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# Association of metabolic syndrome and chronic kidney disease with atrial fibrillation: A nationwide population-based study in Korea <sup>☆</sup>

Won-Seok Choe <sup>a</sup>, Eue-Keun Choi <sup>a,\*</sup>, Kyung-Do Han <sup>b</sup>, Eui-Jae Lee <sup>a</sup>, So-Ryoung Lee <sup>c</sup>, Myung-Jin Cha <sup>a</sup>, Seil Oh <sup>a</sup>

<sup>a</sup> Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

<sup>b</sup> Department of Biostatistics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

<sup>c</sup> Department of Internal Medicine, Soon Chun Hyang University Hospital Seoul, Seoul, Republic of Korea

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## ABSTRACT

**Aims:** Metabolic syndrome (MetS) and chronic kidney disease (CKD) are significant risk factors for incident atrial fibrillation (AF). Few studies have reported the synergistic effect of MetS and CKD on development of AF. We investigated the individual and synergistic effects of MetS and CKD on the risk of incident AF.

**Methods:** We studied a retrospective cohort comprising 22,886,663 Koreans whose data was obtained from the national health claims database established by the Korean National Health Insurance Service between 2008 and 2013. Patients were classified into a MetS and a CKD group and followed-up until 2016 for new-onset AF. A Cox proportional hazards model assessed the independent and synergistic effect of MetS and CKD on the risk of incident AF.

**Results:** The prevalence of MetS and CKD in these patients was 27.4% and 5.4%, respectively. During a mean follow-up of 5.4 years, AF developed in 225,529 patients (1% of the total cohort). The adjusted hazard ratio (HR) for incident AF was 1.38 (95% confidence interval [CI] 1.36–1.39) for MetS, and 1.35 (95% CI 1.34–1.37) for CKD. Patients with MetS and CKD showed a higher risk of AF (HR 1.75, 95% CI 1.73–1.78) than that observed in those without MetS and CKD.

**Conclusions:** The combination of MetS and CKD showed a high risk of development of AF in a large-scale nationwide cohort. Further studies are warranted to determine whether pharmacological and/or lifestyle interventions can control/manage these modifiable risk factors to reduce the risk of development of AF.

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<sup>☆</sup> All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and its interpretation.

\* Corresponding author at: Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.

E-mail address: [choiek17@snu.ac.kr](mailto:choiek17@snu.ac.kr) (E.-K. Choi).

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## 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia observed in clinical practice, and its incidence and prevalence have been progressively increasing with a rise in the aging population and lifestyle changes [1,2]. AF not only affects a patient's quality of life due to distressing symptoms but also leads to serious long-term consequences such as stroke and heart failure [3]. The pathophysiology underlying the onset and progression of AF is a complex process that remains unclear despite thorough investigation over the past 3 decades. Well-established predisposing factors associated with the occurrence of incident AF include conventional cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemia [4,5]. Additionally, metabolically healthy patients with obesity have shown an increased risk of development of AF, which indicates that obesity itself acts as an independent risk factor for development of AF [6].

Metabolic syndrome (MetS) comprises a constellation of interrelated metabolic risk factors associated with development of AF, and several population-based observational studies have reported an association between these 2 common disorders [7,8]. Chronic kidney disease (CKD) is also an important consequence of these cardiovascular risk factors. The relationship is cyclic in nature, and CKD confers a substantial risk for the development of cardiovascular morbidities including AF. Several studies have consistently demonstrated the association between CKD and AF, and that the risk of development of AF increases with worsening renal function [9,10].

Both MetS and CKD are perceived as significant public health problems because they affect a considerable percentage of the adult population. [11,12]. Additionally, Koreans show a high prevalence of cardiovascular risk factors, which predispose the population to an increased risk of AF [13]. However, limited information is available regarding the additive effects of MetS and CKD on the risk of development of AF, particularly in large-scale population analyses. Understanding the epidemiological attributes of AF will help to identify individuals most likely to benefit from primary prevention and early diagnosis of this common arrhythmia with substantial clinical effect/consequences. We aimed to evaluate the synergistic effects of MetS and CKD on the occurrence of incident AF.

## 2. Materials and methods

### 2.1. Data source and study population

This community-based observational cohort study obtained data from the national health claims database established by the Korean National Health Insurance Service (NHIS). The NHIS is a single mandatory health insurance program operated by the NHI Corporation of Korea and provides universal health insurance to nearly the entire Korean population. The NHI Corporation also provides biennial general health screening to all NHI members aged >40 years and also all employed members regardless of age. This screening panel

comprises a physical examination, assessment of biochemical markers in blood and urine, and chest radiography. Thus, the NHIS database comprises information on participants' demographic variables, medical diagnoses, and prescription records registered by medical service providers, and laboratory data from the health screening program [14].

Based on the information obtained from this NHIS cohort database, we enrolled patients who had undergone at least 1 general health screening between January 2009 and December 2012. Using the screening data obtained, we classified baseline comorbidities including the individual components of MetS and CKD. In those who had undergone multiple screening examinations during this period, data from the first examination were used for classification. Patients diagnosed with AF prior to the baseline health screening were excluded from the analysis. The study adhered to the tenets of the Declaration of Helsinki and was exempt from review by the Seoul National University Hospital institutional review board (E-1609-035-789).

### 2.2. Definition of comorbidities

We adopted the modified National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATP III) definition of MetS [15]. MetS was defined as the presence of any 3 of the following 5 attributes: (1) waist circumference  $\geq 80$  cm in women or  $\geq 90$  cm in men (according to the ethnic criteria for Asians), (2) serum triglyceride  $\geq 150$  mg/dL, (3) serum high-density lipoprotein cholesterol  $< 50$  mg/dL in women or  $< 40$  mg/dL in men, (4) blood pressure  $\geq 130/85$  mmHg or drug treatment for elevated blood pressure, and (5) fasting plasma glucose  $\geq 100$  mg/dL or drug treatment for elevated blood glucose.

Patients with a glomerular filtration rate (GFR)  $< 60$  mL/min/1.73 m<sup>2</sup> at the time of baseline evaluation were classified as the CKD group. GFR was estimated using the Modification of Diet in Renal Disease Study equation (GFR =  $175 \times [\text{serum creatinine in mg/dL}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ in women}]$ ) [16]—corresponding to CKD  $\geq$  stage 3 based on the National Kidney Foundation classification, which helps to identify patients with clinically significant CKD [17].

The NHIS cohort database contains diagnoses codified by the Korean Classification of Disease (KCD-5 between 2008 and 2010, KCD-6 between 2011 and 2015), which correspond to the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM). Baseline comorbidities of patients including hypertension, diabetes mellitus, dyslipidemia, heart failure, and history of myocardial infarction or stroke were analyzed based on existing corresponding ICD codes in the claims data, and were validated by previous reports [1,18,19].

### 2.3. Study endpoints

The primary endpoint was the occurrence of incident AF. Patients were followed through December 2015, and those with diagnostic codes indicating paroxysmal, persistent,

and/or permanent AF, as well as atrial flutter (I480-I484 and I489) were considered to meet the criteria. To ensure diagnostic accuracy and to exclude those with transient AF, we defined patients with AF only when the diagnosis had been confirmed at the time of hospital discharge or confirmed more than twice at an outpatient clinic. Patients diagnosed with mitral stenosis (I050, I0520, and I059) or reporting pre-existing mechanical heart valve disorders (Z952–Z945) were excluded from the study to limit our sample to patients with non-valvular AF.

#### 2.4. Statistical analysis

Baseline patient characteristics are presented as mean values and standard deviations (SD) for continuous variables and as numbers and percentages for categorical variables. Differences in baseline characteristics between groups were determined using the Student t-test for continuous and the  $\chi^2$  test for categorical variables. The incidence rate of AF in each group was estimated by dividing the number of incident cases by the person-years of the total observation. The Cox multivariate proportional hazards model was used to identify the comorbidities associated with development of AF. All statistical analyses were performed using the SAS version 9.2 software (SAS Institute, Cary, NC, USA). Two-sided P values <0.05 were considered statistically significant.

### 3. Results

#### 3.1. Baseline patient characteristics

The baseline characteristics of the 22,886,661 patients analyzed have been presented in [Table 1](#). The mean age of the entire cohort was 47.5 years, and men comprised 50.7% of the cohort. During the mean follow-up of 5.4 years (total follow-up duration of 122,564,905 person-years), incident AF was diagnosed in 225,529 (0.98%) patients showing an incidence rate of 1.84 per 1000 person-years. The differential characteristics of patients based on development of AF have been summarized in [Supplementary Table 1](#). Patients who developed AF were more likely to be older, men, and showed a higher prevalence of cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidemia, heart failure, and a history of myocardial infarction, and stroke.

#### 3.2. Risk of incident atrial fibrillation based on the prevalence of components of metabolic syndrome

MetS was diagnosed in 6,270,270 patients (27.4%) at the time of the baseline evaluation based on the NCEP-ATP III definition. A total of 6,052,810 patients (26.4%) presented without any of the 5 MetS components, and 1, 2, 3, 4, and 5 of the MetS components were noted in 5,879,398 (25.7%), 4,684,183 (20.5%), 3,325,698 (14.5%), 2,073,390 (9.1%) and 871,182 (3.8%) patients, respectively. Among the 5 metabolic risk factors, elevated blood pressure was the most prevalent component (43.1% of all patients) in our study population. Those with MetS were significantly older, and more likely to show a higher prevalence of hypertension, diabetes mellitus, dyslipi-

demia, heart failure, and history of myocardial infarction and stroke, as well as a larger waist circumference and higher body mass index than those without MetS.

After adjusting for age, sex, physical activity, alcohol consumption, and smoking status, the hazard ratio (HR) for incident AF in patients with MetS was 1.38 (95% confidence interval [CI] 1.36–1.39) compared to those without MetS. Each MetS component showed an individual/independent association with an increased risk of incident AF after multivariate adjustment with the same variables ([Table 2](#)). Among these, elevated blood pressure was the most potent predictor of AF incidence (HR 1.51, 95% CI 1.50–1.52). We observed a graded risk of AF based on the prevalence of metabolic risk factors (the number of MetS components), and those presenting with all 5 components demonstrated a 2.16-fold risk for incident AF compared to those presenting without any MetS components ([Table 3](#)).

#### 3.3. Risk of incident atrial fibrillation in relation to decreased renal function

The mean estimated GFR (eGFR) in the studied patients was 89.6 (SD 39.5) mL/min/1.73 m<sup>2</sup>, and the overall distribution of eGFR has been shown in [Table 1](#). In all, 1,234,169 patients (5.4%) showed an eGFR < 60 mL/min/1.73 m<sup>2</sup> and were diagnosed with CKD. Among those with CKD, the prevalence of CKD stage 3 (eGFR 30–59 mL/min/1.73 m<sup>2</sup>) and stage 4–5 (eGFR < 30 mL/min/1.73 m<sup>2</sup>) was 80.5% and 19.5%, respectively. Overall, the CKD group demonstrated an epidemiological profile similar to the MetS group, except in terms of female predominance ([Table 1](#)).

The adjusted HR for incident AF in patients with CKD was 1.35 (95% CI 1.34–1.37) compared to those without CKD ([Table 2](#)). Additionally, a graded risk for development of AF was noted based on the severity of renal impairment. The incidence rates and HRs of AF among patients stratified by the eGFR values are shown in [Table 3](#), and those with CKD stage 4–5 showed a 1.84-fold risk for incident AF compared to those without CKD.

#### 3.4. Additive effect of metabolic syndrome and chronic kidney disease on the incidence of atrial fibrillation

Patients with MetS and CKD share a common epidemiological risk profile, and a positive relationship between the prevalence of MetS and CKD was observed in our study. Compared to patients without MetS, CKD was significantly more prevalent among those with MetS, and vice versa ([Table 1](#)). To investigate the synergistic effect of MetS and CKD on development of AF, we divided all patients into 4 groups based on the baseline prevalence of MetS and/or CKD. The crude incidence rate of AF in MetS patients without CKD (MetS+/CKD-) was 3.3 per 1000 person-years, and the adjusted HR for incident AF was 1.33 (95% CI 1.30–1.36) compared to subjects without MetS or CKD (MetS-/CKD-). CKD patients without MetS (MetS-/CKD+) showed a comparable risk for development of AF, with a crude incidence rate of 3.0 per 1000 person-years, and an adjusted HR of 1.36 (95% CI 1.35–1.37). Beyond the independent significant effect of MetS and CKD, we found an additive effect of these comorbidities on the incidence of

**Table 1 – Baseline characteristic of the study population.**

	Total population	Metabolic syndrome		P-value	Chronic kidney disease		
	(N = 22,886,661)	No MetS (N = 16,616,391)	MetS (N = 6,270,270)		No CKD (N = 21,652,492)	CKD (N = 1,234,169)	P-value
MetS	6,270,270 (27.4)	–	–		5,663,319 (26.2)	606,951 (49.2)	<0.0001
CKD	1,234,169 (5.4)	627,218 (3.8)	606,951 (9.7)	<0.0001	–	–	
Age, yrs	47.5 ± 14.3	44.5 ± 13.6	55.5 ± 13	<0.0001	46.8 ± 14	59.4 ± 15	<0.0001
Male	11,602,190 (50.7)	8,389,654 (50.5)	3,212,536 (51.2)	<0.0001	11,122,885 (51.4)	478,634 (38.8)	<0.0001
BMI, kg/m <sup>2</sup>	23.7 ± 3.3	22.9 ± 2.9	25.8 ± 3.2	<0.0001	23.7 ± 3.3	24.2 ± 3.3	<0.0001
Waist circumference, cm	80 ± 9.3	77.5 ± 8.3	86.7 ± 8.1	<0.0001	79.9 ± 9.3	82 ± 9.2	<0.0001
Smoking				<0.0001			<0.0001
None	14,154,666 (61.8)	10,339,599 (62.2)	3,815,067 (60.8)		13,263,033 (61.3)	891,633 (72.3)	
Ex-smoker	3,079,488 (13.5)	2,098,692 (12.6)	980,796 (15.6)		2,912,366 (13.5)	167,122 (13.5)	
Current smoker	5,652,507 (24.7)	4,178,100 (25.1)	1,474,407 (23.5)		5,477,093 (25.3)	175,414 (14.2)	
Alcohol				<0.0001			<0.0001
None	12,219,729 (53.4)	8,540,489 (51.4)	3,679,240 (58.7)		11,356,494 (52.5)	863,235 (69.9)	
Mild	9,148,549 (40.0)	7,059,178 (42.5)	2,089,371 (33.3)		8,821,567 (40.7)	326,982 (26.5)	
Heavy	1,518,383 (6.6)	1,016,724 (6.1)	501,659 (8.0)		1,474,431 (6.8)	43,952 (3.6)	
Regular physical activity	11,368,239 (49.7)	8,438,357 (50.8)	2,929,882 (46.7)	<0.0001	10,815,420 (50.0)	553,496 (44.9)	<0.0001
Hypertension	5,925,310 (25.9)	2,269,848 (13.7)	3,655,462 (58.3)	<0.0001	5,304,774 (24.5)	620,536 (50.3)	<0.0001
Diabetes	2,089,679 (9.1)	519,287 (3.1)	1,570,392 (25.1)	<0.0001	1,843,535 (8.5)	246,144 (19.9)	<0.0001
Dyslipidemia	4,356,614 (19.0)	1,522,319 (9.2)	2,834,295 (45.2)	<0.0001	3,945,903 (18.2)	410,711 (33.3)	<0.0001
Heart failure	135,343 (0.6)	47,123 (0.3)	88,220 (1.4)	<0.0001	106,139 (0.5)	29,204 (2.4)	<0.0001
Previous MI	92,237 (0.4)	29,249 (0.2)	62,988 (1.0)	<0.0001	78,344 (0.4)	13,893 (1.1)	<0.0001
Previous stroke	388,303 (1.7)	131,822 (0.8)	256,481 (4.1)	<0.0001	319,159 (1.5)	69,144 (5.6)	<0.0001
GFR (mL/min/1.73 m)				<0.0001			
≥90	9,765,785 (42.7)	7,589,445 (45.7)	2,176,340 (34.7)		9,765,785 (45.1)	–	
60–89	11,886,707 (51.9)	8,399,728 (50.6)	3,486,979 (55.6)		11,890,000 (54.9)	–	
30–59	993,062 (4.3)	453,556 (2.7)	539,506 (8.6)		–	993,062 (80.5)	
<30	241,107 (1.1)	173,662 (1.1)	67,445 (1.1)		–	241,107 (19.5)	
Blood pressure							
Systole, mmHg	122.2 ± 15.2	118.8 ± 13.8	131.3 ± 14.8	<0.0001	121.9 ± 15.1	126.5 ± 16.5	<0.0001
Diastole, mmHg	76.1 ± 10.1	74.2 ± 9.5	80.9 ± 10.1	<0.0001	76 ± 10.1	77.3 ± 10.3	<0.0001
Cholesterol							
Total, mg/dL	194.8 ± 36.8	191.3 ± 34.2	203.9 ± 41.6	<0.0001	194.5 ± 36.6	199.2 ± 40.3	<0.0001
LDL-C, mg/dL	113.5 ± 33.6	112.1 ± 31.4	117.2 ± 38.8	<0.0001	113.3 ± 33.4	116.9 ± 36.5	<0.0001
HDL-C, mg/dL	55.5 ± 16.7	57.8 ± 16.2	49.3 ± 16.5	<0.0001	55.5 ± 16.1	54.6 ± 24.8	<0.0001

Data have been presented as means ± SDs or n (%). Abbreviations: BMI: body mass index, CKD: chronic kidney disease, GFR: glomerular filtration rate, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, MetS: metabolic syndrome, MI: myocardial infarction, SD: standard deviation.

**Table 2 – Risk associated with the incidence of atrial fibrillation in patients presenting with individual metabolic syndrome components or chronic kidney disease.**

Comorbidities	Prevalence, N (%)	Atrial fibrillation risk				
		Incidence rate (/1000 person-years)	Unadjusted <sup>*</sup> HR	P-value	Adjusted <sup>*</sup> HR	P-value
Metabolic syndrome						
Yes	6,270,270 (27.4)	3.340	2.612 (2.591–2.634)	<0.0001	1.376 (1.364–1.388)	<0.0001
No	16,616,391 (72.6)	1.277				
Elevated waist circumference <sup>†</sup>						
Yes	6,432,097 (28.1)	2.874	1.999 (1.982–2.016)	<0.0001	1.372 (1.360–1.384)	<0.0001
No	16,454,564 (71.9)	1.437				
Elevated triglycerides <sup>†</sup>						
Yes	7,897,866 (34.5)	2.466	1.632 (1.619–1.646)	<0.0001	1.124 (1.115–1.134)	<0.0001
No	14,988,795 (65.5)	1.508				
Reduced HDL-C <sup>†</sup>						
Yes	6,486,065 (28.3)	2.752	1.859 (1.843–1.874)	<0.0001	1.241 (1.230–1.252)	<0.0001
No	16,400,596 (71.7)	1.480				
Elevated blood pressure <sup>†</sup>						
Yes	9,858,545 (43.1)	3.043	3.262 (3.232–3.292)	<0.0001	1.510 (1.495–1.524)	<0.0001
No	13,028,116 (56.9)	0.931				
Elevated fasting glucose <sup>†</sup>						
Yes	7,199,755 (31.5)	2.775	1.963 (1.947–1.979)	<0.0001	1.194 (1.184–1.204)	<0.0001
No	15,686,906 (68.5)	1.414				
Chronic kidney disease <sup>‡</sup>						
Yes	1,234,169 (5.4)	4.995	2.997 (2.962–3.032)	<0.0001	1.353 (1.337–1.369)	<0.0001
No	21,652,492 (94.6)	1.659				

Abbreviations: HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, NCEP-ATP III: National Cholesterol Education Program-Third Adult Treatment Panel.

<sup>\*</sup> The associations were tested using a Cox proportional hazards model adjusted for age, sex, alcohol consumption, smoking status, and physical activity.

<sup>†</sup> The components of metabolic syndrome were defined based on the NCEP-ATP III definition as: (1) waist circumference  $\geq 80$  cm in women or  $\geq 90$  cm in men, (2) serum triglycerides  $\geq 150$  mg/dL, (3) serum high-density lipoprotein (HDL) cholesterol  $< 50$  mg/dL in women or  $< 40$  mg/dL in men, (4) blood pressure  $\geq 130/85$  mmHg or drug treatment for elevated blood pressure, and (5) fasting serum glucose  $\geq 100$  mg/dL or drug treatment for elevated blood glucose.

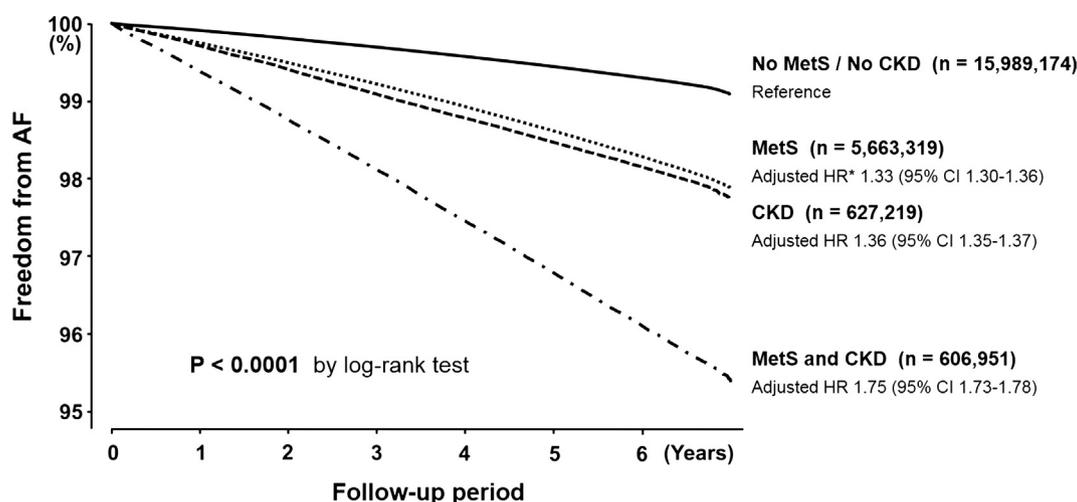
<sup>‡</sup> Chronic kidney disease was defined as a glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup>.

**Table 3 – Risk of incident atrial fibrillation based on the prevalence of metabolic syndrome components (number of components identified in each patient) and the estimated glomerular filtration rate.**

N of subjects (%)	Atrial fibrillation risk				
	Incidence rate (/1000 person-years)	Unadjusted <sup>*</sup> HR	P-value	Adjusted <sup>*</sup> HR	P-value
Metabolic syndrome components, n			<0.0001		<0.0001
0	6,052,810 (26.4)	0.610	1 (Reference)	1 (Reference)	
1	5,879,398 (25.7)	1.322	2.161 (2.125–2.198)	1.283 (1.261–1.305)	
2	4,684,183 (20.5)	2.075	3.392 (3.337–3.448)	1.496 (1.471–1.521)	
3	3,325,698 (14.5)	2.770	4.528 (4.454–4.604)	1.663 (1.635–1.691)	
4	2,073,390 (9.1)	3.664	5.994 (5.892–6.097)	1.866 (1.833–1.899)	
5	871,182 (3.8)	4.771	7.813 (7.664–7.965)	2.155 (2.112–2.198)	
Estimated GFR, ml/min/1.73 m <sup>2</sup>			<0.0001		<0.0001
$\geq 90$	9,765,785 (42.7)	1.233	1 (Reference)	1 (Reference)	
60–89	11,886,707 (51.9)	1.999	1.614 (1.599–1.629)	1.039 (1.029–1.049)	
30–59	993,062 (4.3)	5.596	4.515 (4.454–4.578)	1.346 (1.327–1.366)	
$< 30$	241,107 (1.1)	2.687	2.147 (2.077–2.219)	1.841 (1.781–1.904)	

Abbreviations: GFR: glomerular filtration rate, HR: hazard ratio.

<sup>\*</sup> The associations were tested using a Cox proportional hazards model adjusted for age, sex, alcohol consumption, smoking status, and physical activity.



**Fig. 1** – Kaplan–Meier curves showing the cumulative event-free survival for atrial fibrillation in patients classified into 4 groups based on the presence/absence of metabolic syndrome and chronic kidney disease. \*The associations were tested using a Cox proportional hazards model adjusted for age, sex, alcohol consumption, smoking status, and physical activity. Abbreviations: CI, confidence interval, CKD chronic kidney disease; HR, hazard ratio; MetS, metabolic syndrome.

AF. Kaplan–Meier survival curves demonstrated that patients with both MetS and CKD were at a significantly higher risk for development of AF (Fig. 1). Those with both MetS and CKD (MetS+/CKD+) showed the highest risk for the occurrence of incident AF, with an incidence rate of 6.9 per 1000 person-years and an adjusted HR of 1.75 (95% CI 1.73–1.78). However, our study did not show a multiplicative interaction between MetS and CKD in our patients in terms of the risk for development of AF.

### 3.5. Subgroup analysis

Results of the Cox regression analysis to determine the incidence of AF for different subgroups are shown in [Supplementary Fig. 1](#). The point estimates of HRs of the MetS-/CKD+, MetS+/CKD-, and MetS+/CKD+ groups compared to the MetS-/CKD- group were observed to be consistently >1.0 in all subgroups, and we observed a graded additive risk for the occurrence of incident AF regardless of age, sex, obesity, and history of myocardial infarction, or stroke. The synergistic effect of MetS and CKD on the incidence of AF was most prominently noted in patients aged <60 years. However, we observed a trend showing a reduced risk of AF incidence in patients belonging to the MetS+/CKD- group with concomitant heart failure.

## 4. Discussion

### 4.1. Primary findings

The primary findings of this nationwide population-based study are: (1) Patients with MetS and CKD showed an increased risk for the development of AF, (2) all MetS components showed an individual/independent association with the incidence of AF, and an increase in the prevalence of MetS components (number of MetS components identified in a patient) was associated with a corresponding graded increase

in the risk of development of AF, (3) CKD was also a significant predictor of AF, and those with a lower eGFR were more likely to develop incident AF in a dose-dependent manner, (4) the combined effect of MetS and CKD on the occurrence of incident AF was greater than the individual effect of either disease.

### 4.2. Metabolic syndrome and the risk of atrial fibrillation

MetS represents a cluster of metabolic abnormalities. Despite the use of variable definitions and diagnostic criteria, common key features (which might differ marginally between patients) of MetS include abdominal obesity, elevated blood pressure, glucose intolerance, and dyslipidemia [15,20]. Insulin resistance and visceral obesity underlie these phenotypic clinical components [21] and promote a prothrombotic and proinflammatory environment that enhances the risk of development of multiple cardiovascular diseases including AF [15]. The association between MetS and an increased risk of development of AF has been demonstrated in many community-based epidemiological and observational studies [7,8,22]. The present analysis performed in a large-scale nationwide population-based Korean cohort corroborates the findings of previous reports showing an association between MetS and the incidence of AF. Greater the number of MetS components identified in a patient, higher the risk of occurrence of incident AF in a progressive and graded manner. Each MetS component was independently associated with an increased risk of incident AF. Elevated blood pressure followed by obesity, showed the highest relative effect on the incidence of AF. Notably, an elevated triglyceride level was observed to be a significant risk factor for AF in the current analysis, although the effect size was relatively small (HR 1.11, 95% CI 1.10–1.12)—a finding in disagreement with the results of previously reported major observational studies, which showed that hypertriglyceridemia was not an independent predictor for development of AF [23]. An explanation for

the inconsistency in the association between hypertriglyceridemia and AF remains unclear. Triglyceride levels are known to decrease with advanced age >70 years, whereas the prevalence of AF continuously increases with aging, and it has been proposed that this epidemiological characteristic may offset the effect of hypertriglyceridemia on the incidence of AF in observational studies [24]. Our patients were relatively younger than those enrolled in previous studies—a factor that could have determined the role of hypertriglyceridemia on the risk of development of AF.

#### 4.3. Chronic kidney disease and the risk of atrial fibrillation development

The kidney represents a target organ that is commonly affected by the cardiovascular risk factors associated with MetS. Moreover, CKD is an independent factor for the development of cardiovascular disorders. The association between CKD and AF has been well-established in several population-based observational studies [9,10,25,26]. Although the exact causal mechanism has not been completely understood, pathophysiological conditions observed in CKD including inflammation, activation of the renin-angiotensin-aldosterone system, and hemodynamic overload-induced mechanical atrial stretch have been proposed as possible factors associated with the risk of development of AF [27–29]. Our current study confirmed the significant relationship between CKD and the occurrence of incident AF. The association between CKD and the risk of development of AF was consistently observed in all patients with and without MetS, and Cox regression analysis showed a dose-dependent association between decreased eGFR and an increased risk of incident AF. The overall effect size of CKD (adjusted HR 1.35, 95% CI 1.34–1.37) on the occurrence of incident AF was comparable to that of MetS (adjusted HR 1.38, 95% CI 1.36–1.39), which is a constellation of metabolic disorders that may multiply a patient's risk for development of AF.

#### 4.4. Synergistic effect of metabolic syndrome and chronic kidney disease on atrial fibrillation development

MetS and CKD share common risk factors, and patients diagnosed with MetS are more likely to develop CKD and vice versa. Thus, these multiple risk factors including insulin resistance, abnormal lipid metabolism, hypertension, and systemic inflammation might act synergistically to precipitate AF in patients with MetS and CKD. Our current analysis indicated that the risk of occurrence of incident AF is significantly increased in patients with both MetS and CKD. After adjusting for confounding epidemiological factors, the MetS+/CKD+ showed a 75% increased risk of occurrence of incident AF than the MetS-/CKD- group. Subgroup analysis corroborated the robustness of this relationship. However, the effect of MetS and CKD on the occurrence of incident AF was observed to be additive, and not greater than the sum of the individual components. This finding emphasizes that identification of individual risk factors is important for AF risk stratification, considering the high prevalence of comorbidities.

#### 4.5. Results with different thresholds of abdominal obesity

There is an important issue concerning the multiplicity of diagnostic criteria of the MetS [30]. Specifically, the definition of abdominal obesity using original NCEP-ATP III cut points may underestimate the prevalence of abdominal obesity and MetS in Asians, and different criteria are required in this population. Usually, waist circumferences of  $\geq 80$  cm in women and  $\geq 90$  cm in men are recommended cut points for the diagnosis of abdominal obesity in Asians, but there is no universal agreement with these criteria in different populations [30]. Previously, Lee et al. indicated that cut points of abdominal obesity in the Korean population should be  $\geq 85$  cm in women and  $\geq 90$  cm in men, to reflect the metabolic risk most accurately [31]. To confirm whether our results are significantly affected by different diagnostic cut points, we further analyzed the national registry data by applying these criteria of abdominal obesity (waist circumferences of  $\geq 85$  cm in women and  $\geq 90$  cm in men). As expected, the prevalence of MetS decreased from 27.4% to 20.0% with these higher cut points. However, despite this change in the prevalence of major independent variable, our results have remained consistent. MetS was associated with an increased risk of incident AF by HR of 1.38 (95% CI 1.37–1.39), and the additive effect of MetS and CKD on AF incidence was maintained: the adjusted HR for incident AF in patients with MetS+/CKD-, MetS-/CKD+, and MetS+/CKD+ groups compared to those without any of these diseases were 1.33 (95% CI 1.30–1.35), 1.36 (95% CI 1.35–1.38), and 1.75 (95% CI 1.72–1.78), respectively. These values are nearly identical to the previous analysis with only minor changes in the confidence intervals, and based on these, we concluded that our results are robust, even with substantial changes in the diagnostic criteria of the MetS.

#### 4.6. Study limitations and strengths

Limitations of our study: (1) The study population comprised a homogeneous cohort of Korean ancestry; hence, our findings may not be generalizable, and the reproducibility of the current results should be investigated in other populations. (2) The study population was classified based on a single measurement of the MetS components and eGFR obtained from routine screening evaluation. However, a large sample size generalizes the validity of patient categorization. (3) The diagnosis of incident AF was based on the claims database of the NHIS cohort; thus, some missing data and overestimation of outcomes are expected drawbacks. To avoid the overestimation of incident AF, we used the validated definition of AF from a previous study involving the NHIS cohort database [1]. (3) As is noted with observational and retrospective analyses, our results could not identify causality in the association between MetS and CKD with the incidence of AF. Despite these limitations, this study was the largest population-based study evaluating the synergistic effect of MetS and CKD on development of AF.

## 5. Conclusions

We demonstrated in our large-scale nationwide Korean cohort that the synergistic effect of MetS and CKD represents a strong risk factor for incident AF. MetS and CKD are both individually significant predictors of the development of AF, and their combination further increases the risk of incident AF, independent of baseline confounders. The incidence and prevalence of both disease entities are rapidly growing worldwide, which will therefore significantly affect the development and the consequent medical and socioeconomic consequences of incident AF. Further research is warranted to determine whether pharmacological and/or lifestyle interventions can better manage/control these modifiable risk factors to reduce the risk of development of AF.

## 6. Declarations of interest

None

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2018.12.004>.

## REFERENCES

- [1] Lee SR, Choi EK, Han KD, Cha MJ, Oh S. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA2DS2-VASc score in the entire Korean population. *Int J Cardiol* 2017;236:226–31.
- [2] Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics–2010 update: a report from the American Heart Association. *Circulation* 2010;121:e46–e215.
- [3] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–962.
- [4] Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. Framingham Heart Study. *Jama* 1994;271:840–4.
- [5] Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;96:2455–61.
- [6] Lee H, Choi EK, Lee SH, Han KD, Rhee TM, Park CS, et al. Atrial fibrillation risk in metabolically healthy obesity: a nationwide population-based study. *Int J Cardiol* 2017;240:221–7.
- [7] Tanner RM, Baber U, Carson AP, Voeks J, Brown TM, Soliman EZ, et al. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol* 2011;108:227–32.
- [8] Chamberlain AM, Agarwal SK, Ambrose M, Folsom AR, Soliman EZ, Alonso A. Metabolic syndrome and incidence of atrial fibrillation among blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 2010;159:850–6.
- [9] Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circul Arrhythmia Electrophysiol* 2011;4:26–32.
- [10] Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;123:2946–53.
- [11] Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. *PLoS ONE* 2016;11:e0158765.
- [12] Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA* 2015;313:1973–4.
- [13] Lee SW, Kim HC, Lee HS, Suh I. Thirty-year trends in mortality from cerebrovascular diseases in Korea. *Kor Circul J* 2016;46:507–14.
- [14] Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol* 2017;46:e15.
- [15] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–52.
- [16] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. modification of diet in renal disease study group. *Ann Intern Med* 1999;130:461–70.
- [17] K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Diseases: The Off J Natl Kidney Foundation*. 2002;39:S1–266.
- [18] Kang SH, Choi EK, Han KD, Lee SR, Lim WH, Cha MJ, et al. Underweight is a risk factor for atrial fibrillation: a nationwide population-based study. *Int J Cardiol* 2016;215:449–56.
- [19] Cha MJ, Choi EK, Han KD, Lee SR, Lim WH, Oh S, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation. *Stroke* 2017;48:3040–8.
- [20] Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet (London, England)*. 2005;366:1059–62.
- [21] Meigs JB. Invited commentary: insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. *Am J Epidemiol* 2000;152:908–11. discussion 12.
- [22] Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S, et al. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. *Circulation* 2008;117:1255–60.
- [23] Lopez FL, Agarwal SK, Maclellan RF, Soliman EZ, Sharrett AR, Huxley RR, et al. Blood lipid levels, lipid-lowering medications, and the incidence of atrial fibrillation: the atherosclerosis risk in communities study. *Circul Arrhythmia Electrophysiol* 2012;5:155–62.

- [24] Tadic M, Ivanovic B, Cuspidi C. What do we currently know about metabolic syndrome and atrial fibrillation? *Clin Cardiol* 2013;36:654–62.
- [25] Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, Rahman M, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J* 2010;159:1102–7.
- [26] Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. *Am Heart J* 2009;158:629–36.
- [27] Kulkarni N, Gukathasan N, Sartori S, Baber U. Chronic kidney disease and atrial fibrillation: a contemporary overview. *J Atrial Fibrill* 2012;5:448.
- [28] Khouri Y, Stephens T, Ayuba DG, Al-Ameri H, Juratli N, McCullough PA. Understanding and managing atrial fibrillation in patients with kidney disease. *J Atrial Fibrill* 2015;7:1069.
- [29] Zhang X, Lerman LO. The metabolic syndrome and chronic kidney disease. *Trans Res: J Lab Clin Med* 2017;183:14–25.
- [30] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640–5.
- [31] Lee SY, Park HS, Kim DJ, Han JH, Kim SM, Cho GJ, et al. Appropriate waist circumference cutoff points for central obesity in Korean adults. *Diab Res Clin Pract* 2007;75:72–80.