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Association Between the Number of Deliveries and Cognitive Impairment Considering the Presence of Subclinical Cerebrovascular Diseases: The Ohasama Study

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Although the association between the number of deliveries and cognitive impairment has been previously examined, the influence of subclinical cerebrovascular diseases (SCDs), such as silent cerebrovascular lesions and carotid atherosclerosis, on this association remains unclear. This cross-sectional study aimed to examine whether SCDs mediated the association between the number of deliveries and cognitive impairment. Among 627 Japanese women with a mean age of 73 years, the number of deliveries was collected in the 1998 survey and classified into four groups (0-1, 2, 3, ≥ 4), with two deliveries as the reference. At the annual comprehensive medical examinations, cognitive function was assessed using the Mini-Mental State Examination (MMSE), and SCDs were evaluated using brain magnetic resonance imaging and ultrasonography. Each participant's latest data on these variables and covariates between 1992 and 2018 were used. MMSE scores were divided into three ordinal categories: ≥ 28 (normal), 24-27 (mild cognitive impairment; MCI), and ≤ 23 (severe cognitive impairment). Ordinal logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for cognitive impairment. The ORs for cognitive impairment associated with the number of deliveries were 2.13 (95% CI, 1.21-3.76) in the lowest (0-1) group and 1.45 (0.95-2.23) in the highest (≥ 4) group. These association estimates remained similar after adjusting for SCDs but were weaker in the more recent birth year group. We demonstrated a U-shaped association between the number of deliveries and cognitive impairment, independent of SCDs, and the cohort effect confounded the association.

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Introduction

Dementia is a leading cause of death and disability in older adults worldwide (WHO, World Health Organization 2023). Its prevalence is expected to increase steadily in the coming years (GBD 2019 Dementia Forecasting Collaborators 2022), leading to considerable economic and social burdens (Velandia et al. 2022). Of all dementia cases, Alzheimer's disease accounts for 60-80% and is primarily prevalent in women (WHO 2023). Sex differences in dementia have been linked to neurological, cardiovascular, metabolic, psychological, sociocultural, and health-related behavioral factors (Nebel et al. 2018). Notably, reproductive factor, such as menarche, menopause, pregnancy, and delivery, are experienced exclusively by women.

The number of deliveries, one of the reproductive factors, has been reported to be associated with cognitive impairment and dementia, though the results have been inconsistent. A Mexican cross-sectional study found that having zero or one child, as well as having six or more children, was associated with lower cognitive function, showing a U-shaped association (Saenz et al. 2021). Similarly, a U-shaped association between the number of live births and lower cognitive function was reported in a British cross-sectional study (Ning et al. 2020). In contrast, a British prospective cohort study found that only women with zero or one living child were associated with lower cognitive function (Read and Grundy 2017). Additionally, a pooled analysis of cross-sectional data from 11 population-based cohorts reported that only nulliparity was associated with higher odds of dementia among Asian women (Bae et al. 2020a), whereas a pooled analysis of six prospective cohorts, including European and Asian women, found that only having five or more children was associated with a higher risk of incident non-Alzheimer's dementia (Bae et al. 2020b). Given these results, it can be interpreted that there is evidence of an association between the number of deliveries and cognitive impairment through certain mechanisms; however, the shape of the association remains inconsistent.

Although it is still unknown why the number of deliveries is associated with cognitive impairment or dementia risk, several of the studies described above suggest that the association may be mediated by atherosclerosis or cardiovascular diseases (CVD) (Bae et al. 2020b; Ning et al. 2020). A J-shaped association between the number of deliveries and CVD risk has been reported in a meta-analysis (Li et al. 2019). Our recent study also demonstrated a U-shaped association between the number of deliveries and subclinical cerebrovascular diseases (SCDs), which include silent cerebrovascular lesions and carotid atherosclerosis (Hara et al. 2012), among Japanese women (Sato et al. 2023). These findings suggest that the association between the number of deliveries and atherosclerosis or CVD is J- or U-shaped. Furthermore, non-stroke cardiovascular diseases (including SCDs) are associated with an increased risk of cognitive decline or dementia (Stefanidis et al. 2018). Based on this accumulation of previous evidence, we hypothesized that the association between the number of deliveries and cognitive impairment may be U-shaped, and SCDs could mediate this association. If SCDs mediate the association between the number of deliveries and cognitive impairment, we could prevent cognitive decline in women who have a higher risk of cognitive impairment due to delivery experience by routinely assessing and intervening in atherosclerosis. To date, few studies have investigated whether SCDs mediate the association between the number of deliveries and cognitive function. A Korean cross-sectional study reported that the association between a higher number of deliveries and cognitive function was not mediated by white matter hyperintensities (one of the SCDs) (Jung et al. 2020). However, this Korean study did not examine the mediation of other SCD variables, such as lacunar infarcts, carotid plaque, and carotid intima-media thickness, suggesting that the existing literature provides insufficient evidence to answer our hypothesis. Therefore, the present study aimed to investigate the association between the number of deliveries and cognitive impairment and whether SCDs mediate this association in older Japanese women.

Materials and Methods

Ethical approval

This cross-sectional study was approved by the Institutional Review Boards of Teikyo University Graduate School of Medicine (16–075–6) and Akita University Graduate School of Medicine (No. 2271). The study adhered to the principles outlined in the Declaration of Helsinki and was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al. 2008). All participants provided informed consent.

Study design and eligibility criteria

This study was part of the Ohasama study, the details of which have been described previously (Imai et al. 1993; Ohkubo et al. 2006). Briefly, comprehensive medical examinations were initiated for residents of Ohasama town (currently Hanamaki city), Iwate, in the northern part of Japan, in 1986. Subsequently, their health status was continuously monitored throughout the years. The 1998 questionnaire survey retrospectively collected data on reproductive factors, including age at menarche, age at menopause, and number of deliveries. We restricted the data to women aged 55 years and older in 1998 to include age at menopause as a covariate in this study. Cognitive function tests, carotid ultrasonography (US), and brain magnetic resonance imaging (MRI) were performed annually. Cognitive function, carotid US, brain MRI, and other covariate data were taken from each participant's most recent records between 1992 and 2018. These data were merged using participant ID with reproductive factors obtained from the 1998 questionnaire survey because the number of deliveries reflects a past experience. Individuals with clinically evident dementia were excluded from the study. We excluded participants whose following variables were missing: the number of deliveries, the Mini-Mental State Examination (MMSE) scores, brain MRI and carotid ultrasonography, and home blood pressure (BP) measurements (measured fewer than three).

The reproductive factors

The self-reported number of deliveries, including stillbirths, was collected in the 1998 questionnaire survey. Although the self-reported number of deliveries has yet to be validated among the study participants or Japanese postmenopausal women, its reliability was previously validated among Portuguese postmenopausal women (Lucas et al. 2008). The number of deliveries (range, 0-8) was the exposure variable in this study and was categorized into four groups (0-1, 2, 3, and ≥ 4) based on quartiles. We categorized zero and one delivery as the same group owing to the small number of women with no deliveries (n = 12). A category of two deliveries was used as the reference based on our hypothesis described in the Introduction section. The reproductive period, defined as the years from age at menarche to age at menopause (Shimizu et al. 2019), was used as one of the covariates. Several studies have reported that a higher number of deliveries is associated with later menopause (i.e., a longer reproductive period) (Jeune 1986; Parazzini 1992), and a longer reproductive period is associated with better cognitive function (Li et al. 2016; Gilsanz et al. 2019; Shimizu et al. 2019; Song et al. 2020; Yoo et al. 2020).

Cognitive function

Cognitive function was assessed using the MMSE (Folstein et al. 1975). The scores were classified into three categories: normal (28-30), mild cognitive impairment (MCI) (24-27), and severe cognitive impairment (≤ 23) (Sugishita et al. 2018). The cutoff values among Japanese older people discriminating normal cognition from amnestic MCI due to possible Alzheimer's disease, as diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), are 28/27, with 83.9% sensitivity and 83.5% specificity. Similarly, the cutoff values discriminating MCI from mild probable Alzheimer's disease, diagnosed by DSM-5, are 24/23, with 68.7% sensitivity and 78.8% specificity (Sugishita et al. 2018).

Subclinical cerebrovascular diseases

This study used lacunar infarcts, white matter hyperintensities (WMHs), mean intima-media thickness (IMT), and carotid plaque as SCD variables. Lacunar infarcts and WMHs were assessed using brain MRI. Brain MRI was conducted using a 0.5 T scanner, acquiring T1- and T2-weighted sequences on the axial plane with 10-mm thick slices. Lacunar infarcts were defined as areas of low intensity on T1-weighted images or high intensity on T2-weighted images, ranging 3-15 mm in size, in participants without a history of stroke or transient ischemic attack. Hyperintense punctate lesions appearing only on T2-weighted images were not considered lacunar infarcts. White matter hyperintensities (WMHs) were defined as hyperintensities in the white matter appearing only on T2-weighted sequences and classified into grades 0 (absent), 1 (punctate), 2 (early confluent), and 3 (confluent) (Fazekas et al. 1993). Small caps (< 5 × 10 mm) on the horns of the lateral ventricles and pencil-thin linings around the ventricles were classified as grade 0, whereas larger caps (≥ 5 × 10 mm) were classified as grade 2, based on our previous study (Tsubota-Utsugi et al. 2017). In this study, grades 1-3 were considered to indicate the presence of WMHs, and grade 0 represented their absence.

Mean IMT and carotid plaque were assessed using carotid US. Carotid US was performed using a real-time B-mode US imaging device (Sonolayer SSA-250A; Toshiba, Tokyo, Japan) equipped with a 7.5-MHz annular array probe, providing an axial resolution of 0.25 mm. Measurements were conducted by a physician with participants seated, following a standardized protocol (Hara et al. 2007). The mean IMT was calculated as the average maximum IMT at both the near and far walls of the bilateral common carotid arteries, approximately 10 mm proximal to the carotid sinuses. Carotid plaques were measured bilaterally at the common carotid artery, carotid bifurcation, and internal and external carotid arteries. A carotid plaque was defined as a focal lesion relative to the adjacent segments, either with calcified deposits alone or with a combination of calcified and non-calcified material protruding into the lumen (Bots et al. 1997). Plaque count was categorized as absent, 1, 2, or greater, and further classified as the presence (≥ 1) or absence of carotid plaque. If a carotid plaque was present, IMT was not measured at that site but at an alternate site. In cases where the plaque involved the entire circumference of the artery, three of the four specified locations were measured, and the mean was recorded. The reproducibility of IMT measurement was comparable to other studies (Bots et al. 1997; O'Leary et al. 1999) and was previously validated in this cohort (Hara et al. 2007).

Other covariates

The covariates included birth year, age at the last visit, body mass index (BMI), educational attainment, smoking and drinking statuses, hypertension, diabetes, hypercholesterolemia, and history of CVD. The birth year was divided into quintiles: 1912-1924/1925-1929/1930-1933/1934-1937/1938-1943. BMI was calculated as weight divided by height in meters squared. Educational attainment was categorized into three groups: elementary school, junior high school, and high school or higher. Smoking and drinking statuses were divided into current and non-current smokers/drinkers. Hypertension was defined as the use of antihypertensive medication or a mean home BP ≥ 135/85 mmHg (Umemura et al. 2019). Participants measured their morning BP (after ≥ 2 min of rest in the morning within 1 h after awakening) and evening BP (just before going to bed) every day for 4 weeks (Imai et al. 2012; Umemura et al. 2019). The recorded data were averaged over a 4-week period (Satoh et al. 2023). Diabetes mellitus was defined as either a fasting glucose level ≥ 126 mg/dL, after-2-hour value for a 75-gram oral glucose tolerance test ≥ 200 mg/dL, random plasma glucose level ≥ 200 mg/dL, HbA1c level ≥ 6.5%, or the use of antidiabetic medication (American Diabetes Association Professional Practice Committee 2022). Hypercholesterolemia was defined as a total cholesterol level ≥ 200 mg/dL or the use of lipid-lowering medications (Grundy et al. 2019). Data on CVD history were obtained by asking the participants whether they had a history of stroke or coronary heart disease.

Statistical analysis

Categorical variables were summarized as numbers with percentages, and continuous variables were summarized as means with standard deviations or medians with interquartile ranges. Ordinal logistic regression analyses were conducted to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for cognitive impairment associated with the number of deliveries. The score test was performed to assess whether the models satisfied the proportional odds assumption. This test evaluates whether the association between the number of deliveries and cognitive impairment is consistent across each pair of outcome categories (normal cognition vs. MCI and severe cognitive impairment; normal cognition and MCI vs. severe cognitive impairment). A non-significant result ($p > 0.05$) indicates that the proportional odds assumption holds. The multivariable model was adjusted for birth year (quintiles), age at the last visit (continuous), educational attainment (elementary school/junior high school/high school and above), BMI (continuous), smoking status (current/noncurrent), drinking status (current/noncurrent), diabetes (presence/absence), hypertension (presence/absence), hypercholesterolemia (presence/absence), history of CVD (presence/absence), and reproductive period (continuous). To assess whether the association between the number of deliveries and cognitive impairment was mediated by SCDs, the multivariable model was further adjusted for SCD variables, namely lacunar infarcts (presence/absence), WMHs (presence/absence), mean IMT (continuous), and carotid plaques (presence/absence). Considering the categorical variable of the number of deliveries as ordinal, the P-value of the delivery categories was calculated as the P-value for a linear trend, and the P-value of the quadratic term for the ordinal delivery categories was calculated as the P-value for a quadratic trend.

Given that complete-case analyses ignored missing data and lost 34% (n = 213) of the analytic sample, multiple imputations by chained equations (MICE) were employed to impute missing data (Azur et al. 2011). We generated 50 imputed datasets using all the variables used in the statistical models. Subsequently, analyses were conducted for each imputed dataset, and the estimates were combined across datasets using Rubin's rule (Marshall et al. 2009) with the MI procedure and FCS statement in SAS. We used MICE in all multivariable analyses. In addition, we conducted the following sensitivity analyses. First, previous studies have reported that no pregnancy or delivery was associated with the risk of cognitive impairment (Karim et al. 2016; Read and Grundy 2017; Harville et al. 2020); therefore, we compared the characteristics between women with no delivery and those with one delivery and reran the multivariable model, excluding women with no deliveries. Second, we performed a subgroup analysis divided by the median birth year (1912-1931 vs. 1932-1943), as the total fertility rate in Japan has been declining over the years (World Bank. https://data.worldbank.org/indicator/SP.DYN.TFRT.IN?locations=JP). Additionally, a U.S. cohort study reported that more recent birth cohorts demonstrated higher cognitive function at the same age, and this cohort effect was independent of educational attainment (Dodge et al. 2014). Therefore, the subgroup analysis allowed us to investigate whether the cohort effect might have confounded the association between the number of deliveries and cognitive function.

Statistical significance was set at $p < 0.05$, and all tests were two-sided. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Participants' selection

Out of 1,599 women aged 55 years and older in 1998, we excluded 972 due to the following reasons: 877 for only participating in the 1998 questionnaire survey, 57 for missing the number of deliveries, 20 for missing Mini-Mental State Examination (MMSE) scores, 9 for missing brain MRI and carotid ultrasonography, and 9 for missing home BP measurements. The final analytic sample comprised 627 older women (Fig. 1). The included sample in the study was born later, had a lower BMI, had less hypertension, had slightly better cognitive function, and had fewer lacunar infarcts than the excluded sample (Supplementary Table S1).

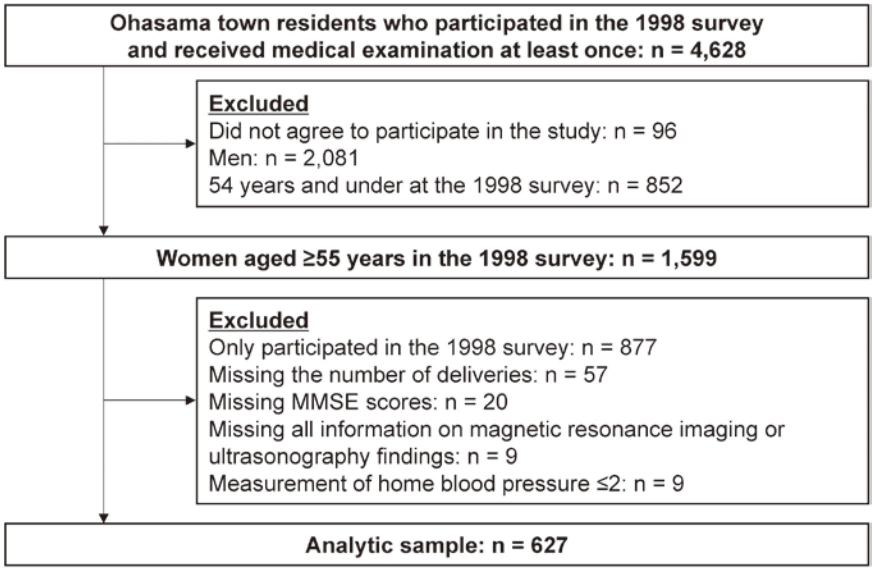

Fig. 1. Participants' enrollment flow chart.

Total characteristics of participants

Table 1 presents the overall participants' characteristics. The median birth year was 1932, and the mean age at the last visit was 73 years. The median number of deliveries was 3, with 12 women having no delivery history. The median MMSE score was 27; at the last visit of each participant, 38% of the patients had MCI, whereas 15% had severe cognitive impairment. Table 1 also shows participants' characteristics by cognitive function categories. Women with MMSE scores ≤ 23 were born earlier, had lower educational attainment and lower BMI, were non-current drinkers, and more likely to have lacunar infarcts, WMHs, and carotid plaque than those with MMSE scores ≥ 28.

Table 2 presents the characteristics of participants across the delivery categories. Participants with four or more deliveries were more likely to born earlier, be older, and had lower educational attainment, CVD histories, WMHs, thicker mean IMT, and carotid plaque than those with two deliveries. In contrast, those with zero or one delivery were more likely to have lower educational attainment and WMHs and less likely to have CVD history and carotid plaques than those with two deliveries.

Compared to participants with one delivery, those with no deliveries were more likely to have higher educational attainment, a history of CVD, a later age at menarche, a shorter reproductive period, better cognitive function, and WMHs. They were also less likely to have carotid plaque (Supplementary Table S2). Compared to the older birth cohort, the more recent birth cohort was likely to have higher educational attainment, experience fewer deliveries, and have higher cognitive function, although the age at MMSE assessment was similar (Supplementary Table S3).

Univariable association between delivery, SCDs, and cognitive impairment

Crude odds ratios of cognitive impairment associated with the number of deliveries, SCDs, and covariates are presented in Supplementary Table S4. Women with zero or one delivery had higher odds of cognitive impairment compared to those with two deliveries (OR, 2.46; 95% CI, 1.42-4.26). Similarly, women with four or more deliveries had higher odds of cognitive impairment (OR, 2.27; 95% CI, 1.54-3.35). Among SCDs, the presence of lacunar infarcts (OR, 1.70; 95% CI, 1.17-2.48) and mean IMT (OR, 4.79; 95% CI, 1.24-18.55) were associated with higher odds of cognitive impairment.

Influence of SCDs on the association between the number of deliveries and cognitive impairment

Fig. 2 and Supplementary Tables S5 show the ORs and 95% CIs from the multivariable model and the SCDs further-adjusted model. Women with zero or one delivery had higher odds of cognitive impairment compared to those with two deliveries (OR, 2.13; 95% CI, 1.21-3.76). Similarly, women with four or more deliveries had higher odds of cognitive impairment than those with two deliveries, although the association was not statistically significant (OR, 1.45; 95% CI, 0.95-2.23). The P-value for the linear trend of the number of deliveries was 0.862, and the P-value for the quadratic trend was 0.006. In the SCDs further-adjusted multivariable model, the estimates were similar to those without SCD adjustment (zero or one delivery; OR, 2.12; 95% CI, 1.20-3.77; four or more deliveries; OR, 1.44; 95% CI, 0.93-2.22), with the P-value for the linear trend was 0.819 and the P-value for the quadratic trend was 0.006.

Sensitivity analyses

After excluding women with no delivery history, hav-

Table 1. Participants' characteristics.

Variables	Overall n = 627	Mini-Mental State Examination score ≤ 23 n = 97	24-27 n = 237	≥ 28 n = 293
Birth year, median (IQR)	1932 (1926-1937)	1929 (1923-1934)	1932 (1926-1936)	1933 (1928-1938)
Age at the last visit, mean (SD)	73 (6)	73 (6)	73 (6)	72 (6)
Educational attainment, n (%)				
Elementary school	115 (18)	36 (37)	48 (20)	31 (11)
Junior high school	414 (66)	55 (57)	160 (68)	199 (68)
High school and over	98 (16)	6 (6)	29 (12)	63 (21)
Body mass index (kg/m^2), mean (SD)	23.5 (3.3)	23.3 (3.5)	23.5 (3.2)	23.6 (3.2)
Body mass index, n (%)				
< 18.5 kg/m^2	37 (6)	12 (12)	10 (4)	15 (5)
≥ 18.5, < 25 kg/m^2	392 (63)	53 (55)	150 (63)	189 (65)
≥ 25 kg/m^2	198 (32)	32 (33)	77 (32)	89 (30)
Hypertension, n (%)	475 (76)	70 (72)	182 (77)	223 (76)
Diabetes, n (%)	94 (15)	12 (12)	38 (16)	44 (15)
Hypercholesterolemia, n (%)	315 (50)	45 (46)	117 (49)	153 (52)
Current smoker, n (%)	7 (1)	1 (1)	2 (1)	4 (1)
Current drinker, n (%)	52 (9)	1 (1)	22 (11)	29 (11)
History of cardiovascular disease, n (%)	106 (17)	21 (22)	35 (15)	50 (17)
Age at menarche, median (IQR)	15 (14-16)	15 (14-16)	15 (14-16)	15 (14-16)
Age at menopause, median (IQR)	50 (48-52)	50 (48-52)	50 (47-52)	50 (48-53)
Reproductive period (years), median (IQR)	35 (32-38)	34 (32-37)	35 (32-37)	36 (33-38)
Number of deliveries, median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-3)
Outcome				
MMSE score, median (IQR)	27 (25-29)			
MMSE score, n (%)				
≥ 28	293 (47)			
24-27	237 (38)			
≤ 23	97 (15)			
Silent cerebrovascular diseases				
Lacunar infarcts (presence), n (%)	147 (35)	38 (51)	53 (33)	56 (30)
White matter hyperintensity (presence), n (%)	241 (57)	52 (70)	88 (55)	101 (54)
Mean IMT (mm), mean (sd)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)
Carotid plaque (presence), n (%)	235 (38)	39 (42)	91 (39)	105 (37)

Missing values were excluded, and percentages for each variable were calculated after excluding missing data. The reproductive period was calculated as the age at menopause minus the age at menarche. IQR, interquartile range; SD, standard deviation; MMSE, Mini-Mental State Examination; IMT, intima-media thickness.

ing one delivery was significantly associated with cognitive impairment compared to having two deliveries, with the estimated odds ratio slightly higher than when including women with no deliveries (Supplementary Table S6). Subgroup analysis divided by median birth year showed that the association between the number of deliveries and cognitive impairment was weaker in the more recent birth year group (born in 1932-1943) compared to the older group (born in 1912-1931) (Supplementary Table S7).

Discussion

In the present study, we hypothesized that the association between the number of deliveries and cognitive impairment is U-shaped, and that SCDs mediate this association. Although only women with zero or one delivery had more than twice the odds of cognitive impairment compared to those with two deliveries, a quadratic trend in the association between the number of deliveries and cognitive impairment was obtained. The observed association did not change after further adjustment for SCDs, suggesting that there was little evidence that SCDs mediated the association. Furthermore, subgroup analyses by the median birth year showed that the association between the number of deliveries and cognitive impairment was weaker in the more recent birth year group than in the older group, suggesting that the association was confounded by the cohort

Table 2. Participants' characteristics categorized by quartile based on the number of deliveries.

	The number of deliveries			
	0-1	2	3	≥ 4
Variables	n = 56	n = 231	n = 182	n = 158
Birth year, median (IQR)	1932 (1924-1937)	1935 (1929-1939)	1932 (1928-1937)	1927 (1923-1931)
Age at the last visit, mean (sd)	72 (6)	72 (6)	73 (5)	74 (5)
Educational attainment, n (%)				
Elementary school	11 (20)	20 (9)	23 (13)	61 (39)
Junior high school	35 (63)	159 (69)	135 (74)	85 (54)
High school and over	10 (18)	52 (23)	24 (13)	12 (8)
Body mass index (kg/m^2), mean (sd)	23.5 (3.2)	23.5 (3.4)	23.7 (3.2)	23.2 (3.2)
Body mass index, n (%)				
< 18.5 kg/m^2	3 (5)	15 (7)	7 (4)	12 (8)
≥ 18.5, < 25 kg/m^2	35 (63)	141 (61)	113 (62)	103 (65)
≥ 25 kg/m^2	18 (32)	75 (33)	62 (34)	43 (27)
Hypertension, n (%)	39 (70)	178 (77)	138 (76)	120 (76)
Diabetes, n (%)	10 (18)	31 (13)	26 (14)	27 (17)
Hypercholesterolemia, n (%)	25 (45)	108 (47)	106 (58)	76 (48)
Current smoker, n (%)	1 (2)		02 (1)	4 (3)
Current drinker, n (%)	4 (8)	21 (10)	13 (8)	14 (10)
History of cardiovascular disease, n (%)	4 (7)	44 (19)	22 (12)	36 (23)
Age at menarche, median (IQR)	15 (14-16)	15 (14-16)	15 (14-16)	15 (14-16)
Age at menopause, median (IQR)	50 (46-51)	50 (48-53)	50 (48-53)	50 (48-53)
Reproductive period (years), median (IQR)	34 (32-37)	35 (33-38)	36 (33-38)	35 (31-37)
Outcome				
MMSE score, n (%)				
≥ 28	17 (30)	129 (56)	91 (50)	56 (35)
24-27	28 (50)	74 (32)	68 (37)	67 (42)
≤ 23	11 (20)	28 (12)	23 (13)	35 (22)
Silent cerebrovascular diseases				
Lacunar infarcts (presence), n (%)	13 (30)	37 (29)	41 (35)	56 (42)
White matter hyperintensity (presence), n (%)	24 (55)	60 (48)	66 (56)	91 (69)
Mean IMT (mm), mean (sd)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.8 (0.1)
Carotid plaque (presence), n (%)	15 (28)	73 (32)	69 (39)	78 (50)

Missing values were excluded, and percentages for each variable were calculated after excluding missing data. The reproductive period was calculated as the age at menopause minus the age at menarche. IQR, interquartile range; SD, standard deviation; MMSE, Mini-Mental State Examination; IMT, intima-media thickness.

effect.

A Korean cross-sectional study reported that a higher number of deliveries was not associated with WMHs but was associated with hippocampal and cortical atrophy (Jung et al. 2020). Additionally, the association between a higher number of deliveries and cognitive impairment was observed, but it was no longer significant after adjusting for hippocampal and cortical atrophy (Jung et al. 2020). The results imply that increasing the number of deliveries directly affected hippocampal and cortical atrophy through mechanisms other than SCDs. In addition to the Korean study, the present study further investigated whether other SCD factors, namely lacunar infarcts, IMT, and carotid plaque, played a mediating role in the association between the number of deliveries and cognitive impairment. Contrary to our prior hypothesis, the present study reinforced the findings that there is little evidence of SCDs mediating the association between the number of deliveries and cognitive impairment.

Several studies have reported a U-shaped association between the number of deliveries and cognitive function (Read and Grundy 2017; Ning et al. 2020; Saenz et al. 2021). In line with these previous studies, we observed a U-shaped association between the number of deliveries and cognitive function, although the association between four or more deliveries and cognitive impairment was weak. Possible explanations for the results, aside from SCDs, are as follows. First, regarding the association between fewer deliveries and cognitive impairment, a British cohort study reported that women with zero or one living child had lower

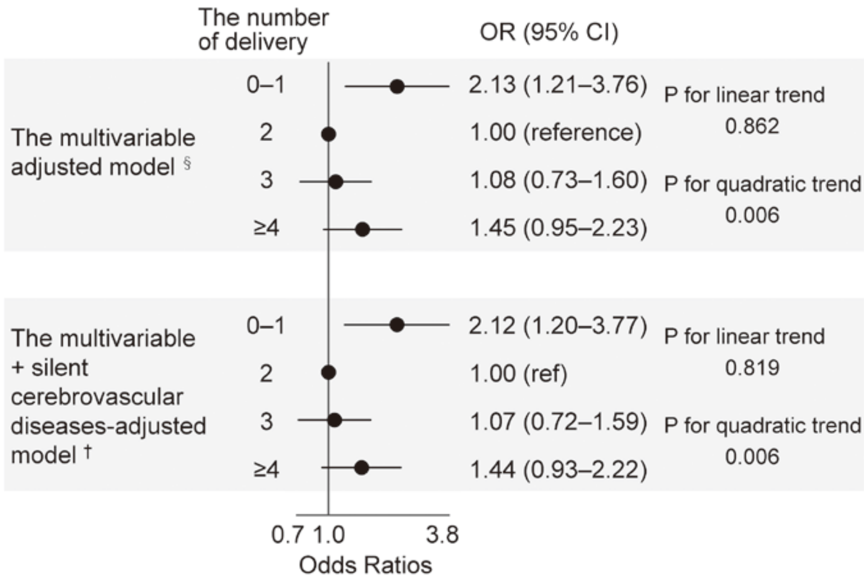

Fig. 2. Multivariable analyses of the association between cognitive impairment, number of deliveries, and silent cerebrovascular diseases.

§Multivariable-adjusted models were adjusted for birth year (quintile, 1912-1924/1925-1929/1930-1933/1934-1937/1938-1943), age at the last visit (continuous), educational attainment (elementary school/junior high school/high school and over), BMI (continuous), smoking status (current/non-current), drinking status (current/non-current), diabetes (presence/absence), hypertension (presence/absence), hypercholesterolemia (presence/absence), history of cardiovascular disease (presence/absence), and reproductive period (continuous).

†Adjusted for covariates in the multivariable model plus lacunar infarcts (presence/absence) and white matter hyperintensity (presence/absence), mean intima-media thickness (continuous), and carotid plaque (presence/absence).

MMSE, Mini-Mental State Examination; OR, odds ratio; CI, confidence interval.

cognitive function than women with two children even after adjusting for socioeconomic status, health-related lifestyles, chronic diseases, mental illness, marital status, and social interactions (Read and Grundy 2017). Similar findings were reported in a Mexican cross-sectional study (Saenz et al. 2021). These studies suggest that socioeconomic status may not confound the association, and lifestyle, psychological, and social factors may not mediate the association. Considering the total fertility rate in Japan at the time when the participants were still fertile (World Bank. https://data.worldbank.org/indicator/SP.DYN.TFRT.IN?locations=JP), zero or one delivery was uncommon. Therefore, these women might have experienced involuntary factors leading to a lower number of deliveries. The most common cause of infertility is ovulatory dysfunction, and the causes of ovulatory dysfunction are associated with an increased risk of cognitive impairment or Alzheimer's disease (Bae et al. 2020a). Furthermore, if women with zero or one delivery experienced recurrent miscarriage, they might have the apolipoprotein E ε4 allele, which increases the risk of cognitive impairment associated with Alzheimer's disease (Bae et al. 2020a). In addition, women with infertility might have repeatedly experienced stigmatization or negative interactions with family or society. It is possible that those experiences induced psychological distress and negatively affected the brain (Saenz et al. 2021). However, the present study was unable to investigate the above possible mechanisms due to the lack of data on these factors; therefore, future studies are needed.

Second, the risk of cognitive impairment among women with more deliveries might be explained by biological, psychological, and socioeconomic factors. It has been hypothesized that increasing the number of deliveries reduces lifetime endogenous estrogen exposure, and it directly affects brain and conveys the risk of cognitive impairment or dementia (Deems and Leuner 2020; Szoeke et al. 2021). The more children women care for, the more psychological and financial stress they may experience, potentially harming brain health, including cognitive function (Blanchflower and Clark 2019; Saenz et al. 2021). Additionally, a previous British cohort study reported that the association between having four or more children and cognitive impairment became null after adjusting for socioeconomic status, including educational attainment, employment, residence, wealth, and income (Read and Grundy 2017). Similar findings have been reported in other studies (Gemmill and Weiss 2022; Zhang et al. 2023). These findings suggest that socioeconomic status may primarily confound the association between a higher number of deliveries and cognitive impairment. In the present study, women with four or more deliveries had the lowest educational attainment, and we adjusted for educational attainment in the multivariable model. Therefore, the observed weak association between four or more deliveries and cognitive impairment might be partly due to confounding by educational attainment. Although we measured educational attainment, other biological, psychological, and socioeconomic factors mentioned above, which were possible mediators or confounders, were not measured in this study. Therefore, we were unable to examine these potential explanations. Future studies are warranted to explore the influence of those factors on the association between higher number of deliveries and cognitive impairment.

Furthermore, the results of the subgroup analyses by birth year suggest that the cohort effect confounded the association between the number of deliveries and cognitive impairment. A U.S. cohort study reported that more recent birth cohorts demonstrated higher cognitive function at the same age, and this cohort effect was independent of educational attainment (Dodge et al. 2014). In the present study, the more recent birth cohort was likely to have higher educational attainment, experience fewer deliveries, and have higher cognitive function than the older cohort, although the age at MMSE assessment was similar. Therefore, it is possible that the number of deliveries is partly accounted for by birth year if diverse generations are included in a single population.

This study had several limitations. First, our sample consisted of 627 participants, representing only 18% of the female population aged 50 years and older in this region in 2000 (3,572 individuals) (Statistics Bureau of Japan 2017). Additionally, the analyzed population differed slightly from the excluded sample (Supplementary Table S1), potentially introducing sampling bias that could have reduced generalizability. Second, previous meta-analyses have shown that the association between the number of deliveries and dementia risk varies according to the dementia type (Bae et al. 2020a; Bae et al. 2020b). As our study only measured cognitive function using MMSE, future research should investigate whether these associations differ according to the cause of dementia. Third, we assessed the covariates and outcomes simultaneously, which prevented the measurement of factors that occurred when the participants were younger, such as health-related lifestyle habits. The results of the present study may have been under- or overestimated due to such unmeasured confounders. Therefore, a prospective study is needed to address the confounding factors. Fourth, the participants in this study were residents who had visited the health examination site. Previous studies have reported a significant J- or U-shaped association between the number of deliveries and the incidence of CVD or CVD-related deaths (Parikh et al. 2010; Li et al. 2019). If CVD onset led to severe disability or death, those individuals could have been excluded from the study. This introduces a potential selection bias due to competing risks, which may have underestimated the association between the number of deliveries and cognitive impairment. Fifth, we added SCDs to the multivariable models to assess their mediation on the association between the number of deliveries and cognitive function. However, merely controlling for the mediator may introduce bias toward over- or underestimation if there are unmeasured common causes of both the mediator and the outcome (i.e., SCDs and cognitive impairment in the present study) (VanderWeele 2016). Future studies should use alternative methodologies, such as causal mediation analysis (VanderWeele 2016), to accurately estimate the mediating effects of atherosclerosis on the association between delivery and cognitive function.

In conclusion, we observed a U-shaped association between the number of deliveries and cognitive impairment, without mediation by SCDs. Moreover, the association was weaker among women born more recently. Further studies are warranted to clarify the underlying mechanisms of the association between the number of deliveries and cognitive impairment, aside from atherosclerosis, while carefully considering confounders such as the cohort effect, socioeconomic status, and others. Given the lack of clarity regarding the underlying mechanisms, caution should be exercised when communicating findings about the association between a lower or higher number of deliveries and cognitive impairment, as there is potential for misunderstanding or stigmatization.

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Author Contributions

T.Y.: conceptualization, formal analysis, investigation, methodology, validation, visualization, and writing of the original draft. K.N.: conceptualization, formal analysis, investigation, methodology, project administration, validation, visualization, review, and editing. M.S.: data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualization, review, and editing. A.H., Y.K., T.H., R.I., and T.T.: investigation, methodology, project administration, review, and editing. M.T.U., T.M., K.A., Y.T., H.M., and Y.I.: funding acquisition, investigation, methodology, project administration, review, and editing. M.K. and A.H.: data curation, funding acquisition, investigation, methodology, project administration, review, and editing. T.O.: a principal investigator of the Ohasama study; conceptualization, funding acquisition, investigation, methodology, project administration, visualization, review, and editing. All authors saw and approved the final manuscript.

Conflict of Interest

Dr. Michihiro Satoh received a scholarship donation (Academic support program) from Bayer Yakuhin Co., Ltd. Dr. Kei Asayama, Dr. Hirohito Metoki, Dr. Yutaka Imai, and Dr. Takayoshi Ohkubo concurrently held the position of director of the Tohoku Institute for Management of Blood Pressure, supported by Omron Healthcare Co., Ltd. Dr. Kei Asayama received honoraria from Takeda Pharmaceutical Co., Ltd. Dr. Kei Asayama and Takayoshi Ohkubo received a joint research grant from Omron Healthcare Co., Ltd. All other authors declare no conflict of interest.

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Supplementary Files

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