보건학 석사학위논문

Association between Metabolically Healthy Obesity and the Risk of Incident Chronic Kidney Dysfunction

대사적으로 건강한 비만과 만성 신기능 저하 발생 위험 간의 연관성

2018년 8월

서울대학교 보건대학원

보건학과 보건학전공

조 수 영

Association between Metabolically Healthy Obesity and the Risk of Incident Chronic Kidney Dysfunction

지도교수 조 성 일

이 논문을 보건학 석사학위논문으로 제출함

2018년 5월

서울대학교 보건대학원

보건학과 보건학전공

조 수 영

조수영의 보건학 석사학위논문을 인준함

2018년 6월

위 원 장 성 주 헌 (인)

부위원장 원 성 호 (인)

위 원 조 성 일 (인)

ABSTRACT

Association between Metabolically Healthy Obesity and the Risk of Incident Chronic Kidney Dysfunction

Su Yeong Jo

Department of Epidemiology

Graduate School of Public Health

Seoul National University

Introduction: Chronic kidney disease (CKD), known as a global public health problem, has also become important issues threatening public health in Korea. Many epidemiological studies have investigated the association between obesity and kidney disease, supporting that obesity increases the risk of kidney disease. It has been known that most of the increased risk of CKD in obese individuals is primarily due to cardiometabolic factors associated with excess adiposity. However, not all the obese people have metabolic abnormality, and obese people with no metabolic dysfunction have been

existed. They have been reported as metabolically healthy obesity (MHO) phenotype. The association between MHO and kidney dysfunction is well unknown, and it is yet to be determined whether MHO is associated with kidney dysfunction. The objective of this study is to investigate the association between MHO and the risk of incident chronic kidney dysfunction for general population of Korea.

Methods: From the Ansung and Ansan community cohort of the Korean Genome and Epidemiology Study (KoGES) data, 8,608 participants were analyzed. The main exposure of this study is MHO. This concept is a combination of metabolic phenotype and the presence or absence of obesity. The participants were divided into four groups based on the body mass index (≥28kg/㎡ as obesity) and the metabolic healthy status by using Adult Treatment Panel-III (ATP-III): Metabolically healthy non-obesity (MHNO), Metabolically healthy obesity (MHO), Metabolically unhealthy non-obesity (MUNO), and metabolically unhealthy obesity (MUO). The outcome of the present study is kidney dysfunction defined as eGFR <60ml/min/1.73㎡. To control the potential confounding, socio-demographic variables, behavioral factors, and biochemical factors were adjusted. Cox proportional hazard regression was used to calculate the hazard ratio (HR) with 95% confidence interval (CI) and MHNO is used as the reference. All statistical analyzes are

done by using R 3.4.3.

Results: The MHO phenotype represented 4.1% (n=351) of the total analytic sample and 29.9% of the obese population. After adjusting for all covariates, the HR of MHO individuals for incident kidney dysfunction was 1.59 (95% CI, 1.24-2.04), the HR of MUNO individuals was 1.69 (95% CI, 1.51-1.89), and the HR of MUO individuals was 2.03 (95% CI, 1.73-2.38). The HRs of all groups were statistically significant higher, compared MHNO individuals, and presented a linear trend, in order of linearity: MHO, MUNO, MUO.

Conclusion: This study indicated that metabolically healthy obesity may increase the risk of incident kidney dysfunction in Korean adults. We suggest that different obese phenotype have different effect on the risk of incident kidney dysfunction and MHO is not a benign condition. Therefore, it is crucial to identify obesity-metabolic status phenotype in predicting kidney dysfunction incidence risk. Moreover, the proper prevention and treatment of chronic disease including CKD according to the obesity subtype are needed.

Keyword: Metabolic syndrome, Obesity, Metabolically healthy obesity, Chronic kidney disease, kidney dysfunction, cox proportional hazard regression

Student Number: *2016-26888*

CONTENTS

TABLES

FIGURES

Chapter 1. Introduction

1.1 Background

As the elderly population increases worldwide, the number of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is increasing rapidly (1). Kidney disease has now supposed epidemic proportions and is also one of the major causes of death caused by chronic diseases in today's industrialized world, while in the past cardiovascular disease and cancer were dominant (2). In accordance with the 2010 Global Burden of Disease study (3), while CKD placed as the 27th cause of death in 1990, it rose to rank as the 18th by 2010. Early stage of CKD is even more prevalent, which can progress to ESRD, cardiovascular disease, and premature death (2). CKD, already known as a global public health problem, has also become an important issue threatening public health in Korea (4). The prevalence of CKD, defined as an estimated glomerular filtration rate (eGFR) lower than 60mL/min/1.73㎡, is estimated through KNHANES (Korean National Health and Nutrition Examination Survey) since 2008. According to KNHANES results (5), the number of CKD patients aged over 30 are increasing overall.

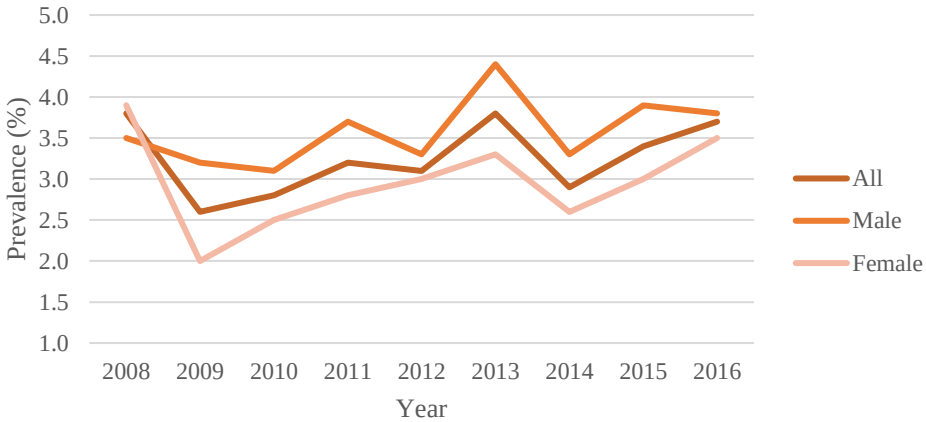

Figure 1. Trends in the prevalence (%) of chronic kidney disease (CKD) by sex, KNHANES 2008-2016

The best resolution to reduce the global burden of CKD is the prevention of progression of renal diseases, and early detection of CKD (6). Therefore, it is necessary to identify modifiable risk factors for kidney disease.

A number of epidemiologic studies have examined obesity as a risk factor for various non-communicable diseases such as cardiovascular disease, diabetes mellitus, CKD and an array of musculoskeletal disorders (7). In the United States, obesity is the second main cause of morbidity and mortality following smoking (8). Many epidemiological studies have investigated the association between obesity and kidney disease, supporting that obesity increases the risk of kidney disease although the pathological mechanism for

the impacts of obesity on kidney disease is unexplained accurately (8). In spite of the negative effects of obesity increasing the incidence of cardiovascular risk factors and the prevalence of cardiovascular disease, many studies over the past decade discussed whether obesity can be ‘healthy’ (9). It has been known that in most cases, increased risk of kidney disease in obese individuals is primarily due to cardiovascular disease associated with excess adiposity (10). Some researchers have proposed that the harmful effects of obesity other than metabolic abnormality could be ignored since most of the increased risk associated with obesity could be induced cardiometabolic factors (9). However, not all obese people have metabolic abnormality, and obese people with no metabolic dysfunction have existed. They have been reported as metabolically healthy obesity (MHO) phenotypes (11). However, the association between MHO and kidney dysfunction is well unknown, and it is yet to be determined whether MHO increases the risk of incident chronic kidney dysfunction.

1.2 Literature Review

1.2.1 Metabolically healthy obesity

As stated above, obese individuals who may be absent of metabolic abnormalities have been defined as "Metabolically healthy obesity." The concept of MHO has been known since 1980s (12). Notwithstanding growth of interest in the obesity paradox which has identified since 1980s, the standard criteria in MHO has still not been defined for research protocols nor in clinical practice (11). Therefore, the definition used differs for each study. In some studies, MHO was defined as obesity in the absence of metabolic diseases, for example hypertension, diabetes mellitus, and dyslipidemia (13-16). In other studies, MHO was identified by low insulin resistance (16, 17). A few studies determined MHO as the absence of both metabolic diseases and low insulin resistance (18). Various definitions of MHO could illustrate the wide variation of prevalence as well as study design and population differences (11).

Potential underlying mechanisms of MHO are fat distribution patterns, and most importantly the amount of skeletal muscle and liver fat contents (19). Liver fat content leads to insulin resistance and is much more relevant than

visceral fat mass (19). In another study (20), high liver fat mass raised the risk of incident type 2 diabetes, independent of known influences. Therefore, a low-risk phenotype is characterized by the absence of fatty liver. In other words, when compared to metabolically unhealthy obese individuals, individuals with MHO have more subcutaneous, less visceral fat mass, and lower ectopic fat deposition in the liver and in the skeletal muscle (21). In addition, the release of pro-inflammatory hepatokines, which intervenes lipid-induced insulin resistance and sub-clinical inflammation, is low in metabolically healthy fatty liver (21). Decreased infiltration of immune cells into adipose tissue was found in MHO individuals (21).

The lack of a single standard definition of MHO makes it unclear how the concept of MHO can be integrated into clinical practice. The primary interventions for all obese individuals are dietary methods and encouraging physical activity. If this intervention does not improve obesity status and metabolic phenotype, a specific intervention is needed (21). It is effective to distinguish subgroups of obesity to not ignore the heterogeneity and differences among obese individuals (11). In the future, various perspective for MHO individuals should need: an establishment of the standard definition of MHO, appraisal of differences in metabolically healthy factors between male and female and between subgroups depending on age and race, and lastly,

cost-benefit analyses for the subgroup of obesity treatment on the basis of MHO stratification (21).

1.3 Objective

The objective of this study is to investigate the association between MHO and the risk of chronic kidney dysfunction for general population of Korea. Since the association of MHO to incidents of chronic kidney dysfunction has yet to be confirmed accurately, the result of this study will provide support to one side of the controversy on the risk of MHO. Moreover, this study will also analyze the effect of MHO on the development of kidney dysfunction stratified by some criteria.

Chapter 2. Method

2.1 Study population

This study is a prospective, community-based cohort study. The data used in this study were derived from the Korean Genome and Epidemiology study (KoGES), which is composed of six kinds of cohorts. Of these cohorts, community-based Ansung and Ansan cohorts were used for this study. While Ansan cohort represents an urban community, Ansung cohort represents a rural community. Details of the study design and procedures have been provided in a previous report (22). In summary, these cohorts began in 2001, and recruited 10,030 participants aged 40-69 years who had undergone comprehensive health examinations at the baseline between 2001 and 2002. They were followed up biennially and the present study was based on the data from the baseline through the seventh follow-up examination between 2013 and 2014. Of 10,030 participants, participants with kidney dysfunction, defined as an eGFR lower than 60 mL/min/1.73㎡ at the baseline exam (*n*=225), or missing information about kidney dysfunction or metabolic components (*n*=6) were excluded. Among the participants who took part in

the baseline, all those who did not participate in any of the followed-up examination after the baseline exam (*n*=1,191) were also excluded. In the end, the number of final participants were 8,608 (Figure 2).

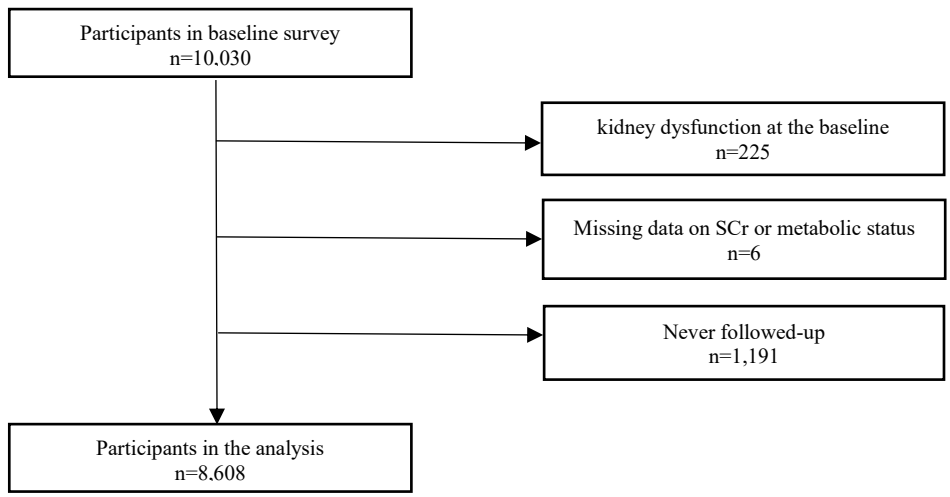

Figure 2. Study flow diagram showing inclusions of participants in analyses

All participants in this study participated voluntarily, and informed consent was obtained in all cases. The study protocol was approved by the Institutional Review Board (IRB) of Seoul National University (IRB No. E1804/003-003).

2.2 Measurement

2.2.1 Exposure

The main exposure of this study is metabolically healthy obesity (MHO). This concept is a combination of metabolic phenotype and the presence or absence of obesity.

There are many reliable measures to classify obesity. Underwater weighing (densitometry), dual-energy X-ray absorptiometry (DXA), and dilution techniques measure total body fat accurately while imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are highly accurate in defining local fat storage and fat distribution. However, CT and MRI are less useful to measure total body fat storage. Bio-impedance analysis techniques are also used widely, but they are of moderate use in estimating total body fat and it is hard to estimate fat distribution (23). Despite these advantages, the equipment mentioned above are expensive and not available for researchers to measure obesity status of a large population (11). Instead, body mass index (BMI) provides an estimate of body fat and it is also related to disease risk, Therefore, BMI is applicable in large studies (23). BMI was used to define obesity in this study. It was

calculated as weight in kilograms divided by height in meters squared and rounded off to the nearest hundredth. Although the Asia-Pacific BMI criteria is well known to define obesity for Asian population, it is controversial whether it can accurately predict the risks of diseases. Therefore, in accordance with the results of a previous study of the Chinese population (24), the participants who had BMI ≥28kg/㎡ were classified as obese, and BMI <28kg/㎡ were classified as non-obese in this study.

We used standard protocols to measure the various components to define metabolic phenotype. Metabolic health status was determined by the presence of ≥2 components of metabolic syndrome using the modified National Cholesterol Education Project Adult Treatment Panel (NCEP-ATPⅢ) criteria. The waist circumference criterion was not used because of its collinearity with BMI. The components of metabolic syndrome used for classification were ① high blood pressure (systolic blood pressure ≥130mmHg and/or diastolic blood pressure ≥85mmHg) or anti-hypertensive drugs; ② hyperglycemia (fasting plasma glucose ≥100mg/dL) or medications for diabetes (insulin or oral anti-diabetic); ③ hypertriglyceridemia (fasting plasma triglycerides ≥150mg/dL); and ④ low HDL cholesterol (fasting HDL cholesterol <40mg/dL for male, <50mg/dL for female). We used these

definitions alongside data on obesity to classify four phenotypes; metabolically healthy non-obesity (MHNO), metabolically healthy obesity (MHO), metabolically unhealthy non-obesity (MUNO), and metabolically unhealthy obesity (MUO).

2.2.2 Outcome

The outcome variable of this study is chronic kidney dysfunction. Basically, GFR was decreased in the incipient stage of CKD where pathologic disturbances or markers of kidney damage had changed (25). In several cases, decreased GFR is considered the earliest sign of kidney disease. Thus, kidney dysfunction was defined as eGFR lower than 60 mL/min/1.73㎡ in this study. There are some equations that estimated GFR. It is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) guidelines that leads to the least bias when diagnosing kidney dysfunction (25). Therefore, the CKD-EPI equation was used for this study, and is as follows:

$$\mathbf{GFR = 141 \times \min(Scr/\kappa, 1)\alpha \times \max(Scr/\kappa, 1) - 1.209 \times 0.993 Age \times 1.018\ [if\ female]}$$

In this equation, Scr means serum creatinine, κ is 0.7 for female and 0.9 for male, α is -0.329 for female and -0.411 for male, ‘min’ indicates the minimum of Scr/κ or 1, and ‘max’ indicates the maximum of Scr/κ or 1.

2.2.3 Covariates

In addition to the main exposure, other factors which may affect the results were also considered such as socio-demographic variables, behavioral factors, and biochemical factors. Except biochemical factors, self-reported questionnaires at the baseline were used to investigate information about socio-demographic variables and behavioral factors. Socio-demographic variables included age, sex, living region, marital status, level of education, and monthly household income. Region was classified into Ansung, or Ansan. Marital status was categorized as single, married/cohabiting, and divorce/separation. Level of education was divided into two levels: high school graduate or above ($\geq$12 years), and non-high school graduate (<12 years). Occupation was classified into housewife, blue-collar (manufacturing, and agriculture worker), white-collar (professional, and administrative worker), pink-collar (service, and sales worker) and others. Monthly household income was categorized as three levels; one million won or less, more than one million won and less than two million won, and more than two million won. Behavioral factors included smoking status, alcohol intake, and physical activity. Smoking status was classified into non-smoker, former smoker, and current smoker. Alcohol consumption was divided into four

categories which are ‘abstainer’, ‘average volume drinking category Ⅰ’ defined as pure alcohol intake <20/day for female or <40g/day for male, ‘average volume drinking category Ⅱ’ defined as 20-39.99g/day for female or 40-59.99g/day for male, or ‘average volume drinking categoryⅢ’ defined as ≥40g/day for female or ≥60g/day for male (26). Physical activities were categorized as ‘inactive’ defined as doing no or very little physical activity, ‘insufficiently active’ defined as doing some physical activity but <150minutes of moderate-intensity physical activity or <60minutes of vigorous-intensity physical activity a week, and ‘sufficiently active’ defined as ≥150minutes of moderate-intensity physical activity or ≥60minutes of vigorous-intensity physical activity a week (27). Biochemical factors included aspartate aminotransferase (AST), alanine aminotransferase (ALT), and high-sensitivity c-reactive protein (hsCRP). The value of hsCRP was classified into two levels; hsCRP≤0.3mg/dL as normal, and the other as inflammation status. This cutoff was defined according to AHA(American Heart Association)/CDC(Centers for Disease Control and Prevention) guideline.

2.3 Study design

In this study, four models were fitted to adjust potential confounders for Korean population. Model 1 was unadjusted. In addition to exposure, socio-demographic variables including sex, age, living region, marital status, job, education year, and monthly household income were fitted (Model 2). In addition to model 2 with demographic characteristics, behavioral factors involving alcohol intake, current smoking status, and physical activity were added in Model 3. In the end, biochemical factors such as ALT, and hsCRP were considered as additional confounders (Model 4).

For subgroup analysis, all models were analyzed for male and female respectively, and analysis stratified by age group was also done. Age group was classified into two groups based on the age of 60. A middle-aged group was less than 60 years old, and elderly group was 60 years old or above. Furthermore, additional analysis stratified by hypertension were done. Although insulin resistance is associated with hyperinsulinemia, obesity and the dyslipidemia, whether hypertension is associated with insulin resistance is controversial. In other words, of metabolic components, hypertension is homogeneous (28).

2.4 Statistical analysis

The general characteristics of the participants were presented as mean ± standard deviation (SD) for continuous variables and as percentage (%) for categorical variables by metabolic phenotype and as a function of BMI categories. To analyze the difference between four groups—MHNO, MHO, MUNO, and MUO—continuous variables were analyzed by ANOVA test with Scheffe's method for *post hoc* analysis, and the chi-square test with false discovery rate (FDR) for *post hoc* analysis were used for categorical variables. The Kaplan-Meier survival function was used to examine the chronic kidney dysfunction over time in order to enable visual inspection of trends, and a log-rank test was performed to analyze the statistical differences between four groups.

To examine the association between MHO and the risk of incident kidney dysfunction, cox proportional-hazard regression model was used to calculate the hazard ratio (HR) with 95% confidence interval (CI), and MHNO was used as reference. In addition, ANOVA test was used to determine whether the differences within each group and the difference between the groups were significant. All statistical analyses were done by using R 3.4.3.

Chapter 3. Results

3.1 Descriptive analysis of the study participants

Table 1-1, Table 1-2, and Table 1-3 show the baseline general characteristics of the participants which are socio-demographic variables (Table 1-1), behavioral factors (Table 1-2), clinical and biochemical factors (Table 1-3) according to obesity-metabolic status phenotype; 51.5% (*n*=4,430) of the participants were metabolically healthy, and 13.6% (*n*=1,172) were obese. The MHO phenotype represented 4.1% (*n*=351) of the total analytic sample and 29.9% of the obese population. There was no statistically significant difference in the proportion of 'physical activity' individuals, and the mean of blood pressure, ALT, and hsCRP among four groups.

Compared to MHNO individuals, MHO individuals were more likely to be female, lower single rates in marital status, less educated, higher proportions of housewife and pink-collars, non-smoker, and to have a less favorable risk profile. There was no statistically significant difference in the proportion of 'age group' individuals, 'region' individuals, 'monthly household income' individuals, and 'alcohol consumption' individuals,

between MHO and MHNO groups.

Compared to MUO individuals, participants with MHO were characterized by female, younger age, more living people in Ansan, lower rates of ‘lower than one million won monthly household income’, and higher rates of non-smoker. They also displayed a more favorable risk profile than MUO individuals. There was no difference in the proportion of ‘marital status’ individuals, ‘occupation’ individuals, and ‘alcohol consumptions’ individuals between MHO and MUO groups.

Compared to MUNO individuals, these individuals showed more female, younger age, living in Ansan, higher proportions of housewife and pink-collars, and lower proportions of blue-collar and pink-collar, and non-smoker. Those two groups had favorable risk profile similarly. There was also no statistically significant difference in the proportion of ‘marital status’ individuals, ‘education year’ individuals, and ‘alcohol consumptions’ individuals.

Table 1-1. Baseline socio-demographic characteristics of the study participants according to metabolic phenotype and obesity

Variables	Non-obesity		Obesity		*p*-value
	Metabolically healthy (MHNO) (*n*=4,079)	**Metabolically unhealthy (MUNO) (*n*=3,357)**	**Metabolically healthy (MHO) (*n*=351)**	**Metabolically unhealthy (MUO) (*n*=821)**	
Sex					
Male (n,%)	2,047 (50.2)[a]	1,655 (49.3)[a]	106 (30.2)	301 (36.7)	<0.001
Female (n,%)	2,032 (49.8)	1,702 (50.7)	245 (69.8)	520 (63.3)	
Age					
Age (years, mean±SD)	50.5±8.6[a]	53.8±8.8	50.8±8.1[a]	52.7±8.5	<0.001
40-59 (n,%)	3,268 (80.1)[a]	2,275 (67.8)	285 (81.2)[a]	607 (73.9)	<0.001
60-69 (n,%)	811 (19.9)	1,082 (32.2)	66 (18.8)	214 (26.1)	
Region					
Ansung (n,%)	1,910 (46.8)[a]	1,821 (54.2)[b]	169 (48.1)[a]	455 (55.4)[b]	<0.001
Ansan (n,%)	2,169 (53.2)	1,536 (45.8)	182 (53.2)	366 (44.6)	
Marital status					
Single (n,%)	3,745 (92.4)	2,972 (89.1)[a]	312 (88.9)[a]	720 (88.0)[a]	
Married/Cohabiting (n,%)	58 (1.4)	40 (1.2)	3 (0.9)	7 (0.9)	<0.001
Divorce/Separation (n,%)	250 (6.2)	324 (9.7)	36 (10.3)	91 (11.1)	
Education year					
12yrs or above (n,%)	2,020 (49.9)	1,329 (39.9)[a]	144 (41.4)[a]	300 (36.8)[a]	<0.001
0-11 (n,%)	2,028 (50.1)	2,000 (60.1)	204 (58.6)	515 (63.2)	
Occupation					
Housewife (n,%)	1,099 (27.1)[a]	877 (26.3)[a]	132 (37.8)[b]	291 (35.6)[b]	
Blue-collar (n,%)	1,365 (33.7)	1,183 (35.5)	91 (26.1)	230 (28.2)	
White-collar (n,%)	380 (9.4)	270 (8.1)	18 (5.2)	65 (8.0)	<0.001
Pink-collar (n,%)	641 (15.8)	510 (15.3)	71 (20.3)	129 (15.8)	
others (n,%)	568 (14.0)	496 (14.9)	37 (10.6)	102 (12.5)	
Monthly household income					
≤100 (n,%)	1,202 (30.0)[a]	1,287 (39.0)[b]	106 (31.0)[a]	328 (40.7)[b]	
100-200 (n,%)	1,228 (30.6)	924 (28.0)	119 (34.8)	224 (27.8)	<0.001
≥200 (n,%)	1,579 (39.4)	1,089 (33.0)	117 (34.2)	253 (31.4)	

[a b] Same letters indicate a statistically insignificant difference.

Table 1-2. Baseline behavioral characteristics of the study participants according to metabolic phenotype and obesity

Variables	Non-obesity		Obesity		*p*-value
	Metabolically healthy (MHNO) (*n*=4,079)	**Metabolically unhealthy (MUNO) (*n*=3,357)**	**Metabolically healthy (MHO) (*n*=351)**	**Metabolically unhealthy (MUO) (*n*=821)**	
Smoking status					
Non-smoker (n,%)	2,336 (57.8) [a]	1,870 (56.5) [a]	260 (75.1)	542 (67.0)	
Former smoker (n,%)	622 (15.4)	567 (17.1)	37 (10.7)	115 (14.2)	<0.001
Current smoker (n,%)	1,082 (26.8)	873 (26.4)	49 (14.2)	152 (18.8)	
Alcohol consumption					
Abstainer (n,%)	1,980 (50.1) [a]	1,795 (55.2) [b]	187 (54.7) [abc]	489 (60.8) [c]	
Category I (n,%)	1,668 (42.2)	1,174 (36.1)	130 (38.0)	239 (29.7)	<0.001
Category II (n,%)	145 (3.7)	145 (4.5)	13 (3.8)	39 (4.9)	
Category III (n,%)	163 (4.1)	140 (4.3)	12 (3.5)	37 (4.6)	
Physical Activity					
Inactive (n,%)	3,051 (75.7)	2,540 (76.4)	249 (71.6)	595 (72.9)	
Insufficiently active (n,%)	257 (6.4)	223 (6.7)	22 (6.3)	57 (7.0)	0.124
Sufficiently active (n,%)	724 (18.0)	561 (16.9)	77 (22.1)	164 (20.1)	

[a b c] Same letters indicate a statistically insignificant difference.

Table 1-3. Baseline clinical and biochemical characteristics of the study participants according to metabolic phenotype and obesity

Variables	Non-obesity		Obesity		*p*-value
	Metabolically healthy (MHNO) (*n*=4,079)	**Metabolically unhealthy (MUNO) (*n*=3,357)**	**Metabolically healthy (MHO) (*n*=351)**	**Metabolically unhealthy (MUO) (*n*=821)**	
Anthropometric factors					
BMI (kg/㎡)	23.2±2.4	24.5±2.2	29.9±1.9 [a]	29.9±1.8 [a]	<0.001
Systolic BP (mmHg)	114.4±15.3	128.7±18.4	118.8±16.6	132.6±18.4	0.811
Diastolic BP (mmHg)	76.1±10.1	84.4±11.5	79.3±10.8	87.6±11.1	0.791
Biochemical factors					
Fasting glucose (mg/dL)	82.6±12.0 [a]	91.4±26.8 [b]	84.5±14.0 [a]	93.4±22.6 [b]	<0.001
Total cholesterol (mg/dL)	186.0±33.2	194.0±35.9 [a]	195.2±33.4 [a]	201.9±36.3	<0.001
Triglyceride (mg/dL)	112.4±44.3 [a]	210.8±118.1	119.8±49.4 [a]	227.4±142.2	<0.001
HDL-cholesterol (mg/dL)	49.1±9.9 [a]	40.2±8.0 [b]	47.7±8.9 [a]	39.5±7.2 [b]	<0.001
AST (IU/L)	28.4±18.5 [a]	30.5±18.1 [b]	29.3±15.0 [ab]	31.6±14.8 [b]	<0.001
ALT (IU/L)	24.9±31.3	30.3±22.5	29.2±21.7	35.1±24.2	0.750
hsCRP (mg/L)	0.2±0.5	0.2±0.6	0.3±0.5	0.3±0.4	0.667
HOMA-IR index score *	1.4±0.9	1.8±1.5 [a]	1.9±1.3 [a]	2.3±1.5	<0.001
eGFR (ml/min/1.73 ㎡)	94.3±13.1	91.8±12.7 [a]	92.1±13.7 [a]	91.4±12.8 [a]	<0.001

[a b] Same letters indicate a statistically insignificant difference.

* HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) was calculated as fasting plasma glucose (mmol/L) × fasting insulin(μU/L) / 22.5

Figure 3 shows the prevalence of metabolic components such as high blood pressure (BP), high fasting plasma glucose (FPG), high triglyceride (TG), and low high-density lipoprotein cholesterol(HDL-C) in four groups according to baseline obesity-metabolic status phenotype. The prevalence of high BP, high TG, and low HDL-C was the lowest in the MHNO group. However, the prevalence of high FPG in the MHO group is the lowest. While the prevalence of high FPG is 2.9% in MHNO group, the prevalence is 2.6% in MHO group. On the other hand, the prevalence of all components was the highest in MUNO group. Overall, the prevalence of metabolically unhealthy groups is higher than that of metabolically healthy groups in all four metabolic components.

Overall, trend of eGFR mean in the four groups is decreasing by rounds, since kidney function decreases with age. All four groups show similar patterns of increase and decrease. The eGFR mean of MUO group is the lowest at every round (Figure 4).

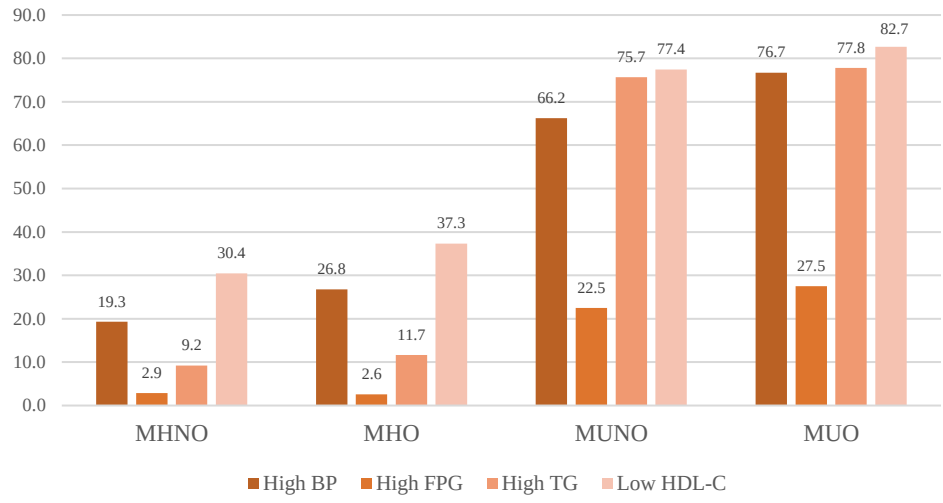

Figure 3. Prevalence of metabolic components in the four groups according to baseline obesity-metabolic status phenotype

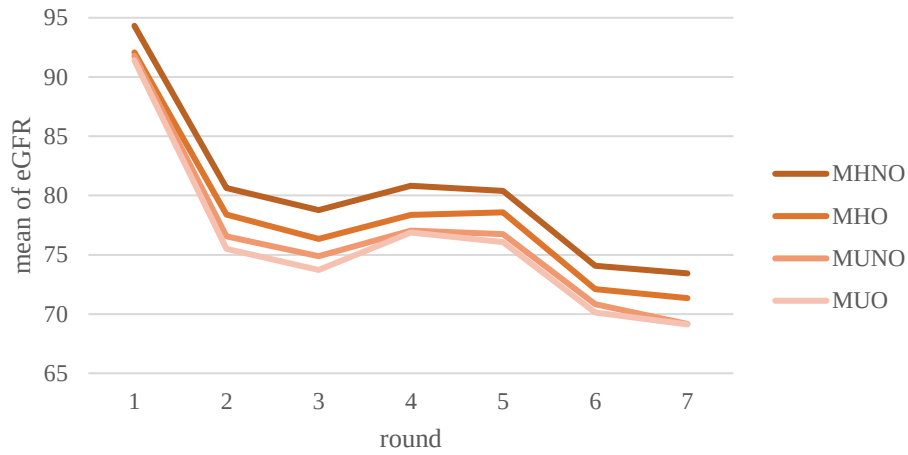

Figure 4. Change of eGFR mean by rounds in the four groups according to baseline obesity-metabolic status phenotype

To determine whether the proportional hazard assumption is satisfied, the log-log plot should be graphed, which is−log[−log(Survival probability)] versus log of survival time graph. The space between the curves should be constant overtime. In Figure 5, curves for each group are generally parallel. Therefore, the proportional hazard assumption is established in this study.

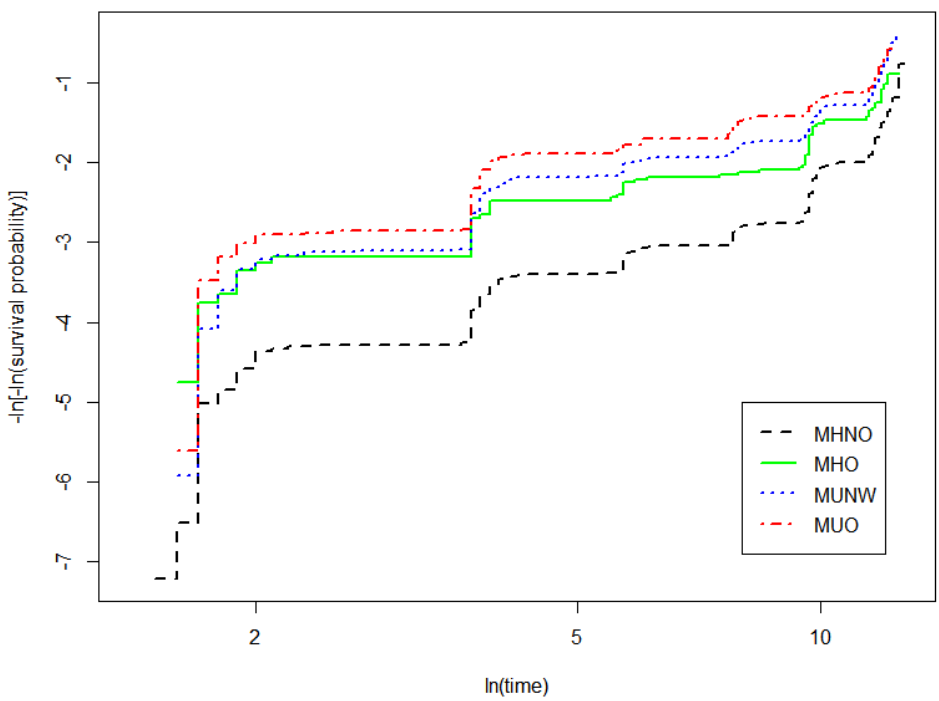

Figure 5. Log-log plot to evaluate the proportional hazard assumption of the Cox-model for each four groups

The Kaplan-Meier survival analysis for incident chronic kidney dysfunction-free survival as a function of obesity-metabolic status phenotype are shown in Figure 6 and Figure 7 to compare survival rates among four groups. Figure 6 is by follow-up year, and Figure 7 is by time between round. Compared to the MHNO group, the participants who included the other three groups (that is, MHO, MUNO, and MUO) had higher probabilities of developing incident kidney dysfunction by follow-up year (log-rank test, $P<0.05$ for all three comparisons). Compared to the MHO group, the participants in MUO group had higher probabilities of developing incident kidney dysfunction (log-rank test, $P<0.05$ for all comparisons), but MUNO individuals had not significantly higher (log-rank test, $P=0.051$). The survival rate of the MUNO group was not also significantly higher than that of MUO group (log-rank test, $P=0.060$). To analyze the pairwise log-rank test, FDR was used to adjust *p*-value.

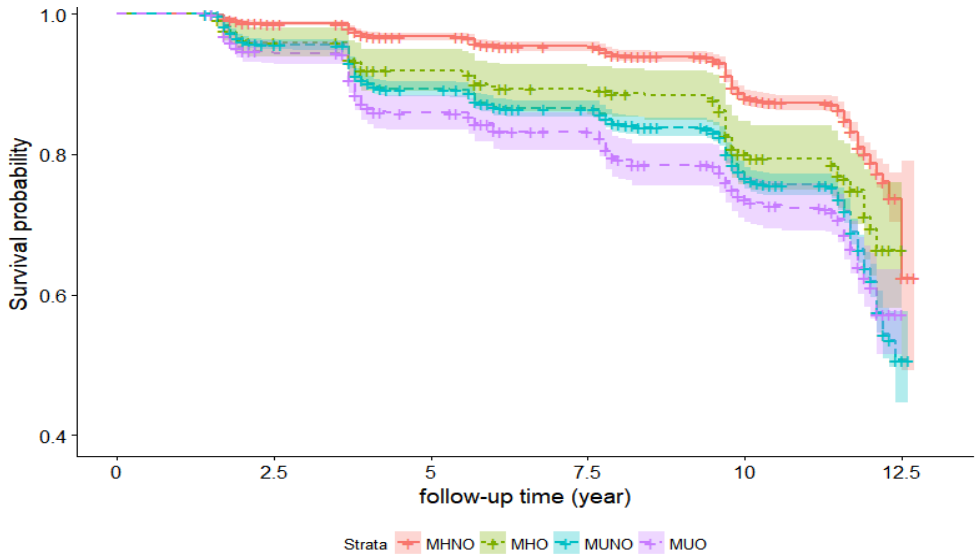

Figure 6. Kaplan-Meier curves showing the association obesity-metabolic status phenotype with kidney dysfunction by follow-up year

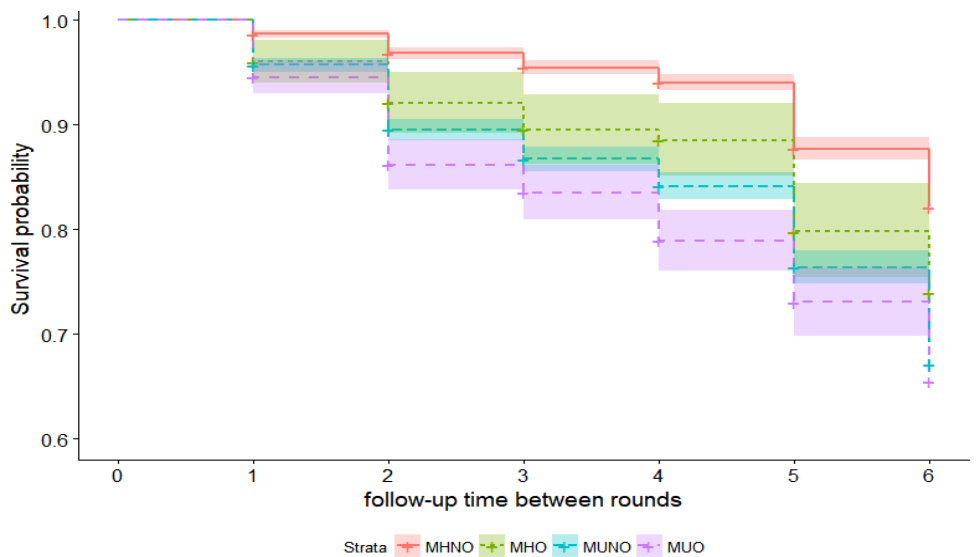

Figure 7. Kaplan-Meier curves showing the association obesity-metabolic status phenotype with kidney dysfunction by follow-up time between rounds

3.2 Association between metabolically healthy obesity and kidney dysfunction

Association between obesity-metabolic status phenotype and kidney dysfunction is presented in Table 2. In model 1, unadjusted HR of MHO individuals for incident kidney dysfunction (MHNO group as reference) was 1.65 (95% CI, 1.30-2.09), the HR of MUNO individuals was 2.11 (95% CI, 1.91-2.35), and the HR of MUO individuals was 2.38 (95% CI, 2.05-2.76). The risk of kidney dysfunction in all groups were significantly higher than MHNO groups, and the risk of MUNO individuals was the highest. In model 2, the HR of MHO individuals for incident kidney dysfunction was 1.62 (95% CI, 1.27-2.07), the HR of MUNO individuals was 1.74 (95% CI, 1.56-1.93), and the HR of MUO was 2.16 (95% CI, 1.85-2.52). In model 3, the HR of MHO individuals was 1.64 (95% CI, 1.28-2.10) and the HR of MUNO and MUO individuals were 1.71 (95% CI, 1.53-1.91), and 2.10 (95% CI, 1.80-2.46) respectively. The risk of incident chronic kidney dysfunction in all groups were still statistically significant and higher than MHNO group after adjusted socio-demographic variables and behavioral factors. In model 4, the HR of MHO individuals for incident kidney dysfunction was 1.59 (95% CI, 1.24-2.04), the HR of MUNO individuals was 1.69 (95% CI, 1.51-1.89), and

the HR of MUO individuals was 2.03 (95% CI, 1.73-2.38). After additional adjustment for biochemical factors, the further covariates did not alter the associations. The HRs of all groups still were statistically significantly higher, compared to MHNO individuals, and presented a significantly linear trend, in order of linearity: MHO, MUNO, and MUO. The difference between the groups was significant (P<0.001). However, the difference between MHO group and MUNO group was not significant (P=0.627). On the other hands, according to akaike information criterion (AIC) of each model, AIC of model 4 was lowest. Therefore, adjustment for socio-demographic variables, behavioral factors, and biochemical factors was the best fitted model. To understand the association between MHO and chronic kidney dysfunction in the final model, each HR of obesity-metabolic status phenotypes and covariates for kidney dysfunction is presented in Table 3.

Table 2. Hazard ratios (HR) for the incident kidney dysfunction according to obesity-metabolic status phenotype

	Model 1	Model 2	Model 3	Model 4
MHNO	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
MHO	1.65 (1.30-2.09)	1.62 (1.27-2.07)	1.64 (1.28-2.10)	1.59 (1.24-2.04)
MUNO	2.11 (1.91-2.35)	1.74 (1.56-1.93)	1.71 (1.53-1.91)	1.69 (1.51-1.89)
MUO	2.38 (2.05-2.76)	2.16 (1.85-2.52)	2.10 (1.80-2.46)	2.03 (1.73-2.38)
AIC	30804.37	28490.88	27463.31	27420.12

Results are reported as hazard ratio (95% confidence interval). P<0.05 vs referent group.

AIC: Akaike information criterion

Model 1 was unadjusted.

Model 2 was adjusted for socio-demographic variables.

Model 3 was adjusted for the variables in model 2, plus behavioral factors.

Model 4 was adjusted for the variables in model 3, plus biochemical factors.

Table 3. Hazard ratios of all covariates for kidney dysfunction in Model 4

Variables		Hazard Ratio (95% CI)	*p*-value
Sex (REF: Male)	Female	1.05 (0.88-1.26)	0.588
Age (REF: 40-59)	60-69	4.02 (3.58-4.52)	< .001
Region (REF: Ansung)	Ansan	1.07 (0.93-1.22)	0.347
Marital status (REF: single)	Married/Cohabiting	0.76 (0.47-1.23)	0.264
	Divorce/Separation	1.11 (0.96-1.30)	0.165
Occupation (REF: Housewife)	Blue-collar	0.76 (0.66-0.88)	< .001
	White-collar	0.75 (0.58-0.97)	0.028
	Pink-collar	0.81 (0.67-0.99)	0.039
	others	0.96 (0.81-1.15)	0.677
Education year (REF: 12yrs or above)	0-11yr	1.18 (1.04-1.35)	0.010
Monthly household income (REF: ≤100)	100-200	0.84 (0.74-0.96)	0.009
	≥200	0.89 (0.77-1.04)	0.153
Smoking status (REF: Non-smoker)	Former smoker	1.10 (0.91-1.33)	0.329
	Current smoker	1.07 (0.89-1.27)	0.473
Alcohol consumption (REF: Abstainer)	Category I	0.81 (0.72-0.92)	< .001
	Category II	0.76 (0.56-1.02)	0.071
	Category III	0.81 (0.61-1.08)	0.150
Physical Activity (REF: inactive)	Insufficiently active	1.06 (0.86-1.30)	0.591
	Sufficiently active	1.09 (0.96-1.25)	0.187
ALT (IU/L)		1.00 (1.00-1.00)	0.781
inflammation (REF: CRP≥0.3)	<0.3	1.28 (1.14-1.44)	< .001
MHO phenotype (REF: MHNO)	MHO	1.59 (1.24-2.04)	< .001
	MUNO	1.69 (1.51-1.89)	< .001
	MUO	2.03 (1.73-2.38)	< .001

3.3 Association between metabolically healthy obesity and kidney dysfunction stratified by sex

Table 4-1 is the males' results of cox regression stratified by sex. In model 1, unadjusted HR of MHO individuals for incident kidney dysfunction was 1.56 (95% CI, 0.99-2.45), the HR of MUNO individuals was 1.88 (95% CI, 1.60-2.21), and the HR of MUO individuals was 2.15 (95% CI, 1.66-2.78). In model 2, the HR of MHO individuals for incident chronic kidney dysfunction was 1.74 (95% CI, 1.09-2.79). After adjustment the HR of MHO individuals was statistically significant. The HR of MUNO individuals was 1.95 (95% CI, 1.65-2.30), and the HR of MUO was 2.88 (95% CI, 2.22-3.75). In model 3, the HR of MHO individuals was 1.79 (95% CI, 1.12-2.86) and the HR of MUNO and MUO individuals were 1.95 (95% CI, 1.65-2.31) and 2.82 (95% CI, 2.15-3.69) respectively. In model 4, the HR of MHO individuals for kidney dysfunction was 1.73 (95% CI, 1.08-2.78), the HR of MUNO individuals was 1.98 (95% CI, 1.67-2.34), and the HR of MUO individuals was 2.83 (95% CI, 2.15-3.73). The HRs of the incident Chronic kidney dysfunction showed a significantly linear trend (P<0.001). The difference between the groups was significant (P<0.001), but the difference between MHO group and MUNO group was not significant (P=0.573).

According to AIC, model 4 was the best fitted model (Table 4-1).

Table 4-2 shows the HR for the development of incident kidney dysfunction according to obesity-metabolic status phenotype in female. In model 1, unadjusted HR of MHO individuals for incident kidney dysfunction was 1.58 (95% CI, 1.20-2.10), the HR of MUNO individuals was 2.31 (95% CI, 2.02-2.65), and the HR of MUO individuals was 2.39 (95% CI, 1.98-2.88). In model 2, the HR of MHO individuals for kidney dysfunction was 1.46 (95% CI, 1.09-1.95). The HR of MUNO individuals was 1.52 (95% CI, 1.31-1.75), and the HR of MUO was 1.75 (95% CI, 1.45-2.13). In model 3, the HR of MHO individuals was 1.46 (95% CI, 1.09-1.96), and the HR of MUNO individuals and MUO individuals were 1.48 (95% CI, 1.28-1.72) and 1.72 (95% CI, 1.41-2.10) respectively. In model 4, the HR of MHO individuals for incident chronic kidney dysfunction was 1.42 (95% CI, 1.06-1.90), the HR of MUNO individuals was 1.44 (95% CI, 1.24-1.67), and the HR of MUO individuals was 1.63 (95% CI, 1.34-1.99). In female group, the difference between the groups was significant (P<0.001), but the difference between MHO group and MUNO (P=0.921) were not statistically significant. Of four models, model 4 was the best fitted model according to AIC of each model (Table 4-2).

Table 4-1. Hazard ratios (HR) for the incident kidney dysfunction according to obesity-metabolic status phenotype in male

	Model 1	Model 2	Model 3	Model 4
MHNO	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
MHO	1.56 (0.99-2.45)	1.74 (1.09-2.79)	1.79 (1.12-2.86)	1.73 (1.08-2.78)
MUNO	1.88 (1.60-2.21)	1.95 (1.65-2.30)	1.95 (1.65-2.31)	1.98 (1.67-2.34)
MUO	2.15 (1.66-2.78)	2.88 (2.22-3.75)	2.82 (2.15-3.69)	2.83 (2.15-3.73)
AIC	10910.87	10269.32	9840.41	9833.52

Table 4-2. Hazard ratios (HR) for the incident kidney dysfunction according to obesity-metabolic status phenotype in female

	Model 1	Model 2	Model 3	Model 4
MHNO	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
MHO	1.58 (1.20-2.10)	1.46 (1.09-1.95)	1.46 (1.09-1.96)	1.42 (1.06-1.90)
MUNO	2.31 (2.02-2.65)	1.52 (1.31-1.75)	1.48 (1.28-1.72)	1.44 (1.24-1.67)
MUO	2.39 (1.98-2.88)	1.75 (1.45-2.13)	1.72 (1.41-2.10)	1.63 (1.34-1.99)
AIC	17418.31	15882.17	15368.47	15333.46

Results are reported as hazard ratio (95% confidence interval). P<0.05 vs referent group.

AIC: Akaike information criterion

Model 1 was unadjusted.

Model 2 was adjusted for socio-demographic variables.

Model 3 was adjusted for the variables in model 2, plus behavioral factors.

Model 4 was adjusted for the variables in model 3, plus biochemical factors.

3.4 Association between metabolically healthy obesity and kidney dysfunction stratified by age group

Table 5-1 shows the HR for the development of incident chronic kidney dysfunction according to obesity-metabolic status phenotype in middle-aged group. In model 1, unadjusted HR of MHO individuals for incident kidney dysfunction was 1.83 (95% CI, 1.34-2.49), the HR of MUNO individuals was 1.87 (95% CI, 1.61-2.17), and the HR of MUO individuals was 2.39 (95% CI, 1.94-2.95). In model 2, the HR of MHO individuals for kidney dysfunction was 1.74 (95% CI, 1.27-2.39). The HR of MUNO individuals was 1.78 (95% CI, 1.52-2.08), and the HR of MUO was 2.26 (95% CI, 1.83-2.80). In model 3, the HR of MHO individuals was 1.84 (95% CI, 1.34-2.53), the HR of MUNO individuals was 1.75 (95% CI, 1.49-2.05), and the HR of MUO individuals was 2.21 (95% CI, 1.78-2.74). Further adjustment for behavioral factors had an impact on the HR. Unlike previous results, the risk of MHO individuals was higher than that of MUNO individuals. In model 4, the HR of MHO individuals for incident CKD was 1.80 (95% CI, 1.31-2.47), the HR of MUNO individuals was 1.72 (95% CI, 1.47-2.02), and the HR of MUO individuals was 2.09 (95% CI, 1.67-2.61). The HRs of kidney dysfunction incidence showed a significantly linear trend, in order of linearity: MUNO,

MHO, MUO (P<0.001). The difference between the groups was significant (P<0.001), and the difference between MHO group and MUNO group was significant in middle-aged group (P=0.040). In the other hand, model 4 was the best fitted model according to AIC of each model (Table 5-1).

Table 5-2 is the cox regression result of the elderly group stratified by age group. In model 1, unadjusted HR of MHO individuals for incident chronic kidney dysfunction was 1.58 (95% CI, 1.09-2.27), the HR of MUNO individuals was 1.73 (95% CI, 1.50-2.00), and the HR of MUO individuals was 2.19 (95% CI, 1.76-2.71). In model 2, the HR of MHO individuals for incident CKD was 1.38 (95% CI, 0.93-2.05). The HR of MUNO individuals was 1.62 (95% CI, 1.39-1.89), and the HR of MUO was 1.91 (95% CI, 1.52-2.40). In model 3, the HR of MHO individuals was 1.33 (95% CI, 0.89-1.99), the HR of MUNO and MUO individuals were 1.60 (95% CI, 1.37-1.88), and 1.89 (95% CI, 1.50-2.38) respectively. In model 4, the HR of MHO individuals for incident kidney dysfunction was 1.31 (95% CI, 0.87-1.96), the HR of MUNO individuals was 1.61 (95% CI, 1.37-1.88), and the HR of MUO individuals was 1.88 (95% CI, 1.48-2.38). Except unadjusted model, the HRs of MHO individuals in all three models were not statistically significant. The estimates of HR for incident kidney dysfunction presented a linear trend (P<0.001). The difference between the groups was significant (P<0.001), but

the difference between MHO group and MUNO group was not significant (P=0.295). Of four models, model 4 was the best fitted model according to AIC of each model (Table 5-2).

Table 5-1. Hazard ratios (HR) for the incident kidney dysfunction according to obesity-metabolic status phenotype in middle-aged group

	Model 1	Model 2	Model 3	Model 4
MHNO	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
MHO	1.83 (1.34-2.49)	1.74 (1.27-2.39)	1.84 (1.34-2.53)	1.80 (1.31-2.47)
MUNO	1.87 (1.61-2.17)	1.78 (1.52-2.08)	1.75 (1.49-2.05)	1.72 (1.47-2.02)
MUO	2.39 (1.94-2.95)	2.26 (1.83-2.80)	2.21 (1.78-2.74)	2.09 (1.67-2.61)
AIC	14016.91	13556.65	13040.98	13035.83

Table 5-2. Hazard ratios (HR) for the incident kidney dysfunction according to obesity-metabolic status phenotype in elderly group

	Model 1	Model 2	Model 3	Model 4
MHNO	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
MHO	1.58 (1.09-2.27)	1.38 (0.93-2.05)	1.33 (0.89-1.99)	1.31 (0.87-1.96)
MUNO	1.73 (1.50-2.00)	1.62 (1.39-1.89)	1.60 (1.37-1.88)	1.61 (1.37-1.88)
MUO	2.19 (1.76-2.71)	1.91 (1.52-2.40)	1.89 (1.50-2.38)	1.88 (1.48-2.38)
AIC	13365.02	12561.50	12139.28	12104.75

Results are reported as hazard ratio (95% confidence interval). P<0.05 vs referent group.

AIC: Akaike information criterion

Model 1 was unadjusted.

Model 2 was adjusted for socio-demographic variables.

Model 3 was adjusted for the variables in model 2, plus behavioral factors.

Model 4 was adjusted for the variables in model 3, plus biochemical factors.

3.5 Association between metabolically healthy obesity and kidney dysfunction stratified by hypertension

Table 6-1 is the results of cox regression in non-hypertensive group. In model 1, unadjusted HR of MHO individuals for incident kidney dysfunction was 1.47 (95% CI, 1.01-1.98), the HR of MUNO individuals was 1.66 (95% CI, 1.42-1.95), and the HR of MUO individuals was 1.79 (95% CI, 1.29-2.48). In model 2, the HR of MHO individuals for incident chronic kidney dysfunction was 1.43 (95% CI, 1.05-1.95). The HR of MUNO individuals was 1.53 (95% CI, 1.29-1.80), and the HR of MUO was 1.74 (95% CI, 1.25-2.43). In model 3, the HR of MHO individuals was 1.46 (95% CI, 1.07-1.99) and the HR of MUNO and MUO individuals were 1.50 (95% CI, 1.27-1.77) and 1.73 (95% CI, 1.24-2.42) respectively. In model 4, the HR of MHO individuals for kidney dysfunction was 1.44 (95% CI, 1.06-1.96), the HR of MUNO individuals was 1.49 (95% CI, 1.26-1.76), and the HR of MUO individuals was 1.68 (95% CI, 1.20-2.35). The HRs of the incident chronic kidney dysfunction showed a significantly linear trend (P<0.001). The difference between the groups was significant (P<0.001). However, the difference between MHO group and MUNO group (P=0.855), between MHO group and MUO (P=0.483), and MUNO and MUO (P=0.501) were not

significant. According to AIC, model 4 was the best fitted model (Table 6-1).

Table 6-2 shows the HR for the development of incident kidney dysfunction according to obesity-metabolic status phenotype in hypertensive group. In model 1, unadjusted HR of MHO individuals for incident kidney dysfunction was 1.86 (95% CI, 1.25-2.76), the HR of MUNO individuals was 1.76 (95% CI, 1.47-2.10), and the HR of MUO individuals was 1.88 (95% CI, 1.52-2.32). In model 2, the HR of MHO individuals for kidney dysfunction was 1.97 (95% CI, 1.30-2.98). The HR of MUNO individuals was 1.69 (95% CI, 1.40-2.03), and the HR of MUO was 2.06 (95% CI, 1.65-2.58). In model 3, the HR of MHO individuals was 1.93 (95% CI, 1.26-2.94), and the HR of MUNO individuals and MUO individuals were 1.63 (95% CI, 1.35-1.97) and 1.97 (95% CI, 1.57-2.47) respectively. In model 4, the HR of MHO individuals for incident chronic kidney dysfunction was 1.84 (95% CI, 1.20-2.81), the HR of MUNO individuals was 1.61 (95% CI, 1.34-1.96), and the HR of MUO individuals was 1.92 (95% CI, 1.52-2.42). In hypertensive group, the difference between the groups was significant (P<0.001), but the difference between MHO group and MUNO (P=0.535) and between MHO group and MUO (P=0.828) was not statistically significant while the difference between MUNO and MUO was statistically significant (P=0.044).

Table 6-1. Hazard ratios (HR) for the incident kidney dysfunction according to obesity-metabolic status phenotype in non-hypertensive group

	Model 1	Model 2	Model 3	Model 4
MHNO	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
MHO	1.47 (1.10-1.98)	1.43 (1.05-1.95)	1.46 (1.07-1.99)	1.44 (1.06-1.96)
MUNO	1.66 (1.42-1.95)	1.53 (1.29-1.80)	1.50 (1.27-1.77)	1.49 (1.26-1.76)
MUO	1.79 (1.29-2.48)	1.74 (1.25-2.43)	1.73 (1.24-2.42)	1.68 (1.20-2.35)
AIC	12091.65	11190.60	10818.14	10816.95

Table 6-2. Hazard ratios (HR) for the incident kidney dysfunction according to obesity-metabolic status phenotype in hypertensive group

	Model 1	Model 2	Model 3	Model 4
MHNO	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
MHO	1.86 (1.25-2.76)	1.97 (1.30-2.98)	1.93 (1.26-2.94)	1.84 (1.20-2.81)
MUNO	1.76 (1.47-2.10)	1.69 (1.40-2.03)	1.63 (1.35-1.97)	1.61 (1.34-1.96)
MUO	1.88 (1.52-2.32)	2.06 (1.65-2.58)	1.97 (1.57-2.47)	1.92 (1.52-2.42)
AIC	16194.29	14961.70	14389.96	14353.92

Results are reported as hazard ratio (95% confidence interval). P<0.05 vs referent group.

AIC: Akaike information criterion

Model 1 was unadjusted.

Model 2 was adjusted for socio-demographic variables.

Model 3 was adjusted for the variables in model 2, plus behavioral factors.

Model 4 was adjusted for the variables in model 3, plus biochemical factors.

Chapter 4. Discussion and Conclusion

4.1 Discussion

In this prospective Korean population-based study of 8,608 participants, 13.6% of the population was obese and 29.9% was 'metabolically healthy', using the ATP-Ⅲ criteria to define metabolic health. The main result of this study is that MHO individuals were significantly at higher risk of incident chronic kidney dysfunction compared to the MHNO individuals after adjusting for socio-demographic variables, behavioral factors, and biochemical factors. However, no significant difference in the risk of kidney dysfunction incidence was shown between MHO individuals and MUNO individuals. Meanwhile, the HR of MUO individuals were significantly higher than the risk of MHO individuals. According to these results, healthy metabolic profile does not protect obese individuals from incident chronic kidney dysfunction. This study can suggest that MHO should not be considered as a benign condition. In addition, we support that different obese phenotype have different effect on the risk of incident kidney dysfunction in Korean population.

Although several previous studies identified the effect of MHO on CKD incidence, the association between two is still controversial. Some reports (4,10,29), but not all (30-32), have presented higher risk of MHO compared to MHNO. This debate might be due to the different criteria used to define MHO. In previous articles (33), it was suggested that the prevalence of MHO varied due to various definition of MHO. We used ATP-Ⅲ definition to define metabolic health, while Chen's study (30) used HOMA-IR score index and hsCRP cutoff in addition to ATP-Ⅲ. The differences of study population characteristics also could be the reason of this debate. Hashimato (32) used the Oike Health Survey that healthy employees from various companies participated. In this case, healthy worker effect could lead to such discrepancy.

According to the result of additional analysis divided by sex, the association of MHO individuals with the risk of incident chronic kidney dysfunction was still statistically significant in both male and female in the final model. In male group compared to female group, overall, the HRs were highest in MHO, MUNO, MUO groups in order. Thus, association between obesity-metabolic status phenotype and the incident chronic kidney dysfunction was stronger in males. On the other hand, the result of analysis stratified by age group showed that the risk of MHO and MUNO groups were significantly higher compared to MUNO in middle-aged group. After

adjusting for all covariates, the point estimate of HR in MHO individuals was higher than that in MUNO individuals, but those were not significantly different. Only in the elderly group was the risk of MHO individuals not statistically significantly higher than the risk of MHNO individuals. The reason why there were differences between middle-aged and elderly groups might be the age difference in the prognostic significance of eGFR. Age is a crucial effect modifier in CKD. Thus, a similar value of eGFR may affect different prognosis in different-aged patients (34). According to hypertension subgroup analysis, the risk of MHO compared to MUNO in both non-hypertensive and hypertensive group also statistically higher. In hypertensive group compared to non-hypertensive group, overall, the HRs were highest in MHO, MUNO, MUO groups in order. Thus, association between obesity-metabolic status phenotype and the incident chronic kidney dysfunction was stronger in the hypertensive group. Furthermore, according to the result of hypertensive group, obesity may be more likely to affect incident kidney dysfunction than cardiometabolic factors in hypertensive group. The risk of MHO group is similar to the risk of MUO and is higher than the risk of MUNO.

The mechanisms behind how obesity and the metabolic syndrome affect renal function deterioration still remain elusive. Some possible mechanisms

explain the association between obesity, metabolic syndrome, and CKD (4). Obesity could enhance kidney injury directly through hemodynamic and hormonal effects or indirectly through development of diabetes and hypertension (8). Leptin, a hormone mainly produced in the adipose tissue, has a potential role in renal dysfunction associated with obesity. Leptin has a direct influence on renal function (35). An inflammatory process is also suggested as a mechanism for obesity-related renal changes (35). Obesity leads to a state of low-grade systemic inflammation in which adipose cells create cytokines, and CRP levels increase (35).

Notable strengths of the present study are that it was a Korean population-based cohort study of a large sample size, and that the evaluation of outcomes was conducted over a 14-year follow-up period. To reduce the potential bias for confounding, we adjusted for diverse variables to that of other preceding research, including socio-economic status (SES), marital status, occupation, living region, smoking status, alcohol consumption, physical activity, and some biochemical factors. The study also has several limitations. First, this analysis did not reflect the change of obesity-metabolic status over the course of follow-up time. Secondly, we used BMI as the criteria of obesity without considering fat distribution. As mentioned at literature review, difference in fat distribution is a potential underlying

mechanism of the MHO effect on chronic disease. Thirdly, in this study, we estimated GFR by using the CKD-EPI equation based on serum creatinine rather than direct measurement. Compared to real GFR value, eGFR could be overestimated or underestimated. In addition, we did not include the incident proteinuria, known as one of the CKD definitions, but only eGFR cutoff to define kidney dysfunction. Therefore, this might have underestimated the incidence of kidney dysfunction. Lastly, in present study, the timing of the incident chronic kidney dysfunction detection might not be accurate because that was the time of the follow-up examination, not of real kidney dysfunction development.

4.2 Conclusion

This study indicated that metabolically healthy obesity may increase the risk of incident chronic kidney dysfunction in Korean adults. We suggest that different obese phenotype have different effect on the risk of incident CKD and MHO is not a benign condition. Therefore, it is crucial to identify obesity-metabolic status phenotype in predicting CKD incidence risk. Moreover, the proper prevention and treatment of chronic disease including CKD according to the obesity subtype are needed. To better understand the health risk associated with the MHO, more attention is required on how to define the metabolic health and what health effects are considered.

REFERENCES

1. Kang EJ, Han MY, Kim HS, *et al*. Baseline General Characteristics of the Korean Chronic Kidney Disease: Report from the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD). *J Korean Med Sci.* 2017;32(2):221-230.

2. Eknoyan G, Lameire N, Barsoum R, *et al*. The burden of kidney disease: improving global outcomes. *Kidney Int*. 2004;66(4):1310-4.

3. Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2013; 380:2095–2128.

4. Song YM, Sung JH, Lee KY. Longitudinal relationships of metabolic syndrome and obesity with kidney function: Healthy Twin Study. *Clin Exp Nephrol*. 2015; 19:887-894.

5. Korean National Health and Nutrition Examination Survey.

6. Schieppati A, Remuzzi G. The future of renoprotection: Frustration and promises. *Kidney Int*. 2003;64(6):1947-55.

7. GBD 2015 Obesity Collaboration. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med.* 2017; 377: 13–27.

8. Wang Y, Chen X, Song Y, Caballero B, and Cheskin LJ. Association between obesity and kidney disease: A systematic review and meta-analysis. *Kidney Int.* 2008;73(1):19-33.

9. Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. *Nat Rev Endocrinol*. 2015;11(1):55-62.

10. Lin L, Peng K, Du R, Huang X, Lu J, Xu Y, Xu M, Chen Y, Bi Y, Wang W. Metabolically healthy obesity and incident chronic kidney disease: The role of systemic inflammation in a prospective study. *Obesity (Silver Spring)*. 2017 Mar;25(3):634-641.

11. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev Endocr Metab Disord*. 2013;14(3):219-27.

12. Ruderman NB, Schneider SH, Berchtold P. The "metabolically-obese," normal-weight individual. *Am J Clin Nutr*. 1981;34(8):1617-21.

13. Camhi SM, Waring ME, Sisson SB, Hayman LL, Must A. Physical activity and screen time in metabolically healthy obese phenotypes in adolescents and adults. *J Obes*. 2013; 2013:1-10.

14. Appleton SL, Seaborn CJ, Visvanathan R *et al*. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care*. 2013; 36: 2388–2394.

15. Lynch LA, O'Connell JM, Kwasnik AK, Cawood TJ, O'Farrelly C, O'Shea DB. Are natural killer cells protecting the metabolically healthy obese patient? *Obesity (Silver Spring).* 2009;17(3):601-5

16. Meigs JB1, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM, D'Agostino RB. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 2006;91(8):2906-12.

17. Calori G, Lattuada G, Piemonti L *et al*. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. *Diabetes Care*. 2011; 34: 210–215.

18. Kuk JL, Ardern CI. Are metabolically normal but obese individuals at lower risk for all-cause mortality? *Diabetes Care*. 2009; 32: 2297–2299.

19. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, Balletshofer B, Machicao F, Fritsche A, Häring HU. Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med.* 2008;168(15):1609-16.

20. Kim CH, Park JY, Lee KU, Kim JH, Kim HK. Fatty liver is an independent risk factor for the development of Type 2 diabetes in Korean adults. *Diabet Med*. 2008;25(4):476-81.

21. Stefan N, Häring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol*. 2013;1(2):152-62.

22. Kim YJ, Han BG, Ko GESg. Cohort profile: the Korean Genome and epidemiology study (KoGES) consortium. *Int. J. Epidemiol.* 2016.

23. Kopelman PG, Caterson ID, Dietz WH. Clinical obesity in adults and children. *Blackwell Publishing*, Oxford, UK; 2010.

24. Zhou BF, Cooperative Meta-Analysis Group of Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci*. 2002;15(1):83-96.

25. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am* J Kidney Dis 2010; 55(4): 622-627.

26. Rehm J, Room R, Monterio M, *et al*. Alcohol use. In: Ezzati M, Lopez AD, Rodegers A, Murray CJL, eds. Comparative quantification of health risks. Global and regional burden of disease attributable to selected major risk factors (vol 1). Geneva: World Health Organization, 2004: 959-1109.

27. Fiona CB, Timothy PA, Tracy D, et al. Physical inactivity. In: Ezzati M, Lopez AD, Rodegers A, Murray CJL, eds. Comparative quantification of health risks. Global and regional burden of disease attributable to selected major risk factors (vol 1). Geneva: World Health Organization, 2004: 959-1109.

28. Chen CH, Lin KC, Tsai ST, Chou P. Different association of hypertension and insulin-related metabolic syndrome between men and women in 8437 nondiabetic Chinese. *Am J Hypertens*. 2000;13(7):846-53.

29. Jung CH, Lee MJ, Kang YM, et al. The risk of chronic kidney disease in a metabolically healthy obese population. *Kidney Int.* 2015;88(4):843-50.

30. Chen S, Zhou S, Wu B, et al. Association between metabolically unhealthy overweight/obesity and chronic kidney disease: the role of inflammation. *Diabetes Metab*. 2014;40(6):423-30.

31. Wang C, Liang K, Zhang X, Li C, Yang W, Ma Z, Sun Y, Song J, Lin P, Gong L, Wang M, Liu F, Li W, Xiao J, Yan F, Yang J, Wang L, Tian M, Liu J, Zhao R, Hou X, Chen L. Metabolic abnormalities, but not obesity, contribute to the mildly reduced eGFR in middle-aged and elderly Chinese. *Int Urol Nephrol.* 2014;46(9):1793-9

32. Hashimoto Y, Tanaka M, Okada H, et al. Metabolically healthy obesity and risk of incident CKD. *Clin J Am Soc Nephrol*. 2015;10(4):578-83.

33. Velho S1, Paccaud F, Waeber G, Vollenweider P, Marques-Vidal P. Metabolically healthy obesity: different prevalences using different criteria. *Eur J Clin Nutr*. 2010;64(10):1043-51.

34. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, Walter LC, Mehta KM, Steinman MA, Allon M, McClellan WM, Landefeld CS. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. 2007;18(10):2758-65.

35. de Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL; PREVEND study group. Obesity and target organ damage: the kidney. *Int J Obes Relat Metab Disord*. 2002;26 Suppl 4:S21-4.

Abstract in Korean

국문초록

대사적으로 건강한 비만과 신기능 저하 발생 위험 간의 연관성

조수영

보건학과 역학전공

서울대학교 보건대학원

연구배경 및 목적: 전 세계의 공중보건학적 문제로 알려진 만성 콩팥병은 한국에서도 보건학적으로 매우 중요하게 다뤄지는 만성질환이다. 비만과 만성 콩팥병의 연관성에 대한 많은 역학 연구 결과, 비만이 만성 콩팥병 위험을 높인다고 밝혔으며 비만이 만성 콩팥병을 일으키는 기전은 지방세포 과다로 인한 대사적인 요소와 관련되었다고 알려져 있다. 그러나 비만한 사람 중에서도 대사적 이상이 없는 집단이 존재하여, 비만하지만 대사적으로 건강한 집단(MHO)에

대한 연구가 진행되어 왔다. 대사적으로 건강한 비만과 만성 콩팥병의 연관성은 정확하게 알려진 바가 없으며, 대사적으로 건강한 비만이 만성 콩팥병 발생 위험을 증가시키는 지에 대해서도 논란이 계속되고 있다. 따라서, 본 연구의 목적은 한국인 일반 인구집단을 대상으로 대사적으로 건강한 비만과 만성 신기능 저하 간의 연관성을 확인하는 것이다.

연구방법: 한국인 유전체 역학조사 사업 중 지역사회 기반 코호트인 안산 및 안성 코호트를 이용하여 총 8,608명의 대상자를 분석하였다. 주요 노출변수는 비만 여부와 대사적 건강여부에 따라 4가지 그룹으로 분류하였다. 체질량 지수가 28kg/㎡ 이상인 경우 비만으로 정의하고, ATP-Ⅲ를 이용하여 대사적 건강 여부를 정의하여 다음과 같이 분류하였다: 대사적으로 건강하고 비만이 아닌 그룹 (MHNO), 대사적으로 건강한 비만 그룹 (MHO), 대사적으로 건강하지 않고 비만이 아닌 그룹 (MUNO), 대사적으로 건강하지 않은 비만 그룹 (MUO). 결과변수는 만성 신기능 저하이며 추정한 사구체 여과율이 60ml/min/1.73㎡ 미만인 경우로 정의하였다. 교란변수를 통제하기 위해 사회 인구학적 변수, 건강 행태적 요인, 생화학적 변수를 보정하였으며, 콕스 비례위험 회귀모형을 이용하여 대사적으로 건강하고 비만이 아닌 그룹을 기준으로 하는 위험비와 95% 신뢰구간을 구하였다. 모든 분석에는 R 3.4.3을 이용하였다.

연구결과: 전체 인구집단의 4.1% (351명), 비만 집단의 29.9%가 대사적으로 건강한 비만이었다. 잠재적인 교란 변수를 모두 보정한 후, 대사적으로 건강한 비만 그룹의 만성 신기능 저하 발생 위험비는 1.59 (95% 신뢰구간: 1.24−2.04)였으며, 대사적으로 건강하지 않고 비만이 아닌 그룹의 위험비는 1.69 (95% 신뢰구간: 1.51−1.89), 대사적으로 건강하지 않은 비만 그룹은 2.03 (95% 신뢰구간: 1.73−2.38)였다. 대사적으로 건강하고 비만이 아닌 그룹에 비해 나머지 모든 그룹의 위험비는 통계적으로 유의하게 높았다. 또한 대사적으로 건강한 비만 그룹, 대사적으로 건강하지 않고 비만이 아닌 그룹, 대사적으로 건강하지 않은 비만 그룹 순으로 위험비가 선형적인 경향을 보였다.

결론: 본 연구는 한국 성인을 대상으로 대사적으로 건강한 비만이 아닌 집단에 비해 대사적으로 건강한 비만이 만성 신기능 저하 발생 위험을 높인다는 것을 보여주었으며, 대사적으로 건강한 비만집단은 건강한 상태(benign condition)라고 볼 수 없다. 또한, 본 연구의 결과를 바탕으로 비만의 하위 집단별 차이에 따라 만성 신기능 저하 발생 위험 차이를 보이기 때문에 만성 콩팥병 발생 위험을 예측할 때 비만의 하위 집단의 특성을 고려하는 것이 중요하며, 하위 집단에 따라 적절한 예방과 치료를 하는 것이 필요하다고 제안할 수 있다.

주요어: 대사증후군, 비만, 대사적으로 건강한 비만, 만성 콩팥병, 신기능 저하, 콕스 비례위험 모형

학 번: *2016-26888*