The Association Between Metabolic Syndrome and Heart Failure in Middle-aged Men and Women : Population-Based Study of 2 Million Individuals

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Abstract

Background: Although the association between metabolic syndrome (MetS) and heart failure (HF) risk is known, large longitudinal studies that can permit causal inferences are limited. In this study, we investigated metabolic status as a risk factor for HF in middle-aged men and women and evaluated sex differences in various risk factors for HF using nationwide real-world data.

Methods: Data obtained from the Korean National Health Insurance Service from 2009 to 2016 were analyzed. A total of 2151597 middle-age subjects (1149642 men and 1001955 women) (between 50 and 59 years old) without a history of Cardiovascular or cerebrovascular disease or malignancy were enrolled. Subjects were divided into three groups according to the number of MetS components: 0 (normal), 1–2 (Pre-MetS) or 3–5 (MetS) based on the National Cholesterol Education Program Adult Treatment Panel III criteria. Cox proportional hazard models were used to estimate the association between MetS and incident HF after adjusting for clinical risk factors.

Results: At baseline, MetS existed in 23.77% of men and 10.58% of women. Pre-MetS and MetS increased the risk of HF: the hazard ratio (95% confidence interval) of pre-MetS was 1.508 (1.287-1.767) in men and 1.395 (1.158-1.681) in women; the hazard ratio (95% confidence interval) of MetS was 1.711 (1.433-2.044) in men and 2.144 (1.674-2.747) in women. Current smoking, low hemoglobin level, underweight (BMI<18.5) and high creatinine level as well as acute myocardial infarction were also predictors of HF in both men and women.

Conclusions: This study confirmed that pre-MetS and MetS are risk factors for HF in middle-aged men and women. The effect of MetS on the occurrence of HF was stronger in women than in men. Pre-MetS was also a predictor of HF but was associated with a lower risk than MetS.

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by a reduced ability to eject and/or accommodate blood within physiological pressure levels.^{1,2} Unlike other cardiac disorders, the prognoses of which have been markedly improved, only modest survival improvement has been observed in HF patients and the prevalence of HF is rising.^{3,4}

Metabolic syndrome (MetS), a clustering of cardiovascular risk factors that includes hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia, is common around the world. The prevalences of MetS in men and women are 35.6% and 30.3% in the United States⁵ and are 41% and 38% in Europe.⁶ Although the pathophysiologic mechanism of MetS has not been fully elucidated, obesity and insulin resistance are believed to play a critical role in the pathogenesis of MetS.⁷

Many studies have demonstrated the association between HF and MetS. Miura et al.⁸ reported that the prevalence of MetS is 2-fold higher in patients with HF than in the general population, and Li et al.⁹ found that MetS was associated with an approximately 2-fold increased likelihood of self-reported HF in a

population-based cross-sectional study. Various studies have reported the association between MetS and the prognosis of HF.^{10,11} Although the underlying pathophysiologic mechanisms of the association between MetS and HF remain to be fully elucidated, metabolic stress caused by elevated glucose and free fatty acids, including dysregulated insulin signaling, impaired mitochondrial respiration and reactive oxygen species formation, is thought to decrease adenosine triphosphate (ATP) production, resulting in impaired contraction, myocellular hypertrophy, and fibrosis of the heart, subsequently leading to HF.¹²

Despite the evidence showing the association between MetS and HF, longitudinal studies that can permit causal inferences are limited, and most of them were performed in elderly populations. Thus, in this study, we investigated MetS as a predictor of HF in middle-aged men and women using the National Health Insurance Service (NHIS) database. Additionally, we investigated the difference in the degree of the risk of MetS associated with HF between men and women.

Methods

Database source

This study used the NHIS database, which is the universal health insurance system in South Korea. The NHIS covers more than 97% of the population and contains information on patients' demographics (age, sex and socioeconomic variables, etc.), prescribed drugs (generic drug name, prescription date, duration and route of administration) and use of medical care institutions (hospital admissions, outpatient department visits, pharmaceutical visits, etc.). The NHIS also provides an annual or biennial health screening examination called the National Health Screening Program (NHSP) to the population aged 20 years and older, which includes questionnaires on lifestyle and behavior, physical examinations, and blood tests. In the NHIS database, diagnoses are coded according to the International Classification of Diseases-10th revision (ICD-10). The data were provided by NHIS after deidentification. This study was approved by the NHIS of Korea (No. NHIS-2020-1-153) and the Institutional Review Board of Konkuk University Medical Center (No. KUH 2020-07-096).

Study population

The number of individuals who underwent health screening examinations between January 2009 and December 2009 in South Korea was 9,927,538. Among the 9,927,538 participants, 7,775,941 were excluded for the following reasons: 1) < 50 years old or $\geq$ 60 years old, 2) history of malignancy (ICD-10 codes C00.X-C99.X) or 3) history of cardiovascular or cerebrovascular disease, including AF (ICD-10 codes I48), coronary artery disease (procedure codes M6561-4), myocardial infarction (ICD-10 codes I21), HF (ICD-10 codes I42 or I50), cerebrovascular accident (ICD-10 codes I60.X-I609. X), and peripheral arterial disease (ICD-10 codes I73 or I74). HF was diagnosed when the diagnostic code of HF occurred and there was any history of admission to hospital. The final number of participants in the study was 2,151,597. These subjects were then divided into three groups for each sex according to the number of MetS components: normal group (0), pre-MetS group (1–2), and MetS group (3–5). We analyzed follow-up data until December 31, 2016 (Fig. 1).

Definition of metabolic syndrome

According to the modified criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria,¹³ a diagnosis of MetS was made when at least three of the following five components were present: (1) abdominal obesity (WC $\geq$ 90 cm for men, $\geq$ 85 cm for women); (2) elevated BP (systolic BP $\geq$ 130 mmHg or diastolic BP $\geq$ 85 mmHg or treatment of previously diagnosed HTN); (3) elevated fasting glucose ($\geq$ 100 mg/dL or treatment of previously diagnosed DM); (4) high triglycerides (TGs) ($\geq$ 150 mg/dL or drug treatment for high TGs); and (5) low high-density lipoprotein cholesterol (HDL-C) ($<$ 40 mg/dL for men, $<$ 50 mg/dL for women or drug treatment for low HDL-C). Subjects with one or two MetS components were defined as having pre-MetS, and those with no MetS components were defined as normal.

Primary outcome and follow-up

The primary outcome of this analysis was the incidence of HF during follow-up period. We defined an HF event using newly occurring ICD-10 codes for HF (I50). Follow-up was initiated at the date of the health screening examination and ended at the incidence of HF, death, or 31 December 2016, whichever came first.

Statistical analysis

Descriptive statistics were used to present the characteristics of the study subjects. The comparisons of baseline characteristics among metabolic syndrome were performed by χ^2 -test.

Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of HF during the follow-up period. The models were initially unadjusted, and further adjustments were made for demographic characteristics (age, smoking status, and exercise status) (model 1). Model 2 was adjusted for the same covariates as model 1 plus family history of HTN, stroke and DM. Covariates were added to those of previous models step by step; thus, model 3 was adjusted for body mass index (BMI) and laboratory results (hemoglobin, creatinine, total cholesterol, low-density lipoprotein cholesterol, and alanine aminotransferase (ALT)) as well as demographic characteristics and family history. In model 4, the final model was adjusted for demographic characteristics, family history, BMI, laboratory results and occurrence of acute myocardial infarction (AMI) during follow-up period. All tests were two-sided, with a significance level of 0.05. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

A total of 1,149,642 men and 1,001,955 women were included in this analysis. At baseline, MetS existed in 23.77% of men and 10.58% of women. The prevalence of pre-MetS was 55.64% and 50.86% in men and women, respectively. Table 1 presents baseline characteristics by MetS status. The prevalence of

MetS was significantly associated with smoking status, alcohol consumption and frequency of exercise. The prevalence of MetS also exhibited a significant association with family histories of HTN, DM and stroke; BMI; and clinical laboratory results of total cholesterol, hemoglobin, creatinine and ALT (Table 1) in both sexes.

Table 1
Baseline characteristics of study population according to metabolic syndrome status

Baseline characteristics of study population according to metabolic syndrome status								
	Male				Female			
	Normal N = 236669 (20.59)	Pre- MetS N = 639704 (55.64)	MetS N = 273269 (23.77)	P- value	Normal N = 386,322 (38.56)	Pre- MetS N = 509,614 (50.86)	MetS N = 106,019 (10.58)	P- value
Smoking status								
Non-smoker	69695 (23.23)	166871 (55.62)	63454 (21.15)	< 0.0001	367335 (38.69)	483018 (50.87)	99076 (10.44)	< 0.0001
Ex-smoker	61530 (19.97)	172740 (56.08)	73774 (23.95)		5641 (39.69)	6929 (48.75)	1642 (11.55)	
Current smoker	103969 (19.42)	296719 (55.43)	134594 (25.14)		10503 (33.77)	16075 (51.68)	4525 (14.55)	
Alcohol consumption								
No drink	76042 (24.28)	172399 (55.04)	64770 (20.68)	< 0.0001	270576 (38.33)	359005 (50.85)	76363 (10.82)	< 0.0001
2–3 per month	114928 (20.92)	305899 (55.68)	128574 (23.4)		94636 (39.97)	119561 (50.50)	22545 (9.52)	
1–4 per week	32605 (15.79)	116225 (56.28)	57695 (27.94)		11672 (34.71)	17863 (53.13)	4089 (12.16)	
≥ 5 per week	10238 (14.87)	38795 (56.36)	19803 (28.77)		3835 (33.26)	6098 (52.89)	1597 (13.85)	
Exercise								
No exercise	93741 (20.12)	257668 (55.3)	114561 (24.59)	< 0.0001	193655 (37.68)	263109 (51.19)	57202 (11.13)	< 0.0001
1–4 per week	47105 (20.44)	127964 (55.53)	55388 (24.03)		71043 (39.03)	92188 (50.65)	18771 (10.31)	
≥ 5 per week	93704 (21.11)	248941 (56.08)	101220 (22.8)		119010 (39.76)	150914 (50.43)	29360 (9.81)	

Unit: persons(%)

Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome

P-value by X²-test

	Male				Female			
Family history of hypertension								
Yes	18324 (15.33)	65336 (54.64)	35905 (30.03)	< 0.0001	40687 (31.85)	68343 (53.50)	18707 (14.64)	< 0.0001
No	145852 (21.44)	378540 (55.63)	156040 (22.93)		213678 (39.88)	268648 (50.14)	53509 (9.99)	
Family history of diabetes mellitus								
Yes	17843 (16.18)	59802 (54.24)	32617 (29.58)	< 0.0001	34730 (33.88)	52863 (51.57)	14922 (14.56)	< 0.0001
No	146165 (21.21)	383657 (55.68)	159236 (23.11)		219524 (39.15)	283972 (50.64)	57220 (10.20)	
Family history of stroke								
Yes	16413 (19.26)	47273 (55.47)	21534 (25.27)		23950 (36.59)	33966 (51.90)	7533 (11.51)	< 0.0001
No	47711 (20.67)	396629 (55.49)	170413 (23.84)		230167 (38.53)	302655 (50.67)	64531 (10.80)	
Total cholesterol (mg/dL)								
< 200	151035 (25.05)	332175 (55.09)	119760 (19.86)	< 0.0001	245784 (41.12)	301128 (50.38)	50829 (8.5)	< 0.0001
200–239	70069 (17.51)	226451 (56.58)	103697 (25.91)		114051 (37.05)	156365 (50.8)	37389 (12.15)	
> 239	15565 (10.63)	81078 (55.36)	49812 (34.01)		26487 (27.47)	52121 (54.06)	17801 (18.46)	
ALT (IU/L)								
< 40	216861 (23.54)	526325 (57.13)	178156 (19.34)	< 0.0001	376523 (39.49)	485460 (50.91)	91557 (9.6)	< 0.0001

Unit: persons(%)
Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome
P-value by X ² -test

	Male				Female			
40–99	18121 (8.6)	105617 (50.1)	87087 (41.31)		8696 (19.87)	21857 (49.95)	13209 (30.18)	
> 100	1687 (9.65)	7762 (44.42)	8026 (45.93)		1103 (23.71)	2297 (49.37)	1253 (26.93)	
Hemoglobin (g/dL)								
< 13.5(Male), < 12(Female)	23156 (26.5)	48700 (55.74)	15510 (17.75)	< 0.0001	90985 (40.86)	112912 (50.7)	18792 (8.44)	< 0.0001
13.5– 17.5(Male), 12-15.5 (Female)	212536 (20.25)	584907 (55.73)	252155 (24.02)		13166 (37.99)	394040 (50.89)	86041 (11.11)	
> 17.5(Male), > 15.5(Female)	977 (7.71)	6097 (48.09)	5604 (44.2)		1151 (23.3)	2619 (53.02)	1170 (23.68)	
Creatinine (mg/dL)								
≤ 1.5	228987 (20.67)	616190 (55.63)	262468 (23.70)	< 0.0001	381018 (38.59)	501914 (50.84)	104342 (10.57)	< 0.0001
> 1.5	7660 (18.27)	23478 (56.00)	10788 (25.73)		5281 (36.11)	7671 (52.45)	1674 (11.45)	
Body Mass Index (kg/m²)								
< 18.5	8184 (48.01)	8264 (48.48)	599 (3.51)	< 0.0001	15574 (61.25)	9535 (37.50)	319 (1.25)	< 0.0001
18.5–22.9	123762 (34.53)	205799 (57.42)	28877 (8.06)		243305 (49.84)	227833 (46.67)	17019 (3.49)	
23-24.9	68418 (21.00)	201763 (61.92)	55641 (17.08)		85685 (35.64)	133579 (55.57)	21128 (8.79)	
25-29.9	36122 (8.74)	214726 (51.95)	162486 (39.31)		41084 (18.76)	126189 (57.63)	51685 (23.60)	
≥30	183 (0.52)	9152 (26.15)	25666 (73.33)		674 (2.32)	12478 (43.00)	15868 (54.68)	
Unit: persons(%)								
Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome								
P-value by X ² -test								

Association between MetS status and HF

The incidence rate of HF was associated with MetS status. The incidences increased as pre-MetS progressed to MetS and were higher in men than in women. The rates per 100,000 person-years in the normal population were 19.2 in men and 13.38 in women, and the rates in the pre-MetS and MetS populations were 35.88 and 55.05, respectively, in men and 19.42 and 34.91, respectively, in women (Fig. 2).

Table 2 compares the baseline characteristics of the population with HF and those without HF. Both in men and women, the frequency of HF was higher in populations with MetS than in the normal population. The pre-MetS population also showed a higher frequency of HF than the normal population, although the proportion was lower than that of the MetS group.

Table 2
Baseline characteristics of study population according to heart failure

Baseline characteristics of study population according to heart failure						
	Male			Female		
	non-HF	HF	p-value	non-HF	HF	p-value
Metabolic status						
Normal	236373 (99.87)	296 (0.13)	< 0.0001	386025(99.92)	297(0.08)	< 0.0001
Pre-MetS	638221 (99.77)	1483 (0.23)		509001(99.88)	612(0.12)	
MetS	272285 (99.64)	984 (0.36)		105769(99.76)	250(0.24)	
Smoking status						
Non-smoker	299458 (99.81)	562 (0.19)	< 0.0001	948372 (99.89)	1056 (0.11)	< 0.0001
Ex-smoker	307501 (99.82)	543 (0.18)		14191 (99.85)	21 (0.15)	
Current smoker	533637 (99.69)	1645 (0.31)		31028 (99.76)	75 (0.24)	
Alcohol consumption						
No drink	312309 (99.71)	902 (0.29)	< 0.0001	705123 (99.88)	820 (0.12)	0.2241
2–3 per month	548255 (99.79)	1146 (0.21)		236485 (99.89)	257 (0.11)	
1–4 per week	206048 (99.77)	477 (0.23)		33585 (99.88)	39 (0.12)	
≥ 5 per week	68622 (99.69)	214 (0.31)		11510 (99.83)	20 (0.17)	
Exercise						
No exercise	464750 (99.74)	1220 (0.26)	0.0005	513340 (99.88)	626 (0.12)	0.0963
1–4 per week	229928 (99.77)	529 (0.23)		181793 (99.89)	209 (0.11)	

Unit: persons(%)

Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome; HF, heart failure

P-value by X²-test

	Male			Female		
≥ 5 per week	442872 (99.78)	993 (0.22)		298969 (99.90)	314 (0.10)	
Family history of hypertension						
Yes	119251 (99.74)	314 (0.26)	0.0308	127569 (99.87)	168 (0.13)	0.0124
No	678868 (99.77)	1564 (0.23)		535269 (99.89)	566 (0.11)	
Family history of diabetes mellitus						
Yes	109954 (99.72)	308 (0.28)	0.0011	102395 (99.88)	120 (0.12)	0.4831
No	687487 (99.77)	1571 (0.23)		560104 (99.89)	612 (0.11)	
Family history of stroke						
Yes	85003 (99.75)	217 (0.25)	0.2137	65377 (99.89)	72 (0.11)	0.9986
No	713089 (99.77)	1664 (0.23)		596696 (99.89)	657 (0.11)	
Total cholesterol (mg/dL)						
< 200	601702 (99.79)	1268 (0.21)	< 0.0001	597109 (99.89)	631 (0.11)	0.0002
200–239	399277 (99.77)	940 (0.23)		307422 (99.88)	383 (0.12)	
> 239	145900 (99.62)	555 (0.38)		96264 (99.85)	145 (0.15)	
ALT (IU/L)						
< 40	919272 (99.78)	2070 (0.22)	< 0.0001	952491 (99.91)	1048 (0.09)	< 0.0001
40–99	210218 (99.71)	607 (0.29)		43668 (99.88)	337(0.12)	
Unit: persons(%)						
Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome; HF, heart failure						
P-value by X ² -test						

	Male			Female		
> 100	17389 (99.51)	86 (0.49)		159829(99.86)	231(0.14)	
Hemoglobin (g/dL)						
< 13.5(Male), < 12(Female)	87087 (99.68)	279 (0.32)	< 0.0001	222419 (99.88)	270 (0.12)	< 0.054
13.5–17.5(Male), 12-15.5 (Female)	1047180 (99.77)	2418 (0.23)		773363 (99.89)	878 (0.11)	
> 17.5(Male), > 15.5(Female)	12612 (99.48)	66 (0.62)		4929 (99.78)	11(0.22)	
Creatinine (mg/dL)						
≤ 1.5	1105044(99.77)	2601(0.23)	< 0.0001	986158(99.89)	1115(0.11)	< 0.0001
> 1.5	41764(99.61)	162(0.39)		14582(99.70)	44(0.30)	
Body Mass Index (kg/m²)						
< 18.5	16995(99.69)	52(0.31)	< 0.0001	25396(99.87)	32(0.13)	< 0.0001
18.5–22.9	357675(99.79)	763(0.21)		487723(99.91)	433(0.09)	
23-24.9	325142(99.79)	680(0.21)		240123(99.89)	269(0.11)	
25-29.9	412217(99.73)	1117(0.27)		218619(99.85)	339(0.15)	
≥30	34850(99.57)	151(0.43)		28934(99.70)	86(0.30)	
Unit: persons(%)						
Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome; HF, heart failure						
P-value by X ² -test						

In addition to MetS status, there were statistically significant differences in baseline characteristics between populations with and without HF. Both in men and women, current smokers showed a higher proportion of HF than ex-smokers or nonsmokers. An occurrence of AMI during follow-up period is definitely related to a higher frequency of HF. In comparison to the normal BMI group, both the underweight and overweight (obese) groups showed higher HF frequency in both sexes. Laboratory findings including cholesterol, creatinine and ALT and family history of hypertension were also related to

the frequency of HF in both sexes. The differences in HF frequency according to alcohol consumption, frequency of exercise and family history of DM and hemoglobin level were shown only in men (Table 2).

Risk factors for HF

Multivariable Cox regression analysis was performed to evaluate risk factors for HF (Table 3, 4). Without other covariates, the HRs of pre-MetS and MetS for HF were 1.867 (95% CI, 1.599–2.18) and 3.016 (2.569–3.541), respectively, in men and 1.605 (1.34–1.923) and 3.349 (2.706–4.145), respectively, in women (model 1). Considering age; smoking; alcohol consumption; exercise; family histories of heart disease, HTN, DM and stroke; laboratory results; and occurrence of AMI during follow-up period as covariates, the occurrence of HF was still significantly higher in subjects with pre-MetS or MetS than in normal individuals, with higher HRs observed in MetS patients than pre-MetS patients. The risk of HF associated with pre-MetS was slightly higher in men than in women, whereas that associated with MetS was higher in women than in men (HR (95% CI) of pre-MetS: 1.508 (1.287–1.767) in men and 1.395 (1.158–1.681) in women; HR (95% CI) of MetS: 1.711 (1.433–2.044) in men and 2.144 (1.674–2.747) in women) (model 5) (Table 3, 4).

Table 3
Risk of heart failure in male: Cox proportional hazard model.

	Non-Adjusted HR (95% CI)	Multivariable HR (95% CI)			
Metabolic status	Model 1	Model 2	Model 3	Model 4	Model 5
Normal	1	1	1	1	1
Pre-metabolic synd.	1.867 (1.599–2.18)	1.846 (1.581–2.156)	1.839 (1.575–2.148)	1.778 (1.517–2.083)	1.508 (1.287–1.767)
Metabolic synd.	3.016 (2.569–3.541)	2.93 (2.494–3.442)	2.901 (2.469–3.41)	2.584 (2.167–3.081)	1.711 (1.433–2.044)
Age		1.067 (1.05–1.084)	1.067 (1.05–1.085)	1.069 (1.051–1.086)	1.034 (1.017–1.051)
Smoking status					
Non-smoker		1	1	1	1
Ex-smoker		0.994 (0.858–1.151)	0.982 (0.848–1.138)	0.971 (0.838–1.125)	0.906 (0.782–1.05)
Current smoker		1.8 (1.592–2.035)	1.787 (1.58–2.02)	1.772 (1.567–2.005)	1.19 (1.051–1.348)
Alcohol consumption					
No drink		1	1	1	1
2–3 per month		0.64 (0.573–0.714)	0.638 (0.571–0.712)	0.643 (0.576–0.718)	0.814 (0.729–0.909)
1–4 per week		0.666 (0.58–0.765)	0.665 (0.579–0.764)	0.674 (0.587–0.774)	0.975 (0.848–1.12)
≥ 5 per week		0.806 (0.667–0.974)	0.807 (0.668–0.975)	0.816 (0.675–0.986)	1.162 (0.961–1.404)
Exercise					
No exercise		1	1	1	1

Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome, HR, hazard ratio

*Occurrence of Acute myocardial infarction during follow-up period

	Non-Adjusted HR (95% CI)	Multivariable HR (95% CI)		
1–4 per week	0.936 (0.826– 1.062)	0.933 (0.822– 1.058)	0.928 (0.818– 1.052)	0.927 (0.817– 1.051)
≥ 5 per week	0.964 (0.869– 1.069)	0.956 (0.862– 1.06)	0.954 (0.86– 1.059)	0.985 (0.888– 1.094)
Family history of heart disease				
No		1	1	1
Yes		1.328 (1.108– 1.593)	1.339 (1.117– 1.605)	1.153 (0.964– 1.38)
Family history of hypertension				
No		1	1	1
Yes		1.033 (0.904– 1.18)	1.042 (0.912– 1.189)	0.991 (0.869– 1.13)
Family history of diabetes mellitus				
No		1	1	1
Yes		1.11 (0.972– 1.267)	1.116 (0.978– 1.274)	1.055 (0.926– 1.203)
Family history of stroke				
No		1	1	1
Yes		0.985 (0.845– 1.148)	0.997 (0.855– 1.162)	0.982 (0.844– 1.143)
Body mass index				
< 18.5			1.629 (1.154– 2.298)	1.786 (1.266– 2.52)
18.5–22.9			1	1
Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome, HR, hazard ratio				
*Occurrence of Acute myocardial infarction during follow-up period				

	Non-Adjusted HR (95% CI)	Multivariable HR (95% CI)	
23-24.9		0.926 (0.813– 1.053)	0.883 (0.776– 1.005)
25-29.9		1.008 (0.89– 1.142)	0.929 (0.82– 1.052)
≥ 30		1.34 (1.066– 1.686)	1.223 (0.972– 1.54)
Hemoglobin (g/dL)			
< 13.5(Male), < 12(Female)		1.498 (1.273– 1.763)	1.553 (1.319– 1.829)
13.5–17.5(Male), 12-15.5 (Female)		1	1
> 17.5(Male), > 15.5(Female)		1.446 (1.047– 1.999)	1.081 (0.782– 1.494)
Creatinine (mg/dL)			
≤ 1.5		1	1
> 1.5		1.735 (1.455– 2.068)	1.624 (1.362– 1.937)
Total cholesterol (mg/dL)			
< 200		1	1
200–239		1.066 (0.96– 1.184)	0.888 (0.799– 0.986)
> 239		1.606 (1.417– 1.821)	0.974 (0.857– 1.107)
ALT (IU/L)			
< 40		1	1

Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome, HR, hazard ratio

*Occurrence of Acute myocardial infarction during follow-up period

	Non-Adjusted HR (95% CI)	Multivariable HR (95% CI)
40–99		1.092 (0.973– 1.226)
> 100		1.436 (1.067– 1.933)
Acute myocardial infarction*		
No		1
Yes		130.854 (118.389– 144.631)
Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome, HR, hazard ratio		
*Occurrence of Acute myocardial infarction during follow-up period		

Table 4
Risk of heart failure in female: Cox proportional hazard model.

	Non-Adjusted HR (95% CI)	Multivariable HR (95% CI)			
Metabolic status	Model 1	Model 2	Model 3	Model 4	Model 5
Normal	1	1	1	1	1
Pre-metabolic synd.	1.605 (1.34– 1.923)	1.555 (1.298– 1.864)	1.548 (1.291– 1.856)	1.436 (1.193– 1.73)	1.395 (1.158– 1.681)
Metabolic synd.	3.349 (2.706– 4.145)	3.118 (2.515– 3.866)	3.086 (2.486– 3.83)	2.324 (1.817– 2.973)	2.144 (1.674– 2.747)
Age		1.056 (1.029– 1.084)	1.056 (1.029– 1.085)	1.057 (1.029– 1.085)	1.051 (1.023– 1.079)
Smoking status					
Non-smoker		1	1	1	1
Ex-smoker		0.839 (0.434– 1.624)	0.838 (0.433– 1.622)	0.84 (0.434– 1.626)	0.847 (0.437– 1.639)
Current smoker		1.99 (1.452– 2.726)	1.99 (1.452– 2.727)	1.995 (1.455– 2.735)	1.721 (1.254– 2.362)
Alcohol consumption					
No drink					1
2–3 per month		0.942 (0.787– 1.127)	0.942 (0.787– 1.127)	0.952 (0.795– 1.14)	0.964 (0.805– 1.154)
1–4 per week		0.909 (0.603– 1.37)	0.909 (0.603– 1.37)	0.924 (0.613– 1.392)	0.931 (0.618– 1.403)
≥ per week		1.353 (0.787– 2.324)	1.354 (0.788– 2.326)	1.363 (0.793– 2.341)	1.435 (0.837– 2.461)
Exercise					
No exercise		1	1	1	1

Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome, HR, hazard ratio

*Occurrence of Acute myocardial infarction during follow-up period

	Non-Adjusted HR (95% CI)	Multivariable HR (95% CI)		
1–4 per week	0.941 (0.769– 1.151)	0.938 (0.767– 1.148)	0.939 (0.767– 1.149)	0.943 (0.771– 1.155)
≥ 5 per week	0.898 (0.755– 1.066)	0.894 (0.752– 1.063)	0.901 (0.758– 1.07)	0.915 (0.77– 1.088)
Family history of heart disease				
No		1	1	1
Yes		1.08 (0.792– 1.474)	1.088 (0.797– 1.484)	1.088 (0.798– 1.485)
Family history of hypertension				
No		1	1	1
Yes		1.13 (0.942– 1.356)	1.126 (0.939– 1.351)	1.086 (0.905– 1.303)
Family history of diabetes mellitus				
No		1	1	1
Yes		0.976 (0.795– 1.197)	0.972 (0.792– 1.193)	0.985 (0.802– 1.209)
Family history of stroke				
No		1	1	1
Yes		0.966 (0.753– 1.238)	0.972 (0.758– 1.246)	0.974 (0.76– 1.249)
Body mass index				
< 18.5			1.647 (1.043–2.6)	1.663 (1.053– 2.624)
18.5–22.9			1	1

Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome, HR, hazard ratio

*Occurrence of Acute myocardial infarction during follow-up period

	Non-Adjusted HR (95% CI)	Multivariable HR (95% CI)	
23-24.9		1.233 (1.014-1.5)	1.226 (1.008– 1.492)
25-29.9		1.305 (1.07– 1.593)	1.273 (1.042– 1.554)
>=30		2.152 (1.571– 2.946)	2.085 (1.523– 2.853)
Hemoglobin (g/dL)			
< 13.5(Male), < 12(Female)		1.207 (1.009– 1.444)	1.203 (1.006– 1.439)
13.5–17.5(Male), 12-15.5 (Female)		1	1
> 17.5(Male), > 15.5(Female)		1.562 (0.775– 3.148)	1.496 (0.742– 3.015)
Creatinine (mg/dL)			
≤ 1.5		1	1
> 1.5		2.3 (1.603– 3.298)	2.167 (1.51– 3.109)
Total cholesterol (mg/dL)			
< 200		1	1
200–239		0.966 (0.818– 1.14)	0.977 (0.827– 1.153)
> 239		1.038 (0.818– 1.318)	1.011 (0.797– 1.283)
ALT (IU/L)			
< 40		1	1
40–99		1.643 (1.265– 2.132)	1.551 (1.193– 2.016)
Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome, HR, hazard ratio			
*Occurrence of Acute myocardial infarction during follow-up period			

	Non-Adjusted HR (95% CI)	Multivariable HR (95% CI)
> 100		1.942 (0.963– 3.914)
1.753 (0.869– 3.537)		
Acute myocardial infarction*		
No		1
Yes		82.637 (61.643– 110.781)
Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome, HR, hazard ratio		
*Occurrence of Acute myocardial infarction during follow-up period		

In addition, the occurrence of AMI during follow-up period was associated with a 131-fold and 83-fold higher risk for HF in men and women, respectively. Although the study participants were all in their fifties, the risk of HF increased with increasing age. Current smoking increased the risk of HF by 1.2-fold (HR (95% CI): 1.19 (1.051–1.348)) in men and 1.7-fold in women (HR (95% CI): 1.721 (1.254–2.362)). Low hemoglobin levels and elevated creatinine levels were also risk factors for HF. The HR (95% CI) of low hemoglobin was 1.553 (1.319–1.829) in men and 1.203 (1.006–1.439) in women; the HR (95% CI) of elevated creatinine level was 1.624 (1.362–1.937) in men and 2.167 (1.51–3.109) in women.

BMI as a risk factor for HF showed different results by sex. Overweight was a significant risk factor for HF in women with obesity (BMI ≥ 30 kg/m²), increasing the risk by 2-fold (HR (95% CI): 2.085 (1.523–2.853)), whereas overweight was not a risk factor for HF in men. Underweight (BMI < 18.5 kg/m²) increased the risk of HF in both men and women by 1.8-fold (HR (95% CI): 1.786 (1.266–2.52)) and 1.7-fold (HR (95% CI): 1.663 (1.053–2.624)), respectively.

Alcohol consumption, total cholesterol and ALT level exhibited inconsistent relationships with the occurrence of HF by sex. Only in men, the consumption of 2–3 servings of alcohol per month and slight elevation of total cholesterol (200–239 (mg/dL)) decreased the risk of HF by 19% (HR (95% CI): 0.814 (0.729–0.909)) and 11% (HR (95% CI): 0.888 (0.799–0.986)), respectively). Slight elevation of the ALT level (40–99 (IU/L)) increased the risk of HF (HR (95% CI): 1.551 (1.193–2.016)) only in women, and an elevation of the ALT level over 100 (IU/L) increased the risk of HF (HR (95% CI): 1.591 (1.183–2.139)) only in men.

Discussion

The associations between the prevalence or prognosis of HF and MetS have been shown in many studies.^{8–11} However, most of these studies were cross-sectional in design, which prevents drawing

causal inferences, and only a few longitudinal studies have been reported. A longitudinal study with 2314 middle-aged men reported that MetS was a significant risk factor for HF, with an HR (95% CI) of 1.80 (1.11 to 2.91).¹⁶ A study of elderly individuals in their seventies reported that MetS increased the occurrence of HF, with an HR (95% CI) of 1.49 (1.10-2.00),¹⁷ and another study of elderly individuals with a mean age of 69 years also reported that MetS was a predictor of HF with an HR (95% CI) of 1.58 (1.16–2.15).¹⁸ In contrast, in a study of participants with a mean age of 62 years old, MetS was not a significant risk factor for HF.¹³ The present study was a large population-based study that included over 2 million individuals in their fifties. MetS was a significant risk factor for HF, and the HR in men was similar to that reported in a study of middle-aged men.¹⁶ Although the results of studies in elderly populations were inconsistent, the HR in the present study was higher than that in a study conducted with elderly participants in which MetS was reported to be a significant risk factor for HF.^{17, 18}

The present study revealed that the effect of MetS on HF differs by sex. The HR (95% CI) in men was 1.711 (1.433–2.044) and that in women was 2.144 (1.674–2.747), showing a higher risk of MetS associated with HF in women than in men. To the best of our knowledge, this is the first study to demonstrate the sex difference of MetS as a risk factor for HF.

In this study, we considered the known risk factors for HF as covariates for adjustment in the Cox regression analysis. It is well known that AMI is a major risk factor for HF. In the study with a median follow-up time of 3.2 years, 31% of men and 46% of women developed HF among those hospitalized due to AMI.¹⁹ Another study reported that approximately 84% of patients with coronary heart disease developed HF during the 19-year follow-up.²⁰ In the present study, AMI increased the risk of HF by 131-fold in men and 83-fold in women, which are considerably higher risks than those previously reported. In the National Health and Nutrition Examination Survey (NHANES) study,²⁰ the relative risk of AMI was 8, and in the Framingham study,²¹ the HR was 6. The reason that the HR of AMI was extremely high in our study was thought to be that as the study population was composed of relatively healthy individuals and patients with a history of cardiocerebral vascular diseases were excluded; additionally, the follow-up period was relatively short compared to that of the NHANES study or Framingham study. Namely, in subjects who do not have underlying disease that can lead to HF, the effect of AMI on the occurrence of HF within a short period is suspected to be critical. The HR of AMI for HF was higher in men than in women, which coincided with the findings of a previous report.²⁰

The association between BMI and HF exhibited obvious sex differences. In women, BMI of 23.0-29.9 kg/m² increased the risk of HF by 1.2- to 1.3-fold, and obesity (BMI $\geq$ 30 kg/m²) increased it by 2.1-fold, whereas in men, overweight was not a significant risk factor for HF. This result is consistent with many studies that reported that overweight increased the HF risk in women more significantly than in men.^{20, 22–24} In the present study, underweight (BMI < 18.5 kg/m²) increased the risk of HF in both men and women. Although various studies reported the association between BMI and HF, underweight has rarely been separately evaluated.^{25–27} The increased risk of HF by underweight is supported by a recent study that reported associations among obesity degree, glycemic status, and risk of HF.²⁸

In this study, low hemoglobin was a risk factor for HF; however, high hemoglobin levels were not a risk factor despite the significantly high prevalence of HF in the high hemoglobin level population. Low hemoglobin levels and lower blood viscosity, hypoxia and enhanced nitric oxide (NO) activity induce reduced vascular resistance, followed by increased cardiac output. Increased cardiac output leads to left ventricular hypertrophy and cardiac enlargement, which can eventually lead to HF.²⁹ Different results have been reported regarding the association between HF and hemoglobin level; while Klip et al.³⁰ reported that both low levels and high levels of hemoglobin increased the risk of HF compared to the risk associated with normal hemoglobin levels, Coglianese et al.³¹ reported that high and normal hematocrit levels were associated with a higher risk of HF than low hematocrit levels. These reports explained that a high level of hemoglobin increases vascular resistance by scavenging nitric oxide, a vasodilator, which induces hypertension, left ventricular hypertrophy and finally HF. These different associations between hemoglobin level and HF risk are suspected to result from the different follow-up periods and different study populations. While the follow-up period of our study was relatively short, with a maximum of 8 years, the study of hematocrit and HF³¹ was performed over 20 years, and the study of hemoglobin and HF had a follow-up of a median of 6 years.³⁰ Additionally, while our study was performed in a healthy population without underlying cardiovascular disease, which is closely related to HF, the study of hemoglobin and HF³⁰ did not exclude the population with those underlying diseases.

Despite the positive aspects of the present study, there were some limitations that should be addressed. First, this study evaluated the subjects' metabolic status based on data from 2009. Even if a subject who had been classified into the normal group on the basis of the data from 2009 developed MetS during the follow-up period, the subject was analyzed in the normal group. Although the number of subjects whose metabolic status was changed may not be substantial considering the total study population, there can be an effect on the accuracy of the results. Second, our study excluded subjects with a history of malignancy or cardiocerebral vascular disease; thus, the association between MetS status and HF risk was analyzed in a relatively healthy population, which means that this result may not be generalizable to high-risk populations.

Conclusion

In summary, this study evaluated the association between MetS and the risk of HF in middle-aged men and women using nationwide real-world data. MetS was a risk factor for HF, and its effect on HF was stronger in women than in men. Not only MetS but also pre-MetS was a predictor of HF, but pre-MetS was associated with a lower risk than MetS.

Declarations

- Ethics approval and consent to participate

Institutional Review Board of Konkuk University Medical Center (No. KUH 2020-07-096)

- Consent for publication

Not applicable

- Availability of data and materials

The data that support the findings of this study are available from National Health Insurance Service (NHIS) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of NHIS.

- Competing interests

The authors declare that they have no competing interests

- Funding

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- Authors' contributions

Tae-Eun Kim: analysis and interpretation of data; drafting and revision of manuscript

Hyeongsu Kim: design of the work; analysis and interpretation of data; revision of manuscript

JiDong Sung: interpretation of data; revision of manuscript

Duk-Kyung Kim: interpretation of data; revision of manuscript

[Myoung-Soon](#) Lee: interpretation of data; revision of manuscript

Seong Woo Han: interpretation of data; revision of manuscript

Hyun-Joong Kim: interpretation of data; revision of manuscript

Sung Hea Kim: conception and design of the study; interpretation of data; revision of the manuscript

Kyu-Hyung Ryu: conception and design of the study; interpretation of data; revision of the manuscript

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Figures

Figure 1

Flow diagram of study population. Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome; AF, atrial fibrillation; HF, heart failure; CAD, coronary artery disease; MI, myocardial infarction; CVA, cerebrovascular accident; PAD, peripheral arterial disease

Figure 2

Incidence rate of heart failure (Abbreviation: Pre-MetS, pre-metabolic syndrome; MetS, metabolic syndrome)