Meta-analysis of association between TCF7L2 polymorphism rs7903146 and type 2 diabetes mellitus

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Abstract

Background: Large scale association studies have found a significant association between type 2 diabetes mellitus (T2DM) and transcription factor 7-like 2 (TCF7L2) polymorphism rs7903146. However, the quality of data varies greatly, as the studies report inconsistent results in different populations. Hence, we perform this meta-analysis to give a more convincing result.

Methods: The articles, published from January 1st, 2000 to April 1st, 2017, were identified by searching in PubMed and Google Scholar. A total of 56628 participants (34232 cases and 22396 controls) were included in the meta-analysis. A total of 28 studies were divided into 4 subgroups: Caucasian (10 studies), East Asian (5 studies), South Asian (5 studies) and Others (8 studies). All the data analyses were analyzed by the R package meta.

Results: The significant association was observed by using the dominant model (OR = 1.41, CI = 1.36 - 1.47, p < 0.0001), recessive model (OR = 1.58, CI = 1.48 - 1.69, p < 0.0001), additive model (CT vs CC) (OR = 1.34, CI = 1.28-1.39, p < 0.0001), additive model (TT vs CC) (OR = 1.81, CI = 1.69-1.94, p < 0.0001) and allele model (OR = 1.35, CI = 1.31-1.39, p < 0.0001).

Conclusion: The meta-analysis suggested that rs7903146 was significantly associated with T2DM in Caucasian, East Asian, South Asian and other ethnicities.

Keywords: T2DM, Polymorphism, rs7903146, Meta-analysis

Background

Diabetes is one of the largest global health emergencies in the twenty-first century. According to the International Diabetes Federation (IDF) [1], 46.5% of the adults with diabetes are undiagnosed, and 1 in 11 adults, about 415 million people, have diabetes. Every 6 s a person dies of diabetes (5.0 million deaths per year). By 2040, 1 in 10 adults, approximately 642 million people, will have diabetes. Notably, 12% of the global health expenditure, up to $673 billion, is dedicated to diabetes treatments, and the related take up most of the total expenditure.

The most prevalent form of diabetes is type 2 diabetes mellitus (T2DM), and in the developed countries up to 91% of the adults, who are being troubled by the diabetes, have T2DM. Excess body weight, physical inactivity, poor nutrition, genetics, family history of diabetes, past history of gestational diabetes and older age are risk factors that increase the rate of T2DM. Besides, T2DM is a complex disease, and and the function of the glycosylation plays a significant role [2, 3].

The SNP rs7903146(C/T) is a common variant in the gene TCF7L2, and allele T is the risk allele related to T2DM. The gene TCF7L2 is a transcription factor involved in the Wnt signaling pathway, and acts as a critical component of Wnt signalling and action [4–6]. The TCF7L2 gene product, a high mobility group box-containing transcription factor previously implicated in blood glucose homeostasis, is considered to act through the regulation of proglucagon gene expression in enteroendocrine cells via the Wnt signaling pathway [7]. In human islets, TCF7L2 expression associates positively with insulin gene expression [8, 9].
To address the genetic variations of T2DM, many scholars devoted themselves to the related research [10–16]. The common Pro12Ala polymorphism rs1801282 in PPARγ, the E23K variant rs5219 in KCNJ11, the polymorphism of the 5-HT2C receptor rs3813929 and the VKORC1 polymorphism rs9923231 were found to be associated with T2DM [17–20]. In 2006, Grant SF, et al. [7] confirmed a strongly significant association between susceptibility related to T2DM and common variants in transcription factor 7-like 2 (TCF7L2) in Icelandic subjects, and the result was the same with case-control method in Danish cohort and U.S. cohort. In 2006, Cauchi et al. [21] reported that the T-allele of the single nucleotide polymorphism (SNP) rs7903146 increased the risk of T2DM in the French population with 2367 cases and 2499 controls. The same results were shown by Horikoshi, Yu and Barra in case of the Japanese population, African American population and Brasilia [22–24]. However, Zheng et al. [25] found no association between rs7903146 and T2DM in the Chinese population.

The quality of the data varies greatly, is one of the reasons that the studies report inconsistent results, and the small sample size is another reason. The statistical efficiency can be improved after combining some samples together. The collected data in the control group was tested by the Hardy-Weinberg Equilibrium (HWE) in view of the quality of data. Therefore, we conducted a meta-analysis of published studies involving rs7903146 and T2DM to achieve a more comprehensive result. Finally, a total of 28 studies from 26 single studies [4, 22–46] were collected to reevaluate the association between rs7903146 and T2DM.

Methods
Search strategy
The articles, published from January 1st, 2000 to April 1st, 2017, were identified by searching the keywords “rs7903146” and “type 2 diabetes mellitus” in PubMed and Google Scholar. The selected articles were written in English.

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**Fig. 1** The flow chart of collecting articles for analyzing the association. And a total of 355 articles were identified by the search strategy. Firstly, a total of 230 articles were removed according to the title and abstract, and 45 articles were removed as the studies did not use case-control method, and 26 articles were removed as the studies did not have sufficient data to calculate OR, and 10 articles were excluded as they did not evaluate the association between rs7903146 and T2DM. After that 44 articles remained. Then, 5 articles were excluded as the control groups didn’t meet the Hardy-Weinberg Equilibrium (HWE), 9 articles were excluded when we made subgroup analyses and reduced the heterogeneity, and 4 articles were excluded as some LADA or type 1 diabetes patients were included in the case groups. Finally 28 studies from 26 articles were left.
Study selection criteria
We selected studies according to the following criteria: (1) The study was designed based on the case-control method. (2) The study evaluated the association between rs7903146 and T2DM. (3) The number of genotypes in case-controls groups was provided for calculating Odds Ratios (ORs). (4) The control group meets HWE. Besides, the $p$ value of HWE was calculated by R program HWE version 1.2 [47]. If $p < 0.05$, the article was preserved, otherwise the article was removed.

Data extraction
We extracted the following information from each study: (1) the first author of each article; (2) the publication year of each article; (3) the population of the study; (4) the ethnicity of individuals in each study; (5) the number of the rs7903146 genotypes both in cases and controls; (6) $p$ value of HWE in the control group. We used R package meta to analyze the data. We also referred to some other methods [48–51] to conduct the meta-analysis.

Choice of genetic model
The rs7903146 has two alleles: C and T. We analyzed the association between rs7903146 and T2DM by using the dominant model (TT+CT versus CC), recessive model (TT versus CC+CT), additive model (CT versus CC), additive model (TT versus CC) and allele model (T versus C), respectively [52].

Table 1 The primary characteristics of the 28 studies

| Study          | Year | Population    | Ethnicity   | T2DM | Control |
|----------------|------|---------------|-------------|------|---------|
| Ezzidi et al.  | 2009 | Arabic Tunisian| Arab        | CC   | 250     |
| Saadi et al.   | 2008 | Arab          | Arab        | CT   | 396     |
| Humphries et al.| 2006| Afro-Caribbean| Black African| TT   | 217     |
| Yu et al.      | 2009 | American      | Black African|     |         |
| Danquah et al. | 2013 | Ghanaiian     | Black African|     |         |
| Yu et al.      | 2009 | USA Caucasian | Caucasian   |     |         |
| Groves et al.  | 2006 | English       | Caucasian   |     |         |
| Humphries et al.| 2006| European      | Caucasian   |     |         |
| Cauchi et al.  | 2006 | Austrian      | Caucasian   |     |         |
| Dahlgren et al.| 2007| Swedish       | Caucasian   |     |         |
| Mayans et al.  | 2007 | Swedish       | Caucasian   |     |         |
| Van et al.     | 2007 | Dutch         | Caucasian   |     |         |
| Kimber et al.  | 2007 | English       | Caucasian   |     |         |
| De Silva et al.| 2007| English       | Caucasian   |     |         |
| Vcelak et al.  | 2012 | Czech         | Caucasian   |     |         |
| Hayashi et al. | 2007 | Japanese      | East Asian  |     |         |
| Honikoshi et al.| 2007| Japanese      | East Asian  |     |         |
| Kuzuaki et al. | 2008| Japanese      | East Asian  |     |         |
| Yasuharu et al.| 2009| Japanese      | East Asian  |     |         |
| Zheng et al.   | 2011 | Chinese       | East Asian  |     |         |
| Marquezine et al.| 2007| Brazilian     | Brazilian   |     |         |
| Barra et al.   | 2013 | Brazilian     | Brazilian   |     |         |
| Assmann et al. | 2014| Brazilian     | Brazilian   |     |         |
| Bodhini et al. | 2007| Asian Indian  | South Asian |     |         |
| Chandak et al. | 2007| Indian        | South Asian |     |         |
| Rees et al.    | 2008| UK South Asian| South Asian |     |         |
| Gupta et al.   | 2010| Indian        | South Asian |     |         |
| Hussain et al. | 2014| Indian        | South Asian |     |         |

A total of 56628 participants (34,232 cases and 22,396 controls) of 28 studies from 26 articles were included in the study. The name of the first author, the publication year of, the population of the study, the ethnicity of the study, the genotypes of the case-control group and the $p$ value of HWE. If the $p$ value of HWE in control group met the selection criteria ($p > 0.05$), it would be preserved, otherwise the data would be removed.
Table 2 The result of the heterogeneity in subgroup analyses

| Subgroup    | Dominant I² | P | Recessive I² | P | Additive (CT vs CC) I² | P | Allele I² | P | Additive (TT vs CC) I² | P |
|-------------|-------------|---|--------------|---|------------------------|---|-----------|---|------------------------|---|
| Caucasian   | 28.00%      | 0.18 | 0.00%        | 0.51 | 9.00%                  | 0.36 | 38.00%     | 0.1 | 20.00%                  | 0.26 |
| East Asian  | 0.00%       | 0.9  | 0.00%        | 0.85 | 0.00%                  | 0.96 | 0.00%      | 0.82 | 0.00%                   | 0.84 |
| South Asian | 0.00%       | 0.9  | 0.00%        | 0.47 | 0.00%                  | 0.97 | 0.00%      | 0.7  | 0.00%                   | 0.44 |
| Others      | 0.00%       | 0.62 | 0.00%        | 0.19 | 0.00%                  | 0.81 | 17.00%     | 0.29 | 29.00%                  | 0.19 |
| Total       | 5.00%       | 0.39 | 9.00%        | 0.33 | 0.00%                  | 0.76 | 29.00%     | 0.08 | 22.00%                  | 0.15 |

The I² and P value were used to test the heterogeneity by the dominant model (TT+CT versus CC), recessive model (TT versus CC+CT), additive model (CT versus CC), additive model (TT versus CC) and allele model (T versus C), respectively.

Fig. 2 The funnel plots of publication bias in different models. The funnel plots showed the results of the publication bias analyses between rs7903146 and T2DM by using a Dominant Model, b Recessive Model, c Additive Model (CT vs CC), d Allele Model and e Additive Model (TT vs CC). The Y-axis indicated the standard error of each study, and the standard error was smaller, the effect of the meta-analysis would be better.
Heterogeneity test

Odds Ratios and 95% confidence intervals (CIs) were calculated to assess the association between rs7903146 and T2DM. The two quantities, Cochran’s Q and I², were adopted to evaluate the heterogeneity in different kinds of ethnic groups. Q approximately follows a chi square distribution with k-1 degrees of freedom (where k is the number of studies), and the p value can be used to measure the significance level of the heterogeneity. The value of I², ranging from 0 to 100%, is calculated according to the formula, which is I² = (Q-(K-1))/Q*100%. The low, moderate, and high heterogeneity were labelled by I² levels of 25%, 50% and 75%, respectively. If I² is less than 50%, or p is more than 0.10, the fixed effect model is used, otherwise the random effect model is adopted.

Meta-analysis and subgroup analysis

After the heterogeneity test, we used the R package meta to perform the experiment with the fixed effect model [53].

Publication bias analysis and sensitivity analysis

Begg’s test [54] and Egger’s test [55] were selected for testing the publication bias. When a two-tailed value is less than 0.05, the publication bias is significant.

Results

Literature search

A flow diagram for the study selection process was shown in Fig. 1. A total of 355 articles were identified by the search strategy, and 28 studies from 26 articles were left. The detailed information about

| Study | Experimental Events | Control Events | Odds Ratio | OR 95%−CI | Weight |
|-------|---------------------|----------------|------------|-----------|--------|
| Subgroup = Caucasian | | | | | |
| Cauchi et al., 2006 | 286 | 806 | 200 | 755 | 1.53 | [1.23; 1.90] | 3.2% |
| Dallgren et al., 2008 | 201 | 490 | 67 | 563 | 1.92 | [1.37; 2.69] | 1.2% |
| Groves et al., 2006 | 1230 | 2531 | 771 | 1946 | 1.44 | [1.28; 1.62] | 10.8% |
| Humphries et al., 2006 | 1858 | 2058 | 601 | 1896 | 1.54 | [1.35; 1.76] | 8.8% |
| Kimber et al., 2007 | 1820 | 3397 | 1405 | 3119 | 1.41 | [1.28; 1.55] | 16.3% |
| Mayans et al., 2007 | 372 | 860 | 452 | 984 | 1.52 | [1.25; 1.85] | 3.8% |
| Vriel-Oostrijk et al., 2007 | 299 | 741 | 203 | 662 | 1.48 | [1.19; 1.88] | 3.1% |
| Silva et al., 2007 | 686 | 1735 | 420 | 1452 | 1.54 | [1.33; 1.79] | 6.8% |
| Vcex et al., 2012 | 199 | 370 | 148 | 353 | 1.61 | [1.20; 2.16] | 1.7% |
| Yan et al., 2009 | 493 | 577 | 430 | 4725 | 1.21 | [1.05; 1.38] | 9.1% |
| Fixed effect model | 17363 | 16455 | | | 1.46 | [1.38; 1.52] | 64.7% |
| Heterogeneity: I² = 58%, I² = 0.0026, p = 0.18 | | | | | |
| Subgroup = East Asian | | | | | |
| Miyake et al., 2008 | 233 | 371 | 1921 | 3617 | 1.49 | [1.20; 1.86] | 3.2% |
| Hayashi et al., 2007 | 169 | 256 | 1450 | 2430 | 1.31 | [1.00; 1.72] | 2.3% |
| Morikoshi et al., 2007 | 24 | 45 | 165 | 408 | 1.74 | [0.84; 3.22] | 0.4% |
| Yashin et al., 2009 | 47 | 73 | 434 | 806 | 1.55 | [0.94; 2.55] | 0.6% |
| Zheng et al., 2011 | 26 | 38 | 202 | 341 | 1.32 | [0.66; 2.68] | 0.3% |
| Fixed effect model | 783 | 7610 | | | 1.44 | [1.24; 1.64] | 6.6% |
| Heterogeneity: I² = 0%, I² = 0, p = 0.90 | | | | | |
| Subgroup = Others | | | | | |
| Amsel et al., 2008 | 343 | 564 | 179 | 304 | 1.08 | [0.82; 1.44] | 2.2% |
| Assmann et al., 2014 | 571 | 845 | 382 | 643 | 1.42 | [1.16; 1.76] | 3.4% |
| Barra et al., 2012 | 64 | 133 | 49 | 119 | 1.33 | [0.80; 2.18] | 0.6% |
| Humphries et al., 2006 | 166 | 316 | 141 | 302 | 1.26 | [0.92; 1.73] | 1.8% |
| Danquah et al., 2013 | 401 | 534 | 273 | 455 | 1.39 | [1.07; 1.79] | 2.4% |
| Marquezine et al., 2007 | 67 | 798 | 45 | 609 | 1.15 | [0.78; 1.70] | 1.1% |
| Saadi et al., 2008 | 65 | 182 | 30 | 101 | 1.31 | [0.76; 2.22] | 0.6% |
| Yan et al., 2009 | 260 | 1346 | 255 | 1411 | 1.09 | [0.90; 1.31] | 4.8% |
| Fixed effect model | 4778 | 3564 | | | 1.24 | [1.12; 1.35] | 16.8% |
| Heterogeneity: I² = 0%, I² = 0, p = 0.62 | | | | | |
| Subgroup = South Asian | | | | | |
| Bodhini et al., 2007 | 569 | 1052 | 462 | 1017 | 1.42 | [1.19; 1.68] | 5.2% |
| Chandak et al., 2007 | 564 | 758 | 391 | 596 | 1.52 | [1.21; 1.93] | 2.7% |
| Gupta et al., 2010 | 140 | 239 | 55 | 117 | 1.59 | [1.02; 2.49] | 0.7% |
| Hussain et al., 2014 | 43 | 85 | 25 | 64 | 1.90 | [0.98; 3.66] | 0.3% |
| Rees et al., 2008 | 476 | 686 | 352 | 574 | 1.43 | [1.13; 1.81] | 2.8% |
| Fixed effect model | 2817 | 2372 | | | 1.47 | [1.31; 1.64] | 11.7% |
| Heterogeneity: I² = 0%, I² = 0, p = 0.90 | | | | | |
| Fixed effect model | 25741 | 30381 | | | 1.41 | [1.36; 1.47] | 100.0% |

Fig. 3 The forest plots for the meta-analysis of rs7903146 by using the dominant model. The data of CC/CT/TT was used in the dominant model (CT + TT vs CC)
the search strategy was displayed in Additional file 1: Table S1.

**Study characteristics**

As shown in Table 1, a total of 56628 participants (34232 cases and 22396 controls) of 28 studies from 26 articles were included in this meta-analysis. The studies were divided into Caucasian (10 studies) [4, 22, 29–36], East Asian (5 studies) [23, 25, 37–39], South Asian (5 studies) [42–46] and Others (Arab (2 studies) [26, 27], Black African (3 studies) [22, 28, 29] and Brazilian (3 studies) [24, 40, 41]) subgroups. The collected data, performed with the R package meta in this meta-analysis, was displayed in Additional file 1: Table S2.

**Heterogeneity test**

According to the genotypes shown in Table 1, a total of 28 studies were analyzed by the dominant model, recessive model, additive model and allele model, respectively. The heterogeneity of subgroups was shown in Table 2. According to the data displayed in Table 2, we didn't get the significant heterogeneity in the dominant model ($p = 0.39$ and $I^2 = 5.00$%), recessive model ($p = 0.33$ and $I^2 = 9$%), additive model (CT vs CC: $p = 0.76$ and $I^2 = 0.00$%), additive model (TT vs CC: $p = 0.15$ and $I^2 = 22$%) and allele model ($p = 0.08$ and $I^2 = 29$%). As the $p$ value was more than 0.1, we selected the fixed effect model.

**Publication bias analysis and sensitivity analysis**

The publication bias was not found in all models below. The $p$ values of Begg's test and Egger's test for the dominant, recessive, additive (CT vs CC), additive (TT vs CC) and allele model are 0.7821 and 0.7352, 0.3635 and 0.441, 0.6354 and 0.5673, respectively. The
results were reflected in the funnel plots Fig. 2(a-e) directly.

**Association between rs7903146 and type 2 diabetes mellitus**

The association between rs7903146 and T2DM was shown in the forest plots: Figs. 3, 4, 5, 6 and 7 were the forest plots of the dominant model (TT + CT versus CC), recessive model (TT versus CC), additive model (CT versus CC), allele model (T versus C) and additive model (TT versus CC), respectively. We made the Z test, and the result was displayed in the Table 3.

In Caucasian subgroup, the results were shown as follows: dominant model (TT + CT vs CC): (OR = 1.45, CI = 1.38 - 1.52, p < 0.0001); recessive model (TT vs CC + CT): (OR = 1.66, CI = 1.53 - 1.79, p < 0.0001); additive model (CT vs CC): (OR = 1.36, CI = 1.29 - 1.43, p < 0.0001); additive model (TT vs CC): (OR = 1.91, CI = 1.76 - 2.08), p < 0.0001); allele model (T vs C): (OR = 1.37, CI = 1.32 - 1.43, p < 0.0001).

In East Asian subgroup, the results were shown as follows: dominant model (TT + CT vs CC): (OR = 1.44, CI = 1.24 - 1.68, p < 0.0001); recessive model (TT vs CC + CT): (OR = 2.82, CI = 1.00 - 7.98, p = 0.0509); additive model (CT vs CC): (OR = 1.42, CI = 1.21 - 1.65, p < 0.0001); additive model (TT vs CC): (OR = 1.81, CI = 1.69 - 1.94, p < 0.0001); allele model (T vs C): (OR = 1.37, CI = 1.32 - 1.43, p < 0.0001).

In South Asian subgroup, the results were shown as follows: dominant model (TT + CT vs CC): (OR = 1.41, CI = 1.31 - 1.64, p < 0.0001); recessive model (TT vs CC + CT): (OR = 1.52, CI = 1.26 - 1.83, p < 0.0001); additive model (CT vs CC): (OR = 1.42, CI = 1.29 - 1.43, p < 0.0001); additive model (TT vs CC): (OR = 1.81,

### Table 3

| Study              | Experimental Events | Total Events | Control Total | Odds Ratio | OR 95% CI | Weight |
|--------------------|---------------------|--------------|---------------|------------|-----------|---------|
| **Subgroup = Caucasian** |                     |              |               |            |           |         |
| Cauchi et al. 2006 | 208                 | 640          | 200           | 1.34       | 1.06:1.68 | 3.2%    |
| Dahlgrem et al. 2008 | 83                 | 410          | 67            | 1.88       | 1.32:2.67 | 1.2%    |
| Groves et al. 2006 | 960                 | 2044         | 771           | 1.35       | 1.19:1.53 | 10.8%   |
| Humphries et al. 2006 | 865             | 1866         | 601           | 1.43       | 1.25:1.64 | 8.7%    |
| Kimber et al. 2007 | 1459               | 2788         | 1405          | 1.34       | 1.21:1.48 | 16.4%   |
| Mayans et al. 2007 | 318                 | 571          | 452           | 1.48       | 1.29:1.62 | 3.8%    |
| Vladd-Obstaphneuk et al. 2007 | 221        | 586          | 203           | 1.37       | 1.08:1.73 | 3.1%    |
| Silva et al. 2007 | 507                 | 1394         | 420           | 1.40       | 1.20:1.64 | 6.8%    |
| Voelax et al. 2012 | 156                 | 303          | 148           | 1.47       | 1.08:2.00 | 1.7%    |
| Yan et al. 2009 | 392                 | 3783         | 430           | 1.15       | 1.02:1.33 | 8.9%    |
| Fixed effect model | 14185              | 1655         |               | 1.36       | 1.29:1.43 | 64.5%   |
| Heterogeneity: p^2 = 9%, p^2 = 0.0007, p = 0.36 |
| **Subgroup = East Asian** |                     |              |               |            |           |         |
| Miyake et al. 2008 | 224                 | 365          | 1921          | 1.47       | 1.18:1.83 | 3.4%    |
| Hayashi et al. 2007 | 165                 | 250          | 1450          | 1.31       | 1.00:1.73 | 2.4%    |
| Horiohsh et al. 2007 | 22            | 43           | 135           | 1.59       | 0.85:2.99 | 0.4%    |
| Yasahara et al. 2009 | 45                | 71           | 434           | 1.48       | 0.90:2.45 | 0.7%    |
| Zheng et al. 2011 | 24                  | 37           | 202           | 1.27       | 0.83:2.58 | 0.4%    |
| Fixed effect model | 796                | 7610         |               | 1.42       | 1.21:1.65 | 7.2%    |
| Heterogeneity: p^2 = 0%, p^2 = 0, p = 0.96 |
| **Subgroup = Others** |                     |              |               |            |           |         |
| Asmann et al. 2008 | 253                 | 415          | 179           | 1.09       | 0.81:1.47 | 2.1%    |
| Asmann et al. 2014 | 415                 | 630          | 382           | 1.32       | 1.06:1.66 | 3.3%    |
| Barra et al. 2012 | 47                  | 110          | 49            | 1.07       | 0.63:1.80 | 0.7%    |
| Humphries et al. 2008 | 136          | 260          | 141           | 1.25       | 0.90:1.75 | 1.6%    |
| Danquah et al. 2013 | 323                 | 488          | 273           | 1.31       | 1.00:1.70 | 2.5%    |
| Marquezone et al. 2007 | 54          | 657          | 45            | 1.12       | 0.74:1.69 | 1.1%    |
| Saadi et al. 2008 | 54                  | 148          | 30            | 1.36       | 0.79:2.34 | 0.6%    |
| Yan et al. 2009 | 215                 | 1133         | 255           | 1.04       | 0.85:1.28 | 4.8%    |
| Fixed effect model | 3841               | 3944         |               | 1.18       | 1.06:1.31 | 16.7%   |
| Heterogeneity: p^2 = 0%, p^2 = 0, p = 0.81 |
| **Subgroup = South Asian** |                     |              |               |            |           |         |
| Bodhini et al. 2007 | 455                 | 846          | 462           | 1.40       | 1.16:1.68 | 5.0%    |
| Chandak et al. 2007 | 423                 | 583          | 391           | 1.39       | 1.08:1.78 | 2.7%    |
| Gupta et al. 2010 | 96                  | 174          | 55            | 1.39       | 0.87:2.22 | 0.8%    |
| Hussain et al. 2014 | 36                | 71           | 25            | 1.77       | 0.90:3.48 | 0.3%    |
| Rees et al. 2008 | 360                 | 526          | 352           | 1.37       | 1.07:1.75 | 2.7%    |
| Fixed effect model | 2200                | 2372         |               | 1.40       | 1.24:1.58 | 11.6%   |
| Heterogeneity: p^2 = 0%, p = 0.97 |
| **Fixed effect model** | **20992**          | **30381**    |               | **1.34**   | **1.28:1.39** | **100.0%** |

Fig. 5 The forest plots for the meta-analysis of rs7903146 by using the additive model. The data of CC/CT/TT was used in the additive model (CT vs CC).
Fig. 6 The forest plots for the meta-analysis of rs7903146 by using the allele model. The data of CC/CT/TT was used in the allele model (T vs C).

CI = 1.69 - 1.94, \( p < 0.0001 \); additive model (TT vs CC): (OR = 1.77, CI = 1.46 - 2.15, \( p < 0.0001 \)) allele model (T vs C): (OR = 1.44, CI = 1.24 - 1.67, \( p < 0.0001 \)).

In Others subgroup, the results were shown as follows: dominant model (TT + CT vs CC): (OR = 1.41, CI = 1.36 - 1.47, \( p < 0.0001 \)); recessive model (TT vs CC + CT): (OR = 1.43, CI = 1.36 - 1.50, \( p = 0.0002 \)); additive model (CT vs CC): (OR = 1.48, CI = 1.26 - 1.75, \( p < 0.0001 \)); allele model (T vs C): (OR = 1.37, CI = 1.25 - 1.49, \( p < 0.0001 \)).

In total groups, the results were shown as follows: dominant model (TT + CT vs CC): (OR = 1.41, CI = 1.36 - 1.47, \( p < 0.0001 \)); recessive model (TT vs CC + CT): (OR = 1.58, CI = 1.48 - 1.69, \( p < 0.0001 \)); additive model (CT vs CC): (OR = 1.34, CI = 1.28 - 1.39, \( p = 0.0001 \)); additive model (TT vs CC): (OR = 1.81, CI = 1.69 - 1.94, \( p < 0.0001 \)); allele model (T vs C): (OR = 1.35, CI = 1.31 - 1.39, \( p < 0.0001 \)).

Discussion

In the meta-analysis, 56628 participants (34232 cases and 22396 controls) of 28 studies from 26 articles were included. The result of the four subgroups (Caucasian, East Asian, South Asian and Others) suggested that rs7903146 was significantly associated with T2DM in all subgroups and the total groups.

We removed each one of the studies in the groups or any subgroups in the dominant, recessive, additive and allele model for testing the robustness of results, respectively. The results did not change significantly, which displayed that the conclusion was robust. The heterogeneity and publication bias were not found in our meta-analysis.

We used the keywords “rs7903146”, “type 2 diabetes” and “meta-analysis” to search in PubMed, and got nine articles [46, 56–63]. Our work was different from others. We analyzed the association between rs7903146 and T2DM in Caucasian, East Asian, South Asian and Others groups. We did not find a significant heterogeneity in all...
subgroup analyses, so the fixed effect model was used. We found that rs7903146 was associated with T2DM in Caucasian, East Asian, South Asian and other ethnicities significantly.

Some limitations existed in this meta-analysis. Firstly, considering the heterogeneity in all subgroup analyses, we excluded 9 articles. More articles should be added into the meta-analysis. Secondly, some of the same cases or controls may be used in different studies.

**Conclusion**

The meta-analysis suggested that rs7903146 was significantly associated with T2DM in Caucasian, East Asian, South Asian and other ethnicities.

**Table 3** The result of the Z test in subgroup analyses

| Subgroup    | Dominant | Recessive | Additive (CT vs CC) | Allele | Additive (TT vs CC) |
|-------------|----------|-----------|---------------------|--------|---------------------|
|             | Z        | P         | Z                   | P      | Z                   | P         |
| Caucasian   | 14.86    | <0.0001   | 12.35               | <0.0001| 11.67               | <0.0001   |
| South Asian | 4.69     | <0.0001   | 1.95                | 0.0509 | 4.42                | <0.0001   |
| East Asian  | 6.61     | <0.0001   | 4.47                | 0.0001 | 5.45                | <0.0001   |
| Others      | 4.17     | <0.0001   | 3.75                | 0.0002 | 3.11                | 0.0019    |
| Total       | 17.2     | <0.0001   | 13.53               | <0.0001| 13.73               | <0.0001   |

The Z test was performed with the dominant model (TT+CT versus CC), recessive model (TT versus CC+CT), additive model (CT versus CC), additive model (TT versus CC) and allele model (T versus C), respectively.
Additional file

Additional file 1: Table S1. The detailed information about the search strategy. Table S2. The collected data in the meta-analysis. (XLSX 13 kb)

Abbreviations
Cis. Confidence intervals; HWE: Hardy-Weinberg Equilibrium; ORs: Odds ratio; SNP: Single nucleotide polymorphism; T2DM: Type 2 diabetes mellitus; TCF7L2: Transcription factor 7-like 2

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Availability of data and materials
All the data generated or analyzed in this study was included in this manuscript.

Authors’ contributions
WYD wrote the paper. SLJ and LX revised the paper. WYD, ZJH, LJZ and SLJ collected and selected the data, designed and performed the experiment. QJU and ZW conducted the project. ZJH and SLJ helped interpret the results. WYD and LX developed analytical tools. All authors discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

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