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Life Course Reproductive Factors and Stroke Incidence and Progression in Women: Research Advances Postprint

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Abstract

Stroke is one of the leading causes of global disease and death burden, and also ranks first among causes of death in the Chinese population, having become a major public health problem that threatens public health and social development. Previous studies have shown that stroke exhibits significant sex differences in disease risk, influencing factors, and prognostic outcomes. Influenced by sex-specific reproductive factors, women typically face higher lifetime stroke risk and poorer post-stroke functional recovery, with the stroke-related disease burden in this population increasingly intensifying. Identifying key influencing factors specific to stroke onset in women and constructing a scientific early risk stratification system are critical pathways to achieving precision primary prevention and optimizing medical resource allocation. This article provides a comprehensive review of research on reproductive factors across the female life cycle and stroke occurrence and development, aiming to summarize the current research status of the impact of reproductive factors on stroke risk in women, thereby promoting in-depth research and clinical practice innovation in the field of women' s stroke.

Full Text

Review and Monograph: Research Progress on Lifetime Reproductive Factors and Stroke Development in Women

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Abstract

Stroke represents one of the leading causes of morbidity and mortality worldwide, ranking as the foremost cause of death in China and emerging as a critical public health challenge that threatens both population health and social development. Accumulating evidence demonstrates significant sex disparities in stroke risk, influencing factors, and prognostic outcomes. Due to sex-specific reproductive profiles, women generally face a higher lifetime risk of stroke and experience poorer post-stroke functional recovery compared to men, with stroke-related disease burden escalating in this population. Identifying female-specific determinants of stroke incidence and establishing scientific early risk stratification systems constitute essential pathways for achieving precise primary prevention and optimizing healthcare resource allocation. This review provides a comprehensive synthesis of research on women' s lifetime reproductive factors and stroke occurrence and progression, aiming to summarize the current state of evidence regarding how reproductive factors influence stroke risk in women and to promote further in-depth research and clinical innovation in women' s stroke.

Keywords: Stroke; Women; Reproductive factors; Life course; Risk prediction; Review

Introduction

Stroke refers to acute focal neurological dysfunction caused by sudden infarction or hemorrhage in the brain, retina, or related spinal cord regions, with symptoms persisting for more than 24 hours [1]. According to the Global Burden of Disease Study 2021 (GBD 2021), global stroke prevalence reached 93.8 million cases, with 11.9 million new cases and 7.3 million deaths accounting for 10.7% of total mortality, making stroke the third leading cause of death worldwide [2]. In China, the disease burden of stroke exceeds the global average. In 2021, China' s age-standardized stroke prevalence was 1,301.42 per 100,000, with age-standardized prevalence and incidence rates of ischemic stroke ranking highest globally [3]. As the leading cause of death among Chinese populations, stroke caused 2.19 million deaths in 2019, representing a 59.0% increase over the past 30 years and constituting a major public health problem that cannot be ignored [4-5]. Beyond individual health and social functioning, stroke imposes severe economic burdens on families, healthcare systems, and society at large [6]. Therefore, effective identification of major risk factors influencing stroke occurrence and development, coupled with targeted early prevention and intervention strategies, is crucial for reducing stroke-related disease burden in China.

Existing research indicates significant sex differences in stroke risk, influencing factors, and prognosis. With advancing age, women exhibit more pronounced

increases in stroke risk and face more severe adverse outcomes [7-8]. In low- and middle-income countries, female stroke mortality exceeds that of males [9]. Regarding cardiovascular risk factors, studies confirm that traditional risk factors such as smoking and diabetes exert significantly greater effects on women than men [10]. Beyond these conventional factors, women bear additional burdens from sex-specific risk factors, particularly key events in the female reproductive cycle that may exert short- or long-term effects on cardio-cerebrovascular metabolism [11]. The Lancet' s 2021 "Women and Cardiovascular Disease Commission" highlighted that research limitations, knowledge gaps, and inadequate diagnosis and treatment of cardiovascular disease in women persist globally, urgently requiring more sex-disaggregated research to collect accurate epidemiological data across gender groups, reveal potential sex-specific biological mechanisms, and address disparities in stroke prevention, diagnosis, and treatment to reduce the global burden of stroke in women [9].

The World Stroke Organization' s 2022 Global Stroke Fact Sheet revealed that 56% of stroke survivors globally are women [12]. GBD 2021 data showed approximately 46 million (43.5–48.8 million) prevalent cases and 5.7 million (5.1–6.3 million) incident cases among women, with 72.2 million disability-adjusted life years (DALYs) and 3.5 million deaths attributable to stroke [2,13]. Stroke ranks as the second leading cause of cardiovascular death in women worldwide, while in East Asia, Southeast Asia, high-income Asia Pacific regions, and southern sub-Saharan Africa, it is the foremost cause of cardiovascular mortality. Studies from the United States, Canada, and the Netherlands indicate that young women have stroke incidence rates equal to or higher than men, whereas middle-aged men show higher incidence than women—a gap that narrows after menopause and reverses after age 80 [14]. Due to women' s longer average lifespan, their lifetime cumulative stroke risk is higher. The Framingham Study estimated lifetime stroke risk at 20–21% for middle-aged women versus 14–17% for middle-aged men [15]. While hypertension, diabetes, atrial fibrillation, dyslipidemia, smoking, and obesity constitute common stroke risk factors, primary studies and meta-analyses demonstrate that atrial fibrillation and diabetes exert more pronounced effects on stroke risk in women compared to men [15-21].

China has undergone rapid health transitions and socioeconomic development in recent decades. Concurrently, lifestyle changes and environmental factors have elevated the prevalence of stroke risk factors such as hypertension, smoking, and obesity, significantly exacerbating China' s stroke burden [22]. A national stroke epidemiology survey revealed an age-standardized stroke prevalence of 1,426.2 per 100,000 among Chinese women, increasing continuously with age from 17.0 per 100,000 in the 20–29 age group to 4,805.4 per 100,000 in those $ $80 years [23]. The age-standardized incidence rate was 226.9 per 100,000 person-years, with an age-standardized mortality of 142.2 per 100,000 [23]. Between 1990 and 2019, China' s age-standardized overall stroke incidence decreased by 10.1%, while ischemic stroke incidence increased by 31.4% and DALYs grew by 21.5% [23].

1. Current Epidemiology of Stroke in Women

Stroke is characterized by sudden onset, rapid progression, high disability rates, and poor prognosis, causing severe harm to patients' health and lives [24]. A meta-analysis of 13 population-based stroke incidence surveys showed higher crude mortality rates in women at 1 and 5 years (mortality rate ratios [MRR] of 1.35 and 1.24, respectively), but this reversed after adjusting for age, pre-stroke functional limitations, stroke severity, and atrial fibrillation history (MRR of 0.81 and 0.76), suggesting women' s higher post-stroke mortality may be attributed to older age, more severe post-stroke symptoms, and higher atrial fibrillation prevalence [25]. Furthermore, female stroke patients generally experience poorer prognostic outcomes and lower health-related quality of life [26-27]. Women demonstrate inferior performance across multiple dimensions including pain, anxiety, depression, frailty, and functional activity, partially explained by older age, lack of social support, and greater emotional sensitivity to stressful events such as widowhood [28-30]. Female patients are also more prone to post-stroke depression. A systematic review of 45 primary studies reported a 78% higher risk of post-stroke depression in women [31], while another 2018 systematic review confirmed women had higher prevalence, incidence, or severity of depressive symptoms even after adjusting for age and stroke severity [32]. A prospective study of UK stroke patients over 25 years of follow-up found more severe anxiety symptoms and worse activities of daily living outcomes in female patients [33].

Findings regarding post-stroke cognitive dysfunction remain controversial. A US study of 1,227 first-time stroke patients examining cognitive function at 90 days post-stroke found significantly lower cognitive function in women, but this difference became non-significant after adjusting for covariates such as widowhood, education level, and pre-stroke cognitive function, suggesting these factors primarily drive female post-stroke cognitive impairment [34]. Another cohort study of US community-dwelling adults found that even after controlling for pre-stroke cognitive indicators, women still had higher post-stroke cognitive impairment incidence than men, particularly in the short term following stroke [35].

2. Health Hazards of Stroke in Women

Beyond the acute clinical manifestations, stroke' s long-term consequences disproportionately affect women across physical, psychological, and social domains. The higher mortality rates observed in women appear largely attributable to demographic and clinical characteristics rather than sex-specific biological factors, though the persistence of worse functional and quality-of-life outcomes suggests unique vulnerabilities. The elevated risk of post-stroke depression and anxiety in women warrants particular clinical attention, as these neuropsychiatric complications significantly impede rehabilitation and recovery. While cognitive outcomes show mixed patterns depending on adjustment for confounding variables, the overall evidence indicates women face a more challenging post-stroke

trajectory that demands sex-tailored interventions.

3. Association Between Women' s Lifetime Reproductive Factors and Stroke Risk

In addition to environmental and lifestyle-related cardiovascular risk factors, female-specific reproductive factors represent sex-specific risks that uniquely and profoundly influence women' s health across the lifespan. From menarche to menopause, women experience a series of physiological events throughout their reproductive cycle, with fluctuations in estrogen and progesterone levels and vascular endothelial changes that may contribute to vascular complications and potentially increase future cardio-cerebrovascular disease risk [11,36-39]. For instance, WELTEN et al. [40] reported that premature menopause was associated with increased ischemic stroke risk among Dutch postmenopausal women. A European study found that higher parity and early menarche were both associated with elevated stroke risk in women [41], while evidence also links miscarriage and stillbirth to stroke occurrence [42]. Consequently, scholars have recommended incorporating sex-specific risk factors into cardiovascular disease prediction models to avoid misclassifying women into low-risk categories [10].

3.1.1 Menarche Age Menarche marks the beginning of a woman' s reproductive cycle and signifies reproductive system maturation and endocrine function activation [43]. Previous research demonstrates that menarche age affects women' s cardiometabolic health, though findings remain inconsistent. The US Nurses' Health Study (NHS) found that women with menarche age $ 10*yearshadhighercardiovasculardiseaserisk*(*includingcoronaryheartdiseaseandstroke*)*comparedtothosew* *shapedassociationwithfatalstrokerisk*, *withbothearly*($12 or 13 years) and late (17–18 years) menarche associated with higher risk [37]. A large UK female cohort study observed a similar U-shaped association, with menarche age $ $10 years and $ $17 years associated with 16% and 13% increased stroke risk, respectively, compared to menarche at age 13 [45]. The association between menarche age and stroke and its underlying mechanisms remain under-investigated. Potential mechanisms linking early menarche to stroke risk include mediating effects of hypertension, diabetes, and hyperlipidemia [46], as well as shared risk factor pathways for early menarche and late cardiovascular events, including low birth weight and childhood overweight/obesity [37]. Conversely, later menarche age has been associated with increased brachial artery diameter and impaired flow-mediated dilation, with this endothelial dysfunction leading to systemic subclinical atherosclerosis that may partially explain the excess stroke risk associated with delayed menarche [47].

3.1.2 Adolescent Pregnancy Adolescent pregnancy severely impacts individual health and social development, representing a global public health priority identified by WHO and the UN Sustainable Development Goals [48]. Previous studies show adolescent pregnancy significantly increases risks of preeclampsia, systemic infection, preterm birth, and puerperal endometritis, which may

be associated with long-term cardio-cerebrovascular disease development [49]. Two Korean studies of postmenopausal women found that pregnancy before age 19 significantly increased hypertension and diabetes risks [50-51], both critical stroke risk factors. Potential biological mechanisms may involve abnormal early-life estrogen exposure, with the dramatic estrogen elevation during adolescent pregnancy overstimulating immature organ systems and disrupting physiological homeostasis [50]. Additionally, adolescent mothers often belong to socioeconomically disadvantaged groups with lower health literacy, unhealthy lifestyle patterns, and poorer healthcare access—factors persisting throughout the reproductive lifecycle that may exacerbate multiple stroke risk indicators including smoking, overweight/obesity, hypertension, and hyperglycemia [52-53].

3.2.1 Pregnancy and Delivery Pregnancy-related stroke refers to ischemic or hemorrhagic stroke occurring during pregnancy or the perinatal period. Evidence indicates approximately 30 per 100,000 pregnant women experience pregnancy-related stroke, with incidence about three times higher than in non-pregnant women of similar age [54]. By subtype, hemorrhagic stroke (including subarachnoid and intracerebral hemorrhage) and cerebral venous sinus thrombosis constitute higher proportions of pregnancy-related stroke, with major pathogenic mechanisms including cardioembolism, carotid artery dissection, reversible cerebral vasoconstriction syndrome, and vascular malformations [55-56]. Pregnancy-specific physiological remodeling imposes substantial vascular load through hemodynamic and vascular system changes, increased coagulation factor activity, and upregulated immune system sensitivity [54]. To meet increasing metabolic demands of mother and fetus, blood volume and cardiac output increase by approximately 45% compared to pre-pregnancy levels, potentially worsening pre-existing cardiac conditions and increasing vascular thrombotic events [57]. Additionally, pregnant women may experience systemic vasodilation and decreased resistance leading to venous stasis, compounded by increased coagulation factor activity and decreased physiological anticoagulants, creating a hypercoagulable state that elevates thrombosis risk 4–10-fold and may trigger embolic events including stroke [58]. Immune system regulation plays crucial roles in early placental implantation and perinatal induction and delivery, but dysregulated immune responses causing excessive inflammation may lead to endothelial dysfunction and increased stroke risk [59]. Other pregnancy complications such as gestational hypertension, preeclampsia, and gestational diabetes also constitute stroke risk factors [8]. Pregnancy and delivery effects extend beyond the perinatal period, influencing future health trajectories. A Chinese study showed women with multiple deliveries had higher future stroke risk compared to those with one delivery, with a dose-response relationship between live birth number and stroke risk [60]. A US cohort study found women with $ $5 live births had higher stroke risk than those with 1–2 live births, though this association became non-significant after adjusting for baseline BMI [61]. The relationship between childbearing age and future stroke risk has also attracted research

attention. Some studies suggest early childbearing age increases stroke risk, potentially related to low socioeconomic status and education, while others indicate later childbearing age also elevates risk through mechanisms including reduced vascular elasticity and impaired regulatory function in older mothers [62-64].

3.2.2 Breastfeeding Breastfeeding is crucial for infant development while conferring long-term health benefits to mothers [65]. A US cohort study of postmenopausal women found ever-breastfeeding was associated with 23% lower future stroke risk compared to never-breastfeeding, with risk decreasing further as lactation duration increased [66]. A large Chinese prospective cohort of postmenopausal women found significant inverse associations between lifetime lactation duration and incident ischemic and hemorrhagic stroke. Specifically, women with lifetime lactation >7 months had lower stroke risk compared to never-breastfeeding women [67]. The protective mechanisms of breastfeeding against stroke remain unclear. Previous research suggests breastfeeding may reset postpartum maternal metabolism, improving visceral fat accumulation and insulin resistance during pregnancy and maintaining cardiovascular health [11]. Additionally, breastfeeding stimulates oxytocin secretion, triggering neuroendocrine stress responses that reduce maternal inflammatory responses, creating a balanced cardiovascular environment that lowers atherosclerosis and stroke risk [67]. Some hypothesize breastfeeding reduces cardiovascular risk by mobilizing excess fat reserves accumulated during pregnancy, but studies show cardiovascular risk remains lower in breastfeeding women even after BMI adjustment [68], indicating protective effects extend beyond fat reduction through other unexplored mechanisms.

3.2.3 Pregnancy Loss Pregnancy loss events, including miscarriage and stillbirth, may cause potential vascular injury. An NHS II cohort study found women with miscarriage history had 20% higher stroke incidence, without significant mediation by hypertension, hyperlipidemia, or type 2 diabetes [69]. A meta-analysis of 18 studies showed women experiencing miscarriage or stillbirth had higher stroke risk, with each additional miscarriage or stillbirth increasing stroke risk by 13% and 25%, respectively. Recurrent miscarriage and stillbirth were associated with 42% and 14% excess stroke risk [70]. A potential linking mechanism involves vascular endothelial dysfunction, a common cause of miscarriage that also relates to late stroke development. Additionally, immune and inflammatory responses play important roles in pregnancy loss, particularly recurrent miscarriage, with alloimmune and autoimmune responses not only causing hemolysis and miscarriage but also promoting arterial thrombosis. Elevated antiphospholipid antibodies are significantly associated with ischemic stroke development [71].

3.3 Perimenopause and Postmenopause Menopause age and hormone therapy: Menopause marks the end of female fertility and the reproductive cy-

cle. With aging, ovarian function gradually declines and endogenous estrogen secretion with cardiovascular protective effects decreases, making menopause an important temporal factor influencing female cardiovascular disease incidence [72]. The 2021 ESC Guidelines on cardiovascular disease prevention and the 2019 ACC/AHA Guideline on primary prevention of cardiovascular disease both identify premature menopause as a "risk enhancer" or "risk modifier" for atherosclerotic cardiovascular disease to guide risk assessment [73-74]. Premature natural and surgical menopause are associated with traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes) as well as atrial fibrillation, venous thromboembolism, and stroke [11]. A European cohort study of postmenopausal women found those with menopause before age 40 had 48% higher stroke risk compared to those with menopause at 50–54 years, with each additional year of menopause age reducing stroke risk by 2% [40]. Some research suggests bidirectional associations between premature menopause and cardiovascular risk, where poor pre-menopausal cardiovascular health may lead to early menopause [11]. The relationship between menopausal hormone therapy and cardiovascular disease has received extensive attention. Clinical trial data indicate estrogen alone or combined estrogen-progestin therapy increases stroke risk (particularly ischemic stroke) [75], though some studies suggest low-dose estrogen formulations effectively alleviate menopausal symptoms without affecting late stroke risk [13].

3.4 Lifetime Cumulative Estrogen Exposure As research on female reproductive factors advances, scholars have proposed comprehensive reproductive indicators to assess the joint impact of life course events on women' s health. Reproductive lifespan, defined as the interval from menarche to menopause, serves as an indicator reflecting lifetime endogenous estrogen exposure. A large pooled study found women with reproductive lifespan <30 years had 75% higher stroke risk compared to those with 36–38 years, with the association remaining significant after adjusting for menarche and menopause ages [76]. Another study proposed a more complex comprehensive indicator of lifetime cumulative estrogen exposure, integrating reproductive lifespan, parity, pregnancy loss, lactation duration, and oral contraceptive use through detailed formulas to represent endogenous and total estrogen exposure patterns, then assessing associations with late stroke [77]. Research found that among Chinese postmenopausal women, the highest quartile of reproductive lifespan had lower risks of overall stroke, ischemic stroke, and intracerebral hemorrhage, with longer endogenous and total estrogen exposure associated with lower stroke risk [77]. Life course epidemiology provides theoretical frameworks and multiple applicable models for assessing cumulative effects of multiple risk factor exposures in chronic diseases, offering suitable methodological foundations for measuring combined reproductive factor impacts [78]. A prospective study of Chinese postmenopausal women used life course cumulative risk models to calculate contributions of multiple reproductive risk factor exposures to stroke burden, estimating that approximately 17.2% of incident stroke cases were attributable to combined reproductive factor influ-

ences [79]. Current empirical research on lifetime estrogen exposure and stroke development remains insufficient, with limited studies exploring overall effects and comprehensive evaluations of multiple reproductive factors. Existing composite indicators have limitations including incomplete coverage of reproductive factors and poor interpretability. Future women' s stroke research should increase attention to female-specific reproductive factors, reveal sex differences in stroke pathophysiological mechanisms, and optimize female-specific stroke prevention and control decision-making to reduce stroke-related health risks and safeguard women' s cardio-cerebrovascular health.

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