

# Risk factor modification reduced incidence of atrial fibrillation in an 18-year prospective cohort study: a time-updated analysis

**Mi Kyoung Son**

Korea National Institute of Health

**Dae Sub Song**

Korea National Institute of Health

**Kyoungho Lee**

Korea National Institute of Health

**Hyun-Young Park** (✉ [mdhypark@gmail.com](mailto:mdhypark@gmail.com))

Korea National Institute of Health

---

## Research Article

**Keywords:** atrial fibrillation, modifiable risk factors, time-updated model

**Posted Date:** September 15th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-882356/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

## Background

Although atrial fibrillation (AF) is an increasing health burden worldwide, strategies for AF prevention are lacking. This study aimed to identify modifiable risk factors (MRF) for and estimate their impact on AF risk in the midlife general population.

## Methods

We assessed 9,049 participants who were free of prevalent AF at baseline from the Korean Genome and Epidemiology Study. Cox models with time-varying assessment of risk factors were used to identify significant MRF for incident AF. The MRF burden was defined as the proportion of times presented MRF during follow-up, based on the number of visits.

## Results

Over a median follow-up of 13.1 years, 182 (2.01%) participants developed AF. In time-updated multivariable models accounting for changes in risk factors, three MRF including systolic blood pressure (SBP) more than 140 mmHg, obesity with central obesity, and an inactive lifestyle were significantly associated with incident AF. Compared to subjects with three MRF, those with one or no MRF had a decreased risk of AF (hazard ratio [95% CI] for one MRF, 0.483 [0.256–0.914]; and for no MRF, 0.291 [0.145–0.583]). A decreasing MRF burden was associated with reduced AF risk (hazard ratio [95% CI] per 10% decrease in SBP more than 140 mmHg, 0.937 [0.880–0.997]; in obesity with central obesity, 0.942 [0.907–0.978]; in inactivity, 0.926 [0.882–0.973]).

## Conclusions

Maintenance or achievement of optimal MRF control was associated with decreased AF risk, suggesting that minimizing the burden of MRF might help prevent AF.

## Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia, is a leading cause of mortality and ischemic stroke (1–2). The prevalence of AF is expected to increase due to a growing burden of risk factors, such as an aging population, hypertension, obesity, diabetes mellitus and ischemic heart disease (3). AF also results in significant use of health care resources and causes a substantial economic burden, with AF-related Medicare expenses being approximately \$16 billion annually in the United States (4). Although catheter ablation has been shown to be effective in suppressing AF, it is invasive and has the potential for serious complications despite improved experience and advances in ablation technology (5, 6). Thus, a

focus on primary prevention is a critical component of strategies to control the growing burden of AF at a population level.

Many studies of incident AF have focused primarily on risk prediction, AF treatment and AF-related stroke prevention (6–11). However, there is limited information on preventive strategies to reduce the incidence of AF. Earlier studies on modifiable and non-modifiable risk factors focused mainly on baseline assessment, and the results may therefore have immortal time bias. For primordial prevention interventions, an appropriate level of control of modifiable risk factors (MRF) is important.

In the present study, we aimed to identify the MRF for incident AF using a time-updated model, investigate the cumulative effects of the MRF burden on AF risk, and provide targets for prevention of AF in a longitudinal population-based cohort.

## **Results**

### **Baseline characteristics**

In 9,049 participants without AF at baseline, 182 participants developed new-onset AF over a median follow-up of 13.1 years (range, 1.4 to 16.6 years). Participants with AF, when compared with people who did not develop AF, were more likely to be older, male, rural, to have CVD, higher WC, higher BP, and lower LTPA (Table 1).

Table 1  
Baseline characteristics of study population (n = 9,094)

<b>Variables</b>	<b>No AF (N = 8,867)</b>	<b>AF (N = 182)</b>	<b>P-value</b>
<b>Age, yrs</b>	52.16 ± 8.9	57.95 ± 8.0	< 0.001
<b>Sex, male</b>	4171 (47.0))	122 (67.0)	< 0.001
<b>Area, rural</b>	4582 (51.7)	118 (64.8)	< 0.001
<b>Clinical</b>			
<b>BMI, kg/m<sup>2</sup></b>	24.58 ± 3.1	25.02 ± 3.4	0.063
<b>WC, cm</b>	82.75 ± 8.8	85.50 ± 8.9	< 0.001
<b>BMI and WC category</b>			0.081
Non-obese without central obesity	4577 (51.6)	85 (46.7)	
Obese without central obesity	1632 (18.4)	31 (17.0)	
Non-obese with central obesity	498 (5.6)	7 (3.9)	
Obese with central obesity	2160 (24.4)	59 (32.4)	
<b>Systolic blood pressure, mmHg</b>	121.5 ± 18.2	127.7 ± 20.0	< 0.001
<b>Systolic blood pressure category, mmHg</b>			< 0.001
< 120	4496 (50.7)	68 (37.4)	
120–139	2968 (33.5)	72 (39.6)	
≥140	1403 (15.8)	42 (23.1)	
<b>Diastolic blood pressure, mmHg</b>	80.30 ± 11.3	82.85 ± 11.46	0.003
<b>LTPA, min/week</b>	75.29 ± 164.5	53.78 ± 122.0	0.021
<b>LTPA category</b>			0.206
Inactivity, 0 min/week	6396 (72.1)	139 (76.4)	
Active, > 0 min/week	2471 (27.9)	43 (23.6)	
<b>CKD, eGFR &lt; 60 mL/min</b>	641 (7.2)	16 (8.8)	0.422
<b>CVD</b>	250 (2.8)	15 (8.2)	< 0.001
Continuous variables are reported as mean ± standard deviation, and categorical variables are reported as n (%).			
AF = atrial fibrillation; BMI = body mass index; WC = waist circumference; CKD = chronic kidney disease; CVD = cardiovascular disease; LTPA = leisure time physical activity			

Variables	No AF (N = 8,867)	AF (N = 182)	P-value
<b>Laboratory examinations</b>			
HbA1c, %	5.79 ± 0.9	5.78 ± 0.8	0.957
Total cholesterol, mg/dL	191.10 ± 35.4	188.00 ± 36.1	0.246
Continuous variables are reported as mean ± standard deviation, and categorical variables are reported as n (%).			
AF = atrial fibrillation; BMI = body mass index; WC = waist circumference; CKD = chronic kidney disease; CVD = cardiovascular disease; LTPA = leisure time physical activity			

## Modifiable risk factors for AF

As expected, the incidence rates of AF increased during follow-up (110.10 and 153.55/100,000 person-years in 2003–2004 and 2017–2018, respectively), were consistently higher among males than females, and increased substantially with age (**Table S1**).

In time-updated multivariable models accounting for changes in risk factors after the baseline survey, three MRF (SBP  $\geq$ 140 mmHg, obesity with central obesity, and inactivity) were each significantly associated with the development of incident AF (Table 2). Non-modifiable risk factors associated with new-onset AF included age  $\geq$ 70 years, male sex, and history of CVD. The most significant risk occurred in those with SBP  $\geq$ 140 mmHg (HR: 1.539; 95% CI: 1.007 to 2.350;  $p = 0.046$ ) when compared with SBP < 120 mmHg, and increasing SBP was associated with a significantly increased risk of incident AF (multivariable-adjusted HR: 1.145, 95% CI: 1.051 to 1.247 [per 10 mmHg increase];  $p = 0.002$ , data not shown). To assess the joint impact of obesity and central obesity, subjects were classified into four groups. Obese individuals with central obesity had a higher risk of AF (HR: 1.681; 95% CI: 1.194 to 2.366;  $p = 0.003$ ) compared to non-obese individuals without central obesity. Inactivity, when compared with low or high levels of LTPA (> 0 min/weeks), was associated with a 42% higher risk of AF. At baseline, 81.2% of all participants had at least one MRF associated with AF risk, and the incidence of AF increased markedly with increasing numbers of MRF (**Table S2**).

Table 2  
Risk factors for incident atrial fibrillation using a time-updated model

	<b>Multivariable-Adjusted HR (95% CI)*</b>	<b>P-value</b>
<b>Modifiable risk factors</b>		
<b>Systolic blood pressure, mmHg</b>		
< 120	Reference	
120–139	1.215 (0.874–1.688)	0.246
≥140	1.539 (1.007–2.350)	0.046
<b>Combinations of obesity and central obesity</b>		
Non-obese without central obesity	Reference	
Obese without central obesity	1.166 (0.699–1.945)	0.557
Non-obese with central obesity	1.246 (0.748–2.075)	0.399
Obese with central obesity	1.681 (1.194–2.366)	0.003
<b>LTPA</b>		
Active	Reference	
Inactivity	1.420 (1.042–1.936)	0.026
<b>Other significant risk factors</b>		
<b>Age, ≥70 years</b>	1.653 (1.110–2.462)	0.013
<b>Sex, male</b>	2.635 (1.914–3.628)	< 0.001
<b>Cardiovascular disease</b>	1.841 (1.223–2.771)	0.003
HR = hazard ratio; CI = confidence interval; LTPA = leisure time physical activity		
*Multivariable adjustment was for sex, area and time-updated assessment of age, systolic blood pressure, combinations of obesity and central obesity, LTPA, chronic kidney disease, cardiovascular disease, HbA1c and total cholesterol.		

Additionally, assuming a causal relationship between MRF and AF, 28.7% (95% CI: 14.6–40.4%) of incident AF in the study population was attributable to these three MRF, with inactivity being the greatest contributing risk factor. (Table 3).

Table 3  
The population attributable fractions (PAF) and 95% CI of individual risk factors

Risk factors	PAF (95% CI)
<b>All 3 modifiable risk factors*</b>	28.7 (14.6–40.4)
SBP $\geq$ 140 mmHg	9.5 (2.4–16.1)
Obesity with central obesity	10.7 (2.2–18.4)
No LTPA (inactivity)	15.6 (2.2–27.2)
<b>Age, <math>\geq</math>60 yrs</b>	34.0 (24.3–42.4)
<b>Sex, male</b>	38.4 (27.0–48.1)
<b>CVD</b>	5.8 (1.7–9.8)
*The PAF for all 3 risk factors is numerically smaller than the individual sum of PAF estimates as the summative PAF accounts for overlap in the prevalence of risk factors	
CVD, cardiovascular disease; SBP, systolic blood pressure; LTPA, leisure time of physical activity; CI, confidence interval	

## Optimal levels of modifiable risk factor control for risk reduction of AF

To assess the joint impact and find optimal levels of these MRF to impact on the incidence of AF, we used multivariable adjusted models with time-updated assessment of risk factors after baseline, as well as baseline models (Fig. 1). In the time-updated model, compared with subjects with three MRF, those who maintained or achieved MRF  $\leq$ 1 had a progressively decreased risk of AF (hazard ratio [95% CI] for one MRF, 0.483 [0.256–0.914]; and for no MRF, 0.291 [0.145–0.583]), with a graded reduction in risk across progressively more optimal risk factor levels. Patients with optimal levels of all three modifiable risk factors (SBP  $\geq$ 140 mmHg, obesity with central obesity, inactivity) had a 71% lower risk of incident AF compared with participants with the least favourable risk factor profile (three MRF). These results were similar to those using the baseline model, where participants with  $\leq$ 1 MRF had a lower risk of incident AF compared with participants with three MRF.

## Impact of modifiable risk factor burden on the risk of AF

Figure 2 depicts the risk of AF associated with continuous measures of MRF burden during follow-up, using restricted cubic spline analysis (with a burden of 100% as reference). The proportion of participants with more than two MRF (burden of more than two MRF) was significantly associated with the risk of AF (hazard ratio [95% CI] per 10% decrease, 0.906 [0.865–0.949] (Fig. 2A). In particular, when the burden of more than two MRF is less than two-thirds, the risk of AF decreased more than 50%. Similarly, a decrease in the proportion of each MRF exposure continuously decreased the adjusted risk of AF (hazard ratio [95% CI] per 10% decrease for SBP  $\geq$ 140 mmHg, 0.937 [0.880–0.997]; for obesity with central obesity,

0.942 [0.907–0.978]; for inactivity, 0.926 [0.882–0.973]). In addition, MRF burdens < 72% for high SBP, 89% for obesity with central obesity, and 88% for inactivity lowered the risk of incident AF by more than 50%.

## Discussion

This study had three principal findings. Firstly, in a time-updated model, three MRF (SBP  $\geq$ 140 mmHg, obesity with central obesity, and inactivity) were significant in the midlife general population. Secondly, participants who maintained or achieved an optimal risk factor profile had a significantly reduced risk of AF. These findings highlight the potential population and individual level impact of risk factor modification on AF risk. Thirdly, decreased MRF burden was associated with a decreased risk of AF. Our study shows that reducing the MRF burden and maintenance or achievement of MRF  $\leq$ 1 plays a crucial role in reducing the risk of AF.

Worldwide, a rapid upward trajectory of prevalence and incidence of AF is occurring (12). The global burden-of-disease study highlighted an alarming twofold increase in AF-related mortality between 1990 and 2010 (7), as well as estimated death rates of 20% and 50%, one and five years, respectively, after initial diagnosis of AF in older adults (13). The burden of AF in Asia is rapidly increasing given the proportional increase in the older population (14, 15). In Korea, a large sample cohort study based on nationwide health insurance data showed that the prevalence of AF increased from 0.36% in 2003 to 0.89% in 2013 (16). In addition, hospitalization rates and costs for AF have increased exponentially over the past 10 years, with a decrease in mortality associated with AF hospitalizations (17). AF will represent a significant public health burden in the near future. Thus, strategies for AF prevention are of paramount importance to prevent morbidity, mortality, and complications associated with AF.

Studies have reported that the independent risk factors for incident AF include aging, hypertension, congestive heart failure, coronary artery disease, valvular heart disease, diabetes mellitus, male sex, obesity, and excessive alcohol use (8, 18). Furthermore, increased numbers of unhealthy lifestyle factors, including current smoking, heavy drinking (30 g/day) and lack of regular exercise, were associated with a higher risk of incident AF (19). These risk factors play a crucial role in abnormal atrial remodelling, disease progression, and recurrence (20). Similarly, the current study showed that an SBP of more than 140 mmHg, obesity with central obesity, inactivity for leisure time, aging, male sex, and CVD were significant risk factors for AF incidence. Particularly, 81.2% of all participants had at least one MRF, and 72.2% (n = 6535) had leisure-time inactivity. In addition, 28.7% of incident AF appears to be attributable to these three MRF, with inactivity during leisure time being the greatest contributing risk factor, indicating the importance of MRF management, especially increasing LTPA.

Although studies for risk prediction and treatment of AF have been extensive, AF prevention has received relatively little attention (7–10). Current international guidelines recommend modifying an inappropriate diet, quitting smoking, abstaining from alcohol and recreational drugs, and participating in regular physical activity programs as key health behaviours to prevent the development of AF (10). However,

many earlier studies also usually assessed risk factors and risk prediction of AF using a single measurement for risk factors (baseline cox model) and provided no information regarding risk factor changes during the follow-up period. These results may have immortal time bias, which can lead to overestimation of the outcome event rate in the unexposed group, underestimation of the event rate in the exposed group, or both (21, 22). When incorporating time-updated assessments of directly significant MRF, there is limited information on the association between optimal levels of risk factors and AF risk reduction. Our results showed that maintaining or achieving  $MRF \leq 1$  significantly reduced the risk of AF. In particular, we identified a consistent decrement in AF risk with progressively optimal risk factor profiles, with a striking 71% lowering of AF risk with optimal levels of MRF (reversing SBP of more than 140 mmHg, obesity with central obesity and inactivity for leisure time). Our study suggests that risk factor improvement may decrease AF risk in general population. Similarly, Du X et al. reported that a high proportion of AF can be prevented by combining strategies, focusing on the high-risk population for better risk factor management, and emphasizing healthy lifestyle choices in the whole population (6). Our findings indicate that it is possible to prevent approximately 29% of AF cases through risk factor modification. Unfortunately, we did not find significant associations between MRF combinations and AF risk, as the sample size was too small and statistical power was too low to analyse these outcomes. However, we believe that our findings provide firmer evidence to establish strategies for AF prevention in the general population.

Although the Framingham Heart Study reported that the risk factor burden, comprising modifiable risk factors, and having multiple morbidities play a crucial role in the lifetime risk of AF, associations between MRF burden and incidence of AF have not been previously reported (23). Our findings showed that the risk of AF progressively decreases according to the decrease in the proportion of visits with more than two MRF during the follow-up period. These results indicate that even if the durations of exposure to MRF are the same, the risk of AF may be lower in those who have a longer period of non-exposure to MRF. We suggest that lengthening the period of non-exposure to MRF (especially when the number of MRF is one or less) during a lifetime could help reduce the risk of AF. Moreover, a log-linear association of high SBP burden with AF incidence suggests that there are cumulative effects of high SBP on the risk of AF. Although we did not find a progressive decrease according to the decreases in the burdens of obesity with central obesity and that of inactivity, an MRF burden of < 72% for high SBP, 89% for obesity with central obesity, and 88% for inactivity lowered the risk of incident AF more than 50%, compared with an MRF burden of 100%. Therefore, minimizing the MRF burden by early intervention and control could reduce the incidence of AF. There is also potential for the burden and costs of AF to be reduced. Our findings provide a necessary evidence base to support future investment in intervention trials aimed at modification of risk factors for AF in the general population without AF.

## Strengths and limitations

This study had several limitations that need to be addressed. First, the study population comprised healthy and middle-aged subjects recruited from two specific communities in Korea (Ansan and Ansong). Thus, the PAF estimated in this study, which is population-specific, may not be applicable to the general

Korean population. Second, self-reporting questionnaires may not have accurately reflected the level of LTPA. In addition, the LTPA was divided into only two groups (inactive vs. active), because the majority of the study population had 0 min/week of LTPA (inactivity) and a small event size when categorizing the active group. Thus, we could not assess the association between LTPA intensity and incidence of AF. Third, information regarding some AF risk factors (e.g., smoking, drinking and sleep apnoea) were not available, due to missing data. We also conducted multivariate model analysis for these factors after excluding missing data, but significant associations between these factors and incident AF were not found. Fourth, AF was identified biennially using a standard 12-lead ECG, therefore some cases of paroxysmal AF could have been missed. Instead, we additionally analysed the incidence of AF using the Korean Classification of Diseases-7 (KCD-7) codes, which is similar to the International Classification of Diseases-10 (ICD-10), for 7,620 participants who consented to data linkage between KoGES and the Korean National Health Insurance Service (NHIS) database. We confirmed that the overall incidence rate of AF using KCD-7 codes was 2.5%, which was similar to our results (2.0%).

However, the study had several strengths. The main strengths were its community-based prospective design and the long follow-up period. In addition, to our knowledge, this is the first study to investigate the association between MRF for incident AF using a time-updated model and assessing the cumulative effects of MRF burden on AF risk in South Korea.

## Conclusions

In a prospective cohort study in Korea, our findings provide support for the concept that targeting MRF, including high SBP, obesity with central obesity, and inactivity for leisure-time, has the potential to significantly reduce the individual risk and population burden of AF. Future studies on appropriate level of control of MRF may provide insights into an efficient approach to reduce AF risk or burden in general population. Presently, this needs to be scrutinized by prospective intervention trials to find suitable level of control of MRF.

## Methods

### Data source and study population

Data were obtained from the Ansan-Ansung cohort within the Korean Genome and Epidemiology Study (KoGES) which is conducted by the Korea National Institute of Health. The Ansan-Ansung cohort is an ongoing, prospective, community-based cohort study that was initiated in 2001–2002. The aim of this cohort study is to ascertain the relationships between genetic, environmental, and lifestyle determinants of chronic diseases such as diabetes mellitus, cerebrovascular disease, and hypertension in Korean people (24). The participants are residents of both urban (Ansan) and rural (Ansung) areas. Enrolment in the study was based on the characteristics of the communities and the most efficient method of recruitment of a representative sample of the Korean population. Initially, the cohort comprised 10,030 participants that were 40–69 years old between 2001 and 2002. Follow-up examinations were conducted

biennially between 2003 and 2018. All the participants provided written informed consent. The study protocol was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention. All research procedures were performed in accordance to the relevant guidelines and regulations.

In the current study, participants with AF at baseline (n = 39), those with missing values for electrocardiography (ECG) at baseline (n = 12), those without ECG tests during follow-up (n = 55) and those lost to follow-up (n = 875) were excluded from the analysis (**Figure S1**). The final study cohort included 9,049 subjects.

## Case ascertainment and follow-up

All participants underwent the 12-lead standard ECG at every visit to identify AF. The mortality data for participants lost to follow-up were ascertained by examination of National Death Records. The participants in this study cohort were followed until the index date (AF, death, or end of the study period [December 31, 2018], whichever came first). The primary outcomes were incident AF or AF-related mortality.

## Risk factor ascertainment

Information on the presence of cardiovascular disease (CVD), including myocardial infarction, coronary artery disease, congestive heart failure and stroke/transient ischemic attack, were obtained using a questionnaire at every visit. The questionnaires were administered by trained interviewers according to a specified protocol. Blood pressure was measured using a mercury sphygmomanometer, by trained examiners, at least twice at the level of the heart, in a sitting position, and averaged. Systolic blood pressure (SBP) was classified into three categories: <120 mmHg, 120–139 mmHg, and  $\geq$ 140 mmHg. Body mass index (BMI) was calculated as body mass in kilograms divided by height in meters squared. Waist circumference (WC) was measured at the mid-point between the lower ribs and the top of the iliac crest in the standing position. Central obesity was defined as a WC  $\geq$ 85 cm in women and  $\geq$ 90 cm in men (25). Obesity was defined as a BMI  $\geq$  25 kg/m<sup>2</sup>, in accordance with the World Health Organization criteria for individuals of Asian descent (26). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Study (CKD-EPI) equation, and chronic kidney disease (CKD) was defined as an eGFR  $\leq$ 60 mL/min/1.73 m<sup>2</sup>. Leisure time physical activity (LTPA); including aerobics, jogging, swimming, tennis, golf, bowling, fitness club exercise, walking, and climbing, was assessed using a questionnaire to quantify activities in the leisure time domain. All participants were asked about the types, duration, and frequency of their LTPA. LTPA was then categorized into no physical activity (inactivity) and > 0 min/weeks (active).

## Statistical analysis

Baseline characteristics, according to incident AF at the index date, were captured. Continuous variables were expressed as mean  $\pm$  standard deviation and compared using t-tests; categorical variables were

expressed as frequency (percentage) and compared using chi-square tests. Incidence rates of AF were reported as number of patients per 100,000 person-years.

To reduce the possibility of immortal biased effect estimates, we constructed Cox models with time-varying assessment of risk factors to identify significant MRF for incident AF. Models were initially adjusted for sex, area, and time-updated assessment of age, SBP, combinations of obesity and central obesity, LTPA, CKD, CVD, HbA1c and total cholesterol. To estimate the joint risk reduction associated with risk factor modification, we constructed a risk factor score composed of significant MRF (one point each for: SBP  $\geq$ 140 mmHg, obesity with central obesity and inactivity). Using Cox models with and without time-varying assessment of risk factors (**Figure S2**), we compared multivariable-adjusted hazard ratios (HR) for participants with the least favourable risk factor profile (three points) to those with progressively favourable profiles (two, one, and zero points). The proportional hazards assumption was tested using the scaled Schoenfeld residuals (27). For all the above-mentioned outcomes, we calculated the population attributable fractions (PAF), which reflect the fraction of the event rate or risk, in a given period, attributable to the exposure of interest (assuming a causal relationship). The PAF were computed using indirect standardization using the SAS procedure STDRAE.

To investigate the cumulative effect of MRF on AF risk, we assessed the association with each participant's MRF burden during follow-up. In this study, MRF burden was defined as the proportion of times MRF appeared during follow-up, based on the number of visits (**Figure S3**). We constructed restricted cubic spline curves to identify the association between MRF burden and AF risk.

All statistical tests were two-tailed and *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS software (ver. 9.4; SAS Institute, Cary, NC, USA) and R 3.5.3 (R Foundation, Vienna, Austria).

## Declarations

### Acknowledgements

The data in this study is from the Korean Genome and Epidemiology Study (KoGES 4851-302), Korea National Institute of Health, Republic of Korea.

The authors wish to thank the participants and staff of the KoGES.

We would like to thank Editage ([www.editage.co.kr](http://www.editage.co.kr)) for English language editing.

### Funding

This research received no external funding

### Conflicts of interest

The authors declare that there is no conflict of interest.

## Author contributions

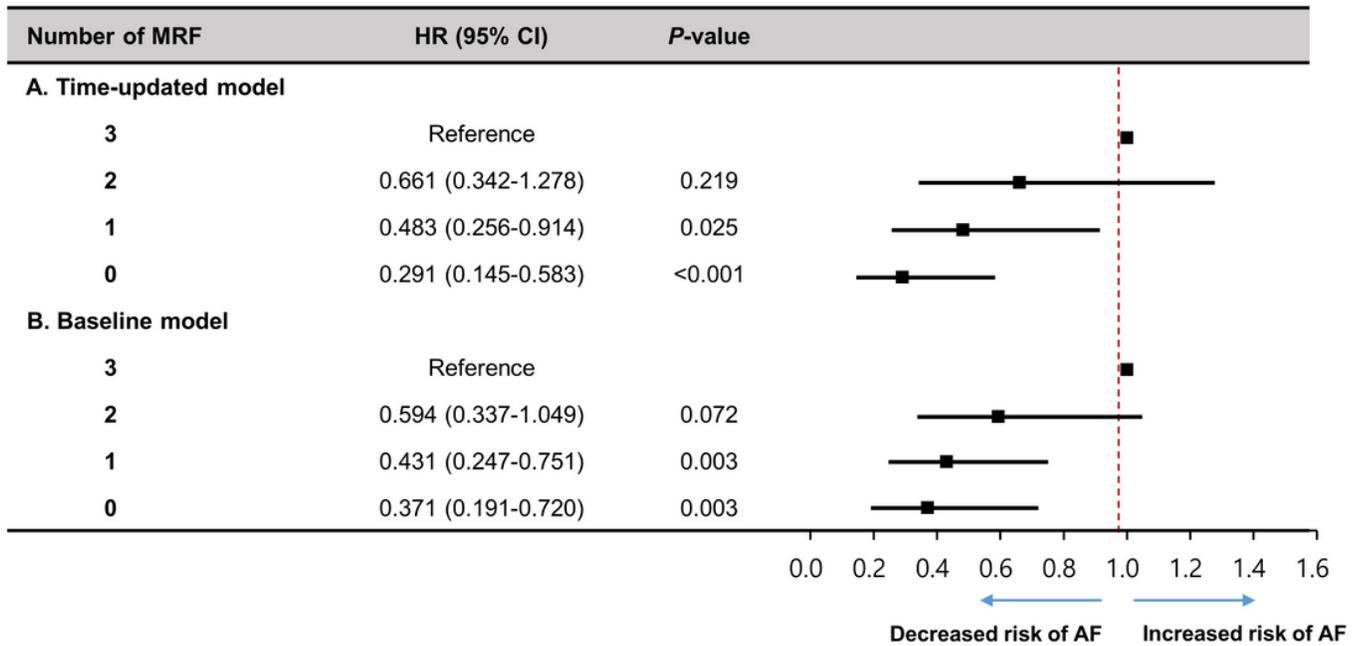
MKS designed the study, interpreted the findings, and drafted the manuscript. MKS and DSS performed the statistical analysis. KL contributed to the discussion. HYP participated in the design of the study, revised the manuscript for important intellectual content and provided final approval of the version to be published. All authors have read and approved the final manuscript.

## References

1. Kaarisalo, M. M. *et al.* Atrial fibrillation and stroke. Mortality and causes of death after the first acute ischemic stroke., **28**, 311–315 (1997).
2. Kannel, W. B., Wolf, P. A., Benjamin, E. J. & Levy, D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol*, **82**, 2–9 (1998).
3. Batul, S. A. & Gopinathannair, R. Atrial fibrillation in heart failure: a therapeutic challenge of our times. *Korean Circ J*, **47**, 644–662 (2017).
4. Reddy, V. Y. *et al.* Time to cost-effectiveness following stroke reduction strategies in AF: warfarin versus NOACs versus LAA closure. *J Am Coll Cardiol*, **66**, 2728–2739 (2015).
5. Neyt, M., Van Brabandt, H. & Devos, C. The cost-utility of catheter ablation of atrial fibrillation: a systematic review and critical appraisal of economic evaluations. *BMC Cardiovasc Disord*, **13**, 78 (2013).
6. Du, X., Dong, J. & Ma, C. Is atrial fibrillation a preventable disease? *J Am Coll Cardiol*, **69**, 1968–1982 (2017).
7. Chugh, S. S. *et al.* Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study., **129**, 837–847 (2014).
8. Benjamin, E. J. *et al.* Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. *JAMA*, **271**, 840–844 (1994).
9. Benedetto, L. D., Michels, G., Luben, R., Khaw, K. T. & Pfister, R. Individual and combined impact of lifestyle factors on atrial fibrillation in apparently healthy men and women: The EPIC-Norfolk prospective population study. *Eur J Prev Cardiol*, **25**, 1374–1383 (2018).
10. Gorenek, B. *et al.* European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS). *Eur J Prev Cardiol*, **24**, 4–40 (2017).
11. Son, M. K., Lim, N. K., Kim, H. W. & Park, H. Y. Risk of ischemic stroke after atrial fibrillation diagnosis: a national sample cohort. *PLoS One*, **12**, e0179687 (2017).
12. Lip, G. Y. H., Brechin, C. M. & Lane, D. A. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe., **142**, 1489–1498 (2012).

13. Piccini, J. P. *et al.* Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke. *Eur Heart J*, **35**, 250–256 (2014).
14. Guo, Y. *et al.* Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation., **147**, 109–119 (2015).
15. Tse, H. F. *et al.* Stroke prevention in atrial fibrillation—an Asian stroke perspective. *Heart Rhythm*, **10**, 1082–1088 (2013).
16. Son, M. K., Lim, N. K. & Park, H. Y. Trend of prevalence of atrial fibrillation and use of oral anticoagulation therapy in patients with atrial fibrillation in South Korea (2002–2013). *J Epidemiol*, **28**, 81–87 (2018).
17. Kim, D. *et al.* Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015., **104**, 2010–2017 (2018).
18. Rangnekar, G. The characterisation of risk factors, substrate and management strategies for atrial fibrillation [dissertation]. School of Medicine, The University of Adelaide; 2015.
19. Lee, S. R. *et al.* Association between clustering of unhealthy lifestyle factors and risk of new-onset atrial fibrillation: a nationwide population-based study. *Sci Rep*, **10**, 19224 (2020).
20. Lau, D. H., Nattel, S., Kalman, J. M. & Sanders, P. Modifiable risk factors and atrial fibrillation., **136**, 583–596 (2017).
21. Yadav, K. & Lewis, R. J. Immortal time bias in observational studies. *JAMA*, **325**, 686–687 (2021).
22. Suissa, S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol*, **167**, 492–499 (2008).
23. Staerk, L. *et al.* Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ*, **361**, k1453 (2018).
24. Kim, Y., Han, B. G. & KoGES group. Cohort profile: the Korean Genome and Epidemiology Study (KoGES) consortium. *Int J Epidemiol*, **46**, e20 (2017).
25. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies., **363**, 157–163 (2004).
26. World Health Organization. *Regional Office for the Western Pacific. The Asia-Pacific perspective: redefining obesity and its treatment* (Health Communications Australia, Sydney, 2000).
27. Schoenfeld, D. Partial residuals for the proportional hazards regression model., **69**, 239–241 (1982).

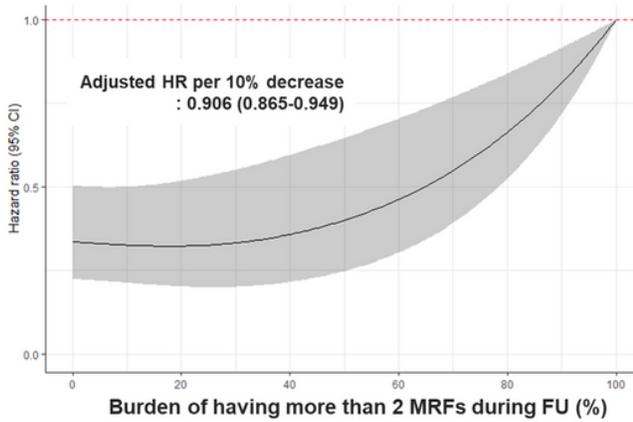
## Figures



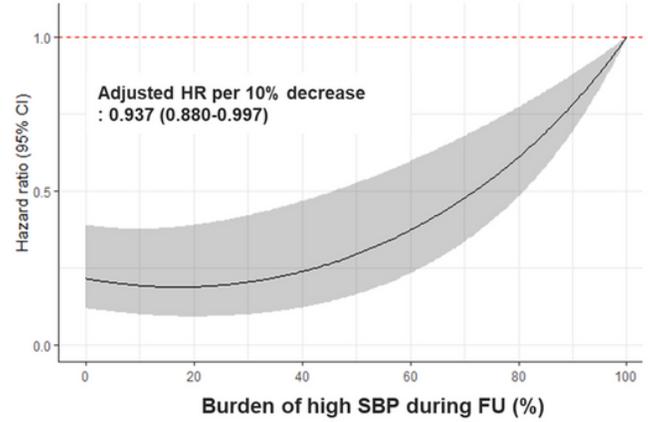
**Figure 1**

Modifiable risk factors and AF risk in general population using baseline and time-updated models. Modifiable risk factors include time-updated systolic blood pressure  $\geq 140$  mmHg, obesity with central obesity, and inactivity. Hazard ratios (HR) for the baseline model were adjusted for age, sex, area, chronic kidney disease, cardiovascular disease, HbA1c and total cholesterol at baseline. Time-updated models were adjusted for sex and area at baseline, and time-updated assessment of age, chronic kidney disease, cardiovascular disease, HbA1c and total cholesterol. MRF=modifiable risk factor; HR=hazard ratio; AF=atrial fibrillation

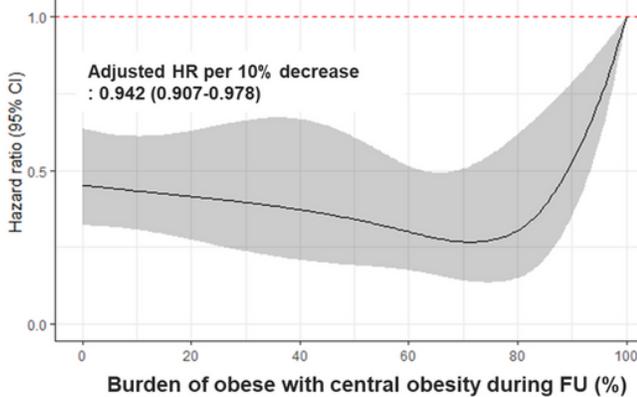
**A. More than 2 MRFs**



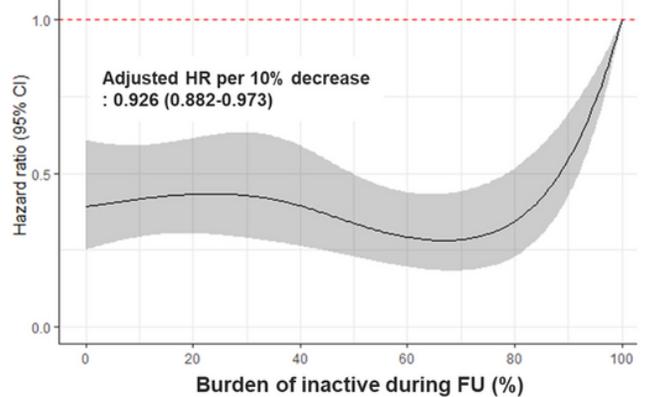
**B. SBP  $\geq$ 140 mmHg**



**C. Obese with central obesity**



**D. No LTPA**



**Figure 2**

Associations between MRF burden and risk of AF. The solid black line and shaded gray areas represent hazard ratio and 95% confidence bands. Restricted cubic splines for hazard ratios were calculated with a burden of 100% as a reference. MRF=modifiable risk factor; SBP=systolic blood pressure; LTPA=leisure time physical activity; HR=hazard ratio; CI=confidence interval; AF=atrial fibrillation

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [FigureS1.docx](#)
- [FigureS2.docx](#)
- [FigureS3.docx](#)
- [TableS1.docx](#)
- [TableS2.docx](#)