Meta-analysis of the association of *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* polymorphisms and endometriosis risk in Asians

Neng-neng Zheng¹ · Ya-ping Bi² · Ying Zheng¹ · Ruo-heng Zheng³

Received: 25 March 2015 / Accepted: 1 June 2015 / Published online: 23 June 2015
© Springer Science+Business Media New York 2015

Abstract

Purpose Several studies have suggested an association between the polymorphisms *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* and endometriosis, but results have been inconclusive. The aim of the present study was to assess these associations by meta-analysis.

Methods Eligible literatures were retrieved from PubMed, ISI Web of Science, Elsevier Science Direct, and several Chinese databases. The pooled odds ratios (ORs) and the corresponding 95 % confidence intervals (CIs) were calculated with a random or fixed-effect model.

Results A total of six eligible studies were included. Regarding the *AhR Arg554Lys* and *ARNT Val189Val* polymorphisms, no obvious associations were found in either overall analysis or subgroup analysis based on the country, source of control, sample size, and genotyping method. For the *AhRR Pro185Ala* polymorphism, overall results suggested a marginal association with endometriosis susceptibility under the

dominant model (OR=1.65, 95 % CI=1.00–2.72). Furthermore, a significantly increased risk for endometriosis was found in the subgroups which used the TaqMan method for genotype analysis or had a sample size ≥ 200 .

Conclusions This meta-analysis suggested that the polymorphisms of *AhR Arg554Lys* and *ARNT Val189Val* are not associated with endometriosis, while the *AhRR Pro185Ala* polymorphism may be associated with endometriosis risk. However, further case–control studies with larger sample sizes are needed to confirm our results.

Keywords Endometriosis · *AhR* · *ARNT* · *AhRR* · Polymorphism · Meta-analysis

Capsule This meta-analysis suggested that the polymorphisms of *AhR Arg554Lys* and *ARNT Val189Val* are not associated with endometriosis, while the *AhRR Pro185Ala* polymorphism may be associated with endometriosis risk.

Neng-neng Zheng and Ya-ping Bi contributed equally to this work.

✉ Ruo-heng Zheng
rouheng_zheng@126.com

¹ Department of Gynecology and Obstetrics, Tongde Hospital of Zhejiang Province, Hangzhou, Zhejiang 310012, China

² Department of Laboratory Medicine, First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, China

³ Institution of Obstetrics and Gynecology, Zhejiang Medical College, 481 Bin-Wen Road, Bin Jiang District, Hangzhou, Zhejiang 310053, China

Introduction

Endometriosis is a common gynecological disease defined as the occurrence of endometrial glands and stroma outside of the uterine cavity with diverse symptoms, such as dysmenorrhea, infertility, and chronic pelvic pain [1, 2]. The most common lesion locations of endometriosis are the peritoneum, ovaries, utero-sacral ligaments, and pouch of Douglas. Although retrograde menstruation of endometrial cells and their subsequent attachment in the pelvic cavity is the primary explanation for the pathogenesis of endometriosis, this hypothesis is inadequate considering that retrograde menstruation occurs in up to 90 % of menstruating women with patent fallopian tubes while the prevalence of endometriosis is much lower [3]. There is growing evidence that endometriosis is likely a multifactorial disease. Complex interactions between genetic, immunologic, hormonal, and environmental factors likely contribute to the pathogenesis of endometriosis [4–6]. However, the exact etiology and pathogenesis of the disease remain unclear.

Recently, epidemiological investigations and animal experiments have shown that exposure to environmental contaminants may contribute to endometriosis susceptibility [7, 8]. According to previous studies, dioxins are a typical environmental contaminant stimulating the growth of endometrial lesions and increasing the risk of endometriosis [8, 9]. The aryl hydrocarbon receptor (*AhR*) is a ligand-dependent transcription factor localized to cytoplasm. When bound to dioxin ligands, *AhR* translocates from the cytoplasm to the nucleus and heterodimerizes with *AhR* nuclear translocator (*ARNT*), contributing to the activation of target genes by binding to the xenobiotic response element [10, 11]. Activation of these pathways may give rise to endocrine abnormality, immunotoxicity, and even cause cancer [11, 12]. The *AhR* repressor (*AhRR*) regulates *AhR* signaling by competing for dimerization to *ARNT* to downregulate gene expression [13]. *AhR*, *ARNT*, and *AhRR* are all expressed in the female reproductive system and can change expression under specific pathologic conditions [14]. Based upon the possible contribution of dioxin to the pathogenesis of endometriosis, it has been hypothesized that variants of the *AhR*, *ARNT*, and *AhRR* genes which affect the xenobiotic detoxification process may also be associated with the risk of endometriosis.

A number of previous studies have investigated the association between the *AhR Arg554Lys* (AGA to AAA, codon 554 in exon 10), *AhRR Pro185Ala* (CCC to GCC, codon 185 in exon 5), and *ARNT Val189Val* (GTG to GTC, codon 189 in exon 7) polymorphisms and endometriosis in Asian populations [15–20] but have failed to reach a definite conclusion. Each of these studies was limited by inclusion of only one ethnic group and a small sample size. Therefore, we conducted a meta-analysis combining currently available data to examine the association between the *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* polymorphisms and endometriosis.

Materials and methods

Publication search

To collect eligible literature, we conducted a systematic search in PubMed, ISI Web of Science, Elsevier Science Direct, and several Chinese databases (Biomedical Literature Database, Chinese National Knowledge Infrastructure, and Chinese Wanfang Data) using different combinations of the following search terms: “Aryl hydrocarbon receptor” or “*AhR*,” “*AhR* repressor” or “*AhRR*,” “*AhR* nuclear translocator” or “*ARNT*,” and “polymorphism” or “variation” or “variant” or “mutation” and “endometriosis”. There was no language restriction, and the last search was updated on February 15, 2015. All references listed in the eligible studies were checked for other relevant literature. All clearly irrelevant studies, case

reports, and editorials were excluded. Review articles were also searched to avoid omission of any potential relevant studies.

Inclusion and exclusion criteria

Studies meeting the following criteria were included in the meta-analysis: (1) The study was a case–control design conducted in humans; (2) the study assessed the relationship between the polymorphisms of *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* and endometriosis; and (3) the study provided sufficient genetic information to calculate the odds ratio (OR) and its corresponding 95 % confidence interval (CI). Studies were excluded based on the following criteria: (1) The study was not relevant to the association of the polymorphisms *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* with endometriosis; (2) no useful data were provided on genetic polymorphisms; (3) the study was not clinical; and (4) the study was a review article or commentary.

Data extraction

The following information was extracted from every eligible study: Name of first author, year of publication, country of origin, ethnicity of the study population, number of cases and controls, mean age of subjects and controls, the source of control, the genotyping method, genotype distributions in cases and controls, and probability (*p*) value for the test of Hardy–Weinberg equilibrium (HWE) in controls.

Quality evaluation

The quality of every included study was assessed according to the Newcastle–Ottawa scale (NOS). The NOS consists of three parts with nine items (one point for each item): selection of the study groups (four items), comparability of the groups (two items), and outcome measurements (three items) [21]. A score greater than 5 was regarded as high quality; otherwise, the study was considered low quality [22].

Statistical analysis

Data analysis was performed using STATA statistical software (version 12.0; Stata Corporation, College Station, TX, USA). ORs with their corresponding 95 % CIs were calculated to estimate the strength of the association of the *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* polymorphisms with endometriosis. Analysis of the polymorphisms was conducted in at least two studies. The pooled OR was calculated for the allele model, homozygote comparison, heterozygote comparison, dominant model, and recessive model. The significance of the pooled OR was determined by *Z* test, and a *p* < 0.05 was considered statistically significant [1]. The heterogeneity among eligible studies was calculated by chi-square-based *Q*

test [23]. The existence of heterogeneity was regarded as significant at $p < 0.1$; in which case, a random-effect model using the DerSimonian–Laird method was applied [24]. Otherwise, a fixed-effect model (Mantel–Haenszel method) was used to calculate the pooled OR [25]. To explore the reasons for heterogeneity, subgroup analyses were applied based on the country, source of control, genotyping method, and sample size. In addition, sensitivity analyses were performed to validate the credibility of outcomes in this meta-analysis by deleting single studies one at a time [26]. The publication bias was evaluated by Begg’s test and Egger’s test and was regarded as statistically significant when $p < 0.05$ [27, 28].

Results

Characteristics of eligible studies

A total of 56 published articles were identified as potentially relevant through our search strategy, with 32 articles excluded for duplication. After review of the abstracts and titles from the remaining articles, 11 studies were eliminated because they were not related to *AhR*, *ARNT*, *AhRR*, or endometriosis. Of these studies, seven articles were excluded because they (1) were reviews, (2) lacked meaningful data, (3) were without

controls, or (4) were not human studies. In the end, a total of six studies were included in this meta-analysis. A flow chart of the inclusion/exclusion steps applied to studies is displayed in Fig. 1, and characteristics of the eligible studies are listed in Table 1. All of the identified studies were considered high quality (NOS > 5) and did not deviate from HWE ($p > 0.05$). Among the six eligible studies, five studies examined the *AhR Arg554Lys* polymorphism, five studies examined the *AhRR Pro185Ala* polymorphism, and three studies concerned the *ARNT Val189Val* polymorphism. However, the article by Matsuzaka et al. [17] only provided data on allele frequency, while data from Wu et al. [18] were based on the dominant model alone. In the current study, although the association of endometriosis with the *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* polymorphisms was assessed under all five genetic models, we have only shown the overall and subgroup results under the allele and dominant models in Table 2.

Association of *AhR Arg554Lys* polymorphism and endometriosis

A total of 776 cases and 980 controls were included to assess the association between the *AhR Arg554Lys* polymorphism and risk for endometriosis. Overall results from the five

Fig. 1 The study selection process

Table 1 Characteristic of the studies included in this meta-analysis

Study	Year	Country	NOS score	Age (year), mean (SD)		Sample size		Source of control	Genotyping method	Polymorphisms	Genotype (case/control)			P_{HWE}^h
				Cases	Controls	Cases	Controls				11	12	22	
Watanabe et al. [16]	2001	Japan	6	NA	NA	45	108	HB	Pyrosequencing	<i>Ahr Arg554Lys</i>	16/30	23/60	6/18	0.19
										<i>AhrRR Pro185Ala</i>	20/39	20/49	5/20	0.51
Tsuchiya et al. [15]	2005	Japan	7	32	33	79	59	HB	TaqMan PCR	<i>Ahr Arg554Lys</i>	24/22	35/29	20/8	0.75
										<i>AhrRR Pro185Ala</i>	20/27	47/27	12/5	0.63
										<i>ANRT Val189Val</i>	26/19	40/28	13/14	0.55
Kim et al. [20]	2007	Korea	6	29.6 (4.3)	36.9 (9.2)	316	256	HB	TaqMan PCR	<i>AhrRR Pro185Ala</i>	122/119	148/109	66/28	0.69
Wu et al. [18]	2011	China	7	30.9 (6.3)	29.1 (4.3)	121	171	PB	Pyrosequencing	<i>Ahr Arg554Lys</i>	102/138	19/33 ^a	NA	>0.05
										<i>AhrRR Pro185Ala</i>	21/61	100/110 ^b	NA	>0.05
										<i>ANRT Val189Val</i>	41/52	80/119 ^c	NA	>0.05
Wang et al. [19]	2011	China	6	NA	NA	431	499	HB	TaqMan PCR	<i>Ahr Arg554Lys</i>	197/230	192/209	42/60	0.24
										<i>ANRT Val189Val</i>	58/78	206/258	167/163	0.15
Matsuzaka et al. [17]	2012	Japan	7	38 (4.8)	43 (12.3)	100	143	HB	Pyrosequencing	<i>Ahr Arg554Lys</i>	109/131 ^d	NA	91/155 ^e	>0.05
										<i>AhrRR Pro185Ala</i>	131/183 ^f	NA	69/103 ^g	>0.05

For *Ahr Arg554Lys*, 11 = GG and 22 = AA; for *AhrRR Pro185Ala*, 11 = CC and 22 = GG; for *ANRT Val189Val*, 11 = GG and 22 = CC

NOS Newcastle–Ottawa scale, SD standard deviation, NA not available, PB population-based, HB hospital-based, HWE Hardy–Weinberg equilibrium, PCR polymerase chain reaction

^a GA + AA

^b CG + GG

^c GC + CC

^d Allele frequency for G

^e Allele frequency for A

^f Allele frequency for C

^g Allele frequency for G

^h p value for HWE in controls

genetic models indicated no statistically significant association between the *AhR Arg554Lys* polymorphism and endometriosis (allele model: OR=0.93, 95 % CI=0.80–1.08; homozygote comparison: OR=0.92, 95 % CI=0.64–1.34; heterozygote comparison: OR=1.03, 95 % CI=0.81–1.32; dominant model: OR=0.98, 95 % CI=0.79–1.22; recessive model: OR=0.93, 95 % CI=0.66–1.32). Subgroup analyses based on country, source of control, sample size, and genotyping method also showed no statistically significant association under all genetic models (Table 2, Fig. 2).

Association of *AhRR Pro185Ala* polymorphism and endometriosis

A total of five studies with 661 cases and 737 controls were identified to evaluate the association between the *AhRR Pro185Ala* polymorphism and endometriosis risk.

The overall results from the allele model, homozygote comparison, heterozygote comparison, and recessive model demonstrated no statistically significant association between the *AhRR Pro185Ala* polymorphism and endometriosis (allele model: OR=1.18, 95 % CI=0.81–1.71; homozygote comparison: OR=1.60, 95 % CI=0.59–4.34; heterozygote comparison: OR=1.34, 95 % CI=0.99–1.79; recessive model: OR=1.38, 95 % CI=0.64–3.00). However, the overall results did suggest a marginal association of this polymorphism with endometriosis susceptibility under the dominant model (OR=1.65, 95 % CI=1.00–2.72; Table 2). Furthermore, subgroup analysis based on the genotyping method demonstrated that the *AhRR Pro185Ala* polymorphism was significantly associated with endometriosis using the TaqMan genotyping method under all genetic models (allele model: OR=1.55, 95 % CI=1.25–1.93;

Table 2 Meta-analysis of *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* gene polymorphisms and endometriosis

Polymorphisms	Comparison	No. of studies	Allele model ^a		Dominant model ^b	
			OR (95 % CI)	<i>P</i> _H	OR (95 % CI)	<i>P</i> _H
<i>AhR Arg554Lys</i>			A vs. G		AA + GA vs. GG	
	Overall	5	0.93 (0.80–1.08) ^F	0.109	0.98 (0.79–1.22) ^F	0.526
	Hospital-based control	4	0.93 (0.80–1.08) ^F	0.109	1.01 (0.80–1.27) ^F	0.440
	Country					
	Japan	3	0.89 (0.69–1.14) ^R	0.054	0.99 (0.59–1.66) ^F	0.202
	China	2	0.96 (0.79–1.16)	–	0.98 (0.77–1.24) ^F	0.439
	Sample size					
	<200	2	1.09 (0.77–1.54) ^R	0.086	0.99 (0.59–1.66) ^F	0.202
	≥200	3	0.89 (0.75–1.06) ^F	0.146	0.98 (0.77–1.24) ^F	0.439
	Genotyping method					
<i>AhRR Pro185Ala</i>			G vs. C		GG + CG vs. CC	
	Overall	5	1.18 (0.81–1.71) ^R	0.012	1.65 (1.00–2.72) ^R	0.022
	Hospital-based control	4	1.18 (0.81–1.71) ^R	0.012	1.40 (0.78–2.52) ^R	0.045
	Japan	3	1.05 (0.65–1.73) ^R	0.032	1.32 (0.39–4.55) ^R	0.015
	Sample size					
	<200	2	1.13 (0.46–2.78) ^R	0.012	1.32 (0.39–4.55) ^R	0.015
	≥200	3	1.21 (0.77–1.93) ^R	0.039	1.77 (1.33–2.45) ^F	0.100
	Genotyping method					
	TaqMan PCR	2	1.55 (1.25–1.93) ^F	0.540	1.66 (1.23–2.24) ^F	0.225
	Pyrosequencing	3	0.85 (0.63–1.15) ^F	0.406	1.39 (0.38–5.06) ^R	0.004
<i>ARNT Val189Val</i>			C vs. G		CC + GC vs. GG	
	Overall	3	1.14 (0.96–1.35) ^F	0.192	1.04 (0.79–1.36) ^F	0.536
	Hospital-based control (TaqMan PCR)	2	1.14 (0.96–1.35) ^F	0.192	1.13 (0.82–1.57) ^F	0.533
	China (sample size ≥200)	2	1.19 (0.99–1.43)	–	1.06 (0.79–1.42) ^F	0.289

OR odds ratio, CI confidence interval, No. number, *P*_H *p* value of Q test for heterogeneity test, vs. versus, R random-effect model, F fixed-effect model

^a The study by Wu et al. was not included since they just presented the data on dominant model in cases and controls

^b The study by Matsuzaka et al. was not included since they just presented the data on allele model in cases and controls

Fig. 2 Forest plot for the correlation of *AhR Arg554Lys* polymorphism with risk of endometriosis based on the dominant model (AA + GA vs. GG; stratified by country)

homozygote comparison: OR=2.42, 95 % CI=1.52–3.87; heterozygote comparison: OR=1.47, 95 % CI=1.07–2.02; dominant model: OR=1.66, 95 % CI=1.23–2.24; recessive model, OR=1.98, CI=1.28–3.07). Finally, subgroup analysis by sample size found a statistically significant association between the *AhRR Pro185Ala* polymorphism and endometriosis under the dominant model when the sample size was equal to or greater than 200 (OR=1.77, 95 % CI=1.33–2.45; Table 2, Fig. 3).

Association of *ARNT Val189Val* polymorphism and endometriosis

Three studies with 631 cases and 729 controls were included to examine the association between the *ARNT Val189Val* polymorphism and risk of endometriosis. Under all genetic models, no significant association was found when all studies were pooled into the meta-analysis (allele model: OR=1.14, 95 % CI=0.96–1.35; homozygote comparison: OR=1.24, 95 % CI=0.86–1.79; heterozygote comparison: OR=1.07,

Fig. 3 Forest plot for the correlation of *AhRR Pro185Ala* polymorphism with risk of endometriosis based on the dominant model (GG + CG vs. CC; stratified by sample size)

95 % CI=0.76–1.51; dominant model: OR=1.04, 95 % CI=0.79–1.36; recessive model: OR=1.22, 95 % CI=0.95–1.58). Subsequent subgroup analyses also showed no statistically significant association between this polymorphism and endometriosis risk (Table 2, Fig. 4).

Heterogeneity test and sensitivity analysis

In studies examining the association of the *AhR Arg554Lys* and *ARNT Val189Val* polymorphisms with endometriosis, there was no heterogeneity among studies in overall comparisons ($p>0.10$). However, for the *AhRR Pro185Ala* polymorphism studies, between-study heterogeneity was statistically significant ($p<0.10$). To explore sources of heterogeneity across studies, subgroup analyses based on the country, source of control, genotyping method, and sample size were conducted, but none of these variables were able to explain the heterogeneity. In order to assess the stability our meta-analysis results, sensitivity analyses were applied by deleting one study at a time. This procedure confirmed that our results regarding the association of the *AhR Arg554Lys*, *ARNT Val189Val*, and *AhRR Pro185Ala* polymorphisms and endometriosis susceptibility were both reliable and robust (Fig. 5).

Publication bias

Begg's test and Egger's test were performed to evaluate potential publication bias among studies included in this meta-analysis. Results showed no publication bias for the studies we examined ($p>0.05$).

Discussion

Endometriosis is a complicated pathological condition which is not fully understood. It has recently been noted that the incidence of endometriosis among reproductive-aged women is increasing [19]. A large number of studies have been conducted to explore the correlation of genetic mutations, including the *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ANRT Val189Val* polymorphisms, with endometriosis, but results have not been consistent even in the same population. Therefore, our meta-analysis should be of great value in identifying the association of *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ANRT Val189Val* polymorphisms with endometriosis risk.

To the best of our knowledge, this is the first meta-analysis to assess the relationship between these three gene polymorphisms and risk of endometriosis. Our meta-analysis failed to find a significant association between the *AhR Arg554Lys* and *ARNT Val189Val* polymorphisms and endometriosis susceptibility in the overall population and in further subgroup analyses. However, it is worth mentioning that the present meta-analysis was limited to the Asian population. Inconsistent results might be obtained from different genetic backgrounds in different ethnicities. Furthermore, for complex gynecologic conditions such as endometriosis, gene-environmental interactions may be more important and relevant than genetic background alone [29, 30]. Further studies in other ethnic groups, such as Caucasian populations, may help to fully understand the influence of these polymorphisms on endometriosis susceptibility. Additionally, in this meta-analysis, the majority of studies enrolled control subjects from women who were hospitalized with the absence of endometriosis and not from healthy volunteers. In fact, two of the studies [15, 17]

Fig. 4 Forest plot for the correlation of *ARNT Val189Val* polymorphism with risk of endometriosis based on the dominant model (CC + GC vs. GG; stratified by country)

Fig. 5 Sensitivity analysis of the summary odds ratio (OR) coefficients on the associations of the *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* polymorphisms with risk of endometriosis based on the dominant model. **a** *AhR Arg554Lys*. **b** *AhRR Pro185Ala*. **c** *ARNT Val189Val*

recruited controls with health histories of unexplained infertility, which may have produced unreliable results because hospital-based controls are less representative of the general population, particularly when the disorders that hospital-based controls may have are expected to be related to the polymorphisms under investigation [31, 32].

For the *AhRR Pro185Ala* polymorphism, we did find a marginal association with endometriosis in the overall population under the dominant model. Furthermore, this polymorphism was significantly associated with endometriosis using the TaqMan genotyping method under all genetic models. One possible explanation is that different genetic methods vary in sensitivity and specificity. It was reported that TaqMan, gene chip, and mass array genotyping methods provide the best sensitivity and accuracy in single-nucleotide polymorphism (SNP) genotyping under optimized condition [33–35], and use of less sensitive methods may have produced discrepant results. The results of our study also showed that the association of the *AhRR Pro185Ala* polymorphism and endometriosis was statistically significant when the sample size was equal to or greater than 200 under the dominant model. As the limited study numbers and relatively small sample sizes may have resulted in small study bias [36], large-scale studies are necessary to further confirm the association between *AhR Arg554Lys*, *AhRR Pro185Ala*, and *ARNT Val189Val* polymorphisms and endometriosis risk.

Although no significant association was found between the *AhR Arg554Lys* and *ARNT Val189Val* polymorphism and endometriosis susceptibility in the present study, the combination of *AhR* with dioxins has been shown to cause high expression of target genes including cytochrome P450 1A1 (*CYP1A1*), which is considered harmful because it creates active oxygen and mutagenic metabolites [37]. The level of *CYP1A1* expression was reported greater in patients with endometriosis than in a non-endometriosis control group [38, 39]. *AhR* signaling is regulated in part by *AhRR*, which is located in the nucleus and functions to downregulate *AhR* interaction with *ARNT*. The exact mechanism controlling the association between the *AhRR* polymorphism and endometriosis is still unclear, but it has been shown that *AhRR* polymorphisms altered *AhR*-mediated signaling [40]. Therefore, loss or reduction of *AhRR* expression in cells may result in increased susceptibility to the toxic effects of dioxins by reducing the negative regulatory effects of *AhRR* [20] and may facilitate proliferation of endometrial cells through diminished downregulation of *AhR*-mediated signaling [18].

Some limitations should be noted in this meta-analysis. First, the results of our meta-analysis should be interpreted with caution because the number of studies and the sample sizes used in the studies were relatively small. There were only six studies included in our meta-analysis, and two of the studies [17, 18] presented data based on a single genetic model, which limited our ability to conduct more meaningful subgroup analyses. Second, the pooled results were based on unadjusted estimates, and potential covariates which might influence the effect estimates were not controlled for the lack of information. Third, between-study heterogeneity was significant in studies of the *AhRR Pro185Ala* polymorphism, even though sensitivity analysis demonstrated no substantial impact of a single study on the overall results. Thus, further studies with larger sample sizes will be required to provide more detailed information on the relationship between genetic polymorphisms and endometriosis susceptibility.

Conclusions

In summary, the results of this meta-analysis indicate that the *AhRR Pro185Ala* polymorphism may be associated with the endometriosis, while the *AhR Arg554Lys* and *ARNT Val189Val* polymorphisms are not likely associated. It is critical that large-scale and well-designed studies be performed to re-evaluate these potential relationships.

Acknowledgments This work was financially supported by the Science and Technology Foundation of Public Welfare Profession of Zhejiang Province (grant no. 2015C33198) and Foundation of Health Bureau of Zhejiang Province (grant no. 2012KYA159).

Competing interests The authors declare that they have no competing interests.

References

1. Missmer SA, Cramer DW. The epidemiology of endometriosis. *Obstet Gynecol Clin North Am.* 2003;30(1):1–19.
2. Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL. Economic burden of endometriosis. *Fertil Steril.* 2006;86(6):1561–72.
3. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol.* 1984;64(2):151–4.
4. Vigano P, Somigliana E, Vignali M, Busacca M, Blasio AM. Genetics of endometriosis: current status and prospects. *Front Biosci.* 2007;12(9):3247–55.
5. Bischoff FZ, Simpson JL. Heritability and molecular genetic studies of endometriosis. *Hum Reprod Update.* 2000;6(1):37–44.
6. Goetzl EJ, Sreedharan SP. Mediators of communication and adaptation in the neuroendocrine and immune systems. *FASEB J.* 1992;6(9):2646–52.
7. Porpora MG, Medda E, Abballe A, Bolli S, De Angelis I, di Domenico A, et al. Endometriosis and organochlorinated

- environmental pollutants: a case control study on Italian women of reproductive age. *Environ Health Perspect.* 2009;117(7):1070–5.
8. Eskenazi B, Mocarelli P, Warner M, Samuels S, Vercellini P, Olive D, et al. Serum dioxin concentrations and endometriosis: a cohort study in Seveso. Italy *Environ Health Perspect.* 2002;110(7):629–34.
 9. Bellelis P, Podgaec S, Abrão MS. Environmental factors and endometriosis. *Rev Assoc Med Bras.* 2011;57(4):448–52.
 10. Guo SW. The association of endometriosis risk and genetic polymorphisms involving dioxin detoxification enzymes: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2006;124(2):134–43.
 11. Guo SW, Simsa P, Kyama CM, Mihályi A, Fulöp V, Othman EE, et al. Reassessing the evidence for the link between dioxin and endometriosis: from molecular biology to clinical epidemiology. *Mol Hum Reprod.* 2009;15(10):609–24.
 12. Urban JD, Budinsky RA, Rowlands JC. Single nucleotide polymorphisms in the human arhl hydrocarbon receptor nuclear translocator gene. *Drug Metab Pharmacokinet.* 2011;26(6):637–45.
 13. Mimura J, Ema M, Sogawa K, Fujii-Kuriyama Y. Identification of a novel mechanism of regulation of Ah (dioxin) receptor function. *Genes Dev.* 1999;13(1):20–5.
 14. Khorram O, Garthwaite M, Golos T. Uterine and ovarian aryl hydrocarbon receptor (AhR) and aryl hydrocarbon receptor nuclear translocator (ARNT) mRNA expression in benign and malignant gynaecological conditions. *Mol Hum Reprod.* 2002;8(1):75–80.
 15. Tsuchiya M, Katoh T, Motoyama H, Sasaki H, Tsugane S, Ikenoue T. Analysis of the AhR, ARNT, and AhRR gene polymorphisms, genetic contribution to endometriosis susceptibility and severity. *Fertil Steril.* 2005;84(2):454–8.
 16. Watanabe T, Imoto I, Kosugi Y, Fukuda Y, Mimura J, Fujii Y, et al. Human arylhydrocarbon receptor repressor (AHRR) gene, genomic structure and analysis of polymorphism in endometriosis. *J Hum Genet.* 2001;46(6):342–6.
 17. Matsuzaka Y, Kikuti YY, Goya K, Suzuki T, Cai LY, Oka A, et al. Lack of an association human dioxin detoxification gene polymorphisms with endometriosis in Japanese women, results of a pilot study. *Environ Health Prev Med.* 2012;17(6):512–7.
 18. Wu CH, Guo CY, Yang JG, Tsai HD, Chang YJ, Tsai PC, et al. Polymorphisms of dioxin receptor complex components and detoxification-related genes jointly confer susceptibility to advanced-stage endometriosis in the Taiwanese Han population. *Am J Reprod Immunol.* 2012;67(2):160–8.
 19. Wang YF, Zong LL, Zhao X, Mao T, Fu YG, Zeng J, et al. No association of AhR gene 1661G/a and ARNT gene 567G/C polymorphisms with endometriosis in southern Han Chinese women. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi.* 2011;28(2):195–8.
 20. Kim SH, Choi YM, Lee GH, Hong MA, Lee KS, Lee BS, et al. Association between susceptibility to advanced stage endometriosis and the genetic polymorphisms of aryl hydrocarbon receptor repressor and glutathione-S-transferase T1 genes. *Hum Reprod.* 2007;22(7):1866–70.
 21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25(9):603–5.
 22. Yang B, Fan S, Zhi X, Li Y, Liu Y, Wang D, et al. Associations of MTHFR gene polymorphisms with hypertension and hypertension in pregnancy: a meta-analysis from 114 studies with 15411 cases and 21970 controls. *PLoS One.* 2014;9(2), e87497.
 23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557–60.
 24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177–88.
 25. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst.* 1959;22(4):719–48.
 26. Thakkinstant A, McElduff P, D'Este C, Duffy D, Attia J. A method for meta-analysis of molecular association studies. *Stat Med.* 2005;24(9):1291–306.
 27. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50(4):1088–101.
 28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629–34.
 29. Asada H, Yagihashi T, Furuya M, Kosaki K, Takahashi T, Yoshimura Y. Association between patient age at the time of surgical treatment for endometriosis and aryl hydrocarbon receptor repressor polymorphism. *Fertil Steril.* 2009;92(4):1240–2.
 30. Kennedy S. The genetics of endometriosis. *Eur J Obstet Gynecol Reprod Biol.* 1999;82(2):129–33.
 31. Zondervan KT, Cardon LR, Kennedy SH. What makes a good case-control study? Design issues for complex traits such as endometriosis. *Hum Reprod.* 2002;17(6):1415–23.
 32. Ruano-Ravina A, Perez-Rios M, Barros-Dios JM. Population-based versus hospital-based controls: are they comparable? *Gac Sanit.* 2008;22(6):609–13.
 33. Zhou C, Ni J, Zhao Y, Su B. Rapid detection of epidermal growth factor receptor mutations in non-small cell lung cancer using real-time polymerase chain reaction with TaqMan-MGB probes. *Cancer J.* 2006;12(1):33–9.
 34. Heller T, Kirchheiner J, Armstrong VW, Luthe H, Tzvetkov M, Brockmüller J, et al. AmpliChip CYP450 GeneChip: a new gene chip that allows rapid and accurate CYP2D6 genotyping. *Ther Drug Monit.* 2006;28(5):673–7.
 35. Li L, Li CJ, Zhang YJ, Zheng L, Jiang HX, Si-Tu B. Simultaneous detection of CYP3A5 and MDR1 polymorphisms based on the SNaPshot assay. *Clin Biochem.* 2011;44(5-6):418–22.
 36. Serrano NC, Díaz LA, Páez MC, Mesa CM, Cifuentes R, Monterrosa A, et al. Angiotensin-converting enzyme I/D polymorphism and preeclampsia risk: evidence of small-study bias. *PLoS Med.* 2006;3(12), e520.
 37. Nebert DW, Roe AL, Dieter MZ, Solis WA, Yang Y, Dalton TP. Role of the aromatic hydrocarbon receptor and [Ah] gene battery in the oxidative stress response, cell cycle control, and apoptosis. *Biochem Pharmacol.* 2000;59(1):65–85.
 38. Bulun SE, Zeitoun KM, Kilic G. Expression of dioxin-related transactivating factors and target genes in human eutopic endometrial and endometriotic tissues. *Am J Obstet Gynecol.* 2000;182(4):767–75.
 39. Bofinger DP, Feng L, Chi LH, Love J, Stephen FD, Sutter TR, et al. Effect of TCDD exposure on CYP1A1 and CYP1B1 expression in explant cultures of human endometrium. *Toxicol Sci.* 2001;62(2):299–314.
 40. Soneda S, Fukami M, Fujimoto M, Hasegawa T, Koitabashi Y, Ogata T. Association of micropenis with Pro185Ala polymorphism of the gene for aryl hydrocarbon receptor repressor involved in dioxin signaling. *Endocr J.* 2005;52(1):83–8.