The genome-wide supported CACNA1C gene polymorphisms and the risk of schizophrenia: an update meta-analysis

Yongping Liu
China Medical University
Xue Wu
China Medical University
Xi Xia
China Medical University
Jun Yao
China Medical University
Bao-jie Wang (wangbj77@163.com)
China Medical University https://orcid.org/0000-0003-1931-423X

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Abstract

Background: The CACNA1C gene was defined as the risk gene for schizophrenia in a large GWAS of European ancestory by Psychiatric Genomics Consortium. Previous meta-analyses have focused on the association between CACNA1C gene rs1006737 and schizophrenia. However, the present study focused on whether there was a racial difference in the effect of CACNA1C gene rs1006737 on schizophrenia. In addition, rs2007044 and rs4765905 were used to analyzed the risk of schizophrenia.

Methods: The pooled analysis, subgroup analysis, sensitivity analysis and publication bias were conducted.

Results: A total of 18 studies met the inclusion criteria, 14 for rs1006737 (15,213 cases and 19,412 controls), 3 for rs2007044 (6007 cases and 6,518 controls), and 2 for rs4765905 (2,435 cases and 2,639 controls). Rs2007044 and rs4765905 were also related to schizophrenia in the only conducted allele model. For rs1006737, the allele contrast model, dominant model, recessive model, codominance models, and complete overdominance model were performed, and the overall meta-analysis showed significant differences between rs1006737 and schizophrenia. However, race-based subgroup analysis of rs1006737 and found that the genotypes GG and GG+GA were only protective factors for schizophrenia in European populations, while the GA genotype of rs1006737 only reduced the risk of schizophrenia in Asian populations.

Conclusions: Rs1006737, rs2007044 and rs4765905 of CACNA1C gene were associated with susceptibility to schizophrenia. However, the influence model of rs1006737 on schizophrenia in Asian and European populations have both similarities and differences.

1. Introduction

Schizophrenia is a chronic, disabling brain disease that characterized by delusions, hallucinations and formal thought disorder, together with a decline in socio-occupational functioning [1]. Studies from twins [2] and adoptive families [3] have shown that genetic factor is an important cause of schizophrenia. It has been pointed out that L-type voltage gated calcium channel plays a unique role in behavioral extinction [4], inhibitory learning, and the maturation of adult cognitive function [5]. The two principal pore-forming subunits of L-type calcium channels expressed in neurons are the α1C or α1D subtypes [6]. Theα1C subtype is encoded by the *CACNA1C* gene, which was defined as the risk gene for schizophrenia in a large genome-wide association study (GWAS) of European ancestory by Psychiatric Genomics Consortium (PGC) [7]. Since then, a growing body of research has provided evidence for the key role of *CACNA1C* in schizophrenia in European populations. Ivorra *et al.* [8] has shown that rs1006737 polymorphism in the *CACNA1C* gene was strongly associated with schizophrenia and bipolar disorder in the Spanish population. Wolf *et al.* [9] suggested that the *CACNA1C* genotype may explains interindividual differents in amygdala volume among patients with schizophrenia in the German population. And it has been proven that the amygdala is not only involved in associative learning, but

also regulates additional cognitive processes, such as memory or attention [10]. Fatima *et al.* [11] detected a significant difference in the genotype and allele frequencies for rs4765905 between the patients and controls, confirming the hypothesis that *CACNA1C* gene was associated with schizophrenia in Pakistani population.

So, we were curious to see if *CACNA1C* gene had the same effect on schizophrenia in the Asian population as it did in the European population. The meta-analysis of Zheng *et al.* [12] and Jiang *et al.* [13] also proved that there was no heterogeneity between the two samples of *CACNA1C* gene rs1006737 in east Asian and European populations. The research of Kuanjun *et al.* [14] showed that rs1006737 in the *CACNA1C* gene was associated with both schizophrenia and major depressive disorder in the Han Chinese population. A meta-analysis about rs1006737 conducted by Nie *et al.* [15] provides additional evidence for association with SZ both in the European and Asian populations when they stratified the samples by ethnicity. However, to follow up on top European GWAS hits, Takahashi *et al.* [16] genotyped implicated loci in additional schizophrenia family samples from China and Japan, founding no association between 12 polymorphisms (including rs4765905 in the *CACNA1C* gene) and schizophrenia. Consistent with this, Hori *et al.* [17] found no significant difference in the genotype or allele frequency of rs1006737 in the *CACNA1C* gene between schizophrenia patients and controls in the Japanese population. In addition, Sudesh *et al*. [18] analyzed 12 single nucleotide polymorphism (SNPs), including rs4765905, in 536 Asian families and found no evidence of any SNP association with schizophrenia.

In summary, there is no consensus on whether *CACNA1C* is associated with schizophrenia and whether there are differences in susceptibility to schizophrenia between Asian and European populations. Hence, we provide a more comprehensive and updated meta-analysis of the association between polymorphisms of *CACNA1C* gene and schizophrenia by including case-control studies.

2. Methods

2.1. Literature search strategy

Eligible studies were identified by searching two online electronic databases (PubMed and the China National Knowledge Infrastructure [CNKI]). PubMed (2011–present) were used to retrieve English studies only, while the CNKI (2013–present) was used to retrieve Chinese studies only. Only completed peer-review studies are likely to be included in our research. The last search update was November 2019. The search terms were rs1006737, rs2007044, rs4765905, *CACNA1C* and schizophrenia. The studies included in our meta-analysis met the following inclusion criteria: (1) included patients with schizophrenia; (2) contained detailed genotype and allele frequencies; (3) included healthy controls; (4) stated that *CACNA1C* is susceptible to schizophrenia; and (5) were case-control studies. The case-control studies met the following exclusion criteria: (1) no patients with schizophrenia; (2) lacked genotype frequency data; (3) no control population; (4) abstracts, reviews and meta-analyses; (5) duplicate sample information; and (6) data included in the PGC GWAS from 2014.

2.2 Data extraction

The methods of data extraction, publication bias assessment, heterogeneity detection, sensitivity detection and statistical analysis are the same as our previous meta-analysis [19], as follows: data extraction was carried out independently by two authors (initials) in strict accordance with the inclusion and exclusion criteria of this meta-analysis. Disagreement between the two authors was negotiated until a consensus was reached. The following data were extracted: (1) basic information such as the first author's last name and publication year; (2) sample information such as the region, race, source of control, mean age of the control group, gender index of the case and control groups and number of individuals in the case and control groups; and (3) number of genotypes between cases and controls.

2.3. Assessment of publication bias

Publication bias was assessed by funnel plots; the x-axis represents the log of the risk ratio and the y-axis represents the standard error of the log of the OR. By observing the symmetry of the funnel plots, it can be judged whether publication bias exists in the included study. The degree of publication bias was evaluated using Egger's test [20]; P values > 0.05 indicate publication bias.

2.4. Statistical analysis

Pearson's chi-square test was used to assess the Hardy–Weinberg equilibrium (HWE) for the controls in each study. The strength of association between the rs1006737, rs2007044 and rs4765905 polymorphism and the risk of schizophrenia was measured by odd ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity among studies was tested by the χ^2-based Cochran's Q-test [21] and I^2 statistics [22]. For the qualitative Cochran's Q-test, a *P* value > 0.1 indicates a lack of heterogeneity; thus, the fixed effects model (Mantel–Haenszel method) was used. On the contrary, a *P* value < 0.1 indicates the existence of heterogeneity; thus, the random effects model (M–H heterogeneity method) was used [23]. For quantitative I^2 statistics, the I^2 statistic represents the variation between studies as a percentage of the total variation. The degree of heterogeneity was divided into low (< 25%), moderate (25–75%) and high (> 75%) groups. Firstly, the allele contrast model (A vs. a) was used to estimate the effect of the risk allele on schizophrenia risk (A = risk allele). Subsequently, multiple pairwise comparisons (e.g. AA vs. aa; AA vs. Aa or Aa vs. aa) were used to indicate the most appropriate genetic model (A = risk allele). Subgroup analyses were conducted to evaluate the effects of race on the risk of schizophrenia.

Sensitivity analysis was carried out to assess not only the stability and reliability of the combined results of the meta-analysis but also whether the pooled results were affected by a single study.

All statistical tests were performed using State version 12.0 (StataCorp LP, College Station, TX, USA). A *P* value < 0.05 is considered statistically significant (two tailed).

3. Results

A total of 67 articles were identified by PubMed and CNKI database searches. Excluding those that did not meet the inclusion criteria, 18 studies remained. Specifically, 14 studies with 15213 cases and 19412

controls involved rs1006737, 3 studies with 6007 cases and 6518 controls involved rs2007044, and 2 studies with 2435 cases and 2639 controls involved rs4765905. A PRISMA flowchart describing the selection and screening of studies for meta-analysis is shown in Fig.1. The main characteristics of the included studies are listed in Table 1 and the allele frequencies and genotype distributions in all studies are shown in Table 2.

Table 1. The main characteristics of the studies included in the meta-analysis

Author	Year	Country	Racial	Source of control group	Mean age of control group	Gender index (case)	Gender index (control)	Case/Control
Rs1006737								
Fatima [11]	2017	Pakistani	Caucasian	Population based	44	0.33	0.71	508/300
Lubeiro [24]	2018	Spain	Caucasian	Population based	29.52	0.72	0.98	50/101
Mallas [25]	2016	Mixed	Mixed	Population based	35.79	0.26	0.85	63/124
Porcelli [26]	2015	Korean	Asian	Hospital based	45.36	0.73	1.22	176/326
Ivorra [8]	2014	Spain	Caucasian	Mixed	43.61	0.79	0.75	3063/2847
He [14]	2013	China	Asian	Population based	30.6	0.53	0.86	1235/1235
Guan [27]	2013	China	Asian	Population based	34.2	0.87	0.83	1430/1570
Galaktionova [28]	2013	Russia	Caucasian	Population based	36	2.24	0.90	188/192
Zheng [12]	2013	China	Asian	Population based	32.4	1.05	1.04	5893/6319
Hori [17]	2012	Japan	Asian	Population based	46	0.82	1.93	552/1132
Zhang [29]	2011	China	Asian	Population based	22.3	0.49	0.60	318/401
Nyegaard [30]	2010	Denmark	Caucasian	Population based	-	-	-	976/1489
Bigos [31]	2010		Caucasian	Population based	33.09	0.230	1.16	282/440
Green [32]	2009	UK	Caucasian	Population based	-	0.47	1.04	479/2936
Rs2007044								
Bustillo [33]	2017	United States	Caucasian	Population based	36	0.26	0.37	53/129
Zhang [34]	2018	China	Asian	Hospital based	27.14	0.15	0.28	53/129
Rs4765905								
Sudesh [18]	2018	India	Indian	Population based	38.73	1.01	0.483	1005/1069

Notes: Gender index = female/male; Guan's study included the main characteristics of both rs1006737 and rs4765905; Zheng's study included the main characteristics of both rs1006737 and rs2007044.

Table 2. The distributions of the allele frequency and genotype in the included studies

Author	Year	Genotype distribution						*P*HWE	Allele frequency			
		Cases, n			Controls, n				Cases (%)		Control (%)	
		AA	Aa	aa	AA	Aa	aa		A	a	A	a
Rs1006737												
Lubeiro	2018	25	23	2	58	38	5	0.70	73	27	154	48
Fatima	2017	393	84	17	235	54	9	0.01	870	118	524	72
Mallas	2016	23	30	10	56	51	17	0.33	76	50	163	85
Porcelli	2015	153	23	0	301	23	2	0.11	329	23	625	27
Ivorra	2014	1417	1271	293	1420	1124	240	0.41	4105	1857	3964	1604
He	2013	996	220	14	1053	166	9	0.39	2212	248	2272	184
Guan	2013	1061	343	26	1223	327	20	0.72	2465	395	2773	367
Galaktionova	2013	78	85	23	80	90	22	0.66	241	131	250	134
Zheng	2013	5239	635	19	5706	597	16	0.93	11113	673	12009	629
Hori	2012	480	70	2	1002	127	3	0.63	1030	74	2131	133
Zhang	2011	280	37	1	357	42	2	0.53	597	39	756	46
Nyegaard	2010	402	444	130	656	675	158	0.42	1248	704	1987	991
Bigos	2010	120	115	47	191	205	44	0.31	355	209	587	293
Green	2009	205	208	66	1367	1233	336	0.02	618	340	3967	1095
Rs2007044												
Zheng	2014	2797	2540	559	3166	2597	559	0.42	8134	3658	8929	3715
Bustillo	2017	26	23	9	35	21	11	0.02	75	41	91	43
Zhang	2018	24	25	4	58	57	14	1.00	73	33	173	85
Rs4765905												
Guan	2013	1307	360	33	1195	352	24	0.74	2434	426	2741	399
Sudesh	2018	579	307	51	668	286	38	0.29	1465	409	1622	362

Notes: P_{HWE}, *P*-value of the Hardy–Weinberg equilibrium; A is the wild-type allele, and a is the mutant allele.

3.1. Rs1006737 polymorphism of *CACNA1C*

In the present study, A was defined as the risk allele. The allele contrast model (A vs. G), dominant model (GA+AA vs. GG) recessive model (AA vs. GG+GA), codominance models (AA vs. GG and GA vs. GG), and complete overdominance model (GG+AA vs. GA) were used to calculate the pooled ORs. All models except for codominance models (GA vs. GG) was performed in the fixed effects model (M–H) due to the low heterogeneity, while codominance models (GA vs. GG) was performed in the random effects model (M-H) due to it's high heterogeneity (I^2=99%).

First, the overall meta-analysis of rs1006737 was conducted. Significant differences between rs1006737 and schizophrenia risk were observed in the allele contrast model (A vs. G), OR = 1.151, 95% CI = 1.100-1.204, I^2 = 0.0%, *P* heterogeneity = 0.867, *P* = 0.000; dominant model (GA+AA vs. GG), OR = 1.169, 95% CI = 1.107-1.234, I^2 = 0.0%, *P* heterogeneity = 0.786, *P* = 0.000; recessive model (AA vs. GG+GA), OR = 1.215, 95% CI = 1.085-1.360, I^2 = 0.0%, *P* heterogeneity = 0.999, *P* = 0.001; codominance models (AA vs. GG), OR = 1.296, 95% CI = 1.151-1.459, I^2 = 0.0%, *P* heterogeneity = 0.993, *P* = 0.000; codominance models (GA vs. GG), OR = 0.064, 95% CI = 0.024-0.169, I^2 = 99%, *P* heterogeneity = 0.000, *P* = 0.000; and complete overdominance model (GG+AA vs. GA), OR = 0.897, 95% CI = 0.849-0.948, I^2 = 26.1%, *P* heterogeneity = 0.173, *P* = 0.000. The main results are listed in Table 3.

Then, subgroup analysis based on race was performed for rs1006737. For Caucasian population, there were 7 studies including 5546 patients with schizophrenia and 8305 controls were included. Rs1006737 was associated with schizophrenia in all genetic models (A vs. G, OR = 1.121, 95% CI = 1.060-1.186, *P* =

0.000; GA+AA vs. GG, OR = 1.127, 95% CI = 1.047-1.213, *P* = 0.001; AA vs. GG+GA, OR = 1.203, 95% CI = 1.067-1.357, *P* = 0.003; AA vs. GG, OR = 1.284, 95% CI = 1.131-1.456, *P* = 0.000; GA vs. GG, OR = 0.279, 95% CI = 0.132-0.587, *P* = 0.001) except the complete overdominance model (GG+AA vs. GA, OR = 0.959, 95% CI = 0.891-1.033, *P* = 0.272).

While for Asian population, there were 6 studies including 9604 patients with schizophrenia and 10983 controls were included. Rs1006737 was associated with schizophrenia in allele contrast model (A vs. G), OR = 1.206, 95% CI = 1.117 - 1.303, *P* = 0.000, dominant model (GA+AA vs. GG), OR = 1.219, 95% CI = 1.123 - 1.323, *P* = 0.000, codominance models (GA vs. GG), OR = 0.008, 95% CI = 0.004 - 0.017, *P* = 0.000, and complete overdominance model (GG+AA vs. GA), OR = 0.827, 95% CI = 0.761-0.899, *P* = 0.000, but not in the recessive model (AA vs. GG+GA), OR = 1.336, 95% CI = 0.922-1.936, *P* = 0.125 and codominance models (AA vs. GG), OR = 1.384, 95% CI = 0.955-2.006, *P* = 0.086. The main results are listed in Table 4.

3.2. Rs2007044 and rs4765905 polymorphisms of *CACNA1C*

Allele G of rs2007044 and allele C of rs4765905 were defined as the risk allele, respectively. Since relatively few studies related to rs2007044 and rs4765905 were included, only the allele model for these two polymorphisms was analyzed. Significant differences between patients and controls were observed both in rs2007044 (G vs. A, OR = 1.080, 95% CI = 1.023-1.139, *P* = 0.006) and in rs4765905 (C vs. G, OR = 1.225, 95% CI = 1.100-1.364, *P* = 0.000). The main results are listed in Table 3.

Table 3. The main results of the overall meta-analysis of polymorphisms in *CACNA1C*.

Genetic model	OR	95% CI	*P*-value	I^2(%)	P_h	Combination method
Rs1006737						
Allele contrast	1.151	1.100-1.204	**0.000**	0.0	0.867	fixed effects model
Dominant	1.169	1.107-1.234	**0.000**	0.0	0.786	fixed effects model
Recessive	1.215	1.085-1.360	**0.001**	0.0	0.999	fixed effects model
Codominance AA vs. GG	1.296	1.151-1.459	**0.000**	0.0	0.993	fixed effects model
Codominance GA vs. GG	0.064	0.024-0.169	**0.000**	99.0	**0.000**	random effects model
Complete overdominance	0.897	0.849-0.948	**0.000**	26.1	0.173	fixed effects model
Rs2007044						
Allele contrast	1.080	1.023-1.139	**0.006**	0.0	0.785	fixed effects model
Rs4765905						
Allele contrast	1.225	1.100-1.364	**0.000**	0.0	0.719	fixed effects model

Notes: I^2 represents the variation in OR attributable to heterogeneity. P_h represents the *P*-value of the Q-test for heterogeneity

Abbreviations: CI, confidence interval; OR, odds ratio

Table 4. Subgroup analysis of the association between rs1006737 and the risk of schizophrenia

Race	Summary of pooled ORs			Heterogeneity test	
	OR	95% CI	*P*-value	I^2(%)	P_h
Asian					
Allele contrast	1.206	1.117 -1.303	**0.000**	0.0	0.583
Dominant	1.219	1.123 -1.323	**0.000**	0.0	0.484
Recessive	1.336	0.922-1.936	0.125	0.0	0.939
Codominance AA vs. GG	1.384	0.955-2.006	0.086	0.0	0.932
Codominance GA vs. GG	0.008	0.004 -0.017	**0.000**	83.6	**0.000**
Complete overdominance	0.827	0.761-0.899	**0.000**	0.0	0.434
Caucasian					
Allele contrast	1.121	1.060-1.186	**0.000**	0.0	0.964
Dominant	1.127	1.047-1.213	**0.001**	0.0	0.919
Recessive	1.203	1.067-1.357	**0.003**	0.0	0.987
Codominance AA vs. GG	1.284	1.131-1.456	**0.000**	0.0	0.893
Codominance GA vs. GG	0.279	0.132-0.587	**0.001**	98.0	**0.000**
Complete overdominance	0.959	0.891-1.033	0.272	0.0	0.457

Notes: I^2 represents the variation in OR attributable to heterogeneity. P_h represents the *P*-value of the Q-test for heterogeneity **Abbreviations:** CI, confidence interval; OR, odds ratio

3.3. Sensitivity analysis

Following sequential exclusion of each study, the combined effect obtained by the new meta-analysis was compared with the total effect. No statistical significance was observed, indicating that our analysis results are reliable and stable, and the range of OR estimates (Table 5) shows that none of the individual studies "reversed" the observed total effect.

Table 5. Results of the sensitivity analysis of rs1006737 in *CACNA1C*.

Excluded					
Study	**Sample**	**OR**	**95% CI**	***P*-value**	P_h
Lubeiro	Caucasian	1.1506206	1.0998443-1.2037411	0.000	0.815
Fatima	Caucasian	1.1546086	1.1033095-1.2082929	0.000	0.878
Mallas	Mixed	1.1497633	1.0989355-1.202942	0.000	0.826
Porcelli	Asian	1.1485037	1.0978361-1.2015097	0.000	0.903
Ivorra	Caucasian	1.166579	1.1047648-1.2318518	0.000	0.866
He	Asian	1.1393697	1.0879437-1.1932266	0.000	0.981
Guan	Asian	1.1452636	1.0925845-1.2004827	0.000	0.847
Galaktionova	Caucasian	1.1542471	1.1029066-1.2079774	0.000	0.863
Zheng	Asian	1.1498204	1.094684-1.2077338	0.000	0.815
Hori	Asian	1.1508508	1.0996418-1.2044445	0.000	0.814
Zhang	Asian	1.1517017	1.1007836-1.204975	0.000	0.821
Nyegaard	Caucasian	1.154137	1.0994588-1.2115344	0.000	0.821
Bigos	Caucasian	1.1496404	1.0980188-1.2036888	0.000	0.818
Green	Caucasian	1.151419	1.0981367-1.2072866	0.000	0.814

Notes: P_h represents the *P*-value of the Q-test for heterogeneity

Abbreviations: CI, confidence interval; OR, odds ratio

3.4. Publication bias

The symmetry of the funnel plots was used to detect the existence of publication bias (Figures 2–9), while Egger's test quantitatively detected symmetry. Due to the lack of studies on rs4765905, the efficacy of Egger's test was limited, so that the symmetry of funnel plot could not be detected. No publication bias was detected for rs2007044 and in the allele contrast model (G vs. A), t = -0.43, P = 0.743. No publication bias was detected for rs1006737 in the allele contrast model (A vs. G), t = 0.86, P = 0.407, dominant model (GA+AA vs. GG), t = 0.52, P = 0.613, recessive model (TT vs. GG+GT), t = -0.68, P = 0.507, codominance models (AA vs. GG), t = -0.38, P = 0.713, and complete overdominance model (GG+TT vs. GT), t = -0.31, P = 0.762 . However, there was a publication bias for rs1006737 in the codominance models (AA vs. GG), t = -3.88, P = 0.002.

4. Discussion

CACNA1C was associated with bipolar disorder [35], autism spectrum disorder [36], major depression [14] and other central nervous system (CNS) disorders [37]. However, the association between the *CACNA1C* gene and schizophrenia has not been determined. It is also unclear whether *CACNA1C* gene has the same effect on schizophrenia in Asian and European populations. Therefore, we conducted a more detailed and comprehensive meta-analysis on the association between rs1006737, rs2007044 and rs4765905 of *CACNA1C* gene and schizophrenia. In the overall analysis, rs1006737 was associated with the risk of schizophrenia in all five genetic models, and rs2007044 and rs4765905 were also related to schizophrenia in the only conducted allele model, implying *CACNA1C* gene may influence the risk of schizophrenia. This view is consistent with the results of previous meta-analyses [12, 13, 15, 18, 38, 39].

However, we conducted a race-based subgroup analysis of rs1006737 and found that the effects of rs1006737 on schizophrenia in Asian and European populations have both similarities and differences. According to the analysis results of allele model (A vs. G) and dominant model (GA+AA vs. GG), the effect of rs1006737 on schizophrenia in European and Asian populations was consistent: allele A and genotype GA+AA are protective factors for the development of schizophrenia. However, analysis of the recessive (AA vs. GG+GA) and codominant (AA vs. GG) models showed that the genotypes GG+GA was only risk factors for schizophrenia in European populations, but had no effect on Asian populations. In addition, in the complete overdominance model (GG+AA vs. GA), the GA genotype of rs1006737 only reduced the risk of schizophrenia in Asian populations, but did not affect the susceptibility of schizophrenia in European populations. Thus, we suggest that the effect of rs1006737 on schizophrenia is racially diverse.

The current study has two limitations: due to significant heterogeneity (I^2=99.0%) and publication bias (Egger's test P = 0.002), the codominant model (GA vs. GG) was not reliable and were not analyzed as a valid gene model for rs1006737. In addition, since there are few studies on the association between rs2007044 and rs4765905 and schizophrenia, more relevant high-quality studies are needed to support our analysis.

The advance of the current study as compared to the literature that already exists were: Firstly, the current study included more detailed and comprehensive studies. A recent meta-analysis of the *CACNA1C* gene

and schizophrenia [38] included 9 studies on the association between rs1006737 and schizophrenia, while the current study included 14 studies on the association between rs1006737 and schizophrenia, including 8 articles [11, 12, 14, 17, 27, 29, 30, 32] identical to [38] and 6 studies [8, 24-26, 28, 31] not included in [38]. Secondly, compared with most of the meta-analysis of *CACNA1C* and schizophrenia, the current study included not only studies on rs1006737 and schizophrenia, but also studies on the association between rs2007044 and rs4765905 and schizophrenia. Although the study of Xiao *et al.* [39] also included these three sites, it only included samples from Asian populations. While the current study included samples from Asian and European populations, providing a richer source of samples. Thirdly, the current study focused on comparing the impact of rs1006737 on Asian and European population. The conclusion is that the influence model of rs1006737 on schizophrenia in Asian and European populations have both similarities and differences. This was a novel and objective conclusion we put forward based on the analysis results.

5. Conclusion

CACNA1C genes rs1006737,rs2007044 and rs4765905 were associated with susceptibility to schizophrenia. However, the influence model of rs1006737 on schizophrenia in Asian and European populations have both similarities and differences.

Abbreviations

GWAS – genome-wide association study;

SNP – single nucleotide polymorphism;

PGC – Psychiatric Genomics Consortium;

OR – odds ratio;

95% CI – 95% confidence interval

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analyzed during this study are include in this published article.

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Figures

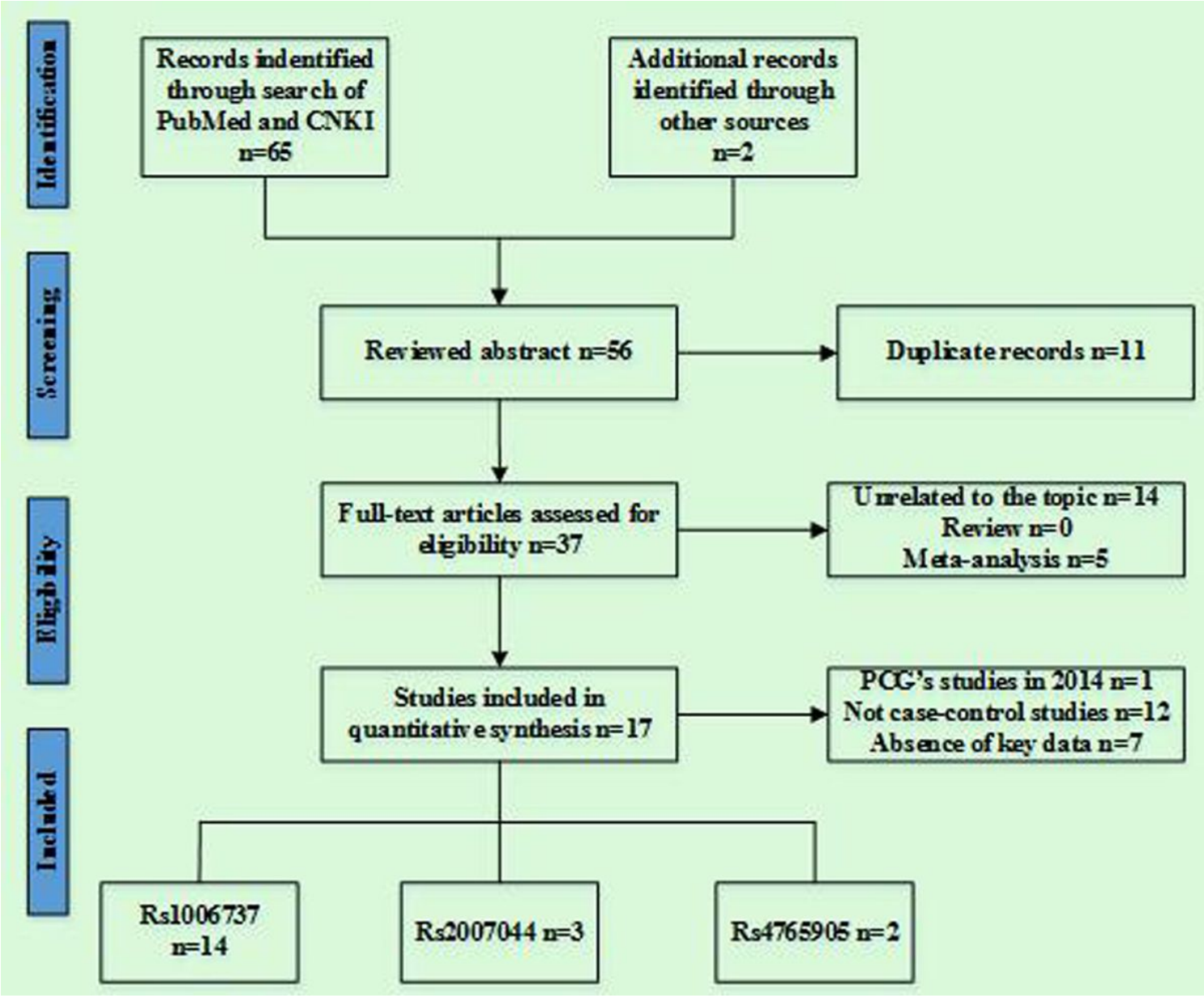

Figure 1

Flow diagram for the search and selection of included studies. A total of 67 relevant English studies were retrieved from the PubMed and CNKI databases. Following removal of studies that did not meet our inclusion criteria, a total of 19 studies were included in our meta-analysis, including 14 studies for rs1006737, 3 studiies for rs2007044, and 2 studies for rs4765905.

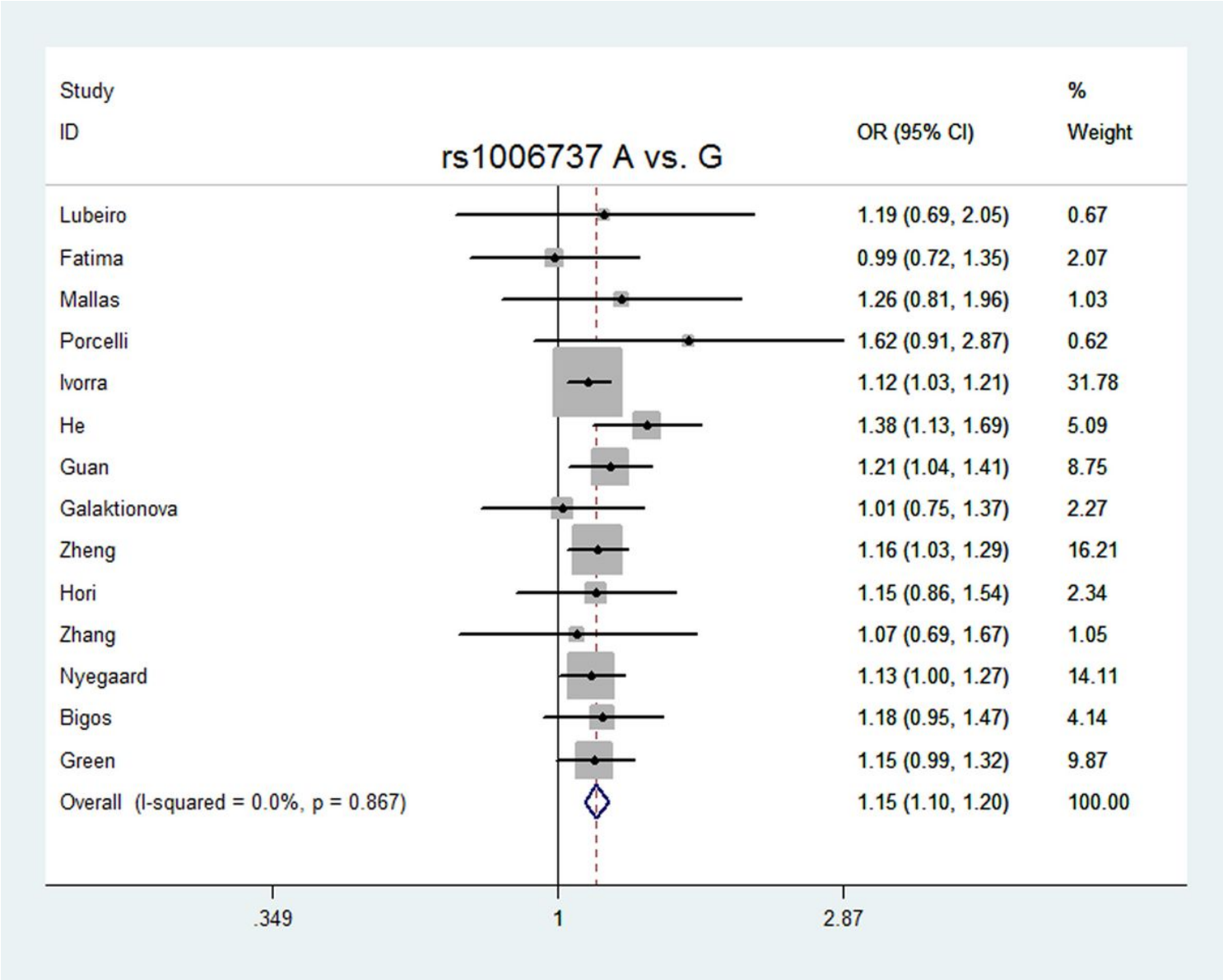

Figure 2

Forest plot of the allele contrast model (A vs. G) of rs1006737. Significant differences between rs1006737 and schizophrenia risk were observed in the allele contrast model (T vs. G), OR = 1.151, 95% CI = 1.100–1.204, P heterogeneity = 0.867, P = 0.000.

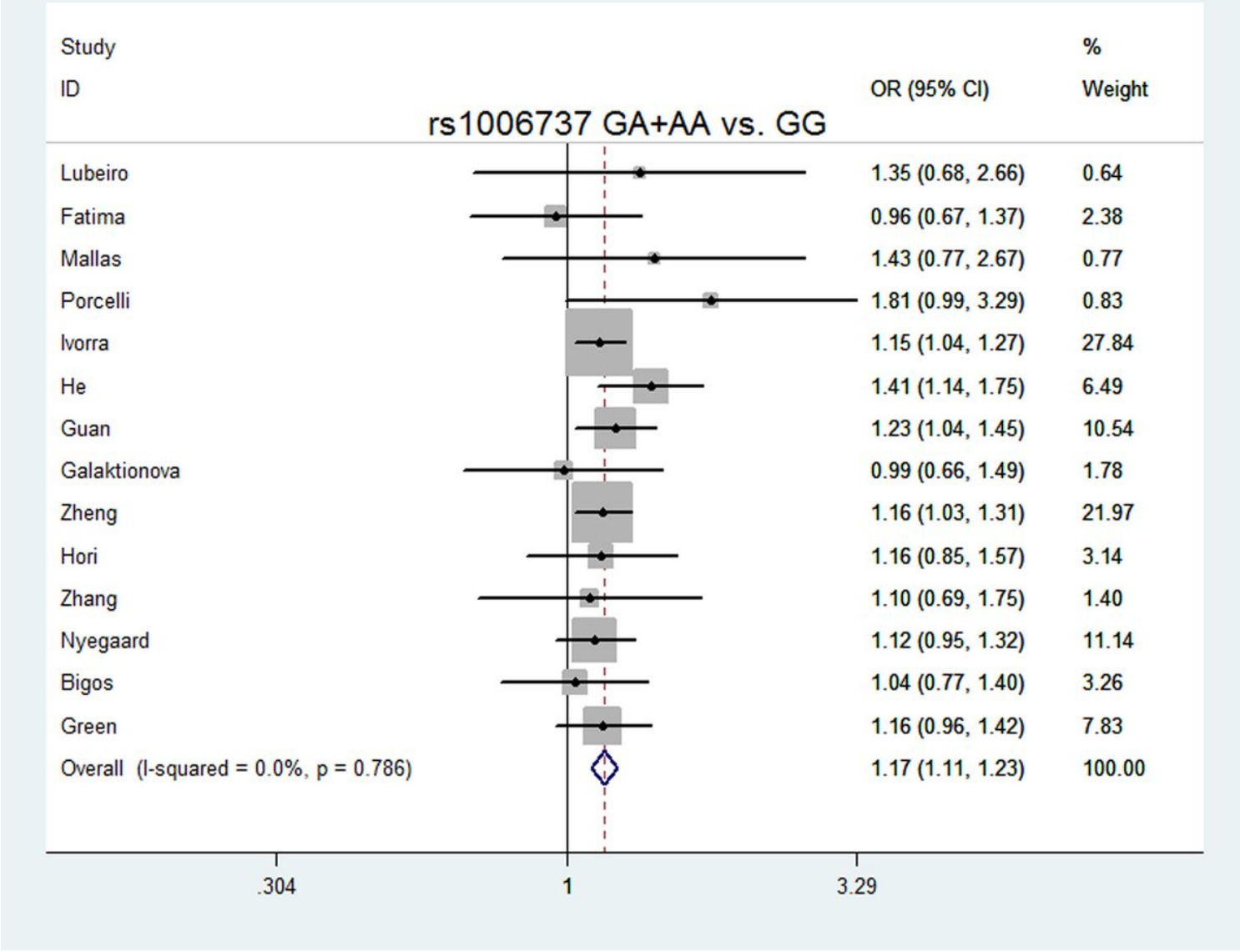

Figure 3

Forest plot of the dominant model (GA+AA vs. GG) of rs1006737. Significant differences between rs1006737 and schizophrenia risk were observed in the dominant model (GA+AA vs. GG), OR = 1.169, 95% CI = 1.107–1.234, P heterogeneity = 0.786, P = 0.000.

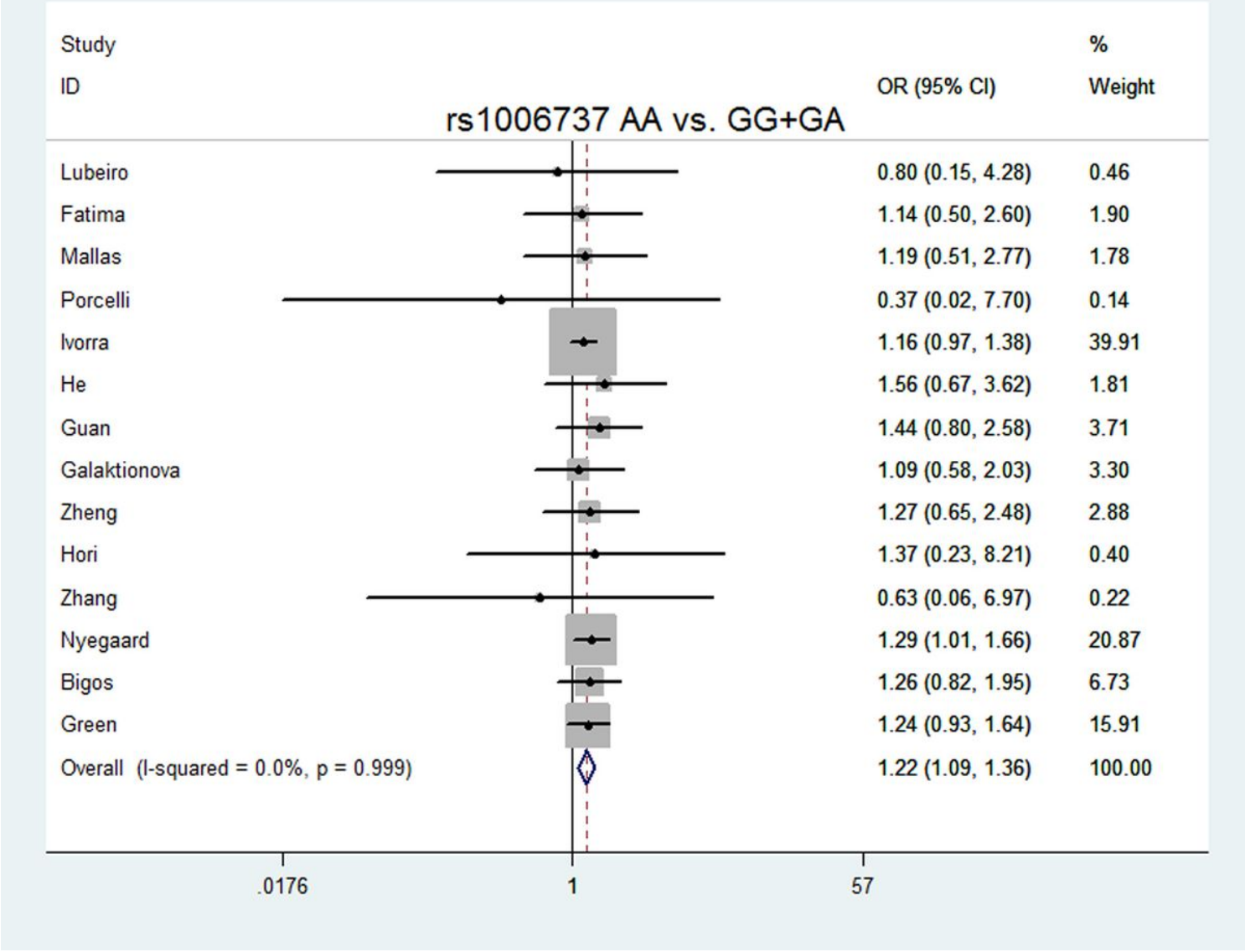

Figure 4

Forest plot of the recessive model recessive model (AA vs. GG+GA) of rs1006737. Significant differences between rs1006737 and schizophrenia risk were observed in the recessive model (AA vs. GG+GA), OR = 1.215, 95% CI = 1.085−1.360, P heterogeneity = 0.999, P = 0.001.

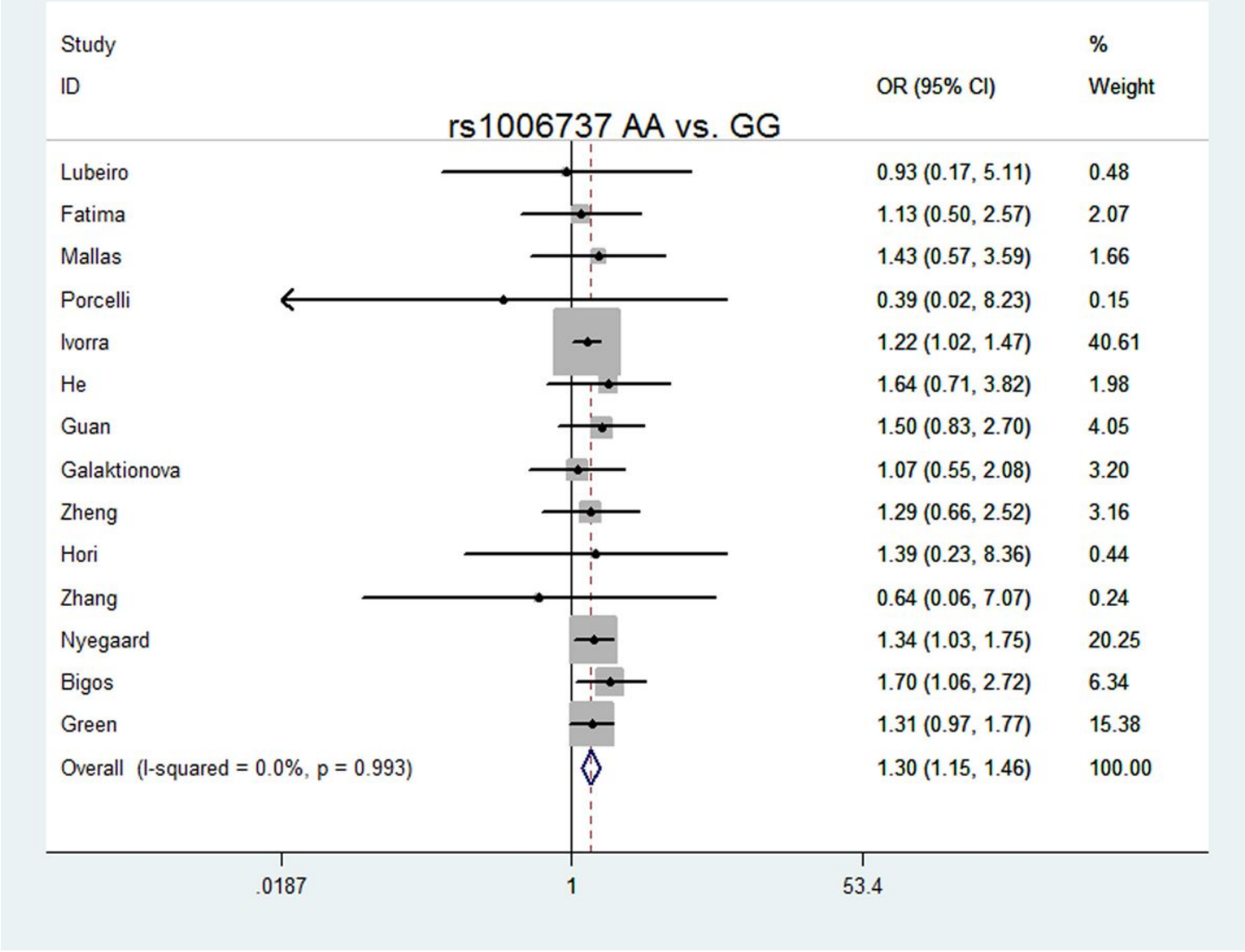

Figure 5

Forest plot of the complete codominance models (AA vs. GG) of rs1006737. Significant differences between rs1006737 and schizophrenia risk were observed in the codominance models (AA vs. GG), OR = 1.296, 95% CI = 1.151−1.459, P heterogeneity = 0.993, P = 0.000.

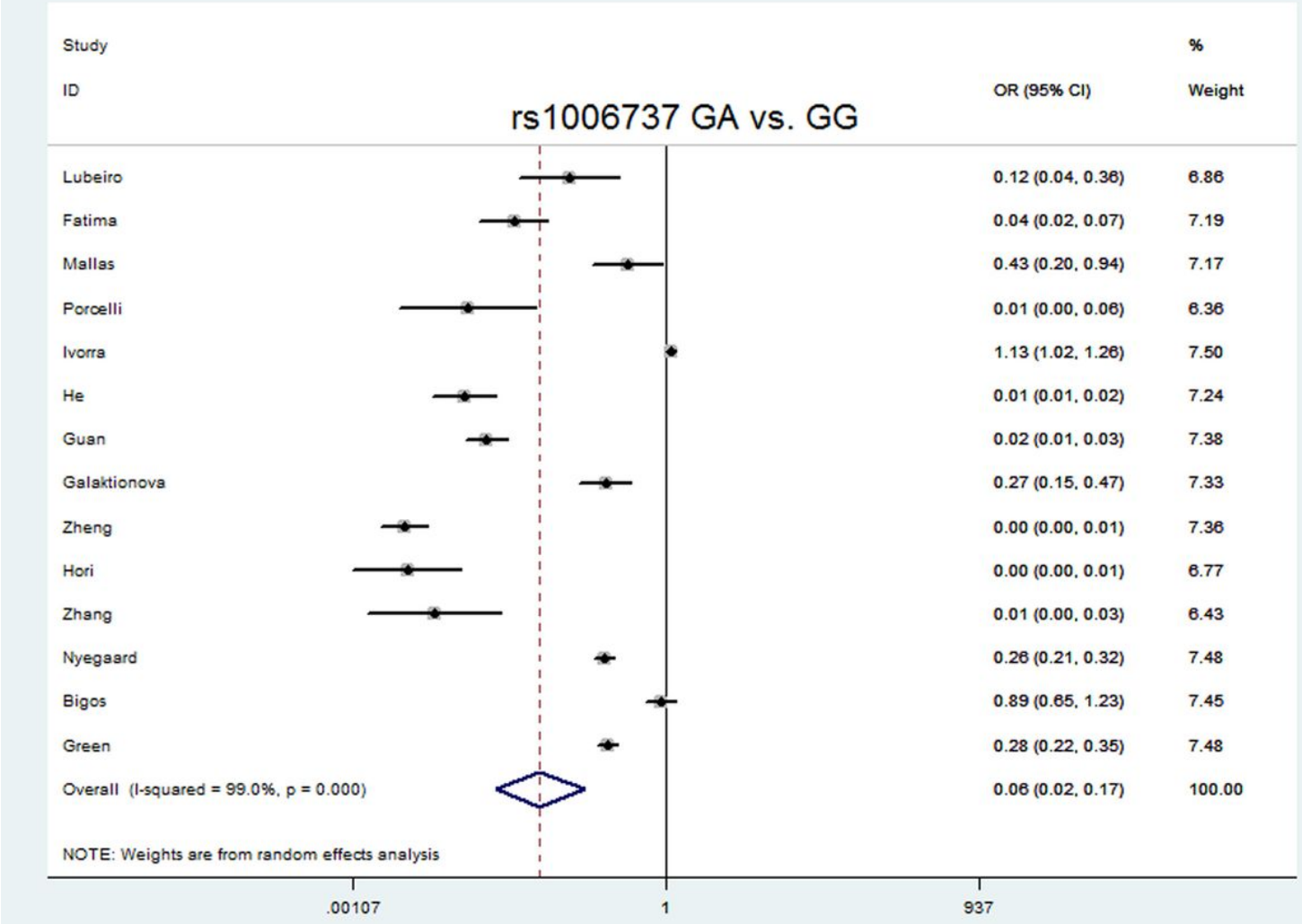

Figure 6

Forest plot of the codominance models (GA vs. GG) of rs1006737. Significant differences between rs1006737 and schizophrenia risk were observed in the codominance models (GA vs. GG)., OR = 0.064, 95% CI = 0.024–0.169, P heterogeneity = 0.000, P = 0.000.

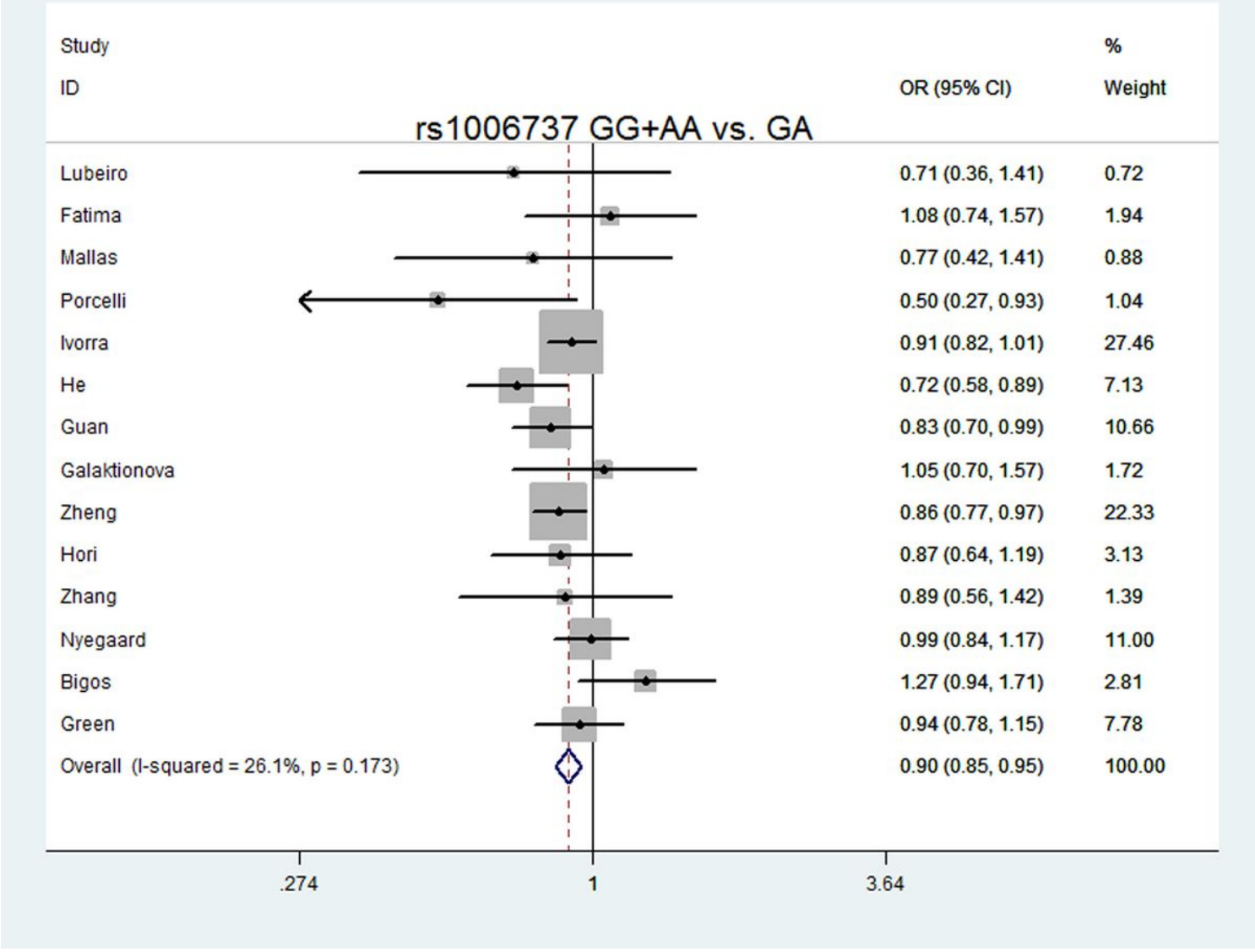

Figure 7

Forest plot of the complete overdominance model (GG+AA vs. GA) of rs1006737. Significant differences between rs1006737 and schizophrenia risk were observed in the complete overdominance model (GG+AA vs. GA). OR = 0.897, 95% CI = 0.849–0.948, P heterogeneity = 0.173, P = 0.000.

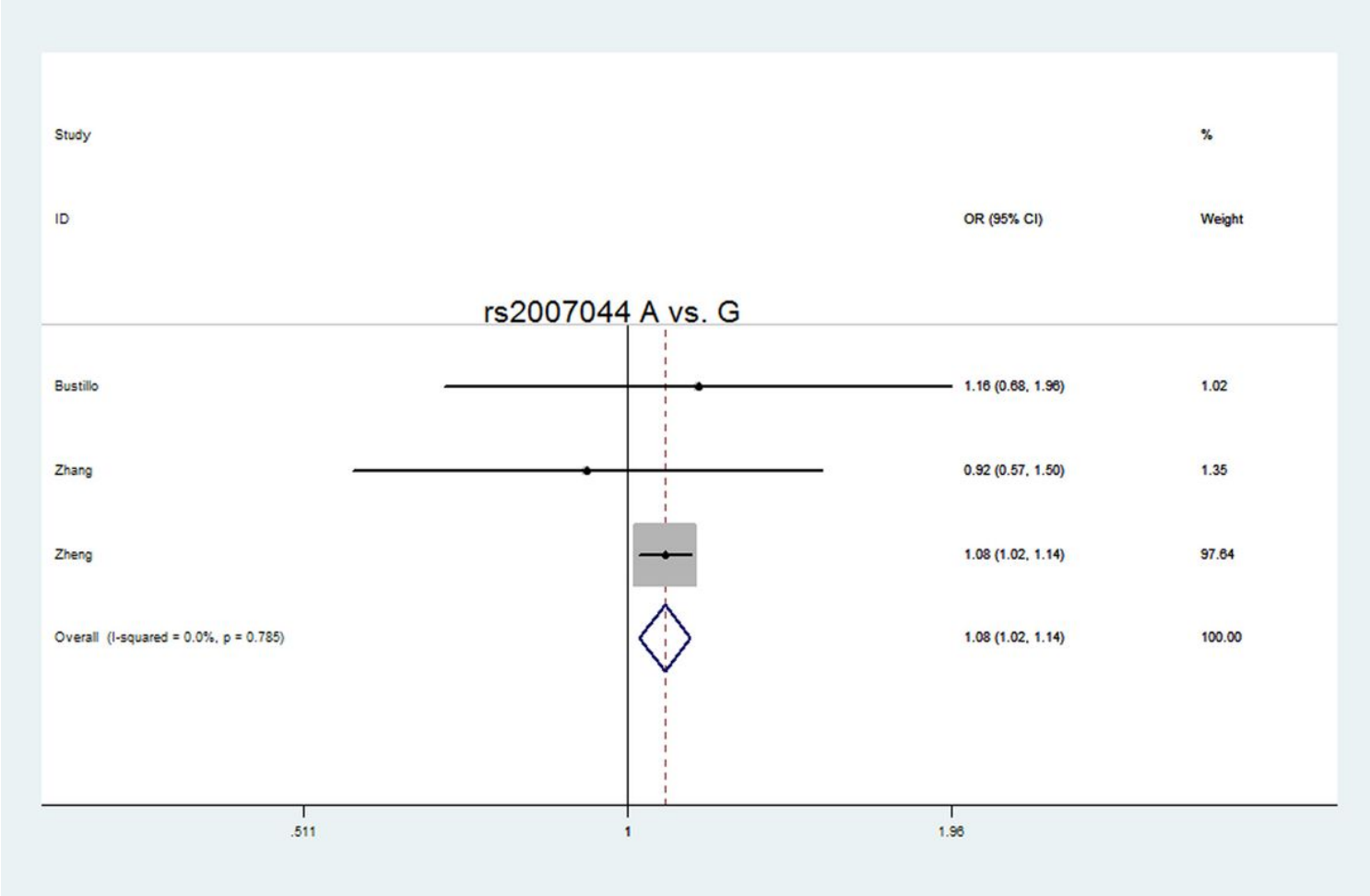

Figure 8

Forest plot of the allele contrast model (A vs. G) of rs2007044. Significant differences between rs2007044 and schizophrenia risk were observed in the allele contrast model (A vs. G). OR = 1.080, 95% CI = 1.023–1.139, P heterogeneity = 0.785, P = 0.006.

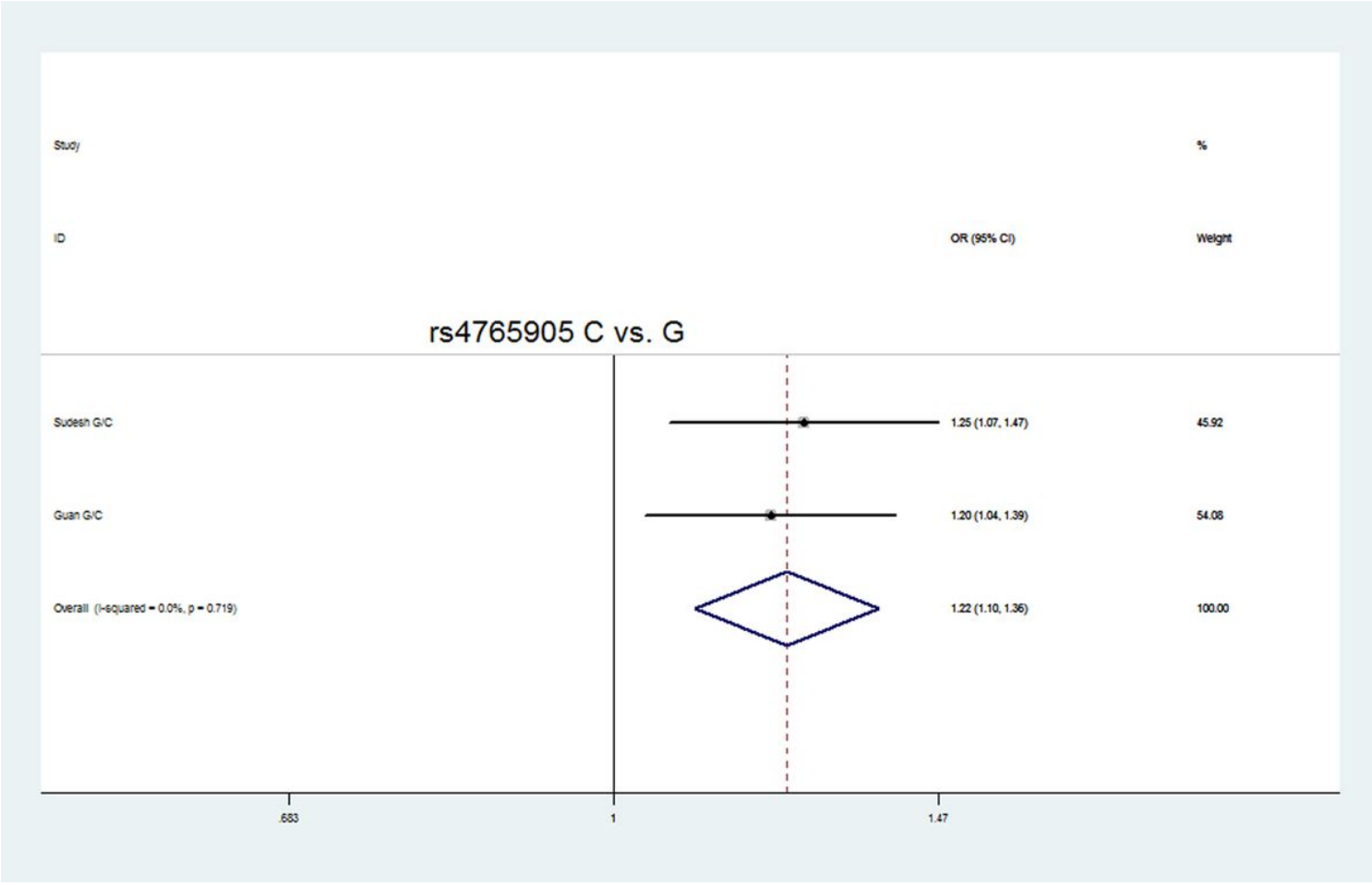

Figure 9

Forest plot of the allele contrast model (C vs. G) of rs4765905. Significant differences between rs4765905 and schizophrenia risk were observed in the allele contrast model (C vs. G). OR = 1.225, 95% CI = 1.100−1.364, P heterogeneity = 0.719, P = 0.000.

Supplementary Files

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

- PRISMANMAchecklist.docx