Int J Clin Exp Med 2019;12(1):86-97
www.ijcem.com /ISSN:1940-5901/IJCEM0062721

Review Article

Association between interleukin-6 rs1800795 polymorphism and the decreased risk of type 2 diabetes mellitus: an updated meta-analysis

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Received May 24, 2017; Accepted March 1, 2018; Epub January 15, 2019; Published January 30, 2019

Abstract: It has been reported that the single nucleotide polymorphism (SNP) rs1800795 in interleukin-6 (IL-6) gene is associated with the susceptibility to type 2 diabetes mellitus (T2DM). However, the conclusions in several recent reports remained controversial. Herein, we performed this meta-analysis to investigate the relationship of rs1800795 and T2DM risk. A systematic search of relevant literatures was conducted through the databases of PubMed, Embase, and CBMdisc up to December 2016. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association between rs1800795 and T2DM risk in four genetic models. Twelve case-control studies were included in the final meta-analysis. Overall, our results showed that rs1800795 was associated with the decreased risk of T2DM in allelic and recessive models, but not dominant or addictive models. No obvious published bias was found in any models for the SNP. In conclusion, the current meta-analysis demonstrated that the SNP of IL-6 gene was correlated with the decreased risk of T2DM. However, studies including a larger number of subjects with more detailed individual information are needed for further validation of our conclusion.

Keywords: Interleukin-6, rs1800795, polymorphism, Type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is a common noncommunicable disease and results in significant morbidity and mortality all around the world [1]. Type 2 diabetes mellitus (T2DM), as the main type of DM, is a heterogeneous metabolic disease caused by the combination of lifestyle and genetic factors [2, 3]. It is estimated that more than 200 million people worldwide suffer from T2DM. And it is scheduled to double in the following generation [4]. Previous studies have demonstrated that chronic low grade systemic inflammation is correlated with the increased risk of impaired glucose tolerance and T2DM [5]. Subsequently, it is proved that the chronic activation of immune system, companied with the high number of white cell, resulted in the decreased insulin sensitivity and the development of T2DM [6].

Interleukin-6 (IL-6), a classic inflammation factor, plays a prominent role in inflammatory response. It has been demonstrated that IL-6 contributes to insulin-resistant state and T2DM [7]. During the process, both protective and pathogenic roles of IL-6 in T2DM are discussed [8, 9]. A previous study indicated that the high IL-6 concentration in plasma could predict the progress of T2DM [10]. More than that, a plenty of genetic, epidemiological, human, and rodent studies have investigated the potential role of IL-6 in the pathogenesis of T2DM. Among them, genetic susceptibility attracts increasing attention.

The IL-6 gene is located at chromosome 7p21. The gene including seven exons covers approximately 12.8 kb of genomic DNA [11]. The single nucleotide polymorphism (SNP) rs1800795, also named -174 G>C in the promoter region of

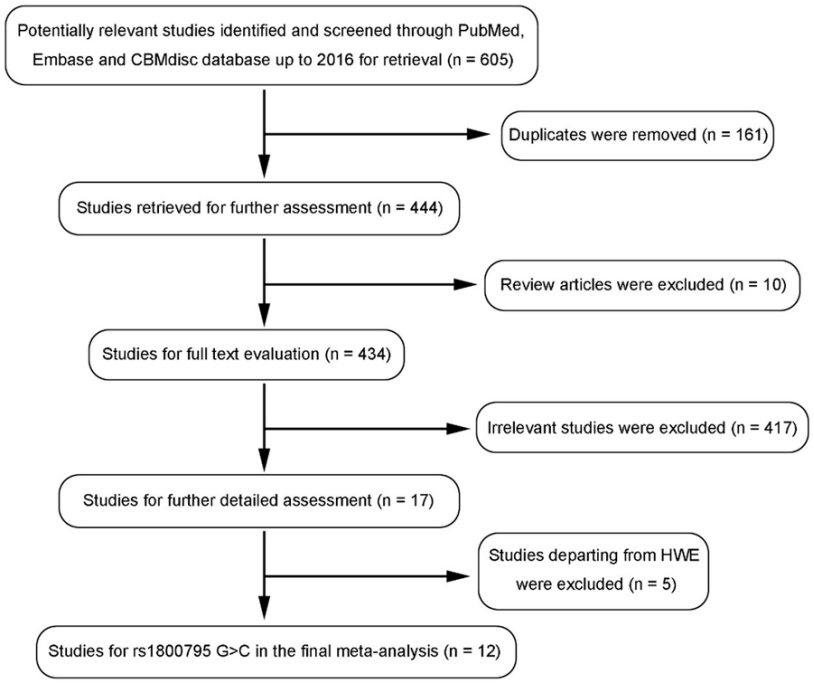

Figure 1. Flow diagram of study search and selection in the current meta-analysis for the association between IL-6 rs1800795 polymorphism and type 2 diabetes mellitus susceptibility.

IL-6 gene, could modulate IL-6 expression [12]. Contrary to the C allele, the pro-inflammatory G allele is the main cause for the elevated plasma levels of IL-6 in healthy subjects [12]. These prior studies imply that the genetic variation in IL-6 would lead to metabolic and cytokine modulation. And these changes may be the main contributor to T2DM [13].

The significant association between rs1800795 and the decreased risk of T2DM was first demonstrated in U.S. Pima Indians and Spanish Caucasians [14]. Soon after, one study confirmed the result [13]. However, no evidence for the association between rs1800795 and T2DM susceptibility was found in the studies carried out by Tsiavou A or Hamid YH [15, 16]. Therefore, Huth C and Qi L performed meta-analyses to provide conclusive evidence for the relationship of T2DM risk and rs1800795 in 2006, respectively [17, 18]. And their results showed that rs1800795 was associated with the decreased risk of T2DM. In the last ten years, some research on the association has been carried out. And several studies among them showed that no significant association between rs1800795 and T2DM susceptibility was observed [19-22]. For the association between rs1800795 and T2DM risk remains controversial to this day, we performed this updated meta-analysis. In this study, the recent studies were included to clarify the association between the SNP and the risk of T2DM. Meanwhile, we attempted to learn the role of the SNP in the development of T2DM and illustrate the possible reasons for these conflicting results in previous studies.

Material and methods

Search strategy

We systematically searched literature from the databases of PubMed, Embase, and CBMdisc for all relevant studies up to December 2016. The search terms were as follows: “type 2 diabetes mellitus or type 2 diabetes or diabetes mellitus or T2DM” and “interleukin-6 or IL-6” and “polymorphism or mutation or variant or genotype”. Furthermore, hand searching of the references in the identified articles was performed.

Inclusion criteria

All of the included studies should meet the major inclusion criteria: (a) evaluating the association between rs1800795 and T2DM risk; (b) case-control study; (c) written in English or Chinese; (d) sufficient information including available phenotype or allele frequencies of rs1800795 in cases and controls to calculate the odds ratios (ORs) and 95% confidence intervals (CIs).

Exclusion criteria

Criteria for exclusion were as follow: (a) the repeated studies; (b) no detailed genotyping information was provided in studies; (c) the reviews or abstracts from conferences; (d) the studies without control.

Table 1. Characteristics of the studies included in this meta-analysis

Author	Year	Region	Ethnicity	Source	Genotyping method	Sample size		Score
						Case	Control	
Bouhaha R	2010	Tunisia	African	HB	Fluorescent	169	281	7
Buraczynska M	2015	Poland	Caucasian	HB	PCR-RFLP	1090	612	6
Danielsson P	2005	Sweden	Caucasian	HB	PCR-RFLP	57	220	4
Dhamodharan U	2015	India	Asian	HB	PCR-RFLP	139	106	5
Eze IC	2016	Switzerland	Caucasian	PB	TaqMan	286	5554	6
Ghavimi R	2016	Iran	Asian	PB	PCR-RFLP	120	120	5
Gueuvoghlanian-Silva BY	2011	Brazil	Latinos	HB	PCR-RFLP	79	165	6
Hamid HY	2005	Sweden	Caucasian	PB	MassARRAY	1389	6164	6
Helaly MA	2013	Egypt	African	HB	PCR-RFLP	69	98	5
Karadeniz M	2014	Turkey	Caucasian	HB	PCR-RFLP	86	340	4
Mohlig M	2004	Germany	Caucasian	PB	PCR-RFLP	188	376	7
Mukhopadhyaya PN	2010	India	Asian	PB	PCR-RFLP	40	40	6
Ng DP	2008	USA	Caucasian	HB	TaqMan	295	174	4
Saxena M	2014	India	Asian	HB	PCR-RFLP	213	145	5
Stephens JW	2004	UK	Caucasian	HB	PCR-RFLP	563	2652	4
Tsiavou A	2004	Greece	Caucasian	HB	PCR-SSP	31	39	5
Vozarova B-Spain	2003	Spain	Caucasian	PB	PCR-RFLP	211	118	7

Table 2. Genotype and allele frequencies distribution of IL-6 rs1800795 polymorphism in the studies included in this meta-analysis

Author	Case			Control			MAF		HWE
	GG	CG	CC	GG	CG	CC	Case	Control	
Bouhaha R	125	40	4	210	64	7	0.142	0.139	0.428
Buraczynska M	316	534	240	195	288	129	0.465	0.446	0.238
Danielsson P	58	108	54	10	35	12	0.491	0.518	0.083
Dhamodharan U	92	46	1	50	44	12	0.173	0.321	0.626
Eze IC	111	135	40	2081	2614	865	0.376	0.391	0.352
Ghavimi R	40	62	18	29	64	27	0.408	0.492	0.463
Gueuvoghlanian-Silva BY	47	24	8	104	52	9	0.253	0.212	0.463
Hamid HY	402	659	328	1246	2133	1022	0.473	0.475	0.062
Helaly MA	2	49	18	5	87	6	0.616	0.505	0.000*
Karadeniz M	53	27	6	143	171	26	0.227	0.328	0.009*
Mohlig M	53	103	32	97	208	71	0.444	0.465	0.030*
Mukhopadhyaya PN	6	11	23	15	13	12	0.713	0.463	0.029*
Ng DP	146	100	38	72	74	22	0.310	0.351	0.665
Saxena M	163	46	4	105	21	19	0.127	0.203	0.000*
Stephens JW	239	254	70	846	1320	486	0.350	0.432	0.466
Tsiavou A	17	11	3	25	11	3	0.274	0.218	0.281
Vozarova B-Spain	84	110	17	34	65	19	0.341	0.436	0.193

*means $P<0.05$.

Data extraction

The following elements in each eligible study were independently collected by two authors (J. Xia and R. Sun): the first author's name, year of publication, country of region, ethnicity of the sample population, the total number of case and control subjects, the frequency distribution of rs1800795, and minor allele frequency (MAF). The Newcastle-Ottawa scale was used

Table 3. Meta-analysis of IL-6 rs1800795 polymorphism and the risk of type 2 diabetes mellitus

Genetic comparison	Number of studies	P_Q	I^2	Random model 95% CI	P_Z
Overall					
G vs. C	12	0.000	74.90%	0.86 (0.75-0.99)	0.035
GG + CG vs. CC	12	0.005	58.50%	0.87 (0.70-1.07)	0.180
GG vs. CG + CC	12	0.000	68.00%	0.82 (0.69-0.98)	0.028
GG vs. CC	12	0.000	70.70%	0.77 (0.58-1.02)	0.067
Caucasian					
G vs. C	8	0.000	75.20%	0.89 (0.77-1.02)	0.103
GG + CG vs. CC	8	0.029	55.00%	0.89 (0.73-1.08)	0.235
GG vs. CG + CC	8	0.001	72.50%	0.84 (0.69-1.02)	0.083
GG vs. CC	8	0.001	71.90%	0.80 (0.60-1.05)	0.108
Non-Caucasian					
G vs. C	4	0.004	77.70%	0.80 (0.52-1.22)	0.299
GG + CG vs. CC	4	0.014	71.70%	0.65 (0.23-1.86)	0.425
GG vs. CG + CC	4	0.040	63.80%	0.78 (0.51-1.19)	0.244
GG vs. CC	4	0.006	75.80%	0.57 (0.17-1.85)	0.349
HB					
G vs. C	8	0.000	78.60%	0.88 (0.70-1.09)	0.237
GG + CG vs. CC	8	0.009	62.70%	0.93 (0.65-1.32)	0.670
GG vs. CG + CC	8	0.000	73.90%	0.82 (0.62-1.08)	0.157
GG vs. CC	8	0.000	74.10%	0.81 (0.51-1.30)	0.389
PB					
G vs. C	4	0.046	62.50%	0.87 (0.74-1.03)	0.113
GG + CG vs. CC	4	0.066	58.20%	0.82 (0.60-1.10)	0.184
GG vs. CG + CC*	4	0.174	39.60%	0.92 (0.83-1.03)	0.167
GG vs. CC	4	0.025	67.90%	0.73 (0.49-1.07)	0.105

*The result was calculated in the fixed-effect model.

to assess the quality of the studies included in this meta-analysis (low quality studies with score ≤3, medium quality studies with score 4-6, and high quality studies with score >6). Any disagreements were resolved through discussion to achieve consensus.

Statistical analysis

All data in this meta-analysis were analyzed by STATA software, version 11.0 (STATA Corp., College Station, TX, USA).

Hardy-Weinberg equilibrium (HWE) in allele frequencies was examined in the control of each study. P<0.05 was considered as deviation from HWE. The ORs and 95% CIs in four genetic models (including allelic model, dominant model, recessive model, and additive model) were assessed using Z test. P<0.05 was regarded as statistically significant difference.

The Chi square-based Q-test was performed and I^2 index was calculated to evaluate the heterogeneity among studies. If P<0.10 for the Q-test or I^2>50%, between-study heterogeneity was significant and the pooled OR was calculated in random-effect model. Otherwise, the fixed-effect model was used. Stratification and meta-regression analyses were conducted to explore the potential source of heterogeneity across studies. Furthermore, stratification analysis was conducted by ethnicity. Sensitivity analysis was performed to assess the quality and consistency of the results. Both Begg's test and Egger's test were used to evaluate the possible publication bias among literatures. All of the P<0.05 were considered statistically significant.

Results

Study selection and characteristics

The literature search and selection process in the current meta-analysis is showed in **Figure 1**. A total of 605 articles were initially identified (PubMed: 235, Embase: 358, and CBMdisc: 12). Of these, 161 studies were duplicate. Thus, 444 articles were retrieved based on the search terms. Among them, 10 review articles and 417 irrelevant studies were excluded after full text assessment. Therefore, the remaining 17 studies were selected and the data from them were extracted. However, the distributions of the control genotypes in 5 studies were not in HWE. Finally, a total of 12 case-control studies (including 4,429 cases and 16,205 controls) were selected to evaluate the possible association between rs1800795 and T2DM risk [13-16, 19-26]. The main characteristics of these included studies are showed in **Table 1**. The genotype frequencies distribution of rs1800795 in 12 studies are listed in **Table 2**.

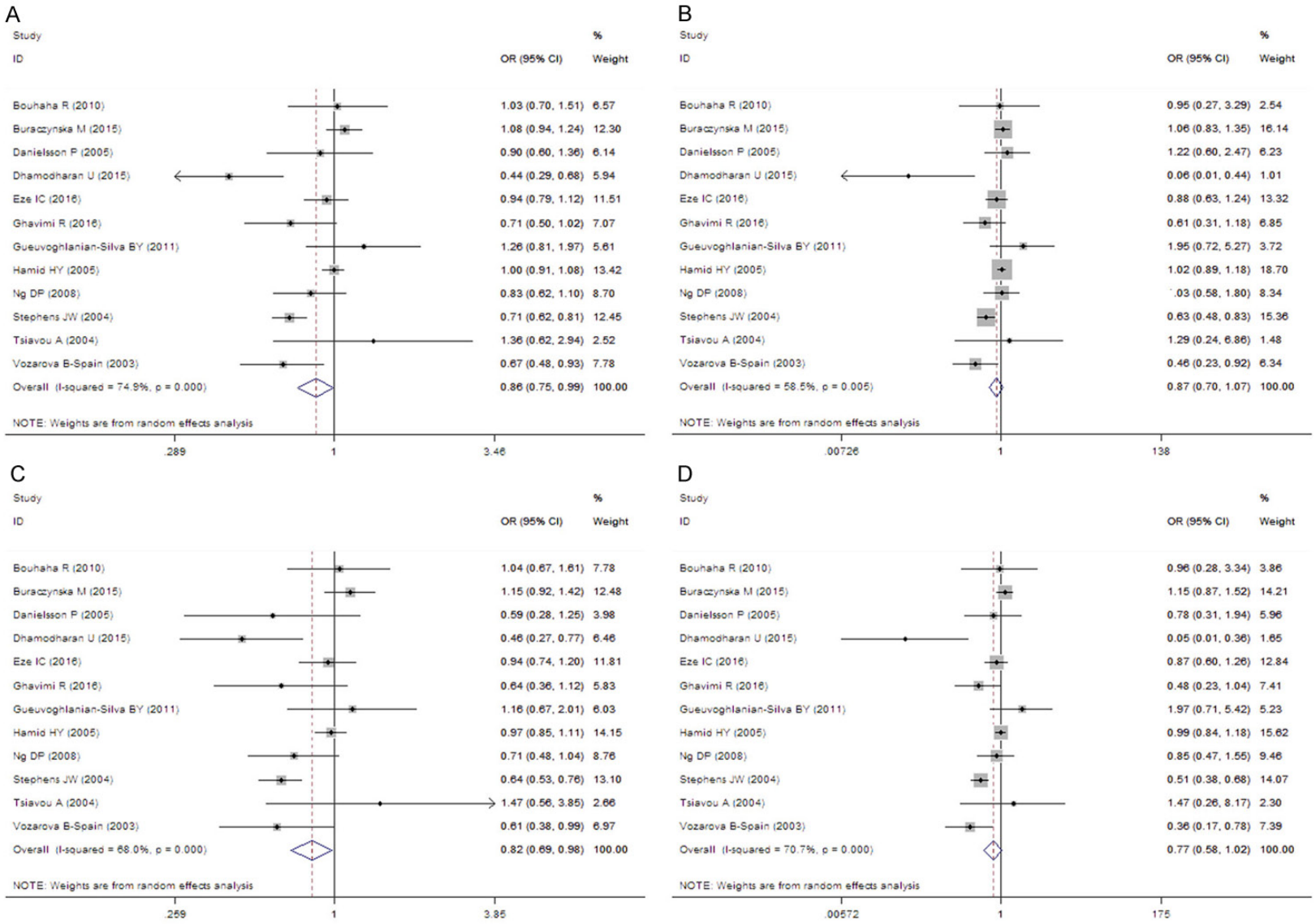

Figure 2. Forest plots for meta-analysis of rs1800795 polymorphism and the risk of type 2 diabetes mellitus in overall populations. A. Allelic model (G vs. C). B. Dominant genetic model (GG + CG vs. CC). C. Recessive genetic model (GG vs. CG + CC). D. Addictive genetic model (GG vs. CC).

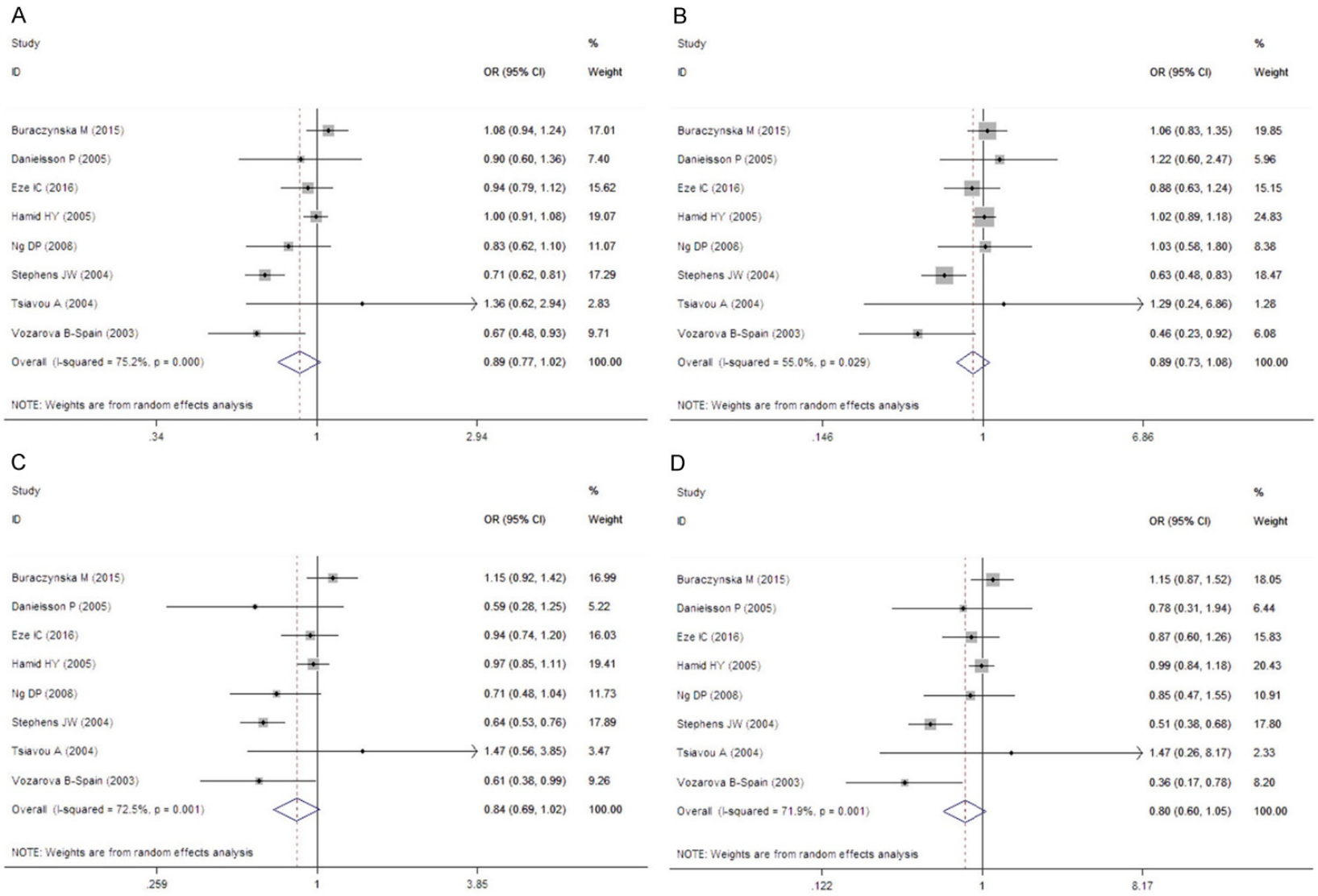

Figure 3. Forest plots for meta-analysis of rs1800795 polymorphism and the risk of type 2 diabetes mellitus in Caucasian populations. A. Allelic model (G vs. C). B. Dominant genetic model (GG + CG vs. CC). C. Recessive genetic model (GG vs. CG + CC). D. Addictive genetic model (GG vs. CC).

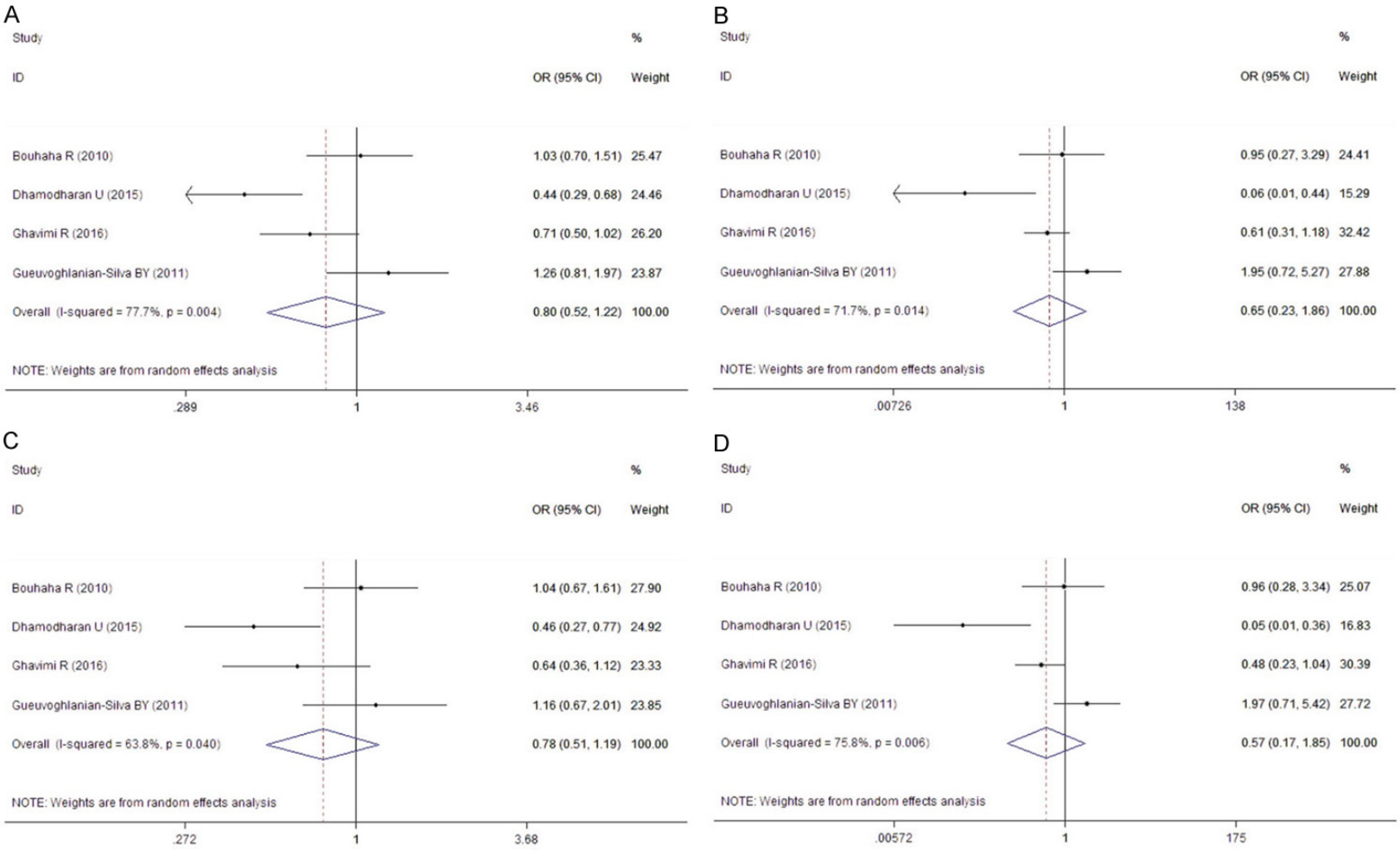

Figure 4. Forest plots for meta-analysis of rs1800795 polymorphism and the risk of type 2 diabetes mellitus in non-Caucasian populations. A. Allelic model (G vs. C). B. Dominant genetic model (GG + CG vs. CC). C. Recessive genetic model (GG vs. CG + CC). D. Addictive genetic model (GG vs. CC).

Table 4. Meta-regression of IL-6 rs1800795 polymorphism and the risk of type 2 diabetes mellitus

Covariate	Genetic comparison	Heterogeneity	t	P>|t|	95% CI
Year	G vs. C	+	0.04	0.972	-0.04, 0.04
	GG + CG vs. CC	+	0.27	0.796	-0.05, 0.06
	GG vs. CG + CC	+	0.58	0.573	-0.03, 0.05
	GG vs. CC	+	0.46	0.654	-0.06, 0.09
Ethnicity	G vs. C	+	-0.44	0.666	-0.34, 0.23
	GG + CG vs. CC	+	0.10	0.926	-0.58, 0.63
	GG vs. CG + CC	+	-0.50	0.627	-0.39, 0.25
	GG vs. CC	+	0.08	0.934	-0.67, 0.72

Meta-analysis results

The results of IL-6 rs1800795 G>C polymorphism and T2DM risk are showed in **Table 3** and **Figures 2**-**4**. The clear heterogeneity was observed in four genetic models. Therefore, the pooled ORs and their corresponding 95% CIs were calculated in random-effect model. We found that rs1800795 was significantly associated with the decreased risk of T2DM in allelic model (**Figure 2A**) and recessive model (**Figure 2C**), but not dominant model (**Figure 2B**) or addictive model (**Figure 2D**), in overall populations (**Table 3**).

Stratification analysis was performed by ethnicity design (**Table 3** and **Figures 3**, **4**). However, our results indicated that no evidence for significant association between rs1800795 and T2DM risk was observed in allelic model (**Figure 3A**), dominant model (**Figure 3B**), recessive model (**Figure 3C**), or addictive model (**Figure 3D**) in Caucasian populations. At the meantime, no obvious association between rs1800795 and the risk of T2DM was observed in allelic model (**Figure 4A**), dominant model (**Figure 4B**), recessive model (**Figure 4C**), or addictive model (**Figure 4D**) in non-Caucasian populations. More than that, the similar results were also observed in the stratification analysis for study design (**Table 3**).

Heterogeneity and sensitivity analyses

Considering the publication year and ethnicity as possible covariates, meta-regression was performed for rs1800795 to explore the source of heterogeneity. No covariate significantly contributing to the heterogeneity was found in the four genetic models (**Table 4**).

Sensitivity analysis showed that rs1800795 was not associated with T2DM risk in the four genetic models, when Dhamodharan U's study was omitted. The similar results were also found after omitting the studies conducted by Ghavimi R, Ng DP, Stephens JW, or Vozarova B (**Table 5**). More than that, when the studies performed by Buraczynska M or Gueuvoghlanian-Silva BY were not included, rs1800795 was significantly associated with the decreased risk of T2DM in allelic, recessive and addictive genetic models (**Table 5**).

These data suggested that our meta-analysis results remained robust in dominant model in overall populations. However, they were unstable in the allele, recessive, or additive models for rs1800795.

Publication bias

The Begg's test and Egger's test were conducted to assess publication bias. No obvious publication bias or trending bias was obtained (**Table 6**).

Discussion

T2DM is a complex disease involved in various factors. The disease exerts a negative effect on the quality of the life of patients and brings about large economic burden on society [27, 28]. It has been demonstrated that inflammatory response plays an important role in the development of T2DM [7, 9, 29]. Furthermore, the complications that usually occur in diabetic population are always due to inflammatory cytokines [30, 31]. As a prominent cytokine, IL-6 affects not only inflammation and infection but also the nervous and endocrine systems. And it has previously been linked to diabetes and various diabetic complications [32, 33].

Several epidemiological studies have found that the increased circulatory level of IL-6 is associated with the increased risk of T2DM. The certain SNPs, including IL-6 rs1800795 (-174 G>C) and IL-6 rs1800796 (-572 C>G), have been demonstrated to modulate the level of IL-6 in plasma [34, 35]. These evidences

Table 5. Sensitivity analysis of the meta-analysis

Author	G vs. C		GG + CG vs. CC		GG vs. CG + CC		GG vs. CC	
	95% CI	P_z	95% CI	P_z	95% CI	P_z	95% CI	P_z
Bouhaha R	0.85 (0.74-0.98)	0.030	0.86 (0.69-1.07)	0.184	0.81 (0.67-0.97)	0.022	0.76 (0.57-1.02)	0.066
Buraczynska M	0.84 (0.72-0.97)	0.019	0.83 (0.64-1.07)	0.148	0.79 (0.66-0.94)	0.009	0.72 (0.52-0.99)	0.041
Danielsson P	0.86 (0.75-0.99)	0.041	0.84 (0.68-1.06)	0.137	0.84 (0.70-1.00)	0.046	0.77 (0.57-1.03)	0.079
Dhamodharan U	0.90 (0.80-1.02)	0.100	0.89 (0.74-1.07)	0.218	0.86 (0.73-1.02)	0.076	0.81 (0.63-1.04)	0.104
Eze IC	0.85 (0.73-1.00)	0.045	0.86 (0.67-1.10)	0.221	0.81 (0.66-0.98)	0.032	0.75 (0.54-1.04)	0.081
Ghavimi R	0.88 (0.76-1.01)	0.069	0.89 (0.71-1.11)	0.288	0.84 (0.70-1.00)	0.052	0.80 (0.60-1.07)	0.129
Gueuvoghlanian-Silva BY	0.85 (0.74-0.97)	0.018	0.84 (0.68-1.04)	0.106	0.81 (0.67-0.96)	0.019	0.73 (0.55-0.97)	0.031
Hamid HY	0.85 (0.72-0.99)	0.040	0.83 (0.64-1.08)	0.166	0.80 (0.65-0.98)	0.032	0.73 (0.52-1.03)	0.071
Ng DP	0.87 (0.75-1.00)	0.056	0.85 (0.68-1.07)	0.164	0.84 (0.69-1.00)	0.056	0.76 (0.56-1.03)	0.076
Stephens JW	0.90 (0.79-1.02)	0.093	0.93 (0.76-1.14)	0.468	0.87 (0.74-1.02)	0.089	0.84 (0.65-1.09)	0.201
Tsiavou A	0.85 (0.74-0.98)	0.025	0.86 (0.69-1.07)	0.170	0.81 (0.68-0.97)	0.019	0.76 (0.57-1.01)	0.057
Vozarova B-Spain	0.88 (0.77-1.02)	0.082	0.90 (0.74-1.11)	0.339	0.84 (0.70-1.01)	0.061	0.82 (0.62-1.08)	0.161

Table 6. Publication bias analysis of the meta-analysis

Genetic comparison	Test	t	*P* value	95% CI
G vs. C	Begg's Test		0.945	
	Egger's Test	-0.86	0.408	-3.23, 1.42
GG + CG vs. CC	Begg's Test		0.537	
	Egger's Test	-1.06	0.316	-2.30, 0.82
GG vs. CG + CC	Begg's Test		0.945	
	Egger's Test	-0.79	0.448	-2.99, 1.42
GG vs. CC	Begg's Test		0.451	
	Egger's Test	-1.12	0.287	-2.86, 0.94

suggest that the genetic factors involved in IL-6 expression may be associated with the development of T2DM [10, 36].

The first report on the association between rs1800795 and T2DM risk was published in 2003 [14]. After that, some studies focused on the relationship [13, 15, 16]. Unfortunately, the results among these studies were not consistent. A meta-analysis study was carried out to demonstrate the significant association between the SNP of IL-6 and the decreased risk of T2DM ten years ago [17]. However, the evidence from recent research showed that different results still existed [19-22]. The discrepancy of these results might result from the genetic heterogeneity across different regions worldwide. Although a single included study also could verify the significant association between rs1800795 and T2DM risk, the false positive result in each literature could not be completely avoided due to a small number of samples. Therefore, the conclusion in the study with relative small sample size might not be able to reveal real gene-disease association.

Meta-analysis is a powerful method to resolve inconsistent results from a relative large number of samples covering different countries or ethnicity. Therefore, it can acquire more reliable conclusion than a single study. To investigate the association between the IL-6 rs1800795 and the decreased risk of T2DM, we performed the updated meta-analysis including eight new reports. In this study, all the collected data represented eleven different countries and covered four kinds of ethnicity.

Our results indicated that rs1800795 was significantly associated with the decreased risk of T2DM in allelic model and recessive model. And no association between this SNP and T2DM risk was observed in dominant model or addictive model. However, sensitivity analysis showed that the results were not robust in allelic, recessive, or addictive genetic models. These results should nonetheless be applied cautiously due to the instability. Sensitivity analysis showed that the result not influenced by omitting any studies in dominant genetic model was robust.

The instability of our results may be attributed to the heterogeneity among the studies included in the meta-analysis. We performed meta-regression and found that the publication year and ethnicity considered as possible covariates

were not the significant contributor to the heterogeneity. In addition, stratification analysis by ethnicity showed that rs1800795 was not associated with T2DM risk in four genetic models. These results may suggest that more studies are needed to explore the association between rs1800795 and T2DM risk.

Each study included in the current meta-analysis met our inclusion criteria and no obvious publication bias was observed. However, some limitations that existed in this meta-analysis had to be considered. First, only published literatures in English or Chinese were included in this meta-analysis. Second, some valuable information from individual participants was not considered in our research (for example, lifestyle). Third, we conducted meta-regression considering only the publication year and ethnicity without other factors.

Despite some limitations, this meta-analysis still provides new insights into the relationship of IL-6 gene and the occurrence of T2DM. This is an updated meta-analysis. Our results were consistent with the conclusion in previous relevant meta-analysis. However, the limit numbers of studies and subjects could reduce the statistical power for confirming the relationship of IL-6 gene polymorphism and T2DM risk in this study. Therefore, the study with larger number of subjects should be performed to identify the association.

In summary, the present meta-analysis demonstrates the significant association between IL-6 rs1800795 and the decreased risk of T2DM. The result suggests that the SNP has the potential to be the biomarker for low susceptibility to T2DM. However, large-scale studies with more detailed individual information are needed for further validation of our conclusion.

Acknowledgements

This work was supported by the Outstanding Young Personnel Research Fund of Zhejiang Provincial People's Hospital (No. ZRY2016C0-04).

Disclosure of conflict of interest

None.

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