ORIGINAL RESEARCH ARTICLE

Trajectories of Cardiovascular Risk Factors and Incidence of Atrial Fibrillation Over a 25-Year Follow-Up

The ARIC Study (Atherosclerosis Risk in Communities)

BACKGROUND: Timing and trajectories of cardiovascular risk factor (CVRF) development in relation to atrial fibrillation (AF) have not been described previously. We assessed trajectories of CVRF and incidence of AF over 25 years in the ARIC study (Atherosclerosis Risk in Communities).

METHODS: We assessed trajectories of CVRF in 2456 individuals with incident AF and 6414 matched control subjects. Subsequently, we determined the association of CVRF trajectories with the incidence of AF among 10 559 AF-free individuals (mean age, 67 years; 52% men; 20% blacks). Risk factors were measured during 5 examinations between 1987 and 2013. Cardiovascular events, including incident AF, were ascertained continuously. We modeled the prevalence of risk factors and cardiovascular outcomes in the period before and after AF diagnosis and the corresponding index date for control subjects using generalized estimating equations. Trajectories in risk factors were identified with latent mixture modeling. The risk of incident AF by trajectory group was examined with Cox models.

RESULTS: The prevalence of stroke, myocardial infarction, and heart failure increased steeply during the time close to AF diagnosis. All CVRFs were elevated in AF cases compared with controls >15 years before diagnosis. We identified distinct trajectories for all the assessed CVRFs. In general, individuals with trajectories denoting long-term exposure to CVRFs had increased AF risk even after adjustment for single measurements of the CVRFs.

CONCLUSIONS: AF patients have increased prevalence of CVRF many years before disease diagnosis. This analysis identified diverse trajectories in the prevalence of these risk factors, highlighting their different roles in AF pathogenesis.

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a lifetime risk of 1 in 4 in the general population and an increasing prevalence as the population ages.[1] Major risk factors for AF include age, white race, obesity, smoking, hypertension, diabetes mellitus, and a history of myocardial infarction (MI) and heart failure (HF).[2–6] These risk factors are similar to the risk factors for cardiovascular disease in general, and these cardiovascular outcomes often precede an AF event.[7] The development of AF is also associated with subsequent increased risk of cardiovascular death,[8,9] HF,[10] MI,[11,12] and stroke.[13]

Despite the extensive literature on risk factors for AF, little attention has been devoted to the timing of risk factor development in relation to AF diagnosis; exceptions are stroke as an outcome of AF and HF as both a risk factor for and outcome of AF. Although it is known that AF is a risk factor for stroke and therefore most often precedes it,[14] AF and HF show a bidirectional relation, and the existing severity of specific cardiovascular risk factors, along with age and sex, may determine whether AF or HF occurs first.[15,16] However, no information exists on the timing relative to the AF diagnosis of the development of other AF risk factors such as hypertension and

obesity. This information can be useful to better understand the factors that influence the progress of the cardiac substrate facilitating the onset of AF and therefore develop preventive strategies.

Furthermore, health care use, particularly cardiovascular-related use, is higher among patients with AF than among individuals without AF even after adjustment for cardiovascular risk factors.[17] Exploring how trajectories in cardiovascular risk factor prevalence differ between individuals with and without AF could help us understand observed differences in healthcare use. Risk factor trajectories could also be clinically relevant and informative in the prevention of AF and may provide more information than a 1-time measurement. With the overall goal of assessing the association of trajectories of cardiovascular risk factors and outcomes with AF, we established the following 2 aims: (1) to describe the long-term prevalence of risk factors preceding AF diagnosis and the subsequent development of cardiovascular outcomes after diagnosis and compare the risk factors and outcomes by AF status and (2) to identify subgroups of individuals with similar trajectories of risk factors and outcomes and determine the association of these trajectory subgroups with the subsequent development of AF. The ARIC study (Atherosclerosis Risk in Communities), a population-based study with a 25-year follow-up and a large number of incident AF cases, provides an exceptional opportunity to describe these trajectories and to assess their impact on AF risk.

METHODS

Study Population

The ARIC study is a mostly biracial, prospective cohort study of cardiovascular disease and atherosclerosis risk factors.[18] Participants at baseline (1987–1989) included 15 792 men and women 45 to 64 years of age recruited from 4 communities in the United States (Washington County, MD; the northwest suburbs of Minneapolis, MN; Jackson, MS; and Forsyth County, NC). ARIC participants were mostly white in the Washington County and Minneapolis centers and only black in the Jackson center; both races were included in Forsyth County. After the initial assessment, study participants were examined 4 additional times (1990–1992 [visit 2], 1993–1995 [visit 3], 1996–1998 [visit 4], 2011–2013 [visit 5]). Additionally, ARIC participants receive annual follow-up calls, with response rates of ≥90% among survivors.

Of the 15 792 participants who attended visit 1 in the ARIC study, we excluded individuals who were of a racial group other than white or black and nonwhites in the Minneapolis and Washington County field centers (n=103), those with prevalent AF at visit 1 (n=37), and those with low-quality or missing ECGs (n=242). After exclusions, our study population included 15 410 participants (26% black, 45% male). For aim 1, our analysis included 2456 individuals with AF diagnosed during the follow-up and 6414 matched control subjects without AF. For aim 2, we included 10 559 individuals with measured risk factors at the first 4 visits and without prevalent AF at visit 4.

This study was approved by institutional review boards at each participating center, and all study participants provided written informed consent.

AF Ascertainment

AF diagnoses were ascertained by 3 different sources in the ARIC study: ECGs performed at study visits, hospital discharge codes, and death certificates.[3] At each ARIC study visit, a 10-second 12-lead ECG was performed with a MAC PC cardiograph (Marquette Electronics Inc, Milwaukee, WI) and transmitted to the ARIC ECG Reading Center for coding, interpretation, and storage. All ECGs automatically coded as AF were visually checked by a trained cardiologist to confirm AF diagnosis.[19] Annual follow-up calls and review of local hospital discharges identified hospitalizations in ARIC participants through the end of 2012. *International Classification of Diseases (ICD), 9th Revision, Clinical Modification* (*ICD-9-CM*) codes of 427.31 (AF) or 427.32 (atrial flutter) listed as a discharge diagnostic code in any position defined AF cases. AF events associated with cardiac surgery were not included in this study. Validity of *ICD* codes for AF is adequate; ≈90% of the cases were confirmed in a physician review of discharge summaries from 125 possible AF cases.[3] AF cases were also identified if *ICD-9* code 427.3 or *International Classification of Diseases, 10th Revision* code I48 was listed as a cause of death. In this analysis, the AF incident date was defined as the date of the first ECG showing AF (4% of our AF cases), as the first hospital discharge with AF coded (96% of AF cases), or when AF was listed as a cause of death (0.1% of cases), whichever occurred earlier.

Risk Factor and Outcome Ascertainment

At baseline and during follow-up examinations, participants reported information on smoking, history of cardiovascular disease, and use of medications and underwent a physical examination. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured with a random-zero sphygmomanometer after 5 minutes of rest in the sitting position and was defined as the average of the second and third measurements taken. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertension medications. In analysis using continuous SBP, a constant of 10 mm Hg was added to the participant's measure if he or she was taking antihypertension medications.[20] Diabetes mellitus was defined as fasting glucose ≥126 mg/dL (7.0 mmol/L), nonfasting glucose ≥200 mg/dL (11.1 mmol/L), treatment for diabetes mellitus, or self-reported physician diagnosis of diabetes mellitus. Prevalent HF was defined as the reported use of HF medication in the previous 2 weeks, presence of HF according the Gothenburg criteria (only at the baseline visit), or having had a HF hospitalization since the previous visit.[21] Incident HF was defined as the first occurrence of any listing of an *ICD-9-CM* code 428 for a hospitalization during follow-up.[22] Prevalent MI at baseline was defined as a self-reported physician-diagnosed MI or presence of an MI by ECG, and incident MI was ascertained by study visit ECGs or the ARIC Morbidity and Mortality Classification Committee by using data from follow-up calls, hospitalization records, and death certificates.[23] Prevalent stroke at baseline was defined as the self-reported physician diagnosis of a stroke before visit 1, and incident stroke was defined as the sudden or rapid onset of neurological symptoms lasting for at least 24 hours or leading to death in the absence of evidence for a nonstroke cause and was validated with the use of established criteria with physician review of records.[24]

Covariates measured at baseline (visit 1) included sex, race, and study center. Information on smoking, obesity, hypertension, diabetes mellitus, HF, MI, stroke, and AF was obtained during each of the 5 study examinations between 1987 and 2013. AF, HF, MI, and stroke also were ascertained from annual surveillance.

Statistical Analysis

For aim 1, to assess the prevalence of cardiovascular risk factors and outcomes in persons with AF versus AF-free control subjects, we compared risk factors and outcomes both before and after AF diagnosis with those in individuals without AF. Each AF case was matched with up to 3 controls by age (±2 years), sex, race, and field center. We defined index date (time t=0) as the date of AF diagnosis for each case and the same date for the corresponding matched controls. Time to each visit was recalculated in relation to the index date as follows: time at visit i (t_i)=visit i date–index date (in years). Negative and positive values correspond to examinations before and after the study index date, respectively.

Using a data set with 1 observation per person-visit (maximum, 5 observations per participant), we fit generalized estimating equation models with a logistic link with time in years before/after index date as the main independent variable. Time was categorized in 5-year periods (<−17.5, −17.5 to <−12.5, −12.5 to <−7.5, −7.5 to <−2.5, −2.5 to 2.5 (reference), and >2.5 years). We chose a reference time of ±2.5 years to account for imprecise AF diagnosis and chose 5-year increments for easy descriptive purposes. Separate models were used to predict the prevalence of risk factors and cardiovascular outcomes (hypertension, smoking, obesity, diabetes mellitus, HF, MI, and stroke) in each time period separately for AF cases and controls and by race. To describe the changes in risk factors and cardiovascular outcomes over time in those with and without AF, adjusted odds ratios were calculated from the same generalized estimating equation models and with the index date ±2.5 years used as the reference group. The interaction of time with AF status was used to test for differences in the odds ratio trajectories in cases and controls.

For aim 2, we included 10 559 individuals with measurements at the first 4 visits (during 1987–1998) and without AF at the time of visit 4 and identified risk factor trajectories during those years. Then we determined the association of each trajectory with the risk of incident AF through the end of 2013. We used latent class models to identify distinct subgroups within the ARIC cohort sharing a similar underlying trajectory for each risk factor. These models were fit with the use of SAS Proc Traj.[25–27] The online-only Data Supplement includes additional details on the trajectory modeling process. The association of each trajectory group with the risk of incident AF was modeled with Cox proportional hazards models comparing the risk in each trajectory group with the reference trajectory group. Models were adjusted for age, sex, race, and each of the other risk factors (BMI, smoking,

diabetes mellitus, hypertension, and a history of MI, HF, or stroke) measured at visit 4. An additional model adjusted for the measure of the continuous variable risk factor at visit 4 to determine whether the previous trajectory itself provided more predictive information on the association with AF than a 1-time measurement. This additional adjustment was possible for BMI, SBP, and current smoking but not for diabetes mellitus, HF, MI, or stroke because of model fit issues derived from complete separation of the data. Follow-up time for Cox models began at visit 4 and continued until the date of AF, the end of follow-up (2013), death, or the date of last contact. All statistical analyses were performed with SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

For aim 1, during a median follow-up of 24 years (interquartile range, 20.5–25.0 years), 2456 cases of AF were detected (19% in blacks; 54% in men) and matched with 6414 controls without AF. Characteristics of AF cases and controls at the index date are given in Table 1. Compared with controls, AF cases had higher BMI and a greater prevalence of current smoking, hypertension, diabetes mellitus, HF, MI, and stroke. The mean number of visits attended by AF cases and matched controls was

Table 1.   Prevalent Characteristics in AF Cases at the Time of AF Diagnosis and in Matched Controls at the Corresponding Index Date, ARIC, 1987 to 2013

	AF Cases (n=2456)	Controls (n=6414)
Calendar year of diagnosis/index date	2003 (6.6)	2003 (6.6)
Matched variables		
Age, y	66.7 (8.7)	67.4 (8.4)
Black race, %	18.9	20.5
Male sex, %	53.6	51.2
Other variables		
Obese (BMI >30 kg/m^2), %	35.1	28.5
BMI, kg/m^2	28.9 (5.9)	28.0 (5.1)
Current smoker, %	17.3	14.3
Hypertension, %	69.8	57.4
SBP, mm Hg	130.0 (21.9)	128.5 (19.7)
Diastolic blood pressure, mm Hg	70.5 (12.5)	69.6 (10.8)
Diabetes mellitus, %	32.3	22.4
HF, %	25.3	5.0
MI, %	19.7	8.3
Stroke, %	8.2	3.4

Values correspond to mean (SD) unless otherwise noted.

AF indicates atrial fibrillation; ARIC, Atherosclerosis in Communities; BMI, body mass index; HF, heart failure; MI, myocardial infarction; and SBP, systolic blood pressure.

3.8 and 4.1, respectively. The mean calendar year of AF diagnosis was 2003.

The age- and sex-adjusted prevalence of risk factors and cardiovascular outcomes by AF status and race is depicted in Figure 1. Cardiovascular risk factors and outcomes were more prevalent in AF cases than in matched controls. This increased prevalence was present for all risk factors and outcomes from the beginning of the follow-up and was significantly higher for obesity, smoking, and HF even in the period <−17.5 years before the index date (P<0.05). Blacks with AF had the highest prevalence for each risk factor and cardiovascular outcome both before and after developing AF, whereas the prevalences were lowest in white controls. For both race groups, the prevalence of hypertension and diabetes mellitus increased gradually over time, up to and after the index date. The prevalence of smoking and obesity increased slightly during follow-up but started to decline around the index date. The prevalence of HF, stroke, and MI in AF cases had a J-shape pattern, with low prevalence in the 10+ years before AF and steep increases in prevalence during the period of time close to AF diagnosis. The prevalence of HF, stroke, and MI in controls remained low throughout follow-up for both blacks and whites.

Figure 2 depicts the change in the prevalence of risk factors and cardiovascular outcomes in AF cases adjusted for age, race, and sex. We observed diverse odds ratio trajectories in the prevalence of risk factors and cardiovascular outcomes among AF patients, with steep increases in the prevalence of stroke, MI, and HF during the time period closest to the AF diagnosis. Odds ratio trajectories for hypertension and diabetes mellitus showed monotonic increases over time, and those for smoking and obesity suggested decreases after AF diagnosis. An odds ratio <1 or >1 can be interpreted as a lower or higher odds, respectively, of the corresponding risk factor or outcome at a particular time period compared with the odds at the time of AF diagnosis date. The odds of having HF around 10 years before AF diagnosis is ≈50% lower compared with having HF at the time of AF, whereas the odds of having diabetes mellitus or hypertension is only ≈20% lower 10 years before the AF diagnosis. The odds ratios over time for hypertension, obesity, HF, stroke, and MI were significantly different on the basis of AF status (P<0.05 for all the interaction terms), with lower increments among those without AF.

For aim 2, trajectories for each of the cardiovascular risk factors and outcomes were fit to the 10559 participants who participated in the first 4 visits and were free of AF at visit 4. These trajectories are depicted in Figure 3. Five distinct trajectories were identified for BMI, obesity, and SBP, and 4 distinct trajectories were identified for hypertension, smoking, diabetes mellitus, HF, MI, and stroke. The trajectory analysis for BMI and
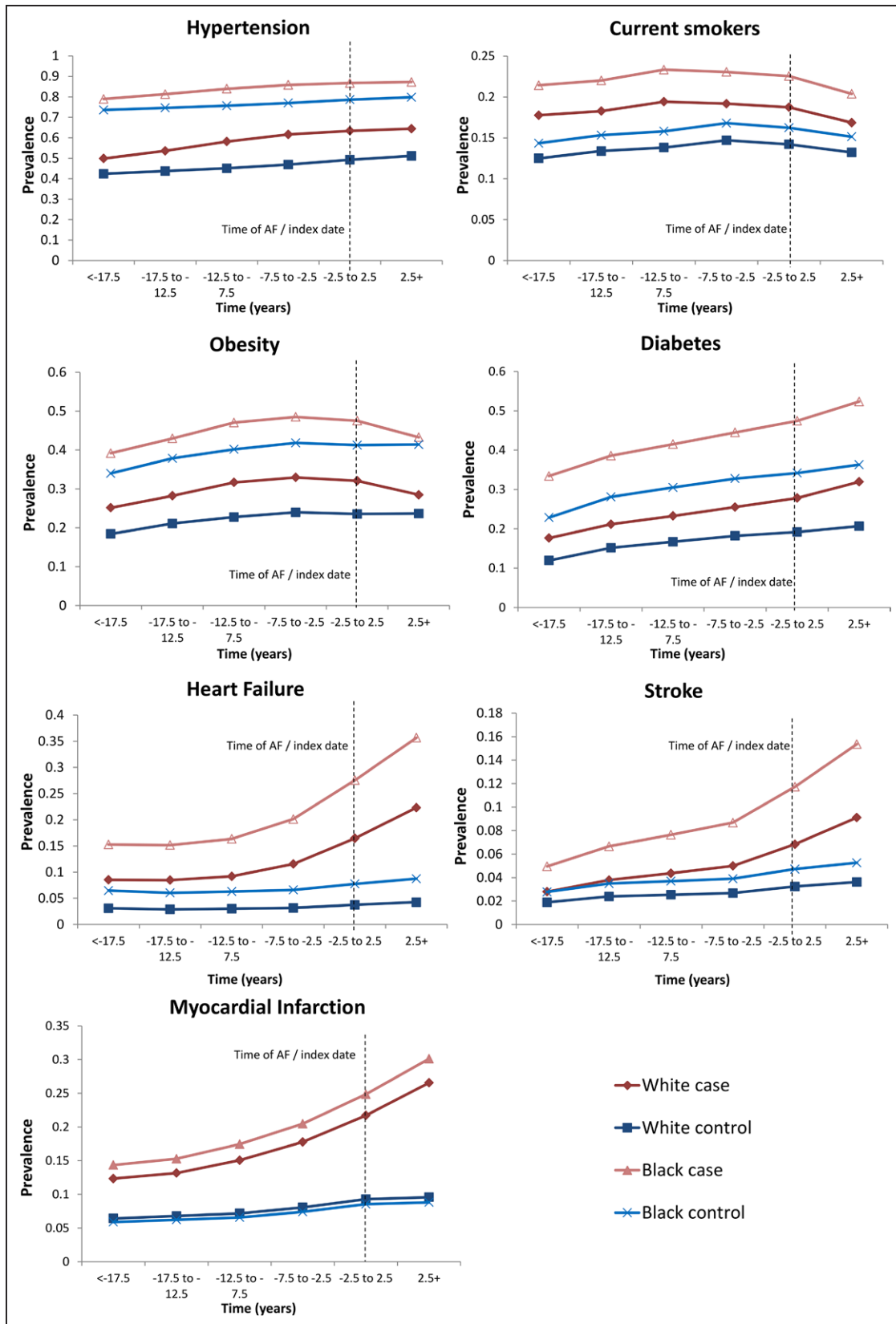
Figure 1. Predicted prevalence of cardiovascular risk factors and outcomes over time by atrial fibrillation (AF) status, ARIC (Atherosclerosis Risk in Communities), 1987 to 2011. Adjusted prevalence was modeled with general estimating equations held constant for age, race, and sex. Predicted probabilities of cardiovascular risk factors and outcomes were then calculated on the basis of a 65-year-old man and stratified by race.
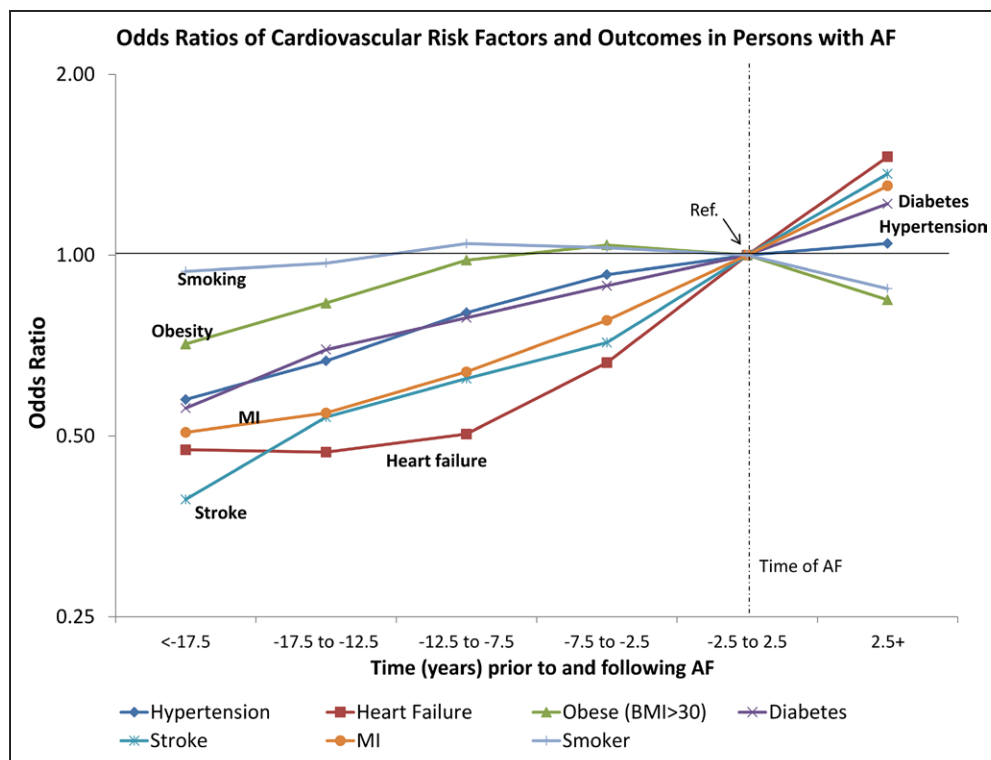
Figure 2. Odds ratios (ORs) of cardiovascular risk factors and outcomes over time based on atrial fibrillation (AF) status and adjusted for age, race, and sex.
An OR <1 or >1 can be interpreted as a lower or higher odds, respectively, of the risk factor or cardiovascular outcome at a particular time period compared with the odds at the time of AF diagnosis date. MI indicates myocardial infarction.

SBP identified subsets with different baseline values but parallel increases in the values of the risk factor during the 9-year period. In contrast, for obesity, hypertension, diabetes, HF, MI, and stroke, we identified a group without the condition during the 9-year period, a group with prevalence close to 100% during the follow-up, and 2 or 3 intermediate groups in which the prevalence increased at different rates during the 9-year period. For smoking, the trajectory analysis identified a group of nonsmokers (77% of the cohort), a group of long-term current smokers (11% of the cohort), and 2 smaller groups who quit smoking at similar rates.

During follow-up of these trajectory groups (median follow-up, 15 years), 1507 cases of incident AF were detected. The association of each trajectory group with each risk factor and outcome is presented in Table 2. For each risk factor, the trajectory group with the most favorable profile (group 1) was the reference to which the other trajectory groups were compared. For all risk factors, risk of incident AF was highest among individuals in the trajectory group with the highest prevalence of risk factor values and lowest in the reference trajectory group. The long-term obese (obesity trajectory group 5) had a 39% (95% confidence interval, 14–70) increased risk of AF compared with the reference trajectory group (nonobese), even after adjustment for BMI measured at

visit 4. Similarly, the SBP trajectory groups with high and very high long-term SBP who had average SBP >140 mm Hg for >9 years had an increased risk of AF even after adjustment for SBP measured at visit 4. These results were consistent with the hypertension analysis in which hypertension trajectory group 4 (long-term hypertensives) had a hazard ratio of 1.31 (95% confidence interval, 1.14–1.51) compared with the reference group even after adjustment for visit 4 SBP. Compared with long-term nonsmokers (smoking trajectory group 1), the long-term current smokers (trajectory group 4) had increased risk of AF even after adjustment for smoking status at visit 4. The risk of AF among those who quit (trajectory groups 2 and 3) was intermediate. The risk of AF was higher in the trajectories containing participants with long-term (trajectory group 4) or newly diagnosed (trajectory groups 2 and 3) diabetes mellitus, HF, MI, and stroke compared with those without the disease (trajectory group 1).

DISCUSSION

In this large population-based study describing the timing of risk factors and outcomes in relation to AF diagnosis, we observed diverse trajectories in the prevalence of risk factors and cardiovascular outcomes. We also found that

Circulation. 2016;134:599–610. DOI: 10.1161/CIRCULATIONAHA.115.020090
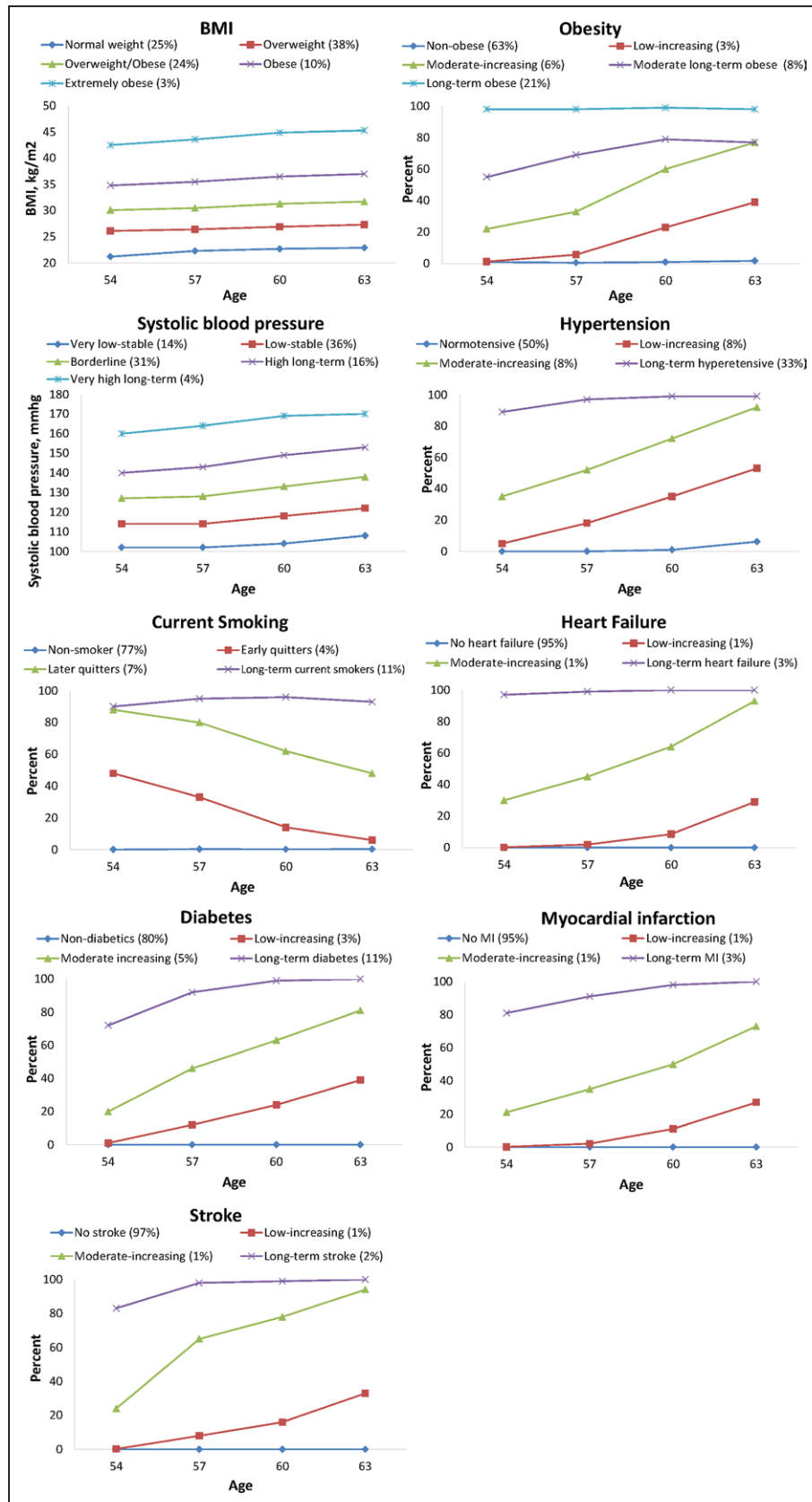
Figure 3. Trajectories in risk factors and outcomes over time, ARIC (Atherosclerosis Risk in Communities), 1987 to 1998.
Groups are trajectory groups (percentage of the population in each group). BMI indicates body mass index.

Table 2. Adjusted Hazard Ratios (95% Confidence Intervals) of AF by Risk Factor Trajectory Groups, ARIC, 1998 to 2013

Risk factor	Trajectory Groups				
	1	**2**	**3**	**4**	**5**
BMI	Normal weight	Overweight	Overweight/obese	Obese	Extremely obese
n (%)	2607 (25)	4025 (38)	2548 (24)	1086 (10)	293 (3)
AF, n	325	535	401	187	59
Model 1	1 (Referent)	0.98 (0.85–1.12)	1.33 (1.14–1.55)	1.66 (1.37–2.01)	2.56 (1.91–3.43)
Model 1+V4 BMI	1 (Referent)	0.90 (0.75–1.07)	1.13 (0.87–1.47)	1.28 (0.86–1.90)	1.70 (0.92–3.14)
Obesity (≥30 kg/m²)	Nonobese	Low, increasing	Moderate, increasing	Moderate long-term obese	Long-term obese
n (%)	6615 (63)	292 (3)	605 (6)	802 (8)	2245 (21)
AF, n	837	57	87	100	426
Model 1	1 (Referent)	1.03 (0.78–1.35)	1.35 (1.08–1.69)	1.18 (0.96–1.45)	1.68 (1.48–1.91)
Model 1+V4 BMI	1 (Referent)	0.93 (0.70–1.23)	1.21 (0.95–1.54)	1.07 (0.86–1.34)	1.39 (1.14–1.70)
SBP	Very low, stable	Low, stable	Borderline	High long-term	Very high long-term
n (%)	1464 (14)	3773 (36)	3228 (31)	1713 (16)	381 (4)
AF, n	170	450	490	312	85
Model 1	1 (Referent)	1.02 (0.86–1.22)	1.32 (1.11–1.59)	1.73 (1.42–2.10)	2.52 (1.92–3.30)
Model 1+V4 SBP	1 (Referent)	0.96 (0.79–1.16)	1.16 (0.93–1.46)	1.43 (1.08–1.89)	1.94 (1.32–2.86)
Hypertension	Normotensive	Low, increasing	Moderate, increasing	Long-term hypertensive	
n (%)	5321 (50)	878 (8)	866 (8)	3494 (33)	
AF, n	583	178	99	647	
Model 1	1 (Referent)	1.43 (1.21–1.70)	1.30 (1.04–1.61)	1.57 (1.39–1.77)	
Model 1+V4 SBP	1 (Referent)	1.23 (1.02–1.47)	1.10 (0.88–1.39)	1.31 (1.14–1.51)	
Current smoking	Nonsmoker	Early quitters	Later quitters	Long-term current smokers	
n (%)	8175 (77)	439 (4)	743 (7)	1202 (11)	
AF, n	1116	50	132	209	
Model 1	1 (Referent)	1.22 (0.92–1.63)	1.57 (1.31–1.88)	1.78 (1.53–2.07)	
Model 1+V4 current smoking	1 (Referent)	1.23 (0.92–1.64)	1.48 (1.21–1.81)	1.43 (1.03–2.00)	
Diabetes mellitus	Nondiabetics	Low, increasing	Moderate, increasing	Long-term diabetes mellitus	
n (%)	8497 (80)	328 (3)	529 (5)	1205 (11)	
AF, n	1096	85	91	235	
Model 1	1 (Referent)	1.29 (1.03–1.62)	1.28 (1.03–1.59)	1.57 (1.36–1.82)	
Heart failure	No heart failure	Low, increasing	Moderate, increasing	Long-term heart failure	
n (%)	10 066 (95)	77 (1)	60 (1)	356 (3)	
AF, n	1368	29	22	88	
Model 1	1 (Referent)	1.91 (1.31–2.78)	3.06 (1.99–4.70)	1.59 (1.27–1.98)	
MI	No MI	Low, increasing	Moderate, increasing	Long-term MI	
n (%)	10 035 (95)	84 (1)	120 (1)	320 (3)	
AF, n	1360	29	34	84	
Model 1	1 (Referent)	1.82 (1.25–2.64)	2.02 (1.43–2.85)	1.77 (1.41–2.21)	
Stroke	No stroke	Low, increasing	Moderate, increasing	Long-term stroke	
n (%)	10 229 (97)	74 (1)	76 (1)	180 (2)	
AF, n	1434	19	17	37	
Model 1	1 (Referent)	1.37 (0.87–2.16)	1.57 (0.96–2.54)	1.68 (1.21–2.33)	

AF indicates atrial fibrillation; ARIC, Atherosclerosis in Communities; BMI, body mass index; HF, heart failure; MI, myocardial infarction; SBP, systolic blood pressure; and V4, visit 4. Model 1 was adjusted for age, sex, race, BMI, smoking, diabetes mellitus, hypertension, history of MI, history of HF, and history of stroke when appropriate.

trajectories of risk factors are associated with the future risk of AF, providing additional information beyond that obtained from single risk factor measurements. In the first aim, there were steep increases in the prevalence of stroke, MI, and HF during the years proximal to the AF diagnosis, whereas prevalences for hypertension and diabetes mellitus showed monotonic increases over time and those for smoking and obesity suggested decreases in prevalence after AF diagnosis. The odds ratios over time for hypertension, obesity, HF, stroke, and MI were significantly different on the basis of AF status, with lower increments among those without AF. Additionally, we found that the prevalence of most cardiovascular risk factors was higher in individuals with AF compared with AF-free controls even ≥15 years before the diagnosis of AF. In aim 2, we observed that those with prevalent risk factors and those who have had them for a longer duration had an increased risk of AF. Participants with high blood pressure or who have been obese for a longer period of time have an even higher risk, and the time since onset may be important. These results underscore the role of factors such as hypertension and obesity in contributing to the development of the atrial substrate that eventually leads to the clinical onset of AF and the need to act earlier in the pathogenic process to prevent this common arrhythmia.

Few studies have considered the timing of risk factor development in relation to AF diagnosis. Most current information consists of the well-known association of increased stroke risk after an AF event,[14] and for this reason, the 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guideline for the management of patients with AF recommends oral anticoagulation in patients with a moderate or greater risk of ischemic stroke.[28] The studies that address the timing of AF and HF development show a bidirectional association, and the existing severity of specific cardiovascular risk factors such as BMI, diabetes mellitus, and previous MI, along with age and sex, may determine whether AF or HF occurs first in the individual.[15,16] Which event develops first also may be indicative of the overall health of the patient. It has been shown that among hospitalized patients with both AF and HF, AF more frequently developed first.[29] HF onset in patients with previous AF has been associated with an increased risk of morbidity and mortality.[16,30]

Although less documented, it appears that MI and AF also can occur concurrently. In a meta-analysis, AF onset in MI patients was associated with higher mortality (odds ratio, 1.46; 95% confidence interval, 1.35–1.58), and this worse prognosis persisted regardless of the timing of AF, suggesting that AF is a major adverse health event for those with MI.[31,32] Several other studies have shown that AF is associated with an increased risk of MI,[11,33] particularly non–ST segment–elevation MI, and that this association was stronger in women.[12]

Although stroke, MI, and HF are all relatively discrete cardiovascular events with the highest prevalence after AF diagnosis, the trajectories in prevalence of traditional risk factors such as hypertension and diabetes mellitus are much different, showing monotonic increases over time. Both hypertension and diabetes mellitus are associated with increased risk of AF independently of other risk factors, and the trajectories depicted in this analysis corroborate that the long-term effects of each chronic condition could take many years, even decades, to appear. Several mechanisms have been proposed to explain the role of hypertension as a risk factor for AF over time. Chronic increased systemic blood pressure leads to left ventricular hypertrophy, impaired ventricular filling, left atrial enlargement, and slowing of atrial conduction velocity.[34] High blood pressure causes structural and functional changes in the myocardium, leading to an increased risk of arrhythmia.[35] Similarly, the damaging impact of diabetes mellitus on AF risk occurs after prolonged exposure to diabetes mellitus, and several mechanisms have been proposed. Diabetes mellitus could place metabolic stress on the atrium or through association with systemic illnesses such as infection or renal failure.[36] Additionally, high hemoglobin A_{1c} levels, the severity of diabetes mellitus, and long-term cumulative exposure to hyperglycemia could induce AF.[37] Several other theories involve atrial dilation, elevated inflammation factors such as C-reactive protein, and electric remodeling of atria.[38]

Obesity is associated with higher risk of AF, possibly through an increased risk of diabetes mellitus and hypertension and through the association of high body mass with the metabolic syndrome, chronic inflammation, and stress. Obesity also increases atrial size and is associated with left ventricular hypertrophy.[34,35] Smoking is associated with AF in both current and former smokers, and the association is higher in those with more pack-years.[7,39] Nicotine increases heart rate and blood pressure, and smoking causes decreased lung function and leads to chronic obstructive pulmonary disorder, which are also risk factors for AF.[4,39] In this analysis, we see a higher prevalence of smoking and obesity in AF cases throughout the entire follow-up, increasing slightly over time up to AF diagnosis and then decreasing around the time of AF and afterward. This decrease could be due to either health issues causing weight loss or a diagnosis of AF instigating lifestyle changes leading to weight loss and smoking cessation.

As previously shown in the ARIC study, AF is more common in whites than in blacks, despite the higher prevalence of comorbidities and cardiovascular outcomes in blacks.[3] This new analysis reports a higher prevalence of all risk factors and cardiovascular outcomes in blacks with AF or without AF compared with their white counterparts throughout the entire follow-up, with the highest prevalence in blacks with AF.

This study describing the prevalence and trajectories of cardiovascular risk factors and outcomes in AF cases has relevant clinical and public health implications.

First, it reinforces the concurrent nature of cardiovascular events such as HF, MI, and stroke as major adverse events that tend to cluster around the time of AF. For patients with newly diagnosed AF, treatment should involve the prevention and early detection of these other cardiovascular events. For patients with previous MI or HF, prevention and early detection of AF could lead to better outcomes. Second, this study implies that chronic conditions such as diabetes mellitus, hypertension, smoking, and obesity cause damage to the cardiovascular system over an extended period of time. Targeting these upstream risk factors could prevent AF in addition to other cardiovascular diseases. Treatment for these conditions should emphasize long-term control to minimize the risks of eventual cardiovascular events such as AF. The decreased risk of AF in former smokers compared with current smokers could have clinical implications, and future studies should explore the effects of improvement in risk factors, including smoking cessation, on the risk of AF. Third, the timing of cardiovascular risk factors and outcomes relative to the AF diagnosis is useful to better understand the pathogenesis of AF and should be used to further causation theories and to develop preventive strategies. Fourth, the distinct trajectory groups could contribute to identify subsets of AF patients with shared pathogenesis and pathophysiological mechanisms, which may result in more targeted treatments and preventive strategies. Lastly, these trajectories could be used to help explain observed differences in healthcare use in those with and without AF and can be used to develop plans for healthcare resource allocation.

Limitations of this study include possible misclassification of the HF and AF diagnoses, which were based mostly on *ICD* discharge codes. Similarly, outpatient AF cases were not captured, so it is possible that some paroxysmal/intermittent AF cases were undetected. Bias may also have occurred if AF was detected as an incidental finding during a hospitalization for some other reason such as a cardiovascular event. However, it has been shown that AF diagnosed by *ICD* codes and from study visit ECGs has a positive predictive value of ≈90%,[3] and the validity of HF in ARIC is ≈90%.[40] For aim 1, we used the AF diagnosis date ±2.5 years to capture the time period around the diagnosis because participants could have had episodes of AF before they were diagnosed. Selection bias is a concern, particularly after the index date, because those who live longer may have an overall healthier cardiovascular profile compared with someone who died shortly after AF.

Despite these limitations, our study has numerous key strengths. This is a large community-based cohort with a biracial sample, repeat study visits with comparable assessment of risk factors over time, and long-term annual follow-up, giving us the ability to observe health trends over 25 years. There are a large number of cardiovascular and AF events with good-quality data on risk factors and detailed ascertainment and adjudication of cardiovascular risk factors and outcomes.

CONCLUSIONS

In this large population-based study, we report an increased prevalence of cardiovascular risk factors in AF patients >15 years before their diagnosis. The prevalence of cardiovascular outcomes increased after AF diagnosis, and trajectories differed by AF status. We also found diverse trajectories in the prevalence of risk factors and cardiovascular outcomes, suggesting that they could have different roles in the pathogenesis of AF.

ACKNOWLEDGMENT

SOURCES OF FUNDING

DISCLOSURES

None.

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FOOTNOTES

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Circulation

Trajectories of Cardiovascular Risk Factors and Incidence of Atrial Fibrillation Over a 25-Year Follow-Up: The ARIC Study (Atherosclerosis Risk in Communities)
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Norby et al*. Trajectories of Cardiovascular Risk Factors and Incidence of Atrial Fibrillation over a 25-year Follow-up: the Atherosclerosis Risk in Communities Study*

Supplemental Methods

Trajectory Modeling

SAS Proc Traj can be used for estimating developmental trajectories, and fits longitudinal data as a discrete mixture of two or more latent trajectories via maximum likelihood.[1-3] The procedure is based on a semiparametric, group-based modeling strategy which incorporates the traditional methods for analyzing developmental trajectories – hierarchical modeling and latent growth curve modeling.[1] The model allows us to simultaneously estimate the probabilities for multiple trajectories as opposed to simply fitting the overall population mean, and assumes that the population is made up of multiple trajectory groups. To find the best trajectory model fit for our population, we tested models with different numbers of trajectory groups and different forms of potential trajectories (linear, quadratic or cubic). Model fit was assessed using the Bayesian Information Criterion (BIC). We used a censored normal model appropriate for continuous outcomes and a logistic model for binary outcomes. Mean age at each visit for the eligible cohort was used as the time variable. Starting with all trajectory groups in quadratic form we examined models with 5 trajectory groups, then compared the BIC of that model with models fitting 4, 3, 2, and 1 groups respectively. We discovered that BMI, SBP and obesity models had the best fit with 5 groups, and the rest of the outcomes fit best with 4 trajectory groups. Once we had identified the model with the best group number fit, we then compared the model fit with different functional forms. Our final models for SBP, HF, MI and stroke consist of classes with quadratic order terms. Our final models for BMI, obesity, smoking and diabetes are a mixture of cubic order terms and quadratic order terms. From these final models, we calculated the posterior predicted probability for

each individuals of being a member in each of the defined classes. Participants were assigned to the

trajectory group for which they had the greatest posterior predictive probability. All the final models

classified participants into trajectory groups with good discrimination: the mean probability of final

group membership was 0.85 (range 0.74-0.95 across the trajectory groups).

Supplemental References

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