Infertility, recurrent pregnancy loss, and risk of stroke: pooled analysis of individual patient data of 618 851 women

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Abstract

Objective
To examine the associations of infertility, recurrent miscarriage, and stillbirth with the risk of first non-fatal and fatal stroke, further stratified by stroke subtypes.

DESIGN
Individual participant pooled analysis of eight prospective cohort studies.

SETTING
Cohort studies across seven countries (Australia, China, Japan, Netherlands, Sweden, the United Kingdom, and the United States) participating in the InterLACE (International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events) consortium, which was established in June 2012.

PARTICIPANTS
618 851 women aged 32.0-73.0 years at baseline with data on infertility, miscarriage, or stillbirth, at least one outcome event (non-fatal or fatal stroke), and information on covariates were included; 93 119 women were excluded. Of the participants, 275 863 had data on non-fatal and fatal stroke, 54 716 only had data on non-fatal stroke, and 288 272 only had data on fatal stroke.

MAIN OUTCOME AND MEASURES
Non-fatal strokes were identified through self-reported questionnaires, linked hospital data, or national patient registers. Fatal strokes were identified through death registry data.

RESULTS
The median follow-up for non-fatal stroke and fatal stroke was 13.0 years (interquartile range 12.0-14.0) and 9.4 years (7.6-13.0), respectively. A first non-fatal stroke was experienced by 9265 (2.8%) women and 4003 (0.7%) experienced a fatal stroke. Hazard ratios for non-fatal or fatal stroke were stratified by hypertension and adjusted for race or ethnicity, body mass index, smoking status, education level, and study. Infertility was associated with an increased risk of non-fatal stroke (hazard ratio 1.14, 95% confidence interval 1.08 to 1.20). Recurrent miscarriage (at least three) was associated with higher risk of non-fatal and fatal stroke (1.35, 1.27 to 1.44, and 1.82, 1.58 to 2.10, respectively). Women with stillbirth were at 31% higher risk of non-fatal stroke (1.31, 1.10 to 1.57) and women with recurrent stillbirth were at 26% higher risk of fatal stroke (1.26, 1.15 to 1.39). The increased risk of stroke (non-fatal or fatal) associated with infertility or recurrent stillbirths was mainly driven by a single stroke subtype (non-fatal ischaemic stroke and fatal haemorrhagic stroke), while the increased risk of stroke (non-fatal or fatal) associated with recurrent miscarriages was driven by both subtypes.

CONCLUSION
A history of recurrent miscarriages and death or loss of a baby before or during birth could be considered a female specific risk factor for stroke, with differences in risk according to stroke subtypes. These findings could contribute to improved monitoring and stroke prevention for women with such a history.

WHAT IS ALREADY KNOWN ON THIS TOPIC?
Evidence on the links of infertility, miscarriage, and stillbirth with stroke has been inconclusive

Limited evidence is available on the association of infertility, miscarriage, and stillbirth with stroke by subtype

WHAT THIS STUDY ADDS
Infertility and pregnancy loss, especially recurrent miscarriage (at least three) and recurrent stillbirth (at least two), increased women's later risk of non-fatal and fatal stroke

The risk of non-fatal or fatal stroke associated with infertility or recurrent stillbirths was mainly driven by a single subtype of stroke (non-fatal ischaemic stroke or fatal haemorrhagic stroke); the risk of non-fatal or fatal stroke associated with recurrent miscarriages was driven by both subtypes

A history of recurrent pregnancy loss could be considered a female specific risk factor for stroke

Introduction
Globally, stroke is one of the leading causes of mortality and disability in women.[1] In 2019, around three million women died from stroke, and women lost over 10 million years of healthy life due to disability caused by stroke—44% higher than the number for men.[2] Current stroke prevention guidelines have identified some risk factors, such as obesity, hypertension, and diabetes, but these are insufficient to explain the difference in risk of stroke between women and men. Female specific risk factors might be needed to identify women at higher risk of stroke.

To date, multiple studies have generated an expanding body of evidence on the association between pregnancy complications (eg, gestational diabetes and preeclampsia) and the long term risk of stroke, but studies on associations with infertility, miscarriage, or stillbirth have produced mixed evidence.[3 4] Infertility, miscarriage, and stillbirth could increase the risk of stroke through the background of endocrine disorders (such as, low oestrogen or insulin resistance), systematic inflammation, endothelial dysfunction, psychological disorders, unhealthy behaviours (eg, smoking), and obesity.[5-9] The inconclusive findings could be owing to methodological differences and limitations, such as inadequate follow-up, inconsistent definitions for outcomes, and lack of adjustment for residual confounders. Additionally, little evidence is available on whether the relations differ by non-fatal and fatal stroke, or by stroke subtypes. Research has suggested that risk factors, such as smoking, blood pressure, atrial fibrillation, and diabetes, are higher for fatal stroke than for non-fatal stroke, and such differences might also exist for the associations with infertility, miscarriage, and stillbirth.[10] Stroke subtypes have divergent pathophysiology (brain vessel obstruction or bleeding) and would be linked through different mechanisms. Analysis by stroke subtypes would provide basic information for future studies on underlying mechanisms.

This study used pooled individual participant data from studies contributing to the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) consortium.[11] The aim was to assess the association of infertility, recurrent miscarriage, and stillbirth with the risk of first non-fatal and fatal stroke, further stratified by stroke subtypes.

Methods

Study participants

We analysed data from the InterLACE consortium, which was established in June 2012 and provides pooled individual level data on reproductive health and chronic disease.[11] Currently, InterLACE is composed of 27 observational studies with over 850 000 women from 12 countries. The design and data harmonisation used with InterLACE have been reported previously.[12] Eight studies from seven countries (Australia, China, Japan, Netherlands, Sweden, the United Kingdom, and the United States) that collected data on infertility, miscarriage, or stillbirth were included (n=711 970): Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), China Kadoorie Biobank, Japan Nurses' Health Study (JNHS), UK MRC National Survey of Health and Development (NSHD), the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, Netherlands (Prospect-EPIC), US Study of Women's Health Across the Nation (SWAN), UK Biobank, and the Swedish Women's Lifestyle and Health Study (WLH; table S1).

All studies began between 1990 and early 2000, with the exception of NSHD (1946 British birth cohort), in which participants were recruited at birth in 1946.[13] For the present analysis, baseline was considered as the first time when infertility, miscarriage, or stillbirth was determined, except for NSHD. NSHD first collected information on stroke in 1982 (when participants were aged 36), and the history of infertility and miscarriage was retrospectively collected in 1989 (aged 43); therefore, 1982 was used as the baseline year for this analysis. Women with data on at least one of infertility, miscarriage, or stillbirth, at least one outcome (first non-fatal stroke or fatal stroke), and covariates (race or ethnicity, body mass index, smoking status, education level, and hypertension) were included (fig S1). Women with non-fatal stroke before the age of 40 were excluded because they might have experienced stroke before a history of infertility, miscarriage, or stillbirth could be fully established.

Infertility, miscarriage, and stillbirth

Information on infertility, miscarriage, and stillbirth was mostly obtained through questionnaires at baseline, or in some studies at repeated follow-up surveys (table S2). Women provide information on their reproductive history according to their understanding, previous diagnosis, or treatment by a physician. Questions related to infertility were asked, such as whether the woman had tried to become pregnant during a period of 12 months or more without success, consulted a doctor for infertility, had a diagnosis of infertility from a doctor, or been treated for infertility. Women with any of the above experiences were identified as having experienced infertility. For miscarriage and stillbirth, the outcome of each pregnancy (livebirth, miscarriage, or stillbirth), number of miscarriages, and number of stillbirths were recorded. The numbers of miscarriages and stillbirths were categorised into four categories (0, 1, 2, and ≥3) and three categories (0, 1, and ≥2), respectively.[14 15] Recurrent miscarriages was defined as three or more miscarriages, and recurrent stillbirths was defined as two or more stillbirths, which could be interspersed with livebirths.

First non-fatal and fatal stroke

The first non-fatal stroke event was identified through self-reported questionnaires (physician diagnosed or treated) or linked hospital data (table S2). All studies provided survey data on stroke; additionally, ALSWH-mid, Prospect-EPIC, UK Biobank, and WLH included linked hospital data, coded according to the 9th or 10th versions of the international classification of diseases (ICD-9 and ICD-10). Fatal stroke was identified through death registries in five studies (ALSWH-mid, China Biobank, Prospect-EPIC, JNHS, and UK Biobank; table S2), using ICD-9 or ICD-10 codes.

The following ICD codes were used to define stroke from hospital records and death registries: ICD-9 (430, 431, 433, 434, 436) and ICD-10 (I60, I61, I63, I64, I69.0, I69.1, I69.3, I69.4).[16] Subtypes of stroke were classified as haemorrhagic stroke (ICD-9: 430, 431; ICD-10: I60, I61, I69.0, I69.1) and ischaemic stroke (ICD-9: 433, 434, 436; ICD-10: I63, I64, I69.3, I69.4).[16] Only JNHS, in which participants were registered nurses, collected self-reported data on stroke subtypes (subarachnoid haemorrhage, cerebral haemorrhage, and cerebral infarction). Any stroke event, not specified as haemorrhagic or ischaemic stroke, was classified as unspecified stroke.

Covariates

Information on covariates was collected at baseline. For women who were not Asian, body mass index was categorised into underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), and obese (≥30).[17] For Asian women, the categories were defined as underweight (<18.5), normal (18.5-22.9), overweight (23-27.4), and obese (≥27.5).[18] Other covariates included race or ethnicity (white, Asian, or others), current smoking status (yes or no), education level (≤10, 11-12, or >12 years), hypertension (yes or no), and diabetes mellitus (yes or no).

Statistical analysis

Baseline characteristics were presented as medians and interquartile ranges for continuous variables, and as numbers and percentages for categorical variables. Kaplan-Meier survival curves were drawn to show the probability of stroke among women with and without infertility, miscarriage, or stillbirth. We fit Cox proportional hazards survival time models to estimate the associations between infertility, miscarriage, stillbirth, and outcomes (first non-fatal stroke, fatal stroke, or subtypes of stroke), providing hazard ratios and 95% confidence intervals. The proportional hazards assumption was tested using Schoenfeld residuals. We adjusted the survival time models for race or ethnicity, body mass index, smoking status, and education level. To account for the time varying effects of hypertension, a stratified analysis was conducted through an option of strata in the proportional hazards regression procedure.[19] However, because the proportion of women with diabetes was too low for stratified analysis, diabetes was taken into consideration in the sensitivity analyses.[19] In the stratified proportional hazards model, the regression coefficients were assumed to be the same for each stratum, and the baseline hazard functions might be different. We took study variability into account by including an indicator for study as a covariate, and robust variance estimators were used to account for potential within study correlation.[20] In the analysis of non-fatal stroke, survival times were age at first non-fatal stroke or age at last update of non-fatal data, and women without stroke were censored. In the analysis of fatal stroke, survival times were age at death or age at last update of death data, and women who had not died were censored. We restricted analyses for miscarriage and stillbirth to women who had ever been pregnant.

To account for the possible bias arising from competing risks across groups, we also calculated Fine-Gray subdistribution hazards for subtypes of non-fatal stroke, fatal stroke, and subtypes of fatal stroke.[21] When one subtype of non-fatal stroke was the event of interest, other subtypes of non-fatal stroke were incorporated as competing events. When fatal stroke or one subtype of fatal stroke was the event of interest, deaths of other causes were treated as competing events. Because of insufficient outcome events, neither the association of fatal stroke (n=204) with infertility nor the associations of unspecified fatal stroke (n=161) with miscarriage and stillbirth were assessed.

We conducted several sensitivity analyses to examine the robustness of findings. Firstly, data from a subset of studies (ALSWH-mid, Prospect-EPIC, UK Biobank, and WLH) were analysed, in which linked hospital data were used to identify non-fatal stroke events. This resulted in the exclusion of 19 114, 15 837, and 15 709 women in the analysis for infertility, miscarriage, and stillbirth, respectively. Secondly, women with infertility who did not have a diagnosis of infertility, meet the definition of infertility (unsuccessfully trying to be pregnant for 12 months or more), or receive maternal treatment of infertility were excluded (n=32 737). Thirdly, the baseline of NSHD was changed from 1982 (when the women were aged 36) to 1989 (aged 43), so that the women's age was more comparable to the data in other included studies. Because fewer data were missing in the 1989 survey, 250, 113, and 88 more women were included in the analysis for infertility, miscarriage, and stillbirth, respectively.

Fourthly, the survival time models were additionally adjusted for a history of the oral contraceptive pill use (yes or no) and of hormone replacement therapy (yes or no) at baseline; these data were not available in the JNHS and China Biobank studies. This resulted in the exclusion of 63 354, 23 597, and 13 317 women before assessing the associations of infertility, miscarriage, and stillbirth with the risk of non-fatal stroke, and 310 828 and 300 593 women before estimating the associations between miscarriage, stillbirth, and fatal stroke. Fifthly, data from women without a history of diabetes were analysed to exclude the influence of diabetes. For non-fatal stroke, 1919, 9786, and 9490 women were excluded from the analysis of infertility, miscarriage, and stillbirth. For fatal stroke, 25 013 and 24 719 women were excluded from the analysis of miscarriage and stillbirth. Sixthly, associations of infertility, miscarriage, and stillbirth with combined stroke event (first non-fatal or fatal stroke) were explored. Finally, missing data on covariates were imputed using multiple imputation (10 times), and imputed datasets were used to assess the validity of results. We also assessed associations in single studies. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

Patient and public involvement

Because the study was a pooled analysis of pre-existing datasets, no patients were involved in setting the research questions or outcome measures, nor were they involved in developing the plan for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. However, their contributions to the respective studies are acknowledged.

Results

Study characteristics

Overall, 618 851 women from eight studies were included, aged from 32.0 to 73.0 years at baseline. The median follow-up for non-fatal stroke was 13.0 years

Table 1 | Baseline characteristics of study participants by history of infertility, miscarriage, and stillbirth. Data are numbers (%)

	Infertility (n=94 286)		Miscarriage (n=550 853)		Stillbirth (n=540 638)	
Characteristics	Never	Ever	Never	Ever	Never	Ever
Sample size	78 055 (82.79)	16 231 (17.21)	459 284 (83.38)	91 569 (16.62)	515 765 (95.40)	24 873 (4.60)
Race or ethnicity						
White	63 738 (81.66)	13 804 (85.05)	177 722 (38.70)	60 207 (65.75)	221 459 (42.94)	6710 (26.98)
Asian	13 276 (17.01)	2160 (13.31)	275 992 (60.09)	29 093 (31.77)	287 215 (55.69)	17 608 (70.79)
Others	1041 (1.33)	267 (1.65)	5570 (1.21)	2269 (2.48)	7091 (1.37)	555 (2.23)
Body mass index						
Underweight	4051 (5.19)	917 (5.65)	13 566 (2.95)	2490 (2.72)	13 968 (2.71)	1429 (5.75)
Normal	46 223 (59.22)	9914 (61.08)	176 583 (38.45)	34 955 (38.17)	197 260 (38.25)	9453 (38.01)
Overweight	20 328 (26.04)	3895 (24.00)	186 293 (40.56)	34 689 (37.88)	208 466 (40.42)	9653 (38.81)
Obese	7453 (9.55)	1505 (9.27)	82 842 (18.04)	19 435 (21.22)	96 071 (18.63)	4338 (17.44)
Current smoker						
No	62 816 (80.48)	12 649 (77.93)	429 192 (93.45)	82 966 (90.60)	480 771 (93.22)	23 060 (92.71)
Yes	15 239 (19.52)	3582 (22.07)	30 092 (6.55)	8603 (9.40)	34 994 (6.78)	1813 (7.29)
Education level						
≤10	23 600 (30.24)	4397 (27.09)	320 770 (69.84)	55 316 (60.41)	350 177 (67.89)	20 679 (83.14)
11-12	18 534 (23.74)	4113 (25.34)	63 985 (13.93)	11 763 (12.85)	72 174 (13.99)	1861 (7.48)
>12	35 921 (46.02)	7721 (47.57)	74 529 (16.23)	24 490 (26.74)	93 414 (18.11)	2333 (9.38)
Hypertension						
No	62 505 (80.08)	13 373 (82.39)	317 457 (69.12)	63 644 (69.50)	358 816 (69.57)	14 254 (57.31)
Yes	15 550 (19.92)	2858 (17.61)	141 827 (30.88)	27 925 (30.50)	156 949 (30.43)	10 619 (42.69)
Diabetes mellitus						
No	76 502 (98.06)	15 862 (97.78)	438 278 (95.50)	87 260 (95.43)	492 462 (95.57)	23 160 (93.20)
Yes	1511 (1.94)	360 (2.22)	20 649 (4.50)	4176 (4.57)	22 843 (4.43)	1689 (6.80)

Infertility: women from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), Swedish Women's Lifestyle and Health Study (WLH), United Kingdom MRC National Survey of Health and Development (NSHD), United States Study of Women's Health Across the Nation (SWAN), Japan Nurses' Health Study (JNHS), and Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, Netherlands (Prospect-EPIC) were included. Miscarriage: women from NSHD, SWAN, UK Biobank, China Biobank, and Prospect-EPIC were included. Among the 550 583 women, 67 345 (12.23%) had one miscarriage, 16 101 (2.92%) had two miscarriages, and 8064 (1.46%) had three or more miscarriages. Stillbirth: women from NSHD, SWAN, UK Biobank, China Biobank, and Prospect-EPIC were included. Among the 540 638 women, 19 937 (3.69%) had one stillbirth, and 4924 (0.91%) had two or more stillbirths. Body mass index: for Asian women, the classifications of body mass index are <18.5 (underweight), 18.5-22.9 (normal), 23-27.4 (overweight), and ≥27.5 (obese); for others, the classifications of body mass index are <18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight), and ≥30 (obese).

(interquartile range 12.0-14.0), and for fatal stroke it was 9.4 years (7.6-13.0). In total, 275 863 women had data on non-fatal and fatal stroke, 54 716 women only had data on non-fatal stroke, and 288 272 only had data on fatal stroke. Among these, 9265 (2.8%) women experienced a first non-fatal stroke at a median age of 62.0 (interquartile range 54.0-70.0), and 4003 (0.7%) had fatal stroke at a median age of 71.0 (64.0-76.0). The proportion of women who experienced infertility, miscarriage, and stillbirth was 17.2%, 16.6%, and 4.6%, respectively (table 1). Table 1 presents the baseline characteristics of women with and without such reproductive histories. Less than 7.0% of women were excluded owing to missing data, and they are more likely to be underweight, current smokers, and less educated (tables S3, S4).

Infertility
Women with a history of infertility were at higher risk of non-fatal stroke compared with women without infertility (hazard ratio 1.14, 95% confidence interval 1.08 to 1.20; table 2, fig S2). Analyses by subtypes of non-fatal stroke showed infertility was associated with an increased risk of ischaemic stroke (1.15, 1.07 to 1.23; fig 1).

Miscarriage
Among women who had ever been pregnant, a history of miscarriage was associated with 11% higher risk of non-fatal stroke compared with women without miscarriage (hazard ratio 1.11, 95% confidence interval 1.07 to 1.15; table 2, fig S3). The risk of non-fatal stroke increased with the number of miscarriages (1, 2, and ≥3), with adjusted hazard ratios of 1.07 (1.04 to 1.10), 1.12 (1.07 to1.17), and 1.35 (1.27 to 1.44), respectively (table 2, fig S4). Women with recurrent miscarriage (≥3) were more likely to experience ischaemic and haemorrhagic non-fatal stroke than women without miscarriage (1.37, 1.23 to 1.53, and 1.41, 1.08 to 1.84, respectively; fig 2).

For fatal stroke, the results showed a similar pattern (table 2, figs S5, S6). Women with one or more miscarriages (1, 2, and ≥3) had a higher risk of fatal stroke compared with women without miscarriages, with adjusted hazard ratios of 1.08 (0.96 to 1.21), 1.26 (1.07 to 1.49), and 1.82 (1.58 to 2.10), respectively. Women with recurrent miscarriages were more likely to experience ischaemic and haemorrhagic fatal stroke (1.83, 1.39 to 2.41, and 1.84, 1.39 to 2.44, respectively; fig 2).

Stillbirth
Among women who have ever been pregnant, a history of stillbirth was associated with 31% increased risk of non-fatal stroke compared with women without stillbirth (hazard ratio 1.31, 95% confidence interval 1.10 to 1.57; table 2, fig S7). Adjusted hazard ratios for single and recurrent stillbirths were 1.32 (1.15 to 1.51) and 1.29 (0.84 to 1.98), respectively, which are consistent with the Kaplan-Meier plot (table 2, fig S8). Women with recurrent stillbirths were more likely to

Table 2 | Association of infertility, miscarriage, and stillbirth with non-fatal and fatal stroke

	Non-fatal stroke					Fatal stroke				
Reproductive histories	Sample size	No of events	Incidence rate	Crude HR (95% CI)	Adjusted HR (95% CI)	Sample size	No of events	Incidence rate	Crude HR (95% CI)	Adjusted HR (95% CI)
Models with single reproductive histories										
History of infertility*										
Never	77 976	2292	47.6	Reference	Reference	34 488	177	7.6	—	—
Ever	16 211	453	46.0	1.13 (1.05 to 1.21)	1.14 (1.08 to 1.20)	5168	27	7.8	—	—
History of miscarriage†										
Never	197 303	5812	43.0	Reference	Reference	455 363	3255	11.3	Reference	Reference
Ever	65 315	2124	47.7	1.11 (1.08 to 1.15)	1.11 (1.07 to 1.15)	89 983	712	11.8	1.18 (1.04 to 1.35)	1.17 (1.07 to 1.29)
No of miscarriages†										
0	197 303	5812	43.0	Reference	Reference	455 363	3255	11.3	Reference	Reference
1	46 681	1454	45.6	1.06 (1.04 to 1.09)	1.07 (1.04 to 1.10)	66 227	479	10.8	1.08 (0.91 to 1.28)	1.08 (0.96 to 1.21)
2	11 988	395	48.4	1.13 (1.07 to 1.18)	1.12 (1.07 to 1.17)	15 805	137	12.9	1.26 (1.18 to 1.36)	1.26 (1.07 to 1.49)
≥3	6588	271	58.1	1.44 (1.34 to 1.56)	1.35 (1.27 to 1.44)	7897	96	18.0	1.93 (1.72 to 2.16)	1.82 (1.58 to 2.10)
History of stillbirth‡										
Never	243 859	7070	42.4	Reference	Reference	510 586	3479	10.7	Reference	Reference
Ever	8547	411	69.5	1.46 (1.18 to 1.82)	1.31 (1.10 to 1.57)	24 673	451	27.1	1.13 (1.08 to 1.18)	1.07 (1.00 to 1.13)
No of stillbirths‡										
0	243 859	7070	42.4	Reference	Reference	510 586	3479	10.7	Reference	Reference
1	7310	349	68.9	1.46 (1.23 to 1.72)	1.32 (1.15 to 1.51)	19 749	275	20.8	1.02 (0.97 to 1.06)	0.97 (0.91 to 1.03)
≥2	1225	62	73.6	1.53 (0.93 to 2.53)	1.29 (0.84 to 1.98)	4914	176	51.1	1.38 (1.27 to 1.50)	1.26 (1.15 to 1.39)
Model with miscarriage and stillbirth§										
No of miscarriages										
0	190 991	5554	42.5	Reference	Reference	449 055	3236	11.4	Reference	Reference
1	43 855	1321	44.2	1.04 (1.02 to 1.06)	1.05 (1.02 to 1.08)	63 509	469	11.1	1.07 (0.91 to 1.27)	1.08 (0.96 to 1.21)
2	11 147	350	46.2	1.08 (1.05 to 1.12)	1.08 (1.04 to 1.12)	14 988	132	13.1	1.23 (1.14 to 1.33)	1.23 (1.04 to 1.46)
≥3	6032	236	57.9	1.38 (1.27 to 1.50)	1.31 (1.23 to 1.41)	7351	91	18.3	1.85 (1.67 to 2.06)	1.76 (1.53 to 2.03)
No of stillbirths										
0	243 589	7056	42.4	Reference	Reference	510 320	3477	10.7	Reference	Reference
1	7231	344	68.6	1.43 (1.21 to 1.68)	1.29 (1.13 to 1.47)	19 689	275	20.9	1.01 (0.96 to 1.05)	0.96 (0.90 to 1.02)
≥2	1205	61	73.7	1.45 (0.90 to 2.32)	1.23 (0.81 to 1.85)	4894	176	51.4	1.34 (1.23 to 1.45)	1.23 (1.12 to 1.34)

Incidence rate (per 100 000 person years). Crude hazard ratios (HRs) took the cluster and fixed effects of study into account. Adjusted HRs were additionally adjusted for race or ethnicity, body mass index, smoking status, and education level, and stratified by history of hypertension.

*Six studies (Australian Longitudinal Study on Women's Health 1946-51 cohort—ALSWH-mid, Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, Netherlands—Prospect-EPIC, Japan Nurses' Health Study—JNHS, United Kingdom MRC National Survey of Health and Development—NSHD, United States Study of Women's Health Across the Nation—SWAN, and Swedish Women's Lifestyle and Health Study—WLH) and two studies (ALSWH-mid and JNHS) were included for non-fatal and fatal stroke, respectively.

†Six studies (ALSWH-mid, China Biobank, Prospect-EPIC, NSHD, SWAN, and UK Biobank) and four studies (ALSWH-mid, China Biobank, Prospect-EPIC, and UK Biobank) were included for non-fatal and fatal stroke, respectively.

‡Five studies (China Biobank, Prospect-EPIC, NSHD, SWAN, and UK Biobank) and three studies (China Biobank, Prospect-EPIC, and UK Biobank) were included for non-fatal and fatal stroke, respectively.

§Five studies (China Biobank, Prospect-EPIC, NSHD, SWAN, and UK Biobank) and three studies (China Biobank, Prospect-EPIC, and UK Biobank) were included for non-fatal and fatal stroke, respectively.

experience ischaemic non-fatal stroke than women without stillbirth (1.77, 1.54 to 2.02; fig 3).

Women with stillbirth were also at higher risk of fatal stroke than women without stillbirth (hazard ratio 1.07, 95% confidence interval 1.00 to 1.13; table 2, fig S9), and the risk increased with the number of stillbirths (1 *v* 0: 0.97, 0.91 to 1.03; ≥2 *v* 0: 1.26, 1.15 to 1.39; table 2, fig S10). Women with recurrent stillbirths were more likely to have haemorrhagic fatal stroke (1.44, 1.35 to 1.53; fig 3).

In this study, miscarriage and stillbirth acted independently on the risk of non-fatal and fatal stroke. Including miscarriage and stillbirth as separate variables in the same model produced almost no changes in the hazard ratios for each variable (table 2). Additionally, models with an eight level variable that combined the history of miscarriage (0, 1, 2, ≥3) and stillbirth (0, ≥1; Akaike information criterion 164 358.7 for non-fatal stroke and 84 611.5 for fatal stroke) did not fit the data better than the models with separate variables of miscarriage and stillbirth (Akaike information criterion 164 355.7 for non-fatal stroke and 84 604.7 for fatal stroke).

Sensitivity analyses

Firstly, studies with hospital data on non-fatal stroke were included. Estimated hazard ratios generally remained unchanged, except for an increase for recurrent stillbirth (table S5). Secondly, a separate analysis that included studies determining infertility through a strict definition (physician diagnosis, maternal treatment, and having difficulty conceiving for 12 months or more) was conducted, and the results were consistent with the main analysis (table S6).[22] Thirdly, redefining the baseline of NSHD had almost no influence on the results (table S7). Fourthly, additional adjustment for a history of oral contraceptive pill and hormone replacement therapy use did not change the associations, but the 95% confidence intervals of subtypes of fatal stroke became wider owing to the smaller sample size (tables S8, S9). Fifthly, restricting the analysis to women without diabetes had similar results to the main analysis (tables S10, S11). Sixthly, when the associations of infertility, miscarriage, and stillbirth with combined outcome (non-fatal or fatal stroke) were observed, recurrent miscarriages and stillbirths were still associated with the risk of stroke

Subtypes	Comparison	Exposed	Unexposed	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Non-fatal stroke					
All	Ever *v* never	453/16 211	2292/77 976		1.14 (1.08 to 1.20)
Haemorrhagic stroke	Ever *v* never	91/16,211	408/77 976		1.13 (0.94 to 1.36)
Ischaemic stroke	Ever *v* never	217/16 211	1020/77 976		1.15 (1.07 to 1.23)
Unspecified stroke	Ever *v* never	158/16 211	904/77 976		1.15 (0.93 to 1.42)

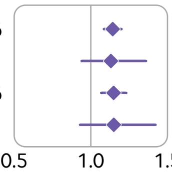

Fig 1 | Association between infertility and first non-fatal stroke overall and by subtypes. Individual level data of 94 187 women were pooled from six studies (Australian Longitudinal Study on Women's Health 1946-51 cohort—ALSWH-mid, Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, Netherlands—Prospect-EPIC, Japan Nurses' Health Study—JNHS, United Kingdom MRC National Survey of Health and Development—NSHD, United States Study of Women's Health Across the Nation—SWAN, and Swedish Women's Lifestyle and Health Study—WLH). Hazard ratios were adjusted for race or ethnicity, body mass index, smoking status, education level, and study, and stratified by history of hypertension

(table S12). Finally, estimates from the imputed datasets had almost no changes from the main analysis (tables S13, S14). The associations of infertility, miscarriage, and stillbirth with non-fatal and fatal stroke in each study separately are also provided in the supplement (figs S11-S15).

Examination of the Schoenfeld residuals did not support violation of the proportional hazard assumptions (table S15). Even though the residuals were correlated with survival time for some variables (eg, education level ≤10 years, obesity, and other races), the correlation coefficients were quite small (<0.08) though statistically significant owing to the large sample size; the inclusion of interaction terms with time did not improve the model fit.

Discussion

Summary of findings

This pooled analysis of 618 851 women (275 863 with data on non-fatal and fatal stroke, 54 716 with data on non-fatal stroke only, and 288 272 with data on fatal stroke only) showed that infertility, miscarriage, and stillbirth were all associated with increased risk of stroke, especially recurrent miscarriages and stillbirths. The increased risk of stroke associated with infertility or recurrent stillbirths was mainly driven by a single subtype of stroke (non-fatal ischaemic stroke or fatal haemorrhagic stroke, respectively), whereas the risk of stroke associated with recurrent miscarriages was driven by both subtypes.

Infertility and stroke

Previous studies on the association between infertility and stroke have been inconsistent. Three cohort studies from Canada, Sweden, and Denmark did not find evidence of an association when infertility was identified through fertility treatment.[23-25] Another study using American Optum's Clinformtics Data Mart showed 26% increased risk of cerebrovascular disease among women with a diagnosis of infertility or who had received treatment or testing for infertility.[26] In this study, women with infertility diagnosis, fertility treatment, infertility consultation, or an experience of trying unsuccessfully to become pregnant for 12 months or more were considered as infertile. Compared with previous studies, the present study included women who met the definition of infertility but had not sought medical help.

In the present study, women with infertility were found to be at increased risk of non-fatal stroke, which was mainly driven by the ischaemic subtype. Infertility might be pathologically linked to stroke through a background of ovarian disorders.[27 28] Polycystic ovary syndrome and premature ovarian insufficiency are two of the main ovarian disorders related to female infertility. Polycystic ovary syndrome is associated with a higher risk of insulin resistance, glucose intolerance, and an increased prothrombotic state, which would lead to vascular dysfunction and long term risk of stroke.[5] Premature ovarian insufficiency is accompanied by decreased levels of oestrogen, and would increase the risk of stroke through the loss of potential neuroprotective and anti-inflammatory properties from oestrogen.[6 29] Meanwhile, in the case of infertility due to polycystic ovary syndrome or premature ovarian insufficiency, a higher prevalence of thyroid autoimmunity has been documented, which would further increase the risk of ischaemic stroke through thyrotoxic atrial fibrillation and hypercoagulability state.[28 30] Additionally, women with infertility are more likely to be smokers, have obesity, and experience anxiety and depression, which would increase future risk of stroke through the toxic effects of smoking, insulin resistance, increased inflammation, and enhanced platelet aggregation.[4 8 31 32]

Miscarriage, stillbirth, and stroke

Even though a few cohort studies from China, the UK, Denmark, and Sweden have shown miscarriage and stillbirth to be associated with increased risk of stroke,[33-37] other studies have not.[38-42] A recent meta-analysis pooled the results of 13 cohort studies and found associations between miscarriage, stillbirth, and the risk of stroke.[43] However, the definitions of outcomes were inconsistent across the included studies (non-fatal stroke only, fatal stroke only, and both non-fatal and fatal stroke).[43] In the present study, the associations for non-fatal and fatal stroke

Subtypes	Comparison	Exposed	Unexposed	Hazard ratio (95% CI)
Non-fatal stroke				
All	Ever *v* never	2124/65 315	5812/197 303	1.11 (1.07 to 1.15)
	1 *v* 0	1454/46 681	5812/197 303	1.07 (1.04 to 1.10)
	2 *v* 0	395/11 988	5812/197 303	1.12 (1.07 to 1.17)
	≥3 *v* 0	271/6588	5812/197 303	1.35 (1.27 to 1.44)
Haemorrhagic stroke	Ever *v* never	398/65 315	1173/197 303	1.04 (1.01 to 1.07)
	1 *v* 0	280/46 681	1173/197 303	1.03 (0.96 to 1.10)
	2 *v* 0	62/11 988	1173/197 303	0.88 (0.73 to 1.06)
	≥3 *v* 0	56/6588	1173/197 303	1.41 (1.08 to 1.84)
Ischaemic stroke	Ever *v* never	936/65 315	2699/197 303	1.08 (1.03 to 1.13)
	1 *v* 0	619/46 681	2699/197 303	1.01 (0.96 to 1.06)
	2 *v* 0	191/11 988	2699/197 303	1.21 (1.09 to 1.33)
	≥3 *v* 0	124/6588	2699/197 303	1.37 (1.23 to 1.53)
Unspecified stroke	Ever *v* never	819/65 315	2027/197 303	1.17 (1.08 to 1.27)
	1 *v* 0	579/46 681	2027/197 303	1.17 (1.10 to 1.25)
	2 *v* 0	145/11 988	2027/197 303	1.12 (0.97 to 1.29)
	≥3 *v* 0	93/6588	2027/197 303	1.27 (1.06 to 1.53)
Fatal stroke				
All	Ever *v* never	712/89 983	3255/455 363	1.17 (1.07 to 1.29)
	1 *v* 0	479/66 227	3255/455 363	1.08 (0.96 to 1.21)
	2 *v* 0	137/15 805	3255/455 363	1.26 (1.07 to 1.49)
	≥3 *v* 0	96/7897	3255/455 363	1.82 (1.58 to 2.10)
Haemorrhagic stroke	Ever *v* never	429/89 983	1964/455 363	1.23 (0.98 to 1.53)
	1 *v* 0	287/66 227	1964/455 363	1.12 (0.89 to 1.40)
	2 *v* 0	87/15 805	1964/455 363	1.40 (1.07 to 1.83)
	≥3 *v* 0	55/7897	1964/455 363	1.84 (1.39 to 2.44)
Ischaemic stroke	Ever *v* never	278/89 983	1209/455 363	1.12 (0.98 to 1.30)
	1 *v* 0	188/66 227	1209/455 363	1.05 (0.92 to 1.20)
	2 *v* 0	49/15 805	1209/455 363	1.09 (0.84 to 1.41)
	≥3 *v* 0	41/7897	1209/455 363	1.83 (1.39 to 2.41)
Unspecified stroke	Ever *v* never	712/89 983	3255/455 363	
	1 *v* 0	479/66 227	3255/455 363	
	2 *v* 0	137/15 805	3255/455 363	
	≥3 *v* 0	96/7897	3255/455 363	

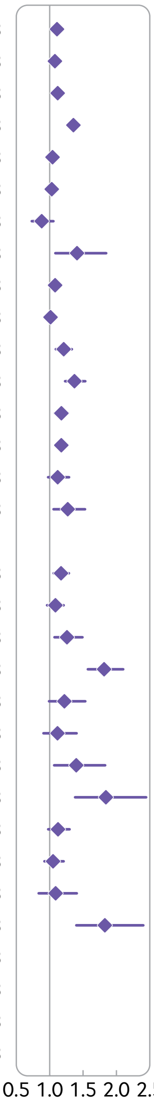

Fig 2 | Association of miscarriage with first non-fatal and fatal stroke overall and by subtypes. Non-fatal stroke: individual level data of 262 618 women were pooled from six studies (Australian Longitudinal Study on Women's Health 1946-51 cohort—ALSWH-mid, China Biobank, Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, Netherlands—Prospect-EPIC, United Kingdom MRC National Survey of Health and Development—NSHD, United States Study of Women's Health Across the Nation—SWAN, and UK Biobank). Fatal stroke: individual level data of 545 346 women were pooled from four studies (ALSWH-mid, China Biobank, Prospect-EPIC, and UK Biobank). Hazard ratios were adjusted for race or ethnicity, body mass index, smoking status, education level, and study, and stratified by history of hypertension

were explored separately. Women with stillbirth or miscarriage, especially recurrent miscarriages or stillbirths, were found to be at increased risk of non-fatal and fatal stroke.

Analysis by subtypes of stroke showed that women with recurrent miscarriages (at least three) were at higher risk of haemorrhagic and ischaemic stroke (non-fatal or fatal), and recurrent stillbirths (at least two) were associated with increased risk of ischaemic non-fatal stroke and haemorrhagic fatal stroke. An underlying mechanism for the risk of stroke associated with recurrent miscarriages or stillbirths would be endothelial dysfunction. Endothelial dysfunction might lead to pregnancy loss through placentation related defects, persist after a complicated pregnancy, and contribute to the development of stroke through reduced vasodilation, proinflammatory status, and prothrombic properties.[7 44] Meanwhile, antiphospholipid antibodies, which are characterised by pregnancy loss attributed to thrombosis of placental vessels, cause stroke through the induction of a prothrombotic state.[45] Binding by antiphospholipid antibodies to endothelial cells deranges normal endothelial anticoagulant function and promotes thrombosis, which would evolve in the development of ischaemic stroke.[46] Women with

Subtypes	Comparison	Exposed	Unexposed	Hazard ratio (95% CI)
Non-fatal stroke				
All	Ever *v* never	411/8547	7070/243 859	1.31 (1.10 to 1.57)
	1 *v* 0	349/7310	7070/243 859	1.32 (1.15 to 1.51)
	≥2 *v* 0	62/1225	7070/243 859	1.29 (0.84 to 1.98)
Haemorrhagic stroke	Ever *v* never	65/8547	1441/243 859	1.15 (1.00 to 1.33)
	1 *v* 0	59/7310	1441/243 859	1.21 (1.01 to 1.45)
	≥2 *v* 0	6/1225	1441/243 859	0.81 (0.59 to 1.11)
Ischaemic stroke	Ever *v* never	194/8547	3337/243 859	1.38 (1.35 to 1.41)
	1 *v* 0	161/7310	3337/243 859	1.33 (1.25 to 1.40)
	≥2 *v* 0	33/1225	3337/243 859	1.77 (1.54 to 2.02)
Unspecified stroke	Ever *v* never	155/8547	2392/243 859	1.29 (0.94 to 1.77)
	1 *v* 0	132/7310	2392/243 859	1.34 (1.02 to 1.78)
	≥2 *v* 0	23/1225	2392/243 859	1.08 (0.57 to 2.03)
Fatal stroke				
All	Ever *v* never	451/24 673	3479/510 586	1.07 (1.00 to 1.13)
	1 *v* 0	275/19 749	3479/510 586	0.97 (0.91 to 1.03)
	≥2 *v* 0	176/4914	3479/510 586	1.26 (1.15 to 1.39)
Haemorrhagic stroke	Ever *v* never	302/24 673	2065/510 586	1.19 (1.09 to 1.30)
	1 *v* 0	183/19 749	2065/510 586	1.08 (0.98 to 1.19)
	≥2 *v* 0	119/4914	2065/510 586	1.44 (1.35 to 1.53)
Ischaemic stroke	Ever *v* never	136/24 673	1339/510 586	0.89 (0.71 to 1.10)
	1 *v* 0	83/19 749	1339/510 586	0.80 (0.68 to 0.95)
	≥2 *v* 0	53/4914	1339/510 586	1.06 (0.74 to 1.52)
Unspecified stroke	Ever *v* never	20/24 673	141/510 586	
	1 *v* 0	14/19 749	141/510 586	
	≥2 *v* 0	6/4914	141/510 586	

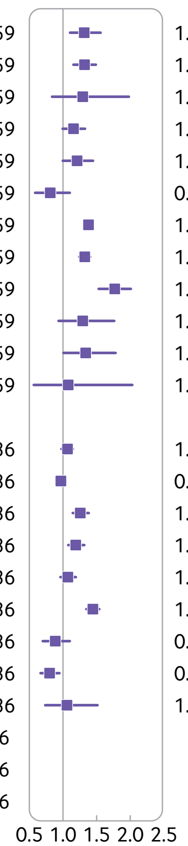

Fig 3 | Association of stillbirth with first non-fatal and fatal stroke overall and by subtypes. Non-fatal stroke: individual level data of 252 406 women were pooled from five studies (China Biobank, Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, Netherland—Prospect-EPIC, United Kingdom MRC National Survey of Health and Development—NSHD, United States Study of Women's Health Across the Nation—SWAN, and UK Biobank). Fatal stroke: individual level data of 535 259 women were pooled from three studies (China Biobank, Prospect-EPIC, and UK Biobank). Hazard ratios were adjusted for race or ethnicity, body mass index, smoking status, education level, and study, and stratified by history of hypertension

recurrent pregnancy loss are also more likely to have unhealthy behaviours (eg, smoking), to have obesity, and to experience depression, which could contribute to later risk of stroke.[8 47-49]

Clinical implications
The findings from this pooled study provided robust evidence for future clinical practice and guidelines. Having a history of recurrent pregnancy loss might be considered a female specific risk factor for stroke. Compared with the overall rates of non-fatal and fatal stroke (2.8% and 0.7%), the rates among women with recurrent miscarriages (at least three) or stillbirths (at least two) increased up to five times (recurrent miscarriage 4.1% and 1.2%; recurrent stillbirth 5.1% and 3.6%). We suggest early monitoring of women with recurrent miscarriages or stillbirths for stroke risk factors (eg, raised blood pressure, blood sugar, blood lipids), and promoting a healthy lifestyle programme (eg, smoking cessation, maintaining healthy weight, exercise) to reduce their excess risk of stroke in later life.

Strengths
This study pooled individual level data from divergent geographical regions and racial groups to quantify the association between infertility, recurrent miscarriages, recurrent stillbirths, and stroke risk, which increases the generalisability of the study findings. All the variables were harmonised with common definitions and coding rules.[12] This reduced potential bias from inconsistent classifications of reproductive histories or outcomes. Additionally, with a large sample size, sufficient power exists to detect the association of rare events (eg, recurrent miscarriages and recurrent stillbirths) with the risk of non-fatal and fatal stroke, further stratified by stroke subtypes, which is often not possible in any single study.

Limitations
Some limitations need to be considered in interpreting the findings. Information on infertility, miscarriage, and stillbirth was collected from questionnaires, which might induce recall bias. Previous studies have found that compared with medical records, self-reported

infertility (sensitivity 72.0%, specificity 70.0%) and pregnancy loss (sensitivity 73.5%, specificity 99.4%) would be reliable, but stillbirth might be over reported (sensitivity 100.0%, specificity 30.0%).[50-52] Therefore, it is plausible to assume that for this study the impact of recall bias was limited.

The definitions of infertility, miscarriage, and stillbirth might not be the same in each of the included studies because women reported according to their understanding of the definition of their reproductive history, previous diagnosis, or treatment by physicians. Additionally, the effects of different causes or treatments related to these reproductive histories were not explored owing to limited data. Only two studies (ALSWH-mid and WLH) and one study (JNHS) had data on infertility treatment and causes of infertility, respectively, and none of the studies had data on causes or treatment of pregnancy loss.

Among 12.1% of the included women, information on non-fatal stroke was collected through questionnaires only. Engstad and colleagues, and Jackson and colleagues have shown, however, that self-reported stroke was reliable (sensitivity 80%, specificity 99%; and sensitivity 78.6%, specificity 99.3%, respectively).[53 54] In this study, sensitivity analysis using hospital data showed consistent results with the main analysis, which indicated that this limitation should have little influence on the results. Also, around 4.0% (161/4003) of fatal strokes and 33.0% (3053/9265) of non-fatal strokes were categorised as unspecified subtype because information on the subtypes of stroke was not available or missing for patients with stroke identified from questionnaires, derived hospital records, or death registry codes, which might affect the strength of association for ischaemic or haemorrhagic stroke.

Although the models were adjusted for a range of covariates, including hypertension and diabetes, some comorbidities of interest, such as thyroid disorders, endometriosis, and pelvic inflammatory disease, were not available in all studies. Finally, some women were excluded owing to missing data, which could lead to sample bias. The proportions of women with missing data were less than 7.0%, and the findings from multiple imputations were consistent with the main analysis.

Conclusions

Infertility and pregnancy loss, especially recurrent miscarriages, and stillbirths, were associated with women's later risk of non-fatal and fatal stroke. The risk of stroke (non-fatal or fatal) associated with infertility or recurrent stillbirths was mainly driven by a single subtype of stroke (non-fatal ischaemic stroke or fatal haemorrhagic stroke, respectively), whereas the risk of stroke (non-fatal or fatal) associated with recurrent miscarriages was driven by both subtypes.

These findings extend our current knowledge on the associations of infertility, miscarriage, and stillbirth with stroke, and highlight the need for future studies on the underlying mechanisms, linking the subtype, severity, and prognosis of stroke. A history of recurrent miscarriages and death or loss of a baby before or during birth should be considered a female specific risk factor for stroke. Early monitoring of women with recurrent miscarriages or stillbirths and tailored healthy lifestyle interventions are recommended to lower the risk of stroke.

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Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organisation.

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Data sharing: No additional data available.

The lead author (GDM) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The dissemination plan targets a wide rangeing audience, including patients, public communities, health professionals, and experts in related fields through social media, websites, conferences, and scientific events. The results will be presented at conferences and disseminated through press releases and social media.

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Web appendix: Supplementary tables and figures