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ORIGINAL RESEARCH

Association between IL-17A G197A polymorphism and gastric cancer risk: an updated meta-analysis based on 6,624 cases and 7,631 controls

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Purpose: Previous studies investigating the association between interleukin-17A (IL-17A) G197A polymorphism and gastric cancer risk have provided inconsistent results. We, therefore, conducted this meta-analysis to clarify the association between IL-17A G197A polymorphism and gastric cancer risk.

Methods: We searched PubMed, Excerpta Medica Database, and CNKI databases to identify relevant studies up to June 10, 2017. A total of 16 case-control studies including 6,624 cases and 7,631 controls were identified.

Results: Overall, significant associations between IL-17A G197A polymorphism and gastric cancer risk were observed (A vs G: OR =1.24, 95% CI =1.14–1.36; AA vs GG: OR =1.63, 95% CI =1.35–1.96; GA vs GG: OR =1.12, 95% CI =1.01–1.25; AA+GA vs GG: OR =1.23, 95% CI =1.11–1.35; AA vs GA+GG: OR =1.54, 95% CI =1.27–1.87). Similar associations were also observed in Asian population (A vs G: OR =1.25, 95% CI =1.15–1.37; AA vs GG: OR =1.62, 95% CI =1.33–1.97; GA vs GG: OR =1.16, 95% CI =1.07–1.25; AA+GA vs GG: OR =1.24, 95% CI =1.15–1.33; AA vs GA+GG: OR =1.51, 95% CI =1.23–1.85), in Caucasian population (AA vs GA+GG: OR =2.19, 95% CI =1.40–3.44), and in the hospital-based controls' subgroup (A vs G: OR =1.30, 95% CI =1.17–1.45; AA vs GG: OR =1.81, 95% CI =1.46–2.25; AA+GA vs GG: OR =1.27, 95% CI =1.12–1.43; AA vs GA+GG: OR =1.71, 95% CI =1.34–2.18).

Conclusions: The current meta-analysis suggests that IL-17A G197A polymorphism might enhance gastric cancer risk.

Keywords: gastric cancer, polymorphism, meta-analysis, interleukin-17A, rs2275913

Introduction

Interleukin-17 (IL-17) is a relatively newly described family of pro-inflammatory cytokines that consists of six family members (IL-17A–F).[1] IL-17 is produced by $CD4^+$ memory T cells, and it is involved in both innate and adaptive immune responses.[2,3] It has been reported that IL-17A, a pro-inflammatory cytokine, is associated with the pathogenesis of chronic inflammatory diseases, autoimmune diseases,[4,5] and cancer progression.[6,7]

There are many studies that focus on the relationship between IL-17A G197A polymorphism and gastric cancer.[8–23] These studies are all based on experimental results, but their results are always inconsistent. Since 2015, only one meta-analysis has been conducted, and 11 case-control studies were included in this meta-analysis.[24] Today, more than five studies that assessed the association between IL-17A G197A polymorphism and the risk of gastric cancer have been published. Therefore, we performed

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an updated meta-analysis to further determine an accurate relationship between IL-17A G197A polymorphism and gastric cancer susceptibility.

Materials and methods

Publication search

We conducted a publication search in PubMed, Excerpta Medica Database, and CNKI databases (up to June 10, 2017) using the following search strategy: "interleukin-17A or interleukin 17A or IL-17A or IL17A", "polymorphism", and "gastric cancer". No language restrictions were applied. Studies had to meet the following criteria: 1) case-control studies; 2) diagnoses of all patients with malignant tumors were confirmed by pathological or histological examination; 3) the study assessed the association between gastric cancer risk and the IL-17A G197A polymorphism. The following exclusion criteria were used: 1) unpublished studies or abstracts; 2) duplicate publications; and 3) insufficient data were reported.

Data extraction

For each study, the following characteristics were extracted: first author, year of publication, ethnicity, sample size (total cases and controls), source of controls, genotype distributions in cases and controls, and *P*-value of Hardy–Weinberg equilibrium (HWE).[25] Disagreements were resolved by discussion.

Statistical analysis

Odds ratios (ORs) with corresponding 95% CIs were calculated to clarify the strength of the association between IL-17A G197A polymorphism and gastric cancer risk. Five genetic models were assessed: homozygote model (AA vs GG), heterozygote model (GA vs GG), recessive model (AA vs GA+GG), dominant model (AA+GA vs GG), and allele model (A vs G). Subgroup analyses were conducted according to ethnicity and source of controls.

Heterogeneity was calculated by using both χ^2-based *Q*-statistic and I^2-statistic.[26] If $P \geq 0.1$ and $I^2 < 50\%$, the fixed-effects model (Mantel–Haenszel method) was chosen.[27] Otherwise, the random effects model (Der Simonian–Laird method) was used.[28] Moreover, sensitivity analysis was performed to assess the stability of the results. Publication bias was assessed with funnel plots and Egger's test.[29] All of the statistical tests were carried out with STATA version 12.0 (Stata corporation, College Station, TX, USA). $P < 0.05$ was considered significant, and all *P*-values were two sided.

Results

Characteristics of eligible studies

A flow diagram illustrating the study selection process is shown in Figure 1. Through literature search and selection, a total of 16 publications[8–23] including 6,624 cases and 7,631 controls were included in the meta-analysis. Table 1 shows the main characteristics of the included studies.

Meta-analysis

Overall, the IL-17A G197A polymorphism was associated with an increased gastric cancer risk in all genetic models (A vs G: OR =1.24, 95% CI =1.14–1.36, Figure 2; AA vs GG: OR =1.63, 95% CI =1.35–1.96, Figure 3; GA vs GG: OR =1.12, 95% CI =1.01–1.25, Figure 4; AA+GA vs GG: OR =1.23, 95% CI =1.11–1.35, Figure 5; AA vs GA+GG: OR =1.54, 95% CI =1.27–1.87, Figure 6). The HWE of each study was taken into consideration. After eliminating studies whose distribution of genotype in controls deviated from HWE, the outcome remained statistically significant. These results are shown in Table 2.

When subgroup analysis was carried out based on ethnicity, significant associations were found in all five genetic models in Asian population (A vs G: OR =1.25, 95% CI =1.15–1.37; AA vs GG: OR =1.62, 95% CI =1.33–1.97; GA vs GG: OR =1.16, 95% CI =1.07–1.25; AA+GA vs GG: OR =1.24, 95% CI =1.15–1.33; AA vs GA+GG: OR =1.51, 95% CI =1.23–1.85), and statistically significant

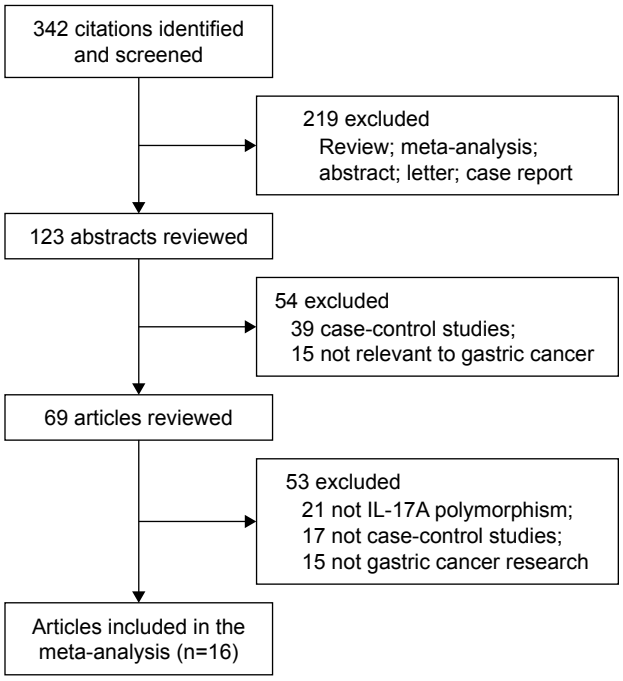

Figure 1 Flow diagram of the study selection process.

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Ethnicity	Source of controls	Cases	Controls	Case			Control			HWE
						GG	GA	AA	GG	GA	AA	
Shibata et al[8]	2009	Asian	Hospital-based	287	523	94	124	69	175	299	49	<0.001
Chen[17]	2010	Asian	Population-based	1,042	1,090	300	522	220	325	541	224	0.967
Wu et al[9]	2010	Asian	Population-based	945	768	210	485	250	193	371	204	0.351
Arisawa et al[10]	2012	Asian	Hospital-based	333	583	112	137	84	218	293	72	0.08
Rafiei et al[11]	2013	Caucasian	Population-based	161	171	56	61	44	78	72	21	0.491
Qinghai et al[12]	2014	Asian	Hospital-based	293	550	126	122	45	273	216	61	0.069
Kutikhin et al[13]	2014	Caucasian	Population-based	60	300	24	26	10	99	165	36	0.009
Gonzalez-Hormazabal et al[14]	2014	Mixed	Hospital-based	147	172	103	36	8	105	59	8	0.937
Wang et al[15]	2014	Asian	Hospital-based	462	462	160	211	91	214	190	58	0.124
Zhang et al[16]	2014	Asian	Population-based	260	512	110	102	48	258	187	67	<0.001
Wu et al[18]	2014	Asian	Hospital-based	945	768	210	485	250	193	371	204	0.351
Gao et al[19]	2015	Asian	Hospital-based	572	573	239	250	83	260	241	72	0.17
Hou and Yang[20]	2015	Asian	Hospital-based	326	326	121	149	56	161	136	29	0.001
Qi et al[21]	2015	Asian	Hospital-based	252	252	100	110	42	122	105	25	0.73
Yang et al[22]	2016	Asian	Hospital-based	386	374	200	128	58	203	123	48	<0.001
Zhao et al[23]	2016	Asian	Hospital-based	153	207	51	76	26	95	94	18	0.437

Abbreviation: HWE, Hardy–Weinberg equilibrium.

associations were found in the following genetic model in Caucasian population (AA vs GA+GG: OR =2.19, 95% CI =1.40–3.44).

When results were stratified by source of controls, IL-17A G197A polymorphism was associated with a significantly increased gastric cancer risk in the hospital-based controls' subgroup (A vs G: OR =1.30, 95% CI =1.17–1.45; AA vs GG: OR =1.81, 95% CI =1.46–2.25; AA+GA vs GG: OR =1.27, 95% CI =1.12–1.43; AA vs GA+GG: OR =1.71, 95% CI =1.34–2.18). However, no associations were

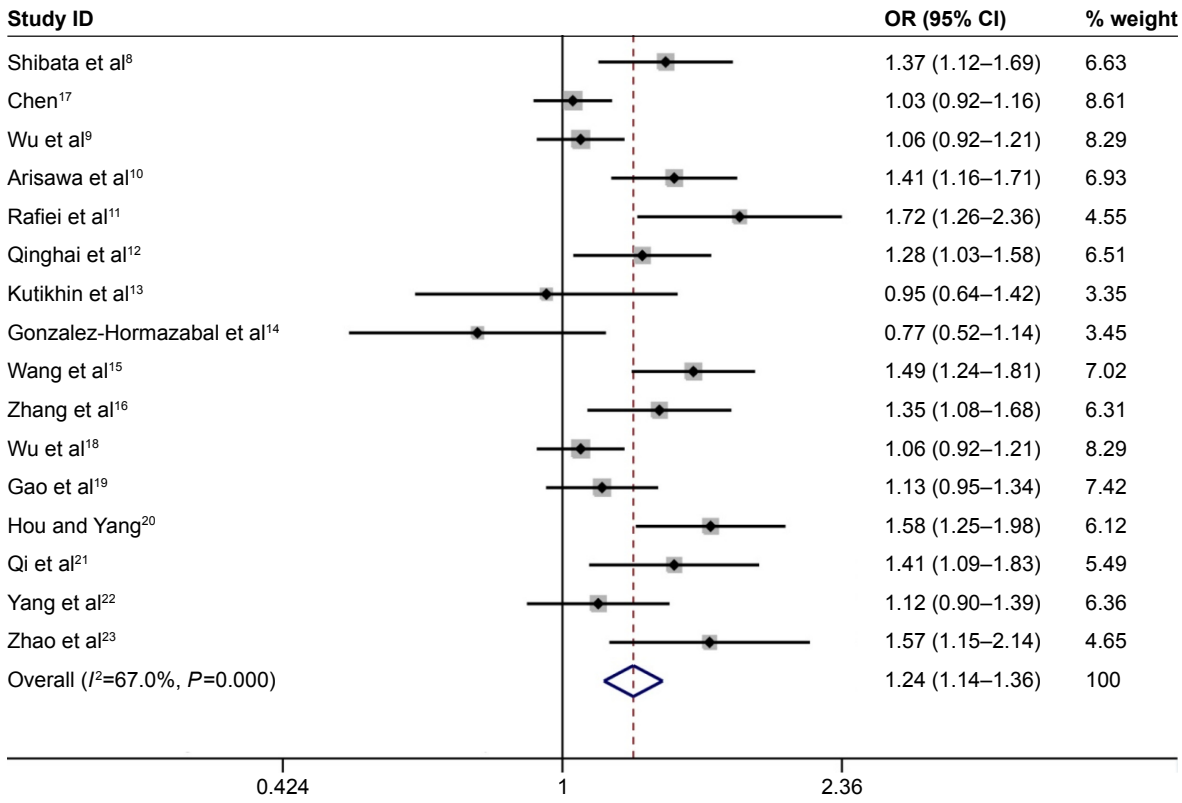

Figure 2 Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the allele model (A vs G) among the overall populations.
Note: Weights are from random effects analysis.
Abbreviations: IL, interleukin; OR, odds ratio.

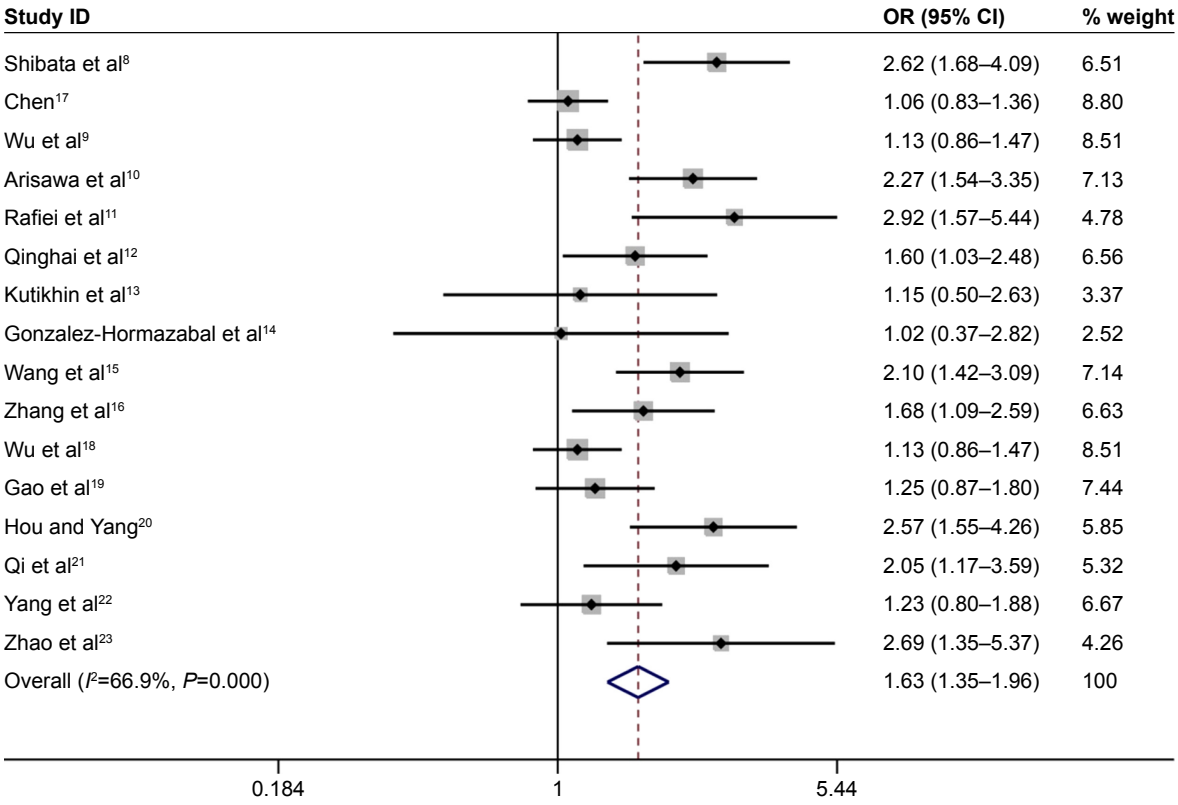

Figure 3 Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the homozygote model (AA vs GG) among the overall populations.
Note: Weights are from random effects analysis.
Abbreviations: IL, interleukin; OR, odds ratio.

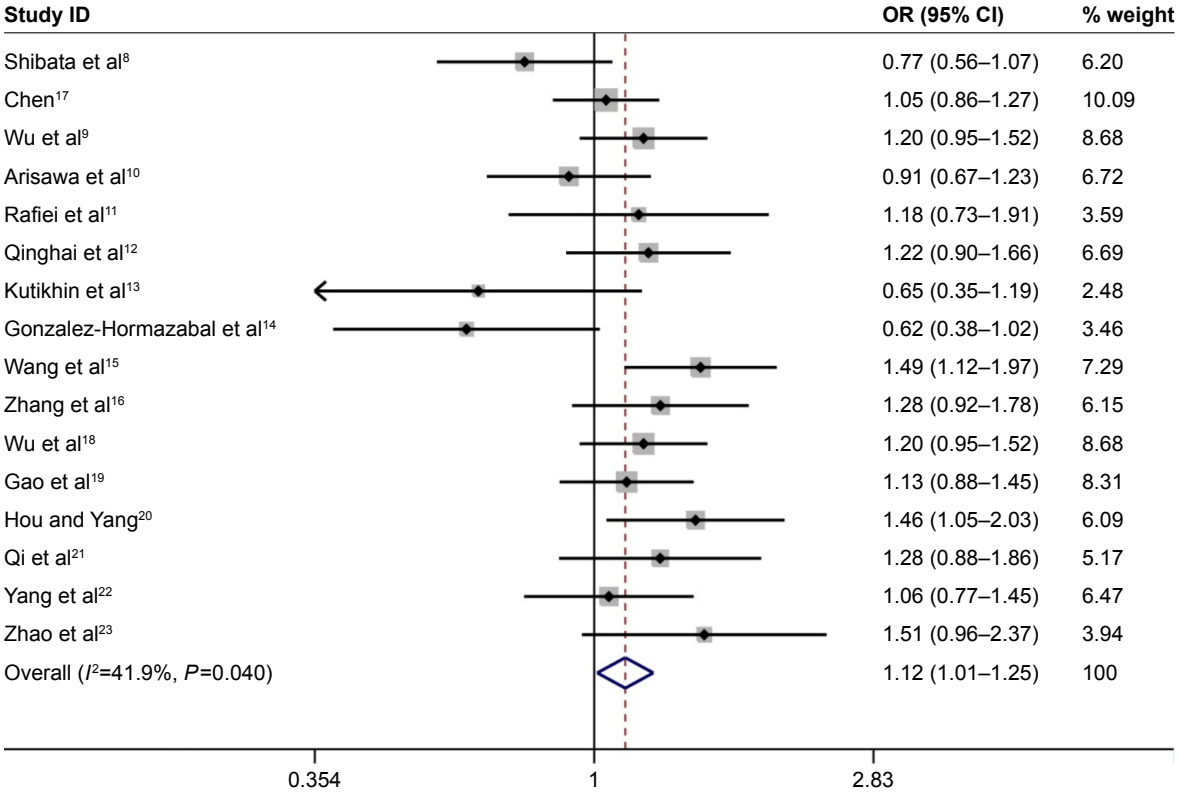

Figure 4 Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the heterozygote model (GA vs GG) among the overall populations.
Note: Weights are from random effects analysis.
Abbreviations: IL, interleukin; OR, odds ratio.

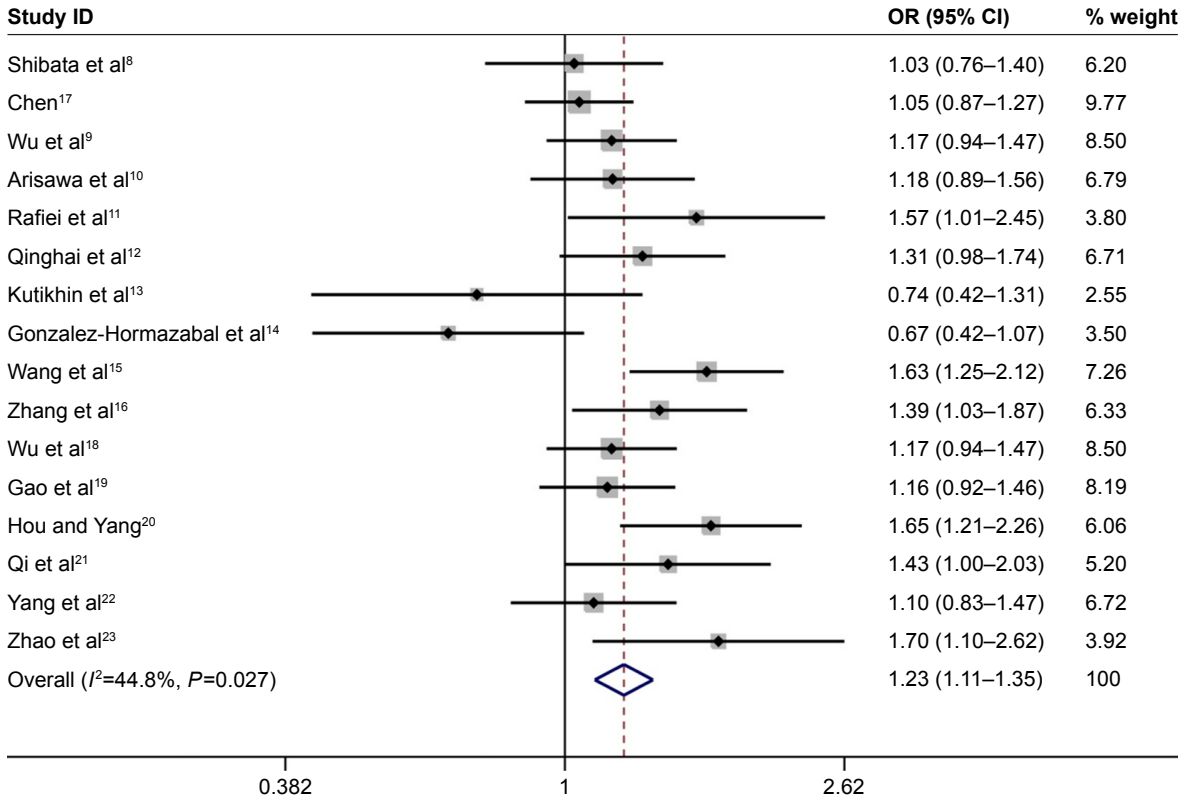

Figure 5 Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the dominant model (AA+GA vs GG) among the overall populations.
Note: Weights are from random effects analysis.
Abbreviations: IL, interleukin; OR, odds ratio.

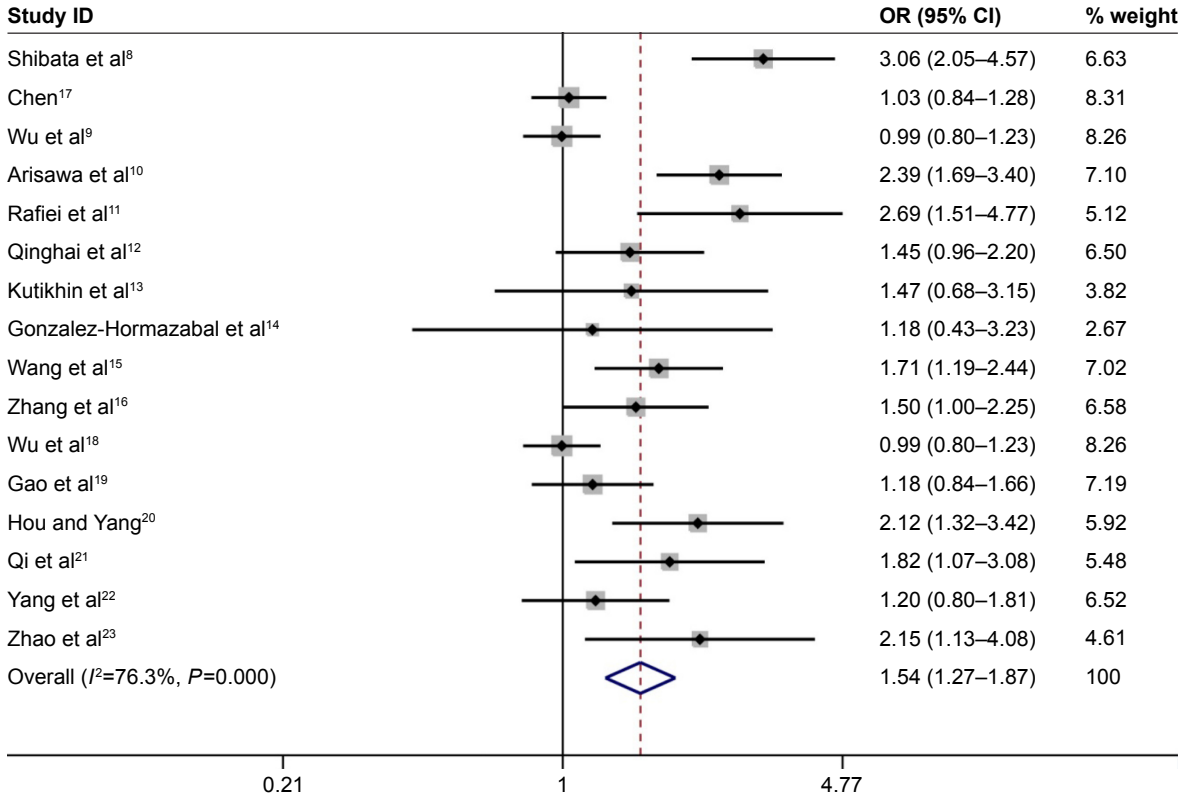

Figure 6 Forest plot of the association between IL-17A G197A polymorphism and gastric cancer risk in the recessive model (AA vs GA+GG) among the overall populations.
Note: Weights are from random effects analysis.
Abbreviations: IL, interleukin; OR, odds ratio.

Table 2 Meta-analysis of the IL-17A polymorphism and gastric cancer risk

Groups and subgroups	Comparison	Test of association			Test of heterogeneity	
		OR	95% CI	*P*-value	*P*-value	I^2 (%)
Total studies	A vs G	1.24	1.14–1.36	0.000	0.000	67.0
	AA vs GG	1.63	1.35–1.96	0.000	0.000	66.9
	GA vs GG	1.12	1.01–1.25	0.030	0.040	41.9
	AA+GA vs GG	1.23	1.11–1.35	0.000	0.027	44.8
	AA vs GA+GG	1.54	1.27–1.87	0.000	0.000	76.3
HWE (yes)	A vs G	1.23	1.10–1.37	0.000	0.000	71.4
	AA vs GG	1.56	1.26–1.94	0.000	0.000	68.4
	GA vs GG	1.15	1.05–1.25	0.002	0.160	30.0
	AA+GA vs GG	1.23	1.10–1.38	0.000	0.050	45.3
	AA vs GA+GG	1.44	1.16–1.78	0.001	0.000	75.0
Ethnicity						
Asian	A vs G	1.25	1.15–1.37	0.000	0.001	65.0
	AA vs GG	1.62	1.33–1.97	0.000	0.000	69.8
	GA vs GG	1.16	1.07–1.25	0.000	0.160	28.3
	AA+GA vs GG	1.24	1.15–1.33	0.000	0.169	27.4
	AA vs GA+GG	1.51	1.23–1.85	0.000	0.000	79.0
Caucasian	A vs G	1.30	0.73–2.32	0.377	0.023	80.7
	AA vs GG	1.91	0.77–4.75	0.166	0.078	67.9
	GA vs GG	0.94	0.64–1.37	0.743	0.133	55.8
	AA+GA vs GG	1.10	0.53–2.31	0.797	0.040	76.3
	AA vs GA+GG	2.19	1.40–3.44	0.001	0.213	35.4
Source of controls						
Hospital-based	A vs G	1.30	1.17–1.45	0.000	0.001	63.8
	AA vs GG	1.81	1.46–2.25	0.000	0.002	62.7
	GA vs GG	1.13	0.99–1.29	0.067	0.031	48.1
	AA+GA vs GG	1.27	1.12–1.43	0.000	0.040	46.1
	AA vs GA+GG	1.71	1.34–2.18	0.000	0.000	75.2
Population-based	A vs G	1.08	0.99–1.17	0.078	0.184	37.9
	AA vs GG	1.16	0.99–1.37	0.073	0.341	10.4
	GA vs GG	1.10	0.97–1.26	0.147	0.215	32.8
	AA+GA vs GG	1.12	0.99–1.28	0.070	0.205	34.6
	AA vs GA+GG	1.07	0.93–1.23	0.317	0.272	23.1

Abbreviations: IL, interleukin; OR, odds ratio; HWE, Hardy–Weinberg equilibrium.

observed in population-based controls' subgroup in all five comparison models. All comparisons are listed in Table 2.

Sensitivity analysis and publication bias

Sensitivity analyses showed that omitting an individual study from all the analyses did not affect the pooled ORs significantly and no substantial change was detected, indicating that the overall results of the present study are stable (Figure 7).

Begg's funnel plot was used to assess the publication bias of included literature. The shapes of the funnel plots did not show any evidence of obvious asymmetry, indicating the absence of publication bias (Figure 8).

Discussion

Genetic and environmental factors, life style, and *Helicobacter pylori* infections have been considered as playing essential roles in the development of gastric cancer,[30,31] but the precise etiology of the disease remains inconsistent.

IL-17 is a critical inflammatory cytokine that plays an important role in chronic inflammation, autoimmune diseases, and cancer.[32] The IL-17A G197A is located in the 5′ region near the *IL-17A* gene, and it may regulate the gene transcription.[33] A previous study has conflicting results about the association between IL-17A G197A polymorphism and gastric cancer risk, which may be because of relatively small sample size and different genetic background.[8] Meta-analysis is a powerful method to evaluate gene–disease associations, by collecting all available published studies to obtain more precise results.[34]

With the development of molecular epidemiology, numerous studies explored the effects of IL-17A G197A polymorphism on gastric cancer susceptibility. In 2014, Yu et al[35] carried out a meta-analysis and revealed that the IL-17A G197A polymorphism was associated with a significantly increased gastric cancer risk. In their work, they identified only six case-control studies evaluating the

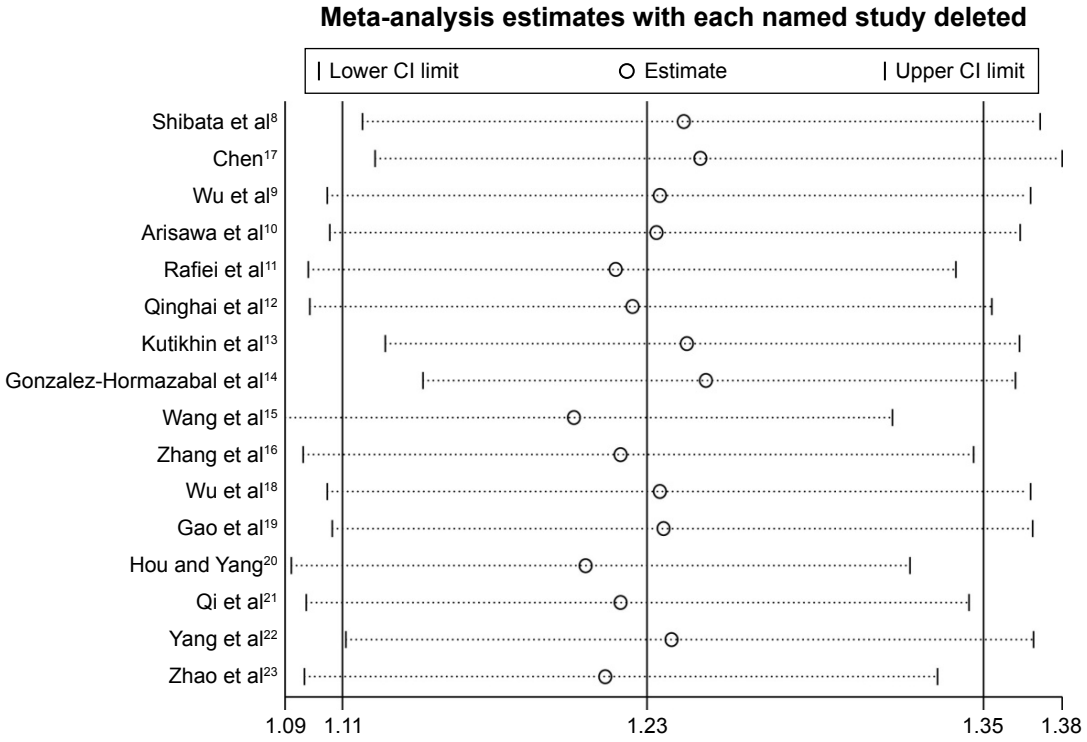

Figure 7 Sensitivity analysis about IL-17A G197A polymorphism and gastric cancer risk in the dominant model (AA+GA vs GG).

association between the IL-17A G197A polymorphism and gastric cancer risk. In 2015, Li et al[24] conducted a meta-analysis to assess the association between IL-17A G197A polymorphism and gastric cancer susceptibility with 11 case-control studies and revealed that IL-17A G197A polymorphism was associated with gastric cancer risk. Therefore, we collected all available published literature and performed an updated meta-analysis of 16 independent case-control studies containing 6,624 cases and 7,631 controls. In the meta-analysis, significant associations between IL-17A G197A polymorphism and gastric cancer risk were observed in all five genetic models. The HWE of each study was taken into consideration. After eliminating studies whose distribution of genotype in controls deviated from HWE, the outcome remained statistically significant. Similar associations were also observed in Asian population (A vs G: OR =1.25, 95% CI =1.15–1.37; AA vs GG: OR =1.62, 95% CI =1.33–1.97; GA vs GG: OR =1.16, 95% CI =1.07–1.25; AA+GA vs GG: OR =1.24, 95% CI =1.15–1.33; AA vs GA+GG: OR =1.51, 95% CI =1.23–1.85), in Caucasian population (AA vs GA+GG: OR =2.19, 95% CI =1.40–3.44), and in the hospital-based controls' subgroup (A vs G: OR =1.30, 95% CI =1.17–1.45; AA vs GG: OR =1.81, 95% CI =1.46–2.25; AA+GA vs GG: OR =1.27, 95% CI =1.12–1.43; AA vs GA+GG: OR =1.71, 95% CI =1.34–2.18).

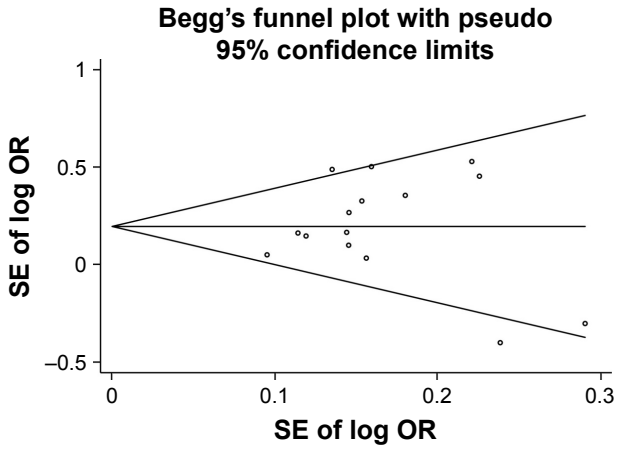

Figure 8 Begg's funnel plots to examine publication bias between IL-17A G197A polymorphism and gastric cancer risk in the dominant model (AA+GA vs GG).
Notes: Plots are shown with pseudo 95% confidence limits. Each point represents a separate study for the indicated association.
Abbreviations: SE, standard error; OR, Odds ratio.

Several limitations need to be addressed. First, due to heterogeneity, the results of our meta-analysis should be interpreted. Second, the overall outcomes were based on unadjusted ORs. Lacking the information on detailed individual data limited our more precise analysis on adjusted estimates by other factors like age and sex. This limitation may cause serious confounding bias. Third, meta-analysis is a type of retrospective study, and recall and selection bias may be present.

In conclusion, our meta-analysis revealed that IL-17A G197A polymorphism may increase gastric cancer risk. However, larger studies are still required to assess the

interaction of IL-17A G197A polymorphism with gastric cancer risk.

Disclosure

The authors report no conflicts of interest in this work.

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