Effects of Postmenopausal Hormone Replacement Therapy (HRT) and Early Age at Menopause on Endothelial Function among Korean Living in Rural Area

Yunsu Choi

Graduate School of Public Health

Yonsei University

Department of Epidemiology and Health Promotion

Effects of Postmenopausal Hormone Replacement Therapy (HRT) And Early Age at Menopause on Endothelial Function among Korean Living in Rural Area

Directed by Professor Sun Ha Jee

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Yunsu Choi

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This certifies that the master's thesis

of Yunsu Choi is approved.

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Thesis Supervisor: [Sun Ha Jee]

_____

Thesis Committee Member #1: Bo Youl Choi

_____

Thesis Committee Member #2: Sohee Park

Graduate School of Public Health

Yonsei University

August 2017

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ABSTRACT

Effects of Postmenopausal Hormone Replacement Therapy (HRT) And Early Age at Menopause on Endothelial Function among Korean Living in Rural Area

Yunsu Choi

Graduate School of Public Health

Yonsei University

Directed by Professor Sun Ha Jee, Ph.D.

Introduction: The second leading cause of death in Korea is cardiovascular disease. Women' menopause is known as a risk factor of cardiovascular disease, and endothelial dysfunction is an independent risk factor for coronary artery disease. Postmenopausal hormone replace therapy has many side effects and benefits, but there is still much controversy about cardiovascular disease.

Objectives: We investigate the effect of postmenopausal period and hormone replacement therapy on endothelial function after adjusted coronary risk scores, marital status, abdominal obesity, and Obstetrics & Gynecological history.

Methods: A total of 251 women who underwent the FMD test and had no missing variables were analyzed for the Health and Aging Cohort (HAC_YangPyeong). In the final regression analysis, a reweighting method was used for outliers.

Results: Endothelial function was 1.75%p (p=0.04) lower in 51(20.3) women who had HRT and 51(20.3) women who experienced early menopause had 3.92%p (p=0.0002) lower. The short-term HRT usage were 2.07%p (p=0.054) lower and the long-term HRT usage were 1.31%p (p=0.285) lower than non-user. Decreased endothelial function when abdominal obesity defined were as WHR (p=0.012), long-term gynecological age (p=0.0006), high of KRS (p=0.005), and long postmenopausal period (p=0.059). In contrast, women who live alone was significantly higher than women who live together after the marriage (p=0.012).

Conclusion: At the onset of HRT, the current age and the type of menopause as well as the coronary risk scores and duration of age at menarche to age at menopause should be considered.

Keywords: Hormone replacement therapy (HRT), menopause, cardiovascular disease, endothelial function (FMD), early menopause, gynecological age

Ⅰ. INTRODUCTION

1. Background

Korea reached an aging society at 2000, also the elderly population is over 13% of the total population and entered the aged society. The death rate from heart disease was 55.6 deaths per 100,000 populations, 56.2 deaths per 100,000 of Korean women were found to be caused by heart disease. The second of common causes of death in Korea. The death from circulatory disease averaged 2.6%p increase over the previous year, also women were 13.8%p higher than men (KOSIS, 2017). The prevalence was higher in postmenopausal women (PMW) than men of the same age in chronic lifestyle-related diseases that require management such as obesity, total cholesterol, blood pressure and stroke according to Korea National Health & Examination Survey (KNHNES) in 2016.

Multiple previous studies suggested menopause is a risk factor for cardiovascular disease and cause of the decrease in endothelial function (Colditz et al., 1987; He et al., 2012). The cause of increased circulatory disease in PMW is the loss of estrogenic cardioprotective function and exposure to various risk factors (Colacurci et al., 2003; Gray et al., 2001; Grodstein and Stampfer, 1998; Sader and

Celermajer, 2002). The vascular endothelial function is the difference between vasodilatation and stabilization by nitric oxygen (NO). The NO in the body decreases gradually as aging, and the endothelial function also decreases (Raitakari and Celermajer, 2000). Decreasing endothelial function is an important independent indicator of the early abnormalities of cardiovascular and is associated with atherosclerosis and cardiovascular disease occurrence (Fathi et al., 2004; Synn, Bae and Kim, 2004). Coronary heart disease (CHD) would be directly or indirectly association with severe vascular related diseases such as heart or kidney failure, and ischemic stroke, cerebral infarction, cerebral hemorrhage.

In Japan, the hormonal changes according to the menstrual cycle had a significant association with the endothelial function test (Flow-mediated dilatation, FMD). The Blood flow was higher in the luteal phase and the follicular phase just before ovulation than in the menstrual period (Hashimoto et al., 1995). The results suggest that hormone exposure through the female menstrual cycle has a protective effect on cardiovascular disease. Another study, in Italy, that considered time since menopause suggested endothelial function was relatively higher in women who had early HRT after menopause and was more relevant than the change due to aging (Vitale et al., 2008).

The postmenopausal hormone replacement therapy (HRT) is used to relieve menopause symptoms such as hot flashes, night sweats, sleep disorder, vaginal dryness and weight gain with a slow metabolism (Barrett-Connor, 1998; Manson and Martin, 2001). HRT consists of patches, injections, oral pills, and has been

reported to vary in effectiveness depending on the combination of regimens. A single long-term use of estrogen has a preventive effect on osteoporosis. It also reduces the risk of CHD and affects the survival rate of women, while increasing the risk of endometrial cancer, stroke, and fracture, the risk of breast cancer during treatment (Barrett-Connor, 1998; Manson and Martin, 2001). Because of these prevention or risk effects of HRT, it is necessary to consider the timing of treatment, the type of preparations, the period of usage, in addition, diseases history of the patient and their family.

Postmenopausal women's HRT may be used for prevention of cardiovascular diseases, but the cardio-protective effect was decreased as the aging progressed after HRT. In some studies, there was no cardio-protective effect of when the women who has many years since menopause (Vitale et al., 2008) or older who experienced any kind of menopause, probably due to an estrogen receptor that could not overcome the effects of aging on endothelial function and predicted that was would be related genetic methylation (Herrington et al., 2001; Kalantaridou et al., 2006).

Women affected not only menopausal hormone changes but also the risk of cardiovascular disease due to periodic hormone exposure by the menstrual cycle. Exposure of hormones does not only affect women's menstrual characteristics but also is closely related to the history of obstetrics and gynecology such as the frequency of deliveries, age at first pregnancy, breast-feeding and oral contraceptive pill use, etc.

However, they could not consider about CHD risk. The studies of coronary artery disease have been ongoing, and many studies have identified risk factors. Based on these risk factors, the Framingham risk scores (FRS) equation for Caucasian was developed in the Framingham Heart Study (Wilson et al., 1998). The calculation method is the coronary artery disease risk scores using categorized such as blood pressure, total cholesterol, HDL and LDL. There is a difference in the risk of racial cardiovascular disease because the equation does not consider it. The commonly used Framingham risk scores (FRS) tends to be overestimated for coronary heart disease (CHD) predictions when applied to Koreans (Jee et al., 2014). The coronary risk scores for Korean (KRS) has ranges from 0 to 1, and the closer to 1 that higher the risk of CHD. Therefore, the effect of hormone therapy should be confirmed by using the risk scores of coronary heart disease developed for Koreans.

The aim of this study is to investigate the relationship between HRT and time of age at menopause with endothelial-dependent function adjusted KRS and to confirm association with endothelial-dependent vasodilation function and the HRT for prevention of cardiovascular disease among Korea rural area Postmenopausal women.

2. Objectives

In this study, we selected subjects who completed all the tests for calculating coronary risk scores among postmenopausal women (PMW) who participated in an FMD test in 2011 and 2013.

The specific aim of the study is as follows.

1. To confirm the relationship between the HRT at postmenopausal and difference in endothelium-dependent function measured by FMD in Korean rural area.

2. To determine the relationship between the endothelium-dependent function by the time of menopause (early menopause, normal or late menopause) and coronary risk scores for Korean (KRS).

3. To confirm the correlation between social factors, health behaviors, history of disease and OB/GY history affecting the duration of hormone exposure that was related to the risk of endothelium-dependent function.

Ⅱ. MATERIALS AND METHODS

1. Study Design

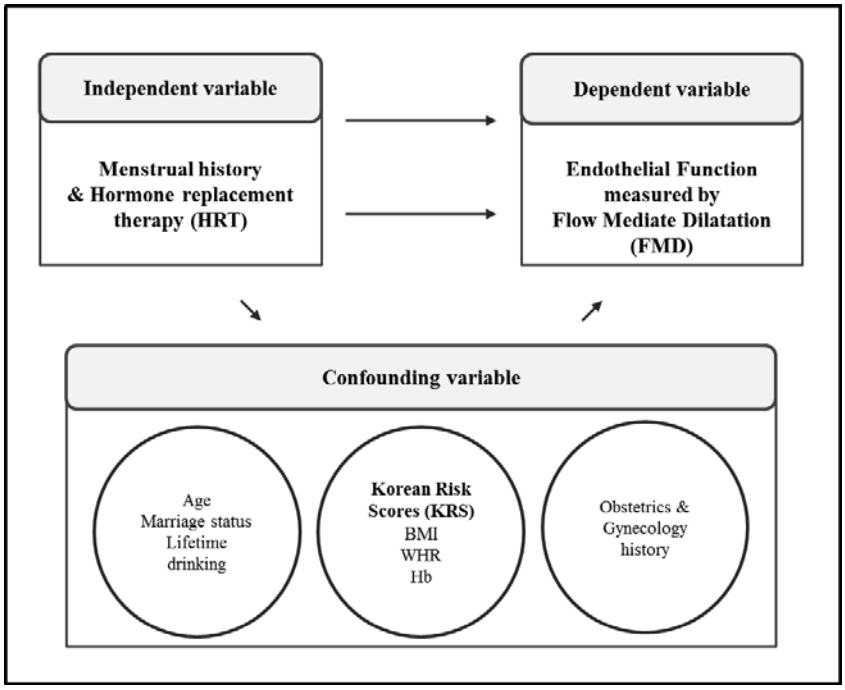

Figure 1. The frame of study

This study was to investigate the effect of HRT among PMW and Time of age at menopause on endothelial function. The vascular endothelial function is assessed by the change rate measured as a Flow-mediate dilatation (FMD) test.

The confounding variables include age, sociological factors, the coronary risk scores for Korean (KRS), anthropometric measurements, menstrual characteristics and Obstetrics & Gynecological history.

2. Study Participants

The Health and Aging Cohort_YangPyeong (HAC_YangPyeong) data, which was designed prospective cohort study to research the prevalence and risk factors developing assessment tools for health, disease, and disability among the elderly in the rural community. At the time of the analysis, this study was used as cross-sectional considered repeated data within the prospective data.

The study target population were women who experienced menopause and got a FMD result living in rural areas (Yangpyeong, Gyeonggi, Republic of Korea). For the calculation of Korean CHD risk scores (KRS), the participants who have missed one of the variables that blood pressure, High-density lipoprotein (HDL), Total cholesterol, smoking status and diabetes history were excluded from the analysis. In addition, by confirming the association with females, the participants who answered all the answers of the obstetrics & gynecological history were selected. Among 3,565 individuals, 2,196 of the women (61.6%) who underwent the FMD test in 2011 or 2013 for baseline or repeat survey, thus 251 adults (mean age; 62.2) included who had no missing in the main questionnaire were selected (Figure 2).

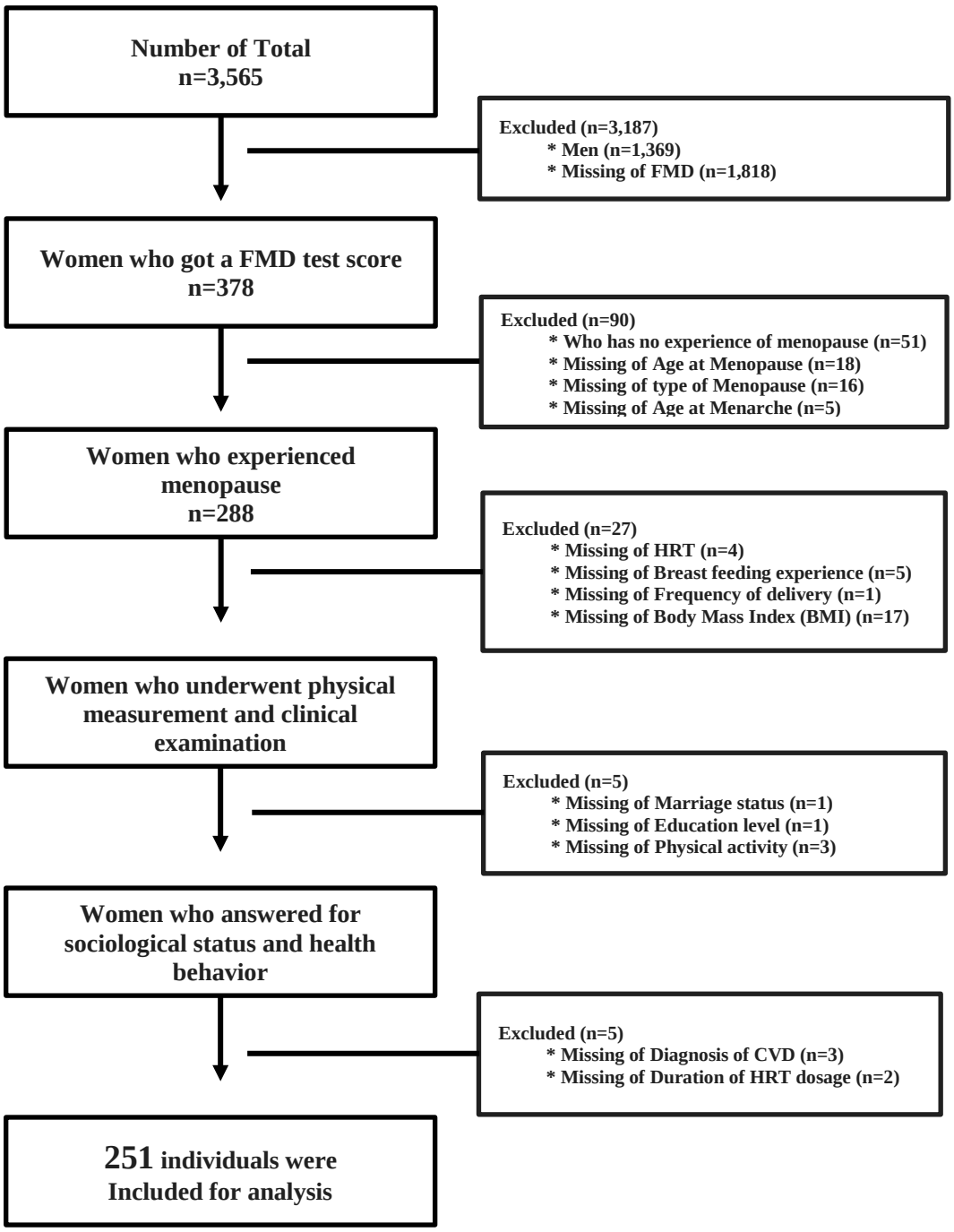

Figure 2. Exclusion criteria for research participants

3. Data Collection

3.1. Survey Questionnaire

Questions that are not likely to change about experienced once in a lifetime, such as “At what age did you have menarche?” was open-ended and asked at the time of the baseline survey. However, questions that could be changed consistently such as “Have you ever been diagnosed with a new disease from a doctor since your last survey?” were reviewed for changes at the last repeated surveys.

3.2. Blood Test Results and Anthropometry Variables

Blood tests which once in each investigation are performed on fasting status. All individuals have undergone tests at repeated survey after the baseline survey, and only once of the twice results were diagnosed if they were included in the reference range. Hemoglobin is relatively likely to change using the results at the time of FMD test.

The changeable anthropometry variable such as height, weight, waist circumference, and hip circumference in the elderly used the results at the time of FMD test. In the case of blood pressure, which can be changed according to condition, time and place at the time of measurement, based on twice in each investigation. The average value of each investigation was calculated and diagnosed when the average value was included in the reference range more than once.

3.3. Measurement of Endothelial Function

Endothelial function was assessed by measuring endothelium-dependent vasodilation using Pulsed Doppler. The vasodilation is calculated by the diameter varying with the degree of vasodilation. After sufficient rest, the baseline diameter in ballast condition is measured. The upper arm is wrapped with a compression pad, the compression band is inflated with a pressure of 250 mmHg for 5 minutes to block blood flow to the upper arm, and the increased blood flow and the diameter of the maximum in the brachial artery are measured while relaxing the compression arm. The FMD was calculated by the percentage of the difference between the diameter of baseline and the diameter of the maximum is divided by the baseline diameter (Corretti et al., 2002; Thijssen et al., 2011).

3.4. Hormone Replacement Therapy (HRT)

“Have you taken hormone medication for postmenopausal treatment?”. The former and the current users were defined as those who experienced HRT and included in the analysis only for those who clearly answered the duration of HRT usage. The subjects who did not receive HRT defined of the duration of HRT usage as 0 month and included in the analysis.

3.5. Operational Definition of Variables (Table 1)

Age is redefined as the age at which the FMD test was performed. The Korean CHD risk scores (KRS) were used to predict the risk of CHD. The KRS is a coronary risk score equation for Koreans considering gender, age, hypertension, HDL, total cholesterol, smoking status and diabetes (Jee et al., 2014).

Hypertension is measured twice in each investigation, it is defined that the average is calculated for each cycle of investigation, in addition, blood sampling such as total cholesterol, HDL and FBS are performed once in a single investigation. The diagnosis was defined as when at least once in the baseline or repeated survey is included in the reference range.

About the reason for menopause, except for natural menopause, menopause due to drugs, uterus or ovary excision was classified as surgical menopause. Menopause was divided into early menopause (under 45 years), normal menopause (46-55 years) and delayed menopause (over 56 years), while Menarche was divided normal menarche (under 16 years) and delayed menarche (over 17 years). Gynecological age was defined as the duration between age at menarche and age at menopause. Age at first pregnancy was defined as the age of 30 years or older, considering that the participants are elderly persons.

Body mass index (BMI) was calculated as weight (kg) / height ^{2} (m) that are measured at the time of the FMD test. BMI is defined that used WHO standard BMI cutoff as normal or underweight (less than 23 kg/m^2), overweight (less than 25 kg/m^2), obesity (equal or over 25 kg/m^2). Abdominal circumference is defined as

abdominal obesity when the female standard exceeds 85cm (Lee et al., 2006). The WHR (Waist-Hip Ratio) is calculated as the ratio of waist to hip measured at the time of FMD test and is classified as a risk group when it exceeds 0.86. Hemoglobin levels are measured at the time of FMD test and defined as anemia if is less than 12 g/dL.

Table 1. Operational definition of variables

Variable	Operational Definition
Age	Age at got a FMD test (as of 2011 or 2013)
FMD (%)	$\frac{(\text{Maximun Diameter} - \text{Baseline Diameter})}{\text{Baseline Diameter}} \times 100$ * Higher is better, Endothelial dysfunction; ≤8
Coronary Risk Scores	The Korean CHD Risk Scores (KRS) for women (Jee et al. 2014)
Blood pressure (mmHg)	JNCⅦ Criteria Normal: SBP<120 , DBP<80 Pre-HTN: 120≤SBP<140, 80≤DBP<90 Stage 1 HTN: 140≤SBP, 90≤DBP<100 Stage 2 HTN: 160≤SBP, 100≤DBP
Total cholesterol (mg/dL)	<160, 160≤ TC <200, 200≤ TC <240, 240≤ TC <280, 280≤
High Density Lipoprotein (mg/dL)	<35, 35≤ HDL <45, 45≤ HDL <50, 50≤ HDL <60, 60≤
Fasting Blood Glucose (mg/dL)	Normal: <126 mg/dL Diabetes mellitus: ≥126 mg/dL
Type of menopause	Natural menopause: menopause due to aging Surgical menopause: menopause due to drugs, uterus or ovary excision
Age at menopause	Early menopause: ≤45 years Normal menopause: 46-55 years Delayed menopause: ≥56 years
Age at menarche	Normal menarche: ≤16 years Delayed menarche: ≥17 years
Gynecological age	Duration between menarche with menopause (= Age at menopause - Age at menarche)
Age at first pregnancy	Pregnancy of young maternal age: <20 years pregnancy of advanced maternal age: ≥30 years
Body Mass Index (kg/m^2)	BMI = weight (kg) / height^2 (m) WHO Asia Pacific criteria Normal or less : <23 kg/m^2, Overweight: <25 kg/m^2, Obesity: ≥25 kg/m^2
Abdominal obesity	Abdominal circumference ≥ 85 cm (Lee et al. 2006)
Waist-Hip Ratio (WHR)	$\frac{\text{Waist circumference}}{\text{Hip circumferece}}$
Hemoglobin (g/dL)	Anemia: <12 Normal: ≥12

4. Statistical Analysis

All variables requiring mathematical computations such as KRS, BMI, WHR, and gynecological age used statistical programs. The general linear model (GLM) procedure was used for the variance comparison and the LSMEANS option was used for the age-adjusted mean. To classify the age effects, both of crude and age-adjusted model probabilities are presented. The final model analysis was a linear regression analysis as a continuous variable using REG procedure. The variable of multiple models was excluded when VIF >10. For the optimal regression equation, the stepwise method of multivariable selection of the REG procedure was used. The significance level for entry (SLE) into regression model is defined 0.15. The final regression equation was dealt outliers and influences defined as when the student residuals do not include -2 to 2. The subjects who are classified into outliers and influences used the REWEIGHT statement of REG procedure rather than the exclusion or imputation method. The reweighted value was defined as 0.8 (when the residual absolute value was between 2 to 3), 0.6 (between 3 to 5), 0.4(between 5 to 7), and 0.05 (over 7). The covariates were selected for a final model consider the effect modification (interaction) between covariate. P-value <0.05 were considered statistically significant. We used statistical program, SAS Enterprise Guide version 9.4 (SAS Institute Inc., North Carolina, USA) to analyze.

Ⅲ. RESULTS

1. General characteristics

The 251 women aged 45 to 88 years who underwent FMD and experienced menopause in the Yangpyeong area's mean age was 62.2 years (mean ± SE, 62.2 ± 0.52). The 207(82.5%) women were married or living together, and about 233(92.8%) had an education level below high school graduation. The mean of the FMD test was 6.9% and 161(64.1%) had vascular endothelial dysfunction. The 43(17.2%) of women were diagnosed with CVD such as hypertension and myocardial infarction. Blood pressure, total cholesterol, HDL, smoking status and diagnosis of diabetes mellitus were categorized for KRS (0.01 ± 0.009). Except for the pre-hypertension group, the 63(25.1%) were hypertensive and the 48(19.1%) had HDL less than 45 mg/dL. Also, 30(11.9%) had a diagnosis of diabetes or more than 126 mg/dL at FBS test. In a survey of health behavior, the 91(36.3%) had experience of lifelong drinking. The 215(85.7%) of the participants experienced natural menopause. The 176(70.1%) experienced normal menarche, and 200(79.7%) experienced normal or late menopause. A mean of gynecological age were 33 years, and 148(59.0%) had more than mean gynecological age. The 57(22.7%) had undergone menopause within 5 years. Experience with lifetime hormone

replacement therapy (HRT), including past and current, was 51(20.3%) in all, and 59(23.5%) of patients who took oral contraceptives. Only 10(4.0%) of subjects was pregnant at an old age. The 168(66.9%) were overweight or over, and 197(78.5%) had abdominal obesity. The 19(7.6%) women had anemia. (Table 2)

Table 2. General characteristics of participants

Variable	N (%) (n=251)	Variable	N (%) (n=251)
Age (yr) *	**62.2 ± 0.52**	**Type of Menopause**	
45-49	12(4.8)	Natural menopause	215(85.7)
50-59	99(39.4)	Surgical menopause	36(14.3)
60-69	95(37.9)	**Age at Menarche (yr) ***	**15.5 ± 0.12**
70-88	45(17.9)	Normal menarche (≤16)	176(70.1)
Marrital status		Delayed menarche (≥17)	75(29.9)
Marriage / Living together	207(82.5)	**Age at menopause (yr) ***	**48.4 ± 0.31**
Seperation / Divorce / Bereavement	44(17.5)	Early menopause (≤45)	51(20.3)
Education level		Normal menopause (46-55)	191(76.1)
Middle school or less	120(47.8)	Late menopause (≥56)	9(3.6)
High school or less	113(45.0)	**Gynecological age (yr) ***	**33.0 ± 0.32**
College or less	10(4.0)	<33	103(41.0)
Graduate school or more	8(3.2)	≥33	148(59.0)
Flow mediated dilatation (FMD, %) *	**6.9 ± 0.43**	**Years since menopause (yr) ***	**13.7 ± 0.60**
Endothelial dysfunction (≤8.0)	161(64.1)	≤5	57(22.7)
Normal (>8.0)	90(35.9)	>5	194(77.3)
Diagnosis of CVD †		**Hormone replacement teraphy (HRT)**	
Before menopause	10(4.0)	None use	200(79.7)
After menopause	33(13.2)	User (Past/Current)	51(20.3)
Korean CHD risk scores (KRS) *	**0.01 ± 0.009**	**Duration of HRT usage (months)**	
≤0.01280	169(67.3)	≤12	29(11.5)
≤0.13330 ‡	82(32.7)	>12	22(8.8)
Hypertension (JNCⅦ)		**Take an oral contraceptive pill**	
None	72(28.7)	None use	192(76.5)
Pre-hypertension	116(42.2)	User (Past/Current)	59(23.5)
Stage 1 hypertension	46(18.3)	**Age at first pregnant ***	**23.7 ± 0.22**
Stage 2 hypertension	17(6.8)	<20	24(9.5)
Total cholesterol (mg/dL)		20-30	217(86.5)
<160	12(4.8)	>30	10(4.0)
160-199	81(32.3)	**Frequency of deliveries ***	**3.1 ± 0.09**
200-239	108(43.0)	≤3	171(68.1)
240-279	41(16.3)	>3	80(31.9)
≥280	9(3.6)	**Breast feeding**	
High density lipoprotein (mg/dL)		No	16(6.4)
<35	6(2.4)	Yes	235(93.6)
35-44	42(16.7)	**Body Mass Index (kg/m^2) ***	**24.9 ± 0.21**
45-49	41(16.3)	Normal weight or less (<23.0)	83(33.1)
50-59	89(35.5)	Over weight (<25.0)	58(23.1)
≥60	73(29.1)	Obesity (≥25.0)	110(43.8)
Smoking		**Abdominal circumference (cm) ***	**86.4 ± 0.52**
Non-smoker	247(98.4)	≤85	106(42.2)
Ever smoker	4(1.6)	>85 (Abdominal obesity)	145(57.8)
Diabetes mellitus		**Waist - Hip ratio (WHR) ***	**0.9 ± 0.004**
No	221(88.1)	≤0.86	54(21.5)
Yes	30(11.9)	>0.86 (Abdominal obesity)	197(78.5)
Alcohol intake		**Hemoglobin (g/dL) ***	**13.2 ± 0.06**
Non-drinker	160(63.8)	<12 (Anemia)	19(7.6)
Drinker (including past drinker)	91(36.3)	≥12	232(92.4)

* Mean ± SE † Cardiovascular disease such as hypertension, myocardial infarction, and angina pectoris ‡ Tertile 3 (≥67%)

2. The association between key variables

2.1. Relevance according to FMD levels

FMD levels were classified as a normal group (> 8) and endothelial dysfunction group (≤ 8). There was no difference in the mean between Korean coronary risk scores. (Figure 3)

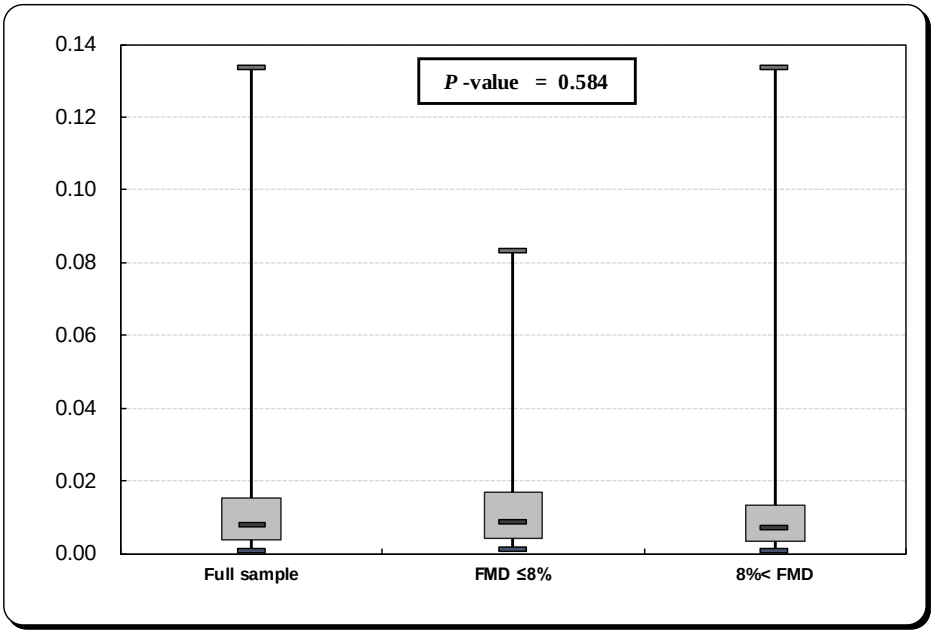

Figure 3. The Korean coronary risk scores for women by FMD levels

The difference in FMD levels with age at menarche, age at menopause and gynecological age was the normal group's time of menarche and menopause was later than endothelial dysfunction group. However, the gynecological age was slightly shorter. The difference between the groups was not significant. (Figure 4)

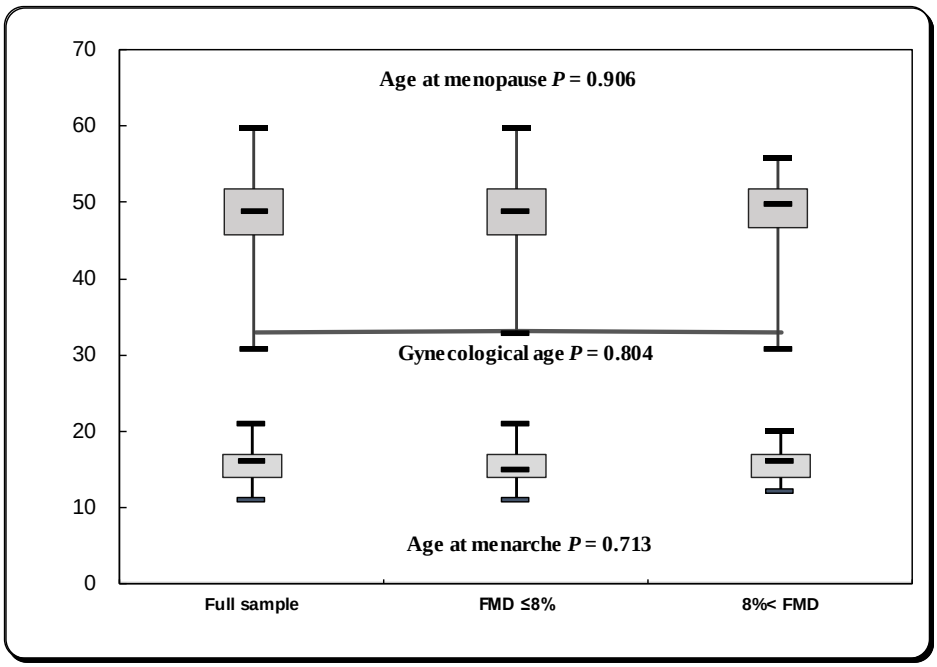

Figure 4. Menstrual characteristics by FMD levels.

2.2. Relevance according to time of age at menopause

Korean coronary risk scores differ according to the time of age at menopause, and there was a significant difference between early or normal menopause with delayed menopause. (Figure 5)

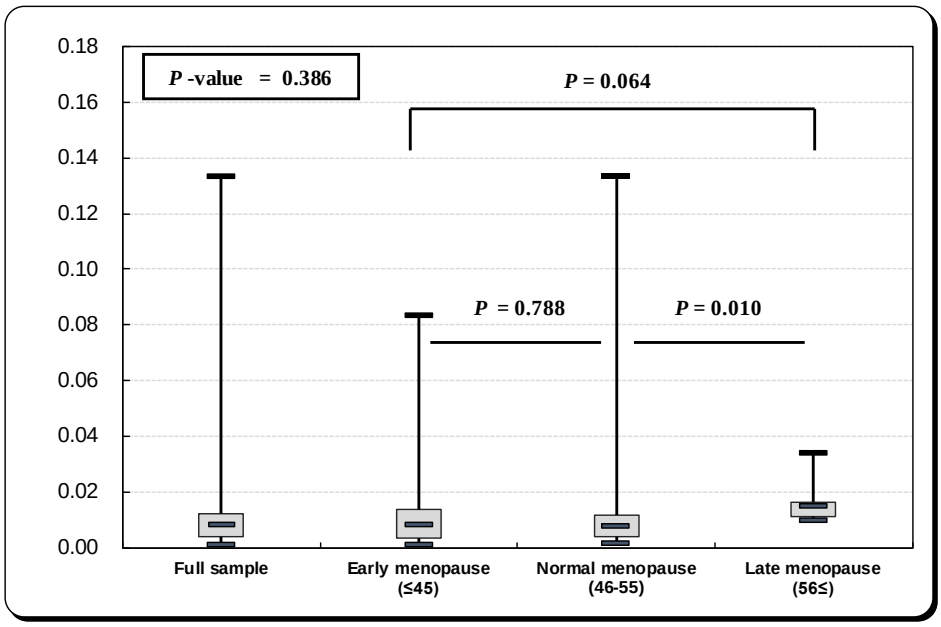

Figure 5. Korean coronary risk scores by time of age at menopause

Depending on the time of age at menopause, the endothelial function dropped immediately after the menopause and the FMD increased slowly with years since menopause, then decreased again. It showed different morphology between the group. (Figure 6)

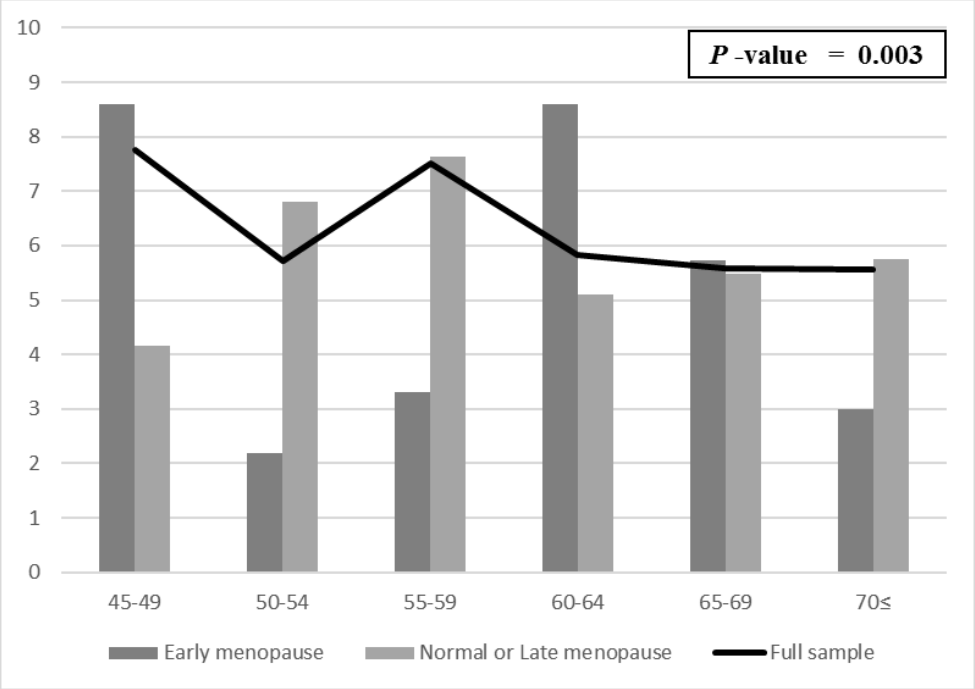

Figure 6. Difference in median of endothelial function with age by time of age at menopause

2.3. Relevance according to Hormone replacement therapy

The endothelial function was significantly decreased in the menopausal period (45 to 50 years) in relation to age and endothelial function according to hormone therapy. There was a tendency for FMD to recover after age 55 in all groups, regardless of hormone therapy, and decreased again after age 60 years. The age-related changes in all groups were similar, however, the differences between the groups according to hormone treatment were statistically significant. (Figure 7)

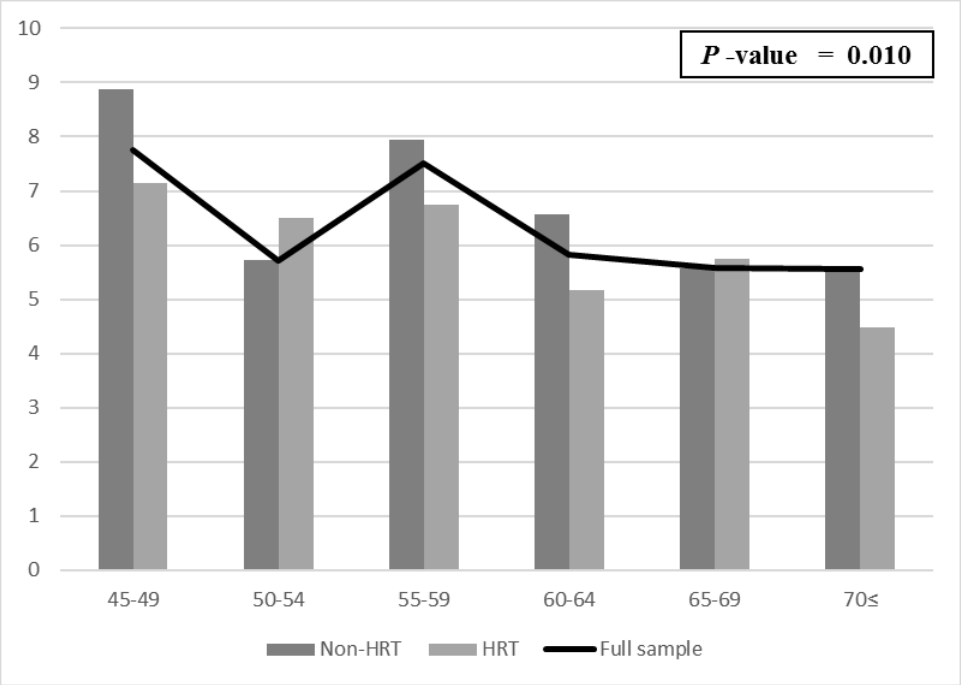

Figure 7. Difference in median of endothelial function with age by HRT usage

The difference of coronary risk scores according to hormone therapy was lowered in the hormone treated group than in the untreated group. This is statistically significant. (Figure 8)

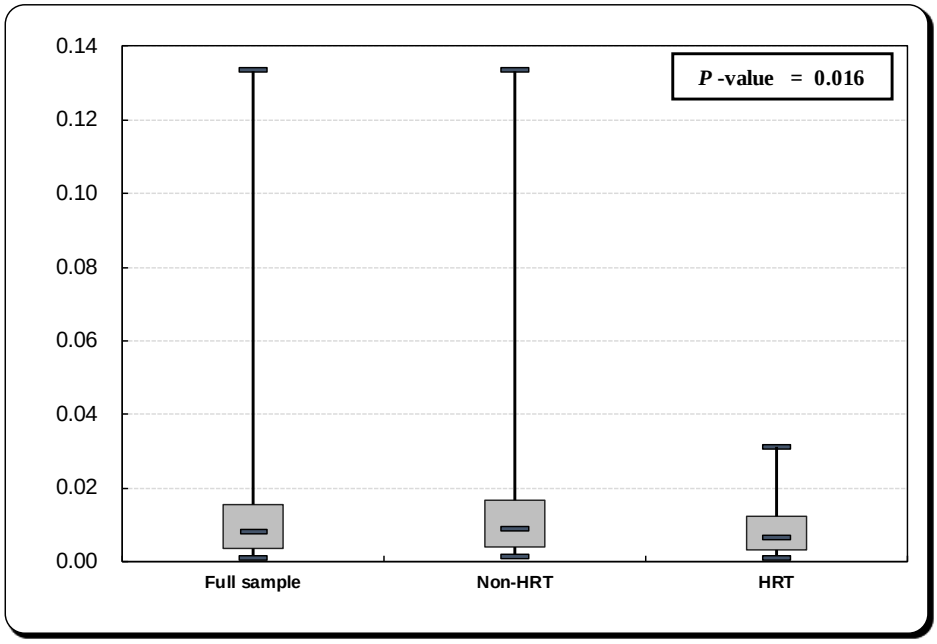

Figure 8. Korean coronary risk scores by HRT usage

3. The mean difference of endothelial function

3.1. The endothelial function comparison with sociological status and health behavior

The FMD tended to decrease with increasing age (crude p = 0.475). The FMD mean indicates women who are living alone had higher FMD than those who were married or living together, moreover, the difference existed in the age-adjusted mean (age adjusted p = 0.024). There was no difference according to the level of education, however, the age-adjusted mean was lower for college graduates or more (age adjusted p = 0.738). At the time of the diagnosis of CVD, diagnosis of CVD at before the menopause group had a higher mean of FMD rather than diagnosis at after the menopause or never diagnosed, however, there was no statistically significant difference (crude p = 0.136, age-adjusted p = 0.263). The FMD mean was not statistically significant in the components for KRS calculation (age, blood pressure, total cholesterol, HDL, smoking status, diabetes mellitus), however, the FMD was lower as the calculated KRS score increased (crude p = 0.044). Alcohol intake (crude p = 0.857, age-adjusted p = 0.555). (Table 3a)

Table 3a. The linear model analysis (GLM) for FMD with sociological status and health behavior

Variable	FMD	Crude *p* value	FMD	Age adjusted *p* value
	Mean ± SE*		Mean †± SE	
FMD (n=251)	6.89 ± 0.43			
Age (yr)				
45-49	7.90 ± 1.98			
50-59	7.63 ± 0.69	0.475	-	-
60-69	6.34 ± 0.71			
70-88	6.17 ± 1.02			
Marrital status				
Marriage / Living together	6.58 ± 0.48	0.117	6.41 ± 0.48	0.024
Seperation / Divorce / Bereavement	8.37 ± 1.03		9.15 ± 1.09	
Education level				
Middle school or less	6.85 ± 0.63		7.25 ± 0.67	
High school or less	6.97 ± 0.65	0.982	6.67 ± 0.67	0.738
College or more	6.67 ± 1.63		5.94 ± 1.68	
Diagnosis of CVD ‡				
None	7.18 ± 0.47		7.13 ± 0.48	
Before menopause	8.07 ± 2.16	0.136	8.01 ± 2.17	0.263
After menopause	4.71 ± 1.19		5.03 ± 1.24	
Korean CHD risk scores (KRS)				
≤0.01280	7.50 ± 0.53	0.044	-	-
≤0.13330 §	5.64 ± 0.75			
Hypertension (JNCⅦ)				
None	7.40 ± 0.81		7.11 ± 0.84	
Pre-hypertension	7.04 ± 0.64	0.605	7.13 ± 0.64	0.680
Stage 1 hypertension	5.69 ± 1.02		5.77 ± 1.02	
Stage 2 hypertension	6.94 ± 1.67		7.41 ± 1.70	
Total cholesterol (mg/dL)				
<160	7.44 ± 1.99		7.20 ± 1.99	
160-199	7.69 ± 0.77		7.69 ± 0.76	
200-239	6.45 ± 0.66	0.598	6.47 ± 0.66	0.653
240-279	6.84 ± 1.08		6.83 ± 1.07	
≥280	4.42 ± 2.30		4.65 ± 2.30	
High density lipoprotein (mg/dL)				
<35	9.64 ± 2.80		9.78 ± 2.80	
35-44	6.37 ± 1.06		6.41 ± 1.06	
45-49	7.86 ± 1.07	0.420	7.86 ± 1.07	0.412
50-59	6.03 ± 0.73		6.03 ± 0.73	
≥60	7.47 ± 0.80		7.44 ± 0.80	
Smoking				
Non-smoker	6.83 ± 0.44	0.232	6.82 ± 0.44	0.217
Ever smoker	10.97 ± 3.43		11.09 ± 3.42	
Diabetes mellitus				
No	6.83 ± 0.46	0.680	6.80 ± 0.46	0.555
Yes	7.38 ± 1.26		7.59 ± 1.26	
Alcohol intake				
Non-drinker	6.83 ± 0.54	0.857	6.90 ± 0.55	0.970
Drinker (including past drinker)	7.00 ± 0.72		6.87 ± 0.73	

* Standard Error (SE) † Age adjusted mean ‡ Cardiovascular disease such as hypertension, myocardial infarction, and angina pectoris § Tertile 3 (≥67%)

3.2. The endothelial function comparison with Obstetrics & gynecological characteristics and anthropometry

The mean FMD of postmenopausal women according to their gynecological history and anthropometry was compared. The mean FMD in the women who experienced surgical menopause was lower than that compared with natural menopause, and the difference was similar after age-adjusted model (crude p = 0.337, age-adjusted p = 0.261). The age-adjusted mean was 0.95%p higher in delayed menopause (over 17 years) compared with the normal menopause. There was no significant difference between the two groups (crude p = 0.486, age-adjusted p = 0.323). The years since menopause being less than 5 years, FMD was 2.7 higher (crude p = 0.009, age-adjusted p = 0.031) than more of 5 years group. Compared with the untreated, postmenopausal hormone replacement therapy was 2.3%p higher (p = 0.031), and 2.7%p higher after age-adjusted (p = 0.014). However, there was no difference of age-adjusted FMD mean according to lifetime oral contraceptive use (p = 0.329), and 1.3%p higher when the frequency of delivery was below 3 (p = 0.245). Also, age-adjusted FMD mean of breastfeeding were 1.0 lower in the women who experienced breastfed (p = 0.575). The age-adjusted FMD mean compared to the first pregnancy age was 3.4%p lower in advanced maternal age group (≥30) than normal group (< 30 years) (age-adjusted p = 0.121).

FMD was highest when body mass index (BMI) was normal, and lowest when overweight (age adjusted p = 0.426). In the case of abdominal obesity confirmed only by abdominal circumference, it was 0.6%p lower than normal group (age-

adjusted p = 0.455). The WHR based on the ratio of abdominal and hip circumference was 2.8%p lower than the normal group (age-adjusted p = 0.011). The women who have anemia were 2.8%p lower than normal group (crude p = 0.145, age-adjusted p = 0.090), however, there was no significant difference. (Table 3b)

Table 3b. The Linear model analysis (GLM) for FMD with Obstetrics & gynecological characteristics and anthropometry

Variable	FMD	Crude *p* value	FMD	Age adjusted *p* value
	Mean ± SE*		Mean †± SE	
FMD (n=251)	6.89 ± 0.43			
Type of Menopause				
Natural menopause	7.06 ±0.47	0.337	7.09 ±0.47	0.261
Surgical menopause	5.87 ±1.14		5.69 ±1.15	
Age at Menarche (yr)				
Normal menarche (≤16)	6.69 ±0.52	0.486	6.61 ±0.52	0.323
Delayed menarche (≥17)	7.36 ±0.79		7.56 ±0.80	
Age at menopause (yr)				
Early menopause (≤45)	4.33 ± 0.95	0.003	4.26 ± 0.94	0.002
Normal or late menopause (>46)	7.54 ± 0.48		7.56 ± 0.48	
Gynecological age (yr)				
<33	7.06 ± 0.68	0.740	7.18 ± 0.68	0.588
≥33	6.77 ± 0.57		6.69 ± 0.57	
Years since menopause (yr)				
≤5	8.97 ± 0.90	0.009	8.98 ± 1.05	0.031
>5	6.28 ± 0.49		6.28 ± 0.51	
Hormone replacement teraphy (HRT)				
None use	7.36 ± 0.48	0.031	7.43 ± 0.48	0.014
User (Past/Current)	5.03 ± 0.95		4.76 ± 0.96	
Duration of HRT usage (months)				
None use	7.36 ± 0.48	0.063	7.43 ± 0.48	0.034
≤12	5.81 ± 1.27		5.48 ± 1.27	
>12	4.02 ± 1.45		3.82 ± 1.45	
Take an oral contraceptive pill				
None use	7.16 ± 0.50	0.273	7.13 ± 0.50	0.329
User (Past/Current)	6.03 ± 0.89		6.12 ± 0.89	
Frequency of deliveries				
≤3	7.41 ± 0.52	0.078	7.30 ± 0.56	0.245
>3	5.77 ± 0.76		6.02 ± 0.87	
Breast feeding				
No	6.92 ± 0.45	0.770	6.96 ± 0.45	0.575
Yes	6.40 ± 1.72		5.94 ± 1.74	
Age at first pregnant				
≤30	7.02 ± 0.44	0.131	7.03 ± 0.44	0.121
>30	3.68 ± 2.17		3.59 ± 2.16	
Body Mass Index (kg/m^2)				
Normal weight or less (<23.0)	7.40 ± 0.75		7.48 ± 0.75	
Over weight (<25.0)	5.93 ± 0.90	0.446	5.95 ± 0.90	0.426
Obesity (≥25.0)	7.01 ± 0.66		6.94 ± 0.66	
Abdominal circumference (cm)				
Normal	7.36 ± 0.67	0.353	7.27 ± 0.67	0.455
Abdominal obesity	6.55 ± 0.57		6.61 ± 0.57	
Waist - Hip ratio (WHR)				
Normal	9.24 ± 0.92	0.004	9.07 ± 0.96	0.011
Abdominal obesity	6.25 ± 0.48		6.29 ± 0.49	
Hemoglobin (g/dL)				
Normal	9.10 ± 1.57	0.145	9.48 ± 1.58	0.090
Anemia	6.71 ± 0.45		6.68 ± 0.45	

* Standard Error (SE) † Age adjusted mean

4. The frequency analysis according to HRT usage

4.1. The HRT usage comparison with sociological status and health behavior

The elderly group mostly did not receive hormone treatment and the distribution was similar in all age group (crude p = 0.002). There was no difference of frequency in marital status (crude p = 0.426, age-adjusted p = 0.846) and education levels (crude p = 0.570, age-adjusted p = 0.877). Most of the diagnosis of CVD before the menopause women did not receive HRT, and there was no difference in HRT along with diagnosis of CVD after the menopause (crude p = 0.711, age-adjusted p = 0.407). The KRS was higher in untreated group (crude p = 0.059), per contra no significant correlation in KRS components such as blood pressure (crude p = 0.343, age adjusted p = 0.631), total cholesterol (crude p = 0.659, age adjusted p = 0.666), HDL (crude p = 0.571, age adjusted p = 0.608), smoking status (crude p = 0.815, age adjusted p = 0.762) and diabetes mellitus (crude p = 0.313, age adjusted p = 0.484). Lifetime drinking experience was higher in the untreated group (crude p = 0.144, age adjusted p = 0.055). (Table 4a)

Table 4a. The HRT usage comparison with sociological status and health behavior

Variable	N (%)		Crude *p* value	Age adjusted *p* value
	HRT Non-user	HRT User		
N	200(79.7)	51(20.3)		
FMD *	7.43 ± 0.48	4.76 ± 0.96	-	0.014
Age (yr)				
45-49	6(3.0)	6(11.8)	0.002	-
50-59	79(39.5)	20(39.2)		
60-69	72(36.0)	23(45.1)		
70-88	43(21.5)	2(3.9)		
Marrital status				
Marriage / Living together	163(81.5)	44(86.3)	0.426	0.846
Seperation / Divorce / Bereavement	37(18.5)	7(13.7)		
Education level				
Middle school or less	99(49.5)	21(41.2)	0.570	0.877
High school or less	87(43.5)	26(51.0)		
College or more	14(7.0)	4(7.8)		
Diagnosis of CVD †				
None	165(82.5)	43(84.3)	0.711	0.407
Before menopause	9(4.5)	1(2.0)		
After menopause	26(13.0)	7(13.7)		
Korean CHD risk scores (KRS)				
≤0.01280	129(64.5)	40(78.4)	0.059	-
≤0.13330 ‡	71(35.5)	11(21.6)		
Hypertension (JNCⅦ)				
None	54(27.0)	18(35.3)	0.343	0.631
Pre-hypertension	91(45.5)	25(49.0)		
Stage 1 hypertension	40(20.0)	6(11.8)		
Stage 2 hypertension	15(7.5)	2(3.9)		
Total cholesterol (mg/dL)				
<160	8(4.0)	4(7.8)	0.659	0.666
160-199	65(32.5)	16(31.4)		
200-239	88(44.0)	20(39.2)		
240-279	33(16.5)	8(15.7)		
≥280	6(3.0)	3(5.9)		
High density lipoprotein (mg/dL)				
<35	6(3.0)	0(0.0)	0.571	0.608
35-44	35(17.5)	7(13.7)		
45-49	30(15.0)	11(21.6)		
50-59	71(35.2)	18(35.3)		
≥60	58(29.0)	15(29.4)		
Smoking				
Non-smoker	197(98.5)	50(98.0)	0.815	0.762
Ever smoker	3(1.5)	1(2.0)		
Diabetes mellitus				
No	174(87.0)	47(92.2)	0.313	0.484
Yes	26(13.0)	4(7.8)		
Alcohol intake				
Non-drinker	123(61.5)	37(72.6)	0.144	0.055
Drinker (including past drinker)	77(38.5)	14(27.5)		

* Age adjusted mean ± SE † Cardiovascular diseases such as hypertension, myocardial infarction, and angina pectoris ‡ Tertile 3 (≥67%)

4.2.The HRT usage comparison with obstetrics & gynecological characteristics and anthropometry

The 17(33.3%) women of those who received HRT were experienced surgical menopause, and most of the women who experienced menopause due to aging did not receive HRT (crude p <0.0001, age-adjusted p <0.0001). Women who experienced normal age at menarche (crude p = 0.148, age-adjusted p = 0.334) or normal or late age at menopause (crude p = 0.306, age-adjusted p = 0.366) were more likely to receive HRT, no one received HRT who experienced delayed menopause (46 years or more). There was no difference in frequency of HRT according to gynecological age (crude p = 0.734, age-adjusted p = 0.461) and years since menopause (crude p = 0.367, age-adjusted p = 0.430). The HRT usage was positively related to oral contraceptive pills (crude p = 0.064, age-adjusted p = 0.034). Relatively who experienced deliveries less than 3 babies (crude p = 0.005, age-adjusted p = 0.116), and did not experienced breastfeed (crude p = 0.873, age-adjusted p = 0.509) was more received HRT. There was no difference in HRT according to the first age at pregnancy (crude p = 0.440, age-adjusted p = 0.478).

There was no association with hormone therapy according to BMI (crude p = 0.677, age-adjusted p = 0.681). Women who has abnormal range of waist circumference (crude p = 0.273, age adjusted p = 0.451) and WHR (crude p = 0.021, age adjusted p = 0.112) more received HRT. There was no difference according to Hb (crude p = 0.934, age adjusted p = 0.622). (Table 4b)

Table 4b. The HRT usage comparison with Obstetrics & gynecological characteristics and anthropometry

Variable	N (%)		Crude *p* value	Age adjusted *p* value
	HRT Non-User	HRT user		
N	200(79.7)	51(20.3)		
Type of Menopause				
Natural menopause	181(90.5)	34(66.7)	<0.0001	<0.0001
Surgical menopause	19(9.5)	17(33.3)		
Age at Menarche (yr)				
Normal menarche (≤16)	136(68.0)	40(78.4)	0.148	0.334
Delayed menarche (≥17)	64(32.0)	11(21.6)		
Age at menopause (yr)				
Early menopause (≤45)	38(19.0)	13(25.5)	0.306	0.366
Normal or late menopause (>46)	162(81.0)	38(74.5)		
Gynecological age (yr)				
<33	81(40.5)	22(43.1)	0.734	0.461
≥33	119(59.5)	29(56.9)		
Years since menopause (yr)				
≤5	43(21.5)	14(27.5)	0.367	0.430
>5	157(78.5)	37(72.6)		
Take an oral contraceptive pill				
None use	158(79.0)	34(66.7)	0.064	0.034
User (Past/Current)	42(21.0)	17(33.3)		
Frequency of deliveries				
≤3	128(64.0)	43(84.3)	0.005	0.116
>3	72(36.0)	8(15.7)		
Breast feeding				
No	13(6.5)	3(5.9)	0.873	0.509
Yes	187(93.5)	48(94.1)		
Age at first pregnant				
≤30	193(96.5)	48(94.1)	0.440	0.478
>30	7(3.5)	3(5.9)		
Body Mass Index (kg/m^2)				
Normal weight or less (<23.0)	68(34.0)	15(29.4)		
Over weight (<25.0)	44(22.0)	14(27.5)	0.677	0.681
Obesity (≥25.0)	88(44.0)	22(43.1)		
Abdominal circumference (cm)				
Normal	81(40.5)	25(49.0)	0.273	0.451
Abdominal obesity	119(59.5)	26(51.0)		
Waist - Hip ratio (WHR)				
Normal	37(18.5)	17(33.3)	0.021	0.112
Abdominal obesity	163(81.5)	34(66.7)		
Hemoglobin (g/dL)				
Normal	15(7.5)	4(7.8)	0.934	0.622
Anemia	185(92.5)	47(92.2)		

5. The frequency analysis according to the time of age at menopause

5.1. The time of age at menopause comparison with sociological status and health behavior

Women who had experienced early menopause was less of age-adjusted FMD mean 3.3%p (age adjusted p = 0.002), compared to women with normal or late menopause. The rate of early menopause was highest in middle-aged (<50) women (crude p = 0.008). Women who are married or living together relatively experienced normal menopause (crude p = 0.398, age-adjusted p = 0.228). Besides, Education levels had positive relation to early menopause (crude p = 0.225, age-adjusted p = 0.305). There was an inverse correlation between KRS and age at menopause (crude p = 0.436), the KRS components such as blood pressure (crude p = 0.364, age-adjusted p = 0.323), total cholesterol (crude p = 0.336, age-adjusted p = 0.381), HDL (crude p = 0.426, age-adjusted p = 0.440), smoking status (crude p = 0.138, age-adjusted p = 0.133), and diabetes mellitus (crude p = 0.598, age-adjusted p = 0.662) was a weak association between time of age at menopause, however there was no statistically significance. Lifetime drinking experience was higher in women who experienced early menopause (crude p = 0.415, age-adjusted p = 0.480) (Table 5a).

Table 5a. The time of age at menopause comparison with sociological status and health behavior

Variable	N (%)		Crude *p* value	Age adjusted *p* value
	Early menopause	Normal or Late menopause		
N	51(20.3)	200(79.7)		
FMD *	4.26 ± 0.94	7.56 ± 0.48	-	0.002
Age (yr)				
45-49	7(13.7)	5(2.5)	0.008	-
50-59	16(31.4)	83(41.5)		
60-69	19(37.3)	76(38.0)		
70-88	9(17.7)	36(18.0)		
Marrital status				
Marriage / Living together	40(78.4)	167(83.5)	0.398	0.228
Seperation / Divorce / Bereavement	11(21.6)	33(16.5)		
Education level				
Middle school or less	19(37.3)	101(50.5)	0.225	0.305
High school or less	27(52.9)	86(43.0)		
College or more	5(9.8)	13(6.5)		
Diagnosis of CVD †				
None	40(78.4)	168(84.0)	0.046	0.021
Before menopause	0(0.0)	10(5.0)		
After menopause	11(21.6)	22(11.0)		
Korean CHD risk scores (KRS)				
≤0.01280	32(62.8)	137(68.5)	0.436	-
≤0.13330 ‡	19(37.3)	63(31.5)		
Hypertension (JNCⅦ)				
None	16(31.4)	56(28.0)	0.364	0.323
Pre-hypertension	20(39.2)	96(48.0)		
Stage 1 hypertension	9(17.7)	37(18.5)		
Stage 2 hypertension	6(11.8)	11(5.5)		
Total cholesterol (mg/dL)				
<160	2(3.9)	10(5.0)	0.336	0.381
160-199	12(23.5)	69(34.5)		
200-239	22(43.1)	86(43.0)		
240-279	12(23.5)	29(14.5)		
≥280	3(5.9)	6(3.0)		
High density lipoprotein (mg/dL)				
<35	0(0.0)	6(3.0)	0.426	0.440
35-44	9(17.7)	33(16.5)		
45-49	5(9.8)	36(18.0)		
50-59	20(39.2)	69(34.5)		
≥60	17(33.3)	56(28.0)		
Smoking				
Non-smoker	49(96.1)	198(99.0)	0.138	0.133
Ever smoker	2(3.9)	2(1.0)		
Diabetes mellitus				
No	46(90.2)	175(87.5)	0.598	0.662
Yes	5(9.8)	25(12.5)		
Alcohol intake				
Non-drinker	30(58.8)	130(65.0)	0.415	0.480
Drinker (including past drinker)	21(41.2)	70(35.0)		

* Age adjusted mean ± SE † Cardiovascular diseases such as hypertension, myocardial infarction, and angina pectoris ‡ Tertile 3 (≥67%)

5.2. The time of age at menopause comparison with Obstetrics & gynecological characteristics and anthropometry

The 20(39.2%) women of those who experienced early menopause as a surgical menopause had a significant difference from normal menopause (crude p <0.0001, age-adjusted p <0.0001). The age at menarche and menopause were positively correlated (crude p = 0.148, age-adjusted p = 0.185), and 98% of women experienced early menopause have a gynecological age less than a mean (crude p <0.0001, age-adjusted p <0.0001). Most early menopause women had years since menopause of more than 5 years (crude p = 0.004, age-adjusted p <0.0001). There was no significant relation between oral contraceptive use (crude p = 0.997, age-adjusted p = 0.943) and the frequency of deliveries (crude p = 0.932, age-adjusted p = 0.692). Furthermore, the most women with breastfeeding have normal or later of age at menopause (crude p = 0.002, age-adjusted p = 0.003). Women who experienced first pregnancy at the old age were relatively fast in age at menopause (crude p = 0.115, age-adjusted p = 0.120).

In a correlation with anthropometry and clinical examination, there was no difference in the time of age at menopause according to BMI (crude p = 0.994, age adjusted p = 0.983). The waist circumference (crude p = 0.644, age adjusted p = 0.717), WHR (crude p = 0.696, age adjusted p = 0.864), Hb (crude p = 0.5010, age adjusted p = 0.426) were not significantly associated with time of age at menopause. (Table 5b)

Table 5b. The time of age at menopause comparison with Obstetrics & gynecological characteristics and anthropometry

Variable	N (%)		Crude *p* value	Age adjusted *p* value
	Early menopause	Normal or Late menopause		
N	51(20.3)	200(79.7)		
Type of Menopause				
Natural menopause	31(60.8)	184(92.0)	<0.0001	<0.0001
Surgical menopause	20(39.2)	16(8.0)		
Age at Menarche (yr)				
Normal menarche (≤16)	40(78.4)	136(68.0)	0.148	0.185
Delayed menarche (≥17)	11(21.6)	64(32.0)		
Gynecological age (yr)				
<33	50(98.0)	53(26.5)	<0.0001	<0.0001
≥33	1(2.0)	147(73.5)		
Years since menopause (yr)				
≤5	4(7.8)	53(26.5)	0.004	<0.0001
>5	47(92.2)	147(73.5)		
Duration of HRT usage (months)				
None use	38(74.5)	162(81.0)	0.306	0.366
User (Past/Current)	13(25.5)	38(19.0)		
Duration of HRT dosage (months)				
None use	38(74.5)	162(81.0)		
≤12	5(9.8)	24(12.0)	0.145	0.157
>12	8(15.7)	14(7.0)		
Take an oral contraceptive pill				
None use	39(76.5)	153(76.5)	0.997	0.943
User (Past/Current)	12(23.5)	47(23.5)		
Frequency of deliveries				
≤3	35(28.6)	136(68.0)	0.932	0.692
>3	16(31.4)	64(32.0)		
Breast feeding				
No	8(15.7)	8(4.0)	0.002	0.003
Yes	43(84.3)	192(96.0)		
Age at first pregnant				
≤30	47(92.2)	194(97.0)	0.115	0.120
>30	4(7.8)	6(3.0)		
Body Mass Index (kg/m^2)				
Normal weight or less (<23.0)	17(33.3)	66(33.0)		
Over weight (<25.0)	12(23.5)	46(23.0)	0.994	0.983
Obesity (≥25.0)	22(43.1)	88(44.0)		
Abdominal circumference (cm)				
Normal	23(45.1)	83(41.5)	0.644	0.717
Abdominal obesity	28(54.9)	117(58..5)		
Waist - Hip ratio (WHR)				
Normal	12(23.5)	42(21.0)	0.696	0.864
Abdominal obesity	39(76.5)	158(79.0)		
Hemoglobin (g/dL)				
Normal	5(9.8)	14(7.0)	0.501	0.426
Anemia	46(90.2)	186(93.0)		

6. The multiple linear regression analysis of FMD with HRT

6.1. The linear regression analysis between FMD and HRT usage

To confirm the correlation of HRT according to the adjusted variable in the linear regression analysis, the parameters were sequentially corrected for 5 models. The KRS equation is calculated using age, therefore age was excluded from the regression model.

In unadjusted model was a simple relation between FMD and HRT that was shown 2.3%p lower in women who experienced HRT ($p = 0.031$). In the KRS - adjusted model, the frequency of FMD in the group with HRT was 2.6%p lower, which was stronger ($p = 0.015$). FMD was 2.1%p lower in the highest KRS group ($p = 0.021$).

The model 1 adjusted sociological and health behavior. Furthermore, it excluded the education levels and moderate physical activity, which were not related to previous analysis. The FMD and HRT still had an inversely correlation and directionality were similar with the previous model ($p = 0.015$). Unusually, the living alone women have higher FMD compared with married or living together ($p = 0.029$). However, alcohol intake was not significantly associated with FMD ($p = 0.660$).

In a model 2, which was adjusted obstetrics & gynecological history, thereby the explanatory power was increased (adjusted R^2; 11.5%). HRT was more strongly associated with its directionality and FMD was 2.8%p lower in women who

experienced HRT (p = 0.012). After adjusted OB & GY history, the effect of KRS was weakened (p = 0.077), and the difference in marital status increased (p = 0.010). There was no significant correlation between the type of menopause (p = 0.645). However, FMD was decreased, women who have an early age at menopause (p=0.0005) or a gynecological age (p = 0.005) longer than mean, which is strongly related than HRT. Although not statistically significant, the frequency of deliveries (p = 0.076), oral contraceptive use (p = 0.664), the first age at pregnancy (p = 0.141) and breastfeeding experience (p = 0.991) was showed inverse relation.

The anthropometry results were adjusted for model 3. HRT was still closely related to FMD, after the adjusted various variables (p = 0.006). The effect of reduced KRS in model 2 was not statistically related, however, showed a tendency to decrease as increasing the risk scores for coronary heart disease. The history of OB & GY, which showed inverse relation, tended to weaken while still statistically significant. Especially, time of age at menopause (p = 0.0007) and gynecological age (p = 0.015) were strongly related. Although not statistically significant, FMD was a positive correlation with BMI, and decreasing in higher abdominal obesity defined by WHR (p = 0.024) or anemia (p = 0.066).

The model 4 was adjusted for diagnosis of cardiovascular diseases such as hypertension and myocardial infarction before the menopause, there was no significant difference in the effect of HRT on FMD (p = 0.702). (Table 6a)

Table 6a. The multiple linear regression between endothelial function (FMD) and HRT usage

Variable	Unadjusted		KRS adjusted		Model 1		Model 2		Model 3	
	β	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value
Model fit										
R^2 (%)	1.9	0.031	4.0	0.007	5.8	0.005	16.1	<0.0001	19.3	<0.0001
Adjusted R^2 (%)	1.5		3.2		4.3		11.5		13.0	
Hormone replacement teraphy (HRT)										
User (Past/Current)	-2.32	0.031	-2.62	0.015	-2.62	0.015	-2.78	0.012	-3.05	0.006
Korean coronary risk scores (KRS)										
> 0.01280 *			-2.13	0.021	-2.70	0.005	-1.80	0.077	-1.77	0.082
Marrital status										
Seperation / Divorce / Bereavement					2.55	0.029	3.05	0.010	3.07	0.009
Alcohol intake										
Drinker (including past drinker)					-0.39	0.660	-0.71	0.424	-1.03	0.251
Type of Menopause										
Surgical menopause							0.62	0.645	0.41	0.762
Age at Menarche (yr)										
Delayed menarche (≥17)							0.26	0.789	0.18	0.852
Age at menopause (yr)										
Early menopause (≤45)							-4.87	0.0005	-4.72	0.0007
Gynecological age (yr)										
≥33							-3.16	0.005	-2.76	0.015
Years since menopause (yr)										
>5							-2.45	0.034	-1.87	0.107
Take an oral contraceptive pill										
User (Past/Current)							-0.44	0.664	-0.53	0.612
Frequency of deliveries										
> 3							-1.82	0.076	-1.69	0.105
Breast feeding										
Yes							-0.02	0.991	-0.21	0.908
Age at first pregnant										
>30							-3.23	0.141	-3.11	0.156
Body Mass Index (kg/m^2)										
Over weight (<25.0)									0.08	0.945
Obesity (≥25.0)									1.12	0.260
Waist - Hip ratio (WHR)										
Abdominal obesity									-2.47	0.024
Hemoglobin (g/dL)										
Anemia									-3.03	0.066
Diagnosis of CVD† before menopause										
Yes									0.82	0.702

* Tertile 3 (≥67%) † Cardiovascular disease such as hypertension, myocardial infarction

6.2.The linear regression analysis between FMD and duration of HRT usage

The multiple linear regression analysis was performed to determine whether there was a change in outcome according to the duration of the hormone treatment. All regression analysis models were applied in the same order as the analysis of hormone treatment use.

In the unadjusted model, compared with women who did not receive HRT, women who received HRT for one year or less has 1.55%p lower ($p = 0.252$) and women who received HRT greater than 1 year has 3.34%p lower ($p = 0.030$).

In the KRS adjusted model, women who have a duration of HRT greater than 1 year ($p = 0.016$) were closely related after adjusted for coronary risk scores for Korean ($p = 0.020$).

In the model 1, the FMD of the separated/divorced / bereavement women ($p = 0.025$) was 2.62%p higher than the women who are married and living together, and the women who received HRT for more than 12 months ($p = 0.012$) were 3.85%p lower than the women who did not receive HRT. The FMD was lower as the coronary risk scores for Korean was higher ($p = 0.004$).

In the model 2, the FMD in women who had experienced HRT for greater than 1 year ($p = 0.012$), who with KRS top 33% ($p = 0.070$) and who were separated / divorced / bereavement ($p = 0.008$) had a stronger correlation than in previous models. The FMD among women who experienced early menopause ($p = 0.0006$) was 4.8%p lower than normal or late menopause women, and 3.18 lower among

women who got gynecological age above average (p = 0.005). However, there were no significant associations between types of menopause (p = 0.616) and age at menarche (p = 0.772). In addition, the women over 5 years since (p = 0.037) menopause was 2.42%p lower, on the other hand, no significant relationship was found between oral contraceptive use (p = 0.651), frequency of deliveries (p = 0.072), and the first age at pregnant (p = 0.128).

In the model 3, there was no significant difference in women who had HRT of 12 months or less (p = 0.049), however there was a faintly significant association in the final model. Women who experienced treatment for more than 1 year (p = 0.025) were 3.48%p lower and who with the highest KRS top of 33% (p = 0.080) and those who were not living together after marriage (p = 0.009) had a significant impact of FMD changes. Time of age at menopause (p = 0.0007) and gynecological age (p = 0.015) were still significantly associated, and FMD among women who are abdominal obesity based on WHR (p = 0.030) was 2.4%p lower than normal group. The FMD of women with anemia (p = 0.077) was 2.94%p lower. The years since menopause, which showed a significant correlation in the previous model, was not statistically significant in this model (p = 0.107). In addition, there were no significant associations between FMD and lifetime drinking behavior (p = 0.253), type of menopause (p = 0.745), age at menarche (p = 0.843), oral contraceptive use (p = 0.609), frequency of deliveries (p = 0.104), breastfeeding (p = 0.899), age at first pregnancy (p = 0.150), BMI (p = overweight; p = 0.919, obesity; p = 0.267) and diagnosis of CVD before menopause (p = 0.689). (Table 6b)

Table 6b. The multiple linear regression between endothelial function (FMD) and duration of HRT usage

Variable	Unadjusted		KRS adjusted		Model 1		Model 2		Model 3	
	β	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value
Model fit										
R^2 (%)	2.2	0.063	4.3	0.012	6.3	0.007	16.5	<0.0001	19.3	<0.0001
Adjusted R^2 (%)	1.4		3.2		4.4		11.5		12.7	
Duration of HRT usage (months)										
≤12	-1.55	0.252	-1.80	0.183	-1.70	0.208	-1.97	0.145	-2.72	0.049
>12	-3.34	0.030	-3.71	0.016	-3.85	0.012	-3.89	0.012	-3.48	0.025
Korean coronary risk scores (KRS)										
> 0.01280 *			-2.15	0.020	-2.74	0.004	-1.84	0.070	-1.78	0.080
Marrital status										
Seperation / Divorce / Bereavement					2.62	0.025	3.12	0.008	3.11	0.009
Alcohol intake										
Drinker (including past drinker)					-0.40	0.652	-0.72	0.419	-1.03	0.253
Type of Menopause										
Surgical menopause							0.68	0.616	0.44	0.745
Age at Menarche (yr)										
Delayed menarche (≥17)							0.28	0.772	0.19	0.843
Age at menopause (yr)										
Early menopause (≤45)							-4.80	0.0006	-4.69	0.0007
Gynecological age (yr)										
≥33							-3.18	0.005	-2.78	0.015
Years since menopause (yr)										
>5							-2.42	0.037	-1.88	0.107
Take an oral contraceptive pill										
User (Past/Current)							-0.46	0.651	-0.54	0.609
Frequency of deliveries										
>3							-1.85	0.072	-1.70	0.104
Breast feeding										
Yes							-0.10	0.957	-0.23	0.899
Age at first pregnant										
>30							-3.35	0.128	-3.17	0.150
Body Mass Index (kg/m^2)										
Over weight (<25.0)									0.12	0.919
Obesity (≥25.0)									1.11	0.267
Waist - Hip ratio (WHR)										
Abdominal obesity									-2.40	0.030
Hemoglobin (g/dL)										
Anemia									-2.94	0.077
Diagnosis of CVD† before menopause										
Yes									0.86	0.689

* Tertile 3 (≥67%) † Cardiovascular disease such as hypertension, myocardial infarction

7. The multiple linear regression analysis models with disposing of outliers and influences

A stepwise variable selection method was used to select statistically appropriate variables among the all the independent variables included in multiple regression analysis (all the processes are presented in appendix tables). The seven individuals were defined as outliers, and 244 individuals were included in the final regression model. The explanatory power of regression model without outliers and influences are increased slightly than before the disposing, however that were same directionality with less effective of overall.

In the model including the HRT usage (Table 7a), the FMD of the early menopause group was 3.92 lower ($p = 0.0002$), and the abdominal obesity defined as WHR was 2.13 lower ($p = 0.012$). Women who has gynecological age more than average ($\geq$33yr) was 3.02 lower ($p = 0.0006$). The women take a HRT were 1.75 lower ($p = 0.040$). Furthermore, the greater than 5 years since menopause group was 1.65 lower ($p = 0.059$). Women with the highest 33% risk for KRS was 2.21 lower of FMD ($p = 0.005$). On the other hand, in marriage status with only positive correlation, the FMD of the separated/divorced / bereavement women was significantly 2.34 higher than the women who marriage and living together ($p = 0.011$).

In other models including the duration of HRT usage (Table 7b), the FMD was 3.95 lower in early age at menopause group ($p = 0.0002$), 2.20 lower in abdominal

obesity group (p = 0.011) and 2.99 lower in gynecological age over 33 years (p = 0.0007). The years since menopause greater than 5 years was 1.64 lower (p = 0.060) and 2.18 lower in the highest KRS group (p = 0.005). The women who experience separation / divorce / bereavement was 2.32%p higher at (p = 0.012). However, in the duration of HRT usage, an inverse correlation between HRT, the FMD was 2.07 lower in short-term users (less than 12 months; p = 0.054) and 1.31 lower in long-term users (greater than 12months; p = 0.285), there was no statistically significant at the 5% significance level.

Table 7a. The final regression analysis without outliers and influences (HRT usage)

Variable	Step 1			
	β	*p* value	*β*	*p* value
N	**251**		**251**	
Outliers & influences	**7 †**			
Model fit				
R^2 (%)	16.1	<0.0001	16.6	<0.0001
Adjusted R^2 (%)	13.7		14.2	
Age at menopause (yr)				
Early menopause (≤45)	-4.91	0.0001	-3.92	0.0002
Waist - Hip ratio (WHR)				
Abdominal obesity	-2.59	0.012	-2.13	0.012
Gynecological age (yr)				
≥33	-3.06	0.004	-3.02	0.0006
Hormone replacement teraphy (HRT)				
User (Past/Current)	-2.77	0.007	-1.75	0.040
Years since menopause (yr)				
>5	-2.05	0.0001	-1.65	0.059
Korean coronary risk scores (KRS)				
> 0.01280 *	-2.07	0.029	-2.21	0.005
Marrital status				
Seperation / Divorce / Bereavement	2.43	0.030	2.34	0.011

* Tertile 3 (≥67%) † Reweighted

Table 7b. The final regression analysis without outliers and influences (duration of HRT usage)

Variable	Step 1			
	β	*p* value	*β*	*p* value
N	**251**		**251**	
Outliers & influences	**7 †**			
Model fit				
R^2 (%)	16.2	<0.0001	16.7	<0.0001
Adjusted R^2 (%)	13.4		13.9	
Age at menopause (yr)				
Early menopause (≤45)	-4.87	0.0001	-3.95	0.0002
Waist - Hip ratio (WHR)				
Abdominal obesity	-2.51	0.017	-2.20	0.011
Gynecological age (yr)				
≥33	-3.09	0.004	-2.99	0.0007
Duration of HRT usage (months)				
≤12	-2.35	0.072	-2.07	0.054
>12	-3.30	0.024	-1.31	0.285
Years since menopause (yr)				
>5	-2.05	0.053	-1.64	0.060
Korean coronary risk scores (KRS)				
> 0.01280 *	-2.11	0.027	-2.18	0.005
Marrital status				
Seperation / Divorce / Bereavement	2.45	0.028	2.32	0.012

* Tertile 3 (≥67%) † Reweighted

Ⅳ. DISCUSSION AND CONCLUSION

The aim of this study is to confirm the relationship between several postmenopausal characteristics and endothelial function after adjusted coronary risk scores for Korean. Vascular endothelial dysfunction affects cardiac function (Maruhashi et al., 2013), and heart disease is the leading cause of death in Korean women. Menopause, an inevitable physical change in women, is known to increased risk for related diseases due to metabolic degradation such as hyperlipidemia, abdominal obesity, hot flushes, bone loss and inflammatory changes, etc. (Li et al., 2012; Stefanick, 2010).

The estrogen has a positive effect on lipid metabolism, it lowers LDL and increases HDL, thereby increasing vascular nitrogen oxides (NO) and reducing the risk of cardiovascular disease (Best et al., 1998). In other studies, however, postmenopausal women's estradiol (E2) concentration had a significant relation to myocardial fat in the low-estradiol group and increased CVD-related risk, depending on the type of estrogen, even though secreted estrone (E1) from women's body fat (El Khoudary et al., 2017). Nevertheless, there is no definitive prophylactic hormone replacement treatment for the increased risk of vascular disease in postmenopausal women.

The most representative type of HRT, a single regimen method: only administers estrogen regimen, and a combination method: uses estrogen plus progestin. Postmenopausal HRT for the first-line prevention of women tends to reduce the risk of CHD, Moreover, the blood estrogen levels have a protective effect against cardiovascular disease (Farhat, Lavigne and Ramwell, 1996). As is known, a single dose of estrogen effects to cardioprotective, however, the combined use of estrogen plus progestin increases the risk of cardiovascular disease, breast cancer. Besides, both of treatment method were increase of risk of veno-thrombotic episodes, stroke and cholecystitis (FALKEBORN et al., 1992; Grodstein et al., 1996; Investigators, 2002; Koo, Song and Na, 2012; Manson et al., 2003; Miller et al., 1995; Rossouw et al., 2007). When the women receive naïve HRT, who may experience side effects such as vaginal bleeding, mood changes, and indigestion during short-term. In some cases, the symptoms are considered to change medication prescription. Continuous therapy has prophylactic effects on osteoporosis and coronary artery disease. On the other hand, HRT may not be recommended for all postmenopausal women because of the increased risk of breast cancer, endometrial cancer, gallbladder disease, stroke and fracture in long-term usage.

In this study, individuals who postmenopausal women have 62 years mean of age. Older group (age over 70) are 18% of the total, there was no significant difference in FMD mean by age, the FMD of married women with separated/divorced/ bereavement (mean age; 68.6 years) was significantly higher

than women who live together after marriage (60.8 years). In addition, mean of gynecological age was lower (31.8 years) compared with women who living together after the marriage (33.2 years), and there was no significant difference in postmenopausal age. However, women who living alone experienced (mean; 21.2 years) many years since of menopause compared with women who live together (12.2 years). Thus, it was found that marital status of women was independently related to after the menstrual characteristics. It is anticipated the stress from a patriarchal culture which is a characteristic of the Korean society in the past, in fact, because most of the individuals are elderly who has a mind of women's responsibility in the house such as housework. Rather, the decrease in endothelial function was greater immediately after menopause. that suggest the years since menopause was strongly related with endothelial function.

The difference in the risk scores for coronary artery disease for Korean (KRS) according to the time of age at menopause was significantly higher in the late menopause women than the early or normal menopause group. The mean age of the nine late menopause women was 65.9 years, which was older than early menopause (61.4 years) and normal menopause women (62.2 years). KRS was significantly lower in the women experienced HRT compared with non-experienced HRT. The median difference of endothelial function, by the age group, was higher during menopause in each group, then gradually decreased after the menopause. There was no significant difference, by the HRT usage, whereas the lower in HRT usage women. These results suggest HRT is associated with the prevention of coronary

risk scores. The endothelial dysfunction which independent association with the occurrence of coronary artery disease (Sader and Celermajer, 2002) had an inverse relation with KRS after the adjusted with menstrual characteristics variables suggest that has a strong association within.

Unlike the previous results, when adjusted for endothelial function and the variables affecting women's health, FMD was significantly lower in the women who experienced HRT than non-use group. Because this study designed a cross-sectional study using cohort data, it is unclear of timing at HRT is initiated. Therefore, if HRT is initiated after the onset of deterioration of endothelial function due to aging or other causes, furthermore, the reverse causation can occur in rural women who are less likely to be prescribed HRT for the prevention of disease. Nevertheless, when further analysis of the duration of HRT was undertaken, FMD was lower in women who underwent HRT within 12 months compared with those who used HRT over 12 months. The mean age of women who received HRT usage during short-term (≤12 months) was 58.8 years, those who were younger than HRT non-users (62.9 years) and long-term users (>12 months, 60.1 years). The mean of years since menopause was 11.3 years was shorter than the other groups (non-users; 14 years, long-term users; 14.5 years). The women with short-term used of HRT have recently been menopause. That suggest FMD is lowered the Immediately afterward of menopause than after many years since menopause.

Among the FMD was 3.3%p lower in the early menopause group, that suggest the decrease endothelial function of women whose hormone decreasing started at a relatively early age is weaker. In order to confirm the accuracy, we calculated the gynecological age (duration between from age at menarche to age at menopause) and included in the analysis, In the Korean Heart Study (KHS) which is large-scale population study, the shorter the hormone exposure period, the risk of cardiovascular disease was increased (Jung et al., 2016). However, we found women who has a longer gynecological age (≥33 years) has significantly decreased in endothelial function. In fact, although gynecological age is not long in all late menopause women, in this study, only one woman had a long gynecological age in early menopause (mean; 28.2 years). Most of the normal or late menopause group has an average or more of gynecological age. The women who were shorter than 33 years of gynecological age had a relatively length years since menopause (mean; 19.3 years), which was longer than who has longer gynecological age (9.9 years). These findings suggest when the estradiol concentration goes lowering in the menopausal woman's body, the endothelial function is sharply lowered.

The endothelium-dependent function is an inverse relation with weight (Arkin et al., 2008). The previous study suggests the WHR, among a healthy overweight woman, is a closely independent predict factors for endothelial function (Brook et al., 2001). In this study, no mean difference of FMD between abdominal obesity defines as a waist circumference only, however, the abdominal obesity women

based on WHR is a significant correlation with endothelial function. Abdominal obesity is a risk factor for various metabolic diseases. This result suggests there is a strong correlation between endothelial function and abdominal obesity, which is not simply based on waist circumference, but the excess accumulation of fat in the abdomen compared to a balanced body. In contrast to previous results, abdominal obesity group (mean age; 63 years) was older than normal group (56.5 years). Obviously, the postmenopausal period was shorter in the normal group (median; 8 years) than in the abdominal obesity group (14 years). Nevertheless, decreased endothelial function in the abdominal obesity group is because obesity itself affects weakens of vessel function (Stapleton et al., 2008).

Postmenopausal women experience loss of estradiol in the body, moreover decreased the function of related receptors affect the dysfunction of endothelial cells, as a result in decreased metabolic function and increased risk of vascular disease (Li et al., 1999). Previous studies have shown estrogen elevation via HRT reduces cell transition by aging through estrogen receptors and contributes to nitric oxide (NO) release, thereby improving endothelial function (Hayashi et al., 1995; Khalil, 2013; Li et al., 1999). In contrast, in older postmenopausal women should be considered in prescribing because the effects of aging are stronger than the prophylactic effects of HRT (Compston, 1997).

We could confirm the association endothelium-dependent function with various menstrual characteristics in postmenopausal women living in Korea rural areas. As a result, women who has a gynecological age was over 33 years, the years

since menopause more than 5 years, the upper 33% of KRS, the abdominal obesity by WHR, women who are living together after the marriage had 13%p lower on endothelial function. In this study, older postmenopausal women who experienced HRT usage and early age at menopause have a negative effect on postmenopausal endothelium-dependent function. In addition, years since menopause, must be considered when deciding to initiate HRT. The longer of period, the weakens of hormone receptor and the prophylactic effect of HRT cannot be expected. That suggest the backup previous hypothesis, in older, postmenopausal women may increase risk rather than preventive effects.

From another perspective, HRT is more likely to be recommended because women with severe menopause symptoms or poor of health condition, that may visit the hospital frequently. Besides, women with cardiovascular risk factors may growth plaques of vascular wall and increased risk of myocardial infarction after the HRT (Medina et al., 2003). In some, women who started HRT early after the menopause, risk of mortality, heart failure and myocardial infarction was reduced without an increased risk of stroke, some of cancer, and venous thromboembolism when HRT usage (Schierbeck et al., 2012).

Nevertheless, there are many side effects and benefits in HRT, and since there are still no clear guidelines, prior to exogenous HRT, postmenopausal women need to increase the intake of foods rich in phytoestrogen, such as soy, fruits and improve their lifestyles to prevent chronic diseases caused by hormone decrease and metabolic degradation. The timing of HRT initiation should be based on family

history, individual health status, cardiovascular risk factors such coronary risk scores (KRS). Furthermore, duration of HRT usage should be decided accordingly. We anticipate that the relatively inhabitants of rural areas in the elderly will lack knowledge which preventive treatment due to information asymmetry. In Korea, rural area where women's chronic diseases and deaths from heart disease are increasing, the municipality should be developed programs and implemented to prevent diseases through related women's health education. This is could be a policy to reduce the sociological cost of the disease.

The limitation of this study was designed cross-sectional, thus, the timing of postmenopausal HRT is unclear in this data. Moreover, to examine the individuals were specific women living in rural area (Yangpyeong, Gyeonggi) in Korea. There was not enough randomized assignment in the selection process. Besides, that may have an error in performing an endothelium-dependent vasodilation test that is sensitive to the measurement environment and the skill of the tester. More prospective studies will need to be undertaken to investigate the history of HRT such as the timing of HRT initiation, regimen, and dosage, etc., and the broader area not only rural area.

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APPENDIX

Table A1. Process of selection independent variables by stepwise method for linear regression equation (HRT usage)

Variable	Step 1		Step 2		Step 3		Step 4		Step 5		Step 6		Step 7	
	β	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value
Model fit														
R^2 (%)	3.6	0.003	6.9	0.0001	9.3	<0.0001	11.5	<0.0001	13.3	<0.0001	14.4	<0.0001	16.1	<0.0001
Adjusted R^2 (%)	3.2		6.2		8.2		10.0		11.6		12.3		13.7	
Age at menopause (yr)														
Early menopause (≤45)	-3.21	0.003	-3.29	0.002	-5.17	<0.0001	-4.96	0.0001	-4.86	0.0001	-5.03	<0.0001	-4.91	0.0001
Waist - Hip ratio (WHR)														
Abdominal obesity			-3.07	0.003	-2.94	0.004	-3.30	0.001	-2.79	0.007	-2.55	0.014	-2.59	0.012
Gynecological age (yr)														
≥33					-2.63	0.012	-2.56	0.014	-3.06	0.004	-3.34	0.002	-3.06	0.004
Hormone replacement teraphy (HRT)														
User (Past/Current)							-2.56	0.014	-2.64	0.011	-2.81	0.007	-2.77	0.007
Years since menopause (yr)														
>5									-2.37	0.023	-1.93	0.069	-2.05	0.053
Korean coronary risk scores (KRS)														
> 0.01280 *											-1.65	0.077	-2.07	0.029
Marrital status														
Seperation / Divorce / Bereavement													2.43	0.030

* Tertile 3 (≥67%)

Table A2. Process of selection independent variables by stepwise method for linear regression equation (duration of HRT usage)

Variable	Step 1		Step 2		Step 3		Step 4		Step 5		Step 6		Step 7	
	β	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value	*β*	*p* value
Model fit														
R^2 (%)	3.6	0.003	6.9	0.0001	9.3	<0.0001	11.0	<0.0001	12.2	<0.0001	13.6	<0.0001	16.2	<0.0001
Adjusted R^2 (%)	3.2		6.2		8.2		9.5		10.4		11.4		13.4	
Age at menopause (yr)														
Early menopause (≤45)	-3.21	0.003	-3.29	0.002	-5.17	<0.0001	-5.08	<0.0001	-4.94	0.0001	-5.11	<0.0001	-4.87	0.0001
Waist - Hip ratio (WHR)														
Abdominal obesity			-3.07	0.003	-2.94	0.004	-2.44	0.019	-2.53	0.015	-2.26	0.029	-2.51	0.017
Gynecological age (yr)														
≥33					-2.63	0.012	-3.10	0.004	-2.82	0.009	-3.07	0.004	-3.09	0.004
Years since menopause (yr)														
>5							-2.27	0.031	-2.47	0.019	-2.01	0.060	-2.05	0.053
Marrital status														
Seperation / Divorce / Bereavement									2.03	0.067	2.49	0.028	2.45	0.028
Korean coronary risk scores (KRS)														
> 0.01280 *											-1.86	0.052	-2.11	0.027
Duration of HRT usage (months)														
≤12													-2.35	0.072
>12													-3.30	0.024

* Tertile 3 (≥67%)

ABSTRACT (IN KOREAN)

한국 농촌지역 여성의 폐경 후 호르몬대체요법과 조기 폐경이 내피세포기능에 미치는 영향

최윤수

연세대학교 보건대학원

지도교수 지선하

연구배경 및 목적

심혈관질환은 국내 성인 사망원인 2 위이다. 여성의 폐경은 심혈관 질환의 위험인자로 알려져 있으며, 내피 세포 기능 장애는 관상 동맥 질환의 독립적인 위험인자이다. 폐경 후 호르몬대체요법에는 많은 부작용과 이점이 있지만 심혈관 질환에 대해서는 여전히 많은 논란이 있다. 본 연구에서는 관상 동맥 질환 위험도 등을 보정한 후 폐경 시기와 호르몬 대체요법이 내피세포 기능에 미치는 영향을 알아보고자 한다.

연구방법

경기도 양평 지역에서 시행된 장수 코호트 자료에서 FMD 검사를 받고 설문조사에 결측이 없는 251 명의 여성을 대상으로 하였다. 최종 회귀분석에서 이상치 처리를 위해 가중치 재부여 방법을 사용하였다.

연구결과

호르몬 재배치 치료를 받은 51 명(20.3%)의 여성의 내피 기능은 1.75%p (p=0.04)낮았고, 조기 폐경을 경험한 여성 51 명(20.3%)은 3.92%p (p=0.0002) 낮았다. 호르몬 치료를 경험하지 않은 여성에 비해 단기간 호르몬 치료를 경험한 여성은 2.07%p(p=0.054), 장기간 호르몬 치료를 경험한 여성은 1.31%p(p=0.285) 낮았다. WHR 로 정의된 복부비만 (p=0.012)이거나, 월경 기간(초경부터 폐경까지의 기간)이 평균 이상 (p=0.0006)이면서, KRS 가 높고(p=0.005) 폐경 후 기간이 긴(p=0.059) 여성은 내피 기능이 감소했다. 대조적으로, 독거 중인 폐경 후 노인 여성은 결혼 후 동거중인 여성에 비해 내피세포 기능이 유의하게 높았다(p=0.012).

결론

호르몬 재배치 치료를 시작할 때, 현재 나이와 폐경의 종류만이 아니라 관상 동맥 질환 위험 점수, 월경 기간 등을 모두 고려해야한다.

핵심 단어:

폐경, 호르몬대체요법, 내피세포기능, 심혈관 질환, 조기 폐경, 월경 기간