Independent Association between Age at Natural Menopause and Hypercholesterolemia, Hypertension, and Diabetes Mellitus: Japan Nurses’ Health Study

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Aim: Menopause is considered a cardiovascular risk factor (CRF), but age at menopause (AAM) varies considerably and could affect the risk among post-menopausal women. The aim of the study was to clarify whether AAM is associated with hypertension, diabetes mellitus (DM) and hypercholesterolemia, independent of chronological age, lifestyle and hormone replacement therapy (HRT), in a sizeable number of Japanese women.

Methods: A retrospective study was conducted using the baseline survey of the ongoing large prospective Japan Nurses’ Health Study. The prevalence of hypertension, DM, and hypercholesterolemia of pre-menopausal and three post-menopausal AAM groups (early: < 45 years, intermediate: 45-53 years, late: > 53 years) was compared among 22,426 women aged 40-59 years. Daily lifestyle such as smoking, alcohol consumption, and physical activity were included.

Results: The estimated risk (odds ratio: OR) was significantly higher in post-menopausal women and linearly elevated according to the AAM groups, and the late AAM group was more likely to have hypertension, DM, or hypercholesterolemia; however, after adjustment for age, BMI (kg/m²), HRT and lifestyle, menopause and AAM showed a significant association with only hypercholesterolemia and the early AAM group had the highest OR (2.72 (1.93-3.82)). Menopause and AAM did not show any independent association with the risk of hypertension and DM in the fully adjusted model.

Conclusions: Among the post-menopausal women, early menopause increased the risk for hypercholesterolemia independently. AAM can be a useful screening tool to identify women at high risk for adverse post-menopausal lipid profiles in the Japanese.


Key words; Age at menopause, Cardiovascular risk factor, Hormone replacement therapy, Lifestyle, Menopause

Introduction

The primary cause of death in women is cardio-

vascular disease (CVD), including heart disease and cerebrovascular disease1, 2. CVD is relatively rare among young women and tends to develop around 10 years later than in men, with a marked increase after menopause2. This increase is believed to be due to increases in conventional cardiovascular risk factors (CRF), including hypertension, diabetes mellitus (DM), dyslipidemia and obesity accompanying menopause; however, menopause-related factors contributing to a high risk for developing CRF have not been fully
understood among post-menopausal women.

While age at menopause (AAM) varies considerably\(^3\), AAM, whether naturally or medically induced, is a noteworthy candidate for easily identifying high-risk women in primary clinical settings. Women with early menopause have elevated CVD\(^4, 5\), and late menopause has shown reduced CVD\(^6, 7\); however, the independent influence of natural AAM on CRF remains unclear.

Associations between menopause or AAM and CRF could be largely confounded by chronological age\(^8-11\) and daily lifestyle, such as body weight, smoking, alcohol consumption, or physical activity\(^10-12\). Chronological age and lifestyle are recognized as influential factors on CRF\(^1, 13\) and are mutually correlated\(^14, 15\). Many studies have also suggested that estrogen has protective effects on the cardiovascular system\(^16, 17\), but in light of inconsistent findings on the protective effects of hormone replacement therapy (HRT) on CVD, the role of a sudden change in estrogen has been questioned\(^18\).

Japanese women have the longest life expectancy in the world\(^19\). The leading cause of death is also CVD\(^20\), and a larger number of women are under medical treatment due to CVD after midlife than men\(^21\). Furthermore, conventional CRF are also important risk factors in Japanese women\(^22\), and they have a long duration of treatment for CRF during later life because of their longer life span; however, Japanese women have much lower body weight and smaller changes of body weight during mid-life due to their different lifestyle from women in western countries\(^23\). It is critical to understand the influential factors unique to women so that new strategies for early detection and early management of CRF in women can be considered in Japan.

To examine whether both the natural menopause status and natural AAM are associated with CRF and whether chronological age, lifestyle, or HRT modulate these associations is potentially important for identifying women at high risk for adverse postmenopausal CRF profiles. As far as we know, however, no study has measured all of these factors simultaneously in a sizeable number of Japanese women. The Japanese Nurses’ Health Study (JNHS) provided the opportunity to examine the association between natural menopause or AAM and hypertension, DM, and hypercholesterolemia independent of chronological age, major lifestyle, and HRT.

The purpose of the present study was to clarify whether there is an association between natural menopause status or AAM and CRF independent of chronological age, lifestyle, and HRT.

### Methods

#### Study Population

The JNHS is an ongoing prospective large cohort study to investigate the effects of lifestyle and health-care practices on Japanese women’s health\(^24\). The enrollment was initiated in 2001, with a seven-year entry period and a proposed ten-year follow-up\(^25\). Participants consisted of female registered nurses, licensed practical nurses, public health nurses, and midwives aged 30 years and older residing in Japan at the baseline survey. Thus, the survey results concerning medical information were expected to be comparatively accurate.

A self-administered questionnaire was distributed with an invitation letter and a stamped self-addressed envelope, requesting demographic information, lifestyle, physical condition, reproductive health, and disease history. Respondents who agreed to participate in the JNHS completed the questionnaire, sealed the envelope, and mailed it back to the JNHS coordination center. A total of 49,927 women from all 47 prefectures in Japan responded to the baseline survey. Participants are undergoing a biennial follow-up survey. The details of the study purpose and design have been reported\(^24, 25\).

This study was approved by the Ethics Committee of the Graduate School of Medicine, Gunma University, Japan.

#### Measurements

##### Natural Menopause Status and Age at Menopause

The study target women were limited to 26,034 women whose chronological age at baseline was 40 to 59 years old because the current study purpose was to investigate the independent associations between natural menopause or AAM and CRF.

The baseline questionnaire included the age at which periods ceased and the cause of period cessation (natural, surgical, other). In post-menopausal women (PMW), participants were excluded if they had no information on AAM or cause of menopause (remaining \(n=25,187\)). In order to focus on natural menopause, women whose menopause occurred medically, i.e. surgery, radiotherapy or chemotherapy, were excluded, and only women who had ceased menstruating naturally for at least 1 year were included in the analysis (remaining \(n=22,426\)). AAM was retrospectively assigned as the self-reported age at the last menstrual period. Menopause status was defined as premenopause or post-menopause.
**Definition of Hypertension, Diabetes Mellitus, and Hypercholesterolemia**

In the baseline survey, participants were requested to report the results of their blood pressure, serum total cholesterol (TC), and fasting plasma glucose (FPG) measurements within 2 years. The questionnaire also asked whether they were currently taking medication for any of these three CRF.

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg, or if they were currently using any anti-hypertensive medication. DM was defined as FPG ≥126 mg/dL, or if they were currently taking any medication for DM. Hypercholesterolemia was defined as TC ≥240 mg/dL, or if they were currently taking medication for hypercholesterolemia.

**Baseline Covariates**

The following baseline factors were considered as covariates: chronological age at survey (years), BMI (body weight (kg)/height (m)²), and use of HRT (never, past, or currently) to relieve menopausal symptoms. For daily lifestyle, smoking, alcohol drinking, and physical activity were also used.

Smoking was categorized as never, past, or currently, and drinking was categorized as <3 times·week⁻¹ or ≥3 times·week⁻¹, according to the national recommended level.

Physical activity was evaluated using a validated self-reported questionnaire. Participants were queried about the number of hours of sleep and of moderate, hard, and very hard physical activity during the previous seven days. A list of example activities in each category was provided. In order to assess the physical activity level, metabolic equivalents (METs) were assigned to three categories of activity: moderate=3 METs; hard=6 METs; and very hard=8 METs. MET-hours per week of these 3 activities were totaled and assessed according to the national recommended level of physical activity (<23 MET-h·week⁻¹ or ≥23 MET-h·week⁻¹).

**Statistical Analysis**

Among the study women, pre-menopausal women were used as a reference group, and PMW were further classified into three groups according to their AAM to examine the influence of AAM on the risk of CRF. The 10th percentile and 90th percentile of the AAM were ages 45 years and 55 years, respectively, and these cutoff points were used to classify into three PMW: early AAM (<45 years), intermediate AAM (45-53 years), and late AAM (>53 years).

The relative risk was estimated as the odds ratio (OR) and its 95% confidence intervals (95% CI) using logistic regression analyses. To confirm the association between menopause or AAM and CRF, univariate logistic regression analysis was performed. To test whether there is an association between menopause or AAM and CRF independent of chronological age, or chronological age, BMI, lifestyle, and HRT, multiple logistic regression analysis was conducted.

All statistical data analyses were carried out using SAS ver. 9.2 (SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was considered significant.

**Results**

In total, 22,426 women fulfilled the eligibility criteria for the study purpose. Average chronological age was 46.7 ± 4.9 years. Overall, 19.3% (n=4,318) of the women had experienced natural menopause, and the median AAM was 50 years old.

Baseline characteristics according to the menopause or AAM are shown in Table 1. Compared to pre-menopausal women, PMW were more likely to be older and tended to have heavier body weight and higher SBP, DBP, TC, and FPG. PMW were more likely to have a higher prevalence of hypertension, DM, and hypercholesterolemia than pre-menopausal women.

Among the PMW, the mean chronological age linearly increased with AAM, and the means of BMI, SBP and DBP also linearly increased; however, the means of TC and FPG were not significantly different among the three AAM groups. The prevalence of hypertension tended to be higher with AAM, but the prevalence of DM and hypercholesterolemia was not significantly different among the three AAM groups.

Around 12.0% had used HRT (previously or currently) among the PMW and the prevalence of ever using HRT significantly declined with AAM. Only around 1.6% had used HRT in pre-menopausal women.

The prevalence of past and current smoking was significantly lower in PMW than in pre-menopausal women and decreased with AAM. There was no significant difference in the prevalence of habitual alcohol drinking between pre- and PMW or among the three AAM groups. The prevalence of physically active women (≥23 MET-h·week⁻¹) was significantly higher in PMW, but there were no significant differences among the AAM groups.

To examine the influence of menopause or AAM on the risk of hypertension, DM, and hypercholesterolemia, the OR and 95% CI using univariate logistic regression analysis are shown in Fig. 1 (open bars).
PMW showed a significantly higher risk for hypertension, DM, and hypercholesterolemia than pre-menopausal women, and the risk for hypertension, DM, and hypercholesterolemia linearly increased according to the AAM. All the OR were statistically significant, except for the OR of DM in the early AAM group. The late AAM group was more likely to have hypertension, DM, and hypercholesterolemia than the other two AAM groups.

Table 2 shows the results of multiple logistic regression analysis. First, the chronological age-adjusted logistic model showed that the OR of hypertension and DM in PMW or in all AAM groups became <1.00, but OR of hypercholesterolemia was continuously >1.00 in PMW or in all AAM groups even after adjustment for age, and the early AAM group was most likely to have hypercholesterolemia among the three AAM groups. Chronological age itself significantly increased the risk for hypertension, DM, and hypercholesterolemia.

The results after further adjustment for chronological age, BMI, HRT, and lifestyle as covariates are shown in Fig. 1 (black bars) and Table 2. The OR of hypertension and DM in PMW or in all AAM groups were not significant after adjustment for these covariates; however, PMW was significantly associated with

Table 1. Baseline characteristics according to natural menopause and age at menopause among women in the Japan Nurses’ Health Study (n=22,426)

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>p 1</th>
<th>&lt;45</th>
<th>45-53</th>
<th>&gt;53</th>
<th>p 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18,108</td>
<td>4,318</td>
<td></td>
<td>305</td>
<td>3,710</td>
<td>303</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mean ± SD</td>
<td>44.9 ± 3.6</td>
<td>53.5 ± 3.3</td>
<td>&lt;0.001</td>
<td>49.4 ± 4.6</td>
<td>53.6 ± 2.8</td>
<td>57.1 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.3 ± 3.0</td>
<td>22.6 ± 2.8</td>
<td>&lt;0.001</td>
<td>22.3 ± 3.2</td>
<td>22.6 ± 2.8</td>
<td>23.0 ± 2.9</td>
<td>0.006</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114.5 ± 13.8</td>
<td>120.4 ± 15.7</td>
<td>&lt;0.001</td>
<td>115.1 ± 15.1</td>
<td>120.5 ± 15.6</td>
<td>123.3 ± 15.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>69.2 ± 10.8</td>
<td>73.6 ± 11.5</td>
<td>&lt;0.001</td>
<td>70.2 ± 11.9</td>
<td>73.8 ± 11.4</td>
<td>75.3 ± 11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>192.3 ± 35.4</td>
<td>215.1 ± 36.0</td>
<td>&lt;0.001</td>
<td>213.1 ± 34.5</td>
<td>215.3 ± 36.4</td>
<td>214.4 ± 32.0</td>
<td>0.622</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>90.4 ± 12.0</td>
<td>93.2 ± 14.9</td>
<td>&lt;0.001</td>
<td>91.3 ± 11.8</td>
<td>93.3 ± 15.1</td>
<td>93.7 ± 14.7</td>
<td>0.135</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Never (%)</td>
<td>1,733 (9.6)</td>
<td>963 (22.4)</td>
<td>&lt;0.001</td>
<td>39 (12.8)</td>
<td>843 (22.8)</td>
<td>81 (26.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past (%)</td>
<td>275 (1.5)</td>
<td>140 (3.3)</td>
<td>&lt;0.001</td>
<td>6 (2.0)</td>
<td>122 (3.4)</td>
<td>12 (4.0)</td>
<td>0.358</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>1,322 (7.4)</td>
<td>1,118 (26.4)</td>
<td>&lt;0.001</td>
<td>77 (25.6)</td>
<td>948 (26.1)</td>
<td>93 (31.0)</td>
<td>0.167</td>
</tr>
</tbody>
</table>

Mean ± SD; t-test or ANOVA, number of women (%); χ² test.

p 1: p value of the comparison between pre- and post-menopausal women.
p 2: p value of the comparison among three age at menopause groups.

* Body mass index.
* Systolic blood pressure.
* Diastolic blood pressure.
* Total cholesterol.
* Fasting plasma glucose.
* SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or under hypertension treatment or using medicine.
* FPG ≥ 126 mg/dL or under diabetes treatment or using medicine.
* TC ≥ 240 mg/dL or under treatment or using medicine.
* Hormone replacement therapy.
* Metabolic equivalent.
Menopausal Age and Cardiovascular Risk Factor

number of studies have reported changes in BP28 or FPG accompanying menopause, but a large number of studies29, 30, including our study, could not observe significant differences with menopause after adjustment for age. An earlier study31 showed that hysterectomized women had an increased prevalence of hypertension, regardless of the number of intact ovaries, or use of HRT, but contrasting results have also been reported32.

The contradictory study results might be attributed to the causes of menopause. The current study focused on natural menopause, and the results are consistent with most of the previous studies which rejected an increased risk for hypertension or DM8, 9, 29, 30, 33. Body weight, smoking, alcohol consumption, and physical activity are now well-known influential factors on blood pressure and glucose metabolism. Thus, we included these covariates in the multivariate model. Unlike hypercholesterolemia, hypertension and DM seem to be unaffected by the decreased secretion of estrogen per se due to menopause.

Before and after adjustment for age and/or BMI, lifestyle, and use of HRT, the risk for hypercholesterolemia significantly increased in PMW, and early AAM showed the highest risk and were likely to have around 2.7 times higher risk for hypercholesterolemia than pre-menopausal women after adjustment for covariates.

Discussion

The purpose of the study was to clarify which women were at high risk for adverse post-menopausal CRF profiles among Japanese women. We assessed the association between menopause or AAM and the risks for hypertension, DM and hypercholesterolemia independent of chronological age, lifestyle, and HRT among Japanese women for the first time. This is the only study to measure all of these covariates simultaneously in a sizeable number of Japanese women. The most relevant findings were that natural menopause itself increased the risk for hypercholesterolemia independently, and early AAM women had the highest risk and were likely to have around 2.7 times higher risk for hypercholesterolemia than pre-menopausal women after adjustment for covariates.

Before adjustment for covariates, all the risks for hypertension, DM, or hypercholesterolemia were significantly increased in PMW and were linearly elevated according to the AAM. After adjustment for covariates, however, neither the risk for hypertension nor the risk for DM was significant in the PMW and in all AAM groups. There have been conflicting study results regarding changes in blood pressure and glucose metabolism with menopause. A relatively small number of studies have reported changes in BP28 or FPG accompanying menopause, but a large number of studies29, 30, including our study, could not observe significant differences with menopause after adjustment for age. An earlier study31 showed that hysterectomized women had an increased prevalence of hypertension, regardless of the number of intact ovaries, or use of HRT, but contrasting results have also been reported32.

The contradictory study results might be attributed to the causes of menopause. The current study focused on natural menopause, and the results are consistent with most of the previous studies which rejected an increased risk for hypertension or DM with menopause.8, 9, 29, 30, 33 Body weight, smoking, alcohol consumption, and physical activity are now well-known influential factors on blood pressure and glucose metabolism. Thus, we included these covariates in the multivariate model. Unlike hypercholesterolemia, hypertension and DM seem to be unaffected by the decreased secretion of estrogen per se due to menopause.

Both before and after adjustment for age and/or BMI, lifestyle, and use of HRT, the risk for hypercholesterolemia significantly increased in PMW, and early AAM showed the highest risk for hypercholesterolemia. An increase in serum cholesterol in PMW is generally considered a result of a decrease in serum estradiol34 and a decrease in the number of low-density lipoprotein cholesterol (LDL-C) receptors35. The reduced activity of hepatic LDL receptors due to decreased estrogen concentration has been speculated as a mechanism36. Higher hepatic lipase activity, which is inhibited by estrogen and stimulated by androgen, was proposed as a key enzyme increasing
only a few studies have examined the effects of AAM on CRF in Japan. Similar to our study results, a prospective study conducted in Nagasaki also rejected a menopausal effect on SBP, but women with AAM younger than 45 years showed a great increase in TC. The raised risk of early AAM might be explained by prolonged exposure to those hormonal changes and could contribute to the elevated risk for hypercholesterolemia.

Among the covariates, our study results revealed

### Table 2. Associations of natural menopause or age at menopause and hypertension, diabetes mellitus, and hypercholesterolemia

<table>
<thead>
<tr>
<th>Chronological age-adjusted logistic model</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopause</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
</tr>
<tr>
<td>Post-menopause</td>
<td>0.84 (0.74-0.95)</td>
<td>0.78 (0.58-1.06)</td>
<td>1.87 (1.63-2.13)</td>
</tr>
<tr>
<td>Chronological age (y)</td>
<td>1.15 (1.14-1.17)</td>
<td>1.13 (1.10-1.16)</td>
<td>1.12 (1.10-1.13)</td>
</tr>
</tbody>
</table>

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<th>Diabetes mellitus</th>
<th>Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopause</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
</tr>
<tr>
<td>&lt;45 years old</td>
<td>0.70 (0.49-0.99)</td>
<td>0.72 (0.31-1.65)</td>
<td>2.65 (2.01-3.50)</td>
</tr>
<tr>
<td>45-53</td>
<td>0.86 (0.75-0.98)</td>
<td>0.79 (0.58-1.08)</td>
<td>1.79 (1.56-2.05)</td>
</tr>
<tr>
<td>&gt;53 years old</td>
<td>0.67 (0.50-0.89)</td>
<td>0.64 (0.33-1.24)</td>
<td>1.57 (1.18-2.09)</td>
</tr>
<tr>
<td>Chronological age (y)</td>
<td>1.15 (1.14-1.17)</td>
<td>1.13 (1.10-1.16)</td>
<td>1.12 (1.10-1.13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate logistic model after adjustment for chronological age, BMI, HRT, and daily lifestyle</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopause</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
</tr>
<tr>
<td>&lt;45 years old</td>
<td>0.81 (0.52-1.26)</td>
<td>0.82 (0.29-3.23)</td>
<td>2.72 (1.93-3.82)</td>
</tr>
<tr>
<td>45-53</td>
<td>0.93 (0.79-1.10)</td>
<td>0.98 (0.67-1.43)</td>
<td>1.77 (1.50-2.09)</td>
</tr>
<tr>
<td>&gt;53 years old</td>
<td>0.72 (0.51-1.04)</td>
<td>0.71 (0.32-1.61)</td>
<td>1.52 (1.07-2.14)</td>
</tr>
<tr>
<td>Chronological age (y)</td>
<td>1.15 (1.14-1.17)</td>
<td>1.12 (1.08-1.16)</td>
<td>1.11 (1.10-1.13)</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;a&lt;/sup&gt; (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.24 (1.22-1.26)</td>
<td>1.24 (1.20-1.27)</td>
<td>1.10 (1.08-1.12)</td>
</tr>
<tr>
<td>Use of HRT&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
</tr>
<tr>
<td>Past</td>
<td>1.12 (0.83-1.51)</td>
<td>0.63 (0.28-1.45)</td>
<td>1.45 (1.11-1.90)</td>
</tr>
<tr>
<td>Current</td>
<td>0.90 (0.62-1.29)</td>
<td>1.23 (0.56-2.68)</td>
<td>0.83 (0.58-1.17)</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Never</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
</tr>
<tr>
<td>Past</td>
<td>1.12 (0.95-1.31)</td>
<td>0.65 (0.42-1.01)</td>
<td>1.02 (0.86-1.20)</td>
</tr>
<tr>
<td>Current</td>
<td>1.15 (0.99-1.33)</td>
<td>0.97 (0.68-1.38)</td>
<td>1.00 (0.86-1.17)</td>
</tr>
<tr>
<td>Drinking</td>
<td></td>
<td></td>
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<tr>
<td>&lt;3 times/week</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
</tr>
<tr>
<td>≥3 times/week</td>
<td>1.36 (1.21-1.53)</td>
<td>0.59 (0.42-0.82)</td>
<td>0.73 (0.64-0.83)</td>
</tr>
<tr>
<td>Daily physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥23 MET&lt;sup&gt;c&lt;/sup&gt;-hours·week&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
<td>1.00 ref.</td>
</tr>
<tr>
<td>&lt;23 MET&lt;sup&gt;c&lt;/sup&gt;-hours·week&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>1.06 (0.88-1.27)</td>
<td>0.81 (0.55-1.21)</td>
<td>1.07 (0.89-1.29)</td>
</tr>
<tr>
<td>≥3 times/week</td>
<td>1.36 (1.21-1.53)</td>
<td>0.59 (0.42-0.82)</td>
<td>0.73 (0.64-0.83)</td>
</tr>
</tbody>
</table>

Odds ratio (OR) (95% Confidence interval (CI)) using logistic regression analysis; reference category: pre-menopause.

<sup>a</sup>Body mass index, <sup>b</sup>Hormone replacement therapy, <sup>c</sup>Metabolic equivalent.

LDL-C in PMW<sup>37</sup>; thus, the difference in the prevalence of hypercholesterolemia was assumed to reflect the change of LDL-C.

However, the mechanism by which early AAM had the highest risk for hypercholesterolemia could not be clearly explained from the current study design. It is speculated that a relationship between early AAM and hypercholesterolemia might depend upon the early AAM itself or on the duration of those hormonal changes related to the menopause. As far as we know,
that BMI significantly and independently increased the risk for hypertension, DM, and hypercholesterolemia irrespective of menopausal status. In the current study, mean BMI was significantly different between pre- and PMW but the magnitude of difference was comparatively small (0.3 ± 3.0 kg/m²). Increasing BMI in PMW could be attributed to an increase in intra-abdominal fat[11, 32, 39]. Even a small increase in body weight in Japanese PMW accompanied a relatively large increase in visceral fat and consequently led to the risk of hypertension, DM, and hypercholesterolemia.

The present study results showed that habitual alcohol drinking (more than 3 times a week) increased the risk for hypertension but decreased the risk for DM and hypercholesterolemia. Drinking could affect both LDL- and HDL-cholesterol metabolism[40, 41], while consumption of a large amount of alcohol is associated with elevated blood pressure[42]. A further study focusing on the appropriate amount, frequency, and type of alcoholic beverage to control overall CRF in Japanese women will be needed.

Past HRT use showed a significant increase in the risk for hypercholesterolemia in the current study results. HRT showed beneficial effects on body composition[39] and vasomotor symptoms but adverse effects on lipid profiles and other CRF. The risks and benefits persist after stopping HRT use[47] and conflicting results remain whether HRT increases the risk of CRF. Recently, the “timing hypothesis” has becomes noted for its emphasis on the timing of HRT initiation[42]. On the other hand, baseline CRF might modulate the outcome of HRT.

Other covariates, i.e. smoking status and physical activity, did not have independent effects on CRF. Physical activity in PMW is generally considered as an indirect effect on CRF through preventing or attenuating changes in body composition[40], and smoking status also has been associated with lower body weight and early AAM[12]. Almost all of the current study population included professional working women, and the body weight difference between pre- and PMW was relatively small. Moreover, they had a relatively small range of physical activity and a lower smoking rate than women in western countries. These characteristics might explain why the smoking status and physical activity did not show significant results. A further study will be required, focusing on lifestyle changes with menopausal transition using prospective data.

To date, epidemiological studies have reported that AAM could predict CVD[4-7]; however, there is no uniform definition of the AAM cutoff point, and the AAM cutoff point used in those studies ranged from 40 to 50 years[4-6, 43]. AAM younger than 40 years is generally used as a premature menopausal cutoff point, including medically induced menopause. In the current study, we used the 10th percentile of natural AAM as the cutoff point and found an independent and significant association of elevated hypercholesterolemia; therefore, using 45 years as the AAM cutoff point for early management of CRF would be useful in the primary clinical setting. A further study concerning endocrinopathic mechanisms to decide the natural AAM cutoff point useful for screening high-risk women will be needed. A simple question regarding AAM in the primary clinical setting could be a useful screening tool to identify women who need intervention, follow-up, and careful evaluation to manage lipid profiles and to prevent CVD.

There are several limitations of the current study. Firstly, all the analyzed data were based on a self-administered questionnaire; however, all the participants were currently working nurses so the medical information was considered to be comparatively accurate, and self-reported body weight and CRF have shown significant predictive power for the mortality and/or morbidity of CVD and cancer in large prospective studies[44], including Japanese[45]. Secondly, this study was conducted retrospectively using baseline data of JNHS; thus, an observational study with prospective follow up should be conducted. Thirdly, genetic factors were not included in this study. Genetic variation in the action of estrogen plays a role in regulating circulating levels of adiponectin[46], which may influence the change of CRF because of menopause. Further studies are needed to identify women at high risk after menopause due to genetic factors.

**Conclusion**

Menopause itself independently contributed to the risk for hypercholesterolemia, and early menopausal women had the highest risk for hypercholesterolemia.

AAM can be a useful screening tool to identify women at high risk for adverse post-menopausal lipid profiles in the Japanese. A simple inquiry regarding AAM can help to identify those women who need monitoring for early management of lipid profiles.

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**Conflict of Interest**

None.

**References**


3) Treloar SA, Do KA, Martin NG: Genetic influences on the age at menopause. Lancet, 1998; 352: 1084-1085


6) van der Schouw YT, van der GY, Eijkemaans JC, Banga JD: Age at menopause as a risk factor for cardiovascular mortality. Lancet, 1996; 347: 714-718


18) Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progesterin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA, 2002; 288: 321-333


