Pre-eclampsia and risk of subsequent hypertension: in an American Indian population

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Background and Objectives: Pre-eclampsia (PE) shares a number of proposed pathophysiological mechanisms related to those implicated in cardiovascular disease (CVD), such as endothelial dysfunction, inflammation, insulin resistance, and impaired renal regulation. PE has also been associated with subsequent hypertension, CVD, and related mortality in later life. Methods: At follow-up, the four most recent blood pressures, body mass index (BMI), and use of hypertensive medications were recorded from clinic visits of 130 PE cases and 289 normal pregnancies. Student’s t test, Chi-square testing, multivariate linear, and logistic regression were used in analysis. Results: Follow-up measurements occurred a mean of 13.11 years post PE pregnancy. Multivariate linear regression showed a significant and independent association between current systolic blood pressure and previous history of PE ($β = 4.47$, $p = 0.04$), while adjusting for age, BMI, and blood pressure from 1 year prior to and up to the 20th week of gestation. A similarly adjusted multivariate logistic regression model found an odds ratio of 3.43, 95% CI 1.83–6.43, $p = 0.001$ for subsequent hypertension. Logistic regression analysis of the quartile with follow-up of less than 7.19 years also shows independent association of prior PE with subsequent hypertension. Discussion and Conclusions: PE appears to confer risk of subsequent hypertension on this cohort of American Indian women within as little as 8 years. This risk is independent of additional risk factors such as increased age, BMI, and blood pressure prior to 20 weeks of gestation. There is evidence of increased risk among those with more severe PE.

Introduction

Pre-eclampsia (PE) and the more severe “eclampsia” together affect approximately 2%–8% of pregnancies and result in more than 50,000 maternal deaths globally (1). The incidence of hypertensive disorders of pregnancy in the US appears to have increased 25% in the last two decades (2), and is a leading contributor to maternal and infant morbidity and mortality (3). Diagnostic criteria have recently been revised to de-emphasize the previously required documentation of proteinuria and to allow greater emphasis on clinical findings (4). None the less, PE has been classically based on the new onset of hypertension and proteinuria after 20 weeks of gestation (5). With severe PE, multiple organ systems can be affected, potentially resulting in complications such as renal failure, stroke, congestive heart failure, disseminated intravascular coagulopathy, and liver failure. Obstetric risk factors for development of PE have previously been identified, such as primiparity, multifetal pregnancy, and prior pregnancy with PE. In addition, traditional cardiovascular disease (CVD) risk factors, such as increased age, obesity, altered glucose metabolism, and pre-existing hypertension, also play a role (4). Specific details of the underlying etiology of PE are unknown; but the condition seems to develop initially from reduced placental perfusion, which leads to systemic inflammatory, metabolic, and thrombotic changes that impair maternal vascular function and lead to multiorgan damage (6).

Although the blood pressure (BP) and albuminuria of patients with PE typically return to normal values within months of delivery, evidence is accumulating that acute episodes of PE are linked to future CVD. From a few reports beginning in 1976 (7) to increasingly strong analyses in the past two decades, evidence is showing that women who experience PE have an increased risk of hypertension and other cardiovascular conditions in later life (8–10). In addition to a four-fold increased risk of hypertension (5), PE is also associated with increased risk of other serious morbidity, including myocardial infarction (11), renal disease (12), diabetes (13), and stroke (14). There also appears to be a
“dose effect” (15,16) with those experiencing more severe or earlier manifestations of PE being at increased risk of adverse outcomes, compared with those having had less severe PE.

One interpretation of these findings is that PE and CVD share risk factors that may be subtle or currently unrecognized in young, pregnant women; and that the additional physiologic stress of pregnancy unmasks this predisposition years ahead of its eventual manifestation. Thus, PE is viewed as a positive “stress test,” predictive of future CVD (17).

Regardless of whether PE is an independent factor in the causal chain of future CVD or simply shares other primary risk factors with CVD, PE was identified by the American Heart Association and the American College of Cardiology as a useful, clinical risk factor for heart disease and stroke. Indeed, the additional risk of future CVD attributed to a history of PE is comparable to that of smoking (9).

The purpose of this study was to determine if there is an association between a history PE and future development of hypertension in an American Indian population.

Methods

This investigation utilized data of American Indian women from a previously described case–control study of genetic influences on risk of PE (18). Case status is equivalent to exposure status in this analysis. A retrospective review of medical records was conducted of women with and without PE that gave birth from January 1, 1995, to December 31, 2012. Institutional Review Board (IRB) permission for this study was obtained from the Indian Health Service facility in the northern plains, the American Indian community, and the University of North Dakota. Cases comprised of women with PE (N = 130), of which 96 met criteria as severe PE as defined by the American College of Obstetrics and Gynecology (19). Controls are women (N = 288) that did not meet criteria for PE.

Hospital diagnostic codes were searched from 1995 forward to ascertain potential cases. Criteria for the case and control definitions of PE in this study are fully described in previous publications (18). In brief, cases were defined as those meeting criteria for PE if at least two of the following were identified:

1. At least two BP values above either 140 mmHg systolic or 90 mmHg diastolic on separate occasions at least 4 hours apart; and absence of a diagnosis of, or treatment for hypertension (during the year prior to conception and the first 20 weeks of gestation).
2. Proteinuria as indicated by a 24-h excretion of >300 mg, or at least two +1 dipstick measurements in the absence of prior proteinuria.
3. A diagnosis of PE, eclampsia, or the hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome by an attending physician after 20 weeks of gestation.

Potential controls were chosen by contacting the two women delivering just prior and after the case; and repeating the process until two control women consented to participate. Both cases and controls were excluded if they had a clinical diagnosis of hypertension prior to the identified pregnancy. The two highest BP readings recorded within the period from 1 year prior to the pregnancy up to 20 weeks of gestation were collected. When available, the mean of both the systolic and diastolic pressures was calculated and used as covariates to adjust models.

The electronic medical records were searched for the four most recent BP readings that were measured on separate office visits during the 2 years prior to follow-up and if a hypertensive medication were prescribed in the past two years. Antihypertensive medications (AHMs) included angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and/or thiazide diuretics. The mean systolic and diastolic BPs were calculated from at least two of the four possible measurements. Defining criteria for “subsequent” hypertension of both cases and controls were a mean systolic BP ≥140 … AND a mean diastolic ≥90 … OR a prescription for AHM. The most recent body mass index (BMI) during the prior 3 years was also recorded. The BMI calculated at the time of pregnancy used the recorded weight and height at the first prenatal visit.

The statistical software, SPSS 13.0.1 for Windows, was used to analyze demographic and clinical characteristics of patients. Frequencies and relative percentages were computed for each categorical variable. Chi-square tests and Fisher’s exact tests were performed to determine which categories were significantly different from one another, and Student’s t-test was used to compare continuous variables. Cytel Studio software, version 11.0.0, was used to calculate logistic regression results. All p-values were two-sided, and a p-value < 0.05 was considered significant. Missing data were excluded from analysis.

Results

The relevant baseline characteristics of the cases and controls are shown in Table 1. Women with a history of PE were more likely to be primiparous, have a higher BMI, have higher recorded BPs prior to 20 weeks of gestation.
gestation, and have exhibited gestational diabetes during their pregnancy. The mean gestational age at the time of first prenatal visit (when BMI was calculated) was 13.02, and only 4.7% of cases and controls attended their first prenatal visit at 30 weeks of gestation or later. Smoking prevalence was similar between cases and controls.

Characteristics of women at follow-up are found in Table 2. Follow-up occurred at a mean (standard deviation, minimum, maximum) of 13.5 years (7.1, 3.6, 36.7) for cases and 12.9 years (6.7, 3.6, 36.6) for controls. There was no significant difference in length of follow-up between cases and controls ($p = 0.421$). At follow-up, cases had higher mean BMI, systolic and diastolic BP, prevalence of AHM, and study-defined hypertension, but otherwise were of similar age.

The results of linear regression models are shown in Table 3. This analysis shows increased subsequent systolic BP of approximately 3 mm of mercury among those with a history of prior PE, even when simultaneously adjusted for age, BMI, and average systolic pressure prior to 20 weeks of gestation. The association is also seen when the analysis is limited to those participants in the lowest quartile of follow-up time (between 3.59 and 7.19 years) as detailed in Table 3, along with summary results from the remaining quartiles. If baseline (rather than current) measures of age and BMI were used as adjusting covariates in these linear models, the covariate association with follow-up BPs lost independent significance. Models including gestational diabetes failed to show significant, independent association in either the linear or logistic regression analyses. Analysis of controls only indicates significant and independent association between BPs prior to 20 weeks of gestation, age, and BMI.

Table 4 indicates the results of multivariate logistic regression analysis with subsequent, study-defined hypertension as the outcome and adjusting covariates as noted for the linear analyses. This also shows the

### Table 1. Characteristics of cases and controls at the time of pregnancy.

| Characteristic                          | Cases     | Controls   | $p$-value |
|-----------------------------------------|-----------|------------|-----------|
| Age, mean years (SD)                    | 26.5 (35.7)| 23.9 (7.3) | 0.411     |
| Parity (% primiparous)                  | 88/130 (67.7%) | 123/286 (43.0%) | 0.001    |
| Mean systolic BP < 20-week gestation    | 133.2 (20.3) | 122.3 (17.7) | 0.001    |
| Mean diastolic BP < 20 week gestation   | 79.2 (12.7) | 71.7 (11.6) | 0.001    |
| Body mass index (SD) at first prenatal visit | 30.5 (7.09) | 28.0 (7.08) | 0.001    |
| Gestational diabetes (% yes)            | 17/129 (13.2%) | 12/220 (5.5%) | 0.007    |
| Maternal smoking (% yes)                | 34/87 (39.1%) | 85/173 (49.1%) | 0.125    |

### Table 2. Characteristics of cases and controls at follow-up.

| Characteristic                          | Cases     | Controls   | $p$-value |
|-----------------------------------------|-----------|------------|-----------|
| Current age, mean (SD)                  | 36.1 (9.6) | 35.9 (9.0) | 0.832     |
| Current body-mass index (SD)            | 34.3 (7.24) | 31.6 (7.53) | 0.001    |
| Mean systolic BP                        | 127.2 (13.2) | 121.3 (12.1) | 0.001    |
| Mean diastolic BP                       | 76.2 (9.0) | 72.6 (8.6) | 0.001    |
| Hypertensive medication use (% yes)     | 35/130 (26.9%) | 25/288 (8.7%) | 0.001    |
| Study-defined, subsequent hypertension, any BMI increase | 41/130 (31.5%) | 29/288 (10.1%) | 0.001    |
| Subsequent hypertension among those with less than median BMI increase | 22/60 (36.7%) | 14/140 (10.0%) | 0.001    |
| Subsequent hypertension among those with more than median BMI increase | 17/65 (26.2%) | 15/135 (11.1%) | 0.012    |
| Follow-up time from pregnancy to current analysis (years) | 13.5 (7.1) | 12.9 (6.7) | 0.421    |

### Table 3. Multivariate linear regression model analyses.

| Linear regression model, systolic blood pressure, $N = 337^*$ | $B^{**}$ | SE | $B^{***}$ | $p$-Value |
|---------------------------------------------------------------|----------|----|----------|-----------|
| Previous pre-eclampsia                                       | 2.75     | 1.33 | 0.109    | 0.040     |
| Mean prior systolic BP****                                   | 0.14     | 0.03 | 0.220    | 0.001     |
| Current age                                                   | 0.19     | 0.07 | 0.138    | 0.007     |
| Current BMI                                                   | 0.28     | 0.09 | 0.170    | 0.002     |
| Linear regression model, diastolic blood pressure, $N = 337$ |          |    |          |           |
| Previous pre-eclampsia                                       | 1.74     | 0.96 | 0.182    | 0.070     |
| Mean prior systolic BP                                        | 0.08     | 0.03 | 0.179    | 0.001     |
| Current age                                                   | 0.12     | 0.05 | 0.129    | 0.013     |
| Current BMI                                                   | 0.20     | 0.06 | 0.170    | 0.002     |
| Participants in first quartile with shortest follow-up       |          |    |          |           |
| Linear regression model, systolic blood pressure, $N = 69$    |          |    |          |           |
| Previous pre-eclampsia                                       | 4.26     | 2.68 | 0.188    | 0.116     |
| Mean prior systolic BP                                        | 0.20     | 0.09 | 0.273    | 0.038     |
| Current age                                                   | 0.233    | 0.21 | 1.093    | 0.278     |
| Current BMI                                                   | 0.16     | 0.17 | 0.115    | 0.362     |
| Remaining quartiles, same model, results given for previous pre-eclampsia only |          |    |          |           |
| Second quartile of follow-up, $N = 89$                       | 2.45     | 2.52 | 0.106    | 0.335     |
| Third quartile, $N = 91$                                     | 4.22     | 2.77 | 0.154    | 0.131     |
| Fourth quartile, $N = 89$                                    | 1.81     | 2.93 | 0.070    | 0.523     |
| Linear regression model, diastolic blood pressure, $N = 69$  |          |    |          |           |
| Previous pre-eclampsia                                       | 3.35     | 1.67 | 0.217    | 0.049     |
| Mean prior diastolic BP****                                  | 0.26     | 0.09 | 0.319    | 0.007     |
| Current age                                                   | 0.35     | 0.13 | 0.271    | 0.012     |
| Current BMI                                                   | 0.09     | 0.10 | 0.102    | 0.360     |
| Remaining quartiles, same model, results given for previous pre-eclampsia only |          |    |          |           |
| Second quartile of follow-up, $N = 89$                       | 1.83     | 1.97 | 0.102    | 0.356     |
| Third quartile, $N = 91$                                     | 0.31     | 1.92 | 0.017    | 0.672     |
| Fourth quartile, $N = 89$                                    | −1.02    | 1.95 | −0.058   | 0.601     |
| Cases excluded, Controls only                                |          |    |          |           |
| Linear regression model, systolic blood pressure, $N = 211$  |          |    |          |           |
| Mean prior systolic BP                                        | 0.13     | 0.04 | 0.20     | 0.003     |
| Current age                                                   | 0.25     | 0.09 | 0.19     | 0.003     |
| Current BMI                                                   | 0.43     | 0.11 | 0.272    | 0.001     |
| Linear regression model, diastolic blood pressure, $N = 211$ |          |    |          |           |
| Mean prior diastolic BP                                       | 0.15     | 0.05 | 0.21     | 0.001     |
| Current age                                                   | 0.18     | 0.06 | 0.19     | 0.004     |
| Current BMI                                                   | 0.30     | 0.07 | 0.26     | 0.001     |

*N = the number of participants with available covariates for a particular analysis.

**Unstandardized regression coefficient.

***Standardized regression coefficient.

**** Mean systolic or diastolic blood pressure, one year pre-pregnancy through 20 weeks gestation.
analyses contrasting those above and those below the BMI increase from pregnancy to follow-up.

Among those with the lesser change (mean and median change of –0.53, and +0.37 BMI units, respectively), both the linear and logistic regression relationship to history of PE remained significant and strong. Among those with the greater change in BMI (mean and median change of +8.08 and +7.08 units, respectively), the linear models now showed no association with systolic or diastolic pressure, whereas the logistic models continued to show statistically significant association with future hypertension as defined (OR 2.67, 95% CI 1.06–7.00, p = 0.036). Last, an additive model, attempting to scale the effects of PE and increasing

Table 4. Multivariate logistic regression model analyses.

| Logistic regression (subsequent hypertension as the outcome), N = 337* | OR** | 95% CI | p-Value |
|---|---|---|---|
| Previous pre-eclampsia | 3.43 | 1.83–6.43 | 0.001 |
| Mean prior systolic BP*** | 1.02 | 1.00–1.04 | 0.032 |
| Current age | 1.08 | 1.04–1.11 | 0.001 |
| Current BMI | 1.01 | 0.97–1.06 | 0.505 |
| Participants in quartile with shortest follow-up, N = 69 |
| Logistic regression (subsequent hypertension as the outcome) | OR | 95% CI | p-Value |
| Previous pre-eclampsia | 11.31 | 1.15–111.2 | 0.038 |
| Mean prior systolic BP | 1.06 | 0.99–1.13 | 0.090 |
| Current age | 1.09 | 0.93–1.29 | 0.270 |
| Current BMI | 0.85 | 0.72–1.01 | 0.062 |
| Remaining quartiles, same model, results given for previous pre-eclampsia only |
| Second quartile of follow-up, N = 89 | 3.52 | 0.69–18.1 | 0.132 |
| Third quartile, N = 91 | 3.65 | 1.05–12.7 | 0.042 |
| Fourth quartile, N = 89 | 2.20 | 0.80–6.08 | 0.128 |
| Cases excluded, controls only, N = 211 |
| Logistic regression (subsequent hypertension as the outcome) | OR | 95% CI | p-Value |
| Mean prior systolic BP | 1.04 | 1.00–1.07 | 0.041 |
| Current age | 1.12 | 1.05–1.18 | 0.001 |
| Current BMI | 1.05 | 0.98–1.13 | 0.188 |

*N = the number of participants with available covariates for a particular analysis.

**Odds ratio.

***Mean systolic or diastolic blood pressure, 1-year pre-pregnancy through 20-week gestation.

The inclusion of pre-natal tobacco use showed only marginally significant association with systolic BP (p = 0.055) and no association in other fully adjusted linear or logistic models for diastolic pressure and subsequent hypertension, respectively. Results of logistic regression analysis of the controls alone indicated significant, independent association with prior systolic BP and age, but not BMI.

A number of analyses were conducted in an attempt to separate the effects of PE per se from the effects of increasing obesity during the follow-up period. As seen in Table 2, the prevalence of hypertension among cases was nominally lower (17/65 = 26.2%) among those with the greatest increase in BMI, compared with (22/60 = 36.7%) among those with the least, but this was not statistically significant (p = 0.463). The participants were stratified into those with a change in BMI below or above the median increase of 3.7 BMI units; and these results are presented in Table 5. Among those with the lesser change (mean and median change of –0.53, and +0.37 BMI units, respectively), both the linear and logistic regression relationship to history of PE remained significant and strong. Among those with the greater change in BMI (mean and median change of +8.08 and +7.08 units, respectively), the linear models now showed no association with systolic or diastolic pressure, whereas the logistic models continued to show statistically significant association with future hypertension as defined (OR 2.67, 95% CI 1.06–7.00, p = 0.036). Last, an additive model, attempting to scale the effects of PE and increasing

Table 5. Analyses contrasting those above and those below the median change in BMI from pregnancy to follow-up.

| Linear regression model, systolic blood pressure |
|---|---|---|---|
| Above median change in BMI, N = 162* | \(\beta\) | SE | p-Value |
| Previous pre-eclampsia | –1.17 | 1.85 | 0.529 |
| Mean prior systolic BP*** | 0.23 | 0.07 | 0.279 |
| Current age | 0.17 | 0.09 | 0.13 | 0.072 |
| Current BMI | 0.31 | 0.14 | 0.18 | 0.028 |
| Below median change in BMI, N = 167 |
| Previous pre-eclampsia | 6.26 | 1.93 | 0.001 |
| Mean prior systolic BP | 0.13 | 0.05 | 0.21 | 0.008 |
| Current age | 0.26 | 0.11 | 0.18 | 0.016 |
| Current BMI | 0.12 | 0.14 | 0.07 | 0.393 |
| Linear regression model, diastolic blood pressure |
| Above median change in BMI, N = 162* | \(\beta\) | SE | p-Value |
| Current BMI | 0.20 | 0.07 | 0.003 |
| Current age | 0.06 | 0.07 | 0.387 |
| Current BMI | 0.25 | 0.10 | 0.19 | 0.015 |
| Below median change in BMI, N = 167 |
| Previous pre-eclampsia | 3.10 | 1.29 | 0.018 |
| Mean prior diastolic BP | 0.19 | 0.05 | 0.029 | 0.001 |
| Current age | 0.13 | 0.07 | 0.036 |
| Current BMI | 0.11 | 0.09 | 0.09 | 0.222 |

Logistic regression model (subsequent hypertension as outcome)

| Additive model, N = 329 |
|---|---|---|---|
| Additive risk score**** | 1.55 | 1.16–2.06 | 0.003 |
| Current age | 1.03 | 1.01–1.05 | 0.009 |
| Current BMI | 1.08 | 1.05–1.12 | 0.001 |
| Current BMI | 1.00 | 0.96–1.05 | 0.994 |

*N = the number of participants with available covariates for a particular analysis.

**Unstandardized regression coefficient.

***Standardized regression coefficient.

****Mean systolic blood pressure, 1-year pre-pregnancy through 20 weeks gestation.

*****0=no PE, below median BMI increase (\(\Delta\) BMI), 1 = no PE, above median BMI increase (\(\Delta\) BMI), 2 = +PE, v BMI, 3 = +PE, \(\Delta\)BMI
BMI over time, showed a strong relationship to subsequent hypertension, as seen in Table 5. Women with a history of PE were also more likely to be prescribed AHM (OR 3.07, 95% CI 1.60–5.91, p = 0.001) compared to women experiencing normal pregnancies.

**Discussion**

Our findings clearly demonstrate that this cohort of American Indian women with a history of PE have an increased risk of future hypertension both over relatively short and longer periods of follow-up. This is in agreement with several investigations, primarily conducted among European populations (8,13,20,21). Bellamy et al. (15) conducted a meta-analysis of 13 studies with a mean follow-up of 14.1 years, finding a composite relative risk (RR 3.70, 95% CI 2.70–5.05) for subsequent hypertension, albeit with significant heterogeneity between studies (smaller studies showing increased RR). This result is nearly identical to our present study. Of note, case–control studies were excluded in this meta-analysis of cohorts, of which all but three (8,14,22) evaluated fewer cases and controls than the present study. Only one of the larger cohorts (14) adjusted for BMI and obtained an odds ratio of 3.98 for a physician’s diagnosis of hypertension.

Although not our primary objective and well-established in the literature (23), we provide additional evidence of the association between obesity and hypertension, both as an independent factor in the relationship between PE and subsequent hypertension and among those with previously normal pregnancies. The lack of a difference in hypertension prevalence between those with greater or lesser increases in BMI supports the independent influence of PE on the risk of subsequent hypertension. The stratified analysis showing a strong association with PE and subsequent hypertension among those with less than the median increase in BMI during follow-up gives further weight to the hypothesis that risk of future hypertension is not due merely to a tendency of those with PE toward obesity. Interestingly, those with the greatest increase in BMI continued to show a relationship between hypertension and PE in logistic analysis, but not in linear analysis of BP. This may be due to the increased effect of obesity overwhelming the influence of prior PE. There are relatively few studies of PE associated with an outcome of hypertension that are adjusted for BMI, but one moderate-sized investigation (14) found an odds ratio of 2.62 (95% CI 1.77–3.86, p = 0.001).

We have been able to identify only three reports relating PE to hypertension among non-European populations. These include studies among Samoan (24), Jordanian (25), and primarily African American (22). There is no prior information available regarding subsequent hypertension among American Indian women.

An interesting question is whether the pathophysiologic changes of PE alter the cardiovascular system of women in a lasting way that increases the risk of future hypertension and CVD events, or whether the stress of pregnancy merely unmasks the underlying pathophysiology that is common to both PE and CVD. This debate is well described in a review by Garovic et al. (26); but remains unresolved. The current study offers additional support for PE as an independent, intrinsic risk factor, in that those with a lesser increase in BMI during follow-up continued to show a strong association with PE, discounting the theory that obesity is perhaps one of multiple primary risk factors for future hypertension. While the addition of BP prior to pregnancy and up to 20 weeks of gestation attenuates the association of PE with subsequent BPs in both linear and logistic analyses, a couple of caveats need to be considered. First, the BP at follow-up will be lessened in those under treatment for hypertension, thus decreasing the power of these linear analyses. The logistic models take into account hypertensive treatment and thus capture this potential effect of PE exposure. Second, a large portion of the “prior” BP measures were obtained during the first 20 weeks of gestation and could well have captured mild elevations from PE that preceded the formal definition of PE (i.e., “after 20 weeks of gestation”). Thus, the use of these prior BPs as a covariate may result in “overadjustment.” The results of logistic models showing subsequent hypertension significantly and independently associated with a history of PE, even among those with the shortest follow-up, are especially impressive in the light of these caveats.

Other studies provide clear evidence of persisting abnormalities in cardiovascular function (27) and even anatomy (28) post PE, but no comparable measures from these women prior to pregnancy. To know whether PE directly affects these changes, detailed longitudinal studies of a cohort of women from pre-pregnancy to a couple years post pregnancy would be ideal, but would be difficult due to the large population needed, continuing difficulty discriminating between possibly distinct forms of PE (e.g., early versus late pregnancy, young versus older women), and the need to control or adjust for pre-existing risk factors. This question is not without practical implications. If PE is the cause of a persistent increase in CVD risk, then management of women with PE may require more aggressive interventions to prevent adverse outcomes (26).
Strengths of this study include PE as a well-defined exposure, confirmed by clinical measures and a conservative definition, and similarly reliable clinical measures of outcome (BP and prescribed medications). Important covariates were also well-documented, in some cases both during pregnancy and at the end of follow-up; and there was adequate power to analyze both long- and short-term outcome. These results from a non-European population support the view that there is a generalizable physiology underlying this association.

Limitations to this investigation include the possibility that some BMIs from the time of pregnancy were obtained during a late prenatal visit, and thus biased upward, although the proportion of women over 30 weeks gestation at first prenatal was less than 5%. It is possible that some women were seen and actively treated for hypertension at a facility other than the Indian Health Service in this community. If there was a systematic bias in loss to follow-up, this could have affected the results. Reassuringly, although abstraction was limited to about 200 per abstractor due to time constraints, of the 418 abstracted (out of a potential 542), all but one had at least three BPs measured within the prior 3 years (resulting in a minimum follow-up of 77%). Loss to follow-up did occur due to death for two control women from the original study; and the cause is unknown. We also caution that these findings from a single community may not generalize to other American Indian populations; and further studies in other areas would be useful.

CVD is the leading cause of death for women ≥65 years of age in the United States (29), and the American Heart Association has recognized the importance of PE as a CVD risk factor (30), which is comparable to the effects of smoking (9). These insights and the development of clinical recommendations for the prevention and treatment of PE have made vital contributions to women’s health (31).

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Declaration of interest
The authors report no conflicts of interest.

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