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Non-genetic risk factors for atrial fibrillation are equally important in both young and old age: A nationwide population-based study

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Abstract

Aims: There are several non-genetic risk factors for new-onset atrial fibrillation, including age, sex, obesity, hypertension, diabetes, and alcohol consumption. However, whether these non-genetic risk factors have equal significance among different age groups is not known. We performed a nationwide population-based analysis to compare the clinical significance of non-genetic risk factors for new-onset atrial fibrillation in various age groups.

Methods and results: A total of 9,797,409 people without a prior diagnosis of atrial fibrillation who underwent a national health check-up in 2009 were included. During 80,130,090 person-years of follow-up, a total of 196,136 people were diagnosed with new-onset atrial fibrillation. The impact of non-genetic risk factors on new-onset atrial fibrillation was examined in different age groups. Obesity, male sex, heavy alcohol consumption, smoking, hypertension, diabetes and chronic kidney disease were associated with an increased risk of new-onset atrial fibrillation. With minor variations, these risk factors were consistently associated with the risk of new-onset atrial fibrillation among various age groups. Using these risk factors, we created a scoring system to predict future risk of new-onset atrial fibrillation in different age groups. In receiver operating characteristic curve analysis, the predictive value of these risk factors ranged between 0.556 and 0.603, and no significant trends were observed.

Conclusions: Non-genetic risk factors for new-onset atrial fibrillation may have a similar impact on different age groups. Except for sex, these non-genetic risk factors can be modifiable. Therefore, efforts to control non-genetic risk factors might have relevance for both the young and old.

Keywords

Atrial fibrillation, risk factors, primary prevention, upstream therapy

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Introduction

Atrial fibrillation, the most frequent tachyarrhythmia, is a significant global health burden.[1,2] There are two major problems related to atrial fibrillation: (a) symptoms that impair quality of life and (b) major adverse cardiovascular events such as ischemic stroke, systemic embolism, congestive heart failure and increased overall mortality.[3–8] Substantial efforts have been made to treat atrial fibrillation and manage its complications, but the underlying pathophysiology and best

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approaches for primary prevention of atrial fibrillation deserve more attention.[9,10]

There are established risk factors for atrial fibrillation such as age, sex, body-mass index, systolic blood pressure, hypertension, PR interval, clinically significant cardiac murmur, heart failure and genetic predisposition.[11,12] Age is one of the most important risk factors for new-onset atrial fibrillation, with older people having a significantly higher risk than young people.[13] Although atrial fibrillation is relatively rare in young people, it is challenging to manage, especially when the atrial fibrillation is highly symptomatic and uncontrolled. Various side effects limit lifelong antiarrhythmic drug therapy, and the use of radiofrequency catheter ablation in young patients is undermined due to the potential risk of decreased left atrial function.[14,15] Therefore, identification of potential risk factors for new-onset atrial fibrillation in young people is critical, as it could enable primary prevention of atrial fibrillation in these people.

It is generally assumed that new-onset atrial fibrillation in young people is more often due to genetic predisposition as compared with elderly people.[16,17] However, the relative contribution of non-genetic risk factors and genetic risk factors in young and old has not yet been determined. Furthermore, whether established risk factors of atrial fibrillation such as hypertension, diabetes mellitus, obesity, heavy alcohol consumption and sex status are equally important in young people has not been addressed, mainly due to the small sample size in previous studies.[13] We performed this population-based analysis to evaluate the influence of non-genetic risk factors in various age groups.

Methods

Patients

The Korean National Health Insurance Service (K-NHIS) database was used for this study. The majority of Koreans (97.1%) are mandatory subscribers to the K-NHIS, a single medical insurer in the Republic of Korea that is managed by the government. Consequently, the K-NHIS database represents the entire population of the Republic of Korea, and contains baseline demographics, diagnosis codes of various diseases, use of inpatient and outpatient services, pharmacy dispensing claims and mortality data. The K-NHIS offers a regular national health check-up for all subscribers that includes the following: a health questionnaire including alcohol consumption, smoking status and physical activity; laboratory tests such as lipid profile, serum creatinine and fasting blood sugar (FBS); and measurement of blood pressure, body weight, height and waist circumference. The database is open for medical researchers if study protocols are approved by the official review committee (https://nhiss.nhis.or.kr/).

Participants who underwent a national health check-up in 2009 were included in this study. The screening period was from January 2002 to December 2008. The screening period was used to identify medical history such as atrial fibrillation, hypertension, diabetes or dyslipidemia in a given people. The follow-up period was from the date of the national health check-up to the date of new-onset occurrence of atrial fibrillation or December 2017 if no new-onset atrial fibrillation was detected. Patients were excluded if they had already been diagnosed with atrial fibrillation during the screening period or if they were younger than 20 years old. Since diagnostic codes related to atrial fibrillation were retrieved, we were able to analyze the impact of non-genetic risk factors for atrial fibrillation throughout various age groups using a large number of patients with a sufficient follow-up duration.

Definitions

The diagnosis of atrial fibrillation required two outpatient records or one inpatient record of International Classification of Disease, Tenth Revision (ICD-10) codes in the K-NHIS database. The robustness of this definition has been validated in previous studies.[18,19] The exact diagnosis codes for atrial fibrillation and other diseases are described in Supplementary Material Table S1 online.

Body weight status was classified into five groups according to body mass index (BMI): underweight ($BMI < 18.5$ (kg/m^2)), normal reference ($18.5 \leq BMI < 23.0$), upper normal ($23.0 \leq BMI < 25.0$), overweight ($25.0 \leq BMI < 30.0$) and obese ($BMI \geq 30.0$). Waist circumference (WC) was also utilized to complement BMI and was classified into six stages: (a) $WC < 80.0$ (cm), $80.0 \leq WC < 85.0$, $85.0 \leq WC < 90.0$, $90.0 \leq WC < 95.0$, $95.0 \leq WC < 100.0$, and $WC \geq 100.0$ for males and (b) $WC < 75.0$, $75.0 \leq WC < 80.0$, $80.0 \leq WC < 85.0$, $85.0 \leq WC < 90.0$, $90.0 \leq WC < 95.0$, and $WC \geq 95.0$ for females.

Smoking status was defined as follows: 1) current-smokers were those who had smoked at least 100 cigarettes in their lifetime, and continued smoking within one month of the 2009 national health check-up; 2) ex-smokers were those who had smoked at least 100 cigarettes in their lifetime, but had not smoked within one month of the 2009 national health check-up; and 3) never-smokers were those who had smoked <100 cigarettes in their lifetime.

Based on the total amount of alcohol intake per week, patients were classified as follows: (a)

non-drinker, 0 g of alcohol per week; (b) mild- to moderate-drinker, less than 210 g but more than 0 g of alcohol per week; and (c) heavy-drinker, 210 g or more of alcohol per week.

Diabetes was classified into four stages: non-diabetic (FBS $<$ 100 mg/dl), impaired fasting glucose (IFG) (fasting blood sugar 100–125 mg/dl), new-onset diabetes (first detection of fasting blood sugar $\geq$126 mg/dl or physician-diagnosed diabetes) and diabetes requiring medication.

Hypertension was classified into three stages: (a) hypertension, either systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg; (b) pre-hypertension, either 120 mmHg $\leq$SBP $<$ 140 mmHg or 80 mmHg $\leq$SBP $<$ 90 mmHg; and (c) non-hypertension, SBP $<$ 120 mmHg and DBP $<$80 mmHg.

Chronic kidney disease was diagnosed if the estimated glomerular filtration rate was $<$60 ml/min per 1.73 m^2.

Based on a questionnaire acquired during nationwide health check-up, people who had one or more sessions in a week with high (such as running, climbing, intense bicycle activities) or moderate physical activity (such as walking fast, tennis, moderate bicycle activities) were assumed to have regular physical activity.

Age

People were classified according to their age at 2009 when they had a national health check-up by decades: 20s, 30s, 40s, 50s, 60s and $\geq$70 years old. The impacts of non-genetic risk factors on new-onset atrial fibrillation were tested on the different age groups.

Study endpoints

The occurrence of new-onset atrial fibrillation was the endpoint of this study. The incidence of new-onset atrial fibrillation was defined as the number of new-onset atrial fibrillation cases calculated for 1000 patient-years of follow-up. The impact of the aforementioned non-genetic risk factors was evaluated in various age groups.

Statistical analysis

Student's *t*-test was used to compare continuous variables, which are described as mean $\pm$ standard deviation. Categorical variables are presented as percentile values and were compared with a chi-square test or Fisher's exact test as appropriate. Univariate and multivariate Cox regression analyses were performed to calculate the hazard ratio and its 95% confidence interval for each independent variable. A multivariate model was adjusted for age, sex, alcohol consumption, smoking status, physical activity, income level, diabetes, hypertension, dyslipidemia and chronic kidney disease. Receiver operating characteristic (ROC) curve analysis with area under curve (AUC) calculation was performed to evaluate the predictive value of non-genetic risk factors. All tests were two-tailed, and p values $\leq$0.05 were considered statistically significant. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina, USA).

Results

Patients

A total of 9,797,409 patients were included in the analysis, with a total of 80,130,090 person-years of follow-up. A flowchart of study population enrollment is summarized in Figure 1. Baseline clinical characteristics of study patients stratified by age group are summarized in Table 1. Significant differences in all baseline characteristics were observed among the different age groups. However, our main analysis was performed for each age group separately.

Waist circumference and BMI

The impact of BMI and waist circumference on new-onset atrial fibrillation is summarized in Table 2. Overweight and obesity had significantly higher risks for new-onset atrial fibrillation in patients who were $\geq$30 years old. In 20s, overweight and obesity was not associated with increased risk of new-onset atrial fibrillation and the impact of obesity on new-onset atrial fibrillation was more pronounced in old age people (p for interaction $<$0.001). Underweight was associated with an increased risk of new-onset atrial fibrillation in patients who were $\geq$60 years old. The risk of new-onset atrial fibrillation increased gradually as waist circumference increased in patients who were $\geq$40 years old. Such association was weakened in the 30s and not obvious in the 20s. In the subgroup analysis, similar trends were observed for both men and women. However, underweight was associated with new-onset atrial fibrillation in male patients $\geq$60 years old and not in females.

Sex, smoking, alcohol and regular exercise

The association between sex and lifestyles with new-onset atrial fibrillation is described in Table 3. Throughout all age groups, female sex was associated with a decreased risk of new-onset atrial fibrillation. Current-smokers aged between 30 and 70 years had an increased risk of new-onset atrial fibrillation. Ex-smokers were at increased risk of new-onset atrial fibrillation if they were 30 to 60 years old. In subgroup

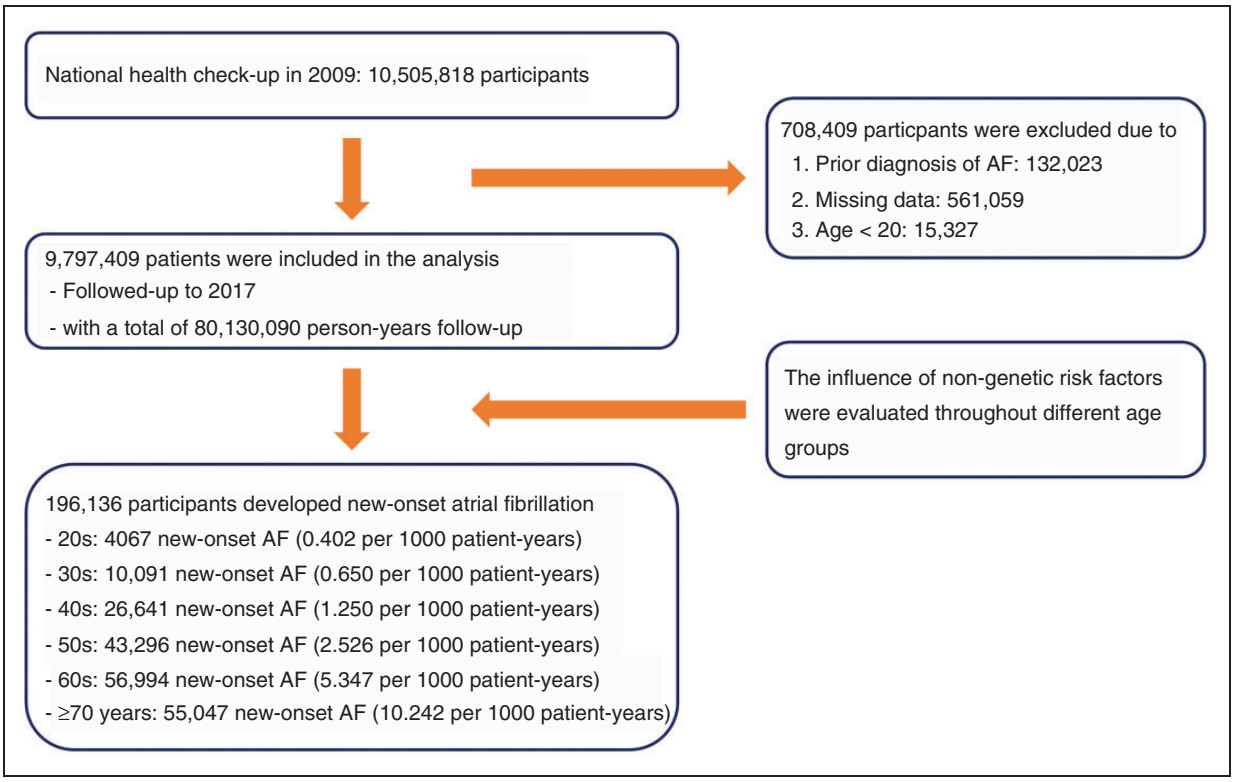

Figure 1. Flowchart of the study.
AF: atrial fibrillation

analysis, smoking had more deleterious effects on female patients throughout the various age groups. Heavy-drinkers had a significantly increased risk of new-onset atrial fibrillation if they were ≥30 years old. No significant association was observed in the 20 s. Mild- to moderate-drinkers showed increased risk of atrial fibrillation only if they were ≥60 years old. In the subgroup analysis, the association between heavy-drinking and new-onset atrial fibrillation was weakened in female patients. Regular exercise was associated with a decreased risk of new-onset atrial fibrillation in patients who were ≥50 years old.

Metabolic disorders

The associations between metabolic disorders and new-onset atrial fibrillation are summarized in Table 4. Pre-hypertension was associated with an increased risk of new-onset atrial fibrillation among all age groups except for those ≥70 years old. Presence of hypertension significantly increased the risk of new-onset atrial fibrillation in all age groups. There was a trend towards higher risk in younger patients (p for interaction <0.001). Similar trends were observed for both sex categories. Diabetes requiring medication was a strong risk factor for new-onset atrial fibrillation and the degree of increased risk was higher in young patients (p for interaction <0.001). Diabetic patients not taking medication were also at increased risk of new-onset atrial fibrillation, but to a lesser degree than those taking medication. In addition to overt diabetes, IFG was also a significant risk factor for new-onset atrial fibrillation in patients who were 20 to 50 years old. Increased low-density lipoprotein level was not associated with new-onset atrial fibrillation. Chronic kidney disease was associated with a significantly increased risk of new-onset atrial fibrillation in patients ≥30 years old. The hazard ratios of different non-genetic risk factors in various age groups are depicted in Figure 2.

Predictive value of non-genetic risk factors

Non-genetic risk factors including waist circumference, sex, smoking history, alcohol consumption pattern, hypertension, diabetes and chronic kidney disease were used to create a scoring system for the prediction of future risk of new-onset atrial fibrillation (Table 5). Risk score allocation was based on hazard ratios obtained from multivariate Cox-regression model for each risk factor (Tables 2–4) and feasibility of calculation was also considered. In the ROC curve analysis,

Table 1. Baseline demographic of patients with and without diabetes.

	20s $n = 1{,}218{,}426$	30s $n = 1{,}874{,}612$	40s $n = 2{,}580{,}705$	50s $n = 2{,}085{,}182$	60s $n = 1{,}320{,}850$	≥70 s $n = 717{,}634$	p value
Male sex	638,193 (52.38%)	1,362,762 (72.7%)	1,370,866 (53.12%)	1,027,291 (49.27%)	639,645 (48.43%)	318183 (44.34%)	<0.001
Smoking							<0.001
Non-smoker	737,478 (60.53%)	832,138 (44.39%)	1,508,675 (58.46%)	1,318,282 (63.22%)	903,831 (68.43%)	531,660 (74.09%)	
Ex-smoker	91,851 (7.54%)	268,576 (14.33%)	386,463 (14.98%)	336,353 (16.13%)	209,992 (15.9%)	100,933 (14.06%)	
Current-smoker	389,097 (31.93%)	773,898 (41.28%)	685,567 (26.57%)	430,547 (20.65%)	207,027 (15.67%)	85,041 (11.85%)	
Alcohol consumption							<0.001
Non-drinker	442,180 (36.29%)	670,169 (35.75%)	1,242,796 (48.16%)	1,220,977 (58.55%)	905,354 (68.54%)	555,695 (77.43%)	
Mild-drinker	683,114 (56.07%)	1,043,687 (55.67%)	1,141,393 (44.23%)	731,916 (35.10%)	351,233 (26.59%)	136,174 (18.98%)	
Heavy-drinker	93,132 (7.64%)	160,756 (8.58%)	196,516 (7.61%)	132,289 (6.34%)	64,263 (4.87%)	25,765 (3.59%)	
Regular exercise, yes	654,066 (53.68%)	1,042,880 (55.63%)	1,409,515 (54.62%)	1,069,003 (51.27%)	602,023 (45.58%)	244,624 (34.09%)	<0.001
Income, lower quartile	407,740 (33.46%)	370,802 (19.78%)	655,943 (25.42%)	601,574 (28.85%)	397,824 (30.12%)	156,781 (21.85%)	<0.001
Hypertension							<0.001
Non-hypertension	805,606 (66.12%)	1,022,744 (54.56%)	1,334,215 (51.70%)	828,175 (39.72%)	372,468 (28.20%)	151,688 (21.14%)	
Pre-hypertension	357,414 (29.33%)	661,378 (35.28%)	790,550 (30.63%)	570,336 (27.35%)	289,194 (21.89%)	126,939 (17.69%)	
Hypertension	55,406 (4.55%)	190,490 (10.16%)	455,940 (17.67%)	686,671 (32.93%)	659,188 (49.91%)	439,007 (61.17%)	
Dyslipidemia	49,014 (4.02%)	184,830 (9.86%)	374,554 (14.51%)	540,235 (25.91%)	411,777 (31.18%)	213,150 (29.70%)	<0.001
Diabetes stages							<0.001
Non-diabetic	1,061,859 (87.15%)	1,461,546 (77.97%)	1,810,669 (70.16%)	1,287,465 (61.74%)	732,280 (55.44%)	385,264 (53.69%)	
Impaired fasting glucose	145,338 (11.93%)	361,080 (19.26%)	614,985 (23.83%)	554,367 (26.59%)	352,996 (26.72%)	186,713 (26.02%)	
New-onset diabetes	9,538 (0.78%)	37,928 (2.02%)	78,598 (3.05%)	81,525 (3.91%)	51,554 (3.90%)	28,274 (3.94%)	
Diabetes on medication	1,691 (0.14%)	14,058 (0.75%)	76,453 (2.96%)	161,825 (7.76%)	184,020 (13.93%)	117,383 (16.36%)	
Age, years	26.19 ± 2.31	34.46 ± 2.90	44.24 ± 2.99	53.81 ± 2.76	63.90 ± 2.85	74.33 ± 4.22	<0.001
Height, cm	167.97 ± 8.40	169.27 ± 7.97	164.36 ± 8.34	161.66 ± 8.20	159.4 ± 8.32	156.00 ± 9.06	<0.001
Weight, kg	63.37 ± 13.31	68.13 ± 12.79	64.49 ± 11.20	63.21 ± 10.05	61.75 ± 9.50	57.64 ± 9.85	<0.001
Body mass index, kg/m^2	22.30 ± 3.49	23.65 ± 3.41	23.77 ± 3.04	24.12 ± 2.92	24.27 ± 2.99	23.64 ± 3.22	<0.001
Waist circumference, cm	75.12 ± 9.66	79.89 ± 9.29	79.58 ± 8.73	81.36 ± 8.27	83.08 ± 8.08	83.00 ± 8.58	<0.001
Systolic blood pressure, mmHg	116.23 ± 12.41	119.84 ± 13.12	120.56 ± 14.22	124.00 ± 15.03	128.15 ± 15.67	130.74 ± 16.38	<0.001
Diastolic blood pressure, mmHg	72.70 ± 8.77	75.41 ± 9.45	76.00 ± 10.16	77.61 ± 10.12	78.27 ± 9.95	78.18 ± 10.10	<0.001
Fasting glucose, mg/dl	88.38 ± 12.87	92.68 ± 17.61	96.67 ± 22.09	100.68 ± 25.81	103.08 ± 26.76	103.19 ± 26.61	<0.001
Total cholesterol, mg/dl	178.40 ± 31.51	191.13 ± 34.65	195.91 ± 35.09	203.22 ± 37.35	200.36 ± 38.32	197.27 ± 38.81	<0.001
High-density lipoprotein, mg/dl	59.07 ± 16.55	54.71 ± 16.59	55.49 ± 17.75	55.15 ± 18.53	54.25 ± 21.48	53.90 ± 25.79	<0.001

Table 2. Waist circumference and body mass index.

	All patients					
Age group	20s	30s	40s	50s	60s	≥70s
WC						
80/75	0.801 (0.709–0.905)	0.834 (0.776–0.895)	0.828 (0.791–0.866)	0.847 (0.818–0.877)	0.901 (0.874–0.929)	0.981 (0.953–1.011)
85/80	0.861 (0.752–0.986)	0.932 (0.867–1.002)	0.930 (0.889–0.972)	0.923 (0.893–0.954)	0.925 (0.899–0.951)	0.985 (0.957–1.014)
90/85	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
95/90	0.954 (0.795–1.146)	1.028 (0.941–1.123)	1.128 (1.072–1.188)	1.146 (1.106–1.186)	1.101 (1.070–1.132)	1.072 (1.042–1.104)
100/95	1.161 (0.928–1.454)	1.110 (0.990–1.245)	1.186 (1.107–1.270)	1.282 (1.226–1.340)	1.222 (1.181–1.264)	1.187 (1.148–1.228)
100–/95–	1.014 (0.782–1.316)	1.529 (1.353–1.729)	1.408 (1.294–1.532)	1.487 (1.407–1.571)	1.477 (1.419–1.538)	1.315 (1.265–1.368)
BMI						
<18.5	0.986 (0.855–1.138)	1.016 (0.881–1.171)	1.072 (0.951–1.208)	0.972 (0.874–1.081)	1.142 (1.062–1.229)	1.109 (1.055–1.165)
18.5–23	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
23–25	1.142 (1.029–1.266)	1.008 (0.943–1.077)	1.059 (1.016–1.103)	1.035 (1.003–1.068)	1.024 (0.997–1.051)	1.013 (0.988–1.039)
25–30	1.083 (0.973–1.206)	1.067 (1.002–1.137)	1.163 (1.118–1.210)	1.190 (1.155–1.225)	1.153 (1.125–1.181)	1.108 (1.082–1.135)
30–	1.123 (0.923–1.366)	1.306 (1.176–1.450)	1.380 (1.282–1.485)	1.512 (1.432–1.596)	1.551 (1.483–1.622)	1.392 (1.325–1.462)
	Male patients					
WC						
80/75	0.779 (0.679–0.893)	0.805 (0.746–0.869)	0.799 (0.755–0.845)	0.842 (0.804–0.882)	0.903 (0.867–0.940)	1.003 (0.962–1.045)
85/80	0.836 (0.721–0.969)	0.918 (0.851–0.990)	0.919 (0.872–0.968)	0.922 (0.885–0.961)	0.951 (0.917–0.987)	1.005 (0.964–1.046)
90/85	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
95/90	0.978 (0.804–1.189)	1.019 (0.930–1.117)	1.120 (1.056–1.188)	1.159 (1.110–1.210)	1.113 (1.072–1.156)	1.122 (1.075–1.171)
100/95	1.213 (0.954–1.542)	1.126 (1.000–1.267)	1.212 (1.120–1.311)	1.316 (1.245–1.392)	1.243 (1.185–1.304)	1.243 (1.179–1.310)
100–/95–	1.011 (0.756–1.354)	1.524 (1.340–1.734)	1.471 (1.333–1.624)	1.583 (1.473–1.701)	1.533 (1.444–1.627)	1.291 (1.207–1.381)
BMI						
<18.5	0.794 (0.585–1.078)	0.989 (0.807–1.212)	0.884 (0.734–1.064)	0.957 (0.835–1.097)	1.170 (1.070–1.281)	1.193 (1.117–1.274)
18.5–23	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
23–25	1.099 (0.974–1.239)	1.002 (0.932–1.078)	1.053 (1.000–1.110)	1.025 (0.985–1.068)	1.009 (0.976–1.044)	1.001 (0.967–1.036)
25–30	1.084 (0.961–1.223)	1.084 (1.013–1.160)	1.172 (1.116–1.230)	1.176 (1.133–1.221)	1.121 (1.085–1.158)	1.095 (1.058–1.133)
30–	1.152 (0.926–1.435)	1.354 (1.212–1.512)	1.435 (1.311–1.571)	1.538 (1.427–1.658)	1.527 (1.420–1.641)	1.366 (1.239–1.506)
	Female patients					
WC						
80/75	0.924 (0.690–1.237)	1.057 (0.846–1.320)	0.878 (0.812–0.948)	0.854 (0.809–0.901)	0.900 (0.859–0.944)	0.959 (0.919–1.001)
85/80	1.020 (0.725–1.434)	1.108 (0.859–1.430)	0.961 (0.882–1.046)	0.924 (0.875–0.975)	0.890 (0.851–0.929)	0.968 (0.929–1.009)
90/85	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

(continued)

Table 2. Continued.

	All patients					
Age group	20s	30s	40s	50s	60s	≥70s
95/90	0.810 (0.481–1.363)	1.166 (0.830–1.638)	1.159 (1.043–1.289)	1.121 (1.055–1.190)	1.084 (1.039–1.131)	1.031 (0.991–1.073)
100/95	0.895 (0.475–1.687)	0.924 (0.579–1.475)	1.109 (0.961–1.279)	1.222 (1.135–1.315)	1.194 (1.137–1.254)	1.147 (1.097–1.199)
100–/95–	1.065 (0.591–1.919)	1.644 (1.104–2.447)	1.263 (1.076–1.482)	1.358 (1.247–1.478)	1.422 (1.346–1.502)	1.312 (1.250–1.377)
BMI						
<18.5	1.050 (0.890–1.239)	1.047 (0.855–1.282)	1.244 (1.063–1.455)	0.992 (0.837–1.176)	1.084 (0.955–1.231)	1.007 (0.935–1.086)
18.5–23	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
23–25	1.257 (1.023–1.544)	1.056 (0.892–1.251)	1.069 (0.999–1.144)	1.047 (0.997–1.100)	1.045 (1.003–1.088)	1.027 (0.991–1.065)
25–30	0.954 (0.735–1.237)	0.917 (0.757–1.111)	1.138 (1.063–1.219)	1.205 (1.150–1.263)	1.194 (1.150–1.239)	1.121 (1.085–1.158)
30–	0.926 (0.587–1.461)	0.923 (0.649–1.313)	1.258 (1.107–1.428)	1.470 (1.359–1.590)	1.576 (1.487–1.671)	1.404 (1.325–1.488)

Hazard ratios are adjusted for age, sex, smoking status, alcohol consumption, physical activity, income level, hypertension, diabetes, dyslipidemia and chronic kidney disease.
BMI: body-mass index; WC: waist circumference.

non-genetic risk factors were able to predict the future risk of new-onset atrial fibrillation in all age groups. AUC values were between 0.556 and 0.603, suggesting that non-genetic risk factors predicted a similar risk of atrial fibrillation across all age groups (Table 5).

Discussion

The primary finding of our study is that non-genetic risk factors for new-onset atrial fibrillation were important in both young and old people. However, the relative importance of each risk factor was not equal among the various age groups. Due to its significantly large sample size, our study was powered to evaluate various risk factors for new-onset atrial fibrillation in different age groups. According to our study, the non-genetic portion of the underlying pathophysiology of new-onset atrial fibrillation might be similar between young and old people, and modifying non-genetic risk factors can be equally important regardless of age.

Body weight status and new-onset atrial fibrillation

In accordance with previous reports, BMI and waist circumference were significant risk factors for new-onset atrial fibrillation.[11,20] We found that the influence of BMI and waist circumference was maintained throughout different age groups, except for the 20s. Furthermore, a previously reported increased risk of new-onset atrial fibrillation in low BMI people (<18.5 kg/m^2) was observed in only those who were ≥ 60 years old.[21] We also observed that the impact of higher BMI was more profound in older people (Table 2).

Social risk factors

Female sex was associated with a decreased risk of new-onset atrial fibrillation throughout all age groups, with some variation in degree of protection; females in their 50s or 60s had the lowest hazard ratio compared with males. The reason for the lower risk of new-onset atrial fibrillation in females is not fully understood. Since various risk factors such as body weight status, alcohol consumption, hypertension or diabetes mellitus were adjusted in our study, the decreased risk of new-onset atrial fibrillation in females might originate from hormonal effects, socioeconomic stress or genetic predisposition.

Previous studies report increased risk of new-onset atrial fibrillation in well-trained athletes.[22,23] However, our study showed that regular physical activity in the general population was associated with a decreased risk of new-onset atrial fibrillation in people 50 years or older and had a neutral effect in younger people.

Table 3. Sex, smoking, alcohol, and regular exercise.

	All patients					
Age group	20s	30s	40s	50s	60s	≥70s
Female sex	0.836 (0.756–0.925)	0.805 (0.742–0.874)	0.810 (0.774–0.848)	0.700 (0.678–0.724)	0.717 (0.698–0.736)	0.744 (0.726–0.762)
Smoking history						
Current-smoker	1.026 (0.932–1.130)	1.087 (1.019–1.159)	1.054 (1.007–1.103)	1.062 (1.026–1.100)	1.086 (1.054–1.119)	1.024 (0.991–1.059)
Ex-smoker	1.102 (0.960–1.265)	1.184 (1.096–1.278)	1.107 (1.053–1.163)	1.066 (1.029–1.105)	1.011 (0.982–1.042)	1.006 (0.977–1.037)
Non-smoker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Alcohol intake						
Heavy-drinker	0.959 (0.830–1.108)	1.126 (1.032–1.228)	1.069 (1.010–1.131)	1.218 (1.166–1.272)	1.192 (1.144–1.243)	1.154 (1.098–1.213)
Mild- to moderate-drinker	0.879 (0.807–0.957)	0.959 (0.906–1.016)	0.945 (0.912–0.980)	1.005 (0.978–1.034)	1.030 (1.006–1.056)	1.035 (1.009–1.063)
Non-drinker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Regular exercise	1.046 (0.969–1.130)	1.034 (0.984–1.087)	0.991 (0.960–1.023)	0.952 (0.930–0.975)	0.951 (0.933–0.970)	0.938 (0.919–0.957)
	Male patients					
Smoking history						
Current-smoker	1.026 (0.922–1.141)	1.078 (1.008–1.152)	1.015 (0.967–1.065)	1.035 (0.998–1.074)	1.069 (1.036–1.104)	0.986 (0.950–1.023)
Ex-smoker	1.142 (0.975–1.337)	1.179 (1.089–1.277)	1.076 (1.022–1.133)	1.044 (1.006–1.084)	0.994 (0.964–1.025)	0.999 (0.969–1.031)
Non-smoker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Alcohol intake						
Heavy-drinker	1.013 (0.862–1.191)	1.133 (1.035–1.240)	1.091 (1.026–1.160)	1.235 (1.180–1.294)	1.192 (1.142–1.244)	1.155 (1.098–1.216)
Mild- to moderate-drinker	0.903 (0.806–1.011)	0.958 (0.898–1.022)	0.972 (0.928–1.017)	1.019 (0.986–1.054)	1.028 (1.000–1.056)	1.026 (0.996–1.057)
Non-drinker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Regular exercise	1.080 (0.980–1.190)	1.053 (0.997–1.112)	1.024 (0.985–1.066)	0.959 (0.931–0.988)	0.945 (0.921–0.969)	0.923 (0.898–0.950)
	Female patients					
Smoking history						
Current-smoker	1.081 (0.835–1.399)	1.335 (1.019–1.750)	1.378 (1.203–1.578)	1.249 (1.128–1.382)	1.162 (1.058–1.276)	1.221 (1.132–1.317)
Ex-smoker	0.940 (0.690–1.279)	1.081 (0.766–1.525)	1.184 (0.971–1.442)	1.233 (1.060–1.434)	1.343 (1.181–1.526)	0.966 (0.862–1.083)
Non-smoker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Alcohol intake						
Heavy-drinker	0.627 (0.394–1.000)	0.770 (0.409–1.450)	1.097 (0.857–1.404)	1.125 (0.912–1.388)	1.210 (0.923–1.585)	1.153 (0.819–1.622)
Mild- to moderate-drinker	0.844 (0.741–0.961)	0.961 (0.848–1.089)	0.899 (0.845–0.956)	0.980 (0.932–1.031)	1.044 (0.993–1.098)	1.079 (1.022–1.139)
Non-drinker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Regular exercise	0.989 (0.871–1.123)	0.945 (0.838–1.066)	0.936 (0.888–0.987)	0.942 (0.908–0.978)	0.961 (0.933–0.990)	0.954 (0.927–0.983)

Hazard ratios are adjusted for age, sex, waist circumference, smoking status, alcohol consumption, physical activity, income level, hypertension, diabetes, dyslipidemia and chronic kidney disease.

Table 4. Hypertension, diabetes mellitus, dyslipidemia and chronic kidney disease.

	All patients					
Age group	20s	30s	40s	50s	60s	≥70s
Hypertension						
Hypertension	1.634 (1.398–1.910)	1.777 (1.653–1.911)	1.637 (1.573–1.703)	1.454 (1.413–1.496)	1.406 (1.370–1.442)	1.298 (1.262–1.334)
Pre-hypertension	1.256 (1.154–1.366)	1.192 (1.128–1.259)	1.177 (1.133–1.223)	1.065 (1.030–1.101)	1.045 (1.011–1.080)	1.000 (0.964–1.037)
Non-hypertension	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Diabetes mellitus						
Diabetes on medication	2.351 (1.355–4.080)	1.426 (1.194–1.703)	1.256 (1.179–1.338)	1.100 (1.062–1.140)	1.017 (0.990–1.043)	0.973 (0.949–0.999)
New-onset diabetes	1.895 (1.408–2.552)	1.229 (1.065–1.419)	1.171 (1.086–1.263)	1.069 (1.013–1.127)	1.006 (0.959–1.055)	1.015 (0.967–1.065)
Impaired fasting glucose	1.327 (1.197–1.471)	1.219 (1.151–1.290)	1.103 (1.064–1.143)	1.010 (0.984–1.038)	1.003 (0.98–1.026)	1.002 (0.979–1.025)
Non-diabetes	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Dyslipidemia						
LDL ≥150 mg/dl on statin	0.912 (0.761–1.093)	0.974 (0.902–1.051)	1.011 (0.970–1.054)	0.965 (0.939–0.992)	0.891 (0.871–0.911)	0.886 (0.866–0.907)
LDL ≥150 mg/dl without statin	0.895 (0.812–0.987)	0.879 (0.831–0.930)	0.918 (0.885–0.951)	0.864 (0.840–0.888)	0.843 (0.822–0.864)	0.855 (0.834–0.876)
LDL < 150 mg/dl	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Chronic kidney disease	1.043 (0.855–1.273)	1.207 (1.059–1.377)	1.049 (0.977–1.127)	1.263 (1.207–1.321)	1.227 (1.195–1.260)	1.173 (1.147–1.200)
	Male patients					
Hypertension						
Hypertension	1.545 (1.300–1.837)	1.725 (1.598–1.863)	1.565 (1.490–1.644)	1.380 (1.329–1.433)	1.369 (1.321–1.418)	1.230 (1.184–1.279)
Pre-hypertension	1.327 (1.201–1.466)	1.185 (1.116–1.258)	1.137 (1.085–1.192)	1.036 (0.993–1.081)	1.061 (1.016–1.108)	0.990 (0.941–1.040)
Non-hypertension	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Diabetes mellitus						
Diabetes on medication	2.466 (1.272–4.780)	1.466 (1.218–1.766)	1.258 (1.169–1.353)	1.090 (1.043–1.138)	1.020 (0.986–1.056)	0.975 (0.939–1.013)
New-onset diabetes	1.882 (1.350–2.626)	1.230 (1.059–1.428)	1.194 (1.099–1.297)	1.056 (0.993–1.123)	1.014 (0.957–1.075)	1.050 (0.983–1.121)
Impaired fasting glucose	1.341 (1.190–1.511)	1.221 (1.149–1.298)	1.076 (1.031–1.123)	1.019 (0.986–1.055)	1.013 (0.982–1.044)	0.991 (0.959–1.024)
Non-diabetes	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Dyslipidemia						
LDL ≥150 mg/dl on statin	0.902 (0.731–1.112)	0.958 (0.884–1.038)	0.979 (0.931–1.029)	0.978 (0.944–1.014)	0.911 (0.883–0.939)	0.913 (0.883–0.945)
LDL ≥150 mg/dl without statin	0.894 (0.795–1.005)	0.862 (0.811–0.916)	0.901 (0.862–0.941)	0.853 (0.823–0.884)	0.849 (0.822–0.877)	0.867 (0.837–0.898)
LDL < 150 mg/dl	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Chronic kidney disease	0.994 (0.739–1.337)	1.245 (1.069–1.450)	1.069 (0.978–1.169)	1.274 (1.202–1.351)	1.229 (1.182–1.277)	1.157 (1.116–1.200)
	Female patients					
Hypertension						
Hypertension	2.522 (1.743–3.648)	2.361 (1.883–2.960)	1.771 (1.655–1.896)	1.560 (1.493–1.629)	1.450 (1.396–1.506)	1.375 (1.320–1.431)
Pre-hypertension	1.052 (0.889–1.246)	1.193 (1.032–1.378)	1.250 (1.170–1.335)	1.097 (1.040–1.158)	1.017 (0.967–1.070)	1.013 (0.960–1.069)

(continued)

Table 4. Continued.

	All patients					
Age group	20s	30s	40s	50s	60s	≥70s
Non-hypertension	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Diabetes mellitus						
Diabetes on medication	2.056 (0.757–5.583)	1.099 (0.597–2.023)	1.226 (1.079–1.393)	1.127 (1.060–1.198)	1.012 (0.973–1.052)	0.971 (0.937–1.006)
New-onset diabetes	1.934 (0.996–3.758)	1.290 (0.781–2.131)	1.032 (0.855–1.246)	1.119 (1.005–1.246)	0.992 (0.911–1.079)	0.978 (0.911–1.050)
Impaired fasting glucose	1.286 (1.046–1.582)	1.200 (1.014–1.420)	1.170 (1.096–1.248)	0.993 (0.949–1.038)	0.991 (0.957–1.026)	1.012 (0.981–1.045)
Non-diabetes	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Dyslipidemia						
LDL ≥ 150 mg/dl on statin	0.946 (0.662–1.352)	1.105 (0.861–1.418)	1.091 (1.009–1.178)	0.946 (0.905–0.989)	0.868 (0.839–0.897)	0.864 (0.838–0.891)
LDL ≥ 150 mg/dl without statin	0.901 (0.756–1.074)	0.988 (0.853–1.145)	0.951 (0.893–1.011)	0.879 (0.839–0.920)	0.831 (0.800–0.863)	0.841 (0.814–0.870)
LDL < 150 mg/dl	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Chronic kidney disease	1.102 (0.842–1.443)	1.103 (0.853–1.427)	1.014 (0.902–1.141)	1.243 (1.158–1.334)	1.222 (1.178–1.269)	1.184 (1.150–1.219)

Hazard ratios are adjusted for age, sex, waist circumference, smoking status, alcohol consumption, physical activity, income level, hypertension, diabetes, dyslipidemia and chronic kidney disease.
LDL: low-density lipoprotein.

Therefore, regular exercise can be recommended to the general population, especially those who are ≥50 years old.

The impact of smoking needs further validation. A recent meta-analysis reported an increased risk of new-onset atrial fibrillation in smokers.[24] The univariate analysis in our study also revealed a significantly increased risk of new-onset atrial fibrillation throughout all age groups to a similar degree found in the previous meta-analysis.[24] However, this association was significantly weakened after multivariate adjustment to a 5.4–8.7% increase in people aged between 30 and 69 years.

Previous study suggested that maintaining normal body weight, stop smoking and reducing alcohol intake were associated with a significant reduction in the risk of new-onset atrial fibrillation.[25] Physical activity was able to offset some, although not all, risk of new-onset atrial fibrillation associated with obesity.[26] The importance of these adequate lifestyle modifications should be kept in mind in both physicians and atrial fibrillation patients. Increased incidence of atrial fibrillation-related emergency department visit due to short-term exposure to particulate matter ≤2.5 μm raises concern about the atrial fibrillation-triggering effect of air pollutants and is an important area of future research.[27]

Metabolic disorders

In accordance with previous studies, hypertension and diabetes mellitus were significant risk factors for new-onset atrial fibrillation.[19,20] Our study revealed that such increased risk was maintained throughout different age groups but to a different degree; the increased risk was most profound in young people (Table 4). Pre-hypertension and IFG were also associated with new-onset atrial fibrillation but to a lesser degree. Our results indicate that prevention and control of hypertension and diabetes mellitus are important in young people to prevent new-onset atrial fibrillation.

Interestingly, high low-density lipoprotein (LDL) was not associated with an increased risk of new-onset atrial fibrillation in our cohort. The univariate analysis showed some association between high LDL and new-onset atrial fibrillation in people aged between 30 and 59 years old. However, such associations were lost after multivariate adjustment.

Young versus old age

Genetic predisposition is generally considered to have a bigger impact in younger people. However, we found that non-genetic risk factors for new-onset

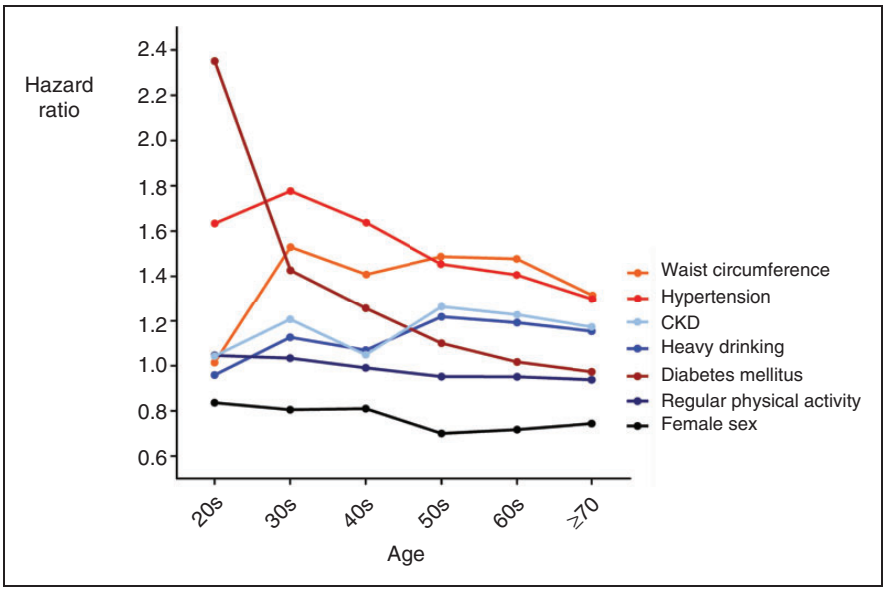

Figure 2. Relative importance of each risk factor.
Hazard ratios of each risk factor are depicted for different age groups.
CKD: chronic kidney disease

Table 5. Risk prediction model for new-onset atrial fibrillation.

A: Scoring system	Score
Age, years	
20 ≤ age < 30	0
30 ≤ age < 40	1
40 ≤ age < 50	2
50 ≤ age < 60	3
60 ≤ age < 70	4
Age ≥ 70	5
Sex	
Male	1
Body mass index	
<18.5	1
18.5–23	0
23–25	0
25–30	1
30–	2
Hypertension	
Non-hypertension	0
Pre-hypertension	1
Hypertension	2
Diabetes	
Non-diabetic	0
Impaired fasting glucose	1
Diabetes	2
Alcohol consumption	
Non- to moderate-drinker	0
Heavy-drinker	1
Smoking	
Non-smoker	0
Ex- or current-smoker	0.5
Chronic kidney disease	
No	0
Yes	1
Score range	
0–15	
B: ROC curve analysis	AUC (95% CI)
20s	0.580 (0.512–0.649)
30s	0.566 (0.517–0.615)
40s	0.603 (0.548–0.658)
50s	0.597 (0.576–0.619)
60s	0.574 (0.564–0.584)
≥70	0.556 (0.545–0.584)
Total, including age	0.747 (0.739–0.755)

Stated variable for ROC curve analysis was new-onset atrial fibrillation occurrence within up to five years of follow-up.
AF: atrial fibrillation; AUC: area under curve; CI: confidence interval; ROC: receiver operating characteristic.

atrial fibrillation were equally important in the young and the old. ROC curve analysis revealed that the predictive value of non-genetic risk factors for new-onset atrial fibrillation did not differ among different age groups. Lifestyle modifications such as maintaining optimal body weight, smoking cessation and reducing alcohol consumption are important regardless of age.

Limitations

The current study has several limitations. First, our analysis was based on a nationwide administrative database. Accordingly, the results might have been contaminated by coding inaccuracies, although our coding strategy has been validated in multiple previous studies.[18–20] Second, our analysis was based on South Korean patients and caution is required when applying our results to other ethnic groups. Third, we were not able to distinguish specific types of atrial fibrillation such as paroxysmal, non-paroxysmal, or valvular atrial fibrillation, which might have different pathophysiology. Identifying unique risk factors for non-paroxysmal atrial fibrillation would guide a more targeted treatment strategy. Fourth, the event number (new-onset atrial fibrillation) was significantly lower in younger people, which may have limited statistical power. Finally, there can be genetic predisposition for hypertension, diabetes, chronic kidney disease and obesity. Therefore, the influence of these risk factors on new-onset atrial fibrillation may not be fully modifiable.

Author contribution

YGK and KDH contributed equally to this work. JIC and YGP had full access to all data in this study and take responsibility for data integrity and analytical accuracy. Concept and design of the study was made by YGK, KDH, JIC, YGP and YHK. Data analysis and interpretation was performed by YGK, KDH, KYB, DYK, JSK and JIC. The manuscript was drafted by YGK, KDH and JIC. Statistical analysis was performed by YGK, KDH, KNL and JIC. Data collection was performed by YGK, KDH, JS and JIC.

Declaration of conflicting interests

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