



## Original Article

G276T polymorphism in the *ADIPOQ* gene is associated with a reduced risk of polycystic ovarian syndrome: A meta-analysis of Asian population

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## ABSTRACT

**Objective:** The etiology of polycystic ovarian syndrome (PCOS) has not yet been fully explained. Several studies suggested an association between two single nucleotide polymorphisms (T45G and G276T) of the *ADIPOQ* gene that encodes for the hormone adiponectin and PCOS susceptibility. Hence, we performed a meta-analysis to investigate the relationship of the two further.

**Materials and methods:** Literature search was conducted in PubMed up to June 22, 2018, for related publications written in English. Selected data were extracted from the included studies and was subjected to analysis using Review Manager 5.3. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed and pooled from the resulting studies. Subgroup analysis by ethnicity was also performed.

**Results:** Overall analysis showed that women with the G276T polymorphism have reduced susceptibility to PCOS (OR: 0.68; 95% CI: 0.60–0.78;  $P^A < 0.001$ ). While no significant association was observed for the T45G polymorphism (OR: 1.07; 95% CI: 0.93–1.24;  $P^A = 0.34$ ). Subgroup analysis, on the other hand, showed significant associations among East Asians (OR: 0.69; 95% CI: 0.57–0.82;  $P^A < 0.001$ ) for the G276T association.

**Conclusion:** Results of this meta-analysis suggests that women with the G276T polymorphism are less likely to develop PCOS. However, more studies are needed to confirm the claims of this meta-analysis.

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## Introduction

Polycystic ovarian syndrome (PCOS) is a malady of the endocrine system affecting approximately 5–10% of women within the reproductive age group and is considered as one of the leading cause of infertility among females [1–3]. The symptoms of the disease vary significantly among individuals. Usual symptoms include polymorphic clinical manifestations, including biochemical and clinical hyperandrogenism, chronic oligo- or anovulation, insulin resistance, and obesity. These symptoms also predispose women to type 2 diabetes mellitus (T2DM) and cardiovascular

diseases [4–10]. Up to date, the etiology of PCOS has not been fully explained. Some studies suggest that multiple genetics play an essential role in the development of PCOS [11,12]. Therefore, the identification of a PCOS candidate gene may not only reveal its mechanism but also enhance its current prevention and therapeutic strategies.

Adiponectin (ADP) is the most abundant adipose-specific adipocytokine in the plasma, accounts for 0.01% of total plasma proteins, and is the product of the human *ADIPOQ* gene expression by white adipose tissues [13–16]. ADP reduces the risk of developing several disorders and is thought to have anti-atherogenic, anti-inflammatory, and cardioprotective properties [16,17]. Numerous studies have shown that ADP plays a vital role in the process of glucose regulation and lipid metabolism. It increases the oxidation of skeletal muscle fatty acid and peripheral tissue sensitivity to insulin. Aside from that, it can also cause inhibition of hepatic

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gluconeogenesis thereby, lowering the risk of developing T2DM [18,19]. Interestingly, several studies have also drawn an association between ADP levels and the development of PCOS. These studies revealed that women with PCOS tend to have 0.5x to 1.5x lower ADP levels when compared to those without [20–22].

The *ADIPOQ* gene is composed of three exons and two introns spanning a 17-kb region [23]. The two single nucleotide polymorphisms (SNPs), T45G (*rs2241766*) in exon 2 and G276T (*rs1501299*) in intron 2 of the *ADIPOQ* gene have shown surprising correlation with high risk of insulin resistance, obesity, and T2DM [24–26]. Variations in the intron affect the splicing of the mRNA that can change the level of gene expression which leads to either an over or underproduction of proteins. Whereas, mutations in the exon can drastically affect the phenotypic characteristics of the organism [27]. These two SNPs were proposed to be connected with the alteration of serum concentrations of ADP either by increasing (G276T SNP) or decreasing (T45G SNP) its levels [28].

Similarly, several studies have tried to link the relationship concerning T45G and G276T polymorphisms and the susceptibility to PCOS however, no consensus was reached due to conflicting results and lack of evidence that further support the association [29–36]. The lack of consistency might be attributed to the small effect of the polymorphisms on susceptibility to PCOS, diversity of ethnicity, relatively small sample size in each study or probably other limitations in study design. As such, in order to shed some light and provide a better understanding, we performed a meta-analysis to thoroughly investigate the correlation of the two SNPs and susceptibility to PCOS in an Asian population.

## Materials and methods

### Search strategy and study selection

A comprehensive electronic search of PubMed was conducted until June 22, 2018, using the key search terms “adiponectin gene,” “polymorphism,” “polycystic ovarian syndrome,” and “Asia.” Studies were included in the meta-analysis if: (i) written in English; (ii) contains case-control data regarding the association of ADP gene T45G and G276T polymorphism with PCOS; (iii) studies that used the Rotterdam criteria for PCOS classification; and (iv) studies were conducted in an Asian population. Titles and abstracts of the resulting studies were initially screened to filter appropriate studies. After removal of duplicates and irrelevant studies, the full text of the resulting articles was manually checked to determine their relevance. Cited references from selected publications were also manually checked to identify additional eligible studies. Additional articles were obtained by checking the references of the included studies. All publications identified were investigated independently for eligibility by two of the authors.

### Data extraction

Two authors independently extracted data and reached an agreement on all the items. For each included study, the following information was extracted: the first author's last name, publication year, country, sources of controls, criteria used for PCOS diagnosis, genotyping method, the total number of participants, number of cases and controls, and genotypic and allelic frequencies for each SNP.

### Derived data

Studies that lacked data regarding allelic frequencies were computed manually. Frequencies of the variant allele deviations of

controls for each study was also calculated using the Hardy-Weinberg Equilibrium (HWE).

### Quality assessment of the included studies

The Newcastle-Ottawa Scale (NOS) [37] assessment was used to check for the quality of the included studies. All studies were assessed based on three parameters: selection, comparability, and exposure. The rating system has scores ranging from 0 (worst) to 9 (best) points. Studies scoring  $\geq 7$  points were regarded as high-quality studies whereas, studies scoring 5–6 points were regarded as moderate-quality.

### Meta-analysis protocol

Susceptibility to PCOS in relation to the *ADIPOQ* gene polymorphism G276T and T45G was estimated for each study and then, overall and subgroup effects were obtained. Review Manager 5.3 (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2014) was used to analyze the collected data for this meta-analysis. Data from T45G and G276T polymorphism were analyzed separately. The protocol used for this meta-analysis was based on the procedure of Pabalan et al. [38–40] with some modifications. Pooled odds ratio (OR) and 95% confidence interval (CI) were analyzed using either the fixed- [41] or random-effects [42] model. To address the importance of heterozygous genotype, three genotypic models and an allelic model were used for evaluation, namely: dominant (T45G: GG + TG vs. TT; G276T: GT + TT vs. GG), recessive (T45G: GG vs. TG + TT; G276T: TT vs. GG + GT), co-dominant (T45G: GG vs. TT; G276T: TT vs. GG), and allele (T45G: G vs. T; G276T: T vs. G). Given the low power of the test caused by the few numbers of included studies, the significance threshold ( $P^H$ ) was set at 0.10 for heterogeneity testing [43]. Presence of heterogeneity across the studies was tested using Chi-square based Q test [44], and the degree of inconsistency was quantified with the

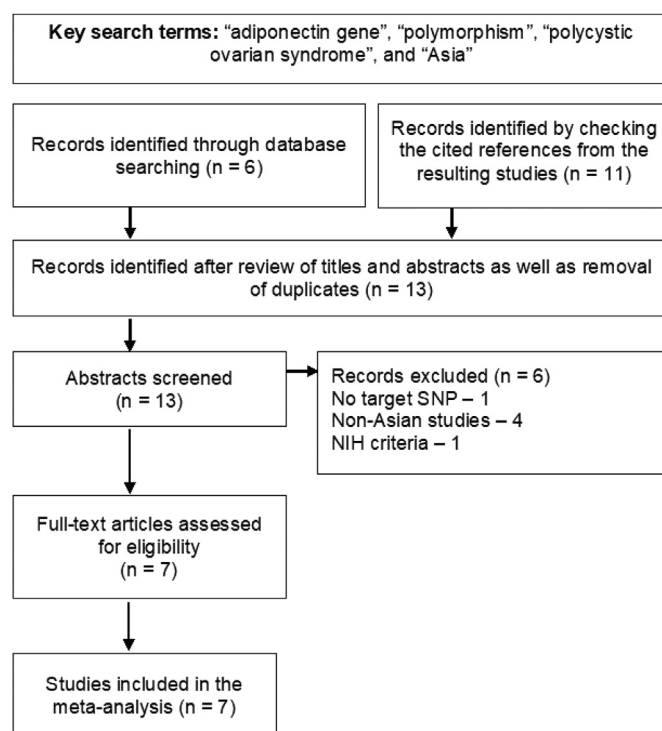


Fig. 1. Summary of literature search. SNP: single nucleotide polymorphism.

$I^2$  statistics [45]. Subgroup analysis was also performed and was based on Asian ethnicity (East Asian vs. West Asian) and the diagnostic criteria used (Rotterdam criteria). Sensitivity analysis was used to determine the robustness of the overall summary effects. Here, the influence of each study on the pooled ORs was examined by systematic removal of one study at a time. Publication bias was no longer tested due to the low sensitivity of the qualitative and quantitative tests when the number of studies is lower than 10 [46]. All  $p$ -values were two-sided with significance threshold ( $P^A$ ) set at <0.05 except for heterogeneity estimation.

## Results

### Characteristics of the included studies

Summary of the literature search is summarized in Fig. 1 whereas, the characteristics of the individual studies are summarized in Table 1.

Overall, a total participant for the meta-analysis is 2084 (1059 cases/1025 controls) for the T45G polymorphism and 1895 (966 cases/929 controls) for the G276T polymorphism. All the included

**Table 1**  
Characteristics of the included study.

First Author	Publication Year	Country	Sources of Control	Genotyping Method	N	HWE		NOS
						T45G	G276T	
Alfaqih [48]	2018	Jordan	Hospital	PCR-RFLP	303	0.008*	<0.001*	7
Demirci [34]	2010	Turkey	Hospital	PCR	189	0.09	—	6
Li [50]	2011	Korea	Hospital	PCR-RFLP	303	<0.001*	0.13	6
Nambiar [47]	2015	India	Population	PCR-RFLP	482	<0.001*	0.06	8
Yoshihara [50]	2009	Japan	Population	TaqMan	362	0.004*	<0.001*	6
Zhang [36]	2008	China	Hospital	PCR	156	0.51	0.08	8
Zhang [49]	2014	China	Hospital	PCR	240	0.37	0.46	7

PCR: polymerase chain reaction; NIH: National Institute of Health; RFLP: restricted fragment length polymorphism; N: total number of participants; HWE: Hardy–Weinberg Equilibrium; NOS: Newcastle–Ottawa Scale.

\*Significant at  $p < 0.05$ .

**Table 2**  
Summary of overall and subgroup effects for the allelic models.

Polymorphism	N	Allelic Model			
		OR (95% CI)	$P^A$	$P^H$	AM
T45G					
Overall	7	1.07 (0.93–1.24)	0.34	0.23	F
Overall in HWE	4	1.14 (0.93–1.40)	0.20	0.13	F
East Asians	4	1.03 (0.78–1.37)	0.83	0.09**	R
East Asians in HWE	3	1.12 (0.72–1.60)	0.54	0.09**	R
West Asians	3	1.01 (0.80–1.28)	0.92	0.23	F
G276T					
Overall	6	0.68 (0.60–0.78)	<0.001*	0.52	F
Overall in HWE	4	0.64 (0.54–0.74)	<0.001*	0.98	F
East Asians	4	0.69 (0.57–0.82)	<0.001*	0.47	F
East Asians in HWE	3	0.65 (0.54–0.79)	<0.001*	0.98	F
West Asians	2	0.68 (0.55–0.84)	<0.001*	0.20	F

N: number of studies; OR: odds ratio; CI: confidence interval;  $P^A$ :  $p$ -value for association;  $P^H$ :  $p$ -value for heterogeneity; AM: analysis model; F: fixed-effect model; R: random-effect model.

\*Significant at  $p < 0.05$ .

\*\*Significant at  $p < 0.10$ .

**Table 3**  
Summary of overall and subgroup effects for the dominant, recessive, and co-dominant genotypic models.

Polymorphism	N	Dominant Model				Recessive Model				Co-Dominant Model			
		OR (95% CI)	$P^A$	$P^H$	AM	OR (95% CI)	$P^A$	$P^H$	AM	OR (95% CI)	$P^A$	$P^H$	AM
T45G													
Overall	7	1.09 (0.91–1.31)	0.34	0.20	F	1.06 (0.79–1.42)	0.69	0.42	F	1.10 (0.82–1.49)	0.51	0.46	F
Overall in HWE	4	1.24 (0.96–1.61)	0.10	0.34	F	0.98 (0.64–1.72)	0.95	0.19	F	1.08 (0.67–1.75)	0.75	0.16	F
East Asians	4	1.06 (0.72–1.56)	0.78	0.06**	R	1.00 (0.63–1.60)	1.00	0.16	F	1.06 (0.66–1.72)	0.81	0.19	F
East Asians in HWE	3	1.21 (0.92–1.60)	0.18	0.21	F	0.90 (0.54–1.48)	0.67	0.16	F	0.98 (0.59–1.65)	0.95	0.13	F
West Asians	3	1.19 (0.89–1.58)	0.24	0.81	F	1.10 (0.76–1.60)	0.61	0.67	F	1.32 (0.71–2.44)	0.87	0.59	F
G276T													
Overall	6	0.76 (0.62–0.94)	<0.01*	0.28	F	0.55 (0.43–0.70)	<0.001*	0.54	F	0.49 (0.36–0.67)	<0.001*	0.51	F
Overall in HWE	4	0.66 (0.51–0.84)	<0.001*	0.74	F	0.56 (0.43–0.74)	<0.001*	0.56	F	0.45 (0.31–0.66)	<0.001*	0.47	F
East Asians	4	0.67 (0.53–0.86)	<0.01*	0.45	F	0.51 (0.35–0.75)	<0.001*	0.59	F	0.44 (0.30–0.66)	<0.001*	0.39	F
East Asians in HWE	3	0.63 (0.48–0.81)	<0.001*	0.89	F	0.46 (0.30–0.70)	<0.001*	0.78	F	0.38 (0.24–0.59)	<0.001*	0.82	F
West Asians	2	1.03 (0.71–1.51)	0.87	0.67	F	0.58 (0.42–0.80)	<0.001*	0.16	F	0.58 (0.35–0.95)	0.03*	0.41	F

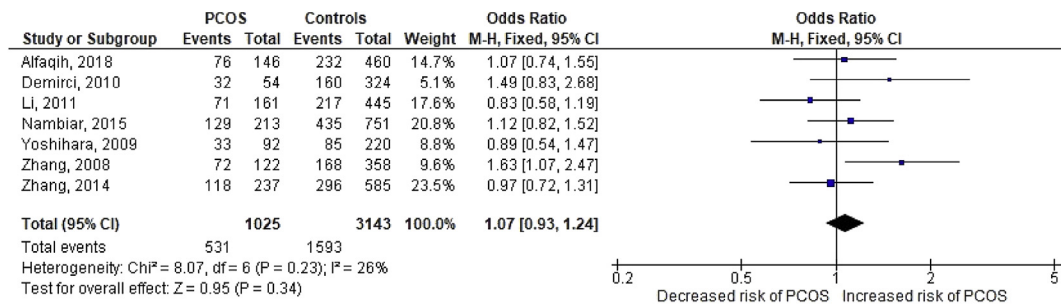
N: number of studies; OR: odds ratio; CI: confidence interval;  $P^A$ :  $p$ -value for association;  $P^H$ :  $p$ -value for heterogeneity; AM: analysis model; F: fixed-effect model; R: random-effect model.

\*Significant at  $p < 0.05$ .

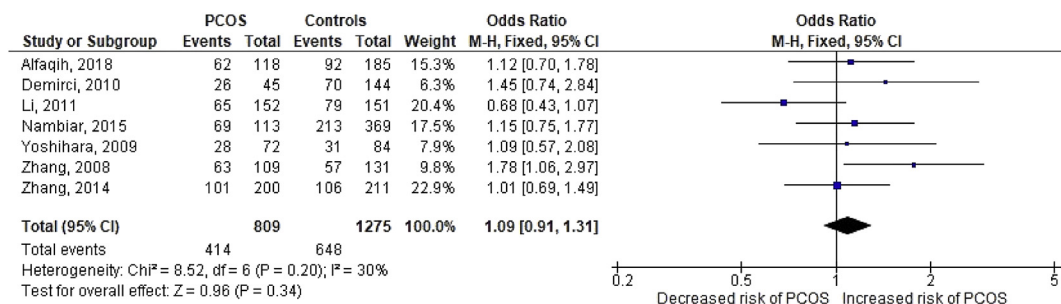
<sup>b</sup>Significant at  $p < 0.10$ .

**a**

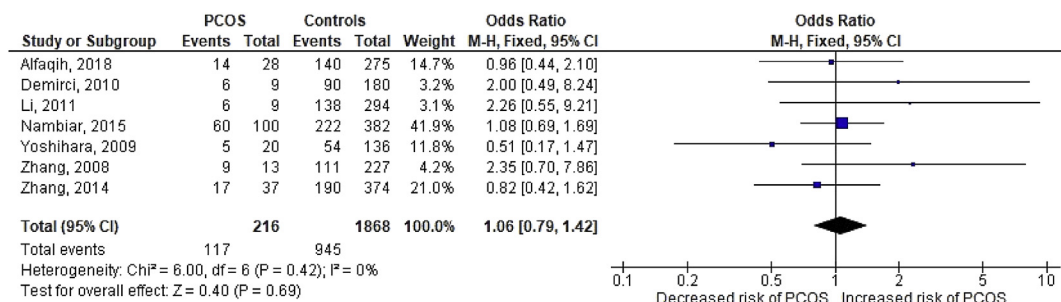
PCOS: polycystic ovarian syndrome; CI: confidence interval; df: degrees of freedom

**b**

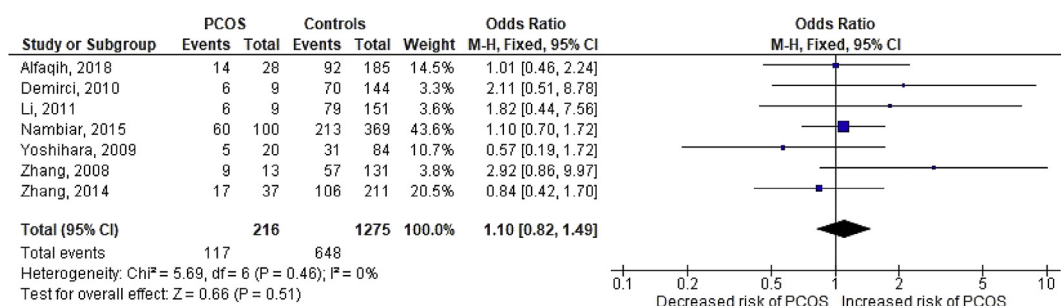
PCOS: polycystic ovarian syndrome; CI: confidence interval; df: degrees of freedom

**c**

PCOS: polycystic ovarian syndrome; CI: confidence interval; df: degrees of freedom

**d**

PCOS: polycystic ovarian syndrome; CI: confidence interval; df: degrees of freedom





studies fulfilled the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) Rotterdam consensus criteria [34,36,47–50] for PCOS diagnosis. Controls were predominantly healthy subjects with regular menstrual cycles and without any signs of hyperandrogenism. Articles included were published between 2008 and 2018. Sample population consisted of East Asians [36,49,50] and West Asians [34,47,48]. Majority of the controls were from hospitals [34,36,48–50] while the rest are from the community [47,50]. As for the genotyping method, four studies included used polymerase chain reaction (PCR) – restricted fragment length polymorphism (RFLP) [47,48,50], three used PCR [34,36,49], and one used TaqMan [50]. Four studies from the T45G polymorphism association [47,48,50] and two studies from the G276T polymorphism association deviated from the HWE [48,50]. NOS scoring showed the mean and standard deviation to be  $6.9 \pm 0.9$  and a median of 7 indicating that the included studies were of moderate quality.

#### Association of T45G ADIPOQ gene polymorphism with PCOS

A total of seven studies were included in the overall analysis for the association of the T45G polymorphism with PCOS (Tables 2 and 3). The G allele was considered as the mutational allele for this polymorphism. Overall analysis showed that there is no significant heterogeneity ( $P^H = 0.23$ ) for the allelic model. Pooled ORs using the fixed-effects model (Fig. 2a) suggest that there was no significant association (OR: 1.07; 95% CI: 0.93–1.24;  $P^A = 0.34$ ) between the T45G polymorphism and PCOS susceptibility in the allelic model. Removal of the studies that deviated from the HWE was not responsible for these results. Subgroup analysis stratified by ethnicity also yielded non-significant results with small to moderate heterogeneity between studies (Tables 2 and 3). No significant associations were found for the three genotypic models either (Fig. 2b–d). Sensitivity analysis by omitting one study at a time did not alter the results of the overall analysis (data not shown).

#### Association of G276T ADIPOQ gene polymorphism with PCOS

In total, six studies were included in the overall analysis for the association of G276T polymorphism with PCOS (Tables 2 and 3). In this association, the T allele was considered as the mutational allele. The overall analysis for determining the association of G276T polymorphism with PCOS susceptibility in the allelic model showed that there was no significant heterogeneity across all the studies ( $P^H = 0.52$ ) and the pooled OR analyzed using the fixed-effects model (Fig. 3a) showed significant association (OR: 0.68; 95% CI: 0.60–0.78;  $P^A < 0.001$ ). Overall subgroup analysis on the other hand showed that association was detected using the fixed-effects model for both East Asian population (OR: 0.69; 95% CI: 0.57–0.82;  $P^A < 0.001$ ) and West Asian population (OR: 0.68; 95% CI: 0.55–0.84;  $P^A < 0.001$ ). The three genotypic models produced similar results as that of the allelic model for the overall analysis (Fig. 3b–d). Sensitivity analysis by study omission did not alter the results of the overall analysis (data not shown), and exclusion of the studies that deviated from the HWE did not change the results either (Tables 2 and 3).

## Discussion

### Summary and interpretation of findings

The results of the overall analysis indicate that the G276T polymorphism may confer protection against PCOS, while the T45G polymorphism showed no significant association. Although heterogeneity was observed for the T45G association, sensitivity analysis did not alter the results for both the overall and subgroup analysis, indicating that our results were robust. Based on the pooled ORs, those that have a G276T polymorphism in the ADIPOQ gene are less likely to develop PCOS. Further analysis by subgroup stratification showed that G276T polymorphism was significantly related to reduced susceptibility to PCOS among East Asians but not among West Asians. These findings suggest that East Asians are less likely to develop PCOS if they have the polymorphism.

### ADP levels and PCOS pathophysiology

The pathophysiology of PCOS has not yet been clearly explained, but clinical studies indicate the role of androgen overproduction in the ovaries, environmental, and genetic factors in the onset of the disease. Deregulation of androgen synthesis in the ovary at the early stage of folliculogenesis is a crucial factor in PCOS pathophysiology [51]. PCOS is said to be associated with components of metabolic syndrome, namely, T2DM, insulin resistance, obesity, and cardiovascular complications [49]. ADP is the most abundant adipokine that exerts the action of sensitizing insulin and contains anti-inflammatory and anti-atherogenic activities. The receptors of ADP are usually expressed in human pituitary, and the hormone itself is localized in the follicle stimulating hormone- (FSH), luteinizing hormone- (LH), and growth hormone-producing cells. Therefore, patients diagnosed with PCOS have increased levels of LH and decreased levels of ADP [52]. Disruption of adipokine and its receptors may affect the role on the pathogenesis of hyperandrogenism in PCOS [51].

### T45G ADIPOQ gene polymorphism and PCOS susceptibility

Considering the metabolic features of PCOS as well as other conditions associated with abnormal ADP levels, mutations in this protein is being considered as one of the possible causes of PCOS development. However, the results of our study did not show any significant association (OR: 1.07; 95% CI: 0.93–1.24;  $P^A = 0.34$ ). Three other studies supported findings of our meta-analysis. In the studies of Xian et al. [53], Panidis et al. [29], and Li et al. [50] no significant association between the T45G polymorphism and PCOS susceptibility was observed. Instead, the polymorphism was associated with other features of PCOS such as obesity and insulin resistance. The low levels of ADP in PCOS are independent of the T45G polymorphism as mentioned by a previous meta-analysis [54]. It is suggested that low ADP in patients with PCOS cannot be directly attributed to the T45G ADP gene polymorphism, rather it is associated with insulin resistance and hyperinsulinemia naturally present in the disease [34].

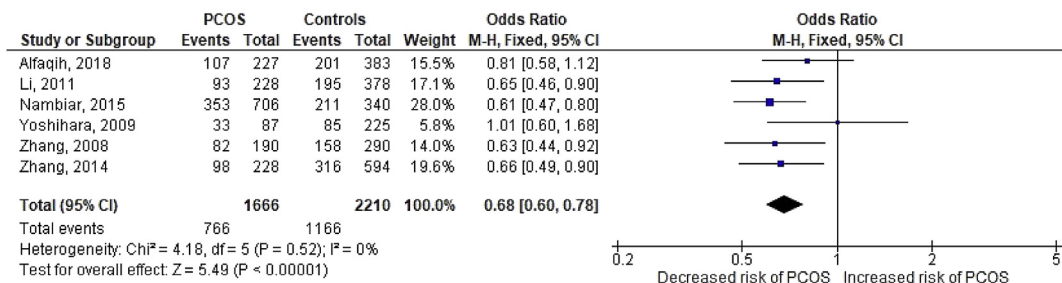
### G276T ADIPOQ gene polymorphism and PCOS susceptibility

The results of this meta-analysis suggest that G276T polymorphism has a protective role against PCOS (OR: 0.68; 95% CI:

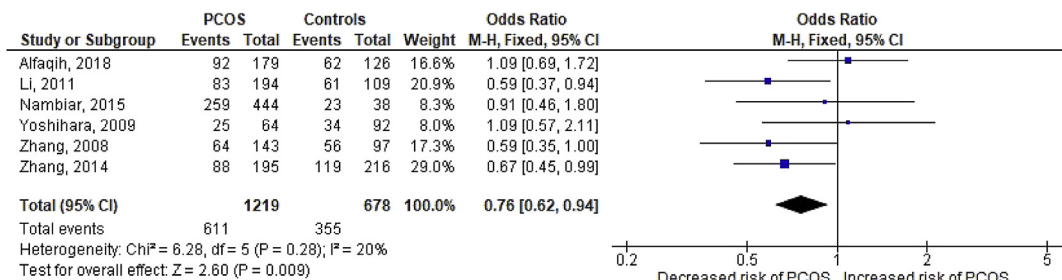
**Fig. 2.** a. Forest plot analysis for the overall association of the T45G SNP (allelic model) with PCOS susceptibility. b. Forest plot analysis for the overall association of the T45G SNP (dominant model) with PCOS susceptibility. c. Forest plot analysis for the overall association of the T45G SNP (recessive model) with PCOS susceptibility. d. Forest plot analysis for the overall association of the T45G SNP (co-dominant model) with PCOS susceptibility.

**a**

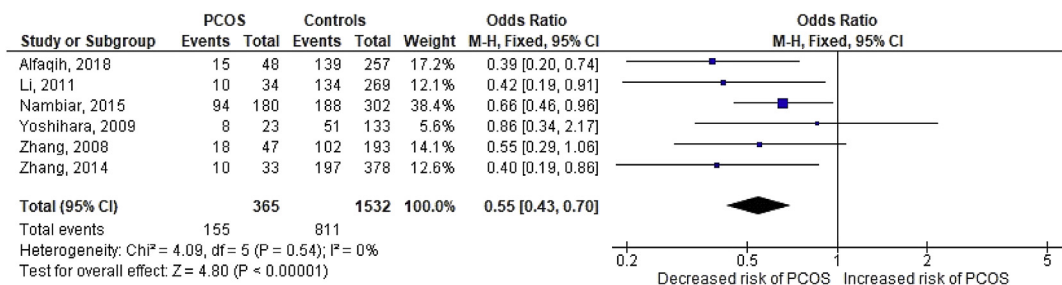
PCOS: polycystic ovarian syndrome; CI: confidence interval; df: degrees of freedom

**b**

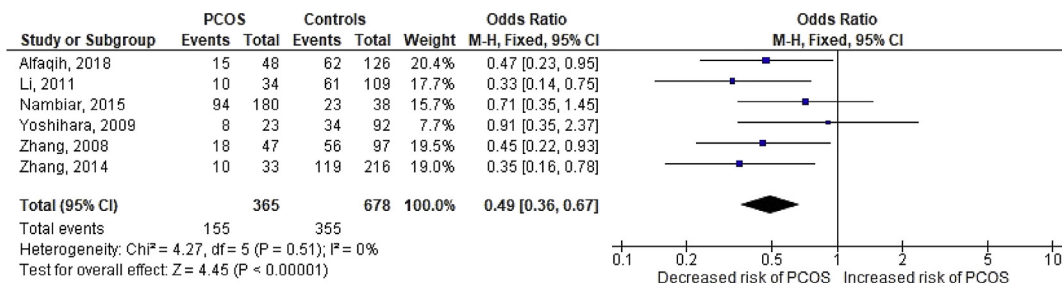
PCOS: polycystic ovarian syndrome; CI: confidence interval; df: degrees of freedom

**c**

PCOS: polycystic ovarian syndrome; CI: confidence interval; df: degrees of freedom

**d**

PCOS: polycystic ovarian syndrome; CI: confidence interval; df: degrees of freedom



**Fig. 3.** a. Forest plot analysis for the overall association of the G276T SNP (allelic model) with PCOS susceptibility. b. Forest plot analysis for the overall association of the G276T SNP (dominant model) with PCOS susceptibility. c. Forest plot analysis for the overall association of the G276T SNP (recessive model) with PCOS susceptibility. d. Forest plot analysis for the overall association of the G276T SNP (co-dominant model) with PCOS susceptibility.

0.60–0.78;  $P^A < 0.001$ ). Our results are similar to two other studies. In the study of Jia et al. [55], they have shown that G276T polymorphism is significantly related to reduced susceptibility to PCOS among East Asians but not among Caucasians. It is presumed that the protective effects of G276T polymorphism among patients with PCOS might be attenuated among Caucasians. Also, in another study, they mentioned that the T allele in the *ADIPOQ* G276T polymorphism is significantly correlated with the decreased susceptibility to PCOS among Asians but not for Caucasians [53]. Aside from the possible influence of ethnicity, other studies [20,25,36,54] noted that the G276T polymorphism is significantly associated with higher levels of circulating ADP. ADP is considered an important factor that plays a critical role in glucose and fat metabolism. It regulates the uptake of glucose as well as fatty acid oxidation in the skeletal muscle, whereas, in the liver, it regulates the process of gluconeogenesis and fatty acid oxidation [56]. Previous studies have demonstrated the insulin-sensitizing, anti-atherogenic and cardioprotective properties of ADP [57–59]. Hence, because of its pivotal functions, high ADP levels are negatively correlated with metabolic syndrome [60], which is an essential feature of PCOS.

#### Difference with previous meta-analyses

The present meta-analysis aims to determine the association of two SNPs in the *ADIPOQ* gene with the risk of developing PCOS. Other meta-analyses [52,53,55] regarding the topic were previously conducted back in 2011 and 2012. However, those studies catered a large variety of ethnic groups whereas, our study focused only on the Asian population. The previous meta-analysis covered 8 to 11 studies in general with two to five studies that included Asian descent. We covered seven studies that included Asians as the participants. Regarding comparison, only one meta-analysis [55] performed subgroup stratification by ethnicity. In their study, only three studies were included under the Asian strata. In our study, sub-group analysis by Asian ethnicity was performed. We opted to perform a meta-analysis investigating Asian population in order to intensify the results obtained by the study of Jia et al. [55]. In their study, they noted that the G276T polymorphism is associated with PCOS susceptibility among Asians but not with Caucasians. According to Jia et al., possible reasons why such results were observed include: (1) the genetic profiles of the two strata were different, wherein, T allele frequencies were higher among Asians than Caucasians; and (2) the selection criteria used may have impacted the results of the genetic association. Little is still known with regards to the relationship of the *ADIPOQ* gene polymorphism with PCOS susceptibility in various ethnic groups. Hence, it is recommended to determine the effect of ethnic diversity with the polymorphism and the gene-environment interaction in future studies.

#### Limitations of the study

Overall, the findings of this meta-analysis suggest that G276T polymorphism is protective against PCOS while no association was observed for the T45G polymorphism. However, interpreting this study warrants awareness of its limitations, namely: (i) effect of gene-gene interaction was not tested; (ii) since T45G and G276T are only 200 bp apart, their possible interaction was not considered; (iii) differences with the genotyping method was observed and might have led to inconsistencies in the results; (iv) participants are heterogeneous due to the differences of ethnicity (East Asians and West Asians), sources of controls (Hospitals and Community), and the diagnostic criteria used (NIH and Rotterdam criteria); and (v) susceptibility to PCOS may be attributed to other factors which were not examined in this meta-analysis.

## Conclusion

To our knowledge, this is the first meta-analysis that investigated the association of the T45G and G276T polymorphism of the *ADIPOQ* gene with PCOS in an Asian population. With this, we hope we have contributed to a better understanding of the pathophysiological mechanism involved in the onset of PCOS. Generally, our results suggest that women with the G276T polymorphism are less likely to develop PCOS while T45G polymorphism did not show any significant association with susceptibility to the disease. Given the limitations mentioned above, these findings should be treated with caution when applied to clinical practice. More studies are needed to confirm the claims of our results.

## Conflicts of interest

The authors declare that they have no conflict of interest.

## Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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