RESEARCH ARTICLE

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 % Cl = 1.14–1.57, homozygous: OR = 1.66, 95 % Cl = 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 (SER-PINE) 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 SNPrs1799889 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 casecontrol 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 randomeffects 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 betweenstudy 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;

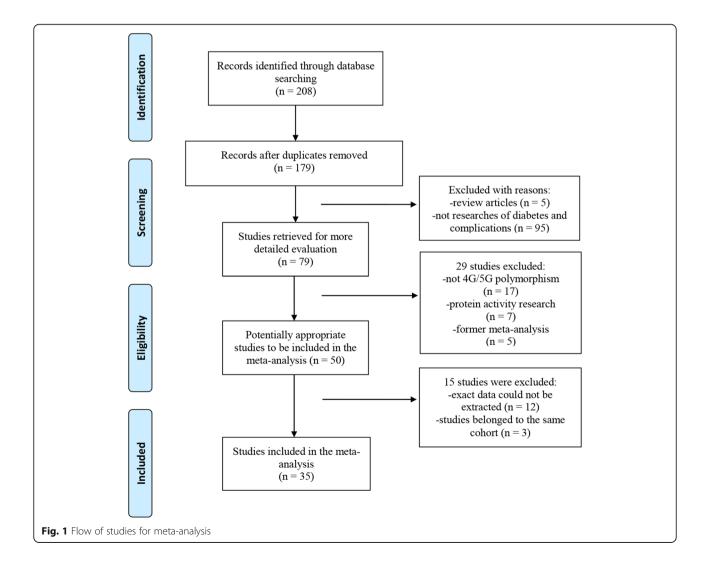
Table 1 Characteristics and genotype frequencies for the SERPINE1 rs1799889 SNP in the included studies

Study	Year	Country	Ethnicity	Sam		Study type	Outcomes	Genotyping	5G allel	e frequency	HWE
				size Cont	Case/ rol			methods	Case/Co	ntrol (%)	
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	Υ
Broch et al	1998	Spain	European	82	95	Hospital based	DR & NIDDM	PCR	51.2	54.7	Υ
Kimura et al	1998	Japan	Asian	208	177	Population based	NIDDM	PCR	41.3	40.1	Υ
				110	98	Population based	PDR & NIDDM	PCR	42.7	39.8	Υ
				110	98	Population based	DN & NIDDM	PCR	41.8	40.9	Υ
De Cosmo et al	1999	Italy & UK	European	311	200	Population based	IDDM	PCR	48.6	49.0	Υ
				175	136	Population based	DN & IDDM	PCR	47.1	50.4	Υ
Wong et a	2000	Hong Kong	Asian	84	57	Hospital based	DR & NIDDM	PCR	40.5	47.4	Υ
				95	46	Hospital based	DN & NIDDM	PCR	39.5	51.1	Υ
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	Υ
				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	Υ
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	Sam	•	Study type	Outcomes	Genotyping	5G alle	e frequency	HWE
				size Con	Case/ trol			methods	Case/Co	ontrol (%)	
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 noninsulin-dependent diabetes mellitus, PTDM post-transplant diabetes mellitus, PCR polymerase chain reaction, HWE Hardy-Weinberg equilibrium, Y Yes



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 SER-PINE1 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 metaanalysis presented were statistically robust (Table 6).

Discussion

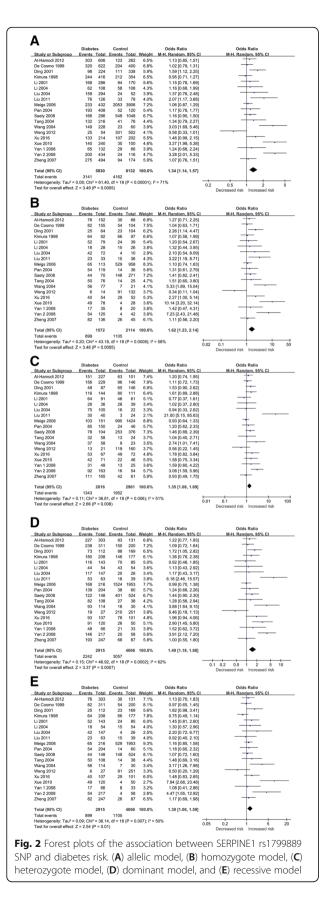
The current meta-analysis suggests that the SERPINE1 rs1799889 4G polymorphism possesses a genetic modulatory function in overall DM populations and in diabetic renal vascular complications, which can be ethnically divergent according to the results. Genetic factors have long been considered a substantial 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, largescale 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

Categories	Categories n 4G vs. 5G			4G4G vs. 5G5G			4G5G vs. 5G5G			4G4G + 4G5G vs. 5G5G	's. 5G5G		4G4G vs. 5G5G + 5G4G	+ 5G4(
	OR (95%	CI)	OR (95% CI) P I ² (%)/Ph	OR (95% CI)	P0.00	OR (95% CI) P0.00 1 ² (%)/Ph0.00/0.00 OR (95%	OR (95% CI)	٩	l²(%)/Ph	OR (95% CI)	٩	l²(%)/ <i>P</i> h	OR (95% CI)	م	1 ² (%)/ <i>P</i> h
Overall	19 1.34 (REM) (1.14–1.57)	() ()	19 1.34 (REM) 0.001 71 % 0.001 1.62 (REM) (1.14-1.57) (1.23-2.14) (1.23-2.14)		0.001	0.001 58 %/0.001	1.35 (REM) (1.08–1.69)	0.001	51 %/0.01	0.001 51%/0.01 1.49 (REM) (1.18–1.88)	0.001	0.001 62%/0.001 1.30 (REM) (1.06–1.59)	1.30 (REM) (1.06–1.59)	0.01	0.01 50 %/0.01
Subgroup (by population)	Ē														
European	3 1.07(0.94-	1.23) 0.31	European 3 1.07(0.94–1.23) 0.31 0 %/0.76	1.15(0.88–1.50) 0.31	0.31	0 %/0.69	1.10(0.86–1.40) 0.45	0.45	7 %/0.34	7 %/0.34 1.12(0.89–1.40) 0.35	0.35	0 %/0.43	1.08(0.88-1.33) 0.46 0 %/0.78	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	0.001 63 %/0.001	1.46 (1.09–1.96)	0.01	0.01 58 %/0.001
Others	1 1.13(0.85-1.51) 0.41 N/A	1.51) 0.41	N/A	1.27(0.71–2.25) 0.42	0.42	N/A	1.20(0.74-1.95) 0.47 N/A	0.47	N/A	1.22(0.77–1.93) 0.39	0.39	N/A	1.13(0.70–1.83) 0.63	0.63	N/A
n: study numk Effects Model	bers, OR: odds	ratio, CI:	confidence inte	erval, bold values	represer	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	cant findings, <i>P</i> h.	: P hete	rogeneity (P	< 0.1 was consi	dered a:	s a significan	it difference), REM	A: Rano	mo

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

 Categories n
 4G vs. 5G5
 4G
 4G

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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 insertiondeletion 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

Categories		Categories n 4G vs. 5G			4G4G vs. 5G5G			4G5G vs. 5G5G			4G4G + 4G5G vs. 5G5G	s. 5G5((7	4G4G vs. 5G5G + 5G4G	564G	
		OR (95% CI)	٩	l ² (%)/ Ph	OR (95% CI) P I ² (%)/ Ph OR (95% CI)	P0.00	P0.00 1 ² (%)/ Ph0.00/0.00	OR(95% CI)	Р	l ² (%)/ Ph	P 1 ² (%)/ Ph OR(95% CI) P 1 ² (%)/ Ph C	٩	l ² (%)/ Ph	OR(95% CI) P I ² (%)/ Ph	٩	l ² (%)/ Ph
Overall	10	1.08(0.97-1.20)	0.15	28 %/0.19	Dverall 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	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)	dod /	ulation)														
European	Ś	1.12(0.98-1.27)	0.09	0 %/0.66	uropean 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	0.98		1.38(1.11–1.71) 0.001 26 %/0.25	0.001	26 %/0.25
Asian	4	0.90(0.73-1.11) 0.34 22 %/0.28	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	-	1.61(1.04–2.48) 0.03	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	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

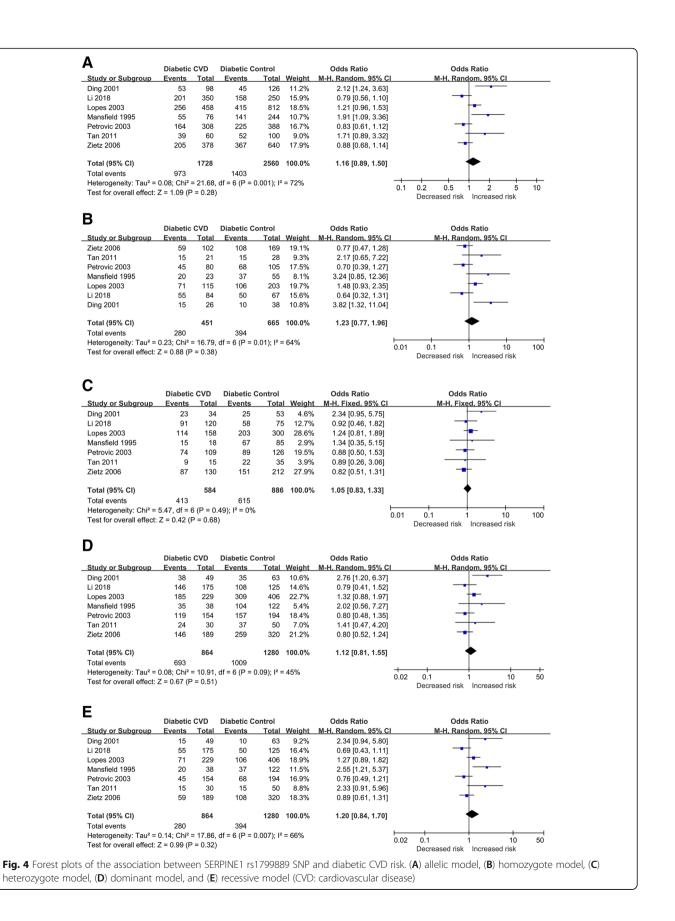
Table 3 Overall and subgroup meta-analysis of the association between SERPINE1 rs1799889 SNP and risk of diabetic retinopathy Categories

o	Diabatic	athy	Diabeti-	ontr-1		Odda D-4:-	Odda Patia
	Diabetic retinopa Events	athy Total	Diabetic C Events		Weight	Odds Ratio M-H. Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup Broch 1998	80	164	Events 86	190	6.3%	1.15 [0.76, 1.75]	
Ezzidi 2009	321	766	350	946	6.3% 27.9%	1.15 [0.76, 1.75]	- -
Globocnik-Petrovic 2003	136	248	350 90		27.9% 7.6%		
				160		0.94 [0.63, 1.41]	
Kimura 1998	126	220	126	196	8.7%	0.74 [0.50, 1.11]	-
Liu 2004	56	112	103	182	6.0%	0.77 [0.48, 1.23]	
Murata 2004	242	376	121	184	8.9%	0.94 [0.65, 1.36]	
Nagi 1997	72	140	81	204	4.9%	1.61 [1.04, 2.48]	·
Santos 2003	89	198	103	222	8.2%	0.94 [0.64, 1.39]	
Wong 2000	100	168	60	114	4.4%	1.32 [0.82, 2.14]	
Zietz 2006	221	384	347	624	17.2%	1.08 [0.84, 1.40]	
Total (95% CI)		2776		3022	100.0%	1.08 [0.97, 1.20]	◆
Total events	1443		1467				
Heterogeneity: Chi ² = 12.53		$l^2 = 28^{\circ}$					
Test for overall effect: Z = 1							0.5 0.7 1 1.5 2
	,						Decreased risk Increased risk
_							
В	Diabetic retinopa	athy	Diabetic C	Control		Odds Ratio	Odds Ratio
Study or Subgroup		Total	Events		Weight	M-H, Fixed, 95% CI	M-H. Fixed. 95% Cl
Broch 1998	17	36	19	47	6.0%	1.32 [0.55, 3.17]	
Ezzidi 2009	77	216	54	231	23.3%	1.82 [1.20, 2.74]	
Globocnik-Petrovic 2003	39	66	25	40	8.8%	0.87 [0.39, 1.94]	
Kimura 1998	32	48	32	44	7.7%	0.75 [0.31, 1.83]	
Liu 2004	15	30	27	42	7.8%	0.56 [0.21, 1.44]	
Murata 2004	78	102	43	57	9.0%	1.06 [0.50, 2.26]	
Nagi 1997	14	26	18	57	3.6%	2.53 [0.98, 6.55]	
Santos 2003	24	58	22	52	9.4%	0.96 [0.45, 2.06]	
Wong 2000	31	46	16	29	4.4%	1.68 [0.64, 4.37]	
Zietz 2006	68	107	98	161	19.8%	1.12 [0.68, 1.86]	
			50	.01			
Total (95% CI)		735		760	100.0%	1.25 [1.01, 1.56]	•
Total events	395		354	100	/0		· ·
		12 - 000					
Heterogeneity: Chi ² = 11.26		i [*] = 20%	70				0.2 0.5 1 2 5
Test for overall effect: Z = 2	2.04 (P = 0.04)						Decreased risk Increased risk
-							
С							
	Diabetic retinopat		Diabetic Co			Odds Ratio	Odds Ratio
Study or Subgroup			Events			M-H, Random, 95% C	I M-H. Random. 95% CI
Broch 1998	46	65	48	76	9.3%	1.41 [0.69, 2.87]	
Ezzidi 2009	167	306	242	419	19.1%	0.88 [0.65, 1.18]	
Globocnik-Petrovic 2003	58	85	40	55	8.7%	0.81 [0.38, 1.70]	
Kimura 1998	62	78	54	66	7.5%	0.86 [0.37, 1.98]	
Liu 2004	26	41	49	64	7.2%	0.53 [0.22, 1.25]	
Murata 2004	86	110	35	49	8.4%	1.43 [0.67, 3.09]	
Nagi 1997	44	56	45	84	8.4%	3.18 [1.47, 6.86]	
Santos 2003	41	75	59	89	10.6%	0.61 [0.33, 1.15]	
Wong 2000	38	53	28	41	6.8%	1.18 [0.48, 2.86]	
	85	124	151	214	14.0%	0.91 [0.56, 1.47]	
Zietz 2006							
Zietz 2006							
Total (95% CI)	650	993		1157	100.0%	1.00 [0.76, 1.32]	+
Total (95% CI) Total events	653 Chi ² = 16.13. df = 9		751		100.0%	1.00 [0.76, 1.32]	+ + + + + + + + + + + + + + + + + + + +
Total (95% CI)	Chi ² = 16.13, df = 9		751		100.0%	1.00 [0.76, 1.32]	0.1 0.2 0.5 1 2 5 10 Decreased risk
Total (95% CI) Total events Heterogeneity: Tau² = 0.08;	Chi ² = 16.13, df = 9		751		100.0%	1.00 [0.76, 1.32]	0.1 0.2 0.5 1 2 5 10 Decreased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0.	Chi ² = 16.13, df = 9 .03 (P = 0.97)	9 (P = 0.	751 .06); I² = 44	1%	100.0%	1.00 [0.76, 1.32]	
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0.	Chi ² = 16.13, df = 9 .03 (P = 0.97) Diabetic retinopa	9 (P = 0. athy	751 .06); I² = 44 Diabetic C	l% Control		Odds Ratio	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D	Chi ² = 16.13, df = 9 .03 (P = 0.97) Diabetic retinopa Events	9 (P = 0. athy Total	751 .06); I² = 44 Diabetic C <u>Events</u>	l% Control Total	Weight	Odds Ratio M-H. Fixed. 95% CI	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998	Chi ² = 16.13, df = 9 .03 (P = 0.97) Diabetic retinopa	9 (P = 0. athy	751 .06); I² = 44 Diabetic C	l% Control		Odds Ratio	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D	Chi ² = 16.13, df = 9 .03 (P = 0.97) Diabetic retinopa Events	9 (P = 0. athy Total	751 .06); I² = 44 Diabetic C <u>Events</u>	l% Control Total	Weight	Odds Ratio M-H. Fixed. 95% CI	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998	Chi ² = 16.13, df = 9 .03 (P = 0.97) Diabetic retinopa <u>Events</u> 63	9 (P = 0. athy <u>Total</u> 82	751 .06); I ² = 44 Diabetic C <u>Events</u> 67	1% Control <u>Total</u> 95	Weight 5.7%	Odds Ratio <u>M-H. Fixed, 95% CI</u> 1.39 [0.70, 2.73]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globacnik-Petrovic 2003	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopa <u>Events</u> 63 244	9 (P = 0. athy <u>Total</u> 383 124	751 .06); l ² = 44 Diabetic C <u>Events</u> 67 296 65	Control Total 95 473	<u>Weight</u> 5.7% 37.9% 6.8%	Odds Ratio <u>M-H. Fixed. 95% Cl</u> 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneiity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzdi 2009 Globocnik-Petrovic 2003 Kimura 1998	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopa Events 63 244 97 94	athy Total 82 383 124 110	751 .06); I ² = 44 Diabetic C <u>Events</u> 67 296 65 86	Control Total 95 473 80	Weight 5.7% 37.9% 6.8% 5.2%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopa Events 63 244 97 94 41	athy Total 82 383 124 110 56	751 0.06); l ² = 44 Diabetic C Events 67 296 65 86 86 76	2000 Total 95 473 80 98 91	Weight 5.7% 37.9% 6.8% 5.2% 6.1%	Odds Ratio M-H, Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopa Events 63 .244 .97 .94 .41 .164	e (P = 0. athy <u>Total</u> 82 383 124 110 56 188	751 006); I ² = 44 Diabetic C Events 67 296 65 86 76 78	20000000000000000000000000000000000000	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.38] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Nagi 1997	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopa <u>Events</u> 63 244 97 94 41 164 44	e (P = 0. athy <u>Total</u> 82 383 124 110 56 188 56	751 .06); ² = 44 Diabetic C Events 67 296 65 86 78 66 78 63	20000000000000000000000000000000000000	Weight 5.7% 6.8% 5.2% 6.1% 5.3% 3.8%	Odds Ratio <u>M-H. Fixad. 95% CI</u> 1.59 [0.70, 2.73] 1.55 [0.79, 1.39] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [107, 4.82]	Decreased risk Increased risk Odds Ratio
Total (95% C1) Total events Heterogeneity: Tau ⁵ = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Globocnik-Petrovic 2003 Kimura 1997 Santos 2003	Chi ^p = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopa <u>Events</u> 244 97 94 41 164 45	athy Total 82 383 124 110 56 188 56 99	751 (06); l ² = 44 Diabetic C Events 67 296 65 86 76 78 63 86 78 83 81	Control Total 95 473 80 98 91 92 102 111	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Nagi 1997 Santos 2003	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopa <u>Events</u> 63 244 94 41 164 44 65 69	athy <u>Total</u> 82 383 124 110 56 188 56 99 84	751 .06); i² = 44 Diabetic C Events 67 296 65 86 76 78 63 81 44	Control Total 95 473 80 98 91 92 102 102 111 57	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3% 3.7%	Odds Ratio <u>M-H. Fixed. 95% CI</u> 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.82 [0.37, 1.83] 0.42 [0.37, 1.83] 0.42 [0.37, 1.83] 0.45 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13]	Decreased risk Increased risk Odds Ratio
Total (95% C1) Total events Heterogeneity: Tau ⁵ = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Globocnik-Petrovic 2003 Kimura 1997 Santos 2003	Chi ^p = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopa <u>Events</u> 244 97 94 41 164 45	athy Total 82 383 124 110 56 188 56 99	751 (06); l ² = 44 Diabetic C Events 67 296 65 86 76 78 63 86 78 83 81	Control Total 95 473 80 98 91 92 102 111	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3% 3.7%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Nagi 1997 Santos 2003 Wong 2000 Zietz 2006	Chi ² = 16.13, df = § .03 (P = 0.97) Diabetic retinopa <u>Events</u> 63 244 97 94 41 164 44 65 69 153	e (P = 0. athy <u>Total</u> 82 383 124 110 56 188 56 99 84 192	751 .06); i² = 44 Diabetic C Events 67 296 65 86 76 78 63 81 44	Control Total 95 473 80 98 91 92 102 111 57 312	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3% 3.7% 15.2%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.33 [0.41, 1.68] 0.62 [0.37, 1.83] 0.64 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Nagi 1997 Santos 2003 Zietz 2006 Total (95% CI)	Chi ² = 16.13, df = 5 Chi ² = 16.13, df = 5 Chi ² = 10, 37 Diabetic retinopa <u>Events</u> 63 244 97 94 41 164 44 65 69 153	athy <u>Total</u> 82 383 124 110 56 188 56 99 84	751 Diabetic C Events 67 296 65 86 76 65 86 76 63 81 44 249	Control Total 95 473 80 98 91 92 102 111 57 312	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3% 3.7%	Odds Ratio <u>M-H. Fixed. 95% CI</u> 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.82 [0.37, 1.83] 0.42 [0.37, 1.83] 0.44 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ⁵ = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Globocnik-Petrovic 2003 Kimura 1999 Santos 2003 Wong 2000 Zietz 2006 Total (95% CI) Total events	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopz <u>Events</u> 63 244 97 94 41 164 44 65 69 153 1034	athy Total 82 383 124 110 56 188 56 99 84 192 1374	751 06); ² = 44 Diabetic C Events 67 296 65 86 76 78 83 81 44 249 1105	Control Total 95 473 80 98 91 92 102 111 57 312	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3% 3.7% 15.2%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.33 [0.41, 1.68] 0.62 [0.37, 1.83] 0.64 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55]	Decreased risk Increased risk Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Murata 2004 Murata 2004 Nagi 1997 Santos 2003 Zietz 2006 Total (95% CI) Total events Heterogeneity: Ch ² = 10.34	Chi ² = 16.13, df = § Chi ² = 16.13, df = § Diabetic retinopa <u>Events</u> 63 244 94 41 164 44 65 69 153 1034 4, df = 9 (P = 0.32);	athy Total 82 383 124 110 56 188 56 99 84 192 1374	751 06); ² = 44 Diabetic C Events 67 296 65 86 76 78 83 81 44 249 1105	Control Total 95 473 80 98 91 92 102 111 57 312	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3% 3.7% 15.2%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.33 [0.41, 1.68] 0.62 [0.37, 1.83] 0.64 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55]	Decreased risk Odds Ratio M-H. Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Tau ⁵ = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Globocnik-Petrovic 2003 Kimura 1999 Santos 2003 Wong 2000 Zietz 2006 Total (95% CI) Total events	Chi ² = 16.13, df = § Chi ² = 16.13, df = § Diabetic retinopa <u>Events</u> 63 244 94 41 164 44 65 69 153 1034 4, df = 9 (P = 0.32);	athy Total 82 383 124 110 56 188 56 99 84 192 1374	751 06); ² = 44 Diabetic C Events 67 296 65 86 76 78 83 81 44 249 1105	Control Total 95 473 80 98 91 92 102 111 57 312	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3% 3.7% 15.2%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.33 [0.41, 1.68] 0.62 [0.37, 1.83] 0.64 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55]	Odds Ratio M-H. Fixed, 95% Cl
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Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Murata 2004 Murata 2004 Nagi 1997 Santos 2003 Zietz 2006 Total (95% CI) Total events Heterogeneity: Ch ² = 10.34	$\begin{array}{l} {\rm Chi}^{2}=16.13,{\rm df}=5\\ .03({\rm P}=0.97)\\ \hline \\ \hline \\ {\rm Diabetic retinops}\\ \hline \\ {\rm Events}\\ \hline \\ 63\\ 2244\\ 94\\ 41\\ 164\\ 44\\ 65\\ 69\\ 153\\ \hline \\ 1034\\ 4,{\rm df}=9({\rm P}=0.32);\\ .37({\rm P}=0.71)\\ \end{array}$	9 (P = 0. athy Total 82 383 124 110 56 99 84 192 1374 I ² = 13 ⁹	751 Diabetic C Events 67 296 65 86 76 65 86 78 63 81 44 249 1105 %	Control Total 95 473 80 91 92 102 1111 57 312 1511	Weight 5.7% 37.9% 6.8% 5.2% 6.1% 5.3% 3.8% 10.3% 3.7% 15.2%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.62 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23]	Decreased risk Increased risk
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Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Murata 2004 Murata 2004 Murata 2004 Murata 2004 Murata 2004 Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003	Chi ² = 16.13, df = § .03 (P = 0.97) Diabetic retinopz <u>Events</u> 63 244 94 41 164 44 65 69 153 1034 4, df = 9 (P = 0.32); .37 (P = 0.71) Diabetic retinopz <u>Events</u> 17 77 39	θ (P = 0. athy Total 82 383 124 110 56 99 84 192 1374 1 ² = 13 ⁹ athy Total 82 383 124 1374 12 1374 12 12 12 12 1374 12 12 12 12 12 12 1374 12 12 12 12 1374 12 12 1374 12 12 1374 12 1374 12 1374 12 1374 12 1374 12 1374 12 1374 12 1374 12 1374 12 1374 12 1374 12 12 1374 12 12 1374 12 12 1374 12 12 1374 12 12 12 1374 12 12 12 1374 12 12 12 1374 12 12 12 12 12 1374 12 12 12 12 12 1374 12 12 12 12 12 1374 12 12 12 12 12 1374 12 12 12 12 12 12 1374 12 12 12 12 12 12 12 1374 12 12 12 12 12 12 12 12 1374 12 12 12 12 12 12 12 12 12 12	751 0.06); ² = 44 Diabetic C Events 67 296 65 86 76 65 86 78 63 81 44 249 1105 % Diabetic C Events 1105 %	% Control Total 95 473 80 98 97 102 102 102 102 102 102 102 102	Weight 5.7% 6.8% 5.2% 10.3% 3.7% 100.0% Weight 6.0% 8.9%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.63 [0.53, 1.55] 1.03 [0.87, 1.23] Odds Ratio M-H. Fixed, 95% CI 1.05 [0.50, 2.18] 1.95 [1.34, 2.85] 1.01 [0.55, 1.85]	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1997 Santos 2003 Vong 2000 Zietz 2006 Total (95% CI) Total (95% CI) Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998	Chi ² = 16.13, df = § .03 (P = 0.97) Diabetic retinopa <u>Events</u> 63 244 94 41 164 44 65 66 9 153 1034 4, df = 9 (P = 0.32); .37 (P = 0.71) Diabetic retinopa <u>Events</u> 17 77 39 32	 e) (P = 0. athy Total 82 383 124 110 56 188 56 99 84 192 1374 I² = 139 athy Total 82 383 124 110 	751 Diabetic C Events 67 296 65 86 78 63 81 44 249 1105 % Diabetic C Events 10 54 25 32	50000000000000000000000000000000000000	Weight 5.7% 5.2% 6.8% 5.2% 5.3% 3.8% 3.7% 10.3% 3.7% 10.3% 15.2% 100.0%	Odds Ratio <u>M-H. Fixed. 95% C1</u> 1.59 [0.70, 2.73] 1.55 [0.79, 1.39] 0.82 [0.37, 1.83] 0.42 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio <u>M-H. Fixed. 95% C1</u> 1.05 [0.47, 1.53] 0.55 [0.47, 1.53]	Decreased risk Increased risk
Total (95% C1) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Murata 2004 Murata 2004 Nagi 1997 Santos 2003 Wong 2000 Zietz 2006 Total (95% C1) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004	Chi ² = 16.13, df = § .03 (P = 0.97) Diabetic retinopz Events 63 244 94 41 164 44 65 69 153 1034 4, df = 9 (P = 0.32); .37 (P = 0.71) Diabetic retinopz Events 17 77 39 32 15	 θ (P = 0. athy Total 82 383 124 1374 82 84 192 1374 1374 82 383 124 110 56 	751 0.06); ² = 44 Diabetic C Events 67 296 65 86 76 63 81 44 249 1105 % Diabetic C Events 19 54 25 32 27	% Control <u>Total</u> 95 473 80 98 91 102 102 102 111 57 312 1511 57 57 312 1511 57 57 312 1511 57 57 312 1511 57 57 312 1511 57 57 57 151 1511 57 151 151	Weight 5.7% 6.8% 5.2% 6.1% 5.3% 3.3% 3.7% 15.2% 100.0% Weight 16.5% 8.9% 10.3%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [10.7, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio M-H. Fixed, 95% CI 1.05 [0.50, 2.18] 1.95 [1.34, 2.86] 1.01 [0.55, 1.85] 0.87 [0.41, 1.82]	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1997 Santos 2003 Vong 2000 Zietz 2006 Total (95% CI) Total (95% CI) Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998	Chi ² = 16.13, df = § .03 (P = 0.97) Diabetic retinopa <u>Events</u> 63 244 94 41 164 44 65 66 9 153 1034 4, df = 9 (P = 0.32); .37 (P = 0.71) Diabetic retinopa <u>Events</u> 17 77 39 32	 e) (P = 0. athy Total 82 383 124 110 56 188 56 99 84 192 1374 I² = 139 athy Total 82 383 124 110 	751 Diabetic C Events 67 296 65 86 78 63 81 44 249 1105 % Diabetic C Events 10 54 25 32	50000000000000000000000000000000000000	Weight 5.7% 5.2% 6.8% 5.2% 5.3% 3.8% 3.7% 10.3% 3.7% 10.3% 15.2% 100.0%	Odds Ratio <u>M-H. Fixed. 95% C1</u> 1.59 [0.70, 2.73] 1.55 [0.79, 1.39] 0.82 [0.37, 1.83] 0.42 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio <u>M-H. Fixed. 95% C1</u> 1.05 [0.47, 1.53] 0.55 [0.47, 1.53]	Decreased risk Increased risk
Total (95% C1) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Murata 2004 Murata 2004 Nagi 1997 Santos 2003 Wong 2000 Zietz 2006 Total (95% C1) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004	Chi ² = 16.13, df = § .03 (P = 0.97) Diabetic retinopz Events 63 244 94 41 164 44 65 69 153 1034 4, df = 9 (P = 0.32); .37 (P = 0.71) Diabetic retinopz Events 17 77 39 32 15	 θ (P = 0. athy Total 82 383 124 1374 82 84 192 1374 1374 82 383 124 110 56 	751 0.06); ² = 44 Diabetic C Events 67 296 65 86 76 63 81 44 249 1105 % Diabetic C Events 19 54 25 32 27	% Control <u>Total</u> 95 473 80 98 91 102 102 102 111 57 312 1511 57 57 312 1511 57 57 312 1511 57 57 312 1511 57 57 312 1511 57 57 57 151 1511 57 151 151	Weight 5.7% 6.8% 5.2% 6.1% 5.3% 3.3% 3.7% 15.2% 100.0% Weight 16.5% 8.9% 10.3%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [10.7, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio M-H. Fixed, 95% CI 1.05 [0.50, 2.18] 1.95 [1.34, 2.86] 1.01 [0.55, 1.85] 0.87 [0.41, 1.82]	Decreased risk Increased risk
Total (95% C1) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Magi 1997 Santos 2003 Zietz 2006 Total (95% C1) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Murata 2004 Magi 1997	Chi ² = 16.13, df = § .03 (P = 0.97) Diabetic retinops <u>Events</u> 63 244 94 44 164 44 65 69 153 1034 4, df = 9 (P = 0.32); 0.37 (P = 0.71) Diabetic retinops <u>Events</u> 17 77 39 32 15 78	θ (P = 0. athy <u>Total</u> 82 383 124 110 56 99 984 192 1374 I ² = 139 82 383 82 383 124 110 56 82 1374 12 1374 12 1374 12 1374 124 137	751 0.06); ² = 44 Diabetic C 67 296 65 86 76 63 81 44 249 1105 % Diabetic C Events 19 54 25 32 27 43	Sontrol Total 95 473 90 80 91 92 102 111 57 312 1511 Control 95 473 95 473 90 91 92	Weightt 5.7% 6.8% 6.1% 5.2% 6.1% 5.3.8% 10.3% 10.2% 10.0.0%	Odds Ratio <u>M-H. Fixed, 95% CI</u> 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.83 [0.41, 1.68] 0.22 [0.71, 183] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [10.7, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio <u>M-H. Fixed, 95% CI</u> 1.05 [0.50, 2.18] 1.95 [1.34, 2.85] 1.04 [0.54, 1.82] 0.87 [0.41, 1.82] 0.87 [0.41, 1.82] 0.81 [0.42, 4.253]	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Magi 1997 Santos 2003 Vietz 2006 Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 Broch 1998 Ezidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 1909 Slobocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Maria 1997 Santos 2003	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopy <u>Events</u> 63 244 94 44 45 69 153 1034 4, df = 9 (P = 0.32); .37 (P = 0.71) Diabetic retinopy <u>Events</u> 17 77 39 32 15 78 14 24	e) (P = 0. athy Total 82 383 124 110 56 84 192 1374 ² = 139 athy Total 82 383 124 1374 ² = 139 124 1374 ² = 139 ³ = 139 	751 .06); ² = 44 Events 67 296 65 86 76 65 86 76 78 63 81 44 249 1105 % Diabetic C Events 19 54 25 32 27 43 18 22	Scontrol Total 95 473 80 98 192 102 1111 57 1511 57 1511 55 473 312 1511 57 56 473 312 1511 95 473 80 98 98 99 98 91 92 95 473 80 98 91 92 102 102 102 102 102 102 102 10	Weight 5.7% 6.8% 5.2% 6.8% 10.3% 10.3% 10.3% 10.3% 10.0% Weight 4.6% 6.6% 4.4% 5.0%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.33 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [10.7, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] M-H. Fixed, 95% CI 1.05 [1.34, 2.85] 1.01 [0.55, 1.85] 0.87 [0.41, 1.82] 0.81 [0.49, 1.33] 1.79 [0.67, 2.49] 1.29 [0.67, 2.49]	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0.0 D Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Marata 2004 Magi 1997 Santos 2003 Viong 2000 Zietz 2006 Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Murata 2004 Murata 2004 Magi 1997 Santos 2003	Chi ² = 16.13, df = § .03 (P = 0.97) Diabetic retinopa Events 63 244 97 94 41 164 44 65 66 9 153 1034 4, df = 9 (P = 0.32); 0.37 (P = 0.71) Diabetic retinopa Events 17 77 39 32 15 78 14 24 31	Θ (P = 0. athy Total 82 383 124 110 56 188 56 99 84 192 1374 I ² = 13 ⁹ athy Total I ² = 13 ⁹ 1374 I ² = 13 ⁹ 110 56 1374 I ² = 13 ⁹ 110 110 56 82 84 84 84 84 84 84 84 84 84 84	751 0.06); I ² = 44 0.06); I ² = 44 67 296 65 86 76 78 63 81 44 249 1105 % Diabetic C Events 19 54 25 32 27 43 18 22 16	% Control Total 95 473 80 98 91 92 102 111 57 312 1511 1511 57 7 312 1511 1511 757 80 98 91 92 92 92 92 92 92 92 93 94 93 94 95 95 95 95 95 95 95 95 95 95 95 95 95	Weight: 5.7% 6.8% 6.1% 5.3% 6.1% 5.3% 10.3% 10.3% 10.0% 100.0%	Odds Ratio <u>M-H. Fixed. 95% CI</u> 1.39 [0.70, 2.73] 1.55 [0.79, 1.39] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [107, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio <u>M-H. Fixed. 95% CI</u> 1.05 [0.50, 2.18] 1.95 [1.34, 2.85] 1.01 [0.55, 1.85] 0.87 [0.41, 1.82] 0.87 [0.41, 1.82] 0.81 [0.49, 1.33] 1.71 [0.54, 2.53] 1.29 [0.67, 2.41] 1.50 [0.7, 2.310]	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Magi 1997 Santos 2003 Vietz 2006 Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 Broch 1998 Ezidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 1909 Slobocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Maria 1997 Santos 2003	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinopz <u>Events</u> 63 244 94 44 164 44 65 69 153 1034 4, df = 9 (P = 0.32); .37 (P = 0.71) Diabetic retinopz <u>Events</u> 17 77 39 32 15 78 14 24	e) (P = 0. athy Total 82 383 124 110 56 84 192 1374 ² = 139 athy Total 82 383 124 1374 ² = 139 124 1374 ² = 139 ³ = 139 	751 .06); ² = 44 Events 67 296 65 86 76 65 86 76 78 63 81 44 249 1105 % Diabetic C Events 19 54 25 32 27 43 18 22	Scontrol Total 95 473 80 98 192 102 1111 57 1511 57 1511 55 473 312 1511 57 57 473 312 1511 95 473 80 98 98 99 98 91 92 95 473 80 98 91 92 95 95 95 95 95 95 95 95 95 95	Weight 5.7% 6.8% 5.2% 6.8% 10.3% 10.3% 10.3% 10.3% 10.0% Weight 4.6% 6.6% 4.4% 5.0%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.70, 2.73] 1.05 [0.79, 1.39] 0.33 [0.41, 1.68] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [10.7, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] M-H. Fixed, 95% CI 1.05 [1.34, 2.85] 1.01 [0.55, 1.85] 0.87 [0.41, 1.82] 0.81 [0.49, 1.33] 1.79 [0.67, 2.49] 1.29 [0.67, 2.49]	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0.0 D Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Marata 2004 Magi 1997 Santos 2003 Viong 2000 Zietz 2006 Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Murata 2004 Murata 2004 Magi 1997 Santos 2003	Chi ² = 16.13, df = 5 .03 (P = 0.97) Diabetic retinops <u>Events</u> 63 244 94 41 164 44 65 69 153 1034 4, df = 9 (P = 0.32); 0.37 (P = 0.71) Diabetic retinops <u>Events</u> 17 77 39 32 15 78 14 24 31 68	Θ (P = 0. athy Total 82 383 124 110 56 188 56 99 84 192 1374 I ² = 13 ⁹ athy Total I ² = 13 ⁹ 1374 I ² = 13 ⁹ 110 56 1374 I ² = 13 ⁹ 110 110 56 82 84 84 84 84 84 84 84 84 84 84	751 0.06); I ² = 44 0.06); I ² = 44 67 296 65 86 76 78 63 81 44 249 1105 % Diabetic C Events 19 54 25 32 27 43 18 22 16	% Control Total 95 473 80 98 91 92 102 1111 57 312 1511 Control Total 473 80 0 8 91 122 1511 57 312 1511 57 312 1511 1511 57 312 1511 157 1511 157 1511 157 1511 157 151 157 151 157 151 157 157	Weight: 5.7% 6.8% 6.1% 5.3% 6.1% 5.3% 10.3% 10.3% 10.0% 100.0%	Odds Ratio <u>M-H. Fixed. 95% CI</u> 1.39 [0.70, 2.73] 1.05 [0.79, 1.38] 0.82 [0.37, 1.83] 0.42 [0.37, 1.83] 0.44 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio <u>M'H. Fixed. 95% CI</u> 1.05 [0.50, 2.18] 1.95 [1.34, 2.85] 1.01 [0.55, 1.85] 0.47 [0.49, 1.33] 1.77 [0.54, 2.53] 1.29 [0.67, 2.49] 1.50 [0.72, 3.10] 1.20 [0.82, 1.75]	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Ezzidi 2009 Globconik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Nagi 1997 Santos 2003 Vieng 2000 Zietz 2006 Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Ezzidi 2009 Globconik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2000 Zietz 2006 Total (95% CI)	$\begin{array}{l} {\rm Chi}^{2}=16.13,{\rm df}=5\\ .03({\rm P}=0.97)\\ \hline \\ {\rm Diabetic retinopr}\\ \hline {\rm Events}\\ \hline \\ 63\\ 244\\ 94\\ 41\\ 164\\ 45\\ 69\\ 153\\ \hline \\ 1034\\ 4,{\rm df}=9({\rm P}=0.32);\\ {\rm argmatrix}\\ 1034\\ 4,{\rm df}=9({\rm P}=0.32);\\ {\rm argmatrix}\\ \hline \\ {\rm Diabetic retinopr}\\ \hline \\ \hline \\ {\rm Events}\\ \hline \\ 17\\ 77\\ 39\\ 32\\ 15\\ 78\\ 14\\ 24\\ 31\\ 68\\ \end{array}$	θ (P = 0. athy Total 82 383 124 110 56 188 56 99 84 192 1374 192 1374 82 383 124 192 1374 82 383 124 192 1374 82 383 124 192 1374 82 383 124 192 1374 82 84 105 105 105 105 105 105 105 105	751 0.06); ² = 44 Diabetic C Events 67 296 65 86 76 63 81 44 249 1105 % Diabetic C Events 10 54 25 32 27 43 18 22 16 98	% Control Total 95 473 80 98 91 92 102 1111 57 312 1511 Control Total 473 80 0 8 91 122 1511 57 312 1511 57 312 1511 1511 57 312 1511 157 1511 157 1511 157 1511 157 151 157 151 157 151 157 157	Weight 5.7% 6.8% 6.1% 5.3% 6.1% 5.3% 10.3% 10.0% 100.0%	Odds Ratio <u>M-H. Fixed. 95% CI</u> 1.39 [0.70, 2.73] 1.55 [0.79, 1.39] 0.82 [0.37, 1.83] 0.54 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [107, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio <u>M-H. Fixed. 95% CI</u> 1.05 [0.50, 2.18] 1.95 [1.34, 2.85] 1.01 [0.55, 1.85] 0.87 [0.41, 1.82] 0.87 [0.41, 1.82] 0.81 [0.49, 1.33] 1.71 [0.54, 2.53] 1.29 [0.67, 2.41] 1.50 [0.7, 2.310]	Decreased risk Increased risk
Total (95% CI) Total events Heterogeneity: Tau ² = 0.08; Test for overall effect: Z = 0. D Study or Subgroup Broch 1998 Eizzidi 2009 Globocnik-Petrovic 2003 Kimura 1997 Santos 2003 Vong 2000 Zietz 2006 Total (95% CI) Total (95% CI) Total (95% CI) Total events Heterogeneity: Chi ² = 10.34 Test for overall effect: Z = 0 E Study or Subgroup Broch 1998 Eizidi 2009 Globocnik-Petrovic 2003 Kimura 1998 Liu 2004 Murata 2004 Nagi 1997 Santos 2003 Vong 2000 Zietz 2006	Chi ² = 16.13, df = \S Diabetic retinopy <u>Events</u> 63 244 94 41 164 44 65 69 153 1034 4, df = $\$$ (P = 0.32);).37 (P = 0.71) Diabetic retinopy <u>Events</u> 17 77 39 32 15 78 14 24 31 68 395	Θ (P = 0. athy Total 82 383 124 110 56 99 84 192 1374 P = 139 athy Total P = 139 124 110 110 56 99 84 1374 P = 139 124 110 56 99 84 122 1374 110 102 1374 124 1374 124 1374 124 1374 1374 1383 124 1374	751 .06); ² = 44 Events 67 296 65 86 76 65 86 76 78 63 81 44 249 1105 % Diabetic C Events 19 54 25 22 7 43 18 22 27 43 18 22 27 43 18 22 27 43 18	% Control Total 95 473 80 98 91 92 102 1111 57 312 1511 Control Total 473 80 0 8 91 122 1511 57 312 1511 57 312 1511 1511 57 312 1511 157 1511 157 1511 157 1511 157 151 157 151 157 151 157 157	Weight 5.7% 6.8% 6.1% 5.3% 6.1% 5.3% 10.3% 10.0% 100.0%	Odds Ratio <u>M-H. Fixed. 95% CI</u> 1.39 [0.70, 2.73] 1.05 [0.79, 1.38] 0.82 [0.37, 1.83] 0.42 [0.37, 1.83] 0.44 [0.24, 1.21] 1.23 [0.60, 2.50] 2.27 [1.07, 4.82] 0.71 [0.39, 1.28] 1.36 [0.59, 3.13] 0.99 [0.63, 1.55] 1.03 [0.87, 1.23] Odds Ratio <u>M'H. Fixed. 95% CI</u> 1.05 [0.50, 2.18] 1.95 [1.34, 2.85] 1.01 [0.55, 1.85] 0.47 [0.49, 1.33] 1.77 [0.54, 2.53] 1.29 [0.67, 2.49] 1.50 [0.72, 3.10] 1.20 [0.82, 1.75]	Decreased risk Increased risk

Fig. 3 Forest plots of the association between SERPINE1 rs1799889 SNP and DR risk. (A) allelic model, (B) homozygote model, (C) heterozygote model, (C) heterozygote model, (D) dominant model, and (E) recessive model (DR: diabetic retinopathy)

Table 4 Overall and su Categories n	Table 4 Overall and subgroup meta-analysis of the asso Categories 4646 vs. 565	up meta-analy	/sis of the association bet 4646 vs. 5656	tween SERPINE1	cciation between SERPINE1 rs1799889 SNP and risk of diabetic CVD 4656 vs. 5656 48. 4656 vs. 5656	isk of diabe	of diabetic CVD 4646 + 4656 vs. 5656	4646 v	4646 vs. 4656 + 5656	5656	
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		OR (95% CI) P I ² (%)/ Ph OR (95% CI)	٩	l ² (%)/ Ph	OR (95% CI)	P0.00	P0.00 I ² (%)/ Ph0.00/0.00 OR(95% CI)	OR(95% CI) P	٩	l ² (%)/ Ph	I ² (%)/ Ph OR(95% CI)	٩	l ² (%)/ Ph	P I ² (%)/ Ph OR(95% CI) P I ² (%)/ Ph	٩	l² (%)/ Ph
Overall	~	7 1.16(0.89–1.50) 0.28 72 %/0.001 1.23(0.77–1.96)	0.28	72 %/0.001	1.23(0.77–1.96)	0.38	0.38 64 %/0.01	1.05 (FEM)(0.83-1.33) 0.68 0%/0.49 1.12(0.81-1.55)	0.68	0 %/0.49	1.12(0.81-1.55)	0.51	45 %/0.09	0.51 45 %/0.09 1.20(0.84–1.70) 0.32 66 %/0.01	0.32	66 %/0.01
Subgroup (by population)	lod (c	pulation)														
European		4 1.07(0.81-1.42) 0.63 70%/0.02 1.08(0.65-1.80)	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	.00 (FEM)(0.77–1.31) 0.97 0%/0.56 1.12 (FEM)(0.89–1.40) 0.35 0%/0.43	0.35	0 %/0.43	1.13(0.76–1.68) 0.54 67 %/0.03	0.54	67 %/0.03
Asian	\sim	3 1.37(0.69–2.73) 0.37 82 %/0.001 1.64(0.52–5.23)	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	0.50 32 %/0.23 1.41(0.63-3.13)	0.40	63 %/0.07	0.40 63 %/0.07 1.45(0.57–3.65) 0.43 77 %/0.01	0.43	77 %/0.01
n: study numbers, OR: c Cardiovascular disease	mber Ilar d	rs, OR: odds ratio, lisease	, CI: co	nfidence inte	rval, bold values	represen	t statistically significar	1: 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: ardiovascular disease	geneit	y (P < 0.1 wa	s considered as a sign	ificant	difference), F	EM: Fix Effects N	lodel, (Ö



Categories n 4G vs. 5G	c	4G vs. 5G			4G4G vs. 5G5G			4G5G vs. 5G5G			4G4G + 4G5G vs. 5G5G	ğ		4G4G vs. 5G5G + 5G4G	i + 5G4G	
		OR (95 %CI)	Ь	l ² (%)/ Ph	OR (95 %CI) P I ² (%)/ Ph OR (95 %CI)	P0.00	l ² (%)/ Pho.00/0.00	P0.00 1 ² (%)/ Ph0.00/0.00 OR(95 %CI) P 1 ² (%)/ Ph OR(95 %CI) P 1 ² (%)/ Ph OR(95 %CI) P 1 ² (%)/ Ph	4	l ² (%)/ Ph	OR(95 %CI)	Ь	l ² (%)/ Ph	OR(95 %CI)	Р	l ² (%)/ Ph
Overall	15	Overall 15 1.48 (REM) 0.001 83 %/0.001 1.92 (REM) (1.15-1.90) (1.15-2.95)	0.001	83 %/0.001		0.001	0.001 74 %/0.001	1.13 (REM)(0.83-1.53) 0.43 58 %/0.001 1.41 (REM) (1.01-1.97)	0.43	58 %/0.001	1.41 (REM) (1.01–1.97)	0.04	70 %/0.001	0.04 70%/0.001 1.78 (REM) (1.27–2.51)	0.001	0.001 77 %/0.001
Subgroup (by population)	y pop	vulation)														
European	m	European 3 1.06(0.91–1.24) 0.45 0 %/0.82	0.45	0 %/0.82	1.16(0.84-1.60)	0.37	0 %/0.90	1.17(0.88–1.57) (0	0.28	38 %/0.20	0.28 38 %/0.20 1.16(0.88–1.53)	0.28	0.28 0 %/0.59	1.04(0.74–1.46) 0.84	0.84	46 %/0.15
Asian	11	11 1.70 (REM) 0.01 84 %/0.001 2.46 (REM) (1.17–2.47) (1.30–4.66)	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)	0.56	65 %/0.001	1.59 (REM)(0.94–2.69)	0.08	75 %/0.001		0.001	0.001 75 %/0.001
Others	-	Others 1 1.12(0.86–1.47) 0.40 N/A	0.40		1.25(0.73–2.14)	0.41 N/A		0.88(0.55-1.41) 0.59 N/A	0.59		0.99(0.64-1.55)	0.98	0.98 N/A	1.36(0.88–2.11) 0.16	0.16	N/A
n: study nur	nbers	i, OR: odds ratio,	CI: con	fidence inter-	val, bold values r	.ebresen	t statistically significan	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	ogeneit	:y (P < 0.1 w	as considered as a sig	Inificant	difference),	REM: Random E	ffects M	odel

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Study or Subgroup	Diabetic nephro Events	pathy Total	Control Events 1		Weight	Odds Ratio M-H. Random. 95% Cl	Odds Ratio M-H. Random, 95% Cl	
De Cosmo 1999	185	350	135	272	7.5%	1.14 [0.83, 1.56]		
Kimura 1998 Li 2001	114 96	196 158		220 128	7.0% 6.5%	0.96 [0.65, 1.42] 1.20 [0.75, 1.93]	—	
Liu 2004	88	154	71	140	6.6%	1.30 [0.82, 2.05]	+	
Liu 2011 Martin 2007	32 254	58 444	44 401	68 722	5.0% 7.9%	0.67 [0.33, 1.38] 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 Wang 2004	212 109	394 152	40	382 76	7.7% 5.9%	1.00 [0.75, 1.32] 2.28 [1.29, 4.04]	·	
Wong 2000	115	190	45	92	6.3%	1.60 [0.97, 2.64]		
Xu 2016	81 111	130 140	52	84 100	5.9%	1.02 [0.58, 1.79]		
Xue 2010 Yan 2 2008	144	140 250	56	100 184	5.8% 7.0%	9.37 [5.17, 16.98] 3.11 [2.08, 4.64]	 '	
Zheng 2007	198	334	77	160	7.1%	1.57 [1.07, 2.29]		
Total (95% CI)		3460	5	3176 1	100.0%	1.48 [1.15, 1.90]	◆	
Total events Heterogeneity: Tau ² =	2024 0.20: Chi ² = 82.18		1630					
Test for overall effect:	Z = 3.05 (P = 0.002	2)	- 0.0000	.,,	0070		0.1 0.2 0.5 1 2 5 10 decreased risk increased risk	
В								
Study or Subgroup	Diabetic nephro Events		Control Events 1		Weight	Odds Ratio M-H. Random, 95% CI	Odds Ratio M-H. Random, 95% Cl	
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]	<u>+</u>	
Li 2001 Liu 2004	31 30	45 49	21 12	34 23	6.6% 6.3%	1.37 [0.54, 3.50] 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]	T	
Tang 2004 Tarnow 2000	33 54	44 93	17 63	32 111	6.5% 8.3%	2.65 [1.00, 7.01] 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 Xue 2010	24 45	32 49	16 4	22 29	5.4% 4.5%	1.13 [0.33, 3.86] 70.31 [16.17, 305.69]		
Yan 2 2008	45	69	10	29 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 1	100.0%	1.92 [1.26, 2.95]	•	
Total (95% CI) Total events	625	900	423	JV# 1		1.02 [1.20, Z.95]	-	
Heterogeneity: Tau ² =	0.49; Chi ² = 54.48,	df = 14 (F)1); l² =	74%		0.005 0.1 1 10 200	
Test for overall effect:	Z = 3.00 (P = 0.003	3)					decreased risk increased risk	
C								
Shudu or Colores	Diabetic nephro		Control		Mainte	Odds Ratio	Odds Ratio	
Study or Subgroup De Cosmo 1999	Events 81	Total 123	Events 7 75	Total V 106	Weight 8.9%	M-H. Random, 95% CI 0.80 [0.46, 1.40]	M-H. Random. 95% Cl	
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 Liu 2011	28 12	47 19	47 18	58 21	6.2% 3.0%	0.34 [0.14, 0.83] 0.29 [0.06, 1.33]		
Liu 2011 Martin 2007	12 114	19 152		21 250	3.0% 9.9%	0.29 [0.06, 1.33] 1.19 [0.75, 1.88]	+	
Prasad 2010	90	139	117	173	9.8%	0.88 [0.55, 1.41]	-	
Tang 2004 Tarnow 2000	15 104	26 143	17 80	32 128	5.1% 9.4%	1.20 [0.42, 3.41] 1.60 [0.96, 2.67]		
Wang 2004	23	33	80 14	25	9.4% 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 Yan 2 2008	21 56	25 81	21 36	46 82	4.2% 8.1%	6.25 [1.85, 21.10] 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 1	100.0%	1.13 [0.83, 1.53]	+	
Total events Heterogeneity: Tau ² =	774 0 19: Cbi? = 33 12	df = 14 /	784 P = 0.003)	12 - 64	R%			
Test for overall effect:			- 5.003),	,, - 00			0.05 0.2 1 5 20 decreased risk increased risk	
D								
	Diabetic nephro	pathy Total	Control	l Fairt 1	Waint	Odds Ratio	Odds Ratio	
Study of Cuk			Event		reight	M.H Dandom Ordi		×
Study or Subgroup De Cosmo 1999	Events 133	175	Events 1 105	136		M-H. Random, 95% Cl 0.93 [0.55, 1.59]	M-H. Random, 95% CI	
De Cosmo 1999 Kimura 1998	133 86	175 98	105 94	136 110	8.3% 6.5%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72]	M-H, Random, 95% Cl	
De Cosmo 1999 Kimura 1998 Li 2001	133 86 65	175 98 79	105 94 51	136 110 64	8.3% 6.5% 6.3%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74]	M-H. Random, 95% Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004	133 86 65 58	175 98 79 77	105 94 51 59	136 110 64 70	8.3% 6.5% 6.3% 6.4%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74] 0.57 [0.25, 1.30]	M-H. Random, 95% Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2011 Martin 2007	133 86 65 58 22 184	175 98 79 77 29 222	105 94 51 59 31 290	136 110 64 70 34 361	8.3% 6.5% 6.3% 6.4% 3.5% 8.9%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74] 0.57 [0.25, 1.30] 0.30 [0.07, 1.31] 1.19 [0.77, 1.83]	MH, Kandom, 95% Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2011 Martin 2007 Prasad 2010	133 86 65 58 22 184 147	175 98 79 77 29 222 196	105 94 51 59 31 290 169	136 110 64 70 34 361 225	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 8.9%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74] 0.57 [0.25, 1.30] 0.30 [0.07, 1.31] 1.19 [0.77, 1.83] 0.99 [0.64, 1.55]	M-H. Random. 95% Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2011 Martin 2007 Prasad 2010 Tang 2004	133 86 65 58 22 184 147 48	175 98 79 77 29 222 196 59	105 94 51 59 31 290 169 34	136 110 64 70 34 361 225 49	8.3% 6.5% 6.4% 3.5% 8.9% 8.9% 6.0%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74] 0.57 [0.25, 1.30] 0.30 [0.07, 1.31] 1.19 [0.77, 1.83] 0.99 [0.64, 1.55] 1.93 [0.79, 4.70]	M-H. Kandom. 95% Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2011 Martin 2007 Prasad 2010	133 86 65 58 22 184 147	175 98 79 77 29 222 196	105 94 51 59 31 290 169	136 110 64 70 34 361 225	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 8.9%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74] 0.57 [0.25, 1.30] 0.30 [0.07, 1.31] 1.19 [0.77, 1.83] 0.99 [0.64, 1.55]	MH.Kandom.9%.Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2011 Martin 2007 Prasad 2010 Tang 2004 Tarnow 2000 Wang 2004 Wong 2000	133 86 65 58 22 184 147 48 158 66 76	175 98 79 77 29 222 196 59 197 76 95	105 94 51 290 169 34 143 27 37	136 110 64 70 34 361 225 49 191 38 46	8.3% 6.5% 6.4% 3.5% 8.9% 6.0% 8.6% 5.6% 6.0%	0.93 (0.55, 1.59) 1.22 (0.55, 2.72) 1.18 (0.57, 2.74) 0.57 (0.25, 1.30) 0.30 (0.07, 1.31) 1.19 (0.77, 1.83) 0.99 (0.64, 1.55) 1.93 (0.79, 4.70) 1.36 (0.84, 2.20) 2.69 (1.02, 7.07) 0.97 (0.40, 2.38)	MH.Kandom. 95% CL	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2011 Martin 2007 Prasad 2010 Tang 2004 Tango 2004 Wang 2000 Xu 2016	133 86 65 58 22 184 147 48 158 66 76 57	175 98 79 77 29 222 196 59 197 76 95 65	105 94 51 290 169 34 143 27 37 36	136 110 64 70 34 361 225 49 191 38 46 42	8.3% 6.5% 6.4% 3.5% 8.9% 6.0% 8.6% 5.6% 6.0% 4.7%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74] 0.57 [0.25, 1.30] 0.30 [0.07, 1.31] 1.19 [0.77, 1.83] 0.99 [0.64, 1.55] 1.93 [0.79, 4.70] 1.36 [0.84, 2.20] 2.69 [1.02, 7.07] 0.97 [0.40, 2.36] 1.19 [0.38, 3.70]	MH. Kandom 9% Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2004 Liu 2011 Martin 2007 Prasad 2010 Tang 2004 Wang 2004 Wang 2004 Wong 2000 Xu 2016 Xue 2010	133 86 65 58 22 184 147 48 158 66 76 57 66	175 98 79 77 29 222 196 59 197 76 95 65 70	105 94 51 59 31 290 169 34 143 27 37 36 25	136 110 64 70 34 361 225 49 191 38 46 42 50	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 8.9% 6.0% 8.6% 5.6% 6.0% 4.7% 4.7%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74] 0.57 [0.25, 1.30] 0.30 [0.07, 1.31] 1.19 [0.77, 1.83] 0.99 [0.64, 1.55] 1.93 [0.79, 4.70] 1.36 [0.84, 2.20] 2.69 [1.02, 7.07] 0.97 [0.40, 2.36] 1.19 [0.38, 3.70] 1.650 [5.22, S2, 19]	MH. Kandom 9% Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2011 Martin 2007 Prasad 2010 Tang 2004 Tango 2004 Wang 2000 Xu 2016	133 86 65 58 22 184 147 48 158 66 76 57	175 98 79 77 29 222 196 59 197 76 95 65	105 94 51 290 169 34 143 27 37 36	136 110 64 70 34 361 225 49 191 38 46 42	8.3% 6.5% 6.4% 3.5% 8.9% 6.0% 8.6% 5.6% 6.0% 4.7%	0.93 [0.55, 1.59] 1.22 [0.55, 2.72] 1.18 [0.51, 2.74] 0.57 [0.25, 1.30] 0.30 [0.07, 1.31] 1.19 [0.77, 1.83] 0.99 [0.64, 1.55] 1.93 [0.79, 4.70] 1.36 [0.84, 2.20] 2.69 [1.02, 7.07] 0.97 [0.40, 2.36] 1.19 [0.38, 3.70]	MH. Kandom. 95%. Cl.	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2014 Liu 2010 Martin 2007 Prasad 2010 Tang 2004 Wang 2004 Wang 2000 Xu 2016 Xue 2010 Yan 2 2008 Zheng 2007	133 86 65 58 22 184 147 48 158 66 76 57 66 100	175 98 79 77 29 222 196 59 197 76 95 65 70 125 167	105 94 51 290 169 34 143 27 37 36 25 46 60	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 8.9% 8.6% 5.6% 6.0% 4.7% 4.7% 4.7% 7.8% 7.6%	$\begin{array}{c} 0.93 \ [0.55, 1.59] \\ 1.22 \ [0.55, 2.72] \\ 1.16 \ [0.55, 2.72] \\ 1.16 \ [0.55, 2.72] \\ 1.16 \ [0.55, 2.72] \\ 1.16 \ [0.57, 1.23] \\ 0.30 \ [0.07, 1.31] \\ 1.19 \ [0.77, 1.83] \\ 0.99 \ [0.64, 1.55] \\ 1.93 \ [0.79, 4.70] \\ 2.69 \ [1.02, 707] \\ 0.97 \ [0.44, 2.20] \\ 2.69 \ [1.02, 707] \\ 0.97 \ [0.44, 2.20] \\ 2.69 \ [1.02, 707] \\ 0.97 \ [0.44, 2.20] \\ 2.69 \ [1.02, 7.20] \\ 1.19 \ [0.38, 3.70] \\ 16.50 \ [5.22, 52.19] \\ 1.30 \ [0.69, 2.45] \\ 1.30 \ [0.69, 2.45] \end{array}$	MH. Kandom 95, Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2014 Martin 2007 Prasad 2010 Tango 2004 Tango 2004 Wang 2004 Wang 2004 Wang 2004 Xu 2016 Xu 2016 Xu 2010 Yan 2 2008 Zheng 2007 Total (95% CI)	133 86 55 58 22 184 184 188 66 57 66 57 66 100 133	175 98 79 77 29 222 196 59 197 76 95 65 70 125	105 94 51 290 169 34 143 27 37 36 25 46 60	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 8.9% 8.6% 5.6% 6.0% 4.7% 4.7% 7.8%	$\begin{array}{c} 0.93 \ [0.55, 1.59] \\ 1.22 \ [0.55, 2.72] \\ 1.16 \ [0.51, 2.74] \\ 0.57 \ [0.25, 1.30] \\ 0.30 \ [0.07, 1.31] \\ 1.19 \ [0.77, 1.83] \\ 0.99 \ [0.64, 1.55] \\ 1.93 \ [0.79, 4.70] \\ 1.36 \ [0.64, 1.55] \\ 1.93 \ [0.79, 4.70] \\ 2.69 \ [1.02, 707] \\ 0.97 \ [0.40, 2.36] \\ 1.19 \ [0.38, 3.70] \\ 16.50 \ [5.22, 52.19] \\ 4.00 \ [2.20, 7.28] \end{array}$	MH.Kandom 95, CL	
De Cosmo 1999 Li 2001 Li 2011 Liu 2011 Liu 2011 Liu 2017 Martin 2007 Prasad 2010 Tang 2004 Wang 2004 Wang 2000 Xiu 2016 Xiu 2016 Xiu 2016 Yan 2 2008 Zheng 2007 Total (95% CI) Total (95% CI)	133 86 55 58 22 184 147 48 158 66 76 57 66 100 133	175 98 79 222 196 59 197 76 95 65 70 125 167	105 94 51 290 169 34 143 27 37 36 25 46 60 1 1207	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 6.0% 8.6% 5.6% 6.0% 4.7% 4.7% 7.8% 7.6%	$\begin{array}{c} 0.93 \ [0.55, 1.59] \\ 1.22 \ [0.55, 2.72] \\ 1.18 \ [0.51, 2.74] \\ 0.57 \ [0.25, 1.30] \\ 0.07, 1.31] \\ 1.91 \ [0.77, 1.83] \\ 0.99 \ [0.64, 1.55] \\ 1.93 \ [0.79, 4.70] \\ 1.36 \ [0.64, 2.20] \\ 2.69 \ [1.02, 7.07] \\ 0.97 \ [0.40, 2.36] \\ 1.19 \ [0.38, 3.70] \\ 1.50 \ [5.22, 52.10] \\ 1.30 \ [0.69, 2.45] \\ 1.41 \ [1.01, 1.97] \end{array}$		
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2014 Martin 2007 Prasad 2010 Tango 2004 Tango 2004 Wang 2004 Wang 2004 Wang 2004 Xu 2016 Xu 2016 Xu 2010 Yan 2 2008 Zheng 2007 Total (95% CI)	133 86 65 58 22 184 147 48 158 66 57 66 57 66 100 133 1399 0.28; Ch ² = 46.37,	175 98 79 77 29 222 196 59 197 76 95 65 70 125 167 1730 , df = 14 (F	105 94 51 290 169 34 143 27 37 36 25 46 60 1 1207	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 6.0% 8.6% 5.6% 6.0% 4.7% 4.7% 7.8% 7.6%	$\begin{array}{c} 0.93 \ [0.55, 1.59] \\ 1.22 \ [0.55, 2.72] \\ 1.18 \ [0.51, 2.74] \\ 0.57 \ [0.25, 1.30] \\ 0.07, 1.31] \\ 1.91 \ [0.77, 1.83] \\ 0.99 \ [0.64, 1.55] \\ 1.93 \ [0.79, 4.70] \\ 1.36 \ [0.64, 2.20] \\ 2.69 \ [1.02, 7.07] \\ 0.97 \ [0.40, 2.36] \\ 1.19 \ [0.38, 3.70] \\ 1.50 \ [5.22, 52.10] \\ 1.30 \ [0.69, 2.45] \\ 1.41 \ [1.01, 1.97] \end{array}$	MH. Kandom 95% Cl	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2011 Martin 2007 Prasad 2010 Trang 2004 Wang 2004 Wang 2004 Wang 2004 Wang 2004 Yang 2008 Zheng 2007 Total (95% CI) Total (95% CI) Total (95% CI) Total (95% CI)	133 86 65 58 22 184 147 48 158 66 57 66 57 66 100 133 1399 0.28; Ch ² = 46.37,	175 98 79 77 29 222 196 59 197 76 95 65 70 125 167 1730 , df = 14 (F	105 94 51 290 169 34 143 27 37 36 25 46 60 1 1207	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 6.0% 8.6% 5.6% 6.0% 4.7% 4.7% 7.8% 7.6%	$\begin{array}{c} 0.93 \ [0.55, 1.59] \\ 1.22 \ [0.55, 2.72] \\ 1.18 \ [0.51, 2.74] \\ 0.57 \ [0.25, 1.30] \\ 0.07, 1.31] \\ 1.91 \ [0.77, 1.83] \\ 0.99 \ [0.64, 1.55] \\ 1.93 \ [0.79, 4.70] \\ 1.36 \ [0.64, 2.20] \\ 2.69 \ [1.02, 7.07] \\ 0.97 \ [0.40, 2.36] \\ 1.19 \ [0.38, 3.70] \\ 1.50 \ [5.22, 52.10] \\ 1.30 \ [0.69, 2.45] \\ 1.41 \ [1.01, 1.97] \end{array}$		
De Cosmo 1999 Kimura 1998 Li 2001 Lu 2014 Lu 2014 Lu 2014 Marina 2010 Tanga 2004 Wang 2004 Wang 2004 Wang 2004 Wang 2004 Wang 2004 Yang 2008 Zue 2016 Yang 2008 Zue 2016 Yang 2008 Total (95% CI) Total (95	133 86 65 58 22 184 147 48 158 66 57 66 57 66 100 133 1339 0.28; Ch ² = 46.37, Z = 2.01 (P = 0.04) Diabetic nephro	175 98 79 29 29 29 196 59 197 76 95 65 70 125 167 1730 4730 475 475 475 475 475 475 475 475 475 475	105 94 51 59 31 290 169 34 143 27 36 25 46 60 1 1207 > < 0.0001	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 1588 1	8.3% 6.5% 6.4% 3.5% 8.9% 6.0% 8.6% 6.0% 4.7% 4.7% 4.7% 7.8% 7.8% 7.6%	0.33 (0.5, 1.69) 1.22 (0.55, 2.72) 1.8 (0.51, 2.74) 0.67 (0.25, 1.30) 0.30 (0.07, 1.31) 1.19 (0.77, 1.83) 0.33 (0.79, 4.70) 1.36 (0.44, 2.20) 2.69 (1.02, 707) 1.36 (0.44, 2.20) 2.69 (1.02, 707) 0.67 (0.40, 2.36) 1.19 (0.38, 3.70) 0.67 (0.40, 2.36) 1.19 (0.38, 3.70) 1.50 (5.22, 52, 19) 4.00 (2.20, 7.28) 1.30 (0.69, 2.45) 1.41 (1.01, 1.97)	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Kimura 1998 Li 2001 Lu 2014 Lu 2014 Lu 2014 Lu 2014 Yang 2004 Wang 2004 Wang 2004 Wang 2004 Wang 2004 Yang 2008 Zheng 2007 Total (95% cl) Total eyesin Heterogeneity: Tar¥ = Test for overall effect:	133 86 65 58 22 184 147 147 147 158 66 76 66 100 133 1399 0.28; Ch [*] = 46.37, Z = 2.01 (P = 0.04)	175 98 79 29 29 29 196 59 197 76 95 65 70 125 167 1730 4730 475 475 475 475 475 475 475 475 475 475	105 94 51 59 31 290 169 34 143 27 36 25 46 60 1 1207 > < 0.0001 Events 1	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 1588 1	8.3% 6.5% 6.4% 3.5% 8.9% 6.0% 8.6% 6.0% 4.7% 4.7% 4.7% 7.8% 7.8% 7.6%	0.83 (0.5, 1.69) 1.22 (0.55, 2.72) 1.81 (0.51, 2.74) 0.67 (0.25, 1.30) 0.00 (0.07, 1.31) 1.91 (0.77, 1.83) 0.96 (0.64, 1.55) 1.33 (0.79, 4.70) 1.36 (0.64, 2.50) 1.36 (0.64, 2.50) 1.36 (0.64, 2.50) 1.37 (0.69, 2.45) 1.30 (0.69, 2.45) 1.41 [1.01, 1.97] Odds Ratio McH. Random, 9%; CI	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Li 2001 Li 2001 Li 2001 Li 2011 Martin 2007 Prasad 2010 Tango 2004 Wong 2004 Wong 2004 Wong 2004 Wong 2004 Wong 2004 Wong 2004 Vang 2004	133 86 65 88 22 184 45 86 66 75 75 75 76 100 100 100 100 100 100 100 100 100 10	175 98 79 77 29 222 196 59 197 76 65 70 125 167 1730 , df = 14 (F 9 9 8 9 8 9 8 9 8 9 8	105 94 51 59 31 290 169 34 143 27 37 36 25 46 60 1 1207 > < 0.0001 Events _ 30 36	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 1588 1 1588 1 1588 1 10 17 136	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 6.0% 8.6% 6.0% 8.6% 6.0% 4.7% 4.7% 7.6% 100.0% 7.6%	0.83 (0.5, 1.69) 1.22 (0.55, 2.72) 1.81 (0.51, 2.74) 0.57 (0.25, 1.30) 0.00 (0.07, 1.31) 1.19 (0.77, 1.83) 0.09 (0.64, 1.55) 1.83 (0.79, 4.70) 1.36 (0.84, 2.20) 1.19 (0.36, 3.70) 1.63 (0.52, 5.2) 1.30 (0.69, 2.45) 1.41 (1.04, 1.97] Odds Ratio MH. Random, 93%, CI 1.49 (0.82, 4.51) 1.49 (0.82, 4.51, 1.49)	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2004 Liu 2010 Martin 2007 Prasad 2010 Wang 2004 Wang 2	133 86 65 88 22 184 48 48 48 48 76 76 76 76 66 76 60 103 1399 9 0.28; Ch ^o = 46.37; 2 = 2.01 (P = 0.04) Diabetic nephro Events 28 28 31	175 98 79 77 29 222 196 59 197 76 95 65 70 125 167 1730 df = 14 (F) 75 98 79	105 94 51 59 31 290 169 34 143 27 36 25 46 60 1 1207 2 < 0.0001 1 200 1 200 1 2 30 36 21	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 80 81 1588 1 1588 1 1, ² = 7 1 136 110 136 110 138 158 1 10 10 10 10 10 10 10 10 10	8.3% 6.5% 6.4% 3.5% 8.9% 6.0% 8.6% 8.6% 5.6% 4.7% 7.6% 7.6% 70%	0.33 (0.5, 1.59) 1.22 (0.55, 2.72) 1.8 (0.51, 2.74) 0.67 (0.25, 1.30) 0.30 (0.07, 1.31) 1.19 (0.77, 1.83) 0.30 (0.77, 1.83) 0.30 (0.79, 1.90) 1.30 (0.44, 2.20) 2.69 (1.02, 707) 1.30 (0.44, 2.20) 2.69 (1.02, 707) 1.30 (0.84, 2.20) 1.30 (0.89, 2.45) 1.30 (0.89, 2.45) 1.30 (0.89, 2.45) 1.44 (1.04, 1.97) 0.46 Ratio M:H.Random, 95% CL 1.49 (0.89, 2.51) 0.22 (0.45, 1.49) 1.22 (0.66, 2.64)	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Li 2001 Li 2001 Li 2001 Li 2010 Martin 2007 Prasad 2010 Tango 2004 Wang 2007 Total (events Heterogeneity, Tau ⁺ = Test for overall effect B Study or Subgroup Li 2001 Li 2001 Li 2004 Li 2007 Li	133 86 65 88 22 184 48 147 48 86 66 76 76 76 76 76 76 76 76 70 133 00 133 00 28 CM* = 45.37 2 = 2.01 (P = 0.04) Diabetic nephro <u>Events</u> 2 2 2 3 1 3 0	175 98 79 77 29 222 196 59 197 76 65 70 125 167 1730 . df = 14 (F 9 5 95 65 70 125 167 1730 . df = 14 (F 9 5 9 77 7 98 79 77	105 94 51 59 31 290 169 34 143 27 36 25 46 60 0 1 1207 2 < 0.0001 Events 1 30 6 21 200 2 36 21 122	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 (); ² = 7 1 10 110 110 110 110 110 110	8.3% 6.5% 6.3% 6.4% 3.5% 8.9% 8.9% 6.0% 8.9% 6.0% 4.7% 4.7% 4.7% 4.7% 4.7% 4.7% 4.7% 4.7	0.83 (0.55, 1.69) 1.22 (0.55, 2.72) 1.81 (0.51, 2.74) 0.57 (0.25, 1.30) 0.00 (0.07, 1.31) 1.19 (0.77, 1.83) 0.09 (0.64, 1.55) 1.53 (0.79, 4.70) 2.66 (1.02, 7.07) 2.66 (1.02, 7.07) 1.19 (0.36, 3.70) 1.53 (0.52, 5.21) 1.40 (0.86, 2.45) 1.41 (1.01, 1.97] Odds Ratio M.H. Random, 35%, CI 1.44 (0.82, 2.51) 0.42 (0.45, 1.49) 1.42 (0.66, 2.45, 1.49) 1.42 (0.66, 2.44, 1.49) 1.42 (0.46, 3.64) 1.43 (0.44, 3.66)	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Kimura 1998 Li 2001 Liu 2004 Liu 2004 Liu 2010 Martin 2007 Prasad 2010 Wang 2004 Wang 2	133 86 65 88 22 184 48 48 48 48 76 76 76 76 66 76 60 103 1399 9 0.28; Ch ^o = 46.37; 2 = 2.01 (P = 0.04) Diabetic nephro Events 28 28 31	175 98 79 77 29 222 196 59 197 76 95 65 70 125 167 1730 df = 14 (F) 75 98 79	105 94 51 59 31 290 169 34 143 27 37 36 60 25 46 60 1 1207 ><0.0001 Events 30 30 36 21 12 13	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 80 81 1588 1 1588 1 1, ² = 7 1 136 110 136 110 138 158 1 10 10 10 10 10 10 10 10 10	8.3% 6.5% 6.4% 3.5% 8.9% 6.0% 8.6% 8.6% 5.6% 4.7% 7.6% 7.6% 70%	0.33 (0.5, 1.59) 1.22 (0.55, 2.72) 1.8 (0.51, 2.74) 0.67 (0.25, 1.30) 0.30 (0.07, 1.31) 1.19 (0.77, 1.83) 0.30 (0.77, 1.83) 0.30 (0.79, 1.90) 1.30 (0.44, 2.20) 2.69 (1.02, 707) 1.30 (0.44, 2.20) 2.69 (1.02, 707) 1.30 (0.84, 2.20) 1.30 (0.89, 2.45) 1.30 (0.89, 2.45) 1.30 (0.89, 2.45) 1.44 (1.04, 1.97) 0.46 Ratio M:H.Random, 95% CL 1.49 (0.89, 2.51) 0.22 (0.45, 1.49) 1.22 (0.66, 2.64)	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Li 2001 Li 2001 Li 2004 Liu 2014 Liu 2004 Liu 2014 Liu 2014 Liu 2014 Liu 2010 Yang 2004 Wang 2004 Wang 2004 Wang 2004 Yang 2004 Liu 2011 Liu 2014 Liu 2011 Marin 2007 Prasad 2019	133 86 65 88 22 184 147 48 158 66 66 100 133 1399 0.28; Chi ⁴ = 46.37, 2 = 2.01 (P = 0.04) Diabetic nephro 52 83 31 10 70 77	175 98 97 77 72 92 222 196 55 50 197 76 95 56 55 70 125 57 167 1730 df = 14 (F 1730 df = 14 (F 2017) 125 167 167 1730 125 167 167 167 1730 125 167 167 167 167 177 177 177 177 177 177	105 94 51 59 93 1290 27 37 6 25 25 25 25 25 25 25 25 25 25 25 25 25	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 1588 1 10 110 110 110 110 110 110	8.3%, 6.5%, 6.3%, 6.4%, 8.9%, 8.9%, 8.9%, 8.9%, 8.9%, 5.6%, 6.0%, 4.7%, 7.6%, 100.0%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 8.4%, 8.4%, 5.7%, 5.3%, 5.3%, 5.3%, 5.3%, 5.5%, 8.4%, 5.5%, 5.5%, 5.5%, 5.5%, 5.5%, 7.6%	0.33 (0.5, 1.69) 1.22 (0.55, 2.72) 1.8 (0.51, 2.74) 0.67 (0.25, 1.30) 0.30 (0.07, 1.31) 1.19 (0.77, 1.83) 1.39 (0.64, 1.56) 1.39 (0.64, 1.56) 1.39 (0.64, 1.56) 1.39 (0.64, 2.76) 1.39 (0.64, 2.76) 1.39 (0.64, 2.76) 1.49 (0.68, 2.74) 1.40 (0.69, 2.51) 0.42 (0.69, 2.45) 1.44 (1.04, 1.97) 1.20 (0.68, 2.44) 1.20 (0.68, 2.4	0.02 0.1 10 50 decreased risk	
Kimura 1996 Li 2001 Liu 2004 Liu 2011 Marin 2007 Prasad 2010 Tang 2004 Xiu 2016 Xiu 2016 Xiu 2016 Xiu 2016 Xiu 2016 Xiu 2016 Xiu 2016 Xiu 2016 Xiu 2016 Total (195% cl) Total	133 86 65 88 22 184 147 48 96 66 76 75 76 86 100 133 103 10 70 75 22 23 147 45 86 100 133 102 102 24 25 25 26 20 20 20 20 20 20 20 20 20 20	1755 98 98 97 77 72 29 222 29 222 197 76 59 55 167 1730 df = 14 (F 70 1730 df = 14 (F 70 175 98 59 77 72 98 59 977 77 77 78 98 79 99 78 79 77 78 79 79 77 79 79 79 77 79 79 79 79 79 79	105 94 94 51 59 31 290 34 41 37 37 36 60 25 5 < 0.0001 1 20001 1 20001 1 200001 1 200001 1 200001 1 200001 1 200001 1 200000 1 200000000	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 1); I ² = 7 I Total V 136 64 42 50 92 138 109 138 109 138 109 138 109 109 109 109 109 109 109 109	8.3%, 6.5%, 6.4%, 8.9%, 8.9%, 6.0%, 8.9%, 6.0%, 8.8%, 6.0%, 7.8%, 7.8%, 7.8%, 7.8%, 7.8%, 7.8%, 7.8%, 5.0%, 8.4%, 8.1%, 6.3%, 6.3%, 8.4%, 8.1%, 6.3%, 8.4%, 8.5%, 6.3%, 6.4%, 8.4%, 6.5%, 6.4%, 6.5%, 6.4%, 8.9%, 6.4%, 8.9%, 6.4%, 8.9%, 6.4%, 8.9%, 6.4%, 8.9%, 6.4%, 8.9%, 6.0%, 8.9%, 7.0%, 7.8%, 7.0%,	0.33 (0.5, 1.69) 1.22 (0.55, 2.72) 1.8 (0.51, 2.74) 0.67 (0.25, 1.30) 0.30 (0.07, 1.31) 1.30 (0.44, 1.55) 1.30 (0.44, 1.55) 1.30 (0.44, 1.55) 1.30 (0.44, 1.55) 1.30 (0.44, 1.55) 1.30 (0.44, 1.25) 1.30 (0.44, 1.25) 1.30 (0.44, 1.25) 1.30 (0.46, 1.25) 1.30 (0.46, 2.20) 2.69 (1.02, 7.07) 1.30 (0.46, 2.26) 1.30 (0.46, 2.46) 1.30 (0.46, 2.46) 1.31 (0.46, 2.46) 1.32 (0.46, 2.46) 1.34 (0.46, 2.4	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Li 2001 Li 2001 Li 2001 Li 2010 Marin 2007 Prasad 2010 Trang 2004 Wong 2004 Wong 2004 Wong 2004 Wong 2004 Yang 2008 Zheng 2007 Total (95% CI) Total (95% CI) Tot	133 86 65 88 22 184 147 48 158 66 66 67 7 67 67 66 60 100 103 133 2 2 201 (P = 0.04) 133 2 2 = 2.01 (P = 0.04) 133 2 2 = 2.01 (P = 0.04) 133 2 2 = 2.01 (P = 0.04) 133 2 2 2 3 1 0 0 2 5 7 5 7 5 2 2 3 3 3 5 4	175 98 97 77 72 92 222 196 55 50 197 76 95 56 55 70 125 57 167 1730 df = 14 (F 1730 df = 14 (F 2017) 125 167 167 1730 125 167 167 167 1730 125 167 167 167 167 177 177 177 177 177 177	105 94 51 59 1290 169 189 189 27 37 34 4143 34 1207 27 52 60 60 1 1207 2 2 5 4 6 60 1 2 1207 2 7 30 6 3 6 2 5 1 1207 2 7 30 1 2 9 0 0 0 1 1 2 9 0 1 1 2 9 0 1 1 2 9 0 1 1 2 9 0 1 1 2 9 1 1 2 9 0 1 1 2 9 1 1 2 9 1 1 2 9 0 1 1 2 9 1 1 2 9 1 1 2 9 1 1 2 9 1 1 2 9 1 1 2 9 1 1 2 7 7 3 7 3 7 3 7 3 7 3 7 3 7 3 7 3 7 3	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 1588 1 10 110 110 110 110 110 110	8.3%, 6.5%, 6.3%, 6.4%, 8.9%, 8.9%, 8.9%, 8.9%, 8.9%, 5.6%, 6.0%, 4.7%, 7.6%, 100.0%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 7.6%, 8.4%, 8.4%, 5.7%, 5.3%, 5.3%, 5.3%, 5.3%, 5.5%, 8.4%, 5.5%, 5.5%, 5.5%, 5.5%, 5.5%, 7.6%	0.33 (0.5, 1.69) 1.22 (0.55, 2.72) 1.81 (0.51, 2.74) 0.67 (0.25, 1.30) 0.30 (0.07, 1.31) 1.19 (0.77, 1.83) 0.39 (0.24, 1.55) 1.39 (0.74, 1.70) 1.39 (0.74, 1.70) 1.39 (0.74, 1.70) 1.39 (0.74, 1.70) 1.39 (0.74, 1.70) 1.39 (0.74, 1.70) 1.39 (0.74, 1.70) 1.30 (0.89, 2.45) 1.41 (1.01, 1.97) 0.47 (0.46, 1.44) 1.42 (0.29, 2.51) 1.44 (0.24, 1.44) 1.52 (0.25, 2.45) 1.44 (0.24, 1.44) 1.52 (0.25, 2.45) 1.44 (0.24, 1.44) 1.52 (0.25, 2.45) 1.44 (0.24, 1.44) 1.52 (0.25, 2.45) 1.44 (0.24, 1.44) 1.52 (0.25, 1.45) 0.45 (0.30, 2.39) 1.54 (0.88, 2.11) 2.39 (0.58, 2.	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Li 2001 Li 2001 Li 2001 Li 2011 Martin 2007 Prasad 2010 Tamov 2004 Vivong 2000 Vivong 2000 Vivong 2007 Total (995% GI) Total 2011 Martin 2007 Prasad 2010 Tang 2004 Viong 2000 Viong 2000 Viong 2000	133 86 65 58 22 184 147 48 158 66 66 77 77 77 77 100 103 133 0.0.8; Chi ^a = 46.37, Z = 2.01 (P = 0.04) Diabetic nephro S2 28 30 00 70 77 57 53 33 54 43 39	1755 98 98 79 77 22 29 222 196 59 197 76 59 65 70 125 167 1730 (d = 14 (f 70 125 167 1730 (d = 14 (f 95) 97 77 29 222 196 65 97 197 76 97 20 222 196 65 97 197 76 97 20 22 22 20 22 20 22 20 22 20 22 20 22 20 22 20 22 20 22 20 20	105 94 94 51 59 31 290 34 41 37 37 36 60 25 5 < 0.0001 1 20001 1 20001 1 200001 1 200001 1 200001 1 200001 1 200001 1 200000 1 200000000	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 1); I ² = 7 1 1 1 1 1 1 1 1 1 1 1 1 1	8.3% 6.5% 6.3% 6.4% 8.9% 6.0% 8.9% 6.0% 8.8% 5.6% 6.0% 8.8% 7.6% 7.8% 7.6% 7.8% 7.6% 7.0%	0.33 (0.5, 1.69) 1.22 (0.55, 2.72) 1.81 (0.51, 2.74) 0.67 (0.25, 1.30) 0.00 (0.07, 1.31) 1.19 (0.77, 1.83) 0.09 (0.64, 1.56) 1.33 (0.79, 1.70) 1.39 (0.74, 1.70) 1.30 (0.64, 2.56) 1.40 (0.2, 2.52, 1.91) 1.50 (0.22, 2.52, 1.91) 1.50 (0.52, 2.52, 1.91) 1.50 (0.	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Li 2001 Li 2001 Li 2014 Li 2016 Li 201	133 86 65 88 22 184 46 46 66 67 67 66 76 66 76 76 66 00 103 133 99 0.28; C34 = 46.37, 70 0.28; C34 = 46.37, 70 2 = 2.01 (P = 0.04) 133 2 = 2.01 (P = 0.04) 133 133 30 10 77 75 54 43 30 30 30 31 33 33 33 33 34 34 34 34 34 34 34 34 34	1755 98 79 77 20 222 99 222 196 59 9 65 70 107 76 9 65 70 125 167 70 125 167 70 125 167 70 0 4 df = 14 (F 730 9 9 9 9 77 77 76 9 9 9 9 9 9 9 9 77 77 76 9 9 9 9	105 94 61 189 31 290 34 143 27 36 60 1 1 207 25 46 60 1 1 207 25 46 60 1 1 207 27 25 20,0001 1 1 207 27 1 207 27 27 1 30 200 1 31 1 207 27 1 30 1 207 27 1 30 1 200 34 1 37 1 200 37 1 200 37 1 37 1 200 37 1 37 1 200 37 1 200 37 1 37 1 200 37 1 37 1 200 37 1 200 37 1 37 1 200 200 37 1 200 200 200 200 200 200 200 200 200 2	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 10; i ² = 7 136 110 138 46 42 10; i ² = 7 136 110 64 70 34 361 225 49 191 38 46 42 42 42 42 49 42 42 42 42 43 44 42 43 44 44 44 44 44 45 46 44 45 46 44 46 46 46 46 46 47 47 49 46 46 46 47 49 47 49 49 49 49 49 49 49 49 49 40 49 49 49 49 49 49 49 49 49 49 49 49 49	8.3% 6.5% 6.3% 6.4% 6.3% 8.9% 6.0% 6.0% 6.0% 6.0% 6.0% 6.7% 7.8% 7.8% 7.8% 7.8% 7.8% 7.8% 7.8% 7	0.33 (0.5, 1.69) 1.22 (0.55, 2.72) 1.8 (0.51, 2.74) 0.67 (0.25, 1.30) 0.30 (0.07, 1.31) 1.19 (0.77, 1.85) 0.33 (0.79, 4.70) 1.36 (0.44, 2.20) 2.69 (1.02, 7.07) 1.36 (0.44, 2.20) 2.69 (1.02, 7.07) 1.36 (0.44, 2.20) 2.69 (1.02, 7.07) 1.30 (0.69, 2.45) 1.30 (0.69, 2.45) 1.30 (0.69, 2.45) 1.30 (0.69, 2.45) 1.30 (0.69, 2.45) 1.32 (0.66, 2.64) 3.30 (1.43, 0.68) 1.32 (0.66, 2.64) 3.30 (1.43, 0.68) 1.35 (0.68, 2.11) 2.25 (0.63, 2.12) 2.37 (1.20, 0.73) 1.31 (1.39, 7.66) 3.31 (1.39, 7.6	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Li 2001 Li 2001 Li 2001 Li 2010 Martin 2007 Presad 2010 Tamov 2040 Yang 2000 Yang 2000 Yang 2008 Yang 2007 Total (95% CI) Total (95	133 86 65 58 22 184 147 48 158 66 75 77 57 75 77 57 22 20 100 103 133 1399 0.28; Ch ² = 46.37, Z = 2.01 (P = 0.04) Diabetic nephro Events 22 23 30 0 77 57 57 52 23 33 35 4 43 39 24 45	1755 98 79 77 29 222 196 59 197 76 59 65 65 167 1730 125 167 1730 47 6 4 5 9 6 5 70 125 167 1730 175 9 8 70 77 72 9 222 21 176 9 77 77 76 9 9 20 21 21 9 6 5 9 197 76 9 77 77 76 9 20 21 9 20 21 21 9 6 5 9 197 76 9 20 21 21 9 6 5 9 197 76 9 20 21 21 9 6 5 9 197 76 9 20 21 21 9 6 5 9 197 76 9 20 21 21 9 6 5 9 197 76 5 9 20 21 22 196 6 5 9 197 76 70 197 76 197 76 197 70 197 76 197 70 1175 70 1175 70 1175 70 1175 1177 70 1175 70 1177 70 1175 1177 70 1175 1177 1175 1177 1175 1177 1175 1	105 94 94 51 1290 34 169 34 169 34 17 7 7 36 6 0 1 1 1207 < 30 6 21 2 5 25 4 6 0 0 1 1 207 36 21 1207 36 21 11 30 6 21 11 30 6 21 1207 36 13 36 25 25 25 25 25 36 13 1207 36 143 27 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	136 110 64 70 34 361 225 49 191 38 46 42 50 1588 1 1 10 10 10 10 10 10 10 10	8.3% 6.5% 6.3% 3.5% 8.9% 6.4% 3.5% 8.9% 6.0% 4.7% 7.8% 7.8% 7.8% 7.8% 7.6% 100.0%	0.33 (0.5, 1.69) 1.22 (0.55, 2.72) 1.81 (0.51, 2.74) 0.67 (0.25, 1.30) 0.07 (0.13) 1.19 (0.77, 1.83) 0.09 (0.64, 1.55) 1.33 (0.79, 4.70) 1.39 (0.64, 2.56) 1.39 (0.64, 2.56) 1.49 (0.22, 2.52, 10) 1.50 (0.22, 2.52, 10)	0.02 0.1 10 50 decreased risk	
De Cosmo 1999 Li 2001 Li 2001 Li 2014 Li 2016 Li 201	133 86 65 88 22 184 46 46 66 67 67 66 76 66 76 76 66 00 103 133 99 0.28; C34 = 46.37, 70 0.28; C34 = 46.37, 70 2 = 2.01 (P = 0.04) 133 2 = 2.01 (P = 0.04) 133 133 30 10 77 75 54 43 30 30 30 31 33 33 33 33 34 34 34 34 34 34 34 34 34	1755 98 79 77 20 222 99 222 99 2196 59 95 65 70 70 125 167 70 125 167 70 125 167 70 0 4 df = 14 (F 730 0 4 df = 14 (F 76 95 9 9 77 77 76 9 9 9 9 9 9 9 77 77 76 9 9 9 9	105 94 61 189 31 290 34 143 27 36 60 1 1 207 25 46 60 1 1 207 25 46 60 1 1 207 27 25 46 60 21 1 21 27 27 30 30 30 30 30 31 1207 27 13 30 30 13 13 13 143 143 143 143 27 143 143 27 143 27 143 27 143 27 143 27 143 27 143 27 143 27 143 27 143 27 143 27 143 27 27 25 25 26 27 143 27 143 27 27 27 27 27 27 27 27 27 27 27 27 27	136 110 64 70 34 361 225 49 191 38 46 42 50 92 80 1588 1 10; i ² = 7 136 110 136 110 64 70 136 140 10; i ² = 7 136 110 10 10 10 10 10 10 10 10 10 10 10 10	8.3% 6.5% 6.3% 6.4% 6.3% 8.9% 6.0% 6.0% 6.0% 6.0% 6.0% 6.7% 7.8% 7.8% 7.8% 7.8% 7.8% 7.8% 7.8% 7	0.33 (0.5, 1.69) 1.22 (0.55, 2.72) 1.8 (0.51, 2.74) 0.67 (0.25, 1.30) 0.30 (0.07, 1.31) 1.19 (0.77, 1.85) 0.33 (0.79, 4.70) 1.36 (0.44, 2.20) 2.69 (1.02, 7.07) 1.36 (0.44, 2.20) 2.69 (1.02, 7.07) 1.36 (0.44, 2.20) 2.69 (1.02, 7.07) 1.30 (0.69, 2.45) 1.30 (0.69, 2.45) 1.30 (0.69, 2.45) 1.30 (0.69, 2.45) 1.30 (0.69, 2.45) 1.32 (0.66, 2.64) 3.30 (1.43, 0.68) 1.32 (0.66, 2.64) 3.30 (1.43, 0.68) 1.35 (0.68, 2.11) 2.25 (0.63, 2.12) 2.37 (1.20, 0.23) 1.31 (1.39, 7.66) 3.31 (1.39, 7.6	0.02 0.1 10 50 decreased risk	
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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-an	lysis
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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	0.00
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 Dominant model	-0.11 0.61	0.91 0.55	0.00 0.69	1.00 0.49
Recessive model	3.05	0.01	2.18	0.03

 $P \prec 0.05$ 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 geneenvironmental interactions might also trigger the heterogeneity of genetic effects between individual studies.

There were several limitations included in our metaanalysis: (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; Cl: 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.

Acknowledgements

The authors gratefully acknowledge the financial supports by Tianjin Chest Hospital Labor Union (HL Cong's model worker innovation studio), and Tianjin Eye Institute, Tianjin Key Lab of Ophthalmology and Visual Science for their linguistic assistance during the preparation of this manuscript.

Authors' contributions

H.L.C. and Y.W. designed the study. J.Y.C. and C.N.Z. prepared the original manuscript, performed statistical analysis and participated in most of the study steps. Z.Q.W. constructed the manuscript revision. Z.Q.W. and R.L. prepared the manuscript and assisted in the study processes. W.J.W., K.H. and M.A. assisted in the data collection, and helped in the interpretation of the study. All authors read and approved the final manuscript.

Funding

The present study was funded by National Natural Science Foundation of China (No. 81670884 and No. 81873684) and Youth Program of National Natural Science Foundation of China (No. 81900828). The funding body of the study (No. 81670884, 81873684 and 81900828) had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. The corresponding author (Hongliang Cong & Yan Wang) had full access to all the data and final responsibility for the decision to submit for publication.

Availability of data and materials

The data analysed during the current meta-analysis is included in this published article and its supplementary information files, and other relevant data is available from the corresponding author on reasonable request.

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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Received: 25 March 2020 Accepted: 10 August 2021 Published online: 30 September 2021

References

 Castañeda-Delgado JE. Diabetic complication could get a gene therapy boost. Gene Ther. 2018;25(6):401.

- Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2): 88–98.
- Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev. 2016;37(3):278–316.
- Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of Diabetes 2017. J Diabetes Res. 2018;2018:3086167.
- Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365(9467):1333–46.
- Mutch NJ, Thomas L, Moore NR, Lisiak KM, Booth NA. TAFIa. PAI-1 and alpha-antiplasmin: complementary roles in regulating lysis of thrombi and plasma clots. J Thromb Haemost. 2007;5(4):812–7.
- Westrick RJ, Eitzman DT. Plasminogen activator inhibitor-1 in vascular thrombosis. Curr Drug Targets. 2007;8(9):966–1002.
- Festa A, D'Agostino R, Mykkänen L, et al. Relative contribution of insulin and its precursors to fibrinogen and PAI-1 in a large population with different states of glucose tolerance. The Insulin Resistance Atherosclerosis Study (IRAS). Arterioscler Thromb Vasc Biol. 1999;19(3):562–8.
- Eriksson P, Kallin B, van 't Hooft FM, Båvenholm P, Hamsten A. Allele-specific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. Proc Natl Acad Sci U S A. 1995; 92(6):1851–5.
- Zhang T, Pang C, Li N, Zhou E, Zhao K. Plasminogen activator inhibitor-1 4G/5G polymorphism and retinopathy risk in type 2 diabetes: a metaanalysis. BMC Med. 2013;11:1.
- Xu K, Liu X, Yang F, et al. PAI-1 -675 4G/5G polymorphism in association with diabetes and diabetic complications susceptibility: a meta-analysis study. PLoS One. 2013;8(11):e79150.
- Li G, Liu Y, Li X, et al. Association of PAI-1 4G/5G Polymorphism with Ischemic Stroke in Chinese Patients with Type 2 Diabetes Mellitus. Genet Test Mol Biomarkers. 2018;22(9):554–60.
- Xu F, Liu H, Sun Y. Association of plasminogen activator inhibitor-1 gene polymorphism and type 2 diabetic nephropathy. Ren Fail. 2016;38:157–62.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9, W64.
- Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010, 25(9):603-605.10.1007/s10654-010-9491-z.
- 16. Robins J, Greenland S, Breslow NE. A general estimator for the variance of the Mantel-Haenszel odds ratio. Am J Epidemiol. 1986;124(5):719–23.
- Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ. 1997;315(7121):1533–7.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.
- Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101.
- Mansfield MW, Stickland MH, Grant PJ. Plasminogen activator inhibitor-1 (PAI-1) promoter polymorphism and coronary artery disease in non-insulindependent diabetes. Thromb Haemost. 1995;74(4):1032–4.
- Nagi DK, McCormack LJ, Mohamed-Ali V, Yudkin JS, Knowler WC, Grant PJ. Diabetic retinopathy, promoter (4G/5G) polymorphism of PAI-1 gene, and PAI-1 activity in Pima Indians with type 2 diabetes. Diabetes Care. 1997; 20(8):1304–9.
- Broch M, Gutierrez C, Aguilar C, Simon I, Richart C, Vendrell J. Genetic variation in promoter (4G/5G) of plasminogen activator inhibitor 1 gene in type 2 diabetes. Absence of relationship with microangiopathy. Diabetes Care. 1998;21:463.
- Kimura H, Gejyo F, Suzuki Y, Suzuki S, Miyazaki R, Arakawa M. Polymorphisms of angiotensin converting enzyme and plasminogen activator inhibitor-1 genes in diabetes and macroangiopathy1. Kidney Int. 1998;54:1659–69.
- De Cosmo S, Margaglione M, Tassi V, Garrubba M, Thomas S, Olivetti C, et al. ACE, PAI-1, decorin and Werner helicase genes are not associated with the development of renal disease in European patients with type 1 diabetes. Diabetes Metab Res Rev. 1999;15:247–53.

- Wong TY, Poon P, Szeto CC, Chan JC, Li PK. Association of plasminogen activator inhibitor-1 4G/4G genotype and type 2 diabetic nephropathy in Chinese patients. Kidney Int. 2000;57:632–8.
- Ding GX, SHEN J, CHEN JW. Relationship between Polymorphisms of PAI-1 Gene, ATN Gene and Coronary Heart Disease in Type 2-DM: Report of 281 Cases. Acta Nanjing Med Univ. 2001;21:95–8.
- Petrovic D, Globocnik-Petrovic M, Peterlin B. 4G4G genotype of PAI-1 gene promoter polymorphism is not associated with myocardial infarction in Caucasians with type-2 diabetes. Cardiology. 2003;100(3):157–8.
- Globocnik-Petrovic M, Hawlina M, Peterlin B, Petrovic D. Insertion/deletion plasminogen activator inhibitor 1 and insertion/deletion angiotensinconverting enzyme gene polymorphisms in diabetic retinopathy in type 2 diabetes. Ophthalmologica. 2003;217:219–24.
- Lopes C, Dina C, Durand E, Froguel P. PAI-1 polymorphisms modulate phenotypes associated with the metabolic syndrome in obese and diabetic Caucasian population. Diabetologia. 2003;46(9):1284–90.
- Liu SG, Xue YM, Yang GC, He FY, Zhao XS. Relationship between plasminogen activator inhibitor-1 gene 4G/5G polymorphism and type 2 diabetic nephropathy in Chinese Han patients in Guangdong Province. Journal of first military medical university. 2004;24:904–7.
- Pan SZ, Yan XF, Lin JY, Yang LY. Association of ACE and PAI-1 gene polymorphisms with plasma PAI-1 level in type 2 diabetic patients. Chinese journal endocrinol metabolics. 2004;20:451–2.
- 34. Santos KG, Tschiedel B, Schneider J, Souto K, Roisenberg I. Diabetic retinopathy in Euro-Brazilian type 2 diabetic patients: relationship with polymorphisms in the aldose reductase, the plasminogen activator inhibitor-1 and the methylenetetrahydrofolate reductase genes. Diabetes Res Clin Pract. 2003;61(2):133–6.
- Meigs JB, Dupuis J, Liu C, O'Donnell CJ, Fox CS, Kathiresan S, et al. PAI-1 Gene 4G/5G polymorphism and risk of type 2 diabetes in a populationbased sample. Obesity (Silver Spring). 2006;14:753–8.
- Zietz B, Leonhardt K, Schäffler A. [Candidate genes and polymorphism analysis in type 2 diabetes mellitus]. Med Klin (Munich). 2006;101(8):605–16.
- Saely CH, Muendlein A, Vonbank A, et al. Type 2 diabetes significantly modulates the cardiovascular risk conferred by the PAI-1 -675 4G/5G polymorphism in angiographied coronary patients. Clin Chim Acta. 2008; 396(1–2):18–22.
- Yan XF, PAN SZ, Yan SJ, Zhang SQ. Relationship between plasminogen activator inhibitor 1 gene polymorphism and the level of endothelium-dependent vasodilatation in patients with type 2 diabetes. Clinical Medicine of China. 2008;24:708–10.
- Li P, Song GY. The study of plasma plasminogen activator inhibitor type-1 (PAI-1)activity and the polymorphism of PAI-1 gene in the NGT first degree relatives of type 2 diabetes. Hebei Medical University 2004:1–37.
- Ezzidi I, Mtiraoui N, Chaieb M, Kacem M, Mahjoub T, Almawi WY. Diabetic retinopathy, PAI-1 4G/5G and – 844G/A polymorphisms, and changes in circulating PAI-1 levels in Tunisian type 2 diabetes patients. Diabetes Metab. 2009;35(3):214–9.
- Al-Hamodi Z, Saif-Ali R, Ismail IS, Ahmed KA, Muniandy S. Effect of plasminogen activator inhibitor-1 and tissue plasminogen activator polymorphisms on susceptibility to type 2 diabetes in Malaysian subjects. J Biomed Biotechnol. 2012. 2012: 234937.
- Weng SC, Shu KH, Tarng DC, Wu MJ, Chen CH, Yu TM, et al. Gene polymorphisms are associated with posttransplantation diabetes mellitus among Taiwanese renal transplant recipients. Transplant Proc. 2012;44:667–71.
- Yan XF, Pan SZ, Yang LY, Huang LN, Zhao SH. Correlation Analysis of Polymorphisms of Angiotensin Converting Enzyme Gene, Plasminogen Activator Inhibitor-1 Gene and Nephropathy in Type 2 Diabetes. China Med. 2008;3:81–3.
- 44. Shu YT, Tian JL. The association study of PAI-1 gene polymorphism and diabetic CAD. Clin Res. 2011;6:86–8.
- 45. Murata M, Maruyama T, Suzuki Y, Saruta T, Ikeda Y. Paraoxonase 1 Gln/Arg polymorphism is associated with the risk of microangiopathy in Type 2 diabetes mellitus. Diabet Med. 2004;21:837–44.
- Tarnow L, Stehouwer CD, Emeis JJ, Poirier O, Cambien F, Hansen BV, Parving HH. Plasminogen activator inhibitor-1 and apolipoprotein E gene polymorphisms and diabetic angiopathy. Nephrol Dial Transplant. 2000;15:625–30.
- Martin RJ, Savage DA, Patterson CC, Brady HR, Maxwell AP. Common polymorphisms of the PAI1 gene do not play a major role in the development of diabetic nephropathy in Type 1 diabetes. Diabet Med. 2007;24:259–65.

- Prasad P, Tiwari AK, Kumar KM, Ammini AC, Gupta A, Gupta R, Thelma BK. Association analysis of ADPRT1, AKR1B1, RAGE, GFPT2 and PAI-1 gene polymorphisms with chronic renal insufficiency among Asian Indians with type-2 diabetes. BMC Med Genet. 2010;11:52.
- Li CG, Dong YH, Wang HY. Association of plasminogen activator inhibitor type-1 4G/5G polymorphism and type 2 diabetic with nephropathy. Circulation. 2001;9:333–6.
- Wang L, Liu Y. The relationship between polymorphisms of PAI-1 gene, PAI-1 antigen in plasma with diabetes nephropathy. Jilin University; 2004: p. 1-52.
- Tang KX. The association between gene expression of PAI-1 in adipose tissue of type 2 diabetes and vascular disease. Clin Chim Acta. 2004;15:1126–8.
- Zheng TS, Liu LM, Zhou WR. Correlation of plasminogen activator inhibitorgene polymorphism with type 2 diabetic nephropathy in Chinese. J Shanghai Jiaotong University (Med Sci). 2007;27:774–6.
- Xue J, Tian GS, Shi FH, Ge B. Polymorphisms of plasminogen activator inhibitor-I genes in type 2 diabetes with nephropathy in Han in Baotou. Chin Med J Metall Ind. 2010;27:373–5.
- Liu MY, Yang ZS, Shen LY, Sun SY, Li H. Association of plasminogen activator inhibitor-1 4G/5G polymorphism and type 2 diabetes with early nephropathy. Acta Acad Med Qingdao Univ. 2006;47:31–2.
- 55. Pierce M, Keen H, Bradley C. Risk of diabetes in offspring of parents with non-insulin-dependent diabetes. Diabet Med. 1995;12(1):6–13.
- Kaprio J, Tuomilehto J, Koskenvuo M, et al. Concordance for type 1 (insulindependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia. 1992;35(11):1060–7.
- 57. Effect of intensive diabetes treatment on the development. and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Diabetes Control and Complications Trial Research Group. J Pediatr. 1994;125(2):177–88.
- Intensive blood-glucose. control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837–53.
- Nyaga DM, Vickers MH, Jefferies C, Perry JK, O'Sullivan JM. The genetic architecture of type 1 diabetes mellitus. Mol Cell Endocrinol. 2018;477:70–80.
- Ahmad S, Ahluwalia TS. Editorial. The Role of Genetic and Lifestyle Factors in Metabolic Diseases. Front Endocrinol (Lausanne). 2019;10:475.
- 61. Flannick J, Mercader JM, Fuchsberger C, et al. Exome sequencing of 20,791 cases of type 2 diabetes and 24,440 controls. Nature. 2019;570(7759):71–6.
- 62. Ahluwalia TS, Kilpeläinen TO, Singh S, Rossing P. Editorial: Novel Biomarkers for Type 2 Diabetes. Front Endocrinol (Lausanne). 2019;10:649.
- Cesari M, Pahor M, Incalzi RA. Plasminogen activator inhibitor-1 (PAI-1): a key factor linking fibrinolysis and age-related subclinical and clinical conditions. Cardiovasc Ther. 2010;28(5):e72–91.
- Hamsten A, de Faire U, Walldius G, et al. Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. Lancet. 1987;2(8549):3–9.
- Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. N Engl J Med. 2000;342(24):1792–801.
- Festa A, D'Agostino R, Tracy RP, Haffner SM. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes. 2002; 51(4):1131–7.
- Festa A, Williams K, Tracy RP, Wagenknecht LE, Haffner SM. Progression of plasminogen activator inhibitor-1 and fibrinogen levels in relation to incident type 2 diabetes. Circulation. 2006;113(14):1753–9.
- Huang J, Sabater-Lleal M, Asselbergs FW, et al. Genome-wide association study for circulating levels of PAI-1 provides novel insights into its regulation. Blood. 2012;120(24):4873–81.
- Rosito GA, D'Agostino RB, Massaro J, et al. Association between obesity and a prothrombotic state: the Framingham Offspring Study. Thromb Haemost. 2004;91(4):683–9.
- Liu Y, Cheng J, Guo X, Mo J, Gao B, Zhou H, et al. The roles of PAI-1 gene polymorphisms in atherosclerotic diseases: A systematic review and metaanalysis involving 149,908 subjects. Gene. 2018;673:167–73.
- Gao WF, Guo YB, Bai Y, Ding XY, Yan YJ, Wu ZQ. Association between PAI-1 4G/5G polymorphism and diabetic nephropathy: a meta-analysis in the Chinese population. Int Urol Nephrol. 2016;48:1483–9.

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