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ORIGINAL RESEARCH

Insomnia and the Risk of Atrial Fibrillation: A Nationwide, Real-World Cohort Study

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BACKGROUND: Insomnia is one of the most prevalent diseases observed in clinical practice, contributing to increased death and a range of chronic diseases. While numerous studies have explored the relationship between insomnia and cardiovascular disease, research on its association with atrial fibrillation (AF) remains limited. This study aimed to investigate the association between insomnia and incident AF in the general population by comprehensive, nationwide, real-world data in Japan.

METHODS: A total of 1 780 764 individuals without prior cardiovascular disease including AF from the DeSC database were included between April 2014 and August 2023. Insomnia was defined by *International Classification of Diseases*, *Tenth Revision* (*ICD-10*) codes (F510, G470) before the baseline health checkup. The primary outcome was incident AF (I480–I482 and I489). Cox proportional hazards models were used to estimate hazard ratios of AF according to present insomnia (versus absent).

RESULTS: Insomnia was observed in 216 919 individuals (12.2%), showing a significant association with incident AF after adjusting for potential confounding factors (adjusted hazard ratio, 1.14 [95% CI, 1.10–1.18]). Among subgroups, a similar pattern in the association between insomnia and incident AF was seen, while the association was stronger in younger individuals aged <65 years (versus ≥65 years) and women (versus men) (*P* for interaction=0.01 and 0.03, respectively).

CONCLUSIONS: Insomnia was significantly associated with the risk of AF. It highlighted the importance of recognizing insomnia as a risk factor for AF, given its high prevalence in the general population and the substantial impact of AF on quality of life and prognosis.

Key Words: atrial fibrillation ■ insomnia ■ risk factors ■ sleep apnea syndrome ■ sleep disorder

Atrial fibrillation (AF) is the most common supraventricular arrythmia in older adults and a public health concern that influences patient prognosis and quality of life. Hypercoagulation due to irregular left atrial motion during AF may cause a left atrial thrombus, leading to the risk of systemic thrombosis.[1] AF is also a strong risk factor for heart failure and valvular disease as the result of structural remodeling when AF persists for a long period.[2–4] For the management of AF, the guidelines recommend an appropriate medication for prevention of systemic thrombosis and early treatment of rhythm control via catheter ablation or antiarrhythmic drugs.[5] Additionally, the management of risk factors for AF such as sleep apnea syndrome and alcohol intake is another cornerstone in the treatment of AF[6]; however, exploring potential risk factors of AF is not well elucidated.

Insomnia is another global health issue and widely recognized as a common disorder regardless of

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CLINICAL PERSPECTIVE

What Is New?

- Insomnia is one of the most prevalent diseases observed in clinical practice, contributing to increased death and a range of chronic diseases, and numerous studies have explored the relationship between insomnia and cardiovascular disease; however, research on its association with atrial fibrillation (AF) remains limited.
- In this retrospective cohort study using nationwide real-world data, the DeSC database including 1 780 764 individuals without prior cardiovascular disease including AF between April 2014 and August 2023, insomnia was significantly associated with incident AF (hazard ratio, 1.14 [95% CI, 1.10–1.18]) after adjustment for traditional risk factors, including sleep apnea syndrome.

What Are the Clinical Implications?

- Our study highlighted the importance of recognizing insomnia as a risk factor for AF beyond the issue of quality of life, suggesting the need for focusing on sleep in AF prevention, and warrants further study assessing a potential association between insomnia and the risk of AF.

patient age, sex, and condition. A recent cohort study has shown that the prevalence of insomnia is ≈20% in the adult population, of which ≈40% is a long-standing persistent condition.[7] Although insomnia is a risk factor for mental health disorders due to impaired quality of life (eg, fatigue and decreased concentration), a recent study suggests a significant association between insomnia and patient prognosis.[8] Physiologically, insomnia could cause abnormal modulation of the autonomic nervous system, elevated sympathetic nervous system activity, hormonal dysregulation, and increased systemic inflammation.[9–12] These mechanisms also elevate the risk of metabolic and cardiovascular disease (CVD) including diabetes, ischemic heart disease, and stroke.[13,14]

While a link between insomnia and AF has been suggested, literature on this topic remains sparse.[15–17] For instance, a cohort study of US veterans who were discharged from military service reported that insomnia was associated with a 32% greater adjusted risk of AF (95% CI, 1.21–1.43).[15] Nevertheless, several knowledge gaps persist on this relationship. First, in contrast with the extensive research linking insomnia to other CVDs such as myocardial infarction and hypertension, investigations into AF are comparatively rare. Given that 1 large-scale population-based study found no significant link,[18] the association remains controversial. Second, most studies relied on a specific population rather than the healthy community,[15] leaving the impact of insomnia on AF incidence within the broader general population uncertain. Finally, to the best of our knowledge, no study has evaluated whether insomnia can improve AF risk prediction beyond traditional risk factors. Furthermore, the independent risk of insomnia after adjusting for sleep apnea syndrome remains to be fully elucidated.

The aim of this study is to investigate the association between insomnia and subsequent AF in the general population by leveraging a nationwide, real-world database in Japan.

METHODS

Data described in this article will not be publicly available because of the confidentiality agreement related to the data. This is a retrospective cohort study using nationwide, real-world data: the DeSC database (DeSC Healthcare, Inc., Tokyo, Japan). The DeSC database is highly representative of the Japanese population, as it integrates data from 3 major insurers in the national health care insurance system in Japan: the National Health Insurance, Health Insurance Societies, and Late-Stage Elderly Health Insurance system.[19] The database collects data on individual health insurance records and health checkup data (eg, anthropometric measurements and blood tests).[20] This database also stores inpatient and outpatient administrative claims data. Diagnoses (confirmed or suspected) are registered using the *International Classification of Diseases, Tenth Revision* (*ICD-10*). This comprehensive coverage ensures a wide age range, from young adults to older adults. The database's robust structure enables longitudinal follow-up through the linkage of specific health checkup records and enrollee registries.

We identified 3 218 173 individuals for whom we could obtain data on health checkups from April 2014 through August 2023 (Figure 1). Individuals were excluded from study participation if they met any of the following criteria: prior history of CVD including myocardial infarction, angina pectoris, stroke, heart failure, and AF (N=591 128); prior history of kidney replacement therapy (eg, dialysis) (N=594); missing data on cigarette smoking (N=277 505); missing data on alcohol consumption (N=224 382); and missing data on physical inactivity (N=343 800). Finally, the study cohort included 1 780 764 individuals.

Ethical Considerations

The present study was approved by the Ethics Committee of the University of Tokyo (Approval No. 2021010NI) and was conducted in accordance with the Declaration of Helsinki. Because all data in the

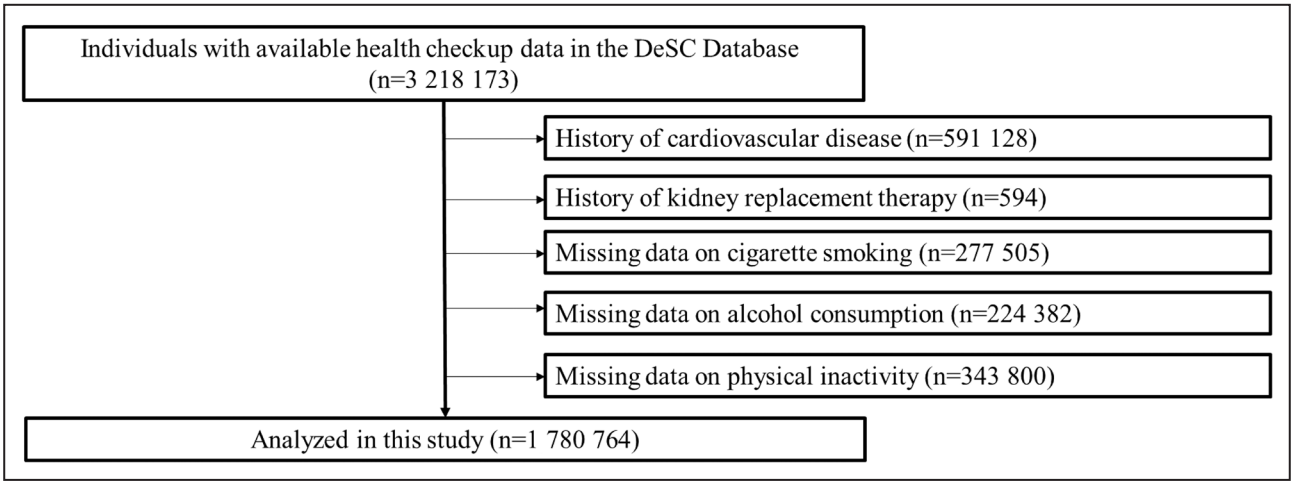

Figure 1. Study flow diagram.
We identified 3 218 173 individuals for whom we could obtain data on health checkups from April 2014 through August 2023. Individuals were excluded from study participation if they met any of the following criteria: prior history of cardiovascular disease including myocardial infarction, angina pectoris, stroke, heart failure, and atrial fibrillation (N=591 128); prior history of kidney replacement therapy (eg, dialysis) (N=594); missing data on cigarette smoking (N=277 505); missing data on alcohol consumption (N=224 382); and missing data on physical inactivity (N=343 800). Finally, the study cohort included 1 780 764 individuals.

DeSC database are anonymized, informed consent of individual participants was not required.

Definition of Insomnia

Individuals with insomnia were defined as those with a confirmed diagnosis of insomnia (*ICD-10* codes F510 and G470) before the initial health checkup.

Outcomes

The primary end point was defined as incident AF (*ICD-10* codes I480–I482 and I489). To ensure specificity, we restricted the definition to confirmed diagnosis records, strictly excluding any suspected cases. Clinical outcomes were ascertained between April 2014 and August 2023. The baseline (time 0) was defined as the date of the initial health checkup during the study period. Participants were censored at the time of AF diagnosis, death, or the end of the observation period in August 2023.

Covariates

Covariate data were ascertained from the initial health checkup and prescription records in the database. Obesity was defined as a body mass index ≥25 kg/m^2. Hypertension was identified by systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications. Diabetes was defined as a hemoglobin A_{1c} level ≥6.5% or current treatment with antidiabetic medications (including insulin). Dyslipidemia was defined as a low-density lipoprotein cholesterol level ≥140 mg/dL, a high-density lipoprotein cholesterol level <40 mg/dL, triglyceride level ≥150 mg/dL, or the use of antihyperlipidemic medications. Sleep apnea syndrome was identified using *ICD-10* code G473. Lifestyle factors, including smoking status (current or noncurrent/never smoker), alcohol consumption frequency (daily versus or nondaily), and physical activity (active versus inactive) were categorized on the basis of self-administered questionnaires.

Statistical Analysis

Basic characteristics, stratified by insomnia status, were reported as median with interquartile range (quartiles 1–3) for continuous variables and as number (percentage) for categorical variables. Between-group comparisons were performed using the Mann–Whitney *U* test or the χ^2 test, as appropriate. We estimated the cumulative incidence of AF using the Kaplan–Meier method and compared curves using the log-rank test. To quantify the association between insomnia and incident AF, we estimated hazard ratios (HRs) and 95% CIs using Cox proportional hazards models. We constructed 3 models: model 1 (unadjusted), model 2 (adjusted for age and sex), and model 3 (further adjusted for body mass index, hypertension, diabetes, dyslipidemia, sleep apnea syndrome, cigarette smoking, alcohol consumption, and physical inactivity).

We performed several sensitivity analyses to test the robustness of our findings. First, we restricted the analysis to individuals prescribed insomnia medications. Second, to minimize confounding by secondary insomnia, we excluded individuals with a history of other psychiatric or neurodevelopmental disorders (*ICD-10* codes F00–F99). Third, to mitigate reverse causality, we introduced a 1-year lag period (excluding events

within the first year as the induction period). Fourth, we used Fine–Gray subdistribution hazard models to account for death as a competing risk. Fifth, we performed subgroup analyses stratified by age (<65 versus ≥65 years), sex, and hypertension status. Finally, to evaluate potential detection bias (or observer bias), we used inguinal hernia (*ICD-10* codes K400–404 and K409) as a negative control outcome (falsification end point).[21] All sensitivity analyses used the fully adjusted Cox model strategy. Statistical significance was set at a 2-tailed *P* value <0.05. All statistical analyses were conducted using Stata version 18 (StataCorp LLC, College Station, TX).

RESULTS

Baseline Characteristics

The study cohort included 1 780 764 individuals with a median age of 63 (interquartile range, 49–68) years, and 45.5% were men. Among them, 216 919 individuals (12.2%) had a history of insomnia. The baseline characteristics of the participants are summarized in Table 1. Compared with individuals without a history of insomnia, those with insomnia were older and there was a higher proportion of women and a higher prevalence of CVD risk factors, including hypertension, diabetes, dyslipidemia, and sleep apnea syndrome. For the specific risk factors for AF, the proportion of alcoholic consumption was less frequently observed in those with insomnia compared with those without insomnia.

Table 2. Association Between Insomnia and the Risk for Atrial Fibrillation

	Insomnia absent	Insomnia present
Number	1 563 845	216 919
Number of events	21 381	4398
Incidence (per 10 000 person-years)	35.4 (34.9–35.9)	57.8 (56.1–59.6)
Model 1, HR (95% CI)	1 (Reference)	1.62 (1.57–1.67)
Model 2, HR (95% CI)	1 (Reference)	1.15 (1.11–1.19)
Model 3, HR (95% CI)	1 (Reference)	1.14 (1.10–1.18)

Model 1, unadjusted; model 2 adjusted for age and sex; and model 3 further adjusted for body mass index, hypertension, diabetes, dyslipidemia, cigarette smoking, alcohol consumption, physical inactivity, and sleep apnea syndrome. Participants were categorized into 2 groups according to the absence or presence of insomnia.

Insomnia and Incident AF

During a median follow-up period of 3.7 (interquartile range, 1.8–5.8) years in overall (those with and without insomnia: 3.5 [interquartile range, 1.7–5.0] and 3.8 [interquartile range, 1.8–5.9] years, respectively), 25 779 individuals (1.4%) were newly diagnosed with AF (Table 2; Table S1). Individuals with a history of insomnia had a significantly higher incidence of AF compared with those without insomnia (57.8 versus 35.4 per 10 000 person-years; log-rank test, *P*<0.001 in Table 2 and Figure 2). Insomnia was significantly associated with the risk of subsequent AF (HR, 1.62 [95% CI, 1.57–1.67] for model 1 in Table 2). After adjusting traditional risk factors of AF, insomnia showed an attenuated but significant association with the risk of AF

Table 1. Baseline Characteristics

	Total	Insomnia absent	Insomnia present	
	n=1 780 764	n=1 563 845	n=216 919	*P* value
Age, y	63 (49–68)	62 (48–68)	67 (58–72)	<0.001
Men	810 085 (45.5)	735 541 (47.0)	74 544 (34.4)	<0.001
Body mass index, kg/m^2	22.6 (20.4–25.0)	22.6 (20.4–24.9)	22.6 (20.4–25.1)	<0.001
Systolic blood pressure, mm Hg	126 (114–138)	126 (114–138)	127 (116–138)	<0.001
Diastolic blood pressure, mm Hg	75 (67–82)	75 (67–83)	74 (67–82)	<0.001
Hypertension	703 165 (39.5)	591 113 (37.8)	112 052 (51.7)	<0.001
Diabetes	161 664 (9.1)	136 273 (8.7)	25 391 (11.7)	<0.001
Dyslipidemia	974 795 (54.7)	837 880 (53.6)	136 915 (63.1)	<0.001
Sleep apnea syndrome	15 595 (0.9)	11 971 (0.8)	3624 (1.7)	<0.001
Cigarette smoking	296 589 (16.7)	267 407 (17.1)	29 182 (13.5)	<0.001
Alcohol consumption	406 111 (22.8)	366 966 (23.5)	39 145 (18.0)	<0.001
Physical inactivity	766 764 (43.1)	672 931 (43.0)	93 833 (43.3)	0.046
Hemoglobin A_{1c}, %	5.5 (5.3–5.8)	5.5 (5.3–5.8)	5.6 (5.4–5.9)	<0.001
Low-density lipoprotein cholesterol, mg/dL	122 (102–144)	123 (102–144)	120 (101–141)	<0.001
High-density lipoprotein cholesterol, mg/dL	62 (52–75)	62 (52–75)	62 (52–75)	<0.001
Triglycerides, mg/dL	94 (66–137)	93 (65–136)	100 (72–143)	<0.001

Values are shown as n (%) or median (interquartile range). *P* values were calculated using a χ^2 test for categorical variables and Mann–Whitney *U* test for continuous variables.

Figure 2. Insomnia and incident AF.
Cumulative incidence of incident AF between the presence or absence of insomnia (orange and green lines). A total of 25 779 events were recorded during a median follow-up period of 3.7 (interquartile range, 1.8–5.8). A significantly higher incidence of incident AF was observed in individuals with insomnia compared with those without insomnia (log-rank, *P*<0.001). AF indicates atrial fibrillation.

(models 2 and 3). Specifically, insomnia was an independent risk factor for AF after accounting for sleep apnea syndrome (ie, HR, 1.14 [95% CI, 1.10–1.18] for model 3).

For the prediction of future AF, the addition of insomnia to traditional risk factors resulted in a comparable c-index for incident AF; however, the analysis of the net reclassification improvement showed a modest but significant enhancement in the discriminatory ability for predicting future AF (Table S2).

Sensitivity Analysis

Overall, the sensitivity analyses showed patterns consistent with the original analysis. First, after excluding individuals with a diagnosis of insomnia who were not receiving insomnia medications, the results remained largely consistent with the original findings (Table S3). Second, after excluding individuals with psychiatric disorders other than insomnia, the association between insomnia and incident AF was slightly attenuated but still significant as the original analysis (Table S4). Third, insomnia showed a significant association with incident AF after an induction period of 1 year (Table S5). Fourth, even after accounting for a competing risk of all-cause death, the association remains unchanged (Table S6). Fifth, subgroup analyses also showed a similar pattern in the association between insomnia and incident AF as the original results, while the association was stronger in younger individuals aged <65 years (versus ≥65 years) and women (versus men) (*P* for interaction=0.01 and 0.03, respectively; Figure 3). Finally, in the falsification end point analysis, no significant association was observed between insomnia and the incidence of inguinal hernia (Table S7).

DISCUSSION

In this large-scale cohort study using nationwide, real-world data from Japan, we examined the association between insomnia and the future incidence of AF in the general population. Our findings demonstrated that insomnia was significantly associated with the development of AF, even after adjustment for traditional AF risk factors including sleep apnea syndrome. Moreover, the addition of insomnia to traditional AF risk factors showed a possibility of further improvement in the prediction for future AF development. Finally, each sensitivity analysis showed a consistent result as our original analysis, suggesting a stronger association in specific subgroups including younger individuals and women.

Although our findings were generally consistent with previous studies,[15–17,22,23] there are several strengths in

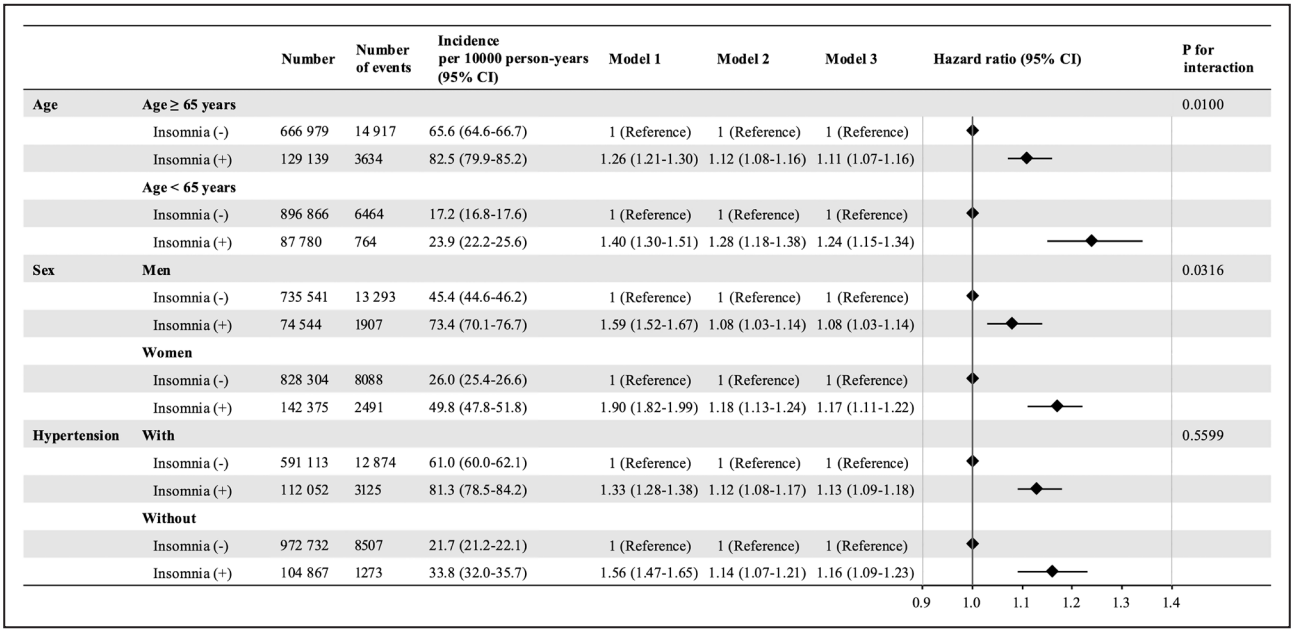

Figure 3. Subgroup analyses of association between insomnia and AF.
We assessed the association among several subgroups including age (<65 and ≥65 y), sex, and with or without hypertension. We estimated hazard ratio (diamonds) and 95% CI (horizontal lines) using the same Cox models as our original analysis: model 1 for an unadjusted model; model 2 adjusted for age and sex; and model 3 further adjusted for body mass index, hypertension, diabetes, dyslipidemia, sleep apnea syndrome, cigarette smoking, alcohol consumption, and physical inactivity (Models for subgroups did not adjust for the stratified variable itself). In the subgroup analysis, there was a similar pattern in the association between insomnia and incident AF as the original results, while the association was stronger in younger individuals of <65 y (vs ≥65 years) and women (vs men) (*P* for interaction=0.01 and 0.03, respectively). AF indicates atrial fibrillation.

the present study. First, since the present study was based on the DeSC database, which is a nationwide, real-world cohort including the general population in Japan, the findings may provide widely acceptable evidence compared with a few previous studies including a biased population (eg, younger veterans). Second, considering sleep apnea syndrome, which could be an important confounder between insomnia and AF, it may be notable that the present study clearly demonstrated the independent association between insomnia and the risk of AF. Finally, the results were widely similar among subgroups, with a more pronounced association between insomnia and the risk of AF in younger adults and women, who are generally considered at low risk in incident AF.

The findings of the present study support that insomnia could be an important risk factor for incident AF. The mechanisms of insomnia and AF are not fully understood but could be explained by the physiologic mechanisms of insomnia. Insomnia can lead to hypothalamic–pituitary–adrenal axis dysregulation, increased systemic inflammation, and enhanced sympathetic activity,[11,24,25] resulting in elevated cortisol and catecholamine levels. These changes may cause elevated blood pressure, heart rate variability, and atherosclerosis, which are the risk factors for CVD.[26,27] These mechanisms are also thought to contribute to the development of AF. Increased sympathetic activity may enhance atrial triggers,[28] while cortisol is thought to contribute to the atrial substrate by promoting structural remodeling through hypertension.[29] In addition, systemic inflammation may be involved in atrial fibrosis,[30] which serves as a substrate for AF. It has been reported that sleep deprivation was associated with increased maximum P-wave duration and P-wave dispersion.[31] Additionally, even a single night of sleep loss has been shown to increase the risk of atrial electromechanical delay in healthy young adults.[32] These suggest insufficient sleep itself could be a potential risk factor for AF with a possible common pathogenesis among insomnia, sleep apnea syndrome, and alcohol intake–related poor sleep quality.

In the subgroup analysis of the present study, younger individuals (<65 years) and women showed stronger association between insomnia and incident AF compared with older adults (≥65 years) and men. These findings suggest that insomnia may play an important role in the development of AF, even in populations generally considered to have fewer conventional risk factors for AF. The results are consistent with a previous study including young adults[15]; thus, insomnia could be an underlying contributor of AF in younger individuals or women who are not at risk for AF. According to these findings, the present study may

provide a few clinically meaningful implications in AF management. Clinicians should be aware of insomnia as an important and independent risk factor for AF as sleep apnea syndrome, particularly in individuals at low risk of AF including traditional risk factors (eg, hypertension, diabetes, alcohol intake). Active assessment of insomnia may be human- and time-resource consuming in daily clinical practice; however, the use of sleep-related questionnaires at clinic visits could be the most realistic approach. On the other hand, rising digital health technology including wearable devices (eg, smartwatches) may be promising to be able to visualize nighttime health such as the amount of sleep and its quality. The present study also suggests a public health impact of insomnia in the development of AF; thus, authorities and stakeholders should enhance outreach activities in the general population and further investigation for the association between sleeping disorders including insomnia and AF.

This study has several limitations. First, it was based on the DeSC database, which primarily includes Japanese individuals, and caution is needed when generalizing the findings to other races or ethnicities.[33] Second, the definitions of exposure and outcome in this study relied on *ICD-10* codes. This approach may lead to an underestimation of the true prevalence of insomnia and AF, as these codes may not fully capture all diagnoses. A limitation of this study is that the definition of insomnia was not adjudicated by a panel of physicians, potentially affecting the accuracy of the diagnostic classification. As a sensitivity analysis, we excluded individuals with *ICD-10* codes for insomnia but without a corresponding prescription for medication. This approach may have mitigated the overestimation of symptomatic insomnia within the secondary data, such as data from the DeSC database. In this regard, integrating symptom survey data with administrative claims data could compensate for the inherent limitations of each data source. These findings suggest that future prospective studies are warranted to more accurately assess the relationship between insomnia and incident AF. Additionally, the present study did not measure the amount of sleep (eg, sleeping hour) and its quality. It has been reported that insomnia and frequent nocturnal awakenings had a greater impact on the risk of developing AF than total sleep duration.[34] This suggests a possible dose–response relationship between sleep quantity or quality and the risk of AF, and further prospective studies are warranted. Third, individuals with missing values in questionnaires for lifestyle (eg, smoking status, alcohol consumption, daily physical activity) were excluded from the present study. Since the DeSC database integrates data from 3 different insurers in the national health care insurance system in Japan, those with missing value in the questionnaire data are thought to be the cases when the questionnaires were not performed in exactly the same manner or when information about the questionnaires was not provided to the insurer. However, the exact reason for the missingness is uncertain. Finally, although we adjusted for potential confounders as much as possible, unmeasured or residual confounding cannot be ruled out.[21] Therefore, the findings of this study should be interpreted as exploratory.

CONCLUSIONS

In a nationwide, large-scale, real-world cohort study in Japan, insomnia was significantly associated with the risk of AF. It also highlighted the importance of recognizing insomnia as a risk factor for AF, given its high prevalence in the general population and the substantial impact of AF on quality of life and prognosis. Our study also supports the need for focusing on sleep in AF prevention and warrants further study assessing the potential association between insomnia and the risk of AF.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7

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