

# Aldehyde dehydrogenase 2 rs671 G>A polymorphism and ischemic stroke risk in Chinese population: a meta-analysis

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**Introduction:** Recently, molecular epidemiological studies have suggested that *aldehyde dehydrogenase 2 (ALDH2)* rs671 G>A polymorphism may be a risk factor for ischemic stroke (IS). However, the results reported have not been consistent.

**Methods:** We conducted the meta-analysis to explore the precise association between *ALDH2* rs671 G>A polymorphism and IS risk. Five online databases were searched and the relative studies were reviewed from inception to October 1, 2018. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated in each genetic model of the general and subgroup. Furthermore, the heterogeneity, accumulative analyses, sensitivity analyses and publication bias were calculated simultaneously.

**Results:** Overall, nine case-control studies involving 6,129 subjects were included in this meta-analysis. All studies were focused on the Chinese population and some significant associations were found between *ALDH2* rs671 G>A polymorphism and IS risk (A vs G: OR=1.29, 95% CI=1.01–1.65,  $P=0.04$ ,  $I^2=78.2\%$ ; AA vs GG: OR=1.86, 95% CI=1.27–2.21,  $P<0.01$ ,  $I^2=11.3\%$ ; AA vs GG + GA: OR=1.67, 95% CI=1.27–2.19,  $P<0.01$ ,  $I^2=0\%$ ). Some significant and similar results were also observed in the subgroup analysis.

**Conclusion:** Our meta-analysis indicates that the *ALDH2* rs671 G>A polymorphism may play an important role in the occurrence of IS by reducing the activity of ALDH2 and interfering with the metabolic processes involving acetaldehyde.

**Keywords:** aldehyde dehydrogenase 2, rs671, ischemic stroke, polymorphism, meta-analysis

## Introduction

Stroke is the second most common cause of death globally and contributes to 9% of all deaths.<sup>1</sup> According to recent epidemiological research, an estimated 6.2 million deaths occur per year due to stroke.<sup>2</sup> Due to the aging of the global population, the prevalence of stroke is continuously increasing. Stroke cases and related deaths are projected to increase among people from China, India and other developing countries.<sup>3,4</sup> Stroke and its sequela, such as post-stroke hemiplegia, depression and impairment of movement and cognition, were thought to be one of the five leading causes of reduced disability-adjusted life years in 2017. This ranking is expected to rise to the fourth place by the year 2030 in developed countries.<sup>5,6</sup>

Ischemic stroke (IS) accounts for more than 80% of diagnosed stroke cases in adults.<sup>7</sup> High blood pressure, insufficient physical activity, apolipoprotein (Apo)B/ApoA1 ratio, unhealthy living habits and diabetes mellitus contribute to more than 90% of the population attributable risks for IS worldwide.<sup>8</sup> However, differences in

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susceptibility to stroke in individuals of different ethnicities and regions have not been fully explained.

The gene for *aldehyde dehydrogenase-2* (*ALDH2*) is located on chromosome 12q24.12 and contains 13 exons and 12 introns. It encodes a crucial mitochondrial enzyme that is distributed throughout in human cells. The enzyme is known to participate in aldehyde substrate metabolism and detoxification. *ALDH2* is the most important enzyme for metabolizing short chain aliphatic aldehydes and promotes the conversion of acetaldehyde to acetate. *ALDH2* is widely expressed in neurons in the brain and is believed to have protective effect.<sup>9</sup>

Single nucleotide polymorphisms (SNPs) are the most common heritable variation in the human genome. Such genetic modification can alter amino acid and their partial structure, influence the expression level and activities of target proteins, and contribute to the risk of various diseases.<sup>10</sup> The rs671 polymorphism, which is located in exon 12 and comprises a base substitution from G to A, results in an amino acid change from glutamate to lysine. This is considered the most common locus for polymorphisms in *ALDH2*, which lead to significant decreases in its enzymatic activity.<sup>11</sup> There are differences in the frequency of the rs671 G>A polymorphism between individuals of different ethnic groups. The A-allele of the *ALDH2* gene is rarely found in Caucasians, Africans and other ethnicities, but is highly prevalent in Asians (between 20% and 50%).<sup>12–14</sup> In 2012, Sun conducted the first case-control study of the association between *ALDH2* polymorphism and IS, and found that the GA/AA genotype was significantly associated with IS risk.<sup>15</sup> Since then, some new studies have addressed the association between the rs671 G>A polymorphism and IS risk. These studies were mostly performed in Chinese populations, but have had inconsistent results. We performed a meta-analysis of all eligible case-control studies to precisely assess the association between the rs671 G>A polymorphism and IS risk.

## Methods

This present meta-analysis was conducted with guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>16</sup> All included data were collected from published studies, and no ethical issues were involved.

## Search strategy

Five online databases (PubMed, Embase, Web of Science, CNKI and Wanfang) were searched for relevant studies on the association between the rs671 G>A polymorphism and IS risk from inception to October 1, 2018. Only studies written in English and Chinese were included. The bibliographies of the collected studies and relevant reviews were also reviewed to identify potential additional articles. The following search terms and strategy was adopted “*Aldehyde dehydrogenase 2*”, “*Aldehyde Dehydrogenase-2*”, “*ALDH2*”, “polymorphism”, “variant”, “mutation”, “stroke”, “ischemic stroke”, “cerebral infarction”.

## Eligibility criteria

All studies included in this meta-analysis were required to meet the following criteria: 1) case-control studies focused on the relationship between rs671 G>A polymorphism and IS risk; 2) studies with sufficient data on the genotypes in the case and control groups to evaluate the crude odds ratios (ORs) and 95% confidence intervals (CIs); 3) studies published only in English or Chinese; and 4) only the largest or most recently updated sample data when some overlapping or duplicate publications were available on the same theme.

## Data extraction and quality evaluation

Xu and Hu reviewed and extracted the following information from all included studies independently: name of the first author, publishing date, control design, genotyping method, sample sizes of the cases and controls, genotype frequency distribution, Hardy-Weinberg equilibrium (HWE) and minor allele frequency assessment in controls, and adjusted factors. Quality evaluation of the included studies was performed by the above authors using the modified Newcastle-Ottawa scale (NOS).<sup>17</sup> The scores ranged from 0 (worst) to 11 points (best) (Table 1). Studies with a score of 8 or higher were classified as high quality.

## Statistical analysis

Crude ORs and 95% CIs were calculated to assess the statistical power of the association between the rs671 G>A polymorphism and IS risk. Five genetic models were examined, including the allele contrast model (A vs G), co-dominant models (GA vs GG and AA vs GG), dominant model (GA + AA vs GG) and recessive model (AA vs GG + GA). Heterogeneity among the included studies was calculated using Cochran’s Q test and the  $I^2$

**Table 1** Scale for quality evaluation

Criteria	Score
<b>Representativeness of cases</b>	
Consecutive/randomly selected cases with clearly defined sampling frame	2
Not consecutive/randomly selected case or without clearly defined sampling frame	1
Not described	0
<b>Source of controls</b>	
Population-based	2
Hospital-bases or Not described	1
<b>Hardy-Weinberg equilibrium in controls</b>	
Hardy-Weinberg equilibrium	2
Hardy-Weinberg disequilibrium	1
Not available	0
<b>Genotyping examination</b>	
Genotyping done under "blinded" condition and repeated again	2
Genotyping done under "blinded" condition or repeated again	1
Unblinded done or not mentioned and unrepeated	0
<b>Subjects</b>	
Number >500	1
Number <500	0
<b>Association assessment</b>	
Assess association between genotypes and ischemic stroke with appropriate statistics and adjustment for confounders	2
Assess association between genotypes and ischemic stroke with appropriate statistics and without adjustment for confounders	1
Inappropriate statistics used	0

test.<sup>18</sup> The fixed-effect model was adopted when  $I^2 \leq 40\%$ . Otherwise, a random-effects model was adopted.<sup>19,20</sup> Subgroup analyses were conducted in accordance with the control design (population base and hospital base), subject number and NOS evaluation. Meta-regression was performed to identify the factors contributing to existing heterogeneity.<sup>21</sup> Cumulative meta-analyses were performed to assess the statistical tendencies of the results. Sensitivity analyses were performed to examine the stability of the results by removing each study individually. Potential publication biases were assessed using Egger's linear regression test and Begg's funnel plots. All statistical analyses were performed with STATA version 14.0

(Stata Corporation, College Station, TX, USA). Two-sided  $P$ -values less than 0.05 were considered statistically significant.

## Results

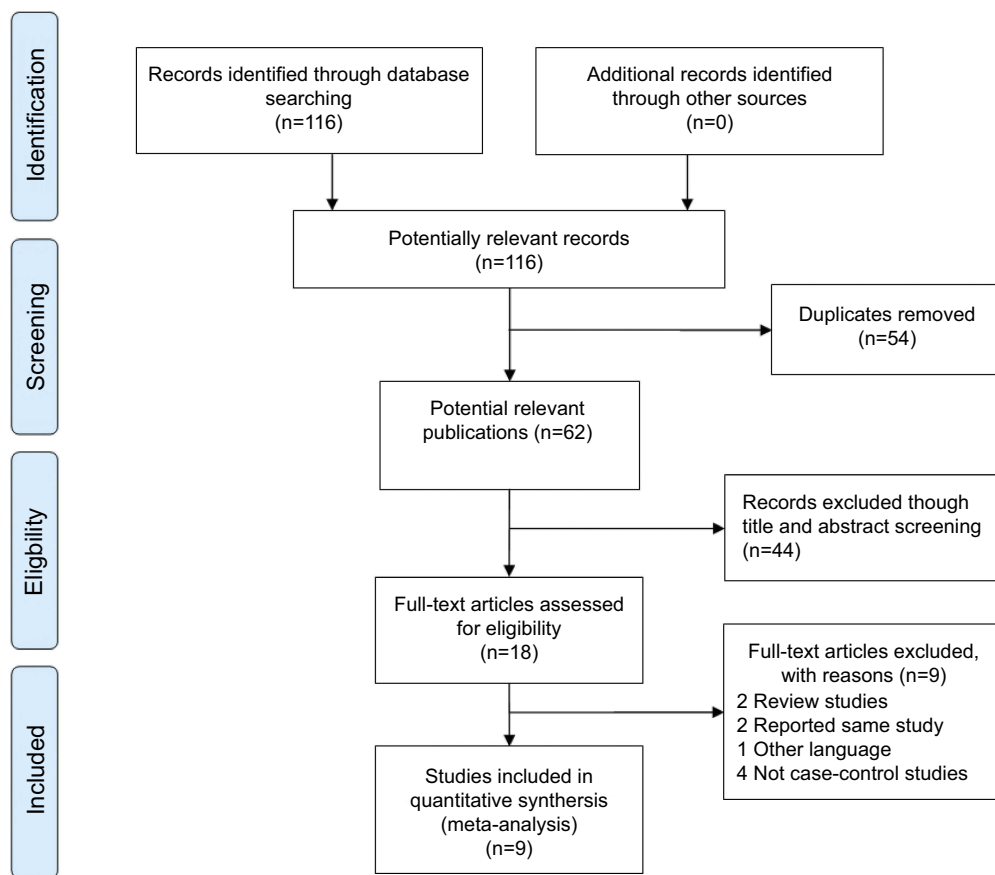
### Study characteristics

In total, 116 studies were found in the first step of the systematic literature search. Figure 1 illustrates the inclusion procedures used to select the related studies. Following analysis of the titles and abstracts and full article screenings, 107 articles were excluded and nine studies involving 3,236 patients and 2,893 controls were included in our meta-analysis.<sup>15,22–29</sup> These nine studies focused on Chinese populations, and the genotype distributions in the control groups in all nine studies satisfied Hardy-Weinberg equilibrium (HWE). Five studies used polymerase chain reaction (PCR)-sequencing, one study used PCR-restriction fragment length polymorphism, one study used PCR-amplified product length polymorphism and another study used the MassARRAY method. All of the information from the collected studies included in our analysis is listed in Table 2.

### Quantitative and subgroup analyses

Overall, the pooled results revealed an increased IS risk associated with the rs671 G>A polymorphism in the allele contrast (A vs G: OR=1.29, 95% CI=1.01–1.65,  $P=0.04$ ,  $I^2=78.2\%$ ); homozygote model (AA vs GG: OR=1.68, 95% CI=1.27–2.21,  $P<0.01$ ,  $I^2=11.3\%$ , Figure 2) and recessive model (AA vs GG+GA: OR=1.67, 95% CI=1.27–2.19,  $P<0.01$ ,  $I^2=0\%$ ) (Figure S1 for other models). In the subsequent analysis, which was based on control design, there were also significant associations between rs671 G>A polymorphism and IS risk, for example in the subgroups of hospital-based controls (A vs G: OR=1.34, 95% CI=1.03–1.73,  $P=0.03$ ,  $I^2=74.0\%$ ; AA vs GG: OR=1.71, 95% CI=1.25–2.34,  $P<0.01$ ,  $I^2=18.9\%$ ; AA vs GG + GA: OR=1.68, 95% CI=1.24–2.29,  $P<0.01$ ,  $I^2=0\%$ ). In addition, elevated IS risk was observed in the subgroups of subject number and NOS evaluation analysis (Table 3). Heterogeneity was observed in the allele contrast, heterozygote and dominant models. Meta-regression analysis was conducted with the aforementioned three stratified factors, but no apparent factor was found to contribute to the existent heterogeneity. (eg, A vs G model:  $P=0.99$  for control design,  $P=0.38$  for subject number and  $P=0.34$  for NOS evaluation).

Accumulative analysis was also conducted and revealed an apparently increased risk from 2014 when



**Figure 1** Flow diagram of the study selection process.

the report by Zhou et al. was included (Figure 3 for AA vs GG model) (Figure S2 for other models). Sensitivity analyses were conducted by removing each included study sequentially based on the published date, which indicated that only the study by Xu et al. influenced the corresponding result in the allele contrast, heterozygote and dominant models (Figure 4 for AA vs GG model) (Figure S3 for other models).

Publication bias was evaluated, and the examination did not reveal any significant asymmetry in any of the funnel plots (Figure 5 for AA vs GG model) (Figure S4 for other models). The results of the Egger's test were also evaluated (A vs G,  $P=0.33$ ; GA vs GG:  $P=0.24$ ; AA vs GG,  $P=0.31$ ; GAh + AA vs GG,  $P=0.28$ ; AA vs GG + GA,  $P=0.39$ ).

## Discussion

Based on the data from the Sino-MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Beijing project from 1984 to 2004, the incidence of IS in China increased along with the fast-growing economy.

This observation indicates that IS continues to account for most cases of stroke.<sup>30</sup> IS is a complex disease and is pathologically based on atherosclerosis which can affect the interactions between genomic abnormalities and various environmental factors, and has become a major public health burden in China.<sup>31</sup>

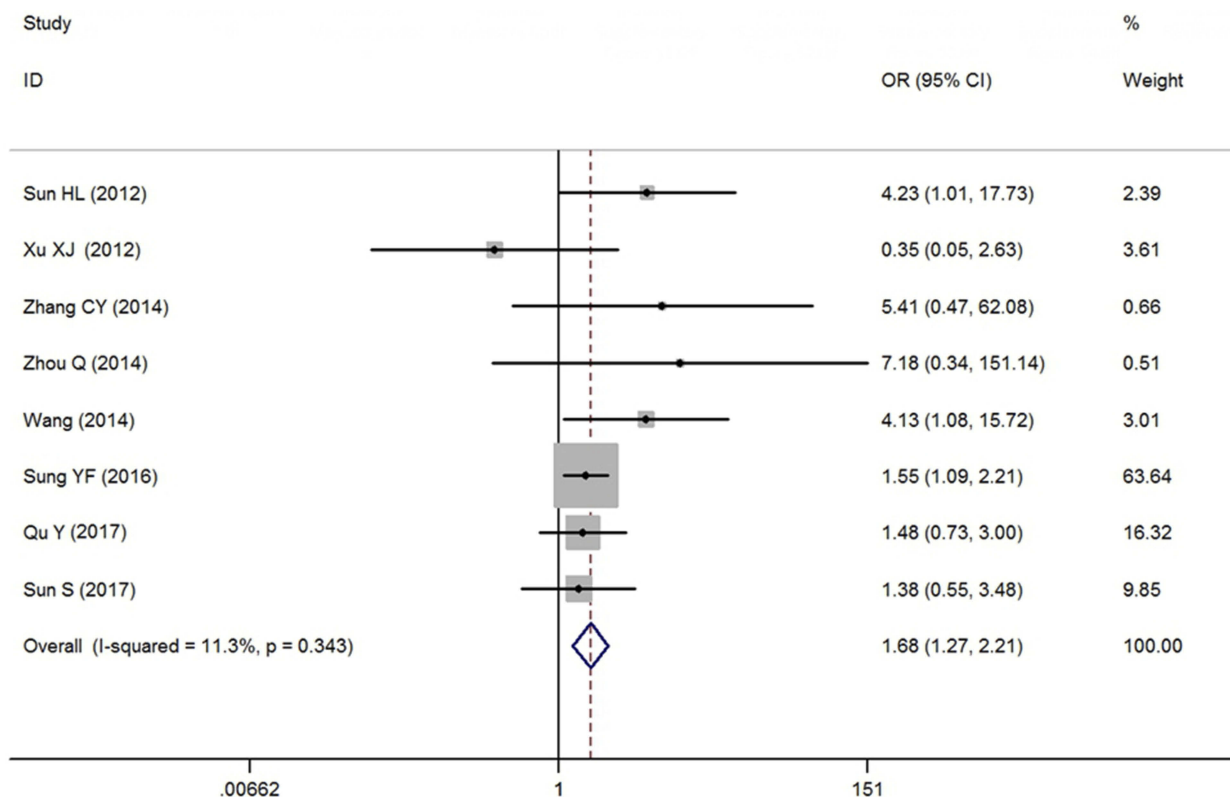
Previous epidemiological studies have suggested that alcohol consumption exerts dual effects on the incidence of IS due to ethnic diversity, sex differences and difference in amounts of alcohol consumed.<sup>32–34</sup> ALDH2 plays a critical role during the metabolism of ethanol and aldehyde detoxification. ALDH2 is an enzyme responsible for the rapid conversion of acetaldehyde to acetic acid in liver mitochondria. The rs671 G>A polymorphism in *ALDH2* results in an inactive A-allele and a dramatic reduction in the enzyme's activity. This remarkable decrease in activity subsequently leads to dysfunctional acetaldehyde metabolism.<sup>35,36</sup> Compared with the wild-type homozygous GG genotype, the heterozygous GA genotype and homozygous AA genotype lead to forms of the enzyme with only approximately 16% of its original effectiveness.

**Table 2** Characteristics of case-control studies on ALDH2 rs671 G>A polymorphism and ischemic stroke risk included in the meta-analysis

First author	Year	Control design	Genotype method	Case	Control	Genotype distribution						P for HWE <sup>a</sup>	MAF	NOS evaluation	Adjusted factors
						Case			Control						
						GG	GA	AA	GG	GA	AA				
Sun HL	2012	HB	PCR-RFLP	78	80	27	44	7	49	28	3	0.68	0.21	7	Age, gender, smoking and alcohol status, total cholesterol, HDLC
Xu XJ	2012	PB	PCR-microarray	100	50	82	16	2	29	19	2	0.61	0.23	8	Age, gender, TC, glucose, LDLC, HDLC, ApoA1, ApoB100
Zhang CY	2014	NA	PCR-sequencing	53	106	27	24	2	73	32	1	0.21	0.16	6	Age, gender, smoking status, TC, TG, LDL
Zhou Q	2014	PB	PCR-sequencing	117	148	96	19	2	138	10	0	0.67	0.03	8	Age, gender, smoking and alcohol status, BP, DM, heart disease
Wang GY	2014	HB	PCR-sequencing	156	160	80	67	9	110	47	3	0.43	0.17	8	Age, gender, height, weight, BP, DM
Li QY	2015	HB	PCR-sequencing	369	247	619 <sup>b</sup>		119 <sup>c</sup>	431 <sup>b</sup>		63 <sup>c</sup>	NA	0.13	7	Age, BMI, BP, DM, tobacco habits, alcohol consumption
Sung YF	2016	HB	PCR-APLP	914	746	474	338	102	389	303	54	0.63	0.28	9	Age, BMI, BP, DM, hypercholesterolemia, coronary artery disease, atrial fibrillation, smoking, alcohol drinking and history
Qu Y	2017	PB	PCR-sequencing	394	406	254	120	20	264	128	14	0.75	0.19	9	Age, gender, smoking and alcohol status, DM, TC, TG, LDLC, HDLC, UA
Sun S	2017	HB	MassARRAY	488	503	369	108	11	371	124	8	0.52	0.14	8	Age, gender, smoking and alcohol status, residential region, ethnicity and family history

**Notes:** <sup>a</sup>HWE in control. <sup>b</sup>: only the G-allele were collected; <sup>c</sup>: only the A-allele were collected.

**Abbreviations:** NOS, Newcastle-Ottawa scale; HB, hospital based; PB, population based; MAF, minor allele frequency in control group; NA, not available; HDLC, high-density lipoprotein cholesterol; TC, total cholesterol; LDLC, low density lipoprotein cholesterol; ApoA1, apolipoproteinA1; ApoB100, apolipoproteinB100; TG, three acylglycerol; DM, diabetes mellitus; BP, blood pressure; BMI, body mass index; UA, uric acid.



**Figure 2** OR and 95% CIs of the associations between *ALDH2* rs671 G>A polymorphism and ischemic stroke risk in AA vs GG model.

This may lead to high acetaldehyde concentrations. Individuals with the latter two genotypes have been shown to be more susceptible to various diseases, including digestive system cancer, diabetes and cardio-cerebrovascular disease.<sup>37</sup>

Since 2012, several case-control studies have been published regarding *ALDH2* rs671 G>A polymorphism and IS risk. However, the results of these studies have been inconsistent. Sun firstly reported an increased risk with the A-allele in Shandong Province, China. Similar increases in IS risk were reported by Wang et al.<sup>24</sup> and Zhou.<sup>25</sup> In contrast, Xu et al. found that the prevalence of the G-allele of *ALDH2* in the rs671 G>A polymorphism was higher in controls than in patients with IS, and stated that the A-allele and the GA genotype exerted protective effects against IS (A vs G, OR=0.37, 95% CI=0.19–0.72; GA vs GG, OR=0.30, 95% CI=0.14–0.65).<sup>22</sup> Other studies, such as those by Qu et al.<sup>29</sup> and Sun et al.,<sup>28</sup> did not find any significant relationship between the *ALDH2* rs671 G>A polymorphism and IS risk.

By reviewing the above-collected studies, we found that the included sample sizes ranged from hundreds to thousands of subjects. In molecular epidemiological studies, small sample sizes may lead to false results and the

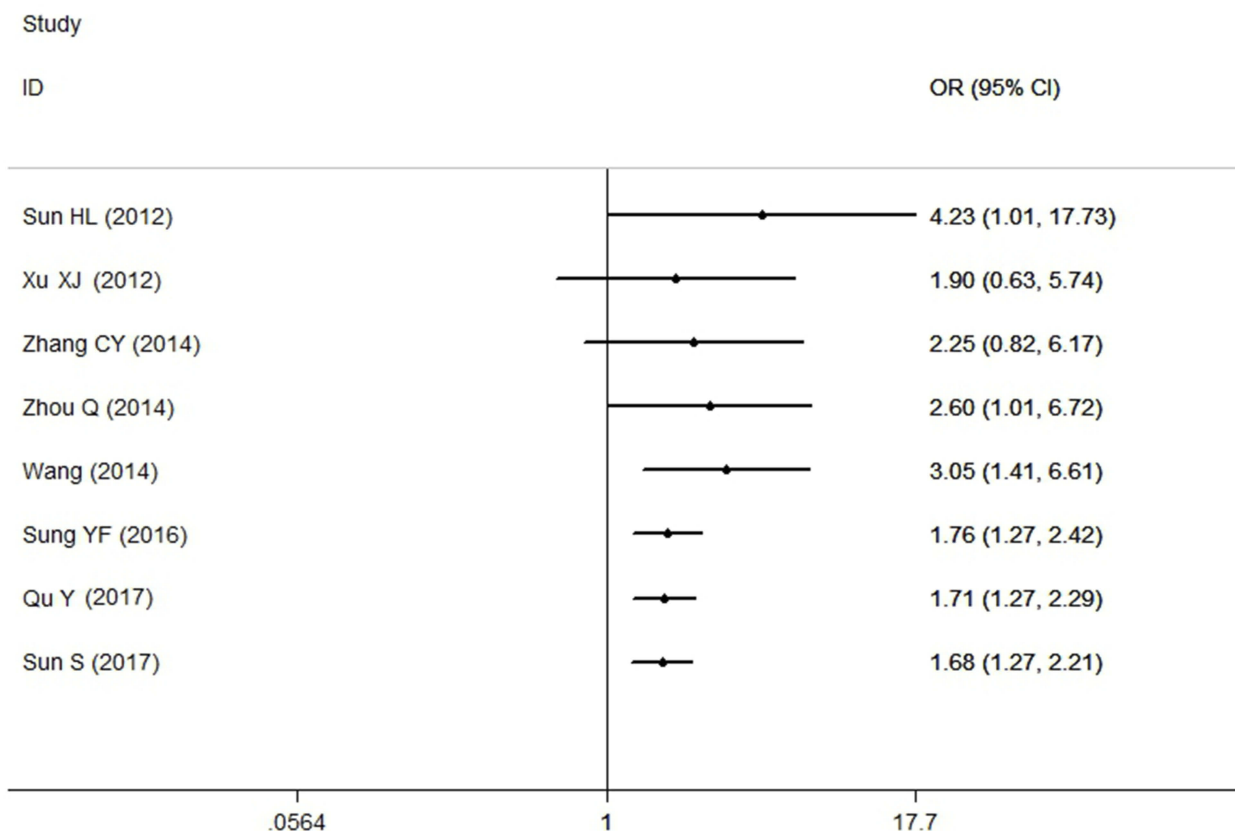
drawing of inaccurate conclusions. Thus, we conducted this meta-analysis using nine published case-control studies to enlarge the sample size and investigate the association between the *ALDH2* rs671 G>A polymorphism and IS risk. To our knowledge, this study is the first meta-analysis of this particular association. Our results strongly suggest that the polymorphic locus of *ALDH2* rs671 G>A may be an independent risk factor for IS. Moreover, the quantitative increase in risk can be observed in all subgroup analyses based on control design, subject number and NOS evaluation groups. Some studies have shown that heterozygous and homozygous mutants of *ALDH2* rs671 G>A polymorphism block aldehyde metabolism and result in acetaldehyde accumulation, which in turn leads to significant impairments in cardiovascular vasorelaxation.<sup>38</sup> Animal studies indicate that *ALDH2*-knockout mice would progressively develop age-related heart dysfunction and show reduction in life span, which strongly suggests that *ALDH2* ablation leads to cardiac aging.<sup>39</sup> In *ALDH2* (-/-) mice, some exhibitions of endothelial dysfunction, increased amyloid-beta in cerebral microvessels and atrophy were observed in the brain.<sup>40</sup> These evidences suggested that the decreased activity of *ALDH2* would

**Table 3** Summary ORs and 95% CI of ALDH2 rs671G>A polymorphism and ischemic stroke risk

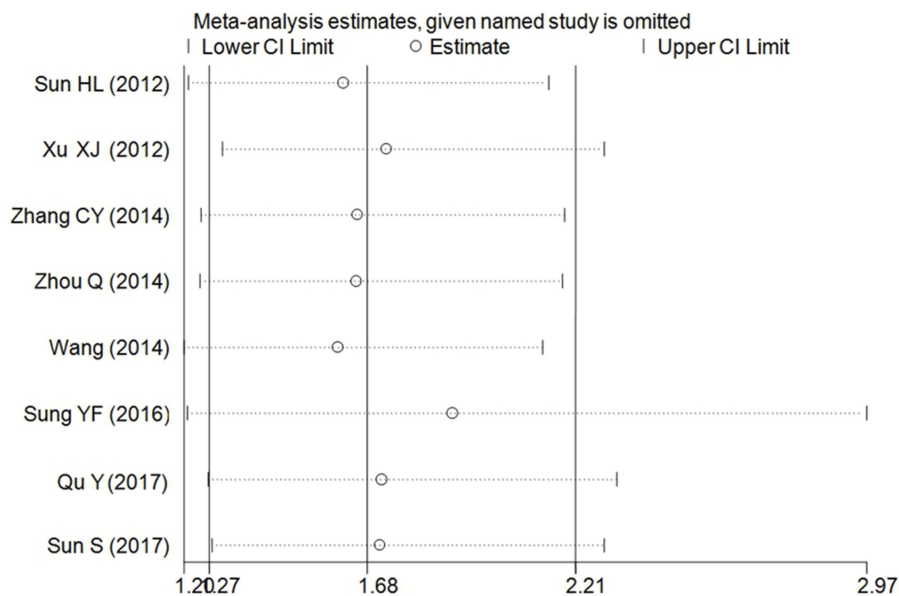
	N*	A vs G				GA vs GG				AA vs GG				GA+AA vs GG				AA vs GG+GA			
		OR	95% CI	P	I <sup>2</sup> (%)	OR	95% CI	P	I <sup>2</sup> (%)	OR	95% CI	P	I <sup>2</sup> (%)	OR	95% CI	P	I <sup>2</sup> (%)	OR	95% CI	P	I <sup>2</sup> (%)
Total	9	1.29	1.01–1.65	0.04	78.2	1.24	0.87–1.76	0.23	81.3	1.68	1.27–2.21	<0.01	11.3	1.31	0.93–1.86	0.13	82.6	1.67	1.27–2.19	<0.01	0
Design																					
HB	5	1.34	1.03–1.73	0.03	74.0	1.34	0.86–2.09	0.20	83.8	1.71	1.25–2.34	<0.01	18.9	1.42	0.92–2.21	0.11	84.3	1.68	1.24–2.29	<0.01	0.0
PB	3	1.06	0.42–2.67	0.91	88.5	0.93	0.35–2.47	0.88	86.6	1.43	0.76–2.30	0.27	32.2	0.98	0.35–2.70	0.96	88.2	1.41	0.70–2.86	0.24	3.6
NA	1	1.88	1.07–3.31	0.03	NA	2.03	1.02–4.04	0.04	NA	5.41	0.47–62.08	0.18	NA	2.13	1.08–4.19	0.03	NA	4.12	0.36–46.48	0.25	NA
Subjects																					
<500	5	1.56	0.85–2.87	0.15	83.6	1.59	0.78–3.24	0.21	82.6	3.05	1.14–6.61	0.01	25.2	1.67	0.80–3.49	0.17	84.5	2.45	1.14–5.26	0.02	0
>500	4	1.09	0.98–1.22	0.12	0	0.92	0.79–1.06	0.26	0	1.52	1.13–2.05	0.01	0	0.99	0.86–1.44	0.87	0	1.57	1.17–2.11	<0.01	0
NOS evaluation																					
NOS ≥8	6	1.14	0.85–1.53	0.39	81.1	1.04	0.73–1.46	0.85	79.4	1.59	1.19–2.11	<0.01	3.7	1.10	0.77–1.56	0.60	81.4	1.60	1.21–2.13	<0.01	0.0
NOS <8	3	1.59	1.24–2.04	<0.01	37.6	2.42	1.50–3.91	<0.01	0	4.49	1.30–15.47	0.02	0	2.54	1.59–4.06	<0.01	0	2.85	0.85–9.54	0.09	0.0

Notes: \*Numbers of comparisons. I<sup>2</sup> for Heterogeneity test.

Abbreviations: HB, hospital based; PB, population based; NA, not available; NOS, Newcastle-Ottawa scale.



**Figure 3** Cumulative meta-analyses according to publication year in AA vs GG model of ALDH2 rs671G>A polymorphism.

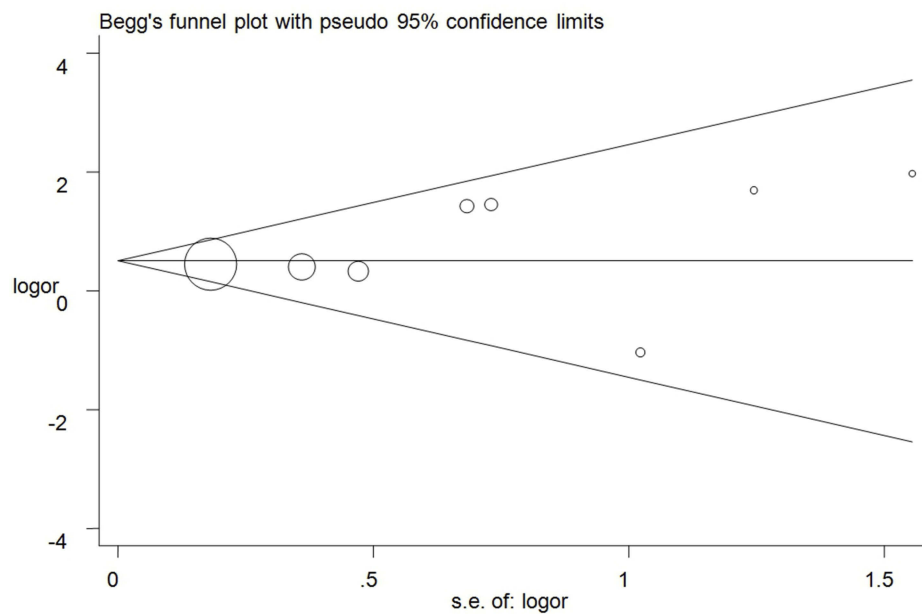


**Figure 4** Sensitivity analysis involving deletion of each study to reflect the influence of the individual dataset to the pooled ORs in AA vs GG model of ALDH2 rs671G>A polymorphism.

aggravate oxidative stress responses and aging of the cerebrovascular system, and increase the risk of IS. Other studies have reported that the proportion of GA

and AA genotypes were higher in subjects with carotid atherosclerosis than in control subjects. This observation indicates that the rs671 G>A polymorphism is





**Figure 5** Funnel plot analysis to detect publication bias for AA vs GG model of *ALDH2* rs671 G>A polymorphism. Circles represent the weight of the studies.

associated with the severity and thickness of carotid atherosclerosis in Asians, and that carotid atherosclerosis is the main pathological mechanism underlying IS.<sup>41–43</sup> All these observations imply that the rs671 G>A polymorphism in *ALDH2* may play an indirect role in IS development.

This analysis integrated all published case-control studies on *ALDH2* rs671 G>A polymorphism and IS risk with both a large sample size and the use of rigorous statistical methods. However, some limitations remain due to the inherent deficiencies of meta-analyses. First, the subjects in all of the included studies were mainly Chinese. Therefore, the results of this analysis may not represent those obtained in all ethnic populations. A recently published genome-wide association study in Caucasian populations had reported that the *ALDH2* rs10744777 polymorphism but not the rs671 polymorphism was associated with IS risk.<sup>44</sup> So, further studies are needed to verify the potential correlation between *ALDH2* rs671 G>A polymorphism and IS risk in Caucasians. Second, only one SNP locus (*ALDH2* rs671 G>A polymorphism) was examined, and the investigation was not adjusted for interfering gene–gene and gene–environment factors. The absence of such adjustments may have led to bias in the general conclusions. Finally, some heterogeneity emerged in the included studies. Meta-regression was performed but failed to identify any factor that contributed to the heterogeneity.

## Conclusion

The data from all the included studies suggest that the *ALDH2* rs671 G>A polymorphism may be a risk factor for IS development. Additional case-control studies including gene–environment interactions in diverse populations are needed to explore the underlying mechanisms of this potential association.

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## Disclosure

The authors report no conflicts of interest in this work.

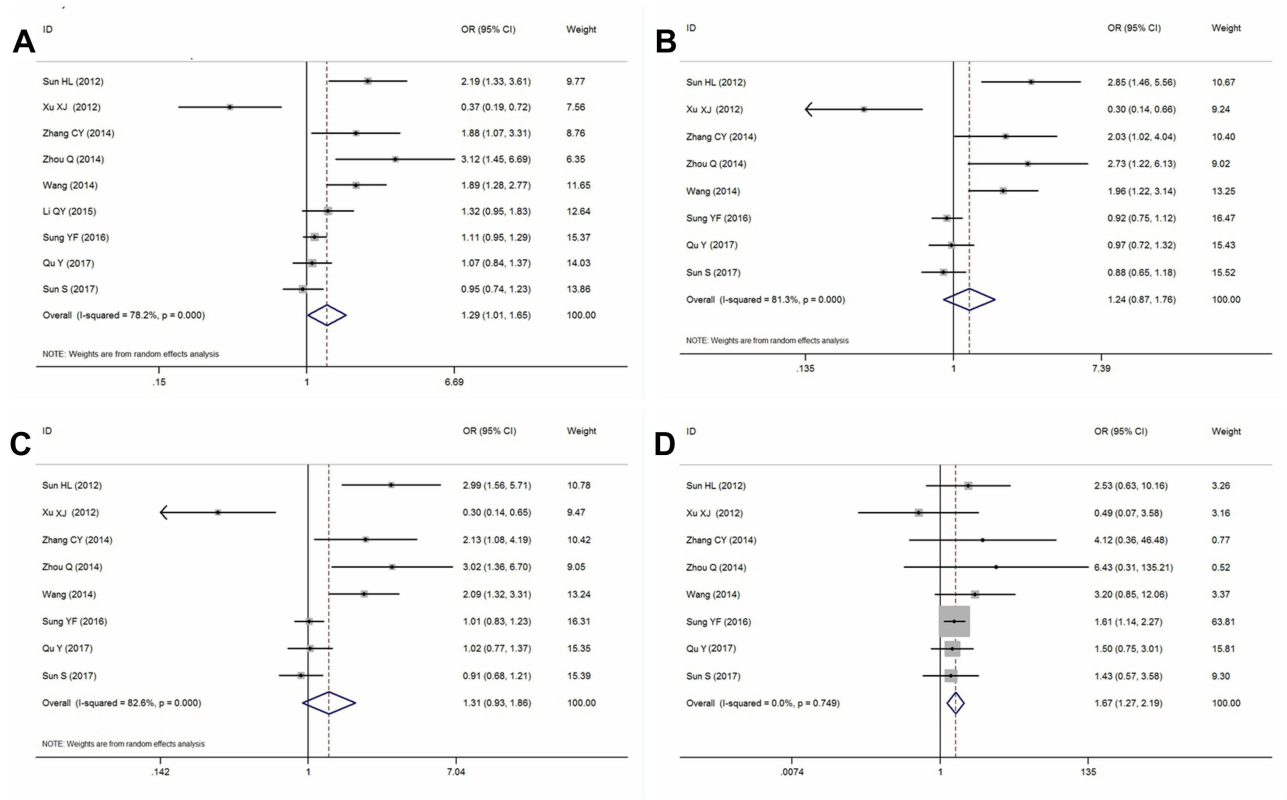
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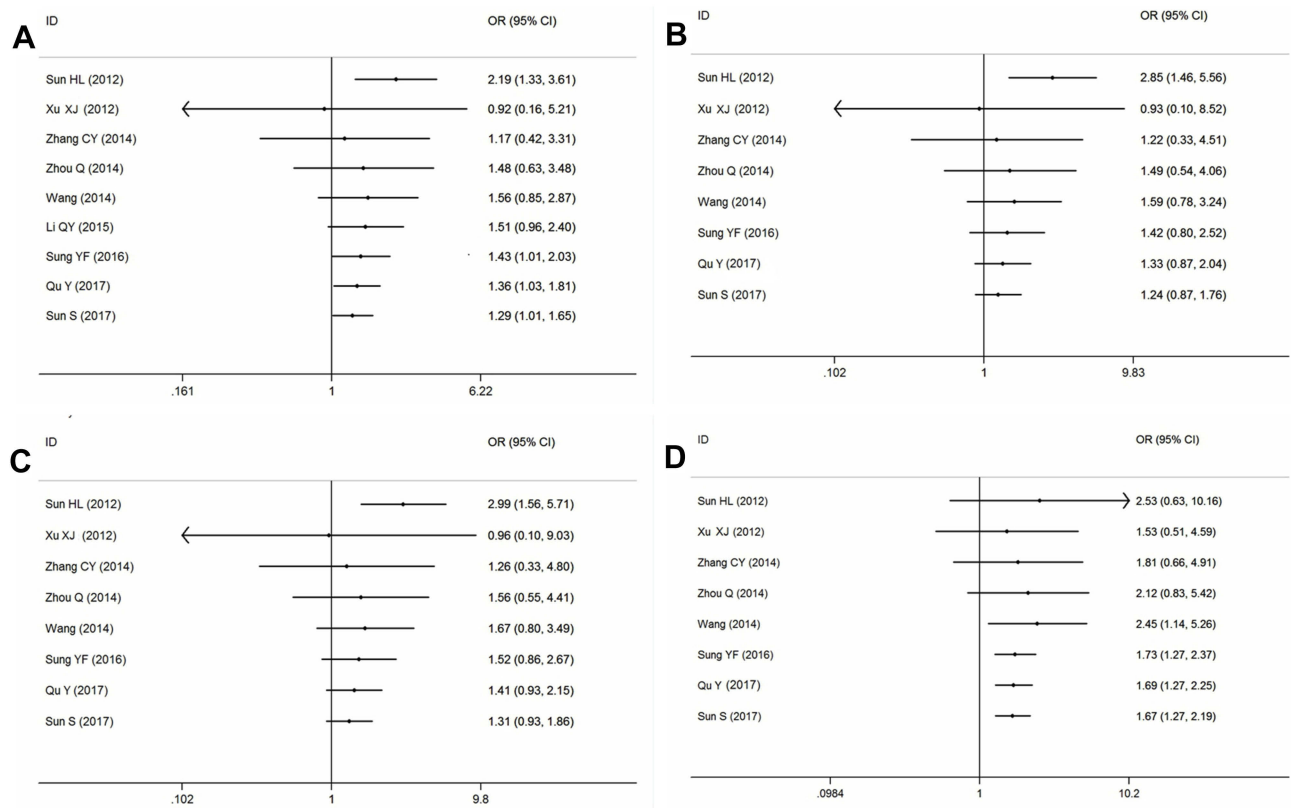
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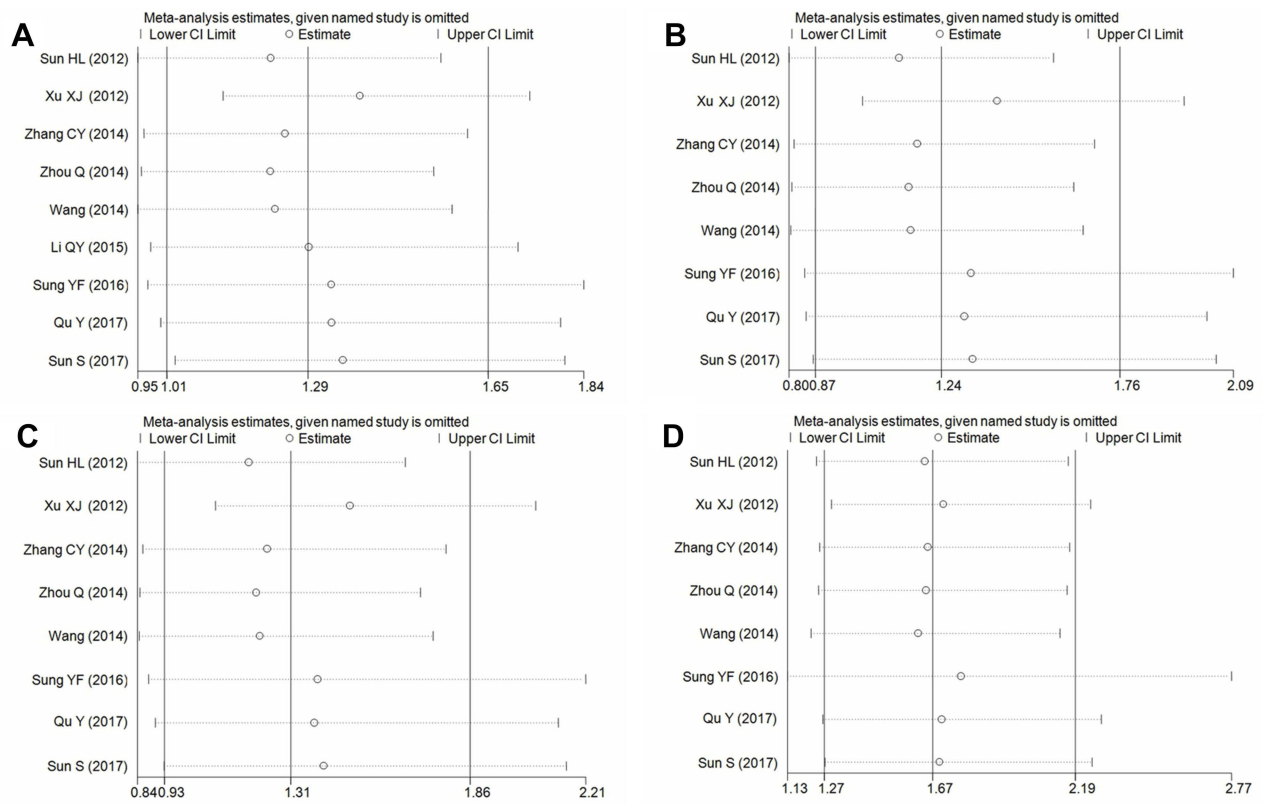
# Supplementary materials



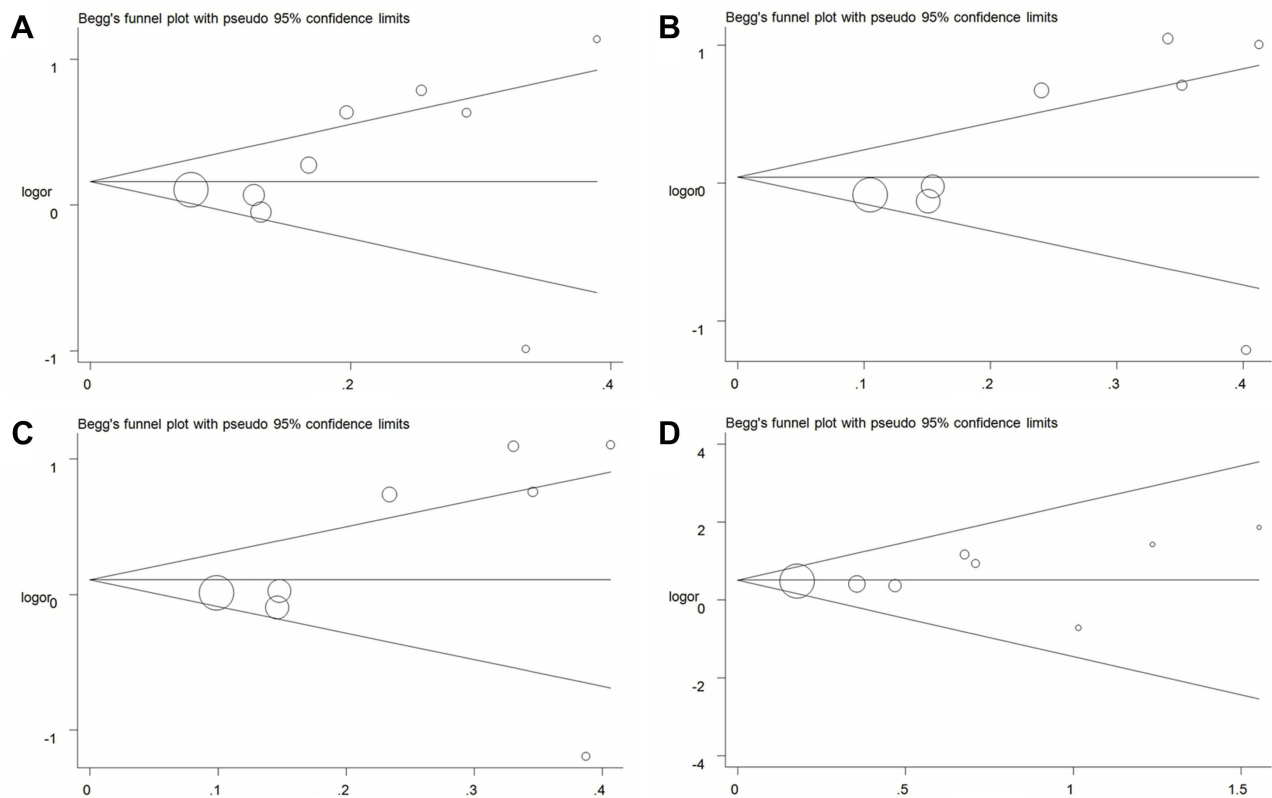
**Figure S1** OR and 95% CIs of the associations between *ALDH2* rs671G>A polymorphism and ischemic stroke risk (**A** for A vs G model; **B** for GA vs GG model; **C** for GA + AA vs GG model; **D** for AA vs GG + GA model).



**Figure S2** Cumulative meta-analyses according to publication year in *ALDH2* rs671G>A polymorphism and ischemic stroke risk (**A** for A vs G model; **B** for GA vs GG model; **C** for GA + AA vs GG model; **D** for AA vs GG + GA model).



**Figure S3** Sensitivity analysis through deleting each study to reflect the influence of the individual dataset to the pooled ORs in *ALDH2* rs671G>A polymorphism and ischemic stroke risk (**A** for A vs G model; **B** for GA vs GG model; **C** for GA + AA vs GG model; **D** for AA vs GG + GA model).



**Figure S4** Funnel plot analysis to detect publication bias in *ALDH2* rs671G>A polymorphism (**A** for A vs G model; **B** for GA vs GG model; **C** for GA + AA vs GG model; **D** for AA vs GG + GA model). Circles represent the weight of the studies.

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