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ORIGINAL RESEARCH

Temporal Trends in Pregnancy-Associated Stroke and Its Outcomes Among Women With Hypertensive Disorders of Pregnancy

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BACKGROUND: Stroke is a serious complication of hypertensive disorders of pregnancy (HDP), with potentially severe and long-term sequelae. However, the temporal trends, predictors, and outcomes of stroke in women with HDP at delivery remain unknown.

METHODS AND RESULTS: All HDP delivery hospitalizations with or without stroke event (ischemic, hemorrhagic, or unspecified) between 2004 and 2014 in the United States National Inpatient Sample were analyzed to examine incidence, predictors, and prognostic impact of stroke. Of 4 240 284 HDP delivery hospitalizations, 3391 (0.08%) women had stroke. While the prevalence of HDP increased over time, incident stroke rates decreased from 10 to 6 per 10 000 HDP delivery hospitalizations between 2004 and 2014. Women with stroke were increasingly multimorbid, with some risk factors being more strongly associated with ischemic strokes, including congenital heart disease, peripheral vascular disease, dyslipidemia, and sickle cell disease. Delivery complications were also associated with stroke, including cesarean section (odds ratio [OR], 1.58; 95% CI, 1.33–1.86), postpartum hemorrhage (OR, 1.91; 95% CI, 1.33–1.86), and maternal mortality (OR, 99.78; 95% CI, 59.15–168.31), independently of potential confounders. Women with stroke had longer hospital stays (median, 6 versus 3 days), higher hospital charges (median, $14 655 versus $4762), and a higher proportion of nonroutine discharge locations (38% versus 4%).

CONCLUSIONS: The incidence of stroke in women with HDP has declined over time. While a relatively rare event, identification of women at highest risk of ischemic or hemorrhagic stroke on admission for delivery is important to reduce long-term sequelae.

Key Words: preeclampsia/pregnancy ■ pregnancy ■ stroke in young adults

See Editorial by Salehi Omran and Leppert

Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal morbidity and mortality worldwide,[1–4] affecting almost 10% of all pregnancies.[5] Chronic hypertension is defined as hypertension diagnosed before pregnancy or before 20 weeks of gestation; gestational hypertension is hypertension diagnosed during pregnancy at or after 20 weeks of gestation, delivery, or postpartum; while preeclampsia or eclampsia is hypertension diagnosed during pregnancy at or after 20 weeks of gestation, delivery, or postpartum with proteinuria or multisystem organ failure.[6] Women with HDP are at increased risk of stroke long-term,[7] while during the pregnancy almost 50% of pregnancy-associated strokes are associated with preeclampsia or eclampsia.[8]

Pregnancy-associated stroke is the most common cause of serious long-term disability following pregnancy[9] and accounts for 7.7% of maternal

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CLINICAL PERSPECTIVE

What Is New?

- The incidence of peripartum stroke in women with hypertensive disorders of pregnancy has declined over time.
- In this population, women with ischemic versus hemorrhagic strokes had moderately different clinical profiles whereby some stroke predictors were more strongly associated with ischemic than hemorrhagic strokes, including congenital heart disease, peripheral vascular disease, and dyslipidemia.
- Peripartum stroke is associated with increased odds of cesarean section and excessive in-hospital mortality risk in women with hypertensive disorders of pregnancy at 1.5- and 100-fold, respectively.

What Are the Clinical Implications?

- Clinicians should be encouraged to actively investigate and treat pregnant women with features suggestive of stroke, especially in the high-risk population of women with hypertensive disorders of pregnancy.
- The assessment of these women for their risk of ischemic or hemorrhagic stroke on admission for delivery is needed so that measures, such as closer blood pressure monitoring, may be instigated to improve their intrapartum care.

Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
HDP	hypertensive disorders of pregnancy
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
IQR	interquartile range
NIS	National Inpatient Sample
OR	odds ratio

deaths in the United States. Furthermore, maternal deaths from stroke in women with HDP may be underestimated, as they may be categorized as deaths attributable to HDP.[10] In the United States, 6.9% of maternal mortality is attributable to HDP.[10] Although there are known risk factors for peripartum strokes in preeclampsia, including older age, black race, infections, and prothrombotic or inflammatory disorders,[11] pregnancy-associated strokes continue to be difficult to predict and prevent.

Approximately 40% of pregnancy-associated strokes occur during hospital admissions for delivery,[1,12,13] with the highest risk occurring the day before or 2 days after delivery.[14] Most of the literature has not assessed the risk of stroke in women with HDP during this high-risk period,[15] when it may be possible to implement preventative strategies for these devastating events. The few larger studies in the context of HDP delivery outcomes are limited by the fact that they reported outcomes from selected preeclampsia cohorts,[11,16] lacked specific delivery admissions data,[1] included only selected risk factors and comorbidities,[1,16] were derived from limited geographic areas,[11,16] and lacked stroke subtype comparisons.[11,16] A nationally representative database, such as the National Inpatient Sample (NIS) containing discharge data from US hospitals, offers the opportunity to study rare events such as pregnancy-associated strokes during hospital delivery and fill current knowledge gaps to accelerate the progress in peripartum stroke prevention.

The current study used a national cohort of over 4 million delivery hospitalization episodes with HDP that occurred between 2004 and 2014. We aimed to assess the temporal trends in the incidence of stroke, patient characteristics, and comorbidities, as well as the associations of stroke with delivery complications, stratified by type of stroke.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. We conducted a cross-sectional study using the nationally representative NIS database, the largest all-payer inpatient healthcare database within the United States sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project.[17] It contains information on 7 million to 8 million hospital discharges per year.

We identified all women with a delivery hospitalization over 11 calendar years between January 2004 and December 2014 using a validated protocol that has been previously published (Data S1).[18] Following this, we established delivery hospitalizations that also had diagnosis codes for HDP using codes from previous publications on the NIS (Table S1).[19–22] Within these hospitalizations, we extracted records of a stroke event during the admission episode. This was stratified into ischemic (acute ischemic stroke, cerebral venous thrombosis, and transient ischemic attack), hemorrhagic (acute hemorrhagic stroke) and unspecified (stroke in puerperium or iatrogenic stroke, unspecific in nature) stroke (Table S1). In parallel, we also stratified the hospitalizations into HDP subgroups (chronic hypertension, gestational hypertension,

preeclampsia, and superimposed preeclampsia on chronic hypertension).

Relevant treatments (angiography, thrombolysis, and thrombectomy), delivery complications (maternal mortality, preterm birth, stillbirth, cesarean section, postpartum hemorrhage), and cost outcomes (length of stay and total hospital charge) were determined from the data set using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes from previous studies (Table S1).[19–21,23–28] We grouped the years (2004–2007, 2008–2011, and 2012–2014) in the temporal trend analyses.

Covariates on patient demographics, obstetric factors, and all Agency for Healthcare Research and Quality Elixhauser comorbidity measures were extracted, except for weight loss, metastatic cancer, solid tumor without metastasis, lymphoma, and blood loss, which are deemed either too uncommon in pregnancy or too common in our delivery cohort (Data S1). Neurological disorders included multiple sclerosis and epilepsy. Cardiovascular disease (CVD) was defined as a composite of arrhythmia, valvular disease, ischemic heart disease, peripheral vascular disease, heart failure, or peripartum cardiomyopathy. The *ICD-9-CM* codes used were based on previous publications and presented in Table S1.[26,27,29,30] This study involved the analysis of deidentified data and therefore did not require institutional review board review in accordance with the Code of Federal Regulations, 45 CFR 46.

Stata/MP version 14.0 statistical package was used to perform all analyses. Continuous variables are presented as medians and interquartile ranges (IQRs), and categorical data are presented as numbers and percentages. As recommended by Agency for Healthcare Research and Quality, to account for the survey design of the NIS database, the survey estimation commands were used (*svy* prefix in Stata) for all analyses.

We conducted binary logistic regression analyses to determine the association of potential risk factors with pregnancy-associated stroke, as well as the association between stroke and delivery complications of interest. The following potential risk factors were adjusted for in all fully adjusted analyses: year of admission, age, weekday/weekend admission, race and ethnicity, median zip code income quartile, hospital region, smoking, congenital heart disease, dyslipidemia, ischemic heart disease, peripartum cardiomyopathy, arrhythmias, previous stroke, sickle cell disease, obstetric factors associated with gestational hypertension or coagulopathy (gestational diabetes mellitus, fetal growth restriction, placenta previa, and multiple pregnancy), and selected Agency for Healthcare Research and Quality Elixhauser comorbidity measures (obesity, heart failure, diabetes mellitus, valvular disease, pulmonary circulation disorders, peripheral vascular disease, neurological disorders, chronic pulmonary disease, hypothyroidism, renal failure, liver disease, HIV and AIDS, rheumatoid arthritis/collagen vascular diseases, fluid and electrolyte disorders, deficiency anemias, alcohol abuse, drug abuse, depression, psychosis, coagulopathy, paralysis, and peptic ulcer). All odds ratios (ORs) were presented with the corresponding 95% CIs. We ensured that our study adhered to the recommended methodology standards[31] and an extension of the Strengthening the Reporting of Observational Studies in Epidemiology checklist, the Reporting of Studies Conducted Using Observational Routinely Collected Data checklist,[32] is shown in Table S2.

RESULTS

A total of 4 240 284 delivery hospitalization episodes with HDP, including 3391 (0.08%) women with stroke, between 2004 and 2014 were included (Figure 1). There was an increase in the proportion of HDP delivery hospitalizations episodes from 8.4% to 10.9% of a total of 44 801 002 hospitalizations between 2004 and 2014 (Figure 2A). However, the proportion of HDP delivery hospitalizations with

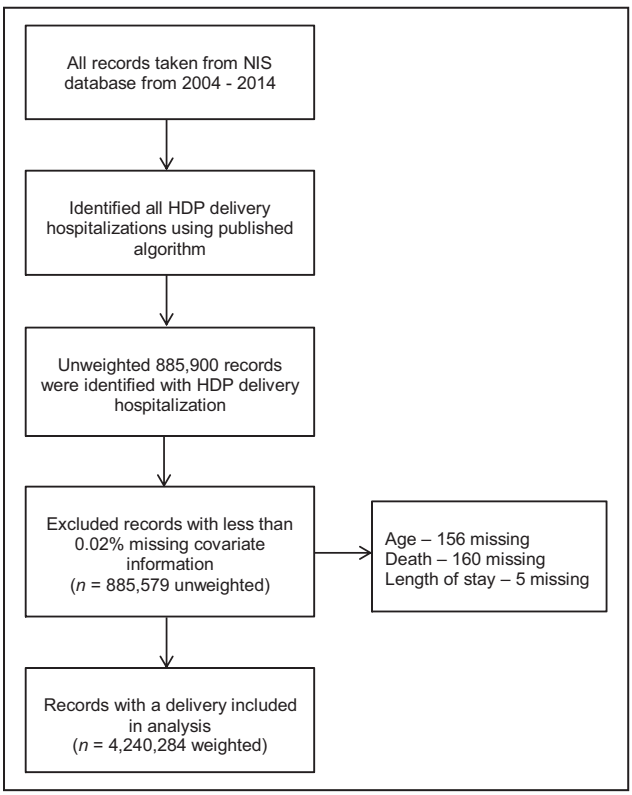

Figure 1. Flow diagram of included/excluded records.
HDP indicates hypertensive disorders of pregnancy; and NIS, National Inpatient Sample.

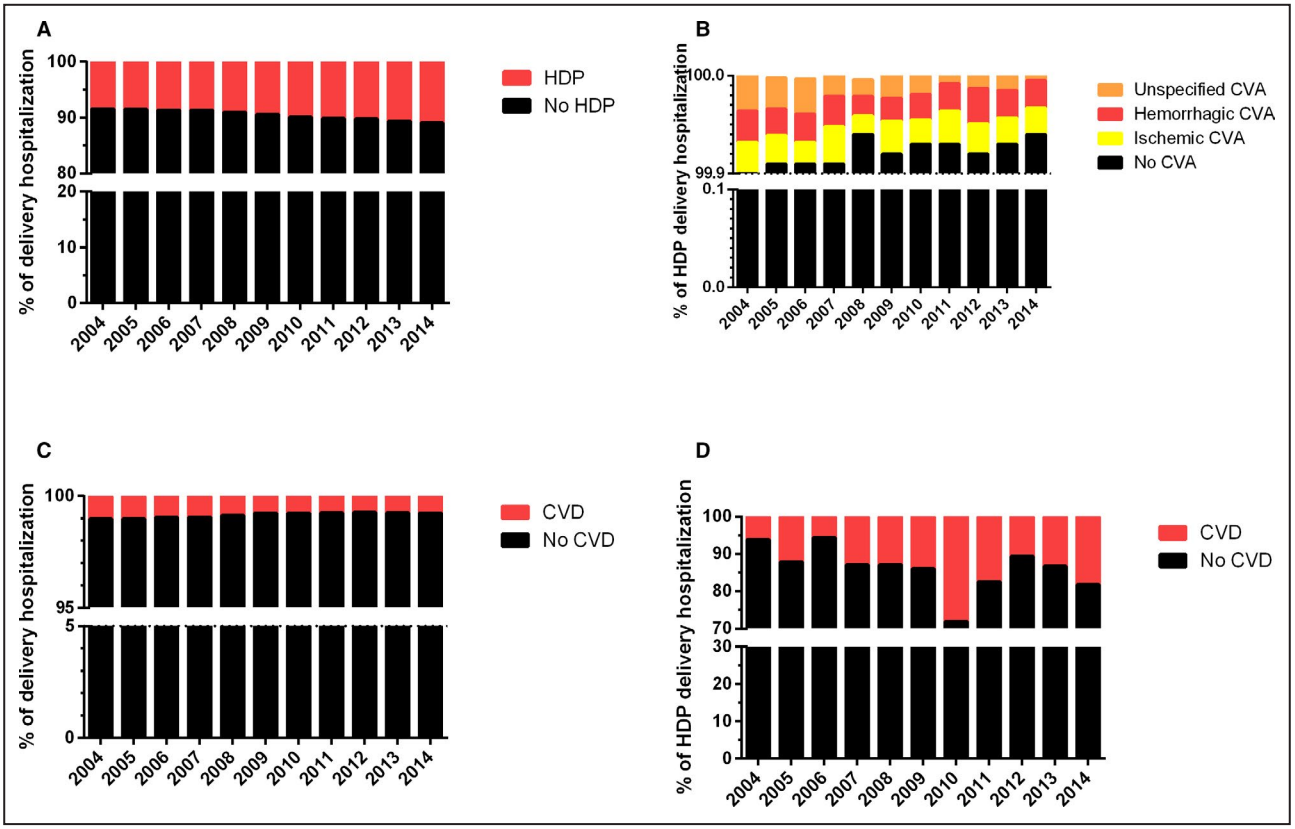

Figure 2. Comparison of hypertensive disorders of pregnancy (HDP) population in the delivery hospitalizations and stroke subpopulation in the HDP delivery hospitalizations over 1 decade.
A, Percentage of HDP diagnosis in delivery hospitalizations. **B**, Percentage of stroke (cerebrovascular accident [CVA]) diagnosis within the HDP delivery hospitalization population. A comparison of cardiovascular disease (CVD) diagnosis was also made between (**C**) HDP and (**D**) stroke populations.

a recorded stroke diagnosis decreased from 10 per 10 000 HDP delivery hospitalizations in 2004 to 6 per 10 000 HDP delivery hospitalizations in 2008, then remained stable until 2014 (Figure 2B). Next, we examined the temporal trends of demographic factors that may affect women with HDP with stroke, such as age, race and ethnicity, median income, and prevalent CVD. In both the HDP population and its stroke subpopulation, the median age and the composition of race groups remained relatively constant over time (Table S3). Although median income (Figure S1A) and prevalent CVD (Figure 2C) within the HDP population have remained unchanged over the decade, there was a proportional increase of women in the wealthiest income quartile (6%–17%; Figure S1B) and with CVD (6%–18%; Figure 2D) in women with HDP with stroke during this study period.

Table S4 shows the characteristics of our study population. Women with stroke comprised 0.08% of the HDP delivery population. They were older (median age, 30 versus 28) and had a higher proportion of black ethnicity (24% versus 17%). These women had more comorbidities, such as congenital heart disease, ischemic heart disease, peripheral vascular disease, heart failure, peripartum cardiomyopathy, coagulopathy, dyslipidemia, and previous stroke. Longer hospital stays (median, 6 versus 3 days) and higher hospital charges (median, $14 655 versus $4762), compared with women without stroke, were evident in women within the stroke group.

More women with stroke had ischemic or hemorrhagic strokes (36% or 35% of all stroke population), while the remaining 28% had unspecified strokes. The ischemic stroke group had a higher proportion of Hispanic women, and women with ischemic heart disease, peripheral vascular disease, heart failure, peripartum cardiomyopathy, previous stroke, dyslipidemia, sickle cell disease, and obesity. Conversely, the prevalence of valvular disease and coagulopathy was higher in the hemorrhagic compared with the ischemic group.

The temporal changes in the prevalence of recorded stroke risk factors and comorbidities in the HDP delivery hospitalization episodes within the stroke and no-stroke groups showed increased recorded prevalence of all risk factors and comorbidities over time in women with stroke (Table S5), except for valvular disease, ischemic heart disease, renal failure, and rheumatoid

Table 1. Association Between Stroke Risk Factors and Comorbidities With Subgroups of Stroke

	Stroke				No Stroke (n=4 236 893)
	All Stroke (n=3391)	Ischemic (n=1229)	Hemorrhagic (n=1187)	Unspecified (n=975)	
	OR (95% CI); n				
Neurological disorders	17.35 (13.42–22.43) n=730	15.99 (10.82, 23.62) n=255	18.94 (12.87–27.86) n=276	17.23 (10.63–27.92) n=199	1.00 (reference) n=34 319
Peripheral vascular disease	10.03 (3.98–25.25) n=54	24.16 (8.47–68.90) n=40	6.26 (1.18–33.18) n=10	1.40 (0.09–21.21) n=4	1.00 (reference) n=1695
Congenital heart disease	7.38 (3.85–14.16) n=81	7.70 (2.90–20.43) n=29	3.49 (0.93–13.05) n=14	12.31 (4.46–33.96) n=38	1.00 (reference) n=6779
Fluid and electrolyte disorders	5.90 (4.65–7.49) n=661	6.66 (4.39–10.09) n=269	8.50 (6.03–11.96) n=291	2.46 (1.41–4.30) n=101	1.00 (reference) n=72 875
Previous stroke	4.77 (2.09–10.87) n=55	3.67 (0.96–14.03) n=20	* n=0	14.09 (5.20–38.18) n=35	1.00 (reference) n=36
Coagulopathy	4.71 (3.80–5.84) n=639	3.92 (2.74–5.61) n=210	6.71 (4.83–9.31) n=300	3.45 (2.18–5.46) n=129	1.00 (reference) n=129 225
Arrhythmia	2.86 (1.94–4.21) n=203	2.58 (1.41–4.72) n=77	2.77 (1.50–5.14) n=67	3.39 (1.57–7.29) n=59	1.00 (reference) n=30 082
Ischaemic heart disease	2.84 (1.25–6.46) n=53	3.21 (0.84–12.26) n=29	2.61 (0.65–10.48) n=9	2.54 (0.58–11.09) n=15	1.00 (reference) n=3813
Drug abuse	1.99 (1.35–2.94) n=173	1.87 (0.92–3.79) n=63	1.94 (1.07–3.53) n=57	2.23 (1.09–4.54) n=53	1.00 (reference) n=72 451
Sickle cell disease	1.94 (0.68–5.50) n=23	6.81 (2.21–20.99) n=23	* n=0	* n=0	1.00 (reference) n=4237
Peripartum cardiomyopathy	1.89 (0.70–5.06) n=82	2.54 (0.64, 10.14) n=44	0.55 (0.03–9.95) n=9	2.30 (0.43, 12.23) n=29	1.00 (reference) n=11 016
Heart failure	1.66 (0.74–3.69) n=91	2.51 (0.79–7.94) n=49	0.48 (0.01–15.22) n=9	1.80 (0.51–6.40) n=33	1.00 (reference) n=12 287
Renal failure	1.36 (0.68–2.73) n=65	0.94 (0.26–3.44) n=20	0.89 (0.25–3.15) n=15	2.86 (0.99–8.25) n=30	1.00 (reference) n=13 558
Rheumatoid arthritis/collagen vascular diseases	1.23 (0.64–2.36) n=55	0.30 (0.04–2.27) n=5	0.96 (0.29–3.21) n=14	2.85 (1.25–6.51) n=36	1.00 (reference) n=20 761
Depression	1.02 (0.68–1.52) n=147	0.63 (0.29–1.38) n=35	1.12 (0.56–2.25) n=54	1.44 (0.77–2.69) n=58	1.00 (reference) n=117 362
Obesity	0.87 (0.67–1.13) n=342	1.01 (0.67–1.54) n=153	0.75 (0.47–1.20) n=98	0.82 (0.48–1.40) n=91	1.00 (reference) n=469 024
Smoking	0.87 (0.62–1.21) n=259	1.01 (0.63–1.64) n=111	0.78 (0.43–1.40) n=75	0.78 (0.41–1.46) n=73	1.00 (reference) n=286 838
Valvular disease	0.87 (0.39–1.94) n=69	0.33 (0.06–1.68) n=15	1.81 (0.62–5.28) n=26	1.03 (0.31–3.42) n=28	1.00 (reference) n=26 269

(*Continued*)

Table 1. Continued

	Stroke				No Stroke (n=4 236 893)
	All Stroke (n=3391)	Ischemic (n=1229)	Hemorrhagic (n=1187)	Unspecified (n=975)	
	OR (95% CI); n				
Diabetes mellitus	0.57 (0.38–0.86) n=152	0.54 (0.26–1.10) n=59	0.38 (0.18–0.82) n=34	0.85 (0.42–1.73) n=59	1.00 (reference) n=165 239
Gestational diabetes mellitus	0.49 (0.36–0.68) n=192	0.53 (0.32–0.88) n=73	0.38 (0.20–0.70) n=52	0.60 (0.34–1.06) n=67	1.00 (reference) n=446 145
Alcohol abuse	0.16 (0.02–1.51) n=5	* n=0	* n=0	0.63 (0.08–5.07) n=5	1.00 (reference) n=6355

Data expressed as odds ratios (OR) and 95% CIs. n indicates weighted number of cases.
*An odds ratio could not be calculated because of lack of cases in subgroup.

arthritis or collagen vascular diseases. No obvious differences in stroke risk factors or comorbidities were found between the stroke subgroups.

Angiography was most commonly conducted in hemorrhagic strokes, while for ischemic strokes, thrombolysis was performed more frequently than thrombectomy (Table S6). The prevalence of all delivery complications was higher in women with strokes compared with women without strokes (Table S6). Maternal mortality, stillbirth, and postpartum hemorrhage occurred most frequently in hemorrhagic strokes, whereas preterm birth occurred most frequently in ischemic strokes. No obvious temporal patterns were detected for treatments and delivery complications both overall and in the stroke subgroups (Table S5).

Multivariable analyses were conducted to examine the independent association of risk factors and stroke subgroups (ischemic, hemorrhagic, and unspecified) (Table 1). Preexisting neurological disorders (adjusted OR, 17.35; 95% CI, 13.42–22.43), peripheral vascular disease (OR, 10.03; 95% CI, 3.98–25.25), congenital heart disease (OR, 7.38; 95% CI, 3.85–14.16), fluid and electrolyte disorder (OR, 5.90; 95% CI, 4.65–7.49), and previous stroke (OR, 4.77; 95% CI, 2.09–10.87) had the highest ORs in association with all stroke. We performed a separate analysis to study the independent predictors of ischemic and hemorrhagic strokes. Generally, the risk factors associated with stroke were the same for ischemic and hemorrhagic strokes, although congenital heart disease, peripheral vascular disease, dyslipidemia, and sickle cell disease were more strongly associated with ischemic stroke.

We also examined the association of stroke with delivery complications (Table 2). This showed that all stroke was associated with a 100-fold increase in risk of maternal mortality (OR, 99.78; 95% CI, 59.15–168.31), which was even greater in the case of hemorrhagic stroke (OR, 260.80; 95% CI, 138.10–492.51). There was an almost double risk of postpartum hemorrhage (OR, 1.91; 95% CI, 1.54–2.37) and 1.5-fold risk for cesarean section (OR, 1.58; 95% CI, 1.33–1.86) for women with strokes. Over the 11-year study period, there was no change in the association between stroke and delivery complications (Figure S2).

Women with stroke had longer lengths of hospital stays (6 days; IQR, 3–10) compared with women without stroke (3 days; IQR, 2–4), with hemorrhagic stroke being associated with the longest duration (7 days; IQR, 3–12) out of all stroke subgroups (ischemic, hemorrhagic, unspecified) (Table S4). Similarly, the total charge was higher for women with stroke ($14 655; IQR, $8494–$27 895) compared with women without stroke ($4762; IQR, $3278–$7036), with the highest charge seen in hemorrhagic stroke ($20 532; IQR, $10 256–$41 042) (Table S4). No temporal changes were detected in the length of stay and total charge outcomes (Table S5). Additional sensitivity analyses on delivery complications and cost outcomes were conducted to examine for the effects of excluding records with missing data (Table S7). This showed no important changes in the ORs.

As a surrogate of disability following stroke, we examined the discharge locations following delivery hospitalizations (Table S4, Figure 3). Women with stroke (Figure 3B) had a higher proportion of discharges to facilities other than routine at own home compared with women without stroke (Figure 3A). The hemorrhagic stroke population (Figure 3D) had a greater proportion of discharges to short-term hospitals and other care facilities, compared with ischemic (Figure 3C) and unspecified (Figure 3E) stroke populations. In contrast, there was a greater proportion of discharges to home care in women with ischemic (Figure 3C) and unspecified (Figure 3E) compared with hemorrhagic strokes (Figure 3D).

We also stratified the data according to subgroups of HDP (chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia). Over half of the strokes (52.5%) occurred in women with preeclampsia (Table S8). We then reassessed the prognostic association of stroke risk factors with stroke and the delivery complications associated with strokes for each HDP subgroup (Table S9). The gestational hypertension subgroup had the highest increase in risk of maternal mortality and preterm birth following stroke, while for the preeclampsia group, the highest increase in risk occurred in postpartum hemorrhage and cesarean section.

DISCUSSION

Our study is the first to consider the temporal trends of the clinical profile and delivery complications of women with HDP with stroke during hospital admissions for delivery, a time of increased stroke risk. Our analysis of over 4.2 million HDP delivery hospitalizations show that while the prevalence of HDP has increased over time, incident stroke rates have declined but remain important predictors of delivery complications, including mortality and cesarean section. Women with stroke are increasingly multimorbid with distinctive risk profiles for ischemic and hemorrhagic complications. Congenital heart disease, peripheral vascular disease, dyslipidemia, and sickle cell disease were more strongly associated with ischemic stroke compared with hemorrhagic stroke.

Previous studies have suggested the incidence of peripartum stroke is increasing over time but without considering the effects of concurrent increase in the incidence of HDP. We are the first to compare the temporal trends in the characteristics of the HDP population with its stroke subpopulation. Our analysis shows that the proportion of incident stroke within the HDP delivery population is actually decreasing. This finding is consistent with previous research showing a decline in overall stroke hospitalizations in the general population over time, which was more pronounced in women.[33,34] This may be attributable to improvements in CVD prevention efforts. However, this downward trend in stroke incidence is at risk of being lost because of other emerging patterns such as increasing sedentary lifestyle, substance abuse, and social isolation, as well as the obesity/metabolic syndrome epidemic.

We comprehensively assessed comorbidities using Elixhauser comorbidity measures and showed that an increasing proportion of women with multimorbidity with HDP suffer strokes, despite the reduction in overall incident stroke in HDP over time. However, this may simply reflect the general trend of more women with multimorbidity conceiving successfully.[22] There was an increase in HDP pregnancy admissions in women who reside in wealthier zip codes over the years, this may be related to increasing access to fertility treatments, as HDP is associated with fertility treatments.[35,36]

There is limited literature on peripartum outcomes of women with HDP with stroke, as the majority have studied stroke in the wider pregnant population.[15,37,38] A previous study using the 1994–2011 NIS database examined hospitalizations with HDP and stroke during the whole pregnancy, rather than the delivery period that we have studied, and showed an event rate of 0.02% for stroke.[1] In contrast to our study, they found that stroke in HDP pregnancy hospitalizations increased over their

Table 2. Association Between Subgroups of Stroke and Delivery Complications

	All stroke (n=3391)	Stroke			No Stroke (n=4 236 893)
		Ischemic (n=1229)	Hemorrhagic (n=1187)	Unspecified (n=975)	
	OR (95% CI); n				
Maternal mortality	99.78 (59.15–168.31) n=297	30.34 (12.32–74.73) n=59	260.80 (138.10–492.51) n=193	40.34 (14.16–114.87) n=45	1.00 (reference) n=847
Postpartum hemorrhage	1.91 (1.54–2.37) n=531	1.98 (1.38–2.83) n=194	2.03 (1.46–2.82) n=223	1.65 (1.01–2.68) n=114	1.00 (reference) n=205 913
Stillbirth	1.68 (1.00–2.82) n=96	0.93 (0.34–2.69) n=21	1.67 (0.70–4.00) n=35	2.84 (1.33–6.07) n=40	1.00 (reference) n=37 285
Cesarean section	1.58 (1.33–1.86) n=2084	1.62 (1.22–2.16) n=761	1.44 (1.08–1.91) n=708	1.71 (1.26–2.30) n=615	1.00 (reference) n=1 961 258
Preterm birth	1.22 (0.99–1.49) n=797	1.34 (0.98–1.82) n=303	1.25 (0.91–1.73) n=283	1.02 (0.68–1.54) n=211	1.00 (reference) n=637 229

Data expressed as odds ratios (OR) and 95% CIs. n indicates weighted number of cases.

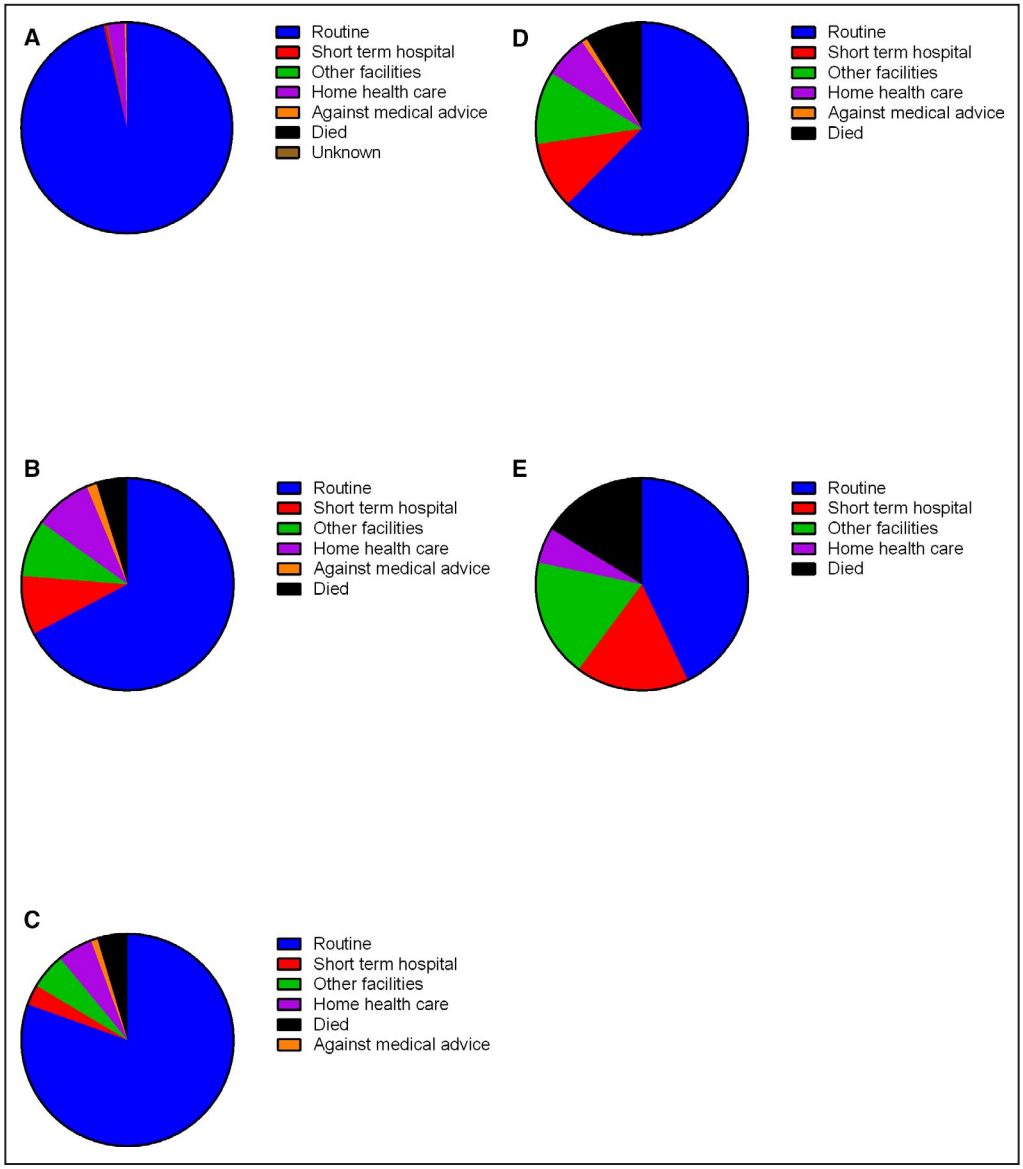

Figure 3. Discharge locations of women with hypertensive disorders of pregnancy and (A) no stroke, (B) any stroke, (C) ischemic stroke, (D) hemorrhagic stroke, or (E) unspecified stroke.

study period.[1] This discrepancy may be attributable to the different study population. Furthermore, different clinical outcomes were examined, with ours focusing on delivery complications, while the other study assessed stroke-related outcomes, such as mechanical ventilation, pneumonia, and seizure.[1] Other national studies on HDP delivery hospitalizations evaluated only women with preeclampsia without other HDP subgroups.[11,16,39,40] These focused on stroke risk factors and did not consider adverse outcomes following stroke. A regional study on HDP delivery hospitalizations in New York showed an incidence rate of 0.13% for stroke.[41] However, most of the analyses in this study included stroke only in a composite cardiovascular morbidity outcome.

Traditional stroke risk factors have been shown to increase the risk for any stroke in women with HDP during pregnancy.[1] We demonstrated that there are some risk factors that are more strongly associated with ischemic than hemorrhagic strokes. A previous study on the whole pregnancy period also identified sickle cell disease as a risk factor for ischemic stroke.[1] Consistent with our findings, diabetes mellitus was not found to increase the risk for pregnancy-associated stroke in this study on HDP pregnancy hospitalizations.[1] Unique to our study is the fact that we are the first to stratify stroke predictors by specific HDP subgroups.

There are some possible mechanisms for the stroke predictors we identified. The most common

mechanism of stroke associated with congenital heart disease is paradoxical embolism, where right-to-left shunts allow thromboemboli to reach into the arterial circulation without traversing the lungs.[42] Moreover, while pregnancy increases the risk of thromboembolism 6-fold, this risk is further increased in women with HDP.[43,44] Both peripheral vascular disease and dyslipidemia increase the risk of atherosclerosis, which in turn causes ischemic stroke. In addition to the physiological hyperlipidemia of pregnancy,[45] women with dyslipidemia have increased risk of preeclampsia.[46] Therefore, women with HDP are a particularly high-risk group for ischemic stroke. Women with sickle cell disease are at high risk for HDP and stroke. Moreover, the stress of delivery can precipitate vaso-occlusive crisis, a cause of stroke in sickle cell disease.[47]

We are the first to show that peripartum stroke is independently associated with increased odds of cesarean section and excessive in-hospital mortality risk in the HDP population at 1.5- and 100-fold, respectively. It is worth noting that pregnant women suffering stroke usually undergo cesarean sections. Comparable to our findings, prior research that examined stroke in pregnancy admissions showed a 1.8-fold risk of postpartum hemorrhage.[13] It is possible that postpartum hemorrhage is caused by stroke treatment; however, as there are no data on chronicity in our data set, we can only speculate. In a longer-term setting, the adjusted incident rate ratio for death from stroke for preeclampsia/eclampsia was 3.59 (95% CI, 1.04–12.4).[48]

Stroke is often misdiagnosed in pregnant women as representing more benign conditions, such as migraines or seizures.[49] Compounded with clinicians' general reluctance to give medication and/or perform nonobstetric surgery in pregnant women, these patients may miss the chance to receive timely effective treatment. Prior research has shown that even for minor symptoms of nausea and vomiting, general practitioners were reluctant to start antiemetic treatment in pregnancy unless the symptoms have progressed to a severe stage.[50] Therefore, clinicians should be encouraged to actively investigate and treat pregnant women with features suggestive of stroke, especially in the high-risk HDP population.

The strengths of this study include the large number of HDP hospital admission episodes, the comprehensive capture of delivery hospitalizations, and the diversity of the HDP population in terms of geography and race or ethnicity. This allows us to have statistical power to examine disease patterns of rare events such as stroke. With 3391 stroke events in our population, we were also able to examine the temporal trends in the prevalence, comorbidities, and associated delivery complications.

A limitation of our study is that our results are national estimates based on sampling weights. As the unweighted events for stroke subtype are low, some of the calculated ORs in the subgroup analyses have wide CIs. Another limitation is the lack of information relevant to patient prognosis after stroke, for example, time to diagnosis, imaging modality, and pharmacotherapy. However, other available data could provide further information. For example, the arrhythmia comorbidity may be a surrogate for warfarin use. We captured data only on women admitted to the hospital without considering stroke in the community. Similarly, we have not captured births in the community. However, US national statistics show that >98% of births occur in hospitals.[51] Because of the design of the NIS, we were unable to track patients over the years and could consider only in-hospital outcomes. Therefore, one woman could have had multiple deliveries during the study period. As there was no information on timing of events, we could not conduct analyses on time to events, such as delivery complications, or effects of chronicity on comorbidities. In addition to mortality, we examined other delivery complications, such as cesarean section and postpartum hemorrhage, which could have contributed to the cause of mortality. However, we did not consider mortality as a competing risk for other delivery complications. Since we did not adjust for multiple testing, some of the statistically significant results may be attributable to chance. Errors may arise from inaccurate physician and administrative reporting of *ICD* codes. Furthermore, chronic conditions are usually undercoded in administrative data sets, with low to moderate sensitivity for the majority of conditions. Finally, for the temporal analyses, the accuracy may have improved over time because of improved diagnosis or better coding from changes in guidelines or incentives.

In conclusion, our analysis showed that over a decade, the incidence of stroke reduced in an increasingly complex HDP delivery population. Women with HDP with ischemic versus hemorrhagic strokes had moderately different clinical profiles whereby some stroke predictors were more strongly associated with ischemic than hemorrhagic strokes and therefore represent underlying differences in the populations at risk. The assessment of women with HDP for their risk of ischemic or hemorrhagic stroke on admission for delivery is needed so that measures such as closer blood pressure monitoring may be instigated to improve their intrapartum care.

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Disclosures

None.

Supplementary Materials

Data S1
Tables S1–S9
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Study design and variables

All eligible discharges with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 650 (*Normal delivery),* V27 (*Outcome of delivery),* selected delivery related procedures and diagnosis-related group (DRG) delivery codes were used to identify the delivery population. As each pregnancy will result in only one delivery hospitalisation per year, the discharge record is linked to each pregnancy. However, many women have more than one pregnancy, and therefore one woman can have multiple delivery hospitalisation episodes over the study period. Codes for hypertensive disorders of pregnancy (HDP) (Table S1) were then applied to the delivery population in order to identified the HDP population in this study.

Patient demographics that were extracted include: age, race and ethnicity, median household income according to ZIP code, admission day (weekday or weekend), hospital region, and patient comorbidity conditions. As each discharge record included information on up to 30 diagnoses that the patient had (15 between 2004 and 2008, 25 between 2009 and 2013 and 30 in 2014), we used these diagnosis codes to identify the comorbidity conditions recorded during the delivery hospitalisation.

To account for the complex survey design of the NIS database, the survey estimation commands were used (svy prefix in Stata) for all analyses. As the discharge records were not sampled individually but by hospitals, the survey estimation accounted for the clustering of records within hospitals by defining each hospital to be the primary sampling unit. In order to calculate national estimates and variances, we used sampling weights for each individual discharge provided by the AHRQ. The sampling weights are needed because of the study design where different observations may have different probabilities of selection.

There has been a change in sampling strategy over time to generate more generalizable estimates by reducing sampling bias. Before 2012 the NIS retained all discharges from a sample of hospitals, but since then the NIS samples discharges from all hospitals participating in HUCP, which approximates a 20% stratified sample of all discharges from U.S. hospitals. In order to ensure the data were comparable across all years of the study period, two sets of weights (pre-2012 and 2012 onwards) were used as there was a redesign of the NIS dataset in 2012.

As the total charge recorded in the NIS database is the amount of the hospital bill and not representative of the actual cost of hospital services, we used a charge to cost conversion ratio provided by AHRQ to convert the reported charge into actual cost for the payer.

Table S1. Search codes.

Variables	ICD-9-CM / ICD-9-CM PR / DXCCS codes
Hypertensive disorders of pregnancy	
Preeclampsia/eclampsia	6424x, 6425x, 6426x
Gestational hypertension	6423x
Chronic hypertension	6420x, 6421x, 6422x, 6429x or Elixhauser comorbidity hypertension variable =1 in NIS dataset
Superimposed preeclampsia on chronic hypertension	6427x or a combination of chronic hypertension and preeclampsia as defined above
Type of stroke	
Acute ischaemic stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.x, 435.8-9, 436, 671.5, 325
Acute haemorrhagic stroke (subarachnoid, intracerebral haemorrhage)	430, 431, 432.x
Cerebral venous thrombosis	437.6, 671.5, 325
Transient ischaemic attack	435.x
Stroke, unspecified	674.0x, 997.02
Treatments / Complications	
Angiography	PR 98841
Thrombolysis	PR 9910
Thrombectomy	PR 3974
Mortality	7616 or DIED variable =1 in NIS dataset
Preterm birth	644x
Stillbirth	6564x, v271x, v273x, v274x, v276x, v277x, 7680, 7681
Postpartum haemorrhage	666x
Caesarean section	PR 740 741 742 744 7499
Comorbidities	
Smoker	V1582, 3051x, 6490x, 98984
Congenital heart disease	6485, 745x, 746x, 747x, DXCCS 213
Dyslipidaemia	DXCCS 53
Ischaemic heart disease	410x, 411x, 412, 413x, 4140x, 4142, 4143, 4144, 4148, 4149
Peripartum cardiomyopathy	425x, 6745x
Arrhythmia	426x, 427x
Previous stroke	V1254
Sickle cell disease	2826x
Gestational diabetes	6488x
Fetal growth restriction	6565x
Placenta praevia	6410x, 6411x
Multiple pregnancy	V272x, v273x, v274x, v275x, v276x, v277x, 651x

Selected Elixhauser comorbidities (obesity, heart failure, diabetes, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, other neurological disorders, chronic pulmonary disease, hypothyroidism, renal failure, liver disease, HIV and AIDS, rheumatoid arthritis/collagen vascular diseases, fluid and electrolyte disorders, deficiency anaemia, alcohol abuse, drug abuse, depression, psychosis, coagulopathy, paralysis, peptic ulcer abuse, depression)	List of comorbidities and associated ICD-9-CM code can be found (Quan 2005 et al.) at: http://czresearch.com/dropbox/Quan_MedCare_2005v43p1130.pdf

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification. PR, procedural. DXCCS, Diagnosis Clinical Classification Software.

Table S2. The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported (page)	RECORD items	Location in manuscript where items are reported (page)
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	4	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	4
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	7		
Objectives	3	State specific objectives, including any prespecified hypotheses	8		
Methods					

Study Design	4	Present key elements of study design early in the paper	8		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	8-9 Table S1	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Table S1
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9		
Bias	9	Describe any efforts to address potential sources of bias	10		
Study size	10	Explain how the study size was arrived at	8		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	NA		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	9-10		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	8

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	8
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	NA
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Figure 1

Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Table S4 Figure 1 8		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures	Table S4		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2 NA NA		

Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Table S7		
Discussion					
Key results	18	Summarise key results with reference to study objectives	14		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-19		
Generalisability	21	Discuss the generalisability (external validity) of the study results	18		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19		

Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	In supplemental materials

Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Table S3. Temporal trends of median age in (A) HDP stroke population and (B) HDP population; and race and ethnicity groups in (C) HDP stroke population and (D) HDP population, between 2004-2014. HDP, hypertensive disorders of pregnancy.

A.

	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
All stroke	29	32	29	29.5	32	31	30	30	30	31	30
Ischaemic stroke	28	30	29	27	34	31	30	27	32	32.5	28
Haemorrhagic stroke	30	34	31	30	30	24	29	34	29	31	32
Unspecified	30	32	29	31	34	33	31	34	30	27	31

B.

	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
HDP	28	28	27	28	28	28	28	28	29	29	29

C.

	2004	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
White	23.15%	36.08%	28.41%	24.96%	31.69%	35.12%	48.17%	35.89%	27.27%	33.33%	27.27%
Black	31.81%	15.56%	18.64%	18.41%	17.89%	22.40%	21.96%	29.18%	28.79%	31.67%	29.09%
Hispanic	18.64%	15.89%	22.91%	21.48%	23.97%	19.91%	13.39%	18.89%	19.70%	26.67%	25.45%
Asian/Pacific Islander	5.88%	0%	2.53%	6.45%	4.58%	0%	5.21%	4.99%	4.55%	3.33%	5.45%
Native American	0%	1.55%	1.43%	1.21%	0%	1.43%	1.48%	0%	1.52%	0%	0%
Other	3.39%	2.58%	4.22%	2.59%	2.24%	4.87%	1.76%	3.44%	12.12%	1.67%	3.64%
Missing	17.12%	28.34%	21.85%	24.91%	19.63%	16.27%	8.03%	7.62%	6.06%	3.33%	9.09%

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	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
White	40.07%	39.37%	36.59%	35.33%	44.29%	43.64%	46.74%	45.84%	50.23%	50.09%	50.15%
Black	14.90%	12.02%	12.94%	15.63%	14.83%	17.60%	20.59%	19.61%	20.50%	20.38%	20.35%
Hispanic	14.21%	14.25%	16.31%	14.93%	14.74%	15.61%	15.11%	18.04%	15.87%	16.27%	16.23%
Asian/Pacific Islander	2.45%	2.37%	1.54%	2.22%	2.58%	2.38%	3.31%	2.58%	3.01%	3.10%	3.16%
Native American	0.38%	0.65%	0.75%	0.79%	0.75%	0.90%	0.82%	0.80%	0.99%	0.78%	0.71%
Other	2.52%	3.37%	2.95%	2.94%	2.84%	3.76%	3.03%	3.80%	4.21%	3.44%	3.65%
Missing	25.47%	27.98%	28.92%	28.17%	19.97%	16.10%	10.40%	9.33%	5.18%	5.94%	5.74%

Table S4. Patient characteristics stratified by subgroups of stroke.

	No stroke	All stroke	Stroke		
			Ischaemic	Haemorrhagic	Unspecified
HDP delivery hospitalisation	99.92%	0.08%	0.029%	0.028%	0.023%
Number of deliveries, weighted	4,236,893	3,391	1,229	1,187	975
		Demographics			
Age, median (IQR)	28 (23-33)	30 (24-35)	29 (24-35)	31 (24-35)	31 (25-35)
Race and ethnicity:					
1. White	44.1%	31.6%	31.0%	27.7%	37.1%
2. Black	17.3%	24.2%	27.0%	24.1%	20.7%
3. Hispanic	15.6%	20.5%	16.9%	25.1%	19.3%
4. Asian / Pacific Islander	2.6%	3.9%	4.0%	3.9%	3.9%
5. Native American	0.8%	0.8%	0.4%	1.2%	0.9%
6. Other	3.3%	0.4%	3.9%	5.8%	1.8%
7. Missing	16.3%	15.0%	16.8%	12.2%	16.3%
Median ZIP code income:					
1. 1st quartile	25.0%	25.0%	26.6%	23.2%	24.9%
2. 2nd quartile	20.9%	20.7%	19.6%	23.3%	18.9%
3. 3rd quartile	19.7%	18.9%	18.3%	19.4%	19.1%
4. 4th quartile	15.9%	13.3%	15.3%	13.1%	11.0%
5. Missing income	18.5%	22.1%	20.2%	21.0%	26.1%
Weekday admission	85.9%	79.9%	77.7%	78.9%	83.9%
Hospital region:					
1. Northeast	14.7%	15.4%	11.2%	18.0%	17.6%
2. Midwest	20.8%	16.8%	16.9%	17.1%	16.2%
3. South	43.9%	42.4%	47.8%	38.6%	40.3%
4. West	20.6%	25.4%	24.1%	26.3%	25.9%

Discharge location: 1. Routine	96.46%	62.39%	67.25%	42.88%	80.45%
2. Short-term hospital	0.48%	10.27%	9.00%	17.31%	3.11%
3.Other facilities	0.09%	11.08%	8.66%	18.09%	5.46%
4. Home health care	2.63%	6.63%	8.78%	5.43%	5.37%
5. Against medical advice	0.31%	0.84%	1.53%	0%	1.00%
6. Died	0.02%	8.79%	4.78%	16.29%	4.61%
7. Unknown, alive	0.01%	0%	0%	0%	0%
Risk factors and comorbidities					
Alcohol abuse	0.15%	0.14%	0%	0%	0.48%
Arrhythmia	0.71%	5.97%	6.28%	5.65%	6.10%
Coagulopathy	3.05%	18.89%	17.10%	25.24%	13.27%
Congenital heart disease	0.16%	2.38%	2.36%	1.17%	3.90%
Depression	2.77%	4.31%	2.81%	4.53%	5.98%
Diabetes	3.90%	4.46%	4.78%	2.87%	6.04%
Drug abuse	1.71%	5.09%	5.10%	4.77%	5.48%
Dyslipidaemia	0.34%	3.02%	4.85%	1.23%	2.89%
Fluid and electrolyte disorders	1.72%	19.52%	21.88%	24.48%	10.33%
Gestational diabetes	10.53%	5.68%	5.94%	4.42%	6.92%
Heart failure	0.29%	2.70%	4.02%	0.77%	3.41%
Ischaemic heart disease	0.09%	1.60%	2.40%	0.80%	1.57%
Neurological disorders	0.81%	21.52%	20.73%	23.26%	20.38%
Obesity	11.07%	10.09%	12.41%	8.27%	9.36%
Peripartum cardiomyopathy	0.26%	2.43%	3.58%	0.79%	2.98%
Peripheral vascular disease	0.04%	1.60%	3.22%	0.83%	0.46%
Previous stroke	0.00086%	1.59%	1.61%	0%	3.54%
Renal Failure	0.32%	1.92%	1.63%	1.27%	3.09%
Rheumatoid arthritis / collagen vascular diseases	0.49%	1.60%	0.39%	1.22%	3.65%
Sickle cell disease	0.10%	0.69%	1.90%	0%	0%
Smoking	6.77%	7.65%	9.03%	6.36%	7.49%

Valvular disease	0.62%	2.02%	1.18%	2.16%	2.92%
Cost outcomes					
Length of stay, median (IQR)	3 (2-4)	6 (3-10)	6 (4-11)	7 (3-12)	5 (3-7)
Total charge, $, median (IQR)	4,762 (3,278-7,036)	14,655 (8,494-27,895)	15,738 (9,613-27,007)	20,532 (10,256-41,042)	$10,651 ($5,358-$17,193)

Table S5. Patient characteristics, risk factors, comorbidities, treatments, and delivery complications from 2004 to 2014.

	No stroke			All stroke			Stroke								
							Ischaemic			Haemorrhagic			Unspecified		
	2004-2007	2008-2011	2012-2014	2004-2007	2008-2011	2012-2014	2004-2007	2008-2011	2012-2014	2004-2007	2008-2011	2012-2014	2004-2007	2008-2011	2012-2014
Demographics															
Age, median (IQR)	28 (22-33)	28 (23-33)	29 (24-33)	30 (24-35)	31 (25-36)	30 (25-35)	28 (22-33)	30 (25-36)	31 (24-36)	31 (23-36)	31 (24-35)	31 (26-35)	31 (25-35)	33 (27-37)	28 (24-33)
Race and ethnicity:															
1. White	37.77%	45.14%	50.17%	27.86%	38.02%	29.28%	19.59%	40.34%	34.29%	24.22%	33.28%	26.32%	39.01%	40.55%	25.71%
2. Black	13.90%	18.16%	20.40%	21.32%	23.20%	29.83%	24.05%	28.84%	28.57%	23.08%	17.73%	31.58%	17.12%	21.91%	28.57%
3. Hispanic	14.93%	15.88%	16.12%	19.78%	18.74%	23.76%	22.56%	10.91%	17.14%	24.39%	28.86%	22.37%	12.92%	17.43%	40.00%
4. Asian / Pacific Islander	2.14%	2.71%	3.09%	3.89%	3.53%	4.42%	4.14%	1.20%	7.14%	4.02%	4.97%	2.63%	3.54%	5.06%	2.86%
5. Native American	0.64%	0.82%	0.82%	1.02%	0.79%	0.55%	0%	1.06%	0%	2.08%	0%	1.32%	1.03%	1.38%	0%
6. Other	2.94%	3.36%	3.76%	3.18%	3.19%	6.08%	3.93%	3.57%	4.29%	3.12%	5.35%	9.21%	2.53%	0%	2.86%
7. Missing	27.66%	13.93%	5.63%	22.94%	12.53%	6.08%	25.73%	14.07%	8.57%	19.10%	9.81%	6.58%	23.85%	13.67%	0%
Median ZIP code income:															
1. 1st quartile	15.37%	29.55%	30.96%	18.91%	25.69%	33.15%	22.01%	25.27%	34.29%	18.01%	20.87%	31.58%	16.83%	32.17%	34.29%
2. 2nd quartile	12.68%	25.10%	25.39%	12.93%	26.53%	25.41%	11.43%	26.79%	21.43%	14.87%	28.93%	27.63%	12.56%	23.22%	28.57%
3. 3rd quartile	11.99%	24.01%	23.49%	12.31%	23.53%	23.20%	12.45%	19.44%	24.29%	9.79%	29.16%	21.05%	14.49%	22.41%	25.71%
4. 4th quartile	10.37%	19.25%	18.41%	5.55%	21.59%	14.92%	5.64%	23.94%	17.14%	7.32%	18.37%	14.47%	3.84%	22.20%	11.43%
5. Missing income	49.58%	2.08%	1.76%	50.30%	2.67%	3.31%	48.46%	4.56%	2.86%	50.01%	2.66%	5.26%	52.28%	0%	0%
Weekday admission	86.3%	86.0%	85.2%	78.03%	83.30%	78.45%	75.7%	81.5%	75.7%	77.7%	81.6%	77.6%	80.6%	88.0%	85.7%

Length of stay, median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	6 (3-10)	5 (3-11)	6 (3-10)	6 (4-10)	6 (3-11)	5 (4-10)	7 (2-12)	6 (3-11)	7 (3-16)	4 (3-7)	5 (3-9)	5 (3-7)
Total charge, $, median (IQR)	4,368 (3,007-6,479)	4,976 (3,419-7,395)	4.962 (3,469 - 7,228)	12,822 (6,860 - 24165)	16,531 (9,092 - 35771)	14,455 (9,338-31,745)	14,593 (9,613-26,213)	16,384 (9,764-32,042)	15,166 (9,464 - 26,879)	19,769 (9,986 - 32,085)	21,179 (9,856 - 41,042)	20,051 (10,925-58,351)	8,658 (4,839 - 15,327)	14,526 (5,942 - 31,703)	11,194 (7,460 - 14,306)
Hospital region:															
1. Northeast	15.2%	14.3%	14.7%	16.8%	11.9%	17.7%	13.3%	10.0%	10.0%	21.3%	13.8%	18.4%	16.0%	12.0%	31.4%
2. Midwest	20.7%	20.9%	20.8%	16.5%	15.4%	18.8%	15.6%	14.6%	21.4%	12.2%	20.1%	19.7%	21.4%	10.9%	11.4%
3. South	43.5%	43.9%	44.3%	43.9%	43.9%	41.4%	45.7%	52.9%	44.3%	40.8%	33.7%	40.8%	39.3%	43.5%	37.2%
4. West	20.6%	20.9%	20.2%	24.8%	28.9%	22.1%	25.4%	22.5%	24.3%	25.7%	32.4%	21.1%	23.3%	33.6%	20.0%
Discharge location:															
1. Routine	96.27%	96.44%	96.73 %	63.91 %	61.38 %	61.33%	68.86%	63.29%	70.00 %	41.12 %	45.75 %	42.11 %	80.18 %	77.80 %	85.71 %
2. Short term hospital	0.47%	0.50%	0.47 %	10.88 %	9.77%	9.94%	10.52%	8.93%	7.14%	19.80 %	15.94 %	15.79 %	3.02%	3.41%	2.86%
3.Other facilities	0.10%	0.08%	0.10%	10.14 %	9.54%	14.36%	7.36%	6.60%	12.86 %	14.43 %	20.73 %	19.74 %	8.83%	0%	5.71%
4. Home health care	2.85%	2.63%	2.35%	7.63%	6.30%	5.52%	10.19%	10.97%	4.29%	6.84%	1.22%	7.89%	5.95%	5.91%	2.86%
5. Against medical advice	0.29%	0.32%	0.34%	1.35%	0.45%	0.55%	3.07%	1.15%	0%	0%	0%	0%	0.96%	0%	2.86%
6. Died	0.02%	0.02%	0.01%	6.09%	12.57 %	8.29%	0%	9.06%	5.71%	17.82 %	16.35 %	14.47 %	1.06%	12.88 %	0%
7. Unknown, alive	0.005%	0.002%	0.001 %	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Risk factors and comorbidities															
Alcohol abuse	0.13%	0.15%	0.20%	0%	0.42%	0%	0%	0%	0%	0%	0%	0%	0%	1.51%	0%
Arrhythmia	0.53%	0.72%	0.91%	2.40%	10.39 %	6.08%	2.10%	11.14%	5.71%	1.08%	7.41%	9.21%	3.97%	13.01 %	0%
Coagulopathy	2.11%	3.22%	3.96%	11.49 %	25.88 %	21.55%	10.14%	19.73%	22.86 %	19.88 %	33.19 %	23.68 %	5.08%	25.62 %	14.29 %

Congenital heart disease	0.11%	0.16%	0.21%	1.98%	2.55%	2.76%	3.11%	1.17%	2.86%	0%	2.40%	1.32%	2.74 %	4.67 %	5.71 %
Depression	2.01%	2.88%	3.54%	2.04%	7.05%	4.42%	0%	4.55%	4.29%	2.06%	9.42%	2.63%	3.96%	7.67%	8.57%
Diabetes	3.44%	3.97%	4.38%	3.45%	4.85%	5.52%	3.15%	5.72%	5.71%	2.22%	3.90%	2.63%	4.85 %	4.81 %	11.43 %
Drug abuse	1.38%	1.58%	2.25%	4.42%	4.66%	6.63%	7.28%	2.28%	5.71%	4.06%	3.74%	6.58%	2.04%	9.13%	8.57%
Dyslipidaemia	1.57 %	3.59 %	5.36 %	0.99 %	2.56 %	6.63 %	0 %	4.56 %	11.43 %	1.06 %	0 %	2.63 %	1.87 %	2.87 %	5.71 %
Fluid and electrolyte disorders	1.48%	1.77%	1.94%	12.23 %	24.19 %	24.86%	14.42%	25.41%	27.14 %	15.70 %	28.95 %	30.26 %	0.70%	16.63 %	8.57%
Gestational diabetes	9.36%	10.57%	11.87 %	5.09%	4.73%	7.73%	4.28%	7.89%	5.71%	4.14%	2.53%	6.58%	6.73 %	2.96 %	14.29 %
Heart failure	0.31%	0.30%	0.27%	2.03%	3.93%	2.21%	3.23%	3.46%	5.71%	0%	2.47%	0%	2.77%	6.39%	0%
Ischaemic heart disease	0.07%	0.10%	0.11%	1.40%	2.26%	1.10%	2.04%	3.59%	1.43%	0%	1.21%	1.32%	2.07%	1.69%	0%
Neurological disorders	0.69%	0.80%	0.94%	22.09 %	17.15 %	25.97%	22.01%	16.45%	24.29 %	20.26 %	20.97 %	28.95 %	23.85 %	13.47 %	22.86 %
Obesity	5.82%	11.50%	16.79 %	4.64%	15.15 %	12.15%	6.07%	21.08%	10.00 %	2.10%	11.90 %	11.84 %	5.61 %	10.76 %	17.14 %
Peripartum cardiomyopathy	0.24%	0.28%	0.27%	1.40%	3.42%	2.76%	1.00%	4.53%	5.71%	0%	1.19%	1.32%	3.07%	4.58%	0%
Peripheral vascular disease	0.026%	0.037%	0.049 %	0.36%	1.27%	3.87%	0%	2.23%	8.57%	1.11%	0%	1.32%	0%	1.46%	0%
Previous stroke	0.004%	0.104%	0.161 %	0.34%	1.25%	3.87%	1.040%	0%	4.286 %	0%	0%	0%	0%	4.559 %	11.429 %
Renal failure	0.25%	0.34%	0.40%	1.82%	2.25%	1.66%	1.13%	2.33%	1.43%	2.31%	0%	1.32%	2.03%	4.90%	2.86%
Rheumatoid arthritis / collagen vascular diseases	1.02%	1.21%	1.29%	1.41%	2.25%	1.10%	0.22%	0.27%	0.33%	0.60%	0.83%	0.85%	0.16%	0.21%	0.26%
Sickle cell	0.10%	0.10%	0.10%	0.35%	1.24%	0.55%	1.05%	3.19%	1.43%	0%	0%	0%	0%	0%	0%
Smoking	4.65%	6.94%	9.10%	3.93%	9.47%	11.05%	4.18%	9.82%	14.29 %	2.25%	8.29%	9.21%	5.24%	10.41 %	8.57%
Valvular disease	0.87%	0.55%	0.41%	2.03%	2.75%	1.10%	2.15%	1.14%	0%	0.96%	3.09%	2.63%	2.92%	4.62%	0%
Treatments (per 10,000 hospitalizations)															
Angiography	1.89	1.10	0.65	706	692	1326	9.44	651	1142	794	924	1974	401	464	286

Thrombectomy	0	0	0	0	45	110	0	0	143	NA	NA	NA	0	0	0
Thrombolysis	0.262	0.598	1184	35	0	221	1.07	0	4.29	NA	NA	NA	0	0	0
Delivery complications (per 10,000 hospitalizations)															
Caesarean section	4565	4698	4619	6374	5775	6243	6768	5984	5714	6173	5352	6316	6187	5998	7143
Maternal mortality	22	24	14	609	1257	828	0	9057	5714	178158	163542	144737	1063	12881	0
Preterm birth	1690	1591	1173	2569	2322	2044	3146	2238	1857	2331	2587	2237	2244	2116	2000
Postpartum haemorrhage	474	477	512	1486	2101	1050	1660	1736	1286	1635	2880	1184	1184	167	286
Stillbirth	89	87	89	256	300	301	0	252	303	135	312	462	594	358	0

Table S6. Treatments and delivery complications (per 10,000 hospitalisations) stratified by subgroups of stroke.

	No stroke	All stroke	Stroke		
			Ischaemic	Haemorrhagic	Unspecified
Treatments					
Angiography	1.2	868	899	1212	4
Thrombectomy	0	45	41	NA	0
Thrombolysis	0.39	74	162	NA	0
Delivery complications					
Caesarean section	4629	6144	6195	5963	6303
Maternal mortality	2	879	478	1629	461
Postpartum haemorrhage	486	1569	1580	1878	1172
Preterm birth	1504	2347	2462	2381	2159
Stillbirth	88	282	169	297	411

Table S7. Sensitivity analysis of association between subgroups of stroke and delivery complications and cost outcomes, comparing the fully adjusted model with complete case analysis which excluded hospitalisation episodes with missing information on race and ethnicity and median ZIP code income variables.

	All stroke	Stroke		
		Ischaemic	Haemorrhagic	Unspecified
Caesarean section				
Fully adjusted model	1.58 (1.33, 1.86)	1.62 (1.22, 2.16)	1.44 (1.08, 1.91)	1.71 (1.26, 2.30)
Excluded missing records on race and ethnicity and median ZIP code income variables	1.64 (1.32, 2.03)	1.68 (1.18, 2.39)	1.43 (1.02, 2.01)	1.91 (1.26, 2.91)
Maternal Mortality				
Fully adjusted model	99.78 (59.15, 168.31)	30.34 (12.32, 74.73)	260.80 (138.10, 492.51)	40.34 (14.16, 114.87)
Excluded missing records on race and ethnicity and median ZIP code income variables	109.37 (60.48, 197.80)	30.82 (10.01, 94.91)	271.34 (132.25, 556.71)	42.96 (14.07, 131.17)
Postpartum haemorrhage				
Fully adjusted model	1.91 (1.54, 2.37)	1.98 (1.38, 2.83)	2.03 (1.46, 2.82)	1.98 (1.50, 2.61)
Excluded missing records on race and ethnicity and median ZIP code income variables	1.62 (1.23, 2.13)	1.70 (1.07, 2.70)	1.93 (1.30, 2.84)	1.04 (0.52, 2.09)
Preterm birth				
Fully adjusted model	1.22 (0.99, 1.49)	1.34 (0.98, 1.82)	1.25 (0.91, 1.73)	1.02 (0.68, 1.54)
Excluded missing records on race and ethnicity and	1.29 (1.00, 1.65)	1.45 (0.99, 2.12)	1.45 (1.00, 2.11)	0.90 (0.54, 1.49)

median ZIP code income variables				
		Stillbirth		
Fully adjusted model	1.68 (1.00, 2.82)	0.93 (0.34, 2.69)	1.67 (0.70, 4.00)	2.84 (1.33, 6.07)
Excluded missing records on race and ethnicity and median ZIP code income variables	1.56 (0.84, 2.89)	0.98 (0.30, 3.18)	1.81 (0.69, 4.70)	2.08 (0.74, 5.91)
		Length of stay		
Fully adjusted model	3.99 (3.06, 4.92)	3.72 (2.41, 5.02)	5.74 (3.67, 7.81)	2.18 (1.05, 3.31)
Excluded missing records on race and ethnicity and median ZIP code income variables	3.74 (2.59, 4.89)	3.50 (2.11, 4.90)	5.08 (2.54, 7.62)	2.28 (0.73, 3.83)
		Total charge		
Fully adjusted model	19806.53 (16048.09, 23564.97)	20479.98 (13422.27, 27537.70)	28272.45 (20881.17, 35663.74)	8722.65 (5013.95, 12431)
Excluded missing records on race and ethnicity and median ZIP code income variables	19056.83 (14721.76, 23391.91)	20972.16 (12140.99, 29803.32)	25025.00 (17521.54, 32528.47)	8308.50 (4293.06, 12323.95)

Data expressed as odds ratios and 95% confidence intervals for categorical variables or beta coefficients and 95% confidence intervals for continuous variables.

Table S8. Study population stratified by hypertensive disorders of pregnancy subgroups.

	Superimposed pre-eclampsia		Preeclampsia		Gestational hypertension		Chronic hypertension	
HDP delivery hospitalisation	6.1%		38.1%		34.0%		21.8%	
Number of deliveries, weighted	257,385		1,615,972		1,443,817		923,110	
	No stroke	**All stroke**	**No stroke**	**All stroke**	**No stroke**	**All stroke**	**No stroke**	**All stroke**
HDP delivery hospitalisation with stroke	---	18.8%	---	52.5%	---	8.7%	---	20.0%
Number of deliveries, weighted	256,749	636	1,614,191	1,781	1,443,521	296	922,432	678

Table S9. Association of stroke with risk factors, comorbidities and delivery complications, stratified by hypertensive disorders of pregnancy subgroups.

	Superimposed preeclampsia	Preeclampsia	Gestational hypertension	Chronic hypertension
Risk factors and comorbidities				
Alcohol abuse	1.17 (0.17, 7.92)	*	*	*
Arrhythmia	5.80 (3.13, 10.76)	2.03 (0.98, 4.18)	5.59 (1.64, 19.07)	1.80 (0.79, 4.13)
Coagulopathy	3.57 (2.07, 6.18)	*	3.57 (1.50, 8.49)	1.74 (0.76, 3.99)
Congenital heart disease	2.31 (0.39, 13.55)	6.23 (2.33, 16.66)	12.52 (1.94, 80.83)	14.42 (4.99, 41.69)
Depression	0.87 (0.38, 2.01)	0.95 (0.49, 1.84)	0.45 (0.06, 3.58)	1.27 (0.62, 2.58)
Diabetes	0.56 (0.29, 1.09)	0.35 (0.14, 0.90)	*	0.67 (0.35, 1.27)
Drug abuse	2.16 (1.08, 4.34)	1.96 (1.10, 3.51)	1.46 (0.22, 9.67)	1.50 (0.66, 3.40)
Dyslipidaemia	1.40 (0.26, 7.70)	4.43 (1.67, 11.76)	32.83 (8.64, 124.75)	4.22 (1.98, 9.02)
Fluid and electrolyte disorders	5.32 (3.27, 8.65)	4.73 (3.42, 6.55)	11.91 (4.72, 30.03)	4.87 (2.66, 8.94)
Gestational diabetes	0.53 (0.27, 1.03)	0.43 (0.26, 0.73)	0.38 (0.12, 1.22)	0.58 (0.32, 1.06)
Heart failure	0.34 (0.06, 1.83)	2.87 (0.93, 8.91)	*	3.69 (1.32, 10.33)
Ischaemic heart disease	2.69 (0.59, 12.20)	2.08 (0.40, 10.77)	*	3.73 (1.07, 12.98)
Neurological disorders	11.81 (6.07, 22.99)	22.64 (16.76, 30.59)	20.66 (8.58, 49.76)	8.82 (4.77, 16.32)
Obesity	0.94 (0.58, 1.51)	0.83 (0.53, 1.30)	1.24 (0.53, 2.90)	0.68 (0.40, 1.16)
Peripartum cardiomyopathy	4.58	0.76	6.25	0.73

	(1.11, 18.83)	(0.13, 4.51)	(1.96, 19.91)	(0.13, 4.21)
Peripheral vascular disease	7.81 (1.86, 32.76)	9.59 (0.99, 93.19)	16.31 (2.11, 126.02)	10.58 (2.67, 41.85)
Previous stroke	3.62 (0.61, 21.55)	6.92 (1.84, 25.94)	30.00 (3.40, 264.62)	3.12 (0.57, 17.06)
Renal failure	0.38 (0.11, 1.32)	4.45 (0.96, 20.63)	*	1.92 (0.69, 5.33)
Rheumatoid arthritis / Collagen vascular diseases	1.31 (0.46, 3.76)	0.47 (0.11, 2.02)	*	2.31 (0.77, 6.87)
Sickle cell disease	*	2.89 (0.88, 9.44)	*	2.63 (0.34, 20.45)
Smoking	0.76 (0.38, 1.52)	0.67 (0.39, 1.16)	1.43 (0.52, 3.97)	1.26 (0.71, 2.24)
Valvular disease	2.34 (0.89, 6.16)	1.41 (0.45, 4.38)	*	0.25 (0.02, 3.02)
Delivery complications				
Caesarean section	1.20 (0.81, 1.79)	1.68 (1.32, 2.13)	1.58 (0.88, 2.81)	0.92 (0.65, 1.32)
Maternal mortality	87.92 (31.38, 246.30)	91.96 (47.75, 177.08)	340.94 (25.94, 4480.86)	54.54 (7.67, 387.92)
Postpartum haemorrhage	1.32 (0.74, 2.35)	2.08 (1.61, 2.70)	0.84 (0.29, 2.47)	2.06 (1.06, 4.00)
Preterm birth	0.58 (0.37, 0.91)	1.16 (0.92, 1.47)	2.50 (1.22, 5.14)	0.70 (0.39, 1.24)
Stillbirth	2.32 (0.89, 6.02)	1.35 (0.65, 2.82)	*	1.17 (0.35, 3.91)

Figure S1. Comparison of median income quartile (Qrtl) between (A) hypertensive disorders of pregnancy (HDP) population in the delivery hospitalizations and (B) the stroke subpopulation in the HDP delivery hospitalizations over one decade.

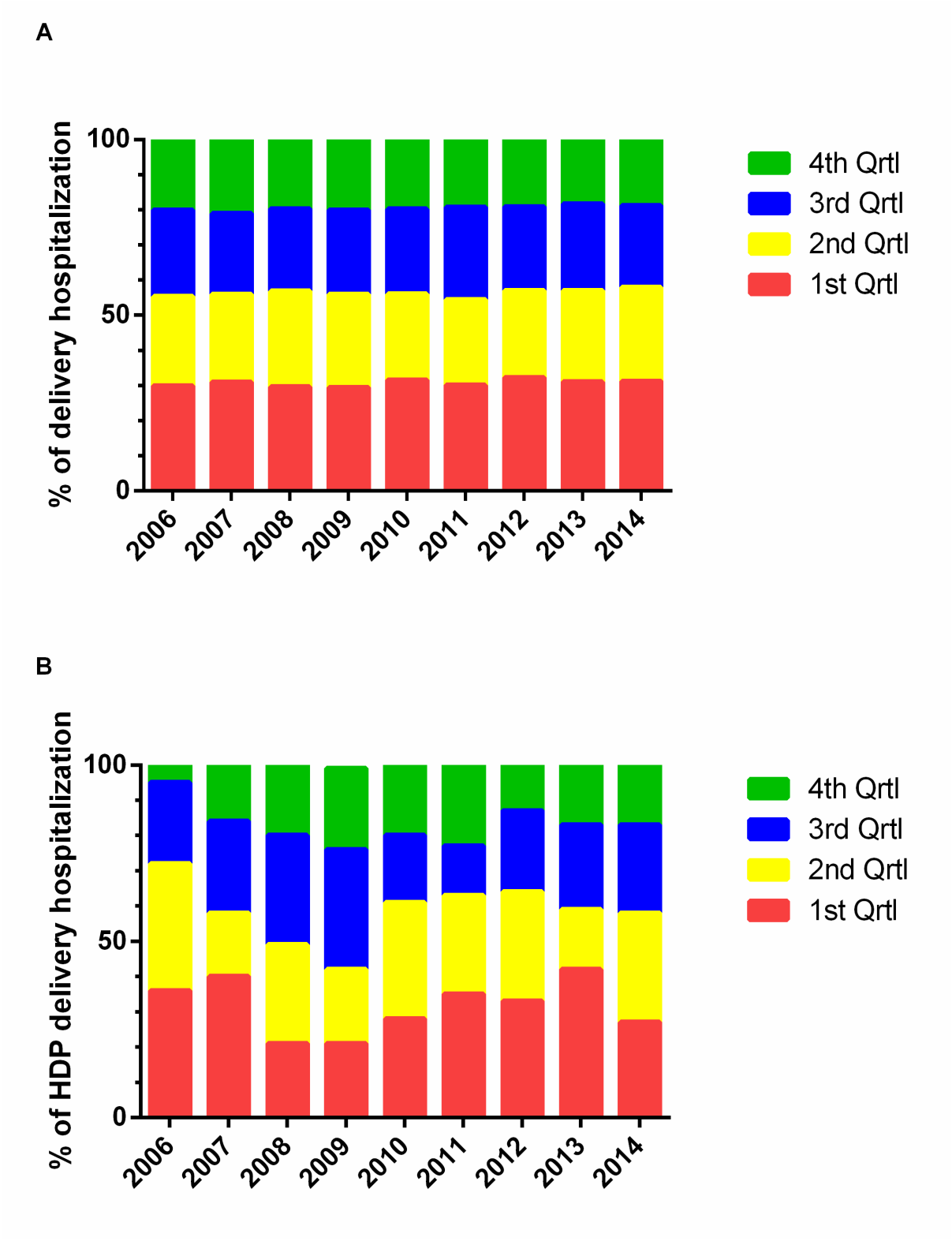

Figure S2. Risk of delivery complications in women with hypertensive disorders of pregnancy and stroke between 2004 and 2014. (A) Mortality (B) Preterm birth (C) Stillbirth (D) Postpartum haemorrhage and (E) Caesarean section.