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Thirty-Year Trends in the Incidence of Atrial Fibrillation: The Atherosclerosis Risk in Communities study

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By

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Bachelor of Dental Surgery

Pravara Institute of Medical Sciences University

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Faculty Thesis Advisor: Alvaro Alonso, MD, PhD

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Abstract

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By
Kunali Parimal Ghelani

Objective: To evaluate the 30-year trends in the incidence of atrial fibrillation (AF) in the Atherosclerosis Risk in Communities (ARIC) cohort and identify race and sex differences in these trends.

Background: Long-term data to study recent trends in the incidence of AF, overall and across sex and race groups, are scarce.

Methods: We included 15,343 men and women aged 45 to 64 in 1987-89 without AF from 4 US communities in the ARIC cohort. Incident AF was identified based on study electrocardiograms, hospital discharge codes, and death certificates through 2017. We calculated age and time period-specific incidence rates (IR) of AF. We used Poisson regression to calculate IR ratios of AF over time adjusting for age, sex and race.

Results: A total of 3,241 AF cases were identified during a mean (SD) follow up of 22 (8.4) years (599 in African Americans, 2642 in whites, 1582 in women, 1659 in men). Overall, the IR of AF in the ARIC cohort was 9.6 per 1000 person-years (6.9 in African American, 10.5 in whites, 8.1 in women, and 11.6 in men). Age-specific IR by time-period did not show significant changes over time. In a model adjusted for sex, race, and age group, the rate of AF did not change from 1987-1991 to 2012-2017 (IR ratio=1.10, 95% CI = 0.89-1.36 comparing 2012-2017 to 1987-1991). Similarly, no evidence of changes over time in AF rates were identified in men or women, whites or African Americans separately.

Conclusions: Even though the incident rates of AF increase as age increases, our analysis provided evidence suggesting that the overall rates of AF have not changed over time in a multicenter cohort of African American and white individuals in the US from 1987 to 2017.

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CONTENTS

Background:

Atrial Fibrillation (AF) is one of the most common clinically relevant cardiac arrythmias, characterized by abnormal electrical activity of the heart that causes the atria to fibrillate. The burden of AF has increased over time and varies regionally with low-middle income countries experiencing lower prevalence compared to high-income countries.[1] The Global Burden of Disease 2010 study estimated 33.5 million (20.9 million men [95% uncertainty interval (UI), 19.5-22.2 million] and 12.6 million women [95% UI, 12.0-13.7 million]) individuals globally with prevalent AF.[2] AF is predicted to affect 17.9 million individuals in Europe and 6-12 million people in United States by 2060.[1]

Heart Failure, cerebral emboli leading to ischemic stroke and early mortality are some of the clinical consequences of AF.[3] This common cardiac arrythmia is associated with a 6-fold increase in stroke and a 1.5-2-fold increase in both cardiovascular and all-cause mortality. Known risk factors for AF include advancing age, male sex, diabetes, hypertension, obesity, valvular disease, myocardial infarction (MI) and heart failure.[4] A substantial proportion of risk factors for AF like tall stature, increased epicardial fat, high birth weight, alcohol consumption and smoking have received less attention.[4,5] The lifetime risk of developing AF was approximately 1 in 3 (33%) in whites and 1 in 5 (21%) in African Americans, in a large biracial cohort in the United States.[6] Specifically, the cumulative risk of developing AF from 45 to 92 years was 36% in white men, 30% in white women, 22% in African American men and 22% in African American women.[6]

AF is more common in men than in women (1.1% vs 0.8%) and in whites compared to African-Americans (2.2% vs 1.5%) across all age groups in the ATRIA study.[7] An increase in the burden of AF has been reported by several studies in the past. The Framingham Heart Study (1958 to 2007) and a study in Olmsted County, Minnesota for the period 1980-2000, both consisting of predominantly white populations, reported an increase in the incidence of AF over time.[8, 9] In contrast, a study of Medicare insured population from 1993 to 2007, a more recent analysis in Olmsted County, Minnesota (2000 to 2010), and the UK study Clinical Practice Datalink Study (CPRD) from 1998 to 2010 reported the incidence rates of AF being fairly stable over time.[10, 11, 12] Questions still remain on the accuracy of these contrasting results, whether these results can be generalized to other communities and other racial and ethnic groups, and whether they apply to the last decade. Current figures for trends in the incidence of AF in diverse communities in the US are not available.

To address these gaps, we evaluated the trends in the incidence of AF among >15,000 white and African American participants from the Atherosclerosis Risk in Communities (ARIC) study, who were followed up for over 30 years. The results obtained from this study will provide insights into the future burden of AF in the general population.

Methods:

Study Population:

The ARIC Study is a population-based prospective cohort study consisting of participants sampled from 4 US Communities (mostly whites from suburbs of Minneapolis, Minnesota, and Washington County, Maryland; African Americans from Jackson, Mississippi; and whites and African Americans from Forsyth County, North Carolina). The procedures were reviewed and approved by the institutional review board at the participating centers. A written informed consent was obtained from all the participants. A detailed phone interview and clinical examination were done to check the eligibility of the participants and collect baseline information. A cohort of 15,792 participants aged 45-64 years were enrolled during the period 1987-1989 (55% women, 27%

African Americans). After an initial assessment, the participants were reexamined roughly every 3 years for 3 additional times until 1998, with further examinations in 2011-2013, 2016-2017 and 2018-2019.[6] Response rates for first, second and third follow up examinations was 93%, 86% and 80% respectively. Contact with the participants was maintained yearly by phone (biannual since 2012) to ascertain their health status and obtain information about hospital admissions.[13,14] For the purpose of the analysis, we included follow-up information through December 31, 2017.

Among the 15,792 participants, individuals with self-identified race non-white or non-African American (n=48) and non-whites from Minnesota and Maryland sites (n=55) were excluded, due to small numbers. Individuals with prevalent AF on ECG (n=37) and whose ECG was missing or unreadable (n=309) at baseline were excluded from the study. We included a total of 15,343 participants in the final study population for analysis purposes.

AF Event Ascertainment:

Diagnosis of AF was obtained from 3 sources: ECG at study exams, recorded with MAC PC ECG machines (Marquette Electronics, Milwaukee, WI) in all clinical centers, hospital discharge records, and death certificates. A resting 12-lead ECG recording was performed during the first five exams for all ARIC participants. ECGs were transmitted to the ARIC Central ECG Reading Center by telephone for interpretation, storage and coding. Trained cardiologist visually rechecked all automatically coded ECG recordings for AF to confirm the diagnosis.

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM codes 427.31 or 427.32) and Tenth Revision, Clinical Modification (ICD-10-CM, I48.x) hospital discharge diagnoses in the absence of cardiac procedures were obtained from hospitalization records to identify AF events. AF occurring during open heart surgeries was excluded. Finally, if AF (ICD-10 code I48 or ICD-9 code 427.3) was mentioned as a cause of death in the death certificate or in vital statistics obtained from National Death Index, then ARIC participants were classified as AF cases. The sensitivity and specificity by this approach was 80% and 99% respectively in African Americans and 85% and 99% respectively in whites.[14] The incident date of AF was established as the date for the first ECG showing AF, the first hospital discharge with an AF or atrial flutter, or death by AF, whichever occurred earlier.

Ascertainment of other variables:

Data at baseline were collected for body mass index (BMI), education level of the participant, smoking status, hypertension and diabetes. Hypertension was defined as use of antihypertensive medication or a systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90mm Hg. Evidence of previous myocardial infarction on ECG at baseline or a self-reported physician diagnosed myocardial infarction was considered as having a history of myocardial infarction.[14,13] Participants self-reported their smoking status and education level at baseline. Gothenburg criteria or treatment of heart failure (HF) in the past two weeks at baseline was identified as having prevalent heart failure.[15]

Statistical Analysis:

Baseline characteristics for participants, stratified by race and sex were summarized as percentages for categorical variables and mean (standard deviation) for continuous variables.

We computed participants person-years of follow up from the date of first examination to the earliest of diagnosis of AF, loss of follow up, or death. Age-specific incidence rates were calculated by 5-year age groups and calendar time by 5-year periods. The last calendar time period was defined as a 6-year period (2012-2017), in order to include the most updated data. The crude incidence rate was reported as the total number of events divided by the person-years of follow up.

Temporal trends were reported using age-specific incidence rates of AF by 5-year calendar year periods. To visually assess the existence of temporal trends, age-specific crude incidence rates of AF by 5-year time periods were graphically plotted. We calculated incident rate ratios (IRR) and their corresponding 95% CI for time period using Poisson regression models adjusting for age, sex and race. Analysis was performed using SAS 9.4 statistical software for all the data collected.

Results:

We analyzed 15,343 participants without AF at baseline and aged 45-64 years. Table 1 reports the baseline characteristics of the included participants by race and sex. The proportion of current smokers was highest among African American men. Likewise, the proportion of participants with only basic education was higher among African Americans. Overall prevalence of risk factors for AF was higher in African Americans as compared to whites.

A total of 3,241 AF cases were identified during a mean (SD) follow up of 22 (8.4) years (599 in African Americans, 2642 in whites, 1582 in women, 1659 in men). Table 2 shows the different sources of AF ascertainment used to identify new incidence of AF during the follow up years. Hospital discharge code only identified 82% of all AF cases, with 16% of the cases identified from two or more sources. The IR of AF in the entire cohort was 9.6 per 1000 person-years. Incidence of AF increased with increasing age (1.1 for <55 years, 4.1 for 55-64 years, 10.2 for 65-74 years, 22.6 for 75-84 years and 39.3 per 1000 person-years for ≥ 85 years), and was higher in men compared to women and whites compared to African Americans (11.6 in men, 8.1 in women, 10.5 in whites and 6.9 per 1000 person-years in African American). Race/center-specific IR were 11.8 per 1000 person-years for whites in Washington County, 9.4 per 1000 person-years for whites in Minneapolis, 7.0 per 1000 person-years for African Americans in Jackson, 10.3 per 1000 person-years for whites in Forsyth and 6.0 per 1000 person-years for African Americans in

Forsyth. Age-specific IR by 5-year time-period did not show meaningful changes over time (Table 3 and Figure 1). Similarly, there was no strong evidence of increases over time in age-specific IR when stratified by race and sex group (Figure 2).

The rate of AF was 45% higher in men compared to women (RR=1.45, 95% CI 1.36, 1.56). and 32% higher in whites compared to African Americans (RR=1.32, 95% CI 1.20, 1.44) adjusting for age and time period, in addition to including sex and race. In a model adjusted for sex, race, and age group, the RR of AF in 2012-2017 compared to 1987-1991 was 1.10 (95% CI = 0.89-1.36). Likewise, no evidence of changes over time in AF rates were identified in men or women, whites or African Americans separately (Table 4).

Discussion:

In our analysis of 15,343 participants aged 45-64 followed for up to 30 years, we did not find any evidence of increased rates of AF over time. Also, and as previously described, despite the risk factors being higher in African Americans the incidence rates of AF were higher in whites. Consistent with previous population-based studies in the US, the incidence of AF increased exponentially with age and was greater in men than in women.[8,16] Age-adjusted incidence in white men compared to white women were higher in both Framingham Heart Study and Olmsted county study. Comparable to the incidence rates being higher in whites, a prior analysis in the ARIC cohort reported a lifetime risk of developing AF of 1 in 3 among whites and 1 in 5 among African Americans.[6]

According to the Olmsted County, Minnesota study there was an increasing trend in the age and sex-adjusted incidence of AF from 1980 to 2000 (3.04 vs 3.68 per 1000 person-years).[8] Similar to these study results, the Framingham Heart Study also showed an increase in the age-adjusted IR (1.83 per 1000 person-years in 1958-1967 vs 3.75 per 1000 person-years in 1998-2007) over time.[16] In contrast, a study of UK CPRD from 1998 to 2010 however showed fairly stable IR over time (1.11 in 1998–2001, 1.33 in 2002–2006 and 1.33 in 2007–2010).[12] Also, a more recent study of AF incidence in Olmsted County, Minnesota (2000-2010) did not report continued increases in AF incidence.[10] Our findings are consistent with both the UK CPRD study and the recent Olmsted County .[12,11] Inconsistencies across studies can be due to the underlying populations and the periods under consideration, which a more diverse population and more recent time periods in our analysis of the ARIC cohort.

Though African Americans have an underlying higher burden of risk factors compared to whites, we found lower overall rates of AF among this racial group. These findings are similar to those in other populations.[17,18,19] Reasons for this difference are unknown, but it does not seem to be explained by the difference is socio-economic status in prior analysis in ARIC cohort.[20]

In the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study consisting of a large ethnically diverse population the prevalence of AF was strongly associated with age.[7] Comparable results of increase in the prevalence of AF with age were seen in a retrospective study of Medicare beneficiaries between 1993 and 2007 where the mean annual increase in prevalence of AF was 5% and in population based longitudinal Cardiovascular Health study.[10,21] Even without increases in the incidence of AF over time, the aging of the overall population is leading to dramatic increases in the overall burden of AF.[7,8] The increasing burden of AF may eventually lead to growing burden of AF-related complications, including stroke, heart failure (HF), cognitive impairment and dementia, chronic and end-stage renal disease, myocardial infarction (MI) and all-cause mortality.

Several studies across Europe,[22,23,24] New Zealand[25], Western Australia[26], Japan[27] and US[28,29] have demonstrated decreasing trends in stroke and coronary heart disease incidence over the last few decades. This decline in cardiovascular disease incidence has been attributed to reductions in the prevalence of risk factors for cardiovascular disease, better management of these risk factors, and improved medical care.[30] These positive trends in stroke and coronary heart disease, however, have not been accompanied by reductions in AF incidence, as shown in our current analysis of the ARIC cohort and other studies, despite some risk factors being shared between these conditions. These discrepancies highlight the importance of developing specific strategies for the prevention of AF that go beyond current approaches for prevention and control of overall cardiovascular disease.

Strengths and Limitations:

The ARIC cohort has a large sample size and a diverse population with an extended follow up time, which allows the estimated incident rates to be precise, even across race and sex groups. As this is one of the longest follow-up studies with a biracial population in four communities across US, the cohort is more diverse than other studies, thus facilitating generalizability of the results. The study also benefits from excellent follow-up, careful participant assessments, and availability of repeated electrocardiograms and information on hospitalizations.

One major limitation of the study is the ascertainment of AF. Asymptomatic AF or those cases managed in outpatient care will be missed as the ascertainment of AF is based primarily on hospital discharge codes. In addition, we are unable to differentiate between paroxysmal AF and persistent AF based on study ECG and hospital discharge records. Finally, since most of the black participants come from the Jackson site, it is not possible to perfectly disentangle race differences from differences in location.

Conclusion:

We report that the incidence rates of AF in a large biracial population-based closed cohort in 4 different US communities did not change over time from 1987-2017. The increasing incidence of AF with increasing age helps to understand the burden of AF and its public health impact. A careful evaluation is needed to fully understand the risk factors and get insights into the mechanism causing racial discrepancy in the incidence of AF. Future studies should address the issue of continuous monitoring of participants for subclinical AF as well as develop strategies aimed to reducing the burden of AF in the population.

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Table 1: Baseline characteristics of study participants in the ARIC Study, 1987-89.

	White Men	**White Women**	**African American Men**	**African American Women**
N (%)	5332 (34.8)	5948 (38.8)	1539 (10.0)	2524 (16.4)
Age (years) [mean (SD)]	54.8 ± 5.7	54.0 ± 5.7	54.0 ± 6.0	53.3 ± 5.7
BMI (kg/m2) [mean (SD)]	27.4 ± 4.0	26.6 ± 5.5	27.7 ± 5.0	30.8 ± 6.5
Education level, (%)				
-Basic Education	960 (18.0)	978 (16.5)	677 (44.1)	1007 (40.0)
-Intermediate Education	2093 (39.3)	3022 (50.9)	400 (26.1)	747 (29.7)
-Advanced Education	2271 (42.7)	1943 (32.7)	457 (29.8)	764 (30.3)
Smoking, n (%)				
-Current	1311 (24.6)	1480 (24.9)	589 (38.3)	625 (24.8)
-Former	2534 (47.5)	1454 (24.5)	520 (33.8)	442 (17.5)
-Never	1486 (27.9)	3008 (50.6)	429 (27.9)	1451 (57.6)
Hypertension, n (%)	1510 (26.2)	1551 (28.5)	839 (54.6)	1424 (56.7)
Diabetes, n (%)	542 (10.2)	484 (8.2)	277 (18.3)	509 (20.8)
Prevalent Heart failure at Baseline, n (%)	148 (4.8)	280 (2.8)	65 (4.3)	216 (8.6)
Prevalent Coronary Heart Disease, n (%)	464 (8.9)	109 (1.9)	89 (5.8)	73 (2.9)
Previous history of myocardial infarction, n (%)	381 (7.2)	91 (1.5)	82 (5.4)	69 (2.8)
Prevalence of Stroke, n (%)	93 (1.9)	53 (1.0)	53 (4.2)	57 (2.7)

Table 2: Sources of incident cases of atrial fibrillation (AF), ARIC Study, 1987-2017

Source	**AF cases [n (%)]**
Hospital discharge code only	2670 (82.3)
Exam ECG only	32 (1)
Death certificate only	31 (1)
Both hospital discharge code and death certificate, no exam ECG	247 (7.6)
Both hospital discharge code and exam ECG, no death certificate	217 (6.7)
Both exam ECG and death certificate, no hospital discharge code	2 (0.1)
All three sources	42 (1.3)
Total	3241 (100)

Table 3: Crude AF Rates (per 1000 Person-Years [PY]) Stratified by 5-Year Age Group and 5-Year Calendar Year

	Calendar Year of Follow-up					
Age Group, y	**1987-1991**	**1992-1996**	**1997-2001**	**2002-2006**	**2007-2011**	**2012-2017**
45-49						
IR(95%CI)	0.68 (0.3-1.3)	1.5 (0.2-5.5)				
Cases/PY	7/10928	2/1318				
50-54						
IR(95%CI)	1.4 (0.8, 2.1)	1.2 (0.7, 1.9)	0.8 (0.02, 4.4)			
Cases/PY	21/15467	19/15260	1/1275			
55-59						
IR(95%CI)	2.7 (1.9, 3.7)	2.9 (2.2, 3.7)	3.8 (2.8, 4.9)	4.1 (1.5, 9.1)		
Cases/PY	39/14593	55/19115	55/14596	5/1206		
60-64						
IR(95%CI)	4.5 (3.5, 5.8)	5.3 (4.2, 6.5)	4.5 (3.5, 5.6)	5.5 (4.4, 6.9)	5.3 (1.9, 11.6)	
Cases/PY	61/13465	92/17462	80/17865	76/13684	6/1123	
65-69						
IR(95%CI)	9.3(6.5, 12.8)	8.9 (7.5, 10.6)	7.1 (5.9, 8.8)	7.1 (5.9, 8.5)	6.9 (5.5, 8.5)	15.9 (9.1, 25.8)
Cases/PY	37/3992	132/14808	113/15837	115/16264	86/12497	16/1005
70-74						
IR(95%CI)		13.1 (9.6, 17.6)	14.3 (12.3, 16.5)	12.2 (10.5, 14.2)	11.6 (9.9, 13.5)	14.6 (12.4, 17.5)
Cases/PY		45/3426	183/12787	168/13704	166/14266	161/11017
75-79						
IR(95%CI)			15.1 (10.9, 20.4)	20.3 (17.6, 23.2)	20.8 (18.2, 23.6)	19.0 (16.7, 21.6)
Cases/PY			42/2780	209/10290	231/11096	237/12459
80-84						
IR(95%CI)				23.3 (17.5, 30.6)	32.1 (28.1, 36.5)	27.3 (23.9, 31.0)
Cases/PY				49/2097	233/7251	235/8598
85-89						
IR(95%CI)					47.9 (36.6, 61.1)	36.7 (31.4, 42.5)
Cases/PY					61/1273	173/4715
90-94						
IR(95%CI)						41.6 (28.1, 59.3)
Cases/PY						30/721

Table 4: Rate Ratio for AF by sex, race, age and period in the Atherosclerosis Risk in Communities Study, 1987-2017

	Rate Ratio	**95% CI**	**p-value**
Sex (Men vs Women)	1.45	1.36, 1.56	<0.0001
Race (White vs African American)	1.32	1.20, 1.44	<0.0002
5-year Age category			
45-49	1	Ref	
50-54	1.65	0.80, 3.41	0.18
55-59	3.96	2.01, 7.82	<0.0001
60-64	6.26	3.19, 12.2	<0.0001
65-69	9.63	4.90, 18.9	<0.0001
70-74	16.2	8.22, 32.0	<0.0001
75-79	24.1	12.2, 47.7	<0.0001
80-84	34.9	17.6, 69.3	<0.0001
85-89	47.8	23.9, 95.5	<0.0001
90-94	52.4	24.2, 113	<0.0001
5-year Period			
1987-1991	1	Ref	
1992-1996	1.11	0.92, 1.35	0.26
1997-2001	1.05	0.87, 1.28	0.60
2002-2006	1.05	0.86, 1.29	0.62
2007-2011	1.12	0.91, 1.38	0.27
2012-2017	1.10	0.89, 1.36	0.37

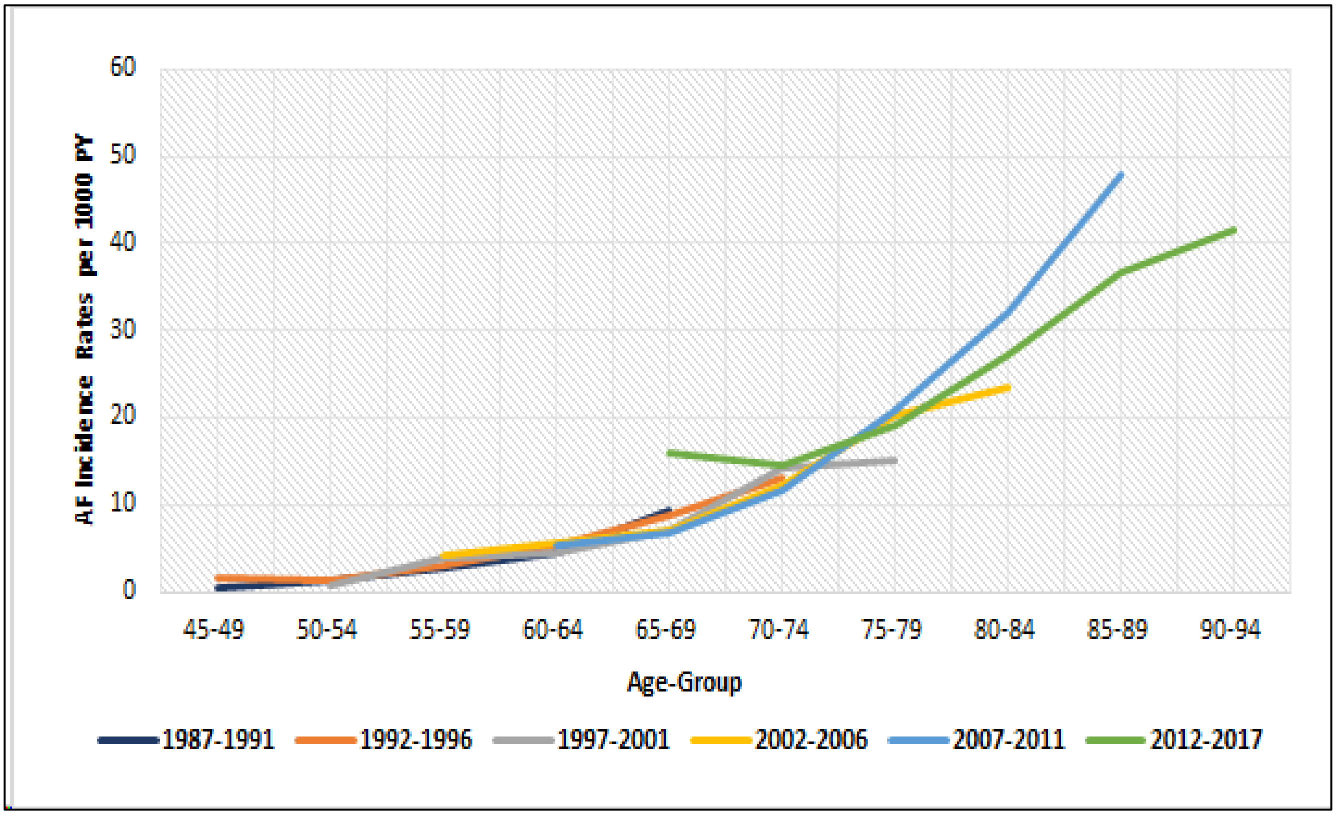

Figure 1: Age-specific incident rates of AF by period in the ARIC cohort, 1987 to 2017

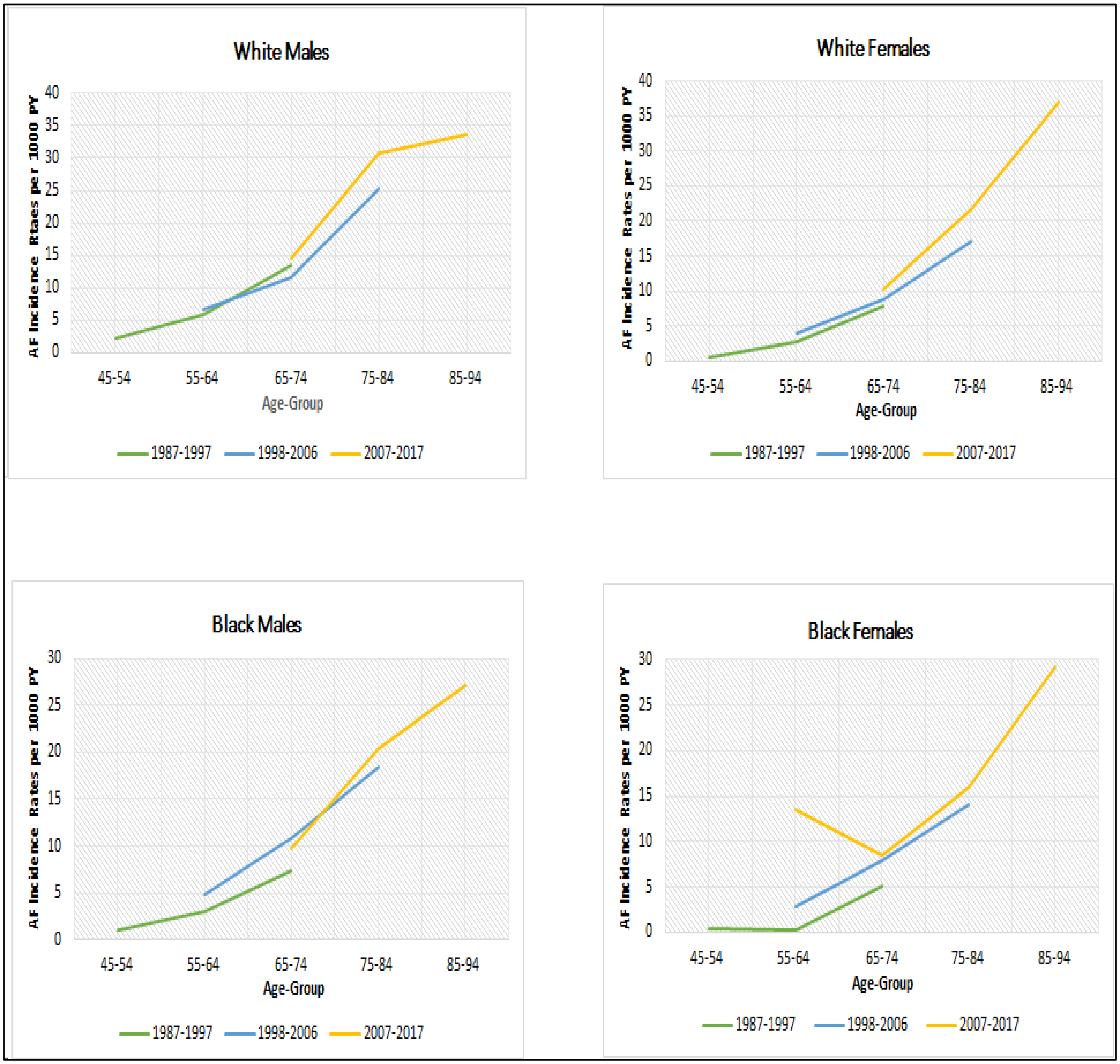

Figure 2: Age-specific incident rates of AF by race, sex and period, ARIC Cohort, 1987-2017