Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Estrogen receptor α gene *Pvu*II polymorphism and coronary artery disease: a meta-analysis of 21 studies*

Jie DING[1], Hui XU[2], Xiang YIN[1], Fu-rong ZHANG[1], Xiao-ping PAN[3], Yi-an GU[4], Jun-zhu CHEN[1], Xiao-gang GUO[†‡1]

([1]*Department of Cardiology, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*)

([2]*Xiuzhou District, Gaozhao Street Community Health Service Center, Jiaxing 314031, China*)

([3]*State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*)

([4]*Columbia University Medical Center, New York, NY 10032, USA*)

[†]E-mail: gxg22222@zju.edu.cn

Received Aug. 20, 2013; Revision accepted Nov. 17, 2013; Crosschecked Feb. 19, 2014

Abstract: The association between the estrogen receptor α gene (*ESR1*) *Pvu*II polymorphism (c.454-397T>C) and coronary artery disease (CAD) is controversial. Thus, we conducted a meta-analysis to evaluate the relationship. Data were collected from 21 studies encompassing 9926 CAD patients and 16710 controls. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the relationship between *Pvu*II polymorphism and CAD. The polymorphism in control populations in all studies followed Hardy-Weinberg equilibrium. We found a significant association between *ESR1 Pvu*II polymorphism and CAD risk in all subjects. When the data were stratified by region, a significant association between *ESR1 Pvu*II polymorphism and CAD risk was observed in Asian populations but not in Western populations. The current study suggests that *ESR1 Pvu*II polymorphism has an important role in CAD susceptibility.

Key words: Estrogen receptor α gene, Polymorphism, Meta-analysis, Coronary artery disease (CAD)
doi:10.1631/jzus.B1300220 **Document code:** A **CLC number:** R541.4

1 Introduction

Coronary artery disease (CAD) is the most common chronic disease in humans and has extremely complex etiology. Epidemiological studies demonstrated that the incidences of CAD and sequelae such as myocardial infarction (MI) are lower in pre-menopausal women than in age-matched men (Tunstall-Pedoe *et al.*, 1999). However, cardiovascular morbidity and mortality increase sharply after the onset of menopause, suggesting that endogenous estrogen protects women against CAD (Gurevitz *et al.*, 2000). Clinical trials of postmenopausal estrogen therapy in CAD have yielded mixed results. Results from a study of nurses suggested that women who used postmenopausal hormones had a lower mortality than non-users (Grodstein *et al.*, 1997). In particular, there was a reduction in death due to coronary heart disease (Grodstein *et al.*, 1997). However, the results from a randomized controlled primary prevention trial, the Women's Health Initiative Trial, showed that the regimen of estrogen plus progestin brought more health risks than benefits, and indicated that hormone therapy did not decrease the risk of cardiovascular events in women with CAD (Rossouw *et al.*, 2002). These findings underscore the complexity of the cardiovascular effects of estrogen and support the

‡ Corresponding author

* Project supported by the Zhejiang Provincial Natural Science Foundation of China (No. LY12H02006) and the Health Bureau of Zhejiang Province (No. 2011RCB016), China

need for a better understanding of its role in cardiovascular biology and of population-level genetic variation in the sex steroid hormone system. It has been suggested that the cardiovascular functions of estrogen depend on estrogen receptors α (ERα) and β (ERβ) encoded by separate genes, *ESR1* and *ESR2*, respectively (Mendelsohn and Karas, 2005). ERα plays a more important role than ERβ in cardioprotection, and is involved in vasodilation (Figtree *et al.*, 2003), attenuation of cardiac cell apoptosis (Wang *et al.*, 2010; Liu *et al.*, 2011), and stimulation of neovascularization (Hamada *et al.*, 2006; Jesmin *et al.*, 2010).

ESR1, located on chromosome 6, locus 6q24-q27, comprises eight exons and seven introns. There are two common site polymorphisms in the first intron, located at the recognition sites of the restriction enzymes known as *Pvu*II and *Xba*I, respectively (Mansur *et al.*, 2005; Rokach *et al.*, 2005). The *Pvu*II polymorphism, also known as c.454-397T>C or rs2234693, results from a T/C transition (Yaich *et al.*, 1992). *ESR1 Pvu*II polymorphism might affect *ESR1* gene expression by altering the binding of transcription factors (Herrington *et al.*, 2002) and influencing the splicing of the *ESR1* gene. Previous studies have suggested that the *Pvu*II polymorphism is related to many diseases, such as breast cancer (St-Hilaire *et al.*, 2011), hypertension (Peter *et al.*, 2005), blood lipid changes (Klos *et al.*, 2008), and coronary atherosclerosis (Figtree *et al.*, 2009).

The relationship between the *ESR1* gene *Pvu*II polymorphism and cardiovascular disease is still controversial. Shen *et al.* (2012) showed that it conferred an increased risk of CAD in Chinese men. Almeida and Hutz (2006) also suggested that the *ESR1 Pvu*II polymorphism was associated with CAD severity independent of gender. However, Matsubara *et al.* (1997) found no significant association between the *ESR1* c.454-397T>C polymorphism and CAD in a Japanese population. Similarly, a large study with 3657 patients and 1211 controls, from a predominantly European population, showed that the genotype distribution of the *ESR1 Pvu*II polymorphism was not significantly different between the case and control groups (Koch *et al.*, 2005). Overall, the current evidence on the link between *ESR1 Pvu*II polymorphism and CAD risk is inconsistent. In addition, individual studies have been limited by small sample sizes and often involved populations of a single ethnicity. Therefore, we performed a meta-analysis of 21 studies, aiming to summarize and clarify the relationship between *ESR1 Pvu*II polymorphism and CAD risk.

2 Materials and methods

2.1 Search methods and selection criteria

The present meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria. Relevant studies published or presented up to 30th May 2013 were searched in several sources including MEDLINE, Cochrane database, Embase, PubMed, SinoMed (China Biological Medicine Database), and CNKI (China National Knowledge Infrastructure). We used various combinations of the following keywords and MeSH (Medical Subject Headings) terms: "estrogen receptor", "estrogen", "receptor", "polymorphism", "gene", "coronary artery disease", "CAD", and "cardiovascular". To search as completely as possible, we also retrieved potential studies via "related articles" in the identified articles. The relevant studies included in this meta-analysis had to meet all the following inclusion criteria: (1) They used a case-control design or cohort or cross-sectional study design; (2) They were studies of human subjects without country and language restrictions; (3) If studies were performed by the same researchers, the one with the largest sample size was selected; (4) The studies provided sufficient data of genotype and allele frequencies for analysis; (5) The genotype distribution of the control group had to correspond with Hardy-Weinberg equilibrium (HWE).

CAD was defined as angiographic evidence of ≥50% stenosis in at least one coronary artery or major branch segment together with clinical symptoms of angina, and/or acute coronary syndrome (ACS), including unstable angina pectoris, fatal or non-fatal MI confirmed by objective clinical evidence, such as the presence of typical electrocardiographic changes and elevation in the levels of cardiac biomarkers of necrosis (Wright *et al.*, 2011; Jneid, 2012). The selection process is shown in Fig. 1.

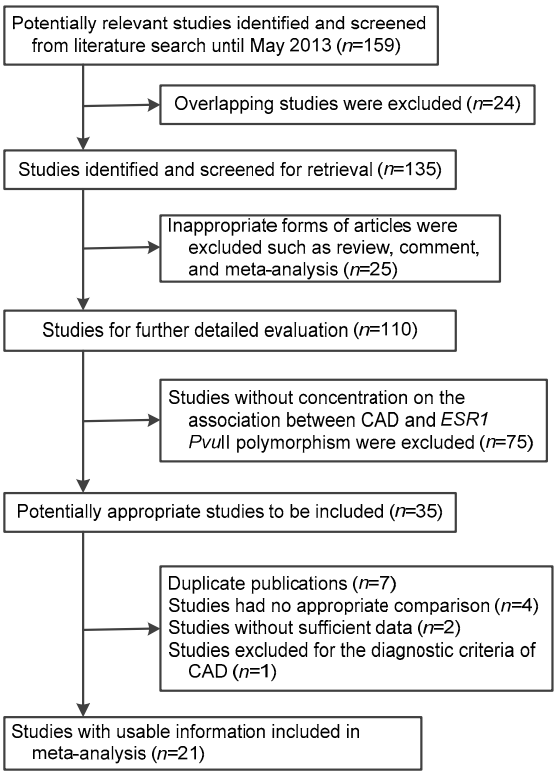

Fig. 1 Flow chart of the selection process used for the meta-analysis of the relationship between *ESR1 Pvu*II polymorphism and CAD risk

2.2 Data extraction

To extract sufficient and useful data from the articles included in this meta-analysis, we reviewed the full text of eligible studies. Characteristics of the studies were gathered including the name of the first author, year of publication, country, type of study design, sample size, mean age, source of the control population, method of genotyping, criteria for matching between case and control, quality score of each study, and HWE of control groups (Table 1). The distribution of genotype and allele frequencies in each study, the sample sizes of cases and controls, and the *P*-values of the HWE of control groups are summarized in Table 2. Data were carefully extracted independently by two reviewers (X.G. GUO and J. DING) according to the eligibility criteria listed above. When the two investigators made different recommendations about a particular study, either they reached a consensus by discussion, or another reviewer intervened to make a decision.

2.3 Quality assessment

Two reviewers (J. DING and X. YIN) independently assessed the quality of the included studies, according to a set of criteria (Table 3) modified on the basis of previous studies (Thakkinstian *et al.*, 2005; Camargo *et al.*, 2006). Scores ranged from 0 to 13, with 0 as the lowest and 13 as the highest quality.

2.4 Statistical analysis

To investigate the association of *Pvu*II polymorphism and CAD, we performed the meta-analysis using a series of models, including allele genetic model (C vs. T), homozygote comparison (CC vs. TT), dominant genetic model (CC/CT vs. TT), and recessive genetic model (CC vs. CT/TT) separately. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to measure the strength of the relationship between *Pvu*II polymorphism and CAD. We conducted chi-square-based *Q*-tests to assess the heterogeneity among different studies (Higgins and Thompson, 2002). The index I^2 was used to quantify the effect of heterogeneity. The value of I^2 indicates the percentage of variation caused by heterogeneity rather than by chance among the studies (Higgins *et al.*, 2003). If the *P*-value of a *Q*-test was not larger than 0.1, we used a random-effect model to test the existence of significant heterogeneity. Otherwise, we chose a fixed-effect model (Cochran, 1968). We also performed sensitivity analyses and meta-regression analysis to evaluate the heterogeneity more clearly. A *P*-value of less than 0.1 was considered to be significant.

The HWE of control groups was examined using chi-square tests. The genotype distributions and allele frequencies of control populations were considered to be consistent with HWE if the *P*-value was less than 0.05. Funnel plot, Egger's linear regression (Egger *et al.*, 1997), and Begg's test (Begg and Mazumdar, 1994) were used to estimate potential publication bias. *P*-values of less than 0.05 from Egger's test and Begg's test indicated that publication bias existed.

Statistical analysis was performed using Review Manager (RevMan) 5.2 (http://ims.cochrane.org/revman/download) and STATA11.0 (STATA Corp., College Station, Texas, USA).

Table 1 Main characteristics of relevant studies selected for meta-analysis

Study	Country	Type of study	Sample size (% women)		Mean age (year)		Control source	Genotyping method	Matching criteria	Quality score	HWE
			Case	Control	Case	Control					
Matsubara *et al.* (1997)	Japan	Case-control	87 (25.3)	94 (20.2)	M: 58.2±9.4 F: 64.7±6.2	M: 49.0±5.5 F: 61.8±8.3	PB	PCR-RFLP	BMI	9.0	Y
Guo *et al.* (2002)	China	Case-control	72 (19.4)	53 (22.6)	65.1±5.6	64.3±4.2	HB, PB	PCR-RFLP	Age/sex	9.5	Y
Huang *et al.* (2002)	China	Case-control	135 (40.0)	118 (57.6)			PB	PCR-RFLP	Age/BMI	8.0	Y
Lu *et al.* (2002)	Japan	Case-control	119 (20.0)	176 (42.0)	M: 50.3±11.7 F: 61.4±7.1	M: 52.3±12.8 F: 63.3±7.4	HB	PCR-RFLP	Age	11.0	Y
Zheng (2002)	China	Case-control	51 (100.0)	54 (100.0)	64.2±9.8	62.1±7.8	HB	PCR	Age/sex	7.0	Y
Shearman *et al.* (2003)	USA	Cohort study	178 (31.5)	1561 (51.8)			PB	PCR-RFLP	Age/BMI	11.0	Y
Schuit *et al.* (2004)	Netherlands	Cohort study	440 (38.2)	5968 (60.7)			PB	TaqMan	Unknown	12.0	Y
Koch *et al.* (2005)	Germany	Case-control	3657 (24.2)	1211 (49.4)	64.0±12.0	60.3±11.9	PB	TaqMan	Unknown	12.0	Y
Mansur *et al.* (2005)	Brazil	Case-control	153 (40.0)	142 (51.0)	43.4±7.5	44.2±11.8	PB	PCR-RFLP	Age/sex	8.0	Y
Almeida and Hutz (2006)	Brazil	Case-control	210 (28.6)	143 (55.9)	M: 61.0±10.4 F: 64.0±10.5	M: 59.0±11.2 F: 58.0±8.8	PB	PCR	BMI	10.0	Y
Cheng *et al.* (2006)	China	Case-control	200 (47.5)	190 (48.4)	56.5±0.4	52.4±0.6	PB	PCR-RFLP	Age/sex	8.0	Y
Li *et al.* (2006)	China	Case-control	165 (100.0)	80 (100.0)	61.7±8.2	59.9±7.7	HB	PCR-RFLP	Age/BMI/sex	9.0	Y
Alevizaki *et al.* (2007)	Greece	Case-control	87 (100.0)	70 (100.0)	65.0±0.95	65.0±0.95	HB	PCR	Unknown	11.0	Y
Kjaergaard *et al.* (2007)	Denmark	Case-control	2495 (27.8)	4447 (60.0)			PB	TaqMan	Unknown	12.0	Y
Yilmaz *et al.* (2007)	Turkey	Case-control	168 (35.7)	99 (62.6)	57.02±8.62	55.9±9.97	HB	PCR-RFLP	Age	11.0	Y
Tang *et al.* (2008)	China	Case-control	161 (0.0)	158 (0.0)	61.4±8.1	60.9±6.4	PB	PCR-RFLP	Age/sex	9.0	Y
Xu *et al.* (2008)	China	Case-control	210 (44.8)	174 (51.1)	56.0±7.3	55.0±8.6	PB	PCR	Age/sex	11.0	Y
Boroumand *et al.* (2009)*	Iran	Case-control	210 (31.4)	240 (61.7)	58.79±10.44	55.1±10.2	HB	PCR-RFLP	Unknown	11.0	Y
Karadağ *et al.* (2009)	Turkey	Cross-sectional	140 (32.1)	47 (44.7)	60.7±12.3	56.2±15.1	HB	PCR-RFLP	Sex	10.0	Y
Lluís-Ganella *et al.* (2009)	Spain	Case-control	423 (25.0)	1269 (25.0)	61.21±11.16	60.72±10.65	PB	TaqMan	Age/sex	12.0	Y
Jin *et al.* (2010)	China	Case-control	236 (28.4)	117 (35.9)	64.0±11.0	62.0±11.0	HB, PB	PCR-RFLP	Age/sex	9.5	Y
Shen *et al.* (2012)	China	Case-control	539 (46.4)	539 (46.9)	57.3±7.2	56.4±9.1	PB	PCR-RFLP	Age/sex	12.0	Y

M: male; F: female; PB: population-based; HB: hospital-based; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; BMI: body mass index; HWE: Hardy-Weinberg equilibrium; Y: genotype distribution and allele frequency of control group followed HWE. * This study was excluded because of its criterion for diagnosis of CAD (Gensini score>6)

Table 2 Summarization of the distribution of genotype and allele frequencies, the sample sizes of cases and controls, and the *P*-values of the HWE of control groups

Included study	Group	Sample size	Genotype			Allele (%)		*P* of HWE
			TT	TC	CC	T	C	
Matsubara *et al.* (1997)	Case	87	27	47	13	58.0	42.0	
	Control	94	34	46	14	60.6	39.4	0.81
Guo *et al.* (2002)	Case	72	10	42	20	43.1	56.9	
	Control	53	23	23	7	65.1	34.9	0.74
Huang *et al.* (2002)	Case	135	80	41	14	74.4	25.6	
	Control	118	51	54	13	66.1	33.9	0.82
Lu *et al.* (2002)	Case	119	35	50	34	50.4	49.6	
	Control	176	67	74	35	59.1	40.9	0.08
Zheng (2002)	Case	51	9	35	7	52.0	48.0	
	Control	54	18	30	6	61.1	38.9	0.21
Shearman *et al.* (2003)	Case	178	50	86	42	52.2	47.8	
	Control	1561	475	776	310	55.3	44.7	0.83
Schuit *et al.* (2004)	Case	440	87	216	137	44.3	55.7	
	Control	5968	1305	2958	1705	46.6	53.4	0.74
Koch *et al.* (2005)	Case	3657	1074	1781	802	53.7	46.3	
	Control	1211	360	595	256	54.3	45.7	0.73
Mansur *et al.* (2005)	Case	153	17	85	51	38.9	61.1	
	Control	142	26	69	47	42.6	57.4	0.94
Almeida and Hutz (2006)	Case	210	72	96	42	57.1	42.9	
	Control	143	54	72	17	62.9	37.1	0.34
Cheng *et al.* (2006)	Case	200	65	92	43	55.5	44.5	
	Control	190	67	85	38	57.6	42.4	0.25
Li *et al.* (2006)	Case	165	33	88	44	46.7	53.3	
	Control	80	21	36	23	48.8	51.3	0.37
Alevizaki *et al.* (2007)	Case	87	25	45	17	54.6	45.4	
	Control	70	32	31	7	67.9	32.1	0.90
Kjaergaard *et al.* (2007)	Case	2495	740	1268	487	55.1	44.9	
	Control	4447	1296	2237	914	54.3	45.7	0.37
Yilmaz *et al.* (2007)	Case	168	8	117	43	39.6	60.4	
	Control	99	22	53	24	49.0	51.0	0.48
Tang *et al.* (2008)	Case	161	48	76	37	53.4	46.6	
	Control	158	46	79	33	54.1	45.9	0.93
Xu *et al.* (2008)	Case	210	92	88	30	64.8	35.2	
	Control	174	82	78	14	69.5	30.5	0.44
Karadağ *et al.* (2009)	Case	140	40	68	32	52.9	47.1	
	Control	47	8	29	10	47.9	52.1	0.11
Lluís-Ganella *et al.* (2009)	Case	423	117	231	75	55.0	45.0	
	Control	1269	383	636	250	55.2	44.8	0.63
Jin *et al*. (2010)	Case	236	84	105	47	57.8	42.2	
	Control	117	49	57	11	66.2	33.8	0.33
Shen *et al.* (2012)	Case	539	245	226	68	66.4	33.6	
	Control	539	274	217	48	71.0	29.0	0.59

Table 3 Scale for quality assessment

Criteria	Score
Representativeness of cases	
Consecutively/randomly selected from case population with clearly defined sampling frame	2
Consecutively/randomly selected from case population without clearly defined sampling frame or with extensive inclusion/exclusion criteria	1
No method of selection described	0
Representativeness of controls	
Population-based or community-based	2
Both population-based and hospital-based/ healthy volunteers/blood donors	1.5
Hospital-based controls without CAD	1
Not described	0
Ascertainment of CAD	
Clearly described objective criteria for diagnosis of CAD, histological confirmation	2
Diagnosis of CAD by patient self-report or by patient history	1
Not described	0
Ascertainment of controls	
Controls were tested to screen out CAD	2
Controls were subjects who did not report CAD: no objective testing	1
Not described	0
Genotyping examination	
Genotyping done under "blinded" condition	1
Unblinded or not mentioned	0
Hardy-Weinberg equilibrium	
Hardy-Weinberg equilibrium in control group	2
Hardy-Weinberg disequilibrium in control group	1
No checking for Hardy-Weinberg equilibrium	0
Association assessment	
Assess association between genotypes and CAD with appropriated statistics and adjustment for confounders	2
Assess association between genotypes and CAD with appropriated statistics without adjustment for confounders	1
Inappropriate statistics used	0

3 Results

3.1 Characteristics of studies

After searching the electronic databases as described above, we identified a total of 159 potentially relevant studies. According to the inclusion criteria defined previously, 21 eligible studies with sufficient data were finally included in this meta-analysis (Fig. 1). The study by Boroumand *et al.* (2009) was excluded because CAD was diagnosed by the Gensini score. The characteristics of the relevant studies are described in Table 1. In all studies, blood samples were used to determine genotypes. The genotype distributions and allele frequencies of these studies are summarized in Table 2. Based on the *P*-values of the HWE of control groups, no study was found to be in disequilibrium.

Eleven of the 21 selected studies consisted of 1975 CAD patients and 1753 controls from the Asian region (Matsubara *et al.*, 1997; Guo *et al.*, 2002; Huang *et al.*, 2002; Lu *et al.*, 2002; Zheng, 2002; Cheng *et al.*, 2006; Li *et al.*, 2006; Tang *et al.*, 2008; Xu *et al.*, 2008; Jin *et al.*, 2010; Shen *et al.*, 2012). The remaining 10 studies with 7951 patients and 14957 controls were from Western countries (Shearman *et al.*, 2003; Schuit *et al.*, 2004; Koch *et al.*, 2005; Mansur *et al.*, 2005; Almeida and Hutz, 2006; Alevizaki *et al.*, 2007; Kjaergaard *et al.*, 2007; Yilmaz *et al.*, 2007; Karadağ *et al.*, 2009; Lluís-Ganella *et al.*, 2009). Both population-based (PB) and hospital-based (HB) studies were included in the analysis. Thirteen studies were PB (Matsubara *et al.*, 1997; Huang *et al.*, 2002; Shearman *et al.*, 2003; Schuit *et al.*, 2004; Koch *et al.*, 2005; Mansur *et al.*, 2005; Cheng *et al.*, 2006; Almeida and Hutz, 2006; Kjaergaard *et al.*, 2007; Tang *et al.*, 2008; Xu *et al.*, 2008; Lluís-Ganella *et al.*, 2009; Shen *et al.*, 2012), six were HB (Lu *et al.*, 2002; Zheng, 2002; Li *et al.*, 2006; Alevizaki *et al.*, 2007; Yilmaz *et al.*, 2007; Karadağ *et al.*, 2009), and the others had both PB and HB controls (Guo *et al.*, 2002; Jin *et al.*, 2010).

3.2 Main results of the meta-analysis

We used four inheritance models of *ESR1 Pvu*II separately to investigate the potential association between *ESR1 Pvu*II polymorphism and CAD risk. When all the eligible studies were pooled into the analysis, the association between *Pvu*II polymorphism and CAD was significant under the allele genetic model (C vs. T: OR=1.14, 95% CI=1.05–1.23, P=0.002, I^2=56%, $P_{\text{Heterogeneity}}$=0.0009) (Fig. 2a), homozygote comparison (CC vs. TT: OR=1.36, 95% CI=1.14–1.62, P=0.0005, I^2=60%, $P_{\text{Heterogeneity}}$=0.0003) (Fig. 2b), dominant genetic model (CC+CT vs. TT: OR=1.20, 95% CI=1.05–1.38, P=0.007, I^2=64%, $P_{\text{Heterogeneity}}$<0.0001) (Fig. 2c), and recessive genetic model (CC vs. CT+TT: OR=1.15, 95% CI=1.03–1.28, P=0.02, I^2=31%, $P_{\text{Heterogeneity}}$=0.08) (Fig. 2d).

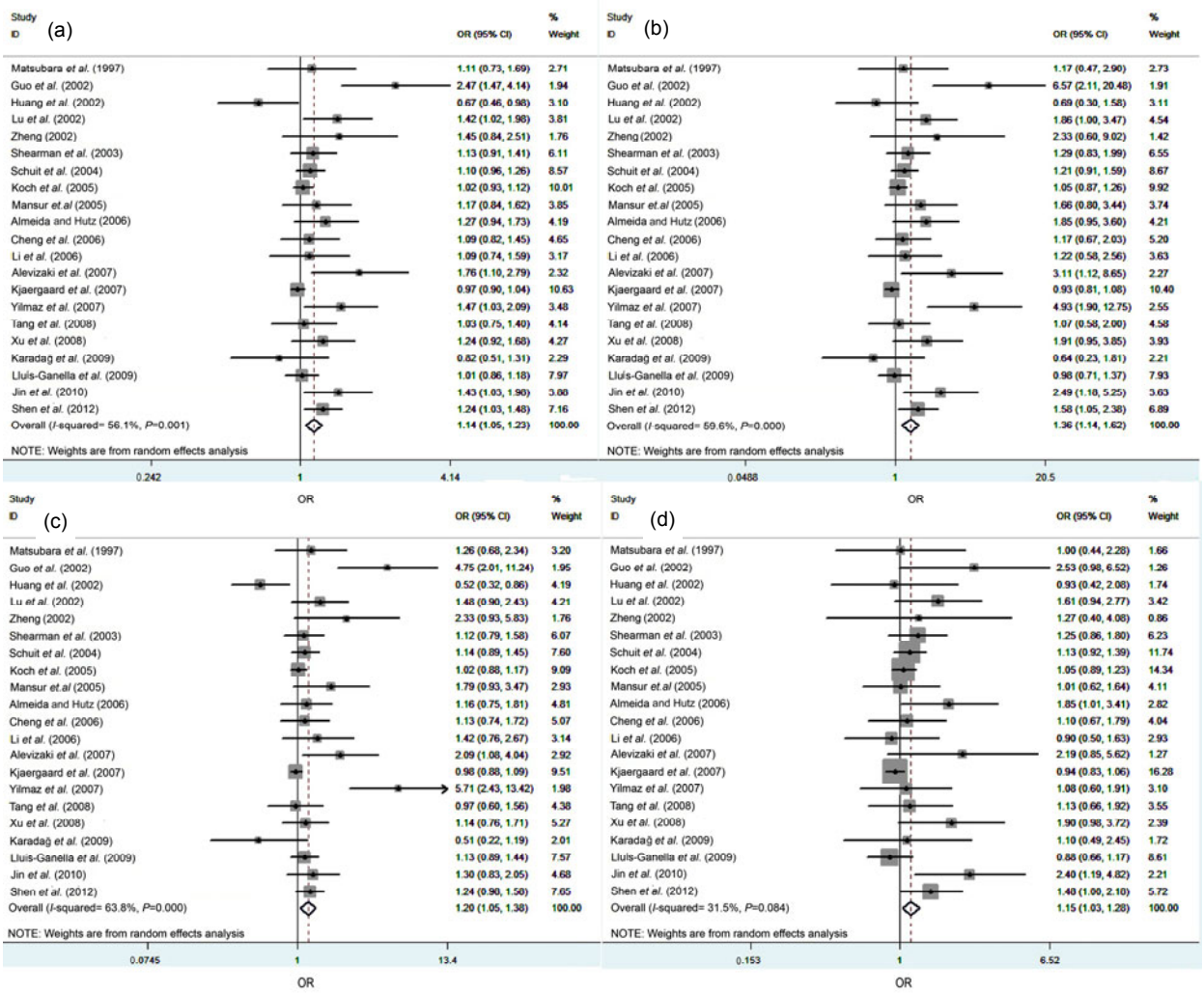

Fig. 2 Forest plots of the association of *ESR1 Pvu*II polymorphism and CAD risk in total population
(a) Allele genetic model (C vs. T); (b) Homozygote comparison (CC vs. TT); (c) Dominant genetic model (CC+CT vs. TT); (d) Recessive genetic model (CC vs. CT+TT)

3.3 Heterogeneity test and sensitivity analysis

Q-test and I^2 index were used to evaluate the heterogeneity in each genetic model. The heterogeneity among different studies was significant in most models (P<0.1). To explore the potential sources of heterogeneity among studies, we performed a meta-regression. According to the characteristics of studies included in our meta-analysis, we considered the following as potential confounding factors: publication year, region of study population, source of population of control group, total sample size of study population, and ratio of CAD group sample size to control group sample size (RR). Among these factors, the source of the control group (P=0.03) might have contributed to the heterogeneity. The low heterogeneity seen in subgroup analysis by source of control supports this explanation.

Sensitivity analysis, carried out by excluding each study sequentially in the allele genetic model (C vs. T), showed that the studies by Guo *et al.* (2002) and Kjaergaard *et al.* (2007) might have contributed to the heterogeneity. When we omitted these two studies from allele genetic model (I^2=56%, OR=1.14, 95% CI=1.05–1.23), the heterogeneity among the remaining studies decreased markedly (I^2=48% after deleting the study of Kjaergaard *et al.* (2007), and I^2=46% after omitting the study of Guo *et al.* (2002)). We also assessed whether each individual study influenced the pooled ORs by sequential omission of

individual studies. No individual study seemed to affect the results significantly in the total population (Fig. 3).

3.4 Subgroup analysis

To investigate whether the association between *ESR1 Pvu*II polymorphism and CAD varies among different populations, we performed subgroup analysis based on the region of origin of the study population. We found an increased risk of CAD in Asian populations under the allele genetic and recessive genetic models (for C vs. T: OR=1.20, 95% CI=1.04–1.39, I^2=51.9%; for CC vs. CT+TT: OR=1.36, 95% CI=1.13–1.63, I^2=1.4%) (Table 4). In contrast, no significant relationship was observed between *Pvu*II polymorphism and CAD in Western populations (Table 4).

In the subgroup analysis stratified by source of control, we found an increased risk of CAD in HB studies (OR=1.3, 95% CI=1.07–1.59) and in studies with both PB and HB controls (OR=1.81, 95% CI=1.07–3.07) under the allele genetic model (C vs. T), but not in PB studies (OR=1.06, 95% CI=0.99–1.12) (Table 4). Furthermore, no significant association of *Pvu*II polymorphism and CAD risk was found in PB studies either under the recessive genetic model or under the dominant genetic model (Table 4).

3.5 Publication bias

A funnel plot of publication bias (Fig. 4) showed that the symmetry of the patterning was not ideal. To detect publication bias in a visual and quantified manner, Begg's test (Fig. 5) and Egger's test (Fig. 6) were used. The Egger's test (t=3.22, P=0.004)

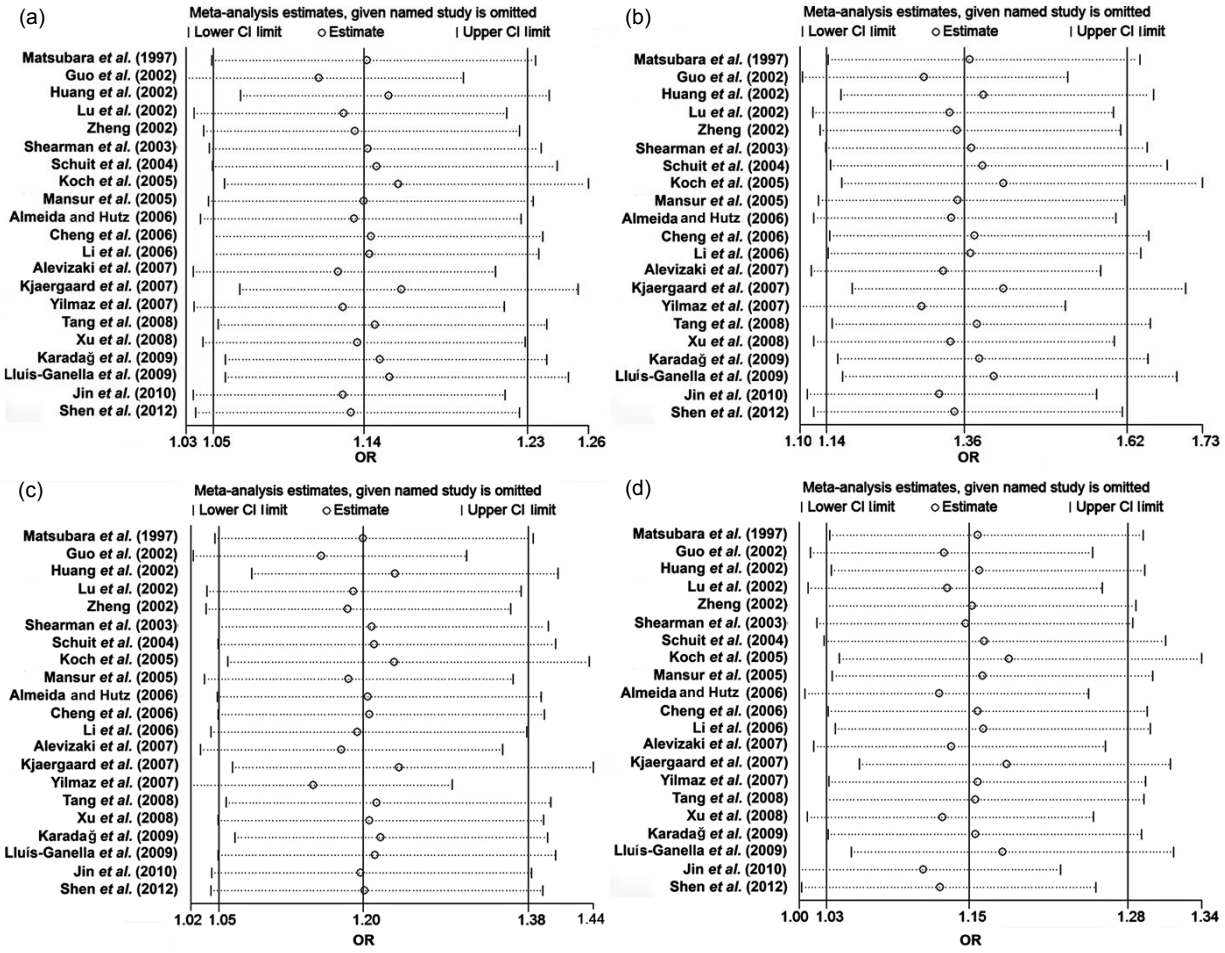

Fig. 3 Sensitivity analysis to examine the influence of individual studies on the pooled ORs

The circles represent the pooled ORs when the given named study on the left is omitted, and the dotted lines between "Lower CI limit" and "Upper CI limit" indicate the 95% CIs. Random-effect model was used. (a) Allele genetic model (C vs. T); (b) Homozygote comparison (CC vs. TT); (c) Dominant genetic model (CC+CT vs. TT); (d) Recessive genetic model (CC vs. CT+TT)

Table 4 Pooled ORs and 95% CIs of the stratified meta-analysis

Stratification	*n*	OR (95% CI)			
		CC vs. TT	CC+CT vs. TT	CC vs. CT+TT	C vs. T
CAD	21	1.36 (1.14–1.62)*	1.20 (1.05–1.38)*	1.15 (1.03–1.28)*	1.14 (1.05–1.23)*
Source of control					
HB	6	1.89 (1.11–3.23)*	1.74 (1.02–2.96)*	1.24 (0.94–1.64)	1.30 (1.07–1.59)*
PB	13	1.13 (1.00–1.28)	1.06 (0.97–1.16)	1.07 (0.97–1.19)	1.06 (0.99–1.12)
PB & HB	2	3.67 (1.45–9.30)*	2.36 (0.67–8.35)	2.44 (1.39–4.28)*	1.81 (1.07–3.07)*
Region					
Asia	11	1.53 (1.17–2.00)*	1.25 (0.99–1.57)	1.36 (1.13–1.63)*	1.20 (1.04–1.39)*
Western	10	1.22 (1.00–1.49)	1.17 (0.99–1.38)	1.04 (0.94–1.16)	1.07 (0.99–1.16)

n: number of studies involved; CC vs. TT: homozygote comparison; CC+CT vs. TT: dominant genetic model; CC vs. CT+TT: recessive genetic model; C vs. T: allele genetic model. CAD: coronary artery disease; PB: population-based; HB: hospital-based. The random model was chosen for data pooling when $P<0.10$; otherwise, the fixed model was used. * OR had statistical significance with corresponding 95% CI not including 1

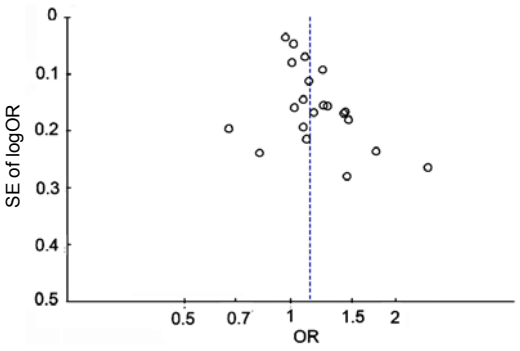

Fig. 4 Funnel plot of publication bias for the meta-analysis under the allelic genetic model (C vs. T)
The SE of logOR is plotted against the OR for each study. The dotted line indicates the estimated OR. OR: odds ratio; SE: standard error

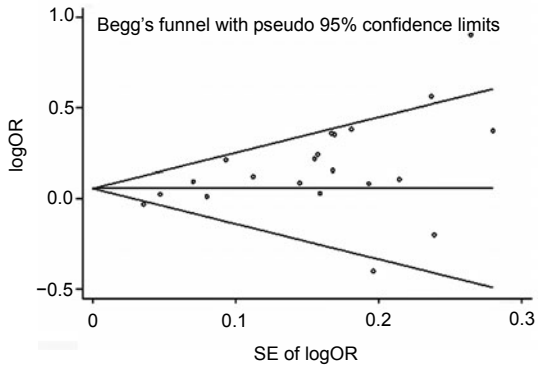

Fig. 5 Begg's funnel plot of publication bias in the meta-analysis of the association of *ESR1 Pvu*II polymorphism and CAD risk under the allelic genetic model (C vs. T)
Each point represents an individual study included in this meta-analysis. OR: odds ratio; SE: standard error

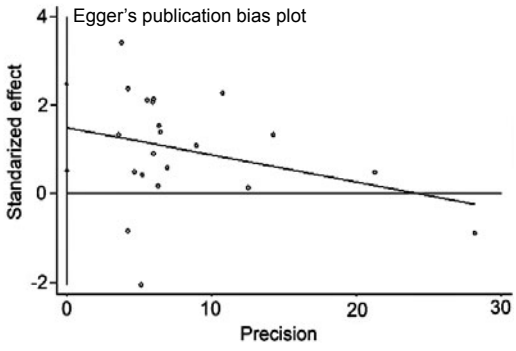

Fig. 6 Egger's linear regression analysis of publication bias for the meta-analysis under the allelic genetic model (C vs. T) (P=0.004, t=3.22)
The standard normal deviation (SND) was regressed against the estimated precision (p). The regression equation is SND=a+bp, where SND is the odds ratio (OR) divided by its standard error (SE), a is the intercept of the regression line, b is the slope of the regression line, and p is precision, the inverse of the SE

suggested the presence of a potential publication bias, a language bias, inflated estimates by a flawed methodological design in smaller studies, and/or a lack of publication of small trials with opposite results. Although sensitivity analysis by sequential omission of individual studies suggested that the results of our meta-analysis were fairly stable and no individual study was found to affect the results significantly, the results of the present meta-analysis should be interpreted cautiously in the context of this limitation.

4 Discussion

Our study found that the *ESR1 Pvu*II polymorphism was significantly associated with CAD risk under the allele genetic model, homozygote comparison, dominant genetic model, and recessive genetic model. To our knowledge, the present study is the largest systematic review by means of meta-analysis to investigate the association between the *ESR1 Pvu*II polymorphism and CAD risk. A previous meta-analysis by Wei *et al.* (2013), which found that the CC genotype of the *ESR1 Pvu*II polymorphism was significantly associated with an increased risk of CAD in Chinese populations, included 10 studies with 1853 CAD patients and 1544 controls. With 9926 CAD cases and 16710 controls, our meta-analysis had a much larger sample size and covered a wider range of countries or regions and languages.

The association between *ESR1 Pvu*II polymorphism and CAD susceptibility was significant in Asian populations in stratification analysis by region. However, no significant results were observed among the Western populations. Our results are consistent with a previous meta-analysis by Kjaergaard *et al.* (2007) which reported that the *ESR1 Pvu*II polymorphism did not influence the risk of CAD in Western populations. Several reasons might explain the contrasting results between Asian and Western populations. Firstly, racial differences between Eastern and Western populations may lead to differences in CAD susceptibility (Thomas *et al.*, 2010; Batchelor *et al.*, 2013), due to potential differences in genetic expression and epigenetic effects. Secondly, it is known that CAD is a complicated disease caused by multiple genetic and environmental factors as well as gene-environment interactions, such that differences in lifestyles, geographic conditions, and climate, for example, may influence the role of the genes (Ioana *et al.*, 2012; Labonté *et al.*, 2012; Yu *et al*., 2012). Finally, the number of eligible studies included in the stratified analysis of Western populations was relatively small. Thus, the lack of association between the *ESR1 Pvu*II polymorphism and CAD among Western populations might be due to insufficient statistical power.

In the present meta-analysis, the source of controls was considered as one source of heterogeneity based on the meta-regression. After adjusting for the source of controls, no significant heterogeneity was observed in PB studies (I^2=30.7%) or HB studies (I^2=29.5%) under genetic models, while significant heterogeneity still existed in the subgroup with both PB and HB sources of controls (I^2=67.1%). The association between the *ESR1 Pvu*II polymorphism and CAD risk was still significant in HB studies and in studies with both PB and HB sources of controls, but not in PB studies, under the allele genetic model (C vs. T). The control population of HB studies might be disease-related, and therefore not representative of the general population. This could affect the reliability and authenticity of the findings. Therefore, the results of our present meta-analysis should be interpreted with caution.

There are several limitations in this current meta-analysis. First, the Egger's test suggested the presence of a potential publication bias. Inevitable literature retrieval bias may exist in our study because we searched papers published in only English or Chinese language. Second, this meta-analysis focused only on the association between *ESR1* c.454-397T>C single nucleotide polymorphisms (SNPs) and CAD risk, while potential interactions between genes were not considered. For example, Schuit *et al.* (2004) reported that postmenopausal women who carried the *ESR1* haplotype 1 c.454-397 T allele and the c.454-351 A allele (T-A) had a higher susceptibility to MI. Third, due to incomplete information about the study populations, such as mean age and sex structure, we could not perform further analysis based on these potential confounding factors. The gender-specific role of the *ESR1 Pvu*II polymorphism in CAD risk was reported previously. Kunnas *et al.* (2000) suggested that the *ESR1 Pvu*II polymorphism contributed to a higher risk of CAD only in men in a Finnish population. Shearman *et al.* (2003) also reported that men with the *Pvu*II CC genotype had a higher risk of MI. In contrast, Alevizaki *et al.* (2007) reported that the *ESR1* polymorphism might influence the severity of CAD in postmenopausal women. In addition, as some young controls currently without CAD may suffer from CAD later in life, and age may also have an impact on the final results. The use of much stricter matching criteria between cases and controls may control these possible confounding factors to some extent.

In conclusion, our meta-analysis suggested that the *ESR1 Pvu*II polymorphism may be associated

with CAD susceptibility, especially among Asian populations. The results of the present meta-analysis may have important implications for clinical decisions, for example, whether to use hormone replacement therapy (HRT) (Stampfer and Colditz, 1991; Grady *et al.*, 1992) for patients with cardiovascular diseases. Additionally, it raises the question of whether the *ESR1 Pvu*II polymorphism could be considered as a candidate genetic marker to identify genetic susceptibility to CAD. Further well-designed studies with larger sample sizes are needed to clarify the effects of estrogen on the cardiovascular system and to elucidate the mechanism of action more clearly.

Acknowledgements

We thank Prof. R. H. ZHUGE from the University of Massachusetts Medical School (USA) for critical reading and language revision of the manuscript.

Compliance with ethics guidelines

Jie DING, Hui XU, Xiang YIN, Fu-rong ZHANG, Xiao-ping PAN, Yi-an GU, Jun-zhu CHEN, and Xiao-gang GUO declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Alevizaki, M., Saltiki, K., Cimponeriu, A., *et al*., 2007. Severity of cardiovascular disease in postmenopausal women: associations with common estrogen receptor α polymorphic variants. *Eur. J. Endocrinol.*, **156**(4): 489-496. [doi:10.1530/EJE-06-0685]

Almeida, S., Hutz, M.H., 2006. Estrogen receptor 1 gene polymorphisms and coronary artery disease in the Brazilian population. *Braz. J. Med. Biol. Res.*, **39**(4):447-454. [doi:10.1590/S0100-879X2006000400004]

Batchelor, W.B., Ellis, S.G., Ormiston, J.A., *et al*., 2013. Racial differences in long-term outcomes after percutaneous coronary intervention with paclitaxel-eluting coronary stents. *J. Interv. Cardiol*., **26**(1):49-57. [doi:10.1111/j.1540-8183.2012.00760.x]

Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**(4):1088-1101.

Boroumand, M., Ghaedi, M., Mohammadtaghvaei, N., *et al*., 2009. Association of estrogen receptor α gene polymorphism with the presence of coronary artery disease documented by coronary angiography. *Clin. Biochem.*, **42**(9):835-839. [doi:10.1016/j.clinbiochem.2009.01.005]

Camargo, M.C., Mera, R., Correa, P., *et al*., 2006. Interleukin-1β and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.*, **15**(9):1674-1687. [doi:10.1158/1055-9965.EPI-06-0189]

Cheng, A.J., Fu, N.K., Xu, J., *et al*., 2006. A study of the correlation between estrogen receptor gene polymorphism and coronary heart disease as well as serum lipid levels in postmenopausal women. *Hebei Med. J.*, **28**(7): 568-570 (in Chinese).

Cochran, W.G., 1968. The effectiveness of adjustment by subclassification in removing bias in observational studies. *Biometrics*, **24**(2):295-313.

Egger, M., Davey Smith, G., Schneider, M., *et al*., 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**(7109):629-634. [doi:10.1136/bmj.315.7109.629]

Figtree, G.A., McDonald, D., Watkins, H., *et al*., 2003. Truncated estrogen receptor α 46-kDa isoform in human endothelial cells: relationship to acute activation of nitric oxide synthase. *Circulation*, **107**(1):120-126. [doi:10.1161/01.CIR.0000043805.11780.F5]

Figtree, G.A., Noonan, J.E., Bhindi, R., *et al*., 2009. Estrogen receptor polymorphisms: significance to human physiology, disease and therapy. *Recent Pat. DNA Gene Seq*., **3**(3):164-171. [doi:10.2174/187221509789318397]

Grady, D., Rubin, S.M., Petitti, D.B., *et al*., 1992. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann. Intern. Med*., **117**(12):1016-1037. [doi:10.7326/0003-4819-117-12-1016]

Grodstein, F., Stampfer, M.J., Colditz, G.A., *et al.*, 1997. Postmenopausal hormone therapy and mortality. *N. Engl. J. Med.*, **336**(25):1769-1775. [doi:10.1056/NEJM199706193362501]

Guo, Z.G., Zheng, H., Wu, S.Z., *et al*., 2002. Relationship between estrogen receptor gene polymorphism and coronary heart disease. *Chin. J. Geriatr. Cardiovasc. Cerebrovasc. Dis.*, **4**(6):374-377 (in Chinese).

Gurevitz, O., Jonas, M., Boyko, V., *et al*., 2000. Clinical profile and long-term prognosis of women ≤50 years of age referred for coronary angiography for evaluation of chest pain. *Am. J. Cardiol.*, **85**(7):806-809. [doi:10.1016/S0002-9149(99)00871-1]

Hamada, H., Kim, M.K., Iwakura, A., *et al.*, 2006. Estrogen receptors α and β mediate contribution of bone marrow-derived endothelial progenitor cells to functional recovery after myocardial infarction. *Circulation*, **114**(21): 2261-2270. [doi:10.1161/CIRCULATIONAHA.106.631465]

Herrington, D.M., Howard, T.D., Brosnihan, K.B., *et al.*, 2002. Common estrogen receptor polymorphism augments effects of hormone replacement therapy on E-selectin but not C-reactive protein. *Circulation*, **105**(16):1879-1882. [doi:10.1161/01.CIR.0000016173.98826.88]

Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. *Stat. Med.*, **21**(11):1539-1558. [doi:10.1002/sim.1186]

Higgins, J.P., Thompson, S.G., Deeks, J.J., *et al*., 2003. Measuring inconsistency in meta-analyses. *BMJ*, **327**(7414):557-560. [doi:10.1136/bmj.327.7414.557]

Huang, X.Z., Zhang, P.A., Li, Y., *et al*., 2002. Association of

estrogen receptor gene polymorphism with coronary heart disease. *Chin. J. Cardiol.*, **30**(2):78-81 (in Chinese).

Ioana, M., Ferwerda, B., Plantinga, T.S., *et al.*, 2012. Different patterns of Toll-like receptor 2 polymorphisms in populations of various ethnic and geographic origins. *Infect. Immun.*, **80**(5):1917-1922. [doi:10.1128/IAI.00121-12]

Jesmin, S., Mowa, C.N., Sultana, S.N., *et al.*, 2010. VEGF signaling is disrupted in the hearts of mice lacking estrogen receptor alpha. *Eur. J. Pharmacol.*, **641**(2-3): 168-178. [doi:10.1016/j.ejphar.2010.05.020]

Jin, L.Z., Chen, X.C., Ma, Y.D., *et al*., 2010. Association of estrogen receptor α gene *Pvu*II and *Xba*I polymorphisms with coronary artery disease. *Chin. J. Biomed. Eng.*, **16**(2):136-139 (in Chinese).

Jneid, H., 2012. The 2012 ACCF/AHA focused update of the unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) guideline: a critical appraisal. *Methodist Debakey Cardiovasc. J.*, **8**(3):26-30.

Karadağ, B., Güven, M., Hacioğlu, Y., *et al*., 2009. Relationship between two estrogen receptor-α gene polymorphisms and angiographic coronary artery disease. *Anadolu Kardiyol. Derg.*, **9**(4):267-272.

Kjaergaard, A.D., Ellervik, C., Tybjærg-Hansen, A., *et al*., 2007. Estrogen receptor α polymorphism and risk of cardiovascular disease, cancer, and hip fracture: cross-sectional, cohort, and case-control studies and a meta-analysis. *Circulation*, **115**(7):861-871. [doi:10.1161/CIRCULATIONAHA.106.615567]

Klos, K.L., Boerwinkle, E., Ferrell, R.E., *et al*., 2008. *ESR1* polymorphism is associated with plasma lipid and apolipoprotein levels in Caucasians of the Rochester Family Heart Study. *J. Lipid Res.*, **49**(8):1701-1706. [doi:10.1194/jlr.M700490-JLR200]

Koch, W., Hoppmann, P., Pfeufer, A., *et al*., 2005. No replication of association between estrogen receptor α gene polymorphisms and susceptibility to myocardial infarction in a large sample of patients of European descent. *Circulation*, **112**(14):2138-2142. [doi:10.1161/CIRCULATIONAHA.105.545913]

Kunnas, T.A., Laippala, P., Penttilä, A., *et al*., 2000. Association of polymorphism of human α oestrogen receptor gene with coronary artery disease in men: a necropsy study. *BMJ*, **321**(7256):273-274. [doi:10.1136/bmj.321.7256.273]

Labonté, B., Suderman, M., Maussion, G., *et al.*, 2012. Genome-wide epigenetic regulation by early-life trauma. *Arch. Gen. Psychiatry*, **69**(7):722-731. [doi:10.1001/archgenpsychiatry.2011.2287]

Li, L.H., Zhao, F.M., Li, G.Q., *et al*., 2006. Association between estrogen receptor alpha gene variation and risks of cardiovascular disease. *Mol. Cardiol. China*, **6**(2):90-94 (in Chinese).

Liu, H., Pedram, A., Kim, J.K., 2011. Oestrogen prevents cardiomyocyte apoptosis by suppressing p38α-mediated activation of p53 and by down-regulating p53 inhibition on p38β. *Cardiovasc. Res.*, **89**(1):119-128. [doi:10.1093/cvr/cvq265]

Lluís-Ganella, C., Lucas, G., Subirana, I., *et al*., 2009. Qualitative assessment of previous evidence and an updated meta-analysis confirms lack of association between the *ESR1* rs2234693 (*Pvu*II) variant and coronary heart disease in men and women. *Atherosclerosis*, **207**(2):480-486. [doi:10.1016/j.atherosclerosis.2009.05.038]

Lu, H., Higashikata, T., Inazu, A., *et al*., 2002. Association of estrogen receptor-α gene polymorphisms with coronary artery disease in patients with familial hypercholesterolemia. *Arterioscler. Thromb. Vasc. Biol*., **22**(5):817-823. [doi:10.1161/01.ATV.0000014424.18209.21]

Mansur, A.P., Nogueira, C.C.M., Strunz, C.M.C., *et al*., 2005. Genetic polymorphisms of estrogen receptors in patients with premature coronary artery disease. *Arch. Med. Res.*, **36**(5):511-517. [doi:10.1016/j.arcmed.2005.04.002]

Matsubara, Y., Murata, M., Kawano, K., *et al*., 1997. Genotype distribution of estrogen receptor polymorphisms in men and postmenopausal women from healthy and coronary populations and its relation to serum lipid levels. *Arterioscler. Thromb. Vasc. Biol.*, **17**(11):3006-3012. [doi:10.1161/01.ATV.17.11.3006]

Mendelsohn, M.E., Karas, R.H., 2005. Molecular and cellular basis of cardiovascular gender differences. *Science*, **308**(5728):1583-1587. [doi:10.1126/science.1112062]

Peter, I., Shearman, A.M., Zucker, D.R., *et al.*, 2005. Variation in estrogen-related genes and cross-sectional and longitudinal blood pressure in the Framingham Heart Study. *J. Hypertens.*, **23**(12):2193-2200. [doi:10.1097/01.hjh.0000188728.66183.92]

Rokach, A., Pollak, A., Rosen, L., *et al*., 2005. Estrogen receptor α gene polymorphisms are associated with the angiographic extent of coronary artery disease. *J. Clin. Endocrinol. Metab.*, **90**(12):6556-6560. [doi:10.1210/jc.2005-0236]

Rossouw, J.E., Anderson, G.L., Prentice, R.L., *et al.*, 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*, **288**(3):321-333. [doi:10.1001/jama.288.3.321]

Schuit, S.C.E., Oei, H.H., Witteman, J.C.M., *et al.*, 2004. Estrogen receptor α gene polymorphisms and risk of myocardial infarction. *JAMA*, **291**(24):2969-2977. [doi:10.1001/jama.291.24.2969]

Shearman, A.M., Cupples, L.A., Demissie, S., *et al*., 2003. Association between estrogen receptor α gene variation and cardiovascular disease. *JAMA*, **290**(17):2263-2270. [doi:10.1001/jama.290.17.2263]

Shen, C., Chen, J., Fan, S., *et al*., 2012. Association between the polymorphism of estrogen receptor α and coronary artery disease in a Chinese population. *Eur. J. Intern. Med.*, **23**(2):175-178. [doi:10.1016/j.ejim.2011.05.006]

Stampfer, M.J., Colditz, G.A., 1991. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev. Med.*, **20**(1):47-63. [doi:10.1016/0091-7435(91)90006-P]

St-Hilaire, S., Mandal, R., Commendador, A., *et al*., 2011. Estrogen receptor positive breast cancers and their association with environmental factors. *Int. J. Health Geogr*., **10**:32. [doi:10.1186/1476-072X-10-32]

Tang, Z.Z., Li, X.P., Yang, J.H., *et al*., 2008. Relationship of estrogen receptor α gene polymorphism and risk of cardiovascular diseases. *Mil. Med. J. South China*, **22**(2): 35-37 (in Chinese).

Thakkinstian, A., McEvoy, M., Minelli, C., *et al.*, 2005. Systematic review and meta-analysis of the association between β_2-adrenoceptor polymorphisms and asthma: a HuGE review. *Am. J. Epidemiol.*, **162**(3):201-211. [doi:10.1093/aje/kwi184]

Thomas, K.L., Honeycutt, E., Shaw, L.K., *et al*., 2010. Racial differences in long-term survival among patients with coronary artery disease. *Am. Heart J.*, **160**(4):744-751. [doi:10.1016/j.ahj.2010.06.014]

Tunstall-Pedoe, H., Kuulasmaa, K., Mähönen, M., *et al*., 1999. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. *Lancet*, **353**(9164):1547-1557. [doi:10.1016/S0140-6736(99)04021-0]

Wang, F., He, Q., Sun, Y., *et al*., 2010. Female adult mouse cardiomyocytes are protected against oxidative stress. *Hypertension*, **55**(5):1172-1178. [doi:10.1161/HYPERTENSIONAHA.110.150839]

Wei, C.D., Zheng, H.Y., Wu, W., *et al*., 2013. Meta-analysis of the association of the rs2234693 and rs9340799 polymorphisms of estrogen receptor alpha gene with coronary heart disease risk in Chinese Han population. *Int. J. Med. Sci.*, **10**(4):457-466. [doi:10.7150/ijms.5234]

Wright, R.S., Anderson, J.L., Adams, C.D., *et al.*, 2011. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.*, **57**(19):e215-e367. [doi:10.1016/j.jacc.2011.02.011]

Xu, H., Hou, X., Wang, N., *et al.*, 2008. Gender-specific effect of estrogen receptor-1 gene polymorphisms in coronary artery disease and its angiographic severity in Chinese population. *Clin. Chim. Acta*, **395**(1-2):130-133. [doi:10.1016/j.cca.2008.06.004]

Yaich, L., Dupont, W.D., Cavener, D.R., *et al*., 1992. Analysis of the *Pvu*II restriction fragment-length polymorphism and exon structure of the estrogen receptor gene in breast cancer and peripheral blood. *Cancer Res.*, **52**(1):77-83.

Yilmaz, A., Menevse, S., Erkan, A.F., *et al*., 2007. The relationship of the *ESR1* gene polymorphisms with the presence of coronary artery disease determined by coronary angiography. *Genet. Test.*, **11**(4):367-371. [doi:10.1089/gte.2007.0019]

Yu, Q., Liu, E.Q., Zhao, S.H., *et al.*, 2012. Association between *TaqIB* polymorphism of cholesteryl ester transfer protein and coronary artery disease in the Chinese population. *J. Zhejiang Univ.-Sci. B (Biomed. & Biotechnol.)*, **13**(5):342-347. [doi:10.1631/jzus.B1100264]

Zheng, H.M., 2002. Association of Estrogen Receptor (ER) Polymorphisms with Coronary Artery Disease and the Lipoprotein Metabolism in Women. MS Thesis, Hebei Medical University, Hebei, China (in Chinese).

中文概要：

本文题目：雌激素受体 α 基因 *Pvu*II 基因多态性与冠心病关系的 meta 分析

Estrogen receptor α gene *Pvu*II polymorphism and coronary artery disease: a meta-analysis of 21 studies

研究目的：系统评价雌激素受体 α 基因 *Pvu*II 基因多态性与冠心病的关系。

创新要点：目前关于雌激素受体 α 基因 *Pvu*II 基因多态性 （c.454-397T>C）与冠心病的关系仍存在争议。因此本研究针对这一问题系统收集国内外符合纳入与排除标准的研究，通过 meta 分析，系统地评估雌激素受体 α 基因 *Pvu*II 基因多态性与冠心病的关系。

研究方法：针对研究问题系统检索国内外相关数据库，根据事先制定的纳入与排除标准及质量评价量表，筛选出符合标准的研究文献。利用 STATA11.0 和 RevMan 5.2 软件对纳入的 21 篇研究（包括 9926 病例和 16710 对照）进行定量分析。优势比（OR）值及 95%置信区间（CI）用来衡量雌激素受体 α 基因 *Pvu*II 基因多态性与冠心病的关系。

重要结论：Meta 分析结果提示，雌激素受体 α 基因 *ESR1 Pvu*II 基因多态性与冠心病的关系在研究的整体人群中有重要意义。地区亚组分析显示，在亚洲人群中，雌激素受体 α 基因 *Pvu*II 基因多态性与冠心病相关，然而这种相关性不存在于西方人群。

关键词组：雌激素受体 α；基因多态性；冠心病；Meta 分析