Asian Nursing Research 15 (2021) 265–271

Contents lists available at ScienceDirect

Asian Nursing Research

journal homepage: www.asian-nursingresearch.com

Research Article

Incidence and Risk Factors of Cardio-Cerebrovascular Disease in Korean Menopausal Women: A Retrospective Observational Study using the Korean Genome and Epidemiology Study data

Jin-Hee Park, Eun Ji Seo, Sun Hyoung Bae*

College of Nursing·Research Institute of Nursing Science, Ajou University, Suwon, Republic of Korea

ARTICLE INFO

Article history:
Received 13 May 2021
Received in revised form
19 July 2021
Accepted 17 August 2021

Keywords:
Cardiovascular diseases
Heart disease risk factors
Incidence
Menopause
Middle aged

SUMMARY

Purpose: Cardio-cerebrovascular diseases constitute the most common and fatal disease among menopausal women. However, the risk of cardio-cerebrovascular diseases in menopausal women compared to men has been underestimated, with insufficient related studies. Therefore, we examined the incidence and risk factors of cardio-cerebrovascular diseases among Korean menopausal women.
Methods: A retrospective observational study design with secondary analysis was conducted using data from the Korean Genome and Epidemiology Study survey. We used the study's data of 1,197 menopausal women, aged 40–64 years, who did not have cardio-cerebrovascular diseases at baseline and their related data from the biennial follow-ups over 14 years. Cardio-cerebrovascular diseases were defined as hypertension, coronary artery disease, or stroke. The incidence of cardio-cerebrovascular diseases was calculated per person-years, and multivariate Cox proportional hazards models were used to determine the predictors of cardio-cerebrovascular diseases during the follow-up period.
Results: Of the 1,197 cases, 264 were early or surgical menopausal women. The overall incidence of cardio-cerebrovascular diseases was 18.75 per 1,000 person-years. Early or surgical menopause (HR = 4.32, $p < .001$), along with family history of cardiovascular disease (HR = 1.87, $p = .024$), elevated blood pressure (HR = 1.79, $p < .001$), abdominal obesity (HR = 1.37, $p = .046$), or duration of menopause at the same age (HR = 1.01, $p = .001$), were strong predictors of cardio-cerebrovascular diseases.
Conclusion: Based on the results of this study, it is necessary to identify and closely monitor women with early or surgical menopause for cardiovascular and cerebrovascular diseases prevention. Also, prevention of cardio-cerebrovascular diseases through blood pressure and abdominal obesity management is vital for menopausal women.

Introduction

Cardio-cerebrovascular diseases, including cardiovascular and cerebrovascular diseases [1], are the leading cause of death for women worldwide, especially after the age of 40 years, increasing their mortality rate to exceed that of men in their 60s [2,3]. This tendency is caused by a decrease in estrogen levels after menopause, which worsens the functions of vascular endothelial cells, vascular responsiveness, and blood lipids, thereby accelerating the body mass index (BMI), fasting blood sugar, blood pressure (BP), and dyslipidemia [2,3]. Nonetheless, it has been reported that women underestimate the risk of cardio-cerebrovascular diseases due to low awareness and minimal engagement with preventive health practices [4]. Therefore, screening and prevention of cardio-cerebrovascular diseases are necessary for middle-aged women before and after menopause.

Furthermore, early menopause, in which a woman's menstruation stops before the age of 45 [5], and surgical menopause, due to removal of both ovaries before natural menopause [6,7], are hypothesized to be detrimental for cardiovascular health because of the early cessation of the protective effect of endogenous estrogen. Consequently, prolonged duration since the onset of menopause could result in a greater risk of cardio-cerebrovascular diseases [8]. The two-fold increase of cardio-cerebrovascular diseases risk in

Jin-Hee Park: https://orcid.org/0000-0002-0069-7819; Eun Ji Seo: https://orcid.org/0000-0002-6565-0093; Sun Hyoung Bae: https://orcid.org/0000-0002-4890-619X

* Correspondence to: Sun Hyoung Bae, College of Nursing·Research Institute of Nursing Science, Ajou University, 164, World cup-Ro, Yeongtong-Gu, Suwon, 16499, South Korea.

E-mail address: shyoung@ajou.ac.kr

https://doi.org/10.1016/j.anr.2021.08.002
p1976-1317 e2093-7482/

women below the age of 60 years who have experienced early menopause is troubling and necessitates advocacy, especially in the case of younger women. However, although postmenopausal women face more risks of developing various chronic diseases and require special attention and management [3,8], studies regarding the incidence of cardio-cerebrovascular diseases after menopause are limited. Also, the risk of cardio-cerebrovascular diseases in women is being ignored, with a common misconception among health professionals and the general public that cardio-cerebrovascular diseases predominantly affect men [4].

The topics predominantly explored encompass cross-sectional prevalence rates or risk assessment for individual chronic diseases [9] and research on acute health problems, such as hot flashes and depression [10,11]. Although women experiencing early or surgical menopause are subjected to a greater risk of chronic diseases [12], it is difficult to find a study validating the associated risk factors or differences with women undergoing natural menopause. Moreover, age at menopause is a significant factor for classifying menopausal types, such as early menopause and natural menopause. Interestingly, there are only a few studies on how age at menopause determines the risk factors and incidences of chronic diseases, although such issues are directly related to women's health.

Therefore, we aimed to identify the incidence of cardio-cerebrovascular diseases in Korean menopausal women and the factors affecting the incidence of cardio-cerebrovascular diseases. A large-scale cohort analysis is ideal for identifying incidences and risk factors for health problems by menopausal type because the incidence of early menopausal women in Korea, derived from national cohort data, is estimated at approximately 7%, which includes artificial menopause [13,14]. Accordingly, this study used the Korean Genome and Epidemiology Study (KoGES) data, a large cohort study of the Korean general population, to evaluate the incidence and risk factors of cardio-cerebrovascular diseases in menopausal women.

Methods

Study design and population

This study involved a retrospective observational study design with secondary analysis using the national cohort data drawn from the KoGES. Details of the KoGES and the methods used have been comprehensively explored [15]. The KoGES Ansan and Ansung study, a large population-based study, recruited 10,030 Korean adults aged 40–69 at baseline from 2001 to 2002. The survey consisted of sociodemographic, lifestyle, and health questionnaires, a dietary interview, and anthropometric and clinical measurements. Follow-up surveys, from baseline, were conducted a further seven times biennially; thus, eight datasets were analyzed. To determine the development of cardio-cerebrovascular diseases in menopausal women during the 14-year data period, we excluded the following participants based on the baseline dataset: (1) those aged 65–69 years during the baseline survey (n = 1,313); (2) men (n = 4,165); (3) those with incomplete data at baseline (n = 684); (4) those with a history of hypertension, coronary artery disease (CAD), or stroke at baseline (n = 1,055); (5) those with history and/or treatment of cancer (n = 10); and (6) those still menstruating (n = 1,606). Finally, 1,197 participants were included in this study (Figure 1).

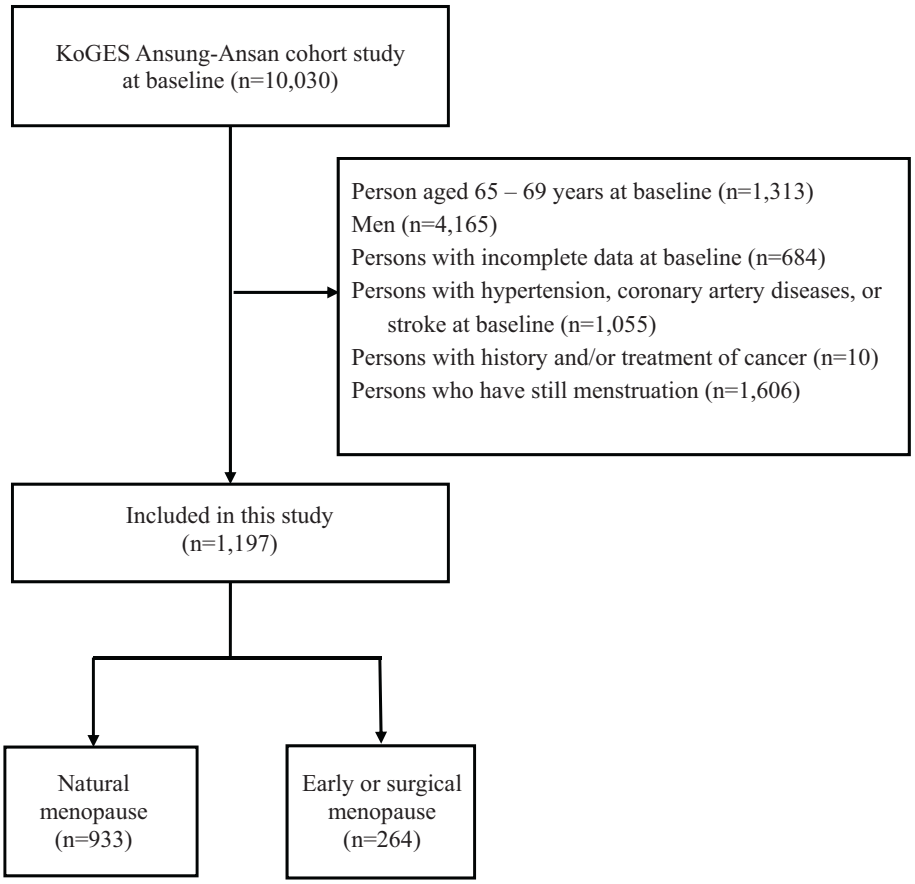

Figure 1. Flow chart of this study.

Measurement

The KoGES data were measured by trained interviewers using a questionnaire that included participants' sociodemographic information, lifestyle (i.e., smoking and drinking), perceived health status, medical information (i.e., personal and family medical history; the current status of disease treatment), and reproductive information (i.e., menopausal status and age at menopause). Anthropometric parameters (i.e., weight, height, and waist circumference) and BP were measured by a trained interviewer using standard methods. Blood samples were collected after at least 8 hours of fasting to measure lipid profiles, including total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels; low-density lipoprotein (LDL) cholesterol was calculated [16].

Study variables

Cardio-cerebrovascular diseases

Cardio-cerebrovascular diseases included cardiovascular diseases (e.g., CAD, hypertension, etc.) and cerebrovascular diseases (e.g., cerebral hemorrhage, cerebral thrombosis, etc.) [1]. In this study, the presence of cardio-cerebrovascular diseases was identified in individuals with at least one of the following diseases: hypertension, CAD, or stroke. We established that the disease occurred if the participants answered yes to either of the following questions: (1) Have you been diagnosed with the above diseases by a physician since the last survey? (2) Have you been treated or medicated for the above diseases. The onset time of each disease was the age at which the participant reported the disease being first diagnosed or treated during a 14-year follow-up period.

Risk factors of cardio-cerebrovascular diseases

We identified certain sociodemographic, lifestyle, and health-related factors as risk factors for cardio-cerebrovascular diseases based on previous studies [9,17,18]. The sociodemographic factors included age, education, and monthly income. Age was reported during the baseline survey. Education was divided into three categories: elementary, middle, and above high school levels. Monthly income (Korean won) was divided as follows: low (<1 million), middle (≥1 million and <3 million), and high (≥3 million) levels.

Lifestyle and health-related factors included smoking, drinking, perceived health status, BMI, type of menopause, duration of menopause, family history of cardiovascular diseases, history of diabetes, BP, waist circumference, and LDL. Smoking and drinking were reclassified into the "No" (never and former smoker/drinker) and "Yes" (current smoker/drinker) groups. Perceived health status was reclassified into three categories (healthy, usual, and unhealthy) from a five-point Likert scale (*very healthy* to *very unhealthy*). BMI was categorized as normal (<23 kg/m^2) and overweight (≥23 kg/m^2) based on Korean population classification [19].

Menopause is classified into two types: natural and early or surgical. Based on the menopause guidelines [5,20], natural menopause is menopause in women over 45 years old who naturally experienced no periods for at least 12 months and had not been using hormonal contraception [20]. Therefore, we defined natural menopause as the menopausal state, which is not the consequence of medical treatment, hysterectomy, or bilateral oophorectomy in women over 45 years old. The standard age was set at 45 years because early menopause is defined as menopause onset at younger than 45 years old [5,20]. Early menopause was defined as the onset before the age of 45 due to occurring primary ovarian insufficiency or some unknown cause [5]. Surgical menopause was defined as menopause induced by a bilateral oophorectomy or a hysterectomy before the onset of natural menopause [6,7]. The duration of menopause was defined as the period from the age at onset of menopause to the age at onset of cardio-cerebrovascular diseases.

BP was classified into two categories, namely normal BP (<120/80 mmHg), elevated BP (≥120/80 mmHg) based on the standard reported by the Korean Society of Hypertension [21]. Waist circumference was categorized into normal (<85 cm) and abdominal obesity (≥85 cm) groups [19]. LDL cholesterol was categorized into normal (<130 mg/dL) and high (≥130 mg/dL) groups.

Procedures and statistical analysis

Participants with an onset of cardio-cerebrovascular diseases were integrated as event cases; participants without cardio-cerebrovascular diseases up to the seventh follow-up survey and those without further follow-up data were censored. Descriptive statistics were used to summarize the baseline sociodemographic, lifestyle, and health-related factors. Hazard ratios (HRs) and 95% confidence interval (CI) were estimated to determine the association between risk factors (sociodemographic, lifestyle, and health-related factors) and incidence of cardio-cerebrovascular disease using Cox proportional hazards regression analysis based on the univariate and multivariate model. In the Cox proportional hazards regression analysis, the event was the occurrence of cardio-cerebrovascular diseases. Time-to-event for each patient was estimated from the baseline date to the date of reported diagnosis or treatment of cardio-cerebrovascular diseases, the date when the participant was censored due to withdrawal from the KoGES database (e.g., moving, refusing to participate, or dying), or the last date of follow-up. Before estimating the Cox proportional hazards models, we checked the basic assumption of the proportional hazard model by model fitness test using log minus log survival plot and confirmed that the incidence curve for cardio-cerebrovascular diseases according to risk factors maintains a constant vertical distance [22]. Second, as the duration of menopause was a time-varying covariate, a significance test was performed on the interaction between the covariate and time using the time-dependent Cox regression model [22,23]. After confirming that the proportional hazards assumption was satisfied, we used the Cox proportional hazards models.

In addition, the incidence of cardio-cerebrovascular diseases was calculated per person-years (py). Person-years is a statistic that represents how many new events occurred within the subject group during a specific period. Person-years of cardio-cerebrovascular diseases were calculated from the baseline data to the event development, or until the time of the last available follow-up data. The 14-year incidence of cardio-cerebrovascular diseases was calculated per 1,000 py by dividing the number of individuals who developed cardio-cerebrovascular diseases during follow-up by the total person-time. All analyses were performed using a 95% CI. Data analysis was performed using IBM SPSS Statistics version 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Incidence analyses were performed using R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical consideration

The study protocol was approved by the Ethics Committee of the Korean Center for Disease Control and the Institutional Review Board of the author's institution (Approval no. AJIRB-SBR-EXP-19-136). The study was performed in accordance with the ethical standards outlined in the Declaration of Helsinki (as revised in Brazil 2013).

Results

Baseline sociodemographic and lifestyle, and health-related factors of participants

The mean age of participants was 54.57 ± 6.15 years. Women perceived as unhealthy accounted for up to 42.3%, and those who were overweight were 69.5% of the total sample. Most of the women did not have a family history of cardiovascular diseases or a history of diabetes. Among the 1197 menopausal women, 264 (22.1%) were categorized under early or surgical menopause, and the mean duration of menopause was 17.31 ± 7.67 years. The mean waist circumference and LDL cholesterol levels were 81.65 (±9.15 cm) and 119.87 (±32.18 mg/dL), respectively, and approximately 60% of the total sample was labeled normal BP, waist circumference, and LDL cholesterol levels (Table 1).

Incidence of cardio-cerebrovascular diseases during the 14-year follow-up

The total follow-up person-years was 12,108 years. Out of 1,197 menopausal women, a total of 227 developed cardio-cerebrovascular diseases. The incidence of cardio-cerebrovascular diseases was 18.75 per 1,000 py. Notably, hypertension had the highest incidence (16.21 per 1000 py) among these individual diseases (Table 2).

Table 1 *Baseline Sociodemographic and Lifestyle and Health-related Factors of Participants (N = 1,197).*

Characteristics	Categories	*n* (%)	Mean ± Standard Deviation
Age, in years	40–49	266 (18.3)	54.57 ± 6.15
	50–59	613 (42.3)	
	≥60	318 (39.4)	
Education	Elementary	640 (53.5)	
	Middle	267 (22.3)	
	Above high school	290 (24.2)	
Monthly income	High	134 (11.2)	
	Middle	527 (44.0)	
	Low	536 (44.8)	
Smoking	No	1149 (96.0)	
	Yes	48 (4.0)	
Drinking	No	874 (73.0)	
	Yes	323 (27.0)	
Perceived health status	Healthy	312 (26.0)	
	Usual	379 (31.7)	
	Unhealthy	506 (42.3)	
Body mass index, kg/m^2	<23 (Normal)	365 (30.5)	24.60 ± 3.15
	≥23 (Overweight)	832 (69.5)	
Type of menopause	Natural	933 (77.9)	
	Early or surgical	264 (22.1)	
Duration of menopause, in years	≤10	231 (19.3)	17.31 ± 7.67
	11-20	595 (49.7)	
	>20	371 (31.0)	
Family history of cardiovascular disease	No	1137 (95.0)	
	Yes	60 (5.0)	
History of diabetes	No	1127 (94.2)	
	Yes	70 (5.8)	
Blood pressure, mmHg	Normal (<120/80)	721 (60.2)	
	Elevated (≥120/80)	476 (39.8)	
Waist circumference, cm	<85 (Normal)	774 (64.7)	81.65 ± 9.15
	≥85 (Abdominal obesity)	423 (35.3)	
Low-density lipoprotein, mg/dL	<130 (Normal)	759 (63.4)	119.87 ± 32.18
	≥130 (High)	438 (36.6)	

Risk factors for the incidence of cardio-cerebrovascular diseases in menopausal women

The log minus log survival plot indicated that the cardio-cerebrovascular disease incidence curve according to risk factors was maintained at a constant distance [22]. Also, in the time-dependent Cox regression model, the significance probability of the duration of menopause was not statistically significant ($p = .944$) [22,23]. Thus, the proportional hazards assumption was satisfied; because the duration of menopause was significantly associated with age ($r = .436$, $p < .001$), the interaction term of the duration of menopause and age was included in the multivariate Cox proportional hazard models.

Using Cox proportional hazard models, we investigated the risk factors for the development of cardio-cerebrovascular diseases during the follow-up period. In the univariate model, age, education (high school and above), monthly income (low), history of diabetes, elevated BP, and duration of menopause were revealed as independent risk factors of cardio-cerebrovascular diseases, respectively. In the multivariate model, early or surgical menopause was a strong risk factor of cardio-cerebrovascular diseases (HR = 4.32, 95% CI = 2.93-6.36). Additionally, having a family history of cardiovascular diseases (HR = 1.87, 95% CI = 1.09-3.21), elevated BP (HR = 1.79, 95% CI = 1.37-2.36), abdominal obesity (HR = 1.37, 95% CI = 1.01–1.86), and a long duration of menopause at the same age (HR = 1.01, 95% CI = 1.00–1.01) were also independently associated with progression to cardio-cerebrovascular diseases (Table 3).

Discussion

This study evaluated the incidence as well as the risk factors of the development of cardio-cerebrovascular diseases in a representative sample of Korean menopausal women, including residents of both rural and urban areas. Early or surgical menopause, family history of cardiovascular diseases, elevated BP, abdominal obesity, and a long duration of menopause at the same age were critical factors influencing the incidence of cardio-cerebrovascular diseases in women.

In this cohort, the overall incidence of cardio-cerebrovascular diseases was 18.75 per 1,000 py during a 14-year follow-up. Among the cardio-cerebrovascular diseases, the incidence of hypertension was high at 16.21 per 1000 py, but the incidence rates of CAD and stroke were low at 2.53 and 1.92 per 1000 py, respectively. These findings indicate that hypertension is a common disease compared to CAD or stroke in Korean menopausal women over time. Among menopausal women, hypertension is highly prevalent and is a crucial health problem [24,25], yet less than half of those with hypertension receive adequate treatment and care [25]. Therefore, behavioral interventions are essential to reduce the occurrence of hypertension among menopausal women during this transition. In addition, the incidence of hypertension and CAD in this study is relatively higher than those in previous studies [24,26,27]. This may be due to several factors, including survey area,

Table 2 *Incidence of Cardio-Cerebrovascular Diseases during 14-year Follow-up.*

	Cardio-cerebrovascular diseases	Hypertension	Coronary artery disease	Stroke
Event, *n*	227	212	33	25
Person-year [a]	12.108	13.081	13.060	13.046
Incidence	18.75	16.21	2.53	1.92

[a] In thousands.

Table 3 *Risk Factors of the Incidence of Cardio-cerebrovascular Diseases.*

Characteristics	Categories	Unadjusted		Adjusted	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age, in years		1.05 (1.03–1.08)	<.001	1.09 (1.02–1.16)	.012
Education	Middle	0.73 (0.52–1.01)	.054	0.94 (0.66–1.35)	.743
(vs. Elementary)	Above high school	0.51 (0.35–0.72)	<.001	0.75 (0.49–1.14)	.176
Monthly income	Middle	1.51 (0.86–2.65)	.155	1.26 (0.71–2.24)	.429
(vs. High)	Low	2.34 (1.35–4.07)	.003	1.59 (0.88–2.88)	.124
Smoking (vs. No)	Yes	1.06 (0.52–2.14)	.874	1.21 (0.58–2.53)	.616
Drinking (vs. No)	Yes	0.93 (0.69–1.25)	.616	1.03 (0.76–1.41)	.847
Perceived health status	Usual	1.09 (0.76–1.56)	.631	1.05 (0.73–1.51)	.797
(vs. Healthy)	Unhealthy	1.27 (0.91–1.77)	.163	1.14 (0.81–1.61)	.451
Body mass index (vs. Normal)	Overweight	1.17 (0.87–1.57)	.292	0.98 (0.70–1.37)	.898
Type of menopause (vs. Natural)	Early or surgical	0.83 (0.60–1.15)	.270	4.32 (2.93–6.36)	<.001
Duration of menopause, in years		0.92 (0.90–0.94)	<.001	0.57 (0.46–0.72)	<.001
Family history of CVD (vs. No)	Yes	1.19 (0.70–2.00)	.523	1.87 (1.09–3.21)	.024
History of diabetes (vs. No)	Yes	1.67 (1.06–2.64)	.029	1.35 (0.84–2.17)	.215
Blood pressure (vs. Normal)	Elevated	2.24 (1.72–2.91)	<.001	1.79 (1.37–2.36)	<.001
Waist circumference (vs. Normal)	Abdominal obesity	1.54 (1.19–2.00)	.001	1.37 (1.01–1.86)	.046
LDL cholesterol (vs. Normal)	High	1.08 (0.83–1.41)	.579	1.09 (0.83–1.44)	.528
Age * Duration of menopause				1.01 (1.00–1.01)	.001

Note. CI = confidence interval; CVD = cardiovascular diseases; HR = hazard ratio; LDL = low-density lipoprotein.

sex and age of participants, and longer follow-up period. This study used the national data that recruited a large cohort and followed up for 14 years using sampling designs and standardized data collection. Thus, it can be said that the incidence of cardio-cerebrovascular diseases specified in this study represents the incidence of Korean menopausal women.

Among risk factors of the incidence of cardio-cerebrovascular diseases, early or surgical menopause was the most important factor influencing future cardio-cerebrovascular diseases in a population-based sample of Korean menopausal women. Our findings align with other large-scale epidemiologic studies of early menopause and cardio-cerebrovascular diseases [12,28], which reported that early menopause had a significantly higher risk of developing cardiovascular disease and stroke than natural menopause. Furthermore, not only the type of menopause but also the time since onset of menopause has been reported as a factor affecting the occurrence of CAD and cardiovascular diseases [8,10,18]. Meta-analysis showed that women with higher age of menopause and shorter periods of time after the onset of menopause had a relatively low risk of CAD [8,18]. Ley et al [10] reported that a shorter period of reproductive life is associated with a high risk of cardiovascular diseases. This phenomenon is in line with the aforementioned outcomes denoting that the longer the menopause period, the higher the risk of cardiovascular diseases. The most noticeable physiological change during menopause is decreased endogenous estrogen and a subsequent change in ovarian function [3,8,18]. Therefore, early estrogen loss in menopausal women might be associated with adverse cardiovascular disease risk factors, such as impairment of vascular function and increased expression of inflammatory cytokines [3,29]. These factors are associated with obesity, diabetes, and hypertension [8]. Therefore, it is necessary to regularly monitor women experiencing early menopause to determine whether they develop cardio-cerebrovascular diseases and provide active lifestyle modification interventions to prevent these diseases.

Our analysis also revealed that women with a family history of cardiovascular diseases had a higher risk of cardio-cerebrovascular diseases than women who did not. This finding is in line with previous studies that show that the incidence of cardiovascular diseases is high for any family history of CAD [30]. Notably, family history is a cardinal factor in a patient's health history, as there can be shared family health-related behaviors, environmental traits, and genetic traits [31,32]. Nonetheless, screening tests for high-risk patients with a family history are often neglected in clinical settings, and significant data, including sex, onset age, number of relatives, and prognosis of families with cardiovascular diseases, have not been collected adequately [32]. Considering that a family history of cardiovascular diseases has been regarded as a prime risk factor for developing future cardiovascular diseases [31,32], a proactive assessment of family histories and targeted risk reduction interventions should be conducted during initial assessments for high-risk groups.

Notably, women with elevated BP were found to experience a higher risk of developing cardio-cerebrovascular diseases than those with normal BP levels. This outcome is similar to the results of previous meta-analyses of prospective cohort studies [33,34], which indicate that elevated BP is associated with a significant risk of developing or dying from cardio-cerebrovascular diseases. In this study, the rate of elevated BP was 39.8%, which is higher than the average rate of 36.7% reported for Asian adults [34]. This difference is because, unlike previous studies with adults over the age of 20 years, this study targeted middle-aged or older women (40–64 years old). However, given that elevated BP is likely to develop into hypertension, it is necessary to screen these high-risk patients and initiate aggressive interventions focused on lifestyle modification to achieve BP goals.

Next, abdominal obesity was a significant risk factor for cardio-cerebrovascular diseases in this study. Our findings agree with previous studies, including population-based cross-sectional studies that have depicted that abdominal obesity is associated with a higher risk of coronary heart disease in Korean and American adults [35,36]. During menopause, women undergo inevitable changes in the accumulation of body fat, thereby increasing lipids and accelerating blood vessel remodeling. Obesity is known to be closely related to the occurrence of cardio-cerebrovascular diseases, but recent studies have reported that higher waist circumference increases the risk of CAD even after BMI adjustment [8,36]. Therefore, to identify high-risk groups, we need to measure the level of general adiposity using BMI and body composition by simultaneously measuring waist circumference.

Our study has several limitations. First, since data about the occurrence of cardio-cerebrovascular diseases is dependent on the participants' self-report without medical record confirmation,

the possibility that the occurrence of cardio-cerebrovascular diseases has been underreported cannot be excluded. Therefore, further studies are needed to investigate connections using claims-based databases. Second, information about hormone therapy-related characteristics (i.e., hormone use, age at use, or dose after menopause) and psychosocial characteristics (i.e., depression and anxiety) were not obtained. Considering that these characteristics may be potential confounding variables for the cardio-cerebrovascular diseases, it is necessary to conduct follow-up studies that include this data. Third, there may be differences in the duration of the reproductive life span between patients with surgical menopause close to a natural menopause and younger patients with surgical menopause before 45 years of age. Further research is needed to confirm the difference in the incidence rate of cardio-cerebrovascular diseases and risk factors between subgroups according to the cause of menopause. Finally, since this study was based on data from community residents in Korea, and although this national population cohort was recruited using sampling designs and standardized data collection, attention should be paid while generalizing the results to the entire Korean population.

Conclusions

The results of this study revealed a high risk of cardio-cerebrovascular disease, especially in women experiencing early or surgical menopause and long periods of menopause. In addition to that, family history of cardiovascular diseases, elevated BP, and abdominal obesity have also been found to be independent risk factors of cardio-cerebrovascular diseases in women. Therefore, in order to prevent cardio-cerebrovascular disease in menopausal women, health providers should evaluate both types and duration of menopause to screen and monitor high-risk groups. In addition, in public health promotion and health care services, it is essential to provide comprehensive interventions focusing on managing blood pressure and abdominal obesity for menopausal women. In the future, it is suggested to conduct a multiregional cohort study to identify risk factors for cardio-cerebrovascular disease, targeting early menopausal women.

Author Contributions

Jin-Hee Park: Conceptualization and methodology, Formal analysis, Writing—original draft preparation and writing—review and editing, Supervision, Funding acquisition; **Eun Ji Seo:** Conceptualization, Formal analysis, Writing—original draft preparation, Visualization; **Sun Hyoung Bae:** Conceptualization, Formal analysis, Writing—original draft preparation and writing—review and editing.

Data statement

The data in this study were obtained from the KoGES (4851-302), National Research Institute of Health, Centers for Disease Control and Prevention, Ministry for Health and Welfare, Republic of Korea. All data generated or analyzed during this study are included in this published article.

Consent for publication

As part of the informed consent process, permission was sought from the participants to be able to use the collected data in a publication, with the participants remaining anonymous.

Funding

This research was supported by a 2019 grant from the Department of Nursing Science, Graduate School, Ajou University. The data in this study were obtained from the Korean Genome and Epidemiology Study (KoGES) (4851-302), National Research Institute of Health, Centers for Disease Control and Prevention, Ministry for Health and Welfare, Republic of Korea. The study sponsor was not involved in the design of the study, the collection, analysis and interpretation of data, writing the report, or the decision to submit the report for publication.

Ethics approval and consent to participate

Informed written consent was obtained from all participants in accordance with the Declaration of Helsinki guidelines. The Institutional Review Board of Ajou University approved the study protocol (IRB No. AJIRB-SBR-EXP-19-136).

Conflict of interest

The author declare no conflicts of interest.

Acknowledgments

We would like to acknowledge Professor Bumhee Park and his medical statistics team in the Medical Research Collaboration Center, Ajou Research Institute for Innovation Medicine, Ajou University Medical Center for statistical consultation.

References

1. Luepker RV, Lakshminarayan K. 9.2 Cardiovascular and cerebrovascular diseases. In: Oxford Textbook of Public Health [Internet]. 5th ed. London: Oxford University Press; 2009 [cited 2021 May 6]. Available from: https://oxfordmedicine.com/view/10.1093/med/9780199218707.001.0001/med-9780199218707-chapter-0902
2. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis. 2015;241(1):211–8. https://doi.org/10.1016/j.atherosclerosis.2015.01.027
3. Maffei S, Guiducci L, Cugusi L, Cadeddu C, Deidda M, Gallina S, et al. Women-specific predictors of cardiovascular disease risk - new paradigms. Int J Cardiol. 2019;286:190–7. https://doi.org/10.1016/j.ijcard.2019.02.005
4. Daugherty SL, Blair IV, Havranek EP, Furniss A, Dickinson LM, Karimkhani E, et al. Implicit gender bias and the use of cardiovascular tests among cardiologists. J Am Heart Assoc. 2017;6(12):e006872. https://doi.org/10.1161/JAHA.117.006872
5. National Health Service. Early menopause [Internet]. London: NHS; 2021 [cited 2021 May 6]. Available from: https://www.nhs.uk/conditions/early-menopause/
6. Georgakis MK, Beskou-Kontou T, Theodoridis I, Skalkidou A, Petridou ET. Surgical menopause in association with cognitive function and risk of dementia: a systematic review and meta-analysis. Psychoneuroendocrinology. 2019;106:9–19. https://doi.org/10.1016/j.psyneuen.2019.03.013
7. Kingsberg SA, Larkin LC, Liu JH. Clinical effects of early or surgical menopause. Obstet Gynecol. 2020;135(4):853–68. https://doi.org/10.1097/AOG.0000000000003729
8. Muka T, Oliver-Williams C, Kunutsor S, Laven JSE, Fauser BCJM, Chowdhury R, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. JAMA Cardiol. 2016;1(7):767–76. https://doi.org/10.1001/jamacardio.2016.2415
9. Sun Y, Ruan X, Mueck AO. Dependency of cardiovascular risk on reproductive stages and on age among middle-aged Chinese women. Climacteric. 2017;20(5):484–90. https://doi.org/10.1080/13697137.2017.1357691
10. Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, et al. Duration of reproductive life span, age at menarche, and age at menopause are associated with risk of cardiovascular disease in women. J Am Heart Assoc. 2017;6(11):e006713. https://doi.org/10.1161/jaha.117.006713
11. Mishra GD, Kuh D. Health symptoms during midlife in relation to menopausal transition: British prospective cohort study. BMJ. 2012;344(1):e402. https://doi.org/10.1136/bmj.e402
12. Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of

Atherosclerosis. Menopause. 2012;19(10):1081–7. https://doi.org/10.1097/gme.0b013e3182517bd0
13. Choe SA, Sung J. Trends of premature and early menopause: a comparative study of the US National Health and Nutrition Examination survey and the Korea National Health and Nutrition Examination survey. J Kor Med Sci. 2020;35(14):e97. https://doi.org/10.3346/jkms.2020.35.e97
14. Hong JS, Yi SW, Kang HC, Jee SH, Kang HG, Bayasgalan G, et al. Age at menopause and cause-specific mortality in South Korean women: Kangwha cohort study. Maturitas. 2007;56(4):411–9. https://doi.org/10.1016/j.maturitas.2006.11.004
15. Kim Y, Han BG, KoGES group. Cohort profile: the Korean Genome and epidemiology study (KoGES) consortium. Int J Epidemiol. 2017;46(4):e20. https://doi.org/10.1093/ije/dyv316
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499–502. https://doi.org/10.1093/clinchem/18.6.499
17. Park CY, Lim JY, Park HY. Age at natural menopause in Koreans: secular trends and influences thereon. Menopause. 2018;25(4):423–9. https://doi.org/10.1097/gme.0000000000001019
18. Zhu D, Chung HF, Dobson AJ, Pandeya N, Brunner EJ, Kuh D, et al. Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: pooled analysis of individual data from 10 international studies. Hum Reprod. 2020;35(8):1933–43. https://doi.org/10.1093/humrep/deaa124
19. Seo MH, Kim YH, Han K, Jung JH, Park JG, Lee SS, et al. Prevalence of obesity and incidence of obesity-related comorbidities in Koreans based on national health insurance service health checkup data 2006-2015. J Obes Metab Syndr. 2018;27(1):46–52. https://doi.org/10.7570/jomes.2018.27.1.46
20. National Institute for Health and Care Excellence. Menopause: diagnosis and management [Internet]. London: NICE; 2015 [cited 2020 Nov 18]. Available from: https://www.nice.org.uk/guidance/ng23/
21. Kim HC, Ihm SH, Kim GH, Kim JH, Kim K, Lee HY, et al. 2018 Korean Society of Hypertension guidelines for the management of hypertension: part I-epidemiology of hypertension. Clin Hypertens. 2019;25(1):16. https://doi.org/10.1186/s40885-019-0121-0
22. Bae JM, Park GH. An illustrated guide to medical statistics using SPSS. Seoul: Hannarae; 2012. p. 293–322. Korean.
23. Song KL, Chon JS. Survival analysis using SPSS. Seoul: Hannarae; 2013. p. 159–208. Korean.
24. Lacruz ME, Kluttig A, Hartwig S, Löer M, Tiller D, Greiser KH, et al. Prevalence and incidence of hypertension in the general adult population: results of the CARLA-Cohort Study. Medicine. 2015;94(22):e952. https://doi.org/10.1097/md.0000000000000952
25. Sylvester MA, Brooks HL. Sex-specific mechanisms in inflammation and hypertension. Curr Hypertens Rep. 2019;21(7):53. https://doi.org/10.1007/s11906-019-0959-2
26. Kim JY, Hong JY, Kim DK. Association of sudden sensorineural hearing loss with risk of cardiocerebrovascular disease: a study using data from the Korea National Health Insurance Service. JAMA Otolaryngol Head Neck Surg. 2018;144(2):129–35. https://doi.org/10.1001/jamaoto.2017.2569
27. Kim JY, Kim MS, Kim MH, Kim DK, Yu MS. Bell palsy and the risk of cardiocerebrovascular disease: a population-based follow-up study. Laryngoscope. 2019;129(10):2371–7. https://doi.org/10.1002/lary.27802
28. Honigberg MC, Zekavat SM, Aragam K, Finneran P, Klarin D, Bhatt DL, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. JAMA. 2019;322(24):2411–21. https://doi.org/10.1001/jama.2019.19191
29. Young L, Cho L. Unique cardiovascular risk factors in women. Heart. 2019;105(21):1656–60. https://doi.org/10.1136/heartjnl-2018-314268
30. Moonesinghe R, Yang Q, Zhang Z, Khoury MJ. Prevalence and cardiovascular health impact of family history of premature heart disease in the United States: analysis of the National Health and Nutrition Examination Survey, 2007-2014. J Am Heart Assoc. 2019;8(14):e012364. https://doi.org/10.1161/jaha.119.012364
31. Centers for Disease Control and Prevention. Know your risk for heart disease [Internet]. Atlanta: CDC; 2019 [cited 2020 Nov 20]. Available from: https://www.cdc.gov/heartdisease/risk_factors.htm
32. Imes CC, Lewis FM. Family history of cardiovascular disease, perceived cardiovascular disease risk, and health-related behavior: a review of the literature. J Cardiovasc Nurs. 2014;29(2):108–29. https://doi.org/10.1097/jcn.0b013e31827db5eb
33. Guo X, Zhang X, Guo L, Li Z, Zheng L, Yu S, et al. Association between prehypertension and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Curr Hypertens Rep. 2013;15(6):703–16. https://doi.org/10.1007/s11906-013-0403-y
34. Huang Y, Cai X, Liu C, Zhu D, Hua J, Hu Y, et al. Prehypertension and the risk of coronary heart disease in Asian and Western populations: a meta-analysis. J Am Heart Assoc. 2015;4(2):e001519. https://doi.org/10.1161/jaha.114.001519
35. Kim HY, Kim JK, Shin GG, Han JA, Kim JW. Association between abdominal obesity and cardiovascular risk factors in adults with normal body mass index: based on the sixth Korea National Health and Nutrition Examination Survey. J Obes Metab Syndr. 2019;28(4):262–70. https://doi.org/10.7570/jomes.2019.28.4.262
36. Sun Y, Liu B, Snetselaar LG, Wallace RB, Caan BJ, Rohan TE, et al. Association of normal-weight central obesity with all-cause and cause-specific mortality among postmenopausal women. JAMA Netw Open. 2019;2(7):e197337. https://doi.org/10.1001/jamanetworkopen.2019.7337