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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

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Aim: In this study, we aimed to evaluate the association between age at menarche and risk of cardiovascular disease mortality.

Methods: In total, 54,937 women aged 40–79 years old between 1988 and 1990 without a history of cardiovascular disease were eligible for analysis and were followed through December 2009. We used the Cox proportional hazards models to examine the association between age at menarche and risk of cardiovascular disease.

Results: Compared with women with age at menarche of 15 years, the hazard ratios (95% confidence intervals) of stroke were 1.22 (0.85–1.75) for women with age at menarche of 9–12 years, 1.08 (0.85–1.36) for those of 13 years, 1.23 (1.02–1.47) for those of 14 years, 1.27 (1.07–1.50) for those of 16 years, 1.16 (0.95–1.41) for those of 17 years, and 1.39(1.16–1.68) for those of 18–20 years (*P* for trend=0.045). A similar pattern was observed for hemorrhagic stroke, ischemic stroke, and total cardiovascular disease. No such association was found for coronary heart disease. When stratified by age, for women aged 40–59 at baseline, the similar U-shaped association was observed. In contrast, for women aged 60–79 years at baseline, a significantly high hazard ratio was noted in the group of late age at menarche, but not in the group of early age at menarche.

Conclusions: Both women with early and late age at menarche were determined to have higher risk of death from stroke and cardiovascular disease.

Key words: Epidemiology, Cohort study, Prospective study, Reproductive health

Introduction

Menarche is a developmental, physiological, and reproductive turning point for adolescent girls that is based on hormonal changes in the hypothalamic-pituitary-ovarian system[1]. High body mass index (BMI), fat percentage, and bone mineral density in childhood were associated with an earlier menarche[2-4]. On the other hand, childhood undernutrition delays the age of menarche[5]. It is also known that health status in childhood is related to lifestyle-related diseases in later life. For example, low-birth-weight babies had a higher risk of hypertension and glucose intolerance in middle age than those who were not[6]. Children with high serum total cholesterol levels were likely to have higher serum total cholesterol levels in adulthood[7].

Previous studies showed that early age at menarche was associated with risk of cardiovascular disease (CVD)[2, 8, 9], ischemic heart disease[8, 10], and

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stroke[8]. Others reported that the relationship of age at menarche to CVD was U-shaped[11-13]. By contrast, a study in Japan reported no association between age at menarche and stroke or CVD[14].

Previously, we reported that in women followed from 1988 through 1999, late age at menarche tended to be associated with an increased risk of mortality from stroke[15]. However, at that time, the number of cases was insufficient to conduct an age-specific analysis. A previous study indicated a temporary increase in the age at menarche among Japanese women during the World War II and a rapid decrease after the war[16]. Among the participants of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) some had their first menstruation during the World War II, while others had it after the war. We thus hypothesized that the association between age at menarche and risk of CVD mortality may differ between these two groups and conducted an analysis to clarify the long-term effect of age at menarche on the risk of CVD mortality stratified by age among Japanese women.

Methods

Study Cohort and Baseline Questionnaire

The JACC Study is a cohort study conducted by the Ministry of Education, Culture, Sports, Science and Technology. Of a total of 110,585 people (46,395 men, 64,190 women) between the ages of 40 and 79 years in 45 communities of Japan, 63,359 women of 44 communities, where a questionnaire including questions about age at menarche was administered, were enrolled in this study from 1988 through 1990 in the baseline survey. The participants were asked to fill out a questionnaire as regards their medical history and lifestyle habits, including physical activity, alcohol consumption, smoking, and daily sleep time. The women were also asked for their age at menarche, age at menopause, type of menopause, and number of childbirths. For age at menarche, age at menopause, and number of childbirths, the participants were asked to enter the actual values.

Before completing the questionnaire, the participants or community representatives gave informed consent to their participation in this epidemiological study in accordance with the guidelines of the International Council of Medical Organizations[17]. Individual informed consent before participation in this study was obtained in 36 of the 45 communities (written consent in 35 communities and oral consent in 1 community); in the remaining 9 communities, group consent from the area leader was obtained, which was an accepted practice in Japan at that time[18]. The JACC Study protocol was approved by the institutional review boards of Hokkaido University, Osaka University, and the University of Tsukuba.

Among the 63,359 women, 3183 women with a history of cancer, stroke, or myocardial infarction at baseline were excluded. In addition, 5078 women with missing or invalid response about age at menarche in the survey and 161 women with age at menarche younger than 9 years or older than 21 years were excluded. Finally, 54,937 women participated in the analyses.

Mortality Surveillance

In Japan, registration of death is required by the Family Registration Law and is followed throughout the country. Therefore, all deaths that occurred in the cohort were confirmed through death certificates. The only exception was participants who died after leaving their original community, in which case they were treated as censored cases.

We continued to follow-up from the time of the baseline survey through the end of 2009 except for the 10 communities that ended their follow-up before 2009 (4 in 1999, 4 in 2003, and 2 in 2008). The average follow-up period for these participants was 18.8 years.

We used the underlying cause of death coded according to the 9th and 10th versions of the International Statistical Classification of Diseases (ICD-9 and ICD-10) to determine CVD (ICD-9th, codes 390-459; ICD-10th, codes I01-I99), coronary heart disease (410-414; I20-25), and total stroke (430-438; I60-I69) including stroke subtypes such as subarachnoid hemorrhage (430 and I60), intraparenchymal hemorrhage (431 and I61), and ischemic stroke (433 and I63). We then defined hemorrhagic stroke as subarachnoid hemorrhage (430 and I60) and intraparenchymal hemorrhage (431 and I61).

Statistical Analysis

We divided the participants according to age at menarche: 9–12 years (n=3490), 13 years (n=7817), 14 years (n=12,276), 15 years (n=12,160), 16 years (n=8902), 17 years (n=5057), and 18–20 years (n=5235). Because the median age of menarche for this population was 15 years old, we used the category of age at menarche of 15 years as the reference.

We calculated the age-adjusted means and proportions of selected cardiovascular risk factors and reproductive factors according to age at menarche and tested the overall difference by analysis of covariance. Duration of reproductive years was defined as the

number of years between age at menarche and age at menopause. For each participant, we calculated the person-years of follow-up from baseline in 1988–1990 to the first endpoint (date of death, moving out of the community, or the end of 2009, whichever occurred first).

The hazard ratio (HR) with 95% confidence interval (CI) of each mortality outcome was calculated according to the age at menarche by using the Cox proportional hazards model, stratifying jointly by areas (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu), and adjusting for age (continuous). In the multivariable model, we further adjusted for potential confounding variables including BMI (quintiles), history of hypertension (yes or no), history of diabetes (yes or no), alcohol intake (never, former, or current), smoking (never, former, or current), sleeping hours per day (<6, 6–7, 7–8, 8–9, or >9 h/day), walking time (never, 0.5, 0.5–1, or >1 h/day), sport participation (never, 1–2, 3–4, or >5 h/week), number of childbirths (never, 1, 2, 3, or <4), age at menopause (≦44, 45–46, 47–48, 49–50, or ≥ 51 years), and education level (elementary school, junior high school, high school, and college or graduate school).

We also stratified the group into two age groups: 40–59 years at baseline, which corresponds to women who mostly had their first menstruation after the World War II, and 60–79 years at baseline, which corresponds to women who mostly had their first menstruation during the war. The significance of the interaction between age and age at menarche in relation to each outcome was tested in a multivariate model using cross-product terms for age 40–59 years and age 60–79 years and seven groups for age at menarche.

All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA). All the probability values for the statistical tests were two-tailed, and values below 0.05 were regarded as significant.

Results

During the 916,858 person-year follow-up, we observed 2960 deaths from CVD including 1292 deaths from stroke, 512 from hemorrhagic stroke, 416 from ischemic strokes, and 564 from ischemic heart disease.

As shown in **Table 1**, a higher age at menarche was associated with older-age at baseline, lighter weight at baseline and at age 20 years, shorter height, lower mean BMI, more smoking, smaller percentage of patients with preexisting hypertension or diabetes, more sleep, higher percentage of menopausal state, shorter duration of reproductive years, and lower education level. In the analysis by age at baseline among the 40–59-year-old group and the 60–79-year-old group, the trend was generally the same, but as for the menopause rate, the older the age of menarche, the lower the menopause rate. Distribution of age at menarche was lower in participants aged 40–59 years than those aged 60–79 years: Among the participants aged 40–59, 2799 (8.7%) had an age of menarche of 9–12 and 2169 (6.8%) had an age of menarche of 18–20, whereas the respective numbers were 691 (3.0%) and 3066 (13.4%) among participants aged 60–79 years. Participants aged 60–79 years were more likely to have a history of hypertension and diabetes and less likely to have a college education or higher.

As shown in **Table 2**, there was a U-shaped association between age at menarche and risk of mortality from stroke. Compared with women with age at menarche of 15 years, the HR (95% CI) of the multivariable adjusted model was 1.22 (0.85–1.75) for women with age at menarche of 9–12 years, 1.08 (0.85–1.36) for those with age at menarche of 13 years, 1.23 (1.02–1.47) for those with age at menarche of 14 years, 1.27 (1.07–1.50) for those with age at menarche of 16 years, 1.16 (0.95–1.41) for those with age at menarche of 17 years, and 1.39 (1.16–1.68) for those with age at menarche of 18–20 years. A similar pattern was observed for hemorrhagic stroke, ischemic stroke, and total CVD. For ischemic stroke, the elevated risk was not observed for ages 9–12 years of age at menarche probably due to the small number at risk in that group. When we collapsed the groups of age at menarche of 9–12 and 13, the multivariable adjusted HR was 1.44 (0.98–2.10) (not shown in the table). No such association was found for coronary heart disease.

Since the U-shaped association was observed for stroke, we further stratified by the age at baseline into 40- to 59-year-old and 60- to 79-year-old groups and examined the associations with stroke **(Table 3)**. For women aged 40–59 at baseline, the similar U-shaped association was observed. In contrast, for women aged 60–79 years at baseline, a significantly high HR was found in the group of late age at menarche, but not significant in the group of early age at menarche.

Discussion

In this large cohort study of women, a U-shaped association was found between age at menarche and risks of mortality from stroke and total CVD. The U-shaped association between age at menarche and stroke was confined to women aged 40–59, but no

Table 1. Age-adjusted means of cardiovascular risk factors and factors related to reproduction, such as menarche, by the seven categories of age at menarche

	Age at menarche (year) for ages of 40-79							*P* for difference
	9-12	13	14	15	16	17	18-20	
Women (*n* = 54,937)								
Number of subjects	3,490	7,817	12,276	12,160	8,902	5,057	5,235	
Age, yrs	50.1	52.7	54.6	57.4	61.0	62.3	61.9	<.001
Weight, kg	53.4	52.9	52.5	52.3	52.3	51.7	51.4	<.001
Weight at age twenty, kg	50.4	50.1	49.9	50.0	49.8	49.5	49.4	<.001
Height, cm	151.3	151.4	151.4	151.3	151.0	150.7	150.5	<.001
Mean body mass index, kg/m^2	23.3	23.1	22.9	22.9	22.9	22.8	22.7	<.001
Current smoker, %	5.9	4.7	4.7	5.1	6.0	6.1	6.4	<.001
Current drinker, %	25.4	25.0	24.7	24.5	25.2	24.5	24.9	0.83
History of hypertension, %	24.0	23.6	22.3	22.4	22.4	20.8	20.7	<.001
Currently treatment of hypertension, %	14.7	14.8	13.5	13.1	13.3	12.0	11.3	<.001
History of diabetes, %	4.8	4.6	4.3	3.5	3.5	2.8	3.3	<.001
Currently treatment of diabetes, %	2.9	2.9	2.4	1.9	2.0	1.5	1.5	<.001
Hours of sleep, hour/day	7.0	7.0	7.1	7.1	7.1	7.1	7.2	<.001
Walking time >0.5hour/day, %	69.4	71.8	71.4	71.8	73.3	72.8	73.0	0.005
Sports ≥ 5 hour/week, %	4.7	4.5	4.4	4.4	4.8	4.6	4.5	0.89
Number of birth	2.8	2.7	2.7	2.7	2.7	2.8	2.7	<.001
Menopause, %	62.3	65.3	67.0	69.7	71.7	72.4	73.5	<.001
Age at menopause, yrs	48.1	48.4	48.6	48.7	48.7	48.7	48.4	<.001
Duration of reproductive year, yrs	36.2	35.4	34.6	33.7	32.7	31.7	29.9	<.001
College or higher education, %	15.4	11.6	10.1	9.5	9.7	8.6	8.7	<.001
	Age at menarche (year) for ages of 40-59							*P* for difference
	9-12	13	14	15	16	17	18-20	
Women (*n* = 32,026)								
Number of subjects	2,799	5,663	8,388	7,165	3,851	1,991	2,169	
Age, yrs	46.4	47.7	49.0	50.7	53.1	54.2	54.8	<.001
Weight, kg	54.8	54.2	53.7	53.4	53.2	52.8	52.7	<.001
Weight at age twenty, kg	50.1	50.0	49.8	49.9	49.8	49.8	49.8	0.24
Height, cm	152.4	152.7	152.7	152.7	152.5	152.3	152.2	<.001
Mean body mass index, kg/m^2	23.6	23.2	23.0	22.9	22.9	22.8	22.8	<.001
Current smoker, %	5.6	4.9	5.0	5.4	7.0	7.0	8.0	<.001
Current drinker, %	28.1	27.7	27.7	28.0	29.0	30.4	29.8	0.19
History of hypertension, %	16.6	15.2	14.0	14.6	14.9	12.7	13.6	0.005
Currently treatment of hypertension, %	8.8	8.2	7.4	7.3	7.4	6.3	6.2	0.013
History of diabetes, %	2.5	2.3	2.3	1.8	2.5	1.9	2.6	0.11
Currently treatment of diabetes, %	1.4	1.3	1.1	0.9	1.2	0.8	1.0	0.13
Hours of sleep, hour/day	6.9	6.9	6.9	7.0	7.0	7.0	7.0	<.001
Walking time >0.5hour/day, %	69.6	72.1	71.3	71.5	71.7	70.6	72.2	0.42
Sports ≥ 5 hour/week, %	2.6	2.8	2.6	2.8	3.1	3.3	3.6	0.34
Number of birth	2.4	2.3	2.3	2.4	2.4	2.4	2.4	0.003
Menopause, %	53.0	51.7	50.8	50.8	50.4	51.1	50.3	0.03
Age at menopause, yrs	47.8	48.1	48.3	48.4	48.2	48.2	47.7	<.001
Duration of reproductive year, yrs	35.9	35.1	34.3	33.4	32.2	31.2	29.3	<.001
College or higher education, %	16.4	12.6	10.7	10.9	12.0	10.1	10.0	<.001

(Cont. Table 1)

	Age at menarche (year) for ages of 60-79							*P* for difference
	9-12	13	14	15	16	17	18-20	
Women (n = 22,911)								
Number of subjects	691	2,154	3,888	4,995	5,051	3,066	3,066	
Age, yrs	65.5	65.8	66.5	67.0	67.1.	67.5	66.9	<.001
Weight, kg	52.3	51.7	51.1	50.7	50.5	49.9	49.3	<.001
Weight at age twenty, kg	51.1	50.4	50.1	50.2	49.9	49.4	49.2	<.001
Height, cm	150.0	149.7	149.5	149.4	148.8	148.6	148.3	<.001
Mean body mass index, kg/m^2	23.2	23.1	22.9	22.8	22.8	22.6	22.5	<.001
Current smoker, %	6.1	3.9	4.2	4.7	5.2	5.4	5.3	0.05
Current drinker, %	21.6	21.4	20.4	19.4	20.3	18.1	19.3	0.07
History of hypertension, %	34.3	36.9	35.2	34.1	33.8	32.6	31.7	0.006
Currently treatment of hypertension, %	23.0	25.1	22.6	21.8	22.1	20.7	19.5	<.001
History of diabetes, %	8.8	8.3	7.5	6.2	5.7	5.1	5.5	<.001
Currently treatment of diabetes, %	5.4	5.7	4.5	3.4	3.5	3.1	3.0	<.001
Hours of sleep, hour/day	7.2	7.2	7.2	7.3	7.3	7.3	7.4	<.001
Walking time >0.5hour/day, %	69.3	71.2	71.5	72.3	74.5	74.3	73.4	0.007
Sports ≥ 5 hour/week, %	7.1	6.5	7.1	6.7	7.6	7.0	6.8	0.78
Number of birth	3.2	3.1	3.1	3.2	3.3	3.3	3.3	<.001
Menopause, %	95.3	95.1	94.1	94.0	93.7	94.0	92.5	0.004
Age at menopause, yrs	48.9	49.0	49.0	49.0	49.0	48.8	48.4	<.001
Duration of reproductive year, yrs	37.1	36.0	35.0	34.0	33.0	31.8	30.0	<.001
College or higher education, %	12.8	9.6	9.4	7.7	7.4	6.9	7.5	<.001

Table 2. Hazard rations and 95% confidence intervals of mortality from total stroke, stroke types, coronary heart disease and total cardiovascular disease according to age at menarche, JACC study, 1988-2009

	Age at menarche (year)							
	9-12	13	14	15	16	17	18-20	*P* for trend
Number at risk	3,490	7,817	12,276	12,160	8,902	5,057	5,235	
Person-years	59,193	132,383	207,670	204,631	145,747	82,205	85,029	
Total stroke								
Number of case	35	100	222	244	308	178	205	
Model 1	1.24 (0.87-1.77)	1.11 (0.88-1.40)	1.23 (1.02-1.47)	1.00	1.28 (1.08-1.52)	1.18 (0.97-1.43)	1.43 (1.19-1.73)	0.03
Model 2	1.22 (0.85-1.75)	1.08 (0.85-1.36)	1.23 (1.02-1.47)	1.00	1.27 (1.07-1.50)	1.16 (0.95-1.41)	1.39 (1.16-1.68)	0.045
Hemorrhagic stroke								
Number of case	21	40	88	107	118	58	80	
Model 1	1.25 (0.78-2.01)	0.85 (0.59-1.22)	1.01 (0.76-1.34)	1.00	1.22 (0.94-1.59)	0.99 (0.72-1.37)	1.39 (1.04-1.86)	0.04
Model 2	1.25 (0.77-2.00)	0.84 (0.58-1.21)	1.02 (0.77-1.35)	1.00	1.20 (0.92-1.56)	0.98 (0.71-1.35)	1.37 (1.02-1.83)	0.05
Ischemic stroke								
Number of case	6	39	73	70	104	60	64	
Model 1	0.87 (0.38-2.00)	1.67 (1.13-2.48)	1.48 (1.07-2.05)	1.00	1.43 (1.06-1.94)	1.30 (0.92-1.83)	1.50 (1.07-2.11)	0.72
Model 2	0.85 (0.37-1.98)	1.60 (1.08-2.38)	1.46 (1.05-2.03)	1.00	1.42 (1.04-1.92)	1.27 (0.90-1.79)	1.43 (1.02-2.01)	0.82
Coronary heart diseases								
Number of case	13	49	85	137	113	75	92	
Model 1	0.81 (0.46-1.44)	0.96 (0.69-1.33)	0.84 (0.64-1.10)	1.00	0.84 (0.65-1.08)	0.89 (0.67-1.18)	1.15 (0.88-1.50)	0.19
Model 2	0.80 (0.45-1.42)	0.91 (0.66-1.27)	0.84 (0.64-1.10)	1.00	0.85 (0.66-1.10)	0.88 (0.66-1.16)	1.15 (0.88-1.50)	0.16
Total cardiovascular disease								
Number of case	81	240	495	634	653	412	445	
Model 1	1.14 (0.90-1.43)	1.04 (0.90-1.21)	1.06 (0.95-1.20)	1.00	1.04 (0.93-1.16)	1.04 (0.92-1.18)	1.20 (1.06-1.35)	0.12
Model 2	1.12 (0.89-1.41)	1.02 (0.88-1.18)	1.07 (0.95-1.20)	1.00	1.03 (0.93-1.15)	1.03 (0.91-1.16)	1.17 (1.03-1.32)	0.20

Model 1 was stratified by area and adjusted for age Model 2 was further adjusted for body mass index, history of hypertension, history of diabetes, alcohol intake, smoking status, walking time, sport participation, sleeping hours, number of birth, menopausal age, and education level.

Table 3. Age specific hazard rations and 95% confidence intervals of mortality from stroke and total cardiovascular disease for 40~59 and 60~79 years old according to age at menarche

	9-12	13	14	15	16	17	18-20	*P* for trend
Ages of 40-59								
Number at risk	2,799	5,663	8,388	7,165	3,851	1,991	2,169	
Person-years	49,489	100,978	150,366	129,187	69,425	35,925	38,648	
Total stroke								
Number of cases	15	30	58	45	34	13	26	
Model 1	1.28 (0.70-2.31)	1.10 (0.69-1.75)	1.27 (0.86-1.88)	1.00	1.14 (0.73-1.79)	0.78 (0.42-1.46)	1.39 (0.85-2.27)	0.90
Model 2	1.21 (0.66-2.20)	1.06 (0.66-1.69)	1.27 (0.86-1.88)	1.00	1.10 (0.70-1.73)	0.76 (0.41-1.42)	1.23 (0.75-2.02)	0.69
Ages of 60-79								
Number at risk	691	2,154	3,888	4,995	5,051	3,066	3,066	
Person-years	9,704	31,405	57,304	75,445	76,322	46,280	46,381	
Total stroke								
Number of cases	20	70	164	199	274	165	179	
Model 1	1.09 (0.69-1.73)	1.07 (0.82-1.41)	1.19 (0.97-1.46)	1.00	1.31 (1.09-1.58)	1.24 (1.01-1.53)	1.47 (1.20-1.80)	0.003
Model 2	1.10 (0.69-1.75)	1.03 (0.78-1.36)	1.19 (0.97-1.46)	1.00	1.30 (1.08-1.56)	1.23 (1.00-1.51)	1.44 (1.18-1.77)	0.004

Model 1 was stratified by area and adjusted for age
Model 2 was adjusted further for body mass index, history of hypertension, history of diabetes, alcohol intake, smoking status, walking time, sport participation, sleeping hours, number of birth, menopausal age, and education level.

significant risk elevation was found for the group of early age at menarche for women aged 60–79.

According to previous large cohort studies, the associations of age at menarche with risks of coronary heart disease[11], stroke[13], and CVD[9] were generally U-shaped, while others reported an inverse association with risks of stroke[8], ischemic heart disease[8, 10], coronary heart disease[2], and CVD[2]. We found a basically U-shaped association between age at menarche and mortality from stroke.

In this present study, no significant association was found between age at menarche and risk of mortality from coronary heart disease. Previous cohort studies in the UK showed a U-shaped[11] or inverse association[2] between age at menarche and risk of coronary heart disease. One of the reasons for this discrepancy may be the characteristics of low levels of coronary risk factors and risk of coronary heart diseases among Japanese women. For example, the mean BMI was 26.1 kg/m^2 in UK women aged 50–64 [11], while that in our study was 22.9 kg/m^2. Mortality from coronary heart disease in Japanese women was approximately one-third of that in UK in 2009 [19], which may obscure the association between age at menarche and risk of coronary heart disease. The risk of coronary heart disease was either not detected in a large cohort study in China[13].

The elevated risk of stroke in early menarche was confined to women aged 40–59 years at baseline, who mostly had their first menstruation after the World War II, but it was not observed for those aged 60–79 years, who mostly had their first menstruation during the war. Childhood undernutrition causes delayed age at menarche[5], and thus delayed age at menarche may be a marker of low nutritional status in childhood, which may be responsible for increased risk of stroke. People exposed to undernutrition in childhood as well as in fetal life and in adolescence can have an increased risk of stroke in later life compared with those not exposed[20]. Taken together, a high menarche age may reflect undernutrition in childhood, which could explain our observation that a positive menarche age–stroke association was more pronounced in the older-age group, who mostly experienced starvation as adolescents during the World War II. On the other hand, earlier age at menarche has been associated with higher blood pressure[11, 21], which may explain the higher risk of stroke in women with an earlier age of menarche. Meanwhile, in our study, the proportion of number at risk of the groups of early menarche among women aged 60–79 was small, and this may be one of the reasons for the non-elevated risk of stroke in groups of early menarche in this age stratum.

The strengths of this study were that it is a large, nationwide, community-based prospective cohort study with almost complete follow-up. Some limitations should be noted. First, as we used self-reports of age at menarche, the participants may not have accurately remembered their menarche that occurred more than 20 years ago, which could have resulted in misclassification. A previous study reported that two interviews on age at menarche, conducted a

few months to 4 years apart, showed high agreement in the responses (kappa=0.81)[22], but the repeatability may be lower for long-term memories. Second, as discussed, only 6% of the participants in this study were aged younger than 12 years at menarche, which may be insufficient for an analysis of the association between early menarche and risk of stroke. Finally, the age of menarche among Japanese girls is becoming younger[16], and the health burden associated with older menarche may become smaller for modern Japanese women. However, even in today and in the future, low nutrition in childhood caused by poverty[23], young women's desire to light weight[24], and excessive pressure on young athletes in terms of extreme diet and weight control[25] are emerging issues in Japan, which may cause delayed menstruation. In addition, our finding could be useful to identify stroke risk for women in developing countries and countries that are undergoing wars and currently facing undernutrition.

Conclusion

Both women with early and late age at menarche had higher risk of death from stroke and cardiovascular disease. In populations that experience childhood undernutrition, the cardiovascular disease risk for those with a later age of menarche should be noted. Cardiovascular risk factors in midlife associated with early age at menarche, such as high BMI and blood pressure, should also be considered in future stroke prevention strategies.

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Conflict of Interest

No conflicts of interest to declare. The funding agencies for this study made no decisions regarding its study design, data collection, data analysis, manuscript preparation, or decision to publish.

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