Independent Contribution of Diabetes to Increased Prevalence and Incidence of Atrial Fibrillation

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OBJECTIVE — Diabetes has long been recognized as a risk factor for atrial fibrillation, but its independent contribution to atrial fibrillation has not been fully evaluated. We sought to compare the prevalence and incidence of atrial fibrillation in age- and sex-matched patients with and without type 2 diabetes.

RESEARCH DESIGN AND METHODS — Using an observational cohort design, we selected 10,213 members of an HMO diabetes registry as of 1 January 1999 plus 7,159 patients who entered the registry by 31 December 2004 and matched them to patients without diabetes on year of birth and sex. All patients were followed until they died, left the health plan, or until 31 December 2008. We compared the baseline prevalence of atrial fibrillation and then followed patients without atrial fibrillation to compare atrial fibrillation incidence while controlling for known risk factors.

RESULTS — Atrial fibrillation prevalence was significantly greater among patients with diabetes (3.6 vs. 2.5%, $P < 0.0001$). Over a mean follow-up of 7.2 ± 2.8 years, diabetic patients without atrial fibrillation at baseline developed atrial fibrillation at an age- and sex-adjusted rate of 9.1 per 1,000 person-years (95% CI 8.6–9.7) compared with a rate of 6.6 (6.2–7.1) among nondiabetic patients. After full adjustment for other risk factors, diabetes was associated with a 26% increased risk of atrial fibrillation among women (hazard ratio 1.26 [95% CI 1.08–1.46]), but diabetes was not a statistically significant factor among men (1.09 [0.96–1.24]).

CONCLUSIONS — In this population, diabetes was an independent determinant of atrial fibrillation prevalence but predicted incidence only among women. These findings have potential public health implications and emphasize the need for further investigation of the mechanistic links between diabetes and atrial fibrillation.

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More than 23 million U.S. adults have diabetes (1), a figure that is growing by ~1 million each year (2). An additional 57 million U.S. residents are estimated to have pre-diabetes (1). Atrial fibrillation, the most common arrhythmia diagnosis in the world, afflicts approximately 2.2 million U.S. adults (3), and that number could more than double by 2050 (4). Other analyses have shown that the rising prevalence and incidence of atrial fibrillation cannot be explained by aging alone (5,6). Recent findings indicate that atrial fibrillation may be relatively common in diabetic patients and should be regarded as a marker of particularly adverse outcomes, prompting aggressive management of all risk factors (7). The overlap of diabetes and atrial fibrillation also contributes to a well-established increased risk of thromboembolic stroke (8).

Although diabetes and atrial fibrillation undoubtedly share common antecedents such as hypertension, atherosclerosis, and obesity (9–11), the confluence of these two conditions clearly warrants additional study. Diabetes has long been recognized as a risk factor for atrial fibrillation (12), which was subsequently reaffirmed in several studies (10,13,14). However, the potential independent contribution of diabetes to the prevalence and incidence of atrial fibrillation has not been evaluated. We therefore performed comparative analyses of the prevalence and incidence of atrial fibrillation in patients with and without diabetes.

RESEARCH DESIGN AND METHODS

— The study site was Kaiser Permanente Northwest (KPNW), a 480,000-member group-model HMO that uses clinical practice guidelines to assist clinicians with patient management. We used an observational longitudinal study design that capitalizes on the comprehensive medical utilization data maintained by KPNW, including an electronic medical record of all patient encounters, laboratory results that are analyzed by a single regional laboratory using standardized methods, and dispenses from pharmacies located in all clinics. The institutional review board of the Kaiser Permanente Center for Health Research reviewed and approved the study.

Sample selection

Since 1989, KPNW has maintained a registry of patients with known diabetes. The criteria for registry entry include an inpatient or outpatient diagnosis of diabetes (ICD-9-CM codes 250.xx), use of an antihyperglycemic drug, or at least two blood glucose test results above diagnostic levels for diabetes. For the current study, we selected 10,213 patients who were members of the diabetes registry as of 1 January 1999 and 7,159 patients who entered the registry by 31 December 2004 (total = 17,372), defining the study index date as either 1 January 1999 (for pre-1999 registrants) or date of registry entry. We then matched these patients to KPNW members without diabetes on year of birth and sex. For these nondiabetic subjects, we defined their index date as that of their matched diabetic subject. The prevalence of atrial fibrillation was calculated as of the index date. To conduct incidence

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analyses, we excluded patients with prevalent atrial fibrillation and 1,143 patients who had a history of stroke. The remaining patients were then followed until they died, left the health plan, or until 31 December 2008, whichever came first.

Outcomes and covariates

Patients were identified with prevalent atrial fibrillation if they had a diagnosis (ICD-9-CM 427.31) recorded in the medical record on or before their index date. Incident diagnoses were similarly identified any time after index until the end of follow-up among those patients who did not have prevalent atrial fibrillation. We also identified comorbidities present at baseline (ICD-9-CM code), including ischemic heart disease (410.x–414.x), history of stroke or cerebrovascular disease (430.x, 431.x, 432.x, 434.x, 435.x, 436.x, and 437.1), valvular disease (424.0–424.3), heart failure (428.x), hypertension (401.x–405.x), and history of depression (296.2x, 296.3x, 300.4, 309.1, and 311). Height, weight, and blood pressure were captured in the electronic medical record: for this study, baseline values of weight and blood pressure were the last measures before the index date. Baseline laboratory values, including LDL cholesterol, HDL cholesterol, triglycerides, serum creatinine (for estimation of glomerular filtration rate), and A1C (among patients with diabetes) were also those recorded latest on or before index date.

Statistical analyses

We conducted bivariate comparisons of baseline covariates among patients with and without diabetes using *t* tests for continuous variables and χ^2 tests for categorical variables. We calculated and compared age- and sex-adjusted incidence rates of atrial fibrillation per 1,000 person-years using regression for incidence densities. We then used Cox proportional hazards regression analysis to determine risk of incident atrial fibrillation for diabetes, controlling for other risk factors. All analyses were conducted with SAS (version 8.2; SAS Institute, Cary, NC).

Table 1—*Baseline characteristics of patients with and without diabetes*

	Diabetes	No diabetes	*P*
n	17,372	17,372	—
Age (years)	58.4 ± 11.5	58.4 ± 11.5	—
Sex (% male)	51.2	51.2	—
Ethnicity (% nonwhite)	11.9	6.4	<0.0001
Ever smoked (%)	22.2	25.4	<0.0001
Diabetes duration (years)	2.6 ± 3.8	—	—
BMI (kg/m^2)	33.6 ± 7.3	28.9 ± 5.7	<0.0001
Systolic blood pressure (mmHg)	136 ± 19	132 ± 18	<0.0001
Diastolic blood pressure (mmHg)	80 ± 10	79 ± 10	<0.0001
LDL cholesterol (mg/dl)	118 ± 34	132 ± 37	<0.0001
HDL cholesterol (mg/dl)	44 ± 13	52 ± 16	<0.0001
Triglycerides (mg/dl)	225 ± 211	164 ± 108	<0.0001
Estimated glomerular filtration rate (ml/min)	90 ± 30	84 ± 23	<0.0001
A1C (%)	7.8 ± 1.7	—	—
Comorbidities (%)			
Ischemic heart disease	10.6	9.8	0.014
History of stroke	4.4	2.9	<0.0001
Valvular disease	1.7	1.7	0.834
Hypertension	47.1	26.9	<0.0001
Heart failure	4.4	1.8	<0.0001
History of depression	15.8	11.7	<0.0001

Data are means ± SD or %.

RESULTS — Mean age of the study sample was 58.4 ± 11.5 years, and 51.2% were men (Table 1). Patients with diabetes were more likely to be nonwhite (11.9 vs. 6.4%, $P < 0.0001$), to have a higher BMI (33.6 ± 7.3 vs. 28.9 ± 5.7 kg/m^2, $P < 0.0001$), and to have higher blood pressure (136/80 vs. 132/79 mmHg, $P < 0.0001$). Comorbidities were more common among patients with diabetes, including ischemic heart disease (10.6 vs. 9.8%, $P = 0.014$), history of stroke (4.4 vs. 2.9%, $P < 0.0001$), hypertension (47.1 vs. 26.9%, $P < 0.0001$), heart failure (4.4 vs. 1.8%, $P < 0.0001$), and history of depression (15.8 vs. 11.7%, $P < 0.0001$).

The prevalence of atrial fibrillation was significantly greater among patients with diabetes (3.6 vs. 2.5%, $P < 0.0001$) (Fig. 1*A*). Prevalence increased with age in both groups but was significantly exaggerated among diabetic patients. These same relationships were observed among men (Fig. 1*B*) and women (Fig. 1*C*). Although men had a higher prevalence of atrial fibrillation in all age-groups regardless of diabetes, the difference in prevalence between those with and without diabetes was greater in women than in men. For example, among men aged 65–74 years, atrial fibrillation was 30% more prevalent among patients with diabetes (7.9 vs. 6.1%, $P = 0.037$). Among women, atrial fibrillation prevalence was 61% higher in diabetic patients in the 65–74 years age-group (6.1 vs. 3.8%, $P = 0.002$).

Over a mean follow-up of 7.2 ± 2.8 years, the 16,057 diabetic patients without prevalent atrial fibrillation or a history of stroke at baseline developed atrial fibrillation at an age- and sex-adjusted incidence rate of 9.1 per 1,000 person-years (95% CI 8.6–9.7) compared with a rate of 6.6 (6.2–7.1) among the 16,471 nondiabetic patients (Fig. 2*A*). Thus, the age- and sex-adjusted relative risk of atrial fibrillation was 38% (28–49%) greater among individuals with diabetes. Among men, the age-adjusted incidence of atrial fibrillation per 1,000 person-years was 10.8 (9.9–11.7) and 8.3 (7.6–9.1), respectively, for patients with and without diabetes (Fig. 1*B*), producing a 30% (17–43%) greater relative risk among men with diabetes. Among women, age-adjusted atrial fibrillation incidence was 7.6 (6.9–8.4) and 5.0 (4.5–5.6), respectively (Fig. 1*C*), with a higher relative risk attributable to diabetes of 52% (34–70%).

Table 2 displays the Cox regression models of time to development of atrial fibrillation. After controls were included for other known risk factors, patients with diabetes had a 16% greater risk of developing atrial fibrillation (hazard ratio [HR] 1.16 [95% CI 1.05–1.28]). However, atrial fibrillation risk associated with diabetes was substantially higher among women (1.26 [1.08–1.46]) and was not statistically significant among men (1.09 [0.96–1.24]). In addition, age ≥65 years tripled the risk of atrial fibrillation overall

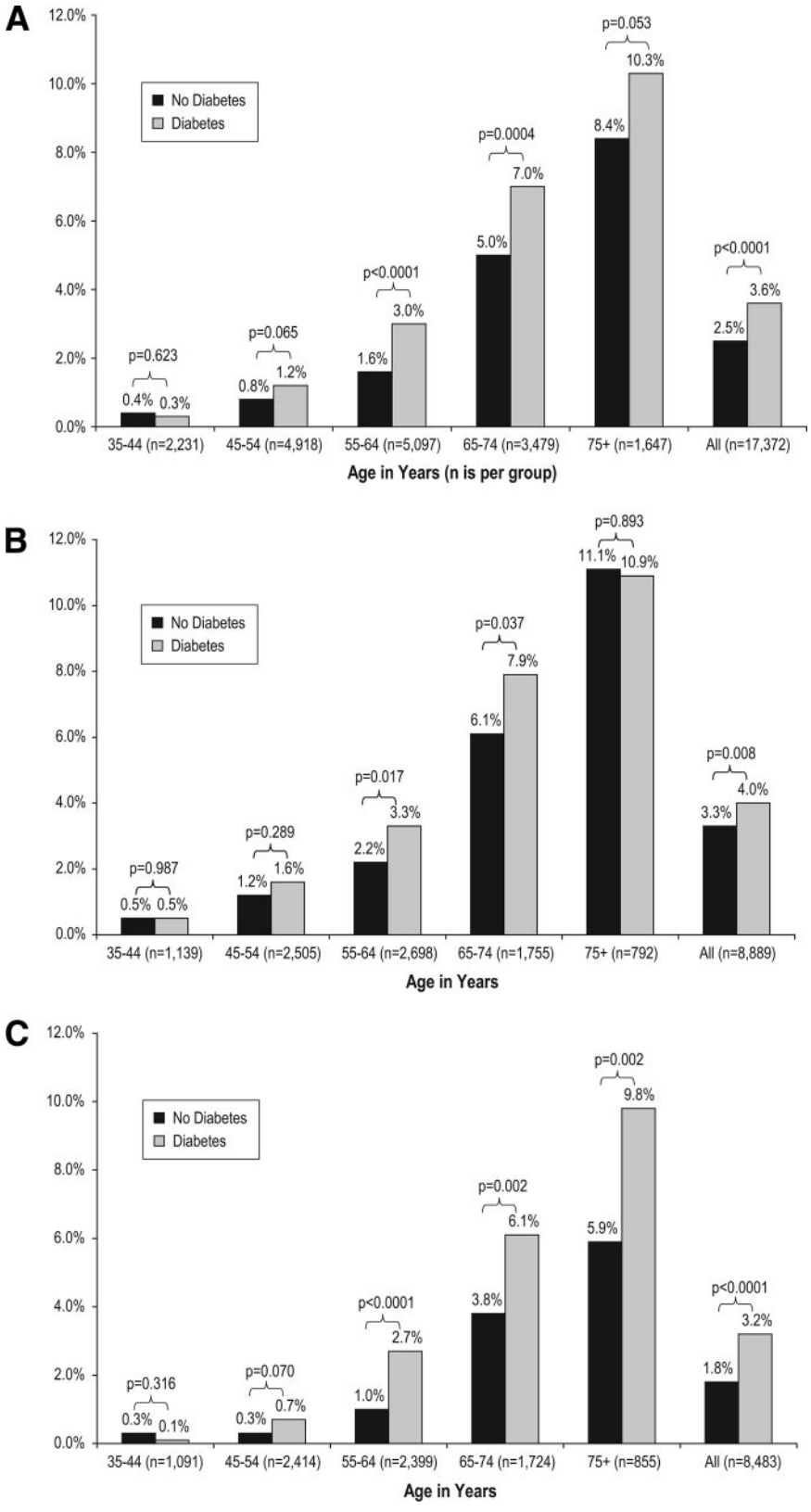

Figure 1—*Prevalence of atrial fibrillation by age and diabetes status. A: Data for all subjects. B: Data for men only. C: Data for women only.*

but had a greater effect among women, whereas BMI ≥30 kg/m^2 increased atrial fibrillation risk among men but was not a significant predictor in the women only model. White race, systolic blood pressure ≥140 mmHg, ischemic heart disease, valvular disease, hypertension, and heart failure were all significantly associated with atrial fibrillation risk in both sexes.

CONCLUSIONS — In this observational, age- and sex-matched cohort, longitudinal study of 34,744 patients with and without diabetes, we found that atrial fibrillation was 44% more prevalent and 38% more likely to develop when diabetes was present. Controlling for other known risk factors such as hypertension and heart failure approximately halved the risk of incident atrial fibrillation. However, this finding differed between men and women. Diabetes was not a significant predictor of atrial fibrillation among men after controlling for other risk factors but was highly significant among women.

Recent studies have provided evidence of how comorbidities can have important modulatory effects on the progression and complications of atrial fibrillation (15). Thus far, studies evaluating the specific role of diabetes have been lacking. In the recent development of a risk score for atrial fibrillation, the Framingham Heart Study did not find diabetes to be a significant predictor of atrial fibrillation risk (16). This finding is contrary to a previous Framingham report that found diabetes to be a strong independent risk factor (10). Consistent with the latter study, our findings suggest that in the present population, diabetes made a significant contribution to the prevalence and incidence of atrial fibrillation, independent of other established risk factors such as hypertension and congestive heart failure. Although this result needs to be confirmed in other populations, there may be important public health implications. The steadily rising prevalence of diabetes may further increase the prevalence of atrial fibrillation, already the most common arrhythmia diagnosis around the globe. Conversely, any efforts made to prevent and treat diabetes may reduce the burden of atrial fibrillation.

Potential mechanisms

These findings also underscore the importance of understanding the mechanistic links responsible for this association. Published studies point to abnormalities of the autonomic nervous system as being an important mechanism in initiation and maintenance of atrial fibrillation. In observational clinical studies, initiation of atrial fibrillation episodes have been ascribed to variations in autonomic tone

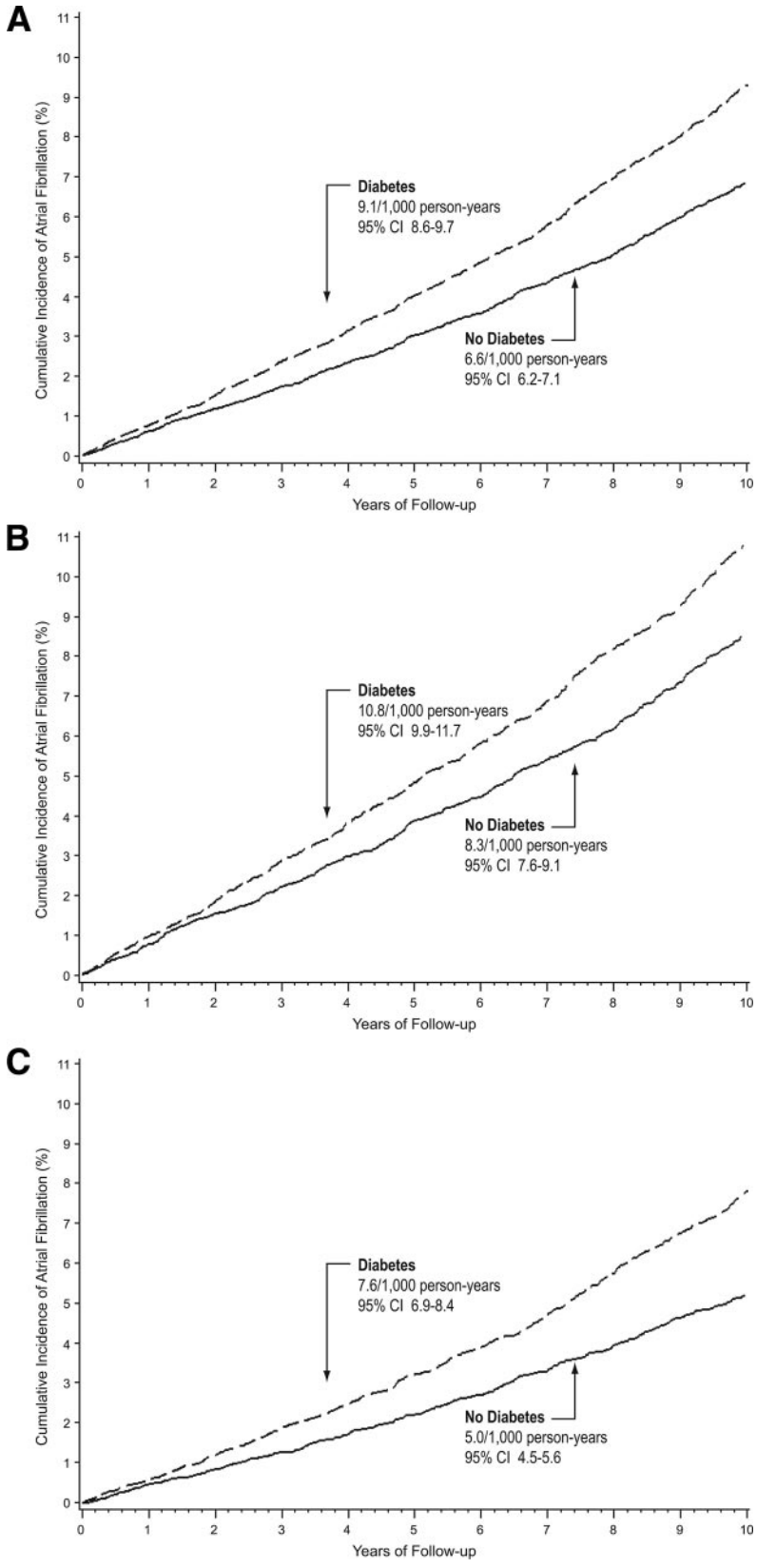

Figure 2—*Cumulative age- and sex-adjusted incidence of atrial fibrillation by diabetes status among patients who did not have atrial fibrillation at baseline.* A*: Data for all subjects.* B*: Data for men only. C: Data for women only.*

(17). Similar associations with altered autonomic tone have been made in conditions such as sleep apnea (18). This work has been extended in a canine model of atrial fibrillation in which researchers have observed that discharges from the stellate ganglia and vagal nerves often precede the onset of paroxysmal atrial fibrillation (19). In fact, targeted ablation of these latter structures appears to prevent the onset of paroxysmal atrial fibrillation in dogs, and such therapies are being evaluated in humans (20–22). Analogous to the well-described peripheral autonomic neuropathy observed in diabetes, cardiac autonomic neuropathy is a serious but overlooked complication of diabetes (23,24). Taken together, these findings lend credence to the hypothesis that cardiac autonomic dysfunction may be an important mechanism for the increased propensity for atrial fibrillation in diabetes and warrants further careful study.

The increased predilection for atrial fibrillation among female diabetic subjects compared with male diabetic subjects is a novel finding that needs to be explored further. A prolonged intrinsic QT interval is a well-recognized sex-related difference in cardiac electrophysiological properties. Women have a longer intrinsic QT interval, a phenomenon that has been attributed to higher levels of estrogens affecting the cardiac repolarizing potassium ion channels (25). Although this finding is unlikely to affect the propensity for atrial fibrillation, there could be other, yet undiscovered, sex differences in atrial ion channel properties or the remodeling of the autonomic tone in female diabetic subjects that could account for the current observations.

Limitations

An observational study has some inherent limitations. In a subgroup of patients, atrial fibrillation is an asymptomatic and paroxysmal phenomenon, such that it may escape detection unless it is observed incidentally. It is possible that patients with diabetes may be more likely to have electrocardiograms or ambulatory monitoring in the absence of symptomatic atrial fibrillation compared with nondiabetic patients. Conversely, diabetes is undiagnosed in ~25% of individuals (1), suggesting that the prevalence of diabetes may have been underestimated in this population. If so, we may be underestimating the effect of diabetes on increased prevalence of atrial fibrillation in this population. Finally, unmeasured

Table 2—*Cox regression analysis of time to atrial fibrillation among patients without atrial fibrillation or stroke at baseline*

	Men and women		Men only		Women only	
	HR (96% CI)	*P*	HR (96% CI)	*P*	HR (96% CI)	*P*
Diabetes	1.16 (1.05–1.28)	0.003	1.09 (0.96–1.24)	0.170	1.26 (1.08–1.46)	0.003
Age ≥65 years	3.10 (2.81–3.43)	<0.001	2.69 (2.37–3.07)	<0.001	3.80 (3.24–4.46)	<0.001
Male sex	1.37 (1.24–1.50)	<0.001	—	—	—	—
White race	1.60 (1.30–1.96)	<0.001	1.58 (1.20–2.07)	0.001	1.61 (1.18–2.19)	0.002
Ever smoked	1.02 (0.91–1.15)	0.751	1.02 (0.88–1.18)	0.812	1.02 (0.84–1.24)	0.845
BMI ≥30 kg/m^2	1.22 (1.11–1.34)	<0.001	1.29 (1.13–1.46)	<0.001	1.13 (0.97–1.31)	0.115
Systolic blood pressure ≥140 mmHg	1.24 (1.13–1.36)	<0.001	1.29 (1.13–1.46)	<0.001	1.17 (1.01–1.35)	0.032
Ischemic heart disease	1.71 (1.53–1.93)	<0.001	1.62 (1.40–1.88)	<0.001	1.93 (1.60–2.33)	<0.001
Valvular disease	2.18 (1.73–2.74)	<0.001	2.05 (1.50–2.81)	<0.001	2.40 (1.71–3.36)	<0.001
Hypertension	1.32 (1.20–1.46)	<0.001	1.29 (1.13–1.46)	<0.001	1.34 (1.15–1.55)	<0.001
Heart failure	2.33 (1.95–2.78)	<0.001	2.39 (1.86–3.07)	<0.001	2.18 (1.68–2.82)	<0.001

variables such as socioeconomic status, education, and alcohol intake could account for some of the differences we report.

Summary

In conclusion, in this population, diabetes was an independent determinant of atrial fibrillation prevalence and incidence. Prevalence was higher at baseline and there was an exaggerated increase of atrial fibrillation incidence over time in diabetic versus nondiabetic patients. Women with diabetes had an unexplained higher predilection for atrial fibrillation compared with men. These findings have potential public health implications, especially in women, and emphasize the need for further investigation of the mechanistic links between diabetes and atrial fibrillation.

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No potential conflicts of interest relevant to this article were reported.

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