Int J Clin Exp Med 2017;10(2):1953-1966
www.ijcem.com /ISSN:1940-5901/IJCEM0033546

Review Article

Relationship between polymorphisms of CYP19A1 gene and hypertension: a meta-analysis

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Received June 11, 2016; Accepted October 30, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Objective and Background: Several published studies have investigated the relationship between the rs700518 and rs4646 polymorphisms in the CYP19A1 gene and the risk of hypertension; however, their results were inconsistent. To examine these inconclusive findings, we performed a meta-analysis to investigate the relationships between genetic polymorphisms of the CYP19A1 gene and the risk of hypertension. Methods: By searching PubMed, ISI Web of Science and Embase, as well as the Wanfang Database, the Chinese National Knowledge Infrastructure (CNKI) Database, the Weipu Database and the Chinese Academic Journal Full-text Database, we extracted data from eligible studies and included these data in our meta-analysis. The relationships between the rs700518 and rs4646 polymorphisms and hypertension were estimated using pooled odds ratios (ORs) and 95% confidence intervals (95% CIs). Heterogeneity was investigated and measured using Cochran's Q test and the inconsistency index (I^2) test. Meta-analysis was conducted using Review Manager Software (version 5.3). Results: A total of six studies from five articles including 1446 subjects with hypertension and 1658 healthy individuals were included in this meta-analysis. No relationship was found between the rs700518 and rs4646 polymorphisms in the CYP19A1 gene and the risk of hypertension (for rs700518, allele model: A *vs*. G, OR = 1.03, 95% CI: 0.93-1.13, *P* = 0.59; dominant model: AA *vs*. AG+GG, OR = 1.10, 95% CI: 0.95-1.27, *P* = 0.20; recessive: model: GG *vs*. AG+AA, OR = 1.04, 95% CI: 0.88-1.22, *P* = 0.65; for rs4646, allele model: G *vs*. T, OR = 1.00, 95% CI: 0.89-1.12, *P* = 0.98; GG *vs*. dominant model: GT+TT, OR = 1.02, 95% CI: 0.88-1.18, *P* = 0.80; recessive model: TT *vs*. GT+GG, OR = 0.97, 95% CI: 0.73-1.28, *P* = 0.83). However, if the data were stratified by gender (men and women), a relationship between the rs4646 polymorphism in the CYP19A1 gene and the risk of hypertension among female subjects under the recessive model (TT *vs*. GT+GG: *P* = 0.04) was found using a fixed-effect model. Conclusion: The results of our meta-analysis suggest that neither the rs700518 polymorphism nor the rs4646 polymorphism in the CYP19A1 gene is a genetic marker of hypertension susceptibility. Other factors, such as gender, appear to play a role in the relationship between the rs4646 polymorphism and the risk of hypertension.

Keywords: CYP19A1, hypertension, polymorphisms, meta-analysis

Introduction

Hypertension currently represents a major cause of cardiovascular morbidity and mortality and causes more than 7 million deaths every year worldwide [1, 2]. This condition has become a major global public health burden, affecting more than one-quarter of adults, and this proportion is expected to increase to one-third of adults by 2025 [3]. Hypertension is a common, polygenic, complex disorder resulting from the interactions of several genes with each other and with environmental factors [4]. Current evidence estimates that genetic factors account for approximately 30%-50% of variations associated with hypertension [5]. The genetic factors underlying hypertension are still unknown [6].

The CYP19A1 gene is located on the long arm of chromosome 15 (15q21.1) and encodes the aromatase enzyme, which is responsible for the biosynthesis of estrogens [7]. Several previous studies have indicated that estrogen plays a protective role in the cardiovascular system [8-10], but only a few studies have focused on

genetic polymorphisms in the CYP19A1 gene with respect to cardiovascular disease [11]. In recent years, increasing numbers of studies have tested the effects of genetic variations in the CYP19A1 gene on hypertension and coronary artery disease. However, the relationship between genetic polymorphisms in the CYP19A1 gene and hypertension risk remains controversial. In 2008, Masanori Shimodaira *et al*. identified two loci (rs1870049 and rs10046) on the CYP19A1 gene which are associated with essential hypertension (EH) [12]. Then, these authors conducted a haplotype-based case-control study and noted relationships between genetic polymorphisms in the CYP19A1 gene and preeclampsia (PE) and gestational hypertension (GH). The rs700158 polymorphism in the CYP19A1 gene is linked to PE by analyzing a dominant model (AG+GG), and the frequency of the G allele is significantly higher in patients with PE than in controls [13]. In 2010, Beitelshees AL *et al.* analyzed two independent populations and noted a significant effect of the interaction between the CYP19A1 genotype and sex differences on cardiovascular outcomes [14]. The study by Reposo Ramirez-Lorca showed that the CYP19A1 gene might be involved in regulation of blood pressure in female subjects [15]. Recently, an investigation of the Framingham Heart Study offspring cohort found evidence suggestive of gender-specific contributions of the CYP19A1 gene to blood pressure variations [16]. However, Ayelet Ziv-Gala *et al.* and Peter I *et al.* found that the rs700518 and rs4646 polymorphisms in the CYP19A1 are not associated with hypertension in a sample of middle-aged female subjects [17, 18]. Two additional independent studies that included 270 women and 729 individuals, respectively, also did not find a significant association between CYP19A1 genetic polymorphisms and blood pressure [19, 20].

There were substantial differences in the sample sizes of the above studies. Additionally, the analyses regarding gender differences, which may be related to estrogen levels, yielded inconsistent results, so it is difficult to draw any conclusions regarding the relationship between CYP19A1 gene polymorphisms and hypertension. To determine whether CYP19A1 gene polymorphisms are associated with the risk of hypertension, we selected 2 genotyped intragenic polymorphisms, rs700518 and rs4646, and performed a meta-analysis to investigate the association between these polymorphisms and hypertension risk.

Materials and methods

Literature search strategy

We conducted literature searches for articles published before October 2015 in PubMed, ISI Web of Science and Embase, as well as the Wanfang Database, the Chinese National Knowledge Infrastructure (CNKI) Database, the Weipu Database and the Chinese Academic Journal Full-text Database. We attempted to identify as many studies as possible using the following key words: “CYP19A1” and “polymorphism” and “hypertension” or “blood pressure”. We retrieved articles containing these terms and reviewed their reference lists to identify additional eligible and relevant studies. We limited our searches to studies published in English and Chinese.

Inclusion criteria and data extraction

Studies were included in this meta-analysis if they met the following inclusion criteria: (1) they evaluated the associations between CYP19A1 polymorphisms (rs700518 and rs4646) and hypertension; (2) they used a case-control or cohort design and included a control group that included healthy or relatively healthy individuals without hypertension; (3) they defined hypertension as a systolic blood pressure of at least 140 mmHg, a diastolic blood pressure of at least 90 mmHg, a previous diagnosis of hypertension or the use of antihypertensive medications; (4) and their control groups were in agreement with Hardy-Weinberg equilibrium (P>0.05). If more than one article was published using the same sample, only the study with largest sample size was included. All relevant information was independently extracted from eligible publications by two authors according to the above-listed inclusion criteria. A third person (Zhenyan Fu) decided whether to include an article when the two authors (Yajie Meng and Dilare Adi) disagreed. The following information was extracted from each study: (1) the first author, (2) the publication year, (3) the ethnicity of the studied population, (4) the SNP research in the paper, (5) the mean age of the study population, (6) the mean BMI, (7) the genotyping methods, (8) agreement with Hardy-

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

Studies	Year	Ethnicity	SNP		Age (mean ± SD)	BMI	Genotyping	HWE	Sample size	
									Cases	Controls
Amber L. Beitelshees	2010	American	rs700518	INFORM:	Male: 61±12 Female: 64±13	Male: 29.0±5.5 Female: 30.1±6.5	Taqman	>0.6	337 Male: 194 Female: 143	207 Male: 157 Female: 50
				INVEST:	Male: 69±9 Female: 73±10	Male: 28.8±4.3 Female: 28.1±5.9		>0.8	148 Male: 74 Female: 74	447 Male: 221 Female: 226
			rs4646	INFORM:	Male: 61±12 Female: 64±13	Male: 29.0±5.5 Female: 30.1±6.5		>0.5	344 Male: 201 Female: 143	233 Male: 184 Female: 49
				INVEST:	Male: 69±9 Female: 73±10	Male: 28.8±4.3 Female: 28.1±5.9		>0.6	302 Male: 76 Female:226	301 Male: 74 Female: 227
Masanori Shimodaira	2012	Japanese	rs700518, rs4646		29.48±5.03	20.60±2.92	TaqMan® PCR	>0.8	131	122
Masanori Shimodaira	2008	Japanese	rs700518, rs4646		Cases Men: 50.2±6.7 Women: 51.1±5.3 Controls Men: 50.0±5.6 Women: 50.9±13.1	Cases Men: 24.8±3.6 Women: 24.8±4.1 Controls Men: 23.0±2.9 Women: 22.4±3.2	TaqMan® PCR	>0.8	223 Men: 142 Women: 81	220 Men:144 Women: 76
Ayelet Ziv-Gala	2012	American	rs700518		45 to 49: 396 50 to 54: 221	<25.0: 265 25.0 to 29.9: 169 >30.0: 182	PCR	>0.6	208	417
Inga Peter	2009	American	rs700518, rs4646		Men: 62±10 Women: 62±9	Men: 28.6±4.5 Women: 27.3±5.5	TaqMan	>0.9	610 Men: 308 Women: 302	651 Men: 296 Women: 355

Table 2. Genotyping characteristics of the all included studies in the meta-analysis

rs700518

First author	Year	Sample size		Genotypes distribution (case/control)					Sex (Male/Females)	
		Case	Control	AA	AG	GG	A	G	Case	Control
Amber L. Beitelshees1	2010	337	207	91/54	164/102	82/43	346/210	328/188	194/143	157/50
Amber L. Beitelshees2	2010	148	447	36/111	75/226	37/110	147/448	149/446	74/221	74/226
Masanori Shimodaira	2012	131	122	47/54	63/55	21/13	157/163	105/81	-/131	-/122
Masanori Shimodaira	2008	218	225	88/82	95/111	35/32	271/275	165/175	142/76	144/81
Ayelet Ziv-Gala	2012	208	417	81/110	90/209	37/90	252/429	164/389	-/208	-/417
Inga Peter	2009	610	651	165/176	305/325	141/150	635/677	587/625	308/302	296/355

rs4646

First author	Year	Sample size		Genotypes distribution (case/control)					Sex (Male/Females)	
		Case	Control	GG	GT	TT	G	T	Case	Control
Amber L. Beitelshees1	2010	337	207	178/114	139/76	27/16	495/304	193/108	194/143	157/50
Amber L. Beitelshees2	2010	150	453	80/237	58/184	12/32	218/658	82/248	74/221	74/226
Masanori Shimodaira	2012	131	122	72/56	52/54	7/12	196/166	66/78	-/131	-/122
Masanori Shimodaira	2008	218	225	114/119	83/85	21/21	311/323	125/117	142/76	144/81
Inga Peter	2009	610	651	343/366	229/244	38/41	915/976	305/326	308/302	296/355

Weinberg equilibrium and (9) the numbers of patients with hypertension and controls. Detailed information regarding the characteristics of the included studies is shown in **Table 1**. The relationship between genetic polymorphisms of the CYP19A1 gene and hypertension is shown in **Table 2**.

Statistical analyses

ORs and 95% CIs were applied to assess the strength of the associations between CYP19A1 polymorphisms (rs700518 and rs4646) and hypertension. Deviations from Hardy-Weinberg equilibrium (HWE) among the SNPs in the

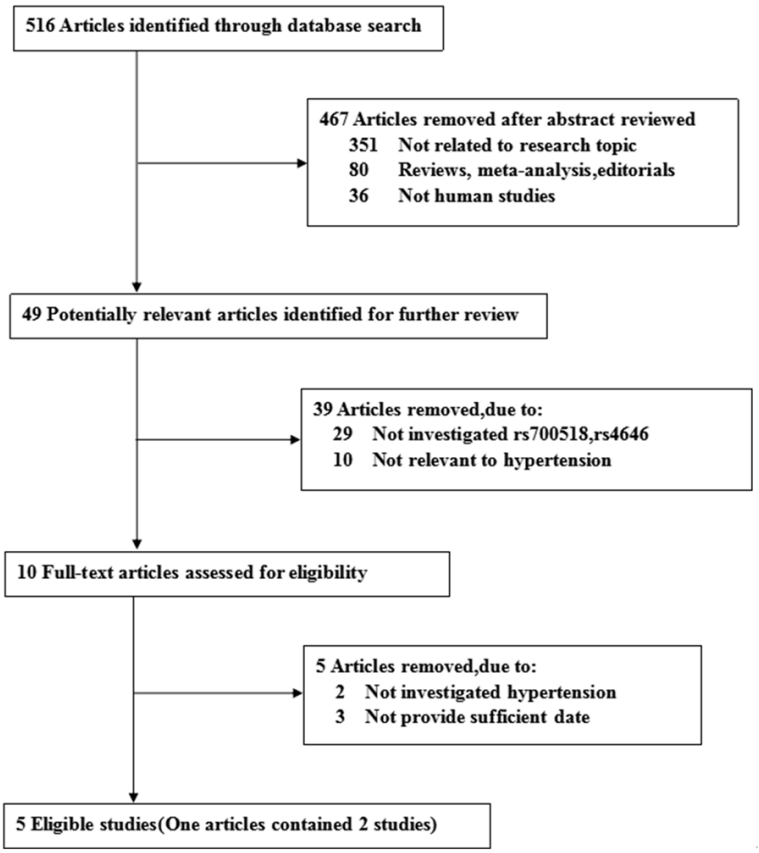


Figure 1. Searching process for eligible studies of the relationship between genetic polymorphisms of CYP19A1 gene with hypertension.

healthy control groups were tested via χ^2 analysis. Pooled ORs were calculated via a Z-test (P<0.05 was considered significant). The Q test was performed to examine whether variations were related to heterogeneity. If an article did not have significant heterogeneity (I^2<50%), the Mantel-Haenszel method [18] was used to calculate pooled ORs and 95% CIs. Alternatively, the DerSimonian-Laird method [22] was used to calculate pooled ORs and 95% CIs when significant heterogeneity (I^2<50%) was noted. Sensitivity analysis was performed to assess the stability of the results after excluding one study at a time. Funnel plots [23] were used as visual tools to investigate the studies for publication bias and other types of bias or systematic heterogeneity. All analyses were conducted using RevMan 5.3 software (website: http://www.cc-ims.net/RevMan).

Results

Characteristics of the studies

Based on our search strategy, we identified 516 potentially relevant articles. By scanning the titles and abstracts, we excluded 467 articles and selected 49 potentially relevant articles for further review. Thirty-nine of these studies were excluded for the following reasons: 29 did not pertain to the rs700518 and rs4646 polymorphisms in the CYP19A1 gene, and 10 did not pertain to hypertension. Ten full-text articles were assessed for eligibility. Three studies were excluded because they investigated the relationship between the rs700518 and rs4646 polymorphisms and coronary heart disease, and 2 studies were excluded because they did not provide sufficient data. Finally, six studies from five articles [12-14, 17, 18] were included in the meta-analysis. The genotype distributions among the control groups of all studies were in agreement with Hardy-Weinberg equilibrium. The characteristics of the selected studies are summarized in **Figure 1**.

Quantitative synthesis

Our meta-analysis included a total of six studies from five articles including 1446 hypertension patients and 1658 healthy individuals. **Table 3**; **Figures 2** and **3** showed the results of the meta-analysis of these six studies regarding the correlation between hypertension and the CYP19A1 polymorphisms rs700518 and rs4646. Systematic reviews of the included studies were included in the above table and figures, including information regarding the numbers of case and control groups, weights, ORs, and 95% CIs.

Figure 2A, **2B** and **Table 3** showed the results of the meta-analysis of the relationship between CYP19A1 polymorphisms (rs700518 and rs4646) and hypertension risk under different genetic models. Unfortunately, we found no associations between the rs700518 polymorphism and the risk of hypertension under an allele model (A *vs*. G, OR = 1.03, 95% CI: 0.93-1.13, P = 0.59), a dominant model (AA *vs*. AG+GG, OR = 1.10, 95% CI: 0.95-1.27, P =

Table 3. Meta-analysis of the relationship between genetic polymorphisms of CYP19A1 gene with hypertension

rs700518	A allele vs. G allele (Allele model)			AA vs. AG+GG (Dominant model)			GG vs. AG+AA (Recessive model)			AA vs. GG (Homozygous model)			GG vs. AG (Heterozygous model)		
	OR	95% CI	*P*	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Amber L. Beitelshees1 2010	0.94	0.74-1.21		1.05	0.71-1.55		1.23	0.81-1.86		0.88	0.54-1.46		1.16	0.79-1.69	
Amber L. Beitelshees2 2010	0.96	0.76-1.28		0.97	0.63-1.50		1.02	0.66-1.57		0.96	0.57-1.64		1.03	0.67-1.58	
Ayelet Ziv-Gala 2012	1.39	1.10-1.77		1.78	1.25-2.54		0.79	0.51-1.20		2.68	1.66-4.32		0.62	0.44-0.88	
Inga Peter 2009	1.00	0.85-1.17		1.00	0.78-1.28		1.00	0.77-1.31		1.00	0.73-1.36		1.01	0.79-1.29	
Masanori Shimodaira 2008	1.05	0.80-1.37		1.18	0.80-1.73		1.15	0.69-1.94		0.98	0.56-1.73		0.85	0.58-1.24	
Masanori Shimodaira 2012	0.74	0.52-1.07		0.70	0.43-1.1		1.60	0.76-3.36		0.54	0.24-1.19		1.42	0.86-2.35	
Total	1.03	1.93-1.13	0.59	1.10	0.95-1.2	0.20	1.04	0.88-1.22	0.65	1.11	0.92-1.34	0.29	0.95	0.82-1.10	0.50
rs4646	G allele vs. T allele (Allele model)			GG vs. GT+TT (Dominant model)			TT vs. GT+GG (Recessive model)			GG vs. TT (Homozygous model)			TT vs. GT (Heterozygous model)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Amber L. Beitelshees1 2010	0.91	0.69-1.20		0.91	0.65-1.29		1.01	0.54-1.90		0.93	1.21		1.21	0.86-1.72	
Amber L. Beitelshees2 2010	1.00	0.75-1.34		1.04	0.72-1.51		1.14	0.57-2.28		0.90	0.44-1.83		0.96	0.66-1.39	
Inga Peter 2009	1.00	0.84-1.20		1.00	0.80-1.25		0.99	0.63-1.56		1.01	0.63-1.61		1.00	0.80-1.25	
Masanori Shimodaira 2008	0.90	0.67-1.21		0.98	0.67-1.42		1.04	0.55-1.96		0.96	0.50-1.85		1.02	0.71-1.49	
Masanori Shimodaira 2012	1.40	0.95-2.06		1.44	0.88-2.36		0.52	0.02-1.36		2.20	0.81-5.96		0.70	0.42-1.14	
Total	1.00	0.89-1.12	0.98	1.02	0.88-1.18	0.80	0.97	0.73-1.28	0.83	1.03	0.78-1.37	0.82	1.00	0.86-1.16	1.00

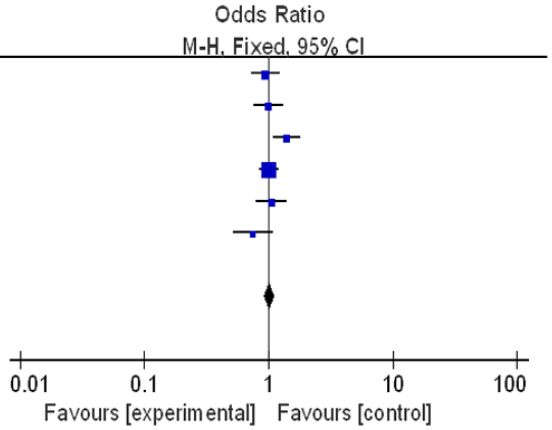
A

a

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	346	674	210	398	15.3%	0.94 [0.74, 1.21]
Amber L. Beitelshees2 2010	147	296	448	894	13.4%	0.98 [0.76, 1.28]
Ayelet Ziv-Gala 2012	252	416	429	818	13.6%	1.39 [1.10, 1.77]
Inga Peter 2009	635	1222	677	1302	37.5%	1.00 [0.85, 1.17]
Masanori Shimodaira 2008	271	436	275	450	12.2%	1.05 [0.80, 1.37]
Masanori Shimodaira 2012	157	262	163	244	8.1%	0.74 [0.52, 1.07]
Total (95% CI)		3306		4106	100.0%	1.03 [0.93, 1.13]
Total events	1808		2202			

Heterogeneity: Chi² = 9.95, df = 5 (P = 0.08); I² = 50%

Test for overall effect: Z = 0.55 (P = 0.59)

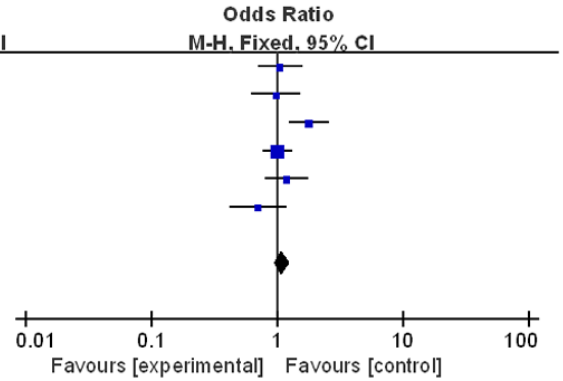


b

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	91	337	54	207	14.2%	1.05 [0.71, 1.55]
Amber L. Beitelshees2 2010	36	148	111	447	12.2%	0.97 [0.63, 1.50]
Ayelet Ziv-Gala 2012	81	208	110	417	13.0%	1.78 [1.25, 2.54]
Inga Peter 2009	165	610	176	651	36.2%	1.00 [0.78, 1.28]
Masanori Shimodaira 2008	88	218	82	225	14.0%	1.18 [0.80, 1.73]
Masanori Shimodaira 2012	47	131	54	122	10.4%	0.70 [0.43, 1.17]
Total (95% CI)		**1652**		**2069**	**100.0%**	**1.10 [0.95, 1.27]**
Total events	508		587			

Heterogeneity: Chi² = 11.16, df = 5 (P = 0.05); I² = 55%

Test for overall effect: Z = 1.28 (P = 0.20)

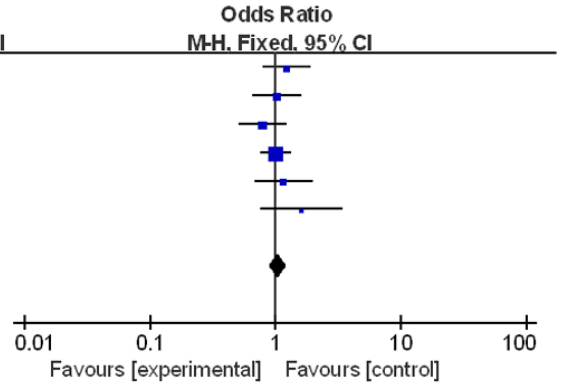


c

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	82	337	43	207	14.4%	1.23 [0.81, 1.86]
Amber L. Beitelshees2 2010	37	148	110	447	14.7%	1.02 [0.66, 1.57]
Ayelet Ziv-Gala 2012	37	208	90	417	17.6%	0.79 [0.51, 1.20]
Inga Peter 2009	141	610	150	651	39.9%	1.00 [0.77, 1.31]
Masanori Shimodaira 2008	35	218	32	225	9.4%	1.15 [0.69, 1.94]
Masanori Shimodaira 2012	21	131	13	122	4.0%	1.60 [0.76, 3.36]
Total (95% CI)		**1652**		**2069**	**100.0%**	**1.04 [0.88, 1.22]**
Total events	353		438			

Heterogeneity: Chi² = 3.79, df = 5 (P = 0.58); I² = 0%

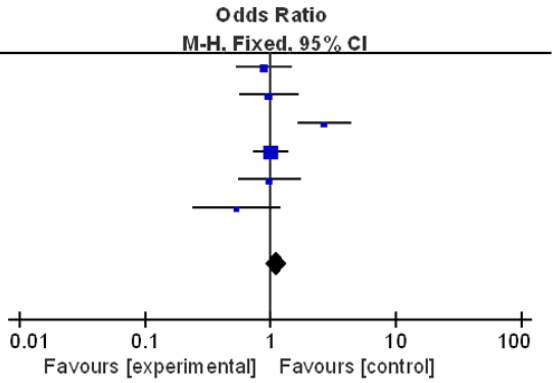
Test for overall effect: Z = 0.45 (P = 0.65)



d

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	91	173	54	97	16.3%	0.88 [0.54, 1.46]
Amber L. Beitelshees2 2010	36	73	111	221	13.9%	0.96 [0.57, 1.64]
Ayelet Ziv-Gala 2012	81	118	90	200	10.4%	2.68 [1.66, 4.32]
Inga Peter 2009	165	306	176	326	39.0%	1.00 [0.73, 1.36]
Masanori Shimodaira 2008	88	123	82	114	12.0%	0.98 [0.56, 1.73]
Masanori Shimodaira 2012	47	68	54	67	8.3%	0.54 [0.24, 1.19]
Total (95% CI)		**861**		**1025**	**100.0%**	**1.11 [0.92, 1.34]**
Total events	508		567			

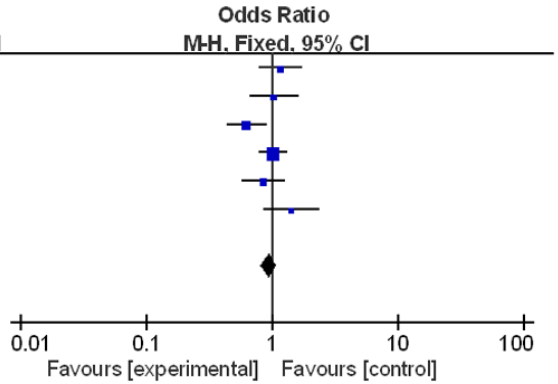
Heterogeneity: Chi² = 17.88, df = 5 (P = 0.003); I² = 72%
Test for overall effect: Z = 1.06 (P = 0.29)



e

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	246	337	145	207	13.0%	1.16 [0.79, 1.69]
Amber L. Beitelshees2 2010	112	148	336	447	10.9%	1.03 [0.67, 1.58]
Ayelet Ziv-Gala 2012	127	208	299	417	20.8%	0.62 [0.44, 0.88]
Inga Peter 2009	446	610	475	651	33.2%	1.01 [0.79, 1.29]
Masanori Shimodaira 2008	130	218	143	225	15.3%	0.85 [0.58, 1.24]
Masanori Shimodaira 2012	84	131	68	122	6.8%	1.42 [0.86, 2.35]
Total (95% CI)		**1652**		**2069**	**100.0%**	**0.95 [0.82, 1.10]**
Total events	1145		1466			

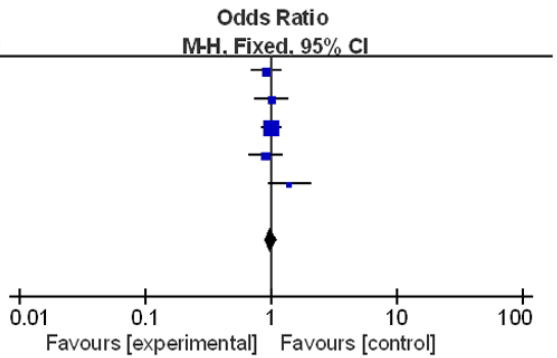
Heterogeneity: Chi² = 9.86, df = 5 (P = 0.08); I² = 49%
Test for overall effect: Z = 0.67 (P = 0.50)



B a

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	495	688	304	412	18.8%	0.91 [0.69, 1.20]
Amber L. Beitelshees2 2010	218	300	658	906	15.8%	1.00 [0.75, 1.34]
Inga Peter 2009	915	1220	976	1302	41.6%	1.00 [0.84, 1.20]
Masanori Shimodaira 2008	311	436	323	440	16.2%	0.90 [0.67, 1.21]
Masanori Shimodaira 2012	196	262	166	244	7.6%	1.40 [0.95, 2.06]
Total (95% CI)		**2906**		**3304**	**100.0%**	**1.00 [0.89, 1.12]**
Total events	2135		2427			

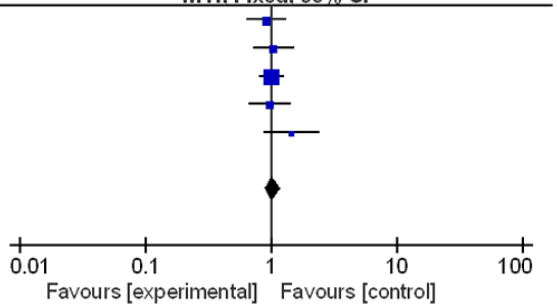
Heterogeneity: Chi² = 3.75, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)



b

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	178	337	114	207	18.6%	0.91 [0.65, 1.29]
Amber L. Beitelshees2 2010	80	150	237	453	15.3%	1.04 [0.72, 1.51]
Inga Peter 2009	343	610	366	651	43.2%	1.00 [0.80, 1.25]
Masanori Shimodaira 2008	114	218	119	225	15.6%	0.98 [0.67, 1.42]
Masanori Shimodaira 2012	72	131	56	122	7.3%	1.44 [0.88, 2.36]
Total (95% CI)		**1446**		**1658**	**100.0%**	**1.02 [0.88, 1.18]**
Total events	787		892			

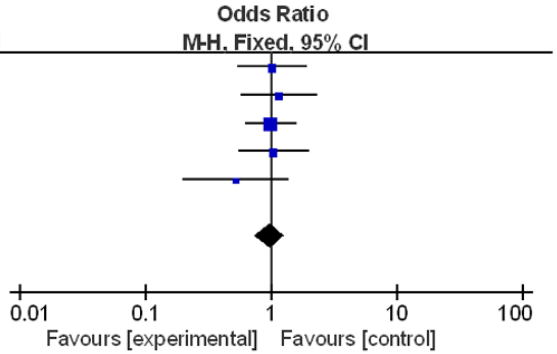
Heterogeneity: Chi² = 2.33, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)



c

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	27	688	16	412	18.9%	1.01 [0.54, 1.90]
Amber L. Beitelshees2 2010	12	150	32	453	14.4%	1.14 [0.57, 2.28]
Inga Peter 2009	38	610	41	651	36.6%	0.99 [0.63, 1.56]
Masanori Shimodaira 2008	21	218	21	225	18.4%	1.04 [0.55, 1.96]
Masanori Shimodaira 2012	7	131	12	122	11.6%	0.52 [0.20, 1.36]
Total (95% CI)		**1797**		**1863**	**100.0%**	**0.97 [0.73, 1.28]**
Total events	105		122			

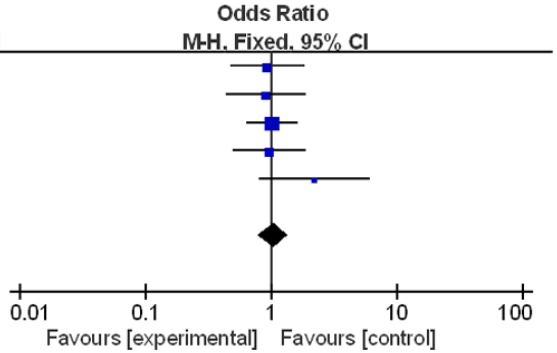
Heterogeneity: Chi² = 1.91, df = 4 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)



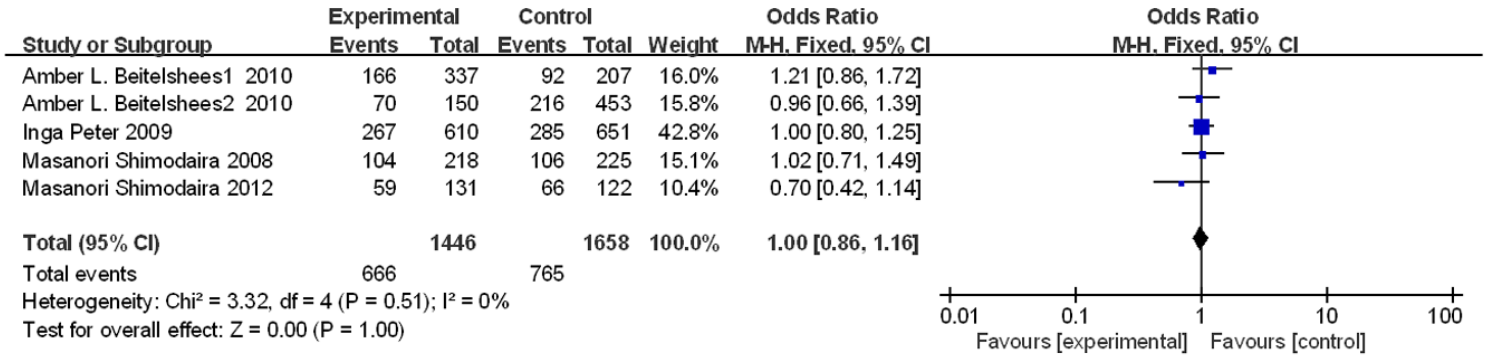
d

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amber L. Beitelshees1 2010	178	205	114	130	19.8%	0.93 [0.48, 1.79]
Amber L. Beitelshees2 2010	80	92	237	269	17.0%	0.90 [0.44, 1.83]
Inga Peter 2009	343	381	366	407	38.0%	1.01 [0.63, 1.61]
Masanori Shimodaira 2008	114	135	119	140	19.6%	0.96 [0.50, 1.85]
Masanori Shimodaira 2012	72	79	56	68	5.7%	2.20 [0.81, 5.96]
Total (95% CI)		**892**		**1014**	**100.0%**	**1.03 [0.78, 1.37]**
Total events	787		892			

Heterogeneity: Chi² = 2.54, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)



e



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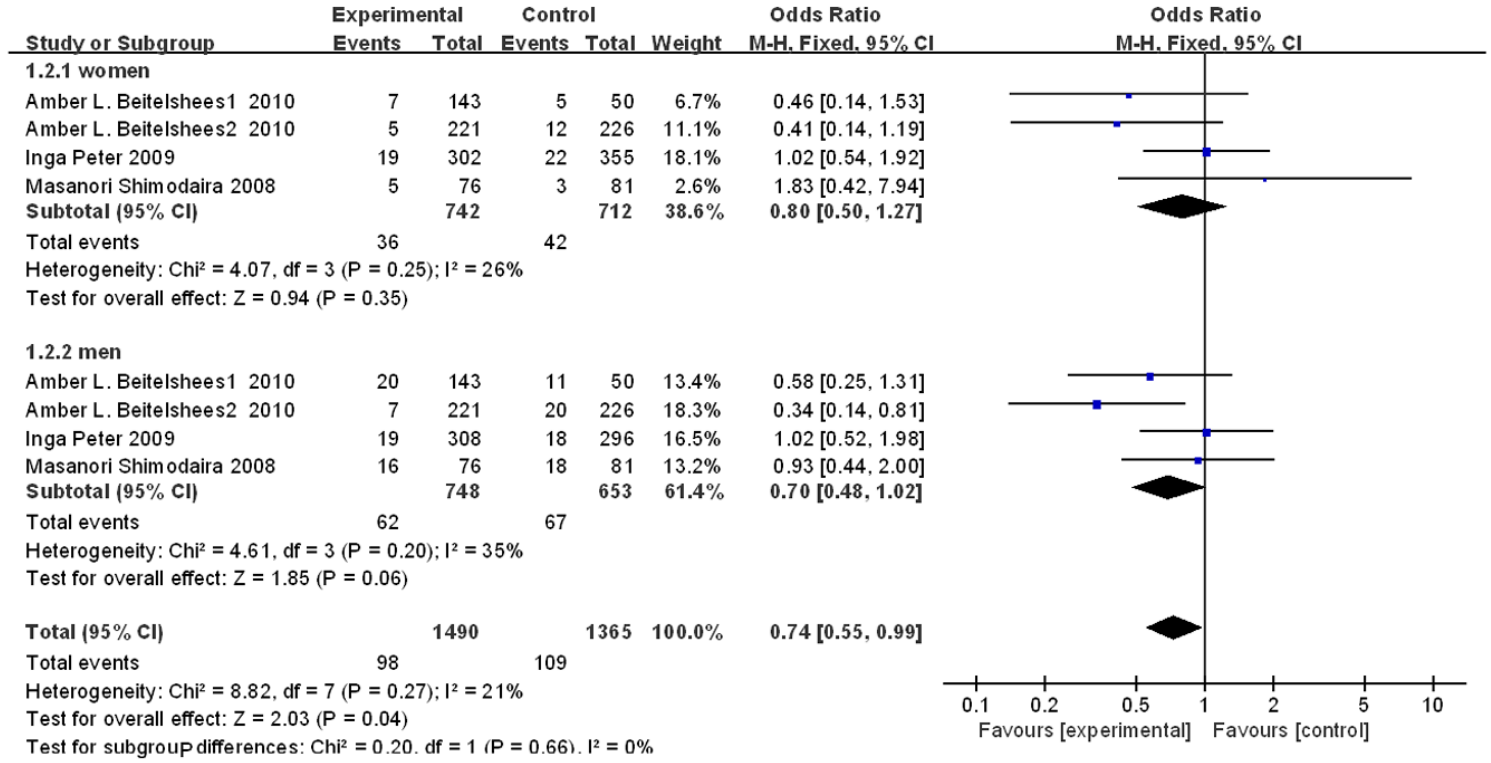
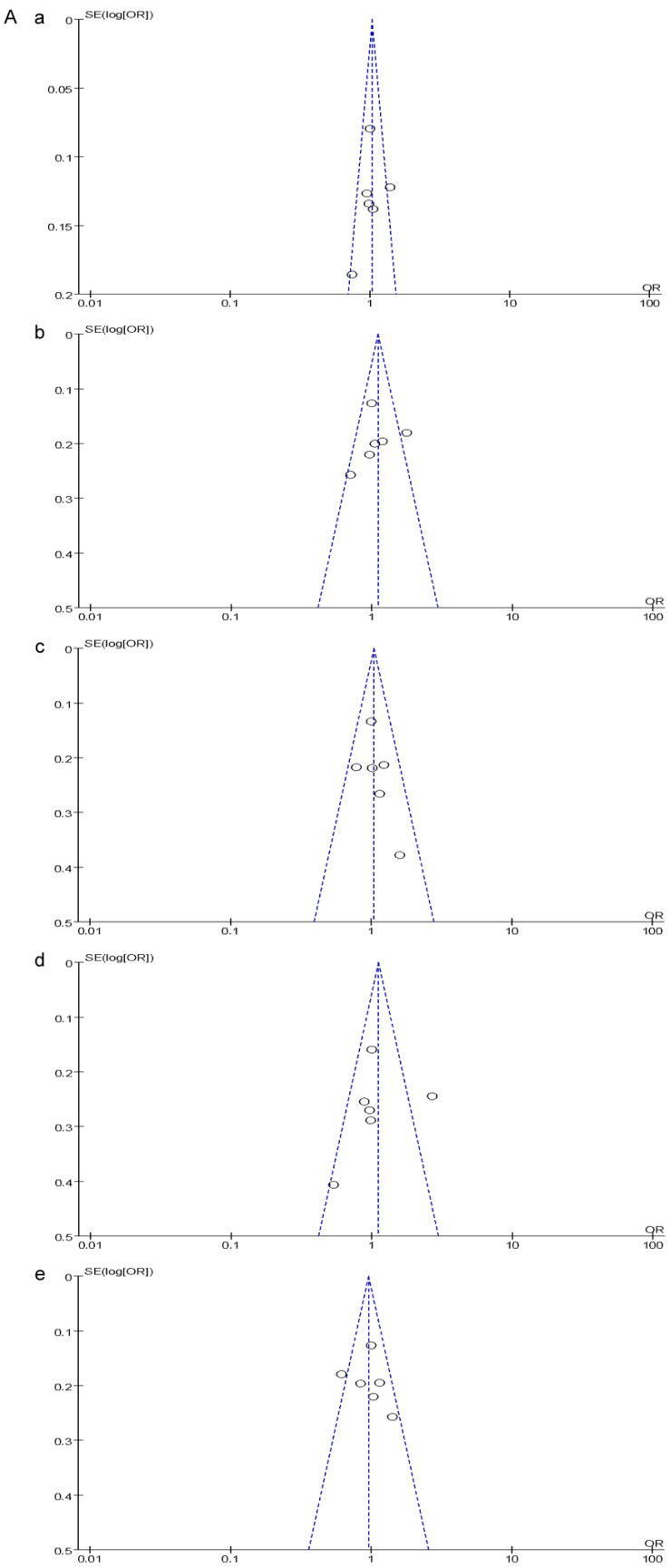


Figure 2. A. Forest plot for CYP19A1 gene rs700518 polymorphism and hypertension risk in different genetic models: a. (Allele model: A allele vs. G allele); b. (Dominant model: AA vs. AG+GG); c. (Recessive: GG vs. AG+AA); d. (Homozygous model: AA vs. GG); e. (Heterozygous model: GG vs. AG). B. Forest plot for CYP19A1 gene rs4646 polymorphism and hypertension risk in different genetic models: a. (Allele model: G allele vs. T allele); b. (Dominant model: GG vs. GT+TT); c. (Recessive model: TT vs. GT+GG); d. (Homozygous model: GG vs. TT); e. (Heterozygous model: TT vs. GT). C. Forest plot for CYP19A1 gene rs4646 polymorphism Recessive model (TT vs. GT+GG) and hypertension risk in subgroup include man and women.

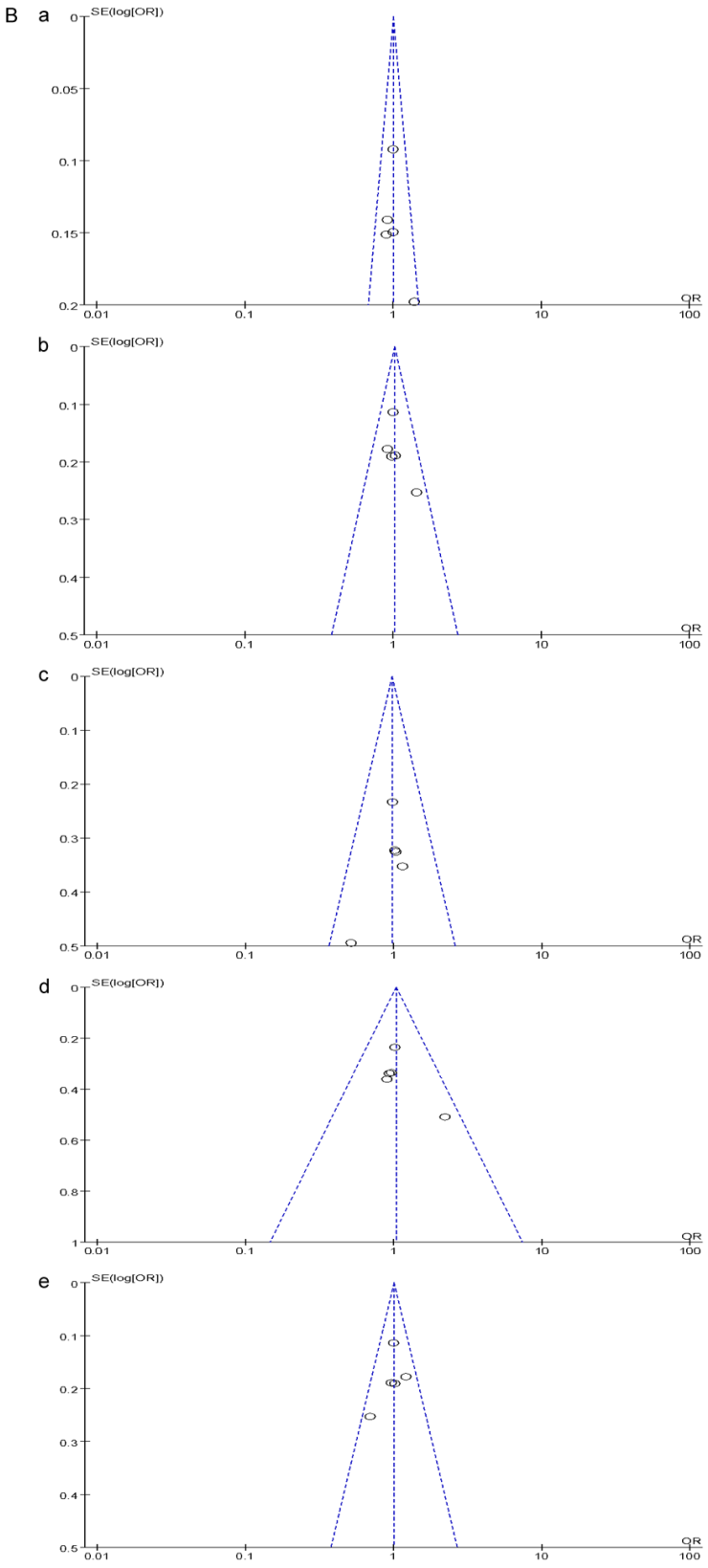


0.20), and a recessive model (GG *vs.* AG+AA, OR = 1.04, 95% CI: 0.88-1.22, *P* = 0.65). We also found no associations between the rs4646 polymorphism and the risk of hypertension under an allele model (G *vs.* T, OR = 1.00, 95% CI: 0.89-1.12, *P* = 0.98), a dominant model (GG *vs.* GT+TT, OR = 1.02, 95% CI: 0.88-1.18, *P* = 0.80), and a recessive model (TT *vs.* GT+GG, OR = 0.97, 95% CI: 0.73-1.28, *P* = 0.83). However, if the data were stratified by gender, we found that the rs4646 polymorphism might be correlated with the risk of hypertension under the recessive model (TT *vs.* GT+GG: *P* = 0.04; I^2 = 0%) using a fixed-effect model, as shown in **Figure 2C**.

Sensitivity and publication bias analyses

In this meta-analysis, in order to assess the sensitivity, the contribution of each study to the pooled estimate was determined. We recalculated the pooled *P* value or OR estimates for the remaining studies. As a result, all of the included studies did not substantially change the pooled point estimates when the random-effects model was converted to the fixed effects model, indicating the reliability of our results.

We used RevMan 5.3 software to analyze the studies for publication bias, and the funnel plots (**Figure 3**) showed that most of the data points were within the 95% confidence interval, and the shapes of funnel plots showed no obvious asymmetry, which indicated that there was no publication bias and that the results of the studies were credible.



Discussion

We conducted a meta-analysis of eligible published studies by collecting summary statistics regarding the association between SNPs (rs700518 and rs4646) in the CYP19A1 gene and the risk of hypertension, using different genetic models. We found that the rs4646 polymorphism might be correlated with the risk of hypertension under a recessive model by conducting a subgroup analysis based on gender.

For many years, researchers and clinicians have observed gender-related differences in the patterns of hypertension. A previous study consisting of women aged 44-56 years indicates that the risk of hypertension increases markedly in women [24]. The results of previous reports noting that BP and hypertension were significantly associated with menopausal status are consistent with those of the above study [25-33]. Estrogen plays key roles in women after menopause and in hypertension. Recent experimental and epidemiological findings support the hypothesis that estrogen deficiency may induce endothelial and vascular dysfunction and potentiate age-related increases in systolic blood pressure possibly as a consequence of reduced large-artery compliance. In menopause, estrogen deficiency may affect the balance among various vasoactive hormones and the proliferation and function of vascular smooth muscle cells possibly by altering the electrolyte composition of the

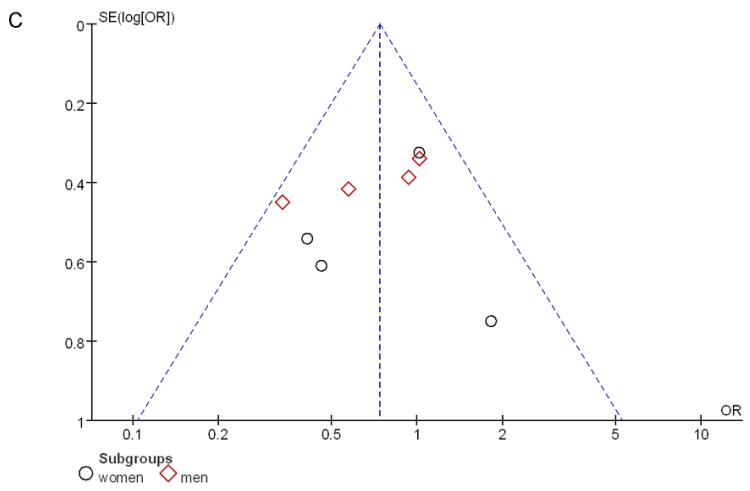


Figure 3. A. Funnel plots for CYP19A1 gene rs700518 polymorphism and hypertension risk in different genetic models: a. (Allele model: A allele vs. G allele); b. (Dominant model: AA vs. AG+GG); c. (Recessive: GG vs. AG+AA); d. (Homozygous model: AA vs. GG); e. (Heterozygous model: GG vs. AG). B. Funnel plots for CYP19A1 gene RS4646 polymorphism and hypertension risk in different genetic models: a. (Allele model: G allele vs. T allele); b. (Dominant model: GG vs. GT+TT); c. (Recessive: TT vs. GT+GG); d. (Homozygous model: GG vs. TT); e. (Heterozygous model: TT vs. GT). C. Funnel plots for CYP19A1 gene rs4646 polymorphism Dominant model and hypertension risk in subgroup include man and women.

intra- or extracellular milieu [34]. The human CYP19A1 gene is located on chromosome 15q21.2, encoding a length of ~130 kb and being composed of nine (II-X) coding exons [35]. In postmenopausal women, a critical step in estrogen biosynthesis involves the formation of C18 estrogens estrone and estradiol) from C19 androgens (rostenedione and testosterone). CYP19A1 is the key to this transformation [36, 37] and thus directly affects estrogen levels. Therefore, it is not surprising that CYP19A1 polymorphisms appear to be associated with hypertension.

The rs700518 and rs4646 polymorphisms are the result of synonymous and 3'UTR mutations in exon 3, respectively. Most previous studies focused only on the relationship between the rs700518 and rs4646 polymorphisms in the CYP19A1 gene and breast cancer [38-41]. Several recent studies have further analyzed these polymorphisms and found that they are associated with the risk of hypertension. In the Framingham Heart Study, Peter et al. found evidence suggesting that the rs4646 polymorphism was associated with higher diastolic blood pressure in women and lower pulse pressure in men [16]. A new study by Neslihan Coban *et al*. demonstrated that the rs10046 polymorphism is associated with cardiovascular risk factors [42]. By contrast, several studies have demonstrated no association between CYP19A1 genetic polymorphisms and the risk of hypertension [16, 19, 20]. At present, whether the CYP19A1 gene is associated with hypertension is controversial.

In our study, we found that the rs700518 and rs4646 polymorphisms in the CYP19A1 gene were weakly associated with hypertension based on the pooled results of 6 studies from 5 published articles. Our study had several strengths. First, it was the first meta-analysis to report the relationship between genetic polymorphisms of the CYP19A1 gene and the risk of hypertension. Second, various methods of analysis (e.g. subgroup analysis, cumulative meta-analysis, and sensitivity analysis) were performed appropriately to investigate the abovementioned relationship. Finally, we investigated the relationship among estrogen, the CYP19A1 gene and hypertension. We performed a subgroup analysis based on gender and determined that female gender may be a key factor in the relationship between the CYP19A1 gene and hypertension.

However, this meta-analysis had some limitations. First, the number of studies included in the meta-analysis was small. Second, the included studies were relatively heterogeneous with respect to ethnicity and age. Third, no prospective studies have addressed the association between CYP19A1 polymorphisms and the risk of hypertension; thus, no such studies were included in this analysis. Finally, due to the limitations of the case-control study design, we cannot exclude the possibility of undetected bias.

In conclusion, the results of the current meta-analysis suggest that the rs4646 polymorphism in the CYP19A1 gene is weakly associated with the risk of hypertension. Gender-

related differences in this association may be mediated by serum estrogen concentrations. Elucidation of the relationship among estrogen, the CYP19A1 gene and hypertension is a task for future prospective studies and large-scale studies, which must also account for the effects of gender, ethnicity and age to obtain more robust results regarding the relationship between CYP19A1 gene polymorphisms and the risk of hypertension.

Acknowledgements

This work was supported financial by National Natural Science Foundation of China (8156-0069) and Key Laboratory project of Xinjiang, China (2015KL011).

Disclosure of conflict of interest

None.

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