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SG13S114 and SG13S32 polymorphism of ALOX5AP in Chinese with ischemic stroke: A Meta-analysis

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Abstract:	Objective: To investigate the relationship between SG13S114 and SG13S32 polymorphism of ALOX5AP and Chinese ischemic stroke. Methods: We conducted a systematic search in Web of Science, PubMed, Chinese National Knowledge Infrastructure, CBM and Wanfang Database, collecting literatures about the association between SG13S114 and SG13S32 gene polymorphism of ALOX5AP and ischemic stroke. The search time was set from database establishment to October 2016. Two researchers separately conducted literature screening, data extraction and quality evaluation, according to the inclusion and exclusion criteria. The meta-analysis was performed by STATA 12.0. Results: A total of 20 independent researchers were included. Among these researchers were 17 studies of SG13S114 and 12 of SG13S32 variants, comprising 7471 cases and 8458 controls, 4731 cases and 4858 controls, respectively. As for SG13S114, the comparison of A with T generated a significant 12.5% increased ischemic stroke risk (A vs. T: OR=1.125, 95%CI: 1.000-1.266, P=0.050) while the comparison of TA+AA with TT generated a significant 13.6% increased ischemic stroke risk (TA+AA vs. TT: OR=1.136, 95%CI: 1.006-1.283, P=0.040). However, there was no significant association between SG13S32 variant and ischemic stroke under all three genetic model. Conclusion: SG13S114 A allele of ALOX5AP may be a risk factor to ischemic stroke for Chinese.

SG13S114 and SG13S32 polymorphism of *ALOX5AP* in Chinese with ischemic stroke: A Meta-analysis

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Abstract

Objective: To investigate the relationship between SG13S114 and SG13S32 polymorphism of ALOX5AP and Chinese ischemic stroke.

Methods: We conducted a systematic search in Web of Science, PubMed, Chinese National Knowledge Infrastructure, CBM and Wanfang Database, collecting literatures about the association between SG13S114 and SG13S32 gene polymorphism of *ALOX5AP* and ischemic stroke. The search time was set from database establishment to October 2016. Two researchers separately conducted literature screening, data extraction and quality evaluation, according to the inclusion and exclusion criteria. The meta-analysis was performed by STATA 12.0.

Results: A total of 20 independent researchers were included. Among these researchers were 17 studies of SG13S114 and 12 of SG13S32 variants, comprising 7471 cases and 8458 controls, 4731 cases and 4858 controls, respectively. As for SG13S114, the comparison of A with T generated a significant 12.5% increased ischemic stroke risk (A vs. T:

OR=1.125, 95%*CI*: 1.000-1.266, *P*=0.050) while the comparison of TA+AA with TT generated a significant 13.6% increased ischemic stroke risk (TA+AA vs. TT: *OR*=1.136, 95%*CI*: 1.006-1.283, *P*=0.040). However, there was no significant association between SG13S32 variant and ischemic stroke under all three genetic model.

Conclusion: SG13S114 A allele of *ALOX5AP* may be a risk factor to ischemic stroke for Chinese.

Key words: ALOX5AP; ischemic stroke; polymorphism; meta-analysis

1. Introduction

It is estimated that about 6 million people died of stroke worldwide each year. China, as the country with the highest incidence, there are approximately 2.5 million new cases and 1.6 million deaths during to stroke every year. [1]. WHO data show that the disability adjustment life year (DALY) caused by stroke in China is about 10 to14 years, which is a heavy burden to our society. Ischemic stroke, accounts for about 87% of all strokes [2], is a complex disease influenced by both genetic and environmental factors. A large number of clinical data on twins showed that the genetic factor plays a very important role in the occurrence and development of ischemic stroke [3].

ALOX5AP gene, with a size of 31 kb, is located in the chromosome 13q12-13, containing five exons and four introns. It encodes five

lipoxygenase activating protein (FLAP), which converts nonesterified arachidonic acid (AA) to leukotriene A4 [4]. Leukotriene A4 as an unstable epoxide is hydrolyzed to leukotriene B4 or conbined with glutathione to yield leukotriene C4 by leukotriene A4 hydrolase and leukotriene C4 synthetase. The leukotrienes participate in many kinds of proinflammatory processes [5, 6], accelerate the formation of thrombus and atherosclerosis, and finally lead to stroke or myocardial infarction. A study showed that HapA (SG13S25, SG13S114, SG13S89 and SG13S32), a four single-nucleotide polymorphism (SNP) haplotype , was associated with a nearly 1.8 fold greater risk for myocardial infarction (MI) and 1.7 fold for stroke in an Icelandic population [7]. However, Zee et al. found no association between HapA and stroke in a US population [8]. Since there is a great difference between different regions, the association between the *ALOX5AP* gene polymorphism and the risk of stroke needs to be verified among different populations. Therefore, we conducted the present meta-analysis to evaluate whether *ALOX5AP* gene polymorphism was a risk factor of ischemic stroke in the Chinese population.

2. Materials and Methods

2.1. Data source and searches

We conducted a systematic search in Web of Science, PubMed, Chinese National Knowledge Infrastructure, CBM and Wanfang Database, using

following search terms: ALOX5AP, 5-lipoxygenase activating protein, stroke, cerebrovascular accident, CVA, cerebrovascular event, cerebrovascular disease, brain hemorrhage, intracranial hemorrhage, cerebral hemorrhage, cerebral infarction, cerebral ischemia, polymorphism, variation, allele, genotype, case control, case-control. The search time was set from database establishment to October 2016. Identify studies published in Chinese or English. Additionally, we screened the reference lists of relevant review articles and included studies for additional information.

2.2. Study selection

Studies investigating the relationship between SG13S114 and SG13S32 gene polymorphism of *ALOX5AP* and ischemic stroke were included. And they must meet the following criteria:1）with a design of case-control study; 2）available and sufficient data for calculation of OR and 95%CI. If multiple publications were available for a study, we included the report with the most detailed information and most extensive population. Studies with unclear diagnosis and review articles were excluded.

2.3. Data extraction

Following information was extracted independently by two

investigators: first author, year of publication, origin, number of cases and controls, study population characteristics (mean age, gender, ethnicity), genotype distribution in cases and controls. The differences between these were resolved through discussion and consensus with another of our authors.

2.4. Quality assessment

Quality assessment was performed according to the Newcastle-Ottawa Quality Assessment Scale (NOS), which is a validated scale for non-randomized studies in meta-analyses. The NOS tool contains nine items, 4 for selection of participants and measurement of exposure, 2 for comparability of cohorts on the basis of the design or analysis, and 3 for assessment of outcomes and adequacy of follow-up and each item is assigned with a star if a study meets the criteria of the item. We considered a study having high quality if it scored more than 6.

2.5. Statistical analysis

The OR and 95%CI were calculated according to allele model (A vs. T for SG13S114 and C vs. A for SG13S32), dominant model (TA+AA vs. TT for SG13S114 and AC+CC vs. AA for SG13S32), recessive model (AA vs. TA+TT for SG13S114 and CC vs. AC+AA for SG13S32). Heterogeneity was examined by Q test and I^2 tests. A random effect

model was taken when P_q <0.1 or I^2>50%; otherwise, a fixed effect model was used. Subgroup analyses and sensitivity analyses were performed to explore the source of heterogeneity. To assess the potential publication bias, Begg's correlation and Egger's regression were used. All tests were two-sides with a significance level of 0.05 and analyses were performed with STATA version 12.0.

3. Results

3.1. Study and data included in the meta-analysis

As shown in Fig. 1, 214 potential relevant studies were identified, while only 20 studies met all criteria. Among these studies, 17 researches focused on SG13S114 and 12 on SG13S32 variants, including 7471 cases and 8458 controls, 4731 cases and 4858 controls, respectively. Detailed characteristics and genotype distribution of all included studies were listed in Table 1 and Table 2.

3.2. Pooled analysis

7471 cases and 8458 controls from 17 studies were included in the meta-analysis on SG13S114 variant. Based on the high heterogeneity (A vs. T：P=0.000，I^2=83.6%；AA vs. TA+TT: P=0.000，I^2=86.5%; TA+AA vs. TT: P=0.000，I^2=67.7%), random effects models were used under three models (allele, recessive and dominant model). There was no

significant association between SG13S114 variant and ischemic stroke under recessive genetic model (AA vs. TA+TT: *OR*=1.245, 95%*CI*: 0.966-1.604, *P*=0.090). In the allele model, the comparison of allele A with T generated a significant 12.5% increased ischemic stroke risk (A vs. T: *OR*=1.125, 95%*CI*: 1.000-1.266, *P*=0.050) (Fig.2) while the comparison of TA and AA with TT generated a significant 13.6% increased ischemic stroke risk (TA+AA vs. TT: *OR*=1.136, 95%*CI*: 1.006-1.283, *P*=0.040) (Fig.3).

12 studies comprising 4731 cases and 4858 controls were included in the present meta-analysis on SG13S32 variant. Based on the values of heterogeneity (C vs. A: *P*=0.000, I^2=87.9%; CC vs. AC+AA: *P*=0.000, I^2=80.1%; AC+CC vs. AA: *P*=0.000, I^2=86.5%), random effects models were used under three models (allele, recessive and dominant model). There was no significant association between SG13S32 variant and ischemic stroke under all three genetic model (C vs. A: *OR*=0.896, 95%*CI*: 0.752-1.068, *P*=0.220; CC vs. AC+AA: *OR*=0.923, 95%*CI*: 0.689-1.236, *P*=0.591; AC+CC vs. AA: *OR*=0.888, 95%*CI*: 0.704-1.120, *P*=0.315).

3.3. Subgroup analysis

In the subgroup analysis, studies were categorized by respective mean age and gender ration of cases and controls. Subgroup by mean age

(case) showed that SG13S114 gene polymorphism of *ALOX5AP* was associated with ischemic stroke among the older (more than 60) under allele (*OR*=1.179, 95%*CI*: 1.018-1.365, *P*=0.028) and recessive (*OR*=1.402, 95%*CI*: 1.093-1.799, *P*=0.008) genetic model, while under dominant model, the subgroup with mean age no more than 60 had a significant association between SG13S114 gene polymorphism of *ALOX5AP* and ischemic stroke(*OR*=1.237, 95%*CI*: 1.010-1.515, *P*=0.040). In addition, stratified by mean age (control), we found that SG13S114 gene polymorphism of *ALOX5AP* was associated with ischemic stroke among the older (more than 60) under recessive (*OR*=1.335, 95%*CI*: 1.026-1.736, *P*=0.031) genetic model and among the younger (no more than 60) under dominant model (*OR*=1.182, 95%*CI*: 1.030-1.358, *P*=0.018). Furthermore, a significant association was shown between SG13S114 gene polymorphism of *ALOX5AP* and ischemic stroke among gender ratio less than 1.5 (both among cases and controls) under allele and dominant model (Table 3). The subgroup results of SG13S32 gene showed that SG13S32 gene polymorphism of *ALOX5AP* was associated with ischemic stroke among the younger (no more than 60) under allele (*OR*=0.651, 95%*CI*: 0.437-0.971, *P*=0.035) and dominant (*OR*=0.589, 95%*CI*: 0.386-0.900, *P*=0.014) genetic model (Table 4) when stratified by mean age (control).

3.4. Sensitivity analyses

Sensitivity analyses were performed to explore sources of heterogeneity and the results showed that our conclusions were statistically stable. We chose 50.0% as the cut-off of I^2 and drop the study one by one until I^2<50.0%. Except the recessive model of SG13S114, there were no variations in the pooled ORs after the exclusion of one study every turn, which mean that our results were stable (Table 5). As for the recessive model of SG13S114, Qianqian Yao[16], Xuewen Feng[20], Zhuo Gao[21] and Chen Xu[23] may be sources of heterogeneity.

3.5. Publication bias

Begg's correlation and Egger's regression were used to assess the potential publication bias. There was not statistically detected in all genetic models for SG13S114(A vs. T: Egger: *P*=0.932, Begg's: *P*=0.967; AA vs. TA+TT: Egger: *P*=0.962, Begg's: *P*=0.967; TA+AA vs. TT: Egger: *P*=0.596, Begg's: *P*=0.837) and for SG13S32(C vs. A: Egger: *P*=0.275, Begg's: *P*=0.631; CC vs. AC+AA: Egger: *P*=0.067, Begg's: *P*=0.150; AC+CC vs. AA: Egger: *P*=0.629, Begg's: *P*=0.451).

4. Discussion

Cerebrovascular disease has been ranked first in the cause of disability and death both in China's urban and rural, and the incidence is

increasing year by year. There are now existing more than 7 million patients with cerebrovascular disease in China, and 70% of which is ischemic stroke. With the aging of China's population, the change of life style and the rapid development of economic level, the incidence of ischemic stroke will increase significantly and the burden of disease will continue to grow in the next 25 years [29]. Therefore, our study including 20 studies which were conducted at Zhejiang, Beijing, Liaoning, Shandong, Ningxia, Henan, Heilongjiang and other regions aimed to do a meta-analysis. We found that SG13S114 gene polymorphism of *ALOX5AP* was associated with ischemic stroke in the Chinese population and A allele would be a risk factor. Speculate the possible mechanism as follows. *ALOX5AP* gene encodes five lipoxygenase activating protein (FLAP). FLAP as an activator protein could converts nonesterified arachidonic acid (AA) to leukotriene A4. Leukotriene A4, as an unstable epoxide, is hydrolyzed to leukotriene B4 or conjugated with glutathione to yield leukotriene C4 by leukotriene A4 hydrolase and leukotriene C4 synthetase. The leukotrienes participate in many kinds of proinflammatory processes [30, 31], accelerate the formation of atherosclerosis and thrombus, and eventually lead to cerebral apoplexy and myocardial infarction [32-36]. Thus, *ALOX5AP* gene is considered to be the key regulator of inflammatory factors. Since a study showed that SG13S114 genotypes modulate mRNA levels of *ALOX5AP* and mRNA

levels were higher in IS cases than in controls [37]. The individual with SG13S114 mutations may lead to *ALOX5AP* gene overexpression and induce a large number of proinflammatory cytokines leukotriene B4 (LTB4). And then LTB4 affect the incidence of stroke by increasing the inflammatory response to the arterial wall. However, no statistical association was found between SG13S32 gene polymorphism of *ALOX5AP* and ischemic stroke in the Chinese population. The specific mechanism is still need more research to further explore. Since the aging and the male are defined risk factors of stroke, we chose the mean age and gender ratio to do a subgroup analysis, and there were some discrepancies between studies with a different mean age and gender ratio.

In addition, our study has the following limitations: First, studies included in our meta-analysis were all case-control studies, thus the strength of the evidence may insufficient. Secondly, our research were only included few regions of China, which may make our results lack of representation. Finally, a larger sample size is needed for better subgroup analysis.

In conclusion, SG13S114 A allele of *ALOX5AP* may be a risk factor to ischemic stroke for Chinese. However, there was no significant association between SG13S32 variant and Chinese ischemic stroke in our study.

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Table 1: Characteristics of the 17 studies about SG13S114 included in the current meta-analysis.

First author	Year	Region	Ethnicity	Male(T/C)	Female(T/C)
Minjie Shao[9]	2013	Zhejiang	/	233/217	161/165
Jianhua Ma[10]	2013	Xinjiang	Uygur/Han	454/454	336/336
Jiannan Wang[11]	2015	Beijing	/	234/194	162/106
Hairong Wu[12]	2013	Shandong	/	208/192	93/103
Yinglei He[13]	2009	Zhejiang	/	236/228	176/140
Lei Sun[14]	2012	Shandong	/	291/314	149/172
Jialiang Xu[15]	2009	Liaoning	Han	283/183	189/129
Qianqian Yao[16]	2013	Shandong	Han	274/304	138/168
Zhisong Gao[17]	2008	Ningxia	/	65/60	35/40
Duanxiu Liao[18]	2016	/	/	235/222	161/156
Wanzhang Chi[19]	2014	Zhejiang	/	231/231	180/180
Xuewen Feng[20]	2016	Zhejiang	/	135/144	155/146
Zhuo Gao[21]	2010	Liaoning	Han	239/141	220/225
Weili Zhang[22]	2006	multi-clinical centers	/	497/982	285/731
Chen Xu[23]	2013	Shanghai	Han	/	/
Dongzhi Yang[24]	2014	Henan	Han	290/268	202/222
Zhengyi Qu[25]	2015	Heilongjiang	Han	297/301	159/151

Age(T/C)	Hardy–Weinberg equilibrium	NOS	Sample size(T/C)	Genotype(T/C)		
				TT	TA	AA
68.60±11.09/64.06±9.12	Yes	6	394/382	124/128	200/203	70/51
59.21±11.02/59.28±10.76	Yes	8	790/790	281/328	363/357	146/105
68.12±12.01/64.15±10.34	/	7	396/300	124/100	201/160	71/40
65.52±9.2/64.88±8.6	Yes	7	301/295	125/152	135/118	41/25
71.5±7.8/70.3±6.9	Yes	8	412/368	152/152	202/182	58/34
66.58±8.40/66.10±5.18	Yes	8	440/486	177/252	206/198	57/36
61.62±10.34/62.73±10.19	Yes	8	472/312	229/161	197/128	46/23
64.72±9.08/64.60±9.31	Yes	8	412/472	182/144	186/240	44/88
57.3±6.9/60.0±7.5	Yes	8	100/100	50/51	40/40	10/9
68.79±11.11/64.98±10.29	Yes	6	396/378	127/131	201/195	68/52
69.30±10.30/68.90±10.20	/	7	411/411	145/165	194/197	72/49
42.5±6.21/41.6±6.32	/	8	290/290	23/42	193/108	74/140
63.44±23.89/56.8±21.78	Yes	8	380/425	38/47	120/225	218/153
61.5±8.5/59.6±8.5	Yes	8	782/1713	376/859	319/687	87/167
/	Yes	5	547/794	215/292	252/357	78/137
56.7±8.3/56.2±8.9	Yes	8	492/490	178/214	222/232	92/44
59.7±11.5/53.7±8.2	Yes	7	456/452	198/189	205/206	53/57

Allele(T/C)	
T	A
448/459	340/305
925/1013	655/567
449/360	343/240
385/422	217/168
506/486	318/250
560/702	320/270
655/450	289/174
550/528	274/416
140/142	60/58
455/457	337/299
484/527	338/295
239/192	341/388
196/319	556/531
1071/2405	493/1021
682/941	408/631
578/660	406/320
601/584	311/320

Table 2: Characteristics of the 12 studies about SG13S32 included in the current meta-an

First author	Year	Region	Ethnicity	Male(T/C)	Female(T/C)
Lei Sun[14]	2012	Shandong	/	291/314	149/172
Jialiang Xu[15]	2009	Liaoning	Han	283/183	189/129
Qianqian Yao[16]	2013	Shandong	Han	274/304	138/168
Duanxiu Liao[18]	2016	/	/	235/222	161/156
Xuewen Feng[20]	2016	Zhejiang	/	135/144	155/146
Zhuo Gao[21]	2010	Liaoning	Han	239/141	220/225
Chen Xu[23]	2013	Shanghai	Han	/	/
Dongzhi Yang[24]	2014	Henan	Han	290/268	202/222
Zhengyi Qu[25]	2015	Heilongjiang	Han	297/301	159/151
Meng Liu[26]	2015	Xinjiang	Uygur	117/117	80/80
Haixian Li[27]	2013	Shandong	/	203/162	154/138
Lifen Chi[28]	2013	Zhejiang	Han	173/149	119/110

ıalysis.

Age(T/C)	Hardy–Weinberg equilibrium	NOS	Sample size(T/C)	Genotype(T/C)	
				AA	AC
66.58±8.40/66.10±5.18	Yes	8	440/486	218/232	174/210
61.62±10.34/62.73±10.19	Yes	8	472/312	226/170	135/82
64.72±9.08/64.60±9.31	Yes	8	412/472	162/212	198/216
68.79±11.11/64.98±10.29	Yes	6	396/378	140/147	192/178
42.5±6.21/41.6±6.32	/	8	290/290	191/113	83/104
63.44±23.89/56.8±21.78	Yes	8	380/425	229/186	92/191
/	Yes	5	547/794	251/348	211/349
56.7±8.3/56.2±8.9	Yes	8	492/490	226/190	208/228
59.7±11.5/53.7±8.2	Yes	7	456/452	215/206	202/198
60.96±11.91/60.54±11.33	Yes	8	197/200	8/23	189/161
65.3±9.4/64.8±8.5	Yes	8	357/300	156/101	151/158
68.56±11.09/63.92±9.29	Yes	6	292/259	103/101	148/122

	Allele(T/C)	
CC	A	C
48/44	610/674	270/298
111/60	587/422	357/202
52/44	522/640	302/304
64/53	472/472	320/284
16/73	465/330	115/250
50/40	550/563	192/271
67/91	713/1045	345/531
58/72	660/608	324/372
39/48	632/610	280/294
0/16	205/207	189/193
50/41	463/360	251/240
41/36	354/324	230/194

Table3

Table 3: Stratification analyses of the ALOX5AP SG13S114 polymorphism on Chinese ischemic stroke ri

Variables	N	A vs. T		TA+AA vs. TT	
		OR（95%CI）	*P*	OR（95%CI）	*P*
Mean age(case)					
＞60	11	1.179(1.018,1.365)	0.028	1.122(0.954,1.319)	0.164
≤60	5	1.060(0.827,1.359)	0.644	1.237(1.010,1.515)	0.040
other	1	0.892(0.761,1.046)	0.159	0.907(0.725,1.136)	0.396
Mean age(control)					
＞60	9	1.144(0.967,1.353)	0.116	1.129(0.919,1.387)	0.249
≤60	7	1.141(0.941,1.383)	0.179	1.182(1.030,1.358)	0.018
other	1	0.892(0.761,1.046)	0.159	0.907(0.725,1.136)	0.396
Gender ratio(case)					
＜1.5	10	1.197(1.057,1.355)	0.004	1.221(1.113,1.339)	0.000
≥1.5	6	1.059(0.823,1.363)	0.657	1.058(0.782,1.431)	0.717
other	1	0.892(0.761,1.046)	0.159	0.907(0.725,1.136)	0.396
Gender ratio(control)					
＜1.5	9	1.184(1.036,1.354)	0.013	1.194(1.094,1.304)	0.000
≥1.5	7	1.090(0.859,1.384)	0.477	1.079(0.809,1.440)	0.605
other	1	0.892(0.761,1.046)	0.159	0.907(0.725,1.136)	0.396

isk.

AA vs. TA+TT	
OR（95%CI）	*P*
1.402(1.093,1.799)	0.008
1.050(0.535,2.061)	0.888
0.791(0.585,1.071)	0.129
1.335(1.026,1.736)	0.031
1.212(0.740,1.986)	0.444
0.791(0.585,1.071)	0.129
1.394(0.984,1.973)	0.061
1.103(0.751,1.621)	0.618
0.791(0.585,1.071)	0.129
1.341(0.930,1.933)	0.116
1.205(0.825,1.760)	0.334
0.791(0.585,1.071)	0.129

Table4

Table 4: Stratification analyses of the ALOX5AP SG13S32 polymorphism on Chinese ischemic stroke ris

Variables	N	C vs. A		AC+CC vs. AA	
		OR（95%CI）	*P*	OR（95%CI）	*P*
Mean age(case)					
＞60	8	1.015(0.886,1.164)	0.827	1.024(0.771,1.360)	0.871
≤60	3	0.627(0.357,1.098)	0.102	0.620(0.354,1.087)	0.095
other	1	0.952(0.807,1.124)	0.563	0.876(0.702,1.093)	0.241
Mean age(control)					
＞60	7	1.068(0.955,1.195)	0.247	1.119(0.893,1.402)	0.329
≤60	4	0.651(0.437,0.971)	0.035	0.589(0.386,0.900)	0.014
other	1	0.952(0.807,1.124)	0.563	0.876(0.702,1.093)	0.241
Gender ratio(case)					
＜1.5	8	0.838(0.641,1.096)	0.196	0.852(0.591,1.228)	0.390
≥1.5	3	1.039(0.882,1.224)	0.646	1.029(0.849,1.247)	0.771
other	1	0.952(0.807,1.124)	0.563	0.876(0.702,1.093)	0.241
Gender ratio(control)					
＜1.5	8	0.838(0.641,1.096)	0.196	0.852(0.591,1.228)	0.390
≥1.5	3	1.039(0.882,1.224)	0.646	1.029(0.849,1.247)	0.771
other	1	0.952(0.807,1.124)	0.563	0.876(0.702,1.093)	0.241

k.

CC vs. AC+AA	
OR（95%CI）	*P*
1.208(1.000,1.459)	0.050
0.484(0.204,1.149)	0.100
1.111(0.793,1.555)	0.541
1.169(0.946,1.445)	0.147
0.640(0.299,1.370)	0.250
1.111(0.793,1.555)	0.541
0.802(0.508,1.265)	0.342
1.113(0.792,1.565)	0.536
1.111(0.793,1.555)	0.541
0.802(0.508,1.265)	0.342
1.113(0.792,1.565)	0.536
1.111(0.793,1.555)	0.541

Table5

Table 5: Sensitivity analyses.

		I^2	tau^2	OR（95%CI）	P
	allele model				
	include[16][20][21][23]	83.60%	0.0499	1.125(1.000,1.266)	0.050
	exclude[16][20][21][23]	41.70%	0.0070	1.204(1.120,1.294)	0.000
	dominant model				
SG13S114	include[16]	67.70%	0.0418	1.136(1.006,1.283)	0.040
	exclude[16]	34.40%	0.0105	1.183(1.084,1.292)	0.000
	recessive model				
	include[16][20][21][23]	86.50%	0.2372	1.245(0.966,1.604)	0.090
	exclude[16][20][21][23]	26.20%	0.0147	1.441(1.264,1.643)	0.000
	allele model				
	include[20][21][24]	87.90%	0.0838	0.896(0.752,1.068)	0.220
	exclude[20][21][24]	42.80%	0.0085	1.033(0.941,1.133)	0.496
	dominant model				
SG13S32	include[20][21][24][26][27]	86.50%	0.1405	0.888(0.704,1.120)	0.315
	exclude[20][21][24][26][27]	32.80%	0.0093	1.061(0.936,1.203)	0.354
	recessive model				
	include[20]	80.10%	0.1994	0.923(0.689,1.236)	0.591
	exclude[20]	39.50%	0.0310	1.092(0.922,1.293)	0.308

Figure2

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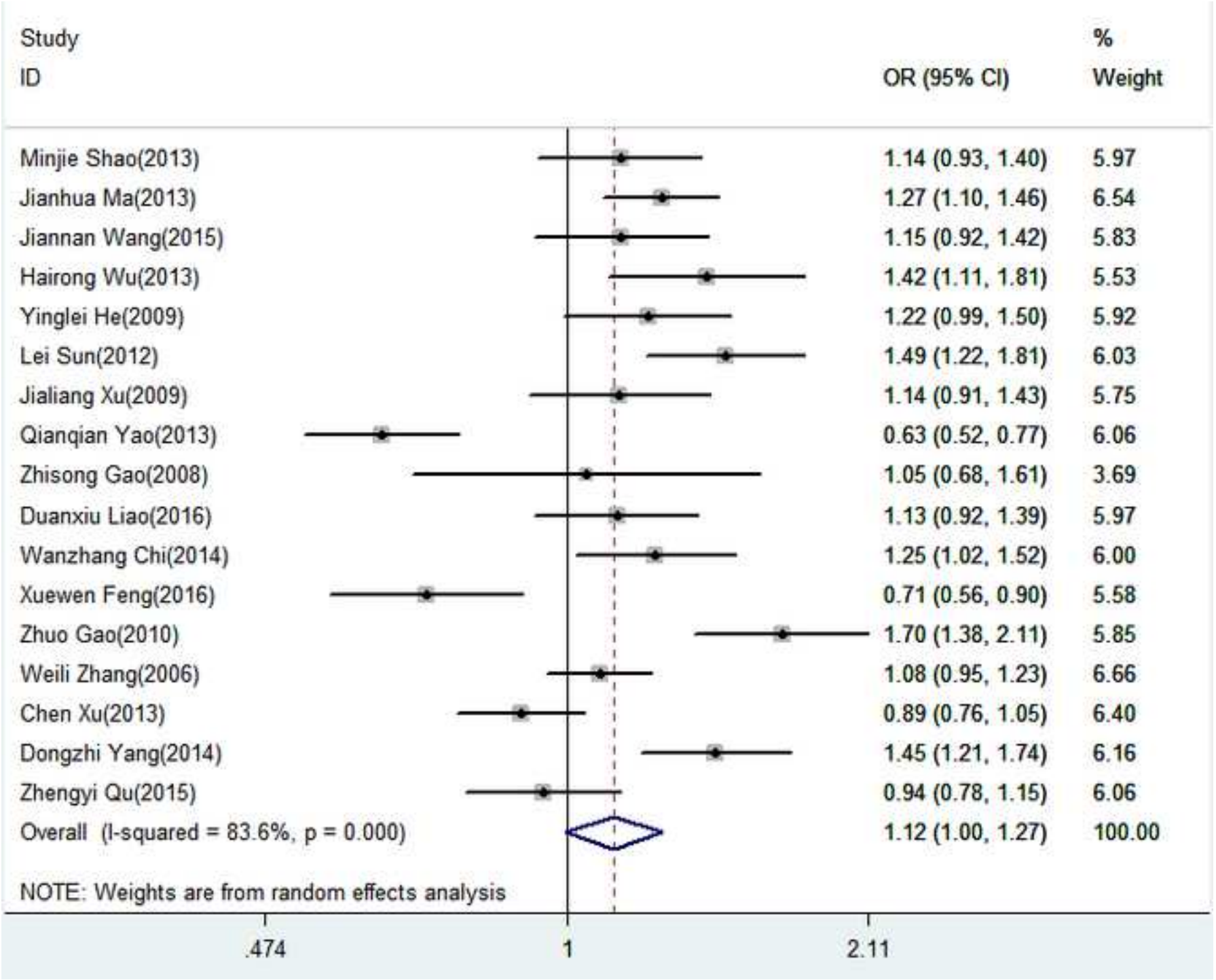

Figure3

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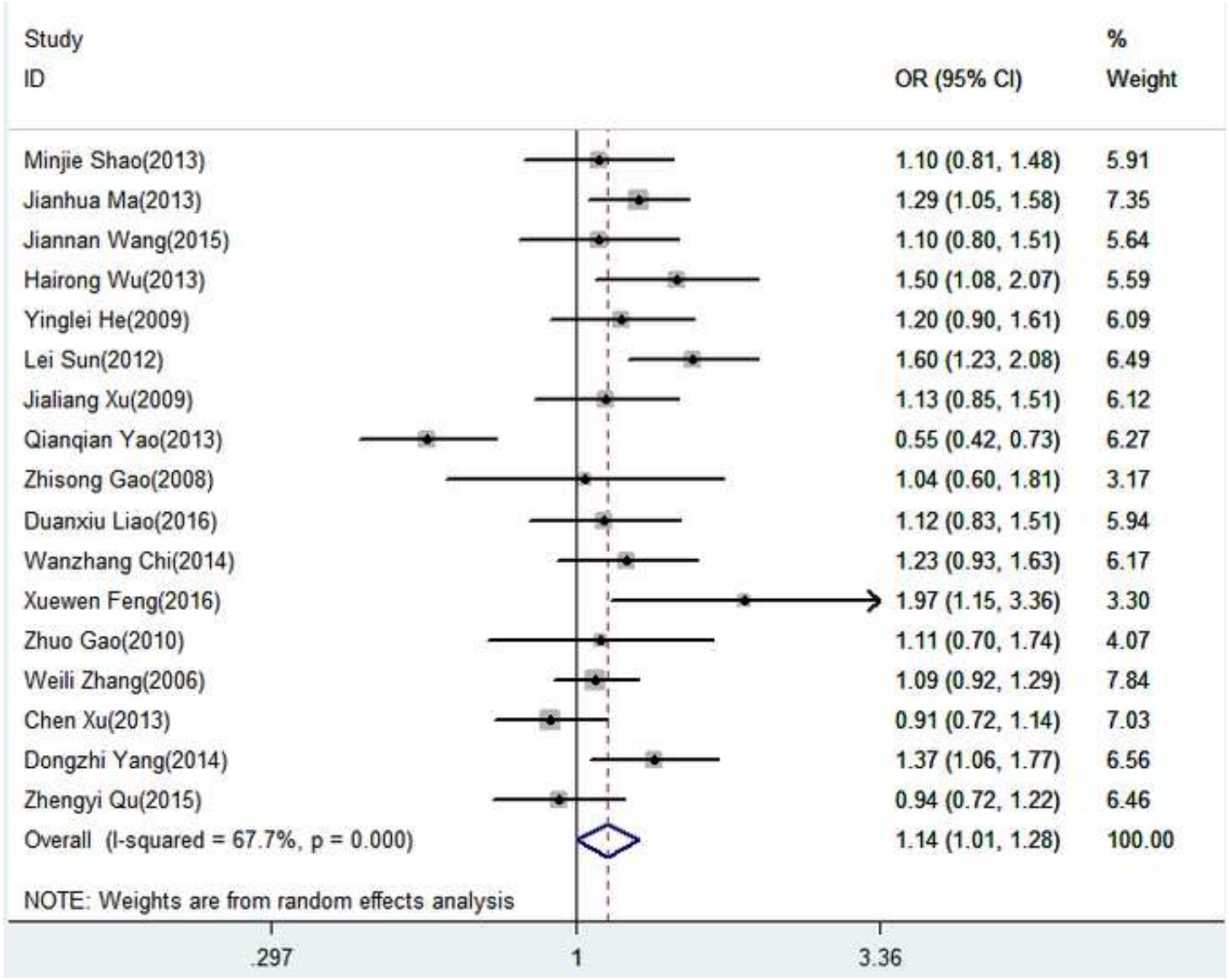

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2-3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	no

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Flow Diagram(Fig.1)

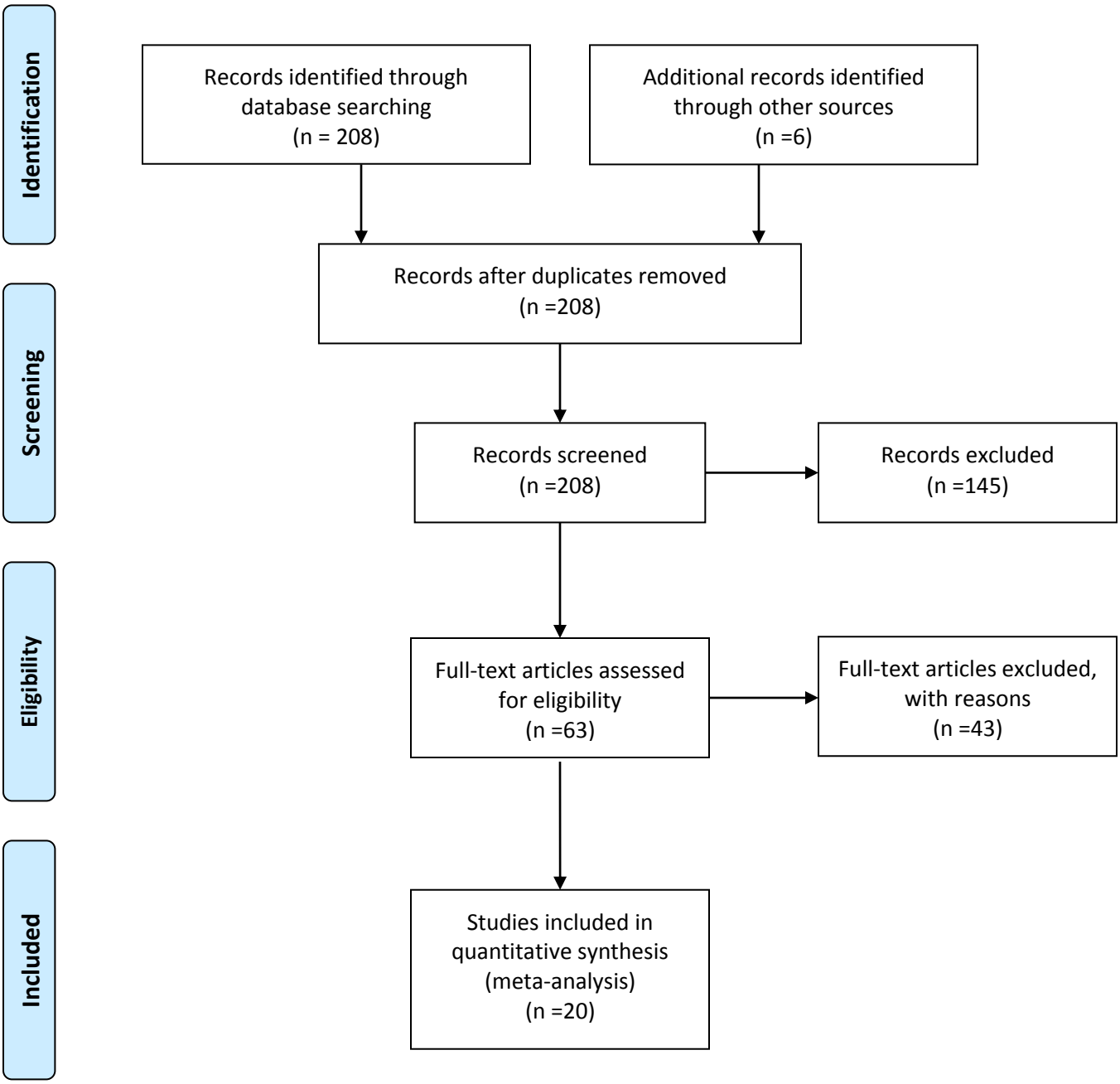

Figure 1: Flow diagram of the process of study selection.