Parity As a Protective Biomarker Against Silent Brain Infarction in Community-Dwelling Older Adults: The Sefuri Study

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Background: Although several studies have reported an association between parity and increased risk of stroke, this relationship remains controversial. *Aims*: The present study aimed to determine whether parity is associated with silent brain infarction (SBI), independent of other confounders. *Methods*: We analyzed the brain magnetic resonance imaging findings in 576 of community-dwelling older adults with a mean age of 72.1 years. All female participants were asked to provide information regarding the total number of live births, their age at the last parity, and their age at menopause. *Results*: The prevalence of SBI and the number of infarcts per participant were higher in men than in women. Although all women who had given birth (0, 1-2, 3-4, or 5+ times) exhibited lower age-adjusted odds ratios (ORs) for SBI than men, a significant difference was observed between women with ≧5 births and men after adjustment for common vascular risk factors (OR: .348, 95% confidence interval [95% CI]: .123-.986). Among women who had given birth, the relationship between fertility and SBI was attenuated, but was enhanced after adjustment for age at the last parity (OR: .300, 95% CI: .102-.886). *Conclusions*: Our findings indicate that fertile women may be protected against SBI or cerebral small vessel disease via the biological effects associated with reproductive activity, and that high fertility may be a marker of protection against SBI. However, late childbearing may blunt protective effects of fertility against SBI.

Key Words: Silent stroke—parity—pregnancy—menopause—magnetic resonance imaging—vascular risk factors

Introduction

Because stroke is less common among women than men, researchers have speculated that female sex may be a strong protective factor against stroke.[1] The incidence of silent brain infarction (SBI) is 5 times higher than that of incident stroke in the general population, and most cardiovascular or stroke risk factors increase the risk of SBI.[2] Hence, SBI may be a better surrogate marker of cerebral arteriosclerosis than symptomatic stroke. Our previous study demonstrated that male predominance of SBI was largely due to the higher prevalence of cigarette smoking and alcohol use among men than among women.[3,4] In women, however, adverse outcomes of pregnancy such as preeclampsia and gestational diabetes may increase the risk of cardiovascular disease in later life.[5-7] In fact, although several studies have reported an association between parity and increased risk of stroke,[8-11] this remains controversial.[12,13] The disposable soma theory emphasizes the optimal balance between somatic maintenance/repair versus reproduction (i.e., the trade-off between longevity and reproduction).[14,15] Nonetheless, the ability to have many children may be a marker for

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slow aging and longevity.[16,17] Within this context, we hypothesized that the beneficial effects of biological sex on SBI can be predicted based on the number of births, even after adjustment for common vascular risk factors. However, to date, no study has examined the risk of SBI in relation to parity or female fertility. Therefore, the present study aimed to analyze the risk of SBI in relation to reproductive history (particularly number of births).

Methods

Participants and Protocol Approval

Between1997 and 2017, we performed a cross-sectional observational study in the rural community of Sefuri village (Saga, Japan), which had a total population of 1739 as of April 2014. We performed a total of 1805 magnetic resonance imaging (MRI) scans in 832 older adults living independently at home and without apparent dementia. We excluded individuals aged <60 years (n = 155). A total of 101 individuals were further excluded due to claustrophobia or contraindications for MRI (n = 9), a history of stroke (n = 30), brain tumor (n = 5), psychiatric disorders including dementia (n = 17), a history of head trauma (n = 5), renal failure (n = 3), Parkinson's disease (n = 1), and insufficient clinical information (n = 31).

The National Hospital Organization Hizen Psychiatric Center Institutional Review Board approved the study (approval number: 15-1 and 24-4). In 1997, informed consent was obtained by T.Y.; since 1998, written informed consent was obtained by T.Y. or H.Y. from all participants.

Clinical Assessments

Participants underwent a structured clinical interview, general hematology tests, and biochemical tests. After a 5 minutes resting period, blood pressure was measured in the sitting position using a standard cuff method. Beginning in 2013, simultaneous blood pressure measurements were recorded from both arms using a pair of automated sphygmomanometers (Omron model HEM-1020, Omron, Japan). The blood pressure values obtained from the right arm were used throughout the current study. Mean blood pressure was calculated as diastolic blood pressure plus one-third of the pulse pressure. Vascular risk factors were defined as previously described.[18] Briefly, arterial hypertension was considered present in participants with a history of repeated blood pressure recordings above 140/90 mm Hg, and in those being treated for hypertension. Diabetes mellitus was defined as fasting plasma glucose greater than 6.99 mmol/L (126 mg/dL) and/or HbA1c greater than 6.5%, or a previous diagnosis of diabetes mellitus. Hyperlipidemia was considered present in participants with a total serum cholesterol concentration greater than 5.69 mmol/L (220 mg/dL), and in those being treated for hyperlipidemia. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation for the Japanese modification: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine [mg/dL])$^{-1.094}$ × (age)$^{-.287}$ × (.739 if female). Smoking was defined when the participant had smoked at least an average of 10 cigarettes per day, while former smokers were considered nonsmokers. Alcohol use was defined when the participant reported drinking 1 or more alcoholic beverages (10 g of ethanol) per week.

Reproductive History

All female participants were asked to provide information regarding the total number of live births, the age at which they had given birth to their last child, and the age at menopause using a questionnaire.[4] Grand multiparity was defined as parity of 5 or more according to the consensus that parity ≧5 is associated with a higher rate of obstetric complications (e.g., gestational diabetes and gestational hypertension), neonatal morbidity, and perinatal death.[19,20] Natural menopause was considered to have occurred if a woman had ceased menstruating naturally for at least 1 year, and the age at natural menopause was defined as the self-reported age at the last menstrual period. Early menopause was defined as menopause prior to the age of 40 years. Women were also asked to provide information regarding the cause of menopause (natural, surgical, or other), whether a hysterectomy was performed, the number of ovaries removed, and the use of hormone replacement therapy.

Assessment of MRI Findings

A combination of T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images is required to accurately detect both SBI and white matter lesions.[21] Between 1997 and 2009, T1-weighted (repetition time [TR]/echo time [TE] = 510/12 ms), T2-weighted (TR/TE = 4 300/110 ms), and FLAIR (TR/inversion time [TI]/TE = 6750/1600/22 ms) images with a slice thickness of 6 mm and an interslice gap of 1 mm were obtained using a 1.0 T MRI scanner (Magnex XP, Shimadzu, Japan). Beginning in 2010, we used 1.5 T MRI scanner (Achieva, Philips, the Netherlands) with essentially the same parameters to obtain T1-weighted, T2-weighted, and FLAIR images. The definitions and imaging methods utilized in the present study were concurrent with the neuroimaging standards for studies on small vessel disease.[22] SBI was defined by low signal intensities on T1-weighted images, and high signal intensity areas on T2-weighted images, and their size was 3 mm or larger as previously described.[18] We differentiated enlarged perivascular spaces from SBI based on their location, shape, and size; lesions of less than 3 mm in diameter are more likely to be perivascular space than lacunes. White matter lesions (deep white matter lesions and periventricular hyperintensities) were defined as isointense with normal brain

parenchyma on T1-weighted images, and high signal intensity areas on T2-weighted images.[23] Two authors (H. Y. and A.U.), who were blinded to all clinical data, independently reviewed all scans.

Statistical Analysis

We excluded 40 cases with missing data (no MRI [n = 9], or insufficient clinical information largely due to missing data regarding reproductive history [n = 31]), analyzing data from a final total of 576 participants without imputation. All clinical variables are presented as the mean ± standard deviation. All tests were 2-sided, and the level of statistical significance was set at $P < .05$. The data were analyzed using IBM SPSS Statistics version 18 for Windows (SPSS Japan Inc., Tokyo, Japan).

For the univariate analysis, chi-square or Fisher's exact tests were used to investigate between-group differences in categorical variables, while unpaired *t* tests were used to investigate differences in continuous variables. Pearson correlation coefficients were used to assess the relationship between the number of births and birth year or age at the last parity. Multiple comparisons were performed using analysis of variance followed by Bonferroni testing. Analysis of covariance (ANCOVA) was used to examine independent dose−effect relationships between the number of births and cholesterol levels/mean blood pressure with age as the covariate. The homogeneity of regression assumption was investigated by including independent variable/covariate interactions in the initial analysis step of ANCOVA.

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for SBI were estimated via binary logistic regression analysis. We hypothesized that a categorical variable subdivided according to the number of births (0, 1-2, 3-4, or 5 +) would represent the extent of sex-related protection against SBI. Because this protection should be at a minimum in men, men were served as the reference category. The association between SBI and the number of births was tested using logistic regression models adjusted for age (model 1); adjusted for age, hypertension, diabetes mellitus, hyperlipidemia, renal function (model 2); and further adjusted for alcohol use and smoking (model 3). In the sensitivity analysis, we excluded participants born after1936 or included women only. We also evaluated whether age at the last parity was associated with SBI, using the same logistic regression models.

Results

Background Characteristics

The present study included 576 community-dwelling adults (246 men and 330 women) with a mean age of 72.1 years. Diabetes mellitus, alcohol use, and smoking were more prevalent in men, while hyperlipidemia was more prevalent in women (Table 1). SBI was detected in 100 (17.4%) participants. SBI was more frequent in men than in women (21.1% versus 14.5%, $P = .039$), and the number of infarcts per participant was larger in men than in women (2.2 ± 1.7 versus 1.6 ± .9, $P = .034$; Table 2). A total of 188 lacunes were observed in 100 participants (109 in the basal ganglia, 21 in the thalamus, 47 in the corona radiata, and 11 in the hindbrain); there were no differences in the locations of SBI between men and women. No significant difference in the prevalence of white matter lesions was observed between men and women.

Among the 330 women, the mean age at natural menopause was 48.6 ± 4.6 years, the mean number of children was 3.2 ± 1.3, and the mean age at the last parity was 31.0 ± 4.6 years. A total of 22 (6.7%) participants reported no births, while 49 (14.8%) reported 5 or more births. The number of births was gradually decreased over time (Fig 1). Four participants reported undergoing hormone replacement therapy.

The ANCOVA homogeneity of regression slopes assumption—with age as the covariate—was met for high-density lipoprotein (HDL) cholesterol but not for total cholesterol. The mean value of HDL cholesterol was lower in participants with ≧5 births than in those with <5 births (57.1 [95% CI: 51.3-62.9] mg/dL versus 64.2 [95% CI: 62.3-66.1] mg/dL, respectively).

Although the prevalence of hypertension did not significantly differ between men and women, we further compared mean blood pressure levels between the each of the parity groups and men. The ANCOVA homogeneity of regression slopes assumption—with age as the covariate—was met for mean blood pressure, and mean blood pressure values did not significantly differ between groups.

Association between Reproductive Activity and SBI

Logistic regression analysis revealed that women with ≧5 births had the lowest OR (.243 [95% CI: .091-.645]) for SBI adjusted for age, hypertension, diabetes, hyperlipidemia, and eGFR (Table 3, all participants, model 2). This OR was attenuated to .348 (95% CI: .123-.986) after adjustment for smoking and alcohol use, yet remained significant (Table 3, all participants, model 3), suggesting the presence of fertility-related protection against SBI independent of common vascular risk factors. Sensitivity analysis indicated that the observed relationship between the number of births and SBI remained significant when the analysis was limited to participants born prior to 1935 (n = 311; Table 3, birth year: 1904-1935). We also performed the same analyses with excluding participants who had undergone obstetric/gynecological surgery (n = 59). Although the level of significance was slightly attenuated, the results were not substantially different from those obtained in analyses of all participants (Table 3, exclusion of participants with a history of obstetric/gynecological surgery).

Table 1. *Characteristics of the study population*

	Female: number of birth									
	0	(n = 22)	1-2	(n = 97)	3-4	(n = 162)	5≦	(n = 49)	Male (n = 246)		*P* for trend
Age, mean (SD), years	72.4	(5.5)	70.5	(7.5)	72.5	(6.7)	78.6	(7.1)	71.2	(7.5)	<.001
Education, mean (SD), years	9.5	(2.3)	10.2	(2.3)	9.6	(2.0)	8.0	(1.5)	10.5	(2.5)	<.001
Body mass index, mean (SD), kg/m^2	23.0	(2.7)	23.0	(3.3)	23.2	(3.7)	22.7	(3.3)	23.0	(3.2)	NS
Hypertension, n (%)	7	(31.8)	42	(43.3)	69	(42.6)	25	(51.0)	100	(40.7)	NS
Antihypertensive medication, n (%)	7	(31.8)	41	(42.3)	67	(41.4)	25	(51.0)	88	(35.8)	NS
Systolic BP, mean (SD), mmHg	146.3	(24.2)	146.0	(21.8)	142.3	(19.7)	149.0	(24.8)	142.5	(21.1)	.198
Diastolic BP, mean (SD), mmHg	79.2	(10.1)	78.9	(11.0)	76.6	(10.6)	74.1	(10.0)	81.3	(10.0)	<.001
Diabetes mellitus, n (%)	2	(9.1)	6	(6.2)	13	(8.0)	4	(8.2)	39	(15.9)	.039
Hyperlipidemia, n (%)	8	(36.4)	33	(34.0)	40	(24.7)	4	(8.2)	36	(14.6)	<.001
Total cholesterol, mean (SD), mg/dL	205.8	(38.2)	210.1	(33.4)	200.5	(34.4)	197.7	(33.9)	188.0	(36.5)	<.001
HDL cholesterol, mean (SD), mg/dL	58.6	(13.7)	66.1	(16.2)	63.9	(16.6)	59.2	(13.5)	60.3	(16.5)	.009
Alcohol, n (%)	4	(18.2)	5	(5.2)	14	(8.6)	5	(10.2)	162	(65.9)	<.001
Smoking, n (%)	0	(.0)	0	(.0)	4	(2.5)	1	(2.0)	62	(25.8)	<.001
Ischemic heart disease, n (%)	1	(4.5)	8	(8.2)	10	(6.2)	4	(8.2)	18	(7.3)	NS
Chronic kidney disease, n (%)	2	(9.1)	12	(12.4)	35	(21.6)	16	(32.7)	45	(18.3)	.028
eGFR, mean (SD), mL/min/1.73 m^2	71.9	(12.8)	73.4	(14.5)	70.9	(15.7)	66.8	(17.1)	73.8	(15.7)	.036
Silent brain infarction, n (%)	3	(13.6)	12	(12.4)	27	(16.7)	6	(12.2)	52	(21.1)	NS
Deep white matter lesions, n (%)	11	(50.0)	42	(43.3)	74	(45.7)	23	(46.9)	102	(41.5)	NS
Periventricular hyperintensities, n (%)	7	(31.8)	18	(18.6)	36	(22.2)	20	(40.8)	69	(28.0)	.033

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein. NS, $P > .2$.

Table 2. *MRI findings*

	Female n = 330	Male n = 246	*P*
Silent brain infarction, n (%)	48 (14.5)	52 (21.1)	.039
Number of infarcts per participant, mean ± SD	1.6 ± .9	2.2 ± 1.7	.034
Locations of silent brain infarction			N.S.
Basal ganglia, n (%)	41 (53.9)	68 (60.7)	
Thalamus, n (%)	8 (10.5)	13 (11.6)	
Corona radiata, n (%)	22 (28.9)	25 (22.3)	
Brainstem/Cerebellum, n (%)	5 (6.6)	6 (5.4)	
Deep white matter lesions, n (%)	150 (45.5)	102 (41.5)	N.S.
Periventricular hyperintensities, n (%)	81 (24.5)	69 (28.0)	N.S.

Age at the last parity was—as expected—positively associated with the number of births (r = .476, $P < .001$). When analyses were restricted to women who had given birth, the association between the number of births and SBI was attenuated (Table 4, models 1 and 2). However, the OR was enhanced after further adjustment for age at the last parity (OR: .300, 95% CI .102-.886) (Table 4, model 3), suggesting that older age at the last parity or late childbearing blunted the protective effects of fertility against SBI.

Discussion

In the present cross-sectional study, we observed that women with ≧5 births exhibited significantly lower ORs for SBI than men, independent of common vascular risk factors. Indeed, extremely low prevalence of smoking in women (n = 5 of 330, 1.5%) accounted for a substantial portion of the low prevalence of SBI in women, although the effects of parity remained significant even after adjusting for smoking status. Protection against SBI in women was associated with the number of births, suggesting that fertility-related biological factors exert protective effects against the development of cerebral arteriosclerosis. Nonetheless, we cannot completely rule out unmeasured lifestyle-related confounders associated with low SBI prevalence. Endogenous estradiol may be an indicator of stroke risk or general health status,[24,25] while previous studies have indicated that postmenopausal hormone replacement therapy increases the incidence of stroke, in contrast to a hypothesized major risk reduction.[26] However, longer life time exposure to endogenous estrogen has been shown to protect against ischemic stroke.[27] Therefore, a healthy lifestyle and uneventful or active reproductive history may explain the lower risk of stroke among women than among men. Hence, our findings indicate that a history of high fertility may be a unique biomarker or a protective factor against SBI in healthy older women. In contrast, higher age at the last parity or late childbearing appeared to attenuate the protective effects associated with high fertility (i.e., a trade-off between fertility and higher age at childbearing).

Recent studies have reported controversial results regarding the relationship between parity and stroke. In a large population-based cohort study of Chinese women, women with ≧5 pregnancies exhibited a hazard ratio of 1.45 (95% CI 1.18-1.77) for incident stroke after adjustment for potential confounders; furthermore, lifestyle risk

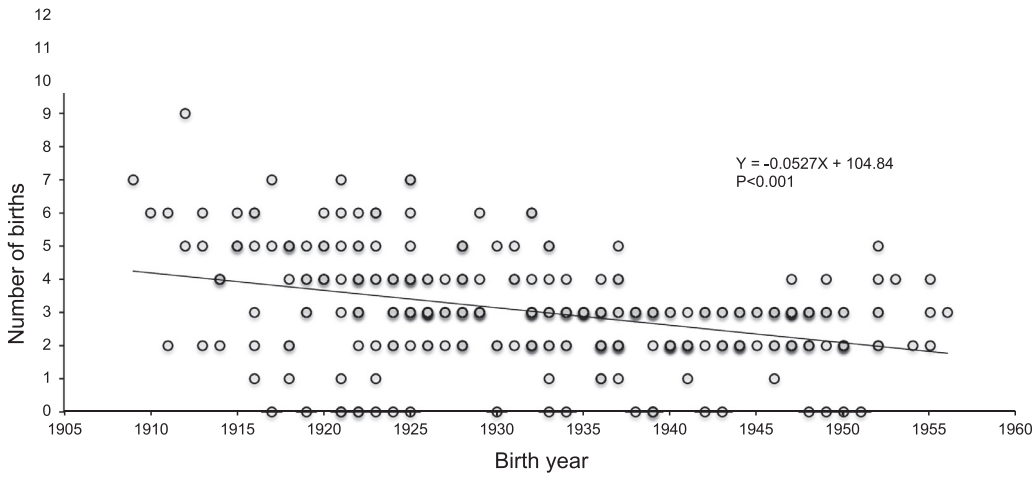

Figure 1. ***Relationship between the birth years of the mother and number of births.*** *Birth number had decreased with the times in female subjects of the present study; at birth year of 1910, the mean number of births was about 4, which decreased to about 2 at 1950.*

Table 3. *Logistic regression analysis for the association between number of births and silent brain infarction*

		Model 1			Model 2			Model 3		
Number of births	n	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
All subjects										
0	22	.554	.155-1.977	.363	.642	.175-2.351	.503	.998	.256-3.883	.998
1-2	97	.536	.266-1.077	.080	.532	.256-1.105	.090	.847	.357-2.011	.706
3-4	162	.671	.395-1.141	.141	.650	.375-1.126	.125	.984	.496-1.952	.962
5≦	49	.269	.103-.702	.007	.243	.091-.645	.005	.348	.123-.986	.047
Birth year 1904-1935										
0	12	.833	.209-3.322	.796	.824	.195-3.485	.792	1.623	.341-7.728	.543
1-2	34	.544	.212-1.398	.206	.492	.176-1.378	.177	.921	.285-2.970	.890
3-4	98	.593	.313-1.122	.108	.522	.264-1.035	.063	.922	.399-2.130	.849
5≦	47	.245	.092-.649	.005	.189	.068-.524	.001	.317	.104-.961	.042
Excluding obstetric and gynecology surgery										
0	17	.792	.213-2.939	.727	.953	.247-3.673	.944	1.602	.385-6.668	.517
1-2	78	.501	.228-1.103	.086	.451	.197-1.035	.060	.767	.292-2.017	.591
3-4	131	.718	.409-1.262	.250	.683	.381-1.224	.200	1.087	.527-2.241	.822
5≦	45	.271	.103-.716	.008	.236	.087-.638	.004	.350	.121-1.014	.053

Model 1: adjusted for age; Model 2: adjusted for age, hypertension, diabetes, hyperlipidemia, and eGFR; and Model 3: further adjusted for alcohol habit, and smoking.

factors and the social or emotional factors associated with child rearing—in addition to biological factors—may explain the increased risk of coronary heart disease and stroke in both sexes (i.e., also among spouses of women).[9] A recent cross-sectional study in China also revealed that women who had experienced 3 or more live births exhibited a higher risk of stroke.[10] One previous study reported that increases in the number of births were associated with increases in the risk of brain hemorrhage and subarachnoid haemorrhage,[11] while another study demonstrated that parous women exhibited a lower risk of hemorrhagic but not ischemic stroke than nulliparous women.[12] In contrast to the findings of earlier studies,[9,10] our present results suggest that high fertility protects against SBI or stroke. Such discrepancies may be due to differences in adverse metabolic changes or pregnancy complications, risk factor profiles, or socioeconomic status among studies. Additionally, the relationship between the type of stroke lesion (i.e., SBI) and its contributing factors may have been more accurately evaluated in the present study, as SBI was identified based on MRI findings.

Several adverse factors associated with pregnancy (i.e., preeclampsia, gestational diabetes, obesity, and metabolic syndrome) may increase the risk of stroke.[5-7] Among these pregnancy-related risk factors, hypertension is one of the major risk factors for SBI or stroke. Preeclampsia and pregnancy-induced hypertension are the 2 most common important hypertensive disorders of pregnancy. While the first pregnancy is traditionally considered to impose an increased risk of preeclampsia, multiparity—in addition to age, obesity, and history of hypertensive disorders—is also a risk factor for pregnancy-induced hypertension.[28,29] However, the number of births was not significantly associated with the prevalence of hypertension or levels of blood pressure in the present study. Women with mild glucose intolerance during pregnancy who developed diabetes thereafter may be at risk for cardiovascular disease; alternatively, type 2 diabetes and cardiovascular disease may develop in parallel.[30] In the present study, however, other metabolic indicators such as diabetes and body mass index did not significantly differ based on the number of births.

The transition to menopause has been associated with changes in lipid levels; total and low-density lipoprotein cholesterol levels increase during this transition, while the greatest increase in HDL cholesterol occurs prior to the transition, following which a gradual decrease is observed.[31] However, among postmenopausal women aged 60 years or older, we observed gradual decrease in total cholesterol with only slight or no change in levels of

Table 4. *Logistic regression analysis for the association between grand multiparity and silent brain infarction*

		Model 1			Model 2			Model 3	
Age at the last parity	OR	95% CI	*P*	OR	95% CI	p	OR	95% CI	*P*
Number of barths ≧5	.415	.153-1.124	.084	.412	.150-1.135	.086	.300	.102-.886	.029
Age at the last parity, /10 y		—			—		2.009	.934-4.324	.074

Model 1: adjusted for age; Model 2: adjusted for age, hypertension, diabetes, hyperlipidemia, and eGFR; and Model 3: further adjusted for age at the last parity.

HDL cholesterol. Age-adjusted levels of "beneficial" HDL cholesterol were lower in women with ≧5 births than in those with <5 births, suggesting that levels of HDL cholesterol did not contribute to the protective effects of parity ≧5 against SBI.

Our study possesses several limitations of note, including its cross-sectional study design, which limits the interpretation of our results with respect to cause and effect; this study is unable to elucidate whether parity is a protective biomarker of SBI. However, in the present study, the age at the last parity was below 60 years, and SBI usually occurs in patients aged 60 years or older. Therefore, these findings strongly suggest that reproductive history reflects the cause rather than the result. Second, we were unable to investigate the effects of pregnancy complications such as preeclampsia, gestational diabetes, and low birth weight on later cardiovascular outcomes, as such information on these events during the reproductive years was unavailable. Nonetheless, the prevalence of vascular risk factors was quite similar among the groups of women subdivided according to the number of births. Also, we could not determine the exposure time or control state of risk factors; this point is another limitation of the present cross-sectional study. Third, such analysis as the number of births may be influenced by socioeconomic status or historical factors; this point is discussed below.

Our previous study indicated that natural early menopause may increase the risk of SBI in community-dwelling older adults, based on the data in 1997-2010.[4] However, during the analysis of the revised data set (1997-2017), we observed that the birth years of individuals who had experienced natural early menopause were within a narrow range centered around 1922 (range: 1914-1931; unpublished observation). Thus, individuals with natural early menopause were at maturation and reproductive age during and just after World War II, when socioeconomic disasters may have influenced the timing of menopause.[32] This observation demonstrates that historical factors are important when evaluating the effects of reproductive activity on stroke incidence. Furthermore, the number of children born to each woman has declined in developed countries,[33] complicating the analysis of the effects of biological sex on stroke incidence. Our study is advantageous in that we were able to obtain data regarding reproductive history prior to the era in which this decrease had begun (i.e., the natural conception cohort). Furthermore, we utilized a community-based design that included a relatively large number of MRI examinations. Such natural fertility cohorts represent biologically maximal fertility conditions.

In conclusions, our findings indicate that women with high parity exhibited a lower risk of SBI than men, and that fertile women may be protected against SBI or small vessel disease via the biological effects of sex. However, higher age at the last parity or late childbearing may blunt the fertility-related protection against SBI. Further studies are required to elucidate the mechanisms by which parity is associated with a lower risk of SBI.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Hiroshi Yao contributed to drafting/revising the manuscript, study concept, interpretation of data, statistical analysis, obtaining funding, and study supervision. Kenji Fukuda contributed to drafting/revising the manuscript, study concept, and interpretation of data. Yuko Araki contributed to statistical analysis and interpretation of data. Yuki Takashima contributed to acquisition of data, study coordination, and obtaining funding. Akira Uchino contributed to interpretation of MRI findings. Takefumi Yuzuriha contributed to study coordination and study supervision. Manabu Hashimoto contributed to acquisition of data, the clinical evaluation of cognitive function, study coordination, obtaining funding, and study supervision.

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