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Interleukin-10 −592C/A, −819C/T and −1082A/G Polymorphisms with Risk of Type 2 Diabetes Mellitus: A HuGE Review and Meta-analysis

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Abstract

Background: Several studies have been conducted in recent years to evaluate the risk of type 2 diabetes mellitus (T2DM) and polymorphisms of interleukin (IL)-10. However, the results remain conflicting rather than conclusive. This meta-analysis aimed to summarize the current evidence from case-control studies that evaluated this association.

Methods: We carried out a search in Medline, EMBASE, and the Chinese National Knowledge Infrastructure (CNKI) database for relevant studies. Data were extracted using a standardized form and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association.

Results: 10 studies were included in our meta-analysis and systemic review. Our meta-analysis indicated that IL-10 −1082A/G polymorphism was associated with the risk of T2DM (GA vs. AA: OR = 1.21, 95% CI = 1.03–1.14; GA/GG vs. AA: OR = 1.22, 95% CI = 1.05–1.41), whereas there was no association between IL-10 −592C/A (CC/CA vs. AA: OR = 1.07, 95% CI = 0.59–1.93) or -819C/T (CC/CT vs. TT: OR = 0.93, 95% CI = 0.49–1.75) polymorphism and T2DM risk was found in our study.

Conclusions: This meta-analysis provides strong evidence that IL-10 −1082A/G polymorphism associated with risk of T2DM. However, no association of the IL-10 −592C/A or −819C/T polymorphism with T2DM risk was found. Additional well-designed large studies were required for the validation of our results.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Type 2 diabetes mellitus (T2DM) is one of the main chronic diseases and its complications have become a major cause of morbidity, mortality, and disability in the World. It has been estimated that the number of people with type 2 diabetes will double to at least 350 million worldwide by 2030 unless appropriate action is taken [1]. However, up to date, the mechanism of the disease is still not fully understood. In recent years, published data showed that genetic polymorphisms might explain individual differences in T2DM risk [2,3]. Several candidate genes are implicated in the pathogenesis of T2DM, one of which is interleukin (IL)-10.

Exel and colleagues discovered that low IL-10 production capacity is associated with the metabolic syndrome and T2DM [4]. The capacity for IL-10 production in individuals has been shown to be correlated with genetic composition of the IL-10 locus [5]. Thus, examination of genetic polymorphisms of IL-10 may explain individual differences in T2DM risk. Several molecular epidemiological studies were conducted in recent years to evaluate the risk of T2DM associated with the polymorphisms of IL-10 [5–14]. However, the results remain conflicting rather than conclusive. Considering the relatively small sample size in each study, it is possible to perform a quantitative synthesis of the evidence with rigorous methods. To investigate a possible association between IL-10 −592C/A, −819C/T and −1082A/G polymorphisms and T2DM, we performed a meta-analysis from all of the available relevant studies.

Materials and Methods

Identification and Eligibility of Relevant Studies

We carried out a search in Medline, EMBASE, and Chinese National Knowledge Infrastructure (CNKI), covering all papers published up to Aug 2012, using the search terms: ("Interleukin-10" OR "IL-10") AND ("gene" OR "polymorphism" OR "genetic variant") AND ("type 2 diabetes mellitus" OR "T2DM" OR "diabetes mellitus" OR "type 2 diabetes"). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Only published studies with full-text articles were included.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) published in English or in Chinese; (b) used a case-control design; (c) supplied the available genotype frequencies in cases and controls; and (d) sufficient
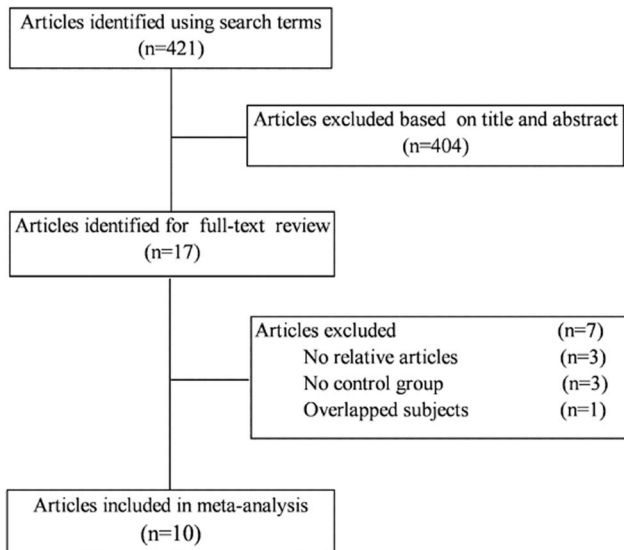
Articles identified using search terms
(n=421)

Articles excluded based on title and abstract
(n=404)

Articles identified for full-text review
(n=17)

Articles excluded   (n=7)
   No relative articles   (n=3)
   No control group   (n=3)
   Overlapped subjects   (n=1)

Articles included in meta-analysis
(n=10)

Figure 1. Flow diagram of the literature search and trial selection process.
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published data for estimating an odds ratio (OR) with 95% confidence interval (CI). Major reasons for exclusion of studies were (a) no control group; (b) duplicate of previous publication.

Data Extraction

Two investigators reviewed the articles independently to exclude irrelevant and overlapping studies. The results were compared, and disagreements were resolved by discussion and consensus. From each study, the following information was extracted: first author's surname, year of publication, ethnic descent of the study population (European, Asian and African), definition of case, age, characteristics of controls, numbers of eligible cases and controls, and genotype distributions in cases and controls.

Statistical Analysis

The Hardy-Weinberg equilibrium (HWE) was utilized to compare the observed genotype frequencies with expected genotype frequencies in controls for all studies. OR and 95% CI were used to assess the strength of association between IL-10

polymorphisms and the risk of T2DM under homozygote comparison, heterozygote comparison, dominant and recessive genetic model comparison. The significance of the combined OR was determined by the Z-test, in which $P<0.05$ was considered significant. Stratified analyses were performed by ethnicity, age and sources of control. The $\chi2$-based Q statistical test was used for the assessment of the between-study heterogeneity, which was considered significant for $P<0.1$ [15]. In analyses, if the heterogeneity was low then we used a fixed-effect model, or else applied the random-effect model. Sensitivity analyses were also performed to assess the stability of the results [16]. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias [17]. All analyses were performed with Stata (Version10.0, Stata Corporation) and Review Manager (version 5.0.16, The Cochrane Collaboration) using two sided P values.

Results

Characteristics of Studies

The search initially identified 421 potentially eligible articles. Of these, the first screening excluded 404 citations based on abstracts or titles, leaving 17 articles for full-text review. The excluded 7 articles had no relative outcomes, no control group, and duplicate of previous publication. We finally included 10 studies in our systematic review and meta-analysis [5–14]. The detailed steps of our literature search are shown in Figure 1.

The characteristics of 10 included studies are summarized in Table 1. There are eight case-control studies concerning −592C/A polymorphism [5–12], four case-control studies concerning −819C/T polymorphism [5–8], and six case-control studies concerning −1082A/G polymorphism [6–9,13,14]. Controls were selected from healthy population in all the studies and most studies used frequency-matched controls to the cases by age, sex, residence, or ethnicity. The genotype distributions among the controls of all studies were in agreement with HWE except for three studies for the −592C/A [8,10,12], one study for the −819C/T [8], and two for the −1082A/G [8,13].
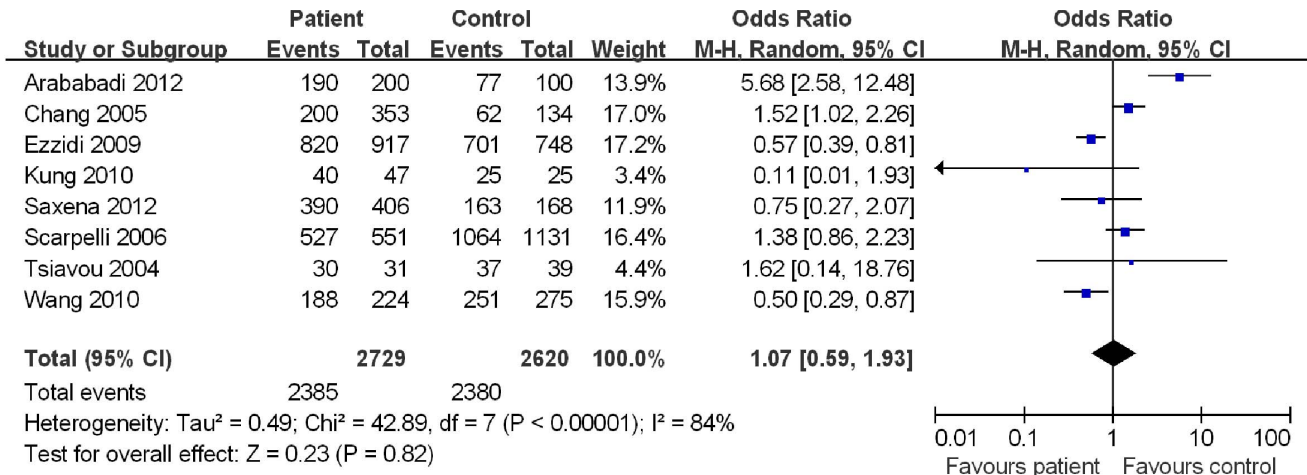
Quantitative Synthesis

IL-10 -592C/A. The evaluation of association between IL-10 polymorphisms and T2DM risk was presented in Table 2. Overall, no significant association was found between IL-10 −592C/A polymorphism and risk of T2DM (CC/CA *vs.* AA: OR = 1.07, 95% CI = 0.59–1.93; Figure 2A). We further performed a

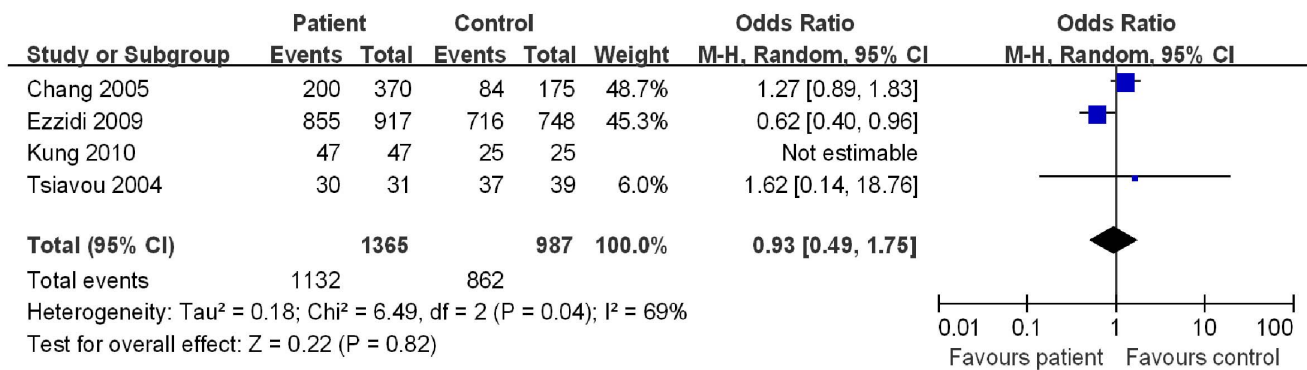**Table 1.** Study characteristics of inclulded studies in this meta-analysis.

Author	Year	Country	Ethnicity	Source of controls	SNPs studied	Sample size	HWE
Chang [5]	2005	China	Asian	Healthy Control	−592C/A, −819C/T	370/175	0.86, 0.87
Ezzidi [6]	2009	Tunisia	African	Healthy Control	−592C/A, −819C/T, −1082G/A	917/748	0.41, 0.41, 0.14
Tsiavou [7]	2004	Greece	European	Healthy Control	−592C/A, −819C/T, −1082G/A	31/39	0.38, 0.38, 0.82
Kung [8]	2010	China	Asian	Healthy Control	−592C/A, −819C/T, −1082G/A	47/25	<0.01, <0.01, <0.01
Scarpelli [9]	2006	Italy	European	Healthy Control	−592C/A, −1082G/A	551/1131	0.21, 0.68
Saxena [10]	2012	India	Asian	Healthy Control	−592C/A	406/168	0.01
Arababadi [11]	2012	Iran	Asian	Healthy Control	−592C/A	200/100	0.32
Wang [12]	2010	China	Asian	Healthy Control	−592C/A	224/275	0.04
Kolla [13]	2009	India	Asian	Healthy Control	−1082G/A	198/202	<0.01
Erdogan [14]	2012	Turkey	Asian	Healthy Control	−1082G/A	91/112	0.68

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A

Study or Subgroup	Patient Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Arababadi 2012	190	200	77	100	13.9%	5.68 [2.58, 12.48]
Chang 2005	200	353	62	134	17.0%	1.52 [1.02, 2.26]
Ezzidi 2009	820	917	701	748	17.2%	0.57 [0.39, 0.81]
Kung 2010	40	47	25	25	3.4%	0.11 [0.01, 1.93]
Saxena 2012	390	406	163	168	11.9%	0.75 [0.27, 2.07]
Scarpelli 2006	527	551	1064	1131	16.4%	1.38 [0.86, 2.23]
Tsiavou 2004	30	31	37	39	4.4%	1.62 [0.14, 18.76]
Wang 2010	188	224	251	275	15.9%	0.50 [0.29, 0.87]
Total (95% CI)		2729		2620	100.0%	1.07 [0.59, 1.93]
Total events	2385		2380			

Heterogeneity: Tau² = 0.49; Chi² = 42.89, df = 7 (P < 0.00001); I² = 84%
Test for overall effect: Z = 0.23 (P = 0.82)

B

Study or Subgroup	Patient Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chang 2005	200	370	84	175	48.7%	1.27 [0.89, 1.83]
Ezzidi 2009	855	917	716	748	45.3%	0.62 [0.40, 0.96]
Kung 2010	47	47	25	25		Not estimable
Tsiavou 2004	30	31	37	39	6.0%	1.62 [0.14, 18.76]
Total (95% CI)		1365		987	100.0%	0.93 [0.49, 1.75]
Total events	1132		862			

Heterogeneity: Tau² = 0.18; Chi² = 6.49, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.22 (P = 0.82)

C

Study or Subgroup	Patient Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Erdogan 2012	69	91	68	112	4.6%	2.03 [1.10, 3.74]
Ezzidi 2009	796	917	642	748	29.4%	1.09 [0.82, 1.44]
Kolla 2009	74	198	54	202	10.5%	1.64 [1.07, 2.50]
Kung 2010	45	47	25	25	0.5%	0.36 [0.02, 7.72]
Scarpelli 2006	332	551	646	1131	52.9%	1.14 [0.93, 1.40]
Tsiavou 2004	21	31	22	39	2.0%	1.62 [0.61, 4.34]
Total (95% CI)		1835		2257	100.0%	1.22 [1.05, 1.42]
Total events	1337		1457			

Heterogeneity: Chi² = 6.52, df = 5 (P = 0.26); I² = 23%
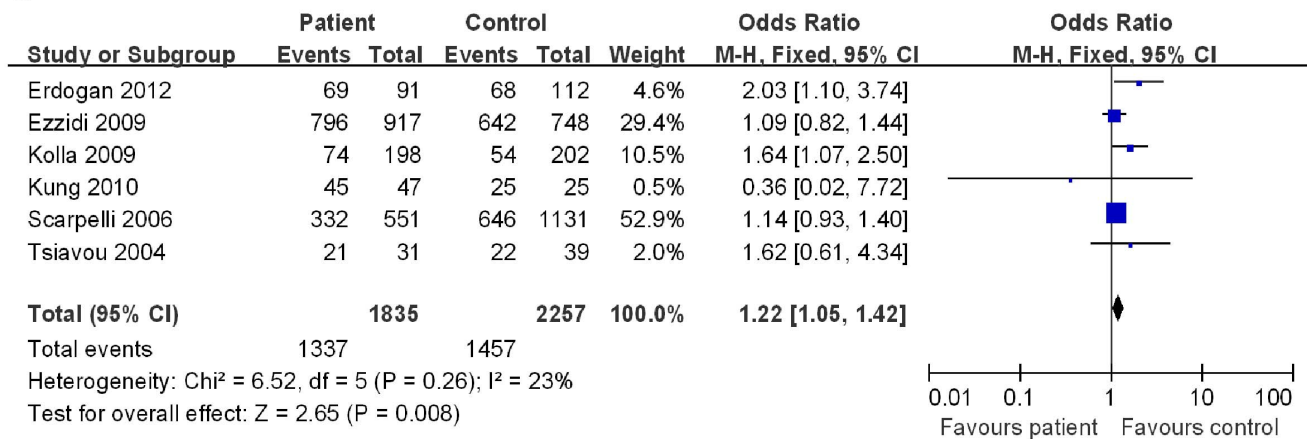Test for overall effect: Z = 2.65 (P = 0.008)

Figure 2. Meta-analysis with a random-effect model for the ORs of type 2 diabetes mellitus risk associated with interleukin-10 polymorphisms in dominant genetic model comparison. (A: −592C/A; B: −819C/T; C: −1082A/G.).
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subgroup analysis by ethnicity and obtained statistically similar results in European descendents and Asian descendents. However, a statistically significant association of IL-10 −592C/A polymorphism and T2DM risk were found in African descendents (CC/CA vs. AA: OR = 0.58, 95% CI = 0.41–0.82),

IL-10 −819C/T. There was no statistically significant differences between IL-10 −819C/T polymorphism and T2DM risk (CC/CT vs. TT: OR = 0.93, 95% CI = 0.49–1.75; Figure 2B). In the stratified analyses for the −819C/T polymorphism, there was a significantly increased risk was observed among African

Table 2. Total and stratified analyses of the interleukin-10 polymorphisms on type 2 diabetes mellitus risk.

Variables	No.[a]	Cases/ Controls	Homozygote OR(95%CI)	P^b	Heterozygote OR(95%CI)	P^b	Dominant Model OR(95%CI)	P^b	Recessive Model OR(95%CI)	P^b
−592C/A	8	2729/2620	1.17[0.54,2.55]	0.00[c]	1.05[0.66,1.68]	0.00[c]	1.07[0.59,1.93]	0.00[c]	1.13[0.79,1.61]	0.00[c]
European	2	582/1170	1.36[0.86,2.13]	0.84	1.38[0.87,2.18]	0.99	1.37[0.88,2.12]	0.90	1.02[0.84,1.25]	0.64
Asian	5	1203/702	1.27[0.32,5.05]	0.00[c]	1.08[0.52,2.23]	0.00[c]	1.11[0.44,2.80]	0.00[c]	1.39[0.65,2.96]	0.00[c]
African	1	917/748	0.53[0.37,0.75]	NA	0.65[0.45,0.94]	NA	0.58[0.41,0.82]	NA	0.74[0.61,0.90]	NA
−819C/T	4	1365/987	0.99[0.37,2.69]	0.01[c]	1.02[0.77,1.36]	0.41	0.93[0.49,1.75]	0.04[c]	0.93[0.49,1.78]	0.03[c]
European	1	31/39	1.72[0.17,17.75]	NA	1.41[0.13,15.13]	NA	1.58[0.16,15.94]	NA	1.27[0.50,3.25]	NA
Asian	2	417/200	1.63[0.87,3.03]	NA	1.20[0.82,1.75]	NA	1.27[0.89,1.83]	NA	1.40[0.77,2.55]	0.12
African	1	917/748	0.54[0.35,0.82]	NA	0.81[0.52,1.27]	NA	0.63[0.41,0.95]	NA	0.64[0.52,0.77]	NA
−1082G/A	6	1835/2257	1.37[0.84,2.25]	0.01[c]	1.21[1.03,1.14]	0.19	1.22[1.05,1.41]	0.26	1.25[0.76,2.03]	0.00[c]
European	2	582/1170	1.22[0.88,1.69]	0.24	1.14[0.92,1.41]	0.81	1.15[0.94,1.41]	0.49	1.14[0.84,1.55]	0.23
Asian	3	336/339	0.56[0.01,29.63]	0.00[c]	1.60[0.81,3.17]	0.12	1.69[1.21,2.38]	0.33	0.38[0.00,47.72]	0.00[c]
African	1	917/748	1.03[0.76,1.39]	NA	1.15[0.85,1.54]	NA	1.09[0.82,1.44]	NA	0.92[0.76,1.13]	NA

a numberof studies; b P value of Q-test for heterogeneity test; c Random-effects model was used when P value for heterogeneity test <0.10; otherwise, fixed-effects model was used; 0.00 means value <0.01; NA not applicable.
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descendents (CC/CT *vs.* TT: OR = 0.63, 95% CI = 0.41–0.95), while these association were not found in European descendents or Asian descendents in the four tested models.

IL-10 −1082A/G. Significant association between IL-10 −1082A/G polymorphism and risk of T2DM was observed under heterozygote comparison (GA *vs.* AA: OR = 1.21, 95% CI = 1.03–1.14) and dominant genetic model (GA *vs.* GG *vs.* AA: OR = 1.22, 95% CI = 1.05–1.41; Figure 2C). In the stratified analysis by ethnicity, IL-10 −1082A/G polymorphism was associated with a significantly increased risk of T2DM in Asian descendents under dominant genetic model (GA/GG *vs.* AA: OR = 1.69, 95% CI = 1.21–2.38). However, no significant association was found in European descendents or African descendents in all tested models.

Test of Heterogeneity

There was significant heterogeneity in our meta-analysis. We then assessed the source of heterogeneity for homozygote comparison by ethnicity and sample size. As a result, for −592C/A and −819C/T, ethnicity ($x^2 = 12.32$, $P = 0.002$; $x^2 = 8.46$, $P = 0.01$; respectively), but not sample size ($x^2 = 1.10$, $P = 0.29$; $x^2 = 0.73$, $P = 0.39$; respectively), was found to contribute to substantial heterogeneity. However, neither ethnicity ($x^2 = 1.77$, $P = 0.41$) nor sample size ($x^2 = 2.34$, $P = 0.13$) was found to contribute to substantial heterogeneity for −1082A/G.

Sensitivity Analysis

Although the distribution of genotypes in the controls in some studies did not follow HWE, the corresponding pooled OR and between-study heterogeneity were not significant altered without these studies (CC *vs.* AA: OR = 1.87, 95% CI = 0.66–5.30, $P_{heterogeneity} < 0.01$ for −592C/A; CC *vs.* CT/TT: OR = 1.00, 95% CI = 0.51–1.96, $P_{heterogeneity} = 0.02$ for −819C/T). However, sensitivity analysis indicated the studies by Kung et al. and Kolla et al. were the main origin of heterogeneity for −1082A/G. The heterogeneity significantly decreased when excluding the two studies ($P_{heterogeneity} = 0.13$), while the value of pooled OR was not significantly altered without the two studies (GG *vs.* AA OR = 1.11, 95% CI = 0.74–1.65).

Publication Bias

We used Funnel plot and Egger's regression asymmetry test to access the publication bias of literatures. The data suggested that there was no evidence of publication bias in dominant genetic model comparison (t = 0.74, $P = 0.486$ for −592C/A; t = 0.80, $P = 0.507$ for −819C/T; t = 1.49, $P = 0.209$ for −1082A/G; Figure 3).

Discussion

In the present study, a meta-analysis was performed to examine the association between three IL-10 polymorphisms and T2DM risk, by critically reviewing 8 studies on IL-10 −592C/A polymorphism (2,729 patients and 2,620 controls), 4 studies on IL-10 −819C/T polymorphism (1,365 patients and 987 controls), and 6 studies on IL-10 −1082A/G polymorphism (1,835 patients and 2,257 controls). To the best of our knowledge, this is the first comprehensive meta-analysis to date investigating the association between IL-10 −819C/T and −1082A/G polymorphisms and T2DM risk. In addition, more studies were included in our study than a recently published meta-analysis concerning −592C/ polymorphisms and T2DM risk [18].

The findings from our study indicated that IL-10 −1082A/G polymorphism associated with risk of T2DM. However, no association of the IL-10 −592C/A or −819C/T polymorphism with T2DM risk was found. There was evidence of heterogeneity between studies in our analyses. We then assessed the source of heterogeneity for homozygote comparison by ethnicity and sample size. As a result, ethnicity was found to contribute to heterogeneity for IL-10 −592C/A and −819C/T polymorphisms. However, the reasons for heterogeneity in the analysis of −1082A/G were unclear. It may be due to other factors, including the selection of methods, definition of cases, and sample sizes [19]. We further performed a sensitivity analysis and found the studies by Kung et al. [8] and Kolla et al. [13] were the main origin of heterogeneity for −1082A/G.

Allele frequency might reflect the natural selection pressures or a balance by other related functional genetic variants and environmental exposures [20,21]. Thus, a subgroup analysis by

A

Begg's funnel plot with pseudo 95% confidence limits

B

Begg's funnel plot with pseudo 95% confidence limits

C

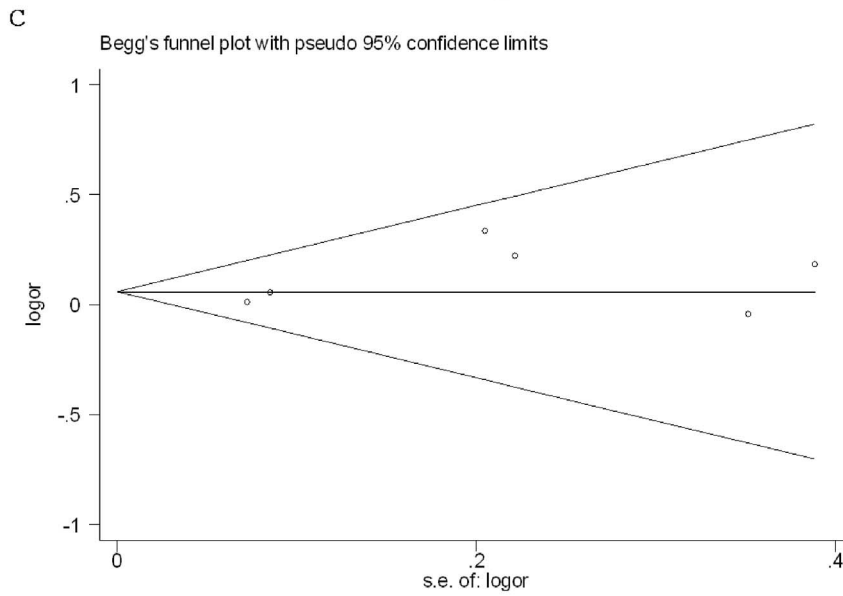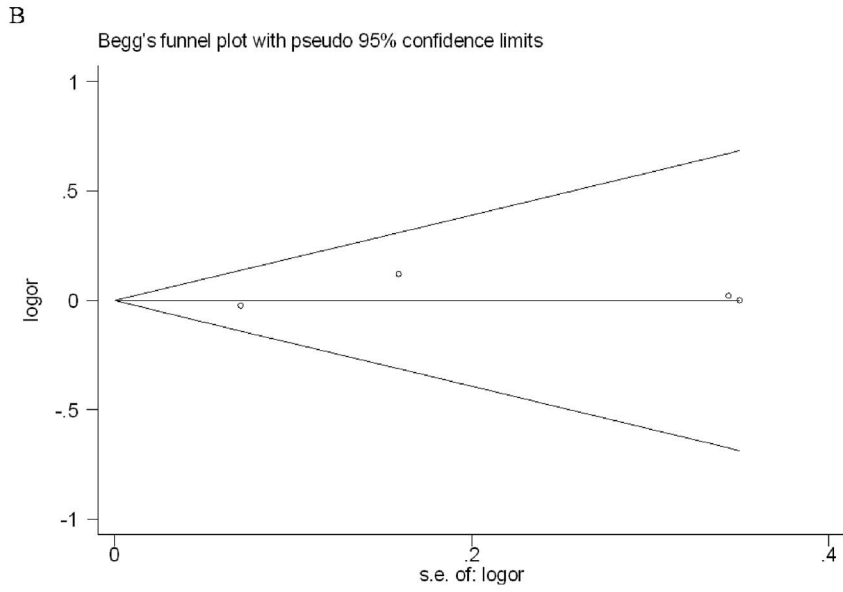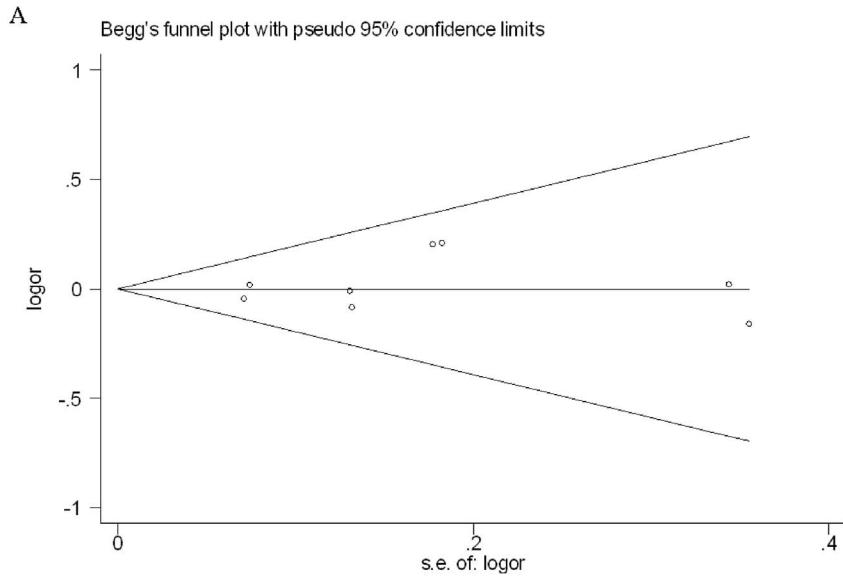Begg's funnel plot with pseudo 95% confidence limits

Figure 3. Funnel plot for publication bias of the meta-analysis of type 2 diabetes mellitus risk and interleukin-10 polymorphisms in dominant genetic model comparison. (A: −592C/A; B: −819C/T; C: −1082A/G.).
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ethnicity was performed in our meta-analyses. In stratified analyses, we observed a significant association between IL-10 −592C/A and −819C/T polymorphisms and T2DM risk in Africans. At the same time, it is worth emphasizing that IL-10 −1082A/G polymorphism contributed to an increase in T2DM susceptibility in Asians, but not for Europeans and Africans. Different genetic background and environmental exposures might contribute to this ethnic difference. However, there are only one study included in the analysis of African descendents with limited sample sizes, the result should be interpreted with caution, therefore, more studies based on larger population should be conducted to further examine those associations.

There are some limitations of this meta-analysis should be acknowledged. Firstly, detailed information, such as environmental exposures and gene-gene interactions, were unavailable in most studies, which limited our further assessment of those confounding factors at the patient level, and were incorporated into the analysis. Secondly, some studies with small sample size appear to overestimate the true association due to lack of sufficient power to detect such an association. Thirdly, only English and Chinese language studies were included in this meta-analysis might have led to bias.

Even though, our meta-analysis has some advantages. Firstly, the search and selection studies were conducted very strictly, which significantly increased statistic power of this meta-analysis. Secondly, all the studies included in this meta-analysis were case-control researches and contained available genotype frequency, which met our including criterion well. Third, controls in all the included studies were healthy population, which avoided occurring population stratification bias.

In conclusion, our meta-analysis suggested that IL-10 −592C/A or −819C/T polymorphism had no association with T2DM risk in all examined patients, whereas there was an association between IL-10 −1082A/G polymorphism and risk of T2DM. However, additional large studies are warranted to validate our findings. Future studies should include multi-ethnic groups and use standardized unbiased genotyping methods, different grades of asthma patients, and well-matched controls.

Author Contributions

Conceived and designed the experiments: YH JS. Performed the experiments: YH JS YS YX XY. Analyzed the data: YH JS YS. Contributed reagents/materials/analysis tools: YH JS YS YX XY. Wrote the paper: YH JS. Study supervision: YS YX XY.

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