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Association between Obesity and Heart Failure and Related Atrial Fibrillation: Patient-Level Data Comparisons of Two Cohort Studies

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Purpose: Heart failure (HF) and atrial fibrillation (AF) frequently coexist, with over 50% patients with HF having AF, while one-third of those with AF develop HF. Differences in obesity-mediated association between HF and HF-related AF among Asians and Europeans were evaluated.

Materials and Methods: Using the Korean National Health Insurance Service-Health Screening (K-NHIS-HealS) cohort and the UK Biobank, we included 394801 Korean and 476883 UK adults, respectively aged 40–70 years. The incidence and risk of HF were evaluated based on body mass index (BMI).

Results: The proportion of obese individuals was significantly higher in the UK Biobank cohort than in the K-NHIS-HealS cohort (24.2% vs. 2.7%, $p<0.001$). The incidence of HF and HF-related AF was higher among the obese in the UK than in Korea. The risk of HF was higher among the British than in Koreans, with adjusted hazard ratios of 1.82 [95% confidence interval (CI), 1.30–2.55] in K-NHIS-HealS and 2.00 (95% CI, 1.69–2.37) in UK Biobank in obese participants (p for interaction <0.001). A 5-unit increase in BMI was associated with a 44% greater risk of HF-related AF in the UK Biobank cohort ($p<0.001$) but not in the K-NHIS-HealS cohort ($p=0.277$).

Conclusion: Obesity was associated with an increased risk of HF and HF-related AF in both Korean and UK populations. The higher incidence in the UK population was likely due to the higher proportion of obese individuals.

Key Words: Obesity, heart failure, atrial fibrillation, body mass index

INTRODUCTION

Heart failure (HF) and atrial fibrillation (AF) frequently coexist and contribute majorly to morbidity, mortality, and hospital admission. Over 50% of patients with HF have AF, while one-third of those with AF develop HF.[1] This "dual epidemic" affects millions of people worldwide, and both conditions are among the most common cardiovascular diagnoses associated with hospital admissions, morbidity, and mortality. Furthermore, the incidence of HF and AF vary significantly among different ethnic populations, with African-Americans and Hispanics having a higher prevalence of HF than Caucasians.[2] Conversely, AF is more common in Caucasians than in Asians or Afro-Caribbean or other races.[3-6] Obesity, a known risk factor for both of these conditions, may partially explain these ethnic disparities.[7,8]

Obesity has been linked to a range of adverse effects on the heart, particularly the left ventricular systolic and diastolic functions. Multiple studies have established obesity as a significant risk factor for the development of HF, with every 1-unit increase in body mass index (BMI) increasing the incidence

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of HF by 5% and 7% in male and female, respectively, after adjusting for other risk factors.[9] This risk persists across the entire BMI spectrum, with obesity and associated conditions accounting for up to 60% of documented increases in AF cases in the population.[10-12] Weight gain and higher midlife BMI have also been strongly correlated with the incidence of AF later in life, with every 5-unit increase in BMI conferring a 29% greater risk of incident AF.[13] However, in the Asian population, a J-shaped association was found between continuous BMI variables and AF risk.[8]

We hypothesized that the population-based differences in BMI values could contribute to the ethnic disparities in the incidence of HF and HF-related AF. We compared patient-level data from two cohorts, the Korea National Health Insurance Service-Health Screening (K-NHIS-HealS) and the UK Biobank, with the aim to investigate whether obesity mediates association between HF and HF-related AF in European and Asian populations.

MATERIALS AND METHODS

Study design and participants

This study is based on data from the K-NHIS-HealS cohort released in 2015, the profile for which has been described previously.[14] K-NHIS-HealS is derived from national health screening programs in Korea that gather information from insured adults. These individuals are eligible to participate in a general health check-up program conducted every 2 years, starting at the age of 40 years. The K-NHIS-HealS cohort, initiated in 2002, included 457510 Koreans aged 40–79 years, and data related to lifestyle and behavior were collected through 2013 via questionnaires and major health examination results. The cohort consisted of a random sample of 10% of all individuals who underwent health examinations from 2002 to 2003.

The UK Biobank cohort included 502422 male and female aged 40–69 years from 22 assessment centers across England, Scotland, and Wales, and their data were collected between 2006 and 2010. Details of the study design and data collection have been described previously.[15] The UK Biobank is a large prospective cohort study, primarily initiated to examine the factors related to genetic and lifestyle that influence various diseases in the middle and later stages of life. At the time of recruitment, detailed questionnaires, physical assessments, and biochemical assays from collected biological specimens were used to acquire detailed data. Additionally, an ongoing program for enhanced data collection is being conducted within significant subsets of the cohort.

In the present study, the two cohorts were established using similar enrollment methods. However, age restrictions (40–70 years) were applied as the UK Biobank cohort included people ≤70 years of age. Furthermore, owing to the distinct follow-up periods within the two cohorts, we focused our analysis exclusively on participants who were enrolled between March 2006 and December 2010. We examined the incidence of the disease at the 7-year mark in both cohorts. Consequently, the following were excluded from the K-NHIS-HealS cohort: 1) individuals who were enrolled prior to March 2006 or after December 2010 (n=726); 2) individuals aged below 40 years or above 70 years (n=51532); 3) individuals with HF [International Classification of Diseases, 10th revision (ICD-10) codes I11.0, I50, and I97.1] before health check-up (n=10334); and 4) individuals with missing data regarding BMI or other variables (n=117). Finally, a total of 394801 participants from this cohort were included in this study (Fig. 1). The current analysis excluded the following participants from the UK Biobank cohort: 1) individuals who were enrolled prior to March 2006 or after December 2010 (n=113); 2) those aged below 40 years or above 70 years (n=10591); 3) those with HF (ICD-10 codes I11.0, I50, and I97.1) before health check-up (n=11957); and

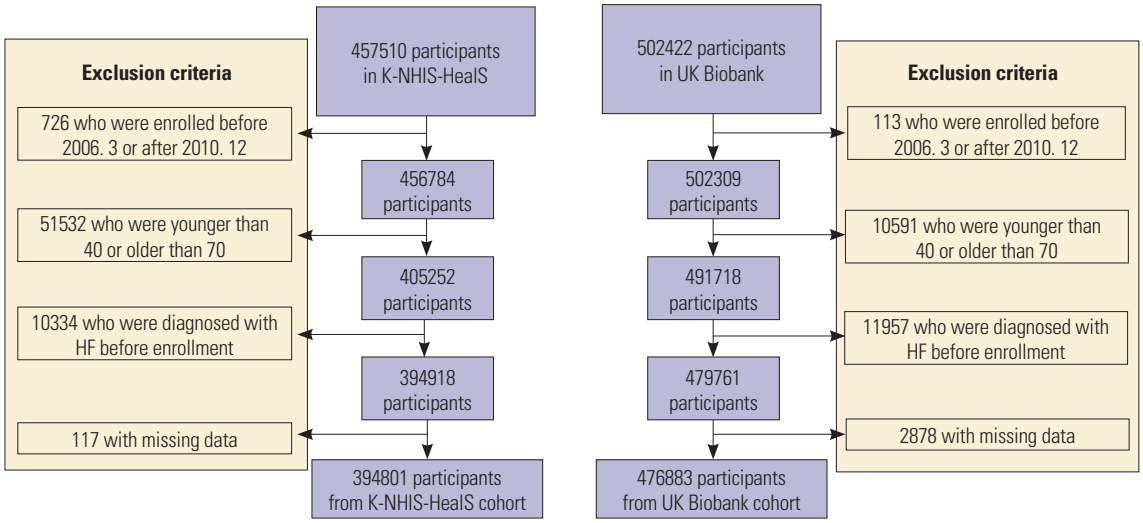

Fig. 1. Flow diagram of the study population. K-NHIS-HealS, Korean National Health Insurance Service-Health Screening; HF, heart failure.

4) those with missing data regarding BMI or other variables (n=2878). In total, the present study included 476883 participants from this cohort (Fig. 1).

Ethical approval

This retrospective study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, and was approved by the Institutional Review Board of Yonsei University Health System (4-2023-0377). The requirement for informed consent was waived by the Institutional Review Board due to the retrospective nature of the data. The UK Biobank study received approval from the Northwest Multicenter Research Ethics Committee. Participants who chose to withdraw their consent after the initial enrollment were not included in this study. Both studies followed the relevant regulations.

Outcome ascertainment

In the K-NHIS-HealS cohort, HF was defined as the first occurrence during more than two different days of hospital visits (outpatient) or the first admission with a diagnosis of HF using the ICD-10 code (I11.0, I50, and I97.1). New-onset AF was defined as the first occurrence during more than two different days of hospital visits (outpatient) or the first admission with a diagnosis of AF using the ICD-10 code (I48).

In the UK Biobank study, HF was defined as having multiple admissions or two primary medical records containing ICD-10 codes within the database. Additionally, self-reported codes (1076) were taken into account. New-onset AF was determined based on more than one hospital inpatient admission or two primary care records containing the relevant ICD-10 codes within the database. Similarly, self-reported non-cancer illness codes (1471, 1483) were considered. Detailed definitions of the comorbidities and outcomes are presented in Supplementary Tables 1 and 2 (only online).

Statistical methods

Data are presented as mean±SD for continuous variables and proportions for categorical variables. The Student's t-test was used to compare continuous variables, while the chi-squared test was used to analyze categorical variables. For comparing continuous variables among different BMI groups, one-way ANOVA and either the chi-squared test or Fisher's exact test as a post-hoc analysis were used. BMI was assessed as both categorical and continuous variable, following the classification system of the World Health Organization (underweight, <18.5; normal, 18.5 to <25.0; overweight, 25.0 to <30.0; obese, >30.0; and severely obese, ≥40.0 kg/m^2; respectively). Abdominal obesity was defined as waist circumference (WC) measurements ≥90 cm for male and ≥80 cm for female.[8,16]

This study employed Cox proportional hazards regression analysis to evaluate the relationship between BMI, WC, and the risk of developing HF and HF-related AF. Adjustment for clinical variables was performed, including age, sex, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, chronic kidney disease, transient ischemic attack or stroke, heavy alcohol consumption, and former or current smoking. For estimating HF, the Fine and Gray method was used to re-

Table 1. Baseline Characteristics of the Total Population of the Korean NHIS-HealS and UK Biobank Cohorts

	Korean NHIS-HealS (n=394801)	UK Biobank (n=476883)	*p* value
Age, yr	53.8±7.2	56.7±8.0	<0.001
Male	217892 (55.2)	216404 (45.4)	<0.001
BMI, kg/m^2	24.0±2.9	27.4±4.8	<0.001
BMI categories			<0.001
Underweight (<18.5 kg/m^2)	7184 (1.8)	2506 (0.5)	
Normal (18.5 to <25.0 kg/m^2)	250751 (63.5)	156476 (32.8)	
Overweight (25.0 to <30.0 kg/m^2)	126352 (32.0)	202409 (42.4)	
Obese (30.0 to <40.0 kg/m^2)	10450 (2.6)	106422 (22.3)	
Severely obese (≥40.0 kg/m^2)	64 (0.0)	9070 (1.9)	
WC, cm	82.0±7.8	90.1±13.4	<0.001
Abdominal obesity	117481 (31.2)	319187 (66.9)	<0.001
SBP, mm Hg	125.2±16.3	137.8±18.7	<0.001
DBP, mm Hg	78.3±10.7	82.3±10.2	<0.001
Hypertension	106574 (27.0)	129091 (27.1)	0.283
Diabetes mellitus	28398 (7.2)	23818 (5.0)	<0.001
Ischemic stroke or TIA	13642 (3.5)	4941 (1.0)	<0.001
Previous MI	2953 (0.7)	9809 (2.1)	<0.001
Hyperthyroidism	9718 (2.5)	4764 (1.0)	<0.001
Hypothyroidism	9979 (2.5)	25567 (5.4)	<0.001
Osteoporosis	47603 (12.1)	10724 (2.2)	<0.001
Dyslipidemia	91456 (23.2)	66688 (14.0)	<0.001
ESRD or CKD	2454 (0.6)	4460 (0.9)	<0.001
COPD	7520 (1.9)	7562 (1.6)	<0.001
History of malignant neoplasm	24037 (6.1)	45166 (9.5)	<0.001
Aspirin	64554 (46.3)	0 (0)	NA
P2Y12 inhibitor	7830 (21.3)	0 (0)	NA
Statin	41510 (29.3)	0 (0)	NA
ACEi or ARB	50138 (39.2)	0 (0)	NA
Betablocker	57792 (50.5)	0 (0)	NA
Glucose, mg/dL	98.2±26.6	92.2±22.1	<0.001
Creatinine, mg/dL	1.0±1.0	0.8±0.2	<0.001
Cholesterol, mg/dL	198.9±36.8	220.2±44.0	<0.001
Triglycerides, mg/dL	144.1±97.9	154.6±91.1	<0.001
LDL, mg/dL	119.2±38.1	137.6±33.4	<0.001
HDL, mg/dL	55.6±30.0	56.0±14.7	0.071

NA, not available; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NHIS-HealS, National Health Insurance Service-Health Screening; SBP, systolic blood pressure; TIA, transient ischemic attack; WC, waist circumference; COPD, chronic obstructive pulmonary disorder.
Values are presented as mean±SD or n (%).

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gard death as a competing risk.[17] The proportional hazards assumption test, utilizing scaled Schoenfeld residuals, was performed to evaluate the adherence of the Cox regression model to the proportional hazards assumption.

Statistical significance was defined as two-sided p values< 0.05. All statistical analyses were conducted using the R version 4.2.2 (www.R-project.org; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Table 1 compares the baseline characteristics of individuals in both populations. In the K-NHIS-HealS cohort, which included 394801 participants with a mean age of 53.8 years (55.2% male), 7184 (1.8%) were classified as underweight, 250751 (63.5%) as normal weight, 126352 (32.0%) as overweight, and 10514 (2.7%) as obese. In the UK Biobank cohort, which included 476883 participants with a mean age of 56.7 years (45.4% male), 2506 (0.5%) were underweight, 156476 (32.8%) were normal weight, 202409 (42.4%) were overweight, and 115492 (24.2%) were obese. The UK Biobank cohort showed significantly higher percentage of obese and severely obese participants compared to the K-NHIS-HealS cohort (p<0.001). In addition, the proportion of participants with abdominal obesity was significantly higher in the UK population than in the Korean population (66.9 vs. 31.2%, p<0.001). Supplementary Tables 3 and 4 (only online) provide the baseline characteristics for the BMI categories.

HF and obesity

During the follow-up period, 683 (0.17%) individuals (57.0% male) developed HF at 7 years in the K-NHIS-HealS cohort. Table 2 presents the adjusted incidence rates of HF based on different BMI categories in the Korean cohort. The age- and sex-adjusted HF incidence rates per 1000 person-years were 0.50, 0.20, 0.27, and 0.52 for the underweight, normal weight, overweight, and obese groups, respectively. In the UK Biobank cohort, 1247 (0.26%) participants (66.9% male) developed HF at 7 years. In this cohort, the total age - and sex-adjusted incidence of HF per 1000 person-years were 0.50, 0.18, 0.29, and 0.73 for the underweight, normal weight, overweight, and obese groups, respectively (Table 2). The overall age- and sex-adjusted HF incidence rate was significantly higher in the UK cohort than in the Korean cohort (0.36 vs. 0.24 per 1000 person-years, p<0.001). The accumulated incidence of HF was higher in overweight and obese individuals than in the normal weight group in both cohorts. (p<0.001) (Supplementary Fig. 1A, only online).

Regressions with the four BMI categories were assessed to examine the impact of BMI (Table 3). After adjustment for covariates, it was confirmed that obesity was associated with HF occurrence in both the Korean and UK populations [subdistribution hazard ratio (sHR), 1.82; 95% confidence interval (CI), 1.30–2.55 (Korea) vs. sHR, 2.00; 95% CI, 1.69–2.37 (UK)] (p< 0.001 for interaction) (Table 3). In the Korean cohort, the analysis of spline curve showed a J-shaped relationship between the continuous BMI variables and the risk of developing HF (Fig. 2A). A 5-unit increase in BMI was found to be correlated with a 44% higher risk of HF in the UK Biobank cohort (p<0.001), but not in the K-NHIS-HealS cohort (p= 0.277) (Table 3).

HF-related AF and obesity

In the K-NHIS-HealS cohort, 236 (0.06%) individuals (65.7% male) developed HF-related AF, whereas in the UK Biobank cohort, 618 (0.13%) participants (69.7% male) developed HF-related AF at 7 years. The age- and sex-adjusted incidence of HF-related AF was significantly greater in the UK population than in the Korean population (0.18 vs. 0.08 per 1000 person-years, p<0.001). In both cohorts, the age- and sex-adjusted HF-related AF incidence increased in obese and overweight groups, regardless of sex (Table 4, Fig. 2B). In addition, the accumulated incidence of HF-related AF was higher in overweight and

Table 2. Age- and Sex-Adjusted Incidence of HF by BMI

	Korean NHIS-HealS				UK Biobank			
	Underweight (n=7184)	Normal (n=250751)	Overweight (n=126352)	Obese (n=10514)	Underweight (n=2506)	Normal (n=156476)	Overweight (n=202409)	Obese (n=115492)
Overall								
Numbers of events/PYRs	26/51638	370/1839943	248/923737	39/75510	9/17845	201/1134277	427/1465800	610/832919
HF incidence (/1000 PYRs)*	0.50	0.20	0.27	0.52	0.50	0.18	0.29	0.73
Female								
Numbers of events/PYRs	10/24099	144/846091	118/376666	22/42018	6/14354	89/742270	116/693765	202/440610
HF incidence (/1000 PYRs)†	0.41	0.17	0.31	0.52	0.42	0.12	0.17	0.46
Male								
Numbers of events/PYRs	16/27539	226/993852	130/547071	17/33492	3/3521	112/392008	311/772036	408/392310
HF incidence (/1000 PYRs)†	0.58	0.23	0.24	0.51	0.85	0.29	0.40	1.04

HF, heart failure; BMI, body mass index; NHIS-HealS, National Health Insurance Service-Health Screening; PYRs, person-years.
*Age- and sex-adjusted HF incidence; †Age-adjusted HF incidence.

Table 3. HF Risk of BMI According to the Age-, Sex-, and Clinical Variable–Adjusted Model in the Total Population

	Korean NHIS-HealS		UK Biobank		*p* for interaction
	sHR (95% CI)	*p* value	sHR (95% CI)	*p* value	
With BMI as a 1-SD increase	1-SD (2.9 kg/m^2)		1-SD (4.8 kg/m^2)		
Age, sex adjusted	1.14 (1.06–1.23)	<0.001	1.73 (1.66–1.81)	<0.001	<0.001
Adjusted for clinical variables*	1.04 (0.97–1.12)	0.277	1.42 (1.35–1.49)	<0.001	<0.001
With BMI as 5-unit increase					
Age, sex adjusted	1.26 (1.11–1.43)	<0.001	1.77 (1.70–1.85)	<0.001	<0.001
Adjusted for clinical variables*	1.08 (0.94–1.23)	0.277	1.44 (1.37–1.51)	<0.001	<0.001
With BMI as a categorical variable					
Age, sex adjusted					<0.001
Underweight (<18.5 kg/m^2)	2.10 (1.41–3.13)	<0.001	3.53 (1.81–6.89)	<0.001	
Normal (18.5 to <25 kg/m^2)	1 (reference)		1 (reference)		
Overweight (25 to <30 kg/m^2)	1.27 (1.08–1.49)	0.004	1.28 (1.08–1.51)	0.005	
Obese (≥30 kg/m^2)	2.43 (1.74–3.38)	<0.001	3.45 (2.94–4.05)	<0.001	
Adjusted for clinical variablesa					<0.001
Underweight (<18.5 kg/m^2)	2.40 (1.61–3.58)	<0.001	3.33 (1.71–6.51)	<0.001	
Normal (18.5 to <25 kg/m^2)	1 (reference)		1 (reference)		
Overweight (25 to <30 kg/m^2)	1.10 (0.94–1.30)	0.233	1.04 (0.90–1.27)	0.429	
Obese (≥30 kg/m^2)	1.82 (1.30–2.55)	<0.001	2.00 (1.69–2.37)	<0.001	

HF, heart failure; BMI, body mass index; NHIS-HealS, National Health Insurance Service-Health Screening; sHR, subdistribution hazard ratio; CI, confidence interval; TIA, transient ischemic attack; MI, myocardial infarction; ESRD, end stage renal disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder.
*Adjusted for age, sex, and clinical variables such as hypertension, diabetes mellitus, ischemic stroke or TIA, previous MI, hyperthyroidism, hypothyroidism, osteoporosis, dyslipidemia, ESRD or CKD, COPD, and history of malignant neoplasm.

Table 4. Age- and Sex-Adjusted Incidence of HF-Related AF by BMI

	Korean NHIS-HealS				UK Biobank			
	Underweight (n=7182)	Normal (n=250731)	Overweight (n=126341)	Obese (n=10511)	Underweight (n=2505)	Normal (n=156453)	Overweight (n=202351)	Obese (n=115398)
Overall								
Number of events/PYRs	10/51658	125/1840540	87/924118	14/75574	4/17883	92/1134390	207/1465940	315/832981
HF incidence (/1000 PYRs)*	0.19	0.07	0.09	0.19	0.22	0.08	0.14	0.38
Female								
Number of events/PYRs	3/24107	40/846333	31/379866	7/42055	2/14362	35/742356	55/693803	95/440701
HF incidence (/1000 PYRs)†	0.12	0.05	0.08	0.17	0.14	0.05	0.08	0.22
Male								
Number of events/PYRs	7/27551	85/994207	56/547252	7/33519	2/3522	57/392034	152/772136	220/392280
HF incidence (/1000 PYRs)†	0.25	0.09	0.10	0.21	0.57	0.15	0.20	0.56

HF, heart failure; AF, atrial fibrillation; BMI, body mass index; NHIS-HealS, National Health Insurance Service-Health Screening; PYRs, person-years.
*Age- and sex-adjusted HF-related AF incidence; †Age-adjusted HF-related AF incidence.

obese individuals than in the normal weight group in both cohorts (p<0.001) (Supplementary Fig. 1B, only online).

After adjustment for clinical variables, it was confirmed that obesity was associated with HF-related AF occurrence in both cohorts [sHR, 2.21; 95% CI, 1.26–3.88 (Korea) vs. sHR, 2.24; 95% CI, 1.76–2.86 (UK)] (p<0.001 for interaction) (Table 5). A 5-unit increase in BMI was associated with a 52% (p<0.001) greater risk of HF-related AF in the UK population, but not in the Korean population (p= 0.275) (Table 5).

HF and HF-related AF according to abdominal obesity

Participants with abdominal obesity had a higher risk of developing HF and HF-related AF than those without abdominal obesity, as demonstrated by the age- and sex-adjusted incidence rates in both the Korean and UK populations. Additionally, each 1-SD increase in WC was associated with an increased risk of these conditions in both cohorts (Supplementary Table 5–8, Supplementary Fig. 2, only online). In the UK cohort, a linear relationship was observed between WC and the risks of HF and HF-related AF, and this trend was more prominent than that in the Korean cohort (Supplementary Fig. 3, only online).

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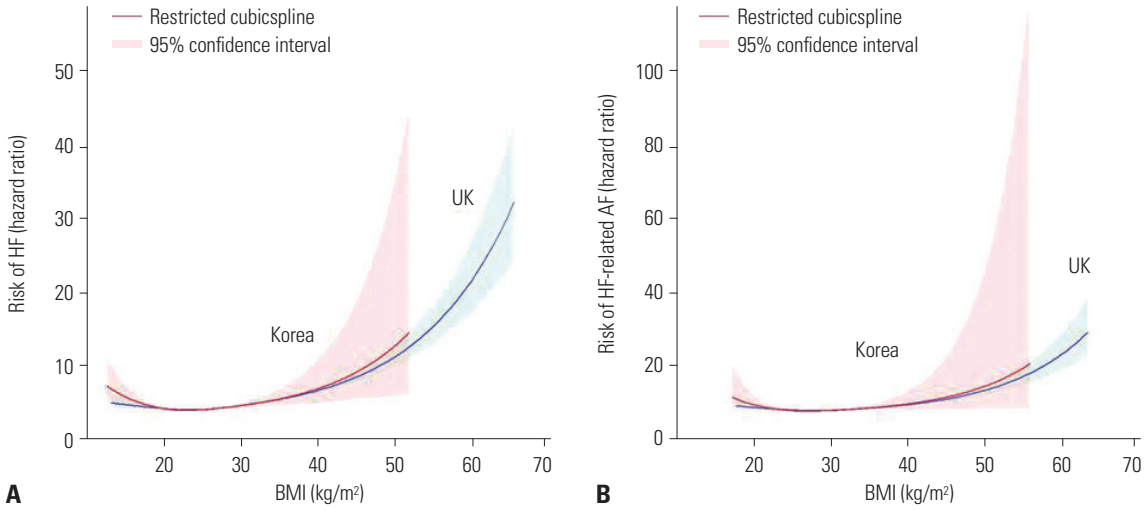

Fig. 2. Cubic spline graph for adjusted hazard ratio for (A) HF and (B) HF-related AF according to BMI in Korean-NHIS-HealS and UK Biobank cohort. Adjusted for age, sex and clinical variables such as hypertension, diabetes mellitus, ischemic stroke or TIA, previous MI, hyperthyroidism, hypothyroidism, osteoporosis, dyslipidemia, ESRD or CKD, COPD, history of malignant neoplasm. HF, heart failure; AF, atrial fibrillation; BMI, body mass index; NHIS-HealS, National Health Insurance Service-Health Screening; TIA, transient ischemic attack; MI, myocardial infarction; ESRD, end stage renal disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder.

Table 5. HF-Related AF Risk of BMI According to Age-, Sex-, and Clinical Variable–Adjusted Model in the Total Population

	Korean NHIS-HealS		UK Biobank		*p* for interaction
	sHR (95% CI)	*p* value	sHR (95% CI)	*p* value	
With BMI as 1-SD increase	1-SD (2.9 kg/m²)		1-SD (4.8 kg/m²)		
Age, sex adjusted	1.15 (1.02–1.30)	0.028	1.80 (1.70–1.91)	<0.001	<0.001
Adjusted for clinical variables*	1.07 (0.95–1.22)	0.275	1.50 (1.40–1.60)	<0.001	<0.001
With BMI as 5-unit increase					
Age, sex adjusted	1.27 (1.03–1.58)	0.028	1.85 (1.74–1.97)	<0.001	<0.001
Adjusted for clinical variables*	1.13 (0.91–1.41)	0.275	1.52 (1.42–1.64)	<0.001	<0.001
With BMI as a categorical variable					
Age, sex adjusted					<0.001
Underweight (<18.5 kg/m²)	2.36 (1.24–4.50)	0.009	3.56 (1.31–9.70)	0.013	
Normal (18.5 to <25 kg/m²)	1 (reference)		1 (reference)		
Overweight (25 to <30 kg/m²)	1.33 (1.01–1.75)	0.042	1.32 (1.03–1.69)	0.029	
Obese (≥30 kg/m²)	2.77 (1.59–4.82)	<0.001	3.83 (3.04–4.84)	<0.001	
Adjusted for clinical variables[2]					<0.001
Underweight (<18.5 kg/m²)	2.55 (1.33–4.88)	0.005	3.60 (1.32–9.82)	0.012	
Normal (18.5 to <25 kg/m²)	1 (reference)		1 (reference)		
Overweight (25 to <30 kg/m²)	1.20 (0.91–1.58)	0.202	1.09 (0.85–1.40)	0.485	
Obese (≥30 kg/m²)	2.21 (1.26–3.88)	0.006	2.24 (1.76–2.86)	<0.001	

HF, heart failure; AF, atrial fibrillation; BMI, body mass index; NHIS-HealS, National Health Insurance Service-Health Screening; sHR, subdistribution hazard ratio; CI, confidence interval; TIA, transient ischemic attack; MI, myocardial infarction; ESRD, end stage renal disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder.
*Adjusted for age, sex, and clinical variables, such as hypertension, diabetes mellitus, ischemic stroke or TIA, previous MI, hyperthyroidism, hypothyroidism, osteoporosis, dyslipidemia, ESRD or CKD, COPD, and history of malignant neoplasm.

Sensitivity analysis

The age- and sex-adjusted HF and HF-related AF incidence rates were examined in the overall population, which included participants aged below 40 years or above 70 years. The results are presented in Supplementary Table 9 (only online). The adjusted risks for HF and HF-related AF in the total population are presented in Supplementary Table 10 (only online). It was observed that both the incidence and risk of HF and HF-related AF increased with higher BMI. The age- and sex-adjusted incidence rates and adjusted risks of HF and HF-related AF were found to be higher in the UK population than in the Korean population.

DISCUSSION

The principal finding of this analysis was that the prevalence of obesity in the UK was nearly nine times higher than that in Korea. Second, it was consistently observed that the overall frequency of incident HF and HF-related AF was higher in the UK cohort than in the Korean cohort. Third, when BMI was analyzed as a categorical variable, obesity was identified as a significant risk factor for HF and HF-related AF in both cohorts. However, a 5-unit increase in BMI was found to be a significant risk factor for HF and HF-related AF only in the UK cohort, suggesting that the increases in the incidence of HF and HF-related AF in Western populations compared to Asians are related to the higher number of obese individuals. Our findings indicated that among Korean female, a 5-unit increase in BMI correlated with a 26% higher risk of HF (p<0.013), while no significant correlation was observed among Korean male (p=0.276). Notably, even with higher obesity rates in the UK cohort compared to South Korea, this suggests that genetic predisposition, hormonal disparities, inflammatory reactions, and environmental factors could contribute to these outcomes. Additionally, unadjusted underlying diseases and medications might also influence HF and associated AF.

Ethnic differences in HF and HF-related AF

This study found a significantly higher prevalence of HF and HF-related AF in Caucasians than in Asians, a previously unidentified ethnic difference. Recently, Choi, et al.[6] reported that age- and sex-adjusted incidence rates of AF were greater in participants from the UK Biobank cohort than in the K-NHIS-HealS cohort (4.30 vs. 3.04 per 1000 person-years). In a large survey study of veterans, the age-adjusted incidence of AF was observed to be 5.7% in Caucasians and 3.6% in Asians.[18] It is noteworthy that the long-term risk of AF was higher in Caucasians than in non-Caucasians. For instance, the Atherosclerosis Risk in Communities study reported that the long-term prevalence of AF is higher in white Europeans than in non-whites (36%, 30%, 21%, and 22% in white male, white female, African-American male, and African-American female, respectively). Furthermore, it is recognized that the incidence of stroke and bleeding associated with oral anticoagulants use in patients with AF can differ among different racial groups.[19,20] The reasons for these differences remain unclear, but they may be related to the higher prevalence of cardiovascular risk factors and diseases, including smoking, obesity, hypertension, ischemic heart diseases, and diabetes, in Western countries.[21]

Obesity causes ethnic differences in HF and HF-related AF

The prevalence of overweight and obesity is higher in Western populations than in Asian populations. In fact, this study found that the proportion of obesity (BMI >30 kg/m^2) in the UK was nearly nine times higher than that in Korea (2.7% vs. 24.2%, respectively). Our investigation revealed that obesity may play a significant role in the higher incidence of HF and HF-related AF in the UK compared to Korea. Excessive accumulation of fat in the heart and liver leads to an increase in blood volume and release of inflammatory factors. This, in turn, contributes to elevated stroke volume and myocardial injury, ultimately resulting in the development of concentric left ventricular hypertrophy and both diastolic and systolic cardiac failure.[4,22,23] BMI is commonly used as a measure of obesity and considered as a main risk factor for cardiometabolic diseases and overall mortality. Numerous community-based cohorts have shown a link between general obesity, increased BMI, and an elevated risk of AF during follow-up periods.[24-26] Moreover, obesity progression has been observed, with a BMI in the range of 30–34.9 kg/m^2 being associated with a 54% increased likelihood of transitioning from paroxysmal to permanent AF and class 2 obesity (BMI: 35.0–39.9 kg/m^2) being associated with an 87% higher risk.[27] Notably, when adjustments were made for left atrial size in the Framingham study, the association between BMI and AF was less significant, suggesting that the presence of left atrial enlargement in obese individuals might play a crucial role in contributing to the development of AF. Additionally, WC is considered a sensitive measure of central obesity,[28] and both WC and waist-to-hip circumference ratio are associated with an elevated risk of AF.[8,26]

Study limitations

This study has some limitations that need to be considered. First, there may be a selection bias as the recommendation for health examinations was not mandatory in the K-NHIS-HealS cohort, unlike in the UK Biobank cohort, which had participants screened and investigated in detail. Second, the study had a relatively short follow-up duration; also, participants who died during the study period may have already experienced serious health problems. Third, individuals who were not included due to missing data may have differed from those included, which could have underestimated the health inequalities in the study. However, missing data were imputed and the results remained similar. Fourth, the detection of incident HF-related AF during hospitalization may miss shorter and fewer symptomatic/asymptomatic/subclinical episodes of the disease. Fifth, it is notable that the genetic background and environmental influences of the participants in both cohorts were not comprehensively accounted for. Therefore, we recommend including an additional discussion that delves into these factors to elucidate the racial disparities observed in the outcomes. Finally, HF-related AF was defined when AF developed in patients with HF. However, the relationship between AF and HF could not be identified.

In conclusion, obesity was associated with an increased risk of HF and HF-related AF in both Korean and UK populations. However, the higher incidence of HF and HF-related AF in the UK population was likely due to the higher proportion of obese

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individuals in that cohort, particularly those in the obese BMI category.

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REFERENCES

1. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation 2016;133:484-92.
2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation 2020;141:e139-596.
3. Zhang J, Johnsen SP, Guo Y, Lip GYH. Epidemiology of atrial fibrillation: geographic/ecological risk factors, age, sex, genetics. Card Electrophysiol Clin 2021;13:1-23.
4. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC Jr, et al. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the multi-ethnic study of atherosclerosis. Ann Epidemiol 2015;25:71-6.e1.
5. Chen ML, Parikh NS, Merkler AE, Kleindorfer DO, Bhave PD, Levitan EB, et al. Risk of atrial fibrillation in black versus white medicare beneficiaries with implanted cardiac devices. J Am Heart Assoc 2019;8:e010661.
6. Choi SH, Yang PS, Kim D, Sung JH, Jang E, Yu HT, et al. Association of obesity with incident atrial fibrillation in Korea and the United Kingdom. Sci Rep 2023;13:5197.
7. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014;64:2222-31.
8. Baek YS, Yang PS, Kim TH, Uhm JS, Park J, Pak HN, et al. Associations of abdominal obesity and new-onset atrial fibrillation in the general population. J Am Heart Assoc 2017;6:e004705.
9. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-13.
10. Wong CX, Brooks AG, Lau DH, Leong DP, Sun MT, Sullivan T, et al. Factors associated with the epidemic of hospitalizations due to atrial fibrillation. Am J Cardiol 2012;110:1496-9.
11. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011;123:1501-8.
12. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet 2015;386:154-62.
13. Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, et al. Obesity and the risk of incident, post-operative, and post-ablation atrial fibrillation: a meta-analysis of 626,603 individuals in 51 studies. JACC Clin Electrophysiol 2015;1:139-52.
14. Lim YM, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Body mass index variability and long-term risk of new-onset atrial fibrillation in the general population: a Korean nationwide cohort study. Mayo Clin Proc 2019;94:225-35.
15. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
16. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new worldwide definition. A consensus statement from the international diabetes federation. Diabet Med 2006;23:469-80.
17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
18. Borzecki AM, Bridgers DK, Liebschutz JM, Kader B, Kazis LE, Berlowitz DR. Racial differences in the prevalence of atrial fibrillation among males. J Natl Med Assoc 2008;100:237-45.
19. Lee KB, Kim TH, Park J, Park JK, Kang KW, Kim J, et al. Stroke and systemic thromboembolism according to CHA2DS2-VASc score in contemporary Korean patients with atrial fibrillation. Yonsei Med J 2022;63:317-24.
20. Park H, Yu HT, Kim TH, Park J, Park JK, Kang KW, et al. Oral anticoagulation therapy in atrial fibrillation patients with advanced chronic kidney disease: CODE-AF registry. Yonsei Med J 2023;64:18-24.
21. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 2009;158:111-7.
22. Neeland IJ, Gupta S, Ayers CR, Turer AT, Rame JE, Das SR, et al. Relation of regional fat distribution to left ventricular structure and function. Circ Cardiovasc Imaging 2013;6:800-7.
23. Murase T, Hattori T, Ohtake M, Abe M, Amakusa Y, Takatsu M, et al. Cardiac remodeling and diastolic dysfunction in DahlS.Z-Lepr(fa)/Lepr(fa) rats: a new animal model of metabolic syndrome. Hyper-

tens Res 2012;35:186-93.
24. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). J Am Coll Cardiol 2010;55:2319-27.
25. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15000 middle-aged men and women (the Renfrew-Paisley study). Eur Heart J 2006;27:96-106.
26. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292:2471-7.
27. Tsang TS, Barnes ME, Miyasaka Y, Cha SS, Bailey KR, Verzosa GC, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J 2008;29:2227-33.
28. Rankinen T, Kim SY, Pérusse L, Després JP, Bouchard C. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. Int J Obes Relat Metab Disord 1999;23:801-9.

https://doi.org/10.3349/ymj.2023.0264