The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

CC BY NC SA

Original Article

J Atheroscler Thromb, 2022; 29: 000-000. http://doi.org/10.5551/jat.63592

Female Reproductive Events and Subclinical Atherosclerosis of the Brain and Carotid Arteriopathy: the Ohasama Study

Wakana Sato[1], Kyoko Nomura[2, 3], Michihiro Satoh[4, 5], Azusa Hara[6], Megumi Tsubota-Utsugi[3], Takahisa Murakami[4, 5, 7], Kei Asayama[3, 8], Yukako Tatsumi[3], Yuki Kobayashi[2], Takuo Hirose[9], Ryusuke Inoue[10], Tomoko Totsune[11], Masahiro Kikuya[3, 8], Atsushi Hozawa[5], Hirohito Metoki[4, 5, 8], Yutaka Imai[8], Hiroyuki Watanabe[1] and Takayoshi Ohkubo[3, 8]

Wakana Sato and Kyoko Nomura contributed equally to this work.

[1]Department of Cardiovascular Medicine, Akita University Graduate School of Medicine, Akita, Japan
[2]Department of Environmental Health Science and Public Health, Akita University Graduate School of Medicine, Akita, Japan
[3]Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
[4]Division of Public Health, Hygiene and Epidemiology, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Japan
[5]Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan
[6]Division of Drug Development and Regulatory Science, Faculty of Pharmacy, Keio University, Tokyo, Japan
[7]Division of Aging and Geriatric Dentistry, Department of RehabilitationDentistry, Tohoku University Graduate School of Dentistry, Sendai, Japan
[8]Tohoku Institute for Management of Blood Pressure, Sendai, Japan
[9]Department of Endocrinology and Applied Medical Science, Tohoku University Graduate School of Medicine, Sendai, Japan
[10]Department of Medical Information Technology Center, Tohoku University Hospital, Sendai, Japan
[11]Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

Aims: Few studies have investigated the subclinical atherosclerotic changes in the brain and carotid artery, and in East Asian populations. We sought to investigate whether gravidity, delivery, the age at menarche and menopause and estrogen exposure period are associated with subclinical atherosclerosis of the brain and carotid arteriopathy.

Methods: This cross-sectional study formed part of a cohort study of Ohasama residents initiated in 1986. Brain atherosclerosis and carotid arteriopathy were diagnosed as white matter hyperintensity (WMH) and lacunae evident on brain magnetic resonance imaging (MRI) and carotid intimal media thickness (IMT) or plaque revealed by ultrasound, respectively. The effect of the reproductive events on brain atherosclerosis and carotid arteriopathy was investigated using logistic regression and general linear regression models after adjusting for covariates.

Results: Among 966 women aged ≥ 55 years in 1998, we identified 622 and 711 women (mean age: 69.2 and 69.7 years, respectively) who underwent either MRI or carotid ultrasound between 1992–2008 or 1993–2018, respectively. The highest quartile of gravidity (≥ 5 vs. 3) and delivery (≥ 4 vs. 2), and the highest and second highest (3 vs. 2) quartiles of delivery were associated with an increased risk of WMH and carotid artery plaque, respectively. Neither of age at menarche, menopause, and estrogen exposure period estimated by subtracting age at menarche from age at menopause was associated with atherosclerotic changes of brain and carotid arteries.

Conclusions: Higher gravidity and delivery are associated with subclinical atherosclerosis of the brain and carotid plaque.

Key words: Carotid plaque, Delivery, Gravidity, Lacunar, Menarche, Menopause, Plaque, Reproductive events, White matter hyperintensity

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Introduction

Reproductive life events such as gravidity, delivery, and age at menarche and menopause have been identified as risk factors for cardiovascular disease (CVD)[1-8]. There is an association between early menopause and a higher risk of CVD, coronary heart disease (CHD), and stroke[3, 4, 7, 9-13]. Similarly, early menarche has also been reported to be associated with a higher risk of stroke, CVD, and CHD mortality[14-19], but the literature results are inconsistent[9, 11, 16-19] and furthermore, two studies reported that late menarche and menopause was associated with the increased CVD risk[17, 19]. Ever parity has been inconsistently reported to have a statistically significant nonlinear inverse association with CVD mortality (with U- or J-shaped relationships)[5-6]. These inconsistencies could be due to varied outcome subgroups (events or mortality by stroke, CVD, or CHD), demographics of the target population, and unadjusted confounders of estrogen exposure periods[7].

The endocrinology underlying these observations is possibly linked to sex hormones such as estrogen. A previous study demonstrated that activation of the silent information regulator 2 (Sir2) proteins, plays a crucial role in the effect of estrogen on retarding arterial senescence and atherosclerotic development through increasing endothelial nitric oxide synthase (eNOS) activation, reducing oxidative stress, inflammation, and DNA damage[20]. Changes in vascular properties such as blood volume, heart rate, oxidative stress, and other gestational factors (age at first childbirth and preterm birth) during pregnancy and childbirth may increase abdominal fat accumulation and serum lipids that could further aggravate endothelial dysfunction and systemic inflammation, with resultant CVD progression[21-23]. A large-scale epidemiological study among working age population demonstrated that the number of abnormal lipid profiles and incident myocardial infarction was pronounced in men than in women[24], suggesting that women who have menstruation may be protected with sex hormone. Despite the suggestive association between reproductive events and CVD risk, the pathological mechanism remains unclear. Considering the CVD outcomes and events of previous studies, which were either based on the vital status (death registry) or retrospective medical records, few studies have investigated the subclinical atherosclerotic changes in the brain, heart, and carotid artery. Furthermore, very few studies have examined these factors in East Asian populations[9]. We hypothesized that the effect of gravidity differs from that of parity, and the age of menarche or menopause is not individually associated with CVD risk and rather estrogen period estimated the difference between menarche and menopause may have an impact on the atherosclerotic progression.

Aim

This study aimed to investigate the association between the reproductive events of gravidity, pregnancy, age at menarche and menopause, and brain atherosclerosis and carotid arteriopathy among Japanese women using magnetic resonance imaging (MRI) and carotid ultrasound (US).

Methods

Study Population

This cross-sectional study formed part of an ongoing cohort study since 1986 involving the inhabitants of Ohasama, a rural town in Iwate Prefecture in northern Japan[25]. This cohort study is particular interested in investigating hypertension and cardiovascular events and participants are periodically assessed by MRI or ultrasound (US). For the MRI imaging, since the imaging modalities changed in 2008, this study only included participants who were followed from 1992 to 2008. For US imaging, there were no such restrictions in the follow-up period. In 1998, we measured the reproductive events at the age at menarche, and menopause, gravidity, and parity in the extended survey. We identified a total of 966 female patients aged ≥ 55 years in the 1998 survey who provided informed consent. Those with invalid responses to a self-administered questionnaire in 1998 (n=41), a history of stroke and ischemic heart disease (n=84), and blood pressure measured at home for less than 3 days (n=8) were excluded. Furthermore, patients were excluded if they did not undergo an MRI (n=211) and/or carotid US (n=122) between 1986 and 2008. Finally, a total of 622 and 711 female patients were identified, respectively.

Address for correspondence: Kyoko Nomura, Chair Professor, Department of Environmental Health Science and Public Health,Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita 010-8543 Japan E-mail: knomura@med.akita-u.ac.jp, nomurakyoko@gmail.com

Received: April 3, 2022 Accepted for publication: August 26, 2022

Copyright©2022 Japan Atherosclerosis Society
This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Ethics Statement

The study was approved by the Institutional Review Boards of the Teikyo University Graduate School of Medicine (16-075-6) and Akita University Graduate School of Medicine (No.2271). The study conformed to the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants.

Brain Atherosclerosis and Carotid Arteriopathy

Brain atherosclerosis and carotid arteriopathy included white matter hyperintensity (WMH), and lacunae evident on brain MRI and excessive IMT or plaque revealed by US, respectively. It has been found that carotid IMT and plaque increase the risk of stroke[26-30] and that the risk of stroke due to a high white matter grade is independent of other risk factors, even after controlling for MRI infarcts (subclinical imaging markers of CVD)[31]. Based on previous large cohort study[32] and Task Force Report[33], Carotid IMT ≥ 1mm indicates high risk of atherosclerosis.

Brain MRI

Brain MRI was performed using a 0.5-Tesla superconducting magnet and images in the axial plane (10-mm-thick slices), and T1- and T2-weighted images were collected. A lacunar infarct was defined as an area of low signal intensity of 3–15 mm on T1-weighted images and hyperintense lesions on T2-weighted images of patients without a history of stroke or transient ischemic attack (TIA). Hyperintense punctate lesions, evident only on T2-weighted images, were not considered as lacunar infarcts. WMH was defined as a hyperintensity apparent only on T2-weighted images and was graded as follows: 0, absent; 1, punctate; 2, early confluent; and 3, confluent[34]. Small and large caps (<5×10 mm and ≥ 5×10 mm, respectively) on the horns of the lateral ventricles and pencil-thin linings around the ventricles were considered normal and a grade 2 disease, respectively. This method was previously validated in the Ohasama study[35]. In this study we defined WMH to be grade 1 or larger versus 0.

Carotid Arteriopathy

We used a real-time B-mode US imaging unit (Sonolayer SSA-250A; Toshiba, Tokyo, Japan) fitted with a 7.5-MHz annular array probe that rendered an axial resolution of 0.25 mm. All ultrasonograms, which were taken with the subjects in a seated position, were examined by a physician according to a standardized protocol[36]. The IMTs of both the near and far walls of the bilateral common carotid arteries were measured approximately 1 cm proximal to the carotid bulbs and recorded as the mean maximum thickness. The plaque status of the common carotid artery, carotid bifurcation, and internal and external carotid arteries was examined bilaterally and graded as either absent, 1, 2, or higher. Further, it was defined as a focal lesion relative to the adjacent segments, with either calcified deposits alone or a combination of calcified and noncalcified material protruding into the lumen[26]. The IMT measurements were not recorded at any plaque lesion sites, whereas they were made at an alternative point if plaque was present and at three of the four locations described above where plaque involved the entire circumference of the artery, with the mean value recorded. The IMT measurement reproducibility was comparable to that of other studies[26, 27] and was previously validated in our Ohasama study[35].

Reproductive Events

Data regarding the delivery, gravidity, and age at menarche and menopause retrieved from the 1998 self-administered questionnaire were evaluated as reproductive events. Because the numbers of the missing values of each event are different, we created four samples for analyses; samples who answered the numbers of gravidity, delivery, and the age at menarche and menopause. We also estimated estrogen exposure time by subtracting age at menarche from age at menopause. For estrogen exposure analyses, the sample unit of age at menopause was used because the samples for age at menopause were smaller than those for age at menarche. Considering the accumulated evidence on the non-linear J-shaped dose-response relationship of gravidity and delivery with CVD risk[5, 6], we grouped the continuous variables into quartiles and used the 2nd lowest quartile as a reference: delivery, 0-1, 2 (ref), 3, and 4 ≤ ; gravidity, ≤ 2, 3 (ref), 4, and 5 ≤ ; age at menarche, ≤ 13 years, 14 years (ref), 15 years, and 16 years ≤ ; and age at menopause, ≤ 47 years, 48–49 years (ref), 50-52 years, and 53 years ≤. Because only 9 women in the MRI sample and 12 women in the US sample had never delivered, we combined women who had never had a delivery with those who had one child. We categorized the estrogen exposure period at the 75th percentiles of its distribution as a short (<38 years) and long time (≥ 38 years) period.

Covariates

The confounders of brain atherosclerosis and carotid arteriopathy included the patient's age; smoking and alcohol consumption status (current, past, or never); body mass index (BMI); home-

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

measured systolic and diastolic blood pressure (SBP and DBP); fasting blood glucose (FBS), hemoglobin A1c (HbA1c), and total cholesterol levels; antihypertensive drug use; hypercholesterolemia; diabetes mellitus; and any history of CVD. BP was measured at home and digitally presented using a cuff-oscillometric method (HEM701C, HEM701C, HEM747ICN, and HEM-7080IC; Omron Healthcare Co. Ltd., Kyoto, Japan), which was validated in our previous study[37] and satisfies the criteria of the Association for the Advancement of Medical Instrumentation. The BMI is classified as (kg/m^2): <25 for underweight and normal weight, and ≥ 25 for overweight and obesity. Hypertension was defined as the use of antihypertensive drugs or a mean BP $\geq$ 135/85 mmHg. All subjects were asked to measure BP every morning and evening[38] and to record the results over a 4-week period. Diabetes mellitus was defined as either an FBS level $\geq$ 200 mg/dL, HbA1c proportion $\geq$ 6.5%, or the use of anti-diabetic medication. Hyperlipidemia was defined as either a LDL (low-density lipoprotein) cholesterol $\geq$ 160 mg/dL or the use of lipid-lowering medication.

Statistical Analysis

The covariates were compared across the quartiles of gravidity, delivery, ages at menarche and menopause and between short and long estrogen exposure period using a chi-squared or Fisher's exact test for categorical data and Student's *t*-test or analysis of variance test for continuous data. Linearity trend for the proportion of WMH, lacunar, and plaque lesions among the quartiles of the five reproductive events was assessed by using Cochran-Armitage trend test while the trend test for mean of IMT, age, BMI, SBP, and DBP among the quartiles of the four events and short or long period of estrogen exposure time was assessed by Jonckheere–Terpstra test embedded in STATA and a *t*-test, respectively. Logistic regression was used to investigate whether any quartiles of either delivery, gravidity, or age at menarche and menopause, and long estrogen exposure period were associated with brain atherosclerosis and carotid arteriopathy. Crude and adjusted odds ratios (ORs) were estimated using 95% confidence intervals (CIs). For IMT, we used the Spearman coefficient for simple correlation and general linear regression models associated with quartiles of delivery, gravidity, age at menarche and menopause, and estrogen exposure period. Covariates in the multivariate models included the patient's age, BMI, diabetes and hypercholesterolemia status, current smoking and alcohol consumption, mean SBP, and hypertension based on the defined criteria. When we examined sample for age at menopause, we adjusted for a length after menopause by subtracting age at menopause from age at the time of MRI or US investigation. In addition, when we examined sample for age at menarche and menopause, we adjusted for each other.

The p value <0.05 was considered statistically significant, and all analyses were performed using SAS software ver. 9.3 (SAS Institute Inc., Cary, NC, USA) and Stata version 17 (STATA Corp, LLC, College Station, Texas, USA).

Results

The mean age at the latest year for MRI and US image investigation was 67.9 (SD, 6.1) and 69.7 (SD, 7.0) years, with a median of 2003 (range, 1992–2008) and 2010 (range, 1993–2018), respectively **(Supplementary Table 1)**. Among those who had the MRI images (the MRI samples), 157 (25%) and 283 (46%) patients had lacunar infarcts and WMH, respectively; among the US samples, plaque was observed in 191 patients (27%; **Table 1**), and the median IMT was 0.67 mm (interquartile range, 0.63–0.75 mm; data not shown). After excluding the missing data on the reproductive events, the number of subjects in the MRI and US sample units were 571 and 665 patients for gravidity **(Supplementary Table 2)**, 582 and 672 patients for delivery **(Supplementary Table 3)**, 509 and 616 patients for age at menarche **(Supplementary Table 4)**, and 462 and 449 patients for age at menopause **(Supplementary Table 5)**, respectively. The median and inter quartiles of the number of gravidity and delivery were 3(2-5) and 3(2-3), respectively in MRI sample and 3(2-4) and 2(2-3), respectively in US sample **(Supplementary Table 1)**.

Fig. 1 shows unadjusted measures of brain atherosclerosis and carotid arteriopathy across the five reproductive events. The quartiles of gravidity were linearly associated with the proportions of WMH and plaque lesions, and mean IMT (all trend $p<0.05$). The quartiles of delivery were linearly associated with the proportions of lacunar, WMH, and plaque lesions (all trend $p<0.010$). The quartiles of age at menarche were linearly associated with the proportions of WMH and plaque lesions, and mean IMT (all trend $p<0.010$). On the other hand, the linearity of age at menopause and estrogen exposure period was not significantly observed with any of the atherosclerotic changes of the brain and carotid artery.

Table 1 shows baseline characteristics according to carotid and brain atherosclerotic lesions. The mean age was linearly and positively correlated with IMT ($p<0.001$), and significantly higher in those with brain atherosclerotic lesions and carotid plaque than in

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Table 1. Baseline characteristics according to carotid and brain atherosclerotic lesions

	MRI sample (n=622)						US sample (n=711)				
	Lacunar infarcts			WMH			Plaque			IMT	
	(+) n=157 (25%)	(-) n=465 (75%)	p	(+) n=283 (46%)	(-) n=339 (54%)	p	(+) n=191 (27%)	(-) n=520 (73%)	p	Correlation coefficient (r)	p
mean ± sd											
Age	70.8 ± 5.9	66.9 ± 5.9	<0.001	70.3 ± 5.4	65.8 ± 5.9	<0.001	72.8 ± 6.1	68.6 ± 6.9	<0.001	0.315	<0.001
BMI, kg/m^2	23.4 ± 3.4	24.0 ± 3.2	0.079	23.4 ± 3.2	24.2 ± 3.3	0.004	23.2 ± 3.3	23.9 ± 3.4	0.014	0.053	0.162
Home-measured mean SBP, mmHg	130.6 ± 14.3	127.6 ± 15.1	0.033	130.8 ± 13.8	126.4 ± 15.6	<0.001	131.3 ± 13.9	129.2 ± 14.7	0.093	0.266	<0.001
Home-measured mean DBP, mmHg	74.6 ± 7.9	74.2 ± 8.9	0.572	75.2 ± 8.6	73.5 ± 8.7	0.017	73.4 ± 8.0	74.6 ± 8.6	0.091	0.046	0.221
median, interquartile range											
Gravidity	4 (3–5)	3 (2–4)	0.008	4 (3–5)	3 (2–4)	0.040	4 (2–5)	3 (2–4)	0.005	0.084	0.030
Delivery	3 (2–4)	2 (2–3)	0.001	3 (2–4)	2 (2–3)	<0.001	3 (2–4)	2 (2–3)	<0.001	0.070	0.069
Age at menarche	15 (14–16)	15 (14–16)	0.505	15 (14–16)	14 (14–16)	0.006	15 (14–16)	14 (13–15)	<0.001	0.280	<0.001
Age at menopause	50 (48–52)	50 (48–53)	0.263	50 (48–52)	50 (48–52)	0.672	50 (47–52)	50 (48–52)	0.919	0.036	0.449
n (%)										Mean ± SD	
Educational attainment			<0.001			<0.001			<0.001		<0.001
Elementary school	31 (21)	51 (12)		48 (18)	34 (10)		21 (12)	28 (6)		0.77 ± 0.12	
Middle school	97 (67)	290 (65)		181 (70)	206 (62)		122 (68)	288 (57)		0.70 ± 0.11	
High school	18 (12)	104 (23)		31 (12)	91 (28)		37 (20)	187 (37)		0.65 ± 0.11	
Lifestyle											
Smoker	1 (1)	5 (1)	0.627	3 (1)	3 (1)	0.824	2 (1)	6 (1)	0.905	0.67 ± 0.13	0.574
Drinker	21 (13)	59 (13)	0.824	34 (12)	46 (14)	0.564	19 (10)	77 (15)	0.093	0.68 ± 0.12	0.520
History											
DM	24 (15)	51 (11)	0.151	38 (13)	37 (11)	0.338	36 (19)	58 (11)	0.007	0.72 ± 0.11	0.006
HL	77 (49)	264 (57)	0.092	149 (53)	192 (57)	0.320	103 (54)	313 (60)	0.133	0.68 ± 0.11	0.050
Hypertension*	88 (56)	213 (46)	0.026	168 (59)	133 (39)	<0.001	120 (63)	299 (58)	0.201	0.71 ± 0.12	<0.001

BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; IMT, intima-media thickness; MRI, magnetic resonance imaging; SBP, systolic blood pressure; US, ultrasound; WMH, white matter hyperintensity

*Based on antihypertensive drug use or mean home-measured BP ≥ 135/85 mmHg.

those without (p<0.001). The mean SBP was significantly higher in those with lacunar infarcts (p=0.033), and WMHs (p<0.001), while DBP was significantly higher in those with WMHs (p=0.017). SBP was positively correlated with IMT (p<0.001), and the mean BMI was significantly lower in patients with WMH brain lesions and carotid plaque lesions (all p-values <0.050). The numbers of gravidity and delivery were higher in those with lacunar infarcts than those without (p=0.008 and p=0.001, respectively), those with WMHs than in those without (p=0.040 and p<0.001, respectively), and those with plaque than those without (p=0.005 and p<0.001, respectively), while only gravidity was positively correlated with IMT (p=0.030). Age at menarche was older in those with WMHs than in those without (p=0.006), and in those with plaque than in those without (p<0.001), and was positively correlated with IMT (p<0.001). Lower educational attainment was associated with both brain atherosclerosis and carotid arteriopathy (all p-values <0.001). A history of hypertension was significantly and positively associated with the brain lesions and IMT (all p-values <0.050). Furthermore, diabetes was not associated with brain atherosclerosis but was associated with carotid arteriopathy (plaque, p=0.007; IMT, p=0.006).

The characteristics of the participants according to gravidity, delivery, age at menarche and menopause, and estrogen exposure period are shown in **Supplementary Table 2 to Table 6**, respectively. The age linearly increased with the quartiles of gravidity, delivery (MRI sample only), and age at menarche (all trend P-values <0.001). Those with the highest quartiles of gravidity, delivery, and age at menarche tended to have lower educational attainment (all p-values <0.001; **Supplementary Table 2-4**). The age at menarche was linearly associated with the levels of BMI in the MRI sample (trend p=0.035), and in the US sample (trend p=0.007), and the levels of SBP

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

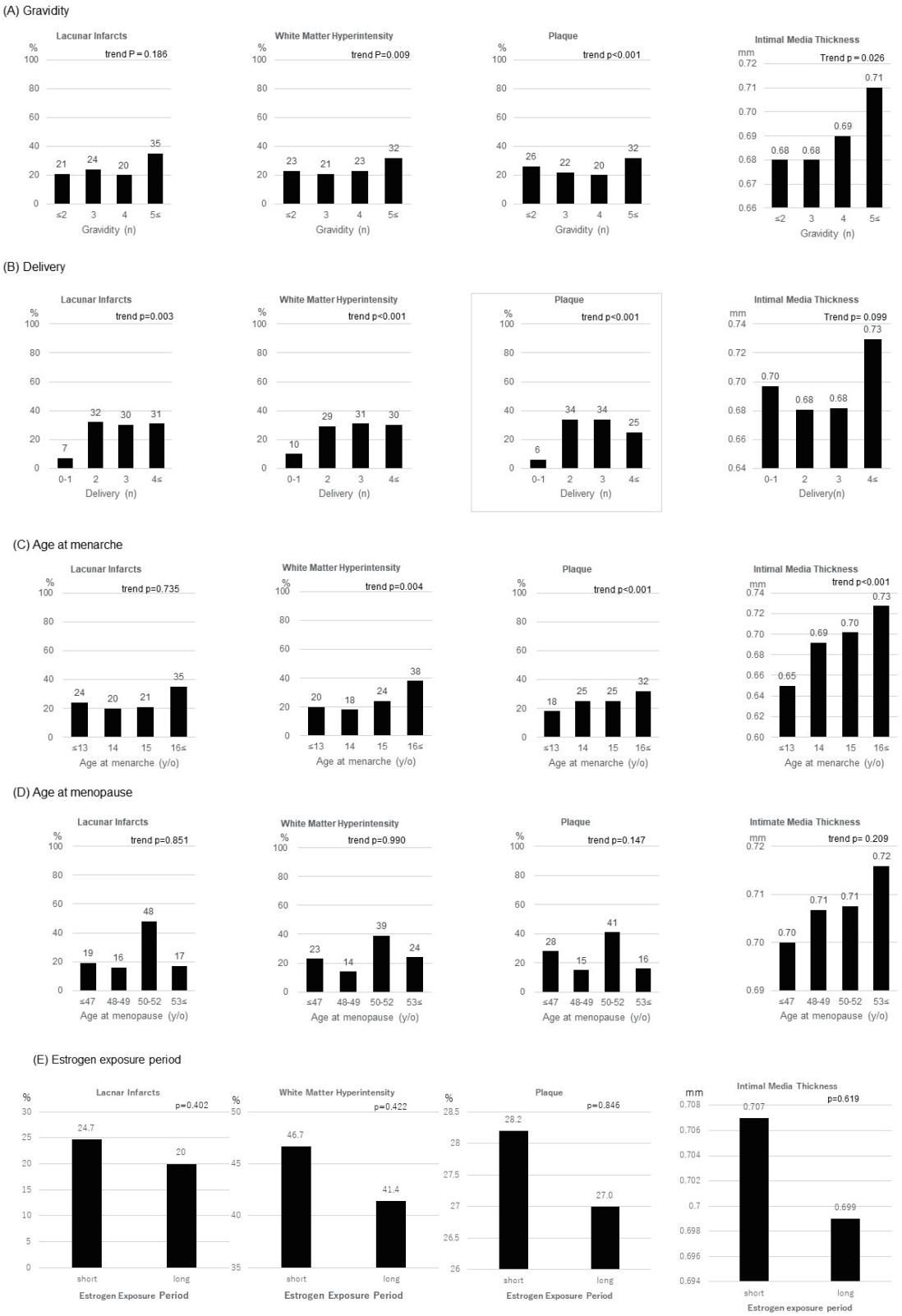


Fig. 1. Unadjusted measures of brain atherosclerosis and carotid arteriopathy across the five reproductive events

The quartiles of gravidity appeared to linearly increase with the proportions of WMH and plaque lesions, and mean IMT. The quartiles of delivery appeared to linearly increase with the proportions of lacunar, WMH, and plaque lesions. The quartiles of age at menarche appeared to linearly increase with the proportions of WMH and plaque lesions, and mean IMT.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

in the US sample (trend p=0.001; **Supplementary Table 4**). Those with the lowest and highest quartiles of age at menopause in the MRI sample tended to have higher proportion of hypertension (p=0.014; **Supplementary Table 5**). Those with long estrogen exposure period tended to have higher mean of BMI both in MRI and US samples (p=0.002 and p=0.014, respectively), and had higher proportion of smoker, drinker, and diabetes in MRI sample (p=0.024, p=0.016, and p=0.022, respectively) compared to those with short period **(Supplementary Table 6)**.

Supplementary Table 7 and 8 shows crude and adjusted odds ratios of brain lesions in relation to quartiles of gravidity, delivery, and age at menarche or menopause, and estrogen exposure period. Multivariate analyses demonstrated that the highest quartile of gravidity (OR, 1.74; 95% CI, 1.02–2.98) and delivery (OR, 1.95; 95% CI, 1.15–3.30) was associated with an increased risk of WMH. Significant covariates observed in these models were age, BMI ≥ 25 kg/m^2, educational attainment, and hypertension **(Supplementary Table 8)**.

Supplementary Table 9 and 10 shows crude and adjusted odds ratios of plaque and unadjusted and adjusted beta estimates of IMT of carotid artery in relation to the quartiles of gravidity, delivery, age at menarche or menopause, and estrogen exposure period. The highest quartiles of gravidity (OR, 1.78; 95% CI, 1.04–3.03) and delivery (OR, 2.32; 95% CI, 1.36–3.94) and the second highest quartile of delivery (OR, 1.57; 95% CI, 1.00–2.44) were associated with an increased risk of plaque lesions **(Supplementary Table 10)**. Significant covariates in these models were age, SBP, educational attainment, and diabetes.

The effects of age at menarche and menopause were consistently insignificant with or without adjustment for each other (i.e., adjusting for age at menarche when examining age at menopause and adjusting for age at menopause when examining age at menarche). The effects of all five reproductive events on the brain and carotid artery lesions were shown in forest plots in **Fig. 2**.

Discussion

This study found the highest quartile of gravidity (≥ 5 vs. 3), and delivery (≥ 4 vs. 2) were associated with an increased risk of WMH in the brain MRI image. Furthermore, the highest quartile of gravidity (≥ 5 vs. 3) and the highest (≥ 4 vs. 2) and second highest (3 vs. 2) quartiles of delivery were associated with an increased risk of plaque in the carotid artery. Previous studies reported a significant association between atherosclerotic changes in coronary artery calcium[39], aortic wall thickness[40], IMT[41], and reproductive factors in women; however, our study is the first to demonstrate a significant association between the reproductive life events of women and subclinical atherosclerotic lesions of the brain by MRI. It is possible that these associations were due to residual confounding; however, adjustment for traditional risk factors and measures of socioeconomic status did not attenuate the associations observed in our models. In addition, in our study, neither age at menarche, menopause, nor estrogen exposure time was associated with any atherosclerotic changes of the brain and carotid artery. Given that the effect of delivery compared to that of gravidity, appeared to have more strong effect on WMH and plaque lesions and the majority of both events are overlapped, it was suggested that multiple pregnancies may influence physiological changes of body and cause the atherogenic milieu, and then eventually increase the risk of atherosclerosis in the brain and carotid arteries.

In our study, we found consistent associations between WMHs and the highest quartiles of gravidity and delivery. Previous studies have suggested that WMHs, and lacunar manifestations vary according to the stage of arteriosclerosis, and advances in brain MRI have revealed earlier WMHs that were less prominent than lacunar lesions[42]. As WMH may trigger ischemic brain dysfunction, prevention or reversal of brain damage caused by small vessel disease at the earliest possible stage is important to ameliorate the potential cognitive, physical, stroke, and dementia consequences[43-46]. The presence of severe WMH at baseline has been reported to double the future risk of stroke[47], and those with severe WMH have been reported to have a more than double and four times risk of future all-cause mortality and subsequent dementia, respectively[48]. These confirmatory data are consistent with risk estimates from other large population-based studies that demonstrate the clinical relevance of WMH[49, 50]. Thus, considering that WMH is associated with a risk of stroke[31], our finding that WMH is associated with gravidity and delivery is clinically meaningful, despite no association with lacunar lesions.

Gravidity is different from delivery with respect to the completion of pregnancies. We confirmed that the numbers of gravidity were higher than the numbers of pregnancy indicating that these two events are overlapped but at the same time, there were some pregnancies terminated (we do not know the reason if the termination is spontaneous or artificial). Pregnancy induced physiological changes that can have adverse effects on incident CVD, which remain even after delivery, including weight gain,

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

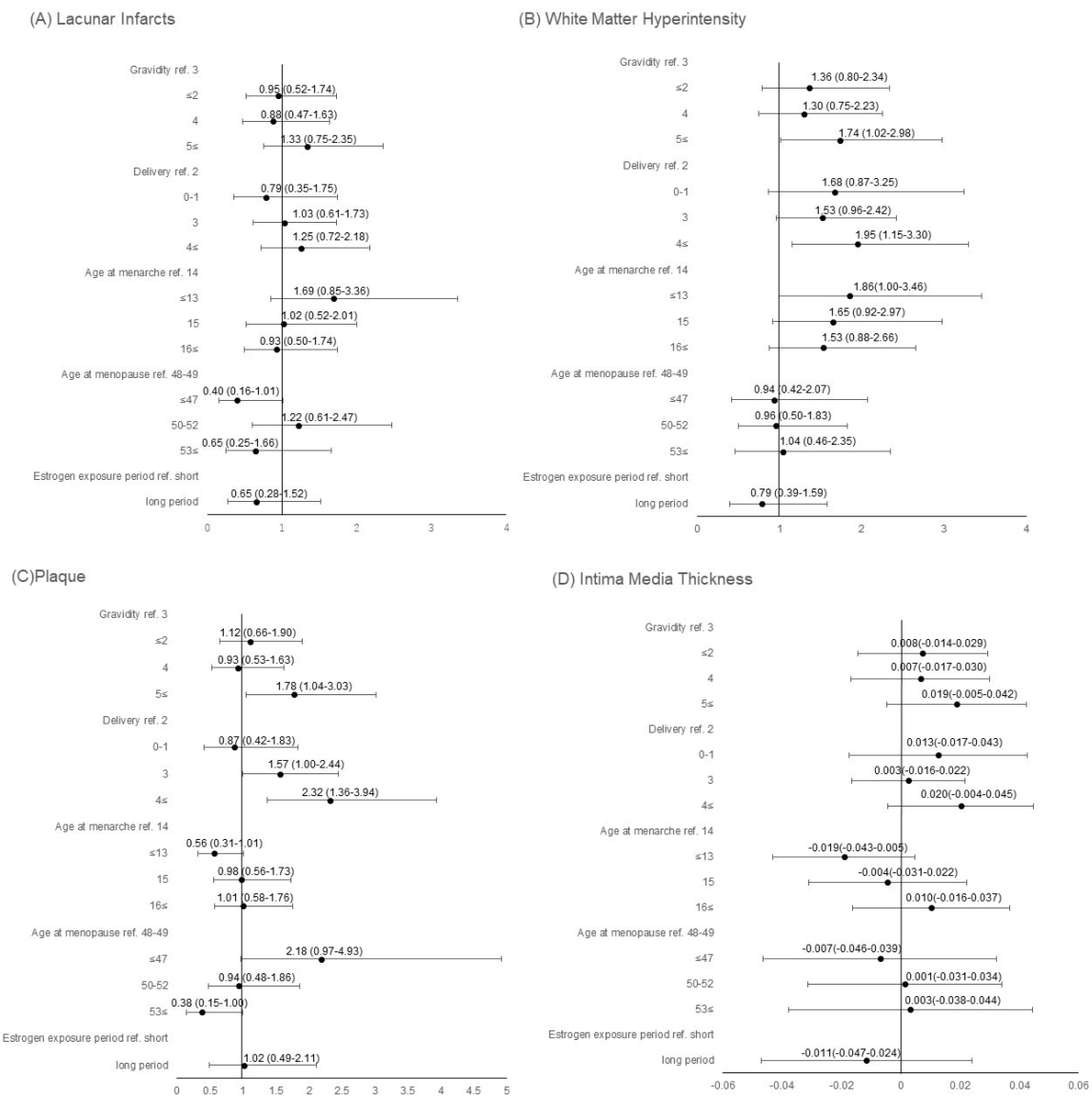


Fig. 2. Adjusted odds ratios and 95% confidence intervals of the effects of gravidity, delivery, and age at menarche and menopause on brain and carotid arteriopathy

The highest quartiles of gravidity and delivery were associated with an increased risk of WMH (B). The highest quartiles of gravidity and delivery and the second highest quartile of delivery were associated with an increased risk of plaque lesions (C).

dyslipidemia, increased plasma glucose levels, and insulin resistance as well as endothelial dysfunction and inflammatory and hemostatic processes[6, 51]. For this reason, we investigated gravidity and pregnancy separately because the impact of these two events on CVD is different. These differences between delivery and gravidity may be explained by more strong effect of delivery observed in our study compared to gravidity: significant findings of the highest category (4 ≥ for delivery vs. 5 ≥ for gravidity) on WHM and the highest and second highest category for delivery vs. the highest category for gravidity on Cardiac US findings.

Previous meta-analysis based on 10 cohort studies the relationship between parity number and CVD mortality compared to nulliparity has either a U- or J-shaped association[5], but such association was not observed in our study. In fact, we had few women without delivery, and the data for these women were grouped with those with a single delivery; this may explain the insignificance observed regarding the 0-1 delivery group that would formulate the left-side of

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

the U- or J-shaped curve. Alternatively, a previous large-scale epidemiological study demonstrated that subfertility, defined as a duration of one year or more of involuntary childlessness, was associated with increased CVD risk when subfertility lasted five or more years[52]. The authors suggested that the nulliparous women in their study population might have had cerebrovascular risk associated underlying illnesses such as polycystic ovary, hypercoaguable states, and hypothyroidism[52]. In this regard, more sophisticate design to collect those obstetrics and gynecological information that could affect fertility may need to be warranted in the future.

We failed to show a significant association between estrogen time and either brain atherosclerosis or carotid arteriopathy. We estimated estrogen exposure period by subtracting age at menarche from age at menopause referring to previous studies that investigated an association between reproductive events and CVD risk[7, 9, 53, 54]. One of these study[53], reported that endogenous estrogen exposure does not add to the predictive value of age at menopause for cardiovascular mortality because of small area under curve. However, a more recent study reported that a longer duration of reproductive years was associated with lower risk of cardiovascular and cerebrovascular diseases among women ≥ 60 years[54]. The insignificant results of both age at menopause and estrogen duration in our study may attribute to several factors including the use of subclinical change outcome, the characteristics of participants, and a lack of information on endogenous estrogen period which included breastfeeding, stillbirths, and miscarriages and hormone use (oral contraceptive pills and menopausal hormone therapy). Unfortunately, our dataset failed to have those information and thus, this is an apparent focus for future research.

We found that significant covariates associated with subclinical atherosclerotic changes of the brain and carotid artery were age, BMI ≥ 25 kg/m^2, educational attainment, and hypertension. Among these, age, educational attainment, and hypertension were independent risk factors for CVD[55], but the protective effect of overweight and obesity needs to be addressed. Our sample is unique because the mean age was 66-67 years and the median of BMI with inter quartile range is 23 (21-26), and the majority are farmers, suggesting that our sample characteristics is quite different from obese people in western countries where obesity is more prevalent. A large-scale cohort study of 179,987 participants of 13 well-qualified cohort studies shows that showed the association between low BMI and elevated mortality in the elderly population with BMI < 29 kg/m^2 [56], suggesting that lower BMI compared to overweight had an increased risk of death and CVD risk.

The strength of this study is that it is the first study to investigate subclinical atherosclerosis of the brain and cervical arteriopathy associated with delivery. Previously, Sanghavi *et al.*[40] reported that subclinical atherosclerosis of brain and cervical arteriopathy were associated with delivery, although the study did not measure home blood pressure, which is considered as gold standard of blood pressure as well as Ambulatory and Home Blood Pressure Measurement. Moreover, there are some limitations to this study that need to be addressed. First, our data may not be generalizable because Ohasama is a countryside and lies in northern Japan, where salt consumption and stroke mortality are very high. Further, most women were farmers who differed in socioeconomic status (income and educational attainment) from the general Japanese population. Second, selection bias may have been present, as only independent participants could participate, and the subjects who underwent MRI were healthier than those who did not. Third, we obtained age at menopause as the age at last menstruation and did not consider surgical menopause such as age at hysterectomy/oophorectomy for treatment purposes. Fourth, although IMT is an independent risk factor for CVD, the mean IMT was 0.7 mm (within the normal range) with the thickest IMT being 0.73 mm, which indicates that the impact of IMT on health may be minimal. Fifth, 0.5-Tesla MRI modality used in this study may affect the accuracy of WMH and lacunar lesions compared to a modality with higher Tesla. Sixth, our dataset did not include maternal information on pregnancy complications. Continuous lifestyle changes (i.e., many pregnancies) have been reported to potentially induce excess gestational weight gain and postpartum obesity, which impacts future health[57]. A more detailed mechanism may be articulated if the metabolic complications during pregnancy, such as glucose intolerance or hypertension, are investigated. Seventh, age at menarche and menopause is more prone to misclassification compared to the number of pregnancies and births, suggesting that non-differential misclassification bias may exist. Finally, there are many unmeasured confounders in this study. Those include underlying illness associated with CVD, including hypercoagulable state, hypothyroidism, polycystic ovary, and socioeconomic factors including influence of the times investigated. Therefore, the interpretation of our results of the present study requires careful consideration.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Conclusion

In summary, we found that a higher gravidity and delivery were associated with an increased risk of subclinical atherosclerotic lesions of the brain and carotid artery while neither of age at menarche nor menopause as well as estrogen exposure period was significant. These findings were consistently observed even after adjusting for conventional risk factors, such as age, BMI, systolic blood pressure, and a history of hypertension. Given that the effect of delivery compared to that of gravidity, appeared to have more strong effect on WMH and plaque lesions and the majority of both events are overlapped, it was suggested that multiple pregnancies may influence physiological changes of body and cause the atherogenic milieu, and then eventually increase the risk of atherosclerosis in the brain and carotid arteries. While these women require close monitoring in clinical practice, further prospective large-scale studies are required to confirm our findings, to make them more applicable to women in modern times, establish causality, and elucidate the underlying mechanism.

Acknowledgements

We thank all the participants and relevant people of Ohasama study.

Conflict of Interest

H.M., K.A., Y.I., and T.O. concurrently held the position of director of the Tohoku Institute for Management of Blood Pressure and were supported by Omron Healthcare Co., Ltd. K.A. and T.O. received a joint research grant from Omron Healthcare Co., Ltd.

Financial Support

This study was supported by Grants for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (17H04126, 17K15853, 17K19930, 18K09674, 18K09904, 18K17396, 19K19466, 19H03908, 19K10662, 20K08612, 21K10452, 21K10478, 21H04854, 21K17313, 21K19670 and 21H03192); internal research grants from Keio University; the Japan Arteriosclerosis Prevention Fund; Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan (H29-Junkankitou-Ippan-003 and 20FA1002); ACRO Incubation Grants of Teikyo University; academic contributions from Pfizer Japan, Inc.; scholarship donations from Chugai Pharmaceutical Co., Ltd. and Daiichi Sankyo Co., Ltd.; research support from Astellas Pharma Inc. and Takeda Pharmaceutical Co., Ltd.; The Health Care Science Institute Research Grant; the Health Science Center Research Grant; and the Takeda Science Foundation.

Author Contributions

WS and KN wrote the draft of this manuscript. KN conceived this study, performed data analyses, completed the draft. Dataset and analyses were supervised by MS, MK, and MT-U. MS, MK and TO were responsible for gathering and screening the data. TO is the principal investigator of the Ohasama study. All authors were involved in data collection and had full access to all data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors have read and approved the final version of the manuscript.

References

1) Charalampopoulos D, McLoughlin A, Elks CE, and Ong KK: Age at menarche and risks of all-cause and cardiovascular death: A systematic review and meta-analysis. Am J of Epidemiol, 2014; 180: 29-40
2) Mishra SR, Chung HF, Waller M, and Mishra GD: Duration of estrogen exposure during reproductive years, age at menarche and age at menopause, and risk of cardiovascular disease events, all-cause and cardiovascular mortality: A systematic review and meta-analysis. BJOG, 2021; 128: 809-821
3) Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, and Franco OH: Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality. JAMA Cardiol, 2016; 1: 767-776
4) Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, Brunner EJ, Kuh D, Hardy R, Avis NE, Gold EB, Derby CA, Matthews KA, Cade JE, Greenwood DC, Demakakos P, Brown DE, Sievert LL, Anderson D, Hayashi K, Lee JS, Mizunuma H, Tillin T, Simonsen MK, Adami HO, Weiderpass E, and Mishra GD: Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Health, 2019; 4: e553-e564
5) Lv H, Wu H, Yin J, Qian J, and Ge J: Parity and cardiovascular disease mortality: A dose-response meta-analysis of cohort studies. Sci Rep, 2015; 5: 13411
6) Li W, Ruan W, Lu Z, and Wang D: Parity and risk of maternal cardiovascular disease: A dose-response meta-analysis of cohort studies. Eur J Prev Cardiol, 2019; 26: 592-602
7) Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, and Rexrode KM: Duration of Reproductive life span, age at menarche, and age at menopause are associated with

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

risk of cardiovascular disease in women. J Am Heart Assoc, 2017; 6: e006713
8) Ness RB, Harris T, Cobb J, Flegal KK, Kelsey JL, Balanger A, Stunkard AJ, and D'Agostino RB: Number of pregnancies and the subsequent risk of cardiovascular disease. N Engl J M, 1993; 328: 1528-1533
9) Jung KJ, Kim MR, Yun YD, Kim HC, and Jee SH: Duration of ovarian hormone exposure and atherosclerotic cardiovascular disease in Korean women: the Korean Heart Study. Menopause, 2016; 23: 60-66
10) Dam V, Van Der Schouw YT, Onland-Moret NC, Groenwold RH, Peters SA,Burgess S, Wood AM, Chirlaque MD, Moons KGM, Oliver-Williams C, Schuit E, Tikk K, Weiderpass E, Holm M, Tjønneland A, Kühn T, Fortner RT, Trichopoulou A, Karakatsani A, Vecchia CL, Ferrari P, Gunter M, Masala G, Sieri S, Tumino R, Panico S, Boer JMA, Verschuren WMM, Salamanca-Fernández E, Arriola L, Moreno-Iribas C, Engström G, Melander O, Nordendahl M, Wennberg P, Key TJ, Colorado-Yohar S, Matullo G, Overvad K, Clavel-Chapelon F, Boeing H, Quiros JR, Angelantonio ED, Langenberg C, Sweeting MJ, Riboli E, Wareham NJ, Danesh J, and Butterworth A: Association of menopausal characteristics and risk of coronary heart disease: a pan-European case-cohort analysis. Int J Epidemiol, 2019; 48: 1275-1285
11) Palmer JR, Rosenberg L, and Shapiro S: Reproductive factors and risk of myocardial infarction. Am J Epidemiol, 1992; 136: 408-416
12) Appiah D, Schreiner PJ, Demerath EW, Loehr LR, Chang PP, and Folsom AR: Association of age at menopause with incident heart failure: a prospective cohort study and meta-analysis. J Am Heart Assoc, 2016; 5: e003769
13) Rahman I, Akesson A, and Wolk A: Relationship between age at natural menopause and risk of heart failure. Menopause, 2015; 22: 12-16
14) Murakami K, Metoki H, Satoh M, Asayama K, Hosaka M, Matsuda A, Inoue R, Tsubota-Utsugi M, Murakami T, Nomura K, Kikuya M, Imai Y, and Ohkubo T: Menstrual factors and stroke incidence in japanese postmenopausal women: the Ohasama study. Neuroepidemiology, 2016; 47: 109-116
15) Mueller NT, Odegaard AO, Gross MD, Koh WP, Yuan JM, and Pereira MA: Age at menarche and cardiovascular disease mortality in Singaporean Chinese women: the Singapore Chinese Health Study. Ann Epidemiol, 2012; 22: 717-722
16) Wu X, Cai H, Kallianpur A, Gao YT, Yang G, Chow WH, Li HL, Zheng W, and Shu XO: Age at menarche and natural menopause and number of reproductive years in association with mortality: results from a median follow-up of 11.2 years among 31,955 naturally menopausal Chinese women. PLoS One, 2014; 9: e103673
17) Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Inaba Y, Tamakoshi A, and JACC Study Group: Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. J Epidemiol, 2006; 16: 177-184
18) Zhang X, Liu L, Song F, Song Y, and Dai HJM: Ages at menarche and menopause, and mortality among postmenopausal women. Maturitas, 2019; 130: 50-56
19) Ota K, Yamagishi K, Kishida R, Kihara T, Cui R, Tamakoshi A, Iso H, and JACC Study group: Relationships between Age at Menarche and Risk of Cardiovascular Disease Mortality among Japanese Women: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) Study. J Atheroscler Thromb, 2022; Online ahead of print. doi; https: //doi.org/10.5551/jat.63321
20) Sasaki Y, Ikeda Y, Miyauchi T, Uchikado Y, Akasaki Y, and Ohishi M: Estrogen-SIRT1 Axis Plays a Pivotal Role in Protecting Arteries Against Menopause-Induced Senescence and Atherosclerosis. J Atheroscler Thromb, 2020; 27: 47-59
21) Skilton MR, Serusclat A, Begg LM, Moulin P, and Bonnet F: Parity and carotid atherosclerosis in men and women: insights into the roles of childbearing and child-rearing. Stroke, 2009; 40: 1152-1157
22) Gunderson EP, Lewis CE, Murtaugh MA, Quesenberry CP, West DS, and Sidney S: Long-term plasma lipid changes associated with a first birth: the Coronary Artery Risk Development in Young Adults Study. Am J Epidemiol, 2004; 159: 1028-1039
23) Rich-Edwards JW, Fraser A, Lawlor DA, and Catov JM: Pregnancy characteristics and women's future cardiovascular health: An underused opportunity to improve women's health? Epidemiol Rev, 2014; 36: 57-70
24) Kamon T, Kaneko H, Itoh H, Okada A, Matsuoka S, Kiriyama H, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H, and Komuro I: Sex Difference in the Association between Lipid Profile and Incident Cardiovascular Disease among Young Adults. J Atheroscler Thromb, 2022; 29; 1475-1486
25) Ohkubo T, Asayama K, and Imai Y: The value of self-measured home blood pressure in predicting stroke. Expert Rev Neurother, 2006; 6: 163-173
26) Bots ML, Hoes AW, Koudstaal PJ, Hofman A, and Grobbee DE: Common carotid intima-media thickness and risk of stroke and myocardial infarction: The rotterdam study. Circulation, 1997; 96: 1432-1437
27) O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, and Wolfson Jr SK: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. N Engl J Med, 1999; 340: 14-22
28) Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, Rosamond WD, and Evans G: Carotid wall thickness is predictive of incident clinical stroke: The atherosclerosis risk in communities (aric) study. Am J Epidemiol, 2000; 151: 478-487
29) Hollander M, Bots ML, Del Sol AI, Koudstaal PJ, Witteman JC, Grobbee DE, Hofman A, and Breteler MMB: Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly: The rotterdam study. Circulation, 2002; 105: 2872-2877
30) Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, Kiyama M, Tanigawa T, Yamagishi K, and Shimamoto T:

Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in japanese elderly men. Stroke, 2004; 35: 2788-2794
31) Kuller LH, Longstreth WT Jr, Arnold AM, Bernick C, Bryan RN, and Beauchamp NJ Jr; Cardiovascular Health Study Collaborative Research Group: White matter hyperintensity on cranial magnetic resonance imaging: A predictor of stroke. Stroke, 2004; 35: 1821-1825
32) Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, and Clegg LX: Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol, 1997; 146: 483-494
33) Naghavi M, Falk E, Hecht HS, Jamieson M J, Kaul S, Berman D, Fayad Z, Budoff MJ, Rumberger J, Naqvi TZ, Shaw LJ, Faergeman O, Cohn J, Bahr R, Koenig W, Demirovic J, Arking D, Herrera VLM, Badimon J, Goldstein JA, Rudy Y, Airaksinen J, Schwartz RS, Riley WA, Mendes RA, Douglas P, Shah PK, and SHAPE Task Forc: From vulnerable plaque to vulnerable patient--Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. Am J Cardiol, 2006; 98: 2H-15H
34) Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, and Lechner H: Pathologic correlates of incidental mri white matter signal hyperintensities. Neurology, 1993; 43: 1683-1689
35) Tsubota-Utsugi M, Satoh M, Tomita N, Hara A, Kondo T, Hosaka M, Saito S, Asayama K, Inoue R, Hirano M, Hosokawa A, Murakami K, Murakami T, Metoki H, Kikuya M, Izumi S, Imai Y, and Ohkubo T: Lacunar infarcts rather than white matter hyperintensity as a predictor of future higher level functional decline: The ohasama study. J Stroke Cerebrovasc Dis, 2017; 26: 376-384
36) Hara A, Ohkubo T, Kikuya M, Shintani Y, Obara T, Metoki H, Inoue R, Asayama K, Hashimoto T, Harasawa T, Aono Y, Otani H, Tanaka K, Hashimoto J, Totsune K, Hoshi H, Satoh H, and Imai Y: Detection of carotid atherosclerosis in individuals with masked hypertension and white-coat hypertension by self-measured blood pressure at home: The ohasama study. J Hypertens, 2007; 25: 321-327
37) Imai Y, Abe K, Sasaki S, Minami N, Munakata M, Sakuma H, Hashimoto J, Sekino H, Imai K, and Yoshinaga K: Clinical evaluation of semiautomatic and automatic devices for home blood pressure measurement: Comparison between cuff-oscillometric and microphone methods. J Hypertens, 1989; 7: 983-990
38) Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, Miyakawa M, and Fukiyama K; Japanese Society of Hypertension: Japanese society of hypertension (jsh) guidelines for self-monitoring of blood pressure at home. Hypertens Res, 2003; 26: 771-782
39) Atsma F, Bartelink ML, Grobbee DE, Rutten A, Bots ML, Prokop M, and Schouw YT: Reproductive factors, metabolic factors, and coronary artery calcification in older women. Menopause (New York, NY), 2008; 15: 899-904
40) Sanghavi M, Kulinski J, Ayers CR, Nelson D, Stewart R, Parikh N, Lemos JA, and Khera A: Association between number of live births and markers of subclinical atherosclerosis: The dallas heart study. Eur J Prev Cardiol, 2016; 23: 391-399
41) Skilton MR, Bonnet F, Begg LM, Juonala M, Kähönen M, Lehtimäki T, Viikari JSA, and Raitakari OT: Childbearing, childrearing, cardiovascular risk factors, and progression of carotid intima-media thickness: the Cardiovascular Risk in Young Finns study. Stroke, 2010; 41: 1332-1337
42) Wardlaw JM, Valdés Hernández MC, and Muñoz-Maniega S: What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J Am Heart Assoc, 2015; 4: 001140
43) The LADIS Study Group, Poggesi A, Pantoni L, Inzitari D, Fazekas F, Ferro J, O'Brien J, Hennerici M, Scheltens P, Erkinjuntti T, Visser M, Langhorne P, Chabriat H, Waldemar G, Wallin A, and Wahlund A: 2001-2011: A decade of the LADIS (Leukoaraiosis And DISability) Study: What have we learned about white matter changes and small-vessel disease? Cerebrovasc Dis, 2011; 32: 577-588
44) Fazekas F, Chawluk JB, Alavi A, Hurtig HI, and Zimmerman RA: Mr signal abnormalities at 1.5 t in alzheimer's dementia and normal aging. AJR Am J Roentgenol, 1987; 149: 351-356
45) Smith EE: Leukoaraiosis and stroke. Stroke, 2010; 41: S139-143
46) Black S, Gao F, and Bilbao J: Understanding white matter disease: Imaging-pathological correlations in vascular cognitive impairment. Stroke, 2009; 40: S48-52
47) Mishra SR, Chung HF, Waller M, Dobson AJ, Greenwood DC, Cade JE, Giles GG, Bruinsma F, Simonsen MK, Hardy R, Kuh D, Gold EB, Crawford SL, Derby CA, Matthews KA, Demakakos P, Lee JS, Mizunuma H, Hayashi K, Sievert LL, Brown DE, Sandin S, Weiderpass E, and Mishra GD: Association between reproductive life span and incident nonfatal cardiovascular disease: A pooled analysis of individual patient data from 12 studies. JAMA Cardiol, 2020; 5: 1410-1418
48) Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, Romero JR, Kase CS, Wolf PA, and Seshadri S: Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: The Framingham Offspring Study. Stroke, 2010; 41: 600-606
49) Vermeer SE, Prins ND, Heijer TD, Hofman A, Koudstaal PJ, and Breteler MMB: Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med, 2003; 348: 1215-1222
50) Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O'Leary DH, and Furberg CD: Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: The cardiovascular health study. Stroke, 2005; 36: 56-61
51) Parikh NI, Cnattingius S, Dickman PW, Mittleman MA, Ludvigsson JF, and Ingelsson E: Parity and risk of later-life maternal cardiovascular disease. Am Heart J, 2010; 159: 215-221
52) Parikh NI, Cnattingius S, Mittleman MA, Ludvigsson JF,

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

and Ingelsson E: Subfertility and risk of later life maternal cardiovascular disease. Hum Reprod, 2012; 27: 568-575
53) Kleijn MJ, Schouw YT, Verbeek AL, Peeters PH, Banga JD, and Graaf Y: Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. Am J Epidemiol, 2002; 155: 339-445
54) Mansoor H, Elgendy IY, Segal R, and Hartzema A: Duration of reproductive years and the risk of cardiovascular and cerebrovascular events in older women: Insights from the National Health and Nutrition Examination Survey. J Womens Health, 2017; 26: 1047-1052
55) Shimamoto T, Iso H, Iida M, and Komachi Y: Epidemiology of cerebrovascular disease: stroke epidemic in Japan. J Epidemiol, 1996; 6: S43-7
56) Hozawa A, Hirata T, Yatsuya H, Murakami Y, Kuriyama S, Tsuji I, Sugiyama D, Satoh A, Tanaka-Mizuno S, Miura K, Ueshima H, and Okamura T: Association Between Body Mass Index and All-Cause Death in Japanese Population: Pooled Individual Participant Data Analysis of 13 Cohort Studies. J Epidemiol, 2019; 29: 457-463
57) Mamun AA, Kinarivala M, O'Callaghan MJ, Williams GM, Najman JM, and Callaway LK: Associations of excess weight gain during pregnancy with long-term maternal overweight and obesity: Evidence from 21 y postpartum follow-up. Am J Clin Nutr, 2010; 91: 1336-1341

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Supplementary Table 1. Baseline characteristics of the MRI sample (n=622) and US sample (n=711)

	MRI sample (n=622)	US sample (n=711)
mean ± sd		
Age, y	67.9 ± 6.1	69.7 ± 7.0
Body Mass Index, kg/m^2	23.8 ± 3.3	23.8 ± 3.4
Home-measured mean SBP, mmHg	128.4 ± 15.0	129.8 ± 14.5
Home-measured mean DBP, mmHg	74.3 ± 8.7	74.3 ± 8.5
median, interquartile range		
Age at menarche	15 (14-16)	14 (13-15)
Age at menopause	50 (48-52)	50 (48-52)
Gravidity	3 (2-5)	3 (2-4)
Delivery	3 (2-3)	3 (2-3)
n (%)		
Educational attainment		
Elementary school	82 (14)	49 (7)
Middle school	387(66)	410(60)
High school	122 (21)	2224(33)
Lifestyle		
Smoker	6 (1)	8 (1)
Drinker	80 (13)	96 (14)
Past history		
Diabetes[a]	75 (12)	94(13)
Dislipidemia[b]	199 (32)	272 (38)
Hypertension[c]	301 (48)	419 (59)

[a]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.
[b]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.
[c]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

Supplementary Table 2. Baseline characteristics according to the quartiles of gravidity in the MRI and US samples

	Gravidity									
	MRI sample (n=571)					US sample (n=665)				
	-2 (n=148)	3 (n=141)	4 (n=133)	5- (n=149)	p	-2 (n=195)	3 (n=170)	4 (n=149)	5- (n=151)	p
mean ± sd										
Age, y	66.8 ± 6.1	67.1 ± 6.1	67.5 ± 6.2	69.7 ± 5.6	<0.001	68.6 ± 6.9	68.8 ± 7.2	70.7 ± 7.1	71.0 ± 6.4	<0.001
Body Mass Index, kg/m^2	23.9 ± 3.1	23.8 ± 3.2	23.9 ± 3.1	23.8 ± 3.6	0.665	23.6 ± 3.2	23.8 ± 3.4	23.9 ± 3.3	23.9 ± 3.6	0.556
Home-measured mean SBP, mmHg	126.5 ± 14.5	129.3 ± 15.6	129.3 ± 15.8	128.5 ± 14.4	0.380	128.5 ± 13.8	129.7 ± 15.1	131.1 ± 14.9	129.9 ± 14.0	0.356
Home-measured mean DBP, mmHg	74.0 ± 8.7	74.5 ± 9.4	75.4 ± 9.0	73.6 ± 8.1	0.660	74.4 ± 8.3	74.1 ± 8.6	75.4 ± 9.1	73.3 ± 8.3	0.463
n (%)										
Educational attainment					<0.001					<0.001
Elementary school	13 (9)	11 (8)	13 (10)	33 (23)		4 (2)	8 (5)	10 (7)	18 (12)	
Middle school	97 (68)	96 (71)	78 (59)	93 (64)		111 (58)	98 (60)	82 (56)	95 (65)	
High school	33 (23)	28 (21)	41 (31)	19 (13)		76 (40)	57 (35)	55 (37)	34 (23)	
Lifestyle										
Smoker	1 (1)	1 (1)	3 (2)	1 (1)	0.490	0 (0)	2 (1)	4 (3)	2 (1)	0.161
Drinker	15 (10)	14 (10)	22 (17)	23 (15)	0.211	30 (15)	21 (12)	17 (11)	25 (17)	0.504
Past history										
Diabetes[a]	14 (9)	16 (11)	14 (11)	24 (16)	0.304	20 (10)	24 (14)	18 (12)	23 (15)	0.519
Dislipidemia[b]	52 (35)	43 (31)	44 (33)	43 (29)	0.668	72 (37)	67 (39)	62 (42)	53 (35)	0.662
Hypertension[c]	67 (45)	65 (46)	73 (55)	67 (45)	0.296	112 (57)	94 (55)	101 (68)	85 (56)	0.095

MRI, magnetic resonance imaging; US, ultrasonography; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.
[b]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.
[c]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Supplementary Table 3. Baseline characteristics according to the quartiles of delivery in the MRI and US samples

	Delivery									
	MRI sample (*n*=582)					US sample (*n*=672)				
	0-1 (*n*=55)	2 (*n*=225)	3 (*n*=174)	4- (*n*=128)	*p*	0-1 (*n*=57)	2 (*n*=292)	3 (*n*=214)	4- (*n*=109)	*p*
mean ± sd										
Age, y	67.5 ± 6.1	66.3 ± 5.8	67.7 ± 6.0	70.8 ± 5.4	<0.001	70.2 ± 6.5	69.3 ± 7.0	69.0 ± 7.1	71.8 ± 6.2	0.080
Body Mass Index, kg/m^2	23.8 ± 3.1	23.8 ± 3.2	24.1 ± 3.2	23.5 ± 3.4	0.746	23.9 ± 3.0	23.7 ± 3.5	23.9 ± 3.2	23.7 ± 3.5	0.747
Home-measured mean SBP, mmHg	126.6 ± 15.7	127.5 ± 15.1	128.9 ± 14.0	130.0 ± 15.8	0.125	127.7 ± 13.0	129.9 ± 14.6	128.8 ± 14.2	132.1 ± 15.1	0.367
Home-measured mean DBP, mmHg	73.9 ± 9.1	74.3 ± 8.7	75.2 ± 8.5	73.3 ± 8.8	0.600	74.4 ± 8.4	74.5 ± 8.3	74.2 ± 8.6	73.7 ± 9.0	0.411
n (%)										
Educational attainment					<0.001					<0.001
Elementary school	6 (11)	11 (5)	17 (10)	41 (33)		1 (2)	7 (2)	13 (6)	23 (22)	
Middle school	35 (64)	151 (69)	112 (67)	70 (57)		38 (67)	164 (57)	121 (59)	65 (61)	
High school	14 (25)	57 (26)	38 (23)	13 (10)		18 (32)	116 (40)	70 (34)	18 (17)	
Lifestyle										
Smoker	2 (4)	1 (1)	2 (1)	1 (1)	0.211	0 (0)	3 (1)	4 (2)	1 (1)	0.646
Drinker	4 (7)	30 (13)	21 (12)	19 (15)	0.545	5 (9)	47 (16)	22 (10)	18 (17)	0.142
Past history										
Diabetes[a]	7 (13)	18 (8)	22 (13)	21 (16)	0.115	10 (18)	32 (11)	26 (12)	17 (16)	0.408
Dislipidemia[b]	20 (36)	75 (33)	60 (35)	31 (24)	0.193	20 (35)	111 (38)	88 (41)	38 (35)	0.677
Hypertension[c]	30 (55)	103 (46)	78 (45)	68 (53)	0.329	35 (61)	174 (60)	125 (58)	62 (57)	0.938

MRI, magnetic resonance imaging; US, ultrasonography; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.
[b]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.
[c]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

Supplementary Table 4. Baseline characteristics according to the quartiles of age at menarche in the MRI and US samples

	Age at menarche									
	MRI sample (*n*=509)					US sample (*n*=616)				
	-13 years (*n*=111)	14 years (*n*=121)	15-16 years (*n*=118)	16- years (*n*=159)	*p*	-13 years (*n*=206)	14 years (*n*=143)	15 years (*n*=123)	16- years (*n*=144)	*p*
mean ± sd										
Age, y	64.8 ± 6.5	66.8 ± 5.7	67.7 ± 5.8	69.9 ± 5.5	<0.001	65.7 ± 6.5	69.1 ± 6.9	71.9 ± 6.1	73.0 ± 5.8	<0.001
Body Mass Index, kg/m^2	24.3 ± 3.3	24.1 ± 3.5	23.9 ± 3.1	23.5 ± 2.9	0.035	24.2 ± 3.4	23.9 ± 3.7	23.7 ± 3.3	23.2 ± 2.7	0.007
Home-measured mean SBP, mmHg	127.8 ± 14.7	128.0 ± 15.6	127.5 ± 14.7	128.9 ± 15.6	0.541	127.2 ± 13.6	128.6 ± 15.0	130.2 ± 13.8	132.4 ± 15.1	0.001
Home-measured mean DBP, mmHg	74.6 ± 8.4	74.1 ± 9.2	75.1 ± 8.9	74.0 ± 8.8	0.975	74.3 ± 9.0	74.5 ± 8.5	73.8 ± 7.9	74.2 ± 8.6	0.857
n (%)										
Educational attainment					<0.001					<0.001
Elementary school	7 (7)	7 (6)	8 (7)	27 (18)		2 (1)	2 (1)	6 (5)	20 (14)	
Middle school	63 (58)	80 (67)	82 (71)	105 (68)		85 (42)	91 (65)	82 (69)	99 (70)	
High school	38 (35)	32 (27)	25 (22)	22 (14)		115 (57)	48 (34)	31 (26)	22 (16)	
Lifestyle										
Smoker	4 (4)	0 (0)	0 (0)	0 (0)	0.002	5 (2)	0 (0)	0 (0)	2 (1)	0.103
Drinker	20 (18)	21 (17)	13 (11)	16 (10)	0.133	37 (18)	18 (13)	12 (10)	18 (13)	0.167
Past history										
Diabetes[a]	14 (13)	11 (9)	14 (12)	16 (10)	0.808	22 (11)	19 (13)	17 (14)	17 (12)	0.819
Dislipidemia[b]	38 (34)	42 (35)	35 (30)	49 (31)	0.790	85 (41)	51 (36)	48 (39)	51 (35)	0.633
Hypertension[c]	53 (48)	57 (47)	48 (41)	82 (52)	0.355	112 (54)	79 (55)	75 (61)	88 (61)	0.475

MRI, magnetic resonance imaging; US, ultrasonography; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.
[b]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.
[c]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Supplementary Table 5. Baseline characteristics according to the quartiles of age at menopause in the MRI and US samples

	Age at menopause									
	MRI sample (*n*=462)					US sample (*n*=449)				
	-47 years (*n*=102)	48-49 years (*n*=66)	50-52 years (*n*=187)	53- years (*n*=107)	*p*	-47 years (*n*=111)	48-49 years (*n*=69)	50-52 years (*n*=173)	53- years (*n*=96)	*p*
mean ± sd										
Age, y	68.2 ± 6.0	68.5 ± 5.9	68.6 ± 5.3	68.7 ± 5.0	0.640	71.2 ± 7.0	71.3 ± 6.6	72.2 ± 5.5	72.4 ± 5.5	0.093
Body Mass Index, kg/m^2	23.8 ± 3.0	23.3 ± 3.3	23.6 ± 3.2	24.5 ± 3.3	0.245	23.8 ± 3.4	23.2 ± 2.8	23.5 ± 3.4	24.2 ± 3.6	0.586
Home-measured mean SBP, mmHg	129.2 ± 15.7	125.9 ± 14.5	126.5 ± 14.8	132.1 ± 14.4	0.240	130.4 ± 14.0	128.5 ± 13.9	129.6 ± 14.4	133.5 ± 12.6	0.155
Home-measured mean DBP, mmHg	75.2 ± 9.6	73.2 ± 7.7	73.4 ± 8.8	74.5 ± 8.1	0.781	74.2 ± 9.1	72.9 ± 7.0	73.8 ± 8.4	74.4 ± 8.4	0.536
n (%)										
Educational attainment					0.416					0.520
Elementary school	12 (12)	13 (20)	19 (10)	11 (11)		10 (9)	8 (12)	13 (8)	3 (3)	
Middle school	69 (71)	38 (57)	126 (68)	71 (68)		69 (65)	44 (64)	117 (68)	69 (74)	
High school	16 (17)	15 (23)	40 (22)	22 (21)		27 (26)	17 (25)	41 (24)	21 (23)	
Lifestyle										
Smoker	1 (1)	0 (0)	2 (1)	1 (1)	0.876	2 (2)	0 (0)	2 (1)	0 (0)	0.446
Drinker	11 (11)	6 (9)	21 (11)	17 (16)	0.509	15 (14)	8 (12)	18 (10)	10 (10)	0.860
Past history										
Diabetes[a]	12 (12)	9 (14)	21 (12)	16 (15)	0.858	15 (14)	13 (19)	20 (12)	16 (17)	0.437
Dislipidemia[b]	34 (33)	22 (33)	58 (31)	38 (35)	0.886	41 (37)	29 (42)	69 (40)	37 (39)	0.914
Hypertension[c]	55 (54)	27 (41)	80 (43)	64 (60)	0.014	69 (62)	39 (57)	103 (60)	67 (70)	0.285

MRI, magnetic resonance imaging; US, ultrasonography; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.
[b]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.
[c]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

Supplementary Table 6. Baseline characteristics according to estrogen exposure period[a]

	Estrogen exposure period[a]					
	MRI sample (*n*=402)			US sample (*n*=393)		
	38> (short) (*n*=332)	≥ 38 (long) (*n*=70)	*p*	38> (short) (*n*=330)	≥ 38 (long) (*n*=63)	*p*
mean ± sd						
Age, y	68.4 ± 5.5	68.4 ± 5.5	0.994	71.9 ± 6.1	71.3 ± 6.3	0.458
Body Mass Index, kg/m^2	23.6 ± 3.1	24.9 ± 3.4	0.002	23.6 ± 3.2	24.7 ± 3.7	0.014
Home-measured mean SBP, mmHg	127.8 ± 15.0	129.8 ± 14.8	0.311	130.6 ± 13.9	129.4 ± 13.0	0.547
Home-measured mean DBP, mmHg	74.1 ± 8.7	73.7 ± 8.9	0.68	74.1 ± 8.4	73.1 ± 8.8	0.399
n (%)						
Educational attainment			0.112			0.103
Elementary school	36 (11)	4 (6)		22 (7)	0 (0)	
Middle school	223 (68)	43 (63)		221 (68)	43 (70)	
High school	67 (21)	21 (31)		82 (25)	18 (30)	
Lifestyle						
Smoker	1 (0)	2 (3)	0.024	2 (1)	1 (2)	0.412
Drinker	36 (11)	15 (21)	0.016	36 (11)	10 (16)	0.261
Past history						
Diabetes[b]	34 (10)	14 (20)	0.022	41 (12)	12 (19)	0.158
Dislipidemia[c]	106 (32)	23 (33)	0.88	125 (38)	27 (43)	0.457
Hypertension[d]	155 (47)	39 (56)	0.17	205 (62)	38 (60)	0.787

MRI, magnetic resonance imaging; US, ultrasonography; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Estimated by subtracting age at menarche from age at menopause and long period is defined as longer years divided at 75 percentiles of its distribution.
[b]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.
[c]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.
[d]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Supplementary Table 7. Crude odds ratios of brain lesions in relation to quartiles of gravidity, delivery, age at menarche or menopause, and estrogen exposure period

Sample unit for analyses	Gravidity (n = 571)		Delivery (n = 582)		Age at menarche (n = 509)		Age at menopause Estrogen exposure period (n = 462)	
Model Outcome	Lacunar infarcts	WMH	Lacunar infarcts	WMH	Lacunar infarcts	WMH	Lacunar infarcts	WMH
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Age	1.13 (1.09-1.17)	1.15 (1.12-1.19)	1.13 (1.09-1.17)	1.16 (1.12-1.20)	1.13 (1.08-1.17)	1.16 (1.12-1.20)	1.13 (1.08-1.18)	1.15 (1.10-1.19)
Body Mass Index								
<25 kg/m^2	—	—	—	—	—	—	—	—
≥ 25 kg/m^2	0.86 (0.57-1.28)	0.70 (0.49-1.0)	0.78 (0.52-1.18)	0.71 (0.50-1.01)	0.80 (0.52-1.24)	0.71 (0.50-1.03)	0.75 (0.47-1.18)	0.72 (0.50-1.06)
Home-measured mean SBP[a]	1.15 (1.01-1.31)	1.24 (1.11-1.39)	1.15 (1.01-1.30)	1.23 (1.10-1.38)	1.13 (0.99-1.29)	1.24 (1.10-1.40)	1.09 (0.95-1.26)	1.21 (1.07-1.38)
Educational attainment								
Elementary school	3.59 (1.79-7.20)	4.62 (2.46-8.69)	3.44 (1.74-6.83)	4.66 (2.51-8.64)	3.13 (1.43-6.83)	4.38 (2.16-8.88)	3.34 (1.43-7.81)	4.00 (1.97-8.13)
Middle school	1.94 (1.11-3.37)	2.46 (1.56-3.89)	1.90 (1.09-3.30)	2.58 (1.63-4.07)	1.85 (1.04-3.28)	2.28 (1.44-3.63)	2.62 (1.33-5.16)	2.80 (1.67-4.69)
High school	—	—	—	—	—	—	—	—
Smoker	0.60 (0.07-5.19)	1.27 (0.25-6.34)	0.62 (0.07-5.33)	1.23 (0.25-6.17)	1.11 (0.11-10.73)	1.31 (0.18-9.34)	1.06 (0.11-10.24)	0.38 (0.03-3.68)
Drinker	1.05 (0.60-1.84)	0.90 (0.55-1.48)	0.99 (0.56-1.76)	0.82 (0.50-1.34)	0.89 (0.48-1.64)	0.85 (0.51-1.42)	0.98 (0.50-1.89)	0.81 (0.46-1.42)
Diabetes[b]	1.30 (0.74-2.28)	1.40 (0.84-2.32)	1.23 (0.70-2.17)	1.35 (0.81-2.24)	1.03 (0.53-1.99)	1.40 (0.80-2.46)	1.21 (0.652-2.24)	1.32 (0.76-2.28)
Dyslipidemia[c]	0.79 (0.52-1.20)	0.93 (0.65-1.32)	0.78 (0.51-1.20)	0.94 (0.66-1.34)	0.77 (0.49-1.23)	0.96 (0.66-1.40)	0.78 (0.49-1.24)	0.90 (0.61-1.33)
Hypertension[d]	1.48 (1.01-2.16)	2.38 (1.69-3.33)	1.51 (1.03-2.20)	2.39 (1.71-3.34)	1.45 (0.96-2.19)	2.39 (1.67-3.42)	1.51 (0.99-2.33)	2.16 (1.49-3.13)
Gravidity								
-2	0.80 (0.46-1.40)	1.04 (0.65-1.66)						
3	—	—						
4	0.84 (0.48-1.48)	1.17 (0.72-1.90)						
5-	1.59 (0.95-2.66)	1.86 (1.17-2.97)						
Delivery								
0-1			0.87 (0.41-1.85)	1.79 (0.99-3.26)				
2			—	—				
3			1.24 (0.77-1.99)	1.78 (1.19-2.68)				
4-			2.04 (1.25-3.32)	3.12 (1.99-4.90)				
Age at menarche								
-13 years					1.32 (0.70-2.49)	1.36 (0.79-2.34)		
14 years					—	—		
15-16 years					1.16 (0.61-2.19)	1.64 (0.96-2.80)		
16- years					1.42 (0.79-2.53)	2.30 (1.40-3.79)		
Age at menopause								
-47 years							0.69 (0.33-1.44)	1.04 (0.55-1.95)
48-49 years							—	—
50-52 years							1.07 (0.57-2.01)	0.96 (0.54-1.68)
53- years							0.49 (0.23-1.04)	1.07 (0.58-1.99)
Long estrogen period[e]								
39 years or longer							0. 76 (0.40-1.44)	0.81 (0.48-1.36)

MRI, magnetic resonance imaging; WMH, white matter hyperintensity. OR, odds ratio; CI, confidence interval. BMI, body mass index; SBP, systolic blood pressure.

[a]per 10-mm Hg Increase

[b]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.

[c]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.

[d]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

[e]Estimated by subtracting age at menarche from age at menopause and long period is defined as longer years divided at 75 percentiles of its distribution.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Supplementary Table 8. Adjusted odds ratios[a] of brain lesions in relation to quartiles of gravidity, delivery, age at menarche or menopause, estrogen exposure period[b]

Sample unit for analyses	Gravidity (n = 571)		Delivery (n = 582)		Age at menarche (n = 509)	
Model Outcome	Lacunar infarcts	WMH	Lacunar infarcts	WMH	Lacunar infarcts	WMH
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Age	1.12 (1.07-1.16)	1.13 (1.08-1.17)	1.12 (1.07-1.16)	1.12 (1.08-1.17)	1.13 (1.08-1.18)	1.14 (1.10-1.19)
Body Mass Index						
< 25 kg/m^2	—	—	—	—	—	—
≥ 25 kg/m^2	0.86 (0.54-1.36)	0.64 (0.42-0.98)	0.84 (0.53-1.32)	0.65 (0.43-0.97)	0.75 (0.45-1.24)	0.65 (0.42-1.01)
Home-measured mean SBP[c]	1.12 (0.92-1.35)	1.06 (0.89-1.26)	1.09 (0.90-1.32)	1.02 (0.86-1.22)	1.09 (0.89-1.35)	1.05 (0.87-1.26)
Educational attainment						
Elementary school	1.65 (0.76-3.55)	2.12 (1.03-4.34)	1.61 (0.74-3.47)	1.91 (0.93-3.89)	1.70 (0.72-3.98)	2.29 (1.03-5.08)
Middle school	1.53 (0.85-2.75)	2.08 (1.25-3.45)	1.51 (0.84-2.71)	2.15 (1.29-3.57)	1.58 (0.86-2.90)	1.94 (1.15-3.27)
High school	—	—	—	—	—	—
Smoker	0.82 (0.08-8.04)	1.96 (0.31-12.39)	0.81 (0.08-8.10)	1.87 (0.28-12.28)	1.74 (0.14-21.95)	2.81 (0.29-27.42)
Drinker	1.27 (0.68-2.37)	1.10 (0.61-1.97)	1.20 (0.64-2.25)	1.02 (0.56-1.84)	1.02 (0.52-2.00)	1.10 (0.60-2.02)
Diabetes[d]	1.20 (0.66-2.20)	1.17 (0.66-2.07)	1.16 (0.63-2.16)	1.01 (0.57-1.82)	0.91 (0.44-1.85)	1.02 (0.54-1.92)
Dyslipidemia[e]	0.76 (0.48-1.22)	0.92 (0.60-1.40)	0.76 (0.48-1.20)	0.92 (0.61-1.40)	0.80 (0.49-1.33)	1.06 (0.68-1.64)
Hypertension[f]	0.99 (0.56-1.75)	1.97 (1.17-3.30)	1.02 (0.58-1.79)	2.07 (1.24-3.44)	0.95 (0.51-1.75)	1.92 (1.11-3.31)
Year after menopause[g]						
Gravidity						
-2	0.95 (0.52-1.74)	1.36 (0.80-2.34)				
3	—	—				
4	0.88 (0.47-1.63)	1.30 (0.75-2.26)				
5-	1.33 (0.75-2.35)	1.74 (1.02-2.98)				
Delivery						
0-1			0.79 (0.35-1.75)	1.68 (0.87-3.25)		
2			—	—		
3			1.03 (0.62-1.73)	1.53 (0.96-2.42)		
4-			1.25 (0.72-2.18)	1.95 (1.15-3.30)		
Age at menarche						
-13 years					1.69 (0.85-3.36)	1.86 (1.00-3.46)
14 years					—	—
15-16 years					1.02 (0.52-2.00)	1.65 (0.92-2.97)
16- years					0.93 (0.50-1.74)	1.53 (0.88-2.66)
Age at menopause						
-47 years						
48-49 years						
50-52 years						
53- years						
Long estrogen period[b]						

MRI, magnetic resonance imaging; WMH, white matter hyperintensity. OR, odds ratio; CI, confidence interval. BMI, body mass index; SBP, systolic blood pressure.

[a]Adjusting for age, body mass index, average systolic home blood pressure, educational attainment, smoker, drinker, diabetes mellitus, serum cholesterol, and hypertension.

[b]Estimated by subtracting age at menarche from age at menopause and long period is defined as longer years divided at 75 percentiles of its distribution.

[c]per 10-mm Hg Increase

[d]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.

[e]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.

[f]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

[g]Estimated by subtracting age at menopause from age at year of MRI or US investigation

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

(Cont. Supplementary Table 8)

Sample unit for analyses	Age at menopause (n = 462)		Estrogen exposure period Age at menopause-age at menarche	
Model Outcome	Lacunar infarcts	WMH	Lacunar infarcts	WMH
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Age	1.06 (0.97-1.16)	1.12 (1.03-1.21)	1.14 (1.05-1.23)	0.79 (0.39-1.59)
Body Mass Index				
< 25 kg/m^2	—	—	—	—
≥ 25 kg/m^2	0.81 (0.47-1.37)	0.72 (0.46-1.12)	0.87 (0.50-1.52)	0.72 (0.45-1.17)
Home-measured mean SBP[c]	0.99 (0.80-1.24)	1.00 (0.82-1.21)	0.97 (0.77-1.23)	1.00 (0.82-1.23)
Educational attainment				
Elementary school	1.98 (0.79-4.97)	2.67 (1.22-5.81)	2.09 (0.79-5.53)	3.09 (1.29-7.39)
Middle school	2.60 (1.26-5.35)	2.86 (1.62-5.03)	2.35 (1.13-4.88)	2.46 (1.38-4.40)
High school	—	—		
Smoker	2.23 (0.19-25.60)	0.50 (0.04-6.40)	5.61 (0.37-84.6)	1.28 (0.08-21.90)
Drinker	1.19 (0.57-2.48)	0.93 (0.49-1.77)	0.93 (0.42-2.06)	0.94 (0.47-1.87)
Diabetes[d]	1.44 (0.73-2.86)	1.27 (0.69-2.34)	1.22 (0.57-2.59)	1.27 (0.65-2.49)
Dyslipidemia[e]	0.61 (0.35-1.04)	0.82 (0.52-1.29)	0.66 (0.37-1.17)	0.96 (0.59-1.56)
Hypertension[f]	1.53 (0.80-2.93)	2.08 (1.20-3.62)	1.35 (0.69-2.64)	2.20 (1.22-3.97)
Year after menopause[g]	1.08 (1.00-1.16)	1.01 (0.94-1.09)	1.01 (0.95-1.08)	1.00 (0.95-1.06)
Gravidity				
-2				
3				
4				
5-				
Delivery				
0-1				
2				
3				
4-				
Age at menarche				
-13 years				
14 years				
15-16 years				
16- years				
Age at menopause				
-47 years	0.40 (0.16-1.01)	0.94 (0.42-2.07)		
48-49 years	—	—		
50-52 years	1.22 (0.61-2.47)	0.96 (0.50-1.83)		
53- years	0.65 (0.25-1.66)	1.04 (0.46-2.35)		
Long estrogen period[b]			0.65 (0.28-1.52)	0.79 (0.39-1.59)

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Supplementary Table 9. Crude odds ratios of plaque and unadjusted beta estimates of IMT of carotid artery in relation to quartiles of gravidity, delivery, and age at menarche or menopause, and estrogen exposure period[a]: univariate analyses

Sample unit for analyses	Gravidity (n = 665)				Delivery (n = 672)			
Model Outcome	Plaque	IMT			Plaque	IMT		
	OR (95%CI)	be	se	p	OR (95%CI)	be	se	p
Age	1.10 (1.07-1.13)	0.005	0.001	<0.001	1.10 (1.07-1.13)	0.005	0.001	<0.001
Body Mass Index								
<25 kg/m^2	—	—	—	—	—	—	—	—
≥ 25 kg/m^2	0.75 (0.52-1.09)	0.003	0.009	0.753	0.69 (0.47-1.00)	0.004	0.009	0.680
Home-measured mean SBP[b]	1.13 (1.00-1.27)	0.019	0.003	<0.001	1.10 (0.98-1.24)	0.020	0.003	<0.001
Educational attainment								
Elementary school	3.00 (1.44-6.23)	-0.020	0.040	0.616	3.15 (1.56-6.35)	0.112	0.018	<0.001
Middle school	2.07 (1.37-3.14)	0.034	0.009	<0.001	2.06 (1.36-3.11)	0.051	0.009	<0.001
High school	—	—	—	—	—	—	—	—
Smoker	0.97 (0.19-4.85)	-0.020	0.040	0.616	0.96 (0.19-4.81)	-0.022	0.041	0.591
Drinker	0.66 (0.38-1.15)	-0.006	0.013	0.666	0.62 (0.35-1.08)	-0.008	0.013	0.557
Diabetes[c]	1.93 (1.20-3.12)	0.036	0.013	0.006	1.91 (1.18-3.08)	0.036	0.013	0.007
Dyslipidemia[d]	1.00 (0.70-1.44)	-0.006	0.009	0.494	0.96 (0.67-1.38)	-0.004	0.009	0.670
Hypertension[e]	1.34 (0.93-1.92)	0.033	0.009	<0.001	1.26 (0.88-1.80)	0.036	0.009	<0.001
Gravidity								
-2	1.05 (0.64-1.72)	0.002	0.012	0.895				
3	—	—	—	—				
4	1.06 (0.63-1.80)	0.012	0.013	0.325				
5-	2.06 (1.26-3.37)	0.034	0.013	0.007				
Delivery								
0-1					0.97 (0.47-1.98)	0.017	0.016	0.296
2					—	—	—	—
3					1.53 (1.00-2.33)	0.004	0.010	0.677
4-					2.75 (1.70-4.47)	0.049	0.013	<0.001
Age at menarche								
-13 years								
14 years								
15-16 years								
16- years								
Age at menopause								
-47 years								
48-49 years								
50-52 years								
53- years								
Long estrogen period								

US, ultrasonography; IMT, intima-media thickness; OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension.

[a]Estimated by subtracting age at menarche from age at menopause and long period is defined as longer years divided at 75 percentiles of its distribution.

[b]per 10-mm Hg Increase

[c]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.

[d]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.

[e]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

(Cont. Supplementary Table 9)

Sample unit for analyses	Age at menarche (n = 616)				Age at menopause Estrogen exposure period (n = 449)			
Model Outcome	Plaque	IMT			Plaque	IMT		
	OR (95%CI)	be	se	p	OR (95%CI)	be	se	p
Age	1.10 (1.07-1.13)	0.005	0.001	<0.001	1.08 (1.04-1.12)	0.002	0.001	0.01
Body Mass Index								
<25 kg/m^2	—	—	—	—	—	—	—	—
≥ 25 kg/m^2	0.66 (0.44-0.99)	0.004	0.010	0.660	0.61 (0.39-0.96)	0.018	0.012	0.126
Home-measured mean SBP[b]	1.10 (0.97-1.25)	0.020	0.003	<0.001	1.04 (0.90-1.20)	0.016	0.004	<0.001
Educational attainment								
Elementary school	2.42 (1.05-5.57)	0.120	0.022	<0.001	1.47 (0.63-3.42)	0.093	0.022	<0.001
Middle school	1.86 (1.22-2.83)	0.052	0.010	<0.001	1.33 (0.80-2.20)	0.026	0.013	0.041
High school	—	—	—	—	—	—	—	—
Smoker	0.52 (0.06-4.31)	-0.043	0.040	0.341	0.81 (0.08-7.84)	-0.046	0.059	0.434
Drinker	0.63 (0.35-1.14)	-0.007	0.014	0.603	0.64 (0.32-1.28)	0.013	0.017	0.447
Diabetes[c]	1.67 (0.99-2.80)	0.034	0.014	0.018	1.56 (0.90-2.71)	0.017	0.016	0.274
Dyslipidemia[d]	0.92 (0.63-1.35)	-0.006	0.010	0.541	0.75 (0.49-1.14)	-0.004	0.011	0.706
Hypertension[e]	1.11 (0.76-1.61)	0.035	0.009	<0.001	1.04 (0.68-1.59)	0.024	0.011	0.033
Gravidity								
-2								
3								
4								
5-								
Delivery								
0-1								
2								
3								
4-								
Age at menarche								
-13 years	0.42 (0.23-0.73)	-0.042	0.012	<0.001				
14 years	—	—	—	—				
15-16 years	1.22 (0.71-2.10)	0.010	0.014	0.456				
16- years	1.41 (0.84-2.35)	0.037	0.013	0.006				
Age at menopause								
-47 years					1.242 (0.64-2.42)	-0.011	0.018	0.558
48-49 years					—	—	—	—
50-52 years					1.18 (0.64-2.20)	0.003	0.002	0.834
53- years					0.77 (0.37-1.57)	0.002	0.018	0.422
Long estrogen period					0.94 (0.51-1.73)	-.0080	0.016	0.619

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

Supplementary Table 10. Adjusted odds ratios of plaque and beta estimates of IMT of carotid artery in relation to quartiles of gravidity, delivery, age at menarche or menopause, and estrogen exposure period[a]: Multivariate analyses[b]

Sample unit for analyses	Gravidity (n = 665)				Delivery (n = 672)				Age at menarche (n = 616)			
Model Outcome	Plaque	IMT			Plaque	IMT			Plaque	IMT		
	Adjusted OR[a] (95%CI)	be	se	p	Adjusted OR[a] (95%CI)	be	se	P	Adjusted OR[a] (95%CI)	be	se	P
Age	1.09 (1.06-1.13)	0.003	0.001	<0.001	1.09 (1.05-1.12)	0.003	0.001	<0.001	1.09 (1.05-1.12)	0.003	0.001	<0.001
Body Mass Index												
<25 kg/m^2	—	—	—	—	—	—	—	—	—	—	—	—
≥ 25 kg/m^2	0.79 (0.52-1.19)	0.006	0.009	0.518	0.73 (0.48-1.10)	0.007	0.009	0.451	0.77 (0.50-1.19)	0.011	0.010	0.252
Home-measured mean SBP[c]	1.10 (0.93-1.29)	0.018	0.004	<0.001	1.06 (0.90-1.25)	0.017	0.004	<0.001	1.11 (0.94-1.32)	0.017	0.004	<0.001
Educational attainment												
Elementary school	1.31 (0.59-2.90)	0.063	0.019	0.001	1.19 (0.54-2.62)	0.069	0.019	<0.001	1.07 (0.43-2.68)	0.071	0.022	0.002
Middle school	1.48 (0.95-2.31)	0.034	0.009	<0.001	1.44 (0.92-2.24)	0.033	0.009	<0.001	1.26 (0.80-2.00)	0.030	0.010	0.003
High school	—	—	—	—	—	—	—	—	—	—	—	—
Smoker	1.79 (0.31-10.49)	-0.001	0.037	0.974	1.60 (0.28-9.27)	-0.002	0.038	0.957	1.05 (0.11-10.01)	-0.008	0.041	0.856
Drinker	0.71 (0.39-1.28)	0.000	0.012	0.991	0.68 (0.37-1.24)	0.000	0.012	1.000	0.69 (0.37-1.31)	0.003	0.013	0.825
Diabetes[d]	1.78 (1.06-2.98)	0.032	0.012	0.011	1.69 (1.00-2.86)	0.030	0.013	0.019	1.53 (0.87-2.69)	0.029	0.014	0.037
Dyslipidemia[e]	1.04 (0.70-1.54)	-0.010	0.009	0.227	0.99 (0.67-1.46)	-0.009	0.009	0.303	0.96 (0.64-1.46)	-0.011	0.009	0.243
Hypertension[f]	0.87 (0.53-1.42)	-0.016	0.011	0.124	0.91 (0.56-1.48)	-0.010	0.011	0.365	0.69 (0.41-1.14)	-0.010	0.011	0.372
Year after menopause[g]												
Gravidity												
-2	1.12 (0.66-1.90)	0.008	0.011	0.501								
3	—	—	—	—								
4	0.93 (0.53-1.63)	0.007	0.012	0.577								
5-	1.78 (1.04-3.03)	0.019	0.012	0.115								
Delivery												
0-1					0.87 (0.42-1.83)	0.013	0.015	0.411				
2					—	—	—	—				
3					1.57 (1.00-2.44)	0.003	0.010	0.781				
4-					2.32 (1.36-3.94)	0.020	0.013	0.107				
Age at menarche												
-13 years									0.56 (0.31-1.01)	-0.019	0.012	0.118
14 years									—	—	—	—
15-16 years									0.98 (0.56-1.73)	-0.004	0.014	0.750
16- years									1.01 (0.58-1.76)	0.010	0.013	0.445
Age at menopause												
-47 years												
48-49 years												
50-52 years												
53- years												
Long estrogen period[a]												

US, ultrasonography; IMT, intima-media thickness; OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension.

[a]Estimated by subtracting age at menarche from age at menopause and long period is defined as longer years at 75 percentiles of its distribution.

[b]Adjusting for age, body mass index, average systolic home blood pressure, educational attainment, smoker, drinker, diabetes mellitus, serum cholesterol, and hypertension

[c]per 10-mm Hg Increase

[d]Based on either an FBS level ≥ 200 mg/dL, HbA1c proportion ≥ 6.5%, or antidiabetic drug use.

[e]Based on either a LDL (low-density lipoprotein) cholesterol ≥ 160 mg/dL or the use of lipid-lowering medication.

[f]Based on either mean home-measured BP values ≥ 135/85 mmHg or antihypertensive drug use.

[g]Estimated by subtracting age at menopause from age at year of MRI or US investigation

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022

(Cont. Supplementary Table 10)

Sample unit for analyses	Age at menopause (n = 449)				Estrogen exposure period Age at menopause-age at menarche			
Model Outcome	Plaque	IMT			Plaque	IMT		
	Adjusted OR[a] (95%CI)	be	se	P	Adjusted OR[a] (95%CI)	be	se	P
Age	1.19 (1.07-1.31)	0.002	0.002	0.221	1.10 (1.03-1.18)	0.004	0.002	0.008
Body Mass Index								
<25 kg/m^2	—	—	—	—	—	—	—	—
≥ 25 kg/m^2	0.68 (0.42-1.11)	0.020	0.012	0.097	0.56 (0.33-0.96)	0.020	0.013	0.128
Home-measured mean SBP[c]	1.08 (0.89-1.30)	0.015	0.005	0.002	1.11 (0.90-1.37)	0.015	0.005	0.005
Educational attainment								
Elementary school	1.08 (0.44-2.64)	0.083	0.023	<0.001	0.56 (0.18-1.77)	0.056	0.028	0.045
Middle school	1.35 (0.79-2.30)	0.024	0.013	0.066	1.16 (0.68-2.00)	0.030	0.013	0.027
High school	—	—	—	—	—	—	—	—
Smoker	0.73 (0.07-7.71)	-0.062	0.058	0.284	N/A	-0.091	0.066	0.171
Drinker	0.58 (0.27-1.21)	0.015	0.017	0.388	0.53 (0.24-1.18)	0.022	0.018	0.227
Diabetes[d]	1.55 (0.84-2.85)	0.015	0.016	0.359	1.20 (0.62-2.32)	0.008	0.017	0.621
Dyslipidemia[e]	0.73 (0.47-1.15)	-0.011	0.011	0.317	0.78 (0.48-1.28)	-0.013	0.012	0.298
Hypertension[f]	0.89 (0.51-1.56)	-0.007	0.014	0.637	0.78 (0.43-1.41)	-0.012	0.015	0.416
Year after menopause[g]	0.91 (0.82-1.00)	-0.001	0.002	0.656	0.98 (0.93-1.04)	-0.002	0.001	0.116
Gravidity								
-2								
3								
4								
5-								
Delivery								
0-1								
2								
3								
4-								
Age at menarche								
-13 years								
14 years								
15-16 years								
16- years								
Age at menopause								
-47 years	2.19 (0.97-4.93)	-0.007	0.020	0.729				
48-49 years	—	—	—	—				
50-52 years	0.94 (0.48-1.86)	0.001	0.017	0.931				
53- years	0.38 (0.15-1.00)	0.003	0.021	0.872				
Long estrogen period[a]					1.01 (0.49-2.09)	-0.011	0.018	0.527

Advance Publication Journal of Atherosclerosis and Thrombosis
Accepted for publication: August 26, 2022 Published online: October 5, 2022