INTRODUCTION

Diabetes mellitus (DM), as the most prevalent metabolic diseases, is a major public health problem worldwide. Its morbidity and mortality rates have increased rapidly over recent decades. According to the reports from the International Diabetes Federation (IDF), approximately 451 million diabetes cases and 5 million deaths worldwide were occurred in 2017, and expected to increase to 693 million cases by 2045 (Cho et al., 2018). Type 2 diabetes mellitus (T2DM) is the most prevalent form of DM, accounting for more than 90% of DM (Chen, Magliano, & Zimmet, 2011). It is a hypothesis

Quantitative assessment of TLR4 gene polymorphisms and T2DM risk: A meta-analysis

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Abstract

Background: Numerous studies have evaluated the association between TLR4 gene polymorphisms and T2DM risk. However, the findings were inconsistent and controversial.

Methods: In order to drive a more precise estimation, we carried out a meta-analysis based on 41 studies involving 23,250 cases and 24,760 controls. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of association.

Results: Our meta-analysis provides evidence that rs4986790 polymorphism was associated with an increased risk of T2DM in Asian (AG vs. AA, OR = 1.23, 95% CI = 1.01–1.50, p = 0.042; G vs. A, OR = 1.21, 95% CI = 1.01–1.44, p = 0.041). Rs4986791 polymorphism was related to an increased risk of T2DM both in Asian (AG vs. AA, OR = 1.76, 95% CI = 1.11–2.80, p = 0.017; G vs. A, OR = 1.63, 95% CI = 1.04–2.55, p = 0.034) and Caucasian (GG vs. AA, OR = 2.42, 95% CI = 1.23–4.75, p = 0.010). Rs11536889 polymorphism may have a protective effect on T2DM in Chinese populations (CC vs. GG, OR = 0.62, 95% CI = 0.40–0.96, p = 0.031; GC vs. GG, OR = 0.77, 95% CI = 0.61–0.98, p = 0.034; CC vs. GC/GG, OR = 0.81, 95% CI = 0.69–0.96, p = 0.013; C vs. G, OR = 0.76, 95% CI = 0.59–0.97, p = 0.027), whereas rs1927911 may have no impact.

Conclusions: These findings supported that rs4986790, rs4986791, and rs11536889 may contribute to the risk of T2DM.

KEYWORDS
meta-analysis, polymorphism, risk, T2DM, TLR4

1 INTRODUCTION

Diabetes mellitus (DM), as the most prevalent metabolic diseases, is a major public health problem worldwide. Its morbidity and mortality rates have increased rapidly over recent decades. According to the reports from the International Diabetes Federation (IDF), approximately 451 million diabetes cases and 5 million deaths worldwide were occurred in 2017, and expected to increase to 693 million cases by 2045 (Cho et al., 2018). Type 2 diabetes mellitus (T2DM) is the most prevalent form of DM, accounting for more than 90% of DM (Chen, Magliano, & Zimmet, 2011). It is a hypothesis
suggest that T2DM is a disease of the innate immune system related to obesity and insulin resistance (Pickup & Crook, 1998). However, the etiology underlying T2DM is still unclear. Accumulating evidence support that the genetic factors may contribute to the development of T2DM. In a nationwide T2DM study with a cohort of 13,888 Finnish twin pairs, the concordance rate for T2DM was much higher among monozygotic twins compared with dizygotic twins (Kaprio et al., 1992). Meanwhile, an increasing number of genetic loci were investigated to be associated with the risk of T2DM (Gaulton, 2017).

Toll-like receptors (TLRs) are the family of the important pathogen recognition receptors involved in regulating the activation of the innate immune response and subsequent pro-inflammatory reactions (Akira, Uematsu, & Takeuchi, 2006). TLR4 (toll-like receptor-4), a key member of the TLRs family, initiates the production of pro-inflammatory cytokines on dendritic cells and macrophages (Zarember & Godowski, 2002). TLR4 plays an important role in the recognition and interaction with lipopolysaccharide (LPS), endogenous ligands, oxidized low-density lipoprotein (LDL), heat shock proteins (HSP) 60 and 70, fibrinogen, and fibronecthin (Peterson, Mart, & Bond, 2014; Rallabhandi et al., 2006). The human TLR4 gene (OMIM# 603030), encoding TLR4, is located on chromosome 9q32–33. Its genetic variations have been reported to modify the function of TLR4 recognition and interaction, and then, change the immune response in the development of T2DM (Armant & Fenton, 2002; Yin, Wang, Sun, Hu, & Liu, 2015). As the most common genetic variation, single nucleotide polymorphisms (SNPs) are becoming more and more popular in T2DM research. Numerous studies have evaluated the association between TLR4 polymorphisms and the risk of T2DM (Aioanei et al., 2019; Bagarolli, Saad, & Saad, 2010; Beijk et al., 2010; Buraczynska, Baranowicz-Gaszczyn, Tarach, & Ksiazek, 2009; Buraczynska, Zukowski, Ksiazek, Wacinski, & Dragan, 2016; Cai, Cai, & Tao, 2013; Degirmenci et al., 2019; Doody et al., 2017; Dzunhur et al., 2012; Gond, Singh, & Agrawal, 2018; Hernesniemi et al., 2006; Huang et al., 2015; Ilig et al., 2003; Jiang, Wang, Jia, Wang, & Liu, 2013; Khaghanzadeh et al., 2020; Kim et al., 2008; Kolek et al., 2004; Peng et al., 2015; Singh et al., 2014; Singh, Singh, Agrawal, Gupta, & Singh, 2013; Xu et al., 2015; Zaharieva, Kamenov, & Savov, 2017). However, these studies reported inconsistent results. This discrepancy may be due to relatively small sample size in each published study. Meta-analysis is an approach to combine various studies to drive more powerful evaluation of these associations. Till now, two meta-analysis explored the possible role of TLR4 polymorphisms and T2DM risk before 2015 (Belforte, 2013; Yin et al., 2015). One only focused on rs4986790 and rs4986791 and the other only on rs1927911. At least another seven studies were published about these two polymorphisms in recent several years. Moreover, we studied all the TLR4 polymorphisms on the risk of T2DM, and more than four publications focused on one polymorphism will be included in our study.

Therefore, we conducted this comprehensive meta-analysis to assess association between T2DM risk and four TLR4 polymorphisms (rs4986790, rs4986791, rs11536889, and rs1927911).

2  |  MATERIALS AND METHODS

2.1  |  Identification and eligibility of relevant studies

A systematic literature search was performed to identify relevant articles published on two widely used electronic literature databases (MEDLINE and EMBASE) up to 24 April 2020. The searching terms were as follows: “Toll-like receptors or Toll-like receptor 4 or TLR4,” “polymorphism or polymorphisms or variant or variation,” and “diabetes or diabetic or T2DM or T2D.” All eligible original studies and other relevant studies were searched manually.

2.2  |  Inclusion criteria and exclusion criteria

We selected studies according to the following criteria: (1) evaluating the association between TLR4 polymorphisms and T2DM risk; (2) based on the case-control or cohort design; (3) with enough information to calculate odds rations (ORs) and 95% confidence intervals (CIs). Exclusion criteria were as follows: (1) reviews, meta-analyses, letters, case reports, and conference abstracts; (2) Non-case-control studies; (3) studies without sufficient data.

2.3  |  Data extraction

Two investigators independently identified the articles for compliance with the inclusion criteria. The following information were extracted from each eligible study: first author’s surname, year of publication, country of origin, ethnicity, source of control, total number of cases and controls, genotype distribution in cases and controls, and Hardy–Weinberg equilibrium (HWE) in controls. Any disagreement was resolved by checking and discussion till consensus was reached. Meanwhile, we categorized ethnicity as Caucasian or Asian, including Indian and Chinese.

2.4  |  Statistical analysis

The HWE for controls of each studies was checked by using a Chi-square test. The strength of association between four
TLR4 polymorphisms (rs4986790, rs4986791, rs11536889, and rs1927911) and T2DM risk was assessed by calculating ORs with the corresponding 95% CIs. For the rs4986790 A > G, the pooled ORs were estimated in homozygous model (GG vs. AA), heterozygous model (AG vs. AA), recessive model (GG vs. AG/AA), dominant model (AG/GG vs. AA), and allele model (G vs. A). As for rs4986791 A > G, rs11536889 G > C, and rs1927911 G > A polymorphism, similar five genetic models were also calculated. We applied Chi-square-based Q-test to assess heterogeneity between studies. A p value greater than 0.10 indicated a lack of heterogeneity, we chose the fixed-effects model (the Mantel–Haenszel method) (Mantel & Haenszel, 1959). Otherwise, we used the random-effects model (the DerSimonian and Laird method) (DerSimonian & Laird, 1986). Funnel plots and Egger’s regression test were applied to assess the publication bias. All the analyses were performed with the STATA software, version 11.0 (Stata Corporation, College Station, TX, USA). All the p values were two-sided and p values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of studies

As shown in Figure 1, 148 potentially relevant publications were identified through database review. Based on a review of title and abstract, 112 obviously irrelevant articles were removed. Of the remaining 36 publications, six were excluded for only case studies, four with insufficient data for further evaluation, and four focused on other polymorphisms because the number of studies on these polymorphisms were less than four. Finally, a total of 22 eligible articles were included in this meta-analysis, including 19 studies on rs4986790 polymorphism (Aioanei et al., 2019; Bagarolli et al., 2010; Beijk et al., 2010; Buraczynska et al., 2009, 2016; Cai et al., 2013; Degirmenci et al., 2019; Doody et al., 2017; Dzumhur et al., 2012; Gond et al., 2018; Hernesniemi et al., 2006; Illig et al., 2003; Jiang et al., 2013; Khaghanzadeh et al., 2020; Kim et al., 2008; Kolek et al., 2004; Singh et al., 2013, 2014; Zaharieva et al., 2017), 13 studies on rs4986791 polymorphism (Aioanei et al., 2019; Bagarolli et al., 2010; Cai et al., 2013; Degirmenci et al., 2019; Gond et al., 2018; Jiang et al., 2013; Kim et al., 2008; Singh et al., 2013, 2014; Zaharieva et al., 2017, Khaghanzadeh et al., 2020), four studies on rs11536889 polymorphism (Cai et al., 2013; Huang et al., 2015; Jiang et al., 2015; Peng et al., 2015), and five studies on rs1927911 polymorphism (Huang et al., 2015; Peng et al., 2015; Singh et al., 2013, 2014; Xu et al., 2015). The characteristics and genotype distributions of the eligible studies are listed in Table 1.

3.2 | Meta-analysis of TLR4 rs4986790 polymorphism and T2DM risk

About 19 studies involving 7150 cases and 9993 controls were included to evaluate the association between TLR4 rs4986790 polymorphism and T2DM risk. About 11 studies focused on Caucasian populations and eight on Asian populations. No significant associations were found between

**FIGURE 1** Flow diagram of the study selection

Potential relevant publications identified through database searching (n=148)

Publications excluded after title and abstract review (n=112)

Publications for full text review (n=36)

Publications excluded (n=14)
6 only case study
4 without sufficient data
4 other SNPs for less than 4 studies

22 articles included in meta-analysis
19 articles for rs4986790 polymorphism
13 articles for rs4986791 polymorphism
4 articles for rs11536889 polymorphism
5 articles for rs1927911 polymorphism
| Surname     | Year | Country | Ethnicity | Source of controls | Cases   | Controls | HWE  |
|-------------|------|---------|-----------|--------------------|---------|----------|------|
|             |      |         |           |                    | Total   | AA       | AG   | GG   | Total | AA    | AG    | GG   |      |
|             |      |         |           |                    | rs4986790 |          |      |      |       |       |       |      |      |
| Illig       | 2003 | Germany | Caucasian | PB                | 217     | 196      | 21   | 0    | 229   | 207   | 20    | 2    | 0.068 |
| Kolek      | 2004 | USA     | Caucasian | HB                | 333     | 315      | 18a  | 18a  | 1561  | 1410  | 151a  |      | \    |
| Hernesniemi | 2006 | Finland | Caucasian | HB                | 107     | 89       | 18a  | 18a  | 550   | 454   | 96a   |      | \    |
| Kim        | 2008 | Korea   | Asian     | HB                | 225     | 225      | 0    | 0    | 153   | 153   | 0     | 0    | 0.069 |
| Buraczynska| 2009 | Poland  | Caucasian | PB                | 864     | 796      | 64   | 4    | 420   | 393   | 27    |      | \    |
| Bagarolli  | 2010 | Brazil  | Caucasian | PB                | 211     | 200      | 11   | 0    | 200   | 178   | 20    | 2    | 0.109 |
| Beijk      | 2010 | Netherlands | Caucasian | HB                | 466     | 411      | 55a  | 55a  | 2890  | 2530  | 360a  |      | \    |
| Dzumhur    | 2012 | Croatia | Caucasian | PB                | 24      | 22       | 2    | 0    | 120   | 98    | 22    |      | 0.269 |
| Cai        | 2013 | China   | Asian     | HB                | 936     | 936      | 0    | 0    | 978   | 978   | 0     | 0    | \    |
| Jiang      | 2013 | China   | Asian     | HB                | 822     | 822      | 0    | 0    | 835   | 835   | 0     | 0    | 0.069 |
| Singh      | 2013 | India   | Asian     | PB                | 125     | 83       | 41   | 1    | 130   | 101   | 29    |      | 0.152 |
| Singh      | 2014 | India   | Asian     | PB                | 378     | 287      | 89   | 2    | 320   | 247   | 73    |      | 0.021 |
| Buraczynska| 2016 | Poland  | Caucasian | PB                | 1090    | 987      | 98   | 5    | 716   | 658   | 57    | 1    | 0.839 |
| Doody      | 2017 | India   | Asian     | PB                | 199     | 153      | 40   | 6    | 203   | 147   | 48    | 8    | 0.118 |
| Zaharijova | 2017 | Bulgaria | Caucasian | PB                | 113     | 105      | 8    | 0    | 28    | 26    | 2     |      | 0.845 |
| Gond       | 2018 | India   | Asian     | PB                | 642     | 476      | 158  | 8    | 260   | 211   | 47    | 2    | 0.725 |
| Aioanei    | 2019 | Romania | Caucasian | PB                | 198     | 150      | 39   | 9    | 200   | 143   | 47    | 10   | 0.026 |
| Degimenci  | 2019 | Turkey  | Caucasian | HB                | 100     | 96       | 4    | 0    | 100   | 96    | 4     |      | 0.838 |
| Khaqanizadeh| 2020| Iran    | Asian     | HB                | 100     | 81       | 19   | 0    | 100   | 88    | 12    |      | 0.523 |
| Kim        | 2008 | Korea   | Asian     | HB                | 225     | 225      | 0    | 0    | 153   | 153   | 0     | 0    | \    |
| Buraczynska| 2009 | Poland  | Caucasian | PB                | 864     | 800      | 62   | 6    | 420   | 394   | 26    |      | 0.513 |
| Bagarolli  | 2010 | Brazil  | Caucasian | PB                | 211     | 208      | 3    | 0    | 200   | 189   | 11    |      | 0.689 |
| Cai        | 2013 | China   | Asian     | HB                | 936     | 936      | 0    | 0    | 978   | 978   | 0     | 0    | \    |
| Jiang      | 2013 | China   | Asian     | PB                | 822     | 822      | 0    | 0    | 835   | 835   | 0     | 0    | \    |
| Singh      | 2013 | India   | Asian     | PB                | 125     | 74       | 45   | 6    | 130   | 109   | 19    | 2    | 0.285 |
| Singh      | 2014 | India   | Asian     | PB                | 378     | 302      | 73   | 3    | 320   | 262   | 54    | 4    | 0.524 |
| Buraczynska| 2016 | Poland  | Caucasian | PB                | 1090    | 995      | 92   | 3    | 716   | 657   | 59    |      | 0.040 |
| Zaharijova | 2017 | Bulgaria | Caucasian | PB                | 110     | 99       | 11   | 0    | 26    | 24    | 2     |      | 0.838 |
| Gond       | 2018 | India   | Asian     | PB                | 652     | 481      | 167  | 4    | 260   | 217   | 41    | 2    | 0.967 |

(Continues)
| Surname       | Year | Country   | Ethnicity | Source of controls | Cases   | Controls | HWE |
|---------------|------|-----------|-----------|--------------------|---------|----------|-----|
| Aioanei       | 2019 | Romania   | Caucasian | PB                 | 198     | 200      | <0.001 |
| Degirmenci    | 2019 | Turkey    | Caucasian | HB                 | 100     | 100      | 0.838 |
| Khaghanzadeh  | 2020 | Iran      | Asian     | HB                 | 100     | 100      | 0.677 |

rs11536889

| Source of controls | Total GG | GC | CC | Total GG | GC | CC | HWE |
|--------------------|----------|----|----|----------|----|----|-----|
| Aioanei            | 198      | 126| 50 | 22       | 200| 152| 35  |
| Degirmenci         | 100      | 95 | 5  | 0        | 100| 96 | 4   |
| Khaghanzadeh       | 100      | 90 | 10 | 0        | 100| 92 | 8   |

rs1927911

| Source of controls | Total GG | GA | AA | Total GG | GA | AA | HWE |
|--------------------|----------|----|----|----------|----|----|-----|
| Cai                | 936      | 675| 215| 46       | 978| 605| 284 |
| Jiang              | 822      | 616| 180| 26       | 835| 527| 247 |
| Huang              | 545      | 306| 204| 35       | 550| 290| 232 |
| Peng               | 3387     | 2014| 1206| 167     | 3385| 1967| 1203| 215 |

Abbreviations: HB, Hospital based; HWE: Hardy–Weinberg equilibrium; PB, Population based.

*The number of the combined AG and GG genotypes, and these studies only involved in the analysis under dominant model.
## TABLE 2

Meta-analysis of the association between TLR4 polymorphisms and T2DM risk

| Variables | rs4986790 | rs4986791 | rs11536889 | rs1927911 |
|-----------|-----------|-----------|------------|-----------|
| **N** | Overall 19,715/9993 | Overall 13,581/4438 | Chinese 4,5690/5748 | Overall 5,4599/4581 |
| **Homozygous** | N/A | GG vs. AA | CC vs. GG | AA vs. GG |
| **OR (95% CI)** | 1.09 (0.65–1.82) | 2.00 (1.17–3.41) | 0.62 (0.40–0.96) | 0.89 (0.59–1.36) |
| **p** | 0.545 | 0.438 | 0.001 | 0.001 |
| **Heterozygous** | N/A | AG vs. AA | GC vs. GG | GA vs. GG |
| **OR (95% CI)** | 1.10 (0.95–1.27) | 1.38 (1.02–1.86) | 0.77 (0.61–0.98) | 0.96 (0.72–1.28) |
| **p** | 0.186 | 0.007 | <0.001 | <0.001 |
| **Recessive** | N/A | GG vs. AG/AA | CC vs. GC/GG | AA vs. GA/GG |
| **OR (95% CI)** | 1.17 (0.68–2.02) | 1.47 (0.73–2.97) | 0.81 (0.69–0.96) | 1.05 (0.93–1.18) |
| **p** | 0.873 | 0.440 | 0.183 | 0.455 |
| **Dominant** | N/A | AG/GG vs. AA | GC/CC vs. GG | GA/AA vs. GG |
| **OR (95% CI)** | 1.01 (0.95–1.07) | 1.01 (0.92–1.11) | 0.95 (0.90–1.10) | 1.00 (0.93–1.18) |
| **p** | 1.00 | 0.984 | 0.426 | <0.001 |
| **Allele** | N/A | G vs. A | C vs. G | A vs. G |
| **OR (95% CI)** | 1.09 (0.96–1.25) | 1.40 (1.07–1.82) | 0.76 (0.59–0.97) | 0.95 (0.77–1.19) |
| **p** | 0.064 | 0.010 | <0.001 | <0.001 |

**Abbreviations:** CI, confidence interval; OR, odds ratio.

Bold values are statistically significant, if the 95% CI excluded 1 or **p** < 0.05.
**3.3 Meta-analysis of rs4986791 polymorphism and T2DM risk**

About 13 studies involving 5811 cases and 4438 controls were included to evaluate the association between TLR4 rs4986791 polymorphism and T2DM risk. Six studies focused on Caucasian populations and seven on Asian populations. The pooled analysis indicated that rs4986791 A > G was related to increased T2DM risk in homozygous, heterozygous, and allelic model (GG vs. AA, OR = 2.00, 95% CI = 1.17–3.41, p = 0.011; AG vs. AA, OR = 1.38, 95% CI = 1.02–1.86, p = 0.035; G vs. A, OR = 1.40, 95% CI = 1.07–1.82, p = 0.013). In a subgroup analysis by ethnicity, a significantly increased association with T2DM risk was found in Caucasian (GG vs. AA, OR = 2.42, 95% CI = 1.23–4.75, p = 0.010) and also in Asian (GG vs. AA, OR = 1.76, 95% CI = 1.11–2.80, p = 0.017; G vs. A, OR = 1.63, 95% CI = 1.04–2.55, p = 0.034) (Table 2 and Figure 2b). No significant publication bias was found in the current meta-analysis by the Egger’s test (GG vs. AA, p = 0.743; AG vs. AA, p = 0.772; GG vs. AG/AA, p = 0.495; AG/GG vs. AA, p = 0.131; G vs. A, p = 0.614, Figure 3b).

**3.4 Meta-analysis of rs11536889 polymorphism and T2DM risk**

Four studies involving 5690 cases and 5748 controls were included to evaluate the association between TLR4 rs11536889 polymorphism and T2DM risk. These four studies all focused on Chinese populations. A significantly decreased association was observed between rs11536889 G > C and T2DM risk.
risk in the Chinese populations (CC vs. GG, OR = 0.62, 95% CI = 0.40–0.96, p = 0.031; GC vs. GG, OR = 0.77, 95% CI = 0.61–0.98, p = 0.034; CC vs. GC/GG, OR = 0.81, 95% CI = 0.69–0.96, p = 0.013; C vs. G, OR = 0.76, 95% CI = 0.59–0.97, p = 0.027) (Table 2 and Figure 2c). Egger’s test indicated no sign of any publication bias (CC vs. GG, p = 0.701; GC vs. GG, p = 0.139; CC vs. GC/GG, p = 0.763; GC/CC vs. GG, p = 0.152; C vs. G, p = 0.327, Figure 3c).

3.5 | Meta-analysis of rs1927911 polymorphism and T2DM risk

Five studies involving 4599 cases and 4581 controls were included to evaluate the association between TLR4 rs1927911 polymorphism and T2DM risk. All the studies focused on Asian populations, including two on Indian populations and three on Chinese populations. No significant association was found between rs1927911 G > A polymorphism and T2DM risk in any genetic models. In the further subgroup analysis by ethnicity, we also did not detect any significant relationship in Indian and Chinese populations (Table 2 and Figure 2d). Meanwhile, no obvious publication bias could be found (AA vs. GG, p = 0.343; GA vs. GG, p = 0.742; AA vs. GA/GG, p = 0.117; GA/AA vs. GG, p = 0.725; A vs. G, p = 0.461, Figure 3d).

4 | DISCUSSION

TLR4 gene, encoding TLR4 protein, has been investigated as a key role in the innate immune response in the metabolic syndrome and induction of insulin resistance. TLR4 not only recognizes the LPS, but also interacts with endogenous ligands, oxidized LDL, HSP 60 and 70, fibrinogen and fibronectin (Peterson et al., 2014; Rallabhandi et al., 2006). Therefore, TLR4 is increasingly being studied for its association with inflammatory diseases, including T2DM. Polymorphisms in TLR4 gene are potential factors in the change in function of its transcription.

Numbers of studies have been carried out to evaluate the association between TLR4 polymorphisms and T2DM risk, and two meta-analyses focused on only two polymorphisms (rs4986790 and rs4986791) before 2015 (Belforte et al., 2013; Yin et al., 2015). However, the results are still inconsistent even in these two studies. Using rs4986790 polymorphism as an example, Yin et al. found no significant association between this polymorphism and T2DM risk (Yin et al., 2015). However, this polymorphism was found to be associated with decreased metabolic disorders risk including T2DM and metabolic syndrome from Belforte et al (Belforte et al., 2013; Rallabhandi et al., 2006). Therefore, it is necessary to conduct this updated meta-analysis.
To the best of our knowledge, this is the first comprehensive meta-analysis to investigate the associations between the TLR4 polymorphisms (rs4986790, rs4986791, rs11536889, and rs1927911) and T2DM risk. We observed some new findings. For rs4986790 polymorphism, there was different results in the previous meta-analysis, and neither did the further subgroup analysis in Asian. However, it was observed to associate to an increased risk in Asian in our study (Figure 2a). The discrepancy may be due to the different sample sizes. Our updated study was the largest and latest including another seven recent studies. For rs4986791 polymorphism, only one previous meta-analysis included eight publications with 4231 cases and 3224 controls showed no association and not do the further subgroup analysis by ethnicity (Yin et al., 2015). In our study, after further adding six more articles with 2250 cases and 1402 controls, we came to a different conclusion that rs4986791 was related to increased T2DM risk under homozygous, heterozygous, and allelic model. Similarly, subgroup analyses indicated that rs4986791 was also related to increased T2DM risk in Caucasian under homozygous model, and in Asian under heterozygous and allelic model. The rs4986790 and rs4986791 have been widely studied in T2DM. However, these two polymorphisms are not polymorphic in Chinese populations, and very low in Asian, but are common among Caucasian ancestry (Yin et al., 2015). This different genetic background may lead to the different results in subgroup analyses. For rs11536889 and rs1927911 polymorphisms, no one has ever performed meta-analysis to drive more precise findings like this before. Huang et al. found neither rs11536889 and rs1927911 related to the risk of T2DM in a case-control study (Huang et al., 2015). However, rs11536889 polymorphism was observed to a significantly decreased in T2DM cases in Jiang’s study (Jiang et al., 2013), and rs1927911 polymorphism was also showed to decrease the risk of T2DM in a study from Xu et al. (Xu et al., 2015). Therefore, it is necessary to perform a meta-analysis to assess the association of the two polymorphism and T2DM. Our findings indicated that rs1927911 polymorphism seem not to be associated with T2DM, but rs11536889 polymorphism associated with decreased risk of T2DM.

Although we included the latest studies for TLR4 polymorphism and T2DM risk, several limitations in this meta-analysis should be addressed. First, only four studies for rs11536889 and five for rs1927911 included in the evaluating of these association of T2DM risk. Second, the sample size of most of these studies are relatively small, especially in the subgroup analysis. Third, we just searched the literatures from MEDLINE and EMBASE database, which may have missed studies for other languages. Forth, lack of the original information, such as age, sex, BMI, smoking, and drinking, limited the further adjusted analyses of these potentially factors.

In conclusion, our meta-analysis provides evidence that rs4986790 polymorphism was associated with an increased risk of T2DM in Asian. Rs4986791 polymorphism was related to an increased risk of T2DM both in Asian and Caucasian. Rs11536889 polymorphism may have a protective effect on T2DM in Chinese populations, whereas rs1927911 may have no impact. Further studies involving different ethnicities and large sample size are warranted to validate our findings.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: Renxian Liang. Selected the studies and collected the data: Jinzhuo Fan and Renxian Liang. Analyzed the data: Jinzhuo Fan and Renxian Liang. Drafted the paper: Renxian Liang. Revised the draft paper: Jinzhuo Fan and Renxian Liang.

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