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Association of Diabetes Mellitus with Incident Dementia in Patients with Atrial Fibrillation in the Atherosclerosis Risk in Communities Cohort

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Master of Public Health

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An abstract of
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Abstract

Association of Diabetes Mellitus with Incident Dementia in Patients with Atrial Fibrillation in the Atherosclerosis Risk in Communities Cohort

By Ashwini Jiayaspathi

Background

Patients with atrial fibrillation (AF) are at increased risk of dementia. Whether diabetes mellitus (DM) is a risk factor for incident dementia in AF has not been explored. This information can enable us to take the necessary steps to prevent dementia in this population.

Objectives

To determine the association between presence of diabetes mellitus at time of AF diagnosis with the risk of incident dementia.

Methods

We identified individuals with an incident diagnosis of AF in the Atherosclerosis Risk in Communities (ARIC) cohort (1987-2017) and determined their diabetes status, blood glucose and HbA1c levels at the time of diagnosis. The primary outcome of incident dementia was defined using information from cognitive assessments, informant interviews and hospitalization surveillance. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia for each level of exposure using Cox models and adjusting for potential confounders.

Results

We analyzed 3,020 patients with AF in the ARIC cohort of which 808 had diabetes and 530 had incident dementia after a mean follow-up of 5.3 years. After multivariable adjustment, AF patients with diabetes had higher rates of dementia than non-diabetics (HR 1.45, 95%CI 1.16, 1.80). Diabetes status, but not fasting blood glucose, was associated with the rates of dementia: compared to non-diabetics with blood glucose <96, the HR and 95%CI of dementia were 0.99 (0.77, 1.29) for non-diabetics with blood glucose between 96 to <105mg/dl, 0.97 (0.74, 1.27) for non-diabetics with blood glucose ≥105mg/dl, 1.74 (1.20, 2.52) for diabetics with blood glucose <131 mg/dl, 1.30 (0.91, 1.86) for diabetics with blood glucose between 131 to < 171mg/dl) and 1.31 (0.87, 1.97) for Diabetics with blood glucose ≥171mg/dl. An increase of 1 unit of HbA1c was associated with a HR 1.29, 95%CI 0.97, 1.71 of dementia.

Conclusions

Patients with AF with diabetes mellitus experienced higher rates of incident dementia compared to non-diabetics. No obvious difference was observed in the rates of dementia upon classifying the patients using blood glucose, independently of their diabetes status.

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Association of Diabetes Mellitus with Incident Dementia in Patients with Atrial Fibrillation in the Atherosclerosis Risk in Communities Cohort

Introduction

According to the World Health Organization, dementia is defined as a syndrome characterized by the deterioration of memory, thinking, behavior and the ability to perform day to day activities (1). It has been estimated that 5.1 million Americans who are older than 65 years of age have Alzheimer's disease, which is considered to be the most common form of dementia, and it has been projected that these numbers may rise to 13.2 million by 2050 (2).

Diabetes mellitus is a major lifestyle-associated chronic disease which is approaching enormous proportions globally. The International Diabetes Federation has estimated that the prevalence of diabetes mellitus is projected to increase from 8.0% to 15.3% by 2025, with the number of people with diabetes worldwide likely to increase from 246 million to 380 million by 2025 (3).

Studies have demonstrated that cardiovascular disorders like atrial fibrillation (AF), which is the most common arrhythmia, are associated with increased risk of dementia even in the absence of associated stroke (4). While studies have been conducted demonstrating the association between midlife cardiovascular risk factors like AF and diabetes with the development of dementia later in life (5), we do not have sufficient evidence to define the role of diabetes mellitus as a risk factor for dementia in patients with AF. Understanding this relationship is important because people with AF are particularly vulnerable to the development of dementia due to their increased risk for irregularities in blood supply to the brain (6-8).

To address these research gaps, we evaluated the association of diabetes and glycemic control markers with the incidence of dementia among individuals newly diagnosed with AF in a community-based cohort study.

Methods

Study population

The study population for this analysis was selected from the Atherosclerosis Risk in Communities Study (ARIC) cohort. ARIC is a prospective cohort study being conducted in 4 US communities, including Forsyth County, NC, Jackson, MS, Minneapolis suburbs, MN, and Washington County, MD. The study recruited 15,792 men and women aged 45 to 64 years of age at baseline in 1987-89. The ARIC study has collected information on the participants medical, social and demographic data as well as information on major cardiovascular events, including AF, heart failure, coronary heart disease, and stroke.

We restricted our analyses to participants who developed incident AF during follow up through 2017 or the latest available year. AF was ascertained in this cohort through 3 main sources: study ECGs, hospital discharge codes, and death certificates. ECGs were performed during the study examinations using MAC PC personal cardiographs where a standard supine 12 lead resting ECG was performed after 12-hour test followed by a light snack and at least 1 hour after smoking tobacco or ingestion of caffeine. These ECGs were at first processed in a central lab at the EPICORE center (University of Alberta, Canada) followed by the EPICARE center (Wake Forest University, Winston-Salem, NC). Visual inspection of the ECGs was performed to assess the quality and look for technical errors (9). In addition, trained abstractors obtained and recorded all hospital discharge diagnosis using ICD 9 CM or ICD 10 CM codes. AF was defined

as ICD 9 CM codes 427.31 or 427.32 and, starting in October 2015, ICD 10 CM codes I48.x, not occurring in the context of open-heart surgery. Finally, the study participants were also labelled as AF patients if the causes of death included AF (ICD 9 code 427.3 or ICD 10 code I48). However, participants identified through this method were not included in the analysis due to lack of follow-up. Our analysis excluded Asians and Native Americans due to their relatively small sample size. In addition, non-whites from Minneapolis and Washington County were also excluded due to very small numbers. Participants with prevalent dementia at the time of AF diagnosis have been excluded from our study. Hence, the baseline population for our study consists of a total of 3,020 participants with AF.

Prevalent Diabetes, Fasting Blood Glucose and Hemoglobin A1C.

The primary exposure of interest is prevalent diabetes mellitus (yes/no) at the time of AF diagnosis. Diabetes was defined in all visits as fasting blood glucose levels ≥126 mg/dl, non-fasting blood glucose levels >=200 mg/dl, self-reported physician diagnosis of diabetes or self-reported use of antidiabetic medications.

For secondary analyses, we considered fasting blood glucose concentrations measured at all study visits and hemoglobin A1c measured at visits 2 (1990-92) and 5 (2011-13) as additional exposures. Serum glucose in the ARIC cohort was measured using the hexokinase method (10). HbA1c was measured in whole blood samples maintained at -80 Celsius using high-performance liquid chromatography using instruments that were standardized to the Diabetes Control and Complications Trial assay (10). We used most recent values of fasting blood glucose and hemoglobin A1c prior to AF diagnosis for the analysis.

Outcome

The primary outcome of interest was incident dementia defined according to standard ARIC procedures (11). There were different approaches used to ascertain dementia. First, ARIC participants taking part in Visits 5 and 6 (2011-2013, 2016-2017) underwent a detailed assessment of neurocognitive functions (12). A subset of these participants was selected to receive a neurological examination and an MRI of the brain. Second, a validated phone-based cognitive assessment, the modified version of the Telephone Interview for Cognitive Status (TICSm), was administered to participants who at the time of Visit 5 were alive but unable or unwilling to participate in an in-person examination. In instances where the participants were deceased or unable to complete the TICSm by themselves, informants provided additional information. Finally, in the full cohort hospitalization codes were used to identify incident dementia occurring from Visit 1 to end of Visit 6. For our analysis, we considered cases of dementia identified through any of these sources. The date of dementia diagnosis was defined depending on the source of dementia diagnosis. In participants who were identified via in-person cognitive evaluations, the date of assessment was used as the date of dementia diagnosis, with an exception of using the hospitalization dates in those with a prior dementia hospitalization. The earliest date from TICSm, informant interview, hospitalization discharge or hospitalization discharge, as applicable, was used for study participants with dementia diagnosis from other sources (5). In study participants who were never diagnosed with dementia, the earliest of the date of visit 6 examination, date of loss to follow-up, or the date of death was used to calculate the follow up time.

Covariates

The covariates used in our analysis included participant demographics, comorbidities as well as the use of certain medications. The demographic information included self-reported age, sex, race (white or black), visit center (Forsyth County, Jackson, Minneapolis suburbs, Washington County), education level (low, medium or high), and smoking and drinker status (current, former, never, missing). The age of the participants was defined at the time of AF diagnosis. Because visit center and the race of participants were correlated, we categorized participants jointly by race and center (whites from Forsyth county, whites from Minneapolis, whites from Washington county, blacks from Forsyth county, and blacks from Jackson).

Incident heart failure was defined as the occurrence of a hospitalization including an ICD 9 CM discharge code of 428.x or using a death certificate with a ICD 9 code of 428 or ICD 10 I50 (13). Incident definite or probable stroke was defined by physician adjudication using eligible hospitalization records, i.e. those with a discharge diagnosis code of ICD 9-CM (codes 430 to 438) and/or if one of the following words were listed in the discharge document: stroke, transient ischemic attack, cerebrovascular disease, cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, cerebral embolus, paralysis, aphasia, diplopia, lacunar infarction, dysarthria, cerebral angiography, carotid or endarterectomy (14). Incident myocardial infarction was defined based on information available on the presence of chest pain, electrocardiogram evidence and biomarker findings which were collected from the hospital records of the study participants. A computer-based algorithm was then used to classify it into Definite MI, Probable MI, Suspect MI and No MI (15). Other comorbidities included were hypercholesterolemia and hypertension, including the use of hypertension lowering medications, as well as use of anticoagulants, statins and aspirin. Total cholesterol was measured at all 6 visits using standard

procedures. The use of hypertension lowering medications, anticoagulants, statins and aspirin were ascertained by self-report at all 6 visits. Systolic and diastolic blood pressure was measured three times, and the mean of the second and third measurements were used for analysis. The APOE genotype, which is a known risk factor for dementia, especially Alzheimer's dementia, was also included in our analysis. Genotyping for APOE polymorphisms in ARIC cohort were performed using the TaqMan assay, where variants on the codons 130 and 176 were assayed separately. The data obtained from these codons were then combined to generate the 6 APOE genotypes, as follows: 22, 23, 33 (used as reference), 24, 34 and 44 (16).

Statistical Analysis

SAS 9.4 and STATA 16.1 were used for statistical analysis. Diabetes status (exposed vs unexposed) in study participants was defined with respect to the date of diagnosis of AF. Baseline characteristics of the study participants with AF were reported stratified by diabetes status. Means and standard deviations were calculated for continuous variables, and frequencies and percentages for categorical variables. Time to event was calculated as the time from diagnosis of AF to time of dementia diagnosis or censoring (death, lost to follow-up, visit 6 date). We calculated incidence rates of dementia diagnosis in diabetics (exposed) and non-diabetics (unexposed). These incidence rates were then used to calculate the incidence rate ratio (non-diabetics as the reference). Cumulative incidence function curves were generated for the association between diabetes and dementia, both before and after accounting for the competing risk of death.

We assessed the association between diabetes diagnosis and incidence of dementia amongst ARIC participants with AF using Cox proportional hazards models to calculate hazard

ratios (HRs) and 95% confidence intervals (CIs). In Model 1 we adjusted for key demographics (age, sex and race/center). In model 2 we additionally adjusted for smoking, drinking, anticoagulant use, aspirin use, antihypertensive use, statin use, CHD, myocardial infarction, stroke, prevalent heart failure, BMI, total cholesterol, systolic blood pressure, diastolic blood pressure and APOE genotype. Effect measure modification by age (categorical), sex (male and female) and race of the association between diabetes and dementia diagnosis was assessed after adjusting for other covariates in model 2. We repeated the analysis using a Fine and Gray subdistribution(17) hazard model considering death as a competing risk and calculating subdistribution HR (SHR) and their 95% Cis (17).

Secondary analysis was performed using glucose tertile cut points as the exposure of interest. These cut points were created separately in both diabetics and non-diabetics and the lowest tertile among non-diabetics were used as the reference category. We assessed the association between these glucose tertile cut points and diagnosis of dementia using Cox proportional hazards models to calculate the respective HRs and 95% CIs. An additional secondary analysis was performed using HbA1c as the exposure of interest. The exposed vs the unexposed were determined using a HbA1c value of 6.5% as the cut point. People with HbA1c values ≥6.5% were considered to be exposed while those with HbA1c values <6.5% were considered to be unexposed. As with the primary analysis, we performed an initial analysis adjusting for demographic variables (Model 1) followed by a model adjusting for multiple covariates (Model 2). We also explored effect measure modification by age, sex and race/center as described above. In addition to this we performed heterogeneity assessment of the HRs obtained by stratification on age, sex and race (18)

For the purpose of interaction assessment by running stratified Cox models we additionally categorized the variable age using the mean value of age for the entire sample as the cut point (age 74).

Results

Baseline Characteristics

Of the 15,792 participants of the ARIC cohort a total of 3,020 with incident AF and without prevalent dementia at the time of AF diagnosis were included in the final analysis. There was a total of 808 participants diagnosed with diabetes mellitus (27%). The baseline characteristics of the study population has been included in ***Table 1.*** Compared to the non-diabetics where 56% of the sample took anti-hypertensives, 80% of diabetics took anti-hypertensives. The mean BMI of diabetics fall in the obese range (32.4) while that of non-diabetics falls within the range for overweight (28.7). 40.5% of the diabetics have a history of incident heart failure while only 27.7% of non-diabetics have a history of the same. The racial and sex distribution was similar between the two exposure groups with majority of them being whites and equal numbers of males and females.

Incidence Rates

There was a total of 530 people with dementia, of which 137 were diabetic and 393 were non-diabetic. The incidence rate of dementia among diabetics was 4.5 (95%CI 3.7, 5.3) per 1,000 person-years, while it was 3.1 (95%CI 2.8, 3.4) per 1,000 person-years among non-diabetics. The incidence rate ratio thus calculated comparing diabetics to non-diabetics was 1.5 (95%CI 1.2, 1.8) (***Table 2***).

Kaplan Meier curves showing the crude incidence of dementia in diabetics vs non-diabetics demonstrate an increased crude incidence of dementia in diabetics with atrial fibrillation compared with non-diabetics with atrial fibrillation (***Figure 1***). Cumulative incidence function curves were also generated after accounting for the competing risk of death. These curves, however, show the cumulative incidence of dementia in diabetics is not different from that in non-diabetics after accounting for the competing risk of death (***Figure 2).***

Results of the Primary Analysis: Exposure – Diabetes (Yes/No)

Cox proportional hazards regression analysis was carried out to study the association between diabetes mellitus and incident dementia in participants with incident AF (***Table 3***). The hazard of incident dementia among diabetics was found to be 58% (HR 1.58, 95%CI 1.29, 1.93) higher than the hazard of incident dementia among non-diabetics after adjustment for demographic variables. A model adjusting for additional covariates also demonstrated an increased hazard of incident dementia among diabetics compared to non-diabetics with a HR of 1.45 (95%CI 1.16, 1.81) in diabetics compared to non-diabetics.

In a competing risks analysis using a Fine and Gray sub-distribution hazard regression model, after accounting for the competing risk of death, there was no association between diabetes and dementia in patients with atrial fibrillation (SHR = 1.01, 95% CI = 0.82, 1.24, in the base model and SHR = 1.02, 95% CI = 0.81, 1.28, in a multivariable model adjusted for all confounders) (***Table 4*).**

Finally, we assessed effect measure modification by age, gender and race of the study participants, and did not find any evidence of heterogeneity by these variables (***Table 5***).

Results of secondary analysis: Exposure- Fasting Blood glucose (mg/dl)

The baseline model for the secondary analysis was similar to that for the primary analysis adjusting for the basic demographics of age, race/center and gender of the participants. There were 6 levels of fasting blood glucose, 3 of which were defined among the diabetics and the other 3 were defined among the non-diabetics. The lowest category among the non-diabetics with a fasting blood glucose value of <96 mg/dl was considered to be the reference for the Cox models. In the baseline model, the hazard for incident dementia was statistically significantly higher among all diabetics independently of their blood glucose levels. After adjusting for all the additional covariates, there was a statistically significant association between fasting blood glucose and incidence of dementia only among participants who were diabetic with fasting blood glucose <131mg/dl with a HR of 1.74 (1.20, 2.52), with non-significant increased risk in those with diabetes and higher glucose levels (***Table 3***). We did not find evidence of heterogeneity in these associations by age, gender or race (***Table 6***).

Results of secondary analysis: Exposure- HbA1c

Using a cutoff for HbA1c of 6.5%, it was observed that in the baseline model there is a 45% (95%CI 1.12-1.89) increased hazard of incident dementia amongst those with HbA1c values ≥ 6.5% compared to those with HbA1c<6.5%. After adjusting for all other covariates in the baseline model the association was attenuated, with a 29% (95%CI 0.97-1.71) increased hazard of incident dementia amongst those with HbA1c values ≥6.5% (***Table 3***)**.** There was no evidence of effect measure modification in these associations by age, gender or race (***Table 7***).

Discussion

In this analysis of a large community-based cohort, we found that amongst individuals with underlying AF a diagnosis of diabetes mellitus was associated higher rates of incident dementia compared to those who were not diabetic. Further detailed analysis of the effects of levels of fasting blood and long-term blood sugar control on incident dementia demonstrated that fasting blood glucose is not associated with increased rates of dementia independently of diabetes status. These associations were similar amongst whites and African Americans, men and women, and did not vary based on age. The associations persisted even after adjusting for confounders in the baseline model.

Our findings suggest that (1) In general a diagnosis of diabetes mellitus without taking into consideration the blood sugar levels or the HbA1c levels was associated with an increased hazard of dementia in patients with underlying atrial fibrillation after adjusting for all covariates, (2) However upon accounting for the competing risk of death in this population, dementia risk among diabetics was similar to that among non-diabetics.

Growing evidence demonstrates that dementia is a frequent adverse outcome of diabetes. A previous study conducted in the ARIC cohort reported an increased risk of dementia hospitalization in those with diabetes (HR 2.2, 95% CI 1.6, 3.0) (16). Positive associations have also been demonstrated between AF and dementia with a HR of 1.14 (95% CI 1.03, 1.26) (19). These positive associations led us to conduct the above analysis to determine the association between diabetes mellitus and dementia in patients with AF to contribute to a deeper understanding of the risk factors and mechanisms linking AF and dementia.

The main mechanisms through which diabetes mellitus-induced hyperglycemia may lead to dementia include inflammation, mitochondrial dysfunction and oxidative stress (20). These in

turn lead to development of brain insulin resistance (caused by hyperglycemia and hyperinsulinemia) and amyloidogenesis, which contributes to the neuropathological manifestations of impaired neuronal integrity and neurodegeneration eventually causing impaired cognitive functioning (20). These processes eventually result in an overall increased risk of dementia among people with diabetes mellitus. Patients with underlying AF also tend to have an increased risk of dementia and cognitive impairment due to increased stroke risk, cerebral hypoperfusion, vascular inflammation, cerebral small vessel disease and brain atrophy (21). Thus, inflammation is an underlying mechanism for dementia in both diabetes mellitus as well as AF. Hence, being a diabetic with AF can put an individual at an increased risk of developing cognitive impairment and dementia.

Upon conducting a Fine and Gray sub-distribution hazards regression, which accounts for the competing risk of death, we found that diabetes was no longer associated with dementia risk in this sample. This can be attributed to the increased risk of death in persons with diabetes, particularly at older age. Thus, participants with diabetes present an overall cumulative risk of dementia that is lower than if the competing risk of death was not present; this reduction is stronger than in those without diabetes, leading to a SHR close to 1. Given the differences between the HR from the standard Cox proportional hazards model and the SHR from the sub-distribution hazards model, we decided to present both (22). However, the final decision on which model to utilize depends on the aim of the research study. While using the Fine and Gray model with the sub-distribution hazard can be useful in prognostic studies (17), epidemiological cohort studies conducted to identify etiological associations in the presence of competing risk should use the standard Cox proportional hazards model. In this particular case, the results show that diabetes is associated with an increased hazard of dementia but the cumulative risk of

dementia in those with and without diabetes is similar (23). When competing risks are present, the assumption of independence between censoring and the outcome is violated, since individuals censored due to the competing risk are no longer at risk of the outcome. Therefore, in prognostic studies, ignoring the fact that an individual dies before developing the outcome actually overestimates cumulative risk (24). However, etiological studies do not have this requirement of maintaining the assumption of independence for censoring, so that we can obtain valid estimates of the association between diabetes and hazard of dementia (23, 25).

Strengths and Limitations

Some limitations of the present analysis need to be mentioned. First, the information on HbA1c was available only from visits 2 and 5 and hence visit 2 information was used for visits 1, 2, 3 and 4, and Visit 5 information was used for visits 5 and 6. Second, the method used for AF ascertainment in the ARIC cohort, which consisted of utilizing information from study ECGs, hospital discharge codes, and death certificates, may miss out on asymptomatic cases of AF as well as those managed exclusively in outpatient settings. Finally, using hospitalization codes as the sole source of incident dementia diagnosis for participants in which no other information was available posed the risk of having limited sensitivity.

In spite of the limitations mentioned above our study had certain strengths that stood out. The most important strength of this study was the long follow-up period lasting for almost 30 years, from 1987 to 2017. Another major strength of this study was the large sample size with the presence of adequate number of events available to perform the analysis. Data completeness was an additional strength, given the lack of significant missing information on covariates considered and adjusted for (<5%). The availability of repeated measurements of glucose and HbA1c helped us pick the value closest to the time of AF diagnosis and hence helped ascertain

the most recent diabetic status of the study participants with respect to the time of development of AF. This helped define a more accurate exposure status at baseline. Finally, the racial diversity of the study population also stands out as a major strength since previous studies conducted for determining dementia incidence were almost entirely whites of European ancestry (26). This helps us gain a better perspective about whether there are racial differences in the development of incident dementia.

Conclusion

In conclusion, our analysis of this large community-based cohort followed for almost 30 years, spanning a total of 6 in-person visits, provides evidence that a diagnosis of diabetes in people with AF is associated with higher hazard of incident dementia compared to people without diabetes. In addition, the association of diabetes mellitus with dementia was independent of fasting blood glucose levels. This information suggests that prevention of diabetes could lead to reduced rates of dementia in persons with AF and provides support to explore pathophysiologic mechanisms responsible for these elevated rates. Replication of results in independent studies is recommended.

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References

1. Organization WH. Dementia. WHO 19 September, 2019.

2. CDC. Cognitive Impairment: A call for action, now. Report. 2011.

3. Tabish SA. Is Diabetes Becoming the Biggest Epidemic of the Twenty-first Century? Int J Health Sci (Qassim). 2007 Jul;1(2):V-viii. PubMed PMID: 21475425. PMCID: PMC3068646. Epub 2007/07/01. eng.

4. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. Cmaj. 2012 Apr 3;184(6):E329-36. PubMed PMID: 22371515. PMCID: PMC3314061. Epub 2012/03/01. eng.

5. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, et al. Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. JAMA Neurol. 2017 Oct 1;74(10):1246-54. PubMed PMID: 28783817. PMCID: PMC5710244. Epub 2017/08/08. eng.

6. Alonso A, Knopman DS, Gottesman RF, Soliman EZ, Shah AJ, O'Neal WT, et al. Correlates of Dementia and Mild Cognitive Impairment in Patients With Atrial Fibrillation: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). J Am Heart Assoc. 2017 Jul 24;6(7). PubMed PMID: 28739861. PMCID: PMC5586306. Epub 2017/07/26. eng.

7. Chen LY, Norby FL, Gottesman RF, Mosley TH, Soliman EZ, Agarwal SK, et al. Association of Atrial Fibrillation With Cognitive Decline and Dementia Over 20 Years: The ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). J Am Heart Assoc. 2018 Mar 7;7(6). PubMed PMID: 29514809. PMCID: PMC5907543. Epub 2018/03/09. eng.

8. Alonso A, Arenas de Larriva AP. Atrial Fibrillation, Cognitive Decline And Dementia. Eur Cardiol. 2016 Summer;11(1):49-53. PubMed PMID: 27547248. PMCID: PMC4988519. Epub 2016/08/23. eng.

9. Soliman EZ, Prineas RJ, Case LD, Zhang ZM, Goff DC, Jr. Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2009 Apr;40(4):1204-11. PubMed PMID: 19213946. PMCID: PMC2685189. Epub 2009/02/14. eng.

10. Ding N, Kwak L, Ballew SH, Jaar B, Hoogeveen RC, Ballantyne CM, et al. Traditional and nontraditional glycemic markers and risk of peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis. 2018 Jul;274:86-93. PubMed PMID: 29753232. PMCID: PMC5999570. Epub 2018/05/13. eng.

11. Knopman DS, Gottesman RF, Sharrett AR, Wruck LM, Windham BG, Coker L, et al. Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Alzheimers Dement (Amst). 2016;2:1-11. PubMed PMID: 26949733. PMCID: PMC4772876. Epub 2016/03/08. eng.

12. Lutsey PL, Chen N, Mirabelli MC, Lakshminarayan K, Knopman DS, Vossel KA, et al. Impaired Lung Function, Lung Disease and Risk of Incident Dementia. Am J Respir Crit Care Med. 2018 Nov 15. PubMed PMID: 30433810. Epub 2018/11/16. eng.

13. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol. 2008 Apr 1;101(7):1016-22. PubMed PMID: 18359324. Epub 2008/03/25. eng.

14. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the

Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1999 Apr;30(4):736-43. PubMed PMID: 10187871. Epub 1999/04/03. eng.

15. Bush M, Sturmer T, Stearns SC, Simpson RJ, Jr., Brookhart MA, Rosamond W, et al. Position matters: Validation of medicare hospital claims for myocardial infarction against medical record review in the atherosclerosis risk in communities study. Pharmacoepidemiol Drug Saf. 2018 Oct;27(10):1085-91. PubMed PMID: 29405474. PMCID: PMC6233317. Epub 2018/02/07. eng.

16. Alonso A, Mosley TH, Jr., Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. J Neurol Neurosurg Psychiatry. 2009 Nov;80(11):1194-201. PubMed PMID: 19692426. PMCID: PMC2783764. Epub 2009/08/21. eng.

17. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999 1999/06/01;94(446):496-509.

18. Kaufman JS, MacLehose RF. Which of these things is not like the others? Cancer. 2013;119(24):4216-22.

19. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, et al. Atrial fibrillation and the risk of incident dementia: a meta-analysis. Heart Rhythm. 2012 Nov;9(11):1761-8. PubMed PMID: 22863685. Epub 2012/08/07. eng.

20. Lee HJ, Seo HI, Cha HY, Yang YJ, Kwon SH, Yang SJ. Diabetes and Alzheimer's Disease: Mechanisms and Nutritional Aspects. Clinical nutrition research. 2018;7(4):229-40. PubMed PMID: 30406052. Epub 2018/10/23. eng.

21. Aldrugh S, Sardana M, Henninger N, Saczynski JS, McManus DD. Atrial fibrillation, cognition and dementia: A review. Journal of cardiovascular electrophysiology. 2017;28(8):958-65. PubMed PMID: 28569383. Epub 2017/06/21. eng.

22. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601-9. PubMed PMID: 26858290. PMCID: PMC4741409. Epub 2016/02/10. eng.

23. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol. 2009 Jul 15;170(2):244-56. PubMed PMID: 19494242. PMCID: PMC2732996. Epub 2009/06/06. eng.

24. Wolters FJ, Rizopoulos D, Ikram MA. Dementia and death: Separate sides of the atrial fibrillation coin? Int J Cardiol. 2017 Jan 15;227:189. PubMed PMID: 27894741. Epub 2016/11/30. eng.

25. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol. 2012 Jun;41(3):861-70. PubMed PMID: 22253319. PMCID: PMC3396320. Epub 2012/01/19. eng.

26. Satizabal C, Beiser AS, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med. 2016 Jul 7;375(1):93-4. PubMed PMID: 27406362. PMCID: PMC6374770. Epub 2016/07/15. eng.

Figure Legends

Figure 1: Cumulative incidence of dementia in atrial fibrillation patients by diabetes status, Kaplan-Meier Estimates, ARIC 1987-2017

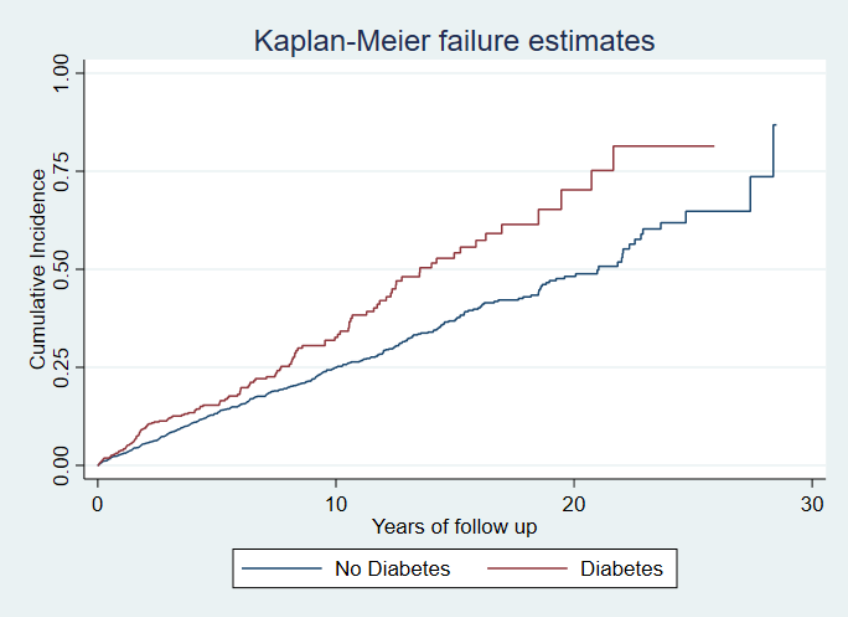
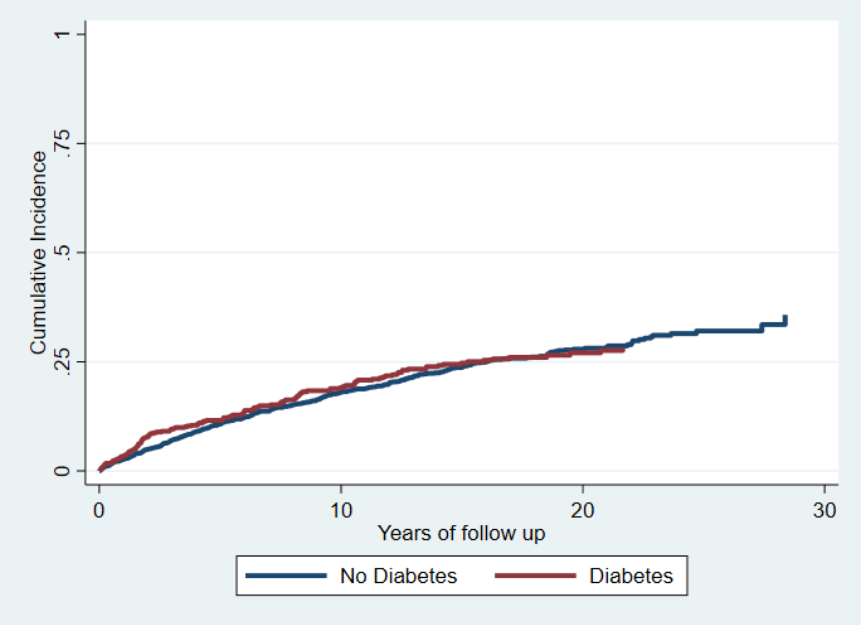


Figure 2: Cumulative incidence of dementia in atrial fibrillation patients by diabetes status accounting for competing risk of death, ARIC 1987-2017



Tables

Table 1: Baseline Characteristics of Patients with Atrial Fibrillation according to their Diabetes Status, ARIC 1987-2017

VARIABLE, N= 3020	Diabetes, N=808	No diabetes, N=2212
	MEAN(SD) OR FREQUENCY(%)	
AGE (years)	73.3(8.2)	73.8(8.2)
GENDER		
Male	407(50.4%)	1151(52.0%)
Female	401(49.6%)	1061(48.0%)
RACE		
Black	212(26.7%)	316(14.3%)
White	596(73.8%)	1896(85.7%)
EDUCATION LEVEL 02		
None of the mentioned categories	4(0.5%)	1(0.1%)
Basic Education or 0 Years Education	253(31.3%)	504(22.8%)
Intermediate Education	333(41.2%)	932(42.1%)
Advanced Education	218(27.0%)	775(35.0%)
SMOKING		
Current smoker	128(15.8%)	431(19.5%)
Former smoker	388(48.0%)	1006(45.5%)
Never smoker	273(33.8%)	742(33.5%)
Unknown	19(2.4%)	33(1.5%)
DRINKING STATUS		
Current drinker	302(37.4%)	1164(52.6%)
Former drinker	302(37.4%)	636(28.8%)
Never drinker	204(25.3%)	411(18.6%)
Unknown	0(0%)	1(0.1%)
ASPIRIN USE		
Yes	522(64.6%)	1390(62.8%)
No	286(35.4%)	822(37.2%)
ANTIHYPERTENSIVE USE		
Yes	645(79.8%)	1245(56.3%)
No	163(20.2%)	967(43.7%)
ANTICOAGULANT USE		
Yes	49(6.1%)	113(5.1%)
No	759(93.9%)	2099(94.9%)
STATIN USE		
Yes	237(29.3%)	394(17.8%)
No	571(70.7%)	1818(82.2%)
TOTAL CHOLESTEROL (mmol/L)	5.03(1.2)	5.08(1.0)

BODY MASS INDEX (kg/m2)	32.4(6.3)	28.7(5.9)
SYSTOLIC BLOOD PRESSURE (mmHg)	134.3(22.5)	130.6(20.9)
DIASTOLIC BLOOD PRESSURE (mmHg)	69.0(12.2)	70.7(11.8)
HISTORY OF MYOCARDIAL INFARCTION		
Yes	176(21.8%)	265(12.0%)
No	637(78.2%)	1947(88.0%)
PREVALENT CHD		
Yes	205(25.4%)	329(14.9%)
No	603(74.6%)	1883(85.1%)
PREVALENT STROKE		
Yes	42(5.2%)	73(3.3%)
No	766(94.8%)	2139(96.7%)
PREVALENT HEART FAILURE		
Yes	327(40.5%)	613(27.7%)
No	481(59.5%)	1599(72.3%)

Table 2: Incidence rates and incidence rate ratios of dementia by diabetes status among participants with AF, ARIC 1987-2017

N	**Diabetes**	**No diabetes**
Incident dementia, n	137	393
Person-years	3,075	12,768
Incidence rate (95%CI)*	4.5 (3.7, 5.3)	3.1 (2.8, 3.4)
Incidence rate ratio (95%CI)	1.45 (1.19, 1.76)	1 (ref.)

* Per 100 person-years

Table 3: Hazard Ratios and 95% confidence intervals of incident dementia for the three different exposures: Diabetes (Primary Analysis), Blood Glucose Levels (Secondary Analysis), HbA1c levels (Secondary Analysis), ARIC 1987-2017

PRIMARY ANALYSIS			
DIABETES	**HR**	**95% CI**	**P VALUE**
MODEL 1	1.58	1.29, 1.93	<0.0001
MODEL 2	1.45	1.16, 1.81	0.0009
SECONDARY ANALYSIS: GLUCOSE LEVELS			
MODEL 1:			
GLUCOSE LEVELS	**HR**	**95% CI**	**P VALUE**
0(<96mg/dl & D=0)	Reference	Reference	Reference
1(96 to <105 mg/dl & D=0	1.02	0.8, 1.31	0.86
2(≥105 mg/dl & D=0)	1.05	0.81, 1.35	0.72
3(<131 mg/dl & D=1)	1.99	1.42, 2.79	<0.0001
4(131 to <171 mg/dl & D=1)	1.41	1.01, 1.96	0.04
5(≥171 mg/dl & D=1)	1.54	1.05, 2.27	0.03
MODEL 2			
1(96 to <105 mg/dl & D=0	0.99	0.77, 1.29	0.95
2(≥105 mg/dl & D=0)	0.97	0.74, 1.27	0.83
3(<131 mg/dl & D=1)	1.74	1.20, 2.52	0.004
4(131 to <171 mg/dl & D=1)	1.30	0.91, 1.86	0.15
5(≥171 mg/dl & D=1)	1.31	0.87, 1.97	0.20
SECONDARY ANALYSIS: HBA1C			
HBA1C (≥6.5% vs. <6.5%)	**HR**	**95% CI**	**P VALUE**
MODEL 1	1.45	1.12, 1.89	0.005
MODEL 2	1.29	0.97, 1.71	0.08

* Model 1: Adjusted for age, gender and race
^ Model 2: Additionally, adjusted for Education, smoking status, drinking status, Total Cholesterol, Body Mass Index, Systolic blood pressure, Diastolic blood pressure, H/O of Myocardial infarction, Prevalent CHD, Prevalent Stroke, Incident Heart Failure, Incident Stroke, Antihypertensive use, Anticoagulant use, Statin use and APOE genotype

Table 4: Side by side comparison of the Cox proportional hazards model with the Sub-distributional hazard's regression model (Primary Analysis: Exposure Diabetes), ARIC 1987-2017

Cox proportional hazards model			
DIABETES	**HR**	**95% CI**	**P VALUE**
MODEL 1	1.58	1.29, 1.93	<0.0001
MODEL 2	1.45	1.16, 1.81	0.0009
Fine Gray sub distribution hazard model			
DIABETES	**SHR**	**95% CI**	**P VALUE**
MODEL 1	1.01	0.82, 1.24	0.91
MODEL 2	1.02	0.81, 1.28	0.86

* Model 1: Adjusted for age, gender and race
^ Model 2: Additionally, adjusted for comorbidities, medications and APOE2 levels

Table 5: Assessment of Effect Measure Modification by Age, Sex and Race of the Study Participants (Primary Analysis: Exposure Diabetes), ARIC 1987-2017

PRIMARY ANALYSIS: DIABETES			
DIABETES	**HR**	**95% CI**	**P VALUE ***
Age < 73.6	1.44	1.00, 2.08	
Age ≥ 73.6	1.21	0.91, 1.61	0.46
Females	1.50	1.08, 2.07	
Males	1.34	0.97, 1.85	0.64
Blacks/African Americans	1.09	0.69, 1.74	
Whites	1.57	1.22, 2.02	0.14

* This p value corresponds to the null hypothesis of no effect measure modification between the exposure and the modifier.

Table 6: Assessment of Effect Measure Modification by Age, Sex and Race of the Study Participants (Secondary Analysis: Exposure Glucose Levels), ARIC 1987-2017

SECONDARY ANALYSIS: GLUCOSE LEVELS			
GLUCOSE LEVELS	**HR**	**95% CI**	**P VALUE ***
Age < 73.6			
1(96 to <105 mg/dl & D=0	0.94	0.61, 1.44	
2(≥105 mg/dl & D=0)	0.90	0.57, 1.41	
3(<131 mg/dl & D=1)	1.82	0.96, 3.44	
4(131 to <171 mg/dl & D=1)	1.52	0.85, 2.73	
5(≥171 mg/dl & D=1)	0.96	0.51, 1.83	
Age ≥ 73.6			
1(96 to <105 mg/dl & D=0	0.82	0.59, 1.14	
2(≥105 mg/dl & D=0)	0.90	0.63, 1.28	
3(<131 mg/dl & D=1)	1.34	0.84, 2.12	
4(131 to <171 mg/dl & D=1)	1.06	0.67, 1.67	
5(≥171 mg/dl & D=1)	0.81	0.46, 1.42	0.38
Females			
1(96 to <105 mg/dl & D=0	1.07	0.75, 1.52	
2(≥105 mg/dl & D=0)	0.80	0.53, 1.19	
3(<131 mg/dl & D=1)	1.92	1.13, 3.27	
4(131 to <171 mg/dl & D=1)	1.26	0.73, 2.17	
5(≥171 mg/dl & D=1)	1.20	0.69, 2.10	
Males			
1(96 to <105 mg/dl & D=0	0.87	0.58, 1.30	
2(≥105 mg/dl & D=0)	1.12	0.76, 1.65	
3(<131 mg/dl & D=1)	1.59	0.91, 2.80	
4(131 to <171 mg/dl & D=1)	1.23	0.74, 2.04	
5(≥171 mg/dl & D=1)	1.26	0.67, 2.37	0.4
Blacks/African Americans			
1(96 to <105 mg/dl & D=0	1.16	0.61, 2.20	
2(≥105 mg/dl & D=0)	0.83	0.43, 1.61	
3(<131 mg/dl & D=1)	1.86	0.81, 4.23	
4(131 to <171 mg/dl & D=1)	0.79	0.35, 1.77	
5(≥171 mg/dl & D=1)	0.94	0.40, 2.23	
Whites			
1(96 to <105 mg/dl & D=0	0.98	0.74, 1.31	
2(≥105 mg/dl & D=0)	1.00	0.74, 1.35	
3(<131 mg/dl & D=1)	1.64	1.07, 2.52	
4(131 to <171 mg/dl & D=1)	1.53	1.03, 2.29	
5(≥171 mg/dl & D=1)	1.51	0.94, 2.41	0.51

Table 7: Assessment of Effect Measure Modification by Age, Sex and Race of the Study Participants (Secondary Analysis: Exposure HbA1C), ARIC 1987-2017

SECONDARY ANALYSIS: HBA1C			
HBA1C	**HR**	**95% CI**	**P VALUE ***
Age < 73.6	1.07	0.67, 1.71	
Age ≥ 73.6	1.08	0.75, 1.56	0.98
Females	1.29	0.87, 1.92	
Males	1.26	0.83, 1.93	0.94
Blacks/African Americans	1.01	0.60, 1.72	
Whites	1.44	1.02, 2.02	0.22

* This p value corresponds to the null hypothesis of no effect measure modification between the exposure and the modifier.