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Socioeconomic variations in the proportions of stroke attributable to reproductive profiles among postmenopausal women in China

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Abstract

Background This prospective study aimed to examine the individual and combined population attributable fractions (PAFs) of stroke and its subtypes associated with reproductive factors among Chinese postmenopausal women, highlighting variations across socioeconomic status (SES) stratas.

Methods Data were from 138,873 Chinese postmenopausal women enrolled in the China Kadoorie Biobank. Reproductive factors evaluated in this study included early age at menarche, early age at menopause, advanced age at first live birth, high parity, history of stillbirth, history of miscarriage or termination, and non-lactation. PAFs were calculated using hazard ratios, estimated using Cox proportional hazard regression, and prevalence of the seven reproductive factors. PAF for each reproductive risk factor and combined PAFs for all factors were estimated in total population and across SES classes.

Results Of the 138,873 included participants, 17,042 developed strokes during a median follow-up period of 8.9 years. Across SES classes, the greatest attributable fractions of total stroke cases were observed for high parity among low-SES women (PAF 17.2%, 95% confidence interval [CI] 13.7%, 20.6%), history of miscarriage or termination among medium-SES women (PAF 11.4%, 95% CI 8.2%, 14.5%), and no history of lactation among high-SES women (PAF 3.1%, 95% CI 1.7%, 4.9%). A multiplicatively estimated 20.5% (95% CI 20.4%, 20.5%) and 3.1% (95% CI 1.7%, 4.9%) of stroke cases were attributable to the seven reproductive risk factors in low-SES and high-SES women, respectively.

Conclusions A large fraction of stroke cases among Chinese postmenopausal women were associated with reproductive factors. Targeted cardiovascular prevention strategies are warranted among women with different SES to mitigate risks associated with different reproductive profiles.

Keywords Stroke, Socioeconomic status, Population attributable fraction, Postmenopausal women, Reproductive factors

Backgrounds

Stroke, a leading cause of morbidity and mortality, has emerged as a global public health concern. In 2019, there were 101 million prevalent stroke cases and 11.6% of total deaths attributable to stroke around the world [1]. In China, the disease burden of stroke is also alarmingly severe, with 24.18 million and 5.94 million prevalent cases of ischemic and hemorrhagic stroke in 2019, posing significant public health challenges to both society and

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the healthcare system [2]. While stroke affects both sexes, disparities in the prevention, treatment, and outcomes of stroke between sexes have been well-documented, with women experiencing a greater increased risk of stroke and more severe consequences as they age [3, 4].

Research into stroke risk factors has traditionally focused on common contributors such as hypertension, diabetes, and lifestyles. However, sex-specific risk factors, particularly those related to reproductive health, affect women disproportionately throughout their lifespan [3]. The reproductive lifespan of women is marked by a series of biological and physiological events, including menarche, pregnancy, delivery, breastfeeding, and menopause [5, 6], which contribute to the development of cardio-cerebrovascular diseases, including stroke [7]. For instance, early menopause and high parity were found associated with an increased risk of ischemic stroke [8, 9]. Number and timing of childbearing both play an important role in the development of stroke [10]. Additionally, adverse pregnancy outcomes, such as pregnancy loss or stillbirth, have also been linked to elevated stroke risks [11, 12]. However, the collective impact of these reproductive events on stroke remains insufficiently understood.

Moreover, socioeconomic status (SES) introduces an additional layer of complexity to the association between reproductive factors and stroke risk [13]. SES, a multifaceted construct encompassing income, occupation, and education, has been suggested to be an effect modifier in the above association through various mechanisms [14], including influencing access to healthcare, health behaviors' formation, and exposure to health risks [15]. The interplay of SES with reproductive health suggests that the impact of reproductive factors on stroke risk may vary across socioeconomic levels, a topic that warrants further investigation. It is imperative to investigate the variations in associations and impacts across different SES groups, in order to better target equitable cardiovascular prevention and intervention strategies for women.

The population attributable fraction (PAF) serves as a metric to estimate the public health impact of risk factors on health conditions and to guide the prioritization of preventive health strategies [16]. To quantify the collective impact of multiple risk factors on diseases, the concept of combined PAF has been introduced, supported by various calculation methods [17, 18]. Despite these methodological advancements, there is a noticeable dearth of research on the PAF of stroke associated with lifetime reproductive factors among Chinese women. Variations in PAFs across different socioeconomic levels also remain largely unexplored.

To fill these research gaps, this prospective cohort study based on the China Kadoorie Biobank (CKB) survey seeks to unravel the association and attributable burdens of stroke with a broad spectrum of reproductive factors among Chinese postmenopausal women, and to explore their variations across SES.

Methods

Study population

Participants in this study were from the CKB, a nationwide prospective cohort study in China [19–21] (www.ckbiobank.org, Request No. DAR-2020–00212). At the baseline survey between June 2004 and July 2008, 512,726 participants aged 30–79 years were recruited from ten geographically diverse areas (five urban districts and five rural counties) across China. Follow-up surveys were subsequently conducted at intervals of every five years until December 2015. Trained staff collected information through laptop-based questionnaires, alongside physical measurements and blood tests. The CKB study obtained ethical approval from the Oxford University Tropical Research Ethics Committee (Approval No. 025–04) and the Chinese Center for Disease Control and Prevention Ethical Review Committee (Approval No. 005/2004). All participants provided written informed consent.

The study flowchart is shown in Fig. 1. For this study, we included only postmenopausal women who had reproductive histories, as well as complete baseline data on reproductive factors and covariates. We excluded male participants ($n=210,204$), women who were not postmenopausal ($n=143,596$), those who had undergone gynecological operations (i.e., breast lumpectomy, hysterectomy, or oophorectomy) or had a history of cancer ($n=14,342$), those with implausible age at menopause (i.e., age at menopause older than age at baseline) ($n=252$), those with incomplete data on reproductive factors ($n=1900$) or covariates ($n=1$), or those who had experienced a stroke prior to the baseline survey ($n=3558$), leaving 138,873 eligible women for further analysis.

Assessment of reproductive factors

Reproductive histories were collected at baseline through a face-to-face interview, including age at menarche, age at menopause, age at first live birth, number of live births, number of stillbirths, number of miscarriages or terminations, and history of lactation. Informed by both the reproductive patterns of our participants and existing literature [22], we categorized these variables into seven dichotomous reproductive risk factors: early age at menarche (≤ 15 years) (Additional file 1: Fig. S1) [23], early age at menopause (≤ 45 years), advanced age at first live birth (>25 years) [24], high parity (number of live births ≥ 3) [25], having a history of stillbirth, having a

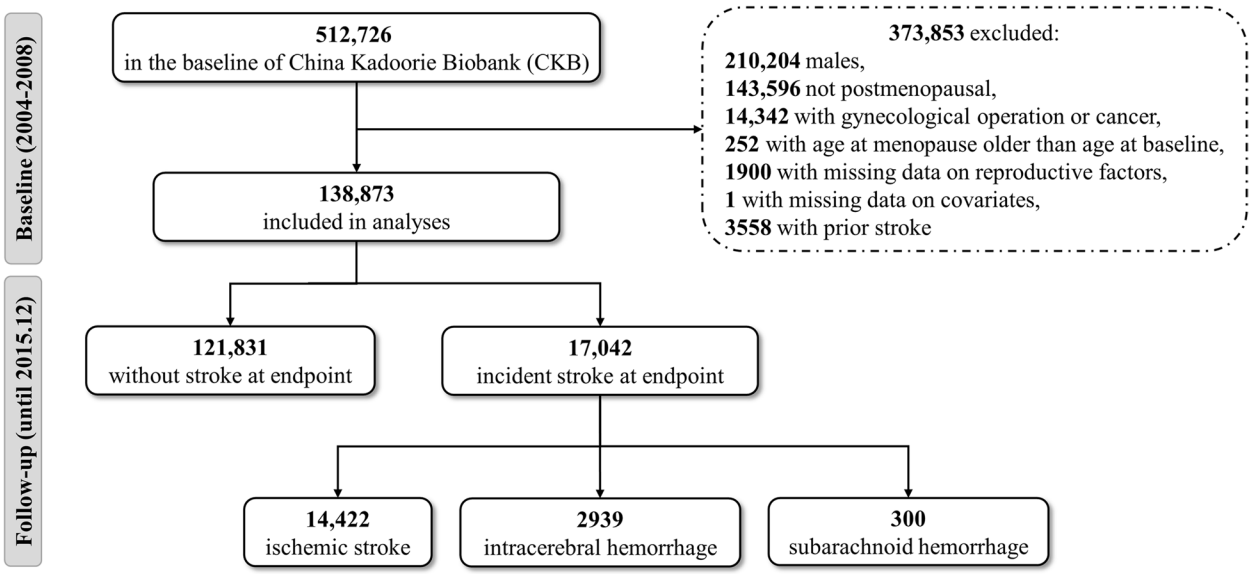

Fig. 1 Flowchart of sample selection. Notes: Total stroke included the first occurrence of a stroke event for each individual

history of miscarriage or termination, and no history of lactation.

Ascertainment of incident stroke

Baseline stroke history was self-reported, with subtype information not specified. Incident strokes during the follow-up were verified by hospitals and further linked to the disease registries and new national health insurance claim databases in China. All stroke events were coded with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (I63 for ischemic stroke, I61 for intracerebral hemorrhage, and I60 for subarachnoid hemorrhage).

Definitions of covariates

Baseline information on demographics, SES variables, lifestyle behaviors, disease, and medication histories was collected through questionnaires [20]. SES components encompassed residence (urban or rural), education (categorized into four levels: primary school or below, middle school, high school, and college or above), occupation (classified as unemployed/retired/others, farmer/worker, sales/self-employed, and manager/professional), and annual household income (divided into < CNY 10,000, CNY 10,000–19,999, CNY 20,000–34,999, and ≥ CNY 35,000). To classify the participants into distinct SES classes, the latent class analysis (LCA) method was employed based on residence, annual household income, education, and occupation. As a form of mixture modeling, LCA helps to assign subgroup labels inferred from observed indicators and is considered a more robust statistical method of clustering [26]. The optimal fit of the classing model was selected based on the theoretical interpretability and fit statistics, including low absolute Akaike information criterion (AIC), low absolute Bayesian information criterion (BIC) values, and high entropy (Additional file 1: Table S1) [26]. Three latent SES classes were finally identified to represent high, medium, and low SES, and class membership was determined by the posterior item probabilities. Age was recorded as a continuous variable. Lifestyle behaviors were assessed through questions on smoking (never vs. ex-/current smoker), passive smoking (yes/no), alcohol consumption (never vs. ex-/current drinker), and physical activity (quantified in metabolic equivalent of task [MET] of hours on all daily activities). Marital status was categorized as married or unmarried (including widowed, separated/divorced, or never married).

Physical examinations and blood tests included measurements of height, weight, waist circumference (WC), blood pressure, and blood glucose [19]. Body mass index (BMI) was calculated by height and weight (kg/m^2) and categorized as underweight (< 18.5 kg/m^2), normal (18.5–23.9 kg/m^2), overweight (24.0–27.9 kg/m^2), and obesity (≥ 28 kg/m^2) [27]. WC was included as a continuous variable and accurate to 0.1 cm. Coronary heart disease history was determined by a positive answer to the question "Has a doctor ever told you that you had coronary heart disease?". Resting blood pressure was measured twice or thrice, with the average of the last two measurements being recorded [19]. Hypertension was defined as blood pressure ≥ 140/90 mmHg, or self-reported physician diagnosis or under treatment. Random blood glucose was measured once by Johnson SureStep Plus, and a

fasting blood glucose test would be conducted on the following day if random blood glucose was between 7.8 and 11.0 mmol/L [19]. Diabetes was defined as self-reported physician diagnosis or under treatment, random blood glucose ≥ 11.1 mmol/L, or fasting blood glucose ≥ 7.0 mmol/L. Medication histories including anticoagulation therapy, hypolipidemic therapy, and oral contraceptive pills usage were recorded with a binary outcome (yes/no).

Statistical analysis

Continuous variables were all skewed from tests for normal distribution and reported as median and interquartile ranges (IQRs). Categorical variables were summarized as counts and percentages (%). The comparison of baseline characteristics between women with and without incident stroke was performed through the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables.

The hazard ratios (HRs) and 95% confidence intervals (CIs) of stroke and its subtypes (i.e., ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage) associated with each of the seven reproductive factors were calculated using Cox proportional hazard regression with stratification by birth year cohorts [28]. The proportional hazards assumption was examined based on Schoenfeld residuals. The time-to-event was calculated from age at baseline until stroke onset, loss to follow-up or December 31, 2015 (the endpoint), whichever came first. A stepwise modeling strategy was adopted: model 1 was adjusted for age at baseline. Model 2 was further adjusted for marital status, BMI, WC, smoking, passive smoking, drinking, physical activity, diabetes, hypertension, coronary heart disease, anticoagulation therapy, hypolipidemic therapy, and oral contraceptive pills usage based on model 1. Model 3 was further adjusted for residence, education, occupation, and annual household income based on model 2. Model 4 mutually involved all seven reproductive factors with the adjustment of covariates in model 3. To further explore the disparities of associations across different SES classes derived using the LCA method, the interaction effects ($P_{interaction}$) of SES with reproductive factors were tested and SES-specific HRs were analyzed with the adjustment of covariates except for SES components.

PAF for each reproductive risk factor among total and SES-specific populations was estimated by Levin's formula [29]: $PAF = \frac{\sum_{j=1}^{n} P_j(RR_j-1)}{\sum_{j=1}^{n} P_j(RR_j-1)+1}$, where P_j was the population prevalence of risk factor j and RR_j was the relative risk of incident stroke with exposure to risk factor j. Our study replaced RRs in the formula with corresponding HRs, and CIs from HRs were used to calculate upper and lower bounds for estimates of PAFs [30]. When considering an array of overlapped risk factors, combined PAF was employed based on two assumptions of the interrelatedness of risk factors. When multiple significant risk factors were assumed to have a multiplicative or additive effect, combined PAF was calculated by Welberry's formulas [17]: $Multiplicative\ combined\ PAF = \frac{\sum_{i=1}^{n}\{[\prod_{j=1}^{k}(x_{ij}RR_j-x_{ij}+1)]-1\}}{\sum_{i=1}^{n}\{[\prod_{j=1}^{k}(x_{ij}RR_j-x_{ij}+1)\}}$; $Additive\ combined\ PAF = \frac{\sum_{i=1}^{n}\{\sum_{j=1}^{k}x_{ij}(RR_j-1)\}}{\sum_{i=1}^{n}\{[\sum_{j=1}^{k}x_{ij}(RR_j-1)]+1\}}$. In the above formulas, x_{ij} was an indicator variable for the ith person and the jth risk factor in a population of n people and a set of k risk factors, and RR_j was the corresponding relative risk, replaced with fully adjusted HRs. The 95% CI was obtained using the bootstrapping method. To verify the robustness of the results, subgroup analyses were further performed within specific categories of each SES component, including residence, annual household income, education, and occupation.

All analyses were performed using Stata statistical software (version 16.0, StataCorp) and R (version 4.2.3). A two-sided P value < 0.05 or a 95% CI that did not cross 1.00 was considered statistically significant.

Results

Baseline characteristics of participants

Characteristics of the postmenopausal women by incident stroke status at the baseline of CKB are shown in Table 1. The median (IQR) age of participants was 58.6 (54.1–65.1) years. Of the 138,873 included postmenopausal women, 17,042 developed stroke during the follow-up, including 14,422 ischemic stroke, 2939 intracerebral hemorrhage, and 300 subarachnoid hemorrhage. Generally, the proportions of early menarche (42.3% vs. 40.2%), early menopause (20.6% vs. 18.8%), high parity (65.6% vs. 52.1%), having stillbirths (10.3% vs. 8.2%), having miscarriages or terminations (55.0% vs. 54.6%), and no history of lactation (2.6% vs. 1.8%) were higher among women with incident total stroke compared to non-stroke ones.

Associations between reproductive factors with stroke and its subtypes among total and SES-stratified populations

There were significant associations between all reproductive factors and incident total stroke (Table 2 and Fig. 2), with fully adjusted HRs (95% CI) of 1.05 (1.02, 1.09) for early age at menarche, 1.09 (1.05, 1.13) for early age at menopause, 1.07 (1.02, 1.11) for advanced age at first live birth, 1.18 (1.14, 1.23) for high parity, 1.07 (1.02, 1.13) for a history of stillbirth, 1.04 (1.01, 1.08) for a history of miscarriage or termination, and 1.33 (1.21, 1.46) for no history of lactation. Similarly, all the included reproductive factors were associated with ischemic stroke. For intracerebral hemorrhage,

Table 1 Characteristics of included women by incident stroke status

Baseline characteristics	Women without incident stroke (*n* = 121,831)	Women with incident stroke				*P* value
		Total stroke (*n* = 17,042)	Ischemic stroke (*n* = 14,422)	Intracerebral hemorrhage (*n* = 2939)	Subarachnoid hemorrhage (*n* = 300)	
Age, year	58.1 (53.8, 64.3)	63.1 (56.8, 68.8)	63.0 (56.8, 68.8)	63.8 (57.3, 69.4)	61.1 (55.4, 67.3)	< 0.001
Residence, *n* (%)						< 0.001
Rural	67,772 (55.6)	8124 (47.7)	6191 (42.9)	2185 (74.3)	164 (54.7)	
Urban	54,059 (44.4)	8918 (52.3)	8231 (57.1)	754 (25.7)	136 (45.3)	
Education, *n* (%)						< 0.001
Primary school and below	90,504 (74.3)	12,215 (71.7)	9959 (69.1)	2549 (86.7)	226 (75.3)	
Middle school	19,307 (15.8)	2719 (16.0)	2486 (17.2)	252 (8.6)	48 (16.0)	
High school	9246 (7.6)	1442 (8.5)	1338 (9.3)	107 (3.6)	19 (6.3)	
College and above	2774 (2.3)	666 (3.9)	639 (4.4)	31 (1.1)	7 (2.3)	
Occupation, *n* (%)						< 0.001
Unemployed, retired or others	64,170 (52.7)	11,421 (67.0)	9932 (68.9)	1670 (56.8)	185 (61.7)	
Farmer or worker	52,024 (42.7)	5145 (30.2)	4048 (28.1)	1239 (42.2)	107 (35.7)	
Sales or self-employed	4105 (3.4)	327 (1.9)	298 (2.1)	26 (0.9)	5 (1.7)	
Manager or professional	1532 (1.3)	149 (0.9)	144 (1.0)	4 (0.1)	3 (1.0)	
Economic status, *n* (%)						< 0.001
< CNY 10,000	40,536 (33.3)	6130 (36.0)	4841 (33.6)	1461 (49.7)	100 (33.3)	
CNY 10,000–19,999	34,680 (28.5)	5396 (31.7)	4674 (32.4)	819 (27.9)	96 (32.0)	
CNY 20,000–34,999	27,547 (22.6)	3311 (19.4)	2906 (20.1)	440 (15.0)	66 (22.0)	
≥ CNY 35,000	19,068 (15.7)	2205 (12.9)	2001 (13.9)	219 (7.5)	38 (12.7)	
Body mass index, kg/m^2	23.6 (21.3, 26.1)	24.3 (21.8, 26.8)	24.5 (22.0, 27.0)	23.4 (20.8, 26.2)	24.0 (21.5, 26.4)	< 0.001
Body mass index status, *n* (%)						< 0.001
Underweight	6872 (5.6)	776 (4.6)	549 (3.8)	242 (8.2)	11 (3.7)	
Normal weight	58,833 (48.3)	7084 (41.6)	5832 (40.4)	1392 (47.4)	138 (46.0)	
Overweight	40,890 (33.6)	6324 (37.1)	5504 (38.2)	918 (31.2)	114 (38.0)	
Obesity	15,236 (12.5)	2858 (16.8)	2537 (17.6)	387 (13.2)	37 (12.3)	
Waist circumference, cm	80.0 (73.0, 86.8)	82.1 (75.3, 89.1)	82.5 (76.0, 89.4)	80.2 (72.8, 87.6)	81.0 (73.8, 88.0)	< 0.001
Ever and current smoker, *n* (%)	6123 (5.0)	1179 (6.9)	981 (6.8)	212 (7.2)	24 (8.0)	< 0.001
Passive smoking, *n* (%)	66,704 (54.8)	8599 (50.5)	7182 (49.8)	1618 (55.1)	143 (47.7)	< 0.001
Ever and current drinker, *n* (%)	5729 (4.7)	747 (4.4)	624 (4.3)	141 (4.8)	17 (5.7)	0.064
Physical activity, MET-hours/day	14.0 (8.9, 22.6)	11.2 (8.4, 16.1)	11.2 (8.4, 15.7)	11.2 (8.4, 19.1)	11.5 (8.4, 17.0)	< 0.001
Marital status, *n* (%)						< 0.001
Unmarried	20,066 (16.5)	3893 (22.8)	3206 (22.2)	765 (26.0)	55 (18.3)	
Married	101,765 (83.5)	13,149 (77.2)	11,216 (77.8)	2174 (74.0)	245 (81.7)	
Diabetes, *n* (%)	9983 (8.2)	2548 (15.0)	2256 (15.6)	362 (12.3)	31 (10.3)	< 0.001
Hypertension, *n* (%)	51,953 (42.6)	10,481 (61.5)	8640 (59.9)	2179 (74.1)	183 (61.0)	< 0.001
Coronary heart disease, *n* (%)	5346 (4.4)	1751 (10.3)	1579 (10.9)	188 (6.4)	19 (6.3)	< 0.001
Oral contraceptive pills usage, *n* (%)	12,275 (10.1)	1240 (7.3)	1085 (7.5)	151 (5.1)	33 (11.0)	< 0.001
Anticoagulation therapy, *n* (%)	1403 (1.2)	372 (2.2)	314 (2.2)	76 (2.6)	4 (1.3)	< 0.001
Hypolipidemic therapy, *n* (%)	361 (0.3)	95 (0.6)	78 (0.5)	24 (0.8)	1 (0.3)	< 0.001
Age of menarche, year	16.0 (15.0, 17.0)	16.0 (15.0, 17.0)	16.0 (15.0, 17.0)	16.0 (15.0, 17.0)	16.0 (15.0, 17.5)	< 0.001

Table 1 (continued)

Baseline characteristics	Women without incident stroke ($n=121,831$)	Women with incident stroke				*P* value
		Total stroke ($n=17,042$)	Ischemic stroke ($n=14,422$)	Intracerebral hemorrhage ($n=2939$)	Subarachnoid hemorrhage ($n=300$)	
Early age at menarche, *n* (%)	48,932 (40.2)	7217 (42.3)	6169 (42.8)	1196 (40.7)	113 (37.7)	< 0.001
Age at menopause, year	49.0 (47.0, 51.0)	49.0 (46.0, 51.0)	49.0 (46.0, 51.0)	49.0 (46.0, 51.0)	50.0 (47.0, 51.0)	0.420
Early age at menopause, *n* (%)	22,961 (18.8)	3503 (20.6)	2886 (20.0)	694 (23.6)	50 (16.7)	< 0.001
Age at first live birth, year	23.0 (20.0, 25.0)	22.0 (20.0, 25.0)	23.0 (20.0, 25.0)	21.0 (19.0, 24.0)	23.0 (20.0, 25.0)	< 0.001
Advanced age at first live birth, *n* (%)	27,114 (22.3)	3799 (22.3)	3444 (23.9)	398 (13.5)	64 (21.3)	0.910
High parity, *n* (%)	63,495 (52.1)	11,181 (65.6)	9248 (64.1)	2227 (75.8)	178 (59.3)	< 0.001
History of stillbirths, *n* (%)	9948 (8.2)	1754 (10.3)	1402 (9.7)	416 (14.2)	40 (13.3)	< 0.001
History of miscarriage or termination, *n* (%)	66,493 (54.6)	9379 (55.0)	8184 (56.7)	1349 (45.9)	174 (58.0)	0.260
No history of lactation, *n* (%)	2241 (1.8)	451 (2.6)	414 (2.9)	45 (1.5)	7 (2.3)	< 0.001

Values are presented as median (interquartile range) for continuous variables and cases (percentage) for categorical variables

MET Metabolic equivalent of task

P value was obtained by comparing women with and without total stroke

higher risks were found among women with early age at menopause (HR 1.14, 95% CI 1.05, 1.25), high parity (HR 1.26, 95% CI 1.14, 1.40), and having a history of stillbirth (HR 1.18, 95% CI 1.06, 1.31). While having a history of stillbirth was the only reproductive risk factor observed significantly associated with subarachnoid hemorrhage (HR 1.53, 95% CI 1.09, 2.16).

There were 77,569, 51,110 and 10,194 women classified into low SES, medium SES, and high SES classes, respectively (Additional file 1: Table S2), and the incidence rate of stroke by the stratas is presented in Additional file 1: Table S3. Significant disparities across the three classes were observed in associations of early age at menarche, high parity, history of stillbirth, history of miscarriage or termination, and no history of lactation with total stroke. Among low-SES individuals, high parity was associated with 34% (HR 1.34, 95% CI 1.25, 1.43) higher risks of ischemic stroke; while in women with high SES, significantly higher risks were only found for those never lactating (HR 1.50, 95% CI 1.26, 1.79). For intracerebral hemorrhage, higher risks were found among low-SES women with early age at menopause and high parity, as well as among high-SES women with history of stillbirth. For subarachnoid hemorrhage, no significant association was found (Additional file 1: Table S4).

The population attributable fractions of reproductive factors with stroke among total and SES-stratified populations

The PAFs quantified the fractions of the stroke burden attributable to reproductive factors among Chinese postmenopausal women (Additional file 1: Table S5 and Fig. 2). Among the total population, high parity contributed to the largest proportion of total stroke cases (PAF 9.0%, 95% CI 6.8%, 11.2%), followed by having a history of miscarriage or termination (PAF 2.4%, 95% CI 0.6%, 4.1%) and early age at menarche (PAF 2.0%, 95% CI 0.8%, 3.3%). Higher incidence of total stroke cases was also attributable to early age at menopause (PAF 1.7%, 95% CI 1.0%, 2.5%), advanced age at first live birth (PAF 1.5%, 95% CI 0.5%, 2.5%), having a history of stillbirth (PAF 0.6%, 95% CI 0.2%, 1.1%), and no history of lactation (PAF 0.6%, 95% CI 0.4%, 0.9%). Taking all seven risk factors into account, 15.9% and 16.7% of total stroke cases were associated with these reproductive factors by additive and multiplicative effect, respectively.

PAFs for reproductive factors varied across SES classes (Table 3 and Fig. 3). For example, no history of lactation accounted for the most total stroke (PAF 3.1%, 95% CI 1.7%, 4.9%) and ischemic stroke (PAF 3.3%, 95% CI 1.8%, 5.1%) cases among high-SES women; while in low-SES women, 17.2% (95% CI 13.7%, 20.6%) and 17.6% (95%

Table 2 HRs and 95% CIs for association of reproductive factors with incident stroke and its subtypes

	Model 1 HR (95% CI)	Model 2	Model 3	Model 4
Total stroke				
Reproductive factors				
Early age at menarche	**1.15 (1.11, 1.18)*** **	**1.09 (1.06, 1.13)*** **	**1.06 (1.03, 1.09)*** **	**1.05 (1.02, 1.09)** **
Early age at menopause	**1.06 (1.02, 1.10)** **	**1.09 (1.05, 1.13)*** **	**1.09 (1.05, 1.14)*** **	**1.09 (1.05, 1.13)*** **
Advanced age at first live birth	**1.20 (1.15, 1.24)*** **	**1.14 (1.10, 1.19)*** **	1.03 (0.99, 1.07)	**1.07 (1.02, 1.11)** **
High parity	**1.04 (1.00, 1.08)***	**1.07 (1.03, 1.11)*** **	**1.16 (1.11, 1.20)*** **	**1.18 (1.14, 1.23)*** **
History of stillbirth	1.02 (0.97, 1.07)	1.03 (0.98, 1.08)	**1.07 (1.02, 1.12)***	**1.07 (1.02, 1.13)** **
History of miscarriage or termination	**1.09 (1.06, 1.12)*** **	**1.07 (1.04, 1.11)*** **	**1.04 (1.01, 1.07)***	**1.04 (1.01, 1.08)** **
No history of lactation	**1.57 (1.43, 1.73)*** **	**1.45 (1.32, 1.60)*** **	**1.31 (1.19, 1.44)*** **	**1.33 (1.21, 1.46)*** **
Ischemic stroke				
Reproductive factors				
Early age at menarche	**1.17 (1.13, 1.21)*** **	**1.10 (1.07, 1.14)*** **	**1.06 (1.02, 1.10)*** **	**1.05 (1.02, 1.09)** **
Early age at menopause	1.03 (0.99, 1.07)	**1.07 (1.03, 1.12)*** **	**1.08 (1.04, 1.13)*** **	**1.08 (1.04, 1.13)*** **
Advanced age at first live birth	**1.31 (1.26, 1.36)*** **	**1.22 (1.18, 1.27)*** **	1.04 (1.00, 1.09)	**1.08 (1.03, 1.13)*** **
High parity	0.96 (0.93, 1.00)	1.01 (0.97, 1.05)	**1.16 (1.11, 1.21)*** **	**1.19 (1.14, 1.25)*** **
History of stillbirth	0.96 (0.91, 1.02)	0.98 (0.93, 1.04)	1.05 (1.00, 1.12)	**1.06 (1.00, 1.12)***
History of miscarriage or termination	**1.16 (1.13, 1.20)*** **	**1.13 (1.09, 1.17)*** **	**1.06 (1.02, 1.09)** **	**1.06 (1.02, 1.10)*** **
No history of lactation	**1.71 (1.55, 1.89)*** **	**1.55 (1.41, 1.71)*** **	**1.34 (1.22, 1.48)***	**1.36 (1.23, 1.50)*** **
Intracerebral hemorrhage				
Reproductive factors				
Early age at menarche	1.06 (0.99, 1.15)	1.07 (0.99, 1.15)	1.07 (0.99, 1.15)	1.05 (0.98, 1.14)
Early age at menopause	**1.24 (1.14, 1.35)*** **	**1.23 (1.13, 1.34)*** **	**1.15 (1.05, 1.25)** **	**1.14 (1.05, 1.25)** **
Advanced age at first live birth	0.65 (0.59, 0.73)	0.72 (0.64, 0.80)	0.98 (0.88, 1.10)	1.04 (0.92, 1.17)
High parity	**1.84 (1.67, 2.03)*** **	**1.66 (1.50, 1.83)*** **	**1.24 (1.12, 1.38)*** **	**1.26 (1.14, 1.40)*** **
History of stillbirth	**1.42 (1.27, 1.57)*** **	**1.30 (1.17, 1.45)*** **	**1.17 (1.05, 1.30)** **	**1.18 (1.06, 1.31)** **
History of miscarriage or termination	0.76 (0.70, 0.81)	0.83 (0.77, 0.89)	0.99 (0.92, 1.07)	1.01 (0.93, 1.09)
No history of lactation	0.87 (0.65, 1.17)	0.93 (0.69, 1.25)	1.18 (0.88, 1.59)	1.20 (0.89, 1.62)
Subarachnoid hemorrhage				
Reproductive factors				
Early age at menarche	0.92 (0.72, 1.16)	0.88 (0.70, 1.12)	0.88 (0.70, 1.12)	0.88 (0.69, 1.12)
Early age at menopause	0.87 (0.64, 1.18)	0.89 (0.65, 1.20)	0.87 (0.64, 1.19)	0.89 (0.65, 1.21)
Advanced age at first live birth	1.01 (0.77, 1.34)	0.96 (0.72, 1.28)	1.02 (0.75, 1.39)	1.00 (0.73, 1.37)
High parity	0.98 (0.75, 1.29)	1.03 (0.78, 1.36)	0.97 (0.72, 1.29)	0.99 (0.73, 1.33)
History of stillbirth	**1.52 (1.09, 2.13)***	**1.55 (1.10, 2.18)***	**1.52 (1.08, 2.14)***	**1.53 (1.09, 2.16)***
History of miscarriage or termination	1.17 (0.93, 1.47)	1.14 (0.90, 1.44)	1.19 (0.93, 1.51)	1.19 (0.94, 1.52)

Table 2 (continued)

	Model 1 HR (95% CI)	Model 2	Model 3	Model 4
No history of lactation	1.27 (0.60, 2.68)	1.19 (0.56, 2.52)	1.25 (0.59, 2.68)	1.26 (0.59, 2.70)

Model 1 was adjusted for age at baseline

Model 2 was further adjusted for body mass index, waist circumference, smoking, passive smoking, drinking, physical activity, marital status, diabetes, hypertension, coronary heart disease, anticoagulation therapy, hypolipidemic therapy, and oral contraceptive pills usage

Model 3 was further adjusted for residence, education, occupation, and annual household income

Model 4 was further adjusted for reproductive factors other than themselves

HR Hazard ratio, *CI* Confidence interval

*** means *P* value <0.001, ** means *P* value <0.01, * means *P* value <0.05

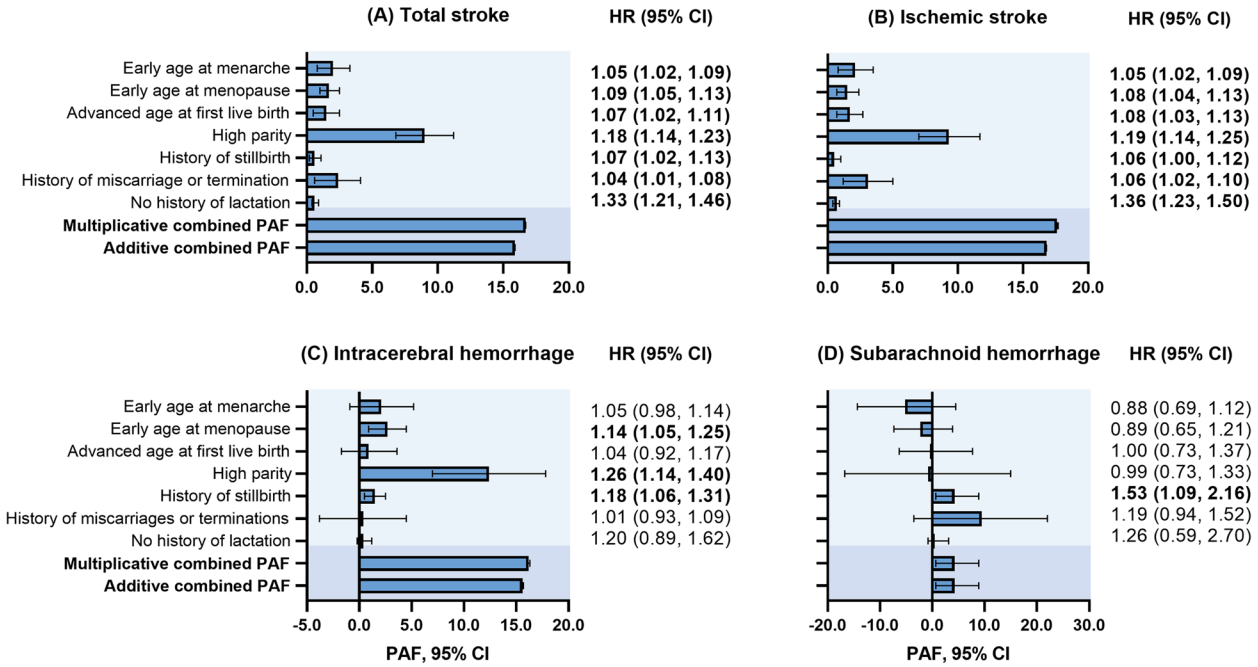

Fig. 2 HRs (95% CIs) and PAFs of reproductive factors with incident stroke and its subtypes among Chinese postmenopausal women. Notes: HR, hazard ratio; CI, confidence interval; PAF, population attributable fraction. Model was adjusted for age, body mass index, waist circumference, smoking, passive smoking, drinking, physical activity, marital status, diabetes, hypertension, coronary heart disease, oral contraceptive pills usage, anticoagulation therapy, hypolipidemic therapy, residence, education, occupation, annual household income, and reproductive factors other than themselves. Bold font means statistical significance

CI 13.7%, 21.4%) of total and ischemic stroke cases were attributable to high parity. The combined PAFs of total stroke with all reproductive factors were the lowest in women with high-SES (both additive and multiplicative combined PAF 3.1%, 95% CI 1.7%, 4.9%) compared with low-SES (additive combined PAF 20.0%, 95% CI 19.9%, 20.1%; multiplicative combined PAF 20.5%, 95% CI, 20.4%, 20.5%) and medium-SES (additive combined PAF 20.6%, 95% CI 20.6%, 20.8%; multiplicative combined PAF 22.2%, 95% CI 22.1%, 22.3%). Similar results were also found for ischemic stroke. For intracerebral hemorrhage, high parity (PAF 19.8%, 95% CI 12.7%, 26.5%), history of miscarriage or termination (PAF 15.0%, 95% CI 4.6%, 24.8%), and history of stillbirth (PAF 4.1%, 95% CI 0.4%, 11.0%) were associated with the greatest fraction of attributable cases in low SES, medium SES, and high SES classes, separately. The greatest combined PAF was found among low-SES women. Additionally, no significant association was found for subarachnoid hemorrhage.

Subgroup analyses within SES components

Residence-stratified results, presented in Tables S6 and S7, found an estimated 14.5% of total stroke cases among urban residents were attributed to the reproductive

Table 3 Population attributable fractions of stroke and its subtypes with reproductive factors across SES classes

	Prevalence, %	Total stroke [a]PAF (95% CI)	Ischemic stroke	Intracerebral hemorrhage	Subarachnoid hemorrhage
Low SES					
Reproductive factors					
Early age at menarche	36.9	0.2 (−1.5, 1.8)	−0.2 (−2.1, 1.7)	2.1 (−1.1, 5.4)	−3.1 (−14.2, 9.2)
Early age at menopause	20.9	**2.0 (0.9, 3.2)**	**1.7 (0.4, 3.1)**	**3.4 (1.2, 5.8)**	2.2 (−5.3, 11.4)
Advanced age at first live birth	10.7	**2.1 (1.2, 3.0)**	**2.8 (1.7, 3.9)**	0.1 (−1.5, 1.9)	−1.4 (−5.7, 5.4)
High parity	63.0	**17.2 (13.7, 20.6)**	**17.6 (13.7, 21.4)**	**19.8 (12.7, 26.5)**	10.2 (−14.6, 31.9)
History of stillbirth	10.6	−0.2 (−0.8, 0.6)	−0.4 (−1.1, 0.5)	0.8 (−0.5, 2.2)	5.1 (−0.2, 12.3)
History of miscarriage or termination	44.3	−2.1 (−4.0, −0.1)	−1.5 (−3.7, 0.8)	−4.0 (−7.7, −0.1)	5.4 (−8.4, 19.4)
No history of lactation	0.8	0.0 (−0.2, 0.2)	−0.1 (−0.3, 0.1)	0.1 (−0.2, 0.7)	−0.2 (−0.7, 3.6)
[b]*Multiplicative combined PAF*		**20.5 (20.4, 20.5)**	**21.1 (21.1, 21.2)**	**22.7 (22.6, 22.8)**	NA
[c]*Additive combined PAF*		**20.0 (19.9, 20.1)**	**20.7 (20.6, 20.7)**	**22.1 (22.0, 22.2)**	NA
Medium SES					
Reproductive factors					
Early age at menarche	41.9	**5.1 (3.0, 7.1)**	**5.3 (3.2, 7.4)**	4.0 (−2.6, 10.7)	−1.5 (−16.6, 14.5)
Early age at menopause	17.2	**1.8 (0.7, 2.9)**	**1.6 (0.5, 2.7)**	2.4 (−1.0, 6.3)	−5.0 (−11.1, 4.1)
Advanced age at first live birth	32.2	**3.7 (1.9, 5.6)**	**4.1 (2.2, 6.0)**	1.8 (−4.2, 8.2)	3.6 (−9.5, 18.4)
High parity	46.4	1.5 (−1.5, 4.4)	1.1 (−1.9, 4.2)	10.0 (−0.1, 20.0)	−7.8 (−29.3, 15.4)
History of stillbirth	6.2	**1.0 (0.4, 1.6)**	**0.9 (0.3, 1.5)**	**3.1 (1.1, 5.5)**	3.3 (−1.0, 10.3)
History of miscarriage or termination	66.2	**11.4 (8.2, 14.5)**	**11.9 (8.6, 15.1)**	**15.0 (4.6, 24.8)**	12.6 (−14.1, 35.2)
No history of lactation	2.6	**1.1 (0.6, 1.6)**	**1.2 (0.7, 1.8)**	0.8 (−0.5, 2.8)	−0.1 (−1.9, 5.0)
[b]*Multiplicative combined PAF*		**22.2 (22.1, 22.3)**	**23.0 (22.9, 23.1)**	**17.8 (17.6, 17.9)**	NA
[c]*Additive combined PAF*		**20.6 (20.6, 20.8)**	**21.4 (21.3, 21.5)**	**17.5 (17.3, 17.6)**	NA
High SES					
Reproductive factors					
Early age at menarche	60.1	−1.2 (−7.4, 4.8)	−0.2 (−6.5, 6.0)	−20.2 (−46.3, 5.4)	−53.7 (−101.2, 4.3)
Early age at menopause	14.2	0.9 (−1.1, 3.1)	1.3 (−0.7, 3.6)	3.6 (−3.9, 14.3)	0.0 (0.0, 0.0)
Advanced age at first live birth	59.9	−3.1 (−9.5, 3.2)	−2.3 (−8.9, 4.1)	−3.7 (−31.0, 21.7)	−26.8 (−83.1, 30.5)
High parity	20.1	−1.5 (−3.8, 1.1)	−1.1 (−3.5, 1.6)	−1.5 (−9.9, 10.2)	−19.9 (−24.1, −2.4)
History of stillbirth	3.1	0.5 (−0.2, 1.5)	0.3 (−0.5, 1.3)	**4.1 (0.4, 11.0)**	8.0 (−0.7, 35.4)
History of miscarriage or termination	75.5	5.3 (−3.4, 13.4)	5.0 (−3.8, 13.4)	6.1 (−32.5, 36.0)	63.9 (−21.9, 91.2)
No history of lactation	6.8	**3.1 (1.7, 4.9)**	**3.3 (1.8, 5.1)**	0.5 (−3.6, 8.5)	6.9 (−3.1, 31.8)
[b]*Multiplicative combined PAF*		**3.1 (1.7, 4.9)**	**3.3 (1.8, 5.1)**	**4.1 (0.4, 11.0)**	NA
[c]*Additive combined PAF*		**3.1 (1.7, 4.9)**	**3.3 (1.8, 5.1)**	**4.1 (0.4, 11.0)**	NA

PAF, population attributable fraction; *CI*, confidence interval; *NA*, not applicable; *SES*, socioeconomic status

Hazard ratios substituting for relative risks (RRs in the formula below) to calculate PAFs were adjusted for age, body mass index, waist circumference, smoking, passive smoking, drinking, physical activity, marital status, diabetes, hypertension, coronary heart disease, anticoagulation therapy, hypolipidemic therapy, and oral contraceptive pills usage

Bold font means statistical significance

[a] $\text{PAF} = \frac{\sum_{j=1}^{n} P_j(RR_j - 1)}{\sum_{j=1}^{n} P_j(RR_j - 1) + 1}$

[b] $\text{Multiplicative combined PAF} = \frac{\sum_{i=1}^{n}\left(\left[\prod_{j=1}^{k}(x_{ij}RR_j - x_{ij} + 1)\right] - 1\right)}{\sum_{i=1}^{n}\left(\prod_{j=1}^{k}(x_{ij}RR_j - x_{ij} + 1)\right)}$

[c] $\text{Additive combined PAF} = \frac{\sum_{i=1}^{n}\left(\sum_{j=1}^{k} x_{ij}(RR_j - 1)\right)}{\sum_{i=1}^{n}\left(\left[\sum_{j=1}^{k} x_{ij}(RR_j - 1)\right] + 1\right)}$

factors other than high parity and advanced age at first live birth. While among rural women, high parity accounted for the greatest proportions of ischemic stroke (16.0%) and intracerebral hemorrhage (15.5%). Similarly, the greatest stroke burdens were associated with high parity within low-income, less-educated individuals and laborers, and the combined PAFs were generally higher among these women (Additional file 1: Tables S8–S13).

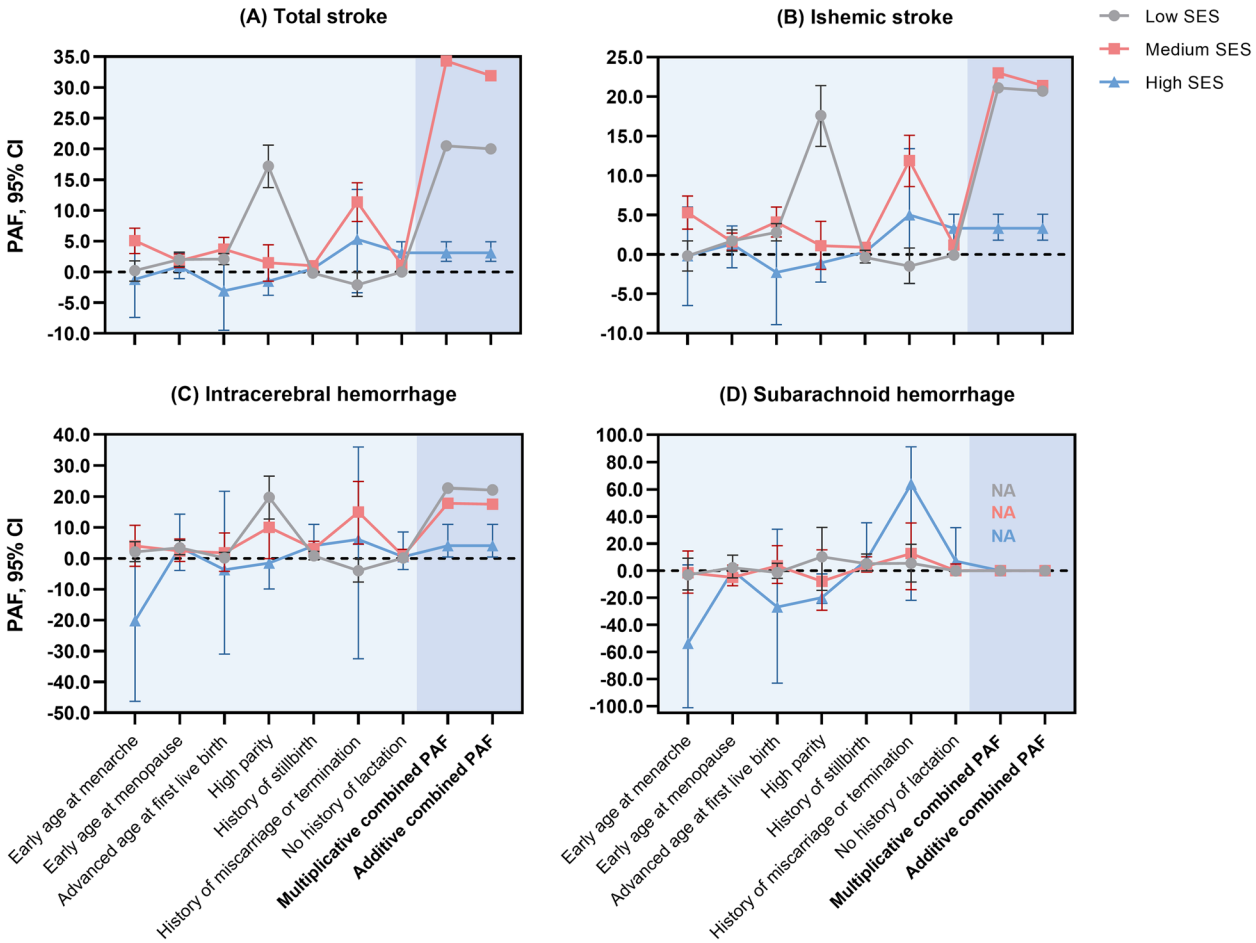

Fig. 3 Population attributable fractions of stroke and its subtypes with reproductive factors across SES classes. Notes: PAF, population attributable fraction; CI, confidence interval; SES, socioeconomic status. Model was adjusted for age, body mass index, waist circumference, smoking, passive smoking, drinking, physical activity, marital status, diabetes, hypertension, coronary heart disease, anticoagulation therapy, hypolipidemic therapy, and oral contraceptive pills usage

Discussion

In this nationwide cohort study of Chinese postmenopausal women, we investigated seven reproductive risk factors and observed significant associations with stroke and its subtypes. The associations and attributable stroke burden varied by SES classes. For instance, no history of lactation and high parity accounted for the most ischemic stroke cases among high-SES (3.3%) and low-SES (17.6%) women, respectively. The lowest combined PAF (3.3%) of multiple reproductive risk factors were found in women with high SES compared with low- and medium-SES ones.

Several studies on the associations between reproductive factors and stroke showed consistent findings with our study. Ardissino et al. have proved the causal relevance of high parity and early age at menarche on stroke among British women using Mendelian randomization [9]. Evidence from China, South Korea, and America also supported that early age at menopause and no history of lactation might be related to higher risks of stroke, respectively [5, 31, 32]. A pooled analysis across seven countries showed that miscarriage and stillbirth were associated with increased risks of stroke, especially among women with more pregnancy loss [33, 34]. Results from the UK Biobank also showed higher stroke risks associated with various reproductive risk factors including early age at menarche or menopause, high parity, and a history of stillbirth [35]. However, there also exists inconsistency. For instance, prospective studies among American and European women indicated stillbirth or miscarriage was not associated with stroke, which might be because of the limited number of stroke events for

subgroup analysis according to specific stroke subtypes [36, 37]. Earlier menopause was found to be associated with increased risks of intracerebral hemorrhage in our study, but not in another study conducted among postmenopausal women in the Netherlands [8]. Comparatively, the differences in women's reproductive patterns between populations and involvement of artificial menopause in the previous study might account for the inconsistency. Additionally, age at first live birth showed contrary associations with stroke risks among Chinese and European populations, possibly due to differences in the study setting and development level [24, 38]. While some prior studies have proposed some composite indicators of reproductive experiences [39, 40], our findings expanded on existing evidence by incorporating a wide spectrum of reproductive factors, providing interpretable results on their separate and combined effects, as well as exploring the socioeconomic variations.

Many researchers have proposed the underlying biological mechanisms behind the association between reproductive factors and stroke. One of the possible pathways was endocrine disorder, including fluctuations of estrogen, progesterone, oxytocin, and adrenocorticotropic hormone levels [41]. In addition, women with premature menopause or pregnancy loss were found more likely to have endothelial dysfunction and further develop into stroke through reduced vasodilation, proinflammatory state, and prothrombic properties [12, 42]. According to different etiology and pathogenesis, stroke can be categorized into heterogeneous subtypes like ischemic stroke and hemorrhagic stroke. Ischemic stroke is the main subtype and generally results from reduced blood flow. The hemorrhagic subtypes, in contrast, are mainly caused by the rupture of cerebral arteries [2, 43]. In our study, history of miscarriage or termination and no lactation were significantly associated with increased risks of ischemic stroke but not hemorrhagic stroke. It was reported that pregnancy loss might be associated with ischemic stroke through shared pathways that could lead to endothelial dysfunction and poor placental function, which was distinct from hemorrhagic stroke [44]. Additionally, compared to hemorrhagic stroke, ischemic stroke benefits more from the cardiovascular health benefits of lactation, which might act through lowering glucocorticoid levels and hypothalamic–pituitary–adrenal axis activity [45, 46].

Notably, we estimated PAFs of stroke related to reproductive risk factors across women with different SES classes and found significant variations, indicating the underlying moderating impact of social determinants. We found that no history of lactation accounted for the most total stroke and ischemic stroke cases among high-SES women, while the largest PAFs were associated with high parity among low-SES women. Previous studies have suggested that the inhibiting effect on blood clotting triggered by increased prolactin and oxytocin, as well as improved glucose and lipid metabolism during lactation, could decrease the risk of stroke [47–49]. In the social context of China, women with higher educational and occupational status are more likely to return to demanding work schedules soon after delivery and interrupt breastfeeding. Workplaces without supportive environments could also make them have a shorter lactation duration and decrease the benefits from lactation [50]. On the other hand, there is a strong association between women's socioeconomic position and parity counts [51]. Low-SES and rural women in China tended to have more children [22], which was likely related to social behavior traits such as education [52]. It has been proposed that reduced estrogen, adverse metabolic changes, and childrearing-related stress induced by high parity may contribute to permanent deleterious effects on postmenopausal women's cardio-cerebrovascular health [14, 53, 54]. Moreover, the combined PAFs of all risk reproductive factors were the lowest in women with high SES. The weathering hypothesis suggests that socially disadvantaged individuals tend to have stronger reactions towards negative exposures [55]. Compared to women with higher SES, low-SES women were more likely to have unhealthier lifestyles and poorer access to healthcare services [54, 56]. Additionally, low SES has been proved as the factor that leads to low health literacy, which could also be considered a modifiable risk factor of socioeconomic disparities in stroke [57]. The weak health awareness and absence of high-quality healthcare throughout the reproductive lifespan among low-SES women pose unfavorable cardiovascular health including high BMI, smoking habit, elevated blood pressure and glucose, all of which are risk factors for stroke [55, 58]. While in our studies, associations between the reproductive factors and stroke remained significant after adjusting with a range of common stroke risk factors, implying that reproductive profiles have unique and independent implications on the development of stroke, not just markers for other risk factors. Our findings also highlight the importance of considering reproductive profiles as well as social contexts when assessing stroke risk. Therefore, it is essential to improve reproductive healthcare services and implement health education in rural and less-developed areas.

This study has several strengths. To our knowledge, this is the first study to explore the PAFs of stroke and its subtypes associated with reproductive factors and the variations across individual SES among Chinese postmenopausal women. Secondly, different subtypes of stroke have been taken into consideration in this study

since stroke is a heterogeneous condition. Thirdly, the design of our study was based on the life-course perspective, which covered reproductive factors at each stage of women. Given that the mechanism for the interaction and combined impact of reproductive factors remains not clear yet, we applied both additive and multiplicative combined PAFs to calculate the joint attributable burden. Moreover, our study was conducted on the basis of the nationwide prospective cohort study of high quality, ensuring the reliability and generalizability of our results.

However, some limitations of the study also warrant a mention. Firstly, there might be potential bias from the self-reported approach to collect information on reproductive factors. However, previous literature has demonstrated great agreements between self-reported data and medical records [59]. Secondly, the results of the present study were derived from Chinese postmenopausal women. As the reproductive patterns varied widely across regions and countries, the generalizability of our findings might be restricted. Thirdly, although our study covered as many confounding factors as possible, there were other factors not included, such as dietary intake, pregnancy complications, and so forth. Fourthly, the potential impact of dynamic changes of occupation over time could not be explored due to lack of data. In addition, since we only utilized bootstrapping methods to generate CIs for the combined PAFs but not for each individual PAF, the potential impact of prevalence uncertainty may still exist. Finally, certain important reproductive factors like hormone replacement therapy were not involved due to data unavailability.

Conclusions

This study demonstrated that reproductive factors were associated with higher risks of stroke in Chinese postmenopausal women, with around 17.0% of strokes being attributable to lifetime reproductive factors. Moreover, high parity and no history of lactation accounted for the most stroke cases among low-SES and high-SES women, respectively. The lowest combined fraction of attributable stroke burden was found for women with high SES. Therefore, the allocation of health resources should also be optimized to improve the accessibility and equity of healthcare services. Also, the popularity of health education on reproductive health ought to increase with diverse focuses within different SES levels.

Abbreviations

SES	Socioeconomic status
PAF	Population attributable fraction
CKB	China Kadoorie Biobank
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
LCA	Latent class analysis
AIC	Akaike information criterion
BIC	Bayesian information criterion
MET	Metabolic equivalent of task
WC	Waist circumference
BMI	Body mass index
IQR	Interquartile range
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03976-5.

Additional file 1: Table S1 Test of goodness of fit of latent class models. Table S2 Characteristics of participants according to SES classes. Table S3 Incidence rate (per 10,000 person-year) of stroke and its subtypes by SES classes. Table S4 HRs and 95% CIs for association of reproductive factors with incident stroke and its subtypes across SES classes. Table S5 Population attributable fractions of reproductive factors with stroke and its subtypes. Table S6 HRs and 95% CIs for association of reproductive factors with incident stroke and its subtypes by residence. Table S7 Population attributable fractions of stroke and its subtypes with reproductive factors by residence. Table S8 HRs and 95% CIs for association of reproductive factors with incident stroke and its subtypes by annual household income. Table S9 Population attributable fractions of stroke and its subtypes with reproductive factors by annual household income. Table S10 HRs and 95% CIs for association of reproductive factors with incident stroke and its subtypes by occupation. Table S11 Population attributable fractions of stroke and its subtypes with reproductive factors by occupation. Table S12 HRs and 95% CIs for association of reproductive factors with incident stroke and its subtypes by education. Table S13 Population attributable fractions of stroke and its subtypes with reproductive factors by education. Fig. S1 Restricted cubic spline for age at menarche and total stroke risk.

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Authors' contributions

PS designed the study. WS managed and analysed the data. JW and WS prepared the first draft. WS, JW, SS, LH, ZL, and JZ reviewed and edited the manuscript, with comments from PS. All authors read and approved the final manuscript.

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Data availability

The raw China Kadoorie Biobank data underlying this article can be accessed via https://www.ckbiobank.org/CKBDataAccess, following the institution's data-access policies. Preliminary event adjudication data are not publicly available.

Declarations

Ethics approval and consent to participate

The CKB study obtained ethical approval from the Oxford University Tropical Research Ethics Committee (Approval No. 025–04) and the Chinese Center for Disease Control and Prevention Ethical Review Committee (Approval No. 005/2004). All participants provided written informed consent.

Consent for publication
This research has been conducted using the China Kadoorie Biobank (CKB) resource (www.ckbiobank.org, Request No. DAR-2020–00212). Publication of results does not require or imply approval by the membership of the CKB Collaborative Group.

Competing interests
The authors declare no competing interests.

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