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Lifetime Cumulative Effect of Reproductive Factors on Stroke and Its Subtypes in Postmenopausal Chinese Women

A Prospective Cohort Study

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Abstract

Background and Objectives

Multiple reproductive factors are associated with stroke. Little is known about the cumulative effects of reproductive factors during a reproductive life course on stroke and its subtypes, especially among female Chinese individuals. The objective of this study was to assess the associations of lifetime cumulative estrogen exposure due to reproductive factors with stroke and its etiologic subtypes among postmenopausal Chinese women.

Methods

Postmenopausal women without prior stroke at baseline (2004–2008) were selected from the China Kadoorie Biobank (CKB). Lifetime cumulative estrogen exposure due to reproductive factors was assessed using 3 composite indicators: reproductive lifespan (RLS), endogenous estrogen exposure (EEE), and total estrogen exposure (TEE). Stroke and its subtypes, ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH), were identified through linkage to a disease registry system and health insurance data during follow-up (2004–2015). Multivariable-adjusted Cox proportional hazards regression models were applied to estimate the adjusted hazard ratio (aHR) and 95% CIs for the risk of stroke by quartiles of RLS, EEE, and TEE, respectively.

Results

A total of 122,939 postmenopausal participants aged 40–79 years without prior stroke at baseline were included. During a median follow-up period of 8.9 years, 15,139 cases with new-onset stroke were identified, including 12,853 cases with IS, 2,580 cases with ICH, and 269 cases with SAH. Compared with the lowest quartile (Q1) of RLS, the highest quartile (Q4) had a lower risk of total stroke (aHR: 0.95, 95% CI 0.92–0.98), IS (aHR: 0.95, 95% CI 0.92–0.98), and ICH (aHR: 0.87, 95% CI 0.81–0.94). Both EEE and TEE displayed a graded association with the subsequent descending risk of total stroke (aHR for Q4 vs Q1: EEE: 0.85, 95% CI 0.82–0.89; TEE: 0.87, 95% CI 0.84–0.90), IS (aHR for Q4 vs Q1: EEE: 0.86, 95% CI 0.83–0.90; TEE: 0.86, 95% CI 0.83–0.89), and ICH (EEE: 0.73, 95% CI 0.65–0.81; TEE: 0.83,95% CI 0.76–0.91), with a p for trend < 0.001 for all these associations.

Discussion

Individuals' cumulative estrogen exposure due to reproductive factors could potentially be a valuable indicator for risk stratification of stroke events after menopause.

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Glossary

aHR = adjusted hazard ratio; **CDC** = Centers for Disease Control and Prevention; **CKB** = China Kadoorie Biobank; **DALYs** = disability-adjusted life-years; **EEE** = endogenous estrogen exposure; **HR** = hazard ratios; **ICD-10** = *International Classification of Diseases, 10th Revision*; **ICH** = intracerebral hemorrhage; **IQRs** = interquartile ranges; **IS** = ischemic stroke; **OCP** = oral contraceptive pill; **RLS** = reproductive lifespan; **SAH** = subarachnoid hemorrhage; **TEE** = total estrogen exposure.

Stroke is a major public health concern worldwide. In 2019, stroke was the third-ranked cause of disability-adjusted life-years (DALYs), accounting for 5.7% of all DALYs and 11.6% of all deaths.[1,2] In China, stroke has become a leading cause of death, with an annual estimated 2.4 million new-onset cases and 1.1 million stroke-related deaths.[3] Stroke has a multidimensional influence on patients' quality of life, with physical, psychological, cognitive, and social interaction domains being most affected.[4] Moreover, the increasing burden of stroke will continue to put a strain not only on stroke patients and their families but also on society.[5] Therefore, it is critical to identify risk factors contributing to stroke and its development, which may help to establish early prevention and management strategies for stroke.[6]

Compared with men, women were reported at a lower risk of stroke at young ages.[7] However, because estrogen production ceases during the postmenopausal phase, such cardiovascular protection decreases.[7,8] Previous research has identified postmenopausal status as an independent risk factor of stroke, in which the reduction of sex hormones has been suggested to be one of the drivers of stroke.[9] Moreover, other reproductive factors, such as early age at menarche, high parity, and no lactation, have been shown to contribute to the development of stroke.[10,11] To better understand the cumulative effect of reproductive experiences across women's reproductive life course, some composite indicators have been proposed by previous studies, including reproductive lifespan (RLS), endogenous estrogen exposure (EEE), and total estrogen exposure (TEE).[12] In previous studies, the lifetime estrogen level was often determined by RLS.[13] For instance, a recent systematic review and meta-analysis showed that female study participants with a shorter RLS duration had a higher risk of stroke than female study participants with a longer RLS.[14] By contrast, EEE and TEE have rarely been used to explore their association with stroke, despite evidence of their impact on stroke.[14] For example, a prospective study observed that a longer duration of EEE was significantly associated with an increased risk of cardiovascular disease mortality.[15]

To date, a few studies have investigated the association between the length of estrogen exposure and stroke risk. However, most of them have focused on cardiovascular disease as a whole or only a specific subtype of stroke and have drawn inconsistent conclusions.[14,16,17] Generally, pathophysiologic mechanisms differ between stroke subtypes. For example, while ischemic stroke (IS) and intracerebral hemorrhage (ICH) can both induce local hypoxia and destroy the brain tissue, IS is caused by the blockage of an artery, whereas ICH is caused by a blood vessel rupture.[18,19] Because of this variation in pathophysiology, it is necessary to distinguish stroke subtypes when exploring risk factors in epidemiologic studies, rather than taking stroke as a single disease entity. In addition, previous studies have mainly focused on female populations in European and American countries, such as the United Kingdom and the United States. Less research has been performed on female populations in Asia, especially in China.[13]

To fill this knowledge gap, this study uses data from the China Kadoorie Biobank (CKB) study to assess the associations of lifetime cumulative estrogen exposure due to reproductive factors with total stroke and various subtypes, including IS, ICH, and subarachnoid hemorrhage (SAH), among postmenopausal Chinese participants.

Methods

Study Design and Data Collection

The CKB study is a population-based longitudinal prospective cohort study. Details of the CKB study protocol have been published elsewhere.[20-22] In brief, the CKB study recruited 512,726 individuals aged 30–79 years from 10 geographical areas (5 urban and 5 rural) across China between June 25, 2004, and July 15, 2008. Baseline data were self-reported by the participants and collected by trained health workers through an interviewer-administered electronic questionnaire, which included questions on sociodemographic characteristics (e.g., age, sex, marital status, residential status, education, occupation, and household income), lifestyle (e.g., tobacco smoking, second-hand smoking, alcohol consumption, and physical activity), medication history (e.g., anticoagulation therapy and hypolipidemic therapy), and medical history (e.g., diabetes and hypertension). Detailed information on participants' reproductive history was also collected. Anthropometric measurements for all participants were recorded, including height, weight, waist circumference, and hip circumference.

Of the population captured by the CKB study, this study included postmenopausal female participants with normal age at menarche (9–18 years) and normal age at menopause

(aged 40 years or older).[23,24] This study excluded those with prior stroke, a history of hysterectomy, the removal of any breast lump or ovary, or a history of cancer. To avoid potential reverse causality, the study also excluded participants who had missing data related to age at menarche and menopause, parity, a history of lactation duration, the number of miscarriages or terminations, and oral contraceptive pill (OCP) use and those with missing data on covariates. Furthermore, the study excluded participants with outliers of RLS, EEE, or TEE (≤0 years). In total, 122,939 participants were included in the final analysis (Figure 1).

Ascertainment of Reproductive Factors

Female participants were asked to provide information on their age at menarche and menopause, parity, number of miscarriages or terminations, history of lactation, and history of OCP use. Age at menarche was divided into quartiles (Q): Q1 (9.0–13.9 years), Q2 (14.0–15.9 years), Q3 (16.0–16.9 years), and Q4 (17.0–18.0 years). Age at menopause was also divided into quartiles: Q1 (40.0–46.9 years), Q2 (47.0–48.9 years), Q3 (49.0–50.9 years), and Q4 (≥51.0 years). The number of pregnancies was classified into 5 groups: 1, 2, 3, 4, and 5 or more. The number of live births was divided into 5 categories: 0, 1, 2, 3, and 4 or more. The number of stillbirths was divided into 0 and 1 or more. The number of miscarriages or terminations was classified into 3 categories: 0, 1, and 2 or more. A history of lactation and a history of OCP use was divided into yes and no, respectively.

Components of Lifetime Cumulative Estrogen Exposure Due to Reproductive Factors

Components of lifetime cumulative estrogen exposure due to reproductive factors in this study include RLS, lifetime live births' duration, lifetime stillbirths' duration, lifetime miscarriages' or terminations' duration, lifetime lactation duration, and OCP use duration. RLS was defined as the age at menarche subtracted from the age at menopause. Lifetime lactation duration was defined as the sum of the lactation duration for each child, and OCP use duration was defined according to pill use years. The cumulative estrogen exposure due to reproductive factors of a woman was assumed to be 9 months for each live birth, 7 months for each stillbirth, and 3 months for each miscarriage or termination. The lifetime live births' duration, lifetime stillbirths' duration, and lifetime miscarriages' or terminations' duration were defined as follows:

$$\text{Lifetime live births}' \text{ duration (years)} = \text{number of live births} \times (9/12 \text{ years}) \quad (1)$$

$$\text{Lifetime stillbirths}' \text{ duration (years)} = \text{number of stillbirths} \times \left(\frac{7}{12} \text{ years}\right) \quad (2)$$

$$\text{Lifetime miscarriages}' \text{ or terminations}' \text{ duration (years)} = \text{number of miscarriages or terminations} \times (3/12 \text{ years}) \quad (3)$$

Indicators of Lifetime Cumulative Estrogen Exposure Due to Reproductive Factors

RLS has been defined as follows:

$$\text{RLS (years)} = \text{age at menopause (years)} - \text{age at menarche (years)} \quad (4)$$

Some studies have shown that estrogen levels decline after pregnancy, especially with lactation.[25,26] Furthermore, taking OCP could alter estrogen levels.[25,27] Based on the above-mentioned evidence, RLS, parity, lactation duration, terminations of pregnancy, and OCP use are all proxy indicators of lifetime EEE.[25] In this study, EEE was calculated by subtracting the following from RLS: lifetime live births' duration, lifetime stillbirths' duration, lifetime miscarriages' or terminations' duration, lifetime lactation duration, and OCP use duration[15]:

$$\begin{aligned}\text{EEE(years)} = \text{RLS (years)} &- \text{lifetime live births}' \text{ duration (years)} \\ &- \text{lifetime stillbirths}' \text{ duration (years)} \\ &- \text{lifetime miscarriages}' \text{ or terminations}' \text{ duration (years)} \\ &- \text{lifetime lactation duration (years)} - \text{OCP use duration (years)} \quad (5)\end{aligned}$$

The hypothesis for TEE was that pregnancy and OCP use represent relatively higher sustained blood estrogen levels.[28,29] Consequently, parity, termination of pregnancy, and OCP use contribute to a higher EEE, whereas lifetime lactation duration was excluded from TEE because it delays regular ovarian activity and the ovarian follicle generation of estradiol and therefore represents a period when estrogen levels are low[30]:

$$\begin{aligned}\text{TEE (years)} = \text{RLS (years)} &+ \text{lifetime live births}' \text{ duration (years)} \\ &+ \text{lifetime stillbirths}' \text{ duration (years)} \\ &+ \text{lifetime miscarriages}' \text{ or terminations}' \text{ duration (years)} \\ &- \text{lifetime lactation duration (years)} + \text{OCP use duration (years)} \quad (6)\end{aligned}$$

Ascertainment of Stroke and Its Subtypes

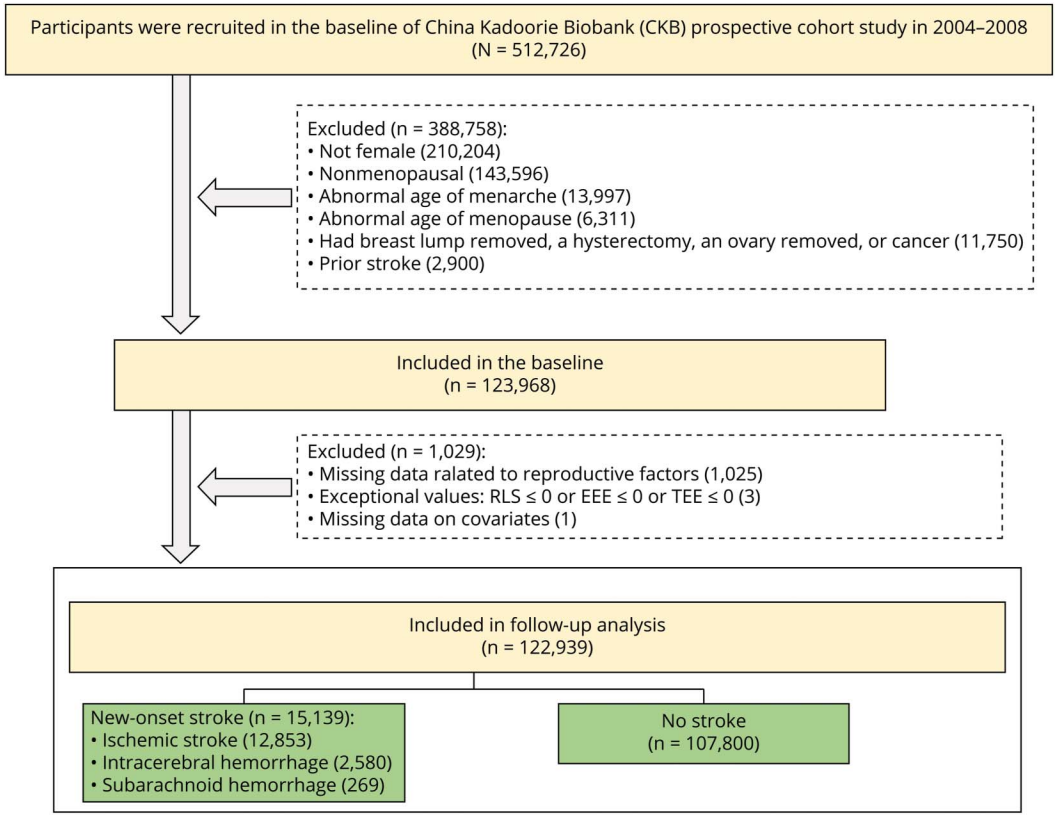
Data on stroke for all hospital admissions were gathered through a continuous linkage to electronic hospital records from the national health insurance system and death registers maintained by China's Disease Surveillance Points and Information System. All fatal and nonfatal cases of stroke reported by various sources were coded by trained medical staff, who were blinded to other personal information, and further reviewed by clinical researchers.

Stroke subtypes were coded according to the ICD-10. The major pathologic types examined in this study were IS (I63), including lacunar infarction and nonlacunar infarction; hemorrhagic stroke (mainly ICH) (I61); SAH (I60); and unspecified stroke (I64).

Definitions of Covariates

Participants' current marital status was classified into 2 groups: never married or separated or widowed or divorced; married. Residential status was divided into rural and urban.

Figure 1 Flowchart



EEE = endogenous estrogen exposure; RLS = reproductive lifespan; TEE = total estrogen exposure.

Education included 4 levels: lower than primary school, middle school, high school, and college and above. Occupation was divided into 5 categories: agriculture or factory worker; administrator or manager or professional or technical; sales or service workers or self-employed; retired or housewife or house husband or unemployed; and other or not stated. Annual household income was classified into 4 levels: <¥10,000, ¥10,000–19,999, ¥20,000–34,999, and ≥¥35,000. Both smoking status and drinking status were classified into 2 categories: never or occasional or former; current. Secondhand smoking was classified as occasionally (<1 time/wk) and frequently (≥1 d/wk). Physical activity was assessed using metabolic equivalents of task by hours per day spent on activities related to occupation, commuting, housework, and nonsedentary leisure time activities.[31] Body mass index was calculated by dividing body weight in kilograms by the square of height in meters (kg/m^2) and was further divided into <18.5 kg/m^2, 18.5–23.9 kg/m^2, 24.0–27.9 kg/m^2, and ≥28.0 kg/m^2. Diabetes was defined as fasting glucose ≥7.0 mmol/L, or random glucose ≥11.1 mmol/L, or self-reported physician diagnosis or under treatment. Hypertension was defined as blood pressure ≥140/90 mmHg or self-reported physician diagnosis or under treatment. The history of anticoagulation therapy, hypolipidemic therapy, stroke, diabetes, and hypertension was divided into yes and no, respectively.

Statistical Analysis

For baseline characteristics, normally distributed continuous variables were presented as mean values with SDs, and nonnormally distributed continuous variables were presented as medians with interquartile ranges (IQRs). Differences among continuous variables were compared using the *t* test or Wilcoxon test. Categorical variables were presented as percentages, and differences were compared using the χ^2 test. The incidence rate of new-onset stroke was calculated as the number of cases per 100,000 person-years.

To assess the association of new-onset stroke and its subtypes with relevant indicators and components of lifetime cumulative estrogen exposure due to reproductive factors, a stratified Cox proportional hazards model with stratification on the birth cohort (in 1-year intervals) and with attained age as the underlying time scale was used. The proportional hazards assumption was examined based on Schoenfeld residuals. Survival time was defined as the period from the date of the baseline interview to the date of diagnosis, the date of death, loss to follow-up, or December 31, 2015, whichever came first. The hazard ratios (HRs) and 95% CIs were estimated using floating absolute risk, which allows acceptable comparisons between any 2 exposure groups and decreases undesired correlation between coefficients.[32-34] Model 1 was adjusted

Table 1 Baseline Characteristics of Postmenopausal Participants Categorized by Incident Stroke

Variables	Total (N = 122,939)	Nonstroke (N = 107,800)	New-onset stroke (N = 15,139)	*p* Value
Age at baseline (y)[a]	58.3 (54.0–65.1)	57.8 (53.7–64.3)	63.0 (56.6–68.8)	<0.001
Age at menarche (y)[a]	16.0 (14.0–17.0)	16.0 (14.0–17.0)	16.0 (14.0–17.0)	<0.001
Age at menopause (y)[a]	49.0 (47.0–51.0)	49.0 (47.0–51.0)	49.0 (47.0–51.0)	0.004
Marital status				<0.001
Never married or separated or widowed or divorced	21,002 (17.1)	17,546 (16.3)	3,456 (22.8)	
Married	101,937 (82.9)	90,254 (83.7)	11,683 (77.2)	
Residential area				<0.001
Rural	66,599 (54.2)	59,514 (55.2)	7,085 (46.8)	
Urban	56,340 (45.8)	48,286 (44.8)	8,054 (53.2)	
Education				<0.001
Lower than primary school	89,238 (72.6)	78,620 (72.9)	10,618 (70.1)	
Middle school	20,276 (16.5)	17,760 (16.5)	2,516 (16.6)	
High school	10,088 (8.2)	8,714 (8.1)	1,374 (9.1)	
College or higher	3,337 (2.7)	2,706 (2.5)	631 (4.2)	
Occupation				<0.001
Agriculture or factory worker	49,487 (40.3)	45,083 (41.8)	4,404 (29.1)	
Administrator or manager or professional or technical	1,619 (1.3)	1,473 (1.4)	146 (0.9)	
Sales and service workers or self-employed	4,068 (3.3)	3,770 (3.5)	298 (2.0)	
Retired or housewife or house husband or unemployed	65,904 (53.6)	55,746 (51.7)	10,158 (67.1)	
Other or not stated	1,861 (1.5)	1,728 (1.6)	133 (0.9)	
Household income (¥/year)				<0.001
<10,000	39,899 (32.5)	34,653 (32.1)	5,246 (34.6)	
10,000–19,999	35,439 (28.8)	30,585 (28.4)	4,854 (32.1)	
20,000–34,999	28,009 (22.8)	24,998 (23.2)	3,011 (19.9)	
≥35,000	19,592 (15.9)	17,564 (16.3)	2,028 (13.4)	
BMI (kg/m^2)				<0.001
<18.5	6,374 (5.2)	5,724 (5.3)	650 (4.3)	
18.5–23.9	56,400 (45.9)	50,384 (46.8)	6,016 (39.7)	
24.0–27.9	43,163 (35.1)	37,428 (34.7)	5,735 (37.9)	
≥28	17,002 (13.8)	14,264 (13.2)	2,738 (18.1)	
WC (cm)[a]	80.2 (73.5–87.1)	80.0 (73.2–87.0)	82.3 (75.6–89.3)	<0.001
Smoking status				<0.001
Never or occasional or former	118,408 (96.3)	103,970 (96.4)	14,438 (95.4)	
Current	4,531 (3.7)	3,830 (3.6)	701 (4.6)	
Secondhand smoking				<0.001
Occasionally	56,434 (45.9)	48,924 (45.4)	7,510 (49.6)	
Most days	66,505 (54.1)	58,876 (54.6)	7,629 (50.4)	
Drinking status				0.050

Continued

Table 1 Baseline Characteristics of Postmenopausal Participants Categorized by Incident Stroke *(continued)*

Variables	Total (N = 122,939)	Nonstroke (N = 107,800)	New-onset stroke (N = 15,139)	*p* Value
Never or occasional or former	118,083 (96.1)	103,498 (96.0)	14,585 (96.3)	
Current	4,856 (3.9)	4,302 (4.0)	554 (3.7)	
Physical activity in MET (h/d)[a]	13.5 (8.9–21.8)	14.0 (8.9–22.5)	11.2 (8.4–16.0)	<0.001
History of anticoagulation therapy				<0.001
No	121,338 (98.7)	106,541 (98.8)	14,797 (97.7)	
Yes	1,601 (1.3)	1,259 (1.2)	342 (2.3)	
History of hypolipidemic therapy				
No	122,532 (99.7)	107,479 (99.7)	15,053 (99.4)	<0.001
Yes	407 (0.3)	321 (0.3)	86 (0.6)	
History of diabetes				<0.001
No	111,607 (90.8)	98,789 (91.6)	12,818 (84.7)	
Yes	11,332 (9.2)	9,011 (8.4)	2,321 (15.3)	
History of hypertension				<0.001
No	67,355 (54.8)	61,555 (57.1)	5,800 (38.3)	
Yes	55,584 (45.2)	46,245 (42.9)	9,339 (61.7)	
No. of pregnancies[a]	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	<0.001
No. of live births[a]	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	<0.001
No. of stillbirths[a]	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	<0.001
No. of miscarriages or terminations[a]	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.162
Lifetime lactation duration (y)[a]	3.0 (2.0–5.0)	3.0 (2.0–5.0)	4.0 (2.0–6.0)	<0.001
History of OCP use				<0.001
No	110,364 (89.8)	96,381 (89.4)	13,983 (92.4)	
Yes	12,575 (10.2)	11,419 (10.6)	1,156 (7.6)	
OCP use duration (y)[a]	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	<0.001
RLS (y)[a]	33.0 (31.0–36.0)	33.0 (31.0–36.0)	34.0 (31.0–36.0)	<0.001
RLS quartiles				<0.001
Q1 (<31 y)	28,956 (23.5)	25,312 (23.5)	3,644 (24.1)	
Q2 (31–32.9 y)	21,375 (17.4)	18,880 (17.5)	2,495 (16.5)	
Q3 (33–35.9 y)	38,075 (31.0)	33,633 (31.2)	4,442 (29.3)	
Q4 (≥36 y)	34,533 (28.1)	29,975 (27.8)	4,558 (30.1)	
EEE (y)[a]	27.3 (23.5–30.7)	27.5 (23.8–30.8)	26.5 (22.4–30.3)	<0.001
EEE quartiles				<0.001
Q1 (<23.5 y)	30,125 (24.5)	25,500 (23.7)	4,625 (30.5)	
Q2 (23.5–27.2 y)	29,936 (24.4)	26,285 (24.4)	3,651 (24.1)	
Q3 (27.3–30.6 y)	31,990 (26.0)	28,587 (26.5)	3,403 (22.5)	
Q4 (≥30.7 y)	30,888 (25.1)	27,428 (25.4)	3,460 (22.9)	
TEE (y)[a]	32.5 (29.3–35.3)	32.5 (29.3–35.3)	32.3 (28.8–35.3)	<0.001

Continued

Table 1 Baseline Characteristics of Postmenopausal Participants Categorized by Incident Stroke *(continued)*

Variables	Total (N = 122,939)	Nonstroke (N = 107,800)	New-onset stroke (N = 15,139)	*p* Value
TEE quartiles				<0.001
Q1 (<29.3 y)	29,760 (24.2)	25,671 (23.8)	4,089 (27.0)	
Q2 (29.3–32.4 y)	31,647 (25.7)	27,873 (25.8)	3,774 (24.9)	
Q3 (32.5–35.2 y)	29,218 (23.8)	25,937 (24.1)	3,281 (21.7)	
Q4 (≥35.3 y)	32,314 (26.3)	28,319 (26.3)	3,995 (26.4)	

Abbreviations: BMI = body mass index; EEE = endogenous estrogen exposure; MET = metabolic equivalents of task; OCP = oral contraceptive pill; RLS = reproductive lifespan; TEE = total estrogen exposure; WC = waist circumference.
Values are presented as number (N) with percent (%).
[a] Represents medians (M) with interquartile ranges (IQRs). *p* values represent statistical measurement of comparing nonstroke with new-onset stroke.

for age at baseline. Model 2 was further adjusted for other covariates defined earlier. Associations of each reproductive factor with the risk of stroke and its subtypes were assessed using a multivariable Cox regression model. In addition, a test for linear trends was conducted.

To examine the robustness of results, several sensitivity analyses were performed: (1) excluding cases of stroke occurring in the first 2 years of follow-up; (2) excluding participants who developed more than 1 subtype of stroke during follow-up; (3) excluding participants who were on medication (i.e., angiotensin-converting enzyme inhibitors, beta-blockers, calcium antagonists, diuretics, aspirin, and statins); and (4) excluding participants who reported having other chronic diseases (i.e., cancer, chronic heart disease, rheumatic heart disease, kidney disease, and psychiatric disorder) at baseline. Age-stratified Cox regression was also performed to deal with the bias caused by age.

Reporting of this study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (eTable 1, links.lww.com/WNL/C612).[35] Statistical significance was set at a 2-tailed $p < 0.05$. All statistical analyses were performed with SAS software, version 9.3, and graphs were plotted using R software, version 3.4.2.

Standard Protocol Approvals, Registrations, and Patient Consents

The CKB study obtained ethical approval from the Oxford Tropical Research Ethics Committee (approval number: 025–04, 3.2.2005; University of Oxford, the United Kingdom); the Chinese Center for Disease Control and Prevention (CDC) Ethical Review Committee (approval number: 005/2004, 9.7.2004; Beijing, China), and the local CDC of each study area. Before the baseline survey, all eligible participants in the CKB cohort provided written informed consent.

Data Availability

Cohort descriptions are available in the cohort profile.[20] Statistical code is available from Dr. Song (email, peigesong@zju.edu.cn). For the dataset, please refer to the CKB study website (ckbiobank.org) for data access policies and procedures.

Results

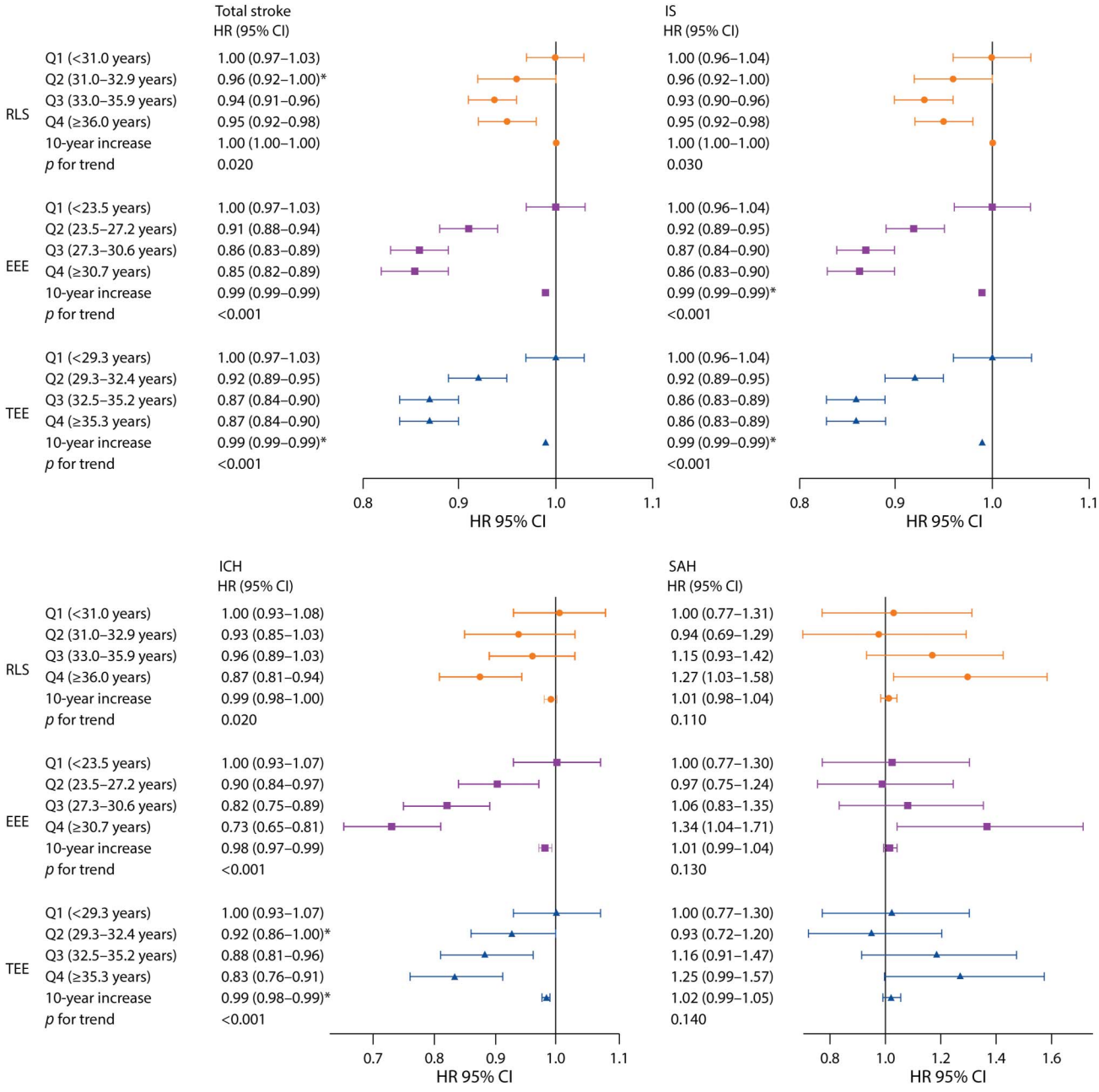
Study Population

The baseline characteristics of the 122,939 postmenopausal participants are summarized in Table 1. Among the included participants, the median age at menarche, menopause, and age at baseline were 16.0 years (IQR: 14.0–17.0), 49.0 years (IQR: 47.0–51.0), and 58.3 years (IQR: 54.0–65.1), respectively. These postmenopausal participants have a median lifetime cumulative estrogen exposure due to reproductive factors of 33.0 years (IQR: 31.0–36.0) for RLS, 27.3 years (IQR: 23.5–30.7) for EEE, and 32.5 years (IQR: 29.3–35.3) for TEE. Participants with new-onset stroke were more likely to have a longer duration of RLS, shorter EEE, and shorter TEE, compared with those without stroke ($p < 0.05$). The baseline characteristics by quartiles of RLS, EEE, and TEE are summarized in eTable 2–4, links.lww.com/WNL/C612. Over a median follow-up period of 8.9 years (IQR: 8.0–10.1), there were a total of 15,139 cases with new-onset stroke, including 12,853 cases of IS, 2,580 cases of ICH, and 269 cases of SAH (Figure 1). The incidence rate was 1,434.9 per 100,000 person-years for total stroke, 1,213.3 per 100,000 person-years for IS, and 234.8 per 100,000 person-years for ICH events after menopause (eTable 5 and eFigure 1, links.lww.com/WNL/C612).

Association of Lifetime Cumulative Estrogen Exposure Due to Reproductive Factors With Stroke

Multivariable associations of indicators for lifetime cumulative estrogen exposure due to reproductive factors with stroke have been shown in Figure 2 and listed in eTable 6, links.lww.com/WNL/C612. Compared with the lowest quartile of RLS, the observed association was more pronounced for the second and above RLS quartiles with total stroke (adjusted hazard ratio [aHR] varying from 0.94 [95% CI 0.91–0.96] to 0.96 [95% CI 0.92–0.997], p for trend = 0.02), for the third and above RLS quartiles with IS (aHR varying from 0.93 [95% CI

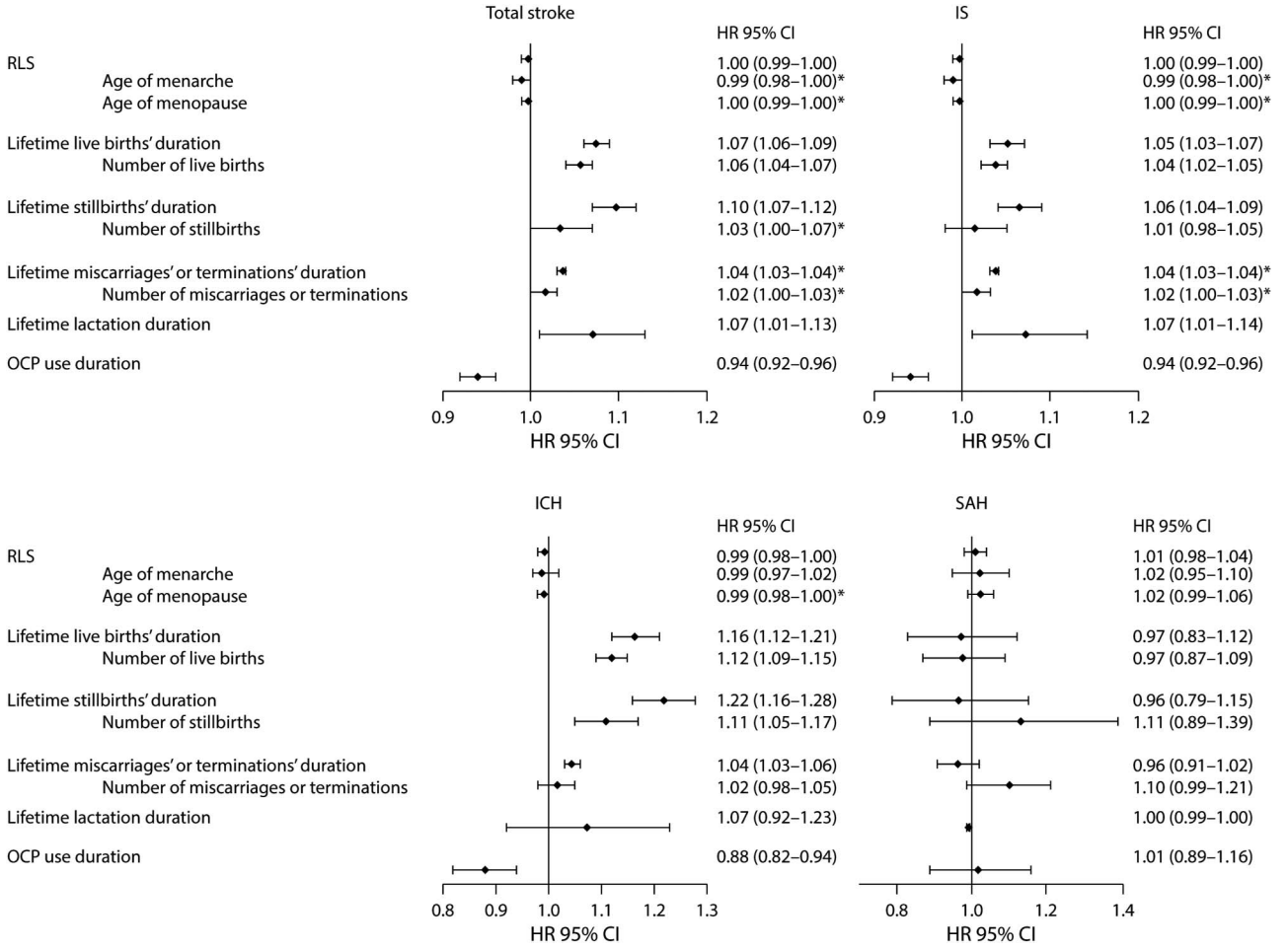
Figure 2 Association Between Indicators of Lifetime Cumulative Estrogen Exposure Due to Reproductive Factors and the Risk of Incident Stroke: Multivariable Cox Regression



*p < 0.05. HR was adjusted for age at baseline, marital status, residential status, education, occupation, household income, body mass index, waist circumference, tobacco smoking, secondhand smoking, alcohol consumption, physical activity in metabolic equivalent (h/d), anticoagulation therapy, hypolipidemic therapy, diabetes, and hypertension. HR = hazard ratio; RLS = reproductive lifespan; EEE = endogenous estrogen exposure; TEE = total estrogen exposure; IS = ischemic stroke; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage.

0.90–0.96] to 0.95 [95% CI 0.92–0.98], p for trend = 0.03), and for the highest quartile of RLS with ICH (aHR: 0.87, 95% CI 0.81–0.94). The increasing levels of EEE were associated with a descending risk of new-onset total stroke (aHR for the highest quartile relative to the lowest: 0.85, 95% CI 0.82–0.89; p for trend < 0.001), IS (aHR Q4 vs Q1: 0.86, 95% CI 0.83–0.90; p for trend < 0.001), and ICH (aHR Q4 vs Q1: 0.73, 95% CI 0.65–0.81; p for trend < 0.001). Similar associations and linear trends were also observed with TEE because higher quartiles of TEE were associated with a reduced risk of total stroke (aHR Q4 vs Q1: 0.87, 95% CI 0.84–0.90; p for trend < 0.001), IS (aHR Q4 vs Q1: 0.86, 95% CI 0.83–0.89; p for trend < 0.001), and ICH (aHR Q4 vs Q1: 0.83, 95% CI 0.76–0.91; p for trend < 0.001). Notably, the associations between these 3 indicators for lifetime cumulative estrogen exposure due to reproductive factors and SAH were relatively weak. Only the highest quartile of RLS and EEE were significant (aHR Q4 vs Q1 for RLS: 1.27, 95% CI

Figure 3 Association Between Components of Lifetime Cumulative Estrogen Exposure to Reproductive Factors and the Risk of Incident Stroke: Multivariable Cox Regression



*$p < 0.05$. HR was adjusted for age at baseline, marital status, residential status, education level, occupation, household income, body mass index, waist circumference, tobacco smoking, secondhand smoking, alcohol consumption, physical activity in metabolic equivalent (h/d), anticoagulation therapy, hypolipidemic therapy, diabetes, and hypertension. HR = hazard ratio; ICH = intracerebral hemorrhage; IS = ischemic stroke; OCP = oral contraceptive pill; RLS = reproductive lifespan; SAH = subarachnoid hemorrhage.

1.03–1.58; aHR Q4 vs Q1 for EEE: 1.34, 95% CI 1.04–1.71), and others were not found to be statistically significant.

Figure 3 shows the association between components of lifetime cumulative exposure due to reproductive factors and the risk of incident stroke. No statistical significance was observed between RLS and stroke. Furthermore, OCP use duration was associated with a decreased risk of new-onset stroke (aHR: 0.94, 95% CI 0.92–0.96), while lifetime live births' duration (aHR: 1.07, 95% CI 1.06–1.09), lifetime stillbirths' duration (aHR: 1.10, 95% CI 1.07–1.12), lifetime miscarriages' or terminations' duration (aHR: 1.04, 95% CI 1.03–1.04), and lifetime lactation duration (aHR: 1.07, 95% CI 1.01–1.13) were associated with an increased risk of stroke. Similar associations were also seen for IS and ICH. As for SAH, none of these components showed statistically significant associations.

Furthermore, the associations of each reproductive factor with stroke and its subtypes were also shown in Figure 3 and eTable 7 (links.lww.com/WNL/C612). Age at menarche (aHR: 0.99, 95% CI 0.98–1.00) and age at menopause (aHR: 1.00, 95% CI 0.99–1.00) were found to have a marginally statistically significant association with stroke. The associations for number of live births, number of stillbirths, and number of miscarriages or terminations with stroke are similar to the corresponding components. As for lactation, the risk of stroke was lower in participants who ever breastfed (aHR: 0.75, 95% CI 0.68–0.83) than those who never breastfed. Moreover, those with fewer stillbirths, miscarriages or terminations, and OCP use were less likely to develop stroke.

Sensitivity Analysis

A series of sensitivity analyses (eTable 8, links.lww.com/WNL/C612) were conducted among those without stroke occurring in the first 2 years of follow-up (N = 120,094), without more than 1 subtype of stroke during follow-up (N = 122,157), not under medication (N = 113,474), or without chronic disease (N = 113,752). The associations of RLS, EEE, and TEE with

stroke and its subtypes in these 4 samples were similar to the main findings. That is, the higher quartiles of EEE and TEE were associated with a lower risk of total stroke, IS, and ICH, respectively. As for RLS, the highest quartile was found to be significantly associated with stroke and its subtypes.

Age-Stratified Analysis

The age-stratified results (eTable 9, links.lww.com/WNL/C612) differed slightly from the main analyses. The associations of RLS with stroke and its subtypes were barely significant despite age stratification. As for EEE and TEE, the associations were hardly changed for total stroke and IS, and the association was weakened for ICH when stratified by age among female participants aged between 50 and 70 years. For postmenopausal participants aged between 40 and 50 years or older than 70 years, the highest quartiles of EEE and TEE were associated with a lower risk of total stroke and IS, while the effect on ICH almost lost statistical significance.

Discussion

This large prospective study in China demonstrated that higher levels of lifetime cumulative estrogen exposure due to reproductive factors were associated with a lower risk of new-onset stroke events among postmenopausal participants. The highest quartile of RLS duration was associated with a lower risk of total stroke, IS, and ICH. As for EEE and TEE, graded associations with a descending risk of total stroke, IS, and ICH were observed.

The association between RLS and the risk of stroke has been examined in previous studies. Overall, previous research has shown that female study participants with a longer RLS duration had a lower risk of stroke. However, there is less evidence demonstrating an association between RLS and IS or ICH. There remains a limited understanding of the association between RLS and stroke, particularly regarding the different etiologies of stroke subtypes. Some studies have found that a longer duration of RLS was associated with a lower risk of stroke.[36,37] Although a multicenter, age-matched, case-control study found that longer RLS duration may protect against noncardioembolic IS, other studies found no statistically significant associations of RLS duration with IS and ICH.[16,17,38] This study found that a longer RLS duration was associated with a decreased risk of IS and ICH, but an increased risk of SAH. By using distinct stroke subtypes, the study was able to show that lifetime estrogen exposure can lead to differential risks regarding the variety of etiologic subtypes, thereby adding nuances to this field.

The findings of longer RLS duration on stroke are mostly consistent with the potential mechanisms explained by previous research. The most common type of stroke, IS, is usually caused by blood clots that block or plug blood vessels in the brain.[18] Estrogen, which could be indirectly reflected by cumulative exposure to reproductive factors, has both rapid and long-term effects on the blood vessel wall.[39] According to current evidence, estrogens cause vasodilation by boosting the synthesis and secretion of nitric oxide and prostacyclin in endothelial cells.[40] They also relax the vascular smooth muscle cells by activating particular calcium channels through a cyclic guanosine monophosphate–dependent mechanism.[41] Unlike IS, ICH is usually caused by the presence of a hematoma and results in localized edema and neuronal damage in the brain parenchyma.[19] Studies have shown estrogens have neuroprotective effects.[42] In addition, the antioxidant properties of the steroid and reduction of NMDA receptor activation have been implicated as possible mechanisms.[43] As for SAH, it is an aneurysm and bleeding on the surface of the brain.[44] Although SAH and ICH have different pathophysiologies, the effect of estrogen on SAH is comparable with that on ICH. According to earlier epidemiologic studies, estrogen has a preventive impact on both conditions.[45,46] However, in this study, the effect of estrogen on SAH is opposite to that on ICH. This study found that the highest quartile of RLS and EEE showed a decreased risk of ICH, but an increased risk of SAH. The inconsistency between the findings from this study and previous epidemiologic research might be due to the limited cases of SAH and the lack of statistical power.

Regarding EEE or TEE, the associations between these indicators and stroke were controversial and less conclusive, given a limited number of studies. One prospective study showed that the highest quartile of EEE was significantly associated with an increased risk of cardiovascular disease mortality, whereas the association between EEE and stroke mortality yielded no statistical significance.[12] Limited by a small number of cases with new-onset stroke in this prospective study, its nonsignificant association between EEE and stroke was difficult to interpret. However, this study involved a large sample size to explore the associations of EEE and TEE with stroke and its subtypes. Furthermore, this study comprehensively incorporated multiple reproductive factors, including stillbirths into the EEE and TEE formulas, which was rarely seen in previous studies.[14] This study found that there were graded associations of longer duration of EEE and TEE, with decreased risks of total stroke, IS, and ICH. One potential explanation for these findings is the cardioprotective effect of estrogen.[39] Estrogen exerts protective effects on the blood-vascular systems, including antioxidant, vasodilating, and cholesterol-lowering effects.[47,48] An earlier study found that adverse changes in lipid and carbohydrate metabolism occur because of low plasma estrogen levels during the menopausal transition and shortly after menopause.[48]

In this study, the effects on RLS differed from those of EEE and TEE. This can at least partially be explained by the relatively crude measurement used for RLS, which only includes age at menarche and age at menopause without considering other reproductive factors. On the contrary, EEE and TEE were assessed more accurately because a considerable amount of detailed information about participants' reproductive history was taken into account in their computing formulas.[14]

Notably, EEE focuses on estrogen exposure originating from endogenous sources, subtracting estrogen exposure caused by pregnancy or OCP use, while TEE is supposed to represent exposure to total estrogen. Despite these differences, the results for EEE and TEE were similar. A possible reason for this is that the number of stillbirths, miscarriages, terminations, or OCP use made marginal contributions in the proposed formula, resulting in similarities between EEE and TEE. Furthermore, the mechanism of their effects was still not clear due to insufficient studies.

In addition, it was found that lifetime live births' duration, lifetime stillbirths' duration, lifetime miscarriages' or terminations' duration, and lifetime lactation duration were each associated with an increased risk of stroke, while OCP use duration was associated with a reduced risk of stroke. By contrast, an umbrella review and another systematic review have reported the increased risk of stroke with each live birth, a history of stillbirth or miscarriage, no lactation, and the use of OCP.[10,11] This difference might be partly explained by the lack of popularity and adoption of OCP within the Chinese population.[49] Because these components represent only 1 aspect of the reproductive system, the cumulative effect of combined reproductive factors on stroke may vary substantially. Hence, a better understanding of comprehensive indicators for cumulative lifetime exposure due to reproductive variables is critically needed.

This study has a number of important strengths. First, it not only used RLS but also EEE and TEE as lifetime cumulative estrogen indicators. Based on the availability of detailed reproductive variables, multiple reproductive factors, including stillbirth, were combined to reflect estrogen exposure levels. The study also explored how each reproductive factor interacted with stroke and its subtypes. All these aid in a better understanding of such interaction and the distinction between the component and calculation formula. Second, focusing on subtypes of stroke is another strength. The study provided complete long-term follow-up data on the incidence densities of stroke and expanded the outcome of stroke by differentiating into stroke subtypes. Third, this study possessed a large sample size from 10 geographical areas across China to investigate the associations of RLS, EEE, and TEE with total stroke and various subtypes. The study focused on the Asian population, which has been historically underrepresented in this research area. Fourth, the Cox models made good use of age as a time scale to shrink the effects of age during the follow-up in this cohort study.

Beyond these strengths, some limitations also warrant mentioning. First, information on reproductive factors was mainly collected based on participants' recall, which could have introduced errors due to recall bias. Second, the study could not adjust for unavailable genetic factors, early life factors, or diet, which might influence EEE and stroke.

Because the direct measures of estrogen exposure are difficult to ascertain, the indirect measures used in this study are important for population-level studies. Lifetime cumulative estrogen exposure due to reproductive factors adopted in our study might act as early warning indicators for stroke and its subtypes. They may also allow for individual reproductive factors to be comprehensively and visibly comparable, and this would be of major clinical and public health importance. Moreover, the findings from this study might help to increase the awareness on sex-specific risk factors for stroke and provide innovation for effective stroke prevention, such as targeting women who have a short duration of estrogen exposure with timely screening.

In conclusion, lifetime cumulative estrogen exposure due to reproductive factors, as indicated by RLS, EEE, and TEE, is associated with stroke events among postmenopausal women. For RLS, those in the highest quartile were found to have a lower risk of total stroke, IS, and ICH. As for EEE and TEE, higher quartiles were found to have a graded association with a descending risk of total stroke, IS, and ICH. Lifetime cumulative estrogen exposure due to reproductive factors could potentially be a useful indicator of women's risk of stroke events after menopause. However, further research is needed on the underlying biological, behavioral, and social mechanisms linking estrogen exposure with stroke risk across women's lifespans.

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Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Appendix Authors

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