Association of candidate gene (*INSR & THADA*) polymorphism with polycystic ovary syndrome: meta-analysis and statistical power analysis

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Abstract

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder that impacts women before reaching menopause. In addition to notable features (irregular ovulation, elevated androgen levels, and the existence of numerous ovarian cysts), individuals with PCOS frequently encounter diverse metabolic, cardiovascular, and psychological conditions. The onset of PCOS is influenced by a combination of factors, and various genetic variations are believed to play a significant role in its progression. The objective of the current study was to explore the link between genetic variations in the candidate genes *thyroid-adenoma-associated (THADA)* gene and insulin receptor (*INSR*) and susceptibility to developing PCOS. We conducted an extensive search across various databases, including Google Scholar, PubMed, Science Direct, Scopus, and EMBASE, to compile relevant case-control studies and literature reviews for subsequent statistical analysis. In the present study, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was followed, a guideline for Systematic Reviews and Meta-Analysis. While a previous meta-analysis explored the correlation between *INSR* rs1799817 and *THADA* rs13429458 and their association with susceptibility to PCOS, our current study did not integrate any findings from these prior investigations. Our research encompassed articles published between 2017 and 2023, and we employed MetaGenyo software to assess the collected data. Statistical power analysis was performed using G*Power 3.1 software. Odds ratios and their corresponding 95% confidence intervals were calculated for each genetic model. Fifteen studies that met the criteria were analyzed. Out of these, ten studies, involving 1,189 cases and 1,005 controls, examined the *INSR* rs1799817 gene polymorphism, while five studies, including 783 cases and 553 controls, investigated the *THADA* rs13429458 gene polymorphism. The meta-analysis results indicated that there was no statistically significant association between the *INSR* rs1799817 gene polymorphism and the risk of PCOS ($p>0.05$). In contrast, the *THADA* rs13429458 gene polymorphism showed a significant association with PCOS risk under the over-dominant model ($p<0.05$). The present meta-analysis demonstrated a notable association between the *THADA* rs13429458 gene polymorphism and the likelihood of developing PCOS. Further rigorous studies with expanded sample sizes and diverse ethnic representation will be important to comprehensively evaluate and validate these findings. (J Turk Ger Gynecol Assoc. 2024; 25: 167-78)

Keywords: PCOS, *INSR*, *THADA*, gene polymorphism, meta-analysis, hyperandrogenism

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Introduction

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that primarily impacts individuals with ovaries and tends to manifest frequently during their reproductive years. PCOS is a multifaceted condition characterized by a variety of symptoms. Irregular menstrual cycles, or in some cases, the absence of menstruation, are common indicators (1). PCOS was initially identified in women by Stein and Leventhal in 1935. It stands as a primary cause of hyperandrogenism and oligoovulation during the reproductive years, often being a significant factor contributing to infertility (2). PCOS is a prevalent issue, impacting approximately 8-21% of women in

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their reproductive years on a global scale. While it can develop post-menarche, most cases are identified between the ages of 20 and 30 years. Worldwide, about 1.55 million women of reproductive age are affected by PCOS, resulting in 0.43 million people living for years with the associated disability (3). While the exact etiology of PCOS remains unclear, a number of different factors are thought to be involved. Primarily, hormonal imbalances, in particular elevated luteinizing hormone (LH) levels and normal or suppressed follicle-stimulating hormone (FSH) levels, resulting in an altered LH/FSH ratio are characteristic. In addition, the clinical signs of hyperandrogenism are linked with hyperinsulinemia and insulin resistance. While the specific predisposing factors for the progress of PCOS are uncertain, there are observations indicating a genetic basis in some cases, and obesity has been identified as a contributing factor due to its association with hyperinsulinemia, potentially increasing the risk of developing PCOS (4). Variations in genetic single nucleotide polymorphisms (SNPs) and single nucleotide variants play a role in affecting steroidogenesis, the activity of ovarian theca cells, and the secretion of hormones from the hypothalamus and pituitary gland (5). Epigenetic elements, like exposure within the womb and increased androgen levels in a mother's environment, may lead to lasting, inheritable traits that contribute to PCOS. This condition, marked by hyperandrogenism, irregular steroid production, insulin resistance, and central obesity, stems from a dysfunctional connection between the hypothalamus, pituitary gland, and ovaries (6). Excessive androgen secretion by ovarian theca cells, triggered by the growth of fatty tissue, leads to the development of numerous small follicles and an imbalance in sex hormones, potentially causing endometrial carcinoma (7). Chronic oxidative stress and inflammatory markers harm both oocyte quality and endothelial function, indicating infertility. Timely screening and diagnosis are vital for preventing PCOS and managing metabolic irregularities. Prioritizing physical and mental well-being, embracing a healthy lifestyle, and fostering a favorable environment all play pivotal roles in mitigating the challenges posed by PCOS (8). According to the latest research, compelling evidence suggests that genetic factors significantly contribute to the development of PCOS. Although various studies have examined gene variants across different biological pathways, the influence of PCOS inheritance patterns on its pathophysiology remains uncertain (9). Candidate genes associated with steroid hormone biosynthesis and metabolism, the action of gonadotropins and gonadal hormones, as well as those related to obesity and energy regulation, insulin secretion, and action, have been investigated and implicated in the development of PCOS (10). Global findings indicate that allelic variants or SNPs within genes related to ovarian steroidogenesis, folliculogenesis, and insulin-regulated glycemic control could potentially disrupt homeostatic signaling mechanisms, ultimately contributing to the development of PCOS (11). It is important to highlight that the pathophysiological pathways in different phenotypes of PCOS may vary, impacted by both genetic and environmental factors. Multiple interlinking aspects could impact the expression of PCOS, making it highly unlikely that a singular cause can be identified for this condition (12). Therefore, it is essential to examine numerous candidate genes linked to PCOS to identify its precise genetic foundation.

Seven Genome-Wide Association Studies have endeavored to establish connections in diverse populations between specific SNPs within candidate genes and PCOS (13-19). The thyroid adenoma-associated protein (THADA), produced by the *THADA* gene, is located on chromosomal band 2p21. This protein is expressed in various tissues, including the pancreas, thyroid, testes, thymus, adrenal gland, small intestine, and stomach (20). The *THADA* gene has been linked to disruptions in energy metabolism, leading to a decrease in energy production and an elevated risk of obesity. This increased susceptibility to obesity, in turn, enhances the likelihood of developing PCOS (21). Notably, *THADA* gene variations impact beta cell function and insulin secretion, potentially influencing insulin resistance in PCOS and diabetes. Endocrinologists are interested in these findings for their relevance to understanding and addressing these conditions (22). Insulin resistance is a key dysfunction associated with PCOS, mainly linked to the *insulin receptor (INSR)* gene located on chromosome 19. Several investigations have additionally indicated that women diagnosed with PCOS face an elevated risk of experiencing gestational diabetes, miscarriages, preeclampsia, and preterm labour (23). The insulin gene is believed to play a crucial role in both insulin secretion and action, as well as in signaling pathways. Any variations in the *INSR* gene can potentially alter INSR function, increasing the susceptibility to developing PCOS (24).

Examining polymorphisms in candidate genes related to the likelihood of developing PCOS offers an insight into the complex interaction between genetic susceptibility and disease development. This method enables researchers and healthcare professionals to explore the underlying genetic predisposition and potential molecular mechanisms influencing PCOS pathogenesis, leading to a more nuanced understanding of the condition. Hence, we undertook a meta-analysis using suitable case-control studies to examine the relationship between the gene polymorphisms of *INSR* and *THADA* and the likelihood of developing PCOS.

Subjects, materials, and methods

During the research, we adhered to the Preferred Reporting Item Guideline for Systematic Reviews and Meta-Analysis

checklist. This meta-analysis was conducted following the guidelines depicted in Figure 1a, b. Additionally, the International Prospective Register of Systematic Reviews (PROSPERO) validated the study's reliability by confirming the registration of its prospective review protocol (PROSPERO ID 502139).

Data source

A comprehensive literature search was carried out across various databases, including Embase, NCBI, Google Scholar, Elsevier, Science Direct, and PubMed from 2017 to 2023, using the following keywords "*PCOS*", "*INSR*", "*THADA*", "gene polymorphism", "case vs. control", "*SNPs*", and "*INSR* gene". The words of Boolean logic, such as OR/AND, were combined with the employed keywords. The database has been updated and eliminating duplicates was performed through screening reviews, recent studies, and past meta-analyses. Furthermore, the reference lists of the identified articles were also screened.

Study selection

Inclusion criteria

This meta-analysis considered the studies that fulfilled the following inclusion criteria: (i) the study had to investigate *INSR* and *THADA* gene polymorphism with PCOS risk; (ii) the research only involved human subjects; (iii) the distribution of allele and genotype information in a case-control study was presented; and (iv) the full text was available in the English language.

Exclusion criteria

Studies were excluded that did not meet the following criteria: (i) studies not investigating *INSR* and *THADA* gene polymorphism and PCOS; (ii) reviews and previous meta-analysis related to PCOS risk; (iii) case reports, animal studies that overlap with other research; and (iv) studies with duplicate data.

Data extraction

Based on the inclusion criteria, we collected the following information in a consistent format, and any discrepancies were reviewed with co-authors until a conclusion could be reached. To learn more about the allelic frequencies and genotypes of the case and control individuals, the retrieved publications were appropriately read. In some cases, not all the genotypic information was shown in the studies. In these situations, the data was calculated using other information, such as allelic frequencies. Research studies where the necessary data was unable to be extracted from the control and case groups were rejected. First author name, PubMed ID, Hardy-Weinberg Equilibrium (HWE) score, year of publication, language, sample size, ethnicity, study

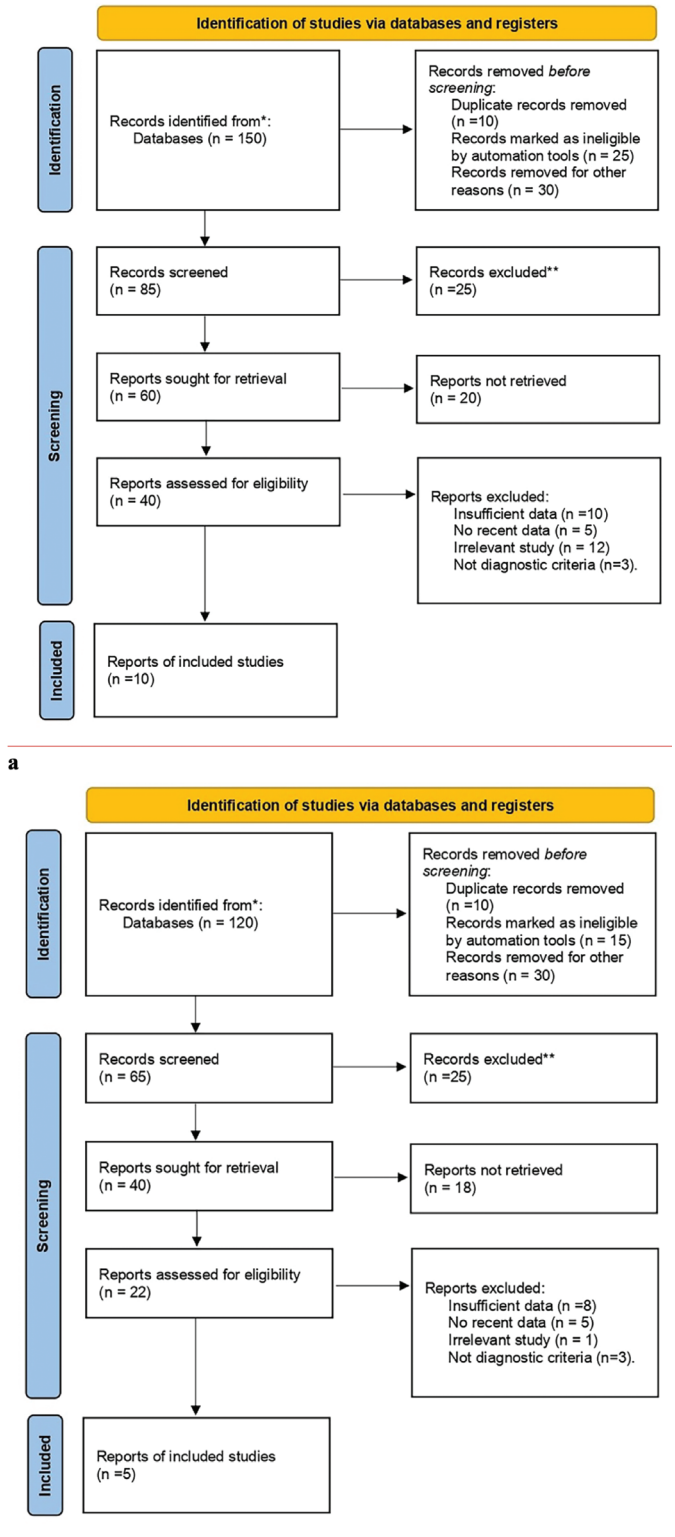


Figure 1. (a) Flow chart for literature screening of *INSR* rs1799817 gene polymorphism. (b) Flow chart for literature screening of *THADA* rs13429458 gene polymorphism
INSR: Insulin receptor, THADA: Thyroid-adenoma-associated gene

design, and other information were taken from each study. To improve screening flexibility, a table for data extraction was created and tested twice. Consistency was maintained throughout the eligibility criteria and data screening process.

Quality of study using risk bias

A thorough risk bias assessment is essential to correctly assessing the methodological quality and possible biases of the studies included in a meta-analysis. In the present study, the risk of bias was assessed using the Cochrane risk of bias tool (ROB2) software. The studies were divided into three categories based on their level of bias: "high risk," "some concern," or "low risk."

Statistical analysis

The relationship between *INSR* and *THADA* gene polymorphisms and PCOS susceptibility was examined using a range of statistical methods. The relationship was estimated by calculating odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). The statistical significance was determined with a threshold set at $p<0.05$. An index of inconsistency (I^2) was employed to assess how consistent the results were across various research efforts in order to measure their uniformity. The I^2 score indicates the extent of variability or diversity among studies, ranging from 0% to 100%. A low I^2 number indicates consistency in results across investigations, while a high value signifies greater diversity or variability. Due to a heterogeneity value below 50%, the research opted for a fixed effect model. If the random effect model with a probability of exceeding 50% was used. The Q statistics were used to conduct a chi-square test to determine the presence of heterogeneity. The test results indicated a statistically significant diversity between the two studies. Summary ORs were evaluated using a Z-test ($p<0.05$), and heterogeneity among studies was assessed using the Q statistic and I^2. Moreover, a sensitivity analysis was carried out to examine the influence of omitting certain studies, especially those where the controls did not adhere to HWE. Furthermore, Egger's regression method was used to evaluate the potential presence of publication bias. All the statistical analyses were conducted using the MetaGenyo software.

Power analysis

The acquired metadata was analyzed through a power assessment under conditions with a 95% CI (0.05 α error). The power for each study sample size (both case and control groups) was combined and examined separately for each chosen gene. The calculation of power was performed using G*Power 3.1 software.

Protein-protein interactions

The STRING (v11.0) online search tool database can predict functional proteins and protein-protein interactions (PPIs) with a score of ≥0.4 for identified PCOS-linked polymorphisms.

Results

Search results

This study sought to investigate the relationship between the gene polymorphisms *INSR* rs1799817 and *THADA* rs13429458 with PCOS risk. A comprehensive search across databases yielded 10 studies comprising 1,189 cases and 1,005 controls for the *INSR* rs1799817 polymorphism, and five studies with 783 cases and 553 controls for *THADA* rs13429458 polymorphism. Table 1 presents key characteristics extracted from the included case-control studies (25-38). Among the 15 selected studies, 14 were conducted within the Asian population, while the remaining study focused on a European population.

Risk bias

ROB2 was used to conduct a thorough assessment of the methodological quality of the included studies, as illustrated in Figure 2a, b. Each row in the chart corresponds to an individual study, while each column indicates a distinct bias category. The color scheme in the image indicates the reviewer's evaluation of the risk level linked to each bias type in each study - red denotes high risk, yellow signifies moderate risk, and green indicates low risk. The majority of the included studies displayed a minimal risk of bias. These findings suggest that most of the studies were executed and documented in ways that effectively minimized the likelihood of bias or systematic errors.

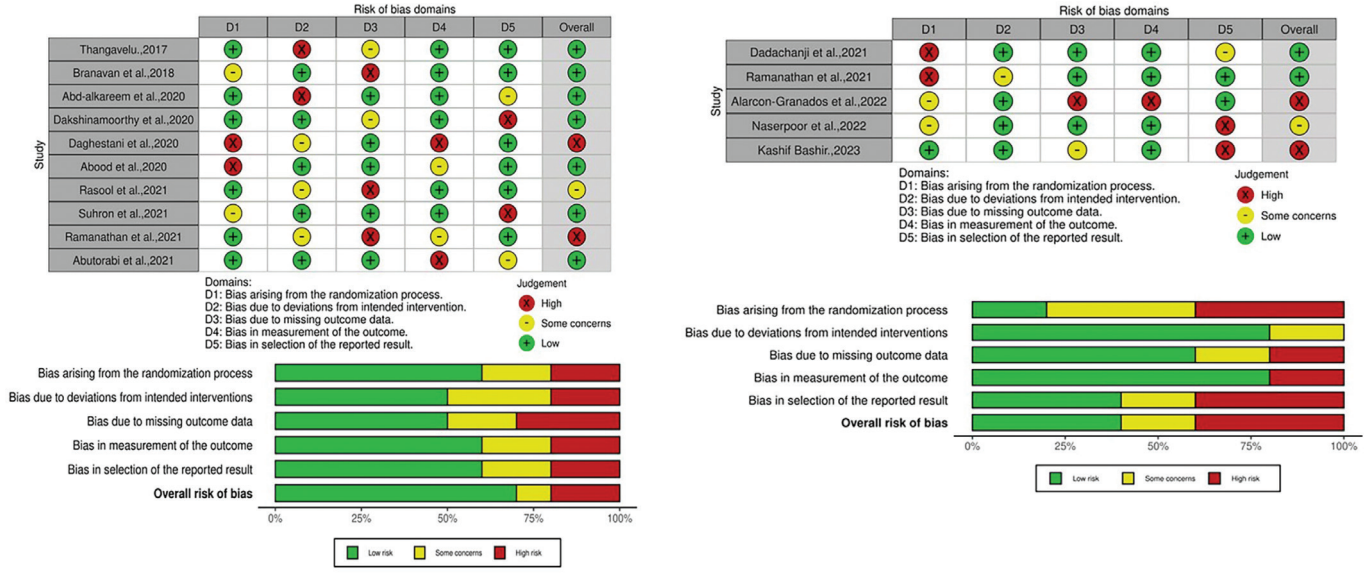
Quantitative data analysis of *INSR* and *THADA* Gene polymorphism with PCOS

Based on the genotypes analyzed in the present meta-analysis, two gene polymorphisms of *INSR* rs1799817 and *THADA* rs13429458 were specifically selected. The investigation into their association with PCOS was conducted using multiple comparison models, taking into consideration the HWE. The *INSR* rs1799817 gene polymorphism showed no significant association in allelic, recessive, dominant, and over-dominant models ($p>0.05$; Table 2). In addition, the subgroup analyses with allelic, recessive, dominant, and over-dominant models were non-significant ($p>0.05$). However, *THADA* rs13429458 gene polymorphism showed significant association with the over-dominant model ($p<0.05$), whereas allelic, recessive, and dominant models showed non-significance ($p>0.05$; Table 3). The results of the subgroup analysis indicated a noteworthy association with the over-dominant model, while other genetic models showed non-significant associations.

Table 1. Characteristics of selected case-control studies for association of *INSR* and *THADA* gene polymorphism with PCOS

SNPs	Study	Country	Ethnicity	Genotype frequency of cases			Genotype frequency of controls			Total cases	Total controls	HWE-p-value
INSR				CC	CT	TT	CC	CT	TT			
rs1799817	Thangavelu et al. (34)	India	Asian	19	76	74	22	67	80	169	169	0.1881
	Branavan et al. (29)	Sri Lanka	Asian	48	1	6	95	1	14	55	110	0
	Abd-alkareem and Omear (25)	Iraq	Asian	8	49	30	2	14	14	87	30	0.5428
	Dakshinamoorthy et al. (26)	India	Asian	81	151	21	30	186	92	253	308	0
	Daghestani (32)	Saudi Arabia	Asian	64	47	15	87	21	10	126	118	0
	Abood et al. (28)	Iraq	Asian	9	20	21	11	36	3	50	50	0.0007
	Rasool et al. (27)	India	Asian	156	74	19	67	21	12	249	100	0.0001
	Suhron and Zainiyah (30)	Indonesia	Asian	12	30	8	10	28	12	50	50	0.3891
	Ramanathan et al. (31)	India	Asian	9	3	8	2	2	6	20	10	0.0976
	Seyed Abutorabi et al. (33)	Iran	Asian	73	56	1	57	2	1	130	60	0.0002
THADA				AA	AC	CC	AA	AC	CC			
rs13429458	Dadachanji et al. (36)	India	Asian	236	101	11	98	49	3	348	150	0.2655
	Ramanathan et al. (31)	Asian	Asian	16	0	4	9	0	1	20	10	0.0016
	Alarcón-Granados et al. (35)	Colombia	European	37	12	0	41	6	2	49	49	0.0202
	Naserpoor et al. (37)	Iran	Asian	32	26	8	26	12	6	66	44	0.0382
	Bashir et al. (38)	Pakistan	Asian	136	54	110	106	100	94	300	300	0

THADA: Thyroid-adenoma-associated gene, INSR: Insulin receptor, PCOS: Polycystic ovary syndrome, SNP: Single nucleotide polymorphisms, HWE: Hardy-Weinberg Equilibrium



a b

Figure 2. (a) Risk of bias summary for *INSR* rs1799817 gene polymorphism. (b) Risk of bias summary for *THADA* rs13429458 gene polymorphism
INSR: Insulin receptor, THADA: Thyroid-adenoma-associated gene

Publication bias and sensitivity analysis

Each variable was carefully examined to detect any potential publication bias caused by constraints in sample size and reporting bias. A forest plot showed heterogeneity (Figures 3-6). A sensitivity analysis was conducted, revealing that excluding individual studies did not significantly alter the

Table 2. Summary estimates for odd ratios and 95% confidence interval in different ethnicity for INSR rs1799817 polymorphism

Model	Study	Number of studies	Test of association			Test of heterogeneity			Publication bias
			OR	95% CI	p-value	Model	p-value	I^2	p-value (Egger's test)
Allele contrast (A vs. a)	Overall	10	0.9231	(0.5775; 1.4755)	0.738194101	Random	0	0.8942	0.1151
Recessive model (AA vs. Aa + aa)	Overall	10	0.8931	(0.4390; 1.8168)	0.755038939	Random	0	0.8795	0.5237
Dominant model (AA + Aa vs. aa)	Overall	10	1.2726	(0.7009; 2.3108)	0.428294474	Random	0	0.7914	0.3975
Overdominant (Aa vs. AA + aa)	Overall	10	1.3952	(0.8632; 2.2552)	0.17400012	Random	0	0.7677	0.5221
OR: Odds ratio, CI: Confidence interval, INSR: Insulin receptor									

Table 3. Summary estimates for odd ratios and 95% confidence interval in different ethnicity for THADA rs13429458 polymorphism

Model	Study	Number of studies	Test of association			Test of heterogeneity			Publication bias
			OR	95% CI	p-value	Model	p-value	I^2	p-value (Egger's test)
Allele contrast (A vs. a)	Overall	5	1.0321	(0.8648; 1.2317)	0.725995	Fixed	0.6913	0	0.0083
Recessive model (AA vs. Aa + aa)	Overall	5	1.1900	(0.9417; 1.5037)	0.145096	Fixed	0.1349	0.4301	0.0684
Dominant model (AA + Aa vs. aa)	Overall	5	0.8072	(0.5919; 1.1008)	0.176014	Fixed	0.6975	0	0.5667
Overdominant (Aa vs. AA + aa)	Overall	5	0.7106	(0.5495; 0.9188)	0.009175	Fixed	0.0011	0.8122	0.3585
OR: Odds ratio, CI: Confidence interval, THADA: Thyroid-adenoma-associated gene									

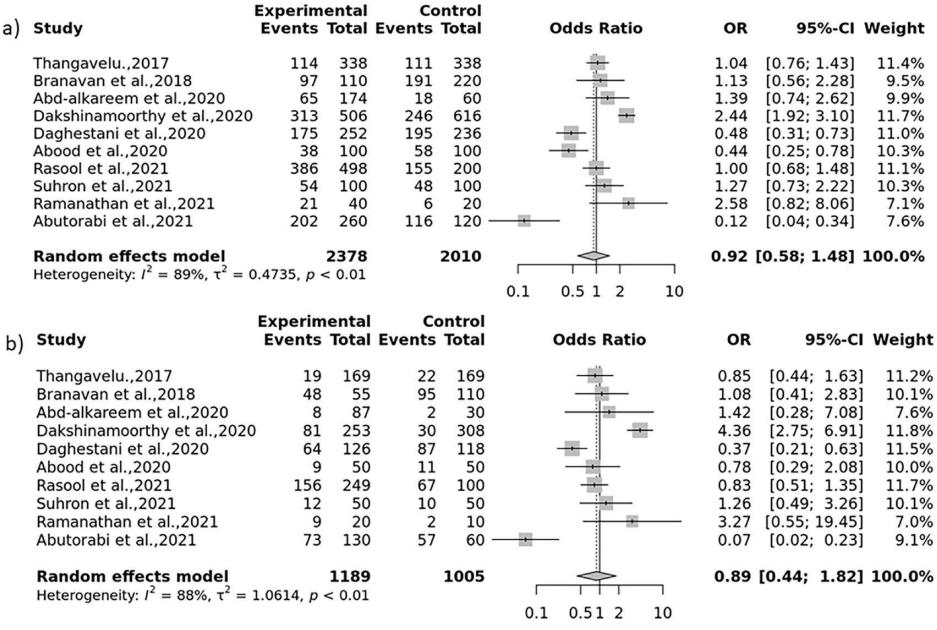


Figure 3. Forest plot for the association of *INSR* rs1799817 gene polymorphism with PCOS risk. (a) Allelic model and (b) Recessive model

INSR: Insulin receptor, PCOS: Polycystic ovary syndrome, OR: Odds ratio, CI: Confidence interval

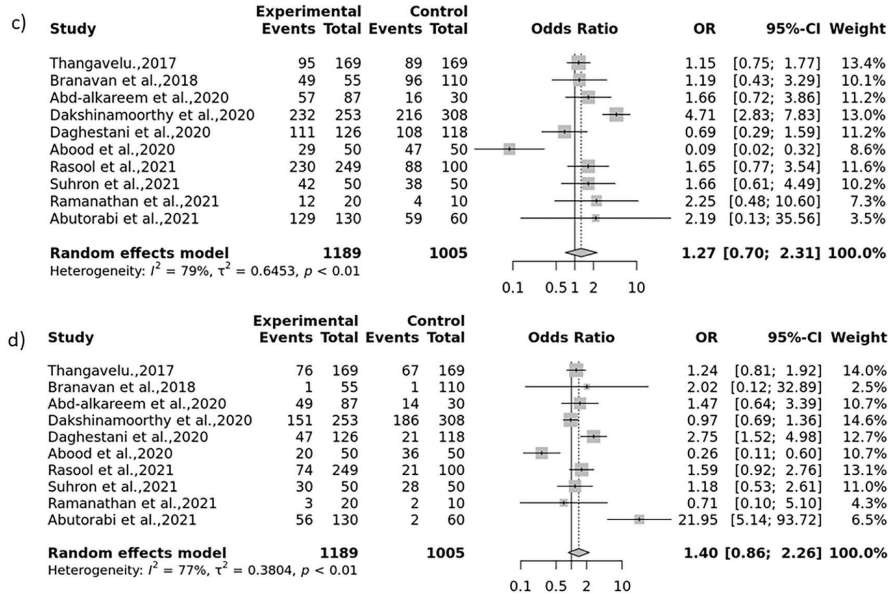


Figure 4. Forest plot for the association of *INSR* rs1799817 gene polymorphism with PCOS risk. (c) Dominant model and (d) Over-dominant model

INSR: Insulin receptor, PCOS: Polycystic ovary syndrome, OR: Odds ratio, CI: Confidence interval

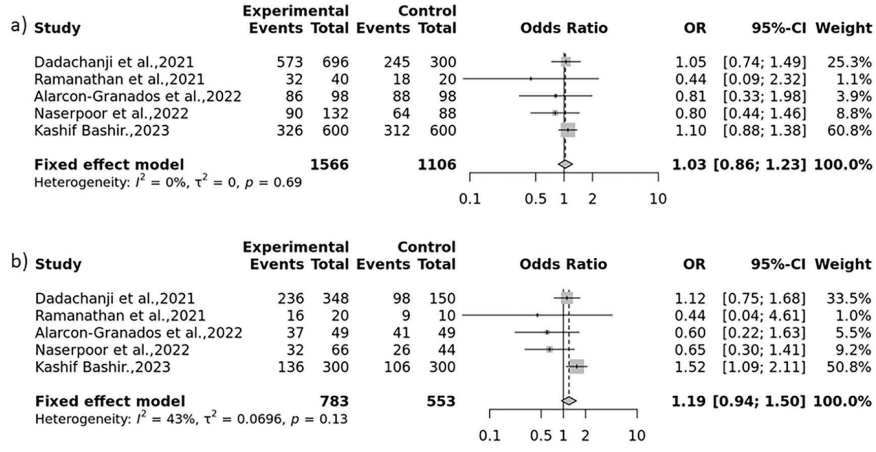


Figure 5. Forest plot for the association of *THADA* rs13429458 gene polymorphism with PCOS risk. (a) Allelic model and (b) Recessive model

THADA: Thyroid-adenoma-associated gene, PCOS: Polycystic ovary syndrome, OR: Odds ratio, CI: Confidence interval

overall outcome. This suggests that our findings are statistically robust and not significantly influenced by the exclusion of any single study (Figure 7). A funnel plot was used to evaluate the possible existence of publication bias. However, no obvious indications of bias were found (Figure 8).

Power analysis, circos plot, and construction of PPI network

We conducted a power analysis to determine the significance level of each study's selected SNPs. According to our findings, the sample size in the selected literature met the significant level requirement, encompassing an α error probability of 1e-007. The findings of the power analysis can be found in Table 4. The Circos plot, arranged from outer to inner, represents annotated genes, chromatin states, transcription factors, and histone modifications, each linked with specific SNPs based on their pairwise linkage disequilibrium (r2) (Figure 9). A PPI network analysis was performed on polymorphic proteins related to *INSR* and *THADA* using the STRING database. The network includes 21 nodes and 123 edges for both *INSR* and *THADA* genes. Although there is no direct interaction, the *INSR* and *THADA* genes are linked through intermediary genes (Figure 10).

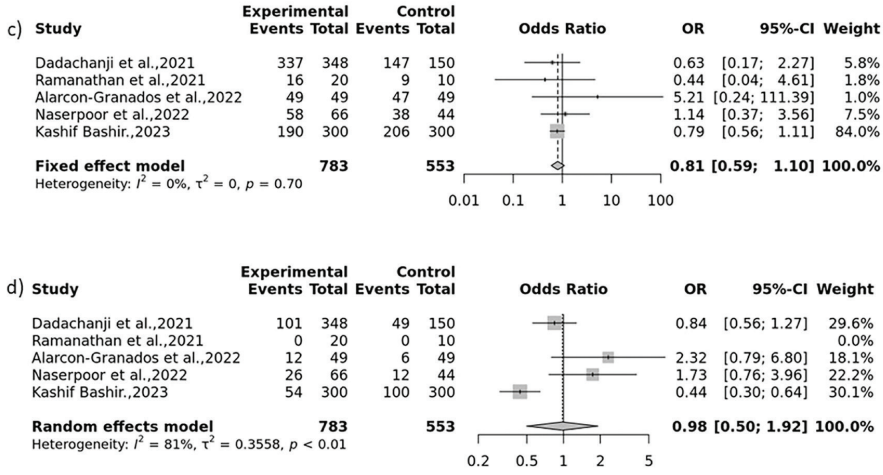


Figure 6. Forest plot for the association of *THADA* rs13429458 gene polymorphism with PCOS risk (c) Dominant model and (d) Over-dominant model

THADA: Thyroid-adenoma-associated gene, PCOS: Polycystic ovary syndrome, OR: Odds ratio, CI: Confidence interval

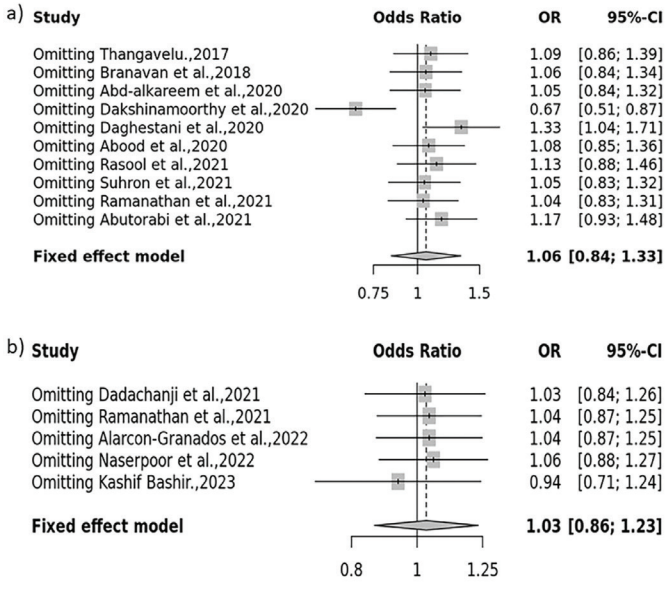


Figure 7. The forest plot representing sensitive analysis between the selected gene polymorphisms and PCOS susceptibility. (a) *INSR* rs1799817 gene polymorphism with the susceptibility of PCOS. (b) *THADA* rs13429458 gene polymorphism with the susceptibility of PCOS

INSR: Insulin receptor, THADA: Thyroid-adenoma-associated gene, PCOS: Polycystic ovary syndrome, OR: Odds ratio, CI: Confidence interval

Discussion

PCOS is a complicated endocrine disorder with multifactorial origins, impacting a significant proportion of reproductive-aged women globally. Its implications extend beyond reproductive ages, persisting throughout a person's lifetime and may often be associated with metabolic disorders such as type 2 diabetes mellitus (DM), obesity, and dyslipidemia. This underscores the substantial impact of PCOS on population health (39). The intricate mechanisms involved in PCOS encompass genetic factors regulating various aspects of steroidogenesis, steroid hormone function, gonadotrophin action, insulin activity, persistent inflammation, and energy metabolism (Figure 11) (40). Candidate genes, *INSR* and *THADA*, have been implicated in PCOS. *INSR* is linked to insulin resistance, a prevalent feature in PCOS contributing to elevated insulin levels and increased risk of metabolic disorders. *THADA*, initially associated with thyroid adenomas, may play a role in PCOS, although the specific mechanisms remain unclear. PCOS is a condition influenced by both genetic and environmental factors, and ongoing research aims to unravel the specific genetic contributions of various genes in its development. According to some study findings, there is no substantial correlation between *PCOS* and *THADA* gene polymorphism (31-36). However, earlier research indicated a notable association between candidate gene polymorphism and PCOS (37,38). A previous meta-analysis investigated the correlation between *INSR* and *THADA* gene polymorphisms and susceptibility to PCOS (41,42). However, the current study did not integrate findings from earlier research. Conducting updated meta-analyses is crucial for maintaining the relevance and accuracy of scientific knowledge. By incorporating the latest research findings, these analyses ensure that conclusions are based on the most current and robust evidence. Our meta-analysis, integrating information from 1,189 cases and 1,005 controls for the *INSR* rs1799817 gene polymorphism, and 783 cases and 553 controls for the *THADA* rs13429458 gene polymorphism, provides valuable insights into their correlation with PCOS. The results indicate that *INSR* rs1799817 gene polymorphism was

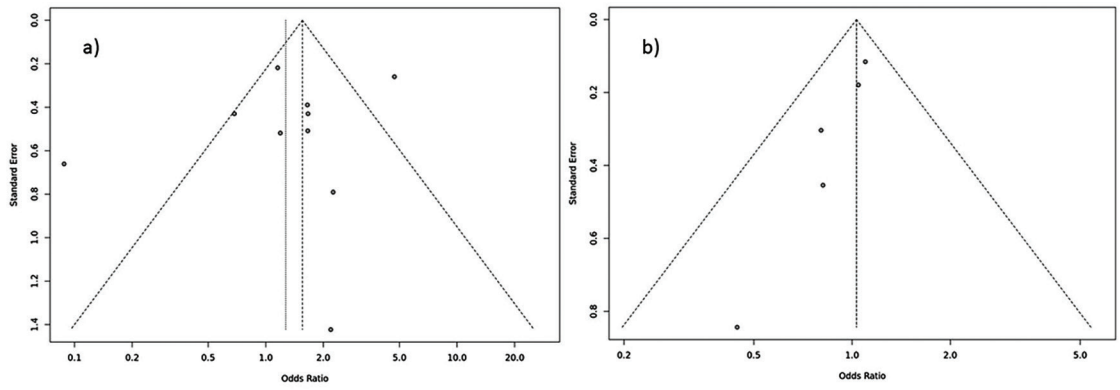


Figure 8. Publication bias was analyzed by funnel plot on the selected gene polymorphisms with the susceptibility of PCOS. (a) *INSR* rs1799817 gene polymorphism with the susceptibility of PCOS. (b) *THADA* rs13429458 gene polymorphism with the susceptibility of PCOS.
INSR: Insulin receptor, THADA: Thyroid-adenoma-associated gene, PCOS: Polycystic ovary syndrome

Table 4. Selecting an appropriate sample size is crucial for reliable findings and accurate statistical evaluation in genetic association studies, particularly when investigating specific polymorphisms. Estimating sample size is critical for determining statistical power

Gene	SNP	No. of studies	Cases	Control	α err prob	Power (1-β err prob)
INSR	rs1799817	10	1189	1005	0.05	0.9500036
THADA	rs13429458	5	783	553	0.05	0.9502123
INSR: Insulin receptor, THADA: Thyroid-adenoma-associated gene, SNP: Single nucleotide polymorphisms						

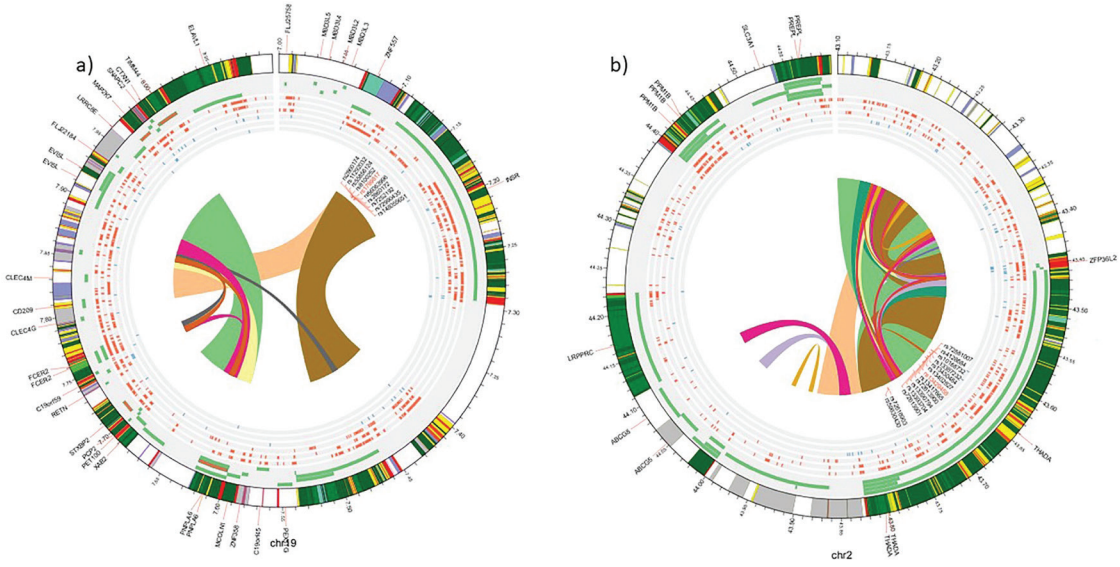


Figure 9. Circos plot that visually represents the chromosomal relationships among the selected SNPs, with a focus on (a) rs1799817 and (b) rs13429458
SNP: Single nucleotide polymorphisms

not associated with PCOS across allelic, recessive, dominant, and over-dominant genetic models, suggesting it may not contribute to PCOS risk. Conversely, *THADA* rs13429458 gene polymorphism significantly correlated with PCOS risk in the over-dominant model but not in other genetic models (allelic, recessive, and dominant), implying its potential contribution to PCOS risk. A sensitivity analysis demonstrates that no single study significantly influences the overall outcomes. Our study concludes that both *INSR* and *THADA* gene polymorphisms adhere to the principles of HWE. To assess publication bias,

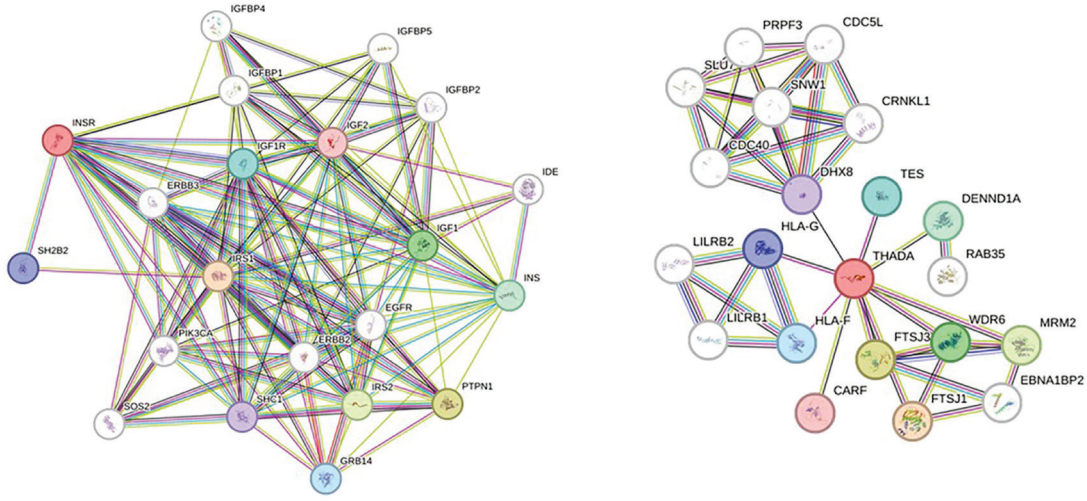


Figure 10. The protein-protein interaction network of differentially expressed genes among the selected genes associated with PCOS
PCOS: Polycystic ovary syndrome

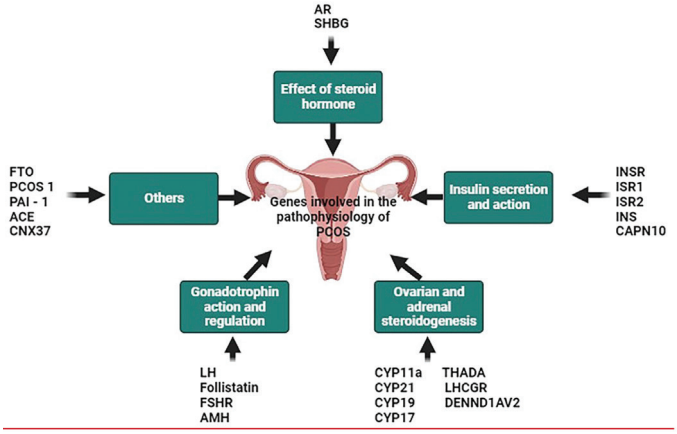


Figure 11. The schematic diagram represents the genes involved in the pathophysiology of PCOS
PCOS: Polycystic ovary syndrome, INSR: Insulin receptor, THADA: Thyroid-adenoma-associated gene, LH: Luteinizing hormone

funnel plots, and Egger's test were employed, revealing no indications of bias. Methodological quality, evaluated using the ROB2 tool, indicated lower risk levels across various aspects of research design in each included study, supporting the reliability of the results. Therefore, our findings are robustly supported by statistical evidence. Rigorous data extraction and analysis procedures were employed, and a power analysis confirmed that the sample size in the selected studies meets the required significance level. According to Albahlol et al. (43) a potential correlation between genetic variations in the *VDR* gene and increased susceptibility to PCOS in Egyptian women was found. Fathy et al. (44) suggested the presence of polymorphism rs6495096 in the *CYP11A1* gene could elevate the susceptibility to PCOS among Iranian women. Alsobaie et al. (45) confirmed that rs8192675 *SLC2A2* is linked to the occurrence of PCOS in women, particularly showing a robust association with those developed type 2 DM in Saudi Arabia. Subbaraj and Sindhu (46) found that *FSHR* (rs6166) was not associated with PCOS. Conversely, they observed a positive correlation between *IL10* (rs1800896) and PCOS, while *IRS-1* (rs1801278) variations were linked to an adverse association (46). Goussalya et al. (47) demonstrated that *IL-6* and *IRS* gene polymorphisms were associated with PCOS. Analyzing gene polymorphisms in PCOS is crucial for understanding its genetic basis, improving diagnostic accuracy, and developing personalized treatments. Genetic variations help identify individuals at risk, allowing for proactive interventions and tailored therapies. Additionally, this research enhances our understanding of PCOS at the molecular level, contributing to advancements in drug development and treatment strategies.

Study limitations

The present study possesses certain limitations. We did not investigate the potential impact of gene-environment interactions and other demographic factors. Subgroup investigation was not carried out due to a lack of sufficient studies, with the majority of the included studies concentrating on Asian populations. It is recommended to conduct further research involving diverse populations to enhance the applicability of the findings.

Conclusion

In summary, the present meta-analysis examined the possible association among polymorphisms in candidate genes, *INSR* and *THADA* and the risk of PCOS by analyzing data from both significant and non-significant studies. The overall findings suggest that there may not be an association between the *INSR* rs1799817 polymorphism and PCOS. Conversely, the *THADA* rs13429458 gene polymorphism seems to be associated with a risk of PCOS. Further research is required with larger sample sizes, environmental datasets, and diverse ethnic populations to validate and support these findings. Regularly updating meta-analyses is essential to incorporate the latest research findings, ensuring that conclusions are based on the most current and robust evidence. This practice enhances the accuracy of results, identifies evolving trends, and guides decision-making with up-to-date insights, contributing to the ongoing improvement of scientific understanding in specific fields.

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