

Association between ALDH2 rs671 polymorphism and risk of ischemic stroke

A protocol for systematic review and meta analysis

Yan Jiang, MD, Jinting He, PhD, Hongyu Liu, PhD, Zhongxin Xu, PhD*

Abstract

In last decades, many scholars have studied the relationship between aldehyde dehydrogenase 2 (*ALDH2*) rs671 and ischemic stroke (IS), however, the results obtained from these studies were inconclusive. The purpose of this study was to investigate the association between rs671 and the risk of IS by systematically review.

Two researchers independently screened relevant published literatures, derived data and estimated the risk of bias of the research in Pubmed, Embase, Ovid, China National Knowledge Infrastructure (CNKI), Cochrane Library and China Biomedical Literature Database throughout March 29, 2020. All statistical analyses were performed with the Stata 12.0 software. The data of the study was analyzed using fixed and random effects models. The results were expressed by odds ratio (OR) and 95% confidence interval (95% CI).

A total of 10 articles were included this study. The total number of samples for all studies was 5265, including 2762 cases and 2503 controls. Statistical results indicated statistical differences between *ALDH2* rs671 polymorphism and IS under dominant model (AA vs. AG + GG) and allelic model (A vs G), ORs (95% CI) were 1.66 (1.27–2.17) ($P = .00$) and 1.34 (1.05–1.71) ($P = .02$), respectively. But there was no statistical difference under recessive model (AA + AG vs GG), OR (95% CI) was 1.40 (0.99–1.97), $P = .06$.

ALDH2 rs671 polymorphism was related to IS risk for Chinese population and the A allele of rs671 may be a risk factor of IS.

Abbreviations: *ALDH2* = aldehyde dehydrogenase 2, CI = cerebral infarction, CNKI = China National Knowledge Infrastructure, GWAS = Genome-wide association studies, HWE = Hardy-Weinberg equilibrium, IS = ischemic stroke, NOS = Newcastle-Ottawa scale, OR = odds ratio (OR), SNP = single nucleotide polymorphisms.

Keywords: *aLDH2*, ischemic stroke, polymorphism, rs671

1. Introduction

Globally, stroke is a major influencing factor of long-term disability and death.^[1] In China, about 1.6 million people die from stroke every year, in other words, there is approximately 157 people killed by stroke in each hundred thousand people, so stroke is the main cause of adult disability and death in Chinese populations.^[2] Ischemic stroke (IS) is the most common type among all stroke types in China. The most common cause for

incident IS was the dearterialization of blood in the human brain. The detailed pathophysiological reasons of IS are still unclear, however, several risk factors such as lifestyle, environmental, immune, inflammatory, and hereditary factors have been reported previously.^[3] Genome-wide association studies (GWAS) have been applied to investigate the relationship between some genetic variants and IS risk previously.^[4,5]

Some studies indicated that the risk of cardiovascular disease (CVD) will be increased, when the activity of *ALDH2* in human body is deficient.^[6,7] *ALDH2* belongs to the stage I oxidase *ALDH* superfamily, which is mainly involved in ethanol metabolism as well as biogenic and xenogenic aldehyde detoxification.^[8,9] The *ALDH2* gene consists of 13 exons and is located at chromosome 12q24 with 46,031 base pairs. The *ALDH2* gene polymorphism has an effect on the concentration of acetaldehyde in blood after alcohol metabolism.^[10,11] A previous study on the rs671G > A polymorphism shows that the prevalence rate is about 30% to 50% in Asian population,^[12] mainly lysine (*Glu487Lys*) substituted glutamine amino acid substitution.^[13] Several studies found that loss of functional variability (*ALDH2* * 1/* 2 and *ALDH2* * 2/* 2) is associated with the prognosis of several common diseases, including coronary heart diseases,^[14] hypertension,^[15] type 2 diabetes^[16] and stroke.^[17] In terms of the association between rs671 and IS susceptibility, some studies suggested that rs671 was a positive,^[18,19] but also a negative^[20] risk factor for IS susceptibility. A recent meta-analysis^[21] was performed on this topic, however, just 9 studies were included in this study, and this our analysis, a new study^[22] published in 2018 was added. Because the previous results have been contradictory, and a new study was published.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Department of Neurology, China-Japan Union Hospital, Jilin University, Changchun, Jilin, China.

* Correspondence: Zhongxin Xu, Department of Neurology, China-Japan Union Hospital, Jilin University, No. 126, Xiantai Street, Erdao District, Changchun 130000, Jilin Province, China (e-mail: xuzhongxx28@163.com).

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Therefore, the purpose of this study was to investigate the extent of connection between rs671 and the risk of IS by screening all available case-control studies for meta-analysis.

2. Materials and methods

2.1. Determination of association research

To confirm all relevant publications on the risk of IS and *ALDH2* gene polymorphisms (rs671 G>A), we conducted a systematic search of related literature through a network database, including Web of Science, Pubmed, Embase, Ovid, China National Knowledge Infrastructure (CNKI), Cochrane Library and the Chinese Biomedical Literature Database. The search date for the literature was until March 29, 2020. These terms were used for retrieval: (“aldehyde dehydrogenase2” or “ALDH2”) AND (“polymorphism” or “polymorphisms” or “variant” or “mutation” or “genotype” or “rs671” or “single nucleotide polymorphisms” or “SNP”) AND (“stroke” or “ischemic stroke” or

“cerebral infarction” or “cerebrovascular disease” or “cerebrovascular disorder” or “cerebral ischemia” or “brain ischemia” or “brain infarction”). We have included studies on humans and searched for articles written in Chinese and English. The detailed search strategy for each electronic database was shown in Table 1.

2.2. Screening criteria

All the researches that met these criteria would be deemed to be eligible including:

1. the articles are complete;
2. IS was verified via computer tomography (CT) or magnetic resonance imaging (MRI);
3. the calculation of studies effect sizes base on enough genotypic data;
4. case-control studies.

All the studies which did not meet the for-mentioned criteria were excluded, including:

Table 1
Search strategy of each electronic database.

Database	Search strategy	Number of searches
Pubmed	((aldehyde dehydrogenase2) OR ALDH2) AND (((polymorphism) OR variant) OR mutation) OR SNP) OR genotype) AND (((ischemic stroke) OR stroke) OR cerebral infarction) OR cerebrovascular disease) OR brain infarction)	26
Web of science	TS=(aldehyde dehydrogenase2 OR ALDH2) TS=(polymorphism OR variant OR genotype OR SNP OR mutation) TS=(ischemic stroke OR stroke OR cerebral infarction OR cerebrovascular disease OR brain infarction) #3 AND #2 AND #1	SCIE:30 MEDLINE:23 TOTAL:53
Ovid	((aldehyde dehydrogenase2) OR ALDH2) AND (((polymorphism) OR variant) OR mutation) OR SNP) OR genotype) AND (((ischemic stroke) OR stroke) OR cerebral infarction) OR cerebrovascular disease) OR brain infarction)	21
Embase	(aldehyde dehydrogenase2 OR ALDH2) AND (polymorphism OR variant OR genotype OR SNP OR mutation) AND (ischemic stroke OR stroke OR cerebral infarction OR cerebrovascular disease OR brain infarction)	25
Cochrane library	#1 (aldehyde dehydrogenase2):ti,ab,kw OR (ALDH2):ti,ab,kw #2 (polymorphism):ti,ab,kw OR (variant):ti,ab,kw OR (mutation):ti,ab,kw OR (SNP):ti,ab,kw OR (genotype):ti,ab,kw #3 (ischemic stroke):ti,ab,kw OR (stroke):ti,ab,kw OR (cerebral infarction):ti,ab,kw OR (cerebrovascular disease):ti,ab,kw OR (brain infarction):ti,ab,kw #1 and #2 and #3	2
Chinese Biomedical Literature Database	((("stroke" [common field: intelligence] or "ischemic stroke" [common field: intelligence] or "cerebral infarction" [common field: intelligence] or "cerebrovascular disease" [common field: intelligence] or "cerebral ischemia" [common field: intelligence]) and ("polymorphism" [common field: intelligence] or "variant" [common field: intelligence] or "genotype" [common field: intelligence] or "rs671" [common field: intelligence] or "Mutation" [common field: intelligence] or "SNP" [common field: intelligence]) and ("aldehyde dehydrogenase" [common field: intelligence] or "aldehyde dehydrogenase 2" [common field: intelligence])) and (("stroke" [common field: intelligence] or "ischemic stroke" [common field: intelligence] or "cerebral infarction" [common field: intelligence] or "cerebrovascular disease" [common field: intelligence] or "cerebral ischemia" [common field: intelligence]) And ("polymorphism" [common field: intelligence] or "variant" [common field: intelligence] or "genotype" [common field: intelligence] or "rs671" [common field: intelligence] or "mutation" [common field: intelligence] or "SNP" [common field: intelligence]) and ("aldehyde dehydrogenase" [common field: intelligence] or "aldehyde dehydrogenase 2" [common field: intelligence])) and (("stroke" [common field: intelligence] or "ischemic stroke" [common field: intelligence] or "cerebral infarction" [common field: intelligence] or "cerebrovascular disease" [common field: intelligence] or "cerebral ischemia" [common field: intelligence]) and ("polymorphism" [common field: intelligence] or "variant" [common field: intelligence] or "genotype" [common field: intelligence] or "rs671" [common field: intelligence] or "mutation" [common field: intelligence] or "SNP" [common field: intelligence]) and ("aldehyde dehydrogenase" [common field: intelligence] or "aldehyde dehydrogenase 2" [common field: intelligence]))))	13
CNKI	Su=(‘ALDH2’+‘ALDH2’) and Su=(‘ischemic stroke’+‘ischemic stroke’+‘cerebral infarction’+‘stroke’+‘cerebrovascular disease’+‘cerebral ischemia’+‘stroke’+‘brain disease’) and Su=(‘polymorphism’+‘allele’+‘variant’+‘mutation’+‘SNP’+‘genotype’+‘rs671’)	14

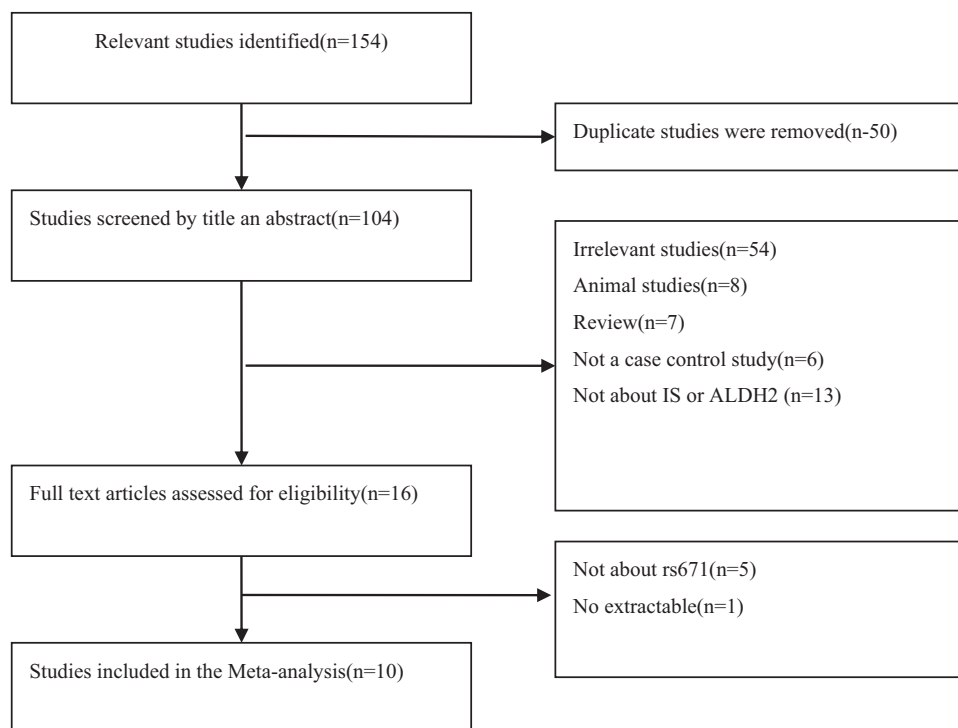


Figure 1. The flow sheet of identification of eligible studies.

Table 2

Characteristic of studies included in the meta-analysis.

Author	year	Age (case)	Age (control)	Genotype methods	Diagnostic criteria	Source of control	NOS score	HWE
Sun HL et al	2012	64.7 ± 13.2	64.0 ± 10.9	PCR-RFLP	CT&MRI	Hospital	8	0.682
Xu XQ et al	2012	66.06 ± 11.75	65.54 ± 11.55	PCR	CT&MRI	Hospital	6	0.607
Wang GY et al	2014	61.77 ± 5.78	57.82 ± 6.09	PCR	CT&MRI	Hospital	7	0.427
Zhang CY et al	2014	Not Know	Not Know	PCR	Not Know	Population	5	0.213
Zhou Q et al	2014	65.02 ± 12.62	58.73 ± 7.47	PCR	CT&MRI	Hospital	7	0.671
Qu Y et al	2017	60.21 ± 10.73	60.99 ± 8.02	PCR	MRI	Population	8	0.753
Liu CM et al	2018	64.59 ± 5.86	64.36 ± 6.59	PCR	CT&MRI	Hospital	5	0.000
Sung YF et al	2016	58.22 ± 12.10	64.83 ± 12.43	PCR	Not Know	Hospital	8	0.632
Li QY et al	2015	64.43 ± 12.87	52.8 ± 15.0	PCR	MRI	Hospital	6	Not Know
Sun SQ et al	2017	63.96 ± 11.06	50.36 ± 7.79	PCR	CT&MRI	Hospital	7	0.517

Table 3

The genotype distribution of ALDH2.

Author	Sample size (case/control)	Female (%) (case/control)	Cases					Controls				
			AA	AG	GG	A	G	AA	AG	GG	A	G
Sun HL et al	78/80	39.7/43.8	7	44	27	58	98	3	28	49	34	126
Xu XJ et al	100/50	18.0/24.0	2	16	82	20	180	2	19	29	23	77
Wang GY et al	156/160	19.9/20.6	9	67	80	85	227	3	47	110	53	267
Zhang CY et al	53/106	Not Know	2	24	27	28	78	1	32	73	34	178
Zhou Q et al	117/148	Not Know	2	19	96	23	211	0	10	138	10	286
Qu Y et al	394/406	27.9/31.0	20	120	254	160	628	14	128	264	156	656
Liu CM et al	93/57	45.2/49.1	7	20	66	34	152	3	4	50	10	104
Sung YF et al	914/746	34.6/53.6	102	338	474	542	1286	54	303	389	411	1081
Li QY et al	369/247	22.2/24.7	–	–	–	119	619	–	–	–	63	431
Sun SQ et al	488/503	33.4/61.2	11	108	369	130	846	8	124	371	140	866

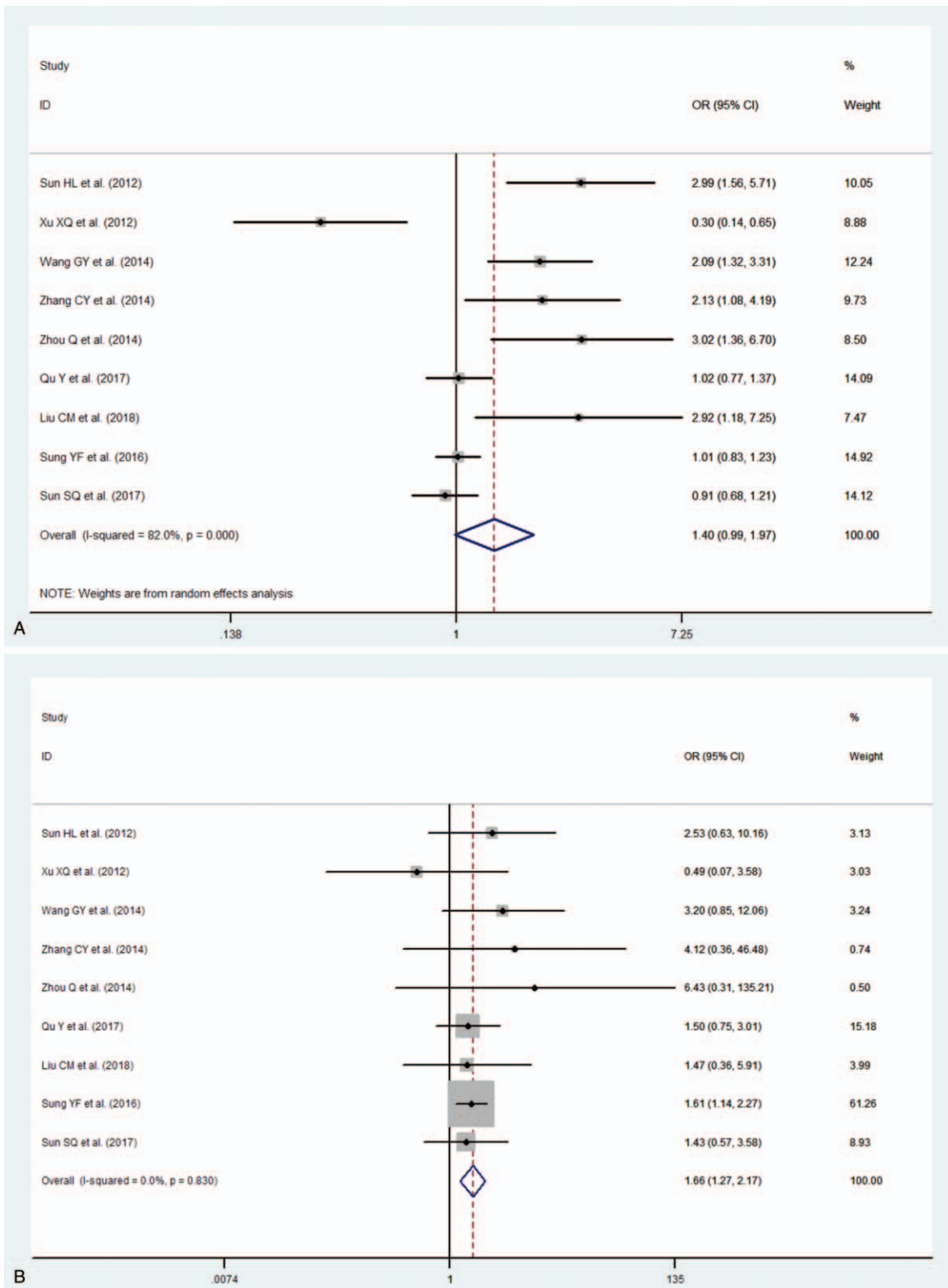


Figure 2. Forest plots of the ALDH2 rs671 polymorphism under different genetic models. a is the dominant model of AA + AG vs GG; b is the recessive model of AA vs AG + GG; c is the allelic model of A vs G.

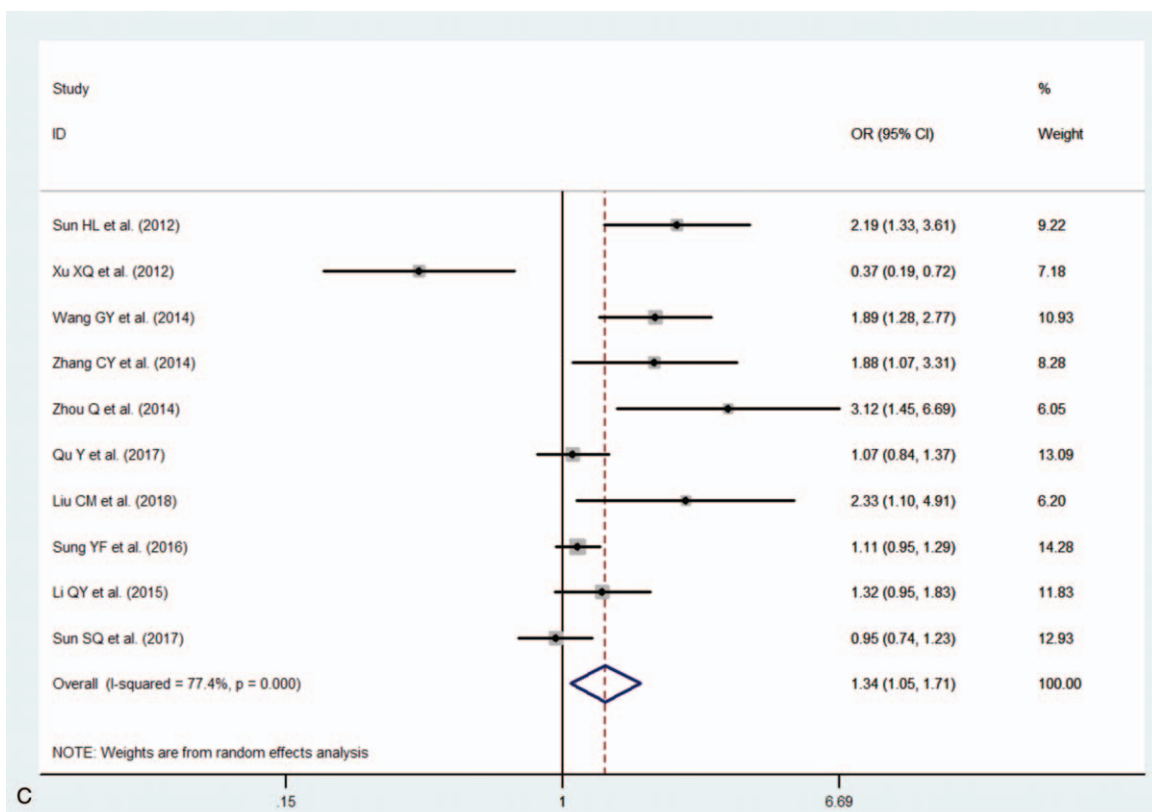


Figure 2. (Continued).

1. the consequence of studies were not from humans;
2. the publications are repetition or plagiarize, or without the authority;
3. the studies lacked genotypic data support;
4. the studies are not case-control study.

This study should follow the relevant requirements of systematic and meta-analysis.^[2,3]

2.3. Data extraction

Data extraction for the enrolled study was independently extracted by 2 researchers using standard data extraction tables. The data collected for each study is as follows:

1. First author;
2. Year of publication;
3. Nationality;
4. Gender and average age of the case and control;
5. Diagnostic criteria of IS;
6. Hardy-Weinberg equilibrium (HWE);
7. The number of cases and controls;
8. Genotyping methods;
9. Sources of control;
10. Number of each genotypes in case and control.

If the same study was published multiple times, the publication with the largest number of samples was selected for inclusion in the study. The differences between the 2 researchers were determined through discussion. For the remaining disagreements, the dispute shall be settled by the third investigator.

2.4. Quality assessment

The 3 authors of the research used the 9-point Newcastle-Ottawa scale (NOS) to evaluate the selected studies separately.^[24] If the score was equal to 6 or more, the study will be considered a “high quality study.” Confirmation of all ratings is subject to discussion by all authors.

2.5. Statistical analysis

HWE for control group of each study was verified by Chi-Squared test. The correlation between *ALDH2* rs671 polymorphism and IS susceptibility was estimated by odds ratio (OR) and 95% confidence interval (95% CI). In the overall meta-analysis, the combined OR values of the dominant models (AA+AG vs GG), the recessive models (AA vs AG+GG), and the allelic models (A vs G) were calculated. Heterogeneity was assessed by Q statistic ($P < .10$) or I^2 statistic (greater or equal to 50% as a basis for significant inconsistency). Once Q-test > 0.10 and $I^2 < 50\%$, the calculation of the combined OR was performed using a fixed effect model (Mantel-Haenszel method), otherwise the random effect model (DerSimonian-Laird method) was applied to calculate the combined OR. The publication bias of the literature was analyzed using Begg funnel plot. Sensitivity analysis was used to analyze the effect of selected individual study groups on combined OR. This study used Stata 12.0 analysis software (STATA Corporation, College Station, TX, USA) to perform statistical analysis on the collected data.

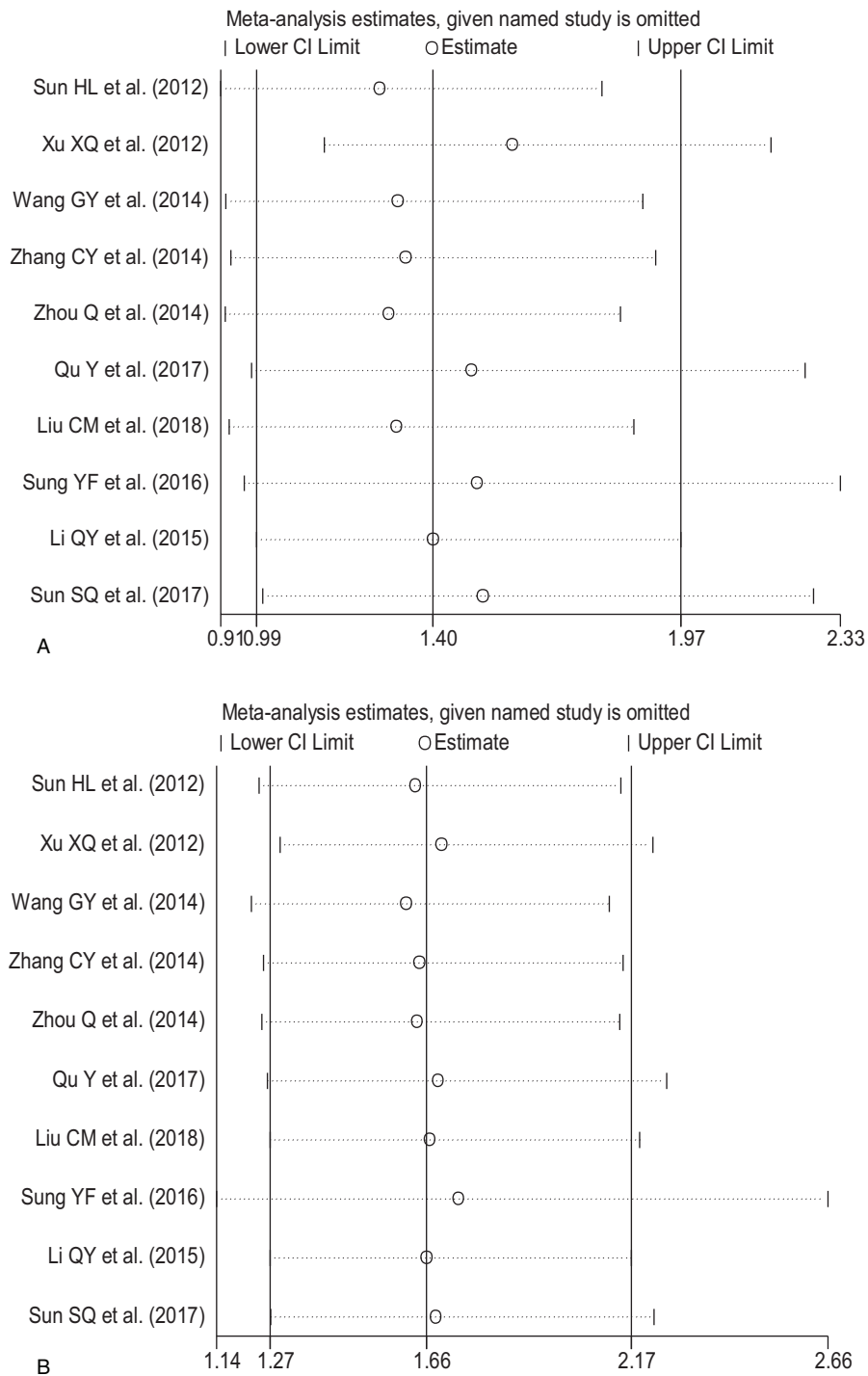


Figure 3. Sensitivity analysis examining the association between the ALDH2 rs671 polymorphism and risk of IS under dominant model (AA + AG vs GG), recessive model (AA vs AG + GG) and allelic model (A vs G).

3. Results

3.1. Overview of selected literatures

The flow chart of the literature search was shown in Figure 1. After completing the initial screening of several major databases, the inclusion of 146 potentially relevant literatures were required further evaluation. Of these, 49 duplicate references were deleted and 97 were further screened and

reviewed by title and abstract. The remaining 11 literatures were reviewed in full text. Finally, 10 literatures were included in this analysis. These literature studies were published from 2012 to 2018. A total of 2503 cases and 2762 controls were included in this study. The genotype frequencies in the control of the 9 studies, except 1 study were distributed accordingly to HWE. The characteristics of the articles involved are summarized in Tables 2 and 3.

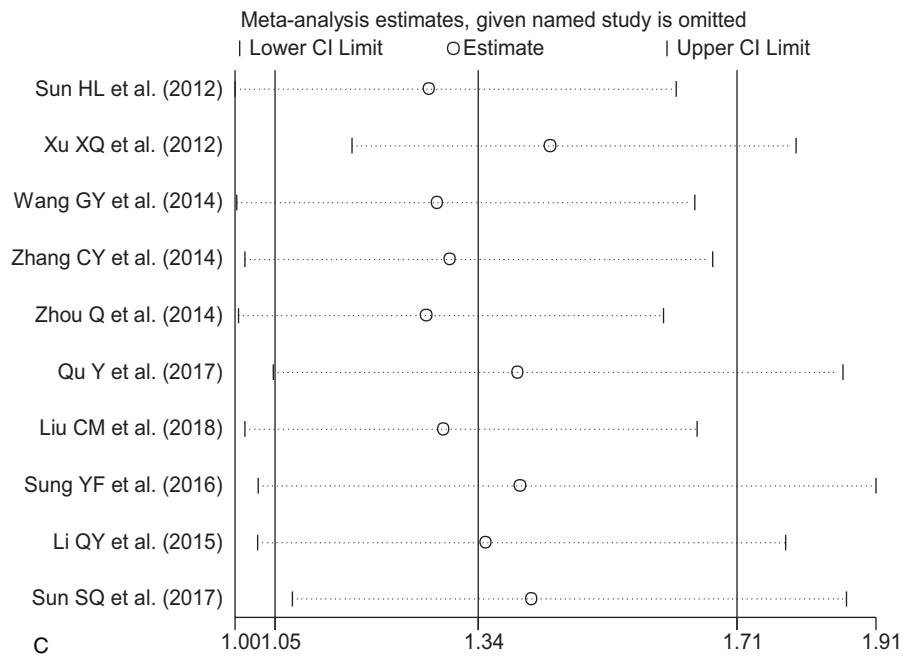


Figure 3. (Continued).

3.2. Meta-analysis results

Heterogeneity in the genetic model was analyzed by Q test and I squared statistics. As shown in Figure 2, a more serious heterogeneity was found under the dominant model ($P=.000$, $I^2=82.0\%$) and allelic model ($P=.000$, $I^2=77.4\%$), therefore we used a random effects model for analysis. No heterogeneity was found under recessive model ($P=.830$, $I^2=0.0\%$), therefore we used a fixed effect model for analysis. Statistical results found statistical differences between *ALDH2* rs671 polymorphism and IS under dominant model (AA vs AG+GG) and allelic model (A vs G), ORs (95% CI) were 1.66 (1.27–2.17) ($P=.00$) and 1.34 (1.05–1.71) ($P=.02$) respectively. But there was no statistical difference under recessive model (AA+AG vs GG), OR (95% CI) was 1.40 (0.99–1.97), $P=.06$.

3.3. Sensitivity analysis

A sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by sequentially removing each eligible study at a time. The results of the study show that no studies have affected the effects of the combined OR (Fig. 3).

3.4. Publication bias

The publication bias of the literature was analyzed using Begg funnel plot. The results of the study showed that there was no publication bias in the 3 genetic models, all P values were more than .05, which means that the examination did not reveal any significant asymmetry in any of the funnel plots (AA+AG vs GG: $P=.466$; AA vs AG+GG: $P=.466$; A vs G: $P=.107$) (Fig. 4).

4. Discussion

There was a great heterogeneity in stroke, and its pathogenesis showed differentiation among individuals. Many genes closely related to CI have been studied by scholars widely, such as interleukin-4,^[25] angiotensin IL-1 receptor,^[26] but the results obtained from these previous studies are still controversial, and the exact mechanism remains to be further studied. As a new biochemical marker of cerebrovascular diseases, *ALDH2* has aroused the attention of scholars wildly. *ALDH2* belongs to acetaldehyde dehydrogenase family, which is an important member of a family with a high genetic polymorphism. *ALDH2* gene is located on chromosome 12q24 and consists of 13 exons. Its coding enzyme protein and peptide chain are composed of 500 amino acid residues.^[10,11] At present, a total of 84 SNPs loci have been found in human *ALDH2* gene, and the rs671G>A is a mutation site in exon 12, and base substitution occurs: G-A, which causes codon change and the loss of catalytic activity.^[6] One study on the rs671G>A polymorphism shows that the prevalence rate in Asian population is about 30% to 50%.^[12] Previously, many scholars have studied the association between *ALDH2* rs671 polymorphism and IS, but these studies concluded the contradictory results.^[18–20] A recent meta-analysis^[21] has been performed on this topic, however, just 9 studies were included in this study, and this our analysis, a new study^[22] published in 2018 for Chinese populations was added. This meta-analysis suggested that the *ALDH2* rs671 G>A polymorphism may play an important role in the incident IS by reducing the activity of *ALDH2* and interfering with the metabolic processes involving acetaldehyde. The recently published article also indicated that the A allele of *ALDH2* gene was an important risk factor for cerebral infarction (CI) incidence. Li et al^[20] indicated that the *ALDH2**2 allele may be an important negative

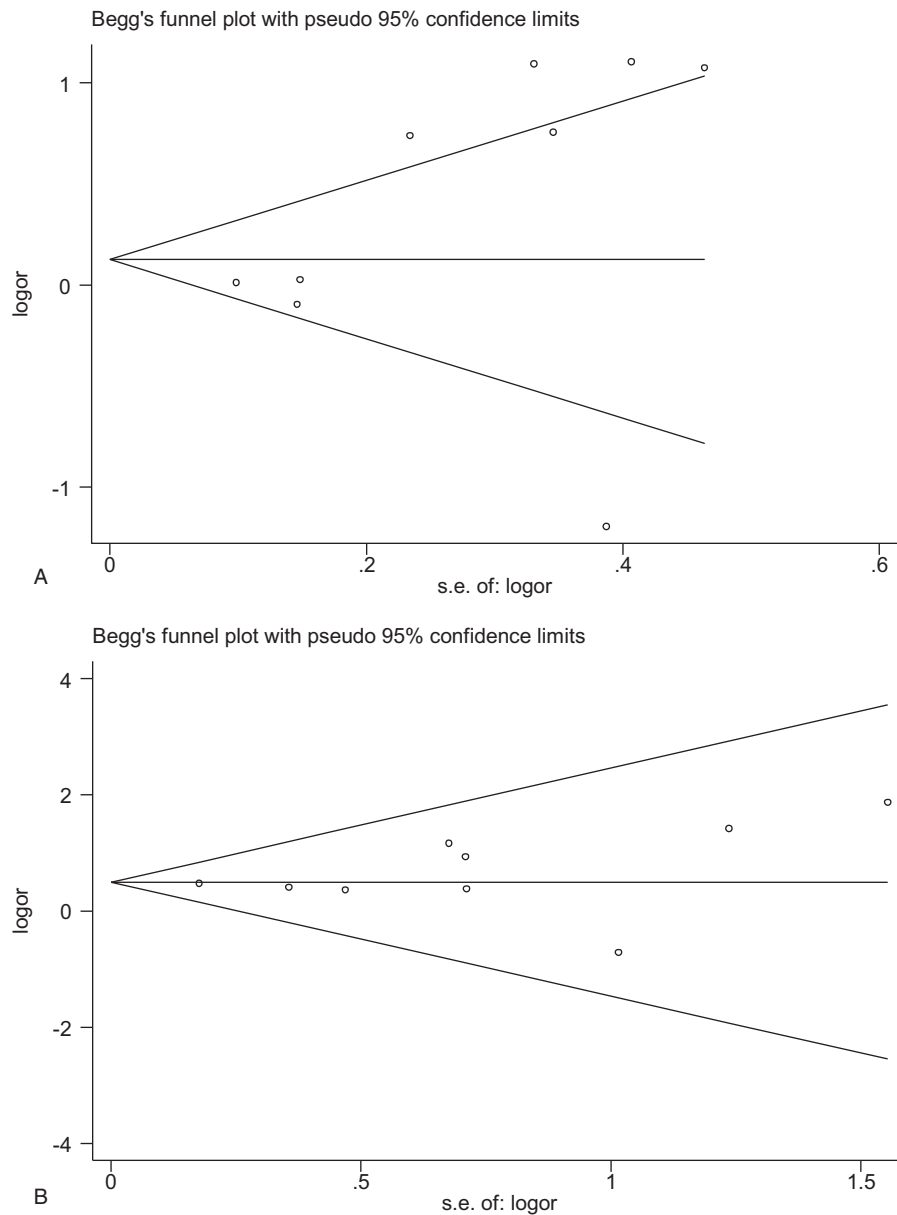


Figure 4. Begg funnel plot for publication bias analysis. a is the dominant model (AA + AG vs GG), b is the recessive model (AA vs AG + GG) and c is the allelic model (A vs G) the dominant model (AA + AG vs GG), recessive model (AA vs AG + GG) and allelic model (A vs G).

risk factor for CI in Chinese women. However, the negative effects of *ALDH2**2 allele on CI were not significant, because of the concealing by other risk factors. Sun et al^[19] randomly selected 6 marker candidate SNPs, including rs671, in a study for the Han population, but they did not find a statistical association between rs671 and IS susceptibility. Another study for the Taiwanese population^[18] showed that *ALDH2* * 2/ * 2 was a possible risk factor for IS in males, but not in females. Wang et al^[27] also suggested that the rs671 polymorphism of *ALDH2* gene was associated with high risk of CI. The rs671 polymorphism of human *ALDH2* gene is related to the stability of carotid artery atherosclerotic plaque in the patients with CI.^[28] Wang et al^[29] also suggested that *ALDH2* gene polymorphism is an

independent risk factor for acute CI in the Han population of Heilongjiang province.

Some limitations for the current study should be addressed. Firstly, the number of enrolled studies was not particularly large, all the enrolled subjects were the Chinese population, and some articles were published in Chinese magazines, further replication studies in different population are warranted to confirm our findings. Secondly, the pathogenic mechanisms of IS were extremely complex, too many factors could significantly influence the susceptibility to IS.

In conclusion, our study indicates that rs671 polymorphism may serve as genetic biomarkers of IS, while rs671 polymorphism may contribute to the higher IS susceptibility. Further research

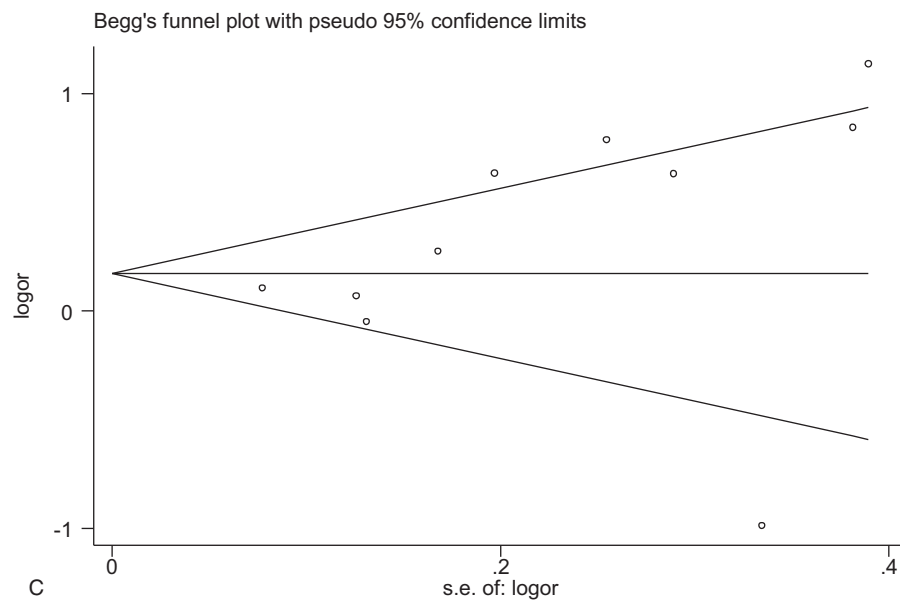


Figure 4. (Continued).

should be conducted in different populations to verify our results, such as different races in Asian, European and American populations, and future investigations also need to explore the possible roles of *ALDH2* gene- gene or gene- environment interactions on IS susceptibility.

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Author contributions

Y Jiang and HY Liu searched literature, extracted data, evaluated study quality, and performed statistical analysis. Y Jiang and JT He drafted the manuscript. ZX Xu and Y Jiang designed the study, interpreted the results, and revised and approved the final manuscript.

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