

## PERINATAL EPIDEMIOLOGY

# Risk of early or severe preeclampsia related to pre-existing conditions

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**Background** Preeclampsia (PE), especially severe or early PE, is a leading cause of morbidity and mortality among mothers and infants. We estimated the population attributable fractions of severe or early PE associated with pre-existing conditions among nulliparous and multiparous women.

**Methods** Among 70 924 women in the Danish National Birth Cohort, we used hospital discharge data to identify 2117 cases of PE, of which 449 were early (<37 weeks), 426 were severe (clinically diagnosed) and 228 were both early and severe. Prospective interview data were supplemented with hospital registry data to identify women with pre-existing conditions. Generalized estimating equations were utilized to estimate adjusted relative risks, and population attributable fractions were calculated with 95% CI.

**Results** Pre-existing hypertension, diabetes, obesity or multiple gestation were associated with 22.3% (19.8–24.9) of all PE cases among nulliparous women. These conditions, or a prior preeclamptic pregnancy, were associated with 52.2% (46.4–57.9) of PE among multiparous women. Early PE was preceded by these pre-existing conditions among 34% (28.3–40.0) of affected nulliparous women and among 50% (37.5–63.4) of multiparous women. The fraction of severe PE associated with these conditions was 23% among nulliparas and 59% among multiparas. Being obese or overweight was associated with 15–17% of the population risk of early PE among nulliparous and multiparous women.

**Conclusions** Pre-existing maternal and obstetric conditions are associated with a high proportion of severe or early cases of PE. Obesity and overweight contributed independently to the risk of pre-term PE, a finding with potentially profound public health implications.

**Keywords** Preeclampsia, attributable fraction, chronic hypertension, obesity

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Preeclampsia (PE), especially early or severe PE, is a leading cause of morbidity and mortality among mothers and infants worldwide.<sup>1,2</sup> This multi-system syndrome, involving systemic endothelial dysfunction and elevations in blood pressure and proteinuria, affects 5–7% of first pregnancies<sup>3</sup> and recurs in 13–18% of subsequent pregnancies.<sup>4,5</sup>

Early onset (between 30 and 36 weeks) or severe PE (severe elevations in blood pressure with proteinuria or involvement of one or more organ systems) represents perhaps one quarter of

all PE and disproportionately causes maternal and neonatal morbidity. Early or severe PE is associated with adverse neonatal outcomes,<sup>6,7</sup> is more likely to recur,<sup>5,8,9</sup> is associated with excess maternal morbidity during pregnancy<sup>9,10</sup> and women with early or severe PE are at high risk for cardiovascular disease later in life.<sup>10–12</sup>

Previous studies have evaluated the occurrence of and morbidity from PE among women with chronic hypertension,<sup>9,13</sup> diabetes mellitus,<sup>14,15</sup> obesity<sup>3,16,17</sup> and twin pregnancies<sup>14,18</sup> separately, and increased risks for these conditions are well-established. However, we are unaware of any study that has considered the cumulative impact of these conditions on the risk for pre-term or severe PE. The attributable fraction is the proportion of cases that can be related to a given factor or

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set of factors, under the condition that they are causally related to PE. The goal of our study was to estimate the risk of PE and severe or early PE attributable to hypertension, diabetes mellitus, obesity and multiple gestation among a large cohort of well-characterized nulliparous and multiparous Caucasian women.

## Materials and methods

The Danish National Birth Cohort is a nationwide longitudinal study of pregnant women and their offspring approved by the Danish National Ethics Board. Details regarding recruitment, retention and data collection are published.<sup>19</sup> Women were identified early in pregnancy via their general practitioner, and about 50% of all general practitioners in Denmark participated. Recruitment took place from 1997 to 2003. Of those women approached to participate, 60% consented and were interviewed twice during pregnancy and twice after delivery. This study combines information from the first three interviews with hospital and birth registries from the Danish National Board of Health that contain all in-patient and out-patient encounters and are linked via a unique personal code.

Of all pregnant women recruited to the Danish National Birth Cohort ( $n = 101\,033$ ), we identified 89 026 women with single or multiple gestation pregnancies who completed the first interview and delivered live born ( $\geq 24$  weeks) or stillborn infants ( $\geq 28$  weeks according to Danish criteria) not complicated by congenital malformations. We excluded 63 women with missing parity values and 807 women with incomplete outcome data. A total of 41 325 nulliparous women were evaluated. Of the 47 053 multiparous women, we limited our analysis to the first multiparous pregnancy in the cohort ( $n = 45\,723$ ) and then required a match to an earlier pregnancy either in the cohort ( $n = 4\,589$ ) or via birth records from 1995 to 2003 ( $n = 25\,232$ ). A total of 29 599 multiparous women were included in the analysis, and for 77% of these women we matched a first birth and report outcomes of the second birth. Final study population was 70 924 women.

Women who reported having chronic hypertension during the first interview (completed at median of 16 weeks, interquartile range 13–19 weeks) and also reported taking antihypertensive medication or indicated that they still had hypertension were categorized with definite hypertension. Those with hypertension, but not on medication or indicated they no longer had hypertension were classified with probable hypertension. Number of previous births, height, and pre-pregnancy weight [used to calculate body mass index (BMI),  $\text{kg}/\text{m}^2$ ] were also reported during this first interview. BMI was categorized as underweight (BMI  $< 18.5$ ), normal weight (18.5–24.9), overweight (25–29.9) and obese ( $\geq 30$ ).<sup>20</sup> Pre-existing diabetes was assessed during the second interview (median of 31 weeks, interquartile range 29–33 weeks), and was supplemented with cases identified via ICD-10 diagnostic codes for insulin dependent or non-insulin-dependent diabetes occurring in the hospital registry prior to the estimated date of conception. Multiple gestation pregnancies were identified via the birth record. Prior PE was determined for multiparous women using discharge diagnoses for prior births occurring from 1995 to 2003. A composite variable was constructed to classify high risk

women as those with one or more of the following: probable or definite hypertension (combined as both contributed independently to risk for PE), BMI  $\geq 30$ , multiple gestation, pre-existing diabetes, or a prior preeclamptic pregnancy (multiparas).

Cases of PE were identified in the hospital registry using ICD-10 codes O14 – O15 ( $n = 2117$ ). These data have been found to have reasonable validity since PE is treated in specialized departments.<sup>19</sup> Danish guidelines define PE as gestational hypertension (blood pressure  $\geq 140/90$  mmHg on at least three occasions) in combination with proteinuria of  $\geq 0.3$  g/l. Cases of PE were further classified as severe based on ICD-10 codes O141 and O150–O159. Current Danish guidelines for severe PE include the presence of a diastolic blood pressure  $\geq 110$  mmHg or a systolic blood pressure  $\geq 180$  mmHg, proteinuria and/or other signs or symptoms involving one or more organ systems.<sup>21</sup> Gestational age of onset was not available, so we defined early PE as those cases delivered  $< 37$  weeks gestation. Gestational age was reported in the birth record, and reflects the clinical evaluation at the time of birth and was based on ultrasound measures. When missing ( $n = 862$ ), gestational age was based on a woman's estimated date of delivery using information reported during the first interview about the last menstrual period.

Possible confounders considered were smoking status, maternal age at delivery and socio-occupational status (from the first interview). Socio-occupational status was based on a woman's current or most recent job (within 6 months) or on the type of education for women who reported being in school.<sup>22</sup> The category of high socio-occupational status included women in management or those with jobs requiring more than 4 years of education beyond high school. Office, service or skilled manual workers and women in the military were classified in the middle category; unskilled workers or unemployed women were classified in the low category. Women who could not be classified (4%) were categorized according to their husband's socio-occupational status. Because multiparous women included in our study were limited to those for whom we could match an earlier delivery occurring from 1995 to 2003, thus over-representing women with shorter pregnancy intervals, we estimated the inter-pregnancy interval for multiparous women. Inter-pregnancy interval was defined as the time between the birth of the first child and the estimated date of conception of the subsequent child.

The chi-square test was used to compare characteristics of women with normal pregnancies and with PE. Generalized estimating equations based on the binomial distribution and log link were used to directly estimate the relative risk (RR) associated with each pre-existing condition for developing PE, severe PE and early PE. Separate models were built for nulliparous and multiparous women, as the aetiology of PE may differ by parity.<sup>23</sup> Multivariable models were used to adjust the RR estimates for maternal age, socio-occupational status, smoking status and inter-pregnancy interval (multiparous women). Additional adjusted models were built to estimate the RR of developing PE associated with BMI as a continuous variable. Curves produced by non-parametric regression smoothing with LOWESS (locally weight regression scatterplot smoother) were created to observe the nature of the association between BMI and PE risk, including early PE.

**Table 1** Frequency of pre-existing conditions and preeclampsia, by parity, Danish National Birth Cohort 1997–03

	Nulliparas ( <i>n</i> = 41 325)		Multiparas ( <i>n</i> = 29 599)		Total ( <i>n</i> = 70 924)	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
<b>Chronic hypertension</b>						
Probable	1171	2.8	746	2.5	1917	2.7
Definite	533	1.3	367	1.2	900	1.3
BMI ≥30	3141	7.6	2481	8.3	5622	7.9
BMI 25–29.9	7407	17.9	5906	20.0	13313	18.8
Diabetes (non-gestational)	146	0.4	127	0.4	273	0.4
Multiple gestation	1204	2.9	596	2.0	1800	2.5
Prior preeclampsia	–	–	1018	3.4		
At least one high risk factor <sup>a</sup>	5705	13.8	4002	13.5	9707	13.7
Preeclampsia	1719	4.2	398	1.3	2117	3.0
Early preeclampsia (<37 weeks)	381	0.9	68	0.2	449	0.6
Severe preeclampsia	361	0.9	65	0.2	426	0.6
Severe and early preeclampsia	197	0.5	31	0.1	228	0.3

<sup>a</sup> Chronic hypertension (probable or definite), BMI ≥30, multiple gestation, diabetes (non-gestational).

The attributable fraction estimates the proportion of PE (and early or severe PE) in the total population that might be explained by each pre-existing condition if the associations are in fact causal. The attributable fraction depends on both the strength of the association between exposure and disease as well as the prevalence of the exposure,<sup>24</sup> and the formula rests upon the multiplicative model.<sup>25</sup> The attributable fraction was estimated for each pre-existing condition, and then again for women with one or more conditions. Separate models were constructed after limiting cases of early PE to those delivered ≤34 weeks gestation to more precisely characterize early onset cases. We also stratified the analysis by maternal age >36; there were too few observations to stratify by young maternal age. 95% confidence limits were constructed for PAR estimates based on the lower and upper bounds of the relative risk<sup>26</sup>.

## Results

Nulliparous women had a higher rate of PE compared with multiparous women (4.2 vs 1.3%, Table 1). Similarly, a higher percentage of nulliparous vs multiparous women experienced severe or early PE, despite the fact that the percentage of women with at least one of the study-defined pre-existing conditions (hypertension, diabetes, obesity and multiple gestation) did not differ by parity. Overall, 25% of PE cases were characterized as severe or early (11% were both severe and early). Among severe PE cases, 54% were delivered pre-term. Additional maternal characteristics are presented in Table 2.

### Occurrence and population risk of PE, nulliparas

In terms of attributable fraction, the presence of at least one pre-existing condition (probable or definite hypertension, pre-existing diabetes, multiple gestation or obesity) was associated with 22.3% (95% CI 19.8–24.9) of all PE cases in nulliparous women (Table 3). Results were not different when limiting analysis to non-severe cases (*n* = 1358, PAR 23.0%, 95% CI 20.1–26.0) There was little overlap of conditions among these

nulliparous women; 87% of women with at least one pre-existing condition had only one. The adjusted RR of PE associated with having two or more conditions vs none was 4.6 (95% CI 3.8–5.5) while the RR associated with having just one pre-existing condition was 2.5 (95% CI 2.3–3.9). However, the prevalence of women with multiple comorbidities was so low (1.2%) that this group only accounted for 4% of PE cases.

Almost 34% (95% CI 28.3–40.0) of early PE was associated with the presence of hypertension, diabetes mellitus, multiple gestation or high BMI. Obesity independently contributed 7.6% and being overweight contributed 6.9% to the occurrence of early PE. The population attributable fraction for definite hypertension was 5.5% and an additional 3.2% of the risk for early PE was associated with probable hypertension. Multiple gestation contributed 12.5% to early PE cases, and pre-existing diabetes contributed only about 1%.

Severe PE was similarly related to these conditions. Twenty-two per cent (95% CI 17.0–28.4) of severe PE was associated with the presence of at least one pre-existing condition, and obesity and overweight were each associated with 8% of the attributable fraction for severe PE. Results were similar when analysis was restricted to women with severe PE who also delivered pre-term (*n* = 197); however, women with definite hypertension had an 8.2-fold (95% CI 5.2–12.9) increase in risk for severe and early PE.

All of these findings held when cases of early PE were limited to those women who delivered ≤34 weeks gestation (*n* = 208). Again, the risk associated with definite hypertension increased to 7.2 (95% CI 4.6–11.6) for delivery ≤34 weeks. The magnitude of the attributable fraction associated with each pre-existing condition separately or in combination did not change significantly when stratified by high (>36 years) maternal age.

### Occurrence and population risk of PE, multiparas

Multiparas for whom we could match a prior pregnancy were, on average, younger than multiparas with births prior to 1995 (28.7 vs 33.5 years, *P* < 0.0001) although they had a similar

**Table 2** Maternal characteristics by presence of preeclampsia (PE), severe preeclampsia, or early (<37 weeks) preeclampsia compared with women without preeclampsia (percentages), Danish National Birth Cohort 1997–2003

	Nulliparas (n = 41 325)				Multiparas (n = 29 599)			
	No PE n = 39 606	PE n = 1719	Severe PE n = 361	Early PE n = 381	No PE n = 29201	PE n = 398	Severe PE n = 65	Early PE n = 68
<b>Mother's age</b>								
<20	1.2	1.0***	0.8	0.8***	1.2	1.8***	3.7***	4.5***
20–25	22.4	23.3	21.9	21.5	24.1	25.5	24.8	31.3
26–30	50.5	47.1	47.6	45.1	24.6	18.6	17.4	14.9
31–35	21.1	23.1	25.6	28.1	39.8	40.2	39.5	40.3
36+	4.8	5.5	5.0	4.5	10.3	14.0	14.7	9
<b>Socio-occupational status</b>								
Low	3.8	4.4	5.0	6.3***	4.6	5.6	3.1	2.9
Middle	29.4	32.1	29.9	31	28.9	32.4	32.3	36.8
High	66.8	63.5	65.1	62.7	66.5	62.0	64.6	60.3
<b>Mother's country of origin</b>								
Denmark <sup>c</sup>	96.5	97.2	96.7	96.3	96.8	97.5	100	96.9
Other Nordic countries	1.0	0.5	0.6	0.8	0.8	1.3	0	3.1
Other	2.6	2.3	2.8	2.9	2.4	1.3	0	0
<b>BMI</b>								
<18.5	4.6	2.3*	2.5*	2.4*	4.7	1.0*	1.5**	1.5**
18.5–24.9	70.1	55.6	58.6	58.1	66.9	48.1	53.9	52.9
25–29.9	18.0	24.1	23.9	23.1	20.1	26.1	24.6	30.9
≥30	7.3	18.0	14.9	16.4	8.3	24.8	20.0	14.7
<b>Smoking in pregnancy</b>								
No	72.9	78.4*	83.3*	78.0	79.3	84	86.2	85.3
Quit before 2nd interview <sup>a</sup>	11.0	10.5	6.4	8.9	5.7	4.8	3.1	5.9
Smoking at 2nd interview <sup>a</sup>	16.0	11.2	10.3	13.1	15.0	11.2	10.8	8.8
Probable hypertension	2.7	6.4*	5.8**	6.1**	2.5	4.8	3.1	1.5
Definite hypertension	1.2	5.6*	8.3*	8.7*	1.1	9.1*	12.9*	7.5*
Diabetes (non-gestational)	0.3	1.2*	0.8	2.9*	0.4	2.0*	0	5.9*
Multiple gestation	2.8	6.5*	7.5*	16.5*	2.0	5.5*	6.2***	16.2*
Prior preeclampsia					3.0	36.2*	41.5*	36.8*
At least one pre-existing condition <sup>b</sup>	13.3	32.8*	31.9*	43.5*	15.2	60.0*	64.1*	58.2*

<sup>a</sup> Median time of the 2nd interview was the 31st week of pregnancy (interquartile range: 29–33 weeks).

<sup>b</sup> Chronic hypertension (probable or definite), BMI ≥30, multiple gestation, diabetes (non-gestational) or prior preeclamptic pregnancy (multiparas).

<sup>c</sup> Includes 412 women from Greenland or Faroe Island.

\*  $P < 0.0001$  chi-square when compared with women with normal pregnancies; \*\* $P < 0.01$  and \*\*\* $P < 0.05$ .

BMI (23.7 vs 23.8,  $P = 0.074$ ). Matched multiparas also had lower rates of PE and severe or early PE ( $P < 0.0001$ ) when compared with multiparas with births prior to 1995. Among the multiparous women we analysed, presence of a prior preeclamptic pregnancy, probable or definite hypertension, multiple gestation, obesity or diabetes mellitus was associated with 52.2% (95% CI 46.4–57.9) of all cases of PE (Table 4). Twenty-six per cent of PE cases were associated with a prior preeclamptic pregnancy, 11% of cases were associated independently with obesity, and 8.3% of cases were associated with being overweight.

Fifty per cent (95% CI 37.5–63.4) of pre-term PE was associated with the presence of at least one study-defined condition. A prior preeclamptic pregnancy accounted for 30.5% of early PE cases. Multiple gestation and being overweight were associated

with 11.7 and 13% of the population risk of early PE, respectively. Fifty-nine per cent (95% CI 44.7–71.7) of severe PE cases among multiparous women were associated with the presence of at least one pre-existing condition, with prior PE accounting for the majority of this risk. When prior PE was removed from the analysis, 29.6% (95% CI 24.1–35.4) of all PE cases, 25.1% (95% CI 12.9–39.1) of early PE and 26.5% (95% CI 13.9–40.9) of severe PE were associated with at least one pre-existing condition.

### BMI, preeclampsia and early preeclampsia

As BMI increased, the predicted probability of PE among nulliparous women increased linearly; this relationship was also apparent, although attenuated, among multiparous women

**Table 3** Risk of preeclampsia, nulliparas ( $n=41\ 325$ ), Danish National Birth Cohort 1997–03

Risk factor	Preeclampsia (%)	Crude RR	Adj RR(95% CI)	Population attributable risk(%)	PAR 95% CI
Chronic hypertension					
Probable	9.3	2.5	2.2 (1.9–2.7)	3.4	(2.4–4.6)
Definite <sup>a</sup>	16.7	4.4	3.4 (2.8–4.1)	3.1	(2.4–4.1)
Multiple gestation <sup>a</sup>	9.2	2.3	2.2 (1.8–2.6)	3.4	(2.3–4.5)
BMI $\geq 30$ <sup>a</sup>	9.7	2.9	2.6 (2.3–2.9)	11.0	(8.9–12.9)
BMI 25–29.9 <sup>a</sup>	5.5	1.6	1.6 (1.4–1.7)	9.2	(6.6–12.0)
Diabetes <sup>a</sup>	13.7	3.3	2.1 (1.4–3.0)	0.4	(0.1–0.7)
At least one high risk factor <sup>b</sup>	9.7	3.0	3.0 (2.8–3.4)	22.3	(19.8–24.9)
None of the risk factors	4.0		1.0		
Risk factor	Early PE (%)	Crude RR	Adj RR <sup>a</sup> (95% CI)	Population attributable risk (%)	PAR 95% CI
Chronic hypertension					
Probable <sup>a</sup>	2.0	2.4	2.2 (1.4–3.3)	3.2	(1.2–6.3)
Definite <sup>a</sup>	6.1	7.6	5.4 (3.8–7.6)	5.5	(3.8–9.0)
Multiple gestation <sup>a</sup>	5.2	6.6	5.9 (4.5–7.8)	12.5	(9.1–16.3)
BMI $\geq 30$ <sup>a</sup>	1.9	2.5	2.1 (1.6–2.7)	7.6	(4.1–11.8)
BMI 25–29.9 <sup>a</sup>	1.2	1.5	1.4 (1.1–1.8)	6.9	(1.7–12.6)
Diabetes <sup>a</sup>	7.5	8.4	3.7 (2.3–6.0)	0.9	(0.5–1.8)
At least one high risk factor <sup>b</sup>	2.9	4.7	4.6 (3.8–5.7)	33.8	(28.3–40.0)
None of the risk factors	0.6		1.0		
Risk factor	Severe PE (%)	Crude RR	Adj RR <sup>a</sup> (95% CI)	Population attributable fraction (%)	PAR 95% CI
Chronic hypertension					
Probable <sup>a</sup>	1.9	2.4	2.2 (1.4–3.5)	4.9	(1.7–9.4)
Definite <sup>a</sup>	5.9	7.3	6.2 (4.2–9.1)	6.5	(4.3–9.9)
Multiple gestation <sup>a</sup>	2.4	2.8	2.6 (1.7–3.9)	4.4	(2.0–7.7)
BMI $\geq 30$ <sup>a</sup>	1.8	2.4	2.1 (1.6–2.9)	7.8	(3.7–15.4)
BMI 25–29.9 <sup>a</sup>	1.2	1.6	1.5 (1.1–1.9)	7.9	(2.5–14.0)
Diabetes <sup>a</sup>	2.3	2.6	1.7 (0.6–5.0)	0.2	(–0.2–1.5)
At least one risk factor <sup>b</sup>	2.2	3.0	3.1 (2.5–3.9)	22.5	(17.0–28.4)
None of the risk factors	0.7		1.00		

<sup>a</sup> Estimates from one model containing probable or definite hypertension, multiple gestation, diabetes, BMI, maternal age, smoking, socio-occupational status; non-smoking women with BMI < 25–9.9 and without any of the study conditions are the referent.

<sup>b</sup> Estimates from one model containing a composite variable (presence of probable or definite hypertension, multiple gestation, diabetes, BMI  $\geq 30$ ) and maternal age, smoking and socio-occupational status; non-smoking women without any of the study conditions are the referent.

(Figure 1). The trend was similar for early PE, although the relationship between BMI and early PE appeared to be different after a BMI of 30 (Figure 2). Each one-unit (adjusted) increase in BMI among nulliparous women conferred a 7% increase in risk for PE (95% CI 1.06–1.08) and a 6% increase in risk for early PE (95% CI 1.05–1.08). Among multiparous women, the effect was similar, although attenuated; each one-unit increase in BMI, adjusted for all other factors, conferred a 3% (95% CI 1.0–1.1) increase in risk for early PE.

## Discussion

Among a population of pregnant women from Denmark, the portion of PE associated with pre-existing and easily identified maternal and obstetric factors ranged from 22% among nulliparous women to 52% among multiparous women. The fraction of early PE preceded by these factors ranged from 34%

among nulliparas to 50% among multiparas. Our results indicate that chronic hypertension confers a 7- to 8-fold increase in risk for the most severe PE cases, those delivered very pre-term or those cases involving both severe maternal symptoms and pre-term delivery.

Our results indicate that pre-existing maternal metabolic and vascular conditions contribute significantly to the risk severe or early PE. Sibai *et al.*<sup>13</sup> found that women with chronic hypertension for at least 4 years prior to pregnancy had more severe PE and higher rates of pre-term delivery and growth-restricted infants. Nulliparous women in our study with definite hypertension also had high rates of PE (16.7%) including severe or early PE. This relatively small group of women (1.3% of nulliparas) accounted for 5% of the early PE cases and 7% of severe PE cases. Prior PE accounted for a large fraction of PE cases among multiparous women in our study. While this finding is certainly relevant from a clinical

**Table 4** Risk of preeclampsia, multiparas ( $n = 29\ 599$ ), Danish National Birth Cohort 1997–03

<b>Risk factor</b>	<b>Preeclampsia (%)</b>	<b>Crude RR</b>	<b>Adj RR<sup>a</sup> (CI)</b>	<b>Population attributable risk (%)</b>	<b>PAR 95% CI</b>
Chronic hypertension					
Probable <sup>a</sup>	2.6	2.1	1.1 (0.7–1.7)	0.3	(–1.1–2.8)
Definite <sup>a</sup>	9.8	8.2	2.0 (1.5–2.8)	1.3	(0.6–2.3)
Multiple gestation <sup>a</sup>	3.7	2.8	2.3 (1.6–3.4)	2.6	(1.2–4.5)
BMI $\geq 30^a$	4.0	4.0	2.4 (1.9–3.1)	10.9	(7.1–15.2)
BMI 25–29.9 <sup>a</sup>	1.7	1.8	1.5 (1.1–1.9)	8.3	(2.9–14.6)
Diabetes <sup>a</sup>	6.3	4.8	1.4 (0.7–2.8)	0.2	(–1.1–0.8)
Prior preeclampsia <sup>a</sup>	14.2	15.9	11.2 (9.0–14.0)	26.1	(22.5–32.0)
At least one risk factor <sup>b</sup>	5.1	7.9	7.8 (6.4–9.6)	52.2	(46.4–57.9)
None of the risk factors	1.3		1.0		
<b>Risk factor</b>	<b>Early PE (%)</b>	<b>Crude RR</b>	<b>Adj RR<sup>a</sup> (CI)</b>	<b>Population attributable risk (%)</b>	<b>PAR 95% CI</b>
Chronic hypertension					
Probable <sup>a</sup>	0.1	0.6	0.3 (0.05–2.4)	–1.7	(–2.5–3.5)
Definite <sup>a</sup>	1.4	6.4	1.1 (0.4–3.0)	0.2	(–0.7–2.5)
Multiple gestation <sup>a</sup>	1.9	9.4	7.6 (4.0–14.5)	11.7	(5.7–21.2)
BMI $\geq 30^a$	0.4	2.2	1.4 (0.7–2.9)	3.5	(–2.6–13.8)
BMI 25–29.9 <sup>a</sup>	0.4	1.9	1.7 (1.0–3.0)	13.0	(0.0–28.0)
Diabetes <sup>a</sup>	3.2	14.5	4.6 (1.7–12.3)	1.5	(0.3–4.7)
Prior preeclampsia <sup>a</sup>	2.5	16.3	13.7 (8.1–23.3)	30.5	(20.4–44.6)
At least one risk factor <sup>b</sup>	0.8	7.3	7.3 (4.5–11.8)	50.0	(37.5–63.4)
None of the risk factors	0.1		1.00		
<b>Risk factor</b>	<b>Severe PE (%)</b>	<b>Crude RR</b>	<b>Adj RR<sup>a</sup> (95% CI)</b>	<b>Population attributable fraction (%)</b>	<b>PAR 95% CI</b>
Chronic hypertension					
Probable <sup>a</sup>	0.3	1.4	0.7 (0.2–3.1)	0.0	0
Definite <sup>a</sup>	2.4	12.3	3.0 (1.4–6.4)	2.5	(0.5–5.7)
Multiple gestation <sup>a</sup>	0.7	3.3	3.0 (1.1–7.9)	3.8	(0.3–12.2)
BMI $\geq 30^a$	0.5	3.0	1.9 (1.0–3.6)	6.9	(–0.2–18.0)
BMI 25–29.9 <sup>a</sup>	0.3	1.5	1.3 (0.7–2.3)	5.1	(–7.1–20.6)
Diabetes <sup>a</sup>	0.0	0.0	0	0.0	0
Prior preeclampsia <sup>a</sup>	3.0	22.3	18.3 (10.7–31.3)	38.4	(25.9–52.3)
At least one risk factor <sup>b</sup>	0.9	9.8	10.1 (6.1–16.8)	59.3	(44.7–71.7)
None of the risk factors	0.1		1.00		

<sup>a</sup> Estimates from one model containing probable or definite hypertension, multiple gestation, diabetes, BMI, maternal age, smoking, socio-occupational status, prior preeclampsia, inter-pregnancy interval.

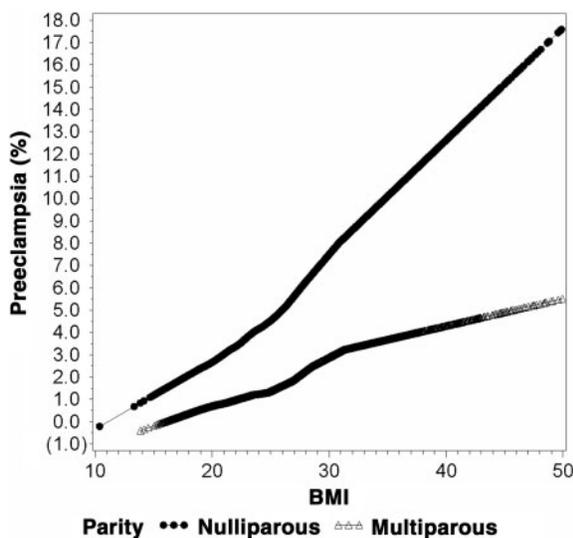
<sup>b</sup> Estimates from one model containing a composite variable (presence of probable or definite hypertension, multiple gestation, diabetes, BMI  $\geq 30$ , prior preeclampsia) and maternal age, smoking and socio-occupational status, inter-pregnancy interval.

perspective, it is also noteworthy that when prior PE was removed from the analysis, pre-existing risk factors accounted for 25–30% of PE, including severe and early cases.

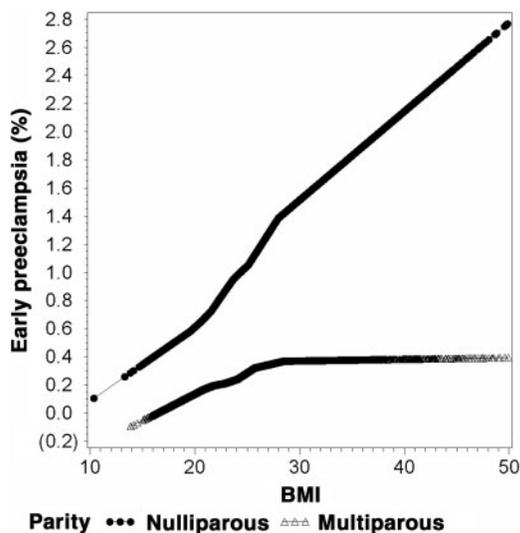
Our findings contribute to a growing body of evidence that pre-pregnancy BMI plays an important role in risk for PE.<sup>17,27,28</sup> We found BMI to be independently associated with the risk for PE in multiparous as well as nulliparous women. In addition, our results suggest that 15–17% of the population risk of early PE is associated with being overweight or obese. Our findings are consistent with those of Bodnar *et al.*<sup>17</sup> that small increases in BMI, even within the normal range, significantly and independently increase a woman's risk of PE. If causal, BMI may be the one modifiable risk related to PE risk, but the

association could also be related to insulin resistance. There is recent evidence that increased physical activity may reduce the risk for PE,<sup>29–31</sup> but there are no published reports, to our knowledge, on weight loss prior to pregnancy and risk for PE and this is an area that requires further study.

There are important strengths of our study. The Danish National Birth Cohort provides a large and well-characterized population in which to study relatively rare pregnancy outcomes, such as severe or early PE. The cohort was established within a stable, universal and tax paid health care system where more than 99% of women access pre-natal care, ensuring standardized and validated diagnostic as well as outcome information.<sup>19</sup>



**Figure 1** Unadjusted probability of preeclampsia according to BMI among nulliparous (top line, dot) and multiparous (bottom line, triangle) women



**Figure 2** Unadjusted probability of early preeclampsia (<37 weeks) according to BMI among nulliparous (top line, dot) and multiparous (bottom line, triangle) women

There are also limitations to our study. The majority of the population in Denmark is Caucasian, thus limiting the generalizability of our results to other ethnic groups. That the magnitude of the relative risks we calculated, as well as our prevalence estimates of prior PE and pre-existing conditions, are similar to those of other studies<sup>3,14</sup> provides reassurance about the applicability of our findings to more diverse populations. The prevalence of obesity and overweight in the US is significantly higher than in Denmark, and we may thus have underestimated the burden of disease attributable to these factors in countries with higher rates of obesity and overweight and overestimated the attributable fraction in leaner populations.

We relied on self-report of some study variables, although we validated these data with diagnostic or other confirmatory information when available. For example, self-reported pre-existing hypertension was classified as definite when women also reported taking antihypertensive medication. However, we were unable to evaluate actual blood pressure measures. Danish criteria for PE are similar to those in other countries, but blood pressure criteria for severe PE is higher (180 vs 160 mmHg). Therefore, while we may have underestimated the occurrence of severe PE and overestimated the occurrence of mild PE, our estimates related to overall PE are unlikely to be misclassified. Although multiparous women with shorter inter-pregnancy intervals were over-represented in our population, we accounted for this in our modelling, and the multiparous women we analysed were younger and had lower rates of PE, suggesting that any bias we have introduced would cause our estimates to be conservative.

Our results among a general, well-characterized population indicate that well-known maternal morbidity and obstetric factors can identify up to 34% of population risk for early PE and 23% of the risk for severe PE among nulliparous women. Among multiparous women, these pre-existing conditions are associated with 50% of early PE and 59% of severe cases. These women represent a subgroup of preeclamptic women with the worst neonatal outcomes and the most severe long-term cardiovascular disease risks. Given that obesity continues to increase in the US and other countries, our findings related to BMI have potentially profound public health implications.

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### KEY MESSAGES

- Pre-existing maternal and obstetric conditions identified up to 34% of the population risk for early PE and 23% of the risk for severe PE.
- Among multiparous women, these pre-existing conditions were associated with 50% of early PE and 59% of severe cases.
- Obesity and overweight contributed independently to the risk of pre-term or severe PE, a finding with potentially profound public health implications.

initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from the Foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation and the Health Foundation. The authors also thank Inge Eisensee for programming assistance.

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