Body Mass Index and Mortality of Cardiovascular Disease by Smoking and Age at menopause among postmenopausal women: A Kangwha Cohort Study

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Nemekhee Odongua

TABLE OF CONTENTS

List of Figures

List of Tables

List of Appendices

Abstract

Body Mass Index and Mortality of
Cardiovascular Disease by Smoking and Age at Menopause among
Postmenopausal Women: A Kangwha Cohort Study

Background and Purpose-The association between body mass index (BMI) and mortality caused by subtypes of stroke among postmenopausal women by smoking status and age at menopause remained controversial.

Methods-The data were derived from a cohort study of 3,321 with 17.8 years of follow-up (1985-2002). Hazard ratios and 95% confidence intervals for strokes as related to BMI were estimated by Cox proportional hazard models adjusted for age, hypertension, smoking, drinking, occupation, education, self-reported health, and age at menopause. A stratified analysis was conducted by age at menopause and smoking status.

Results-The obese group (BMI ≥27.5 kg/m^2) had higher risks of total stroke mortality (hazard ratio [HR] =1.59; 95% confidence interval [CI], 1.05-2.42) and hemorrhagic stroke mortality (HR=2.91; 95% CI, 1.37-6.19) than the normal weight group (18.5≤BMI<23.0). Among ever smokers, the obese group showed significantly increased risks of total stroke mortality (HR=2.33; 95% CI, 1.00-5.43) and ischemic stroke mortality (HR=7.21; 95% CI, 1.18-44.3). Obesity had more effect on stroke mortality among women who experienced menopause at age <50 than women with age ≥50. For the obese group of the none smoker, the

hazard ratio of total stroke was 2.04 (95% CI, 1.25-3.34) and that of hemorrhagic stroke 6.46 (95% CI, 2.42-17.25).

Conclusions-In this prospective study, obesity raised the risks of total stroke mortality and hemorrhagic stroke mortality among Korean menopausal women. It was more evident with women who experienced menopause at age <50. The obese group of ever smokers was at an increased risk of ischemic stroke mortality.

I. Introduction

Obesity is a contemporary global public health problem and there are 315 million people who are obese according to a WHO report (WHO, Global Database on Body Mass Index 2004). Being overweight is a well-documented risk factor for chronic diseases such as cancer, diabetes and cardiovascular diseases (Calle et al. 1999; Jee et al. 2006; Song et al. 2007; Park et al. 2008). However, the association between body mass index (BMI) and coronary heart disease and strokes are less clear (Rexrode et al. 1997; Feigin et al. 2005; Sturgeon et al. 2007). Cardiovascular disease (CVD) is a leading cause of disability and death among elderly women in developed countries (Bushnell et al. 2006). In 2005, the mortality rate from stroke in South Korean women was 67.3 deaths/100,000 person-years (National Statistical Office. Year book of causes of death, 2005. National Statistical Office, Republic of Korea 2005).

Obesity is well documented as being closely related to insulin resistance and is inversely associated with adiponectin plasma concentrations. Overweight and obesity, affecting the majority of the general adult population, are a continuingly increasing problem in also the lower socioeconomic sectors and children (Jurimae et al. 2009). The prevalence of abdominal obesity in the United States continues to grow, even within the 21st century. Waist circumference, a measure of abdominal obesity, is increasing most rapidly in the sub-population of postmenopausal women (Calle et al. 1999; Deurenberg et al. 1999).

Over 19 million American adult women are obese, and the age group in which obesity is most prevalent (over 25%) is the 50–59 year-olds. European countries have slightly lower obesity rates that in the United States among women, these ranged from 6% in France and 8% in Italy, to 20% in Hungary and Rumania. In Israel, about 50% of women were defined overweight in the year 2000

(Creatsas et al. 2005; Manson et al. 1995; Bogers et al. 2007; Rodriguez et al. 2002; Perez et al. 2009). While it is currently unclear if menopausal transition itself brings about weight gain, it is known that this physiological withdrawal of estrogen brings about changes in fat distribution: the proportion of android (upper-body) fat to gynoid (lower-body) fat deposition is greater in postmenopausal than in premenopausal women, and the use of hormone replacement therapy decreases this shift (Crist et al. 2009; Feng et al. 2008). This update will discuss the recent literature on lifestyle changes useful in the treatment of postmenopausal obesity, focusing on diet and physical activity. Age at natural menopause is related to the increase in risk and is also predictive of CVD mortality (Hu et al. 1999; Manson et al. 1995).

As a result, coronary artery disease (CAD) and strokes are the two main contributors to mortality among post-menopausal women. Most women suffer strokes relatively late in life (Hu et al. 1999). Incidence climbs precipitously after menopause and incidence rates are particularly high in Asians and African Americans (Atsma et al. 2006). Although observational studies had suggested that estrogen reduced the risk of cardiovascular diseases (CVD) in postmenopausal women, the two largest randomized clinical trials on estrogen hormone therapy and CVD not only failed to confirm the observational studies but found that estrogen therapy increased both the risk of stroke and of coronary heart diseases (CHD) and did not affect stroke and CHD incidence in postmenopausal women (Tan et al. 2009).

Menopause is a pathophysiological change that begins at an average age of 50 years but the mechanism through which menopause exerts its effect on vascular incidents remains unknown. Also, menopause is known to cause major physiological changes in women (i.e., hormonal profile, blood pressure, lipid levels, and body fat distribution) that might affect the association between BMI

and mortality. The beneficial effects of hormone replacement (HR) in menopausal women on cardiovascular comorbidities are still under consideration. The Heart and Estrogen/ Progestin Replacement Study (HERS) was a secondary prevention study that recruited postmenopausal women who experienced acute myocardial infarction. This study observed an increase in coronary events within the first year of follow-up in women treated with a combination of conjugated estrogens /medroxy progesterone acetate (Rossouw 2008; Rossouw, 2007; Hulley et al. 1998).

The Women's Health Initiative (WHI) was a primary prevention study designed to follow 160 000 postmenopausal women for 15 years. After 5.2 years, the study was halted because of a higher incidence of cerebrovascular events in women with HR compared with women receiving placebo. Additionally, HERS and WHI reported increased risk of venous thromboembolism with the use of HR.A second primary prevention study was the Women's International Study of Long-Duration Oestrogen after Menopause (WISDOM). This study was stopped in light of the WHI observations. The HR intervention in evidence-based guidelines for CVD prevention in women received Class III recommendations (Grady et al. 2002).

The control of other major risk factors of CVD such as lipids, glucose, blood pressure, and weight management, should be according to guidelines. Estrogen and aging are important for vascular health in women. Estrogen withdrawal in women is associated with adverse effects on the cardiovascular system. Hormone replacement therapy has not proved yet to be of beneficial effect in clinical practice in terms of vascular disease prevention. This may be attributed to the fact that clinical studies involved older women (many years after menopause) (Arana et al. 2006). The studies that will involve younger women for HR therapy may be more encouraging. Until then, risk factors, and especially a

pathological lipid profile, should be treated (lifestyle modification or/and hypolidemic drugs) in menopausal women. For a better understanding, the impact of the menopausal status on the association between BMI and mortality needs to be examined according to the specific causes of deaths (Cui et al. 2005).

Smoking as a risk factor for chronic disease is well documented (Kurth et al. 2003; Nakamura et al. 2008; Anderson et al. 2004). Smoking has been shown to decrease age at menopause and is a well-known risk factor for cardiovascular disease (Feigin, 2005). Women with a higher age at menopause may be older at time of inclusion in the study than women with a lower age at menopause. After controlling for confounding by age and smoking, the relationship between postmenopausal status and cardiovascular disease were disappeared. In contrast, the effect of early menopause was more pronounced after controlling for age and smoking. A few studies assessed women who had menopause at younger than normal ages and reported the increased risks of CHD and stroke. However, how differently obesity affects stroke between ever smokers and never smokers or between women going through early menopause and late menopause is not yet clearly established (Prentice et al. 2009; Yi et al. 2009).

Overall, there was no convincing relationship between postmenopausal status and cardiovascular disease. With the increased longevity of women and the growing socioeconomic burden from CVD, we need to identify risk factors pertaining to CVDs of postmenopausal women to help prevent CVD (Lisabeth et al. 2009).

However, there was a modest effect of early menopause on cardiovascular disease. The effect was more pronounced for women with an artificial menopause than for women who underwent natural menopause (Lobo 2007a; Lobo 2007b). Despite the tremendous progress in coronary heart disease (CHD) treatment in the past 25 years, this condition remains the largest cause of mortality among women

in the world, according to the recent American Heart Association (AHA) preventive guidelines (Broderick et al. 2007). Also, menopausal transition is well known to be associated with a greater intra-abdominal fat deposition, a shift toward a more atherogenic lipid profile, impaired glucose-insulin homeostasis, and increased blood pressure. This cluster of complications is now referred to as metabolic syndrome (MS) by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP/ATP III). According to the NCEPATP III guidelines, 5 in women, MS is identified in clinical practice with the presence of three or more of the following criteria: fasting glycemia of 6.1 mmol/L or greater, triglyceride levels 1.69 mmol/L or greater, high-density lipoprotein (HDL) cholesterol (CHOL) levels less than 1.29 mmol/L, resting BP 130/85 mm Hg or greater, and waist circumference greater than 88 (Bogers et al. 2007; Stampfer et al. 1991). Postmenopausal women often display a hyperandrogenic state, which has often been reported to contribute to the emergence of this condition, thus leading to higher CHD risk. Because of the uncertainty of the risks/benefits associated with hormone therapy (HT) use there is an increasing need for alternative therapies that can decrease CHD risk in postmenopausal women (Pelliccia et al. 2009). In this regard, brisk walking is likely to be the most successful physical intervention to reduce CHD risk and mortality in women because of its safety, accessibility, and popularity (Lisabeth et al. 2009).

Previous studies that examined the effects of walking programs different in length, intensity, and duration have shown not only net ameliorations in aerobic fitness but also substantial reductions in the body weight, fat mass and abdominal adiposity of moderately obese postmenopausal women (Prentice et al. 2009). However, substantial difference exists between cardiorespiratory fitness (CRF) improvements and metabolic risk profile changes of overweight to obese dyslipidemic individuals subjected to endurance exercise (Neuhouser et al. 2009).

Although low CRF was considered as one of the strongest risk factors for CHD and related mortality, as well as an independent predictor of MS, the decrease in CHD risk after endurance training depended on reduced body fatness rather than on increased aerobic fitness (Kurth et al. 2006).

II. Objectives

The purpose of this study is to explore and investigate the relationship between body mass index and risk of mortality for cardiovascular disease such as atherosclerotic disease, ischemic heart disease, and strokes by smoking status and age at menopause among postmenopausal women from Kangwha cohort study.

Specially:

1. To estimate the relation between baseline BMI and mortality of atherosclerotic disease, ischemic heart disease, and strokes
2. To stratify analysis according to smoking status (ever smoker, and never smoker)
3. To stratify analysis according to age at menopause status (age at menopause <50, and ≥50)

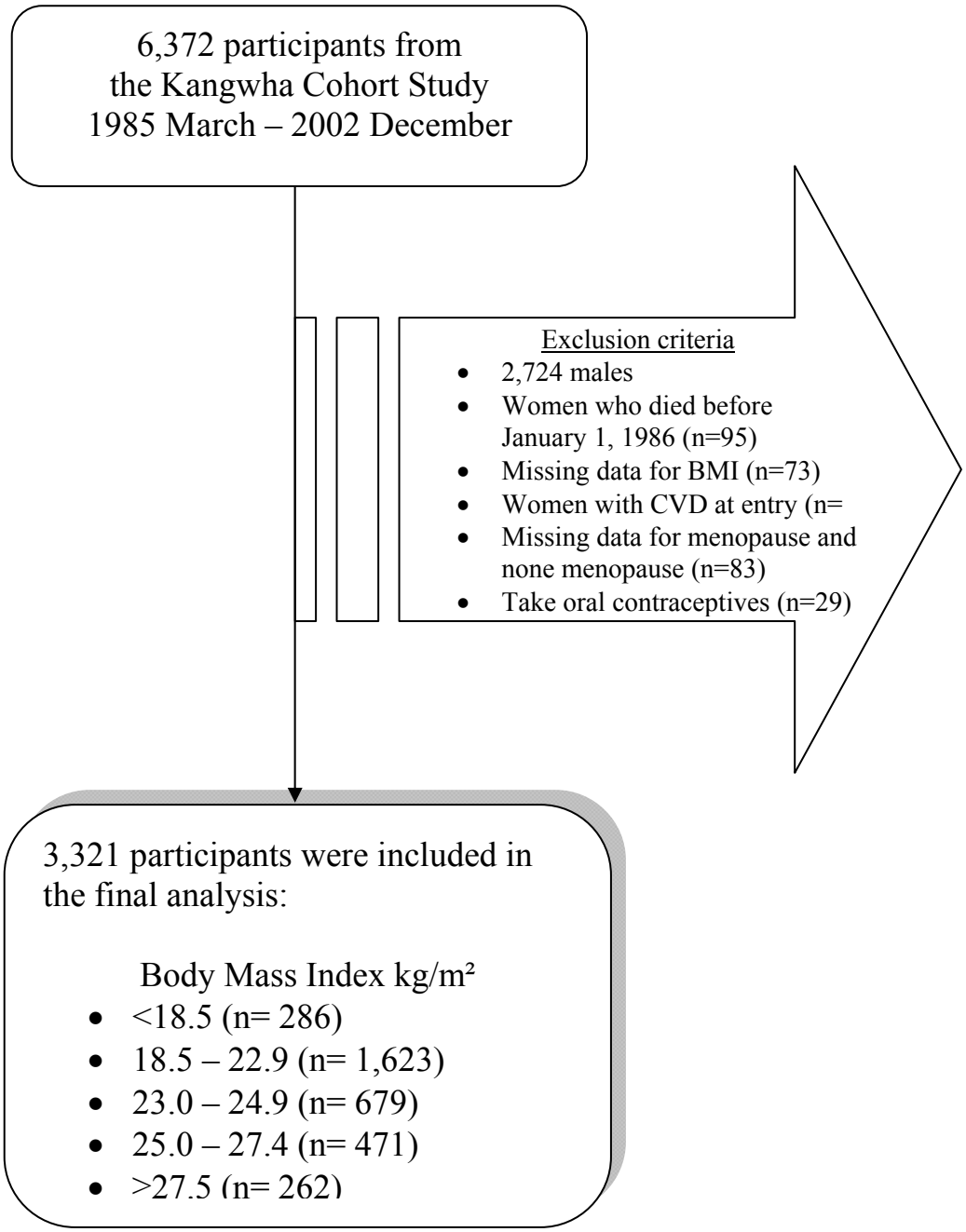

Figure 1. Selection procedure of the study population.

III. Subjects and Methods

1. Study Participants

This study used the data from the Kangwha Cohort study and included 3,648 South Korean women at least 55 years old. The Kangwha Cohort was first established to examine risk factors influencing the development of various cancers, CVD, and other causes of death in the elderly.

Kangwha County consists of several islands located approximately 50km west from Seoul. The population of this county was 71,116 in 1993. The population recruited for Kangwha Cohort study included residents aged ≥55 years who were born before 1930 in 10 administrative districts (eups and myeons in Korean) of Kangwha County on February 28, 1985, based on their resident registration records (total, 9,378; male, 3,938; female, 5,440). Six thousand three hundred, seventy two persons (2,724 males, 3,648 females) agreed to participate in the interview and medical examination in the 1985 survey. The rate of participation was 67.9% (Hong et al. 2007a;, Hong et al. 2007b).

To avoid the confounding of pre-existing diseases, data for 95 women who died or followed up only before January 1, 1986, were excluded from analysis as were data for 73 women with missing BMI information. We also excluded data for women with strokes at entry (n = 47), not having menopause (n = 12), without known menopausal status (n = 71) and who had taken oral contraceptives (n = 29). We then analyzed the remaining dataset for 3,321 postmenopausal subjects.

This study was approved by the Institutional Review Board of Human Research of Yonsei University (Approval No 4-2007-0182).

2. Baseline Data Collection and Follow-Up

Baseline data included self-reported information of study participants. Twenty six trained staff reviewed completed questionnaires and entered the data. Each subject was interviewed using a structured questionnaire for demographic characteristics data: education, occupation, health conditions at entry, health behaviors, diet, and other factors.

Questions on reproductive factors included age at menarche, menopause and first birth, marital status and number of children. Age at menopause was recorded with the age at which each participant reported her last menstruation. Lifestyle related factors, including smoking habits, alcohol drinking were also described. The weight and height measurements were recorded with participants wearing light clothing.

Body mass index (BMI) was calculated as weight (kg) divided by height (m^2) and blood pressure with a standard mercury sphygmomanometer when the individual was seated. The blood pressure measurement training was provided with an educational audio tape that the London School of Hygiene & Tropical Medicine produced; and the interobserver error in blood pressure measurement was with in 2 mmHg. Systolic blood pressure and diastolic blood pressure were measured as the first and fifth Korotkoff sounds, respectively. The blood pressure was measured once per person.

The study subjects were followed up from March 1985 until December 31, 2002, and the follow-up period for each subject was calculated in months. The total observed person-times was 45,362 person years ,median person-times was17.5 person- years (interquartile range, 9.5 to 17.8), and mean person-times was 13.6 person-years.

3. Outcome Ascertainment

In Korea, the Annual Report on the Cause of Death Statistics is published to analyze and provide causes of death in a systematic manner. All deaths were registered within one month after knowing of the death through required papers (Notice of death and medical certificate of death). Death registration is stipulated in the family register law. The local government office accepts the papers after scrutiny, inputs the data to PC, and transmits the data. Lastly, National Statistical Office (NSO) collects and edits the data, and codes the cause of deaths.

In this study, deaths among subjects from January 1, 1992 to December 31, 2002 were confirmed by matching the information to death records from the National Statistical Office. Data for those who died from March 15, 1985 to December 31, 1991 were collected either through calls and visits of trained surveyors twice a year or from records of burial and death certificates of eup and myeon offices that are administrative branch offices of the local government in Korea. Causes of death from 1992 to 2002 which were provided by the National Statistical Office of Korea, were presented in accordance with the International Classification of Disease, Tenth Revision, where as causes of death before 1992 were coded under International Classification of Disease, Tenth Revision (ICD-10) by 2 medical doctors.

The main outcome variables for this study were death due to total, hemorrhagic, and ischemic stroke as defined by International Classification of Disease, Tenth Revision. The ICD-10 codes as following total stroke (I60-I69), ischemic stroke (I63) and hemorrhagic stroke (I60-I62). We noted that there were no cases with I65 and I66 (Suh et al. 2001). However, computed tomography and magnetic resonance imaging are routinely used in the diagnosis of stroke, and a radiologist's reading is required for insurance claims. According to a nationwide

survey of 152 representative hospitals, computed tomography and/or magnetic resonance imaging were used for 89% of hospital admissions for stroke in 2000 (*Ministry of Health and Welfare. Pilot test of National Cardiovascular Disease Surveillance System. Seoul, Korea: Ministry of Health and Welfare, 2000*).

4. Definition of Menopause

The definition of menopause was defined as women were asked of the age when they experienced their last menstruation. In this study chronic diseases, hospitalization history, and, if they had ever been hospitalized, kind of disease were questioned. No one in the study population suffered or had ever suffered cancers of genitourinary system such as uterine cancer or ovarian cancer. Some had diseases of the genitourinary system (ICD9: 580-629) that had been diagnosed during hospitalization, but the number was only 17 and there was no record for operations such as hysterectomy (http://www.menopause.org/). Therefore, all 3,321, the final study population, are supposed to have experienced natural menopause.

Research into the use of HRT was not implemented for this study. This study had 116 women who had used oral contraceptives and we have excluded them from our study. Unfortunately, our data did not contain any information on HT. Research into the use of HT was not implemented for this study. But HRT was rarely introduced in Korea before 1985. Moreover, Kangwha County was a rural island where medical or socio-economical standard was failing behind. Therefore, it is believed that HRT was almost not used in Kangwha County.

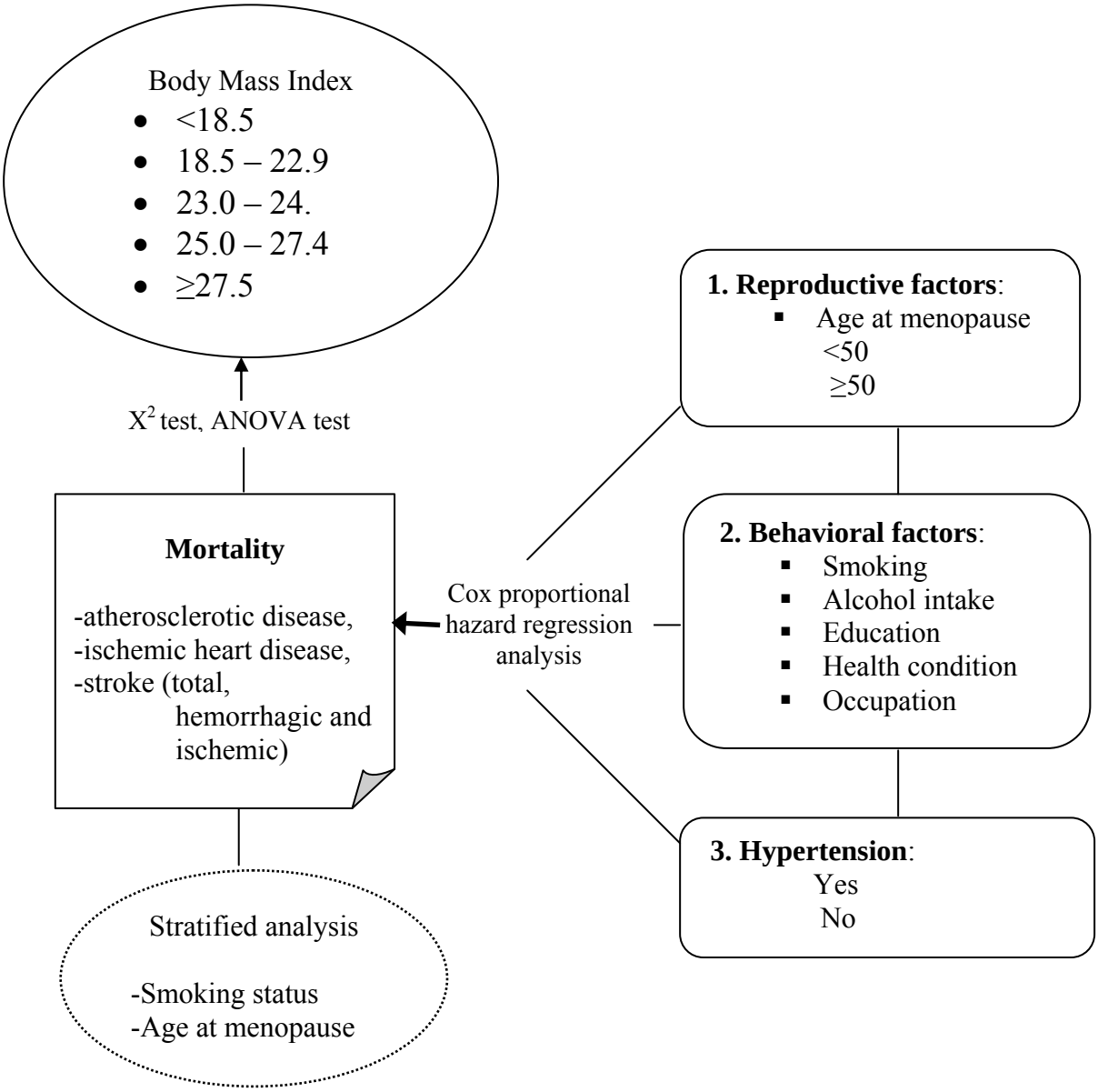

Figure 2. Flow of the study analysis.

5. Statistical analysis

Cox proportional hazards models were used to evaluate the relation between baseline BMI and stroke mortality. Subjects were divided into five groups by BMI: less than 18.5, 18.5 to 22.9, 23.0 to 24.9, 25.0 to 27.4, more than 27.5. Analyses were performed only for postmenopausal women and were adjusted for the following covariates: age at entry in 5-year categories, systolic and diastolic blood pressure (continuous), smoking status (never, ever), alcohol consumption (never, ever), and occupation (agriculture, non-agriculture), age at menopause, and self reported health compared with the same age group (better, similar worse).

Additionally, we performed a stratified analysis according to smoking status and age at menopause (less than 50 [age at early menopause], and over 50 [age at late menopause]). We also accessed potential modification of the effect of BMI by smoking status (two categories, one consisting of current and ex-smokers and one of nonsmokers) and age ate menopause (two categories). Hazard ratios (HRs) and 95% confidence intervals (CIs) were expressed for the results and *P* values were calculated by the two-tail test. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC) (Yun et al. 2006; Odongua et al. 2007).

Also, Endnote program was used to collect bibliography and generate the reference lists for this dissertation.

IV. Results

1. General characteristics of the study population

During the 17.8 years of follow-up, following cardiovascular disease outcomes were identified: 409 all cardiovascular diseases, 26 coronary heart disease, 117 other circulatory diseases, and 236 total strokes 51 hemorrhagic and 137 ischemic stroke causes among the study participants (Table 1).

The average BMI was 22.7 kg/m^2 and majority of subjects had BMI <25.0. Only 7.9% of subjects had BMI >27.5. Mean age at menopause was 46.7, women with higher BMI >27.5 had early menarche age, mean age of first child delivery was 21.7 and mean of number of children was 4.8. Almost more than 60% of women had age at menopause <50 (Table 2).

More than half (59.0%) had hypertension and about 10% had used antihypertensive drugs and alcohol. Past smokers were just 2.0%. Most of subjects engaged in agriculture. Almost all subjects (98.8%) had received no formal education or had been educated only at an elementary school level (Table 3).

Table 1. Study outcomes with *ICD 10* codes and blood pressure by body mass index

Variables	Body mass index				
	<18.5	18.5 – 22.9	23.0 – 24.9	25.0 – 27.5	≥27.5
	Mean ± (SD) *				
Systolic Blood Pressure (mmHg)	144.5 (32.01)	148.0 (53.05)	148.1 (29.72)	150.2 (32.46)	157.8 (32.74)
Diastolic Blood Pressure (mmHg)	63.9 (20.12)	71.1 (50.01)	71.8 (18.44)	74.1 (20.31)	78.7 (20.94)
Mortality	Numbers (%)				
All cardiovascular diseases (I00-I99)	81 (19.94)	78 (19.12)	76 (18.61)	91 (22.32)	83 (20.13)
Coronary heart disease (I20-I25)	6 (23.11)	3 (11.52)	8 (30.83)	7 (26.93)	2 (7.75)
Other circulatory diseases†	30 (25.64)	29 (24.81)	16 (13.74)	23 (19.77)	19 (16.25)
Total strokes (I60 - I69)	43 (18.25)	42 (17.81)	47 (19.97)	52 (22.04)	52 (22.17)
Hemorrhagic strokes (I60-I62)	5 (9.86)	6 (11.82)	13 (25.55)	10 (19.63)	17 (33.37)
Ischemic strokes (I63, I65, I66)	25 (18.26)	29 (21.26)	28 (20.42)	27 (19.74)	28 (20.51)

* Standard deviation

† Other circulatory diseases are included I00.0 – I19.9, I26.0 – 159.9, I70.0 – I99

Table 2. Reproductive factors of all women by body mass index

Variables	Body mass index (kg/m2)					P value*
	<18.5	18.5 – 22.9	23.0 – 24.9	25.0 – 27.5	≥27.5	
No. of women	286	1623	679	471	262	
Person-years of follow up	3,319	21,951	9,535	6,926	3,632	
	Mean (Standard deviation)					
Age at entry (years)	70 (8.61)	67.2 (8.44)	66.1 (7.84)	64.9 (7.34)	64.8 (7.42)	<.0001
Age at menopause (years)	46 (4.81)	46.7 (4.91)	46.7 (4.91)	47 (5.35)	46.9 (5.04)	0.100
Age at menarche (years)	18.0 (5.11)	18.3 (7.21)	17.9 (5.71)	17.6 (4.12)	17.3 (1.78)	0.0871
Age at first delivery	21.6 (7.64)	21.9 (9.84)	21.9 (10.32)	21.2 (5.32)	20.9 (6.98)	0.2079
No of children	4.0 (2.04)	4.9 (6.91)	5.0 (6.64)	4.5 (2.02)	5.4 (8.55)	0.1114
Age at menopause (years)	Numbers (%)					
below 50	198 (69.24)	1049 (64.68)	465 (68.59)	291 (61.82)	166 (63.42)	0.081
50 or above	88 (30.85)	574 (35.49)	214 (31.57)	180 (38.22)	96 (36.65)	

* *P*-value for ANOVA and Chi-square tests

Table 3. Life style factors and health status of study subjects by body mass index

Variables	Body mass index (kg/m2)					P value
	<18.5	18.5 – 22.9	23.0 – 24.9	25.0 – 27.5	≥27.5	
	Numbers (%)					
Antihypertensive therapy	3 (1.04)	17 (1.04)	6 (0.9)	13 (2.8)	13 (3.1)	
Hypertension†						
No	138 (48.3)	714 (44.1)	264 (38.9)	174 (36.9)	71 (27.1)	<.0001
Yes	148 (51.7)	904 (55.9)	415 (61.1)	297 (63.1)	191 (72.9)	
Smoking status						
Never smoked	152 (53.1)	1189 (73.3)	566 (83.4)	384 (81.5)	217 (82.8)	<.0001
Current smoker	129 (45.1)	399 (24.6)	101 (14.9)	76 (16.1)	42 (16)	
Ex smoker	5 (1.7)	35 (2.2)	12 (1.8)	11 (2.3)	3 (1.1)	
Alcohol drinking						
Non drinker	253 (88.5)	1456 (89.7)	612 (90.1)	423 (89.8)	239 (91.2)	0.872
Current drinker	33 (11.5)	167 (10.3)	67 (9.9)	48 (10.2)	23 (8.8)	
Self reported health status						
Better	42 (14.7)	374 (23.1)	157 (23.1)	105 (22.3)	51 (19.5)	0.001
Similar	150 (52.4)	847 (52.3)	382 (56.3)	269 (57.1)	147 (56.1)	
Worse	94 (32.9)	400 (24.7)	140 (20.6)	97 (20.6)	64 (24.4)	
Occupation						
Agriculture	226 (79)	1341 (82.7)	552 (81.3)	365 (77.5)	192 (73.3)	0.002
Education						
No education	248 (86.7)	1311 (80.8)	559 (82.3)	353 (74.9)	201 (76.7)	0.002
Elementary school	37 (12.9)	290 (17.9)	114 (16.8)	107 (22.7)	59 (22.5)	
Middle school or over	1 (0.3)	21 (1.3)	6 (0.9)	11 (2.3)	2 (0.8)	

† Hypertension defined as on hypertension medication or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg

2. Relation between Smoking status and Study Outcomes

Table 4 and 5 showed the hazard ratio of death due to all-cardiovascular disease, coronary heart disease, and other circulatory diseases, and total strokes, hemorrhagic and ischemic strokes by ever smoking status. Total number of deaths was 297, of whom 64 subjects died with strokes. Unadjusted hazard ratio shows that women who had ever smokers with BMI ≥27.5 significantly increased the risk of coronary heart disease, total stroke and hemorrhagic stroke mortality. Among ever smokers, obese women (BMI ≥27.5) had a significantly high unadjusted HR for ischemic stroke mortality and, after adjustment for confounders, were still at significantly high risk for the mortality (HR=7.21)

Table 6 and 7 showed the hazard ratio of death due to all-cardiovascular disease, coronary heart disease, and other circulatory diseases, and total strokes, hemorrhagic and ischemic strokes by never smoking status. Among current and past smokers, unadjusted HR showed that BMI ≥27.5 was significantly associated with total stroke mortality (HR=2.35) and hemorrhagic stroke mortality (HR=5.32). After adjustment for age at entry, hypertension and other variables, women with BMI ≥27.5 had a significantly increased risk of total stroke mortality (p=0.050), which was raised 1.09 times every BMI increase of 1 kg/m2 (p=0.038). After adjustment for confounders, high BMI (BMI ≥27.5) was borderline significantly associated with hemorrhagic stroke mortality (p=0.082).

Table 4. Hazard ratio (HR) for All Cardiovascular Disease (CVD), Coronary heart Disease (CHD), other circulatory disease mortality by ever smoking and body mass index

Variables	Ever smoker			
	No. of Death	Unadjusted HR (95% CI)	Model 1 HR(95% CI)*	Mode2 HR(95% CI)†
ALL CVD				
<18.5	51	1.42 (0.9-2.3)	1.33 (0.8-09)	1.19 0.8-1.7()
18.5-22.9	54	1.00	1.00	1.00
23.0-24.9	53	0.88 (0.5- 1.6)	0.83 (0.5-1.2)	0.93 (0.6-1.3)
25.0-27.4	77	0.99 (0.6-1.5)	0.96 (0.6-1.5)	0.96 (0.5-1.2)
≥27.5	62	0.64 (0.3-1.4)	0.65 (0.3-1.4)	0.65 (0.3-1.4)
Continuous‡	297	1.06 (0.9-1.2)	1.06 (0.9-1.1)	1.06 (0.9-1.2)
CHD				
<18.5	2	4.89 (0.6-39.1)	5.62 (0.6-45)	5.86 (0.7-48.9)
18.5-22.9	2	1.00	1.00	1.00
23.0-24.9	6	0.95 (0.1-5.2)	0.95 (0.1-5.3)	0.90 (0.2-5.1)
25.0-27.4	5	0.24 (0.3-1.3)	0.20 (0.2-1.6)	0.14 (0.0-1.3)
≥27.5	2	0.03 (0.0-1.4)	0.02 (0.0-0.3)	0.01 (0.0-0.2)
Continuous‡	17	1.90 (1.3-2.7)	2.04 (1.3-3.1)	2.17 (1.4-3.3)
Other circulatory diseases				
<18.5	20	0.99 (0.4-2.2)	1.34 (0.4-2.0)	0.93 (0.4-2.1
18.5-22.9	20	1.00	1.00	1.00
23.0-24.9	13	0.71 (0.3- 1.5)	0.93 (0.3-1.6)	0.73 (0.3-1.6)
25.0-27.4	21	1.34 (0.5-3.5)	0.73 (0.4-3.3)	1.28 (0.4-3.3)
≥27.5	14	1.30 (0.2-6.3)	1.28 (0.2-6.3)	1.32 (0.2-6.3)
Continuous‡	88	0.88 (0.7-1.1)	1.31 (0.7-1.1)	0.89 (0.7-1.1)

* Hazard ratio (95% confidence interval) adjusted for age at entry (years) and hypertension, † Hazard ratio (95% confidence interval) adjusted for age at entry (years), hypertension, education (never, elementary school, middle school or over), occupation (agriculture, other), drinking (current drinker, non-drinker), age at menopause (below 50 years old, 50 or above)

‡ Body mass index was used as a continuous variable, per 1 kg/m^2

Table 5. Hazard ratio (HR) for stroke mortality by ever smoking and body mass index

Variables	Ever smoker			
	No. of Death	Unadjusted HR (95% CI)	Model 1 HR(95% CI)*	Mode2 HR(95% CI)†
Total strokes				
<18.5	7	0.89 (0.39-2.01)	0.98 (0.43-2.24)	0.96 (0.42-2.19)
18.5-22.9	32	1.00	1.00	1.00
23.0-24.9	11	1.30 (0.66-2.58)	1.35 (0.68-2.68)	1.34 (0.67-2.67)
25.0-27.4	7	0.99 (0.44-2.25)	1.05 (0.46-2.37)	1.02 (0.45-2.32)
≥27.5	7	2.35 (1.04-5.32)	2.27 (0.99-5.19)	2.33 (1.00-5.43)
Continuous‡	64	1.08 (1.01-1.16)	1.08 (1.00-1.17)	1.09 (1.00-1.17)
Hemorrhagic stroke				
<18.5	0	0.0	0.0	0.0
18.5-22.9	6	1.00	1.00	1.00
23.0-24.9	1	0.64 (0.08-5.29)	0.55 (0.07-4.62)	0.66 (0.08-5.78)
25.0-27.4	2	1.52 (0.31-7.54)	1.38 (0.28-6.85)	1.32 (0.25-6.85)
≥27.5	3	5.30 (1.32-21.21)	3.78 (0.90-15.83)	3.73 (0.84-16.49)
Continuous‡	12	1.21 (1.04-1.41)	1.17 (1.00-1.37)	1.16 (0.98-1.36)
Ischemic stroke				
<18.5	1	1.12 (0.13-10.03)	1.11 (0.12-10.04)	1.19 (0.13-11.10)
18.5-22.9	4	1.00	1.00	1.00
23.0-24.9	1	0.94 (0.11-8.41)	0.95 (0.11-8.53)	0.88 (0.10-8.02)
25.0-27.4	2	2.20 (0.40-12.00)	2.22 (0.40-12.20)	1.98 (0.35-11.23)
≥27.5	2	6.05 (1.11-33.09)	6.25 (1.06-36.76)	7.21 (1.18-44.27)
Continuous‡	10	1.18 (0.99-1.40)	1.18 (0.98-1.42)	1.17 (0.97-1.42)

* Hazard ratio (95% confidence interval) adjusted for age at entry (years) and hypertension, † Hazard ratio (95% confidence interval) adjusted for age at entry (years), hypertension, education (never, elementary school, middle school or over), occupation (agriculture, other), drinking (current drinker, non-drinker), age at menopause (below 50 years old, 50 or above)

‡ Body mass index was used as a continuous variable, per 1 kg/m^2

Table 6. Hazard ratio (HR) for All Cardiovascular Disease (CVD), Coronary Heart Disease (CHD), other circulatory disease mortality by never smoking and body mass index

Variables	Never smoker			
	No. of Death	Unadjusted HR (95% CI)	Model 1 HR(95% CI)*	Mode2 HR(95% CI)†
ALL CVD				
<18.5	30	1.35 (0.7-2.5)	1.34 (0.7-2.5)	1.33 (0.7-2.5)
18.5-22.9	24	1.00	1.00	1.00
23.0-24.9	23	0.94 (0.5- 1.7)	0.95 (0.5- 1.8)	0.85 (0.4-1.6)
25.0-27.4	14	0.58 (0.2-1.3)	0.60 (0.2-1.4)	0.59 (0.2-1.3)
≥27.5	21	0.51 (0.1-1.7)	0.49 (0.1-1.7)	0.47 (0.1-1.6)
Continuous‡	112	1.14 (0.9-1.3)	1.15 (0.9-1.3)	1.14 (0.9-1.3)
CHD				
<18.5	4	5.71 (0.3-95.8)	4.06 (0.2-14.4)	5.39 (0.2-9.9)
18.5-22.9	1			
23.0-24.9	2	1.67 (0.1-27.1)	2.15 (0.1-69.0)	2.66 (0.1-49.4)
25.0-27.4	2	1.35 (0.0-58.7)	2.31 (0.5-40.5)	1.97 (0.4-94.3)
≥27.5	0	0.00 (0.0-0.0)	0.00 (0.0-0.0)	0.00 (0.0-0.0)
Continuous‡	9	1.28 (0.5-3.0)	1.09 (0.4-2.6)	1.22 (0.4-3.06)
Other circulatory diseases				
<18.5	10	0.74 (0.2-2.5)	0.73 (0.2-2.5)	0.72 (0.2-2.5)
18.5-22.9	9			
23.0-24.9	3	0.46 (0.1-1.9)	0.45 (0.1-1.9)	0.36 (0.8-1.5)
25.0-27.4	2	0.44 (0.6-3.0)	0.45 (0.6-3.1)	0.47 (0.6-3.3)
≥27.5	5	1.25 (0.1-14.0)	1.19 (0.9-14.3)	1.14 (0.9-13.9)
Continuous‡	29	0.93 (0.6-1.3)	0.94 (0.6-1.3)	0.92 (0.6-1.3)

*Hazard ratio (95% confidence interval) adjusted for age at entry (years) and hypertension, † Hazard ratio (95% confidence interval) adjusted for age at entry (years), hypertension, education (never, elementary school, middle school or over), occupation (agriculture, other), drinking (current drinker, non-drinker), age at menopause (below 50 years old, 50 or above)

‡ Body mass index was used as a continuous variable, per 1 kg/m^2

Table 7. Hazard ratio (HR) for stroke mortality by never smoking and body mass index

Variables	Never smoker			
	No. of Death	Unadjusted HR (95% CI)	Model 1 HR(95% CI)*	Mode2 HR(95% CI)†
Total strokes				
<18.5	10	1.23 (0.64-2.38)	1.16 (0.60-2.24)	1.09 (0.56-2.12)
18.5-22.9	75	1.00	1.00	1.00
23.0-24.9	48	1.29 (0.90-1.86)	1.24 (0.87-1.79)	1.25 (0.87-1.80)
25.0-27.4	29	1.09 (0.71-1.67)	1.11 (0.72-1.71)	1.15 (0.74-1.77)
≥27.5	22	1.55 (0.97-2.50)	1.46 (0.90-2.35)	1.45 (0.90-2.34)
Continuous‡	184	1.03 (0.98-1.08)	1.03 (0.98-1.08)	1.03 (0.98-1.08)
Hemorrhagic stroke				
<18.5	2	1.32 (0.30-5.79)	1.32 (0.30-5.80)	1.28 (0.29-5.66)
18.5-22.9	14	1.00	1.00	1.00
23.0-24.9	11	1.58 (0.72-3.49)	1.50 (0.68-3.31)	1.57 (0.71-3.48)
25.0-27.4	7	1.40 (0.57-3.48)	1.31 (0.53-3.27)	1.41 (0.56-3.51)
≥27.5	8	3.04 (1.28-7.25)	2.67 (1.11-6.41)	2.75 (1.14-6.63)
Continuous‡	42	1.09 (1.00-1.20)	1.08 (0.98-1.18)	1.08 (0.99-1.19)
Ischemic stroke				
<18.5	1	1.36 (0.17-11.4)	1.37 (0.17-11.2)	1.45 (0.18-11.9)
18.5-22.9	7	1.00	1.00	1.00
23.0-24.9	4	1.14 (0.33-3.89)	1.07 (0.31-3.67)	1.14 (0.33-3.93)
25.0-27.4	4	1.57 (0.46-5.36)	1.45 (0.42-4.98)	1.54 (0.44-5.34)
≥27.5	0	0.0	0.0	0.0
Continuous‡	16	0.93 (0.79-1.10)	0.92 (0.77-1.09)	0.92 (0.78-1.09)

* Hazard ratio (95% confidence interval) adjusted for age at entry (years) and hypertension, † Hazard ratio (95% confidence interval) adjusted for age at entry (years), hypertension, education (never, elementary school, middle school or over), occupation (agriculture, other), drinking (current drinker, non-drinker), age at menopause (below 50 years old, 50 or above) and self-reported health compared to the same age group (better, similar, worse)
‡ Body mass index was used as a continuous variable, per 1 kg/m^2

3. Relation between Smoking status and Study Outcomes

BMI used as a continuous variable, hypertension and BMI ≥27.5 significantly increased the risk of hemorrhagic stroke mortality, whereas women who experienced menopause at age ≥50 had a significantly elevated risk of ischemic stroke mortality. Among women who experienced menopause at age <50, the obese group (BMI ≥27.5) showed higher risks of total stroke mortality and hemorrhagic stroke mortality than the normal weight group (18.5≤BMI<23.0) in both unadjusted analysis and multivariate-adjusted analysis. For hemorrhagic stroke, unadjusted and multivariate-adjusted HRs (95% CI) for women of BMI ≥27.5 were 7.08 (95% CI, 2.73-18.3) and 6.46 (2.42-17.3), respectively. But there was no significant relationship between BMI and ischemic stroke mortality in those early menopause women. Among women who experienced late menopause (age ≥50), BMI was not significantly associated with mortality from total stroke, hemorrhagic stroke or ischemic stroke.

Table 8. Hazard ratio (HR) for All Cardiovascular Disease (CVD), Coronary heart Disease (CHD),, other circulatory disease mortality by age at menopause ≥50 and body mass index

Variables	Age at Menopause ≥50			
	No. of Death	Unadjusted HR (95% CI)	Model 1 HR (95% CI)*	Mode2 HR (95% CI)†
ALL CVD				
<18.5	29	1.11 (0.5-2.1)	0.99 (0.5-1.8)	1.06 (0.5-2.0)
18.5-22.9	28	1.00	1.00	1.00
23.0-24.9	31	0.98 (0.5-1.7)	1.14 (0.6-2.0)	1.16 (0.6-2.0)
25.0-27.4	27	1.07 (0.5-2.2)	1.23 (0.5-2.6)	1.22 (0.5-2.6)
≥27.5	27	1.05 (0.3-3.2)	1.31 (0.4-4.1)	1.23 (0.3-3.9)
Continuous‡	142	0.95 (0.8-1.1)	0.94 (0.7-1.1)	0.95 (0.8-1.1)
CHD				
<18.5	0	-	-	-
18.5-22.9	1	1.00	1.00	1.00
23.0-24.9	3	-	-	-
25.0-27.4	0	-	-	-
≥27.5	1	-	-	-
Continuous‡	5	5.24 (0.6-41.5)	5.31 (0.6-41.4)	6.27 (0.6-62.5)
Other circulatory diseases				
<18.5	14	0.64 (0.2-1.9)	0.55 (0.1-1.7)	0.60 (0.1-1.8)
18.5-22.9	12	1.00	1.00	1.00
23.0-24.9	7	0.79 (0.2-2.2)	0.90 (0.3-2.6)	0.92 (0.3-2.6)
25.0-27.4	5	1.07 (0.2-4.4)	1.23 (0.2-5.2)	1.20 (0.2-5.1)
≥27.5	7	3.04 (0.4-21.6)	3.85 (0.5-28.9)	3.54 (0.4-26.9)
Continuous‡	45	0.74 (0.5-0.9)	0.72 (0.5-0.9)	0.73 (0.5-1.0)

* Hazard ratio (95% confidence interval) adjusted for age at entry (years) and hypertension, † Hazard ratio (95% confidence interval) adjusted for age at entry (years), hypertension, education (never, elementary school, middle school or over), occupation (agriculture, other), drinking (current drinker, non-drinker), age at menopause (below 50 years old, 50 or above)

‡ Body mass index was used as a continuous variable, per 1 kg/m^2

Table 9. Hazard ratio (HR) for stroke mortality by age at menopause ≥50 and body mass index

Variables	Age at Menopause ≥50			
	No. of Death	Unadjusted HR (95% CI)	Model 1 HR (95% CI)*	Mode2 HR (95% CI)†
Total strokes				
<18.5	6	1.11 (0.47-2.62)	1.22 (0.51-2.88)	0.83 (0.10-6.55)
18.5-22.9	41	1.00	1.00	1.00
23.0-24.9	19	1.17 (0.68-2.02)	1.23 (0.71-2.12)	0.67 (0.19-2.40)
25.0-27.4	14	0.99 (0.54-1.82)	1.10 (0.60-2.03)	1.07 (0.34-3.38)
≥27.5	7	0.97 (0.43-2.15)	0.92 (0.41-2.05)	0.87 (0.19-3.98)
Continuous‡	87	0.99 (0.93-1.06)	1.00 (0.93-1.06)	1.00 (0.87-1.15)
Hemorrhagic strokes				
<18.5	1	0.63 (0.08-4.87)	0.75 (0.10-5.77)	0.78 (0.10-6.19)
18.5-22.9	12	1.00	1.00	1.00
23.0-24.9	3	0.64 (0.18-2.27)	0.63 (0.18-2.25)	0.65 (0.18-2.33)
25.0-27.4	4	0.98 (0.32-3.03)	0.98 (0.31-3.06)	1.06 (0.34-3.36)
≥27.5	2	0.95 (0.21-4.23)	0.80 (0.18-3.58)	0.87 (0.19-3.97)
Continuous‡	22	1.01 (0.88-1.15)	0.99 (0.87-1.13)	1.00 (0.88-1.15)
Ischemic strokes				
<18.5	2	2.61 (0.53-12.95)	2.76 (0.55-13.80)	3.14 (0.57-17.46)
18.5-22.9	6	1.00	1.00	1.00
23.0-24.9	2	0.81 (0.16-4.03)	0.82 (0.17-4.07)	0.90 (0.18-4.51)
25.0-27.4	4	1.90 (0.54-6.74)	2.00 (0.56-7.15)	2.05 (0.57-7.44)
≥27.5	1	0.93 (0.11-7.70)	0.86 (0.10-7.22)	0.96 (0.11-8.16)
Continuous‡	15	0.95 (0.80-1.12)	0.95 (0.80-1.12)	0.95 (0.80-1.13)

* Hazard ratio (95% confidence interval) adjusted for age at entry (years) and hypertension, † Hazard ratio (95% confidence interval) adjusted for age at entry (years), hypertension, education (never, elementary school, middle school or over), occupation (agriculture, other), drinking (current drinker, non-drinker), age at menopause (below 50 years old, 50 or above)

‡ Body mass index was used as a continuous variable, per 1 kg/m^2

Table 10. Hazard ratio (HR) for All Cardiovascular Disease (CVD), Coronary heart Disease (CHD),, other circulatory disease mortality by age at menopause <50 and body mass index

Variables	Age at Menopause <50			
	No. of Death	Unadjusted HR (95% CI)	Model 1 HR (95% CI)*	Mode2 HR (95% CI)†
ALL CVD				
<18.5	52	1.51 (0.9-2.3)	1.49 (0.9-2.3)	1.47 (0.9-2.2)
18.5-22.9	50	1.00	1.00	1.00
23.0-24.9	45	0.75 (0.4-1.1)	0.75 (0.4-1.1)	0.74 (0.4-1.1)
25.0-27.4	64	0.79 (0.4-1.3)	0.74 (0.4-1.2)	0.74(0.4-1.2)
≥27.5	56	0.46 (0.2-1.0)	0.42 (0.1-0.9)	0.42 (0.1- 0.9)
Continuous‡	267	1.13 (1.0-1.2)	1.15 (1.0-1.2)	1.15 (1.0- 1.2)
CHD				
<18.5	6	7.82 (1.2-48.7)	8.13 (1.3-50.9)	8.69 (1.3-5.0)
18.5-22.9	2	1.00	1.00	1.00
23.0-24.9	5	1.34 (0.2-8.1)	1.30 (0.2-7.9)	1.47 (0.2-8.9)
25.0-27.4	7	0.86 (0.0-7.9)	0.82 (0.0-7.6)	0.83 (0.1-7.8)
≥27.5	1	0.02 (0.0-2.9)	0.02 (0.0-2.5)	0.02 (0.0-2.3)
Continuous‡	21	1.48 (0.9-2.3)	1.52 (0.9-2.4)	1.54 (0.9-2.4)
Other circulatory diseases				
<18.5	16	1.07 (0.4-2.4)	1.02 (0.4-2.3)	1.01 (0.4-2.3)
18.5-22.9	17	1.00	1.00	1.00
23.0-24.9	9	0.53 (0.2-1.3)	0.52 (0.2-1.2)	0.50 (0.2-1.2)
25.0-27.4	18	0.96 (0.3-2.6)	0.91 (0.3-2.4)	0.90 (0.3- 2.4)
≥27.5	12	0.64 (0.1-3.4)	0.59 (0.1-3.1)	0.60 (0.1-3.1)
Continuous‡	72	1.01 (0.8-1.2)	1.03 (0.8-1.2)	1.02 (0.8-1.2)

* Hazard ratio (95% confidence interval) adjusted for age at entry (years) and hypertension, † Hazard ratio (95% confidence interval) adjusted for age at entry (years), hypertension, education (never, elementary school, middle school or over), occupation (agriculture, other), drinking (current drinker, non-drinker), age at menopause (below 50 years old, 50 or above)

‡ Body mass index was used as a continuous variable, per 1 kg/m^2

Table 11. Hazard ratio (HR) for stroke mortality by age at menopause <50 and body mass index

Variables	Age at Menopause <50			
	No. of Death	Unadjusted HR (95% CI)	Model 1 HR (95% CI)*	Mode2 HR (95% CI)†
Total strokes				
<18.5	11	1.13 (0.59-2.13)	1.02 (0.54-1.93)	0.95 (0.50-1.80)
18.5-22.9	66	1.00	1.00	1.00
23.0-24.9	40	1.30 (0.88-1.93)	1.27 (0.85-1.88)	1.28 (0.86-1.91)
25.0-27.4	22	1.06 (0.66-1.72)	1.08 (0.66-1.75)	1.11 (0.68-1.81)
≥27.5	22	2.07 (1.28-3.35)	2.02 (1.24-3.28)	2.04 (1.25-3.34)
Continuous‡	161	1.06 (1.01-1.11)	1.06 (1.01-1.12)	1.07 (1.02-1.12)
Hemorrhagic strokes				
<18.5	1	0.85 (0.11-6.83)	0.92 (0.11-7.37)	0.79 (0.10-6.39)
18.5-22.9	8	1.00	1.00	1.00
23.0-24.9	9	2.41 (0.93-6.26)	2.30 (0.89-5.98)	2.50 (0.96-6.55)
25.0-27.4	5	1.99 (0.65-6.07)	1.84 (0.60-5.64)	2.00 (0.65-6.20)
≥27.5	9	7.08 (2.73-18.34)	6.23 (2.37-16.42)	6.46 (2.42-17.25)
Continuous‡	32	1.19 (1.08-1.31)	1.17 (1.06-1.29)	1.18 (1.07-1.30)
Ischemic strokes				
<18.5	0	0.0	0.0	0.0
18.5-22.9	5	1.00	1.00	1.00
23.0-24.9	3	1.28 (0.31-5.35)	1.21 (0.29-5.10)	1.35 (0.31-5.79)
25.0-27.4	2	1.23 (0.24-6.35)	1.13 (0.22-5.90)	1.39 (0.27-7.32)
≥27.5	1	1.28 (0.15-10.91)	1.11 (0.13-9.71)	1.26 (0.14-11.12)
Continuous‡	11	1.08 (0.90-1.29)	1.06 (0.88-1.28)	1.08 (0.90-1.29)

* Hazard ratio (95% confidence interval) adjusted for age at entry (years) and hypertension, † Hazard ratio (95% confidence interval) adjusted for age at entry (years), hypertension, education (never, elementary school, middle school or over), occupation (agriculture, other), drinking (current drinker, non-drinker), age at menopause (below 50 years old, 50 or above)

‡ Body mass index was used as a continuous variable, per 1 kg/

4. Effect Modification between BMI and age at menopause and smoking status

In addition, patterns of effect modification between BMI and age at menopause (Fig 1) and smoking status have been explored (Fig 2). Age at menopause significantly interacted with BMI in terms of the overall occurrence of hemorrhagic stroke ($P = 0.02$). Smoking status also positively interacted with BMI in terms of the overall occurrence of hemorrhagic stroke ($P = 0.05$). The association between BMI and total, and ischemic stroke was not statistical significantly modified by age at menopause and smoking status (P for all stroke types ≥ 0.16). Among women who had high BMI, an increased risk of hemorrhagic stroke was more modified by age at menopause and smoking status.

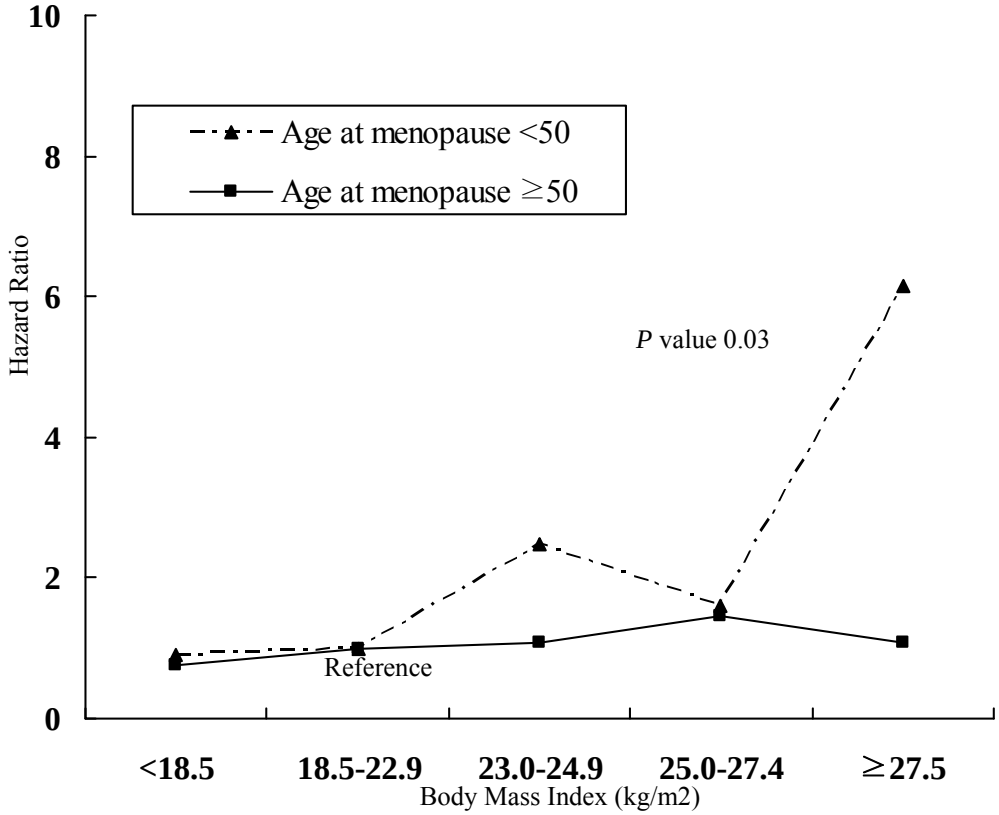

Figure 3. Interaction of Hemorrhagic stroke mortality by age at menopause status, Kangwha Cohort study. Multivariate adjusted for age in five-year categories, systolic and diastolic blood pressure (continuous), smoking status (never, ever), alcohol consumption, and occupation.

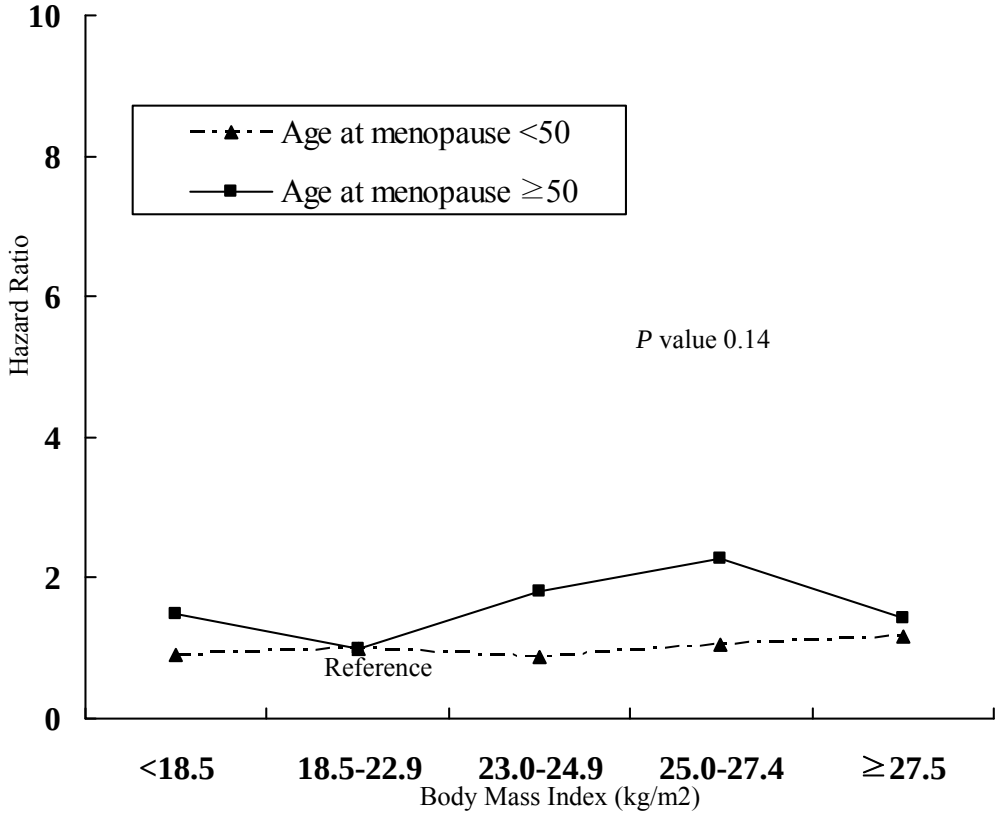

Figure 4. Interaction of Total stroke mortality by age at menopause status, Kangwha Cohort study. Multivariate adjusted for age in five-year categories, systolic and diastolic blood pressure (continuous), smoking status (never, ever), alcohol consumption, and occupation.

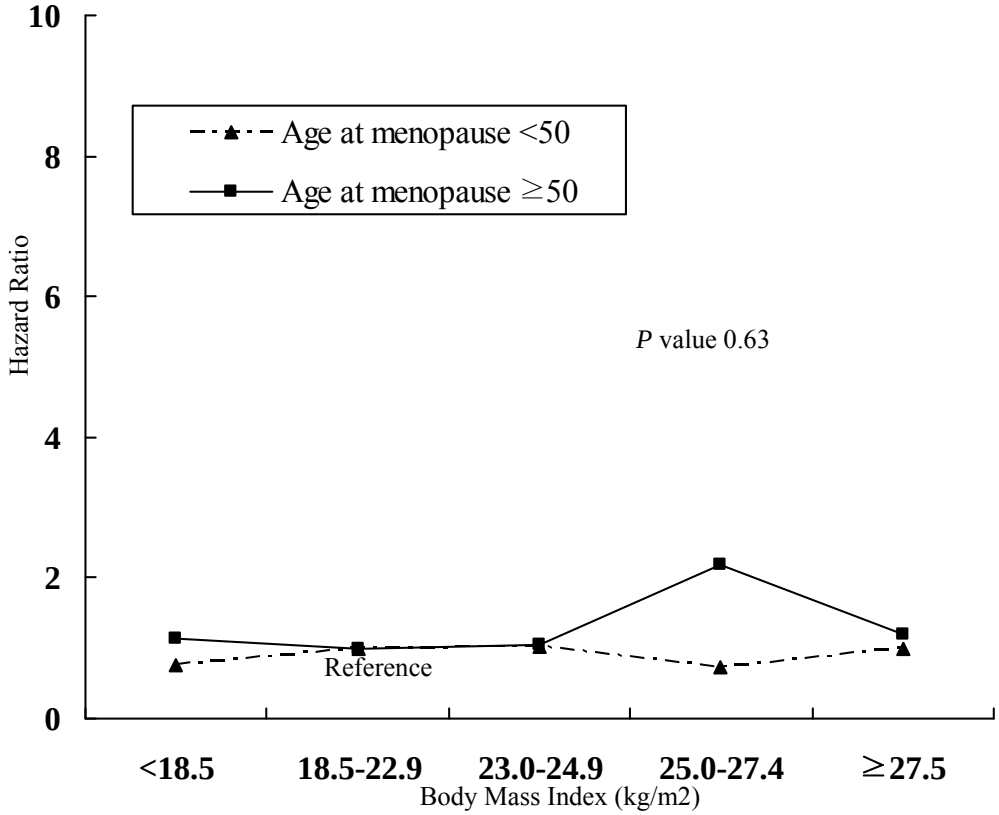

Figure 5. Interaction of Ischemic stroke mortality by age at menopause status, Kangwha Cohort study. Multivariate adjusted for age in five-year categories, systolic and diastolic blood pressure (continuous), smoking status (never, ever), alcohol consumption, and occupation.

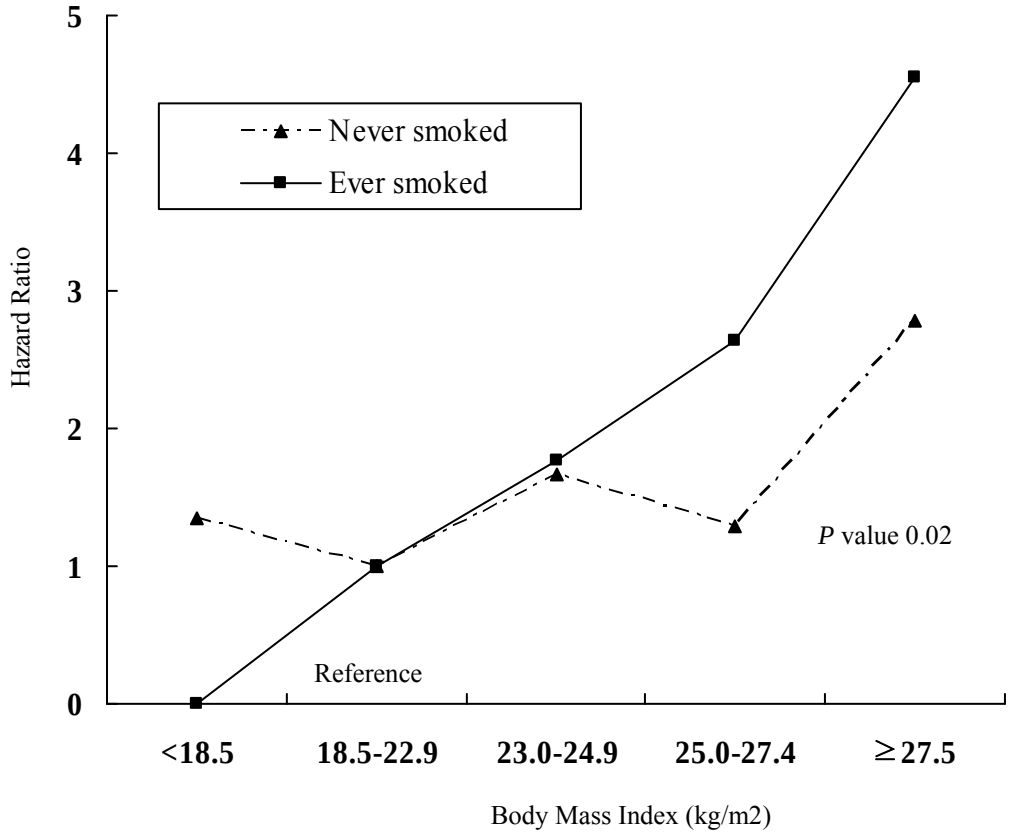

Figure 6. Interaction of Hemorrhagic stroke mortality by smoking status, Kangwha Cohort study. Multivariate adjusted for age in five-year categories, systolic and diastolic blood pressure (continuous), smoking status (never, ever), alcohol consumption, and occupation.

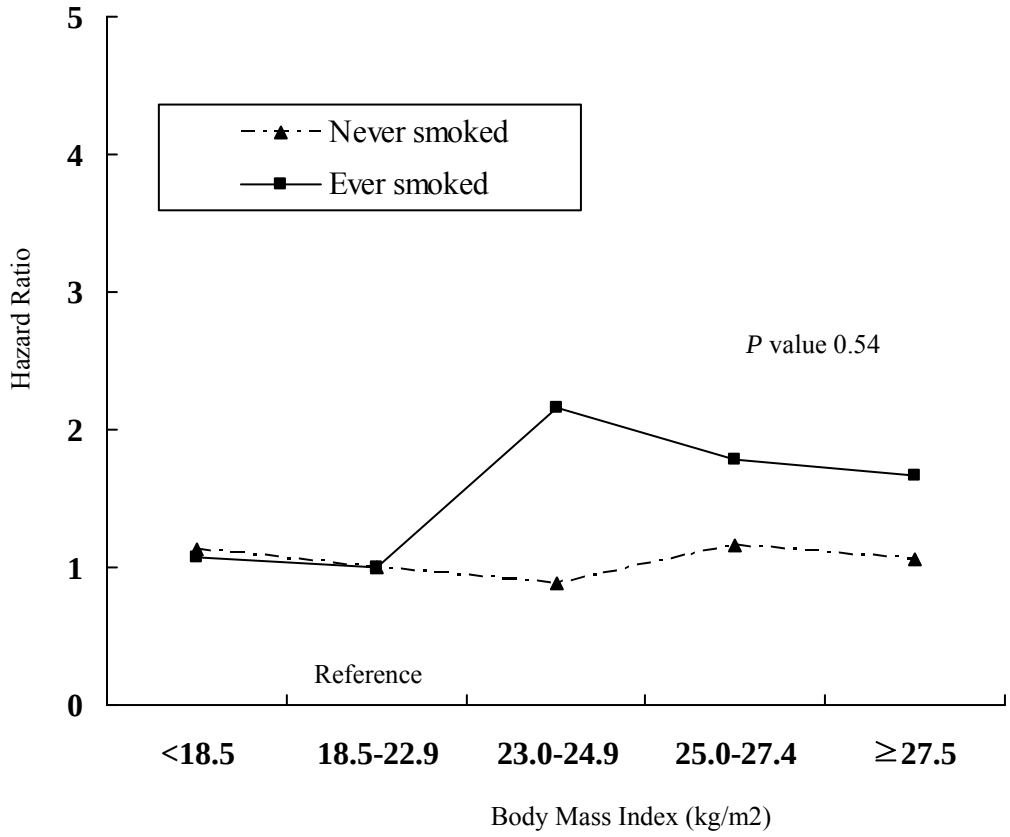

Figure 7. Interaction of Total stroke mortality by smoking status, Kangwha Cohort study. Multivariate adjusted for age in five-year categories, systolic and diastolic blood pressure (continuous), smoking status (never, ever), alcohol consumption, and occupation.

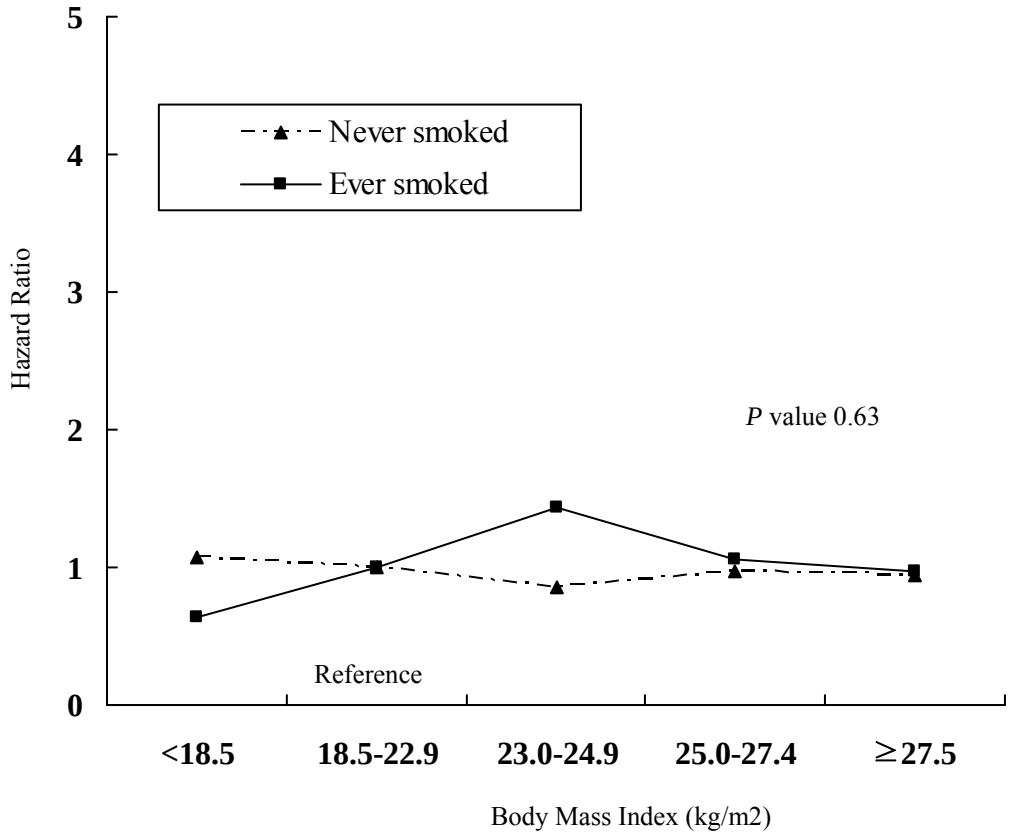

Figure 8. Interaction of Ischemic stroke mortality by smoking status, Kangwha Cohort study. Multivariate adjusted for age in five-year categories, systolic and diastolic blood pressure (continuous), smoking status (never, ever), alcohol consumption, and occupation.

V. Discussion

In this prospective cohort study of Korean postmenopausal women, it is of interest to note that BMI was an independent predictor of mortality for total stroke, particularly for hemorrhagic stroke not for risk factors coronary heart diseases. The association for death due to the total and hemorrhagic stroke mortality was stronger among women who experienced early menopause but not among those experienced late menopause. Meanwhile, among total postmenopausal women, BMI was not associated with ischemic stroke mortality, whereas among smoking postmenopausal women, the obese women (BMI $\geq$27.5 kg/m^2) had a significantly high risk of ischemic stroke mortality (adjusted HR=7.21) in this data.

Although overweight, particularly obesity, is known to be a risk factor for the incidence or death of cardiovascular disease (Villareal et al. 2005; Tice et al. 2006), study results on the relationship between obesity and stroke mortality in Asian populations are not always consistent (Nakamura et al. 2008; Song et al. 2007; Park et al. 2008) . Some studies have also noted a substantially increased risk of total and ischemic strokes among both men and women with a high BMI (Rexrode et al. 1997; Kurth et al. 2005; Jood et al. 2004). However, the association between hemorrhagic stroke and BMI was inconsistent, (Rexrode et al. 1997; Kurth et al. 2006; Rodriguez et al. 2002; Feigin et al. 2005) although another large prospective cohort study among middle aged women in Korea found a positive association. Asian populations have higher incidences of hemorrhagic stroke and also higher percentages of body fat and less muscle mass compared to Western populations (Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies 2004). Our study findings

imply that being overweight or obese may contribute to total and hemorrhagic stroke mortality in Asian populations.

In this study, women who experienced early menopause showed an increased association between BMI and mortality from total strokes, particularly hemorrhagic stroke, whereas no significant association between BMI and stroke mortality was found among women who experienced late menopause. Although Asian women are relatively thin and scarcely show high obesity rate (BMI ≥30), the association between BMI and stroke mortality differs with studies for Asian women. Out of many possible reasons, menopause may be a factor causing the difference. Menopause is known to increase the risk of cardiovascular disease and subsequently the risk of mortality from cardiovascular disease (Hardy et al. 2008). However, only a few studies have examined the relationship between age at menopause and the incidence and death of stroke, and whether BMI affects stroke mortality differently between women who experienced early menopause and late menopause are very rarely studied (Feigin et al. 2003). The findings that BMI may increase cardiovascular disease in elder women remain controversial (Hu et al. 1999). The results of this study imply that the time of menopause has an effect on the relation between BMI and stroke mortality, but the mechanism through which menopause exerts its effect remains unknown (Feldmann et al. 2005).

Among ever smokers, the obese group showed significantly increased risks of mortality from total and ischemic stroke. But no association between BMI and stroke mortality was observed among never smokers (Jacobsen et al. 2004). For hemorrhagic stroke, there was no big difference between BMI and mortality of ever smokers and those of never smokers. The inconsistent results of association between BMI and subtypes of stroke have been reported, and one of the reasons may depend on whether smoking status was stratified (Kanaya et al. 2003). The smoking adversely affects mortality risk and that smokers are known

to be leaner than nonsmokers. Also smoking has been reported to lower the age at menopause. This study stratified subjects into ever smokers and never smokers and examined the relationship between BMI and stroke mortality. Meanwhile, in a Korean study conducted for middle-aged women, among never smokers (Kim et al. 2005), BMI was related with ischemic and hemorrhagic stroke, but among smokers, ischemic stroke was related with high BMI and hemorrhagic stroke was increased at the lowest BMI group (BMI <18.5) (Park et al. 2008). Such differences among studies are supposed to result from study design, age and socioeconomic status of subjects, stroke diagnosis method, and analysis method. Whether stroke risk or mortality differs with smoking status is inconclusive and requires further study (Must et al. 1999; Singh et al. 2001).

The prospective design of this study coupled with long-term follow-up data minimized bias caused by differences in reporting of BMI as a result of stroke mortality. In addition, the self-administered questionnaires and anthropometric measurements were collected by trained surveyors. Thus the probable information bias due to self-reporting was minimized.

This study has several limitations to be discussed. First, women were asked of the age when they experienced their last menstruation, but not questioned to specify whether it was natural or surgical. In this study, chronic diseases, hospitalization history, and, if they had ever been hospitalized, kind of disease were questioned. No one in the study population suffered cancers of genitourinary system. There was no report for operations such as hysterectomy. Women who experienced their last menstruation less than a year ago were just 6. Therefore, our subjects are reasonably supposed to have experienced natural menopause that has no menstruation for more than 12 months. Second, covariates and etiologic mediators such as the use of hormone replacement therapy (HRT), antiplatelet/anticoagulant therapy, diabetes and atrial fibrillation, which may affect stroke mortality, was not

surveyed in details. But HRT, antiplatelet/anticoagulant therapy was rarely introduced in Korea before 1985. Hospitalization experiences for diabetes were 4 cases. Atrial fibrillation was not reported and their prevalence rate was very low. But not to research such factors to adjust must be a limitation. Third, death record follow-up is different between 1985-1991 and 1992-2002. However, stroke deaths from 1985 to 1991 were relatively small as 54 cases (22%), and even when the analysis was made with cases from 1992 to 2002 only, the result was similar. Fourth, the validity of diagnosis of stroke in the death certificates was not examined separately. Computed tomography and magnetic resonance imaging started to be widely used in the diagnosis of stroke in Korea from mid 90's. Therefore, there might be a limitation in the validity of diagnosis of stroke made in late 80's and early 90's. Fifth, subjects were Korean populations of age ≥55, less obese than Western populations, and having scarce HRT experiences. Thus there must be a limitation to generalizing the results of this study and applying them to other populations who are more obese and receive HRT more. Sixth, this study relied on the memory of responders regarding age at menopause, which may be subject to recall bias. Seventh, the sample sizes and numbers of cases were small, which limited to examine association between stroke and all BMI categories of the WHO Asian population classification, and may have limited the statistical power on some analysis.

VI. Conclusion

In this study of Korean postmenopausal women, the obesity group (BMI ≥27.5) had higher risks of mortality from total and hemorrhagic stroke than the normal weight group (18.5≤BMI<23.0). Obesity had particularly more effect on women who experienced early menopause than women who experienced late menopause for the risk of mortality from total and hemorrhagic stroke. Among ever smokers, the obese group showed significantly increased risks of mortality from total and ischemic stroke. But no significant association between BMI and stroke mortality was observed among never smokers, except for hemorrhagic stroke. Further study is required to clarify whether obesity is an independent risk factor for mortality from hemorrhagic stroke and whether BMI, especially obesity, affects the incidence/death of subtypes of stroke differently according to smoking status or age at menopause.

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Abstract in Korean

조기 폐경과 체질량지수가 심혈관질환 사망률에 미치는 영향

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어던과

연구배경 및 목적: 체질량지수 (body mass index, BMI)와 심혈관 질환으로 인한 사망과의 관련성은 알려져 왔으나, 이러한 관련성이 폐경기 여성에 있어서 흡연상태와 폐경연령에 따라 어떤 차이가 있는지 추가 연구가 필요하다. 본 연구에서는 코호트 연구를 통하여 폐경기 여성에서 비만과 뇌졸중 사망과의 관련성을 살펴보고자 하였다.

연구방법: 본 연구는 1985 년에 구축된 ‘ 강화코호트’ 자료를 이용하였다. 면접과 신체검사를 시행할 수 있었던 대상자 중 폐경기 여성 3,321 명을 대상으로 하였으며, 이들은 평균 17.8 년 추적되었다. 비만에 따라서 뇌졸중 사망에 차이가 있는지 살펴보기 위하여 Cox 비례위험회귀모형을 이용하였으며, 위험비(Hazard ratio)와 95% 신뢰구간 (confidence interval, CI) 을 표시하였다. 폐경연령과 흡연상태에 따라 층화하여 분석하였다.

연구결과: 비만군(BMI ≥ 27.5 kg/m^2)의 전체 뇌졸중 사망위험비가 1.59(95% CI: 1.05-2.42)로 정상체중군 (18.5≤ BMI<23.0)에 비해 통계적으로 유의하게 뇌졸중 사망위험이 높았다. 흡연자의 경우 비만군의 전체 뇌졸중 사망위험비와 허혈성 뇌졸중 사망위험비가 각각 2.33(95% CI: 1.00-5.43), 7.21(95% CI: 1.18-44.3)로

정상체중군에 비해 높았다. 비만은 50 세 미만의 조기폐경 여성에서 뇌졸중 사망과의 관련성이 더 높았다. 비흡연자이면서 비만인 그룹의 전체 뇌졸중 사망위험비와 출혈성 뇌졸중의 사망위험비는 각각 2.04(95% CI: 1.25-3.34), 6.46(95% CI: 2.42-17.25) 이었다.

요약 및 결론: 폐경기 여성에서 비만은 전체 뇌졸중과 출혈성 뇌졸중 사망과의 관련성이 있었다. 이러한 결과는 50 세 미만 조기 폐경 여성에서 더 관련성이 높았으며, 과거흡연자이면서 비만한 여성은 허혈성 뇌졸중 사망과 관련성이 있었다.

Appendices

Table 1. Hazard ratio (HR) for stroke mortality by age at menopause and quintile of body mass index by quintile

BMI (kg/m^2)	No. of Cases	Age at Menopause <50		No. of Cases	Age at Menopause ≥50	
		HR (95% CI)*	HR (95% CI)†		HR (95% CI)*	HR (95% CI)†
Total Strokes						
Quintile 1	29	1.00 (0.62-1.67)	0.92 (055-1.53)	14	1.25 (057-2.72)	1.48 (0.67-3.27)
Quintile 2	30	1.00	1.00	12	1.00	1.00
Quintile 3	27	0.96 (0.57-1.62)	0.90 (0.56-1.50)	20	1.56 (0.76-3.21)	1.80 (0.86-3.76)
Quintile 4	33	1.10 (0.67-1.81)	1.05 (0.63-1.72)	19	1.61 (0.78-3.34)	2.27 (1.07-4.83)
Quintile 5	35	1.29 (0.75-2.12)	1.18 (0.71-1.93)	17	1.33 (0.63-2.79)	1.42 (0.67-3.00)
Ischemic strokes						
Quintile 1	17	0.85 (0.45-1.62)	0.77 (0.40-1.47)	8	1.00 (0.38-2.61)	1.14 (0.43-3.04)
Quintile 2	20	1.00	1.00	9	1.00	1.00
Quintile 3	20	1.09 (0.58-2.03)	1.01 (0.54-1.89)	8	0.90 (0.34-2.34)	1.06 (0.39-2.87)
Quintile 4	15	0.75 (0.38-1.47)	0.72 (0.37-1.42)	12	1.37 (0.58-3.26)	2.19 (0.87-5.49)
Quintile 5	19	1.08 (0.57-2.03)	0.98 (0.52-1.85)	9	0.98 (0.39-2.50)	1.19 (0.46-3.12)
Hemorrhagic strokes						
Quintile 1	2	0.56 (0.10-3.11)	0.54 (0.01-2.96)	3	1.56 (0.26-9.35)	1.89 (0.31-2.19)
Quintile 2	4	1.00	1.00	2	1.00	1.00
Quintile 3	5	1.28 (0.35-4.81)	1.24 (0.33-4.69)	8	3.53 (0.75-16.7)	4.12 (0.85-20.1)
Quintile 4	6	1.42 (0.40-5.03)	1.41 (0.39-5.02)	4	2.03 (0.37-11.1)	2.81 (0.49-16.1)
Quintile 5	12	2.86 (0.92-8.88)	2.72 (0.87-8.53)	5	2.26 (0.44-11.6)	2.51 (0.48-13.2)

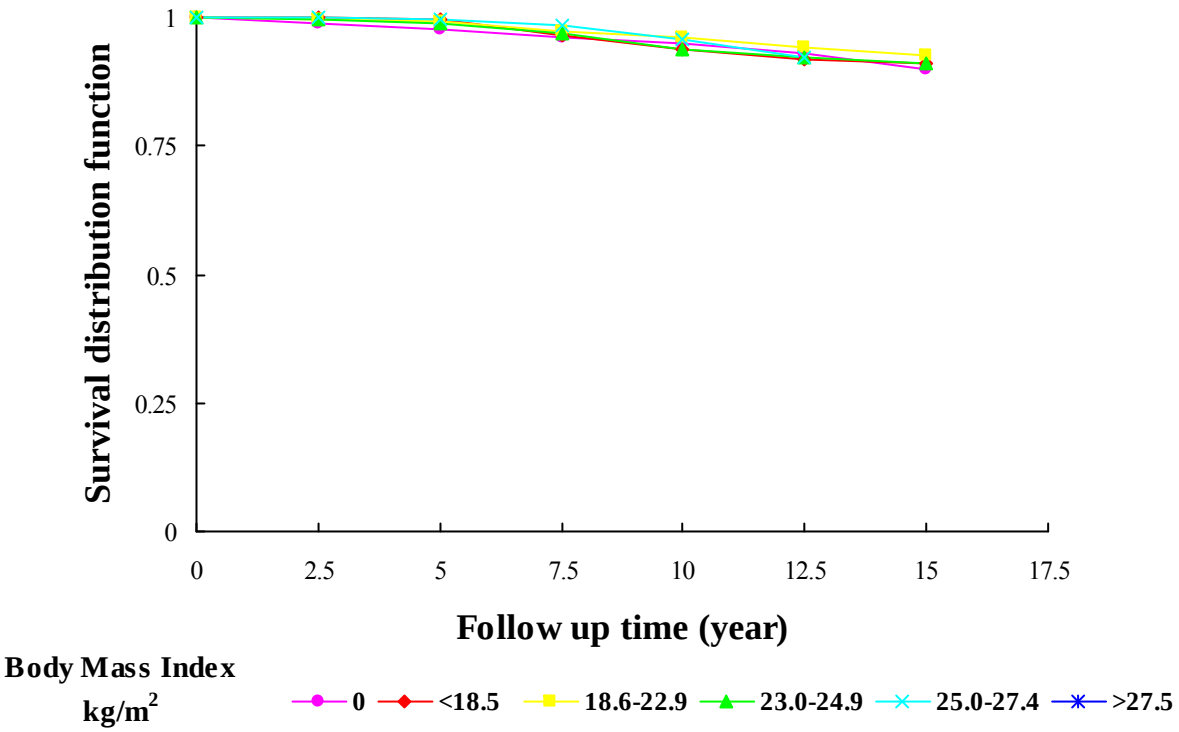

Figure 1. Death of total stroke by body mass index.

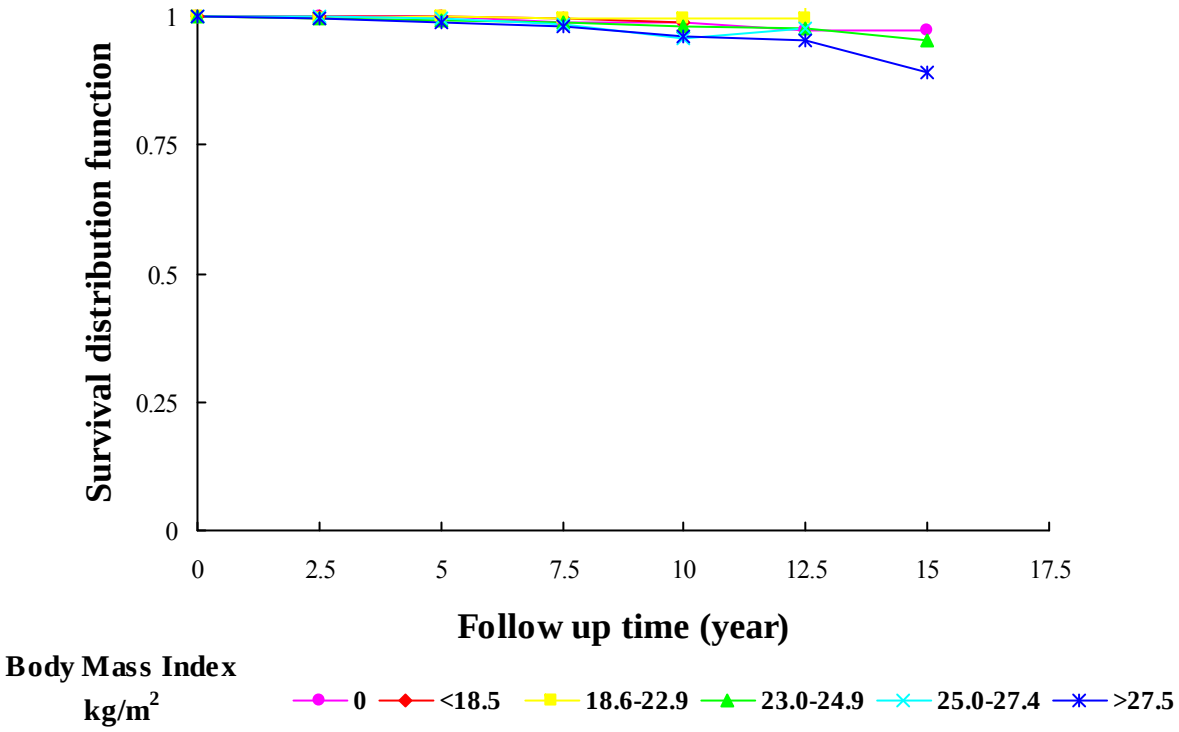

Figure 2. Death of hemorrhagic stroke by body mass index.

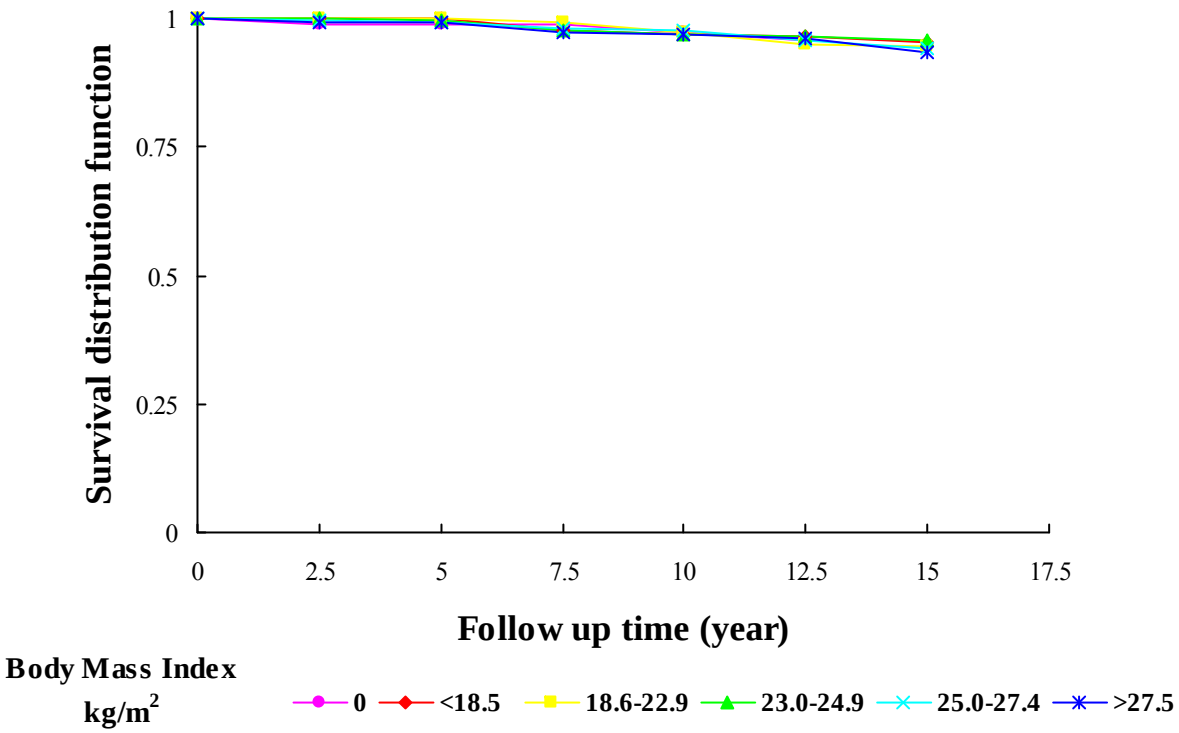

Figure 3. Death of ischemic stroke by body mass index

ICD10 CODES FOR CARDIOVASCULAR DISEASES

All cardiovascular diseases (I00-I99)
Coronary heart disease (I20-I25)
Total strokes (I60 - I69)
Hemorrhagic strokes (I60-I62)
Ischemic strokes (I63, I65, I66)
Other circulatory diseases (I00.0 – I19.9, I26.0 – 159.9, I70.0 – I99)

ICD10M1	Frequency	Percent	Cumulative Frequency	Cumulative Percent
I10	39	2.72	335	23.39
I11	8	0.56	343	23.95
I119	2	0.14	345	24.09
I120	3	0.21	348	24.30
I13	1	0.07	349	24.37
I20	2	0.14	351	24.51
I21	18	1.26	369	25.77
I219	2	0.14	371	25.91
I24	1	0.07	372	25.98
I25	1	0.07	373	26.05
I255	1	0.07	374	26.12
I259	1	0.07	375	26.19
I26	1	0.07	376	26.26
I27	1	0.07	377	26.33
I352	1	0.07	378	26.40
I38	2	0.14	380	26.54
I46	13	0.91	393	27.44
I48	4	0.28	397	27.72
I49	1	0.07	398	27.79
I50	19	1.33	417	29.12
I500	1	0.07	418	29.19
I51	16	1.12	434	30.31
I519	1	0.07	435	30.38
I60	5	0.35	440	30.73
I608	1	0.07	441	30.80
I61	25	1.75	466	32.54
I615	1	0.07	467	32.61
I619	1	0.07	468	32.68
I62	19	1.33	487	34.01
I620	1	0.07	488	34.08
I63	23	1.61	511	35.68
I639	2	0.14	513	35.82
I64	112	7.82	625	43.65
I67	63	4.40	688	48.04
I679	1	0.07	689	48.11
I69	10	0.70	699	48.81
I693	1	0.07	700	48.88
I694	1	0.07	701	48.95
I70	6	0.42	707	49.37
I73	1	0.07	708	49.44
I99	1	0.07	709	49.51