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Aryl hydrocarbon receptor rs2066853 gene polymorphisms and male infertility risk: a meta-analysis

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ABSTRACT

To evaluate the relationship between the aryl hydrocarbon receptor (*AHR*) rs2066853 gene polymorphism and the risk of male infertility. PubMed, Embase, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) were searched for relevant case–control studies up to 31 July 2019. Odds ratio (OR) and 95% confidence interval (95% CI) were used to assess the strength of associations. Finally, seven case–control studies involving 1247 cases and 1762 controls were included in this meta-analysis. The pooled results showed that there was no significant association between *AHR* rs2066853 gene polymorphism and male infertility risk (A vs. G: OR = 1.08, 95% CI = 0.83–1.39; AA vs. GG: OR = 1.16, 95% CI = 0.65–2.04; AA vs. GA + GG: OR = 1.17, 95% CI = 0.66–2.07; AA + GA vs. GG: OR = 0.99, 95% CI = 0.85–1.15). Subgroup analysis by ethnicity showed the same result. However, significant association was found between *AHR* rs2066853 gene polymorphism and male infertility risk in oligoasthenotspermia (A vs. G: OR = 2.52, 95% CI = 1.72–3.70). In conclusion, our meta-analysis indicated that *AHR* rs2066853 gene polymorphism might be associated with an increased susceptibility to oligoasthenotspermia.

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Aryl hydrocarbon receptor; AHR gene; polymorphism; male infertility; meta-analysis

Introduction

Infertility is a worldwide health problem, which affects an estimated 15% of all couples trying to conceive a child [1,2]. Approximately half of all infertility cases caused by factors related to the male partner [3]. The etiology of male infertility is complicated and not yet fully established, environment, lifestyle risk factors and genetic causes may be possible risk factors [4,5]. Genetic causes, such as chromosomal aberrations and single gene mutations, play important roles in developing male infertility among these risk factors [4–6]. Researches have indicated that genetic abnormalities may contribute to approximately 15% of male infertility [6].

The *AHR* is a ligand-activated transcription factor (TF) that belong to the basic helix–loop–helix.

Per-Arnt-Sim (bHLH/PAS) family which regulates a wide range of biological and toxicological effects [7,8]. *AHR*, in association with Hsp90, usually existing in cytoplasm, where dioxins plays as ligands and bind to *AHR*. After translocating to the nucleus, Hsp90 switches to *AHR* nuclear translocator (Arnt) and the ligand-*AHR*-Arnt complex binds to the cognate xenobiotic responsive elements (XREs) in the promoter/enhancer region, which are evolved in the upstream of the target genes for CYP1A1, GST, and others to activate their expressions [9–11]. Seventy-five dioxin congeners and 135 furan congeners, widely existing in environmental pollutants, are capable of binding to and activating the aryl hydrocarbon receptor (*AHR*) signaling pathway [12]. It has been well revealed in animal studies that *AHR* plays an important role in reproductive function in both sexes [13,14]. Adult female animals exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) were found a general decrease in reproductive health, including decreased fertility and litter size, alterations in estrous/menstrual cycles, and an increased abortion rate [15,16]. *AHR* pathway protein distributes widely in the testicular tissues. Testicular functions, especially spermatogenesis and sperm motility, are sufficiently reduced

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by exposure to PAHs through activation of *AHR* [17]. *AHR* plays an important role in mediating the toxic actions of POPs, which inspires researchers to study the association between polymorphisms of genes involved in *AHR* pathway and sensitivity to POPs exposure.

The c.1661G>A transition (rs2066853) is the most widely studied SNP in the *AHR* gene which leads to an arginine to lysine change at codon 554 (p.Arg554Lys) in the transcriptional activation domain (TAD) of the receptor. Several researches have explored the associations between *AHR* rs2066853 gene polymorphism and male infertility risk. However, most of those researches had small patient sample sizes, and the results were inconclusive rather than consistent. Therefore, we conducted a meta-analysis to evaluate the association between the *AHR* rs2066853 gene polymorphism and risk of male infertility.

Materials and methods

Searching strategy

Two authors conducted a systematic search on PubMed, Embase, Web of Science, and CNKI independently up to 31 July 2019. The search terms were used as follows: 'Aryl hydrocarbon receptor or *AHR*' and 'polymorphism or mutation or variant' and 'male infertility'. Moreover, the references of relevant articles were checked to identify additional studies on this topic. Figure 1 shows the strategy flowchart.

Inclusion criteria and exclusion criteria

Studies were considered eligible if they (1) were full text articles; (2) were case–control studies evaluating the association between *AHR* rs2066853 gene

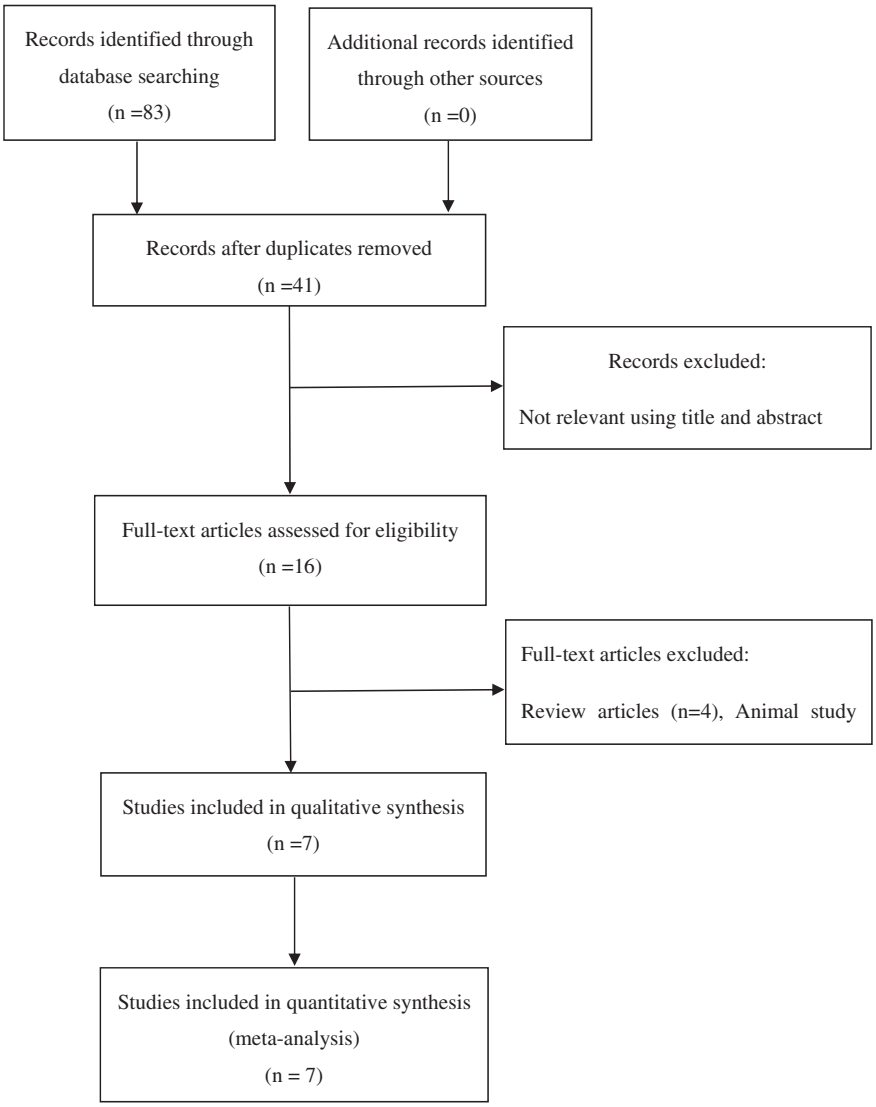

Figure 1. Flowchart of the study selection procedure.

polymorphism and susceptibility to male infertility; (3) included available genotype distributions for both cases and controls; (4) contained no overlapping data. If the studies with the same or overlapping data by the same authors, we selected the ones with the most subjects, (5) were published in Chinese or English. Exclusion criteria including: (1) not for the association between *AHR* rs2066853 gene polymorphism and the male infertility risk; (2) studies with insufficient data; (3) animal studies, conference abstracts, editorial articles, review articles or meta-analyses.

Quality assessment

Two independent authors used the Newcastle-Ottawa scale (NOS) to assess the quality of the included studies [18]. The NOS has eight items with three aspects including selection, comparability, and exposure for both cohort and case–control researches. The methodological quality was evaluated using a 'star' rating system. Researches that scored nine stars were considered high quality, that scored seven or eight stars were considered medium quality, and that scored less than seven stars were considered low quality. Inconsistent opinions were resolved by discussion and consensus with a third author.

Data extraction strategy

Two authors extracted all available data from each study independently using standard data collection form. The following information for each study were collected: first author's name, publication year, country, genotyping method, sample size of the study case and control groups, the results of the Hardy–Weinberg equilibrium test.

Statistical analysis

Reviewer Manager 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata 12.0 software (Stata Corporation, College Station, Texas, USA) were applied for statistical analyses. The strength of association between *AHR* rs2066853 gene polymorphisms and male infertility was evaluated by odds ratios (ORs) with 95% CIs. The pooled ORs were analyzed for four genetic models: allele comparison model, dominant model, recessive model and codominant model, respectively. We used chi-square-based Q-test and the I^2 metric to assess heterogeneity between studies. An I^2 >50% and the p values for heterogeneity <.10 was considered the high level of heterogeneity. If heterogeneity was observed among the individual studies (p values for heterogeneity was >.10 and I^2 < 50%), a random-effect model was applied to evaluate the summary OR. Otherwise, a fixed-effect model was used. The significance of the summary OR was determined by the Z-test which was considered as statistically significant when $p < .05$.The potential publication bias were estimated by Begg's test, Egger's test and funnel plots. As for Sensitivity analysis, we excluded one study each time to evaluate the stability of the results.

Results

Study inclusion and characteristics

Eighty-three case–control studies were identified through first search in PubMed, Embase, Web of Science, and CNKI. Among these search results, 76 studies were excluded for full text review after screening titles and abstracts. Finally, 7 case–control studies involving 1247 cases and 1762 controls were included in this meta-analysis [19–25]. The studies were published from 2004 to 2017. Three of these studies based in Caucasians, three in Asians, and one in African population. The *AHR* gene rs2066853 genotype frequencies of the controls from the seven studies were consistent with HWE. Table 1 shows the main characteristics of all the included studies and Table 2 shows the quality of the included studies based on the NOS score.

Association between the AHR gene rs2066853 polymorphism and male infertility

Seven studies including 3254 individuals totally evaluated the influence of *ARH* rs2066853 gene

Table 1. Main characteristics of studies included in the meta-analysis.

					Case					Control					
Study/year	Country	Genotypingmethod	Case	Control	GG	GA	AA	G	A	GG	GA	AA	G	A	HWE
Aftabi et al. 2017	Iran	PCR-RFLP	135	130	68	62	5	198	72	73	53	4	199	61	0.120
Gu et al. 2011	China	TaqMan	567	573	255	231	81	741	393	249	244	80	742	404	0.108
Liu et al. 2016	China	PCR	136	456	58	57	18	173	93	193	206	55	592	316	0.998
Merisalu et al. 2007	Estonia	ASPCR	110	211	96	14	0	206	14	175	36	0	386	36	0.195
Mostafa et al. 2017	Egypt	Real-time PCR	120	50	43	21	56	107	133	28	15	7	71	29	0.055
Safarinejad et al. 2013	Iran	PCR	176	352	73	89	14	235	117	131	152	69	414	290	0.710
Watanabe et al. 2004	Japan	PCR	123	112	36	64	23	136	110	32	58	22	122	102	0.641

Table 2. Quality assessment for all of the included studies.

First author	Publishing year	Selection	Comparability	Exposure	Total
Aftabi et al.	2017	★★	★★	★★	6
Gu et al.	2011	★★★	★	★★	6
Liu et al.	2016	★★★	★	★★	6
Merisalu et al.	2007	★★	NA	★★	4
Mostafa et al.	2017	★★	★	★★	5
Safarinejad et al.	2013	★★	★★	★★	6
Watanabe et al.	2004	★★	★	★★	5

polymorphism on the risk of male infertility. Figures 2–5 show the meta-analysis results for the allele model (A vs. G), additive model (AA vs. GG), dominant model (AA + GA vs. GG), and recessive model (AA vs. GA + GG), for which the I^2 value, representing the among-study heterogeneity, was 77%, 74%, 29%, and 78%, respectively. Therefore, random-effects models were applied in the allele model (A vs. G), additive

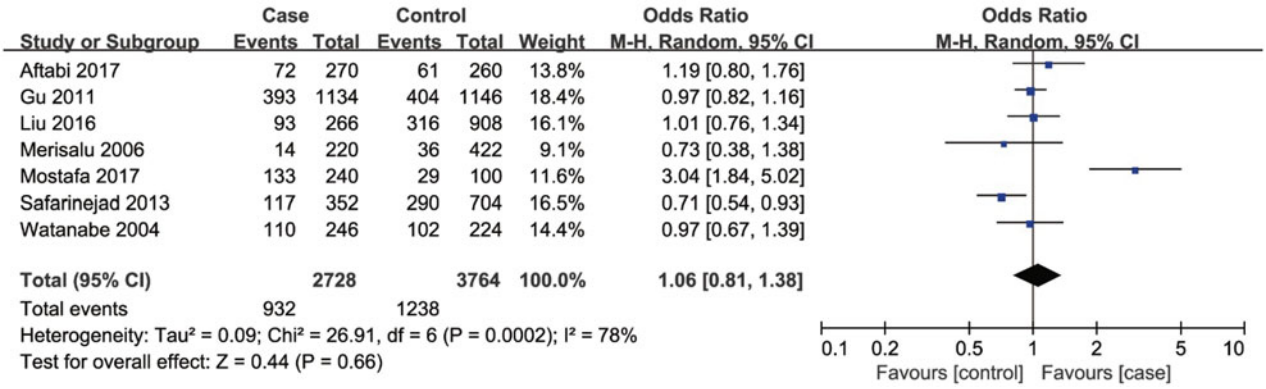

Figure 2. Forest plot of the studies assessing the association between *AHR* rs2066853 gene polymorphisms and male infertility based on allelic model (allele model: A vs. G).

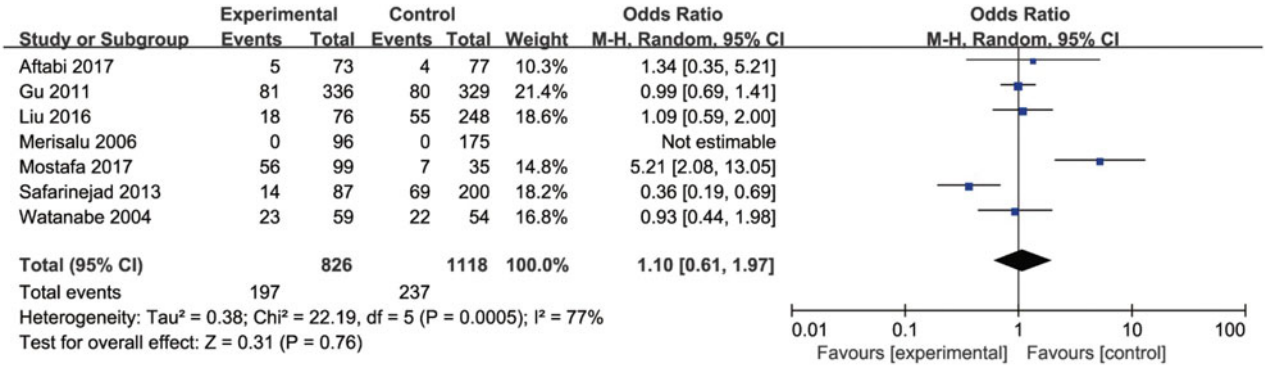

Figure 3. Forest plot of the studies assessing the association between *AHR* rs2066853 gene polymorphisms and male infertility based on additive model (additive model: AA vs. GG).

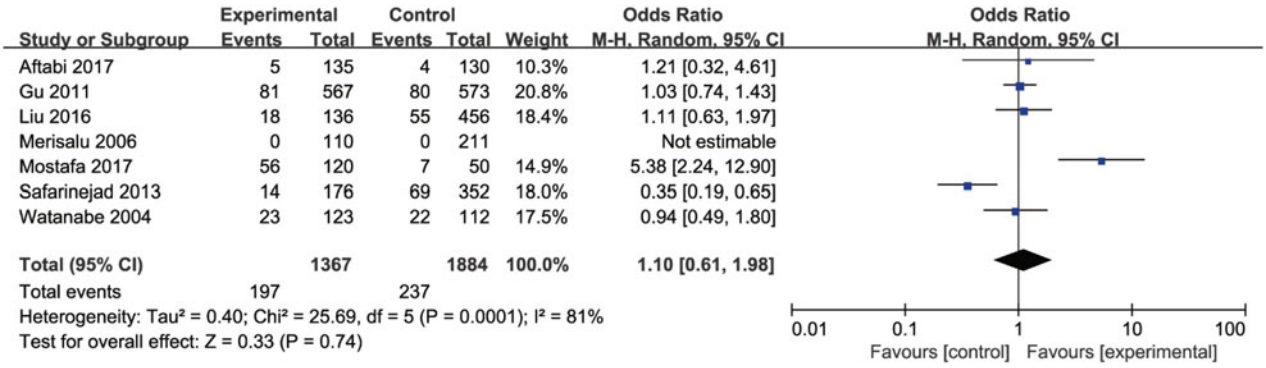

Figure 4. Forest plot of the studies assessing the association between *AHR* rs2066853 gene polymorphisms and male infertility based on recessive model (recessive model: AA vs. GG + GA).

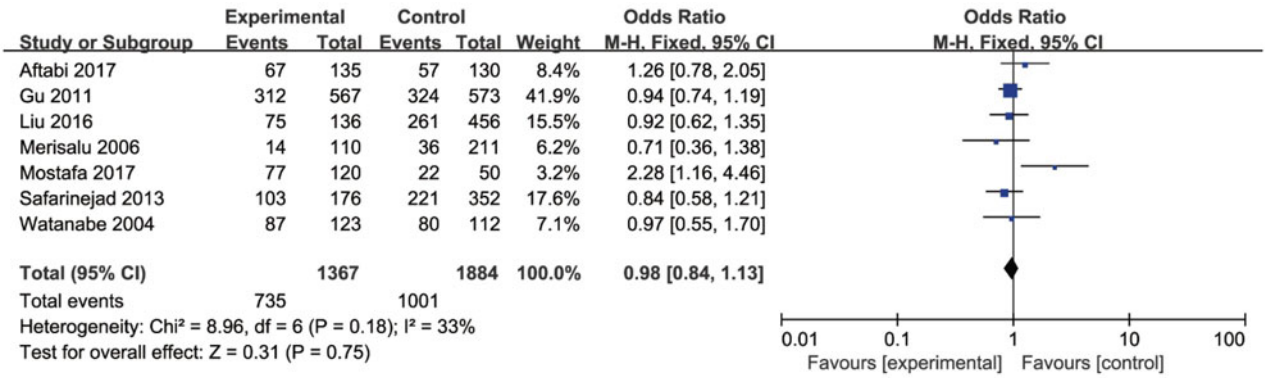

Figure 5. Forest plot of the studies assessing the association between *AHR* rs2066853 gene polymorphisms and male infertility based on dominant model (dominant model: AA + GA vs. GG).

Table 3. Meta-analysis of the association of *AHR* rs2066853 gene polymorphisms with male infertility.

		A vs. G		AA vs. GG		AA vs. GA + GG		AA + GA vs. GG	
	N	OR	P_H	OR	P_H	OR	P_H	OR	P_H
Total	7	1.06 [0.81–1.38]	<0.05	1.10 [0.61–1.97]	<0.05	1.10 [0.61–1.98]	<0.05	0.98 [0.84–1.13]	0.180
Ethnicity									
Asian	3	0.98 [0.86–1.12]	0.980	1.00 [0.75–1.33]	0.940	1.03 [0.79–1.34]	0.930	0.94 [0.78–1.13]	0.990
European	3	0.85 [0.60–1.22]	0.100	0.61 [0.17–2.11]	0.090	0.56 [0.18–1.82]	0.100	0.92 [0.71–1.21]	0.290
African	1	3.04 [1.84–5.02]	–	5.21 [2.08–13.05]	–	5.38 [2.24–12.90]	–	2.28 [1.16–4.46]	–
OA	2	2.52 [1.72–3.70]	0.230	4.66 [2.22–9.80]	0.620	3.99 [2.09–7.61]	0.170	2.36 [1.35–4.13]	0.870

PH: P value for heterogeneity; OA: oligoasthenotspermia.

model (AA vs. GG) and recessive model (AA vs. GA + GG). All in all, the result revealed no significant association between the *ARH* rs2066853 gene polymorphism and male infertility risk (A vs. G: OR = 1.08, 95% CI = 0.83–1.39; AA vs. GG: OR = 1.16, 95% CI = 0.65–2.04; AA vs. GA + GG: OR = 1.17, 95% CI = 0.66–2.07; AA + GA vs. GG: OR = 0.99, 95% CI = 0.85–1.15).

Table 3 presents subgroup analyses results of male infertility risk by ethnicity, there was no significant association between *ARH* rs2066853 gene polymorphism and male infertility risks in Asian, European, and African. However, significant association was found between ARH rs2066853 gene polymorphism and oligoasthenozoospermia (A vs. G: OR = 2.52, 95% CI =1.72–3.70; AA vs. GG: OR = 4.66, 95% CI = 2.22–9.80; AA vs. GA + GG: OR = 3.99, 95% CI = 2.09–7.61; AA + GA vs. GG: OR = 2.36, 95% CI = 1.35–4.13) (Table 3).

Sensitivity analyses and publication bias

Begg's test, Egger's test, and funnel plots were applied to assess the publication bias on *ARH* rs2066853 gene polymorphism. No publication bias was observed based on visual inspection of funnel plots or according to the results of Begg's and Egger's test (Figure 6; Table 4). The sensitivity analyses were performed to calculate the pooled ORs by sequentially excluding individual studies, the results revealed that no individual study influenced the overall pooled ORs, suggesting the results of this meta-analysis are stable (Figure 7).

Discussion

Testis is the most sensitive organ to TCDD toxicity. It was demonstrated that testicular functions, especially spermatogenesis and sperm motility, were specifically reduced by exposure to PAHs due to activation of *AHR* [26–28]. More and more evidence from evidence-based studies certificates the critical role of genetic factors in the development of male infertility. The c.1661G>A transition (rs2066853) is the most widely studied SNP in the *AHR* gene. Hence, we performed a meta-analysis to provide a clear understanding between the *ARH* rs2066853 gene polymorphisms and risk of male infertility.

In the present studies, no overall association was observed between the *ARH* rs2066853 gene polymorphisms and male infertility risk, similar results were obtained in subgroup analysis by ethnicity. However, association between *AHR* rs2066853 gene polymorphisms and oligoasthenotspermia risk was observed significant. The present meta-analysis included only five studies that reported the relationship between the *AHR* rs2066853 gene polymorphisms and male infertility risk

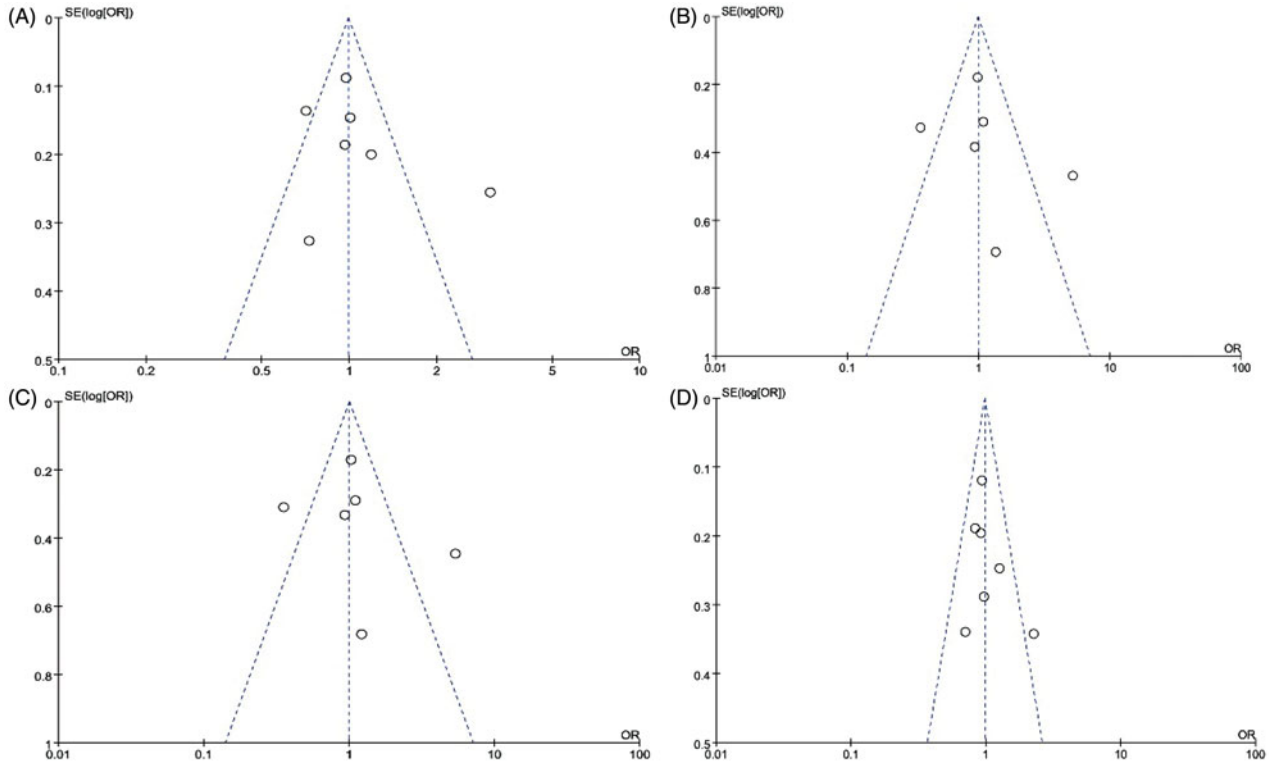

Figure 6. Funnel plot of the studies assessing the association between *AHR* rs2066853 gene polymorphisms and male infertility (allele model: A vs. G; additive model: AA vs. GG; recessive model: AA vs. GG + GA; dominant model: AA + GA vs. GG).

Table 4. Publication bias test for the *AHR* rs2066853 gene polymorphism.

	Egger's test			Begg's test
Comparisons	Coefficient	*p* Value	95 % CI	*p* Value
A vs. G	0.273	.871	−3.823 to 4.369	.548
AA vs. GG	1.125	.760	−8.412 to 10.662	.452
AA vs. GA + GG	0.049	.970	−3.329 to 3.426	.452
AA + GA vs. GG	−1.354	.727	−10.790 to 8.083	.368

in Asian, one study in European and one study in African and two studies reported the relationship between the *AHR* rs2066853 gene polymorphisms and oligoasthenotspermia risk, the sample size was small; Thus, studies with larger sample sizes are demanded for further investigation on the potential relationships between *AHR* rs2066853 gene polymorphisms and male infertility risk.

Safarinejad et al. found strong evidence that *AHR* rs2066853 gene polymorphism significantly contributed to susceptibility of male factor infertility with impaired semen quality in the Iranian population. Similarly, Liu et al. and Mostafa et al. clarified that the *AHR* rs2066853 gene polymorphisms may correlated with sperm quality, which were in contrast to the conclusions of other studies include in the meta-analysis. The inconsistency between the studies could arise from study patients, race, geography or genetic differences of the study population. However, we enrolled only seven studies in the present studies. Well designed, unbiased, and large case–control studies should be performed to acquire a more precise association between the *AHR* rs2066853 gene polymorphism and male infertility risk.

In the current meta-analysis, I^2 statistics and Q-test were performed to evaluate the significance of heterogeneity. Obvious heterogeneity among the included studies was found in Allele model, Recessive model and Additive model. After sub-grouped by ethnicity, the heterogeneity among the studies was removed in Asian population, whereas certain degree of heterogeneity was observed in the Caucasian population. We considered the heterogeneity may result from difference in genotyping method, the intricate substructure in Caucasian population, and some other unknown factors. Sensitivity meta-analyses were performed in this meta-analysis. We removed each study in turn in every comparison, finding that none of the individual studies significantly affected the pooled ORs, and the association between the *AHR* rs2066853 gene polymorphism and male infertility remained unchanged in each genetic models, proving the high stability of the meta-analysis. As well, there were no publication biases in our meta-analysis.

However, some limitations of the present study should be noted. First, heterogeneity is a major issue that needs to be mentioned when interpreting the

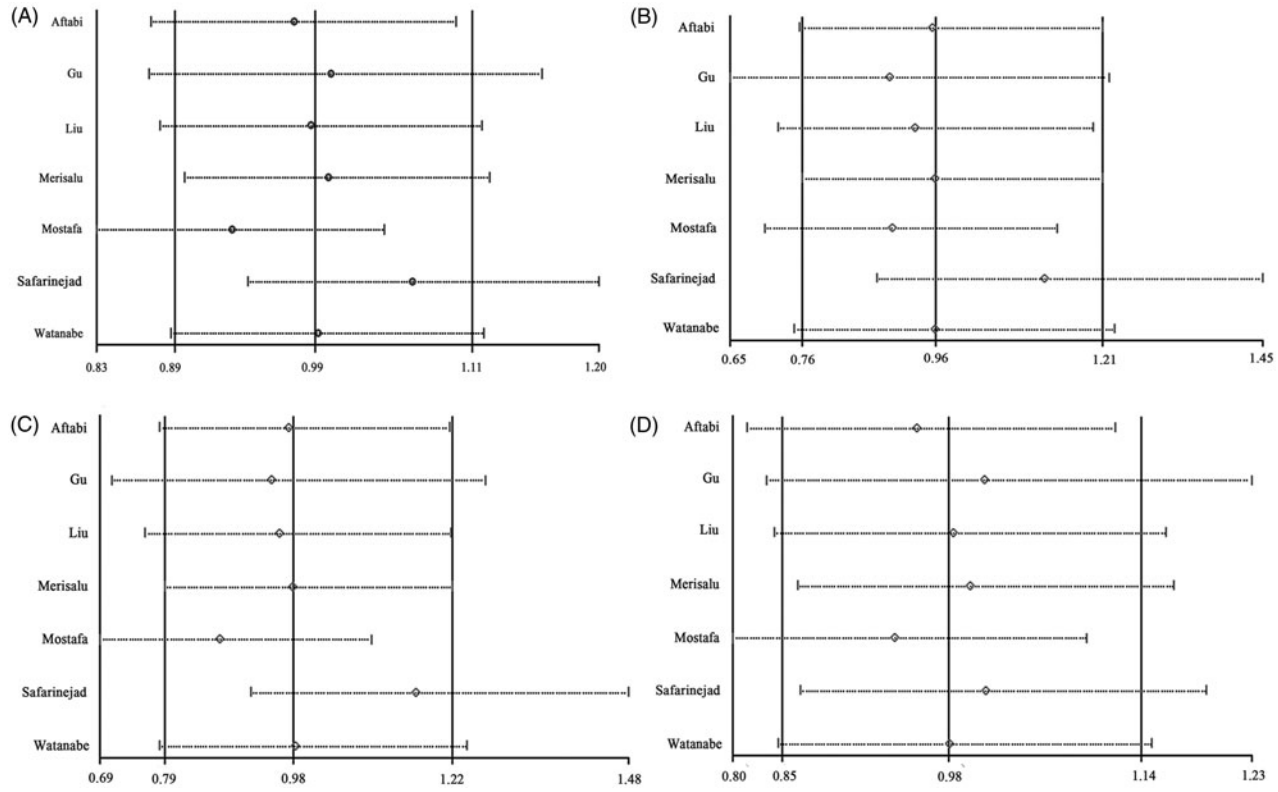

Figure 7. Sensitivity analysis diagram for each study used to assess the relative risk estimates for the *AHR* rs2066853 gene polymorphisms and male infertility in all the included studies (allele model: A vs. G; additive model: AA vs. GG; recessive model: AA vs. GG + GA; dominant model: AA + GA vs. GG).

meta-analysis results, and after performing subgroup analyses by ethnicity, the heterogeneity was effectively reduced or removed in most of genetic models. Second, only seven studies were included in the meta-analysis, the sample sizes were small; therefore, more case–control studies that evaluate the association between *AHR* rs2066853 gene polymorphism and male infertility are needed. Third, the potential gene–gene and gene–environment interactions were not estimated due to the limited information in the original studies. Fourth, sources of control, genotyping procedure, and semen quality were not applied in the pooled results assessment, due to lack of information. Finally, there were no enough studies investigating the association between the *AHR* rs2066853 gene polymorphism and different type of male infertility in this meta-analysis. Thus, the association between the *AHR* rs2066853 gene polymorphism and different type of male infertility needed further confirmation.

Conclusion

Results of the present meta-analysis indicate that the *AHR* rs2066853 gene polymorphism may contribute to genetic susceptibility to the risk of oligoasthenotspermia. Nevertheless, future studies are needed to further investigate the association between the *AHR* gene polymorphisms and different type of male infertility.

Disclosure statement

No potential conflict of interest was reported by the authors.

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