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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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ABSTRACT

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.

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; Helaly 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.

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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 I^2measure, where $I^2 = 100\% \times (Q - df)/Q$ (Higgins and Thompson, 2002). The I^2measure ranges between 0 and 100%, and it represents the proportion of inter-study variability attributable to heterogeneity rather than chance. I^2 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, $p = 0.134$) (Fig. 2) 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, heterozygote and homozygote 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 Hatata, 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 Hatata, 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: 1.001–2.165, $p = 0.049$) (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

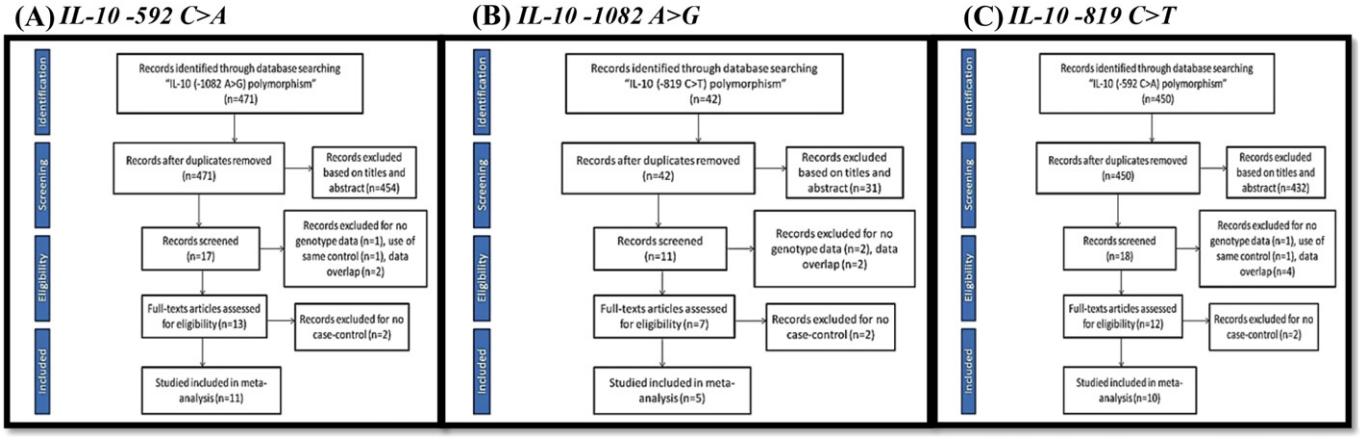

Fig. 1. Flow chart of studies of (A) IL-10 −592 C > A, (B) IL-10 −1082 A > G and (C) IL-10 −819 C > T polymorphisms in the meta-analysis.

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 were 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 (Mtiraoui et al., 2009), and one study was performed on Europeans (Tsiavou 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).

We detected no association between *−819 T* allele and risk of developing T2DM in overall pooled subjects regarding the allele contrast method (T versus C allele; OR = 1.092, 95%CI = 0.786–1.518, $p = 0.600$), dominant model (OR = 1.150, 95% CI = 0.717–1.843, $p = 0.562$) (Fig. 4) neither for the recessive model (OR = 1.144, 95% CI = 0.729–1.794, $p = 0.558$). Regarding the ethnic distribution of subjects, although Asians and Europeans showed no association of *IL-10 −819 C > T* polymorphism and T2DM, interestingly, the T allele was positively

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
				Cases	Controls							
−592 A/C							CC	AC	AA	C	A	
Bai et al.	2014	China	Asian	364	677	Mass array	153/313	162/299	49/65	468/925	260/429	0.59
Saxena et al.	2013	India	Asian	213	140	PCR-RFLP	116/62	87/72	10/6	319/196	107/84	0.008*
García-Elorriaga et al.	2013	Mexico	Mexican	21	47	PCR-RFLP	11/13	9/34	1/0	31/60	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*
Mtiraoui et al.	2009	Tunisia	African	917	748	PCR-ASA	425/403	395/298	97/47	1245/1104	589/392	0.41
Scarpelli et al.	2006	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	464/196	0.88
Tsiavou et al.	2004	Greece	European	31	39	PCR-SSP	17/19	13/18	1/2	47/56	15/22	0.38
−1082G/A							AA	GA	GG	A	G	
Bai et al.	2014	China	Asian	364	677	Mass array	252/495	72/129	40/53	576/1119	152/235	<0.001*
García-Elorriaga et al.	2013	Mexico	Mexican	21	47	PCR-RFLP	6/4	9/18	6/25	21/26	21/68	0.77
Helaly 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*
Mtiraouli et al.	2009	Tunisia	African	917	748	PCR-ASA	121/106	426/326	370/316	668/538	1166/958	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*
Tsiavou et al.	2004	Greece	European	31	39	PCR-SSP	10/17	13/17	8/5	33/51	29/27	0.82
−819 T/C							CC	TC	TT	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*
Mtiraouli 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
Tsiavou 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.

Table 2
Meta-analysis of the association between IL-10-592 C > A polymorphism and T2DM.

Comparison	Population	Sample size		No. of studies	Test of association				Test of heterogeneity			Publication bias
		T2DM	Control		OR	95% CI	*P*-value	Model	Q test	*P*-value	I^2 (%)	*P*-value (Egger's)
A allele versus C allele (allelic contrast)	Overall	5842	6632	10	0.901	0.700–1.161	0.421	R	69.82	<0.001	87.11	0.188
	Asian	2802	2702	6	0.859	0.565–1.304	0.475	R	54.90	<0.001	90.89	0.398
	European	1164	2340	2	0.946	0.805–1.113	0.504	F	0.161	0.688	0.0	NA
	African	1834	1496	1	1.332	1.145–1.550	<0.001	F	0.0	1.0	0.0	NA
AC + AA versus CC (dominant model)	Overall	2921	3316	10	1.106	0.967–1.265	0.140	R	52.37	<0.001	82.81	0.08
	Asian	1401	1351	6	0.725	0.410–1.283	0.270	R	39.67	<0.001	87.40	0.289
	European	582	1170	2	0.980	0.802–1.196	0.840	F	0.227	0.634	0.0	NA
	African	917	748	1	1.352	1.114–1.641	0.002	F	0.0	1.0	0.0	NA
AA versus CC + AC (recessive model)	Overall	2921	3316	10	1.225	0.940–1.596	0.134	R	46.68	<0.001	80.72	0.935
	Asian	1401	1351	6	0.945	0.466–1.917	0.876	R	34.85	<0.001	85.65	0.998
	European	582	1170	2	0.719	0.450–1.149	0.168	F	0.016	0.900	0.0	NA
	African	917	748	1	1.764	1.228–2.536	0.002	F	0.0	1.0	0.0	NA
AC versus CC (heterozygote contrast)	Overall	2533	3010	10	1.074	0.936–1.232	0.310	R	35.47	<0.001	74.62	0.053
	Asian	1136	1161	6	0.760	0.471–1.227	0.261	R	25.47	<0.001	80.37	0.291
	European	557	1101	2	1.017	0.828–1.250	0.871	F	0.230	0.632	0.0	NA
	African	820	701	1	1.257	1.026–1.540	0.027	F	0.0	1.0	0.0	NA
AA versus CC (homozygote contrast)	Overall	1630	1877	10	1.297	0.979–1.718	0.070	R	59.05	<0.001	84.76	0.462
	Asian	753	711	6	0.806	0.298–2.181	0.671	R	47.01	<0.001	89.36	0.556
	European	343	703	2	0.725	0.450–1.168	0.186	F	0.044	0.835	0.0	NA
	African	522	450	1	1.957	1.346–2.845	<0.001	F	0.0	1.0	0.0	NA
AC versus CC + AA (overdominant model)	Overall	2921	3316	10	1.035	0.912–1.174	0.598	R	21.66	0.010	58.45	0.018
	Asian	1401	1351	6	0.888	0.659–1.196	0.433	R	13.99	0.016	64.28	0.170
	European	582	1170	2	1.045	0.854–1.280	0.667	F	0.207	0.649	0.0	NA
	African	917	748	1	1.143	0.939–1.390	0.183	F	0.0	1.0	0.0	NA

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

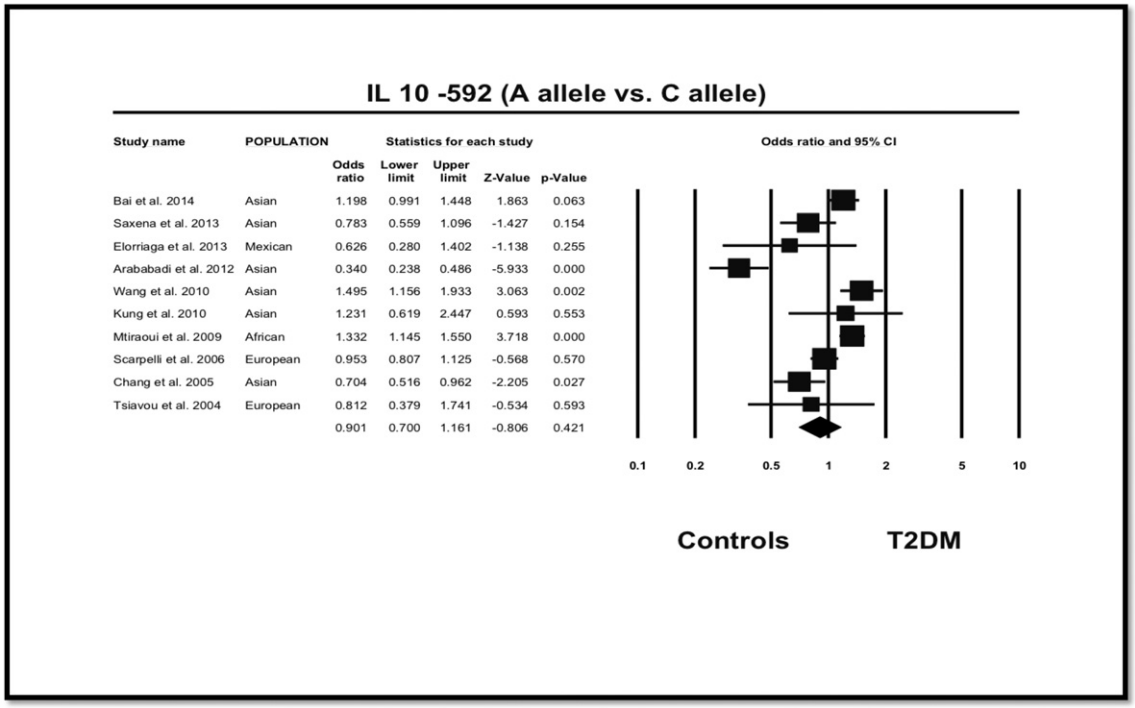

Fig. 2. OR and 95% CI for individual studies and pooled data for the association of *IL-10-592 A* versus C allele.

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		OR	95% CI	*P*-value	Model	Q test	*P*-value	I^2 (%)	*P*-value (Egger's)
G allele versus A allele (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	1.030–2.108	0.034	R	27.44	<0.001	85.42	0.213
	Asian	1218	1808	3	1.370	0.986–1.904	0.061	R	4.67	0.097	57.18	0.914
	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	2.055	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 (recessive model)	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	0.265–35.32	0.370	R	22.09	<0.001	95.47	NA
AG versus AA (heterozygote contrast)	Overall	2148	2884	11	1.118	0.984–1.270	0.086	F	14.32	0.159	30.19	0.699
	European	1006	1499	5	1.158	0.810–1.653	0.421	R	10.67	0.031	62.51	0.898
	Asian	537	838	3	1.123	0.857–1.472	0.400	F	0.670	0.715	0.0	0.490
	African	590	525	2	1.165	0.869–1.562	0.306	F	0.398	0.528	0.0	NA
GG versus AA (homozygote contrast)	Overall	1604	2113	10	1.387	0.957–2.011	0.084	R	29.72	<0.001	69.72	0.716
	European	625	940	5	1.252	0.983–1.594	0.069	F	5.63	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	0.213–75.73	0.353	R	10.21	0.001	90.21	NA
AG versus AA + GG (overdominant model)	Overall	2823	3542	11	0.964	0.739–1.256	0.784	R	38.97	<0.001	74.34	0.439
	European	1207	1745	5	1.072	0.677–1.689	0.767	R	21.96	<0.001	81.79	0.961
	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

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

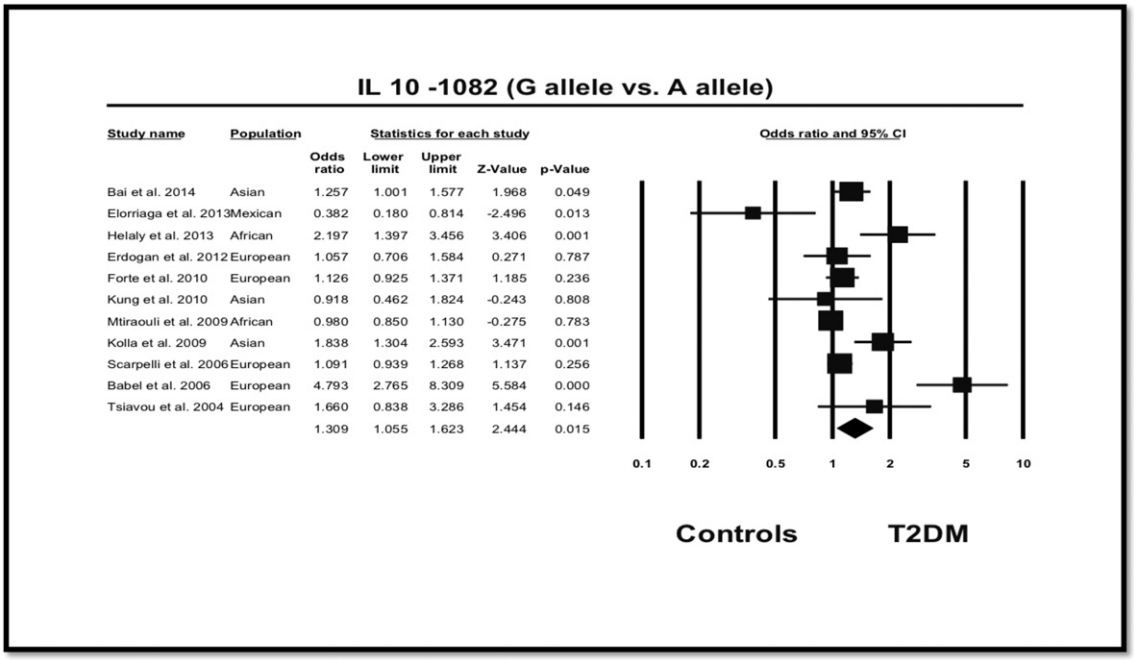

Fig. 3. OR and 95% CI for individual studies and pooled data for the association of *IL-10-1082 G* versus A allele.

Table 4
Meta-analysis of the association between IL-10 −819 C > T polymorphism and T2D.

Comparison	Population	Sample size		No. of studies	Test of association				Test of heterogeneity			Publication bias
		T2DM	Control		OR	95% CI	*P*-value	Model	Q test	*P*-value	I^2 (%)	*P*-value (Egger's)
T allele versus C allele	Overall	2428	3328	5	1.092	0.786–1.518	0.600	R	21.62	<0.001	81.49	0.544
(allelic contrast)	Asian	1562	1754	3	0.986	0.845–1.151	0.860	F	3.31	0.191	39.58	0.859
	European	62	78	1	0.812	0.379–1.741	0.593	F	0.0	1.0	0.0	NA
	African	804	1496	1	1.683	1.379–2.053	<0.001	F	0.0	1.0	0.0	NA
CT + TT versus CC	Overall	1214	1664	5	1.150	0.717–1.843	0.562	R	17.37	0.002	76.97	0.646
(dominant model)	Asian	781	877	3	1.024	0.806–1.301	0.845	F	3.27	0.195	38.90	0.959
	European	31	39	1	0.782	0.304–2.015	0.611	F	0.0	1.0	0.0	NA
	African	402	748	1	1.915	1.496–2.450	<0.001	F	0.0	1.0	0.0	NA
TT versus CC + CT	Overall	1167	1639	4	1.144	0.729–1.794	0.558	R	7.35	0.062	59.19	0.854
(recessive model)	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	0.0	1.0	0.0	NA
	African	402	748	1	1.804	1.080–3.016	0.024	F	0.0	1.0	0.0	NA
CT versus CC	Overall	983	1493	5	1.172	0.752–1.827	0.483	R	14.29	0.006	72.10	0.708
(heterozygote contrast)	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	0.0	1.0	0.0	NA
	African	372	716	1	1.861	1.439–2.407	<0.001	F	0.0	1.0	0.0	NA
TT versus CC	Overall	639	986	4	1.178	0.606–2.292	0.629	R	10.21	0.017	70.61	0.594
(homozygote contrast)	Asian	392	445	2	0.899	0.426–1.899	0.781	R	3.20	0.074	68.76	NA
	European	18	21	1	0.559	0.046–6.727	0.647	F	0.0	1.0	0.0	NA
	African	229	520	1	2.299	1.360–3.885	0.002	F	0.0	1.0	0.0	NA
CT versus CC + TT	Overall	1214	1664	5	1.235	0.900–1.693	0.191	R	10.47	0.033	61.80	0.985
(overdominant model)	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	0.325–2.182	0.724	F	0.0	1.0	0.0	NA
	African	402	748	1	1.723	1.340–2.216	<0.001	F	0.0	1.0	0.0	NA

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 + GG* 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 positive association of *IL-10 −1082 G* allele with the risk of T2DM in European 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 + GG* 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 + GG*) genotypes and the risk of development of T2DM in subjects of various ethnic origins as Egyptians (Helaly and Hatata,

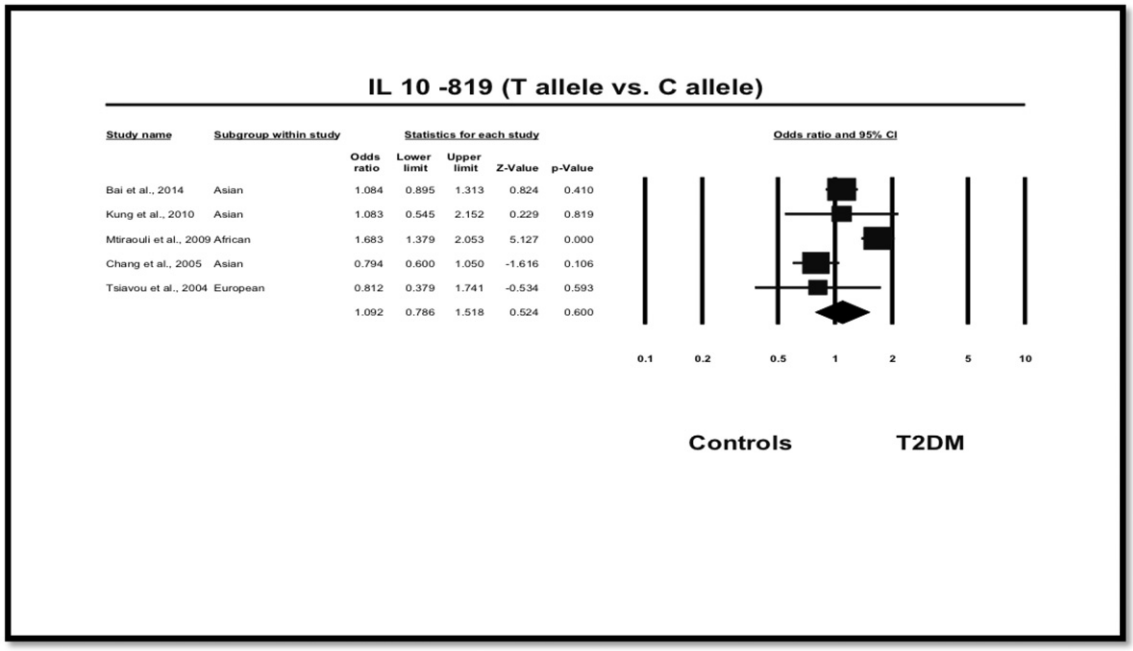

Fig. 4. OR and 95% CI for individual studies and pooled data for the association of *IL-10 −819 T* versus C allele.

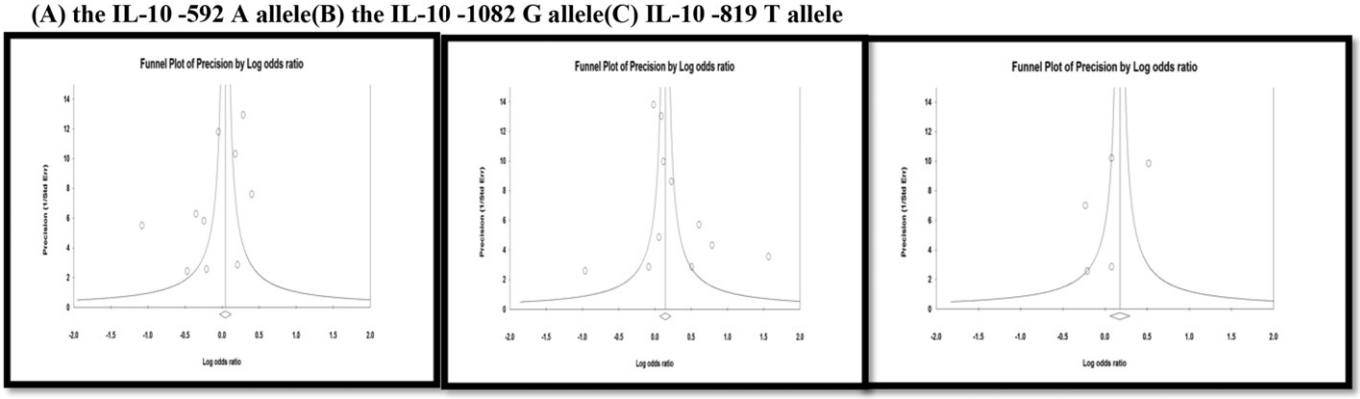

Fig. 5. Funnel plot for the association between (A) the IL-10 −592 A allele, (B) the IL-10 −1082 G allele and (C) IL-10 −819 T allele with T2DM in all study subjects (Egger's regression *P* value = 0.188, 0.277 and 0.544, respectively).

2013), Chinese (Bai et al., 2014), Turkish (Erdogan et al., 2012), Mexican (García-Elorriaga et al., 2013) and Indian (Kolla et al., 2009) subjects. On the contrary, several other studies have revealed no association between *IL-10 −1082 A > G* polymorphism and the risk of development of T2DM in some other populations like that done among Taiwanese (Kung et al., 2010), Greek (Tsiavou et al., 2004), Tunisian (Mtiraoui et al., 2009), Italian (Scarpelli et al., 2006) and Germen (Babel et al., 2006) subjects.

Similar to our findings, some studies revealed no significant association with *IL-10 −592 C* allele carriage (*AC + CC*) genotypes and the risk of development of T2DM like that done among Indian (Saxena et al., 2013), Mexican (García-Elorriaga et al., 2013), Taiwanese (Kung et al., 2010), Italian (Scarpelli et al., 2006) and Greek (Tsiavou et al., 2004) subjects. However, other reports showed significant association of this polymorphism with the risk of development of T2DM like that done among Iranian (Arababadi et al., 2012), Chinese (Bai et al., 2014) and Tunisian (Mtiraoui et al., 2009) subjects. Few reports have studied the association of *IL-10 −819 C > T* polymorphism and the risk of development of T2DM and found no association for this polymorphism like those done among Chinese (Bai et al., 2014), Taiwanese (Kung et al., 2010 and Chang et al., 2005) and Greek (Tsiavou et al., 2004) subjects. Contrastingly, one study reported a positive association between *IL-10 −819 T* allele and *TT* genotype and the risk of development of T2DM among Tunisian subjects (Mtiraoui et al., 2009). This discrepancy in results pertinent to individual genotype association with T2DM might obviously be due to innate genetic diversity among ethnicities in addition to multiple interactive environmental factors as climate, diet, lifestyle and economic status. Factors related to the study design or sample size should also be put into consideration (Brooks et al., 2012 and Li et al., 2013).

In fact, studies concerning IL-10 −592 C > A and −819 C > T polymorphisms among African ethnicities were somewhat lacking. This meta-analysis involved the results of only two studies investigating these polymorphisms among African subjects. In that respect, we recommend undertaking wider scale studies with appropriate sample size of Africans to further evaluate this association.

Despite our efforts in performing a comprehensive analysis, some limitations of this meta-analysis have to be considered including the relatively insufficient raw data in spite of laying down strict search strategy in the study; noting that some relevant studies could not be included in the meta-analysis. In addition, between-studies heterogeneity and publication bias might influence the net results of the meta-analysis. Moreover, some genetic polymorphisms of included studies were deviant from HWE that might imply a potential bias during control selection or genotyping errors. Haplotype analysis was also tried, but due to the lack of enough data it was not presented here, so we also recommend a linkage and haplotype analysis on a larger scale sample in various populations in order to have a better look into the situation 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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