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The susceptibility of SERPINE1 rs1799889 SNP in diabetic vascular complications: a meta-analysis of fifty-one case-control studies

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Abstract

Background: The serine protease inhibitor-1 (SERPINE1) rs1799889 single nucleotide polymorphism (SNP) has been constantly associated with diabetes mellitus (DM) and its vascular complications. The aim of this meta-analysis was to evaluate this association with combined evidences.

Methods: The systematic search was performed for studies published up to March 2021 which assess the associations between SERPINE1 rs1799889 SNP and the risks of DM, diabetic retinopathy (DR), diabetic cardiovascular disease (CVD) and diabetic nephropathy (DN). Only case-control studies were identified, and the linkage between SERPINE1 rs1799889 polymorphism and diabetic vascular risks were evaluated using genetic models.

Results: 51 comparisons were enrolled. The results revealed a significant association with diabetes risk in overall population (allelic: OR = 1.34, 95 % CI = 1.14–1.57, homozygous: OR = 1.66, 95 % CI = 1.23–2.14, heterozygous: OR = 1.35, 95 % CI = 1.08–1.69, dominant: OR = 1.49, 95 % CI = 1.18–1.88, recessive: OR = 1.30, 95 % CI = 1.06–1.59) as well as in Asian descents (allelic: OR = 1.45, 95 % CI = 1.16–1.82, homozygous: OR = 1.88, 95 % CI = 1.29–2.75, heterozygous: OR = 1.47, 95 % CI = 1.08-2.00, dominant: OR = 1.64, 95 % CI = 1.21–2.24, recessive: OR = 1.46, 95 % CI = 1.09–1.96). A significant association was observed with DR risk (homozygous: OR = 1.25, 95 % CI = 1.01–1.56, recessive: OR = 1.20, 95 % CI = 1.01–1.43) for overall population, as for the European subgroup (homozygous: OR = 1.32, 95 % CI = 1.02–1.72, recessive: OR = 1.38, 95 % CI = 1.11–1.71). A significant association were shown with DN risk for overall population (allelic: OR = 1.48, 95 % CI = 1.15–1.90, homozygous: OR = 1.92, 95 % CI = 1.26–2.95, dominant: OR = 1.41, 95 % CI = 1.01–1.97, recessive: OR = 1.78, 95 % CI = 1.27–2.51) and for Asian subgroup (allelic: OR = 1.70, 95 % CI = 1.17–2.47, homozygous: OR = 2.46, 95 % CI = 1.30–4.66, recessive: OR = 2.24, 95 % CI = 1.40–3.59) after ethnicity stratification. No obvious association was implied with overall diabetic CVD risk in any genetic models, or after ethnicity stratification.

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Conclusions: SERPINE1 rs1799889 4G polymorphism may outstand for serving as a genetic synergistic factor in overall DM and DN populations, positively for individuals with Asian descent. The association of SERPINE1 rs1799889 SNP and DR or diabetic CVD risks was not revealed.

Keywords: SERPINE1, rs1799889, 4G/5G polymorphism, Plasminogen activator inhibitor 1, Diabetes, Diabetic vascular disease

Background

Diabetes mellitus (DM) is a major worldwide epidemic that has gained significant public attention. According to recent data from the latest WHO report on diabetes, its world prevalence has been estimated at 8.4 % [1]. Added to this universal health issue, patients with diabetes often develop several vascular and neurogenic complications such as nephropathy, coronary heart disease, myocardial infarction, ischemic stroke, retinopathy, and neuropathy [2]. Most diabetic patients suffer from at least one complication, and vascular complications have become the leading cause of morbidity and mortality, while neurogenic complications such as retinopathy can severely affect quality of life [3].

To date, advances in epidemiological and pathophysiological research on DM have improved our understanding of the underlying pathogenic mechanism of diabetes. The determinants of DM consist of a matrix of genetic susceptibility and epigenetic and lifestyle factors that interact with one another and operate within the larger physical-sociocultural environment [2, 4]. Genetic elements are essentially involved in the pathogenesis of diabetes [5]. Plasminogen activator inhibitor 1 (PAI-1) belongs to the serine protease inhibitor (SERPINE) superfamily and plays a substantial role in the modulation of fibrinolysis and thrombosis [6]. The SERPINE1 gene is commonly recognized in the literature as PAI-1 gene and has been widely studied in epidemiologic studies. A common promoter SNP-rs1799889 consists in an A > G substitution located 2KB upstream the SERPINE1 gene. The 4G allele in the promoter region at nucleotide position-675 is associated with higher PAI-1 levels compared to the 5G allele [7]. PAI-1 levels increase in the pre-diabetic as well as the diabetic state [8]. Moreover, increases in PAI-1 expression may contribute to vascular complications such as nephropathy, coronary heart disease, myocardial infarction, and ischemic stroke [8, 9].

To date, there have been extensive studies conducted investigating the potential role of SERPINE1 rs1799889 polymorphism in DM and subsequent complications. However, former meta-analyses reached inconsistent conclusions on this topic as they might be restrained by sample sizes or an insufficiency of studies [10, 11]. Contradictory as the previous results might be, recent investigations by Li et al. [12] and Xu et al. [13] defined the SERPINE1 rs1799889 SNP genotype dominant allele model as a risk factor for vascular complications in patients with DM. As a result, we felt obliged to perform the updated meta-analysis with larger sample sizes and more sufficient data, intending to better solve the disparity and further evaluate the associations between SERPINE1 rs1799889 SNP polymorphism and DM vascular complications.

Method

Search strategy

The current meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. Potentially related articles were systematically searched in PubMed, Medline, Embase, CNKI, OVID, ScienceDirect and WanFang to identify published literatures up to March 2021 using the following key words: "diabetes mellitus (DM)", "diabetes", "diabetic", and "plasminogen activator inhibitor-1", "PAI-1", "PAI 1", "SERPINE1", "polymorphism, genetic", "polymorphism, single-stranded conformational", "polymorphism, single nucleotide", "polymorphism, restriction fragment length", "variants", "variations, DNA copy number", "genotype", "allele", "mutation", "mutation, frameshift", "INDEL mutation", "rs1799889", "4G", "5G", "4G/5G", and "diabetes complications", "coronary artery/heart disease (CAD/CHD)", "cardiovascular disease (CVD)", "myocardial infarction", "ischemic heart disease", "ischemic stroke", or "nephropathy", "renal disease", or "retinopathy", "diabetic retinopathy", "retinal artery occlusion". No language restrictions were imposed in this meta-analysis. Furthermore, the reference lists of all retrieved articles were screened to identify potentially relevant studies. The literature search was independently performed by two reviewers (JY Chen and CN Zhai).

Inclusion and exclusion criteria

A study included in this meta-analysis must meet with the following criteria: (1) case-control study on correlation analysis between SERPINE1 rs1799889 SNP and the risk of diabetes and associated complications to be assessed; (2) the study must include original and adequate data to allow calculation of odds ratios (ORs) with 95 % confidence intervals (CIs) (independence among studies); (3) evaluation of SERPINE1 rs1799889 polymorphism and the risk of diabetes and its complications.

A study was excluded when fulfilling one of the following criteria: (1) for overlapping-data study, only the most recent

and complete one was enrolled; (2) study with missing information (particularly genotype distributions), while the required information could not be acquired from the corresponding author; (3) genome scans investigating linkages with no detailed genotype frequencies between cases and controls. If inclusions have disagreements, we reached a consensus through discussion. Two reviewers (JY Chen and CN Zhai) independently screened the titles and abstracts for the eligibility criteria. Subsequently, reviewers both read the full text of the studies which potentially met with the inclusion criteria, and the literature was reviewed to determine final inclusive data.

Data extraction

Two reviewers (JY Chen and CN Zhai) conducted the data extraction from each study independently. Any disagreement between the two reviewers was solved by discussion with the third reviewer (ZQ Wang) until reaching a consensus. Three reviewers (JY Chen, CN Zhai, and ZQ Wang) independently evaluated the quality of each case-control study by using the Newcastle–Ottawa Scale criteria [15]. We summarized the information extracted from each literature in Table 1. The characteristics of the selected studies included (1) name of first author; (2) year of publication; (3) country in which the study was done; (4) ethnicity; (5) the number of cases and controls; (6) the genotypic distributions of SERPINE1 rs1799889 polymorphisms in cases and controls; (7) type of disease and outcome. Furthermore, the probability value (*P* value) of Hardy-Weinberg equilibrium (HWE) test was also calculated on the basis of allele frequencies of certain SERPINE1 rs1799889 polymorphisms in the control group.

Statistical analysis

All statistical analyses were conducted using STATA 12.0 (Stata-corp, college station, Tex) and Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). The associations between the SERPINE1 rs1799889 polymorphism and DM and its complications' susceptibility were assessed using the following genetic models: 4G vs. 5G (allelic), 4G4G vs. 5G5G (homozygous), 4G5G vs. 5G5G (heterozygous), 4G4G + 4G5G vs. 5G5G (dominant), and 4G4G vs. 5G5G + 5G4G (recessive). Between-study heterogeneity was tested using Q statistics, and $P < 0.1$ was considered statistically significant. The Mantel-Haenszel method for fixed effects and the Der-Simonian and Laird method for random effects were used to estimate pooled effects [16]. We used fixed-effects methods if the result of the Q test was not significant. Otherwise, we calculated the pooled ORs and 95 % CIs assuming a random-effects model. Fixed effects assume that genetic factors have similar effects on disease susceptibility across all studies and that the observed variations between studies

are caused by chance alone [17]. The random effects model assumes that different studies may have substantial diversity and assesses both within- and between-study variations [18]. A recently developed measure, I^2, was used to quantify the inconsistency among the studies' results with values of 50 % or higher and the large heterogeneity for values of 75 % or higher [19]. The data are shown as the ORs with 95 %CIs, with two-tailed *P*-values; statistical significance was set at $P < 0.05$ (two-tailed). Meta-regression analysis was applied to evaluate the heterogeneity of the studies. Publication bias was conducted statistically via Begg's and Egger's bias test, which measures the degree of funnel plot asymmetry [20, 21]. The Begg's adjusted rank correlation test was used to assess the correlation between test accuracy estimates and their variances. The Egger's bias test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision.

Results

Search results and characteristics of included studies

The study flow chart is summarized in Fig. 1, the primary literature search identified 208 potentially relevant articles. After exclusion of duplicate or irrelevant articles by reading titles and abstracts, and screening through study results, 50 articles were retrieved for further investigation. Another 15 articles were excluded subsequently after full text evaluation. Finally, a total of 35 studies with 51 comparisons containing 15,341 subjects that met our inclusion and exclusion criteria were included [12, 13, 22–54]. The quality of observational studies is presented in Supplementary Material. All of the studies included in the meta-analysis had high quality in their data outcome and clinical design. Characteristics of included studies were summarized in Table 1.

Association of SERPINE1 rs1799889 SNP with overall diabetes risk

In overall population, our meta-analysis revealed a significant association between the SERPINE1 rs1799889 polymorphism and overall diabetes risk, in allelic (4G vs. 5G: OR = 1.34, 95 % CI = 1.14–1.57, p = 0.00), homozygous (4G4G vs. 5G5G: OR = 1.66, 95 % CI = 1.23–2.14, p = 0.00), heterozygous (4G5G vs. 5G5G: OR = 1.35, 95 % CI = 1.08–1.69, p = 0.00), dominant (4G4G + 4G5G vs. 5G5G: OR = 1.49, 95 % CI = 1.18–1.88, p = 0.00),and recessive (4G4G vs. 5G5G + 5G4G: OR = 1.30, 95 % CI = 1.06–1.59, p = 0.01) models. When analyses were subdivided by ethnicity, no obvious associations were noted for the European using any of the five genetic models. For the Asian subgroup, significant associations were observed in all of the five genetic models (allelic: OR = 1.45, 95 % CI = 1.16–1.82, p = 0.00;

Table 1 Characteristics and genotype frequencies for the SERPINE1 rs1799889 SNP in the included studies

| Study	Year	Country	Ethnicity	Sample size Case/ Control		Study type	Outcomes	Genotyping methods	5G allele frequency Case/Control (%)		HWE
Mansfield et al	1995	UK	European	38	122	Hospital based	CAD & NIDDM	PCR	27.6	42.2	Y
Nagi et al	1997	USA	Mix	70	101	Population based	DR & NIDDM	PCR	48.6	60.3	Y
Broch et al	1998	Spain	European	82	95	Hospital based	DR & NIDDM	PCR	51.2	54.7	Y
Kimura et al	1998	Japan	Asian	208	177	Population based	NIDDM	PCR	41.3	40.1	Y
				110	98	Population based	PDR & NIDDM	PCR	42.7	39.8	Y
				110	98	Population based	DN & NIDDM	PCR	41.8	40.9	Y
De Cosmo et al	1999	Italy & UK	European	311	200	Population based	IDDM	PCR	48.6	49.0	Y
				175	136	Population based	DN & IDDM	PCR	47.1	50.4	Y
Wong et a	2000	Hong Kong	Asian	84	57	Hospital based	DR & NIDDM	PCR	40.5	47.4	Y
				95	46	Hospital based	DN & NIDDM	PCR	39.5	51.1	Y
Tarnow et al	2000	Denmark	European	197	191	Hospital based	DN & IDDM	PCR	46.2	46.1	Y
Ding et al	2001	China	Asian	112	169	Hospital based	NIDDM	PCR	56.3	67.2	Y
				49	63	Hospital based	CHD & NIDDM	PCR	54.9	64.3	Y
Li et al	2001	China	Asian	143	85	Hospital based	NIDDM	PCR	41.3	44.7	Y
				79	64	Hospital based	DN & NIDDM	PCR	39.2	43.8	Y
Petrovic et al	2003	Slovenia	European	154	194	Population based	MI & NIDDM	PCR	46.8	42.0	Y
Santos et al	2003	Brazil	European	99	111	Hospital based	DR & NIDDM	PCR	55.1	53.6	Y
Globocnik-P et al	2003	Slovenia	European	124	80	Hospital based	DR & NIDDM	PCR	45.2	43.8	Y
Lopes et al	2003	France	European	229	406	Population based	CHD & NIDDM	PCR	44.1	48.9	Y
Liu et al	2004	China	Asian	147	26	Hospital based	NIDDM	PCR	45.9	53.8	Y
				56	91	Hospital based	DR & NIDDM	PCR	50.0	43.4	Y
				77	70	Hospital based	DN & NIDDM	PCR	42.9	49.3	Y
Pan et al	2004	China	Asian	204	60	Hospital based	NIDDM	PCR	52.7	56.7	Y
Li et al	2004	China	Asian	54	54	Population based	NIDDM	PCR	42.6	46.3	Y
Murata et al	2004	Japan	Asian	188	92	Hospital based	DR & NIDDM	PCR	35.6	34.2	Y
Tang et al	2004	China	Asian	108	38	Hospital based	NIDDM	PCR	38.9	46.1	Y
				59	49		DN & NIDDM	PCR	31.4	48.0	Y
Wang et al	2004	China	Asian	114	30	Hospital based	NIDDM	PCR	34.6	61.7	Y
				76	38	Hospital based	DN & NIDDM	PCR	28.3	47.4	Y
Meigs et al	2006	USA	European	216	1953	Population based	DM	PCR	46.1	47.4	Y
Zietz et al	2006	Germany	European	192	312	Population based	DR & NIDDM	PCR	42.4	44.4	Y
				189	320	Population based	CHD & NIDDM	PCR	45.8	42.7	Y
Martin et al	2007	Ireland	European	222	361	Hospital based	DN & IDDM	PCR	42.8	44.5	Y
Zheng et al	2007	China	Asian	247	87	Hospital based	NIDDM	PCR	44.3	46.0	Y
				167	80	Hospital based	DN & NIDDM	PCR	40.7	51.9	Y
Saely et al	2008	Austria	European	148	524	Population based	NIDDM	PCR	43.9	47.6	Y
Yan et al 1	2008	China	Asian	66	33	Hospital based	NIDDM	PCR	50.8	56.1	Y
Yan et al 2	2008	China	Asian	217	58	Population based	NIDDM	PCR	53.9	79.3	Y
				125	92	Population based	DN & NIDDM	PCR	42.4	69.6	Y
Ezzidi et al	2009	Tunisia	European	383	473	Hospital based	DR & NIDDM	PCR	58.1	63.0	Y
Prasad et al	2010	India	Mix	196	225	Hospital based	DN & NIDDM	PCR	48.0	50.9	Y
Xue et al	2010	China	Asian	120	50	Hospital based	NIDDM	PCR	41.7	70.0	Y
				70	50	Hospital based	DN & NIDDM	PCR	20.7	71.0	Y

Table 1 Characteristics and genotype frequencies for the SERPINE1 rs1799889 SNP in the included studies *(Continued)*

Study	Year	Country	Ethnicity	Sample size Case/Control		Study type	Outcomes	Genotyping methods	5G allele frequency Case/Control (%)		HWE
Liu et al	2011	China	Asian	63	39	Hospital based	NIDDM	PCR	39.7	57.7	Y
				29	34	Hospital based	DN & NIDDM	PCR	44.8	35.3	Y
Tan et al	2011	China	Asian	30	50	Hospital based	CHD & NIDDM	PCR	35.0	48.0	Y
Al-Hamodi et al	2012	Malaysia	Asian	303	131	Population based	NIDDM	PCR	50.0	53.1	Y
Weng et al	2012	Taiwan	Asian	27	251	Hospital based	PTDM	PCR	53.7	40.0	Y
Xu et al	2016	China	Asian	107	101	Hospital based	NIDDM	PCR	37.9	47.0	Y
				65	42	Hospital based	DN & NIDDM	PCR	37.7	38.1	Y
Li et al	2018	China	Asian	175	125	Hospital based	IS & NIDDM	PCR	42.6	36.8	Y

CAD coronary artery disease, *CHD* coronary heart disease, *MI* myocardial infarction, *IS* ischemic stroke, *IDDM* insulin-dependent diabetes mellitus, *NIDDM* non-insulin-dependent diabetes mellitus, *PTDM* post-transplant diabetes mellitus, *PCR* polymerase chain reaction, *HWE* Hardy-Weinberg equilibrium, *Y* Yes

Fig. 1 Flow of studies for meta-analysis
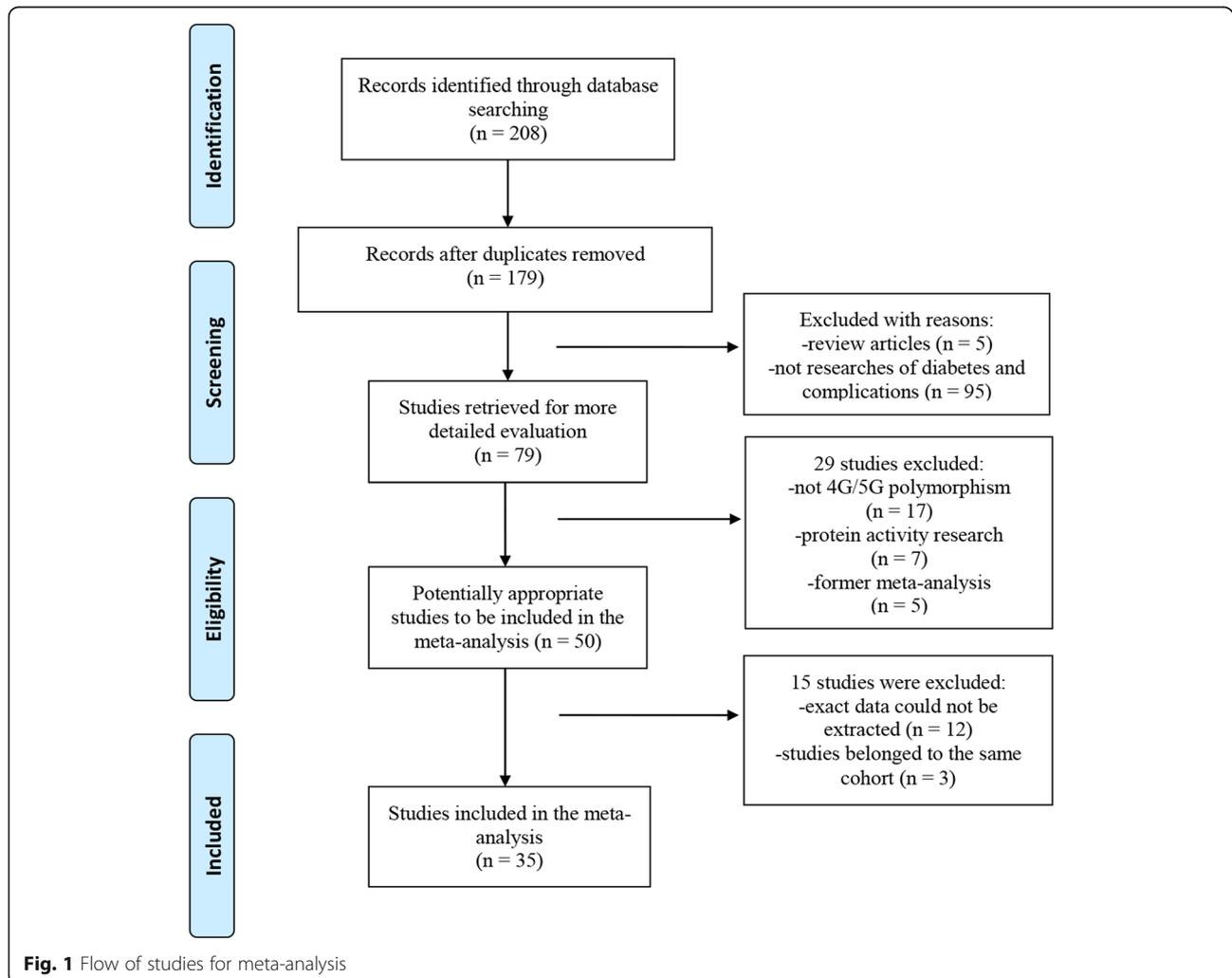
homozygous: OR = 1.88, 95 % CI = 1.29–2.75, p = 0.00; heterozygous: OR = 1.47, 95 % CI = 1.08-2.00, p = 0.01; dominant: OR = 1.64, 95 % CI = 1.21–2.24, p = 0.00; recessive: OR = 1.46, 95 % CI = 1.09–1.96, p = 0.01). Results of pooled analyses are summarized and presented in Table 2; Fig. 2.

Association of SERPINE1 rs1799889 SNP with DR risk
In overall population, a significant association between the SERPINE1 rs1799889 polymorphism and DR risk was observed in homozygous (4G4G vs. 5G5G: OR = 1.25, 95 % CI = 1.01–1.56, p = 0.04) and recessive (4G4G vs. 5G5G + 5G4G: OR = 1.20, 95 % CI = 1.01–1.43, p = 0.04) models, but no association was found in the other three genetic models. For the European subgroup, a significant association was revealed by homozygous (OR = 1.32, 95 % CI = 1.02–1.72, p = 0.04) and recessive model (OR = 1.38, 95 % CI = 1.11–1.71, $p < 0.01$), but no association was observed in the allelic, heterozygote, and dominant models. No significant associations were indicated among Asian descent in all genetic models. Results of pooled analyses are summarized and presented in Table 3; Fig. 3.

Association of SERPINE1 rs1799889 SNP with diabetic CVD risk
No significant association was implied between the SERPINE1 rs1799889 polymorphism and overall diabetic CVD risk in any genetic models. Additionally, after ethnicity stratification, no significant association was revealed either in European or Asian descent. Results of pooled analyses are summarized and presented in Table 4; Fig. 4.

Association of SERPINE1 rs1799889 SNP with DN risk
In overall population, significant associations were shown between the SERPINE1 rs1799889 polymorphism and overall diabetic nephropathy risk, in allelic (4G vs. 5G: OR = 1.48, 95 % CI = 1.15–1.90, p = 0.00), homozygous (4G4G vs. 5G5G: OR = 1.92, 95 % CI = 1.26–2.95, p = 0.00), dominant (4G4G + 4G5G vs. 5G5G: OR = 1.41, 95 % CI = 1.01–1.97, p = 0.04), and recessive (4G4G vs. 5G5G + 5G4G: OR = 1.78, 95 % CI = 1.27–2.51, p = 0.00) models. After subdivided by ethnicity, remarkable associations were observed in allelic (OR = 1.70, 95 % CI = 1.17–2.47, p = 0.01), homozygous (OR = 2.46, 95 % CI = 1.30–4.66, p = 0.01), and recessive (OR = 2.24, 95 % CI = 1.40–3.59, p = 0.00) models for Asian subgroup. On the contrary, no obvious associations were noted for the European using any of the five genetic models. Results of pooled analyses are summarized and presented in Table 5; Fig. 5.

Meta-regression analysis
A meta-regression analysis for the discovery of potential origins of heterogeneity, such as study type, published years, sample sizes, age, gender, ethnicity and outcomes, was conducted. Single covariates were added in the allelic, homozygous, heterozygous, dominant and recessive models. However, the results of meta-regression indicated that none of the above sources contributed to the heterogeneity across all studies of the association between SERPINE1 rs1799889 polymorphism and diabetic vascular susceptibility, since all the p values calculated were larger than 0.05.

Sensitivity analysis and publication bias
Sensitivity analysis with stratified analyses were conducted to examine the stability of our meta-analysis results. The high heterogeneity in some of the genetic models was obvious among studies except for the association with DR risk. On the association with DM and DN risk, a heterogeneity was detected within the overall analysis for the allelic model. On the association with DM, DR and DN risks, the heterogeneity in any genetic model was not significantly varied after either sensitivity analysis or sub-group analysis by ethnicity stratification. On the association with diabetic CVD risk, heterogeneity was noted for allelic/homozygote/recessive models, except for the European sub-group. After the sensitivity analysis, the study from Li et al. [12] were mainly responsible for the observed heterogeneity.

Potential publication bias in the current study was evaluated with Begg's and Egger's bias test. Publication bias was noted within DM sub-group with Egger test and DN sub-group for recessive model. Except for that, no obvious publication bias was observed in other comparisons, which confirmed that the results our meta-analysis presented were statistically robust (Table 6).

Discussion
The current meta-analysis suggests that the SERPINE1 rs1799889 4G polymorphism possesses a genetic modulatory function in overall DM populations and in diabetic renal vascular complications, which can be ethnically divergent according to the results. Genetic factors have long been considered a substantial determinant within the diabetic physical-sociocultural environment [55]. Positive family history might attribute a 2- to 4-fold increase in risk for diabetes [56]. The DCCT (Diabetes Control and Complications Trial) [57] and the EDIC (Epidemiology of Diabetes Interventions and Complications) [58] established that hyperglycemia is modified by both genetic determinants of individual susceptibility and by independent accelerating factors. Recently, large-scale genome wide association studies (GWAS) [59, 60] have identified hundreds of genetic risk variants, which in aggregate could explain the substantial role of genetic predisposition in DM. Additionally, one recent exome sequencing study [61] discovered additional genes and

Table 2 Overall and subgroup meta-analysis of the association between SERPINE1 rs1799889 SNP and risk of diabetes

Categories	n	4G vs. 5G			4G4G vs. 5G5G			4G5G vs. 5G5G			4G4G + 4G5G vs. 5G5G			4G4G vs. 5G5G + 5G4G		
		OR (95% CI)	P	I^2(%)/Ph	OR (95% CI)	P0.00	I^2(%)/Ph0.00/0.00	OR (95% CI)	P	I^2(%)/Ph	OR (95% CI)	P	I^2(%)/Ph	OR (95% CI)	P	I^2(%)/Ph
Overall	19	**1.34 (REM) (1.14–1.57)**	**0.001**	71 %/0.001	**1.62 (REM) (1.23–2.14)**	**0.001**	58 %/0.001	**1.35 (REM) (1.08–1.69)**	**0.001**	51 %/0.01	**1.49 (REM) (1.18–1.88)**	**0.001**	62 %/0.001	**1.30 (REM) (1.06–1.59)**	**0.01**	50 %/0.01
Subgroup (by population)																
European	3	1.07(0.94–1.23)	0.31	0 %/0.76	1.15(0.88–1.50)	0.31	0 %/0.69	1.10(0.86–1.40)	0.45	7 %/0.34	1.12(0.89–1.40)	0.35	0 %/0.43	1.08(0.88–1.33)	0.46	0 %/0.78
Asian	15	**1.45 (REM) (1.16–1.82)**	**0.001**	74 %/0.001	**1.88 (REM) (1.29–2.75)**	**0.001**	62 %/0.01	**1.47 (REM) (1.08–2.00)**	**0.01**	56 %/0.01	**1.64 (REM) (1.21–2.24)**	**0.001**	63 %/0.001	**1.46 (1.09–1.96)**	**0.01**	58 %/0.001
Others	1	1.13(0.85–1.51)	0.41	N/A	1.27(0.71–2.25)	0.42	N/A	1.20(0.74–1.95)	0.47	N/A	1.22(0.77–1.93)	0.39	N/A	1.13(0.70–1.83)	0.63	N/A

n: study numbers, OR: odds ratio, CI: confidence interval, bold values represent statistically significant findings, Ph: P heterogeneity (P < 0.1 was considered as a significant difference), REM: Random Effects Model

Chen *et al. BMC Endocrine Disorders*   (2021) 21:195

Page 8 of 18

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Study or Subgroup	Diabetes Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Hamodi 2012	303	606	123	262	6.5%	1.13 [0.85, 1.51]
De Cosmo 1999	320	622	204	400	6.8%	1.02 [0.79, 1.31]
Ding 2001	98	224	111	338	5.9%	1.59 [1.12, 2.25]
Kimura 1998	244	416	212	354	6.5%	0.95 [0.71, 1.27]
Li 2001	168	286	94	170	5.6%	1.15 [0.78, 1.69]
Li 2004	62	108	58	108	4.3%	1.16 [0.68, 1.99]
Liu 2004	159	294	24	52	3.9%	1.37 [0.76, 2.48]
Liu 2011	76	126	33	78	4.0%	2.07 [1.17, 3.68]
Meigs 2006	233	432	2053	3906	7.2%	1.06 [0.87, 1.29]
Pan 2004	193	408	52	120	5.4%	1.17 [0.78, 1.77]
Saely 2008	166	296	549	1048	6.7%	1.16 [0.90, 1.50]
Tang 2004	132	216	41	76	4.4%	1.34 [0.79, 2.27]
Wang 2004	149	228	23	60	3.9%	3.03 [1.69, 5.46]
Weng 2012	25	54	301	502	4.1%	0.58 [0.33, 1.01]
Xu 2016	133	214	107	202	5.5%	1.46 [0.99, 2.15]
Xue 2010	140	240	30	100	4.6%	3.27 [1.98, 5.38]
Yan 1 2008	65	132	29	66	3.9%	1.24 [0.68, 2.24]
Yan 2 2008	200	434	24	116	4.7%	3.28 [2.01, 5.33]
Zheng 2007	275	494	94	174	5.9%	1.07 [0.76, 1.51]
Total (95% CI)		**5830**		**8132**	**100.0%**	**1.34 [1.14, 1.57]**
Total events	3141		4162			

Heterogeneity: Tau² = 0.08; Chi² = 61.40, df = 18 (P < 0.00001); I² = 71%
Test for overall effect: Z = 3.49 (P = 0.0005)

B

Study or Subgroup	Diabetes Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Hamodi 2012	76	152	30	68	6.9%	1.27 [0.71, 2.25]
De Cosmo 1999	82	155	54	104	7.5%	1.04 [0.63, 1.71]
Ding 2001	25	64	23	104	6.2%	2.26 [1.14, 4.47]
Kimura 1998	64	92	66	97	6.6%	1.07 [0.58, 1.99]
Li 2001	52	79	24	39	5.4%	1.20 [0.54, 2.67]
Li 2004	18	28	15	26	3.8%	1.32 [0.44, 3.95]
Liu 2004	42	72	4	10	2.9%	2.10 [0.54, 8.09]
Liu 2011	23	33	15	36	4.3%	3.22 [1.19, 8.71]
Meigs 2006	65	113	529	958	8.3%	1.10 [0.74, 1.63]
Pan 2004	54	119	14	36	5.6%	1.31 [0.61, 2.79]
Saely 2008	44	70	148	271	7.2%	1.41 [0.82, 2.41]
Tang 2004	50	76	14	25	4.7%	1.51 [0.60, 3.80]
Wang 2004	56	77	7	21	4.1%	5.33 [1.89, 15.04]
Weng 2012	6	14	91	132	3.7%	0.34 [0.11, 1.04]
Xu 2016	40	54	29	52	5.3%	2.27 [1.00, 5.14]
Xue 2010	49	78	4	28	3.6%	10.14 [3.20, 32.14]
Yan 1 2008	17	35	8	20	3.8%	1.42 [0.47, 4.31]
Yan 2 2008	54	125	4	42	3.9%	7.23 [2.43, 21.48]
Zheng 2007	82	136	26	45	6.1%	1.11 [0.56, 2.20]
Total (95% CI)		**1572**		**2114**	**100.0%**	**1.62 [1.23, 2.14]**
Total events	899		1105			

Heterogeneity: Tau² = 0.20; Chi² = 43.18, df = 18 (P = 0.0008); I² = 58%
Test for overall effect: Z = 3.46 (P = 0.0005)

C

Study or Subgroup	Diabetes Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Hamodi 2012	151	227	63	101	7.4%	1.20 [0.74, 1.95]
De Cosmo 1999	156	229	96	146	7.9%	1.11 [0.72, 1.73]
Ding 2001	48	87	65	146	6.9%	1.53 [0.90, 2.62]
Kimura 1998	116	144	80	111	6.4%	1.61 [0.89, 2.88]
Li 2001	64	91	46	61	5.1%	0.77 [0.37, 1.61]
Li 2004	26	36	28	39	3.4%	1.02 [0.37, 2.80]
Liu 2004	75	105	16	22	3.3%	0.94 [0.33, 2.62]
Liu 2011	30	40	3	24	2.1%	21.00 [5.15, 85.63]
Meigs 2006	103	151	995	1424	8.8%	0.93 [0.64, 1.33]
Pan 2004	85	150	24	46	5.7%	1.20 [0.62, 2.33]
Saely 2008	78	104	253	376	7.3%	1.46 [0.89, 2.39]
Tang 2004	32	58	13	24	3.7%	1.04 [0.40, 2.71]
Wang 2004	37	58	9	23	3.5%	2.74 [1.01, 7.41]
Weng 2012	13	21	119	160	3.7%	0.56 [0.22, 1.45]
Xu 2016	53	67	49	72	4.8%	1.78 [0.82, 3.84]
Xue 2010	42	71	22	46	5.0%	1.58 [0.75, 3.34]
Yan 1 2008	31	49	13	25	3.6%	1.59 [0.60, 4.22]
Yan 2 2008	92	163	16	54	5.7%	3.08 [1.59, 5.96]
Zheng 2007	111	165	42	61	5.9%	0.93 [0.49, 1.75]
Total (95% CI)		**2016**		**2961**	**100.0%**	**1.35 [1.08, 1.69]**
Total events	1343		1952			

Heterogeneity: Tau² = 0.11; Chi² = 36.81, df = 18 (P = 0.006); I² = 51%
Test for overall effect: Z = 2.66 (P = 0.008)

D

Study or Subgroup	Diabetes Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Hamodi 2012	227	303	93	131	6.8%	1.22 [0.77, 1.93]
De Cosmo 1999	238	311	150	200	7.2%	1.09 [0.72, 1.64]
Ding 2001	73	112	88	169	6.5%	1.72 [1.05, 2.82]
Kimura 1998	180	208	146	177	6.1%	1.36 [0.78, 2.38]
Li 2001	116	143	70	85	5.0%	0.92 [0.46, 1.85]
Li 2004	44	54	43	54	3.6%	1.13 [0.43, 2.92]
Liu 2004	117	147	20	26	3.4%	1.17 [0.43, 3.17]
Liu 2011	53	63	18	39	3.8%	6.18 [2.46, 15.57]
Meigs 2006	168	216	1524	1953	7.7%	0.99 [0.70, 1.38]
Pan 2004	139	204	38	60	5.7%	1.24 [0.68, 2.26]
Saely 2008	122	148	401	524	6.7%	1.44 [0.90, 2.30]
Tang 2004	82	108	27	38	4.2%	1.28 [0.56, 2.94]
Wang 2004	93	114	16	30	4.1%	3.88 [1.64, 9.15]
Weng 2012	19	27	210	251	3.9%	0.46 [0.19, 1.13]
Xu 2016	93	107	78	101	4.8%	1.96 [0.94, 4.06]
Xue 2010	91	120	26	50	5.1%	2.90 [1.45, 5.80]
Yan 1 2008	48	66	21	33	3.9%	1.52 [0.62, 3.72]
Yan 2 2008	146	217	20	58	5.6%	3.91 [2.12, 7.20]
Zheng 2007	193	247	68	87	5.8%	1.00 [0.55, 1.80]
Total (95% CI)		**2915**		**4066**	**100.0%**	**1.49 [1.18, 1.88]**
Total events	2242		3057			

Heterogeneity: Tau² = 0.15; Chi² = 46.92, df = 18 (P = 0.0002); I² = 62%
Test for overall effect: Z = 3.37 (P = 0.0007)

E

Study or Subgroup	Diabetes Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Hamodi 2012	76	303	30	131	7.1%	1.13 [0.70, 1.83]
De Cosmo 1999	82	311	54	200	8.1%	0.97 [0.65, 1.45]
Ding 2001	25	112	23	169	5.6%	1.82 [0.98, 3.41]
Kimura 1998	64	208	66	177	7.8%	0.75 [0.49, 1.14]
Li 2001	52	143	24	85	6.0%	1.45 [0.81, 2.60]
Li 2004	18	54	15	54	4.0%	1.30 [0.57, 2.96]
Liu 2004	42	147	4	26	2.5%	2.20 [0.72, 6.77]
Liu 2011	23	63	15	39	4.0%	0.92 [0.40, 2.10]
Meigs 2006	65	216	529	1953	9.3%	1.16 [0.85, 1.58]
Pan 2004	54	204	14	60	5.1%	1.18 [0.60, 2.32]
Saely 2008	44	148	148	524	8.1%	1.07 [0.72, 1.60]
Tang 2004	50	108	14	38	4.4%	1.48 [0.69, 3.16]
Wang 2004	56	114	7	30	3.4%	3.17 [1.26, 7.98]
Weng 2012	6	27	91	251	3.3%	0.50 [0.20, 1.29]
Xu 2016	40	107	29	101	6.0%	1.48 [0.83, 2.65]
Xue 2010	49	120	4	50	2.7%	7.94 [2.68, 23.48]
Yan 1 2008	17	66	8	33	3.2%	1.08 [0.41, 2.86]
Yan 2 2008	54	217	4	58	2.8%	4.47 [1.55, 12.92]
Zheng 2007	82	247	26	87	6.5%	1.17 [0.69, 1.98]
Total (95% CI)		**2915**		**4066**	**100.0%**	**1.30 [1.06, 1.59]**
Total events	899		1105			

Heterogeneity: Tau² = 0.09; Chi² = 36.14, df = 18 (P = 0.007); I² = 50%
Test for overall effect: Z = 2.54 (P = 0.01)

Fig. 2 Forest plots of the association between SERPINE1 rs1799889 SNP and diabetes risk. (**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model

pathways for future target gene prioritization efforts and complications in DM [60]. Overall, the evidence jointly supports the theory that genetic factors significantly account for the pathogenesis of DM and its complications.

PAI-1 is a serine protease inhibitor protein encoded by the SERPINE1 gene that plays an important role in regulating fibrinolysis and thrombosis by inhibiting the activity of tissue plasminogen activator and urokinase plasminogen activator, whose activation is driven by tissue-type plasminogen activator (tPA) cleavage of plasminogen [62]. Previous human and animal PAI-1 studies have confirmed its effect on hemostasis and thrombolysis, where suppressing PAI-1 activity would resulted in a reduction of thrombus formation while activation of the PAI-1 promoted thrombus formation [63]. Classic studies have confirmed that high plasma levels of PAI-1 are associated with an increased risk of cardiovascular diseases [64, 65], and SERPINE1 allelic variations are also associated with the pathogenesis of metabolic syndrome, insulin resistance, and diabetes [66–68]. To date, several SERPINE1 polymorphisms have been identified, of which the SERPINE1 rs1799889–4G/5G insertion-deletion variant has been most consistently implicated with the plasma level of PAI-1 [68]. Unlike the 5G allele, which 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 [9]. In diabetic populations, PAI-1 levels are particularly connected to elevated fasting insulin levels and triglycerides, and inhibition of PAI-1 may have merit in patients at high cardiovascular risk [69].

Previous studies of the distribution of the SERPINE1 rs1799889 SNP have been controversial concerning the susceptibility of diabetes among various populations. Saely et al. [37] demonstrated no significant difference in the SERPINE1 4G/5G polymorphism between nondiabetic control subjects and diabetic patients. In contrast, Al-Hamodi et al. [41] suggested that the dominant and additive models showed a weak association with T2DM. Nagi et al. [23] reported preliminary findings indicating that in Pima Indians with type 2 diabetes, the presence of the 4G allele was associated with a higher risk of diabetic retinopathy. However, Santos et al. [34] indicated that the 4G/5G polymorphism was not related to the presence of DR in Euro-Brazilian patients. While Ezzidi et al. [40] identified that genetic variations served as risk factors for DR but not DR severity. Tarnow et al. [46] suggested that the SERPINE1 4G/5G polymorphism might not contribute to the genetic susceptibility to diabetic nephropathy or retinopathy. In contrast, Prasad et al. [48] and Xu et al. [13] demonstrated major associations with the SERPINE1 rs1799889 4G polymorphism and the progression of diabetic nephropathy. Mansfield

Table 3 Overall and subgroup meta-analysis of the association between SERPINE1 rs1799889 SNP and risk of diabetic retinopathy

Categories	n	4G vs. 5G			4G4G vs. 5G5G			4G5G vs. 5G5G			4G4G + 4G5G vs. 5G5G			4G4G vs. 5G5G + 5G4G		
		OR (95% CI)	P	I² (%)/ Ph	OR (95% CI)	P	I² (%)/ Ph	OR(95% CI)	P	I² (%)/ Ph	OR(95% CI)	P	I² (%)/ Ph	OR(95% CI)	P	I² (%)/ Ph
Overall	10	1.08(0.97–1.20)	0.15	28 %/0.19	1.25(1.01–1.56)	**0.04**	23 %/0.23	1.00 (REM)(0.76–1.32)	0.97	44 %/0.06	1.03(0.87–1.23)	0.71	13 %/0.32	1.20(1.01–1.43)	**0.04**	23 %/0.23
Subgroup (by population)																
European	5	1.12(0.98–1.27)	0.09	0 %/0.66	1.32(1.02–1.72)	**0.04**	26 %/0.25	0.88(0.71–1.09)	0.24	0 %/0.55	1.00(0.82–1.22)	0.98	0 %/0.63	1.38(1.11–1.71)	**0.001**	26 %/0.25
Asian	4	0.90(0.73–1.11)	0.34	22 %/0.28	0.94(0.60–1.45)	0.77	0 %/0.56	0.95(0.63–1.45)	0.83	5 %/0.37	0.94(0.63–1.39)	0.75	6 %/0.36	0.93(0.68–1.26)	0.63	0 %/0.56
Others	1	1.61(1.04–2.48)	0.03	N/A	2.53(0.98–6.55)	0.06	N/A	3.18(1.47–6.86)	0.003	N/A	2.27(1.07–4.82)	0.03	N/A	1.17(0.54–2.53)	0.70	N/A

n: study numbers, OR: odds ratio, CI: confidence interval, bold values represent statistically significant findings, Ph: P heterogeneity (*P* < 0.1 was considered as a significant difference), REM: Random Effects Model
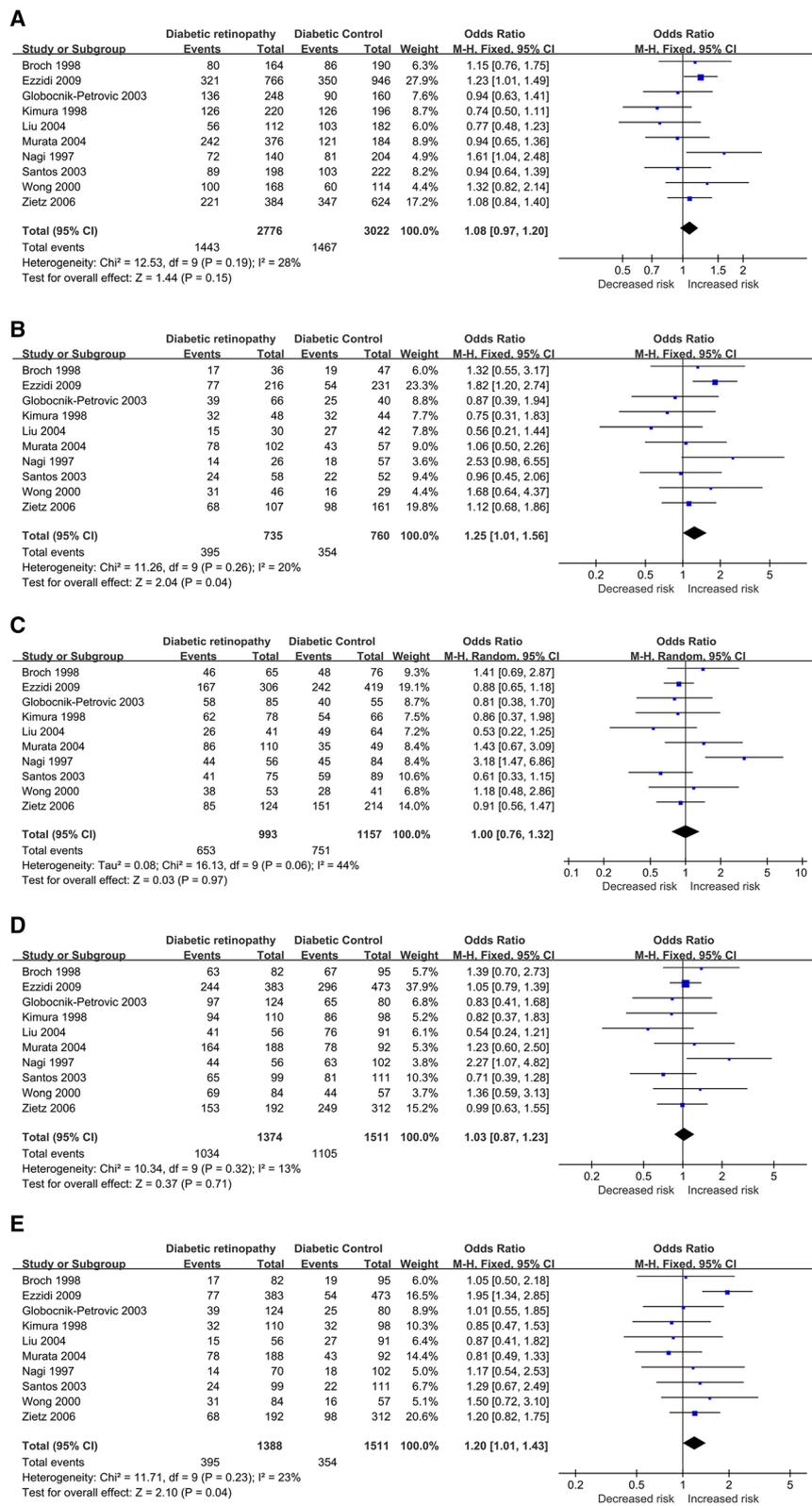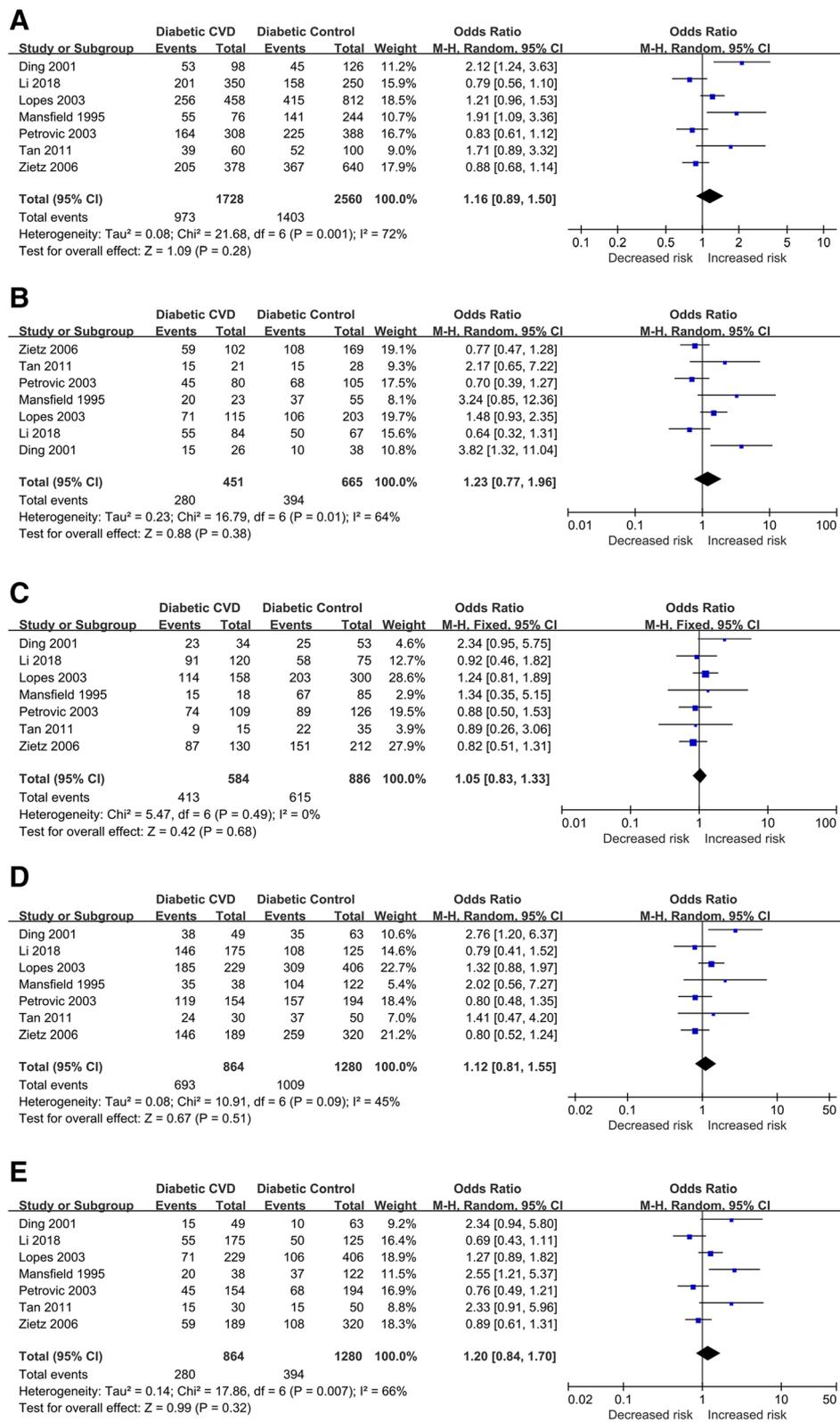
Fig. 3 Forest plots of the association between SERPINE1 rs1799889 SNP and DR risk. (**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model (DR: diabetic retinopathy)

Table 4 Overall and subgroup meta-analysis of the association between SERPINE1 rs1799889 SNP and risk of diabetic CVD

Categories	n	4G vs. 5G			4G4G vs. 5G5G			4G5G vs. 5G5G			4G4G + 4G5G vs. 5G5G			4G4G vs. 4G5G + 5G5G		
		OR (95% CI)	P	I² (%)/ Ph	OR (95% CI)	P0.00	I² (%)/ Ph0.00/0.00	OR(95% CI)	P	I² (%)/ Ph	OR(95% CI)	P	I² (%)/ Ph	OR(95% CI)	P	I² (%)/ Ph
Overall	7	1.16(0.89–1.50)	0.28	72 %/0.001	1.23(0.77–1.96)	0.38	64 %/0.01	1.05 (FEM)(0.83–1.33)	0.68	0 %/0.49	1.12(0.81–1.55)	0.51	45 %/0.09	1.20(0.84–1.70)	0.32	66 %/0.01
Subgroup (by population)																
European	4	1.07(0.81–1.42)	0.63	70 %/0.02	1.08(0.65–1.80)	0.77	62 %/0.05	1.00 (FEM)(0.77–1.31)	0.97	0 %/0.56	1.12 (FEM)(0.89–1.40)	0.35	0 %/0.43	1.13(0.76–1.68)	0.54	67 %/0.03
Asian	3	1.37(0.69–2.73)	0.37	82 %/0.001	1.64(0.52–5.23)	0.40	76 %/0.02	1.24(0.66–2.33)	0.50	32 %/0.23	1.41(0.63–3.13)	0.40	63 %/0.07	1.45(0.57–3.65)	0.43	77 %/0.01

n: study numbers, OR: odds ratio, CI: confidence interval, bold values represent statistically significant findings, *Ph*: *P* heterogeneity (*P* < 0.1 was considered as a significant difference), FEM: Fix Effects Model, CVD: Cardiovascular disease
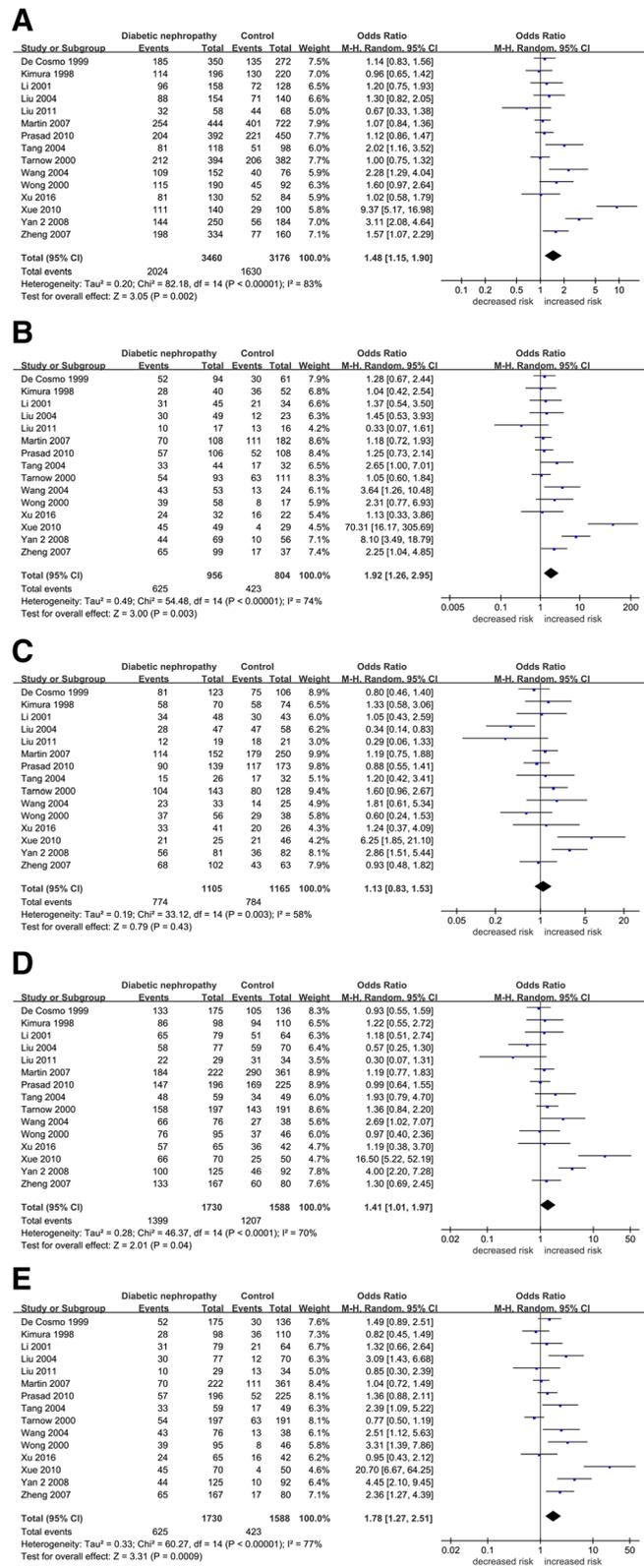
Fig. 4 Forest plots of the association between SERPINE1 rs1799889 SNP and diabetic CVD risk. (**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model (CVD: cardiovascular disease)

Table 5 Overall and subgroup meta-analysis of the association between SERPINE1 rs1799889 SNP and risk of diabetic nephropathy

Categories	n	4G vs. 5G			4G4G vs. 5G5G			4G5G vs. 5G5G			4G4G + 4G5G vs. 5G5G			4G4G vs. 5G5G + 5G4G		
		OR (95 %CI)	P	I² (%)/ Ph	OR (95 %CI)	P0.00	I² (%)/ Ph0.00/0.00	OR(95 %CI)	P	I² (%)/ Ph	OR(95 %CI)	P	I² (%)/ Ph	OR(95 %CI)	P	I² (%)/ Ph
Overall	15	1.48 (REM) (1.15–1.90)	**0.001**	83 %/0.001	1.92 (REM) (1.26–2.95)	**0.001**	74%/0.001	1.13 (REM)(0.83–1.53)	0.43	58 %/0.001	1.41 (REM) (1.01–1.97)	**0.04**	70 %/0.001	1.78 (REM) (1.27–2.51)	**0.001**	77 %/0.001
Subgroup (by population)																
European	3	1.06(0.91–1.24)	0.45	0%/0.82	1.16(0.84–1.60)	0.37	0%/0.90	1.17(0.88–1.57)	0.28	38 %/0.20	1.16(0.88–1.53)	0.28	0 %/0.59	1.04(0.74–1.46)	0.84	46 %/0.15
Asian	11	1.70 (REM) (1.17–2.47)	**0.01**	84%/0.001	2.46 (REM) (1.30–4.66)	**0.01**	76%/0.001	1.15 (REM)(0.71–1.86)	0.56	65 %/0.001	1.59 (REM)(0.94–2.69)	0.08	75 %/0.001	2.24 (REM) (1.40–3.59)	**0.001**	75 %/0.001
Others	1	1.12(0.86–1.47)	0.40	N/A	1.25(0.73–2.14)	0.41	N/A	0.88(0.55–1.41)	0.59	N/A	0.99(0.64–1.55)	0.98	N/A	1.36(0.88–2.11)	0.16	N/A

n: study numbers, OR: odds ratio, CI: confidence interval, bold values represent statistically significant findings, *Ph*: *P* heterogeneity (*P* < 0.1 was considered as a significant difference), REM: Random Effects Model

A

Study or Subgroup	Diabetic nephropathy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
De Cosmo 1999	185	350	135	272	7.5%	1.14 [0.83, 1.56]
Kimura 1998	114	196	130	220	7.0%	0.96 [0.65, 1.42]
Li 2001	96	158	72	128	6.5%	1.20 [0.75, 1.93]
Liu 2004	88	154	71	140	6.6%	1.30 [0.82, 2.05]
Liu 2011	32	58	44	68	5.0%	0.67 [0.33, 1.38]
Martin 2007	254	444	401	722	7.9%	1.07 [0.84, 1.36]
Prasad 2010	204	392	221	450	7.7%	1.12 [0.86, 1.47]
Tang 2004	81	118	51	98	6.0%	2.02 [1.16, 3.52]
Tarnow 2000	212	394	206	382	7.7%	1.00 [0.75, 1.32]
Wang 2004	109	152	40	76	5.9%	2.28 [1.29, 4.04]
Wong 2000	115	190	45	92	6.3%	1.60 [0.97, 2.64]
Xu 2016	81	130	52	84	5.9%	1.02 [0.58, 1.79]
Xue 2010	111	140	29	100	5.8%	9.37 [5.17, 16.98]
Yan 2 2008	144	250	56	184	7.0%	3.11 [2.08, 4.64]
Zheng 2007	198	334	77	160	7.1%	1.57 [1.07, 2.29]
Total (95% CI)		3460		3176	100.0%	1.48 [1.15, 1.90]
Total events	2024		1630			

Heterogeneity: Tau² = 0.20; Chi² = 82.18, df = 14 (P < 0.00001); I² = 83%
Test for overall effect: Z = 3.05 (P = 0.002)

B

Study or Subgroup	Diabetic nephropathy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
De Cosmo 1999	52	94	30	61	7.9%	1.28 [0.67, 2.44]
Kimura 1998	28	40	36	52	6.8%	1.04 [0.42, 2.54]
Li 2001	31	45	21	34	6.6%	1.37 [0.54, 3.50]
Liu 2004	30	49	12	23	6.3%	1.45 [0.53, 3.93]
Liu 2011	10	17	13	16	4.2%	0.33 [0.07, 1.61]
Martin 2007	70	108	111	182	8.6%	1.18 [0.72, 1.93]
Prasad 2010	57	106	52	108	8.4%	1.25 [0.73, 2.14]
Tang 2004	33	44	17	32	6.5%	2.65 [1.00, 7.01]
Tarnow 2000	54	93	63	111	8.3%	1.05 [0.60, 1.84]
Wang 2004	43	53	13	24	6.1%	3.64 [1.26, 10.48]
Wong 2000	39	58	8	17	5.9%	2.31 [0.77, 6.93]
Xu 2016	24	32	16	22	5.4%	1.13 [0.33, 3.86]
Xue 2010	45	49	4	29	4.5%	70.31 [16.17, 305.69]
Yan 2 2008	44	69	10	56	7.1%	8.10 [3.49, 18.79]
Zheng 2007	65	99	17	37	7.4%	2.25 [1.04, 4.85]
Total (95% CI)		956		804	100.0%	1.92 [1.26, 2.95]
Total events	625		423			

Heterogeneity: Tau² = 0.49; Chi² = 54.48, df = 14 (P < 0.00001); I² = 74%
Test for overall effect: Z = 3.00 (P = 0.003)

C

Study or Subgroup	Diabetic nephropathy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
De Cosmo 1999	81	123	75	106	8.9%	0.80 [0.46, 1.40]
Kimura 1998	58	70	58	74	6.5%	1.33 [0.58, 3.06]
Li 2001	34	48	30	43	6.0%	1.05 [0.43, 2.59]
Liu 2004	28	47	47	58	6.2%	0.34 [0.14, 0.83]
Liu 2011	12	19	18	21	3.0%	0.29 [0.06, 1.33]
Martin 2007	114	152	179	250	9.9%	1.19 [0.75, 1.88]
Prasad 2010	90	139	117	173	9.8%	0.88 [0.55, 1.41]
Tang 2004	15	26	17	32	5.1%	1.20 [0.42, 3.41]
Tarnow 2000	104	143	80	128	9.4%	1.60 [0.96, 2.67]
Wang 2004	23	33	14	25	4.9%	1.81 [0.61, 5.34]
Wong 2000	37	56	29	38	5.8%	0.60 [0.24, 1.53]
Xu 2016	33	41	20	26	4.3%	1.24 [0.37, 4.09]
Xue 2010	21	25	21	46	4.2%	6.25 [1.85, 21.10]
Yan 2 2008	56	81	36	82	8.1%	2.86 [1.51, 5.44]
Zheng 2007	68	102	43	63	7.9%	0.93 [0.48, 1.82]
Total (95% CI)		1105		1165	100.0%	1.13 [0.83, 1.53]
Total events	774		784			

Heterogeneity: Tau² = 0.19; Chi² = 33.12, df = 14 (P = 0.003); I² = 58%
Test for overall effect: Z = 0.79 (P = 0.43)

D

Study or Subgroup	Diabetic nephropathy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
De Cosmo 1999	133	175	105	136	8.3%	0.93 [0.55, 1.59]
Kimura 1998	86	98	94	110	6.5%	1.22 [0.55, 2.72]
Li 2001	65	79	51	64	6.3%	1.18 [0.51, 2.74]
Liu 2004	58	77	59	70	6.4%	0.57 [0.25, 1.30]
Liu 2011	22	29	31	34	3.5%	0.30 [0.07, 1.31]
Martin 2007	184	222	290	361	8.9%	1.19 [0.77, 1.83]
Prasad 2010	147	196	169	225	8.9%	0.99 [0.64, 1.55]
Tang 2004	48	59	34	49	6.0%	1.93 [0.79, 4.70]
Tarnow 2000	158	197	143	191	8.6%	1.36 [0.84, 2.20]
Wang 2004	66	76	27	38	5.6%	2.69 [1.02, 7.07]
Wong 2000	76	95	37	46	6.0%	0.97 [0.40, 2.36]
Xu 2016	57	65	36	42	4.7%	1.19 [0.38, 3.70]
Xue 2010	66	70	25	50	4.7%	16.50 [5.22, 52.19]
Yan 2 2008	100	125	46	92	7.8%	4.00 [2.20, 7.28]
Zheng 2007	133	167	60	80	7.6%	1.30 [0.69, 2.45]
Total (95% CI)		1730		1588	100.0%	1.41 [1.01, 1.97]
Total events	1399		1207			

Heterogeneity: Tau² = 0.28; Chi² = 46.37, df = 14 (P < 0.0001); I² = 70%
Test for overall effect: Z = 2.01 (P = 0.04)

E

Study or Subgroup	Diabetic nephropathy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
De Cosmo 1999	52	175	30	136	7.6%	1.49 [0.89, 2.51]
Kimura 1998	28	98	36	110	7.3%	0.82 [0.45, 1.49]
Li 2001	31	79	21	64	6.7%	1.32 [0.66, 2.64]
Liu 2004	30	77	12	70	6.3%	3.09 [1.43, 6.68]
Liu 2011	10	29	13	34	5.0%	0.85 [0.30, 2.39]
Martin 2007	70	222	111	361	8.4%	1.04 [0.72, 1.49]
Prasad 2010	57	196	52	225	8.1%	1.36 [0.88, 2.11]
Tang 2004	33	59	17	49	6.3%	2.39 [1.09, 5.22]
Tarnow 2000	54	197	63	191	8.1%	0.77 [0.50, 1.19]
Wang 2004	43	76	13	38	6.1%	2.51 [1.12, 5.63]
Wong 2000	39	95	8	46	5.8%	3.31 [1.39, 7.86]
Xu 2016	24	65	16	42	6.2%	0.95 [0.43, 2.12]
Xue 2010	45	70	4	50	4.6%	20.70 [6.67, 64.25]
Yan 2 2008	44	125	10	92	6.4%	4.45 [2.10, 9.45]
Zheng 2007	65	167	17	80	7.1%	2.36 [1.27, 4.39]
Total (95% CI)		1730		1588	100.0%	1.78 [1.27, 2.51]
Total events	625		423			

Heterogeneity: Tau² = 0.33; Chi² = 60.27, df = 14 (P < 0.00001); I² = 77%
Test for overall effect: Z = 3.31 (P = 0.0009)

Fig. 5 Forest plots of the association between SERPINE1 rs1799889 SNP and DN risk. (**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model (DN: diabetic nephropathy)

Table 6 Publication bias assessment of this meta-analysis

Genetic model	Egger's test		Begg's test	
	t-value	*p*	t-value	*p*
Diabetes				
Allelic model	2.96	*0.01*	2.72	*0.01*
Homozygote model	2.99	*0.01*	2.96	*0.001*
Heterozygote model	3.11	*0.01*	2.11	0.04
Dominant model	2.48	*0.02*	1.99	0.05
Recessive model	2.23	*0.03*	1.87	0.06
Diabetic retinopathy				
Allelic model	-0.98	0.36	0.00	1.00
Homozygote model	-1.88	0.10	0.36	0.72
Heterozygote model	0.74	0.48	0.54	0.59
Dominant model	0.04	0.97	0.00	1.00
Recessive model	-1.39	0.20	0.00	1.00
Diabetic CVD				
Allelic model	1.88	0.12	1.20	0.23
Homozygote model	1.49	0.20	0.60	0.55
Heterozygote model	0.62	0.56	0.90	0.37
Dominant model	1.13	0.31	0.90	0.37
Recessive model	1.88	0.12	0.30	0.76
Diabetic nephropathy				
Allelic model	1.18	0.09	1.98	0.05
Homozygote model	1.63	0.13	1.48	0.14
Heterozygote model	-0.11	0.91	0.00	1.00
Dominant model	0.61	0.55	0.69	0.49
Recessive model	3.05	*0.01*	2.18	*0.03*

P ≺ 0.05 was considered as a significant difference

et al. [22] and Lopes et al. [31] have proved the synergistic effect between the SERPINE1 4G/5G polymorphism and CVD, suggesting its potential correlation with insulin-resistance and obesity. Nevertheless, Petrovic et al. [29] found no association between this polymorphism and myocardial infarction.

Our results revealed an obvious difference in the association of the SERPINE1 rs1799889 SNP among individuals with Asian and European descent, implying that the heterogeneity is based on ethnicity. Concerning the association with diabetes risk, our results suggested that the 4G polymorphism is a genetic risk factor in overall populations. Moreover, after stratification by ethnicity, the results revealed a remarkable association with Asian descent, while no association was found for European diabetic populations. A previous meta-analysis showed different results [11]. Regarding the association with DR risk, our results differed from Zhang et al. [10] but were in concordance with Xu et al. [11]. In our analysis, we included a novel German study [36]. Additionally, both random and fixed effects model was adapted to

demonstrate less bias and to confirm a robust conclusion. Since our meta-analysis has included recent published studies and larger sample sizes, we suppose it could provide better reliability. We hypothesize that these factors might contribute to the disparities with other studies. Concerning the association with diabetic CVD risk, our results coincided with a previous analysis [11], which proved no significant association despite the inclusion of recent studies [12]. This result was to some extent disparate from other analyses concerning PAI-1 polymorphisms in atherosclerotic diseases [70] and suggests that the underlying mechanism for the SERPINE1 4G/5G polymorphism might be conducted through different pathways in diabetic CVD. Concerning the association with DN risk, our results indicated a strong linkage between SERPINE1 4G polymorphism and DN risk in the overall and Asian populations. This is consistent with former studies [25, 71] and further implies that heterogeneity is affected by ethnicity. Moreover, insufficient genetic data in mix ethnicities could limit the possibility of further discussion regarding this population, which to a considerable extent could alter the overall analyses. To our knowledge, the current meta-analysis includes the largest sample size to date with the most extensive case-control studies, and demonstrates an ethnicity-based evaluation for different results among studies. The association with ischemic stroke in the diabetic population was not further evaluated in the present study owing to limitations of available trails, but would be an important topic for consideration in future studies concerning diabetic atherothrombotic complications. In addition, future investigations are also warranted to discover the possible functions of other SERPINE1 gene polymorphisms in DM and its complications.

Since our meta-analysis was conducted with stratified ethnicity, the origins of heterogeneity must be given thorough discussion. In our analysis, heterogeneity was revealed among people of Asian descent both in the CVD and DN subgroups. We speculate that the sources of heterogeneity in studies might include age and gender proportion, ethnic traits, environmental factors, medication status, health care quality and cultural differences. A meta-regression analysis was done by study type, published years, age, gender, ethnicity, sample sizes, and outcomes. However, the results did not indicate the sources of heterogeneity, since all the p values calculated above were larger than 0.05. As we speculated, meta-regression is usually conducted in studies with larger sample sizes and study sub-groups, whose effect might be restrained in this case. Moreover, the gene-gene and gene-environmental interactions might also trigger the heterogeneity of genetic effects between individual studies.

There were several limitations included in our meta-analysis: (1) insufficient genotyping data of SERPINE1

rs1799889 SNP in mix ethnicity, which limited the possibility to further discussions regarding this population, and (2) potential heterogeneity of study variables, such as the biological parameters of study subjects, clinical history, medication compliance, other diabetic complications, etc. and (3) the Begg's and Egger's test have given some potential publication bias, indicating the importance of a well-matched case-control study population. (4) Sample size is another limitation, some of the original studies analyzed presented relatively small control groups, and the minor allele frequency (G or 5G; MAF) of the control populations analyzed are heterogeneous, between 34.2 and 71 %, including among studies in the same ethnicity group and also in the same study among different analyzed groups. (5) Insufficiency of original studies of type 1 DM has restrained a further subgroup analysis concerning the classification of DM.

Conclusions

Collectively, our meta-analysis demonstrates that the SERPINE1 rs1799889 4G polymorphism may outstand for serving as a genetic synergistic factor in overall DM populations, and overall DN populations. Moreover, it can be positively associated with increased DM and DN risks for individuals with Asian descent. The association of SERPINE1 rs1799889 polymorphisms and DR or diabetic CVD risks was not revealed by our meta-analysis. However, future studies with multiple ethnicities and rigorous designs are still in-need to confirm our conclusions.

Abbreviations
DM: diabetes mellitus; SERPINE1: serine protease inhibitor-1; SNP: single nucleotide polymorphism; PAI-1: plasminogen activator inhibitor-1; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; DR: diabetic retinopathy; DN: diabetic nephropathy; CAD/CHD: coronary artery/ heart disease; CVD: cardiovascular disease; OR: odds ratio; CI: confidence interval; DCCT: Diabetes Control and Complications Trial; EDIC: Epidemiology of Diabetes Interventions and Complications; GWAS: Genome Wide Association Studies; tPA: tissue-type plasminogen activator

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-021-00837-z.

Additional file 1: Supplementary Table 1. Newcastle–Ottawa scale (NOS) for assessing quality of observational studies.

Additional file 2: Supplementary Table 2. Search strategy for PubMed.

Additional file 3: Supplementary Fig. 1. Cumulative meta-analysis of the chronologic integration between SERPINE1 rs1799889 SNP and diabetes risk. (**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model.

Additional file 4: Supplementary Fig. 2. Begg's funnel plot of bias for studies of the association between SERPINE1 rs1799889 SNP and diabetes risk. (**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model.

Additional file 5: Supplementary Fig. 3. Begg's funnel plot of bias for studies of the association between SERPINE1 rs1799889 SNP and DR risk.

(**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model.

Additional file 6: Supplementary Fig. 4. Begg's funnel plot of bias for studies of the association between SERPINE1 rs1799889 SNP and CVD risk. (**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model.

Additional file 7: Supplementary Fig. 5. Begg's funnel plot of bias for studies of the association between SERPINE1 rs1799889 SNP and DN risk. (**A**) allelic model, (**B**) homozygote model, (**C**) heterozygote model, (**D**) dominant model, and (**E**) recessive model.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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

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