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META-ANALYSIS

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Intercellular Adhesion Molecule-1 K469E Polymorphism and Risk of Coronary Artery Disease: A Meta-Analysis

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Intercellular adhesion molecule-1 (*ICAM-1*) K469E polymorphism has been implicated in susceptibility to coronary artery disease (CAD). Several studies investigated the association of this polymorphism with CAD in different populations but the results were contradictory. A meta-analysis was conducted to assess the association between *ICAM-1* K469E polymorphism and CAD susceptibility.

Material/Methods: Databases including PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), and Weipu Database were searched to find relevant studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of associations. A random-effects model was used.

Results: Fifteen case-control studies including 3088 cases and 3466 controls were included. Overall, a significant association between *ICAM-1* K469E polymorphism and CAD was observed in the dominant model (OR=1.80; 95% CI 1.62–2.01; $P<0.00001$; $P_{heterogeneity}=0.40$). In subgroup analysis by ethnicity, a significant association was found among Asians (OR=1.92; 95% CI 1.51–2.43; $P<0.00001$; $P_{heterogeneity}=0.98$) and among Caucasians (OR=1.64; 95% CI 1.30–2.08; $P<0.0001$; $P_{heterogeneity}=0.04$). In the subgroup analysis by age, a significant association was found among young patients (OR=1.46; 95% CI 1.10–1.93; $P=0.008$; $P_{heterogeneity}=0.21$) and old patients (OR=1.92; 95% CI 1.75–2.10; $P<0.00001$; $P_{heterogeneity}=0.99$).

Conclusions: Results of this meta-analysis suggest that *ICAM-1* K469E polymorphism confers a risk factor of CAD.

MeSH Keywords: Coronary Artery Disease • Intercellular Adhesion Molecule-1 • Meta-Analysis • Polymorphism, Single Nucleotide

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Background

Coronary artery disease (CAD) is the leading cause of death worldwide. Genetic susceptibility to CAD may be determined by specific polymorphic variants that encode proteins involved in the atherosclerotic processes. Adhesion molecules are one of the main markers of endothelial dysfunction.

Intercellular adhesion molecule-1 (ICAM-1) is widely distributed and expressed constitutively at low levels on leukocytes, vascular endothelial cells, fibroblasts, and epithelial cells. ICAM-1 specifically participates in trafficking of inflammatory cells, in leukocyte effector functions, in adhesion of antigen-presenting cells to T lymphocytes, in microbial pathogenesis, and in signal transduction pathways through outside-in signaling events [1]. ICAM-1 plays an important role in the adhesion of circulating leukocytes to the blood vessel wall and transendothelial migration to the vascular intima [2]. An elevated level of soluble ICAM-1 (sICAM-1) was observed in patients with confirmed coronary or cerebral atherosclerosis [3]. Furthermore, sICAM-1 concentrations have been associated with future CAD risk [4].

The *ICAM-1* gene is located in 19p13.2 and its K469E polymorphism (rs5498) has been suggested to have functional activity [5]. This polymorphism was suggested to affect mRNA splicing patterns that modify cell–cell interactions and influence inflammatory response [5]. In addition, this variant might have possible functional value in the etiology of atherosclerosis [6]. Studies of the association between *ICAM-1* K469E polymorphism and CAD risk [7–21] have yielded conflicting and inconclusive results. Thus, we carried out a meta-analysis to ascertain whether there was a genetic effect of *ICAM-1* K469E polymorphism on CAD susceptibility.

Material and Methods

Publication search

We conducted a systematic literature search using the databases: PubMed, EMBASE, and Weipu (last search was updated March 2014). The search terms were: ("coronary artery disease" or CAD or "coronary heart disease" or CHD) and ("intercellular adhesion molecule-1" or ICAM-1) and (polymorphism or mutation or variant). No publication date or language restrictions were imposed. All the searched studies were retrieved, and their references were checked for other relevant publications. Review articles were also searched to find additional eligible studies.

Inclusion and exclusion criteria

Case-control or cohort studies with sufficient published data for estimating an odds ratio (OR) and corresponding 95% confidence interval (CI) were included in this meta-analysis. Studies were excluded if any of the following criteria existed: (1) the studies were not relevant to *ICAM-1* K469E polymorphism or CAD, (2) non-clinical studies or the design based on family or sibling pairs, (3) genotype frequencies or number were not reported, or (4) reviews, abstracts, or comments. For overlapping studies, only the 1 with the largest sample size was included.

Data extraction

Two authors independently reviewed full manuscripts of eligible studies. The following variables were extracted from each study, if available: first author's surname, year of publication, ethnicity, age, sample size, and genotype numbers in cases and controls.

Methodological quality assessment

Two authors completed the quality assessment independently. The Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality, which scored studies by the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest [22–24]. We considered a study that was awarded 0–3, 4–6, and 7–9 as a low-, moderate-, or high-quality study, respectively. Discrepancies were resolved by consensus and discussion.

Statistical analysis

Bielinski et al. suggested that *ICAM-1* K469 caused an increase in sICAM-1 expression [25]. Thus, the strength of association between the *ICAM-1* K469E polymorphism and CAD risk was measured by OR and 95% CI in the dominant model (KK + KE *vs.* EE). A random-effects model, using the inverse variance method, was used to calculate the pooled ORs. The statistical significance of an OR was determined with the *Z* test.

Hardy-Weinberg equilibrium (HWE) was tested using the chi-squared test and it was considered statistically significant when $P<0.05$. Heterogeneity was evaluated by *Q* statistic and was considered statistical significant at *P* value <0.10. Subgroup analyses were performed by ethnicity and age. Sensitivity analysis was performed through sequentially excluded individual studies to assess the stability of the results. In addition, sensitivity analysis was also conducted by omitting the studies not in HWE and the studies with small sample size (n<200). Publication bias was analyzed by several methods. Visual inspection of asymmetry in funnel plots was carried out. Egger's test was also used to statistically assess publication bias [26].

All statistical tests were performed by using the Review Manager 5.1.2 (2011, The Cochrane Collaboration) and STATA

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Table 1. Studies and data included in this meta-analysis.

Study	Year	Ethnicity	Age of Case	No. of Case	No. of Control	Case			Control			HWE	Score
						KK	KE	EE	KK	KE	EE		
Jiang	2002	Caucasian	62.2	349	213	139	148	62	60	66	87	No	8
Zak	2005	Caucasian	45.9	146	121	12	86	48	8	68	45	No	6
Shang	2005	Asian	65.9	89	117	33	39	17	32	45	109	No	6
Wang	2005	Asian	64.9	165	199	96	61	8	91	90	18	Yes	7
Podgoreanu	2006	Caucasian	63.7	52	382	14	26	12	50	177	155	Yes	8
Wei	2006	Asian	64.1	225	230	124	84	17	101	103	26	Yes	6
Zhang	2006	Asian	68.0	173	141	111	52	10	69	59	13	Yes	5
Aminian	2007	Caucasian	56.6	303	141	90	144	64	36	69	35	Yes	8
Wen	2008	Asian	64.0	71	164	28	30	13	40	65	59	No	5
Zhou	2008	Asian	59.2	103	197	20	45	38	33	62	102	No	7
Sarecka-Hujar	2009	Caucasian	43.8	191	203	12	118	61	8	122	73	No	8
Sakowicz	2010	Caucasian	41.0	160	131	106*		54	14	69	48	Yes	6
Li	2010	Asian	58.6	93	101	47	39	7	52	36	13	Yes	7
Liu	2011	Asian	64.7	312	302	178	112	22	130	138	34	Yes	8
Buraczynska	2012	Caucasian	62.8	656	824	288	340	28	272	379	173	Yes	9

* The combined number of KK and KE genotypes. HWE – Hardy-Weinberg equilibrium; NA – not available.

11.0 software (Stata Corporation, College Station, TX). A *P* value <0.05 was considered statistically significant.

Results

Study characteristics

A total of 15 case-control studies with 3088 cases and 3466 controls met our inclusion criteria [7–21]. There were 8 studies of Asians and 7 studies of Caucasians. Six studies were performed in young patients (age <60), and 9 studies were conducted in old patients (age >60). Six studies were not in HWE. The quality scores ranged from 5 to 9, suggesting that the methodological quality was generally acceptable. The characteristics of each study and genotype distribution are presented in Table 1.

Quantitative data synthesis

All studies

The pooled OR was 1.80 (95% CI 1.62–2.01) and the *Z* test for overall effect was 10.69 (*P*<0.00001) (Figure 1). There was small heterogeneity (I^2=5% and $P_{heterogeneity}$=0.40).

Subgroup analyses

In the subgroup analysis by ethnicity, a significant association was found among Asians (OR=1.92; 95% CI 1.51–2.43; *P*<0.00001; $P_{heterogeneity}$=0.98) and among Caucasians (OR=1.64; 95% CI 1.30–2.08; *P*<0.0001; $P_{heterogeneity}$=0.04) in the dominant genetic model. In the subgroup analysis by age, a significant association was found among young patients (OR=1.46; 95% CI 1.10–1.93; *P*=0.008; $P_{heterogeneity}$=0.21). There was a significant association between *ICAM-1* K469E polymorphism and CAD risk among old patients (OR=1.92; 95% CI 1.75–2.10; *P*<0.00001; $P_{heterogeneity}$=0.99).

Sensitivity analysis

To assess the stability of the results of the meta-analysis, we performed a sensitivity analysis through sequentially excluding individual studies. Statistically similar results were obtained after sequentially excluding each study (data not shown). Omitting the studies deviating from HWE also did not change the result (OR=1.75; 95% CI 1.52–2.00; *P*<0.00001; $P_{heterogeneity}$=0.35). Additionally, when the studies with small sample sizes were excluded, the result was still significant (OR=1.86; 95% CI 1.70–2.05; *P*<0.00001; $P_{heterogeneity}$=0.42).

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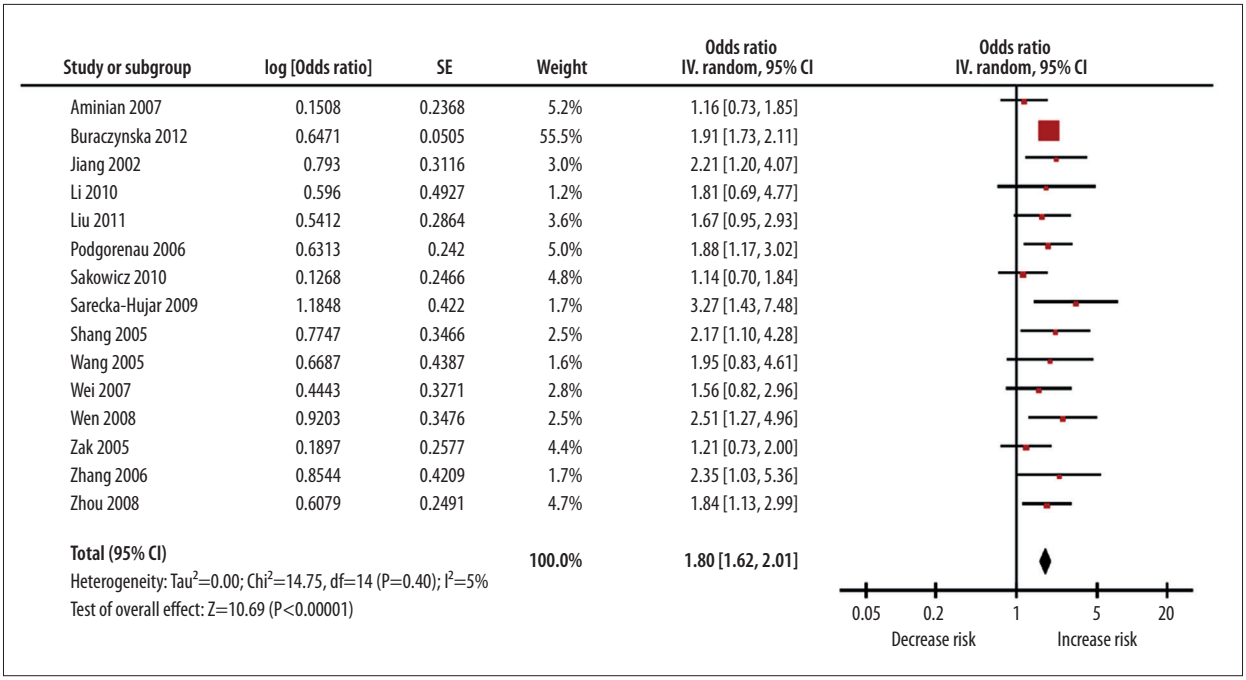

Figure 1. Meta-analysis with a random-effects model for the association between *ICAM-1* K469E polymorphism and CAD risk.

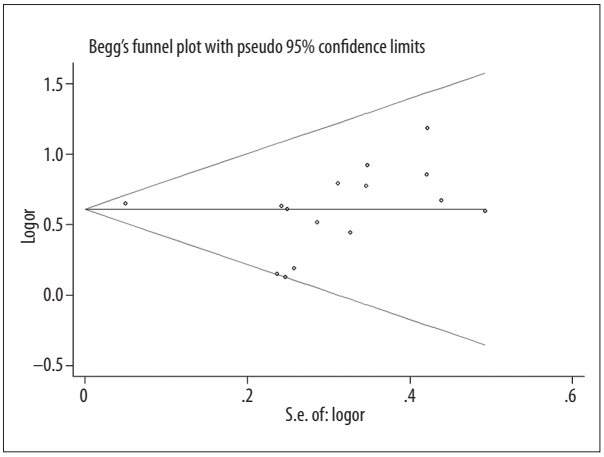

Figure 2. Funnel plot for *ICAM-1* K469E polymorphism and CAD risk.

Publication bias

Funnel plot was performed to assess the publication bias in this meta-analysis; it showed a symmetrical inverse funnel shape (Figure 2). Egger's test also indicated no significant publication bias (*P*=0.584).

Discussion

This meta-analysis of 15 case-control studies including 3088 cases and 3466 controls evaluated the association between *ICAM-1* K469E polymorphism and CAD risk. The result indicate that *ICAM-1* K469E polymorphism might be a risk factor for developing CAD. Our results suggest that individuals who carry the KK or KE genotype may have an 80% increased CAD risk compared with EE genotype carriers. In the subgroup analysis by ethnicity, both significant associations were found in Asians and Caucasians, suggesting that both Asians and Caucasians who carry the KK or KE genotype might have an increased CAD risk. In the subgroup analysis by age, we found *ICAM-1* K469E polymorphism showed increased early-onset CAD risk and late-onset CAD risk. This result indicates that the role of *ICAM-1* K469E polymorphism is not selective by age.

Many recent studies suggest that sICAM-1 plays an important in the development of CAD. For example, Hulthe et al. showed that levels of sICAM-1 were associated with subclinical atherosclerosis and inflammatory variables [27]. Bongard et al. [28] reported that sICAM-1 was independently associated with the risk of having at least 1 carotid plaque and with the risk of having at least 1 femoral plaque. Furthermore, *ICAM-1* K469E polymorphism could influence the levels of sICAM-1. Genome-wide association analysis indicated that *ICAM-1* K469E polymorphism had a role in the genetic regulation of sICAM-1 levels [29]. In addition, Reilly et al. found that *ICAM-1* K469E EE genotype was associated with lower coronary artery calcification (CAC) scores in men [30]. Taken together, these data indicate that *ICAM-1* K469E polymorphism can influence the risk of CAD.

The role of the IL-33/ST2 signaling pathway in ischemic heart disease has been reported [31]. Choi et al. found that IL-33 mediated the expression of ICAM-1 and vascular cell adhesion

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molecule (VCAM)-1 in endothelial cells [32]. sST2 seems to act as a decoy-receptor for IL-33: it binds IL-33, thus, subtracting such a molecule from the interaction with ST2L [31]. Therefore, it is interesting to investigate whether sST2 can influence the expression of ICAM-1.

Heterogeneity is an important issue when interpreting the results of meta-analyses. In our meta-analysis, there was no significant heterogeneity in most of the comparisons and no publication bias was found. Therefore, heterogeneity and publication bias did not influence the results. We also conducted sensitivity analyses and no individual study was found to affect the overall result. Excluding the studies not in HWE or with small sample size also did not influence the overall result. These results indicate that our results are stable and robust. However, several limitations of this study should be addressed. First, the sample size was still relatively small for some stratified analyses. Second, only published studies were included in the meta-analysis; therefore, publication bias may have occurred, even though the use of a statistical test did not show it. Third, we were unable to obtain information from most studies on the presence or absence of a history of smoking, because of lack of the investigation of gene-environment interactions [33]. Finally, our meta-analysis was based on unadjusted estimates, whereas a more precise analysis could be performed if individual data were available and would allow for an adjustment estimate. Despite the limitations, our meta-analysis significantly increased the statistical power of the analysis based on the large number of cases and controls from different studies.

Conclusions

Results of this meta-analysis suggest that the *ICAM-1* K469E polymorphism is a risk factor for CAD. Future large-scale studies are needed to validate our findings.

Conflicts of interest

None.

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