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Original Article

Insulin receptor substrate-1 (IRS-1) rs1801278G>A polymorphism is associated with polycystic ovary syndrome susceptibility: a meta-analysis

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Abstract: The correlation between *insulin receptor substrate-1* (*IRS-1*) rs1801278G>A polymorphism and polycystic ovary syndrome (PCOS) has been widely studied. However, the results of these studies are conflicting. The current study provides an assessment of the association between the genetic susceptibilities of *IRS-1* rs1801278G>A polymorphism and PCOS. A comprehensive meta-analysis was carried out in over 4,555 subjects included in twenty publications which were published up to June 26, 2015. Our findings suggested that the *IRS-1* rs1801278G>A genotype was correlated with the susceptibility of PCOS in the allele comparison, heterozygote comparison and the dominant genetic model. In the dominant genetic model, variant A allele carriers (AA+GA) of *IRS-1* rs1801278G>A polymorphism increased the susceptibility of PCOS comparing to the homozygote GG [odds ratio (OR)=1.82, 95% confidence interval (CI) 1.30-2.53 for AA+GA vs. GG]. The analysis by different ethnicity groups highlighted that Caucasian population (OR=1.96, 95% CI 1.26-3.04 for AA+GA vs. GG) had significant increased PCOS susceptibility. Bias diagnosis indicated there are slight publication biases in some genetic models, suggesting that these findings should be interpreted with very caution. In summary, our findings suggested that *IRS-1* rs1801278G>A polymorphism may be a risk factor for PCOS.

Keywords: Insulin receptor substrate-1, polymorphism, polycystic ovary syndrome, meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism and ovulatory dysfunction and is a common endocrine disorder, which affect approximately 5%-10% of female in reproductive age and is a leading cause of infertility [1, 2]. Biomarker of PCOS involve in ovarian and adrenal steroid hormone, steroidogenesis actions, insulin secretion and action, energy homeostasis, gonadotropin action and regulation and chronic inflammation [3]. Although the potential mechanisms of PCOS are very elusive and has not been identified thoroughly, familial aggregation shows that the genetic factors may play an important role in the aetiology of this disease [4].

Accumulating evidence suggests that insulin resistance (IR) plays a vital role in the pathogenesis of PCOS [5-7]. The insulin receptor consists of two α and two β-dimers. The ligand-binding site lies in the α-subunit, while the ligand-activated tyrosine kinase lies in the β-subunit. Once insulin binds to its receptor, the tyrosine is phosphorylated and then insulin receptor substrate-1 (IRS-1) and IRS-2, two intracellular substrates, are phosphorylated. After this procedure, IRS-1 and IRS-2 combine and activate downstream effectors, including phosphoinositide 3-kinase, to control the metabolism and participate in mitogenic actions of insulin. The *IRS-1* is located on chromosome 2q36. The most common variant, *IRS-1* rs1801278G>A polymorphism (Gly972Arg), was suggested to

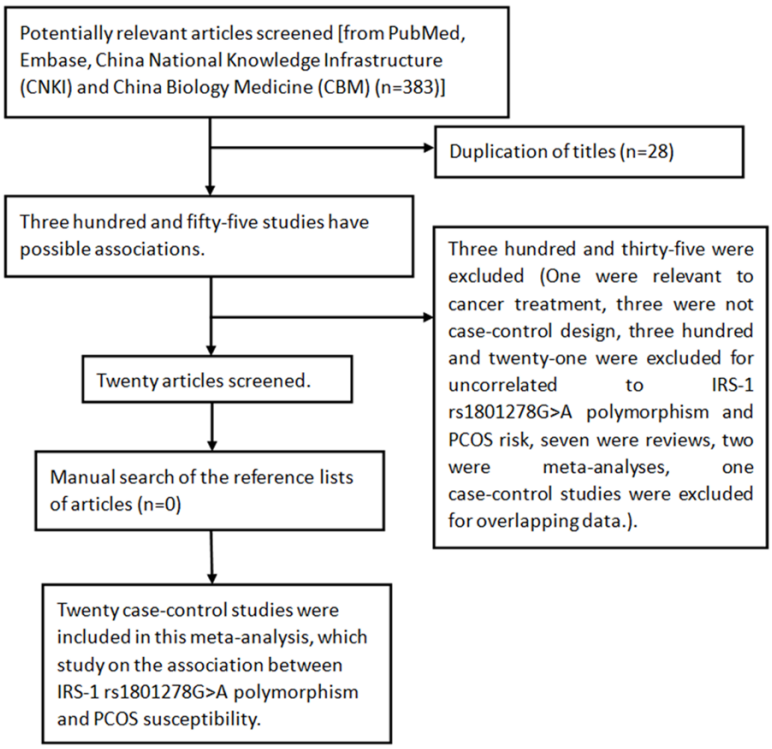

Figure 1. Flow chart shows studies included procedure for meta-analysis.

be correlated with IR, type 2 diabetes mellitus (T2DM) and PCOS [8, 9].

Recently, a meta-analysis yielded a significant correlation between *IRS-1* rs1801278G>A polymorphism and the susceptibility of developing PCOS [10]. In addition, several new case-control studies with relatively large sample sizes reported correlations of *IRS-1* rs1801278G>A variants with PCOS, but the findings were conflicting. Considering the crucial role of *IRS-1* rs1801278G>A polymorphism in PCOS, we conducted an updated meta-analysis to assess the susceptibility of developing PCOS associated with this single nucleotide polymorphism (SNP). To the best of our knowledge, our study is the most comprehensively pooled analysis performed with respect to the associations between *IRS-1* rs1801278G>A polymorphism and the susceptibility of developing PCOS.

Materials and methods

Search strategy

PubMed, EMBASE, China National Knowledge Infrastructure (CNKI) and China Biology Medicine (CBM) databases (the search was updated in June 26, 2015) were searched using the following terms: 'insulin receptor substrate 1' or 'insulin receptor substrate-1' or 'IRS1' or 'IRS-1', 'SNP' or 'polymorphism' or 'variant', and 'polycystic ovary syndrome' or 'PCOS'. The literature search was limited to English or Chinese articles. Additional publications were identified by a manual search based on references of retrieved studies or reviews.

Inclusion and exclusion criteria

The selection criteria were: (1) in a case-control study design, (2) studies that evaluated the relationship between the *IRS-1* rs1801278G>A polymorphism and PCOS, (3) usable data on genotype frequency. Thus, reports without usable data, reviews, comments and duplicated publications were excluded.

Data extraction

The data were collected by two independent reviewers (W. Tang and Y. Wang): (a) the surname of first author, (b) country of origin, (c) ethnicity, (d) year of publication, (e) number of cases and controls, (f) data of genotype frequency, (g) genotyping method and evidence of Hardy-Weinberg equilibrium (HWE) in controls. When come to conflicting assessments, disagreements were settled through a discussion among all authors.

Statistical analysis

The strength of correlation between *IRS-1* rs1801278G>A polymorphism and the susceptibility of developing PCOS was assessed by the crude odds ratios (ORs) with 95% confidence intervals (95% CIs). A $P<0.05$ (two-tailed) was considered as statistical significance. A Chi-square-based I^2 test was used to detect heterogeneity [11] and an $I^2<25\%$ indicates low heterogeneity, $25\%\leq I^2\leq 50\%$ indicates moderate heterogeneity, and $I^2>50\%$ indicates large heterogeneity [12]. When $I^2>50\%$ or $P<0.10$ (two-

Table 1. Characteristics of the individual studies included in the meta-analysis

Study	Year	Country	Ethnicity	Sample size	Genotype method
Lin et al. [18]	2014	China	Asians	248/92	DNA sequencing
Skrgatic et al. [22]	2013	Croatia	Caucasians	150/175	real-time PCR
Dasgupta et al. [19]	2013	India	Asians	250/299	DNA sequencing
Kawamura et al. [20]	2011	Japan	Asians	50/100	TaqMan
Pappalardo et al. [8]	2010	Italy	Caucasians	65/27	PCR-RFLP
Christopoulos et al. [21]	2010	Greece	Caucasians	183/88	PCR-RFLP
Dravecka et al. [23]	2010	Slovakia	Caucasians	53/21	PCR-RFLP
Marioli et al. [24]	2010	Greece	Caucasians	162/122	PCR-RFLP
Valdes et al. [25]	2008	Chile	Caucasians	50/75	PCR-RFLP
Baba et al. [9]	2007	Japan	Asians	123/380	TaqMan
Lin et al. [17]	2006	China	Asians	47/45	PCR-RFLP
Dilek et al. [26]	2005	Turkey	Caucasians	60/60	PCR-RFLP
Villuendas et al. [27]	2005	Spain	Caucasians	103/48	PCR-RFLP
Haap et al. [28]	2005	German	Caucasians	57/316	DNA sequencing
Witchel et al. [29]	2005	USA	Caucasians	114/95	PCR-RFLP
Sir-Petermann et al. [30]	2004	Chile	Caucasians	146/97	PCR-RFLP
El Mkadem et al. [31]	2001	France	Caucasians	53/102	PCR-RFLP
Sir-Petermann et al. [32]	2001	Chile	Caucasians	82/70	PCR-RFLP
Witchel et al. [33]	2001	USA	Caucasians	69/15	PCR-RFLP
Zhen et al. [16]	2000	China	Asians	163/100	PCR-RFLP

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Distribution of *IRS-1* rs1801278G>A polymorphisms genotype and allele among PCOS patients and controls

Study	Year	Case			Control			Case		Control		HWE
		GG	GA	AA	GG	GA	AA	A	G	A	G	
Lin et al.	2014	220	28	0	84	8	0	28	468	8	176	Yes
Skrgatic et al.	2013	131	18	1	142	25	3	20	280	31	309	Yes
Dasgupta et al.	2013	232	18	0	275	24	0	18	482	24	574	Yes
Kawamura et al.	2011	44	6	0	98	2	0	6	94	2	198	Yes
Pappalardo et al.	2010	14	50	1	22	5	0	52	78	5	49	Yes
Christopoulos et al.	2010	127	47	9	76	10	2	65	301	14	162	No
Dravecka et al.	2010	41	12	0	19	2	0	12	94	2	40	Yes
Marioli et al.	2010	148	12	2	112	9	1	16	308	11	233	Yes
Valdes et al.	2008	42	8	0	70	5	0	8	92	5	145	Yes
Baba et al.	2007	110	12	1	362	17	1	14	232	19	741	Yes
Lin et al.	2006	47	0	0	45	0	0	0	94	0	90	No
Dilek et al.	2005	46	14	0	55	5	0	14	106	5	115	Yes
Villuendas et al.	2005	90	13	0	41	7	0	13	193	7	89	Yes
Haap et al.	2005	50	6	0	272	44	0	6	106	44	588	Yes
Witchel et al.	2005	94	15	0	89	6	0	15	203	6	184	Yes
Sir-Petermann et al.	2004	129	14	0	93	4	0	14	272	4	190	Yes
El Mkadem et al.	2001	41	12	0	85	17	0	12	94	17	187	Yes
Sir-Petermann et al.	2001	72	10	0	66	4	0	10	154	4	136	Yes
Witchel et al.	2001	53	16	0	14	1	0	16	122	1	29	Yes
Zhen et al.	2000	130	20	13	83	11	6	46	280	23	177	No

HWE: Hardy-Weinberg equilibrium.

Table 3. Meta-analysis of the *IRS-1* rs1801278G>A polymorphism and PCOS risk

	No. of study	A vs. G			AA vs. GG			AA+GA vs. GG			AA vs. GA+GG			GA vs. GG		
		OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)
Total	20	1.67 (1.25-2.21)	<0.001	0.009	1.56 (0.79-3.08)	0.200	0.728	1.82 (1.30-2.53)	<0.001	0.001	1.39 (0.70-2.75)	0.346	0.854	1.81 (1.30-2.53)	<0.001	0.001
Ethnicity																
Asians	6	1.39 (1.02-1.91)	0.038	0.109	1.51 (0.58-3.90)	0.399	0.565	1.40 (1.00-1.97)	0.051	0.110	1.47 (0.57-3.80)	0.423	0.582	1.39 (0.97-1.98)	0.075	0.119
Caucasians	14	1.75 (1.21-2.53)	0.003	0.011	1.62 (0.61-4.28)	0.332	0.478	1.96 (1.26-3.04)	**0.003**	0.001	1.30 (0.49-3.49)	0.600	0.653	1.96 (1.27-3.03)	**0.002**	0.002
HWE																
≥0.05	17	1.67 (1.21-2.31)	0.002	0.010	1.25 (0.38-4.11)	0.716	0.521	1.83 (1.26-2.67)	0.002	0.001	1.01 (0.30-3.43)	0.990	0.684	1.83 (1.26-2.66)	**0.002**	0.001
<0.05	3	1.75 (0.90-3.41)	0.101	0.098	1.73 (0.75-3.98)	0.201	0.480	1.85 (0.83-4.10)	0.132	0.090	1.59 (0.69-3.68)	0.274	0.600	1.83 (0.77-3.43)	0.175	0.107
Publication year																
>2007	9	1.78 (1.07-2.96)	0.027	0.001	1.62 (0.61-4.28)	0.565	0.478	2.06 (1.11-3.80)	0.021	<0.001	1.30 (0.49-3.49)	0.600	0.653	2.06 (1.12-3.80)	**0.020**	<0.001
≤2007	11	1.59 (1.21-2.08)	0.001	0.361	1.51 (0.58-3.90)	0.399	0.565	1.64 (1.23-2.19)	0.001	0.334	1.47 (0.57-3.80)	0.423	0.582	1.65 (1.22-2.23)	0.001	0.346

HWE: Hardy-Weinberg equilibrium; Bold values are statistically significant ($P<0.05$).

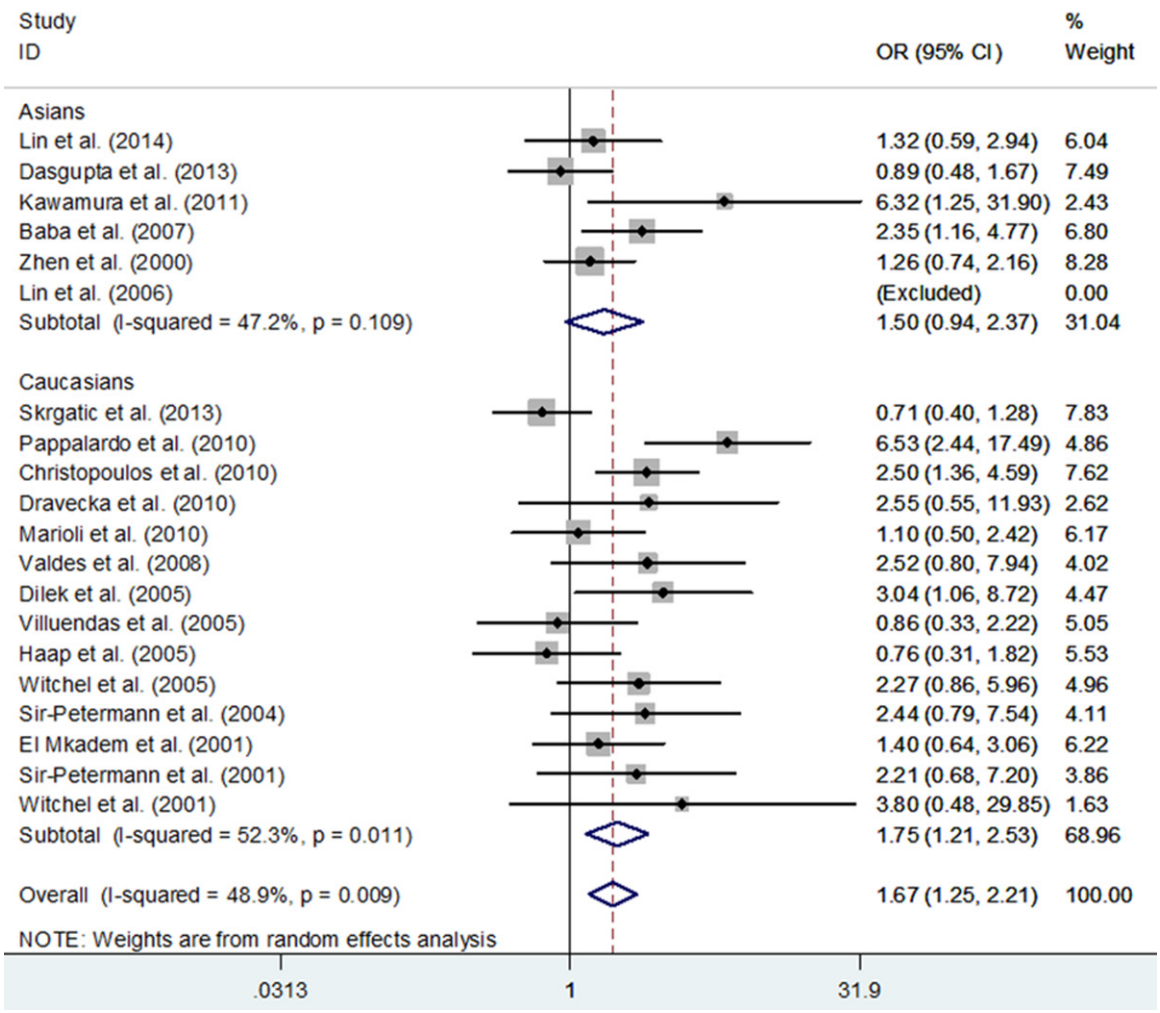

Figure 2. Forest plot of breast cancer risk associated with *IRS-1* rs1801278G>A polymorphism for the A vs. G (random effects model).

sided), the random-effects model (the DerSimonian-Laird method) was utilized to pool the data [13], otherwise the fixed-effects model (the Mantel-Haenszel method) was used [14]. Sub-group analyses were conducted according to different ethnicity to identify the specific effects of heterogeneity. Publication bias was assessed by Begg's funnel plot and Egger's test [15]. Sensitivity analyses were conducted by one-way method. For publication bias test, a $P<0.05$ (two-sided) was considered as statistical significance. All statistical analyses were performed using STATA version 12.0 software (Stata Corporation, College Station, TX).

Results

Characteristics

In total, three hundred and eighty-three articles were retrieved. **Figure 1** summarized the selecting process. Finally, a total of twenty studies met the inclusion criteria [8, 9, 16-33]. Among them, six were from Asia [9, 16-20], fourteen were from Caucasians [8, 21-33]. Characteristics of included studies and the distribution of *IRS-1* rs1801278G>A genotypes as well as the alleles are summarized in **Tables 1** and **2**, respectively.

Quantitative synthesis

There were twenty case-control studies met the major inclusion criteria with 2,228 PCOS cases and 2,327 controls. A total of twenty studies were included in the present pooled analysis. Fourteen case-control studies focused on Caucasians and six focused on Asians. Overall, there was a significant correlation of *IRS-1* rs1801278G>A polymorphism with PCOS risk (OR, 1.67; 95% CI, 1.25-2.21; $P<0.001$ for A *vs.*

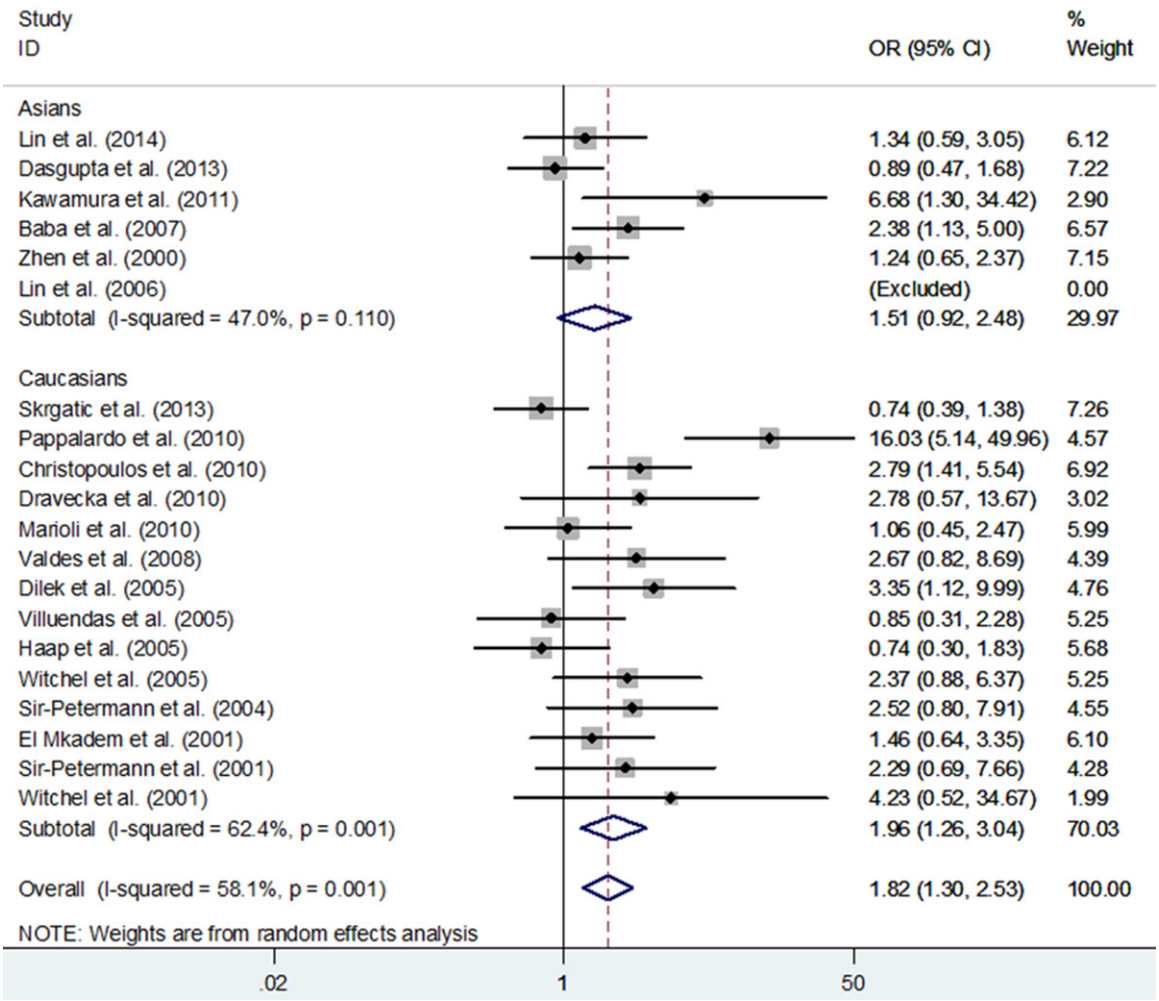

Figure 3. Forest plot of breast cancer risk associated with *IRS-1* rs1801278G>A polymorphism for the AA+GA vs. GG (random effects model).

G; OR, 1.82; 95% CI, 1.30-2.53; *P*<0.001 for AA+GA *vs.* GG and OR, 1.81; 95% CI, 1.30-2.53; *P*<0.001 for GA *vs.* GG; **Table 3**; **Figures 2** and **3**). In a subgroup analysis by ethnicity, *IRS-1* rs1801278G>A variants were correlated with a significantly increased susceptibility of PCOS among Caucasians (OR, 1.75; 95% CI, 1.21-2.53; *P*=0.003 for A *vs.* G; OR, 1.96; 95% CI, 1.26-3.04; *P*=0.003 for AA+GA *vs.* GG and OR, 1.96; 95% CI, 1.27-3.03; *P*=0.002 for GA *vs.* GG; **Table 3**; **Figures 2** and **3**) and among Asians (OR, 1.39; 95% CI, 1.02-1.91; *P*=0.038 for A *vs.* G). Other results were summarized in **Table 3**.

Tests for publication bias, sensitivity analyses, and heterogeneity

Publication bias was assessed by both the Begg's funnel plot and the Egger's test. A slight publication bias was found in some genetic models (A *vs.* G: Begg's test *P*=0.005, Egger's test *P*=0.024; AA *vs.* GG: Begg's test *P*=0.452, Egger's test *P*=0.737; AA+GA *vs.* GG: Begg's test *P*=0.030, Egger's test *P*=0.014; AA *vs.* GA+GG: Begg's test *P*=1.000, Egger's test *P*=0.907, GA *vs.* GG: Begg's test *P*=0.050, Egger's test *P*=0.010; **Figure 4**). Since the publication biases were identified in some genetic models, we performed nonparametric "trim-and-fill" method to measure the stability of our findings. The adjusted ORs and CIs were not materially altered, suggesting that our findings were relatively robust (A *vs.* G: adjusted pooled OR=1.345, 95% CI: 1.00-1.80, *P*=0.048; AA *vs.* GG: adjusted pooled OR=1.49, 95% CI: 0.75-2.98, *P*=0.258; AA+GA *vs.* GG: adjusted pooled OR=1.27, 95% CI: 0.88-1.82, *P*=0.198; AA *vs.* GA+GG: adjusted pooled OR=1.41, 95% CI: 0.70-2.86, *P*=0.341; GA *vs.* GG: adjusted

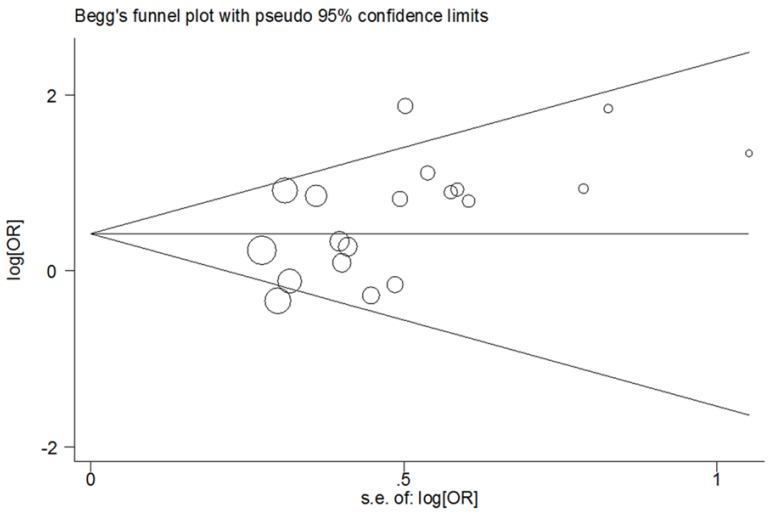

Figure 4. Begg's funnel plot analysis of *IRS-1* rs1801278G>A polymorphism with breast cancer risk for the A vs. G (random-effects model).

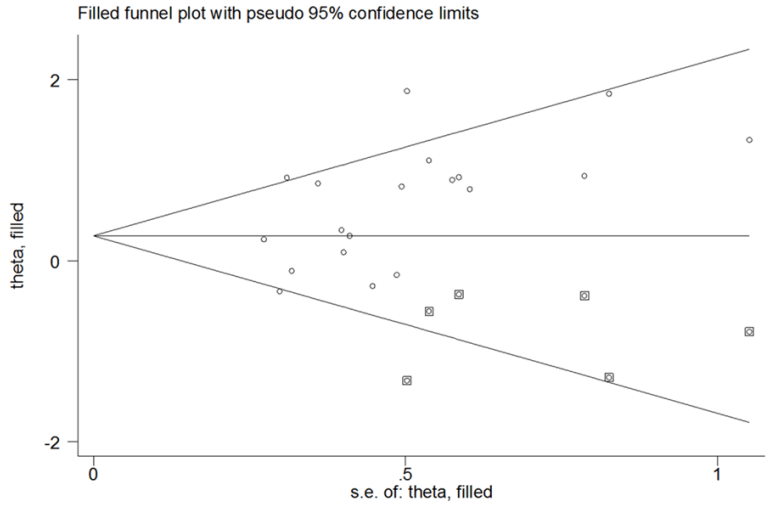

Figure 5. Filled funnel plot of meta-analysis of the association between *IRS-1* rs1801278G>A polymorphism and the risk of PCOS (A vs. G; random-effects model).

pooled OR=1.26, 95% CI: 0.88-1.82, *P*=0.210; **Figure 5**).

We conducted an one-way sensitivity analysis to test the influence of an individual data on the pooled ORs and CIs by eliding a study in turn. These findings suggested that our results were relatively stable (**Figure 6**) (data not shown).

As summarized in **Table 3**, heterogeneity was significant in overall and in some subgroups. Thus, we measured the sources of heterogeneity by subgroup analysis (**Table 3**). The results showed that Caucasian populations, P_{HWE}≥0.05 and publication year (>2007) subgroups may lead to the major sources of heterogeneity.

Discussion

PCOS is one of the leading causes of infertility with a very complex genetic aetiology. PCOS is characterized by several metabolic disorders that include peripheral IR, fasting and glucose-stimulated hyperinsulinemia, abnormalities of energy expenditure and dyslipidemia [34]. Additionally, an increased susceptibility of developing impaired glucose tolerance and T2DM at a relatively younger age is found in PCOS patients. It is highlighted that PCOS patients have significant IR which is due to a disorder of insulin signaling in some classic insulin target tissues, such as adipocytes and skeletal muscle [35]. In view of those findings, the *IRS-1* polymorphisms have been explored for the correlation with PCOS recently. Results of previous meta-analyses highlighted that the *IRS-1* rs1801278 A allele modified the risk of PCOS [10, 36]. Recently, more studies on the association of *IRS-1* rs1801278G>A polymorphism with PCOS risk were conducted; however, the findings were conflicting. In the light of the primary results, we summarized data for 2,228 PCOS cases and 2,327 controls from twenty included case-control studies and attempted to measure the risk of *IRS-1* rs1801278G>A variants to PCOS by a most comprehensive pooled analysis. Our findings suggested that *IRS-1* rs1801278 A allele might increase the risk of PCOS.

The *IRS-1* is situated on chromosome 2q36 and encodes a 131.6 kDa IRS-1 protein. The most common SNP, *IRS-1* rs1801278G>A (Gly972Arg), was considered to be correlated with IR, PCOS and T2DM [8, 9, 37, 38]. Recently,

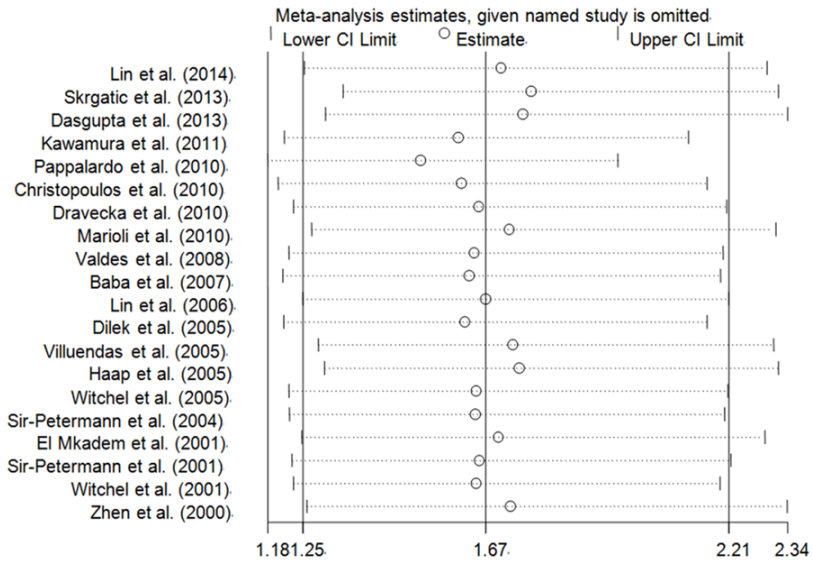

Figure 6. One-way sensitivity analysis of *IRS-1* rs1801278G>A polymorphism with breast cancer risk for the A vs. G (random-effects model).

a handful of case-control studies have explored the relationship of this SNP in *IRS-1* gene with PCOS risk. In 2005, Dilek *et al.* first reported that a G→A mutation in rs1801278 polymorphism was associated with the risk of PCOS [26]. Thereafter, more studies highlighted that *IRS-1* rs1801278G>A polymorhphism increased the risk of PCOS [8, 9, 20]. In this meta-analysis, the results demonstrated that *IRS-1* rs1801278G>A variants were associated with the increased risk of PCOS, which coincide with the findings of prior meta-analyses [10, 36]. A stratified analysis was also carried out regarding different ethnicities for the *IRS-1* rs1801278G>A polymorphism. This polymorhphism was related to the increased risk of PCOS in both Asians and Caucasians. Our results highlighted the influence of *IRS-1* rs1801278 genetic variants and consistency in different races to the risk of PCOS. Genotype distributions in the control subjects in three case-control studies [16, 17, 21] did not accord with the HWE, which suggested the presence of population stratification and/or genotyping errors. Thus, we conducted a subgroup analysis. When we removed these studies that deviated from the HWE, the correlation between *IRS-1* rs1801278G>A polymorphism and PCOS was also significant with respect to the three genetic models (OR, 1.67; 95% CI, 1.21-2.31; *P*=0.002 for A vs. G; OR, 1.83; 95% CI, 1.26-2.67; *P*=0.002 for AA+GA vs. GG and OR, 1.83; 95% CI, 1.26-2.66; *P*= 0.002 for GA vs. GG; **Table 3**).

Some limitations must be acknowledged in the interpretation of our results. First, the Begg's funnel plot test and the Egger's test showed a slight publication bias in some genetic models and although an extensive search was carried out, it is likely that some unpublished data were omitted. Selection bias for this pooled analysis might have occurred. These findings should be interpreted with very cautions. Second, our findings were based on unadjusted ORs and CIs, whereas a more precisely stratified analysis could be performed if the sufficient individual data were available, which might allow for an adjustment by other co-variables including age, body mass index, drinking status, cigarette consumption, other lifestyle factors and other biochemical indicator. Third, all included studies were relatively small sample sizes, which limited the power of the statistical analysis. Finally, due to lack of uniform individual-level data, further stratified analysis to measure any interactions between gene-gene variation and gene-metabolic traits was not performed.

In summary, our findings demonstrates that the *IRS-1* rs1801278G>A polymorphism probably contributes to increased risk of PCOS among both Caucasians and Asians. Nevertheless, for practical reasons, future studies are warranted to confirm or refute these correlations, particularly with respect to the interactions of gene-gene and gene-environment.

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Disclosure of conflict of interest

None.

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