Journal of the American Heart Association

ORIGINAL RESEARCH

Sex Differences in the Association Between Hypertension and Incident Atrial Fibrillation

Satoshi Kanazawa, BS; Hidehiro Kaneko, MD, PhD; Yuichiro Yano, MD; Yuta Suzuki, PhD; Akira Okada, MD; Satoshi Matsuoka, MD; Katsuhito Fujiu, MD; Nobuaki Michihata, MD; Taisuke Jo, MD; Norifumi Takeda, MD; Hiroyuki Morita, MD; Koichi Node, MD; Hideo Yasunaga, MD; Issei Komuro, MD

BACKGROUND: Limited evidence is available on sex differences about the association between hypertension and incident atrial fibrillation (AF).

METHODS AND RESULTS: We used a nationwide health checkup and claims database to analyze 3 383 738 adults (median age, 43 (36–51) years, 57.4% men). We investigated the relationship between hypertension and incident AF in men and women using a Cox regression model. We used restricted cubic spline functions to identify the association of blood pressure (BP) as a continuous parameter with incident AF. We categorized the men and women into 4 groups according to the 2017 American College of Cardiology/American Heart Association BP guidelines. During a mean follow-up of 1199±950 days, 13 263 AF diagnoses were recorded. The incidence (95% CI) of AF was 15.8 (15.5–16.1) per 10 000 person-years in men and 6.1 (5.9–6.3) per 10 000 person-years in women. Compared with normal BP, elevated BP, stage 1 hypertension, and stage 2 hypertension were associated with an increased risk AF in both men and women. However, the hazard ratios were greater in women than in men, and the *P* value for interactions in the multivariable model was 0.0076. The models using restricted cubic spline showed that the risk of AF associated with elevated systolic BP increased steeply above an approximate threshold of systolic BP of 130 mm Hg in men and 100 mm Hg in women. Although our primary findings were consistent across subgroup analyses, this association was most significant in younger individuals.

CONCLUSIONS: Although the incidence of AF was higher in men, the association between hypertension and incident AF was more pronounced in women than in men, suggesting a potential sex difference in the relationship between hypertension and incident AF.

Key Words: atrial fibrillation ■ blood pressure ■ hypertension ■ sex difference

Atrial fibrillation (AF) is increasing in prevalence.[1–3] In the United States, the number of patients with AF is estimated to increase from ≈5.2 million in 2010 to 12.1 million in 2030.[4] Similarly, the prevalence of AF is projected to increase from 8.8 million in 2010 to 17.9 million in 2060 among people aged >55 years in the European Union.[5] Given this epidemiological background, the primary prevention of AF is needed from the public health perspective. For this end, hypertension is one of the important risk factors for cardiovascular disease including AF,[6,7] and the risk stratification of AF using blood pressure (BP) status is clinically important. Regarding the potential sex difference, although the incidence of AF is known to be higher in men than in women,[2,8,9] once AF occurs, women could have adverse clinical events (eg, recurrence, stroke, death).[10–12] Therefore, even if the incidence is low, preventing AF in women is essential. Furthermore, considering the possible sex difference in the relationship between the risk factors and incident cardiovascular events,[13] risk stratification for AF by sex would also be required. However, data on the potential sex difference in the influence of hypertension on

Correspondence to: Hidehiro Kaneko, MD, PhD, The Department of Cardiovascular Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: kanekohidehiro@gmail.com

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026240

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Our analysis of a large-scale real-world data set including >3 million people demonstrated that elevated blood pressure, stage 1 hypertension, and stage 2 hypertension were all associated with a greater risk of developing atrial fibrillation in men and women, and this relationship was more pronounced in women than in men.

What Are the Clinical Implications?

- Women may be more susceptible to increasing blood pressure than men in the development of atrial fibrillation, and we need to recognize that the risk of atrial fibrillation was higher even in elevated blood pressure compared with normal blood pressure in both men and women.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
SBP	systolic blood pressure

incident AF have been limited. In the present study, we examined the association of hypertension with incident AF stratified by sex using a nationwide health checkup and administrative claims data set and aimed to clarify whether sex differences are present in the relationship between hypertension and the risk of developing AF.

METHODS

We used the JMDC Claims Database, commercially available for anyone who would purchase it, from JMDC Inc. (JMDC Inc., Tokyo, Japan; https://www.jmdc.co.jp/en/). JMDC Inc. is a health care venture corporation in Japan.

Study Population

In this retrospective observational cohort study, we used the JMDC Claims Database, consisting of a combined database of health checkup and administrative claims database (both outpatient and inpatient settings) in Japan.[6,14,15] The JMDC Claims Database covered individuals who were mainly employees and their family members in Japan between January 2005 and April 2021. Japan has a universal health insurance system, and the JMDC Claims Database consists of administrative claims records reimbursed by insurance (eg, medical diagnoses, pharmacological prescriptions) from >60 insurers, and medical diagnoses are registered in the form of *International Classification of Diseases, 10th Revision* (*ICD-10*) coding. We identified 4 534 334 individuals with available health checkup data on BP and blood test results. Subsequently, we excluded individuals aged <20 years; those with a history of myocardial infarction, angina pectoris, stroke, heart failure, and AF; those with a history of renal replacement therapy; those taking BP-lowering medications; and those with missing data on cigarette smoking and alcohol consumption. Finally, we obtained 3 383 738 participants in this study (Figure 1). In this study, we used data on BP and the status of BP-lowering medication use only at the initial health checkup.

Ethics

This study was performed in accordance with the ethical guidelines of the University of Tokyo (approval by the Ethical Committee of the University of Tokyo: 2018-10862) and the principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data in the JMDC Claims Database were anonymized and deidentified.

BP Measurement

In Japan, employers are obligated to perform health checkups (generally once a year) for their employees, and we used BP data at health checkup. BP was measured during a health checkup according to the protocol recommended by the Japanese Ministry of Health, Labor, and Welfare by health care professionals after a 5-minute rest (see Data S1).[6,14,15]

BP Categorization

The participants were categorized into 4 groups based on BP at initial health checkup: normal BP (systolic BP (SBP) <120 mm Hg and diastolic BP (DBP) <80 mm Hg), elevated BP (SBP of 120 to 129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (SBP of 130–139 mm Hg or DBP of 80–89 mm Hg), and stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg).[16] Furthermore, we also categorized study participants into normal/elevated BP that was defined as SBP <130 mm Hg and DBP <80 mm Hg, isolated diastolic hypertension defined as SBP <130 mm Hg and DBP ≥80 mm Hg, isolated systolic hypertension defined as SBP ≥130 mm Hg and DBP <80 mm Hg, and systolic diastolic hypertension defined as SBP ≥130 mm Hg and DBP ≥80 mm Hg.

Risk Factors Other Than BP

Data on body mass index (BMI), and fasting laboratory values were obtained using standardized protocols during the health checkups. Information on

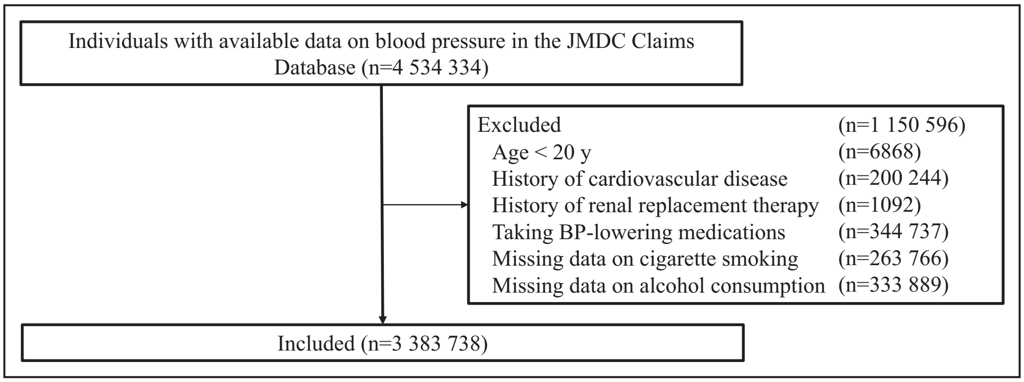

Figure 1. Flowchart.
Study population after applying inclusion and exclusion criteria.

cigarette smoking (current or noncurrent) and alcohol consumption (every day or not every day) were collected from self-reported questionnaires at the health checkup. Overweight and obesity were defined as BMI ≥25 kg/m^2. Diabetes was defined as having a fasting glucose level ≥126 mg/dL or using glucose-lowering medications. Dyslipidemia was defined as low-density lipoprotein cholesterol level ≥140 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, triglyceride level ≥150 mg/dL, or using lipid-lowering medications.

Outcomes

Information on the outcomes was collected between January 2005 and April 2021. The primary outcome was AF (*ICD-10* code: I480–I484, and I489).

Statistical Analysis

We analyzed the study population stratified by sex. The data are expressed as median (Q1–Q3) for continuous variables or number (percentage) for categorical variables. The statistical significance of differences between men and women on clinical characteristics were assessed using unpaired t test and Chi-squared test, for continuous variables and for categorical variables, respectively. We performed analyses using Cox regression to examine the association between BP categories and incident AF. We calculated hazard ratios (HRs) in an unadjusted model (Model 1), an age-adjusted model (Model 2), and after adjustment for age, BMI, diabetes, dyslipidemia, cigarette smoking, and alcohol consumption using the forced entry method (Model 3). To examine whether the BP category had a differential relationship with incident AF by sex, multiplicative interaction terms for sex were calculated. We performed a stratified subgroup analysis by age (≥50 versus <50 years) or alcohol consumption (every day versus not every day). We checked the proportional hazard assumption for Cox proportional hazard models using Schoenfeld residuals.

We evaluated the dose–response relationship of SBP or DBP with the risk of developing AF using a restricted cubic spline regression model. We used 4 knots for SBP and DBP (5th, 35th, 65th, and 95th percentiles), with the reference point set at SBP of 120 mm Hg and DBP of 80 mm Hg. The HR of SBP or DBP as a continuous variable was adjusted for age, BMI, diabetes, dyslipidemia, cigarette smoking, and alcohol consumption.

Four sensitivity analyses were conducted. First, we included individuals taking BP-lowering medications at the initial health checkup; these individuals had been excluded from the main analysis as shown in Figure 1. Second, we imputed missing data on cigarette smoking and alcohol consumption and obtained results, as previously described.[17,18] Briefly, we performed the analysis using the multiple imputation by the chained equation method with 20 iterations described by Aloisio et al,[19] and obtained the HRs with standard errors based on Rubin's rules.[20] Third, because death could be regarded as a competing risks with AF events, we also conducted a competing risks analysis using cause-specific Cox proportional hazard modeling.[21,22] Fourth, we added use of sex hormones or modulators of genital system medications (ATC code of G03) to multivariable Cox regression model (model 3).

Statistical significance was set at a *P* value <0.05. All statistical analyses were conducted using STATA version 17 (StataCorp LLC, College Station, TX, USA).

RESULTS

Clinical Characteristics

The clinical characteristics of the study participants are summarized in Table 1. The median (interquartile range) age was 43 (36–51) years, and 1 943 708 participants (57.4%) were men. The median age was 44 years in women, and 43 years in men. The SBP and DBP were higher in men than in women. Accordingly,

Table 1. Baseline Characteristics

	Men (n=1 943 708)	Women (n=1 440 030)	*P* value
Age, y	43 (36–51)	44 (36–51)	<0.001
Body mass index, kg/m^2	23.1 (21.1–25.3)	20.9 (19.2–23.2)	<0.001
Overweight/obesity, n (%)	548 872 (28.2)	210 716 (14.6)	<0.001
Systolic blood pressure, mm Hg	120 (111–129)	111 (102–122)	<0.001
Diastolic blood pressure, mm Hg	75 (67–82)	68 (61–76)	<0.001
Blood pressure category			<0.001
Normal blood pressure, n (%)	851 494 (43.8)	971 120 (67.4)	
Elevated blood pressure, n (%)	336 104 (17.3)	167 421 (11.6)	
Stage 1 hypertension, n (%)	491 293 (25.3)	199 296 (13.8)	
Stage 2 hypertension, n (%)	264 817 (13.6)	102 193 (7.1)	
Diabetes, n (%)	65 133 (3.4)	16 038 (1.1)	<0.001
Dyslipidemia, n (%)	875 301 (45.0)	387 728 (26.9)	<0.001
Low-density lipoprotein cholesterol, mg/dL	122 (101–144)	113 (94–135)	<0.001
High-density lipoprotein cholesterol, mg/dL	56 (48–67)	70 (61–81)	<0.001
Triglycerides, mg/dL	94 (65–140)	64 (48–89)	<0.001
Fasting plasma glucose, mg/dL	93 (87–100)	89 (84–94)	<0.001
Cigarette smoking, n (%)	707 446 (36.4)	159 791 (11.1)	<0.001
Alcohol consumption, n (%)	552 688 (28.4)	172 932 (12.0)	<0.001

Data are reported as medians (interquartile range) or numbers (percentage), where appropriate.

the prevalence of stage 1 and stage 2 hypertension were higher in men than in women. Moreover, men had a higher BMI and a higher prevalence of diabetes, dyslipidemia, cigarette smoking, and alcohol consumption than women.

BP Category and AF

During a mean follow-up period of 1199±950 days, 10 601 AF diagnoses were recorded in men, and the incidence of AF was 15.8 (95% CI, 15.5–16.1) per 10 000 person-years. In women, 2662 AF events were recorded, and the incidence of AF was 6.1 (95% CI, 5.9–6.3) per 10 000 person-years. The risk of AF increases with increasing BP. Compared with normal/elevated BP, HRs of elevated BP, stage 1 hypertension, and stage 2 hypertension for AF were 1.10 (95% CI, 1.03–1.17), 1.17 (95% CI, 1.11–1.23), and 1.55 (95% CI, 1.47–1.63) in men, respectively. HRs of elevated BP, stage 1 hypertension, and stage 2 hypertension for AF were 1.22 (95% CI, 1.08–1.37), 1.37 (95% CI, 1.23–1.52), and 1.89 (95% CI, 1.68–2.12) in women, respectively. The *P* value for interaction was 0.0076 in the model 3, suggesting that the significant association of the BP category with incident AF was modified by sex (Table 2). We checked the proportional hazard assumption by Schoenfeld residual tests, and there was no breach of this hypothesis (*P*=0.060 for men, *P*=0.462 for women).

The BP category was associated with the incidence of AF in men and women, not only in people aged ≥50 years, but also in those aged <50 years. The *P* value for the interaction assessing the association of BP category with incident AF between men and women was statistically significant in people aged <50 years, but not in those aged ≥50 years. The association of hypertension with incident AF was greater in women than in men among both people with and without alcohol consumption. However, the statistically significant interaction was more robust in people with alcohol consumption (Table 3).

Furthermore, compared with the normal/elevated BP, isolated diastolic hypertension, isolated systolic hypertension, and systolic diastolic hypertension were associated with an increased risk of developing AF in both men and women, and this relationship was more pronounced in women than in men (Table S1). The significant interaction assessing the association of this alternative BP category with incident AF between men and women was only observed in people aged <50 years (Table S2).

Restricted Cubic Spline

Restricted cubic spline showed that the risk of AF associated with elevated systolic BP increased steeply above an approximate threshold of systolic BP of 130 mm Hg in men and 100 mm Hg in women. In men, the risk of AF as a function of DBP was flat (ie, did not increase with respect to DBP) when DBP <80 mm Hg but increased steadily above a threshold

Table 2. Blood Pressure Category and Atrial Fibrillation Stratified by Sex

	Men				Women				*P* for interaction
	Normal blood pressure	Elevated blood pressure	Stage 1 hypertension	Stage 2 hypertension	Normal blood pressure	Elevated blood pressure	Stage 1 hypertension	Stage 2 hypertension	
No. of individuals	851 494	336 104	491 293	264 817	971 120	167 421	199 296	102 193	…
No. of events	3326	1490	3160	2625	1345	371	532	414	…
Incidence per 10 000 person-years	11.4 (11.1–11.8)	13.2 (12.6–13.9)	17.8 (17.2–18.4)	29.1 (28.0–30.3)	4.6 (4.3–4.8)	7.2 (6.5–8.0)	8.7 (8.0–9.5)	14.3 (13.0–15.7)	…
Model 1	1 [Reference]	1.15 (1.08–1.23)	1.54 (1.47–1.62)	2.54 (2.41–2.67)	1 [Reference]	1.57 (1.40–1.77)	1.91 (1.73–2.12)	3.16 (2.83–3.53)	<0.001
Model 2	1 [Reference]	1.13 (1.06–1.20)	1.23 (1.17–1.29)	1.68 (1.59–1.76)	1 [Reference]	1.22 (1.09–1.37)	1.38 (1.24–1.52)	1.91 (1.70–2.14)	0.1525
Model 3	1 [Reference]	1.10 (1.03–1.17)	1.17 (1.11–1.23)	1.55 (1.47–1.63)	1 [Reference]	1.22 (1.08–1.37)	1.37 (1.23–1.52)	1.89 (1.68–2.12)	0.0076

The association between blood pressure category and atrial fibrillation stratified by sex is summarized. The incidence is presented in 10 000 person-years. Model 1=unadjusted model. Model 2=adjusted for age. Model 3=Adjusted for age, body mass index, diabetes, dyslipidemia, cigarette smoking, and alcohol consumption.

of DBP >80 mm Hg. In women, the risk of AF increased steadily throughout the range of DBP, without threshold (Figure 2).

Sensitivity Analyses

First, we added 301 915 individuals taking BP-lowering medications to the population of the main analysis (n=3 383 738) and analyzed 3 685 653 individuals in this sensitivity analysis. In this population, the main results were almost unchanged (Table S3). Second, after multiple imputations, 15 803 AF events were recorded in 3 981 393 individuals. As also seen in this analysis, the association between BP category and incident AF was greater in women than in men (Table S4). Third, our primary results were consistent with those of a competing risks model (Table S5). Fourth, after adding use of sex hormones or modulators of genital system medications to model 3, our primary findings were unchanged (Table S6).

DISCUSSION

The current analyses using a large-scale health checkup and administrative claims database including >3 000 000 individuals demonstrated that hypertension was associated with a higher risk of developing AF in both men and women, and the relationship between hypertension and incident AF was more pronounced in women than in men. This relationship is consistent across a variety of sensitivity analyses. This is the first epidemiological data suggesting a potential sex difference in the association between hypertension and the subsequent risk of AF using a large-scale real-world data set.

In agreement with preceding studies,[2,8,9] the incidence of AF was higher in men than in women. Furthermore, the status of cardiovascular risk factors, including BP, was much better in women than in men. Nevertheless, our analyses demonstrated that the relationship between hypertension and incident AF was more pronounced in women than that in men. The restricted cubic spline suggested that the risk of AF began to increase with SBP or DBP earlier in women than in men. Women may be more susceptible to BP than men are in terms of the risk of developing AF. Several possible explanations for this have been suggested. First, the baseline risk of developing AF is lower in women than in men. Therefore, the influence of hypertension could be more pronounced in women. Accordingly, as shown in Table 3, among older individuals, we did not find the *P* value for the interaction statistically significant. In the older people, the baseline AF risk markedly increases in both men and women, and the menopause-associated changes also increase the risk of AF in women,[9] which would have attenuated the sex difference in the hypertension-AF

Table 3. Subgroup Analysis of Blood Pressure Category and Atrial Fibrillation Stratified by Sex

	Men				Women				
	Normal blood pressure	Elevated blood pressure	Stage 1 hypertension	Stage 2 hypertension	Normal blood pressure	Elevated blood pressure	Stage 1 hypertension	Stage 2 hypertension	*P* for interaction
Age ≥50 y									
No. of individuals	186 761	76 258	174 353	127 596	211 545	65 042	89 931	61 020	…
No. of events	1751	808	1943	1773	588	208	315	304	…
Incidence per 10 000 person-years	26.6 (25.4–27.8)	30.8 (28.8–33.0)	31.9 (30.6–33.4)	43.1 (41.1–45.1)	9.4 (8.7–10.2)	11.2 (9.8–12.9)	12.3 (11.0–13.7)	18.7 (16.7–20.9)	…
Model 1	1 [Reference]	1.16 (1.07–1.26)	1.20 (1.12–1.28)	1.62 (1.52–1.73)	1 [Reference]	1.19 (1.02–1.39)	1.30 (1.13–1.49)	1.99 (1.74–2.29)	0.0630
Model 2	1 [Reference]	1.10 (1.01–1.19)	1.16 (1.09–1.24)	1.51 (1.41–1.61)	1 [Reference]	1.07 (0.91–1.25)	1.18 (1.03–1.35)	1.71 (1.48–1.96)	0.3495
Model 3	1 [Reference]	1.07 (0.98–1.16)	1.12 (1.05–1.19)	1.41 (1.32–1.51)	1 [Reference]	1.06 (0.90–1.24)	1.16 (1.01–1.33)	1.65 (1.43–1.91)	0.2274
Age <50 y									
No. of individuals	664 733	259 846	316 940	137 221	759 575	102 379	109 365	41 173	…
No. of events	1575	682	1217	852	757	163	217	110	…
Incidence per 10 000 person-years	7.0 (6.7–7.4)	7.9 (7.3–8.5)	10.4 (9.9–11.0)	17.4 (16.3–18.6)	3.2 (3.0–3.5)	4.9 (4.2–5.7)	6.2 (5.4–7.0)	8.7 (7.2–10.4)	…
Model 1	1 [Reference]	1.12 (1.02–1.23)	1.45 (1.35–1.57)	2.44 (2.24–2.65)	1 [Reference]	1.50 (1.26–1.77)	1.87 (1.61–2.18)	2.66 (2.18–3.25)	0.0025
Model 2	1 [Reference]	1.17 (1.07–1.27)	1.29 (1.20–1.39)	2.00 (1.84–2.17)	1 [Reference]	1.39 (1.18–1.65)	1.66 (1.43–1.94)	2.20 (1.80–2.70)	0.0201
Model 3	1 [Reference]	1.13 (1.03–1.23)	1.21 (1.12–1.31)	1.79 (1.64–1.96)	1 [Reference]	1.41 (1.19–1.68)	1.69 (1.45–1.98)	2.26 (1.83–2.80)	0.0008
Alcohol consumption: every day									
No. of individuals	192 742	85 481	166 928	107 537	101 316	21 325	32 171	18 120	…
No. of events	1165	551	1394	1254	146	57	92	66	…
Incidence per 10 000 person-years	16.1 (15.2–17.0)	17.4 (16.0–18.9)	21.9 (20.8–23.1)	33.4 (31.6–35.3)	4.9 (4.1–5.7)	9.1 (7.0–11.8)	10.1 (8.2–12.4)	13.8 (10.9–17.6)	…
Model 1	1 [Reference]	1.08 (0.98–1.20)	1.36 (1.26–1.47)	2.09 (1.93–2.26)	1 [Reference]	1.86 (1.37–2.52)	2.07 (1.60–2.69)	2.87 (2.15–3.84)	0.0016
Model 2	1 [Reference]	1.04 (0.94–1.15)	1.14 (1.05–1.23)	1.48 (1.37–1.61)	1 [Reference]	1.55 (1.14–2.11)	1.66 (1.28–2.17)	2.02 (1.49–2.72)	0.0172
Model 3	1 [Reference]	1.02 (0.92–1.13)	1.11 (1.02–1.20)	1.41 (1.30–1.54)	1 [Reference]	1.53 (1.12–2.09)	1.64 (1.25–2.14)	1.96 (1.45–2.66)	0.0150
Alcohol consumption: not every day									
No. of individuals	658 752	250 623	324 365	157 280	869 804	146 096	167 125	84 073	…
No. of events	2161	939	1766	1371	1199	314	440	348	…
Incidence per 10 000 person-years	9.9 (9.5–10.3)	11.6 (10.9–12.3)	15.5 (14.8–16.3)	26.1 (24.8–27.5)	4.5 (4.3–4.8)	6.9 (6.2–7.7)	8.5 (7.7–9.3)	14.4 (13.0–16.0)	…
Model 1	1 [Reference]	1.17 (1.08–1.26)	1.55 (1.46–1.65)	2.62 (2.45–2.81)	1 [Reference]	1.53 (1.35–1.73)	1.87 (1.68–2.09)	3.20 (2.84–3.61)	0.0002
Model 2	1 [Reference]	1.17 (1.08–1.26)	1.25 (1.17–1.33)	1.76 (1.65–1.89)	1 [Reference]	1.18 (1.04–1.33)	1.33 (1.19–1.49)	1.89 (1.67–2.14)	0.6910
Model 3	1 [Reference]	1.14 (1.06–1.23)	1.20 (1.13–1.28)	1.65 (1.54–1.77)	1 [Reference]	1.17 (1.03–1.33)	1.33 (1.18–1.48)	1.88 (1.65–2.14)	0.2729

The incidence is presented in 10 000 person-years. Model 1=unadjusted model. Model 2=Adjusted for age. Model 3=adjusted for age, body mass index, diabetes, dyslipidemia, cigarette smoking, and alcohol consumption. In a subgroup analysis stratified by alcohol consumption, alcohol consumption was excluded from covariate.

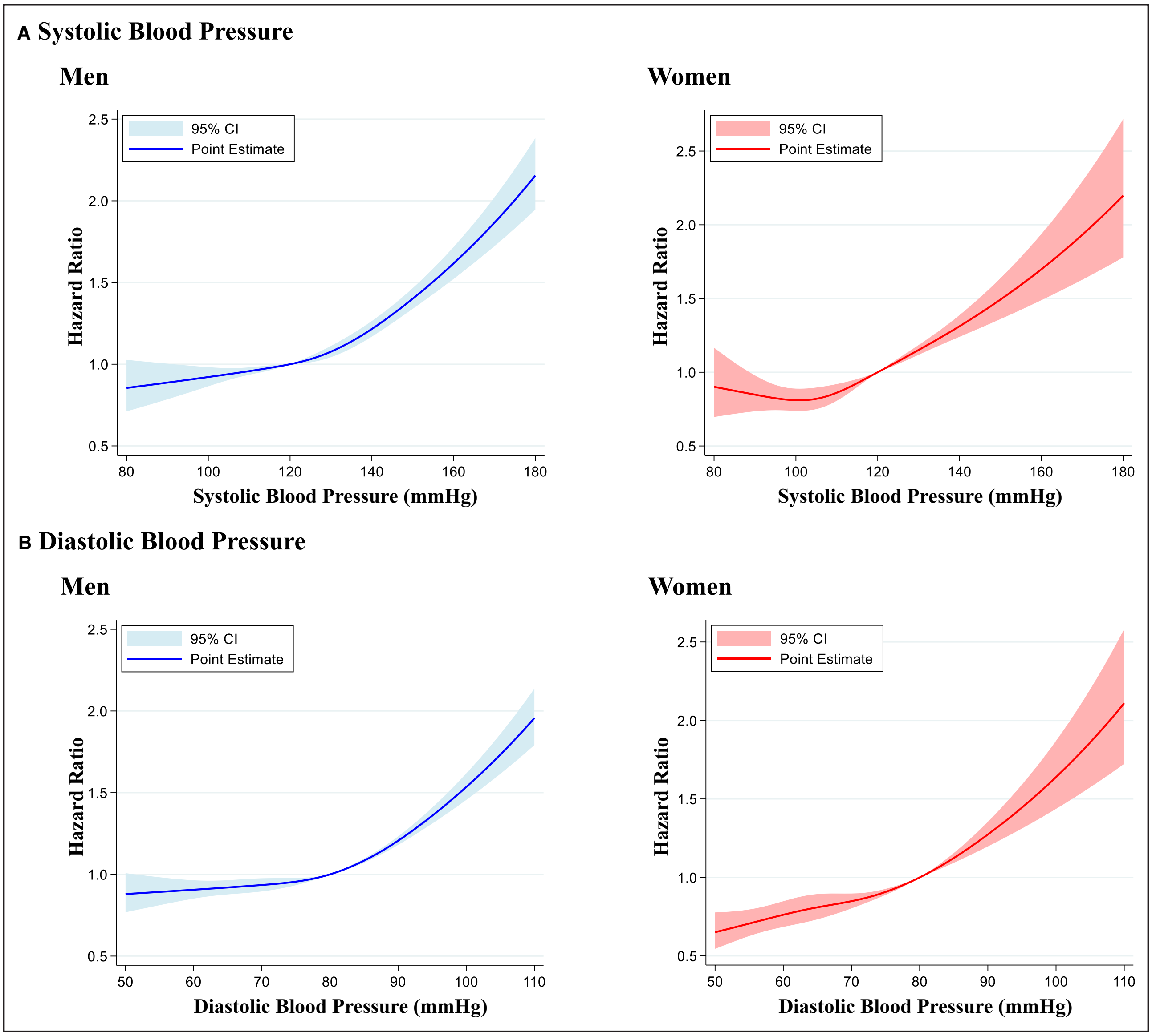

Figure 2. Restricted cubic spline.

Restricted cubic spline of systolic blood pressure (**A**) and diastolic blood pressure (**B**) in the incidence of atrial fibrillation. We used 4 knots for change in systolic blood pressure (5, 35, 65, and 95 percentiles), with the reference point set at systolic blood pressure of 120 mm Hg and diastolic blood pressure of 80 mm Hg. The hazard ratio of systolic or diastolic blood pressure as a continuous variable was adjusted for age, obesity, diabetes, dyslipidemia, cigarette smoking, and alcohol consumption.

relationship. Second, there are various sex differences in the pathological mechanisms of AF (including structural, electrophysiological, and hormonal factors),[23] which may explain our results. For example, sex differences in atrial anatomy or tissue fibrosis are involved in sex-specific responses to hypertension in the development of AF.[24,25] Third, recent advances in basic research have also identified possible sex differences in the pathology of hypertension.[26] For example, the anti-inflammatory profile is greater in females as a compensatory mechanism for hypertension, and this enhanced anti-inflammatory response would be mediated by angiotensin type 2 receptor.[26] Disruption of such regulatory mechanisms may be greater in women than in men, and induce not only hypertension, but also the development of AF. The underlying pathological link between hypertension and AF could explain the sex difference in the relationship between hypertension and incident AF.

Our study has several strengths and clinical implications. Our data set included a large sample size with high retention attributable to the linkage of insurance records, which enabled various sensitivity analyses that strengthened the robustness of our results. Although the incidence of AF was lower in women, our results underscore the importance of BP control in women for the primary AF prevention and should not underestimate the clinical significance of BP in both men and women. Results of subgroup analyses are also important. Subgroup analysis stratified by age showed that the interaction between sex and BP as risk factors for incident AF was most significant in the subgroup of individuals <50 years of age. This might be attributable to a potential complex interaction on the risk of hypertension and AF between age and sex,[27,28] and we need further investigations regarding this point. Subgroup analysis stratified by alcohol consumption showed that the sex-specific relationship between medication-naïve BP and incident AF was more pronounced in people with daily alcohol consumption. Unfortunately, our data set lacks detailed information on alcohol consumption (eg, amount of alcohol consumption), and thus, it is difficult to deepen this result any further. However, given that alcohol drinking is involved in the pathogenesis of both hypertension and AF, and given the results from our subgroup analysis, further studies are needed to explore sex differences in the cardiovascular effects of alcohol consumption. It is also essential that in both men and women, the risk of AF started to increase from BP values much lower than the SBP/DBP of 140/90 mm Hg, which is the classical cut-off value for diagnosing hypertension. Indeed, SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated that intensive BP-lowering treatment in patients with hypertension reduced the risk of AF.[29] Furthermore, the results of cubic spline suggest that the optimal BP value would be lower in women than in men. Therefore, our results would be helpful in determining target BP values from the point of view of AF prevention. Because of the retrospective nature of this study, we cannot conclude a causal relationship, and further investigations are required to identify adequate BP management for both men and women from the perspective of primary AF prevention.

This study had several limitations that should be addressed. Most limitations of this study are common to other studies using this health checkup and administrative claims database, as we described previously.[6,14,15] We used BP data measured at health checkups and conducted BP measurement on a single occasion, which may not fully represent the BP phenotype of study participants. Although health care professionals (eg, nurses) are requested to measure BP according to the standardized protocol of the Ministry of Health, Labor, and Welfare, adherence to this protocol might be lenient in a busy clinical setting. Because the JMDC Claims Database primarily includes employed working-age individuals, a selection bias (healthy worker bias) should be considered, and our results need to be validated by other independent data sets. In addition, when compared with countries with a diversity of ethnicities such as the United States, Japan is a relatively homogeneous country; this fact should be considered when our results are applied to other populations. Although we performed multivariable Cox regression analyses, we could not eliminate potential unmeasured confounders and residual bias (eg, salt intake, socioeconomic status, and psychological factors). Moreover, while the accuracy of recorded diagnoses in an administrative claims data set was reported to be high in Japan,[30,31] the recorded diagnoses of administrative data sets should generally be considered as less well-validated. In this study, we focused on the sex difference in the association between medication-naïve BP and the risk of developing AF. However, it is interesting that this sex difference was seemingly attenuated if we included people taking BP-lowering medications as shown in Table S3 and we need further investigations regarding the potential sex difference in the association of BP on BP-lowering treatment and the subsequent risk of AF. Although we used a large-scale database, the number of AF events in women was relatively small, and thus, the CIs for the results in women were wide.

CONCLUSIONS

We analyzed a large-scale health checkup and administrative claims database and found that elevated BP, stage 1 hypertension, and stage 2 hypertension were associated with a higher subsequent risk of AF in both men and women. However, the relationship between the BP category and incident AF was more pronounced in women than in men, suggesting a sex difference in the association between hypertension and incident AF. Therefore, we may need to recognize the significance of hypertension, particularly in women, in the primary prevention of AF.

ARTICLE INFORMATION

Received March 24, 2022; accepted January 19, 2023.

Affiliations

The Department of Cardiovascular Medicine (S.K., H.K., Y.S., S.M., K.F., N.T., H.M., I.K.) and The Department of Advanced Cardiology (H.K., K.F.), The University of Tokyo, Tokyo, Japan; Department of Advanced Epidemiology, NCD Epidemiology Research Center, Shiga University of Medical Science, Shiga, Japan (Y.Y.); The Department of Family Medicine and Community Health, Duke University, Durham, NC (Y.Y.); Center for Outcomes Research and Economic Evaluation for Health, National Institute of Public Health, Saitama, Japan (Y.S.); Department of Prevention of Diabetes and Lifestyle-Related Diseases, Graduate School of Medicine (A.O.) and The Department of Health Services Research (N.M., T.J.), The University of Tokyo, Tokyo, Japan; Department of Cardiovascular Medicine, Saga University, Saga, Japan (K.N.); and The Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan (H.Y.).

Sources of Funding

This work was supported by the grants from the Ministry of Health, Labor and Welfare, Japan (21AA2007), and the Ministry of Education, Culture, Sports, Science and Technology, Japan (20H03907, 21H03159, and 21K08123). The funding sources were not related to the current study.

Disclosures

Research funding and scholarship funds (Hidehiro Kaneko and Katsuhito Fujiu) were provided by Medtronic Japan Co., LTD, Boston Scientific Japan Co., LTD, Biotronik Japan, Simplex QUANTUM Co., LTD, and Fukuda Denshi, Central Tokyo CO., LTD.

Supplemental Material

Data S1
Tables S1–S6

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639. doi: 10.1161/CIR.0000000000001052
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125. doi: 10.1161/CIRCULATIONAHA.105.595140
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–2375. doi: 10.1001/jama.285.18.2370
4. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112:1142–1147. doi: 10.1016/j.amjcard.2013.05.063
5. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751. doi: 10.1093/eurheartj/eht280
6. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, et al. Association of blood pressure classification using the 2017 American College of Cardiology/American Heart Association blood pressure guideline with risk of heart failure and atrial fibrillation. *Circulation*. 2021;143:2244–2253. doi: 10.1161/CIRCULATIONAHA.120.052624
7. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med*. 1995;98:476–484. doi: 10.1016/S0002-9343(99)80348-9
8. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154–162. doi: 10.1016/S0140-6736(14)61774-8
9. Ko D, Rahman F, Martins MA, Hylek EM, Ellinor PT, Schnabel RB, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: treatment. *Nat Rev Cardiol*. 2017;14:113–124. doi: 10.1038/nrcardio.2016.171
10. Scheuermeyer FX, Mackay M, Christenson J, Grafstein E, Pourvali R, Heslop C, MacPhee J, Ward J, Heilbron B, McGrath L, et al. There are sex differences in the demographics and risk profiles of emergency department (ED) patients with atrial fibrillation and flutter, but no apparent differences in ED management or outcomes. *Acad Emerg Med*. 2015;22:1067–1075. doi: 10.1111/acem.12750
11. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952. doi: 10.1161/01.CIR.98.10.946
12. Volgman AS, Manankil MF, Mookherjee D, Trohman RG. Women with atrial fibrillation: greater risk, less attention. *Gend Med*. 2009;6:419–432. doi: 10.1016/j.genm.2009.09.008
13. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis*. 2015;241:211–218. doi: 10.1016/j.atherosclerosis.2015.01.027
14. Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, et al. Association of isolated diastolic hypertension based on the cutoff value in the 2017 American College of Cardiology/American Heart Association blood pressure guidelines with subsequent cardiovascular events in the general population. *J Am Heart Assoc*. 2020;9:e017963. doi: 10.1161/JAHA.120.017963
15. Matsuoka S, Kaneko H, Yano Y, Itoh H, Fukui A, Morita K, Kiriyama H, Kamon T, Fujiu K, Seki H, et al. Association between blood pressure classification using the 2017 ACC/AHA blood pressure guideline and retinal atherosclerosis. *Am J Hypertens*. 2021;34:1049–1056. doi: 10.1093/ajh/hpab074
16. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018;138:e484–e594. doi: 10.1161/CIR.0000000000000596
17. Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Morita H, et al. Association of body weight gain with subsequent cardiovascular event in non-obese general population without overt cardiovascular disease. *Atherosclerosis*. 2020;308:39–44. doi: 10.1016/j.atherosclerosis.2020.05.015
18. Yagi M, Yasunaga H, Matsui H, Morita K, Fushimi K, Fujimoto M, Koyama T, Fujitani J. Impact of rehabilitation on outcomes in patients with ischemic stroke: a nationwide retrospective cohort study in Japan. *Stroke*. 2017;48:740–746. doi: 10.1161/STROKEAHA.116.015147
19. Aloisio KM, Swanson SA, Micali N, Field A, Horton NJ. Analysis of partially observed clustered data using generalized estimating equations and multiple imputation. *Stata J*. 2014;14:863–883. doi: 10.1177/1536867X1401400410
20. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;10:585–598. doi: 10.1002/sim.4780100410
21. Morita K, Ono S, Ishimaru M, Matsui H, Naruse T, Yasunaga H. Factors affecting discharge to home of geriatric intermediate care facility residents in Japan. *J Am Geriatr Soc*. 2018;66:728–734. doi: 10.1111/jgs.15295
22. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133:601–609. doi: 10.1161/CIRCULATIONAHA.115.017719
23. Odening KE, Deiss S, Dilling-Boer D, Didenko M, Eriksson U, Nedios S, Ng FS, Roca Luque I, Sanchez Borque P, Vernooy K, et al. Mechanisms of sex differences in atrial fibrillation: role of hormones and differences in electrophysiology, structure, function, and remodelling. *Europace*. 2019;21:366–376. doi: 10.1093/europace/euy215
24. Forleo GB, Tondo C, De Luca L, Dello Russo A, Casella M, De Sanctis V, Clementi F, Fagundes RL, Leo R, Romeo F, et al. Gender-related differences in catheter ablation of atrial fibrillation. *Europace*. 2007;9:613–620. doi: 10.1093/europace/eum144
25. Cochet H, Mouries A, Nivet H, Sacher F, Derval N, Denis A, Merle M, Relan J, Hocini M, Haissaguerre M, et al. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. *J Cardiovasc Electrophysiol*. 2015;26:484–492. doi: 10.1111/jce.12651
26. Gillis EE, Sullivan JC. Sex differences in hypertension: recent advances. *Hypertension*. 2016;68:1322–1327. doi: 10.1161/HYPERTENSIONAHA.116.06602
27. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27:949–953. doi: 10.1093/eurheartj/ehi825
28. Ostchega Y, Fryar CD, Nwankwo T, Nguyen DT. Hypertension prevalence among adults aged 18 and over: United States, 2017–2018. *NCHS Data Brief*. 2020;364:1–8.
29. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, Ghazi L, Blackshear JL, Chonchol M, Fine LJ, et al. Effect of intensive blood pressure lowering on the risk of atrial fibrillation. *Hypertension*. 2020;75:1491–1496. doi: 10.1161/HYPERTENSIONAHA.120.14766
30. Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. *J Epidemiol*. 2017;27:476–482. doi: 10.1016/j.je.2016.09.009
31. Fujihara K, Yamada-Harada M, Matsubayashi Y, Kitazawa M, Yamamoto M, Yaguchi Y, Seida H, Kodama S, Akazawa K, Sone H. Accuracy of Japanese claims data in identifying diabetes-related complications. *Pharmacoepidemiol Drug Saf*. 2021;30:594–601. doi: 10.1002/pds.5213

SUPPLEMENTAL MATERIAL

Data S1. Methods of Blood Pressure Measurement

1. The auscultation method should use an accurately calibrated mercury or aneroid sphygmomanometer. A calibrated electronic sphygmomanometer can also be used.

2. Healthcare professionals should choose the correct cuff size and wrap the cuff around the arm, with the center of the cuff bladder over the brachial artery. The stethoscope, standard sphygmomanometers, and cuff and bulb should be checked regularly to ensure that BP measurements have a standardized high level of accuracy and precision. The appropriate BP cuff size should be determined by measuring the participant's arm circumference at the mid-point between the acromion and olecranon. A cuff with a bladder 13 cm wide and 22–24 cm long should be used for the auscultation method. A pediatric cuff should be used for a brachial girth less than 27 cm, and a large adult cuff for an arm girth ≥34 cm.

3. Caffeine, eating, heavy physical activity, smoking, and talking should be avoided before measurement.

4. Research staff should measure right-arm brachial artery blood pressure two times after the participant had been sitting in a quiet room for 5 minutes in a seated position on a chair with back support and the participant's legs uncrossed. The inner aspect of the bend at the elbow (cubital fossa) should be maintained at heart level.

5. Measurement: The cuff should rapidly be inflated while palpating the radial or brachial artery, and the stethoscope should be applied once the pressure in the blood pressure cuff has risen to 20-30 mmHg or more above the level at which the radial (or brachial) arterial pulse is no longer palpable. Then, the cuff should be slowly deflated (2 mmHg per second). Staff should record the 1st and 5th Korotkoff sounds, rounding the pressure in mmHg to the nearest even number and recording it.

6. The measurements should be performed two times at an interval of ≥ 1 min, and the mean value of two measurements that provide stable values (difference in the values: <5 mmHg) should be used for the analyses.

Table S1. Alternative Blood Pressure Categorization and Atrial Fibrillation Stratified by Sex

	Men				Women				
	Normal/Elevated BP	Isolated Diastolic Hypertension	Isolated Systolic Hypertension	Systolic Diastolic Hypertension	Normal/Elevated BP	Isolated Diastolic Hypertension	Isolated Systolic Hypertension	Systolic Diastolic Hypertension	P for interaction
No. of Individuals	1,187,598	278,915	94,058	383,137	1,138,541	107,489	52,192	141,808	-------
No. of Events	4,816	1,868	620	3,297	1,716	266	178	502	-------
Incidence (10000 person-years)	11.9 (11.6-12.3)	18.5 (17.7-19.3)	19.5 (18.0-21.1)	24.5 (23.7-25.3)	4.9 (4.7-5.2)	8.3 (7.4-9.4)	11.1 (9.6-12.9)	12.0 (11.0-13.0)	-------
Model 1	1 [Reference]	1.54 (1.46-1.63)	1.62 (1.49-1.77)	2.04 (1.95-2.13)	1 [Reference]	1.69 (1.48-1.92)	2.24 (1.92-2.62)	2.42 (2.19-2.68)	0.0002
Model 2	1 [Reference]	1.24 (1.17-1.30)	1.36 (1.25-1.48)	1.41 (1.35-1.48)	1 [Reference]	1.39 (1.22-1.58)	1.38 (1.18-1.62)	1.60 (1.45-1.77)	0.0894
Model 3	1 [Reference]	1.19 (1.12-1.25)	1.31 (1.20-1.42)	1.31 (1.25-1.38)	1 [Reference]	1.38 (1.21-1.57)	1.37 (1.17-1.60)	1.57 (1.42-1.75)	0.0097

Model 1=Unadjusted Model. Model 2=Adjusted for age. Model 3=Adjusted for age, body mass index, diabetes mellitus, dyslipidemia, cigarette smoking, and alcohol consumption.

Table S2. Subgroup Analysis of Alternative Blood Pressure Categorization and Atrial Fibrillation Stratified by Sex

Age ≥ 50 years									
	Men				Women				
	Normal/Elevated BP	Isolated Diastolic Hypertension	Isolated Systolic Hypertension	Systolic Diastolic Hypertension	Normal/Elevated BP	Isolated Diastolic Hypertension	Isolated Systolic Hypertension	Systolic Diastolic Hypertension	P for interaction
No. of Individuals	263,019	100,875	28,015	173,059	276,587	40,512	30,943	79,496	-------
No. of Events	2,559	1,107	411	2,198	796	144	130	345	-------
Incidence (10000 person-years)	27.8 (26.7-28.9)	31.4 (29.6-33.3)	44.7 (40.5-49.2)	38.2 (36.7-39.9)	9.8 (9.2-10.6)	12.4 (10.6-14.6)	15.3 (12.8-18.1)	15.8 (14.2-17.6)	-------
Model 1	1 [Reference]	1.13 (1.05-1.21)	1.61 (1.45-1.78)	1.38 (1.30-1.46)	1 [Reference]	1.27 (1.06-1.51)	1.55 (1.29-1.87)	1.61 (1.42-1.83)	0.1023
Model 2	1 [Reference]	1.16 (1.09-1.25)	1.36 (1.23-1.51)	1.31 (1.24-1.39)	1 [Reference]	1.27 (1.06-1.52)	1.24 (1.03-1.50)	1.46 (1.29-1.66)	0.2354
Model 3	1 [Reference]	1.13 (1.05-1.21)	1.32 (1.18-1.46)	1.24 (1.17-1.31)	1 [Reference]	1.25 (1.05-1.49)	1.22 (1.01-1.47)	1.41 (1.24-1.61)	0.1615
Age < 50 years									
	Men				Women				
	Normal/Elevated BP	Isolated Diastolic Hypertension	Isolated Systolic Hypertension	Systolic Diastolic Hypertension	Normal/Elevated BP	Isolated Diastolic Hypertension	Isolated Systolic Hypertension	Systolic Diastolic Hypertension	P for interaction
No. of Individuals	924,579	178,040	66,043	210,078	861,954	66,977	21,249	62,312	-------
No. of Events	2,257	761	209	1,099	920	122	48	157	-------
Incidence (10000 person-years)	7.2 (7.0-7.6)	11.6 (10.8-12.4)	9.3 (8.1-10.6)	14.2 (13.4-15.1)	3.5 (3.2-3.7)	6.0 (5.0-7.2)	6.4 (4.8-8.5)	7.8 (6.7-9.1)	-------
Model 1	1 [Reference]	1.57 (1.45-1.70)	1.25 (1.08-1.44)	1.91 (1.78-2.06)	1 [Reference]	1.74 (1.44-2.10)	1.81 (1.35-2.42)	2.24 (1.89-2.65)	0.0581
Model 2	1 [Reference]	1.31 (1.20-1.42)	1.36 (1.18-1.57)	1.58 (1.47-1.70)	1 [Reference]	1.57 (1.30-1.90)	1.60 (1.20-2.14)	1.89 (1.59-2.24)	0.1053

Model 3	1 [Reference]	1.24 (1.14-1.35)	1.29 (1.12-1.48)	1.43 (1.32-1.54)	1 [Reference]	1.58 (1.31-1.92)	1.62 (1.21-2.17)	1.91 (1.59-2.28)	0.0068

Model 1=Unadjusted Model. Model 2=Adjusted for age. Model 3=Adjusted for age, body mass index, diabetes mellitus, dyslipidemia, cigarette smoking, and alcohol consumption.

Table S3. Blood Pressure Category and Atrial Fibrillation Stratified by Sex including individuals with taking antihypertensive medications

	Men				Women				
	Normal Blood Pressure	Elevated Blood Pressure	Stage 1 Hypertension	Stage 2 Hypertension	Normal Blood Pressure	Elevated Blood Pressure	Stage 1 Hypertension	Stage 2 Hypertension	P for interaction
No. of Individuals	886,696	362,403	570,015	335,554	992,612	180,759	228,589	129,025	-------
No. of Events	3,857	1,903	4,424	3,891	1,464	464	711	590	-------
Incidence (10000 person-years)	12.8 (12.4-13.2)	15.7 (15.0-16.4)	21.7 (21.1-22.4)	34.3 (33.3-35.4)	4.9 (4.6-5.1)	8.4 (7.7-9.2)	10.3 (9.5-11.0)	16.2 (14.9-17.5)	-------
Model 1	1 [Reference]	1.23 (1.16-1.30)	1.70 (1.62-1.77)	2.69 (2.57-2.81)	1 [Reference]	1.73 (1.55-1.92)	2.11 (1.93-2.31)	3.35 (3.04-3.69)	<0.001
Model 2	1 [Reference]	1.15 (1.09-1.22)	1.28 (1.23-1.34)	1.68 (1.61-1.76)	1 [Reference]	1.27 (1.14-1.41)	1.41 (1.29-1.55)	1.85 (1.68-2.05)	0.1525
Model 3	1 [Reference]	1.11 (1.05-1.17)	1.20 (1.15-1.26)	1.52 (1.45-1.60)	1 [Reference]	1.24 (1.12-1.38)	1.38 (1.25-1.51)	1.78 (1.60-1.93)	0.0175
Model 4	1 [Reference]	1.09 (1.03-1.15)	1.16 (1.11-1.22)	1.45 (1.39-1.52)	1 [Reference]	1.22 (1.10-1.36)	1.31 (1.19-1.44)	1.64 (1.47-1.82)	0.0694

Model 1=Unadjusted Model. Model 2=Adjusted for age. Model 3=Adjusted for age, body mass index, diabetes mellitus, dyslipidemia, cigarette smoking, and alcohol consumption. Model 4=Adjusted for age, body mass index, diabetes mellitus, dyslipidemia, cigarette smoking, alcohol consumption, and the presence of antihypertensive medications.

Table S4. Blood Pressure Category and Atrial Fibrillation Stratified by Sex after Multiple Imputations

	Men				Women				
	Normal Blood Pressure	Elevated Blood Pressure	Stage 1 Hypertension	Stage 2 Hypertension	Normal Blood Pressure	Elevated Blood Pressure	Stage 1 Hypertension	Stage 2 Hypertension	P for interaction
No. of Individuals	1,023,634	411,638	585,119	311,154	1,115,074	192,088	227,479	115,207	-------
No. of Events	3,939	1,800	3,808	3,179	1,565	439	597	476	-------
Incidence (10000 person-years)	10.7 (10.4-11.1)	12.3 (11.7-12.9)	17.2 (16.7-17.8)	28.7 (27.8-29.8)	4.5 (4.3-4.7)	7.2 (6.6-7.9)	8.4 (7.7-9.1)	14.2 (13.0-15.6)	-------
Model 1	1 [Reference]	1.14 (1.08-1.20)	1.59 (1.52-1.66)	2.67 (2.55-2.80)	1 [Reference]	1.60 (1.44-1.78)	1.86 (1.69-2.04)	3.18 (2.87-3.52)	<0.001
Model 2	1 [Reference]	1.14 (1.07-1.20)	1.25 (1.19-1.31)	1.71 (1.63-1.80)	1 [Reference]	1.24 (1.11-1.38)	1.32 (1.20-1.46)	1.89 (1.70-2.11)	0.1433
Model 3	1 [Reference]	1.10 (1.04-1.17)	1.19 (1.13-1.24)	1.58 (1.50-1.66)	1 [Reference]	1.24 (1.11-1.38)	1.31 (1.19-1.45)	1.87 (1.68-2.09)	0.0259

Model 1=Unadjusted Model. Model 2=Adjusted for age. Model 3=Adjusted for age, body mass index, diabetes mellitus, dyslipidemia, cigarette smoking, and alcohol consumption.

Table S5. Blood Pressure Category and Atrial Fibrillation Stratified by Sex using the cause-specific Cox proportional hazard modeling

	Men				Women				
	Normal Blood Pressure	Elevated Blood Pressure	Stage 1 Hypertension	Stage 2 Hypertension	Normal Blood Pressure	Elevated Blood Pressure	Stage 1 Hypertension	Stage 2 Hypertension	P for interaction
No. of Individuals	851,494	336,104	491,293	264,817	971,120	167,421	199,296	102,193	-------
No. of Events	3,326	1,490	3,160	2,625	1,345	371	532	414	-------
Incidence (10000 person-years)	11.4 (11.1-11.8)	13.2 (12.6-13.9)	17.8 (17.2-18.4)	29.1 (28.0-30.3)	4.6 (4.3-4.8)	7.2 (6.5-8.0)	8.7 (8.0-9.5)	14.3 (13.0-15.7)	-------
Model 1	1 [Reference]	1.15 (1.08-1.23)	1.54 (1.47-1.62)	2.54 (2.41-2.67)	1 [Reference]	1.57 (1.40-1.77)	1.91 (1.73-2.12)	3.16 (2.83-3.53)	<0.001
Model 2	1 [Reference]	1.13 (1.06-1.20)	1.23 (1.17-1.29)	1.68 (1.59-1.76)	1 [Reference]	1.22 (1.08-1.37)	1.38 (1.24-1.52)	1.91 (1.70-2.14)	0.1066
Model 3	1 [Reference]	1.10 (1.03-1.17)	1.17 (1.11-1.23)	1.55 (1.47-1.63)	1 [Reference]	1.22 (1.08-1.37)	1.37 (1.23-1.52)	1.89 (1.68-2.12)	0.0076

Model 1=Unadjusted Model. Model 2=Adjusted for age. Model 3=Adjusted for age, body mass index, diabetes mellitus, dyslipidemia, cigarette smoking, and alcohol consumption.

Table S6. Blood Pressure Category and Atrial Fibrillation Stratified by Sex after additional adjustment for use of sex hormones and modulators of the genital system medications

	Men				Women				
	Normal Blood Pressure	Elevated Blood Pressure	Stage 1 Hypertension	Stage 2 Hypertension	Normal Blood Pressure	Elevated Blood Pressure	Stage 1 Hypertension	Stage 2 Hypertension	P for interaction
No. of Individuals	851,494	336,104	491,293	264,817	971,120	167,421	199,296	102,193	-------
No. of Events	3,326	1,490	3,160	2,625	1,345	371	532	414	-------
Incidence (10000 person-years)	11.4 (11.1-11.8)	13.2 (12.6-13.9)	17.8 (17.2-18.4)	29.1 (28.0-30.3)	4.6 (4.3-4.8)	7.2 (6.5-8.0)	8.7 (8.0-9.5)	14.3 (13.0-15.7)	-------
Model 1	1 [Reference]	1.15 (1.08-1.23)	1.54 (1.47-1.62)	2.54 (2.41-2.67)	1 [Reference]	1.57 (1.40-1.77)	1.91 (1.73-2.12)	3.16 (2.83-3.53)	<0.001
Model 2	1 [Reference]	1.13 (1.06-1.20)	1.23 (1.17-1.29)	1.68 (1.59-1.76)	1 [Reference]	1.22 (1.09-1.37)	1.38 (1.24-1.52)	1.91 (1.70-2.14)	0.1525
Model 3	1 [Reference]	1.10 (1.03-1.17)	1.17 (1.11-1.23)	1.55 (1.47-1.63)	1 [Reference]	1.22 (1.08-1.37)	1.37 (1.23-1.52)	1.89 (1.68-2.13)	0.0073

The association between blood pressure category and atrial fibrillation stratified by sex is summarized. The incidence is presented in in 10000 person-years. Model 1=Unadjusted Model. Model 2=Adjusted for age. Model 3=Adjusted for age, body mass index, diabetes mellitus, dyslipidemia, cigarette smoking, alcohol consumption, and use of sex hormones and modulators of the genital system medications.