# Risk of Atrial Fibrillation in Patients with Congenital Heart Disease: Results of a Propensity Score-Matched, Nationwide Cohort Study

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**Aim:** The objective was to compare the rate of atrial fibrillation (AF) onset in patients with congenital heart disease (CHD) compared to controls.

**Methods:** Using a large number of samples extracted from nationwide cohort data in Taiwan, the authors used a propensity-matching procedure and multivariable Cox models to assess the risk of AF by CHD.

**Results:** A cohort of 19,439 CHD patients and a propensity-matched cohort of 19,439 control patients were included in this study. The cumulative incidence of AF was significantly higher in the CHD cohort than in the non-CHD cohort ($p < 0.001$). After controlling for confounding factors, the adjusted hazard ratio (aHR) of AF was 4.23 (95% confidence interval [CI] 3.31–5.41) in the CHD cohort, compared to the non-CHD cohort.

**Conclusions:** A significant association between CHD and AF risk was found.

**Key words:** Atrial fibrillation, Cohort, Congenital heart disease

## Introduction

The lifespan of patients with congenital heart disease (CHD) is longer than before because of improved surveillance, surgical intervention and post-operative care[1, 2]. CHD patients are vulnerable to arrhythmia events, especially atrial fibrillation (AF)[3-6]. Indeed, the relationship between CHD and AF occurrence is clear[3-8]. Patients with CHD-complicated AF may have a higher risk of AF-related complications (stroke, heart failure, and bleeding) resulting in early death; hence, they deserve increased attention[3-8]. Although the association and the underlying mechanism have been explored previously, early studies primarily focused on the association between a certain type of CHD and concerned the risk of AF among CHD patients who were children and young adults[3-8]. To add to the existing literature on patients with CHD and AF from a clinical perspective, using National Health Insurance data, the authors conducted this observational-epidemiology study with propensity score matching analysis and multivariable Cox proportional hazards models to evaluate the risk of AF among CHD patients.

## Methods

### Data Source

In 1995, the government of Taiwan launched the National Health Insurance (NHI) program, which included claims data and covers more than 99% of the country's population[9]. The National Health Research Institutes (NHRI) built the National Health Insurance Research Database (NHIRD). In this retrospective study, we used a subset of the NHIRD containing health care data, including files of the Registry for Catastrophic Illness Patient Database (RCIPD), inpatient claims, and Registry of Beneficiaries. The disease record system in the Taiwan NHI was established according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Research Ethics Committee of China
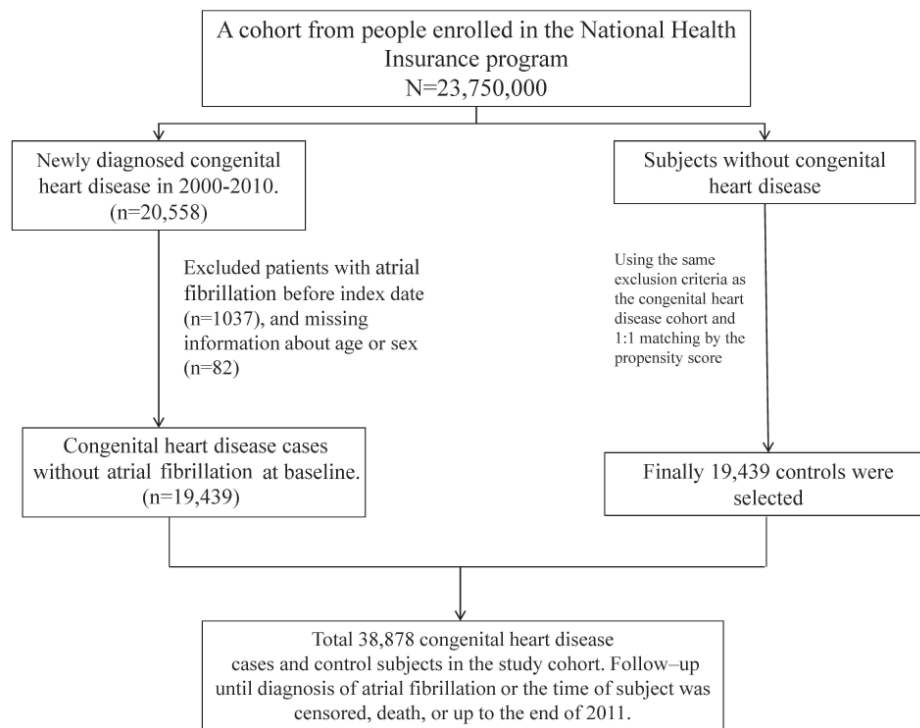
**Fig. 1.** Flowchart of the study design and selection of study subjects

Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115).

### Sampled Participants

Patients with a new diagnosis of congenital heart disease (CHD) (ICD-9-CM codes 745.0, 745.1, 745.2, 745.3, 745.4, 745.5, 745.6, 745.7, 746.0, 746.1, 746.2, 746.3, 746.4, 746.5, 746.6, 746.7, 746.8, 747.0, 747.1, 747.2, 747.3, 747.4) were identified from the RCIPD between 2000 and 2010. 19,439 CHD patients with no history of AF (ICD-9-CM code 427.31) before the index date were selected as the CHD group. Subjects without CHD and AF at baseline were identified as a control cohort. Both cohorts were matched using a 1:1 propensity score to minimize selection bias[10]. The propensity score through nearest neighbor matching was calculated using a logistic regression to estimate the probability of the disease status, including gender, age, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease (CAD), heart failure, chronic obstructive pulmonary disease (COPD), peripheral arterial occlusion disease (PAOD), chronic renal disease, hyperthyroidism, sleep disorders, gout, cerebrovascular disease, chronic liver disease, chromosome anomaly, epilepsy, congenital respiratory anomaly, mental retardation, rheumatologic disease, and cerebral palsy (**Fig. 1**). Therefore,

matches were first made within a caliper width of 0.0000001, and then the caliper width was increased for unmatched cases to 0.1. We reconsidered the matching criteria and performed a rematch (greedy algorithm). For each CHD patient, corresponding comparisons were selected based on the nearest propensity score.

### Outcome

All study subjects were followed up until a diagnosis of AF, loss to follow-up, death, withdrawal from the database, or, by the end of 2011, whichever date came first.

### Statistical Analysis

The distributions of gender, age, and comorbidity (%) between the two cohorts were compared with standardized mean differences. The cumulative incidence of AF for both cohorts and increased aging were plotted using the Kaplan–Meier method, and the log rank test was used to test the curves. The incidence density rates (per 1,000 person-years) were estimated for different risk factors (age, gender, comorbidity) and different CHD types in the two cohorts. Univariable and multivariable Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of incident AF risk among the CHD patients. All data

**Table 1.** Demographic characteristics and comorbidities in patients with and without congenital heart disease

| | Congenital heart disease | | Standardized mean difference[§] |
|---|---|---|---|
| Variables | No (N=19439) | Yes (N=19439) | |
| Gender | | | |
| Women | 9728 (50.0) | 10570 (54.4) | 0.09 |
| Men | 9711 (50.0) | 8869 (45.6) | 0.09 |
| Age stratified | | | |
| <18 | 12959 (66.7) | 13373 (68.8) | 0.05 |
| 18-34 | 2709 (13.9) | 2771 (14.3) | 0.01 |
| 35-49 | 1641 (8.44) | 1685 (8.67) | 0.01 |
| 50+ | 2130 (11.0) | 1610 (8.28) | 0.09 |
| Age, mean ± SD[a] | 14.7 ± 21.5 | 14.9 ± 19.3 | 0.09 |
| Comorbidity | | | |
| Hypertension | 1824 (9.38) | 623 (3.20) | 0.26 |
| Diabetes mellitus | 819 (4.21) | 264 (1.36) | 0.17 |
| Hyperlipidemia | 698 (3.59) | 218 (1.12) | 0.16 |
| CAD | 1227 (6.31) | 588 (3.02) | 0.16 |
| Heart failure | 1513 (7.78) | 1028 (5.29) | 0.10 |
| COPD | 359 (1.85) | 112 (0.58) | 0.12 |
| PAOD | 80 (0.41) | 41 (0.21) | 0.04 |
| Chronic renal disease | 105 (0.54) | 39 (0.20) | 0.06 |
| Hyperthyroidism | 355 (1.83) | 50 (0.26) | 0.16 |
| Sleep disorders | 306 (1.57) | 46 (0.24) | 0.14 |
| Gout | 294 (1.51) | 81 (0.42) | 0.11 |
| Cerebrovascular disease | 540 (2.78) | 152 (0.78) | 0.15 |
| Chronic liver disease | 839 (4.32) | 141 (0.73) | 0.23 |
| Chromosome anomaly | 159 (0.82) | 252 (1.30) | 0.05 |
| Epilepsy | 153 (0.79) | 65 (0.33) | 0.06 |
| Congenital respiratory anomaly | 9 (0.05) | 34 (0.17) | 0.04 |
| Mental retardation | 32 (0.16) | 30 (0.15) | 0.003 |
| Rheumatologic disease | 559 (2.88) | 141 (0.73) | 0.16 |
| Cerebral palsy | 129 (0.66) | 24 (0.12) | 0.09 |

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease
[§]A standardized mean difference of ≤ 0.10 indicates a negligible difference between the two cohorts.

analyses were executed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA). The level of significance was set to $P < .05$ and the tests were 2-tailed.

## Results

**Table 1** showed the gender, age, and comorbidities for patients with CHD ($n=19439$) and without CHD ($n=19439$). Most participants were aged <18 years (68.8% vs 66.7% in both cohorts). The mean ages of the CHD and non-CHD control cohorts were 14.9 (± 19.3 years) and 14.7 (± 21.5 years), respectively. Comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, CAD, COPD, hyperthy-

roidism, sleep disorders, gout, cerebrovascular disease, chronic liver disease, and rheumatologic disease were comparable and significantly different between the two cohorts. The mean follow-up duration for the CHD and non-CHD cohorts was 6.10 ± 3.31 and 6.01 ± 3.17 years, respectively (data not shown).

The cumulative incidence of AF was significantly higher in the CHD cohort than in the non-CHD cohort (**Fig. 2**; $p<0.001$). **Table 2** showed that the overall AF density rates were 2.06 and 0.96 per 1,000 person-years for the CHD cohort and the non-CHD cohort, respectively. After controlling for confounding factors, the adjusted hazard ratio (aHR) of AF was 4.23 (95% CI 3.31–5.41) in the CHD cohort com-
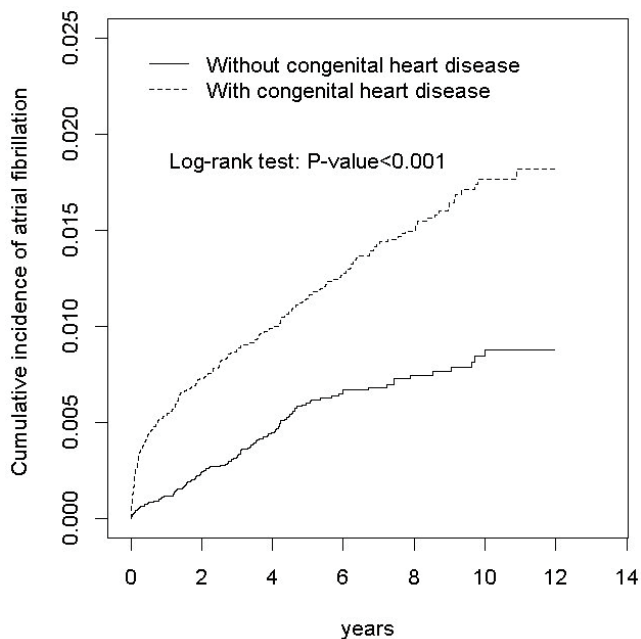
**Fig. 2.** Cumulative incidence curves of new-onset atrial fibrillation for groups with and without congenital heart disease

pared to the non-CHD cohort. Compared to patients aged <18 years, the risk of AF was 16.6-fold higher in those aged 18-34 years (95% CI 7.51-36.7), 58.5-fold higher in those 35-49 years (95% CI 27.8-122.8), and 231.9-fold higher in those aged ≥ 50 years (95% CI 113.3-474.5). AF risk was significantly higher in patients with CAD (aHR=1.43, 95% CI 1.10–1.85), heart failure (aHR=2.35, 95% CI 1.84–3.01), and chronic renal disease (aHR=2.29, 95% CI 1.30–4.05) compared to subjects without these comorbidities.

AF risks were higher in patients with different types of CHD, namely transposition of the great vessels (aHR=8.61, 95% CI 1.19-62.5), Tetralogy of Fallot (aHR=7.03, 95% CI 3.48-14.2), ventricular septal defect (aHR=2.98, 95% CI 2.03-4.38), ostium secundum type atrial septal defect (aHR=6.20, 95% CI 4.71-8.15), Atrioventricular septal defect (aHR=6.94, 95% CI 2.51-19.2), two-chambered heart (aHR=134.7, 95% CI 18.5-982.9), Ebstein's anomaly (aHR=6.09, 95% CI 2.47-15.0), congenital insufficiency of the aortic valve (aHR=3.55, 95% CI 1.79-7.04), other specified congenital anomalies of heart (aHR=2.74, 95% CI 1.26-5.95), patent ductus arteriosus (aHR=5.83, 95% CI 3.33-10.2), and coarctation of the aorta (aHR=8.06, 95% CI 1.97-33.0) (**Table 3**). The cumulative incidence of AF was much higher in CHD patients than in non-CHD patients and increased with age (**Fig. 3**; $p < 0.001$).

## Discussion

This retrospective cohort study was conducted within the Taiwan National Insurance Database. The authors assessed the risk of AF by CHD using a large number of samples and a propensity-matching procedure. Multivariable Cox models showed increased AF risk in CHD patients, and that was statistically significant.

The link between CHD and risk of incident AF has been demonstrated, mainly through underlying medical comorbidities, post-surgery fibrosis, cardiac remodeling, or increased loading condition[3-8, 11-13]. This study is different from other investigations examining the association between CHD and AF in that it does not focus on AF during subsequent years for a certain type of CHD or a specified age group, making this study unique, relevant, and informative[3-8, 11-13].

The incidence of new-onset AF is significantly lower than that reported in previous studies[3-8, 11-13]. Moreover, the incidence of comorbidities at risk for the occurrence of AF is very low in both groups. Some researchers might argue that patients who were hospitalized with a CHD, despite propensity matching on some important variables, would still have a higher risk of AF most likely related to more severe underlying disease not corrected for in matching. Moreover, it is difficult to conclude that a two-chambered heart conferred the highest risk of incident AF compared to other CHDs since there were only five patients with two-chambered hearts. The results should be interpreted with high caution given the very low event rates presented in this study.

Numerous studies have shown that AF patients have much higher morbidity and mortality compared to the general population[14, 15]. As reported in this study, CHD is inextricably linked to incident AF. Given that identifying AF and a high risk of stroke is of great importance, CHD patients should be approached with caution so that early detection and intervention strategy could be applied[16, 17].

Several aspects of the study strengths deserved to be highlighted. First, this nationwide project addressed almost 100% of Taiwan's population. Second, this study has a large population, with 19,439 patients in the CHD and in the comparison group. Finally, the methodology is appropriate for the topic. Patients with and without CHD have few differences, making the correlation highly reliable.

## Limitations

Although this study investigates a topic of high interest, there are still several methodological concerns

**Table 2.** The incidence and risk factors for atrial fibrillation

| Variable | Event | PY | Rate[#] | Crude HR (95% CI) | Adjusted HR[$] (95% CI) |
|---|---|---|---|---|---|
| Congenital heart disease | | | | | |
|   No | 112 | 116778 | 0.96 | 1.00 | 1.00 |
|   Yes | 244 | 118666 | 2.06 | 2.17 (1.73, 2.71)*** | 4.23 (3.31, 5.41)*** |
| Age group, years | | | | | |
|   <18 | 8 | 169387 | 0.05 | 1.00 | 1.00 |
|   18-34 | 26 | 31159 | 0.83 | 17.3 (7.82, 38.2)*** | 16.6 (7.51, 36.7)*** |
|   35-49 | 57 | 17829 | 3.20 | 65.5 (31.2, 137.3)*** | 58.5 (27.8, 122.8)*** |
|   50+ | 265 | 17070 | 15.5 | 308.6 (152.6, 624)*** | 231.9 (113.3, 474.5)*** |
| Gender | | | | | |
|   Women | 191 | 121781 | 1.57 | 1.00 | 1.00 |
|   Men | 165 | 113663 | 1.45 | 0.94 (0.76, 1.15) | |
| Comorbidity | | | | | |
|   Hypertension | | | | | |
|     No | 237 | 224185 | 1.06 | 1.00 | 1.00 |
|     Yes | 119 | 11259 | 10.6 | 9.16 (7.34, 11.4)*** | 1.07 (0.82, 1.39) |
|   Diabetes mellitus | | | | | |
|     No | 307 | 230839 | 1.33 | 1.00 | 1.00 |
|     Yes | 49 | 4606 | 10.6 | 7.10 (5.24, 9.61)*** | 0.86 (0.62, 1.20) |
|   Hyperlipidemia | | | | | |
|     No | 326 | 231081 | 1.41 | 1.00 | 1.00 |
|     Yes | 30 | 4363 | 6.88 | 4.47 (3.07, 6.50)*** | 0.70 (0.47, 1.04) |
|   CAD | | | | | |
|     No | 238 | 227367 | 1.05 | 1.00 | 1.00 |
|     Yes | 118 | 8077 | 14.6 | 12.7 (10.2, 15.9)*** | 1.43 (1.10, 1.85)** |
|   Heart failure | | | | | |
|     No | 222 | 223237 | 0.99 | 1.00 | 1.00 |
|     Yes | 134 | 12208 | 11.0 | 10.3 (8.34, 12.8)*** | 2.35 (1.84, 3.01)*** |
|   COPD | | | | | |
|     No | 321 | 233506 | 1.37 | 1.00 | 1.00 |
|     Yes | 35 | 1939 | 18.1 | 11.6 (8.21, 16.5)*** | 1.39 (0.95, 2.01) |
|   PAOD | | | | | |
|     No | 347 | 234896 | 1.48 | 1.00 | 1.00 |
|     Yes | 9 | 548 | 16.4 | 10.2 (5.27, 19.8)*** | 1.81 (0.92, 3.56) |
|   Chronic renal disease | | | | | |
|     No | 343 | 234948 | 1.46 | 1.00 | 1.00 |
|     Yes | 13 | 497 | 26.2 | 15.1 (8.69, 26.4)*** | 2.29 (1.30, 4.05)** |
|   Hyperthyroidism | | | | | |
|     No | 352 | 233154 | 1.51 | 1.00 | 1.00 |
|     Yes | 4 | 2291 | 1.75 | 1.12 (0.42, 3.00) | |
|   Sleep disorders | | | | | |
|     No | 350 | 233835 | 1.50 | 1.00 | 1.00 |
|     Yes | 6 | 1610 | 3.73 | 2.23 (1.00, 5.00) | |
|   Gout | | | | | |
|     No | 335 | 233747 | 1.43 | 1.00 | 1.00 |
|     Yes | 21 | 1698 | 12.4 | 7.83 (5.03, 12.2)*** | 1.30 (0.82, 2.07) |
|   Cerebrovascular disease | | | | | |
|     No | 330 | 232536 | 1.42 | 1.00 | 1.00 |
|     Yes | 26 | 2908 | 8.94 | 5.55 (3.72, 8.28)*** | 0.78 (0.51, 1.20) |
|   Chronic liver disease | | | | | |
|     No | 326 | 230713 | 1.41 | 1.00 | 1.00 |
|     Yes | 30 | 4732 | 6.34 | 4.15 (2.85, 6.03)*** | 1.23 (0.83, 1.82) |
|   Chromosome anomaly | | | | | |
|     No | 356 | 233085 | 1.53 | 1.00 | 1.00 |
|     Yes | 0 | 2359 | 0.00 | - | |

(Cont Table 2)

| Variable | Event | PY | Rate[#] | Crude HR (95% CI) | Adjusted HR[$] (95% CI) |
|---|---|---|---|---|---|
| Epilepsy | | | | | |
| No | 356 | 234360 | 1.52 | 1.00 | 1.00 |
| Yes | 0 | 1085 | 0.00 | - | |
| Congenital respiratory anomaly | | | | | |
| No | 356 | 235250 | 1.51 | 1.00 | 1.00 |
| Yes | 0 | 195 | 0.00 | - | |
| Mental retardation | | | | | |
| No | 354 | 235118 | 1.51 | 1.00 | 1.00 |
| Yes | 2 | 326 | 6.13 | 3.86 (0.96, 15.5) | |
| Rheumatologic disease | | | | | |
| No | 331 | 231488 | 1.43 | 1.00 | 1.00 |
| Yes | 25 | 3956 | 6.32 | 4.33 (2.89, 6.51)*** | 1.23 (0.81, 1.87) |
| Cerebral palsy | | | | | |
| No | 355 | 234510 | 1.51 | 1.00 | 1.00 |
| Yes | 1 | 934 | 1.07 | 0.71 (0.10, 5.06) | |

CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PAOD, peripheral arterial occlusive disease; PY, person-years; [#]Incidence rate per 1,000 person-years; [$]Multivariable analysis included age, and comorbidity of hypertension, diabetes mellitus, hyperlipidemia, CAD, heart failure, COPD, PAOD, chronic renal disease, gout, cerebrovascular disease, chronic liver disease, and rheumatologic disease; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

**Table 3.** Incidence and hazard ratios of AF between individuals with difference types congenital heart disease and without congenital heart disease

| Variable | N | Event | PY | Rate[#] | Crude HR (95% CI) | Adjusted HR[&] (95% CI) |
|---|---|---|---|---|---|---|
| Congenital heart disease | | | | | | |
| None | 19439 | 112 | 116778 | 0.96 | 1 (Reference) | 1 (Reference) |
| Common truncus | 24 | 0 | 132 | 0.00 | - | - |
| Transposition of the great vessels | 272 | 1 | 1146 | 0.87 | 0.86 (0.12, 6.12) | 8.61 (1.19, 62.5)* |
| Tetralogy of Fallot | 1250 | 9 | 7605 | 1.18 | 1.26 (0.64, 2.48) | 7.03 (3.48, 14.2)*** |
| Common ventricle | 49 | 0 | 203 | 0.00 | - | |
| Ventricular septal defec | 7308 | 41 | 49795 | 0.82 | 0.90 (0.63, 1.28) | 2.98 (2.03, 4.38)*** |
| Ostium secundum type atrial septal defect | 5274 | 139 | 30453 | 4.56 | 4.71 (3.67, 6.03)*** | 6.20 (4.71, 8.15)*** |
| Atrioventricular septal defect | 221 | 4 | 1100 | 3.64 | 3.64 (1.34, 9.87)* | 6.94 (2.51, 19.2)*** |
| Two-chambered heart | 5 | 1 | 38 | 26.2 | 29.9 (4.17, 214.1)*** | 134.7 (18.5, 982.9)*** |
| Anomalies of pulmonary valve congenital | 765 | 2 | 4580 | 0.44 | 0.46 (0.11, 1.87) | 3.31 (0.81, 13.5) |
| Tricuspid atresia and stenosis, congenital | 38 | 0 | 201 | 0.00 | - | |
| Ebstein's anomaly | 135 | 5 | 804 | 6.22 | 6.52 (2.66, 16.0)*** | 6.09 (2.47, 15.0)*** |
| Congenital stenosis of aortic valve | 372 | 7 | 1888 | 3.71 | 3.68 (1.72, 7.90)*** | 1.05 (0.49, 2.28) |
| Congenital insufficiency of the aortic valve | 200 | 9 | 914 | 9.85 | 9.41 (4.77, 18.6)*** | 3.55 (1.79, 7.04)*** |
| Congenital mitral stenosis | 20 | 0 | 98 | 0.00 | | |
| Congenital mitral insufficiency | 102 | 2 | 560 | 3.57 | 3.65 (0.90, 14.8) | 3.52 (0.86, 14.4) |
| Hypoplastic left heart syndrome | 34 | 0 | 22 | 0.00 | | |
| Other specified congenital anomalies of heart | 302 | 7 | 1297 | 5.40 | 5.04 (2.35, 10.8)*** | 2.74 (1.26, 5.95)* |
| Patent ductus arteriosus | 1692 | 15 | 10581 | 1.42 | 1.51 (0.88, 2.58) | 5.83 (3.33, 10.2)*** |
| Co-arctation of the aorta | 188 | 2 | 913 | 2.19 | 2.16 (0.53, 8.74) | 8.06 (1.97, 33.0)** |
| Other congenital anomalies of the aorta | 750 | 0 | 3891 | 0.00 | | |
| Congenital anomalies of the pulmonary artery | 326 | 0 | 1937 | 0.00 | | |
| Anomalies of the great veins | 112 | 0 | 506 | 0.00 | | |

CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PAOD, peripheral arterial occlusive disease; PY, person-years; [#]Incidence rate per 1,000 person-years; [$]Multivariable analysis included age, and comorbidity of hypertension, diabetes mellitus, hyperlipidemia, CAD, heart failure, COPD, PAOD, chronic renal disease, gout, cerebrovascular disease, chronic liver disease, and rheumatologic disease; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
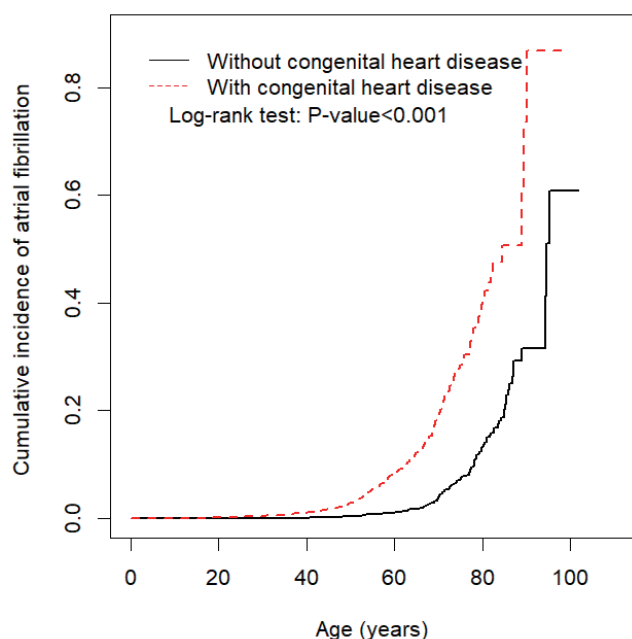
**Fig. 3.** Cumulative incidence of AF was much higher in CHD patients than in non-CHD patients and increased with age

which might limit generalization of the results. The principal limitation, however, is the relatively small prevalence of CHD in the general population and the consequent relatively modest priority. Second, because of the limitations of the national health insurance database, the authors did not mention the methods of AF detection. There was no information on the type of AF (paroxysmal or non-paroxysmal), and this might be a potential bias. In addition, the size of the atrium measured by echocardiography or magnetic resonance was not available although the occurrence of AF is related to the size of the atrium. Third, despite propensity matching, some investigators might be concerned about residual confounding. Finally, all diagnoses were defined using the ICD code, so the reliability might be challenged. However, many validation studies involving this administrative data have been reported, and the result was highly convincing[18-20].

## Conclusion

CHD is significantly associated with new onset of AF.

## Disclosure

None.

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