The incidence of first stroke in pregnant and non-pregnant women of childbearing age: A population-based cohort study from England

Ban, Stroke incidence in childbearing-age women

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Abstract

Background: Pregnant women may have an increased risk of stroke compared to non-pregnant women of similar age, but the magnitude and the timing of such risk are unclear. We examined the risk of first stroke event in women of childbearing age and compared the risk during pregnancy and in the early postpartum period to background risk outside these periods.

Methods and Results: We conducted an open cohort study of 2,046,048 women aged 15-49 years between 1st April 1997 and 31th March 2014 using linked primary (Clinical Practice Research Datalink) and secondary (Hospital Episode Statistics) care records in England. Risk of first stroke was assessed by calculating the incidence rate of stroke in antepartum, peripartum (2 days before until 1 day after delivery), early (first six weeks) and late (second six weeks) postpartum periods, compared with non-pregnant time using a Poisson regression model with adjustment for maternal age, socioeconomic group and calendar time. A total of 2,511 women had a first stroke. The incidence rate of stroke was 25.0 per 100,000 person-years (95% confidence interval 24.0-26.0) in non-pregnant time. The rate was lower antepartum (10.7/100,000 person-years, 7.6-15.1), but 9-fold higher peripartum (161.1/100,000 person-years, 80.6-322.1) and 3-fold higher early postpartum (47.1/100,000 person-years, 31.3-70.9). Rates of ischaemic and haemorrhagic stroke both increased peripartum and early postpartum.

Conclusions: Although the absolute risk of first stroke is low in women of childbearing age, health care professionals should be aware of a considerable increase in relative risk during the peripartum and early postpartum periods.

Key words: epidemiology, women, pregnancy and postpartum, and stroke

Introduction

Stroke is one of the leading causes of death in high-income countries including the United Kingdom (UK).[1] Although the risk of stroke among women under 40 years of age is relatively low compared to older women, pregnancy can substantially increase this risk.[1] Estimates of the absolute risk of stroke in and around pregnancy are therefore crucial for planning health care resource and decision-making. There is, however, large variation in the reported incidence of stroke in pregnant women;[2] reports vary between 1.5 per 100,000 deliveries in the UK[3], 21.5 per 100,000 deliveries in Taiwan[4] and 34.2 per 100,000 deliveries in the United States of America (USA).[5] However, previous large population-based studies did not provide a complete picture of stroke incidence by either missing women in the early antepartum[6–8] or postpartum periods[3], or by not distinguishing between risks in antepartum and postpartum periods.[9,10]

The recent World Stroke Day campaigns in 2014-2016 highlighted the impact of stroke on women and emphasised the importance of preventing stroke in women of all ages in the UK.[11] However, to our knowledge there has been no population-based study in the UK to examine the risk of stroke in pregnancy and postpartum compared to non-pregnant periods in women of childbearing age, which is important for planning preventative strategies. The primary care Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) linked data have given us a unique opportunity to quantify the population level absolute risk of stroke in specific antepartum and postpartum periods by utilising data on more than 2 million women. The aim of this study was to quantify the incidence rates of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage in women of childbearing age and compare the rates in antepartum and in the early postpartum period to background rates outside these periods.

Methods

Database and study population

The Clinical Practice Research Datalink (CPRD) is a routinely collected electronic primary care database of anonymised medical records from over 650 general practitioners (GP) across the UK. Approximately 7% of the UK population are included which are broadly representative of the UK general population in terms of age and sex.[12] GPs are gatekeepers of the National Health Service (NHS) in the UK and are the primary point of contact for non-emergency health care. Around 98% of the UK population is registered with a GP. CPRD contains demographic, medical, prescription and lifestyle related information recorded using Read code system[13] and has been extensively validated for a wide range of diagnoses for epidemiological research.[14] For this study we used a subset of English practices within CPRD that have been linked to the Hospital Episode Statistics (HES), containing details of all hospital admissions to NHS hospitals in England. About 58% of CPRD practices are linked to HES; the linkage is done by a trusted third party using NHS number, date of birth and sex. As HES only covers English hospitals, practices from Northern Island, Wales and Scotland are excluded for the linkage. The CPRD-HES linked data have been compared to Office for National Statistics (ONS) data, showing similar age and sex distribution.[15] Along with basic demographic information, HES contains information on discharge diagnoses (including one primary diagnosis and up to 19 secondary/subsidiary diagnoses) and procedures that are coded using International Classification of Disease (ICD) version 10 and Operation and Procedure Coding Supplement (OPCS) version 4 respectively. Particularly, Maternity HES contains information on all births across England and has been validated against birth registration data and NHS Numbers for Babies data.[16]

We used an open cohort study design including all women aged 15-49 years from the CPRD-HES between 1st April 1997 and 31st March 2014. The follow-up start date for each woman was defined as the start of the CPRD-HES link (1st April 1997), the date of a woman becoming 15 years old, the date of a woman's registration with a general practice or the up-to-standard date of that practice, whichever came latest; whereas the follow-up end date was defined as the last date for CPRD-HES link (31st March 2014), the date before a woman became 50 years old, the date of a woman transferring out from the practice, the date of a woman's death or the last date of data collection, whichever came earliest. Women with a prior history of stroke before the study start date were excluded from this cohort study.

Defining exposure time

For each woman we extracted information on their pregnancy outcome (live birth or stillbirth, date of delivery, and gestation) from Maternity HES. In the UK, stillbirth is defined as a baby dead after 24 completed weeks of pregnancy. Women's follow-up time between age 15 and 49 years was divided into time associated with pregnancy (defined from the date of conception until 12 weeks postpartum) and "non-pregnant time" (all other available follow-up time, which included all time for women who were never pregnant during the study period as previously defined[17]).

The time associated with pregnancy was divided into antepartum (from the date of conception until 3 days before the date of delivery), peripartum (2 days before until 1 day after delivery), and postpartum (from 2 days after delivery until the end of the 12th week postpartum). The period of 2 days before until 1 day after delivery was defined as peripartum based on a previous Swedish study which found that the risk of stroke was high during this period.[6] The antepartum period was further subdivided into trimesters and the postpartum

period was further subdivided into individual weeks and also into early (first six weeks) and late (second six weeks) postpartum.

Outcome

The outcome of this study was first incident stroke during the study period. Stroke diagnosis was identified using ICD-10 codes (I60-I64, O22.5 and O87.3) from hospital records or Read codes from primary care records. We also used Office of National Statistics (ONS) death records linked to CPRD-HES to identify stroke that had resulted in death and may have only been diagnosed post-mortem. Cause of death for stroke was recorded in the ONS data using firstly ICD9 (430-434, 436, and 437) and then ICD10 (I60-I64, O22.5 and O87.3) codes during the study period. We only included deaths that had stroke as the primary cause of death. Since women with a prior history of stroke may have a risk of recurrent stroke and they may have been on secondary prevention to reduce this risk, we excluded women if they had a history of stroke before the start of the study period. For women with an incident stroke during the study period, they were followed until time of the first event for similar reason, i.e. women's clinical follow-up and personal health could be subsequently modified by this event, which could in turn modify the occurrence of a subsequent stroke event. We also excluded women if the first stroke event was recorded in CPRD primary care data within the first month of women's registration with their current general practice but without proximal hospital admission within 30 days, or if the first stroke event recorded in HES was not the primary or the first two secondary diagnoses, as these might be a recording of medical history.

Stroke events were classified as ischaemic stroke (IS), intracerebral haemorrhage (ICH), and subarachnoid haemorrhage (SAH). The type of stroke was identified from the ICD codes in the HES record if a woman's first stroke diagnosis was in HES or if she was hospitalised for stroke within 30 days after a first stroke diagnosis in primary care data. Read codes in the

CPRD record were used to identify stroke type if the woman's first stroke diagnosis was in CPRD and she had no hospitalisation within 30 days. Although it is possible to have more than one type of stroke in close succession (e.g. ICH after acute IS or infarction after SAH),[18] our aim was to identify first incident stroke. Therefore, for women with different types of stroke within the same hospitalisation, only the earliest diagnosis was used to identify the stroke type. In addition, for some women whose stroke type was unspecified, they were classified as having IS if they had a prescription for an antiplatelet or an anticoagulant drug from primary care within two months after the diagnosis. Finally, women with multiple types of stroke but no clear indication of the diagnosis order were classified as having stroke type unspecified.

Statistical analysis

We calculated the absolute rates of stroke per 100,000 person-years with 95% confidence intervals (95% CI) for all time periods and also for different types of stroke. Poisson regression was used to estimate incidence rate ratios (IRR) of stroke in antepartum and postpartum periods compared with the non-pregnant time period with adjustment for maternal age (15-24, 25-34 and 35-49 years), socioeconomic deprivation (defined as quintiles of 2010 English Index of Multiple Deprivation) and calendar time (1997-2002, 2003-2008, 2009-2014). Age and calendar time were treated as time-varying covariates created using Lexis expansion.[19] We also presented stratified analysis by each of these covariates with mutual adjustment for the rest of the covariates. The English Index of Multiple Deprivation measures relative levels of socioeconomic deprivation in small areas of England called lower super output areas[20] which was linked via patient postcode by a trusted third party in CPRD.

We also conducted two sensitivity analyses. Firstly, since stroke events identified only from CPRD and without proximal hospital admission within 30 days afterwards may be existing

diagnoses and not be incident cases, we conducted a sensitivity analysis excluding women with such events. Secondly, since patients with ICH or SAH may start their antithrombotic treatment within 60 days of diagnosis, we used a more strict definition for IS and conducted a second sensitivity analysis excluding women with unspecified stroke and prescribed an antiplatelet or anticoagulant after seven days of diagnosis as having IS.

In addition, for women with first stroke diagnosed in time associated with pregnancy, we also examined their medical records for diagnoses of any hypertensive disorders in pregnancy (HDP), including pre-existing hypertension before pregnancy, gestational hypertension, pre-eclampsia and eclampsia. In addition, for women with first stroke diagnosed around the time of delivery, we examined whether or not they had preterm birth (before 37 completed weeks of gestation) since this could give us some indication about the timing of stroke related to delivery. According to the CPRD license agreement, we have not reported data for cells with fewer than five patients. Missing data for socioeconomic deprivation were included in separate categories. Data analysis was performed using Stata/MP 11.2. The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for database research (ISAC Protocol No: 15_083R). No other ethical approval was needed for this study.

Results

Participant characteristics

We identified 2,046,048 women of childbearing age with no evidence of stroke prior to our study period (Figure 1). Table 1 shows the basic characteristics of the study population. The median length of follow-up was 3.4 years (interquartile range [IQR] 1.4-7.5). Among these women, 337,297 had at least one live birth or stillbirth during the study period. The median age at delivery was 30.1 years (IQR 25.5-34.1). A total of 2,511 women had a first incidence of stroke during the study period with 1,625 (64.7%) first recorded in HES. Of the 886 first identified from CPRD, 133 (15.0%) had hospital admission records from HES within 30 days (the median time difference was 3 days, IQR 1-12). Of the total women with stroke, 1,109 (44.2%) had IS, 705 (28.1%) had SAH and 368 (14.7%) had ICH. There were 329 (13.1%) women with unspecified type of stroke, including 13 (0.5%) with multiple types where the primary diagnosis was not possible to identify.

Absolute and relative risk of stroke

The rate of first stroke in women of childbearing age was 24.7 per 100,000 person-years (95% CI 23.7-25.7). Table 2 shows the absolute rates of stroke per 100,000 person-years in antepartum, peripartum, postpartum and non-pregnant time. The incidence rate was 10.7 (95% CI 7.6-15.1) per 100,000 person-years in antepartum, similar across trimesters, and 14.2 (95% CI 6.8-29.7) in late postpartum, but was higher around the time of delivery (161.1, 95% CI 80.6-322.1) and in early postpartum (47.1, 95% CI 31.3-70.9). Compared to non-pregnant time (25.0, 95% CI 24.0-26.0), women were nine times more likely to develop first stroke in peripartum (IRR=9.4, 95% CI 4.7-18.8) and three times more likely in early postpartum (IRR=2.7, 95% CI 1.8-4.1) after adjustment for maternal age, socioeconomic

deprivation and calendar time (Table 2). We also found a slightly lower incidence rate of stroke in antepartum compared to non-pregnant time (IRR=0.6, 95% CI 0.5-0.9).

Risk of stroke in pregnancy and by stroke type

There were 71 women with first stroke in the time associated with pregnancy, 17 of whom had diagnoses of HDP including seven with diagnoses of pre-eclampsia/pre-eclampsia. Eight women had stroke around the time of delivery of which half had diagnoses of HDP (37.5% with pre-eclampsia/eclampsia) and 12.5% had preterm delivery. In time associated with pregnancy, the most common type of stroke was IS (50.7%) followed by SAH (19.7%) and ICH (15.5%) and a similar pattern was also observed in non-pregnant time. Table 3 shows the incidence rates of different types of stroke. Compared with non-pregnant time, the incidence of IS was higher in peripartum (IRR=8.0, 95% CI 2.6-25.0) and in early postpartum (IRR=4.1, 95% CI 2.4-6.8) but not in antepartum (IRR=0.6, 95% CI 0.3-1.0) or late postpartum (IRR=1.3, 95% CI 0.5-3.2) periods. In terms of haemorrhagic stroke, SAH had increased incidence in peripartum (IRR=12.9, 95% CI 4.1-40.1) but not in other time periods; whereas ICH showed increased incidence only in the early postpartum (IRR=3.6, 95% CI 1.5-8.7).

Risk of stroke by different covariates

Table 4 shows the relative risk of stroke in peripartum and early postpartum compared to non-pregnant time by maternal age, socioeconomic deprivation and calendar time. The incidence rate of stroke increased with age and socioeconomic deprivation. The incidence rate (95% CI) was 4.8 per 100,000 person-years (4.0-5.8) at age 15-24 and 41.0 (39.2-42.8) at age 35-49 years in non-pregnant time and increased risks were also observed in peripartum and early postpartum (Table 4). The relative risk of stroke in peripartum and early postpartum compared to non-pregnant time however was much higher in women aged 15-24 years

(IRR=11.9, 95% CI 5.5-25.6) than in women aged 35-49 years (IRR=2.1, 95% CI 1.1-4.0) (Table 4). For socioeconomic deprivation and calendar time, the relative risk of stroke in peripartum and early postpartum compared to non-pregnant time was broadly similar across different groups (Table 4).

Sensitivity analyses

In the first sensitivity analysis, we excluded 753 women with stroke identified from CPRD without hospital admission information for stroke from HES within 30 days. Similar to results from the main analysis, we found increased incidence of stroke around the time of delivery (IRR=11.8, 95% CI 5.6-24.7) and early postpartum (IRR=3.4, 95% CI 2.2-5.3) but slightly lower incidence of stroke in the antepartum (IRR=0.6, 95% CI 0.4-0.9) compared to non-pregnant time periods (Table 5). In the second sensitivity analysis, we excluded 229 women from the ischaemic stroke group if they had unspecified stroke and were prescribed an antiplatelet or anticoagulant after 7 days of diagnosis. The increased relative risk of stroke around the time of delivery and early postpartum were broadly similar to the main analysis (Table 6).

Discussion

Principal findings

Using data from a large population based cohort, we found that compared to non-pregnant time, the risk of first stroke was slightly lower in antepartum but nine-fold higher in peripartum and three-fold higher in the first six weeks postpartum. The risks of ischaemic and haemorrhagic stroke were both increased during the high-risk period. In addition, the risk of first stroke was increased by age and socioeconomic deprivation. The relative increased risk of stroke in peripartum and early postpartum period was however much higher in women at younger age than at older age.

Strengths and weaknesses in relation to other studies

Our study used information on more than 2 million women age 15-49 years from England providing the most comprehensive and contemporary estimates for stroke risks in antepartum (by trimester), early and late postpartum and time outside these pregnancy-related periods in women of childbearing age. Most previous research estimating the risk of stroke in women of childbearing age has been focused on either pregnancy or periods of different lengths after delivery or has not explored the risk relative to non-pregnant women of similar age. The UK Obstetric Surveillance System (UKOSS) conducted a study between 2007 and 2010[3] and found that the risk of stroke was 1.5 per 100,000 deliveries (95% CI 1.0-2.1) and was higher for ischaemic stroke than haemorrhagic stroke.[3] This estimate was substantially lower than our study as well as studies published in other countries or areas.[4–6] The difference may be due to the fact that the UKOSS study only included women with stroke in antepartum and not the period soon after pregnancy. Our finding of increased risk of ischaemic and

haemorrhagic stroke in the early postpartum compared to non-pregnancy time is in line with previous studies from Japan,[21] Taiwan,[22] and the USA[9,23] utilising hospital discharge records.

In addition, very few studies have been able to examine the period around the time of delivery. For example, a recent study published by Kamel *et al* in 2014 contained over 1.6 million patients identified from US hospital discharge records and found that the risk of stroke was 119 per 100,000 deliveries in the first 6 weeks after delivery (approximately equivalent to 91.5 per 100,000 person-years).[8] However, this U.S. study did not separate the risk around the time of delivery from the rest of the early postpartum period. The only previous study that has specifically examined the stroke risk around the time of delivery was a Swedish study[6] published in 2001. This study used the Swedish Birth Register linked with the Inpatient Register between 1987 and 1995 and found that compared with the risk in the baseline period (which included the period before pregnancy and the first two trimesters), the risk of stroke was higher around delivery and in the first six weeks postpartum.[6] Importantly, this Swedish study included deliveries only between 1987 and 1995 and did not report the risk in the first or second trimester. Our study results are broadly in line with the Swedish study but provide more contemporary and comprehensive estimates for the stroke risk (including in first and second trimesters).

Regarding specific type of stroke, in line with our results, a much older study from USA published in 1996 using hospital discharge records found that the risks of IS and ICH were both increased in the first six weeks after delivery compared to non-pregnant time.[23] Another more recent USA study solely focusing on ICH found that the risk of ICH was 7.1 per 100,000 person-years compared to 5.0 in the general population of similar age but did not provide the estimate for other types of stroke.[24] Swedish studies found that the risks of IS, ICH and SAH were all increased around the time of delivery compared to the period before

pregnancy and the first two trimesters.[6,7] Nevertheless, we did not find any women with ICH around the time of delivery probably due to lack of study power for specific types of stroke, and particularly for ICH.

A limitation of this study is potential misclassification of the incident stroke. Firstly, the median length of prospective follow-up was only 3.4 years (IQR 1.4-7.5) therefore we might have misclassified a recurrent stroke as the first stroke. We however investigated historical stroke events (wherever available) and excluded women with stroke before start of the study in the main analysis. Secondly, 753 women were diagnosed with stroke in primary care without admission to hospital within 30 days. Since such diagnoses might not indicate 'incident' stroke events, we performed a sensitivity analysis by excluding these women. The absolute rates of stroke for each period during and outside pregnancy reduced slightly but remained largely within the confidence limits of the original analysis. The relative rates during pregnancy related time compared with non-pregnant time were extremely similar to the main analysis so this did not change interpretation. Thirdly, since we have only used HES to identify pregnancies, pregnancies ending earlier (not ending in live birth or stillbirth) were not included in this study. Therefore if a woman had a stroke event in pregnancy which did not end in a delivery, such stroke event would be included in non-pregnant time. Fourthly, we should acknowledge that we used date of hospital admission as the date of stroke diagnosis which means there might be some misclassification between antepartum and postpartum stoke. However by creating a third category of peripartum, around the time of delivery, we believe we have reduced its impact.

In addition, we relied on clinician diagnosis to identify stroke and there was no information on CT brain scan nor other aetiological information to validate the stroke diagnosis or allow a mechanism based classification of stroke types. Hospitals in England will of course use CT

and other tests to classify the stoke diagnosis for management and coding in HES, but we were not able to access this information directly and it would not be standardised across all of our cases. For a small proportion of women without stroke type specified at the time of their first stroke diagnosis, prescriptions of antiplatelet and anticoagulant drugs within 60 days after their stroke diagnosis were used to classify IS. By using this approach, it is possible that we might have misclassified some women as having ischaemic stroke when they did not. However, we believe this is unlikely for a number of reasons. Firstly, majority of stroke cases during the time around delivery and early postpartum were identified from HES based on ICD-10 codes with stroke type specified. Secondly, the use of an antiplatelet or anticoagulant after a stroke other than IS would be very unlikely. However, we also conducted a sensitivity analysis which excluded women with unspecified stroke who were prescribed an antiplatelet or anticoagulant after seven days of diagnosis from the ischemic stroke group. We found broadly similar results to the main analysis.

Possible explanations and implications for clinicians and researchers

Our study found that the risk of both ischaemic and haemorrhagic stroke was increased around the time of delivery and in the first six weeks postpartum. In addition, our results suggested that the mechanisms of increased relative risk around the time of delivery and early postpartum are age-dependent and younger women had a higher relative risk of stroke in the high-risk period than older women. Certain delivery-related factors (such as the prothrombotic state) could have substantial impact on the occurrence of ischaemic stroke in the high-risk period. Previous research has found that the risk of first venous thromboembolism is also significantly higher around the time of delivery and early postpartum.[17] In addition, other risk factors unique to pregnancy, such as pregnancy-induced hypertension and pre-eclampsia/eclampsia, especially increase the risk of haemorrhagic

stroke.[25–28] In our study, about 25% of women with stroke in the time associated with pregnancy had diagnoses of HDP, much higher than risk expected in the general population, indicating that HDP is an important risk factor for pregnancy-related stroke. On the other hand, blood pressure normally falls during the first half of pregnancy, which could reduce the risk of haemorrhagic stroke in early pregnancy. In addition, the universal use of free, routinely provided antenatal care in the UK starting from early in the first trimester, could help to identify young women with traditional risk factors for stroke and might lead to monitoring and treatment of high blood pressure in pregnancy. Outside of pregnancy, such women of the same age will less often come into contact with health professionals. Health care professionals should be aware of the pregnancy-related stroke risk and provide women immediate investigation and treatment if stroke symptoms develop**.** Prospective registries recording stroke events in and after pregnancy particularly relative to delivery and labour could be potentially beneficial in monitoring and understanding occurrence of stroke in pregnant women.

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Conflict of Interest Disclosures

None

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Figure legends

Figure 1 Defining study population and stroke types using both Hospital Episode Statistics (HES) and Clinical Practice Research Datalink (CPRD)

Table 1 Basic characteristics of study population

Variables	**N (%)**
Included women in the study	2,046,048
Median follow-up (interquartile range) in years	3.4 (1.4-7.5)
Pregnancy outcome (total pregnancies N=453,800)	
Live births	451,765 (99.55)
Stillbirths	2,035 (0.45)
Study follow-up time in person-years (total person-years=10,170,974)	
Non-pregnant time	9,759,438 (95.95)
Antepartum	308,378 (3.03)
Peripartum	4,967 (0.05)
Postpartum	98,191 (0.97)
Cases of first stroke (total cases=2,511)	
Non-pregnant time	2,440 (97.17)
Pregnant time	71 (2.83)

Table 2 Incidence rates (per 100,000 person-years) of stroke in antepartum, the time of delivery, postpartum and non-pregnant time (N=2,046,048 women)

All strokes	**N stroke cases**	**P-Y**	**Rate**	**95% CI**	**Adjusted rate ratio***	**95% CI**
			(per 100,000 P-Y)			
Non-pregnant time**	2440	9,759,438	25.0	24.0-26.0	reference	
Antepartum	33	308,378	10.7	7.6-15.1	0.6	0.5-0.9
1st trimester	*8*	*94,973*	*8.4*	*4.2-16.8*	*0.5*	*0.3-1.0*
2nd trimester	*13*	*119,521*	*10.9*	*6.3-18.7*	*0.7*	*0.4-1.1*
3rd trimester	*12*	*93,884*	*12.8*	*7.3-22.0*	*0.8*	*0.4-1.3*
Peripartum	8	4,967	161.1	80.6-322.1	9.4	4.7-18.8
Postpartum	30	98,191	30.6	21.4-43.7	1.8	1.2-2.5
Early postpartum	23	48,796	47.1	31.3-70.9	2.7	1.8-4.1
Late postpartum	7	49,395	14.2	6.8-29.7	0.8	0.4-1.7

* Rate ratio adjusted for maternal age, socioeconomic deprivation and calendar time

** Excluding the first 12 weeks postpartum

P-Y=person-years

95% CI=95% confidence interval

Table 3 Incidence rates of different types of stroke in antepartum, the time of delivery, postpartum and non-pregnant time (N=2,046,048 women)

	Ischaemic stroke		Intracerebral haemorrhage		Subarachnoid haemorrhage		Unspecified stroke	
	N cases	**Rate* (95% CI)**	**N cases**	**Rate* (95% CI)**	**N cases**	**Rate* (95% CI)**	**N cases**	**Rate* (95% CI)**
Non-pregnant time**	1073	11.0 (10.4-11.7)	357	3.7 (3.3-4.1)	691	7.1 (6.6-7.6)	319	3.3 (2.9-3.7)
Antepartum	13	4.2 (2.4-7.3)	<5	1.3 (0.5-3.5)	9	2.9 (1.5-5.6)	7	2.3 (1.1-4.8)
Peripartum	<5	60.4 (19.5-187.4)	0		<5	60.4 (19.5-187.4)	<5	40.3 (10.1-161.2)
Early postpartum	15	30.8 (18.5-51.0)	5	10.3 (4.3-24.6)	<5	4.1 (1.0-16.4)	<5	2.1 (0.3-14.6)
Late postpartum	5	10.1 (4.2-24.3)	<5	4.1 (1.0-16.2)	0		0	

* Rate per 100,000 person-years

** Excluding the first 12 weeks postpartum

95% CI=95% confidence interval

According to the data license agreement, we do not report data for cells with fewer than five patients; therefore we use <5 instead.

Table 4 Incidence rates of stroke in non-pregnant time and combination of around the time of delivery and early postpartum by maternal age, socioeconomic status and calendar time

	Non-pregnant time*		Peripartum and early postpartum		Adjusted rate ratio**
	N stroke cases	Rate*** (95% CI)	N stroke cases	Rate*** (95% CI)	(95% CI)
Maternal age, years					
15-24	110	4.8 (4.0-5.8)	7	57.9 (27.6-121.4)	11.9 (5.5-25.6)
25-34	379	13.9 (12.6-15.4)	15	48.8 (29.4-80.9)	3.6 (2.1-6.0)
35-49	1,951	41.0 (39.2-42.8)	9	82.4 (42.9-158.3)	2.1 (1.1-4.0)
Index of Multiple Deprivation****					
Quintile 1 (least deprived)	405	18.0 (16.4-19.9)	<5	26.2 (8.5-81.3)	1.9 (0.6-5.8)
Quintile 2	467	21.7 (19.8-23.7)	6	55.2 (24.8-122.8)	3.5 (1.6-7.8)
Quintile 3	444	23.1 (21.0-25.4)	9	89.2 (46.4-171.5)	5.4 (2.8-10.4)
Quintile 4	554	29.3 (27.0-31.9)	5	46.2 (19.2-110.9)	2.5 (1.0-6.0)
Quintile 5 (most deprived)	562	36.7 (33.8-39.9)	8	76.6 (38.3-153.2)	3.9 (1.9-7.9)
Calendar time					

1997-2002	650	25.8 (23.8-27.8)	6	49.8 (22.4-110.9)	3.0 (1.3-6.7)
2003-2008	949	24.5 (23.0-26.2)	13	60.2 (34.9-103.6)	3.6 (2.1-6.2)
2009-2014	841	25.0 (23.3-26.7)	12	59.7 (33.9-105.1)	3.4 (1.9-6.0)

* Excluding the first 12 weeks postpartum

** Rate ratio mutually adjusted for other co-variates (maternal age, socioeconomic deprivation and calendar time)

*** Rate per 100,000 person-years

**** 4,798 women with missing information

95% CI=95% confidence interval

According to the data license agreement, we do not report data for cells with fewer than five patients; therefore we use <5 instead.

Table 5 Sensitivity analyses after excluding 753 women with stroke recorded in their general practice record but no hospital admission within 30 days: Incidence rates of stroke in antenatal, postnatal and non-pregnant periods

All strokes	**N stroke cases**	**P-Y**	**Rate (per 100,000 P-Y)**	**95% CI**	**Adjusted rate ratio***	**95% CI**
Non-pregnant time**	1,704	9,755,854	17.5	16.7-18.3	reference	
Antepartum	22	308,300	7.1	4.7-10.8	0.6	0.4-0.9
1st trimester	*7*	*94,948*	*7.4*	*3.5-15.5*	*0.6*	*0.3-1.3*
2nd trimester	*7*	*119,491*	*5.9*	*2.8-12.3*	*0.5*	*0.2-1.0*
3rd trimester	*8*	*93,861*	*8.5*	*4.3-17.0*	*0.7*	*0.4-1.4*
Peripartum	7	4,965	141.0	67.2-295.7	11.8	5.6-24.7
Postpartum	25	98,165	25.5	17.2-37.7	2.1	1.4-3.1
Early postpartum	20	48,783	41.0	26.5-63.5	3.4	2.2-5.3
Late postpartum	5	49,382	10.1	4.2-24.3	0.8	0.3-2.0

* Rate ratio adjusted for maternal age, socioeconomic deprivation and calendar time

** Excluding the first 12 weeks postpartum

P-Y=person-years

95% CI=95% confidence interval

Table 6 Sensitivity analysis excluding 229 women with unspecified stroke but with a prescription of an antiplatelet or anticoagulant after 7 days of diagnosis from the ischaemic stroke group: Incidence rates of ischaemic stroke in antepartum, the time of delivery, postpartum and non-pregnant time

	Ischaemic stroke		
	N cases	**Rate* (95% CI)**	**Adjusted RR (95% CI)**
Non-pregnant time**	847	8.7 (8.1-9.3)	1
Antepartum	11	3.6 (2.0-6.4)	0.6 (0.3-1.1)
Peripartum	<5	40.3 (10.1-161.1)	6.4 (1.6-25.6)
Early postpartum	15	30.8 (18.5-51.0)	4.8 (2.9-8.1)
Late postpartum	5	10.1 (4.2-24.3)	1.6 (0.7-3.8)

* Rate per 100,000 person-years

** Excluding the first 12 weeks postpartum

95% CI=95% confidence interval

According to the data license agreement, we do not report data for cells with fewer than five patients; therefore we use <5 instead.