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REVIEW

Association of IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms with susceptibility to chronic and aggressive periodontitis: a systematic review and meta-analysis

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Abstract

Objectives Several epidemiological studies have evaluated association of interleukin 10 (IL-10) polymorphisms with risk of periodontitis. However, the results remain conflicting and inconclusive. Here, we carried out a comprehensive systematic review and meta-analysis to evaluate the association of IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms with risk of chronic (CP) and aggressive (CP) periodontitis.

Methods Electronic databases including PubMed, Science Direct, SciELO, and CNKI were systematically searched to identify all relevant studies published up to 01 June 2020.

Results A total of 60 case–control studies with 5313 cases and 6528 controls met our inclusion criteria. Overall, the pooled data showed that the IL-10 -592C>A polymorphism was statistically associated with increased risk of periodontitis in the overall population, while no significant association was identified for IL-10 -1082A>G and IL-10 -819C>T polymorphisms. The subgroup analysis by ethnicity revealed that the IL-10 -1082A>G polymorphism was significantly associated with periodontitis risk in Caucasians, IL-10 -819C>T polymorphism in mixed population, and IL-10 -592C>A polymorphism in both Asians and mixed populations. When further analyzed by periodontitis type, only the IL-10 -592C>A polymorphism was associated with CP risk, but not AgP; and the IL-10 -1082A>G and -819C>T polymorphisms have not positive association neither in the CP and AgP.

Conclusions The current meta-analysis showed that the IL-10 -592C>A polymorphism was statistically associated with periodontitis risk in the overall population. Moreover, the IL-10 -1082A>G, IL-10 -819C>T, and IL-10 -592C>A polymorphisms were associated with periodontitis risk by ethnicity. Therefore, the IL-10 polymorphisms are of high clinical relevance by ethnicity and would be a useful marker to identify patients who are at higher risk for periodontitis.

Keywords Periodontitis · Chronic · Aggressive · Interleukin-10 · Polymorphism · Meta-analysis

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Introduction

Periodontitis is one of the most common oral health problems which is associated with several systemic conditions and diseases such as diabetes mellitus, cardiovascular disease, rheumatoid arthritis, psoriasis, pregnancy outcomes, and respiratory diseases [1–3]. Periodontitis is a multifactorial inflammatory disease resulting in the destruction of the supporting structures of the teeth [4, 5]. It is caused by the inflammatory response of the gingival tissues and the subjacent bone to the presence of dental plaque and leads to non-reversible loss of tooth support [5, 6]. The manifestation of the periodontitis can range from mild cases of marginal gingival inflammation with slight attachment and bone loss to severe cases of attachment and bone loss [7, 8]. There is a global variation in the prevalence of periodontitis [5, 9]. Population-based periodontitis incidence data estimates that this disease prevalence in the United States adults population ages 30 years and older is 47% (65 million people) and 65 years and older is 70% [10]. Chronic periodontitis (CP) is the most common form of periodontitis among the adult population [11]. Aggressive periodontitis (AgP) differs from the CP primarily by the rapid destruction of the periodontal ligament and alveolar bone [12]. However, there is no consensus in use of criteria to define the different forms of periodontitis in the literature, and the clinical distinction between CP and AgP is not clear cut [13, 14].

Currently, there is a consensus that the etiopathology of periodontitis entails a multifaceted dynamic interaction of periopathogenic microorganisms, innate and adaptive immune responses, and adverse environmental events [15, 16]. It is well established that besides environmental factors, genetic factors are also associated with development of periodontitis [17]. There is good evidence that the pro-inflammatory mediators (IL-6, TNF-α, and MMP-8), and the anti-inflammatory mediators (IL-10 and HDL) play a central role in periodontal inflammation [18, 19]. Interleukin-10 (IL-10) is an anti-inflammatory cytokine that has been implicated in various physiological and pathophysiological processes including periodontal diseases [20].

IL-10 is a multifunctional anti-inflammatory cytokine with both immunosuppressive and anti-angiogenic functions [21]. The human IL-10 gene is located on chromosome 1 at 1q31-32, contains four introns and five exons, and spans about 4.7 kb [22, 23]. Several polymorphic sites have been identified in the promoter region of the IL-10 gene, which associated with low levels of IL-10 production [24]. During the last decade, common promoter region variants of the gene including -1082A>G, -819C>T, and -592C>A polymorphisms had been reported to be associated with susceptibility to periodontitis in different ethnicities [25]. However, those studies results have been inconsistent and inclusive, partly due to periodontitis definition, sample size, source of controls, genotyping methods, and ethnicity. In addition, it is unclear whether IL-10 polymorphisms are associated with different periodontitis subtypes and/or clinical features. Thus, we performed the most comprehensive meta-analysis of all eligible published studies to derive a more precise estimation of the IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms with risk of periodontitis.

Materials and methods

Search strategy

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines. Ethical approval or patient consent was not needed because this is a meta-analysis in which all data were extracted from published literature. A comprehensive literature search was conducted in PubMed, Web of Knowledge, Web of Science, Embase, Islamic World Science Citation Center (ISC), Scientific Information Database (SID), WanFang, VIP, Chinese Biomedical Database (CBD), Scientific Electronic Library Online (SciELO) and China National Knowledge Infrastructure (CNKI) database to identify all relevant studies evaluated the association of the IL-10 promoter region polymorphisms with risk of the periodontitis published up to 01 June 2020. We used the following key words and medical subject headings (MeSH) terms for the research: ("Periodontitis" OR "Periodontal Disease" OR "Chronic Periodontitis" OR "Aggressive Periodontitis" OR "Gingivitis" OR "Alveolar-Resorption" OR "Riggs-Disease" OR "Pyorrhea-Alveolaris") AND ("Interleukin-10" OR "IL-10" OR "Human Cytokine Synthesis Inhibitory Factor" OR "CSIF") AND ("-1082A>G" OR "rs1800896" OR "c.-1117A>G" OR "g.3943A>G") AND ("-819C>T" OR "rs1800871" OR "c.-854 T>C" OR "g.4206 T>C") AND ("-592C>A" OR "rs1800872" OR "c.-627A>C" OR "g.4433A>C") AND ("Gene" OR "Genotype" OR "Allele" OR "Polymorphism" OR "Single nucleotide polymorphisms" OR "SNP" OR "Variation" OR "Mutation"). Additionally, the reference lists of all eligible original studies, review articles and previous meta-analyses were manually searched for more studies not identified in the database search. The searching was done without language limitations and publication date.

Inclusion and exclusion criteria

Studies were included in the current meta-analysis, regardless of the sample size and the population of the studies, if they met the following criteria: (a) case–control or cohort

study published as an original study; (b) evaluated the association of IL-10 promoter region polymorphisms with risk of chronic or aggressive periodontitis; (c) had detailed genotypes frequency in cases and controls or could be calculated from the text; (d) provided sufficient published data for estimating an odds ratio (OR) with a 95% confidence interval (95% CI). Accordingly, studies were excluded if one of the following existed: (a) case only studies or no control group; (b) family based, twin studies, and linkage studies; (c) no report essential information for data extraction; (d) unpublished data, abstracts, comments, conference abstracts, editorials, reviews, meta-analyses, review articles, case reports, animal studies, or editorials; (e) duplicate or overlapping with previous publications. In the case of multiple studies based on the same population, the most recent publication or largest sample size publication providing more information were included.

Data extraction

Data were independently extracted by two investigators from all eligible publications using a data-collecting form according to the inclusion criteria. For each included study, the following data was collected: first author name, publication year, country of origin, ethnicity, total number of cases and controls, the frequencies of genotypes for IL-10 -1082A>G, -819C>T, and -592C>A in cases and controls, type of periodontitis (chronic or aggressive), minor allele frequency (MAF) and p values of Hardy–Weinberg equilibrium (HWE) test in control groups. Diverse ethnicity descents were categorized as Caucasians, Asians, and mixed. When publications included subjects of more than one ethnicity or disease type, genotype data were extracted separately according to type of periodontitis or ethnicities for subgroup analyses. Therefore, it may be a publication included more than one study. Any disagreements were discussed and resolved through consensus with a third investigator. If selected articles did not reported necessary data the corresponding authors was contacted by email to request the missing data.

Statistical analysis

Crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to evaluate the strength the association of IL-10 -1082A>G, -819C>T and -592C>A polymorphisms with risk of periodontitis. The significance of the pooled ORs was determined by a Z_{test} at $p < 0.05$. The pooled ORs for the IL-10 polymorphisms were estimated under all five genetic models, i.e., allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB + BA vs. AA), and recessive (BB vs. BA + AA), which "A" represented the major allele and "B" represented the minor allele. The between-studies heterogeneity was assessed using the chi-squared based Q test. A p value>0.10 for the Q test shows a lack of heterogeneity among the studies. Moreover, a quantitative measure of between-study heterogeneity was tested using the I^2 statistic (range of 0–100%), in which the heterogeneity was considered low, moderate, and high based on I^2 values of 25%, 50%, and 75%, respectively. A fixed-effect model (Mantel–Haenszel method) was used to pool ORs and 95% CI when there was no significant heterogeneity. Otherwise, a random effects model (the DerSimonian and Laird method) was adopted to calculate the pooled OR and 95% CI. The Pearson's χ^2 test was applied to test the Hardy–Weinberg equilibrium (HWE) in healthy controls for the IL-10 polymorphisms, in which p value < 0.05 the genotype distribution of control population conformed to HWE. Stratified analyses were performed by ethnicity, disease type and HWE status. The literature publication bias was assessed visually inspecting the Begg's funnel plot for asymmetry and the Egger' linear regression test statistically. Egger`s linear regression test was used to evaluate the symmetry of the funnel plot in order to minimize the subjective influence of the visual inspection assessment, in which bias was considered with $p < 0.05$ in Egger's test. If publication bias was seen, the "trim and fill" method which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry was used to further analysis the possible effect of publication bias. Sensitivity analysis was carried out to assess the effects of individual study on the pooled OR by iteratively omitting one study. Moreover, sensitivity analysis was performed by removing those studies did not in agreement with HWE in control groups (HWE-violating studies). All the statistical analyses were performed by comprehensive meta-analysis (CMA) 2.0 software (Biostat, USA). Two-sided p values < 0.05 were considered statistically significant.

Result

Characteristics of the studies

A flow chart describing the process of inclusion/exclusion of study is presented in Fig. 1. Initially, we identified 318 potentially relevant publications from database searching and two studies from manual retrieval. After screening of titles and or abstracts, obvious irrelevance studies and duplicates were excluded resulting in 163 publications. An additional 132 publications were excluded because the studies were reviews, case reports, posters, letter to editor, not reporting the usable data and not related to periodontitis. Finally, a total of 60 case–control studies with 5313 cases and 6528 controls were included to the meta-analysis. The characteristics of selected studies to the meta-analysis are

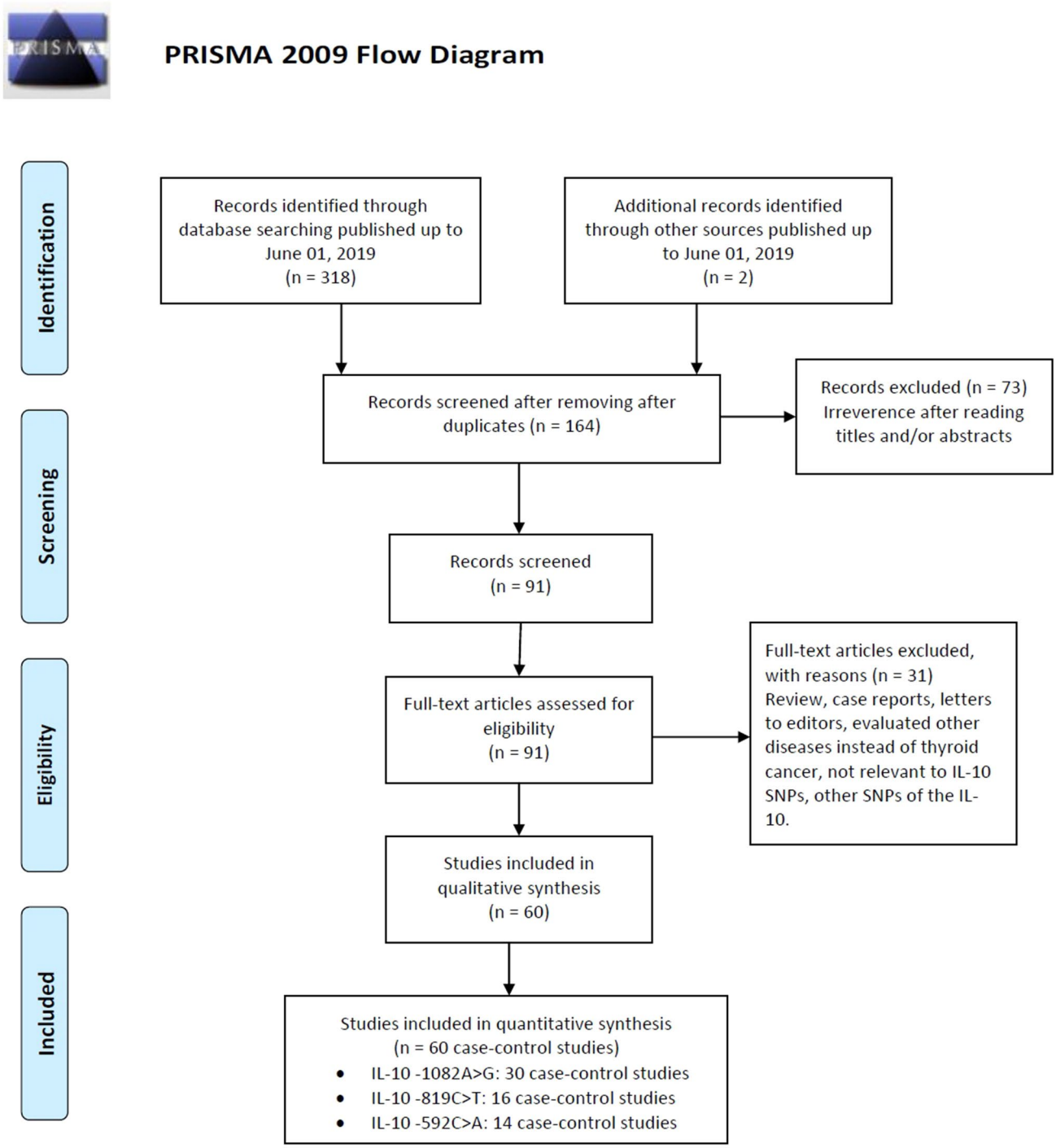

Fig. 1 Flow diagram of search strategy and study selection

Table 1 Characteristics of the studies included in the meta-analysis for the -1082A>G polymorphisms

First author	Country (ethnicity)	Periodontitis type	Case/control	Cases					Controls					MAFs	HWE
				Genotypes			Alleles		Genotypes			Alleles			
				AA	AG	GG	A	G	AA	AG	GG	A	G		
Berglundh (2003)	Sweden (Caucasian)	CP	60/39	14	22	24	50	70	12	19	8	43	35	0.448	0.924
Scarel-Caminaga (2004)	Brazil (Mixed)	CP	67/43	34	25	8	93	42	17	21	5	55	31	0.360	0.697
	Brazil (Caucasian)	CP	48/36	27	15	6	69	27	14	19	3	47	25	0.347	0.324
Brett (2005)	UK (Caucasian)	CP	55/92	18	24	13	60	50	28	47	17	103	81	0.440	0.725
		AgP	48/92	16	17	15	49	47							
Babel (2006)	Germany (Caucasian)	CP	118/114	36	82	–	–	–	30	84	–	–	–	–	–
Mellati (2007)	Iran (Asian)	AgP	53/61	16	27	9	59	45	23	17	7	63	31	0.329	0.212
Tervonen (2007)	Finland (Caucasian)	CP	51/178	19	32	–	–	–	54	124	–	–	–	–	–
Reichert (2008)	Germany (Caucasian)	CP	27/34	5	17	5	27	27	10	18	6	38	30	0.441	0.667
		AgP	32/34	14	15	3	43	21							
Hu (2009)	China (Asian)	CP	145/126	132	13	0	277	13	115	11	0	241	11	0.043	0.608
		AgP	65/126	60	5	0	125	5							
Kobayashi (2009)	Japan (Asian)	CP	117/108	109	8	0	226	8	102	6	0	210	6	0.027	0.766
Moreira (2009)	Brazil (Mixed)	CP	67/43	31	28	8	90	44	16	20	7	52	34	0.395	0.858
		AgP	55/43	26	25	4	77	33							
Wang (2009)	China (Asian)	CP	146/138	134	12	0	280	12	123	15	0	261	15	0.054	0.499
Jaradat (2011)	Jordan (Asian)	CP	105/86	38	47	20	123	87	17	36	33	70	102	0.593	0.218
		AgP	85/86	19	36	30	74	96							
Loo (2012)	China (Asian)	CP	440/850	277	31	132	585	295	782	17	51	1581	119	0.007	≤0.001
Atanasovska-Stojanovska (2012)	Macedonia (Caucasian)	CP	111/299	34	62	15	130	92	70	212	17	352	246	0.411	≤0.001
Ianni (2013)	Italy (Caucasian)	CP	75/470	39	29	7	107	43	168	209	93	545	395	0.420	0.058
Houshmand (2013)	Iran (Asian)	CP	52/30	22	23	7	67	37	3	7	20	13	47	0.783	0.086
Chambrone (2014)	Peru (Mixed)	CP	53/53	22	18	13	62	44	11	16	26	38	68	0.641	0.012
Silvera (2015)	Brazil (Mixed)	CP	60/41	27	25	8	79	41	23	14	4	60	22	0.268	0.404
		AgP	50/41	20	25	5	65	35							
Hannum (2015)	Brazil (Mixed)	CP	36/30	7	16	13	30	42	5	13	12	23	37	0.616	0.647
Crena (2015)	India (Asian)	SCP	46/45	34	11	1	79	13	27	10	8	64	26	0.288	0.002
Gurol (2016)	Turkey (Caucasian)	CP	18/34	1	15	2	17	19	11	21	2	43	25	0.367	0.055
Moudi (2018)	Iran (Asian)	CP	210/100	34	98	78	166	254	38	41	21	117	83	0.415	0.119
Emampanah (2019)	Iran (Asian)	CP	64/128	12	21	5	45	31	19	29	21	67	71	0.514	0.187

CP chronic periodontitis, *AgP* aggressive periodontitis, *MAFs* minor allele frequencies, *HWE* Hardy–Weinberg equilibrium

Table 2 Characteristics of the studies included in the meta-analysis for the IL-10 -819C>T and -592C>A polymorphisms

First author	Ethnicity (country)	Periodontitis type	Case/control	Cases					Control					MAFs	HWE
				Genotypes			Alleles		Genotypes			Alleles			
				CC	TC	TT	C	T	CC	TC	TT	C	T		
IL-10 -819C>T															
Tang (2004)	China (Asian)	CP	142/81	14	83	45	111	153	2	48	31	52	110	0.679	0.001
Scarel-Caminaga (2004)	Brazil (Mixed)	CP	67/43	16	42	9	74	60	21	16	6	58	28	0.325	0.316
	Brazil (Caucasian)	CP	48/36	11	32	5	54	42	19	13	4	51	21	0.291	0.449
Sumer (2007)	Turkey (Caucasian)	CP	75/73	33	32	10	98	52	40	28	5	108	38	0.260	0.973
Reichert (2008)	Germany (Caucasian)	CP	27/34	20	7	0	47	7	23	11	0	57	11	0.161	0.260
Hu (2009)	China (Asian)	CP	145/126	16	52	77	84	206	12	55	59	79	173	0.686	0.874
Kobayashi (2009)	Japan (Asian)	CP	117/108	14	46	57	74	160	14	43	51	71	145	0.671	0.309
Wang (2009)	China (Asian)	CP	146/138	12	59	75	83	209	14	57	67	85	191	0.692	0.715
Atanasovska-Stojanovska (2012)	Macedonia (Caucasian)	CP	111/299	64	43	4	171	51	155	125	19	435	163	0.348	0.348
Houshmand (2013)	Iran (Asian)	CP	82/30	14	32	6	60	44	5	17	8	27	33	0.550	0.427
Taleb (2014)	Syria (Asian)	AgP	83/79	29	27	13	85	53	34	32	10	100	52	0.342	0.573
Silvera (2015)	Brazil (Mixed)	CP	61/61	22	32	7	76	46	28	25	8	81	41	0.336	0.523
		AgP	50/61	21	21	8	63	37							
Gurol (2016)	Turkey (Caucasian)	CP	16/34	1	14	1	168	16	5	29	0	39	29	0.426	≤0.001
Moudi (2018)	Iran (Asian)	CP	210/100	58	138	14	254	166	37	54	9	128	72	0.360	0.085
Emampanah (2019)	Iran (Asian)	CP	64/128	13	25	13	51	51	35	42	25	112	92	0.451	0.088
IL-10 -592C>A				CC	AC	AA	C	A	CC	AC	AA	C	A		
Scarel-Caminaga (2004)	Brazil (Mixed)	CP	67/43	19	46	2	84	50	21	17	5	59	27	0.314	0.589
	Brazil (Caucasian)	CP	48/36	12	34	2	58	38	19	14	3	52	20	0.277	0.853
Sumer (2007)	Turkey (Caucasian)	CP	75/73	24	40	11	88	62	43	29	1	115	31	0.212	0.108
Claudino (2008)	Brazil (Mixed)	CP	116/173	33	65	18	131	101	34	69	20	137	109	0.443	0.129
Reichert (2008)	Germany (Caucasian)	CP	27/34	20	7	0	47	7	23	10	1	56	12	0.176	0.944
Hu (2009)	China (Asian)	CP	145/126	27	32	86	86	204	16	48	62	80	172	0.682	0.174
Wang (2009)	China (Asian)	CP	146/138	13	56	77	82	210	12	61	65	85	191	0.692	0.663
Jaradat (2011)	Jordan (Asian)	CP	105/86	60	32	13	152	58	63	19	4	145	27	0.157	0.125
		AgP	85/86	57	20	8	134	36							
Atanasovska-Stojanovska (2012)	Macedonia (Caucasian)	CP	111/299	62	45	4	169	53	154	117	28	425	173	0.289	0.402
Silvera (2015)	Brazil (Mixed)	CP	61/61	22	32	7	76	46	27	26	8	80	42	0.344	0.662
		AgP	50/61	20	21	9	61	39							
Moudi (2018)	Iran (Asian)	CP	210/100	46	152	12	244	176	29	61	10	119	81	0.405	0.007
Emampanah (2019)	Iran (Asian)	CP	64/128	22	25	6	69	37	53	45	5	151	55	0.267	0.238

CP chronic periodontitis, *AgP* aggressive periodontitis, *MAFs* minor allele frequencies, *HWE* Hardy–Weinberg equilibrium

presented in Tables 1 and 2. Among them, there were 30 case–control studies with 2559 cases and 3653 controls were on -1082A>G [18, 19, 26–44], 16 case–control studies with 1444 cases and 1431 controls on -819C>T [29, 31, 33, 37, 38, 41–43, 45–48], and 14 case–control studies with 1310 cases and 1444 controls were on -592C>A polymorphism [27, 29, 33, 38, 41, 42, 45, 48, 49]. Moreover, there were 30 case–control studies with 4707 cases and 5758 controls on CP and eleven studies with 606 cases and 770 controls on AgP. Twenty of these studies were conducted in Caucasians, 26 studies in Asians, and 14 studies were performed in mixed population. The countries of these studies included Sweden, Brazil, UK, Germany, Iran, Finland, China, Japan, Jordan, Macedonia, Italy, Peru, India, Turkey, and Syria. The distribution of genotypes in the controls of all studies was consistent with HWE, except for six studies including four studies on the -1082A>G and two studies on the -819C>T. The characteristics of each study included in this meta-analysis are presented in Tables 1 and 2.

Quantitative synthesis

IL-10 -1082A>G polymorphism

Table 3 presents the main results of the meta-analysis of the IL-10 -1082 A>G polymorphism and periodontitis risk. A total of 30 case–control studies with 2559 cases and 3653 controls on IL-10 -1082A>G polymorphism were included to the meta-analysis. The pooled ORs based on selected studies did not show a significant association between the IL-10 -1082A>G polymorphism and risk of periodontitis under all five genetic models, i.e., allele (G vs. A: OR 0.896, 95% CI 0.679–1.388, $p=0.623$, Fig. 2a), homozygous (GG vs. AA: OR 0.838, 95% CI 0.395–1.778, $p=0.645$), heterozygous (GA vs. AA: OR 0.941, 95% CI 0.707–1.252, $p=0.676$), dominant (GG + GA vs. AA; OR 0.973, 95% CI 0.624–1.517, $p=0.903$) and recessive (GG vs. GA + AA: OR 0.900, 95% CI 0.465–1.742, $p=0.755$). Stratified analysis by periodontitis type revealed that of the IL-10 -1082 A>G polymorphism was not associated with CP and AgP risk. However, subgroup analysis by the ethnicity showed a significant association between the IL-10 -1082A>G polymorphism and periodontitis risk in Caucasians under the heterozygote model (GA vs. AA: OR 0.706, 95% CI 0.561–0.888, $p=0.003$), but not in the Asians and mixed population.

IL-10 -819C>T polymorphism

Table 4 presents the main results of the meta-analysis of the IL-10 -819C>T polymorphism and periodontitis risk**.** A total of 16 case–control studies with 1444 cases and 1431 controls on IL-10 -819C>T polymorphism were included to the meta-analysis. Five studies were from Caucasians, six were from Asians, and two were from mixed population. The pooled data showed that the IL-10 -819C>T polymorphism was not significantly associated with periodontitis risk in overall population under all five genetic models, i.e., allele (T vs. C: OR 0.840, 95% CI 0.620–1.138, $p=0.261$), homozygous (TT vs. CC: OR 1.061, 95% CI 0.774–1.454, $p=0.714$), heterozygous (TC vs. CC: OR 1.171, 95% CI 0.867–1.582, $p=0.303$, Fig. 2b), dominant (TT + TC vs. CC; OR 0.652, 95% CI 0.321–1.325, $p=0.237$) and recessive (TT vs. TC + CC: OR 0.861, 95% CI 0.701–1.056, $p=0.150$). When stratified analyzed by periodontitis type was performed a significant association did not find between the IL-10 -592C>A polymorphism with CP and AgP. However, subgroup analysis by the ethnicity revealed a significant association between the IL-10 -819C>T polymorphism and periodontitis risk in mixed populations under the heterozygote model (TC vs. CC: OR 2.111, 95% CI 1.102–4.046, $p=0.024$), but not in the Caucasians and Asians.

IL-10 -592C>A polymorphism

Table 5 presents the main results of the meta-analysis of the IL-10 -592C>A polymorphism and periodontitis risk. A total of 14 case–control studies with 1310 cases and 1444 controls on IL-10 -819C>T polymorphism were included to the meta-analysis. The pooled results based on the included studies revealed a significant association between the IL-10 -592C>A polymorphism and an increased risk of periodontitis in overall population under two genetic models, i.e., homozygous (AA vs. CC: OR 1.095, 95% CI 0.647–1.853, $p=0.735$) and dominant (AA + CA vs. CC; OR 1.422, 95% CI 1.044–1.936, $p=0.026$, Fig. 2c). Stratified analysis by periodontitis showed a significant association between the IL-10 -592C>A polymorphism and CP risk under allele model (A vs. C: OR 1.310, 95% CI 1.021–1.682, $p=0.034$), but not with AgP. We then performed stratified analysis by ethnicity and found a significant association between the IL-10 -592C>A polymorphism and increased risk of periodontitis in Asians under the recessive model (AA vs. AC + CC: OR 1.443, 95% CI 1.047–1.988, $p=0.025$), and in the mixed population under two genetic models, i.e., allele (A vs. C: OR 1.444, 95% CI 0.126–1.852, $p=0.004$) and dominant (AA + CA vs. CC; OR 1.930, 95% CI 1.357–2.747, $p\leq 0.001$).

Sensitivity analysis

Sensitivity analyses were performed after sequentially removing each eligible study to assess the influence of the individual data set to the pooled ORs. The results showed that no individual study significantly affected the pooled ORs. Moreover, we carried out sensitivity

Table 3 Summary risk estimates for association of IL-10 -1082A>G polymorphism with periodontitis risk

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	G vs. A	Random	94.27	≤0.001	0.896	0.679–1.388	−0.491	0.623	0.975	0.007
	GG vs. AA	Random	90.07	≤0.001	0.838	0.395–1.778	−0.461	0.645	0.892	0.005
	GA vs. AA	Random	63.45	≤0.001	0.941	0.707–1.252	−0.419	0.676	0.109	0.382
	GG + GA vs. AA	Random	88.37	≤0.001	0.973	0.624–1.517	−0.121	0.903	0.694	0.016
	GG vs. GA + AA	Random	89.93	≤0.001	0.900	0.465–1.742	−0.312	0.755	0.558	0.009
Periodontitis type										
CP	G vs. A	Random	94.50	≤0.001	0.899	0.540–1.497	−0.407	0.684	0.404	0.019
	GG vs. AA	Random	90.90	≤0.001	0.812	0.351–1.878	−0.488	0.626	1.000	0.084
	GA vs. AA	Random	62.58	≤0.001	0.914	0.678–1.232	−0.590	0.555	0.029	0.387
	GG + GA vs. AA	Random	88.70	≤0.001	0.929	0.578–1.494	−0.304	0.761	0.346	0.017
	GG vs. GA + AA	Random	90.71	≤0.001	0.864	0.414–1.801	−0.391	0.696	0.620	0.008
AgP	G vs. A	Fixed	11.42	0.342	0.985	0.793–1.224	−0.137	0.891	1.000	0.681
	GG vs. AA	Fixed	18.75	0.291	0.972	0.615–1.537	−0.120	0.905	0.707	0.493
	GA vs. AA	Fixed	29.14	0.206	1.024	0.729–1.439	0.138	0.890	0.763	0.811
	GG + GA vs. AA	Random	56.26	0.033	1.083	0.668–1.756	0.324	0.746	1.000	0.540
	GG vs. GA + AA	Fixed	23.08	0.260	1.043	0.706–1.540	0.211	0.833	0.452	0.514
By Ethnicity										
Caucasian	G vs. A	Random	63.27	0.012	0.995	0.732–1.353	−0.030	0.976	0.763	0.442
	GG vs. AA	Random	60.14	0.020	1.190	0.610–2.231	0.511	0.609	0.548	0.484
	GA vs. AA	Fixed	0.00	0.452	0.706	0.561–0.888	−2.969	0.003	0.076	0.048
	GG + GA vs. AA	Fixed	3.63	0.405	0.916	0.731–1.149	−0.757	0.449	0.117	0.088
	GG vs. GA + AA	Random	58.66	0.024	1.373	0.767–2.458	1.068	0.286	0.763	0.918
Asian	G vs. A	Random	96.80	≤0.001	0.872	0.309–2.461	−0.0258	0.796	0.901	0.038
	GG vs. AA	Random	95.75	≤0.001	0.550	0.082–3.675	−0.617	0.537	0.806	0.081
	GA vs. AA	Random	76.43	≤0.001	1.205	0.646–2.246	0.586	0.558	0.901	0.246
	GG + GA vs. AA	Random	93.40	≤0.001	1.036	0.391–2.746	0.072	0.943	0.265	0.008
	GG vs. GA + AA	Random	96.24	≤0.001	0.606	0.109–3.383	−0.571	0.568	0.462	0.155
Mixed	G vs. A	Random	62.01	0.032	0.772	0.509–1.171	−1.217	0.224	0.462	0.753
	GG vs. AA	Fixed	36.69	0.177	0.606	0.365–1.005	−1.942	0.052	0.220	0.202
	GA vs. AA	Fixed	17.34	0.304	0.855	0.577–1.267	−0.781	0.435	1.000	0.674
	GG + GA vs. AA	Fixed	49.26	0.096	0.753	0.446–1.272	−1.062	0.288	0.806	0.729
	GG vs. GA + AA	Fixed	23.70	0.263	0.675	0.433–1.051	−1.741	0.822	0.220	0.035
By HWE*										
	G vs. A	Random	70.03	≤0.001	0.866	0.664–1.129	−1.065	0.287	0.276	0.533
	GG vs. AA	Random	67.57	≤0.001	0.773	0.442–1.354	−0.900	0.368	0.837	0.538
	GA vs. AA	Fixed	16.42	0.261	0.821	0.681–0.991	−2.054	0.040	0.035	0.029
	GG + GA vs. AA	Random	52.33	0.006	0.935	0.713–1.227	−0.483	0.629	0.483	0.620
	GG vs. GA + AA	Random	69.22	≤0.001	0.821	0.502–1.344	−0.785	0.433	1.000	0.824

CI confidence interval, *CP* chronic periodontitis, *AgP* aggressive periodontitis, *HWE* Hardy–Weinberg equilibrium

*Excluding the HWE-violating studies

analysis by omitting those studies deviated from the HWE for the IL-10 -1082A>G and -819C>T polymorphisms. Results showed that the significance of pooled ORs in overall analysis under the heterozygote model (GA vs. AA: OR 0.821, 95% CI 0.681–0.991, $p = 0.040$) was influenced by omitting these four studies for IL10 -1082A>G, indicating that the results were relatively unstable (Table 3). However, sensitivity analysis showed that those two studies had not effect on OR values for the IL-10 − 819 polymorphism, which indicated the stability of present work for the IL-10 -819C>T polymorphism (Table 4).

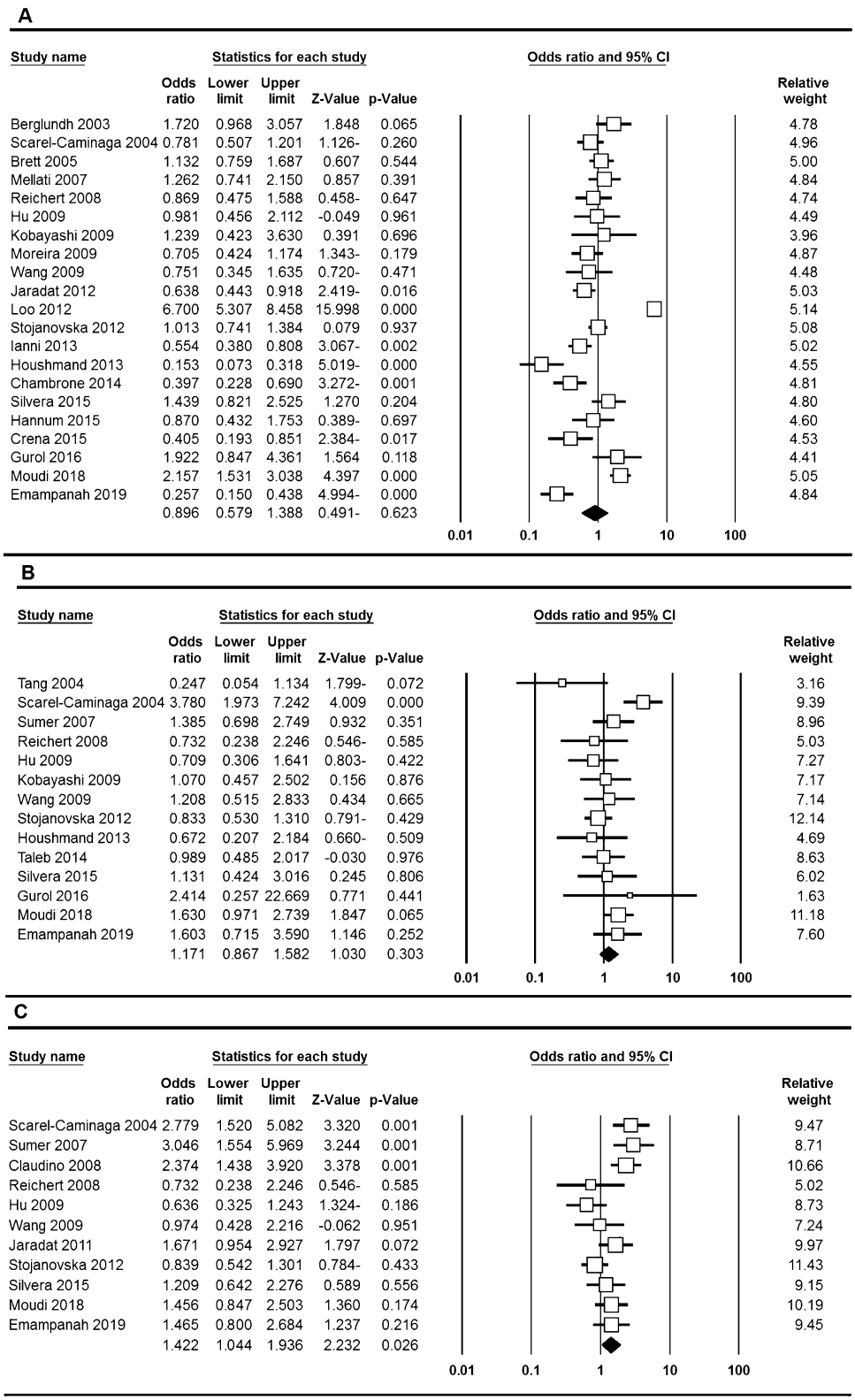

Fig. 2 Forest plots for association between the IL-10 polymorphisms and risk of periodontitis. **a** 1082A>G (allele model: G vs. A); **b** -819C>T (heterozygote model: TC vs. CC); **c** -592C>A (dominant model: AA + CA vs. CC)

Publication bias

Begg's funnel plot and Egger's tests were performed to assess the publication bias of the selected articles. The shapes of the funnel plots did not reveal any evidence of an obvious asymmetry in all comparison models (Tables 3, 4, 5). However, sthe Begg's test is non-parametric, which reduces its power. Therefore, Egger's test

Table 4 Summary risk estimates for association of IL-10 -819C>T polymorphism with periodontitis risk

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	T vs. C	Random	80.85	≤0.001	0.840	0.620–1.138	−1.123	0.261	1.000	0.978
	TT vs. CC	Fixed	36.62	0.106	1.061	0.774–1.454	0.367	0.714	0.533	0.688
	TC vs. CC	Random	46.99	0.027	1.171	0.867–1.582	1.030	0.303	0.631	0.607
	TT + TC vs. CC	Random	88.97	≤0.001	0.652	0.321–1.325	−1.183	0.237	0.631	0.315
	TT vs. TC + CC	Fixed	30.75	0.154	0.861	0.701–1.056	−1.438	0.150	0.640	0.740
Periodontitis type										
CP	T vs. C	Random	82.39	≤0.001	0.828	0.593–1.157	−1.106	0.269	1.000	0.992
	TT vs. CC	Random	70.56	≤0.001	0.753	0.389–1.459	−0.839	0.401	0.720	0.609
	TC vs. CC	Random	60.26	0.005	0.994	0.651–1.516	−0.030	0.976	0.436	0.508
	TT + TC vs. CC	Random	90.55	≤0.001	0.546	0.241–1.250	−1.429	0.153	0.350	0.281
	TT vs. TC + CC	Fixed	65.11	0.002	0.719	0.477–1.085	−1.573	0.116	1.000	0.713
AgP	T vs. C	Fixed	0.00	0.600	1.036	0.726–1.479	0.194	0.846	NA	NA
	TT vs. CC	Random	91.75	≤0.001	0.415	0.031–5.504	−0.667	0.505	NA	NA
	TC vs. CC	Fixed	69.19	0.072	0.676	0.379–1.208	−1.321	0.187	NA	NA
	TT + TC vs. CC	Random	82.65	0.016	0.433	0.114–1.651	−1.226	0.220	NA	NA
	TT vs. TC + CC	Random	86.14	0.007	0.538	0.098–2.964	−0.712	0.476	NA	NA
By Ethnicity										
Caucasian	T vs. C	Random	69.20	0.011	1.062	0.648–1.739	0.237	0.813	0.806	0.963
	TT vs. CC	Fixed	45.53	0.138	1.356	0.674–2.728	0.855	0.393	0.734	0.396
	TC vs. CC	Random	60.27	0.039	1.368	0.729–2.565	0.976	0.329	0.462	0.365
	TT + TC vs. CC	Random	91.75	≤0.001	0.847	0.196–3.658	−0.223	0.824	0.806	0.804
	TT vs. TC + CC	Fixed	25.01	0.261	1.110	0.568–2.170	0.305	0.760	0.734	0.469
Asian	T vs. C	Random	82.27	≤0.001	0.671	0.450–1.001	−1.954	0.051	0.707	0.714
	TT vs. CC	Fixed	38.87	0.147	0.954	0.640–1.420	−0.23	0.816	0.707	0.014
	TC vs. CC	Fixed	0.00	0.556	0.67	0.599–1.255	−0.758	0.448	0.707	0.047
	TT + TC vs. CC	Random	81.34	≤0.001	0.467	0.212–1.029	−1.890	0.059	1.000	0.692
	TT vs. TC + CC	Fixed	48.04	0.087	0.846	0.670–1.069	−1.400	0.161	0.452	0.434
Mixed	T vs. C	Fixed	0.00	0.344	1.360	0.950–1.946	1.681	0.093	NA	NA
	TT vs. CC	Fixed	16.98	0.272	1.156	0.538–2.483	0.371	0.711	NA	NA
	TC vs. CC	Fixed	63.99	0.096	2.111	1.102–4.046	2.252	0.024	NA	NA
	TT + TC vs. CC	Fixed	69.90	0.068	1.832	0.993–3.380	1.937	0.053	NA	NA
	TT vs. TC + CC	Fixed	0.00	0.702	0.792	0.457–1.372	−0.831	0.406	NA	NA
By HWE*										
	T vs. C	Random	82.63	≤0.001	0.849	0.605–1.192	−0.945	0.345	1.000	0.739
	TT vs. CC	Fixed	18.89	0.275	1.118	0.809–1.545	0.678	0.498	0.602	0.261
	TC vs. CC	Random	50.02	0.035	1.135	0.800–1.610	0.707	0.479	0.591	0.773
	TT + TC vs. CC	Random	90.61	≤0.001	0.652	0.304–1.398	−1.099	0.272	0.474	0.253
	TT vs. TC + CC	Fixed	36.91	0.123	0.864	0.642–1.162	−0.967	0.334	0.916	0.742

CI confidence interval, *CP* chronic periodontitis, *AgP* aggressive periodontitis, *NA* not applicable, *HWE* Hardy–Weinberg equilibrium

*Excluding the HWE-violating studies

was used to provide statistical evidence of funnel plot symmetry. The results still did not show any evidence of publication bias for the IL-10 -819C>T and -592C>A polymorphisms and risk of periodontitis. However, the *p* value of Egger's test confirmed the existence of publication bias for the IL-10 -1082A>G polymorphism under the allele model ($P_{Begg's} = 0.575$ and $P_{Egger's} = 0.015$, Fig. 3), the homozygote model ($P_{Begg's} = 0.892$ and $P_{Egger's} = 0.005$), the dominant model ($P_{Begg's} = 0.694$ and $P_{Egger's} = 0.016$), and the recessive model ($P_{Begg's} = 0.558$ and $P_{Egger's} = 0.009$). Then, we used the Duval and Tweedie non-parametric ''trim and fill" method to recalculate the pooled risk estimate. However, analysis demonstrated that

Table 5 Summary risk estimates for association of IL-10 -592C>A polymorphism with periodontitis risk

Subgroup	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall										
	A vs. C	Random	58.01	0.008	1.291	1.057–1.576	2.505	0.012	0.602	0.802
	AA vs. CC	Random	51.53	0.036	1.095	0.647–1.853	0.339	0.735	0.465	0.456
	AC vs. CC	Random	68.73	0.001	1.203	0.805–1.798	0.900	0.361	1.000	0.751
	AA + CA vs. CC	Random	63.65	0.002	1.422	1.044–1.936	2.232	0.026	0.916	0.800
	AA vs. AC + CC	Random	54.45	0.015	1.145	0.759–1.728	0.647	0.517	0.916	0.736
Periodontitis type										
CP	A vs. C	Random	64.61	0.004	1.310	1.021–1.682	2.119	0.034	1.000	0.778
	AA vs. CC	Random	51.61	0.035	1.077	0.627–1.849	0.268	0.789	0.465	0.422
	AC vs. CC	Random	69.90	0.001	1.243	0.817–1.891	1.014	0.310	1.000	0.840
	AA + CA vs. CC	Random	71.61	≤0.001	1.461	0.976–2.188	1.840	0.066	0.754	0.849
	AA vs. AC + CC	Random	55.84	0.020	1.151	0.723–1.833	0.594	0.553	0.916	0.721
AgP	A vs. C	Fixed	0.00	0.669	1.325	0.898–1.955	1.418	0.156	NA	NA
	AA vs. CC	Fixed	0.00	0.661	1.793	0.780–4.121	1.374	0.169	NA	NA
	AC vs. CC	Fixed	0.00	0.907	1.131	0.658–1.942	0.445	0.656	NA	NA
	AA + CA vs. CC	Fixed	0.00	0.812	1.277	0.777–2.099	0.964	0.335	NA	NA
	AA vs. AC + CC	Fixed	0.00	0.643	1.701	0.768–3.767	1.310	0.190	NA	NA
By Ethnicity										
Caucasian	A vs. C	Random	82.36	0.001	1.279	0.643–2.544	0.702	0.483	1.000	0.727
	AA vs. CC	Random	73.44	0.010	1.288	0.197–8.431	0.264	0.792	0.734	0.511
	AC vs. CC	Random	71.57	0.014	1.628	0.799–3.317	1.343	0.179	0.734	0.522
	AA + CA vs. CC	Random	80.00	0.002	1.587	0.696–3.617	1.099	0.272	1.000	0.546
	AA vs. AC + CC	Random	66.96	0.028	0.934	0.180–4.844	-0.082	0.935	0.308	0.563
Asian	A vs. C	Fixed	27.20	0.253	1.24	0.993–1.559	1.896	0.058	1.000	0.076
	AA vs. CC	Fixed	49.05	0.140	1.161	0.714–1.888	0.603	0.547	0.296	0.121
	AC vs. CC	Random	71.42	0.030	0.809	0.364–1.799	-0.520	0.603	1.000	0.550
	AA + CA vs. CC	Fixed	58.25	0.091	1.090	0.744–1.595	0.441	0.659	1.000	0.595
	AA vs. AC + CC	Fixed	0.00	0.496	1.443	1.047–1.988	2.244	0.025	0.296	0.271
Mixed	A vs. C	Fixed	0.00	0.456	1.444	0.126–1.852	2.892	0.004	1.000	0.413
	AA vs. CC	Fixed	0.00	0.576	0.960	0.536–1.718	-0.138	0.890	1.000	0.507
	AC vs. CC	Fixed	57.56	0.095	1.375	0.930–2.033	1.598	0.110	0.296	0.067
	AA + CA vs. CC	Fixed	34.46	0.217	1.930	1.357–2.747	3.655	≤0.001	1.000	0.890
	AA vs. AC + CC	Fixed	46.28	0.155	1.098	0.652–1.850	0.353	0.724	0.296	0.101

CI confidence interval, *CP* chronic periodontitis, *AgP* aggressive periodontitis, *NA* not applicable

the results of our study did not significantly change even after adjusting for the publication bias.

Minor allele frequencies (MAFs)

The MAFs for the IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms in the healthy controls are provided in Tables 1 and 2. The MAF of the IL-10 -1082 in Caucasian controls varied from 0.347 to 0.448, in mixed population from 0.268 to 0.641, but in Asians was from 0.043 to 0.783. The MAF of IL-10 -819C>T in the Caucasian controls was from 0.161 to 0.426, in mixed population from 0.325 to 0.336, but that in Asians was from 0.342 to 0.686. For IL-10 -592C>A the MAF in Caucasian controls varied from 0.176 to 0.289, in mixed population from 0.314 to 0.443, but in Asians was from 0.157 to 0.682.

Discussion

The exact etiology of periodontitis has not known exactly [50]. However, certain interleukins, inflammatory mediators and cellular receptors genes interact with some environmental factors such as microorganisms are related to increasing

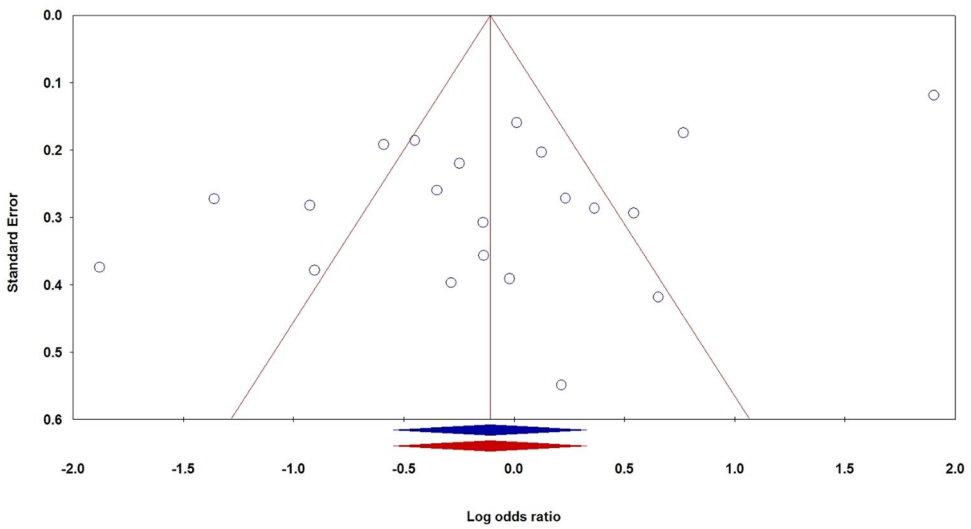

Fig. 3 Begg's funnel plots of IL-10 -1082A>G polymorphism with periodontitis risk for publication bias test under the allele model (G vs. A)

the risk of this disease [51, 52]. Several studies have revealed that the Cytokines such as interleukins (IL-1A, IL-1B, IL-6, and IL-10, among others), surface receptors such as the Fcγ family (FCGRs), and cyclooxygenase- (COX-) 2 and matrix metalloproteinase (MMP) are risk factors in the development and progression of periodontitis [53, 54]. IL-10 is a key immunoregulatory cytokine that may be of significance in the immunopathogenesis of inflammatory diseases such as periodontitis [55]. It has been proposed that IL-10 may attenuate periodontal tissue destruction through the induction of tissue inhibitors of metalloproteinases and the inhibitor of osteoclastogenesis [56, 57].

To date, several epidemiological studies have been conducted to evaluate the association of IL-10 gene promoter region polymorphisms with risk of periodontitis, but results have remained conflicting. For example, regarding the IL-10 -1082A>G polymorphism, Crena et al., have found that the AA genotype was associated with a significant increase in chronic periodontitis risk compared in an Indian population [35]. Atanasovska-Stojanovska et al., reported that the IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms were associated with periodontitis in a Macedonian population [29]. Similar increases in periodontitis risk have also reported in other studies that focused on different ethnicities, whereas other studies failed to show a significant association of the IL-10 polymorphisms and risk of periodontitis [32, 34, 58]. Here, we evaluate the association between three most common promoter polymorphisms of the IL-10 gene and the susceptibility to periodontitis using data from 60 published case–control studies. To our knowledge, this is so far the largest meta-analysis that has evaluated IL-10 gene promoter polymorphisms with risk of chronic and aggressive periodontitis. When all the eligible studies were pooled into the meta-analysis, the IL-10 -592C>A polymorphism was significantly associated with periodontitis under the allele model (A vs. C: OR 1.308, 95% CI 1.026–1.667, $p=0.030$) in overall analysis, while no significant association was identified for IL-10 -1082A>G and IL-10 -819C>T polymorphisms. In the stratified by ethnicity, significantly increased periodontitis risk was observed in Caucasians under the heterozygote model (GA vs. AA: OR 0.706, 95% CI 0.561–0.888, $p=0.003$) for IL-10 -1082A>G polymorphism, in mixed population under heterozygote model (TC vs. CC: OR 2.111, 95% CI 1.102–4.046, $p=0.024$) for IL-10 -819C>T polymorphism, in Asians under recessive model (AA vs. AC + CC: OR 1.443, 95% CI 1.047–1.988, $p=0.025$) and mixed population under the allele model (A vs. C: OR 1.444, 95% CI 0.126–1.852, $p=0.004$) for IL-10 -592 polymorphism. Moreover, in the subgroup analysis by the periodontitis type, only IL-10 -592 polymorphism is associated with CP risk, but not aggressive type; while the IL-10 -1082 and -819 polymorphisms have not positive association neither in the CP and AgP development.

In 2012, Zhong et al., published the first meta-analysis to evaluate the association of IL-10 polymorphisms with risk of periodontitis, which included eleven studies with 1106 cases and 946 controls on -1082, seven studies with 719 cases and 603 controls on -819, and six studies encompassing 576 cases and 587 on -592 polymorphism. They found that IL-10 -1082A>G and -592C>A polymorphisms were associated with CP, especially in Caucasians [25]. In the same year, Albuquerque et al., carried out another meta-analysis regarding association between IL-10 gene polymorphisms and periodontitis risk, in which included six case–control studies on -1082 (with 453 CP patients, 197 AgP patients, and 502 controls), four case–control studies on -819 (with 295 CP patients, 97 AP patients, and 269 controls), and five studies on -592 (with 411 CP patients, 97 AP patients, and 442 controls) [59]. They have also suggested that the IL-10 -819C>T and -592C>A polymorphisms were

associated with increased periodontitis risk in Caucasians. However, their results about IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms and periodontitis risk essentially remains an open field, as the number of studies is considerably smaller than that needed for the achievement of robust conclusions. Compared with the previous meta-analyses, our meta-analysis was more comprehensively searched and included 60 case–control studies, which 30 case–control studies comprising a total of 2285 cases and 2950 controls for -1082A>G, 16 case–control studies with 1170 cases and 1142 for -819C>T, and nine case–control studies with 1036 cases and 1069 controls for -592C>A. In addition, our meta-analysis performed subgroup analysis in the Asians and mixed population and sensitivity analysis. Moreover, we found a significant association between -1082A>G polymorphism and periodontitis risk in Caucasian, but not in the overall, Asians and mixed population. However, in the previous meta-analyses, Zhong et al., and Albuquerque et al., have not found association between IL-10 1082 polymorphism and periodontitis risk (either CP or AgP), even when by subgroup analysis among Caucasians [25, 59]. As to the IL-10 -819C>T and -592C>A polymorphisms, we have found a significant association between IL-10 -819 periodontitis risk in mixed population and IL-10 -592C>A polymorphism in Asian and mixed population, but not Caucasians. However, the previous meta-analyses have been reported a significant association of IL-10 -819C>T and IL-10 -592C>A polymorphisms with risk of periodontitis in Caucasians [59]. These differences may be derived by different genetic backgrounds and environmental exposures, such as the difference of MAFs in the healthy controls among the Caucasian, Asian and mixed population. Therefore, inconsistent associations indicate that there may be differences in the magnitude of the IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms contribution to periodontitis susceptibility by different genetic backgrounds and environmental exposures.

In this meta-analysis, obvious between-study heterogeneity was found in both overall and subgroup analyses. The ethnicity, disease type, HWE and total sample size were regarded as the potential confounding factors [60–64]. Therefore, we explored the source of between-study heterogeneity to ensure the reliability of our results. HWE results showed the *p* values of four studies for IL-10 -1082A>G and two studies for IL-10 -819C>T polymorphism were less than 0.05, which suggested the potential to influence the between-study heterogeneity. Therefore, for the analysis of IL-10 -1082A>G and − 819 polymorphisms, all the studies were stratified according to HWE status. After removing those studies from the overall analysis, the between-study heterogeneity reduced, but not disappeared. Additionally, association between the IL-10 -1082A>G polymorphism and periodontitis risk was revealed. Moreover, sensitivity analysis showed that these studies had minor effect on OR values of IL-10 -819C>T polymorphism, which indicated the stability of present work. It demonstrated that deviation from the HWE was not source of heterogeneity substantially. For IL-10 -592C>A polymorphism, there was significant heterogeneity in the CP and Caucasians subgroups under all of the genetic models, while the heterogeneity did not exist under all of the genetic models in the AgP, Asians, and mixed population. However, further stratification analysis demonstrated that ethnicity, disease type, HWE may be the main source of heterogeneities. Besides, there is other factors did contribute to the source of heterogeneity that cannot be explained.

To the best of our knowledge, our work has provided most robust evidence of association between the IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms and periodontitis risk. However, when explaining the results, some limitations of this meta-analysis should be considered. Firstly, significant between-study heterogeneity existed in some comparisons, especially for IL-10 -1082A>G and -592C>A polymorphism and might have potential impact in the pooled results. Second, some of eligible studies included in the meta-analysis for -1082A>G polymorphism did not include genotype data. Moreover, studies included for analysis of allele model, recessive model, dominant model and homozygote model respectively, were not wholly the same. Therefore, these may have distorted the statistical information of the meta-analysis. Thirdly, the current meta-analysis only included the published studies and the language of the published studies including our meta-analysis was limited on English. Therefore, publication and language bias may exist. Finally, the interaction between different susceptibility genes and environmental factors leaded to the conditions, but our study could not assess gene–gene and gene-environment interactions due the limited information. In addition, haplotype analysis of IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms may have provided more information and would have been more powerful than single polymorphism analysis.

In summary, this meta-analysis result suggested that the IL-10 -592C>A polymorphism was associated with periodontitis risk in overall population. When further analyzed by periodontitis type, only the IL-10 -592C>A polymorphism was associated with CP risk, but not AgP; and the IL-10 -1082A>G and -819C>T polymorphisms have not positive association neither in the CP and AgP. Moreover, the IL-10 -1082A>G, -819C>T, and -592C>A polymorphisms were associated with periodontitis risk by ethnicity. Identification of the association of IL-10 polymorphisms with periodontitis might be important to provide proper dental management necessary these patients. However, further large sample size, well-designed, and population-based studies should be performed to assess possible gene–gene or gene-environment interactions and validate our findings.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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