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Original article

CYP17A1 (*rs*74357) polymorphism and polycystic ovary syndrome risk: A systemic review and meta-analysis

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Abstract. *Background and aim:* To investigate the association between *CYP17A1* (*rs*74357) polymorphism and the risk of Polycystic Ovary Syndrome (PCOS). *Methods:* Literature on the association of *CYP17A1rs*74357 gene polymorphism and susceptibility to PCOS was retrieved by searching databases such as PubMed, Science Direct, Google Scholar and Embase from. The association measure was analyzed using an Odds Ratio (OR) and 95% Confidence Interval (CI). All the statistical analyses were executed using CMA 3.0 Software. *Results:* In the present meta-analysis, 24 studies including 3462 PCOS and 2898 controls were analyzed. The overall results validated that the 17 *CYP17A1* T/C (*rs*74357) gene polymorphism was significantly associated with PCOS risk in five genetic models: recessive model (fixed and random effect), dominant model (random effect), CC *vs*. TT (fixed effect), CT *vs*. TT (fixed effect), and allele contrast (random effect). Stratified analyses by ethnicity/country also detected significant association between Asian and Caucasian under the recessive, dominant, CC *vs*. TT, CC *vs*. CT, and the allele contrast models. *Conclusions*: In the present study, *CYP17A1* T/C (*rs*74357) gene polymorphism increase the susceptibility of PCOS, and the recessive C allele, can be proposed as a predictive factor for the risk of PCOS or an important pathway in PCOS associated metabolic and hormonal imbalance especially insulin resistance. However, larger sample size and multiracial studies are needed in the future to confirm the findings. (www.actabiomedica.it)

Key words: polycystic ovary syndrome, *CYP17A1* gene, single nucleotide polymorphism, *rs*74357, meta-analysis

Introduction

PCOS, or polycystic ovarian syndrome, is one of the most common endocrinopathy, affecting around 5% to 10% of women of reproductive age. On ultrasound examination, cystic ovaries are present, as well as amenorrhea, oligomenorrhea, obesity, hyperandrogenism, and anovulation infertility (1). The main cause of PCOS is CYP17A1 dysregulation by P450 17α-related steroid hormone synthesis. *CYP17A1*gene is located on chromosome 10q24.3 and has 8 exons and 7 introns. The *CYP17A1* gene encodes the key enzyme 17-α-hydroxylase/17-20 lyase (P45017α) that contributes to the androgen synthesis pathway and biosynthesis pathways of the ovary and adrenal (2). The promoter 5 'untranslated region of the *CYP17A1* MSP AI (T-34C/ *rs*743572) has a polymorphism that affects gene expression regulation. The presence of this polymorphism may result in enhanced androgen synthesis. There are conflicting studies on the role of the *CYP17A1* MSP Al polymorphism in PCOS susceptibility (3,4). Over the last two decades, a number of case-control studies were conducted to investigate the association between*CYP17A1*T/C polymorphisms and PCOS risk in humans. But these studies reported conflicting results. Some researchers concluded that this C substitution of the *CYP17A1* gene might be associated to the high risk of PCOS and maybe marked

as a pathogenic gene of PCOS (1,5), whereas others found the contradictory result (6-9). In addition, some scholars issued that the association of *rs*7432592 with PCOS is uncertain (10), as this SNP may indirectly affect PCOS through the association between testosterone level and insulin resistance (11). Different methodologies have been used, but, in particular, most of the studies used a small sample size and it is therefore not surprising that there has been a lack of replication in various studies. Based on the dissimilarity of case-control results and the ambiguous pathological mechanism of PCOS, an updated meta-analysis was designed to characterize better the relationship between *CYP17A1* SNP *rs*743572 and PCOS risk.

Materials and methods

This systematic review and meta-analysis followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (12). As this was a meta-analysis, ethical approval was not required.

Publication search

Studies were searched on PubMed, Science Direct, Google Scholar and Embase databases for all articles on the association between *CYP17A1* T/C polymorphisms and PCOS risk. The following keywords were used: "polycystic ovary syndrome" or "PCOS" or "Stein-Leventhal syndrome" or "multi-pouch ovary syndrome", "17α-hydroxylase" or "CYP17A1", and "SNP" or "polymorphisms" or "mutation" or "genotype" or "variant". The search was without restriction on language, conducted on human subjects. The reference lists of reviews and retrieved articles were hand searched at the same time. If more than one article was published by the same author using the same case series, we selected the study where the most individuals were investigated.

Inclusion and exclusion criteria

Eligible studies were involved if they met many criteria. We first screened by reading the title and abstract and then reviewed the full text according to the following criteria for the second screen: (i). The papers should adopt widely recognized and representative diagnostic criteria for PCOS: NIH criteria (13) or Rotterdam criteria (14) which case-control studies were conducted to evaluate the association between *CYP17A1* T/C polymorphism and PCOS risk; (ii). Sufficient genotype data were presented to calculate the odds ratios (ORs) and 95% confidence intervals (CIs); (iii) the paper should clearly describe PCOS diagnoses and the sources of cases and controls. Major reasons for the exclusion of studies were: (a) duplicate data; (b) abstract, comment, review and editorial; (c) no sufficient data were reported.

Data extraction

Data were extracted from all eligible articles separately. Included papers were organized and the following information was obtained: (i). The first author of the research, publication year, source of control, original country, and the ethnicity of subjects. (ii). Evidence of *Hardy-Weinberg* equilibrium. (iii). Genotyping method. (iv). Genotype frequencies of TT, TC, CC of PCOS group, and control group. After that, a rigorous literature evaluation was carried out. Asian and Caucasian ethnicity have been categorized. If original genotype frequency data were unavailable in relevant articles, a request was sent to the corresponding author for additional data. Furthermore, the *Hardy-Weinberg* equilibrium test was also calculated and adjusted manually.

Statistical analysis

To begin with, the *p*-value of the control group's *Hardy-Weinberg* equilibrium was calculated online (https://wpcalc.com/en/equilibrium-hardy-weinberg/), and the literature with a *p*-value less than 0.05 could be regarded as not in line with HWE. The strength of the association between PCOS and the *CYP17A1*T/C polymorphism was estimated using ORs, with the corresponding 95% CIs and *p*-value calculated by Comprehensive Meta-Analysis (CMA) Software 3.0. The pooled ORs and *p*-value in a fixed-effect model (fixed effect estimate method:

Inverse variance) and a random effect model (Random effect estimate method: DerSimonian-Laird) of the association test were performed under 7 genetic models: for the recessive model (CC *vs*. CT+TT), dominant model (CC+CT *vs*. TT), over-dominant model (CT *vs*. CC+TT), CC *vs*. TT model, CC *vs*. CT model, CT *vs*. TT model, and the allele contrast (C *vs*. T). Forest plot for each model was generated by the CMA software. We also carried out the stratified analyses by ethnicity, country, HWE in controls and study sample size. Both the Cochran's Q statistics to test for heterogeneity and the I^2 statistics to quantify the proportion of the total variation due to heterogeneity were calculated. A *p*-value of more than the nominal level of 0.05 for the Q statistic indicated a lack of heterogeneity across studies, allowing for the use of a fixed-effect model (the Mantel-Haenszel method); otherwise, the random effect model (the Der Simonian and Laird method) was used. To explore sources of heterogeneity across studies, we did logistic meta-regression analyses by CMA Software 3.0 (https://www.meta-analysis.com/).

Heterogeneity, sensitive analysis and publication bias

Several methods were used to assess the potential publication bias. Visual inspection of generated funnel plot asymmetry was conducted. The Begg's rank correlation method and the Egger's weighted regression methods were used to statistically assess publication bias and *p*-value ≤0.05 was considered statistically significant. All analyses were done using CMA software 3.0.

Results

Literature retrieval results and characteristics of studies

According to PRISMA flow diagram guidelines (Figure 1), a total of 88 articles were obtained from the original search after the exclusion of duplicates. The examination of the title and abstract performed on these articles led to the removal of 50 studies and 38 continued to detailed assessment.

After screening the full text of these publications, 14 articles were excluded for not meeting the inclusion criteria. Ultimately, 24 eligible case-control studies were included in this review (1,4-11,15-29). There were 17 studies of Asian patients and 7 studies of Caucasian patients. Studies has been carried out in China, Korea, India, Turkey, the USA, Poland, Greece, Mexico, Afghanistan, Belgium and the Republic of Chile. The retrieval results and detailed characteristics were shown in Table 1.

The 24 studies has been conducted in various countries and ethnicity with 3462 PCOS patients and 2898 control groups involved. 62.5% of the included studies took the Rotterdam criteria, and the remaining 37.5% took NIH criteria (studies performed before 2008). All studies extracted DNA from peripheral blood. Twenty-two of the 24 studies used the classic PCR-RFLP method, and the other two studies used different molecular genotyping methods, such as Taqman, PCR-SSCP.

Quantitative analysis

The main results of this meta-analysis are listed in Table 2 (association test results). Forest plot of meta-analysis comparisons models are presented in Figures 2, 3, 4 and 5.

The overall results validated that the 17 *CYP17A1* T/C (*rs*74357) gene polymorphism was significantly associated with PCOS risk in five genetic models: the recessive model (CC *vs*. CT+TT) fixed and random effect, dominant model (CC+CT *vs*. TT) random effect, CC *vs*. TT (CT *vs*. CC+TT) fixed effect, CT *vs*. TT fixed effect, and allele contrast (C *vs*. T) random effect. However, the variant genotypes (CC and TC) were not associated with PCOS risk, compared with the wild-type TT homozygous under two comparison models: over-dominant model (CT *vs*. CC+TT) and CC *vs*. CT model.

On the basis of the potential overestimation of the true effect of the polymorphism on the PCOS risk, we stratified these studies according to ethnicity, country, HWE in controls and study sample size. Stratified analyses by ethnicity/country also detected significant association under the five genetic models described above in Asian and Caucasian populations:

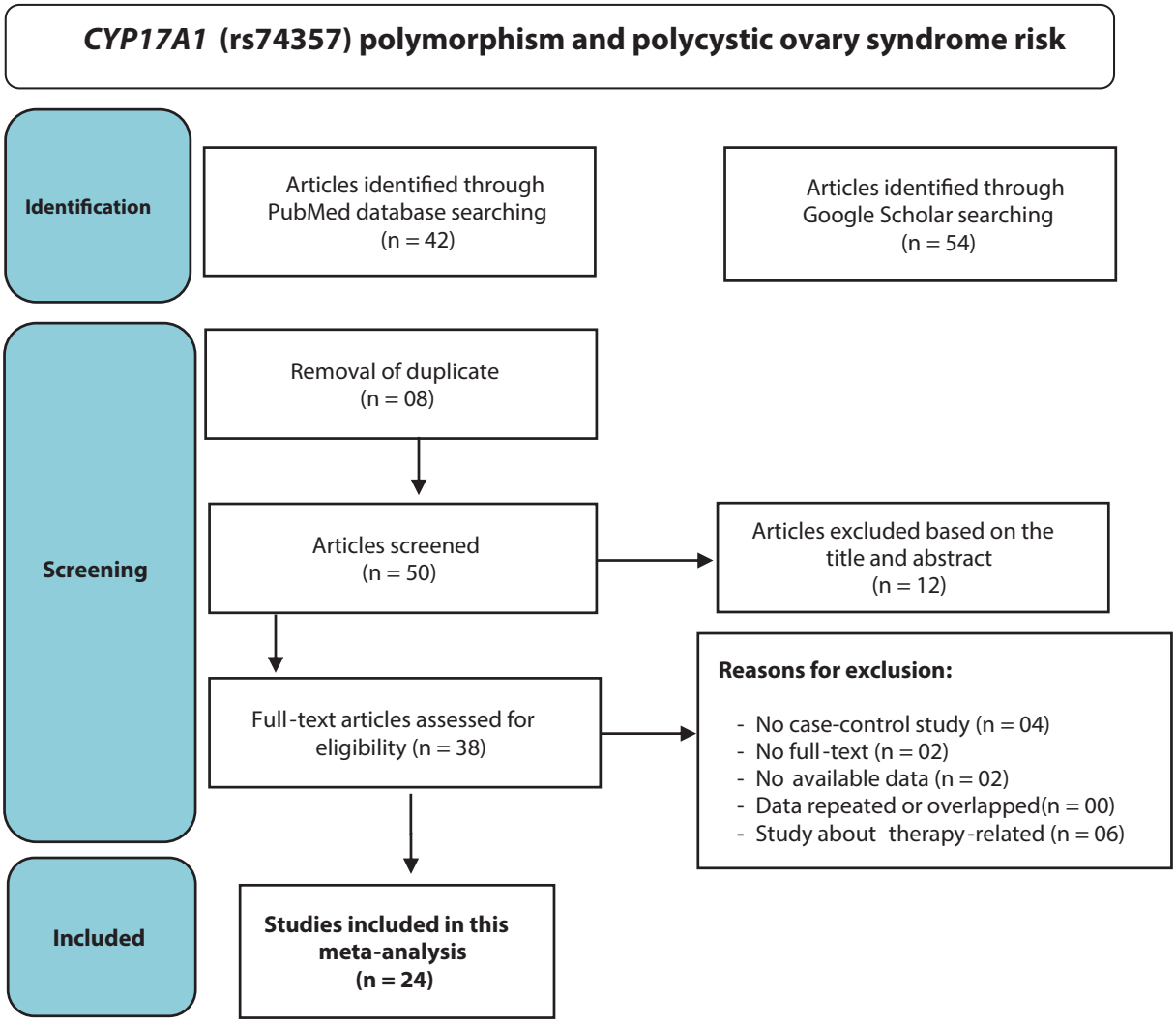

Figure 1. Prisma flow diagram.

recessive model, dominant model, CC *vs*. TT, and allele contrast. However, on the CT *vs*. TT comparison model, significant difference was found only in Asian (Table 3).

Heterogeneity analysis

Statistical analysis shows high heterogeneity under 5 genetic comparison models: dominant model, over-dominant model, CC *vs*. TT, CT *vs*. TT, allele contrast. Due to this high heterogeneity, we conducted logistic meta-regression and subgroup analysis to explore the potential sources of heterogeneity with the following covariates: ethnicity (Asian, Caucasian), country (China or other), HWE in controls (yes or not), diagnostic criteria (Rotterdam criteria, NIH criteria) and genotyping approaches (PCR-RFLP or others). After estimating each covariate's potential contribution to heterogeneity by logistic meta-regression under CMA software, we found that all the *p*-value were > 0.05, which meant the heterogeneity could be attributed to none of the factors above. However, subgroup analysis indicated significantly decreasing heterogeneity in the Caucasian and NIH criteria

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

	Author and year	Country (ethnicity)	No. of Patients	TT	TC	CC	No. of Controls	TT	TC	CC
1	Diamanti et al., 1999	Greece (Caucasian)	50	17	29	4	50	22	28	0
2	Cao et al., 1999	China (Asian)	56	17	17	22	30	8	14	8
3	Marszalek et al., 2001	Poland (Caucasian)	55	17	27	11	56	20	29	7
4	Kahsar-Miller et al., 2004	USA (Caucasian)	259	79	142	38	161	50	94	17
5	Tan et al., 2005	China (Asian)	118	12	66	40	106	21	55	30
6	Ding et al., 2007	China (Asian)	329	55	145	129	275	30	151	94
7	Luo et al., 2007	China (Asian)	74	38	33	3	27	16	10	1
8	Li et al., 2008	China (Asian)	61	11	32	18	45	14	18	13
9	Echiburú et al., 2008	Chili (Caucasian)	159	59	81	19	93	43	36	14
10	Park et al., 2008	South Korea (Asian)	133	40	61	32	99	25	41	33
11	Prez et al., 2008	Argentina (Caucasian)	64	23	26	15	57	16	30	11
12	Unsal et al., 2009	Turkey (Caucasian)	44	15	19	10	50	20	24	6
13	Pusalkar et al., 2009	India (Asian)	100	44	42	14	100	62	30	8
14	Liu et al., 2011	China (Asian)	55	19	23	13	50	17	22	11
15	Zaho et al., 2011	China (Asian)	177	18	100	59	159	32	81	46
16	Cirilo et al., 2012	Brazil (Caucasian)	117	53	46	18	105	65	32	8
17	Dasgupta et al., 2014	India (Asian)	60	15	26	19	54	18	22	14
18	Li et al., 2015	China (Asian)	318	158	139	21	306	137	141	28
19	Banerjee et al., 2016	India (Asian)	75	20	33	22	73	18	35	20
20	Wu et al., 2017	China (Asian)	260	90	109	61	237	81	104	52
21	Kaur et al., 2018	India (Asian)	250	107	118	25	250	146	94	10
22	Rahimi et al., 2019	Iran (Asian)	50	35	15	0	109	92	17	0
23	Ashraf et al., 2021	Kashmir (Asian)	394	115	209	70	306	108	156	42
24	Munawar et al., 2021	Pakistan (Asian)	204	88	112	4	100	86	12	2

subgroups. Thus, it was deduced that ethnicity and diagnosis criteria might be the main source of high heterogeneity.

Sensitivity analysis and publication bias

Begg's Funnel plot and Egger's test were performed to evaluate sensitivity and publication. Displayed a funnel plot that examined the *CYP17A1* T/C polymorphism and overall PCOS risk included in the meta-analysis in the dominant model. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry. The statistical results still did not show publication bias using the seven genetic models: recessive model (P = 0.166), dominant model (P = 0.300), over-dominant model (P = 0.243), CC *vs*. TT model (P = 0.074), CC *vs*. CT model (P = 0.918), CT *vs*. TT model (P = 0.399), and the allele contrast (C *vs*. T) (P = 0.067).

To assess sensitivity and the effect of an individual study on the overall meta-analysis estimate, we excluded one study at a time, and the exclusion of any

Table 2. Association test results.

Model		OR	95%-CI	*p*-value	Adjusted *p*-value
Allele contrast (C *vs.* T)	Fixed effect	1.198	[1.112; 1.291]	< 0.001	< 0.001
	Random effect	1.265	[1.108; 1.445]	< 0.001	**0.003**
Recessive model (CC *vs.* CT+TT)	Fixed effect	1.221	[1.065; 1.400]	0.004	**0.028**
	Random effect	1.221	[1.065; 1.400]	0.004	**0.028**
Dominant model (CC+CT *vs.* TT)	Fixed effect	1.297	[1.160; 1.449]	< 0.001	< **0.001**
	Random effect	1.378	[1.107; 1.714]	0.004	**0.027**
Over-dominant model (CT *vs.* CC+TT)	Fixed effect	1.103	[0.996; 1.222]	0.058	0.40
	Random effect	1.171	[0.965; 1.422]	0.10	0.76
CC *vs.* TT	Fixed effect	1.302	[1.104; 1.536]	0.002	**0.011**
	Random effect	1.369	[1.095; 1.712]	0.005	0.04
CC *vs.* CT	Fixed effect	1.170	[1.012; 1.352]	0.033	0.23
	Random effect	1.170	[1.012; 1.352]	0.033	0.23
CT *vs.* TT	Fixed effect	1.253	[1.114; 1.408]	< 0.001	**0.001**
	Random effect	1.323	[1.052; 1.663]	0.016	0.11

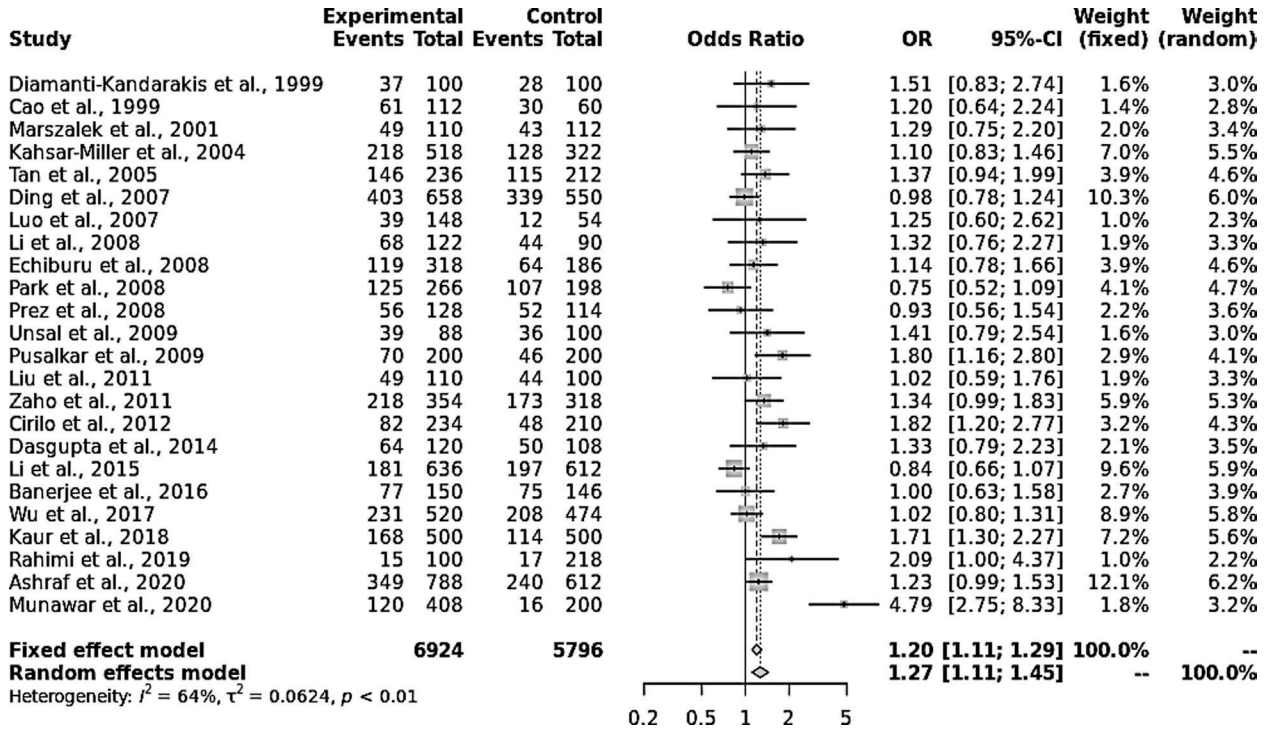

Figure 2. Forest plot of meta-analysis in the allele contrast (C *vs.* T).

single report did not alter the significance of the final decision, suggesting that the outcomes were robust. Finally, the sensitivity analysis demonstrated any individual article did not constitute the source of heterogeneity since removing any single article would not affect the stability of the overall estimate.

Discussion

Polycystic ovarian syndrome is a multifaceted disorder caused by anomalies in genetics, metabolism, endocrine function, and environmental factors. Obesity-related health complications such as diabetes,

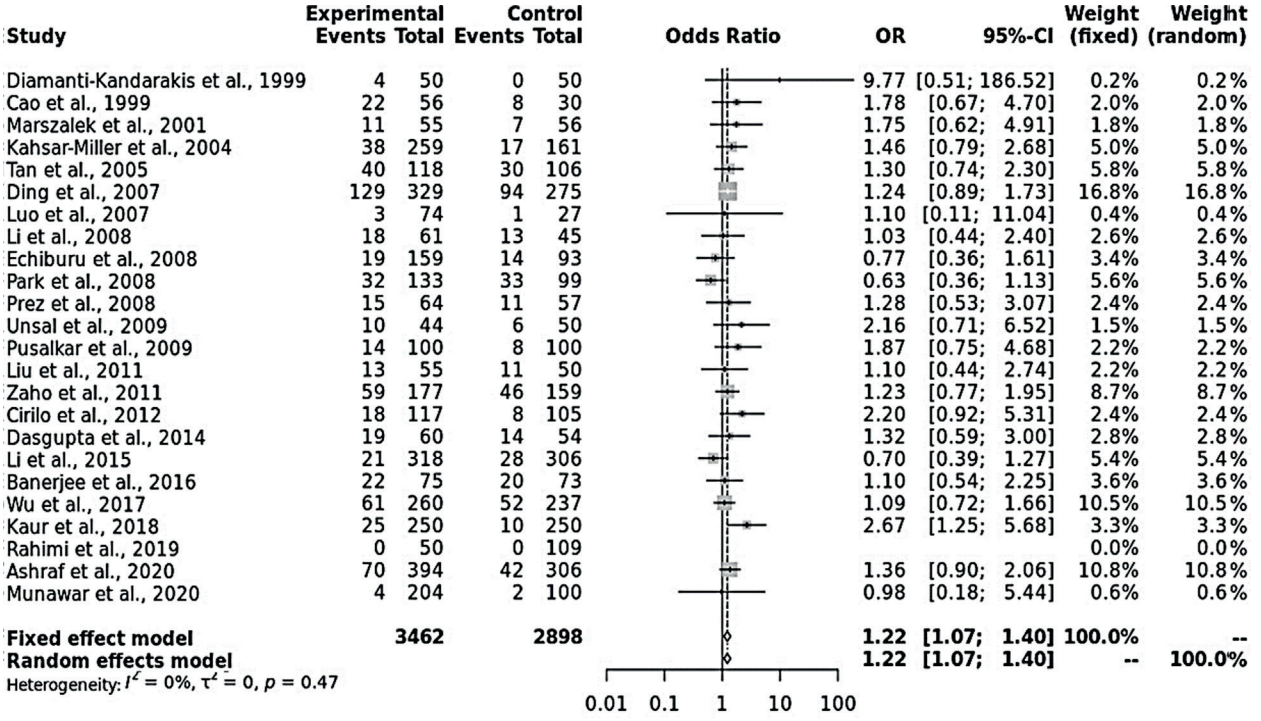

Figure 3. Forest plot of meta-analysis in the recessive model (CC *vs*. CT+TT).

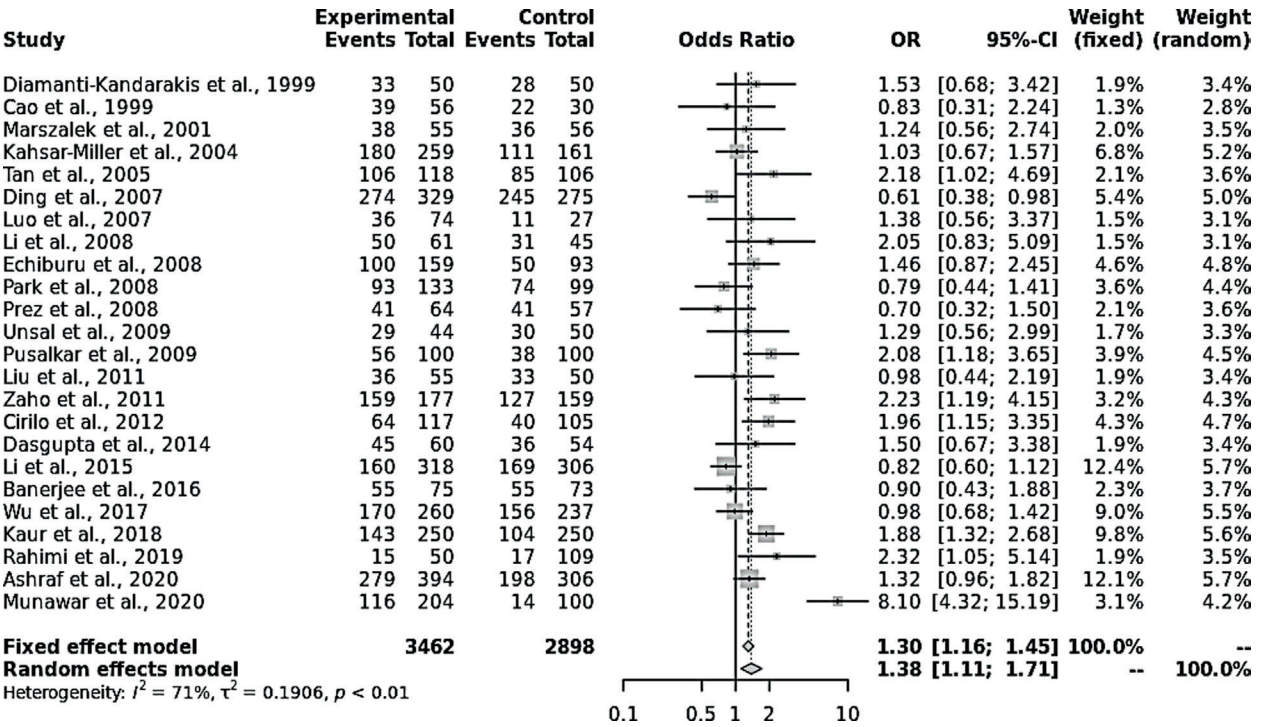

Figure 4. Forest plot of meta-analysis in the dominant model (CC+CT *vs*. TT).

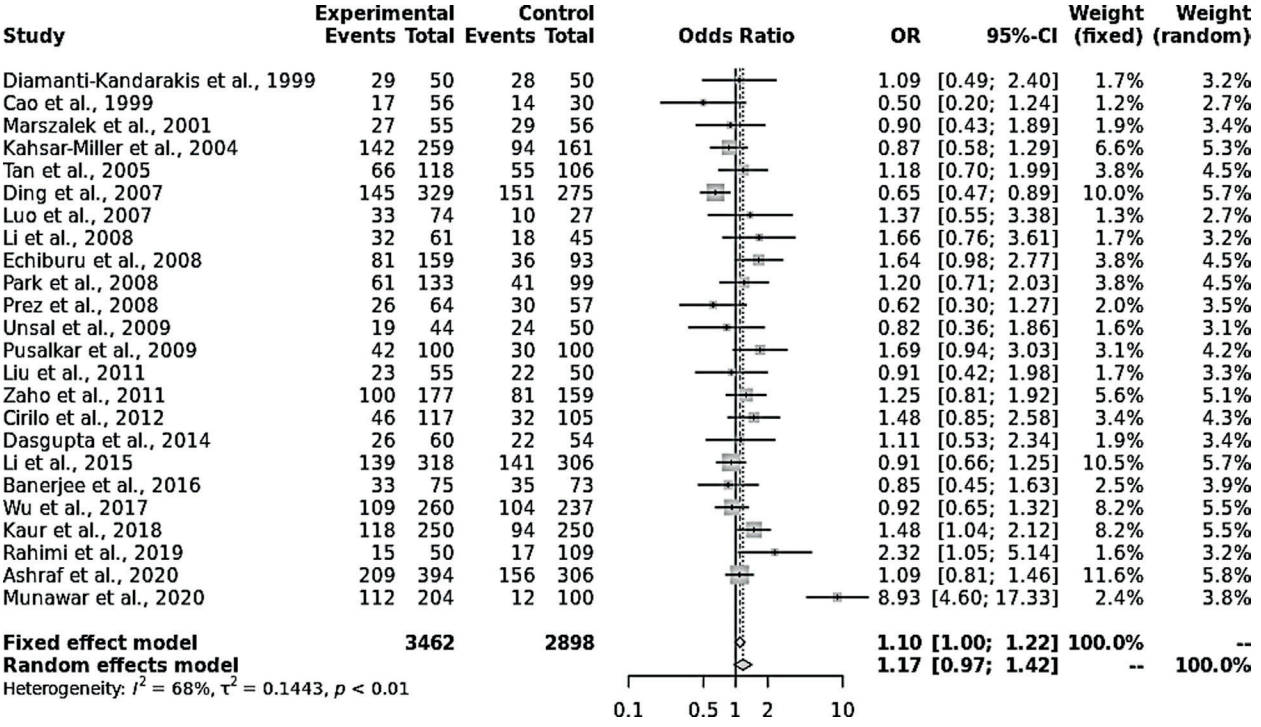

Figure 5. Forest plot of meta-analysis in the over-dominant model (CT *vs*. CC+TT).

hypertension, cardiovascular disorders, anovulation, infertility, trouble in conception, and unfavorable pregnancy outcomes are widely established in PCOS women (30). The indication of family-based and association case-control studies suggests that PCOS has a substantial genetic foundation, although the genes prompting to PCOS have yet to be clearly defined. The candidate genes predisposing to PCOS comprise those indicated in the regulation of ovarian steroidogenesis and also those genes that influence body mass index (BMI) and adiposity (31). It has been proposed that an amplified activity of ovarian P450c17α, a key enzyme in the biosynthesis of androgens, is the fundamental disorder in the ovarian hyperandrogenism observed in this syndrome (9). Consequently, the initial investigations focused on the possible role of *CYP17A1*, the gene that codes for cytochrome P450c17α, located on chromosome 10q24.3. A polymorphism has been found in the regulatory region of the *CYP17A1* gene, being a T to C substitution -34 bp from the translation start point in the promoter region. It has been proposed that this modification may up-regulate the expression of *CYP17A1*, resulting in an increased synthesis of androgens (29). The obvious contribution of the genetic factor to this syndrome was observed, and the involvement of the *CYP17A1* gene polymorphism in raising the probability of PCOS was noted through multiple case control and meta-analysis studies. However, several studies have shown that the T to C substitution at 34 bp upstream the 5' promoter region of the *CYP17A1* gene was associated with PCOS; while some have found the opposite (2).

The present meta-analysis integrated the updated published studies of the *CYP17A1*gene through comprehensive literature retrieval as well as systematic analysis and explored the relationship between the *CYP17A1* gene and PCOS. To the best of our knowledge, *CYP17A1*encodes the enzyme 17-α-hydroxylase/17–20 lyase (P45017α), which is a rate-limiting enzyme in androgen synthesis. Diamanti-Kandarakis *et al*., 1999 was the first to propose that *CYP17A1* T/C gene polymorphism could be responsible for the deregulation of gene *CYP17A1* expression, which aggravated hyperandrogenemia of PCOS (15), which was later supported by Pusalkar *et al*., 2009 (1), who described a strong association of *CYP17A1* T/C gene polymorphism with

Table 3. Subgroup analyses were performed by ethnicity.

Model	Ethnicity	No. of studies	Test of association			Test of heterogeneity		Bias
			OR	95% CI	*p*	Model	*p*	*p*
Allele contrast (C *vs*. T)	Overall	24	1,265	[1.108;1.445]	< **0.001**	Random	< **0.001**	0,06
	Asian	17	1,272	[1.072;1.510]	**0,005**	Random	< **0.001**	0,12
	Caucasian	7	1,242	[1.056;1.460]	**0,008**	Fixed	0,42	0,44
Recessive model (CC *vs*. CT+TT)	Overall	23	1,221	[1.065;1.400]	**0,004**	Fixed	0,46	0,16
	Asian	16	1,181	[1.016;1.371]	**0,029**	Fixed	0,47	0,68
	Caucasian	7	1,443	[1.033;2.015]	**0,031**	Fixed	0,42	0,11
Dominant model (CC+CT *vs*. TT)	Overall	24	1.378	[1.107;1.714]	**0,003**	Random	< **0.001**	0,30
	Asian	17	1,430	[1.072;1.907]	**0,014**	Random	< **0.001**	0,29
	Caucasian	7	1,276	[1.014;1.606]	**0,037**	Fixed	0,39	0,90
Over-dominant model (CT *vs*. CC+TT)	Overall	24	1,171	[0.965;1.422]	0,10	Random	< 0.001	0,24
	Asian	17	1,236	[0.966;1.582]	0,09	Random	< 0.001	0,16
	Caucasian	7	1,045	[0.836;1.306]	0,69	Fixed	0,25	0,71
CC *vs*. TT	Overall	23	1,369	[1.095;1.712]	**0,005**	Random	**0,036**	0,07
	Asian	16	1,317	[1.001;1.733]	**0,048**	Random	**0,019**	0,27
	Caucasian	7	1,530	[1.063;2.202]	**0,021**	Fixed	0,43	0,14
CC *vs*. CT	Overall	23	1,170	[1.012;1.352]	**0,033**	Fixed	0,49	0,91
	Asian	16	1,136	[0.969;1.332]	0,11	Fixed	0,50	0,33
	Caucasian	7	1,352	[0.951;1.924]	0,09	Fixed	0,37	0,18
CT *vs*. TT	Overall	24	1.323	[1.052;1.663]	**0,016**	Random	< **0.001**	0,39
	Asian	17	1,395	[1.032;1.885]	**0,030**	Random	< **0.001**	0,33
	Caucasian	7	1,189	[0.933;1.515]	0,16	Fixed	0,34	0,72

PCOS. In the current study, more frequencies of the polymorphic C allele and CC genotype were discovered in women with PCOS than in controls, which supported the hypothesis that the significance of the association was found to be more significant compared with controls. It was hypothesized that this polymorphism could generate an additional sp1 binding site near the promoter, which enhanced transcription activity of *CYP17A1* expression and produced hyperandrogenism. However, experimental studies have not confirmed this finding (2).This meta-analysis results validated that the 17 *CYP17A1 T/C* (*rs*74357) gene polymorphism was significantly associated with PCOS risk in 5 genetic models: recessive model (fixed and random effect), dominant model (random effect), CC *vs*. TT (fixed effect), CT *vs*. TT (fixed effect), and allele contrast (random effect). Stratified analyses by ethnicity/country also detected significant association between Asian and Caucasian under the recessive, dominant, CC *vs*. TT, CC *vs*. CT, and the allele contrast models. All these data suggest a very strong implication of the studied polymorphism independent of ethnic factors.

This meta-analysis does, however, have certain limitations. First, the number of studies included in the meta-analysis and the number of cases and controls in the studies included in specific subgroups were both limited. As a result, more research with a larger sample size and more detailed information is required. Second, because not all published studies offered adjusted ORs, or when they did, the ORs were not adjusted for

the same possible confounders, such as age, ethnicity, and exposures, our meta-analysis was based on unadjusted OR estimates. The limited information for data analysis could result in substantial confounding bias. Third, investigations of the polymorphism showed high between-study variability, and the genotype distribution included deviated from *HWE* case-control study (15,18,20).

Despite these disadvantages, our meta-analysis has certain advantages. First and foremost, a rigorous search. The use of a computer-assisted search method allowed as many eligible studies to be included as possible. Second, the case-control studies included in this meta-analysis were of acceptable quality and matched our inclusion criteria. Furthermore, the meta-analysis approach was well designed before it was started, with specific methods for research selection, data extraction, and data analysis (PRISMA). Also, the meta-analysis was performed using the latest version (3.0) of the reference software for performing meta-analysis in genetics (Comprehensive Meta Analysis).

Furthermore, more research evaluating the impact of gene–gene and gene-environment interactions could lead to a more complete understanding of the link between the *CYP17A1 T/C* polymorphism and PCOS risk.

Conclusion

The current findings in our meta-analysis result suggest that gene polymorphisms influence the expression and production of *CYP17A1*and the *CYP17A1 T/C* (*rs*74357) gene polymorphism plays an important role in increasing the susceptibility of PCOS when carrying the C allele (genotype TC and CC). Despite the undoubted connection of *CYP17A1*gene polymorphism to PCOS, the range to which *CYP17A1*gene polymorphism contributes to metabolic dysfunction in PCOS is unidentified and needs further study. Meanwhile, due to the strong correlation between PCOS and *CYP17A1rs*7435742 polymorphism, it could be used as a genetic marker for PCOS, and might supply another tool for assessing women's susceptibility. Likewise, the *CYP17A1* could be applied to the treatment of PCOS as a potentially feasible target.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Funding: This work was non-funded.

Ethics Approval: Ethical approval will not be required because this study will retrieve and synthesise data from already published studies.

Authors Contribution: MLR article writing and editing, DE research and collection of DATA, HB research and collection of DATA, DC paper review.

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