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ORIGINAL RESEARCH

The Associations between Paraoxonase 1 L55M/Q192R Genetic Polymorphisms and the Susceptibilities of Diabetic Macroangiopathy and Diabetic Microangiopathy: A Meta-Analysis

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ABSTRACT

Introduction: Plenty of studies have focused on the associations of paraoxonase 1 Q192R and L55M genetic polymorphisms with diabetic macroangiopathy and microangiopathy susceptibility, but these associations remain controversial. Therefore, this meta-analysis was conducted to demonstrate these relationships.

Methods: Relevant studies published in English or Chinese were identified in PubMed, Embase, Wanfang Database, and CNKI by applying specific inclusion and exclusion criteria. Statistical analyses were performed using the STATA 12.0 statistical software.

Results: 25 Case–control studies were included in the meta-analyses: six on the association between paraoxonase 1 L55M genetic polymorphism and diabetic macroangiopathy risk, nine on the association between L55M and diabetic microangiopathy risk, 12 on the association between Q192R and diabetic macroangiopathy risk, and 12 on the association between Q192R and diabetic microangiopathy risk. Paraoxonase 1 L55M genetic polymorphism was significantly associated with diabetic microangiopathy susceptibility in the dominant model [odds ratio (OR) 0.53, 95% confidence interval (CI) 0.33–0.83, $P = 0.006$], the homozygous model (OR 0.37, 95% CI 0.16–0.86, $P = 0.021$), the allelic contrast model (OR 0.62, 95% CI 0.43–0.90, $P = 0.011$), the recessive model (OR 12.04, 95% CI 8.02–18.06, $P = 0.000$), and the heterozygous model (OR 0.57, 95% CI 0.38–0.85, $P = 0.006$), but L55M was not significantly associated with macroangiopathy susceptibility. Paraoxonase 1 Q192R genetic polymorphism was significantly associated with diabetic macroangiopathy susceptibility in the homozygous model (OR 1.88, 95% CI 1.06–3.32, $P = 0.030$), the allelic contrast model (OR 1.31, 95% CI 1.02–1.69, $P = 0.038$), and the recessive model (OR 1.55, 95% CI 1.11–2.16, $P = 0.010$), but not in the dominant and heterozygous models. Meanwhile, there was no significant association between paraoxonase 1 Q192R genetic polymorphism and diabetic microangiopathy susceptibility.

Conclusion: Paraoxonase 1 L55M and Q192R genetic polymorphisms play important roles in

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diabetic macroangiopathy and microangiopathy susceptibility. Further well-designed studies based on large samples are needed to confirm these results.

Keywords: Diabetic macroangiopathy; Diabetic microangiopathy; Paraoxonase 1; Polymorphism

INTRODUCTION

Diabetes mellitus (DM) is a highly investigated and complex chronic disease that has become increasingly prevalent with economic development. In 2016, DM was reported to be the eighth most prevalent cause of disease-related mortality. If DM is not properly managed, it can result in diabetic macroangiopathy (of the heart, brain, lower limb arteries, etc.), a specific form of accelerated atherosclerosis, as well as diabetic microangiopathy (of the kidney or eye, neuropathy, etc.), which are associated with increased morbidity and mortality. It is reported that 20–30% of diabetic patients have diabetic macroangiopathy [1]. Atherosclerosis in DM is more severe and aggressive than that in non-DM patients, and usually involves multiple arteries. DM also adversely affects the microvasculature in many organs, and remains the leading cause of chronic kidney disease and blindness [2]. Therefore, the ultimate goal of managing DM is to lower the risks of diabetic macroangiopathy (DMMA) and highly morbid microangiopathy (DMMI).

There are many risk factors associated with diabetic macroangiopathy and microangiopathy, including genetic factors, dyslipidemia, smoking, alcohol, obesity, exercise, and oxidative stress, but diabetic macroangiopathy and microangiopathy susceptibility is still not completely understood. Paraoxonase 1 is a 354-aa, 45-kDa glycoprotein that is synthesized in the liver and released into the blood, and which binds to high-density lipoprotein in a calcium-dependent manner [3]. Paraoxonase 1 is the main constituent of high-density lipoprotein (HDL), and contributes to the protective role of HDL against vascular diseases [4]. Paraoxonase 1 activity is reported to affect diabetic macroangiopathy and microangiopathy susceptibility [4–6]. There are large ethnic differences in the genetic polymorphisms of paraoxonase 1, according to the 1000 Genomes database [7]. A meta-analysis showed that paraoxonase 1 L55M and Q192R genetic polymorphisms were significantly associated with susceptibility to DM, but there were notable ethnic differences [7]. In 1998, Kao et al. reported that paraoxonase 1 L55M genetic polymorphism was significantly associated with diabetic retinopathy, whereas Q192R was not [8]. In another study, the author found that both (i.e., paraoxonase 1 L55M and Q192R) genetic polymorphisms were significantly related to diabetic complications [9]. Plenty of studies have focused on the associations of paraoxonase 1 Q192R and L55M genetic polymorphisms with diabetic macroangiopathy and microangiopathy susceptibility, but these links remain controversial. Therefore, the meta-analysis reported in the present paper was conducted to demonstrate these relationships.

METHODS

Search Strategy

We carried out literature searches for papers published in English or Chinese in the Embase, PubMed, Wanfang Database, and China National Knowledge Internet (CNKI) databases using the following keywords: “PON1” or “paraoxonase 1,” “diabetes” or “diabetes mellitus” or “DM” or “Type 2 diabetes mellitus (T2DM)” or “Type 1 diabetes mellitus (T1DM),” and “variation” or “polymorphism” or “single nucleotide polymorphism” or “SNP.” We also searched through relevant articles manually to find additional reports.

Inclusion and Exclusion Criteria

Articles were included in this meta-analysis if they complied with the following criteria: (1) they were published as original case–control studies; (2) they reported the relationship(s) of paraoxonase 1 L55M and/or Q192R genetic

polymorphisms with diabetic macroangiopathy and/or diabetic microangiopathy susceptibility; (3) they used DM without any complication as a control. When the same series of patients were used in more than one article, we used the latest and most complete study.

Data Extraction

WCF and WDL screened all of the articles found in the searches and extracted data from all eligible publications independently. For each study included in our meta-analysis, we carefully extracted the following information: first author, published year, country, ethnicity, type of DM, diagnostic criteria used for diabetic complications, and paraoxonase 1 L55M and/or Q192R genotypes in each group. If there were any discrepancies between the data extracted by WCF and WDL, they attempted to resolve the disagreement through discussion; if no agreement was reached, another author was consulted to resolve the dispute.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Statistical Analysis

Our meta-analysis followed the recommendations of the PRISMA statement and used the Newcastle–Ottawa Scale (NOS) criteria to assess study quality. Studies that met five or more of the NOS criteria were considered of high quality. Pooled odds ratios (ORs) were used to explore the relationships of paraoxonase 1 L55M and Q192R polymorphisms with the susceptibilities to diabetic macroangiopathy and/or diabetic microangiopathy. Heterogeneity was measured using the chi-square-based Q test. A random effects model was applied when $I^2 > 50\%$ and $P < 0.05$. Otherwise, a fixed effects model was used. Publication bias was investigated using Egger's test and a funnel plot. This meta-analysis was performed using STATA 12.0 software (Stata Corporation, TX, USA). $P < 0.05$ was taken to imply statistical significance.

RESULTS

Study Characteristics

As shown in Fig. S1 of the Electronic supplementary material (ESM), 332 publications were identified, among which 111 duplicates and 57 irrelevant papers were subsequently excluded. Of the remaining 164 papers, 139 were excluded for the following reasons: the paper was a review, no diabetic macroangiopathy or microangiopathy groups were included, there was no DM without complication group, the paper was a duplicate, and other paraoxonase 1 genetic polymorphisms were studied. Thus, 25 articles were ultimately included in the present meta-analysis. Eleven publications were written in English [8–18] and 14 were written in Chinese [19–32]. Table 1 shows detailed information on those 25 studies. The name of the first author, the year published, country, ethnicity, the type of DM, the numbers and ages of the cases and controls, the diagnostic criteria used for diabetic complications, and the genetic polymorphisms of paraoxonase 1 studied in each work are presented. All studies were found to be of high quality according to the NOS criteria.

Paraoxonase 1 L55M Genetic Polymorphism and Risk of Diabetic Macroangiopathy

As shown in Table 2, six studies probed the association between paraoxonase 1 L55M genetic polymorphism and the risk of diabetic macroangiopathy; these studies included 431 cases and 640 DM patients without complications as the control. Two studies were performed in Europe [10, 17], and four were carried out in Asia [9, 16, 31, 32]. The results indicated that there was no heterogeneity in the dominant model (LM + MM vs LL: $I^2 = 0.0\%$, $P = 0.447$, Fig. 1a, Table 4), homozygous model (MM vs LL: $I^2 = 30.7\%$, $P = 0.217$, Fig. 1b,

Table 1 Characteristics of the studies included in the meta-analysis of paraoxonase 1 L55M and Q192R in relation to diabetes complications

First author	Published year	Country	Ethnicity	DM patients without complications/ with DMMA/ with MDMI	Type of DM	Type(s) of complication(s)	Diagnostic criteria used for the diabetic complications	Gene polymorphism	Median (or mean) age (range or SD) year (DM/ DMMA/ DMMI)
Ei-Lebedy [16]	2014	Egypt	Egyptian	68/66/–	T2DM	DMMA (H)	American Diabetes Association Classification 2010	L55M Q192R	51.75 (6.00)/ 58.20 (7.12)
Shao [32]	2014	China	Chinese	177/202/–	T2DM	DMMA (H)	ECG, BET; coronarography	L55M Q192R	63.3 (10.9)/ 62.4 (12.5)
Zheng [19]	2012	China	Chinese	90/–/94	T2DM	DMMI (E)	OBCMA 1985	L55M Q192R	57.08 (11.97)/ 58.00 (7.80)
Chen [20]	2011	China	Chinese	97/–/113	T2DM	DMMI (K)	ACR	Q192R	59.9 (10.6)/ 61.6 (9.3)
Ergun [9]	2011	Turkey	Turkish	131/40/–	T2DM	DMMA (H)	ECG, exercise-stress ECG, ultrasound, echocardiography	L55M Q192R	NM
Tiwari [14]	2009	India	Indian	207/–/186	T2DM	DMMI (E&K)	E (fundoscopic, fluoroangiographic); K (creatinine $\geq$ 2 mg/dl, diabetes duration > 2 years)	Q192R	60.64 (10.66[a])/ 54.86 (11.31[a])
Flekac [10]	2008	Czekh	Czech	120/45/167	T1DM & T2DM	DMMA (H&B&L)/ DMMI (E&N)	H (ECG, coronarography); B (clinic, CT); L (angiography); E (ophthalmoscopy); N (clinical, physical examination)	L55M Q192R	NM

Table 1 continued

First author	Published year	Country	Ethnicity	DM patients without complications/ with DMMA/ with MDMI	Type of DM	Type(s) of complication(s)	Diagnostic criteria used for the diabetic complications	Gene polymorphism	Median (or mean) age (range or SD) year (DM/ DMMA/ DMMI)
Qi [27]	2007	China	Chinese	93/90/–	T2DM	DMMA (H&B&L)	H (ISFC/WHO criteria for CHD 1979); B (CT or MRI); L (ultrasound)	Q192R	56.6 (7.0)/62.1 (9.3)
Shi [21]	2007	China	Chinese	92/–/87	T2DM	DMMI (K)	UAER $\geq$ 20 μg/ml or ACR $\geq$ 25 mg/g	Q192R	60.9 (7.3)/62.5 (7.1)
Hofer [18]	2006	Australia	Caucasian	138/–/10	T1DM	DMMI (E&K)	UAER	L55M	NM
Shao [31]	2006	China	Chinese	50/42/–	T2DM	DMMA (H)	ECG, coronarography	L55M	61.5 (3.3)/64.3 (5.67)
Sun [30]	2005	China	Chinese	162/–/147	T2DM	DMMI (K)	WHO criteria for CKD	L55M Q192R	64.5 (10.3)/ 64.7 (11.2)
Li [23]	2004	China	Chinese	36/27/–	T2DM	DMMA (H)	NM	Q192R	56 (8)/61 (9)
Murata [11]	2004	Japan	Japanese	92/–/188	T2DM	DMMI (E&K)	NM	Q192R	47.9 (8.40)/ 49.0 (11.4)
Zhang [22]	2004	China	Chinese	56/60/–	T2DM	DMMA (B)	CT or MRI	Q192R	63.6 (11.4)/ 64.5 (11.3)
Ma [28]	2003	China	Chinese	80/96/–	T2DM	DMMA (H)	H (ISFC/WHO criteria for CHD 1979)	Q192R	64 (8)/65 (7)
Pu [25]	2003	China	Chinese	30/26/44	T2DM	DMMA (H&B&L)/ DMMI (E&K)	H (disease history, ECG or Holter); B (CT or MRI); L (clinical, ultrasound); E (OBCMA 1985); K (Mogensen criteria)	Q192R	67 (5)/66 (5)/ 67 (5)

Table 1 continued

First author	Published year	Country	Ethnicity	DM patients without complications/ with DMMA/ with MDMI	Type of DM	Type(s) of complication(s)	Diagnostic criteria used for the diabetic complications	Gene polymorphism	Median (or mean) age (range or SD) year (DM/ DMMA/ DMMI)
Qian [29]	2003	China	Chinese	121/125/–	T2DM	DMMA (H)	WHO criteria for CHD 1979	Q192R	57.8 (5.7)/57.7 (6.5)
Ren [24]	2003	China	Chinese	69/–/126	T2DM	DMMI (E&K)	E (retinal photography); K (UAER)	Q192R	NM
Wang [26]	2003	China	Chinese	36/39/–	T2DM	DMMA (H)	WHO criteria for CHD	Q192R	64.8 (11.9)/ 72.7 (8.3)
Letellier [17]	2002	France	Caucasian	96/36/35	T2DM	DMMA (H)/ DMMI (E&K)	H (clinic, ultrasound); E (fundus eye examination); K (microalbuminuria)	L55M Q192R	56.76 (10.72)/ NM
Kao [13]	2002	Australia	Caucasian	198/–/171	T1DM	DMMI (E&K)	E (retinal photography); K (UAER)	L55M	13.00 (11.8–14.7)/ 14.8 (13.2–16.5)
Kordonouri [15]	2001	Australia	Caucasian	117/–/73	T1DM	DMMI (E)	Retinal photography	L55M	NM
Araki [12]	2000	USA	Caucasian	179/–/188	T1DM	DMMI (K)	ACR	L55M Q192R	36 (7)/35 (6)

Table 1 continued

First author	Published year	Country	Ethnicity	DM patients without complications/ with DMMA/ with MDMI	Type of DM	Type(s) of complication(s)	Diagnostic criteria used for the diabetic complications	Gene polymorphism	Median (or mean) age (range or SD) year (DM/ DMMA/ DMMI)
Kao [8]	1998	Australia	Caucasian	119/–/80	IDDM	DMMI (E)	NM	L55M Q192R	13.9 (0.55[a])/ 15.40 (0.67[a])

DM diabetes mellitus, *T2DM* type 2 diabetes mellitus, *T1DM* type 1 diabetes mellitus, *IDDM* insulin-dependent diabetes mellitus, *NM* not mentioned, *DMMA* diabetic macroangiopathy, *DMMI* diabetic microangiopathy, *H* heart, *E* eye, *K* kidney, *B* brain, *P* peripheral artery disease, *L* lower limbs, *N* neuropathy, *OBCMA* Ophthalmology Branch of the Chinese Medical Association, *ISFC* International Society of Federation of Cardiology, *ACR* urinary albumin to creatinine ratio, *CKD* chronic kidney disease, *UAER* urinary albumin excretion rate, *ECG* electrocardiogram, *BET* bicycle ergometer test, *CHD* coronary heart disease

[a] The standard deviation (SD) calculated from the original paper

Table 4), allelic contrast model (M vs L: I^2 = 16.8%, P = 0.305, Fig. 1c, Table 4), recessive model (MM vs LL + LM: I^2 = 19.9%, P = 0.288, Fig. 1d, Table 4), and heterozygous model (LM vs LL: I^2 = 0.0%, P = 0.610, Fig. 1e, Table 4). Meta-analysis suggested that there was no significant association of paraoxonase 1 L55M genetic polymorphism with susceptibility to diabetic macroangiopathy in all five models (LM + MM vs LL: OR 0.98, 95% CI 0.69–1.38, P = 0.996, Fig. 1a; MM vs LL: OR 1.30, 95% CI 0.81–2.08, P = 0.279, Fig. 1b; and M vs L: OR 1.10, 95% CI 0.87–1.39, P = 0.414, Fig. 1c; MM vs LLLM: OR 1.30, 95% CI 0.99–1.90, P = 0.176, Fig. 1d; LM vs LL: OR 0.90, 95% CI 0.62–1.30, P = 0.569, Fig. 1e; Table 4). When the effects models were altered, the significances of these three models did not change statistically significantly (data not shown). Based on the funnel plot and Egger's test, none of the three models had significant publication bias (LM + MM vs LL: t = − 0.040, P = 0.970; MM vs LL: t = 0.300, P = 0.781; M vs L: t = − 0.340, P = 0.752; MM vs LL + LM: t = 0.69, P = 0.539; LM vs LL: t = − 0.10, P = 0.923; data not shown).

Paraoxonase 1 L55M Genetic Polymorphism and Susceptibility to Diabetic Microangiopathy

As shown in Table 2, nine studies focused on the association of paraoxonase 1 L55M genetic polymorphism with the risk of diabetic microangiopathy; these studies included 992 cases and 1212 controls [8, 10, 12, 13, 15, 17–19, 30]. The results showed that there was significant heterogeneity in the dominant model (LM + MM vs LL: I^2 = 81.0%, P = 0.000, Fig. 2a, Table 4), homozygous model (MM vs LL: I^2 = 80.9%, P = 0.000, Fig. 2b, Table 4), allelic contrast model (M vs L: I^2 = 84.1%, P = 0.000, Fig. 2c, Table 4), recessive model (MM vs LL + LM: I^2 = 68.6%, P = 0.001, Fig. 2d, Table 4), and heterozygous model (LM vs LL: I^2 = 71.1%, P = 0.000, Fig. 2e, Table 4). Thus, subgroup analysis of ethnicity, type of DM, and Hardy–Weinberg equilibrium (HWE) was performed, and the results indicated that ethnicity

Table 2 Characteristics of the studies included in this meta-analysis of the relationship between paraoxonase 1 L55M polymorphism and risk of diabetes complications

Author	Year	Type of DM	Country	Ethnicity	DM without complications			HWE (control)		Diabetic macroangiopathy			Diabetic microangiopathy		
					LL	LM	MM	χ^2	*P*	LL	LM	MM	LL	LM	MM
Ei-Lebedy [16]	2014	T2DM	Egypt	Egyptian	11	34	23	0.070	0.791	12	32	22			
Shao [32]	2014	T2DM	China	Chinese	159	16	2	2.660	0.103	180	18	4			
Zheng [19]	2012	T2DM	China	Chinese	82	7	1	1.740	0.187				86	8	0
Ergun [9]	2011	T2DM	Turkey	Turkish	25	35	71	19.50	**0.000**	10	10	20			
Flekac [10]	2008	T1DM & T2DM	Czekh	Czech	37	58	23	0.001	0.975	8	21	16	47	83	37
Hofer [18]	2006	T1DM	Australia	Caucasian	50	69	19	0.391	0.532				7	2	1
Shao [31]	2006	T2DM	China	Chinese	46	4	0	0.167	0.683	39	3	0			
Sun [30]	2005	T2DM	China	Chinese	66	79	12	3.247	0.072				55	71	11
Letellier [17]	2002	T2DM	France	Caucasian	31	55	10	4.071	**0.044**	15	14	7	19	13	3
Kao [13]	2002	T1DM	Australia	Caucasian	45	111	42	2.929	0.087				89	75	7
Kordonouri [15]	2001	T1DM	Australia	Caucasian	31	60	26	0.089	0.766				45	25	3
Araki [12]	2000	T1DM	USA	Caucasian	68	90	21	1.158	0.284				80	84	24
Kao [8]	1998	IDDM	Australia	Caucasian	32	71	16	5.595	**0.019**				40	37	3

DM diabetes mellitus, *T2DM* type 2 diabetes mellitus, *T1DM* type 1 diabetes mellitus, *IDDM* insulin-dependent diabetes mellitus, *HWE* Hardy–Weinberg equilibrium

Boldface means statistical significance ($P < 0.05$)

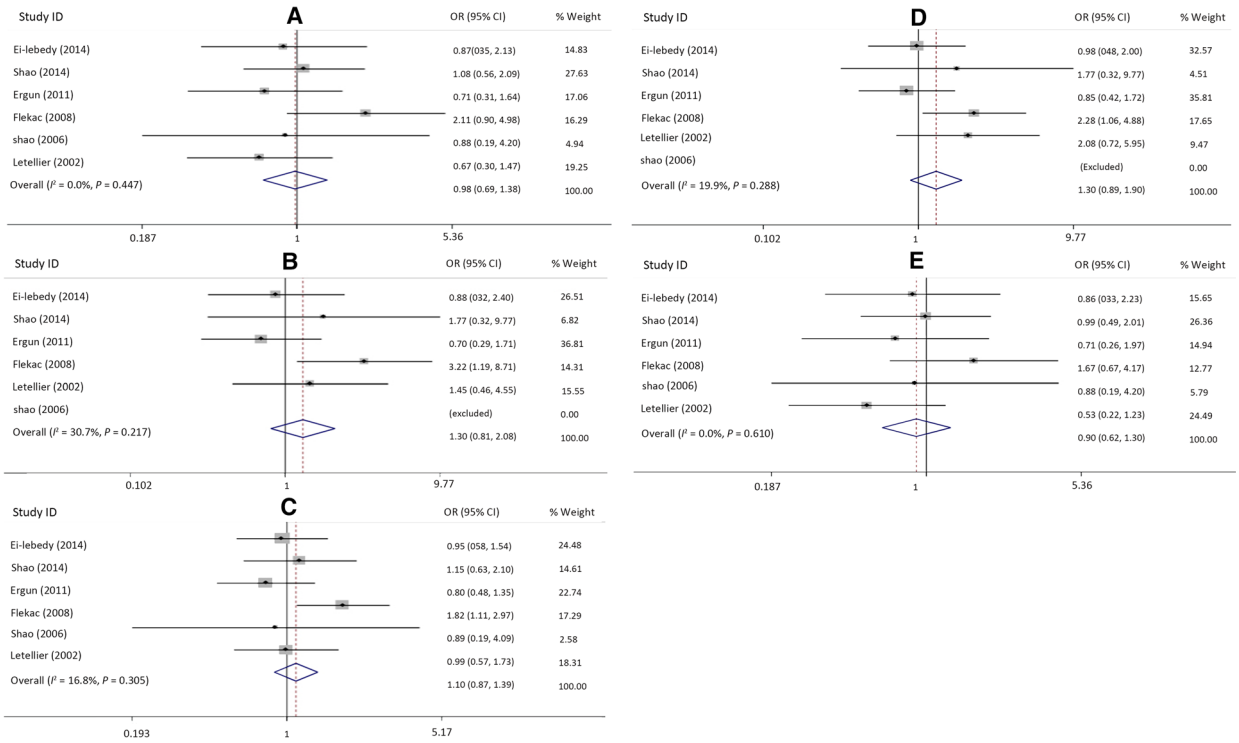

Fig. 1a–e Forest plots for the association of paraoxonase 1 L55M genetic polymorphism with diabetic macroangiopathy. **a** Dominant model, LM + MM vs LL; **b** homozygous model, MM vs LL; **c** allelic contrast model, M vs L; **d** recessive model, MM vs LL + LM; **e** heterozygous model, LM vs LL

and type of DM can explain the heterogeneity in the recessive model, but not the heterogeneity in the other models (Table 4). Meta-regression analysis was then performed using the covariates published year, sample size, ethnicity, type of DM, and HWE to investigate the sources of the between-study heterogeneity, but it failed to identify those sources (Table 5). Paraoxonase 1 L55M genetic polymorphism was clearly related to diabetic microangiopathy susceptibility in the dominant model (OR 0.53, 95% CI 0.33–0.83, $P = 0.006$, Fig. 2a, Table 4), the homozygous model (OR 0.37, 95% CI 0.16–0.86, $P = 0.021$, Fig. 2b, Table 4), the allelic contrast model (OR 0.62, 95% CI 0.43–0.90, $P = 0.011$, Fig. 2c, Table 4), the recessive model (OR 12.04, 95% CI 8.02–18.06, $P = 0.000$, Fig. 2d, Table 4), and the heterozygous model (OR 0.57, 95% CI 0.38–0.85, $P = 0.006$, Fig. 2e, Table 4). When the effects models were changed, the statistical significance did not alter (data not shown). Meanwhile, the funnel plot and Egger's test indicated that there was no significant publication bias in the models (LM + MM vs LL: $t = -0.640$, $P = 0.543$; MM vs LL: $t = -1.750$, $P = 0.124$; M vs L: $t = -0.710$, $P = 0.503$; LM vs LL: $t = -0.540$, $P = 0.607$; data not shown) except for the recessive model (MM vs LL + LM: $t = 2.580$, $P = 0.037$, data not shown).

Paraoxonase 1 Q192R Genetic Polymorphism and Susceptibility to Diabetic Macroangiopathy

As shown in Table 3, twelve studies focused on the association of paraoxonase 1 Q192R genetic polymorphism with the risk of diabetic macroangiopathy; these studies included 827 cases and 1069 controls [9, 10, 16, 17, 22, 23, 25–29, 32]. The results showed that there was significant heterogeneity in the dominant model (QR + RR vs QQ: $I^2 = 63.6\%$, $P = 0.001$, Fig. 3a, Table 4), homozygous model (RR vs QQ: $I^2 = 64.5\%$, $P = 0.001$, Fig. 3b, Table 4), allelic contrast model (R vs Q: $I^2 = 66.5\%$, $P = 0.001$,

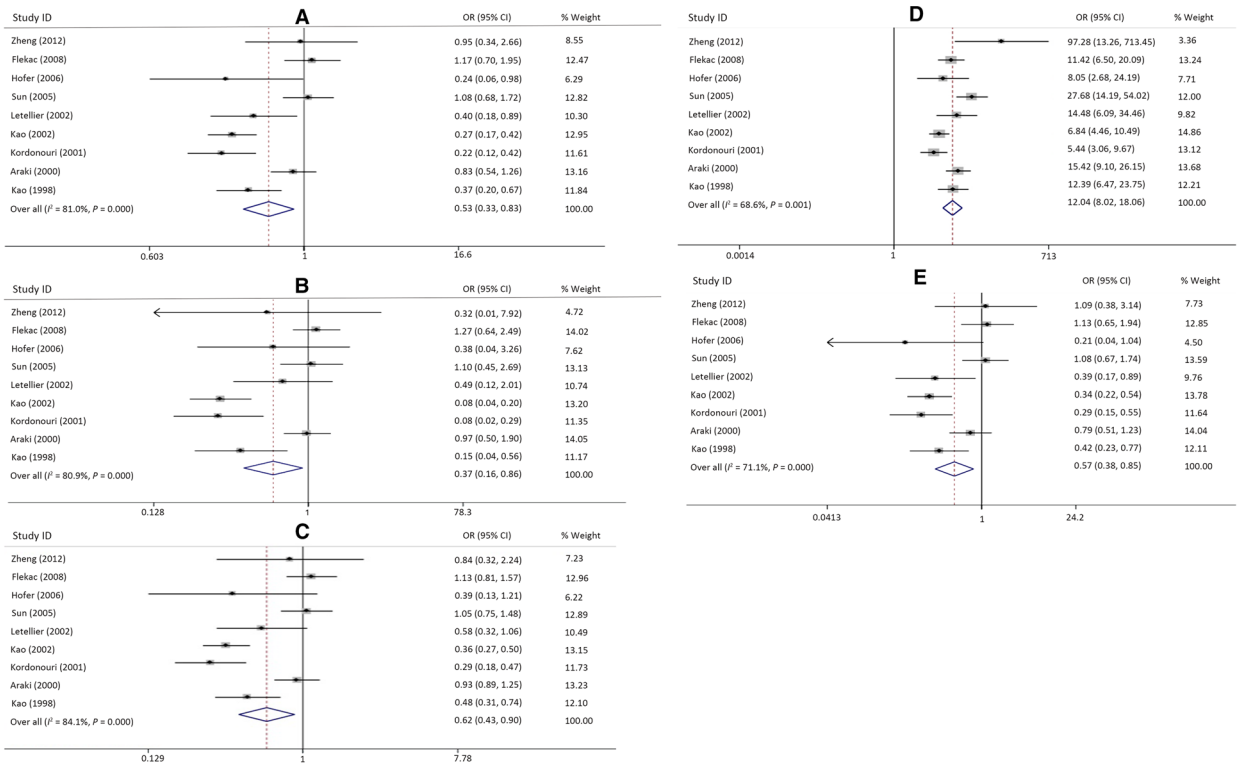

Fig. 2a–e Forest plots for the association of paraoxonase 1 L55M genetic polymorphism with diabetic microangiopathy. **a** Dominant model, LM + MM vs LL; **b** homozygous model, MM vs LL; **c** allelic contrast model, M vs L; **d** recessive model, MM vs LL + LM; **e** heterozygous model, LM vs LL

Fig. 3c, Table 4), recessive model (RR vs QQ + QR: I^2 = 45.7%, P = 0.042, Fig. 3d, Table 4), and heterozygous model (QR vs QQ: I^2 = 52.5%, P = 0.017, Fig. 3e, Table 4). Subgroup analysis of ethnicity, type of DM, and HWE was therefore conducted, but it failed to find the sources of heterogeneity (Table 4). Meta-regression analysis was then performed using the covariates published year, sample size, ethnicity, type of DM, and HWE. The results showed that sample size could explain the heterogeneity in the dominant allelic and heterozygous models, and HWE could explain the heterogeneity in the homozygous and recessive models (Table 5). Paraoxonase 1 Q192R genetic polymorphism was significantly related to diabetic macroangiopathy susceptibility in the homozygous model (OR 1.88, 95% CI 1.06–3.32, P = 0.030, Fig. 3b, Table 4), allelic contrast model (OR 1.31, 95% CI 1.02–1.69, P = 0.038, Fig. 3c, Table 4), and recessive model (OR 1.55, 95% CI 1.11–2.16, P = 0.010, Fig. 3d, Table 4), but not the dominant model (OR 1.35, 95% CI 0.88–2.08, P = 0.163, Fig. 3a, Table 4) or heterozygous model (OR 1.20, 95% CI 0.81–1.78, P = 0.370, Fig. 3e, Table 4). Sensitivity analysis indicated that when the effects models were changed, the statistical significance did not alter (data not shown). Meanwhile, there was no significant publication bias according to the funnel plot and Egger's test (QR + RR vs QQ: t = 1.44, P = 0.179; RR vs QQ: t = 1.46, P = 0.174; R vs Q: t = 1.00, P = 0.343; RR vs QQ + QR: t = 1.30, P = 0.224; QR vs QQ: t = 1.03, P = 0.326; data not shown).

Paraoxonase 1 Q192R Genetic Polymorphism and Susceptibility to Diabetic Microangiopathy

As shown in Table 3, twelve studies focused on the association of paraoxonase 1 Q192R genetic polymorphism with the risk of diabetic

Table 3 Characteristics of the studies included in this meta-analysis of the relationships between paraoxonase 1 Q192R polymorphism and the risks of diabetic macroangiopathy and microangiopathy

Author	Year	Type of DM	Country	Ethnicity	DM without complications			HWE (control)		Diabetic macroangiopathy			Diabetic microangiopathy		
					QQ	QR	RR	χ^2	*P*	QQ	QR	RR	QQ	QR	RR
Ei-Lebedy [16]	2014	T2DM	Egypt	Egyptian	39	23	6	0.867	0.352	21	36	9			
Shao [32]	2014	T2DM	China	Chinese	19	95	88	0.860	0.354	31	78	68			
Zheng [19]	2012	T2DM	China	Chinese	6	32	52	0.124	0.725				15	34	45
Chen [20]	2011	T2DM	China	Chinese	14	53	30	1.487	0.223				9	56	48
Ergun [9]	2011	T2DM	Turkey	Turkish	74	37	20	12.78	**0.000**	17	13	10			
Tiwari [14]	2009	T2DM	India	Indian	29	100	78	0.115	0.735				34	82	70
Flekac [10]	2008	T1DM & T2DM	Czekh	Czech	80	36	4	0.000	0.984	35	9	1	112	50	5
Qi [27]	2007	T2DM	China	Chinese	17	48	28	0.205	0.651	15	49	26			
Shi [21]	2007	T2DM	China	Chinese	22	38	32	2.481	0.115				11	31	45
Sun [30]	2005	T2DM	China	Chinese	29	81	52	0.069	0.793				24	80	43
Li [23]	2004	T2DM	China	Chinese	8	15	13	0.813	0.367	8	9	10			
Murata [11]	2004	T2DM	Japan	Japanese	15	46	31	0.090	0.765				11	98	79
Zhang [22]	2004	T2DM	China	Chinese	11	22	23	1.736	0.188	5	19	36			
Ma [28]	2003	T2DM	China	Chinese	8	42	30	1.508	0.219	8	42	46			
Pu [25]	2003	T2DM	China	Chinese	4	18	8	1.497	0.221	1	15	10	1	31	12
Qian [29]	2003	T2DM	China	Chinese	20	85	16	20.61	**0.000**	9	75	41			
Ren [24]	2003	T2DM	China	Chinese	5	30	34	0.221	0.638				17	65	44
Wang [26]	2003	T2DM	China	Chinese	13	19	4	0.580	0.446	5	22	12			
Letellier [17]	2002	T2DM	France	Caucasian	55	38	3	1.516	0.218	22	11	3	15	18	2
Araki [12]	2000	T1DM	USA	Caucasian	86	79	14	0.512	0.474				84	81	23
Kao [8]	1998	IDDM	Australia	Caucasian	60	39	20	7.928	**0.005**				35	26	19

DM diabetes mellitus, *T2DM* type 2 diabetes mellitus, *T1DM* type 1 diabetes mellitus, *HWE* Hardy–Weinberg equilibrium
Boldface means statistical significance ($P < 0.05$)

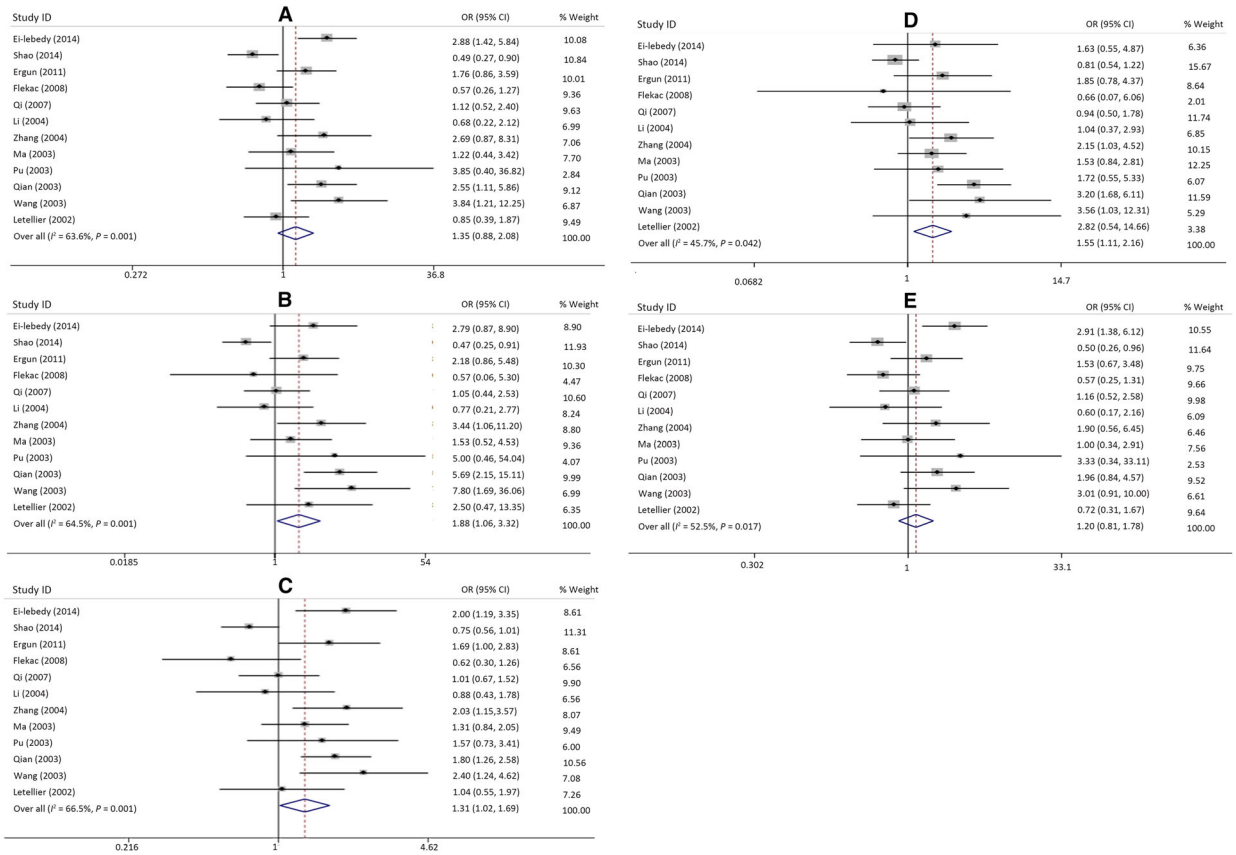

Fig. 3a–e Forest plots for the association of paraoxonase 1 Q192R genetic polymorphism with diabetic macroangiopathy. **a** Dominant model, QR + RR vs QQ; **b** homozygous model, RR vs QQ; **c** allelic contrast model, R vs Q; **d** recessive model, RR vs QQ + QR; **e** heterozygous model, QR vs QQ

microangiopathy; these studies included 1455 cases and 1353 controls [8, 10–12, 14, 17, 19–21, 24, 25, 30]. The results showed that there was significant heterogeneity in the dominant model (QR + RR vs QQ: I^2 = 53.5%, P = 0.014, Fig. 4a, Table 4), homozygote model (RR vs QQ: I^2 = 60.4%, P = 0.004, Fig. 4b, Table 4), and allelic contrast model (R vs Q: I^2 = 59.3%, P = 0.005, Fig. 4c, Table 4) but not in the recessive model (RR vs QQ + QR: I^2 = 39.8%, P = 0.075, Fig. 4d, Table 4) and heterozygous model (QR vs QQ: I^2 = 35.1%, P = 0.109, Fig. 4e, Table 4). Subgroup analysis of ethnicity, type of DM, and HWE and meta-regression analysis using the covariates published year, sample size, ethnicity, type of DM, and HWE were therefore performed to investigate the sources of heterogeneity. Unfortunately, the sources of heterogeneity were not found (Tables 4, 5). There was no marked association between paraoxonase 1 Q192R genetic polymorphism and susceptibility to diabetic microangiopathy in the dominant model (OR 1.21, 95% CI 0.90–1.64, P = 0.209, Fig. 4a, Table 4), the homozygous model (OR 1.33, 95% CI 0.86–2.05, P = 0.119, Fig. 4b, Table 4), the allelic contrast model (OR 1.12, 95% CI 0.93–1.35, P = 0.227, Fig. 4c, Table 4), the recessive model (OR 1.12, 95% CI 0.93–1.33, P = 0.225, Fig. 4d, Table 4), and the heterozygous model (OR 1.12, 95% CI 0.92–1.36, P = 0.272, Fig. 4e, Table 4). Sensitivity analysis indicated that when the effects models were changed, the statistical significances did not alter (data not shown). Meanwhile, according to the funnel plot and Egger's test, there was no significant publication bias in the models (QR + RR vs QQ: t = 2.19,

Table 4 Main results of the pooled data in this meta-analysis

	Dominant model			Homozygous model			Allelic model			Recessive model			Heterozygous model		
	OR (95% CI)	*P*	I2,% (*P*)	OR (95% CI)	*P*	I2,% (*P*)	OR (95% CI)	*P*	I2,% (*P*)	OR (95% CI)	*P*	I2,% (P)	OR (95% CI)	*P*	I2,% (P)
L55M DMMA															
Total	0.98(0.69-1.38)	0.996	0.0(0.447)	1.30(0.81-2.08)	0.279	30.7(0.217)	1.10(0.87-1.39)	0.414	16.8(0.305)	1.30(0.89-1.90)	0.176	19.9(0.298)	0.90(0.62-1.30)	0.569	0.0(0.610)
L55M DMMI															
Total	0.53(0.33-0.83)	**0.006**	81.0(**0.000**)	0.37(0.16-0.86)	0.021	80.9(**0.000**)	0.62(0.43-0.90)	0.011	84.1(**0.000**)	12.04(8.02-18.06)	**0.000**	68.6(**0.001**)	0.57(0.38-0.85)	**0.006**	71.1(**0.000**)
Asian	1.06(0.69-1.62)	0.794	0.0(0.827)	1.01(0.43-2.38)	0.988	0.0(0.465)	1.03(0.74-1.42)	0.871	0.0(0.676)	38.41(11.68-126.37)	**0.000**	40.0(0.197)	1.08(0.70-1.67)	0.729	0.0(0.986)
NAS	0.44(0.26-0.74)	**0.002**	81.1(**0.000**)	0.31(0.12-0.84)	**0.022**	84.4(**0.000**)	0.55(0.36-0.84)	**0.006**	85.7(**0.000**)	9.73(7.06-13.41)	**0.000**	46.2(0.084)	0.48(0.31-0.74)	**0.001**	69.8(**0.003**)
T2DM	0.77(0.41-1.46)	0.424	55.8(0.104)	0.83(0.40-1.73)	0.614	0.0(0.531)	0.86(0.58-1.26)	0.435	29.8(0.241)	25.4(11.28-57.48)	**0.000**	49.0(0.141)	0.79(0.40-1.54)	0.483	56.7(0.099)
Other	0.44(0.25-0.80)	**0.006**	84.1(**0.000**)	0.29(0.09-0.89)	**0.031**	87.0(**0.000**)	0.54(0.34-0.88)	**0.014**	88.1(**0.000**)	9.33(6.60-13.19)	**0.000**	50.8(0.071)	0.49(0.30-0.80)	**0.004**	74.1(**0.002**)
HWE	0.57(0.33-1.01)	0.053	84.5(**0.000**)	0.40(0.15-1.10)	0.076	84.3(**0.000**)	0.95(0.41-1.02)	0.061	87.4(**0.000**)	11.92(7.12-19.96)	**0.000**	75.9(**0.000**)	0.62(0.39-1.01)	0.055	76.2(**0.000**)
NH	0.38(0.33-0.83)	**0.000**	0.0(0.862)	0.26(0.08-0.86)	**0.024**	30.8(0.229)	0.51(0.43-0.90)	**0.000**	0.0(0.620)	13.11(7.79-22.06)	**0.000**	0.0(0.778)	0.41(0.25-0.66)	**0.000**	0.0(0.882)
Q192R DMMA															
Total	1.35(0.88-2.08)	0.163	63.6(**0.001**)	1.88(1.06, 3.32)	**0.030**	64.5(**0.001**)	1.31(1.02, 1.69)	**0.038**	66.5(**0.001**)	1.55(1.11-2.16)	**0.010**	45.7(**0.042**)	1.20(0.81-1.78)	0.370	52.5(**0.017**)
Asian	1.58(0.98-2.56)	0.061	63.5(**0.003**)	1.97(1.05-3.69)	0.034	69.9(**0.000**)	1.41(1.07-1.86)	**0.013**	68.5(**0.001**)	1.55(1.09-2.21)	**0.014**	52.9(**0.024**)	1.39(0.90-2.16)	0.142	51.3(**0.030**)
NAS	0.70(0.40-1.23)	0.213	0.0(0.482)	1.44(0.35-5.89)	0.611	8.4(0.296)	0.82(0.50-1.36)	0.448	11.0(28.9)	1.66(0.42-6.59)	0.474	7.0(0.300)	0.64(0.36-1.16)	0.141	0.0(0.694)
T2DM	1.48(0.95-2.29)	0.082	61.8(**0.003**)	1.99(1.10-3.59)	**0.022**	66.9(**0.001**)	1.38(1.07-1.78)	0.014	65.5(**0.001**)	1.58(1.13-2.23)	**0.008**	49.6(**0.031**)	1.30(0.86-1.95)	0.216	50.5(**0.027**)
Other	NA	NA	NA (NA)	NA	NA	NA (NA)	NA	NA	NA (NA)	NA	NA	NA (NA)	NA	NA	NA (NA)
HWE	1.23(0.75-2.01)	0.414	65.0(**0.002**)	1.59(0.86-2.93)	0.138	58.9(**0.009**)	1.22(0.92-1.63)	0.167	65.2(**0.002**)	1.31(0.96-1.80)	0.088	25.8(0.206)	1.11(0.69-1.76)	0.672	56.3(**0.014**)
NH	2.06(1.20-3.54)	**0.009**	0.0(0.504)	3.47(1.35-3.32)	**0.010**	49.2(0.161)	1.76(1.31-2.37)	**0.000**	0.0(0.835)	2.63(1.57-4.41)	**0.000**	0.6(0.316)	1.73(0.8-1.78)	0.070	0.0(0.680)
Q192R DMMI															
Total	1.21(0.90-1.64)	0.209	53.5(**0.014**)	1.33(0.86-2.05)	0.119	60.4(**0.004**)	1.12(0.93-1.35)	0.227	59.3(**0.005**)	1.12(0.93-1.33)	0.225	39.8(0.075)	1.12(0.92-1.36)	0.272	35.1(0.109)
Asian	1.22(0.72-2.08)	0.456	68.0(**0.003**)	1.26(0.68-2.34)	0.468	72.9(**0.001**)	1.07(0.83-1.40)	0.595	71.0(**0.001**)	1.06(0.87-1.28)	0.579	55.0(**0.030**)	1.12(0.84-1.50)	0.430	54.8(**0.030**)
NAS	1.19(0.91-1.54)	0.2	0.0(0.626)	1.57(0.98-2.52)	0.06	0.0(0.818)	1.21(0.99-1.48)	0.067	0.0(0.611)	1.50(0.96-2.36)	0.076	0.0(0.873)	1.11(0.85-1.47)	0.444	0.0(0.692)
T2DM	1.28(0.80-2.05)	0.311	65.2(**0.003**)	1.31(0.73-2.36)	0.368	69.7(**0.001**)	1.11(0.86-1.42)	0.422	68.7(**0.001**)	1.06(0.88-1.29)	0.537	49.7(**0.044**)	1.18(0.90-1.55)	0.230	51.5(**0.036**)
Other	1.31(0.85-1.49)	0.398	0.0(0.756)	1.53(0.94-2.49)	0.09	0.0(0.702)	1.17(0.94-1.45)	0.149	0.0(0.570)	1.49(0.93-2.36)	0.095	0.0(0.725)	1.05(0.78-1.41)	0.752	0.0(0.945)
HWE	1.21(0.86-1.69)	0.274	57.5(**0.009**)	1.30(0.80-2.11)	0.284	63.4(**0.002**)	1.10(0.90-1.34)	0.336	61.7(**0.004**)	1.09(0.91-1.31)	0.346	42.5(0.066)	1.12(0.90-1.38)	0.306	41.0(0.075)
NH	NA	NA	NA (NA)	NA	NA	NA (NA)	NA	NA	NA (NA)	NA	NA	NA (NA)	NA	NA	NA (NA)

DMMA diabetic macroangiopathy, *DMMI* diabetic microangiopathy, *T2DM* type 2 diabetes mellitus, *NAS* non-Asian, *NA* not available, *HWE* Hardy-Weinberg equilibrium, *NH* non-HWE

$P = 0.054$; RR vs QQ: $t = 1.35$, $P = 0.207$; R vs Q: $t = 0.69$, $P = 0.505$, RR vs QQ + QR: $t = 0.61$, $P = 0.555$; data not shown) except in the heterozygous model (QR vs QQ: $t = 2.36$, $P = 0.040$, data not shown).

DISCUSSION

This study is the first to demonstrate that paraoxonase-1 L55M and Q192R genetic polymorphisms are associated with susceptibility to diabetic macroangiopathy and microangiopathy. The results showed that paraoxonase 1 L55M genetic polymorphism was significantly related to diabetic microangiopathy susceptibility, but not diabetic macroangiopathy susceptibility, in the dominant, homozygous, and allelic contrast models. There was also a significant association of paraoxonase 1 Q192R genetic polymorphism with diabetic macroangiopathy susceptibility in the homozygous and allelic contrast models, but not in the dominant model. Meanwhile, there was no significant relationship between paraoxonase 1 Q192R genetic polymorphism and susceptibility to diabetic microangiopathy.

Paraoxonase 1 has been shown to have antioxidant properties and to protect low-

Table 5 The meta-regression results for the associations between paraoxonase 1 genetic polymorphism and diabetes macroangiopathy/microangiopathy susceptibility

Subject	Genetic model	Covariate	Coefficient	Standard error	*Z* value	*P* value	95% confidence interval
L55M & DMMI	Dominant	Published year	0.1090745	0.0956685	1.14	0.254	− 0.0784323 to 0.2965813
		Sample size	0.005215	0.0039579	1.32	0.188	− 0.0025424 to 0.0129723
		Ethnicity	− 0.4837321	1.204749	− 0.40	0.688	− 2.844998 to 1.877533
		Type of DM	− 0.0062408	1.085109	− 0.01	0.995	− 2.133016 to 2.120534
		HWE	0.7979578	1.054773	0.76	0.449	− 1.269359 to 2.865275
	Homozygous	Published year	0.1041156	0.2001671	0.52	0.603	− 0.2882047 to 0.4964358
		Sample size	0.0066319	0.0168507	0.39	0.694	− 0.0263948 to 0.0396586
		Ethnicity	0.5950655	2.73419	0.22	0.828	− 4.763848 to 5.953979
		Type of DM	− 0.9519258	2.401169	− 0.40	0.692	− 5.658131 to 3.754279
		HWE	0.136136	2.350938	0.06	0.954	− 4.471617 to 4.743889
	Allelic	Published year	0.0845667	0.0786569	1.08	0.282	− 0.069598 to 0.2387315
		Sample size	0.0020688	0.0016197	1.28	0.201	− 0.0011057 to 0.0052433
		Ethnicity	− 0.1843924	0.9877488	− 0.19	0.852	− 2.120345 to 1.75156
		Type of DM	− 0.1308186	0.884981	− 0.15	0.882	− 1.865349 to 1.603712
		HWE	0.6506242	0.8619522	0.75	0.450	− 1.038771 to 2.340019
	Recessive	Published year	0.07039	0.0809792	0.87	0.385	− 0.0883263 to 0.2291063
		Sample size	0.0019382	0.0025359	0.76	0.445	− 0.0030321 to 0.0069084
		Ethnicity	− 1.124716	1.01324	− 1.11	0.267	− 3.11063 to 0.8611974
		Type of DM	− 0.0469295	0.8809193	− 0.05	0.958	− 1.7735 to 1.679641
		HWE	0.8786279	0.8244041	1.07	0.287	− 0.7371745 to 2.49443
	Heterozygous	Published year	0.1017681	0.0861222	1.18	0.237	− 0.0670283 to 0.2705645
		Sample size	0.0050425	0.0041101	1.23	0.220	− 0.0030132 to 0.0130982
		Ethnicity	− 0.519662	1.07313	− 0.48	0.628	− 2.622959 to 1.583635
		Type of DM	0.1723669	0.952935	0.18	0.856	− 1.695351 to 2.040085
		HWE	0.6634776	0.9138099	0.73	0.468	− 1.127557 to 2.454512

Table 5 continued

Subject	Genetic model	Covariate	Coefficient	Standard error	*Z* value	*P* value	95% confidence interval
Q192R & DMMA	Dominant	Published year	− 0.0035683	0.0456424	0.08	0.938	− 0.0858892 to 0.0930259
		Sample size	− 0.0047061	0.002193	− 2.15	**0.032**	− 0.0090043 to − 0.0004079
		Ethnicity	− 0.685705	0.6208855	− 1.10	0.269	− 1.902618 to 0.5312082
		Type of DM	− 0.2674995	0.7910298	− 0.34	0.735	− 1.817889 to 1.282891
		HWE	0.5332051	0.4344049	1.23	0.220	− 0.3182129 to 1.384623
	Homozygous	Published year	− 0.1084717	0.0911813	− 1.19	0.234	− 0.2871837 to 0.0702404
		Sample size	− 0.0027179	0.0069887	− 0.39	0.697	− 0.0164154 to 0.0109797
		Ethnicity	0.09757	0.9376981	0.10	0.917	− 1.740284 to 1.935425
		Type of DM	0.189628	1.00174	0.19	0.850	− 1.773747 to 2.153003
		HWE	1.037982	0.3995946	2.60	**0.009**	0.2547913 to 1.821173
	Allelic	Published year	0.025372	0.0549197	0.46	0.644	− 0.0822686 to 0.1330126
		Sample size	− 0.007117	0.004638	− 1.53	0.125	− 0.0162074 to 0.0019733
		Ethnicity	− 0.3534767	0.7241402	− 0.49	0.625	− 1.772765 to 1.065812
		Type of DM	− 0.1464683	0.8657358	− 0.17	0.866	− 1.843279 to 1.550343
		HWE	0.6639624	0.5398508	1.23	0.219	− 0.3941256 to 1.722051
	Recessive	Published year	− 0.0428223	0.0361368	− 1.19	0.236	− 0.1136492 to 0.0280046
		Sample size	− 0.0010928	0.0015401	− 0.71	0.478	−0.0041113 to 0.0019257
		Ethnicity	0.4832858	0.8650459	0.56	0.576	− 1.212173 to 2.178745
		Type of DM	− 1.159989	1.422063	− 0.82	0.415	− 3.947182 to 1.627204
		HWE	0.6748508	0.3036949	2.22	**0.026**	0.0796197 to 1.270082
	Heterozygous	Published year	0.0653146	0.0423903	1.54	0.123	− 0.017769 to 0.1483981
		Sample size	− 0.0121148	0.0035643	− 3.40	**0.001**	− 0.0191008 to − 0.0051289
		Ethnicity	− 0.3397478	0.5238912	− 0.65	0.517	− 1.366556 to 0.6870602
		Type of DM	− 0.1798542	0.6317462	− 0.28	0.776	− 1.418054 to 1.058346
		HWE	0.4497992	0.3550472	1.27	0.205	− 0.2460806 to 1.145679

Table 5 continued

Subject	Genetic model	Covariate	Coefficient	Standard error	*Z* value	*P* value	95% confidence interval
Q192R & DMMI	Dominant	Published year	− 0.0687371	0.0683063	− 1.01	0.314	− 0.202615 to 0.0651409
		Sample size	− 0.0022643	0.003068	− 0.74	0.460	− 0.0082774 to 0.0037489
		Ethnicity	− 0.2406894	0.9342698	− 0.26	0.797	− 2.071825 to 1.590446
		Type of DM	− 0.0557483	1.057836	0.05	0.958	− 2.017572 to 2.129068
		HWE	− 0.4900475	1.000762	− 0.49	0.624	− 2.451505 to 1.47141
	Homozygous	Published year	− 0.0595551	0.0942681	− 0.63	0.528	− 0.2443173 to 0.125207
		Sample size	− 0.005957	0.0080294	− 0.74	0.458	− 0.0216943 to 0.0097802
		Ethnicity	0.0377475	1.445747	0.03	0.979	− 2.795865 to 2.87136
		Type of DM	0.2128231	1.782176	0.12	0.905	− 3.280177 to 3.705823
		HWE	− 0.5056941	1.352152	− 0.37	0.708	− 3.155863 to 2.144475
	Allelic	Published year	− 0.0151024	0.0391517	− 0.39	0.700	− 0.0918383 to 0.0616335
		Sample size	− 0.0001761	0.0008283	− 0.21	0.832	− 0.0017995 to 0.0014473
		Ethnicity	0.2495559	0.5697268	0.44	0.661	− 0.8670881 to 1.3662
		Type of DM	− 0.2526901	0.658074	− 0.38	0.701	− 1.542492 to 1.037111
		HWE	0.0773636	0.6056003	0.13	0.898	− 1.109591 to 1.264318

DMMA diabetic macroangiopathy, *DMMI* diabetic microangiopathy, *DM* diabetes mellitus, *HWE* Hardy–Weinberg equilibrium

Boldface means statistical significance ($P < 0.05$)

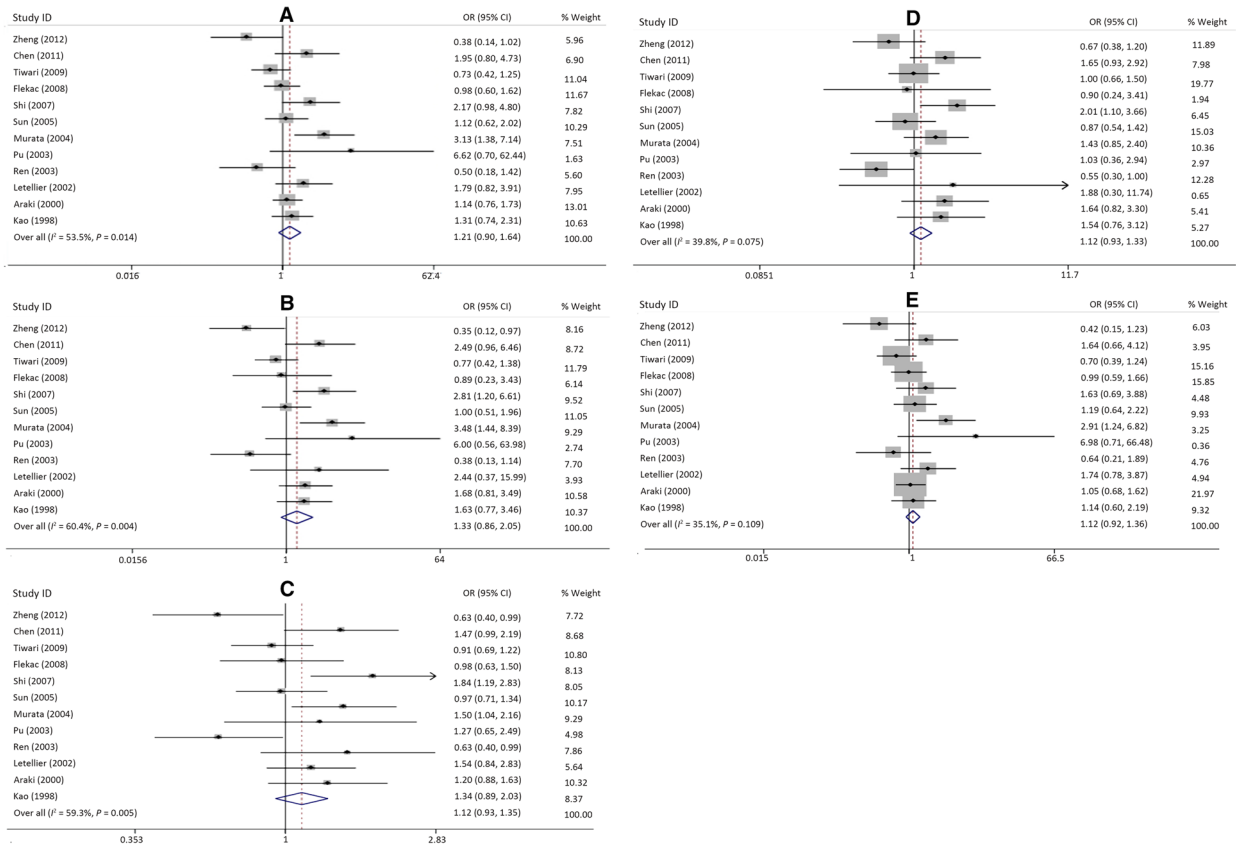

Fig. 4a–e Forest plots for the association of paraoxonase 1 Q192R genetic polymorphism with diabetic microangiopathy. **a** Dominant model, QR + RR vs QQ; **b** homozygous model, RR vs QQ; **c** allelic contrast model, R vs Q; **d** recessive model, RR vs QQ + QR; **e** heterozygous model, QR vs QQ

density lipoprotein from oxidative damage. The 192Q allele of paraoxonase 1 is more effective than 192R at preventing low-density lipoprotein oxidation [33]. The 192R allele was found to be significantly associated with lower serum paraoxonase 1 activity in DM patients in an Egyptian population [16]. A recent meta-analysis also demonstrated that Q192R genetic polymorphism was significantly related to the risk of type 2 diabetes mellitus, although there were some ethnic differences [7]. However, the relationships between paraoxonase 1 Q192R genetic polymorphism and various diabetic complications are considered to be rather unclear. Therefore, the meta-analysis reported in the present paper was performed to examine these relationships, and we found that there was a significant relationship between paraoxonase 1 Q192R genetic polymorphism and susceptibility to diabetic macroangiopathy in the homozygous and allelic contrast models, but not in the dominant model. Meanwhile, there was no significant association between paraoxonase 1 Q192R genetic polymorphism and diabetic microangiopathy susceptibility. However, there were significant heterogeneities in all three of these models when the associations of Q192R with diabetic macroangiopathy and microangiopathy susceptibility were analyzed. Meta-regression analysis was performed using the covariates published year, sample size, ethnicity, and type of DM, but it failed to identify the sources of heterogeneity.

Paraoxonase 1 L55M genetic polymorphism, another common single nucleotide polymorphism of paraoxonase 1, can affect the enzyme activity of paraoxonase 1, with the L allele linked to a higher serum concentration and

greater stability to proteolysis [33, 34]. A recent meta-analysis found that L55M polymorphism was significantly associated with many diseases, such as any cancer, breast cancer [35], and diabetes mellitus [7]. Paraoxonase 1 L55M genetic polymorphism was also found to be significantly associated with diabetic retinopathy in a meta-analysis which included just two articles [36]. Thus, before the present meta-analysis was carried out, the relationships of L55M genetic polymorphism with diabetic macroangiopathy and microangiopathy were not very clear. In this meta-analysis, L55M genetic polymorphism was found to be significantly associated with susceptibility to diabetic microangiopathy but not susceptibility to diabetic macroangiopathy in the dominant, homozygous, and allelic contrast models. Thus, subgroup analysis and meta-regression were conducted, and the results showed that type of DM was able to explain the heterogeneity in the recessive model, but not in the other models.

It is important to note the limitations of this meta-analysis. First, only articles written in English and Chinese were included in this study, and there may have been some publication bias, although Egger's test and a funnel plot did not point to any significant publication bias. Second, we used composites of diabetic complications in the present meta-analysis. Although macroangiopathy and microangiopathy are two kinds of diabetic vascular complications, the pathophysiological mechanisms and the contributions of genetic polymorphisms were probably different for these complications. Third, significant heterogeneity was found in our analysis, but subgroup analysis and meta-regression failed to find any of the sources of the between-study heterogeneity in the associations of paraoxonase 1 L55M/Q192R genetic polymorphisms with the risk of diabetic microangiopathy. Therefore, further well-designed studies with large samples are needed to confirm the results of this meta-analysis.

CONCLUSIONS

Paraoxonase 1 L55M and Q192R genetic polymorphisms play important roles in the susceptibility to diabetic macroangiopathy and microangiopathy.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets obtained during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Madonna R, Pieragostino D, Balistreri CR, et al. Diabetic macroangiopathy: pathogenetic insights and novel therapeutic approaches with focus on high glucose-mediated vascular damage. Vasc Pharmacol. 2018;S1537-1891:30322–1.

2. Barrett EJ, Liu Z, Khamaisi M, et al. Diabetic microvascular disease: an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2017;102(12):4343–410. https://doi.org/10.1210/jc.2017-01922.

3. Vakili L, Navab KD, Shabihkhani M, et al. Systemic inflammation, intestine, and paraoxonase-1. Adv Exp Med Biol. 2014;824:83–8.

4. Poh R, Muniandy S. Paraoxonase 1 activity as a predictor of cardiovascular disease in type 2 diabetes. Southeast Asian J Trop Med Public Health. 2010;41:1231–46.

5. Mackness B, Durrington PN, Abuashia B, Boulton AJ, Mackness MI. Low paraoxonase activity in type II diabetes mellitus complicated by retinopathy. Clin Sci (Lond). 2000;98:355–63.

6. Abdin AA, Hassanien MA, Ibrahim EA, El-Noeman SD. Modulating effect of atorvastatin on paraoxonase 1 activity in type 2 diabetic Egyptian patients with or without nephropathy. J Diabetes Complicat. 2010;24:325–33.

7. Luo JQ, Ren H, Liu MZ, Fang PF, Xiang DX. European versus Asian differences for the associations between paraoxonase-1 genetic polymorphisms and susceptibility to type 2 diabetes mellitus. J Cell Mol Med. 2018;22:1720–32.

8. Kao YL, Donaghue K, Chan A, Knight J, Silink M. A variant of paraoxonase (PON1) gene is associated with diabetic retinopathy in IDDM. J Clin Endocrinol Metab. 1998;83:2589–92.

9. Ergun MA, Yurtcu E, Demirci H, et al. PON1 55 and 192 gene polymorphisms in type 2 diabetes mellitus patients in a Turkish population. Biochem Genet. 2011;49:1–8.

10. Flekac M, Skrha J, Zidkova K, Lacinova Z, Hilgertova J. Paraoxonase 1 gene polymorphisms and enzyme activities in diabetes mellitus. Physiol Res. 2008;57:717–26.

11. 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.

12. Araki S, Makita Y, Canani L, Ng D, Warram JH, Krolewski AS. Polymorphisms of human paraoxonase 1 gene (PON1) and susceptibility to diabetic nephropathy in type I diabetes mellitus. Diabetologia. 2000;43:1540–3.

13. Kao Y, Donaghue KC, Chan A, Bennetts BH, Knight J, Silink M. Paraoxonase gene cluster is a genetic marker for early microvascular complications in type 1 diabetes. Diabet Med. 2002;19:212–5.

14. Tiwari AK, Prasad P, Thelma BK, et al. Oxidative stress pathway genes and chronic renal insufficiency in Asian Indians with Type 2 diabetes. J Diabetes Complicat. 2009;23:102–11.

15. Kordonouri O, James RW, Bennetts B, et al. Modulation by blood glucose levels of activity and concentration of paraoxonase in young patients with type 1 diabetes mellitus. Metabolism. 2001;50:657–60.

16. El-Lebedy D, Kafoury M, Abd-El Haleem D, Ibrahim A, Awadallah E, Ashmawy I. Paraoxonase-1 gene Q192R and L55M polymorphisms and risk of cardiovascular disease in Egyptian patients with type 2 diabetes mellitus. J Diabetes Metab Disord. 2014;13:124.

17. Letellier C, Durou MR, Jouanolle AM, Le Gall JY, Poirier JY, Ruelland A. Serum paraoxonase activity and paraoxonase gene polymorphism in type 2 diabetic patients with or without vascular complications. Diabetes Metab. 2002;28:297–304.

18. Hofer SE, Bennetts B, Chan AK, et al. Association between PON 1 polymorphisms, PON activity and diabetes complications. J Diabetes Complicat. 2006;20:322–8.

19. Zheng Y, Lei Y, Gong J, Zhong X, Pan T. Association of paraoxonase 1 gene polymorphisms with retinopathy in type 2 diabetes mellitus. Acta Universitatis Medicinalis Anhui. 2012;47:1206–8.

20. Chen X, Pan S, Zeng J. Relationship between PON1, PON2 polymorphism and type 2 diabetic nephropathy. Med J Chin. 2011;22:153–6.

21. Shi G, Wu N. Relationship between paraoxonase 1 genetic polymorphism with type 2 diabetic nephropathy. Clin Med China. 2007;23:134–6.

22. Zhang Z, Li J, Zhang C. PON1 gene polymorphism in NIDDM patients with cerebral infarction. Acta Academinae Medicine Qingdao Universitatis. 2004;40:336–8.

23. Li S, Li J, Wei G, Ji Q, Wang P. Study on the relationship between paraoxonase 1 and type 2 diabetes mellitus complicated by coronary artery disease. Tianjin Med J. 2004;32:273–6.

24. Ren T, Xiang K, Liu L. An association study of diabetic neruopathy with polymorphisms of eNOS,

PON1, RAGE and ALR2 genes. Shanghai Med J. 2003;26:24–7.

25. Pu X, Zeng F, Zeng Z, Liu W, Ke X. Study on relationship between paraoxonase 1 and type 2 diabetes mellitus in the elderly. Chin J Geriatr. 2003;22:466–8.

26. Wang Y, Chang Z. The relationship between PON1 192 Gln/Arg gene polymorphism and type 2 diabetes mellitus complicated with coronary disease. Guangdong Med J. 2003;24:598–600.

27. Qi L, Lu Z, Dong Y. The association of paraoxonase-1 192 Gln/Arg and paraoxonase-2 311 Cys/Ser gene polymorphisms with macrovascular disease in type 2 diabetes mellitus patients. Chin J Arterioscler. 2007;15:703–7.

28. Ma R, Yan S, Yu H, Zhao S, Wang Y, Miao Z. The association of paraoxonase 192 Gln/Arg gene polymorphism with coronary heart disease with type 2 diabetes mellitus. Chin J Diabetes. 2003;11:29–33.

29. Qian Q, Qian S, Wang S. Association of paraoxonase 1 arylersterase gene polymorphism in patients with type 2 diabetes and coronary heart disease. J Clin Cardiol (China). 2003;19:606–9.

30. Sun Y, Sun S, Zuo J, Lin Y, Kan Y, Shao H. Polymorphism of paraoxonase in diabetic nephropathies. J Jilin Univ (Med Ed). 2005;31:598–601.

31. Shao H, Zhang Y. The association of paraoxonase gene polymorphism and coronary disease in patients with type 2 diabetes mellitus. Shanxi Med J. 2006;35:1432–3.

32. Shao Z, Li J, Wang X. Analysis of paraoxonase 1 gene polymorphisms in type 2 diabetic patients with coronary artery disease. Chin J Cardiovasc Med. 2014;19:426–9.

33. James RW, Deakin SP. The importance of high-density lipoproteins for paraoxonase-1 secretion, stability, and activity. Free Radic Biol Med. 2004;37:1986–94.

34. Leviev I, Deakin S, James RW. Decreased stability of the M54 isoform of paraoxonase as a contributory factor to variations in human serum paraoxonase concentrations. J Lipid Res. 2001;42:528–35.

35. Chen L, Lu W, Fang L, et al. Association between L55M polymorphism in paraoxonase 1 and cancer risk: a meta-analysis based on 21 studies. Onco Targets Ther. 2016;9:1151–8.

36. Wang J, Yang MM, Rong SS, Ng TK, Li YB, Liu XM. Association of paraoxonase gene polymorphisms with diabetic nephropathy and retinopathy. Mol Med Rep. 2013;8:1845–51.