Temporal trends in lifetime risks of atrial fibrillation and its complications between 2000 and 2022: Danish, nationwide, population based cohort study

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ABSTRACT

OBJECTIVES

To examine how the lifetime risks of atrial fibrillation and of complications after atrial fibrillation changed over time.

DESIGN

Danish, nationwide, population based cohort study.

SETTING

Population of Denmark from 1 January 2000 to 31 December 2022.

PARTICIPANTS

3.5 million individuals (51.7% women and 48.3% men) who did not have atrial fibrillation at 45 years of age or older were followed up until incident atrial fibrillation, migration, death, or end of follow-up, whichever came first. All 362 721 individuals with incident atrial fibrillation (46.4% women and 53.6% men), but with no prevalent complication, were further followed up until incident heart failure, stroke, or myocardial infarction.

MAIN OUTCOME MEASURES

Lifetime risk of atrial fibrillation and lifetime risks of complications after atrial fibrillation over two prespecified periods (2000-10 *v* 2011-22).

RESULTS

The lifetime risk of atrial fibrillation increased from 24.2% in 2000-10 to 30.9% in 2011-22 (difference 6.7% (95% confidence interval 6.5% to 6.8%)). After atrial fibrillation, the most frequent complication was heart failure with a lifetime risk of 42.9% in 2000-10 and 42.1% in 2011-22 (−0.8% (−3.8% to 2.2%)). Individuals with atrial fibrillation lost 14.4 years with no heart failure. The lifetime risks of stroke and of myocardial infarction after atrial fibrillation decreased slightly between the two periods, from 22.4% to 19.9% for stroke (−2.5% (−4.2% to −0.7%)) and from 13.7% to 9.8% for myocardial infarction (−3.9% (−5.3% to −2.4%). No evidence was reported of a differential decrease between men and women.

CONCLUSION

Lifetime risk of atrial fibrillation increased over two decades of follow-up. In individuals with atrial fibrillation, about two in five developed heart failure and one in five had a stroke over their remaining lifetime after atrial fibrillation diagnosis, with no or only small improvement over time. Stroke risks and heart failure prevention strategies are needed for people with atrial fibrillation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Once atrial fibrillation develops, patient care has focused on the risk of stroke

Long term downstream consequences of atrial fibrillation, including stroke, heart failure, and myocardial infarction, must be better studied

Changes over time in the lifetime risks of atrial fibrillation and of complications after atrial fibrillation remain to be fully explored with new stroke prevention treatment for atrial fibrillation

WHAT THIS STUDY ADDS

In registry analyses of the entire population in Denmark over 2000-22, the lifetime risks of complications after atrial fibrillation were high

The most common complication was heart failure (lifetime risk 41%), followed by stroke (21% for any stroke and 13% for ischaemic stroke) and myocardial infarction (12%)

From 2000-10 to 2011-22, virtually no improvement was reported in the lifetime risk of heart failure after atrial fibrillation (−0.8%) and only slight decreases in the lifetime risks of stroke (−2.5% for any stroke, −5.2% for ischaemic stroke) and myocardial infarction (−3.9%) after atrial fibrillation

Introduction

Atrial fibrillation is estimated to affect 17.9 million people in Europe by 2060 and 15.9 million people in the US by 2050.[1 2] All cause and cardiovascular mortality among individuals with atrial fibrillation has improved over time, although the excess mortality associated with atrial fibrillation is still high.[3-5] Atrial fibrillation is also associated with increased risks of stroke,[6] heart failure,[7] and myocardial infarction.[8] Therefore, prevention of atrial fibrillation is a major public health priority.

Effective risk assessment for atrial fibrillation and its complications is key to primary and secondary prevention by increasing awareness of the condition.[9-11] In this context, the residual lifetime risk measures the cumulative risk for developing a disease over the remaining lifespan among individuals who attained a given index age disease-free.[12 13] Lifetime risk is a tractable quantity that can help to promote lifestyle change using recommendations and is an important communication tool to the public.[14 15] Population and community based cohort studies have reported on the lifetime risk of atrial fibrillation, which is estimated as affecting one in three in individuals of European ancestry in Europe and the US.[16-18]

Patients are commonly told that the main danger after being diagnosed with atrial fibrillation is the increased risk of stroke, but atrial fibrillation is associated with increased risk of other complications. Quantification of the long term downstream consequences of atrial fibrillation will further improve our understanding of the burden of atrial fibrillation and how to communicate risks to the public, but previous investigations do not appear to have addressed this question. Furthermore,

data for temporal trends in the lifetime risks of atrial fibrillation and of subsequent complications are absent. Monitoring temporal changes in atrial fibrillation burden is critical to indirectly measure the effectiveness of improvements in atrial fibrillation management and of primary and secondary prevention strategies, particularly in the new phase of stroke prevention therapy for atrial fibrillation. In this study of the Danish population, we aimed to estimate the lifetime risk of atrial fibrillation and of complications after atrial fibrillation, and to examine their temporal trends over 2000-22.

Methods

Setting, data sources, and study population

We conducted a nationwide cohort study from 1 January 2000 to 31 December 2022 in Denmark. We estimated the lifetime risk of atrial fibrillation among individuals who did not have atrial fibrillation and were aged 45 to 95 years. Among individuals with newly diagnosed atrial fibrillation, we estimated the lifetime risks of subsequent complications, including heart failure, any stroke, ischaemic stroke, myocardial infarction, and systemic embolism. To assess temporal trends, we compared two periods: 2000-10 and 2011-22.

Study populations and data were obtained from administrative nationwide registries. Firstly, we used the Danish National Patient Registry to identify inpatient hospital stays and outpatient contacts. We retrieved individual level information on dates of hospital admission and discharge, procedures performed, and primary and several secondary diagnoses per discharge. Diagnoses were coded according to the International Classification of Diseases 8th Revision (ICD-8) before 1994 and to the 10th revision (ICD-10) from 1994. Supplemental table 1 gives the ICD codes we used. We used the admission dates for outpatient contacts and discharge dates for inpatients contacts. In the third version of the Danish National Patient Registry, which was implemented in early 2019, information to classify hospital contacts as inpatients or outpatients was no longer available, and we used admission dates for all diagnoses. Secondly, we extracted individual level information on sex, date of birth, vital status, and migration from the Civil Registration System.[19] Thirdly, we retrieved information on pharmacological treatments from the Danish National Prescription Registry.[20] Medications were coded in accordance with the anatomical therapeutic chemical classification system. The codes we used are given in supplemental table 1.

Participants and outcomes for lifetime risk of atrial fibrillation

In each period (2000-22, 2000-10, and 2011-22), we included all Danish individuals aged 45 years or older and who did not have atrial fibrillation. We excluded participants aged 95 or older. To enable medical history assessment, we further excluded individuals who had been Danish residents for fewer than five years. Participants were followed up until the earliest of incident atrial fibrillation, death, age of 95 years, emigration, or the end of the period. In the primary analysis, 45 years was the index age. In secondary analyses, we repeated the analyses for the following index ages: 55 years or older, 65 years or older, and 75 years or older.

To assess newly diagnosed atrial fibrillation, we identified individuals with an incident hospital primary or secondary diagnosis of atrial fibrillation or atrial flutter (supplemental table 1). In the Danish National Patient Registry, the positive predictive value of atrial fibrillation or atrial flutter ICD code is 94-95% for inpatients and outpatients.[21 22]

Participants and outcomes for lifetime risks of complications after atrial fibrillation

In each period, all patients with incident atrial fibrillation were further followed up for complications after their incident hospital diagnosis of atrial fibrillation up until death, age 95 years, emigration, or the end of the period. The population was restricted to patients with newly diagnosed atrial fibrillation in the study period and did not include prevalent patients to prevent survival bias. We identified the first occurrence after atrial fibrillation, if any, of each of the following outcomes: heart failure, any stroke, ischaemic stroke, myocardial infarction, and systemic embolism. For each outcome, we excluded patients with a prevalent diagnosis of the complication of interest at the time of incident atrial fibrillation. For example, when examining heart failure after atrial fibrillation, patients with a history of heart failure at or before the diagnosis of atrial fibrillation were excluded. To limit the possibility of misclassification, we did not use information about previous coronary artery bypass grafting or primary coronary intervention to identify prior myocardial infarction. Both procedures may be used for severe chronic coronary syndrome with no evidence of acute myocardial infarction. We also excluded patients who experienced a complication of interest fewer than seven days after newly diagnosed atrial fibrillation to ensure temporal separation between the diagnoses. All complications were identified as primary or secondary diagnoses (definitions in supplemental table 1). The positive predictive values of ICD codes were more than 80% for heart failure,[23] more than 90% for ischaemic stroke,[24] more than 70% for intracerebral haemorrhage,[24] and more than 97% for myocardial infarction,[22] while the value is unknown for systemic embolism. We conducted analyses for each of the index ages 45, 55, 65, and 75 years.

Covariates

To characterise the study populations, we assessed history of hypertension, diabetes, dyslipidaemia, heart failure, myocardial infarction, any stroke, cardiomyopathy, valvular heart disease, chronic obstructive pulmonary disease, chronic kidney disease, ischaemic stroke, and systemic embolism. Furthermore, we assessed family income and

educational attainment from Statistics Denmark. Details are in the appendix. Information was assessed among individuals who did not have atrial fibrillation at cohort entry and among people who had atrial fibrillation at the time of incident atrial fibrillation (definitions in supplemental table 1).

Statistical methods

Age was the time scale in all analyses. We used the Aalen-Johansen estimator to calculate the cumulative incidence of atrial fibrillation and of complications after atrial fibrillation, accounting for left truncation and for the competing risk of death. The time at risk started at the exact entry age: index age or older for the lifetime risk of atrial fibrillation, and age at the diagnosis of incident atrial fibrillation for the lifetime risks of complications. The time at risk ended at the individual's age at the earliest of the following dates: first incident atrial fibrillation or complication after atrial fibrillation, death, age 95 years, emigration, or end of study period. The lifetime risk was the cumulative incidence at the age of 95 years. We used the pseudo-value regression approach on the lifetime risk to obtain 95% confidence intervals (CI) and P values.[13] We tested for differences in lifetime risks between men and women and between period 1 and period 2.

To translate the lifetime risk into the time domain, we estimated the restricted mean time lost as the area under the cumulative incidence function from the index age of 45 years up to 95 years.[25] For the lifetime risk of atrial fibrillation, the restricted mean time lost gives the mean atrial fibrillation-free time lost between 45 and 95 years. For the lifetime risk of complications after atrial fibrillation, for example heart failure, the restricted mean time lost gives the mean time lost with no heart failure.

We repeated these analyses with adjustment for the covariates listed above. We estimated a propensity score to be in period 2 versus 1 by using all covariates in a logistic regression model. We then applied stabilised inverse propensity weights to the pseudo-value regression.

We also performed subgroup analyses for the lifetime risk of atrial fibrillation and of complications after atrial fibrillation (appendix). Subgroups were defined by sex, cardiometabolic risk factors, clinical comorbidities, and social factors, as aforementioned. We tested for differences in lifetime risks between subgroups and we tested for interaction between temporal trends across periods and subgroups.

Analyses were performed in Stata (StataCorp 2019: release 17.0, College Station, TX, USA).

Patient and public involvement statement

No funding was available to support patients or members of the public in the study design, interpretation of results, or development of the dissemination strategy. We appraised the registry based data and analysed them without public or patient involvement.

Results

Characteristics of participants

We included 3 574 903 individuals who did not have atrial fibrillation at index age 45 years or older, of whom 1 727 703 were men (48.3%) and 1 847 200 were women (51.7%). Flow diagrams showing the selection of participants are in supplemental figure 1. Participant characteristics are summarised in table 1 as well as supplemental tables 2 and 3 by sex. Among participants free of atrial fibrillation at entry, the prevalence of hypertension, diabetes, dyslipidaemia, and stroke increased from 2000-10 to 2011-22. Moreover, we followed up 362 721 individuals with newly diagnosed atrial fibrillation, of whom 194 505 were men and 168 216 were women. At diagnosis of atrial fibrillation, the distribution of age was similar between periods, while the prevalence of hypertension, dyslipidaemia, and diabetes increased over time, and the prevalence of heart failure and myocardial infarction decreased over time.

Lifetime risk of atrial fibrillation

At the index age of 45 years, the lifetime risk of atrial fibrillation over 2000-22 was 27.7% ((95% CI 27.6% to 27.8%); table 2 and supplemental table 4). The lifetime risk of atrial fibrillation was higher among men, individuals with history of hypertension, heart failure, myocardial infarction, cardiomyopathy, dyslipidaemia, valvular heart disease and individuals with higher educational attainment and higher family income. History of stroke, chronic obstructive pulmonary disease, and chronic kidney disease were associated with lower lifetime risk of atrial fibrillation because they were also associated with considerably higher mortality (supplemental table 5 and supplemental figures 2-13).

From 2000-10 to 2011-22, the overall lifetime risk of atrial fibrillation increased from 24.2% (95% CI 24.1% to 24.3%) to 30.9% (30.8% to 31.0%), an absolute increase of 6.7% ((6.5% to 6.8%); table 3 and supplemental tables 6). Findings were similar after adjustment for covariates at entry (supplemental table 7). Over time, the lifetime risk of atrial fibrillation increased across all subgroups (supplemental table 8 and supplemental figures 2-13). The increase in lifetime risk was slightly higher among men, individuals with a history of heart failure or stroke, and among individuals with no dyslipidaemia.

All findings at index ages 55, 65, and 75 years were consistent. Across 2000-22, the lifetime risk of atrial fibrillation was 27.6% at 55 years, 26.9% at 65 years, and 24.3% at 75 years (supplemental table 9), and the lifetime risk of atrial fibrillation increased between the two periods by an absolute value of 6.5%, 6.3%, and 5.6% at index ages 55, 65, and 75 years (supplemental table 10).

Lifetime risk of complications after atrial fibrillation

Among patients with an incident diagnosis of atrial fibrillation, heart failure was the most frequent complication with a lifetime risk of 41.2% (95% CI

Table 1 | Characteristics of the study populations. Data are number (percentage), unless otherwise specified

Characteristics	No atrial fibrillation and aged ≥45 years			Atrial fibrillation diagnosis		
	Overall (n=3 574 903)	Period 1 (n=2 776 110)	Period 2 (n=2 924 053)	Overall (n=362 721)	Period 1 (n=151 757)	Period 2 (n=210 964)
Age, median (IQR), years	48 (45-62)	54 (45-66)	55 (45-66)	76 (67-83)	76 (67-83)	75 (68-83)
Men	1 727 703 (48.3)	1 322 685 (47.7)	1 409 879 (48.2)	194 505 (53.6)	78 722 (51.9)	115 783 (54.9)
Cardiometabolic risk factors:						
Hypertension	353 899 (9.9)	307 138 (11.1)	624 931 (21.4)	213 433 (58.8)	81 081 (53.4)	132 352 (62.7)
Diabetes	125 352 (3.5)	100 953 (3.6)	180 765 (6.2)	52 836 (14.6)	18 562 (12.2)	34 274 (16.2)
Dyslipidaemia	124 823 (3.5)	87 555 (3.2)	510 845 (17.5)	125 767 (34.7)	34 589 (22.8)	91 178 (43.2)
Clinical comorbidities:						
Heart failure	34 732 (1.0)	32 675 (1.2)	38 340 (1.3)	62 078 (17.1)	31 168 (20.5)	30 910 (14.7)
Myocardial infarction	77 075 (2.2)	73 114 (2.6)	77 935 (2.7)	45 985 (12.7)	21 483 (14.2)	24 502 (11.6)
Any stroke	83 737 (2.3)	75 280 (2.7)	96 604 (3.3)	51 652 (14.2)	21 305 (14.0)	30 347 (14.4)
Cardiomyopathy	5092 (0.1)	3507 (0.1)	8739 (0.3)	7494 (2.1)	2854 (1.9)	4640 (2.2)
Valvular heart disease	17 966 (0.5)	15 301 (0.6)	31 163 (1.1)	36 967 (10.2)	13 390 (8.8)	23 577 (11.2)
Chronic obstructive pulmonary disease	55 871 (1.6)	51 600 (1.9)	75 262 (2.6)	44 086 (12.2)	18 382 (12.1)	25 704 (12.2)
Chronic kidney disease	47 059 (1.3)	36 623 (1.3)	52 806 (1.8)	22 405 (6.2)	8,078 (5.3)	14 327 (6.8)
Ischaemic stroke	44 043 (1.2)	39 840 (1.4)	51 393 (1.8)	26 059 (7.2)	12 760 (8.4)	13 299 (6.3)
Systemic embolism	6518 (0.2)	5869 (0.2)	5742 (0.2)	3189 (0.9)	1632 (1.1)	1557 (0.7)
Social factors:						
Higher family income*	1 752 996 (50.0)	1 366 706 (50.0)	1 436 612 (50.0)	181 298 (50.0)	75 868 (50.0)	105 430 (50.0)
Educational attainment†						
Lower	1 088 261 (33.5)	953 943 (38.3)	833 889 (29.8)	145 309 (44.6)	61 080 (50.8)	84 229 (40.9)
Medium	1 355 019 (41.7)	1 005 325 (40.4)	1 211 401 (43.2)	122 228 (37.5)	40 851 (34.0)	81 377 (39.5)
Higher	806 789 (24.8)	530 0173 (21.3)	757 152 (27.0)	58 459 (17.9)	18 274 (15.2)	40 185 (19.5)

Overall is from 2000 to 2022, period 1 is from 2000 to 2010, and period 2 is from 2011 to 2022.
IQR=interquartile range.
*Five year mean annual family income higher than calendar year-specific median value.
†Lower: early childhood, primary education, and lower secondary education (ISCED 0-2). Medium: general upper secondary education and vocational upper secondary education (ISCED 3). Higher: short cycle tertiary, medium length tertiary, bachelor's level educations or equivalent, second cycle, Master's level or equivalent, and PhD level (ISCED 5-8). ISCED 4 does not exist in Denmark.
Missing values among atrial fibrillation-free participants: education: 324 834 (9.1%); income: 68 894 (1.9%). Missing values among atrial fibrillation participants: education 36 725 (10.1%); income: 117 (0.03%).

39.8% to 42.7%) from index age 45 years (table 2, fig 1, supplemental table 11-12). The lifetime risks of any stroke and ischaemic stroke after atrial fibrillation were 21.4% (20.6% to 22.3%) and 13.1% (12.4% to 13.8%). The lifetime risk of myocardial infarction after atrial fibrillation was 11.5% (10.9% to 12.2%) and diagnosed systemic embolism after atrial fibrillation was uncommon, with a lifetime risk of 1.8% (1.6% to 2.0%).

Associations between covariates and lifetime risk of complications following atrial fibrillation are summarised in supplemental tables 13-17 and supplemental figures 14-74. Men had a higher lifetime risk of complications after atrial fibrillation compared with women for heart failure (44.2% *v* 34.6%) and myocardial infarction (12.2% *v* 10.2%), while the lifetime risk of stroke after atrial fibrillation was lower in men than in women (20.6% *v* 22.6%). Individuals who had a history of hypertension had a larger lifetime risk of heart failure, ischaemic stroke, myocardial infarction, and systemic embolism compared with those who did not. Additionally, people with history of myocardial infarction (58.4% *v* 39.6%), cardiomyopathy (84.5% *v* 39.9%), or valvular

Table 2 | Lifetime risks of atrial fibrillation and of complications after atrial fibrillation at index age 45 years, 2000-22

Outcome	Lifetime risk, % (95% confidence interval)					Restricted mean time lost, years (95% confidence interval)			
	Overall	Men	Women	Absolute difference, men v women	P value	Overall	Men	Women	Absolute difference, men v women
Atrial fibrillation	27.7 (27.6 to 27.8)	29.9 (29.8 to 30.0)	25.6 (25.5 to 25.7)	4.3 (4.1 to 4.5)	<0.001	5.3 (5.3 to 5.4)	6.3 (6.3 to 6.4)	4.4 (4.4 to 4.4)	1.9 (1.9 to 1.9)
Heart failure	41.2 (39.8 to 42.7)	44.2 (42.3 to 46.1)	34.6 (32.6 to 36.6)	9.6 (6.8 to 12.3)	<0.001	13.6 (12.9 to 14.3)	15.1 (14.2 to 16.0)	10.2 (9.2 to 11.3)	4.9 (3.4 to 6.3)
Any stroke	21.4 (20.6 to 22.3)	20.6 (19.6 to 21.7)	22.6 (21.2 to 24.0)	−2.0 (−3.7 to −0.2)	0.03	6.2 (5.9 to 6.6)	6.2 (5.7 to 6.6)	6.4 (5.7 to 7.0)	−0.2 (−1.0 to 0.6)
Ischaemic stroke	13.1 (12.4 to 13.8)	12.6 (11.8 to 13.4)	13.8 (12.6 to 15.0)	−1.2 (−2.7 to 0.3)	0.11	3.8 (3.5 to 4.2)	3.8 (3.4 to 4.2)	3.9 (3.3 to 4.5)	−0.1 (−0.8 to 0.6)
Myocardial infarction	11.5 (10.9 to 12.2)	12.2 (11.3 to 13.1)	10.2 (9.3 to 11.2)	1.9 (0.6 to 3.2)	0.003	3.6 (3.3 to 3.9)	3.9 (3.5 to 4.3)	3.0 (2.6 to 3.4)	0.9 (0.3 to 1.5)
Systemic embolism	1.8 (1.6 to 2.0)	1.7 (1.5 to 2.0)	2.0 (1.6 to 2.3)	−0.3 (−0.7 to 0.2)	0.24	0.6 (0.5 to 0.6)	0.6 (0.5 to 0.7)	0.6 (0.4 to 0.7)	0.0 (−0.2 to 0.2)

Lifetime risk is cumulative incidence function at age 95 years. Restricted mean time lost is the number of disease-free years lost by age 95 years.

Table 3 | Temporal trends in lifetime risks of atrial fibrillation and complications after atrial fibrillation, at index age 45 years

	Lifetime risk, % (95% confidence interval)			Restricted mean time lost, years (95% confidence interval)		
Outcome	Overall	Men	Women	Overall	Men	Women
Atrial fibrillation						
2000-10	24.2 (24.1 to 24.3)	25.7 (25.5 to 25.8)	22.8 (22.6 to 22.9)	4.8 (4.8 to 4.8)	5.6 (5.6 to 5.6)	4.0 (4.0 to 4.1)
2011-22	30.9 (30.7 to 31.0)	33.6 (33.4 to 33.7)	28.2 (28.1 to 28.4)	5.8 (5.8 to 5.8)	6.9 (6.9 to 6.9)	4.7 (4.7 to 4.8)
Absolute difference	6.7 (6.5 to 6.8)	7.9 (7.7 to 8.1)	5.5 (5.3 to 5.7)	1.0 (1.0 to 1.1)	1.3 (1.3 to 1.4)	0.7 (0.7 to 0.8)
Trend P value	<0.001	<0.001	<0.001	—	—	—
Complications after atrial fibrillation						
Heart failure:						
2000-10	42.9 (40.7 to 45.1)	46.3 (43.5 to 49.1)	35.0 (32.4 to 37.6)	14.4 (13.2 to 15.5)	16.2 (14.7 to 17.7)	10.2 (9.2 to 11.2)
2011-22	42.1 (40.1 to 44.2)	44.8 (42.0 to 47.6)	35.7 (32.4 to 38.8)	14.4 (13.4 to 15.4)	15.7 (14.4 to 17.0)	11.2 (9.4 to 13.0)
Absolute difference	−0.8 (−3.8 to 2.2)	−1.5 (−5.5 to 2.4)	0.6 (−3.5 to 4.7)	0.0 (−1.5 to 1.5)	−0.5 (−2.5 to 1.4)	1.0 (−1.0 to 3.1)
Trend P value	0.62	0.44	0.74	—	—	—
Any stroke:						
2000-10	22.4 (21.1 to 23.6)	21.9 (20.3 to 23.6)	22.7 (20.8 to 24.6)	6.7 (6.2 to 7.3)	6.9 (6.1 to 7.6)	6.3 (5.6 to 7.1)
2011-22	19.9 (18.7 to 21.0)	18.8 (17.4 to 20.1)	22.0 (19.7 to 24.0)	5.9 (5.4 to 6.4)	5.6 (5.0 to 6.1)	6.7 (5.6 to 7.7)
Absolute difference	−2.5 (−4.2 to −0.7)	−3.1 (−5.3 to −1.0)	−0.8 (−3.7 to 2.1)	−0.8 (−1.6 to −0.1)	−1.3 (−2.3 to −0.4)	0.3 (−1.0 to 1.6)
Trend P value	0.005	0.004	0.60	—	—	—
Ischaemic stroke:						
2000-10	16.1 (15.0 to 17.1)	15.9 (14.6 to 17.2)	15.9 (14.4 to 17.5)	4.8 (4.4 to 5.3)	5.0 (4.4 to 5.6)	4.4 (3.8 to 5.0)
2011-22	10.8 (9.8 to 11.8)	10.0 (9.0 to 11.0)	12.4 (10.4 to 14.5)	3.3 (2.8 to 3.7)	3.0 (2.5 to 3.4)	3.9 (2.9 to 4.9)
Absolute difference	−5.2 (−6.7 to −3.8)	−5.9 (−7.6 to −4.3)	−3.5 (−6.0 to −0.9)	−1.6 (−2.2 to −1.0)	−2.0 (−2.8 to −1.3)	−0.5 (−1.7 to 0.7)
Trend P value	<0.001	<0.001	0.005	—	—	—
Myocardial infarction:						
2000-10	13.7 (12.7 to 14.8)	14.2 (12.9 to 15.6)	12.6 (11.9 to 14.2)	4.28 (3.81 to 4.75)	4.6 (4.0 to 5.2)	3.7 (3.0 to 4.4)
2011-22	9.8 (8.9 to 10.8)	10.6 (9.3 to 11.9)	8.3 (7.2 to 9.5)	3.14 (2.69 to 3.60)	3.5 (2.8 to 4.1)	2.5 (2.0 to 3.0)
Absolute difference	−3.9 (−5.3 to −2.4)	−3.6 (−5.5 to −1.7)	−4.3 (−6.3 to −2.3)	−1.1 (−1.79 to −0.49)	−1.1 (−2.0 to −0.2)	−1.2 (−2.1 to −0.3)
Trend P value	<0.001	<0.001	<0.001	—	—	—
Systemic embolism:						
2000-10	2.0 (1.6 to 2.3)	1.8 (1.4 to 2.3)	2.1 (1.6 to 2.7)	0.6 (0.5 to 0.7)	0.6 (0.4 to 0.9)	0.6 (0.4 to 0.8)
2011-22	1.7 (1.5 to 2.0)	1.7 (1.4 to 2.0)	1.8 (1.3 to 2.3)	0.6 (0.5 to 0.7)	0.6 (0.4 to 0.7)	0.6 (0.4 to 0.8)
Absolute difference	−0.2 (−0.7 to 0.2)	−0.1 (−0.7 to 0.4)	−0.3 (−1.0 to 0.4)	−0.0 (−0.2 to 0.2)	−0.0 (−0.3 to 0.2)	−0.0 (−0.3 to 0.3)
Trend P value	0.32	0.58	0.41	—	—	—

Lifetime risk is the cumulative incidence function at age 95 years. Restricted mean time lost is the number of disease-free years lost by age 95 years.

heart disease (62.5% *v* 39.6%) had notably higher lifetime risks of heart failure after atrial fibrillation. Conversely, individuals with prior chronic obstructive pulmonary disease or chronic kidney disease and lower family income generally had lower lifetime risks of complications following atrial fibrillation because of the association that these risk factors have with higher overall mortality rates (supplemental figures 14-74).

Over time, lifetime risk of heart failure after atrial fibrillation did not change (42.9% in 2000-10 *v* 42.1% in 2011-22) and slight decreases were noted in the lifetime risk for any stroke (−2.5% (−4.2% to −0.7%)), ischaemic stroke (−5.2% (−6.7% to −3.8%)), and myocardial infarction after atrial fibrillation (−3.9% (−5.3% to −2.4%) (table 3, supplemental tables 18-19). Analyses adjusted for covariates at the time of atrial fibrillation diagnoses showed consistent findings (supplemental table 20).

No evidence suggested differential temporal trends for all complications after atrial fibrillation according to sex and most covariates (fig 2, table 3, supplemental tables 21-25, supplemental figures 14-74). However, the lifetime risk of heart failure decreased from 2000-10 to 2011-22 among patients with atrial fibrillation and a history of hypertension (52.6% *v* 41.8%) or dyslipidaemia (52.1% *v* 44.5%). Additionally, the decrease from 2000-10 to 2011-22 in the lifetime risk of myocardial infarction after atrial fibrillation was larger among patients with dyslipidaemia versus people with normal lipids (−11.1% *v* −3.7%).

The analyses of secondary index ages showed consistent findings. The lifetime risk of each complication was smaller with increasing index age (supplemental tables 26-28). Moreover, we found evidence of decrease over time in the lifetime risks for heart failure and systemic embolism after atrial fibrillation at index ages 55 and 75 years.

Discussion

Principal findings

In this nationwide study, the lifetime risk of newly diagnosed atrial fibrillation increased from approximately one in four in 2000-10 to one in three in 2011-22. The lifetime risk of atrial fibrillation increased across all subgroups over time, but the increase was larger among men and individuals with heart failure, myocardial infarction, stroke, diabetes, and chronic kidney disease. Among patients with newly diagnosed atrial fibrillation, heart failure was the most frequent complication after atrial fibrillation, with a lifetime risk of about two in five, twice as large as the lifetime risk of stroke after atrial fibrillation and four times greater than the lifetime risk of myocardial infarction after atrial fibrillation. Overall, lifetime risk

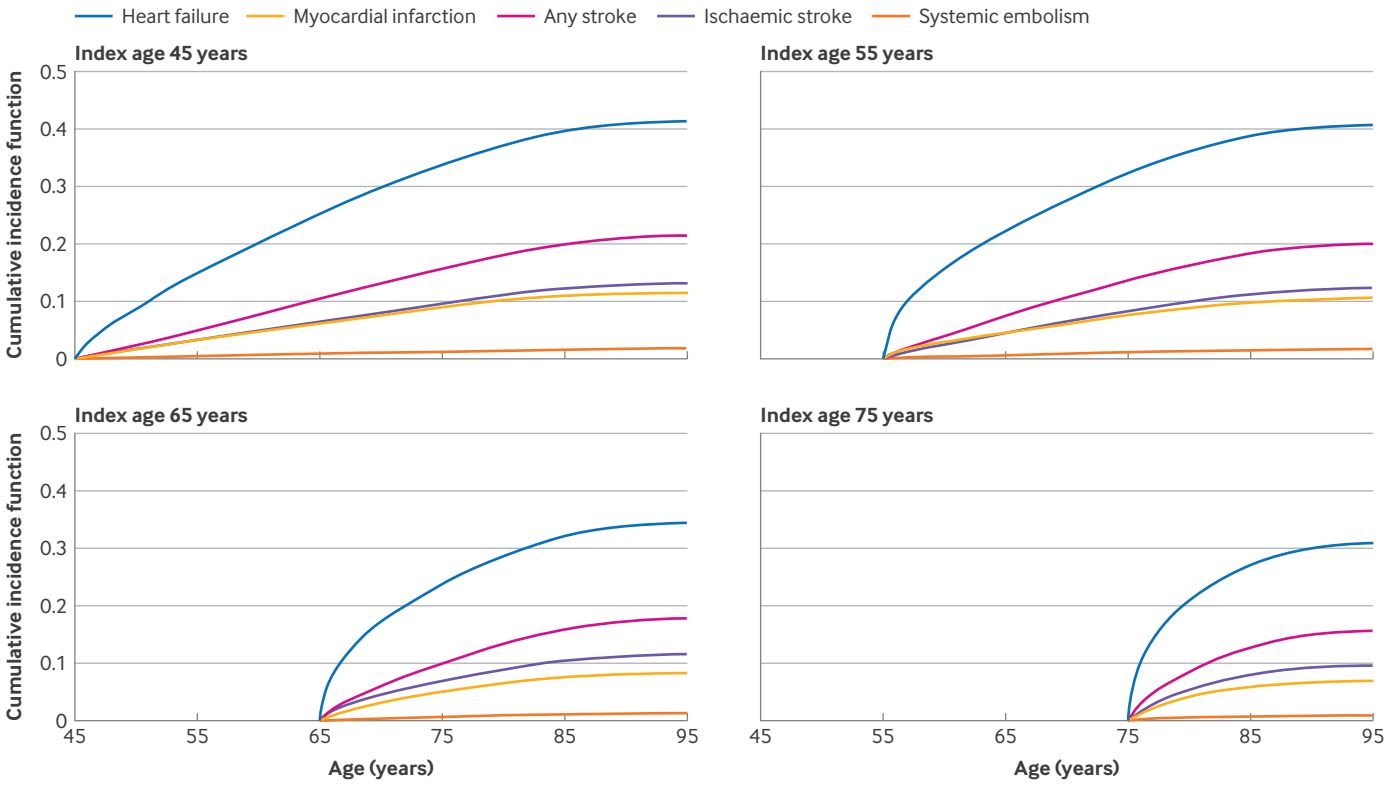

Fig 1 | Cumulative incidence of complications after atrial fibrillation

of heart failure after atrial fibrillation showed almost no change, and only a slight decrease in the lifetime risks of any stroke, ischaemic stroke, and myocardial infarction after newly diagnosed atrial fibrillation. These slight improvements were similar among men and women. However, the lifetime risk of heart failure decreased from 2000-10 to 2011-22 for patients with history of hypertension and dyslipidaemia.

Comparison with other studies

In Europe, a study reported cumulative incidences of atrial fibrillation of about 27% at the age of 90 years in both men and women based on data from the BiomarCaRE Consortium.[16] Another used data from the Rotterdam Study and noted a lifetime risk of atrial fibrillation at the index age of 55 years of 23.8% in men and 22.2% in women.[26] A study in China reported a lifetime risk of 21% in women and 17% in men using a Chinese medical insurance database.[27] In Taiwan, a study used the National Taiwanese Health Insurance Research Database and reported a lifetime risk of 15% among men and 17% among women.[28] Additionally, in the US, data from the Framingham Heart Study were used and a lifetime risk of 37% for the index age of 55 years was reported.[17] The Atherosclerosis Risk in Communities study was used to report a lifetime risk of 36% in white men, 30% in white women, 21% in African American men, and 22% in African American women.[18] Data from prospective cohort studies are strengthened by systematic follow-up and may be limited by self-selection bias and under-representation of specific groups.[29] However, our findings originate from national data and are consistent with prior estimates. No study has thus far examined the lifetime risks of complications following atrial fibrillation.

Interpretation of temporal trends

To our knowledge, the temporal trends in lifetime risks of atrial fibrillation and complications after atrial fibrillation have not been reported previously. The underlying reasons for the observed trends are speculative but likely multifactorial. For lifetime risk of atrial fibrillation, the detection of atrial fibrillation significantly improved over the past two decades, primarily due to advancements in technology, changes in clinical practice, and increased awareness. Approximately a third of patients with atrial fibrillation are asymptomatic,[30] and enhanced detection over time may lead to increased lifetime risk of diagnosed atrial fibrillation. Another possible reason is the global increase in life expectancy. Additionally, survival after myocardial infarction and heart failure has improved, which increases the likelihood of developing atrial fibrillation and having atrial fibrillation detected due to increased surveillance. The lifetime risk increased slightly more in some subgroups, particularly those with history of heart failure or stroke, and improved attention on developing comorbidities may partially explain the increase. Finally, the observed increasing prevalence of key risk factors for atrial fibrillation

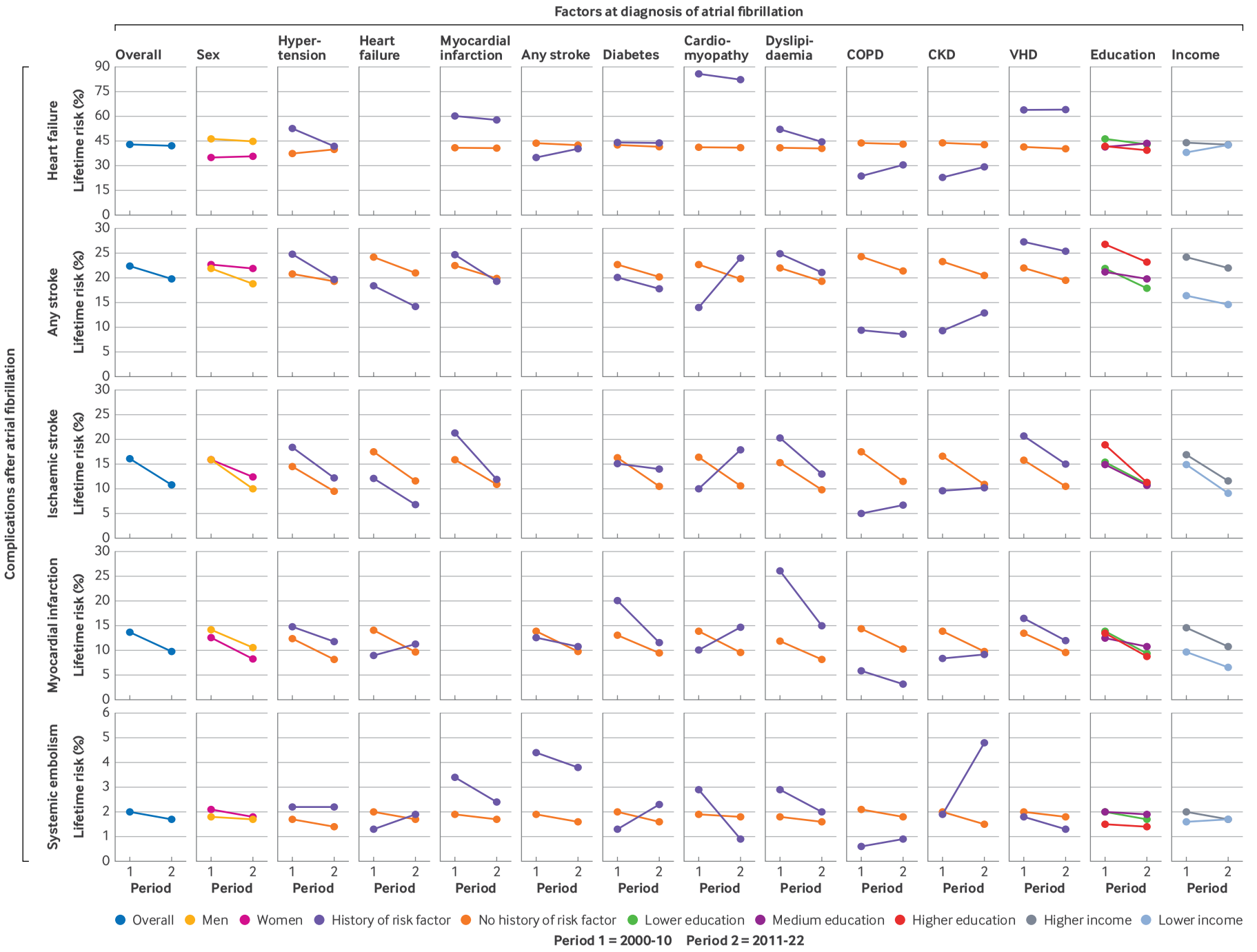

Fig 2 | Summary plot of temporal trends in lifetime risk of complications by subgroups. CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; VHD=valvular heart disease

over time, such as hypertension, dyslipidaemia, and diabetes, could also explain the increasing lifetime risk of atrial fibrillation. Although we did not have data for body mass index, the prevalence of obesity has increased over the past two decades in Denmark.[31] However, the temporal trend of atrial fibrillation remained after adjustment for all available risk factors at entry.

Regarding complications after atrial fibrillation, lifetime risks of stroke and ischaemic stroke remained high, with only about 4-5% decrease between 2000-10 and 2011-22. Clinical guidelines for the treatment of atrial fibrillation have been published regularly since 2001,[32] and new evidence supporting better treatment modalities, including target specific anticoagulants, has been incorporated since then.[11 33] These improvements in atrial fibrillation management may translate into a larger decline in lifetime risks of complications after atrial fibrillation over longer periods. Another reason for the decreasing risk over time is the potential early identification of patients with atrial fibrillation at low risk because of enhanced awareness. For instance, patients with persistent atrial fibrillation have a higher risk of stroke than patients with paroxysmal atrial fibrillation.[34] The lifetime risk of heart failure after atrial fibrillation did not change overall, but over time heart failure substantially decreased among patients with history of hypertension and dyslipidaemia at atrial fibrillation diagnosis. The lifetime risk of myocardial infarction also had larger decrease among patients with dyslipidaemia. These trends may reflect the effect of anti-hypertensive and lipid lowering drugs. Key risk factors have increased over time, particularly hypertension, dyslipidaemia, and diabetes. The increasing prevalence may be explained by improvement of screening protocols for risk factors, leading to more comprehensive detection rates. The criteria for diagnosing hypertension and diabetes have changed over the timeline investigated in this study, with the thresholds for blood pressure and glycaemic concentrations being updated. Finally, lifestyle changes and an increase in risk factors in the general population, such as obesity and sedentary behaviour, may also play a role in the uptick of these conditions. Despite increasing prevalence of risk factors, our analyses adjusting for risk factors at the diagnosis of atrial fibrillation were consistent with the primary analysis.

Implications

Lifetime risk estimates provide epidemiological insights into the public health impact presented by atrial fibrillation and its complications. Communication of lifetime risk estimates may motivate preventive strategies, such as beneficial changes in lifestyle and strengthening of the focus on quality in medical care settings. Preventive strategies require knowledge of different components of long term risk after atrial fibrillation. However, the main body of data on the absolute risk of complications after atrial fibrillation originates from short term studies, and 11 years seems to be the maximum follow-up period.[7 35-37] By adopting a lifetime perspective, we provided evidence on the actual disease burden associated with atrial fibrillation.

Estimates of the lifetime risk of complications after atrial fibrillation indicate the burden of the different complications, and such information may be essential to facilitate prioritisation and development of preventive efforts against complications, prediction of complications, and management of health policy. In Denmark, more than 85% of patients with atrial fibrillation initiate oral anticoagulation, and the one year and two year persistence are both above 85%.[38] Despite a high rate of anticoagulation treatment, we observed that stroke risk remains a very important problem after atrial fibrillation. These findings underscore the need for treatments to further decrease stroke risk. Factor XIa inhibitors and left atrial appendage closure are currently evaluated in randomised controlled trials as first line stroke prevention measures. Moreover, although atrial fibrillation guidelines principally focus on stroke prevention,[11 33] our findings indicate that heart failure was the major complication after incident atrial fibrillation, with a lifetime risk of two in five patients with atrial fibrillation, twice greater than that of stroke. Our findings encourage greater attention to secondary prevention of heart failure after atrial fibrillation, and in line with a recent report from the National Heart, Lung, and Blood Institute, relevant future initiatives include development of non-anticoagulant pharmacotherapies, effective implementation of weight loss, and risk factor modification, and designing successful programmes for cardiac rehabilitation.[10] As atrial fibrillation is a common arrhythmia, a lower incidence of complications may reduce the future economic costs in healthcare.

Limitations of the study

The data used in this study originate from a tax supported universal healthcare system with no substantial loss to follow-up of patients. The Danish National Patient Registry provided information on admissions to hospital for atrial fibrillation, but we were unable to examine individuals clinically to confirm the diagnosis. Furthermore, we could not use electrocardiogram monitoring devices such as Holter monitoring, and therefore, we may have missed patients with undiagnosed atrial fibrillation. We had no specific data for the proportion of patients with incident atrial fibrillation who were not captured by the Danish National Patient Registry. However, as the Danish guidelines recommend referral of patients with newly diagnosed atrial fibrillation to a public hospital for further examination, most patients with atrial fibrillation will be registered, and only a few cardiologists work outside of the public healthcare system in Denmark.[38] In Sweden, where the healthcare system is very similar to the Danish system, a study using data from 2004 to 2010 from the Swedish National Patient Registry and a central

electrocardiogram database found that 93.2% of patients with electrocardiogram confirmed atrial fibrillation had a recording in the Swedish National Patient Registry.[39] Additionally, validation studies reported a high positive predictive value of atrial fibrillation and atrial flutter in the Danish National Patient Registry.[21 22] We could not differentiate between atrial fibrillation and atrial flutter; however, atrial accounts for approximately 5% of the ICD-10 I48 diagnoses.[21] The positive predictive values for stroke, heart failure, and myocardial infarction also seem adequate.[22-24] The positive predictive value of ICD-10 I45 codes for systemic embolism is unknown. The diagnostic validity is likely to be even higher in a cohort of patients with a history of atrial fibrillation because these individuals are likely to be under closer medical surveillance. We had no information on the cause of death, and accordingly, we may have underestimated the true number of incident events and the lifetime risk. We also did not have information on lifestyle factors, such as obesity, smoking status, and physical activity.

Assessing temporal trends in lifetime risk of atrial fibrillation and its complications requires extended follow-up durations of population based samples with minimal loss to follow-up. The Danish registries offer these unique features. However, we were able to assess the lifetime risks over only two periods. Moreover, lifetime risks of atrial fibrillation and subsequent complications may vary according to race and ethnic group, geographical location, health system, and country income, and our results may not be transportable to other countries or settings. Lastly, we did not separate calendar temporal trends from birth cohort effects, although analyses with age as the time scale partially address this limitation.[40]

Conclusions

Our nationwide study shows that the lifetime risk of atrial fibrillation increased over the past two decades from one in four to one in three. After atrial fibrillation, heart failure was the most frequent complication, with a lifetime risk of two in five, twice greater than the lifetime risk of stroke after atrial fibrillation. The lifetime risks of stroke, ischaemic stroke, and myocardial infarction following atrial fibrillation improved only modestly over time and remained high, while virtually no improvement was noted in the lifetime risk of heart failure after atrial fibrillation. Our novel quantification of the long term downstream consequences of atrial fibrillation highlights the critical need for treatments to further decrease stroke risk as well as for heart failure prevention strategies among patients with atrial fibrillation.

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Contributors: NV, LF, EJB, and LT developed the hypothesis. NV, LF, and LT developed the study design. NV, PC, and LT did the statistical analysis. NV and LT wrote the first and successive drafts of the manuscript. All authors contributed to analysis and interpretation of data and drafting or critical revision of the manuscript for important intellectual content or additionally to data acquisition. NV and PC had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. NV and LT are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The Danish Health Data Authority, Statistics Denmark, and the Danish Data Protection Agency approved this study. Registry-based studies do not require approval from an ethics committee according to Danish law.

Data sharing: Permission to access the data used in this study can be obtained following approval from the Danish Health Authority.

Transparency: NV and LT affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: The study's findings will be disseminated through press releases, media engagement, and social media outreach. We also will present findings at conferences oriented towards clinicians that manage patients with atrial fibrillation and those at risk for developing atrial fibrillation. Our target audiences include the general public, including patients with atrial fibrillation and those at risk for developing atrial fibrillation, as well as healthcare professionals (eg, cardiologists, general practitioners, and nurses) and public health and cardiovascular health researchers.

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1 Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;34:2746-51. doi:10.1093/eurheartj/eht280

2 Dai H, Zhang Q, Much AA, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. *Eur Heart J Qual Care Clin Outcomes* 2021;7:574-82. doi:10.1093/ehjqcco/qcaa061

3 Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;386:154-62. doi:10.1016/S0140-6736(14)61774-8
4 Kornej J, Huang Q, Preis SR, et al. Temporal trends in cause-specific mortality among individuals with newly diagnosed atrial fibrillation in the Framingham Heart Study. *BMC Med* 2021;19:170. doi:10.1186/s12916-021-02037-x
5 Vinter N, Huang Q, Fenger-Grøn M, Frost L, Benjamin EJ, Trinquart L. Trends in excess mortality associated with atrial fibrillation over 45 years (Framingham Heart Study): community based cohort study. *BMJ* 2020;370:m2724. doi:10.1136/bmj.m2724
6 Christiansen CB, Gerds TA, Olesen JB, et al. Atrial fibrillation and risk of stroke: a nationwide cohort study. *Europace* 2016;18:1689-97. doi:10.1093/europace/euv401
7 Schnabel RB, Rienstra M, Sullivan LM, et al. Risk assessment for incident heart failure in individuals with atrial fibrillation. *Eur J Heart Fail* 2013;15:843-9. doi:10.1093/eurjhf/hft041
8 Frederiksen TC, Dahm CC, Preis SR, et al. The bidirectional association between atrial fibrillation and myocardial infarction. *Nat Rev Cardiol* 2023;20:631-44. doi:10.1038/s41569-023-00857-3
9 Benjamin EJ, Chen PS, Bild DE, et al. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. *Circulation* 2009;119:606-18. doi:10.1161/CIRCULATIONAHA.108.825380
10 Benjamin EJ, Al-Khatib SM, Desvigne-Nickens P, et al. Research priorities in the secondary prevention of atrial fibrillation: a national heart, lung, and blood institute virtual workshop report. *J Am Heart Assoc* 2021;10:e021566. doi:10.1161/JAHA.121.021566
11 Hindricks G, Potpara T, Dagres N, et al, ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42:373-498. doi:10.1093/eurheartj/ehaa612
12 Beiser A, D'Agostino RBSr, Seshadri S, Sullivan LM, Wolf PA. Computing estimates of incidence, including lifetime risk: Alzheimer's disease in the Framingham Study. The Practical Incidence Estimators (PIE) macro. *Stat Med* 2000;19:1495-522. doi:10.1002/(SICI)1097-0258(20000615/30)19:11/12<1495::AID-SIM441>3.0.CO;2-E
13 Conner SC, Beiser A, Benjamin EJ, LaValley MP, Larson MG, Trinquart L. A comparison of statistical methods to predict the residual lifetime risk[published Online First: 20220103]. *Eur J Epidemiol* 2022;37:173-94. doi:10.1007/s10654-021-00815-8
14 Karmali KN, Lloyd-Jones DM. Adding a life-course perspective to cardiovascular-risk communication. *Nat Rev Cardiol* 2013;10:111-5. doi:10.1038/nrcardio.2012.185
15 Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol* 2007;6:1106-14. doi:10.1016/S1474-4422(07)70291-0
16 Magnussen C, Niiranen TJ, Ojeda FM, et al, BiomarCaRE Consortium. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation* 2017;136:1588-97. doi:10.1161/CIRCULATIONAHA.117.028981
17 Staerk L, Wang B, Preis SR, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ* 2018;361:k1453. doi:10.1136/bmj.k1453
18 Mou L, Norby FL, Chen LY, et al. Lifetime risk of atrial fibrillation by race and socioeconomic status: ARIC study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol* 2018;11:e006350. doi:10.1161/CIRCEP.118.006350
19 Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-9.
20 Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(Suppl):38-41. doi:10.1177/1403494810394717
21 Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449-90. doi:10.2147/CLEP.S91125
22 Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;6:e012832. doi:10.1136/bmjopen-2016-012832
23 Delekta J, Hansen SM, AlZuhairi KS, Bork CS, Joensen AM. The validity of the diagnosis of heart failure (I50.0-I50.9) in the Danish National Patient Register. *Dan Med J* 2018;65:A5470.
24 Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology* 2007;28:150-4. doi:10.1159/000102143
25 Conner SC, Trinquart L. Estimation and modeling of the restricted mean time lost in the presence of competing risks. *Stat Med* 2021;40:2177-96. doi:10.1002/sim.8896
26 Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949-53. doi:10.1093/eurheartj/ehi825
27 Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GYH. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. *Chest* 2015;147:109-19. doi:10.1378/chest.14-0321
28 Chao TF, Liu CJ, Tuan TC, et al. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan Nationwide AF Cohort Study. *Chest* 2018;153:453-66. doi:10.1016/j.chest.2017.10.001
29 Goldberg M, Chastang JF, Leclerc A, et al. Socioeconomic, demographic, occupational, and health factors associated with participation in a long-term epidemiologic survey: a prospective study of the French GAZEL cohort and its target population. *Am J Epidemiol* 2001;154:373-84. doi:10.1093/aje/154.4.373
30 Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. *Circ Res* 2020;127:4-20. doi:10.1161/CIRCRESAHA.120.316340
31 Tolstrup JS, Bramming M, Davidsen M, Schramm S. Time trends in body mass index distribution in the general population in Denmark from 1987 to 2021. *Dan Med J* 2023;70:A09220573.
32 Fuster V, Rydén LE, Asinger RW, et al, American College of Cardiology/American Heart Association Task Force on Practice GuidelinesEuropean Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation)North American Society of Pacing and Electrophysiology. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology. *Circulation* 2001;104:2118-50. doi:10.1161/circ.104.17.2118
33 Joglar JA, Chung MK, Armbruster AL, et al. ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2023;2023. doi:10.1016/j.jacc.2023.08.017
34 Steinberg BA, Hellkamp AS, Lokhnygina Y, et al, ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J* 2015;36:288-96. doi:10.1093/eurheartj/ehu359
35 Schmidt M, Ulrichsen SP, Pedersen L, Bøtker HE, Nielsen JC, Sørensen HT. 30-year nationwide trends in incidence of atrial fibrillation in Denmark and associated 5-year risk of heart failure, stroke, and death. *Int J Cardiol* 2016;225:30-6. doi:10.1016/j.ijcard.2016.09.071
36 Naser N, Kulic M, Dilic M, et al. The cumulative incidence of stroke, myocardial infarction, heart failure and sudden cardiac death in patients with atrial fibrillation. *Med Arch* 2017;71:316-9. doi:10.5455/medarh.2017.71.316-319
37 Son MK, Lim NK, Kim HW, Park HY. Risk of ischemic stroke after atrial fibrillation diagnosis: a national sample cohort. *PLoS One* 2017;12:e0179687. doi:10.1371/journal.pone.0179687
38 Frost L, Joensen AM, Dam-Schmidt U, et al. The Danish atrial fibrillation registry: a multidisciplinary national pragmatic initiative for monitoring and supporting quality of care based on data retrieved from administrative registries. *Clin Epidemiol* 2023;15:1259-72. doi:10.2147/CLEP.S443473
39 Norberg J, Bäckström S, Jansson JH, Johansson L. Estimating the prevalence of atrial fibrillation in a general population using validated electronic health data. *Clin Epidemiol* 2013;5:475-81. doi:10.2147/CLEP.S53420
40 Vinter N, Cordsen P, Johnsen SP, et al. Birth cohort effects on diagnosed atrial fibrillation incidence: nationwide cohort study from 1980 to 2018. *Heart* 2024; doi:10.1136/heartjnl-2023-323737.

Web appendix: Supplementary material