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META-ANALYSIS

Association between SHBG (TAAAA)n and AR (CAG)n polymorphisms and PCOS risk: A meta-analysis

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Abstract

AIM: To systematically assess the association between sex hormone-binding globulin (SHBG) (TAAAA)n and androgen receptor (AR) (CAG)n polymorphisms and polycystic ovarian syndrome (PCOS) risk.

METHODS: We searched MEDLINE (PubMed), EMBASE and Web of Science database from inception to May 2014. To avoid missing any additional studies, we looked through all the references of relevant articles. Case-control studies concerning the (CAG)n variants in the *AR* gene or the (TAAAA)n polymorphism in the *SHBG* gene in PCOS patients were included. Five studies regarding the (TAAAA)n polymorphism in the *SHBG* gene and 14 studies regarding the (CAG)n polymorphism in the AR gene met our criteria. Odd ratio (OR) and weighted mean difference (WMD) were selected as the effect size measurements to evaluate the influence of the (TAAAA)n polymorphism and (CAG)n variants on PCOS risk. Begg's test was used for the evaluation of publication bias.

RESULTS: With respect to the relationship between the (TAAAA)n polymorphism and PCOS risk, the statistical results showed that there was no significant difference between PCOS patients and controls in the alleles of TAAAA (S: OR = 0.91, 95%CI: 0.78-1.05; L: OR = 1.10, 95%CI: 0.95-1.27). Subgroup analyses of the combination of alleles indicated similar results (short-short: OR = 0.87, 95%CI: 0.66-1.14; short-long: OR = 1.12, 95%CI: 0.86-1.46; long-long: OR = 1.03, 95%CI: 0.72-1.47). As for the relationship between the (CAG)n polymorphism and PCOS risk, we found no association between CAG repeat variants and PCOS risk (WDM = 0.03, 95%CI: -0.13-0.08). Subgroup analyses by race and diagnosis criteria indicated the same results (Asian: WMD = -0.03, 95%CI: -0.14-0.07; Caucasian: WMD = -0.02, 95%CI: -0.24-0.21; the criteria of Rotterdam: WMD = 0.01, 95%CI: -0.01-0.03).

CONCLUSION: There is no association between (TAAAA)n polymorphism in SHBG gene, (CAG)n repeat variants in *AR* gene and PCOS.

Key words: Sex hormone-binding globulin; TAAAA; Androgen receptor; CAG; Polycystic ovarian syndrome

Core tip: Our study investigated the association between sex hormone-binding globulin (SHBG) (TAAAA)n and androgen receptor (AR) (CAG)n polymorphisms and polycystic ovarian syndrome (PCOS) risk. Five studies regarding the (TAAAA)n polymorphism in the *SHBG* gene and 14 studies regarding the (CAG)n polymorphism in the *AR* gene were included based on the strict inclusion criteria. The overall meta-analysis, as well as the subgroup analysis, showed that there was no association between PCOS risk and the SHBG (TAAAA)n polymorphism or AR (CAG)n repeat variants.

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INTRODUCTION

The morbidity of polycystic ovarian syndrome (PCOS) is estimated to be 7%[1] in women of reproductive age and it is characterized by hyperandrogenism, chronic anovulation and polycystic ovaries[2]. There are three main diagnostic guides for PCOS, including the 1990 National Institutes of Health criteria, the 2003 Rotterdam criteria and the 2006 Androgen Excess and PCOS Society criteria[3-5]. Hyperandrogenism plays an important part in these PCOS diagnostic features and is increasingly considered a main pathogenic factor of PCOS[4]. Recently, the genetic aspects of PCOS have been clarified to prove the presence of genetic abnormalities in PCOS patients. Although the specific genetic alterations that contribute to the development of PCOS remain unclear, several candidate genes have been proposed, including the sex hormone-binding globulin (*SHBG*) gene and the androgen receptor (*AR*) gene[6].

The *SHBG* gene (17p13-p12) encodes a 373 amino acid polypeptide that regulates the bioavailability of sex steroids by binding androgens, particularly testosterone and estrogens[7,8]. The free SHBG levels frequently diminish in patients with hyperandrogenism, especially in those who have PCOS, which may result in an increase in free androgen levels and magnify the biological impact of androgens. SHBG can be influenced by many factors, including gender, age, metabolic, genetic and nutritional factors, with genetic factors being more important[9,10]. A (TAAAA)n repeat variant in the 5' non-coding region of SHBG promoter has been described and its influence on *in vitro* transcriptional activity has been reported[11]. Compared with normal women, those with PCOS tend to have a significantly greater frequency of longer (TAAAA)n alleles (more than eight repeats)[10]. However, the genetic association studies between (TAAAA)n repeat polymorphism of SHBG and PCOS risk show controversial results, which make it difficult to judge PCOS by the number of SHBG (TAAAA)n repeats.

The *AR* gene (Xq11-q12)[12] consists of eight exons and seven introns. The CAG trinucleotide repeats in exon 1 ranged in length from 8 to 35 in healthy individuals and have been reported to influence the transcriptional activity of AR[13]. Chamberlain *et al*[13] reported that there was a negative correlation between the number of CAG repeats and the AR activity, which means that a higher number of CAG repeats is associated with a lower AR biological activity. There are several studies focusing on the relationship between CAG repeat number and PCOS risk, but inconsistent results make it hard to assess the importance of CAG repeat number in PCOS.

Currently, there is no consensus regarding the relationship between SHBG (TAAAA)n polymorphism, AR CAG length and PCOS, although this relation may influence the time to diagnosis and drug intervention. For this reason, we conducted this meta-analysis to address such inconsistency.

MATERIALS AND METHODS

Data sources and searches

We underwent a systematic search of MEDLINE (PubMed), EMBASE, and Web of Science database with the assistance of computer from inception to May 2014, attempting to find all publications about the relationship between (TAAAA)n SHBG and (CAG)n AR polymorphisms and PCOS. Key words for the search of MEDLINE were as follows: ("sex hormone-binding globulin" or "SHBG") and "TAAAA" and ("polycystic ovarian syndrome" or "PCOS") for the *SHBG* gene and ("androgen receptor" or "AR") and "CAG" and ("polycystic ovarian syndrome" or "PCOS") for the *AR* gene. We used similar strategies to search EMBASE. The abstracts of additional meetings were mainly from Web of Science. To avoid missing any additional studies, we looked through all the references of relevant articles.

Study selection

We skimmed titles and abstracts of identified papers to exclude studies that clearly not meeting the inclusion criteria and retrieved the full texts of selected studies for further review and evaluation.

The inclusion criteria for studies were as follows: (1) studies concerning the association between the (CAG)n polymorphism in the *AR* gene or (TAAAA)n variants in the *SHBG* gene and PCOS risk; (2) independent case-control study; (3) specific diagnosis criteria for PCOS; (4) hospital-based healthy women were selected as controls; and (5) data were enough for our further analysis. In order to avoid overlapping data, only the latest study or the study having the most sufficient data was enrolled in our analysis if several studies were conducted by the same author.

Data extraction

Two authors (Jin JW and Chen SL) extracted data from

Table 1 Characteristics of studies on (TAAAA)n sex hormone-binding globulin polymorphism and polycystic ovarian syndrome

Ref.	Year	Country	Race	PCOS women	Controls	PCOS alleles (2 n)		Controls alleles (2 n)		PCOS women genotype			Controls genotype			PCOS diagnostic criteria
						S (< 8 repeats)	L (≥ 8 repeats)	S (< 8 repeats)	L (≥ 8 repeats)	SS	SL	LL	SS	SL	LL	
Xita *et al*[10]	2003	Greece	Caucasian	185	324	230	140	446	202	NR	NR	NR	NR	NR	NR	A
Zhao *et al*[24]	2005	China	Asian	157	156	180	134	175	137	48	84	25	48	79	29	B
Ferk *et al*[26]	2007	Slovenia	Caucasian	123	110	155	91	151	69	54	48	21	52	47	11	C
Liu *et al*[27]	2008	China	Asian	187	176	216	158	210	142	59	96	32	66	78	32	C
Díaz *et al*[25]	2010	Spain	Caucasian	70	107	102	38	139	75	NR	NR	NR	NR	NR	NR	D

A: The 1990 National Institutes of Health–National Institute of Child Health and Human Development conference on PCOS; B: (1) Amenorrhoea or oligomenorrhoea; (2) LH/FSH ⩾ 2.5 or T ⩾ 1.56; (3) More than 10 follicles measuring 2-8 mm in diameter at least in one ovary; and (4) Exclusion of congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumor, hyperprolactinaemia and thyroid dysfunction; C: The criteria of Rotterdam Revised 2003 (two of three) diagnosis; D: (1) Hirsutism; (2) Amenorrhoea or oligomenorrhoea; (3) Increased serum T and/or androstenedione and 17OH-P hyperresponse to GnRH agonist; and (4) Hyperinsulinaemia during an oral glucose tolerance test. PCOS: Polycystic ovarian syndrome; S: Short alleles; L: Long alleles; SS: Short-short genotype; SL: Short-long genotype; LL: Long-long genotype; NR: Non-reported.

each selected article independently and the specific items were as follows: (1) first author; (2) year of publication; (3) regions of the population investigated; (4) diagnosis criteria for PCOS; (5) size of controls and PCOS patients; (6) the number of cases and controls for SHBG (TAAAA)n alleles and genotype; and (7) the mean and standard deviation of cases and controls for AR (CAG)n repeats. We extracted quantitative data directly from articles or using original information provided in the tables and figures[14].

Statistical analysis

We used STATA Statistical Software for all the analyses (version 12.0, STATA Corporation, United States). The evaluation indicators were odd ratio (OR) with 95%CI for the *SHBG* gene and weighted mean difference (WMD) with 95%CI for the *AR* gene.

Meta-analysis

We used two models to calculate the pooled OR and WMD estimates with 95%CI: a fixed-effects model known as Mantel Haenszel method[15] or a random-effects model known as Der Simonian-Laird method[16]. We used the χ^2 test to evaluate the heterogeneity of the studies[17] and the quantity I^2 was also calculated[18,19]. I^2 is the percentage of between-study variation in total variation. The value of 25% is regarded as low heterogeneity while the value of 75% represents high heterogeneity. While I^2 was over 50%, the random-effect model was used instead of the fixed-effect model.

Publication bias was evaluated to find whether the results of the studies were homogeneous[20], and the Egger regression asymmetry test[21] and the Begg-Mazumdar adjusted rank correlation test[22] were used. When the *P*-value of the Egger's test or Begg's test was < 0.05, we considered significant bias among the studies.

RESULTS

Search results

For the (TAAAA)n polymorphism in the *SHBG* gene, 22 records were found in electronic databases, including 8 records in MEDLINE, 11 records in Web of Science database and 3 records in EMBASE. According to the selection criteria, we ultimately identified 5 studies for our final statistical analysis (Figure 1). Table 1 summarizes the characteristics of all the included studies. For the (CAG)n repeats in the *AR* gene, a total of 65 studies were found, including 26 records in MEDLINE, 37 records in Web of Science database and 2 references from reference lists. According to the selection criteria, we identified 14 studies for our meta-analysis (Figure 2) and present their characteristics in Table 2.

Meta-analysis of the SHBG (TAAAA)n polymorphism and PCOS risk

We involved 5 studies, a total of 722 cases and 873 controls, to compare short (S) alleles and long (L) alleles in PCOS patients with those in controls. Because heterogeneity

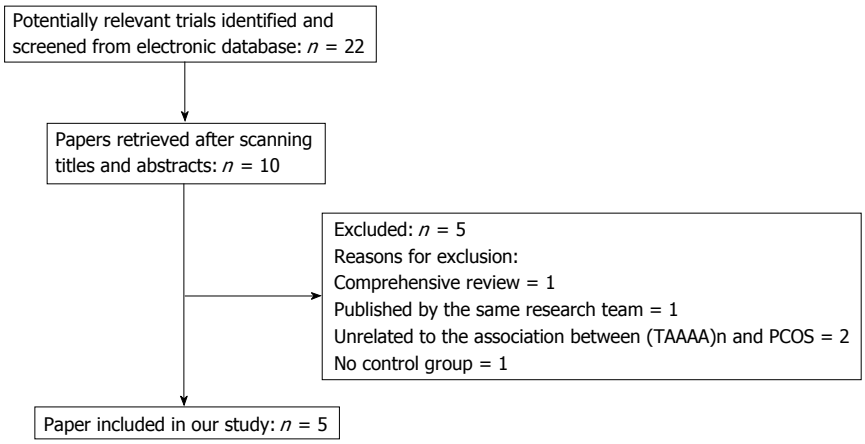

Figure 1 Strategy for searching studies concerning the association between the (TAAAA)n sex hormone-binding globulin polymorphism and polycystic ovarian syndrome risk. PCOS: Polycystic ovarian syndrome.

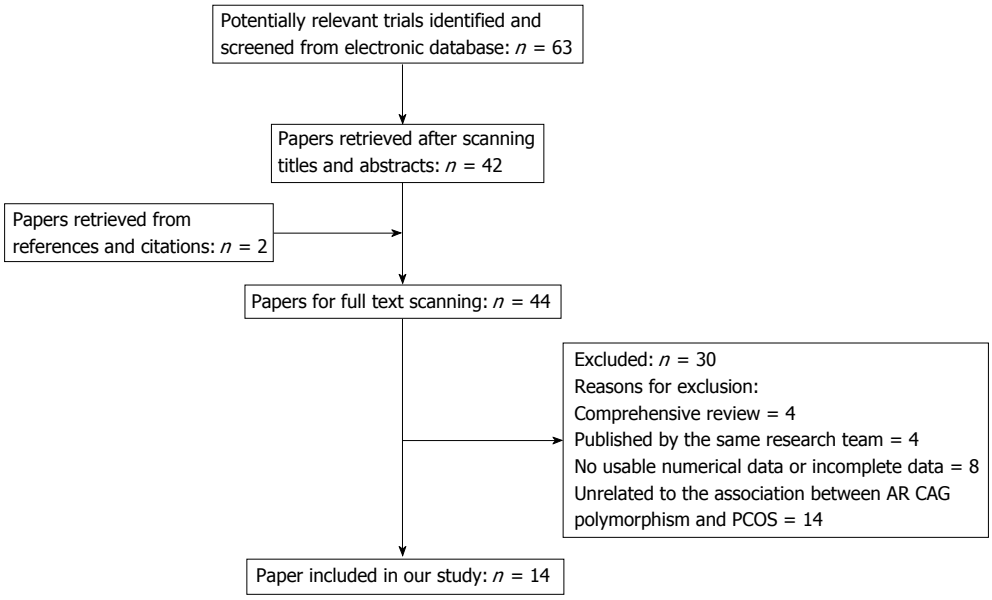

Figure 2 Strategy for searching studies concerning the association between the (CAG)n androgen receptor polymorphisms and polycystic ovarian syndrome risk. AR: Androgen receptor; PCOS: Polycystic ovarian syndrome.

was moderate (I^2 = 47.8% < 50%), we calculate the pooled OR estimates with 95%CI using the fixed-effects model (S: OR = 0.91, 95%CI: 0.78-1.05; L: OR = 1.10, 95%CI: 0.95-1.27) (Figure 3 and Table 3). We considered there was no significant association between PCOS and (TAAAA)n SHBG allele. No obvious publication bias was found in all the selective studies.

On the other hand, we identified 3 studies to compare short-short (SS) genotype, short-long (SL) genotype and long-long (LL) genotype in PCOS patients with those in controls. Because heterogeneity was low (SS: I^2 = 0; SL: I^2 = 0; LL: I^2 = 29.6%), we calculated OR using the fixed-effects model (SS: OR = 0.87, 95%CI: 0.66-1.14; SL: OR = 1.12, 95%CI: 0.86-1.46; LL: OR = 1.03, 95%CI: 0.72-1.47) (Figure 4 and Table 3). Similar to the results of alleles, there was no association between PCOS and (TAAAA)n SHBG genotype. No obvious publication bias was found in all the selective studies.

Meta-analysis of the AR (CAG)n polymorphism and PCOS risk

We involved 14 studies (1882 cases and 1988 controls in total) to compare biallelic mean of CAG length in PCOS patients with controls. Because heterogeneity was moderate (I^2 = 51.0% > 50%), we calculate the pooled WMD estimates with 95%CI using the random-effects model (WMD = 0.03, 95%CI: -0.13-0.08) (Figure 5 and Table 4). Begg's test (P = 0.621) and Egger's test (P = 0.866) showed no obvious publication bias. Further, subgroup analyses were done by race and diagnosis criteria. Because the heterogeneity was high in subgroup by race (Asian: I^2 = 72.9%; Caucasian: I^2 = 41.9%) and low by diagnosis criteria (The criteria of Rotterdam: I^2 = 0), random and fixed models were used, respectively.

Table 2 Characteristics of studies on (CAG)n androgen receptor polymorphism and polycystic ovarian syndrome

Ref.	Year	Country	Race	PCOS			Controls			PCOS diagnostic criteria
				Size	Mean	Std dev	Size	Mean	Std dev	
Mifsud *et al*[23]	2000	Singapore	Asian	91	22.97	0.24	112	23.09	0.23	A
Hickey *et al*[37]	2002	Australia	Caucasian	122	23	2.025	83	22.34	2.094	B
Jääskeläinen *et al*[43]	2005	Finland	Caucasian	106	21.5	2.2	112	21.5	2.1	C
Kim *et al*[39]	2008	South Korea	Asian	114	23.3	1.8	205	23.1	2	D
Ferk *et al*[38]	2008	Slovene	Caucasian	102	22.4	3.5	110	21.9	3.5	E
Liu *et al*[27]	2008	China	Asian	148	22.88	1.76	104	22.85	1.6	D
Shah *et al*[36]	2008 (1)	America	Caucasian	270	21.8	3.1	165	22.3	3.11	B
Shah *et al*[36]	2008 (2)	America	Black	37	20.1	3.44	84	20.2	3.08	B
Van Nieuwerburgh *et al*[40]	2008	Belgium	Caucasian	97	21.93	2.122	31	21.823	3.112	NC
Dasgupta *et al*[41]	2010	India	Asian	250	18.74	0.13	299	18.73	0.12	D
Laisk *et al*[34]	2010	Estonia	Caucasian	32	21.5	1.6	79	21.6	1.8	D
Robeva *et al*[44]	2010	Bulgaria	Caucasian	52	21.6	2.62	41	21.3	3.71	D
Skrgatic *et al*[42]	2011	Croatia	Caucasian	214	22.1	3.4	209	21.9	3.2	D
Schüring *et al*[35]	2011	Germany	Caucasian	72	21.43	1.87	179	21.99	2.07	D
Rajender *et al*[47]	2013	India	Asian	169	17.39	2.29	175	17.43	2.43	D

A: (1) Proven fertility; (2) No history of subfertility treatment; and (3) Normal menstrual cycles (25-32 d); B: National Institutes of Health criteria; C: (1) Non-hirsute; (2) Proven fertility; (3) Regular menstrual cycles; and (4) Normal ovaries; D: The criteria of Rotterdam Revised 2003 (two of three); E: (1) Oligo-/amenorrhea; (2) Polycystic ovaries; and (3) Hyper-androgenism. PCOS: Polycystic ovarian syndrome; NC: Unclear.

Table 3 Meta-analysis of (TAAAA)n sex hormone-binding globulin polymorphism and polycystic ovarian syndrome

	No. of studies	OR (95%CI)	Heterogeneity			Publication bias	
			χ^2	I^2 (%)	*P*	Begg's *P*	Egger's *P*
S (< 8 repeats)	5	Fixed, 0.91 (0.78-1.05)	7.59	47.8	0.108	0.221	0.221
L (≥ 8 repeats)	5	Fixed, 1.10 (0.95-1.27)	7.30	45.2	0.121	0.221	0.225
SS	3	Fixed, 0.87 (0.66-1.14)	0.60	0.0	0.749	1.000	0.564
SL	3	Fixed, 1.12 (0.86-1.46)	1.64	0.0	0.441	0.296	0.072
LL	3	Fixed, 1.03 (0.72-1.47)	2.84	29.6	0.242	1.000	0.256

OR: Odd ratio; S: Short alleles; L: Long alleles; SS: Short-short genotype; SL: Short-long genotype; LL: Long-long genotype.

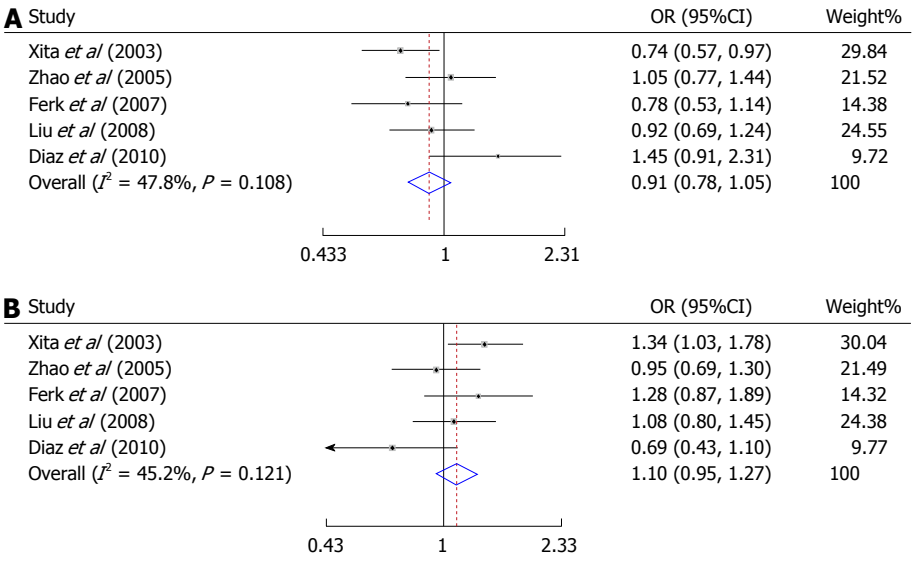

Figure 3 Association between polycystic ovarian syndrome risk and (TAAAA)n sex hormone-binding globulin alleles. A: Comparison of short alleles in the PCOS group with those in the control group; B: Comparison of long alleles in the PCOS group with those in the control group. PCOS: Polycystic ovarian syndrome.

We found that the (CAG)n repeats in race group (Asian: WMD = -0.03, 95%CI: -0.14-0.07; Caucasian: WMD = -0.02, 95%CI: -0.24-0.21) (Figure 6 and Table 4) and in diagnosis criteria group (the criteria of Rotterdam: WMD

Table 4 Meta-analysis of (CAG)n androgen receptor polymorphism and polycystic ovarian syndrome

		Number of studies	WMD (95%CI)	Heterogeneity			Publication bias	
				χ^2	I^2 (%)	*P*	Begg's *P*	Egger's *P*
All		15	Random, -0.03 (-0.13, 0.08)	28.55	51.0	0.012	0.621	0.866
Race	Asian	5	Random, -0.03 (-0.14, 0.07)	14.74	72.9	0.005	0.806	0.875
	Caucasian	9	Fixed, -0.02 (-0.24, 0.21)	13.77	41.9	0.088	0.175	0.596
The criteria of Rotterdam		8	Fixed, 0.01 (-0.01, 0.03)	5.91	0.0	0.550	1.000	0.784

WMD: Weighted mean difference.

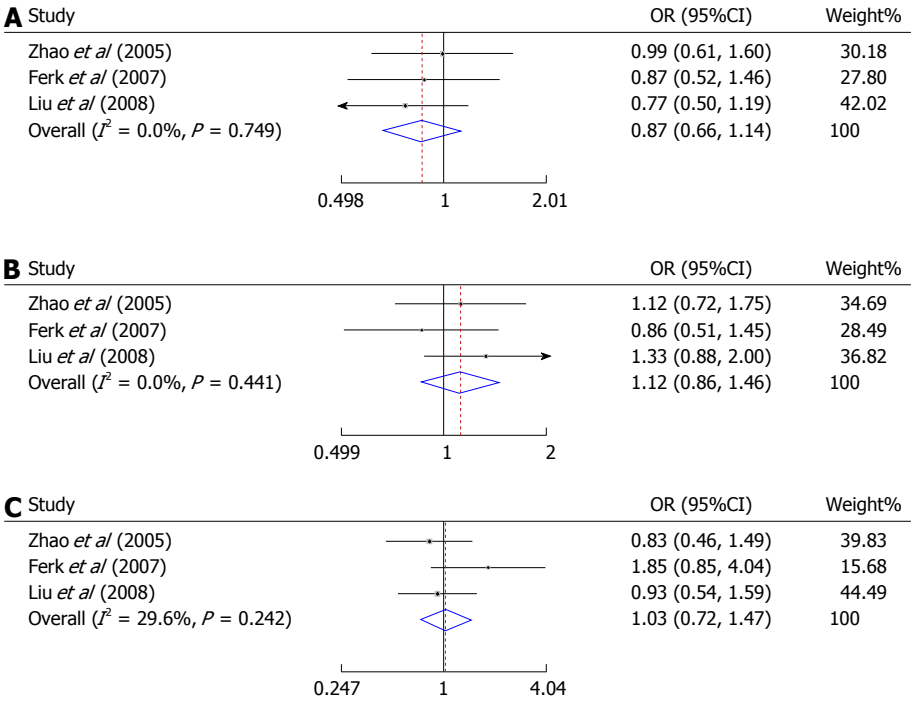

Figure 4 Association between polycystic ovarian syndrome risk and (TAAAA)n sex hormone-binding globulin genotypes. A-C: Comparison of short-short (A), short-long (B), long-long (C) genotype in the PCOS group with those in the control group. PCOS: Polycystic ovarian syndrome.

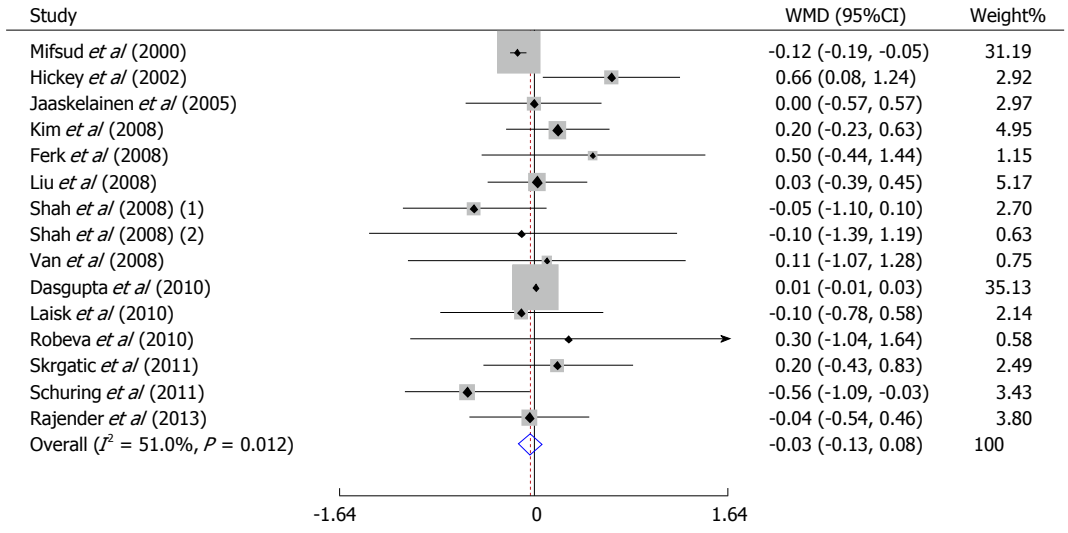

Figure 5 Association between polycystic ovarian syndrome risk and (CAG)n repeats in androgen receptor in all selected studies. WMD: Weighted mean difference.

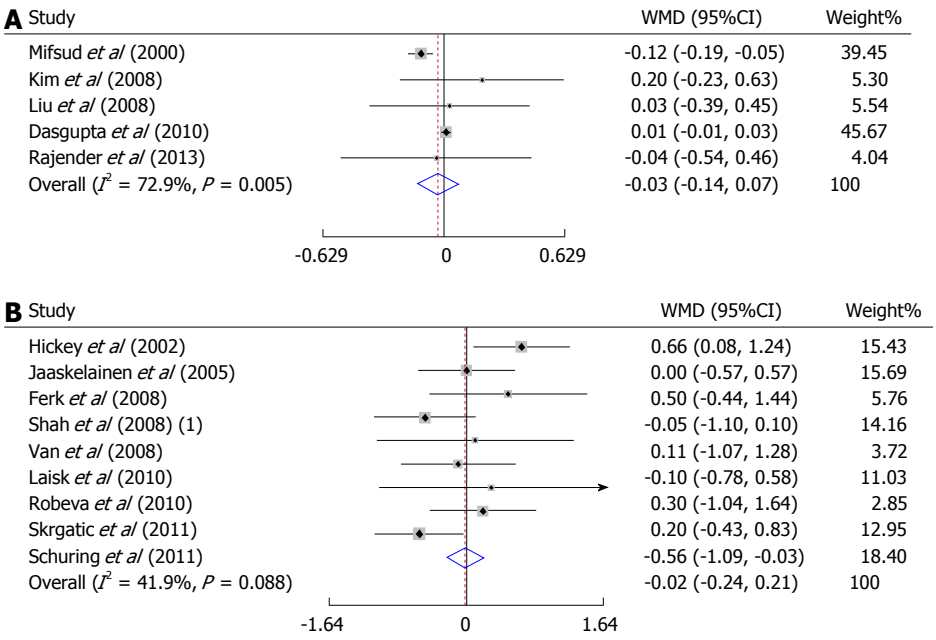

Figure 6 Association between polycystic ovarian syndrome risk and (CAG)n repeats in polycystic ovarian syndrome by race. A: Asian; B: Caucasian. WMD: Weighted mean difference.

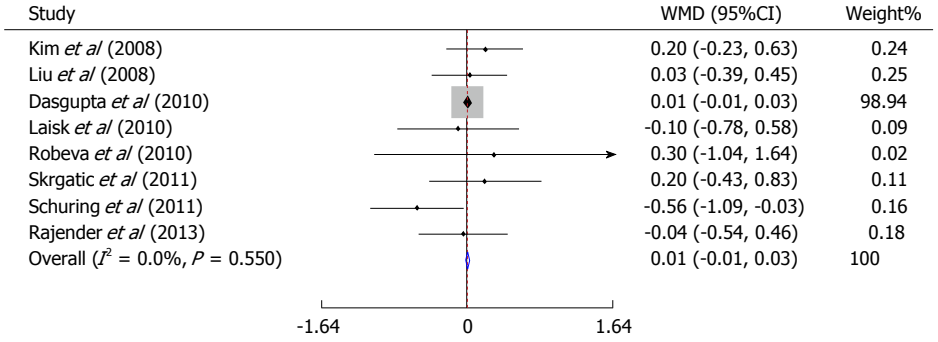

Figure 7 Association between polycystic ovarian syndrome diagnosed according to the criteria of Rotterdam Revised 2003 and (CAG)n repeats in androgen receptor. WMD: Weighted mean difference.

= 0.01, 95%CI: -0.01-0.03) (Figure 7 and Table 4) had no association with PCOS, which was similar to the previous results.

DISCUSSION

PCOS is a multifactorial disorder of unclear etipathogenesis. Hyperandrogenism is gradually being the hallmark of PCOS, and it is an item included in all the three worldwide diagnostic guides. SHBG regulates the bioavailability of sexual hormones to target tissues and is the primary plasma transport protein for those hormones, while AR is the protein to bind androgen and activate the downstream pathway in target cells. Since Xita *et al*[10] first reported PCOS risk in association with genetic variants in SHBG and Mifsud e*t al*[23] reported the relationship between PCOS risk and AR polymorphic CAG repeat, a series of following studies were performed. If there was a definite conclusion of PCOS risk with SHBG or AR polymorphism, PCOS could been caught earlier and prognosis would be better.

For the *SHBG* gene, Xita *et al*[10] discovered that PCOS women had a greater frequency of longer (TAAAA)n (more than 8 repeats) than normal women and proposed that (TAAAA)n repeat variants may be implicated in the development of PCOS. Whereafter, some case-control experiments proved this[24], but others did not[25-27]. In our meta-analysis, we selected OR as the effect size measurement to estimate the influence of (TAAAA)n repeat variants on PCOS risk. The summary ORs for TAAAA alleles (including S and L) indicated that there was no association between the TAAAA polymorphism and PCOS risk. Furthermore, the ORs of the combination of TAAAA alleles (SS, SL and LL) showed no differences between PCOS patients and controls either. These results indicate that the (TAAAA)n polymorphism has no influence on the development of PCOS. As Martínez-García *et al*[28] proposed SHBG as a candidate gene for PCOS, our result may be partly explained by the influence of other single nucleotide polymorphisms in the *SHBG*

gene, such as *rs1799941*[29], *rs2075230*[30], *rs6257* (T/C)[31], *rs727428*[32] and *rs6259*[28].

Our analysis on the *SHBG* gene has several strengths: (1) selection of different combinations of alleles; (2) comprehensive search for original case-control studies without limitation of language; and (3) adoption of bias measurements to avoid publication bias in study selection and data abstraction. On the other hand, limitations exist in this meta-analysis: (1) the numbers of studies and subjects included in this meta-analysis were small; (2) the diagnosis criteria for PCOS in selected studies were different and could not guarantee that involved PCOS cases had similar characteristics; and (3) only publications were enrolled in our meta-analysis, resulting in potential publication bias which was inevitable.

For the *AR* gene, there has been a study showing that higher AR activity correlated with shorter CAG and speculating that the CAG repeat variants were a sign in the development of PCOS[23]. A series of following case-control studies were performed to confirm this result. After scanning titles, abstracts and full texts, fourteen studies were included in our analysis. Among those, four showed that there were more short CAG alleles in PCOS patients compared with controls[33-36], while eight reported the opposite results[27,37-42] and the remaining two found no significant difference between the two groups[43,44]. We selected WMD as the effect size measurement to estimate the association between (CAG)n repeat variants and PCOS risk. The summary WMD for mean of CAG alleles showed that there was no statistical relationship between CAG repeat variants and PCOS risk. Furthermore, the WMD of CAG biallelic mean in subgroups (by race: Asian and Caucasian; by diagnosis criteria: the Rotterdam criteria) displayed no difference between cases and controls. These statistical results indicate that the CAG repeat variants have no influence on the development of PCOS, which was similar to the conclusions of three other meta-analysis[45-47].

Our meta-analysis on the *AR* gene has several strengths: (1) subgroup analysis was performed by race and diagnosis criteria; (2) comprehensive search for original case-control studies was done without limitation of language; and (3) most studies were proved to be homogeneous. Further, there are some limitations in our study: (1) only biallelic mean of CAG repeat variants was analyzed, without analysis on CAG alleles and genotype; (2) the number of studies focusing on Black was small, making it hard to analyze the association in the Black population; and (3) most results were not adjusted because of the inconsistent characteristics of participants among different studies.

In summary, there is no association between SHBG (TAAAA)n and AR (CAG)n polymorphisms and PCOS risk. In order to further understand the relationship between gene polymorphisms and PCOS risk, more studies should be launched to enlarge the sample size and variety of gene polymorphisms with unified diagnostic criteria, which will make the meta-analysis more convincing and useful.

COMMENTS

Background

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age and its risk is increasing in the association with genetic variants. The (TAAAA)n polymorphism in the sex hormone-binding globulin (*SHBG*) gene and the (CAG)n polymorphism in the androgen receptor (*AR*) gene are two hotspots, but there are no definite results regarding the association between those two genetic variants and PCOS risk.

Research frontiers

Over the past two decades, many studies have been performed to understand the associations between SHBG (TAAAA)n and AR (CAG)n repeat variants and PCOS risk. Moreover, several systematic reviews were recently performed to investigate these associations. However, the inclusion criteria varied greatly among those reviews and thus could not achieve a comprehensive conclusion.

Innovations and breakthroughs

Based on this meta-analysis, neither the TAAAA polymorphism in the *SHBG* gene nor the CAG polymorphism in the *AR* gene has no influence on the risk of PCOS. Similar results were indicated in subgroup analyses of the combination of alleles by race and diagnosis criteria, which were not presented clearly in previous reviews.

Applications

SHBG (TAAAA)n and AR (CAG)n repeat variants have no association with PCOS risk, which prompts a further investigation of other single nucleotide polymorphisms in those genes, including *rs1799941*, *rs2075230*, *rs6257* (T/C), *rs727428* and *rs6259*.

Terminology

Polymorphism is the regular and simultaneous occurrence in a single interbreeding population of two or more discontinuous genotypes. The concept includes differences in genotypes ranging in size from a single nucleotide site to large nucleotide sequences visible at the chromosomal level.

Peer review

This is a good meta-analysis in which the authors investigated the association among SHBG (TAAAA)n and AR (CAG)n polymorphisms and PCOS risk. The result definitely proved the results of previous reviews and informed that other polymorphisms in the *SHBG* and *AR* genes may contribute to PCOS risk. The meta-analysis is innovative and the manuscript is well written.

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