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Diabetes, prediabetes, and atrial fibrillation—A population-based cohort study based on national and regional registers

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Background. Previous studies have shown an increased risk for atrial fibrillation and atrial flutter (AF) in people with type 2 diabetes and prediabetes. It is unclear whether this increase in AF risk is independent of other risk factors for AF.

Objective. To investigate the association between diabetes and different prediabetic states, as independent risk factors for the onset of AF.

Methods. We performed a population-based cohort study in Northern Sweden, including data on fasting plasma glucose, oral glucose tolerance test, major cardiovascular risk factors, medical history, and lifestyle factors. Participants were divided into six groups depending on glycemic status and followed through national registers for AF diagnosis. Cox proportional hazard model was used to assess the association between glycemic status and AF, using normoglycemia as reference.

Results. The cohort consisted of 88,889 participants who underwent a total of 139,661 health examinations. In the model adjusted for age and sex, there was a significant association between glycemic status and development of AF in all groups except the impaired glucose tolerance group, with the strongest association for the group with known diabetes (p-value <0.001). In a model adjusted for sex, age, systolic blood pressure, body mass index, antihypertensive drugs, cholesterol, alcohol, smoking, education level, marital status, and physical activity, there was no significant association between glycemic status and AF.

Conclusions/interpretation. The association between glycemic status and AF disappears upon adjustment for potential confounders. Diabetes and prediabetes do not appear to be independent risk factors for AF.

Keywords: atrial fibrillation, diabetes, glucose, oral glucose tolerance test, prediabetes

Introduction

Atrial fibrillation and atrial flutter (AF) are the most common cardiac arrythmias requiring treatment [1] and are associated with four-to-five times increased risk for ischemic stroke [2]. The prevalence of AF in Sweden is almost 3% [3, 4]. The incidence increases sharply with age; at the age of 75 years, the prevalence of AF is 12% [5] and 27.5 per 1000 person-years in persons aged 80 years or more [6]. Important risk factors for developing AF are hypertension, ischemic heart disease, atrial volume, and high body mass index (BMI) [7–9].

Worldwide, impaired fasting glucose (IFG) is the third largest risk factor for death after hypertension and smoking [10]. IFG, together with impaired glucose tolerance (IGT) during an oral glucose tolerance test (OGTT), and elevated levels of glycated hemoglobin A1c (HbA1c) not fulfilling the criteria for diabetes, are sometimes collectively referred to as prediabetes [11]. Previous studies have shown

that people with type 2 diabetes (T2D) have two-to-four times increased risk of cardiovascular events compared to the population as a whole [12].

An association between T2D and AF has been suggested [13], but the putative relationship between prediabetes and risk of AF is less well studied. A meta-analysis published in 2018 showed that diabetes was associated with a 28% increased risk of developing AF and that prediabetes was associated with a 20% increased risk of developing AF [14]. However, it is not clear whether hyperglycemia is an independent risk factor for AF, or whether the increased risk seen in people with diabetes and prediabetes is mediated through other cardiovascular risk factors and possibly coronary artery disease. It is important to note that the meta-analysis from 2018 includes different study designs, and many of the studies did not assess hyperglycemia as the primary exposure, but only as a covariate.

Our aim was to investigate if there is an independent association between diabetes, different components of prediabetes, and the onset of AF, adjusted for all major AF risk factors.

Methods

We created a cohort study, linking data from the Västerbotten Intervention Programme (VIP) to the Swedish National Patient Register through the unique personal identification number given to all Swedish residents.

VIP invites 40-, 50-, and 60-year-olds in Västerbotten County to a health examination to increase the awareness of lifestyle factors influencing the risk of cardiovascular disease [15]. The participation rate has increased over the years, from 56% in 1995 to 73% in 2011 [16].

The Swedish National Patient Register includes International Classification of Diseases (ICD) codes for all admissions to inpatient care from 1987 and specialist outpatient care from 2001 [17]. A previous study in the county of Västerbotten found that the Swedish National Patient Register included 93.2% of all AF cases in a population of 75,000 individuals [4]. Information about death was collected from the National Cause of Death Register, and information about migration was collected from the Swedish Tax Agency.

For this study, participants in VIP between January 1, 1988, and September 5, 2014, were included. Participants who had a diagnosis of AF or a history of myocardial infarction at baseline were excluded; prediabetes is a well-established risk factor for ischemic heart disease [18], which in turn increases the risk of AF [19]. A total of 23 people got the AF diagnosis on the same date as their health examination and were therefore not included in the analysis.

Measurements and definitions

Fasting plasma glucose (FPG) was analyzed after a minimum of 8 h of fasting. An OGTT was performed, using a 75 g oral glucose load. The FPG and the OGTT 2-h post-load plasma glucose (2HPG) were capillary samples. The WHO definition of IFG and IGT was used [20]. IFG was defined as FPG between 6.1 and 6.9 mmol/L, and IGT was defined as 2-h plasma glucose between 8.9 and 12.1 mmol/L. Previously unknown diabetes was defined as FPG $\geq$7.0 mmol/L, or a 2-h oral glucose tolerance plasma glucose of $\geq$12.2 mmol/L without previously diagnosed diabetes. Known diabetes was defined as self-reported diabetes or self-reported treatment with antidiabetics.

BMI (measured in kg/m^2) was calculated after measuring height and weight in light clothing and without shoes. It was classified as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obesity ($\geq$30 kg/m^2). Hypertension was defined as systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or as self-reported use of antihypertensive medication during the last 2 weeks. Blood pressure was measured after a minimum of 5 min of rest.

History of myocardial infarction, smoking habits, educational level, physical activity, and marital status was collected from a questionnaire. Alcohol habits were assessed using the CAGE questions (cut down, annoyance, guilt, eye-opener) and analyzed as a number of positive answers [21]. Smoking was classified as smoker, previous smoker, or never smoker. Previous smoking was not defined according to any time criterion in the questionnaire but was based on how the participants defined themselves. Marital status was defined as unmarried, married/living with partner, divorced/separated, or widow/widower. Educational level was divided into four categories: primary school, lower secondary school, upper secondary school, or university degree. Physical

activity was categorized as inactive, moderately inactive, moderately active, or active, based on the Cambridge index, a validated instrument used to assess physical activity both at work and during leisure time [22].

Statistical analyses

Baseline characteristics were presented stratified for glycemic status and described as means and standard deviations for continuous variables, and numbers and proportions for categorical variables. We performed a complete-case analysis.

Cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between glycemic status, categorized as normoglycemic, IFG, IGT, IFG in combination with IGT, previously unknown diabetes, and known diabetes, according to the definitions above, and AF diagnosis. Time at risk was calculated from the date of participation in VIP until the date of event, death, moving from Västerbotten county, or the end of the study, September 5, 2014, whichever came first. An event was defined as the first occasion with a diagnosis of AF (ICD-10 code I48 or ICD-9 code 427.3). Model 1 was adjusted for sex and age. Model 2 was adjusted for sex, age, and BMI. Model 3 was adjusted for sex, age, BMI, and systolic blood pressure. Model 4 was adjusted for the covariates in model 3 as well as the use of antihypertensive drugs, total cholesterol, alcohol, smoking, education level, marital status, and physical activity. Systolic blood pressure, total cholesterol, BMI, and age were handled as continuous variables, and sex, alcohol, smoking, educational level, marital status, and physical activity were handled as categorical variables. Some covariates in this study may be both confounders and mediators. This is particularly true for blood pressure, which is often elevated in people with diabetes and prediabetes, although the causal direction of the association has not been established. We refrained from a formal mediation analysis due to the complexity of interrelated data. Each participation in VIP was entered as one recording in the analysis. One participant could thus have several observations in the analysis, which was accounted for using a robust variance estimator [23]. Analyses were also performed stratified for age, sex, BMI, and systolic blood pressure. We have chosen to stratify for this as they are known and easily accessible risk factors for diabetes and AF, and the limits are chosen to be clinically well established but also to obtain reasonably equal-sized groups [24].

Sensitivity analyses, including data from each participant's most recent health examination, were performed in which the association between glycemic status and risk of AF was analyzed with Cox proportional hazards regression. A further sensitivity analysis was performed, analyzing FPG and 2HPG as continuous variables and their association with risk of AF. We also performed a sensitivity analysis regarding the association between prediabetes and diabetes (with normoglycemia as reference category) and the risk of AF. Prediabetes was defined as IFG, IGT, or IFG + IGT. Diabetes was defined as previously unknown diabetes or known diabetes. We performed a further sensitivity analysis regarding the association between prediabetes and diabetes, and the risk of AF, including participants with a previous myocardial infarction (in contrast to the main analysis where participants with a previous myocardial infarction had been excluded). These sensitivity analyses were successively adjusted for variables in models 1–4 as described above, and with the year of health examination as an additional adjustment variable.

The participants in VIP that donated blood for future research provided written consent, and all participants were informed that their health data is collected in a database and that it may be used for future research. They were given the option to be removed from the database. The study was approved by the Regional Ethics Review Board, Umeå, Sweden (approval number 2015-50-31 M).

The descriptive statistics and Cox regression sensitivity analyses were calculated using IBM SPSS statistics for Macintosh, Versions 27.0.1.0 and 28.0.1.1 (IBM Corp). The main Cox regression analyses were performed using Stata 16 MP (Stata Corporation).

Results

Overall, 139,661 observations from 88,889 unique individuals were included in the analyses (Table 1 and Fig 1). Baseline data based on exposure is presented in Table 1, and baseline data based on outcome is presented in Table S1. Overall, 51.8% of the included observations were from female participants and the mean age at health examination was 49 years (SD 8.9). The proportion of participants with missing data was low (Table 1).

Table 1. *Baseline characteristics of the study population.*

	Total	Normoglycemia	IFG	IGT	IFG + IGT	Previously unknown diabetes	Known diabetes	Missing, no (%)
Observations, no (%)	139,661	111,964 (80.2)	13,290 (9.5)	5306 (3.8)	2656 (1.9)	3808 (2.7)	2637 (1.9)	
Unique participants, no (%)	88,889	73,452 (82.6)	7462 (8.4)	2970 (3.3)	1387 (1.6)	2195 (2.5)	1423 (1.6)	
Age (years), mean (SD)	49.0 (8.9)	48.1 (8.9)	51.0 (8.1)	53.2 (7.8)	54.1 (7.3)	54.1 (7.4)	54.5 (7.5)	
Sex, no (%)								
Male	67,327 (48.2)	53,161 (47.5)	7220 (54.3)	2024 (38.1)	1252 (47.1)	2129 (55.9)	1530 (58.0)	
Female	72,334 (51.8)	58,782 (52.5)	6070 (45.7)	3282 (61.9)	1404 (52.9)	1679 (44.1)	1107 (42.0)	
Alcohol use habits, no (%)								2789 (2.0)
CAGE 0	113,614 (81.3)	91,020 (81.3)	10,658 (80.2)	4466 (84.2)	2208 (83.1)	3079 (80.9)	2183 (82.8)	
CAGE 1	13,965 (10.0)	11,343 (10.1)	1387 (10.4)	433 (8.2)	224 (8.4)	346 (9.1)	232 (8.8)	
CAGE 2	7105 (5.1)	5762 (5.1)	720 (5.4)	208 (3.9)	126 (4.7)	185 (4.9)	104 (3.9)	
CAGE 3	1641 (1.2)	1250 (1.1)	192 (1.4)	55 (1.0)	31 (1.2)	69 (1.8)	44 (1.7)	
CAGE 4	547 (0.4)	419 (0.4)	61 (0.5)	20 (0.4)	10 (0.4)	26 (0.7)	11 (0.4)	
BMI (kg/m^2), no (%)								281 (0.2)
Underweight (<18.5)	945 (0.7)	833 (0.7)	55 (0.4)	25 (0.5)	7 (0.3)	20 (0.5)	5 (0.2)	
Normal weight 18.5–24.9	60,697 (43.5)	53,094 (47.4)	4326 (32.6)	1589 (29.9)	502 (18.9)	674 (17.7)	512 (19.4)	
Overweight 25.0–29.9	55,863 (40.0)	43,912 (39.2)	5952 (44.8)	2327 (43.9)	1148 (43.2)	1497 (39.3)	1027 (38.9)	
Obese ≥30	21,875 (15.7)	13,915 (12.4)	2933 (22.1)	1349 (25.4)	993 (37.4)	1602 (42.1)	1083 (41.1)	
Hypertension, no (%)								3402 (2.4)
No	98,900 (70.8)	84,134 (75.1)	8654 (65.1)	2675 (50.4)	1086 (40.9)	1514 (39.8)	837 (31.7)	
Yes	37,359 (26.7)	24,980 (22.3)	4358 (32.8)	2542 (47.9)	1525 (57.4)	2235 (58.7)	1719 (65.2)	

(*Continued*)

Table 1. *(Continued)*

	Total	Normoglycemia	IFG	IGT	IFG + IGT	Previously unknown diabetes	Known diabetes	Missing, no (%)
Systolic blood pressure (mm Hg), mean (SD)	126.5 (17.3)	124.8 (16.5)	129.6 (17.4)	134.8 (19.8)	138.6 (19.4)	139.5 (19.8)	135.4 (18.0)	655 (0.5)
Cholesterol (mmol/L), mean (SD)	5.5 (1.1)	5.5 (1.1)	5.5 (1.1)	5.7 (1.1)	5.6 (1.1)	5.6 (1.2)	5.2 (1.2)	373 (0.3)
Smoking, no (%)								1914 (1.4)
Yes	25,836 (18.5)	20,151 (18.0)	3042 (22.9)	850 (16.0)	484 (18.2)	826 (21.7)	483 (18.3)	
Previous smoker	42,870 (30.7)	33,562 (30.0)	4449 (33.5)	1711 (32.2)	938 (35.3)	1291 (33.9)	919 (34.9)	
Never smoker	69,041 (49.4)	56,748 (50.7)	5627 (42.3)	2677 (50.5)	1190 (44.8)	1626 (42.7)	1173 (44.5)	
Physical activity, no (%)								8925 (6.4)
Inactive	19,752 (14.1)	15,411 (13.8)	2052 (15.4)	856 (16.1)	455 (17.1)	619 (16.3)	359 (13.6)	
Moderately inactive	40,144 (28.7)	31,842 (28.4)	3899 (29.3)	1593 (30.0)	800 (30.1)	1232 (32.4)	778 (29.5)	
Moderately active	38,052 (27.2)	30,768 (27.5)	3605 (27.1)	1415 (26.7)	694 (26.1)	943 (24.8)	627 (23.8)	
Active	32,788 (23.5)	27,373 (24.4)	2845 (21.4)	951 (17.9)	459 (17.3)	628 (16.5)	532 (20.2)	
Education level, no (%)								829 (0.6)
Primary school	26,516 (19.0)	19,507 (17.4)	2973 (22.4)	1349 (25.4)	744 (28.0)	1124 (29.5)	819 (31.1)	
Lower secondary school	25,361 (18.2)	19,134 (17.1)	2852 (21.5)	1218 (23.0)	623 (23.5)	908 (23.8)	626 (23.7)	
Upper secondary school	46,738 (33.5)	38,837 (34.7)	4027 (30.3)	1502 (28.3)	683 (25.7)	1028 (27.0)	661 (25.1)	
University degree	40,217 (28.8)	33,874 (30.3)	3349 (25.2)	1201 (22.6)	587 (22.1)	704 (18.5)	502 (19.0)	
Marital status, no (%)								979 (0.7)
Unmarried	13,846 (9.9)	10,652 (9.5)	1380 (10.4)	590 (11.1)	306 (11.5)	504 (13.2)	414 (15.7)	
Married	111,586 (79.9)	90,217 (80.6)	10,461 (78.7)	4139 (78.0)	2032 (76.5)	2833 (74.4)	1904 (72.2)	
Divorced	10,899 (7.8)	8640 (7.7)	1077 (8.1)	402 (7.6)	227 (8.5)	335 (8.8)	218 (8.3)	
Widowed	2351 (1.7)	1702 (1.5)	261 (2.0)	141 (2.7)	70 (2.6)	99 (2.6)	78 (3.0)	

Abbreviations: CAGE, cut down, annoyance, guilt, eye-opener; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; SD, standard deviation.

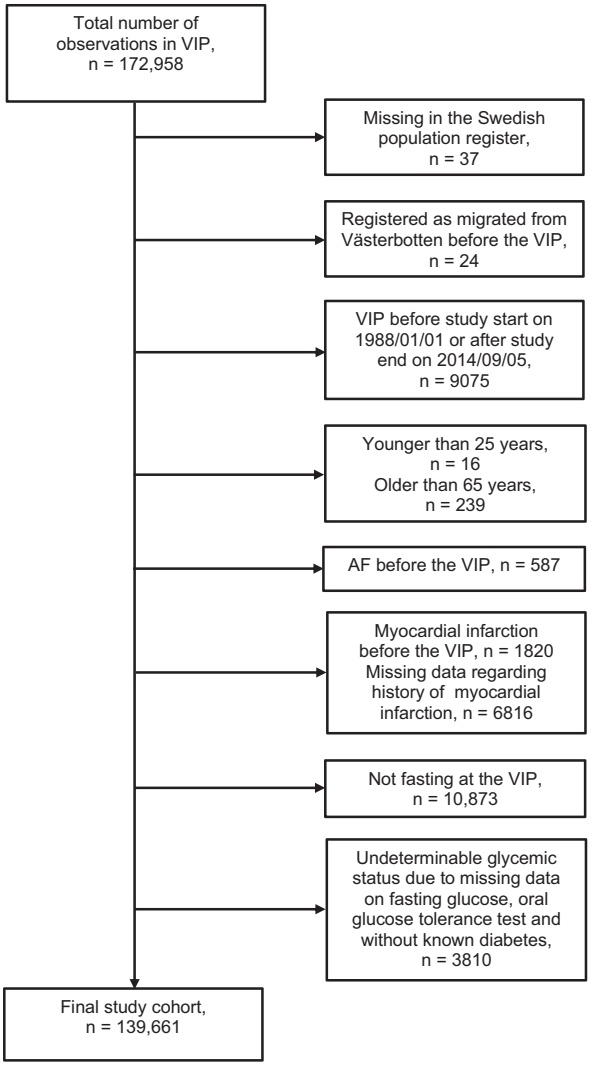

Fig. 1 *Inclusion of Västerbotten Intervention Programme (VIP) observations in the study cohort.*

During follow-up, 4948 participants had an incident hospital-based diagnosis of AF, with mean age at AF diagnosis of 65 years (SD 8.4), and a median time-to-AF-event of 10.2 years. Among the participants who developed AF, 37% were women.

The risk for AF for participants in different glucose categories compared to normoglycemia is presented in Table 2 and Fig. 2. In model 1, there was a significant association between glycemic status and higher risk of developing AF for all prediabetic and diabetic categories except in the IGT

Table 2. *Association between glycemic status and AF.*

	Observations with AF/total number of observations (% with AF)	Model 1 (HR 95% CI)	*p*	Model 2 (HR 95% CI)	*p*	Model 3 (HR 95% CI)	*p*	Model 4 (HR 95% CI)	*p*
Normoglycemia	3587/111,943 (3.2)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
IFG	580/13,290 (4.4)	1.17 (1.07–1.28)	0.001	1.10 (1.00–1.20)	0.05	1.08 (0.99–1.18)	0.10	1.03 (0.93–1.14)	0.52
IGT	227/5304 (4.3)	1.05 (0.92–1.21)	0.45	0.98 (0.85–1.12)	0.73	0.91 (0.79–1.05)	0.21	0.86 (0.74–1.01)	0.07
IFG + IGT	138/2656 (5.2)	1.23 (1.03–1.47)	0.02	1.05 (0.87–1.26)	0.61	0.98 (0.82–1.17)	0.81	0.90 (0.73–1.10)	0.29
Previously unknown diabetes	243/3808 (6.4)	1.41 (1.23–1.61)	<0.001	1.17 (1.02–1.35)	0.02	1.10 (0.96–1.26)	0.17	1.01 (0.86–1.18)	0.92
Known diabetes	172/2637 (6.5)	1.55 (1.31–1.82)	<0.001	1.30 (1.10–1.54)	0.002	1.25 (1.05–1.47)	0.01	1.07 (0.88–1.30)	0.49

Note: Model 1: adjusted for sex, age; model 2: adjusted for sex, age, BMI; model 3: adjusted for sex, age, BMI, systolic blood pressure; model 4: adjusted for sex, age, systolic blood pressure, BMI, antihypertensive drugs, cholesterol, alcohol, smoking, education level, marital status, physical activity.
Abbreviations: AF, atrial fibrillation or atrial flutter; BMI, body mass index; CI, confidence Interval; HR, hazard ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

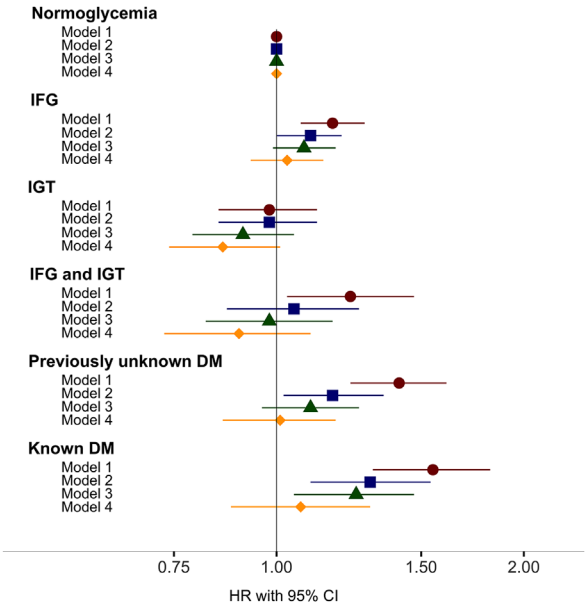

Fig. 2 *Association between glycemic status and risk of atrial fibrillation. Model 1 shown in red circles, model 2 shown in blue squares, model 3 shown in green triangles, and model 4 in yellow diamonds. Model 1: adjusted for sex and age; model 2: adjusted for sex, age, and body mass index (BMI); model 3: adjusted for sex, age, BMI, and systolic blood pressure; model 4: adjusted for sex, age, BMI, systolic blood pressure, antihypertensive drugs, cholesterol, smoking, education level, marital status, and physical activity. CI, confidence interval; DM, diabetes; HR, hazard ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.*

group, ranging from IFG (HR: 1.17; 95% CI: 1.07–1.28) to the known diabetes group (HR: 1.55; 95% CI: 1.31–1.82). In model 2, adjusted for sex, age, and BMI, there was no association between prediabetic status and the risk of AF, and the association between known diabetes and the risk of AF was attenuated (HR: 1.30; 95% CI: 1.10–1.54). In model 3, adjusted for sex, age, BMI, and systolic blood pressure, the only remaining significant association was in the known diabetes group (HR: 1.25; 95% CI: 1.05–1.47). In model 4, adjusted for the covariates in model 3 and use of antihypertensive drugs, total cholesterol, alcohol, smoking, education level, marital status, and physical activity, there was no significant association between glycemic status and the risk of AF.

Analyses stratified for age, sex, BMI, and systolic blood pressure are presented in Table S2, fully adjusted according to model 4. In summary, IGT was associated with a lower risk of AF in elderly, overweight, and people with elevated systolic blood pressure, whereas no glucose category was consistently associated with an increased risk of AF in more than one subgroup.

The sensitivity analysis, including data from each participant's most recent health examination, confirmed the association between IGT and a decreased risk of AF (HR 0.83; 95% CI 0.71–0.99 adjusted for the variables in model 4 and health examination year; Table S3), as did the analysis including 2HPG as a continuous variable (HR 0.97; 95% CI 0.95–0.99 adjusted for the variables in model 4 and health examination year; Table S3). There were no significant association among IFG, IFG + IGT, or diabetes and risk of AF in the analysis using data from the most recent health examination, nor in the analysis assessing FPG as a continuous variable (HR 1.01; 95% CI 0.98–1.04 adjusted for the variables in model 4 and health examination year; Table S3). There was no association between prediabetes (defined as IFG, IGT, or both) or diabetes and the risk of AF; see Table S4. There was no association between prediabetes (HR 0.93; 95% CI 0.85–1.01) or diabetes (HR 0.97; 95% CI 0.85–1.10) and risk of AF adjusted for the variables in model 4 and health examination year when including individuals with a previous myocardial infarction in the study population.

Discussion

Our study found a clear association between glycemic status and the risk of AF in the analyses that only adjusted for age and sex, which was attenuated with increasing adjustment and disappeared in the fully adjusted model. These findings indicate that diabetes and prediabetes are not independently associated with the risk of AF; but rather that the increased risk associated with hyperglycemia can be explained by other factors.

Some previous studies reported an increased risk of AF in people with diabetes and prediabetes. A meta-analysis published in 2018 found that diabetes was associated with a 28% increased risk of AF, and that prediabetes was associated with a 20% increased risk of AF [14]. However, the design of the included studies differed a lot; many of the included studies did not assess glycemic status as the primary exposure, but only as a covariate, which may have affected the analytical strategy and choice of covariates, and thus the results.

Huxley et al. studied the association among diabetes, prediabetes, and the risk of AF and found no association between prediabetes and AF. However, they found an association between fasting serum glucose (FSG) in people with diabetes and AF risk after adjustment for confounders, including BMI and systolic blood pressure (FSG 100–125 mg/dL: HR: 1.99; 95% CI 0.46–8.67. FSG ≥126 mg/dL HR: 2.89; 95% CI 0.71–11.8, compared to FSG <100 mg/dL, *p*-value for trend 0.04). However, the association was no longer significant after adjustment for the history of coronary heart disease (FSG ≥126 mg/dL HR: 2.63; 95% CI 0.64–10.7, *p*-value for trend 0.11) [25]. This result is consistent with our findings, showing no association between glycemic status and risk of AF in the fully adjusted analyses.

A Danish registry-based study reported an association between diabetes and an increased risk of AF. This association was more pronounced in younger participants and not detectable in people aged 75 years or older [26]. However, this study lacked information about BMI, a major potential confounder due to its association with both hyperglycemia and AF [27, 28]. The fact that BMI increases the risk of many conditions that are known to increase the risk of AF, such as hypertension, obstructive sleep apnea syndrome, and atherosclerotic cardiovascular disease, underlines the importance of adjustment for BMI to explore a possible causal role of hyperglycemia in AF [29–31]

Some studies indicate that lean body mass rather than fat mass is associated with the risk of incident AF, and that BMI is therefore not an optimal measurement for this relationship [32, 33]. Frost et al. found an association between fat mass and atrial fibrillation, but the association was attenuated when adjusting for lean body mass. They also found an association between lean body mass and risk of incident AF, and when adjusting for fat mass, this association remained significant [34]. This may be related to the fact that heart size, which is an important driver of AF, is more strongly associated with lean body mass than fat mass, and a study from 2004 demonstrated that the association between BMI and AF disappeared when adjusting for atrial diameter [35]. Unfortunately, we do not have access to data on lean body mass in our study cohort.

In a recently published study, using European cohorts, different biomarkers were studied as predictors of atrial fibrillation. The analyses in this study were extensively adjusted, and no association between glucose levels and AF was found [36].

A strength of our study is that the number of participants is considerably larger than that of previous studies, with extensive follow-up, resulting in more than 1.1 million person-years at risk. This allows us to detect smaller differences between groups than other studies with fewer participants would be able to do. In our study, we can thus, with high certainty, exclude an increased risk for AF associated with prediabetes and a risk increase of 30% or more for people with known diabetes. Interestingly, our analyses suggested an inverse association between IGT and AF for several subgroups, as well as for 2HPG assessed as a continuous variable. These findings need to be interpreted with caution.

Our study has some limitations. First, people with low income and single households tend to participate to a lesser extent in VIP, raising the possibility of a healthy participant bias. Second, most of the included participants were of Northern European ancestry [16]. An American study found that black Americans, Asian Americans, and Hispanic Americans had an increased risk for diabetes at lower BMI levels compared to White Americans [37]. Furthermore, a British study suggested ethnicity-specific BMI cutoffs for overweight, since people from, for example, Asia tend to have an increased risk for hyperglycemia at lower BMI levels [38]. Interestingly, however, a systematic review from 2018 described a lower risk of AF in Asians, Blacks, and Hispanics compared to Caucasian, despite an increased prevalence of previously known AF risk factors in these ethnical groups [39]. Our results should therefore be applied with caution to other ethnic groups.

Third, it is not possible to separate atrial fibrillation from atrial flutter in our study as the ICD-9 code 427.3 and the ICD-10 code I48.9, which are used to identify persons with incident AF in our study, include both atrial fibrillation and atrial flutter. Hence, we have decided to include both atrial fibrillation and atrial flutter, even though the pathogenesis for these conditions partly differs.

Fourth, the questionnaire used to collect data on several lifestyle factors has not been separately validated. On the other hand, several previous

studies using the data from the same VIP health examinations have found associations between the recorded risk factors (e.g., studies regarding the association between alcohol consumption and risk of AF, and anthropometric factors and risk of AF) that are consistent with findings from other cohorts [40, 41]. We also lack information on some conditions associated with both hyperglycemia and AF, for example, heart failure and obstructive sleep apnea [29, 42, 43], and we do not have information about the duration or severity of hypertension. However, the cohort is relatively young, and people with a history of myocardial infarction before the health examination are excluded; so the potential impact of undiagnosed heart failure should be limited. Possibly, the risk for residual confounding due to sleep apnea is decreased as we have adjusted for BMI [30].

Lastly, the blood analyzed in this study was from capillary samples, which have a lower analytical precision, compared to venous samples (which is WHO standard) [44]. We also lack data on HbA1c, which, in addition to FPG and OGTT, is commonly used to diagnose diabetes and prediabetes. However, as we did not find an association between neither diabetes nor prediabetes and AF, it seems unlikely that there would be an association between prediabetic HbA1c and AF.

In summary, this study implies that blood glucose is not an independent risk factor for AF. Rather, the increased risk of AF seen in people with diabetes and prediabetes seems to be related to the higher prevalence of other risk factors.

Conflict of interest statement

The authors declare no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: Baseline data.
Table S2: Association between glycemic status and risk of AF. Analyses stratified by age, sex, BMI, and systolic blood pressure.

Table S3: Association between glycemic status at the most recent health examination and risk of AF.
Table S4: Association between prediabetes, diabetes, and risk of atrial AF based on data from the most recent health examination. Associations presented as hazard ratios with 95% confidence intervals.