

Gestational Hypertension, Preeclampsia, and Eclampsia and Future Neurological Disorders

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 Supplemental content

IMPORTANCE Gestational hypertension, preeclampsia, and eclampsia are established risk factors for stroke and dementia later in life. Whether these pregnancy complications are associated with an increased risk of new-onset neurological disorders within months to years after giving birth is not known.

OBJECTIVE To explore whether gestational hypertension, preeclampsia, and eclampsia are associated with new-onset migraine, headache, epilepsy, sleep disorder, or mental fatigue within months to years after giving birth.

DESIGN, SETTING, AND PARTICIPANTS In this register-based cohort study, exposures were identified in the Swedish Medical Birth Register from 2005 to 2018. Follow-up was conducted using the National Patient Register, containing diagnoses from specialized inpatient and outpatient care. Follow-up started 42 days after delivery and continued until the first event, death, emigration, or the end of the follow-up period (2019). The risk was calculated with Cox regression analysis and expressed as adjusted hazard ratio (aHR) with a 95% CI. Through the Swedish Medical Birth Register, 659 188 primiparous women with singleton pregnancies between 2005 and 2018 were identified. Women with a diagnosis of chronic hypertension (n = 4271) or a prepregnancy neurological disorder (n = 6532) were excluded. The final study population included 648 385 women. Data analyses were conducted in 2023.

EXPOSURES Gestational hypertension, preeclampsia, and eclampsia.

MAIN OUTCOME The primary outcome was a composite neurological outcome of migraine, headache, epilepsy, sleep disorder, or mental fatigue.

RESULTS The study included 648 385 women with a mean age of 28.5 (SD, 5.0) years at the time of their first pregnancy. Women with gestational hypertension (n = 11 133), preeclampsia (n = 26 797), and eclampsia (n = 625) all had an association with increased risk for a new-onset neurological disorder compared with women with normotensive pregnancies. The aHR for gestational hypertension was 1.27 (95% CI, 1.12-1.45), 1.32 (95% CI, 1.22-1.42) for preeclampsia, and 1.70 (95% CI, 1.16-2.50) for eclampsia. When exploring individual outcomes, women with eclampsia were associated with more than a 5 times increased risk of epilepsy (aHR, 5.31; 95% CI, 2.85-9.89).

CONCLUSION AND RELEVANCE In this study, gestational hypertension, preeclampsia, and eclampsia were associated with an increased risk of new-onset migraine, headache, epilepsy, sleep disorder, or mental fatigue within months to years after giving birth. Guidelines recommend follow-up after delivery for women with gestational hypertension and preeclampsia for their increased risk of cardiovascular disease. At these visits, caregivers should also pay attention to persisting or new-onset of neurological symptoms, since this group of women appears to be vulnerable to developing or experiencing neurological disorders.

JAMA Neurol. doi:10.1001/jamaneurol.2024.4426
Published online December 23, 2024.

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Acute cerebral complications in preeclampsia, such as eclampsia and cerebral edema, have long been considered reversible. However, magnetic resonance imaging (MRI) follow-up studies have shown increased cerebral white matter lesions, smaller brain volumes, reduction in cortical gray matter volume, and persistent blood-brain barrier leakage years after a pregnancy complicated by preeclampsia.¹⁻⁴ In addition, small observational studies have reported both subjective and objective cognitive impairment months to years after giving birth in women with gestational hypertension, preeclampsia, and eclampsia.⁵⁻⁷

Larger register-based studies and recent systematic reviews have established that gestational hypertension, preeclampsia, and eclampsia are associated with an increased risk of stroke⁸⁻¹⁰ and vascular dementia¹¹⁻¹⁴ later in life. A connection between preeclampsia and Alzheimer disease has also been proposed, but results are conflicting.^{12,13} Thus, it appears that women with gestational hypertension, preeclampsia, and eclampsia may have long-lasting brain abnormalities, potentially translating into later neurological disorders, such as cognitive decline, stroke, and dementia.

The association between gestational hypertension, preeclampsia, and eclampsia and neurological disorders in proximity to childbirth is less explored. Two smaller studies and 1 Canadian register-based study have shown an association between preeclampsia and eclampsia and later seizure disorder.¹⁵⁻¹⁷ There is a lack of large-scale data confirming these findings. From clinical experience, some women affected by preeclampsia and, in particular, eclampsia report persisting neurological symptoms, such as headache, concentration difficulties, fatigue, dizziness, and migraine after pregnancy. These symptoms have not been reported in the preeclampsia literature. Thus, there is a gap in knowledge regarding the presence of neurological disorders during the years following birth after preeclampsia.

We therefore aimed to address this gap by using high-quality Swedish national registers to explore whether gestational hypertension, preeclampsia, and eclampsia are associated with new-onset migraine, headache, epilepsy, sleep disorder, or mental fatigue within months to years after giving birth.

Methods

Ethics

The study was approved by the Uppsala ethical review board (approval number 2019-04925). The dataset received by the researchers was pseudonymized using a unique serial number. Register-based studies using pseudonymized data are exempt from consent requirements according to Swedish data protection legislation.

Study Design

This was a Swedish nationwide register-based cohort study. When reporting this observational study, the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed.

Key Points

Question Is there an increased risk of developing new-onset neurological disorders in the months to years after having a pregnancy complicated by gestational hypertension, preeclampsia, or eclampsia?

Findings In this Swedish register-based cohort study, including 648 385 primiparous women, gestational hypertension, preeclampsia, and eclampsia were associated with an increased risk of migraine, headache, epilepsy, sleep disorder, or mental fatigue during a follow-up time of up to 15 years after giving birth. The strongest association was seen between eclampsia and future epilepsy.

Meaning Caregivers should inquire about neurological symptoms in women with a history of gestational hypertension, preeclampsia, and eclampsia.

Data Sources

The Swedish Medical Birth Register holds information on 98% of all pregnancies and deliveries in Sweden, containing data on both mother and infant.¹⁸ Registration starts at the first antenatal visit and information is collected prospectively throughout pregnancy, delivery, and the neonatal period in standardized medical records and reported to the Medical Birth Register after delivery.^{19,20} Complications during pregnancy and the perinatal period are classified according to the Swedish version of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)*, at discharge from the hospital. The Swedish National Patient Register contains nationwide information on ICD-coded diagnoses and dates of hospital admissions, discharges, and outpatient visits. However, it does not cover conditions diagnosed in primary health care.²¹

The Swedish Cause of Death Register comprises data on ICD-coded cause(s) of death and when death occurred.²² The Swedish Total Population Register contains information about the population, eg, country of birth and migration.²³ The Swedish Education Register holds longitudinal data on the education of the Swedish population.²⁴ Each individual living in Sweden is assigned a unique personal identification number upon birth or immigration, enabling data linkage between national registers.²⁵

Study Population

We included women with singleton pregnancies who were giving birth to their first infant at 22 + 0 gestational weeks or later. The birth needed to occur between January 1, 2005, and December 31, 2018, according to the Swedish Medical Birth Register. Women with chronic hypertension at the index pregnancy were excluded in order to exclude women with a potential cardiovascular dysfunction prior to pregnancy that could affect the outcome. We also excluded women with a diagnosis of any of the neurological outcomes: migraine, headache, epilepsy, sleep disorder, and mental fatigue, before or during pregnancy or within 42 days after giving birth to avoid symptoms relating to the index pregnancy. Data on diagnoses were obtained from the Swedish National Patient

Register. Since the Swedish Medical Birth Register only provides birth by year and month to protect confidentiality, all births were set to the 15th of the respective month. Follow-up started 42 days after the set birthdate, ie, 27 to 57 days after the actual date of birth.

Data on early pregnancy maternal characteristics, such as age, weight, height, smoking, cohabitation status, pregestational diseases, and gestational diabetes, were collected from the Swedish Medical Birth Register. Early pregnancy maternal body mass index (BMI) was calculated as weight in kilograms divided by self-reported height in meters squared.² A registered BMI less than 15 or more than 55 was assumed to have been entered incorrectly in the register, and thus, replaced by a missing value. Data on country of birth were retrieved from the Total Population Register. The level of education was retrieved from the Education Register and was measured as the highest achieved level of education until 2020, irrespective of the date and year of their first birth.

Infant characteristics on gestational age at birth, sex, birth weight, small for gestational age, and stillbirth were available from the Swedish Medical Birth Register. Preterm birth was defined as birth before 37 + 0 weeks of gestation. Gestational length was primarily established by a first or early second trimester ultrasound (more than 90% of women in this cohort). Small for gestational age was defined as birth weight being less than -2 SDs of expected birth weight according to gestational length and sex.²⁶ Stillbirth included antenatal and intrapartum stillbirths. Data on the definitions of covariates and maternal and infant characteristics, including their ICD codes and from which registries they were obtained, are summarized in the eTable in Supplement 1.

Exposures

Exposures were gestational hypertension, preeclampsia, and eclampsia identified in the Swedish Medical Birth Register. Gestational hypertension was clinically defined as new-onset high systolic blood pressure 140 mm Hg or higher and/or diastolic blood pressure 90 mm Hg or higher measured on 2 subsequent occasions more than 4 hours apart, in the absence of proteinuria, after 20 weeks' gestation. During the study period, preeclampsia was defined as gestational hypertension accompanied by proteinuria (300 mg or more for 24 hours, 2 or more positive results on dipstick, or 1 positive result on dipstick on 2 separate occasions with more than 4 hours apart) according to Swedish clinical practice.²⁷ Eclampsia was defined as tonic-clonic seizures without other etiology, accompanied by a diagnosis of preeclampsia. For the main analysis, the cohort was divided into 1 reference group (normotensive pregnancies) and 3 exposure groups: women with gestational hypertension, women with preeclampsia without eclampsia, and women with eclampsia.

In a subgroup analysis, all women with preeclampsia (with or without eclampsia) were allocated into 1 of 2 groups: either with preterm (less than 37 weeks) or term (37 weeks or more) delivery. Women with gestational hypertension (n = 11 133) and women with missing data on gestational length at delivery (n = 160) were excluded from the subgroup analysis.

Outcome

Our main outcome was the development of a new-onset medium-term neurological disorder during a time frame ranging from a minimum of 42 days (27 to 57 days) after childbirth to the longest possible follow-up time of 15 years. The neurological outcome disorders were migraine, headache, epilepsy, sleep disorder, and mental fatigue (neurasthenia), identified by ICD-10 codes in the Swedish National Patient Register (eTable in Supplement 1).

The primary outcome was a composite of these 5 diagnoses, where 1 of these diagnoses was sufficient. Our secondary outcomes were migraine, headache, epilepsy, sleep disorder, and mental fatigue as individual outcomes.

Statistical Analysis

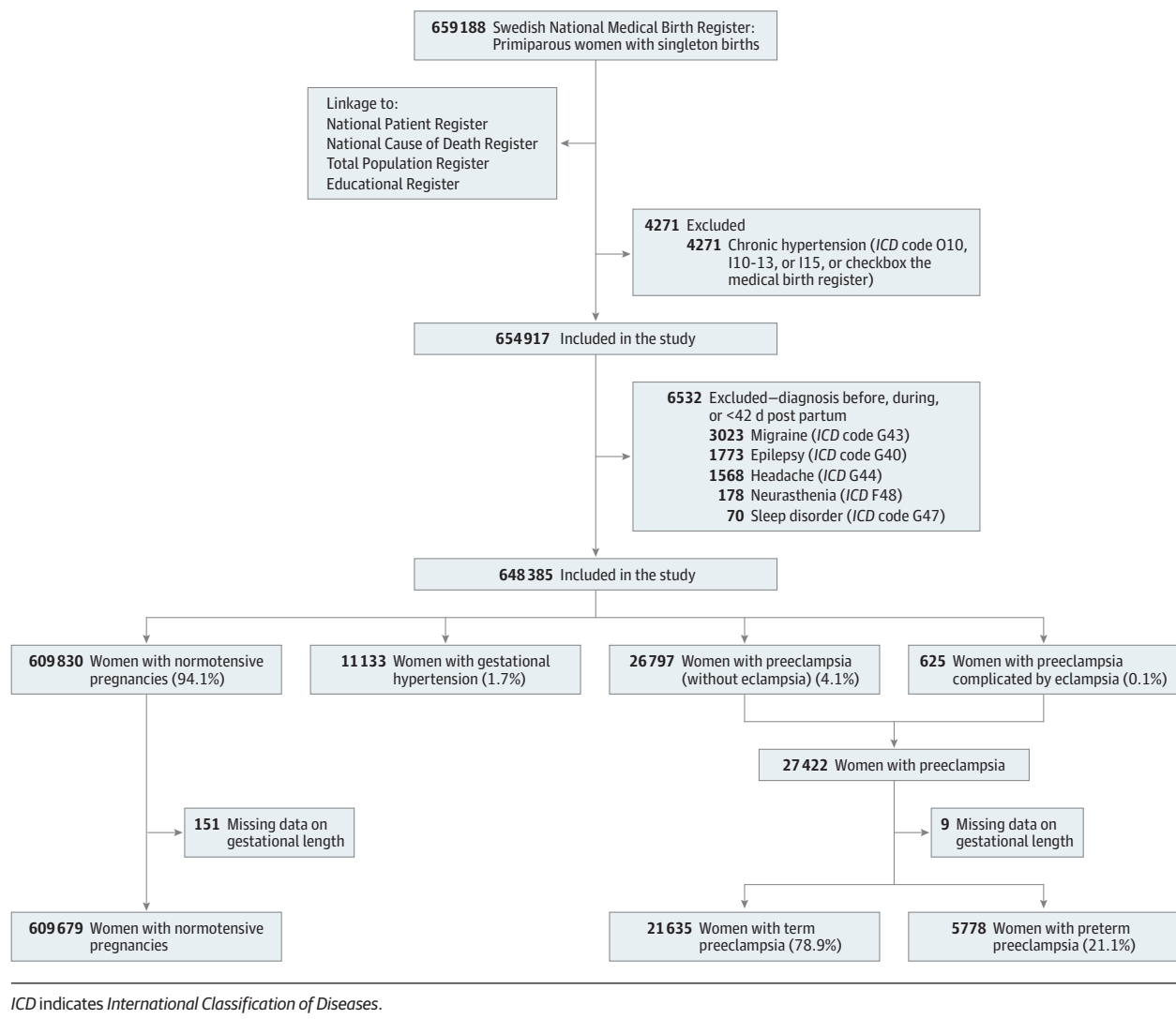
Descriptive statistics were presented with mean (SD) and frequencies as numbers (%). Data were analyzed using time-to-event methods for the different exposure groups and incidence rates were calculated. The start of follow-up was 42 days after the set birthdate. Follow-up ended at the first event of neurological outcome, death, emigration, or December 31, 2019. This would allow a minimum time of follow-up of 1 year post partum and avoid any acute neurological events in relation to index pregnancy and childbirth.

A directed acyclic graph²⁸ was created to obtain a systematic representation of assumptions about the relationship between pregnancy-induced hypertension and the neurological disorders. In addition, the directed acyclic graph was used to conclude which confounders to include in the adjusted analysis (eFigure in Supplement 1). The covariates related to maternal characteristics that were considered potential confounders of the composite outcome included maternal age at childbirth, early pregnancy BMI, country of birth, smoking habits, education level, as well as pregestational and gestational diabetes, kidney disease, and systemic lupus erythematosus.

In the analyses of the composite outcome, only the first recorded diagnosis per woman was used. For the secondary outcomes all diagnoses were included; thus, women with multiple outcome diagnoses could be represented in several secondary analyses.

Associations between gestational hypertension, preeclampsia (without eclampsia) and eclampsia, and the composite neurological outcome were explored through Cox regression analysis. Women with normotensive pregnancies were used as the reference group. Assessment of proportional hazards was tested by plotting of Schoenfeld residuals for estimation of the time-dependent coefficient $\beta(t)$. The analysis suggested that the assumption of proportional hazards was met. Risks were expressed as crude and adjusted hazard ratios (aHRs) with 95% CIs. First, we performed analyses on the crude dataset. In total, 63 140 women (9.7%) had 1 or more missing covariate(s). Hence, we ran analyses on the dataset with complete data and these results are the aHRs presented in the abstract and main text. Then, we imputed missing values of covariates, using the multiple imputation chained equations (MICE) approach with the R package mice.²⁹ Imputation was made 5 times, resulting in 5 completed datasets. The results

Figure 1. Flowchart of the Study Population



of the Cox regression analysis from each of these datasets were combined applying the Rubin rules to generate the imputed dataset's result (eMethods in Supplement 1).

Thereafter, we explored associations between gestational hypertension, preeclampsia, and eclampsia, and the individual components in the composite neurological outcome (migraine, headache, epilepsy, sleep disorder, and mental fatigue) using the same methods as described above. Mental fatigue was reported in fewer than 5 outcomes per group and was therefore omitted from the analysis. Kaplan-Meier survival analyses were generated to estimate cumulative event rates in relation to exposure groups.

Lastly, in a subanalysis, we explored the associations between preterm and term preeclampsia and the composite neurological outcome through Cox regression analysis. The reference group was women with normotensive pregnancies.

Statistical analyses were performed using SPSS software version 28.0 (IBM) and R version 4.2.3 (R Project).

Results

The study included 648 385 primiparous women (Figure 1). There were 609 830 women with a normotensive pregnancy, 11 133 women with gestational hypertension, 26 797 women with preeclampsia without eclampsia, and 625 women with eclampsia. Among women with preeclampsia, 5778 had preeclampsia with preterm birth (21.1%) and 21 635 had preeclampsia with term birth (78.9%) (Figure 1). The total follow-up time of the entire study population was more than 5 million person-years. Mean follow-up time per individual was 7.7 years.

Maternal and Infant Characteristics

Background characteristics of the population is presented in Table 1. Women with gestational hypertension and preeclampsia seemed to have a higher mean BMI and to be more likely

Table 1. Maternal and Infant Characteristics in a Cohort of Primiparous Women Giving Birth to Singletons in Sweden, 2005 Through 2018, (N = 648 385)

Characteristic	No. (%)			
	Normotensive pregnancy	Gestational hypertension	Preeclampsia ^a	Eclampsia
Total cohort	609 830 (94.1)	11 133 (1.7)	26 797 (4.1)	625 (0.1)
Maternal characteristics				
Age, y				
Mean (SD)	28.5 (5.0)	29.8 (5.3)	28.9 (5.4)	27.8 (5.7)
<25	137 323 (22.5)	1749 (15.7)	5825 (21.7)	197 (31.5)
25-34.9	401 090 (65.8)	7293 (65.5)	16 900 (63.1)	348 (55.7)
≥35	71 417 (11.7)	2091 (18.8)	4072 (15.2)	80 (12.8)
BMI ^{b,c}				
Mean (SD)	24.1 (4.4)	26.4 (5.4)	26.3 (5.6)	25.1 (5.1)
<18.5	17 122 (3.0)	112 (1.1)	395 (1.6)	17 (3.0)
18.5-24.9	364 584 (64.6)	4838 (46.4)	11 981 (48.3)	330 (57.5)
25.0-29.9	127 838 (22.7)	3124 (30.0)	6999 (28.2)	132 (23.0)
≥30	54 834 (9.7)	2348 (22.5)	5422 (21.9)	95 (16.5)
Missing	45 452	711	2000	51
Location of birth				
Sweden	470 770 (77.2)	9618 (86.4)	22 225 (83.0)	473 (75.7)
Europe	53 652 (8.8)	746 (6.7)	1679 (6.3)	46 (7.4)
Rest of the world ^d	85 279 (14.0)	768 (6.9)	2889 (10.8)	106 (17.0)
Missing	129	1	4	0
Daily cigarette smoking in early pregnancy				
No	542 133 (94.1)	10 073 (95.6)	24 094 (95.4)	555 (94.1)
Yes	34 079 (5.9)	459 (4.4)	1153 (4.6)	35 (5.9)
Missing	33 618	601	1550	35
Cohabitation				
Yes ^e	530 532 (91.5)	9789 (92.4)	23 240 (91.5)	510 (85.9)
Other ^f	49 176 (8.5)	802 (7.6)	2164 (8.5)	84 (14.1)
Missing	30 204	543	1396	32
Highest level of education				
≤ Upper secondary school degree	85 919 (14.2)	1137 (10.3)	3790 (14.2)	117 (18.9)
<2 y postsecondary education	157 359 (26.0)	3109 (28.1)	7766 (29.2)	174 (28.1)
≥2 y of university	362 036 (59.8)	6826 (61.7)	15 070 (56.6)	329 (53.1)
Missing	4532	61	172	5
Pregestational diabetes	2998 (0.5)	165 (1.5)	787 (2.9)	20 (3.2)
Gestational diabetes	5852 (1.0)	248 (2.2)	598 (2.2)	10 (1.6)
Kidney disease	2437 (0.4)	50 (0.4)	186 (0.7)	6 (1.0)
SLE	645 (0.1)	15 (0.1)	57 (0.2)	1 (0.2)
Infant characteristics				
Gestational age, wk, mean (SD)	39.9 (1.9)	39.8 (1.9)	38.4 (3.0)	37.7 (3.8)
Born preterm (yes) ^g	31 235 (5.1)	639 (5.7)	5596 (20.9)	182 (29.1)
Missing	151	1	9	0
Sex				
Female	296 035 (48.5)	5258 (47.2)	12 791 (47.7)	286 (45.7)
Male	313 804 (51.5)	5875 (52.8)	14 006 (52.3)	339 (54.3)
Missing	9	0	0	0
Birth weight, g, mean (SD)	3462 (543)	3416 (616)	3091 (831)	2973 (919)
SGA (yes) ^h	17 476 (2.9)	760 (6.8)	3497 (13.0)	83 (13.3)
Missing	1044	17	51	1
Stillborn (yes)	2298 (0.4)	29 (0.2)	138 (0.5)	6 (1.0)

Abbreviations: BMI, body mass index; SGA, small for gestational age; SLE, systemic lupus erythematosus.

^a Preeclampsia without eclampsia.

^b Excluding women with BMI less than 15 and 55 or more.

^c Calculated as weight in kilograms divided by height in meters squared.

^d Includes Africa, Asia, North America, Oceania, and South America.

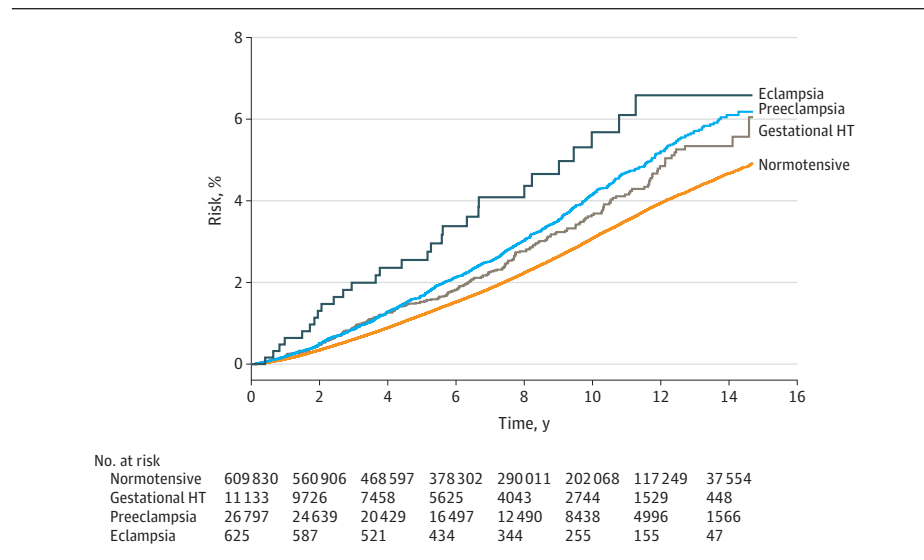
^e Includes women, married or unmarried, who are cohabiting with the other parent.

^f Includes women, with or without a partner, who are not cohabiting with the other parent.

^g Defined as born before 37 + 0 weeks.

^h Defined as a birth weight less than 2 SDs from the mean birth weight for the gestational age.

Figure 2. Kaplan-Meier Curve Illustrating the Cumulative Event Rate for a Composite of Neurological Disorders, per Exposure Group, in the Main Analysis



Women who experienced eclampsia during their first pregnancy were at the highest risk of developing future neurological disorders, with the highest cumulative event rate in the first 4 years after giving birth. After that, the cumulative event rate decreased and became similar to the rate of women with gestational hypertension (HT) and preeclampsia.

to have pregestational diabetes, kidney disease, and systemic lupus erythematosus than women with normotensive pregnancies.

Composite Neurological Outcomes

The cumulative event rate of the composite neurological outcome, by exposure group, is illustrated in Figure 2. Women with normotensive pregnancies had the lowest cumulative event rate of the 4 groups. Women with gestational hypertension and preeclampsia had around 1% incidence of the composite neurological event 4 years after giving birth, whereas the corresponding incidence was 2% for those who had experienced eclampsia. Subsequently, the incidence for all exposure groups increased by almost 2% for every 4 years.

Women with gestational hypertension, preeclampsia, and eclampsia had higher incidence rates (3.6, 4.0, and 5.4 per 1000, respectively) of developing a new-onset neurological disorder compared with women with a normotensive pregnancy (3.0 per 1000) (Table 2).

After adjustment for confounders, there was an association with increased risk of the composite outcome for women with gestational hypertension (aHR, 1.27; 95% CI, 1.12-1.45), women with preeclampsia (aHR, 1.32; 95% CI, 1.22-1.42), and women with eclampsia (aHR, 1.70; 95% CI, 1.16-2.50), compared with normotensive pregnancies (Table 2). After imputation of missing confounding data, the aHR remained essentially unchanged (Table 2).

Individual Neurological Outcomes

After adjustment for confounders, migraine was associated with an increased risk in women with gestational hypertension (aHR, 1.39; 95% CI 1.19-1.63) and preeclampsia (aHR, 1.25; 95% CI 1.13-1.38) compared with women with a normotensive pregnancy (Table 2). Preeclampsia was also associated with an increased risk of headache (aHR, 1.51; 95% CI, 1.33-1.71) and epilepsy (aHR, 1.32; 95% CI, 1.07-1.63) compared with women

with a normotensive pregnancy. Women with eclampsia were associated with a 5-time increased risk (aHR, 5.31; 95% CI, 2.85-9.89) for epilepsy during the follow-up time compared with women with normotensive pregnancies (Table 2).

Outcomes After Preterm and Term Preeclampsia

Women with preterm and term preeclampsia had higher incidence rates (4.8 and 3.9 per 1000, respectively) of developing a new-onset neurological disorder compared with women with a normotensive pregnancy (3.0 per 1000) (Table 3).

After adjustment for confounders, there was an association with increased risk for the composite neurological outcome for women with preterm preeclampsia (aHR, 1.54; 95% CI, 1.34-1.79) and women with term preeclampsia (aHR, 1.27; 95% CI, 1.17-1.38) compared with women with normotensive pregnancies. Both preterm and term preeclampsia were associated with increased risks of the individual outcomes migraine and headache, with higher aHRs for preterm than term preeclampsia. Women with term preeclampsia also had an association with increased risk for epilepsy (aHR, 1.41; 95% CI, 1.13-1.77) compared with women with a normotensive pregnancy (Table 3).

Discussion

In this study, women with gestational hypertension, preeclampsia, and eclampsia had an association with 20% to 70% increased risk of developing neurological disorders (migraine, headache, epilepsy, sleep disorder, or mental fatigue) in the years following their first birth. When investigating the neurological outcomes individually, the strongest association was found between women with eclampsia and epilepsy, with a 5-fold increased risk compared with women with a normotensive pregnancy. In the subanalysis, aHRs for migraine and headache were higher after preeclampsia with

Table 2. Risk of Developing a Neurological Disorder After a First Pregnancy Complicated by Gestational Hypertension, Preeclampsia, and Eclampsia, Main Analysis (N = 648 385)

Outcome	Normotensive pregnancy (n = 609 830)	Gestational hypertension (n = 11 133)	Preeclampsia (n = 26 797) ^a	Eclampsia (n = 625)
Primary outcome				
Composite of neurological disorders ^b				
Total PY of follow-up	4 728 612	74 614	205 470	5330
No. of events (%)	14 221 (2.3)	269 (2.4)	828 (3.1)	29 (4.6)
Event rate per 1000 PY	3.0	3.6	4.0	5.4
HR (95% CI), crude	1 [Reference]	1.24 (1.10-1.40)	1.35 (1.25-1.44)	1.77 (1.23-2.55)
aHR (95% CI), complete dataset	1 [Reference]	1.27 (1.12-1.45)	1.32 (1.22-1.42)	1.70 (1.16-2.50)
aHR (95% CI), imputed dataset	1 [Reference]	1.27 (1.12-1.43)	1.32 (1.23-1.42)	1.70 (1.18-2.44)
Secondary outcomes				
Migraine				
No. of events (%)	8309 (1.4)	179 (1.6)	458 (1.7)	13 (2.1)
Event rate per 1000 PY	1.7	2.4	2.2	2.4
HR (95% CI), crude	1 [Reference]	1.41 (1.22-1.64)	1.27 (1.16-1.40)	1.34 (0.78-2.31)
aHR (95% CI), complete dataset	1 [Reference]	1.39 (1.19-1.63)	1.25 (1.13-1.38)	1.47 (0.86-2.54)
aHR (95% CI), imputed dataset	1 [Reference]	1.43 (1.23-1.66)	1.26 (1.15-1.39)	1.32 (0.76-2.27)
Headache				
No. of events (%)	4473 (0.7)	76 (0.7)	283 (1.1)	6 (1.0)
Event rate per 1000 PY	0.9	1.0	1.4	1.1
HR (95% CI), crude	1 [Reference]	1.12 (0.89-1.40)	1.46 (1.29-1.65)	1.15 (0.52-2.55)
aHR (95% CI), complete dataset	1 [Reference]	1.27 (1.01-1.61)	1.51 (1.33-1.71)	1.00 (0.42-2.40)
aHR (95% CI), imputed dataset	1 [Reference]	1.21 (0.96-1.52)	1.47 (1.30-1.66)	1.08 (0.48-2.39)
Epilepsy				
No. of events (%)	1671 (0.3)	29 (0.3)	109 (0.4)	12 (1.9)
Event rate per 1000 PY	0.4	0.4	0.5	2.2
HR (95% CI), crude	1 [Reference]	1.13 (0.78-1.62)	1.50 (1.24-1.82)	6.26 (3.55-11.05)
aHR (95% CI), complete dataset	1 [Reference]	1.14 (0.78-1.66)	1.32 (1.07-1.63)	5.31 (2.85-9.89)
aHR (95% CI), imputed dataset	1 [Reference]	1.08 (0.75-1.56)	1.36 (1.12-1.66)	5.75 (3.26-10.15)
Sleep disorder				
No. of events (%)	352 (0.1)	3 (0.0)	23 (0.1)	1 (0.2)
Event rate per 1000 PY	0.1	0.0	0.1	0.2
HR (95% CI), crude	1 [Reference]	0.57 (0.18-1.78)	1.51 (0.99-2.30)	2.39 (0.34-17.04)
aHR (95% CI), complete dataset	1 [Reference]	0.59 (0.19-1.84)	1.28 (0.81-2.02)	2.43 (0.34-17.29)
aHR (95% CI), imputed dataset	1 [Reference]	0.54 (0.17-1.67)	1.33 (0.87-2.04)	2.17 (0.30-15.46)

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; PY, person-years.

^a Preeclampsia without eclampsia.

^b The composite outcome includes migraine, headache, epilepsy, neurasthenia, and sleep disorder.

preterm than term delivery; however, confidence intervals were overlapping.

Most studies on maternal long-term outcomes after gestational hypertension, preeclampsia, and eclampsia have focused on cardiovascular disease or long-term neurological complications, such as stroke, dementia, and cognitive impairment.^{5,8,12} There are few reports on future risks of short-term to medium-term neurological disorders. Two case series of patients with epilepsy and eclampsia reported eclampsia as a potential risk factor for epilepsy, though lacking a control group.^{15,16} There is 1 previous publication from a register-based study reporting on epilepsy after preeclampsia

that reported similar results as our study.¹⁷ They reported associations between preeclampsia (aHR, 1.96; 95% CI, 1.21-3.17) and eclampsia (aHR, 5.42; 95% CI, 2.42-12.12), and future seizure disorders.¹⁷ While their definition of the outcome was more comprehensive, we chose to include only epilepsy, a well-defined disorder caused by unusual electric activity in the brain, which is most often diagnosed after 2 seizures.³⁰ This stricter classification will avoid other causes of seizures, eg, caused by mental stress or a physical condition. The underlying mechanism of the association between eclampsia and epilepsy is unclear. However, hypertensive disorders during pregnancy, in particular eclampsia, are asso-

Table 3. Risk of Developing a Neurological Disorder After a First Pregnancy Complicated by Preeclampsia With Preterm or Term Delivery, Subanalysis (N = 637 092)

Outcome	Normotensive pregnancy (n = 609 679)	Preeclampsia, preterm (n = 5778) ^a	Preeclampsia, term (n = 21 635) ^b
Primary outcome			
Composite of neurological disorders ^c			
Total PY of follow-up	4 727 008	44 870	165 845
No. of events (%)	14 218 (2.3)	217 (3.8)	640 (3.0)
Event rate per 1000 PY	3.0	4.8	3.9
HR (95% CI), crude	1 [Reference]	1.61 (1.41-1.84)	1.29 (1.19-1.39)
aHR (95% CI), complete dataset	1 [Reference]	1.54 (1.34-1.79)	1.27 (1.17-1.38)
aHR (95% CI), imputed dataset	1 [Reference]	1.57 (1.37-1.79)	1.27 (1.17-1.37)
Secondary outcomes			
Migraine			
No. of events (%)	8307 (1.4)	119 (2.1)	352 (1.6)
Event rate per 1000 PY	1.8	2.6	2.1
HR (95% CI), crude	1.0	1.50 (1.25-1.80)	1.21 (1.09-1.35)
aHR (95% CI), complete dataset	1.0	1.53 (1.26-1.85)	1.18 (1.05-1.32)
aHR (95% CI), imputed dataset	1.0	1.49 (1.25-1.79)	1.20 (1.08-1.34)
Headache			
No. of events (%)	4472 (0.7)	84 (1.5)	205 (0.9)
Event rate per 1000 PY	0.9	1.9	1.2
HR (95% CI), crude	1 [Reference]	1.97 (1.59-2.45)	1.31 (1.14-1.51)
aHR (95% CI), complete dataset	1 [Reference]	1.83 (1.44-2.32)	1.40 (1.21-1.62)
aHR (95% CI), imputed dataset	1 [Reference]	1.94 (1.57-2.41)	1.32 (1.15-1.52)
Epilepsy			
No. of events (%)	1671 (0.3)	29 (0.5)	92 (0.4)
Event rate per 1000 PY	0.4	0.6	0.5
HR (95% CI), crude	1 [Reference]	1.82 (1.26-2.63)	1.57 (1.27-1.94)
aHR (95% CI), complete dataset	1 [Reference]	1.45 (0.96-2.19)	1.41 (1.13-1.77)
aHR (95% CI), imputed dataset	1 [Reference]	1.61 (1.11-2.33)	1.44 (1.16-1.78)
Sleep disorder			
No. of events (%)	352 (0.1)	5 (0.1)	19 (0.1)
Event rate per 1000 PY	0.1	0.1	0.1
HR (95% CI), crude	1 [Reference]	1.49 (0.61-3.59)	1.55 (0.97-2.45)
aHR (95% CI), complete dataset	1 [Reference]	1.48 (0.61-3.58)	1.26 (0.76-2.09)
aHR (95% CI), imputed dataset	1 [Reference]	1.29 (0.53-3.12)	1.37 (0.86-2.18)

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; PY, person-years.

^a Defined as birth before 37 + 0 weeks.

^b Defined as birth at 37 + 0 weeks or later.

^c The composite outcome includes migraine, headache, epilepsy, neurasthenia, and sleep disorder.

ciated with impaired cerebral autoregulation, blood-brain barrier disruption, and neuroinflammation, which are possible underlying causes of cerebral edema formation.^{4,31-34} In addition, preeclampsia and, in particular, eclampsia, can result in irreversible subclinical cerebral infarcts found in areas of cerebral edema.^{35,36} These findings are important and could be linked to the association with increased risk of epilepsy in women with preeclampsia and eclampsia. In other diseases associated with an acute brain injury, such as sepsis, a similar association to later epilepsy has been found.³⁷

To our knowledge, our study is the first to show an association between gestational hypertension and preeclampsia and a later diagnosis of migraine, as well as the association between preeclampsia and a later diagnosis of headache. The association between gestational hypertension and preeclampsia with migraine suggests that there might be a common underlying vascular component,³⁸ which is plausible since preeclampsia is a risk factor for cardiovascular morbidity later in life.^{8,9}

We did not find associations between gestational hypertension, preeclampsia, and eclampsia, and future increased risks of sleep disorder or mental fatigue. However, the prevalence of these outcomes was low and we cannot exclude that an existing association remains undetected. According to our clinical experience, many women describe symptoms corresponding to mental fatigue. They report feeling mentally tired, experiencing more fatigue after mental tasks, and having difficulties concentrating or multitasking after severe preeclampsia and eclampsia. This observation is in line with previous reports of patients experiencing problems with memory and concentration,⁵ as well as documentation of long-term cognitive impairment after gestational hypertension and preeclampsia.^{2,7} It may be that other similar diagnoses, such as depression, exhaustion disorder, or myalgic encephalomyelitis, are more commonly used and may overlap with mental fatigue/neurasthenia.^{39,40} To further examine mental fatigue and sleep disorders, case-control studies, studies using ques-

tionnaires, or qualitative studies may be better suited or complementary to register-based studies. Another approach to investigate mental fatigue would be to use sick leave or length of parental leave as potential outcomes. Prolonged periods of absence from work may reflect that women exposed to preeclampsia, for various reasons, are not ready to take up their work or enter the labor market again.

Obstetricians and gynecologists, as well as other health care professionals within maternal health, should be aware of the association with increased risk of persisting or new-onset neurological signs and symptoms after gestational hypertension, preeclampsia, and eclampsia. At follow-up visits, health care personnel should inquire about neurological symptoms in women affected by these disorders.

Strengths and Limitations

A strength of this population-based study is the large amount of data, with almost 650 000 women included. Due to the use of registry data, there was minimal loss to follow-up. The registries used in this study are of high quality and have population-based coverage.¹⁸ Our exposures are considered to have good to very good validity in the Swedish Medical Birth Register.¹⁸ Validation of the diagnosis of preeclampsia in the Norwegian Medical Birth Register, which holds great similarities with the Swedish registry, ascertained high positive predictive value concerning the diagnosis of preeclampsia.⁴¹

Limitations include the lack of diagnoses from primary health care, which resulted in low absolute frequencies of our outcomes. The epilepsy diagnosis is expected to be well covered in our dataset, given that all patients with a new onset of

epilepsy/seizures should be referred to a neurologist or internal medicine specialist for clinical and neuroradiological/physiological examination before diagnosis.³⁰ The diagnoses migraine, headache, and sleep disorder are more prevalent in primary health care, which entails a risk of type 2 error due to the falsely low incidence in our dataset. We could only identify the most severe cases, ie, women referred to specialized care. Lastly, since Swedish registers do not hold information on race or ethnicity, no such information could be included and no analyses could be conducted with respect to this. Racial differences have been demonstrated in the risk of cardiovascular outcomes after preeclampsia. Whether our findings regarding neurological outcomes extend to populations of all backgrounds remains to be explored.

Conclusions

In this study, women with gestational hypertension, preeclampsia, and eclampsia were associated with an increased risk of neurological disorders months to years after giving birth, including migraine, headache, epilepsy, sleep disorder, and mental fatigue. We speculate that differing pathophysiological mechanisms may underlie these neurological disorders, depending on which hypertensive disorder the woman was exposed to. Our findings warrant further investigations of neurological complications after gestational hypertension, preeclampsia, and eclampsia. They also highlight the need for follow-up regarding neurological disorders in women affected by these pregnancy-complications.

ARTICLE INFORMATION

Accepted for Publication: October 29, 2024.

Published Online: December 23, 2024.
doi:10.1001/jamaneurol.2024.4426

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Author Contributions: Dr Friis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtained funding: Wikström.

Administrative, technical, or material support: Hesselman, Wikström.

Supervision: Bergman, Cluver, Escudero, Wikström.

Conflict of Interest Disclosures: Dr Bergman reported grants from the Wallenberg Center for Molecular and Translational Medicine, the Swedish Research Council, Vera and Emil Cornell's Foundation, and the Swedish Society of Medicine, support for a prediction study from Perkin Elmer, Thermo Fisher, and Roche, and drug and placebo provided by Merck for a clinical trial outside the submitted work. Dr Hesselman reported grants from Centrum för klinisk forskning Dalarna during the conduct of the study. No other disclosures were reported.

Funding/Support: The Swedish Research Council (2020-01640).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank Katja Gabrysch, PhD, Uppsala Clinical Research Center, for valuable statistical support and Per Wikman, MSc, Department of Women's and Children's

Health, Uppsala University, for assistance with database management.

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