Original Article

Association between triglyceride glucose index and atrial fibrillation: A systematic review and meta-analysis

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Background and Objectives: Previous studies have demonstrated that insulin resistance (IR) is associated with atrial fibrillation (AF). As a reliable indicator of IR, the triglyceride glucose (TyG) index has been extensively studied in relation to AF. We aimed to investigate the relationship between the TyG index and AF through a systematic review and meta-analysis. **Methods and Study Design:** We systematically searched studies published up to August 2024 in online databases including PubMed, Embase, Web of Science, Wanfang, and the China National Knowledge Internet database. Seventeen studies involving 57,213 patients were included in the analysis. A random-effects model and exposure-effect analysis were used to calculate the pooled effect estimate and compute the linear trend. **Results:** A significantly higher TyG index was observed in AF patients (standardized mean difference [SMD]: 0.78; 95% CI: 0.43- 1.13; p<0.001). The TyG index was associated with the risk of AF in both continuous analysis (odds ratio [OR]: 1.80; 95% CI: 1.50-2.17; p<0.001) and category analysis (odds ratio [OR]: 1.98; 95% CI: 1.35-2.91]; p<0.001). Exposure-effect analysis confirmed a linear positive relationship between the TyG index and the risk of AF ($p_{linearity}$ = 0.006). **Conclusions:** The TyG index is associated with an increased risk of AF, including pure AF, post-operative AF and AF recurrence after ablation. Further studies are needed to confirm the causal relationship between the TyG index and AF.

Key Words: triglyceride and glucose index, atrial fibrillation, systematic review, exposure-effect, meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent sustained tachyarrhythmia in clinical practice,[1-3] which is associated with high risk of mortality, stroke, and heart failure and significantly impairs patients' quality of life.[4-6] Previous studies have shown that the global incidence and prevalence of AF are steadily rising, with projections suggesting that the number of individuals affected by AF in Asia may exceed 72 million by 2050, indicating a growing burden of AF-relevant events.[7-8] Among the numerous risk factors for AF, diabetes is one of the most significant. A prospective cohort study revealed that diabetes not only elevates the risk of AF but is also associated with a higher symptom burden, reduced quality of life, and higher rates of hospitalization and mortality.[9] Furthermore, several studies have suggested that the complex underlying pathophysiology is linked to metabolic syndrome and increased sympathetic activity, with glucose-lowering therapies potentially influencing AF development.[10-11]

Insulin resistance (IR), a pathological condition characterized by a diminished response of tissues or cells to insulin, is a hallmark of diabetes and has been identified as a risk factor for AF, even before the onset of diabetes.[12] The homeostasis model assessment index for insulin resistance (HOMA-IR), regarded as the gold standard for assessing IR, is widely used in clinical practice.[13] However, its high cost and complexity limit its widespread application. Therefore, recent studies have proposed a novel measure, the triglyceride glucose (TyG) index, which is more convenient and has been validated as an effective estimator of IR.[14-15] Additionally, several epidemiological studies have reported that, compared with HOMA-IR, the TyG index may offer greater reliability and advantages for predicting IR risk.[16-17]

Previous studies have reported that a higher TyG index is associated with an increased risk of cardiovascular events and subclinical cardiovascular disease.[18-20] Moreover, the relationship between the TyG index and AF has been extensively investigated,[21-37] including its associations with new-onset atrial fibrillation (NOAF), recurrent AF after radiofrequency catheter ablation (RFCA), and post-operative atrial fibrillation (POAF). There has been sustained and significant interest in the TyG index and AF in recent years. Therefore, we aimed to conduct an updated systematic review and meta-analysis to evaluate the predictive value of the TyG index for AF.

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METHODS

This systematic review and meta-analysis was conducted in accordance with the guidelines of the updated Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[38] This study protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO), with the registration number CRD42024581745.

Literature search

A comprehensive systematic literature search was performed in online databases including PubMed, Embase, Web of Science, Wanfang, and China National Knowledge Internet databases from their respective dates of inception until August 22, 2024. Our comprehensive search terms included "Atrial Fibrillation" OR "Auricular Fibrillation" AND "TyG" OR "triglyceride glucose" OR "triglyceride-glucose" OR "triacylglycerol glucose" OR "triacylglycerol-glucose". The search was carried out by combining subject words and free words and restricted to full-length human studies in English or Chinese. In addition, the references of all eligible articles were manually examined to identify any potentially relevant studies. Details of the search strategy and the retrieved studies are available in Supplementary Table 1.

Study selection

Two investigators (QC and JZ) independently assessed each study based on preestablished inclusion and exclusion criteria. During the data extraction process, we carefully reviewed each included study to identify any instances of incomplete or missing data for key variables such as the TyG index and AF outcomes. Studies with significant missing data that could not be estimated or obtained were excluded from the analysis to ensure the reliability and validity of our findings. The eligibility criteria for the potentially included studies were as follows according to the PICOS: The participants (P) included adults (age > 18 years) of any ethnicity and both sexes. For the intervention/exposure (I), the TyG index was measured, and AF patients and participants with the highest-category TyG index were considered as exposure. Accordingly, the patients without AF and participants with the lowest-category TyG index were considered as comparisons separately (C). To determine the outcomes (O), the mean TyG index was compared between participants with and without AF, and the association between TyG index and risk of AF was evaluated. The study design (S) included observational studies, including case-control (CC) studies, cross-sectional (CS) studies, prospective cohort (PC) studies, and retrospective cohort (RC) studies. The exclusion criteria were as follows: (1) studies including children or adolescents; (2) studies that did not evaluate the TyG index or report the outcome of AF; (3) studies with data that could not be extracted or were not reported; or (4) preclinical studies, reviews, meta-analyses, abstract-only articles or editorials. Studies were included if they measured the TyG index and reported data on AF outcomes, regardless of whether the TyG index or AF was the primary focus. The flow of the selection process for potentially eligible trials and reasons for exclusion are illustrated in Figure 1.

Data extraction and quality assessment

Two authors (QC and JZ) independently extracted the relevant information from the eligible studies by screening all full-text articles, and subsequently input the data into a pre-piloted, standardized Excel spreadsheet: first author name and publication year, source of participants, definition of case and control groups, country or region, design of study, sex ratio, age, sample size, TyG index and main findings. Additionally, we extracted the hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (CI) from the most adjusted model. The studies included in this analysis were observational, therefore, the Newcastle-Ottawa scale was used to assess the quality and risk of bias of the included studies. Two independent authors (QC and JZ) assessed the qualities, and in cases of disagreement, the corresponding author (WW) resolved the issue.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the included studies. For variables reporting median and interquartile range (IQR) or median and range, we calculated mean and standard deviation through the methods suggested by Luo et al. and Wan et al.[39,40] To evaluate the mean TyG index in patients with or without AF, we employed the Hedges's standardized mean differences (SMD) with their matching 95% confidence intervals (CIs) by random-effect meta-analysis.[41] For studies that reported the TyG index as a categorical variable, we summarized the effect estimates of the highest TyG index group versus the lowest TyG index group. For analysis of continuous variables, the effect estimates of the TyG index per 1-unit increment were assessed. For the meta-analysis, the total effectiveness rates of dichotomous data were pooled using odds ratios (ORs) with 95% CIs. The statistical heterogeneity was evaluated using the Cochrane Q-test and I^2 statistics, with an I^2 value greater than 75% indicating high heterogeneity.[42] Considering the influence of heterogeneity, a random-effects model was conducted to combine the results. Sensitivity analysis was assessed by applying a "leave-one-out" approach. To assess the publication bias, funnel plot, Egger's test and Begg's test were employed. Meta-regression based on publication year, sample size, mean age, male percentage, different outcomes and study type was performed to assess their effect on overall heterogeneity. Subgroup analyses were conducted based on different types of AF. Besides, for exposure-effect analysis, variance-weighted least-squares regression analysis was used to compute the linear trend.[43] The meta-analysis, subgroup analysis, and heterogeneity analysis were conducted using RevMan (Version 5.3; Cochrane Collaboration, Oxford, UK). Sensitivity analysis, assessment of publication bias, meta-regression analysis, and exposure-effect analysis were performed using Stata software (Version 16.0; Stata Corporation, College Station, TX, USA). A two-sided $p<0.05$ indicates statistical significance.

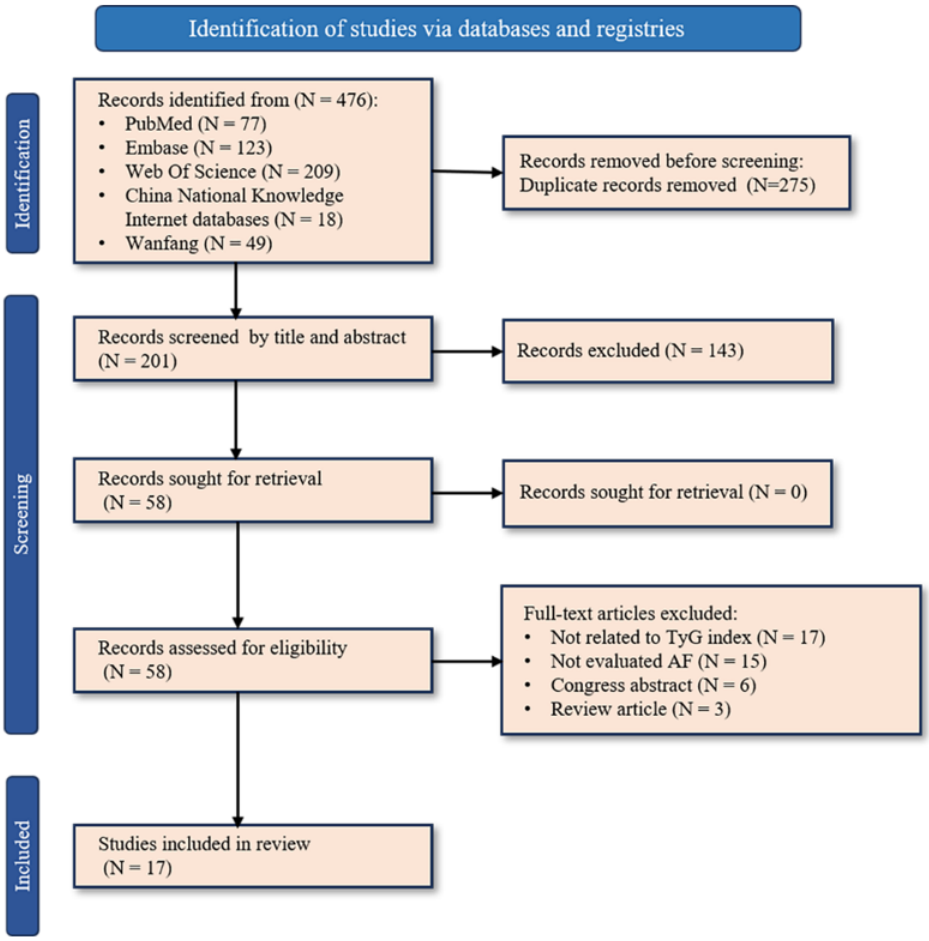


Figure 1. Flow chart of the study selection process.

RESULTS

Study selection and baseline characteristics

Our comprehensive literature search identified 476 studies, of which 275 were duplicates. After the initial screening of titles and abstracts, 58 studies were selected for full-text screening. Finally, a total of 17 studies were included in the present research (Figure 1).[21-37] Table 1 summarizes the characteristics of included study, including author, publication year, source of participants, definition of case and control groups, country or region, design of study, sex ratio, age, sample size, TyG index and main findings. These studies, published between 2021 and 2024, involved sample sizes ranging from 226 to 32,899, with a total of 57,213 participants. Most of the studies were conducted in China,[21-33,36] followed by Turkey,[34] United States[35] and Sweden.[37] The mean age of participants ranged from 45 to 70.2 years, with the proportion of men ranging from 26.8% to 82.1%. Six studies analyzed the relationship between the TyG levels and AF,[21-24,35,37] seven studies for the TyG levels with recurrent AF after RFCA[25-31] and four studies for the TyG levels with post-operative atrial fibrillation.[32-34,36] Meta-regression analyses assessing the effect of each variable are summarized in Table 2. The quality of the studies included in the analysis is summarized in Supplementary Table 2. All studies had NOS 7-8, indicating good methodological quality based on the established criteria.

Meta-analysis of TyG levels in patients with AF

We identified thirteen studies to compare the mean TyG index between patients with and without AF. As shown in Figure 2, the pooled results showed a significantly higher TyG index in patients with AF overall (SMD: 0.78; 95% CI: 0.43-1.13; I^2=98%; p<0.001). Subgroup analysis was then performed based on different types of AF. As shown in Figure 2, no significant difference was observed between patients with pure AF and non-AF (SMD: 1.12; 95% CI: -0.10-2.34; I^2=99%; p=0.07). In contrast, the subgroup analysis revealed a significantly higher TyG index in patients with late AF recurrence after ablation (SMD: 0.65; 95% CI: 0.31-0.99; I^2=96%; p< 0.001) compared to those without late AF recurrence, as well as in patients with AF after procedure (SMD: 0.73; 95% CI: 0.13-1.33; I^2=95%; p=0.02) compared to those without AF undergoing the same procedures [percutaneous coronary intervention (PCI), septal myectomy, or coronary artery bypass grafting (CABG)].

Association between the TyG and risk of AF (Per 1 unit increase)

Sixteen studies were involved in examining the TyG index as a continuous variable to assess its association with AF risk. The overall pooled estimate indicated that each unit increase in the TyG index was associated with an 80% higher risk of AF (OR: 1.80; 95% CI: 1.50-2.17; I^2=88%; p<0.001). Subgroup analyses further

Table 1. Characteristics of included studies in this meta-analysis

Study	Groups	Population	AF definition	Country	Design
Shi et al. (2022)[21]	AF Non-AF	Diabetic patients	AF was diagnosed a standard 12-lead ECG recording of ≥30s showing heart rhythm with no discernible repeating P waves and irregular RR intervals and the subject's self-report of AF history with clear medical examination evidence	China	CS
Chen et al. (2022)[22]	AF Non-AF	Patients from the Department of Cardiology	AF was diagnosed based on ECG findings (absence of consistent P waves, presence of rapid, irregular f waves with a frequency of 350-600 b.p.m. and an irregular ventricular response)	China	RC
Zhang et al. (2023)[23]	NAFLD + AF NAFLD+non-AF	Patients diagnosed with NAFLD via ultrasonography	AF defined as standard 12-lead ECG showing a≥30-s rhythm, undiscernible P-waves, and irregular RR intermittent and self-reporting histories of AF with clear physical evidence.	China	CC
Bai et al. (2024)[24]	CHF+AF CHF+non-AF	CHF patients hospitalized in the Department of Cardiovascular	AF was diagnosed a standard 12-lead ECG recording of ≥30s showing heart rhythm with no discernible repeating P waves and irregular RR intervals	China	CC
Tang et al. (2022)[25]	Recurrent AF Non-recurrent AF	Nondiabetic AF patients after RFCA	AF recurrence was defined as AF, atrial flutter, or atrial tachycardia lasting>30 s recorded by any type of ECG or Holter monitoring after a three-month blanking period	China	RC
He et al. (2023)[26]	Recurrent AF Non-recurrent AF	Nondiabetic patients with persistent AF after RFCA	AF recurrence was defined as AF, atrial flutter, or atrial tachycardia lasting>30 s recorded by any type of ECG or Holter monitoring after a three-month blanking period	China	RC

Study	Total, n	Male, %	Age, year	TyG index	Main findings
Shi et al.	213	72.3	55.97±13.25	9.51±0.74	TyG index was positively associated with AF (OR = 1.406, 95% CI 1.197-1.650, p<0.001)
(2022)[21]	3031	53.7	56.21±10.67	9.17±0.67	
Chen et al.	179	53.1	67.3±9.0	Not provide	TyG index was positively associated with AF (OR = 2.092, 95% CI 1.412-3.100, p<0.001).
(2022)[22]	179	51.4	67.0±9.0		TyG index was associated with AF (OR = 3.065, 95% CI, 1.819-5.166, p<0.001) in non-diabetic subjects. However, TyG index was not associated with AF in diabetic subjects
Zhang et al.	204	64.7	68.78±11.15	9.12±0.53	TyG was an independent risk factor for AF (OR=4.84, 95% CI 2.98–7.88, p < 0.001)
(2023)[23]	708	60.6	56.25±10.31	8.01±0.44	
Bai et al.	138	51.4	66.95±9.74	8.63±0.54	TyG was an independent risk factor for AF (OR=2.360，95%CI 1.397-3.987，p=0.001)
(2024)[24]	279	53.0	65.95±9.69	8.41±0.45	
Tang et al.	70	75.7	64.38±8.04	9.42±0.60	TyG index was an independent risk factor for late recurrence of AF after RFCA (HR=2.015,
(2022)[25]	205	67.3	55.07±8.93	8.68±0.70	95% CI 1.408–4.117, p=0.009)
He et al.	52	46.2	64. 54±9. 95	8. 67±0. 57	TyG index was an independent risk factor for late recurrence of AF after RFCA (HR=1.836,
(2023)[26]	190	57.9	63. 03±12. 32	8. 46±0. 53	95% CI 1. 063-3. 171, p=0.029)

AF atrial fibrillation; CABG coronary artery bypass grafting; CC case control; CHF chronic heart failure; CS cross-sectional; ECG electrocardiogram; HR hazard ratio; NAFLD non-alcoholic fatty liver disease; NOAF new-onset atrial fibrillation; OPCABG off-pump coronary artery bypass grafting; OR odds ratio; PC prospective cohort; PCI percutaneous coronary intervention; POAF post-operative atrial fibrillation; RC retrospective cohort; RFCA radiofrequency catheter ablation; STEMI ST-segment elevation myocardial infarction; TyG triglyceride-glucose index.

Table 1. Characteristics of included studies in this meta-analysis (cont.)

Study	Groups	Population	AF definition	Country	Design
Zhang(2) et al. (2023)[27]	Recurrent AF Non-recurrent AF	Patients who underwent valvular surgery with concurrent Cox-maze IV ablation	AF recurrence was defined as any AF lasting>30 s recorded by any type of ECG or Holter monitoring after a three-month blanking period	China	CC
Wang et al. (2024)[28]	Recurrent AF Non-recurrent AF	AF patients after RFCA	The definition of AF recurrence was any atrial tachyarrhythmia lasting for more than 30 s in electrocardiogram or Holter monitoring after the 3-month blanking period	China	RC
Jia et al. (2024)[29]	Recurrent AF Non-recurrent AF	AF patients after RFCA	AF recurrence was defined as the presence of sustained atrial tachyarrhythmias enduring for 30 s or more recorded by any type of ECG or Holter monitoring after a three-month blanking period	China	RC
Luo et al. (2024)[30]	Recurrent AF Non-recurrent AF	AF patients after RFCA	AF recurrence was defined as all 30-second AF events continuously recorded by any ECG or Holter monitoring device after the 90-day gap period	China	RC
Xiong et al. (2024)[31]	Recurrent AF Non-recurrent AF	AF patients after RFCA	AF recurrence was defined as all 30-second AF events continuously recorded by any ECG or Holter monitoring device after the 3-month blanking period	China	CC
Ling et al. (2021)[32]	NOAF after PCI No-AF after PCI	STEMI patients after PCI	NOAF was explained as the detection of AF lasting ≥30 s during post-PCI hospi-talization	China	RC

Study	Total, n	Male, %	Age, year	TyG index	Main findings
Zhang(2) et al. (2023)[27]	117 307	71.8 70.4	61.7±12.7 56.8±13.7	9.21±0.38 8.34±0.72	TyG index was an independent risk factor for recurrence of AF (HR=2.021, 95% CI 1.374~3.245, p<0.001)
Wang et al. (2024)[28]	711 1531	60.2 64.9	61.57±11.30 60.35±11.27	8.63±0.54 8.55±0.54	TyG level was an independent risk factor for AF recurrence (HR = 1.18, 95% CI 1.02–1.36, p=0.024)
Jia et al. (2024)[29]	200 797	67.0 62.2	63.37±9.81 63.17±9.86	8.68±0.60 8.54±0.55	TyG level was an independent risk factor for AF recurrence (HR = 1.255, 95% CI 1.087–1.448, p=0.002)
Luo et al. (2024)[30]	189 721	39.7 26.8	67.2±9.71 65.66±10.43	7.14±0.59 7.01±0.55	TyG level was an independent risk factor for AF recurrence (HR = 1.472, 95% CI 1.158–1.870, p=0.002)
Xiong et al. (2024)[31]	31 195	41.9 42.1	66.72±10.07 65.56±9.31	8.75±0.53 8.24±0.41	TyG level was an independent risk factor for AF recurrence (OR = 1.302, 95% CI 1.011–1.513, p=0.037)
Ling et al. (2021)[32]	42 507	71.4 80.5	70.2±7.1 62.6±14.1	9.48±0.75 8.75±0.64	The TyG index was an independent predictor of NOAF (OR=8.884, 95% CI 1.570–50.265, p = 0.014)

AF atrial fibrillation; CABG coronary artery bypass grafting; CC case control; CHF chronic heart failure; CS cross-sectional; ECG electrocardiogram; HR hazard ratio; NAFLD non-alcoholic fatty liver disease; NOAF new-onset atrial fibrillation; OPCABG off-pump coronary artery bypass grafting; OR odds ratio; PC prospective cohort; PCI percutaneous coronary intervention; POAF post-operative atrial fibrillation; RC retrospective cohort; RFCA radiofrequency catheter ablation; STEMI ST-segment elevation myocardial infarction; TyG triglyceride-glucose index.

Table 1. Characteristics of included studies in this meta-analysis (cont.)

Study	Groups	Population	AF definition	Country	Design
Wei et al. (2021)[33]	POAF Non-POAF	Patients with hypertrophic obstructive cardiomyopathy after septal myectomy	POAF was defined as the presence of AF that lasted ≥5 min or required cardio-version with antiarrhythmic drugs	China	RC
Erbay et al. (2024)[34]	POAF Non-POAF	Patients undergoing isolated off-pump CABG	POAF was described as AF lasting at least 5 minutes or requiring cardioversion with electrical or antiarrhythmic drugs	Turkey	RC
Liu et al. (2023)[35]	TyG<8.8 8.8≤TyG≤9.2 9.2 <TyG	Individuals without known cardiovascular diseases	AF: fatal AF event; AF event at visit 2, 3, 4, or 5 determined by ECG readings; AF event determined by hospital discharge codes	USA	PC
Peng et al. (2023)[36]	TyG≤8.45 8.45<TyG≤8.80 8.80<TyG	Participants who underwent OPCABG	POAF is defined as atrial fibrillation (AF) episodes lasting >30 seconds captured during the period from immediately after surgery to discharge	China	RC
Muhammad et al. (2023)[37]	TyG Q1 TyG Q2 TyG Q3 TyG Q4	General population	Incident AF (ICD-9 codes: 427D)	Sweden	PC

Study	Total, n	Male, %	Age, year	TyG index	Main findings
Wei et al. (2021)[33]	61 348	52.5 52.0	56.75±12.35 49.92±12.35	7.41±0.67 6.90±0.55	The TyG was an independent risk factors for POAF in patients undergoing septal myectomy (OR=4.218, 95% CI 2.381–7.473, $p < 0.001$)
Erbay et al. (2024)[34]	310 416	75.5 79.0	63.6±31.28 63.05±33.48	9.84±2.76 9.28±2.53	TyG index independently contributed to the risk of POAF (OR=6.824, 95% CI 3.511–13.264, $p<0.001$)
Liu et al. (2023)[35]	7605 2477 1769	40.3 49.9 54.4	53.61±5.73 54.65±5.75 55.08±5.54	8.30±0.32 8.98±0.12 9.57±0.32	Both < 8.80 (HR=1.15, 95% CI 1.02–1.29) and > 9.20 levels (HR=1.18, 95% CI 1.03–1.37) of the TyG index were associated with AF compared with the middle TyG index category (8.80–9.20)
Peng et al. (2023)[36]	181 185 176	76.2 70.8 71.6	62.4±3.1 62.1±2.9 61.9±3.3	Not provide	Fully adjusted HRs of TyG index in tertile 3 versus tertile 1 was 2.88 (1.76–4.71) for POAF, each 1.0 SD increase in the TyG index was related to an increased risk of POAF (HR=1.24, 1.03–1.73).
Muhammad et al. (2023)[37]	8221 8232 8232 8214	50.1 65.0 72.7 82.1	46.41±7.73 45.69±7.48 45.24±7.44 45.26±6.92	3.38-4.38 4.38-4.55 4.55-4.74 4.74-6.70	Per 1-unit increase 0.99 (0.89–1.11) Compared to the reference category (Q1), HR for incident AF for individuals in the fourth quartile of TyG index were 0.96 (0.89–1.04)

AF atrial fibrillation; CABG coronary artery bypass grafting; CC case control; CHF chronic heart failure; CS cross-sectional; ECG electrocardiogram; HR hazard ratio; NAFLD non-alcoholic fatty liver disease; NOAF new-onset atrial fibrillation; OPCABG off-pump coronary artery bypass grafting; OR odds ratio; PC prospective cohort; PCI percutaneous coronary intervention; POAF post-operative atrial fibrillation; RC retrospective cohort; RFCA radiofrequency catheter ablation; STEMI ST-segment elevation myocardial infarction; TyG triglyceride-glucose index.

Table 2. Univariate meta-regression for meta-analysis of TyG and AF

Moderator	No. of studies	Slope	*p*-value	R^2 (%)
Mean TyG				
Publication year	13	-0.2013	0.232	0
Sample size	13	-0.0002	0.352	0
Mean age	13	-0.0375	0.198	0
Male %	13	0.0115	0.549	0
Outcomes	13	-0.1933	0.490	0
Study type	13	-0.2226	0.386	0
Per 1 unit increase				
Publication year	16	-0.1954	0.202	0
Sample size	16	-0.0001	0.068	0
Mean age	16	0.0235	0.038	0
Male %	16	0.0157	0.222	0
Outcomes	16	0.2050	0.320	0
Study type	16	-0.0549	0.756	0
Highest vs. lowest				
Publication year	7	-0.0678	0.856	0
Sample size	7	-0.0001	0.032	25.62
Mean age	7	0.0692	0.318	0
Male %	7	0.0280	0.136	0
Outcomes	7	0.1000	0.778	0
Study type	7	-0.4143	0.037	55.71

AF atrial fibrillation; TyG triglyceride-glucose index

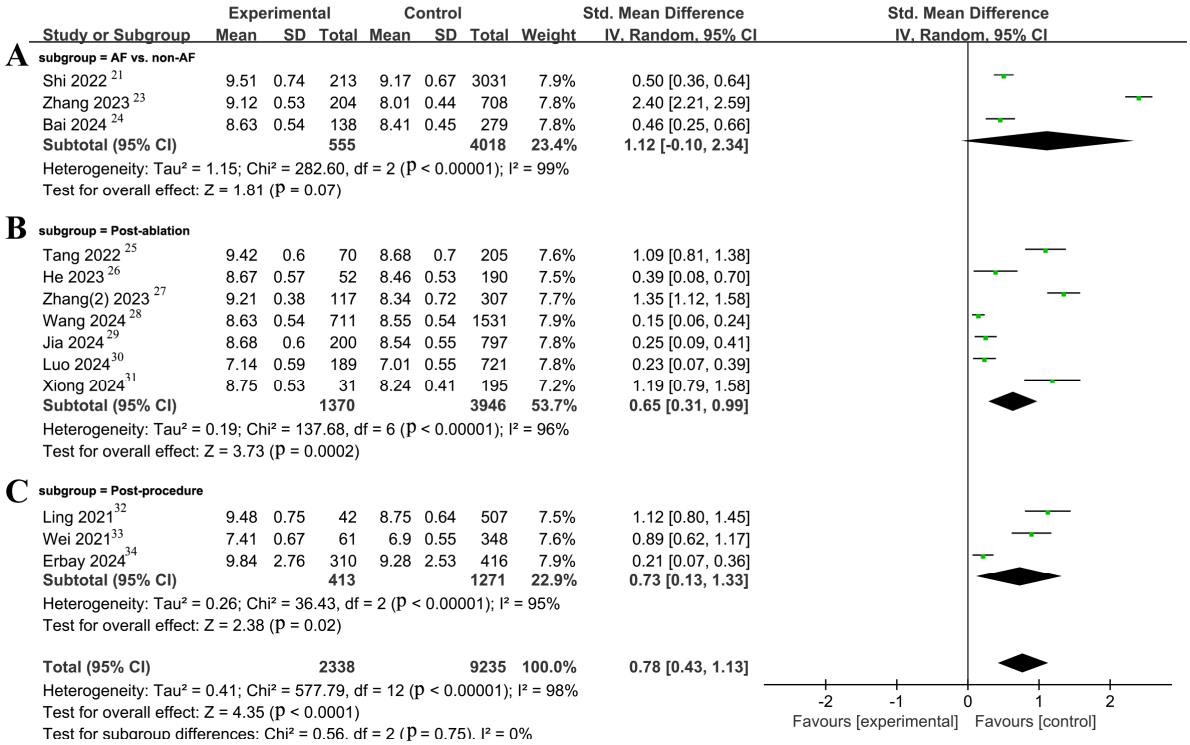


Figure 2. Forest plot and subgroup analysis of the association between mean TyG and AF. Subgroup analysis was conducted based on different types of AF. (A) Forest plots of the association between the TyG index and AF between patients with pure AF and non-AF. (B) Forest plots of the association between the TyG index and AF between patients with late AF recurrence after ablation and without late AF recurrence. (C) Forest plots of the association between the TyG index and AF between patients with AF after procedure and without AF undergoing the same procedure

demonstrated consistent results, showing that each unit increase in the TyG index was associated with an elevated risk of pure AF (OR: 1.91; 95% CI: 1.25-2.92; I^2=94%; *p*=0.003), AF recurrence after ablation (OR: 1.44; 95% CI: 1.24-1.67; I^2=60%; *p*<0.001), and AF after procedure (OR: 3.78; 95% CI: 1.32-10.68; I^2=93%; *p*=0.01). The detailed results of these analyses are presented in Figure 3.

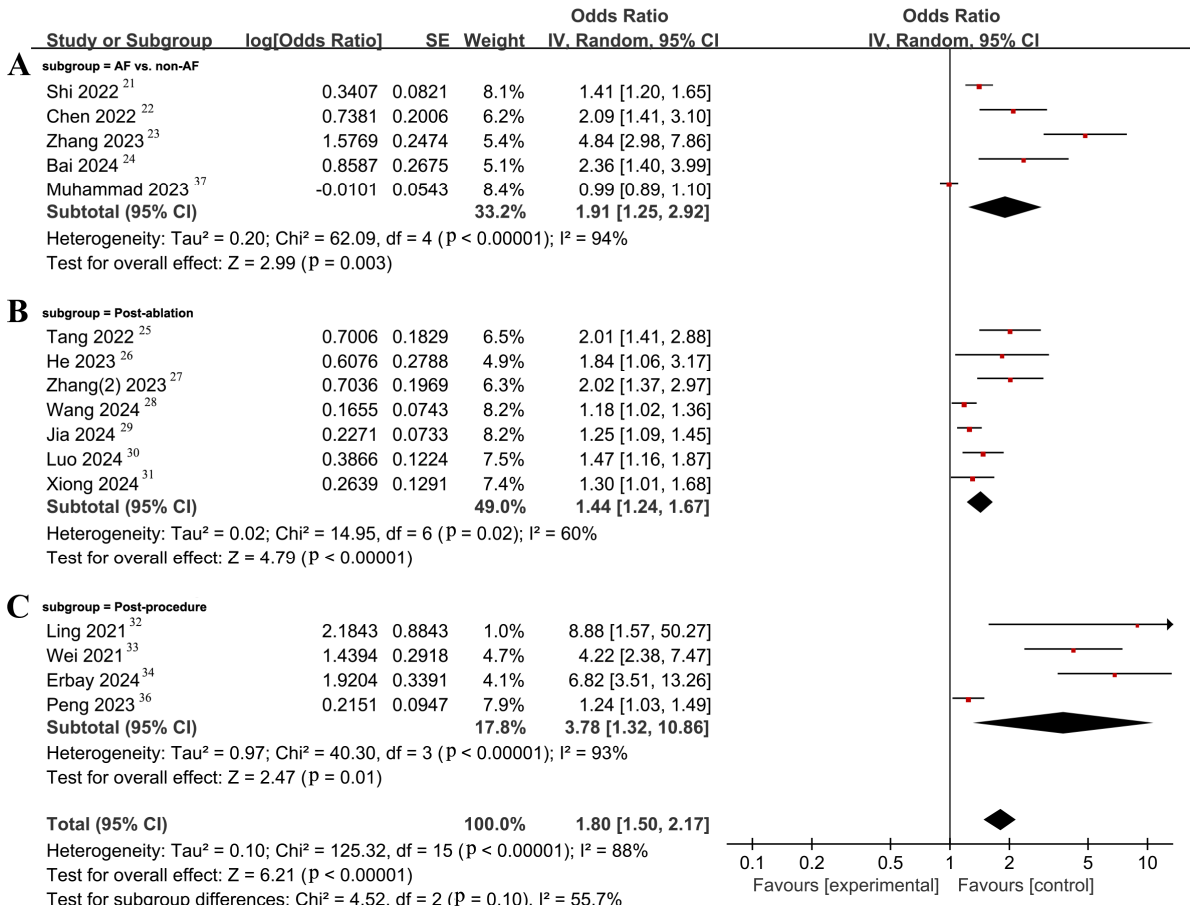


Figure 3. Forest plot and subgroup analysis of the association between TyG (analyzed as continuous variable) and the risk of AF. Subgroup analysis was conducted based on different types of AF. (A) Forest plots of the association between the TyG index (analyzed as continuous variable) and AF between patients with pure AF and non-AF. (B) Forest plots of the association between the TyG index (analyzed as continuous variable) and AF between patients with late AF recurrence after ablation and without late AF recurrence. (C) Forest plots of the association between the TyG index (analyzed as continuous variable) and AF between patients with AF after procedure and without AF undergoing the same procedure.

Association between the TyG and risk of AF (Highest vs. lowest)

Seven studies were involved in examining the TyG index as a categorical variable to assess its association with AF risk. The overall pooled estimate indicated that the highest TyG group was associated with a significant ly greater risk of AF compared to the lowest TyG group (OR:1.98; 95% CI: 1.35-2.91; I^2=92%; p<0.001). Howev er, subgroup analysis revealed no statistically significant difference between the highest and lowest TyG groups in AF after procedure (OR: 1.54; 95% CI: 0.95-2.50; I^2=76%; p=0.08). In contrast, among patients undergoing ablation, those with higher TyG index levels had a significantly increased likelihood of AF recurrence (OR:2.29; 95% CI:1.14-4.58; I^2=93%; p=0.02). The detailed results of these analyses are presented in Figure 4.

Sensitivity analysis and publication bias

We performed sensitivity analyses for each outcome using a "leave-one-out" approach. By sequentially removing one study at a time, the results remained consistent with the primary meta-analysis, indicating the robustness of our findings (Supplementary Figure 1). Additionally, we evaluated publication bias using funnel plots, Egger's test, and Begg's test. For the mean TyG index, the results indicated no significant publication bias. However, for the association between the TyG and risk of AF, both Egger's and Begg's regression tests suggested a potential risk of publication bias. The detailed results of the publication bias assessment are presented in Supplementary Figure 2.

Exposure-effect analysis between the TyG index and AF

Four studies[24, 35-37] were included in the exposure-effect meta-analysis of the TyG index and AF. As shown in Figure 5, variance-weighted least-squares regression analysis confirmed a significant linear positive relationship between the TyG index and AF ($p_{linearity}$ = 0.006). However, no evidence of a nonlinear relationship was observed between the TyG index and AF ($p_{nonlinearity}$ =0.093). The estimated ORs derived from the exposure-effect curve are shown in Supplementary Table 3.

DISCUSSION

In this systematic review and meta-analysis, we investigated the association between the TyG index and AF risk. The results demonstrated that the TyG index was significantly higher in AF patients compared to the general population. Furthermore, a higher TyG index was associated with an increased risk of AF, regardless of whether it was analyzed as a continuous or categorical variable.

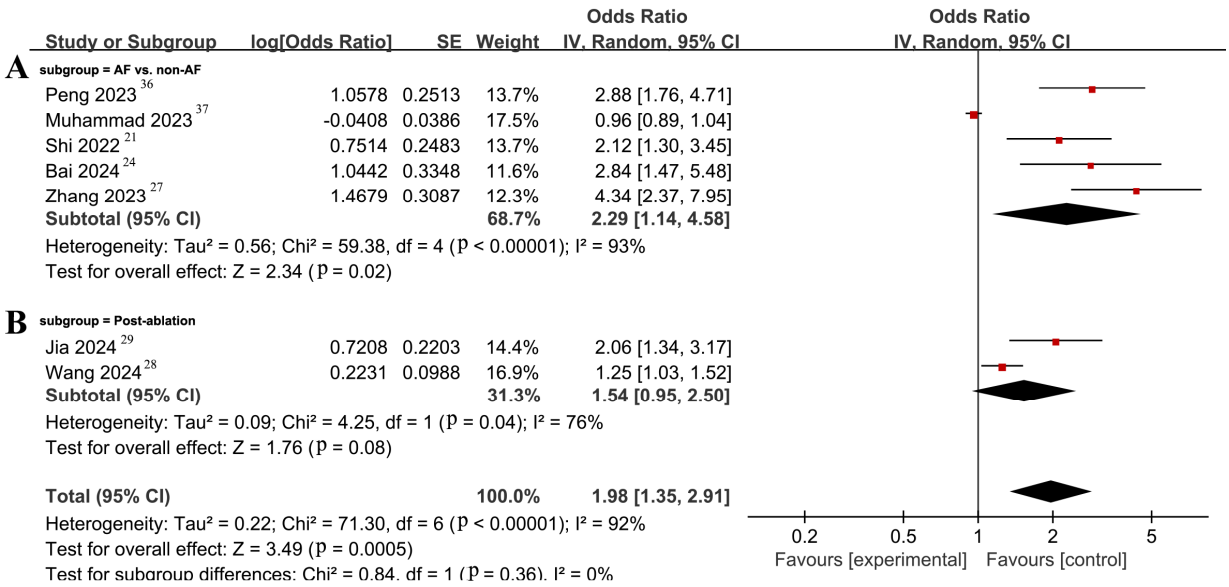


Figure 4. Forest plot and subgroup analysis of the association between TyG (analyzed as categorical variable) and the risk of AF. Subgroup analysis was conducted based on different types of AF. (A) Forest plots of the association between the TyG index (analyzed as categorical variable) and AF between patients with pure AF and non-AF. (B) Forest plots of the association between the TyG index (analyzed as categorical variable) and AF between patients with late AF recurrence after ablation and without late AF recurrence.

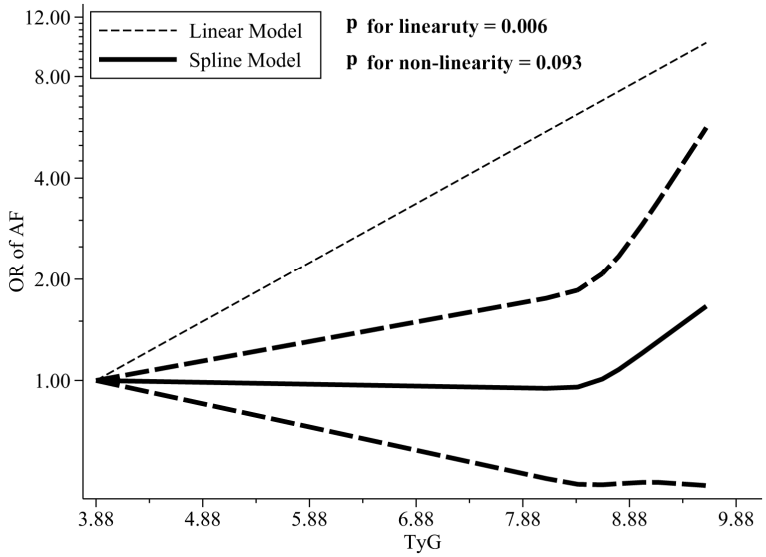
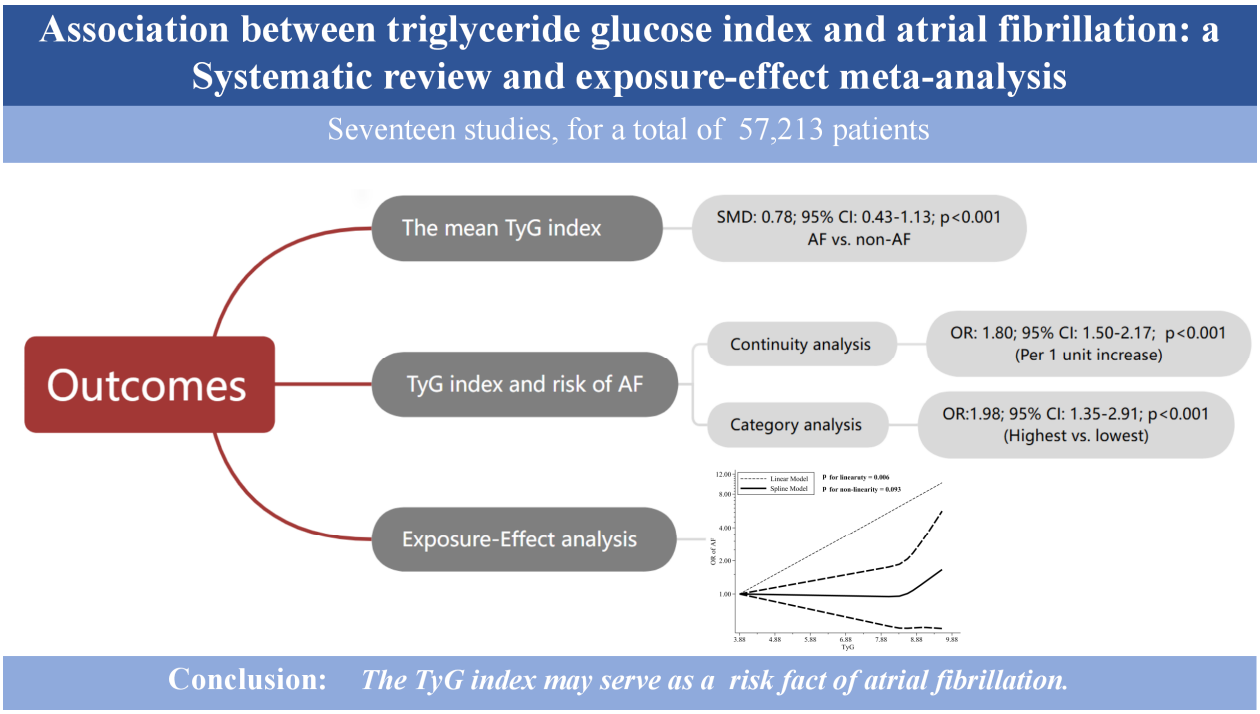


Figure 5. TyG and risk of AF in linear and nonlinear exposure-effect analysis. The bold solid line and the bold dashed lines represent the estimated odd ratio and the 95% confidence interval, respectively

Subgroup analysis yielded largely consistent results. Additionally, exposure-effect analysis confirmed a significant linear positive relationship between the TyG index and the AF risk.

AF is the most common clinical arrhythmia in the general population, and its prevalence increases with age, significantly elevating the risk of heart failure, cardiomyopathies and stroke.[44] RFCA is widely regarded as a highly effective treatment for AF in clinical practice.[1] Despite advances in AF treatment, patients remain at high risk for both the development and recurrence of AF. Therefore, identifying risk factors and predictors of AF is crucial to help clinicians recognize high-risk groups and reduce the incidence and recurrence of this disease.

Previous studies have established that IR is an independent risk factor for AF.[12,45] Shigematsu et al. observed that IR, estimated using HOMA-IR, is highly prevalent among non-diabetic patients with hypertrophic cardiomyopathy, suggesting its potential role in the pathogenesis of AF.46 A community-based, longitudinal study including 8,175 adults reported that higher HOMA-IR was independently associated with new-onset AF and increased the risk of AF by approximately 60%.[47] However, the clinical utility of HOMA-IR is limited by its cost and complexity. Compared to other tools to measure IR in clinical practice, the TyG index has been considered as a more convenient and validated parameter, with a diagnostic and prognostic value. The TyG index is calculated using routine laboratory measurements of fasting triglycerides and glucose, making it an accessible and cost-effective tool.[14-16] This eliminates the need for complex or expensive tests, facilitating its widespread use in both



Graphical abstract.

resource-limited and advanced healthcare settings. In this regard, previous studies have highlighted the great value of the TyG index in predicting the incidence and prognosis of coronary heart disease, hypertension and heart failure.[18,48-50] Additionally, the TyG index has been associated with the development and progression of chronic kidney disease (CKD), particularly in patients with diabetes or hypertension,[51] It serves as a predictor of renal function decline and the need for dialysis, offering a simple yet effective tool for monitoring CKD patients. It also serves as a non-invasive marker for diagnosing and monitoring non-alcoholic fatty liver disease (NAFLD), given its strong correlation with hepatic steatosis and fibrosis.[52]

Extensive research has explored the relationship between the TyG index and atrial fibrillation. A cross-sectional study including 3244 diabetic patients revealed a linear correlation between the TyG index and the prevalent AF in patients with diabetes.[21] Among non-diabetic patients, the TyG index was also proved to be an independent risk factor for AF,[22] while a retrospective study conducted on 912 NAFLD patients demonstrated its association with an increased risk of AF in this population.23 Notably, the TyG index combined with traditional risk factors improved the predictive value for AF. On the other hand, recent studies have also focused on the associations between the TyG index and AF recurrence after ablation or AF after procedure. Current evidence consistently supports the TyG index as an independent risk factor for AF recurrence after RFCA or Cox-maze IV ablation.[25-31] Similarly, its predictive capacity for postoperative AF has been validated in patients undergoing percutaneous coronary intervention,[32] septal myectomy[33] or coronary artery bypass grafting.[34,36] The findings of this meta-analysis align with these studies, and further confirm a linear positive relationship between the TyG index and AF.

Although numerous animal studies and clinical trials have explored the mechanisms underlying the association between IR and AF, such as oxidative stress in myocardial tissue, systemic inflammation and atrial remodeling,[53-55] the precise molecular pathways remain unclear. In diabetic rats, the action potential duration of atrial myocytes was significantly prolonged, accompanied by the downregulation of several ion channel proteins, which increased susceptibility to AF.[56] Chan et al. suggested that IR enhances superoxide production and upregulates calcium-homeostasis-related proteins, thereby increasing AF susceptibility.[12] Additionally, IR, oxidative stress and inflammation may interact and overlap, leading to atrial electrical remodeling, structural remodeling and the formation of low-voltage areas, which are widely recognized as key components of AF pathophysiology.[46,57] Furthermore, IR may eventually lead to compensatory hyperinsulinemia,58 which has been shown to activate the sympathetic nervous system and the renin-angiotensin-aldosterone system, ultimately contributing to autonomic nervous system dysfunction and increased AF susceptibility.[59,60]

It is also important to note that several studies have demonstrated that lifestyle interventions or pharmacotherapy can reduce the risk of AF in patients with DM. Lavie et al. discussed special issues related to AF in obesity and concluded that weight loss, physical activity and improved cardiorespiratory fitness are beneficial for the prognosis of obese patients with AF.[61] It has been proven that intermittent fasting can mitigate obesity-induced atrial hypertrophy and fibrosis, thereby restoring systemic insulin sensitivity and protecting against AF in obese mice.[54] Previous cohort and in vitro studies have found that metformin use protects the diabetic patients from AF, probably via attenuation of atrial cell tachycardia-induced remodeling and oxidative stress.[62] Additionally, sodium glucose cotransporter 2 inhibitor (SGLT2i) have been

associated with a reduced risk of both new-onset AF[63] and AF recurrence after catheter ablation.[64] Based on existing evidence, lifestyle interventions, including weight loss, physical activity, and dietary modifications, can improve insulin sensitivity and reduce the risk of AF, thereby attenuating the TyG index and its association with AF. Furthermore, pharmacological therapies such as metformin and SGLT2 inhibitors have been shown to protect against AF by targeting underlying metabolic dysfunction, which may further modulate the relationship between the TyG index and AF. In summary, IR may play a critical role in the development of AF, providing a mechanistic link that helps explain the association between the TyG index and AF.

The persistent high heterogeneity observed in our meta-analysis, despite subgroup analyses and sensitivity analyses, highlights the complexity of the relationship between the TyG index and AF risk. Heterogeneity in meta-analyses is often multifactorial65 and its clinical implications are noteworthy. The variability across studies underscores the need for personalized risk assessment strategies. Clinicians should consider the TyG index as one of several potential biomarkers for AF risk, while also accounting for individual patient characteristics, such as metabolic health status and comorbid conditions. For patients with an elevated TyG index, clinicians may identify them as high-risk for AF and recommend lifestyle modifications (e.g., Mediterranean diet, physical activity, weight loss), consider initiating metformin to improve insulin sensitivity, and schedule regular follow-ups with ECGs and cardiac monitoring for early AF detection. Future research should focus on identifying patient subgroups who may benefit most from TyG index-based risk stratification, potentially through advanced analytical techniques such as machine learning. The potential for publication bias, as indicated by Egger's and Begg's regression tests, is an important consideration in our study. Publication bias may arise from the tendency of journals to favor studies with statistically significant or positive findings, while studies with null or negative results may remain unpublished.[66] Although our results suggest a significant association between the TyG index and AF risk, the influence of unpublished studies or methodological differences across included studies cannot be excluded. Furthermore, the observed heterogeneity, combined with the potential for publication bias, emphasizes the need for future research to prioritize standardized methodologies, larger sample sizes, and transparent reporting. Such efforts would help reduce both heterogeneity and publication bias, ultimately strengthening the evidence base in this field.

Strengths and limitations

The strength of this study is that it is one of the most comprehensive and up-to-date meta-analyses on this topic and the first analysis of the exposure-effect relationship between the TyG index and AF. Our pooled ORs were derived from multivariate analyses, which helped minimize the influence of various confounders. This study provides a foundation for future studies to assess the potential ability of TyG index in AF pathology and prognosis, suggesting that addressing IR through lifestyle interventions or pharmacotherapy may improve metabolic health and reduce the risk of AF. However, there are several limitations that should be taken into consideration. First, all included studies were observational, so we cannot completely rule out the risk of confounding bias and cannot demonstrate any direct causal association. Second, this study was restricted to English and Chinese studies, potentially excluding relevant data published in other languages. Future research should aim to incorporate non-English studies, particularly those with robust data on the TyG index and AF, to enhance the generalizability and comprehensiveness of the findings. Third, the cut-off values for the TyG index varied among included studies, which may lead to differences in dividing individuals into the high or low TyG groups. Furthermore, the high heterogeneity observed in our analysis is a significant limitation that should be considered when interpreting the results. Although subgroup and sensitivity analyses were conducted to explore potential sources of heterogeneity, differences in study design, population characteristics, sample size and other unmeasured factors may have influenced the findings. Additionally, the potential for publication bias may have led to an overestimation of the true effect size and reduced the generalizability of the results. To address these limitations, we recommend utilizing larger, multi-center prospective cohorts with standardized data collection methods to minimize bias and confounding factors. Additionally, we propose the design of high-quality randomized controlled trials (RCTs) to evaluate the causal relationship between the TyG index and AF risk. Specifically, future RCTs could investigate whether interventions targeting the TyG index (e.g., lifestyle modifications or pharmacological treatments) effectively reduce the incidence of AF.

Conclusion

Based on our study's findings, the TyG index is associated with an increased risk of AF, including pure AF, postoperative AF and AF recurrence after ablation. Additionally, we identified a linear positive relationship between the TyG index and AF risk. However, we should consider that potential confounding factors, such as lifestyle modifications, pharmacological interventions, and other variables, may have influenced the results. Therefore, further high-quality, large-scale studies are needed to validate the TyG index as a predictor for AF in clinical practice and to strengthen the robustness of these conclusions.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare that there is no conflict of interest.

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