The genome-wide supported *CACNA1C* gene polymorphisms and the risk of schizophrenia: an updated 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

Research article

Keywords: meta-analysis, CACNA1C, rs1006737, rs2007044, rs4765905, schizophrenia

Posted Date: April 17th, 2020

DOI: https://doi.org/10.21203/rs.2.24453/v2

Version of Record: A version of this preprint was published at BMC Medical Genetics on August 8th, 2020. See the published version at https://doi.org/10.1186/s12881-020-01084-0.

Abstract

Background: The *CACNA1C* gene was defined as a risk gene for schizophrenia in a large genome-wide association study of European ancestry performed by the Psychiatric Genomics Consortium. Previous meta-analyses focused on the association between the *CACNA1C* gene rs1006737 and schizophrenia. The present study focused on whether there was a racial difference in the effect of the *CACNA1C* gene rs1006737 on schizophrenia. rs2007044 and rs4765905 were analyzed for their effect on the risk of schizophrenia.

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

Results: A total of 18 studies met the inclusion criteria, including fourteen rs1006737 studies (15,213 cases, 19,412 controls), three rs2007044 studies (6,007 cases, 6,518 controls), and two rs4765905 studies (2,435 cases, 2,639 controls). An allele model study also related rs2007044 and rs4765905 to schizophrenia. The overall meta-analysis for rs1006737, which included the allele contrast, dominant, recessive, codominance, and complete overdominance models, showed significant differences between rs1006737 and schizophrenia. However, the race-based subgroup analysis for rs1006737 found that the genotypes GG and GG + GA were only protective factors for schizophrenia in European populations. In contrast, the rs1006737 GA genotype only reduced the risk of schizophrenia in Asian populations.

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

1. Background

Schizophrenia is a chronic, disabling brain disease characterized by delusions, hallucinations, and formal thought disorders in addition to a decline in socio-occupational functioning [1]. Studies with twins [2] and adoptive families [3] have shown that genetic factors are an important cause of schizophrenia. The L-type voltage-gated calcium channels play a unique role in behavioral extinction [4], inhibitory learning, and the maturation of adult cognitive function [5]. The two principal pore-forming subunits of these channels expressed in neurons are the α1C and α1D subtypes [6]. The α1C subtype is encoded by the *CACNA1C* gene, which is considered a risk factor for schizophrenia based on a large genome-wide association study (GWAS) of European ancestry performed by the Psychiatric Genomics Consortium (PGC) [7]. A growing body of research supports a key role for *CACNA1C* in schizophrenia in European populations. Ivorra *et al.* [8] found that the rs1006737 polymorphism of the *CACNA1C* gene is strongly associated with schizophrenia and bipolar disorder in a Spanish population. Wolf *et al.* [9] suggested that the *CACNA1C* genotype may explain inter-individual differences in the amygdala volume among patients with schizophrenia in the German population. The amygdala is not only involved in associative learning but also regulates additional cognitive processes, such as memory and attention [10]. Fatima *et al.* [11] detected a significant difference in the genotype and allele frequencies for the rs4765905 polymorphism between patients and controls, confirming the hypothesis that the *CACNA1C* gene was associated with schizophrenia in the Pakistani population.

Based on these findings, we were curious to see if the *CACNA1C* gene had the same effect on schizophrenia in Asian populations as it did in the European populations. The meta-analysis of Zheng *et al.* [12] and Jiang *et al.*

[13] showed that there was no heterogeneity between the *CACNA1C* rs1006737 polymorphism in East Asian and European populations. He *et al.* [14] also showed that rs1006737 was associated with both schizophrenia and major depressive disorder in the Han Chinese population. Additional rs1006737 meta-analysis showed an association between this *CACNA1C* polymorphism and schizophrenia in both the European and Asian populations when the samples were stratified by ethnicity [15]. However, in a follow-up to the top European GWAS hits, The genotyping performed by Takahashi *et al.* [16] implicated loci in additional schizophrenia family samples from China and Japan and found no association between 12 polymorphisms (e.g., rs4765905 in the *CACNA1C* gene) and schizophrenia. Consistent with this finding, Hori *et al.* [17] found no significant difference in the genotype or allele frequency of the *CACNA1C* rs1006737 polymorphism between schizophrenia patients and controls in a Japanese population.

In summary, there is no consensus on whether *CACNA1C* is associated with schizophrenia or if there are differences in susceptibility to schizophrenia between Asian and European populations. Therefore, we performed an updated comprehensive meta-analysis on the relationship between *CACNA1C* gene polymorphisms and schizophrenia, which included case-control studies.

2. Methods

2.1. Literature search strategy

Eligible studies were identified by searching two electronic databases (PubMed and the China National Knowledge Infrastructure [CNKI]). PubMed (2011–present) was used to retrieve English studies only, while the CNKI (2013–present) was used to retrieve Chinese studies only. Using these databases, only completed peer-review studies were 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 used in our meta-analysis were based on 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 a susceptible gene for schizophrenia; (5) were case-control studies. Case-control studies were excluded based on the following 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; (6) data included in the PGC GWAS from 2014.

2.2. Data extraction

Data extraction, publication bias assessment, heterogeneity detection, sensitivity detection, and statistical analysis were performed as previously described [19]. Briefly, data extraction was carried out independently by two authors in strict accordance with the inclusion and exclusion criteria. Disagreements between the two authors were negotiated until a consensus was reached. The following data were extracted: (1) basic information (e.g., first author's last name, publi tion year); (2) sample information (e.g., region, race, source of control, mean age of control group, gender index of the case and control groups, and the number of individuals in the case and control groups); (3) the number of genotypes between cases and controls.

2.3. Assessment of publication bias

Publication bias was assessed using funnel plots in which 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, one can judge whether publication bias exists in a study. The degree of publication bias was evaluated using the Egger's test [20]. A *P*-value > 0.05 indicated 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 the association between the rs1006737, rs2007044, and rs4765905 polymorphisms and the risk of schizophrenia was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The heterogeneity among the 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 indicated a lack of heterogeneity. Therefore, the fixed effects model (Mantel-Haenszel method) was used. In contrast, a *P*-value < 0.1 indicated the existence of heterogeneity, and the random effects model (M-H heterogeneity method) was used [23]. For quantitative I^2 statistics, I^2 was the variation between the studies as a percentage of the total variation. The degree of heterogeneity was divided into low (< 25%), moderate (25–75%), and high (> 75%) groups. The allele contrast model (A vs. a) was used to estimate the effect of the risk allele on the risk of schizophrenia (A = risk allele). Subsequently, multiple pairwise comparisons (e.g., AA vs. aa; AA vs. Aa or Aa vs. aa) were used to determine 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. Meta-regression analysis was performed to assess the impact of different variables (mean age of control group and sex indexes) on the analysis.

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

3. Results

A total of 67 articles were identified from the PubMed and CNKI database searches. Eighteen studies remained after excluding those that did not meet the inclusion criteria. Specifically, these 18 studies included 14 rs1006737 studies (15,213 cases and 19,412 controls), three rs2007044 studies (6,007 cases and 6,518 controls), and two rs4765905 studies (2,435 cases and 2,639 controls). A PRISMA flowchart describing the selection and screening of the studies used in the meta-analysis is shown in Fig.1. The main characteristics of the included studies are presented in Table 1. The allele frequencies and genotype distributions for all the 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 (73.0)	27 (27.0)	154 (76.2)	48 (23.8)
Fatima	2017	393	84	17	235	54	9	0.01	870 (88.1)	118 (11.9)	524 (88.0)	72 (12.0)
Ivorra	2014	1417	1271	293	1420	1124	240	0.41	4105 (68.9)	1857 (31.1)	3964 (71.2)	1604 (28.8)
Galaktionova	2013	78	85	23	80	90	22	0.66	241 (64.8)	131 (35.2)	250 (65.1)	134 (34.9)
Nyegaard	2010	402	444	130	656	675	158	0.42	1248 (63.9)	704 (36.1)	1987 (66.7)	991 (33.3)
Bigos	2010	120	115	47	191	205	44	0.31	355 (62.9)	209 (37.1)	587 (66.7)	293 (33.3)
Green	2009	205	208	66	1367	1233	336	0.02	618 (64.5)	340 (35.5)	3967 (67.6)	1095 (32.4)
Mallas	2016	23	30	10	56	51	17	0.33	76 (60.3)	50 (39.7)	163 (65.7)	85 (34.3)
Porcelli	2015	153	23	0	301	23	2	0.11	329 (93.5)	23 (6.5)	625 (95.9)	27 (4.1)
He	2013	996	220	14	1053	166	9	0.39	2212 (89.9)	248 (10.1)	2272 (92.5)	184 (7.5)
Guan	2013	1061	343	26	1223	327	20	0.72	2465 (86.2)	395 (13.8)	2773 (88.3)	367 (11.7)
Zheng	2013	5239	635	19	5706	597	16	0.93	11113 (94.3)	673 (5.7)	12009 (95.0)	629 (5.0)
Hori	2012	480	70	2	1002	127	3	0.63	1030 (93.3)	74 (6.7)	2131 (94.1)	133 (5.9)
Zhang	2011	280	37	1	357	42	2	0.53	597 (93.9)	39 (6.1)	756 (94.3)	46 (5.7)
Rs2007044												
Zhang	2018	24	25	4	58	57	14	1.00	73 (68.9)	33 (31.1)	173 (67.1)	85 (32.9)
Bustillo	2017	26	23	9	35	21	11	0.02	75 (64.7)	41 (35.3)	91 (67.9)	43 (32.1)
Zheng	2014	2797	2540	559	3166	2597	559	0.42	8134 (77.5)	3658 (22.5)	8929 (70.7)	3715 (29.3)
Rs4765905												
Sudesh	2018	579	307	51	668	286	38	0.29	1465 (78.2)	409 (21.8)	1622 (81.8)	362 (18.2)
Guan	2013	1307	360	33	1195	352	24	0.74	2434 (71.6)	426 (28.4)	2741 (87.2)	399 (12.8)

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

3.1. *CACNA1C* Rs1006737 polymorphism

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

After the overall meta-analysis of rs1006737 was conducted, significant differences were observed between rs1006737 and the risk of schizophrenia using the following models: 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 model (GA vs. GG; OR = 0.064, 95% CI = 0.024–0.169, I^2 = 99%, *P* heterogeneity = 0.000, *P* = 0.000); 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 presented in Table 3.

Subsequently, subgroup analysis based on race was performed for rs1006737. For the Caucasian population, there were seven studies that included a total of 5,546 patients with schizophrenia and 8,305 controls. Rs1006737 was associated with schizophrenia using all but one genetic model (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). The complete overdominance model (GG + AA vs. GA) resulted in an OR = 0.959, 95% CI = 0.891–1.033, and *P* = 0.272.

The subgroup analysis also included six studies involving Asian populations with a total of 9,604 patients with schizophrenia and 10,983 controls. Rs1006737 was associated with schizophrenia using the following models: 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 model (GA vs. GG; OR = 0.008, 95% CI = 0.004–0.017, *P* = 0.000); complete overdominance model (GG + AA vs. GA; OR = 0.827, 95% CI = 0.761–0.899, *P* = 0.000). There was no association observed using the recessive (AA vs. GG+GA; OR = 1.336, 95% CI = 0.922–1.936, *P* = 0.125) or codominance model (AA vs. GG; OR = 1.384, 95% CI = 0.955–2.006, *P* = 0.086) models. The main results are shown in Table 4. Neither the mean age of the control group (slope = 0.995, 95% CI = 0.985–1.005, *P* = 0.265) nor the sex indexes (case group, slope = 0.943, 95% CI = 0.797–1.115, *P* = 0.455; control group, slope =1.059, 95% CI = 0.829–1.352, *P* = 0.616) had any significant impact on the results.

3.2. Rs2007044 and rs4765905 polymorphisms of *CACNA1C*

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

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

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 the sequential exclusion of each study, the combined effect obtained by the new meta-analysis was compared to the total effect. No statistically significant differences were observed, indicating that our analysis results were reliable and stable. The range of OR estimates demonstrated that none of the individual studies "reversed" the observed total effect (Table 5).

Table 5. Results of the sensitivity analysis for the *CACNA1C* rs1006737 polymorphism.

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). The Egger's test quantitatively detected symmetry. Due to the lack of studies on rs4765905, the efficacy of the Egger's test was limited, and the symmetry of the funnel plot could not be detected. No publication bias was detected with the allele contrast model for rs2007044 (G vs. A; t = -0.43, P = 0.743) or rs1006737 (A vs. G; t = 0.86, P = 0.407). Furthermore, no publication bias was detected for rs1006737 with the 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 model (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 the rs1006737 polymorphism with the codominance model (AA vs. GG; t = -3.88, P = 0.002).

4. Discussion

CACNA1C is 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 the *CACNA1C* gene has the same effect on schizophrenia in both Asian and European populations. Therefore, we conducted a comprehensive meta-analysis on the association between the *CACNA1C* rs1006737, rs2007044, and rs4765905 polymorphisms 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 allele model, implying that the *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].

When we conducted a race-based subgroup analysis of rs1006737, we found that the effects of rs1006737 on schizophrenia in the Asian and European populations had both similarities and differences. According to the results obtained with the allele (A vs. G) and dominant (GA + AA vs. GG) models, the effect of rs1006737 on the

risk of schizophrenia in the European and Asian populations was consistent (i.e., allele A and genotype GA + AA were protective factors against the development of schizophrenia). However, analysis by the recessive (AA vs. GG + GA) and codominant (AA vs. GG) models showed that the genotype GG + GA was only a risk factor for schizophrenia in the European population. In contrast, according to the complete overdominance model (GG + AA vs. GA), the GA genotype of rs1006737 only reduced the risk of schizophrenia in the Asian population. These data 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, therefore, was not a valid gene model for evaluating the rs1006737 polymorphism. In addition, there were few studies on the association between rs2007044 or rs4765905 and schizophrenia. Thus, additional high-quality studies are needed to support our analysis.

This meta-analysis study advanced our understanding of the relationship between *CACNA1C* polymorphisms and schizophrenia compared to previous literature. First, the current study included more comprehensive studies. A recent meta-analysis of the *CACNA1C* gene and schizophrenia [38] contained nine studies on the association between rs1006737 and schizophrenia. In comparison, the current study included 14 studies on the association between this polymorphism and schizophrenia, including eight articles [11, 12, 14, 17, 27, 29, 30, 32] shared with [38] along with six additional studies [8, 24-26, 28, 31]. Second, compared to most of the meta-analysis on *CACNA1C* and schizophrenia, the current study not only included studies on rs1006737 and schizophrenia but also studies on the association between two other *CACNA1C* polymorphisms (rs2007044 and rs4765905) and schizophrenia. Although the study of Xiao *et al.* [39] also included these three polymorphisms, it only included samples from Asian populations. Because the current study included samples from both Asian and European populations, it used a richer source of samples for the analysis. Finally, the current study focused on comparing the impact of rs1006737 on schizophrenia in Asian and European populations. Based on this analysis, the influence model of rs1006737 on schizophrenia in Asian and European populations identified both similarities and differences between the two populations.

5. Conclusion

The *CACNA1C* rs1006737, rs2007044, and rs4765905 gene polymorphisms were associated with the susceptibility to schizophrenia. However, the influence model for rs1006737 on schizophrenia in Asian and European populations demonstrated both similarities and differences between the two populations.

List Of 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 included in this published article.

Competing interests: The authors declare that they have no competing interests.

Funding: The present research was not funded by any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions: YPL participated in the study design and drafted the manuscript. XW and XX performed the statistical analysis. BJW and JY contributed to the revision of the final manuscript. All authors have read and approved the manuscript.

Acknowledgement

We would like to thank Professor Mei Ding for her guidance and review of the data analysis.

References

[1] Mowry BJ, Nancarrow DJ. Molecular genetics of schizophrenia. Clin Exp Pharmacol Physiol. 2001;28:66-9.

[2] Kendler KS. Overview: a current perspective on twin studies of schizophrenia. Am J Psychiatry. 1983;140:1413-25.

[3] Kety SS. Schizophrenic illness in the families of schizophrenic adoptees: findings from the Danish national sample. Schizophr Bull. 1988;14:217-22.

[4] Soeiro-de-Souza MG, Bio DS, Dias VV, Vieta E, Machado-Vieira R, Moreno RA. The CACNA1C risk allele selectively impacts on executive function in bipolar type I disorder. Acta Psychiatr Scand. 2013;128:362-9.

[5] Barad M. Later developments: molecular keys to age-related memory impairment. Alzheimer Dis Assoc Disord. 2003;17:168-76.

[6] Leitch B, Szostek A, Lin R, Shevtsova O. Subcellular distribution of L-type calcium channel subtypes in rat hippocampal neurons. Neuroscience. 2009;164:641-57.

[7] Cross-Disorder Group of the Psychiatric Genomics C. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013;381:1371-9.

[8] Ivorra JL, Rivero O, Costas J, Iniesta R, Arrojo M, Ramos-Rios R, et al. Replication of previous genome-wide association studies of psychiatric diseases in a large schizophrenia case-control sample from Spain. Schizophr Res. 2014;159:107-13.

[9] Wolf C, Mohr H, Schneider-Axmann T, Reif A, Wobrock T, Scherk H, et al. CACNA1C genotype explains interindividual differences in amygdala volume among patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2014;264:93-102.

[10] Gallagher M, Chiba AA. The amygdala and emotion. Curr Opin Neurobiol. 1996;6:221-7.

[11] Fatima A, Farooq M, Abdullah U, Tariq M, Mustafa T, Iqbal M, et al. Genome-Wide Supported Risk Variants in MIR137, CACNA1C, CSMD1, DRD2, and GRM3 Contribute to Schizophrenia Susceptibility in Pakistani Population. Psychiatry Investig. 2017;14:687-92.

[12] Zheng F, Zhang Y, Xie W, Li W, Jin C, Mi W, et al. Further evidence for genetic association of CACNA1C and schizophrenia: new risk loci in a Han Chinese population and a meta-analysis. Schizophr Res. 2014;152:105-10.

[13] Jiang H, Qiao F, Li Z, Zhang Y, Cheng Y, Xu X, et al. Evaluating the association between CACNA1C rs1006737 and schizophrenia risk: A meta-analysis. Asia Pac Psychiatry. 2015;7:260-7.

[14] He K, An Z, Wang Q, Li T, Li Z, Chen J, et al. CACNA1C, schizophrenia and major depressive disorder in the Han Chinese population. Br J Psychiatry. 2014;204:36-9.

[15] Nie F, Wang X, Zhao P, Yang H, Zhu W, Zhao Y, et al. Genetic analysis of SNPs in CACNA1C and ANK3 gene with schizophrenia: A comprehensive meta-analysis. Am J Med Genet B Neuropsychiatr Genet. 2015;168:637-48.

[16] Takahashi S, Glatt SJ, Uchiyama M, Faraone SV, Tsuang MT. Meta-analysis of data from the Psychiatric Genomics Consortium and additional samples supports association of CACNA1C with risk for schizophrenia. Schizophr Res. 2015;168:429-33.

[17] Hori H, Yamamoto N, Fujii T, Teraishi T, Sasayama D, Matsuo J, et al. Effects of the CACNA1C risk allele on neurocognition in patients with schizophrenia and healthy individuals. Sci Rep. 2012;2:634.

[18] Sudesh R, Thalamuthu A, John S, Thara R, Mowry B, Munirajan AK. Replication of GWAS identified miR-137 and its target gene polymorphisms in Schizophrenia of South Indian population and meta-analysis with Psychiatric Genomics Consortium. Schizophr Res. 2018;199:189-94.

[19] Liu YP, Meng JH, Wu X, Xu FL, Xia X, Zhang XC, et al. Rs1625579 polymorphism in the MIR137 gene is associated with the risk of schizophrenia: updated meta-analysis. Neurosci Lett. 2019;713:134535.

[20] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-34.

[21] Wu R, Li B. A multiplicative-epistatic model for analyzing interspecific differences in outcrossing species. Biometrics. 1999;55:355-65.

[22] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.

[23] Yang X, Wang G, Wang Y, Yue X. Association of metabotropic glutamate receptor 3 gene polymorphisms with schizophrenia risk: evidence from a meta-analysis. Neuropsychiatr Dis Treat. 2015;11:823-33.

[24] Lubeiro A, Fatjo-Vilas M, Guardiola M, Almodovar C, Gomez-Pilar J, Cea-Canas B, et al. Analysis of KCNH2 and CACNA1C schizophrenia risk genes on EEG functional network modulation during an auditory odd-ball task. Eur Arch Psychiatry Clin Neurosci. 2019.

[25] Mallas E, Carletti F, Chaddock CA, Shergill S, Woolley J, Picchioni MM, et al. The impact of CACNA1C gene, and its epistasis with ZNF804A, on white matter microstructure in health, schizophrenia and bipolar disorder(1). Genes Brain Behav. 2017;16:479-88.

[26] Porcelli S, Lee SJ, Han C, Patkar AA, Serretti A, Pae CU. CACNA1C gene and schizophrenia: a case-control and pharmacogenetic study. Psychiatr Genet. 2015;25:163-7.

[27] Guan F, Zhang B, Yan T, Li L, Liu F, Li T, et al. MIR137 gene and target gene CACNA1C of miR-137 contribute to schizophrenia susceptibility in Han Chinese. Schizophr Res. 2014;152:97-104.

[28] Galaktionova D, Gareeva AE, Khusnutdinova EK, Nasedkina TV. [The association of polymorphisms in SLC18A1, TPH1 and RELN genes with risk of paranoid schizophrenia]. Mol Biol (Mosk). 2014;48:629-39.

[29] Zhang Q, Shen Q, Xu Z, Chen M, Cheng L, Zhai J, et al. The effects of CACNA1C gene polymorphism on spatial working memory in both healthy controls and patients with schizophrenia or bipolar disorder. Neuropsychopharmacology. 2012;37:677-84.

[30] Nyegaard M, Demontis D, Foldager L, Hedemand A, Flint TJ, Sorensen KM, et al. CACNA1C (rs1006737) is associated with schizophrenia. Mol Psychiatry. 2010;15:119-21.

[31] Bigos KL, Mattay VS, Callicott JH, Straub RE, Vakkalanka R, Kolachana B, et al. Genetic variation in CACNA1C affects brain circuitries related to mental illness. Arch Gen Psychiatry. 2010;67:939-45.

[32] Green EK, Grozeva D, Jones I, Jones L, Kirov G, Caesar S, et al. The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. Mol Psychiatry. 2010;15:1016-22.

[33] Bustillo JR, Patel V, Jones T, Jung R, Payaknait N, Qualls C, et al. Risk-Conferring Glutamatergic Genes and Brain Glutamate Plus Glutamine in Schizophrenia. Front Psychiatry. 2017;8:79.

[34] Zhang Z, Wang Y, Zhang Q, Zhao W, Chen X, Zhai J, et al. The effects of CACNA1C gene polymorphism on prefrontal cortex in both schizophrenia patients and healthy controls. Schizophr Res. 2018.

[35] Khalid M, Driessen TM, Lee JS, Tejwani L, Rasool A, Saqlain M, et al. Association of CACNA1C with bipolar disorder among the Pakistani population. Gene. 2018;664:119-26.

[36] Li J, Zhao L, You Y, Lu T, Jia M, Yu H, et al. Schizophrenia Related Variants in CACNA1C also Confer Risk of Autism. PLoS One. 2015;10:e0133247.

[37] Moon AL, Haan N, Wilkinson LS, Thomas KL, Hall J. CACNA1C: Association With Psychiatric Disorders, Behavior, and Neurogenesis. Schizophr Bull. 2018;44:958-65.

[38] Zhu D, Yin J, Liang C, Luo X, Lv D, Dai Z, et al. CACNA1C (rs1006737) may be a susceptibility gene for schizophrenia: An updated meta-analysis. Brain Behav. 2019;9:e01292.

[39] Xiao X, Luo XJ, Chang H, Liu Z, Li M. Evaluation of European Schizophrenia GWAS Loci in Asian Populations via Comprehensive Meta-Analyses. Mol Neurobiol. 2017;54:4071-80.

Figures

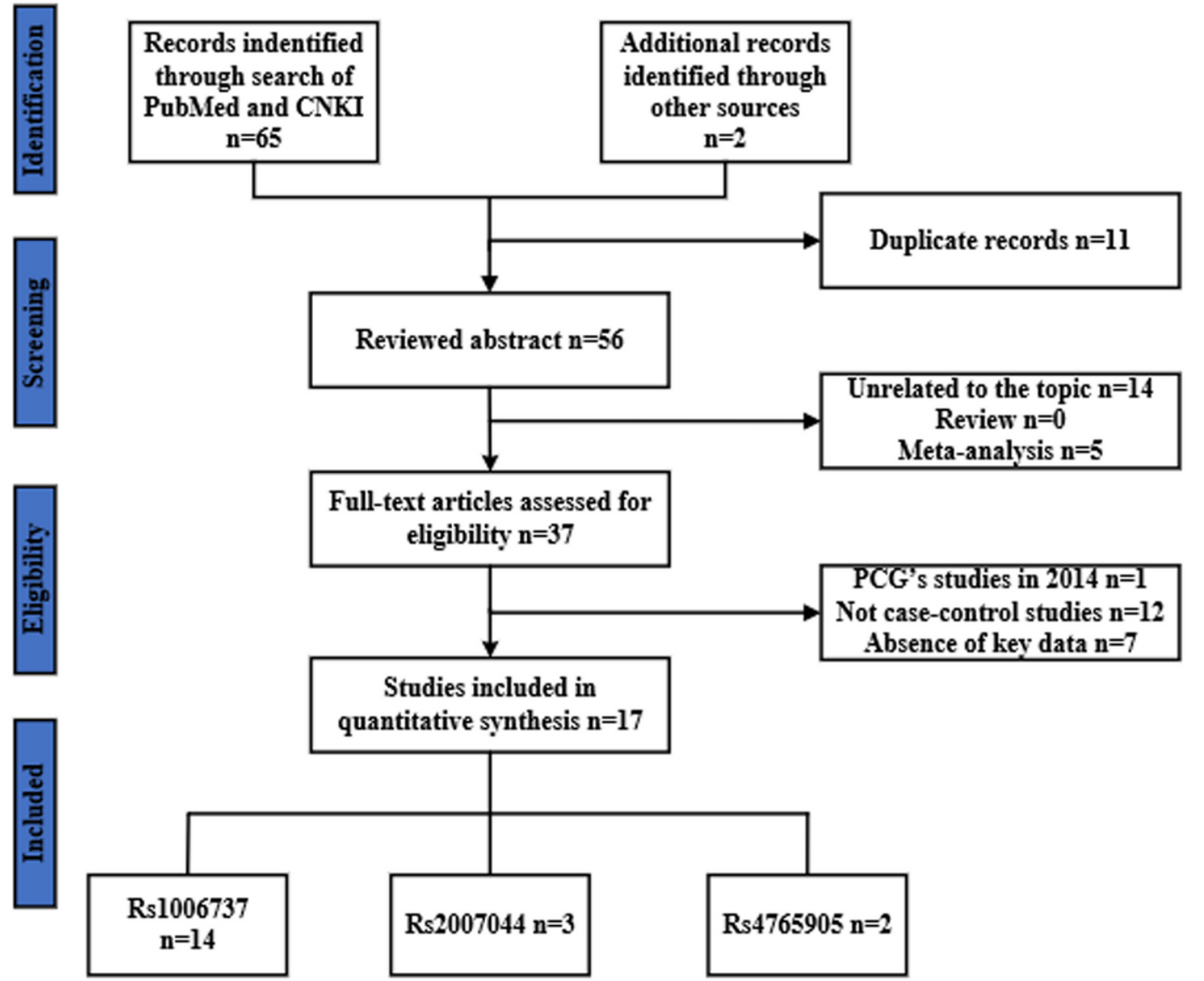

Figure 1

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

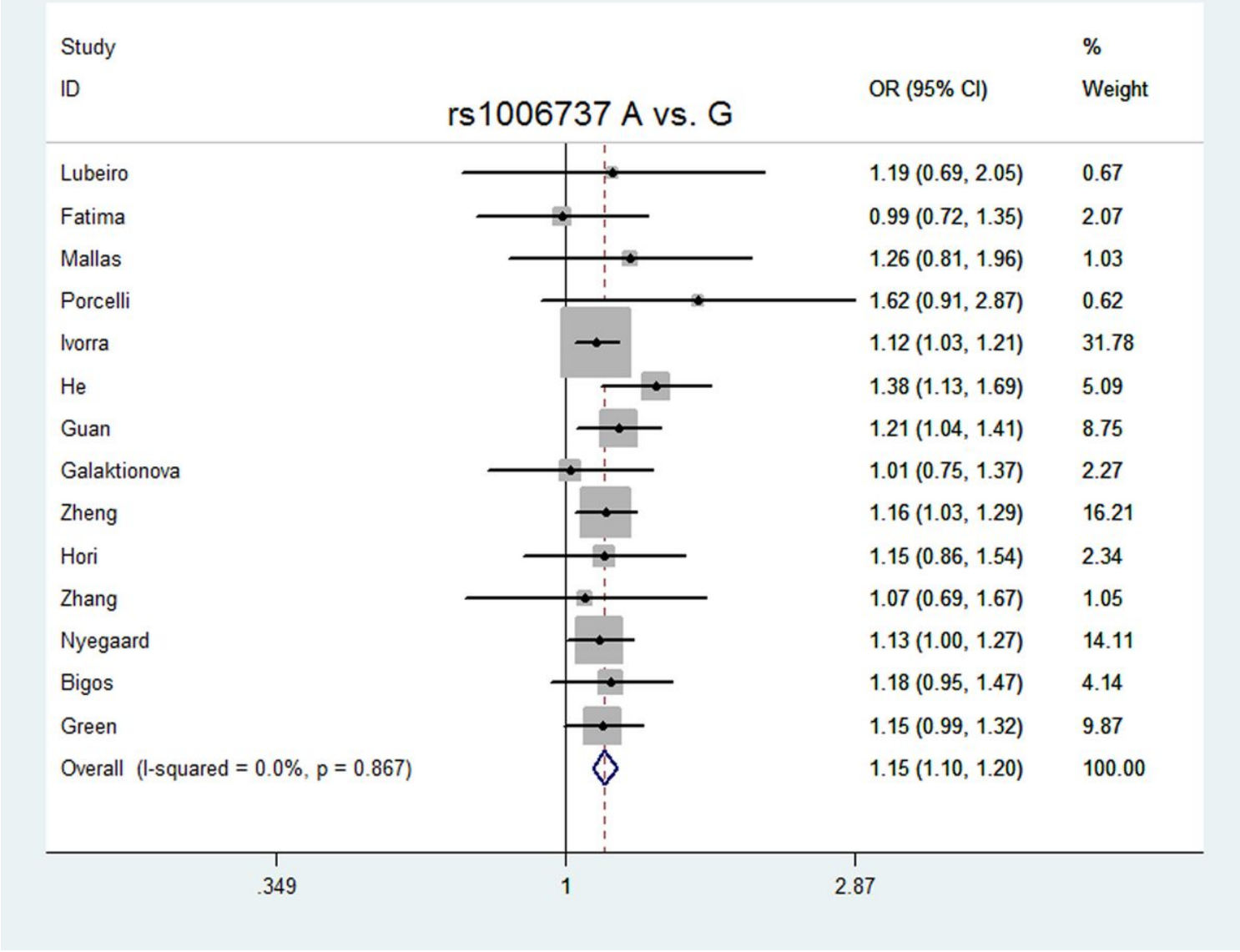

Figure 2

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.

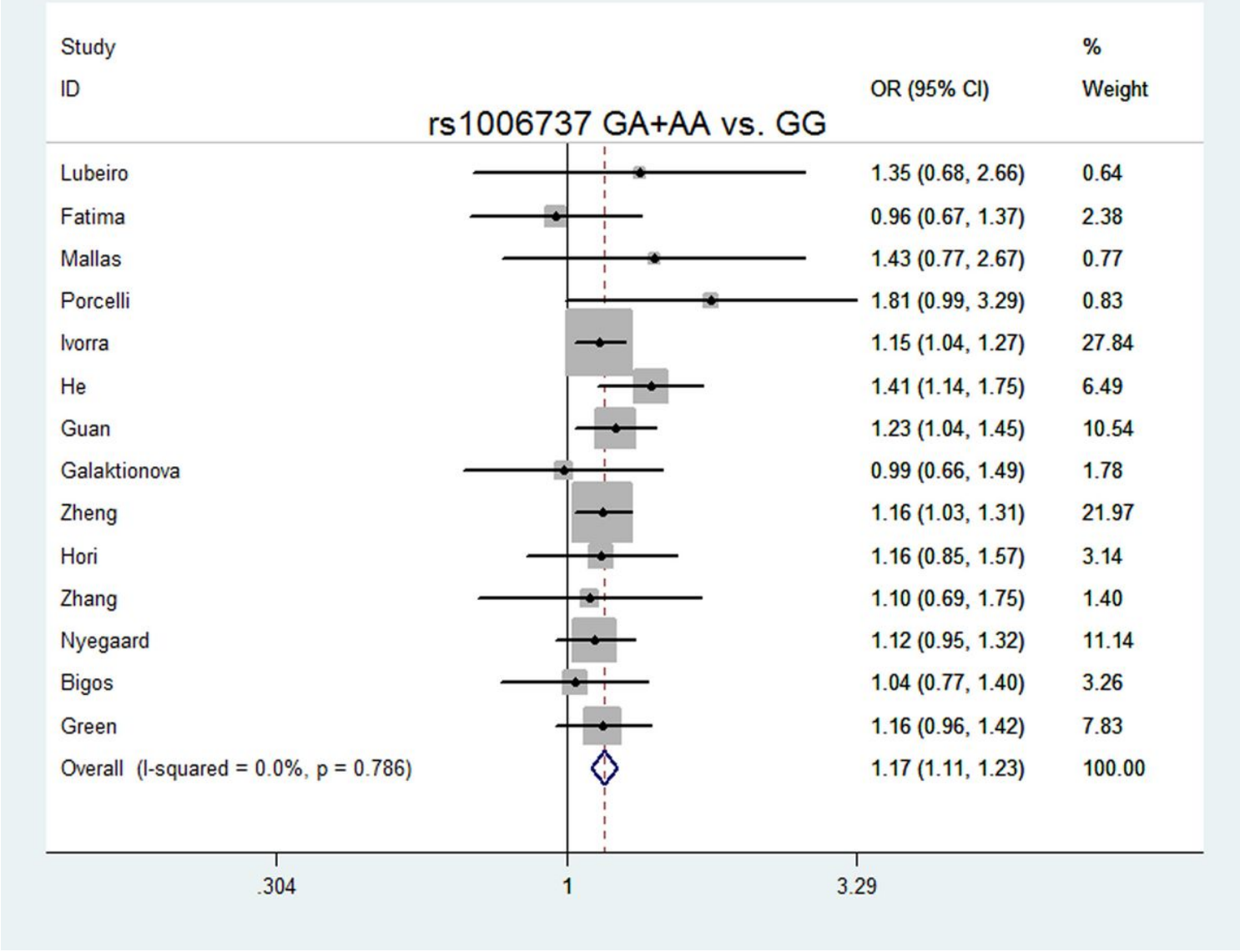

Figure 3

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.

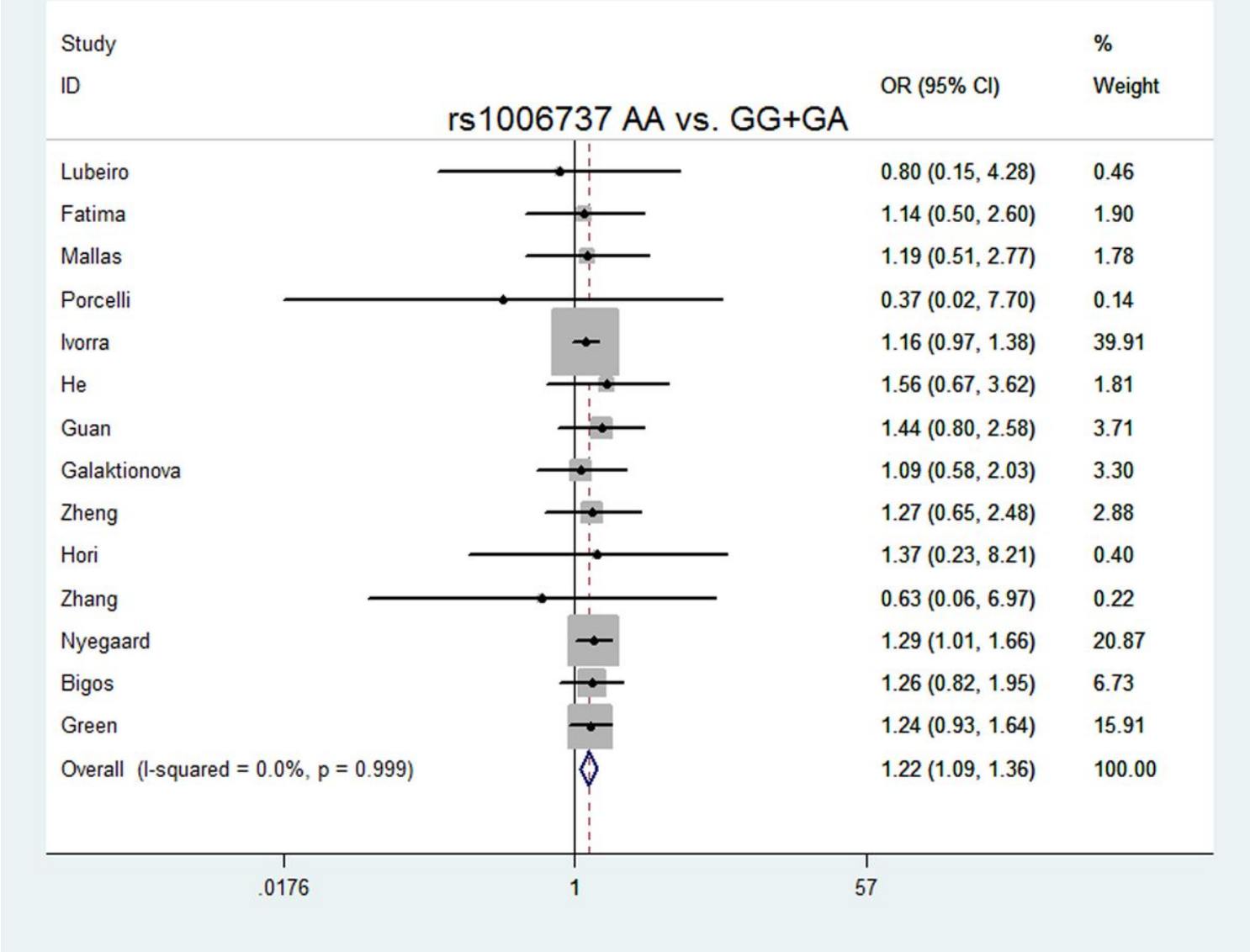

Figure 4

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.

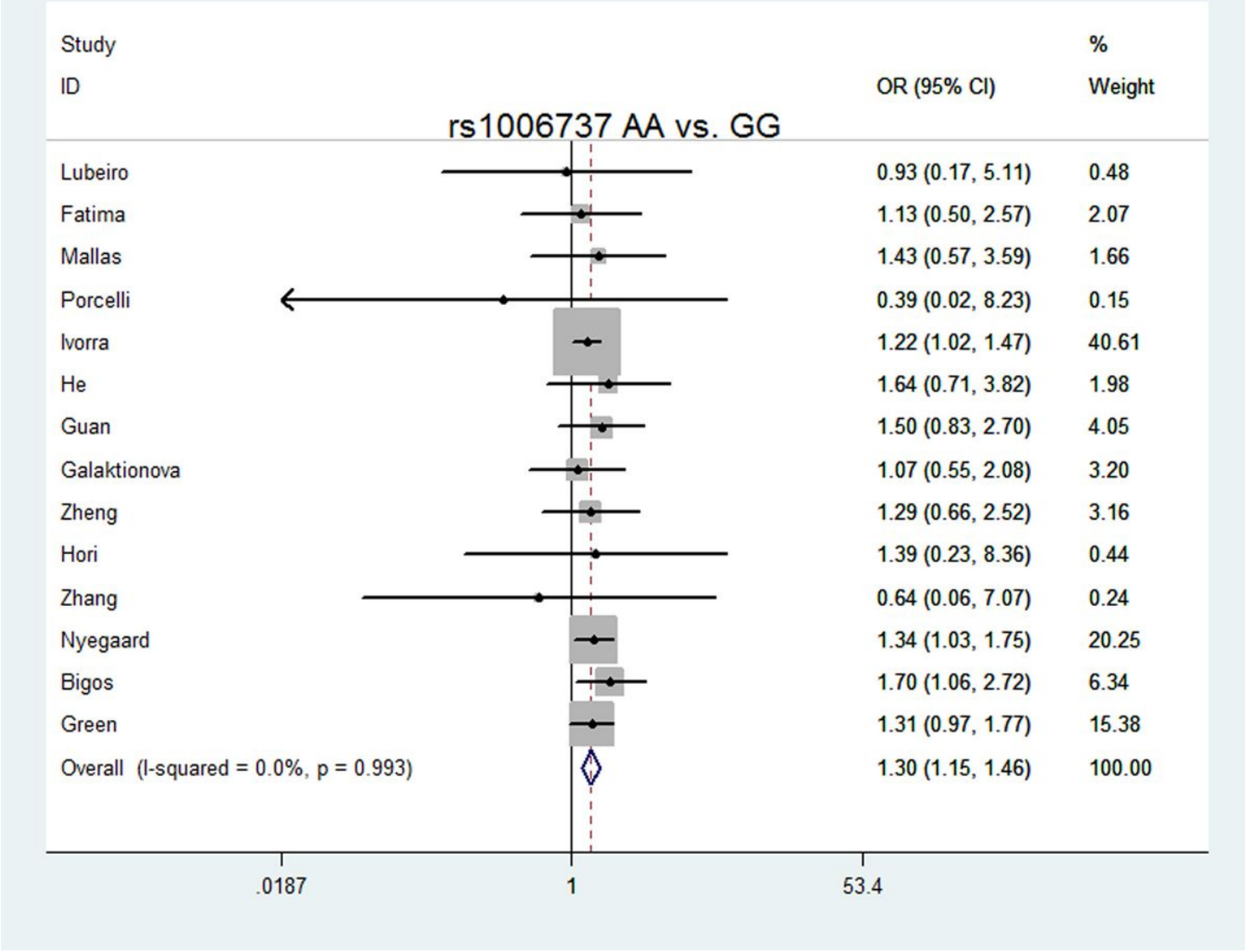

Figure 5

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.

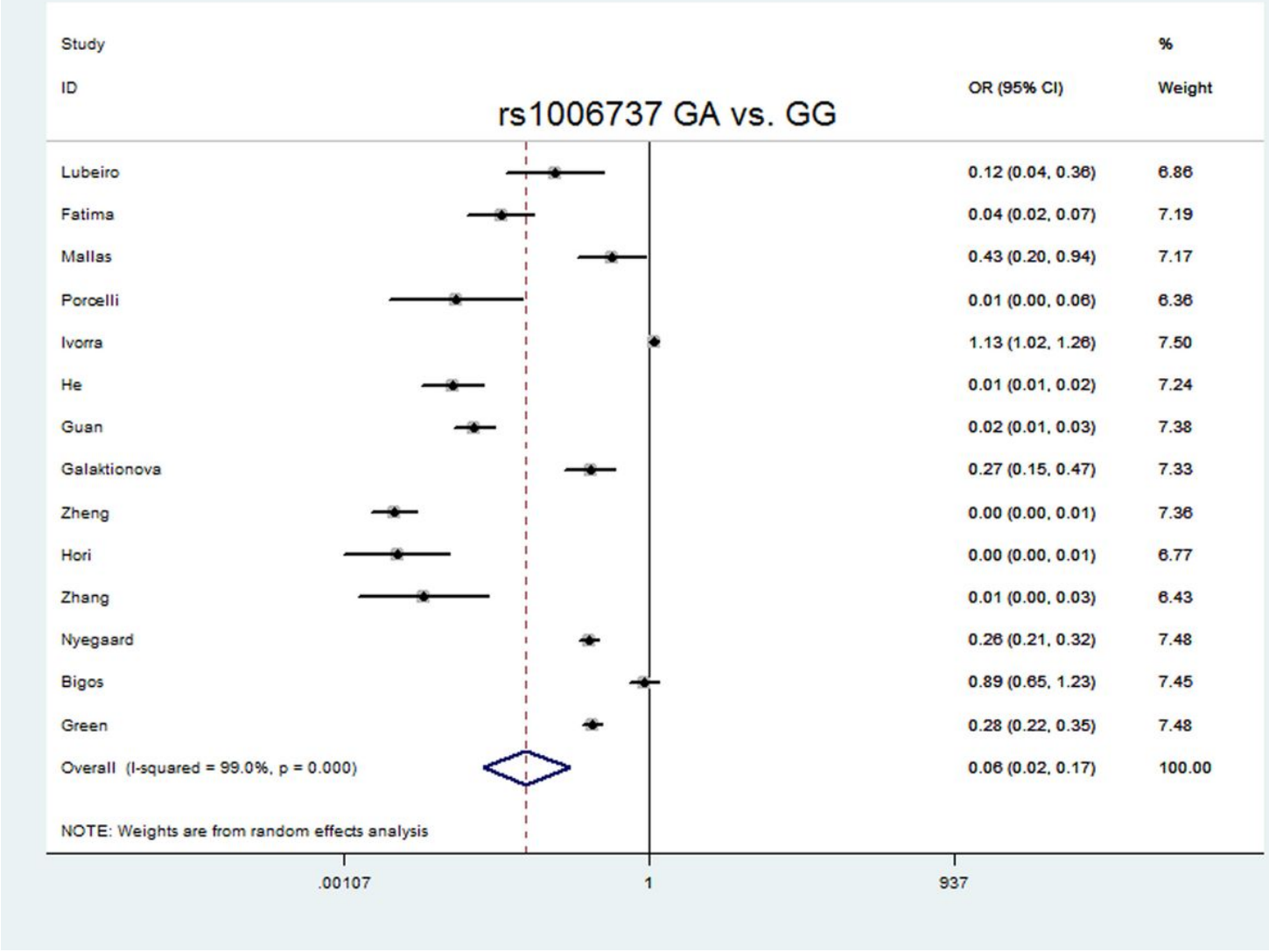

Figure 6

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.

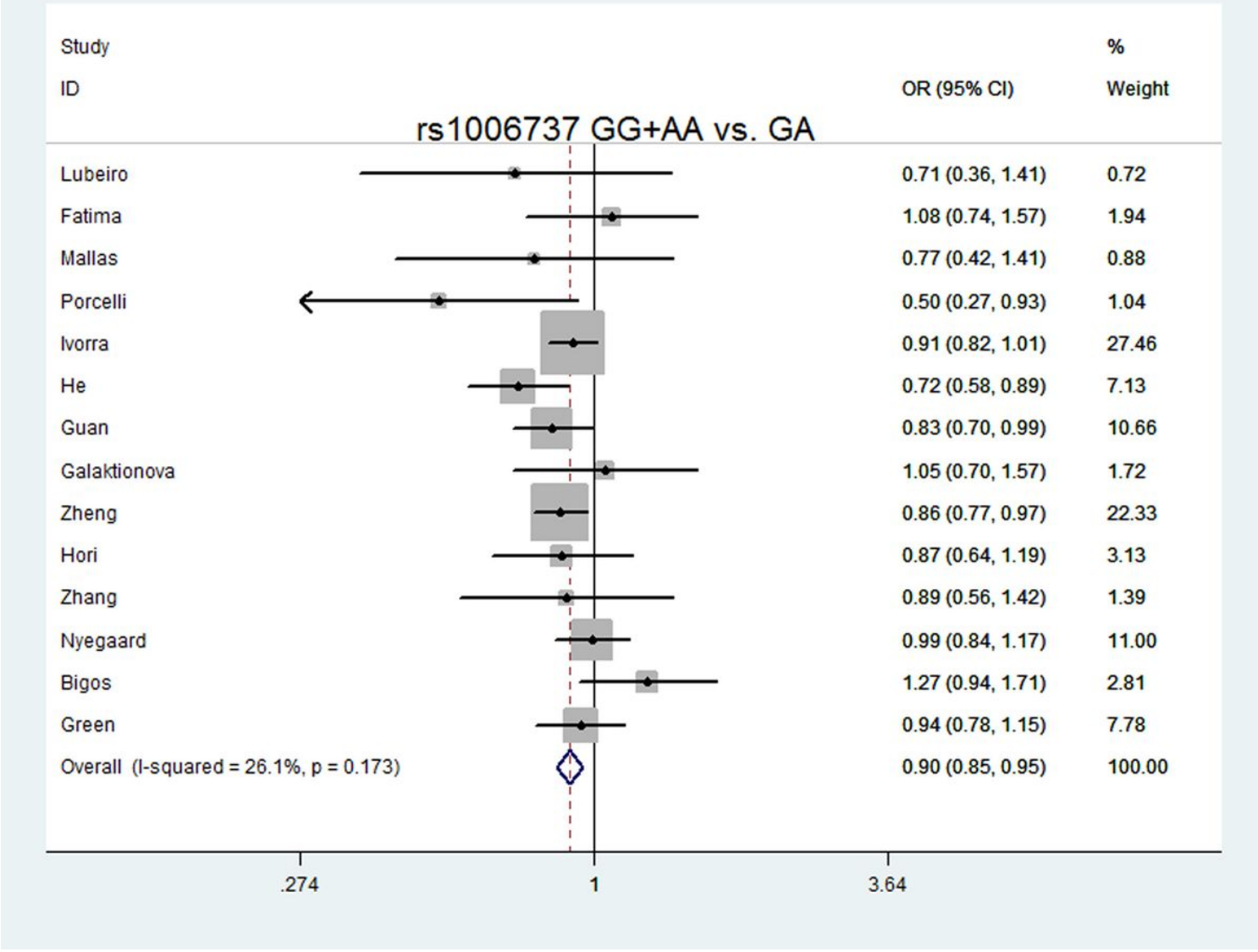

Figure 7

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.

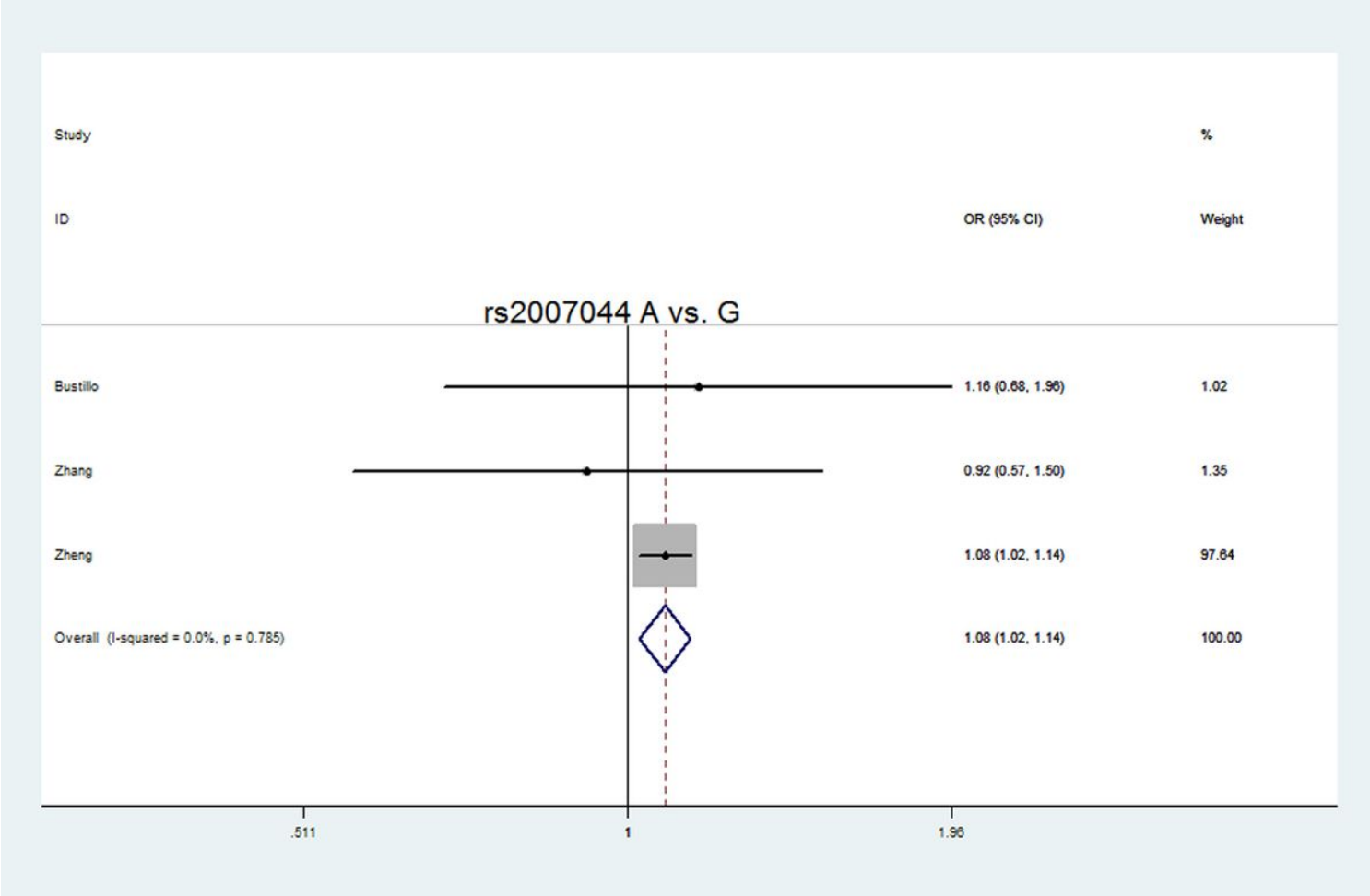

Figure 8

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.

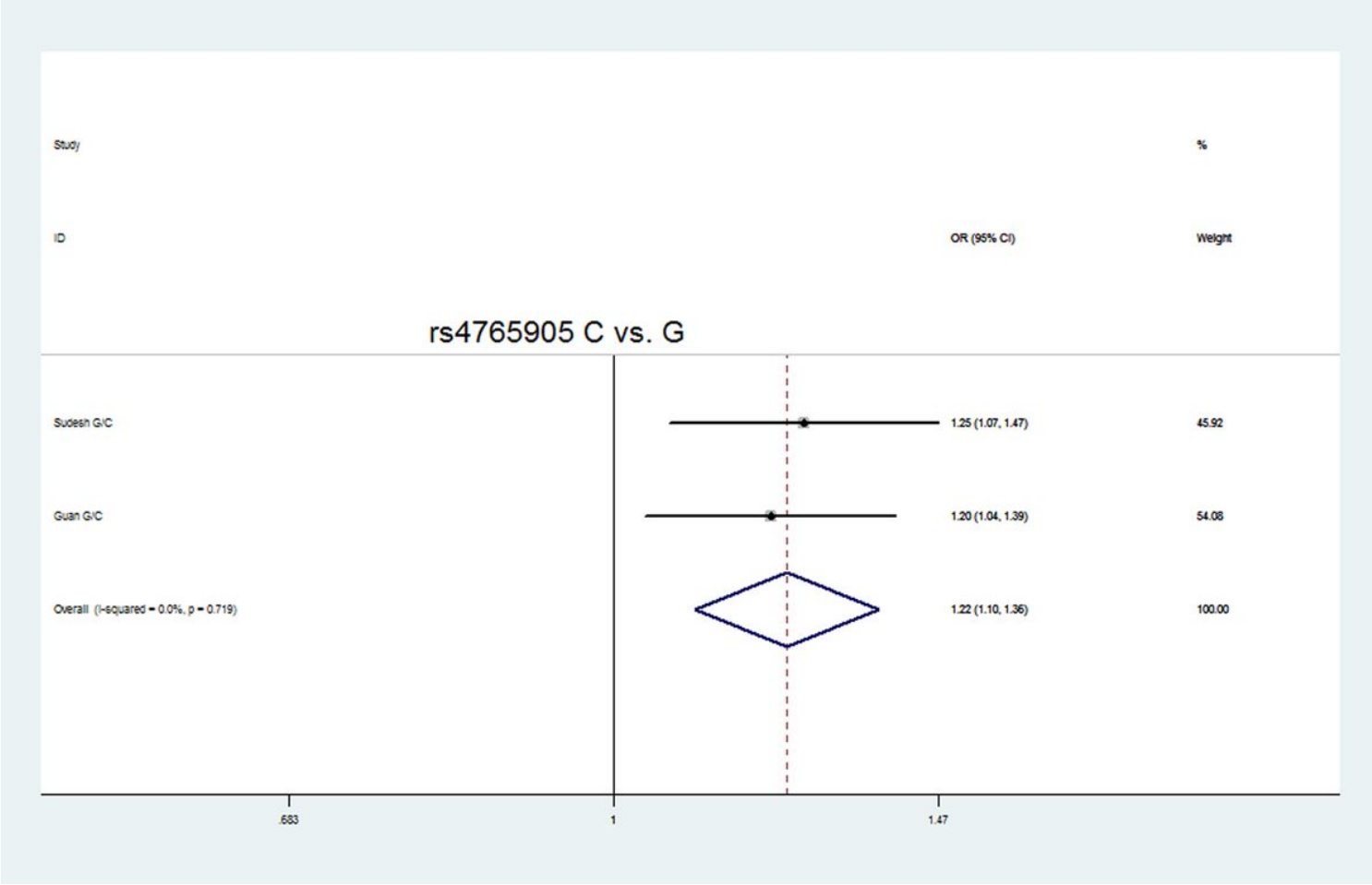

Figure 9

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.pdf