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Tumor necrosis factor-α-308 polymorphism is not associated with Kawasaki disease

A meta-analysis of case–control studies

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Abstract

Background: Genetic factors in the pathogenesis of Kawasaki disease (KD) have received a lot of attention during the past decade. Some studies have reported that tumor necrosis factor (TNF)-α-308 polymorphism has been associated with KD. However, there have been inconsonant results among different studies. To increase the power for clarifying the influence of TNF on KD, a meta-analysis of case–control studies were performed.

Methods: The following databases were searched to identify related studies: PubMed, Embase, Cochrane Library, CNKI, Wanfang, and VIP databases according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Search terms included "Kawasaki disease" or "KD," "tumor necrosis factor-alpha" or "TNF-α," and "polymorphism" or "mutation." Two reviewers independently extracted data and assessed study quality using Newcastle–Ottawa Scale. Odds ratios (ORs) with corresponding 95% confidence intervals (CI) were used to assess the strength of the association. Accounting for heterogeneity, a fixed or random effects model was respectively adopted. Heterogeneity was checked using the *Q* test and the I^2 statistic. A cumulative meta-analysis was conducted to estimate the tendency of pooled OR. Funnel plots and Egger tests were performed to test for possible publication bias and sensitivity analyses were done to ensure authenticity of the outcome.

Results: Eleven separate studies were suitable for the inclusion criterion. The selected studies contained 2582 participants, including 841 in KD group and 1741controls. The pooled odds ratio of G versus A with the random effect model was 1.09 (95% CI = 0.69–1.70, *P* = .72) and the genotype effects for GG versus GA+AA was 1.14 (95% CI = 0.68–1.90, *P* = .62) in the whole population separately. Unfortunately, no significant association was detected between the TNF-α-308 polymorphism and KD risk under allele and genotype model.

Conclusion: No association between the TNF-α-308 polymorphism and KD was found in our meta-analysis and further studies with larger sample size and more ethnicities are expected to be conducted in the future to validate the results.

Abbreviations: CAL = coronary arterial lesion, CBM = China biological medicine database, CI = confidence intervals, HWE = Hardy–Weinberg equilibrium, KD = Kawasaki disease, OR = odds ratios, PRISMA = preferred reporting items for systematic reviews and meta-analyses, TNF = tumor necrosis factor.

Keywords: Kawasaki disease, meta-analysis, polymorphism, tumor necrosis factor-alpha-308

1. Introduction

Kawasaki disease (KD) is an acute potentially fatal multisystem vasculitis most commonly occurring in children <5 years of age[1] and is the leading cause of acquired heart disease in the pediatric age group in the United States and Japan.[2,3] Although the first reports of KD were in Japanese children,[4,5] it is now recognized in children of all races and ethnic groups. Both etiology and pathogenesis of KD have not yet been clarified, but the most accepted hypothesis holds that KD is caused by aberrant pro-inflammatory immune response against a pathogenic noxa in genetically predisposed individuals.[6,7] Recently, predisposing factors such as elevated serum levels of pro-inflammatory cytokines have been the focus of much research. Several studies have shown an association between elevated serum levels of tumor necrosis factor (TNF)-α and KD.[8–12] Previous studies have supported a central role for TNF-α in the pathogenesis of KD.[8,13–15] These results, along with others showing the involvement of TNF-α in the pathogenesis of severe infectious diseases[16,17] suggest that the genetic propensity of the host to produce TNF-α is related to the onset and severity of KD. TNF-α levels are elevated in the majority of children during the acute phase of the disease[10,12,14,18] and are highest in children in whom coronary arterial lesion (CAL) develop.[12,14] In vitro studies using vascular endothelial cells have demonstrated that TNF-α induce the expression of surface antigens that render the cells susceptible to lysis by immunoglobulin G or immunoglobulin M antibodies in the sera of children with acute KD.[18,19] TNF-α, therefore, may play an important role in the pathogenesis of the vascular injury in KD.

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The authors declare that they have no competing interests.

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A genetic influence on disease susceptibility is suspected because Kawasaki syndrome is overrepresented among Asian and Asian-American populations. Moreover, Asian children, especially those of Japanese, Chinese, and Korean descent, have the highest incidence of KD, although all racial groups are affected, strongly suggesting a genetic predisposition for KD.[20] The gene coding for TNF is localized in the short arm of chromosome 6 in the MHC class III region at 250 centromeric Kb from HLA-B locus. The polymorphic nucleotides have been reported to influence the TNF production level: a G/A transition in the TNF gene promoter region (position 308).[21] The TNF-a G allele at -308 has shown association with increased KD prevalence in several separate studies.[22–24] Furthermore, these studies suggest that the TNF-a-308 polymorphism is not only associated with the onset of KD but also the severity of KD and CAL development.[25–30] However, a negative association has been reported between polymorphisms in the TNF gene and susceptibility to KD or CA in the Taiwanese and the Korean populations.[25,27]

Recently, many molecular epidemiological studies[22,23,25–29,31–33] were performed to investigate the association between the TNF-a-308 polymorphism loci and KD. Unfortunately, the results were conflicting or inconsistent, most likely due to small sample size, diverse genetic backgrounds, and potential confounding bias. Meta-analysis is a widely used statistical method in medical study, particularly for a subject being extensively investigated while controversial results are being reported. However, previous meta-analysis only included 6 studies and the literature search was updated in August 2010.[34] Additionally, new molecular epidemiological studies have recently been conducted to investigate the role of TNF gene variations in the occurrence of KD in different populations and provide new evidences that were not included in the previous meta-analysis. Consequently, we carried out an update meta-analysis of studies examining the single nucleotide polymorphism to provide a more comprehensive assessment of the association of TNF-α-308 G/A polymorphism with KD.

2. Methods

This study was approved by the ethics committees of the First Hospital of Jilin University and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant before entry into the study, and all of the procedures were in accordance with institutional guidelines.

2.1. Search strategy and study selection

To search for all the studies that examined the association of the TNF-α-308 polymorphism with KD risk, we conducted a computerized literature search from PubMed, Embase, CBM (China Biological Medicine Database), Wanfang, and VIP databases, using the following keywords and subject terms: ("Kawasaki disease" or "KD") AND ("tumor necrosis factor-alpha" or "TNF-α") AND ("gene or genotype or allele or polymorphisms"). The full text of the retrieved articles was scrutinized to inspect whether data on the topic of interest were included. We systematically searched eligible studies reported before Sep 1, 2018. Eligible publications had to be written in either Chinese or English. The references of all retrieved articles were also screened. To prevent data duplication, when a report overlapped with another study, only the most detailed study was included. If an article reported results on different ethnic subpopulations, each sub-population was treated as a separate study.

2.2. Inclusion/exclusion criteria

Studies included in the meta-analysis had to meet all the following criteria: the evaluation of the relationship between the TNF-α-308 polymorphism and KD; the use of case–control study design or cross-sectional study design; the available genotype/allele frequency of TNF-α-308 polymorphism between cases and controls; all subjects were well ethnicity-matched. If the genotype frequency was not reported, we contacted the original authors by e-mail to obtain the missing data. The excluded literatures were comprised of studies of poor research quality, providing little or insufficient data, violating the inclusion criteria, and repeated publications.

2.3. Data extraction and quality assessment

To minimize the selection bias, the data were independently gathered in duplicate by 2 investigators on the basis of a standard protocol. The data extracted from the studies included such details as the first author, publication year, region, ethnicity, study design, matching criteria, sample size, mean age of cases

Table 1

Characteristics of the included studies.

First author	Year	Region	Ethnicity	Study design	Sample size (n) KD/Control	Mean age, y KD/Control	KD			Control			HWE-*P* value	Quality score
							GG	GA	AA	GG	GA	AA		
Assari et al[31]	2018	Caucasian	Iran	Case–control	55/140	3.3 /3.3	46	9	0	98	39	0	Yes	9
Maggioli et al[23]	2014	Caucasian	Italy	Case–control	74/440	2.1/2.1	48	24	1	270	80	1	Yes	7
Cruz-Olivo et al[22]	2011	Mixed	Mexico	Case–control	48/61	NA/NA	42	0	6	45	6	10	Yes	8
Weng et al[32]	2010	Asian	Taiwanese	Case–control	211/211	2.2/48.9	179	30	2	176	41	4	Yes	8
Cheung et al[26]	2008	Asian	Chinese	Case–control	167/124	8.9/9.7	123	40	4	106	18	0	Yes	9
Xi and Gui[33]	2006	Asian	Chinese	Case–control	100/100	2.5/3.3	87	13	0	93	7	0	Yes	8
Ahn et al[25]	2003	Asian	Korean	Case–control	24/12	2.1/2.7	22	2	0	11	1	0	Yes	7
Chien et al[27]	2003	Asian	Taiwanese	Case–control	18/16	2.1/NA	15	2	1	16	0	0	Yes	7
Quasney (a) et al[29]	2001	Asian	Japanese	Case–control	39/78	NA/NA	39	0	0	36	3	0	Yes	7
Quasney (b) et al[29]	2001	Caucasian	USA	Case–control	46/105	NA/NA	38	8	0	75	26	4	Yes	7
Kamizono et al[28]	1999	Asian	Japanese	Case–control	60/575	9.8/13.5	60	0	0	556	18	1	Yes	7

HWE = Hardy–Weinberg, KD = Kawasaki Disease.

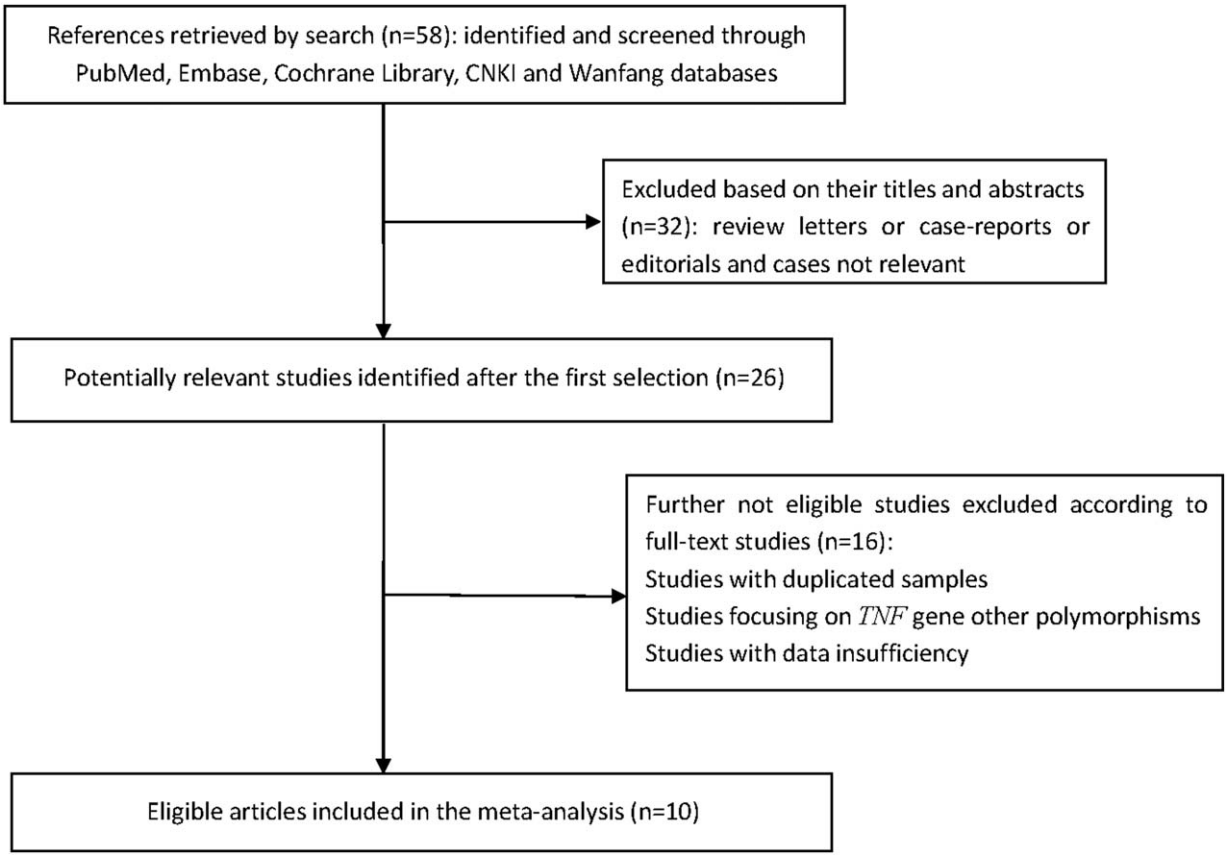

Figure 1. Flowchart of study selection.

and controls, Hardy–Weinberg equilibrium test and Quality score. If the same research result appeared in different articles, the result was only adopted once in the present meta-analysis. The quality of studies was assessed by 2 reviewers (LN and YY) using a modified quality assessment score developed for genetic association studies. These scores were based on both traditional epidemiological considerations, as well as genetic issues. The total quality score can range from 0 (worst) to 10 (best). If there was discrepancy between them, it was settled by discussion until a consensus was reached. These studies will be discarded for insufficient and equivocal data because we tried unsuccessfully to obtain further information from the authors. All of the data were shown in Table 1.

Table 2

Allele frequencies of tumor necrosis factor-a-308 polymorphisms among KD and Non-KD.

	KD		Non-KD			
Authors	**G**	**A**	**G**	**A**	**OR**	**95% CI**
Assari et al[31]	101	9	235	39	1.86	0.87–3.99
Maggioli et al[23]	120	26	620	82	0.61	0.38–0.99
Cruz-Olivo et al[22]	84	12	96	28	1.90	0.90–3.99
Weng et al[32]	388	34	393	49	1.42	0.90–2.25
Cheung et al[26]	286	48	230	18	0.47	0.26–0.82
Xi and Gui[33]	187	13	193	7	0.52	0.20–1.34
Ahn et al[25]	46	2	23	1	1.0	0.09–11.61
Chien et al[27]	32	2	32	0	0.20	0.01–4.33
Quasney (a) et al[29]	78	0	75	3	7.28	0.37–143.29
Quasney (b) et al[29]	84	8	176	34	2.03	0.90–4.57
Kamizono et al[28]	120	0	1130	20	4.37	0.26–72.71

CI = confidence interval, KD = Kawasaki disease, OR = odds ratio.

2.4. Statistical analysis

As case–control or cross-sectional studies were used, odds ratios (ORs) corresponding to a 95% confidence interval (CI) were implemented to assess the intensity of the association between the TNF-α-308 polymorphism and KD, and the ORs were calculated according to the method described by Woolf.[35] The significance of the pooled ORs was determined by the Z-test, and a $P < .05$ was considered significantly.

The pooling of genetic effects was performed using 2 approaches: per-allele and per-genotype analyses. In the first approach, an estimated OR for G versus A allele and its variance were estimated for each included study. For the per-genotype approach, an OR of GG versus GA+AA was estimated because the AA genotype was very rare and could not be identified in either the KD or non-KD groups in some studies. If there was at least 1 zero cell, the OR was calculated by adding 0.5 for continuity correction. To assess heterogeneity across the studies, Cochrane Q test[36] and I^2 statistic[37,38] were calculated. If the studies were shown to be homogeneous with $P \geq .10$ and $I^2 < 50\%$, the fixed-effects model (the Mantel–Haenszel method) was selected. Otherwise, the random-effects model (the DerSimonian and Laird method) was applied. Meta-regression was employed to explore the potential sources of heterogeneity including study quality, mean age of control and case group, and quality score. If

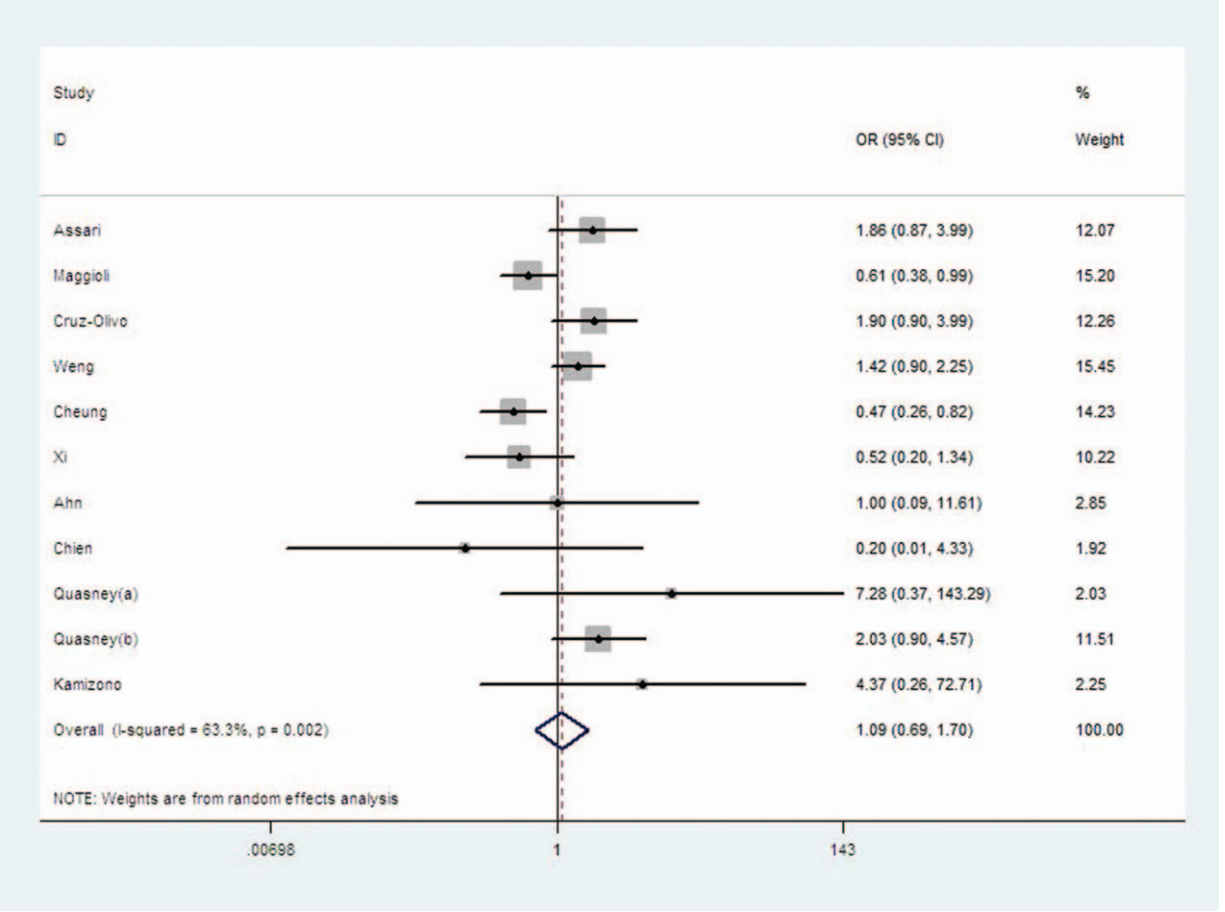

Figure 2. Forest plot of KD and TNF-α-308 in a G versus A model, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. CI = confidence intervals, KD = Kawasaki disease, OR = odds ratios, TNF = tumor necrosis factor.

the outcomes were heterogeneous, prespecified subgroup comparisons were performed to detect the influence of the following factors on the TNF-α-308 polymorphism-KD correlation.

Sensitivity analyses were conducted by deleting a single study each time involved in the meta-analysis to identify the potential influence of the individual data set on the pooled ORs. The funnel plot was used to estimate the potential publication bias. The asymmetry of the funnel plot was assessed by Egger linear regression test.[39] Hardy–Weinberg equilibrium (HWE) was tested with a chi-square test for goodness-of-fit based as applied by a web program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). All other statistical analyses were performed using Review Manager 5.3 and Stata version 13.0 software (Stata Corporation, College Station, TX). All *P* values were two-sided.

3. Results

3.1. Flow of included studies

Characteristics of Eligible Studies. Initially, 58 studies were identified as potentially eligible candidates from the electronic and manual searches. After screening the titles and abstracts, 32 studies were excluded because of not case–control trials or irrelevant studies or no desired polymorphism (including other review papers). Full texts of 26 papers were retrieved and most were excluded because they were duplicate publications or focused on TNF gene other polymorphisms or included no sufficient data. Additionally, studies no satisfying HWE were excluded. Among the 10 eligible studies remaining, 1 study by Quasney et al[29] combined 2 independent studies involving Japanese and Caucasian subjects conducted in different places and using different research methods. We thus counted these studies as 2 different studies and a total of 10 original reports with 11 separate association studies[22,23,25–29,31–33] were included in the final meta-analysis. A flow diagram of the study selection is shown in Fig. 1.

3.2. Study characteristics

All studies were hospital-based case–control designs except 1 study in which controls were selected from a surveillance study of healthy unrelated Japanese children.[28] All studies had enrolled children as cases and controls except 1 study,[29] which had adult volunteers as controls. The ethnicity status was well matched between the study case and control population. Among these studies, 3 in Caucasians and 7 were conducted in Asians. All studies used polymerase chain reaction methods for genotyping and a restriction fragment length method for polymorphism analysis. The genotype frequencies of all the studies were consistent with HWE. In light of Newcastle–Ottawa Scale, 11

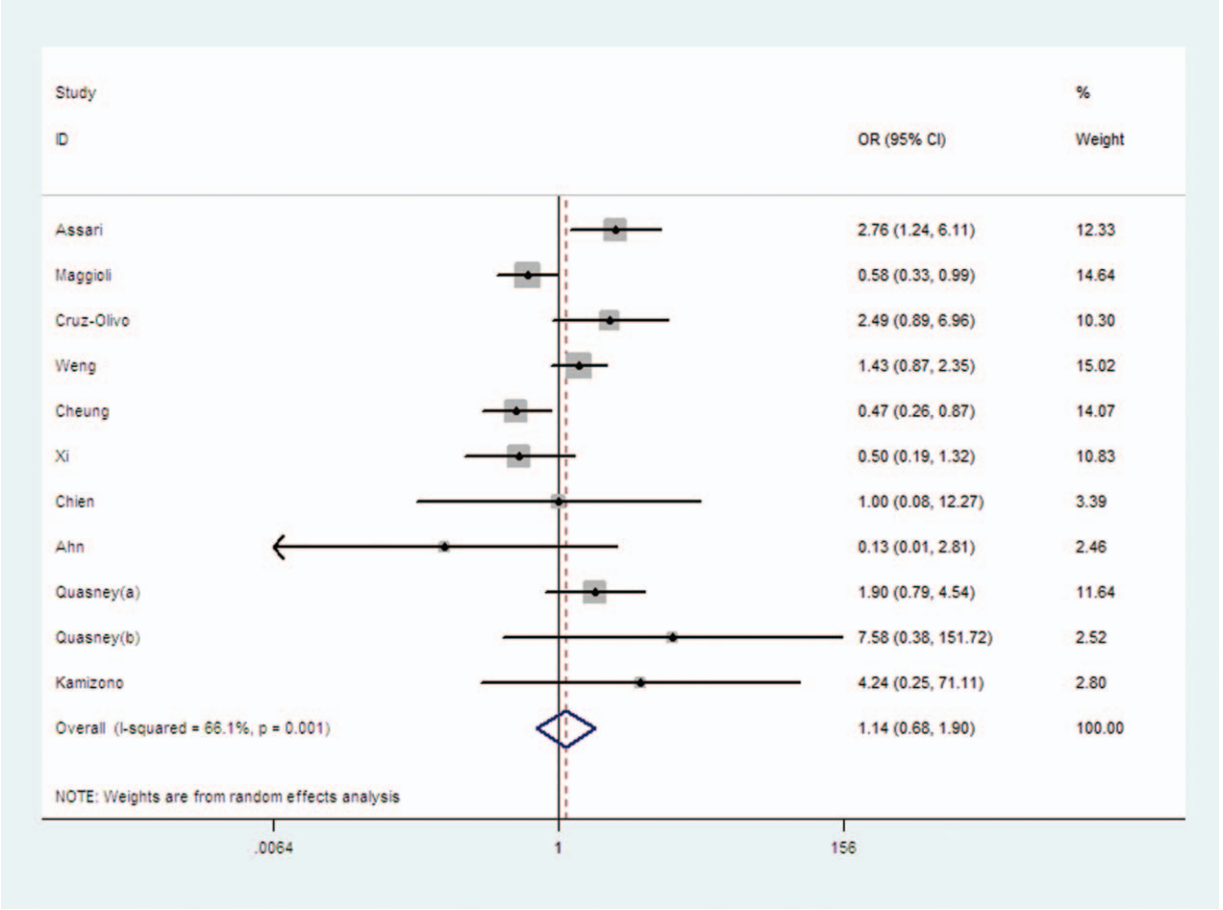

Figure 3. Forest plot of KD and TNF-α-308 in a GG versus GA+AA model, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. CI = confidence intervals, KD = Kawasaki disease, OR = odds ratios, TNF = tumor necrosis factor.

articles are high quality. The quality scores ranged from 7 to 9 out of a best possible score of 10. Characteristics of the studies are shown in Table 1.

3.3. Description of data

Data from control groups of 11 studies were used for pooling allele prevalence (Table 2). The frequency of G allele in KD group and in control group was 47.6% and 47.9%, respectively ($P = .77$). In addition, the prevalence of GG/GA/AA genotypes was 83.1%/15.2%/1.5% in KD group and 84.6%/14.2%/1.1% in control group, respectively.

3.4. Pooled analyses

Eleven studies were included in assessing the association between allele frequency of the TNF-α-308 polymorphism and KD. The TNF-α-308 allele frequencies between case and control groups are described in Table 2. The allele effect (i.e., OR) for the G versus A allele was estimated for each study. There was a large degree of heterogeneity ($Q = 27.2$, $P = 0.002$, $I^2 = 63\%$), so random effect model was used. No significant difference was detected between the TNF-α-308 G allele and A allele, the pooled OR was 1.09 (95% CI: 0.69–1.70; $P = .72$), as displayed in Fig. 2.

The TNF-α-308 genotype frequencies between case and control groups are described in Table 1. The genotype effects for GG versus GA+AA were estimated for each study. There was a large degree of heterogeneity ($Q = 29.5$, $P = .001$; $I^2 = 66\%$) and random effect model was used. No significant difference was seen between the TNF-α-308 and KD under genotype model, the pooled OR was 1.14 (95% CI: 0.68–1.90; $P = .62$), as displayed in Fig. 3.

Meta-regression was used to assess the source of heterogeneity and it was found that ethnicity may explain this heterogeneity. Between-study-variation (tau2) ranged from 0.89 if no variables were included to 0.26 if ethnicity was included in the model. That suggested that the ethnicity could explain the between-study variation for about 63%. We thus performed a subgroup analysis according to ethnicity including 3 studies in Caucasians and 7 studies in Asians. The pooled OR were 1.62 (95% CI: 0.39–6.77) in Caucasian subgroup and 1.04 (95% CI: 0.61–1.78) in Asian subgroup, respectively, Fig. 4. Unfortunately, inter-group heterogeneity has not been removed in the stratified analysis by ethnicity and no association between TNF-α-308 and KD was seen in Caucasian and Asian subgroup populations.

3.5. Publication bias

Begg funnel plot and Egger test revealed that points are evenly distributed and symmetrical, and most of the points are within

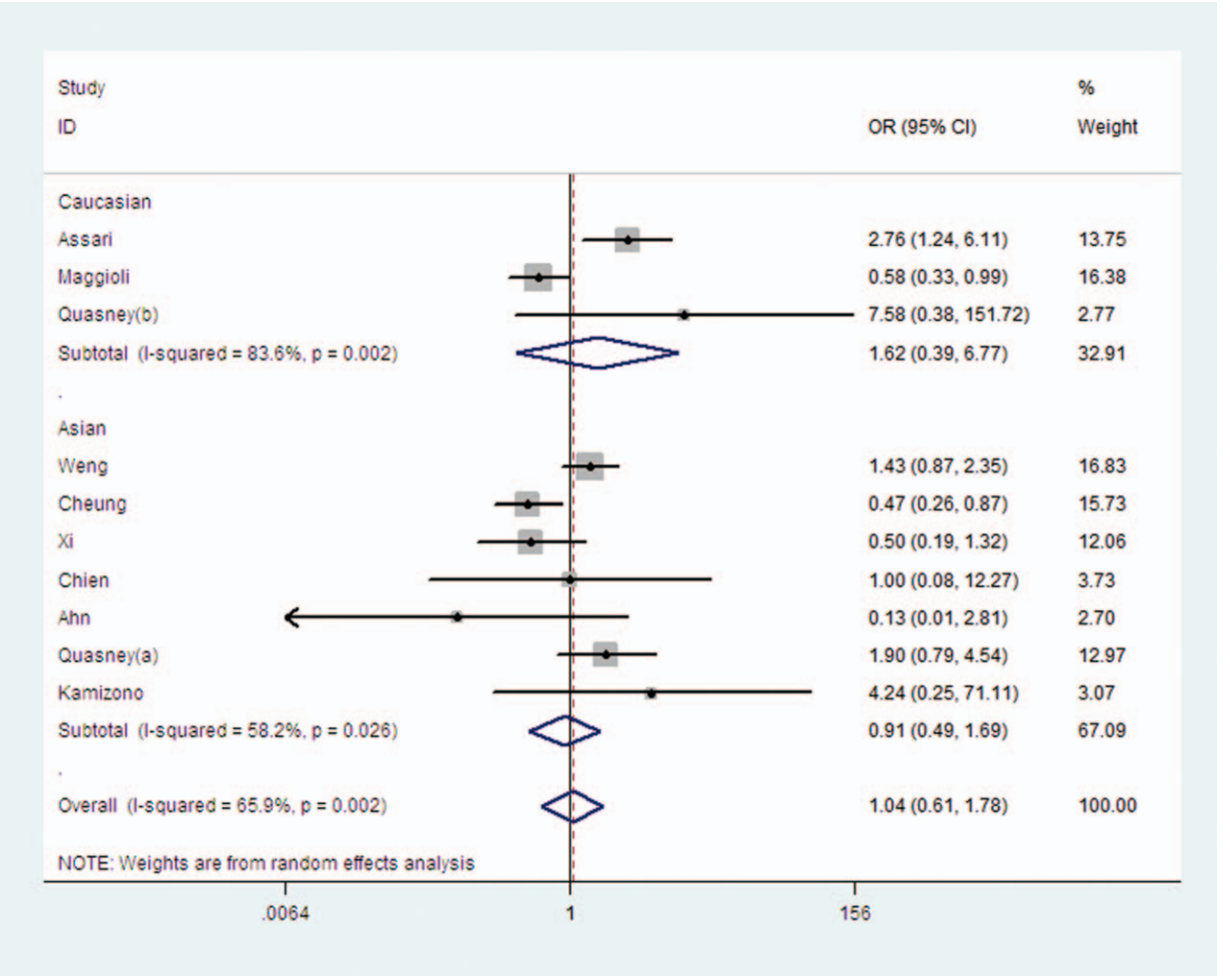

Figure 4. Forest plot of KD and TNF-α-308 in Caucasian and Asian subgroup, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. CI = confidence intervals, KD = Kawasaki disease, OR = odds ratios, TNF = tumor necrosis factor.

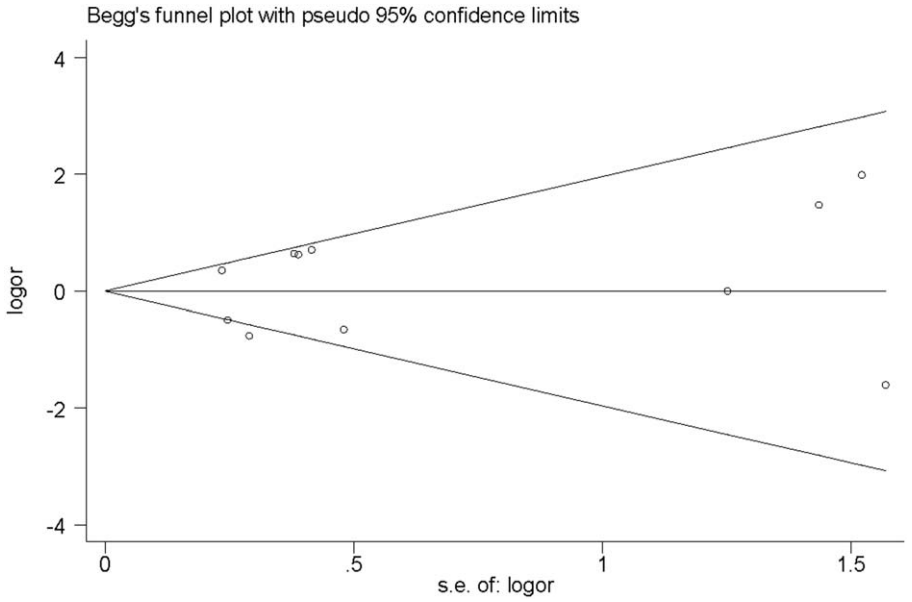

Figure 5. Begg funnel plot for publication bias tests. Each point represents a separate study for the indicated association. Log or represents natural logarithm of OR. Vertical line represents the mean effects size. OR = odds ratios.

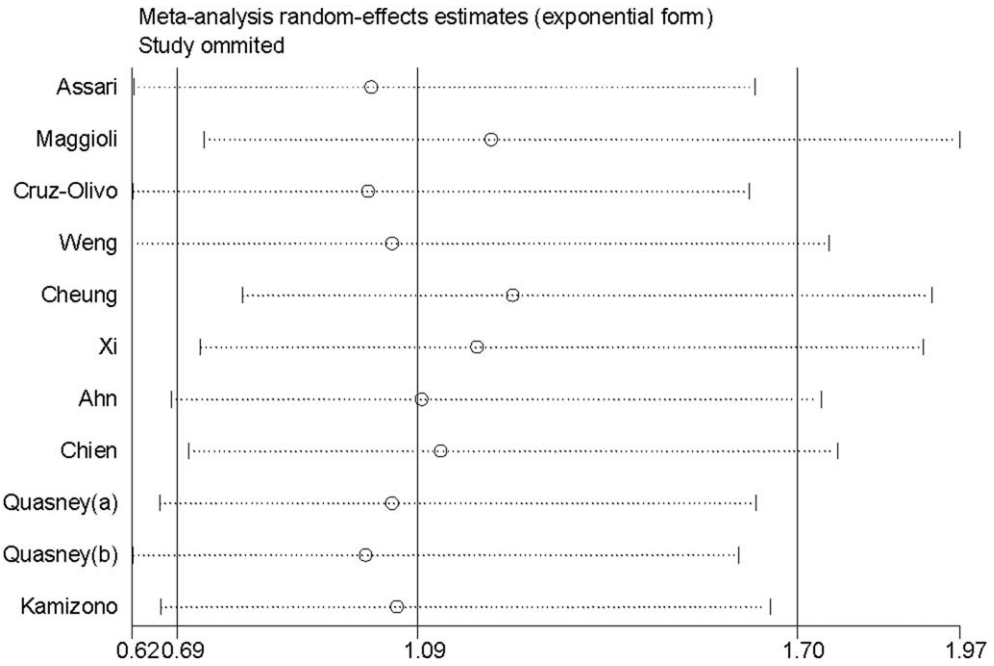

Figure 6. Potential outliers (i.e., data points that are far outside the norm) were identified by a sensitivity analysis.

the 95% CI and the shape of funnel plots showed no obvious asymmetry suggesting that there is no publication bias, and emphasized that the result of the study is credible and dependable. Absence of statistical significance based on Egger test about the value of the funnel plot ($P = .38$) suggested absence of publication bias in this model, Fig. 5.

3.6. Sensitivity analysis

Sensitivity analysis was carried out for each meta-analysis to address the influence of each study. Corresponding pooled ORs showed no significant change when 1 study was omitted at a time from each meta-analysis, implying that the results were stable and reliable, Fig. 6.

4. Discussion

The present meta-analysis containing 11 studies representing a pooled total of 841 cases and 1741 controls had relative larger sample size compared with the previous one that investigated the association between TNF-α-308 gene polymorphism and the occurrence of KD. Previous studies suggested that there is a trend of association between the TNF-α-308 G-allele and KD and having the G allele or the GG genotype might have a similar risk of developing KD compared with the A or GA/AA genotype.[34] In contrast with previous meta-analysis, our results suggested that there was not a significant association between the TNF-α-308 polymorphism and KD in both allele and genotype analyses. To exclude the influence of population stratification, we then divided all data sets into 2 subgroups, Asian population and Caucasian population. However, there was still no significant association between the TNF-α-308 polymorphism and KD in any of the genetic models in the subgroup analysis according to ethnicity.

Several studies have shown conflicting results on the genetic influence in KD. One study showed that the TNF-α-308 A/G genotype was found at a higher frequency among white children with KD who had coronary artery abnormalities compared with controls.[29] However, another study showed no association between the levels of TNF-α production and genetic polymorphisms in the 5′ flanking region of the TNF-α gene in Japanese children with a history of KD, which was consistent with the results of our study.[4] Although several studies support the role of promoter polymorphism in increased TNF-α production, other studies have shown that these polymorphism may not affect production. Some explanations may be that TNF-α production, which is regulated at both the transcriptional and posttranscriptional level, is controlled by multiple genetic factors interacting together and thus polymorphism at position-308 must be present with other polymorphisms or genetic elements to control TNF-α production. The specific genetic mechanism involved in the regulation of TNF-α production remains to be elucidated.

To some extent, the current meta-analysis possessed obvious advantage over the previous study with respect to the following point. We included the recent published studies concerned with the association between TNF-α-308 polymorphism and the occurrence of KD, which could provide more credibility for the final results. In spite of the clear advantages of our study including large-size samples, there are also several limitations in this work. First, this meta-analysis only focused on the articles from English and Chinese databases without language restrictions, which might lead to a potential language bias. Second, the low prevalence of the A allele in the whole population coupled with our small sample size may have precluded our ability to detect a difference. Third, we did not perform an evaluation of potential interactions such as gene–gene or gene–environment, which might be involved in susceptibility to KD. Considering this would lead to low statistical power, future studies with a large

dataset would be necessary for fully establishing the impact on susceptibility to KD.

5. Conclusions

In summary, our results suggest that TNF-α-308 A/G loci was not associated with the risk of KD. Large sample epidemiological studies, especially in different ethnic populations, need to confirm the findings of our meta-analysis and investigate the latent gene–gene and/or gene–environment interactions between the susceptibility gene and KD.

Author contributions

Conceptualization: Jinhua Piao, Na Lu.
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Formal analysis: Ye Yuan, Jinhua Piao, Na Lu.
Investigation: Ye Yuan, Na Lu.
Methodology: Ye Yuan, Jinhua Piao, Na Lu.
Resources: Jinhua Piao, Na Lu.
Software: Ye Yuan.
Supervision: Jinhua Piao, Na Lu.
Validation: Na Lu.
Visualization: Jinhua Piao, Na Lu.
Writing – original draft: Ye Yuan.
Writing – review & editing: Ye Yuan, Jinhua Piao, Na Lu.

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