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Relationship between prediabetes and risk of atrial fibrillation: a meta-analysis

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ABSTRACT

Background Diabetes is an established risk factor for atrial fibrillation (AF). However, whether prediabetes is also a risk factor for AF is unclear. This meta-analysis examined the relationship between prediabetes and AF risk.

Methods EMBASE, MEDLINE, and Publicly Available Contents (from Jan. 1, 1950 to Jan. 29, 2025) were used to comprehensively search for observational studies of the incidence or prevalence of AF among those with prediabetes or normoglycemia. Each relative risk (RR) for prediabetes *vs.* normoglycemia and the population attributable fraction (PAF) of prediabetes to AF incidence in longitudinal studies and the odds ratio (OR) for prediabetes *vs.* normoglycemia in cross-sectional studies were pooled with a random-effects model.

Results Identified were 46 eligible studies. Pooled RR and PAF (95% confidence interval [CI]) were 1.12 (1.06–1.18) and 2.7% (1.4%-4.0%), respectively. Pooled crude RR and crude OR (95% CI) were 1.49 (1.37–1.62) and 1.42 (1.23–1.64), respectively. Higher RR was revealed in populations ≥ 65 years old *vs.* < 65 years old ($P = 0.02$) and in Asian *vs.* non-Asian countries ($P = 0.047$). Higher PAF was revealed in studies with a population ≥ 65 years old *vs.* < 65 years old ($P < 0.001$) and in male-dominant *vs.* female-dominant studies ($P < 0.001$). Only by examining the RR for both diabetes and prediabetes *vs.* normoglycemia, the pooled RR/PAF (95% CI) was 1.12 (1.15–1.20)/1.6% (0.9%-2.3%) for prediabetes and 1.15 (1.10-1.20)/1.0% (0.7%-13%) for diabetes.

Conclusions Prediabetes is a modest but significant risk factor for AF, comparable to that of diabetes. The impact of prediabetes was strong among the elderly, males, and Asian people.

Atrial fibrillation (AF) is the most common clinically important arrhythmia. The prevalence and incidence of AF have increased globally owing to widespread ageing of the population.[1] AF is markedly associated with increases in heart failure, stroke, and all-cause mortality[2] and substantial healthcare costs such as hospitalizations[3] and treatment with oral anticoagulant agents or warfarin.[4] Identifying risk factors for AF and quantitively assessing their contributions to AF are essential to targeting individuals for prevention of AF.

Among non-organic risk factors hypertension is the most common contributor to the incidence of AF.[1] Although diabetes contributes less than hypertension to the incidence of AF, it is a significant risk factor for AF,[5,6] as explained by a biological mechanism such as the prolongation of action potential duration (APD), heterogeneity in cardiac conduction velocity, and the shortening of APD to the increased pacing frequency in the diabetic atrium.[7,8] Prediabetes refers to a condition in which gluc-

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ose levels do not meet the criteria for diabetes but indicate abnormal carbohydrate metabolism.[9] As prediabetes has a prevalence of approximately 2.5-fold that of diabetes,[10] its contribution to a disease such as AF could be large even if the risk magnitude is not as large as that of diabetes.

It is unclear whether prediabetes as well as diabetes significantly elevates the risk of AF. A previous meta-analysis indicated that pre-diabetes and diabetes increased the risk of AF by 20% and 28%, respectively.[11] However, that meta-analysis focused on diabetes and insufficiently reviewed studies that examined the association of prediabetes with AF risk. In addition to the finding that diabetes is a risk factor for AF, it was noted that patients with AF had a higher prevalence of diabetes than those without AF.[12] However, it is also unclear whether the relationship between prediabetes and AF can be explained by a sequence of events (i.e., prediabetes precedes AF), coexistence (i.e., AF coexists with prediabetes or prediabetes coexists with AF), or both a sequence of events and the coexistence of a condition. The current meta-analysis primarily examined the relationship between prediabetes and AF risk and secondarily compared the impact on AF risk between prediabetes and diabetes.

METHODS

Protocol

Before performing this meta-analysis, we registered the protocol in the international prospective register of systematic reviews (PROSPERO) (CRD42025631067).

Search Strategy and Inclusion Criteria

A systematic literature search for which EMBASE, MEDLINE, and Publicly Available Contents (from Jan. 1, 1950 to Jan. 29, 2025) were used was conducted to obtain observational studies that examined the relationship between prediabetes and AF. Search keywords were text words and thesaurus terms related to the following elements: (1) effect measures (relative risk (RR) and odds ratio (OR)), (2) prediabetes, and (3) AF (Supplementary Material 1). Inclusion criteria were: (1) observational study; (2) exposure was prediabetes; (3) non-exposure was normoglycemia; and (4) outcome was incident AF for a longitudinal study or prevalent AF for a cross-sectional study.

Exclusion Criteria

(1) The cut-off value for differentiating pre-diabetes and normoglycemia varied among studies. We fundamentally accepted any cut-off value even if it was inconsistent with the present definition of prediabetes.[9] However, studies were excluded if the cut-off value was hemoglobin A1c (A1C) ≥ 6.5%, fasting plasma glucose (FPG) ≥ 7.0 mmol/L, or 2-h oral glucose tolerance test (OGTT) ≥ 11.1 mmol/l because those values indicated that the exposure was diabetes not prediabetes.

(2) Even if the cut-off value for prediabetes was A1C < 6.5%, FPG < 7.0 mmol/L, or OGTT < 11.0 mmol/L studies were excluded if it was indicated that participants with diabetes were included in the non-exposed groups. It was possible that participants with prediabetes and diabetes were mixed in the exposed group such as when the criterion for hyperglycemia in metabolic syndrome (i.e., FPG < 5.6 or 6.1 mmol/L) was used as the cut-off value. Studies were included if it was not mentioned that some participants in the non-exposed group had diabetes.

Effect Measures

For this comprehensive meta-analysis, a longitudinal study had to present the RR or a cross-sectional study had to present the OR and its corresponding standard error (SE) of log OR/RR in a comparison with an exposed group to a non-exposed group or if the data required to calculate these values were given. If these were not given, we queried the study author to obtain them only if the study met all inclusion criteria or did not meet any of the exclusion criteria.

In addition, the effect measures included the population attributable fraction (PAF) to assess the contribution of prediabetes to AF risk in longitudinal studies which presented data on the number of participants with incident AF in exposed and non-exposed groups. The PAF is defined as the proportion of the incidence of a disease which is attributable to a risk factor and calculated as follows:

$$PAF = (P_r \times (RR - 1)/(1 + [P_r \times (RR - 1)])$$

where P_r is the proportion of individuals who have a risk factor in the study population.

Study Quality

We used the Newcastle Ottawa Quality Assessment

Scale (NOS) to assess study quality. The NOS consists of the following 3 broad domains: selection of study groups (Selection), comparability of groups (Comparability), and ascertainment of the outcome of interest (Outcome) for longitudinal and cross-sectional studies and Selection, Comparability, and ascertainment of exposure (Exposure) for case-control studies. Each domain consists of 2 to 4 criteria. If a criterion was met, we gave 1 point (exceptionally, 2 points for the first criterion in the Exposure domain of cross-sectional studies). Full marks are 9. Details are described in Supplementary Material 2.

Data Extraction

Two authors (S.K. and K.F.) independently extracted the data. Disagreements were solved by a third author (H.S.). The extracted data were: first author, year, country, study design (i.e., cohort/case-control/cross-sectional), number of participants and cases, mean age, proportion of men, characteristics of the population (if not general population), and follow-up duration. If a study presented data on AF incidence or prevalence according to diabetes status, the crude (non-adjusted) RR/OR was calculated. If zero-event existed, we added 0.5 to each of the 4 values (i.e., number of cases in the exposed group [C_E], number of cases in the non-exposed group [C_{NE}], number of non-cases in the exposed group [NC_E], and the number of non-cases in the non-exposed group [NC_{NE}]) to make it possible to calculate the variance of the logarithm (log) of RR/OR.[13]

$$V_{logRR} = 1/C_E + 1/C_{NE} - 1/(C_E + NC_E) - 1/(C_{NE} + NC_{NE})$$

$$V_{logOR} = 1/C_E + 1/C_{NE} + 1/NC_E + 1/NC_{NE}$$

Data Synthesis

Longitudinal and cross-sectional studies were separately analyzed. To calculate the pooled OR/RR, we used an inverse-variance fixed-effect model if the between-study heterogeneity expressed as I-squared[14] was not significant. Otherwise we used a random-effects model according to the method of DerSimonian & Laird.[15] If two or more OR/RR were presented for the same exposure and outcome, we chose the RR/OR which was the most fully adjusted for covariates. In addition, the pooled PAF was calculated in the analysis of longitudinal studies which presented the number of participants and AF cases in the exposed and non-exposed groups. The pooled PAF was calculated from [1- PAF]. The variance (V) of log [1-PAF] was calculated as follows:[16]

$$V = \frac{PAF^2}{(1-PAF)^2}\left(\frac{V_{logRR}}{(RR-1)^2} + \frac{2}{D_1} + \frac{D_2}{D_1(D_1+D_2)}\right)$$

where V_{logRR} is a variance of log RR and D_1 and D_2 represent the number of incidences with and without a risk factor, respectively.

Sensitivity Analysis

We limited the analysis to studies which provided data on the unadjusted (crude) OR/RR (i.e., number of participants and AF cases according to diabetes status) and the adjusted OR/RR and calculated the pooled adjusted and crude RR/OR and PAF in prediabetes compared with normoglycemia. Stratified analyses were performed according to several key study characteristics that were identified by extracting the data (see Data extraction). In the stratified analysis, we chose categorical data, if provided (e.g., data separately for the male and female populations; and separately for the risks of paroxysmal and non-paroxysmal AF). However, in the overall analysis, we chose the combined data (i.e., data for the population which combined males and females; the risk of outcome which combined paroxysmal AF and non-paroxysmal AF, in the above examples).

We limited the analyses to studies that provided AF risks for both prediabetes and diabetes and calculated the pooled AF risk for prediabetes and diabetes compared with normoglycemia. For each of the sensitivity analyses, a meta-regression analysis was performed to examine the source of heterogeneity in risk magnitude. The statistically significant regression coefficient suggested that the explanatory variable is a determinant which creates differences in the risk magnitude among strata. If there were two or more data with different exposures (e.g., AF risk for high A1C level and that for high FPG level) or different outcomes (e.g., risk of paroxysmal AF and that of non-paroxysmal AF) for the same pair of comparisons or the same referent (i.e., AF risk for prediabetes *vs.* normoglycemia and that for diabetes *vs.* normoglycemia), we used a multi-level mixed meta-regression model which is designed as an extension of meta-regression where two or more data are nested and may be correlated.[17]

Publication bias was assessed for the overall OR/RR and PAF for prediabetes visually using funnel plots and statistically by Begg's and Egger's tests.[18,19] If a publica-

tion bias was statistically significant, we used a trim-fill method to adjust the pooled estimate for the publication bias.[20] This method plots evidence from hypothetically unpublished studies so that the funnel plot can restore asymmetry under the assumption that the funnel plot is symmetrical without publication bias and recalculates the overall estimates combining existing and plotted evidence.

All statistical analyses were performed using STATA statistical software (Version 18, Stata Corporation, College Station, TX, USA). Two-sided *P*-value < 0.05 was considered statistically significant with the exception that *P* value < 0.10 was used to test for publication bias.[21] Since all analyses were based on previously published studies, ethical approval or informed consent was not required.

RESULTS

Included Studies

We retrieved 7364 articles using the study key words. We performed full-paper reviews for 283 articles that consisted of 275 articles after we excluded 7089 articles judging from their titles and abstracts and 8 studies which were obtained from reference lists. Of these 283 articles, 236 studies were excluded because they did not meet all-of the inclusion criteria or met any exclusion criterion (see Inclusion criteria and Exclusion criteria). In one study, the data on effect measures were unclarified. Age-adjusted prevalence according to the 3 diabetes statuses were provided, but ORs were impossible to calculate because the unadjusted prevalence was not provided.[22] We queried the study's authors to clarify this issue. However, they did not respond and the study had to be excluded in this meta-analysis. Finally, 47 studies[23–68] were included in the meta-analysis (Figure 1).

Study Characteristics (Summary is Shown in Table 1)

As to study design, 24 studies[23–29,31–36,38–47,69] used a cohort design while 20 studies[48–67] used a cross-sectional design. One study[37] had two perspectives, those of a longitudinal and a cross-sectional study because it examined the number of patients with a history of AF at baseline and the incidence of paroxysmal AF during the follow-up period. The remaining two studies[30,68] used a case-control design of a hospital-based study population and were analyzed as cross-sectional because the diagnoses of prediabetes and AF were concurrently made.

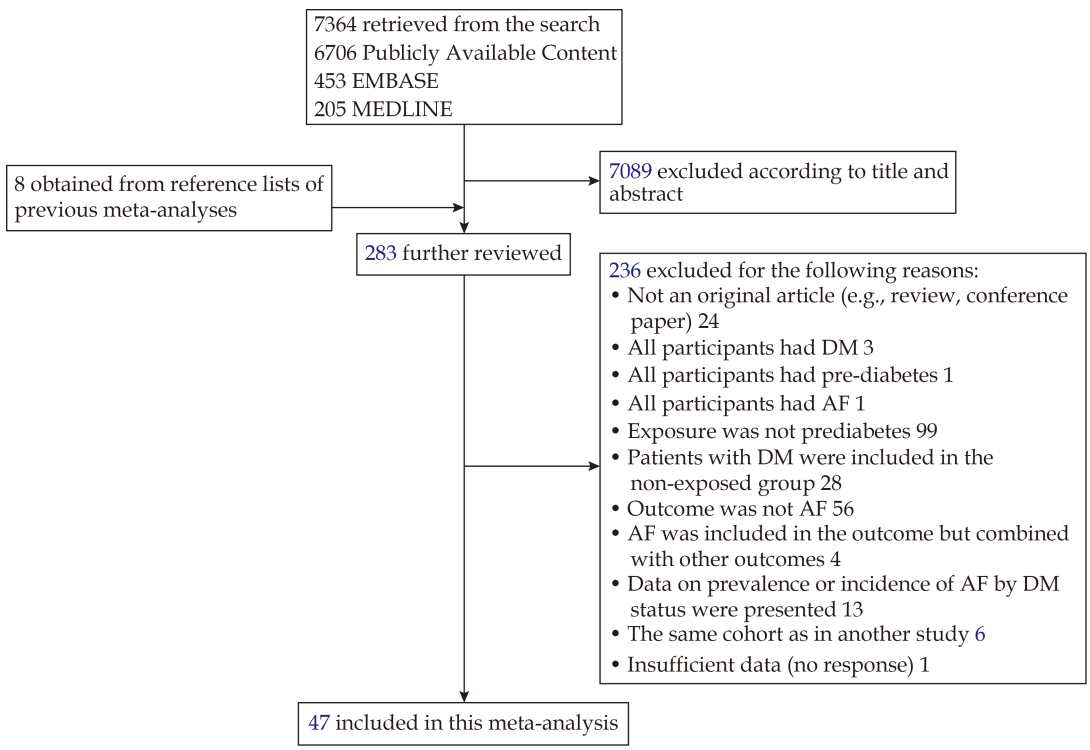


Figure 1 Study flow for choosing eligible studies. AF: atrial fibrillation; DM: diabetes mellitus.

Table 1 Summary of study characteristics.

Study source	Country	No. participants	No. cases	Mean age (yrs) [median]	Men, %	Population (if selected)	Follow-up duration
(a) Longitudinal study							
Yu (2025)[23]	China	11,663	1,343	68	49		11.1 yrs
Hsu (2023)[25]	Taiwan	28,618	1,189	64	46		6 yrs
Kim (2023)[24]	Korea	176,937	2,346	51	53		7.4 yrs
	United Kingdom	167,946	5,314	54	37		11.8 yrs
Johansson (2023)[26]	Sweden	139,661	4,948	49	48		7.9 yrs
Rentsch (2023)[27]	United Kingdom	427,435	23,088	58	46		12 yrs
Rorth (2023)[28]	Denmark	354,807	25,058	55	55		12 yrs
Sumin (2023)[29]	Russia	383	59	59	74	Admission for CABG	12.5 days
Upur (2022)[31]	China	3,330	122	56	78	MI	3.2 yrs
Kaneko (2021)[69]	Japan	1,180,062	5,656	40	57		3.3 yrs
Lind (2021)[32]	Sweden	294,057	135,562	47	54		18.2 yrs
Choe (2019)[33]	Korea	22,886,661	225,529	48	51		5.4 yrs
Yang (2019)[34]	Korea	6,199,629	127,268	48	56		7.2 yrs
Kokubo (2017)[35]	Japan	6,864	311	56	47		13.8 yrs
Lee (2017)[36]	Korea	227,102	1470	39	49		7.7 yrs
Masnaghetti (2017)[37]	Italy	2,490	448	66	69	Cardiac patients	3.1 yrs
AbuShady (2015)[38]	Egypt	60	10	64	63	Acute coronary syndrome	5.2 days
Nystrom (2015)[39]	Sweden	4,021	285	60	48		13.6 yrs
Blasco (2014)[40]	Spain	601	71	62	78	MI	No data
Sandhu (2014)[41]	USA	34,720	690	53	0		16.4 yrs
Sano (2014)[42]	Japan	7,206	296	57	36		6.4 yrs
Huxley (2012)[43]	USA	13,025	1,311	57	44		14.5 yrs
Schoen (2012)[44]	USA	34,720	1,079	53	0		16.4 yrs
Cicek (2011)[45]	USA	374	12	56	85	MI	6.4 days
Watanabe (2008)[46]	Japan	28,449	265	59	34		4.5 yrs
O'Sullivan (2006)[47]	Ireland	165	5	72	59	Admission for vascular surgery	6 moths
(b) Cross-sectional study							
Boxhammer (2024)[48]	Austria	725	36	63	73	MI	
Cheang (2024)[49]	China	12,649	395	62	56	Cancer	
Zaki (2024)[50]	Saudi Arabia	198	2	59	56	MetS	
Kim (2023)[51]	Korea	2,801,153	45629	49	57		
Tang (2023)[52]	Taiwan	172	5	58	45	Dialysis	
Zhang (2023)[53]	China	1,496	107	64	64	Stroke	
*Zhong (2023)[30]	China	1,840	920	68	50		
Djupsjo (2022)[54]	Sweden	618,694	17169	48	48	ED	
Gündoğmuş (2022)[55]	Turkey	527	111	76	52	MI	
Lupu (2022)[56]	Israel	1,412	174	67	69	ICU	
Veugen (2022)[57]	Netherlands	3,410	23	60	51		
Wei (2022)[58]	China	11,384	423	62	80	CAD	

Continued

Study source	Country	No. participants	No. cases	Mean age (yrs) [median]	Men, %	Population (if selected)	Follow-up duration
Kim (2021) [59]	Korea	661	261	69	60	Stroke	
Wnuk (2020)[60]	Poland	181	80	66	51	Stroke	
Fu (2019)[61]	China	11,488	144	58	35		
Nochioka (2019)[62]	Japan	535	226	66	75	CHF	
Khoo (2018)[63]	Australia	1,191	626	81	48	CHF	
Marto (2018)[64]	Portugal	247	16	49	58	Stroke	
Masnaghetti (2017)[37]	Italy	2,490	448	66	69	Cardiac patients	
Zadok (2017)[65]	Israel	3,993	1202	75	57	CHF	
Brunisholz (2016)[66]	USA	33,838	897	51	54	At high risk of diabetes	
Sun (2016)[67]	China	288	6	58	67	Brain hemorrhage	
*Johansen (2008)[68]	Norway	154	46	75	69		

*Case-control study. CABG: coronary artery bypass grafting; CAD: coronary artery disease; CHF: chronic heart failure; ED: emergency disease; ICU: intensive care unit; MetS: metabolic syndrome; MI: myocardial infarction.

Twenty studies[23,25,30,33–36,42,46,49,51–53,58,59,61–63,67,69] were conducted in Asian countries, which included Australia, China, Japan, Korea, and Taiwan, while 26 studies[26–29,31,32,37–41,43–45,47,48,50,54–57,60,64–66,68] were conducted in non-Asian countries which included European countries, Israel, Egypt, Saudi Arabia, Turkey, Russia, and the United States of America (USA). One study[24] was conducted in Korea and the United Kingdom (UK). Mean or median age of study populations ranged from 39 to 81 years (median, 59 years). Proportion of men ranged from 0% to 85% (median, 54%).

With regard to AF outcome, most of the included studies did not differentiate paroxysmal and non-paroxysmal AF with the exceptions that paroxysmal AF was specified in 2 studies[29,37] and paroxysmal and non-paroxysmal AF were separately analyzed in 2 studies.[23,41] One study[23] separately examined the risks of paroxysmal AF, non-paroxysmal AF, and a combination of paroxysmal and non-paroxysmal AF. While most studies did not differentiate valvular and non-valvular AF, valvular AF was specified in 7 studies.[24,25,30,31,33,36,61]

Most of the cross-sectional studies targeted selected patient groups (e.g., history of stroke) while most of the longitudinal studies did not use a selected population. Follow-up period of the included longitudinal studies ranged from 5.2 days to 18.2 years (median, 7.6 years). Among the 25 longitudinal studies, 2[25,31] had a retrospective cohort design and the remaining 23 studies used a prospective cohort.

Table 2 summarizes the criteria for prediabetes and study covariates for which the AF risk was adjusted. Only 5 studies[23,38,43,49,64] used both A1C and FPG and in only 6 studies[25,26,38,62,67,68] were OGTT performed. Five studies[33,39,42,46,50] used only the criterion of hyperglycemia in metabolic syndrome (MetS) as the definition of prediabetes. While no longitudinal study used casual blood glucose, it was used in 3 cross-sectional studies[54,55,65] for ascertaining prediabetes. While most longitudinal and case-control studies adjusted the AF risk for several covariates, no cross-sectional study adjusted for covariates except the one study that adjusted only for age.[61]

Study Quality

Results of assessment of study quality using NOS are presented in Supplementary Material 3. The main reason for a reduced study quality was the recruitment of a selected and/or hospital-based study population. The hospital-based studies[25,29–31,37,38,40,45,47–50,52–56,58–60,62–68] could have a selection bias although 3 of these hospital-based studies[25,30,68] recruited non-specified patients. Other main reasons for the low study quality were insufficient adjustment for study covariates in some studies with a cohort design[24,27–29,31–33,35–38,40,45,47] and all studies with a cross-sectional or case-control design, failure to describe methods for ascertaining AF[29,37,38,41,44,48,56,59,60,62,65–67] and prediabetes,[51,52,57] and missing data that could introduce biases.[35,41,42,44,57]

Studies with a cohort design having a follow-up period < 5 years or that was unclarified[29,31,37,38,40,45–47,69] or did not state that all participants did not have AF at

Table 2 Summary of criteria for prediabetes and covariates.

Study source	Criteria for prediabetes	Covariate
(a) Cohort study		
Yu (2025)[23]	FPG = 5.6–6.9 mmol/L or A1C = 5.7%–6.4%	Age, smoking, alcohol, PA, SBP, DBP, TG, LDL-C, HDL-C, BMI
Hsu (2023)[25]	FPG = 5.6–6.9 mmol/L or 2hPG = 7.8–11.0 mmol/L	Age, sex, BMI, HT, HL, CAD, gout, COPD, CKD, PAD, stroke, NT-po-BNP, LA, LVEF, LV mass
Kim (2023)[24]	FPG = 5.6–6.9 mmol/L	Age, sex, smoking, alcohol, economic status.
Johansson (2023)[26]	FPG = 6.1–6.9 mmol/L or 2hPG = 8.9–12.1 mmol/L	Age, sex, smoking, alcohol, PA, BMI, SBP, TC, BMI, antihypertensive drugs, education, marital status
Rentsch (2023)[27]	A1C = 6.0%-6.4%	Age, TC, GFR, CRP, HT, antihypertensive drugs, FH of CVD
Rorth (2023)[28]	A1C = 42–48 mmol/mol	Age, sex, CHD, cancer, renal disease, COPD, HT
Sumin (2023)[29]	FPG = 6.1–6.9 mmol/L	None
Upur (2022)[31]	FPG = 5.6–6.9 mmol/L	None
Kaneko (2021)[69]	FPG = 5.6–6.9 mmol/L	Age, sex, obesity, high WC, HT, dyslipidemia, smoking, alcohol
Lind (2021)[32]	FPG = 6.1–6.9 mmol/L	Age, sex, TC, TG, economic status, BMI
Choe (2019)[33]	FPG ≥ 5.6 mmol/L or hypoglycemic drugs	Age, sex, smoking, alcohol, PA
Yang (2019)[34]	FPG = 5.6–6.9 mmol/L	Age, sex, smoking, BMI, alcohol, income, PA, HT, dyslipidemia
Kokubo (2017)[35]	FPG = 5.6–6.9 mmol/L	Age, sex
Lee (2017)[36]	FPG = 5.6–6.9 mmol/L	Age, sex, smoking, alcohol
Masnaghetti (2017)[37]	FPG ≥ 6.1 mmol/L	Age, gender, BMI, HT, LVEF, CAD, cardiac surgery, HF
AbuShady (2015)[38]	FPG = 5.6–6.9 mmol/L or A1C = 5.7%–6.4% or 2 hPG = 7.8–11.0 mmol/L	None
Nystrom (2015)[39]	FPG ≥ 5.6 mmol/L or hypoglycemic drugs	Age, sex, smoking, alcohol, PA, components of MetS
Blasco (2014)[40]	A1C = 5.5%–6.4%	None
Sandhu (2014)[41]	A1C ≥ 4.84%	Age, sex, smoking, alcohol, PA, aspirin, vitamin E, beta-carotene, BMI, HT, blood lipids, inflammation score, A1C, GFR, MI, stroke, revascularization
Sano (2014)[42]	FPG ≥ 6.1 mmol/L or hypoglycemic drugs	Age, sex, alcohol, smoking, obesity, HT, HL, abnormal ECG, MI, CHF
Huxley (2012)[43]	FPG = 5.6–6.9 mmol/L or A1C = 5.7%–6.4%	Age, smoking, race, sex, education, income, PH of CVD, BMI, SBP, antihypertensive drugs,
Schoen (2012)[44]	A1C ≥ 4.84%	Age, smoking, PA, alcohol, education, race/ethnicity, hypercholesterolemia, height, HT, BMI
Cicek (2011)[45]	A1C = 5.7%–6.4%	None
Watanabe (2008)[46]	FPG ≥ 5.6/6.1 mmol/L or hypoglycemic drugs	Age, sex, components of MetS
O'Sullivan (2006)[47]	A1C ≥ 6.1%	None
(b) Cross-sectional study		
Boxhammer (2024)[48]	A1C = 5.7%–6.4%	None
Cheang (2024)[49]	FPG = 5.6–6.9 mmol/L or A1C = 5.7%–6.4%	None
Zaki (2024)[50]	FPG ≥ 5.6 mmol/L or hypoglycemic drugs	None

Continued

Study source	Criteria for prediabetes	Covariate
Kim (2023)[51]	FPG = 5.6–6.9 mmol/L	None
Tang (2023)[52]	FPG = 5.6–6.9 mmol/L	None
Zhang (2023)[53]	FPG = 5.6–6.9 mmol/L	None
*Zhong (2023)[30]	FPG = 6.1–6.9 mmol/L	Age, sex, HT, CHD, antihypertensive drugs, statins, TC, LDL-C, HDL-C, APO-A1, APO-B, Cr, Alb
Djupsjo (2022)[54]	Random BG = 7.8–11.0 mmol/L	None
Gündoğmuş (2022)[55]	Random BG ≥ 9.0 mmol/L	None
Lupu (2022)[56]	A1C = 5.7–6.4%	None
Veugen (2022)[57]	Unclear	None
Wei (2022)[58]	A1C = 5.7–6.4%	None
Kim (2021)[59]	A1C = 5.7–6.4%	None
Wnuk (2020)[60]	FPG = 5.6–6.9 mmol/L	None
Fu (2019)[61]	FPG = 5.6–6.9 mmol/L	Age
Nochioka (2019)[62]	FPG = 6.1–6.9 mmol/L or 2hPG = 7.8–11.0 mmol/L	None
Khoo (2018)[63]	A1C = 5.7–6.4%	None
Marto (2018)[64]	A1C = 5.7–6.4% or FPG = 6.1–6.9 mmol/L	None
Masnaghetti (2017)[37]	FPG ≥ 6.1 mmol/L	None
Brunisholz (2016)[66]	FPG = 5.6–6.9 mmol/L	None
Zadok (2017)[65]	random BG = 7.8–11.0 mmol/L	None
Sun (2016)[67]	FPG = 6.1–6.9 mmol/L or 2hPG = 7.8–11.0 mmol/L	None
*Johansen (2008)[68]	FPG = 6.1–6.9 mmol/L or 2hPG = 7.8–11.0 mmol/L	Age**

*Case-control design; **All participants were 75 years old. A1C: hemoglobin A1c; Alb: albumin; Apo-A1: apolipoprotein-A1; Apo-B: apolipoprotein B; BG: blood glucose; BMI: body mass index; CHF: chronic heart failure; CKD: chronic kidney disease; COPD: chronic occlusive pulmonary disease; CHD: coronary heart disease; CRP: C-reactive protein; Cre: creatinine; CRP: C reactive protein; CVD: cardiovascular disease; DBP: diastolic blood pressure; ECG: electrocardiogram; FH: family history; FPG: fasting plasma glucose; GFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; HT: hypertension; HL: hyperlipidemia; LA: left atrial size; LDL-C low-density lipoprotein cholesterol; LV mass: left ventricular mass; LVEF: left ventricular ejection fraction; MetS: metabolic syndrome; NT-proGNP: N-terminal pro b-type natriuretic peptide; PA: physical activity; PAD: peripheral artery disease; PH: past history; SBP: systolic blood pressure; SES: socio-economic status; TC: total cholesterol; TG: triglycerides; 2hPG: 2-h postprandial glucose; WC: waist circumference.

baseline[29,31,37,38,40,45,47] were judged as having low quality. In studies with a cross-sectional design, none justified the sample size and some[49,50,54] did not perform statistical tests to compare participants with and without prediabetes, which could introduce biases.

Association of Prediabetes with AF Risk in Longitudinal Studies (Summary is Shown in Table 3)

Among the 25 longitudinal studies (see Included studies), 2[41,44] had the same cohort. We chose the one study[44] wherein the outcome combined paroxysmal and non-paroxysmal AF. The other study,[41] in which paroxysmal and non-paroxysmal AF were separately analyzed, was not chosen in the overall analysis and was kept for a subsequent stratified analysis. One study[24] consisted of 2 cohorts but we used only the Korean cohort because the other cohort, the UK cohort, overlapped with that of another study.[27] Overall RR (95% CI) for AF of the 24 included studies was 1.12 (1.06–1.18) (Figure 2). There was between-study heterogeneity (I^2 = 92.9 %, P < 0.001).

One study[69] directly provided data on PAF and its corresponding 95% CI. However, the values seemed to be miscalculated; thus, we recalculated them. Twenty studies[23–26,28,29,31–40,43–45,47] presented data on the number of participants and AF cases according to prediabetes and

Table 3 Pooled relative risk (RR) with 95% CI for atrial fibrillation in relation to pre-diabetes.

	No. data	Effect measure (95% CI)	χ^2	*P* for χ^2	I^2	Tau	*Z*	*P* for *Z*	*P* for difference
RR									
Overall RR	32	1.12 (1.06–1.18)	438.7	< 0.001	92.9%	0.0101	4.44	< 0.001	< 0.001
*Crude RR	29	1.49 (1.37–1.62)	1782.4	< 0.001	98.4%	0.0381	9.17	< 0.001	
Overall PAF									
*Overall PAF	29	2.7% (1.4%–4.0%)	1064.5	< 0.001	97.4%	0.0006	4.13	< 0.001	< 0.001
*Crude PAF		8.8% (2.7%–14.8%)	12145.9	< 0.001	99.8%	0.0106	4.17	< 0.001	
Limited to studies which presented both adjusted and crude RR									
Adjusted RR	22	1.10 (1.05–1.16)	404.5	< 0.001	94.8%	0.0098	3.59	< 0.001	< 0.001
Crude RR		1.46 (1.34–1.60)	1774.7	< 0.001	98.8%	0.0381	8.38	< 0.001	
Adjusted PAF	22	2.5% (1.3%–3.7%)	1046.9	< 0.001	98.0%	0.0006	3.85	< 0.001	0.001
Crude PAF		8.5% (4.2%–12.6%)	11520.5	< 0.001	99.8%	0.0107	3.82	< 0.001	

*Analysis was limited to studies which presented data on the number of participants who developed atrial fibrillation in each non-exposed (normoglycemia) and exposed (prediabetes) group. PAF: population attributable fraction; RR: relative risk.

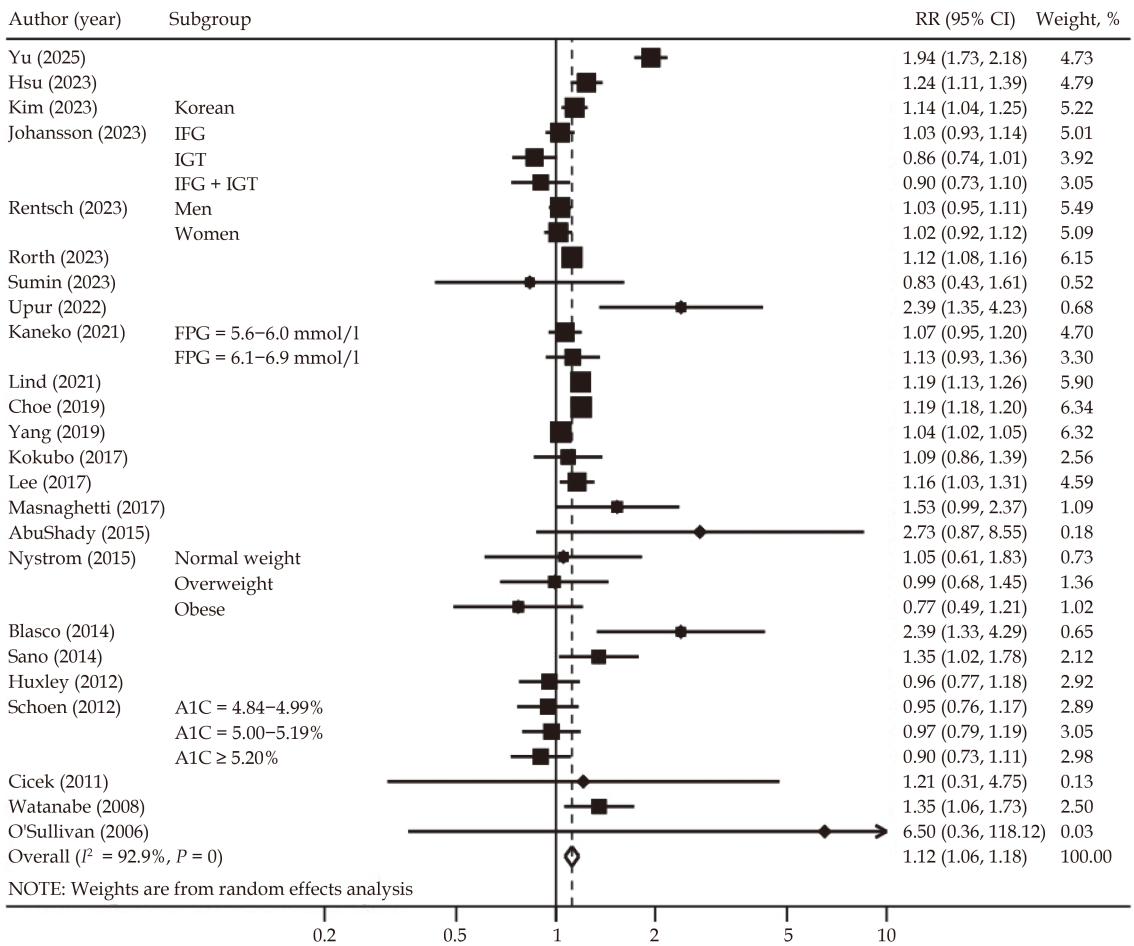


Figure 2 Forest plot of relative risk with 95% CI for AF in prediabetes compared with normoglycemia. The RR in each study is indicated by a square. Area of squares is proportional to the study weight (i.e., inverse of square of the standard error of the RR). Pooled RR is indicated by a diamond. AF: atrial fibrillation; A1C: hemoglobin A1c; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; RR: relative risk.

normoglycemia which made it possible to calculate the PAF in addition to the crude RR. Overall, the PAF (95% CI) was 2.7% (1.4%-4.0%) (Figure 3). There was large between-study heterogeneity (I^2 = 97.4%, P < 0.001). Overall crude RR (95% CI) was 1.49 (1.37–1.62) (Figure 4). Based on the crude RR, the pooled crude PAF (95% CI) was 8.8% (4.7%-12.7%) (Supplementary Material 4).

Among the 25 longitudinal studies, 14 studies[23–26,28,32–36,41,43,44,69] presented the adjusted RR which was adjusted for at least one covariate and the data required for calculating the crude RR. There was a significant difference between the pooled adjusted and crude RR (95% CI) (1.10 [1.04–1.16] *vs.* 1.46 [1.34–1.60]; P < 0.001) (Supplementary Material 5) and between the pooled adjusted and crude PAF (95% CI) (2.5% [1.3%-3.8%] *vs.* 8.5% [4.2%-12.6%]; P = 0.001) (Supplementary Material 6).

Details of results of the stratified analyses of the RR and PAF for AF in relation to prediabetes are provided in Table 4 and Table 5, respectively. Studies of participants with a mean age of ≥ 65 years revealed a significantly higher pooled RR (95% CI) compared with those of participants with a mean age of < 65 years (1.42 [1.04–1.94] *vs.* 1.07 [1.02–1.13]; P = 0.02) and PAF (95% CI) (12.7% [0.4%–23.6%] *vs.* 1.6% [0.2%–2.9%]; P < 0.001). Male-dominant (≥ 50%) longitudinal studies tended to show a higher RR (P = 0.11) and PAF (3.2% *vs.* 0.4%; P < 0.001) than female-dominant studies. When studies from Asian countries were examined, the pooled RR (95% CI) was significantly higher than those from non-Asian countries (1.23 [1.14–1.33] *vs.* 1.03 [0.97–1.10]; P = 0.047). Hospital-based studies revealed a higher pooled RR (95% CI) compared with general population-based studies (1.57 [1.17–2.11] *vs.* 1.10 [1.04–1.15]; P = 0.02). When the outcome included non-paroxysmal AF, the pooled

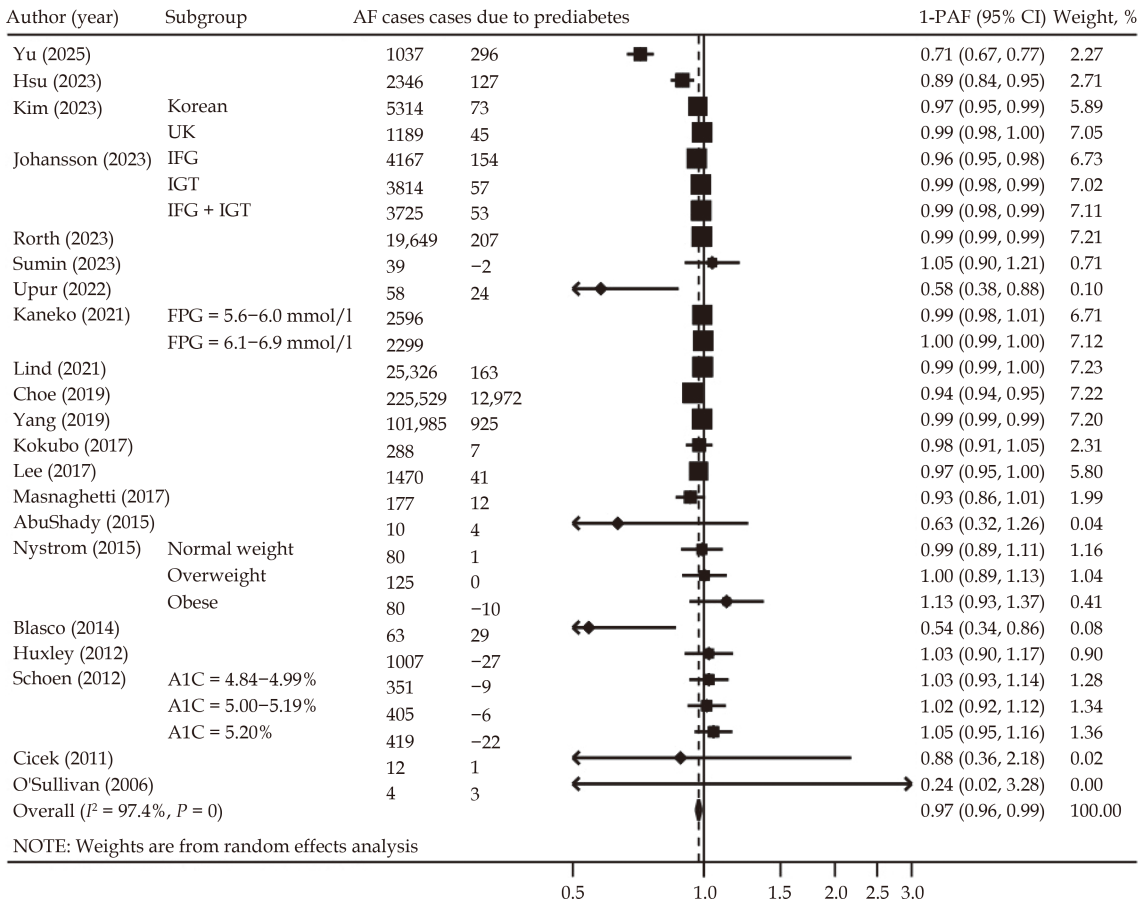


Figure 3 Forest plot of values obtained by subtracting the PAF from 1 [1- PAF] with 95% CI for AF in prediabetes compared with normoglycemia. The [1-PAF] in each study is indicated by a square. Area of squares is proportional to the study weight (i.e., inverse of square of the standard error of the [1-PAF]). Pooled [1-PAF] is indicated by a diamond. PAF was calculated by subtracting [1-PAF] from 1. AF: atrial fibrillation; A1C: hemoglobin A1c; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; PAF: population attributable fraction.

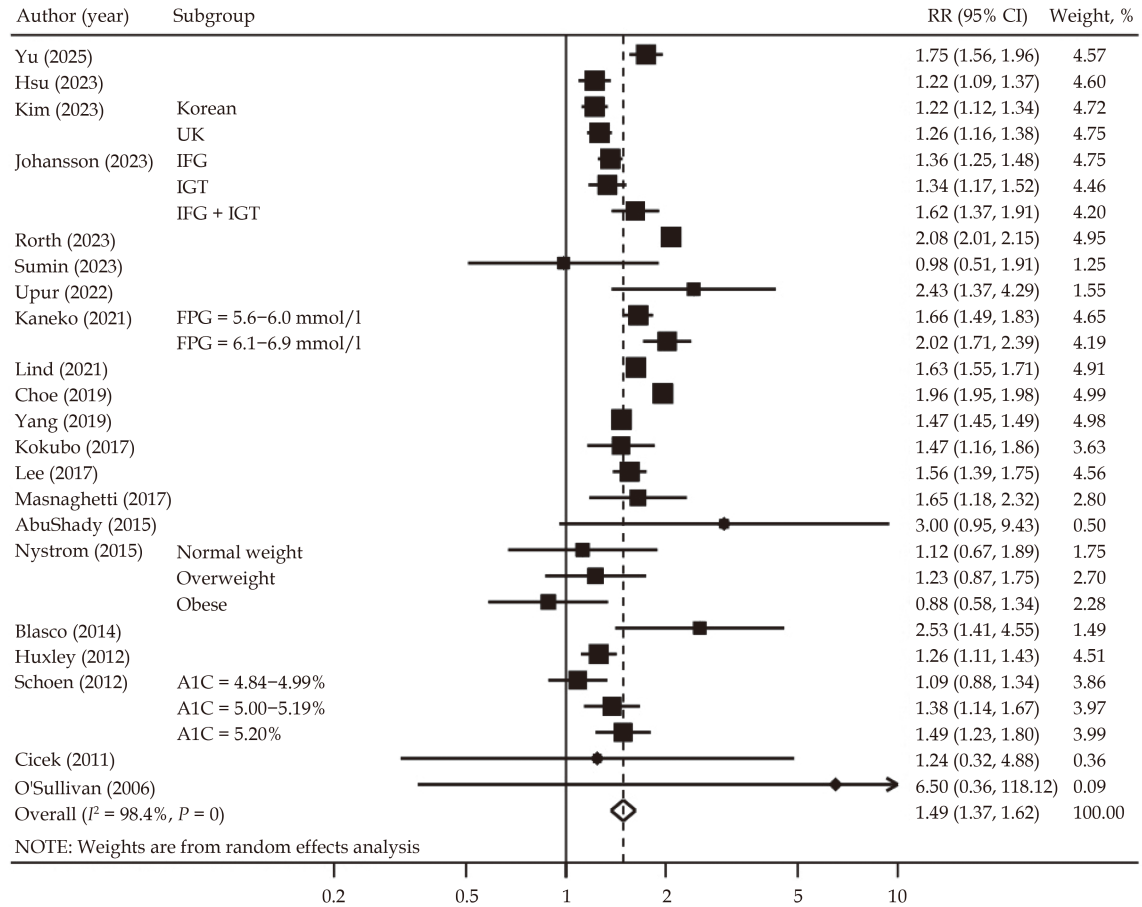


Figure 4 Forest plot of relative risk with 95% CI for AF in prediabetes compared with normoglycemia when the analysis was limited to cohort studies presenting the crude RR. The RR in each study is indicated by a square. Area of squares is proportional to the study weight (i.e., inverse of square of the standard error of the RR). Pooled RR is indicated by a diamond. AF: atrial fibrillation; A1C: hemoglobin A1c; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; UK: United Kingdom.

PAF (95% CI) was lower than when the outcome was limited to paroxysmal AF (2.8% [1.5%–4.1%] *vs.* −0.6% [−5.8%–4.2%]; P = 0.009). As to methods for ascertaining prediabetes, when both A1C and FPG were used for diagnosing prediabetes, the pooled PAF (95% CI) for AF was higher than when either A1C or FPG was used (18.3% [−12.3%–40.5%] *vs.* 2.0% [0.8%–3.3%]; P = 0.003). However, whether criteria of Mets were used did not significantly affect the pooled RR (P = 0.85) and PAF (P = 0.76). Longer follow-up (≥ 5 years) studies tended to reveal a more modest RR (95% CI) than those with a shorter follow-up (1.09 [1.03–1.15] *vs.* 1.26 [1.11–1.43]; P = 0.07). Although studies with adjustment for at least 1 confounder revealed a significantly small pooled RR (P = 0.01), studies which controlled for obesity and hypertension, which could influence study quality (see Supplementary Material 2), did not reveal a significantly different RR (P = 0.84) or PAF (P = 0.82) compared with studies that did not control for these confounders.

Association of Prediabetes with AF risk in Cross-sectional studies (Summary is shown in Table 6)

Overall OR (95% CI) of the 23 cross-sectional studies (see Included studies) was 1.45 (1.26–1.67) (Figure 5). Between-study heterogeneity was highly significant (I^2 = 93.1%, P<0.001). All 23 studies provided the crude OR. The pooled crude OR (95% CI) was 1.42 (1.23–1.64) (Figure 6), which was quite similar to the overall OR because the crude OR was pooled in most of the studies to estimate the overall OR. There were only 2 studies [30,61] which presented the adjusted and crude OR. Pooled adjusted and crude OR (95% CI) were 1.46 (1.12–1.89) and 1.25 (0.75–2.09), respectively (Supplementary Material 7). The difference between the 2 pooled ORs was not significant (P = 0.18).

Stratified analyses of the OR for AF in relation to pre-

Table 4 Stratified analysis of pooled relative risk with 95% confidence interval (CI) for atrial fibrillation (AF).

Characteristic	No. data	RR (95% CI)	χ^2	*P* for χ^2	I^2	Tau	*Z*	*P* for *Z*	Meta-regression
Country									0.047
Asian	12	1.23 (1.14–1.33)	365.0	< 0.001	97.0%	0.012	5.34	< 0.001	
Non-Asian	20	1.03 (0.97–1.10)	53.4	0.001	64.4%	0.007	0.96	0.34	
Mean age*									0.02
≥ 65 yrs	5	1.42 (1.04–1.94)	114.1	< 0.001	96.5%	0.092	2.18	0.03	
< 65 yrs	28	1.07 (1.02–1.13)	341.1	< 0.001	92.1%	0.011	2.59	0.01	
% men*									0.11
≥ 50%	22	1.15 (1.08–1.22)	284.0	< 0.001	92,6%	0.009	4.57	< 0.001	
< 50%	18	1.03 (1.01–1.05)	17.3	0.053	37.8%	0.024	2.52	0.01	
Used MetS criteria for ascertaining prediabetes									0.85
Yes	6	1.19 (1.18–1.20)	6.5	0.26	23.1%	-	41.59	< 0.001	
No	26	1.11 (1.05–1.18)	191.8	< 0.001	87.0%	0.013	3.56	< 0.001	
BG indicator for ascertaining prediabetes*									0.04
Both A1C and FPG	3	1.55 (0.83–2.86)	33.3	< 0.001	94.0%	0.231	1.38	0.17	0.39
A1C only	9	1.04 (0.96–1.13)	20.6	0.008	61.2%	0.006	0.95	0.34	0.16
FPG only	21	1.11 (1.05–1.18)	321.8	< 0.001	93.8%	0.009	3.70	< 0.001	0.44
Used OGTT for ascertaining prediabetes*									0.81
Yes	5	1.03 (0.87–1.22)	19.6	0.024	79.6%	-	0.33	0.75	
No	27	1.14 (1.08–1.20)	411.5	< 0.001	93.7%	0.010	4.71	< 0.001	
Specified outcome to non-valvular AF*									0.15
Yes	6	1.19 (1.18–1.20)	10.8	0.06	53.6%	-	41.89	< 0.001	
No	27	1.09 (1.03–1.16)	180.9	< 0.001	85.6%	0.013	2.94	0.003	
Paroxysmal AF or not*									0.22
Specified paroxysmal AF	6	1.22 (0.69–2.14)	103.4	< 0.001	95.2%	0.460	0.69	0.49	0.08
Both paroxysmal and non-paroxysmal AF	30	1.12 (1.06–1.17)	436.1	< 0.001	93.3%	0.010	4.33	< 0.001	0.38
Specified non-paroxysmal AF	4	1.56 (1.38–1.77)	1.3	0.72	0.0%	-	7.05	< 0.001	0.49
Study population									0.02
General	24	1.10 (1.04–1.15)	418.4	< 0.001	94.5%	0.010	3.50	< 0.001	
hospital-based	8	1.57 (1.17–2.11)	14.36	0.045	51.2%	0.071	3.02	0.003	
Were patients with DM potentially included in the exposed group?									0.57
Yes	13	1.09 (0.995–1.18)	26.9	0.01	55.4%	0.009	1.84	0.06	
No	19	1.19 (1.10–1.28)	185.55	< 0.001	90.3%	0.014	3.80	< 0.001	
Design									0.21
Retrospective	4	1.27 (1.14–1.41)	7.2	0.07	58.4%	-	4.46	< 0.001	
Prospective	28	1.11 (1.05–1.16)	428.0	< 0.001	93.7%	0.010	3.80	< 0.001	
Follow-up duration									0.07
≥ 5 yrs	21	1.09 (1.03–1.15)	415.3	< 0.001	95.2%	0.011	3.02	0.003	

Continued

Characteristic	No. data	RR (95% CI)	χ^2	*P* for χ^2	I^2	Tau	*Z*	*P* for *Z*	Meta-regression
< 5 yrs	11	1.26 (1.11–1.43)	17.5	0.02	53.9%	0.014	3.63	< 0.001	
Covariates									0.01
≥ 1	26	1.11 (1.05–1.16)	421.8	< 0.001	94.1%	0.010	4.00	< 0.001	
None	6	1.84 (1.33–2.53)	8.7	0.12	42.3%	-	3.72	< 0.001	
Included hypertension and obesity or their indicators in the covariates									0.84
Yes	18	1.09 (0.99–1.20)	145.3	< 0.001	88.3%	0.033	1.73	0.08	
No	14	1.14 (1.08–1.20)	51.5	< 0.001	74.7%	0.003	5.15	< 0.001	

*In some studies, data for two or more strata existed. If overall and stratified data were both given, stratified data were chosen. A1C: hemoglobin A1c; AF: atrial fibrillation; DM: diabetes mellitus; FPG: fasting plasma glucose; MetS: metabolic syndrome; OGTT: oral glucose tolerance test; RR: relative risk.

Table 5 Stratified analysis of longitudinal studies for calculating pooled PAF with 95% CI for AF.

	No. data	PAF (95% CI)	χ^2	*P* for χ^2	I^2	Tau	*Z*	*P* for *Z*	Meta-regression
Country									0.13
Asian	8	5.1% (2.7%–7.5%)	633.5	< 0.001	98.6%	0.0012	4.06	< 0.001	
Non-Asian*	19	1.3% (0.8%–1.8%)	44.0	0.001	59.1%	< 0.0001	4.69	< 0.001	
Mean age*									< 0.001
≥ 65 yrs	5	12.7% (0.4%–23.6%)	85.7	< 0.001	95.3%	0.0174	2.01	0.04	
< 65 yrs	25	1.6% (0.2%–2.9%)	1010.3	< 0.001	97.6%	0.0006	2.26	0.02	
% men*									< 0.001
≥ 50%	18	3.2% (1.6%–4.7%)	1020.1	< 0.001	98.3%	0.0007	3.92	< 0.001	
< 50%	14	0.4% (−0.2%–1,1%)	26.1	0.02	50.4%	< 0.0001	1.27	0.21	
Used MetS criteria for ascertaining prediabetes									0.76
Yes	4	5.7% (5.5%–6.0%)	5.0	0.17	40.1%	-	39.98	< 0.001	
No	25	1.7% (1.1%–2.3%)	148.7	< 0.001	83.9%	0.0001	5.14	< 0.001	
BG indicator									< 0.001
Both A1C and FPG	3	18.3% (−12.3%–40.5%)	23.8	< 0.001	91.6%	0.0588	1.24	0.21	< 0.001
A1C only	7	1.0% (0.7%–1.4%)	9.8	0.13	38.9%	-	5.86	< 0.001	0.72
FPG only	19	2.3% (0.8%–3.7%)	948.7	< 0.001	98.1%	0.0007	3.09	0.002	0.17
Used OGTT									0.60
Yes	5	2.6% (1.1%–4.2%)	20.3	< 0.001	80.3%	0.0002	3.35	0.001	
No	24	2.6% (1.0%–4.1%)	1044.1	< 0.001	97.8%	0.0007	3.28	0.001	
Specified outcome of non-valvular AF									0.66
Yes	6	4.4% (1.3%–7.4%)	151.4	< 0.001	96.7%	0.0011	2.78	0.005	
No	23	1.5% (0.8%–2.2%)	125.1	< 0.001	82.7%	0.0001	4.18	< 0.001	
Paroxysmal AF or not**									0.007
Specified outcome of paroxysmal AF	5	−0.6% (−5.8%–4.2%)	8.2	0.09	51.1%	-	−0.25	0.80	0.01
Both paroxysmal and non-paroxysmal AF	27	2.7% (1.4%–3.9%)	1062.1	< 0.001	97.6%	0.0006	4.02	< 0.001	0.02

Continued

	No. data	PAF (95% CI)	χ^2	*P* for χ^2	I^2	Tau	*Z*	*P* for *Z*	Meta-regression
Specified outcome of non-paroxysmal AF	3	16.6% (4.9%–26.9%)	0.2	0.89	0.0%	-	2.72	0.007	0.003
Study population									0.11
General	21	2.3% (1.0%–3.6%)	1038.2	< 0.001	98.1%	0.0006	3.43	0.001	
Hospital-based	8	11.6% (1.7%–20.5%)	15.6	0.026	55.0%	0.0079	2.27	0.02	
Were patients with DM potentially included in the exposed group?									0.24
Yes	11	0.6% (−2.9%–3.9%)	281.1	0.048	96.4%	0.0021	0.34	0.74	
No	18	2.5% (1.4%–3.9%)	1040.1	< 0.001	97.8%	0.0006	3.53	< 0.001	
Design									0.37
Retrospective	4	8.1% (−1.2%–16.6%)	8.7	0.03	65.5%	0.0054	1.71	0.09	
Prospective	22	2.8% (1.4%–4.1%)	1047.2	< 0.001	97.7%	0.0006	3.53	< 0.001	
Follow-up duration									0.96
≥ 5 yrs	19	3.2% (1.5%–4.7%)	770.2	< 0.001	97.7%	0.0008	3.80	< 0.001	
< 5 yrs	10	0.7% (−0.2%–1.6%)	19.6	0.02	54.0%	0.0001	1.51	0.13	
Covariates									0.16
≥ 1	23	2.6% (1.4%–3.9%)	1048.6	< 0.001	97.9%	0.0006	4.02	< 0.001	
None	6	28.8% (−2.1%–50.4%)	14.9	0.01	66.4%	0.1077	1.85	0.07	
Included both hypertension and obesity or their indicators in the covariates									0.82
Yes	16	2.4% (1.1%–3.6%)	119.1	< 0.001	97.9%	0.0003	3.71	< 0.001	
No	13	2.6% (0.3%–4.7%)	897.3	< 0.001	98.7%	0.0008	2.26	0.02	

*In some studies, data for two or more strata existed. AF: atrial fibrillation; A1C: hemoglobin A1c; DM: diabetes mellitus; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; PAF: population attributable fraction.

Table 6 Pooled odds ratio with 95% CI for atrial fibrillation in relation to prediabetes.

	No. data	OR (95% CI)	χ^2	*P* for χ^2	I^2	Tau	*Z*	*P* for *Z*	
All cross-sectional studies									
Overall OR	23	1.45 (1.26–1.67)	320.6	< 0.001	93.1%	0.063	5.09	< 0.001	
*Crude OR	23	1.42 (1.23–1.64)	327.8	< 0.001	93.3%	0.064	4.81	< 0.001	
Limited to studies presenting both adjusted and crude OR									
Adjusted OR	2	1.46 (1.12–1.89)	0.3	0.57	0.0%	-	2.82	0.005	*P* for difference=0.18
*Crude OR		1.25 (0.75–1.09)	4.5	0.03	77.7%	0.106	0.87	0.39	

*Analyzed studies which presented data on the number of participants having atrial fibrillation in each non-exposed (normoglycemia) and exposed (prediabetes) group.

diabetes are presented in Table 7. These meta-regression analyses did not show differences in the pooled OR among strata except that using A1C (i.e., using A1C only or both A1C and FPG) for diagnosing prediabetes resulted in a higher OR (95% CI) than not using A1C for diagnosing prediabetes (2.13 [1.23–3.71] *vs.* 1.20 [1.04–1.39]; *P* for difference = 0.02).

Comparison of Diabetes and Prediabetes for the Strength of Association with AF Risk

The risk measures for AF in prediabetes and diabetes are given in Table 8. Fifteen longitudinal studi-

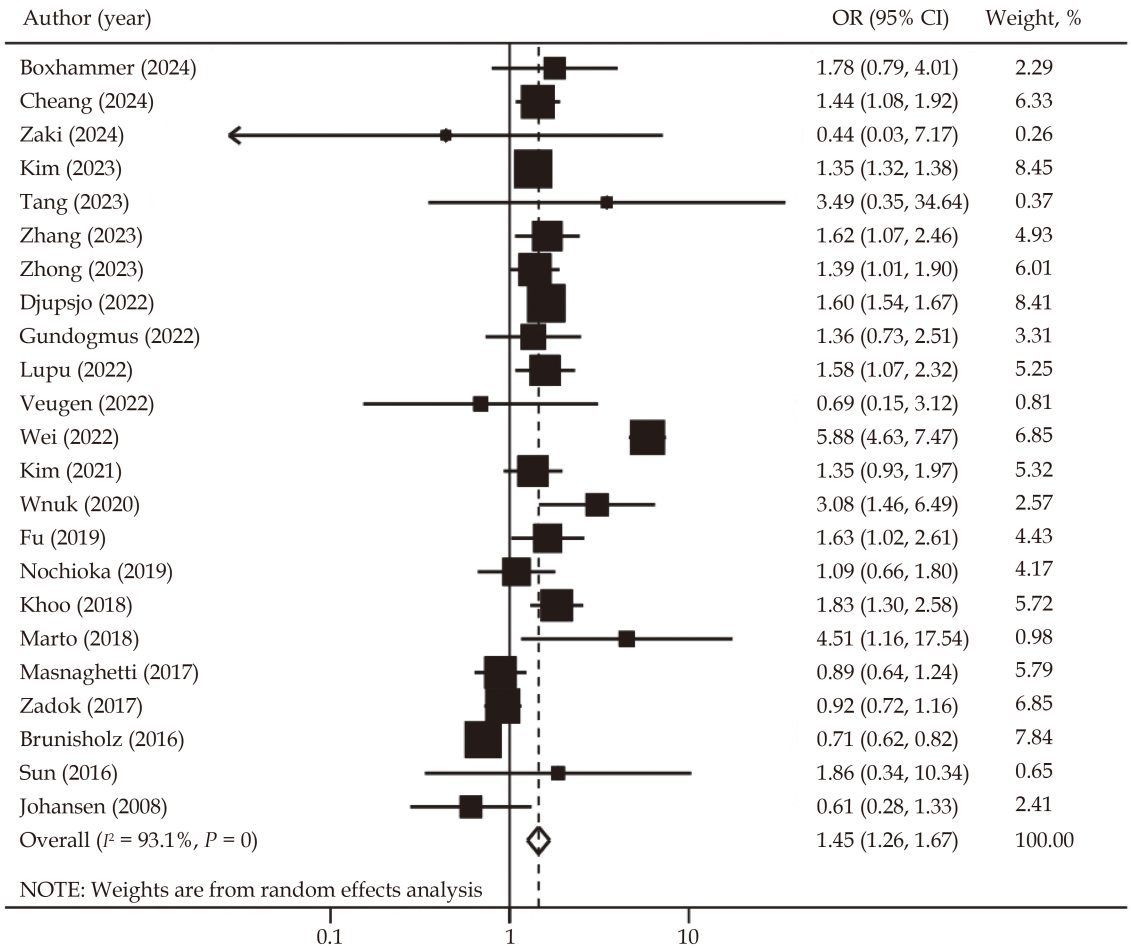


Figure 5 Forest plot of OR with 95% CI for AF in prediabetes compared with normoglycemia. The OR in each study is indicated by a square. Area of squares is proportional to the study weight (i.e., inverse of square of the standard error of the OR). Pooled OR is indicated by a diamond. AF: atrial fibrillation.

es[23,26–29,31,32,34,35,37,40,43,45,47,69] provided data on the RR for AF in relation to both prediabetes and diabetes. The difference was significant (P = 0.003) but modest in the pooled RR value (95% CI) between prediabetes and diabetes (1.12 [1.05–1.20] *vs.* 1.15 [1.10-1.20]) (Figure 7) although the multi-level mixed meta-regression analysis, which considered within-study correlations, showed that the risk magnitude was significantly larger for diabetes than for prediabetes (P = 0.003). Thirteen longitudinal studies[23,26,28,29,31,32,34,35,37,40,43,45,47] presented data on the number of participants and the AF incidence according to both prediabetes and diabetes. The pooled PAF (95% CI) based on these data were 1.6% [0.9%-2.3%] for diabetes and 1.0% (0.7%-1.3%) for prediabetes (Figure 8) with the difference not significant (P = 0.98). There were also no significant differences in the pooled crude RR (P = 0.85) and crude PAF (P = 0.19).

There were 19 cross-sectional studies[30,37,48,49,51,52,54–65,68] which presented the OR for AF in both diabetes and prediabetes. The pooled OR (95% CI) was 1.49 (1.13–1.96) for prediabetes and 1.54 (1.34–1.78) for diabetes (Figure 9) with the difference not significant (P = 0.76). There was also no significant difference in the pooled crude OR (P = 0.89).

Publication Bias

Funnel plots of risk measures in each study are provided in Supplementary Material 8 to Supplementary Material 13. In the funnel plots of longitudinal studies, distributions of plots were visually asymmetrical in estimating the pooled RR and PAF (Supplementary Materials 8, 9, 10, 11) where statistically significant publication biases were detected (Supplementary Material 14) and were almost symmetrical in estimating the pooled

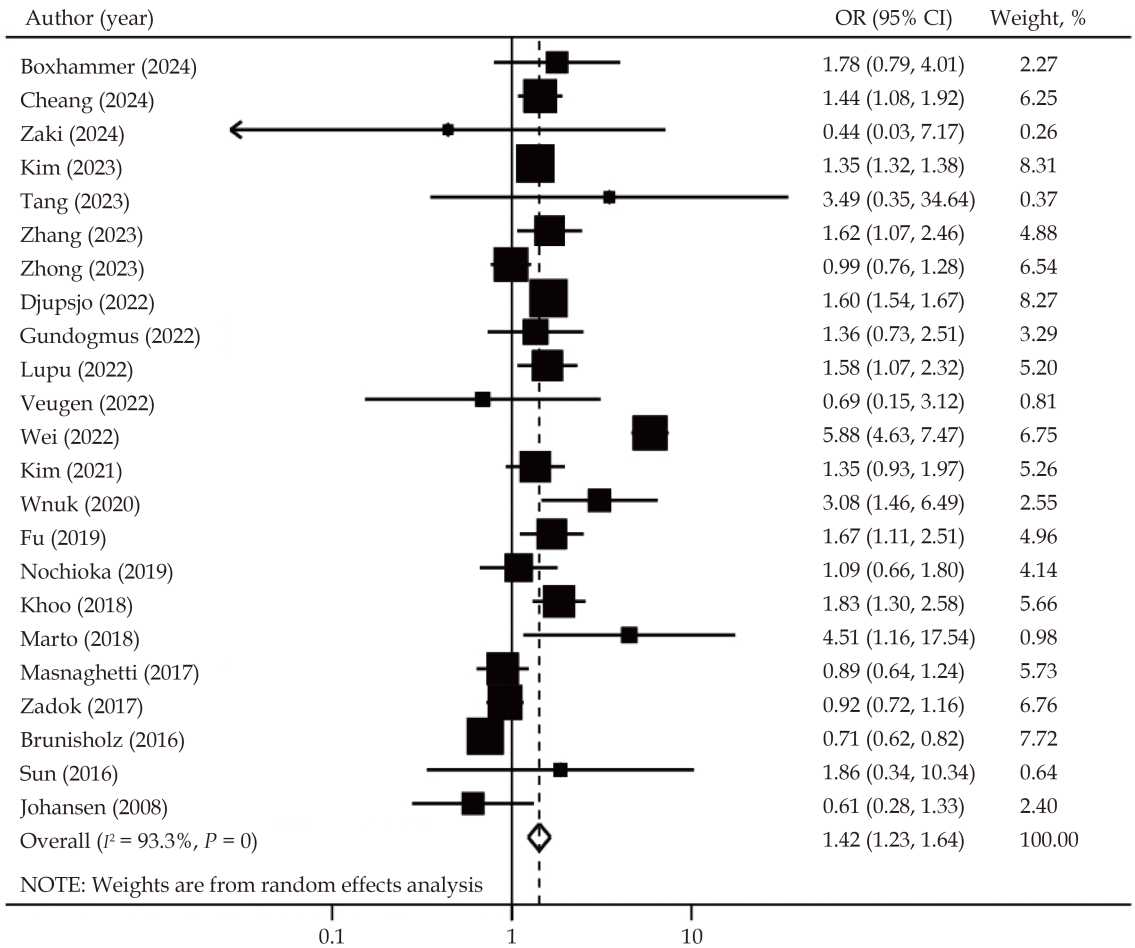


Figure 6 Forest plot of OR with 95% CI for AF in prediabetes compared with normoglycemia when the analyses were limited to cross-sectional studies which presented the crude OR. The OR in each study is indicated by a square. Area of squares is proportional to the study weight (i.e., inverse of square of the standard error of the OR). Pooled OR is indicated by a diamond. AF: atrial fibrillation.

OR (Supplementary Materials 12, 13) where there was no publication bias (Supplementary Material 14). Nevertheless, adjustment for the publication bias by the trim-fill method (see Methods) did not change these pooled estimates (Supplementary Material 14).

DISCUSSION

The overall RR (95% CI) for AF risk (1.12 [1.06–1.18]) indicated that there was a significant association between prediabetes and AF. While we were revising this manuscript, we discovered that a meta-analysis of longitudinal studies that had a theme similar to ours has been published.[70] Also, the conclusion of this study was in line with ours. However, our meta-analysis is novel for two reasons. The first is that our meta-analysis was performed on cross-sectional studies in addition to longitudinal studies. The crude OR estimated from pooling the cross-sectional studies was 1.42, which had a similar risk magnitude to the crude RR (1.49) estimated by pooling the longitudinal studies. If the OR had a larger risk magnitude than the RR, incident AF could have preceded the incident prediabetes instead of the prediabetes leading to AF Although it was impossible to prove a causation, this meta-analysis suggests that prediabetes was a significant risk factor for AF.

The second novelty is that we compared the risk magnitude for AF between prediabetes and diabetes to address the issue of whether the AF risk is elevated in a dose-response fashion according to blood glucose levels. It is important to prove dose dependency for elevating the grade of evidence that prediabetes leads to incident AF,[71] like the association of alcohol intake with AF risk.[72] A previous meta-analysis suggested a dose-re-

Table 7 Stratified analysis of cross-sectional studies for calculating pooled odds ratio with 95% CI for AF.

Characteristic	N of data	OR (95% CI)	χ^2	*P* for χ^2	I^2	Tau	*Z*	*P* for *Z*	**Meta-regression
Country									
Asian	11	1.74 (1.23–2.46)	148.9	< 0.001	93.3%	0.263	3.13	0.002	0.13
Non-Asian	12	1.22 (0.88–1.71)	160.0	< 0.001	93.1%	0.227	1.18	0.24	
Mean age									
≥ 65 years	10	1.27 (1.02–1.58)	26.3	0.002	65.7%	0.076	2.12	0.03	0.26
< 65 years	13	1.64 (1.34–2.00)	288.9	< 0.001	95.8%	0.064	4.88	< 0.001	
% men									
≥ 50%	19	1.42 (1.10–1.83)	258.8	< 0.001	93.0%	0.223	2.68	0.007	0.85
< 50%	5	1.47 (1.10–1.96)	12.8	0.01	68.8%	0.060	2.61	0.009	
Used MetS criteria									
for ascertaining prediabetes									0.43
Yes	1	0.44 (0.03–7.17)	-	-	-	-	−0.58	0.57	
No	22	1.46 (1.26–1.68)	319.9	< 0.001	93.4%	0.063	5.12	< 0.001	
BG indicator									0.17
Both A1C and FPG	2	1.51 (1.14–2.00)	2.6	0.11	61.5%	-	2.89	0.004	0.51
A1C only	5	2.13 (1.08–4.21)	66.7	< 0.001	94.0%	0.548	2.18	0.03	0.04
FPG only	12	1.22 (0.93–1.60)	98.4	< 0.001	88.8%	0.131	1.44	0.15	0.15
Other (casual BG, unclear)	4	1.21 (0.79–1.85)	21.7	< 0.001	86.2%	0.122	0.88	0.38	0.42
Using OGTT									
Yes	3	0.96 (0.64–1.44)	2.2	0.34	6.9%	-	−0.2	0.84	0.23
No	20	1.50 (1.29–1.74)	315.14	< 0.001	94.0%	0.063	5.35	< 0.001	
Specified outcome to non-valvular AF									
Yes	2	1.46 (1.12–1.89)	0.3	0.57	0.0%	-	2.82	0.005	0.95
No	21	1.45 (1.24–1.69)	320.2	< 0.001	93.8%	0.065	4.74	< 0.001	
Study population									
General	3	1.35 (1.32–1.38)	1.4	0.50	0.0%	-	26.83	< 0.001	0.76
Hospital-based	20	1.49 (1.15–1.93)	287.9	< 0.001	93.4%	0.249	3.01	0.003	
Were patients with DM potentially									
included in the exposed group?									
Yes	1	0.44 (0.03–7.17)	-	-	-	-	−0.58	0.57	0.43
No	22	1.46 (1.26–1.68)	319.9	< 0.001	93.4%	0.063	5.12	< 0.001	
Design									
Case-control	2	1.24 (0.92–1.65)	3.7	0.06	0.728	-	1.42	0.16	0.32
Cross-sectional	21	1.49 (1.28–0.73)	316.2	< 0.001	0.937	0.064	5.2	< 0.001	
Covariates									
Used only crude OR	21	1.45 (1.24–1.69)	320.2	< 0.001	93.8%	0.065	4.74	< 0.001	0.95
Used the most fully adjusted data in each study	2	1.46 (1.12–1.89)	0.3	0.57	0.0%	-	2.82	0.005	

AF: atrial fibrillation; A1C: hemoglobin A1c; BG: blood glucose; DM: diabetes mellitus; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.

sponse relationship between blood glucose values and AF risk.[11] However the result of the current meta-analysis showed that the pooled RR/PAF/OR for diabetes and prediabetes were 1.15/1.0%/1.54 and 1.12/1.6%/1.49, respectively (see Table 8), which did not necessarily agree with the suggestion in that previous meta-analysis.

Table 8 Comparison of the impact of pre-DM and DM on atrial fibrillation.

		No. data	RR (95% CI)	χ^2	*P* for χ^2	I^2	Tau	*Z*	*P* for *Z*	*P* for comparison
Cohort study										
RR	Pre-DM	19	1.12 (1.05–1.20)	173.3	< 0.001	89.6%	0.0137	3.19	0.001	0.003
	DM	23	1.15 (1.10–1.20)	132.2	< 0.001	83.4%	0.0052	5.86	< 0.001	
limited to crude RR	Pre-DM	17	1.61 (1.45–1.70)	375.6	< 0.001	95.7%	0.0311	9.11	< 0.001	0.85
	DM	19	1.65 (1.46–1.87)	1106.9	< 0.001	98.4%	0.0514	8.01	< 0.001	
PAF	Pre-DM	17	1.6% (0.9%–2.3%)	126.2	< 0.001	87.5%	0.0001	4.35	< 0.001	0.11
	DM	19	1.0% (0.7%–1.3%)	117.6	< 0.001	84.7%	< 0.0001	6.68	< 0.001	
limited to crude PAF	Pre-DM	17	6.7% (4.0%–9.3%)	1864.3	< 0.001	99.1%	0.0023	4.75	< 0.001	0.19
	DM	19	1.9% (−0.6%–4.4%)	5546.8	< 0.001	99.7%	0.0021	1.52	0.13	
Cross-sectional study										
overall	Pre-DM	20	1.49 (1.13–1.96)	603.5	< 0.001	96.9%	0.3080	2.84	0.004	0.76
	DM	19	1.54 (1.34–1.78)	226.3	< 0.001	92.0%	0.0476	6.06	< 0.001	
limited to crude OR	Pre-DM	20	1.51 (1.15–1.99)	624.0	< 0.001	97.0%	0.3055	2.97	0.003	0.89
	DM	19	1.50 (1.31–1.73)	234.0	< 0.001	92.3%	0.0489	5.70	< 0.001	

DM: diabetes; PAF: population attributable fraction; RR: relative risk.

although our meta-analysis indicated that the RR for AF in diabetes was slightly but significantly higher than in prediabetes ($P = 0.003$). In that previous meta-analysis, the studies that estimated the AF risk in diabetes and those in prediabetes were different. However, these studies were similar in our meta-analysis, which made it possible to directly compare AF risk between diabetes and prediabetes. It is suggested that blood glucose values insufficiently explained the association of prediabetes with AF risk.

A population-based cohort study indicated that participants with a ≥ 1.4 Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) had a 1.61-fold risk of AF than those with < 1.4 HOMA-IR in a non-diabetic population.[73] An animal study showed that insulin-resistance models of rats fed with high-fructose or high-cholesterol diets had a prolonged calcium transient duration, reduced conduction velocity, and development of atrial fibrosis, which could contribute to increased AF susceptivity.[74] It is difficult to explain a plausible mechanism for the current finding. Nevertheless, because insulin resistance is a hallmark of prediabetes,[75] it is hypothesized that insulin resistance rather than the extent of hyperglycemia is a determinant of whether individuals would develop AF. In proving this hypothesis, it would be essential to analyze the population differences among the included studies in the current meta-analysis, which was beyond the scope of that meta-analysis because of lack of data on this issue.

The current meta-analysis indicated that the overall PAF in prediabetes was 2.7%. Previous cohort studies indicated that the estimated PAF for hypertension and obesity were 21.6% and 12.7%, respectively, in the USA;[5] 10-20% and 8–18%, respectively, in Europe;[76] and 26.6% and 4.8%, respectively, in China.[77] Although prediabetes was significantly associated with AF risk, the overall contribution of prediabetes to AF risk was relatively small compared with those above-mentioned risk factors of obesity and hypertension. When the analysis was limited to studies that presented both adjusted and crude RR/PAF, the pooled estimates of the adjusted RR/PAF (1.10/2.5%) were deflated compared with those of crude RR/PAF (1.46/8.5%). If the association of prediabetes with AF risk was substantially explained by the coexistence of prediabetes and hypertension and obesity,[78] the adjustment for obesity and hypertension would deflate the risk magnitude of prediabetes for incident AF. However, this was not supported by our sensitivity analysis because the studies controlling for these confounders did not reveal a stronger RR/PAF than those which did not. Identifying factors that associate prediabetes with AF risk is a topic for future research.

The overall impact of prediabetes on incident AF might be considered to be modest. However, the impact could be strengthened in specific populations. First, the association of prediabetes with AF risk was relatively

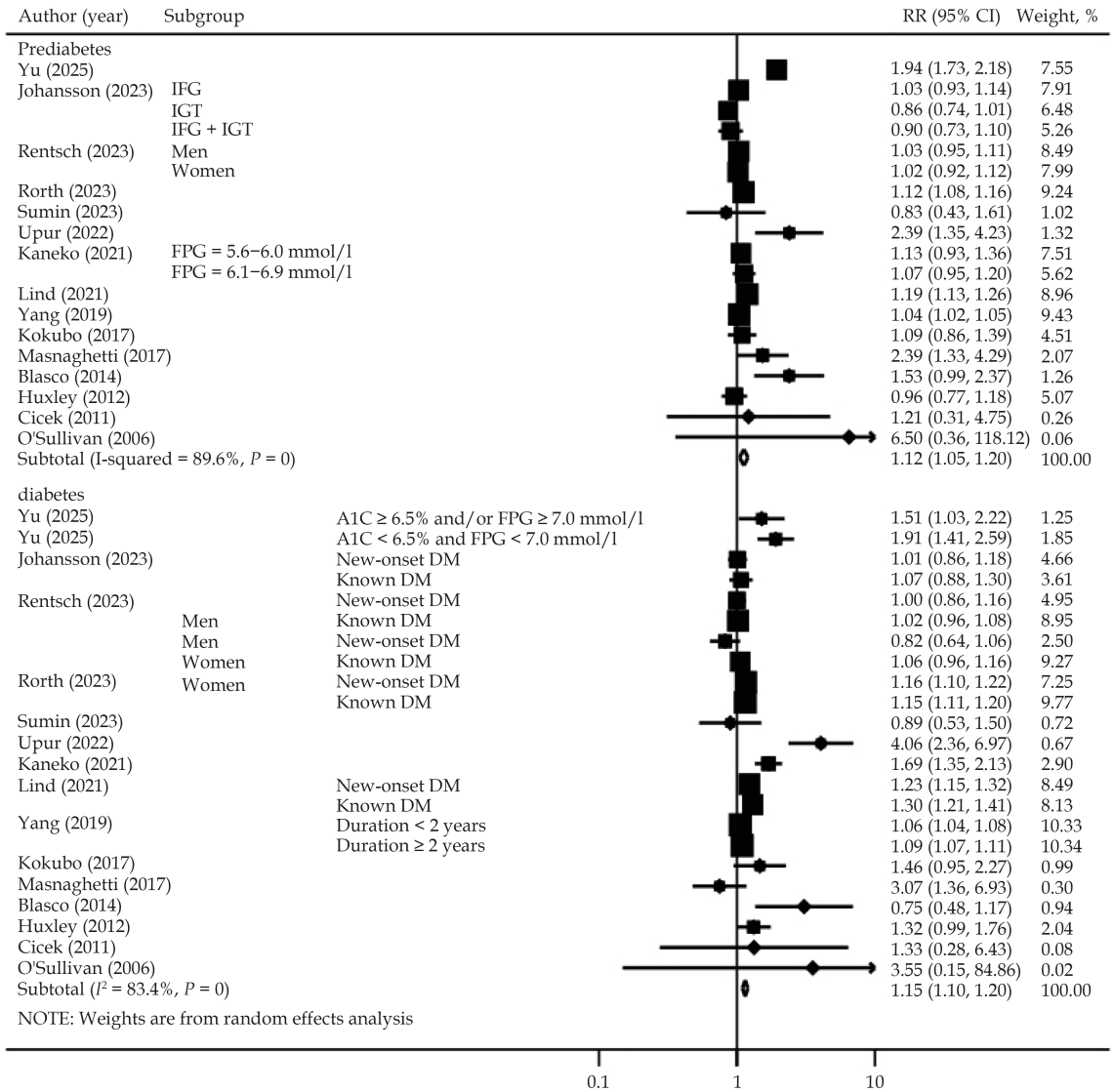


Figure 7 Forest plot of relative risk with 95% CI for AF in prediabetes and diabetes compared with normoglycemia. Analysis was limited to studies which presented RR in relation to both prediabetes and diabetes. The RR in each study is indicated by a square. Area of squares is proportional to the study weight (i.e., inverse of square of the standard error of the RR). Pooled RR is indicated by a diamond. A1C: hemoglobin A1c; AF: atrial fibrillation; DM: diabetes mellitus; FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; RR: relative risk.

strong in the elderly compared with young people and in men compared with women. The plausible explanation is that the genetic contribution to AF risk is relatively large in females compared with males and in young persons compared with the elderly, which could result in a relatively large contribution of prediabetes to AF risk in males and the elderly. A prospective cohort study indicated that the elevated risk of incident AF for high *vs.* low genetic risk scores was more remarkable in women than in men, particularly among participants with high clinical risk scores.[79] A strong familial aggregation of AF was observed among young (< 60 years) populations compared with the elderly (≥ 60 years) populations.[80] In addition, the prevalence of prediabetes increased with age and in men,[78] which would result in the additional contribution of prediabetes to AF risk in the elderly and males given that the PAF was elevated with the increase in prevalent prediabetes as well as its risk magnitude for AF (see Methods). Since the AF incidence was higher in men and the elderly,[81] such individuals would benefit from ameliorating modifiable AF risk factors that include prediabetes compared with wo-

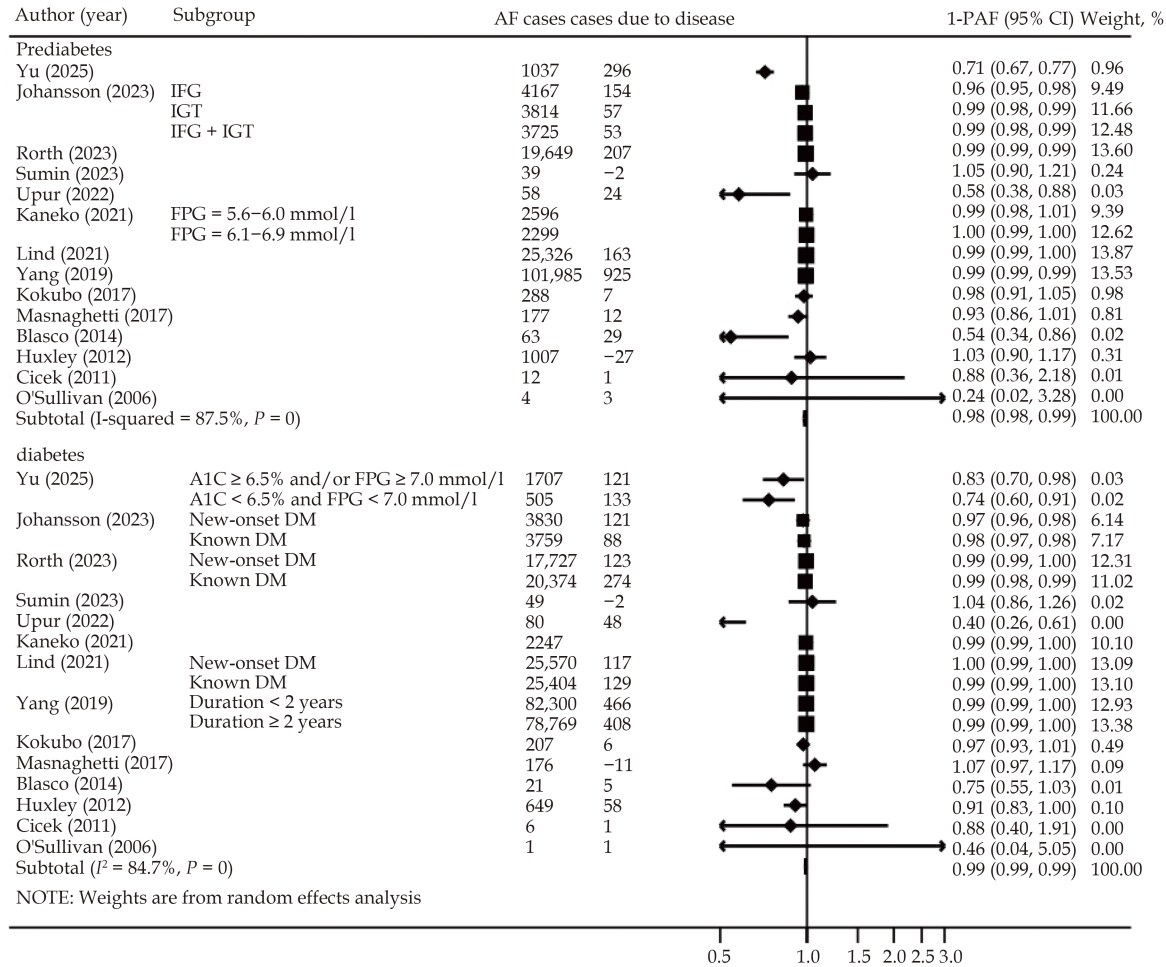


Figure 8 Forest plot of values obtained by subtracting the PAF from [1- PAF] with a 95% confidence interval for AF in prediabetes and diabetes compared with normoglycemia. Analysis was limited to studies which presented the incidence of AF in relation to both prediabetes and diabetes, which made it possible to calculate the PAF. The RR in each study is indicated by a square. Area of squares is proportional to the study weight (i.e., inverse of the square of the standard error of the RR). Pooled RR is indicated by a diamond. AF: atrial fibrillation; A1C: hemoglobin A1c; DM: diabetes mellitus; FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; PAF: population attributable fraction.

men and young people.

Second, the current meta-analysis indicated a stronger association of prediabetes with AF in Asian people than in non-Asian people. One plausible explanation is that the AF risk due to prediabetes is relatively independent of that due to obesity in non-Asian people although obesity inevitably confounds the association of prediabetes with AF risk. In Asians, there was no relationship (*P* trend = 0.90) between the prevalence of prediabetes and obesity status (i.e., underweight/normal/overweight/obesity) while these factors were significantly correlated in White (*P* trend = 0.02) and Black people (*P* trend = 0.04).[82] The relatively low impact of obesity could result in the relatively strong impact of prediabetes on AF risk in Asian people. Another explanation is the racial differences in incident AF. Data on the large hospital-based cohort in California indicated that Whites had a higher incidence of AF than non-Whites (Asians, Hispanics, and Blacks). However, the higher rate of AF among Whites was diminished in the presence of acquired AF risk factors such as hypertension, diabetes, and valvular diseases.[83] If prediabetes was included in such AF comorbid conditions, it is possible that the AF risk among Asians was responsible according to whether they had prediabetes. To determine the population in which prediabetes has a particularly strong impact on AF risk, further studies should directly compare the association of prediabetes with incident AF between men

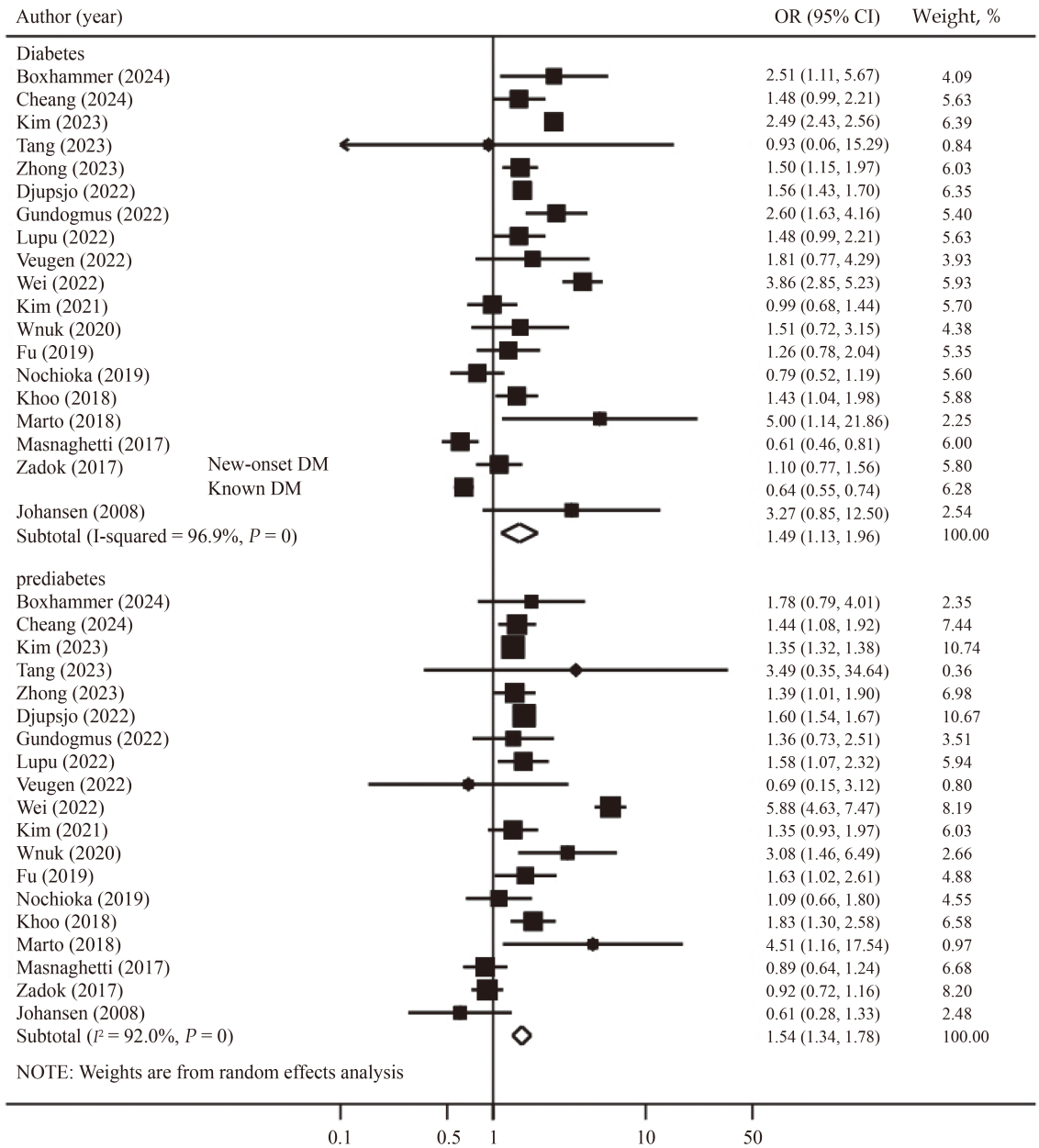


Figure 9 Forest plot of OR with 95% CI for AF in prediabetes and diabetes compared with normoglycemia. Analysis was limited to studies which presented the OR in relation to both prediabetes and diabetes. The OR in each study is indicated by a square. Area of squares is proportional to the study weight (i.e., inverse of square of the standard error of the OR). Pooled OR is indicated by a diamond. AF: atrial fibrillation; DM: diabetes mellitus.

and women, between young and the elderly, and among races.

It is important to discriminate paroxysmal and non-paroxysmal AF although they were not discriminated in most of the included studies in this meta-analysis, given that permanent AF is quite different from paroxysmal AF in management strategies and long-term outcomes.[84] Stratified analysis showed a higher PAF in studies which included non-paroxysmal AF in the outcome compared with outcomes for paroxysmal AF. Patients with persistent or permanent AF, which are progressions of paroxysmal AF, had more cardiovascular risk factors such as diabetes than those with paroxysmal AF.[85] As prediabetes is an established cardiovascular risk factor,[86] prediabetes could be associated with the progression of AF as well as the development of AF, although this was

not explored by our meta-analysis. Examination of whether prediabetes is associated with AF aggravation is suggested for future studies.

Limitations

Several limitations need to be addressed. First, there was large between-study heterogeneity in all pooled estimates, which could downgrade the quality of evidence.[87] Although we performed every possible sensitivity analysis, none of the sensitivity analyses could even insufficiently explain the source of heterogeneity. Thus, it could not be ruled out that the residual heterogeneity affected the robustness of study results. Second, definitions of prediabetes varied among studies. Most of the studies did not use both A1C and FPG and also did not use OGTT for diagnosing prediabetes. The current meta-analysis indicated that using both A1C and FPG resulted in a higher PAF for AF than using either A1C or FPG. It is possible that failure to use either A1C or FPG caused the failure to identify persons with prediabetes who developed AF and consequently underestimated the AF risk from prediabetes. In addition, the failure to measure OGTT could misclassify the diabetes status (i.e., normoglycemia, prediabetes, diabetes). This could bias the relationship between prediabetes and AF although there was no evidence that the misclassification biased the results of this meta-analysis. Third, the current meta-analysis suggested a difference in AF risk between hospital-based and general populations. It was pointed out that profiles differed between the two[88] and could substantially modify the results although we could not find clues to discuss this issue. Fourth, all longitudinal studies fundamentally used baseline exposure status. Ignoring persons who developed prediabetes during the follow-up period could underestimate the long-term risk because such persons had a high risk of incident AF. Actually, the current sensitivity analysis indicated that studies with a long follow-up tended to reveal a smaller RR ($P = 0.07$) compared with those with a short follow-up. Last, there was evidence of publication bias in part of the pooled estimates. The study results were not changed by the adjustment for publication bias by the trim-fill method which is commonly used in meta-analyses. Nevertheless, the possibility of publication bias could not completely be ruled out. In addition, we did not search grey literature such as conference abstracts and clinical trial registries which posed a certain risk of publication bias.

Conclusions

The current meta-analysis indicated that prediabetes is a significant risk factor for AF. Although the risk for AF in those with diabetes was statistically larger than in those with prediabetes, the difference was slight. If we consider PAF in addition to RR, the AF risk magnitude for prediabetes is comparable to that for diabetes. Although the impact of prediabetes on AF risk was modest, it was relatively strong in the elderly, males, and Asians. Further studies should compare the contribution of prediabetes to AF risk according to the characteristics of the study population such as age, sex, and race in terms of determining targets for prevention of prediabetes and subsequent incident AF and should examine whether prediabetes is associated with progression from paroxysmal to permanent AF in terms of determining targets for preventing the progression to AF.

STATEMENTS

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Conflict of interest statement

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Kodama S: Conceptualization, Data collection, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft; Yamada T: Methodology, Project administration; Yagyuda N: Data collection; Ferreira ED: Data collection; Sato T: Data collection; Kitazawa M: Investigation; Matsubayashi Y: Investigation; Fujihara K: Conceptualization, Methodology; Tanaka S: Formal analysis; Horikawa C: Data collection, Methodology; Yachi Y: Investigation, Project administration; Sone H: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review and editing. Each author had access to all study data, takes responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication.

Data Availability Statement

The data that support the findings of this study are available in the supplementary tables and figures in this article.

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DISCLOSURE

Part of the findings in this article were presented at the 40th annual Scientific of the Japan Society of Diabetic Complications, which was held in Tokyo, Japan, on 14–15 Nov. 2025 and the 123th Annual Meeting of the Japanese Society of Internal Medicine, which was held in Tokyo, Japan, on 10-12 Apr. 2026.

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