Association between susceptibility of diabetic nephropathy and gene polymorphisms in ELMO1 and IL-8: a systemic review and meta-analysis

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Abstract

Background: The engulfment and cell motility 1 (ELMO1) and interleukin-8 (IL8) gene polymorphisms have been previously implicated in diabetic nephropathy (DN) susceptibility. However, the results are inconsistent. We aimed to examine this issue by systematic meta-analysis.

Methods: An electronic search was conducted in PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure and Wanfang Database to identify all the eligible studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to investigate the associations. All statistical analyses were performed by STATA 12.0.

Results: Of the 11 studies included, 9 studies were performed to detect EMLO1 rs741301 polymorphism; 5 studies were used to examine IL-8 rs4073 polymorphism. The results revealed no significant association between EMLO1 rs741301 polymorphism and DN risk. While, stratified analysis by ethnicity indicated that EMLO1 rs741301 polymorphism was associated with an increased risk of DN risk among Asians (GG vs. GA +AA: OR= 1.840, 95% CI= 1.338-2.529, P= 0.000; GG vs. AA: OR= 1.834, 95% CI= 1.309-2.569, P= 0.000; G vs. A: OR= 1.222, 95% CI= 1.053-1.417, P= 0.008). As for IL-8 rs4073 polymorphism, a positive correlation between this gene polymorphism and DN risk was found (AA+AT vs. TT: OR= 1.450, 95% CI= 1.166-1.802, P= 0.001; AT vs. TT: OR= 1.420, 95% CI= 1.129-1.786, P= 0.003; AA vs. TT: OR= 1.553, 95% CI= 1.094-2.203, P= 0.014; A vs. T: OR= 1.291, 95% CI= 1.102-1.512, P= 0.002). After stratified population by ethnicity, the results in Caucasians remained significant (AA+AT vs. TT: OR= 1.770, 95% CI= 1.354-2.315, P= 0.000; AT vs. TT: OR= 1.733, 95% CI= 1.304-2.302, P= 0.000; AA vs. TT: OR= 1.939, 95% CI= 1.263-2.976, P= 0.002; A vs. T: OR= 1.494, 95% CI= 1.227-1.820, P= 0.000).

Conclusions: This meta-analysis indicates that the GG genotype of EMLO1 rs741301 polymorphism and the A allele of IL-8 rs4073 polymorphism might be risk factors for the development of DN.

Background

Diabetic nephropathy (DN), characterized by high disability rates and mortality rates, is a serious microvascular complication of diabetes mellitus (DM), leading to the occurrence of end-stage renal failure (ESRD)[1]. Although the exact pathogenesis of DN remains uncertain, it has become evident that environmental factors are likely to cooperate with genetic factors play a vital role in the development and progression of DN[2]. Recent genome-wide association studies (GWAS) have identified that several genetic single nucleotide polymorphisms (SNPs), which is involved in the pathogenesis of nephropathy, are associated with DN susceptibility, such as angiotensin I-converting enzyme (ACE)[3], angiotensin II type–1 receptor (AT1R)[4], vitamin D receptor (VDR)[5], engulfment and cell motility 1 (ELMO1)[6] and interleukin–8 (IL8)[7].

ELMO1, a soluble cytoplasmic protein consisting of 720 amino acids, has been reported to be a key-mediator in the pathogenesis of cytoskeletal rearrangements by interacting with the cytokinesis protein during cell motility and apoptotic cell phagocytosis[8]. It has been demonstrated that high glucose

increases the expression of ELMO1, which inhibits cell adhesion and promotes transcription growth factor-β (TGF-β), collagen type 1, fibronectin as well as integrin-linked kinase expressions to mediate the pathogenesis of DN[9, 10]. ELMO1 gene, located on chromosome 7p14, has been demonstrated to be a new candidate gene for DN in the first GWAS conducted in Japanese individuals[11]. Genetic studies have identified that rs741301 variants in the ELMO1 gene appear to confer risk for DN[12].

The pro-inflammatory chemokine IL−8, regulating inflammatory and immune processes, has been found to be highly expressed in urine of DN patients[13]. IL−8 gene, located on chromosome 4q13-q21, consists of 4 exons, 3 introns, and a promoter region[14]. It has been previously shown that rs4073 polymorphism of IL−8 gene participates in the development of DN among T2DM in the North and South Indian populations[7].

Recently, several genetic studies have reported the association between ELMO1 rs741301 variant or IL−8 rs4073 polymorphism and susceptibility of DN[7, 11, 12, 15–18]. However, these results were controversial and inconsistencies because of the sample size, false positive results and different ethnicities in these publications. Therefore, we performed this meta-analysis to assess the pooled effect of ELMO1 rs741301 variant or IL−8 rs4073 polymorphism that have reproducibly been associated with DN.

Methods

Literature search strategy

The electronic literature search of PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI) and Wanfang Database were comprehensively performed for all the eligible studies published up to July 2019. The search terms were listed as follows: (“engulfment and cell motility 1” or “ELMO1”), (“single nucleotide polymorphism” or “SNP” or “polymorphism” or “variation” or “mutation”) and (“diabetic nephropathy”) or (“interleukin−8” or “IL−8”), (“single nucleotide polymorphism” or “SNP” or “polymorphism” or “variation” or “mutation”) and (“diabetic nephropathy”). Furthermore, the reference lists of all selected articles were manually conducted for further potentially eligible articles. The language, population, publication date, or type of report was not restricted and unpublished data were excluded.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) case-control study; (2) investigating the association between EMLO1 rs741301 polymorphism or IL−8 rs4073 polymorphism and susceptibility of diabetic nephropathy; (3) diabetes mellitus (DM) was defined as control group; (4) complete data on the genotypic and allelic distributions of EMLO1 rs741301 polymorphism or IL−8 rs4073 polymorphism. The major exclusion criteria of this meta-analysis were: (1) not related to DN; (2) without control groups; (3) unavailable genotype information reported; (4) inappropriate article types (reviews, case reports, letters, or

abstracts); (5) duplicated data. For overlapping studies, the largest or most recent publication was selected. All the potential studies were independently selected by two reviewers (Yanting Zhu and Qiong Wang).

Data extraction

The following information from each eligible study was independently extracted by two investigators (Yan Sun and Penghua Zhou) according to the standard protocol: first author, year of publication, country, ethnicity of each study population, duration of DM, number of cases and controls, genotyping method, genotype distribution in cases and controls and P value for Hardy-Weinberg equilibrium (HWE) in controls.

Statistical analysis

STATA version 12.0 software (Stata Corporation, College Station, Texas, USA) was used to perform this meta-analysis. Chi-squared test was carried out to determine whether genotype frequencies in controls of each study were in accordance with Hardy-Weinberg equilibrium (HWE). $P < 0.05$ was considered that control population in study was departed from HWE. Heterogeneity among the included studies was assessed using Chi-square-based Q test and I^2 statistics. $P < 0.10$ was considered that there was a statistical heterogeneity among the studies and the random-effect model was adopted for analysis. Otherwise, the fixed-effect model was applied for analysis as the pooling method ($P \geq 0.1$). Sensitivity analysis of the overall population was tested by sequentially omitting one study in each turn. The combined odds ratio (OR) with its corresponding 95% confidence interval (CI) were calculated to evaluate the associations between EMLO1 rs741301 polymorphism or IL−8 rs4073 polymorphism and susceptibility of DN under five genetic models: recessive model (EMLO1 rs741301: GG vs. GA + AA; IL−8 rs4073: AA vs. AT + TT); dominant model (EMLO1 rs741301: GG + GA vs. AA; IL−8 rs4073: AA + AT vs. TT); codominant model (EMLO1 rs741301: GA vs. AA; IL−8 rs4073: AT vs. TT); homozygote model (EMLO1 rs741301: GG vs. AA; IL−8 rs4073: AA vs. TT); allele model (EMLO1 rs741301: G vs. A; IL−8 rs4073: A vs. T). Z-test was performed for assessing the significance of the pooled OR, with $P < 0.05$ considered statistically significant. Publication bias was estimated by Begg's test and Egger's test and $P < 0.05$ was considered significant publication bias.

Results

Literature search and study characteristics

Initially, a total of 414 articles were identified to be relevant to the search terms from several different databases. After a systematical literature search according to the inclusion and exclusion criteria, 11 case-control studies from 7 published articles with a total of 2215 DN cases and 2001 DM controls investigating the genetic effects of EMLO1 rs741301 polymorphism and IL−8 rs4073 polymorphism on

DN susceptibility, were recruited for this meta-analysis[7, 11, 12, 15–18]. A flow diagram in Figure 1 displayed the selection process with more particulars.

The main characteristics of included studies were summarized in Table 1. Of the 11 studies included, 9 studies from 6 selected articles containing 1879 cases and 1654 controls were performed to detect EMLO1 rs741301 polymorphism[11, 12, 15–18]; 5 studies (661 cases and 674 controls) in 2 published articles were used to examine IL−8 rs4073 polymorphism[7, 17]. In terms of EMLO1 rs741301 polymorphism, 5 studies were performed in Asians[11, 15, 17], 4 studies was undertaken in Caucasians according to ethnicity[12, 16–18]. As for IL−8 rs4073 polymorphism, there were 2 studies carried out of Asian ethnicity[17] and 3 studies conducted of Caucasian ethnicity[7, 17]. Genotype distributions and HWE examination results were exhibited in Table 2. The genotypes of EMLO1 rs741301 polymorphism in the control groups were in agreement with HWE excepted to 1 article[11]. For IL−8 rs4073 polymorphism, HWE deviation existed in control of 1 eligible study[7].

Individual polymorphism meta-analysis and subgroup analysis

The relationship between EMLO1 rs741301 polymorphism or IL−8 rs4073 variant and DN risk were shown in Table 3.

For EMLO1 rs741301 polymorphism, the susceptibility for DN did not show significant difference under the following genetic models: recessive model (GG vs. GA +AA: OR = 1.141, 95% CI = 0.941–1.385, P = 0.179); dominant model (GG+GA vs. AA: OR = 0.999, 95% CI = 0.874–1.142, P = 0.990); codominant model (GA vs. AA: OR = 0.968, 95% CI = 0.840–1.115, P = 0.650); homozygote model (GG vs. AA: OR = 1.120, 95% CI = 0.911–1.378, P = 0.283) and allele model (G vs. A: OR = 1.033, 95% CI = 0.938–1.139, P = 0.506). For studies assessing the relationship between EMLO1 gene polymorphism and DN risk in different ethnicity, significant increase in DN risk was identified in Asians under the recessive model (GG vs. GA +AA: OR = 1.840, 95% CI = 1.338–2.529, P = 0.000), the homozygote model (GG vs. AA: OR = 1.834, 95% CI = 1.309–2.569, P = 0.000) and the allele model (G vs. A: OR = 1.222, 95% CI = 1.053–1.417, P = 0.008) (Figure 2); no significant association was found among Asians in other genetic models (dominant model, GG+GA vs. AA: OR = 1.121, 95% CI = 0.915–1.372, P = 0.271 and codominant model, GA vs. AA: OR = 0.997, 95% CI = 0.805–1.234, P = 0.977). Available data did not suggest an association between this polymorphism and DN risk in Caucasians under all genetic models.

As for IL−8 rs4073 polymorphism, pooled effect among all studies suggested a significant association between the IL−8 rs4073 polymorphism and DN risk in dominant model (AA+AT vs. TT: OR = 1.450, 95% CI = 1.166–1.802, P = 0.001); codominant model (AT vs. TT: OR = 1.420, 95% CI = 1.129–1.786, P = 0.003); homozygote model (AA vs. TT: OR = 1.553, 95% CI = 1.094–2.203, P = 0.014) and allele model (A vs. T: OR = 1.291, 95% CI = 1.102–1.512, P = 0.002); but not in recessive model (AA vs. AT +TT: OR = 1.272, 95% CI = 0.921–1.757, P = 0.144) (Figure 3). When stratified population by the basis of ethnicity, a

positive correlation between this gene polymorphism and DN risk among Caucasians was found under the dominant model (AA+AT vs. TT: OR = 1.770, 95% CI = 1.354–2.315, P = 0.000), codominant model (AT vs. TT: OR = 1.733, 95% CI = 1.304–2.302, P = 0.000), homozygote model (AA vs. TT: OR = 1.939, 95% CI = 1.263–2.976, P = 0.002) and allele model (A vs. T: OR = 1.494, 95% CI = 1.227–1.820, P = 0.000); but not in recessive model (AA vs. AT+TT: OR = 1.419, 95% CI = 0.958–2.104, P = 0.081) (Figure 4). However, IL–8 rs4073 variant was not found to be associated with the risk of DN in Asians under all the genetic models.

Sensitivity analysis

In order to explore the stability of the crude results, sensitivity analysis was performed by sequentially omitting each study.

For EMLO1 rs741301 polymorphism, the result showed that the Bodhini's study influenced the stability of the pooled ORs. Therefore, a systematical meta-analysis was performed after deleting this study. The main result of the relationship between EMLO1 rs741301 polymorphism and diabetic nephropathy risk are presented in Table 4. Overall, the GG genotype of EMLO1 rs741301 polymorphism was a significantly increased risk factor for the development of DN (recessive model, GG vs. GA +AA: OR = 1.496, 95% CI = 1.164–1.922, P = 0.002; homozygote model, GG vs. AA: OR = 1.531, 95% CI = 1.172–1.999, P = 0.002 and allele model, G vs. A: OR = 1.172, 95% CI = 1.039–1.321, P = 0.010). After categorizing subjects into different subgroups on the basis of ethnicity, the results in Asians remained significant. Exclusion of the sensitivity analysis-deviated studies did not meaningfully change the pooled estimates in Asians.

As for IL–8 rs4073 polymorphism, the first study of Ahluwalia's altered the stability of the pooled ORs. After omitting this study, the results showed that a positive correlation was found between IL–8 rs4073 polymorphism and DN in the overall population under the dominant model (AA+AT vs. TT: OR = 1.492, 95% CI = 1.132–1.966, P = 0.005) and codominant model (AT vs. TT: OR = 1.622, 95% CI = 1.213–2.168, P = 0.001). The subgroup analysis by ethnicity was not performed due to the limited data provided in Caucasians and Asians.

Publication bias

Publication bias was evaluated by Begg's funnel plot and Egger's linear regression test. All the shapes of the funnel plots were found to be symmetrical (Figure 5), indicating that there was a lack of publication bias for the association of EMLO1 rs741301 variant and IL–8 rs4073 polymorphism in all the genetic models (Table 5).

Discussion

Results of meta-analysis indicated that there was no significant association between EMLO1 rs741301 polymorphism and DN susceptibility in overall analyses. However, when stratified population by ethnicity, there was a significant increase on DN risk in Asians, but not in Caucasians. The GG genotype of EMLO1 rs741301 might be an increased risk factor for the development of DN. As for IL−8 rs4073 polymorphism, a significantly positive association between IL−8 rs4073 polymorphism and DN risk was found in the overall population. While after categorizing subjects into different subgroups on the basis of ethnicity, the results in Caucasians remained significant.

ELMO1 functions as a guanine nucleotide exchange factor for the small GTPase Rac1 in combination with Dock180, leading to regulation of cell migration, cell motility and apoptotic cell phagocytosis[8, 19, 20]. ELMO1 has been found to be over-expressed in serum of DN patients, which contributes to extracellular matrix (ECM) deposition, and thereby promotes the thickening of glomerular and tubular basement membrane, ultimately results in the occurrence and development of chronic renal injuries under high glucose concentration[10, 21]. Furthermore, recent study has demonstrated that inhibition of ELMO1 expression could be a promising option for slowing or preventing progression of the condition to ESRD[9]. Except for alteration of ELMO1 expression, its genetic polymorphism is also associated with the pathogenesis of DN[22–24]. The gene coding for ELMO1, spans over 590kb on chromosome 7p14 and contains 22 exons and 21 introns[8]. A genome wide association study in Japan has identified that one SNP locus rs741301 in the 18th intron of the ELMO1 gene was found to be strongly associated with DN[11]. In addition, later studies have demonstrated a significant association between rs741301 polymorphism and DN in South Indians[12], Chinese[15] and Iranian population[18]. In contrast, some other studies have shown no significant association between genetic variation in the ELMO1 rs741301 and DN[16]. To date, the effect of ELMO1 rs741301 polymorphism on DN risk has not been examined.

This present meta-analysis synthesized 9 studies from 6 selected articles containing 1879 cases and 1654 controls to detect the relationship between EMLO1 rs741301 polymorphism and DN. The pooled results suggested that no significant association between EMLO1 rs741301 polymorphism and DN susceptibility was found in overall analyses. When stratified population by ethnicity, analysis indicated that a significant increase on DN risk in Asians, but not in Caucasians. Furthermore, results showed that the Bodhini's study influenced the stability of the pooled ORs. Exclusion of the sensitivity analysis-deviated studies did not meaningfully change the pooled estimates in Asians.

IL−8, a member of the C-X-C motif (CXC) subfamily of chemokines, is involved in angiogenesis, tumorigenesis, tissue invasion and metastasis by initiation and amplification of inflammation[25–27]. IL−8 has been found to be a major role in the pathogenesis of DN by promotion of oxidative stress and inflammatory response[28]. It is highly probable that IL−8 polymorphism, affecting the ability of individuals to produce IL−8, is associated with the development of DN[17]. IL−8 is encoded by the CXCL8 gene, which is located on chromosome 4q−13−21 and consists of a proximal promoter region, 4 exons, and 3 introns[14]. Recent study has showed a positive association between IL8 rs4073 polymorphism and DN in Indians, but not in Malays or Chinese[17]. Another study has suggested that IL−8 −251AA

genotype was more prevalent in North Indian DN group[7]. Therefore, this meta-analysis provided a statistical estimation to demonstrate the relationship between IL8 rs4073 variant and DN risk.

5 studies from 2 selected publications with a total of 661 cases and 674 controls were performed to investigate the correlation between IL8 rs4073 variant and DN risk. A positive association was found between the IL−8 rs4073 polymorphism and DN risk in overall population. After stratified population by ethnicity, the results in Caucasians remained significant. Moreover, Ahluwalia's first study altered the stability of the pooled ORs. After omitting this study, the results showed that a significantly increased risk of DN was found in overall population. The A allele of IL−8 rs4073 might be a risk factor for the development of DN.

There are several advantages in the present study. Firstly, the most recent literature was included. Secondly, the sensitivity analysis of each genetic model by sequentially deleting one study at a time was examined to improve the credibility of the results. However, this meta-analysis has some advantages. First, original data in some studies was lacking, which might limit sufficient statistical power to clarify the effect of EMLO1 rs741301 polymorphism and IL−8 rs4073 variant on asthma risk. Second, higher heterogeneity was found in some pooled analyses, which might greatly affect the conclusions of meta-analysis. Some potentially relevant factors except for ethnicity such as age, sex, BMI and drug treatment status may influence the heterogeneity. Third, some studies employed DM only as the control group; whereas others studies used healthy people and DM as the controls, respectively. The difference between DN patients and healthy people in EMLO1 rs741301 polymorphism and IL−8 rs4073 variant was unable to evaluate due to limited availability of published data.

Conclusion

In conclusion, results of meta-analysis demonstrate that there was no significant association between EMLO1 rs741301 polymorphism and DN susceptibility in overall analyses. However, when stratified population by ethnicity, there was a significant increase on DN risk in Asians, but not in Caucasians. The GG genotype of EMLO1 rs741301 might be an increased risk factor for the development of DN. As for IL−8 rs4073 polymorphism, a significantly positive association between IL−8 rs4073 polymorphism and DN risk was found in the overall population. While after categorizing subjects into different subgroups on the basis of ethnicity, the results in Caucasians remained significant.

Abbreviations

DN: diabetic nephropathy; DM: diabetes mellitus; ESRD: end-stage renal disease; GWAS: Genome-wide Association Study; SNPs: single nucleotide polymorphisms; ACE: angiotensin I-converting enzyme; AT1R: angiotensin II type−1 receptor; VDR: vitamin D receptor; ELMO1: engulfment and cell motility 1; IL−8: interleukin−8; TGF-β: transcription growth factor-β; CNKI: China National Knowledge Infrastructure; HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval.

Declarations

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Availability of data and material

Not applicable.

Authors’ contributions

Yanting Zhu: study protocol, literature search, data abstraction for meta-analysis, formulation of protocol, writing manuscript. Xiaoming Wang, Yan Sun, Qiong Wang, Bing Wu and Penghua Zhou: literature search, data abstraction for meta-analysis. Zhenjiang Li: study protocol, third reviewer of data abstraction, supervision of data abstraction, preparation of manuscript, submission for publication. All authors read and approved the final manuscript.

Competing interests

Authors declare no financial affiliations or conflicts of interest in submitting the study for publication.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Tables

Due to technical limitations, all Table(s) are only available as a download in the supplemental files section.

Table S1 Caption

Meta-analysis of EMLO1 rs741301 and IL-8 rs4073 polymorphisms and DN susceptibility in which studies influencing the stability of the pooled ORs were deleted.

OR, odds ratio; CI, confidence interval; R, random effect model; F, fixed effect model.

Figures

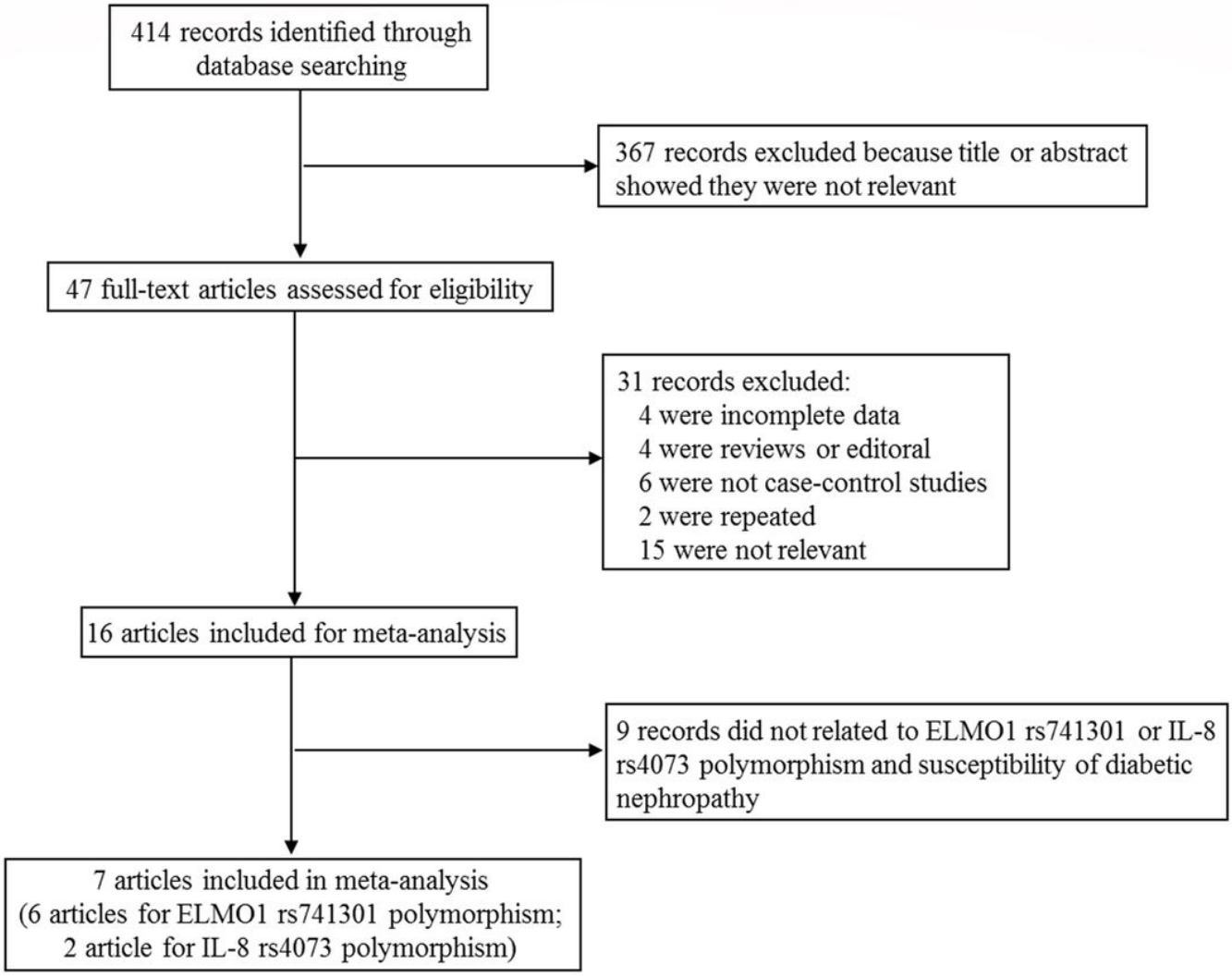

Figure 1

Flowchart of study selection procedure.

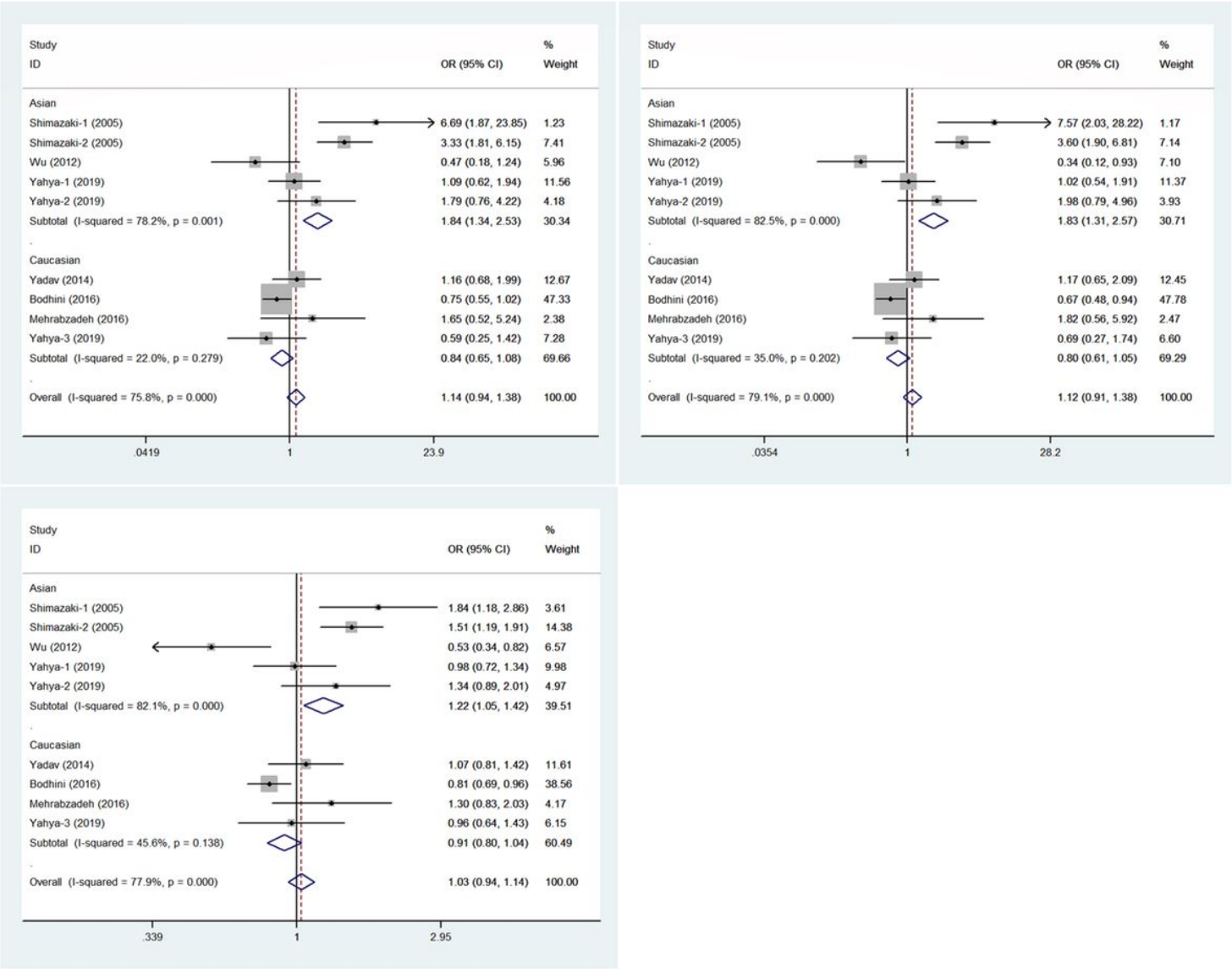

Figure 2

Forest plot of the association between EMLO1 rs741301 polymorphism and DN risk by ethnicity stratification under (A) the recessive model (GG vs. GA+AA), (B) the homozygote model (GG vs. AA) and (C) the allele model (G vs. A).

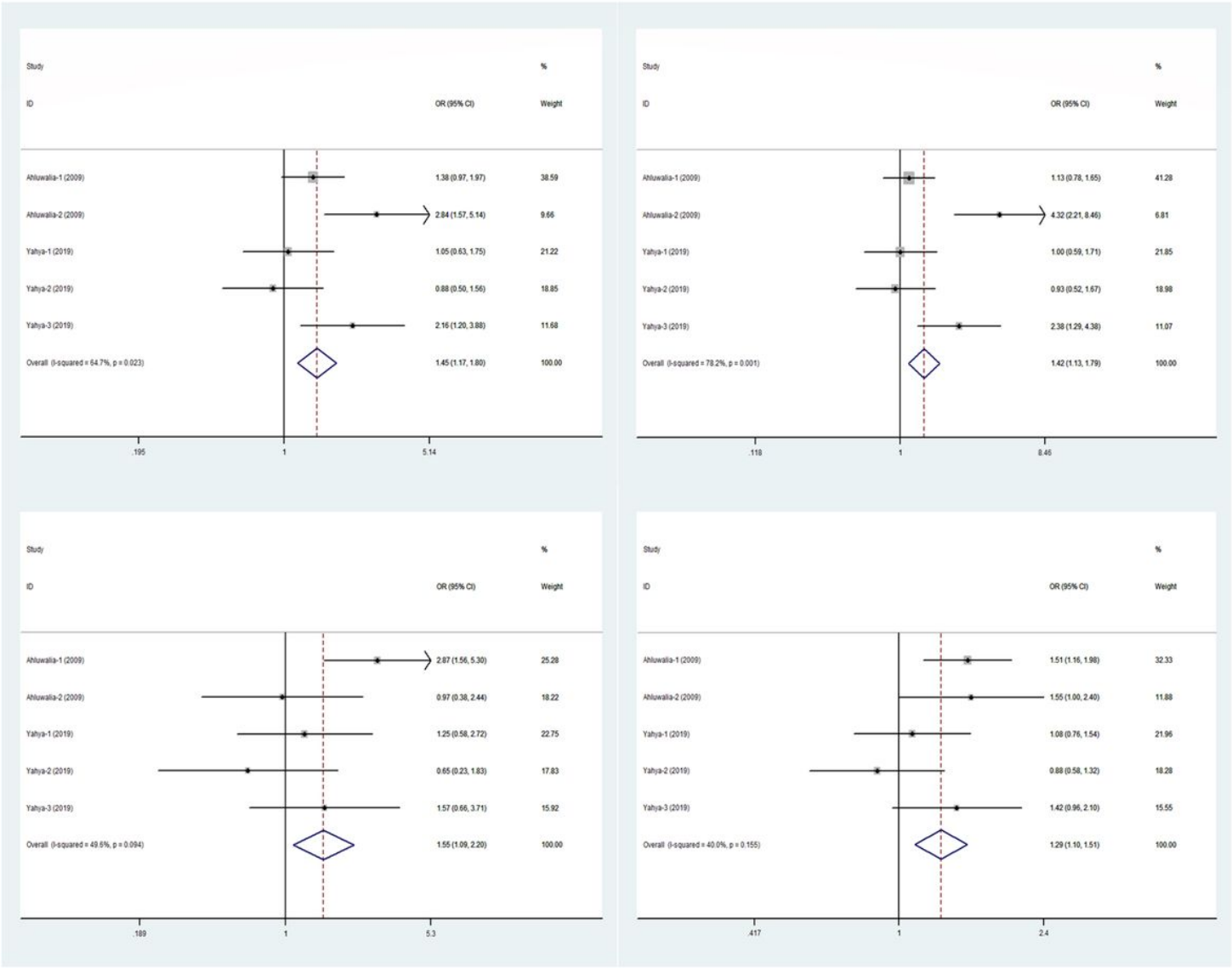

Figure 3

Forest plot of the association between IL-8 rs4073 polymorphism and DN risk under (A) the dominant model (AA+AT vs. TT), (B) the codominant model (AT vs. TT), (C) the homozygote model (AA vs. TT) and (D) the allele model (A vs. T).

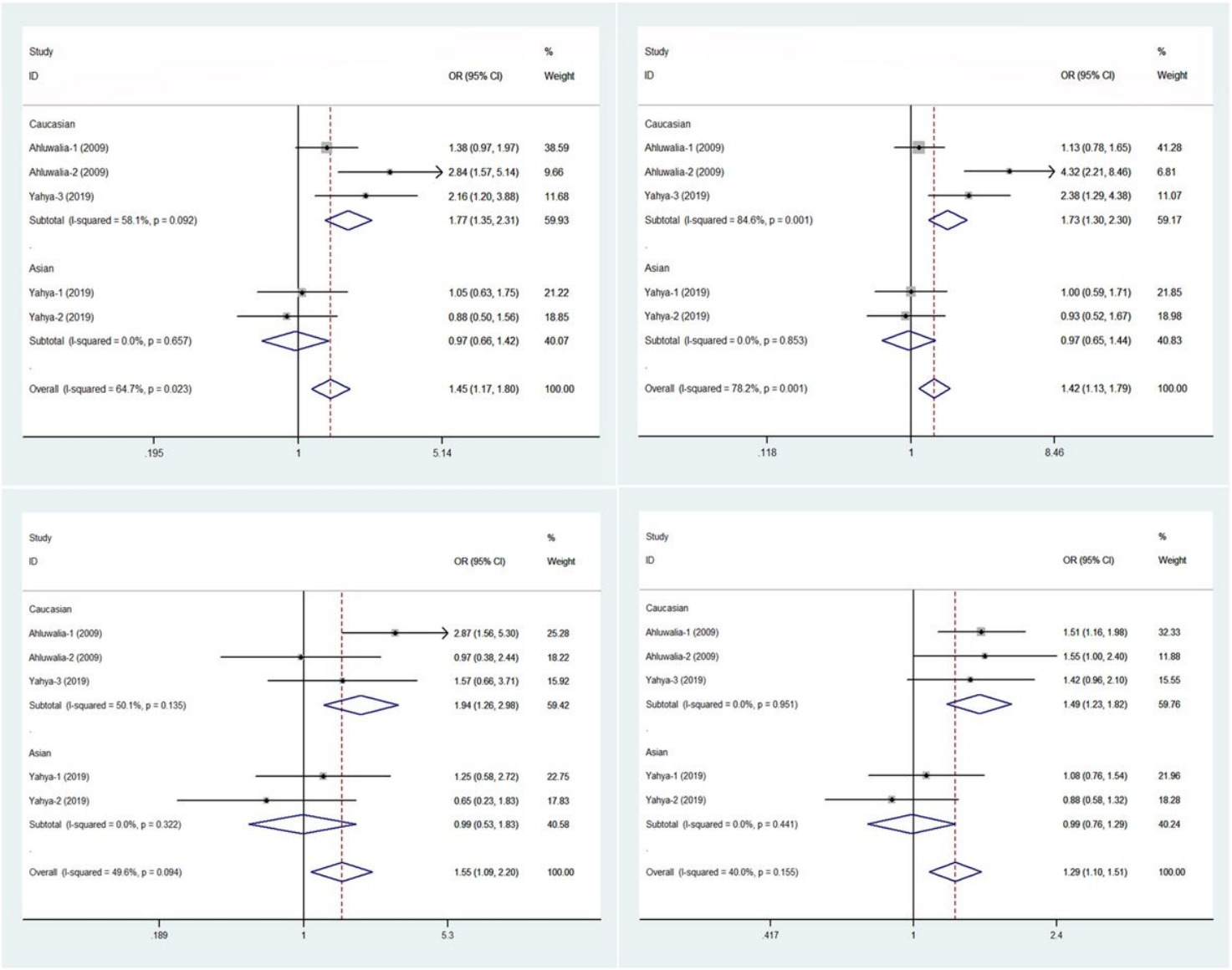

Figure 4

Forest plot of the association between IL-8 rs4073 polymorphism and DN risk stratified by ethnicity under(A) the dminant model (AA+AT vs. TT), (B) the codominant model (AT vs. TT), (C) the homozygote model (AA vs. TT) and (D) the allele model (A vs. T).

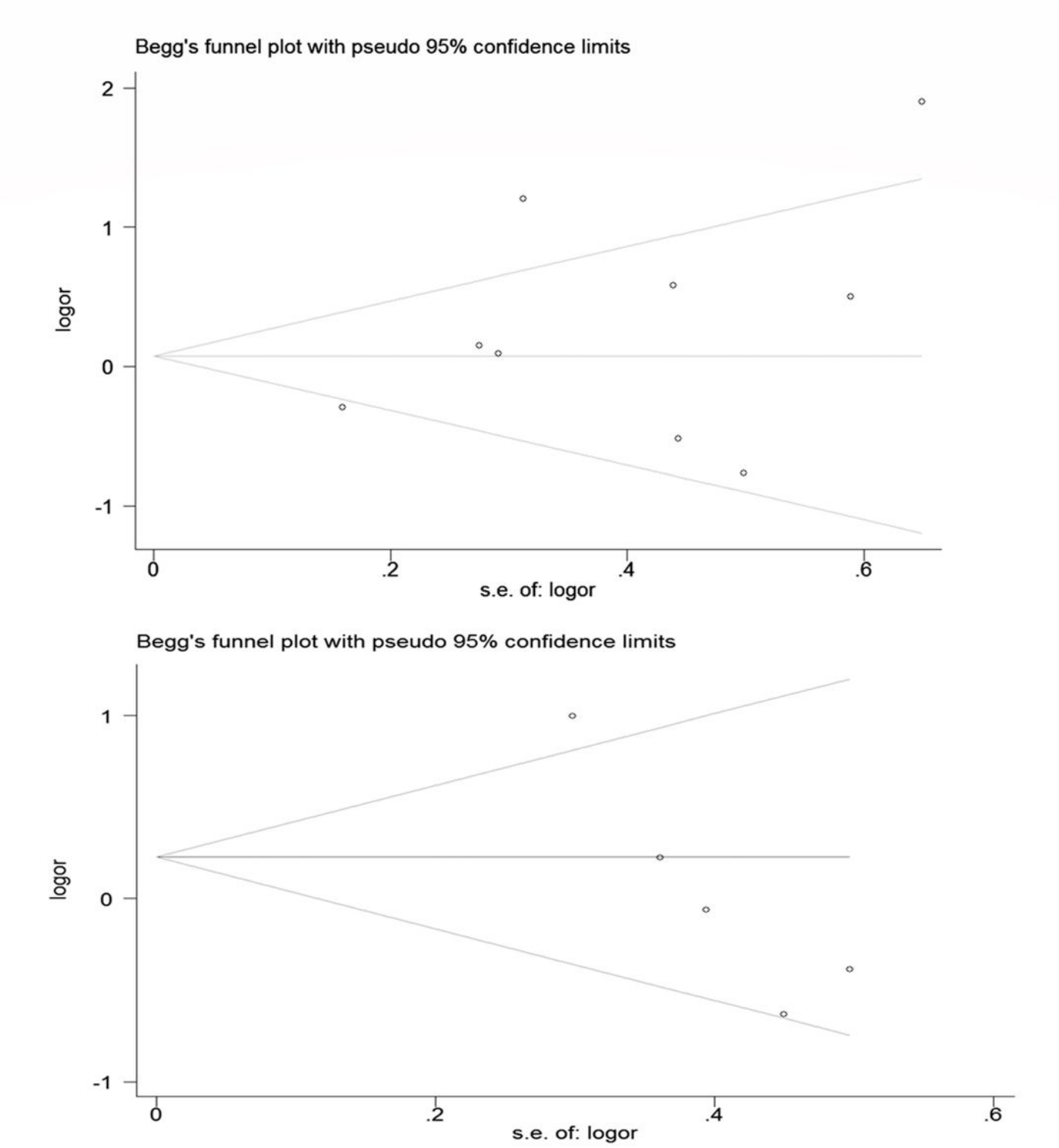

Figure 5

Begg's funnel plot of publication bias for the association between EMLO1 rs741301 and IL-8 rs4073 polymorphisms and DN risk under the recessive models (GG vs. GA+AA; AA vs. AT+TT).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- table3.tif
- table1.tif
- supplementaltable.tif
- table4.tif
- table2.tif