ORIGINAL ARTICLE

Risk factor profile for newly diagnosed atrial fibrillation: 4-year follow-up of annual health examinations in a Japanese Adult Cohort

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Abstract

Background: Detecting unknown atrial fibrillation (AF) would provide an opportunity to prevent ischemic stroke by instituting appropriate anticoagulation. Although opportunistic screening of older patients is recommended in current guidelines, which patients may benefit from intensive AF screening remains unclear. We sought to clarify the risk factor profile for newly diagnosed AF in annual health examinations of a Japanese adult cohort.

Methods: Among 141 441 Japanese patients who underwent annual health examinations in 2014, 87 872 patients aged ≥20 years without known AF who had undergone electrocardiography were analyzed (mean age: 47 ± 12 years; 64% men). The absence of known AF was confirmed by prior electrocardiography in 2012 and/or 2013. Newly diagnosed AF was observed in 244 patients in 2014–2017 (mean age: 62 ± 12 years; 83% men).

Results: In the multivariable analysis, waist circumference obesity (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.13–1.99; $p = .005$) high blood pressure (HR, 1.9; 95% CI, 1.01–3.59; $p = .047$), on-treatment hypertension (HR, 1.53; 95% CI, 1.01–2.31; $p = .046$), and daily alcohol drinking (HR, 2.18; 95% CI, 1.52–3.12; $p < .001$) were significantly associated with newly diagnosed AF.

Conclusions: In this Japanese cohort, waist circumference obesity, hypertension, and alcohol drinking were independent predictors of newly diagnosed AF in annual medical examinations. This finding encourages further evaluation of systematic AF screening programs in at-risk populations.

KEYWORDS
atrial fibrillation, electrocardiography, lifestyle, mass screening, risk factors

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia and is a global healthcare problem with evidence suggesting an increasing prevalence and incidence worldwide.[1,2] AF is associated with a high relative risk of dementia, stroke, major adverse cardiac events, and all-cause mortality.[3-6] Many guidelines recommend oral anticoagulation therapy for patients with AF at elevated risk of stroke.[7-9]

The data from the Swedish Riksstroke registry of >94000 strokes have helped identify the major gaps in prevention of AF-related strokes, which represent 33% of all ischemic strokes.[10,11] In 9% of all strokes, the presence of AF is not known prior to stroke. In the Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial, poststroke cardiac rhythm monitoring with an insertable cardiac monitor in patients with cryptogenic stroke showed a 30% detection rate of unknown AF.[12] More effective prevention of AF-related complications would require screening to detect and treat unknown AF.[13] However, AF is often asymptomatic and frequently undetected clinically.[14] Asymptomatic AF is associated with a higher stroke risk and poorer prognosis than that with symptomatic AF.[15] Opportunistic screening of older patients is recommended in current guidelines,[8,16,17] but it is necessary to identify the target population of patients who will benefit most from intensive AF screening.

Japan has a unique health-care system. Annual health checks including 12-lead electrocardiography (ECG) are required for every worker and his or her family members. This systematic screening is efficient in detecting unknown AF. We previously reported that repeat annual screening revealed a consistent new AF yield of 0.33%–0.55% per year in individuals aged ≥65 years, and 73% of new-onset AF was asymptomatic.[18] Therefore, this study was performed to clarify the risk factor profile for newly diagnosed AF from a 4-year follow-up of annual health examinations in a Japanese adult cohort. A distinctive feature of this study is that the risk of new-onset AF was evaluated in subjects who had not been diagnosed with AF, which was confirmed by ECG data of the previous 2 years and medical records, in a provincial city (Toyama Prefecture, Japan). By clarifying the risk factors for newly detected AF, we sought to identify the optimal target for an intensive AF screening program with high cost-effectiveness.

2 | METHODS

2.1 | Study design and population

In this retrospective cohort study, we examined data from annual health examinations performed in Toyama Prefecture by the Hokuriku Health Service Association from 2012 to 2017. All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later

versions. Written informed consent was obtained from all patients included in the study. The patients provided written consent to use their data for research when then provided consent for the examination. The study protocol was approved by the ethics committee of the Hokuriku Health Service Association.

2.2 | Annual health examination

Hokuriku Health Service Association in Toyama Prefecture performs annual health examinations on approximately 150000 workers and their families each year. The annual health examination includes 12-lead ECG, chest X-ray examination, blood pressure (BP) measurement, waist circumference measurement, urinalysis, and blood chemistry testing. The examination also includes a health questionnaire containing items on alcohol consumption, smoking, and history of comorbidities (i.e., history of stroke, myocardial infarction, angina pectoris, arrhythmia, hypertension, dyslipidemia, diabetes mellitus, gout, and other conditions). The participants were asked to indicate how often they consumed alcoholic beverages. There were four predefined categories of the frequency of consumption of alcoholic beverages: never, 1–4 days/week, 5–6 days/week, and daily. Waist circumference obesity was defined as a waist circumference of ≥85 cm for men and ≥90 cm for women in accordance with the Japan Society for the Study of Obesity criteria.[19] According to the generally accepted definition, hypertension was diagnosed if the peripheral BP was ≥140/90 mm Hg.[20] BP was measured a few times at the upper arm in the sitting position using an automatic sphygmomanometer after rest. Participants currently undergoing treatment for hypertension were classified as "on-treatment." Untreated hypertension was classified into three groups with reference to the guideline: systolic BP of <120 mm Hg and diastolic BP of <80 mm Hg, systolic BP of 120–159 mm Hg and/or diastolic BP of 80–99 mm Hg, and systolic BP of ≥160 mm Hg and/or diastolic BP of ≥100 mm Hg.

2.3 | Assessment of AF

Standard 12-lead ECG was performed for approximately 10 s in all participants while in the supine position. A trained cardiologist in Hokuriku Health Service Association used 12-lead ECG to diagnose AF (Minnesota Codes 8-3-1 and 8-3-3) or atrial flutter (Minnesota Codes 8-3-2 and 8-3-4). AF symptoms were determined from information contained in the health questionnaire in the onset year and were classified into typical symptoms (palpitations or erratic pulse), atypical symptoms (dizziness, orthostatic dizziness, dyspnea, and chest pain), or no symptoms.

2.4 | Study participants

Data were retrieved from the electronic records of all 141441 patients who underwent a health examination in 2014, and 12-lead
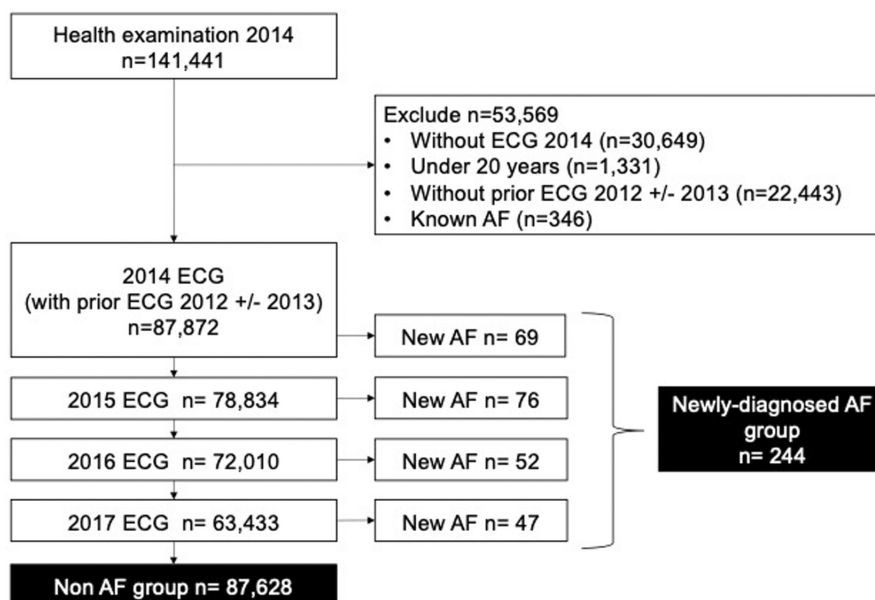
ECG was performed in 110 792 of the examinations (Figure 1). Study participants with AF diagnosed by ECG in either 2012 or 2013 were considered to have "known AF" and were excluded from this study. Only patients aged ≥20 years with a prior ECG recorded in 2012 or 2013 were deemed eligible; therefore, the baseline sample comprised 87 872 participants. All participants without known AF were followed up over 4 years (from 2014 to 2017) with health examinations that included annual ECG. Those with AF diagnosed by ECG during the 4-year follow-up were considered to have "newly diagnosed AF," and those without newly diagnosed AF during the 4-year follow-up were considered to have "non-AF."

2.5 | Statistical analysis

Continuous variables are presented as mean±standard deviation, and categorical variables are presented as number and percentage. The baseline characteristics were compared between participants with newly diagnosed AF and non-AF by the chi-square test or Student's *t* test for categorical and continuous variables, respectively. The overall and yearly incidence rates for newly diagnosed AF were calculated. We calculated the hazard ratios (HR) and 95% confidence interval (CI) for incident AF during the 4-year follow-up period by using multivariable Cox regression models. We examined the associations between cardiovascular risk factors and the risk of new-onset AF using unadjusted and multivariable-adjusted Cox proportional hazard ratios after adjusting for the participants' gender and age (Table S1). All possible interactions between the risk factors and new-onset AF were identified in our univariable model. We created a multivariable Cox model by adjusting for the participants' cardiovascular risk factors (gender, age, blood pressure, waist circumference, alcohol drinking, and on-treatment hypertension) and known risk factors (smoking, ischemic heart disease, dyslipidemia,

and diabetes mellitus).[21,22] Analyses were performed with SPSS software, version 25 (IBM Corp.). A *p* value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

In total, 87 872 patients were enrolled in the cohort analysis. During the 4-year follow-up, newly diagnosed AF occurred in 244 patients (age: 62±12 years; 83% men). The non-AF group comprised 87 628 patients (age: 47±12 years; 64% men). Figure 2 shows the age distribution of all study participants and the patients with newly diagnosed AF. Both men and women were older in the newly diagnosed AF group than those in the non-AF group. Among the study participants, 78 607 (89.7%) in 2015, 72 010 (81.9%) in 2016, and 63 433 (72.2%) in 2017 were able to be followed up for 4 years. The characteristics of the participants who could and could not be followed up are displayed in Table S2.

Table 1 shows the incidence of newly diagnosed AF during the 4-year follow-up. The overall incidence was 0.81 per 1000 person-years (0.72–0.96 per person-year). Figure 3 shows the incidence of newly diagnosed AF by age and gender. The incidence exceeded 1 per 1000 person-years in men aged 50 years and women aged 60 years, and 10 per 1000 person-years in men aged 65 years and women aged 75 years. The characteristics of both groups in this study are summarized in Table 2. Participants with newly diagnosed AF had higher BP and waist circumference than those with non-AF. The prevalence of daily alcohol drinkers was twofold higher in the newly diagnosed AF group than that in the non-AF group. Compared with patients without newly diagnosed AF, patients with newly diagnosed AF had more symptoms of dyspnea, palpitation, and elastic pulse. Most of these patients were asymptomatic (79.5%).
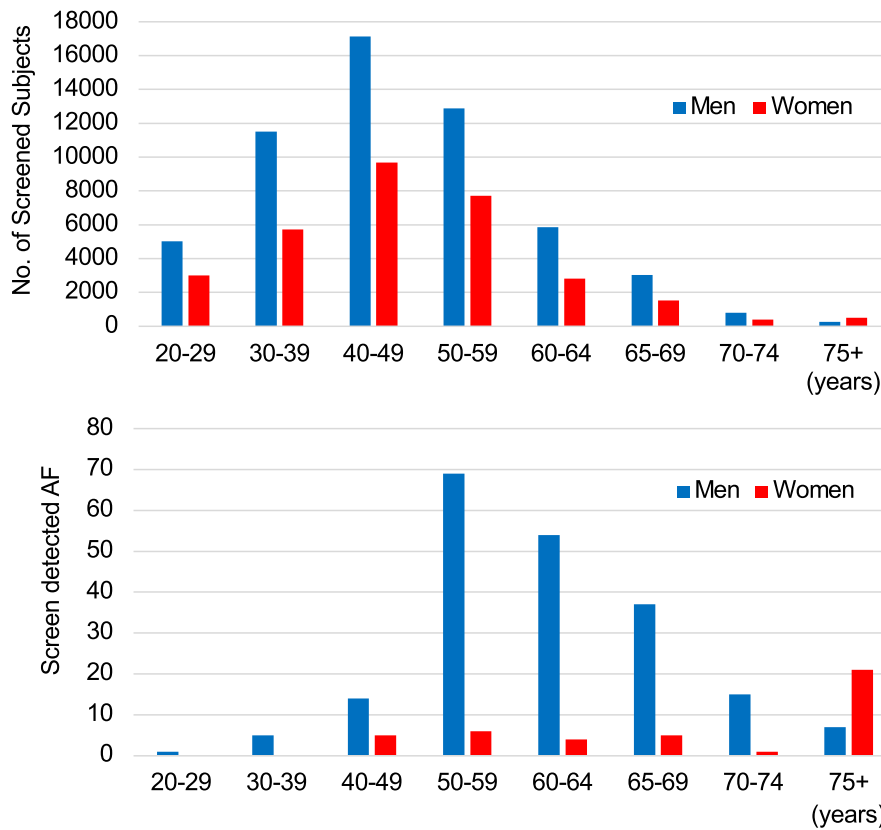
FIGURE 2 Age and gender distribution of the cohort. AF, atrial fibrillation.

3.2 | Multivariable logistic regression analysis for newly diagnosed AF

Table 3 shows the results of the multivariable Cox regression models to compare the contributions of the risk factors for newly diagnosed AF. Compared with non-AF, newly diagnosed AF was strongly correlated with gender and age. Participants aged >50 years were at higher risk, and older age (especially >75 years) was associated with a greater risk of newly diagnosed AF compared with younger age. Among the lifestyle risk factors, obesity, high BP (systolic BP of ≥160 mm Hg and/or diastolic BP of ≥100 mm Hg), on-treatment hypertension, and daily alcohol drinking were more likely to be found in patients with newly diagnosed AF during the 4-year follow-up.

4 | DISCUSSION

In an aging society, detecting unknown AF before the development of stroke could contribute to an extended healthy life expectancy.[23] Detection of unknown AF by opportunistic screening would contribute to decreased AF-related complications. By clarifying the risk factors for newly diagnosed AF, the screening target for unknown AF can be optimized and the cost can be reduced. The systematic screening system in Japan is a unique health-care system. Employers have a legal obligation to provide annual health examinations for their employees and the employees' family members. The government provides access to annual health examinations for everyone else, although attendance is optional. This comprehensive annual

TABLE 1 Incidence rate of newly diagnosed AF over a 4-year follow-up.

	No. of screening (person-year)	No. of newly diagnosed AF (person)	Incidence rate of AF (per 1000 person-years)
2014	87 872	69	0.79
2015	78 834	76	0.96
2016	72 010	52	0.72
2017	63 433	47	0.74
2014–2017	302 149	244	0.81

Abbreviation: AF, atrial fibrillation.

health examination includes screening for respiratory, metabolic, cardiovascular, ophthalmologic, hearing, gynecologic, and lifestyle disorders, and many companies also include 12-lead ECG. This mass screening approach includes a low-risk population that is not recommended for screening of AF. AF screening in a targeted population is likely to yield greater clinical benefit.[24] In previous studies in Western countries, patients who had AF were more likely to be men, older, have a history of stroke, and have hypertension, obesity, a smoking habit, cardiac disease, and diabetes.[25,26] Although the risk factors for AF have been well established in many previous studies, identification of risk factors for newly diagnosed AF might be challenging. To address this issue, we checked the ECG data and medical records from the previous 2 years before enrollment to exclude patients with known AF. Consequently, most (79.5%) of the

FIGURE 3 Incidence of newly diagnosed AF by age and gender. AF, atrial fibrillation.
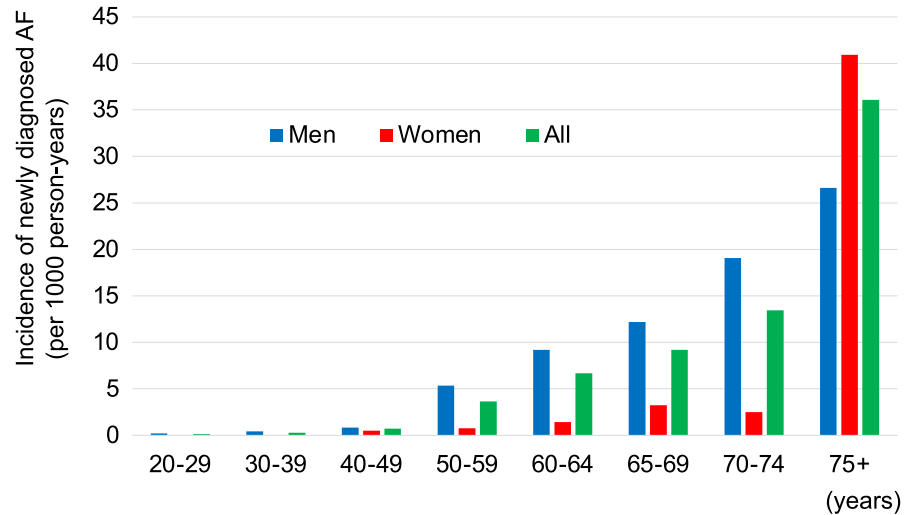
participants with newly diagnosed AF were asymptomatic. As expected, the ratio of asymptomatic AF in this study was higher than that of the Fushimi AF registry (50.3%), which included patients with known AF.[27]

We previously reported that annual ECG screening identified an incremental new AF yield of approximately 0.08% in Japanese people aged ≥65 years with two prior consecutive negative AF screening ECG examinations.[18] The results of our Japanese study indicated that age, obesity, hypertension, and alcohol drinking were risk factors for newly diagnosed AF. Japanese individuals aged >65 years who have these risk factors without AF should be a target population for screening of unknown AF. Not only should these patients undergo regular pulse checks, but they may benefit from use of the latest technology for detecting AF (i.e., long-term Holter monitoring, intermittent smartwatch ECG assessment, and wearable devices).[16]

Previous studies have revealed many risk factors for AF in the Japanese population, including hypertension, diabetes mellitus, dyslipidemia, obesity, alcohol drinking, smoking, cardiac disease, and chronic kidney disease.[22,28–31] Our data show that the risk of AF is high not only in patients with high BP but also in patients with hypertension who are being treated.

In Japan, there are regional differences in lifestyles and food cultures; in particular, alcohol intake, hypertension, and obesity might have impacted the present results. Actually, in Toyama residents, the stroke mortality rate is 1.3 times higher than the national average.[32] Additionally, annual alcohol consumption in Toyama Prefecture is higher than the national average.[33] Several studies have evaluated the risk of incident AF in Japanese subjects. The Hisayama study[21] and the Suita study[22] identified age, male gender, hypertension, and obesity as risk factors, which is consistent with our study findings. Drinking alcohol was identified as a risk factor in the Suita study, but not in the Hisayama study. Nishikawa et al.[30] demonstrated an association between lifestyle behavior and incident AF.

The importance of countermeasures against cardiovascular diseases and cerebrovascular disorders for extending healthy life expectancy has been recognized, and such countermeasures were passed as Japanese law in 2019.[34] One of the important measures is

"prevention of cardiovascular disease and dissemination of correct knowledge." Currently, AF management mainly prevents the development of related diseases, such as brain embolism and heart failure. However, to reduce the complications related to AF, it is important to prevent new-onset AF from a young age. Comprehensive AF risk factor management and intensive AF screening are important to extend people's healthy life expectancy.[16]

4.1 | Limitations

This study had several limitations. First, our data were collected from one site in Toyama Prefecture, Japan; therefore, the data may not be generalizable to other prefectures in Japan or other countries. Second, during the 4-year period, 27.8% of the participants did not receive an ECG. No annual ECG screening was more common among older participants. Under the Industrial Safety and Health Act, ECG is included in the standard items of regular health examinations for employees. ECG is mandatory for workers aged 35 years and in those over 40 years when they join the company; however, many companies provide ECGs for these employees only. Additionally, there were participants in this study who did not undergo health examinations at our facility owing to job changes, retirement, or relocation. Furthermore, in the annual health examinations, examination items may change, depending on the individual's circumstances, instructions from the insurer, and contract details. Therefore, there are participants who do not undergo ECG examination every year. Table S1 shows the differences in characteristics between those who did and did not undergo ECG. Owing to the above legal restrictions and contracts with companies, it is unavoidable that some people have not undergone ECG. Owing to the large number of cases, we consider that the impact on the analysis results was small. Third, 12-lead ECG evaluation was performed by a single cardiologist to limit medical costs. Fourth, the purpose of this study was to examine the relationship between lifestyle habits and patient backgrounds and new-onset AF. However, other risk factors for new-onset AF have been reported. Abnormal

TABLE 2 Characteristics of the study participants.

	Non-AF		Newly diagnosed AF		p value
	n = 87 628		n = 244		
	n	% or Mean ± SD	n	% or Mean ± SD	
Men	56 283	64.2%	202	82.8%	<.001
Age, years	46.7 ± 12.4		62.2 ± 12.3		<.001
Blood pressure, mm Hg					
Systolic blood pressure	122.2 ± 15.8		130.7 ± 18.1		<.001
Diastolic blood pressure	72.9 ± 11.5		77.0 ± 11.8		<.001
Waist circumference, cm	82.0 ± 10.2		87.4 ± 10.1		<.001
Smoking					
None	44 469	51.1%	88	39.6%	<.001
Current	29 035	33.4%	68	31.1%	
Quit	13 530	15.5%	65	29.3%	
Alcohol drinking					
Daily	16 994	19.5%	98	44.1%	<.001
5–6 days/week	8474	9.7%	28	12.6%	
1–4 days/week	18 411	21.2%	39	17.6%	
Never	43 129	49.6%	57	25.7%	
Comorbidity					
Cerebrovascular disease	994	1.1%	7	2.9%	.023
Ischemic heart disease	840	1.0%	10	4.1%	<.001
Hypertension	10 531	12.0%	89	36.5%	<.001
Dyslipidemia	4714	5.4%	18	7.4%	.199
Diabetes mellitus	3522	4.0%	25	10.2%	<.001
Symptoms					
Asymptomatic	77 814	88.8%	194	79.5%	<.001[a]
Atypical	6829	7.8%	13	5.3%	
Orthostatic dizziness	4055	4.6%	14	5.7%	.36
Dizziness	2866	3.3%	6	2.5%	.59
Dyspnea	2024	2.3%	16	6.6%	<.001
Chest pain	1697	1.1%	7	2.9%	.25
Typical	2985	3.4%	37	15.2%	
Palpitations	2470	2.8%	24	9.8%	<.001
Erratic pulse	929	1.1%	25	10.2%	<.001

Abbreviations: AF, atrial fibrillation; SD, standard deviation.
[a]Compared among asymptomatic, atypical, and typical groups.
[Correction added on 6th July 2023 after first online publication: The alignment of table 2 has been changed.]

ECG findings are associated with an increased risk of AF.[35] However, adding ECG findings to the risk model provided insufficient statistical power given the number of new-onset AF cases. Furthermore, embolic risk (congestive heart failure, hypertension, age ≥75 years,

TABLE 3 Results of the multivariable Cox regression models for newly diagnosed AF in patients without known AF in any 2 years prior to the study.

Explanatory variables	HR	95% CIs	p value
Gender			
Men	3.07	1.87–5.03	<.001
Women	Reference		
Age			
<50 years	Reference		
50–64 years	7.05	4.54–10.96	<.001
65–74 years	14.59	8.87–24.02	<.001
≥75 years	25.21	8.57–74.17	<.001
Waist circumference			
<85 cm (men), <90 cm (women)	Reference		
≥85 cm (men), ≥90 cm (women)	1.50	1.13–1.99	.005
Blood pressure			
Systolic BP <120 mm Hg and Diastolic BP <80 mm Hg	Reference		
Systolic BP 120–159 mm Hg and/or Diastolic BP 80–99 mm Hg	0.93	0.64–1.35	.69
Systolic BP ≥160 mm Hg and/or Diastolic BP ≥100 mm Hg	1.90	1.01–3.59	.047
On treatment	1.53	1.01–2.31	.046
Alcohol			
Daily	2.18	1.52–3.12	<.001
5–6 day/week	1.42	0.88–2.27	.15
1–4 day/week	1.41	0.93–2.14	.11
Never	Reference		
Smoking			
Current	0.79	0.56–1.10	.17
Quit	1.13	0.81–1.59	.48
Never	Reference		

Note: HR >1 indicates increased risk for newly diagnosed AF. Data were adjusted for gender, age, waist circumference, blood pressure, dyslipidemia, diabetes mellitus, smoking status, alcohol consumption, and comorbidities (cerebrovascular disease, ischemic heart disease). Abbreviations: AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; HR, hazard ratio.

diabetes, previous stroke [CHADS2] score; CHADS-vascular disease, age 65–74 years, gender category [CHADS-VASc] score)[36,37]; and cancer history[38] have been suggested to influence new-onset AF. However, we did not have data on heart failure and peripheral artery disease in the study dataset, and information on a history of cancer was an optional item in the original database. The association between these risk factors and new-onset AF could not be accurately evaluated. Finally, our data were collected from annual health examination databases, and the data were not linked to our hospital patient information. Therefore, information on Holter ECG monitoring, long-term ECG monitoring, and a history of paroxysmal AF is missing. Long-term ECG recordings, which are a more effective

tool for the detection of AF, were not performed. Consequently, our baseline sample may contain people with undetected paroxysmal AF, and it is possible that our results may have underestimated the prevalence of AF in Toyama prefecture. Additionally, we had no information regarding the treatment of AF. We cannot deny that some participants with AF were likely treated with antiarrhythmics or catheter ablation.

5 | CONCLUSIONS

The 4-year follow-up of annual health examinations in this Japanese cohort revealed that obesity, hypertension, and alcohol drinking were independent predictors of newly diagnosed AF. This finding encourages further evaluation of systematic AF screening programs and primary prevention in at-risk populations.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, Yoshiki Nagata. The data are not publicly available owing to restrictions, such as the data containing information that could compromise the privacy of the research participants.

ETHICS APPROVAL STATEMENT

The study protocol was approved by the ethics committee of the Hokuriku Health Service Association (Reference number: 2020–2).

PATIENT CONSENT STATEMENT

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964

and later versions. Written informed consent was obtained from all patients included in the study. When the patients underwent the health examination, they provided written consent to use their data for research when they provided consent for the examination.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

PREVIOUS PRESENTATION

This study was presented in part as a poster presentation at the American Heart Association Scientific Sessions 2019 as Y Nagata, N Lowres, T Yamagami, H Wang, D Nutbeam, B Freedman: High Risk Population of Screening-Detected Atrial Fibrillation. *Circulation.* 2019;140 (Suppl_1): Abstract 12010.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.