











ORIGINAL RESEARCH

Number of Live Births as a Protective Factor Against Clinical and Covert Brain Infarcts: The Framingham Heart Study

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BACKGROUND: Female-specific reproductive factors have been associated with stroke risk, although evidence for some factors (eg, live births) remains conflicting. We determined the association between number of live births and other female-specific reproductive factors and subsequent risk of stroke and magnetic resonance imaging markers of vascular brain injury in a community-based cohort.

METHODS: This was a prospective cohort study of 1882 (mean age, 61.3±9.6 years) women from the FHS (Framingham Heart Study) Offspring cohort who were stroke free at the baseline examination (1998–2001). Reproductive factors included number of live births, age at menopause, postmenopausal hormone replacement therapy use and serum estradiol and estrone levels. The primary outcome was incident all-cause stroke, with covert brain infarcts and white matter hyperintensity volume on brain magnetic resonance imaging as cross-sectional secondary outcomes.

RESULTS: During a median 18-year follow-up, 126 women had a stroke. On multivariable Cox proportional hazards models controlling for vascular risk factors, ≥3 live births (versus 0, reference) was associated with a reduced risk of stroke (hazard ratio, 0.51 [95% CI, 0.31–0.85]; $P<0.01$). More live births (≥3 versus 0) was cross-sectionally associated with decreased risk of covert brain infarct (odds ratio, 0.52 [95% CI, 0.30–0.92]; $P=0.03$). No significant association was detected between other reproductive factors and incident stroke or magnetic resonance imaging markers of vascular brain injury.

CONCLUSIONS: A greater number of live births was associated with a decreased risk of stroke and covert brain infarct in women and may be an important factor to include in female-specific clinical prediction rules for stroke.

Key Words: reproductive factors ■ risk prediction ■ stroke ■ women

Stroke is a major cause of morbidity and death and disproportionately affects women, with women experiencing a higher lifetime risk of stroke.¹ In the United States, 57% of all strokes occur in women, and by the year 2050, it is estimated that there will be an annual excess of 68 000 stroke deaths among women.^{1–3}

Female-specific reproductive factors, for example, age at menarche, age at menopause, circulating estrogen levels, number of pregnancies, and use of hormone replacement therapy, affect overall lifetime exposure to estrogen³ and have been implicated as important predictors of future stroke risk in women. Indeed, greater

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RESEARCH PERSPECTIVE

What Is New?

- A greater number of live births was associated with a decreased risk of stroke and covert brain infarcts in women.

What Question Should Be Addressed Next?

- Should reproductive factors, such as live births, be included in female-specific clinical prediction rules for stroke?

Nonstandard Abbreviations and Acronyms

CBI	covert brain infarct
FHS	Framingham Heart Study
PAI	physical activity index
pmHRT	postmenopausal hormone replacement therapy
WMHV	white matter hyperintensity volume

endogenous estrogen exposure has recently been associated with a lower burden of cerebral small-vessel disease in women.⁴ However, previous studies exploring the relationship between reproductive factors in women—in particular, number of live births or parity—and stroke risk have reported conflicting findings. For example, a number of studies have reported an association between nulliparity and an increased risk of stroke,^{5,6} while others have reported a reverse association, that is, an association between higher parity and increased stroke risk.^{6–10} In some studies, the association between parity and stroke risk has been obviated after adjusting for baseline cardiovascular risk factors.^{5,11} Many of the prior studies have been limited by a short duration of follow-up, self-reported rather than clinically validated cardiovascular risk factors and retrospective outcome assessment using diagnostic coding data or mortality records.^{5,6,10–13} In addition, subclinical vascular brain injury is more frequent than clinical stroke, and the relation of female-specific reproductive factors with subclinical markers such as covert infarcts and white matter hyperintensity burden remain to be fully elucidated.

Improving our understanding of the effect of reproductive factors in women on clinical stroke risk and subclinical vascular brain injury could help inform more accurate stroke risk prediction and opportunities for stroke risk mitigation in women. In this investigation, we prospectively evaluated the association of

female-specific reproductive factors, namely, number of live births, as well as age at menopause, circulating estrogen levels, and postmenopausal hormone replacement therapy (pmHRT) with stroke risk in a large community-based cohort with robust outcome assessment and longitudinal follow-up. We also assessed the association between these factors and cross-sectional intermediate neuroimaging markers of vascular brain injury, namely, covert brain infarcts (CBIs) and white matter hyperintensity volume (WMHV).

METHODS

Data Availability

The deidentified data used in these analyses can be obtained from the National Heart, Lung, and Blood Institute database and the National Center for Biotechnology Information Database of Genotypes and Phenotypes for the purposes of reproducing the results.

Study Sample

The study sample included participants from the FHS (Framingham Heart Study) Offspring cohort, which enrolled both the offspring of the original FHS cohort and the spouses of the offspring. It consists of 5124 people who were aged between 5 and 70 years at the time of enrollment in 1971. They undergo regular examinations every 4 years. Full details of the cohort and the examination protocol have been published elsewhere.^{14,15} For this study, we included women in the Offspring cohort who attended examination cycle 7 (baseline examination, 1998–2001; n=1914), who were confirmed free of stroke at the time of this examination (n=1885) and had available data on reproductive risk factors at examination 7 (n=1884). For the primary analysis of ischemic stroke, we included individuals who also had available stroke status on follow up (n=1882; Figure). For the secondary analyses, we included those with available data on brain magnetic resonance imaging (n=1171) and who were dementia free at this examination (n=1165; Figure). Written informed consent was obtained from participants at each examination cycle. The study design was approved by the institutional review board of the Boston University Medical Center.

Outcome Measures

The primary outcome was incident stroke (including both ischemic stroke and intracerebral hemorrhage). Stroke was clinically defined as the rapid development of focal neurological dysfunction of presumed vascular pathogenesis lasting for >24 hours. CBI and transient ischemic attack are not included as stroke based

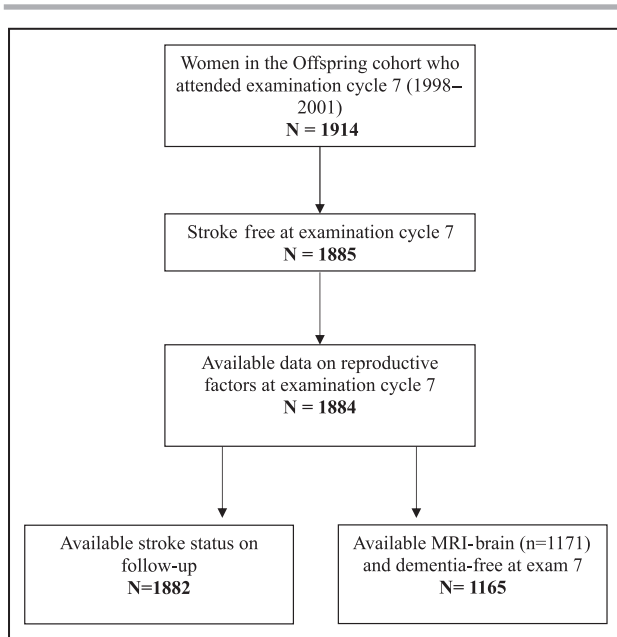


Figure. Selection of study participants. MRI indicates magnetic resonance imaging.

on this definition. Definitions of stroke subtypes were predetermined and were based on clinical features, imaging findings, and autopsy results. A diagnosis of ischemic stroke was made if there was no hemorrhage on imaging or if this diagnosis was reported at autopsy. All cases of stroke were clinically confirmed by an FHS neurologist and verified by a panel of 3 investigators. An independent tracking system is in place to ensure that all relevant clinical events are detected. A full description of the methods used to capture outcomes is available in Supplementary Methods.

The secondary outcomes assessed cross-sectionally were the presence or absence of CBIs on magnetic resonance imaging as well as WMHV. CBIs are defined as focal brain lesions most plausibly attributed to ischemia in the absence of a history of clinical stroke. A detailed description of the imaging methods has been published previously.¹⁶ In brief, the presence of CBIs was determined by 3 independent raters who used an image analysis system that permitted superimposition of the subtraction image, T2-weighted image and proton density image at 3x magnification. Only lesions >3mm were considered candidate CBIs.¹⁶ Values for agreement (κ) among the raters were between 0.73 and 0.90.

White matter hyperintensity volume (WHMV) was adjusted for intracranial volume and was calculated using a multistep imaging and statistical analysis process. First, images were prepared by subtracting the skull volume using an atlas-based method. Collected images were registered nonlinearly to a minimal deformation template synthetic brain image by using a cubic

B-spline. Tissue segmentation into gray matter, white matter, and cerebrospinal fluid was achieved using an expectation–maximization algorithm. The results were then further refined with a Markov random field model and an adaptive prior model. WMV was then calculated from the fluid attenuated inversion recovery sequence and 3-dimensional T1 images using a modified Bayesian probability structure. Prior-probability maps for white matter hyperintensities for use within the FHS were previously derived using imaging data from 700 individuals by combining a semiautomatic detection system with manual review. The likelihood estimates for the original images were obtained through histogram segmentation and thresholding. Initially, segmentation was performed in a standard space, yielding probability values for white matter hyperintensities at each voxel in the white matter. These values were then thresholded at 3.5 SDs above the mean to create a binary white matter hyperintensity mask.

Reproductive Factors

All reproductive factor variables were measured at examination cycle 7 (baseline examination) and were self-reported by participants through completion of a questionnaire at this examination. Number of live births was self-reported by participants and defined as the number of live children born to the participant, categorized as ≥ 3 children, 1 to 2 children, or no children (reference). Age at menopause (participant self-reported) was defined as the age at which periods had been absent for ≥ 1 year and was further categorized into natural, surgical, and chemotherapy/radiotherapy-induced menopause. Categories of menopausal age were ≤ 49 years, 50 to 51 years (reference), and ≥ 52 years. The reference categories for menopause were predefined on the basis of reported mean ages in high-income countries.^{17–20} pmHRT was defined as previous or current use of any product self-reported to be hormone therapy after or around the time of menopause. Serum estradiol and serum estrone concentrations (pm/mL) were measured at examination cycle 7 in samples collected between 7:30 and 9:30 AM after an overnight fast. Values were log transformed to approximate a normal distribution. Serum levels of estradiol and estrone were measured via a liquid chromatography–tandem mass spectrometry assay, which has previously been described,^{21,22} and were certified via the Hormone Standardization Program of the Centers for Disease Control and Prevention. In summary, 200 μ L serum aliquots were spiked with internal standard, extracted, derivatized with dansyl chloride, and then analyzed using liquid chromatography–tandem mass spectrometry 2-dimensional chromatographic separation. For both estradiol and estrone assays, the

lower limit of quantitation was 2 pg/mL; the interassay coefficients of variation for estrone were 4.5%, 7.7%, and 6.9% at concentrations of 8, 77, and 209 pg/mL, respectively, and for estradiol, were 6.9%, 7.0%, and 4.8% at concentrations of 8, 77, and 206 pg/mL, respectively.

Demographics and Clinical Variables

We included demographics and baseline covariates (measured at examination 7), including age, education status, physical activity index (PAI), systolic blood pressure, use of antihypertensive treatment, history of cardiovascular disease, diabetes, current smoking, and history of atrial fibrillation. Education status was categorized as no high school degree, high school but no college degree, and college degree or higher. The PAI was calculated as participant self-reported metabolic work completed during a 24-hour period.²³ Systolic blood pressure was measured at the patient's left arm while seated and was defined as the mean of 2 physician recorded measurements. History of cardiovascular disease included coronary artery disease (comprising previous myocardial infarction, unstable angina, stable angina, and other coronary insufficiency), peripheral vascular disease (including intermittent claudication) and congestive cardiac failure. Diabetes was defined as a fasting plasma glucose ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL, or record of use of an antihyperglycemic medication. Current smoking was participant self-reported and included reported smoking within 1 year of the baseline examination.

Statistical Analysis

Serum levels of estradiol and estrone levels were log transformed, thereby approximating a normal distribution. Cox proportional hazards models were generated to estimate the association between individual reproductive factors and risk of stroke during follow-up. Model 1 (primary model) adjusted for age, cardiovascular disease, diabetes, current smoking, history of atrial fibrillation, baseline systolic blood pressure, and use of antihypertensive therapy. In addition, in the model with pmHRT as the predictor variable, we also adjusted for age at menopause, given that age at menopause may confound this specific association. In addition, in the models with serum estradiol and serum estrone as the predictor variables, we also adjusted for menopausal status and use of pmHRT, given that the use of pmHRT and presence/absence of menopause may confound these specific associations. Model 2 additionally adjusted for education status and PAI. Participants were followed from the time of the baseline examination to the time of incident stroke or time of stroke-free death or date

the participant was last confirmed to be stroke free. In all analyses, proportional hazards assumptions were maintained. Results are reported as hazard ratios (HRs) with 95% CIs.

For secondary outcomes, multivariable linear and logistic regression models were generated to determine the association between reproductive factors and WMHV and CBIs. Model 1 accounted for baseline age, age squared (due to the nonlinear relationship with age), time between the baseline examination and completion of magnetic resonance imaging brain, total intracranial volume (for WMHV), prevalent cardiovascular disease, current smoking, diabetes, history of atrial fibrillation, baseline systolic blood pressure, use of antihypertensive therapy, age at menopause (for the model with pmHRT as predictor variable), menopausal status and use of pmHRT (for the model with serum estradiol and estrone as predictors only), and cause of menopause (surgical versus natural, for analyses with menopausal age as the predictor). Model 2 additionally adjusted for PAI and education status.

We completed a priori sensitivity analyses, (1) including only those with natural menopause and excluding those with surgical-, radiation-, or chemotherapy-induced menopause; and (2) including only those with ischemic stroke (excluding intracerebral hemorrhage). We also completed a post hoc sensitivity analysis, adjusting for baseline serum estrone and estradiol for all outcomes, for the predictor variable of "number of live births." For all analyses, $P < 0.05$ was considered statistically significant, and statistical analyses were completed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

The study sample included 1882 women for the primary outcome of incident stroke. The mean age of participants at baseline was 61.3 ± 9.6 years. The median duration of follow up was 18.2 (interquartile range, 14.2–19.5) years. Full baseline characteristics are shown in [Table 1](#).

Stroke

During the study follow-up period, 126 (6.7%) women had an incident stroke. Using a multivariable Cox proportional hazards model adjusted for major cardiovascular risk factors, a higher number of live births (≥ 3) was associated with a reduced hazard of incident stroke (HR, 0.51 [95% CI, 0.31–0.85]; $P < 0.01$) when compared with nulliparous women. There was no association noted between age at menopause, serum estradiol, serum estrone, or use of pmHRT and risk of incident stroke ([Table 2](#)).

Table 1. Baseline Characteristics

	Overall	No live births	1–2 live births	≥3 live births	P value*
	1882	255/1875 (13.6)	737/1875 (39.3)	883/1875 (47.1)	...
Age, y, mean±SD	61.3±9.6	58.7±10.5	59.1±9.8	63.9±8.4	...
Education					<0.0001
No high school degree	79/1846 (4.3)	7/249 (2.8)	29/724 (4.0)	42/866 (4.9)	...
High school degree but no college degree	1227/1846 (66.5)	137/249 (55.0)	463/724 (63.9)	621/866 (71.7)	...
College degree or higher	540/1846 (29.3)	105/249 (42.2)	232/724 (32.0)	203/866 (23.4)	...
Physical activity index, median (IQR)	36.0 (33.2, 40.4)	35.2 (32.4, 39.4)	35.8 (33.2, 39.8)	36.8 (33.6, 40.7)	0.002
Systolic blood pressure, mean±SD	126.3±20.0	123.5±20.9	124.3±18.8	129.0±20.5	<0.0001
Prevalent cardiovascular disease	152/1882 (8.1)	15/255 (5.9)	51/737 (6.9)	85/883 (9.6)	0.02
Atrial fibrillation	38/1882 (2.0)	6/255 (2.4)	6/737 (0.8)	26/883 (2.9)	0.09
Current smoking	268/1882 (14.2)	42/255 (16.5)	107/737 (14.5)	118/883 (13.4)	0.21
Diabetes	158/1764 (9.0)	16/240 (6.7)	57/693 (8.2)	84/826 (10.2)	0.06
Body mass index, mean±SD	27.6±5.9	27.2±6.7	27.3±5.7	28.0±5.7	0.002
Postmenopausal	1484/1772 (83.8)	174/241 (72.2)	545/697 (78.2)	760/828 (91.8)	...
If yes					...
Natural	1014/1480 (68.3)	129/174 (74.1)	362/544 (66.5)	518/757 (68.4)	...
Other (surgical/chemotherapy/radiation)	466/1480 (31.5)	45/174 (25.9)	182/544 (32.9)	239/757 (31.0)	...
pmHRT use (current or prior)	645/1879 (34.3)	66/255 (25.6)	258/735 (35.1)	319/882 (36.2)	...
Age at menopause, mean±SD	47.0±6.7	46.7±6.9	46.4±6.8	47.56.5	...
Age at menopause, y					...
≤49	796/1484 (53.7)	102/174 (58.6)	317/545 (58.2)	374/760 (49.2)	...
50–51	289/1484 (19.5)	28/174 (16.1)	100/545 (18.4)	160/760 (21.1)	...
≥52	399/1484 (26.9)	44/174 (25.3)	128/545 (23.5)	226/760 (29.7)	...
Serum estradiol, pg/mL, median (IQR)	13 (7, 29)	13.5 (7, 35)	14 (7, 33)	12 (7, 24)	...
Serum estrone, pg/mL, median (IQR)	41 (25, 92)	44 (24, 91)	41 (25, 98.5)	40 (24, 88)	...

Values are presented as n/N (%) unless otherwise specified. IQR indicates interquartile range; and pmHRT, hormone replacement therapy.

*P values for trend were calculated across selected variables using Cochran–Armitage trend tests and linear regression models. Education was coded as 0=no high school degree or high school degree but no college degree and 1=college degree or higher. Log transformations were applied to body mass index and physical activity index to address skewness.

Neuroimaging Outcome Measures

Using multivariable linear and logistic regression models and controlling for age, time to magnetic resonance imaging completion, and vascular risk factors, ≥3 live births compared with no live births, was associated with a reduced risk of CBI (odds ratio, 0.52 [95% CI, 0.30–0.92]; *P*=0.03). There was no association between any reproductive factor and WMHV (Table 3).

Sensitivity Analysis

The association between higher number of live births (≥3) and incident stroke remained significant when the analysis was limited to those with natural menopause only (Tables S1–S2) and when the analysis was limited to only ischemic strokes (Table S2).

DISCUSSION

We found that a higher number of live births was associated with a reduced risk of both clinical stroke and

covert stroke in this community-based prospective cohort study. There was no association between other female-specific reproductive factors and clinical stroke or neuroimaging markers of vascular brain injury, after adjusting for baseline cardiovascular risk.

The association we observed between a higher number of live births and reduced stroke risk persisted, even after accounting for age and vascular risk factors, and remained significant in a sensitivity analysis limited to ischemic stroke events. Due to the small numbers of women with higher-order numbers of live births, we were unable to explore a dose–response relationship beyond the categories of 1 to 2 live births and ≥3 live births. A number of previous studies have assessed the relationship between number of live births (ie, number of babies born alive) or parity (which has been differentially defined as the number of pregnancies carried to at least 24 weeks; the number of pregnancies ≥24 weeks ending in live birth; the number of pregnancies ≥28 weeks ending in live birth; and the number of births, including live births and stillbirths, ≥20 weeks)

Table 2. Reproductive Factors in Women and Risk of Stroke

Predictor variable	Stroke cases/N (%)	Risk of incident stroke					
		Model 1		Model 2		Model 3	
		126/1882					
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age at menopause							
≤49y	59/796 (7.4)	1.28 (0.75–2.17)	0.37	1.08 (0.62–1.86)	0.79	...	
50–51y	19/289 (6.6)	Ref		Ref		...	
≥52	28/399 (7.0)	1.27 (0.71–2.28)	0.42	1.20 (0.66–2.16)	0.55	...	
Number of live births							
0	21/255 (8.2)	Ref		Ref		Ref	
1–2	44/737 (6.0)	0.67 (0.39–1.14)	0.14	0.71 (0.40–1.26)	0.24	0.69 (0.36–1.24)	0.23
≥3	61/883 (6.9)	0.51 (0.31–0.85)	0.01	0.55 (0.32–0.95)	0.03	0.49 (0.27–0.91)	0.02
Serum estradiol	103/1645 (6.3)	1.08 (0.82–1.43)	0.58	1.07 (0.79–1.44)	0.65	...	
Serum estrone	103/1653 (6.2)	1.08 (0.79–1.49)	0.62	1.14 (0.81–1.60)	0.45	...	
Use of pmHRT	126/1879 (6.7)	0.99 (0.61–1.60)	0.96	0.80 (0.47–1.35)	0.41	...	

Serum estradiol and estrone levels were log transformed to approximate a normal distribution. Model 1 adjusted for age, cardiovascular diseases, diabetes, current smoking, history of atrial fibrillation, baseline systolic blood pressure, and use of antihypertensive therapy. In addition, in the model with pmHRT as the predictor variable, we also adjusted for age at menopause, given that age at menopause may confound this specific association. In addition, in the models with serum estradiol and serum estrone as the predictor variables, we also adjusted for menopausal status (presence/absence of menopause) and use of pmHRT, given that use of pmHRT and menopausal status may confound these specific associations. Model 2 additionally adjusted for physical activity index and education status. Model 3 additionally adjusted for baseline serum estradiol and serum estrone (for the model with number of live births as the predictor). HR indicates hazard ratio; and pmHRT, postmenopausal hormone replacement therapy.

and risk of subsequent stroke. Several studies have shown an association between “high parity” (defined as ≥4, ≥5 or ≥6) and increased risk of stroke.^{6,9,10,24} Other studies have found that nulliparity is associated with an increased stroke risk, when compared with ever-parity.⁵ Some studies have demonstrated a dose–response association between number of live births and stroke risk,^{24,25} while others have found no effect.¹¹

There may be several reasons for the inconsistency in findings across studies. Studied populations differ in terms of how they adjusted for background cardiovascular risk factors in their models. Of the large cohort studies we identified that specifically looked at the number of live births or parity,^{9,11,24} none adjusted for the presence of atrial fibrillation, the incidence of which has been associated with increasing number of births.²⁶ Studies also varied in their duration of follow-up (7 years²⁴ to 30 years⁹). Studies of shorter duration, particularly those including younger participants, premenopausal individuals, and those reporting fewer strokes overall,²⁴ may underestimate a potential protective effect of increased estrogen exposure, particularly in the postmenopausal or later-life period. The cited studies also vary in their chosen reference point for number of live births and indeed the way they were ordinally grouped. One of the larger studies that reported a positive association between number of live births and stroke did not include women who had no live births at all and reported a similar level of hazard for all categories above a single live birth,²⁴ which may

explain the discrepancy with our findings. Another large study that reported no association between increasing live births and stroke risk used a reference point of 1 live birth rather than no live births (as in our study).⁹

The cited studies varied significantly in their method of primary outcome assessment, with many using diagnostic coding data as their main measure^{5,6,10,12} rather than clinical validation of stroke, which is more reliable.²⁶ Some studies used parity rather than live births. Although the terms are closely related and are frequently used interchangeably in the literature,⁴ they do differ slightly. Parity refers to all births after 24 weeks, regardless of whether the infant is stillborn, while number of live births refers to all infants born viable, irrespective of gestational age. It is unlikely that number of live births and parity would differ significantly given the relative rarity of viable births <24 weeks²⁷ and stillbirth,²⁸ respectively. Compared with other studies, our findings are strengthened by the inclusion of comprehensive risk factor data, use of clinically validated stroke outcome, and a long duration of follow-up. However, our findings do not prove causality and will require further replication.

Consistent with our findings for the outcome of clinical stroke, a higher number of live births was also associated with a reduced risk of CBIs. Several previous studies have also demonstrated a decreased risk of cerebral small-vessel disease with increasing parity.^{4,29}

One candidate explanation for the association between increased live births and decreased risk of overt

and covert stroke may be that the type of increased circulating estrogen during pregnancy has a neuro-protective effect against stroke.³⁰ Laboratory data demonstrate protective effects of estrogen on the vascular endothelium as well as improved cerebral blood flow and vascular reactivity,^{1,31} while animal model data indicate that extended periods of higher endogenous estrogen exposure, for example, during pregnancy, result in sustained enhancement of endothelial and neuronal estrogen receptors.^{32–35} Furthermore, several studies have demonstrated that indicators of higher lifetime estrogen exposure (such as longer reproductive life span and greater total lifetime endogenous estrogen exposure) are associated with a decreased stroke risk.^{13,36,37} Alternatively, an increasing number of live births may reflect a decreased likelihood of infertility and miscarriage, which themselves are risk factors for stroke.³⁸ Another candidate explanation is that an increased number of live births may reflect decreased duration of time exposed to hormonal contraceptive methods, which can have complex effects on total estrogen exposure^{39,40} and have been independently associated with an increased stroke risk.^{41–46} We did not have reliable data available on oral contraceptives to interrogate this. Hormonal factors other than estrogens may plausibly have a role also. For example, pregnancy is associated with a 9-month bolus of high levels of vascular endothelial growth factor and other angiogenic factors.⁴⁷ These factors have complex vascular effects, which may be sustained after pregnancy.⁴⁸ Finally, the association may be due to the effects of unmeasured confounders, for example, socioeconomic status, marital status and duration, religious beliefs, social and extended family support, healthy lifestyle choices during pregnancy (eg, avoiding alcohol and smoking), and breastfeeding duration, which were not accounted for in our analyses (data unavailable).

We did not find an association between other measured reproductive factors and stroke or neuroimaging outcomes in our study, although associations have been described in the literature. For example, menopause was not associated with incident stroke in our study, despite other studies demonstrating an association between earlier menopause and increased risk of ischemic stroke.^{49,50} However, the attenuation of effect when menopause is surgically induced⁵⁰ along with negative results from a recent Mendelian randomization study⁵¹ have led some to speculate that the association may be the result of confounding. Use of pmHRT was not associated with stroke or neuroimaging markers of vascular brain injury in our study. The nature of the association between stroke and HRT use remains controversial and may depend on timing of commencement (eg, earlier use within 5 years of menopause versus later commencement of use) and duration of use.^{52,53} In our study, we did not have

reliable data available on the timing, type, and duration of use of pmHRT to further explore this.

Our study has several notable strengths, including comprehensiveness of data on exposures and outcomes, clinical confirmation of stroke, a population confirmed to be free from stroke at baseline, an extensive 18-year surveillance period, and inclusion of a community-based cohort. There are, however, several limitations. The population was predominantly White European American, which may restrict the generalizability of our findings. Furthermore, we did not collect data on gestational diabetes, gestational hypertension/preeclampsia, or number of miscarriages, which can have implications on estrogen exposure and stroke risk, and we did not have available data on serum estradiol levels at multiple time points throughout the reproductive life span, including during pregnancy. In addition, we were unable to account for several unmeasured confounders, for example, socioeconomic status, income level, marital status, religiosity, social support, healthy lifestyle during pregnancy, and duration of breastfeeding. In addition, our results were not adjusted for multiple testing. Finally, we did not have neuroimaging data available at baseline, and so we cannot rule out the possibility that the association between the number of live births and CBI is due to reverse causation.

CONCLUSIONS

A greater number of live births was associated with a decreased risk of stroke and covert brain infarcts. Our findings would suggest that reproductive factors, for example, number of live births, may be an additional risk factor to consider when stratifying risk of stroke in women. Inclusion of this risk factor in female-specific clinical prediction rules for stroke may enhance risk prediction in women, but this will require further study.

ARTICLE INFORMATION

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Disclosures

The authors report no conflicts of interest. Dr McGrath had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Supplemental Material

Tables S1–S2

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