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Meta-analysis of Cohort and Case-Control Studies of Type-2 Diabetes Mellitus and Risk of Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is one of the most clinically diagnosed cardiac disturbances but little is known about its risk factors. Previous epidemiological studies have reported on the association between diabetes mellitus (DM) and subsequent risk of AF with inconsistent results. The aim of this study was to conduct a meta-analysis of published studies to reliably determine the direction and magnitude of any association between DM and AF. A systematic review and meta-analysis was conducted. PUBMED and EMBASE were searched to identify prospective cohort and case-control studies that had reported on the association between DM and other measures of glucose homeostasis with incident AF by April 2010. Studies conducted in primarily high-risk populations and participants in randomized controlled trials were excluded. Seven prospective cohort studies and four case-control studies with information on 108,703 cases of AF among 1,686,097 individuals contributed to this analysis. The summary estimate indicated that individuals with DM had an approximate 40% greater risk of AF compared with unaffected individuals: RR 1.39 (95% Confidence Intervals: 1.10 – 1.75; p for heterogeneity <0.001). After correcting for publication bias the RR was XXXXXXXX. Studies that had adjusted for multiple risk factors reported a smaller effect estimate compared with age-adjusted studies: RR 1.24 (95% Confidence Intervals: 1.06 – 1.44) versus 1.70 (1.29 – 2.22); p for heterogeneity = 0.053. The population attributable fraction of AF due to DM was 2.5% (95% CI: 0.1 – 3.9%). In conclusion, DM is associated with an increased risk of subsequent AF but the mechanisms that may underpin the relation between DM and AF remain speculative.

Keywords

Diabetes mellitus; arrhythmias; meta-analysis

BACKGROUND

Aside from age, established risk factors for atrial fibrillation (AF) include heart failure and valvular heart disease, and some cardiovascular risk factors such as elevated blood pressure, obesity and smoking[1]. In addition to these risk factors, observational studies have also reported on the association between diabetes mellitus (DM) and AF but with equivocal results[1–5]. The discrepancies in study findings may be due in part to methodological challenges such as limited power and small effect size. Thus, the aim of this article was to quantify the magnitude and direction of the reported association between DM and AF by

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conducting a systematic review and meta-analysis of published cohort and case-control studies.

METHODS

We performed a systematic review of the available literature according to the MOOSE guidelines for the conduct of meta-analyses of observational studies[6]. Relevant studies were identified by computerized searches from the following data sources: MEDLINE via Ovid (from 1950 through April 2010) and EMBASE (from 1966 through May 2010) using relevant text words and medical subject headings that included all spellings of “type 2 diabetes” OR “diabetes mellitus” OR “glucose intolerance” OR “impaired fasting glucose” and “atrial fibrillation”. The search was limited to prospective cohort and case-control studies in predominantly healthy adult populations without language restriction. Studies of high-risk populations and reports from randomized controlled trials were excluded. (Figure 1).

All cohort studies and case-control studies that had reported on the association between DM and AF were eligible for inclusion. Studies of populations that comprised patients who had undergone cardiac surgery or those with established cardiac disease were excluded.

Quantitative estimates (hazard ratio, relative risk (RR) or odds ratio [OR]) and the 95% confidence intervals (95% CI) (or another measure of variance) of the association between DM and AF were extracted from each study. Where possible both the age-adjusted estimate (and where appropriate, the age- and sex-adjusted estimate) and the multiple-adjusted risk estimate (and corresponding 95% CI) were extracted from individual studies. Additional information on patient characteristics at study baseline (e.g. mean age, gender distribution, race) was also extracted from the published reports. Information on variables included in the multivariable model was also recorded, as was method of case ascertainment and study exposure.

Summary estimates were obtained using a random-effects model to account for between-study heterogeneity. Overall and cohort estimates are presented as relative risks (RR) with 95% CI, and case-control estimates are presented as odds ratios (OR) with 95% CI. For those studies that had reported both multiple risk estimates, only the most-adjusted estimated contributed to the summary estimates. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic[7]. To examine the influence of study-level covariates on the effect of DM on the risk of AF, two meta-regression models on the log(relative risk) scale were constructed. The first examined the impact of study design (i.e., cohort versus case-control), and the second investigated the impact of level of adjustment. For the latter model, studies were classified into “least-adjusted” if they had only adjusted for age and sex and “most adjusted” if they had adjusted for additional variables (Tables 1 and 2) and a corresponding indicator variable was included in the model. Publication bias was assessed using the Egger test[8] and trim and fill analyses were used to adjust the RRs for the presence of publication bias[ref]. A p-value of less than 0.05 was considered statistically significant for all analyses. All statistical analyses were performed with STATA, version 11.1 (Stata, College Station, Texas).

To ascertain what proportion of the burden of AF might theoretically be avoided if DM could be entirely eliminated from the population, we used the following PAR formula[9]: $PAF=PD[(RR-1)/RR]$, where PD is the prevalence of DM among AF cases. This prevalence was estimated using the average prevalence of the case series of included case-control studies.

RESULTS

A total of 6 prospective cohort studies relating DM to subsequent risk of AF involving 5,436 incident cases of AF in 801,837 individuals were identified [1, 10–14]. An additional cohort including 265 incident cases of AF among 28,449 people reported on the association between impaired glucose tolerance and risk of AF[15] (Table 1). Three of the 7 cohort studies provided sex-specific estimates adjusted at least for age, of the association between DM and AF and therefore ten separate estimates of the relation contributed to this analysis. All but one of the studies was from populations in North America (n = 2) or Europe (n = 4) with the remaining study from Japan[15].

The characteristics of cohort study participants are shown in Table 1. Four case-control studies including information on 103,267 cases of prevalent AF among 884,260 individuals included in this review (Table 2) [16–19]. One of the four case-control studies provided sex-specific estimates, hence, there were five separate estimates from these four studies that contributed to this analysis. The following analyses are therefore based on 108,703 cases of AF among 1,686,097 individuals.

Three prospective cohort studies involving 1,104 incident cases of AF among 20,871 individuals and one case-control study involving 42 individuals with AF and 549 control subjects were unable to contribute to the meta-analysis. Although these studies had commented on the direction of the association between DM (or serum blood glucose) with AF, no quantitative estimate was reported (Table 3) [2–5]. In three of these studies, there was no association between DM or blood sugar level with risk of AF. In the remaining study, there was a positive association between glucose level and risk of AF: RR 1.10 (95% CI: 1.04 – 1.17) per mmol/L glucose but it did not provide a quantitative estimate for the DM-AF relation.

The overall summary estimate from the 15 separate risk estimates from the cohort and case-control studies combined indicated that individuals with DM had an approximate 40% greater excess risk of AF compared with unaffected individuals: RR 1.39 (1.10 – 1.75; Figure 2). There was significant heterogeneity ($p < 0.001$) most of which was due to differences between studies (I^2 statistic = 94.2%). There was evidence of publication bias ($p = 0.003$) correcting for which reduced the summary estimate to RR XXXXXXXXXXXXXXXX. The pooled summary estimates from the cohort and case-control studies were broadly comparable with no evidence from the meta-regression analysis that the relative risk estimate varied with study design (RR 1.32 (95% CI: 1.09 – 1.60) versus 1.53 (95% CI: 1.03 – 2.26); $p = 0.50$; Figure 2). Adjusting for publication bias did not alter this finding: RR XXXXXXXXXXXXXXXX and RR XXXXXXXXXXXXXXXX, $p = X$, respectively.

To examine the possible impact of confounding on the relationship requires estimates of effect that are in the first instance age-adjusted only, and then secondly, adjusted for potential confounders. If there is substantial attenuation of the age-adjusted estimate following adjustment for other risk factors then residual confounding may persist.

Only 3 studies reported separate age and multiple-adjusted estimates. In the first study [1], the authors reported age-adjusted estimates of the association between DM and incidence of AF separately for men and women (RR 1.7 [95% CI: 1.2 – 2.3] and 2.1 [1.5 – 2.8], respectively). After adjustment was made for smoking, hypertension and prior cardiac disease there was an approximate 50% attenuation in the magnitude of the relationship: RR 1.4 (95% CI: 1.0 – 2.0) and 1.6 (1.1 – 2.2), in men and women, respectively. In this analysis, the authors did not adjust for obesity and therefore the true estimate of effect is likely to be less than these adjusted estimates would suggest. In the Malmo Diet and Cancer Study[14], in analyses adjusted only for age, DM was a significant risk factor for AF in both men and

women, but after adjusting for BMI and other confounders, the relationship was no longer significant: HR 1.39 (95% CI: 1.02 – 1.90) versus 1.1 (0.84 – 1.59) in men and HR 1.67 (1.15 – 2.43) versus 1.4 (0.95 – 2.05) in women. In the final study of men, the age-adjusted estimate for the relationship between DM and AF was significant (RR 1.8 (95% CI: 1.26 to 2.64)) but after adjusting for cardiac conditions, alcohol consumption, smoking and obesity the relationship was no longer significant (multiple-adjusted estimate was not reported) [10].

The findings from the meta-regression analysis of least-adjusted versus most-adjusted studies indicated a borderline significant greater association of DM with the risk of AF in those studies that had only adjusted for age and sex compared with those that involved a greater level of statistical adjustment: RR 1.70 (95% CI: 1.29 – 2.22) versus RR 1.24 (95% CI: 1.06 – 1.44; $p = 0.053$).

Only one case-control study reported on the association between cumulative exposure to DM and prevalent AF [17]. In that study, compared with individuals without DM, those with DM < 5 years had an approximate 7% higher risk of AF (OR 1.07 [95% CI: 0.75 – 1.51]); those with DM between 5 – 10 years had a 51% greater risk (OR 1.51 [95% CI: 1.05 – 2.16]); and in those with DM for more than 10 years, the risk of prevalent AF was 64% (OR 1.64 [95% CI: 1.22 – 2.20]).

In the one case-control [17] that reported on the association by AF subtype, there was no evidence that the positive relationship between those with treated DM and overall AF varied according to subtype: RR 1.35 (95% CI: 1.03 – 1.78), 1.36 (95% CI: 1.06 – 1.76) and 1.71 (95% CI: 1.17 – 2.49) for paroxysmal, persistent and sustained AF, respectively (p for heterogeneity = 0.51).

Using the average prevalence of DM of case series of included case-control studies (12.7%) and the summary estimate obtained from all studies combined (RR 1.39), the PAF of AF due to DM was 3.6% (95% CI: 1.2 – 5.4%). If the more conservative summary risk estimate derived from those studies that had adjusted for multiple risk factors was used then the proportion of AF explained by DM was reduced to 2.5% (95% CI: 0.07 – 3.9%).

DISCUSSION

In this meta-analysis involving information on 108,703 cases of AF among 1,686,097 individuals from 7 prospective cohort and 4 case-control studies, DM was associated with an overall X% increase in the risk of AF after correcting for the presence of publication bias. The summary estimates for the cohort and case-control studies were broadly similar although the lack of a significant difference between the study designs may have been due to the meta-regression analysis being underpowered.

The overall summary estimate obtained by this review may however be an overestimate of the real association between DM and AF due to the presence of confounding. The level of adjustment for known and putative risk factors that are associated with both DM and AF, such as elevated BMI and prior cardiac disease [1], varied across the studies and hence, it was not possible to fully take into account their possible impact on the association. One method by which to ascertain the likely effect of adjustment for such risk factors on the relationship between DM and AF is to compare the crude and multiple-adjusted estimates of the association from the same study population. Three studies did report separate estimates of effect that in the first instance were adjusted only for age [and sex] and then additionally for other risk factors. In all instances the impact of adjustment for multiple confounders was to either render the crude estimate non-significant or to have attenuated the estimate by approximately 20%. Furthermore, the summary estimate from those studies that had adjusted for multiple risk factors was lower than that obtained from studies that had adjusted

only by age (RR 1.24 versus RR 1.70; $p = 0.053$). Therefore, the true risk between DM and subsequent risk of AF may be closer to 25% rather than 40% as indicated by the overall summary estimate. Assuming this to be true, then DM would explain approximately 2.5% of the burden of AF, similar to the estimate recently reported from a Swedish cohort [14].

The presence of publication bias may also have inflated the estimate of effect between DM and AF. In the current review, 4 studies with 1,146 AF events among 21,462 people could not contribute to the meta-analysis. Although these studies had reported on the direction of association between DM and AF, no quantitative estimate of effect was given. Three of these excluded studies showed no statistically significant association between DM and AF, and hence, had they been included the summary estimate is likely to have been attenuated. But, given the large number of events from the included studies, any change in the summary effect size is likely to have been only modest.

That there is a causal association between DM and AF receives some support from an analysis of the impact of cumulative exposure to DM on risk of prevalent AF. In that study, duration of DM [which was assessed by use of DM medication] and risk of prevalent AF increased over time such that in individuals with DM for more than 10 years, compared with non-diabetics, the risk of prevalent AF was approximately 64%. In contrast, the risk was only 7% in those with DM for less than five years.

Several possible pathways by which elevated glucose levels and DM may exert a pro-arrhythmic effect have been suggested. Aside from a small number of case-report studies [20], there is no evidence to indicate that type-1 diabetes is associated with an increase in the risk of AF, suggesting that it is not the chronic hyperglycaemia associated with DM but rather insulin resistance which might be the mechanism responsible for the observed increased risk of AF among those with DM. Insulin resistance is also considered to be a mechanism by which hypertension and obesity are associated with increased risk of AF [21]. Ostgren and colleagues attempted to examine the potential pathways mediating the association between DM, hypertension and AF in a Swedish community-based cross-sectional study among 915 patients with DM and hypertension and 824 control subjects [22]. In that study, individuals with both risk factors had a three times higher risk of prevalent AF compared with normotensive, non-diabetic controls. However, after adjustment for the Homeostasis Model Assessment Index the association was significantly attenuated and no longer significant suggesting that insulin resistance was the underlying mechanism governing the link between DM, hypertension and AF: OR 3.3 (95% CI: 1.6 – 6.7) versus 1.3 (95% CI: 0.5 – 3.1).

There are several noteworthy limitations of this review in addition to those already discussed. First is the lack of complete data on sub-type of AF which, may or may not, have different risk factors, for example, “binge-drinking” is considered to be a main risk factor in paroxysmal AF, which is the most common form of AF observed in younger people but is not considered to be a risk factor for persistent or permanent AF [23–25]. Only one study reported on the relationship between DM and subtypes of AF. In that study, DM was positively associated with all three forms of AF with no evidence that the relationship differed by subtype [17]. Second, the exclusion of studies of individuals with prior history of AF or high-risk trial populations limits the generalizability of the study. For example, in the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-Atrial Fibrillation trial [26] which included 1442 patients with at least two documented AF episodes in the previous six months, there was no observed significant difference at baseline in the prevalence of DM between the group in whom AF recurred versus the group in whom AF did not recur (13.9% versus 15.4%; $p = 0.44$).

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Figure 1. Flowchart of search strategy. Excluded studies are available online (Web table 1 and Web references)

Figure 2.

The relationship between type 2 diabetes and atrial fibrillation in published cohort and case-control studies. The studies are sorted by statistical weight defined as the inverse of the variance. The center of each black square is placed at the point estimate; the area of the square is proportional to the statistical size; and each horizontal line shows the 95% confidence interval [CI] for the estimate for each study. The open diamonds represent the summary estimates from the pooled cohort and pooled case-control studies and the overall summary estimate.

Baseline characteristics of study participants of cohort studies examining the association between type 2 diabetes and AF

Table 1

First Author (Year)	Date of Enrolment	Country	N (% Female)	Mean age (yrs)	Mean FU (yrs)	Incident Cases AF	IR (per 1000 person-years)	Diabetes diagnosis	AF diagnosis	Covariates in model
Krahn, 1995 (14)	1948	Canada	3983 (0)	72	44	299	0.5 < 50y 2.3 at 60y 16.9 at 85y	NA	ECG	Age, cardiac conditions, alcohol, smoking, obesity
Benjamin, 1998 (3)	1948	USA	4731 (56)	55–94	38	562	6.2 (55–64y, M) 3.8 (55–64y, F) 75.9 (85–94y, M) 62.8 (85–94y, F)	FBG/diabetes medication	ECG	Age, smoking, ECG, hypertension, MI, CHF, valve disease
Watanabe, 2008 (19)	1996–98	Japan	28449 (66)	59	4.5	265	4.1 (M) 1.3 (F)	IGT*/diabetes medication	ECG	Age, sex
Ruigomez, 2002 (15)	1996	UK	703340	40–89	NA	1035	1.7	MR	ECG	Age, sex, CVD morbidity
Frost, 2005 (16)	1993–01	Denmark	47589	50–64	5.7	553	2.9 (M) 1.2 (F)	NA	ECG	BMI, age, height, education, smoking, alcohol, IHD, CHF, hypertension
Rosengren 2009 (17)	1970–73	Sweden	6903 (0)	51	34 (max)	1253	7.5 (non-diabetics) 7.1 (diabetics)	SR	ECG	Age
Gustav Smith, 2010 (18)	1991–96	Sweden	30447 (60%)	44–73	11.2	1430	6.3 (M) 3.1 (F)	SR/diabetes medication	ECG	Age, BMI, smoking, BP, prior cardiac disease

* This study reported on the relationship between impaired glucose tolerance according to the NCEP-ATP III guidelines with risk of AF. ECG = electrocardiogram; NA= information not available; M = male; F = female; MI = myocardial infarction; CHF = congestive heart failure; IHD = ischemic heart disease; CVD = cardiovascular disease; BMI = body mass index; BP = blood pressure; NA = not available; SR = self-report; MR = medical records; IR = incidence rate

Table 2

Baseline characteristics of study participants of case-control studies examining the association between diabetes and AF

Author	Date of Study	Country	N	Prevalent AF	Mean age (yrs, SD)	Diabetes diagnosis	AF diagnosis	Covariates in model
Nichols, 2009 (20)	1999-04	USA	17 372 diabetics 17 373 controls	626 cases (3.6%) 434 (2.5%)	58	Inpatient/outpatient diagnosis	MR	Age, sex, ethnicity, smoking, obesity, hypertension, CAD
Dublin 2010 (21)	2001-04	USA	1410 AF cases 2203 controls	NA	55-94	MR	MR	Adjusted for age, sex, calendar year, treated hypertension and BMI
Movahed, 2005 (22)	1990-00	USA	293124 diabetics 552624 controls	43674 cases (14.9%) 57077 controls (10.3%)	65	MR	MR	CHF, CAD, LVH
Johansen, 2008 (23)	NA	Norway	46 AF subjects 108 controls	NA	75	OGTT	ECG	None

MR = medical records; CHF = congestive heart failure; CAD = coronary artery disease; LVH = left ventricular hypertrophy; BMI = body mass index; NA = information not available.

Table 3
Characteristics of studies that reported on the direction of association but did not report a quantitative estimate

First author	Date of Study	Country	N	Mean age (yrs)	Mean FU (yrs)	Incident Cases AF	IR (per 1000 person-years)	Direction of association of exposure with AF	Covariates in model
Psaty, 1997 (6)	1989–93	USA	4844	>65	3.3	304	17.6 (65–74 yrs, M) 10.1 (65–74 yrs, F)	Positive: 1.10 (95% CI: 1.04–1.17) per mmol/L glucose	Alcohol, SBP, age, hght, TC, ethnicity, B-blockers, diuretics
Wilhelmsen, 2001 (7)	1970–73	Sweden	7495	47–55	25.2	754	NA	No sig. association; no data given	NA
Stewart, 2002 (8)	1972–76	Scotland	8532	45–64	4.1	46	0.54	No sig. association with blood glucose	NA
Agmon, 2001 (9)	NA	USA	42 AF cases 539 controls	82 (cases) 66 (controls)	-	-	-	No association; p = 0.27	None

NA = information not available; AF = atrial fibrillation; IR = incidence rate; yrs = years; SBP = systolic blood pressure; B-blockers = beta-blockers; M = male; F = female; sig = significant; hght = height; TC = total cholesterol.