Incident atrial fibrillation in relation to disability-free survival, risk of fracture, and changes in physical function in the Cardiovascular Health Study

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Abstract

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Background: Atrial fibrillation (AF) is common in older adults and associated with an increased risk of stroke, heart failure, dementia, and death, but important gaps remain in our understanding of the physical and functional consequences of AF. The aim of this study was to investigate the associations of incident AF with disability-free survival, risk of fracture, and changes in gait speed and grip strength in the Cardiovascular Health Study (CHS), a population-based longitudinal cohort study of adults aged 65 years and older.

Methods: The study population included up to 4462 CHS participants enrolled in fee-for-service Medicare, followed between 1991 and 2009. Individuals with prevalent AF or a history of stroke or heart failure at baseline were excluded. Incident AF during cohort follow-up was identified by annual study electrocardiogram (ECG), hospital discharge diagnosis, or AF diagnosis in Medicare inpatient, outpatient, or physician service claims. Disability-free survival was defined as survival free of Activities of Daily Living (ADL) disability. ADLs were self-reported at annual clinic visits or via telephone interview. Fracture (defined as fractures of the hip, distal forearm,

pelvis, or humerus) was identified by hospital discharge diagnosis or Medicare claims. Gait speed (time to walk 15 feet, converted to meters per second) and grip strength (in kilograms) were assessed at annual clinic visits. We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals for the associations of incident AF with disability-free survival and the risk of fracture. Linear mixed effects models were used to examine incident AF and one-year change in grip strength and gait speed. All estimates were adjusted for baseline age sex, race, clinic, education, body mass index, smoking, baseline self-reported physical activity, and time-varying hypertension, use of anti-hypertensive medications, coronary heart disease, and diabetes. Estimates for the associations of incident AF with disability-free survival were further adjusted for interim stroke and heart failure.

Results: Incident AF was associated with decreased disability-free survival (HR for death or ADL disability=1.71, 95% CI 1.55, 1.90, HR for ADL disability=1.36, 95% CI 1.18, 1.58) compared to individuals without incident AF, and this association persisted after adjustment for stroke and heart failure (HR for death or ADL disability=1.50, 95% CI 1.34, 1.66, HR for ADL disability=1.24, 95% CI 1.07, 1.44). Incident AF was not associated with changes in gait speed (estimated one-year change in subjects without AF = -0.011 m/s; with incident AF = -0.013 m/s; difference = -0.002 m/s, 95% CI -0.006, 0.003) or grip strength (estimated one-year change in subjects without AF = -0.47 kg; with incident AF = -0.48 kg; difference = -0.01 kg, 95% CI -0.13, 0.10). Individuals with incident AF were not at higher risk of fracture (adjusted HR=0.97, 95% CI 0.77, 1.21) or hip fracture (adjusted HR=1.09, 95% CI 0.83, 1.42).

Conclusion: The results of this study suggest that incident AF is a risk factor for disability in older adults. However, incident AF does not appear to be a risk factor for fracture and does not appear to accelerate declines in gait speed or grip strength. Additional research is needed to understand the potential mechanisms through which AF influences disability and to examine whether prevention or treatment of AF can reduce the burden of disability in the elderly.

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Chapter 1. Incident atrial fibrillation and disability-free survival

INTRODUCTION

In older adults the onset of disability, whether from a gradual loss of physical function or after a catastrophic event such as a hip fracture, marks a critical turning point in life. It is often followed by a precipitous decline in health, soaring medical costs, and an increased risk of nursing home placement and death.[1, 2] On an individual level, it means a loss of personal autonomy and diminished quality of life in one's final years. Improvements in life expectancy and the burgeoning population of older adults have heightened interest in "successful aging", a concept which includes, amongst other factors, aging with intact physical function and free of disability.[3] Of particular importance is the identification of modifiable risk factors that contribute to the onset of disability.

Atrial fibrillation is one potential risk factor for disability in older adults. AF is the most common cardiac arrhythmia in the U.S. and is prevalent in the elderly, affecting more than 10% of U.S. adults over the age of 80.[4] Symptoms and complications of AF include decreased cardiac and cerebral perfusion, reduced exercise tolerance, weakness, dizziness, and a rapid or irregular heart rate.[5, 6] These in turn may increase the likelihood of disabling falls or promote a sedentary lifestyle, hastening the onset of disability.

AF is associated with an increased risk of stroke[7], heart failure[8], dementia[9, 10], and death[11], but whether AF is associated with disability is largely unknown. One recent post-hoc analysis of two clinical trials suggested an association between AF and incident ADL disability, but was restricted to patients at high cardiovascular risk.[12] The relationship between AF and incident disability or disability-free survival has yet to be studied prospectively in a population generalizable to older U.S. adults. We hypothesized that individuals with AF would be at higher risk of disability or death than those without AF.

METHODS

The Cardiovascular Health Study (CHS) is a population-based, longitudinal cohort study of risk factors for coronary heart disease and stroke in individuals 65 years of age and older.[13] Participants (N=5,888) were recruited from a random sample of Medicare beneficiary lists from four communities across the U.S. (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania). The cohort is comprised of 5,201 participants recruited in 1989-1990 and 687 additional participants, primarily African Americans, recruited in 1992-1993. Individuals were excluded from CHS if they were institutionalized, were wheelchair-bound, planned to move out of the area within three years, or were actively undergoing treatment for a malignant condition. The institutional review boards for each community site approved the study, and all participants provided informed, written consent.

Administrative claims data used to identify incident AF were available from 1991 onward and only in subjects enrolled in fee-for-service Medicare (FFS). Because we used FFS data to identify incident AF, this analysis was restricted to subjects in FFS. Individuals entered the analytic cohort at the start of FFS availability and were censored if they disenrolled from FFS. In addition to excluding subjects not enrolled in FFS (n=810), individuals with ADL disability (n=453), prevalent AF (n=171), a history of stroke or heart failure (n=343), or missing covariate data (n=65) at baseline were also excluded. The final analytic cohort included 4046 individuals. Follow-up extended through June 30, 2009.

Exposure

The primary exposure was incident AF (defined as either atrial fibrillation or atrial flutter), ascertained from three sources: (1) ECGs from annual study examinations which indicate AF, (2) hospital discharge diagnoses indicating AF (from CHS or Medicare data), and (3) diagnoses

of AF from outpatient or physician visits (from Medicare data). Study ECGs were read and interpreted by the CHS Electrocardiography Reading Center using standard methods.[14] For AF identified using hospital discharge or Medicare data, a diagnosis of AF was based on a single inpatient claim or hospital discharge diagnosis or 2 outpatient or physician claims within 365 days (ICD-9-CM code 427.31 or 427.32).[15] The date of AF diagnosis was based on the earlier of: (1) the date of ECG indicating AF, (2) the admission date of the qualifying inpatient claim or hospital discharge diagnosis, or (3) the service date of the second qualifying outpatient or physician claim. Previous validation work in a sub-sample of CHS subjects yielded a positive predictive value of 98% and sensitivity of 71% for the use of hospital discharge codes to identify AF.[16] Once an AF diagnosis was made, participants were classified thereafter as having AF.

Outcomes

The primary outcome was disability-free survival, defined as survival free of ADL disability. For the purposes of risk estimates, a failure was death or ADL disability. We defined ADL disability as reporting any difficulty or inability to perform one or more of the following tasks considered crucial for independent living: bathing, dressing, eating, using the toilet, walking around the home, and getting out of a bed or chair.[17, 18] ADLs were assessed at each clinic visit for the first ten years of the study and by telephone every year thereafter. Because disability can be transient, we also considered whether incident AF was associated with persistent ADL disability, defined as self-reported difficulty in at least one ADL for two consecutive occasions.[3] Individuals with a single occasion of ADL difficulty who subsequently died or were missing all future ADLs were also considered to have persistent ADL disability. Date of persistent ADL disability was the date of the first occurrence of ADL difficulty for qualifying cases.

Covariates

Participant age, year of birth, sex, race (white, non-white), education beyond twelfth grade (yes/no), clinic (Wake Forest, Davis, Hopkins, Pittsburgh), physical activity (kcal/week), alcohol use (mean number of drinks per week) and smoking history (never, former, current) were self-reported at CHS study baseline. Body mass index (kg/m^2) and forced expiratory volume (FEV1) were measured at CHS study baseline. Use of anti-hypertensive medications (yes/no), diabetes (yes/no, either prevalent or newly recognized), and hypertension (yes/no) were assessed and updated at each clinic visit. Antihypertensive medication use was assessed using the method of medication inventory.[19] Diabetes was defined as use of insulin or oral hypoglycemic drugs, or fasting serum glucose $\geq$ 126 mg/dL or, non-fasting serum glucose $\geq$ 200 mg/dL. Hypertension was defined as use of antihypertensive medications plus self-reported history of hypertension, or systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg. Chronic kidney disease (yes/no) was defined as having a creatinine-based estimated glomerular filtration rate of less than 60 ml/min. At least one creatinine measure was available in 3,882 individuals and up to three creatinine measures were available over follow-up. Baseline and incident coronary heart disease, incident stroke, and incident heart failure were identified by the semi-annual contacts (telephone or clinic visit) or through linkage with Medicare hospitalization data, and were confirmed by physician adjudication using medical and hospital records or study ECGs.[20, 21]

Statistical Analysis

Kaplan-Meier curves for disability-free survival were plotted in individuals with and without incident AF and a difference in curves was evaluated using a log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between incident AF, modeled as a time-varying exposure, and the risk of death or ADL disability. The association between incident AF and the risk of incident ADL disability

alone was also estimated. Analyses were repeated for the outcomes of persistent ADL disability or death, and persistent ADL disability alone. All estimates were adjusted for age, sex, race, clinic, education, BMI, FEV1, smoking, alcohol use, physical activity, and time-varying hypertension, anti-hypertensive drug use, coronary heart disease, and diabetes.

We conducted several secondary analyses. To examine whether the relationship between incident AF and death or disability could be due to interim stroke and heart failure, we repeated our analyses adjusting for incident stroke and heart failure during follow-up. Analyses were also repeated after adjusting further for time-varying chronic kidney disease in the subsample of the cohort with at least one measure of creatinine. We also examined whether the relationship between incident AF and disability-free survival differed by sex or race. Wald tests were used to evaluate evidence of effect modification using a significance level of 0.05.

We performed sensitivity analyses including subjects not enrolled in fee-for-service Medicare and ignoring entry and exit from fee-for-service Medicare. Finally, to examine bias due to subjects dropping out of the study prior to death or the onset of disability, sensitivity analyses were performed using inverse probability weighting methods (IPW).[22] The probability of having more than two missing ADL measures (an indicator of early drop-out) was estimated as a function of the following factors at each subject's baseline: age, smoking, BMI, self-reported health, diabetes, coronary heart disease, hypertension, use of anti-hypertensive medications and physical activity level as well as any AF during follow-up, and any stroke or heart failure during follow-up. Statistical analyses were conducted using STATA version 13.0 (Stata Corp, College Station, Texas).

RESULTS

Over a mean follow-up of 7.0 years, 660 individuals (16.3%) developed incident AF. Of the individuals diagnosed with AF, 10% were first identified from study ECG, 65% from an inpatient claim or hospital discharge diagnosis, and 25% from an outpatient or physician claim. Individuals who developed incident AF over follow-up were more likely to be male and white, and had a higher burden of comorbidity than individuals who did not develop AF (Table 1.1). Both individuals with and without incident AF had on average 7 measures of ADLs over follow-up.

The crude incidence rate of death or disability was 100.5 per 1,000 person-years in individuals without incident AF and 207.8 per 1,000 person years in individuals with incident AF. Crude incidence rates for ADL disability alone were 62.5 per 1,000 person-years (41.7 for persistent ADL disability) and 97.8 per 1,000 person-years (86.2 for persistent ADL disability) in individuals without and with incident AF, respectively. Figure 1 displays Kaplan-Meier curves for disability-free survival for individuals with and without incident AF. There was evidence of a difference in the survival curves (log-rank $p<0.001$). Incident AF was associated with a higher risk of death or disability (adjusted HR=1.71, 95% CI 1.55, 1.90) (Table 1.2). Incident AF was also associated with a higher risk of disability (adjusted HR = 1.36, 95% CI 1.18, 1.58). Estimates were similar for the associations of incident AF and persistent ADL disability and persistent disability-free survival. Adjustment for interim stroke and heart failure attenuated, but did not completely remove, the associations between incident AF and death or disability (Table 1.2). Further adjustment for chronic kidney disease among a subsample of the cohort with creatinine measures had no material effect on estimates (Supplemental Table 1.1). Sensitivity analyses including subjects not enrolled in FFS Medicare and ignoring entry to and exit from FFS yielded similar estimates (Supplemental Table 1.1).

There was evidence that the association between incident AF and ADL disability differed by race (Table 1.3). White individuals who developed incident AF were at higher risk of subsequent disability whereas non-whites did not appear to be at higher risk. However, there was no evidence of effect modification by race for the outcome of death or ADL disability and no evidence of effect modification by sex for either outcome.

DISCUSSION

This was the first study to examine the association between incident AF and the risk of disability in a population representative of older U.S. adults. The results of this study suggest that incident AF is a risk factor for disability and is associated with decreased survival free of disability. Importantly, we observed that even after adjustment for interim stroke or heart failure, individuals with incident AF experienced a 50% higher risk of death or disability and 24% higher risk of becoming disabled.

One prior study evaluated the association between AF and the risk of ADL disability using a post-hoc analysis of randomized controlled trial data in patients at high cardiovascular risk.[12] In that study, subjects with prevalent or newly diagnosed AF were at higher risk of ADL disability than subjects without AF, and the magnitude of association was similar to this study (adjusted HR=1.35, 95% 1.19, 1.54).

In our study, white individuals with incident AF were at higher risk of disability than non-white individuals with incident AF but there was no difference in the risk of the outcome of disability or death. These results should be interpreted with caution as they comprised a sub-group analysis and the results may be due to chance. Previous research suggests that African-Americans have a higher risk of disability than whites[23], but are at lower risk of developing AF.[24] Additional

studies in multi-ethnic populations are needed to clarify whether racial differences in the relationship between incident AF and the risk of disability can be confirmed.

The onset of disability can occur as a result of a catastrophic event such as a stroke or hip fracture, or may develop slowly over time.[25] In our study the relationship between incident AF and the risk of death or disability appeared to be partially, but not fully, mediated by the effects of interim stroke and heart failure, suggesting that other mechanisms may be at work. Previous work within CHS found no associations between incident AF and the risk of hip fracture, falls, or longitudinal changes in physical function (see Chapters 2 and 3 of this work). Beyond stroke, AF may exert degenerative effects on the brain via hypoperfusion and or covert infarction.[6] Covert brain infarctions and white matter disease are associated with impaired cognition[26], abnormalities in gait and balance[27-29], disability[29], and a higher risk of falls.[30] Two cross-sectional studies have observed an association between prevalent AF and the presence of white matter abnormalities or covert infarction.[31, 32] However, other cross-sectional studies have found no association between prevalent AF and white matter findings. [33] More research is needed to understand other pathophysiological mechanisms through which AF may lead to disability.

There were several limitations to this study. AF can be transient and asymptomatic, leading to misclassification in AF ascertainment. Assuming that errors in ascertaining AF were non-differential, this would have attenuated the associations between incident AF and the risk of disability or death. Second, we were not able to differentiate between different categories of AF such as paroxysmal, persistent, and permanent on the basis of the diagnosis codes, and the risk of subsequent disability may differ by type of AF. Prior studies have shown that individuals with permanent AF report poor quality of life and have a poorer prognosis compared with

individuals with other types of AF.[34-36] Additional studies are needed to examine whether there are important differences in the risk of disability within subgroups of individuals with AF.

Disability was based on self-reported ADLs. It is possible that individuals with AF were more likely to report a loss of function because their diagnosis made them feel sicker but were not actually more likely to be disabled. Individuals with AF often report feeling anxious, depressed, or a loss of quality of life.[37] If such individuals over-reported difficulties in ADLs, this would overestimate the associations between incident AF and the risk of ADL disability. However, the use of self-reported ADLs is considered a valid, reliable, and clinically important measure of disability.[38, 39] Alternatively, sicker individuals, such as those with AF, may be more likely to die or to drop out of the study before they have the opportunity to report become disabled, or to have missing data on ADLs. One advantage of the use of self-reported ADLs versus the use of a more objective, clinic-based physical performance measure is that it can be assessed quickly and easily over the telephone. Thus, it may be less prone to bias from the non-random missingness that is common in studies of aging.[40] In addition, individuals with incident AF were no more likely than those without AF to have missing data on ADLs.

Our study has a number of strengths. We utilized a large prospective cohort study generalizable to older U.S. adults. We had rich and detailed information about potential confounders and important clinical factors which may mediate the relationship between AF and disability, such as stroke or heart failure. Multiple sources were used to identify incident AF, including AF detected on study clinic ECG as well as AF diagnosed outside of the hospital, which lowered the likelihood of misclassification of AF status. Finally, we attempted to reduce the potential bias from missing data that is common in studies of aging by using IPW.

In conclusion, the results of this study suggest that incident AF is a risk factor for disability in older adults. Additional research is needed to understand the potential mechanisms through which AF influences disability and to examine whether prevention or treatment of AF can reduce the burden of disability in the elderly.

TABLES AND FIGURES

Table 1.1. Baseline characteristics of participants

Characteristic	All N=4046	No AF during follow-up N=3386	Incident AF during follow-up N=660
Age, mean (SD)	73 (5)	73 (5)	74 (5)
Male, %	41.8	39.6	53.0
White, %	86.5	85.6	91.2
Education beyond 12th grade, %	44.5	44.3	45.6
Smoking, %			
Current	12.2	12.3	12.0
Former	41.6	41	44.9
Alcohol use, %	51.7	51.5	52.9
Mean number of drinks per week (SD)	5.0 (9.8)	5.1 (10)	5.0 (8.5)
Physical activity (kcal) per week, mean (SD)	1838 (2071)	1844 (2079)	1805 (2031)
Body mass index (kg/m^2), mean (SD)	26.4 (4.5)	26.4 (4.6)	26.2 (4.0)
FEV1, mean (SD)	2.1 (0.7)	2.1 (0.6)	2.1 (0.7)
Diabetes, %	13.6	13.4	15.0
Coronary heart disease, %	17.4	15.7	26.1
Hypertension, %	55.2	54.5	58.6
Antihypertensive medication use, %	43.7	42.5	49.7

Table 1.2. Incident AF and the risk of incident ADL disability or death

Outcome	Hazard Ratio (95% Confidence Interval)[a]		
	Minimally adjusted[b]	Fully adjusted[c]	Further adjusted for stroke and heart failure[c]
ADL disability or death	1.79 (1.62, 1.98)	1.71 (1.55, 1.90)	1.50 (1.34, 1.66)
ADL disability	1.48 (1.29, 1.71)	1.36 (1.18, 1.58)	1.24 (1.07, 1.44)
Persistent ADL disability or death	1.76 (1.60, 1.94)	1.71 (1.56, 1.89)	1.48 (1.34, 1.64)
Persistent ADL disability	1.53 (1.33, 1.75)	1.40 (1.22, 1.61)	1.26 (1.09, 1.46)

[a] Referent category is No AF

[b] Adjusted for age, sex, race and clinic

[c] Adjusted for age, sex, race, clinic, education, BMI, FEV1, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

Figure 1.1 Kaplan-Meier plots of disability-free survival in individuals with and without incident AF

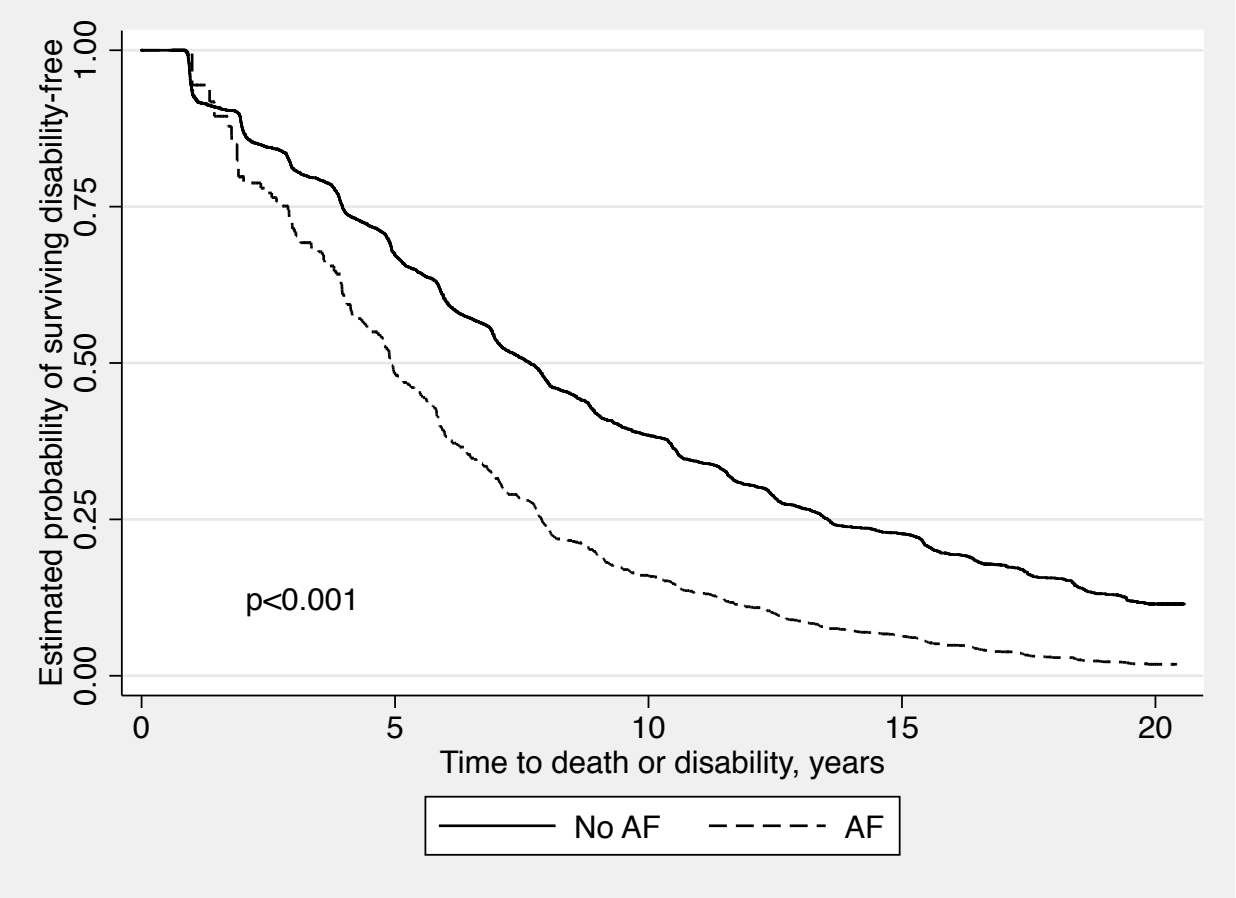


Table 1.3. Incident AF and the risk of ADL disability or death, by selected characteristics

Outcome and characteristic	Hazard Ratio (95% Confidence Interval)[a]	p for interaction
ADL disability or death		
Sex		
Men	1.73 (1.50, 1.99)	0.87
Women	1.70 (1.48, 1.96)	
Race		
White	1.76 (1.59, 1.96)	0.11
Non-white	1.34 (0.97, 1.84)	
ADL disability		
Sex		
Men	1.45 (1.18, 1.78)	0.42
Women	1.30 (1.07, 1.57)	
Race		
White	1.43 (1.24, 1.66)	0.04
Non-white	0.79 (0.46, 1.36)	

[a] Adjusted for age, sex, race, clinic, education, BMI, FEV1, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

SUPPLEMENTAL MATERIALS

Supplemental Table 1.1. Incident AF and the risk of incident ADL disability or death; selected sensitivity analyses and secondary analyses

Analysis and outcome	Hazard Ratio (95% Confidence Interval)[a]
Including non-FFS subjects[ab]	
ADL disability or death	1.84 (1.68, 2.01)
ADL disability	1.40 (1.24, 1.58)
With IPW[c]	
ADL disability or death	1.81 (1.55, 2.10)
ADL disability	1.40 (1.15, 1.71)
Additional adjustment for chronic kidney disease[d]	
ADL disability or death	1.72 (1.55, 1.90)
ADL disability	1.37 (1.18, 1.58)

[a] Adjusted for age, sex, race, clinic, education, BMI, FEV1, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)
[b] N=4259
[c] N=4046
[d] N=3882

Chapter 2. Incident AF and the risk of fracture

INTRODUCTION

More than 1.5 million osteoporotic fractures occur annually in the U.S. and are significant contributors to morbidity and mortality in the elderly.[41-44] As the number of U.S. adults aged 65 years and older is expected to double over the next 25 years, there is a need to identify modifiable risk factors that influence fracture risk in older adults.

Atrial fibrillation (AF) is one potential risk factor for fractures. Stroke and heart failure, two conditions strongly associated with AF, have been associated with a higher risk of hip and other osteoporotic fractures.[45, 46] Aside from hemiplegia-related falls in stroke patients, the precise mechanisms for the associations of stroke and heart failure with fractures remain poorly understood but may reflect shared risk factors like diabetes or physical inactivity, or common pathophysiologic factors such as inflammation or oxidative stress.[47] Symptoms and complications present in these conditions as well as AF such as weakness, dizziness, and decreased cerebral and cardiac perfusion may also increase the likelihood of falls.[5, 6] AF may contribute to cerebral white matter lesions[31, 32], which in turn are associated with abnormalities in gait and balance[27, 28] and a higher risk of falls.[30] In addition, experimental studies in animals have observed that warfarin, an anticoagulant used to prevent stroke in AF, is associated with reduced bone mineral density.[48] Warfarin use has been associated with a higher risk of fracture in some[49, 50], but not all[51, 52], epidemiologic studies.

Whether AF is associated with fracture risk is unknown. No studies to date have examined whether individuals with AF are at higher risk of fractures than those without AF. The goal of this study was to examine the associations of incident AF with the risk of hip and other fractures using data from the Cardiovascular Health Study.

METHODS

The Cardiovascular Health Study (CHS) is a population-based longitudinal cohort study of risk factors for coronary heart disease and stroke in individuals 65 years of age and older. Details about CHS have been published elsewhere.[13] Briefly, participants (N=5,888) were recruited from a random sample of Medicare beneficiary lists between 1989-1993 from four communities across the U.S. (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania). The original CHS cohort (N=5201) was enrolled in 1989-1990 and a cohort of 687 additional participants, predominantly African Americans, was enrolled in 1992-1993. Individuals underwent annual clinic exams for the first ten years of the study that included standardized questionnaires, laboratory tests, and electrocardiograms (ECGs). Individuals were contacted via telephone every six months to ascertain changes in health status, hospitalizations, and medication use. Passive surveillance for AF and fracture events were also conducted through a linkage to Medicare claims data, which captured claims to Medicare for inpatient and outpatient visits as well as physician claims for services covered under Medicare Part B, for subjects enrolled in fee-for-service Medicare (FFS). The institutional review boards for each community site approved the study, and all participants provided informed, written consent.

This analysis includes CHS subjects enrolled in FFS during cohort follow-up. FFS data became available from 1991 onward. Because FFS information was not available until after CHS study baseline, the baseline for individuals in this analysis was at the time of entry into FFS. Follow-up for this analysis extends through June 30, 2009. Individuals with prevalent AF or a history of stroke or heart failure at baseline were excluded from the analysis.

Exposure

The primary exposure was incident AF (defined as either atrial fibrillation or atrial flutter), ascertained from three sources: (1) ECGs from annual study examinations which indicate AF, (2) hospital discharge diagnoses indicating AF (from CHS or Medicare data), and (3) diagnoses of AF from outpatient or physician visits (from Medicare data). Study ECGs were read and interpreted by the CHS Electrocardiography Reading Center using standard methods.[14] For AF identified using hospital discharge or Medicare data, a diagnosis of AF was based on a single inpatient claim or hospital discharge diagnosis or 2 outpatient or physician claims within 365 days (ICD-9-CM code 427.31 or 427.32). The date of AF diagnosis was based on the earlier of: (1) the date of ECG indicating AF, (2) the admission date of the qualifying inpatient claim or hospital discharge diagnosis, or (3) the service date of the second qualifying outpatient or physician claim. In previous validation work within CHS, the use of hospital discharge codes to identify AF had a PPV of 98% and sensitivity of 71%.[16] Once an AF diagnosis was made, participants were classified thereafter as having AF.

Outcomes

Fracture of the hip, distal forearm, humerus, and pelvis were ascertained using hospital discharge diagnoses, outpatient visits, and physician claims. These types of fractures are considered classic osteoporotic fractures because they are associated with older age, low bone mineral density, and falls.[53-55] To minimize misclassification from rule-out diagnoses, diagnosis claims of fractures were required to have concomitant procedure codes consistent with treatment of a fracture, as defined by previously validated algorithms (Supplemental Table 1).[56, 57] The sensitivity and positive predictive value of these algorithms range from 93-98% and 89%-97%, respectively.[56, 58]

Covariates

Participant age, year of birth, sex, race (white, non-white), education beyond twelfth grade (yes/no), clinic (Wake Forest, Davis, Hopkins, Pittsburgh), physical activity (kcal/week), alcohol use (mean number of drinks per week) and smoking history (never, former, current) were self-reported at CHS study baseline. Body mass index (kg/m^2) was measured at CHS study baseline. Use of anti-hypertensive medications (yes/no), warfarin (yes/no), diabetes (yes/no, either prevalent or newly recognized), and hypertension (yes/no) were assessed and updated at each clinic visit. Antihypertensive medication use and use of oral anticoagulants or bisphosphonates were assessed using the method of medication inventory.[19] Diabetes was defined as use of insulin or oral hypoglycemic drugs, or fasting serum glucose $\geq$ 126 mg/dL or, non-fasting serum glucose $\geq$ 200 mg/dL. Hypertension was defined as use of antihypertensive medications plus self-reported history of hypertension, or systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg. Baseline and incident coronary heart disease, incident stroke, and incident heart failure were identified by the semi-annual contacts (telephone or clinic visit) or through linkage with Medicare hospitalization data, and were confirmed by physician adjudication using medical and hospital records or study ECGs.[20, 21] Falls were self-reported at yearly clinic visits or at the time of the telephone interview, with individuals indicating whether they had experienced a fall during the past six months or during the last year.

Statistical Analysis

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between incident AF, modeled as a time-varying exposure, and the risk of any fracture at the selected sites (hip, distal forearm, humerus, and pelvis) and the risk of hip fracture alone. In secondary analyses the association between incident AF and the risk of each fracture type was estimated separately. All estimates were adjusted for age, sex, race, clinic, education, BMI, smoking, alcohol use, physical activity, and time-varying

hypertension, anti-hypertensive drug use, coronary heart disease, and diabetes. Secondary analyses were also conducted to assess whether the association between incident AF and the risk of fracture differed by sex, race, or use of oral anticoagulants or bisphosphonates (both assessed as time-varying covariates). Wald tests were used to assess evidence of any differences in the associations between incident AF and the risk of fracture for each characteristic using a significance level of 0.05.

In the course of this work we discovered that in 21 subjects, AF and fracture were diagnosed on the same date. All cases arose from hospitalizations for either a hip or pelvic fracture where the discharge diagnoses included codes for fracture and AF. The medical records of these subjects were reviewed for evidence of a prior history of AF, or evidence that AF may have developed during the course of the hospital stay. Of the 21 cases, 3 had a prior history of AF documented in the medical records, while 18 had no prior history. In 10 cases, the AF was diagnosed during the course of the hospitalization (usually post-operatively). In three cases, AF was detected at admission in the emergency room, and for 5 we could not determine when AF occurred. Therefore, we decided to treat the 3 subjects with a documented history of AF as having AF prior to fracture, and the remaining 18 as not having AF prior to fracture.

Because one of the mechanisms through which AF may influence the risk of fracture is through a fall, a secondary analysis was conducted to examine whether AF was associated with a higher risk of falling. Data on self-reported falls were only available for the first ten years of the study. For this secondary analysis, follow-up extended through 1999, corresponding to the end of clinic visits. Because falls were self-reported over the entire past year, we could not be certain when a fall occurred. Therefore, we assigned the date of the first reported fall as the midpoint between clinic visits. We used Cox proportional hazards models to estimate the

association between incident AF and the risk of a subsequent fall and adjusted for all covariates included in the primary analysis of incident AF and fracture risk.

To examine the potential bias from excluding individuals not in FFS we conducted a sensitivity analysis, repeating our primary analyses but including individuals not enrolled in FFS and ignoring entry and exit from FFS. All statistical analyses were conducted using STATA version 13.0 (Stata Corp, College Station, Texas).

RESULTS

Of the initial 5,888 individuals in CHS, 4462 were included in the final analysis. Over a mean follow-up of 8.8 years, 1007 (23%) of individuals developed AF and 717 sustained a fracture, 421 at the hip. Of individuals diagnosed with AF during follow-up, 9% were initially identified by study ECG, 66% from an inpatient claim or hospitalization, and 25% from an outpatient or physician claim. Incident AF was more common in men and individuals who developed incident AF were more likely to have hypertension, diabetes, and coronary heart disease at baseline (Table 2.1).

The crude incidence rate of fracture was 22.9 per 1,000 person-years in individuals with AF and 17.7 per 1,000 person-years in individuals without AF. Individuals with incident AF were not shown to be at higher risk of fracture (adjusted HR=0.97, 95% CI 0.77, 1.21) or hip fracture (adjusted HR=1.09, 95% CI 0.84, 1.43) compared with those without AF (Table 2.2). When studying the risk of each fracture type individually, individuals with incident AF were at slightly higher risk of sustaining fractures of the hip, humerus, and pelvis, and at slightly lower risk of distal forearm fracture, although none of the risk estimates reached the level of statistical significance (Supplemental Table 2.2). Estimates including subjects not enrolled in FFS

Medicare and ignoring entry to and exit from FFS yielded similar estimates (Supplemental Table 2.3).

There was evidence that the association between incident AF and the risk of hip fracture may differ by oral anticoagulant use. Among individuals who used oral anticoagulants, those with AF were at nearly three-fold higher risk of hip fracture (adjusted HR=2.94, 95% CI 1.01, 8.54; p for interaction=0.05) compared with those without AF, and were at elevated risk of any fracture, although tests for effect modification were not statistically significant (Table 2.3). Among individuals using bisphosphonates, those with incident AF were also at higher risk of hip or any fracture, but the associations did not reach statistical significance. There was no evidence that the relationship between incident AF and fracture risk differed by sex or race (p>0.05 for all).

The secondary analysis of incident AF and the risk of a subsequent fall included 4402 individuals with data on falls. Over a mean follow-up of 6.3 years, 2112 individuals (48%) experienced at least one fall. Individuals with incident AF were not shown to be at higher risk of sustaining a fall than those without incident AF (adjusted HR=1.06, 95% CI 0.92, 1.21).

DISCUSSION

This is the first study to examine the association of incident AF with the risk of fracture. The main results of this study suggest that individuals with incident AF are not at higher risk of sustaining a fracture than individuals without AF.

We observed that individuals who developed incident AF and used oral anticoagulants were at higher risk of sustaining a hip fracture. Warfarin and other oral anticoagulants influence the formation and function of the matrix protein gamma-carboxyglutamate (Gla), which in turn inhibits the carboxylation of osteocalcin, an important factor in bone metabolism and the

maintenance of bone mineral density.[59] We also observed that individuals with incident AF who used bisphosphonates may also be at higher risk of hip or other fractures, although the associations did not rise to the level of statistical significance. Taken together, these findings suggest that incident AF may be a risk factor for fractures in individuals who are already at an increased risk of fracture, but additional studies are needed to determine whether these subgroup analyses can be replicated in other populations.

One of the primary mechanisms through which we hypothesized that AF would influence the risk of fracture was through an increased risk of falling. We did not observe an association between incident AF and the risk of falls. However, we had insufficient information to determine the exact date of a fall, only that it occurred at some time over the course of one year. This imprecision in estimating the timing of a fall may have obscured any relationship between incident AF and the risk of falls. Additional studies in other populations are needed to investigate this relationship.

All of the fractures studied in this analysis are associated with low bone mineral density and falling, but there are likely other, potentially differing, risk factors for each type of fracture. Prior studies have observed that the risk of hip, pelvic, and humerus fractures increase with advancing age, but distal forearm fractures do not.[60, 61] Other studies have found that individuals with markers of sickness and frailty such as poor mobility or multiple comorbidities are at high risk of hip fracture, whereas distal forearm fractures are more common in individuals with low BMD but who are otherwise healthy.[62-65] Distal forearm fractures were the second most common fracture site, behind hip fractures, and the differing risk factors for each fracture type may have partially obscured any association between incident AF and any fracture. In secondary analyses, we observed that incident AF was associated with a slightly lower risk of distal

forearm fracture and a slightly higher risk of fractures of the hip, pelvis, and humerus, but none of the associations rose to the level of statistical significance.

There were limitations to this study. AF can occur transiently and in the absence of symptoms. Episodes of AF that did not rise to clinical attention and were not detected on ECG during the annual exams through 1999 would have been missed and would have resulted in under-ascertainment of incident AF. Assuming that errors in measuring AF are non-differential, this may have attenuated any associations between incident AF and the risk of fracture. Second, administrative claims data were used to identify both incident AF and fracture. The use of administrative claims data has well-known limitations, including both random and potentially systematic errors in coding diagnoses and procedures.[58, 66] Third, individuals in managed care plans , which comprised approximately 13% of individuals in CHS, were excluded from the primary analysis. Problems with external generalizability may have resulted if individuals who enroll in and remain in FFS are different than those who enroll in managed care. We attempted to reduce the bias from coding inaccuracies in fracture ascertainment by utilizing previously validated algorithms. The use of two outpatient or physician claims was used to minimize the likelihood of rule-out diagnoses of AF.[15] Finally, we tested the generalizability of our findings by conducting sensitivity analyses including subjects not in FFS, which yielded similar estimates.

This study has several strengths. We used a population-based longitudinal cohort study with extensive information on potential confounders, including sociodemographic and clinical risk factors for both AF and fracture, and were able to adjust for a number of important confounders that varied over time. Multiple data sources were used to identify incident AF and fractures, including capturing clinically unrecognized AF and fractures diagnosed and treated outside of the hospital.

In summary, the results of this study suggest that incident AF is not a risk factor for hip or other fractures in community-dwelling older adults. Individuals with incident AF who are already at increased risk of fracture, such as individuals taking oral anticoagulants or bisphosphonates, may comprise a vulnerable subgroup at high fracture risk, but further studies are needed.

TABLES AND FIGURES

Table 2.1. Baseline characteristics of participants

Characteristic	All N=4462	No AF during follow-up N=3455	Incident AF during follow-up N=1007
Age, mean (SD)	74 (5)	73 (5)	74 (5)
Male, %	40.6	38.2	48.5
White, %	85.9	84.8	89.9
Education beyond 12th grade, %	43.8	43.0	46.3
Smoking, %			
Current	12.4	13.1	9.9
Former	41.0	40.2	43.6
Alcohol use, %	50.3	50.1	51.2
Mean number of drinks per week (SD)	5.2 (16.3)	5.3 (18.0)	5.2 (8.6)
Physical activity (kcal) per week, mean (SD)	1791 (2075)	1802 (2094)	1756 (2012)
Body mass index (kg/m^2), mean (SD)	26.6 (4.7)	26.6 (4.7)	26.8 (4.7)
Diabetes, %	14.6	14.1	16.2
Coronary heart disease, %	18.0	16.2	24.3
Hypertension, %	56.1	54.9	60.6
Antihypertensive medication use, %	45.2	43.4	51.2

Table 2.2. Incident AF and the risk of fracture

Outcome	Minimally adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]
Any fracture	1.01 (0.81, 1.26)	0.97 (0.77, 1.21)
Hip fracture	1.15 (0.88, 1.49)	1.09 (0.83, 1.42)

[a] Referent category is No AF. Adjusted for age, sex, race and clinic

[b] Adjusted for age, sex, race, clinic, education, BMI, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

Table 2.3. Incident AF and the risk of fracture, by fracture type and selected characteristics

Outcome and characteristic	Hazard ratio (95% CI)[a]	p for interaction
Any fracture		
Sex		
Men	0.79 (0.51, 1.21)	0.27
Women	1.04 (0.81, 1.34)	
Race		
White	0.96 (0.77, 1.21)	0.95
Non-white	1.00 (0.39, 2.53)	
Oral anticoagulant use		
Yes	1.79 (0.85, 3.79)	0.09
No	0.90 (0.70, 1.17)	
Bisphosphonate use		
Yes	1.44 (0.83, 2.51)	0.13
No	0.90 (0.71, 1.15)	
Hip fracture		
Sex		
Men	0.86 (0.52, 1.42)	0.27
Women	1.19 (0.87, 1.62)	
Race		
White	1.08 (0.82, 1.42)	0.79
Non-white	1.28 (0.38, 4.34)	
Oral anticoagulant use		
Yes	2.94 (1.01, 8.54)	0.05
No	0.98 (0.72, 1.34)	
Bisphosphonate use		
Yes	1.73 (0.90, 3.31)	0.13
No	1.00 (0.75, 1.35)	

[a] Adjusted for age, sex, race, clinic, education, BMI, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

SUPPLEMENTAL MATERIALS

Supplemental Table 2.1. Algorithms used to identify fractures.[a]

Fracture type	ICD-9 diagnosis code	CPT procedure codes
Hip	820.0-820.9	27125-27127, 27130-27131, 27230-27248, 29010-29046, 29305-29365, 29505-29520, 29799,
Distal forearm	813.4-813.5	24580-24588, 25600-25620, 29065-29085, 29105, 29125-29126, 29799
Humerus	812.0-812.5	23600-23630, 23665-23680, 24500-24588, 29035-29065, 29105, 29799
Pelvis	808.0-808.9	27120, 27122, 27130, 27131-27132, 27190-27192, 27200, 27202 27210-27214, 27220-27225

[a] Based on Ray et al[56] and Baron et al[57]

Requirements (all):
Inpatient claims: ICD-9 diagnosis code
Outpatient or physician claims: ICD-9 diagnosis code AND procedure code consistent with fracture treatment
Exclusion codes (all): Concomitant codes consistent with care of old fractures or other bone diseases, such as late effects of fracture (ICD-9 905.4), implant complication (ICD-9 996.4, 996.6, 996.7, E878.1), aseptic necrosis (ICD-9 733.4), malunion of bone (ICD-9 733.8), other disorders of bone or cartilage (ICD-9 733.9), and fracture follow-up care (V540, V664, V674).

Supplemental Table 2.2. Incident AF and the risk of fracture, by fracture site

Outcome	Number of events[a]	Minimally adjusted HR (95% CI)[b]	Fully adjusted HR (95% CI)[c]
Any fracture	717	1.01 (0.81, 1.26)	0.97 (0.77, 1.21)
Hip	421	1.15 (0.88, 1.49)	1.09 (0.83, 1.42)
Distal forearm	209	0.91 (0.58, 1.42)	0.91 (0.58, 1.43)
Humerus	166	1.09 (0.70, 1.69)	1.10 (0.70, 1.71)
Pelvis	86	1.18 (0.67, 2.09)	1.11 (0.62, 1.99)

[a] Events not mutually exclusive; individuals could have sustained fractures at multiple sites

[b] Referent category is No AF. Adjusted for age, sex, race and clinic

[c] Adjusted for age, sex, race, clinic, education, BMI, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

Supplemental Table 2.3. Incident AF and the risk of fracture, including subjects not enrolled in FFS

Outcome	Minimally adjusted HR (95% CI)[a]	Fully adjusted HR (95% CI)[b]
Any fracture	1.05 (0.87, 1.27)	1.02 (0.84, 1.23)
Hip fracture	1.08 (0.86, 1.36)	1.04 (0.83, 1.32)

[a] Referent category is No AF. Adjusted for age, sex, race and clinic

[b] Adjusted for age, sex, race, clinic, education, BMI, smoking, alcohol use, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

Chapter 3. Incident AF and changes in gait speed and grip strength

INTRODUCTION

Physical functioning is a key component of health and well being of older adults. Objective measures of physical function such as gait speed and handgrip strength are useful indicators of health in the elderly because they are simple to perform, relatively easy to interpret, and predict multiple adverse outcomes.[67] Slow gait and decline in gait speed, for example are associated with a higher risk of falls, disability, hospitalization and death.[18, 67, 68] Decline in muscle strength can reflect underlying changes in body composition and predicts future mobility impairment, disability and death.[69, 70]

Atrial fibrillation (AF) may be a risk factor for declining physical function in older adults. AF is the most common cardiac arrhythmia and is prevalent in the elderly, affecting more than 10% of U.S. adults over the age of 80.[4] Sequelae of AF include decreased cardiac and cerebral perfusion, reduced exercise tolerance, weakness, dizziness, and a rapid or irregular heart rate.[5, 6] These in turn may promote a sedentary lifestyle, leading to declines in markers of physical function such as grip strength and gait speed. Stroke and heart failure, conditions with known effects on physical function,[71, 72] are also strongly associated with AF.[7, 73]

Although the clinical outcomes associated with AF (e.g. stroke) are well known, important gaps remain in our understanding of the functional consequences of AF. No studies to date have compared how long-term physical function differs between individuals with and without AF. The goal of this study was to assess the associations of incident atrial fibrillation with the trajectory of changes in physical function, as measured by gait speed and grip strength. We hypothesized that after adjustment for baseline socio-demographic and health-related variables, individuals with AF will experience more rapid declines in gait speed and grip strength over time compared to those without AF.

METHODS

The Cardiovascular Health Study (CHS) is a population-based prospective cohort study of risk factors for coronary heart disease and stroke in individuals 65 years of age and older. Details about the design and recruitment in CHS have been published elsewhere.[13] Briefly, participants (N=5,888) were recruited from a random sample of Medicare beneficiary lists between 1989-1993 from four communities across the U.S. (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania). The original CHS cohort (N=5201) was enrolled in 1989-1990 and a cohort of 687 additional participants, almost all African Americans, was enrolled in 1992-1993. Individuals underwent annual exams for the first ten years of the study that included standardized questionnaires, laboratory tests, electrocardiograms (ECGs), and assessments of physical function. The institutional review boards for each community site approved the study, and all participants provided informed, written consent.

Medicare claims data, which we used to identify incident AF, became available from 1991 onward. Claims data were not available for individuals in managed-care plans. Therefore, this analysis is restricted to individuals enrolled in fee-for-service (FFS) Medicare. Because Medicare claims data were not available until after CHS study baseline, the baseline for individuals in this analysis was the first clinic visit after entry into FFS. For most individuals, this was approximately 1.5 years after entry into CHS. Follow-up for this analysis was through 1999, corresponding to the end of annual clinic exams. Individuals were censored if they left FFS prior to the end of follow-up. Individuals with prevalent AF or a history of stroke or heart failure prior to baseline were excluded from the analysis. Of the initial 5,888 individuals in CHS, 4372 were included in the final analytic cohort (Figure 3.1).

Exposure

The primary exposure was incident AF (defined as either atrial fibrillation or atrial flutter), ascertained from three sources: (1) ECGs from annual study examinations which indicate AF, (2) hospital discharge diagnoses indicating AF (from CHS outcomes ascertainment or Medicare data), and (3) diagnosis of AF from outpatient or physician visits (from Medicare data). The annual ECGs were read and confirmed by the CHS Electrocardiography Reading Center using standard methodology.[14, 16] In previous validation work among a sub-sample of CHS subjects, the use of hospital discharge codes to diagnose AF had a positive predictive value of 98% and a sensitivity of 71%.[16] For AF identified using hospital discharge or Medicare data, a diagnosis of AF was based on a single inpatient claim or hospital discharge diagnosis or 2 outpatient or physician claims within 365 days (ICD-9-CM code 427.31 or 427.32). The date of AF diagnosis was based on the earlier of: (1) the date of ECG indicating AF, (2) the admission date of the qualifying inpatient claim or hospital discharge diagnosis, or (3) the service date of the second qualifying outpatient or physician claim. The use of two outpatient or physician claims is used to minimize misclassification of AF, since an initial diagnosis of AF in an outpatient setting may be recorded when the intention is to rule out AF rather than to diagnose AF.[15] Once an AF diagnosis was made, participants were classified thereafter as having AF.

Outcomes

Two measures of physical function were analyzed longitudinally: (1) gait speed (time to walk 15 feet, converted to meters per second) and (2) grip strength (in kilograms). Each was measured at the annual in-person CHS clinic visit. Gait speed was measured as the time needed to walk a 15-foot course (4.57 meters) at usual pace beginning from a still-standing position.[18] The time was recorded using a stopwatch (to 0.1 seconds). The average time in meters/second of two timed walks was used. Grip strength was measured in kilograms using an adjustable hydraulic dynamometer (Jamar Hand Dynamometer, Fred Sammons, Inc., Burr Ridge, IL).[70] Individuals

made three attempts using the dominant hand and the maximum of these attempts was considered their grip strength at that time.

Covariates

Participant age, year of birth, sex, race (white, non-white), education beyond twelfth grade (yes/no), clinic (Wake Forest, Davis, Hopkins, Pittsburgh), physical activity (kcal/week) and smoking history (never, former, current) were self-reported at CHS study baseline. Body mass index (kg/m^2) and height (cm) were measured at CHS study baseline. Use of anti-hypertensive medications (yes/no), diabetes (yes/no, either prevalent or newly recognized), and hypertension (yes/no) were assessed and updated at each clinic visit. Medication use was assessed using the method of medication inventory.[19] Diabetes was defined as use of insulin or oral hypoglycemic drugs, or fasting serum glucose $\geq$ 126 mg/dL or, non-fasting serum glucose $\geq$ 200 mg/dL. Hypertension was defined as use of antihypertensive medications plus self-report of a physician diagnosis of hypertension, or systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg. Baseline and incident coronary heart disease, incident stroke, and incident congestive heart failure (CHF) were identified by the semi-annual contacts (telephone or clinic visit) or through linkage with Medicare hospitalization data, and were confirmed by physician adjudication using medical and hospital records or study ECGs.[20, 21] The $CHADS_2$ score (an acronym for Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke), a risk score that estimates stroke risk in individuals with AF, was calculated based on the presence of heart failure (1 point), hypertension (1 point), age ($\geq$75 years, 1 point), diabetes (1 point), or a history of stroke (2 points).[74] It is recommended that individuals with $CHADS_2$ scores of 2 or greater receive antithrombotic therapy with warfarin as they are considered at high risk of stroke.[75] Individuals with scores of less than 2 points are considered at low to moderate risk of stroke. For the purposes of this analysis, $CHADS_2$ score was

dichotomized (<2 points, ≥ 2 points) as the trajectories of physical function may differ by an individual's underlying stroke risk.

Statistical Analysis

Linear mixed effects models were used to examine the association between incidence of AF and changes in each physical function measure across age, taking into account the dependency of repeated observations of physical functioning within each subject.[76] One-year change in each measure and 5-year trajectories were estimated across different ages along with their 95% confidence intervals (95% CI). Censoring events included death, disenrollment in FFS Medicare, or loss to follow-up.

The models included both linear and quadratic terms for age. Each model included random effects for the intercept and the linear age term, with an unstructured covariance matrix. Estimates of the rate of change in grip strength and gait speed were adjusted for the following covariates: year of birth, sex, race, clinic, education, height, body mass index, smoking, baseline self-reported physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensive medications (time-varying).Secondary analyses were conducted to examine whether the association between incident AF and changes in each physical function measure differed by sex, race, and incident stroke or incident heart failure. Amongst individuals with incident AF, we also examined whether the rates of decline differed by $CHADS_2$ score (less than 2 points vs. greater than 2 points). Wald tests were used to assess differences in the rate of change in each measure, with a significance level of 0.05.

Several sensitivity analyses were performed. To examine bias from excluding individuals not in FFS or clinic visits conducted outside of Medicare data availability we repeated our analyses

including individuals not enrolled in FFS and ignoring entry and exit from FFS. To examine bias due to individuals dropping out of the study, analyses were repeated using Inverse Probability Weighting Methods (IPW)[22], which weight observations based on the inverse probability of remaining in the study, giving more weight to observations that are likely to be missing, but are in fact observed. The probability of having missing data was estimated as a function of the following factors at each subject's baseline: age, gait speed (or baseline grip strength for analyses of grip strength), sex, education, smoking, BMI, diabetes, self-reported health, height, hypertension, use of anti-hypertensive medications and physical activity levels as well as any AF during follow-up, and any stroke or heart failure during follow-up. Statistical analyses were conducted using STATA version 13.0 (Stata Corp, College Station, Texas).

RESULTS

Over a mean follow-up of 6 years, 568 (13%) of individuals developed AF. Of individuals diagnosed with AF during follow-up, 17% were initially identified by study ECG, 59% from an inpatient claim or hospitalization, and 24% from an outpatient or physician claim. Individuals who developed incident AF were more likely to be male, white, and to be slightly older with a higher burden of coronary heart disease and hypertension at baseline (Table 3.1). Individuals who developed incident AF had slightly slower gait and slightly greater grip strength at baseline than those who did not develop AF. An average of 5.4 measures of gait speed (5.4 in individuals without incident AF and 5.6 in individuals with incident AF) and 5.0 measures of grip strength (5.0 in individuals without incident AF and 5.1 in individuals with incident AF) were available for each individual. An average of 3.1 measures of gait speed and 3.0 measures of grip strength were available in individuals after diagnosis of incident AF.

Incident AF was not associated with changes in gait speed (estimated one-year change in individuals without AF = -0.011 m/s, 95% CI -0.012, -0.001; with incident AF = -0.013 m/s, 95%

CI -0.018, -0.008; difference = -0.002 m/s, 95% CI -0.006, 0.003) or grip strength (estimated one-year change in individuals without AF = -0.47 kg, 95% CI -0.51, -0.44; with incident AF = -0.48 kg, 95% CI -0.60, -0.37; difference = -0.01 kg, 95% CI -0.13, 0.10) (Tables 3.2 and 3.3 and Figures 3.2 and 3.3).

There was evidence that gait speed declines were accelerated in individuals who developed AF and experienced a stroke during follow-up compared with individuals without either condition or only one (p=0.03) (Table 3.5). However, the number of individuals who developed both AF and experienced a stroke during follow-up was small (N=55). Decline in physical function also differed by $CHADS_2$ score. Individuals with incident AF and $CHADS_2$ scores of 2 or higher experienced a more rapid rate of decline in grip strength than those with incident AF and scores of 2 or less or individuals without incident AF, regardless of their $CHADS_2$ score (p=0.04) (Table 3.5). Similarly, gait speed declines were accelerated in individuals with incident AF and $CHADS_2$ scores of 2 or higher compared to those without AF or with AF but with scores of less than 2, but the difference did not reach statistical significance (p=0.13). There was no evidence of differences by sex, race, or incident heart failure for either gait speed or grip strength.

In two sets of sensitivity analyses, 1) using inverse probability weights and 2) including individuals not enrolled in FFS and ignoring entry or exit from FFS, the trajectories of physical function did not significantly differ between individuals with and without incident AF (Supplemental Table 3.1 and Supplemental Figure 3.1).

DISCUSSION

In this population-based cohort study of older adults we observed that individuals with incident AF experienced rates of decline in gait speed and grip strength similar to those of individuals

without AF. To the best of our knowledge this is the first study to examine the association between incident AF and longitudinal changes in gait speed and grip strength.

We observed that the decline in grip strength was accelerated in individuals with incident AF and $CHADS_2$ scores of two points or greater compared to those without incident AF or those with scores of less than two points. Previous studies have found associations between components of the $CHADS_2$ score and physical function, including heart failure[77, 78], hypertension[79], advanced age[80], diabetes[81], and stroke.[82] Therefore, it is not surprising that individuals with these other risk factors would be at higher risk to experience accelerated declines. However, individuals with incident AF and a $CHADS^2$ score of two points or higher experienced the fastest rates of decline, even compared to their counterparts without AF. We also found that individuals who developed AF and suffered a subsequent stroke experienced a faster rate of decline in gait speed than individuals with incident AF or stroke alone. These findings should be taken with caution however, as the number of individuals with both stroke and AF in this study was small and our subgroup analyses were secondary, so significant results could be due to chance. If confirmed in other studies, this could highlight an especially vulnerable population, who may benefit from more intensive rehabilitation efforts and support.

Although incident AF by itself was not associated with the rate of decline in gait speed and grip strength in this study, plausible mechanisms exist through which AF may influence muscle strength and walking speed. AF is linked to impaired hemodynamics and symptoms such as dyspnea, chest pain, and palpitations, which may discourage physical activity and are associated with exercise intolerance in patients with AF.[37, 83] These factors may work to accelerate the loss of muscle mass and strength that occur as part of aging.[84] While gait speed is also linked to changes in skeletal muscle function[85], abnormalities in gait or slow gait are correlated with cognitive function and are believed to reflect underlying neurodegeneration.[18, 84,

[86-88] AF may contribute to structural changes in the brain via decreased cardiac output leading to cerebral hypoperfusion and ischemia.[6] Alternatively, pooling of blood in the fibrillating left atrium promotes the formation of thrombi, which may travel to the brain, resulting in overt stroke or covert infarction.[89]

There were several limitations to this study. AF can be transient and individuals who experience episodes that are more frequent or of longer duration may be at greater risk of accelerated decline in physical function than those with fewer and shorter episodes. Unfortunately, we were not able to differentiate between different types of AF such as paroxysmal, persistent, and permanent on the basis of the diagnosis codes. In addition, AF can be asymptomatic, and episodes of AF that did not rise to clinical attention and were not present during the clinic ECG would be missed, resulting in misclassification of AF status. Missing data are inherent in studies of aging adults, including this one.[40] Individuals who are sicker are generally more likely to have missing data or become lost to follow-up, and they in turn may have a higher risk of AF and lower physical function than healthier individuals. However, the average number of measures of physical function was similar between individuals with and without AF in our study, and individuals had on average three measures of function after incident AF. We attempted to correct for the potential bias from missing data by repeating our analyses using inverse probability weights. Aside from the potential for non-random missing data due to drop-out, some clinic visits (for example, CHS study baseline visit) were excluded from the primary analysis because administrative claims data used to ascertain AF were not yet available. As a result, individuals had on average 1.5 fewer clinic visits available for the analysis than they actually attended, and individuals not enrolled in fee-for-service Medicare were excluded from the primary analysis. We assessed the robustness of our findings by repeating our analyses including individuals not enrolled in fee-for-service Medicare and ignoring enrollment periods for

FFS. In all sensitivity analyses, we did not find that the trajectories of gait speed and grip strength over time differed significantly between individuals with and without incident AF.

There were a number of strengths to this study. The Cardiovascular Health Study is a population-based longitudinal cohort with rich data on potential confounders, including socio-demographic, lifestyle, and clinical factors that influence both the risk of AF and physical function. We had five measures of physical function on average for each individual over more than six years of follow-up, including several years of follow-up in individuals after they developed AF. The size of the population studied and the number of measures per subject provided sufficient powered to detect differences in gait speed and grip strength below those that we observed in this analysis. Finally, we were able to leverage multiple sources to capture incident AF, including AF detected on study clinic ECG as well as AF diagnosed outside of the hospital, decreasing the likelihood of misclassification of AF status.

In summary, incident AF was not associated with changes in gait speed or grip strength in this longitudinal cohort study of older adults. The co-occurrence of AF and other risk factors such as stroke or a high $CHADS_2$ score appeared, however, to act synergistically to hasten declines in gait speed or grip strength in older adults. Additional research is needed to understand the functional consequences of AF in the elderly.

FIGURES AND TABLES

Figure 3.1.
Selection of the analytic cohort

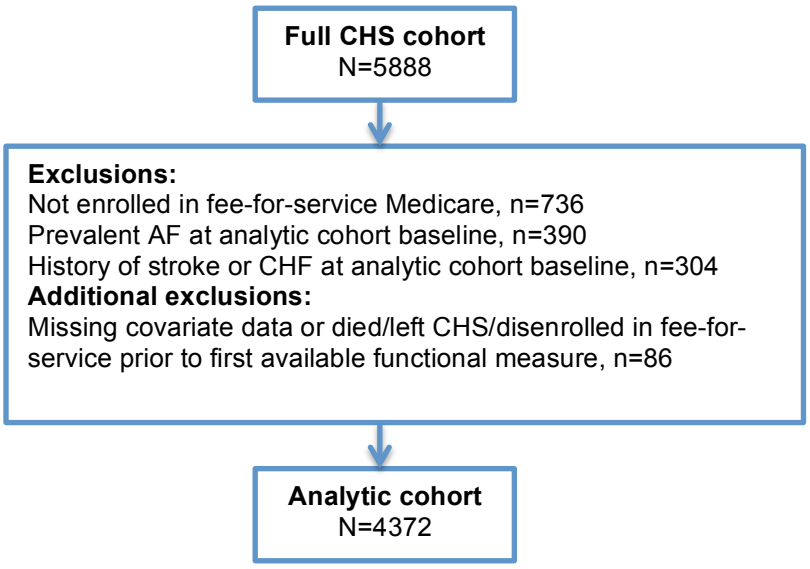


Table 3.1. Baseline characteristics of participants

Characteristic	All N=4372	No AF during follow-up N=3804	Incident AF during follow-up N=568
Age, mean (SD)	74 (5)	74 (5)	75 (6)
Male, %	40.9	39.3	53.0
White, %	85.6	84.8	91.2
Education beyond 12th grade, %	44.1	43.8	46.5
Smoking, %			
Current	11.9	12	11.3
Former	41.6	41.4	42.6
Physical activity (kcal) per week, mean (SD)	1782 (2063)	1799 (2075)	1672 (1977)
Height (cm), mean (SD)	165 (9)	164 (9)	167 (10)
Body mass index (kg/m^2), mean (SD)	26.7 (5)	26.5 (5)	26.7 (5)
Diabetes, %	15.1	15.0	15.7
Coronary heart disease, %	19.2	17.7	29.4
Hypertension, %	54.9	54.2	59.3
Antihypertensive medication use, %	47.9	46.7	55.5
Baseline gait speed (m/s) (SD)	0.91 (0.25)	0.91 (0.25)	0.89 (0.25)
Baseline grip strength (kg) (SD)	28.8 (10.6)	28.7 (10.6)	29.1 (10.8)

Table 3.2 Estimated average 5-year change in gait speed (m/s) (95% CI)[a]

Age	No AF	Incident AF	Difference
65-70	-0.006 (-0.017, 0.005)	-0.030 (-0.072, 0.013)	-0.024 (-0.066, 0.018)
70-75	-0.042 (-0.048, -0.035)	-0.055 (-0.083, -0.027)	-0.013 (-0.041, 0.014)
75-80	-0.077 (-0.083, -0.071)	-0.080 (-0.095, -0.065)	-0.003 (-0.018, 0.011)
80-85	-0.112 (-0.121, -0.104)	-0.105 (-0.120, -0.091)	0.007 (-0.007, 0.021)
85-90	-0.148 (-0.161, -0.135)	-0.131 (-0.157, -0.104)	0.017 (-0.009, 0.043)
Average change per year	-0.011 (-0.012, -0.001)	-0.013 (-0.017, -0.008)	-0.002 (-0.006, 0.002)[b]

[a] Adjusted for birth year, sex, race, clinic, education, height, BMI, smoking, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

[2] p=0.41

Figure 3.2. Estimated trajectory of gait speed over time in individuals with and without incident AF

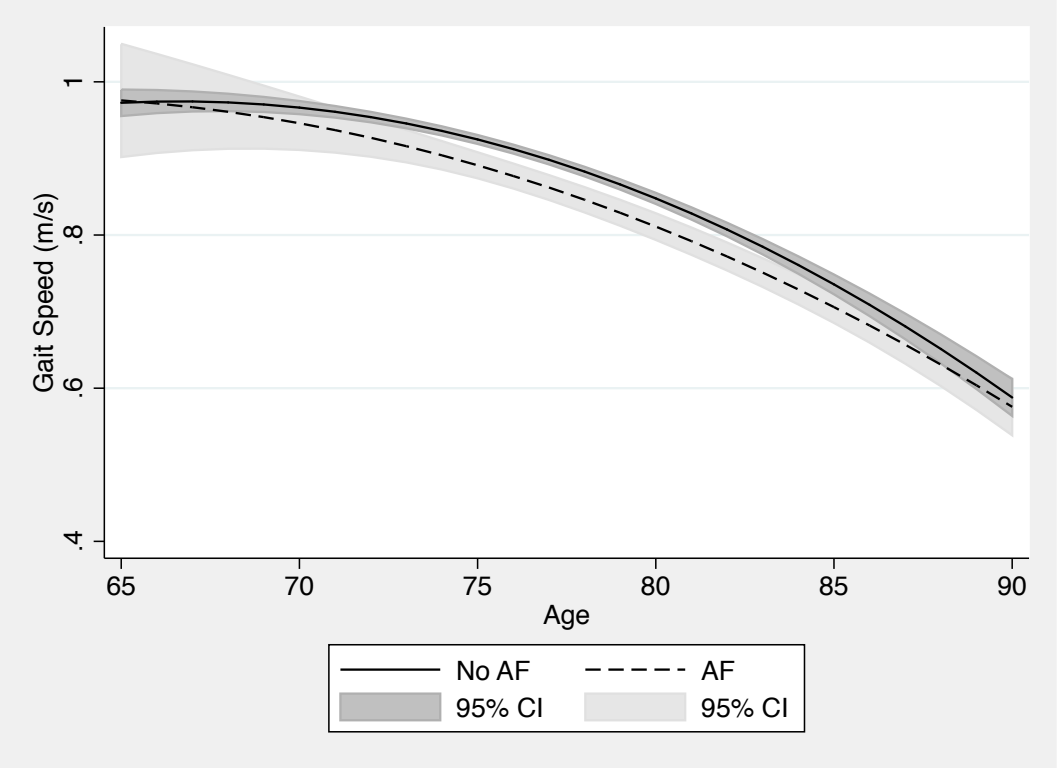


Table 3.3. Estimated average 5-year change in grip strength (kg) (95% CI)[a]

Age	No AF	Incident AF	Difference
65-70	-1.52 (-1.82, -1.23)	-1.76 (-2.81, -0.71)	-0.24 (-1.28, 0.80)
70-75	-2.13 (-2.32, -1.95)	-2.28 (-2.97, -1.60)	-0.15 (-0.82, 0.52)
75-80	-2.74 (-2.89, -2.59)	-2.81 (-3.18, -2.43)	-0.07 (-0.43, 0.30)
80-85	-3.35 (-3.57, -3.13)	-3.33 (-3.68, -2.98)	0.02 (-0.32, 0.36)
85-90	-3.64 (-4.30, -3.61)	-3.85 (-4.50, -3.20)	0.11 (-0.52, 0.74)
Average change per year	-0.47 (-0.51, -0.44)	-0.50 (-0.61, -0.39)	-0.024 (-0.13, 0.08)[b]

[a] Adjusted for birth year, sex, race, clinic, education, height, BMI, smoking, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

[b] p=0.97

Figure 3.3. Estimated trajectory of grip strength over time in individuals with and without incident AF

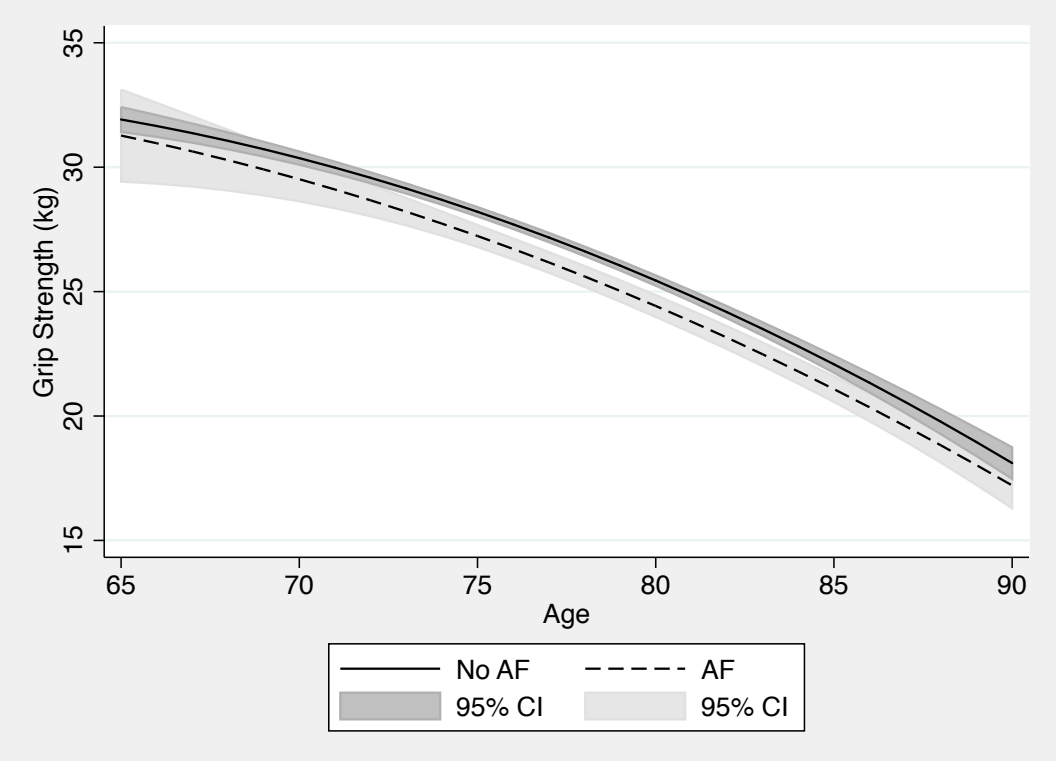


Table 3.4. Association between incident AF and one-year change in gait speed (m/s) by sex, race, incident stroke, and incident CHF (95% CI)[a]

Characteristic	No AF	AF	p for interaction
Sex			
Men	-0.010 (-0.012, -0.008)	-0.006 (-0.040, 0.028)	0.34
Women	0.012 (-0.013, -0.010)	-0.017 (-0.023, -0.010)	
Race			
White	0.011 (-0.012, -0.010)	-0.002 (-0.061, 0.058)	0.54
Non-white	-0.012 (-0.015, -0.009)	-0.020 (-0.032, -0.008)	
Incident stroke			
Yes	-0.014 (-0.024, -0.005)	-0.040 (-0.060, -0.019)	0.03
No	-0.011 (-0.012, -0.009)	-0.012 (-0.016, -0.007)	
Incident CHF			
Yes	-0.008 (-0.016, 0.001)	-0.014 (-0.025, -0.004)	0.44
No	-0.011 (-0.012, -0.010)	-0.012 (-0.017, -0.007)	
$CHADS_2$ score			
≥2 points	-0.012 (-0.015, -0.010)	-0.021 (-0.029, -0.012)	0.13
<2 points	-0.011 (-0.012, -0.009)	-0.010 (-0.015, -0.005)	

[a] Adjusted for birth year, sex, race, clinic, education, height, BMI, smoking, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

Table 3.5. Association between incident AF and one-year change in grip strength (kg) by sex, race, incident stroke, and incident CHF (95% CI)[a]

Characteristic	No AF	AF	p for interaction
Sex			
Men	-0.65 (-0.70, -0.61)	-1.97 (-2.81, -1.11)	0.27
Women	-0.37 (-0.40, -0.33)	-0.37 (-0.41, -0.33)	
Race			
White	-0.45 (-0.48, -0.42)	0.84 (-0.59, 2.27)	0.93
Non-white	-0.63 (-0.71, -0.56)	-0.68 (-0.97, -0.40)	
Incident stroke			
Yes	-0.63 (-0.87, -0.39)	-0.49 (-0.93, -0.05)	0.62
No	-0.46 (-0.50, -0.44)	-0.49 (-0.60, -0.38)	
Incident CHF			
Yes	-0.46 (-0.67, -0.24)	-0.48 (-0.73, -0.24)	0.92
No	-0.47 (-0.50, -0.44)	-0.47 (-0.59, -0.35)	
$CHADS_2$ score			
≥2 points	-0.55 (-0.61, -0.49)	-0.75 (-0.96, -0.54)	0.04
<2 points	-0.45 (-0.48, -0.41)	-0.42 (-0.54, -0.29)	

[a] Adjusted for birth year, sex, race, clinic, education, height, BMI, smoking, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

SUPPLEMENTAL MATERIALS

Supplemental Table 3.1. Estimated average one-year change in gait speed and grip strength (95% CI), with inverse probability weights (IPW) and including individuals not enrolled in fee-for-service Medicare

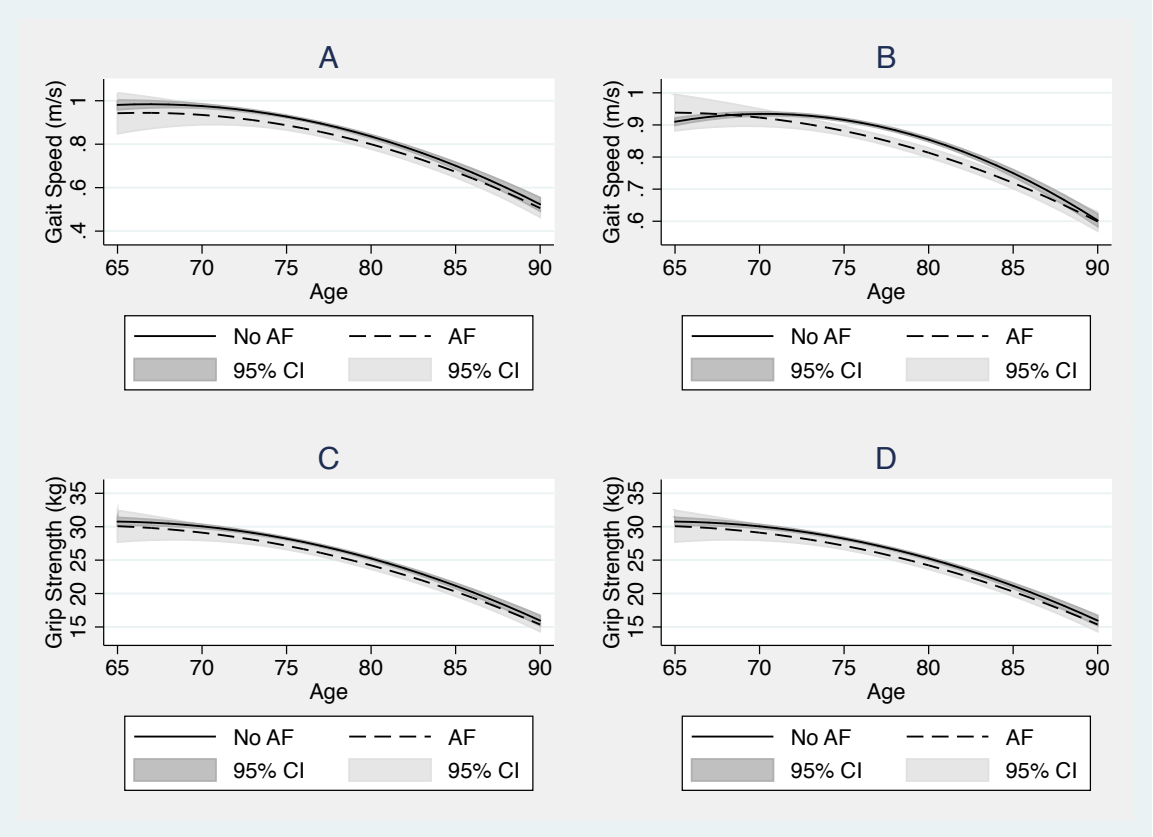
Outcome	No AF	Incident AF	Difference
Gait speed (m/s)			
With IPW[a]	-0.013 (-0.015, -0.012)	-0.012 (-0.018, -0.007)	0.001 (-0.005, 0.006)
With non-FFS subjects[b]	-0.007 (-0.008, -0.006)	-0.010 (-0.014, -0.007)	-0.003 (-0.007, 0.001)
Grip strength (kg)			
With IPW[a]	-0.45 -0.49, -0.42)	-0.47 (-0.60, -0.32)	0.012 (-0.15, 0.13)
With non-FFS subjects[b]	-0.38 (-0.40, -0.36)	-0.41 (-0.50, -0.32)	0.03 (-0.11, 0.06)

[a] N=4372

[b] N=5155; average of 7.0 measures of gait speed and 6.0 measures of grip strength per subject

All models adjusted for birth year, sex, race, clinic, education, height, BMI, smoking, physical activity, hypertension (time-varying), coronary heart disease (time-varying), diabetes (time-varying), and use of anti-hypertensives (time-varying)

Supplemental Figure 3.1. Estimated trajectories in gait speed and grip strength in individuals with and without AF, with IPW and including individuals not in FFS



Legend:
A: Trajectory in gait speed, with IPW
B: Trajectory in gait speed, with individuals not in FFS
C: Trajectory in grip strength, with IPW
D: Trajectory in grip strength, with individuals not in FFS

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