

## Original Article

# Association between “solute carrier family 30 member 8” (*SLC30A8*) gene polymorphism and susceptibility to type 2 diabetes mellitus in Chinese Han and minority populations: an updated meta-analysis

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**Background and Objectives:** In China, some studies have been reported that solute carrier family 30 member 8 (*SLC30A8*) gene polymorphism might increase the risk of T2DM, but some are not. The aim of this meta-analysis was to systematically investigate the association between the rs13266634 polymorphism of the *SLC30A8* gene and T2DM in Chinese Han and ethnic minority populations. **Methods and Study Design:** All published electronic articles were retrieved from Pubmed, Web of Knowledge, Chinese National Knowledge Infrastructure (CNKI), Wanfang database, VIP database and Google scholar. Pooled OR and 95% CI were calculated using random- or fixed-effects models. **Results:** Twenty-five articles involving 62,285 subjects were included in this meta-analysis. Considering the total population, significant associations between the rs13266634 polymorphism and T2DM were observed under the allele model (C vs T: OR=1.23, 95% CI=1.18-1.29), the additive models (CC vs TT: OR=1.44, 95% CI=1.32-1.56; CC vs CT: OR=1.08, 95% CI=1.02-1.15; CT vs TT: OR=1.25, 95% CI=1.15-1.37), the dominant model (CC vs CT+TT: OR=1.24, 95% CI=1.17-1.32) and the recessive model (CC+CT vs TT: OR=1.26, 95% CI=1.16-1.35). Based on subgroup analysis, besides the CC vs CT model, these associations were stronger in the ethnic minority groups than in the Han population. Moreover, no association was observed under the CC vs CT model (OR=1.26, 95% CI=0.95-1.66,  $p=0.105$ ) in ethnic minority groups. **Conclusions:** Chinese C allele carriers could have an increased risk of T2DM. Well-designed future studies should be conducted with a larger sample size to better understand this association in ethnic minority groups.

**Key Words:** SLC30A8, polymorphism, T2DM, Chinese, meta-analysis

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder characterized by insulin resistance and/or impaired insulin secretion.<sup>1</sup> According to a new estimate by the International Diabetes Federation (IDF), the number of individuals aged 20–79 suffering from diabetes worldwide in 2017 was 425 million, and will increase to 700 million by 2045.<sup>2</sup> T2DM accounts for 90% of these cases, and the medical expenses for treatment were as high as 727 billion dollars,<sup>2</sup> which has become a serious and worsening public health problem. In China, the prevalence of diabetes was 11.6% in 2010,<sup>3</sup> which means that more than 100 million of people were suffering from diabetes and China has become one of the largest T2DM population countries in the world.<sup>4</sup> As the disease progresses, T2DM can lead to severe complications such as stroke, cardiovascular disease, renal failure and retinopathy.<sup>5,6</sup> Epidemiological studies including investigations within twins have suggested that the disease is caused by an interplay of environmental and genetic factors.<sup>7,8</sup> Alt-

hough some causal factors have been identified in T2DM, such as obesity, dyslipidemia, hypertension and lack of physical activity,<sup>9,10</sup> more studies are needed to better understand important genetic factors that may play a role in T2DM.

Zinc is an essential trace element that plays a critical role in  $\beta$  cells, promoting insulin crystallization into hexamers.<sup>7</sup> Data from population-based studies and animal experiments indicate that zinc homeostasis is associated with T2DM.<sup>11,12</sup> The zinc transport protein member 8 (ZnT-8) is a trans-membrane protein containing 369 ami-

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no acids which is expressed exclusively in pancreatic islet  $\beta$  cells, and which transports zinc ions from the cytoplasm to insulin secretion vesicles, a key step in the process of insulin synthesis and secretion.<sup>13</sup> (The mechanism's diagram is shown in Figure S1. of supplementary materials). Since ZnT-8 is encoded by the *SLC30A8* gene, it is reasonable to postulate that polymorphism of the *SLC30A8* gene may be involved in the development of T2DM.

A large genome-wide association study (GWAS) performed on 392,935 French subjects by Sladek in 2007 first identified an association between the rs13266634 polymorphism of the *SLC30A8* gene and the risk of developing T2DM.<sup>14</sup> Considering the differences in genetic backgrounds between Europeans and other populations, replication studies were conducted in groups with different ethnic backgrounds. Chang et al. reported that the rs13266634 polymorphism was associated with T2DM in the Chinese Han population after adjusting for age, gender and BMI (OR, 1.30; 95% CI, 1.17-1.45;  $p < 0.001$ ).<sup>15</sup> Similar studies were also conducted in Singapore, Korea, and other Asian countries.<sup>16-18</sup> However, the published results have been inconsistent. In 2009, Jing and colleagues first reported a meta-analysis including European and Asian populations, and the results showed the carriers of the C allele that may be at increased risk of T2DM compared with those carrying the T allele.<sup>19</sup> However, in a more recent meta-analysis, this association was not found in an African population.<sup>20</sup> Perhaps the contribution of the genetic background to T2DM can explain these differences. Therefore, constantly updated studies should help clarify the association between rs13266634 polymorphism and T2DM.

In previous meta-analyses, only a small fraction of the Chinese Han population was included. However, until now, no meta-analysis has been conducted in ethnic minority groups to evaluate the pooled effects of rs13266634 polymorphism on the risk of developing T2DM. China is a multi-ethnic country with a total of 56 ethnic groups. The Han nationality is the largest ethnic group. The remaining 55 ethnic groups are collectively referred to as ethnic minorities, accounting for 9% of the total population, including Muslim, Mongolian, Uyghur, Kazak, and Manchu ethnic groups, etc. The epidemiological survey of T2DM among ethnic minorities by Liu and colleagues suggested that there was a significant difference in the prevalence of T2DM between Han and ethnic minorities.<sup>21</sup> Compared with the ethnic Han, minorities are always distributed in remote areas, have their own special cultural and beliefs, have a small population mobility, and have a stable genetic background. They have more valuable genetic information, especially in genetic polymorphism. Therefore, we conducted an updated meta-analysis evaluating the association between rs13266634 polymorphism and T2DM in Chinese Han and ethnic minority populations.

## METHODS

The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>22</sup> (Details were listed in Table S2).

## Literature search

Pubmed, Web of Knowledge, CNKI, Wanfang, VIP and Google scholar databases were searched until November, 2017 by two investigators employing the following terms: ("*SLC30A8*" or "solute carrier family 30 member 8" or "rs13266634" or "zinc transporter protein member 8" or "ZnT-8" or "Arg325Trp" or "R325W" ) and ("polymorphism" or "variant" or "mutation") and ("diabetes" or "type 2 diabetes" or "T2DM"). In addition, the references from all relevant articles were searched manually.

## Selection criteria

Studies which met all the following criteria were included: (1) case-control design or cohort design; (2) they evaluated the association between rs13266634 polymorphism and T2DM; (3) T2DM diagnosis by World Health Organization-WHO (1999 version) or American Diabetes Association-ADA;<sup>23,24</sup> (3) they provided sufficient data to calculate the OR and 95% CI or the data were available after contacting with the authors by E-mail; (4) they were published in Chinese or English; (5) the subjects were Chinese; (6) the genotype distribution of the controls complied with the Hardy-Weinberg Equilibrium (HWE); (7) if several publications existed based on the same study, only the article with the largest number of cases or the most recently published study was included.

## Data extraction and quality assessment

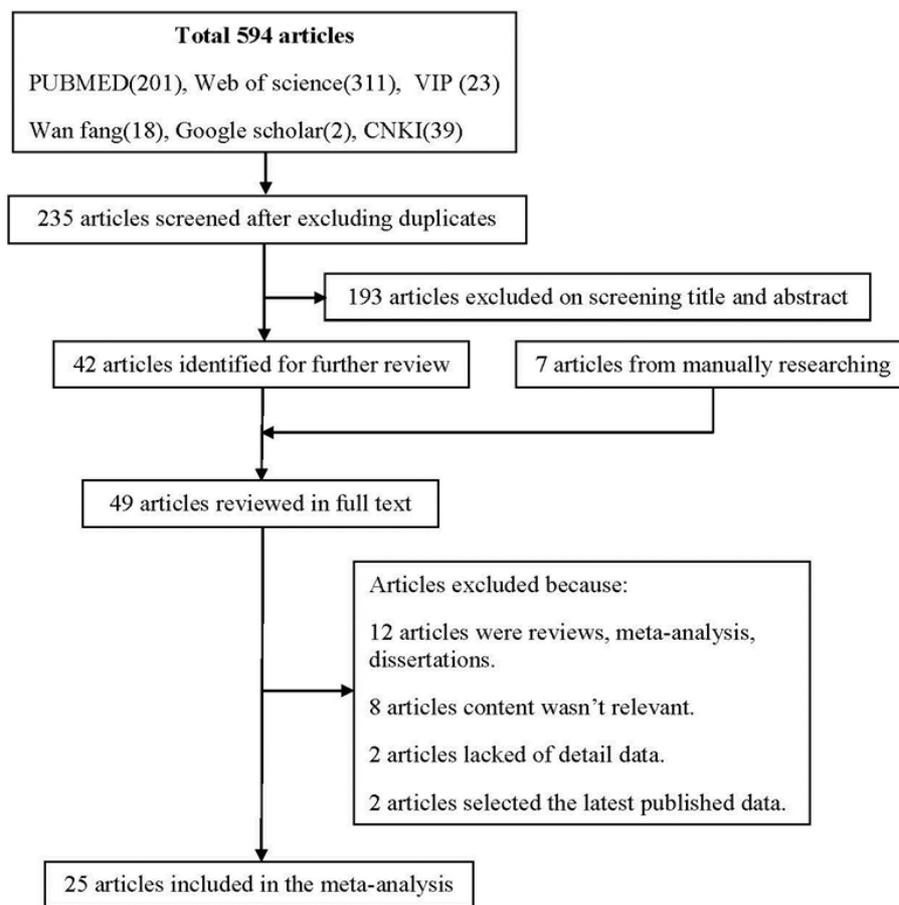
The following information was extracted from each eligible study: first author's surname, year of publication, geographical location and ethnicity of subjects, source of controls, diagnostic criteria, subjects' mean age, number of cases, genotype distribution data and adjusted covariates. Two investigators independently assessed and then discussed the articles in order to reach an agreement on all items.

The quality score of the studies included this meta-analysis was assessed by means of the Newcastle-Ottawa Scale (NOS).<sup>25</sup> Three aspects (selection, comparability and exposure) were estimated and each eligible answer got one point. Studies were regarded as "good" when the score was 8-9, "fair" when the score was 5-7, and "poor" when the score was  $\leq 4$ . Two investigators independently scored all the studies.

All disputes were resolved by discussing the issue with a senior author (WJL).

## Statistical analysis

The pooled OR and corresponding 95% CI were calculated to estimate the strength of association between the rs13266634 polymorphism and T2DM. Six genetic models, the allelic model (C vs T), the additive models (CC vs TT, CC vs CT, CT vs TT), the dominant model (CC vs CT+TT) and the recessive model (CC+CT vs TT) were analyzed.<sup>26</sup> The pooled OR were determined by means of the Z test ( $p < 0.05$  was considered statistically significant). Heterogeneity was evaluated by the Q test and the  $I^2$  test, with  $p < 0.05$  and/or  $I^2 > 50\%$  representing significant heterogeneity, in which case the random-effect model was selected; otherwise, the fixed-effect model was applied.<sup>27</sup> To uncover the source of the heterogeneity, we conducted additional subgroup analyses based on the subjects' mean



**Figure 1.** The article selection flow chart.

age (cut off point at 60 years of age), ethnicity groups (Han or minority), source of controls (population-based or hospital-based), diagnostic criteria (WHO or ADA), geographical location (north or south of China), NOS score (cut off point  $\geq 8$ ),<sup>25</sup> and adjustment for potential confounders (yes or no). In addition, we also employed the leave-one-out sensitivity analysis method to evaluate the impact of individual data on the pooled OR. Egger's tests and Begg's funnel plots were performed to assess publication bias, and  $p < 0.05$  was considered significant.<sup>28</sup> If some publication bias was detected, the Trim and Fill method was used to adjust the meta-analysis results by adding data from potential missing studies or prospective studies.<sup>30</sup> Data were analyzed using the Stata software (Version 11.0, Stata Corp, College Station, TX, USA). All results with  $p$  values  $< 0.05$  were considered significant.

## RESULTS

### Characteristics of the studies

A total of 594 relevant publications were identified following the initial search. After all duplicates had been removed, 235 unique articles remained. Of these, 193 were excluded after screening the title and abstract. The full-text of forty-two potential articles was downloaded for further review. In addition, 7 more articles were included after manually searching the reference lists. Twenty-four other articles were excluded because they did not fulfill the inclusion criteria. The flow diagram showing

the selection process is presented in Figure 1. Finally, 25 articles were included in the meta-analysis.<sup>15,17,31-53</sup> The main characteristics of the articles are listed in Table 1. The 25 selected articles involved 24 studies including 62,285 subjects (30,636 cases and 31,649 controls) and five ethnic groups (one Han and four minority groups). All studies were case-control studies, conducted in 15 provinces, and with sample sizes that varied between 222 and 13,517. The quality of the studies included in this meta-analysis was acceptable (at least 6 points in the NOS score). (Supplementary table 3).

### Meta-analysis results

Twenty-five articles involving 62,285 subjects (57,707 Han/4,578 minority) were selected to evaluate the association between rs13266634 and T2DM under six genetic models. Significant associations between rs13266634 polymorphism and T2DM were found in the combined population under six genetic models (C vs T: OR=1.23, 95% CI=1.18-1.29; CC vs TT: OR=1.44, 95% CI=1.32-1.56; CC vs CT: OR=1.08, 95% CI=1.02-1.15; CT vs TT: OR=1.25, 95% CI=1.15-1.37; CC vs CT+TT: OR=1.24, 95% CI=1.17-1.32; CC+CT vs TT: OR=1.26, 95% CI=1.16-1.35;  $p < 0.001$ ). The pooled results are shown in Figure 2. (detailed data is shown in the supplementary materials section, Figures S2-S7). Clear associations between the rs13266634 polymorphism and T2DM were observed in the Han group under the six genetic models (Figure 2). However, there was no evidence of a similar

**Table 1.** Main characteristics of the rs13266634 polymorphism studies included in this meta-analysis

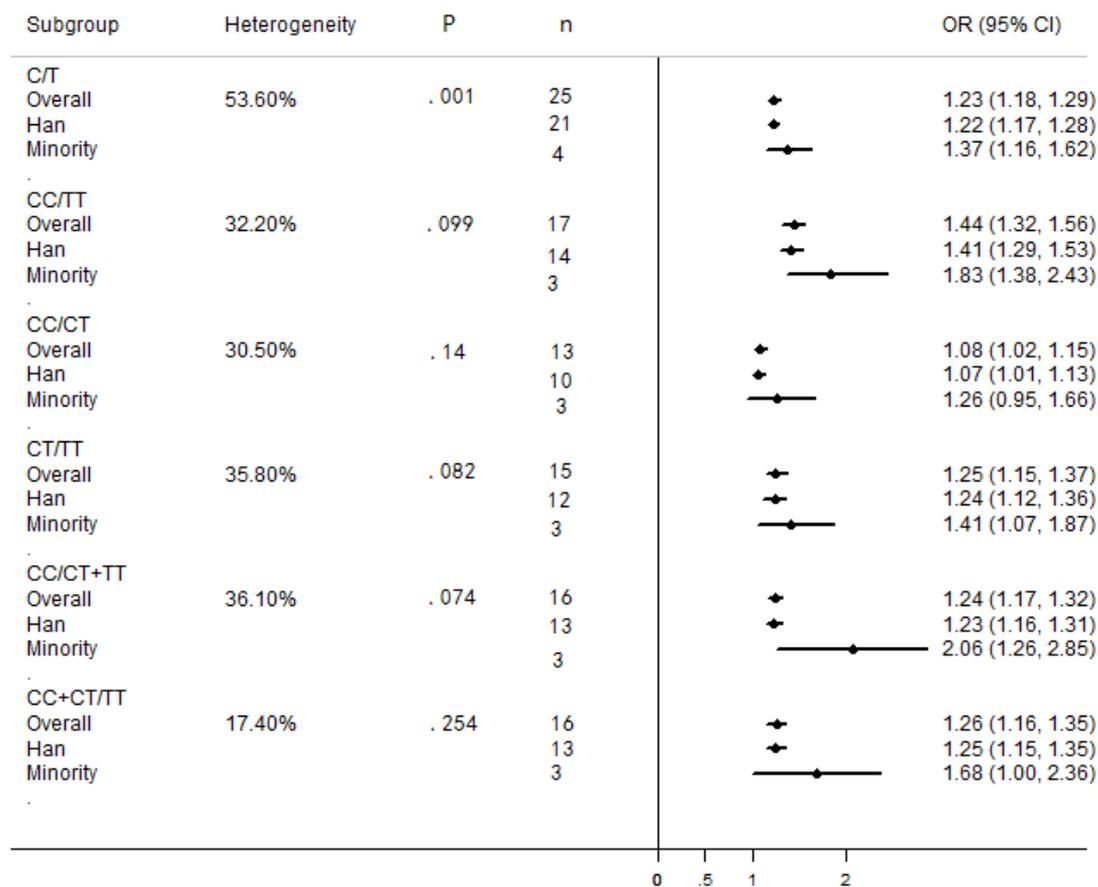
First author and year	Geographical location	Ethnic group	Control source	Diagnostic criteria	Age (y)	Participants (cases)	Genotypes distribution (case/control)			OR and 95% CI (C vs T)	Score
							CC	CT	TT		
Wang, 2008 <sup>31</sup>	Chongqing	Han	HB	WHO	55±12	765 (454)	152/87	219/141	83/83	1.36 (1.11-1.67) <sup>†</sup>	6
Wu, 2008 <sup>32</sup>	Beijing	Han	PB	WHO	58.6±6	2332 (424)	-	-	-	1.09 (0.93-1.27)	7
Xiang, 2008 <sup>33</sup>	Shanghai	Han	PB	WHO	62.6±9.2	1242 (521)	-	-	-	1.22 (1.04-1.43)	7
Ma, 2009 <sup>34</sup>	Shanghai	Han	HB	WHO	65±12	459 (259)	87/34	123/114	49/52	1.59 (1.19-2.12) <sup>†</sup>	7
Hu, 2009 <sup>35</sup>	Shanghai	Han	PB	WHO	61.2±12.6	3634 (1849)	-	-	-	1.25 (1.14-1.37)	7
Han, 2010 <sup>36</sup>	Beijing	Han	PB	WHO	56±12	1985 (992)	386/327	457/487	149/179	1.19 (1.04-1.37) <sup>†</sup>	8
Huang, 2010 <sup>37</sup>	Hunan	Han	HB	WHO	49.1±10.8	672 (443)	134/64	211/93	98/72	1.26 (1.01-1.58)	6
Lin, 2010 <sup>38</sup>	Sichuan	Han	HB	WHO	60.2±10.1	2968 (1529)	-	-	-	1.24 (1.12-1.37)	6
Tan, 2010 <sup>17</sup>	NA	Han	PB	WHO	50.9±11	3737 (1541)	-	-	-	0.98 (0.88-1.09)	8
Xu, 2010 <sup>39</sup>	Shanghai	Han	PB	WHO	63.3±9.7	4025 (1825)	-	-	-	1.20 (1.09-1.32)	7
Li, 2011 <sup>40</sup>	Nei Mongol	Han	HB	WHO	57.9±10.4	222 (125)	36/24	81/55	8/18	1.64 (1.13-2.40)	6
Wang, 2011 <sup>41</sup>	Hunan	Han	HB	WHO	57.4±10.5	454 (236)	82/48	117/95	37/75	1.89 (1.45-2.46)	7
Zheng, 2012 <sup>42</sup>	Chongqing	Han	HB	WHO	54.1±12.9	379 (227)	65/48	114/76	48/28	1.12 (0.84-1.50)	7
Li, 2012 <sup>53</sup>	Beijing	Han	PB	-	56.6±10	13517 (6570)	-	-	-	1.18 (1.07-1.29)	7
Tam, 2013 <sup>43</sup>	Hong Kong	Han	PB	WHO	56.8±13.3	8451 (5882)	-	-	-	1.22 (1.13-1.32)	7
Chen, 2013 <sup>44</sup>	Fujian	She	PB	WHO	54.2±11.3	2210 (443)	-	-	-	1.48 (1.10-2.01)	7
Zhang, 2014 <sup>45</sup>	Gansu	Dong Xiang	HB	WHO	49.8±14.1	252 (123)	48/30	56/69	19/30	1.62 (1.13-2.31)	6
Zhang, 2015 <sup>46</sup>	Gansu	Muslim	HB	WHO	53.6±12.3	252 (125)	51/33	54/65	20/29	1.56 (1.09-2.22)	6
Chang, 2014 <sup>15</sup>	Gansu	Han	HB	WHO	55.8±15.8	273 (138)	56/33	62/76	20/26	1.54 (1.09-2.16)	6
Shan, 2014 <sup>47</sup>	Taiwan	Han	PB	ADA	55.8±15.8	3020 (1502)	-	-	-	1.30 (1.17-1.45) <sup>†</sup>	7
Shan, 2014 <sup>47</sup>	Hubei	Han	HB	WHO	51±10.8	1578 (785)	-	-	-	1.27 (1.08-1.51) <sup>†</sup>	7
Chen, 2015 <sup>48</sup>	Jilin	Han	HB	WHO	-	220 (113)	44/36	55/55	14/16	1.18 (0.80-1.73)	7
Liu, 2015 <sup>49</sup>	Liaoning	Han	HB	WHO	51.4±10.2	281 (136)	52/32	64/84	20/29	1.55 (1.11-2.17)	6
Zhao, 2015 <sup>50</sup>	Jiangsu	Han	PB	WHO	64.31±9.0	3687 (1737)	624/649	837/951	277/350	1.10 (1.00-1.21)	8
Qian, 2015 <sup>51</sup>	Jiangsu	Han	PB	WHO	58.8±10.3	3806 (1725)	593/676	863/1023	269/382	1.13 (1.01-1.26) <sup>†</sup>	8
Su, 2016 <sup>52</sup>	Sin Kiang	Uyghur	HB	ADA	-	1864 (932)	466/432	402/403	64/97	1.19 (1.03-1.36)	6

NA: not available; HB: hospital-based; PB: population-based; WHO: world health organization; ADA: American diabetes association; OR: odds ratio; CI: confidence interval.

Studies were regarded as “good” when the score was 8-10, “fair” when the score was 5-7, and “poor” when the score was ≤4.

<sup>†</sup>Adjusted for confounders: sex, age, BMI (body mass index).

-: no value.



**Figure 2.** Pooled OR and 95% CI showing the strength of association between the rs13266634 polymorphism and T2DM risk in Han and minority populations under six genetic models.

association in ethnic minority groups under the additive model (CC vs CT: OR=1.26, 95% CI=0.95-1.66,  $p=0.105$ ). Nevertheless, under the other five genetic models, these associations were stronger in the ethnic minority than in Han populations.

#### Source of heterogeneity

No obvious heterogeneity was detected under the additive, dominant, or recessive models, and the heterogeneity  $I^2$  results oscillated between 17.4% and 36.1%. In contrast, the between-study heterogeneity for the allelic genetic model was high ( $I^2=53.6%$ ,  $p=0.001$ ). To identify the source of this heterogeneity, we initially conducted subgroup analyses based on the subjects' mean age, ethnicity, source of controls, diagnostic criteria, geographical location, NOS score, and adjustment for potential confounders. These results suggested that variables such as mean age  $\geq 60$  years, minority group ethnicity, inclusion of hospital-based, ADA diagnostic criteria, northern China geographical location, NOS score  $< 8$ , and adjustment for confounders could partly explain the source of the heterogeneity (Table 2). Meanwhile, the leave-one-out analysis showed that the study conducted by Tan<sup>17</sup> was the prominent contributor to the elevated heterogeneity.<sup>17</sup> After excluding this study, the heterogeneity dropped to  $I^2=23.3%$  ( $p=0.146$ ), and the association showed significance (OR=1.21, 95% CI=1.18-1.25,  $p<0.001$ ).

#### Sensitivity analysis and publication bias

By excluding one study at a time, the sensitivity analysis

did not identify any single one which clearly affected the results. Begg's funnel plot and Egger's test were performed to assess publication bias. No significant publication bias was observed under the additive models (CC vs CT: Egger's test,  $t=1.96$ ,  $p=0.075$ ; CT vs TT: Egger's test,  $t=1.33$ ,  $p=0.207$ ). (Supplementary figure 8). However, the shapes of the funnel plots demonstrated obvious asymmetry under other genetic models ( $p<0.05$  from Egger's test). Subsequently, the Trim and Fill method was applied to adjust the results. This methodology indicated that the results would be robust after supplementing (8, 7, 6, 6) potential missing studies in (C vs T, CC vs TT, CC vs CT+TT, CC+CT vs TT) genetic models, respectively. (Figure 3 and Figure 4).

#### DISCUSSION

In the present study we report the results of a meta-analysis based on 24 case-control studies including 62,285 subjects. We observed a significant association between the rs13266634 polymorphism of the *SLC30A8* gene and T2DM in Chinese populations under six genetic models. However, there was no evidence of this association in ethnic minority populations under the additive genetic model (CC vs CT). To our knowledge, this is the first meta-analysis to investigate the effects of the rs13266634 polymorphism on T2DM in both Chinese Han and minority populations.

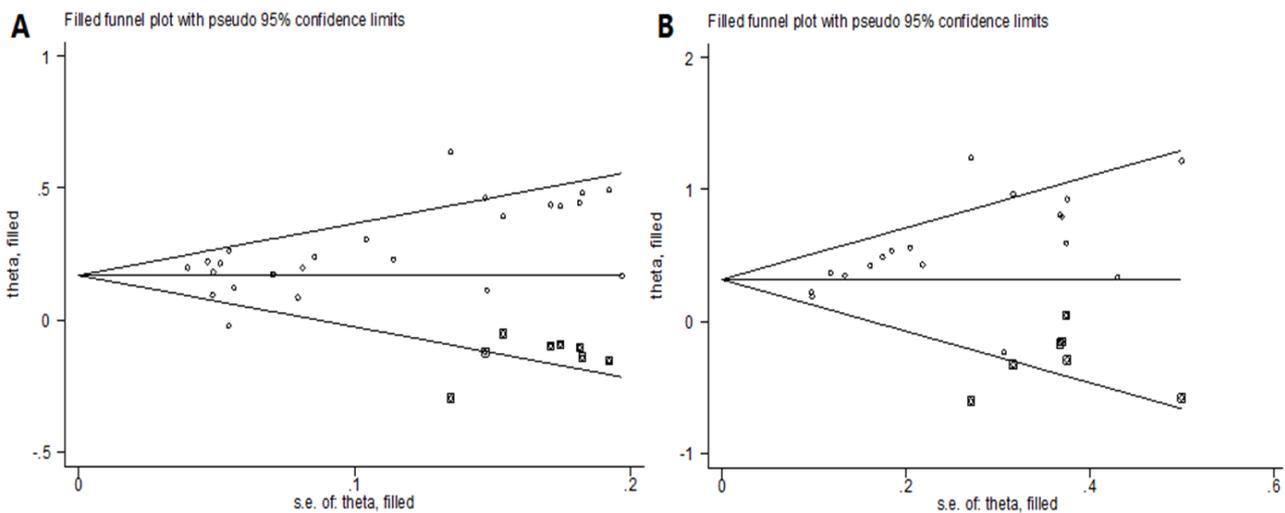
T2DM is a common metabolic disease of multiple etiologies caused by genetic and environmental interactions.<sup>54,55</sup> Accumulating evidence suggests that increased

**Table 2.** Rs13266634 polymorphism and T2DM: subgroup analysis under the allelic genetic model (C/T)

Subgroup	Study number	Effect size	Heterogeneity	
		OR and 95% CI	<i>I</i> <sup>2</sup> (%)	<i>p</i>
Total	25	1.23 (1.18-1.29)	53.6	0.001
Age				
<60	16	1.28 (1.18-1.38)	64.9	<0.001
≥60	6	1.21 (1.14-1.29)	37.6	0.156
Ethnic group				
Han	21	1.22 (1.17-1.28)	55.7	0.001
Minority	4	1.37 (1.16-1.62)	36.6	0.193
Control source				
PB	12	1.17 (1.12-1.23)	52.2	0.018
HB	13	1.35 (1.25-1.46)	32.8	0.113
Diagnostic criteria				
WHO	22	1.24 (1.18-1.31)	57.5	<0.001
ADA	2	1.26 (1.16-1.37)	0.00	0.324
Geographical location				
North China	7	1.32 (1.19-1.47)	23.9	0.239
South China	15	1.24 (1.19-1.30)	44.3	0.033
NOS score				
<8	21	1.27 (1.21-1.32)	29.4	0.097
≥8	4	1.09 (1.01-1.18)	48.2	0.122
Adjust confounders <sup>†</sup>				
Yes	6	1.21 (1.16-1.27)	0.0	0.607
No	19	1.26 (1.18-1.35)	62.1	<0.001

HB: hospital-based; PB: population-based; WHO: world health organization; ADA, American diabetes association; OR: odds ratio; CI: confidence interval; NOS: new castle-ottawa scale.

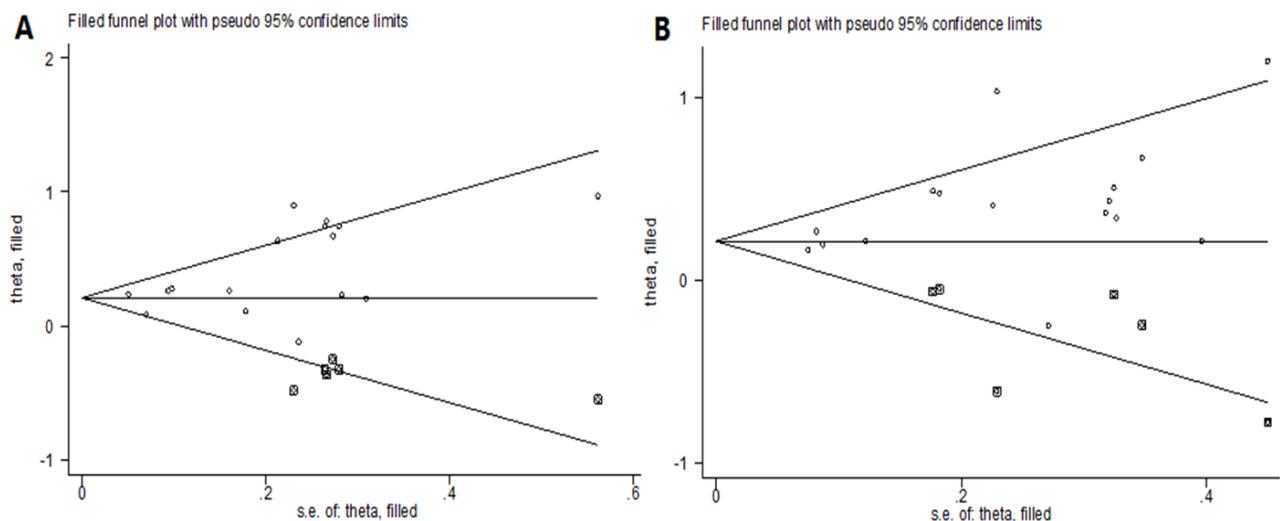
<sup>†</sup>Adjusted for confounders: sex, age, and BMI (body mass index).



**Figure 3.** Funnel plot of rs13266634 polymorphism and T2DM publication bias. (A): C vs T. (B): CC vs TT.

susceptibility to T2DM is largely attributable to genetic factors.<sup>56</sup> In this regard, more than 100 loci have been reported to be associated with susceptibility to T2DM.<sup>57</sup> In 2007, Sladek et al first confirmed the association between the rs13266634 polymorphism and susceptibility to T2DM.<sup>14</sup> Subsequently, numerous replication studies were conducted in multi-ethnic populations. However, the conclusions have been controversial.<sup>17,35,58,59</sup> Considering the low credibility of a single study due to limited sample size, meta-analysis has become the preferred methodology to approach genetic-association studies.<sup>60</sup>

In our meta-analysis, the pooled results from all the population groups suggested that the rs13266634 polymorphism was significantly associated with T2DM, with the OR ranging between 1.08 and 1.44 under six genetic models. Our results are consistent with the findings of previous meta-analysis conducted by Jing and Cheng,<sup>19,20</sup> which showed that the rs13266634 polymorphism was associated with the risk of developing T2DM in Asian populations. However, the present study has some strengths compared with others. Firstly, it includes more publications (25 versus 11) and subjects than the study



**Figure 4.** Funnel plot adjusted using the Trim and Fill method for rs13266634 polymorphism and T2DM publication bias. (A): CC vs CT+TT. (B) CC+CT vs TT.

carried out by Jing,<sup>19</sup> increasing its potential to establish the relationship between the *SLC30A8* genotype and the risk of developing T2DM in Chinese populations. Secondly, the genetic analysis conducted in this study, which assessed under six genetic models, is more comprehensive than the study done by Cheng.<sup>20</sup> Thirdly, this is the first study to analyze the association of this polymorphism with T2DM among ethnic minorities.

No association was found between the rs13266634 polymorphism and T2DM in ethnic minority groups under the additive model (CC vs CT: OR=1.26, 95% CI=0.95-1.66,  $p=0.105$ ), a result that is similar to that reported by Zhang et al in Chinese Dongxiang and Muslim populations.<sup>45,46</sup> Ethnic differences might partly account for the degree of susceptibility to T2DM. Qiu et al found that the SHP70-2 gene polymorphism (+1267) G allele could increase the risk of essential hypertension in the Han population, but the A allele could increase the risk of essential hypertension in the Muslim population.<sup>61</sup> Si et al found that C1GALT1 (rs1008898) polymorphism was related to IgA nephropathy in Han nationality, but no such association was found in the Muslim population.<sup>62</sup> In addition, most studies tested the multiple genetic models for complex diseases, and did not correct for multiple comparisons.<sup>63</sup> Therefore, we suggested that the additive model (CC/CT) might be not the best model to determine the association between polymorphism of rs13266634 and the risk of T2DM in ethnic minority groups. However, this conclusion should be interpreted with caution in our meta-analysis, since these studies have small sample sizes and only investigated four minority ethnic populations.

Between-study heterogeneity is common in genetic association meta-analysis studies.<sup>64</sup> In our meta-analysis, substantial heterogeneity was found in the allele genetic model (C vs T:  $I^2=53.6\%$ ,  $p=0.001$ ). Therefore, subgroup analysis was conducted to explore the source of heterogeneity based on subjects' mean age, ethnic group, source of controls, diagnostic criteria, geographical location, NOS score, and adjustment for covariates (yes or no). We found that all the subgroups partly accounted for the heterogeneity. In addition, the leave-one-out analysis showed that the main contributor to the high level of het-

erogeneity was the study conducted by Tan.<sup>17</sup> The reproduced OR and corresponding 95% CI were 1.21 and 1.18-1.25, respectively, without any notable change, but the heterogeneity dropped to  $I^2=23.3\%$  ( $p=0.146$ ) after excluding Tan's study. Subjects included in the study conducted by Tan were Chinese who have long lived in Singapore, whose lifestyles and behaviors may differ from other subjects lived in China. This may be the main reason for the high heterogeneity of pooled results.

Several potential limitations of our meta-analysis should be acknowledged. First, although we corrected for publication bias using the Trim and Fill method, the impact on the results is not negligible. Some articles that have not been published due to negative results should be mined. Second, due to data limitation, the effects of gene-gene/gene-environment interactions were not addressed in our meta-analysis. Third, inherent in epidemiological designs is participant selection bias and recall bias, which may impact on the measurement of exposures/risk factors. Finally, case-control studies make an assumption that there is an unbiased allele frequency. In spite of these limitations, our meta-analysis also has some strengths. First, the number of participants and cases was sufficient. Second, the NOS score of all the included articles was above 6, which indicates the good quality of the included studies. Third, this is the first comprehensive analysis of ethnic minority populations.

Taken together, the present meta-analysis which includes 24 studies suggests that the rs13266634 polymorphism of the *SLC30A8* gene may be associated with an increased risk of developing T2DM in Chinese populations. In addition, ethnic minorities are more likely to increase the risk of T2DM than Han under a specific genetic model. Therefore, increasing genetic monitoring in ethnic minorities may be an effective method to prevent diabetes. Taking the publication bias and the inclusion of fewer literature on ethnic minorities into consideration, additional well-designed, prospective cohort studies should be conducted in ethnic minorities with a large sample size and better adjustment for all potential confounders.

## AUTHOR DISCLOSURES

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**Supplementary table 1.** Comparison between the present meta-analysis and existing researches

Article	Year	No. of studies	No. of Ethnic groups	No. of Chinese studies	No. of ethnic minority groups	No. of subjects (Cases/Controls)	Genetic models						NOS
							C/T	CC/TT	CC/CT	CT/TT	CC+CT/TT	CC/CT+TT	
No 1. SLC30A8 polymorphism and type 2 diabetes risk: Evidence from 27 study groups	2009	27	3	2	0	2198/2701	√	×	×	×	×	×	×
No 2. Association between SLC30A8 rs13266634 Polymorphism and Type 2 Diabetes Risk: A Meta-Analysis	2015	39	3	11	0	NP	√	√	√	√	√	√	√
No 3. The present meta-analysis	2018	25	1	25	4	30636/31649	√	√	√	√	√	√	√

NP: not provided; NOS: Newcastle-Ottawa Scale.

The number of subjects listed in the table refers to the number of Chinese people. (The total number of article No 1. were 42609/69564).

×: The existing researches did not performed the corresponding analysis; √: The existing researches performed the corresponding analysis

**Supplementary table 2.** PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Protocol not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5

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**Supplementary table S.** PRISMA 2009 Checklist (cont.)

Section/topic	#	Checklist item	Reported on page #
<b>Methods</b>			
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	6-7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
<b>Results</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10 Figure 3 Figure S8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 Figures S2-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2-3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 4 Figure S8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2
<b>Discussion</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Revista Española De Nutrición Humana Y Dietética* 2009; 18:e123

**Supplementary table 3.** Quality assessment of included case-control studies

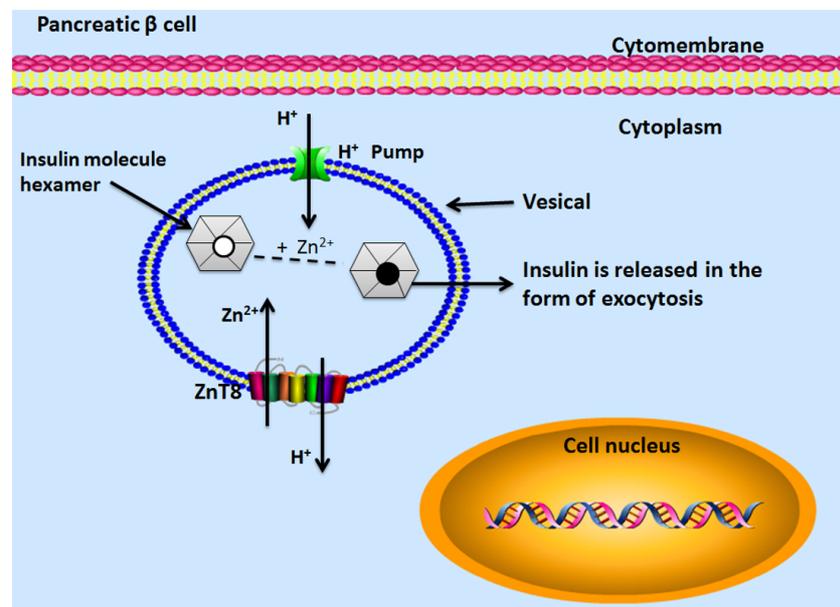
Author (publication year)	Newcastle-Ottawa Scale									Total
	Selection				Comparability		Exposure			
	1 <sup>†</sup>	2 <sup>‡</sup>	3 <sup>§</sup>	4 <sup>¶</sup>	5 <sup>††</sup>	6 <sup>‡‡</sup>	7 <sup>§§</sup>	8 <sup>¶¶</sup>	9 <sup>†††</sup>	
Wang et al (2008)	1	1	0	0	1	1	1	1	0	6
Wu et al (2008)	1	1	1	0	1	1	1	1	0	7
Xiang et al (2008)	1	1	1	0	1	1	1	1	0	7
Ma et al (2009)	1	1	0	1	1	1	1	1	0	7
Hu et al (2009)	1	1	1	0	1	1	1	1	0	7
Han et al (2010)	1	1	1	1	1	1	1	1	0	8
Huang et al (2010)	1	1	0	0	1	1	1	1	0	6
Lin et al (2010)	1	1	0	0	1	1	1	1	0	6
Tan et al (2010)	1	1	1	1	1	1	1	1	0	8
Xu et al (2010)	1	1	1	0	1	1	1	1	0	7
Li et al (2011)	1	1	0	0	1	1	1	1	0	6
Wang et al (2011)	1	1	0	1	1	1	1	1	0	7
Zheng et al (2012)	1	1	0	1	1	1	1	1	0	7
Li et al (2012)	1	1	1	0	1	1	1	1	0	7
Tam et al (2013)	1	1	1	0	1	1	1	1	0	7
Chen et al (2013)	1	1	1	0	1	1	1	1	0	7
Zhang et al (2014)	1	1	0	0	1	1	1	1	0	6
Zhang et al (2015)	1	1	0	0	1	1	1	1	0	6
Chang et al (2014)	1	1	1	0	1	1	1	1	0	7
Shan et al (2014)	1	1	0	1	1	1	1	1	0	7
Chen et al (2015)	1	1	0	1	1	1	1	1	0	7
Liu et al (2015)	1	1	0	0	1	1	1	1	0	6
Zhao et al (2015)	1	1	1	1	1	1	1	1	0	8
Qian et al (2015)	1	1	1	1	1	1	1	1	0	8
Su et al (2016)	1	1	0	0	1	1	1	1	0	6

Selection: <sup>†</sup>Is the case definition adequate; <sup>‡</sup>Representativeness of the case; <sup>§</sup>Selection of controls; <sup>¶</sup>Definition of Controls.

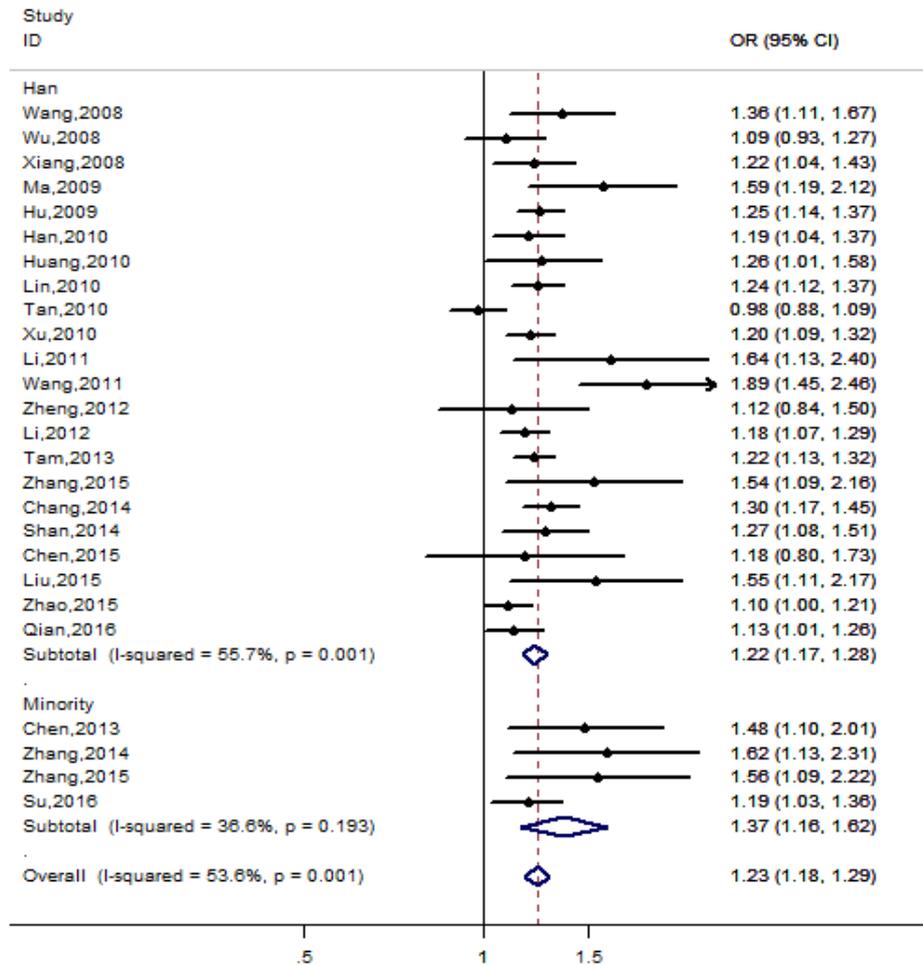
Comparability: <sup>††</sup>Comparability of cases and controls on the basis of the design or analysis (adjusted for gender, age, BMI);

<sup>‡‡</sup>Comparability of cases and controls on the basis of the design or analysis (adjusted for a second important factor).

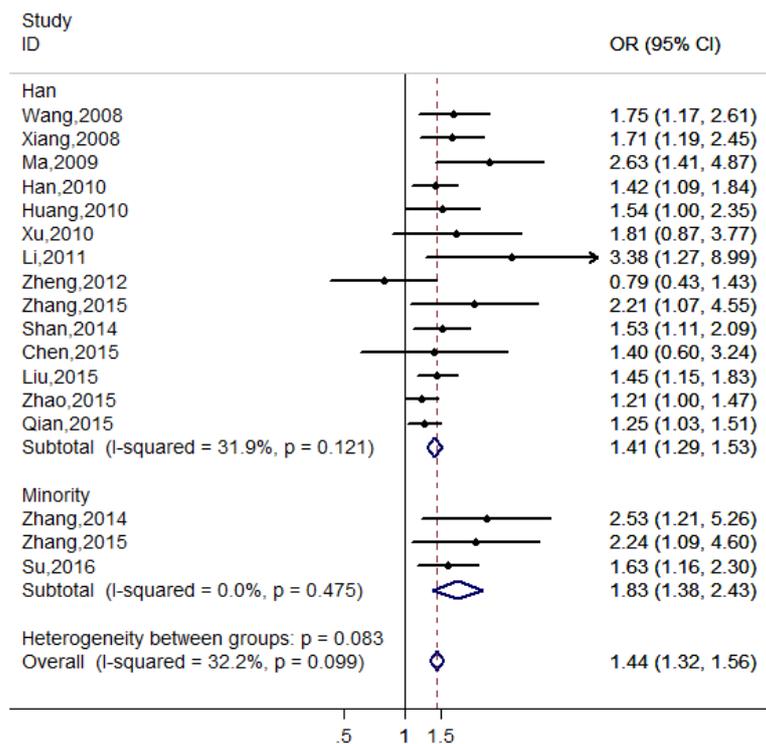
Exposure: <sup>§§</sup>Ascertainment of exposure; <sup>¶¶</sup>Same method of ascertainment for cases and controls; <sup>†††</sup>Non-response rate.



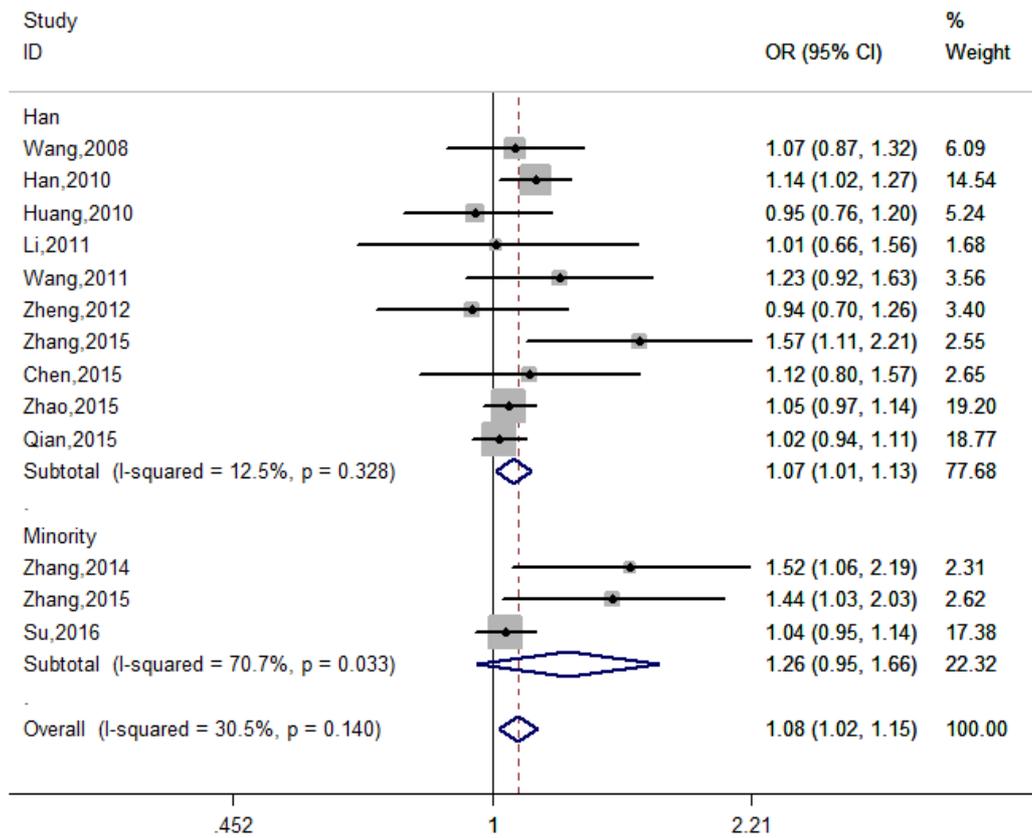
**Supplementary figure 1.** Mechanism of Zinc transport 8 (ZnT8) in insulin secretion process. ZnT-8 is a trans-membrane protein containing 369 amino acids which is expressed exclusively in pancreatic islet β cells. A H<sup>+</sup> pump on the secretory vesicle membrane of the islet cells transports H<sup>+</sup> to the vesicle, resulting in a poor H<sup>+</sup> concentration inside and outside the vesicle. With this concentration difference, ZnT8 transports 2 H<sup>+</sup> and simultaneously transfers 1 Zn<sup>2+</sup>. Two Zn<sup>2+</sup> and six insulin monomers constitute hexamers specifically stored in vesicles.



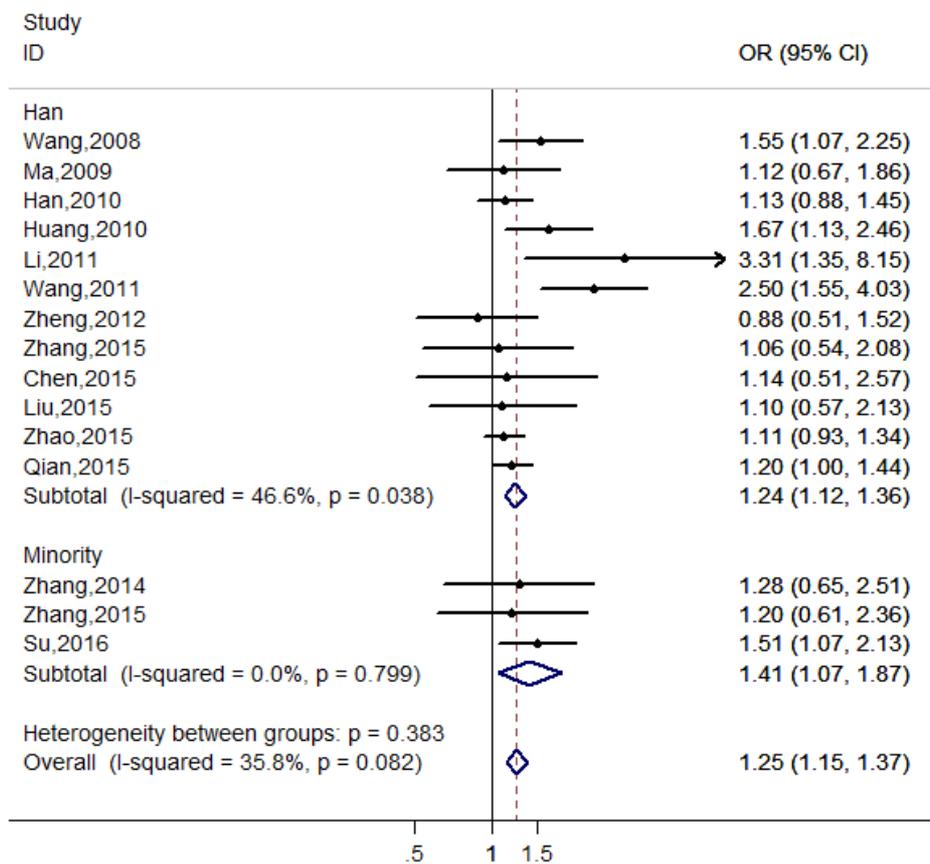
Supplementary figure 2. Forest plot showing the association between the rs13266634 polymorphism and T2DM under the allelic genetic model (C/T).



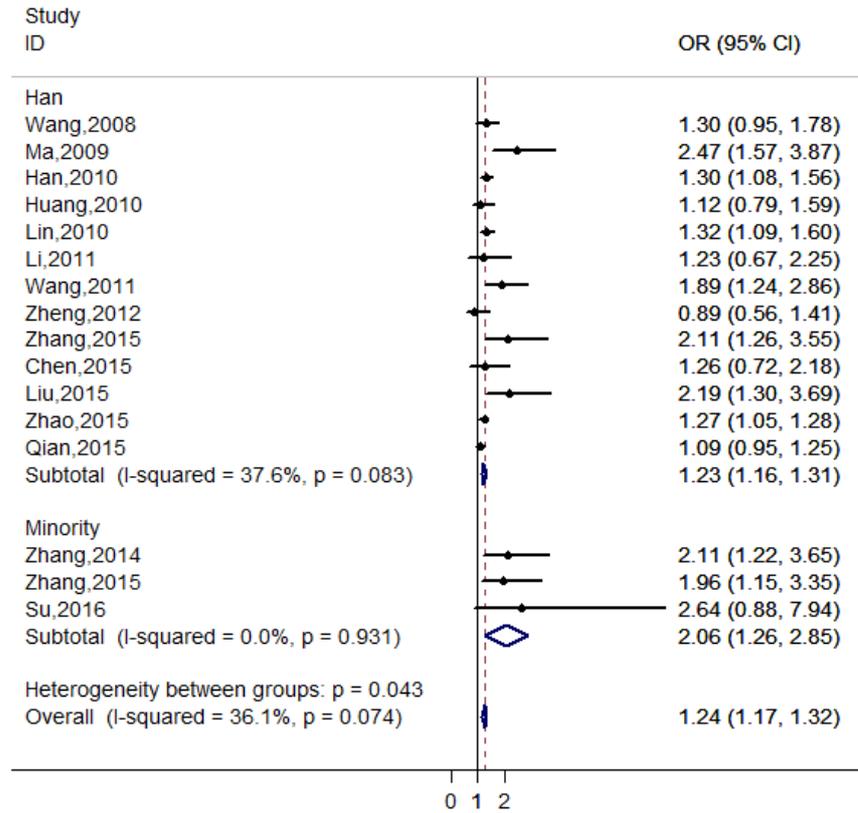
Supplementary figure 3. Forest plot showing the association between the rs13266634 polymorphism and T2DM under the additive genetic model (CC/TT).



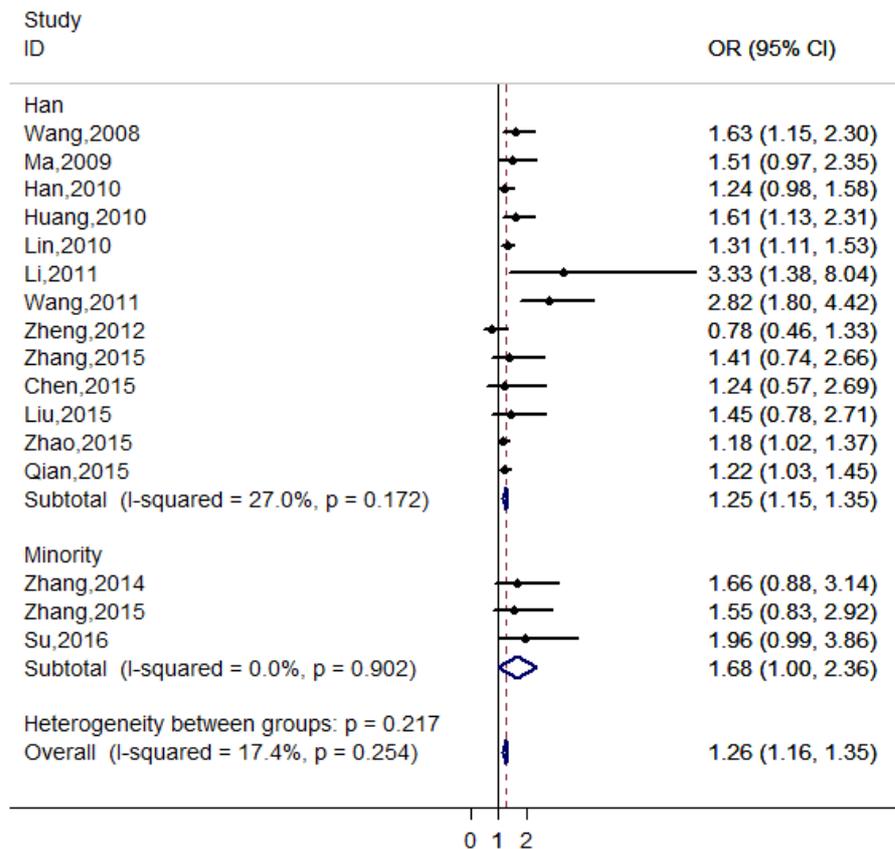
**Supplementary figure 4.** Forest plot showing the association between the rs13266634 polymorphism and T2DM under the additive genetic model (CC/CT).



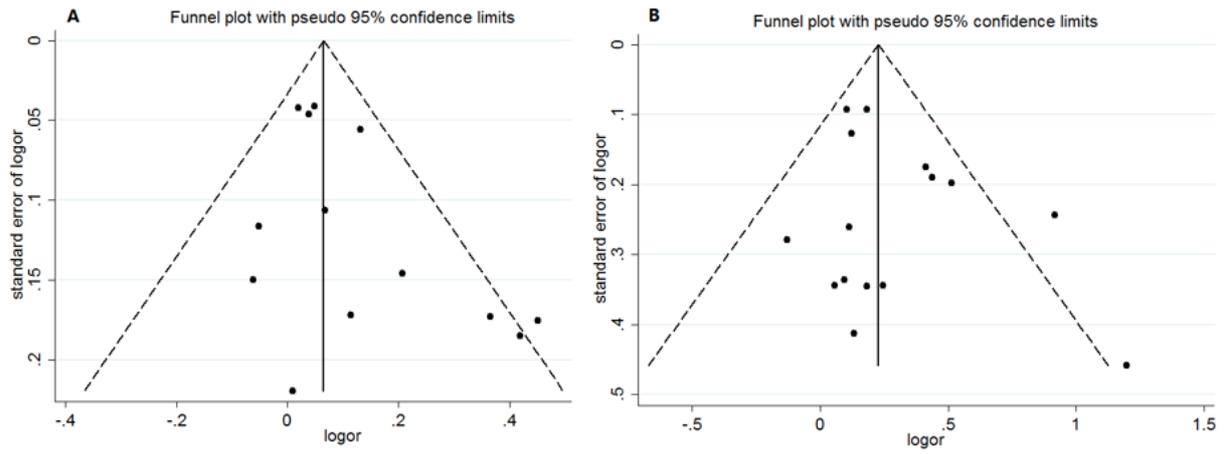
**Supplementary figure 5.** Forest plot showing the association between the rs13266634 polymorphism and T2DM under the additive genetic model (CT/TT).



**Supplementary figure 6.** Forest plot showing the association between the rs13266634 polymorphism and T2DM under the additive genetic model (CC/CT+TT).



**Supplementary figure 7.** Forest plot showing the association between the rs13266634 polymorphism and T2DM under the additive genetic model (CC+CT+TT).



**Supplementary figure 8.** Funnel plot of the meta-analysis of the rs13266634 polymorphism and T2DM under two genetic models.(A): CC vs. CT. (B): CT vs. TT.