REVIEW

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Polymorphisms in *FSHR* modulating susceptibility to polycystic ovary syndrome: an updated meta-analysis



Mandeep Kaur¹, Sukhjashanpreet Singh¹ and Anupam Kaur^{1*}

Abstract

Background Two polymorphisms, rs6165 and rs6166 located in the intracellular domain of FSHR has been reported to affect folliculogenesis, steroidogenesis and oocyte maturation. Several studies have highlighted the role of *FSHR* polymorphisms in PCOS but the findings are conflicting. A meta-analysis was carried out to decipher the emerging perspectives.

Methodology A comprehensive literature search was made using PubMed, PCOSkb, and Google Scholar. New Ottawa Scale has been utilized to evaluate the quality of each article. To evaluate the strength of association under different genetic models of rs6165 and rs6166 polymorphisms, odds ratio with a 95% confidence interval (CI) was calculated.

Results A total of 20 articles were selected for the present study. In pooled analysis and after the stratification by ethnicity, polymorphism rs6165 remains unrelated to the onset of PCOS. Besides, rs6166 exhibits significant protection in the Indian population under recessive, additive, and allele models (OR = 0.7, CI: 0.54-0.9, p = 0.006, OR = 0.65, CI: 0.48-0.89, p = 0.006, OR = 0.82, CI: 0.7-0.95, p = 0.01, respectively) and low to moderate risk in the Caucasian population under allele model (OR = 1.17, CI: 1.04-1.32, p = 0.01).

Conclusion This meta-analysis suggests that GG genotype of rs6166 provides protection against PCOS, in a population-specific manner.

Keywords PCOS, FSHR, Meta-analysis, Genetic models, Polymorphisms

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting females of reproductive age and is the foremost cause of anovulatory infertility [1, 2]. The worldwide prevalence of PCOS is between 6 and 26% [3]. Chronic anovulation, hyperandrogenism, and menstrual irregularities are the characteristic features of PCOS [4],

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¹ Department of Human Genetics, Guru Nanak Dev University, Amritsar, Punjab 143005, India which are additionally accompanied by obesity, insulin resistance and high LH levels [5, 6]. The diagnosis of PCOS is based on Rotterdam criteria 2003 which states that 2 out 3 features: a) Oligo/anovulation, b) clinical or biochemical sign of hyperandrogenism, and c) presence of polycystic ovaries on ultrasonography should be present [7]. It is becoming evident that PCOS can affect a woman anytime. It may start while she is still in the womb and show clinical signs in adolescence which continue throughout her reproductive years. Moreover, even after menopause, PCOS women are more likely to develop metabolic diseases like diabetes, hypertension, and cardiovascular disease [8].



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The precise etiology of PCOS is yet unknown, but it was suggested that the interplay of genetic and environmental factors is responsible for this condition [9]. In PCOS, the levels of gonadotropins such as follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin are abnormal. Due to persistently high-frequency GnRH stimulation, women with hyperandrogenic PCOS exhibit an increased LH pulse frequency and low FSH [10]. Lower FSH levels result in follicular development arrest, contributing to ovulatory dysfunction in PCOS. These alterations in gonadotropin secretion (LH and FSH) in PCOS may also depend on genetic variants of gonadotropic-related genes such as FSHR (FSH receptor) and LHCGR (LH/choriogonadotropin receptor) and are supported by various studies [11].

The FSHR is located on chromosome 2 at position p21-p16 and has 10 exons and 9 introns. The extracellular domain of the receptor is encoded by the first 9 exons. In contrast, the C-terminal end of the extracellular domain, the whole transmembrane domain, and the intracellular domain of the FSHR are all encoded by exon 10. In females, FSHR is expressed in granulosa cells and regulates the development of graffian follicles, granulosa cell proliferation and estrogen synthesis [12]. When FSH binds to its receptor, FSHR, it activates a number of intracellular signalling pathways, and for signal transduction exon 10 is crucial [13, 14]. Mutations in FSHR specifically in exon 10 can lead to the arrest of follicle development at several phases of growth and has several effects on phenotype such as variable development of secondary sex characteristics, primary amenorrhea, hypoplastic ovary and high serum levels of FSH [15, 16]. Ser680Asn (rs6166) and Ala307Thr (rs6165) are the two polymorphisms located in the exon 10 of FSHR and are well known to affect the efficacy of FSHR receptor towards its ligand (FSH), increase FSH levels in a compensatory manner. This increases FSHR resistance leading to reduce estrogen and inhibin B that establish the inhibitory feedback loop in the pituitary gland, resulting in hyperandrogenism which may arrest follicle development [17]. According to different studies, these polymorphisms may affect the menstrual cycle, ovarian hyperstimulation and PCOS development [18, 19]. Several studies have been carried out across the globe to e the genetic association of these SNPs but the results were conflicting. In order to resolve differences in genetic association research, meta-analysis has been a widely known method. It specifically incorporates findings from various studies on the same subject, improving statistical strength and accuracy in effect estimation [20]. Although, meta-analysis has already been done earlier on both variants [21-23], however, there are some additional publications on FSHR polymorphisms [24, 25]. Furthermore,

a recent meta-analysis by [23] includes only Asian studies. Hence, in order to ascertain the relationship between these polymorphisms and PCOS susceptibility in the global population, we further conducted a thorough and updated meta-analysis.

Material and methodology Search strategy

Comprehensive computer-based literature searches on Google Scholar, PubMed, and PCOSkb were used to find each study that has reported the genetic association of Polycystic Ovary Syndrome and *FSHR* polymorphisms (rs6165 and rs6166) without any language barrier (up to March 2023). The following set of MeSH keywords and terms were used: Polycystic Ovary Syndrome or PCOS or Stein Leventhal Syndrome; FSHR or Follicle Stimulating Hormone Receptor or FSH; rs6165 or rs6166 or Ala307Thr or Ser680Asn; gene or allele or genotype or mutation or variant or variation or polymorphism or Genetic variant or Genetic variation. Moreover, manual screening was done on the reference lists of research articles and earlier meta-analyses.

Inclusion/ exclusion criteria

In this meta-analysis, studies fulfilling the following criteria were included: (a) a case–control design (b) evaluation of the association of rs6165 and rs6166 with PCOS (c) genotype frequency of controls in the Hardy Weinberg equilibrium (HWE) (d) provides genotypic data for both cases and control group (e) studies on human blood samples (f) published in the English language. Exclusion criteria were as follows: (a) not the case–control design, (b) Controls genotype frequency deviated from HWE (c) The design is based on family or sibling pairs (d) Animal studies.

Data search and quality assessment

Data were extracted from selected publications based on inclusion criteria. From each study, the following information was gathered: first Author name, year of publication, country of origin, diagnostic criteria of PCOS, method of genotyping, the total number of cases and controls and evidence of HWE in controls.

To check the quality of each publication included in the present meta-analysis New Castle Ottawa scale (NOS) [26] was used. NOS is based on a star scoring system and is categorized into three parts: a) Selection b) Comparability c) Outcome. For the non-randomized meta-analysis, each publication can be given a total of 9 stars, with 0 to 3 stars, 4 to 6 stars, and 7 to 9 stars representing low, moderate, and high quality, respectively. For the current meta-analysis, publications of moderate and high quality were chosen, while publications of low quality were excluded. Finally, PRISMA 2020 (Preferred Reporting

Items for Systematic Reviews and Meta-Analysis) checklist and flow diagram were used for this meta-analysis.

Statistical analysis

The power of the study was calculated using a Cats-power calculator which rendered the power to be>95%. A goodness of fit Chi-square calculation was used to determine any deviations from HWE. Pooled odds ratios (OR) and 95% confidence intervals (CIs) were used to evaluate the strength of the association for the meta-analysis. The association was determined using the following four genetic models: dominant model (GG+AG vs. AA), recessive model (GG vs. AG+AA), additive model (GG vs. AA), and allele model (G vs. A). To assess heterogeneity, the I² statistic was used and a random effect model (REM) was chosen when I² was greater than 50%, indicating that heterogeneity is present, while a fixed effect model (FEM) was chosen when I^2 was less than 50%, indicating that heterogeneity was absent. To assess publication bias, Beggs's funnel plot was used. All data were analysed using Review Manager 5.4.1. Bonferroni correction was applied to *p*-value in order to reduce the type 1 error.

Results

Studies included in the meta-analysis

Figure 1 displays the flowchart for the search process and search results. A total of 156 possible studies were gathered through the use of database search and manual search. Titles and abstracts were carefully examined and 124 papers were eliminated, because they were duplicates, review articles, or case reports. Following full-text analysis, 10 were excluded since they were not case-control studies designed or have enough information for meta-analysis. In addition, two studies that deviated from Hardy Weinberg equilibrium were excluded, and one study was also taken out since it had a low NOS score. There were no additional relevant studies found despite our search of recent reviews and meta-analyses. Eventually, 20 case-control studies were selected for meta-analysis, and of these 20 studies, 16 were on Asians and 4 studies were on Caucasians. Table 1 enlists the distinguishing characteristics of all selected studies. Genotype frequency and HWE p-value of included studies were tabulated in Table 2.



Fig. 1 Flow diagram of the selection process for meta-analysis (according to PRISMA guidelines)

Sr. No	Study	Year	Country	PCOS diagnostic criteria	Variants Studied	Genotyping method	Sample size (Cases/Controls)
1)	Conway et al. [27]	1999	UK	PCO+OA+MD	rs6165, rs6166	PCR-SSCP	93/51
2)	Tong et al. [28]	2001	China	HA+PCO+MD	rs6165	PCR-RFLP	124/236
3)	Sudo et al. [29]	2002	Japan	Rotterdam Criteria	rs6165, rs6166	PCR-RFLP	18/168
4)	Unsal et al. [30]	2009	Turkish	Rotterdam Criteria	rs6165, rs6166	PCR-RFLP	44/50
5)	Valkenburg et al. [17]	2009	Netherlands	Rotterdam Criteria	rs6166	PCR-SSP	495/2912
6)	Du et al. [31]	2010	China	Rotterdam Criteria	rs6165, rs6166	PCR-SSP	55/92
7)	Gu et al. [16]	2010	Korea	Rotterdam Criteria	rs6165, rs6166	PCR-RFLP	235/128
8)	Mohiyiddeen et al. [32]	2012	UK	Rotterdam Criteria	rs6166	Taq man assay	58/83
9)	Fu et al. [33]	2013	China	Rotterdam Criteria	rs6165, rs6166	Sequencing	384/768
10)	Kambalachenu et al. [34]	2013	India	Rotterdam Criteria	rs6166	PCR-RFLP	97/101
11)	Liaqat et al. [35]	2013	Pakistan	Rotterdam Criteria	rs6165, rs6166	PCR-SSP	96/96
12)	Singhasena et al. [36]	2014	Thailand	Rotterdam Criteria	rs6165, rs6166	PCR-RFLP	133/132
13)	Wu et al. [37]	2014	China	Rotterdam Criteria	rs6165, rs6166	PCR-RFLP	215/205
14)	Almawi et al. [38]	2015	Bahrain	Rotterdam Criteria	rs6166	Real-time PCR	203/211
15)	Thathapudi et al. [39]	2016	India	AES	rs6166	PCR-RFLP	204/204
16)	Kim et al. [4]	2017	Japan	Rotterdam Criteria	rs6165, rs6166	Sequencing	377/388
17)	Branavan et al. [40]	2018	Sri Lanka	Rotterdam Criteria	rs6165, rs6166	Real-time PCR	55/110
18)	Wan et al. [23]	2021	China	Rotterdam Criteria	rs6165, rs6166	Sanger sequencing	400/480
19)	Kaur et al. [24]	2023	India	Rotterdam Criteria	rs6165, rs6166	PCR-RFLP	421/322
20)	Vieira et al. [25]	2023	Portugal	Rotterdam Criteria	rs6166	PCR-RFLP	88/80

Table 1 List of included studies in the present meta-analysis

PCO Polycystic Ovary, OA Oligo/annovulation, MD Menstrual irregulation, HA Hypreandrogenism, PCR-SSCP Polymerase Chain Reaction-Single Strand Conformation Polymorphism, PCR-RFLP Polymerase Chain Reaction- Restriction Fragment Length Polymorphism, PCR-SSP Polymerase Chain Reaction- Sequence Specific Priming, AES Androgen Excess Society

Pooled analysis

The findings of the meta-analysis were displayed in Table 3. For rs6165, fixed effect model was chosen for all the genetic models due to low heterogeneity. None of the genetic models confers a significant risk to PCOS in the overall analysis for rs6165 polymorphism (dominant model: OR = 1.04, CI: 0.93–1.16, *p* = 0.49; recessive model: OR-1.19 CI:1.03–1.3, *p*=0.02; additive model: OR-1.2 CI:1.02–1.42, *p*=0.03, allele model: OR=1.07, CI: 0.99– 1.18, p=0.08 respectively) (Table 3; Fig. 2). Significant heterogeneity was observed for the rs6166 polymorphism in the allele, additive, and recessive models ($I^2 = 61\%$, 64%, 64%, respectively); however, genetic models did not indicate any risk for the development of PCOS (dominant model: OR=1.05, CI:0.95–1.15, p=0.34; Recessive model: OR = 0.97, CI:0.78–1.22, *p* = 0.82; Additive model: OR = 0.99, CI:0.76–1.29, *p* = 0.94; Allele model: OR = 1.02, CI: 0.90–1.15, *p*=0.73) (Table 3, Fig. 3).

Subgroup analysis

After the stratification by ethnicity, rs6165 polymorphism did not showed a significant risk of PCOS development in any ethnic group under any genetic model (Fig. 4; Table 3). In the Indian population, rs6166 polymorphism provides significant protection under recessive, additive, and allele models (Recessive model: OR=0.7, CI:0.54–0.9, p=0.006, Additive model: OR=0.65, CI:0.48–0.89, p=0.006, Allele model: OR=0.82, CI:0.7–0.95, p=0.01), while dominant model showed no association (Dominant model: OR=0.84, CI:0.66–1.06, p=0.15). Furthermore, a significant association was also found under the allelic model in other studies (Caucasian studies) (OR=1.17, CI:1.04 -1.32, p=0.01). However, none of the genetic models show any association with the Asian population (Table 3, Fig. 5).

Publication bias and sensitivity of meta-analysis

Begg's funnel plots were used to analyze the publication bias in included studies and, because of their symmetrical design, neither of the studies showed any signs of publication bias. Leave one out sensitivity analysis was performed to check the stability of the study. After systematically excluding each study, statistically comparable results were still obtained, showing statistically valid findings from our meta-analysis.

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	rs6165						HWE <i>p</i> - value	rs6166						HWE <i>p</i> - value
	Cases			Controls				Cases			Controls			
	Thr/Thr	Thr/Ala	Ala/Ala	Thr/Thr	Thr/Ala	Ala/Ala		Asn/Asn	Asn/Ser	Ser/Ser	Asn/Asn	Asn/Ser	Ser/Ser	1
Conway et al. [27]	22	47	24	80	25	18	0.88	23	48	52	18	25	8	0.88
Tong et al. [28]	53	56	15	102	110	24	0.47							
Sudo et al. [29]	ŝ	12	ŝ	73	73	22	0.57	e	12	ŝ	73	73	22	0.57
Unsal et al. [30]	16	19	6	16	25	6	0.88	13	20	11	14	27	6	0.2
Valkenburg et al. [17]	ı	ı					ı	123	248	124	782	1500	630	0.07
Du et al. [31]	26	20	6	40	37	15	0.2	26	26	ŝ	40	34	16	0.07
Gu et al. [16]	81	116	38	50	56	22	0.35	138	91	9	92	35	-	0.23
Mohiyiddeen et al. [32]								14	34	10	20	47	16	0.21
Fu et al. [33]	192	156	36	362	329	77	0.86	187	162	35	357	334	77	0.93
Kambalachenu et al. [34]							ı	25	64	8	31	52	18	0.63
Liaqat et al. [35]	27	47	22	22	49	25	0.83	29	47	20	24	47	25	0.83
Singhasena et al. [36]	70	53	10	70	56	9	0.20	69	59	5	72	54	9	0.29
Wu et al. [37]	93	95	27	91	100	14	0.052	93	94	28	94	98	13	0.057
Almawi et al. [38]	ı	ı		,	,	,	ı	64	92	47	52	107	52	0.83
Thathapudi et al. [39]				,		,	ı	74	66	31	44	90	70	0.14
Kim et al. [4]	145	176	56	181	176	31	0.18	149	178	50	180	176	32	0.22
Branavan et al. [40]	16	26	13	28	53	29	0.7	16	26	13	28	53	29	0.7
Wan et al. [23]	175	175	50	210	222	48	0.33	176	178	46	218	215	47	0.56
Kaur et al. [24]	93	175	153	76	146	100	0.11	119	198	104	92	156	74	0.6
Vieira et al. [25]								28	43	17	30	32	18	0.104
HWE Hardy–Weinberg equilibri	m													

p-value < 0.05 considered as statistically significant

Table 3	Illustration of	pooled and su	b-group analy	/sis under different	aenetic models

	Overall Analysis			Asian Studies	Indian Studies	Other studies
	FEM	REM	l ²	Meta-analysis	Meta-analysis	Meta-analysis
rs6165	OR (CI), <i>p</i> -value					
Dominant Model	1.04(0.93–1.16), 0.49	1.19 (0.92–1.16), 0.54	4%	1.04(0.92–1.18), 0.53	1.09(0.77–1.54), 0.63	0.6(0.25–1.47), 0.26
Recessive Model	1.19(1.03–1.3), 0.02	1.2 (1.01–1.4), 0.04	10%	1.22(1.02–1.46), 0.03	1.27(0.93–1.73), 0.13	0.64(0.3–1.33), 0.23
Additive Model	1.2(1.02–1.42), 0.03	1.19(0.96–1.47), 0.11	27%	1.23(1.02–1.49), 0.03	1.25(0.84–1.85), 0.16	0.48(0.18–1.34), 0.16
Allele Model	1.07(0.99–1.18), 0.08	1.07(0.97–1.17), 0.19	25%	1.07(0.97–1.19), 0.18	1.15(0.93–1.41), 0.19	0.7(0.43–1.14), 0.16
rs6166						
Dominant Model	1.05(0.95–1.15), 0.34	1.04 (0.91–1.2) 0.56	44%	1.07 (0.95–1.2), 0.28	0.84 (0.66–1.06), 0.15	1.15 (0.95–1.39), 0.16
Recessive Model	1.02(0.91–1.15), 0.72	0.97 (0.78–1.22), 0.82	61%	1.11 (0.92–1.32), 0.27	0.7 (0.54–0.9), 0.006*	1.02 (0.91–1.15), 0.11
Additive Model	1.03 (0.90–1.2), 0.67	0.99 (0.76–1.29), 0.94	64%	1.1 (0.91–1.34), 0.33	0.65 (0.48–0.89), 0.006*	1.25 (0.98–1.59), 0.07
Allele Model	1.03(0.96–1.10), 0.4	1.02 (0.90–1.15), 0.78	64%	1.06 (0.95–1.15), 0.19	0.82 (0.7–0.95), 0.01*	1.17 (1.04–1.32), 0.01*

OR Odds Ratio, CI Confidence Interval, FEM Fixed Effect Model, REM Random Effect Model

* *p*-value was considered significant after Bonferroni correction,

Discussion

One of the most prevalent endocrine-metabolic disorders in women of reproductive age is PCOS and anovulation, infertility, and hyperandrogenism are its characteristic featu6res. PCOS is a polygenic condition, and numerous genetic variations are linked to its susceptibility [23]. The involvement of genetic factors in PCOS pathogenesis is evident in familial and genomewide association studies (GWAS) [38, 41–43]. FSHR, LHCGR, THADA, and DENND1A are PCOS-susceptibility loci [41, 44].

Chronic anovulation is a hallmark of PCOS and the mechanism by which follicle selection is blocked in PCOS is still not known. An abnormal endocrine environment may be responsible for the premature arrest of some follicles and the advancement of follicle maturation in others. The suppression of FSH is the primary cause of this "suspension" of follicle growth and it had been reported that after careful administration of low-dose FSH, growth and ovulation of a healthy dominant follicle was reestablished [45-48]. FSH performs by activating a specific receptor (FSHR) on the granulosa cells of the ovary. It was reported that phosphorylation of the Ser and Thr residues in the intracellular domain of FSHR may affect how the protein decouples from adenylyl cyclase. As a result, the function of the receptor, including the efficacy of FSH, may be affected by amino acid alterations linked to the corresponding SNPs (rs6165 and rs6166) [30, 49]. These two polymorphisms are located in exon 10 (rs6165 and rs6166) and are widely studied in different populations [4]; but the results had been inconsistent.

A meta-analysis is a statistical tool used to combine the findings of multiple studies on the same topic, increasing the statistical power to resolve discrepancies, and FSHR polymorphisms have already been meta-analyzed earlier as well [21, 22]. Additional studies on FSHR polymorphisms were found, after thoroughly reviewing the literature. Therefore, the present meta-analysis aims to investigate the association of FSHR exon 10 (rs6165 and rs6166) polymorphisms with PCOS risk. It comprises a total of 20 studies (Table 1). For rs6165, 14 studies were selected which include 2650 PCOS cases and 3226 controls and it was found that rs6165 does not exhibit an association with PCOS in any genetic model (Table 3). For rs6166, 19 studies with 3671 PCOS cases and 6579 controls were chosen and the protective role of Asn680Ser was observed in the Indian population under recessive, additive and allelic model while in the Caucasian population, it was demonstrated that Ser680 provides low to moderate risk under allelic model (OR-1.17, CI- 1.04–1.32, p=0.01), however, in the Asian population, rs6166 polymorphism remained non-associated.

Chen et al. [21] conducted a meta-analysis on rs6165 and rs6166 that included 10 studies with 1720 PCOS cases and 4523 controls for rs6166 and 1097 cases and 1545 controls for rs6165. However, they did not observe any PCOS risk associated with *FSHR* polymorphisms. Another meta-analysis was carried out by Qiu et al. [22]

rs6165 Pooled analysis

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	PCOS Ca	ases	Contro	ols		Odds Ratio			Odds Ratio
Study or Subgroup	Events	Total	Events	Iotal	weight	M-H, Fixed, 95% CI	Year		M-H, Fixed, 95% Cl
Conway et al	/1	93	43	51	2.1%	0.60 [0.25, 1.47]	1999		
Sudo et al	15	124	95	168	0.5%	3 84 [1 07 13 77]	2001		
Unsaletal	28	44	34	50	1.9%	0.82 [0.35, 1.94]	2009		
Duetal	29	55	52	92	3.0%	0.86 [0.44, 1.68]	2010		
Guetal	154	235	78	128	5.6%	1.22 [0.78, 1.90]	2010		+
Fu et al	192	384	406	768	21.7%	0.89 [0.70, 1.14]	2013		
Liaqat et al	69	96	74	96	3.3%	0.76 [0.40, 1.46]	2013		
Singhasena et al	63	133	62	132	5.3%	1.02 [0.63, 1.65]	2014		
Wu et al	122	215	114	205	8.1%	1.05 [0.71, 1.54]	2014		+
Kim et al	232	377	207	388	12.6%	1.40 [1.05, 1.87]	2017		
Branavan et al	39	55	82	110	2.6%	0.83 [0.40, 1.71]	2018		
wan et al	225	400	270	480	17.2%	1.00 [0.77, 1.31]	2021		T
r auf et al	320	421	240	322	3.3%	1.08 [0.77, 1.04]	2025		E Contraction of the second seco
Total (95% CI)		2650		3226	100.0%	1.04 [0.93, 1.16]			•
Total events	1638		1897						
Heterogeneity: Chi ² =	13.59, df=	= 13 (P =	= 0.40); I ^z	= 4%				0.01	
Test for overall effect:	Z = 0.69 (F	P = 0.49)					0.01	U.1 1 10 100 Eavours (control) Eavours (experimental)
									r dreate (control) - dreate (coperintential)
L)									
D)									
,	PCOSC	1565	Contro	als		Odds Ratio			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% CL	Year		M-H. Fixed, 95% Cl
Conway et al	24	93	18	51	5.6%	0.64 [0.30, 1.33]	1999		
Tong et al	15	124	24	236	4.7%	1.22 [0.61, 2.41]	2001		_ -
Sudo et al	3	18	22	168	1.1%	1.33 [0.36, 4.96]	2002		
Unsal et al	9	44	9	50	2.2%	1.17 [0.42, 3.28]	2009		
Du et al	9	55	15	92	3.0%	1.00 [0.41, 2.48]	2010		
Gu et al	38	235	22	128	7.7%	0.93 [0.52, 1.65]	2010		
Fuetal	36	384	77	768	15.0%	0.93 [0.61, 1.41]	2013		-
Liaqat et al	22	96	25	96	6.2%	0.84 [0.44, 1.63]	2013		
Singhasena et al	10	133	6	132	1.8%	1.71 [0.60, 4.84]	2014		
vvu et al	27	215	14	205	4.0%	1.96 [1.00, 3.85]	2014		
nim et al	56	311	31	388	8.4%	2.01 [1.26, 3.20]	2017		
oranavan etal Won otal	13	00 100	29 40	110	4.8%	1.20 [0.41, 1.84]	2018		
Kauretal	163	421	40	322	23.2%	1.25 [0.04, 1.90]	2021		
Naul et al	155	421	100	322	23.270	1.27 [0.85, 1.75]	2023		-
Total (95% CI)		2650		3226	100.0%	1.20 [1.03, 1.39]			•
Total events	465		440						
Heterogeneity: Chi ² =	14.45, df=	: 13 (P =	= 0.34); I ^z	= 10%				0.01	01 1 10 100
Test for overall effect:	Z = 2.36 (F	P = 0.02)					0.01	Favours [control] Favours [experimental]
c)									
-)	PCOS C	2026	Contro	nle		Odds Ratio			Odds Ratio
Study or Subgroup	Evente	Total	Evente	Total	Weight	M.H. Fixed 95% CL	Year		M-H Fixed 95% CI
Composed of Subgroup	24	10101	10	10101	A EQ.	0.40.00.10.1.041	1000		Mi-H, FIXEU, 55% CI
Tong et al	15	040	24	126	4.0%	1 20 [0.10, 1.34]	2001		
Pudo et el	10	00	24	120	0.5%	2 22 10 22 40	2001		
lincolotol	0	25	22	25	2 2 96	1 00 0 22 2 17	2002		
Ductol	0	25	15	55	2.5%	0.0210.25.2.421	2003		
Guetal	20	110	22	70	7.60	1.07 [0.55, 2.42]	2010		
Fuetal	36	228	77	430	19.1%	0.88 [0.57, 2.01]	2010		
lionototol	22	10	25	433	5 7%	0.7210.32 1.601	2013		
Singhocono ot ol	10	90	25	76	2.7%	1.67 [0.52, 1.00]	2013		
Wii of al	27	120	14	105	1 7%	1 80 10 03 3 83	2014		
k/im et al	56	201	31	212	9.0%	2 25 [1 38 3 68]	2017		
Branavan et al	13	201	20	57	A 496	0.78 (0.32, 1.92)	2017		
Wan et al	50	225	48	258	14 296	1 25 [0.80, 1.95]	2010		_ _
Kauretal	153	246	100	176	18 0%	1.25 [0.84 1.85]	2023		
	100	240				1.20 [0.04] 1.00]	2020		
Total (95% CI)		1477		1769	100.0%	1.20 [1.02, 1.42]			◆
Total events	465		440						
Heterogeneity: Chi ² =	17.78, df=	= 13 (P =	= 0.17); l ^a	= 27%				0.01	
Test for overall effect	Z = 2.15 (F	P = 0.03)					0.01	Favours [control] Favours [experimental]
d)									
,	DCORCO	1000	Contra	ale		Odde Datio			Odde Patio
Chudu en Cutano	FUESCO	Tata	Contro	JIS Tet-1	Malate	Ouus Kauo	Mr.		Uuus Rau0
study or Subgroup	Events	rotal	Events	rotal	weight	M-H, FIXed, 95% Cl	rear		M-H, FIXEO, 95% CI
Conway et al	95	186	61	102	3.2%	0.70 [0.43, 1.14]	1999		
Tong et al	86	248	158	472	5.9%	1.06 [0.76. 1.46]	2001		+
Sudo et al	19	26	117	326	U 0 04	1 87 [] 04 2 72	2002		<u> </u>
Juncol et al	10	20	10	100	1.00	0.00 (0.84, 3.73)	2002		
onsarecal	31	88	43	100	1.9%	0.96 [0.54, 1.72]	2009		
Du et al	38	110	67	184	2.7%	0.92 (0.56, 1.51)	2010		
Gu et al	192	470	100	256	6.3%	1.08 [0.79, 1.47]	2010		+
Fu et al	228	768	483	1536	18.7%	0.92 [0.76, 1.11]	2013		+
Liagat et al	91	192	qa	192	4 3%	0.85 (0.57, 1.26)	2013		
Cinchacona at al	70	200	00	261	1 10/	1 00 0 74 1 60	2014		<u> </u>
unigna sella et al	13	200	00	204	4.170	1.05 [0.74, 1.00]	2014		L
vvu et al	149	430	128	410	7.1%	1.17 (U.88, 1.56)	2014		T-
Kim et al	288	754	238	776	12.0%	1.40 [1.13, 1.73]	2017		-
Branavan et al	52	110	111	220	3.2%	0.88 [0.56, 1.39]	2018		-+-
Wan et al	275	800	318	960	15.7%	1.06 [0.87, 1.29]	2021		+
Kauretal	/01	242	346	644	13 0 %	1 15 [0 02 1 //1	2022		-
r\duietai	401	042	340	044	13.970	1.10 [0.85, 1.41]	2023		-
Total (05% CI)		6200		6452	100.0%	1 07 [0 00 4 40]			
Total (95% CI)		2200		0402	100.0%	1.07 [0.99, 1.16]			ľ
Total events	2103		2337						
Heterogeneity: Chi ² =	17.23, df=	: 13 (P =	= 0.19); I ^z	= 25%				0.01	01 1 10 400
Test for overall effect:	Z=1.72 (F	P = 0.08)					0.01	Eavoure [control] Eavoure [constal]
	N								LANDER DATED TO THE TAXABLE PROPERTIES OF TAXABLE PROPER



Pooled analysis (rs6166)

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Study or Subgroup Conway et al Sudo et al Jnsal et al	PCOS C	Cases	Contr	ols		Odde Patio			Odds Ratio
Conwayetal Sudoetal Jnsaletal		Total	Events	Total	Weight	M-H. Fixed, 95% Cl	Year		M-H, Fixed, 95% CI
Sudo et al Jnsal et al	70	93	33	51	1.2%	1.66 [0.79, 3.49]	1999		
/ilsal et al	15	18	95	168	0.3%	3.84 [1.07, 13.77]	2002		
′alkenburα et al	372	44	2130	2912	17.3%	1.11 [0.89, 1.38]	2009		
) u et al	29	55	50	90	2.0%	0.89 [0.46, 1.75]	2010		
Buetal Achieldeen etel	97	235	36	128	3.1%	1.80 [1.13, 2.86]	2010		
u et al	197	384	411	768	15.0%	0.92 [0.72, 1.17]	2012		_ _
(ambalachenu et al	72	97	70	101	2.0%	1.28 [0.69, 2.37]	2013		
iaqatetal	67	96	72	96	2.5%	0.77 [0.41, 1.45]	2013		
inghasena et al	64	133	60	132	3.5%	1.11 [0.69, 1.80]	2014		
lmawi et al	139	203	159	211	5.5%	0.71 [0.46, 1.09]	2015		
'hathapudi et al	130	204	160	204	6.5%	0.48 [0.31, 0.75]	2016		
Branavan et al	39	55	208	110	1.8%	0.83 [0.40, 1.71]	2017		
Van et al	224	400	262	480	11.8%	1.06 [0.81, 1.38]	2021		_ - _
(aur et al	302	421	230	322	8.3%	1.02 [0.74, 1.40]	2023		
rieira et al	60	88	50	80	1.9%	1.29 [0.68, 2.43]	2023		
otal (95% CI)		3671		6579	100.0%	1.05 [0.95, 1.15]			+
otal events	2302		4318						
est for overall effect: .	32.25,011 = Z = 0.95 (F	= 18 (P = P = 0.34)	0.02); I*)	= 44%				0.1 0.2	2 0.5 1 2 5 10 Favours (control) Eavours (experimental)
))									
study or Subgroup	PCOS C	ases Total	Contro	Total	Weight	Odds Ratio M-H Random 95% C	Vear		Odds Ratio
conway et al	11	44	9	50	3.4%	1.52 [0.56, 4.10]	1 1999		
iudo et al	47	203	52	211	7.5%	0.92 [0.59, 1.45]	2002		
Jnsal et al	50	377	32	388	7.3%	1.70 [1.06, 2.72]	2009		
ankenburg et al)u et al	13	55 495	29 630	2912	4.8%	0.86 [0.41, 1.84] 1.21 IO 97 1 51	j ∠009] 2010		
∋uetal	6	235	1	128	1.0%	3.33 [0.40, 27.95]	2010		
lohiyiddeen et al	5	133	6	132	2.6%	0.82 [0.24, 2.76]	2012		
u et al (amhalachenu et cl	3	55 59	16 16	90 83	2.4%	0.27 [0.07, 0.96]	2013		
iaqatetal	20	96	25	96	5.5%	0.75 [0.38, 1.46]	2013		- _
Vu et al	17	88	18	80	4.9%	0.82 [0.39, 1.74]	2014		
linghasena et al	28	215	13	205	5.3%	2.21 [1.11, 4.40]	2014		
innawietal hathapudietal	22	93 204	8 70	51 204	4.0%	1.67 [0.68, 4.07] 0.34 [0.21_0.55]	j ∠015] 2016		
im et al	8	97	18	101	4.0%	0.41 [0.17, 1.00]	2017		
Iranavan et al	3	18	22	168	2.3%	1.33 [0.36, 4.96]	2018		
van et al Gauretal	104	421	74	322	8.6%	1.10 [0.78, 1.55]	2021		
ieira et al	46	400	47	480	7.7%	1.20 [0.78, 1.84]	2023		-+
otal (95% CI)	600	3671	1160	6579	100.0%	0.97 [0.78, 1.22]]		•
otal events leterogeneity: Tau ² = I	583 0.12:Chiᢪ	= 45.70.	df = 18 (P = 0.00	103); I ^z = 6	31%		<u> </u>	
est for overall effect: 2	Z = 0.23 (P	= 0.82)						0.05	0.2 1 5 20 Favours (control) Favours (experimental)
									, areas (council , areas (astronauta)
)									
.)	PCOSC	ases	Contro	ls		Odds Ratio			Odds Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I Year		M-H, Random, 95% Cl
onway et al	22	45	8	26	4.0%	2.15 [0.78, 5.95]	1999		
Conwayetal Gudoetal Josaletal	22 3 11	45 6 24	8 22 9	26 95 23	4.0% 2.0% 3.4%	2.15 [0.78, 5.95] 3.32 [0.62, 17.62] 1.32 [0.41, 4.20]] 1999] 2002] 2009		
conway et al Judo et al Jusal et al Jalkenburg et al	22 3 11 124	45 6 24 247	8 22 9 630	26 95 23 1412	4.0% 2.0% 3.4% 9.1%	2.15 [0.78, 5.95] 3.32 [0.62, 17.62] 1.32 [0.41, 4.20] 1.25 [0.95, 1.64]	1999 2002 2009 2009		
conwayetal cudoetal /nsaletal /alkenburgetal ouetal &uetal	22 3 11 124 3 6	45 6 24 247 29 144	8 22 9 630 16 1	26 95 23 1412 56 93	4.0% 2.0% 3.4% 9.1% 2.8% 1.3%	2.15 (0.78, 5.95) 3.32 (0.62, 17.62) 1.32 (0.41, 4.20) 1.25 (0.95, 1.64) 0.29 (0.08, 1.09) 4 00 (0.47, 33.77)	1999 2002 2009 2009 2009 2010		
conway et al sudo et al Jnsal et al 'alkenburg et al Du et al Su et al fohlyiddeen et al	22 3 11 124 3 6 10	45 6 24 247 29 144 24	8 22 9 630 16 1 16	26 95 23 1412 56 93 36	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9%	2.15 [0.78, 5.95] 3.32 [0.62, 17.62] 1.32 [0.41, 4.20] 1.25 [0.95, 1.64] 0.29 [0.08, 1.09] 4.00 [0.47, 33.77] 0.89 [0.31, 2.54]	1999 2002 2009 2009 2010 2010 2010 2012		
conway et al tudo et al 'alkenburg et al 'u et al bu et al tohiyiddeen et al u et al 'ambalachenu et al	22 3 11 124 3 6 10 35 8	45 6 24 247 29 144 24 222 33	8 22 9 630 16 1 16 77 18	26 95 23 1412 56 93 36 434 49	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 7.9% 4.2%	2.15 [0.78, 5.95] 3.32 [0.62, 17, 62] 1.32 [0.41, 4.20] 1.25 [0.95, 1.64] 0.29 [0.08, 1.09] 4.00 [0.47, 33.77] 0.89 [0.31, 2.54] 0.87 [0.56, 1.34] 0.55 [0.21, 1, 48]] 1999] 2002] 2009] 2009] 2010] 2010] 2012] 2013] 2013		
Conway et al Iudo et al Yasal et al Yalkenburg et al Ju et al Yu et al tohiyiddeen et al ambalachenu et al Jaqat et al	22 3 11 124 3 6 10 35 8 20	45 6 24 247 29 144 24 222 33 49	8 22 9 630 16 1 16 77 18 25	26 95 23 1412 56 93 36 434 49 49	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 7.9% 4.2% 5.2%	$\begin{array}{c} 2.15 \left[0.78, 5.95 \right] \\ 3.32 \left[0.62, 17.62 \right] \\ 1.32 \left[0.041, 4.20 \right] \\ 0.29 \left[0.08, 1.09 \right] \\ 4.00 \left[0.47, 33.77 \right] \\ 0.89 \left[0.31, 2.54 \right] \\ 0.87 \left[0.56, 1.34 \right] \\ 0.55 \left[0.21, 1.48 \right] \\ 0.66 \left[0.30, 1.47 \right] \end{array}$	1999 2002 2009 2010 2010 2010 2012 2012 2013 2013 2013		
conway et al iudo et al /nsal et al (alkenburg et al)u et al tohiyiddeen et al u et al (ambalachenu et al Jaqat et al Vu et al	22 3 11 124 3 6 10 35 8 20 5 28	45 6 24 247 29 144 222 33 49 74 121	8 22 9 630 16 1 16 77 18 25 6 13	26 95 23 1412 56 93 36 434 49 49 78 107	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 4.2% 5.2% 3.1% 5.2%	2.15 [0.78, 5.95] 3.32 [0.62, 17.62] 1.32 [0.41, 4.20] 1.25 [0.95, 1.64] 0.29 [0.08, 1.09] 4.00 [0.47, 33.77] 0.89 [0.31, 2.54] 0.87 [0.55, 1.34] 0.65 [0.21, 1.48] 0.66 [0.30, 1.47] 0.87 [0.25, 2.98] 2.19 [1.05, 4.16]	1999 2002 2009 2010 2010 2012 2013 2013 2013 2013 2013 2013 2013 2013 2013 2014		
conway et al judo et al Jnsal et al (alkenburg et al Du et al to hiyiddeen et al to hiyiddeen et al (ambalachenu et al Jaqat et al Vu et al Imawi et al	22 3 11 124 3 6 10 35 8 20 5 28 47	45 6 24 247 29 144 222 33 49 74 121 111	8 22 9 630 16 1 16 77 18 25 6 13 52	26 95 23 1412 56 93 36 434 49 49 78 107 104	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 7.9% 4.2% 5.2% 3.1% 5.8% 7.1%	$\begin{array}{c} 2.15 \ [0.78, 6.96]\\ 3.32 \ [0.62, 17, 62]\\ 1.32 \ [0.41, 4.20]\\ 1.25 \ [0.95, 16.44]\\ 0.29 \ [0.95, 16.44]\\ 0.29 \ [0.08, 1.09]\\ 4.00 \ [0.47, 33, 77]\\ 0.89 \ [0.31, 2.54]\\ 0.87 \ [0.56, 1.34]\\ 0.66 \ [0.30, 1.47]\\ 0.87 \ [0.25, 2.19]\\ 2.18 \ [1.06, 4.46]\\ 0.73 \ [0.43, 1.26]\end{array}$	1999 2002 2009 2010 2010 2012 2012 2013 2013 2013 2014 2014 2014		
conway et al junsai et al junsai et al alkenburg et al ju et al ju et al iu et al iu et al acmbalachenu et al jaqat et al Wu et al innghasena et al innawi et al hathapudi et al	22 3 11 124 3 6 10 35 8 20 5 28 47 31	45 6 24 247 29 144 24 222 33 49 74 121 111 105	8 22 9 630 16 1 16 77 18 25 6 13 52 70 70	26 95 23 1412 56 93 36 434 49 49 78 107 104 114	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 7.9% 4.2% 5.8% 7.1% 5.8% 7.1% 6.9%	$\begin{array}{c} 2.15 (0.78, 6.68)\\ 3.32 (0.62, 17.62)\\ 1.32 (0.41, 4.20)\\ 1.25 (0.95, 1.64)\\ 0.29 (0.08, 1.09)\\ 4.00 (0.47, 33.77)\\ 0.89 (0.31, 2.64)\\ 0.65 (0.31, 2.64)\\ 0.65 (0.31, 2.64)\\ 0.65 (0.30, 1.47)\\ 0.87 (0.25, 2.88)\\ 2.18 (1.06, 4.68)\\ 0.73 (0.43, 1.26)\\ 0.73 (0.43, 1.26)\\ 0.26 (0.15, 0.46)\\ 0.26$	1999 2002 2009 2010 2010 2012 2013 2013 2013 2014 2014 2015 2014 2015 2016		
conway et al udo et al Insai et al alkenburg et al ue tal tohiyiddeen et al ue tal cambalachenu et al Jaqat et al Imawi et al Imathapudi et al Granavan et al	22 3 11 124 3 6 10 35 8 20 5 28 47 31 50 13	45 6 24 247 29 144 222 33 49 74 121 111 105 199 29	8 22 9 630 16 1 1 6 77 18 25 6 13 52 70 32 29	26 95 23 1412 56 93 36 434 49 78 107 104 114 212 57	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 7.9% 4.2% 5.2% 5.2% 5.8% 7.1% 6.9% 6.9% 4.7%	$\begin{array}{c} 2.15 \ [0.78, 6.56]\\ 3.32 \ [0.62, 1762]\\ 1.32 \ [0.41, 4.20]\\ 1.52 \ [0.95, 184]\\ 0.29 \ [0.08, 109]\\ 4.00 \ [0.47, 33.77]\\ 0.89 \ [0.31, 2.54]\\ 0.87 \ [0.55, 1.34]\\ 0.55 \ [0.21, 1.48]\\ 0.66 \ [0.30, 1.47]\\ 0.87 \ [0.25, 2.98]\\ 2.18 \ [1.66, 4.46]\\ 0.73 \ [0.43, 1.26]\\ 1.69 \ [1.15, 0.46]\\ 1.89 \ [1.15, 0.46]\\ 1.89 \ [1.15, 0.43, 1.26]\\ 0.78 \ [0.32, 1.92$	1999 2002 2009 2009 2010 2010 2012 2013 2013 2014 2015 2016 2016 2016 2017 2018		
Jonway et al Judo et al Jinsal et al (alkenburg et al Ju et al tohkjiddeen et al u et al (ambalachenu et al Jinghasena et al Iinghasena et al Tirmawi et al Tiranayan et al Yan et al	22 3 11 124 3 6 10 35 8 20 5 28 47 31 50 13 46 5	45 6 24 29 144 222 33 49 74 121 111 105 199 222 222	8 22 9 6300 16 17 18 25 6 13 52 70 322 29 47	26 95 23 1412 56 93 36 434 49 78 107 104 114 212 57 265	4.0% 2.0% 3.4% 2.8% 1.3% 3.9% 4.2% 5.2% 3.1% 5.8% 7.1% 6.9% 7.5% 4.7%	$\begin{array}{c} 2.15 \ [0.78, 6.68]\\ 3.32 \ [0.62, 17 \ 622 \\ 1.32 \ [0.41, 4.20]\\ 2.50 \ [0.51, 164]\\ 0.29 \ [0.08, 1.09]\\ 4.00 \ [0.47, 33.77 \\ 0.89 \ [0.31, 2.64]\\ 0.55 \ [0.21, 1.48 \\ 0.55 \ [0.21, 1.48 \\ 0.65 \ [0.25, 2.96]\\ 2.18 \ [1.06, 4.46 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.43, 1.26 \\ 0.73 \ [0.47, 1.15 \\ 0.73 \ [0.77, 1.15 \\ 0.77 \ [0.77, 1.15 \ [0.77, 1.15 \\ 0.77 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 \ [0.77, 1.15 $	1999 2002 2009 2009 2010 2010 2012 2013 2013 2013 2013 2013 2013 2013 2014 2015 2016 2017 2018 2021		
Jonway et al Jonsal et al Aikenburg et al Ju et al Istkenburg et al Ju et al Istolhykiddeen et al Jagat et al Jagat et al Jinghas en a et al Jinghas en a et al Jinghas en a et al Jinghas et al Tranavan et al Van et al Ieira et al	22 3 111 124 3 6 10 35 8 20 5 28 47 31 50 13 46 104 17	45 6 24 29 144 222 33 49 74 121 111 105 199 29 222 223 45	8 22 9 6300 16 17 77 18 25 6 13 52 70 32 29 47 72 29 47 74	26 95 1412 56 93 36 434 49 78 107 104 114 212 57 265 166 48	4.0% 2.0% 3.4% 2.8% 1.3% 7.9% 4.2% 5.2% 3.1% 5.2% 5.2% 6.9% 7.1% 6.9% 7.5% 8.2% 5.0%	$\begin{array}{c} 2.15 \ [0.76, 6.56]\\ 3.32 \ [0.62, 17.62]\\ 1.32 \ [0.41, 4.20]\\ 1.25 \ [0.95, 1.64]\\ 0.29 \ [0.06, 1.09]\\ 1.05 \ [0.47, 33.77]\\ 0.89 \ [0.31, 2.64]\\ 0.87 \ [0.56, 1.34]\\ 0.55 \ [0.21, 1.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.87 \ [0.25, 2.46]\\ 0.75 \ [0.25, 2.46]\\ 0.75 \ [0.25, 2.46]\\ 0.75 \ [0.25, 2.46]\\ 0.75 \ [0.25, 2.46]\\ 0.77 \ [0.25, 2.46]\\ $	1999 2002 2009 2009 2010 2010 2012 2013 2013 2013 2014 2015 2014 2015 2016 2017 2018 2021 2023		
conway et al uido et al linsal et al alikenburg et al liu et al liu et al combalachenu et al laqat et al Yu et al mawi et al hathapudi et al hathapudi et al Yan et al Yan et al Gur et al leira et al	22 3 11 124 3 6 10 35 8 20 5 28 47 31 50 13 50 13 46 104 17	45 6 24 247 29 144 222 33 49 74 1211 105 199 222 223 223 223 5	8 22 9 630 16 16 77 18 25 6 13 52 70 32 29 9 47 74 18	26 95 23 1412 56 93 36 434 49 49 78 107 104 114 212 57 265 166 48	4.0% 2.0% 3.4% 2.8% 1.3% 7.9% 4.2% 3.1% 5.2% 5.2% 6.9% 7.5% 7.8% 8.2% 5.2%	$\begin{array}{c} 2.15 \ [0.76, 6.66] \\ 3.32 \ [0.62, 17.62] \\ 1.32 \ [0.41, 4.20] \\ 1.25 \ [0.96, 1.64] \\ 0.25 \ [0.76, $	1999 2002 2009 2009 2010 2012 2013 2013 2013 2013 2014 2015 2014 2015 2016 2017 2018 2023 2023		
conway et al uduo et al Instail et al alivensumg et al alivensumg et al ue et al ambalachenu et al ambalachenu et al ambalachenu et al ambahapud et al hambapud et a	22 3 11 124 3 6 10 35 8 20 5 28 47 31 50 13 46 104 17 583	45 6 24 247 29 144 222 33 49 74 121 111 105 199 222 223 223 4952	8 22 9 630 16 16 16 77 18 25 6 13 52 70 32 29 47 74 18 1163	26 95 23 1412 56 93 36 434 49 49 78 107 104 212 57 265 166 48 3424	4.0% 2.0% 3.4% 9.1% 2.8% 3.9% 7.9% 5.2% 5.2% 5.2% 5.8% 7.1% 5.8% 7.1% 6.9% 7.5% 4.7% 5.8% 7.5% 4.7% 5.0%	$\begin{array}{c} 2.16 [0.76, 6.96] \\ 3.32 [0.62, 17.62] \\ 3.32 [0.62, 17.62] \\ 3.32 [0.62, 17.62] \\ 3.32 [0.62, 17.62] \\ 3.32 [0.62, 17.62] \\ 3.32 [0.62, 17.62] \\ 3.32 [0.62, 17.62] \\ 4.00 [0.47, 3.377] \\ 0.99 [0.31, 2.54] \\ 0.65 [0.21, 11.46] \\ 0.65 [0.21, 11.4$	1999 2002 2009 2009 2010 2012 2013 2013 2013 2013 2013 2013 2013 2013 2014 2015 2016 2017 2018 2021 2023 2023		
conway et al use of al instal et al instal et al alkenburg et al use tal and t	22 3 11 124 5 6 10 35 8 20 5 28 47 31 50 13 46 104 17 583 0.18; Chi [#]	45 6 24 247 29 144 222 33 49 74 121 111 105 199 222 223 45 1952 = 49.47,	8 22 9 630 16 1 16 77 18 25 52 70 32 29 47 74 18 1163 df = 18 (26 95 23 1412 56 93 36 434 49 78 107 104 114 212 57 265 166 48 3424 P < 0.00	4.0% 2.0% 3.4% 9.1% 2.8% 3.9% 7.9% 5.2% 5.2% 5.2% 5.8% 7.1% 5.8% 7.1% 5.8% 7.5% 4.7% 5.0% 100.0%	$\begin{array}{c} 2.16 \ [0.78, 6.96 \\ 3.32 \ [0.62, 17.62 \\ 1.22 \ [0.41, 4.20 \\ 1.25 \ [0.55, 164 \\ 0.55, 164 \\ 1.25 \ [0.55, 164 \\ 1.25 \ [0.55, 164 \\ 1.25 \ [0.55, 164 \\ 1.25 \ [0.55, 164 \\ 0.55 \ [0.21, 1.46 \\ 0.55 \ [0.21, 1.46 \\ 0.55 \ [0.21, 1.46 \\ 0.55 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.21, 1.46 \\ 0.57 \ [0.22, 1.22 \\ 1.21 \ [0.77, 181 \\ 1.01 \ [0.44, 1.23 \\ 0.59 \ [0.76, 1.29 \\ 0.57 \ [0.56, 1.29 \ [0.56, 1.29 \\ 0.57 \ [0.56, 1.29 \ [0.56, 1.29 \\ 0.57 \ [0.56, 1.29 \ [0$	1998 2002 2009 2009 2010 2010 2012 2013 2013 2013 2013 2014 2014 2016 2017 2018 2021 2023 2023 	0.05	
convayed al uduo et al Instail et al Instail et al Instail et al Use tal Use tal Use tal Use tal Use tal Lochard et al Lochard et	22 3 3 11 124 3 6 10 35 8 20 5 5 28 47 31 50 13 46 104 17 583 0.18; Chi [≢] 2 = 0.07 (P	45 6 24 247 29 144 223 33 49 74 121 105 199 29 222 223 45 1952 = 49.47, 5 = 0.94)	8 22 9 630 16 1 1 16 77 78 25 52 70 32 29 9 47 74 18 1163 df = 18 (26 95 23 1412 56 93 36 434 49 78 104 114 212 57 265 166 48 3424 P < 0.00	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 4.2% 5.2% 3.1% 5.2% 3.1% 5.2% 5.2% 5.0% 4.7% 7.5% 4.7% 7.5% 4.7% 5.0%	$\begin{array}{c} 2,16 [0,76,56]\\ 3,32 [0,62,1762]\\ 1,32 [0,41,420]\\ 1,32 [0,41,420]\\ 1,22 [0,41,420]\\ 0,29 [0,00,100]\\ 4,00 [0,47,3377]\\ 0,99 [0,31,244\\ 0,07 [0,51,136]\\ 0,29 [0,00,13,244\\ 0,07 [0,51,136]\\ 0,12 [0,12,136]\\ 0,1$	1999 2002 2009 2009 2010 2010 2011 2013 2013 2013 2014 2014 2015 2016 2017 2018 2023 2023 	0.05	0.2 Control Favours (control)
conway et al uduo et al Instail et al Instail et al Instail et al ue et al ue et al ambalacheme et al ambalacheme et al ambalacheme et al Immavel at Ambhapudi et al Immavel at Ambhapudi et al Immavel at Immavel at Imma	22 3 11 124 5 6 10 35 8 20 5 28 20 47 31 50 13 46 104 17 583 0.18; Chl [■] z= 0.07 (P	45 6 24 247 29 144 242 223 33 49 9 74 121 111 105 199 29 2223 45 1952 = 49.47, '= 0.94)	8 22 9 6300 16 177 18 25 6 13 52 29 29 47 74 18 1163 df = 18 (26 95 23 1412 93 36 434 49 49 78 107 104 212 7 57 56 5 166 48 3424 P < 0.00	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 4.2% 5.2% 3.1% 5.2% 3.1% 5.2% 5.2% 5.2% 5.0% 100.0%	2.1610.78.630 3.3210.62,17.62 3.3210.41,420 1.2210.41,420 1.2210.41,420 1.2210.41,420 4.00[0.47,337,10,41,120 4.00[0.47,337,10,41,120 0.400[0.47,337,10,41,120 0.400[0.47,337,10,41,120 0.400[0.47,337,10,41,120 0.400[0.47,137,10,41,120 1.210[0.44,42,24] 0.391[0.77,1161 1.091[0.77,1161] 1.091[0.77,1161] 1.091[0.77,1161] 1.091[0.77,1161] 1.091[0.77,1161] 1.091[0.77,1161] 1.091[0.77,1161] 1.091[0.77,1161]	1999 2002 2009 2009 2010 2010 2013 2013 2013 2013 2014 2014 2015 2016 2017 2018 2023 2023 	0.05	0.2 Favours [control] Favours [experimenta]
conway et al uduo et al instai et al alkenburg et al bu et al ambalachene et al anabalachene et al anabalachene et al anabatapud et al instraavan e	22 3 11 12 3 6 10 35 8 20 5 8 20 5 8 20 5 8 20 5 8 20 5 8 31 50 13 46 104 17 7 503 8 0.04 17 7 2 8 47 7 7 2 8 47 7 2 8 47 7 2 8 47 7 8 47 7 8 8 8 47 7 8 9 8 8 9 8 9 8 9 8 9 8 9 8 9 9 9 9	45 6 24 247 29 144 242 223 33 49 74 121 111 105 199 29 2223 45 1952 = 49.47, '= 0.94)	8 22 9 6300 16 18 77 718 25 6 13 52 29 29 47 74 18 1163 df = 18 (26 95 23 1412 93 36 434 49 49 78 107 104 212 7 265 166 48 3424 P < 0.00	4.0% 2.0% 3.4% 9.1% 2.8% 1.3% 7.9% 4.2% 5.2% 3.1% 5.2% 3.1% 5.2% 7.1% 6.9% 7.5% 4.7% 4.7% 4.7% 5.0%	$\begin{array}{c} 2.16 \ (0.76, 6.96)\\ 3.32 \ (0.62, 17.62)\\ 1.25 \ (0.35, 16.46)\\ 1.25 \ (0.35, 16$	1999 2002 2009 2009 2010 2010 2012 2013 2013 2013 2014 2014 2016 2016 2017 2018 2023 2023 	0.05	0.2 Favours [control] Favours [experimental]
convayed al uduo et al Instaid et al Instaid et al Instaid et al Instaid et al Use et al Use et al Lagat et al La	22 3 11 124 3 6 10 35 8 20 5 28 47 7 31 50 104 17 583 0.18; Chi [#] 2 = 0.07 (P	45 6 24 247 29 144 222 33 49 74 121 111 105 5 199 292 223 223 49 222 223 49 29 222 245 1952 = 49.47, 1952	8 22 9 630 16 17 77 18 25 6 13 3 52 70 32 29 9 9 47 74 18 0 47 74 18 0 47 18 0 52 70 0 32 29 9 47 74 18 0 52 70 0 16 6 52 70 0 18 6 52 70 0 18 6 52 70 18 52 70 18 52 70 18 52 70 18 52 70 19 53 77 18 52 70 18 52 70 18 52 70 19 55 77 77 77 77 77 77 77 78 77 77 77 77 77	26 93 1412 56 93 34 49 78 104 104 212 57 265 166 48 3424 P < 0.00	4.0%; 2.0%; 3.4%; 9.1%; 2.8%; 1.3%; 7.9%; 4.2%; 5.2%; 5.8%; 4.7%; 7.1%; 5.0%; 8.2%; 5.0%; 100.0%; 100.0%;	2.1610.78.630 3.3210.62,17.62 1.3220.41,4 20 1.3210.41,4 20 0.2910.061100 4.0010.47,3377 0.9910.31,244 0.0710.56,134 0.0710.56,134 0.0710.56,134 0.0710.57,135 1.0110.44,234 0.9910.77,181 1.05107,142 0.9910.77,181 1.05107,183 0.9910.76,1291 1.05107,183 0.9910.76,1291 1.05107,183 0.9910.76,1291 1.051044,234 0.051044,234 0.001044,234	1999 2002 2009 2010 2010 2012 2013 2013 2013 2014 2014 2014 2014 2014 2015 2016 2017 2018 2023 2023 	0.05	0.2 Favours (control) Favours (experimental)
ionway et al iuduo et al instail et al alkenburg et al bu et al arabalachenu et al arabalachenu et al arabalachenu et al arabalachenu et al inmata al inmata al arabata al ara	22 3 11 124 3 6 5 5 8 8 0 0 0 5 5 8 8 8 8 8 8 8 8 8 8 8	45 6 24 247 29 144 222 33 49 74 121 111 111 105 222 223 45 1952 = 49.47, = 0.94) asses Total	8 29 630 16 77 18 25 52 29 47 74 18 1163 dr = 18 (Contro Events	26 95 92 1412 56 93 36 49 93 36 49 78 107 104 104 114 212 265 57 265 48 3424 P < 0.00 NS Total	4.0%; 2.0%; 9.1%; 9.1%; 1.3%; 3.9%; 4.2%; 5.2%; 5.2%; 5.2%; 5.2%; 5.2%; 5.2%; 5.2%; 5.2%; 5.2%; 5.2%; 5.2%; 5.0%; 100.	2.1610.78.630 3.3210.63,17.62 1.3210.81,47.62 1.3200.81,60 4.0010.47,3377 0.8910.31,2.64 0.6710.56,134 0.6710.56,134 0.6710.25,134 0.6710.25,134 0.6710.25,134 0.6710.25,134 0.7310.43,123 0.2610.15,0.46 1.5911.53 0.2610.15,0.46 1.5911.53 0.2610.15,0.46 1.5911.53 0.2610.15,0.46 1.5911.53 0.2610.15,0.46 1.5911.53 0.2610.15,0.46 1.5911.53 0.2610.15,0.46 1.5910.77,1591 0.9107.15,132 0.910.77,1591 0.9107.15,132 0.910.77,1591 0.9107.15,132 0.910.75,1	2002 2009 2009 2010 2010 2010 2012 2013 2013 2013 2013	0.05	0 ¹ / ₂ Favours [control] Favours [experimental] ²⁰ Odds Ratio M-H, Random, 95% Cl
convayet al uduo et al insaiet al insaiet al insaiet al uo et al ingana et al i	22 311 124 5 8 200 5 28 47 31 50 135 5 28 47 31 104 17 2 8 200 5 28 47 31 104 17 2 8 200 5 28 47 31 1 50 20 13 5 5 28 47 31 1 5 5 28 20 5 5 2 5 28 20 5 5 2 8 2 5 5 2 8 2 5 5 5 2 8 2 5 5 5 2 8 2 5 5 5 2 8 5 2 5 5 5 2 8 2 5 5 5 2 8 5 5 5 5	45 6 24 247 29 144 224 33 49 74 121 111 105 199 222 223 45 1952 = 49.47, = 0.94) asses Total 186	8 22 9 630 16 77 18 25 52 70 32 29 47 74 18 1163 df = 18 (Contro Events 41	26 95 23 1412 56 59 33 36 434 49 78 78 49 78 78 107 104 107 104 107 265 166 6 48 3424 ₽ × 0.000	4.0%; 2.0%; 3.4%; 9.1%; 2.8%; 1.3%; 2.8%; 1.3%; 5.2%; 5.2%; 5.3%; 7.9%; 7.1%; 8.9%; 7.1%; 8.9%; 7.7%; 7.8%; 8.2%; 100.0%; 100.0%; 100.0%; 100.0%; 101; 1° = 6; Weight 3.7%;	2.1610.78.650 3.3210.62,17.62 1.3210.41,4 20 1.3210.41,4 20 1.3210.41,4 20 0.2910.008,100 4.0010.47,3377 0.6910.31,244 0.6710.55,1204 0.6710.55,1204 0.6610.30,147 0.6710.55,1204 0.6610.30,147 0.6710.55,1204 0.6610.30,147 0.6710.55,1204 0.6910.77,161 1.6110.04,4234 0.9910.76,1291 1.0110.44,234 0.9910.76,1291 1.0110.44,234 0.9910.76,1291 1.0110.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910.76,1291 1.1010.44,234 0.9910	1 1999 1 2002 2 2009 2 2009 2 2010 2 2012 2 2013 2 2013 2 2013 2 2013 2 2013 2 2013 2 2013 2 2014 2 2016 2 2017 2 2018 2 2023 2 2023 2	0.05	el.2 Favours [control] Favours [experimental] 20 Odds Ratio M-H, Random, 95% Cl
convayed al used of al Instal et al Instal et al Instal et al Instal et al Instal et al Instal et al Insta	22 3 11 124 3 6 10 35 8 20 5 28 47 31 50 5 28 47 31 50 13 46 104 17 5 8 30.18; Chi ^p 2 = 0.07 (P PCOS Cd Events 92 18	45 6 6 24 247 29 144 222 33 49 42 42 223 349 929 229 223 45 1952 = 49.47, = 0.94) 1952 223 223 223 223 223 223 223 2	8 22 9 6300 16 1 18 25 6 13 52 70 32 29 47 74 18 1163 df = 18 (Contro Events 41 117	266 95 233 1412 56 93 36 434 49 49 49 49 49 78 107 107 107 107 107 57 57 57 57 57 48 3424 P < 0.00 b 5 56 93 36 434 49 49 59 50 56 93 60 57 56 93 60 56 56 93 60 57 56 93 60 56 93 60 57 56 93 60 57 56 93 60 57 56 93 60 57 56 93 60 57 56 93 60 57 56 93 60 57 56 93 60 57 56 93 60 57 56 93 60 78 97 78 78 107 122 56 57 78 78 107 122 56 57 78 107 122 56 57 78 107 122 56 57 78 107 122 56 57 78 107 122 125 107 107 107 107 107 107 107 107 107 107	4.0%; 2.0%; 3.4%; 9.1%; 1.3%; 3.9%; 7.9%; 4.2%; 5.8%; 7.1%; 5.8%; 7.1%; 5.8%; 7.1%; 6.9%; 7.1%; 5.8%; 7.1%; 5.8%; 7.1%; 5.8%; 7.1%; 5.8%; 7.1%; 5.8%; 7.1%; 5.8%; 7.9%; 4.2%; 5.8%; 7.1%; 5.8%; 7.9%; 4.2%; 5.8%; 7.1%; 5.8%; 7.9%; 4.2%; 5.8%; 7.9%; 5.2%;	2.1610.78.630 3.3210.62,17.62 3.3210.41,420 1.2210.41,420 0.2210.01,01 0.2210.00,1100 4.0010.47,3377 0.9910.31,254 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.710.51,120 2.1011.06,440 0.7310.43,120 1.210.07,1131 1.0910.73,153 1.0110.44,234 0.9910.76,1291 0.9910.76,1291 1.2100.77,1131 1.0910.73,153 1.0110.44,234 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1291 0.442,244 0.9910.76,1292 0.442,244 0.9910.44,23	1 1999 2002 2009 2010 2010 2010 2010 2010	0.05	0.2 Favours [control] Favours [experimental] Odds Ratio M-H, Random, 95% Cl
conway et al uduo et al instail et al alixenburg et al bu et al u et al arabilatcheru et al arabilatcheru et al arabilatcheru et al arabitaptione et al imme et al hathapud et al hathapud et al hathapud et al conversione dellorgementi; Ture = 1 est for overall effect 2 conversione test of overall effect 2 conversione conve	22 3 11 124 3 6 0 35 8 20 5 28 20 5 28 20 5 28 20 3 3 13 46 5 5 20 5 20 5 20 5 20 5 5 20 5 5 20 5 5 20 5 5 20 5 5 5 20 5 5 5 20 5 5 5 20 5 5 5 20 5 5 5 20 5 5 5 20 5 5 5 5	46 6 6 24 247 29 144 222 33 349 9 29 223 45 1952 223 45 1952 223 45 1952 223 45 1952 223 45 1952 223 45 1952 223 45 1952 223 45 1952 1952 1953 1952 203 45 1952 1953 1953 1953 1953 1953 1953 1953 1953	e e 22 22 e 22 630 16 16 17 18 25 18 25 29 29 29 29 29 29 47 74 18 1163 32 47 70 07 70 07 70 07 70 47 1163 32 41 117 117 45	26 95 23 1412 56 93 36 49 49 49 49 49 49 49 49 49 49 49 49 49	4.0% 2.0% 2.0% 3.4% 9.1% 2.8% 1.3% 3.9% 7.9% 4.2% 5.2% 5.2% 7.9% 4.2% 5.2% 5.2% 5.6% 7.5% 4.7% 5.0% 100.0% 100.0% 01); * = 6 Weight 3.7% 2.3% 3.1% 5.2% 5.0% 5.0% 5.2% 5.0% 5.2% 5.0% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2	2.1610.78.630 3.3210.63,17.62 1.3210.81,47.62 1.3210.81,47.80 1.3210.81,47.80 4.0010.47,337 0.8910.31,2.54 0.6710.56,134 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.6510.21,140 0.7310.32,122 1.2101.63,440 0.7310.32,122 1.2101.73,163 1.0010.44,234 0.046 Ratio M.H. Random,95% C 1.46[0.89,237 1.48710.94,123 1.1010.44,240 1.46[0.89,237 1.48710.94,137 1.48710.94,373 1.49710.943,132 1.49710.9451,132 1.49710.9451,132 1.49710.9451,132 1.49710.9451,132 1.49710.9451,132 1.49710.9451,132 1.49710.9451,132 1.49710.9451,132 1.49710.9451,135 1.49710	1 1999 2002 2009 2010 2010 2010 2010 2010	0.05	0,2 Favours [control] Favours [experimenta] 20 Odds Ratio M-H, Random, 95% C1
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Fig. 3 The association between FSHR (rs6166) variant and risk of PCOS using different genetic models in overall analysis: a Dominant model (GG+AG vs AA), **b** Recessive model (GG vs AG+AA), **c** Additive model (GG vs AA), **d** Allele model (G vs A). In each model, solid squares represent the OR and horizontal lines represent 95%Cl and diamond represents the pooled OR and 95%Cl

a)

	PCOS C	ases	Contro	ols		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
1.1.1 Asian Studies								
Tong et al	15	124	24	236	4.7%	1.22 [0.61, 2.41]	2001	•
Sudo et al	3	18	22	168	1.1%	1.33 [0.36, 4.96]	2002	
Unsaletal	9	44	9	50	2.2%	1.17 [0.42, 3.28]	2009	
Duetal	9	55	15	92	3.0%	1.00 [0.41, 2.48]	2010	
Guetal	38	235	22	128	7.7%	0.93 [0.52, 1.65]	2010	
Fuetal	36	384	77	768	15.0%	0.93 [0.61, 1.41]	2013	
Liaqat et al	22	96	25	96	6.2%	0.84 [0.44, 1.63]	2013	
Singhasena et al	10	133	6	132	1.8%	1.71 [0.60, 4.84]	2014	
Wu et al	27	215	14	205	4.0%	1.96 [1.00, 3.85]	2014	
Kim et al	56	377	31	388	8.4%	2.01 [1.26, 3.20]	2017	
Branavan et al	13	55	29	110	4.8%	0.86 [0.41, 1.84]	2018	
Wan et al	50	400	48	480	12.3%	1.29 [0.84, 1.96]	2021	
Subtotal (95% CI)		2136		2853	71.2%	1.22 [1.02, 1.46]		◆
Total events	288		322					
Heterogeneity: Chi ² =	11.50, df=	= 11 (P =	= 0.40); l²	= 4 %				
Test for overall effect:	Z = 2.20 (P = 0.03)					
4.4.2 Indian Study								
1.1.2 Indian Study								
Kaur et al	153	421	100	322	23.2%	1.27 [0.93, 1.73]	2023	
Subtotal (95% CI)		421		322	23.2%	1.27 [0.93, 1.73]		
lotal events	153		100					
Heterogeneity: Not ap	opiicable							
Test for overall effect:	2 = 1.51 (P = 0.13	9					
1.1.3 Other studies								
Conway et al	24	93	18	51	5.6%	0.64 (0.30, 1.33)	1999	
Subtotal (95% CI)		93		51	5.6%	0.64 [0.30, 1.33]		
Total events	24		18					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z=1.19 (P = 0.23	0					
Total (95% CI)		2650		3226	100.0%	1.20 [1.03, 1.39]		◆
Total events	465		440					
Heterogeneity: Chi² =	14.45, df=	= 13 (P =	= 0.34); I ^z	= 10%				
Test for overall effect:	Z = 2.36 (P = 0.02)					Eavours [control] Eavours [experimental]
Test for subgroup dif	ferences: (Chi² = 2.	97. df = 2	P = 0	.23), I ² = 0	32.6%		r avouro (control) - r avouro (experimental)

b)

	PCOS C	ases	Contro	ols		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% CI
1.1.1 Asian Studies								
Tong et al	15	68	24	126	5.3%	1.20 [0.58, 2.48]	2001	-
Sudo et al	3	6	22	95	0.5%	3.32 [0.62, 17.62]	2002	
Unsal et al	9	25	9	25	2.3%	1.00 [0.32, 3.17]	2009	
Du et al	9	35	15	55	3.5%	0.92 [0.35, 2.42]	2010	
Gu et al	38	119	22	72	7.6%	1.07 [0.57, 2.01]	2010	
Fuetal	36	228	77	439	18.1%	0.88 [0.57, 1.36]	2013	
Liaqat et al	22	49	25	47	5.7%	0.72 [0.32, 1.60]	2013	
Singhasena et al	10	80	6	76	2.2%	1.67 [0.57, 4.83]	2014	
Wu et al	27	120	14	105	4.7%	1.89 [0.93, 3.83]	2014	+
Kim et al	56	201	31	212	8.9%	2.25 [1.38, 3.68]	2017	
Branavan et al	13	29	29	57	4.4%	0.78 [0.32, 1.92]	2018	
Wan et al	50	225	48	258	14.2%	1.25 [0.80, 1.95]	2021	
Subtotal (95% CI)		1185		1567	77.5%	1.23 [1.02, 1.49]		◆
Total events	288		322					
Heterogeneity: Chi² =	14.60, df=	= 11 (P =	= 0.20); l ²	= 25%				
Test for overall effect:	Z=2.17 (P = 0.03)					
4.4.2 Indian Study								
1.1.2 indian Study								
Kaur et al	153	246	100	176	18.0%	1.25 [0.84, 1.85]	2023	
Subtotal (95% CI)	450	240	400	170	10.0%	1.20 [0.04, 1.00]		
lotal events	153		100					
Heterogeneity: Not ap	plicable	0 - 0 07						
Test for overall effect.	Z=1.11 (P = 0.27)					
1.1.3 Other studies								
Conway et al	24	46	18	26	4.5%	0.48/0.18/1.341	1999	
Subtotal (95% CI)	24	46		26	4.5%	0.48 [0.18, 1.34]	1000	
Total events	24		18					
Heterogeneity: Not ar	nnlicable							
Test for overall effect:	Z = 1.40 (P = 0.16	6					
			, 					
Total (95% CI)		1477		1769	100.0%	1.20 [1.02, 1.42]		◆
Total events	465		440					
Heterogeneity: Chi ² =	17.78, df=	= 13 (P =	= 0.17); l ²	= 27%				
Test for overall effect:	Z = 2.15 (P = 0.03)					Eavours [control] Eavours [experimental]
Test for subaroup dif	ferences: (Chi ² = 3.	19. df = 2	? (P = 0	20), I² = 3	37.3%		avours [control] 1 avours [experimental]

Fig. 4 The association between *FSHR* (rs6165) and PCOS progression using different genetic models in Sub-group analysis: **a** Recessive model (GG vs AG + AA), **b** Additive model (GG vs AA). In each model, solid squares represent the OR and horizontal lines represent 95%Cl and diamond represents the pooled OR and 95%Cl

Sub-group analysis (rs6166)

Study or Subgroup	PCOS Ca Events	ises Total	Contro Events	s Total	Weight I	Odds Ratio I-H, Fixed, 95% Cl	Year	Odds Ratio M-H, Fixed, 95% Cl
Sudo et al Unsal et al	3 11	18 44	22 9	168 50	0.7%	1.33 [0.36, 4.96] 1.52 [0.56, 4.10]	2002	
Du et al Gu et al	3	55 235	16 1	90 128	2.1%	0.27 [0.07, 0.96] 3.33 [0.40, 27.95]	2010	
Fuetal Liaqatetal	35 20	384	25	768	8.7%	0.90 [0.69, 1.37] 0.75 [0.38, 1.46]	2013	
Singhasena et al Almawi et al	28 47	133 215 203	13 52	205 211	2.2%	0.02 [0.24, 2.76] 2.21 [1.11, 4.40] 0.92 [0.59, 1.45]	2014 2014 2015	
Kim et al Branavan et al	50 13	377	32 29	388 110	5.1% 2.8%	1.70 [1.06, 2.72]	2017 2018	
Wan et al Subtotal (95% CI)	46	400 2215	47	480 2826	7.1% 42.1%	1.20 [0.78, 1.84] 1.11 [0.92, 1.32]	2021	+
Heterogeneity: Chi ^a =	267 16.99, df= 7 = 1.10 /P	11 (P = 0 = 0.27)	329 0.11); I⁼=	35%				
5.1.2 Indian Studies	L= 1.10 (P	- 0.27)						
Kambalachenu et al Thathapudi et al	8 31	97 204	18 70	101 204	3.0% 11.1%	0.41 [0.17, 1.00] 0.34 [0.21, 0.55]	2013 2016	
Kaur et al Subtotal (95% CI)	104	421 722	74	322 627	11.8% 25.9%	1.10 [0.78, 1.55] 0.70 [0.54, 0.90]	2023	◆
Heterogeneity: Chi ² = Test for overall effect	143 16.59, df = Z = 2.76 (P	2 (P = 0.) = 0.006)	162 0002); I≅:	= 88%				
5.1.3 Other Studies	2-2.100	- 0.000)						
Conway et al Valkenburg et al	22 124	93 495	8 630	51 2912	1.5%	1.67 [0.68, 4.07] 1.21 [0.97, 1.51]	1999	
Vieira et al Subtotal (95% CI)	10	88 734	18	80 3126	2.8% 32.0%	0.87 [0.36, 2.09] 0.82 [0.39, 1.74] 1.18 [0.96, 1.44]	2012	
Total events Heterogeneity: Chi ² =	173 1.97, df = 3	(P = 0.5	672 8); I ² = 09	6				-
Test for overall effect:	Z = 1.58 (P	= 0.11)						
Total (95% CI) Total events	583 45 70 df -	3671	1163	6579 K= 61 °	100.0%	1.02 [0.91, 1.15]	L	, † ,
Test for overall effect. Test for subgroup diffe	43.70, df = Z = 0.36 (P erences: Cl	+ o (r = 0 = 0.72) hi≇ = 11.1		- 61%	004), I ^a = 8	2.1%	b	05 0.2 1 5 20 Favours [control] Favours [experimental]
b)								
U)								
Study or Subgroup	PCOS C Events	ases Total	Contro Events	ols Total	Weight	Odds Ratio M-H, Fixed, 95% C	<u>Year</u>	Odds Ratio M-H, Fixed, 95% Cl
5.1.1 Asian Studies Sudo et al	3	6	22	95	0.3%	3.32 [0.62. 17 67	2002	
Unsal et al Du et al	11	24	-9 16	23	1.2%	1.32 [0.41, 4.20	1 2009	
Guetal	6	144	1	93	0.3%	4.00 [0.47, 33.77	2010	
Liaqatetal	20	49	25	434	3.6%	0.67 [0.56, 1.34	2013	_
v∜u et al Singhasena et al	5 28	74 121	6 13	78 107	1.3% 2.6%	0.87 [0.25, 2.98 2.18 [1.06, 4.46] 2014 j] 2014	
Almawi et al Kim et al	47	111 199	52 32	104 212	7.5% 5.6%	0.73 [0.43, 1.26	2015	++
Branavan et al Wan et al	13	29	29	57	2.6%	0.78 [0.32, 1.92	1 2018	
Subtotal (95% CI)	40	1230		1573	46.4%	1.10 [0.91, 1.34	1 2021	+
Heterogeneity: Chi ² =	20.86, df=	11 (P =	329 1.03); I⁼:	= 47%				
Test for overall effect:	Z= 0.97 (F	'= 0.33)						
5.1.2 Indian Studies Kambalachenu et al	8	33	18	49	2.7%	0.55 [0.21, 1.48	3 2013	
Thathapudi et al Kaur et al	31 104	105 223	70 74	114 166	11.5% 11.0%	0.26 [0.15, 0.46	2016	
Subtotal (95% CI)	142	361	162	329	25.2%	0.65 [0.48, 0.89	i	◆
Heterogeneity: Chi ² =	16.19, df =	2 (P = 0	.0003); F	'= 88%				
E 4 3 Othor Studios	Z = 2.75 (F	- 0.000	9					
Conway et al	22	45	8	26	1.3%	2.15 [0.78, 5.95] 1999	+
Valkenburg et al Mohiyiddeen et al	124 10	247 24	630 16	1412 36	22.7% 1.8%	1.25 [0.95, 1.64 0.89 [0.31, 2.54] 2009] 2012	
Vieira et al Subtotal (95% CI)	17	45 361	18	48 1522	2.6% 28.4%	1.01 [0.44, 2.34 1.25 [0.98, 1.59	2023	◆
Total events Heterogeneity: Chi² =	173 1.74, df = 3	3 (P = 0 F	672 63); I⁼ = ∩	196				
Test for overall effect:	Z=1.78 (F) = 0.07)		-				
Total (95% CI)		1952		3424	100.0%	1.03 [0.90, 1.18	1	+
Heterogeneity Chi ² -	58.4		1163					1
Test for overall effect	49.47, df =	18 (P <	1163 0.0001);	I ² = 64	%			0.05 0.2 1 5 2
Test for overall effect: Test for subgroup diff	583 49.47, df = Z = 0.43 (F erences: C	:18 (P ≺ ? = 0.67) :hi² = 11.	1163 0.0001); 47, df= :	$I^2 = 64'$ 2 (P = 0	% .003), I² =	82.6%		0.05 0.2 1 5 Favours [control] Favours [experimental]
Test for overall effect: Test for subgroup diff	583 49.47, df = Z = 0.43 (F erences: C	:18 (P ≺ P = 0.67) :hi² = 11.	1163 0.0001); 47, df= :	I ² = 64 2 (P = 0	% .003), I¤=	82.6%		0.05 0.2 5 Favours [control] Favours [experimental]
Test for overall effect. Test for subgroup diff C)	583 49.47, df = Z = 0.43 (F erences: C PCOS Ca Events	: 18 (P < P = 0.67) chi ² = 11.	1163 0.0001); 47, df = 3 Contro Events	I ² = 64' 2 (P = 0 Is Total	% .003), I ² =	82.6% Odds Ratio M-H. Fixed 95% Cl	Year	0.05 0.2 5 2 5 2 5 2 5 5 2 5 5 2 5 5 5 5 5 5 5
Test for overall effect. Test for subgroup diff C) Study or Subgroup 5.1.1 Asian Studies Sudo et al	583 49.47, df = Z = 0.43 (F erences: C PCOS Ca Events	: 18 (P ≺ P = 0.67) chi² = 11. ises <u>Total</u>	1163 0.0001); .47. df = : Contro Events	I ² = 64 ¹ 2 (P = 0 Is <u>Total</u> 336	% .003), I ² = <u>Weight</u> 0.6%	82.6% Odds Ratio M-H, Fixed, 95% CI	Year	0.05 0.2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5
Test for overall effect: Test for subgroup diff C) <u>Study or Subgroup</u> 5.1.1 Asian Studies Sudo et al Unsal et al Du et al	583 49.47, df= Z = 0.43 (F erences: C PCOS Ca Events 18 42 32	:18 (P ≺ >= 0.67) :hi ² = 11. ises <u>Total</u> 36 88 110	1163 0.0001); 47. df = 3 Contro <u>Events</u> 117 45 88	I ² = 64' 2 (P = 0 Is Total 336 180	% .003), I ² = <u>Weight</u> 0.6% 1.2% 1.9%	82.6% Odds Ratio M-H, Fixed, 95% CI 1.87 [0.94, 3.73] 1.12 [0.63, 1.98] 0.71 [0.43, 1.49]	Year 2002 2009 2010	0.05 0.2 5 2 5 2 5 2 5 2 5 5 2 5 5 2 5 5 2 5
Test for overall effect: Test for subgroup diff C) Study or Subgroup 5.1.1 Asian Studies Sudo et al Unsal et al Ou et al Fu et al	983 49.47, df= Z = 0.43 (F erences: C PCOS Ca Events 18 42 32 103 232	:18 (P < P = 0.67) chi [≠] = 11. Ises <u>Total 1</u> 36 88 110 470 768	1163 0.0001); .47. df = : Contro Events 117 45 66 37 488	I ² = 64 2 (P = 0 Is Total 336 100 180 256 1536	% .003), I [≠] = <u>Weight</u> 0.6% 1.2% 1.9% 2.0% 12.1%	Odds Ratio M-H, Fixed, 95% CI 1.87 (0.94, 3.73) 1.12 (0.63, 1.98) 0.71 (0.43, 1.18) 1.66 (1.10, 2.51) 0.93 (0.77, 1.12)	Year 2002 2009 2010 2010 2010	0.05 0.2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5
Test for overall effect Test for subgroup diff C) <u>Study or Subgroup</u> 5.1.1 Asian Studies Sudo et al Unsal et al Du et al Ou et al Evagat et al Wu et al	583 49.47, df = Z = 0.43 (F erences: C PCOS Ca Events 18 42 32 103 232 87 69	= 18 (P < P = 0.67) = 11. =	1163 0.0001); 47, df = : Contro Events 117 45 66 37 488 97 66	I ² = 64 ¹ 2 (P = 0 is <u>Total</u> 336 100 180 256 1536 1536 192 264	Weight 0.003), I [≠] = 0.6% 1.2% 2.0% 12.1% 2.8%	Odds Ratio M-H, Fixed, 95% CI 1.87 (0.94, 3.73) 1.12 (0.63, 1.98) 0.71 (0.43, 1.18) 1.66 (1.10, 2.51) 0.93 (0.77, 1.12) 0.81 (0.54, 1.21) 1.05 (0.71, 1.15%)	Year 2002 2009 2010 2010 2013 2013 2014	0.05 0.2 Favours [control] Favours [experimental] Odds Ratio M.H. Fixed, 95% CI
Test for overall effect. Test for subgroup diff C) Study or Subgroup. 5-1.1 Asian Studies Sudo et al Unsal et al Du et al Gu et al Fu et al Lingat al Singhasena et al Almavi et al	583 49.47, df = Z = 0.43 (F erences: C PCOS Ca Events 18 42 32 32 32 32 32 37 69 150 186	= 18 (P < = 0.67) hi ² = 11. ases Total 36 88 110 470 768 266 430 406	1163 0.0001); 47, df = : Contro Events 117 45 66 37 488 97 97 66 124 211	I ² = 64 ⁴ 2 (P = 0 100 180 256 1536 192 264 410 422	% .003), I* = 0.6% 1.2% 2.0% 12.1% 2.8% 4.4%	Odds Ratio M-H, Fixed, 95% CI 1.87 (0.94, 3.73) 1.12 (0.63, 1.98) 0.71 (0.43, 1.98) 0.71 (0.43, 1.91) 0.80 (0.74, 1.21) 0.81 (0.74, 1.21) 1.05 (0.71, 1.55) 1.24 (0.93, 1.65) 0.85 (0.84, 1.11)	Year 2002 2010 2010 2013 2013 2014 2014 2014	0.05 0.2 Favours [control] Favours [experimental] Odds Ratio M-H, Fixed, 95% CI
Test for overall effect. Test for subgroup diff C) S.1.4 Asian Studies Sudo et al Unsal et al Ou et al Linqui et al Singhasena et al Almawi et al Binghasena et al Almawi et al	583 49.47, df = Z = 0.43 (F erences: C PCOS Ca Events 18 42 32 103 2322 87 69 150 186 278 52	18 (P ≤ = 0.67) chi [≠] = 11. sees Total 1 36 88 110 470 768 192 266 430 406 754 111	1163 0.0001); 47. df = : Contro Events 117 45 66 37 488 97 66 124 211 240 111	I ^P = 64 ¹ 2 (P = 0 15 100 180 256 1536 192 264 410 422 776 220	% 0003), I ^a = 0.6% 1.2% 1.2% 2.0% 2.6% 4.4% 6.0% 8.0% 2.1%	Odds Ratio MH, Fixed, 95% CI 1.87 (0.94, 3, 73) 1.12 (0.63, 1.98) 0.71 (0.43, 1.18) 0.66 (1.10, 2.51) 0.63 (0.77, 1.12) 0.90 (0.77, 1.22) 0.90 (0.74, 1.21) 0.90 (0.64, 1.11) 1.30 (1.05, 1.61) 0.85 (0.64, 1.51)	Year 2002 2009 2010 2010 2013 2013 2013 2014 2014 2015 2017 2018	0.05 0.2 Favours [control] Favours [experimental] Odds Ratio M-H, Fixed, 95% CI
Test for overall effect. Test for subgroup diff C Study or Subgroup 5.1.1 Asian Studies bornal et al Ou et al Ou et al Fu et al Singhasena et al Almawi et al Branavan al Branavan al Branavan al	583 49,47, df = Z = 0.43 (F erences: C PCO\$ Ca Events 18 42 32 103 232 232 87 69 160 186 278 52 270	18 (P ≤ = 0.67) chi [≠] = 11. 1585 Total 1 36 88 110 470 768 192 266 430 406 754 110 800 4430	1163 0.0001); 47, df = : Contro Events 117 45 66 37 488 97 66 124 211 240 111 309	I ² = 64' 2 (P = 0 15 100 180 256 1536 1536 1536 1536 1536 1536 192 264 410 4222 776 220 96052	& Weight 0.6% 1.2% 1.2% 2.0% 2.0% 2.0% 2.8% 2.6% 4.6% 6.0% 8.0% 8.0% 5.1% 9.9% 5.3.7%	Cdds Ratio MH, Fixed, 95% CI 1.87 (0.94, 3.73) 1.12 (0.63, 160) 0.71 (0.43, 1.18) 1.03 (0.74, 1.14) 0.81 (0.54, 1.21) 0.81 (0.54, 1.21) 1.05 (0.74, 1.52) 0.81 (0.54, 1.21) 1.24 (0.93, 1.85) 0.65 (0.64, 1.11) 1.30 (1.06, 1.81) 0.07 (0.56, 1.81) 0.07 (0.56, 1.81) 0.07 (0.56, 1.81) 0.07 (0.56, 1.81)	Year 2002 2009 2010 2013 2013 2014 2015 2014 2016 2017 2018 2021	0.05 0.2 5 Favours [control] Favours [experimental]
Test for overall effect. Test for subgroup diff C Study or Subgroup 5.1.1 Asian Studies Sude et al Du et al Use et al Eve et al Eve et al Singha sena et al Airmavi et al Vian et al Branavan et al Vian et al Branavan et al Heterogenehy: Chi# =	583 49,47, df = Z = 0.43 (f erences: C PCO\$ Cc Events 18 42 32 103 232 87 69 150 186 278 270 1519 21.22, df =	18 (P < P = 0.67) hi ² = 11. 36 88 10 470 768 192 266 430 406 754 110 4430 11 (P = 0	1163 0.0001); 47. df = 1 Contro Events 117 45 66 124 211 240 111 309 1911 .03); ^p =	I ² = 64' 2 (P = 0 15 1536 1536 1536 1536 1536 256 264 412 2776 220 5652 48%	% .003), I [≠] = 0.6% 1.2% 1.2% 2.0% 12.1% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2.1% 9.9% 53.7%	Odds Ratio MH, Fixed, 95% CI 1.97 (0.94, 3.73) 0.71 (0.43, 1.94) 0.71 (0.45, 1.19) 0.93 (0.77, 1.12) 0.81 (0.54, 1.21) 1.26 (0.27, 1.12) 1.30 (1.05, 1.81) 1.30 (0.56, 1.39) 1.30 (0.56, 1.39) 1.07 (0.89, 1.51)	Year 2002 2009 2010 2010 2013 2013 2014 2014 2014 2015 2017 2018 2021	0.05 0.2 Favours [control] Favours [experimental] Odds Ratio M-H, Fixed, 85% CI
Test for overall effect. Test for subgroup diff C) Study or Subgroup 5.1.1 Asian Studies Stude et al Unsal et al Ou et al Fu et al Liagat et al Wu et al Finanaena et al Kim et al Branavan et al Wan et al Subdotal (6% C) Total events Hotal Chiffer C.	233 249.47, df 27=0.43 (F erences: C PCOS Ca Events 18 42 32 103 232 87 69 150 186 278 272 150 186 278 272 150 189 127 127 127 127 127 127 127 127	18 (P ≤ P = 0.67) hi ² = 11. 1505 Total 1 36 88 110 4700 4708 768 430 406 754 110 800 4430 11 (P = 0 = 0.19)	1163 0.0001); 47, df = : Contro Events 117 45 66 66 124 211 240 111 309 1911 03); ⊨ =	I ² = 64' 2 (P = 0 Is Total 336 100 180 256 1536 1536 1536 192 264 410 422 276 220 960 5652 48%	% .003), I [#] = 0.6% 1.2% 1.2% 2.0% 2.6% 4.4% 6.0% 8.0% 8.0% 53.7%	Odds Ratio MH, Fixed, 95% C1 137 (0.94, 3.73) 1.12 (0.63, 198) 0.71 (0.43, 118) 0.68 (1.07, 261) 0.68 (1.07, 261) 0.68 (1.07, 261) 0.68 (0.64, 111) 1.05 (0.77, 1.55) 1.24 (0.93, 185) 1.24 (0.93, 185) 1.26 (0.93, 185) 1.26 (0.97, 1.15)	Year 2002 2009 2010 2013 2013 2014 2014 2014 2016 2017 2018 2021	0.05 0.2 Favours [control] Favours [experimental] Odds Ratio M.H. Fixed, 95% CI
Testfor overall effect Test for subgroup diffect Test for subgroup diffect C Stat Asian Studies Sudo et al Unsal et al Do ut al Fu et al Liagat et al Wu et al Binghasena et al Afmavi et al Binghasena et al Wu et al Tearavan et al Wu et al Franavan et al Wan et al Heterogeneity. Ch" = Test for overall effect : 5.1.2 Indian Studies	49.47, df Z = 0.43 (F erences: C PCOS Cc Events 18 42 32 103 232 87 69 150 186 278 5278 5270 1501 24.270 1501 24.270 1501 2578 5278 5278 5278 5278 5278 5278 5278	: 18 (P < P = 0.67) hi ² = 11. asos <u>Total </u> 36 88 110 768 88 110 768 80 406 754 192 266 430 406 754 192 266 430 406 754 192 266 430 406 719 192 206 100 112 206 112 114 114 110 114 110 114 110 114 110 114 110 114 110 114 110 114 110 114 110 114 114	1163 0.0001); 47, df = : Contro Events 117 488 97 66 124 210 240 111 309 1911 .03); I ^p =	I ^P = 64 ⁴ 2 (P = 0 4s Total 336 100 180 256 1536 1536 1536 1536 264 410 264 410 5652 48% 202	% .003), I [#] = 0.6% 1.2% 1.9% 2.0% 2.6% 4.4% 6.0% 8.0% 53.7%	02.6% Odds Ratio M.H. Fixed, 95% CI 1.37 (0.94, 3.73) 1.12 (0.83, 1.98) 0.71 (0.43, 1.18) 0.38 (0.75, 1.12) 0.49 (0.71, 1.25) 1.24 (0.93, 165) 1.24 (0.93, 165) 0.36 (0.65, 1.39) 1.36 (0.97, 1.15) 0.91 (0.61, 1.35)	Year 2002 2009 2010 2013 2013 2014 2014 2017 2018 2021 2013	0.05 0.2 Favours [control] Favours [experimental] Odds Ratio M-H, Fixed, 95% CI
Test for overall effect. Test for subgroup C) Study or Subgroup S.1.4 Asian Studies Sudo et al Unsal et al Due et al Linque et al Airmavi et al Singhasena et al Airmavi et al Subtotal (69% C)] Total events Heart overall effect. S.1.2 Indian Studies for overall effect.	983 49.47, df 2 = 0.43 (F erences: C PCOS Cc Events 18 42 32 32 32 32 87 69 150 186 278 52 270 1519 21.22, df z = 1.32 (P 80 161 406	18 (P < = 0.67) hi ² = 11. 36 88 110 768 400 406 754 110 266 430 4430 11 (P = 0 = 0.19) 194 408 842	1163 0.0001); 47, df = : Contro Events 117 488 97 66 37 488 97 66 124 211 240 111 110 1911 .03); ⊨ = 88 230 304	2 (P = 0 336 100 1536 192 264 410 422 264 410 5652 264 48% 202 48%	x .003), I ² = 0.6% 1.2% 1.2% 2.0% 12.1% 2.8% 2.0% 4.4% 6.0% 2.1% 9.9% 53.7%	82.6% Odds Ratio M.H, Fixed, 95% CI 1.67 (0.94, 2.73) 1.12 (0.84, 2.73) 1.12 (0.84, 2.16) 0.71 (0.43, 1.18) 0.66 (1.10, 2.61) 0.63 (0.74, 1.21) 1.04 (0.74, 1.66, 1.39) 1.07 (0.88, 1.31) 1.06 (0.97, 1.15) 0.69 (0.64, 1.14) 0.91 (0.61, 1.35) 0.05 (0.38, 0.67) 0.91 (0.61, 1.35) 0.91 (0.68, 1.28)	Year 2002 2009 2010 2010 2013 2014 2014 2014 2014 2017 2018 2021	0.05 0.2 Favours [control] Favours [experimental] Odds Ratio M.H. Fixed, 95% CI
Test for overall effect. Test for subgroup diffect. Test for subgroup diffect. C Sudo et al Unsal et al Ou et al Unsal et al Ou et al Singhasena et al Almowi et al Wat et al Singhasena et al Almowi et al Wat et al Singhasena et al Almowi et al Wat et al Subtotal (6% CI) Total events Kambalachenu et al Subtotal (6% CI) Total events	49.47, df Z = 0.43 (f erences: C PCOS Cc Events 18 42 32 103 232 87 59 150 1519 27.22, df= Z = 1.32, df= 21.22, df= 21.22, df= 80 161 80 161 80 647	18 (P < P = 0.67) hiP = 11. sees Total 1 36 88 110 470 768 192 266 430 406 754 110 800 4430 11 (P = 0 = 0.19) 194 408 842 1444	1163 0.0001); 47, df = : Contro Events 117 45 66 124 211 240 240 1911 103); l ² = 88 230 304 622	2 (P = 0 3366 100 180 1536 192 264 410 422 264 410 5652 48% 202 48%	x .003), I ² = 0.6% 1.2% 1.9% 2.0% 1.21% 2.8% 2.6% 8.0% 2.1% 9.9% 53.7% 2.7% 7.4% 9.9% 19.7%	82.6% Odds Ratio M.H. Fixed, 95% CI 1.97 (0.94, 3.73) 1.77 (0.63, 1.60) 1.66 (1.10, 2.61) 0.63 (0.77, 1.12) 0.81 (0.54, 1.21) 1.52 (0.23, 1.65) 0.30 (1.06, 1.31) 1.07 (0.88, 1.31) 1.06 (0.97, 1.15) 0.91 (0.61, 1.35) 0.50 (0.38, 0.67) 1.00, 0.38 (0.67) 1.00, 0.38 (0.67) 0.50 (0.38, 0.67) 1.00, 0.92 (0.66, 0.98) 0.92 (0.92 (0.98) 0.92 (0.92 (0.98)) 0.92 (0.92 (0.92)) 0.92 (0	Year 2002 2009 2010 2010 2013 2014 2014 2014 2014 2017 2018 2021	0.05 0.2 Favours [control] Favours [experimental] Odds Ratio M-H, Fixed, 95% CI
Test for overall effect. Test for subgroup diffect. Test for subgroup diffect. C) Study or Subgroup 5.1.1 Asian Studies bons at ta Use tai Gue tai Fue tai Singhasen et al Aimway et al Branavan et al Subtoral (ross C) Total events Heterogeneity. Chf# = Test for overall effect.	49,47, df Z = 0.43 (f erences: C PCOS Cc Events 18 42 32 32 103 232 87 59 1560 1866 2782 2702 1519 21.22, df Z = 2.76 (f 80 161 80 161 80 161 81 80 161 81 81 82 81 81 81 81 81 81 81 81 81 81 81 81 81	18 (P < 2 = 0.67) 2 = 0.67) 2 = 0.67) 3	1163 0.0001); 47, df = : Contro Events 117 45 66 124 211 240 240 1911 .03); l ^a = 88 230 304 622 300 304	^P = 64' 2 (P = 0 is <u>Total</u> 3366 192 264 410 410 410 264 410 264 410 264 410 264 410 264 410 264 410 264 410 264 410 264 264 264 264 264 264 264 264	% .003), I [≠] = .06% 1.2% 1.9% 2.0% 1.21% 2.0% 1.21% 2.6% 4.4% 6.0% 3.0% 5.3.7% .2% 19.7%	Odds Ratio M.H. Fixed, 95% CI 1.67 (0.94, 3.73) 1.71 (20, 63, 7.89) 0.71 (0.43, 1.18) 1.72 (0.63, 1.98) 0.71 (0.43, 1.18) 1.75 (0.71, 1.55) 1.24 (0.24, 1.11) 1.05 (0.71, 1.55) 1.24 (0.24, 1.11) 1.06 (0.54, 1.31) 1.07 (0.88, 0.56, 1.39) 1.07 (0.88, 0.57) 1.04 (0.84, 1.28) 0.50 (0.38, 0.57) 1.04 (0.86, 1.28) 0.82 (0.70, 0.55)	Year 2002 2009 2010 2013 2013 2014 2014 2017 2018 2021 2018 2021	0.05 0.2 5 Favours [control] Favours [experimental]
Test for overall effect Test for subgroup diffect Test for subgroup 5.1.1 Asian Studies Study or Subgroup Du et al Du et al Liaqat et al Wu et al Example and the subgroup Cu et al Fu et al Armavi et al Kim et al Branavan et al Wan et al Heterogenehy: Chif = Test for overall effect. Subblack (95% CI) Total events Kubblack (95% CI) Total e	983 49.47, df = 27.043 (F erences: C Events 18 42 32 32 37 69 150 186 278 69 150 186 278 69 150 186 278 69 150 186 278 69 150 161 161 161 270 161 161 270 161 270 161 161 270 161 161 270 161 161 270 161 161 161 161 161 161 161 16	18 (P < 2 = 0.67) chi ² = 11. 366 110 470 768 88 110 470 768 430 440 754 406 754 109 2266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 754 192 266 430 440 440 754 194 201 9 194 402 206 194 201 194 201 194 201 194 201 194 201 194 201 194 201 194 201 194 204 201 194 201 194 204 104 201 194 104 201 194 104 201 104 104 201 105 104 104 104 104 104 104 104 104	1163 0.0001); 47, df = : Contro Events 117 46 67 488 7 97 97 124 211 240 111 309 1911 .03); ⊨ = 88 230 304 304	^P = 64 ⁴ 2 (P = 0 100 100 180 1536 1536 1536 202 410 410 422 264 410 422 264 410 422 264 410 422 8652 48% 202 400 402 400 402 400 402 400 402 400 402 400 402 408 402 408 402 402 402 402 408 402 402 402 402 408 402 402 402 408 408 402 402 408 402 408 408 408 408 408 408 408 408	% .003), I ² = .06% 1.2% 1.9% 2.0% 2.1% 2.0% 2.6% 4.4% 8.0% 53.7% 2.7% 7.4% 19.7%	Odds Ratio Mt4, Fixed, 95% C1 1.87 (0.94, 3.73) 1.12 (0.84, 3.74) 1.12 (0.84, 3.74) 1.12 (0.84, 3.74) 0.68 (1.0, 2.61) 0.61 (0.43, 1.14) 1.05 (0.77, 1.55) 1.24 (0.84, 1.11) 1.05 (0.77, 1.55) 1.24 (0.84, 1.11) 1.05 (0.77, 1.55) 1.24 (0.84, 1.11) 1.05 (0.77, 1.55) 1.24 (0.93, 1.85) 1.05 (0.64, 1.13) 0.05 (0.64, 1.13) 0	Year 2002 2009 2010 2013 2013 2014 2014 2016 2017 2018 2021	0.05 0.2 5 Favours [control] Favours [experimental]
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Fig. 5 The association between FSHR (rs6166) variant and PCOS risk using different genetic models in overall analysis: a Recessive model (GG vs AG + AA), **b** Additive model (GG vs AA), **c** Allele model (G vs A). In each model, solid squares represent the OR and horizontal lines represent 95%CI and diamond represents the pooled OR and 95%CI

with 11 studies on Thr307Ala (1326 cases and 3867 controls) and Asn680Ser (1344 cases and 3885 controls) and their study reported that Asn680Ser under homozygote model and Asn allele might have a protective effect against PCOS. In the sub-group analysis, the Asn680 allele showed a protective role only in Caucasians, not in Asian PCOS women. Wan et al. [23] also did a metaanalysis and they included 8 articles published on the Asian population. The results of a pooled meta-analysis in Asians supported that rs6166 polymorphism was strongly related to PCOS susceptibility. They also did a subsequent stratified study and observed that rs6165 remained unrelated to PCOS susceptibility in Chinese and Koreans, while rs6166 was related to PCOS susceptibility in Koreans but not in Chinese.

Conclusion

Our meta-analysis is the most comprehensive on the FSHR polymorphisms and PCOS risk. We scored each article using the Newcastle-Ottawa Quality Assessment Scale in order to find higher-quality publications, and each study included in the current meta-analysis received a rating of at least five. We examined all the included studies for fixed or random effect models and analyzed the total effects under dominant, recessive, additive, and allele models. This meta-analysis includes a higher number of studies than the earlier ones, thus it provides accurate estimation. In the present meta-analysis, it was concluded that polymorphism rs6166 was found to have a modest impact on PCOS, however, on a specific cohort. In a meta-analysis, if the degree of heterogeneity rises, it gets harder to justify an integrated conclusion. Heterogeneity for rs6166 polymorphism is higher despite of subgroup analysis, therefore these results cannot be generalized. Further studies on homogeneous and larger populations with ethnicity-matched controls are required to strengthen the statistical power and to better understand the role of FSHR polymorphisms with PCOS.

Abbreviations

PCOS	Polycystic Ovary Syndrome
LH	Luteinizing Hormone
ESHRE	European Society of Human Reproduction and Embryology
ASRM	American Society of Reproductive Medicine
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropic Releasing Hormone
FSHR	Follicle Stimulating Hormone Receptor
LHCGR	Luteinizing Hormone/Choriogonadotropin Receptor
PCOSKB	Polycystic Ovary Syndrome Knowledge Base
MeSH	Medical Subject Headings
HWE	Hardy Weinberg Equilibrium
SNP	Single Nucleotide Polymorphism
NOS	New-Castle Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and
	Meta-Analysis
REM	Random Effect Model
FEM	Fixed Effect Model

- PCO Polycystic Ovary
- OA Oligo/anovulation
- MD Menstrual irregulation
- HA Hyperandrogenism
- PCR-SSCP Polymerase Chain Reaction-Single Strand Conformation Polymorphism
- PCR–RFLP Polymerase Chain Reaction- Restriction Fragment Length Polymorphism
- PCR-SSP Polymerase Chain Reaction- Sequence Specific Priming OR Odds Ratio
- CI Confidence Interval
- THADA Thyroid Adenoma Associated
- DENDD1A DENN domain-containing protein 1A

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Authors' contributions

A study design and review of the manuscript was done by AK. A literature review and meta-analysis were conducted by MK and SS. The manuscript was written by MK. All the authors carefully read the manuscript and approved it.

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The authors declare no competing interests.

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