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Association of *TCF7L2* genetic variants rs12255372 and rs7903146 with the polycystic ovary syndrome risk: systematic review and meta-analysis

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Abstract

Background A significant overlap in the pathophysiological features of polycystic ovary syndrome (PCOS) and type 2 diabetes mellitus (T2DM) has been reported; and insulin resistance is considered a central driver in both. The expression and hepatic clearance of insulin and subsequent glucose homeostasis are mediated by *TCF7L2* via Wnt signaling. Studies have persistently associated *TCF7L2* genetic variations with T2DM, however, its results on PCOS are sparse and inconsistent.

Methods We performed a comprehensive literature review of the data published till June 2024, on rs7903146, rs12255372, and PCOS in PubMed, Medline, the Cochrane Library, Google Scholar, Science Direct, Scopus, and Web of Science, followed by a meta-analysis to evaluate the association between these genetic variations and the PCOS risk. Using a random effects model, the pooled odds ratio (OR) and confidence intervals (95%CI) were computed using STATA statistical software.

Results The genotypic data from 3052 controls and 2291 women with PCOS from ten published studies were analysed. The results indicated no cumulative association between the rs7903146 variant and PCOS risk in either the allelic (C vs. T: OR = 1.21; 95% CI: 0.96–1.47, $p > 0.05$) or genotypic models (CC vs. CT + TT: OR = 1.06; 95% CI: 0.90–1.23, $p > 0.05$). Similarly, the genetic variant rs12255372 was not associated with PCOS risk both in the allelic and the dominant inheritance model($p > 0.05$). Unlike East Asians (MAF < 0.025), both variants are highly frequent across other global populations including America, South Asia, and Europe (MAF ≥ 0.19).

Conclusion Unlike T2DM, our results showed that rs7903146 and rs12255372 variants of the *TCF7L2* gene do not modulate the PCOS risk. However, the role of other *TCF7L2* variants remains to be studied in future studies.

Keywords Polycystic ovary syndrome, Gene polymorphism, Menstrual irregularity, Insulin resistance, Diabetes mellitus, *TCF7L2*

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Introduction

Polycystic ovary syndrome (PCOS) is increasingly recognized as the most prevalent (9.2%) endocrine–metabolic disorder in young women of < 40 years of age [1, 2]. The clinical presentation of PCOS includes chronic anovulation, hyperandrogenism, and polycystic ovaries [3, 4]. Globally, the age-standardized PCOS incidence rate in 2017 was reported to be ~ $83/10^5$ in reproductive-aged women [5]. PCOS and Type 2 diabetes mellitus (T2DM) have similar pathophysiological characteristics [1]. T2DM and insulin resistance (IR) are two typical manifestations in women with PCOS. Women with PCOS have been found to have a 3-fold greater risk of impaired glucose tolerance (IGT) when compared to age-matched non-PCOS women. Moreover, elevated oxidative stress [6], and pervasiveness of undiagnosed T2DM in women with PCOS [7], warrants contemplation especially in the Vitamin-D deficient populations [8]. Given these observations, evidence suggests that T2DM, IR, and PCOS are likely to be an outcome of a common dysregulated pathway.

Given a significant overlap in the pathophysiological events between PCOS and T2DM, several genes have been proposed as potential candidates in the poorly understood etiology of PCOS. Among these factors, *TCF7L2* (transcription factor 7-like 2) and *INSR* (insulin receptor) are considered important modulators of PCOS risk. *TCF7L2* is a transcription factor in the Wnt signaling cascade that regulates the transcription of several genes, including those involved in glucose homeostasis [9]. *TCF7L2* mediates the hormone glucagon-like peptide-1 (GLP-1) which in turn enhances the secretion and the production of insulin and inhibits glucagon secretion [10]. Additionally, the synthesis, secretion, and degradation of glucose-dependent insulin-tropic peptide (GIP), insulin-like growth factor-1 (IGF-1), and the functioning of pancreatic beta islets are all downstream effects of this TCF7L2/Wnt signaling cascade [11]. *TCF7L2* imparts an enhanced risk and expedites the development of T2DM in subjects with impaired glucose tolerance [12]. Given that PCOS women possess a seven-fold risk for developing T2DM, a strong association between PCOS and IR and the crucial involvement of *TCF7L2* in glucose homeostasis makes the latter a compelling candidate for understanding PCOS pathogenesis [12]. While few small candidate gene association studies have evaluated the association of *TCF7L2* genetic variants with PCOS risk, no underlying mechanism of the former in the development of PCOS has been established so far.

The complex and heterogeneous clinical presentation of PCOS and its poorly understood multifactorial pathogenesis is modulated by genetic and epigenetic factors [13, 14]. As an essential candidate genetic locus for T2DM, the genetic variations in *TCF7L2* have been persistently linked with the risk of T2DM [15, 16]. However, studies on its association with PCOS are limited and have shown inclusive results [17, 18]. Therefore, based on the published research, we conducted a meta-analysis and assessed the relationship between the persistently investigated *TCF7L2* polymorphic variants (rs12255372 and rs7903146) with the risk of PCOS.

Methodology

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist guidelines were followed for the current study [19].

Search strategy

A comprehensive literature search strategy utilizing a combination of keywords including "TCF7L2" AND "PCOS" OR "Polycystic ovary syndrome" was carried out. Besides, another search strategy with the keywords "rs7903146" PCOS' OR "Polycystic ovary syndrome" and "rs12255372" AND "PCOS" OR "Polycystic ovary syndrome" was used for inclusion/exclusion of studies. The publicly accessible resources such as PubMed, Medline, the Cochrane Library, Google Scholar, Science Direct, Scopus, and Web of Science were accessed. The literature search was conducted between 21st February to May 31st, 2024 and all the papers published till May 31st, 2024 were included in the analysis.

Inclusion and exclusion

During the literature search, restrictions were not placed on country, time, or language of publication. However, due to missing required information, editorial letters, conference proceedings, and practice guidelines were excluded. To confirm eligibility, the data was extracted and read independently by two authors (IAS and RR). The data was made available to other authors for further analysis. The minor allele frequencies of the two studied variants rs7903146 (GRCh37; Chr:10:114758349-C/T) and rs12255372 (GRCh37; Chr:10:114808902-G/T) were also checked at (asia.ensembl.org).

After removing duplicates, titles, and abstracts were screened as per the eligibility criteria. The full-text articles of all the identified abstracts were reviewed independently. Only the case-control studies with (a) well-defined uniform diagnostic criteria for PCOS, (b) evaluating the relationship between the polymorphic variants rs7903146 and rs12255372 of *TCF7L2* and the risk of PCOS, and (c) reporting odds ratios, genotypic and allelic frequencies were included in the current meta-analysis. The exclusion criteria included: (1) studies thar did not providing sufficient data on allelic and genotypic data (2) studies without clear results and in languages other than English (4) Case reports, commentaries, guidelines, editorials, book chapters, letters to editor, reviews, and metanalysis. The

reference lists of previous systematic reviews/metanalysis were also screened for relevant studies. The observational and interventional studies that did meet the eligibility criteria were excluded from the analysis.

Quality assessment

The critical appraisal checklists for research developed by the Joanna Briggs Institute (JBI) [19] were used to assess the quality of the chosen studies and to assess their bias risk. The risk of bias in a study was considered high if the "yes" score was 49% or lower. Studies with a score between 50 and 69% were considered at moderate risk and those with a score of 70% or higher at low risk of bias. All the studies included were evaluated for the risk of bias and then classified accordingly i.e., studies with low risk, high risk of bias, and studies with some concerns. Disagreements between the two independent reviewers were addressed by discussion and consensus.

Statistical analysis

From each study included in the current meta-analysis, the genotypic frequencies, odds ratios (ORs), and 95% confidence intervals (CIs) were retrieved. Individual ORs and 95%CIs were estimated by χ^2 test wherever authors had not reported. To evaluate the relationship between the investigated genetic variations of *TCF7L2* and the risk of PCOS, pooled ORs with 95% CIs were also calculated. Given a variability in the published results on the association of studied genetic variations and the risk of PCOS, we used random effects model for the analysis. To calculate the pooled OR, we employed both the dominant model (CC vs. CT + TT for rs7903146 and GG vs. GT + TT for rs12255372), and the allelic model (C allele vs. A allele and G vs. T). To calculate the statistical significance of pooled ORs, a Z-test was employed. Statistical significance was defined as a two-tailed p-value of <0.05. Any potential heterogeneity between studies was estimated by performing the I^2 test. Studies with $I^2 > 50\%$ were considered substantially heterogeneous. Galbraith plots were also plotted for heterogeneity estimation. The studies were additionally stratified by ethnicities and subpopulations, and pooled ORs were examined using the random effects model. To look for any publication bias, Egger's and Begg's tests were applied. STATA statistical software (version 17.0, Stata Corporation, College Station, TX) was used for the data analysis.

Results

Identification and description of studies

Eighty-eight papers (after deduplication) that were related to *TCF7L2* and PCOS risk were found in the literature review. After applying our predetermined exclusion criteria and reviewing the titles and/or abstracts of the research, 78 papers were removed as having either inadequate data or being ineligible for the meta-analysis (Fig. 1). A detailed summary of the studies included in the current meta-analysis is provided in Table 1. For rs7903146, we examined the genotypes of 3052 controls and 2291 women with PCOS from ten different studies [20–28]. While as the data from 1173 PCOS patients and 1229 controls were analysed from five studies that were eligible for the rs12255372 genetic variation *TCF7L2* study [23, 24, 26, 27, 29]. The studies involved individuals from various ethnic backgrounds, and after dividing them into two groups (Asian and non-Asian), the relationship between genetic variations and the risk of PCOS was assessed.

Association of *TCF7L2* genetic variants rs12255372 and rs7903146 with PCOS

On analysing the association of *TCF7L2* variant rs7903146 and PCOS risk, our results indicated no cumulative association between the rs7903146 variant and PCOS in either the allelic (C vs. T: OR = 1.21; 95% CI: 0.96–1.47, $p > 0.05$) or genotypic models (CC vs. CT + TT: OR = 1.06; 95% CI: 0.90–1.23, $p > 0.05$) (Fig. 2). Similarly, the genetic variant rs12255372 was also not associated with PCOS risk in any model studied: (G vs. T: OR = 1.01; 95%CI:0.70–1.32, $p > 0.05$) or genotypic dominant model (GC vs. GT + TT: OR = 0.99; 95%CI:0.66–1.233 ($p > 0.05$) (Fig. 3). Unlike East Asians (MAF < 0.025), both variants are highly frequent across other global populations (MAF ≥ 0.19) in 1000G or gnomAD databases. Further, there was no correlation between the examined polymorphic variations and the risk of PCOS when the subjects were divided by ethnicity ($p > 0.05$). In the meta-analysis for rs12255372, we discovered heterogeneity across all genetic models examined ($I^2 = 49.25\%$ for the genotypic model and $I^2 = 63.25\%$ for the allelic model).

Publication bias and quality assessment of studies

The cumulative analysis did not reveal any indication of publication bias according to Begg's test or Egger's test ($p > 0.05$) (Supplementary Figure S1). Upon sensitivity analysis the results did not change when omitting one study at a time (Supplementary Figure S2) and no significant heterogeneity between the studies was observed (Supplementary Figure S3).

Discussion

The overlapping pathophysiological events between PCOS and T2DM suggest shared etiological factors as well. The interaction between a Wnt ligand and its receptor triggers a multitude of signaling cascades that in turn orchestrate many cellular functions including polarity, movement, proliferation, differentiation, self-renewal, and survival [30]. The downstream Wnt signaling cascade including regulation of multiple gene expression is

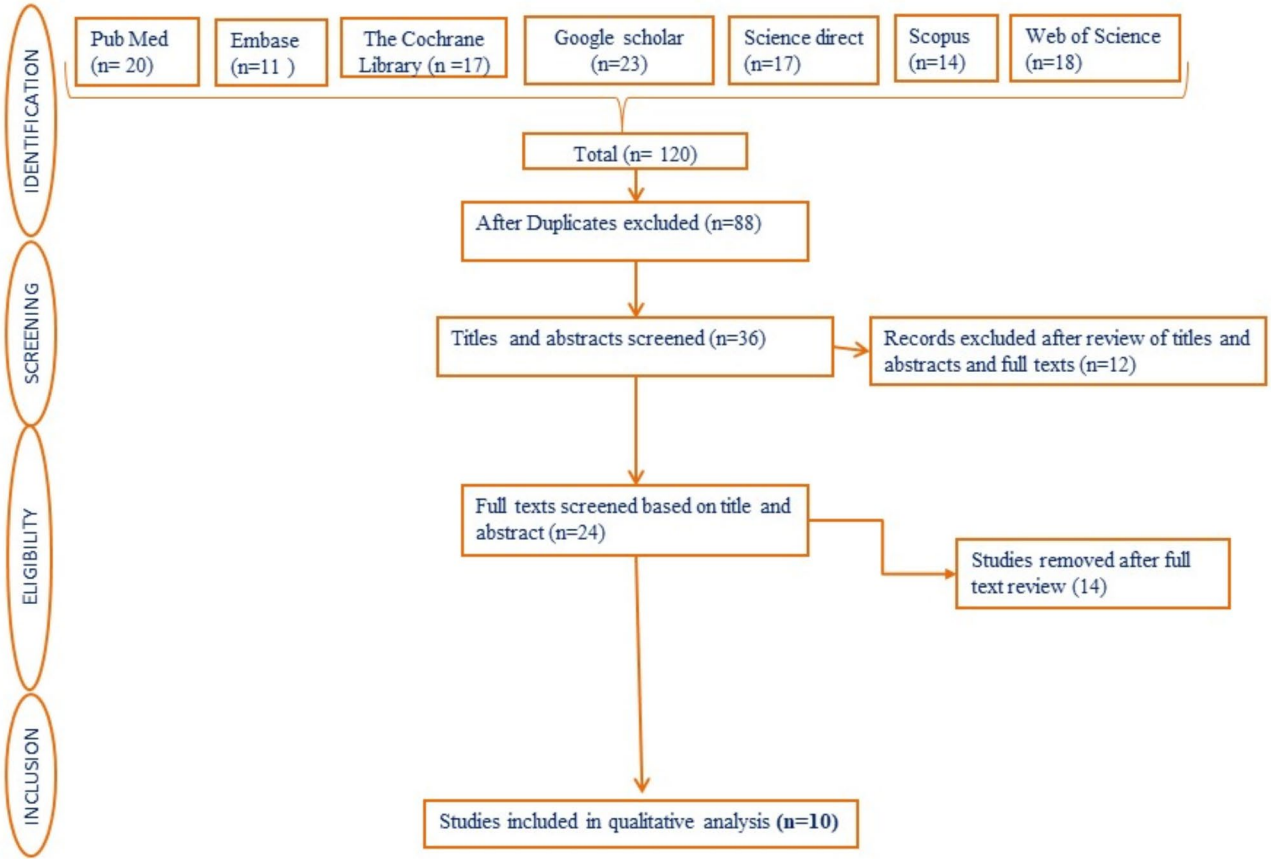

Fig. 1 PRISMA flow diagram of the study selection process

mediated in the nucleus via the interaction of β-catenin and TCF7L2 [31]. Wnt signaling regulates the production and secretion of insulin [10] and inhibits glucagon secretion. Besides synthesis, secretion, and degradation of glucose-dependent insulin-tropic peptide (GIP), insulin-like growth factor-1 (IGF-1), and the functioning of pancreatic beta islets [11] are also regulated by the same pathway. Moreover, in *vitro* pancreatic β-cell depletion of *TCF7L2* in humans has been demonstrated to increase apoptosis, diminish β-cell proliferation, and inhibit the maturation, production, and hepatic clearance of glucose-stimulated insulin [32, 33]. The overexpressing TCF7L2 in human islet cells have shown elevated insulin synthesis and secretion [34]. Given that PCOS women possess an elevated risk for developing T2DM, a strong association between PCOS and IR, and the pivotal role of *TCF7L2* in glucose homeostasis makes latter a compelling candidate for understanding PCOS pathogenesis [12]. However, the direct causal role (if any) needs to be validated in mechanistic studies in the future.

Our present meta-analysis based on 10 studies showed that the polymorphic variants rs12255372 and rs7903146 of *TCF7L2* do not confer any susceptibility to develop PCOS both in Asians or non-Asians (European, Caucasian). *TCF7L2 is* a strong GWAS-identified susceptibility genetic locus persistently associated with T2DM across multiple ethnicities [35]. The *TCF7L2* polymorphic variants have been hypothesized to modulate the glycemic control in the subjects harboring them [36, 37]. However, the underlying pathophysiological mechanisms mediated by these polymorphic variants are poorly understood. Given both variants are intronic, studies have speculated that both of these *TC7L2* variants might modulate the *TCF7L2* gene expression, thereby modulating glucose homeostasis [38]. However, though based on a small sample size, Rashid *et a l* [28] found no variations in the expression levels of *TCF7L2* mRNA in the leukocytes between PCOS cases and controls. An earlier study has reported an elevated expression of TCF7L2 in the granulosa cells of women with PCOS lacking IR [39]. Moreover, *TCF7L2* genetic variations have been reported to impact IR – a clinical manifestation of PCOS, as well [40].

Studies that attempted to assess the association of *TCF7L2* variants (rs7903146 and rs12255372) and the PCOS risk have failed to demonstrate any conclusive results. While a previous meta-analysis discovered a substantial correlation between PCOS risk and

Table 1 Details of the studies included in the current study

Author (year)	Ethnicity	Study type and Outcome	Genotype for rs7903146								Genotype for rs12255372							
			Cases				Controls				Cases				Controls			
			CC	CT	TT	N	CC	CT	TT	N	GG	GT	TT	N	GG	GT	TT	N
Barber et al. (2007)	European British/Irish	CC/NA	177	151	30	358	600	539	104	1243	-	-	-	-	-	-	-	-
Christopoulos et al. (2008)	European (Greece)	CC/WA	43	108	32	183	52	76	20	148	-	-	-	-	-	-	-	-
Xu et al. (2010)	Asian (China)	CC/NA	261	61	4	326	232	56	2	290	-	-	-	-	-	-	-	-
Kim et al. (2012)	Asian (Korea)	CC/NA	350	27	0	377	357	29	0	386	372	5	0	377	383	3	0	386
Vcela´k et al. (2012)	European (Czech Republic)	CC/NA	178	127	24	329	204	147	24	375	189	119	2	310	207	146	23	376
Ramos et al. (2013)	Caucasians (Brazil)	CC/NA	104	55	33	192	51	36	10	97	-	-	-	-	-	-	-	-
A. Ben-Salem et al. (2014)	Tunisian (Tunisia)	CC/NA	37	51	30	118	46	69	32	147	45	42	31	118	44	60	34	138
Reddy et al. (2016)	Asia (India)	CC/NA	122	96	22	240	103	87	16	206	146	92	10	248	132	69	8	209
Taskin et al. (2021)	Turkish (Turkey)	CC/NA	21	21	6	48	22	10	8	40	-	-	-	-	-	-	-	-
Rashid et al. (2022&23)*	Asia (India)	CC/NA/SA	97	21	2	120	100	18	2	120	44	73	3	120	65	55	0	120

N: Sample size

For the column "Study type and Outcome: CC represents case-control study design, NA, WA and SA represent no association, weak association and statistical association of the studied genetic variation with the PCOS risk respectively. *Rashid et al has reported association of rs12255372 variant with the PCOS risk

'-' represents data not available

TCF7L2 variations (rs7903146) [18], two recent investigations found no correlation between the risk of PCOS and rs12255372 [17, 41]. Study designs, varying disease presentations, inconsistent diagnostic criteria, and ethnic disparities have all been linked to the variability in the results [29]. For rs12255372, of all the five studies included in the studies, only Rashid et al. had reported a positive association with PCOS risk [29], however, this study was based on a smaller number of subjects. While as for rs7903146 a marginal risk for PCOS was reported by Christopoulos et al. [21]. However, in the current updated meta-analysis, the two polymorphic variations under study showed no correlation with the incidence of PCOS, according to our findings.

The current study provides an extensive review of the studies on the association between rs12293275 and rs7903146 variants of *TCF7L2* with the PCOS risk, however, the results are based on only 10 published studies and might limit the generalisability of the findings. Besides, while all the studies included in the meta-analysis had used uniform criteria for the diagnosis of PCOS, only two out of 10 studies had ruled out the effect confounding factors in the analysis.

There are more than 1000 genetic variations reported in the *TCF7L2* gene so far in the gnomAD database. The current study evaluated only two commonly studied *TCF7L2* genetic variations, and the effect of other variants on modulating the PCOS cannot be entirely ruled. More studies exploring the association of such variants with the PCOS risk, and mechanistic studies evaluating the underlying pathogenic mechanisms involved are warranted to establish the potential causal link.

In conclusion, our results show that, unlike T2DM, the rs7903146 and rs12255372 variants of the *TCF7L2* gene do not modulate the PCOS risk. However, the role of other *TCF7L2* variants in PCOS remains to be studied in future studies.

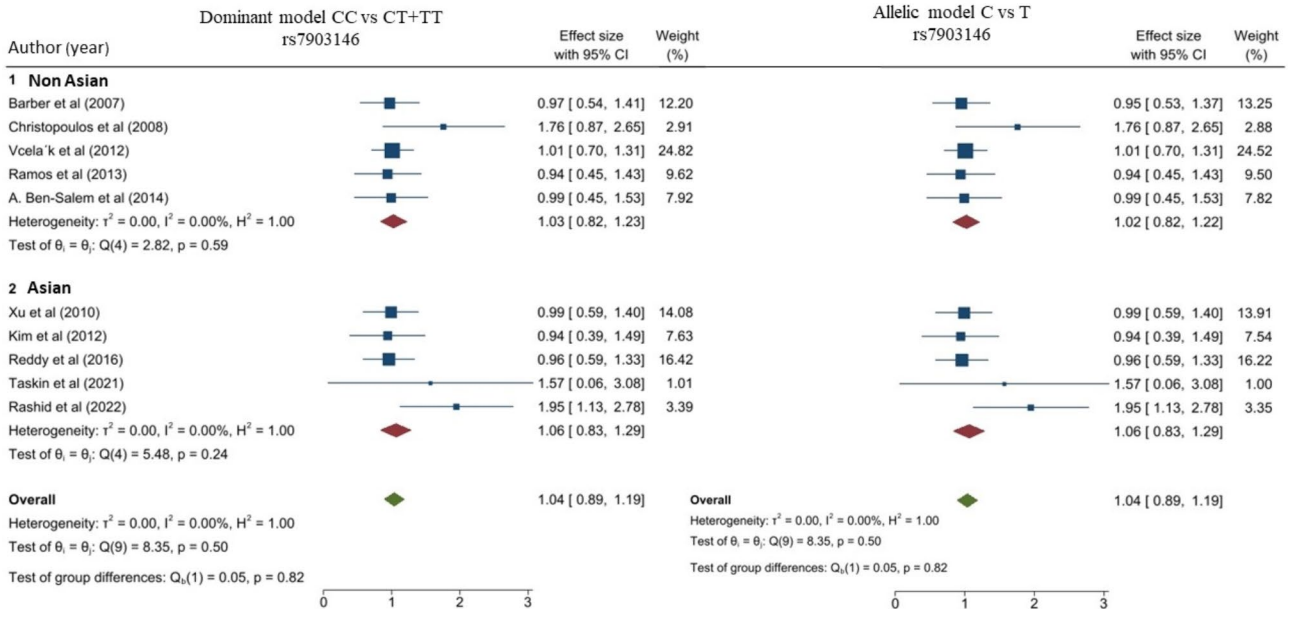

Fig. 2 Forest plot showing association between *TCF7L2* genetic variant rs7903146 and the PCOS risk based on both dominant *genotypic (CC vs. CT + T)*, and the *allelic model* (C vs. T allele) stratified by the population. The countries from Asia included China, Korea and India while Non-Asian countries included studies from Britain/Ireland, Greece, the Czech Republic, Brazil, Tunisia, and Turkey

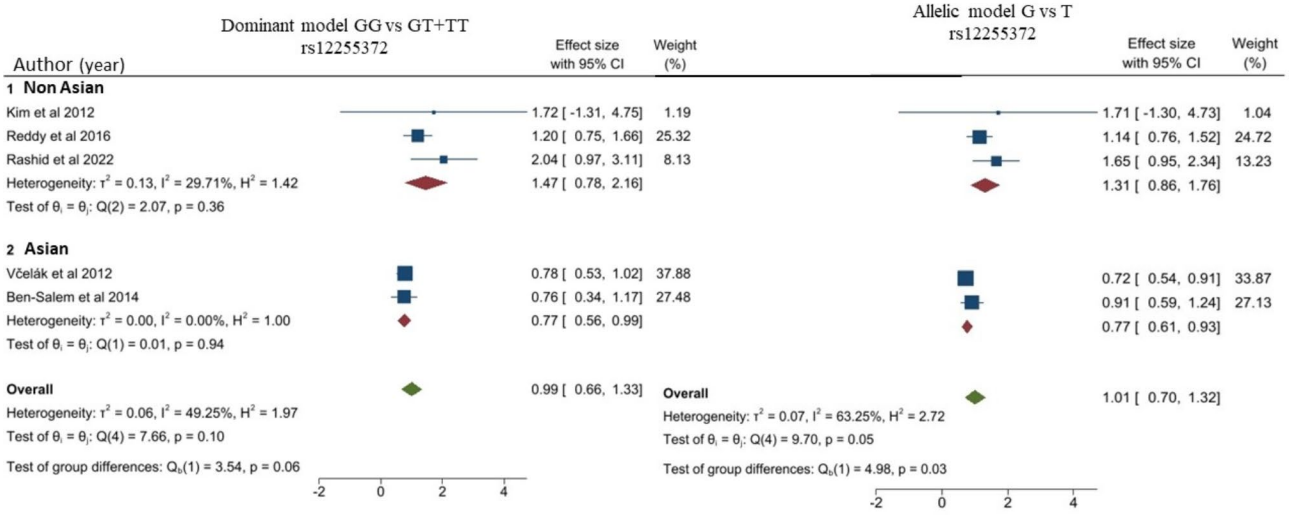

Fig. 3 Forest plot showing association between *TCF7L2* genetic variant rs12255372 and the PCOS risk based on both dominant *genotypic GG vs. GT + T)*, and the *allelic model* (G vs. T allele) stratified by the population. The countries from Asia included China Korea and India while non-Asian countries included studies from Britain/Ireland, Greece, the Czech Republic, Brazil, Tunisia, and Turkey

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-024-01585-z.

Supplementary Material 1

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Author contributions
Study Concept and design: IAS. Data Acquisition and analysis: IAS, RR, HR, AB. Manuscript writing and approval: IAS, HR, RR, AB, MAG.

Data availability
The analysed data can be shared upon a valid request to the corresponding author.

Code availability
Not Applicable

Declarations

Ethics approval
No ethical approval was required for the present study.

Consent to participate
Not applicable.

Consent to publish
Nothing was purchased or copied from a magazine, including any objects or images.

Declaration of generative AI in scientific writing
No AI tool was used in the preparation of the manuscript.

Competing interests
The authors declare no competing interests.

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