# Contents

Characteristics

Table S1. Characteristics of eight studies of women having information on infertility, miscarriage, stillbirth, and stroke in the InterLACE consortium

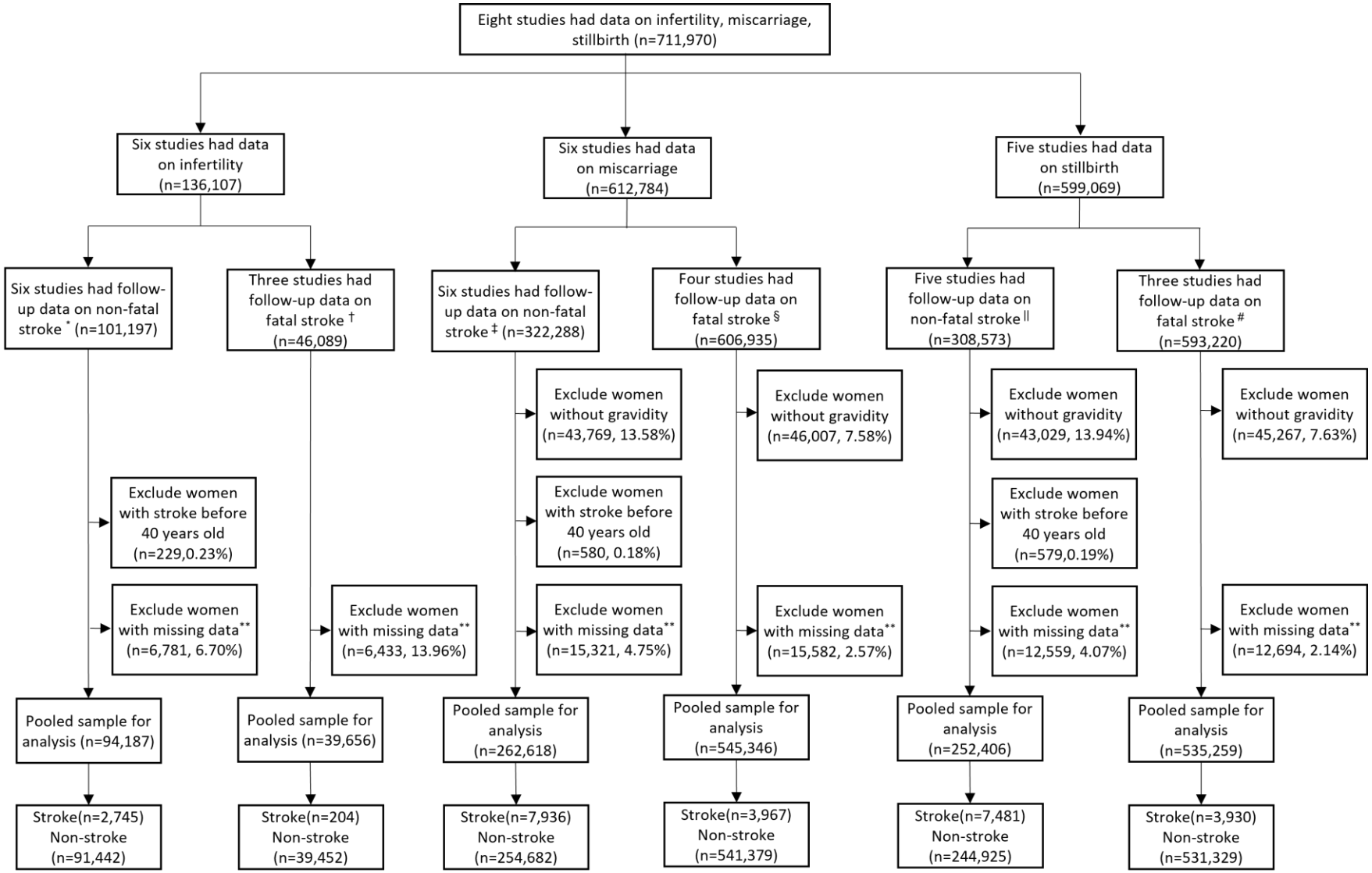
| Study | Country | Study population | Number | Baseline year | Age (Median, IQR) | |
|---|---|---|---|---|---|---|
| | | | | | Baseline | Last follow-up* |
| ALSWH-mid | Australia | Women who are Australian citizens or permanent residents and born between 1946 and 1951 were randomly selected from the universal health insurance data base. | 12,262 | 1996 | 47.6 (46.3,48.9) | 70.0 (69.0,72.0) |
| Prospect-EPIC | Netherlands | women aged 50–69 years living in the city of Utrecht and vicinity who were scheduled for breast cancer screening between 28th June 1993 and 28th November 1997, were invited to join the Prospect-EPIC study. | 16,930 | 1993-1997 | 56.9 (52.1,62.7) | 72.0 (68.0,77.0) |
| China Biobank† | China | Women aged between 30 and 79 years old at baseline, were identified through official residential records and recruited from 10 geographically defined regions (5 urban and 5 rural) of China. | 299,611 | 2004-2008 | 50.9 (42.6,58.8) | 53.7 (45.3,61.1) |
| JNHS | Japan | Female registered nurses, licensed practical nurses, public health nurses, and/or midwives, who were at least 30 years old and resident | 14,770 | 2001-2007 | 41.0 (35.0,48.0) | 50.0 (44.0,57.0) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | in Japan at the baseline survey. The age limit was reduced to 25 years old in 2005. | | | | |
| NSHD‡ | UK | The target sample for the first data collection was all the births in England, Scotland, and Wales in one week in March 1946. Subsequent data collections have been from a sample of all single births to married women with husbands in non-manual and agriculture employment and 1 in 4 of all comparable births to women with husbands in manual employment. | 1,265 | 1989 | 36.0 (36.0,36.0) | 54.0 (54.0,54.0) |
| SWAN | USA | Premenopausal women from the cross-sectional phase of SWAN were enrolled into the longitudinal follow-up study, if they were aged 42-52 years at baseline, had a uterus and at least one intact ovary, reported a menstrual period within the past three months and had not taken hormone medication in the last three months. | 3,175 | 1996-1997 | 46.0 (44.0,48.0) | 54.0 (52.0,57.0) |
| UK Biobank | UK | Women aged 40-69 years who attended one of the 22 centres across the UK between 2006 and 2010 were recruited. | 222,419 | 2006-2010 | 58.0 (51.0,63.0) | 70.0 (63.0,75.0) |

| | | | | | | |
|---|---|---|---|---|---|---|
| WLH | Sweden | Women aged 29-49 years at baseline and resident in the Uppsala Health Care Region were selected randomly from the Swedish Population Registry. | 48,419 | 1991-1992 | 40.0 (35.0,45.0) | 60.0 (55.0,65.0) |

ALSWH-mid: Australian Longitudinal Study on Women's Health 1946-51 cohort; Prospect-EPIC: the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands; JNHS: Japan Nurses' Health Study; NSHD: MRC National Survey of Health and Development Study; SWAN: Study of Women's Health Across the Nation; WLH: Women's Lifestyle and Health Study; IQR: interquartile range; *: last follow-up for non-fatal stroke event; †: In the study of China Biobank, 302,510 women were enrolled. All of them had follow-up data on fatal stroke, and 12,014 of them had follow-up data on non-fatal stroke. ‡: In NSHD (1946 British Birth Cohort) 1982 was used as the baseline year.

Figure S1. Flow chart of sample for analysis of the association between infertility, miscarriage, stillbirth, and stroke in the InterLACE consortium



The eight included studies were Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), Japan Nurses' Health Study (JNHS), MRC National Survey of Health and Development Study (NSHD), Study of Women's Health Across the Nation (SWAN), UK Biobank, and Women's Lifestyle and Health Study (WLH). *: ALSWH-mid, Prospect-EPIC, JNHS, NSHD, SWAN, and WLH. JNHS enrolled 49,927 women, and 15,017 women were followed up for non-fatal stroke. †. ALSWH-mid, Prospect-EPIC and JNHS. In JNHS, 15,017 of 49,927 women were followed up for fatal stroke. ‡. ALSWH-mid, China Biobank, Prospect-EPIC, NSHD, SWAN, and UK Biobank. China Biobank enrolled 302,510 women, and 12,014 women were followed up for non-fatal stroke. §. ALSWH-mid, China Biobank, Prospect-EPIC, and UK Biobank. ‖. China Biobank, Prospect-EPIC, NSHD, SWAN, and UK Biobank. China Biobank enrolled 302,510 women, and 12,014 women were followed up for non-fatal stroke. #. China Biobank, Prospect-EPIC, and UK Biobank. **: Women with missing value on exposure (infertility, miscarriage, or stillbirth), outcome (non-fatal stroke or fatal stroke), or covariates (race/ethnicity, body-mass index, smoking status, education level, hypertension, and study) were excluded.

Table S2. Ascertainment of exposures and outcomes

| Study | Infertility | Miscarriage | Stillbirth | Non-fatal stroke | Fatal stroke |
|---|---|---|---|---|---|
| ALSWH-mid (Survey 1-9) | Questionnaire (survey 3): 1.unsuccessfully to get pregnant? (For 12 months or more) 2.diagnosed as infertile 3.treatment for infertility | Questionnaire (survey 1): number of miscarriages | / | Questionnaire (survey 1-9): diagnosis or treatment of stroke Hospital admission data (until December 2020): ICD 9 (stroke: 430, 431, 433, 434, 436; haemorrhagic stroke: 430, 431; ischaemic stroke: 433, 434, 436) and ICD 10 (stroke: I60, I61, I63, I64, I690, I691, I693, I694; haemorrhagic stroke: I60, I61, I690, I691; ischaemic stroke: I63, I64, I693, I694) Aged care data (up to 2019) | Death registry data (until January 2019): ICD 10 (stroke: I60, I61, I63, I64, I690, I691, I693, I694; haemorrhagic stroke: I60, I61, I690, I691; ischaemic stroke: I63 I64, I693, I694) |
| Prospect-EPIC (Survey 1-5) | Questionnaire (survey 1): sub/infertility and infertility consult | Questionnaire (survey 1): number of miscarriages | Questionnaire (survey 1): number of stillbirths | Questionnaire (survey 1-5): diagnosis or treatment of stroke Hospital admission data (until December 2010, derived): Dutch Hospital Association and Order of | Statistic Netherlands (until December 2010, derived): ICD 9 (stroke: 430, 431, 432, 433, 434, 436; haemorrhagic stroke: 430, 431, 432; ischaemic stroke: 433, 434, 436) and ICD 10 |

| Study | Infertility | Miscarriage | Stillbirth | Non-fatal stroke | Fatal stroke |
|---|---|---|---|---|---|
| | | | | Medical Specialists, ICD 9 (stroke: 430, 431, 432, 433, 434, 436; haemorrhagic stroke: 430, 431, 432; ischaemic stroke: 433, 434, 436) and ICD 10 (stroke: I60, I61, I62, I63, I64, I65; haemorrhagic stroke: I60, I61, I62; ischaemic stroke: I63, I64, I65) | (stroke: I60, I61, I62, I63, I64, I65; haemorrhagic stroke: I60, I61, I62; ischaemic stroke: I63, I64, I65) |
| China Biobank (Survey 1-2) | / | Questionnaire (survey 1-2): number of spontaneous abortions | Questionnaire (survey 1-2): number of still births | Questionnaire (survey 1-2): diagnosis of stroke | Death registry data (until December 2014, derived): ICD 10 (stroke: I60, I61, I63, I64, I690, I691, I693, I694; haemorrhagic stroke: I60, I61, I690, I691; ischaemic stroke: I63 I64, I693, I694) |
| JNHS (Survey 1-6) | Questionnaire (survey 1): 1.have difficulty in becoming pregnant | / | / | Questionnaire (survey 1-6): diagnosis of stroke, subarachnoid hemorrhage, cerebral hemorrhage, cerebral infarction. | Death registry data (until March 2017): ICD 10 (stroke: I60, I61, I63, I64, I690, I691, I693, I694; haemorrhagic |

| Study | Infertility | Miscarriage | Stillbirth | Non-fatal stroke | Fatal stroke |
|---|---|---|---|---|---|
| | for more than 2 years; 2.treatment of infertility | | | | stroke: I60, I61, I690, I691; ischaemic stroke: I63 I64, I693, I694) |
| NSHD* (Survey 1-7) | Questionnaire (survey 6): 1.consult a doctor or other professional about infertility | Questionnaire (survey 6): number of miscarriages | Questionnaire (survey 6): number of stillbirths | Questionnaire (survey 5,6,13): diagnosis of stroke | / |
| SWAN (Survey 1-11) | Questionnaire (survey 1): 1.have a period of 12 months not being able to get pregnant | Questionnaire (survey 1): number of miscarriages, outcome of each pregnancy (e.g., livebirth, stillbirth, miscarriage) | Questionnaire (survey 1): outcome of each pregnancy (e.g., livebirth, stillbirth, miscarriage) | Questionnaire (survey 1-11): diagnosis or treatment for stroke | / |

| Study | Infertility | Miscarriage | Stillbirth | Non-fatal stroke | Fatal stroke |
|---|---|---|---|---|---|
| UK Biobank (Survey 1-3) | / | Questionnaire (survey 1-3): number of miscarriages | Questionnaire (survey 1-3): number of stillbirths | Questionnaire (survey 1-3): diagnosis of stroke<br>Derived hospital records (up to 31 Dec 2016): date of first stroke, ischaemic, intracerebral haemorrhage, subarachnoid haemorrhage<br>Hospital admission data (until March 2021): ICD 9 (stroke: 430, 431, 433, 434, 436; haemorrhagic stroke: 430, 431; ischaemic stroke: 433, 434, 436) and ICD 10 (stroke: I60, I61, I63, I64, I690, I691, I693, I694; haemorrhagic stroke: I60, I61, I690, I691; ischaemic stroke: I63, I64, I693, I694) | Death registry data (until March 2021): ICD 9 (stroke: 430, 431, 433, 434, 436; haemorrhagic stroke: 430, 431; ischaemic stroke: 433, 434, 436) and ICD 10 (stroke: I60, I61, I63, I64, I690, I691, I693, I694; haemorrhagic stroke: I60, I61, I690, I691; ischaemic stroke: I63, I64, I693, I694) |
| WLH (Survey 1-2) | Questionnaire (survey 1-2): | / | / | Questionnaire (survey 1& final): diagnosis of stroke<br>Patient registry data (until 2012) | / |

| Study | Infertility | Miscarriage | Stillbirth | Non-fatal stroke | Fatal stroke |
|---|---|---|---|---|---|
| | 1. have difficulty in becoming pregnant for 1 or more years; 2.treatment of infertility | | | Hospital admission data (until 2010): ICD 9 (stroke: 430, 431, 433, 434, 436; haemorrhagic stroke: 430, 431; ischaemic stroke: 433, 434, 436) and ICD 10 (stroke: I60, I61, I63, I64, I690, I691, I693, I694; haemorrhagic stroke: I60, I61, I690, I691; ischaemic stroke: I63, I64, I693, I694) | |

ALSWH-mid: Australian Longitudinal Study on Women's Health; Prospect-EPIC: the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands; JNHS: Japan Nurses' Health Study; NSHD: MRC National Survey of Health and Development Study; SWAN: Study of Women's Health Across the Nation; WLH: Women's Lifestyle and Health Study.

Table S3. Missing data pattern of the pooled dataset of the eight included studies from the InterLACE

| Group | Education level | BMI | Smoking status | Race | Hypertension | Diabetes mellitus | Study | No. (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | X | X | X | X | X | X | X | 699,740 (98.28%) |
| 2 | X | X | X | X | X | . | X | 612 (0.09%) |
| 3 | X | X | X | X | . | X | X | 757 (0.11%) |
| 4 | X | X | X | X | . | . | X | 374 (0.05%) |
| 5 | X | X | . | X | X | X | X | 2,198 (0.31%) |
| 6 | X | X | . | X | X | . | X | 13 (0.00%) |
| 7 | X | X | . | X | . | X | X | 48 (0.01%) |
| 8 | X | X | . | X | . | . | X | 470 (0.07%) |
| 9 | X | . | X | X | X | X | X | 4,763 (0.67%) |
| 10 | X | . | X | X | X | . | X | 10 (0.00%) |
| 11 | X | . | X | X | . | X | X | 9 (0.00%) |
| 12 | X | . | X | X | . | . | X | 1 (0.00%) |
| 13 | X | . | . | X | X | X | X | 26 (0.00%) |
| 14 | . | X | X | X | X | X | X | 1,881 (0.26%) |
| 15 | . | X | X | X | X | . | X | 26 (0.00%) |
| 16 | . | X | X | X | . | X | X | 28 (0.00%) |
| 17 | . | X | X | X | . | . | X | 13 (0.00%) |
| 18 | . | X | . | X | X | X | X | 182 (0.03%) |
| 19 | . | X | . | X | X | . | X | 4 (0.00%) |
| 20 | . | X | . | X | . | X | X | 7 (0.00%) |
| 21 | . | X | . | X | . | . | X | 780 (0.11%) |
| 22 | . | . | X | X | X | X | X | 18 (0.00%) |
| 23 | . | . | . | X | X | X | X | 3 (0.00%) |
| 24 | . | . | . | X | . | . | X | 7 (0.00%) |

"X" indicates presence of data, and "." indicates missing data.

Table S4. Comparison of women's characteristics in complete dataset used for analysis and the dataset with missing data

| | Infertility and non-fatal stroke | | Miscarriage and non-fatal stroke | | Miscarriage and fatal stroke | |
|---|---|---|---|---|---|---|
| | Competed dataset | Missing data | Competed dataset | Missing data | Competed dataset | Missing data |
| Sample size, No. (%) | 94,187 (93.28) | 6,781 (6.72) | 262,618 (94.49) | 15,321 (5.51) | 545,346 (97.22) | 15,582 (2.78) |
| Race/ethnicity, No. (%) | | | | | | |
| White | 77,474 (82.26) | 6,100 (89.96) | 237,426 (90.41) | 13,620 (88.90) | 233,992 (42.91) | 13,908 (89.26) |
| Asian | 15,405 (16.36) | 490 (7.23) | 17,379 (6.62) | 804 (5.25) | 304,619 (55.86) | 835 (5.36) |
| Others | 1,308 (1.39) | 191 (2.82) | 7,813 (2.98) | 897 (5.85) | 6,735 (1.23) | 839 (5.38) |
| Body-mass index, No. (%) | | | | | | |
| Underweight | 4,965 (5.27) | 1,441 (23.26) | 3,810 (1.45) | 1,390 (12.12) | 15,914 (2.92) | 515 (4.37) |
| Normal | 56,092 (59.55) | 2,510 (40.51) | 100,025 (38.09) | 3,886 (33.88) | 209,229 (38.37) | 4,192 (35.58) |
| Overweight | 24,192 (25.69) | 1,402 (22.63) | 97,953 (37.30) | 3,587 (31.27) | 219,288 (40.21) | 4,198 (35.63) |
| Obese | 8,938 (9.49) | 843 (13.61) | 60,830 (23.16) | 2,607 (22.73) | 100,915 (18.50) | 2,878 (24.43) |
| Current smoking, No. (%) | | | | | | |
| No | 75,385 (80.04) | 3,921 (75.75) | 236,029 (89.88) | 10,923 (86.89) | 507,940 (93.14) | 11,822 (86.10) |
| Yes | 18,802 (19.96) | 1,255 (24.25) | 26,589 (10.12) | 1,648 (13.11) | 37,406 (6.86) | 1,908 (13.90) |
| Education level (years), No. (%) | | | | | | |
| ≤10 | 27,959 (29.68) | 2,999 (54.10) | 139,470 (53.11) | 7,288 (55.15) | 374,174 (68.61) | 7,544 (54.24) |
| 11-12 | 22,626 (24.02) | 974 (17.57) | 36,756 (14.00) | 1,786 (13.52) | 74,428 (13.65) | 2,168 (15.59) |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≥12 | 43,602 (46.29) | 1,570 (28.32) | 86,392 (32.90) | 4,140 (31.33) | 96,744 (17.71) | 4,197 (30.17) |
| Hypertension, No. (%) | | | | | | |
| No | 75,823 (80.50) | 4,308 (76.06) | 189,624 (72.21) | 9,760 (74.17) | 379,244 (69.54) | 10,250 (70.90) |
| Yes | 18,364 (19.50) | 1,356 (23.94) | 72,994 (27.79) | 3,399 (25.83) | 166,102 (30.46) | 4,206 (29.10) |
| Diabetes mellitus, No. (%) | | | | | | |
| No | 92,268 (98.02) | 5,799 (96.97) | 252,832 (96.45) | 13,341 (96.37) | 520,333 (95.49) | 14,240 (95.98) |
| Yes | 1,868 (1.98) | 181 (3.03) | 9,296 (3.55) | 502 (3.63) | 24,554 (4.51) | 597 (4.02) |

| | Stillbirth and non-fatal stroke | | Stillbirth and fatal stroke | |
|---|---|---|---|---|
| | Competed dataset | Missing data | Competed dataset | Missing data |
| Sample size, No. (%) | 252,406 (95.26) | 12,559 (4.74) | 535,259 (97.68) | 12,694 (2.32) |
| Race/ethnicity, No. (%) | | | | |
| White | 227,667 (90.20) | 11,001 (87.59) | 224,359 (41.92) | 11,162 (87.93) |
| Asian | 17,119 (6.78) | 735 (5.85) | 304,357 (56.86) | 768 (6.05) |
| Others | 7,620 (3.02) | 823 (6.55) | 6,543 (1.22) | 764 (6.02) |
| Body-mass index, No. (%) | | | | |
| Underweight | 3,151 (1.25) | 1,235 (13.98) | 15,267 (2.85) | 348 (3.86) |
| Normal | 95,202 (37.72) | 2,649 (29.99) | 204,480 (38.20) | 2,881 (31.94) |
| Overweight | 95,091 (37.67) | 2,817 (31.90) | 216,456 (40.44) | 3,397 (37.66) |
| Obese | 58,962 (23.36) | 2,131 (24.13) | 99,056 (18.51) | 2,393 (26.53) |
| Current smoking, No. (%) | | | | |
| No | 227,705 (90.21) | 9,027 (88.15) | 499,695 (93.36) | 9,846 (87.34) |
| Yes | 24,701 (9.79) | 1,213 (11.85) | 35,564 (6.64) | 1,427 (12.66) |
| Education level (years), No. (%) | | | | |
| ≤10 | 134,244 (53.19) | 5,974 (56.45) | 369,034 (68.94) | 6,143 (55.09) |
| 11-12 | 35,042 (13.88) | 1,337 (12.63) | 72,747 (13.59) | 1,686 (15.12) |
| ≥12 | 83,120 (32.93) | 3,271 (30.91) | 93,478 (17.46) | 3,322 (29.79) |

| | | | | |
|---|---|---|---|---|
| Hypertension, No. (%) | | | | |
| No | 181,596 (71.95) | 7,612 (72.70) | 371,299 (69.37) | 8,018 (68.87) |
| Yes | 70,810 (28.05) | 2,859 (27.30) | 163,960 (30.63) | 3,624 (31.13) |
| Diabetes mellitus, No. (%) | | | | |
| No | 242,916 (96.43) | 10,717 (96.24) | 510,540 (95.46) | 11,493 (95.74) |
| Yes | 9,006 (3.57) | 419 (3.76) | 24,266 (4.54) | 511 (4.26) |

Distributions between complete dataset and the dataset with missing value were compared using Chi-square test. All the p value were <.001, except the p value for diabetes mellitus between women included and excluded in the analysis for miscarriage and non-fatal stroke (p=0.62), the p values for diabetes mellitus between women included and excluded in the analysis for miscarriage and fatal stroke (p=0.005 for diabetes), the p values for hypertension and diabetes mellitus between women included and excluded in the analysis for stillbirth and non-fatal stroke (p=0.09 for hypertension; p=0.29 for diabetes), and p values for hypertension and diabetes mellitus between women included and excluded in the analysis for stillbirth and fatal stroke (p=0.25 for hypertension; p=0.14 for diabetes).

Kaplan-Meier survival plot

Figure S2. Kaplan-Meier survival curves comparing the rate of non-fatal stroke according to the history of infertility

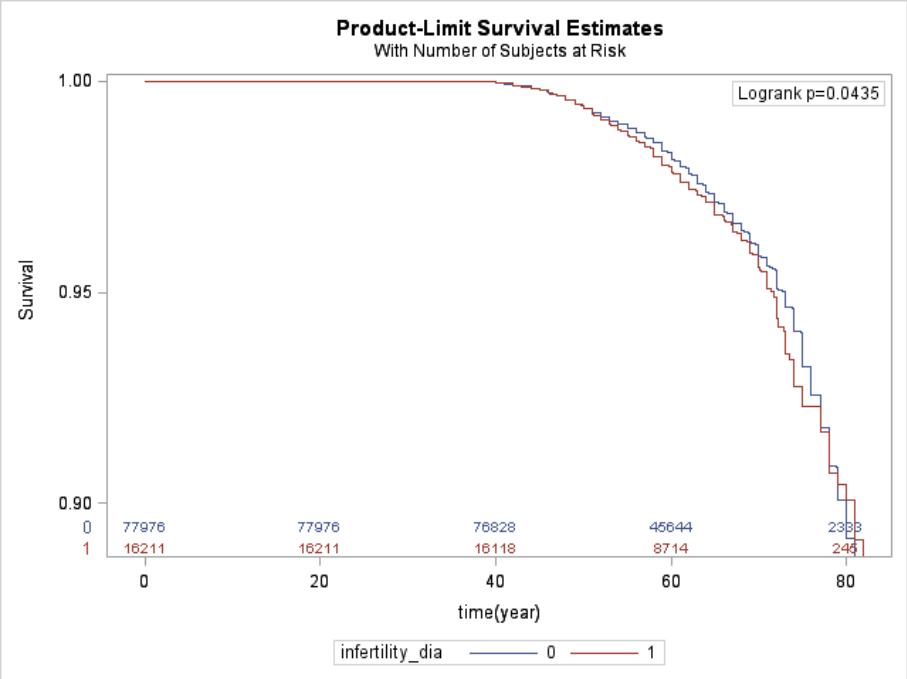


Figure S3. Kaplan-Meier survival curves comparing the rate of non-fatal stroke according to the history of miscarriage

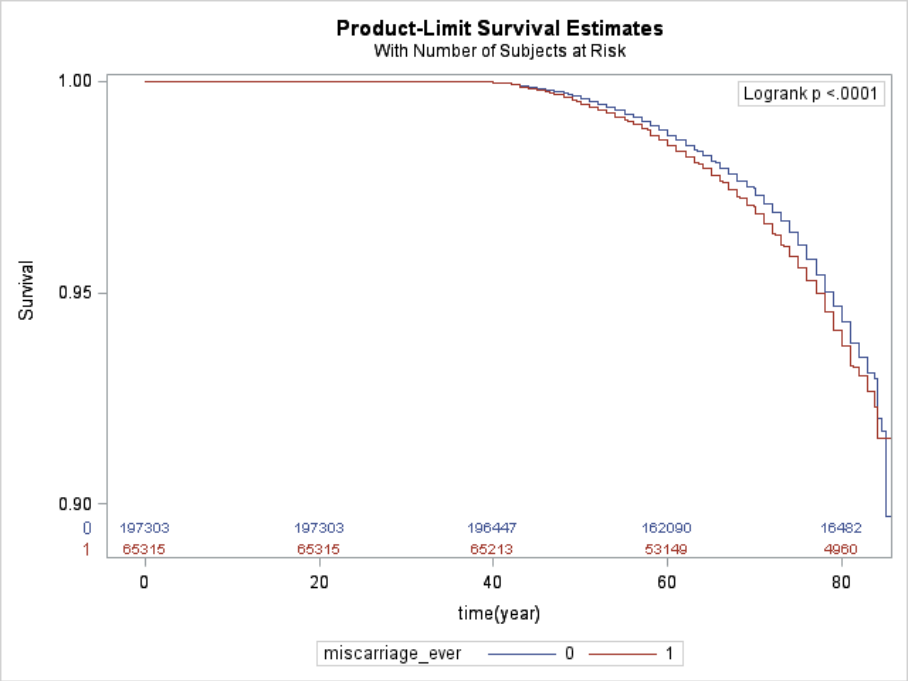



Figure S4. Kaplan-Meier survival curves comparing the rate of non-fatal stroke according to the number of miscarriages

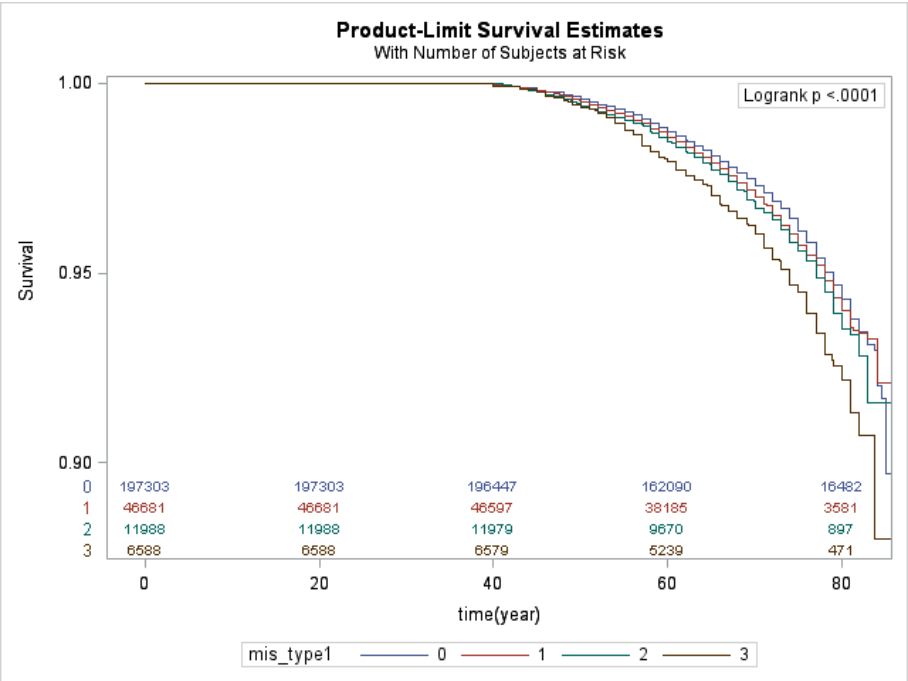


Figure S5. Kaplan-Meier survival curves comparing the rate of fatal stroke according to the history of miscarriage

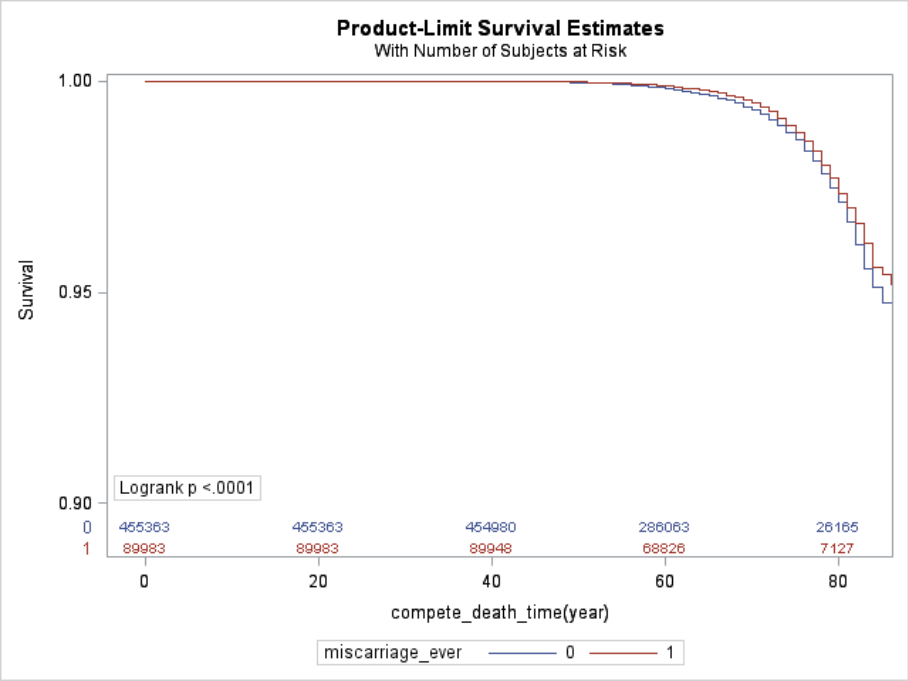



Figure S6. Kaplan-Meier survival curves comparing the rate of fatal stroke according to the number of miscarriages

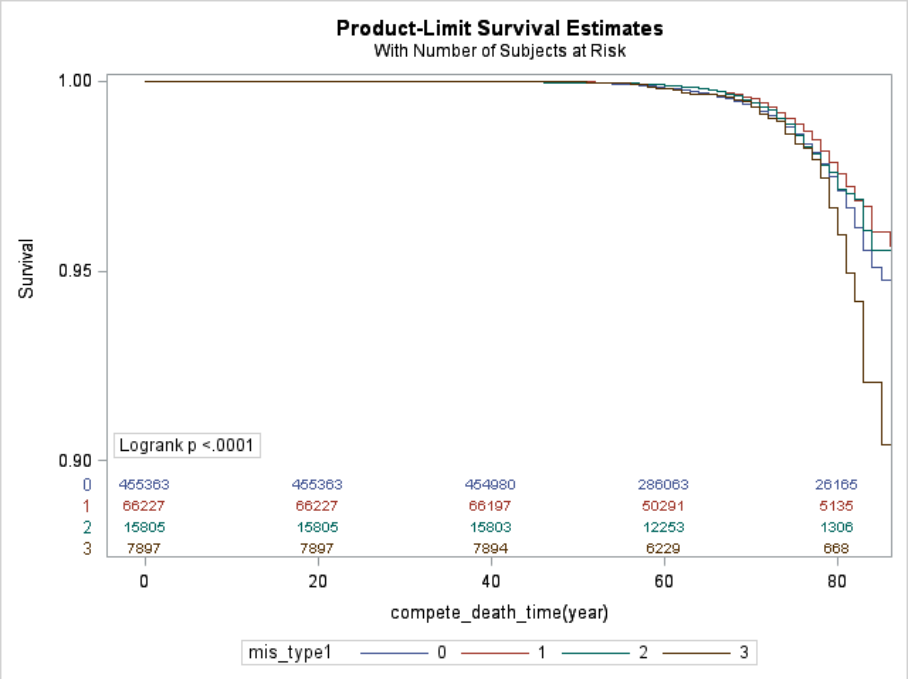


Figure S7. Kaplan-Meier survival curves comparing the rate of non-fatal stroke according to the history of stillbirth

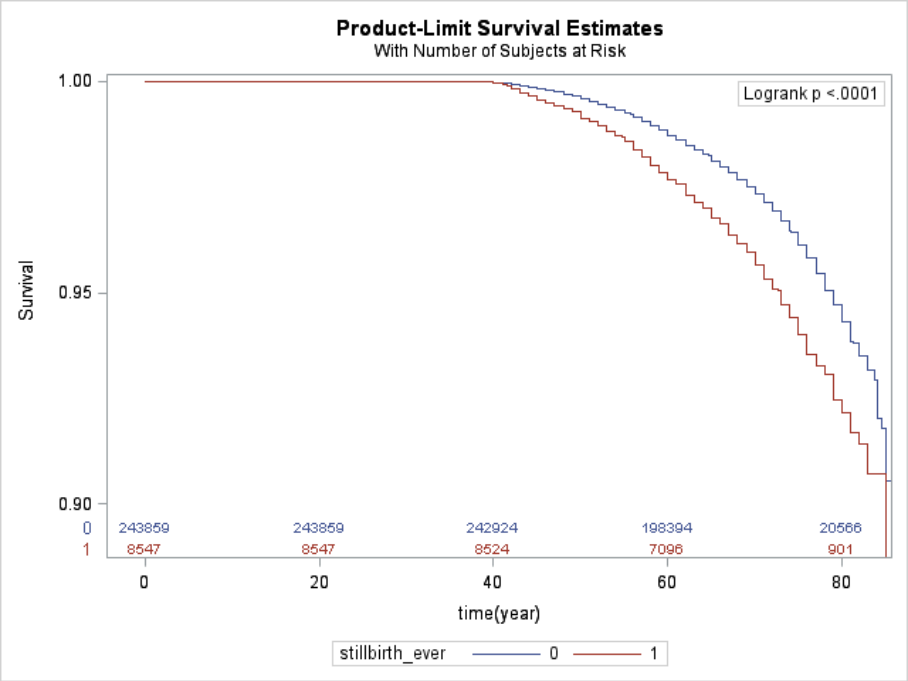



Figure S8. Kaplan-Meier survival curves comparing the rate of non-fatal stroke according to the number of stillbirths

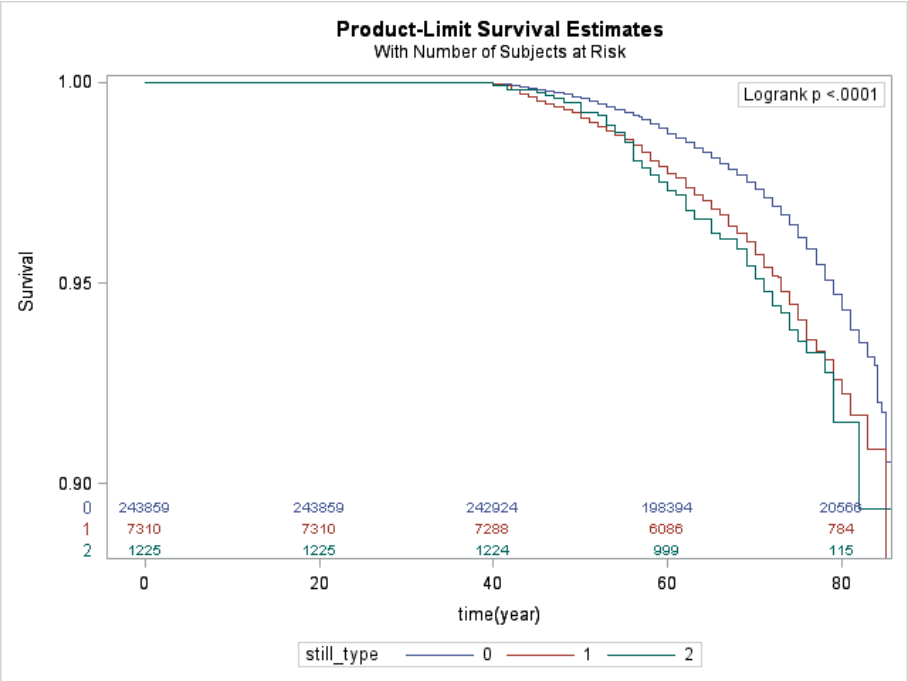


Figure S9. Kaplan-Meier survival curves comparing the rate of fatal stroke according to the history of stillbirth

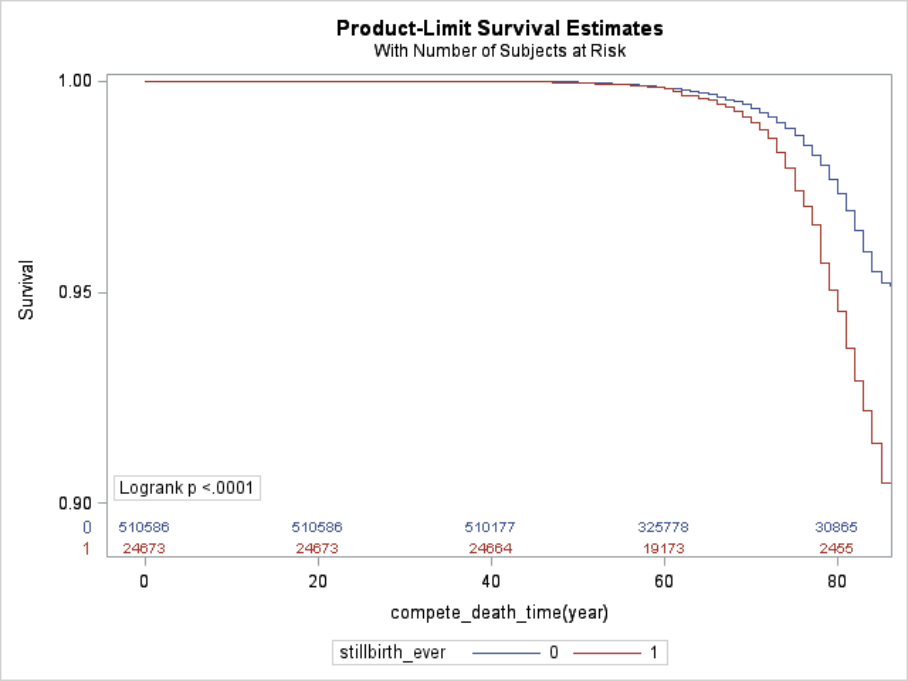
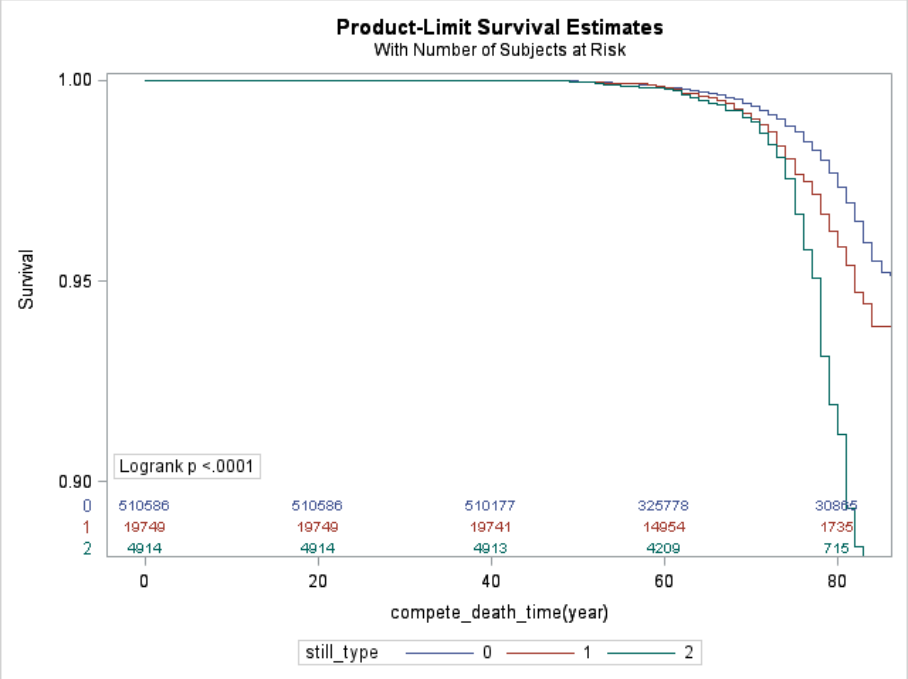



Figure S10. Kaplan-Meier survival curves comparing the rate of fatal stroke according to the number of stillbirths



Sensitivity analysis

Table S5. Sensitivity analysis for the association of infertility, miscarriage, and stillbirth with first non-fatal stroke, subtypes of first non-fatal stroke using hospital data

| | | Non-fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of infertility | Never | 61,741 | 2,038 | Ref. | 370 | Ref. | 888 | Ref. | 813 | Ref. |
| | Ever | 13,332 | 407 | 1.16 (1.12,1.21) | 85 | 1.13 (0.93,1.38) | 197 | 1.16 (1.08,1.24) | 137 | 1.20 (0.96,1.50) |
| History of miscarriage | Never | 184,178 | 5,535 | Ref. | 1,173 | Ref. | 2,699 | Ref. | 1,750 | Ref. |
| | Ever | 62,603 | 2,055 | 1.11 (1.08,1.15) | 398 | 1.04 (1.01,1.07) | 936 | 1.08 (1.03,1.13) | 750 | 1.20 (1.10,1.30) |
| Number of miscarriages | 0 | 184,178 | 5,535 | Ref. | 1,173 | Ref. | 2,699 | Ref. | 1,750 | Ref. |
| | 1 | 44,616 | 1,405 | 1.07 (1.05,1.10) | 280 | 1.03 (0.96,1.10) | 619 | 1.01 (0.96,1.06) | 530 | 1.20 (1.13,1.28) |
| | 2 | 11,528 | 382 | 1.12 (1.07,1.17) | 62 | 0.88 (0.73,1.06) | 191 | 1.21 (1.09,1.33) | 132 | 1.13 (0.97,1.32) |
| | ≥3 | 6,401 | 264 | 1.36 (1.28,1.44) | 56 | 1.41 (1.08,1.84) | 124 | 1.37 (1.23,1.53) | 86 | 1.27 (1.06,1.53) |
| History of stillbirth | Never | 229,283 | 6,754 | Ref. | 1,441 | Ref. | 3,337 | Ref. | 2,076 | Ref. |
| | Ever | 7,414 | 382 | 1.40 (1.32,1.48) | 65 | 1.15 (1.00,1.33) | 194 | 1.38 (1.35,1.41) | 126 | 1.54 (1.24,1.91) |
| Number of stillbirths | 0 | 229,283 | 6,754 | Ref. | 1,441 | Ref. | 3,337 | Ref. | 2,076 | Ref. |
| | 1 | 6,425 | 326 | 1.38 (1.30,1.46) | 59 | 1.21 (1.01,1.45) | 161 | 1.33 (1.25,1.40) | 109 | 1.53 (1.21,1.94) |
| | ≥2 | 978 | 56 | 1.58 (1.55,1.60) | 6 | 0.81 (0.59,1.11) | 33 | 1.77 (1.55,2.02) | 17 | 1.65 (1.41,1.93) |

Women from the studies, in which information on first non-fatal stroke were collected from questionnaires only, were excluded. Infertility: 19,114 women from Japan Nurses' Health Study (JNHS), MRC National Survey of Health and Development Study (NSHD), and Study of Women's Health Across the Nation (SWAN) were excluded. Miscarriage: 15,837 women from China Kadoorie Biobank, MRC National Survey of Health and Development Study (NSHD), and Study of Women's Health Across the Nation (SWAN) were excluded. Stillbirth: 15,709 women from China Kadoorie Biobank, MRC National Survey of Health and Development Study (NSHD), and Study of Women's Health Across the Nation (SWAN) were excluded. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no).

Table S6. Sensitivity analysis for the association between infertility and first non-fatal stroke, subtypes of first non-fatal stroke disaggregated by ascertainment of infertility

| | | Non-fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of infertility | Never | 49,302 | 1,131 | Ref. | 253 | Ref. | 543 | Ref. | 363 | Ref. |
| | Ever | 12,148 | 295 | 1.15 (1.08,1.22) | 71 | 1.16 (0.94,1.44) | 155 | 1.17 (1.10,1.26) | 80 | 1.13 (0.87,1.47) |

32,737 women from Japan Nurses' Health Study (JNHS), MRC National Survey of Health and Development Study (NSHD), and the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC) were excluded, in which infertility were additionally identified through unsuccessfully trying to be pregnant for 2 years or more, or infertility consult. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no).

Table S7. Sensitivity analysis for the association of infertility, miscarriage, and stillbirth with first non-fatal stroke, subtypes of first non-fatal stroke with redefined baseline of NSHD

| | | Non-fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of infertility | Never | 78,203 | 2,293 | Ref. | 408 | Ref. | 1,020 | Ref. | 905 | Ref. |
| | Ever | 16,234 | 453 | 1.14 (1.08,1.20) | 91 | 1.13 (0.94,1.36) | 217 | 1.15 (1.07,1.23) | 158 | 1.15 (0.93,1.42) |
| History of miscarriage | Never | 197,361 | 5,812 | Ref. | 1,173 | Ref. | 2,699 | Ref. | 2,027 | Ref. |
| | Ever | 65,370 | 2,125 | 1.11 (1.07,1.15) | 398 | 1.04 (1.01,1.07) | 936 | 1.08 (1.03,1.13) | 820 | 1.18 (1.09,1.27) |
| Number of miscarriages | 0 | 197,361 | 5,812 | Ref. | 1,173 | Ref. | 2,699 | Ref. | 2,027 | Ref. |
| | 1 | 46,720 | 1,455 | 1.07 (1.04,1.10) | 280 | 1.03 (0.96,1.10) | 619 | 1.01 (0.96,1.06) | 580 | 1.18 (1.10,1.25) |
| | 2 | 11,996 | 395 | 1.12 (1.07,1.17) | 62 | 0.88 (0.73,1.06) | 191 | 1.21 (1.09,1.33) | 145 | 1.12 (0.97,1.29) |
| | ≥3 | 6,596 | 271 | 1.36 (1.28,1.45) | 56 | 1.41 (1.08,1.84) | 124 | 1.37 (1.23,1.53) | 93 | 1.27 (1.06,1.53) |
| History of stillbirth | Never | 243,942 | 7,070 | Ref. | 1,441 | Ref. | 3,337 | Ref. | 2,392 | Ref. |
| | Ever | 8,552 | 412 | 1.32 (1.11,1.58) | 65 | 1.15 (1.00,1.33) | 194 | 1.38 (1.35,1.41) | 156 | 1.30 (0.95,1.78) |
| Number of stillbirths | 0 | 243,942 | 7,070 | Ref. | 1,441 | Ref. | 3,337 | Ref. | 2,392 | Ref. |
| | 1 | 7,315 | 350 | 1.33 (1.16,1.52) | 59 | 1.21 (1.01,1.45) | 161 | 1.33 (1.25,1.40) | 133 | 1.35 (1.03,1.78) |
| | ≥2 | 1,225 | 62 | 1.31 (0.85,2.02) | 6 | 0.81 (0.59,1.11) | 33 | 1.77 (1.54,2.02) | 23 | 1.08 (0.57,2.03) |

After redefining the baseline of MRC National Survey of Health and Development Study (NSHD), 250, 113, and 88 women were further included in the analysis of infertility, miscarriage, and stillbirth, respectively. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no).

Table S8. Sensitivity analysis for the association of infertility, miscarriage, and stillbirth with first non-fatal stroke, subtypes of first non-fatal stroke with additional adjustment of oral contraceptive pill and hormone replacement therapy

| | | Non-fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of infertility | No | 25,796 | 1,299 | Ref. | 163 | Ref. | 509 | Ref. | 634 | Ref. |
| | Yes | 5,037 | 231 | 1.15 (1.05,1.27) | 35 | 1.26 (0.84,1.89) | 96 | 1.16 (1.09,1.22) | 102 | 1.10 (0.81,1.50) |
| History of miscarriage | Never | 179,620 | 5,309 | Ref. | 1,125 | Ref. | 2,620 | Ref. | 1,642 | Ref. |
| | Ever | 59,401 | 1,860 | 1.10 (1.06,1.14) | 364 | 1.03 (1.01,1.05) | 881 | 1.08 (1.03,1.12) | 638 | 1.16 (1.09,1.24) |
| Number of miscarriages | 0 | 179,620 | 5,309 | Ref. | 1,125 | Ref. | 2,620 | Ref. | 1,642 | Ref. |
| | 1 | 42,513 | 1,283 | 1.06 (1.03,1.09) | 261 | 1.03 (0.97,1.10) | 589 | 1.01 (0.97,1.05) | 453 | 1.17 (1.12,1.22) |
| | 2 | 10,888 | 338 | 1.09 (1.04,1.13) | 54 | 0.84 (0.73,0.96) | 176 | 1.18 (1.08,1.29) | 111 | 1.10 (0.94,1.29) |
| | ≥3 | 5,944 | 235 | 1.35 (1.27,1.45) | 49 | 1.38 (1.04,1.83) | 114 | 1.36 (1.22,1.52) | 72 | 1.27 (1.05,1.53) |
| History of stillbirth | Never | 231,641 | 6,800 | Ref. | 1,429 | Ref. | 3,315 | Ref. | 2,154 | Ref. |
| | Ever | 7,448 | 379 | 1.39 (1.31,1.46) | 65 | 1.18 (1.01,1.37) | 189 | 1.36 (1.31,1.41) | 128 | 1.51 (1.22,1.86) |
| Number of stillbirths | 0 | 231,641 | 6,800 | Ref. | 1,429 | Ref. | 3,315 | Ref. | 2,154 | Ref. |
| | 1 | 6,469 | 324 | 1.37 (1.30,1.44) | 59 | 1.23 (1.02,1.48) | 157 | 1.30 (1.22,1.40) | 111 | 1.50 (1.19,1.90) |
| | ≥2 | 967 | 55 | 1.56 (1.51,1.61) | 6 | 0.83 (0.61,1.14) | 32 | 1.74 (1.56,1.94) | 17 | 1.59 (1.35,1.88) |

Women with missing value on oral contraceptive pill or hormone replacement therapy were excluded. Infertility: 63,354 women were excluded, who were from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort,

the Netherlands (Prospect-EPIC), Japan Nurses' Health Study (JNHS), MRC National Survey of Health and Development Study (NSHD), Study of Women's Health Across the Nation (SWAN), or Women's Lifestyle and Health Study (WLH). Miscarriage: 23,597 women were excluded, who were from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), MRC National Survey of Health and Development Study (NSHD), Study of Women's Health Across the Nation (SWAN), or UK Biobank. Stillbirth: 13,317 women were excluded, who were from China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), MRC National Survey of Health and Development Study (NSHD), Study of Women's Health Across the Nation (SWAN), or UK Biobank. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no).

Table S9. Sensitivity analysis for the association of miscarriage and stillbirth with fatal stroke, subtypes of fatal stroke with additional adjustment of oral contraceptive pill and hormone replacement therapy

| | | Fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | |
|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of miscarriage | Never | 176,428 | 627 | Ref. | 323 | Ref. | 327 | Ref. |
| | Ever | 58,090 | 200 | 1.01 (0.84,1.22) | 77 | 0.76 (0.67,0.86) | 129 | 1.25 (1.05,1.49) |
| Number of miscarriages | 0 | 176,428 | 627 | Ref. | 323 | Ref. | 327 | Ref. |
| | 1 | 41,583 | 126 | 0.90 (0.73,1.10) | 48 | 0.66 (0.56,0.79) | 83 | 1.14 (0.93,1.39) |
| | 2 | 10,645 | 40 | 1.10 (0.80,1.50) | 16 | 0.86 (0.57,1.30) | 24 | 1.26 (0.96,1.64) |
| | ≥3 | 5,810 | 34 | 1.71 (1.18,2.48) | 13 | 1.27 (0.57,2.80) | 22 | 2.10 (1.72,2.55) |
| History of stillbirth | Never | 227,366 | 787 | Ref. | 385 | Ref. | 429 | Ref. |
| | Ever | 7,300 | 42 | 1.22 (0.97,1.53) | 16 | 0.99 (0.89,1.10) | 28 | 1.43 (1.03,1.99) |
| Number of stillbirths | 0 | 227,366 | 787 | Ref. | 385 | Ref. | 429 | Ref. |
| | 1 | 6,321 | 32 | 1.07 (0.93,1.24) | 15 | 1.07 (0.95,1.21) | 19 | 1.13 (0.87,1.45) |
| | ≥2 | 969 | 10 | 2.23 (1.21,4.10) | <5 | 0.47 (0.06,4.08) | 9 | 3.49 (2.19,5.57) |

Women with missing value on oral contraceptive pill or hormone replacement therapy were excluded. Miscarriage: 310,828 women were excluded, who were from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), or UK Biobank. Stillbirth: 300,593 women were excluded, who were from China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), or UK Biobank. None of the

included fatal stroke cases were identified as unspecified stroke. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no).

Table S10. Sensitivity analysis for the association of infertility, miscarriage, and stillbirth with first non-fatal stroke, subtypes of first non-fatal stroke among women without diabetes mellitus

| | | Non-fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of infertility | No | 76,425 | 2,139 | Ref. | 399 | Ref. | 939 | Ref. | 840 | Ref. |
| | Yes | 15,843 | 424 | 1.15 (1.10,1.20) | 87 | 1.11 (0.96,1.29) | 206 | 1.18 (1.12,1.26) | 144 | 1.15 (0.90,1.46) |
| History of miscarriage | Never | 190,152 | 5,267 | Ref. | 1,116 | Ref. | 2,404 | Ref. | 1,827 | Ref. |
| | Ever | 62,680 | 1,894 | 1.09 (1.05,1.14) | 382 | 1.06 (1.01,1.11) | 826 | 1.08 (1.03,1.14) | 714 | 1.13 (1.03,1.25) |
| Number of miscarriages | 0 | 190,152 | 5,267 | Ref. | 1,116 | Ref. | 2,404 | Ref. | 1,827 | Ref. |
| | 1 | 44,953 | 1,312 | 1.06 (1.03,1.10) | 269 | 1.04 (0.95,1.14) | 551 | 1.01 (0.96,1.07) | 515 | 1.15 (1.08,1.23) |
| | 2 | 11,465 | 346 | 1.08 (1.02,1.15) | 60 | 0.90 (0.74,1.10) | 167 | 1.20 (1.11,1.30) | 122 | 1.04 (0.86,1.26) |
| | ≥3 | 6,205 | 232 | 1.33 (1.25,1.41) | 53 | 1.45 (1.18,1.77) | 106 | 1.38 (1.25,1.53) | 75 | 1.16 (0.88,1.55) |
| History of stillbirth | Never | 234,959 | 6,382 | Ref. | 1,372 | Ref. | 2,972 | Ref. | 2,131 | Ref. |
| | Ever | 7,957 | 353 | 1.32 (1.14,1.52) | 64 | 1.24 (1.16,1.31) | 163 | 1.37 (1.33,1.41) | 129 | 1.28 (0.93,1.75) |
| Number of stillbirths | 0 | 234,959 | 6,382 | Ref. | 1,372 | Ref. | 2,972 | Ref. | 2,131 | Ref. |
| | 1 | 6,830 | 303 | 1.33 (1.20,1.47) | 58 | 1.29 (1.17,1.41) | 136 | 1.32 (1.25,1.39) | 112 | 1.35 (0.99,1.83) |
| | ≥2 | 1,117 | 50 | 1.26 (0.86,1.85) | 6 | 0.90 (0.60,1.36) | 27 | 1.79 (1.34,2.38) | 17 | 0.98 (0.54,1.76) |

Women with diabetes or having missing value on diabetes were excluded. Infertility:1,919 women were excluded, who were from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands

(Prospect-EPIC), Japan Nurses' Health Study (JNHS), MRC National Survey of Health and Development Study (NSHD), Study of Women's Health Across the Nation (SWAN), or Women's Lifestyle and Health Study (WLH). Miscarriage: 9,786 women were excluded, who were from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), MRC National Survey of Health and Development Study (NSHD), Study of Women's Health Across the Nation (SWAN), or UK Biobank. Stillbirth: 9,490 women were excluded, who were from China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), MRC National Survey of Health and Development Study (NSHD), Study of Women's Health Across the Nation (SWAN), or UK Biobank. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no).

Table S11. Sensitivity analysis for the association of miscarriage and stillbirth with fatal stroke, subtypes of fatal stroke among women without diabetes mellitus

| | | Non-fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of miscarriage | Never | 434,548 | 2,772 | Ref. | 1,727 | Ref. | 976 | Ref. | 123 | Ref. |
| | Ever | 85,785 | 616 | 1.18 (1.04,1.33) | 380 | 1.22 (0.95,1.57) | 231 | 1.13 (0.99,1.29) | 17 | - |
| Number of miscarriages | 0 | 434,548 | 2,772 | Ref. | 1,727 | Ref. | 976 | Ref. | 123 | Ref. |
| | 1 | 63,270 | 412 | 1.08 (0.93,1.25) | 252 | 1.10 (0.84,1.44) | 155 | 1.05 (0.91,1.21) | 12 | - |
| | 2 | 15,041 | 124 | 1.30 (1.08,1.57) | 79 | 1.41 (1.06,1.87) | 44 | 1.17 (0.93,1.46) | <5 | - |
| | ≥3 | 7,421 | 80 | 1.77 (1.49,2.11) | 49 | 1.86 (1.40,2.47) | 32 | 1.76 (1.21,2.55) | <5 | - |
| History of stillbirth | Never | 487,563 | 2,973 | Ref. | 1,821 | Ref. | 1,086 | Ref. | 124 | Ref. |
| | Ever | 22,977 | 380 | 1.04 (0.97,1.11) | 262 | 1.16 (1.08,1.25) | 109 | 0.87 (0.69,1.09) | 16 | - |
| Number of stillbirths | 0 | 487,563 | 2,973 | Ref. | 1,821 | Ref. | 1,086 | Ref. | 124 | Ref. |
| | 1 | 18,420 | 234 | 0.96 (0.89,1.04) | 158 | 1.05 (0.97,1.14) | 68 | 0.81 (0.67,0.99) | 13 | - |
| | ≥2 | 4,549 | 146 | 1.19 (1.08,1.30) | 104 | 1.38 (1.30,1.47) | 41 | 0.99 (0.71,1.37) | <5 | - |

Women with diabetes or having missing value on diabetes were excluded. Miscarriage: 25,013 women were excluded, who were from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), or UK Biobank. Stillbirth: 24,719 women with diabetes or having missing value on diabetes were excluded, who were from China Kadoorie Biobank, the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), or UK Biobank.

HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no).

Table S12. Sensitivity analysis for the association of infertility, miscarriage, and stillbirth with combined outcome (first non-fatal and fatal stroke)

| | | Non-fatal and fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of infertility | Never | 36,052 | 1,621 | Ref. | 239 | Ref. | 625 | Ref. | 779 | Ref. |
| | Ever | 5,341 | 238 | 1.11 (0.96,1.28) | 33 | 1.03 (0.81,1.30) | 81 | 1.04 (0.95,1.14) | 130 | 1.22 (0.97,1.52) |
| History of miscarriage | Never | 184,178 | 5,670 | Ref. | 1,236 | Ref. | 2,774 | Ref. | 1,750 | Ref. |
| | Ever | 62,603 | 2,099 | 1.11 (1.08,1.14) | 411 | 1.01 (0.99,1.03) | 967 | 1.08 (1.04,1.13) | 750 | 1.20 (1.10,1.30) |
| Number of miscarriages | 0 | 184,178 | 5,670 | Ref. | 1,236 | Ref. | 2,774 | Ref. | 1,750 | Ref. |
| | 1 | 44,616 | 1,432 | 1.07 (1.04,1.10) | 287 | 1.00 (0.93,1.07) | 639 | 1.01 (0.97,1.05) | 530 | 1.20 (1.13,1.28) |
| | 2 | 11,528 | 389 | 1.11 (1.07,1.15) | 65 | 0.87 (0.73,1.03) | 195 | 1.19 (1.07,1.31) | 132 | 1.13 (0.97,1.32) |
| | ≥3 | 6,401 | 274 | 1.36 (1.19,1.56) | 59 | 1.39 (1.05,1.84) | 131 | 1.39 (1.28,1.52) | 86 | 1.26 (1.05,1.52) |
| History of stillbirth | Never | 229,283 | 6,918 | Ref. | 1,507 | Ref. | 3,436 | Ref. | 2,076 | Ref. |
| | Ever | 7,414 | 390 | 1.39 (1.28,1.51) | 69 | 1.16 (1.01,1.34) | 200 | 1.38 (1.33,1.42) | 126 | 1.54 (1.24,1.91) |
| Number of stillbirths | 0 | 229,283 | 6,918 | Ref. | 1,507 | Ref. | 3,436 | Ref. | 2,076 | Ref. |
| | 1 | 6,425 | 332 | 1.37 (1.22,1.53) | 62 | 1.21 (1.01,1.45) | 166 | 1.32 (1.24,1.41) | 109 | 1.53 (1.21,1.94) |
| | ≥2 | 978 | 58 | 1.58 (1.39,1.79) | 7 | 0.89 (0.64,1.23) | 34 | 1.76 (1.53,2.02) | 17 | 1.64 (1.41,1.90) |

Infertility: 41,393 women from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC), Japan Nurses' Health Study (JNHS) were included. Miscarriage: 246,781 women from Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWH-mid), the Utrecht contribution to the European Prospective Investigation into Cancer and

Nutrition cohort, the Netherlands (Prospect-EPIC), and UK Biobank. Stillbirth: 236,697 women from the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands (Prospect-EPIC) and UK Biobank were included. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no).

Table S13. Multiple imputation for the association of infertility, miscarriage, and stillbirth with first non-fatal, subtypes of first non-fatal stroke

| | | Non-fatal and fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of infertility | Never | 796,760 | 23,600 | Ref. | 4,190 | Ref. | 10,390 | Ref. | 9,420 | Ref. |
| | Ever | 165,110 | 4,660 | 1.14 (1.08,1.21) | 920 | 1.11 (0.92,1.35) | 2,220 | 1.15 (1.06,1.25) | 1,650 | 1.15 (0.92,1.43) |
| History of miscarriage | Never | 2,021,890 | 59,700 | Ref. | 12,060 | Ref. | 27,810 | Ref. | 20,720 | Ref. |
| | Ever | 670,370 | 21,970 | 1.11 (1.07,1.15) | 4,100 | 1.04 (1.02,1.06) | 9,670 | 1.08 (1.04,1.13) | 8,520 | 1.19 (1.10,1.28) |
| Number of miscarriages | 0 | 2,021,890 | 59,700 | Ref. | 12,060 | Ref. | 27,810 | Ref. | 20,720 | Ref. |
| | 1 | 478,880 | 15,000 | 1.07 (1.04,1.10) | 2,880 | 1.03 (0.97,1.09) | 6,370 | 1.01 (0.96,1.06) | 6,000 | 1.18 (1.12,1.25) |
| | 2 | 122,790 | 4,130 | 1.14 (1.08,1.19) | 660 | 0.91 (0.78,1.07) | 1,980 | 1.22 (1.11,1.33) | 1,540 | 1.16 (1.02,1.32) |
| | ≥3 | 68,110 | 2,800 | 1.35 (1.26,1.44) | 560 | 1.36 (1.05,1.77) | 1,300 | 1.38 (1.22,1.57) | 960 | 1.26 (1.03,1.54) |
| History of stillbirth | Never | 2,496,240 | 72,510 | Ref. | 14,810 | Ref. | 34,380 | Ref. | 24,370 | Ref. |
| | Ever | 87,930 | 4,260 | 1.32 (1.10,1.58) | 680 | 1.16 (0.98,1.37) | 1,990 | 1.37 (1.34,1.39) | 1,620 | 1.33 (0.97,1.83) |
| Number of stillbirths | 0 | 2,496,240 | 72,510 | Ref. | 14,810 | Ref. | 34,380 | Ref. | 24,370 | Ref. |
| | 1 | 75,170 | 3,610 | 1.33 (1.16,1.52) | 600 | 1.19 (0.96,1.46) | 1,660 | 1.32 (1.28,1.36) | 1,380 | 1.38 (1.04,1.83) |
| | ≥2 | 12,640 | 650 | 1.31 (0.86,2.01) | 80 | 1.03 (0.84,1.26) | 330 | 1.68 (1.49,1.91) | 240 | 1.11 (0.58,2.13) |

Education level, body-mass index, smoking status, ethnicity, hypertension, diabetes mellitus and study were included in the imputation procedure. Ten imputed datasets were created. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no)

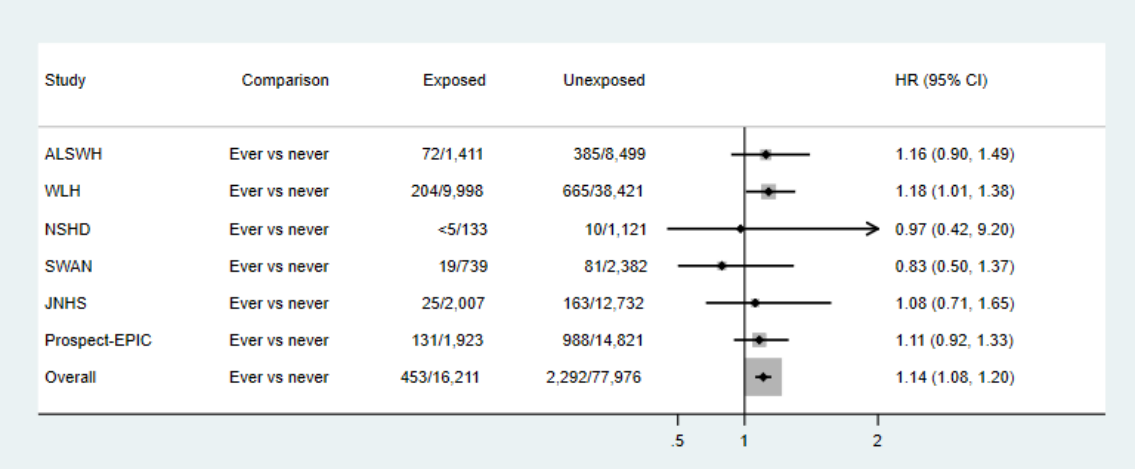
Table S14. Multiple imputation for the association of miscarriage and stillbirth with fatal, subtypes of fatal stroke

| | | Non-fatal and fatal stroke | | | Haemorrhagic stroke | | Ischaemic stroke | | Unspecific stroke | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Comparison | Sample size | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) | No. of events | HR (95% CI) |
| History of miscarriage | Never | 4,600,380 | 32,780 | Ref. | 19,740 | Ref. | 12,230 | Ref. | 1,420 | Ref. |
| | Ever | 916,050 | 7,150 | 1.17 (1.05,1.29) | 4,310 | 1.22 (0.97,1.53) | 2,810 | 1.12 (0.98,1.28) | 190 | - |
| Number of miscarriages | 0 | 4,600,380 | 32,780 | Ref. | 19,740 | Ref. | 12,230 | Ref. | 1,420 | Ref. |
| | 1 | 673,620 | 4,810 | 1.07 (0.95,1.21) | 2,890 | 1.11 (0.89,1.40) | 1,900 | 1.04 (0.91,1.19) | 130 | - |
| | 2 | 160,780 | 1,380 | 1.25 (1.06,1.49) | 870 | 1.39 (1.05,1.83) | 500 | 1.09 (0.84,1.42) | 30 | - |
| | ≥3 | 81,100 | 960 | 1.78 (1.54,2.07) | 550 | 1.82 (1.35,2.45) | 410 | 1.79 (1.38,2.31) | 30 | - |
| History of stillbirth | Never | 5,160,800 | 35,020 | Ref. | 20,760 | Ref. | 13,540 | Ref. | 1,410 | Ref. |
| | Ever | 249,120 | 4,520 | 1.06 (1.00,1.13) | 3,020 | 1.19 (1.08,1.30) | 1,370 | 0.89 (0.71,1.11) | 200 | - |
| Number of stillbirths | 0 | 5,160,800 | 35,020 | Ref. | 20,760 | Ref. | 13,540 | Ref. | 1,410 | Ref. |
| | 1 | 199,500 | 2,760 | 0.97 (0.91,1.03) | 1,830 | 1.07 (0.97,1.19) | 840 | 0.81 (0.67,0.97) | 140 | - |
| | ≥2 | 49,520 | 1,760 | 1.26 (1.15,1.38) | 1,190 | 1.43 (1.34,1.53) | 530 | 1.06 (0.74,1.51) | 60 | - |

Education level, body-mass index, smoking status, ethnicity, hypertension, diabetes mellitus and study were included in the imputation procedure. Ten imputed datasets were created. HRs were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (≤10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no)

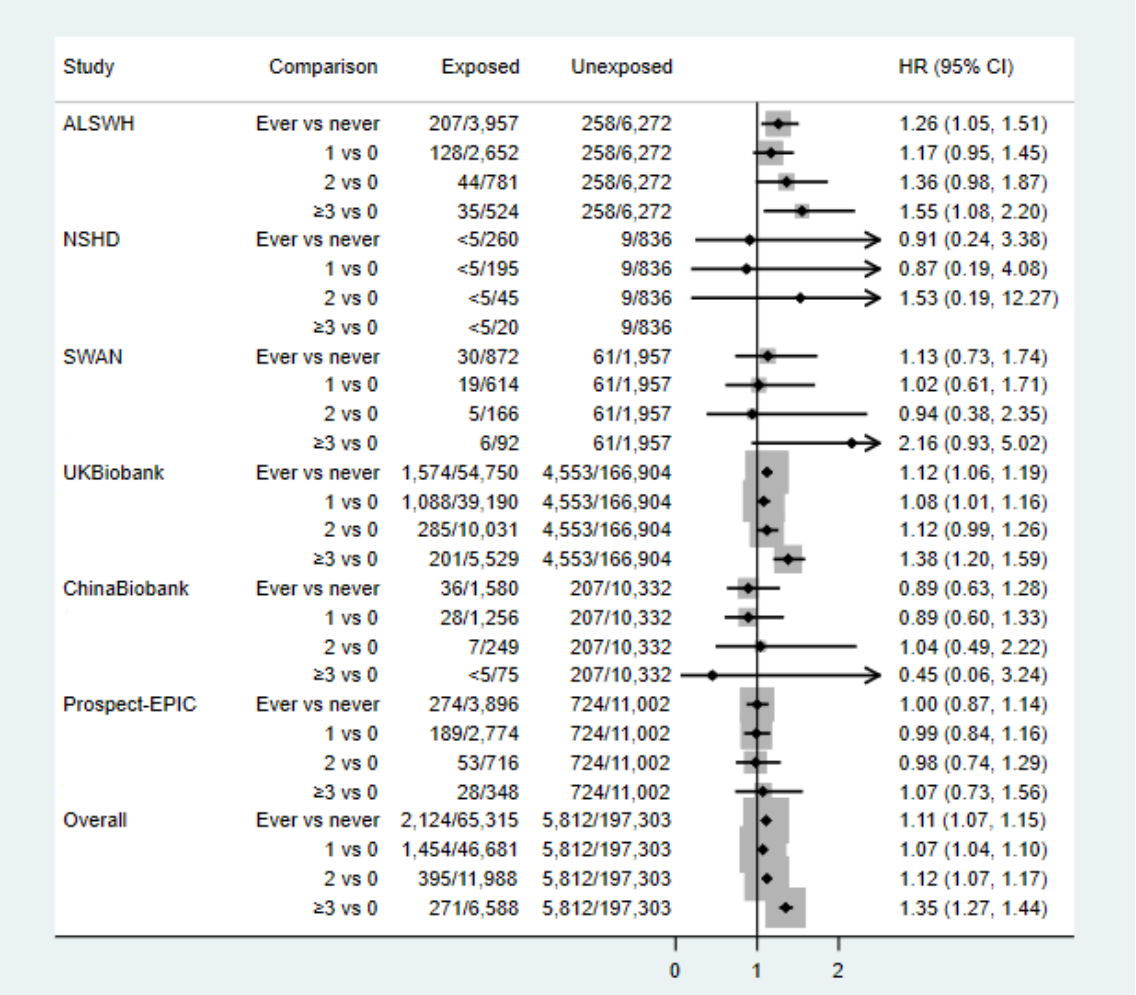
Effect size in single study

Figure S11. Association between infertility and first non-fatal stroke in each study



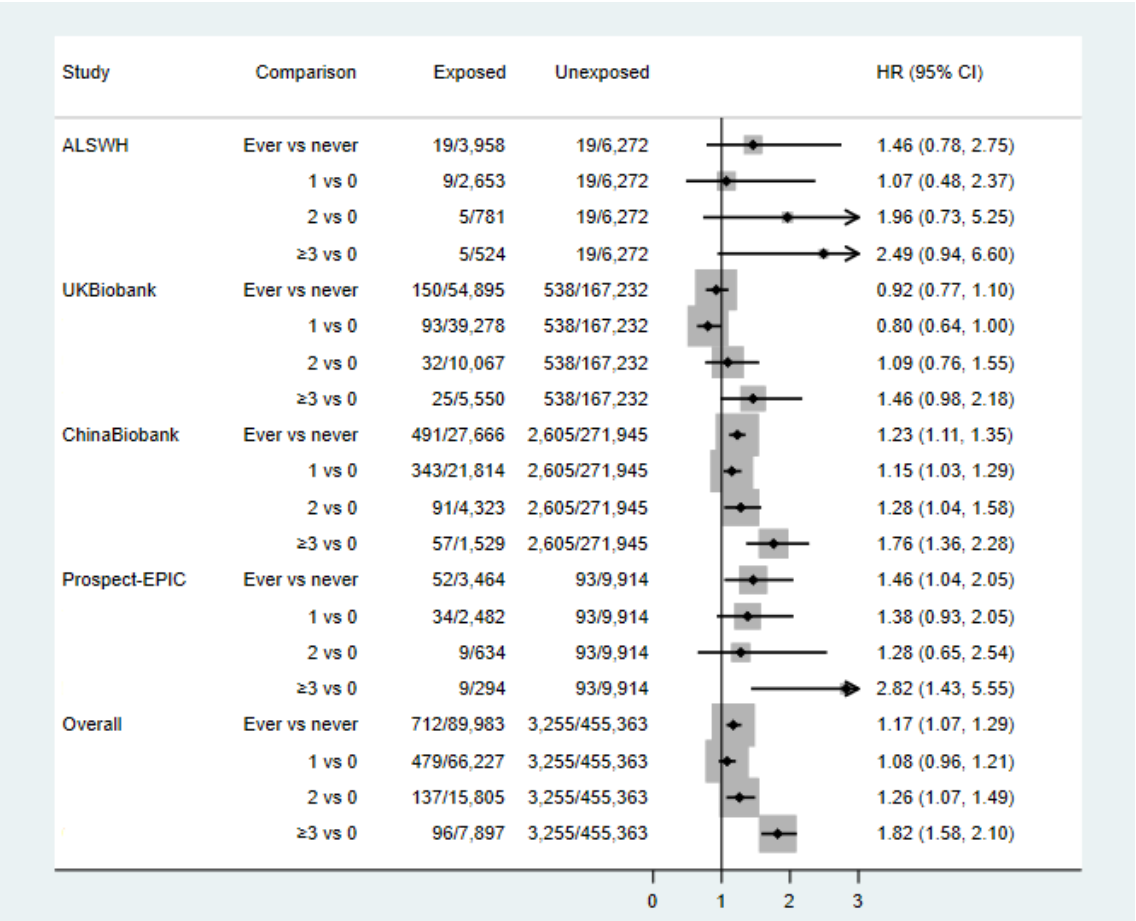

ALSWH: Australian Longitudinal Study on Women's Health 1946-51 cohort; JNHS: Japan Nurses' Health Study; NSHD: MRC National Survey of Health and Development Study; Prospect-EPIC: the Prospect-European Prospective Investigation into Cancer and Nutrition cohort coordinated in the Netherlands; SWAN: Study of Women's Health Across the Nation; WLH: Women's Lifestyle and Health Study. Heterogeneity: $I^2$=0.0%, p=0.82. HR in single study was adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), and education level (≤10, 11-12, and >12 years), and stratified by hypertension (yes and no). Overall HRs were additionally adjusted for study.

Figure S12. Association between miscarriage and first non-fatal stroke in each study



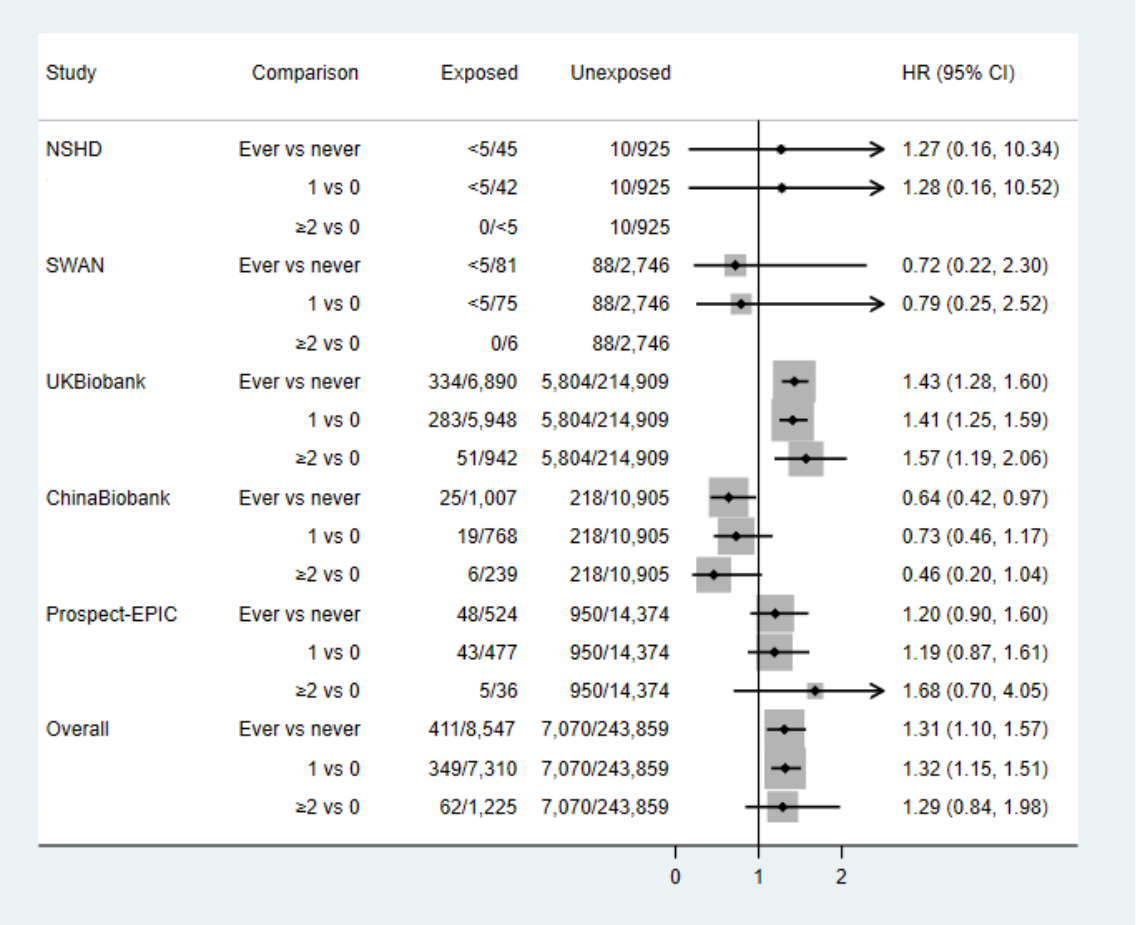

ALSWH: Australian Longitudinal Study on Women's Health 1946-51 cohort; NSHD: MRC National Survey of Health and Development Study; SWAN: Study of Women's Health Across the Nation; Prospect-EPIC: the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands. Heterogeneity: Ever vs never: $I^2$=16.7%, p=0.31; 1 vs 0: $I^2$=0.0%, p=0.76; 2 vs 0: $I^2$=0.0%, p=0.81; ≥3 vs 0: $I^2$=3.6%, p=0.39. HR in single study was adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), and education level (≤10, 11-12, and >12 years), and stratified by hypertension (yes and no). Overall HRs were additionally adjusted for study.

Figure S13. Association between miscarriage and fatal stroke in each study



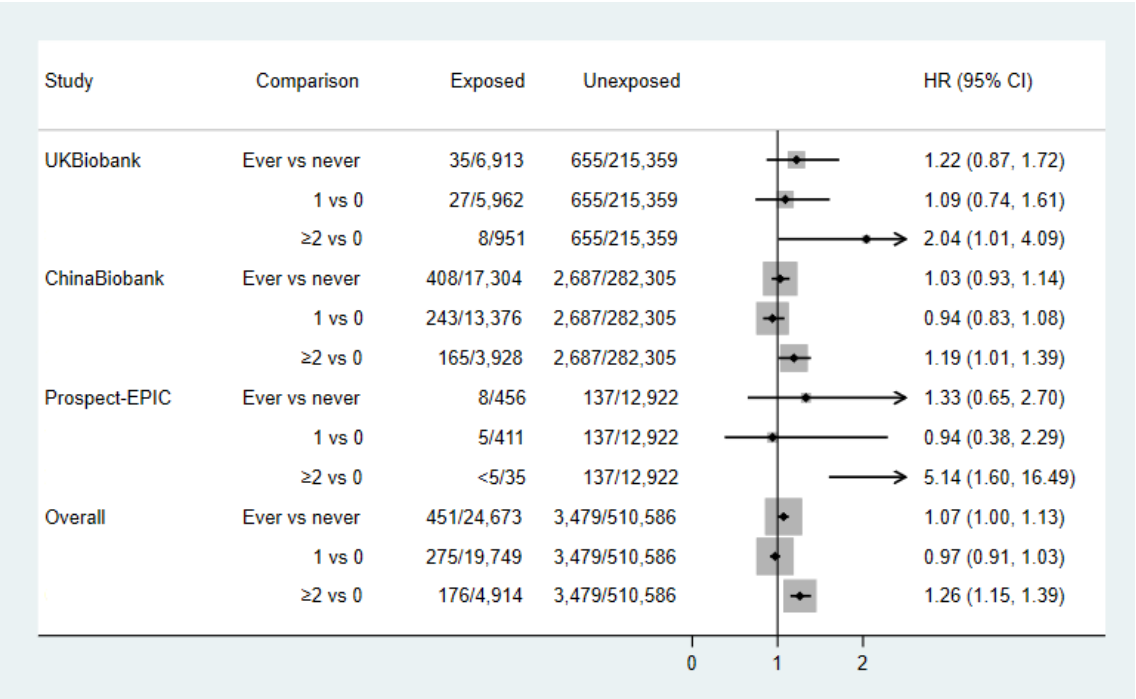

ALSWH: Australian Longitudinal Study on Women's Health 1946-51 cohort; Prospect-EPIC: the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands. Heterogeneity: Ever vs never: $I^2$=72.6%, p=0.01; 1 vs 0: $I^2$=72.7%, p=0.01; 2 vs 0: $I^2$=0.0%, p=0.80; ≥3 vs 0: $I^2$=0.0%, p=0.55. HR in single study was adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), and education level (≤10, 11-12, and >12 years), and stratified by hypertension (yes and no). Overall HRs were additionally adjusted for study.

Figure S14. Association between stillbirth and first non-fatal stroke in each study




NSHD: MRC National Survey of Health and Development Study; SWAN: Study of Women's Health Across the Nation; Prospect-EPIC: the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands. Heterogeneity: ever vs never: $I^2$=83.7%, p<.001; 1 vs 0: $I^2$=67.6%, p=0.02; ≥2 vs 0: $I^2$=85.3%, p<.001. HR in single study was adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), and education level (≤10, 11-12, and >12 years), and stratified by hypertension (yes and no). Overall HRs were additionally adjusted for study.

Figure S15. Association between stillbirth and fatal stroke in each study




Prospect-EPIC: the Utrecht contribution to the European Prospective Investigation into Cancer and Nutrition cohort, the Netherlands. Heterogeneity: ever vs never: $I^2$=0.0%, p=0.60, 1 vs 0: $I^2$=0.0%, p=0.81; ≥2 vs 0: $I^2$=10.2%, p=0.33. HR in single study was adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), and education level (≤10, 11-12, and >12 years), and stratified by hypertension (yes and no). Overall HRs were additionally adjusted for study.

Schoenfeld residuals

Table S15. Correlation between the Schoenfeld residuals and survival time

| | | | Exposure (β, p) | | | Education level (β, p) | | | Body-mass index (β, p) | | Smoking (β, p) | Race (β, p) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Stroke | Ever | 1 | 2/≥2 | ≥3 | <=10 | 11-12 | Underweight | Overweight | Obese | Current | Asian | Others |
| Infertility | Non-fatal | -0.00462 | | | | -0.01739 | -0.013 | 0.01104 | 0.01807 | -0.03713 | 0.00799 | -0.00037 | -0.02419 |
| | (n=2,745) | 0.81 | | | | 0.36 | 0.50 | 0.56 | 0.34 | 0.05 | 0.68 | 0.98 | 0.21 |
| Miscarriage | Non-fatal | -0.02868 | | | | -0.02257 | 0.00407 | -0.00028 | 0.0181 | -0.06761 | -0.00881 | 0.0156 | -0.03675 |
| | (n=7,936) | 0.01 | | | | 0.04 | 0.72 | 0.98 | 0.11 | <.001 | 0.43 | 0.16 | 0.001 |
| | | | -0.01807 | -0.01568 | -0.0118 | -0.02276 | 0.00458 | -0.0001 | 0.01799 | -0.068 | -0.00869 | 0.01559 | -0.03673 |
| | | | 0.11 | 0.16 | 0.29 | 0.04 | 0.68 | 0.99 | 0.11 | <.001 | 0.44 | 0.17 | 0.001 |
| | Fatal | 0.01827 | | | | 0.00192 | -0.02227 | 0.01797 | -0.003 | 0.00479 | -0.01501 | -0.01841 | -0.01322 |
| | (n=3,967) | 0.25 | | | | 0.90 | 0.16 | 0.26 | 0.85 | 0.76 | 0.34 | 0.25 | 0.41 |
| | | | 0.01397 | 0.00082 | 0.00936 | 0.00175 | -0.02224 | 0.01776 | -0.00258 | 0.00495 | -0.0149 | -0.01887 | -0.0131 |
| | | | 0.38 | 0.96 | 0.56 | 0.91 | 0.16 | 0.26 | 0.87 | 0.76 | 0.35 | 0.23 | 0.41 |
| Stillbirth | Non-fatal | -0.0331 | | | | -0.02608 | 0.01011 | -0.00476 | 0.02089 | -0.07456 | -0.01035 | 0.01606 | -0.03811 |
| | (n=7,481) | 0.004 | | | | 0.02 | 0.38 | 0.68 | 0.07 | <.001 | 0.37 | 0.16 | 0.001 |
| | | | -0.03132 | -0.00984 | | -0.02602 | 0.01004 | -0.00475 | 0.02097 | -0.07458 | -0.01037 | 0.01611 | -0.03811 |
| | | | 0.006 | 0.39 | | 0.02 | 0.39 | 0.68 | 0.07 | <.001 | 0.37 | 0.16 | 0.001 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fatal | 0.03857 | | | 0.00098 | -0.02235 | 0.02054 | -0.00151 | 0.00431 | -0.00816 | -0.02544 | -0.0147 |
| (n=3,930) | 0.016 | | | 0.95 | 0.16 | 0.20 | 0.92 | 0.79 | 0.61 | 0.11 | 0.36 |
| | | 0.00375 | 0.04997 | 0.00053 | -0.02201 | 0.02037 | -0.00136 | 0.0047 | -0.00801 | -0.02609 | -0.0146 |
| | | 0.81 | 0.002 | 0.97 | 0.17 | 0.20 | 0.93 | 0.77 | 0.62 | 0.10 | 0.36 |

Models were adjusted for ethnicity (Caucasian, Asian, and other), body-mass index (underweight, normal, overweight, and obese), smoking status (current smoker and not current smoker), education level (⩽10, 11-12, and >12 years), and study, and stratified by hypertension (yes and no). Miscarriage (yes or no) and non-fatal stroke: models with and without interaction term (survival time*miscarriage, survival time*education level, survival time*body-mass index, and survival time*race) fit the data similarly (AIC: 175570.7 vs 175700.9), and 95%CI for HR of interaction terms cross 1. Miscarriage (0, 1, 2, or ≥3) and non-fatal stroke: models with and without interaction term (survival time*education level, survival time*body-mass index, and survival time*race) fit the data similarly (AIC: 175565.8 vs 175599.3), and 95%CI for HR of interaction terms cross 1. Stillbirth (yes or no) and non-fatal stroke: models with and without interaction term (survival time*stillbirth, survival time*education level, survival time*body-mass index, and survival time*race) fit the data similarly (AIC: 164789.0 vs 164832.6), and 95%CI for HR of interaction terms cross 1. Stillbirth (0, 1, or ≥2) and non-fatal stroke: models with and without interaction term (survival time*stillbirth, survival time*education level, survival time*body-mass index, and survival time*race) fit the data similarly (AIC: 164789.9 vs 164832.3), and 95%CI for HR of interaction terms cross 1. Stillbirth (yes or no) and fatal stroke: models with and without interaction term (survival time*stillbirth) fit the data similarly (AIC: 84679.2 vs 84688.6), and HR (95%CI) of interaction term was 1.02 (1.01,1.03). Stillbirth (0, 1, or ≥2) and fatal stroke: models with and without interaction term (survival time*stillbirth) fit the data similarly (AIC: 84670.1 vs 84678.5), and HR (95%CI) of interaction term was 1.02 (1.01,1.02).