Association between glutathione S-transferase M1/T1 gene polymorphisms and susceptibility to endometriosis: A systematic review and meta-analysis

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Abstract. Endometriosis is a polygenic/multifactorial disease caused by interactions between multiple genes and the environment. Findings from studies evaluating the association between the glutathione S-transferase (GST) M1/T1 null genotype and susceptibility to endometriosis are inconsistent. This meta-analysis updated and reevaluated the possible associations between *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* (null genotype versus wild-type) gene polymorphisms and susceptibility to endometriosis. The PubMed, Embase and Chinese BioMedical Literature databases and Google Scholar were searched for case-control genetic association studies on *GSTM1*/*GSTT1* (null genotype versus wild-type) gene polymorphisms and endometriosis in comparison with non-endometriosis or healthy controls. Fixed-effect and random-effect meta-analytical techniques were conducted for the outcome measure and subgroup analyses. The meta-analysis demonstrated significant associations between the *GSTM1* [odds ratio (OR)=1.56; 95% confidence interval (CI): 1.25-1.95; P<0.0001), *GSTT1* (OR=1.31; 95% CI: 1.02-1.68; P=0.037) and *GSTM1*/*GSTT1* (OR=1.68; 95% CI: 1.29-2.17; P<0.0001) null genotypes and increased risk for endometriosis. The results suggest that the *GSTM1*, *GSTT1*, and combined *GSTM1*/*GSTT1* null genotypes increase susceptibility to endometriosis. Additional well-designed studies and precise analyses are warranted to confirm these findings.

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Introduction

Endometriosis manifests as ectopic endometrial cells outside the uterus. It is an intractable disease that causes infertility, dysmenorrhea and pelvic pain. Endometriosis occurs in 10% of women of childbearing age. Notably, the incidence of endometriosis has been rising in recent years (1). The pathogenesis of endometriosis remains to be elucidated.

Published reports indicate that endometriosis is a polygenic/multifactorial disease caused by interactions between multiple genes and the environment (2,3). In particular, a correlation has been identified between endometriosis and exposure to environmental toxins such as dioxin (4); dioxin and dioxin-like compounds have been implicated in the development of endometriosis (5,6).

The phase II conjugation enzymes usually function to inactivate environmental toxins. Among these, glutathione S-transferase (GST) may be critical for the detoxification of dioxins. Human GSTs are classified into two distinct categories: Soluble or cytosolic and membrane-bound microsomal. The soluble or cytosolic GSTs are subdivided into seven families named α, μ, ω, π, σ, θ and ζ (7). Genes in several of these families are polymorphic, including: *GSTA2* in the α family, *GSTM1* and *GSTM3* in the μ family, *GSTP1* in the π family, *GSTO*, *GSTT1*, and *GSTT2* in the θ family, and *GSTZ1* in the ζ family. Heritable allelic differences in *GSTM1*, *GSTM3*, *GSTT1* and *GSTP1* may have marked relevance for individual susceptibility to disease.

GSTM1 and *GSTT1* are two candidate genes that may play an important role in the development of endometriosis. *GSTM1* and *GSTT1* are located on chromosomes 1p13.3 and 22q11.23, respectively. They are critical in the detoxification of the products of oxidative stress produced during the repair of the ovarian epithelium. *GSTM1* and *GSTT1* null alleles have reduced enzyme activity, a state that may contribute to inefficient detoxification of intermediates produced during stress. This may increase damage to various host genes and contribute to the pathogenesis of endometriosis (8,9).

A meta-analysis summarizing the literature up to the year 2005 suggested that the *GSTT1* null genotype, but not the

GSTM1 null genotype, was associated with an increased risk for endometriosis (7). In the years since 2005, additional reports investigating this topic have been published. The objective of the present study was to update the existing meta-analysis and reevaluate the possible associations between *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* (null genotype vs. wild-type) gene polymorphisms and susceptibility to endometriosis.

Materials and methods

Searches. For this systematic review and meta-analysis, PubMed (from January 1996 to January 2014), Embase (from January 1996 to January 2014), Chinese BioMedical Literature database (from January 1996 to January 2014) and Google Scholar (from January 1996 to January 2014) were searched. The following keywords were used: 'endometriosis', 'polymorphisms', 'glutathione S-transferases', '*GSTM1*' and '*GSTT1*' or their combinations.

Reference lists from articles identified by the electronic search were searched by hand. This process was performed iteratively until no additional articles could be identified.

Inclusion and exclusion criteria. Articles published in English or Chinese were included if they reported quantitative outcomes from case-control genetic association studies on *GSTM1*, *GSTT1* or combined *GSTM1*/*GSTT1* (null genotype vs. wild-type) gene polymorphisms and endometriosis versus non-endometriosis or healthy controls.

Studies were excluded if they were case reports, case-only studies, letters, reviews or meta-analyses; included subjects who were related; included cases of adenomyosis, which has unknown etiology (10); reported insufficient data; or were duplicate studies.

Selection of studies. Two reviewers (XYX and ZSJ) independently examined titles and abstracts to select eligible studies. Records were removed that were ongoing or unpublished studies, or were published as abstracts or conference proceedings. Where data sets were overlapping or duplicated, only the most recent information was included. The full text of potentially relevant studies was retrieved. Two reviewers (XYX and HJG) independently examined the full text records to determine which studies met the inclusion criteria. Disagreement about the selection of studies was resolved by discussion and consensus.

Data extraction and management. Two reviewers (XYX and ZSJ) independently extracted data from eligible studies including the first author's last name, publication year, study location, ethnicity, matching variability, diagnostic criteria, stages of disease, source of controls, numbers of cases and controls, and numbers and/or percentages of null genotypes. Disagreement about data extraction was resolved by discussion and consensus.

Assessment of quality of evidence in included studies. Two reviewers (YYL and HJG) independently assessed quality of evidence in the included studies using the 9-star Newcastle-Ottawa Scale, which considers selection, comparability and outcome evaluation criteria.

Assessment of heterogeneity. Heterogeneity was assessed using the χ^2 test and I^2 test. The I^2 statistic was interpreted as follows: I^2=0-40%, heterogeneity may not be important; I^2= 30-60%, heterogeneity may be moderate; I^2=50-90%, heterogeneity may be substantial; and I^2=75-100%, considerable heterogeneity (11). If heterogeneity was present, meta-regression was used to find the source.

Assessment of reporting biases. A funnel plot of effect estimates against their standard errors (SEs) was created to assess possible reporting bias between studies. Funnel plot asymmetry was assessed using Egger's linear regression test and Begg's rank correlation test; $P<0.05$ suggested publication bias.

GSTM1/GSTT1 and risk for endometriosis. Two reviewers (XYX and HJG) independently combined data from trials using a fixed-effect model (DerSimonian and Laird method) when there was no significant heterogeneity in populations (I^2<50%) and a random-effect model (Mantel-Haenszel method) when there was considerable heterogeneity. Variables were synthesized using odds ratios (ORs). A P-value of 0.05 was used as the cut-off value to determine statistical significance, and data are presented as the estimated OR with 95% confidence intervals (CIs). All statistical analyses were performed using STATA software, version 12.0 (StataCorp, College Station, TX, USA). Inconsistencies in data analysis were resolved through consensus and discussion with a third reviewer (ZSJ).

Sensitivity and subgroup analyses. Sensitivity analyses were performed to explore the impact of excluding outlying results. Subgroup analyses were performed by stratifying patients according to ethnicity (Caucasian, Asian or mixed), characteristics of controls (hospital patients or healthy individuals), and quality of evidence (high-quality or low-quality).

Results

Screening and selection. The searches identified 120 articles. Titles and abstracts were screened, and 36 studies were identified as potentially eligible for inclusion. The full text articles for these studies were retrieved. Following analysis of the full text articles, four studies were excluded and 32 studies were found to be eligible for inclusion according to the criteria used for considering studies in this review (Fig. 1).

Included studies. The characteristics of the included studies are shown in Table I. There were 32 case-control genetic association studies involving 3,990 cases of endometriosis and 4,625 controls. One publication addressed two groups of subjects with different ethnicities and was considered as two case-control genetic association studies (12); thus, the total number of studies was considered to be 33. Studies included data relevant to the *GSTM1* genotype, *GSTT1* genotype or the combined *GSTM1*/*GSTT1* genotype. Of the 32 eligible studies, 20 were conducted in Asia (12-31), eight in Europe (32-39), two in North America (40,41), and two in South America (42,43). The evidence reported in 23 studies was identified as high-quality, and that in 10 studies was identified as low-quality.

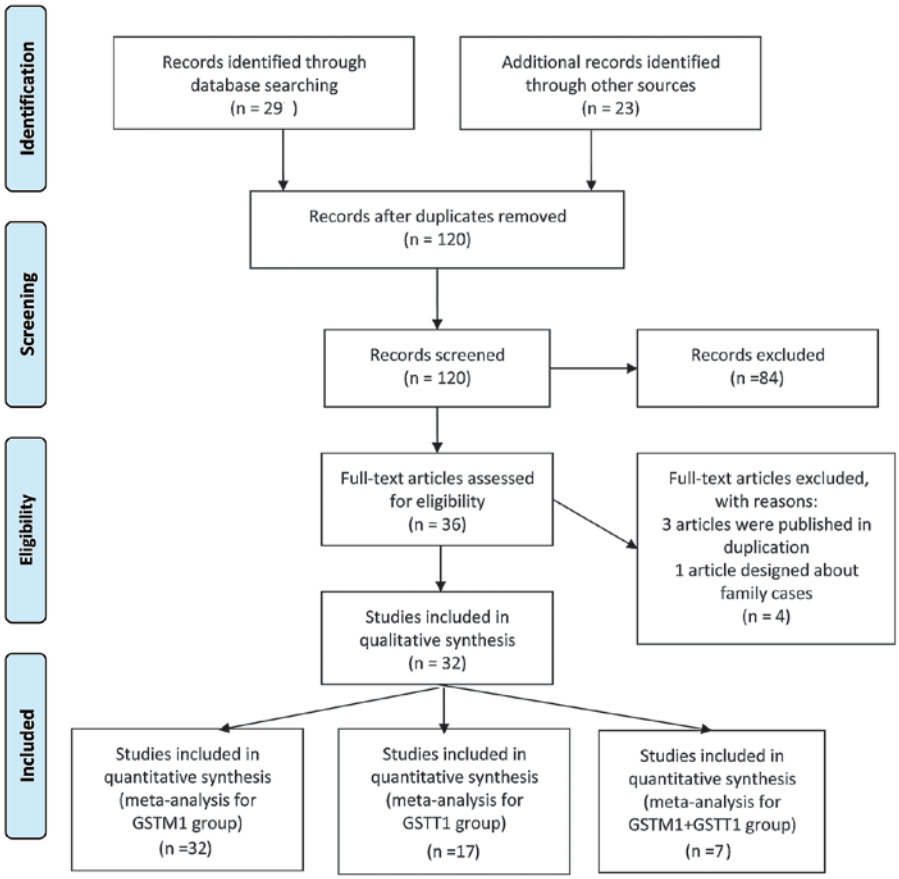

Figure 1. PRISMA 2009 flow diagram showing the article screening and selection process. Using the search strategy, 120 articles were identified by the initial search, and 36 required further assessment. Finally, 32 articles were included in this review, one of which was considered as two studies. GSTM1, glutathione S-transferase μ1; GSTT1, glutathione S-transferase θ1.

Excluded studies. Of the 36 studies that were relevant to the *GSTM1*/*GSTT1* genotype and endometriosis, four were excluded. Of these, three were duplicates (13,14,32), and one included subjects who were related (44).

GSTM1/GSTT1 and risk for endometriosis

GSTM1genotype. Data reporting on the *GSTM1* gene polymorphism are described in 33 case-control studies (3,990 cases of endometriosis and 4,625 controls). The meta-analysis demonstrated that there was a significant association between the *GSTM1* null genotype and an increased risk for endometriosis (OR=1.56; 95% CI: 1.25-1.95; P<0.0001; Fig. 2A).

Subgroup analyses stratified by ethnicity (Caucasian: OR=1.599; 95% CI: 1.205-2.122; P=0.001; Asian: OR=1.772; 95% CI: 1.242-2.528, P=0.002), source of controls (hospital patients: OR=1.561; 95% CI: 1.151-2.117; P=0.004; healthy individuals: OR=1.569; 95% CI: 1.131-2.176; P=0.007), and quality of evidence (high-quality: OR=1.563; 95% CI: 1.253-1.949; P<0.0001) confirmed this finding.

Subgroup analysis stratified for mixed ethnicity (two case control studies involving 111 cases of endometriosis and 78 controls) demonstrated a significant association between the *GSTM1* null genotype and a decreased risk for endometriosis (OR=0.404; 95% CI: 0.219-0.745; P=0.004; Table II). Compared with individual Caucasian and Asian populations, the difference was statistically significant (P<0.001; data shown in Table III).

GSTT1 genotype. Data reporting on the *GSTT1* gene polymorphism are described in 18 case-control studies (2,371 cases of endometriosis and 2,490 controls). The meta-analysis demonstrated a significant association between the *GSTT1* null genotype and an increased risk for endometriosis (OR=1.31; 95% CI: 1.02-1.68; P=0.037; Fig. 2B).

Subgroup analysis stratified by ethnicity demonstrated a significant association between the *GSTT1* null genotype and an increased risk for endometriosis among Asians (OR=1.573; 95% CI: 1.186-2.085; P=0.002), but not among Caucasians (OR=1.124; 95% CI: 0.745-1.697; P=0.577).

Subgroup analyses stratified by the source of controls found no significant association between the *GSTT1* null genotype and an increased risk for endometriosis among hospital-based studies (OR=1.284; 95% CI: 0.963-1.712; P=0.089) or among healthy individuals (OR=1.315; 95% CI: 0.767-2.254; P=0.320).

Subgroup analyses stratified by quality of evidence demonstrated a significant association between the *GSTT1* null genotype and an increased risk for endometriosis among studies considered high-quality evidence (OR=1.376; 95% CI: 1.020-1.858; P=0.037), but not among studies considered low-quality evidence (OR=1.121, 95% CI: 0.646-1.944; P=0.684; Table II).

Combined GSTM1/GSTT1 genotype. Data reporting on the combined *GSTM1*/*GSTT1* gene polymorphism are described in eight case-control studies (1,083 cases of endometriosis and 1,222 controls). The meta-analysis demonstrated a significant

Table I. Characteristics of included studies on the *GSTM1, GSTT1* and combined *GSTM1/GSTT1* gene polymorphisms.

First author, year	Ethnicity	Countries	Source of controls	Quality	*GSTM1* (n)		*GSTT1* (n)		*GSTM1+GSTT1* (n)		Refs.
					Cases /null	Controls /null	Cases /null	Controls /null	Cases /null	Controls /null	
Baranov, 1996	Caucasian	Russia	Healthy individuals	Low	42/34	67/26					(33)
Baranova, 1999	Caucasian	Russia, France	Hospital patients	High	65/50	72/33	65/13	72/7			(32)
Baranov, 1999	Caucasian	Russia	Healthy individuals	Low	150/88	99/42					(34)
Hadfield, 2001	Caucasian	UK	Hospital patients	High	132/59	52/27	116/29	50/14			(35)
Baxter, 2001	Caucasian	England	Healthy individuals	High	84/40	219/107					(36)
Bischoff, 2002	Caucasian	USA	Hospital patients	Low	62/13	36/20					(40)
Ivaschenko, 2003	Caucasian	Russia	Hospital patients	High	74/42	40/17	74/27	40/6	74/16	40/2	(37)
Arvanitis, 2003	Caucasian	Greece	Healthy individuals	High	275/161	346/181	275/24	346/31	275/11	346/16	(38)
Peng, 2003	Asian	China	Hospital patients	High	76/50	80/37					(15)
Lin, 2003	Asian	China	Hospital patients	High	68/49	28/12	68/53	28/9			(16)
Morizane, 2004	Asian	Japan	Healthy individuals	Low	108/57	173/89	108/52	173/71	108/30	173/43	(17)
Hsieh, 2004	Asian	China	Hospital patients	High	150/95	159/8					(18)
De Carvalho, 2004	Mixed	Brazil	Hospital patients	Low	61/21	32/17					(42)
Ding, 2004	Asian	China	Healthy individuals	High	80/46	105/55	80/59	105/47	80/34	105/24	(12)
Ding, 2004	Asian	China	Healthy individuals	High	41/21	107/57	41/15	107/32	41/10	107/14	(12)
Babu, 2005	Caucasian	India	Hospital patients	High	310/121	215/64	310/42	215/34	310/14	215/11	(19)
Hur, 2005	Asian	Korea	Hospital patients	Low	194/112	259/145	194/104	259/125			(20)
Aban, 2007	Caucasian	Turkey	Hospital patients	High	150/88	150/65	150/59	150/44			(21)
Chang, 2007	Asian	China	Hospital patients	High	74/48	65/30	74/46	65/32	74/27	65/13	(30)
Kim, 2007	Asian	Korea	Hospital patients	High	316/183	256/146	316/178	256/124			(22)
Rozati, 2009	Caucasian	India	Hospital patients	High	97/26	102/15					(13)
Yang, 2009	Asian	China	Hospital patients	Low	216/134	216/100					(14)
Cao, 2009	Asian	China	Hospital patients	High	51/33	102/61	51/22	102/39			(23)
Wu, 2009	Asian	China	Hospital patients	High	96/63	85/40					(24)
Huang, 2010	Asian	China	Hospital patients	High	28/12	29/10					(25)
Trabert, 2011	Caucasian	USA	Healthy individuals	High	254/137	567/268					(41)
Hosseinzadeh, 2011	Caucasian	Iran	Healthy individuals	High	120/87	200/80					(26)
Wu, 2012	Asian	China	Healthy individuals	low	121/57	171/52	121/40	171/33	121/23	171/15	(27)
Seifati, 2012	Caucasian	Iran	Hospital patients	High	101/51	142/74					(28)
Vichi, 2012	Caucasian	Italy	Hospital patients	High	181/104	162/85	181/20	162/32			(39)
Matsuzaka, 2012	Asian	Japan	Hospital patients	High	97/43	143/67	97/38	143/56			(29)
Frare, 2013	Mixed	Brazil	Healthy individuals	Low	50/25	46/34	50/16	46/27			(43)
Sachan, 2013	Caucasian	Iran	Healthy people	Low	66/27	100/16					(31)

Null genotype vs. wild type gene polymorphisms and susceptibility to endometriosis. GSTM1, glutathione S-transferase μ1; GSTT1, glutathione S-transferase θ1.

Table II. Meta-analysis of the association between *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* (null genotype vs. wild-type) gene polymorphisms and susceptibility to endometriosis.

Group	No. of studies	No. of subjects (cases/controls)	OR [95%CI]	P-value
Total studies				
GSTM1 genotype	33	3,990/4,625	1.563 [1.253-1.949]	<0.001
GSTT1 genotype	18	2,371/2,490	1.345 [1.044-1.733]	0.022
GSTM1+*GSTT1* genotype	8	1,083/1,222	1.672 [1.291-2.166]	0.005
Caucasian				
GSTM1 genotype	16	2,163/2,569	1.599 [1.205-2.122]	0.001
GSTT1 genotype	7	1,171/1,035	1.124 [0.745-1.697]	0.577
GSTM1+*GSTT1* genotype	3	659/601	1.185 [0.717-1.961]	0.508
Asian				
GSTM1 genotype	15	1,716/1,978	1.772 [1.242-2.528]	0.002
GSTT1 genotype	10	1,150/1,409	1.573 [1.186-2.085]	0.002
GSTM1+*GSTT1* genotype	5	424/621	1.898 [1.404-2.565]	<0.001
Mixed				
GSTM1 genotype	2	111/78	0.404 [0.219-0.745]	0.004
GSTT1 genotype	1	50/46		
GSTM1+*GSTT1* genotype	0			
Controls from hospital patients				
GSTM1 genotype	21	2,599/2,425	1.561 [1.151-2.117]	0.004
GSTT1 genotype	12	1,696/1,542	1.284 [0.963-1.712]	0.089
GSTM1+*GSTT1* genotype	3	458/320	1.797 [1.081-2.989]	0.024
Controls from healthy individuals				
GSTM1 genotype	12	1,391/2,200	1.569 [1.131-2.176]	0.007
GSTT1 genotype	6	675/948	1.315 [0.767-2.254]	0.320
GSTM1+*GSTT1* genotype	5	625/902	1.657 [1.085-2.532]	0.001
High quality				
GSTM1 genotype	23	2,920/3,426	1.563 [1.253-1.949]	<0.001
GSTT1 genotype	14	1,898/1,841	1.376 [1.020-1.858]	0.037
GSTM1+*GSTT1* genotype	6	854/878	1.753 [1.265-2.430]	0.001
Low quality				
GSTM1 genotype	10	1,070/1,199	1.259 [0.785-2.020]	0.340
GSTT1 genotype	4	473/649	1.121 [0.646-1.944]	0.684
GSTM1+*GSTT1* genotype	2	229/344	1.542 [1.009-2.356]	0.045

OR, odds ratio; CI, confidence interval; *GSTM1*, glutathione S-transferase μ1; *GSTT1*, glutathione S-transferase θ1.

association between the combined *GSTM1*/*GSTT1* null genotype and an increased risk for endometriosis (OR=1.68, 95% CI: 1.29-2.17; P<0.0001; Fig. 2C).

This association was unchanged by subgroup analyses stratified by source of controls (hospital-based studies: OR=1.797; 95% CI: 1.081-2.989; P=0.024; healthy individuals: OR=1.657; 95% CI: 1.085-2.532; P=0.001) or quality of evidence (high-quality evidence: OR=1.753; 95% CI: 1.265-2.430; P=0.001; low-quality evidence: OR=1.542; 95% CI: 1.009-2.356, P=0.045; Table II).

Subgroup analysis stratified by ethnicity demonstrated a significant association between the combined *GSTM1*/*GSTT1* null genotype and an increased risk for endometriosis among Asian populations (OR=1.898; 95% CI: 1.404-2.565; P<0.001), but not among Caucasian populations (OR=1.185; 95% CI: 0.717-1.961; P=0.508).

Publication bias. Visual inspection of a Funnel plot, Egger's test and Begg's rank correlation test revealed no significant publication bias for the *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* studies (Fig. 3; Table IV).

Heterogeneity analysis. There was evidence of significant heterogeneity (I^2>50%) between studies of *GSTM1* and *GSTT1*, and those used in subgroup analyses, although not among studies of *GSTM1*/*GSTT1* combined (Table IV). Therefore, the random-effect model was used in all analyses with the exception of the analysis of combined *GSTM1*/*GSTT1* gene polymorphisms. For the *GSTM1* and *GSTT1* gene polymorphisms, a meta-regression was conducted in which publication year, ethnicity, source of controls, sample size, and quality of evidence were covariates. All the covariates were entered into the meta-regression model simultaneously,

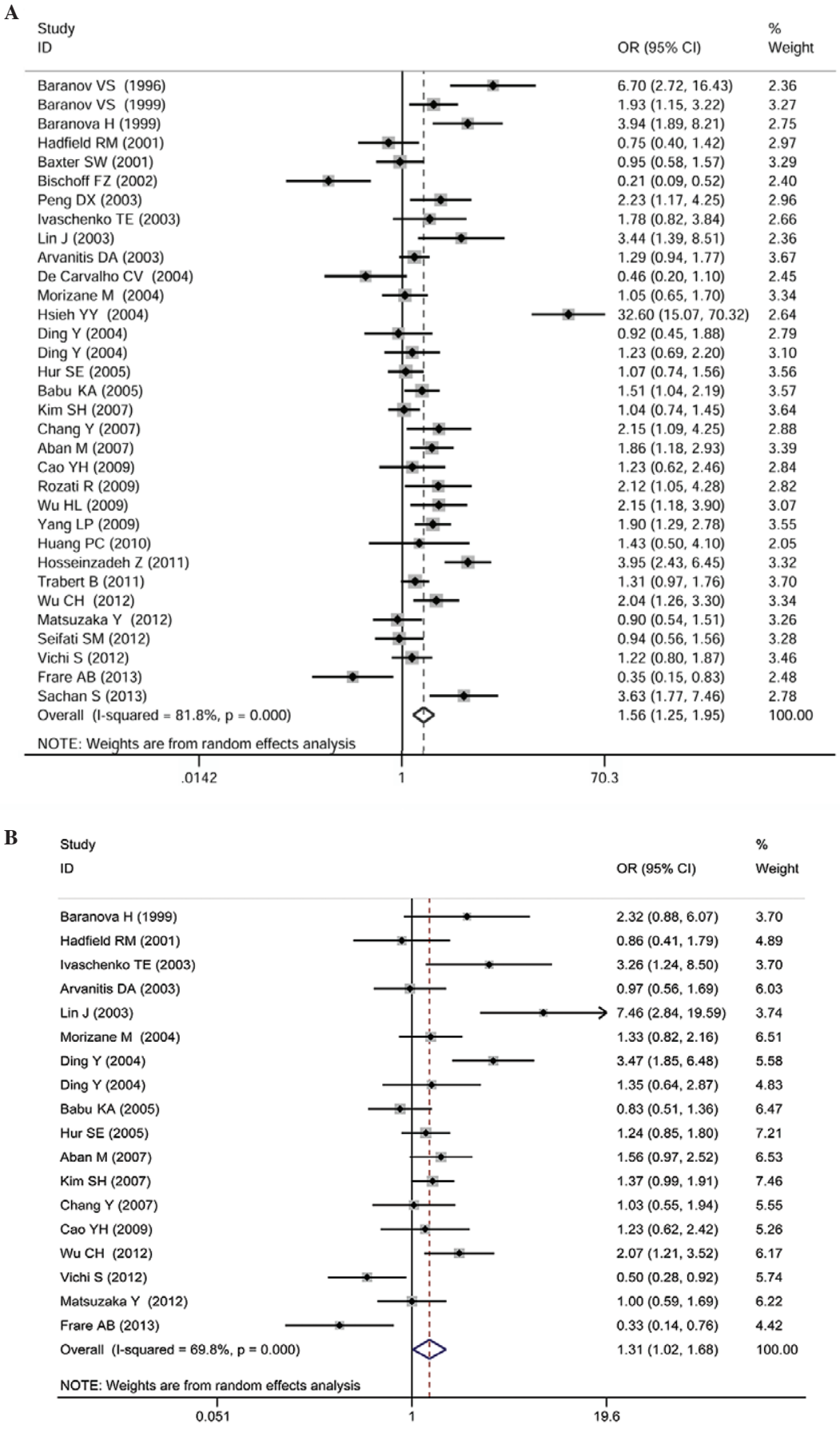

Figure 2. Association between *GSTM1*, *GSTT1* and the combined *GSTM1/GSTT1* null genotypes and susceptibility to endometriosis. (A) A total of 33 studies described the association between the *GSTM1* null genotype and susceptibility to endometriosis [odds ratio (OR)=1.56; 95% confidence interval (CI): 1.25-1.95; P<0.0001]; and (B) 18 studies described the association between the *GSTT1* null genotype and susceptibility to endometriosis (OR=1.31; 95% CI: 1.02-1.68; P=0.037). GSTM1, glutathione S-transferase μ1;. GSTT1, glutathione S-transferase θ1.

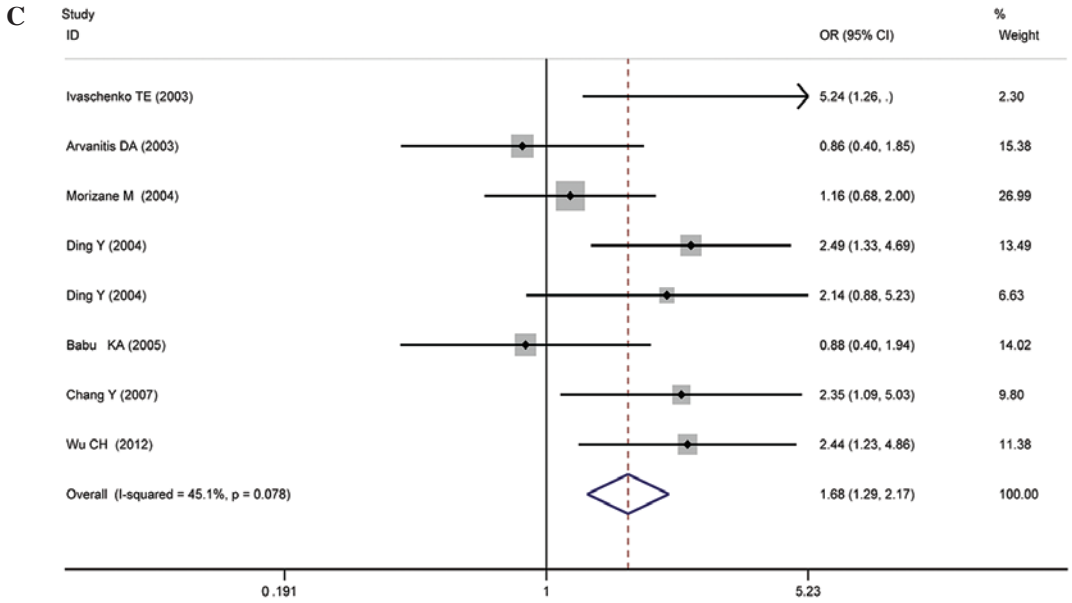

Figure 2. Continued. (C) Eight studies described the association between the combined *GSTM1*/*GSTT1* null genotypes and susceptibility to endometriosis [odds ratio (OR)=1.68; 95% confidence interval (CI): 1.29-2.17; P<0.0001]. GSTM1, glutathione S-transferase μ1;. GSTT1, glutathione S-transferase θ1.

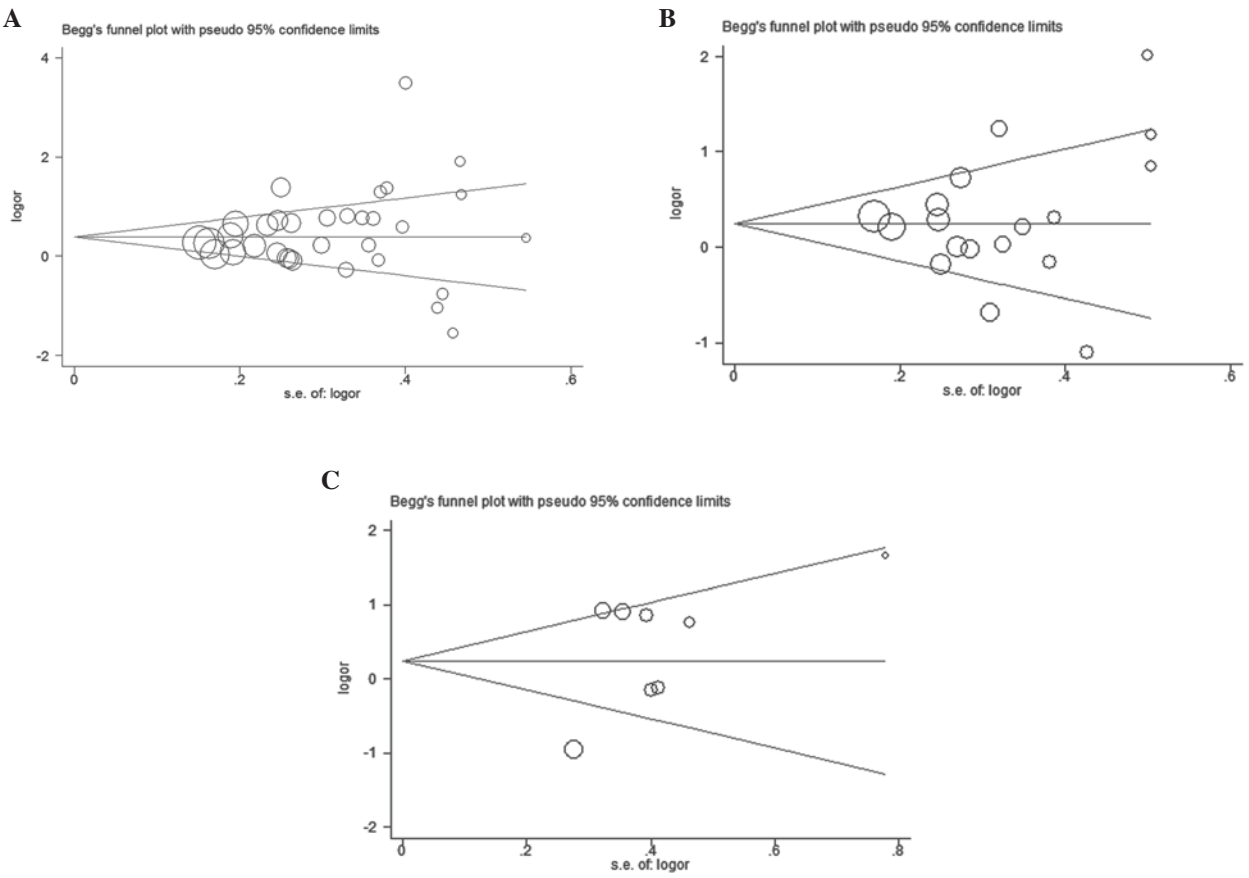

Figure 3. Assessment of publication bias for studies on (A) *GSTM1*, (B) *GSTT1* and (C) combined *GSTM1*/*GSTT1* genotypes. GSTM1, glutathione S-transferase μ1;. GSTT1, glutathione S-transferase θ1.

and the covariates that had the highest P-values were omitted one at a time in order to identify any sources of heterogeneity among them. However, the meta-regression analysis did not identify any of these covariates as a significant source of heterogeneity (Figs. 4 and 5).

Sensitivity analysis. To explore the effects of individual studies on the pooled OR estimates, a sensitivity analysis was performed, with the omission of one study at a time. The OR estimates for the *GSTM1* polymorphism were not notably altered (Fig. 6A). The OR estimates for the *GSTT1* and

Table III. Comparisons of subgroup analyses for *GSTM1*, *GSTT1* and combined *GSTM1/GSTT1* studies.

A, Analysis of the *GSTM1* gene

		GSTM1 (n)			
Subgroup	Subjects	Null	Normal	χ^2	P-value
Ethnicity				3.245	0.72[a]
Caucasian	Cases	1,128	1,035		
	Controls	1,120	1,449		
Asian	Cases	1,003	713		
	Controls	909	1,069		
Mixed	Cases	46	65	18.737	<0.001[b]
	Controls	51	27	23.467	<0.001[c]
Source of controls				0.130	0.718
Hospital patients	Cases	1,397	1,202		
	Controls	1,073	1,352		
Healthy individuals	Cases	780	611		
	Controls	1,007	1,193		
Quality				0.825	0.364
High quality	Cases	1,609	1,311		
	Controls	1,539	1,887		
Low quality	Cases	568	502		
	Controls	541	658		

B, Analysis of the *GSTT1* gene

		GSTT1 (n)			
Subgroup	Subjects	Null	Normal	χ^2	P-value
Ethnicity				6.766	0.009
Caucasian	Cases	214	957		
	Controls	168	867		
Asian	Cases	607	543		
	Controls	568	841		
Source of controls				0.638	0.425
Hospital patients	Cases	631	1,065		
	Controls	522	1,020		
Healthy individuals	Cases	206	469		
	Controls	241	707		
Quality				0.062	0.803
High quality	Cases	625	1,273		
	Controls	507	1,334		
Low quality	Cases	212	261		
	Controls	256	393		

C, Analysis of *GSTM1+GSTT1* genes

		GSTM1+GSTT1 (n)			
Subgroup	Subjects	Null	Normal	χ^2	P-value
Ethnicity				7.642	0.006
Caucasian	Cases	41	618		
	Controls	29	572		

Table III. Continued.

Subgroup	Subjects	Null	Normal	χ^2	P-value
Asian	Cases	124	300		
	Controls	109	152		
Source of controls				0.091	0.763
Hospital patients	Cases	57	401		
	Controls	26	294		
Healthy individuals	Cases	108	517		
	Controls	112	790		
Quality				0.022	0.882
High quality	Cases	112	542		
	Controls	80	598		
Low quality	Cases	53	176		
	Controls	58	286		

[a]Caucasians vs. Asians, [b]Caucasians vs. mixed, [c]Asians vs. mixed.

Table IV. Heterogeneity and publication bias of *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* studies.

	Heterogeneity		Publication bias (P-value)	
Group	I^2 value (%)	P-value	Egger's test	Begg's funnel plot
Total studies				
GSTM1 genotype	81.8	<0.001	0.313	0.412
GSTT1 genotype	69.9	<0.001	0.557	0.705
GSTM1+*GSTT1* genotype	44.7	0.081	0.170	1.000
Caucasian				
GSTM1 genotype	79.2	<0.001	0.454	0.322
GSTT1 genotype	64.7	0.009	0.339	0.764
GSTM1+*GSTT1* genotype	58.5	0.090	0.021	0.296
Asian				
GSTM1 genotype	83.8	<0.001	0.098	0.083
GSTT1 genotype	62.4	0.004	0.160	0.210
GSTM1+*GSTT1* genotype	13.6	0.081	0.340	0.806
Mixed				
GSTM1 genotype	0.0	0.664	<0.001	0.317
Controls from hospital patients				
GSTM1 genotype	83.6	<0.001	0.390	0.506
GSTT1 genotype	65.9	0.001	0.335	0.451
GSTM1+*GSTT1* genotype	62.2	0.071	0.585	1.000
Controls from healthy individuals				
GSTM1 genotype	79.4	<0.001	0.598	0.784
GSTT1 genotype	78.4	<0.001	0.431	0.707
GSTM1+*GSTT1* genotype	45.9	0.116	0.531	1.000
High quality				
GSTM1 genotype	80.9	<0.001	0.042	0.068
GSTT1 genotype	69.9	<0.001	0.530	0.189
GSTM1+*GSTT1* genotype	49.0	0.081	0.641	1.000
Low quality				
GSTM1 genotype	85.1	<0.001	0.788	0.516
GSTT1 genotype	77.2	0.004	0.347	1.000
GSTM1+*GSTT1* genotype	62.9	0.101		

GSTM1, glutathione S-transferase μ1;. GSTT1, glutathione S-transferase θ1.

A

```
. metareg logor publish size ethnicity source quality, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      33
REML estimate of between-study variance           tau2           =    .658
% residual variation due to heterogeneity         I-squared_res  =  84.15%
Proportion of between-study variance explained    Adj R-squared  = -17.93%
Joint test for all covariates                     Model F(5,27)  =    0.34
With Knapp-Hartung modification                   Prob > F       =  0.8865
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
publish	-.0222449	.0523803	-0.42	0.674	-.1297205	.0852307
size	-.0057332	.0930674	-0.06	0.951	-.1966917	.1852253
ethnicity	-.1694732	.2954847	-0.57	0.571	-.7757577	.4368114
source	-.1049237	.3379029	-0.31	0.759	-.7982432	.5883958
quality	.2929028	.362554	0.81	0.426	-.4509965	1.036802
_cons	.5558104	1.054713	0.53	0.603	-1.608282	2.719903

B

```
. metareg logor publish ethnicity source quality, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      33
REML estimate of between-study variance           tau2           =    .6263
% residual variation due to heterogeneity         I-squared_res  =  83.59%
Proportion of between-study variance explained    Adj R-squared  = -12.25%
Joint test for all covariates                     Model F(4,28)  =    0.43
With Knapp-Hartung modification                   Prob > F       =  0.7846
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
publish	-.0228103	.0501709	-0.45	0.653	-.1255807	.07996
ethnicity	-.1629092	.2725722	-0.60	0.555	-.7212481	.3954297
source	-.1010562	.3256125	-0.31	0.759	-.7680431	.5659308
quality	.2884664	.3536127	0.82	0.422	-.4358765	1.012809
_cons	.5321084	.9521008	0.56	0.581	-1.418182	2.482399

C

```
. metareg logor publish ethnicity quality, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      33
REML estimate of between-study variance           tau2           =    .6005
% residual variation due to heterogeneity         I-squared_res  =  83.13%
Proportion of between-study variance explained    Adj R-squared  =  -7.62%
Joint test for all covariates                     Model F(3,29)  =    0.56
With Knapp-Hartung modification                   Prob > F       =  0.6477
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
publish	-.0219724	.0492768	-0.45	0.659	-.1227548	.0788101
ethnicity	-.1670919	.2677483	-0.62	0.537	-.7146988	.3805149
quality	.2682417	.3427604	0.78	0.440	-.4327819	.9692654
_cons	.4010682	.8372382	0.48	0.636	-1.311276	2.113413

D

```
. metareg logor ethnicity quality, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      33
REML estimate of between-study variance           tau2           =    .5775
% residual variation due to heterogeneity         I-squared_res  =  82.56%
Proportion of between-study variance explained    Adj R-squared  =  -3.50%
Joint test for all covariates                     Model F(2,30)  =    0.75
With Knapp-Hartung modification                   Prob > F       =  0.4804
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
ethnicity	-.1886307	.259498	-0.73	0.473	-.7185963	.341335
quality	.2568094	.3371358	0.76	0.452	-.4317137	.9453325
_cons	.30802	.798419	0.39	0.702	-1.322569	1.938609

E

```
. metareg logor quality, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      33
REML estimate of between-study variance           tau2           =    .5648
% residual variation due to heterogeneity         I-squared_res  =  82.23%
Proportion of between-study variance explained    Adj R-squared  =  -1.23%
With Knapp-Hartung modification
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
quality	.3201558	.3226287	0.99	0.329	-.3378498	.9781615
_cons	-.0943798	.5686729	-0.17	0.869	-1.254196	1.065436

Figure 4. Meta-regression for *GSTM1* studies, with publication year, ethnicity, source of controls, sample size, and quality of evidence as covariates. All covariates were entered into the meta-regression model simultaneously, and the covariates with the highest P-values were omitted one at a time to identify sources of heterogeneity. The meta-regression did not identify any of these covariates as a significant source of heterogeneity. Variables were omitted in the following order: Size (A→B), source (B→C), publication year (C→D), ethnicity (D→E). GSTM1, glutathione S-transferase μ1.

A

```
. metareg logor quality ethnicity source publish size, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      18
REML estimate of between-study variance           tau2           =   .2886
% residual variation due to heterogeneity         I-squared_res  =  71.84%
Proportion of between-study variance explained    Adj R-squared  =  -6.38%
Joint test for all covariates                     Model F(5,12)  =    1.16
With Knapp-Hartung modification                   Prob > F       =  0.3826
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
quality	-.1590068	.4528592	-0.35	0.732	-1.145702	.8276887
ethnicity	.271699	.4052781	0.67	0.515	-.6113262	1.154724
source	-.0803778	.3782303	-0.21	0.835	-.9044707	.7437151
publish	-.1704023	.0853161	-2.00	0.069	-.3562901	.0154854
size	-.0645026	.098486	-0.65	0.525	-.2790851	.1500799
_cons	1.239194	.7636197	1.62	0.131	-.4245906	2.902978

B

```
. metareg logor quality ethnicity publish size, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      18
REML estimate of between-study variance           tau2           =   .2512
% residual variation due to heterogeneity         I-squared_res  =  69.50%
Proportion of between-study variance explained    Adj R-squared  =   7.39%
Joint test for all covariates                     Model F(4,13)  =    1.53
With Knapp-Hartung modification                   Prob > F       =  0.2518
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
quality	-.1857158	.4081106	-0.46	0.657	-1.067385	.6959535
ethnicity	.250042	.3759013	0.67	0.518	-.5620434	1.062127
publish	-.1645894	.0793835	-2.07	0.059	-.3360871	.0069084
size	-.0651066	.0939738	-0.69	0.501	-.2681247	.1379114
_cons	1.173268	.6945433	1.69	0.115	-.3272015	2.673738

C

```
. metareg logor ethnicity publish size, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      18
REML estimate of between-study variance           tau2           =   .2216
% residual variation due to heterogeneity         I-squared_res  =  67.69%
Proportion of between-study variance explained    Adj R-squared  =  18.33%
Joint test for all covariates                     Model F(3,14)  =    2.05
With Knapp-Hartung modification                   Prob > F       =  0.1527
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
ethnicity	.1674779	.3162035	0.53	0.605	-.5107112	.845667
publish	-.1629358	.0767844	-2.12	0.052	-.3276219	.0017504
size	-.0722779	.0891182	-0.81	0.431	-.2634175	.1188617
_cons	1.097336	.6596905	1.66	0.118	-.3175592	2.512232

D

```
. metareg logor publish size, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      18
REML estimate of between-study variance           tau2           =   .2043
% residual variation due to heterogeneity         I-squared_res  =  66.88%
Proportion of between-study variance explained    Adj R-squared  =  24.68%
Joint test for all covariates                     Model F(2,15)  =    3.05
With Knapp-Hartung modification                   Prob > F       =  0.0773
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
publish	-.1420633	.0653113	-2.18	0.046	-.2812709	-.0028556
size	-.0925823	.0779051	-1.19	0.253	-.2586331	.0734686
_cons	1.337196	.4586958	2.92	0.011	.3595093	2.314883

E

```
. metareg logor publish, wsse(_selogES) bsest(reml)

Meta-regression                                   Number of obs  =      18
REML estimate of between-study variance           tau2           =   .2125
% residual variation due to heterogeneity         I-squared_res  =  67.21%
Proportion of between-study variance explained    Adj R-squared  =  21.67%
With Knapp-Hartung modification
```

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
publish	-.141961	.0661497	-2.15	0.048	-.2821921	-.0017298
_cons	1.020376	.3760155	2.71	0.015	.2232584	1.817493

Figure 5. Meta-regression for *GSTT1* studies, with publication year, ethnicity, source of controls, sample size, and quality of evidence as covariates. All covariates were entered into the meta-regression model simultaneously, and covariates with the highest P-values were omitted one at a time to identify sources of heterogeneity. Meta-regression identified publication year as a significant source of heterogeneity (P=0.048), but after omitting this covariate heterogeneity remained substantial (I^2=67.21%) Variables were omitted in the order: Source (A→B), quality (B→C), ethnicity (C→D), size (D→E). GSTT1, glutathione S-transferase θ1.

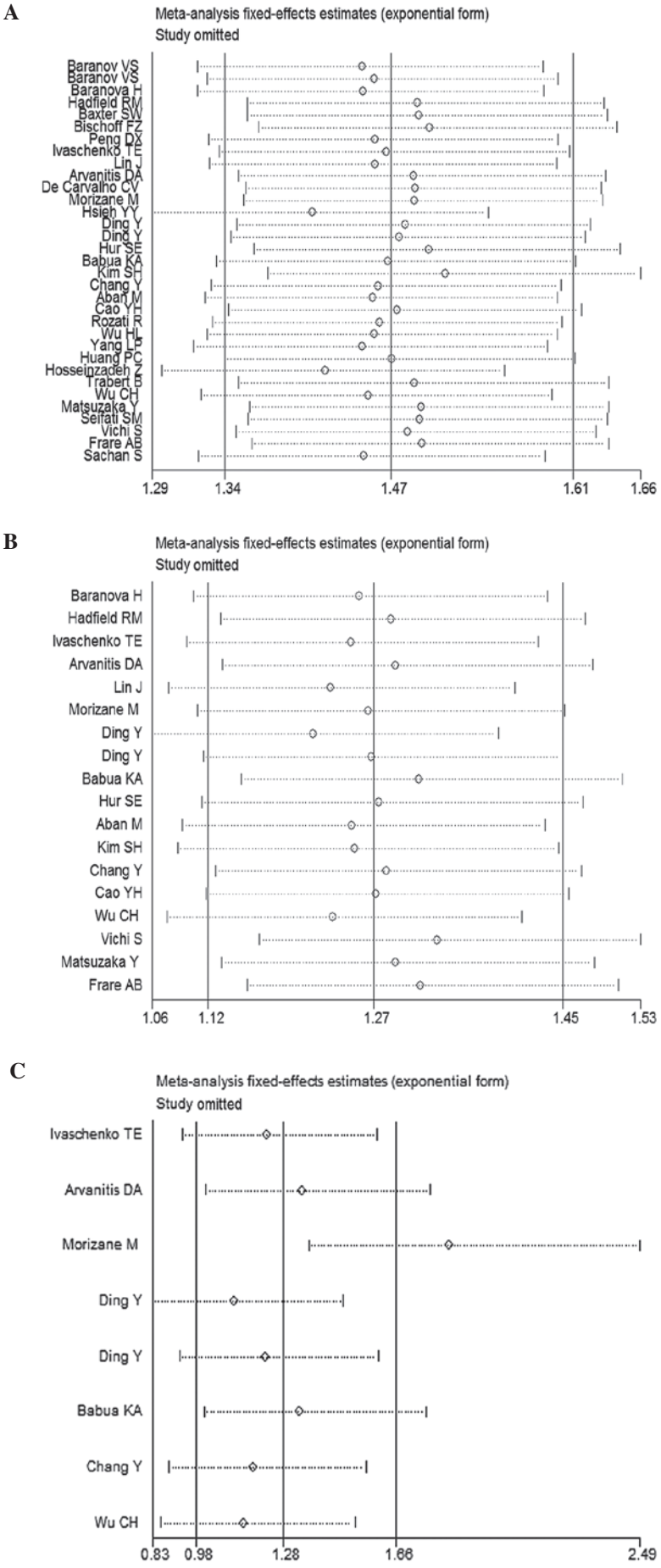

Figure 6. Sensitivity analyses investigating the association between the (A) *GSTM1*, (B) *GSTT1* and (C) combined *GSTM1*/*GSTT1* null genotypes and susceptibility to endometriosis; one study was omitted at a time. GSTM1, glutathione S-transferase μ1;. GSTT1, glutathione S-transferase θ1.

combined *GSTM1*/*GSTT1* polymorphisms were altered when studies were excluded (Fig. 6B and C).

Discussion

In the present study, a meta-analysis of data from 33 studies was conducted to examine the associations between the *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* null genotypes and susceptibility to endometriosis. The risk for endometriosis was significantly increased in the presence of the *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* null genotypes compared with the wild-type. Subgroup analyses stratified by ethnicity, source of controls and quality of evidence confirmed this finding among several subgroups, but particularly among studies considered high-quality evidence. Notably, among patients of mixed ethnicity, the *GSTM1* null genotype was significantly associated with a decreased risk for endometriosis compared with the wild-type.

A similar meta-analysis of 23 studies performed in 2005 demonstrated an increased risk for endometriosis in women with the *GSTT1* null genotype (8). However, the authors requested that their findings be interpreted with caution as asymmetry in the funnel plot was evident, which was likely due to publication bias (8). This previous study did not include subgroup analyses or an evaluation of the combined *GSTM1*/*GSTT1* null genotype-endometriosis association.

Previous meta-analyses have found that the *GSTM1*/*GSTT1* gene polymorphism is associated with cervical cancer (45), breast cancer (46), bladder cancer (47), gastric cancer (48,49) and acute leukemia (50). In accordance with the observations of the present study, several studies have shown that the *GSTM1* (OR=32.6, 95% CI: 15.07-70.32, P<0.0001) (18) and *GSTT1* (OR>3; P<0.0001) null genotypes (12,16) are associated with an increased risk for endometriosis. However, other reports suggest the *GSTM1* (OR=0.21, 95% CI: 0.09-0.52, P<0.0001; OR=0.35, 95% CI: 0.15-0.83, P<0.0001) (40,43), *GSTT1* (OR≥5; P<0.0001) (16) and combined *GSTM1*/*GSTT1* (OR=0.38; P<0.001) (17) null genotypes are associated with a decreased risk for endometriosis. These divergent results may be explained by differences in *GSTM1*/*GSTT1* null genotype frequencies and study locations. The frequency of the *GSTM1*/*GSTT1* null genotype may vary from 10 to 65% depending on the region and population studied (51). Different study locations may introduce confounding variables associated with variations in lifestyles and exposures to toxic substances of the study populations.

The results of the present study must be interpreted with caution due to the presence of substantial heterogeneity. Among analyses of the studies of *GSTM1* and *GSTT1*, the cause of heterogeneity remains unclear, despite meta-regression analyses being conducted. Among the analyses of combined *GSTM1*/*GSTT1* studies, subgroup and sensitivity analyses suggested that studies that included patients with advanced stage endometriosis caused most of the variability. Publication bias was unlikely to have influenced the findings.

In addition to the heterogeneity, there were several limitations to this study. Firstly, the composition of the endometriosis patient and control populations varied between studies. For instance, some studies included only patients with advanced endometriosis (17-20,22,27,35), while control populations consisted of a mixture of infertile (29), postmenopausal (43) and premenopausal (18,35) women, and newborn babies that had not been exposed to the environment (17). Furthermore, patients and controls were not always accurately matched by age or environmental exposures. Secondly, gene-gene or gene-environment interactions may jointly increase the risk for endometriosis; therefore, different lifestyle and environmental factors may contribute to differential genotypic frequencies in cases and controls. Attempts were made to mitigate inaccuracies associated with this limitation through a subgroup analysis stratified according to ethnicity. Thirdly, this study was based on published articles. As a positive result is more likely to be published, publication bias is an inherent limitation of all meta-analyses irrespective of the outcomes of the Egger's linear regression test and Begg's rank correlation test.

In conclusion, the present meta-analysis shows the *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* null genotypes are likely associated with increased susceptibility to endometriosis. These data are in contrast to those reported previously. Therefore, further studies reporting higher quality evidence are necessary to verify these conclusions.

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