Menopause: The Journal of The North American Menopause Society
Vol. 30, No. 1, pp. 88-94
DOI: 10.1097/GME.0000000000002081

OPEN

ORIGINAL STUDY

Changes in cardiovascular disease risk factors during menopausal transition in Japanese women: the Circulatory Risk in Communities Study (CIRCS)

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Abstract

Objective: We aimed to longitudinally clarify the changes in cardiovascular disease risk factors associated with menopause in Japanese women in the 2000s.

Methods: Of the 4,596 women who underwent health examinations between 2007 and 2012 in three communities of the Circulatory Risk in Communities Study, 263 women who reported going through menopause during that period were included in the study. We randomly selected 1,665 men as control subjects who participated in a health examination at least once between 2001 and 2009 and at least once between 2010 and 2018 by 1:1 pair-matching for age, community, and examination year. The health examination data from 3 to 6 years before (2001-2009) and after menopause age (2010-2018) were compared in terms of body mass index, systolic and diastolic blood pressure levels, serum total cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, uric acid, hemoglobin A_{1c}, hemoglobin, aspartate aminotransferase, alanine aminotransferase, and current smoker status.

Results: Compared with the men, the women showed a greater increase in serum total cholesterol (+16.7 vs −3.1 mg/dL, $P < 0.001$), non-high-density lipoprotein cholesterol (+15.9 vs −6.3 mg/dL, $P < 0.001$), fasting triglycerides (+1.2 vs +1.0 mg/dL, $P = 0.027$), triglycerides regardless of fasting status (+1.2 vs −0.9 mg/dL, $P < 0.001$), uric acid (+0.5 vs +0.2 mg/dL, $P = 0.008$), hemoglobin (+0.9 vs −0.3 g/dL, $P < 0.001$), aspartate aminotransferase (+2.9 vs −2.7 IU/L, $P < 0.001$), and alanine aminotransferase (+2.9 vs −2.6 IU/L, $P < 0.001$). No differences were found in the changes in body mass index, systolic and diastolic blood pressures, and hemoglobin A_{1c} between the women and the matched men.

Conclusions: Menopause may be a crucial factor related to changes in serum total cholesterol, non-high-density lipoprotein cholesterol, triglycerides, uric acid, hemoglobin, and liver enzymes.

Key Words: Cardiovascular disease – Cohort study – Postmenopause – Premenopause – Risk factor.

Received May 23, 2022; revised and accepted July 30, 2022.

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Funding/support: This study was supported by a Japan Society for the Promotion of Science Scientific Research B grant (no. 19H03901) and a SPRING grant (no. JPMJSP2124).

Financial disclosure/conflicts of interest: None reported.

Author Contributions: S.T., T.S., K.Y., and H. Iso contributed to the conception or design of the work. All the authors contributed to the acquisition, analysis, or interpretation of data for the work. S.T. drafted the manuscript, and T.S., K.Y., M.U., M.H.-T., I.M., M.T., T.K., T. Ohira, H.I., R.C., Y.S., T. Okada, A.K., M.K., and H.I. revised the manuscript critically for important intellectual content.

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Women generally experience periodic changes in estrogen and progesterone levels during the premenopausal period and substantial reduction in those levels during the postmenopausal period, changes that have a variety of health impacts. Cross-sectional studies have shown that cardiovascular risk factors such as blood pressure, serum total cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, uric acid, serum glucose, aspartate aminotransferase, alanine aminotransferase, body mass index (BMI), and abdominal circumference before menopause age differed from those after menopause age,[1-5] and concordantly, cohort studies have reported that women who experienced early menopause, a short reproductive period, or bilateral ovariectomy had higher overall mortality and increased risk and mortality from cardiovascular disease.[6-11] However, not many longitudinal studies have been conducted focusing on changes in cardiovascular risk factors after menopause age as compared with those before menopause age.[12-16]

We previously reported that women surveyed in the 1980s had higher serum total cholesterol, systolic and diastolic blood pressures, BMI, and subscapular skinfold thickness after menopause age than before.[12] However, the mean serum total cholesterol levels among women in the 1980s were 193.7 mg/dL in a rural area and 208.2 mg/dL in an urban area and increased to 222.4 and 210.8 mg/dL, respectively, in the 2000s,[17] suggesting that current-day women may have even higher serum total cholesterol levels after menopause age. On the other hand, mean systolic blood pressure levels among women, which were 130 mm Hg in the urban area and 132 mm Hg in the rural area in the 1980s, decreased to 128 and 129 mm Hg, respectively, in the 2000s, and the prevalence of hypertension decreased from 29% to 27% in the urban area and from 37% to 34% in the rural area. The mean BMI increased from 22.6 kg/m^2 in the 1980s to 22.8 kg/m^2 in the 2000s in the urban area and from 23.9 kg/m^2 to 24.3 kg/m^2 in the rural area.[17] The results of that study suggest that changes in postmenopausal cardiovascular risk factors in women in the 2000s may not be the same as those in the 1980s. The hypothesis of this present study is that the cardiovascular risk factors described above will change during the menopausal transition, and the purpose of this study was to clarify the changes in cardiovascular risk factors in Japanese women who underwent menopause in the 2000s, including high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol triglycerides, uric acid, hemoglobin A_{1c} (HbA_{1c}), hemoglobin, aspartate aminotransferase, and alanine aminotransferase, which were not examined in the 1980s.[12]

METHODS

Study population

The Circulatory Risk in Communities Study is an ongoing dynamic community-based prospective study involving five communities in Japan. Details of the study protocol have been described elsewhere.[18] The survey areas in this study are Ikawa (Akita prefecture), a farming community in northeastern Japan; Kyowa (Ibaraki prefecture), a farming community in mideastern Japan; and Minami-Takayasu (Osaka prefecture), a suburb near Osaka city in midwestern Japan. The study participants were all residents who were aged 30 to 69 years at baseline and eligible for the health examination. Of these, women who had undergone menopause between 2007 and 2012 were included. Men were included in the analysis and considered as references to investigate changes in cardiovascular risk factors associated with menopause.

Baseline data collection and follow-up

Of the 4,596 women who underwent health examinations between 2007 and 2012, 266 women who reported going through menopause during that period were included in the study. The time of menopause was confirmed by interviews conducted at every visit. Because reproductive hormones may fluctuate during the 2 years after the last menstrual period,[19] the health examination data within 3 to 6 years (2001 and 2009) before menopause age were defined as those of the premenopausal period, and those within 3 to 6 years (2010 and 2018) after menopause age as those of the postmenopausal period. If we had multiple data from the health examinations, the oldest year of data was used for the premenopausal data, and the latest data after menopause age was used for the postmenopausal data. Because it was difficult to match postmenopausal women with premenopausal women of the same age, we randomly selected controls from 1,665 men who participated in a health examination at least once between 2001 and 2009 and at least once between 2010 and 2018 by 1:1 pair-matching for age, community, and examination year with the women. Three women were unmatched with the men. In the end, 263 women and 263 corresponding men were included (Fig. 1).

Baseline examination

We conducted face-to-face interviews to obtain menstrual information. Menopause was defined as menstruation not occurring for 6 months or more, and menopausal age as the age at which the participants reported their menopause status. Information was also obtained on smoking (never, former, current) and on use of antihypertensive, cholesterol-lowering, uric acid-lowering, or antidiabetic medications. Height in socks and weight in light clothing were measured, and 1 kg was subtracted as the clothing weight. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Blood pressures were measured with a standard mercury sphygmomanometer or automatic sphygmomanometer in the right arm of the participants who had been resting for at least 5 minutes before the measurement. If the first systolic blood pressure reading was 140 mm Hg or greater and/or the diastolic blood pressure was 90 mm Hg or greater, the physicians repeated the measurement. The first blood pressure measurement was used in this study. Blood was drawn into plastic serum separator gel tubes from the participants in a sitting position, and the serum was separated by centrifugation within 30 minutes of the blood collection. Serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured by use of a standardized protocol by the laboratory of the Osaka Medical Center for Health Science

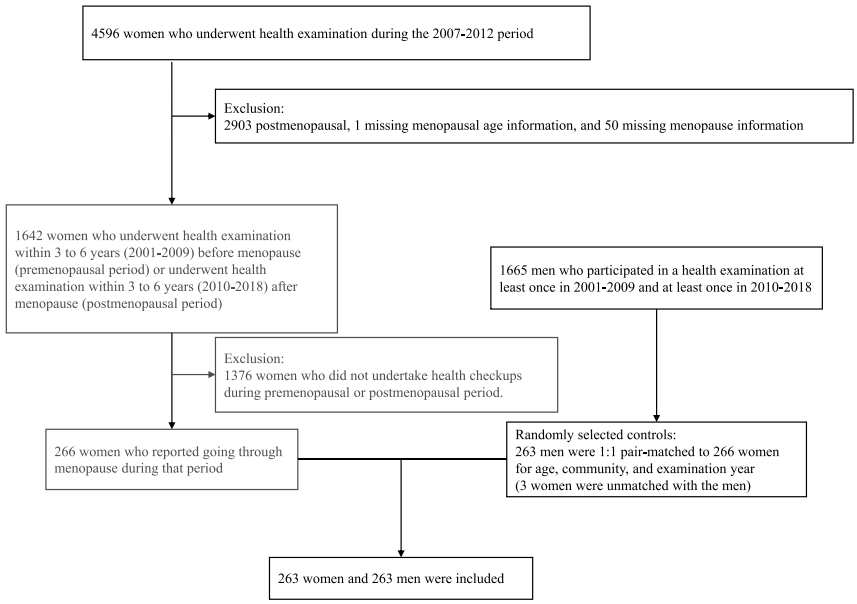

FIG. 1. Flowchart of the selection of the study participants.

and Promotion[20,21] (except for a part of Kyowa) and an enzymatic method by the Ibaraki Health Service Association (high-density lipoprotein cholesterol for a part of Kyowa was measured by use of the direct method). Non-high-density lipoprotein cholesterol was defined as total cholesterol minus high-density lipoprotein cholesterol. Aspartate aminotransferase and alanine aminotransferase were measured according to the Japanese Society for Clinical Chemistry's standard transferable method. Hb A_{1c} levels were measured by means of the latex agglutination reaction method from 2001 to 2011 and by means of the high-performance liquid chromatography method from 2012, whereas Kyowa has been using the enzymatic method since 2011. Uric acid levels were measured by means of the uricase-peroxidase method. Hemoglobin levels were measured by means of the cyanmethemoglobin method.

Statistical analysis

Changes from the premenopausal period to the postmenopausal period for women and from the corresponding periods for men in systolic and diastolic blood pressure levels, BMI, serum total cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, uric acid, HbA_{1c}, hemoglobin, aspartate aminotransferase, alanine aminotransferase, and current smoker status were compared by use of analysis of covariance and logistic regression models, adjusted for age, follow-up years, BMI, BMI change during the follow-up, and medication use status (antihypertensive, cholesterol-lowering, uric acid–lowering, and antidiabetic medications), that is, no continued medication use, initiation of medication use, cessation of medication use, and continued medication use. Smoking was adjusted for the same confounding variable except for medication use status. Triglycerides regardless of fasting status were adjusted for age, follow-up years, BMI, BMI change during the follow-up, and fasting status.

Sex differences in cardiovascular risk factor change were also tested by means of analysis of covariance adjusted for the same confounding variable. For smoking, sex differences in the proportions of cessation of smoking were tested by means of logistic regression models adjusted for age, follow-up years, BMI, and BMI change during the follow-up. Triglycerides, aspartate aminotransferase, and alanine aminotransferase were log-transformed to obtain a normal distribution of the data. The results were expressed as backlogged values. The statistical analysis package SAS version 9.4 (SAS Institute, Cary, NC) was used for all the analyses, and the 2-tailed significance level was set to less than 0.05.

Ethics approval

Because the data were collected as part of municipal government health check activities, we did not obtain individual informed consent from each study participant but provided opt-out opportunities. This study was approved by the ethics committees of the University of Tsukuba (approval no. 66-10), Osaka University (approval no. 14285-9), and the Osaka Center for Cancer and Cardiovascular Disease Prevention (approval no. R2-Rinri-4).

RESULTS

Table 1 shows the mean levels of cardiovascular risk factors before and after menopause age. The age at recruitment was 47.6 years for the premenopausal women and 47.7 years for the matched men, and the postmenopausal age was 58.4 years for both the women and the matched men, with a mean follow-up period of 10.8 years. The mean age at menopause was 51.4 years (range, 39-59 years). As shown in Table 1 and Figure 2, cardiovascular disease risk factors in women, except for BMI, systolic

TABLE 1. *Comparison of changes in cardiovascular risk factors after menopause age from those before in women and in men matched for age, community, and examination year*

	Women (n = 263)					Men (n = 263)					
	Menopausal state	n	Adjusted mean or proportion[a]	Change from before and after menopausal periods[b]	P^b	Menopausal state	n	Adjusted mean or proportion[a]	Change in corresponding periods[b]	P^b	Sex difference P^c
Age, y	Pre	263	47.6	10.8	—	Pre	263	47.7	10.7	—	—
	Post		58.4			Post		58.4			
Menopausal age, y		263	51.4	—	—			—			
Current smoker, %	Pre	261	10.3	−3.0	0.211	Pre	263	40.3	−15.7	<0.001	<0.001
	Post		7.3			Post		23.6			
Body mass index, kg/m^2	Pre	263	22.8 (0.2)	−0.3 (0.1)	0.326	Pre	263	23.8 (0.2)	−0.1 (0.1)	0.532	0.203
	Post		22.5 (0.2)			Post		23.6 (0.2)			
Systolic blood pressure, mm Hg	Pre	258	125.5 (1.0)	1.2 (1.0)	0.331	Pre	258	124.8 (1.0)	3.0 (1.0)	0.038	0.233
	Post		126.9 (1.0)			Post		127.6 (1.0)			
Diastolic blood pressure, mm Hg	Pre	258	75.8 (0.6)	1.5 (0.7)	0.075	Pre	258	79.7 (0.7)	1.5 (0.7)	0.123	0.991
	Post		77.4 (0.6)			Post		81.1 (0.7)			
Antihypertensive medication, %	Pre	263	4.6	—	—	Pre	263	9.1	—	—	—
	Post		17.9			Post		21.7			
Serum total cholesterol, mg/dL	Pre	263	204.8 (2.1)	16.7 (1.6)	<0.001	Pre	262	211.3 (2.1)	−3.1 (1.6)	0.305	<0.001
	Post		221.5 (2.1)			Post		208.2 (2.1)			
Cholesterol-lowering medication, %	Pre	263	1.1	—	—	Pre	263	5.3	—	—	—
	Post		16.3			Post		16.3			
High-density lipoprotein cholesterol, mg/dL	Pre	259	67.9 (0.9)	1.1 (0.7)	0.276	Pre	263	57.9 (0.9)	3.2 (0.7)	0.022	0.028
	Post		69.3 (0.9)			Post		60.7 (0.9)			
Non–high-density lipoprotein cholesterol, mg/dL	Pre	259	137.2 (1.8)	15.9 (1.5)	<0.001	Pre	262	153.3 (2.2)	−6.3 (1.5)	0.059	<0.001
	Post		152.7 (1.8)			Post		147.4 (2.2)			
Fasting triglycerides, mg/dL	Pre	100	67.0 (1.0)	1.2 (1.1)	0.006	Pre	95	105.6 (1.1)	1.0 (1.1)	0.889	0.027
	Post		79.0 (1.0)			Post		106.8 (1.1)			
Triglycerides regardless of fasting status, mg/dL	Pre	259	71.8 (1.0)	1.2 (1.0)	<0.001	Pre	263	121.4 (1.0)	−0.9 (1.0)	0.002	<0.001
	Post		83.7 (1.0)			Post		104.0 (1.0)			
Uric acid, mg/dL	Pre	153	4.0 (0.1)	0.5 (0.1)	<0.001	Pre	153	5.9 (0.1)	0.2 (0.1)	0.038	0.008
	Post		4.5 (0.1)			Post		6.1 (0.1)			
Uric acid–lowering medication, %	Pre	263	9.5	—	—	Pre	263	18.3	—	—	—
	Post		35.4			Post		50.6			
Hemoglobin A_{1c}, %	Pre	244	5.1 (0.0)	0.8 (0.1)	<0.001	Pre	253	5.2 (0.1)	0.8 (0.1)	<0.001	0.674
	Post		5.9 (0.0)			Post		6.0 (0.1)			
Antidiabetic medication, %	Pre	263	0.8	—	—	Pre	263	4.9	—	—	—
	Post		3.8			Post		6.8			
Hemoglobin, g/dL	Pre	244	12.5 (0.1)	0.9 (0.1)	<0.001	Pre	250	15.4 (0.1)	−0.3 (0.1)	0.002	<0.001
	Post		13.4 (0.1)			Post		15.1 (0.1)			
Aspartate aminotransferase, IU/L	Pre	259	18.8 (2.7)	2.9 (2.7)	<0.001	Pre	263	24.8 (2.7)	−2.7 (2.7)	0.136	<0.001
	Post		21.9 (2.7)			Post		24.0 (2.7)			
Alanine aminotransferase, IU/L	Pre	259	14.8 (2.7)	2.9 (2.7)	<0.001	Pre	263	24.8 (2.7)	−2.6 (2.7)	<0.001	<0.001
	Post		17.6 (2.7)			Post		21.7 (2.7)			

Parentheses show standard errors.

[a]Mean value and proportions of premenopausal and postmenopausal periods for women and the corresponding periods for men were calculated by means of analysis of covariance, adjusted for age, follow-up years, body mass index, body mass index change during the follow-up, and medication use status (antihypertensive for blood pressure, cholesterol-lowering for serum total cholesterol and non–high-density lipoprotein cholesterol, uric acid–lowering for uric acid, and antidiabetic medications for hemoglobin A_{1c}). Triglycerides regardless of fasting status were adjusted for the same confounding variables and fasting status except for medication use status.

[b]Differences between premenopausal and postmenopausal periods for women and the corresponding periods for men were compared in terms of means and proportion by use of analysis of covariance and logistic regression models, adjusted for age, follow-up years, body mass index, body mass index change during the follow-up, and medication use status. Triglycerides regardless of fasting status were adjusted for the same confounding variables and fasting status except for medication use status.

[c]Sex differences in change from premenopausal and postmenopausal periods were compared by use of analysis of covariance and logistic regression models adjusted for age, follow-up years, body mass index, body mass index change during the follow-up, and medication use status. Triglycerides regardless of fasting status were adjusted for the same confounding variables and fasting status except for medication use status. For smoking, sex difference in the proportions of cessation of smoking was tested by means of logistic regression models adjusted for age, follow-up years, body mass index, and body mass index change during the follow-up.

and diastolic blood pressure, high-density lipoprotein cholesterol, and current smoker status, significantly increased after menopause from those before. For men, systolic blood pressure levels, high-density lipoprotein cholesterol, uric acid, and HbA_{1c} increased significantly. Compared with the men, the women showed a greater increase in serum total cholesterol (+16.7 mg/dL in women vs −3.1 mg/dL in men, $P < 0.001$), non-high-density lipoprotein cholesterol (+15.9 vs −6.3 mg/dL, $P < 0.001$), fasting triglycerides (+1.2 vs +1.0 mg/dL, $P = 0.027$), triglycerides regardless of fasting status (+1.2 vs −0.9 mg/dL, $P < 0.001$), uric acid (+0.5 vs +0.2 mg/dL, $P = 0.008$), hemoglobin (+0.9 vs −0.3 g/dL, $P < 0.001$), aspartate aminotransferase (+2.9 vs −2.7 IU/L, $P < 0.001$), and alanine aminotransferase (+2.9 vs −2.6 IU/L, $P < 0.001$) (Table 1). The percentage of current smokers was higher in men than in women both before and after menopause age. No significant differences were found in changes

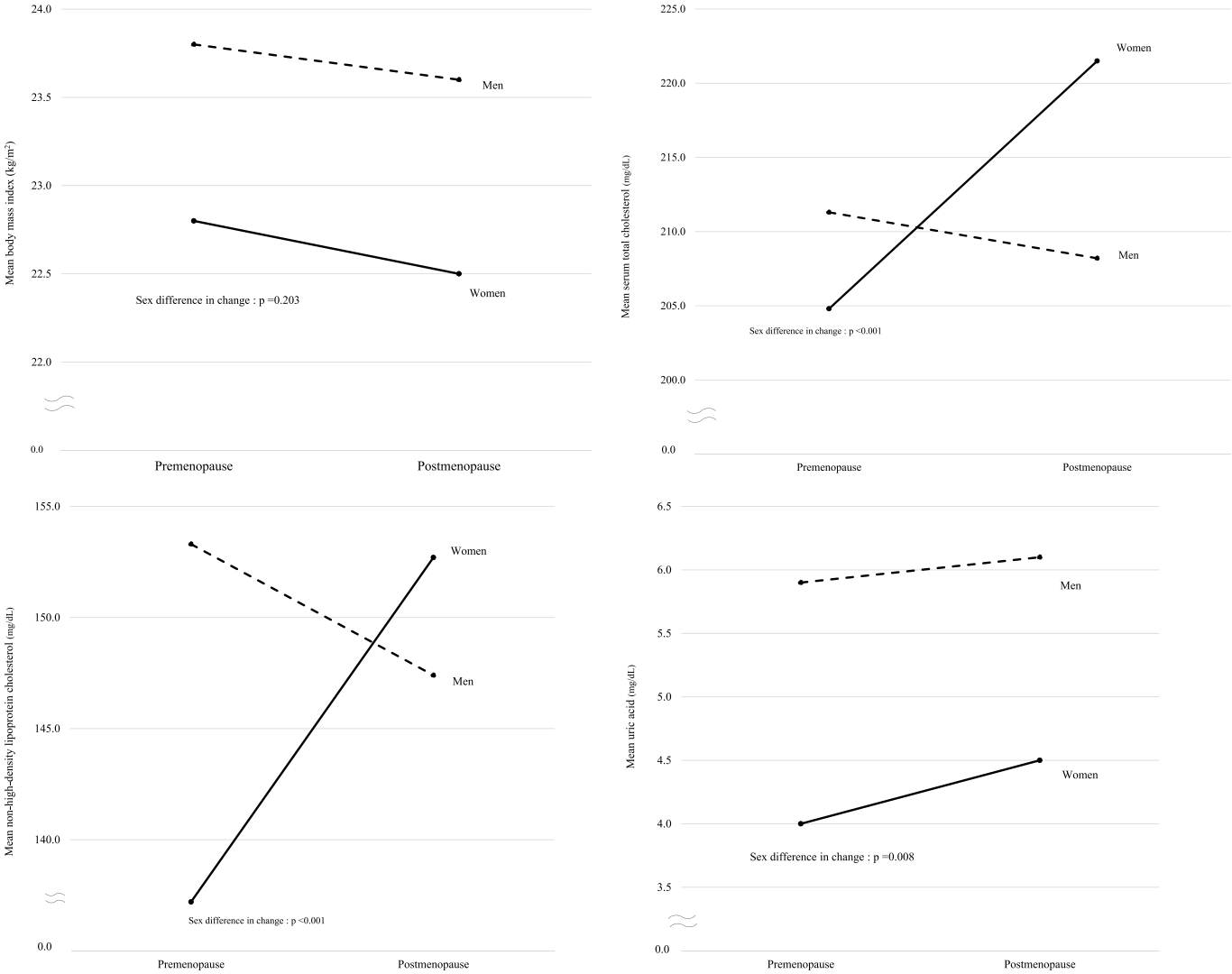

FIG. 2. Changes in mean values of cardiovascular disease risk factors from before to after menopause age. (Continued on next page.)

in BMI, systolic and diastolic blood pressures, or HbA_{1c} between the women and the matched men (Table 1 and Fig. 2).

DISCUSSION

We found that change in serum total cholesterol from before to after menopause age was steeper in women than in matched men and that the mean value for the women was larger than that of the men, consistent with the results of our previous study conducted in the 1980s.[12] Non-high-density lipoprotein cholesterol, triglycerides, uric acid, hemoglobin, and liver enzyme levels also increased among women during the menopausal transition but were still lower than those among men except for non-high-density lipoprotein cholesterol.

The findings of higher serum total cholesterol and triglycerides in postmenopausal than in premenopausal women were generally consistent with those from previous studies.[12-16] As mentioned previously, the women in this study had higher mean values of premenopausal serum total cholesterol than those of the women in our previous study, conducted in the 1980s[12]: the mean serum total cholesterol levels were 204.8 and 183.7 mg/dL, respectively. This may reflect a secular increasing trend for total cholesterol in these two decades in Japan.[17] In that previous study,[12] the unadjusted change in total cholesterol was 16.3 mg/dL (8.9% increase) with a mean interval of 4.3 years before and after menopause age, whereas the unadjusted change observed in the present study was 16.7 mg/dL (8.2% increase) with a longer mean interval of 10.8 years (not shown). The premenopausal-to-postmenopausal interval in the previous studies[12,14] may not have been sufficient to detect changes in cholesterol during reproductive hormone fluctuations.[19] Of note, when we set the premenopausal-to-postmenopausal interval as 4 years, the same as that of the previous study, the increase in cholesterol was 13.2 mg/dL (6.1% increase). A similar increase was observed in Taiwanese women, a 12.9 mg/dL increase from before to after menopause age.[13] The Women's Health Across the Nation, which included non-Hispanic White, African American, Chinese, Hispanic American, and Japanese women living in the United States with a mean follow-up of 3.9 years, showed a 4.3% increase from before to after menopause age, from 196.7 to 205.2 mg/dL.[14]

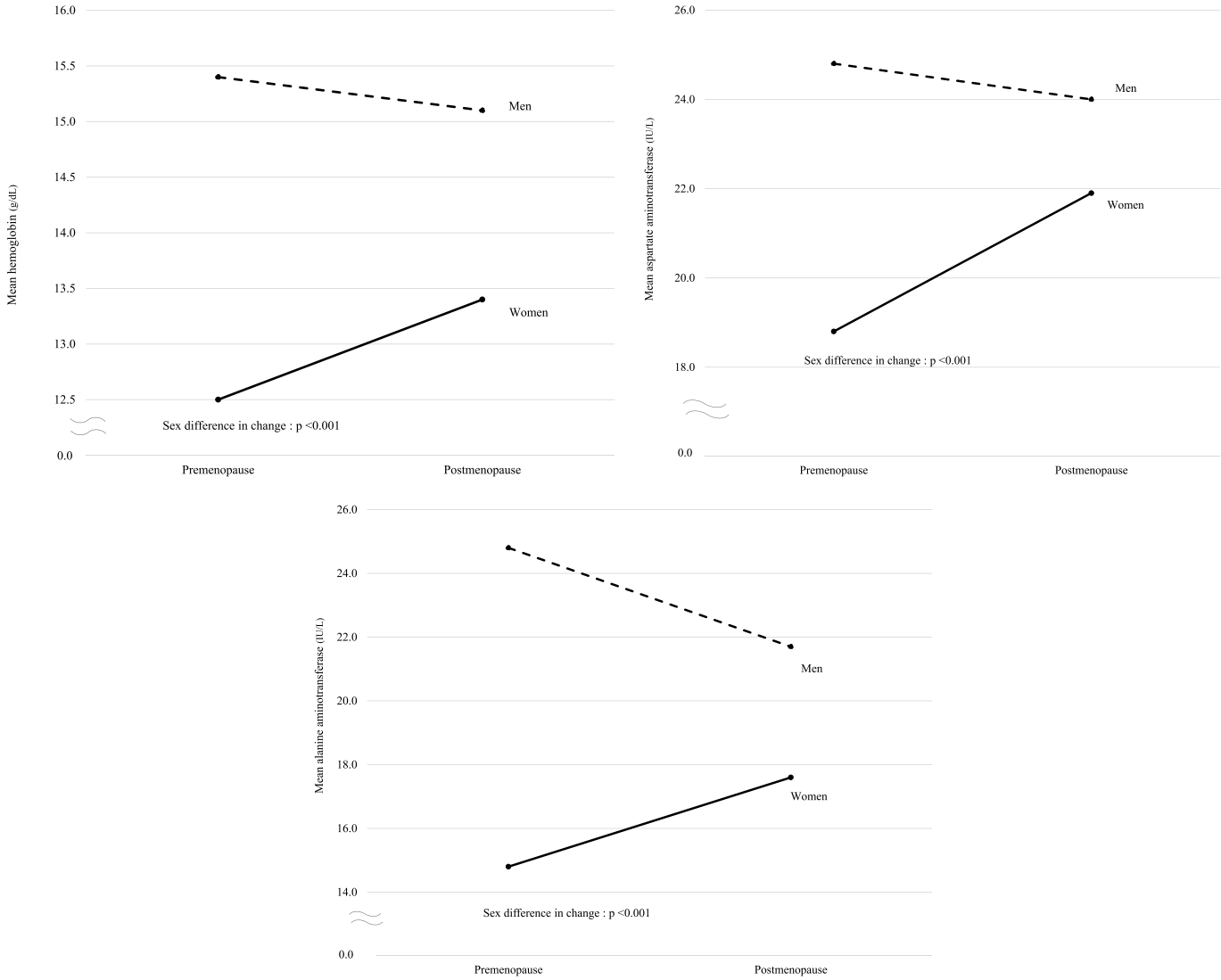

FIG. 2. (Continued.)

Triglycerides, either fasting status or regardless of fasting status, were significantly increased after menopause age from those before menopause age in this study. The Women's Health Across the Nation in the United States showed that the premenopausal fasting triglyceride levels increased from 100.2 to 106.4 mg/dL (6.2% increase) after menopause age.[14] Another cohort study of women (339 White, 31 Black, and 2 from other ethnic groups) aged 40 to 52 years in the United States reported that fasting triglycerides were 81.5 mg/dL before menopause age (mean age, 47.5 years) and increased to 110.7 mg/dL (35.8% increase) after menopause age with a mean follow-up of 5.2 years.[15] The results of the present study showed an increase in fasting triglycerides from 67.0 to 79.0 mg/dL (17.9% increase), indicating that the degree of menopausal increase in triglycerides differed across the studies.

Whereas cross-sectional studies[2-5] have previously been conducted to examine changes in non–high-density lipoprotein cholesterol, uric acid, and liver enzyme levels after menopause age, no such cohort study has yet been conducted.

Non-high-density lipoprotein cholesterol significantly increased during the menopausal transition among women, and the change was larger in women than in men. In a cross-sectional study examining the association between lipids and duration of menopause in women included in the ELSA-Brasil study, non–high-density lipoprotein cholesterol was significantly higher in postmenopausal women of the <2-year, <6-year, <10-year, and >10-year groups than in premenopausal women.[4]

We focused on liver function in this study because a cross-sectional study showed that age- and BMI-adjusted mean values of aspartate aminotransferase and alanine aminotransferase were higher in postmenopausal women than in premenopausal women.[5] Aspartate aminotransferase and alanine aminotransferase in this study were also significantly increased during the menopausal transition.

According to animal studies, the decrease in estrogen levels with menopause age reduced the ability to transport cholesterol to the liver, affecting lipid metabolism.[22,23] In human studies, decreased estrogen and increased follicle-stimulating hormone levels were associated with increased serum total cholesterol, triglycerides, aspartate aminotransferase, and alanine aminotransferase levels and with decreased high-density lipoprotein cholesterol levels.[5,14] Because estrogen promotes the urinary excretion of uric acid and lowers

blood uric acid levels, reduced estrogen causes an increase in blood uric acid levels among postmenopausal women.[24] An increase in hemoglobin levels may be caused by the absence of bleeding due to menopause.

The strength of the present study is its prospective design with updated measurements for cardiovascular risk factors, which allowed examination of their factors during the menopausal transition. The limitations of the study are as follows. First, we were unable to obtain information on whether the menopause was natural or surgical. A previous study showed that compared with natural menopause at 40 years or older, natural menopause and surgical menopause at younger ages were associated with higher risk of incident cardiovascular disease: hazard ratio, 1.36 (95% CI, 1.19-1.56) and 1.87 (95% CI, 1.36-2.58), respectively.[25] Second, information on the use of hormone therapy was not collected in this study. However, the use of hormone therapy in the 2000s was low in Japan, at 13%, as compared with more than 30% in the United States and Europe,[26,27] and thus unlikely to have affected the results materially. Third, because of the performance of multiple tests, we cannot fully rule out the possibility of type I errors. Last, the controls were selected from age-matched men rather than age-matched nonmenopausal women because the latter were rarely identified in this cohort. No cohort studies have examined changes in cardiovascular risk factors during the menopausal transition by comparing with sustained premenopausal women as controls.

CONCLUSIONS

Menopause may be a crucial factor related to changes in serum total cholesterol, non-high-density lipoprotein cholesterol, triglycerides, uric acid, hemoglobin, and liver enzymes. Enhanced lifestyle modifications and clinical management for cardiovascular risk factors among postmenopausal women may be helpful for preventing cardiovascular disease.

Acknowledgments: We thank the staff of Ikawa, Kyowa, and Minami-Takayasu. We also appreciate Ms Flaminia Miyamasu of the Medical English Communications Center, University of Tsukuba, for language revision.

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