## **RESEARCH ARTICLE**

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# 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 = 1.31, 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

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<sup>5</sup>Department of Mathematics, Harbin Institute of Technology, No.92, Xidazhi Street, Nangang District, 150001 Harbin, China 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].



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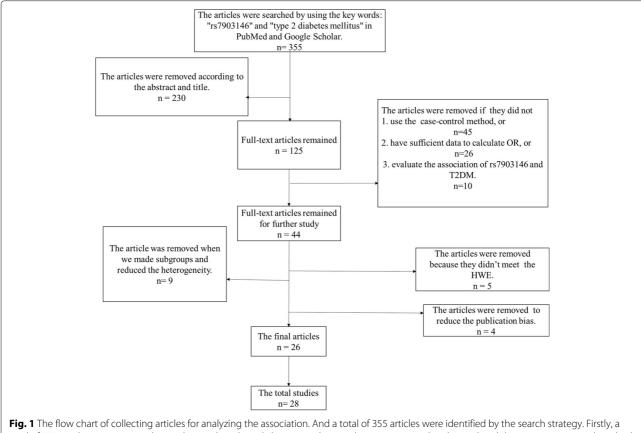
To address the genetic variations of T2DM, many scholars devoted themselves to the related research [10-16].The common Pro12Ala polymorphism rs1801282 in PPAR $\gamma$ , the E23K variant rs5219 in KCNJ11, the polymorphism of the 5-HT2C receptor rs3813929 and the VKORC1 polymorphism rs9923231 were found 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 metaanalysis 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.



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

| Table 1 | The primar | characteristics of the 28 studies |
|---------|------------|-----------------------------------|
|---------|------------|-----------------------------------|

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].

Control

|                   |      |                  |               | T2DM |      |     | Control |      |     |          |
|-------------------|------|------------------|---------------|------|------|-----|---------|------|-----|----------|
| Study             | Year | Population       | Ethnicity     | CC   | CT   | TT  | CC      | CT   | TT  | HWE      |
| Ezzidi et al.     | 2009 | Arabic Tunisian  | Arab          | 250  | 396  | 217 | 181     | 235  | 95  | 0.227155 |
| Saadi et al.      | 2008 | Arab             | Arab          | 30   | 54   | 11  | 71      | 94   | 23  | 0.388992 |
| Humphries et al.  | 2006 | Afro-Caribbean   | Black African | 141  | 136  | 30  | 161     | 124  | 26  | 0.75859  |
| Yu et al.         | 2009 | African American | Black African | 255  | 212  | 48  | 1156    | 921  | 165 | 0.31807  |
| Danquah et al.    | 2013 | Ghanaian         | Black African | 273  | 323  | 78  | 182     | 165  | 28  | 0.257132 |
| Yu et al.         | 2009 | USA Caucasian    | Caucasian     | 430  | 392  | 101 | 4295    | 3391 | 693 | 0.515248 |
| Groves et al.     | 2006 | English          | Caucasian     | 771  | 960  | 270 | 1175    | 1084 | 217 | 0.944175 |
| Humphries et al.  | 2006 | European         | Caucasian     | 601  | 665  | 193 | 1295    | 1001 | 197 | 0.854011 |
| Cauchi et al.     | 2006 | Austrian         | Caucasian     | 200  | 208  | 78  | 555     | 432  | 88  | 0.759981 |
| Dahlgren et al.   | 2007 | Swedish          | Caucasian     | 67   | 83   | 18  | 496     | 327  | 62  | 0.421344 |
| Mayans et al.     | 2007 | Swedish          | Caucasian     | 452  | 318  | 54  | 532     | 253  | 35  | 0.480907 |
| Van et al.        | 2007 | Dutch            | Caucasian     | 203  | 221  | 72  | 459     | 365  | 83  | 0.396927 |
| Kimber et al.     | 2007 | English          | Caucasian     | 1405 | 1459 | 361 | 1714    | 1329 | 248 | 0.662991 |
| De Silva et al.   | 2007 | English          | Caucasian     | 420  | 507  | 161 | 1032    | 887  | 180 | 0.58617  |
| Vcelak et al.     | 2012 | Czech            | Caucasian     | 148  | 156  | 43  | 205     | 147  | 24  | 0.730572 |
| Hayashi et al.    | 2007 | Japanese         | East Asian    | 1450 | 165  | 4   | 980     | 85   | 2   | 0.91209  |
| Horikoshi et al.  | 2007 | Japanese         | East Asian    | 165  | 22   | 2   | 251     | 21   | 0   | 0.507848 |
| Kazuaki et al.    | 2008 | Japanese         | East Asian    | 1921 | 228  | 5   | 1696    | 137  | 1   | 0.29539  |
| Yasuharu et al.   | 2009 | Japanese         | East Asian    | 434  | 45   | 2   | 372     | 26   | 0   | 0.50056  |
| Zheng et al.      | 2011 | Chinese          | East Asian    | 202  | 24   | 1   | 139     | 13   | 0   | 0.581813 |
| Marquezine et al. | 2007 | Brazilian        | Brazilian     | 45   | 54   | 13  | 564     | 603  | 128 | 0.070107 |
| Barra et al.      | 2013 | Brazilian        | Brazilian     | 55   | 49   | 6   | 58      | 40   | 11  | 0.304112 |
| Assmann et al.    | 2014 | Brazilian        | Brazilian     | 382  | 415  | 156 | 261     | 215  | 59  | 0.147418 |
| Bodhini et al.    | 2007 | Asian Indian     | South Asian   | 462  | 455  | 114 | 555     | 391  | 92  | 0.531352 |
| Chandak et al.    | 2007 | Indian           | South Asian   | 391  | 423  | 141 | 205     | 160  | 34  | 0.726021 |
| Rees et al.       | 2008 | UK South Asian   | South Asian   | 352  | 360  | 116 | 222     | 166  | 44  | 0.12238  |
| Gupta et al.      | 2010 | Indian           | South Asian   | 55   | 96   | 44  | 62      | 78   | 21  | 0.64658  |
| Hussain et al.    | 2014 | Indian           | South Asian   | 25   | 36   | 7   | 43      | 35   | 4   | 0.349985 |

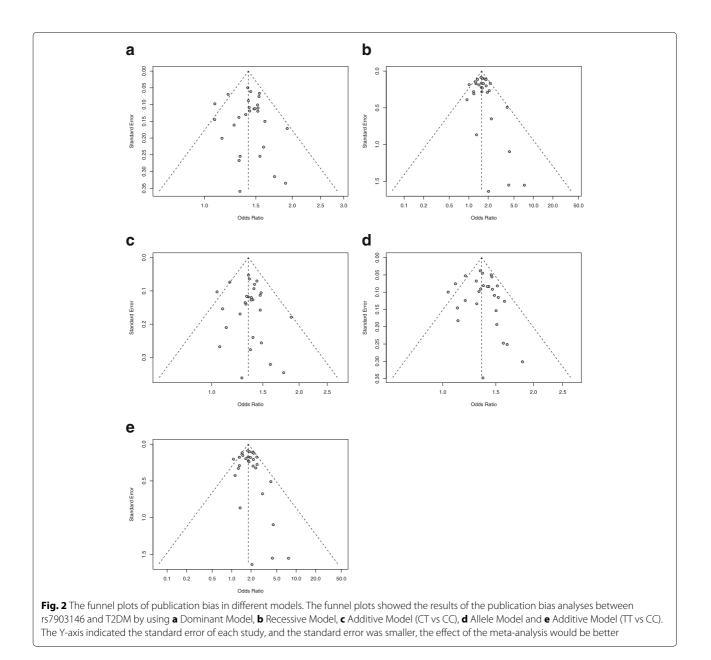
T2DM

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

| Subgroup    | Dominant | Dominant |              | Recessive |              | CT vs CC) | Allele       |      | Additive(TT vs CC) |      |  |
|-------------|----------|----------|--------------|-----------|--------------|-----------|--------------|------|--------------------|------|--|
|             | 2        | Р        | <sup>2</sup> | Р         | <sup>2</sup> | Р         | <sup>2</sup> | Р    | <sup>2</sup>       | Р    |  |
| 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 |  |

Table 2 The result of the heterogeneity in subgroup analyses

The I<sup>2</sup> 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



#### 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 I<sup>2</sup>, 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 I<sup>2</sup>, ranging from 0 to 100%, is calculated according to the formula, which is I<sup>2</sup> = (Q-(K-1))/Q\*100%. The low, moderate, and high heterogeneity were labelled by I<sup>2</sup> levels of 25%, 50% and 75%, respectively. If I<sup>2</sup> 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, abd 28 studies from 26 articles were left. The detailed information about

| Study   | Events   | Total   | Events  | Total   | Odds   | Ratio  | OR  | 95%-CI  | Weight   |
|---|--|---|---|---|--|--|---|---|--|
| Subgroup - Caucasian                              |  |   |   |   |  |  |   |   |  |
|   | 286  | 806   | 200   | 755   |  |  | 1 53 [  | 1 23 1 901  | 3.2%   |
|   |  |   |   |   |  | <u> </u>   |   |   | 1.2%   |
|   |  |   |   |   |  | -  |   |   |  |
| ,   |  |   |   |   |  |  |   |   | 8.8%   |
|   |  |   |   |   |  |  |   |   |  |
|   |  |   |   |   |  |  |   |   | 3.8%   |
|   |  |   |   |   |  |  |   |   |  |
|   |  |   |   |   |  | 5  |   |   |  |
|   |  |   |   |   |  |  |   |   |  |
|   |  |   |   |   |  |  |   |   |  |
|   | -50  |   |   |   |  |  |   |   |  |
|   | 0026 n -   |   |   | 10400   |  |  | 1.45 [  | 1.00, 1.02]   | UT.1 /0  |
| Heterogeneity. $T = 26\%, T = 0.$                 | 0020, <i>p</i> =   | 0.10  |   |   |  |  |   |   |  |
| Subgroup = East Asian                             |  |   |   |   |  |  |   |   |  |
| Miyake et al.,2008                                | 233  | 371   | 1921  | 3617  |  |  |   |   | 3.2%   |
| Hayashi et al.,2007                               |  |   |   |   |  |  |   |   | 2.3%   |
| Horikoshi et al.,2007                             | 24   | 45  |   | 416   | -  | + + +  | — 1.74 [  | 0.94; 3.22]   | 0.4%   |
| Yasuharu et al.,2009                              | 47   |   |   |   | -  | <u> </u>   |   |   | 0.6%   |
| Zheng et al.,2011                                 | 25   | 38  | 202   | 341   |  | + +  | - 1.32 [  | 0.65; 2.68]   | 0.3%   |
|   |  | 783   |   | 7610  |  | $\diamond$   | 1.44 [  | 1.24; 1.68]   | 6.8%   |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $\mu$ | 0 = 0.90   |   |   |   |  |  |   |   |  |
| Subgroup = Others                                 |  |   |   |   |  |  |   |   |  |
| Alsmadi et al.,2008                               | 343  | 564   | 179   | 304   | _  | *  | 1.08 [  | 0.82; 1.441   | 2.2%   |
|   | 571  |   |   |   |  |  |   |   |  |
|   |  |   |   |   |  |  |   |   |  |
|   |  |   |   |   | _  |  |   |   |  |
|   |  |   |   |   |  |  |   |   |  |
|   |  |   |   |   |  |  |   |   |  |
|   |  |   |   | 101   |  |  |   |   |  |
|   |  |   |   | 1411  | -  | - i  |   |   |  |
|   |  |   |   |   |  | $\diamond$   |   |   |  |
|   | 0.62   |   |   |   |  |  | L   | /   |  |
| Subgroup - South Asian                            |  |   |   |   |  |  |   |   |  |
|   | 560  | 1052  | 462   | 1017  |  |  | 1 / 2 1   | 1 10 1 691  | 5.2%   |
| · · · · · · · · · · · · · · · · · · ·             |  |   |   |   |  | <u> </u>   |   |   |  |
|   |  |   |   |   |  |  |   |   |  |
|   |  |   |   |   |  |  |   |   |  |
|   |  |   |   |   |  |  |   |   |  |
|   | 470  |   | 552   |   |  |  |   |   |  |
|   | 0 = 0.90   | 2017  |   | 2012  |  |  | 1.47 [  | 1.01, 1.04]   | 11.7 /0  |
|   |  |   |   |   |  |  |   |   |  |
| Fixed effect model                                |  | 25741   |   | 30381   |  |  | 1.41 [  | 1.36; 1.47]   | 100.0%   |
| Heterogeneity: $I^2 = 5\%$ , $\tau^2 = 0.0$       | 006, <i>p</i> = 0  | .39   |   |   | 0.5  | 1 2  |   |   |  |
|   | Silva et al.,2007<br>Vcelak et al.,2012<br>Yan et al.,2009<br>Fixed effect model<br>Heterogeneity: $l^2 = 28\%$ , $\tau^2 = 0$ .<br>Subgroup = East Asian<br>Miyake et al.,2008<br>Hayashi et al.,2007<br>Horikoshi et al.,2007<br>Yasuharu et al.,2009<br>Zheng et al.,2011<br>Fixed effect model<br>Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p$<br>Subgroup = Others<br>Alsmadi et al.,2018<br>Assmann et al.,2014<br>Barra et al.,2012<br>Humphries et al.,2006<br>Danquah et al.,2013<br>Marquezine et al.,2007<br>Saadi et al.,2008<br>Yan et al.,2009<br>Fixed effect model<br>Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p$<br>Subgroup = South Asian<br>Bodhini et al.,2017<br>Gupta et al.,2017<br>Hussain et al.,2014<br>Rees et al.,2018<br>Fixed effect model<br>Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p$ | Study   Events     Subgroup = Caucasian   Cauchi et al., 2006   286     Dahlgren et al., 2006   1230     Humphries et al., 2006   1230     Humphries et al., 2006   1230     Mayans et al., 2007   1820     Mayans et al., 2007   1820     Mayans et al., 2007   1820     Mayans et al., 2007   688     Viet–Ostaptchouk et al., 2007   688     Voelak et al., 2012   199     Yan et al., 2009   493     Fixed effect model   Heterogeneity: $t^2 = 28\%$ , $\tau^2 = 0.0026$ , $p = 0.90$ Subgroup = East Asian   Miyake et al., 2007   24     Yasuharu et al., 2012   44     Heterogeneity: $t^2 = 0\%$ , $t^2 = 0$ , $p = 0.90$ Subgroup = Others   Alsmadi et al., 2013   401     Marquezine et al., 2014   571     Barra et al., 2012   64     Humphrises et al., 2006   166 | Subgroup = Caucasian   Cauchi et al., 2006 286 806   Dahigren et al., 2006 1230 2531   Humphries et al., 2006 1320 2531   Humphries et al., 2007 1820 3397   Mayans et al., 2007 372 660   Viiet-Ostaptchouk et al., 2007 372 660   Viiet-Ostaptchouk et al., 2017 93 741   Silva et al., 2012 199 370   Yan et al., 2012 199 370   Yan et al., 2009 493 4577   Fixed effect model 17363   Heterogeneity: $f^2 = 28\%$ , $\tau^2 = 0.0026$ , $p = 0.18$ Subgroup = East Asian Miyake et al., 2007 24 45   Yasuharu et al., 2007 24 45 Yasuharu et al., 2007 24 45   Yasuharu et al., 2007 24 45 Yasuharu et al., 2007 24 45   Yasuharu et al., 2007 24 45 Yasuharu et al., 2012 44 43   Eherogeneity: $f^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.90$ 833 564 Assmann et al., 2014 51 845   Barra et al., 2012 <t< td=""><td>Study   Events   Total Events     Subgroup = Caucasian   Cauchi et al.,2006   286   806   200     Dahlgren et al.,2006   1230   2531   771     Humphries et al.,2006   1230   2531   771     Humphries et al.,2007   1820   3397   1405     Mayans et al.,2007   372   660   452     Vliet-Ostaptchouk et al.,2007   293   741   203     Silva et al.,2007   681   7353   420     Viet-Ostaptchouk et al.,2007   168   17363   Heterogeneity: <math>l^2 = 28\%</math>, <math>t^2 = 0.0026</math>, <math>p = 0.18     Subgroup = East Asian   Miyake et al.,2007   169   256   1450     Horikoshi et al.,2007   24   45   165   Yasuharu et al.,2007   24   45   165     Yasuharu et al.,2007   24   45   165   Yasuharu et al.,2011   25   38   202     Fixed effect model   783   Heterogeneity: <math>l^2 = 0\%</math>, <math>t^2 = 0</math>, <math>p = 0.90   Fixed effect model   783     Hayashi et al.,2011   541   133</math></math></td><td>StudyEventsTotalEventsTotalSubgroup = CaucasianCauchi et al., 2006286806200755Dahlgren et al., 2006123025317711946Humphries et al., 2006182025317711946Humphries et al., 20071820339714053119Mayans et al., 20071820339714053119Mayans et al., 200768817354201452Viet-Ostaptchouk et al., 200768817354201452Vcelak et al., 2012199370148353Yan et al., 200949345774304725Fixed effect model1736316455Heterogeneity: <math>r^2 = 28\%</math>, <math>r^2 = 0.0026</math>, <math>p = 0.18</math>7610Miyake et al., 20072445165416Yasuharu et al., 20094773434806Zheng et al., 20072445165416Yasuharu et al., 20094773434806Zheng et al., 201151382643Barra et al., 20126413349Humphries et al., 2006166316141302Danquah et al., 20076779845609Saadi et al., 20086518230101Yan et al., 20086518230101Humphries et al., 200766136141302Danquah et al., 200766136141</td><td>Study   Events   Total   Events   Total   Odds     Subgroup = Caucasian   Cauchi et al.,2006   286   806   200   755     Dahlgren et al.,2006   1230   2531   771   1946     Humphries et al.,2006   1820   3397   1405   3119     Mayans et al.,2007   1820   3397   1405   3119     Mayans et al.,2007   0732   660   452   984     Vilet-Ostaptchouk et al.,2007   293   741   203   662     Silva et al.,2012   199   370   148   353     Yan et al.,2008   493   4577   430   4725     Fixed effect model   17363   16455   166   16     Heterogeneity: <math>f^2 = 28\%</math>, <math>r^2 = 0.026</math>, <math>p = 0.18</math>   203   143   806   143     Yasuharu et al.,2007   24   45   165   416   143     Yasuharu et al.,2007   24   45   165   416   143     Yasuharu et al.,2011   25</td><td>Study   Events   Total   Odds Ratio     Subgroup = Caucasian<br/>Cauchi et al.,2006   286   806   200   755     Dahlgren et al.,2008   101   490   67   563     Groves et al.,2006   1230   2531   771   1946     Humphries et al.,2007   1820   3397   1405   3119     Mayans et al.,2007   1820   3397   1405   3119     Mayans et al.,2007   1820   3397   148   353     Yan et al.,2007   168   17363   16455     Fixed effect model   17363   16455     Heterogeneity: <math>l^2 = 28%</math>, <math>t^2 = 0.0026</math>, <math>p = 0.18</math>   500   2430     Subgroup = East Asian   Miyake et al.,2007   169   256   1450   2430     Horikoshi et al.,2007   129   256   1450   2430   4577   434   806     Zheng et al.,2011   25   38   202   341   54   165   416     Yasuharu et al.,2012   64   133   49</td><td>Study   Events   Total   Code   Ratio   OR     Subgroup = Caucasian   Cauchi et al.,2006   286   806   200   755     Dahlgren et al.,2006   1230   2531   771   1946   1.43     Humphries et al.,2007   1820   3397   1405   3119   1.44     Mayans et al.,2007   1820   3397   1405   3119   1.44     Viet-Ostaptchouk et al.,2007   668   1735   420   1452   1.44     Veclak et al.,2009   493   4577   430   4725   1.44     Havashi et al.,2009   493   4577   430   4725   1.45     Hetarogeneity: <math>l^2 = 285</math>, <math>r^2 = 0.026</math>, <math>p = 0.18</math>   1.45   1.44   1.44     Miyake et al.,2008   233   371   1921   3617     Hayashi et al.,2007   169   256   1450   1.33     Hive deflect model   783   7610   1.44   1.24     Hetarogeneity: <math>l^2 = 0.6</math>, <math>r^2 = 0. p = 0.90</math>   1.44   1.24   1.</td><td>Study   Events   Total   Odds Ratio   OR   95%-CI     Subgroup = Caucasian   Cauchi et al.,2006   286   806   200   755   1.53   11.23; 1.90     Dahigren et al.,2006   1230   2531   771   1946   1.54   1.52; 1.23; 1.90     Humphries et al.,2007   1820   3397   1405   3119   1.44   1.28; 1.62     Mayans et al.,2007   372   660   452   984   1.54   1.33; 1.79     Vcelak et al.,2007   372   660   452   984   1.54   1.38; 1.75     Voelak et al.,2007   668   1735   420   1452   1.54   1.33; 1.79     Voelak et al.,2007   168   1736   16655   1.54   1.33; 1.79     Vise et al.,2007   169   256   1450   2430   1.45   1.38; 1.52     Heterogeneity: <math>I^2 = 0.026</math>, <math>I^2 = 0.020</math>   783   7610   1.44   1.42; 1.16; 1.66     Hatsondi et al.,2007   168   326   431   456   1.55</td></t<> | Study   Events   Total Events     Subgroup = Caucasian   Cauchi et al.,2006   286   806   200     Dahlgren et al.,2006   1230   2531   771     Humphries et al.,2006   1230   2531   771     Humphries et al.,2007   1820   3397   1405     Mayans et al.,2007   372   660   452     Vliet-Ostaptchouk et al.,2007   293   741   203     Silva et al.,2007   681   7353   420     Viet-Ostaptchouk et al.,2007   168   17363   Heterogeneity: $l^2 = 28\%$ , $t^2 = 0.0026$ , $p = 0.18     Subgroup = East Asian   Miyake et al.,2007   169   256   1450     Horikoshi et al.,2007   24   45   165   Yasuharu et al.,2007   24   45   165     Yasuharu et al.,2007   24   45   165   Yasuharu et al.,2011   25   38   202     Fixed effect model   783   Heterogeneity: l^2 = 0\%, t^2 = 0, p = 0.90   Fixed effect model   783     Hayashi et al.,2011   541   133$ | StudyEventsTotalEventsTotalSubgroup = CaucasianCauchi et al., 2006286806200755Dahlgren et al., 2006123025317711946Humphries et al., 2006182025317711946Humphries et al., 20071820339714053119Mayans et al., 20071820339714053119Mayans et al., 200768817354201452Viet-Ostaptchouk et al., 200768817354201452Vcelak et al., 2012199370148353Yan et al., 200949345774304725Fixed effect model1736316455Heterogeneity: $r^2 = 28\%$ , $r^2 = 0.0026$ , $p = 0.18$ 7610Miyake et al., 20072445165416Yasuharu et al., 20094773434806Zheng et al., 20072445165416Yasuharu et al., 20094773434806Zheng et al., 201151382643Barra et al., 20126413349Humphries et al., 2006166316141302Danquah et al., 20076779845609Saadi et al., 20086518230101Yan et al., 20086518230101Humphries et al., 200766136141302Danquah et al., 200766136141 | Study   Events   Total   Events   Total   Odds     Subgroup = Caucasian   Cauchi et al.,2006   286   806   200   755     Dahlgren et al.,2006   1230   2531   771   1946     Humphries et al.,2006   1820   3397   1405   3119     Mayans et al.,2007   1820   3397   1405   3119     Mayans et al.,2007   0732   660   452   984     Vilet-Ostaptchouk et al.,2007   293   741   203   662     Silva et al.,2012   199   370   148   353     Yan et al.,2008   493   4577   430   4725     Fixed effect model   17363   16455   166   16     Heterogeneity: $f^2 = 28\%$ , $r^2 = 0.026$ , $p = 0.18$ 203   143   806   143     Yasuharu et al.,2007   24   45   165   416   143     Yasuharu et al.,2007   24   45   165   416   143     Yasuharu et al.,2011   25 | Study   Events   Total   Odds Ratio     Subgroup = Caucasian<br>Cauchi et al.,2006   286   806   200   755     Dahlgren et al.,2008   101   490   67   563     Groves et al.,2006   1230   2531   771   1946     Humphries et al.,2007   1820   3397   1405   3119     Mayans et al.,2007   1820   3397   1405   3119     Mayans et al.,2007   1820   3397   148   353     Yan et al.,2007   168   17363   16455     Fixed effect model   17363   16455     Heterogeneity: $l^2 = 28%$ , $t^2 = 0.0026$ , $p = 0.18$ 500   2430     Subgroup = East Asian   Miyake et al.,2007   169   256   1450   2430     Horikoshi et al.,2007   129   256   1450   2430   4577   434   806     Zheng et al.,2011   25   38   202   341   54   165   416     Yasuharu et al.,2012   64   133   49 | Study   Events   Total   Code   Ratio   OR     Subgroup = Caucasian   Cauchi et al.,2006   286   806   200   755     Dahlgren et al.,2006   1230   2531   771   1946   1.43     Humphries et al.,2007   1820   3397   1405   3119   1.44     Mayans et al.,2007   1820   3397   1405   3119   1.44     Viet-Ostaptchouk et al.,2007   668   1735   420   1452   1.44     Veclak et al.,2009   493   4577   430   4725   1.44     Havashi et al.,2009   493   4577   430   4725   1.45     Hetarogeneity: $l^2 = 285$ , $r^2 = 0.026$ , $p = 0.18$ 1.45   1.44   1.44     Miyake et al.,2008   233   371   1921   3617     Hayashi et al.,2007   169   256   1450   1.33     Hive deflect model   783   7610   1.44   1.24     Hetarogeneity: $l^2 = 0.6$ , $r^2 = 0. p = 0.90$ 1.44   1.24   1. | Study   Events   Total   Odds Ratio   OR   95%-CI     Subgroup = Caucasian   Cauchi et al.,2006   286   806   200   755   1.53   11.23; 1.90     Dahigren et al.,2006   1230   2531   771   1946   1.54   1.52; 1.23; 1.90     Humphries et al.,2007   1820   3397   1405   3119   1.44   1.28; 1.62     Mayans et al.,2007   372   660   452   984   1.54   1.33; 1.79     Vcelak et al.,2007   372   660   452   984   1.54   1.38; 1.75     Voelak et al.,2007   668   1735   420   1452   1.54   1.33; 1.79     Voelak et al.,2007   168   1736   16655   1.54   1.33; 1.79     Vise et al.,2007   169   256   1450   2430   1.45   1.38; 1.52     Heterogeneity: $I^2 = 0.026$ , $I^2 = 0.020$ 783   7610   1.44   1.42; 1.16; 1.66     Hatsondi et al.,2007   168   326   431   456   1.55 |

(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 Table1, a total of 28 studies were analyzed by the dominant model, recessive

model, additive model and allele model, respectively. The heterogeneity of all 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 0.711, 0.4528 and 0.5199, 0.6927 and 0.5673, respectively. The

| Study                                    | Experim<br>Events  |      | C<br>Events | ontrol<br>Total | Odds    | Ratio        | OR        | 95       | 5%-CI  | Weight |
|--|--------------------|------|-------------|-----------------|---------|--------------|-----------|----------|--------|--------|
|  |                    |      |             |                 |         |              |           |          |        |        |
| Subgroup = Caucasian                     |                    |      |             |                 |         |              |           |          |        |        |
| Cauchi et al.,2006                       | 78                 | 166  | 408         | 1395            |         | 1            | 2.14      |          |        | 3.3%   |
| Dahlgren et al.,2008                     | 18                 | 80   | 150         | 973             |         | +            | 1.59      | [0.92;   | 2.77]  | 1.3%   |
| Groves et al.,2006                       | 270                | 487  | 1731        | 3990            |         | ф<br>Р       | 1.62      |          | 1.96]  | 12.2%  |
| Humphries et al.,2006                    | 193                | 390  | 1266        | 3562            |         |              | 1.78      | [1.44;   | 2.19]  | 9.2%   |
| Kimber et al.,2007                       | 361                | 609  | 2864        | 5907            |         |              | 1.55      | [1.31;   | 1.83]  | 15.9%  |
| Mayans et al.,2007                       | 54                 | 89   | 770         | 1555            |         | ÷            | 1.57      | [1.02;   | 2.43]  | 2.4%   |
| Vliet–Ostaptchouk et al.,20              | 007 72             | 155  | 424         | 1248            |         | *            | 1.69      | [1.20;   | 2.36]  | 3.7%   |
| Silva et al.,2007                        | 161                | 341  | 927         | 2846            |         |              | 1.85      | [1.48;   | 2.32]  | 7.6%   |
| Vcelak et al.,2012                       | 43                 | 67   | 304         | 656             |         | <u>+-</u>    | 2.07      | [1.23;   | 3.50]  | 1.5%   |
| Yan et al.,2009                          | 101                | 794  | 822         | 8508            |         |              | 1.36      | [1.09;   | 1.70   | 8.9%   |
| Fixed effect model                       |                    | 3178 |             | 30640           |         | 6            | 1.66      |          |        | 66.0%  |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$  | 0. p = 0.51        |      |             |                 |         |              |           | L /      |        |        |
|  |                    |      |             |                 |         | 1            |           |          |        |        |
| Subgroup = East Asian                    |                    |      |             |                 |         |              |           |          |        |        |
| Miyake et al.,2008                       | 5                  | 6    | 2149        | 3982            | _       | ;            | - 4.26    | [0.50;   | 36.541 | 0.1%   |
| Hayashi et al.,2007                      | 4                  | 6    | 1615        | 2680            |         | ļ.           |           | [0.24;   |        | 0.2%   |
| Horikoshi et al.,2007                    | 2                  | 2    | 187         | 459             |         |              |           | [0.35; 1 |        | 0.0%   |
| Yasuharu et al.,2009                     | 2                  | 2    | 479         | 877             |         |              |           | [0.20;   |        | 0.0%   |
| Zheng et al.,2011                        | 1                  | 1    | 226         | 378             |         | i.           |           | [0.08;   |        | 0.0%   |
| Fixed effect model                       |                    | 17   | 220         | 8376            |         | in           | 2.82      |          |        | 0.4%   |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$  | 0 0 - 0.95         |      |             | 0370            |         |              | 2.02      | [1.00,   | 7.50]  | 0.470  |
| Helelogeneity. 7 = 0 %, t =              | ο, <i>μ</i> = 0.85 |      |             |                 |         |              |           |          |        |        |
| Subgroup = Others                        |                    |      |             |                 |         |              |           |          |        |        |
| Alsmadi et al.,2008                      | 90                 | 149  | 432         | 719             | +       | ŧ.           | 1.01      | [0.71;   | 1.45]  | 4.3%   |
| Assmann et al.,2014                      | 156                | 215  | 797         | 1273            |         | +            | 1.58      | [1.15;   | 2.18]  | 4.6%   |
| Barra et al.,2012                        | 17                 | 23   | 96          | 229             |         | <del> </del> | 3.93      | [1.49;   | 10.32] | 0.3%   |
| Humphries et al.,2006                    | 30                 | 56   | 277         | 562             | -       | ai.          | 1.19      | [0.68;   | 2.06]  | 1.7%   |
| Danguah et al.,2013                      | 78                 | 106  | 596         | 943             |         | +            | 1.62      | [1.03;   | 2.55]  | 2.3%   |
| Marquezine et al.,2007                   | 13                 | 141  | 99          | 1266            | _       | a.           | 1.20      | [0.65;   | 2.20]  | 1.3%   |
| Saadi et al.,2008                        | 11                 | 34   | 84          | 249             | _       | Ļ.           | 0.94      |          |        | 1.0%   |
| Yan et al.,2009                          | 48                 | 213  | 467         | 2544            |         | <b>-</b>     | 1.29      | [0.92;   | 1.81   | 4.1%   |
| Fixed effect model                       |                    | 937  |             | 7785            |         | ¢.           |           | [1.15;   |        |        |
| Heterogeneity: $I^2 = 30\%$ , $\tau^2 =$ | 0.0232, <i>p</i> = |      |             |                 |         |              |           | L        |        |        |
| Cubarous - Couth Asian                   |                    |      |             |                 |         |              |           |          |        |        |
| Subgroup = South Asian                   |                    | 200  | 017         | 1000            |         |              | 1 00      | 10.06    | 1 711  | E 09/  |
| Bodhini et al.,2007                      | 114                | 206  | 917         | 1863            |         |              | 1.28      |          |        | 5.9%   |
| Chandak et al.,2007                      | 141                | 175  | 814         | 1179            |         | 1            | 1.86      | [1.25;   |        | 3.0%   |
| Gupta et al.,2010                        | 44                 | 65   | 151         | 291             |         |              | 1.94      |          |        | 1.3%   |
| Hussain et al.,2014                      | 7                  | 11   | 61          | 139             | -       | 1:           | 2.24      | [0.63;   | 7.99]  | 0.2%   |
| Rees et al.,2008                         | 116                | 160  | 712         | 1100            |         | 1            | 1.44      |          |        | 3.6%   |
| Fixed effect model                       |                    | 617  |             | 4572            |         | ¢            | 1.52      | [1.26;   | 1.83]  | 14.1%  |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$  | 0, <i>p</i> = 0.47 |      |             |                 |         |              |           |          |        |        |
| Fixed effect model                       |                    | 4749 |             | 51373           |         |              | 1.58      | [1.48:   | 1.691  | 100.0% |
| Heterogeneity: $I^2 = 9\%$ , $\tau^2 =$  | 0.0034, p = 0      |      |             |                 |         |              |           |          |        |        |
|  | , μ = 0            | -    |             | 0               | .01 0.1 | 1 10         | 100       |          |        |        |
|  | c                  |      |             |                 |         |              | of CC/CT/ |          |        |        |

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+CT), 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),

Study

Subgroup = Caucasian Cauchi et al.,2006 Experimental

208

Events Total Events Total

640

*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); additive model(TT vs CC): (OR = 1.81, CI = 1.69 - 1.94, p < 0.0001); additive model(TT vs CC): (OR = 1.81, CI = 1.69 - 1.94, p < 0.0001); additive model(TT vs CC): (OR = 2.90, CI = 1.03 - 8.22, p = 0.0446); 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,

95%-CI Weight

3.2%

OR

1.34 [1.06; 1.68]

|   | 00       | 440   | 07   | 500   |          |                           |
|---|----------|-------|------|-------|----------|---------------------------|
| Dahlgren et al.,2008                              | 83       | 410   | 67   | 563   |          | - 1.88 [1.32; 2.67] 1.2%  |
| Groves et al.,2006                                | 960      | 2044  | 771  | 1946  |          | 1.35 [1.19; 1.53] 10.8%   |
| Humphries et al.,2006                             | 665      | 1666  | 601  | 1896  |          | 1.43 [1.25; 1.64] 8.7%    |
| Kimber et al.,2007                                | 1459     | 2788  | 1405 | 3119  | ***      | 1.34 [1.21; 1.48] 16.4%   |
| Mayans et al.,2007                                | 318      | 571   | 452  | 984   |          | 1.48 [1.20; 1.82] 3.8%    |
| Vliet–Ostaptchouk et al.,2007                     | 221      | 586   | 203  | 662   |          | 1.37 [1.08; 1.73] 3.1%    |
| Silva et al.,2007                                 | 507      | 1394  | 420  | 1452  |          | 1.40 [1.20; 1.64] 6.8%    |
| Vcelak et al.,2012                                | 156      | 303   | 148  | 353   |          | 1.47 [1.08; 2.00] 1.7%    |
| Yan et al.,2009                                   |          | 3783  |      | 4725  | -        | 1.15 [1.00; 1.33] 8.9%    |
| Fixed effect model                                |          | 14185 | 100  | 16455 |          | 1.36 [1.29; 1.43] 64.5%   |
| Heterogeneity: $I^2 = 9\%$ , $\tau^2 = 0.0$       |          |       |      | 10400 |          |                           |
| Subgroup = East Asian                             |          |       |      |       |          |                           |
| Miyake et al.,2008                                | 228      | 365   | 1921 | 3617  | <u> </u> | 1.47 [1.18; 1.83] 3.4%    |
| Hayashi et al.,2007                               | 165      | 250   | 1450 | 2430  |          | 1.31 [1.00; 1.73] 2.4%    |
|   | 22       | 43    |      |       | Ĩ.       |                           |
| Horikoshi et al.,2007                             |          |       | 165  | 416   |          |                           |
| Yasuharu et al.,2009                              | 45       | 71    | 434  | 806   |          | - 1.48 [0.90; 2.45] 0.7%  |
| Zheng et al.,2011                                 | 24       | 37    | 202  | 341   |          | — 1.27 [0.63; 2.58] 0.4%  |
| Fixed effect model                                |          | 766   |      | 7610  |          | 1.42 [1.21; 1.65] 7.2%    |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $\mu$ | 0 = 0.96 |       |      |       |          |                           |
| Subgroup = Others                                 |          |       |      |       |          |                           |
| Alsmadi et al.,2008                               | 253      | 415   | 179  | 304   |          | 1.09 [0.81; 1.47] 2.1%    |
| Assmann et al.,2014                               | 415      | 630   | 382  | 643   |          | 1.32 [1.05; 1.66] 3.3%    |
| Barra et al.,2012                                 | 47       | 110   | 49   | 119   | <b>.</b> | 1.07 [0.63; 1.80] 0.7%    |
| Humphries et al.,2006                             | 136      | 260   | 141  | 302   |          | 1.25 [0.90; 1.75] 1.6%    |
| Danguah et al.,2013                               | 323      | 488   | 273  | 455   |          | 1.31 [1.00; 1.70] 2.5%    |
| Marguezine et al.,2007                            | 54       | 657   | 45   | 609   |          | 1.12 [0.74; 1.69] 1.1%    |
| Saadi et al.,2008                                 | 54       | 148   | 30   | 101   |          | - 1.36 [0.79; 2.34] 0.6%  |
| Yan et al.,2009                                   | 212      | 1133  | 255  | 1411  |          | 1.04 [0.85; 1.28] 4.8%    |
| Fixed effect model                                | 212      |       | 200  |       |          |                           |
|   | 0.04     | 3841  |      | 3944  | <u>_</u> | 1.18 [1.06; 1.31] 16.7%   |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , p     | 0 = 0.81 |       |      |       |          |                           |
| Subgroup = South Asian                            |          |       |      |       |          |                           |
| Bodhini et al.,2007                               | 455      | 846   | 462  | 1017  |          | 1.40 [1.16; 1.68] 5.0%    |
| Chandak et al.,2007                               | 423      | 583   | 391  | 596   |          | 1.39 [1.08; 1.78] 2.7%    |
| Gupta et al.,2010                                 | 96       | 174   | 55   | 117   |          | 1.39 [0.87; 2.22] 0.8%    |
| Hussain et al.,2014                               | 36       | 71    | 25   | 68    |          | —— 1.77 [0.90; 3.48] 0.3% |
| Rees et al.,2008                                  | 360      | 526   | 352  | 574   |          | 1.37 [1.07; 1.75] 2.7%    |
| Fixed effect model                                |          | 2200  |      | 2372  | -<br>-   | 1.40 [1.24; 1.58] 11.6%   |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $\mu$ | 0.97     |       |      |       |          |                           |
| Fixed effect model                                |          | 20992 |      | 30381 |          | 1.34 [1.28; 1.39] 100.0%  |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , $\mu$ |          |       |      |       |          |                           |
| $r = 0, \mu$                                      | - 0.70   |       |      |       | 0.5 1 2  |                           |

Control

755

200

Odds Ratio

| Study                                       | Experir           |       | C<br>Events | ontrol<br>Total | Odds I | Ratio  | OR     | 95%_01                       | Weight  |
|---|-------------------|-------|-------------|-----------------|--------|--|--------|------------------------------|---------|
| Study                                       | Lvents            | Total | LVCIIIS     | Total           | Ouus   | natio  | UN     | 35 /8-01                     | weight  |
| Subgroup = Caucasian                        |                   |       |             |                 |        |  |        |                              |         |
| Cauchi et al.,2006                          | 364               | 972   | 608         | 2150            |        |  | 1.52   | [1.29; 1.78]                 | 3.3%    |
| Dahlgren et al.,2008                        | 119               | 570   | 217         | 1536            |        | <u>+ • • • • • • • • • • • • • • • • • • •</u> |        | [1.25; 2.05]                 | 1.3%    |
| Groves et al.,2006                          | 1500              | 3018  | 2502        | 5936            |        | ÷.   | 1.36   | [1.24; 1.48]                 | 11.7%   |
| Humphries et al.,2006                       | 1051              | 2446  | 1867        | 5458            |        | ÷.   | 1.45   | [1.31; 1.60]                 | 9.1%    |
| Kimber et al.,2007                          | 2181              | 4006  | 4269        | 9026            |        |  | 1.33   | [1.24; 1.43]                 | 16.4%   |
| Mayans et al.,2007                          | 426               | 749   | 1222        | 2539            |        |  | 1.42   | [1.21; 1.68]                 | 3.3%    |
| Vliet-Ostaptchouk et al.,200                | 7 365             | 896   | 627         | 1910            |        |  | 1.41   | [1.19; 1.66]                 | 3.3%    |
| Silva et al.,2007                           | 829               | 2076  | 1347        | 4298            |        | ······································         | 1.46   | [1.31; 1.62]                 | 7.2%    |
| Vcelak et al.,2012                          | 242               | 437   | 452         | 1009            |        |  | 1.53   | [1.22; 1.92]                 | 1.7%    |
| Yan et al.,2009                             | 594               | 5371  | 1252        | 13233           |        |  | 1.19   | [1.07; 1.32]                 | 8.8%    |
| Fixed effect model                          |                   | 20541 |             | 47095           |        | \$   |        | [1.32; 1.43]                 |         |
| Heterogeneity: $I^2 = 38\%$ , $\tau^2 = 0$  |                   |       |             |                 |        | 1  |        | ,                            |         |
|   |                   |       |             |                 |        |  |        |                              |         |
| Subgroup = East Asian                       | 000               | 077   | 4070        | 7500            |        |  | 4 40   | 1 00. 1 0.1                  | 1.00/   |
| Miyake et al.,2008                          | 238               | 377   | 4070        | 7599            |        | _  |        | [1.20; 1.84]                 |         |
| Hayashi et al.,2007                         | 173               | 262   | 3065        | 5110            | F      |  |        | [1.00; 1.68]                 |         |
| Horikoshi et al.,2007                       | 26                | 47    | 352         | 875             | -      |  |        | [1.02; 3.32]                 |         |
| Yasuharu et al.,2009                        | 49                | 75    | 913         | 1683            |        |  |        | [0.98; 2.58]                 |         |
| Zheng et al.,2011                           | 26                | 39    | 428         | 719             |        |  |        | [0.69; 2.69]                 |         |
| Fixed effect model                          |                   | 800   |             | 15986           |        | $\Leftrightarrow$                              | 1.44   | [1.24; 1.67]                 | 4.1%    |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , | p = 0.82          |       |             |                 |        |  |        |                              |         |
| Subgroup = Others                           |                   |       |             |                 |        |  |        |                              |         |
| Alsmadi et al.,2008                         | 433               | 713   | 611         | 1023            |        |  | 1.04   | [0.86; 1.27]                 | 2.7%    |
| Assmann et al.,2014                         | 727               | 1060  | 1179        | 1916            |        |  | 1.36   | [1.16; 1.60]                 | 3.6%    |
| Barra et al.,2012                           | 81                | 156   | 145         | 348             | -      |  | 1.51   | [1.03; 2.21]                 | 0.6%    |
| Humphries et al.,2006                       | 196               | 372   | 418         | 864             | +      |  | 1.19   | [0.93; 1.52]                 | 1.6%    |
| Danguah et al.,2013                         | 479               | 700   | 869         | 1398            |        | é  |        | [1.09; 1.60]                 |         |
| Marquezine et al.,2007                      | 80                | 939   | 144         | 1875            |        | •  | 1.12   | [0.84; 1.49]                 | 1.2%    |
| Saadi et al.,2008                           | 76                | 216   | 114         | 350             |        |  | 1.12   | [0.79; 1.61]                 | 0.8%    |
| Yan et al.,2009                             | 308               | 1559  | 722         | 3955            | +      | -  |        | [0.95; 1.28]                 |         |
| Fixed effect model                          |                   | 5715  |             | 11729           |        | $\diamond$                                     |        | [1.12; 1.29]                 |         |
| Heterogeneity: $I^2 = 17\%$ , $\tau^2 = 0$  | .0025, <i>p</i> = | 0.29  |             |                 |        |  |        | -                            |         |
| Subgroup = South Asian                      |                   |       |             |                 |        |  |        |                              |         |
| Bodhini et al.,2007                         | 683               | 1258  | 1379        | 2880            |        | -  | 1.29   | [1.13; 1.48]                 | 5.3%    |
| Chandak et al.,2007                         | 705               | 933   | 1205        | 1775            |        |  |        | [1.22; 1.75]                 |         |
| Gupta et al.,2010                           | 184               | 304   | 206         | 408             |        |  |        | [1.11; 2.03]                 |         |
| Hussain et al.,2014                         | 50                | 93    | 200         | 207             |        |  |        | [1.00; 2.68]                 |         |
| Rees et al.,2008                            | 592               | 846   | 1064        | 1674            |        |  |        | [1.00, 2.08]<br>[1.12; 1.60] |         |
| Fixed effect model                          | 532               | 3434  | 1004        | 6944            |        | \$   |        | [1.12; 1.00]                 |         |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , | p = 0.70          | 0709  |             | 0011            |        | ¥  | 1.07   | [1120, 1140]                 | 1210/0  |
| Final offerst medal                         |                   | 00400 |             | 01754           |        |  | 1 05 1 | 4 04. 4 003                  | 100.00/ |
| Fixed effect model                          |                   | 30490 |             | 81754           |        |  | 1.35   | [1.31; 1.39]                 | 100.0%  |
| Heterogeneity: $I^2 = 29\%$ , $\tau^2 = 0$  | .0028, <i>p</i> = | 0.08  |             |                 | 0.5    | ,<br>,   |        |                              |         |
|   |                   |       |             |                 | 0.5 1  | 2  |        |                              |         |

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 = 1.24, CI = 1.12 - 1.36, p < 0.0001); recessive model (TT vs CC + CT): (OR = 1.35, CI = 1.15 - 1.58, p = 0.0002); additive model (CT vs CC): (OR = 1.4, CI = 1.24 - 1.58, p = 0.0019); additive model(TT 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

| Study                                       | Experim<br>Events |      |      | ontrol<br>Total | Odds    | Ratio       |     | OR    | 95                 | 5%–CI   | Weight |
|---|-------------------|------|------|-----------------|---------|-------------|-----|-------|--------------------|---------|--------|
|   |                   |      |      |                 |         |             |     |       |                    |         |        |
| Subgroup = Caucasian                        | _                 |      |      |                 |         |             |     |       |                    |         |        |
| Cauchi et al.,2006                          | 78                | 166  | 200  | 755             |         | -           |     |       | [1.74;             |         | 3.3%   |
| Dahlgren et al.,2008                        | 18                | 80   | 67   | 563             |         | <u>+</u>    |     | 2.15  | [1.20;             |         | 1.1%   |
| Groves et al.,2006                          | 270               | 487  | 771  | 1946            |         |             |     | 1.90  | [1.55;             |         | 11.9%  |
| Humphries et al.,2006                       | 193               | 390  | 601  | 1896            |         | +-          | :   | 2.11  | [1.69;             |         | 9.0%   |
| Kimber et al.,2007                          | 361               | 609  | 1405 | 3119            |         | ÷           |     | 1.78  | [1.49;             | 2.12]   | 16.2%  |
| Mayans et al.,2007                          | 54                | 89   | 452  | 984             |         | -8-         |     | 1.82  | [1.17;             | 2.83]   | 2.6%   |
| Vliet-Ostaptchouk et al.,200                | 7 72              | 155  | 203  | 662             |         | +           |     | 1.96  | [1.37;             | 2.80]   | 3.6%   |
| Silva et al.,2007                           | 161               | 341  | 420  | 1452            |         | -           |     | 2.20  | [1.73;             | 2.80]   | 7.3%   |
| Vcelak et al.,2012                          | 43                | 67   | 148  | 353             |         |             | :   | 2.48  | [1.44;             | 4.27]   | 1.5%   |
| Yan et al.,2009                             | 101               | 794  | 430  | 4725            |         | -+-         |     |       | [1.16;             |         | 9.4%   |
| Fixed effect model                          |                   | 3178 |      | 16455           |         | 6           |     |       | [1.76;             |         | 65.8%  |
| Heterogeneity: $I^2 = 20\%$ , $\tau^2 = 0$  |                   |      |      |                 |         |             |     |       | L,                 | 1       |        |
| Subgroup = East Asian                       |                   |      |      |                 |         |             |     |       |                    |         |        |
| Miyake et al.,2008                          | 5                 | 6    | 1921 | 3617            | _       |             |     | 4 4 1 | [0.52;             | 37 821  | 0.1%   |
| Hayashi et al.,2007                         | 4                 | 6    | 1450 | 2430            |         | 1.          |     |       | [0.25;             |         | 0.1%   |
| Horikoshi et al.,2007                       | 2                 | 2    | 1450 | 416             |         |             |     |       | [0.25,<br>[0.36; 1 |         | 0.2%   |
| Yasuharu et al.,2009                        | 2                 | 2    | 434  | 806             |         |             |     |       | [0.30, 1<br>[0.21; |         | 0.0%   |
|   | 2                 |      |      |                 |         |             |     |       |                    |         |        |
| Zheng et al.,2011                           | I                 | 1    | 202  | 341             |         | i~          |     |       | [0.08;             |         | 0.1%   |
| Fixed effect model                          | - 0.01            | 17   |      | 7610            |         |             | 1   | 2.90  | [1.03;             | 0.22]   | 0.4%   |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , | p = 0.84          |      |      |                 |         |             |     |       |                    |         |        |
| Subgroup = Others                           |                   |      |      |                 |         |             |     |       |                    |         |        |
| Alsmadi et al.,2008                         | 90                | 149  | 179  | 304             | -       | ÷:          |     | 1.07  | [0.71;             | 1.59]   | 4.0%   |
| Assmann et al.,2014                         | 156               | 215  | 382  | 643             |         | +           |     | 1.81  | [1.29;             | 2.53]   | 4.6%   |
| Barra et al.,2012                           | 17                | 23   | 49   | 119             |         | <u>+</u> →− |     | 4.05  | [1.49;             | 11.00]  | 0.4%   |
| Humphries et al.,2006                       | 30                | 56   | 141  | 302             | -       | a i         |     | 1.32  | [0.74;             | 2.33]   | 1.8%   |
| Danguah et al.,2013                         | 78                | 106  | 273  | 455             |         | <u>_k</u>   |     | 1.86  | [1.16;             | 2.97]   | 2.4%   |
| Marguezine et al.,2007                      | 13                | 141  | 45   | 609             | -       |             |     | 1.27  | [0.67;             |         | 1.3%   |
| Saadi et al.,2008                           | 11                | 34   | 30   | 101             | _       | ₩÷.         |     | 1.13  | [0.49;             |         | 0.9%   |
| Yan et al.,2009                             | 48                | 213  | 255  | 1411            |         | <b>_</b>    |     | 1.32  | [0.93;             |         | 4.5%   |
| Fixed effect model                          | .0                | 937  | 200  | 3944            |         | 8           |     |       | [1.26;             |         |        |
| Heterogeneity: $I^2 = 29\%$ , $\tau^2 = 0$  | .0257, p = 0      |      |      | 30117           |         |             |     |       | L                  |         | 1010/0 |
| Subgroup = South Asian                      |                   |      |      |                 |         |             |     |       |                    |         |        |
| 0   | 114               | 206  | 460  | 1017            |         | 1           |     | 1 40  | [1 10-             | 2 0 1 1 | 6 00/  |
| Bodhini et al.,2007                         | 114               | 206  | 462  | 1017            |         |             |     | 1.49  | [1.10;             |         | 6.0%   |
| Chandak et al.,2007                         | 141               | 175  | 391  | 596             |         | 1           |     |       | [1.44;             |         | 3.0%   |
| Gupta et al.,2010                           | 44                | 65   | 55   | 117             |         |             |     | 2.36  | [1.25;             |         | 1.1%   |
| Hussain et al.,2014                         | 7                 | 11   | 25   | 68              |         |             |     |       | [0.80;             |         | 0.2%   |
| Rees et al.,2008                            | 116               | 160  | 352  | 574             |         | +           |     |       | [1.13;             |         | 3.7%   |
| Fixed effect model                          |                   | 617  |      | 2372            |         | ¢           |     | 1.77  | [1.46;             | 2.15]   | 14.0%  |
| Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$ , | p = 0.44          |      |      |                 |         |             |     |       |                    |         |        |
| Fixed effect model                          |                   | 4749 |      | 30381           |         | 6           |     | 1.81  | [1.69;             | 1.94]   | 100.0% |
| Heterogeneity: $I^2 = 22\%$ , $\tau^2 = 0$  | .0105, p = 0      | ).15 |      |                 |         | і г         |     |       | - ,                |         |        |
|   |                   |      |      | 0               | .01 0.1 | 1 10        | 100 |       |                    |         |        |
|   |                   |      |      |                 |         |             |     |       |                    |         |        |

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 –  | Dominar | Dominant |       | Recessive |       | (CT vs CC) | Allele |          | Additive(TT vs CC) |          |  |
|-------------|---------|----------|-------|-----------|-------|------------|--------|----------|--------------------|----------|--|
|             | Z       | Р        | Z     | Р         | Z     | Р          | Z      | Р        | Z                  | Р        |  |
| Caucasian   | 14.86   | <0.0001  | 12.35 | <0.0001   | 11.67 | <0.0001    | 16.98  | <0.0001  | 15.15              | <0.0001  |  |
| South Asian | 4.69    | <0.0001  | 1.95  | 0.0509    | 4.42  | <0.0001    | 4.86   | < 0.0001 | 2.01               | 0.0446   |  |
| East Asian  | 6.61    | < 0.0001 | 4.47  | <0.0001   | 5.45  | <0.0001    | 7.12   | <0.0001  | 5.83               | <0.0001  |  |
| Others      | 4.17    | < 0.0001 | 3.75  | 0.0002    | 3.11  | 0.0019     | 4.89   | <0.0001  | 4.65               | < 0.0001 |  |
| Total       | 17.2    | < 0.0001 | 13.53 | < 0.0001  | 13.73 | < 0.0001   | 19.38  | < 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

Cls: Confidence intervals; HWE: Hardy-Weinberg Equilibrium; ORs: Odds ratio; SNP: Single necluotide 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. QHJ 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.

#### Ethics approval and consent to participate

Not applicable.

#### **Consent for publication**

Not applicable.

#### **Competing interests**

The authors declared that they had no competing interests.

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