African vs. Caucasian and Asian difference for the association of interleukin-10 promotor polymorphisms with type 2 diabetes mellitus (a meta-analysis study)

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Background: Interleukin-10 (IL-10) is a multifunctional regulatory cytokine that might be associated with increased risk of type 2 diabetes mellitus (T2DM). IL-10 gene polymorphisms have been reported to be associated with T2DM in several ethnic populations with controversial results. Objectives: This work is an updated meta-analysis aiming at the evaluation of the association between IL-10 gene polymorphisms: rs1800872 (−592 C > A), rs1800896 (−1082 A > G) and rs1800871 (−819 C > T) with the risk of T2DM. Methods: All available full text studies published up to July 2015 were included in this meta-analysis. Mainly Pubmed and Science Direct databases were searched for all eligible studies pertinent to testing the association between IL-10 gene polymorphisms with the susceptibility to T2DM. Further analyses of the pooled and stratified data in terms of individual polymorphic types and subject ethnicity were done and assessed using varied genetic models. Results: Fifteen case-control studies with a total of 26 comparisons (10 for IL-10 −592 C > A rs1800872, 11 for IL-10 −1082 A > G rs1800896 and 5 for IL-10 −819 C > T rs1800871 polymorphisms) met our inclusion criteria. IL-10 −1082 A > G polymorphism was the only one to show an association with T2DM in all pooled sample particularly among Asian and European (high frequency of the G allele) ethnic groups. On the other hand, IL-10 −592 C > A and −819 C > T were significantly associated with T2DM only among African subjects. Conclusions: This meta-analysis demonstrated that IL-10 −1082 A > G polymorphism was associated with increased risk of development of T2DM in total subjects no matter was their ethnic background, while both IL-10 −592 C > A and −819 C > T polymorphisms were associated with that risk only among African subjects.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex disease characterized by progressive β-cell dysfunction with insulin resistance and impaired insulin secretion (Steyn et al., 2009; Lin et al., 2010). The basic etiologic pathology of T2DM is speculated to involve multiple factors including genetic, environmental and immune ones (Pickup, 2004). One of the important cytokines with a probable major role is the interleukin-10 (IL-10) known of its multifunctional role in the inflammatory response of immune disorders (van Exel et al., 2002; Del Prete et al., 1993). The IL-10 gene is located on chromosome 1 (1q31–1q32) which is composed of five exons (Eskdale et al., 1997). Polymorphisms implicated to affect IL-10 transcription and secretion include rs1800872 (−592 C > A), rs1800896 (−1082 A > G) and rs1800871 (−819 C > T) (Eskdale et al., 1997; Kilpinen et al., 2002; Li et al., 2013).

Although several studies and few meta-analyses have evaluated the association between IL-10 gene polymorphisms with the risk of development of T2DM in different ethnic populations, their results showed controversies and inconsistencies that might be due relatively small sample size, selection bias and ethnic difference (Bai et al., 2014; Helal and Hatata, 2013; Kung et al., 2010; Yin et al., 2012; Li et al., 2013; Zhang et al., 2013; Mtiraoui et al., 2009). Another issue of concern is the under-representation of African-based studies. For this reason, we planned this meta-analysis to have an updated evidence based testing for the association of IL-10 gene polymorphisms with the increased risk of T2DM in a pooled sample of subjects of European, Asian as well African origins.
2. Methods

2.1. Study identification and selection

This meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria (Moher et al., 2010). A literature search was conducted using Pubmed and Science Direct citation databases to identify articles (up to July 2015) that examined the association between IL-10 gene (−592 C > A, −1082 A > G and −819 C > T) polymorphisms and risk of T2DM. Combinations of keywords such as: “interleukin-10”, “IL-10”, “−1082 A > G”, “−592 C > A”, “−819 C > T”, “polymorphism”, “variant”, “type 2 diabetes mellitus” and “T2DM” were entered as both Medical Subject Headings (MeSHs) and text words without any restrictions on language or country.

2.2. Inclusion and exclusion criteria

Inclusion criteria were defined as follows: (a) full text articles evaluating the association between genetic polymorphisms of IL-10 (−592 C > A, −1082 A > G and −819 C > T) with the risk of T2DM, (b) the design is a case–controlled study based on unrelated individuals, and (c) sufficient data (genotype distributions for cases and controls) available to estimate an odds ratio (OR) with its 95% confidence interval (CI). Studies were excluded if one of the following existed: (a) reviews and abstracts of meetings or conferences; (b) studies containing overlapping data; (c) studies in which the genotype frequencies or numbers could not be ascertained and (d) studies in which family members were studied, because their analysis is based on linkage considerations. If more than one article were published by the same authors using the same sample series, studies with the recently published ones were included.

2.3. Data extraction

The following information was carefully extracted from all eligible publications independently by two investigators: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity of the studied population; (5) number of cases and controls assigned to certain polymorphism of IL-10 (−592 C > A, −1082 A > G and −819 C > T); (6) genotyping method and (7) Hardy–Weinberg equilibrium (HWE) for controls.

2.4. Statistical analysis

The meta-analysis examined the comparisons between T2DM patients and healthy controls. The Hardy–Weinberg equilibrium (HWE) was evaluated in control groups by chi square test. If the study was found not to be in HWE with p value less than 0.05, it was considered to be in disequilibrium. Allele frequencies of the IL-10 gene (−592 C > A, −1082 A > G and −819 C > T) polymorphisms in each of the studies were determined using the allelic counting method. The strength of association was evaluated by examining the pooled odd ratios (ORs) and their 95% confidence intervals (CIs) for each study while, within and between-study heterogeneity were assessed using Cochran’s Q statistic. The genetic models evaluated for pooled ORs of these three polymorphisms have included allelic contrast, recessive model, dominant model, overdominant model, homozygote contrast and heterozygote contrast. The heterogeneity test was used to assess the probability of the null hypothesis that all studies were evaluating the same effect. The random-effects model was used for meta-analysis when a significant Q statistic (p < 0.10) indicated heterogeneity across studies (DerSimonian and Laird, 1986), while the fixed-effect model was used when heterogeneity was not significant (Mantel and Haenszel, 1959). We quantified the effect of heterogeneity by using the recently developed I² measure, where I² = 100% × (Q − df)/Q (Higgins and Thompson, 2002). The I² measure ranges between 0 and 100%, and it represents the proportion of inter-study variability attributable to heterogeneity rather than chance. I² values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. Funnel plot and Egger’s linear regression test were used to evaluate publication bias (Egger et al., 1997), and a P value <0.1 was considered statistically significant. Statistical manipulations were performed using the comprehensive meta-analysis computer program (Biosta, Englewood, NJ, USA).

3. Results

3.1. Meta-analysis of −592 C > A and T2DM susceptibility

In total, 10 studies including 2921 T2DM cases and 3316 controls investigating the relationship between the IL-10 −592 C > A polymorphism and the development of T2DM were available and met the criteria for this meta-analysis (Fig. 1A). The detailed characteristics of these studies were shown in (Table 1). Among these, six studies were performed among Asians (Wang et al., 2010; Kung et al., 2010; Chang et al., 2005; Arababadi et al., 2012; Saxena et al., 2013; Bai et al., 2014); two studies among Europeans (Tsiavou et al., 2004; Scarpelli et al., 2006); one study among Africans (Mtiraoui et al., 2009), and one among Mexicans (García-Elorriaga et al., 2013). The overall frequencies of IL-10 −592 C > A gene polymorphism in control subjects was consistent with Hardy–Weinberg equilibrium (HWE) in spite of the presence of 4 non-consistent studies (Wang et al., 2010; Kung et al., 2010; García-Elorriaga et al., 2013; Saxena et al., 2013). The results of Eggers test suggested no publication bias for all comparisons (Fig.5A and Table 2).

Analysis showed no significant differences between cases and controls regarding the allelic (OR = 0.901, 95% CI: 0.700–0.161, p = 0.421), dominant (OR = 1.106, 95% CI: 0.967–1.265, p = 0.140) and recessive (OR = 1.225, 95% CI: 0.940–1.596, p = 0.134) models. However, analysis based on the ethnic distribution of subjects, it was found that the IL-10 −592 A allele was only positively associated with T2DM among African population (OR = 1.332, 95% CI: 1.145–1.550, p < 0.001), which was also noted in the dominant, recessive, homozygote and homoyzgote models (Table 2, Fig. 2).

3.2. Meta-analysis of IL-10 −1082 A > G and T2DM susceptibility

In total, 11 studies including 2823 T2DM cases and 3542 controls examined the relationship between the IL-10 −1082 A > G polymorphism and the development of T2DM were available and met the criteria for this meta-analysis (Fig. 1B). The detailed characteristics of the studies included were shown in (Table 1). Among these, five studies were performed among Europeans (Tsiavou et al., 2004; Babel et al., 2006; Scarpelli et al., 2006; Forte et al., 2010; Erdogan et al., 2012), three studies were performed among Asians (Kolla et al., 2009; Kung et al., 2010 and Bai et al., 2014), two studies were performed among Africans (Mtiraoui et al., 2009 and Helaly and Hatafa, 2013), and one among Mexicans (García-Elorriaga et al., 2013). The overall frequencies of IL-10 −1082 A > G gene polymorphism in control subjects was consistent with Hardy–Weinberg equilibrium (HWE) in spite of the presence of 5 non-consistent studies (Bai et al., 2014; Helaly and Hatafa, 2013; Kung et al., 2010; Kolla et al., 2009; Babel et al., 2006). The results of Eggers test suggested no publication bias for all comparisons (Fig. 5B, Table 3).

Overall, a significant association between the −1082 A > G polymorphism and T2DM was found regarding the allelic contrast model (G vs. A allele, OR = 1.309, 95% CI: 1.055–1.623, p = 0.015), dominant model (OR = 1.174, 95% CI: 1.044–1.320, p = 0.008) and recessive model (OR = 1.472, 95% CI: 1.001–2.065, p = 0.049) (Fig. 3). Stratified analyses showed that significant associations were found in European population for the allelic contrast model (ORs of 1.474 and 95% CI = 1.030–2.108, p = 0.034); and in Asian populations for the dominant
model (OR = 1.315 and 95% CI = 1.042–1.660, p = 0.021), recessive model (OR = 1.757 and 95% CI = 1.221–2.529, p = 0.002) and homozygote contrast model (OR = 1.806 and 95% CI = 1.248–2.612, p = 0.002) (Table 3, Fig. 3). On the other hand, African cases showed no significant differences in genotype distribution of −1082 A > G from controls (G vs. A: OR = 1.424 and 95% CI = 0.647–3.135, p = 0.379) (Table 3, Fig. 3).

3.3. Meta-analysis of −819 C > T and T2DM susceptibility

For −819 C > T, there were five studies available involving 1214 cases and 1664 controls and met the criteria for this meta-analysis (Fig. 1C). The detailed characteristics of the studies included are shown in (Table 1). Among these, three studies were performed on Asians (Chang et al., 2005; Kung et al., 2010 and Bai et al., 2014), one study on Africans (Mirrored et al., 2009), and one study was performed on Europeans (Tsivou et al., 2004). The distribution of genotype of the IL-10−819 C > T gene polymorphism in control groups was not consistent with the HWE in two studies but the overall result was coping with the genetic equilibrium (Kung et al., 2010 and Bai et al., 2014). The results of Egger’s test suggested no publication bias for all comparisons (Fig. 5C and Table 4).

![Table 1](image)

**Table 1** Characteristics of studies of IL-10 gene polymorphisms included in the meta-analysis.

| First author [Ref] | Year | Country | Ethnicity | Sample size | Genotyping methods | Cases/controls (genotype) | Case/control (allele) | P (HWE) controls |
|--------------------|------|---------|-----------|-------------|--------------------|--------------------------|----------------------|------------------|
| Bai et al. 2014    | China | Asian   | 364 677   | Mass array  | 153/313 162/299    | 49/65                    | 468/925 260/429     | 0.39             |
| Saxena et al. 2013 | India | Asian   | 213 140   | PCR-RFLP    | 116/62 87/72       | 10/6                    | 319/196 107/84      | 0.008*           |
| Garcia-Eloffinge et al. 2013 | Mexico | Mexican | 21 47    | PCR-RFLP    | 11/13 9/34          | 1.0                    | 31.50 11/34        | <0.001*          |
| Arababadi et al. 2012 | Iran | Asian | 200 100   | PCR-RFLP    | 107/22 83/55       | 10/23                   | 297/99 103/101      | 0.32             |
| Wang et al. 2010   | China | Asian   | 224 275   | PCR-RFLP    | 66/113 122/138     | 36/24                   | 254/364 194/186     | 0.04*            |
| Kung et al. 2010   | Taiwan | Asian | 47 25     | PCR-RFLP    | 4/1 36/24          | 7/0                    | 44/26 50/24        | <0.001*          |
| Mirrored et al. 2009 | Tunisia | African | 425/395 298/97 | PCR-ASA 589/392 | 1245/1104 589/392 | 0.41                  |
| Forte et al. 2010  | Italy | European | 551 1131  | Sequencing   | 301/615 226/449     | 24/67                   | 828/1679 274/583    | 0.21             |
| Chang et al. 2005  | China | Asian   | 353 134   | PCR-RFLP    | 42/10 158/52       | 153/72                  | 242/72 46/196       | 0.88             |
| Tsivou et al. 2004 | Greece | European | 31 39     | PCR-SSP     | 17/19 13/18        | 1/2                    | 47/56 15/22        | 0.38             |

| −1082G/A | | | | | | | | |
| Bai et al. 2013 | China | Asian | 364 677 | Mass array | 252/495 72/129 | 40/53 | 576/1119 152/235 | <0.001* |
| García-Eloffinge et al. 2012 | Mexico | Mexican | 21 47 | PCR-RFLP | 6/4 9/18 | 6/25 | 21/26 21/68 | 0.77 |
| Helély et al. 2013 | Egypt | African | 69 98 | ARMS-PCR | 2/8 41/85 | 26/5 | 45/101 93/95 | <0.001* |
| Erdogan et al. 2012 | Turkey | European | 91 112 | PCR-RFLP | 22/44 69/54 | 0/14 | 113/142 69/82 | 0.68 |
| Forte et al. 2010 | Italy | European | 490 349 | PCR | 161/118 228/176 | 101/55 | 550/412 430/286 | 0.43 |
| Kung et al. 2010 | Taiwan | Asian | 47 25 | PCR-RFLP | 2/0 45/25 | 0/0 | 49/25 45/25 | <0.001* |
| Mirrored et al. 2009 | Tunisia | African | 917 748 | PCR-ASA | 121/106 426/326 | 370/316 | 668/536 116/958 | 0.14 |
| Kolla et al. 2009 | India | Asian | 198 202 | PCR | 124/148 42/41 | 32/13 | 290/337 106/67 | 0.002* |
| Scarpelli et al. 2006 | Italy | European | 551 1131 | Sequencing | 219/485 264/516 | 68/130 | 702/1486 400/776 | 0.68 |
| Babel et al. 2006 | Germany | European | 44 114 | PCR-SSP | 12/30 8/42 | 24/42 | 32/126 56/46 | 0.006* |
| Tsivou et al. 2004 | Greece | European | 31 39 | PCR-SSP | 10/17 13/17 | 8/5 | 33/51 29/27 | 0.82 |

| −819 C/T | | | | | | | | |
| Bai et al. 2014 | China | Asian | 364 677 | Mass array | 151/295 183/336 | 30/46 | 485/926 243/428 | <0.001* |
| Kung et al. 2010 | Taiwan | Asian | 47 25 | PCR-RFLP | 0/1 47/24 | 0/0 | 47/26 47/24 | <0.001* |
| Mirrored et al. 2009 | Tunisia | African | 402 748 | PCR-ASA | 199/488 173/228 | 30/32 | 571/1204 233/292 | 0.41 |
| Chang et al. 2005 | Taiwan | Asian | 370 175 | PCR-RFLP | 41/13 159/71 | 170/91 | 241/97 499/253 | 0.87 |
| Tsivou et al. 2004 | Greece | European | 31 39 | PCR-SSP | 17/19 13/18 | 1/2 | 47/56 15/22 | 0.38 |

* Asterisk indicate significant P of HWE, and it is deviation from this equation.

Fig. 1. Flow chart of studies of (A) IL-10−592 C > A, (B) IL-10−1082 A > G and (C) IL-10−819 C > T polymorphisms in the meta-analysis.
associated with T2DM among only the African population (T vs. C: OR = 1.683, 95% CI = 1.379–2.053, p < 0.001), which was also noted in the dominant, recessive, heterozygote and homozygote models (Table 4, Fig. 4).

3.4. Heterogeneity and publication bias

Between-study heterogeneity concerning the IL-10 −592 C > A and −1082 A > G polymorphisms were significant among all subjects and thus, the random effect model was used (Tables 2 and 3). On the other hand between-study heterogeneity of the other IL-10 −819 C > T polymorphism was not significant among all subjects and thus the fixed effect model was used (Table 4). Funnel plots were performed to assess the possibility of publication bias. The results of Egger’s regression test suggested no publication bias for the three studied meta-analyses (Egger’s regression test P value was > 0.1) (Fig. 5).

4. Discussion

T2DM is a complex heterogeneous status of metabolic disorders including hyperglycemia and impaired insulin function and secretion (Kramer et al., 2015). Several reports have demonstrated the association...
between IL-10 $-592$ C $>$ A, $-1082$ A $>$ G and $-819$ C $>$ T gene polymorphisms and the susceptibility of T2DM with relatively inconclusive conclusions (Bai et al., 2014; Arababadi et al., 2012; Scarpelli et al., 2006; Zhang et al., 2013; Helaly and Hatata, 2013; Erdogan et al., 2012; Mtiraoui et al., 2009; Chang et al., 2005 and Li et al., 2013). Knowing that the meta-analysis is a suitable method for evaluating small effects in human genetic association studies, we have designed this study to investigate and update the results recently given for the association of IL-10 $-592$ C $>$ A, $-1082$ A $>$ G and $-819$ C $>$ T gene polymorphisms with T2DM susceptibility in different ethnic subjects. In this meta-analysis, we updated the data of IL-10 gene in which we added two studies for $-592$ C $>$ A (Bai et al., 2014; García-Elorriaga et al., 2013), three studies for $-1082$ A $>$ G (Bai et al., 2014; García-Elorriaga et al., 2013 and Helaly and Hatata, 2013) in addition to one study for $-819$ C $>$ T (Bai et al., 2014) polymorphisms.

In this meta-analysis, in spite of the negative association of IL-10 $-592$ C $>$ A polymorphism with T2DM susceptibility in total subjects, stratified analysis indicated that the IL-10 $-592$ A allele was significantly associated with T2DM among African but not European and Asian subjects. Interestingly, the IL-10 $-819$ T allele was also significantly associated with T2DM among African but not in European and Asian subjects. On contrast, the IL-10 $-1082$ G allele was significantly associated with T2DM in total subjects, particularly in European and Asian but not in African subjects.

Comparing our updated meta-analysis to the previously done studies, a partial agreement was found. A nearly similar conclusion

### Table 3

Meta-analysis of the association between IL-10 $-1082$ A $>$ G polymorphism and T2D.

| Comparison | Population | Sample size | No. of studies | Test of association | Test of heterogeneity | Publication bias |
|------------|------------|-------------|----------------|---------------------|-----------------------|-----------------|
|            |            |             |                | T2DM                | Control              |                 |
| AG versus AA (allelic contrast) | Overall | 5646 | 7028 | 11 | 1.309 | 1.055–1.623 | 0.015 | R | 56.66 $<$0.001 | 82.35 | 0.227 |
|             | European  | 2414 | 3434 | 5  | 1.474 | 1.303–2.108 | 0.034 | R | 27.44 $<$0.001 | 85.42 | 0.213 |
|             | Asian     | 1218 | 1808 | 3  | 1.370 | 0.586–1.994 | 0.061 | R | 4.67 | 0.097 | 57.18 | 0.014 |
|             | African   | 1972 | 1692 | 2  | 1.424 | 0.647–3.135 | 0.379 | R | 11.10 | 0.001 | 90.99 | NA |
| AG + GG versus AA (dominant model) | Overall | 2823 | 3542 | 11 | 1.174 | 1.044–1.320 | 0.008 | F | 14.24 | 0.162 | 29.79 | 0.963 |
|             | European  | 1207 | 1745 | 5  | 1.155 | 0.987–1.352 | 0.072 | F | 4.45 | 0.350 | 9.86 | 0.407 |
|             | Asian     | 609  | 904  | 3  | 1.315 | 1.042–1.660 | 0.021 | F | 2.065 | 0.358 | 2.655 | 0.801 |
|             | African   | 986  | 846  | 2  | 1.120 | 0.850–1.477 | 0.421 | F | 1.515 | 0.218 | 33.97 | NA |
| GG versus AA + AG (heterozygote contrast) | Overall | 2776 | 3517 | 10 | 1.472 | 1.001–2.165 | 0.049 | R | 46.69 $<$0.001 | 80.72 | 0.337 |
|             | European  | 1207 | 1745 | 5  | 1.338 | 0.857–2.088 | 0.200 | R | 9.96 | 0.041 | 59.82 | 0.792 |
|             | Asian     | 562  | 879  | 2  | 1.757 | 1.221–2.529 | 0.002 | F | 2.56 | 0.109 | 61.02 | NA |
|             | African   | 986  | 846  | 2  | 3.060 | 2.655–33.22 | 0.370 | R | 22.09 $<$0.001 | 95.47 | NA |
| AG versus AA (homozygote contrast) | Overall | 2148 | 2884 | 11 | 1.118 | 0.984–1.270 | 0.086 | R | 14.32 | 0.159 | 30.19 | 0.099 |
|             | European  | 1006 | 1499 | 5  | 1.158 | 0.810–1.653 | 0.421 | R | 10.67 | 0.031 | 62.51 | 0.888 |
|             | Asian     | 537  | 838  | 3  | 1.123 | 0.857–1.472 | 0.400 | F | 0.670 | 0.715 | 0.0 | 0.400 |
|             | African   | 590  | 525  | 2  | 1.165 | 0.869–1.563 | 0.306 | R | 0.398 | 0.528 | 0.0 | NA |
| GG versus AA (overdominant model) | Overall | 1604 | 2113 | 10 | 1.387 | 1.057–2.011 | 0.084 | R | 29.72 $<$0.001 | 69.72 | 0.716 |
|             | European  | 625  | 940  | 5  | 1.252 | 0.983–1.594 | 0.069 | F | 0.53 | 0.228 | 29.01 | 0.710 |
|             | Asian     | 448  | 709  | 2  | 1.806 | 1.248–2.612 | 0.002 | F | 2.71 | 0.100 | 63.05 | NA |
|             | African   | 519  | 435  | 2  | 4.017 | 2.131–75.73 | 0.333 | R | 10.21 | 0.001 | 90.21 | NA |
| AG versus AA + GG (recessive model) | Overall | 2823 | 3542 | 11 | 0.964 | 0.739–1.256 | 0.784 | R | 38.37 $<$0.001 | 74.34 | 0.439 |
|             | European  | 1207 | 1745 | 5  | 1.072 | 0.677–1.689 | 0.767 | R | 21.55 | 0.035 | 2.655 | 0.801 |
|             | Asian     | 609  | 904  | 3  | 1.042 | 0.798–1.360 | 0.763 | F | 0.471 | 0.790 | 0.0 | 0.225 |
|             | African   | 986  | 846  | 2  | 0.524 | 0.108–2.537 | 0.422 | R | 16.39 $<$0.001 | 93.90 | NA |

### Fig. 3.

OR and 95% CI for individual studies and pooled data for the association of IL-10-1082 G versus A allele.
was made by Hau et al., in their meta-analysis study reporting a significant association of IL-10 − 592 CA + AA and − 819 CT + TT polymorphisms in African subjects; and IL-10 − 1082 AG + GC polymorphism among Asian subjects with a negative association in European subjects (Hua et al., 2013). On the other hand, Yin et al., 2012, 2013 reported a significant association of IL-10 gene polymorphism in African subjects with no significant association of IL-10 − 592 C > A polymorphism in all ethnicity-subgroups (Yin et al., 2012; Yin et al., 2013). In agreement with our results, Li et al., revealed a significant association of IL-10 − 1082 (AG + GC vs. AA) with T2DM in overall subjects with no significant associations of IL-10 − 592 A and − 819 T alleles with T2DM in total studied subjects Asian, African and European ethnicities (Li et al., 2013). On contrast, another meta-analysis done by Zhang et al. suggested that variations of the − 1082 G/A and − 819 C/T have a protective effects with decreased risk of T2DM in Caucasian subjects for (the allelic contrast A vs. G; C vs. T, homozygote contrast AA vs. GG; CC vs. TT, dominant model AA + AG vs.GG; CC + CT vs.TT), and in Asian subjects for the homozygote contrast and recessive models of − 1082 G/A (AA vs. GG and AA vs. AG + GG) (Zhang et al., 2013). In addition, several individual studies have evaluated the association between IL-10 − 592 C > A, − 1082 A > G and − 819 C > T gene polymorphisms and the risk of development of T2DM (Bai et al., 2014; Helaly and Hatata, 2013; Li et al., 2013 and Yin et al., 2012). Similar to our results, some reported positive association with IL-10 − 1082 G allele carriage (AG + GC) genotypes and the risk of development of T2DM in subjects of various ethnic origins as Egyptians (Helaly and Hatata,

### Table 4

| Comparison          | Population   | Sample size | No. of studies | Test of association | Test of heterogeneity | Publication bias |
|---------------------|--------------|-------------|----------------|---------------------|-----------------------|-----------------|
|                      |              |             |                | OR      | 95% CI   | P-value | Model | Test of association | Test of heterogeneity | Publication bias |
| T allele versus C allele (allelic contrast) | Overall | 2428 | 3328 | 5 | 1.092 | 0.786−1.518 | 0.600 | R | 21.62 | <0.001 | 81.49 | 0.544 |
|                      | Asian       | 1562       | 1754           | 3              | 0.986 | 0.645−1.511 | 0.860 | F | 5.31   | 0.191 | 39.58 | 0.859 |
|                      | European    | 62         | 78             | 1              | 0.812 | 0.379−1.741 | 0.593 | F | 0.00   | 1.0   | 0.0   | NA   |
|                      | African     | 804        | 1496           | 1              | 1.683 | 1.379−2.053 | <0.001 | F | 0.00   | 1.0   | 0.0   | NA   |
| CT + TT versus CC (dominant model) | Overall | 1214 | 1664 | 5 | 1.150 | 0.717−1.843 | 0.562 | R | 17.37 | 0.002 | 76.97 | 0.646 |
|                      | Asian       | 781        | 877            | 3              | 1.024 | 0.806−1.350 | 0.645 | F | 3.27   | 0.195 | 35.90 | 0.959 |
|                      | European    | 31         | 39             | 1              | 0.782 | 0.304−2.015 | 0.611 | F | 0.00   | 1.0   | 0.0   | NA   |
|                      | African     | 402        | 748            | 1              | 1.915 | 1.496−2.540 | <0.001 | F | 0.00   | 1.0   | 0.0   | NA   |
| TT versus CC + CT (recessive model) | Overall | 1167 | 1639 | 4 | 1.144 | 0.729−1.794 | 0.558 | R | 7.35   | 0.062 | 59.19 | 0.854 |
|                      | Asian       | 734        | 852            | 2              | 0.924 | 0.693−1.232 | 0.589 | F | 2.18   | 0.140 | 54.12 | NA   |
|                      | European    | 31         | 39             | 1              | 0.617 | 0.053−7.134 | 0.699 | F | 0.00   | 1.0   | 0.0   | NA   |
|                      | African     | 402        | 748            | 1              | 1.804 | 1.089−3.016 | 0.024 | F | 0.00   | 1.0   | 0.0   | NA   |
| CT versus CC (heterozygote contrast) | Overall | 983 | 1493 | 5 | 1.172 | 0.752−1.827 | 0.483 | R | 14.29 | 0.006 | 72.10 | 0.708 |
|                      | Asian       | 581        | 740            | 3              | 1.019 | 0.796−1.305 | 0.880 | F | 2.29   | 0.319 | 12.49 | 0.866 |
|                      | European    | 30         | 37             | 1              | 0.807 | 0.307−2.125 | 0.665 | F | 0.00   | 1.0   | 0.0   | NA   |
|                      | African     | 372        | 716            | 1              | 1.861 | 1.439−2.407 | <0.001 | F | 0.00   | 1.0   | 0.0   | NA   |
| TT versus CC (homozygote contrast) | Overall | 639 | 986 | 4 | 1.178 | 0.606−2.292 | 0.629 | R | 10.21 | 0.017 | 70.61 | 0.594 |
|                      | Asian       | 392        | 445            | 2              | 0.899 | 0.426−1.989 | 0.781 | R | 3.20   | 0.074 | 68.76 | NA   |
|                      | European    | 18         | 21             | 1              | 0.559 | 0.046−6.727 | 0.647 | F | 0.00   | 1.0   | 0.0   | NA   |
|                      | African     | 229        | 520            | 1              | 2.299 | 1.360−3.885 | 0.002 | F | 0.00   | 1.0   | 0.0   | NA   |
| CT versus CC + TT (overdominant model) | Overall | 1214 | 1664 | 5 | 1.235 | 0.900−1.693 | 0.191 | R | 10.47 | 0.033 | 61.80 | 0.985 |
|                      | Asian       | 781        | 877            | 3              | 1.058 | 0.859−1.304 | 0.594 | F | 1.17   | 0.557 | 0.0   | 0.022 |
|                      | European    | 31         | 39             | 1              | 0.843 | 0.323−2.182 | 0.724 | F | 0.00   | 1.0   | 0.0   | NA   |
|                      | African     | 402        | 748            | 1              | 1.723 | 1.340−2.216 | <0.001 | F | 0.00   | 1.0   | 0.0   | NA   |

**Fig. 4.** OR and 95% CI for individual studies and pooled data for the association of IL-10 − 819 T versus C allele.
of this cytokine in the pathogenesis of T2DM. In spite of these limitations, this meta-analysis demonstrated that IL-10 − 1082 A > G polymorphism was associated with increased risk of development of T2DM in all subjects while both IL-10 − 592 C > A and − 819 C > T polymorphisms were associated with that risk only among African subjects.

**Conflict of interest**

The authors declare that they have no conflict of interest related to this work.

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