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Type 2 Diabetes Mellitus and Risk of Incident Atrial Fibrillation in Women

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Abstract

Objectives—To assess whether changes of major atrial fibrillation (AF) risk factors and/or intercurrent cardiovascular events could explain the relationship between type 2 diabetes mellitus (T2D) and incident AF.

Background—Prior studies found an increased risk of incident AF among individuals with T2D, but few if any of these studies did take into account changes of AF risk factors over time.

Methods—A total of 34720 female health professionals who participated in the Women's Health Study, and were free of cardiovascular disease and AF at baseline were followed for a median of 16.4 years. Cox proportional-hazards models were constructed to assess the relationship between T2D and incident AF, using either information at baseline or time-varying covariates for both T2D and potential confounders.

Results—At baseline, 937 (2.7 %) women had T2D. Compared to women without T2D, women with T2D had an age-adjusted hazard ratio (HR) for new-onset AF of 1.95 (95% confidence interval (CI), 1.49-2.56, p<0.0001). In multivariable analyses adjusting for baseline confounders, this HR was substantially attenuated, but baseline T2D remained a significant predictor of incident AF (HR 1.37, 95% CI, 1.03-1.83, p=0.03). In time-updated models that adjusted for changes in AF risk factors and intercurrent cardiovascular events, the HR for T2D was attenuated further and became non-significant (HR= 1.14; 95% CI, 0.93 – 1.40, p=0.20).

Conclusions—While this study confirms a significant relationship between baseline T2D and incident AF, our data suggest that the increased risk associated with T2D is mainly mediated by changes of other AF risk factors.

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Keywords

Atrial fibrillation; type 2 diabetes; blood pressure; obesity; women; cardiovascular disease; prospective cohort study

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population (1), and its prevalence is projected to increase substantially over the next decades (2). Individuals suffering from AF have an increased risk of major complications including death, stroke and congestive heart failure even after adjustment for relevant co-morbidities (3–8), such that defining and treating risk factors for AF occurrence is a major public health priority.

Several prospective studies have evaluated the relationship between type 2 diabetes (T2D) and incident AF, and discrepant findings have been reported (9–15). A recent meta-analysis found a modest, but statistically significant increased risk of new-onset AF among individuals with T2D (summary relative risk 1.24 (95% confidence interval (CI), 1.06-1.44)) (16). However, significant between-study heterogeneity was observed, part of which might be explained by the fact that studies with more extensive multivariable adjustment were associated with smaller relative risk estimates than studies with less extensive adjustments (p for heterogeneity 0.053) (16).

Given the close relationship of T2D with obesity and hypertension (17), two of the strongest risk factors for new-onset AF (15, 18–20), adequate adjustment in the evaluation of the association between T2D and AF is a relevant issue. The observed association between baseline T2D and AF may be due to differential changes of these risk factors in diabetic compared with non-diabetic subjects, because of the increased risk of weight gain and hypertension among patients with established T2D (21–23).

Few if any studies on the association between T2D and AF have taken into account changes of risk factors over time after the development of T2D (9–15, 24, 25). Because detailed knowledge of these relationships is important in order to optimize measures for AF disease prevention in the population, the primary aim of this study was to prospectively examine whether changes of major AF risk factors over time and intercurrent cardiovascular events may explain the previously observed association between T2D and AF.

Methods

Study Participants

All study subjects participated in the Women's Health Study (WHS), a completed randomized trial among 39876 women evaluating benefits and risks of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular disease and cancer, using a randomized, double-blind, placebo-controlled study design. Details about the conduct of the study have been published previously (26–28).

Participants were female health professionals in the United States, aged 45 years or older and free of cardiovascular disease, cancer or other major illnesses at study entry. Randomized treatment ended on March 31, 2004, and all women were invited to participate in continued observational follow-up, which for the current analysis was truncated on March 2nd, 2011. Of the original cohort, we excluded 897 women (2.2%) with a history of AF at baseline and 54 (0.1%) women with a confirmed cardiovascular event (stroke, heart failure or myocardial infarction) prior to study entry. In addition, 4205 (10.5%) women did not participate in the observational follow-up, leaving 34720 participants for the current analysis. The study was approved by the institutional review board of Brigham and Women's Hospital, Boston, and was monitored by an external data and safety monitoring board.

Study variables

Mailed questionnaires were used to collect information on baseline characteristics. To obtain information on study outcomes, changes in covariates and other information, follow-up questionnaires were sent to all participants every six months during the first year and every 12 months thereafter. Covariates of interest included age, hypertension, body mass index (BMI) (weight in kilograms divided by height in meters squared), hypercholesterolemia, physical exercise, self-reported race/ethnicity, highest education level, smoking and alcohol consumption.

Ascertainment of incident type 2 diabetes

Details regarding the ascertainment of incident T2D in the WHS have been reported previously (29). Briefly, participants were asked annually whether and when they had been diagnosed with diabetes since baseline. Confirmation of T2D was conducted using American Diabetes Association diagnostic criteria (30). Self-reported cases were investigated by either telephone interview conducted by a physician or a self-administered supplemental questionnaire that inquired about symptoms, diagnostic testing, and use of diabetes medications. In a validation study (31), the self-administered questionnaire proved highly accurate for confirmation of clinical diabetes as compared to medical record review. Thus, since 1999, confirmation of T2D has relied upon supplemental questionnaires. Overall, in 95% of all post-randomization self-reported diabetes, sufficient information for confirmation or disconfirmation of the endpoint was obtained. In addition, among women with available baseline levels of hemoglobin A1c (HbA1c) and without a baseline diagnosis of T2D, the prevalence of HbA1c >6.5% was only 0.5%. Only confirmed cases of incident T2D were included in this study.

Ascertainment of incident atrial fibrillation

Details about AF endpoint confirmation have been published previously (18, 32). Briefly, participating women were asked about incident AF diagnoses at baseline, after 48 months and annually thereafter. Women who participated in the continued observational follow-up who indicated the occurrence of an incident AF event on one or more yearly questionnaires were sent a supplemental questionnaire to collect additional information and to obtain written informed consent for medical record review. For all deceased participants who reported AF during the trial and extended follow-up period, family members were contacted

to obtain consent and additional relevant information. An endpoint committee of cardiovascular physicians reviewed medical records for reported events according to predefined criteria. An AF event was confirmed if there was electrocardiographic evidence of AF or if a medical report clearly indicated a personal history of AF. Only confirmed AF events were included in the present report.

Ascertainment of incident cardiovascular events

Collection of cardiovascular end-points occurred through questionnaires, letters, and phone calls, as described previously (8, 26). A blinded end-point committee of physicians adjudicated all events according to predefined criteria (26). Information on stroke and myocardial infarction was collected from the beginning of the study. Incident diagnoses of congestive heart failure were reported for the first time at the 48-month questionnaire. Heart failure was confirmed if participants met either the Framingham Heart Study (33) or the Cardiovascular Health Study (34) criteria for the presence of heart failure, and both definite and probable cases were included in the analysis.

Measurement of HbA1c levels

Blood samples at study entry were obtained from 28345 women. Levels of HbA1c were estimated using the Tina-Quant turbidimetric inhibition immunoassay (Roche Diagnostics, Indianapolis, IN) on a Hitachi 911 autoanalyzer using packed red blood cells (35). The assay is specific for HbA1c, standardized against the approved International Federation of Clinical Chemists reference method, and traceable to the Diabetes Control and Complications Trial by use of a conversion factor. Values of HbA1c presented in this study are Diabetes Control and Complications Trial aligned. The coefficient of variation for HbA1c computed from blinded simultaneously analyzed quality controls was 7.2%.

Statistical analysis

Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables were used to compare baseline characteristics of women with and without T2D at study entry. Person-years of follow-up were calculated from the date of return of the baseline questionnaire to the first occurrence of new-onset AF, death, loss to follow-up, or March 2nd 2011.

Cox proportional hazards models were constructed to calculate hazard ratios (HRs) and 95% CIs for incident AF and to adjust for potential confounders. Age-adjusted models were further adjusted for adult height, smoking, exercise, alcohol consumption, education, race/ethnicity, and hypercholesterolemia. Because of the close relationship between BMI, hypertension and T2D (17), these variables were added in separate steps to the multivariable models.

To evaluate the influence of covariate changes over time, we then constructed multivariable Cox models where T2D and all other covariates were updated during follow-up whenever follow-up values were available. We adjusted these multivariable models according to the same pre-specified order described above, but added a final step where we additionally adjusted for intercurrent cardiovascular events, defined as stroke, myocardial infarction or

congestive heart failure. Finally, to assess the potential bidirectional nature of the relationship between T2D, hypertension and BMI, we constructed a similar series of multivariable Cox models for BMI and hypertension, where T2D was added as a covariate in a separate step.

In order to get further insights on the role of glucose homeostasis in AF development, we assessed the relationship between approximate quartiles of HbA1c levels and incident AF in age- and multivariable adjusted Cox models among women with available HbA1c levels at baseline. Tests for linear trend were performed by assigning all women the quartile-specific median HbA1c value. To evaluate the effect of elevated HbA1c values, we repeated the same analyses after dichotomizing HbA1c levels at the 95th percentile. Finally, we also specifically assessed the association between HbA1c and incident AF among women with baseline T2D.

Categorical variables were entered in the Cox models using binary indicator variables. Multiplicative interaction terms between T2D and several baseline characteristics were evaluated in the fully adjusted baseline models using likelihood ratio tests. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). A two-tailed P-value <0.05 was pre-specified to indicate statistical significance.

Results

Baseline characteristics

Baseline characteristics stratified by the presence or absence of T2D are presented in Table 1. At study entry, 937 women (2.7 %) had T2D. Women with T2D were significantly older, had a higher BMI, a higher prevalence of hypertension, a lower educational level and exercised less frequently compared with women without T2D (all p<0.0001).

Baseline T2D and new-onset AF

During a median follow-up of 16.4 years (interquartile range 15.6 – 16.8 years), 1079 (3.1%) women developed incident AF. The age-adjusted incidence rate for new-onset AF was 3.97 and 1.99 per 1000 person-years of follow-up among women with and without baseline T2D, respectively (Table 2, upper section). Accordingly, in Cox proportional-hazards models the age-adjusted HR for women with baseline T2D was 1.95 (95% CI, 1.49 – 2.56, p<0.0001). Multivariable adjustment for established cardiovascular risk factors but not BMI and hypertension had little effect on this risk estimate (HR 1.87, 95% CI 1.41–2.47, p<0.0001). While additional adjustment for hypertension and BMI substantially attenuated this relationship, a significant effect of baseline T2D persisted in the fully adjusted model (HR 1.37, 95% CI, 1.03-1.83, p=0.03). BMI and hypertension were strong and significant risk factors of incident AF in all models and the effect of adding T2D to these models was small (Supplementary Tables 1 and 2).

Models with time-updated covariates

Among women without T2D at baseline, 2730 (7.9 %) developed new-onset T2D during follow-up. Sixty-eight (2.5 %) of these women had a subsequent diagnosis of new-onset AF,

which corresponds to an age-adjusted incidence rate of 3.62 events per 1000 person-years among women with new-onset T2D, as shown in Table 2. In multivariable models not adjusting for hypertension and BMI, T2D was significantly associated with incident AF (HR 1.58, 95% CI, 1.30 – 1.93, p<0.0001) (Table 2, lower section). When BMI and hypertension were added to this model, the association between T2D and new-onset AF was weakened and no longer statistically significant (HR 1.19, 95% CI, 0.97 – 1.45, p=0.10).

Among women with T2D, significantly more AF events were preceded by a cardiovascular event compared to women without T2D (16 of 124 (12.9%) versus 39 of 955 (4.1%), p<0.001). After additional adjustment for these intercurrent events, the multivariable adjusted relative risk was further attenuated (HR 1.14, 95% CI, 0.93 – 1.40, p=0.20), as shown in Table 2. Again, BMI and hypertension were strongly associated with incident AF in all models and adding T2D only minimally altered these results, as shown in Supplementary Tables 1 and 2.

Subgroup analyses

Subgroup analyses are displayed in Table 3. The relationship between baseline T2D and incident AF was stronger among women aged <65 years (HR 1.54, 95% CI, 1.13 – 2.11) than among women aged ≥65 years (HR 0.85, 95% CI, 0.42 – 1.74) (p for interaction 0.01). Again, in women aged <65 years, the effect of T2D on incident AF was attenuated in fully adjusted time-updated Cox models (HR 1.24, 95% CI 0.99 – 1.55). Consistent findings with non-significant interaction tests were obtained for all other subgroups assessed.

HbA1c levels and new-onset AF

Among 28345 women with available blood samples at baseline, 25290 were eligible for the current analysis, of whom 24890 (98%) had a valid HbA1c measurement. In this subcohort, 835 confirmed incident AF events occurred. HbA1c at study entry was not significantly associated with incident AF. The age- and multivariable adjusted models for quartiles of HbA1c are shown in Table 4, and the p values for linear trend across quartiles were non-significant. When extremes levels above the 95th percentile (i.e. >5.6%) were examined, the age-adjusted association was significant (HR=1.53; 95% CI 1.20-1.96) but was highly attenuated and became non-significant after multivariable adjustment (HR=1.13; 95% CI 0.87-1.48). Finally, stratifying women by the presence or absence of T2D at baseline provided similar results. Among the 647 women with T2D at baseline, the multivariable HR for each 1% increase in HbA1c was 1.09 (95% CI 0.93-1.27). The corresponding HR among the nondiabetic women was 0.87 (95% CI 0.71-1.07).

Discussion

In this large, prospective cohort of initially healthy middle-aged women, baseline T2D was a modest, but statistically significant risk factor of incident AF after multivariable adjustment. Like in prior studies on this issue, we found that the risk of incident AF among women with T2D was increased approximately twofold after adjustment for age, and that this risk was attenuated to about 1.4 after more extensive multivariable adjustment for baseline risk factors (9, 12, 14, 16). The present study adds to this literature by showing that much of the

remaining association between T2D and AF in these prior studies can be accounted for by the development over time of hypertension, obesity, and cardiovascular disease. We also found that the effect of T2D on incident AF was stronger in younger women (p for interaction 0.01). The reason for this finding is unclear, but it may suggest that environmental factors leading to hypertension and obesity are less important in younger individuals with T2D.

Our data suggest that the adiposity and hypertension associated with T2D are more important for AF development than glucose homeostasis, a concept that is supported by at least two lines of evidence. First, we found no relationship between HbA1c levels and incident AF in women with and without established T2D who had available blood samples. However, a recent study found that elevated HbA1c levels were associated with an increased risk of AF occurrence in the subgroup of participants with established T2D (25). The reason for these differential findings are unclear, but may be related to the fact that a more severe endpoint (AF hospitalizations) was assessed in the earlier study or that a different sample population was evaluated (community based cohort versus initially healthy female health professionals). Alternatively, the relatively small subgroup of women with T2D and available HbA1c levels in our study might have limited our power to detect such an association. The upper limit of the 95% CI in our analysis suggests that our study can't exclude an increased risk of incident atrial fibrillation up to 27% for each 1% increase in HbA1c among women with T2D, an order of magnitude well in line with the risk estimate of the previous analysis (25). By contrast, the tight confidence limits (HR 0.87, 95% CI 0.71-1.07) for HbA1c in the much larger group of non-diabetic women do confidently rule out even a modest increase in risk. Second, recent data from the Framingham Heart Study investigators showed that insulin resistance does not independently increase the risk of incident AF, with a multivariable adjusted HR for new-onset AF associated with insulin resistance of 1.03 (95% CI, 0.72-1.46) (36).

In contrast to these negative findings, the strong and independent relationships of obesity and elevated blood pressure, two important T2D-related co-morbidities (17), with AF development have been demonstrated in several independent studies (18–20, 37). These relationships persisted in models taking into account changes of covariates over time (18, 19), and were only minimally affected in the present study by adding T2D to the models. Population attributable risks around 20% for overweight and obesity (19, 37), and up to 25% for elevated blood pressure (37) further highlight the importance of overweight and elevated blood pressure as AF risk factors. Because patients with T2D are more likely to suffer from additional weight gain and increases in blood pressure, taking into account changes in these risk factors over time is important in order to isolate any residual association attributable to diabetes independent of these factors. Interestingly, obesity, hypertension, T2D and AF have all been strongly related to blood levels of inflammatory biomarkers, such that inflammation may be an important pathophysiological link between these variables (19, 38, 39). With regard to clinical implications, our data suggest that prevention of AF among individuals with T2D should focus on the strict control of body weight and blood pressure (40).

The occurrence of cardiovascular events is a strong risk factor for incident AF (14, 37) and an important determinant of an adverse outcome in AF patients (8). As patients with T2D

have an increased risk of developing cardiovascular events (41), we hypothesized that intercurrent cardiovascular events could also mediate AF risk in these patients. However, although significantly more AF events were preceded by a cardiovascular event in women with T2D, the great majority of AF events occurred independent of an overt cardiovascular event also among individuals with T2D. Accordingly, our multivariable models suggest that once changes in blood pressure and body weight are taken into account, only a small part of the relationship between baseline T2D and new-onset AF may be mediated by nonfatal cardiovascular events.

Strengths and limitations

Strengths of the present study include the prospective design, the large sample size and complete long-term follow-up with a large number of events confirmed by medical record review and regular covariate update. Potential study limitations should also be considered. First, most participants of the present study are Caucasian women and generalization of our findings to different populations should be done cautiously. Second, some AF cases may have gone undetected because of asymptomatic AF episodes. The only way to obtain a true picture of the AF prevalence would be by long-term continuous Holter monitoring, which unfortunately is not feasible in large long term cohort studies of this type. Third, defining the onset of the initial AF episode may be challenging. Fourth, underdiagnosis of T2D may have occurred, given the lack of systematic T2D screening. Fifth, subclinical hyperthyroidism has been repeatedly associated with an increased risk of AF and may also be related to T2D (42, 43). As information on thyroid function is not available in this study, we were unable to assess its role in the relationship between T2D and incident AF.

Conclusion

In this large cohort of initially healthy women, T2D at study entry was associated with a modest increase in risk of incident AF. Most of this increased risk seems to be mediated through excess weight gain and a higher prevalence of hypertension among individuals with T2D, such that the impact of diabetes beyond these risk factors is less important. Therefore, strategies for AF prevention in diabetic patients should focus on the control of T2D-associated co-morbidities, in particular weight maintenance and blood pressure control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AF	atrial fibrillation
BMI	body mass index
CI	confidence interval
HbA1c	glycosylated haemoglobin A1c
HR	hazard ratio
T2D	type 2 diabetes mellitus
WHS	Women's Health Study

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Table 1

Baseline characteristics according to the presence or absence of T2D

Characteristic (n = 34720)	No Baseline T2D (n=33783)	Baseline T2D (n=937)	P value*
Age, years	52.8 (48.9 - 58.7)	55.5 (50.0 - 62.1)	<0.0001
Body mass index, kg/m^2	24.9 (22.5-28.3)	30.0 (26.3-34.6)	<0.0001
Adult height, cm	165 (160 - 168)	165 (160 - 170)	0.23
History of hypertension	8586 (25.4%)	589 (62.9%)	<0.0001
History of hypercholesterolemia	10041 (29.7%)	443 (47.3%)	<0.0001
Smoking			
Current	4179 (12.4%)	127 (13.6%)	0.49
Past	12139 (35.9%)	343 (36.6%)	
Never	17439 (51.6%)	467 (49.8%)	
Alcohol consumption			
Rarely/Never	14706 (43.5%)	655 (69.9%)	<0.0001
1-3 drinks per month	4463 (13.2%)	122 (13.0%)	
3-6 drinks per week	11052 (32.7%)	124 (13.2%)	
1+ drinks per day	3552 (10.5%)	36 (3.8%)	
Highest education level			
Less than a bachelor's degree	18438 (54.6%)	599 (63.9%)	<0.0001
Bachelor's degree	7900 (23.4%)	190 (20.3%)	
Master's degree or doctorate	6876 (20.4%)	127 (13.6%)	
Exercise, times/ week			
Rarely/Never	12646 (37.4%)	446 (47.6%)	<0.0001
< 1	6693 (19.8%)	187 (20.0%)	
1-3	10734 (31.8%)	229 (24.4%)	
>= 4	3695 (10.9%)	75 (8.0%)	

T2D=Type 2 diabetes. Data are median (interquartile ranges) or counts (percentages). Number of observations across categories may not sum to the given number because of missing data.

*Based on Kruskal-Wallis tests for continuous variables and Chi-Square tests for categorical variables.

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Table 2

Risk of incident AF according to the presence or absence of T2D

Models with baseline characteristics only			
	No T2D at Baseline (n = 33783)	**T2D at Baseline (n = 937)**	**P value**
Number of events / person years	1023 / 528,106	56 / 13,192	...
Age-adjusted incidence rate	1.99	3.97	...
Age-adjusted model	Referent	1.95 (1.49 – 2.56)	<0.0001
Multivariable-adjusted model *†	Referent	1.87 (1.41 – 2.47)	<0.0001
+ hypertension†	Referent	1.62 (1.22 – 2.14)	0.0008
+ BMI‡	Referent	1.47 (1.11 – 1.96)	0.008
+ hypertension and BMI‡	Referent	1.37 (1.03 – 1.83)	0.03

Models using time – updated covariates			
	Never T2D (n = 31053)	**Baseline or incident T2D (n = 3667)**	**P value**
Number of events / person years	955 / 507,851	124 / 33,448	...
Age-adjusted incidence rate	1.98	Baseline T2D: 3.97 Incident T2D: 3.62	
Age-adjusted model	Referent	1.63 (1.35 – 1.96)	<0.0001
Multivariable-adjusted model *†	Referent	1.58 (1.30 – 1.93)	<0.0001
+ hypertension†	Referent	1.42 (1.16 – 1.73)	0.0005
+ BMI‡	Referent	1.24 (1.01 – 1.53)	0.04
+ hypertension and BMI‡	Referent	1.19 (0.97 – 1.45)	0.10
+ hypertension, BMI and intercurrent cardiovascular events‡	Referent	1.14 (0.93 – 1.40)	0.20

Data are counts, rates per 1000 person-years of follow-up, or hazard ratios (95% CIs) as appropriate. BMI = body mass index; T2D=Type 2 diabetes

*Adjusted for age, smoking, exercise, alcohol consumption, education, race/ethnicity, hypercholesterolemia, and adult height.

†These models were based on 1040 events in 33757 women because of missing data.

‡These models were based on 1027 events in 33372 women because of missing data.

Table 3

T2D and risk of incident AF, stratified by selected baseline characteristics

Characteristic	No baseline T2D (n=33783)	Baseline T2D(n=937)	P Value*
Age ≥ 65 y			0.01
Yes (n = 3430)			
Events/participants	250/3294	8/136	
HR (95% CI)	1 [Reference]	0.85 (0.42 – 1.74)	
No (n = 31290)			
Events/participants	773/30489	48/801	
HR (95% CI)	1 [Reference]	1.54 (1.13 – 2.11)	
Body mass index			0.10
< 25 kg/m^2 (n = 17720)			
Events/participants	431/17546	3/174	
HR (95% CI)	1 [Reference]	0.53 (0.17 – 1.66)	
25 – 30 kg/m^2 (n = 10707)			
Events/participants	331/10418	16/289	
HR (95% CI)	1 [Reference]	1.19 (0.68 – 2.09)	
> 30 kg/m^2 (n = 6260)			
Events/participants	260/5791	37/469	
HR (95% CI)	1 [Reference]	1.73 (1.21 – 2.48)	
Hypertension			0.70
Yes (n = 9175)			
Events/participants	430/8586	44/589	
HR (95% CI)	1 [Reference]	1.43 (1.03 – 2.00)	
No (n = 25545)			
Events/participants	593/25197	12/348	
HR (95% CI)	1 [Reference]	1.22 (0.69 – 2.17)	
Hypercholesterolemia			0.82
Yes (n = 10484)			
Events/participants	359/10041	27/443	
HR (95% CI)	1 [Reference]	1.37 (0.91 – 2.07)	
No (n = 24236)			
Events/participants	664/23742	29/494	
HR (95% CI)	1 [Reference]	1.35 (0.91 – 2.02)	
Current Smoking			0.98
Yes (n = 4306)			
Events/participants	92/4179	5/127	
HR (95% CI)	1 [Reference]	1.48 (0.57 – 3.84)	
No (n = 30388)			

Characteristic	No baseline T2D (n=33783)	Baseline T2D(n=937)	P Value*
Events/participants	929/29578	51/810	
HR (95% CI)	1 [Reference]	1.35 (1.00 – 1.83)	

T2D=Type 2 diabetes

All hazard ratios were adjusted for age, smoking, exercise, alcohol consumption, education, race/ethnicity, hypercholesterolemia, hypertension, body mass index, and adult height

* P value for interaction based on a likelihood ratio test with and without interaction terms in the models

Table 4

HbA1c and risk of incident AF among 24890 women with available HbA1c levels

	Hemoglobin A1c Quartiles				
N=24890	**1 ≤4.84%**	**2 4.84-5.00%**	**3 5.00-5.19%**	**4 >5.l9%**	**P Trend[§]**
Number of events / participants	170 / 6275	181 / 6149	235 / 6293	249 / 6173	-
Age-adjusted incidence rate	2.05	1.99	2.33	2.37	-
Age-adjusted model	Referent	0.97 (0.79-1.20)	1.12 (0.92-1.37)	1.12 (0.91-1.37)	0.16
Multivariable-adjusted model [*†]	Referent	0.99 (0.80-1.22)	1.07 (0.87-1.31)	1.11 (0.90-1.36)	0.22
+ hypertension and BMI[‡]	Referent	0.95 (0.76-1.17)	0.97 (0.79-1.19)	0.90 (0.73-1.11)	0.35

Data are counts, rates per 1000 person-years of follow-up, or hazard ratios (95% CIs) as appropriate. BMI = body mass index

[*]Adjusted for age, smoking, exercise, alcohol consumption, education, race/ethnicity, hypercholesterolemia, and adult height.

[†]These models were based on 806 events in 24194 women because of missing data.

[‡]These models were based on 794 events in 23921 women because of missing data.

[§]P value for trend across quartiles of HbA1c using quartile-specific medians of HbA1c