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**META-ANALYSIS** 

MONITOR Received: 2015.03.08 Association between SLC30A8 rs13266634 Accepted: 2015.04.03 Published: 2015.07.27 **Polymorphism and Type 2 Diabetes Risk: A Meta-Analysis** ABCDEF 1 Liging Cheng Authors' Contribution: 1 Department of Endocrinology and Metabolism, Southwest Hospital, Third Military Study Design A Medical University, Chongqing, P.R. China BCDEF 2 Dongmei Zhang

2 Department of Dermatology, Southwest Hospital, Third Military Medical Lina Zhou BF 1 Statistical Analysis C University, Chongqing, P.R. China BF 1 Jie Zhao Data Interpretation D Manuscript Preparation E AG 1 Bing Chen Literature Search F Funds Collection G **Corresponding Author:** Bing Chen, e-mail: chenbingtmmu@163.com This study was partly supported by the Scientific and Technological plans of Chongqing (cstc2014yykfA110004) Source of support: Background: Accumulating but inconsistent data about the role of rs13266634 variant of SLC30A8 in type 2 diabetes have been reported, partly due to small sample sizes and non-identical ethnicity. Material/Methods: We searched PubMed and Cochrane Library to identify eligible studies and extract data of baseline characteristics, genotype count, odds ratio (OR), and 95% confidence interval (CI). Both adjusted OR with 95% CI and genotype counts were employed to assess the association. Genotype data were further pooled to provide estimates under different genetic models and the most appropriate model was determined. Sensitivity and cumulative analysis were conducted to assure the strength of results. **Results:** Fifty-five datasets of 39 studies (including 38 of 24 with genotype count) were included. Significant associations were found in allelic contrasts using adjusted ORs and raw genotype count, respectively, overall in Asian and European populations (overall: OR=1.147/1.157, 95% Cl 1.114–1.181/1.135–1.180; Asian: OR=1.186/1.165, 95% CI 1.150–1.222/1.132–1.198: European: OR=1.100/1.151, 95% CI 1.049–1.153/1.120–1.183: All p=0.00). but not in African populations (African: OR=1.255/1.111, 95% CI 0.964–1.634/0.908–1.360, p=0.091/0.305). Further analysis with genotype count under different genetic models all showed that individuals with CC genotype had 33.0% and 16.5% higher risk of type 2 diabetes than those carrying TT and CT genotypes, respectively, under the most likely codominant model. Cumulative analysis indicated gradually improved precision of estimation after studies accumulated. Conclusions: Our results suggest that rs13266634 may be an important genetic factor of type 2 diabetes risk among Asian and European but not African populations. **MeSH Keywords:** Diabetes Mellitus, Type 2 • Meta-Analysis • Polymorphism, Genetic Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/894052





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Data Collection B

# Background

Diabetes is a group of worldwide prevalent, metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Two major etiopathogenetic groups of diabetes mellitus have been defined: type 1 and type 2. Type 1 diabetes is an autoimmune disease. Diabetes type 2 is much more prevalent and has a more complicated etiology involving a combination of genetic to environmental factors. Diabetes mellitus affects approximately 347 million people worldwide[1], 90% of which have type 2 diabetes, and accounts for an estimated 3.4 million death in 2004 [2]. The economic costs and burden of diabetes are considerable, given the substantial morbidity and vital multi-organ complications [3].

In recent years many genes have been identified to be associated with type 2 diabetes susceptibility [4,5]. SLC30A8, as a coding gene of zinc transporter 8 (ZnT8), was reported to contribute to type 2 diabetes susceptibility [6-9]. ZnT8, a novel member of ZnT family, is predominately expressed in pancreatic islet beta cells and is responsible for cellular efflux of zinc from cytoplasm into intracellular vesicles. It localizes into insulin secretory granules and is indispensable for insulin crystallization, storage, and secretion [10–12]. Antibodies against ZnT8 have been identified as novel biomarkers for autoimmune diabetes [13–19]. The association of SLC30A8 variants with type 2 diabetes has also received much attention, with an important polymorphism, rs13266634, being the most studied [19–29]. This non-synonymous variant (rs13266634) is a C-to-T variant (arginine to tryptophan at position 325, R325W) and had been confirmed to be associated with higher risk of type 2 diabetes in various ethnic populations [6-9,30-33].

Although a number of studies, including some meta-analyses, have been conducted to investigate the association between rs13266634, the most common variant of SLC30A8, and the risk of type 2 diabetes in diverse populations, the results were mixed and inconclusive, possibly due to the relatively small sample size in the included studies. Meta-analysis is a cost-effective method to increase sample size by combining data from different independent studies, and is recognized as a ideal tool for summarizing inconsistent results from multiple studies. There has recently been an increase in the number of these studies, but there is no updated meta-analysis investigating the association between them. To provide the most comprehensive assessment of the relationship between rs13266634 variant and type 2 diabetes risk, we performed an updated meta-analysis of all available studies.

# **Material and Methods**

The meta-analysis was conducted according to the PRISMA statement (Preferred reporting items for systematic reviews and meta-analyses, checklist S1) [34] and meta-analysis on genetic association studies (checklist S2).

## Search strategy

We searched PubMed and Cochrane Library from 2007, the year when the association of SLC30A8 and diabetes was first reported [6–9], to identify all relevant papers on humans published in English. The following terms were used in searching: (rs13266634 or zinc transporter protein member 8 or ZnT8 or ZnT-8 or SLC30A8) and (polymorphism or variant or *loci*) and diabetes. All eligible studies were retrieved and their references were checked for other relevant publications in English. The titles and abstracts were scanned to exclude studies that were clearly irrelevant to the current topic. The full text of the remaining articles was read to determine whether they contained information of interest. Two independent reviewers (Cheng and Zhang) performed a systematic search in PubMed and Cochrane databases, with the last search updated on June 25, 2014.

#### Inclusion and exclusion criteria

Studies included in the meta-analysis were required to meet the following criteria: (1) case-control study or prospective study that evaluated the association between rs13266634 and type 2 diabetes in humans; and (2) had an odds ratio (OR) with 95% confidence interval (CI) or detailed genotype data for estimating OR (95% CI). Exclusion criteria are: (1) duplication of previous publications; (2) comment, review, or editorial; and (3) family-based studies of pedigrees.

# **Data extraction**

Two investigators (Cheng and Zhang) independently extracted information from all eligible publications. The results were compared and disagreements were discussed until a consensus was reached. Data extracted from each study included the following characteristics: the first author's name, the year of publication, ethnicity of participants, age, age at diagnosis, body mass index (BMI), fasting plasma glucose (FPG), total number, genotype numbers and frequency, and the most completely adjusted estimate (OR and 95% CI, respectively) of the rs13266634 polymorphism in the cases and controls. If dissent still existed, the third investigator (Zhou) would be involved to adjudicate the disagreements. For those included articles without all desired wanted data, we emailed the authors, providing contact information, to ask for details.

## Quality score assessment

The quality of selected studies was assessed by 3 investigators (Cheng, Zhang, and Zhou) independently scoring studies according to a set of predetermined criteria adjusted from previous reports [35,36]. Quality scores ranged from 0 to 10 and studies were scored as "good" if the score was 8–10, "fair" if the score was 5–7, and "poor" if the score was <4. Discrepancies were resolved by discussion.

### Statistical analyses

All statistical tests were conducted with STATA software version 11.0 (STATA Corp, College Station, Texas).

To investigate the association strength between SLC30A8 rs13266634 polymorphism and the susceptibility of type 2 diabetes, we used adjusted ORs and corresponding 95% CIs from all studies, and calculated ORs from studies with genotype distribution information to pool ORs and corresponding 95% Cls. For those studies with raw genotype count, we then obtained pooled ORs and corresponding 95% CIs from combination of single studies by homozygote and heterozygote comparison (CC vs. TT, OR1; CT vs. TT, OR2; CC vs. CT, OR3), overdominant (CC+CT vs. TT) an dominant and recessive models (CC vs. CT+TT and CC+CT vs. TT), respectively. We also performed subgroup analysis on ethnicity, Hardy-Weinberg equilibrium (HWE), genotyping methods, sample size (large sample ≥1000, small sample <1000), study design (population-based case-control study, hospital-based case-control study, and prospective study), and quality of studies in these comparisons. Environmental effects associated with diabetes, such as diet and exercise, were not analyzed due to limited details. Z-test was used for assessing the significance of the pooled ORs, with p<0.05 considered statistically significant. A biological justification for the choice of the genetic model was estimated according the relationships of OR, OR, and OR, [37]. Cumulative meta-analysis by publication year was conducted to investigate time-based fluctuation and robustness of results.

Heterogeneity among the studies was evaluated as notable by the chi-square-based Q-test (significance level of p<0.10) and/or  $I^2$  index (greater than 50% as evidence of significant inconsistency) [38] and the random-effects model (DerSimonian and Laird method); otherwise, the fixed-effects model (Mantel and Haenszel method) was employed. The significance of pooled ORs was determined by Z-test and p<0.05 was considered as statistically significant. For the controls of each study with detailed genotype count, HWE was evaluated using the goodness-of-fit chi-square test and a p<0.05 was considered to deviate from HWE. To identify the effect of any individual study, especially studies deviating from HWE, we pooled results and assessed the stability of the results. Sensitivity analysis was also carried out by deleting a single study each time to examine the influence of individual data sets on the pooled ORs. Publication bias of literature was examined using Begg's funnel plots and Egger's test [39]. An asymmetrical plot suggests possible publication bias and the p value of Egger's test less than 0.05 was considered the presence of potential publication bias [40].

# Results

#### Flow of included studies and characteristics of studies

Figure 1 is a flow diagram illustrating the strategy used to identify and select studies for inclusion in the meta-analysis. According to the PubMed and Cochrane database with associated key words, a total of 156 articles were retrieved and 2 studies from references were included. After excluding 2 duplicates, 156 articles were screened by titles and abstracts and 106 of them were excluded as review articles or irrelevant studies. Fifty studies appeared to satisfy our criteria and their full texts were evaluated. In further examination, we excluded 11 studies deviating from inclusion criteria. Finally, 39 studies, including 36 case-control studies, 2 prospective studies, and 1 study including both case-control and prospective groups, were eligible and included in our meta-analysis[6–9,28,30,31,33,41–71].

A summary of characteristics of each selected study, including first author, year of publication, ethnicity, genotype distribution, HWE, score of studies, and adjusted estimate (OR and 95% CI).

#### Overall meta-analysis and stratified analysis

We pooled overall and ethnic-specific ORs for allelic contrast with adjusted or calculated ORs, respectively, from the included studies to assess the association between rs13266634 variants and susceptibility to type 2 diabetes (Table 1 and Figure 2). A significant association was identified with adjusted ORs from all eligible studies in the overall population, Asian and European populations, but not in African population (Overall population: OR=1.147, 95% CI 1.114-1.181, p=0.000; Asian: OR=1.186, 95% CI 1.150-1.222, p=0.000; European: OR=1.100, 95% CI 1.049-1.153, p=0.000; African: OR=1.255, 95% CI 0.964-1.634, p=0.091) using the random-effects model from 55 data sets of 39 independent studies with 65 767 cases and 100 182 controls. Similar results were acquired using calculated ORs from 38 datasets of 24 studies with detailed genotype distribution under the fixed-effects model (overall population: OR=1.157, 95% CI 1.135-1.180, p=0.000; Asian: OR=1.165, 95% CI 1.132-1.198, p=0.000; European: OR=1.151, 95% CI 1.120-1.183, p=0.000; African: OR=1.111, 95% CI 0.908-1.360, p=0.305).

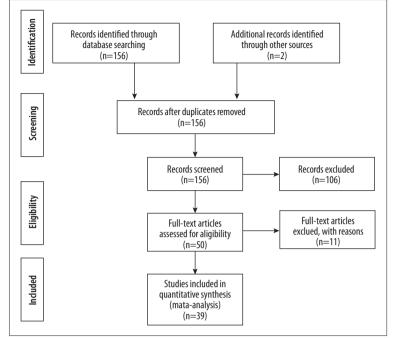


Figure 1. Flow diagram of study selection.

Then 38 data sets from 24 studies with detailed genotype distribution were analyzed employing different genetic models. The fixed-effects model was conducted in all genetic models except for overdominant model analysis, which showed significant heterogeneity (p < 0.1) The pooled analysis of all genetic models yielded significant overall association (CC+CT vs. TT: OR=1.216, 95% CI: 1.123-1.318, p=0.000; CC vs. CT+TT: OR=1.197, 95% CI: 1.165-1.229, p=0.000; CC+TT vs. CT: OR=1.086, 95% CI: 1.050-1.123, p=0.000; CC vs. TT: OR,=1.330, 95% CI: 1.274–1.388, p=0.000; CT vs. TT: OR,=1.136, 95% CI: 1.089-1.184, p=0.000; CC vs. CT: OR<sub>3</sub>=1.165, 95% CI: 1.132–1.198, p=0.000). When stratifying the data by ethnicity, we observed an increased risk among Asians in all except the overdominant model (CC+TT vs. CT, p=0.050). Significant associations were also found among Europeans. Not surprisingly, this polymorphism did not appear to influence risk of African population and type 2 diabetes in all genetic models (Table 1 and Figure 3).

According to the recommendation of Thakkinstian et al. [37], pairwise differences of  $OR_1$ ,  $OR_2$ , and  $OR_3$  were used to indicate the most appropriate genetic model ( $OR_1=OR_3\neq1,OR_2=1$ , recessive model;  $OR_1=OR_2\neq1$ ,  $OR_3=1$ , dominant model;  $OR_2=1,OR_3\neq1$ ,  $OR_1=1$ , overdominant model;  $OR_1>OR_2>1,OR_1>OR_3<1$  or  $OR_1<OR_2<1$ ,  $OR_1<OR_3<1$ , codominant model). The pooled OR1 for CC versus TT, OR2 for CT versus TT, OR3 for CC versus CT( $OR_1=1.330$ ,  $OR_2=1.136$ ,  $OR_3=1.165$ ) suggested that a codominant effect was most likely and that individuals with CC genotype had 33.0% and 16.5% higher risk of type 2 diabetes than those carrying TT and CT genotypes, respectively. We further carried out subgroup analysis under this genetic model

based on HWE, genotyping methods, sample size, study design and quality of studies (conducted by fixed-effects model). We observed increased risk of type 2 diabetes regardless of HWE, genotyping methods, and study design. In subgroup analysis stratified by ethnicity, we found that this polymorphism was associated with type 2 diabetes risk both in Asians and Europeans but not in Africans. In subgroup analysis stratified by sample size, we found increased risk in large sample sizes but not small sample sizes. In subgroup analysis stratified by quality of studies, however, fair quality subgroup in CC vs. CT comparison, unlike that in CC vs. TT comparison, indicated no significant association.

#### Test of heterogeneity and sensitivity analysis

In allelic comparison using adjusted ORs, there was heterogeneity across studies (P=0.000 and I<sup>2</sup>=62.0%); thus, a random-effects model was finally employed to obtain summary OR. The source of heterogeneity was further explored by subgroup analysis based on ethnicity, which indicated that studies of Europeans were mainly responsible for the overall heterogeneity; in allelic comparison using calculated ORs from raw data, there was no heterogeneity across the study (p=0.152 and I<sup>2</sup>=19.2%); thus, a fixed-effects model was finally employed to obtain summary OR. For comparisons using studies with raw genotype count, the fixed-effects model was conducted in all contrasts except overdominant model (CC+CT vs. TT: p=0.182, I<sup>2</sup>=17.1%; CC vs. CT+TT: p=0.120, I<sup>2</sup>=21.7%; CC vs. TT: p=0.369, l<sup>2</sup>=5.7%; CT vs. TT: p=0.126, l<sup>2</sup>=21.2%; CC vs. CT: p=0.122, l<sup>2</sup>=21.6%; CC+TT vs. CT: p=0.048, l<sup>2</sup>=29.4%) due to heterogeneity (Table 1).

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an (2010) uang (2010) n (2010) n (2010) n (2010) n (2010) n (2010) n (2010) u (2012) han (2012) han (2012) han (2012) han (2014) bitotal (I-squared=29.3%, p=0.078) Jropean axena (2007) tott (2008) tott (1-squared=72.6%, p=0.000) frican tienthorsdottir (2007) tottot (2012) tottot (1-squared=72.6%, p=0.000) frican tienthorsdottir (2007) tiraoui (2012) tottot (1-squared=72.6%, p=0.000) frican tienthorsdottir (2007) tottot (1-squared=72.6%, p=0.000) frican tienthorsdottir (2007) tottot (1-squared=72.6%, p=0.000) frican tienthorsdottir (2007) tottot (1-squared=72.6%, p=0.000) frican tienthorsdottir (2007) tottot (1-squared=72.6%, p=0.000) tottot (1-squared=72.6%, p=0.000) tottot (1-squared=72.6%, p=0.000) tottot (1-squared=72.6%, p=0.000) tottot (1-squared=72.6%, p=0.000) tottot (1-squared=72.6%, p=0.000) tottot (1-s	<sup>19</sup>	1.24 (1.17, 1.3
In (2010)       1.37 (1.20, 1.56)       Xu (2010)         In (2010)       1.20 (1.09, 1.32)       Iwata (2012)         Ivata (2012)       1.24 (1.08, 1.44)       Shan(2014)         Ivata (2012)       1.24 (1.08, 1.44)       Shan(2014)         Ivata (2012)       1.24 (1.08, 1.44)       Shan(2014)         Ivata (2012)       1.27 (1.08, 1.51)       Subtotal (1-sc         Ivata (2017)       1.07 (1.00, 1.16)       Scott (2007)         Ivata (2007)       1.07 (1.00, 1.16)       Steinthorsdo         Ivata (2007)       1.09 (0.99, 1.9)       Steinthorsdo         Ivata (2007)       1.12 (1.02, 1.23)       Steinthorsdo         Ivata (2007)       1.12 (1.02, 1.23)       Steinthorsdo         Ivata (2008)       1.12 (1.02, 1.23)       Zeggin (2007)         Ivata (2008)       0.76 (0.59, 0.97)       Zeggin (2007)		1.21 (1.06, 1.3
In (2010) (2010) (2010) (2010) (2010) (2010) (2012) (20	,	1.26 (1.01, 1.5
u (2010)       1.20 (1.09, 1.32)       Zheng (2012)         u (2010)       1.24 (1.08, 1.44)       Shan(2014)         ueng (2012)       1.48, 1.10, 2.01)       Subtotal (1-squared=29.3%, p=0.078)       1.19 (1.15, 1.22)         uropean       scott (2007)       1.07 (1.00, 1.16)       Scott (2007)         acta (2007)       1.07 (1.00, 1.16)       Steinthorsdotti (2007)       Scott (2007)         cott (2007)       1.07 (1.00, 1.16)       Steinthorsdotti (2007)       Steinthorsdotti (2007)         teinthorsdottir (2007)       1.19 (1.25, 1.38)       Steinthorsdotti (2007)       Steinthorsdotti (2007)         teinthorsdottir (2007)       1.11 (1.02, 1.29)       Steinthorsdotti (2007)       Steinthorsdotti (2007)         teinthorsdottir (2007)       1.10 (0.9, 1.33)       Steinthorsdotti (2007)       Steinthorsdotti (2007)         teinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)       Zeggini (2007)         teinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)       Zeggini (2007)         teinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)       Zeggini (2007)         teinthorsdottir (2007)       1.22 (1.08, 1.18)       Steinthorsdot       Zeggini (2007)         teinthorsdottir (2007)       1.22 (1.02, 1.33)       Zeggini (2007)       Zeggini (2007) <td></td> <td>1.48 (1.02, 2.1</td>		1.48 (1.02, 2.1
vara (2012)       1.24 (1.08, 1.44)       Shan(2014)         heng (2012)       0.88 (0.65, 1.9)       Subtotal (1-sc         han (2014)       1.27 (1.08, 1.51)       European         axcena (2007)       1.07 (1.00, 1.16)       Scott (2007)         cott (2007)       1.07 (1.00, 1.16)       Steinthorsdot         cott (2007)       1.14 (1.02, 1.29)       Steinthorsdot         cott (2007)       1.14 (1.02, 1.29)       Steinthorsdot         cott (2007)       1.19 (1.66, 1.38)       Steinthorsdot         ceinthorsdottir (2007)       0.94 (0.57, 1.17)       Steinthorsdot         teinthorsdottir (2007)       1.90 (0.99, 1.19)       Steinthorsdot         teinthorsdottir (2007)       1.90 (0.99, 1.19)       Steinthorsdot         teinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)         constein (2008)       0.76 (0.61, 0.94)       Zeggini (2007)         constein (2008)       0.76 (0.61, 0.94)       Zeggini (2007)         cachi/Meyre (2008)       0.76 (0.61, 0.94)       Zeggini (2007)		1.24 (1.07, 1.4
heng (2012)       0.88 (0.65, 1.19)       Subtotal (I-sci         heng (2012)       1.48, 1.10, 2.01)       Subtotal (I-sci         han (2014)       1.27 (1.08, 1.51)       European         axena (2007)       1.07 (1.00, 1.16)       Statut (2007)         cott (2007)       1.22 (1.08, 1.38)       Statek (2007)         cott (2007)       1.22 (1.08, 1.38)       Steinthorsdot         cott (2007)       1.22 (1.08, 1.38)       Steinthorsdot         cott (2007)       1.22 (1.08, 1.38)       Steinthorsdot         cott (2007)       1.14 (1.02, 1.29)       Steinthorsdot         cott (2007)       1.99 (0.99, 1.19)       Steinthorsdot         teinthorsdottir (2007)       1.99 (0.99, 1.19)       Steinthorsdot         teinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)         cottir (2007)       1.12 (1.04, 1.19)       Zeggini (2007)         cottir (2007)       1.12 (1.04, 1.19)       Zeggini (2000)         cathi/Weyre (2008)       0.76 (0.59, 0.97)       Zeggini (2000)         cathi/Weyre (2008)       0.77 (0.80, 1.18)       Cuachi/Meyre         cuachi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         cuachi/Meyre (2008)       0.99 (0.77, 1.27)       Cuachi/Meyre         cuachi/Meyre (2	<u> </u>	0.89 (0.67, 1.1
hen [2012]       1.48, 1.10, 2.01)       Jubular (FSC)         han (2014)       1.27 (1.08, 1.51)       European         juropean       Scott (2007)       Scott (2007)         act (2007)       1.07 (1.00, 1.16)       Scott (2007)         cott (2007)       1.22 (1.08, 1.38)       Sladek (2007)         cott (2007)       1.22 (1.08, 1.38)       Sladek (2007)         cott (2007)       1.22 (1.08, 1.38)       Steinthorsdo         ieinthorsdottir (2007)       1.9 (1.08, 1.31)       Steinthorsdo         ieinthorsdottir (2007)       1.9 (1.08, 1.31)       Steinthorsdo         ieinthorsdottir (2007)       1.9 (0.99, 1.19)       Steinthorsdo         ieinthorsdottir (2007)       1.9 (0.99, 1.19)       Steinthorsdo         ieinthorsdottir (2007)       1.10 (0.91, 1.33)       Steinthorsdo         ieinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)         ieinthorsdottir (2007)       1.12 (1.04, 1.19)       Zeggini (2007)         ieinthorsdottir (2007)       1.12 (1.04, 1.19)       Zeggini (2007)         ieinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)         ieinthorsdottir (2007)       1.22 (1.04, 1.19)       Zeggini (2007)         ieinthorsdottir (2008)       0.76 (0.59, 0.97)       Zeggini (2002)		1.00 (0.88, 1.1
han (2014) Jbtotal (I-squared=29.3%, p=0.078) Jropean axena (2007) cott (2008) cott (2008) cott (2008) cott (2008) cott (2008) cott (2008) cott (2008) cott (2007) cott (2007) cott (2008) cott (2008) cott (2008) cott (2007) cott (2007) cott (2008) cott (2008) cott (2008) cott (2007) cott (2007) cott (2008) cott (2008) cott (2007) cott (2007) cott (2008) cott (2008) cott (2008) cott (2007) cott (2007) cott (2007) cott (2008) cott (2008) cott (2008) cott (2007) cott (2007) cott (2007) cott (2008) cott (2008) cott (2008) cott (2007) cott (2007) cott (2007) cott (2007) cott (2008) cott (2008) cott (2007) cott (2007)	juared=19.7%, p=0.218)	1.16 (1.13, 1.2
Scott (2007) scort (2007) sott (2007) seinthorsdottir (2008) sachi/Meyre (2008) sachi/Meyre (2008) ssenko (2008) ntheek (2008) ssenko (2008) ntheek (2008) ssenko (2008) ssenko (2008) ssenko (2008) ssenko (2008) titierrez-Vida (2011) titraoui (2012) stottal (I-squared=72.6%, p=0.000) frican seinthorsdottir (2007) sachi/Meyre (2008) subtotal (I-squared=72.6%, p=0.000) frican seinthorsdottir (2007) subtotal (I-squared=72.6%, p=0.000) frican steinthorsdottir (2007) subtotal (I-squared=72.6%, p=0.000) frican subtotal (I-squared=72.6%, p=0.000) frican subtotal (I-squared=72.6%, p=0.000) frican subtotal (I-squared=72.6%, p=0.000) frican subtotal (I-squared=72.6%, p=0.000) frican subtotal (I-squared=72.6%, p=0.000) frican subtotal (I-squared=72.6%, p=0.000)		
Jropean       1.07 (1.00, 1.16)       Scott (2007)         axena (2007)       1.22 (1.08, 1.38)       Sladek (2007)         cott (2007)       1.14 (1.02, 1.29)       Steinthorsdo         adek (2007)       1.14 (1.02, 1.29)       Steinthorsdo         ieinthorsdottir (2007)       1.19 (1.08, 1.31)       Steinthorsdo         ieinthorsdottir (2007)       1.9 (0.99, 1.19)       Steinthorsdo         ieinthorsdottir (2007)       1.00 (0.99, 1.19)       Steinthorsdo         ieinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)         reggini (2007)       1.12 (1.04, 1.19)       Zeggini (2007)         romstein (2008)       1.14 (1.00, 1.30)       Zeggini (2007)         achi/Meyre (2008)       0.76 (0.59, 0.97)       Zeggini (200)         achi/Meyre (2008)       0.76 (0.51, 0.94)       Zeggini (200)         achi/Meyre (2008)       0.76 (0.51, 0.94)       Zeggini (200)         archi/Meyre (2008)       0.77 (0.61, 1.94)       Zeggini (200)         archi/Meyre (2008)       0.76 (0.51, 1.17)       Cuachi/Meyre         archi/Meyre (2008)       0.76 (0.51, 1.17)       Cuachi/Meyre         archi/Meyre (2008)       0.76 (0.51, 1.18)       Cuachi/Meyre         archi/Meyre (2008)       0.76 (0.51, 1.18)       Cuachi/Meyre <td></td> <td></td>		
axena (2007)       1.07 (1.00, 1.16)       Schul (2007)         cott (2007)       1.22 (1.08, 1.38)       Sladek (2007)         teinthorsdottir (2007)       1.14 (1.02, 1.29)       Steinthorsdo         teinthorsdottir (2007)       1.9 (1.08, 1.31)       Steinthorsdo         teinthorsdottir (2007)       1.9 (1.08, 1.31)       Steinthorsdo         teinthorsdottir (2007)       1.51 (1.25, 1.81)       Steinthorsdo         teinthorsdottir (2007)       1.51 (1.25, 1.81)       Steinthorsdo         teinthorsdottir (2007)       1.12 (1.00, 1.10)       Zeggini (2007)         teinthorsdottir (2007)       1.51 (1.25, 1.81)       Steinthorsdo         teinthorsdottir (2007)       1.12 (1.04, 1.23)       Zeggini (2007)         teinthorsdottir (2007)       1.12 (1.04, 1.33)       Steinthorsdo         teinthorsdottir (2007)       1.12 (1.04, 1.23)       Zeggini (2007)         teinthorsdottir (2007)       1.12 (1.04, 1.33)       Zeggini (2007)         tachi/Meyre (2008)       0.76 (0.61, 0.94)       Zeggini (2007)         tachi/Meyre (2008)       <		1.22 (1.09, 1.3
cost (2007)       1.14 (1.02, 1.29)       Steinthorsdot         adek (2007)       1.27 (1.16, 1.38)       Steinthorsdot         ieinthorsdottir (2007)       1.9 (1.08, 1.31)       Steinthorsdot         ieinthorsdottir (2007)       1.9 (1.08, 1.31)       Steinthorsdot         ieinthorsdottir (2007)       1.0 (0.99, 1.19)       Steinthorsdot         ieinthorsdottir (2007)       1.0 (0.91, 1.33)       Steinthorsdot         ieinthorsdottir (2007)       1.12 (1.02, 1.23)       Zeggini (2007)         reggini (2007)       1.12 (1.04, 1.19)       Zeggini (2007)         ronstein (2008)       0.76 (0.59, 0.97)       Zeggini (200         uachi/Meyre (2008)       0.76 (0.51, 0.94)       Zeggini (200         uachi/Meyre (2008)       0.77 (1.07, 1.27)       Cuachi/Meyre         uashence/(2008)       1.12 (1.01, 1.23)       uachi/Meyre         uathence/(2012)       1.10 (0.76, 1.31)       uachi/Meyre         utierrez-Vidal (2011)       1.22 (1.05, 1.41)       Guteirrez-Vida         utierrez-Vidal (2012)       1.37 (1.15, 1.62)       uachi		1.15 (1.02, 1.2
adek (2007)       1.27 (1.16, 1.38)       Steinthorsdottir (2007)         teinthorsdottir (2007)       1.9 (1.08, 1.31)       Steinthorsdottir (2007)         teinthorsdottir (2007)       0.94 (0.57, 1.17)       Steinthorsdottir (2007)         teinthorsdottir (2007)       1.51 (1.25, 1.81)       Steinthorsdottir (2007)         teinthorsdottir (2007)       1.10 (0.91, 1.33)       Steinthorsdot         ggini (2007)       1.12 (1.04, 1.19)       Zeggini (2007)         orostein (2008)       0.76 (0.59, 0.97)       Zeggini (2007)         uachi/Meyre (2008)       0.76 (0.59, 0.97)       Zeggini (2007)         uachi/Meyre (2008)       0.76 (0.61, 0.94)       Zeggini (2007)         uschi/Meyre (2008)       0.76 (0.61, 0.94)       Zeggini (2007)         uschi/Meyre (2008)       1.10 (1.03, 1.18)       Cuachi/Meyre         uschi/Meyre (2008)       1.10 (1.03, 1.18)       Cuachi/Meyre         uschi/Meyre (2008)       1.10 (1.05, 1.15)       van Hoek (2007)         uschi/Meyre (2008)       1.26 (0.88, 1.81)       Subtotal (1-soc)         uschi/Meyr		1.27 (1.16, 1.3
teinthorsdottir (2007) teinthorsdottir (2008) tachi/Meyre (2008) tachi/Meyre (2008) tachi/Meyre (2008) teinthorsdottir (2007) teinthorsdottir (2007) teinthorsdottir (2008) teinthorsdottir (2008) teinthorsdottir (2008) teinthorsdottir (2008) teinthorsdottir (2008) teinthorsdottir (2011) there-Vidal (2012) there-Vidal (2012) there-Vidal (2012) there-Vidal (2012) there-Vidal (2012) there-Vidal (2012) there-Vidal (2012) there-Vidal (2007) teinthorsdottir (2007) te	100 H	1.19 (1.09, 1.3
teinthorsdottir (2007)       1.09 (0.99, 1.19)       Steinthorsdo         teinthorsdottir (2007)       1.51 (1.25, 1.81)       Steinthorsdo         reggini (2007)       1.10 (0.91, 1.33)       Zeggini (2007)         reggini (2007)       1.12 (1.02, 1.23)       Zeggini (2007)         ronstein (2008)       1.14 (1.00, 1.30)       Zeggini (2000)         uachi/Meyre (2008)       0.76 (0.59, 0.97)       Zeggini (2000)         uachi/Meyre (2008)       0.76 (0.51, 0.94)       Zeggini (2000)         uachi/Meyre (2008)       0.77 (0.80, 1.18)       Cuachi/Meyre         uachi/Meyre (2008)       0.97 (0.80, 0.18)       Cuachi/Meyre         uschi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         uschi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         uschi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         uschi/Meyre (2008)       0.110 (1.03, 1.18)       Cuachi/Meyre         uschi/Meyre (2008)       1.12 (1.01, 1.23)       van Hoek (200         utierrez-Vidal (2011)       1.12 (1.01, 1.23)       van Hoek (200         utierrez-Vidal (2012)       1.37 (1.15, 1.62)       van Hoek (200         uschal (I-squared=72.6%, p=0.000)       1.10 (1.05, 1.15)       African         frican       steinthorsdo		0.94 (0.75, 1.1
teinthorsdottir (2007) teinthorsdottir (2007) teinthorsdottir (2007) teinthorsdottir (2007) teinthorsdottir (2007) teinthorsdottir (2008) uachi/Meyre (2008) utirerez-Vidal (2011) amboro-Melendez (2012) ttiraoui (2012) utirerez-Vidal (2011) amboro-Melendez (2012) ttiraoui (2012) ubtotal (I-squared=72.6%, p=0.000) frican teinthorsdottir (2007) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2008) ubtotal (I-squared=72.6%, p=0.000) frican teinthorsdottir (2007) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2008) ubtotal (I-squared=72.6%, p=0.000) frican teinthorsdottir (2007) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyr		1.09 (0.99, 1.1
teinthorsdottir (2007) ggini (2007) ggini (2007) ronstein (2008) uachi/Meyre (2008) usterrez-Vidal (2011) amboro-Melendez (2012) titraoui (2012) ubtotal (I-squared=72.6%, p=0.000) frican teinthorsdottir (2007) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2008) ubtotal (I-squared=72.6%, p=0.000) frican teinthorsdottir (2007) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2008) uachi/Meyre (2007) uachi/Meyre (2008) uachi/Meyre (2008		1.51 (1.25, 1.8
eggini (2007)       1.12 (1.02, 1.23)       Zeggini (200         ggini (2007)       1.12 (1.02, 1.23)       Zeggini (200         ornstein (2008)       1.14 (1.00, 1.30)       Zeggini (200         uachi/Meyre (2008)       0.76 (0.61, 0.94)       Zeggini (200         uachi/Meyre (2008)       0.76 (0.61, 0.94)       Zeggini (200         uachi/Meyre (2008)       0.76 (0.61, 0.94)       Zeggini (200         uachi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         uachi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         uachi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         uschi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         uschi/Meyre (2008)       1.10 (1.03, 1.18)       Cuachi/Meyre         viserez-Vidal (2011)       1.01 (0.76, 1.33)       van Hoek (200         amboro-Melendez (2012)       1.37 (1.15, 1.62)       van Hoek (200         uitraoui (2012)       1.37 (1.15, 1.62)       subtotal (I-so)         uachi/Meyre (2008)       1.26 (0.88, 1.81)       Subtotal (I-so)         wis (2008)       0.99 (0.77, 1.27)       Cuachi/Meyre         uachi/Meyre (2008)       1.26 (0.88, 1.81)       Subtotal (I-so)         uachi/Meyre (2008)       1.26 (0.88, 1.81)       Subtotal (I-so) <td></td> <td>1.10 (0.91, 1.3</td>		1.10 (0.91, 1.3
The second se		1.12 (1.02, 1.2
Jachi/Meyre (2008)       0.76 (0.59, 0.97)       Zegyini (200.700, 0.76)         Jachi/Meyre (2008)       0.76 (0.59, 0.97)       Zegyini (200.700, 0.76)         Jachi/Meyre (2008)       0.77 (0.80, 1.18)       Cuachi/Meyre         Jachi/Meyre (2008)       0.97 (0.80, 0.94)       Zeggini (200.700, 0.94)         Jachi/Meyre (2008)       0.97 (0.80, 0.94)       Cuachi/Meyre         Jachi/Meyre (2008)       0.97 (0.80, 0.94)       Cuachi/Meyre         Jachi/Meyre (2008)       1.17 (1.07, 1.27)       Cuachi/Meyre         Jierrez-Vidal (2011)       0.85 (0.66. (1.10)       Cuachi/Neare         Jutierrez-Vidal (2012)       1.01 (0.76, 1.33)       van Hoek (200         Jutierrez-Vidal (2012)       1.22 (1.05, 1.41)       Gutierrez-Vid         Jubotal (I-squared=72.6%, p=0.000)       1.10 (1.05, 1.15)       African         frican       1.26 (0.88, 1.81)       Subtotal (I-squared-regover)         Juachi/Meyre (2008)       0.99 (0.77, 1.27)       Cuachi/Meyre         Visi (2008)       1.26 (0.48, 1.81)       Subtotal (I-squared-regover)         Juachi/Meyre (2008)       1.26 (0.48, 4.89)       Subtotal (I-squared-regover)         Juachi/Meyre (2008)       1.26 (0.48, 4.89)       Subtotal (I-squared-regover)         Juachi/Meyre (2008)       1.59, 1.14, 2.01)       Subtotal (I-square		1.10 (1.00, 1.2
aachi/Meyre (2008)       0.97 (0.80, 1.18)       Cuachi/Meyre         uachi/Nead (2008)       0.91 (0.83, 0.99)       Cuachi/Meyre         pertel (2008)       0.91 (0.83, 0.99)       Cuachi/Meyre         yssenko (2008)       1.17 (1.07, 1.27)       Cuachi/Meyre         yssenko (2008)       0.85 (0.66. (1.10)       Cuachi/Meyre         n Hoek (2008)       1.12 (1.01, 1.23)       van Hoek (20         namboro-Melendez (2012)       1.12 (1.05, 1.41)       Gutierrez-Vida         titraoui (2012)       1.37 (1.15, 1.62)       Subtotal (I-so)         titraoui (2012)       1.37 (1.15, 1.62)       African         frican       1.26 (0.88, 1.81)       Cuachi/Meyre         wis (2008)       1.26 (0.48, 1.81)       Subtotal (I-so)         ywis (2008)       1.46 (0.43, 4.89)       Subtotal (I-so)         jachi/Meyre       1.59, 1.14, 2.01)       Subtotal (I-so)		1.17, 1.00, 1.3
Jachi/Nead (2008)       0.91 (0.83, 0.99)       Cuachi/Meyri         prtel (2008)       1.17 (1.07, 1.27)       Cuachi/Meyri         yssenko (2008)       1.10 (1.03, 1.18)       Cuachi/Meyri         yssenko (2008)       0.85 (0.66. (1.10)       Cuachi/Meyri         n Hoek (2008)       0.85 (0.66. (1.10)       Cuachi/Neadi         utierrez-Vidal (2011)       1.01 (0.76, 1.33)       van Hoek (2008)         amboro-Melendez (2012)       1.22 (1.05, 1.41)       Gutierrez-Vid         tiraoui (2012)       1.37 (1.15, 1.62)       Subtotal (I-so)         jbotal (I-squared=72.6%, p=0.000)       1.26 (0.88, 1.81)       Steinthorsdo         frican       1.26 (0.88, 1.81)       Cuachi/Meyri         wis (2008)       1.26 (0.48, 4.89)       Subtotal (I-so)         ywis (2008)       1.26 (0.48, 4.89)       Subtotal (I-so)         ywis (2008)       1.59, 1.14, 2.01)       Subtotal (I-so)		1.11 (0.99, 1.2
ertel (2008)       1.17 (1.07, 1.27)       Cuachi/Meyri         rssenko (2008)       1.10 (1.03, 1.18)       Cuachi/Meyri         rssenko (2008)       0.85 (0.66. (1.10)       Cuachi/Negri         ni Hoek (2008)       1.12 (1.01, 1.23)       van Hoek (20         amboro-Melendez (2012)       1.22 (1.05, 1.41)       Guterrez-Vid         tiraoui (2012)       1.37 (1.15, 1.62)       Subtotal (I-squared=72.6%, p=0.000)         frican       1.26 (0.88, 1.81)       Steinthorsdo         usici/Meyre (2008)       1.26 (0.88, 1.81)       Cuachi/Meyre         usici/Meyre (2008)       1.26 (0.88, 1.81)       Subtotal (I-squared=72.6%, p=0.000)         frican       1.26 (0.88, 1.81)       Steinthorsdo         usici/Meyre (2008)       1.46 (0.43, 4.89)       Subtotal (I-squared=72.6%, p=0.000)         frigi (2011)       1.59, 1.14, 2.01)       Subtotal (I-squared=72.6%, p=0.000)		1.13 (0.98, 1.2
rssenko (2008)       1.10 (1.03, 1.18)       Cuachi/Meyre         rssenko (2008)       0.85 (0.66. (1.10)       Cuachi/Nead         am Hoek (2008)       1.12 (1.01, 1.23)       van Hoek (20         itierrez-Vidal (2011)       1.01 (0.76, 1.33)       Gutierrez-Vida         amboro-Melendez (2012)       1.22 (1.05, 1.41)       Gutierrez-Vida         tiraoui (2012)       1.37 (1.15, 1.62)       Subtotal (I-so         jubotal (I-squared=72.6%, p=0.000)       1.26 (0.88, 1.81)       Steinthorsdo         frican       1.26 (0.88, 1.81)       Steinthorsdo         usici/Meyre (2008)       0.99 (0.77, 1.27)       Cuachi/Meyre         ywis (2008)       1.59, 1.14, 2.01)       Subtotal (I-so		1.23 (1.01, 1.4
an Hoek (2008) titierrez-Vidal (2011) amboro-Melendez (2012) tiraoui (2012) ibtotal (I-squared=72.6%, p=0.000) frican reinthorsdottir (2007) iachi/Meyre (2008) wan Hoek (20 1.22 (1.05, 1.41) 0.99 (0.84, 1.18) 1.37 (1.15, 1.62) 1.10 (1.05, 1.15) African Steinthorsdot 0.99 (0.77, 1.27) 1.46 (0.43, 4.89) 5ubtotal (I-squared=72.6%) 1.59 (1.15, 1.62) 1.10 (1.05, 1.15) African Steinthorsdot Cuachi/Meyre Subtotal (I-squared=72.6%) 1.46 (0.43, 4.89) 5ubtotal (I-squared=72.6%) 1.59, 1.14, 2.01)	2 (2008)	1.06 (0.86, 1.3
utierrez-Vidal (2011)       1.01 (0.76, 1.33)       Vali Hoek (20 and the constraint)         amboro-Melendez (2012)       1.22 (1.05, 1.41)       Gutierrez-Vidal (2012)         tiraoui (2012)       1.37 (1.15, 1.62)       Subtotal (I-squared=72.6%, p=0.000)         irican       1.26 (0.88, 1.81)       African         seinthorsdottir (2007)       1.26 (0.88, 1.81)       Steinthorsdo         uachi/Meyre (2008)       1.46 (0.43, 4.89)       Subtotal (I-squared=72.6%)         yis (2008)       1.59, 1.14, 2.01)       Subtotal (I-squared=72.6%)	(2008)	1.13 (1.04, 1.2
amboro-Melendez (2012) tiraoui (2012) ubtotal (I-squared=72.6%, p=0.000) frican einthorsdottir (2007) uachi/Meyre (2008) taig (2011) 1.22 (1.05, 1.41) 0.99 (0.84, 1.18) 1.37 (1.15, 1.62) 1.10 (1.05, 1.5) 1.26 (0.88, 1.81) 0.99 (0.77, 1.27) L46 (0.43, 4.89) 1.59, 1.14, 2.01) Subtotal (I-squared=72.6%) 1.20 (1.05, 1.41) Subtotal (I-squared=72.6%) 1.20 (0.84, 1.18) Subtotal (I-squared=72.6%) 1.20 (0.84, 1.18) Subtotal (I-squared=72.6%) 1.20 (0.84, 1.18) Subtotal (I-squared=72.6%) 1.26 (0.88, 1.81) Steinthorsdo Subtotal (I-squared=72.6%) Subtotal (I-squared=72.	08)	1.12 (1.02, 1.2
titraoui (2012) ubtotal (I-squared=72.6%, p=0.000) frican teinthorsdottir (2007) uachi/Meyre (2008) wis (2008) frigi (2011) teinthorsdottir (2007) uachi/Meyre (2008) tigi (2011)	al (2011)	1.05, 0.82, 1.3
ubtotal (I-squared=72.6%, p=0.000) frican teinthorsdottir (2007) uachi/Meyre (2008) ewis (2008) ifagi (2011) 1.10 (1.05, 1.15) 1.26 (0.88, 1.81) 0.99 (0.77, 1.27) 1.46 (0.43, 4.89) 1.59, 1.14, 2.01) Subtotal (I-so	quared=25.1%, p=0.160)	1.15 (1.12, 1.1
frican teinthorsdottir (2007) Jachi/Meyre (2008) wis (2008) ifagi (2011)		
teinthorsdottir (2007) uachi/Meyre (2008) ewis (2008) ifagi (2011)		
uachi/Meyre (2008) ewis (2008) ifagi (2011) 0.99 (0.77, 1.27) Cuachi/Meyre 1.46 (0.43, 4.89) Subtotal (I-so	ttir (2007)	1.33 (0.93, 1.9
ewis (2008) ifagi (2011) 1.46 (0.43, 4.89) 1.59, 1.14, 2.01) Subtotal (I-so		1.02 (0.80, 1.3
ifagi (2011) 1.59, 1.14, 2.01)	guared=29.0%, p=0.235)	1.11 (0.91, 1.3
		(, 115
ubtotal (I-squared=51.1%, p=0.105) 1.26 (0.96, 1.63) verall (I-squared=62.0%, p=0.000) 1.15 (1.11, 1.18) Overall (I-squ	lared=19.2%, p=0.152)	1.16 (1.13, 1.1
veran (1-3quareu-02.070, μ-0.000)   φ 1.13 (1.11, 1.18) Ονεταπ (1-3qu	(100 15.270, p=0.152)	
ote: Weights are from random effects analysis		

Figure 2. Stratified analysis based on ethnicity for the association between SLC30A8 polymorphism rs13266634 and type 2 diabetes risk under allelic model. (A) Using individual adjusted ORs from all original articles, (B) using individual calculated ORs from studies with detailed genotype distribution. Each study is shown by the point estimate of the odds ratio, and a horizontal line denotes the 95% confidence interval. The pooled odds ratio is represented by a diamond. The area of the grey squares reflects the weight of the study in the meta-analysis.

 Table 1. Meta-analysis of the association between rs13266634 variant and susceptibility to type 2 diabetes (all conducted under fixedeffects model except those marked with an asterisk).

Genetic contrasts	Ethnia anoun	Data este (r)	n) OR (95% CI)		Heterogeneity test	
	Ethnic group	nnic group Data sets (n)		Р	l² (%)	P (Q)
C vs. T(ajusted ORs)*	Overall	55	1.147 (1.114–1.181)	0.000	62.0	0.000
	Asian	27	1.186 (1.150–1.222)	0.000	29.3	0.078
	European	24	1.100 (1.049–1.153)	0.000	72.6	0.000
	African	4	1.255 (0.964–1.634)	0.091	51.1	0.105
C vs. T (calculated ORs)	Overall	38	1.157 (1.135–1.180)	0.000	19.2	0.152
	Asian	18	1.165 (1.132–1.198)	0.000	19.7	0.218
	European	18	1.151 (1.120–1.183)	0.000	25.1	0.160
	African	2	1.111 (0.908–1.360)	0.305	29.0	0.235
CC + CT vs. TT	Overall	38	1.216 (1.123–1.318)	0.000	17.1	0.182
	Asian	18	1.221 (1.160–1.286)	0.000	47.5	0.014
	European	18	1.221 (1.149–1.298)	0.000	0.0	0.793
	African	2	1.207 (0.575–2.533)	0.618	0.0	0.730
CC vs. CT + TT	Overall	38	1.197 (1.165–1.229)	0.000	21.7	0.120
	Asian	18	1.215 (1.167–1.266)	0.000	9.9	0.336
	European	18	1.185 (1.143–1.228)	0.000	34.2	0.078
	African	2	1.118 (0.895–1.397)	0.326	23.1	0.254
CC + TT vs. CT*	Overall	38	1.086 (1.050–1.123)	0.000	29.4	0.048
	Asian	18	1.056 (1.000–1.116)	0.050	38.3	0.050
	European	18	1.108 (1.062–1.156)	0.000	21.7	0.196
	African	2	1.112 (0.855–1.446)	0.428	21.4	0.259
CC vs. TT(OR1)	Overall	38	1.330 (1.274–1.388)	0.000	5.7	0.369
	Asian	18	1.346 (1.270–1.426)	0.000	31.0	0.103
	European	18	1.312 (1.230–1.398)	0.000	0.0	0.665
	African	2	1.213 (0.577–2.552)	0.611	0.0	0.718
CT vs. TT(OR2)	Overall	38	1.136 (1.089–1.184)	0.000	21.2	0.126
	Asian	18	1.141 (1.080–1.206)	0.004	51.5	0.005
	European	18	1.128 (1.058–1.203)	0.000	0.0	0.853
	African	2	1.144 (0.532–2.459)	0.731	0.0	0.938
CC vs. CT(OR3)	Overall	38	1.165 (1.132–1.198)	0.000	21.6	0.122
	Asian	18	1.176 (1.126–1.228)	0.000	17.7	0.242
	European	18	1.155 (1.115–1.202)	0.000	31.4	0.100
	African	2	1.109 (0.882–1.394)	0.377	19.5	0.265

Α		В	
Study ID	OR (95% CI)	Study ID	Study ID
Asian Horikoski (2007) Steinthorsdottir (2007) Furukawa (2008) Horikawa (2008) Lee (2008) Omori (2008) Sanghera (2008) Rong (2009) Tabara (2009) Tabara (2009) Tabara (2009) Takeuchi (2009) Takeuchi (2009) Han (2010) Huang (2010) Xu (2012) Zheng (2012)	1.29 (0.99, 1.69) 1.39 (1.10, 1.76) 1.27 (0.82, 1.97) 1.29 (1.07, 1.57) 1.63 (1.18, 2.26) 1.23 (1.07, 1.42) 1.33 (1.05, 1.68) 0.85 (0.51, 1.43) 0.74 (0.37, 1.51) 1.34 (0.90, 1.98) 1.48 (1.20, 1.82) 1.54 (1.36, 1.74) 1.54 (1.36, 1.74) 1.54 (1.00, 2.35) 1.81 (0.87, 3.77) 1.47 (1.11, 1.95) 0.79 (0.43, 1.43)	Asian Horikoski (2007) Steinthorsdottir (2007) Furukawa (2008) Lee (2008) Ng (2008) Omori (2008) Sanghera (2008) Rong (2009) Takeuchi (2009) Takeuchi (2009) Han (2010) Huang (2010) Xu (2010) Iwata (2012) Zheng (2014)	1.15 (0.93, 1.42) 1.30 (1.07, 1.57) 1.02 (0.74, 1.40) 1.19 (1.02, 1.38) 1.12 (0.88, 1.43) 1.22 (1.09, 1.35) 1.13 (0.96, 1.34) 1.07 (0.80, 1.42) 1.13 (0.93, 1.37) 0.88 (0.66, 1.19) 1.02, 0.87, 1.19) 1.25 (1.14, 1.36) 1.26 (1.04, 1.53) 0.92 (0.63, 1.36) 2.31 (1.32, 4.05) 1.16 (0.92, 1.46) 0.90 (0.56, 1.45) 1.73 (1.01, 1.60)
Shan (2014) Subtotal (I-squared=31.0%, p=0.103)	1.00 (0.79, 1.27) 1.35 (1.27, 1.43)	Shan(2014) Subtotal (I-squared=17.7%, p=0.242)	1.27 (1.01, 1.60) 1.18 (1.13, 1.23)
European Scott (2007) Scott (2007) Sladek (2007) Steinthorsdottir (2007) Steinthorsdottir (2007) Steinthorsdottir (2007) Steinthorsdottir (2007) Zeggini (2008) Guterrez-Vidal (2011) Subtal (I-squared=0.0%, p=0.665)	$\begin{array}{c} 1.36 \ (1.06, 1.76) \\ 1.29 \ (1.01, 1.65) \\ 1.53 \ (1.24, 1.87) \\ 1.44 \ (1.18, 1.76) \\ 0.79 \ (0.49, 1.25) \\ 1.26 \ (1.02, 1.55) \\ 1.29 \ (1.20, 2.96) \\ 1.21 \ (0.76, 1.92) \\ 1.35 \ (1.07, 1.70) \\ 1.15 \ (0.91, 1.46) \\ 1.48 \ (1.02, 2.15) \\ 1.27 \ (0.96, 1.67) \\ 1.18 \ (0.88, 1.59) \\ 1.50 \ (0.94, 2.39) \\ 1.22 \ (1.01, 1.46) \\ 1.21 \ (1.03, 1.68) \\ 1.24 \ (0.65, 2.36) \\ 1.31 \ (1.23, 1.40) \end{array}$	European Scott (2007) Scott (2007) Sladek (2007) Steinthorsdottir (2007) Steinthorsdottir (2007) Steinthorsdottir (2007) Steinthorsdottir (2007) Steinthorsdottir (2007) Zeggini (2008) Guachi/Meyre (2008) Guachi/Meyre (2008) Gutierrez-Vidal (2011) Subtotal (I-squared=31.4%, p=0.100)	$\begin{array}{c} 1.39 \ (1.16, 1.65) \\ 1.17 \ (0.98, 1.39) \\ 1.29 \ (1.16, 1.45) \\ 1.16 \ (1.02, 1.31) \\ 1.09 \ (0.79, 1.49) \\ 1.02 \ (0.90, 1.16) \\ 1.67 \ (1.30, 2.15) \\ 1.09 \ (0.84, 1.41) \\ 1.07 \ (0.94, 1.21) \\ 1.14 \ (1.00, 1.30) \\ 1.11 \ (0.90, 1.36) \\ 1.09 \ (0.93, 1.29) \\ 1.24 \ (1.00, 55, 1.58) \\ 1.23 \ (0.95, 1.58) \\ 1.06 \ (0.82, 1.38) \\ 1.16 \ (1.04, 1.28) \\ 1.00 \ (0.71, 1.39) \\ 1.16 \ (1.12, 1.20) \\ \end{array}$
African Steinthorsdottir (2007) Cuachi/Meyre (2008) Subtotal (I-squared=0.0%, p=0.718)	1.60 (0.29, 8.77) 1.13 (0.49, 2.60) 1.21 (0.58, 2.55)	African Steinthorsdottir (2007) Cuachi/Meyre (2008) Subtotal (I-squared=19.5%, p=0.265)	1.32 (0.90, 1.93) 1.00 (0.75, 1.34) 1.11 (0.88, 1.39)
Overall (I-squared=5.7%, p=0.369)	1.33 (1.27, 1.39)	Overall (I-squared=21.6%, p=0.122)	1.16 (1.13, 1.20)
.5 11.33 2		.247 1	4.05

**Figure 3.** Stratified analysis based on ethnicity for the association between SLC30A8 polymorphism rs13266634 and type 2 diabetes risk under codominant genetic model. (A) CC vs. TT, (B) CC vs. CT. Each study is shown by the point estimate of the odds ratio, and a horizontal line denotes the 95% confidence interval. The pooled odds ratio is represented by a diamond. The area of the grey squares reflects the weight of the study in the meta-analysis.

To evaluate the effect of each individual study, especially studies deviating from HWE, on the pooled estimate, we performed a sensitivity analysis by deleting 1 study each time in turn. It showed that all the results hardly changed after sequential removal of each study from the total analysis, indicating the robustness of these results (data not shown). We also observed that the significance of the overall data for the different genetic models was not statistically altered under either random- or fixed-effects models.

#### **Cumulative meta-analysis**

Cumulative meta-analysis was also performed in allelic contrast with adjusted and calculated ORs by gradually including each additional study according to published year. The pooled genetic risk effect of both adjusted and calculated allelic contrasts remained significant in the entire period studied and the 95% CI for pooled ORs became progressively narrower after adding 1 more study, indicating that the precision of our estimation was gradually improved after adding more studies (Figure 4).

A Study ID		OR (95% CI)	B Study ID		Study ID
Horikoski (2007)		1.19 (0.69, 2.06)	Horikoski (2007)	<b></b>	1.15 (1.00, 1.32)
Saxena (2007)		1.09 (0.85, 1.41)	Scott (2007)		1.19 (1.09, 1.30)
Scott (2007) Scott (2007)	<b>—</b>	1.12 (0.90, 1.40) 1.13 (0.92, 1.37)	Scott (2007)		1.17 (1.09, 1.26)
Sladek (2007)	<b>—</b> •	1.16 (0.92, 1.37)	Sladek (2007)		1.21 (1.15, 1.28)
Steinthorsdottir (2007)		1.17 (1.00, 1.36)	Steinthorsdottir (2007)		
Steinthorsdottir (2007)	<b>—</b>	1.16 (1.00, 1.36)	( )	-	1.21 (1.15, 1.26)
Steinthorsdottir (2007) Steinthorsdottir (2007)	<b></b>	1.15 (1.00, 1.33) 1.16 (1.01, 1.34)	Steinthorsdottir (2007)	<b>+</b>	1.19 (1.14, 1.25)
Steinthorsdottir (2007)	<b>—</b> •	1.16 (1.01, 1.34)	Steinthorsdottir (2007)	+	1.17 (1.13, 1.22)
Steinthorsdottir (2007)		1.16 (1.02, 1.33)	Steinthorsdottir (2007)	<b>  +</b>	1.19 (1.14, 1.23)
Steinthorsdottir (2007)	<b>—</b>	1.16, 1.02, 1.33)	Steinthorsdottir (2007)	<b>↔</b>	1.18 (1.14, 1.23)
Zeggini (2007) Zeggini (2007)	<b></b>	1.16 (1.03, 1.31) 1.15 (1.03, 1.29)	Steinthorsdottir (2007)	•	1.18 (1.14, 1.23)
Bronstein (2008)		1.15 (1.03, 1.29)	Steinthorsdottir (2007)	•	1.18 (1.14, 1.23)
Cuachi/Meyre (2008)		1.15 (1.03, 1.27)	Zeggini (2007)		1.18 (1.14, 1.23)
Cuachi/Meyre (2008)	<b>–</b>	1.14 (1.02, 1.27)	Zeggini (2007)		1.17 (1.13, 1.21)
Cuachi/Meyre (2008) Cuachi/Meyre (2008)	<b>-</b>	1.13 (1.02, 1.26) 1.13 (1.02, 1.26)	55		
Cuachi/Nead (2008)		1.11 (1.01, 1.23)	Zeggini (2007)	•	1.17 (1.13, 1.21)
Furukawa (2008)	<b>—</b>	1.11 (1.01, 1.23)	Zeggini (2007)	<b>+</b>	1.16 (1.13, 1.20)
Hertel (2008)	-0-	1.12 (1.01, 1.23)	Cuachi/Meyre (2008)	•	1.16 (1.13, 1.20)
Horikawa (2008) Lee (2008)		1.12 (1.02, 1.23) 1.12 (1.02, 1.23)	Cuachi/Meyre (2008)	<b>+</b>	1.16 (1.13, 1.20)
Lewis (2008)	<b>T</b>	1.12 (1.02, 1.23)	Cuachi/Meyre (2008)	<b>e</b>	1.16 (1.13, 1.20)
Lyssenko (2008)	- <b>ē</b> -	1.12 (1.03, 1.22)	Cuachi/Meyre (2008)	•	1.16 (1.13, 1.19)
Lyssenko (2008)		1.12 (1.02, 1.21)	Cuachi/Nead (2008)	•	1.16 (1.12, 1.19)
Ng (2008) Omori (2008)		1.12 (1.03, 1.21) 1.12 (1.03, 1.21)	Furukawa (2008)		1.15 (1.12, 1.19)
Sanghera (2008)	-	1.12 (1.03, 1.21)	Horikawa (2008)		1.15 (1.12, 1.18)
van Hoek (2008)	- <b>e</b> -	1.12 (1.03, 1.21)			
Wu (2008)		1.12 (1.03, 1.21)	Lee (2008)		1.16 (1.13, 1.19)
Xiang (2008) Hu (2009)		1.12 (1.04, 1.21) 1.12 (1.04, 1.21)	Ng (2008)	•	1.15 (1.13, 1.18)
Rong (2009)	- <b>ē</b> -	1.12 (1.04, 1.21)	Omori (2008)	•	1.15 (1.13, 1.18)
Tabara (2009)	- <del>•</del>	1.12 (1.04, 1.21)	Sanghera (2008)	<b>e</b>	1.15 (1.12, 1.18)
Takeuchi (2009)		1.13 (1.05, 1.21)	van Hoek (2008)	•	1.15 (1.12, 1.18)
Chauhan (2010) Chauhan (2010)	-	1.14 (1.06, 1.22) 1.14 (1.06, 1.22)	Rong (2009)		1.15 (1.12, 1.17)
Han (2010)	- <del>•</del>	1.14 (1.06, 1.22)	Tabara (2009)		1.15 (1.12, 1.17)
Huang (2010)		1.14 (1.07, 1.22)	Takeuchi (2009)		1.15 (1.12, 1.17)
Lin (2010) Tan (2010)	T T	1.14 (1.07, 1.22)	Takeuchi (2009)		1.16 (1.14, 1.18)
Xu (2010)	-	1.15 (1.07, 1.23) 1.14 (1.07, 1.22)			
Xu (2010)	<b>  ⊕</b>	1.14 (1.07, 1.22)	Han (2010)		1.16 (1.14, 1.18)
Gutierrez-Vidal (2011)	1	1.14 (1.07, 1.22)	Huang (2010)		1.16 (1.14, 1.18)
Kifagi (2011) Gaboa-Melendez (2012)	l <b>∓</b>	1.14 (1.07, 1.22) 1.14 (1.07, 1.22)	Xu (2010)	•	1.16 (1.14, 1.19)
lwata (2012)	╺┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿┿	1.14 (1.07, 1.22)	Gutierrez-Vidal (2011)	•	1.16 (1.14, 1.18)
Mitraoui (2012)		1.15 (1.08, 1.22)	lwata (2012)	•	1.16 (1.14, 1.19)
Mitraoui (2012)	-	1.14 (1.07, 1.22)	Zheng (2012)	<b>e</b>	1.16 (1.14, 1.18)
Zheng (2012) Chen (2013)	- <b>•</b> -	1.15 (1.08, 1.22) 1.14 (1.08, 1.22)	Shan (2014)	•	1.16 (1.13, 1.18)
Shan (2014)	•	1.14 (1.08, 1.22)	2011	-	
I .5	1 1.15	2		1 1.16	2

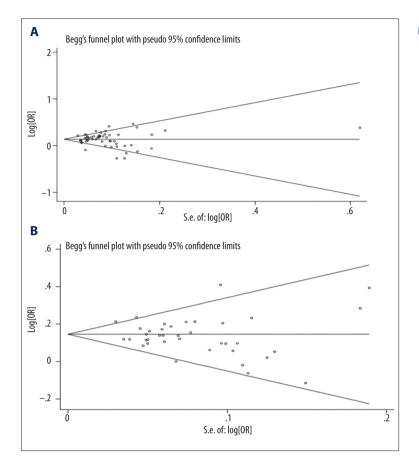
Figure 4. Cumulative meta-analysis of associations between the rs13266634 variant of SLC30A8 with type 2 diabetes risk in allelic contrasts sorted by publication year. The horizontal line shows the accumulation of estimates as each study was added, and is not the estimate of a single study. (A) Using individual adjusted ORs from all original articles, (B) using individual calculated ORs from studies with detailed genotype distribution.

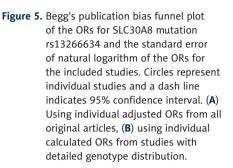
# **Publication bias**

Funnel plot and Egger's test were performed to assess the publication bias of included studies. As shown in Figure 5, the shapes of the Begg's funnel plot did not reveal any evidence of obvious asymmetry in both stages. Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not show any evidence of publication bias (p=0.496/0.249, respectively).

# Discussion

So far, 3 previous meta-analysis have been conducted to explore the function of SLC30A8 gene polymorphisms in type 2





diabetes [72-74]. One of them pooled allelic ORs but provided no details about selecting criteria, another also conducted allelic contrast with adjusted individual OR, and the last one carried out contrasts under different genetic models with calculated individual OR. Although all 3 articles indicated increased risk of type 2 diabetes with polymorphism rs13266634, they employed either adjusted or calculated individual OR only rather than both, and did not conclude which was the appropriate genetic model. Additionally, considering several new original studies on this variant, we therefore decided to perform this updated meta-analysis, with more samples (including 38 studies, involving 65 767 type 2 diabetes patients and 100 182 controls) and more comprehensive comparisons (using both adjusted and calculated individual OR, under most likely and overall genetic models), to elucidate the relationship between rs13266634 variant and type 2 diabetes. The summary results from adjusted ORs demonstrated that C allele carriers of rs13266634 are strongly associated with type 2 diabetes risk in the total population. Subgroup analysis by ethnicity showed the same result in Asian and European populations but not in African populations. Furthermore, metaanalysis with calculated raw ORs generated similar results in overall and ethnic populations under different s models. Finally, we decided on the most likely genetic model, the codominant model, and performed subgroup analysis based on HWE, genotyping methods, sample size, study design, and quality of studies, and observed increased risk of type 2 diabetes in all populations except Africans, small sample size subgroups, and fair subgroup in CC vs. CT comparison. Hence, the result of subgroup analysis also confirmed the association between polymorphism rs13266634 and risk of type 2 diabetes. This differences in ethnicity may be due to the different genetic backgrounds of and limited articles on the African population. The difference in sample size subgroup is reasonable and indicates the importance of sample size in research. The difference in study quality subgroup between CC vs. TT and CC vs. CT contrasts may result from gene additive effect besides quality itself. Cumulative meta-analysis indicated a consistent and more precise estimation as evidence from published studies accumulated according to year published.

To date, 5 genome-wide association studies (GWAS) involving type 2 diabetes and SLC30A8 polymorphism rs13266634 have been published [6-9, 64], which were all included in this metaanalysis. Four of them reported that this common variant is also associated with the risk of type 2 diabetes in Europeans (combined OR=1.12 and 95% CI=1.07–1.16), although data from 1 study were less compelling (p=0.90 in the genome scan and p=0.01 in replication samples) [9]. One replication in Asians also showed similar results as in Europeans (OR=1.16 and 95% CI=1.05-1.27). Therefore, results from GWAS were consistent with that of our meta-analysis, which indicated that SLC30A8 polymorphism rs13266634 confers risk of type 2 diabetes.

Potential mechanisms whereby rs13266634 variant of ZnT8 may modulate insulin biophysiological activities and plasma glucose metabolism have been extensively studied. There are several possible explanations for the association between type 2 diabetes risk and rs13266634. Firstly, given the significant role of ZnT8 in insulin activities, this mutation may affect the basal function of ZnT8 and subsequent insulin synthesis. Zinc is essential for the correct processing, storage, secretion, and action of insulin in pancreatic  $\beta$  cells [75–77]. The W325 variant displayed higher zinc transport activity than R325 ZnT8 in a murine  $\beta$ -cell line[78] and protective effect against cyclosporin A-induced suppression of insulin secretion [79]. Similarly, studies also demonstrated that this polymorphism is strongly associated with abnormal insulin behaviors in humans, including decreased insulin secretion response to glucose stimulations, lower fasting insulin levels, reduced disposition index, and decreased proinsulin-to-insulin conversion [56,80-82]. Controversially, the risk C-allele does not affect ex-vivo insulin secretion and SLC30A8 expression in isolated human islets [74]. Secondly, this mutation may regulate plasma insulin concentration via decreasing hepatic insulin clearance. A recent study revealed that humans carrying rs13266634 exhibited increased insulin clearance, as assessed by c-peptide/ insulin ratio, and mice with beta cell-specific SLC30A8 knockout demonstrated the similar results; thus, we speculate that the rs13266634 variant may result in the same consequence [83]. The studies cited above suggest that rs13266634 variant can modulate plasma glucose homeostasis via full-scale insulin activities from synthesis to clearance [56,80-82].

Several strengths of this meta-analysis could be listed. First of all, we followed a rigorous protocol of meta-analysis [34] and meta-analysis of genetic association studies [37]. We performed subgroup analysis, HWE test, sensitivity analysis, and funnel plots to explore the source of heterogeneity, indicating the reliability of our study. Next, we included more original studies and more samples than previous studies to enhance

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the statistical power of the study. Moreover, we used adjusted and calculated ORs to summarize estimate and raw genotype count, respectively, analyzed under different genetic models with the codominant model deemed to be most likely. All previous meta-analyses used either adjusted or calculated ORs and did not specify a most likely genetic model. Lastly, we conducted cumulative meta-analysis to investigate the dynamic change trend of the research results and the potential impact of small samples on estimate effect size. The small sample sizes without cumulative analyses may have influenced the strength of results of previous studies.

Unavoidable limitations of this meta-analysis should also be pointed out. The first limitation comes from multiple and diverse methods for SNP detection in different studies. The second limitation is that type 2 diabetes is a complex and multifactorial disorder and potential interactions among gene-gene and gene-environment should be considered; however, insufficient information, including nutrient, lifestyle behavior, and demographic details, hinder us from performing further adjusted analysis. The third limitation is that although we tried our best to contact the corresponding authors of published articles, we could not get information on gain genotypes data of all studies. The final limitation is that studies of Africans and prospective research were limited; thus, the interpretation of results should be cautious.

# Conclusions

The present meta-analysis suggests that SLC30A8 gene polymorphism rs13266634 may be an important genetic factor in the risk for developing type 2 diabetes among Asian and European populations but not African populations. Mechanism studies are needed to explain and support this finding in various ethnic groups.

# Disclosure

No competing financial interests exist.

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