Impact of Pre-eclampsia/eclampsia on Hemorrhagic and Ischemic Stroke Risk: A 17 years Follow-up Nationwide Cohort Study

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Abstract

Objective No study ever investigated the long-term risk of stroke in women with pre-eclampsia/eclampsia. The purpose of this study is to explore long-term stroke risks, differentiating subtypes and their time trends. Design Nationwide population-based cohort study Methods Between 2000 and 2017, 1,384,427 pregnant women were registered in the National Health Insurance Research Database in Taiwan. After excluding women with previous stroke history and exact matching with all confounders, 6,053 women with pre-eclampsia/eclampsia and 24,212 controls were recruited. Main Outcome Measures Hemorrhagic and ischemic strokes after child-birth Results Over the 17-year follow-up, the adjusted hazard ratio (aHR) for stroke in women with a history of pre-eclampsia/eclampsia was 2.05 (95% confidence interval, CI = 1.67-2.52, p<0.001). The 17 years overall risks of both ischemic and hemorrhagic stroke were 1.98 and 3.45, respectively (p<0.001). The stroke subtypes, hemorrhagic and ischemic, had different time trend risks, and hemorrhagic stroke risks kept higher than that of ischemic stroke. The ischemic stroke risk peaked during 1-3 years after childbirth (aHR=3.09). The hemorrhagic stroke risk peaked during 3-5 years (aHR=7.49). Conclusions Stroke risk persisted even after decades, for both ischemic and hemorrhagic subtypes. Women with pre-eclampsia/eclampsia history should be aware of the long-term risk of stroke. Tweetable abstract Both ischemic and hemorrhagic stroke risks persisted high even after decades, while their time trend risks were different. Keywords: pre-eclampsia/eclampsia; ischemic stroke; hemorrhagic stroke

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Objective

No study ever investigated the long-term risk of stroke in women with pre-eclampsia/eclampsia. The purpose of this study is to explore long-term stroke risks, differentiating subtypes and their time trends.

Design

Nationwide population-based cohort study

Methods

Between 2000 and 2017, 1,384,427 pregnant women were registered in the National Health Insurance Research Database in Taiwan. After excluding women with previous stroke history and exact matching with all confounders, 6,053 women with pre-eclampsia/eclampsia and 24,212 controls were recruited.

Main Outcome Measures

Hemorrhagic and ischemic strokes after child-birth

Results

Over the 17-year follow-up, the adjusted hazard ratio (aHR) for stroke in women with a history of pre-eclampsia/eclampsia was 2.05 (95% confidence interval, CI = 1.67-2.52, p<0.001). The 17 years overall risks of both ischemic and hemorrhagic stroke were 1.98 and 3.45, respectively (p<0.001). The stroke subtypes, hemorrhagic and ischemic, had different time trend risks, and hemorrhagic stroke risks kept higher than that of ischemic stroke. The ischemic stroke risk peaked during 1-3 years after childbirth (aHR=3.09). The hemorrhagic stroke risk peaked during 3-5 years (aHR=7.49).

Conclusions

Stroke risk persisted even after decades, for both ischemic and hemorrhagic subtypes. Women with pre-eclampsia/eclampsia history should be aware of the long-term risk of stroke.

Tweetable abstract

Both ischemic and hemorrhagic stroke risks persisted high even after decades, while their time trend risks were different.

Keywords: pre-eclampsia/eclampsia; ischemic stroke; hemorrhagic stroke

Introduction

Pre-eclampsia/eclampsia, a hypertensive disorder of pregnancy, is a serious and common obstetric complication[1]. The incidence of pre-eclampsia/eclampsia in pregnant women is 5-8% worldwide, and it is a major cause of maternal morbidity and mortality[2-4]. Pre-eclampsia/eclampsia is defined as hypertension with high levels of protein in their urine (i.e. proteinuria) after 20 weeks of gestation. Severe pre-eclampsia/eclampsia is a serious threat to the lives of mothers and fetuses, leading to cardiovascular and metabolic complications for mothers and persistent bradycardia, hypotension, and neonatal hypoglycemia for fetuses[5-7]. Pre-eclampsia/eclampsia may lead to serious kidney, brain, and blood clotting problems which cause 10-15% of maternal deaths in lower-income countries[8,9].

Among these different sequelae of pre-eclampsia/eclampsia, stroke is a serious one. The incidence of stroke[10-13], both ischemic and hemorrhagic subtypes[14,15], increased in the peripartum and postpartum stages.

Stroke is an important issue not only in the elderly, but also in pregnant women. Stroke incidence ranges from 1.5 to 34.2 per 100,000 deliveries in pregnancy and the puerperium[16,17]. It has been reported that pre-eclampsia/eclampsia-related stroke would cause direct obstetric death[18,19]. The incidence of stroke in pregnant women in previous studies is varied according to different preexisting risk factors[16,20].

It has been reported that the probability of cardiovascular[7] and cerebrovascular disease[10,21]in the next few years after childbirth in women with ever pre-eclampsia/eclampsia would to be higher than that in the general population. However, long-term impact of pre-eclampsia/eclampsia on cerebrovascular disease is unknown.

In this study, we aimed to utilize a nationwide database to explore the long-term overall, ischemic, and hemorrhagic stroke risks in women with a history of pre-eclampsia/eclampsia, after decades follow up.

Materials and Methods

This study was conducted following the Declaration of Helsinki. The study protocol was also approved by the Institutional Review Board (IRB) of Dalin Tzu Chi Hospital of Buddhist Tzu Chi Medical Foundation (approval number, B10402022). The IRB absolved the requirement for written informed consent due to no direct contact with individual patients from this de-identified database.

We used the Taiwan National Health Insurance Research Database (NHIRD) to analyze the incidence rate of stroke in women with pre-eclampsia/eclampsia and compared it to those without pre-eclampsia/eclampsia. Taiwan NHIRD contains all the records of diagnosis and treatment of approximately 99% of people from inpatient, outpatient, and emergency departments[22]. The data collection of pregnant women from the Taiwan NHIRD ranged from 2000 to 2017, and it was included in this study for statistical analysis. The data included were evaluated by the National Health Insurance Administration (NHIA) quarterly expert reviews on every 50 to 100 ambulatory and inpatient claims filed by each medical institution[23]. False diagnostic reports are subject to severe penalties from the NHIA[24].

Records of pregnant women in this database were collected and categorized into two groups women, those with and without pre-eclampsia/eclampsia. Based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes for pregnant women, the codes were 650, 651, 652, and 653, while those for pregnant women with pre-eclampsia/eclampsia were 642.4, 642.5, 642.6, and 642.7. The primary outcomes included: codes for hemorrhagic stroke being 430, 431, 432, and codes for ischemic stroke being 433, 434, 435, 436, and 437.

Between 2001 and 2017, 1,384,427 pregnant women with delivery were registered in the Taiwan NHIRD. We included all pregnant women in Taiwan with different socioeconomic statuses, living areas (such as metropolises to rural), and hospital levels. The sample size exceeded million people. Figure 1 shows our study's flow diagram. We excluded 38,707 cases with missing confounders and 566 cases with stroke history. In addition, we only included women with the delivery age between 18 to 45 years. Finally, we enrolled 1,338,334 cases in this study, divided into groups of normal delivery with (N=8,077) and without (N=1,316,550) pre-eclampsia/eclampsia.

In this study, we used exact matching method to control covariates, that is, these two cohorts had the same age, same distribution for comorbidities, and socioeconomic status (all p= 1.000). After 1:4 exact matching, 6,053 cases were selected in the pre-eclampsia/eclampsia group and 24,212 in the non-pre-eclampsia/eclampsia group. The follow-up time in this study was from 2000 to 2017. We divided the 17 years follow up into short (0-1, 1-3, 3-5 years), intermediate (5-10), and long (10-15 years), to further differentiate the risks at different intervals.

Covariates included were age, season, cesarean section or normal spontaneous delivery, multiple gestations, hospital levels, and comorbidities. The hospital level was included in the analysis, account for different care qualities during pregnancy at different hospital levels. The comorbidities included hypertension, gestational diabetes mellitus (GDM), anemia, and delivery conditions such as antepartum hemorrhage (APH) and postpartum hemorrhage (PPH). These young women, age 18 to 45, had no comorbidities, such as chronic

3

kidney disease, heart failure, hypercholesterolemia, peripheral vascular disease, heart valve disorders, after matching. Socioeconomic variables, including geographic region, urbanization level, and monthly income-based insurance premiums were analyzed to reduce bias resulting from lifestyle.

Statistical methods

The basic characteristics between the two study groups were compared by Chi-square test. We used a Cox regression model to compare the adjusted hazard ratio (aHR) and 95% confidence interval (CI) for stroke occurrence. Cumulative incidence functions for the first occurrence of stroke episode between pre-eclampsia/eclampsia and non-pre-eclampsia/eclampsia women were compared using the Kaplan–Meier model. The SAS software (version 9.2; SAS Institute, Inc., Cary, NC) was used for all statistical analyses. A two-sided P-value of <0.05 was considered statistically significant.

Results

Demographic characteristics of pre-eclampsia/eclampsia and non-pre-eclampsia/eclampsia cohorts

The mean ages of the groups with and without pre-eclampsia/eclampsia were 32.04 and 31.84 years, respectively. No statistically differences in distribution of the all demographic characteristics and comorbidities between two groups after exact matching.

Prevalence rates of stroke in these matched cohorts

During this 17-year follow up time, 2.15% (130 over 6,053) women in the pre-eclampsia/eclampsia group, ever had stroke which was higher than that in the non-pre-eclampsia/eclampsia group (1.23%, p< 0.001) (Table 1). The prevalence rates of ischemic and hemorrhagic stroke in the pre-eclampsia/eclampsia group were also higher than that in the non-pre-eclampsia/eclampsia group (1.88% versus 1.12%, 0.55% versus 0.18%, respectively, both p< 0.001).

Risks of stroke

Table 2 presents the aHRs of stroke after adjusting for covariates. Stroke risk was significantly higher in the pre-eclampsia/eclampsia group than in the non-pre-eclampsia/eclampsia group (aHR = 2.05, 95% CI =1.67-2.52, $p < 0.001$).

Women with old delivery age had higher risk of stroke than that of women with young delivery age (Table 2), with highest risk being 2.61 ($p < 0.001$) for age >35 years, compared to women with age at delivery <30 years.

From the Cox regression analysis results presented in Table 3, delivery-related variables, such as cesarean section, multiple gestation, hospital level, and the season of maternal delivery did not have significant risk for stroke.

For comorbidities, Hypertension increased risks for stroke with aHR 3.35 (95% CI = 1.99-5.63, p <0.001) in these two matched cohorts. APH had a significant risk for stroke. Other comorbidities such as GDM, anemia, and PPH had no significant impact on stroke occurrence.

Socioeconomic variables, such as geographic region and urbanization level, had no significant stroke risk except family income. Women in median or high-income families had a higher risk of stroke than that of women in low-income families.

Risks of stroke for different stroke subtypes

Table 3 presents the aHRs of ischemic stroke, and hemorrhagic stroke, after adjusting for covariates. The aHR of ischemic stroke was 1.98 (95% CI = 1.59-2.46, $p < 0.001$) and the aHR of hemorrhagic stroke 3.45 (95% CI = 2.18-5.47, $p < 0.001$), respectively, for overall 17 years follow-up.

Risks of stroke for different follow-up time interval

4

We also observed stroke risk in women with pre-eclampsia/eclampsia at intervals of 0-1, 1-3, 3-5, 5-10, and 10-15 years (see Table 3). Overall, the stroke risk reach peak within 1-3 years after child delivery (aHR 3.20, 95% CI=1.82-5.63, p <0.001). The risk time trends for these two stroke subtypes were different (Table 3 and as illustrated in Figure 2). The ischemia stroke risk reach peak within 1-3 after child delivery (aHR 3.09, 95% CI=1.71-5.58, p <0.001), while hemorrhage stroke reach peak within 3-5 years after child delivery (aHR 7.49, 95% CI=1.18-47.33, p =0.032). Besides, the hemorrhagic stroke risk was higher than the ischemic risk at each follow-up time interval.

Cumulative incidence rates of stroke

The 17 years cumulative incidence rates of overall stroke, ischemic and hemorrhagic stroke were all higher in women with pre-eclampsia/eclampsia history than that in women without pre-eclampsia/eclampsia (6.00% versus 3.01%, 5.05% versus 2.62%, 1.95% versus 0.57%, all p< 0.001) as Figure 3.

Discussion

Main Findings

Overall, women with pre-eclampsia/eclampsia in pregnancy significantly increased the future occurrence rate of stroke, both ischemic and hemorrhagic stroke, even after 10 to 15 years. The risks of hemorrhagic stroke at different follow up periods were all higher than that of ischemic stroke, with different risk time trends. The peak of ischemic stroke risk was 1-3 years after childbirth; while for the peak of hemorrhagic stroke risk was 3-5 years after childbirth.

Strengths and Limitations

First, this study's major strength is exploring the association between pre-eclampsia/eclampsia and stroke in a nationwide scope cohort study. Second, this study reported the two different stroke subtypes and divided the long follow-up duration into different follow-up durations to provide information regarding the time-trend effects of pre-eclampsia/eclampsia on stroke. Finally, because of the large number of women in this nationwide study, we used exact matching to control all covariates, that is, women with the same age, same comorbidity distributions, and same socioeconomic status, which could reduce statistical bias in this study.

This study has several limitations. First, our health insurance database provides no information on laboratory data, nor the severity of pre-eclampsia/eclampsia. Second, smoking habits, alcohol consumption, or body weight/body mass index are not available in our database. Therefore, we could not evaluate the effects of these factors on stroke.

Interpretation

Our results show that a history of pre-eclampsia/eclampsia in pregnancy significantly increased the future occurrence rate of stroke, both ischemic and hemorrhagic stroke, even after 10 to 15 years. In this study, after adjusting for potential confounding variables, women with history of pre-eclampsia/eclampsia still had a 2-fold higher long-term stroke risk. Nearly 2-fold higher ischemic stroke risk and up to 3-fold higher hemorrhagic stroke risk were observed.

Reviewing the literature, it has been often reported that pre-eclampsia/eclampsia would increase stroke risk during the pregnancy process, both ischemic and hemorrhagic stroke, a dangerous complication of pregnancy[11,25-30]. In those studies, pre-eclampsia/eclampsia generally increased a woman's stroke risk and hypertension between 2~4-fold during pregnancy, respectively[14,30-33], and also leads to higher mortality of pregnancy and delivery[2,34,35]. In a case-control stroke study, Kittner and colleagues found that the adjusted relative risk (aRR) of stroke (both cerebral infarction and intracerebral hemorrhage) during pregnancy and the 6-week postpartum period was 2.4 (95 % CI, 1.6 to 3.6)[36]. The aRR during pregnancy was 1.1 (95 % CI, 0.6 to 2.0), while for risk during the 6-week postpartum period alone the aRR increased to 7.9 (95 % CI, 5.0–12.7). Compared to our cohort study, our study showed aHR was 1.65 during 0- 1 years after childbirth, 3.20 during 1- 3 years, and 1.80 during 10- 15 years.

5

In the literature, another case-control study with follow-up time prolonging to one year after childbirth, Tang et al. evaluated the aRRs of ischemic and hemorrhagic stroke during pregnancy and the first postpartum year [14]. In that study, they found a U-shape trend of hemorrhagic stroke risk from antepartum to 1-year postpartum (aRR 10.68, to 6.45, to 5.61, to 11.76, to 19.90 for 3 months antepartum, and 3 days, 6 weeks, 6 months, 12 months postpartum, respectively). Compared to that U shape of that short postpartum case-control study, our long-term cohort study showed a reverse-U shape in decade follow-up for hemorrhagic stroke with a peak of aHR 7.49 during 3-5 years after childbirth. .

For the ischemic stroke risk, Tang's study showed aRR as high as 40.86 within 3 months antepartum, then decrease to 11.23 from 3 days to 6 weeks postpartum, and further decreased to 4.35 from 6 months to 12 months postpartum. In our cohort study, the aHR for ischemic stroke increased from 1.82 during the first year after childbirth, with peak 3.09 during 1-3 years, and then decreased to 1.58 after 10 years.

In the literature, it has been reported that ischemic stroke had two peaks of occurrence, in the first and third trimesters of pregnancy: 24/27 (89%), while intracerebral hemorrhage was more frequently observed during the third trimester: 15/23 (65%)[37]. Different from previous studies, in our long-term follow-up study, we noted that stroke risk would reach peak during 1-3 years after childbirth for ischemic stroke and during 3-5 years for hemorrhagic stroke. Based on short-term follow-up studies in the past and this long-term study, it is found consistently that ischemic stroke occurs faster and earlier than hemorrhagic stroke.

The role of hypertension in women with pre-eclampsia/eclampsia is also worth to note in this study. In previous studies, compared to patients without pre-existing hypertension those with higher blood pressure have smaller amount of salvageable tissue and obvious intracranial occlusion and thus worsen stroke outcome[38-41]. Both of the elevation of systolic and diastolic blood pressure increase stroke risk of 2.9-fold for women[42,43]. In addition, recent study further identifies related genes of predisposing to hypertension may associate with pre-eclampsia/eclampsia in Asian women[44]. Our study confirm the role of hypertension on stroke in women with history of pre-eclampsia/eclampsia with aHR 3.35 (95% CI 1.99-5.63). For women with pre-eclampsia/eclampsia, the role of hypertension is a red flag in aggravating probability of future stroke occurrence.

Age may also have significant influence on stroke. Previous studies ever discussed the impact of maternal age on stroke risk[13,45,46]. For example, women aged >39 years and those aged >29 years are significant hemorrhagic and ischemic stroke factors associated with increased risk, respectively[46]. This is consistent with our results, which showed women with an age at delivery >35 years had a significantly high aHR of hemorrhagic stroke risk.

For socioeconomic status, previous studies suggest that socioeconomic deficiency is associated with increased stroke severity and incidence at young age population[47], and stroke mortality[47,48]. This influence of socioeconomic deficiency may have a greater impact on pregnant women, which may cause pregnant women to have a higher stroke risk than other groups[49]. Our long-term study also showed that women with lowest family income had elevated stroke risk than women with other family income levels.

Conclusions

In summary, our results indicate that the ischemic and hemorrhagic stroke risk of women with pre-eclampsia/eclampsia history remained high for a long time. Women with pre-eclampsia/eclampsia history should be aware of stroke risk, even 10 to 15 years after childbirth.

Disclosure of interests

All authors declare that they have no competing interests.

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6

the statistical analyses. WYC and HJY wrote the first draft of the manuscript. All authors interpreted the data and contributed to the writing of the paper. All authors revised and approved the final version.

Details of Ethics approval

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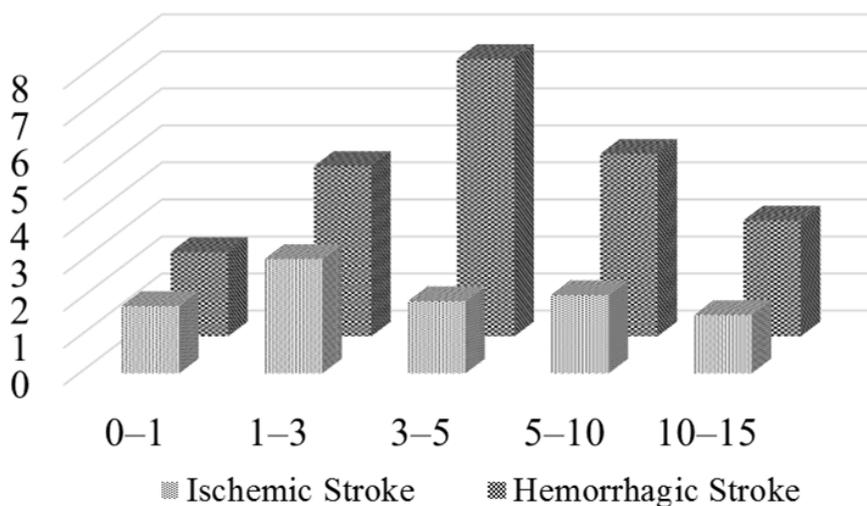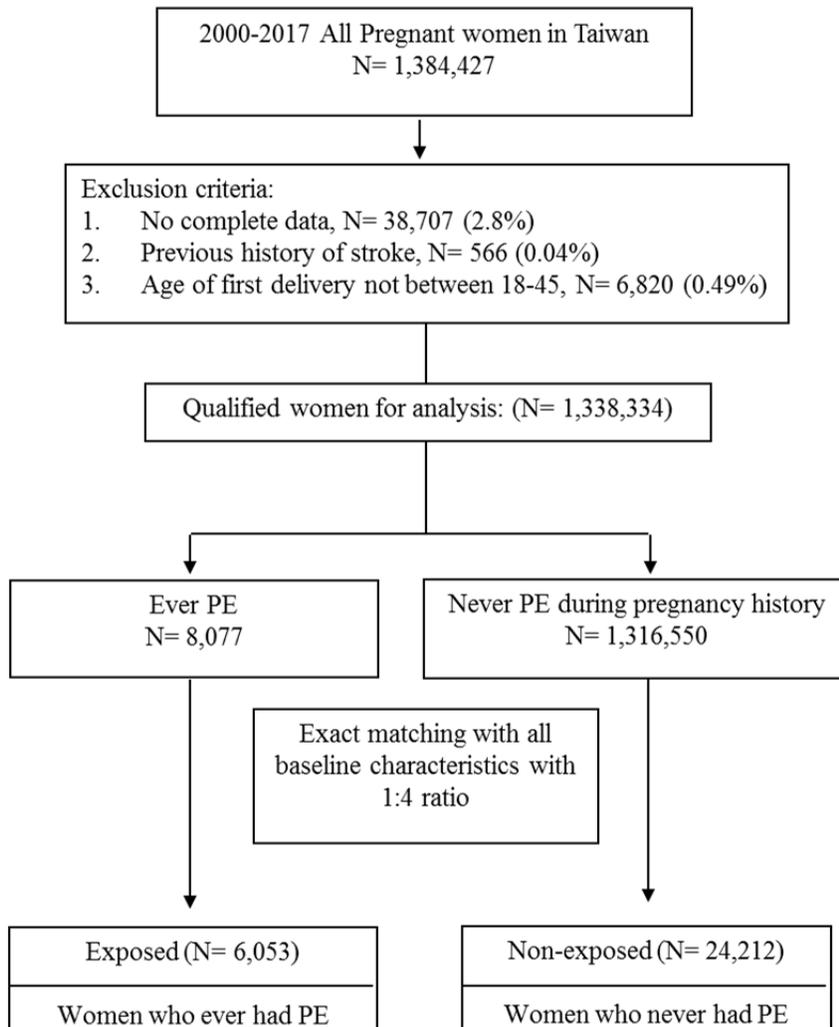
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Figure legends

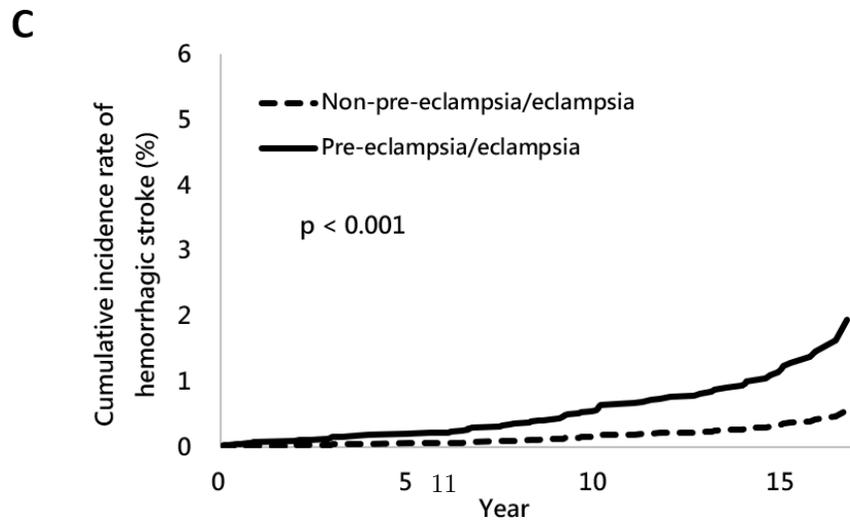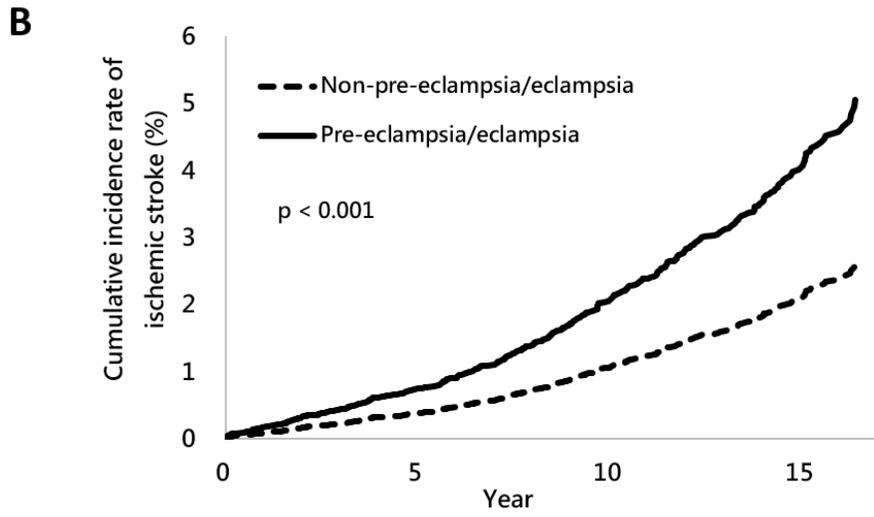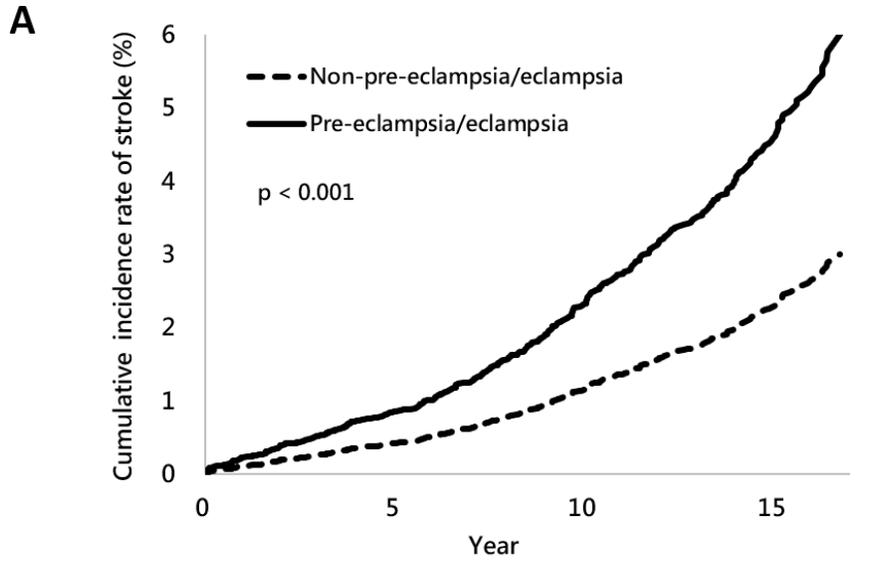Figure 1. A flow chart illustrating the selection procedure of study subjects. PE; pre-eclampsia/eclampsia.

Figure 2. The risk time trends of ischemic and hemorrhagic stroke in women with a history of pre-eclampsia/eclampsia.

Figure 3. Cumulative event rates of overall strokes (A), ischemic stroke (B), and hemorrhagic stroke (C) among women with and without history of pre-eclampsia/eclampsia.

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┌─────────────────────────────────────┐
│   2000-2017 All Pregnant women in Taiwan │
│          N= 1,384,427                │
└─────────────────────────────────────┘
                    │
                    ▼
┌──────────────────────────────────────────────────┐
│ Exclusion criteria:                                │
│ 1.   No complete data, N= 38,707 (2.8%)            │
│ 2.   Previous history of stroke, N= 566 (0.04%)    │
│ 3.   Age of first delivery not between 18-45, N= 6,820 (0.49%) │
└──────────────────────────────────────────────────┘
                    │
                    ▼
┌──────────────────────────────────────────────────┐
│   Qualified women for analysis: (N= 1,338,334)     │
└──────────────────────────────────────────────────┘
```

```
┌─────────────────┐          ┌──────────────────────────────┐
│  Ever PE         │          │  Never PE during pregnancy history │
│  N= 8,077        │          │  N= 1,316,550                │
└─────────────────┘          └──────────────────────────────┘
```

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            ┌─────────────────────────┐
            │  Exact matching with all │
            │  baseline characteristics with │
            │       1:4 ratio          │
            └─────────────────────────┘
```

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┌──────────────────────────┐       ┌──────────────────────────┐
│  Exposed (N= 6,053)       │       │  Non-exposed (N= 24,212)  │
│ ─────────────────────────│       │ ─────────────────────────│
│  Women who ever had PE    │       │  Women who never had PE   │
└──────────────────────────┘       └──────────────────────────┘
```


0–1   1–3   3–5   5–10   10–15

▒ Ischemic Stroke   ▓ Hemorrhagic Stroke

A

B

C

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(+)Table 1_preeclampsia.docx available at https://authorea.com/users/449371/articles/547916-impact-of-pre-eclampsia-eclampsia-on-hemorrhagic-and-ischemic-stroke-risk-a-17-years-follow-up-nationwide-cohort-study

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(+)Table 2_preeclampsia.docx available at https://authorea.com/users/449371/articles/547916-impact-of-pre-eclampsia-eclampsia-on-hemorrhagic-and-ischemic-stroke-risk-a-17-years-follow-up-nationwide-cohort-study

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(+)Table 3_preeclampsia.docx available at https://authorea.com/users/449371/articles/547916-impact-of-pre-eclampsia-eclampsia-on-hemorrhagic-and-ischemic-stroke-risk-a-17-years-follow-up-nationwide-cohort-study