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Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the Atherosclerosis Risk in Communities Study

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Abstract

Objective—Type 2 diabetes has been inconsistently associated with risk of atrial fibrillation (AF) in previous studies that have frequently been beset by methodological challenges.

Design—Prospective cohort study.

Setting—The Atherosclerosis Risk in Communities Study.

Participants—Detailed medical histories were obtained on 13025 participants. Individuals were categorized as having no diabetes, pre-diabetes or diabetes based on the 2010 American Diabetes Association criteria at study baseline (1990–92).

Main Outcome Measures—Diagnoses of incident AF were obtained through 2007. Associations between type 2 diabetes and markers of glucose homeostasis with the incidence of AF were estimated using Cox proportional hazards models after adjusting for possible confounders.

Results—Type 2 diabetes was associated with a significant increase in risk of AF (HR 1.35, 95% confidence interval [CI]: 1.14–1.60) after adjustment for confounders. There was no indication that individuals with pre-diabetes or those with undiagnosed diabetes were at increased risk of AF compared to those without diabetes. We observed a positive linear association between HbA1c and risk of AF in those with and without diabetes: 1.13 (1.07–1.20) and 1.05 (0.96–1.15) per 1% point increase, respectively. There was no association between fasting glucose or insulin ($p>0.05$) in those without diabetes but a significant association with fasting glucose in those with the condition ($p=0.0002$). Results were similar in whites and African Americans.

Conclusions—Diabetes, HbA1c level and poor glycemic control are independently associated with increased risk of AF, but the underlying mechanisms governing the relationship are unknown and warrant further investigation.

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Keywords

Atrial fibrillation; risk factors; macrovascular disease

INTRODUCTION

Atrial fibrillation (AF) is one of the most frequently sustained cardiac arrhythmias seen in clinical practice.[1] Type-2 diabetes is a well-established risk factor for coronary heart disease (CHD) and stroke,[2] and has been reported by some [3–5] but not all,[6] observational studies to be associated with an increased risk of AF. The inconsistencies between study findings may in part be due to methodological challenges such as small sample size, limited adjustment for potential confounders, misclassification of exposure and using different methods of AF ascertainment. Further, the relationships between common clinical markers of glucose homeostasis with incident AF has not been widely studied.

The Atherosclerosis Risk in Communities study (ARIC) provides an excellent opportunity to prospectively examine the association between diabetes and markers of glucose homeostasis with incident AF in a population of whites and African-Americans [7] for whom there are no existing studies on this topic. The aims of this study were two-fold: first, to determine the risk of AF among individuals with diabetes compared with unaffected individuals; and second, to investigate the relationships between levels of fasting serum glucose (FSG), fasting insulin and HbA1c levels with incident AF in those individuals with, and without, diabetes.

METHODS

The ARIC Study is a community-based prospective cohort study of 15792 participants aged 45–64 years at baseline and recruited from four communities in the United States.[7] The first examination occurred 1987–89, with three follow-up visits taking place, each three years apart. Participants (or proxy) are contacted annually by telephone to ascertain information on hospitalizations and deaths. Active community-wide surveillance of local hospitals was performed to identify additional hospitalizations. Visit 2 (1990–92) was the only visit for which stored whole blood samples were available for the measurement of HbA1c; this was the baseline for the present study unless otherwise stated. There were 14348 participants who attended visit 2 of whom 1323 individuals were excluded for the following reasons: non-white and non-African-American (n=91); prevalent AF or atrial flutter (n=114); no electrocardiogram (ECG) or unreadable at baseline (n=273); non-fasting (<8 hours) blood sample (n=471); missing information on exposure or covariates of interest (n=374). The final sample size was 13025 individuals. The ARIC Study protocol was approved by institutional review boards at each site and informed consent was obtained from all study participants.

Blood collection and processing techniques from visit 2 have been previously described.[8] Briefly, glucose was measured in serum using a hexokinase/glucose-6-phosphate dehydrogenase method. Insulin was measured by radioimmunoassay (125Insulin kit; Cambridge Medical Diagnosis, Bilerica, MA) in Visit 1 samples only.[8] HbA1c was measured using high-performance liquid chromatography (Tosoh 2.2 Plus Glycohemoglobin Analyzer in 2003–2004 and the Tosoh G7 in 2007–2008, Tosoh Corporation) on all participants with available stored whole blood at Visit 2.[9] The reliability of measurements from these stored samples has been previously reported.[10] Attained educational level, income, cigarette smoking and use of antihypertensive and diabetic medications in the past two weeks were obtained from questionnaires and from documentation of medications.[8]

Sitting systolic BP was measured three times using a random-zero sphygmomanometer after 5 minutes of rest. The mean of the last two measurements were used for the analysis. BMI (kg/m^2) was computed from weight in a scrub suit and standing height.

Study participants with a FSG <100 mg/dL, a HbA1c<5.7%, no use of diabetic medication, and no history of physician-diagnosed diabetes were considered to have an optimal level of blood glucose and were categorized as having no diabetes.[11] Individuals with a FSG 100–125 mg/dL or HbA1c 5.7–6.4%, no use of diabetic medication, and no history of physician-diagnosed diabetes were considered to have a sub-optimal glucose profile and classified as having pre-diabetes. Those with FSG≥126 mg/dL or HbA1c≥6.5% or use of diabetic medication or history of physician-diagnosed diabetes were categorized as having diabetes. Individuals with FSG≥126 mg/dL or HbA1c≥6.5% but no history of diabetic medication usage or physician-diagnosed diabetes were categorized as having undiagnosed diabetes.

Individuals with evidence of AF or atrial flutter on an ECG at visits 1 or 2, or a hospitalization for AF between both visits, were excluded from this analysis. Diagnoses of incident AF and atrial flutter were obtained through the end of 2007 from three sources: ECGs done at study visits 3 and 4, presence of an ICD9 code for AF/atrial flutter (427.31 or 427.32) listed on the hospital discharge record, or AF listed as any cause of death on the death certificate. Hospitalizations with AF associated with open cardiac surgery were not considered events. Date of AF incidence was the earliest of any AF diagnosis. All ARIC examination ECGs were recorded using MAC PC Personal Cardiographs (Marquette Electronics, Inc, Milwaukee, WI). A standard supine 12-lead resting ECG was recorded at each clinic visit and was transmitted by modem to the ARIC ECG Reading Center for automatic reading and coding. All AF events that were automatically detected from the study ECGs were visually rechecked by a cardiologist.[12]

Means (or percentages) and standard deviations (SD) were calculated separately in those with diabetes, pre-diabetes and those without diabetes. The age-standardized incidence of AF for both diabetes and pre-diabetes was calculated. Associations between diabetes and pre-diabetes with AF were estimated using time-dependent Cox proportional hazards models with time to AF as the dependent variable. Separate race and gender analyses were conducted; models were adjusted for age, study site, education, income, prevalent CHD, BMI, systolic BP, antihypertensive medications, and smoking. Additional analyses included FSG in the model as a means to control for differences in control of diabetes. We explored the assumption of proportional hazards by computation of Schoenfeld residuals, and inspection of log(−log[survival function]) curves.

Initially, we explored the association between measures of diabetes markers and AF risk modeling FSG, fasting insulin, and HbA1c using restricted cubic splines. After confirming linearity, the association between FSG, fasting insulin and HbA1c levels with incident AF was examined separately in diabetics and non-diabetics using Cox models with adjustment for the same covariates as previously described. Chi-square tests for trend were conducted across categorical levels and tests for interaction with gender and race were performed. P-values <0.05 were considered significant.

We conducted sensitivity analyses excluding individuals with a history of CHD prior to visit 2. Prevalent CHD included individuals with a history of myocardial infarction (MI), MI adjudicated from the baseline ECG, or history of coronary bypass or angioplasty. We also examined the associations between tertiles of FSG and HbA1c with incident AF after reclassifying individuals as diabetic or not based on prior history of treatment for diabetes and self-reported history of diabetes (Y/N). To examine the relationship between duration of diabetes and risk of AF, self-reported age of diabetes diagnosis was obtained during an

annual phone follow-up between between 1994–96 among 10371 individuals free of AF at visit 4 (1996–98).

RESULTS

Baseline characteristics and diabetes prevalence of study participants

At study baseline, the mean age of the 13025 participants included in this analysis was 57.0 years (Table 1). One third (33.7%) of the study population did not have diabetes, 51.4% had pre-diabetes and 14.9% had diabetes. Of those with diabetes, 50.6% were previously undiagnosed. During a mean follow-up of 14.5 years there were 1311 cases of incident AF. Of these, 98.9% were identified from hospitalizations, 6.6% from study ECGs, and 5.6% from death certificates (some cases were identified by more than one method).

Incidence of atrial fibrillation by diabetic status

In the overall cohort, individuals with diabetes had an age-adjusted incidence rate of AF that was twice that of those without diabetes 9.02 vs. 4.51 per 1000 person-years, $p < 0.0001$). Those classified as having 'pre-diabetes' had incidence rates of AF that were intermediate (5.14). Compared with those individuals who received a physician-diagnosis of diabetes, those with undiagnosed diabetes had lower incidence rates of AF (10.8 vs 7.38; p=0.0008).

Association between diabetic status and risk of atrial fibrillation

Individuals with diabetes had one third greater risk of incident AF compared with those without diabetes after adjustment with no evidence of interactions with race or gender (HR 1.35 (95% CI: 1.14–1.60; Figure 1). When FSG was included in the model to adjust for diabetes control the risk of AF associated with diabetes was no longer significant (1.07 ([0.87–1.33]). After excluding those with prevalent CHD (n=12307; 1150 AF cases) the adjusted association between diabetes and risk of AF was attenuated: HR 1.27 (95% CI: 1.06–1.52). After additional adjustment was made for FSG the relationship was no longer significant (1.04 [0.83–1.31]).

The positive association was observed in individuals with previously diagnosed diabetes but not in those with undiagnosed diabetes: HR 1.61 (95% CI: 1.33–1.96) vs 1.11 (0.89–1.37; Figure 1). In individuals with diagnosed diabetes there was no interaction with race (p=0.59) but the association tended to be stronger in women than in men (p=0.03; Figure 1). There was no evidence of an increased risk of AF in persons with pre-diabetes compared with those without diabetes after multivariable adjustment (0.96 [0.84–1.10]) in any of the race or gender groups (all p-values for interaction>0.35).

Association between fasting serum glucose with risk of atrial fibrillation

Among individuals without diabetes, there was no evidence to suggest that FSG was independently associated with incident AF (p for trend=0.93) both overall, or in any of the race-gender subgroups (all p-values for interaction>0.30). Exclusion of those with prevalent CHD and undiagnosed diabetes did not materially alter these results (p for linear trend=0.13; both p-values for interaction>0.13). Similarly, when diabetes was defined based only on history of medication use or self-report there was no evidence of an independent positive association between tertiles of FSG and risk of AF among those without diabetes (p=0.63; Table 2).

In individuals with diabetes there was a significant linear association between FSG and risk of AF: HR 1.03 (95% CI: 1.01–1.05 per 10 mg/dl increase in FSG; p=0.0002) with no significant interaction by race (p=0.89) or gender (p=0.09). These results did not substantially change when individuals with undiagnosed diabetes were excluded (HR 1.03;

p=0.002), or after further exclusion of those with prevalent CHD (HR 1.02; p=0.03). When diabetes was defined based only on history of medication use or self-report there was similar evidence of a positive, independent association across tertiles of FSG and AF (p=0.04; Table 3).

Association between HbA1c with risk of atrial fibrillation

In individuals without diabetes, there was a linear trend between incident AF with HbA1c level after adjusting for confounders; HR 1.05 (95% CI: 0.96–1.15; p=0.07) for every 1% point increase in HbA1c. Exclusion of undiagnosed diabetics did not alter the results (HR 1.05) nor did the estimates differ by race (p=0.92) or gender (p=0.29). After excluding individuals with prevalent CHD (n=642; 131 AF cases) the positive trend between HbA1c and incident AF was no longer apparent: HR 1.00 (95% CI: 0.90–1.11). Similar results were observed when diabetes was defined on the basis of medication use or self-report (Table 3).

In those with diabetes, HbA1c levels were positively and independently associated with incident AF: HR 1.13 (95% CI: 1.07–1.20; p<0.001) per 1% point increase in HbA1c level. The result remained unchanged after excluding those with undiagnosed diabetes (HR 1.13; p=0.001) and those with prevalent CHD (HR 1.14; p<0.0001). Among all individuals with diabetes, after additionally adjusting for FSG, the relationship between HbA1c level and AF risk was attenauted HR 1.11 (0.99–1.24; p=0.07). Similar results were observed when diabetes was defined on the basis of medication use or self-report (Table 3).

Association between fasting insulin with risk of atrial fibrillation

In an analysis based on 1530 AF events among 14644 individuals there was no evidence of an association across quartiles of fasting insulin with risk of incident AF in those with or without diabetes (both p for trends>0.50).

Association between duration of self-reported diabetes with risk of atrial fibrillation

Among 1541 persons with diagnosed diabetes at visit 4 with information on age at diagnosis, there were 179 incident cases of AF during follow-up beyond visit 4. There was an independent linear relationship between duration of self-reported diabetes with incident AF (p for trend=0.0006). Compared with unaffected individuals, those who reported having diabetes for <5 years, had a 25% (95% CI: 1–56%) greater risk of AF, and in those with diabetes for >10 years, the risk was more than 50% (HR 1.58, 95% CI: 1.17–2.13) higher.

DISCUSSION

Findings from this large community-based prospective cohort suggest that individuals with diagnosed diabetes, irrespective of race and gender, have one-third greater risk of incident AF compared with individuals without diabetes consistent with earlier studies.[13, 14] Furthermore, FSG was independently associated with greater risk of AF in people with diabetes, an association which remained after excluding individuals with undiagnosed diabetes and prevalent CHD. This finding is consistent with a report from the US Cardiovascular Health Study that showed an independent positive association between FSG and AF in older adults in the US.[4]

There was no evidence however to support the hypothesis that individuals with pre-diabetes are at increased risk of AF compared with those without diabetes. Similarly, in individuals without diabetes, there was no association between FSG with AF, which is in agreement with findings from a Scottish cohort which reported no significant association between FSG and AF in healthy middle-aged participants.[5]

The current study however does support a positive and independent relationship between HbA1c levels with incident AF in both individuals with and without diabetes. Moreover, our finding of a strong positive association between HbA1c level with risk of AF in people with diabetes supports the hypothesis that poor glycemic control is an independent risk factor for AF.

To the best of our knowledge this is only the second report, and the first cohort study, to assess the association between HbA1c levels and risk of AF. In a previous case-control study a 1% point higher HbA1c level was associated with a 1.14 (95% CI: 0.96 to 1.35) greater odds of AF [15]: however, as people with diabetes were included in that analysis, it is uncertain whether the association was due, in part, to a treatment effect. In the current study, we surmounted this limitation by stratifying the analysis by diabetic status; in unaffected individuals, a 1% point increase in HbA1c level was associated with a non-significant 5% greater risk of AF and a significant 13% greater risk in those with diabetes.

The lack of any association between markers of glucose homeostasis with incident AF in those without diabetes suggests that the relationship between diabetes and AF may be a function of the severity of diabetes and apparent only after long-term cumulative exposure to hyperglycemia. This hypothesis is supported by our findings of a stronger association of diabetes with AF among persons with longer duration of diabetes consistent with an earlier report.[15] Alternatively, the association between those with diagnosed diabetes and subsequent AF may be due to surveillance bias; as patients with diabetes have a greater likelihood of developing co-morbidities, they are more likely to have more contact with the health care system compared with those without a diagnosis of diabetes. Hence, increased surveillance of patients with diabetes for other medical conditions, including AF, may explain the stronger association with AF than among patients without diagnosed diabetes, who are less likely to receive the same level of medical scrutiny.

The mechanisms by which diabetes may increase the risk of AF are largely unknown. Previous reports have shown that insulin resistance is associated with increased risk of left ventricular hypertrophy which is itself a major risk factor for AF.[16] Although we did not observe an association between fasting insulin and incident AF, we cannot preclude a possible causative role for insulin resistance in the aetiology of AF for three reasons: first, we were limited by only having a single measure of insulin, the variability around which was high, and therefore any association may have been diluted; second, a single measurement of insulin is a crude marker of insulin resistance; and third, in a previous publication from ARIC, individuals with the metabolic syndrome (of which, insulin resistance is a key component) had significantly greater risk of AF compared with unaffected individuals.[17]

The main strengths of this study are its prospective study design, its long-term follow-up of more than 14 years and standardized, detailed information on a large number of possible confounders. There are however some limitations. First is the lack of complete data on subtypes of AF which may have different associations with diabetes, although there is no reported evidence of heterogeneity in the magnitude or direction of the positive association between diabetes and subtype of AF.[15] Second, as discussed in a previous ARIC publication as cases of AF were mainly ascertained through hospital discharge codes, this may have led to under-ascertainment of events that perhaps, were not severe enough to warrant hospitalization.[18]

In summary, individuals with diagnosed diabetes are at increased risk of subsequent AF compared with those without the condition. The lack of clear evidence for an association between pre-diabetes, those with undiagnosed diabetes, and with several indices of glucose

control, suggests that the detrimental impact of diabetes on AF risk occurs only after prolonged exposure to diabetes.

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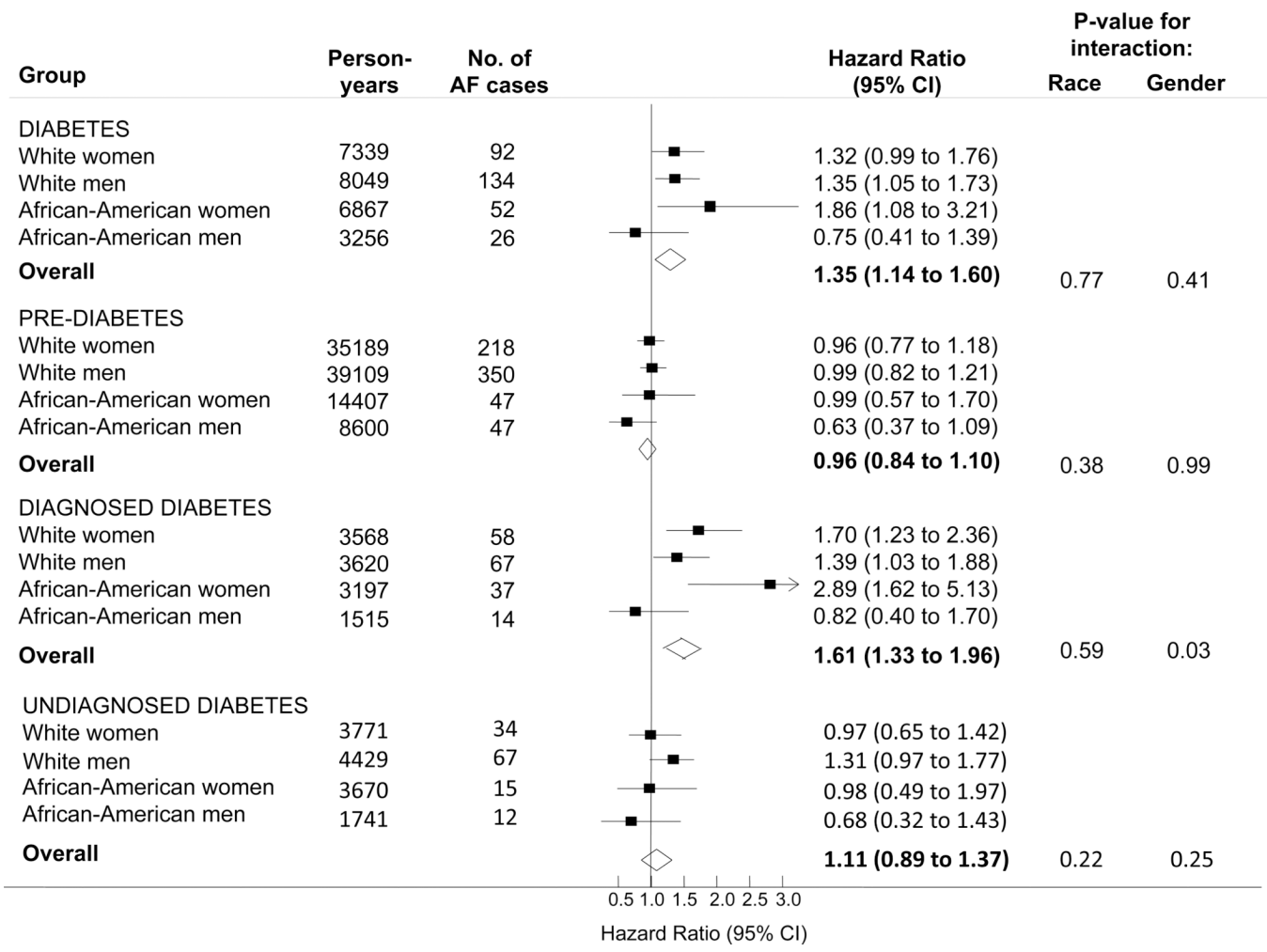

Figure 1.

Relationship between diabetes, pre-diabetes and physician-diagnosed diabetes with incident atrial fibrillation among whites and African-Americans in ARIC by gender (1990–2007). Individuals without diabetes comprised the reference group for each comparison. Diabetes included all individuals with FSG ≥126 mg/dL or HbA1c > 6.5% or use of diabetic medication or history of physician-diagnosed diabetes. Undiagnosed diabetes = FSG ≥126 mg/dL or HbA1c > 6.5% but no history of diabetic medication usage or physician-diagnosed diabetes. The black boxes represent the estimate of effect adjusted for age, education, income, prior history of cardiovascular disease, body mass index, systolic blood pressure, use of hypertensive medications, and cigarette smoking. Horizontal lines represent the 95% confidence intervals. Open diamond represents the estimate of effect for the overall population.

Table 1

Descriptive statistics by type 2 diabetes status* at baseline, ARIC, 1990–1992

	Total (n =13025)	**No diabetes (n = 4390)**	**Pre-diabetes (n = 6693)**	**Diagnosed Diabetes (n = 959)**	**Undiagnosed diabetes (n = 983)**
Age (years)	57.0 (5.7)	56.1 (5.6)	57.2 (5.7)	58.6 (5.6)	57.8 (5.7)
Race (% African American)	22.9	15.0	23.4	39.7	38.9
Gender (% Female)	55.9	66.0	49.6	55.9	52.9
Income (%):< $16,000	18.7	13.6	18.4	35.1	28.1
$16,000 – <$35,000	31.5	30.5	31.9	32.6	33.1
$35,000 – <$50,000	19.2	21.6	19.0	14.4	14.9
$50,000+	24.9	28.9	25.2	11.8	17.3
Unknown/Refused	5.7	5.5	5.6	6.1	6.7
Education (%):					
< High school	21.0	14.7	21.7	34.7	30.6
College level	42.0	44.2	41.1	40.3	39.5
Graduate level	37.1	41.1	37.2	25.0	29.9
Cigarette Smoking (%):					
Current	21.9	20.8	23.2	18.7	21.6
Former	38.1	35.8	39.3	37.9	40.4
Never	40.0	43.4	37.5	43.5	38.1
Fasting serum glucose (mg/dL)	112.2 (38.1)	93.1 (4.7)	107.0 (7.4)	199.7 (80.9)	147.0 (43.4)
Fasting insulin* (pmol/L)	88.7 (153.6)	59.3 (44.8)	80.8 (59.2)	243.8 (502.8)	124.8 (82.3)
HbA1c levels (%)	5.7 (1.1)	5.2 (0.3)	5.5 (0.4)	8.3 (2.2)	6.7 (1.3)
Body mass index (kg/m^2)	28.0 (5.4)	26.0 (4.5)	28.2 (5.2)	31.0 (6.0)	31.4 (5.9)
Systolic BP (mm Hg)	121.4 (18.7)	117.2 (18.0)	122.1 (18.1)	128.2 (20.1)	128.1 (18.9)
Hypertension medication (%)	32.1	21.4	32.6	58.5	50.5
Prior coronary heart disease (%)	5.5	3.8	5.3	12.9	7.7

Values correspond to mean (standard deviation) unless otherwise stated; BP = blood pressure;

* Insulin available at visit 1, 1987–89.

* No-diabetes = study participants with a FSG <100 mg/dL, a HbA1c < 5.7%, no use of diabetic medication, and no history of physician-diagnosed diabetes. Pre-diabetes = FSG 100–125 mg/dL or HbA1c 5.7–6.4%, no use of diabetic medication, and no history of physician-diagnosed diabetes. Diabetes = FSG ≥126 mg/dL or HbA1c > 6.5% or use of diabetic medication or history of physician-diagnosed diabetes. Undiagnosed diabetes = FSG ≥126 mg/dL or HbA1c > 6.5% but no history of diabetic medication usage or physician-diagnosed diabetes.

Table 2

Hazard ratios (95% confidence intervals) for atrial fibrillation by fasting serum glucose and HbA1c levels in individuals without type 2 diabetes (defined by no history of medication use or no self-report of diabetes) (n = 12 066), ARIC, 1990–2007

	Fasting Serum Glucose (mg/dl)			P-value for trend	P-values for interactions	
	<100	100–125	≥126		Gender	Race
No. AF cases	405	626	104			
Person-years	73322	92274	11544			
HR (95% CI) Model 1	1(REF)	1.07 (0.94–1.21)	1.48 (1.19–1.84)	0.005	0.64	0.24
HR (95% CI) Model 2	1 (REF)	0.92 (0.81–1.05)	1.02 (0.82–1.28)	0.63	0.50	0.31
HR (95% CI) excl. prev..CHD*	1 (REF)	0.90 (0.70–1.03)	0.92 (0.71–1.17)	0.20	0.82	0.21
		HbA1c (%)				
	< 5.7	5.7 – 6.4	≥ 6.5			
No AF cases	788	280	67			
Person-years	136022	33695	7422			
HR (95% CI) Model 1	1 (REF)	1.39 (1.21–1.60)	1.67 (1.30–2.15)	<0.0001	0.21	0.25
HR (95% CI) Model 2	1 (REF)	1.13 (0.98–1.30)	1.19 (0.92–1.54)	0.06	0.07	0.58
HR (95% CI) excl. prev..CHD*	1REF)	1.09 (0.94–1.27)	1.02 (0.76–1.36)	0.45	0.17	0.73

HR: Hazard ratio (95% confidence intervals); Model 1: Adjusted for age, race and sex; Model 2: Adjusted for model 1 + center, education, income, smoking status, prevalent CHD, systolic blood pressure, hypertensive medications and body mass index;

*HR (95% CI) excluding prev. CHD: Adjusted hazard ratio (Model 2) and 95% confidence intervals after excluding those with prevalent CHD.

Table 3

Hazard ratios (95% confidence intervals) for atrial fibrillation by fasting serum glucose and HbA1c levels in individuals with type 2 diabetes (defined by history of medication use or self-report of diabetes) (n = 959), ARIC, 1990–2007

	Fasting Serum Glucose (mg/dl)			P-value for trend	P-values for interactions	
	<100	**100–125**	**≥126**		**Gender**	**Race**
No. AF cases	2	18	156			
Person-years	542	1675	9683			
HR (95% CI) Model 1	1(REF)	2.53 (0.58–11.0)	4.10 (1.01–16.7)	0.005	0.79	0.79
HR (95% CI) Model 2	1(REF)	1.99 (0.46–8.67)	2.89 (0.71–11.8)	0.04	0.78	0.80
HR (95% CI) excl. prev. CHD*	1 (REF)	2.07 (0.47–9.05)	2.63 (0.64–10.7)	0.11	0.89	0.54
		HbA1c (%)				
	< 5.7	5.7 – 6.4	≥ 6.5			
No AF cases	8	16	152			
Person-years	1135	1714	9049			
HR (95% CI) Model 1	1 (REF)	1.30 (0.56–3.05)	2.77 (1.36–5.65)	0.0002	0.76	0.79
HR (95% CI) Model 2	1(REF)	1.18 (0.50–2.77)	2.11 (1.02–4.37)	0.007	0.66	0.52
HR (95% CI) excl. prev. CHD*	1 (REF)	1.22 (0.49–3.05)	2.21 (1.01–4.83)	0.009	0.84	0.79
HR(95%CI) + adj FSG**	1 (REF)	1.12 (0.48–2.64)	1.69 (0.78–3.66)	0.09	0.73	0.56

HR: Hazard ratio (95% confidence intervals); Model 1: Adjusted for age, race and sex;Model 2: Adjusted for model 1 + center, education, income, smoking status, prevalent CHD, systolic blood pressure, hypertensive medications and body mass index;

*HR (95% CI) excluding prev. CHD: Adjusted hazard ratio (Model 2) and 95% confidence intervals after excluding those with prevalent CHD;

**Hazard ratio (95% confidence intervals) from Model 2 + adjustment for fasting serum glucose among all persons with type 2 diabetes