.60-5.18]
Private Medical Sector		0.84[0.69-1.02]	0.89[0.73-1.08]	0.89[0.72-1.10]
Other source		3.16[1.31-7.59]	3.08[1.27-7.44]	2.57[1.05-6.33]
Food and micronutrient intake				
Diversified dietary intake				
Inadequate [Ref]			1	1
Adequate			1.54[1.16-2.04]	1.46[1.10-1.94]
Intake of Iron and folic acid supplementation				
No [Ref]			1	1
Yes			1.20[0.81-1.29]	1.11[0.87-1.41]
Milk or curd				
Never/occasionally [Ref]			1	1
Daily/weekly			0.87[0.71-1.07]	1.06[0.85-1.31]
Pulses or beans				
Never/occasionally [Ref]			1	1
Daily/weekly			0.76[0.58-1.00]	0.80[0.60-1.07]
Vegetables				
Never/occasionally [Ref]			1	1
Daily/weekly			0.90[0.65-1.25]	0.81[0.58-1.13]
Fruits				
Never/occasionally [Ref]			1	1

Daily/weekly	0.92[0.73-1.15]	1.05[0.82-1.33]
Eggs		
Never/occasionally [Ref]	1	1
Daily/weekly	0.90[0.70-1.16]	0.80[0.62-1.03]
Fish		
Never/occasionally [Ref]	1	1
Daily/weekly	1.76[1.38-2.25]	1.12[0.87-1.46]
Chicken/meat		
Never/occasionally [Ref]	1	1
Daily/weekly	0.60[0.45-0.80]	0.75[0.56-1.02]
Socioeconomic and demographic characteristics		
Age		
15-19 [Ref]		1
20-24		0.83[0.58-1.18]
25-29		0.71[0.49-1.02]
30-34		0.86[0.58-1.27]
35-39		1.25[0.81-1.91]
40-44		0.99[0.53-1.86]
45-49		1.49[0.60-3.68]
Education		
No education [Ref]		1
Primary		0.92[0.68-1.25]
Secondary		1.15[0.87-1.52]
Higher		0.96[0.53-1.74]
Employment status		
Currently not working [Ref]		1
Working		1.21[0.91-1.38]
Religion		
Hindu [Ref]		1
Muslim		1.00[0.74-1.35]
Christian		1.53[0.90-2.60]
Sikhs		0.79[0.27-2.31]
Others		0.65[0.29-1.47]
Caste/tribe		
Scheduled caste [Ref]		1
Scheduled tribes		0.97[0.68-1.38]
Other backward class		0.65[0.50-0.85]
General		1.11[0.83-1.49]
Missing caste		0.48[0.24-0.95]
Wealth index		
Lowest [Ref]		1
Second		0.89[0.68-1.16]
Middle		0.80[0.58-1.09]
Fourth		0.76[0.52-1.11]
Highest		0.45[0.27-0.78]
Place of residence		
Urban [Ref]		1
Rural		1.01[0.77-1.34]
Geographic Regions		
North [Ref]		1
Northeast		1.82[1.06-3.13]
Central		0.93[0.62-1.39]

East	2.68[1.83-3.93]
West	0.69[0.42-1.15]
South	1.28[0.82-1.99]
Number of cases	34978

*Note: [Ref] denotes reference category; Model 1 unadjusted; Model 2 adjusted for BMI, tobacco smoking, alcohol drinking, TV watching and access to healthcare; Model 3 adjusted for Model 2+ specific dietary intakes; Model 4 adjusted for all

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Section of manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and abstract, p. 1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract, p. 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Intro paras 1&2; What is already known, p. 4
Objectives	3	State specific objectives, including any pre specified hypotheses	Intro para 3
Methods			
Study design	4	Present key elements of study design early in the paper	Secondary analysis of NFHS-3/2005-06 data as referenced in Methods para 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Secondary analysis of NFHS-3/2005-06 data – referenced in Methods para 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Secondary analysis of NFHS-3/2005-06 data – referenced in Methods 2,3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods paras 2, 3,4,5. Full survey report including questionnaire referenced Methods para 1
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Questionnaire and survey report referenced Methods para 1
Bias	9	Describe any efforts to address potential sources of bias	Methods para 6,7
Study size	10	Explain how the study size was arrived at	Methods para2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods paras 4 & 5; groupings shown in Table 1
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods para 6
		(*b*) Describe any methods used to examine subgroups and	Methods para 6

		interactions	
		(*c*) Explain how missing data were addressed	Methods para 5; Results para 1
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Methods para 6
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results para 1
		(b) Give reasons for non-participation at each stage	Results para 1
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Results para 1; Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	Results; Tables 3-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion paras 1 and 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion para 5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion para 5
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion para 2
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding statement in the Acknowledgement section

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.