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Original Article

Plasminogen activator inhibitor-1 4G/5G polymorphism is associated with coronary artery disease risk: a meta-analysis

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Abstract: Background: The aim of the current study was to evaluate the association of *PAI-1* 4G/5G polymorphism with coronary artery disease (CAD) risk using a meta-analysis. Methods: All eligible studies were identified through a search of PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), Database of Chinese Scientific and Technical Periodicals, and China Biology Medical literature database (CBM) before June 2014. The association between the *PAI-1* 4G/5G polymorphism and CAD risk was estimated by odds ratio (OR) and 95% confidence interval (CI). Results: A total of 72 studies including 23557 cases and 21526 controls were eventually collected. The *PAI-1* 4G/5G polymorphism was significant associated with CAD risk in overall population (OR=1.19, 95% CI 1.10-1.28, $P < 0.00001$). The combination of adjusted ORs for CAD was 1.20 (95% CI 1.03-1.40, $P=0.02$). This polymorphism was associated with CAD risk in Caucasians (OR=1.10, 95% CI 1.02-1.19, $P=0.01$) and Asians (OR=1.46, 95% CI 1.21-1.75, $P < 0.0001$). This polymorphism significantly increased MI risk (OR=1.15, 95% CI 1.06-1.25, $P=0.001$). In the subgroup analysis by age, this polymorphism was significantly associated with early-onset CAD risk (OR=1.21, 95% CI 1.02-1.43, $P=0.03$). In the gender subgroup analyses, a statistically significant association was found in male CAD patients (OR=1.10, 95% CI 1.01-1.20, $P=0.04$). Both T2DM patients and non-T2DM patients carrying 4G allele showed increased CAD risks (OR=2.23, 95% CI 1.27-3.92, $P=0.005$ and OR=1.64, 95% CI 1.19-2.25, $P=0.002$, respectively). Conclusions: This meta-analysis suggested that *PAI-1* 4G/5G polymorphism was a risk factor for CAD.

Keywords: Coronary artery disease, plasminogen activator inhibitor-1, meta-analysis, genetic

Introduction

Cardiovascular diseases, the first cause of death in the Western countries are a real common health problem. Despite the high responsibility of factors such as high level of total cholesterol, systemic hypertension, smoking, type 2 diabetes (T2DM) in coronary artery disease (CAD), evidence from family studies show that genetic factors contribute to the predisposition to CAD.

The plasminogen activator inhibitor-1 (*PAI-1*), a 52 kDa glycoprotein belong to the serine proteinase inhibitor super family, is a multifaceted proteolytic factor. It is the principal inhibitor of tissue and urinary plasminogen activators, and therefore constitutes an important regulatory protein in fibrinolysis [1]. Impaired fibrinolysis due to high *PAI-1* activity has been shown to be associated with an increased risk of thrombotic events [2]. *PAI-1* overexpression may also promote development of weak plaques with thin fibrous caps by inhibiting both u-PA receptor- and integrin-mediated cell adhesion and migration [3]. In addition, increased plasma *PAI-1* levels have been reported in survivors of myocardial infarction (MI) compared with the general population [4]. Therefore, *PAI-1* might play an important role in the pathogenesis of CAD.

The *PAI-1* gene, located in 7q21.3-22, spans 12.3 kb and contains 9 exons and 8 introns. The polymorphism of the 4G/5G gene is located in the *PAI-1* gene promoter region. The most commonly studied functional variant in the

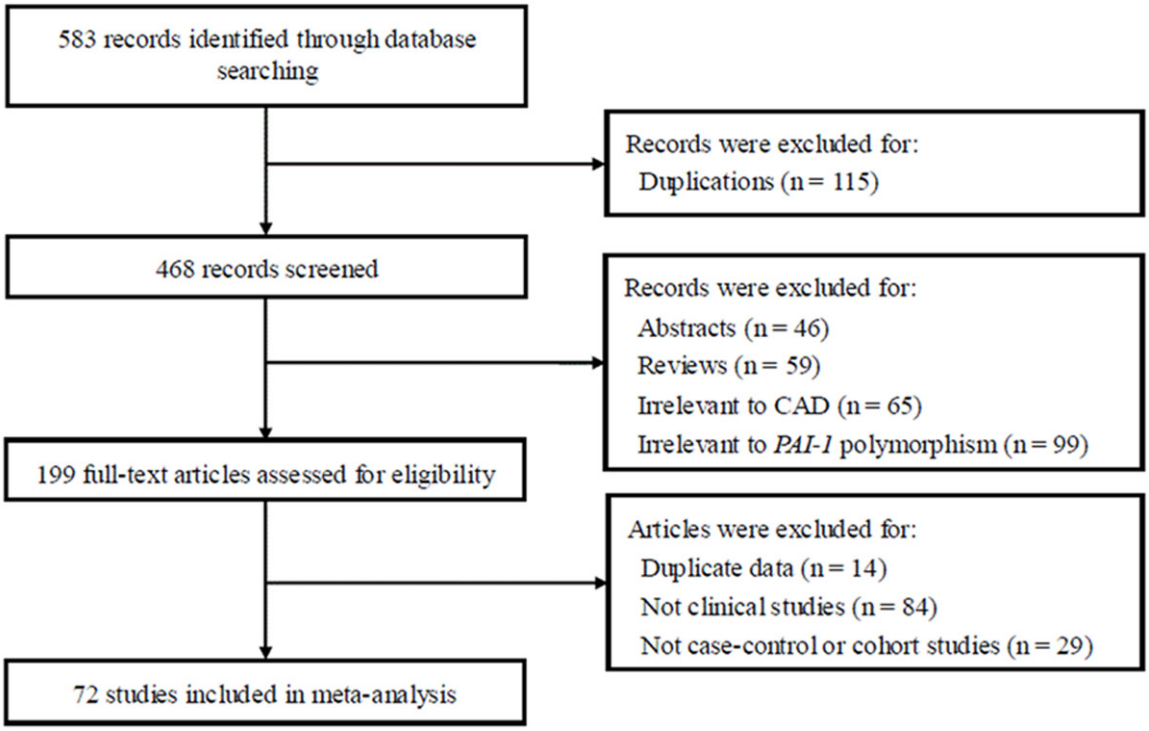

Figure 1. Flow of study identification, inclusion, and exclusion.

Table 1. Characteristics of the included studies

					Age		Case	Control	
First author	Year	Country	Ethnicity	Endpoint	of patients	Female (%)	(n)	(n)	Adjustment for covariates
Dawson	1993	Sweden	Caucasian	MI	< 45 (39.9±0.4)	14	107	73	NA
Eriksson	1995	Sweden	Caucasian	MI	< 45	0	93	100	NA
Ye	1995	France/UK	Caucasian	MI	25-64	0	476	601	NA
Mansfield	1995	UK	Caucasian	CAD	61-70	0	38	122	NA
Burzotta	1997	Italy	Caucasian	MI	> 45 (59±7)	25	108	175	NA
Ridker	1997	USA	Caucasian	MI	62.9±8.8	0	374	495	NA
Ossei-Gerning	1997	UK	Caucasian	MI	59.8	NA	158	150	NA
Iwai	1998	Japan	Asian	MI	59.3±10.3	22.5	204	148	NA
Kohler	1998	Finland	Caucasian	MI	57-59	27.7	181	188	NA
Margaglione	1998	Italy	Caucasian	MI	22-65	23	198	981	NA
Pastinen	1998	Finland	Caucasian	MI	58.1±4.9	19.2	151	150	NA
Junker	1998	Germany	Caucasian	MI	38.6±4.4	0	241	179	NA
Sugano	1998	Japan	Asian	MI	63.1±9.2	12.1	66	62	NA
Ardissino	1999	Italy	Caucasian	MI	40.7±4.1	7.5	200	200	NA
Anderson 1	1999	USA	Caucasian	MI	63.7±11.6	23	375	978	NA
Anderson 2	1999	USA	Caucasian	CAD	62.5±10.9	20	898	329	NA
Doggen	1999	Netherlands	Caucasian	MI	56.1±9.0	0	331	302	NA
Gardemann 1	1999	Germany	Caucasian	CAD	62.7	0	1791	594	NA
Gardemann 2	1999	Germany	Caucasian	MI	62.2	0	1214	1351	NA
Grancha	1999	Spain	Caucasian	CAD	56±5	100	41	62	NA
Beneš	2000	Czech	Caucasian	CAD	49.5±4.5	0	175	222	NA
Canavy	2000	France	Caucasian	CAD/MI	55	22	244	244	NA
Hooper	2000	USA	African	MI	60.7±9.2	53	110	185	NA
Mikkelsson	2000	Finland	Caucasian	MI	47.9±9	0	68	164	NA
Song	2000	Korea	Asian	CAD	60.7±9.2	37.3	158	139	NA

Fu	2000	China	Asian	MI	51.3±6.7	42.5	87	92	NA
Viitanen	2001	Finland	Caucasian	CAD	56±1	40.7	118	110	NA
Dai	2001	China	Asian	CAD/MI	57±9	NA	250	95	NA
Fu	2001	China	Asian	CAD	66±10	50	123	172	NA
Shang	2001	China	Asian	CAD	NA	NA	38	80	NA
Ortlepp	2002	Germany	Caucasian	CAD	58±12.8	68	100	100	NA
Yamada	2002	Japan	Asian	MI	62.5±10.8	100	589	704	NA
Guan	2002	China	Asian	CAD	34-90	38.1	126	121	NA
Li	2002	China	Asian	CAD	60 ± 8	33.3	36	16	NA
ATVBISG	2003	Italy	Caucasian	MI	< 45	12.3	1210	1210	Smoking, diabetes, hypertension, family history, body mass index, hypercholesterolemia, alcohol, cocaine, physical exercise
Crainich	2003	USA	Caucasian	MI	73.5±5.5	40.2	264	753	NA
Juhan-Vague	2003	Europe	Caucasian	MI	< 60	0	483	507	NA
Leander 1	2003	Sweden	Caucasian	MI	58.3±7.1	0	851	1051	Age, residential area
Leander 2	2003	Sweden	Caucasian	MI	61.5±6.8	100	361	505	Age, residential area
Petrovič	2003	Slovenia	Caucasian	MI	58.3±11.3	33.8	154	194	NA
Zhan	2003	China	Asian	MI	67.1±10.4	21.4	56	83	NA
Ding 1	2003	China	Asian	CAD	NA	NA	60	109	Age, body mass index, family history
Ding 2	2003	China	Asian	CAD	NA	NA	49	63	Age, body mass index, family history
Wang	2003	China	Asian	CAD	59±12	24	67	30	NA
Zhai	2003	China	Asian	CAD	62.8±9	32	122	172	NA
Tobin	2004	UK	Caucasian	MI	61.9±9.2	32	547	505	NA
Pegoraro	2005	Indian	Asian	MI	< 45	NA	195	300	NA
Whiting	2005	USA	Caucasian	CAD	NA	NA	881	261	Diabetes, family history
Zak	2005	Poland	Caucasian	CAD	45.9±6	34.9	146	121	NA
Agirbasli	2006	Turkey	Caucasian	CAD	< 55	20	100	100	NA
Su	2006	China	Asian	CAD	54.5±8.9	21.6	812	931	Age, sex, BMI, HDL-C, LDL-C, hypertension, diabetes, and smoking
Xia	2006	China	Asian	CAD	57.7±8.1	28.6	166	63	NA
Morange	2007	France	Caucasian	MI	51.91±5.44	0	510	543	NA
Sampaio	2007	Brazil	Caucasian	MI	34.4±4.9	38.1	115	104	Age, gender, ethnic background, hypertension, diabetes, hypercholesterolemia, obesity, smoking, stress, and sedentary lifestyle
Taymaz	2007	Turkey	Caucasian	CAD	NA	NA	115	41	NA
Onalan	2008	Turkey	Caucasian	MI	59±11	19.9	156	281	NA
Saely	2008	Austria	Caucasian	CAD	NA	NA	406	266	Age, gender, BMI, smoking, hypertension, LDL cholesterol, HDL cholesterol, triglycerides, and use of aspirin, statins, angiotensin converting enzyme inhibitors and beta adrenoreceptor blocking agents
Sarecka	2008	Poland	Caucasian	CAD	43.8±6.1	32.6	178	202	Smoking, elevated level of total cholesterol, LDL-cholesterol, triacylglycerols, overweight or obesity
Zhang	2008	China	Asian	CAD	63.6±4.9	27	155	190	NA
Isordia-Salas	2009	Mexico	Caucasian	MI	40±4.6	16.5	127	127	NA
Tàssies	2009	Spain	Caucasian	CAD	60±13	23	248	200	NA
Var	2009	Turkey	Caucasian	CAD	55.3±11.3	35	86	90	Age, sex, smoking and hypertension
Chen	2009	China	Asian	CAD	60±11	51	293	178	NA

Abboud	2010	Tunisia	African	MI	59.0±12.0	19	305	328	NA
Cao	2010	China	Asian	MI	64.62	33.6	116	60	NA
Koch	2010	Germany	Caucasian	MI	64±12	24.2	3657	1211	Age, gender, history of arterial hypertension, history of hypercholesterolaemia, current cigarette smoking, and diabetes mellitus
Agirbasli	2011	Turkey	Caucasian	CAD	45.4±7	43.3	90	90	NA
Ahmed	2011	Pakistan	Caucasian	MI	52.1±11.3	19.7	229	217	NA
Ashavaid	2011	India	Asian	CAD	58.6±10.4	19.7	446	473	NA
Lima	2011	Brazil	Caucasian	CAD	60	50	123	38	NA
Zhao	2012	China	Asian	CAD	40-82	32.9	146	113	NA
Lin	2012	China	Asian	CAD	43±14	38	65	132	NA

MI, myocardium infarction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; NA, not available.

Table 2. Distribution of *PAI-1* -675 4G/5G polymorphism among patients and controls

	Case			Control			
Study	4G/4G	4G/5G	5G/5G	4G/4G	4G/5G	5G/5G	HWE
Dawson	29	51	27	23	24	26	No
Eriksson	40	38	15	26	54	20	Yes
Ye	148	230	98	189	271	141	No
Mansfield	20	15	3	37	67	18	Yes
Burzotta	32	46	30	52	86	37	Yes
Ridker	101	191	82	133	247	115	Yes
Ossei-Gerning	59	73	26	36	65	49	Yes
Iwai	83	99	22	53	76	19	Yes
Kohler	66	91	27	54	86	48	Yes
Margaglione	68	85	45	239	493	249	Yes
Pastinen	46	74	31	30	80	40	Yes
Junker	86	112	43	52	93	34	Yes
Sugano	5	28	33	6	27	29	Yes
Ardissino	38	93	69	32	102	66	Yes
Anderson 1	105	193	77	303	457	218	Yes
Anderson 2	267	433	198	97	155	77	Yes
Doggen	88	170	73	84	150	68	Yes
Gardemann 1	624	985	362	167	305	122	Yes
Gardemann 2	382	606	226	409	684	258	Yes
Grancha	6	23	12	11	30	21	Yes
Beneš	53	91	31	77	103	42	Yes
Canavy	48	97	56	64	121	59	Yes
Hooper	7	42	59	11	79	104	Yes
Mikkelsson	18	38	12	29	78	57	Yes
Song	62	64	32	54	60	25	Yes
Fu	39	29	19	25	45	22	Yes
Viitanen	29	65	24	28	51	31	Yes
Dai	85	110	55	12	48	35	Yes
Fu	58	49	16	38	85	49	Yes
Shang	13	18	7	20	37	23	Yes
Ortlepp	36	48	16	24	54	22	Yes
Yamada	215	300	75	315	316	73	Yes

PAI-1 gene is the guanine deletion polymorphism at position -675 nucleotides relative to the transcription start site (rs179-9889). The *PAI-1* -675 4G allele has higher transcriptional activity than the *PAI-1* -675 5G allele and homozygous possession of -675 4G is associated with higher plasma *PAI-1* levels [5]. A number of papers investigated the association between this polymorphism and CAD risk. However, the results remained inconclusive [6-73]. Metaanalysis is a useful method for investigating associations between genetic factors and diseases, because a quantitative approach is used to combine the results from different studies on the same topic, thereby providing more reliable conclusions. Thus, we performed a meta-analysis to clarify the association of *PAI-1* 4G/5G polymorphism with CAD.

Methods

Publication search

A computerized literature search was performed to identify the relevant studies from five electronic databases including PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), Database of Chinese Scientific and Technical Periodicals, and China

Guan	50	52	24	23	70	28	Yes
Li	13	18	5	5	11	0	Yes
ATVBISG	335	589	286	342	588	280	Yes
Crainich	70	136	58	200	387	166	Yes
Juhan-Vague	125	249	109	133	269	105	Yes
Leander 1	256	415	153	283	542	203	Yes
Leander 2	103	180	61	153	226	110	Yes
Petrovič	45	74	35	68	89	37	Yes
Zhan	40	14	2	25	52	6	No
Ding 1	8	26	26	15	39	55	Yes
Ding 2	15	23	11	10	25	28	Yes
Wang	8	35	24	2	7	21	Yes
Zhai	58	49	16	38	85	49	Yes
Tobin	159	280	108	162	237	106	Yes
Pegoraro	42	99	54	65	132	103	Yes
Whiting	263	427	191	78	121	62	Yes
Zak	34	74	38	44	58	19	Yes
Agirbasli	28	46	26	23	60	17	Yes
Su	272	390	150	275	446	210	Yes
Xia	79	67	20	18	28	17	Yes
Morange	105	236	120	96	254	124	Yes
Sampaio	23	47	45	16	45	43	Yes
Taymaz	31	58	26	15	20	6	Yes
Onalan	51	75	30	73	112	96	Yes
Saely	NA	NA	NA	NA	NA	NA	Yes
Sarecka	38	94	46	69	103	30	Yes
Zhang	58	62	35	52	87	51	Yes
Isordia-Salas	9	64	54	17	38	72	Yes
Tàssies	56	121	71	48	92	60	Yes
Var	43	24	19	24	36	30	Yes
Chen	100	140	53	47	99	32	Yes
Abboud	88	156	61	42	180	106	Yes
Cao	61	41	14	15	27	18	Yes
Koch	1091	1787	779	360	590	261	Yes
Agirbasli	36	35	19	24	43	23	Yes
Ahmed	64	86	79	52	89	76	Yes
Ashavaid	112	218	116	113	247	113	Yes
Lima	46	34	43	12	12	14	Yes
Zhao	46	68	32	23	57	33	Yes
Lin	29	28	8	34	63	35	Yes

HWE, Hardy-Weinberg equilibrium.

Biology Medical literature database (CBM). The search terms were used as follows: (coronary artery disease or coronary heart disease or atherosclerosis) and (polymorphism or variant or mutation) and (plasminogen activator inhibitor-1 or *PAI-1*). All searched studies were retrieved and the bibliographies were checked for other relevant publications.

Inclusion and exclusion criteria

The following criteria were used for the literature selection: first, studies should concern the association of *PAI-1* 4G/5G polymorphism with CAD risk; second, studies must be observational studies (case-control or cohort); third, papers must offer the size of the sample, odds ratios (ORs) and their 95% confidence intervals (CIs), the genetic distribution or the information that can help infer the results. Studies were excluded if one of the following existed: first, studies were not relevant to *PAI-1* or CAD; second, the design based on family or sibling pairs; third, sample size or OR and 95% CI were not reported; fourth, reviews and abstracts. As for the studies from the same institution, only the one with the largest sample size was included. No language restrictions were imposed.

Data extraction

Data were extracted by two authors independently. If encountered the conflicting evaluations, an agreement was reached following a discussion; if could not reached agreement, another author was consulted to resolve the debate. The following information was extracted from each study: first author, year of publication, original country, ethnicity, endpoint, age, gender, sample size, covariates.

Statistical analysis

OR and 95% CI were employed to evaluate the strength of the association between 4G/5G polymorphism and the risk of CAD in dominant model. Departure from Hardy-Weinberg equilibrium (HWE) in controls was tested by the chi-square test. The Q statistic and the I^2 statistic were used to assess the degree of heterogeneity among the studies included in the meta-analysis. The random-effects model was used to estimate the pooled OR (the DerSimonian and Laird method).

Table 3. The effect of *PAI-1* -675 4G/5G polymorphism on CAD risk

		No. of	Test of association			Heterogeneity		
Comparison	Study	studies	OR (95% CI)	*Z*	*P* Value	χ^2	*P* Value	I^2 (%)
4G/4G + 4G/5G vs. 5G/5G	Overall	72	1.19 (1.10-1.28)	4.54	< 0.00001	144.13	< 0.00001	51
4G/4G + 4G/5G vs. 5G/5G	Adjusted	10	1.20 (1.03-1.40)	2.29	0.02	13.95	0.12	36
4G/4G + 4G/5G vs. 5G/5G	Caucasian	45	1.10 (1.02-1.19)	2.54	0.01	70.61	0.007	38
4G/4G + 4G/5G vs. 5G/5G	Asian	24	1.46 (1.21-1.75)	4.03	< 0.0001	55.19	0.0002	58
4G/4G + 4G/5G vs. 5G/5G	African	2	1.38 (0.70-2.70)	0.93	0.35	5.12	0.02	80
4G/4G + 4G/5G vs. 5G/5G	MI	39	1.15 (1.06-1.25)	3.27	0.001	68.35	0.002	44
4G/4G + 4G/5G vs. 5G/5G	Early-onset	12	1.21 (1.02-1.43)	2.20	0.03	6.31	0.71	0
4G/4G + 4G/5G vs. 5G/5G	Late-onset	4	0.90 (0.72-1.13)	0.89	0.37	1.83	0.61	0
4G/4G + 4G/5G vs. 5G/5G	Male	13	1.10 (1.01-1.20)	2.10	0.04	7.23	0.84	0
4G/4G + 4G/5G vs. 5G/5G	Female	4	1.03 (0.89-1.19)	0.34	0.73	4.54	0.21	34
4G/4G + 4G/5G vs. 5G/5G	T2DM	4	2.23 (1.27-3.92)	2.80	0.005	0.48	0.79	0
4G/4G + 4G/5G vs. 5G/5G	Non-T2DM	3	1.64 (1.19-2.25)	3.03	0.002	0.57	0.75	0

MI, myocardium infarction; T2DM, type 2 diabetes.

Subgroup analyses were carried out by ethnicity, endpoint, age, gender and T2DM. We defined the early-onset CAD was the first event before 50 years old. Sensitivity analysis was performed through sequentially excluded individual studies to assess the stability of the results. The potential publication bias was examined visually in a funnel plot of log [OR] against its standard error (SE), and the degree of asymmetry was tested using Egger's test [74].

All statistical tests were performed using Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX, USA). A *P* value < 0.05 was considered statistically significant, except for tests of heterogeneity where a level of 0.10 was used.

Results

Study characteristics

The flow chart in **Figure 1** summarizes this literature review process. In this current study, a total of 68 eligible studies met the inclusion criteria [6-73]. Four articles reported two cohorts, and each cohort was considered as a case-control study. Finally, a total of 72 studies involving 23557 cases and 21526 controls were included in this meta-analysis. There were 24 studies performed using Asians, 45 studies using Caucasians, and 2 studies using Africans. Thirteen studies included only male CAD patients, and four studies included female CAD patients. Ten studies reported adjusted ORs and CIs and four studies reported the information of T2DM. Three studies were not in HWE. The characteristics of each study included in this meta-analysis are presented in **Table 1**. Genotype frequencies and HWE examination results are listed in **Table 2**.

Quantitative data synthesis

The results of this meta-analysis are shown in **Table 3**. We found that *PAI-1* 4G/5G polymorphism was significant associated with CAD risk in overall population (OR=1.19, 95% CI 1.10-1.28, *P* < 0.00001, **Figure 2**). The combination of adjusted ORs for CAD was 1.20 (95% CI 1.03-1.40, *P*=0.02). In the subgroup analysis according to ethnicity, the results suggested that *PAI-1* 4G/5G polymorphism was associated with CAD risk in Caucasians (OR=1.10, 95% CI 1.02-1.19, *P*=0.01) and Asians (OR=1.46, 95% CI 1.21-1.75, *P* < 0.0001). However, no significant association was observed in Africans (OR=1.38, 95% CI 0.70-2.70, *P*=0.35). In terms of subgroup analyses by endpoint, the *PAI-1* 4G/5G polymorphism significantly increased MI risk (OR=1.15, 95% CI 1.06-1.25, *P*=0.001). In the subgroup analysis by age, the *PAI-1* 4G/5G polymorphism was significantly associated with early-onset CAD risk (OR=1.21, 95% CI 1.02-1.43, *P*=0.03) but not with late-onset CAD risk (OR=0.90, 95% CI 0.72-1.13, *P*=0.37). In the gender subgroup analyses, a statistically significant association was found in male CAD patients (OR=1.10, 95% CI 1.01-1.20, *P*=0.04) but not with female CAD patients (OR=1.03, 95% CI 0.89-1.19, *P*=0.73). Stratification by T2DM status showed that both T2DM patients and non-T2DM patients carrying 4G allele were associated with increased CAD risks (OR=2.23, 95% CI 1.27-3.92, *P*=0.005 and OR=1.64, 95% CI 1.19-2.25, *P*=0.002, respectively).

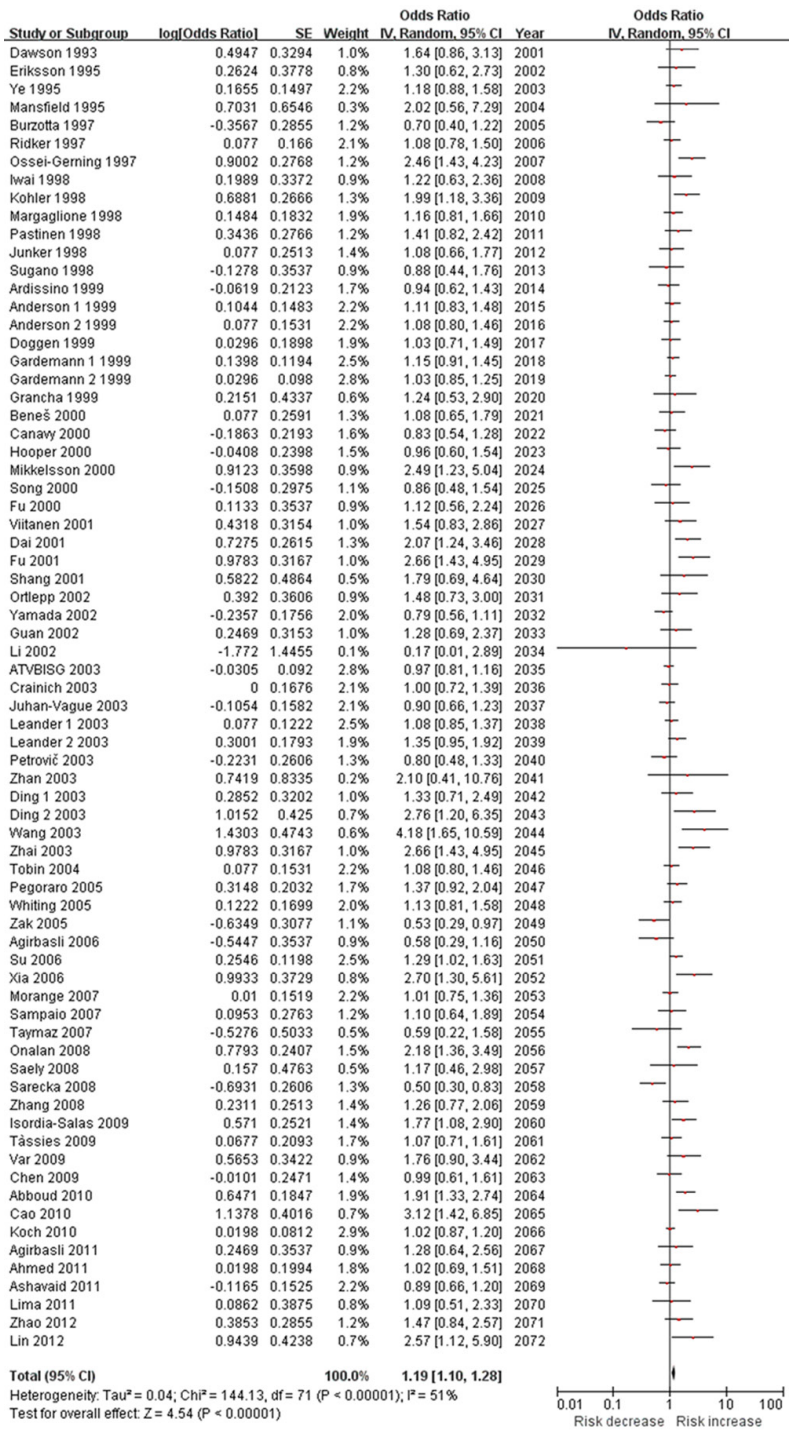

Figure 2. Meta-analysis of the association between the *PAI-1* 4G/5G polymorphism and CAD risk.

Sensitivity analysis was used to evaluate the stability of the overall results by sequential omission of individual studies. In this meta-analysis, the results of sensitive analysis showed that any single study did not influence the overall results qualitatively (data not shown).

Funnel plots and the Egger's test were used to assess publication bias. In the funnel plot analysis, the shape of the funnel plot seemed symmetrical (**Figure 3**). Furthermore, Egger's test did not detect any publication bias (P=0.239). Therefore, there was no significant publication bias in the studies included in current analyses.

Discussion

This present meta-analysis investigating the relationship between *PAI-1* 4G/5G polymorphism and risk of CAD. Seventy-two studies with a total of 45083 subjects were eligible. At the overall analysis, the *PAI-1* 4G/5G polymorphism was significantly associated with CAD risk. Even the studies reporting adjusted ORs were included, the result was still significant. We also found that this polymorphism increased MI risk significantly. In the subgroup analysis by ethnicity, we noted that Asians and Caucasians carrying the 4G allel had an increased CAD risk. Only two studies investigated the association between *PAI-1* 4G/5G polymorphism and risk of CAD in Africans. Therefore, more studies are still needed. In the stratified analysis by age, we found *PAI-1* 4G/5G polymorphism showed increased early-onset CAD risk but not late-onset CAD risk. There were only four studies about late-onset CAD risk, the positive association between *PAI-1* 4G/5G polymorphism and late-onset CAD risk could not be ruled out, because studies with small sample size may have insufficient statistical

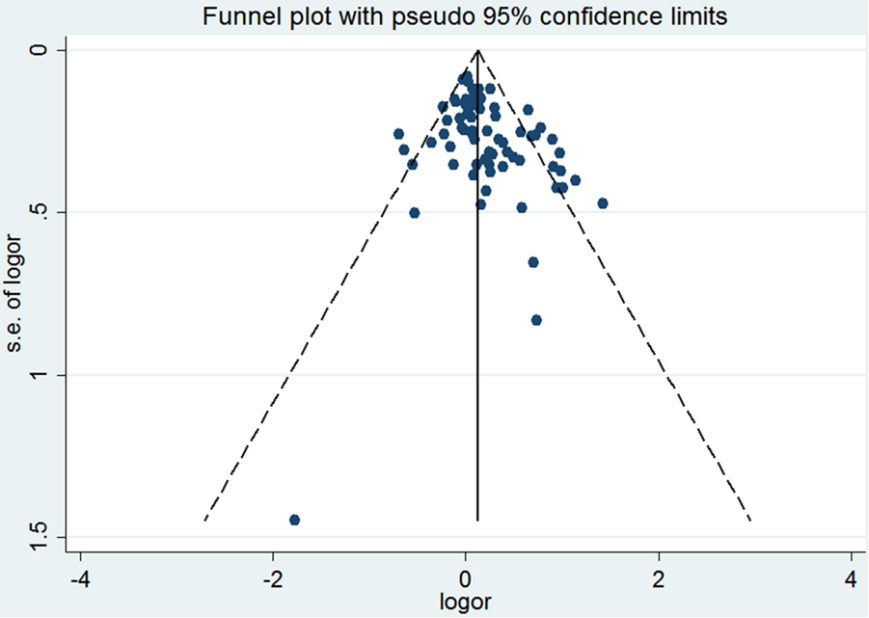

Figure 3. Funnel plot of the association between the *PAI-1* 4G/5G polymorphism and CAD risk.

power to detect a slight effect. The subgroup analysis based on gender found that this polymorphism showed increased CAD risk in male patients but not in female patients. Since the number of studies included in female subgroup analysis was small, the results lacked sufficient reliability to confirm or refute an association in a definitive manner. In the future, more studies should be designed to analyze these associations. When subgroup analysis was performed according to T2DM status, significant associations were showed in T2DM patients and non-T2DM patients. This result suggested that T2DM did not change the effect of *PAI-1* 4G/5G polymorphism on CAD. Previous meta-analysis has assessed the association between *PAI-1* 4G/5G polymorphism and risk of CAD. For example, Koch and coworkers found that the risk of MI in 4G allele carriers was found to be significantly elevated [67]. Li suggested that *PAI-1* 4G/5G polymorphism was associated with increased CAD risk in Chinese Han population [75]. Nikolopoulos et al. also indicated that *PAI-1* 4G allele slightly increased the risk for MI [76]. These results were all in line with our results. However, our study had some advantages. First, it was the first time studying T2DM and *PAI-1* 4G/5G polymorphism interactions. Second, we sought to find as many publications as we could by means of various searching approaches. Third, the main result remained statistically signifiant when the adjusted ORs were combined.

PAI-1 is a glycoprotein that belongs to the serine protease inhibitor superfamily. It is equimolecularly combined with the tissue plasminogen activator (tPA) single chain, double chains, and double chain urokinase plasminogen activator (uPA). Consequently, tPA and uPA activities are rapidly inhibited by *PAI-1*. Mice in which *PAI-1* gene was invalidated were protected from thrombotic risk after vascular injury [77]. Case-control studies in humans have shown that high *PAI-1* plasma levels were associated with an increased risk of CAD and that plasma levels of *PAI-1* were higher in patients with MI than in control individuals [78]. Therefore, *PAI-1* might be involved in the development of CAD. *PAI-1* 4G/5G polymorphism is one of the DNA sequence variations that plays a key rolein regulating *PAI-1* gene expression. Studies have shown that the *PAI-1* activity of the 4G allele promoter is higher than that of 5G in a cytokine-stimulated state. Unlike the 5G allele that binds a transcription repressor protein, resulting in low *PAI-1* expression, the 4G allele does not bind a transcription repressor, thus conferring a high *PAI-1* expressor nature to the allele [5].

Some limitations should be addressed. First, there was only two case-control study investigated the association of *PAI-1* 4G/5G polymorphism and risk of CAD in Africans. Therefore, more studies with large sample sizes are needed to further identify the association among Africans. Second, because small negative studies are less likely to be published, the possibility of publication bias cannot be ruled out completely, even though the Egger's test and funnel plots did not provide the evidence of publication bias in this meta-analysis. Third, a lack of original data from the eligible studies limited evaluation of the effects of the gene-gene and

gene-environment interactions during CAD development.

In conclusion, this meta-analysis suggested that *PAI-1* 4G/5G polymorphism was associated with increased CAD risk. Further studies with large sample size were needed to confirm our findings.

Disclosure of conflict of interest

None.

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