The association between paraoxonase 1 activity and the susceptibilities of diabetes mellitus, diabetic macroangiopathy and diabetic microangiopathy

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Abstract
We carried out this meta-analysis to explore the influence of paraoxonase 1 activity on the susceptibility of diabetes mellitus (DM), diabetic macroangiopathy and diabetic microangiopathy. Relevant studies were identified from PubMed, Web of Science and CNKI without language limitation, following the inclusion and exclusion criteria. Statistical analyses were implemented with the STATA 12.0 statistical software. Thirty-six case-control studies were included in the meta-analyses, in which 35 for the association between paraoxonase 1 activity and DM risk, 8 for diabetic macroangiopathy and 7 for diabetic microangiopathy. Paraoxonase 1 activity was significantly associated with the susceptibility of DM in pooled population (SMD = 1.37, 95% CI = 0.96 - 1.79, P = .000), and Asians (SMD = 2.00, 95% CI = 1.44 - 2.56, P = .000), but not in non-Asians (SMD = 0.44, 95% CI = 0.03 - 0.91, P = .069). However, marked heterogeneity was existed (I² = 98.10%, P = .000) and subgroup analyses failed to investigate the sources of heterogeneity. Then, meta-regression was performed and found that ethnicity could explain the observed between-study heterogeneity (P = .002). Meanwhile, significant associations were found between paraoxonase 1 activity and diabetic macroangiopathy (SMD = 1.06, 95% CI = 0.48 - 1.63, P = .000) and diabetic microangiopathy (SMD = 0.72, 95% CI = 0.13 - 1.32, P = .018). In conclusion, paraoxonase 1 activity plays important roles in the risk of DM, diabetic macroangiopathy and microangiopathy with ethnicity differences. Further studies with large sample and well design are needed to confirm these results.

KEYWORDS
activity, diabetes mellitus, meta-analysis, paraoxonase 1

1 | INTRODUCTION

Diabetes mellitus (DM) is one of the most serious health-related diseases all over the world, characterized by recurrent or persistent hyperglycaemia. It was estimated that approximately 90% DM were type 2 diabetes mellitus (T2DM), which occurs due to cells developing a resistance to insulin. DM prevalence is rapidly increasing in developing countries with the development of economics. When DM was not properly managed, it can lead to life-threatening complications, including diabetic macroangiopathy (heart, brain, etc.), diabetic microangiopathy (kidney, eye, etc.), and neuropathy. DM is an important risk factor that leads to ischaemic stroke, and DM complicated with ischaemic stroke can aggravate the mortality and morbidity of patients. Various factors contributed to the occurrence of DM, including genetic factors, lifestyle factors, and environmental factors. Genetic factors include polymorphisms in the genes encoding paraoxonase 1 (PON1), which is involved in the metabolism of organophosphate and paraoxon hydrolysis. PON1 polymorphisms have been associated with the risk of DM and its complications. The association between PON1 activity and the susceptibility of DM, diabetic macroangiopathy and diabetic microangiopathy is unclear. Therefore, we carried out this meta-analysis to explore the influence of paraoxonase 1 activity on the susceptibility of DM, diabetic macroangiopathy and diabetic microangiopathy.
and development of DM, such as genetic, psychological, lifestyle and environment. Among these influential factors in DM, the serum level, the activity and gene polymorphisms of paraoxonase 1 played important roles in the susceptibility of DM.

Paraoxonase 1, a member of hydrolases with a glycoprotein structure, is a 354 aa glycoprotein of about 45 kD that is synthesized in the liver, released to the blood and binds to the high-density lipoprotein in calcium-dependent manner. Paraoxonase 1 has been demonstrated approximately 200 nucleotide polymorphisms, such as Q192R polymorphism, which was significantly associated with the susceptibility to T2DM by meta-analysis. Paraoxonase 1 is a multifunctional enzyme with functions of arylesterase, paraoxonase and lactonase. Serum level and activity of paraoxonase 1 are different from individuals. Paraoxonase 1 activity is affected by age, sex, lifestyle and genetic polymorphisms.

It has been reported that paraoxonase 1 activity was decreased in heart disease, and a large number of studies have been conducted over the last two decades to demonstrate the relationship of paraoxonase 1 activity and the susceptibility to DM and DM complications. Mackness et al. firstly found that paraoxonase 1 activity was significantly higher in diabetic population than non-diabetic population in 1998. While, Kopprasch et al. showed no significant difference in paraoxonase 1 activity between DM and non-DM in different population. Meanwhile, Mackness et al. firstly described that paraoxonase 1 activity was significantly higher in DM patients without complications than that with retinopathy in 2000. Subsequently, there were some studies on the associations between paraoxonase 1 activity and the susceptibilities of DM and DM complications. However, the previously published results remain contentious. Therefore, to firmly demonstrate the association of paraoxonase 1 activity (paraoxon as substrate) with the susceptibility to DM, diabetic macroangiopathy and diabetic microangiopathy, we performed this meta-analysis of data from thirty-six studies.

2 | METHODS

We carried out literature searches in PubMed, Web of Science and China National Knowledge Internet (CNKI) without language limitation, using the following key words: “PON1” or “paraoxonase 1,” “diabetes” or “diabetes mellitus” or “DM” or “T2DM” or “T1DM,” and “activity.” On the other hand, relevant articles were hand searched to identify additional reports.

2.1 | Inclusion and exclusion criteria

The following criteria were used to select articles included in this meta-analysis: (1) published as original case-control studies; (2) paraoxonase 1 activity was detected in serum using paraoxon as the substrate; (3) reported an association between paraoxonase 1 activity and the susceptibilities of DM, diabetic macroangiopathy and/or diabetic

![Flow diagram of the search strategy and study selection](image-url)
microangiopathy. When the same series of patients were used in more than one article, we used the latest and most complete one.

2.2 Data extraction

WDL and WCF screened all searched articles and extracted data from all eligible publications independently. For each study, we carefully extracted the following information: name of the first author, published year, country, ethnicity, type of DM, type of control and paraoxonase 1 activity (mean ± SD) in each group. If there were any discrepancies, an agreement was reached after discussion; otherwise, another author was consulted to resolve the dispute.

### TABLE 1 Characteristics of studies included in this meta-analysis for the relationship between paraoxon activity and diabetes risk

| Author      | Year | Type of DM | Type of control | Country      | Ethnicity | Paraoxon activity (DM) Mean± SD | N | Paraoxon activity (Control) Mean± SD | N |
|-------------|------|------------|----------------|--------------|-----------|----------------------------------|---|-------------------------------------|---|
| Inoue       | 2000 | T2DM       | Healthy control| Japan        | Japanese  | 116 ± 55                         | 108| 162 ± 57                           | 161|
| Mackness    | 2002 | T1DM       | Healthy control| English      | Englishman| 178.8 ± 71.23                    | 152| 214.6 ± 99.08                      | 282|
| Letellier    | 2002 | T2DM       | Healthy control| France       | French    | 217.63 ± 130.1                   | 167| 259 ± 154.3                        | 105|
| Kopprasch    | 2003 | T2DM       | Healthy control| Finland      | Caucasian | 5.33 ± 0.5                       | 75 | 4.67 ± 0.27                        | 403|
| Rosenblat    | 2006 | NIDDM      | Healthy control| Israel       | Israeli   | 183 ± 35                         | 3  | 340 ± 37                           | 3   |
| Mastonikou   | 2006 | T2DM       | Healthy control| English      | Englishman| 113.6 ± 92.3                     | 36 | 269.4 ± 104.75                     | 19  |
| Singh        | 2007 | T2DM       | Healthy control| India        | Indian    | 58.36 ± 26.03                    | 57 | 64.92 ± 32.92                      | 191 |
| Flekac       | 2008 | T2DM       | Healthy control| Czech Republic| Czech     | 118 ± 69                         | 246| 203 ± 58                           | 110 |
| Unur         | 2008 | T2DM       | Healthy control| Turkey       | Turk      | 135.7 ± 71.1                     | 51 | 364.2 ± 26.7                       | 53  |
| Poh          | 2010 | T2DM       | Healthy control| Malaysia     | Malaysian | 486.31 ± 284.94                  | 140| 581 ± 315                          | 153 |
| Abdin        | 2010 | T2DM       | Healthy control| Egypt        | Egyptian  | 18.79 ± 6.44                     | 40 | 39.66 ± 12.38                      | 30  |
| Nowak        | 2010 | T1DM       | Healthy control| Poland       | Polish    | 266.83 ± 164.94                  | 76 | 312.04 ± 129.77                    | 35  |
| Stefanovic   | 2010 | T2DM       | Healthy control| Serbia       | Serbian   | 199.4 ± 154.73                   | 114| 299.5 ± 285.61                     | 91  |
| Altunuer     | 2011 | T2DM       | Healthy control| Turkey       | Turk      | 80.02 ± 12.94                    | 100| 94.12 ± 6.79                       | 50  |
| Ergun        | 2011 | T2DM       | Healthy control| Turkey       | Turk      | 134.67 ± 66.99                   | 171| 244.45 ± 114.2                     | 80  |
| Gelisenac    | 2011 | GDM        | Without DM     | Turkey       | Turk      | 95.31 ± 18.57                    | 23 | 133.15 ± 18.88                     | 22  |
| Gupta        | 2011 | T2DM       | Healthy control| Turkey       | Turk      | 114.2 ± 47.38                    | 250| 178 ± 63.58                       | 300 |
| Liu          | 2011 | T2DM       | Healthy control| China        | Chinese   | 142 ± 55                         | 100| 222 ± 99                           | 50  |
| Tabak        | 2011 | T2DM       | Healthy control| Turkey       | Turk      | 111.42 ± 62.38                   | 69 | 260.55 ± 76                        | 20  |
| Ames         | 2012 | T2DM       | Healthy control| Mexico       | Mexican   | 289.4 ± 61.9                    | 75 | 282.6 ± 70.2                      | 86  |
| Gbandjabaca  | 2012 | DM         | Healthy control| Morocco      | Moroccan  | 67.83 ± 89.58                    | 84 | 68.91 ± 99.51                      | 87  |
| Guo          | 2012 | T2DM       | Healthy control| China        | Chinese   | 102.24 ± 14.95                   | 108| 183.52 ± 49.45                     | 50  |
| Murakami     | 2013 | T2DM       | Healthy control| Japan        | Japanese  | 261 ± 47                         | 36 | 309 ± 32                           | 9   |
| Bansal      | 2013A| T2DM       | Healthy control| India        | Indian    | 228.34 ± 37.83                   | 157| 379 ± 31.5                         | 40  |
| Bansal      | 2013B| T2DM       | Healthy control| India        | Indian    | 209.7 ± 45.77                    | 265| 381 ± 30.33                        | 171 |
| Budak       | 2013 | T2DM       | Healthy control| Turkey       | Turk      | 210.81 ± 46.89                   | 54 | 258 ± 60                           | 24  |
| Helaly       | 2013 | T2DM       | Healthy control| Egypt        | Egyptian  | 89.1 ± 11.4                      | 100| 239.6 ± 49.3                      | 100 |
| Fekih       | 2014 | T1DM       | Healthy control| Tunisia      | Tunisian  | 330 ± 198                        | 122| 334 ± 220                          | 97  |
| Srecekovic   | 2014 | GDM        | Without DM     | Austria      | Austrian  | 35 ± 9                          | 9  | 75 ± 18                           | 11  |
| Craciun      | 2016 | T1DM       | Healthy control| Romania      | Romanian  | 181 ± 38.83                      | 82 | 215 ± 83.75                       | 41  |
| Muhtaroglu   | 2016 | DM         | Healthy control| Turkey       | Turk      | 73.15 ± 19.98                    | 60 | 97.7 ± 23.175                      | 30  |
| Shakeri      | 2017 | T2DM       | Healthy control| Iran         | Iranian   | 770.95 ± 320.47                  | 90 | 2185.64 ± 428.76                   | 90  |
| Sun          | 2017 | DM         | Without DM     | China        | Chinese   | 309.4 ± 116.8                    | 51 | 366.8 ± 120.8                      | 135 |
| Crow         | 2018 | T2DM       | Without DM     | America      | American  | 51.1 ± 35.5                      | 117| 52.4 ± 32.9                       | 117 |

DM, diabetes mellitus; SD, standard deviation; N, number; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; NIDDM, non-independent diabetes mellitus; GDM, gestational diabetes mellitus.

*The unit of paraoxonase 1 activity is nmol/min/mL.

Means calculated data from articles.

The unit of paraoxonase 1 activity is U/mL.
2.3 Statistical analysis

Paraoxonase 1 activity in each group was described as mean ± SD. Standard mean differences (SMD) were used to evaluate the association between paraoxonase 1 activity and the susceptibilities of DM, diabetic macroangiopathy, and/or diabetic microangiopathy. Heterogeneity was measured using a Chi-square-based Q test. The fixed effect model was used to calculate pooled SMD, when $I^2 < 50\%$ and $P > .05$. Otherwise, the random effect model was applied. Meta-regression analyses on published year, ethnicity, sample size, type of control and type of DM, and subgroup analyses on type of control, ethnicity, and type of DM were conducted to assess heterogeneity sources across the study. Publication bias was investigated using Egger’s test and funnel plot. STATA 12.0 software (Stata corporation, TX, USA) was used in this meta-analysis. $P < .05$ means statistical significance.

3 RESULTS

3.1 Study characteristics

Relevant publications were searched and preliminarily reviewed. As shown in Figure 1, 564 publications were identified, in which 137 duplicates and 344 irrelevant papers were excluded. Then eighty-three citations remaining for further review. Eight original articles lacking of controls, twenty-nine articles used other paraoxonase 1 substrates, two reviews, one performed not in serum, one with paraoxonase 1 gene polymorphism, four with other diseases or protein and one without data of paraoxonase 1 activity were all excluded. Two studies used the same case series, respectively, so the most recent publication was included. Lastly, 36 case-control studies were included in the meta-analyses. Thirty-four publications were written in English, and two were written in Chinese. The detailed information is shown in Tables 1 and 2. The first author, published year, country, ethnicity, the types and numbers of cases and controls, and levels of paraoxonase 1 activity for each study were presented.

3.2 Paraoxonase 1 activity and DM risk

As shown in Table 1, thirty-four articles studied the association between paraoxonase 1 activity and risk of DM included 3474 DM patients and 3246 controls. Twenty-one studies were performed in Asian countries, and other thirteen in non-Asian. Twenty-three articles were focused on T2DM, one on T1DM and T2DM, four on TDM, two on GDM or one on NIDDM, and one without data of paraoxonase 1 activity were all excluded. Two studies used the same case series, respectively, so the most recent publication was included. Thirty-four case-control studies were included in the meta-analyses. Thirty-four publications were written in English, and two were written in Chinese. The detailed information is shown in Tables 1 and 2. The first author, published year, country, ethnicity, the types and numbers of cases and controls, and levels of paraoxonase 1 activity for each study were presented.

TABLE 2 Characteristics of studies included in this meta-analysis for the relationship between paraoxon activity and risk of diabetes complications

| Author   | Year | Type of DM | Country  | Ethnicity | DM without complications | DM with macroangiopathy | DM with microangiopathy |
|----------|------|------------|----------|-----------|--------------------------|-------------------------|-------------------------|
|          |      |            |          |           | Mean ± SD | N | Mean ± SD | N | Mean ± SD | N |
| Mackness | 2000 | T2DM       | English  | Englishman| 164.1 ± 76.6 | 93 | 113.4 ± 68.6 | 101 |
| Letellier | 2002 | T2DM       | France   | French    | 211 ± 189  | 36 | 254 ± 155  | 35 |
| Abdin    | 2010 | T2DM       | Egypt    | Egyptian  | 14.25 ± 6.13 | 20 | 14.25 ± 6.13 | 20 |
| Nowak    | 2010 | T1DM       | Poland   | Polish    | 289.87 ± 157.07 | 35 | 227.66 ± 123.57 | 41 |
| Poh      | 2010 | T2DM       | Malaysia | Malaysian | 583 ± 342  | 44 | 442 ± 244  | 96 |
| Liu      | 2011 | T2DM       | China    | Chinese   | 152 ± 67   | 50 | 110 ± 46   | 50 |
| Guo      | 2012 | T2DM       | China    | Chinese   | 125.14 ± 34.22 | 29 | 94.49 ± 28.87 | 37 |
| Gupta    | 2012 | T2DM       | Turkey   | Turk      | 114.2 ± 47.42 | 250 | 51 ± 15.75 | 300 |
| Bansal   | 2013A| T2DM       | India    | Indian    | 276 ± 49.75 | 57 | 198 ± 35    | 47 |
| Bansal   | 2013B| T2DM       | India    | Indian    | 246 ± 40.33 | 135 | 172 ± 30.17 | 130 |
| Budak    | 2013 | T2DM       | Turkey   | Turk      | 221 ± 52    | 29 | 199 ± 39    | 25 |
| Sun      | 2017 | DM         | China    | Chinese   | 352 ± 184  | 10 | 299 ± 96   | 41 |

DM, diabetes mellitus; SD, standard deviation; N, number; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus.

*aThe unit of paraoxonase 1 activity is nmol/min/mL.
*bMeans calculated data from articles.
**FIGURE 2** Forest plot for the association between paraoxonase 1 activity with DM, subgrouped by type of diabetes mellitus

**TABLE 3** The meta-regression results for the association between paraoxonase activity and susceptibility of diabetes mellitus

| Covariates                  | Coefficient | Standard error | Z value | P value | 95% confidence interval |
|-----------------------------|-------------|----------------|---------|---------|-------------------------|
| Published year              | –0.0329444  | 0.0581352      | –0.57   | .571    | –0.1468872–0.0809985    |
| Sample size                 | 0.0022293   | 0.0018531      | 1.20    | .229    | –0.0014027–0.0058613    |
| Ethnicity                   | –1.465915   | 0.4797128      | –3.06   | .002*   | –2.406135–0.5256954     |
| Type of control              | –0.139538   | 1.085985       | –0.13   | .898    | –2.268029–1.988953      |
| Type of diabetes mellitus    | 0.2003757   | 0.3617462      | 0.55    | .580    | –0.5086338–0.9093852    |

*P < .05.
CI = −1.79 ~ −0.96, P = .000, Figure 2). Risk of DM obviously increased with low levels of paraoxonase 1 activity. Subgroup analysis on type of DM showed significant relationships found in T2DM subgroup (SMD = −1.54, 95% CI = −2.10 ~ −0.98, P = .000), T1DM subgroup (SMD = −0.55, 95% CI = −1.03 ~ −0.08, P = .023) and other types of DM (SMD = −1.26, 95% CI = −2.00 to −0.52, P = .001) (Figure 2). Meanwhile, the result of subgroup analysis on ethnicity showed significant associations between paraoxonase 1 activity and DM in Asian group (SMD = −2.00, 95% CI = −2.56 ~ −1.44, P = .000, Supporting information Figure S1), but not in non-Asian group (SMD = −0.44, 95% CI = −0.91 ~ 0.03, P = .069, Supporting information Figure S1). Significant publication bias was found using funnel plot and Egger’s test (P = .008, data not shown).

3.3 | Paraoxonase 1 activity and susceptibility of diabetic macroangiopathy

As shown in Table 2, eight articles focused on the association of paraoxonase 1 activity and the risk of diabetic macroangiopathy, including 737 cases and 671 controls.17,18,22,30,34,35,44 The results showed that significant heterogeneity was found (I² = 94.90%, P = .000, Figure 3A). Paraoxonase 1 activity was significantly associated with the susceptibility of diabetic macroangiopathy (SMD = −1.06, 95% CI = −1.63 ~ −0.48, P = .000, Figure 3A).

There was no significant publication bias existed, demonstrated by funnel plot and Egger’s test (P = .116, data not shown).

3.4 | Paraoxonase 1 activity and susceptibility of diabetic microangiopathy

As shown in Table 2, seven articles focused on the association of paraoxonase 1 activity and the risk of diabetic microangiopathy, including 317 cases and 359 controls.15,17,23,31,35,38,43 The results showed that significant heterogeneity was found (I² = 92.0%, P = .000, Figure 3B). Paraoxonase 1 activity was significantly associated with the susceptibility of diabetic microangiopathy (SMD = −0.72, 95% CI = −1.32 ~ −0.13, P = .018, Figure 3B). Meanwhile, there was no significant publication bias, according to funnel plot and Egger’s test (P = .533, data not shown).

4 | DISCUSSION

Our meta-analysis firstly demonstrated the associations between paraoxonase 1 activity and DM, diabetic macroangiopathy and diabetic microangiopathy by polling the individual data set. In the overall meta-analysis of paraoxonase 1 activity, susceptibility of DM significantly increased with low levels of paraoxonase 1 activity, but strong between-study heterogeneity was found. Therefore, to
address the substantial heterogeneity, subgroup analyses on ethnicity, type of control and type of DM were conducted. But significant heterogeneity was still existed. Then, meta-regression was performed using the following covariates: published year, sample size, ethnicity, type of control and type of DM and the results showed that ethnicity could explain the observed between-study heterogeneity. In addition, subgroup analysis showed significant associations between paraoxonase 1 activity and DM in Asian group, but not in non-Asian group. Paraoxonase 1 activity was different from ethnicity, and significantly higher in Malays and Chinese than Indians. A recent meta-analysis on the associations of paraoxonase 1 Q192R/L55M genetic polymorphisms with susceptibility to T2DM also suggested a significant ethnicity differences. There are huge racial and regional differences in the genetic polymorphisms of paraoxonase 1, according to the 1000 genomes database. Genetic polymorphisms of paraoxonase 1 have been demonstrated to affect the paraoxonase 1 activity. Regarding the paraoxonase 1 Q192R polymorphism, paraoxonase 1 activity was different from genotypes, with the highest level in genotype RR in an Egyptian population, and the lowest level in genotype QQ in an African population. Paraoxonase 1 activity was significantly lower in the genotype QQ of paraoxonase 1 Q192R polymorphism than genotypes QR and RR in the patients with diabetic macroangiopathy. Meanwhile, paraoxonase 1 activity was significantly lower in the genotype LL of the paraoxonase 1 L55M polymorphism than genotypes LM and MM in the patients with diabetic macroangiopathy and microangiopathy in an Egyptian population, while no difference between L and M alleles. So the effect of interaction between paraoxonase 1 activity and genetic polymorphisms on the susceptibility of DM regarding the ethnic difference needs to be studied in the further.

Diabetic macroangiopathy is one of the most common complications of DM, which reduced the mortality and life quality of DM patients. It is a specific type of accelerated atherosclerosis. In this meta-analysis, paraoxonase 1 activity was significantly associated with the susceptibility of diabetic macroangiopathy. Diabetic microangiopathy including diabetic nephropathy and diabetic retinopathy is also one of the most common complications. Diabetic nephropathy is the leading global cause of end-stage renal disease. In this meta-analysis, paraoxonase 1 activity was significantly associated with the susceptibility of diabetic microangiopathy.

Paraoxonase 1 can cleave oxidized lipids from low-density lipoproteins. High-density lipoproteins diminish the accumulation of lipid peroxides in low-density lipoproteins mainly due to paraoxonase 1 activity. Paraoxonase 1 activity in human beings is very low at birth and increases with time. As our meta-analysis has demonstrated the significant role of paraoxonase 1 activity in DM and diabetic complications, therapeutic strategies targeting this enzyme maybe reasonable. Therapeutic strategies can be focused on lifestyle modification and increasing the level of paraoxonase 1 activity.

In this meta-analysis, there existed some limitations. First, only articles with English and Chinese language were included in this study, some publication bias may exist. Second, significant heterogeneity was found in our analysis about the association between paraoxonase 1 activity and susceptibility of DM and diabetic complications, and for DM, ethnicity might explain some of the sources of between-study heterogeneity. But there were only 8 and 7 articles included for analysis of the association between paraoxonase 1 activity and diabetic macroangiopathy and microangiopathy, respectively, so we failed to find the sources of heterogeneity. Thus, large sample and well-designed studies needed to demonstrate the result in the further.

In conclusion, paraoxonase 1 activity plays important roles in the risk of DM, diabetic macroangiopathy and microangiopathy with ethnicity differences. Further studies with large sample and well design are needed to confirm these results.

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CONFLICT OF INTEREST

All authors declared that there were no potential conflict of interests.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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