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The association between insulin resistance and QT interval: A systematic review and Meta-Analysis

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Abstract

Background Insulin resistance (IR) is a major health concern associated with various diseases, and prolonged QT interval can potentially lead to life-threatening arrhythmias and death. There are conflicting views on the relationship between IR and QT interval. This meta-analysis aims to comprehensively investigate the association between IR and QT interval.

Methods An extensive search in databases PubMed, Scopus, Cochrane Library, Embase, and Web of Science up to October 2024 was conducted. Cohort studies which reported means and standard deviations for the QTc interval across the case and control groups with and without insulin resistance based on HOMA-IR were eligible for inclusion. Research with partial or inaccessible primary data, those involving participants with pre-existing cardiac conditions, and those with ambiguous results were excluded. The evaluation of study quality utilized the Newcastle-Ottawa Scale. A random-effects model was applied for the meta-analysis, and Egger's test was used to assess publication bias. GRADEproGDT was used to evaluate the certainty of the evidence.

Results Five studies, encompassing 603 participants, met the inclusion criteria. A significant positive association was observed between IR and QT interval (Weighted Mean Difference [WMD] = 12.38, 95% Confidence Interval [CI]: 5.51, 19.25). All included studies demonstrated high methodological quality. Assessment for publication bias revealed no significant findings (p-value for Egger's test = 0.39). The quality of evidence for the main outcome was moderate. Subgroup analyses revealed a significant link between IR and QT interval in studies from Turkey and India, with samples over fifty, and involving adults.

Conclusions This meta-analysis highlights that IR is linked to an elevated risk of QT prolongation. Early identification of IR is crucial to mitigate the risk of QT prolongation and subsequent arrhythmias, thus emphasizing the importance of early intervention to prevent adverse cardiac outcomes and sudden cardiac death. Caution is needed when

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interpreting our results due to study heterogeneity, certainty of evidence, and sensitivity analysis findings. More rigorous research on this subject is required.

Keywords Insulin resistance, QT interval, QT prolongation, Meta-analysis

Introduction

Insulin resistance is mainly brought on by insulin's incapacity to activate the insulin receptor substrate (IRS) in an effective manner. This diminished IRS activation impairs the function of GLUT4 in the context of glucose transport. Moreover, the diminished capacity of IRS-1/2 to activate glycogen uptake in the liver in an effective manner inhibits glycogen synthesis. Finally, abnormalities result in elevated blood glucose levels [1]. Additionally, the equilibrium between the supply and consumption of glucose can be altered by insulin resistance, which can lead to elevated blood sugar levels. This can subsequently exacerbate conditions including metabolic syndrome [2], cancer [2], and coronary heart disease [3]. Insulin resistance causes cardiac repolarization to take longer, which lengthens the QT interval [4, 5].

It is generally acknowledged that prolonged QTc is linked to potentially fatal outcomes like sudden cardiac death (SCD) and potentially life-threatening ventricular arrhythmias (VAs) like torsades de pointes (Tdp) [6]. Around 180–250,000 instances of SCD are reported to occur annually in the US, whereas 4–5 million cases are thought to occur worldwide [7]. Studies have demonstrated that insulin improves long-QT in insulin-resistant aged rats by enhancing the ventricular AP repolarization through reversing the depressed IKs via modulation of the β3 -ARs signaling pathway [8].

Some investigations have demonstrated a relationship between IR and QT prolongation However, others have shown either no association or a weak association between IR and QT prolongation [9, 10]. Given the conflicting results and gaps, we aimed to conduct a systematic review and meta-analysis on this topic, which has not been previously undertaken. Our aim is to elucidate the association between IR and QT interval, thereby enabling the prediction and mitigation of the adverse effects of QT prolongation.

Materials and methods

Search strategy

Our systematic review was conducted in accordance with the Cochrane Collaboration guidelines and PRISMA statement [11]. The research protocol was registered on the PROSPERO platform (CRD42024590336), and the data gathering and analysis were carried out as outlined. Because only published and anonymized data were utilized, it was not required to obtain approval from an Ethics Committee. We performed a systematic search in the databases PubMed, Scopus, Cochrane library, Embase, and Web of sciences to find relevant investigations up to October 29, 2024. Additionally, we searched Google Scholar and reviewed the reference lists of previous investigations and selected articles to spot additional pertinent literature. Our search strategy combined the terms ("insulin resistance" OR "insulin sensitivity" AND "QT prolongation" OR "ventricular arrhythmia" OR "cardiac disease"). All searches were conducted by a trained librarian using EndNote software version X6. All the search syntaxes for the different databases are presented in the Supplementary file.

Inclusion criteria

We included original observational studies meeting the following criteria: (a) Examined both IR and QTc interval, (b) Published in English with full-text availability, (c) Utilized Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), (d) Reported means and standard deviations for the QTc interval across the case and control groups with and without insulin resistance based on HOMA-IR.

HOMA-IR in each study was determined by multiplying the fasting insulin level (in μIU/mL) with the fasting glucose level (in mmol/L) and dividing the result by 22.5 [12]. Insulin resistance was assessed using various cutoffs of HOMA-IR, based on study age groups and geographic location (Table 1). To enable a more detailed analysis and obtain specific results, we divided the studies into two subgroups: (1) studies with an IR population size of more than 50, and (2) studies with an IR population size of less than 50.

Electrocardiography (ECG) measurements in all investigations were performed using a 12-lead ECG at 25 mm/s and 10 mm/mV while the patient was supine. QT interval was measured from the QRS complex start to T-wave intersection with the isoelectric line. QTc was calculated as QT/√RR (Bazzet formula) in all studies [13].

Exclusion criteria

We excluded studies with the following criteria: (a) review articles, (b) editorials or commentaries, (c) in vivo and in vitro studies, (d) clinical trials, (e) studies involving participants with pre-existing cardiac disease, and (f) studies with unclear or ambiguous results. Additional reasons for exclusion during the full-text review are presented in the PRISMA flowchart of the study (Fig. 1).

Table 1 Study characteristics

Study	Study design	Location	Population	Period	Sample size (Case/Control)	HOMA-IR cutoff for Insulin resistance	Mean ± SD of QTc for case group	Mean ± SD of QTc for control group	NOS assessment
Kumar et al. (2024)	Cross sectional cohort study	India	Non-diabetic patients 18–60 years of age attended to Medicine OPD, LLRM Medical College	Not mentioned	100 (37/63)	≥ 6	431.24 ± 31.2	408.83 ± 16.96	High quality
I dil et al. (2023)	Prospective cohort study	Turkey	Children aged 2–18 years with obesity based on BMI above 95% or + 2 SDS or body weight above 99% or + 2 SDS	2020	50 (25/25)	≥ 2.5 in prepubertal patients and ≥ 4 in pubertal patients	386 ± 43	382 ± 33	High quality
I lhan et al. (2022)	Prospective cohort study	Turkey	Obese patients 6–18 years of age referred to the pediatrics clinic	2018–2019	50 (25/25)	> 2.2 in girls and > 2.6 in boys in the prepubertal period and > 3.8 in girls and > 5.2 in boys in the pubertal period	426.5 ± 17.4	420.9 ± 21.4	High quality
Matsumoto et al. (2019)	Prospective cohort study	Japan	Urban and rural resident who received health checkups	2008–2014	153 (25/128)	≥ 1.73	407.7 ± 26.6	402.2 ± 21.2	High quality
Kuzu et al. (2019)	Cross sectional cohort study	Turkey	Patients followed-up in the endocrinology and metabolism disorders clinic	2015–2017	250 (110/140)	≥ 2.5 in prepubertal patients and ≥ 4 in pubertal patients	430.9 ± 18	414.2 ± 23	High quality

Abbreviations: SDS, Standard Deviation Score; NOS, Newcastle Ottawa Scale (risk of bias tool for observational studies)

Case group: Insulin resistance (HOMA-IR of appropriate cutoff or above); Control group: Insulin sensitive (HOMA-IR below the appropriate cutoff)

Data extraction

Two researchers (S.B. and S.S.) collected and extracted data independently for each study, including study characteristics (author's name, title, study type, publication year, location, population, and sample size), participant information (age, gender, metabolic syndrome status, cardiovascular status, and BMI status), and outcome measures (IR status, mean QTc interval). Any discrepancies were resolved through discussion, with agreement reached by the two investigators; if not resolved, a third researcher (M.F.) was involved.

Quality assessment

We conducted methodological quality assessment utilizing Newcastle Ottawa Scale, allocating a total of nine points across three areas: (1) the process of selecting the sample, which involves four important factors, (2) ensuring comparability between different groups, which involves two factors, and (3) accurately determining the exposure and outcomes, which involves three factors for cohort studies. Studies scoring more than 7 were categorized as high quality [14]. Two investigators (M.M. and S.B.) conducted the quality assessment process, and challenges were addressed by engaging in dialogue until a mutual agreement was established; if unresolved, a third researcher (M.F.) was brought in.

Statistical analysis

The relationship between IR and QTc interval outcomes were presented with weighted mean differences (WMD) and their 95% confidence intervals (95% CIs). Before conducting a meta-analysis, all effect estimates from each study were standardized to a HOMA-IR change in insulin levels. Heterogeneity within the studies was assessed by employing the I2 statistic., where values less than 25% indicated no homogeneity, 25–50% represented moderate heterogeneity, 50–75% showed substantial heterogeneity, whereas 75–100% demonstrated considerable

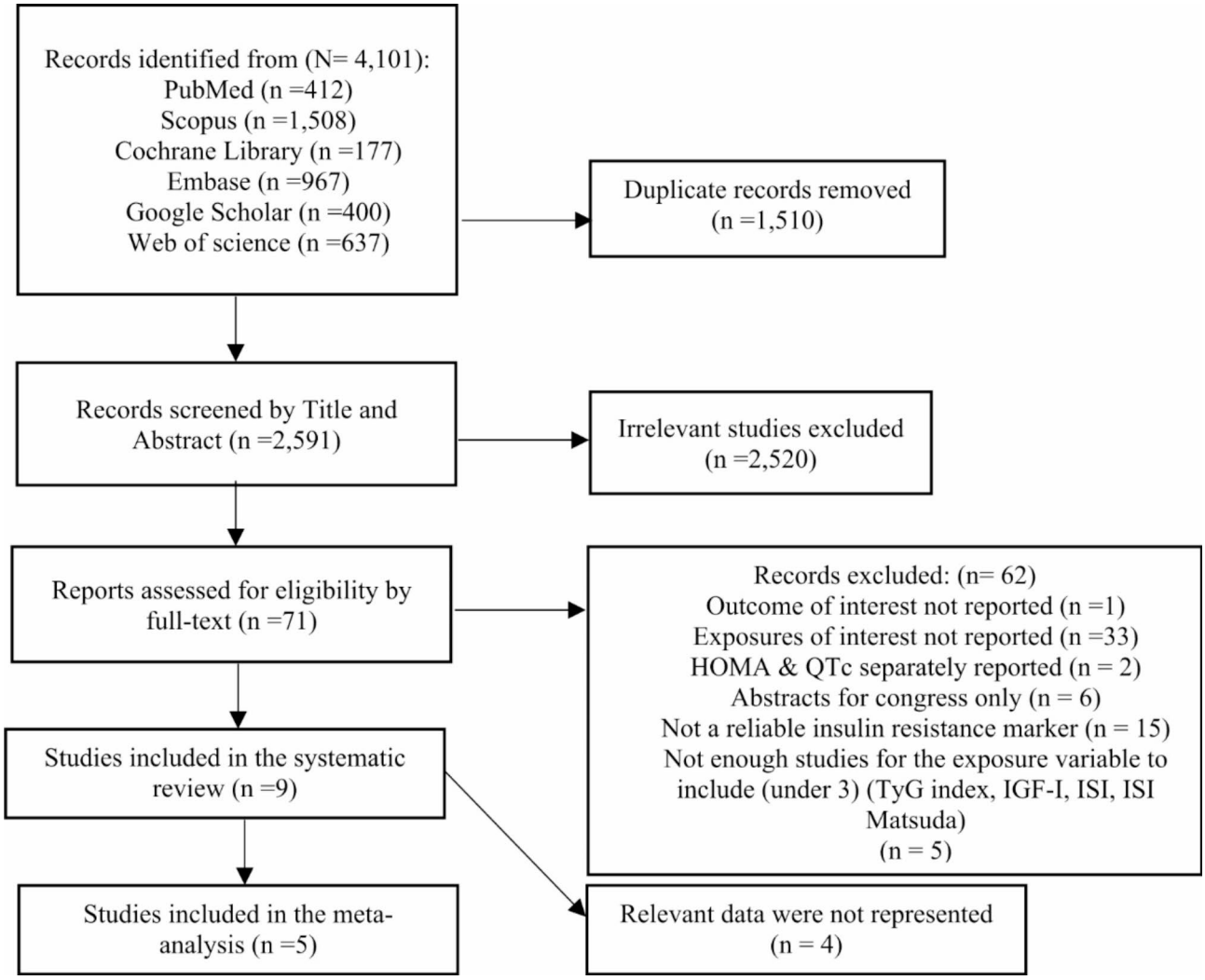

Fig. 1 PRISMA flowchart of the study selection

heterogeneity [15]. Random-effects model was utilized to pool the effect sizes (ESs) depending on the presence of heterogeneity.

Additional analyses, such as sensitivity analysis and subgroup analyses, were carried out to detect the root causes of inter-study heterogeneity. The potential publication bias was assessed through both statistical and visual analysis using Egger's test and funnel plot among studies, respectively. We performed all analyses using the STATA version 16.0 software. Statistical significance was considered if the p-value was less than 0.05.

GRADE analysis

Additionally, according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [16] (GRADEproGDT, www.gradepro.org [17]), the certainty of the evidence was rated as high, moderate, low and very low, by considering the items of risk of bias, inconsistency of findings, indirectness of evidence, imprecision, dose response analysis, publication bias, plausible confounding and large effect.

Results

Search strategy

In the preliminary search phase, a sum of 4101 pertinent studies were found. Firstly, duplicate records were removed ($n = 1510$). Then, after screening for title and abstract, 2520 studies were excluded. Lastly, we did full-text evaluation, during which 66 studies were excluded due to the mentioned reasons (Fig. 1). Finally, 5 studies [18–22] were included in the analysis.

Study characteristics

Table 1 displays the principal features of the four studies that were incorporated. Three of these studies were prospective cohort studies [18, 19, 21], while two were cross-sectional [20, 22]. The studies were carried out in Turkey, Japan, and India with a total of 603 participants

recruited. Participants from various age groups (2–70 year) contributed in this meta-analysis. Included studies were published from 2019 to 2024. They applied data that collected in 2008–2020. HOMA scale was utilized in these studies to define IR and investigate its effect on QTc interval.

Quality assessment results

Each study was of superior quality. The evaluation of quality yielded scores of seven for three of the studies and eight for the remaining two. The studies were notably high-quality in terms of adequate case definition, determination of exposure, selection and definition of controls, and adjustment for confounding factors (Supplementary Table 1).

Systematic review results

Four studies on HOMA-IR lacked the numeric data needed for inclusion in the meta-analysis. Among them, Hlaing et al. reported a significant positive correlation between HOMA-IR and QTc in 100 healthy adult men ($r = 0.41$, $p < 0.001$), with an insulin resistance cutoff of 3.8 associated with a 3.4-fold higher likelihood of QT prolongation [23]. Similarly, Timar et al. found a significant correlation in 104 patients with type 2 diabetes ($r = 0.38$, $p < 0.001$), supported by a multivariate model (B = 1.76, 95% CI 1.3–2.2) [24]. Shin et al., in a study of 874 health checkup participants, found a significant correlation only in women ($r = 0.17$, $p < 0.001$); however, the overall multivariate analysis also showed an association (B = 3.508, $p = 0.033$) [25]. Alexandra et al. observed a significant correlation in 50 patients with metabolic syndrome ($r = 0.38$, $p < 0.01$) [26].

For the meta-analysis, studies with consistent designs reporting QTc means and standard deviations in case and control groups (with and without insulin resistance based on HOMA-IR) were included. Two cross-sectional studies reported significantly higher QTc in insulin-resistant individuals: 16.7 milliseconds in Kuzu et al. [27] and 22.41 milliseconds in Kumar et al. [22] Three prospective studies reported smaller differences, which were not statistically significant: 5.5 milliseconds in Matsumoto et al. (healthy adults) [21], 5.6 milliseconds in Ihan et al. (obese children) [19], and 4 milliseconds in Idil et al. (obese children) [28].

Meta-analysis results

Pooling the data from the five studies, our meta-analysis demonstrated a positive association between IR and QT interval (WMD = 12.38, 95% CI: 5.51, 19.25). Subgroup analysis based on sample size revealed that IR had a significant impact on QT interval, increasing the risk of QT prolongation in studies with a sample size greater than fifty (WMD = 15.25, 95% CI: 7.32, 23.17), employing cross-sectional designs (WMD = 17.72, 95% CI: 13.11, 22.33), and encompassing adult populations (individuals over 18 years of age) (WMD = 15.25, 95% CI: 7.32, 23.17). Furthermore, subgroup analysis based on study location showed a positive relationship between IR and QT interval in studies conducted in Turkey (WMD = 11.24, 95% CI: 2.24, 20.24), whereas the study conducted in Japan did not demonstrate a significant relation (WMD = 5.50, 95% CI: -5.55, 16.55) (Fig. 2; Table 2).

Leave-one-out sensitivity analysis

Sensitivity analyses revealed a notable change in the impact of IR on the risk of QT prolongation after excluding the study by Kuzu et al. [20] (WMD = 10.20, 95% CI: 0.90, 19.49) (Fig. 3).

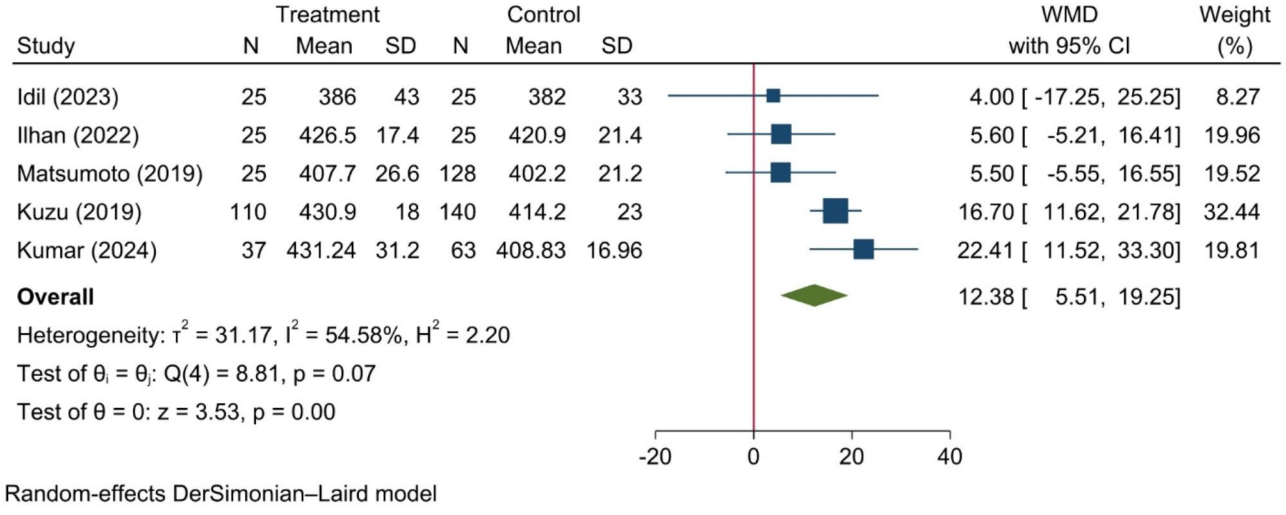

Fig. 2 IR and QT interval, Meta-analysis results

Table 2 Final meta-analysis results and subgroup analysis

Sub groups		Study	Effect size (WMD)	I^2 value	*P*-value for heterogeneity
Overall		I dil et al. I lhan et al. Kuzu et al. Matsumoto et al. Kumar et al.	12.38 (5.51, 19.25)	54.6%	0.07
Based on location	Turkey	I dil et al. I lhan et al. Kuzu et al.	11.24 (2.24, 20.24)	52.9%	0.120
	Japan	Matsumoto et al.	5.50 (-5.55, 16.55)	-	-
	India	Kumar et al.	22.41 (11.52, 33.30)	-	-
Based on study design	Prospective	I dil et al. I lhan et al. Matsumoto et al.	5.37 (-1.89, 12.63)	0.0%	0.991
	Cross sectional	Kuzu et al. Kumar et al.	17.72 (13.11, 22.33)	0.0%	0.352
Based on sample size	More than 50	Kuzu et al. Matsumoto et al. Kumar et al.	15.24 (7.32, 23.17)	58.91%	0.00
	Less than 50	I dil et al. I lhan et al.	5.27 (-4.36, 14.90)	0.0%	0.991
Based on age	More than 18	Kuzu et al. Matsumoto et al. Kumar et al.	15.25 (7.32, 23.17)	58.91%	0.08
	Less than 18	I dil et al. I lhan et al.	5.27 (-4.36, 14.91)	0.0%	0.9

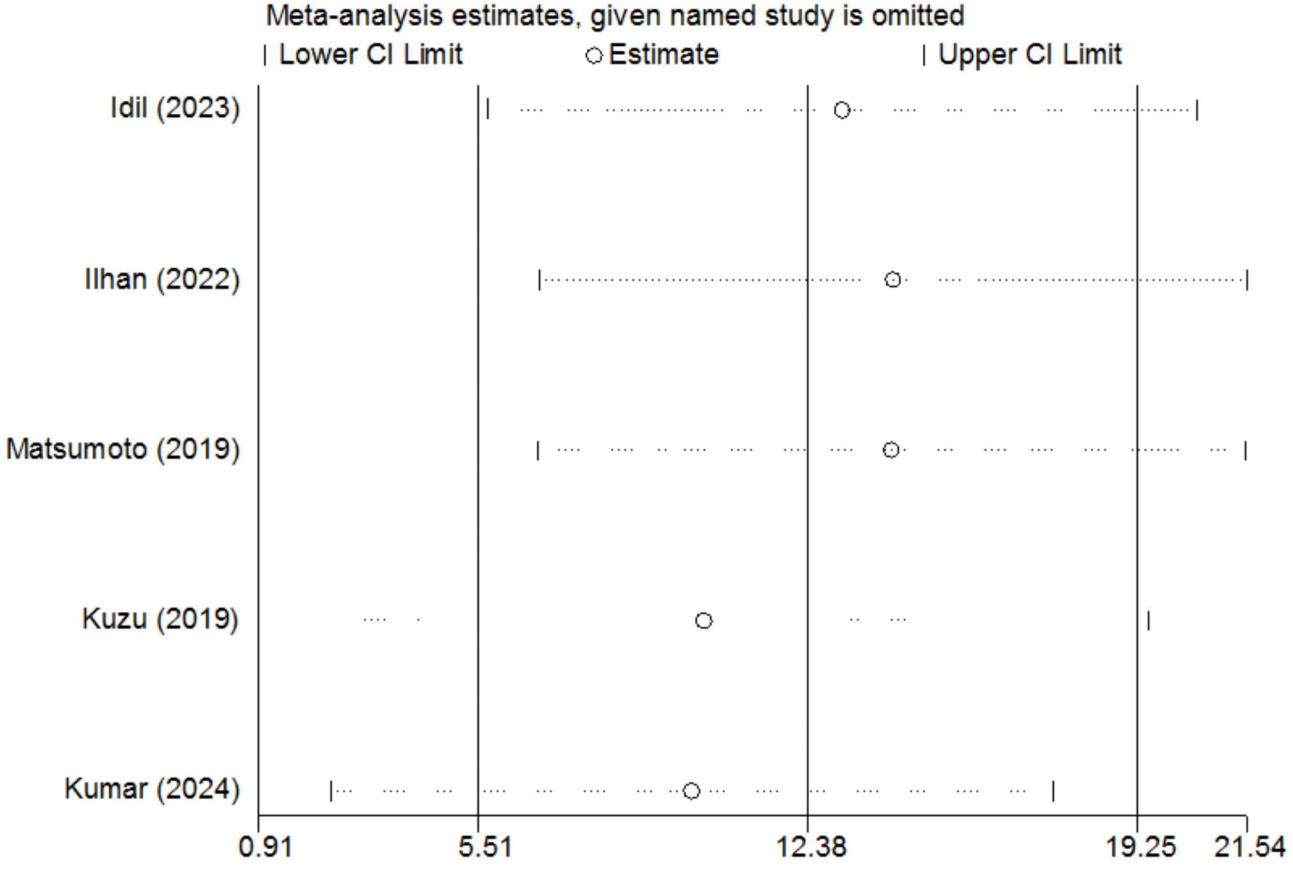

Fig. 3 IR and QT interval, leave-one-out sensitivity analysis

Table 3 GRADE evidence profile of the association between insulin resistance and QT interval

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Participants	WMD	(95% CI)		
5	observational studies	not serious	not serious	not serious	not serious	Dose-Response	603	12.38	(5.51, 19.25)	⨁⨁⨁◯ Moderate	CRITICAL

Abbreviations: WMD: Weighted mean difference; **CI**: Confidence interval

Quality of the evidence and publication bias

Based on the GRADE assessment, the quality of evidence for main outcome was moderate (Table 3). No considerable publication bias was observed in the meta-analyses of IR in relation to QT interval across the included studies (p-value for Egger's test = 0.39).

Discussion

This meta-analysis has methodically assessed the relationship between IR and the QT interval, which is a cardiac repolarization measure associated with a higher risk of sudden cardiac death. Our results demonstrated a strong positive correlation between IR and QTc interval in our meta-analysis, which included five observational studies. In view of the noted heterogeneity, subgroup analyses were performed. In studies, particularly those carried out in Turkey and India, with sample numbers more than fifty, and involving adult populations (individuals over 18 years of age) a substantial and direct link between IR and QT interval was discovered.

Research has shown that IR has a significant impact on a variety of medical conditions, such as hyperlipidemia [29], cardiovascular diseases [30], and renal disease [31]. There is particular evidence from several research that IR and QT interval are positively correlated [32, 33]. A weak or nonexistent correlation has been documented by some research, whilst others have indicated that IR may potentially impact the QT interval and cause its extension [34, 35]. Several studies that measured insulin resistance using the well-known HOMA-IR index have presented contradictory results, with some reporting significant associations [22, 26, 27], and others reporting no association with QTc [19, 21, 28].

Many pathogenic hypotheses seek to explain the link between IR and QT interval. QT prolongation is one possible mechanism by which IR affects the cardiovascular system. Increased heart rate and cardiac contractility can affect the QT interval, as can increased sympathetic nervous system activity brought on by IR [36]. Metabolic diseases associated with IR, such as dyslipidemia and altered glucose metabolism, may worsen QT prolongation [37, 38], Heart myocytes may be affected by certain conditions. Hyperinsulinemia, which raises cellular potassium uptake and causes hypokalemia, is commonly associated with IR [39]. The QT interval may be further prolonged by hypokalemia in addition to other electrolyte abnormalities such as hypomagnesemia and hypocalcemia, which are frequent in insulin-resistant people [40–42]. Additionally, by lowering vasodilation and increasing arterial stiffness, IR-associated endothelial dysfunction [43] may have an impact on the cardiovascular system and result in QT prolongation. Moreover, changes in the heart's structure caused by IR, such as left ventricular hypertrophy, might potentially affect QT prolongation [44]. Furthermore, drugs that prolong the QT interval may also be taken by individuals with IR. Higher plasma levels also increase the chance of QTc prolongation since IR hinders medication metabolism.

These findings emphasize the need of continuously assessing cardiovascular health in individuals with IR, which has important therapeutic ramifications. When assessing cardiovascular risk, clinicians should be aware of the possibility of QTc prolongation in this patient group. These findings highlight the critical role that IR management plays in preventing type 2 diabetes, controlling other metabolic issues, and reducing the incidence of cardiac arrhythmias. Further research needs to focus on elucidating the processes behind the correlation between IR and QTc prolongation. Additionally, they ought to investigate the potential of reversing or stopping QTc prolongation using insulin sensitivity therapies. Randomized controlled trials and longitudinal investigations are required to prove causation and the efficacy of treatment approaches.

This study of meta-analysis included advantages as well as disadvantages. This study represents the first meta-analysis to assess the association between IR and QT prolongation, given the increasing prevalence of IR and its critical role in the development of arrhythmias and SCD. The dearth of studies in this field was, however, a disadvantage. Additionally, our findings may not have been as applicable to all included research because of the lack of geographical and participant demographic diversity. Due to the lack of a sufficient number of studies with consistent and comparable results for pooling and conducting a meta-analysis, the analyses were performed on studies with varying designs and populations. Despite subgroup analyses based on study design, this variability reduces

the precision of the results and requires cautious interpretation. Additionally, most included studies had small sample sizes and low methodological quality, which weakens the strength of the evidence. Further studies are needed to evaluate this association, with larger sample sizes and more robust designs across diverse populations. This would enable future meta-analyses to pool more consistent results and yield more reliable conclusions.

Our study focused on the more widely accepted and standardized HOMA-IR index, as sufficient studies using other indices were not available for meta-analysis. However, we included a table summarizing studies that have investigated the association between IR and the QTc interval in various ways. This table serves as a guide for future meta-analyses and provides additional context for readers interested in the background of our research idea (Supplementary Table 2). The table is categorized based on the type of insulin resistance index evaluated.

Conclusion

In conclusion, the meta-analysis affirms that there is a relationship between IR and QTc interval. Our study highlights the significance of IR as a factor affecting QT interval. Physicians must recognize IR in its early phases in order to minimize its negative consequences on human health, including those on the cardiovascular system and QT interval. We can lessen the likelihood of QT prolongation and the potentially harmful side effects that go along with it by managing and reducing IR, one of the factors that contributes to QT prolongation. When interpreting our results, care should be used because of the heterogeneity of the studies, certainty of evidence findings, and the sensitivity analysis results.

Abbreviations

IR	Insulin Resistance
IRS	Insulin Receptor Substrate
SCD	Sudden Cardiac Death
Vas	Ventricular Arrhythmias
Tdp	Torsades de Pointes
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
ECG	Electrocardiography
WMD	Weighted Mean Differences
CI	Confidence Interval
ES	Effect Size
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
NOS	Newcastle-Ottawa Scale

Supplementary Information

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Supplementary Material 1

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Author contributions

Conceptualization: M.F. Systematic search: Z.KM. and S.B. Screening: S.B. and S.S. Data Extraction: S.B. and S.S. Quality assessment: M.MS. and S.B. Analysis: R.T. Writing (original draft preparation): M.MS. and S.B. Writing (review and editing): S.B. Supervision: S.B., M.F. Validation: M.F., R.T., and S.B. Visualization: R.T. Project administration: M.F. and R.T.; All authors have read and approved the final version.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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