Inflammation Research (2019) 68:275–284
https://doi.org/10.1007/s00011-019-01220-4

Inflammation Research

ORIGINAL RESEARCH PAPER

# The influence of ICAM1 rs5498 on diabetes mellitus risk: evidence from a meta-analysis

**Wensheng Mi**[1,2] · **Yan Xia**[1,2] · **Yanhui Bian**[1,2]

Received: 30 December 2018 / Revised: 12 February 2019 / Accepted: 19 February 2019 / Published online: 23 February 2019


## Abstract

**Objectives** Both type 1 diabetes (T1D) and type 2 diabetes (T2D) are classified as forms of diabetes mellitus (DM) and commonly considered inflammatory process. Intercellular adhesion molecule-1 (ICAM-1) is involved in the development and progression of diabetes mellitus. However, the genetic association between ICAM-1 rs5498, and T1D and T2D risk was inconclusive.

**Materials and methods** A meta-analysis by searching the PubMed, Embase, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) databases was performed out. The pooled odds ratio (OR) and 95% confidence interval (CI) were used to describe the strength of association of T1D and T2D risk.

**Results** A total of 14 studies encompassing 3233 cases and 2884 controls were included in the present meta-analysis. Significant associations were found between the allele and recessive models of ICAM1 rs5498 and DM in Asian population (allele: OR 1.13; 95% CI 1.03–1.23, $p=0.008$; recessive: OR 1.25; 95% CI 1.06–1.48, $p=0.008$), but not in Caucasian population ($p>0.05$). In addition, the allele model of rs5498 was found to be significantly associated with the increased risk of T2D (OR 1.10; 95% CI 1.01–1.21, $p=0.03$), but not T1D ($p>0.05$).

**Conclusions** The ICAM1 rs5498 might be a susceptible factor for T2D, but not T1D. And the allele and recessive models of ICAM1 rs5498 might be a risk factor in Asian population.

**Keywords** Diabetes mellitus (DM) · Intercellular adhesion molecule-1 (ICAM-1) · Genetic association · Meta-analysis

## Introduction

Diabetes mellitus (DM) is a major endocrine disorder characterized by chronic hyperglycemia that results from inefficient insulin secretion and impaired glucose metabolism [1–3]. By the year 2030, the number of persons with DM will increase to 366 million in the whole world [4]. There are three types of DM including type 1 diabetes, type 2 diabetes and gestational diabetes [5]. T1D caused by autoimmunity against pancreatic beta cells, resulting in insulin deficiency, and T2D initiated by metabolic changes that render target tissues resistant to insulin [6, 7]. The metabolic, genetic and environmental factors, as well as inflammatory mediators were shown to play an important role in the pathogenesis of T1D and T2D [8–13].

Commonly, T1D and T2D are considered inflammatory processes [14–17]. Pro-inflammatory cytokines such as IL-6, IL-18, IL-1 and TNF-α, as well as chemokines including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and nuclear transcription factor κB (NF-κB) were reported to be significantly increased in patients with T1D and T2D [18–21]. The ICAM-1, a well-characterized transmembrane glycoprotein, is known to be expressed on the surface of endothelial cell, vascular endothelial cells, macrophages, and activated lymphocytes [22, 23]. A previous study has approved that

Responsible Editor: John Di Battista.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00011-019-01220-4) contains supplementary material, which is available to authorized users.

✉ Yan Xia
xiayancsmu518@sina.com

[1] Department of Pathophysiology, School of Basic Medical Science, Changsha Medical University, Changsha 410219, People's Republic of China

[2] Department of Human Anatomy, Histology and Embryology, Institute of Neuroscience, Changsha Medical University, Changsha 410219, People's Republic of China

elevated ICAM-1 levels were independently associated with insulin resistance [24]. Clinical investigations have shown that increased serum ICAM-1 levels are associated with all caused mortality and cardiovascular morbidity in T1D and T2D [25, 26]. Lines of evidence have emphasized the importance of ICAM-1 for the pathogenesis of DM and indicated on ICAM1 as a candidate gene in the DM susceptibility [27, 28].

The ICAM1 gene is located on chromosome 19p13 within the linkage region of diabetes [29]. Several studies have demonstrated that single-nucleotide polymorphisms (SNPs) in the ICAM-1 gene such as rs5498 E469K (A/G) and rs1799969 R241G (A/G) were associated with coronary heart disease [30], ischaemic stroke [31], diabetic retinopathy (DR) [19, 29, 30], and diabetic nephropathy (DN) [32, 33]. Furthermore, the frequencies of the allelic (G vs. A) and the dominant models (GG + GA vs. AA) of ICAM1 rs5498 were higher than that in patients with T2D [33]. However, most of other studies have shown no association between ICAM1 rs5498 and T2D risk [34, 35]. In addition, significant association was also detected between the recessive model of ICAM1 rs5498 and T1D risk in Swedish [28], while negative results were reported in Finlish [38] and Japanese [39].

Due to relatively small sample sizes and inconsistent results in previous individual studies, we aimed to systematically evaluate the genetic association between ICAM1 rs5498, and T1D and T2D using a meta-analysis.

## Materials and methods

### Search strategy

This meta-analysis followed the Cochrane collaboration definition and PRISMA 2009 guidelines for meta-analysis and systematic review [40]. A comprehensive literature search throughout PubMed, Embase, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) databases was performed out to retrieve the genetic association studies of ICAM1 polymorphisms and DM risk. The following search terms were used: "diabetes mellitus", "Type 1 diabetes mellitus", "Type 2 diabetes mellitus", "DM", "T1D", "T2D", "Intercellular adhesion molecule-1", "ICAM-1", "polymorphism", "variant". No language and published year was limited. Other relevant references of identified studies were retrieved by cross-references. The latest search was updated on August 1, 2018.

Inclusion criteria: (1) case–control study. The cases should be patients with T1D or T2D without DR or DN and the control group consisted of unrelated healthy subjects, (2) regarding the genetic association between ICAM1 polymorphisms and T1D or T2D risk, (3) the allele and genotype frequencies in cases and controls were available, (4) the genotype distribution in control group was in Hardy–Weinberg equilibrium (HWE).

Exclusion criteria: (1) duplicated study, (2) review, letter, abstract, brief communication, and case report, (3) irrelevant to the association between ICAM1 polymorphisms and T1D or T2D risk, (4) insufficient data for genotypes.

### Data abstraction and quality assessment

Two authors (Mi WS and Bian YH) independently reviewed the relevant articles and extracted the following data: the first author, year of publications, ethnicity, age of cases and controls, duration year of DM, percent of males, body mass index (BMI), level of fasting glucose, type of DM, number of cases and controls, genotype and allele frequency, and evidence of HWE in controls. All discrepancies were resolved by discussion. The study quality was assessed by the Newcastle–Ottawa Scale (NOS) [41]. Total score ranged from 0 (lowest quality) to 8 (highest quality). A score of 6 or higher was selected in present study.

### Statistical analysis

The association between the allele, dominant, and recessive models of ICAM-1 rs5498 and the risk of T1D and T2D was evaluated by crude OR and 95% CI. The significance of the pooled OR was assessed by the $Z$ test. Subgroup analyses were performed stratified by ethnicity and type of DM (T1D or T2D). Heterogeneity was evaluated by the chi-square-based $Q$ statistic and $I^2$ statistic. When the heterogeneity $< 50\%$ or $p > 0.05$, a fixed-effect model was used. Otherwise, a random effect model was selected. To evaluate the stability of the overall results, sensitivity analyses by omitting each study was performed. Potential publication bias was assessed using Begg's and Egger's test. A $p$ value of less than 0.05 was considered to be significant. The STATA 12.0 software (Stata Corp, College Station, TX, USA) and Revman 5 (Cochrane Collaboration, London, UK) were used in statistical analyses.

## Results

### Study selection and characteristics

According to the inclusion criteria, 673 publications were identified from the initial search. Of these, 126 studies were excluded for being replications. After screening the titles and abstracts, 92 were excluded for being review, abstracts, or letter. 417 were excluded for being not related to the association between ICAM1 rs5498 and DM risk. In addition, 16 were excluded for being not case–control-designed study. 8

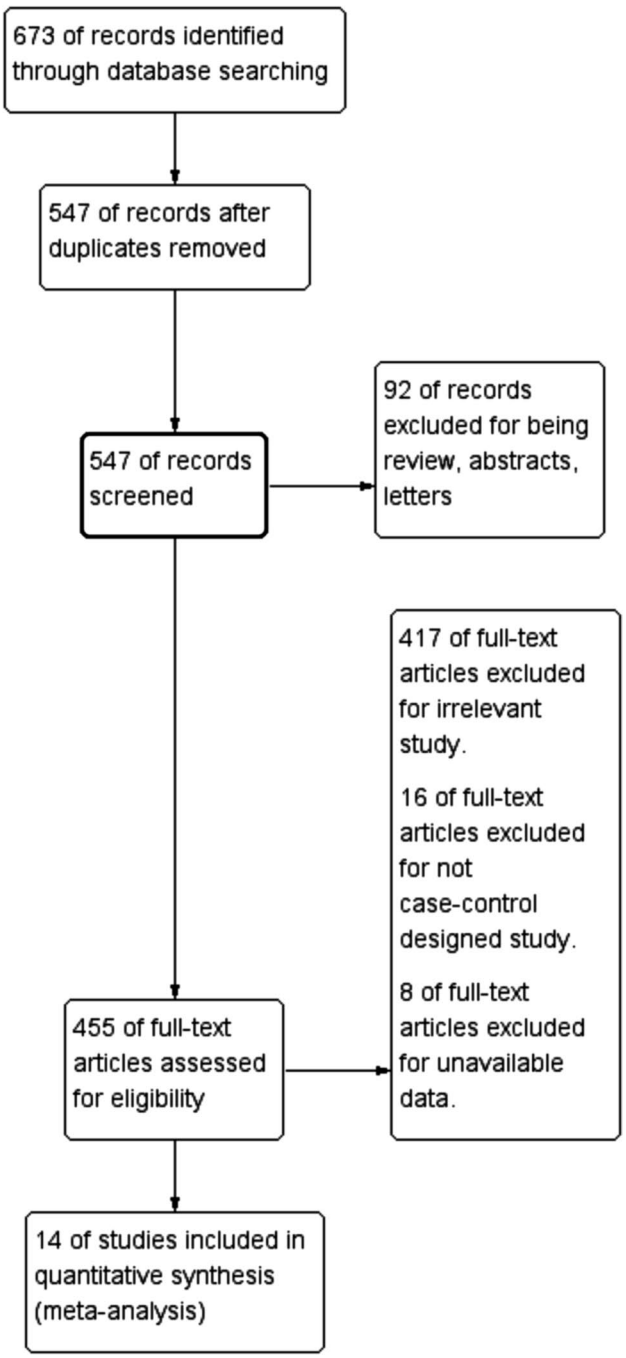



**Fig. 1** PRISMA flow chart of studies inclusion and exclusion

were excluded for unavailable data. Therefore, a total of 14 publications encompassing 3233 cases and 2884 controls were included in the final meta-analysis. Selection for eligible papers included in this meta-analysis is presented in Fig. 1. The detailed characteristics of individual study are listed in Table 1. The NOS scores ranged from six to eight stars, indicating that all the included studies of high quality (Suppl Table s1). Among the studies, 3 articles were in

**Table 1** Characteristics of included studies

| First author | Year | Ethnicity | Duration (years) | Age (years) | *M* (%) | BMI (kg/m$^2$) | Fasting glucose (mmol/l) | Type of DM | Case | Control | HWE | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ma | 2006 | Swedish | 31 ± 11 | 45 ± 12/48 ± 5 | 37.9/45.8 | 25.3 ± 3.44/23.0 ± 1.82 | NA | T1D | 187 | 432 | $p > 0.05$ | 7 |
| Nejentsev | 2000 | Finland | NA | NA | NA | NA | NA | T1D | 218 | 212 | $p > 0.05$ | 6 |
| Nishimura | 2000 | Japanese | NA | NA | NA | NA | NA | T1D | 164 | 171 | $p > 0.05$ | 6 |
| Liu | 2005 | Chinese | 13.7 ± 1.90 | 61.5 ± 11.53/50.2 ± 10.64 | 47.5/50 | NA | 7.9 ± 3.91/5.0 ± 0.66 | T2D | 40 | 80 | $p > 0.05$ | 7 |
| Popović | 2016 | Slovakia | 11.25 ± 7.88 | 61.38 ± 9.65/60.07 ± 9.18 | 56.8/46 | 30.96 ± 4.74/27.90 ± 4.42 | 8.04 ± 2.57/5.27 ± 0.87 | T2D | 595 | 200 | $p > 0.05$ | 8 |
| Ren | 2015 | Chinese | 15.6 ± 5.9 | 66.4 ± 11.2/50.0 ± 16.1 | 53.1/49.6 | 26.0 ± 8.7/23.0 ± 3.5 | 7.5 ± 2.7/5.0 ± 0.4 | T2D | 385 | 672 | $p > 0.05$ | 8 |
| Seman | 2015 | Malaysia | 13 ± 8 | 56 ± 11/44 ± 15 | 50.5/52.8 | 27.9 ± 5.3/25.8 ± 6.1 | 5.3 ± 2.1/4.9 ± 1.0 | T2D | 580 | 562 | $p > 0.05$ | 8 |
| Yokoyama | 2005 | Japanese | NA | 55.2 ± 12.1/55.2 ± 11.5 | 48/48 | 24.4 ± 4.4/24.4 ± 2.6 | NA | T2D | 360 | 152 | $p > 0.05$ | 7 |
| Chen | 2010 | Chinese | NA | 57.69 ± 9.72/55.2710.13 | 45.4/48.6 | NA | NA | T2D | 189 | 111 | $p > 0.05$ | 6 |
| Wang | 2006 | Chinese | 9.7 ± 6.1 | 60.2 ± 6.9/60.8 ± 7.0 | 50/51 | 25.8 ± 2.4/24.5 ± 2.4 | NA | T2D | 100 | 98 | $p > 0.05$ | 7 |
| Oguz | 2015 | Turkish | NA | 54.77 ± 2.49/50.1 ± 8 | 35.5/33.3 | 32 ± 4.9/23.92 ± 3.3 | 9.94 ± 1.24/5.2 ± 0.51 | NA | 138 | 138 | $p > 0.05$ | 7 |
| Zhou | 2010 | Chinese | NA | 56.3 ± 9.4/55.3 ± 8.6 | 51.6/52 | NA | NA | T2D | 120 | 150 | $p > 0.05$ | 7 |
| Zhu | 2010 | Chinese | NA | NA | NA | NA | NA | T2D | 40 | 30 | $p > 0.05$ | 6 |
| Mao | 2008 | Chinese | 4.1 ± 1.8 | 46.5 ± 5.4/45.3 ± 6.6 | NA/55.3 | NA | NA | T2D | 70 | 121 | $p > 0.05$ | 7 |

*NA* not available, *M* male, *BMI* body mass index, *DM* diabetes mellitus, *HWE* Hardy–Weinberg equilibrium, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *NOS* Newcastle–Ottawa Scale

Caucasian, 11 were in Asian. In addition, three articles were carried out in subjects with T1D; the remaining ten studies were carried out in subjects with T2D.

### Results of meta-analysis

A fixed effects model was conducted for allele model (G vs. A), dominant model (GG + GA/AA) and recessive model (GG/GA + GG) without significant heterogeneity. As shown in Table 2, no statistically significant association was detected between the allele, dominant, and recessive models of ICAM1 rs5498 and DM (allele: OR 1.08; 95% CI 1.00–1.16, $p = 0.05$; dominant: OR 1.13; 95% CI 1.00–1.27, $p = 0.05$; recessive: OR 1.11; 95% CI 0.96–1.27, $p = 0.16$). Stratified analyses were performed based on ethnicity. The results indicated that the allele and recessive models of rs5498 were significantly associated with the increased risk of DM in Asian (allele: OR 1.13; 95% CI 1.03–1.23, $p = 0.008$; recessive: OR 1.25; 95% CI 1.06–1.48, $p = 0.008$), but not in Caucasian ($p > 0.05$). In the stratified analysis by the type of DM, we found the allele model of rs5498 was significantly associated with the increased risk of T2D (OR 1.10; 95% CI 1.01–1.21, $p = 0.03$), but not T1D ($p > 0.05$) (Table 2; Fig. 2).

We carried out sensitivity analysis by omitting individual study once at a time. The pooled ORs for all the genetic models of rs5498 polymorphism for DM risk indicated that our data were stable and trustworthy (Fig. 3). Both Egger's and Begg's tests were used to evaluate the publication bias of this meta-analysis. The results revealed that there was no obvious publication bias in overall analysis for ICAM1 rs5498 (Fig. 4).

## Discussion

In present study, we detected a significant association between the allelic and recessive models of ICAM1 rs5498 and DM risk in Asian population, but not Caucasian population. In addition, the rs5498G might be a risk factor for T2D, but not T1D.

ICAM1 is a cell surface adhesion molecule and expressed in endothelial cells and leukocytes in the immune system [42, 43]. The ICAM-1 molecule has been shown to play an important role in stabilizing cell–cell interactions, facilitating leukocyte endothelial transmigration, as well as T-cell receptor-mediated activation of resting T cells [44, 45]. The role of ICAM1 in T1D has been concentrically investigated in NOD mice, an animal model resembling human T1D [46]. It serves as a receptor for the leukocyte function-associated antigen-1 (LFA-1) and the macrophage differentiation antigen-1 (Mac-1). ICAM1 and LFA1 expression are restricted to regions of immune cell infiltration. Significant prevention of the onset of diabetes was detected in NOD mice using monoclonal antibodies against LFA1 and ICAM1 [47, 48].

Type 1 diabetes is an organ-specific autoimmune disease that selectively destroys islet beta cells [49]. The major genetic T1D component resides in regions mapping to 6q21

**Table 2** The association between ICAM1 rs5498 and diabetes mellitus

| SNP (minor allele) | Genetic model | Subgroup | Number of studies | Numbers | | Test of association | | Model | Test of heterogeneity | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | OR (95% CI) | *p* value | | *p* value | $I^2$ (%) |
| Rs5498 (G) | Allelic (G vs. A) | Total | 14 | 6466 | 5768 | 1.08 (1.00, 1.16) | 0.05 | F | 0.82 | 0 |
| | | Asian | 11 | 4372 | 4570 | 1.13 (1.03, 1.23) | 0.008 | F | 0.95 | 0 |
| | | Caucasian | 3 | 2094 | 1198 | 0.96 (0.83, 1.12) | 0.62 | F | 0.57 | 0 |
| | | T1D | 3 | 1232 | 1140 | 0.98 (0.83, 1.15) | 0.79 | F | 0.32 | 13 |
| | | T2D | 10 | 4958 | 4352 | 1.10 (1.01, 1.21) | 0.03 | F | 0.92 | 0 |
| | Dominant (GG + GA/AA) | Total | 14 | 3233 | 2884 | 1.13 (1.00, 1.27) | 0.05 | F | 0.07 | 39 |
| | | Asian | 11 | 2186 | 2285 | 1.15 (1.00, 1.32) | 0.05 | F | 0.04 | 46 |
| | | Caucasian | 3 | 1047 | 599 | 1.07 (0.85, 1.35) | 0.58 | F | 0.30 | 17 |
| | | T1D | 3 | 616 | 570 | 1.10 (0.85, 1.42) | 0.46 | F | 0.92 | 0 |
| | | T2D | 7 | 2479 | 2176 | 1.14 (0.99, 1.31) | 0.07 | R | 0.03 | 52 |
| | Recessive (GG/GA + GG) | Total | 14 | 3233 | 2884 | 1.11 (0.96, 1.27) | 0.16 | F | 0.04 | 44 |
| | | Asian | 11 | 2186 | 2285 | 1.25 (1.06, 1.48) | 0.008 | F | 0.86 | 0 |
| | | Caucasian | 3 | 1047 | 599 | 0.82 (0.64, 1.06) | 0.13 | R | 0.004 | 82 |
| | | T1D | 3 | 616 | 570 | 0.83 (0.62, 1.10) | 0.19 | R | 0.001 | 85 |
| | | T2D | 7 | 2479 | 2176 | 1.18 (1.00, 1.40) | 0.05 | F | 0.32 | 13 |

*ICAM1* intercellular adhesion molecule-1, *SNP* single-nucleotide polymorphism, *R* random model, *F* fixed model, *OR* odds ratios, *CIs* confidence intervals

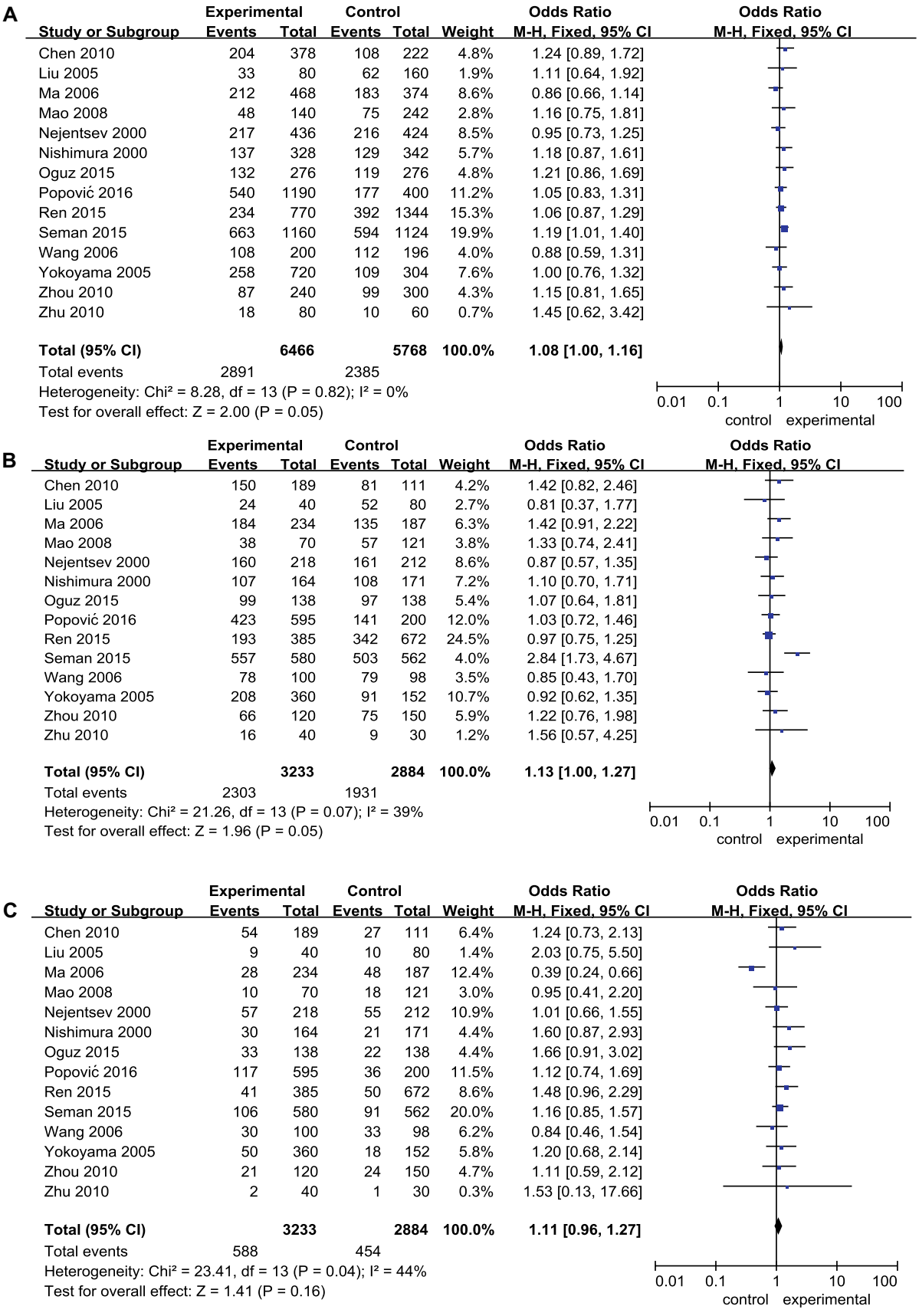



**Fig. 2** Forest plots of odds ratios for the association between ICAM1 rs5498 and diabetes mellitus. **a** Allele model, **b** dominant model, **c** recessive model

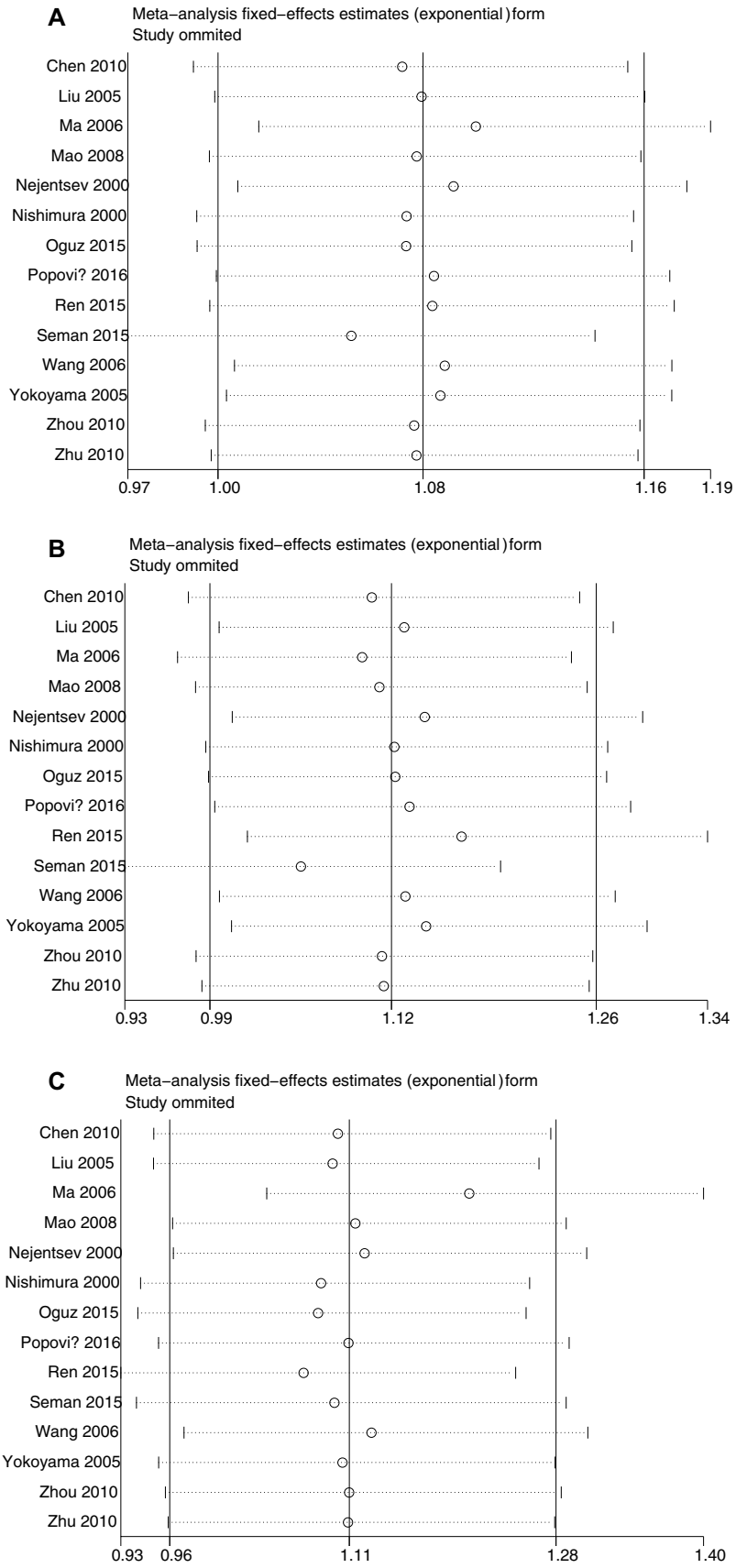
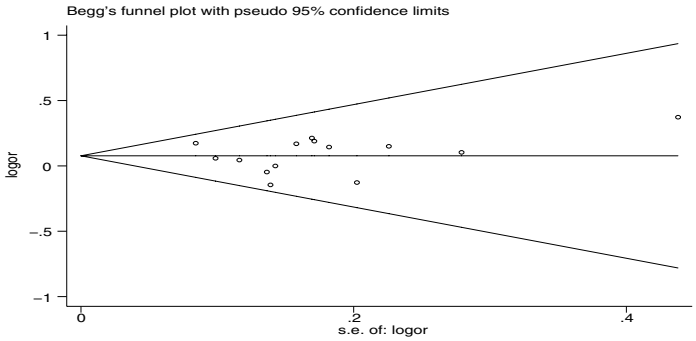


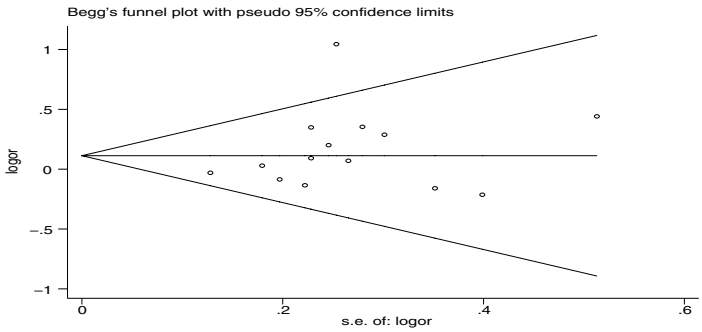

**Fig. 3** Sensitivity analyses between ICAM1 rs5498 and diabetes mellitus. **a** Allele model, **b** dominant model, **c** recessive model

**A**



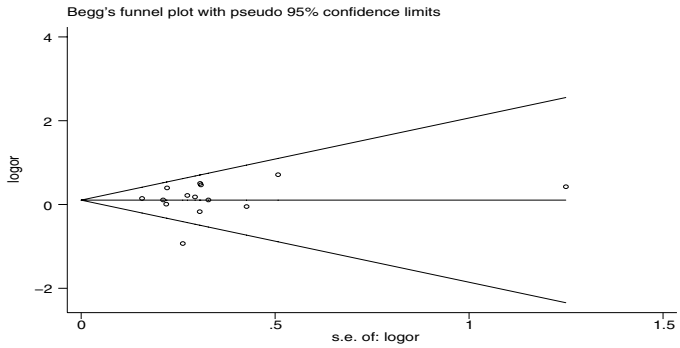

| Std_Eff | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| slope | -.0597932 | .4918037 | -0.12 | 0.906 | -1.172331 | 1.052744 |
| bias | -1.433159 | 3.792616 | -0.38 | 0.714 | -10.01265 | 7.146335 |

**B**




| Std_Eff | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| slope | -.0464061 | .3535203 | -0.13 | 0.898 | -.8461245 | .7533124 |
| bias | .2675036 | 1.780476 | 0.15 | 0.884 | -3.760212 | 4.295219 |

**C**




| Std_Eff | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| slope | -.0541566 | .4441261 | -0.12 | 0.906 | -1.05884 | .9505266 |
| bias | .679105 | 1.793918 | 0.38 | 0.714 | -3.379019 | 4.737229 |

**Fig. 4** Publication bias of literatures for ICAM1 rs5498 and diabetes mellitus were tested by Begg's funnel plot and Egger's test. **a** Allele model, **b** dominant model, **c** recessive model

(MHC) and 19p13 (ICAM1) [28, 50]. K469E, a frequent exon 6 substitution, which encodes Ig-like domain 5-Lys (AAG) or Glu (GAG), has been investigated in DM in small samples, with variable results [51]. The first study conducted by Nishimura et al. [39] showed that the frequency of ICAM-1 469AG genotype was significantly higher in the adult-onset T1D patients than that in controls. Subsequently, Ma et al. suggested that the ICAM-1 rs5498 polymorphism was associated with T1D [28]. A combined analysis of the transmission disequilibrium test from T1D families with 728 affected offspring of Romanian, Finnish and Danish ancestry has suggested association between ICAM1 E469 allele and T1D ($p = 0.013$) [52]. However, our combined analysis of case–control data with 616 cases and 570 controls suggested no association between ICAM1 K469E and T1D risk. Notable, only three studies were included in the

analysis of correlation of ICAM1 K469E and T1D, which may reduce the statistical power to evaluate the precise association between ICAM1 K469E and T1D risk for the relatively small sample size. To further investigate the association between ICAM1 K469E and T1D risk, larger number of case–control studies with more subjects is necessary in the future.

T2D is a so-called multifactorial disease in which the genes (loci) not only interact with each other but also with environmental factors such as age, physical activity, diet, and obesity [53]. Oxidative stress, inflammation, and endothelial dysfunction may be ameliorated by a healthy diet and lifestyle, and have also been linked to the etiology of T2D [54]. It has been suggested that an acute increase of plasma glucose may produce an oxidative stress in man [55]. In vitro studies have demonstrated that high glucose and free radicals may induce cellular expression of ICAM-1 [56]. Odegaard et al. has reported a higher incidence rate of T2D with higher levels of ICAM-1 regardless of oxidized LDL level in young adults [54]. Thus, ICAM-1 may play an important role in oxidative stress through by high glucose in T2D. Both T1D and T2D show a familial predisposition, which is a strong indication for the involvement of genes in people's susceptibility to the disease. Notable, the ICAM1 rs5498 allele was significantly associated with T2D, but not with T1D. Although T1D and T2D share some clinical similarities, these diseases are the result of distinct biological mechanisms. T1D is caused by autoimmunity against pancreatic beta cells, resulting in insulin deficiency and typically presents in childhood, while T2D is initiated by metabolic changes that render target tissues resistant to insulin and typically presents in adults (> 40 years of age). Despite suggestions that genetic similarities exist between T1D and T2D [57], few genes were shown to be associated with both the T1D and T2D. And the loci reported for each of these phenotypes appear largely different from one another which further supports the fact that these are two distinct diseases [58, 59]. In our meta-analysis, the ICAM1 rs5498 allele was found to be significantly associated with T2D, but not T1D, which may indicate the etiology underlying types 1 and 2 is different and different genes are likely to be involved in each type of diabetes mellitus.

Interesting, significant association between the allele and recessive models of ICAM1 rs5498 and DM in Asian, but not in Caucasian, was observed, which may indicate an important role of genetic background in the pathogenesis of DM. The average frequency of ICAM1 rs5498G in patients with DM in Caucasian was not significantly different from that in Asian (Caucasian 0.463; Asian 0.407). Among the included studies, only Seman et al. has shown significant association between ICAM1 rs5498 and DM in Malaysian. After excluded this study, significant associations were also detected between allele and recessive models of ICAM1 rs5498 and DM risk in Asian, which indicate the ICAM1 rs5498 might contribute to the pathogenesis of DM in Asian, but not in Caucasian. However, there were only three studies included in Caucasian subgroup, which may partly influence the evaluation of the precise correlation of ICAM1 rs5498 and DM in Caucasian.

The limitations of this study should be mentioned. First, the sample size was relatively small, especially for the analysis of ICAM1 K469E and T1D. Several studies enrolled only dozens of patients. Large-scale case–controls would have improved the accuracy of the present findings. Second, the results have shown the importance of gene background in the pathogenesis of DM. However, the subgroup analysis stratified by ethnicity was performed out in only Asian and Caucasian. The results may be need further accessed in multiple ethnicity groups. Third, multiple factors can influence the development of DM, especially the gene–gene interaction and gene–environment interaction. The age and gender were important factors in the pathologenesis of DM. However, we failed to evaluate the effect of these two factors in the association between ICAM1 rs5498 and DM risk for lack of sufficient data.

## Conclusion

The ICAM1rs5498 might be a susceptible factor for T2D, but not T1D. In addition, the allele and recessive models of ICAM1 rs5498 were associated with DM in Asian, but not in Caucasian. For the limited studies included in present study, it is necessary to investigate the genetic association between ICAM1 rs5498 and DM risk using a case–control-designed study with larger number of subjects.

**Acknowledgements** This study was funded by the Youth Foundation of the Education Department of Hunan (17B035) and the construct program of the key discipline in Hunan province.

### Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

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