The association between ethnicity and pre-eclampsia in Australia: A multicentre retrospective cohort study

Ziad TA AL-RUBAIE, H Malcolm HUDSON, Gregory JENKINS, Imad MAHMOUD, Joel G RAY, Lisa M ASKIE, Sarah J LORD

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Background: Rates of pre-eclampsia vary between countries and certain ethnic groups. However, there is limited evidence about the impact of ethnicity on risk of pre-eclampsia, beyond established clinical risk factors.

Aims: To assess the association between ethnicity and pre-eclampsia in Australia's diverse multiethnic population.

Materials and Methods: We conducted a retrospective cohort study using the ObstetriX dataset. We included all women with a birth between January-2011 and December-2014, at ~~[A]~~Auburn, ~~[B]~~Blacktown/Mount-Druitt and ~~[C]~~Westmead hospitals in the ~~[X]~~Western Sydney Local Health District. We estimated the pre-eclampsia rate overall, and by maternal ethnic group, defined by country-of-birth and primary language. We developed multivariable logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CIs) for pre-eclampsia, adjusting for maternal age, body mass index, autoimmune disease, chronic hypertension, chronic renal disease, diabetes mellitus (type 1 or 2), and multiple pregnancy. A secondary analysis was restricted to nulliparous women.

Results: 40,824 women were evaluated, including 12,743 nulliparous women. 1448 (3.5%) women developed pre-eclampsia (range: Australian/New Zealand-born English-speakers 735/15,422 (4.8%); North-East Asian women 51/4470 (1.1%)). Relative to Australian/New Zealand-born English-speakers, immigrants had a lower risk of pre-eclampsia overall (adjusted OR 0.67 (95% CI 0.60-0.75)); as did the three largest immigrant groups examined: Southern Asian (0.73 (0.62-0.85)), Middle-Eastern/African (0.55 (0.47-0.66)) and North-East Asian (0.33 (0.25-0.45)) women. Findings were similar for nulliparous women.

Conclusions: Certain immigrant groups are at lower risk of pre-eclampsia than Australian/New Zealand-born English-speaking women. Understanding why this is so may lead to better screening and preventive strategies in higher risk women.

INTRODUCTION

Australian antenatal guidelines list clinical risk factors for pre-eclampsia and recommend routine risk assessment in early pregnancy to identify moderate- to high-risk women for preventive strategies such as aspirin.[1,2] There is international evidence that risk of pre-eclampsia also varies between countries and between ethnic groups,[3,4] but limited evidence on the impact of ethnicity on pre-eclampsia in Australia's diverse multiethnic antenatal population, beyond established clinical risk factors.

In Australia, approximately one-third of births are to immigrant women.[5] An international analysis of immigrant status and pre-eclampsia that used population-based datasets from the USA, Canada, Denmark, Sweden, Spain and Australia (over 9,000,000 births, 1995-2010) reported immigrant women from Sub-Saharan Africa and Latin America and the Caribbean to be at higher risk of pre-eclampsia than non-immigrant women; while East-Southeast Asian and North-African/Middle-Eastern women were at lower risk than non-immigrant women.[3] However, the effect of ethnicity appeared to vary by receiving country.[3] In particular, in the Australian dataset, immigrant groups, including Sub-Saharan African women, had a similar or lower risk of pre-eclampsia than Australian-born women. However, study estimates of the effect of ethnicity on pre-eclampsia were not adjusted for important clinical risk factors which may explain the variation observed between ethnic groups. In contrast, a prospective cohort study in Australia that adjusted for risk factors for pre-eclampsia indicated that East-Asian and South-Asian women may be at higher risk of early-onset pre-eclampsia than Caucasian women, although this study was limited by the small sample size and these findings were not statistically significant.[6]

The aim of the current study was to assess the association between ethnicity and pre-eclampsia to address this gap.

MATERIALS AND METHODS

Design, population and setting

We used a retrospective cohort study design. The study sample was drawn from the three public hospitals (Auburn, Blacktown/Mount-Druitt and Westmead) in the ~~[X]~~Western Sydney Local Health District (~~[X]~~WSLHD) providing different healthcare levels.[7]

We extracted study data from the ObstetriX database held by the maternity unit at each hospital. This database collects information for women from the first antenatal visit until delivery and discharge from hospital.[8]

We included all women with a birth recorded between 1st January-2011 and 31st December-2014 regardless of parity. Exclusion criteria were: women with missing information for pre-eclampsia, parity or ethnicity. We also excluded women who were prescribed antiplatelet therapy in the first trimester given the effectiveness of these agents for preventing pre-eclampsia.

Study data were provided de-identified with a waiver for patient consent approved by the Notre Dame and ~~[X]~~WSLHD ethics committees. (Notre Dame HREC approval number: 016071S; and ~~[X]~~WSLHD HREC approval number: LNR/16/WMEAD/239, LNR SSA/16/WMEAD/256, LNR SSA/17/WMEAD/113, LNR SSA/17/WMEAD/117).

Outcomes

The primary outcome was pre-eclampsia (any severity or timing). During the study period, clinical guidelines defined pre-eclampsia as hypertension with new onset of significant proteinuria at or beyond 20 weeks' gestation.[9] Secondary outcomes were early-onset pre-eclampsia (requiring

delivery before 34 weeks' gestation) and preterm pre-eclampsia (requiring delivery before 37 weeks' gestation).

Study data

For each participant, we extracted information about hospital site; gestational age at first visit; socio-demographic characteristics (maternal age, country of birth, primary language spoken at home and socioeconomic status classified from postcode using the Index of Relative Socio-economic Advantage and Disadvantage from the Socio-Economic Indexes for Areas (SEIFA))[10], clinical risk factors for pre-eclampsia (parity, body mass index (BMI), autoimmune disease, chronic hypertension, chronic renal disease, diabetes mellitus (type 1 or 2), multiple pregnancy, family history of pre-eclampsia); and study outcomes.

We selected clinical risk factors from antenatal guidelines[1,11,12] and published risk prediction models for pre-eclampsia[13] that were available in the ObstetriX database (see details, Supplementary Appendix).

We classified women as immigrant or non-immigrant based on country-of-birth; and geographically into six ethnic groups based on country-of-birth and, for women born in Australia and New Zealand, primary language spoken at home: Australian/New Zealand-born English-speakers, Middle-Eastern/African, South-East Asian, North-East Asian, Southern Asian, and Others (Supplementary Appendix).

Women with missing values for study variables were excluded from the analysis requiring that variable.

Statistical analysis

We summarised maternal characteristics for the total study sample, and for each hospital site. For categorical variables, we calculated the count and percentage. For continuous variables, we calculated the mean and standard deviation (SD), median, range and interquartile range (IQR). We calculated the rate of pre-eclampsia among all women and for the subgroup of nulliparous women, overall and by hospital.

For ethnicity and each pre-defined pre-eclampsia risk factor, we assessed the association with pre-eclampsia using univariable and multivariable logistic regression models to estimate unadjusted odds ratios (OR), adjusted OR (aOR), and their 95% confidence intervals (CIs). The multivariable logistic regression models included risk factors for pre-eclampsia listed in clinical guidelines: autoimmune disease, chronic hypertension, chronic renal disease, diabetes mellitus (type 1 or 2), multiple pregnancy, maternal age (<25, 25-29, 30-34, ≥35 years) and BMI (<25, 25-29, 30-34, ≥35 kg/m^2). As we did not have information about any past pregnancy history, the main analyses were re-run, but restricted to nulliparous women.

We tested for differences in the prevalence of risk factors by ethnicity using a chi-square test for categorical variables and ANOVA for continuous variables. We assessed for heterogeneity in the effect size for each risk factor between ethnic groups by estimating the adjusted OR and 95% CIs for each risk factor within each ethnic group and testing for an interaction between ethnicity and the risk factor using the Wald test.

We performed secondary analyses for Sub-Saharan Africa and Latin America and the Caribbean born women, given international evidence of increased risk of pre-eclampsia for these groups;[3] and for women who identify as Aboriginal and/or Torres Strait Islander in the ObstreriX database, given evidence of their increased risk of pre-eclampsia reported in NSW.[8]

We also performed secondary analyses to assess the association between each risk factor, and ethnicity, and early-onset and preterm pre-eclampsia for all women and for the subgroup of nulliparous women. We excluded women who did not have gestational age at delivery recorded from the analyses of early-onset and pre-term pre-eclampsia.

We performed two post-hoc sensitivity analyses to explore the impact of potential study limitations on our estimates of the effect of ethnicity on pre-eclampsia. First, we excluded ~~[C]~~Westmead hospital participants to examine the potential for selection bias from including births from this tertiary referral hospital that receives transfers of high-risk women outside of ~~[X]~~WSLHD. Second, we excluded women with high-risk factors to minimise the risk of residual confounding. For the latter analysis, we anticipated under-reporting of risk factors more likely for immigrant women than Australian/New Zealand-born English-speakers.

Statistical significance was set at a p-value of <0.05. We used SPSS version 24 and R statistical software for analyses.

RESULTS

We received data for 41,175 women giving birth between 2011 and 2014. After exclusions, 40,824 women were included in the analysis, including 12,743 nulliparous women (Figure S1). ~~[C]~~Westmead hospital contributed more than 50% of the participants.

Approximately two-thirds of women (64.0%) were born overseas and participant socio-demographic characteristics varied by hospital (Table 1). Overall, 21.5% were of Southern Asian ethnicity and

17.1% were Middle-Eastern/African (Table 1). One-third of women were nulliparous 12,743 (31.2%), with similar proportions across the three hospitals.

The mean age of participants was 29.3 years (SD 5.3). The median gestational age at delivery was 39.3 weeks (IQR 38.4-40.3). 3166 women (7.8%) had preterm deliveries before 37 weeks' gestation, and 1197 women (2.9%) had deliveries before 34 weeks.

1331 women (3.2%) had a multiple pregnancy. The rates of chronic hypertension, chronic renal disease and diabetes mellitus (type 1 or 2) were each approximately 1%, with the highest rates in ~~[C]~~Westmead hospital and lowest rates in ~~[A]~~Auburn hospital (Table 1). Autoimmune disease was recorded in 59 women (0.1%). Family history of pre-eclampsia was recorded in 104 women (0.3%). 345 women (0.8%) received antiplatelet therapy after the first trimester.

The rate of pre-eclampsia was 3.5% (n=1448 women) and lowest in ~~[A]~~Auburn hospital (1.9%) (Table S1). The prevalence of risk factors varied between ethnic groups (p <0.001, Table S2).

Risk factors for pre-eclampsia

All women

The rate of pre-eclampsia varied by ethnic group with the lowest rate among North-East Asian women (1.1%) and the highest among Australian/New Zealand-born English-speaking women (4.8%) (Table 2, Figure 1). After adjusting for other risk factors, immigrants had a lower risk of pre-eclampsia than Australian/New Zealand-born English-speakers (aOR 0.67, 95% CI 0.60-0.75). Middle-Eastern/African (aOR 0.55 (0.47-0.66)), North-East Asian (aOR 0.33 (0.25-0.45)) and Southern Asian (aOR 0.73 (0.62-0.85)) ethnic groups had a lower risk of pre-eclampsia compared to Australian/New

Zealand-born English-speaking women, but not South-East Asians (aOR 0.98 (0.79-1.23)). Nulliparous women had a lower risk of pre-eclampsia than parous women (aOR 0.74 (0.64-0.85)).

Women aged 35 years or older had a 54% higher relative odds of pre-eclampsia than women aged 25-29 years (aOR 1.54 (1.32-1.79)). Women with a BMI of 35 kg/m^2 or higher had a 3.5-fold increased relative odds of pre-eclampsia compared to those with a BMI less than 25 kg/m^2 (aOR 3.51 (2.98-4.13)). We also observed an association between assisted method of conception and risk of pre-eclampsia (Table 2).

Of the established clinical risk factors, chronic hypertension, renal disease and family history were the strongest risk factors in our study sample, associated with a four-fold or higher increased relative odds of pre-eclampsia (aOR 4.29 (2.03-9.05, aOR 3.99 (2.96-5.39), aOR 5.65 (3.25-9.84) respectively). Autoimmune disease was rare (n=59) thus our estimate is surrounded by a wide confidence interval (aOR 2.41 (1.04-5.59)) (Table 2).

Variation between the effect of risk factors and ethnicity was not statistically significant except for multiple pregnancy where the effect was greatest among North-Asian women (*p*-heterogeneity=0.003, Table S3).

Nulliparous women

There were 308 cases of pre-eclampsia in 12,743 nulliparous women (2.4%), and the rate varied between ethnic groups (Table 2). The size of the association between each risk factor and pre-eclampsia were similar to those observed for all women, with the exception of diabetes mellitus (type 1 or 2) which were not associated with pre-eclampsia after adjustment for other risk factors (Table 2).

Ethnicity results were consistent in the sensitivity analyses excluding ~~[C]~~Westmead hospital and high-risk women (immigrants versus Australian/New Zealand-born English-speakers, aOR 0.58 (0.49-0.70) and 0.66 (0.57-0.75) respectively).

The study sample included 1030 (2.5%) women from Sub-Saharan Africa and 290 (0.7%) women from Latin America and Caribbean. The rate of pre-eclampsia was 3.5% (n=36) and 3.4% (n=10) in these groups respectively, with an aOR for pre-eclampsia of 0.63 (95% CI 0.44-0.90) and 0.64 (95% CI 0.33-1.26) compared to Australian/New Zealand-born English-speakers. 774 (1.9%) women were recorded as Aboriginal and/or Torres Strait Islander in the ObstreriX database. Of these, 44 (5.7%) women had pre-eclampsia with an aOR of 1.28 (95% CI 0.92-1.78) compared to other Australian/New Zealand-born English-speakers.

Early-onset and pre-term pre-eclampsia

Of 40,810 women included in the analysis of early-onset and preterm pre-eclampsia, there were 150 early-onset (0.4%) and 386 preterm (0.9%) pre-eclampsia events (Table S1).

The rates of early-onset and pre-term pre-eclampsia were lower among immigrant women compared to Australian/New Zealand-born English-speaking women, but these findings were not statistically significant (aOR 0.84 (0.59-1.21) and 0.91 (0.73-1.14) respectively, Table S4). Middle-Eastern/African women had the lowest rate of early-onset pre-eclampsia compared to Australian/New Zealand-born English-speaking group (aOR 0.45 (0.24-0.86)); and North-East Asian women had the lowest rate of preterm pre-eclampsia (0.5%), compared to Australian/New Zealand-born English-speakers (aOR 0.59 (0.36-0.96)).

The analyses for nulliparous women were limited by small numbers but demonstrated results consistent to those for all women (Table S5).

DISCUSSION

We demonstrate the risk of pre-eclampsia varies widely between ethnic groups in Australia, independent of established risk factors. In the ~~[X]~~WSLHD study sample, Australian/New Zealand-born English-speaking women are at highest risk (4.8%, 95% CI 4.4-5.1%); while Southern Asian, Middle-Eastern/African, North-East Asian women, representing three of the four most common immigrant groups among women giving birth in Australia, each have a substantially lower risk of pre-eclampsia than locally born English-speakers, with the lowest rate among North-East Asian women (1.1%, 95% CI 0.9-1.5%).

Prior studies have largely focused on identifying immigrant groups at higher risk of pre-eclampsia than locally born women. Our findings that Australian immigrant groups are at lower risk than Australian/New Zealand-born English-speaking women contrast to findings from other countries[3,14] but are supported by the Australian subset findings from Urquia's international study that included 636,042 deliveries in Victoria,1999-2008 (Southern Asian OR 0.58, 95% CI 0.55-0.62, East-Southeast Asian OR 0.64, 95% CI 0.58-0.71 and Middle-Eastern/North-African women OR 0.69, 95% CI 0.63-0.77, adjusted by maternal age and parity).[3] The present study adds to these findings by demonstrating the ethnic differences in pre-eclampsia rates in Australia cannot be entirely explained by differences in the prevalence of known risk factors between ethnic groups, which we demonstrate also vary widely between groups.

For North-East Asian women (includes China, Japan, Korea, Taiwan), our finding of a substantially lower risk of pre-eclampsia than Australian/New Zealand-born English-speakers is also consistent

with estimates of the rate of pre-eclampsia in China;[15] and studies comparing Chinese-born versus locally born women in New Zealand (aOR 0.56 (0.41-0.76))[16] and the USA (aOR 0.80 (0.70-0.80)),[17] although only the former study fully adjusted for known risk factors. We defined ethnicity based on geographical region of birth and primary language spoken at home as a pragmatic, albeit imperfect, measure of race and culture that is currently used by the Australian Institute of Health and Welfare (AIHW). Research to identify genetic factors that may help explain differences between countries is still ongoing.[18,19] Research to identify environmental risk/protective factors associated with culture will be particularly valuable if modifiable for risk reduction.

The main study strengths are our large study sample of women from ~~[X]~~WSLHD, one of the most ethnically diverse communities in Australia, providing a rich dataset to assess the impact of ethnicity.

The main study limitation is the potential under-ascertainment of study variables in the ObstetriX database.[20] This appeared to be the case for family history of pre-eclampsia which was reported in only 0.3% of women. We also considered the possibility that high-risk factors may be more poorly identified for non-English-speaking women which may confound our assessment of the independent effect of ethnicity. However, we did not find evidence to support this concern from our sensitivity analysis excluding women with recorded high-risk factors.

Women giving birth in private hospitals were not included in the present analysis, thus we are unable to assess whether hospital setting impacts the Australian/New Zealand-born effect, for example due to differences in the risk of pre-eclampsia and ethnic composition between public and private hospitals. However, we note Urquia et al. reported similar findings from a population-based sample of women that included both public and private hospitals in Victoria.[3] The latter study provides support for the generalisability of our findings to antenatal care beyond the ~~[X]~~WSLHD.

In conclusion, our finding that certain immigrant groups are at lower risk of pre-eclampsia than Australian/New Zealand-born English-speaking women may be explained in part by a 'healthy migrant effect', due to as yet unknown factors (not accounted for by established risk factors). This raises the importance of further research to understand the underlying causes for the ethnic differences observed, which may provide valuable insights that lead to improved prevention or treatment strategies.

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TABLE 1 Maternal characteristics overall and by hospital, ~~[X]~~WSLHD, 2011-2014. All data are presented as a number (%) unless otherwise indicated

Characteristic	All women (N=40,824)†	~~[A]~~Auburn Hospital (N=5702)†	~~[B]~~Blacktown/Mount-Druitt Hospital (N=12,906)†	~~[C]~~Westmead Hospital (N=22,216)†
Ethnicity				
Australian/New Zealand-born English-speakers	15422 (37.8)	1192 (20.9)	6195 (48.0)	8035 (36.2)
Middle-Eastern/African	6977 (17.1)	1576 (27.6)	1464 (11.3)	3937 (17.7)
South-East Asian	2725 (6.7)	270 (4.7)	1173 (9.1)	1282 (5.8)
North-East Asian	4470 (10.9)	1503 (26.4)	410 (3.2)	2557 (11.5)
Southern Asian	8762 (21.5)	1008 (17.7)	2639 (20.4)	5115 (23.0)
Others	2468 (6.0)	153 (2.7)	1025 (7.9)	1290 (5.8)
Maternal and clinical factors				
Parity				
Parous	28081 (68.8)	3870 (67.9)	9231 (71.5)	14980 (67.4)
Nulliparous	12743 (31.2)	1832 (32.1)	3675 (28.5)	7236 (32.6)
Gestational age at first visit (weeks)				
Median (IQR)	12.0 (6.0-18.0)	19.0 (15.0-23.0)	15.0 (12.0-18.0)	8.0 (5.0-13.0)
<12 weeks' gestation	18434 (45.2)	1008 (17.7)	3162 (24.5)	14264 (64.2)
12-28 weeks' gestation	20304 (49.7)	4120 (72.3)	8944 (69.3)	7240 (32.6)
>28 weeks' gestation	2086 (5.1)	574 (10.1)	800 (6.2)	712 (3.2)
Gestational age at delivery (weeks) , N=40810				
Median (IQR)	39.3 (38.4-40.3)	39.4 (38.6-40.3)	39.3 (38.4-40.3)	39.3 (38.3-40.2)
<34 weeks' gestation	1197 (2.9)	40 (0.7)	174 (1.3)	983 (4.4)
34-36^{+6} weeks' gestation	1969 (4.8)	149 (2.6)	588 (4.6)	1232 (5.5)
≥37 weeks' gestation	37644 (92.2)	5511 (96.7)	12142 (94.1)	19991 (90.0)
Maternal age (years)				
Mean (SD)	29.3 (5.3)	28.4 (5.3)	29.0 (5.5)	29.8 (5.1)
≤24	7621 (18.7)	1514 (26.6)	2692 (20.9)	3415 (15.4)
25-29	13704 (33.6)	1908 (33.5)	4298 (33.3)	7498 (33.8)
30-34	12805 (31.4)	1537 (27.0)	3887 (30.1)	7381 (33.2)
≥35	6694 (16.4)	743 (13.0)	2029 (15.7)	3922 (17.7)
Body mass index (kg/m2), N=40109				
Mean (SD)	25.5 (5.9)	24.6 (5.3)	27.0 (6.2)	24.9 (5.7)
≤24	22338 (55.7)	3478 (61.7)	5713 (44.5)	13147 (60.7)
25-29	10417 (26.0)	1400 (24.8)	3864 (30.1)	5153 (23.8)
30-34	4491 (11.2)	499 (8.9)	1900 (14.8)	2092 (9.7)
≥35	2863 (7.1)	259 (4.6)	1348 (10.5)	1256 (5.8)
Socioeconomic status‡, N=40773				
1	8816 (21.6)	3001 (52.7)	2337 (18.1)	3478 (15.7)
2	4765 (11.7)	756 (13.3)	128 (1.0)	3881 (17.5)
3	8776 (21.5)	1189 (20.9)	5731 (44.4)	1856 (8.4)
4	9705 (23.8)	357 (6.3)	1849 (14.3)	7499 (33.8)
5	8711 (21.4)	394 (6.9)	2851 (22.1)	5466 (24.6)
Smoking status, N=40635				
Current smokers	3510 (8.6)	279 (4.9)	1562 (12.1)	1669 (7.6)
Family history of PE				
Yes	104 (0.3)	2 (0.0)	27 (0.2)	75 (0.3)
Conception method, N=40626				
Assisted§	1697 (4.2)	182 (3.2)	385 (3.0)	1130 (5.1)

Characteristic	All women (N=40,824)†	[A]Auburn Hospital (N=5702)†	[B]Blacktown/Mount-Druitt Hospital (N=12,906)†	[C]Westmead Hospital (N=22,216)†
Autoimmune disease¶, N=40645				
Yes	59 (0.1)	1 (0.0)	12 (0.1)	46 (0.2)
Chronic hypertension, N=40652				
Yes	411 (1.0)	24 (0.4)	102 (0.8)	285 (1.3)
Chronic renal disease, N=40620				
Yes	361 (0.9)	15 (0.3)	115 (0.9)	231 (1.0)
Diabetes mellitus (type 1 or 2), N=40646				
Yes	325 (0.8)	28 (0.5)	100 (0.8)	197 (0.9)
Multiple pregnancy				
Yes	1311 (3.2)	63 (1.1)	263 (2.0)	985 (4.4)
Antiplatelet therapy¥				
Yes	345 (0.8)	15 (0.3)	42 (0.3)	288 (1.3)

IQR, interquartile range; PE, pre-eclampsia; SD, standard deviation; [X]WSLHD, [X]Western Sydney Local Health District.
†The total for each characteristic varies from the overall total due to missing data.
‡Classification of socioeconomic status into quintiles using Australian Bureau of Statistics (ABS) Socio-Economic Index for Australia (SEIFA) advantage/disadvantage by postcode (1=most disadvantaged, 5=most advantaged).
§Assisted by use of medications or fertilization procedures (includes intrauterine insemination, in-vitro fertilization, intracytoplasmic sperm injection).
¶Autoimmune disease includes systemic lupus erythematosus and antiphospholipid syndrome.
¥Antiplatelet therapy, includes aspirin or clexane, received after first trimester.

TABLE 2 Association between maternal ethnicity, other socio-demographic, and clinical risk factors and pre-eclampsia, all women and nulliparous women, ~~[X]~~WSLHD, 2011-2014

Characteristic	All women (N=40,824)				Nulliparous women (N=12,743)			
	PE	Total†	OR (95% CI)	Adjusted OR (95% CI)¥	PE	Total†	OR (95% CI)	Adjusted OR (95% CI)¥
Ethnicity								
Australian/New Zealand-born English-speakers	735	15422	1.00	1.00	160	4297	1.00	1.00
Middle-Eastern/African	182	6977	0.54 (0.45-0.63)	0.55 (0.47-0.66)	21	1716	0.32 (0.20-0.51)	0.34 (0.21-0.56)
South-East Asian	110	2725	0.84 (0.69-1.03)	0.98 (0.79-1.23)	22	840	0.70 (0.44-1.09)	0.95 (0.59-1.53)
North-East Asian	51	4470	0.23 (0.17-0.31)	0.33 (0.25-0.45)	14	1596	0.23 (0.13-0.40)	0.32 (0.18-0.57)
Southern Asian	255	8762	0.60 (0.52-0.69)	0.73 (0.62-0.85)	76	3613	0.56 (0.42-0.73)	0.78 (0.57-1.06)
Others	115	2468	0.98 (0.80-1.19)	0.96 (0.78-1.19)	15	681	0.58 (0.34-1.00)	0.68 (0.40-1.18)
Maternal and clinical factors								
Parity								
Parous	1140	28081	1.00	1.00				
Nulliparous	308	12743	0.59 (0.52-0.67)	0.74 (0.64-0.85)	------	------	----------	----------
Maternal age (years)								
Total	1448	40824	1.05 (1.04-1.06)	1.03 (1.02-1.04)	308	12743	1.04 (1.02-1.06)	1.02 (0.99-1.04)
≤24	213	7621	1.01 (0.85-1.19)	0.99 (0.83-1.18)	91	3779	1.42 (1.06-1.91)	1.40 (1.03-1.91)
25-29	381	13704	1.00	1.00	89	5205	1.00	1.00
30-34	496	12805	1.41 (1.23-1.61)	1.30 (1.13-1.49)	91	2916	1.85 (1.38-2.49)	1.69 (1.25-2.30)
≥35	358	6694	1.98 (1.71-2.29)	1.54 (1.32-1.79)	37	843	2.64 (1.79-3.90)	1.84 (1.21-2.80)
Body mass index (kg/m²)								
Total	1422	40109	1.08 (1.07-1.08)	1.07 (1.06-1.07)	301	12542	1.09 (1.07-1.10)	1.08 (1.06-1.10)
≤24	499	22338	1.00	1.00	155	8340	1.00	1.00
25-29	390	10417	1.70 (1.49-1.95)	1.61 (1.40-1.85)	58	2683	1.17 (0.86-1.58)	1.13 (0.83-1.54)
30-34	281	4491	2.92 (2.52-3.39)	2.58 (2.21-3.01)	37	973	2.09 (1.45-3.01)	1.92 (1.32-2.78)
≥35	252	2863	4.22 (3.61-4.94)	3.51 (2.98-4.13)	51	546	5.44 (3.92-7.56)	4.26 (3.00-6.06)
Socioeconomic status‡								
1	303	8816	1.00	1.00	48	2418	1.00	1.00
2	136	4765	0.83 (0.67-1.01)	0.85 (0.69-1.06)	24	1477	0.82 (0.50-1.34)	0.82 (0.49-1.36)
3	319	8776	1.06 (0.90-1.24)	1.04 (0.88-1.22)	66	2701	1.24 (0.85-1.80)	1.18 (0.80-1.74)
4	365	9705	1.10 (0.94-1.28)	1.15 (0.98-1.36)	90	3248	1.41 (0.99-2.01)	1.33 (0.92-1.94)
5	322	8711	1.08 (0.92-1.27)	1.14 (0.96-1.35)	79	2881	1.39 (0.97-2.00)	1.38 (0.94-2.02)
Smoking status								
Non-smokers	1302	37125	1.00	1.00	288	12004	1.00	1.00

Characteristic	All women (N=40,824)				Nulliparous women (N=12,743)			
	PE	Total†	OR (95% CI)	Adjusted OR (95% CI)¥	PE	Total†	OR (95% CI)	Adjusted OR (95% CI)¥
Current smokers	137	3510	1.12 (0.93-1.34)	1.02 (0.85-1.23)	18	686	1.10 (0.68-1.78)	0.95 (0.58-1.57)
Family history of PE								
No	1431	40720	1.00	1.00	304	12708	1.00	1.00
Yes	17	104	5.37 (3.18-9.05)	5.65 (3.25-9.84)	4	35	5.27 (1.85-15.01)	4.44 (1.47-13.42)
Conception method								
Natural	1342	38929	1.00	1.00	270	11934	1.00	1.00
Assisted§	95	1697	1.66 (1.34-2.06)	1.29 (1.02-1.62)	35	745	2.13 (1.49-3.05)	1.23 (0.81-1.87)
Autoimmune disease¶								
No	1432	40586	1.00	1.00	304	12683	1.00	1.00
Yes	8	59	4.29 (2.03-9.05)	2.41 (1.04-5.59)	1	10	4.52 (0.57-35.82)	5.17 (0.62-34.10)
Chronic hypertension								
No	1345	40241	1.00	1.00	289	12592	1.00	1.00
Yes	94	411	8.58 (6.77-10.86)	4.62 (3.55-6.01)	18	103	9.63 (5.77-16.06)	5.83 (3.28-10.35)
Chronic renal disease								
No	1359	40259	1.00	1.00	288	12577	1.00	1.00
Yes	63	361	6.05 (4.59-7.98)	3.99 (2.96-5.39)	14	110	6.22 (3.51-11.03)	4.40 (2.41-8.06)
Diabetes mellitus (type 1 or 2)								
No	1403	40321	1.00	1.00	300	12623	1.00	1.00
Yes	37	325	3.56 (2.52-5.04)	1.65 (1.12-2.41)	5	73	3.02 (1.21-7.54)	0.93 (0.39-2.86)
Multiple pregnancy								
No	1352	39513	1.00	1.00	277	12396	1.00	1.00
Yes	96	1311	2.23 (1.80-2.76)	1.95 (1.55-2.46)	31	347	4.29 (2.91-6.32)	3.97 (2.60-6.06)

CI, confidence interval; OR, odds ratio; PE, pre-eclampsia; ~~[X]~~WSLHD, ~~[X]~~Western Sydney Local Health District.

†The total for each characteristic varies from the overall total due to missing data.

‡Classification of socioeconomic status into quintiles using Australian Bureau of Statistics (ABS) Socio-Economic Index for Australia (SEIFA) advantage/disadvantage by postcode (1=most disadvantaged, 5=most advantaged).

§Assisted by use of medications or fertilization procedures (include intrauterine insemination, in-vitro fertilization and intracytoplasmic sperm injection).

¶Autoimmune disease includes systemic lupus erythematosus and antiphospholipid syndrome.

¥Adjusted for: autoimmune disease, chronic hypertension, chronic renal disease, diabetes mellitus (type 1 or 2), multiple pregnancy, maternal age group and body mass index group.