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ORIGINAL RESEARCH

Associations between dopamine D2 receptor gene polymorphisms and schizophrenia risk: a PRISMA compliant meta-analysis

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Objective: To determine the relationships between dopamine D2 receptor gene polymorphisms and the risk of schizophrenia using meta-analysis.

Method: The PubMed, Embase, and China National Knowledge Infrastructure databases were searched to identify relevant literature published up to February 2016. The allele contrast model was used. Stata software was used for statistical analysis, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated to evaluate the associations between dopamine D2 receptor gene polymorphisms and the risk of schizophrenia. Meta-regression and publication bias, trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analyses were also performed.

Results: This meta-analysis included 81 studies. The rs1801028 and rs1799732 were associated with schizophrenia risk among Asians (P=0.04, OR =1.25, 95% CI =1.01–1.55; P<0.01, OR =0.76, 95% CI =0.63–0.92, respectively), while the rs6277 was associated with schizophrenia risk in Caucasians (P<0.01, OR=0.72, 95% CI =0.66–0.79). The rs1800497 was also associated with schizophrenia risk in population-based controls (P<0.01, OR =0.84, 95% CI =0.72–0.97). The rs6275, rs1079597, and rs1800498 were not associated with schizophrenia risk. In addition, meta-regression indicated that the controls may be sources of heterogeneity for the rs1801028 single-nucleotide polymorphism (SNP), while ethnicity may be sources of heterogeneity for the rs6277 SNP. Publication bias was significant for the rs1801028 SNP, and this result changed after the publication bias was adjusted using the trim-and-fill method.

Conclusion: This meta-analysis demonstrated that the rs1801028 may be a risk factor for susceptibility to schizophrenia among Asians, while the rs1799732 may be a protective factor for that population. Large-sample studies are necessary to verify the results of this meta-analysis.

Keywords: dopamine D2 receptor, polymorphisms, schizophrenia

Introduction

Schizophrenia is a severe mental disorder characterized by changes in its higher functions and deterioration of behavior, cognition, emotions, motivation, and perception, and is marked by socio-occupational dysfunction. Schizophrenia manifests with a wide variety of positive (auditory hallucinations and paranoid delusions), negative (affective flattening, anhedonia, and alogia), and cognitive (declined attention and memory) symptoms.[1] It is a complex multifactorial psychiatry disorder involving genetic and environmental factors, with a global lifetime prevalence of 0.5%–1%.[2]

Family, twin, and adoption studies have shown that genetic factors play a significant role in the pathogenesis of schizophrenia, with the heritability of schizophrenia being estimated at 70%–80%.[3,4] Additionally, Lee et al estimated that 23% of variation in

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liability to schizophrenia is captured by single-nucleotide polymorphisms (SNPs).[5] For schizophrenia, some genetic factors were shared with other psychiatric disorders (bipolar disorder, major depressive disorder, autism spectrum disorders, and attention-deficit/hyperactivity disorder),[6] and some genetic factors associated with its risk were overlapped with those associated with reproduction traits (eg, age at first birth).[7] In short, schizophrenia is highly polygenic.[8]

The dopamine hypothesis is one of the main ideas for explaining the etiology of schizophrenia.[9] There are several lines of evidence implicating dopamine D2 receptor (DRD2) as the main candidate gene for the risk of schizophrenia.[10] In humans, the *DRD2* gene is located on chromosome 11 at q22–q23, extends over 270 kb, and has eight exons.[11] Associations between schizophrenia risk and four SNPs have been widely studied: rs1799732 (–141C Ins/Del), rs1801028 (311 Ser/Cys), rs1800497 (TaqIA), and rs6277 (C957T).[12,13] The rs1799732 SNP is located in the *DRD2* promoter region and has been demonstrated to affect gene expression in vitro.[14] The rs1801028 SNP is the missense variant 960C/G in exon 7 of the *DRD2* gene[15] that can alter the physiology and function of the D2 receptor.[12] The rs1800497 SNP was previously thought to be located in the *DRD2* 3′-untranslated region and was recently identified as being in exon 8 of the ankyrin repeat and kinase domain containing 1 (ANKK1) gene. This SNP has been considered to alter substrate-binding specificity.[16] The rs6277 SNP is located in exon 7 of the *DRD2* gene and alters mRNA folding, leading to a decrease in mRNA stability and translation, and markedly changing dopamine-induced up-regulation of *DRD2* expression.[17] In addition, associations between schizophrenia risk and the rs6275 (C939T), rs1079597 (TaqIB), and rs1800498 (TaqID) SNPs have been widely reported.[18,19]

While associations between *DRD2* gene polymorphisms and the risk of schizophrenia have been studied extensively, there are still some uncertainties about these associations. The present meta-analysis was therefore performed to further identify the associations between *DRD2* gene polymorphisms and schizophrenia risk. Meta-regression and publication bias, nonparametric trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analyses were also performed.

Method

Search strategy

The PubMed, Embase, and China National Knowledge Infrastructure databases were independently searched by two reviewers (He and Wu) to collect the literature related to associations between *DRD2* gene polymorphisms and schizophrenia risk. The last search update was performed in February 2016, and the following keywords were used in the literature search: "schizophrenia", "psychosis", "schizophrenic," "DRD2," "dopamine receptor 2," "dopamine receptor D2", "dopamine D2 receptor", "polymorphism", "variant", "variation", "allele", and "genotype". The species was limited to human. Moreover, the literature references in all of the included documents were searched to find more studies that were consistent with the eligibility criteria.

Eligibility criteria

1. Studies that met the following inclusion criteria were included:
   a) Research study with a case–control design.
   b) Written in Chinese or English.
   c) Investigation of the associations between *DRD2* gene polymorphisms and the risk of schizophrenia.
   d) Providing sufficient allele or genotype distribution data of the included cases and controls.
2. Studies that met any of the following exclusion criteria were excluded:
   a) Repetition of information in other literature.
   b) A review, comment, or conference proceedings.
   c) Results obtained in an animal model.
   d) Series of reports or case reports.

Research screening

The studies were first screened by browsing the titles and abstracts of the identified documents. Secondary screening was then performed by reading the full text of selected reports. Finally, data extraction and quality assessment were performed for the included studies.

Data extraction

In our present study, two reviewers (He and Wu) independently extracted the following information from the included literature: first author, publication year, mean age of the cases and controls, country, ethnicity, source of controls, numbers of cases and controls, *DRD2* gene locus, diagnostic criteria of schizophrenia, genotyping method, and conformity with Hardy–Weinberg equilibrium (HWE) for the controls. If the allele or genotype distribution data of the cases and controls were not reported in the original articles, the corresponding author was contacted by mail to obtain this information.

Quality assessment

Two authors (HH and HW) independently performed quality assessment using quality scoring criteria[20] based on criteria previously applied in observational studies for addressing genetic epidemiological issues, with the scores ranging from

0 points (worst) to 9 points (best) (Table S1). A study was classified as being of low quality when it scored <6 points. Sensitivity analysis was conducted by deleting these low-quality studies.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strengths of the associations between *DRD2* gene polymorphisms and schizophrenia risk. Pooled effect sizes were calculated using the random-effects model. This model evaluated different underlying influences considering both within- and between-study variations, which provided the advantage of accommodating diversity between studies and yielding a more conservative estimate of the assessed effect.[21] The present study used an allele comparison model because this maximized the number of included studies.

Cochran's *Q* statistic was used to estimate the degree of heterogeneity in the included studies. Heterogeneity was considered to be high when the *P*-value was <0.1. The heterogeneity was also quantified using the I^2 statistic and was considered high when I^2>50%. Based on clinical knowledge, the ethnicity and source of controls were considered to be responsible for heterogeneity, and so these parameters were set as covariates in the meta-regression. A subgroup analysis was also conducted.

Publication bias was analyzed using Begg's funnel plots. An asymmetrical funnel plot indicated the presence of significant publication bias. The symmetry of Begg's funnel plots was judged using Egger's linear regression, and a *P*-value of <0.05 was considered to indicate that the funnel plots were significantly asymmetrical. The trim-and-fill method was used to correct for publication bias and also to assess the impact of publication bias on the results.

Sensitivity analysis was used to assess both the potential impact of single studies on the pooled effect size and the impact of removing low-quality studies on the obtained results. Cumulative analysis by publication year was used to explore temporal trends in the results. Finally, the fail-safe number of negative studies that would be required to nullify (ie, make *P*>0.05) the effect size was calculated.

All of the statistical analyses were conducted using Stata software, version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

A flow chart of the study selection procedure is shown in Figure 1. Briefly, 1,267 studies were identified after eliminating 304 duplications. After reviewing the abstracts or reading full texts carefully according to eligibility criteria,

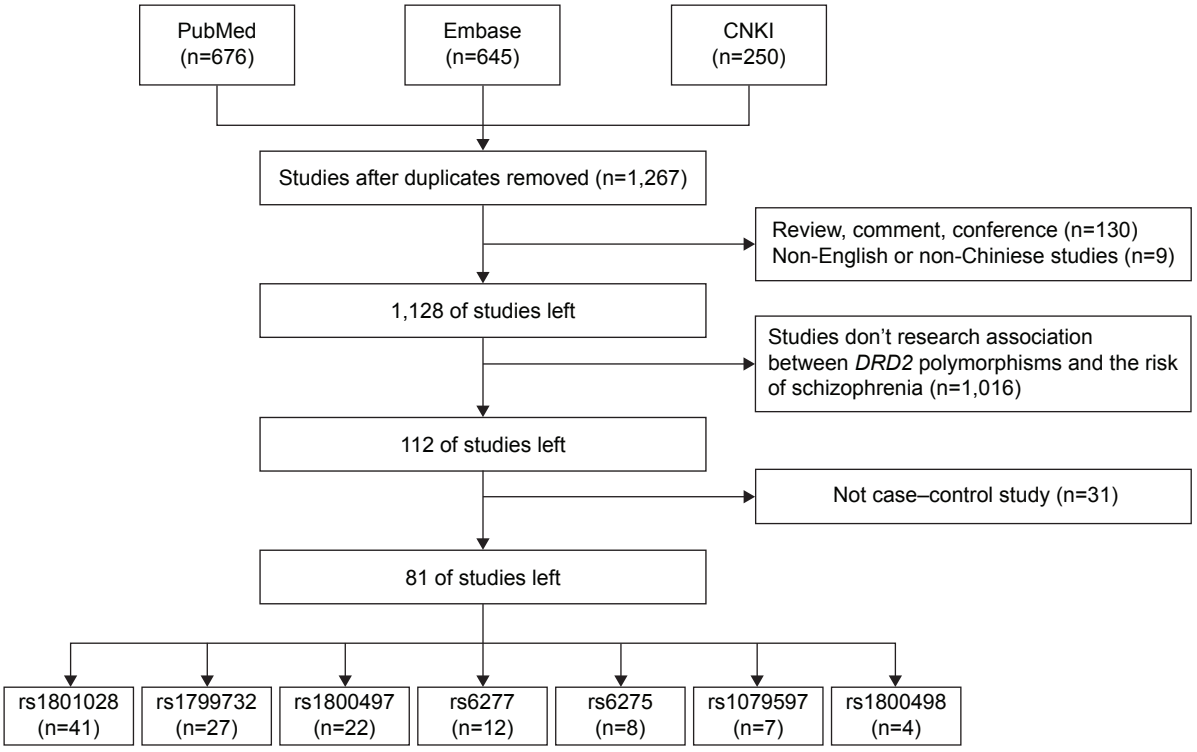

Figure 1 Flow diagram of the study selection process.
Abbreviations: CNKI, China National Knowledge Infrastructure; DRD2, dopamine D2 receptor.

a further 1,186 studies were excluded. Finally, 81 studies were identified for exploring the associations between *DRD2* gene polymorphisms and susceptibility to schizophrenia in a meta-analysis.

The main features of the included studies are listed in Table 1. The 81 studies comprised 45 studies focused on Caucasians, 34 on Asians, and 2 on mixed populations. The distributions of genotypes in the control groups deviated from HWE for the rs1801028, rs1800497, and rs1800498 SNPs in seven studies.[11,22–27] The quality assessment revealed that four studies were of low quality.[26,28–30]

Association between the rs1801028 (311 Ser/Cys) and schizophrenia risk

A meta-analysis of 42 case–control studies (9,771 cases and 11,900 controls) revealed that the variant allele G (Cys) was associated with increased schizophrenia risk in all populations (P=0.009, OR =1.23, 95% CI =1.05–1.44; Figure 2A). The fail-safe number was 104.52, and there was moderate heterogeneity (I^2=35%). Meta-regression indicated that the source of controls may have been responsible for this heterogeneity (P<0.01). The subgroup analysis, whose results are presented in Table 2, revealed that the G allele was associated with increased susceptibility to schizophrenia in Asians (P=0.04, OR =1.25, 95% CI =1.01–1.55) and hospital-based controls (P<0.01, OR =1.91, 95% CI =1.39–2.61).

Sensitivity analysis indicated that no single study qualitatively changed the pooled ORs (Figure 3). Removing the low-quality studies[26,29,30] did not change the results. Four of the studies deviated from HWE,[22,24,26,27] but removing them from the analysis did not change the results. Cumulative analysis by publication year confirmed that pooled ORs and 95% CIs were stable and that there was a reliable temporal trend in the results from 1996[31] (Figure 4).

In terms of publication bias, Egger's linear regression showed that the funnel plots were asymmetrical (P=0.023). The trim-and-fill method suggested that eight studies were missing, and the results for the association between the rs1801028 SNP and schizophrenia changed after replacing the data for these eight studies (OR =1.063, 95% CI =0.892–1.266; Figure 5). This indicates that our analyses were not stable and that future research is very likely to produce different results.

Association between the rs6277 (C957T) and schizophrenia risk

A meta-analysis of 12 case–control studies (2,919 cases and 3,600 controls) revealed that the variant allele T was associated with decreased schizophrenia risk (P=0.002, OR =0.80, 95% CI =0.69–0.92; Figure 2B). The fail-safe number was 91.00, there was high heterogeneity (I^2=58.5%), and meta-regression indicated that ethnicity may have been responsible for this heterogeneity (P<0.01). A subgroup analysis based on ethnicity showed that the T allele was associated with decreased susceptibility to schizophrenia in Caucasians (P<0.01, OR =0.72, 95% CI =0.66–0.79).

Cumulative analysis by publication year did not show a reliable temporal trend. Sensitivity analysis showed that no single study qualitatively changed the pooled ORs. In terms of publication bias, Egger's linear regression showed that the funnel plots were symmetrical (P=0.119).

Association between the rs1799732 (−141C Ins/Del) and schizophrenia risk

A meta-analysis of 27 case–control studies (6,770 cases and 7,347 controls) demonstrated that the rs1799732 SNP was not associated with schizophrenia risk (P=0.26, OR =0.91, 95% CI =0.78–1.07; Figure 2C). There was high heterogeneity (I^2=76%), and meta-regression indicated that neither ethnicity (P=0.119) nor the source of controls (P=0.452) was responsible for this heterogeneity. A subgroup analysis based on ethnicity showed that the variant type (−141C Del) was associated with decreased susceptibility to schizophrenia in Asians (P=0.004, OR =0.76, 95% CI =0.63–0.92). A subgroup analysis based on the source of controls found no significant association between the rs1799732 SNP and schizophrenia risk in population-based controls or hospital-based controls. In terms of publication bias, Egger's linear regression showed that the funnel plots were symmetrical (P=0.173).

Association between the rs1800497 (TaqIA) and schizophrenia risk

A meta-analysis of 22 case–control studies (4,017 cases and 4,209 controls) demonstrated that the rs1800497 SNP was not associated with schizophrenia risk (P=0.06, OR =0.87, 95% CI =0.75–1.01; Figure 2D). There was high heterogeneity (I^2=72%), and meta-regression indicated that neither ethnicity (P=0.612) nor the source of controls (P=0.372) was responsible for this heterogeneity. A subgroup analysis based on the source of controls revealed that the variant allele A (A2) was associated with decreased schizophrenia risk in population-based controls (P<0.01, OR =0.84, 95% CI =0.72–0.97). A subgroup analysis based on ethnicity revealed that the rs1800497 SNP was also not associated with susceptibility to

Table 1 Characteristics of case–control studies on *DRD2* gene polymorphisms and schizophrenia risk included in the meta-analysis

Author	Year	Country	Ethnicity	No of sample		Control sources	Mutation analysis method	Criteria	SNP	HWE (*P*-value)	Quality score
				Cases	Controls						
Caprini et al[28]	2011	Scandinavia	Caucasians	837	1,471	PB	–	ICD-10 + DSM-III-R + DSM-IV	TaqID	Yes	5
Dollfus et al[35]	1996	France	Caucasians	62	161	PB	PCR-RFLP	DSM-III-R	TaqIA	Yes	8
Luo[24]	2008	China	Asians	211	201	PB	Direct sequencing	DSM-IV	−141C Ins/Del	Yes	6
Watanabe et al[36]	2012	Japan	Asians	648	664	PB	TaqMan	DSM-IV	Ser311Cys	Yes	7
Crawford et al[31]	1996	America	Caucasians	84	81	HB	Direct sequencing	DSM-III-R	Ser311Cys	Yes	6
Dubertret et al[13]	2010	France	Caucasians	50	50	PB	PCR	DSM-IV	TaqIB	–	–
									TaqIA	Yes	7
Himei et al[37]	2002	Japan	Asians	190	103	PB	PCR-RFLP	DSM-IV	Ser311Cys	Yes	7
									−141C Ins/Del	Yes	7
Jonsson et al[87]	1996	Sweden	Caucasians	118	78	PB	PCR	DSM-III-R	TaqIA	Yes	7
Kunii et al[62]	2014	Japan	Asians	12	12	PB	PCR-RFLP	DSM-IV	TaqIA	Yes	8
Srivastava et al[4]	2010	India	Caucasians (Indians)	233	224	PB	PCR-RFLP	DSM-IV	−141C Ins/Del	Yes	8
									TaqIA	Yes	8
									TaqIB	–	–
									Ser311Cys	Yes	8
Arinami et al[47]	1996	Japan	Asians	136	279	PB	PCR	ICD-10 + DSM-III-R	Ser311Cys	Yes	7
Arinami et al[57]	1997	Japan	Asians	260	312	PB	PCR-RFLP	DSM-III-R	−141C Ins/Del	Yes	7
Aslan et al[23]	2010	Turkey	Caucasians	99	109	PB	PCR	DSM-IV	TaqIA	No	6
Behravan et al[11]	2008	Iran	Caucasians	38	63	PB	PCR	DSM-IV	TaqIB	Yes	7
									TaqIA	No	6
Betcheva et al[1]	2009	Bulgaria	Caucasians	255	556	PB	PCR	DSM-IV	C957T	Yes	8
									C939T	Yes	8
Breen et al[63]	1999	England	Caucasians	439	437	PB	PCR	DSM-III-R + DSM-IV	−141C Ins/Del	Yes	7
Chen et al[38]	1996	China	Asians	114	88	PB	PCR	DSM-III-R	Ser311Cys	Yes	6
Cordeiro et al[14]	2009	Brazil	Mixed	229	733	PB	–	DSM-IV	−141C Ins/Del	Yes	8
Cordeiro and Vallada[16]	2014	Brazil	Mixed	235	834	PB	PCR	DSM-IV	TaqIA	Yes	8
Dubertret et al[15]	2004	France	Caucasians	103	83	PB	PCR-RFLP	DSM-IV	−141C Ins/Del	Yes	7
									TaqIB	–	–
									TaqID	–	–
									Ser311Cys	Yes	7
									TaqIA	Yes	7
Dubertret et al[13]	2010	France	Caucasians	144	142	PB	TaqMan	DSM-IV	TaqIA	Yes	8
									C957T	–	–
									Ser311Cys	Yes	8
									−141C Ins/Del	Yes	8
									TaqID	–	–
									TaqIB	–	–
Fan et al[39]	2010	China	Asians	421	404	PB	PCR	DSM-IV	Ser311Cys	Yes	7
									C957T	Yes	7
									C939T	Yes	7
Golimbet et al[40]	2011	Russia	Caucasians	366	387	PB	PCR	ICD-10	Ser311Cys	Yes	8
Gupta et al[41]	2009	India	Caucasians (Indians)	254	225	PB	PCR	DSM-IV	−141C Ins/Del	Yes	8

(*Continued*)

Table 1 (*Continued*)

Author	Year	Country	Ethnicity	No of sample		Control sources	Mutation analysis method	Criteria	SNP	HWE (*P*-value)	Quality score
				Cases	Controls						
									Ser311Cys	Yes	8
									C957T	Yes	8
									C939T	Yes	8
Hanninen et al[64]	2006	Finland	Caucasians	188	384	PB	PCR	DSM-IV	C957T	Yes	8
Harano[42]	1997	Japan	Asians	70	101	HB	PCR	DSM-III-R	Ser311Cys	Yes	6
Hoenicka et al[65]	2006	Spain	Caucasians	131	364	PB	PCR	DSM-IV	C957T	Yes	7
Hori et al[43]	2001	Japan	Asians	241	201	PB	PCR	DSM-IV	Ser311Cys	Yes	7
									−141C Ins/Del	Yes	7
Iwata et al[44]	2003	Japan	Asians	51	63	PB	PCR-RFLP	DSM-IV	Ser311Cys	Yes	7
Jonsson et al[66]	1999	Sweden	Caucasians	129	179	HB	PCR	DSM-III-R	−141C Ins/Del	Yes	6
Jonsson et al[45]	2003	Sweden	Caucasians	173	236	HB	PCR	DSM-III-R	Ser311Cys	Yes	6
Kaneshima et al[46]	1997	Japan	Asians	78	112	PB	PCR	RDC + DSM-IV	Ser311Cys	Yes	7
Kukreti et al[2]	2006	India	Caucasians (Indians)	101	145	PB	PCR	DSM-IV	C957T	Yes	8
									C939T	Yes	8
Kurt et al[67]	2011	Turkey	Caucasians	73	60	PB	PCR-RFLP	DSM-IV	−141C Ins/Del	Yes	7
Lafuente et al[68]	2008	Spain	Caucasians	243	291	HB	PCR	DSM-IV	TaqIB	Yes	7
									TaqIA	Yes	7
									−141C Ins/Del	Yes	7
Laurent et al[48]	1994	France	Caucasians	113	184	PB	–	DSM-III-R	Ser311Cys	Yes	6
Lawford et al[10]	2005	Australia	Caucasians	154	148	PB	PCR	DSM-IV	C957T	Yes	7
Li et al[70]	1998	England	Caucasians	151	145	HB	PCR	DSM-IV + DSM-III-R	−141C Ins/Del	Yes	6
Monakhov et al[69]	2008	Russia	Caucasians	311	364	PB	PCR	DSM-IV	C957T	Yes	7
									C939T	Yes	7
									TaqIA	Yes	7
Ohara et al[3]	1996	Japan	Asians	153	121	PB	PCR	DSM-IV	Ser311Cys	Yes	7
Ohara et al[71]	1998	Japan	Asians	170	121	PB	PCR	DSM-IV	−141C Ins/Del	Yes	8
Parsons et al[25]	2007	Spain	Caucasians	119	165	PB	PCR-RFLP	DSM-IV	−141C Ins/Del	Yes	7
									TaqIA	No	6
Saiz et al[72]	2010	Spain	Caucasians	288	421	PB	PCR-RFLP	DSM-IV	−141C Ins/Del	Yes	9
Sanders et al[49]	2008	Europe	Caucasians	1,870	2,002	PB	TaqMan	DSM-IV	Ser311Cys	Yes	8
									−141C Ins/Del	Yes	8
Sasaki et al[26]	1996	Europe	Caucasians	273	255	HB	PCR	DSM-III-R	Ser311Cys	Yes	5
Spurlock et al[50]	1998	Europe	Caucasians	373	413	PB	PCR	DSM-III-R	Ser311Cys	Yes	7
Stöber et al[73]	1998	German	Caucasians	260	290	PB	PCR	ICD-10	−141C Ins/Del	Yes	7
Tallerico et al[74]	1999	America	Caucasians	50	51	PB	PCR	DSM-III-R	−141C Ins/Del	Yes	7
Tanaka et al[51]	1996	Japan	Asians	106	106	PB	PCR	DSM-III-R	Ser311Cys	Yes	7
Tsutsumi et al[22]	2011	Japan	Asians	407	384	PB	PCR-RFLP	DSM-IV	C957T	Yes	7
									Ser311Cys	No	6
Verga et al[52]	1997	Italy	Caucasians	103	97	PB	PCR	DSM-III-R	Ser311Cys	Yes	7
Fujiwara et al[54]	1997	Japan	Asians	52	26	PB	PCR	DSM-IV + ICD-10	Ser311Cys	Yes	7
Kampman et al[75]	2003	Finland	Caucasians	93	94	PB	PCR	DSM-IV	−141C Ins/Del	Yes	7
Morimoto et al[55]	2002	Japan	Asians	48	48	PB	PCR	DSM-IV + ICD-10	Ser311Cys	Yes	7
Vijayan et al[19]	2007	India	Caucasians (Indians)	213	196	PB	PCR	DSM-IV	TaqIB	Yes	8

									TaqIA	Yes	8
									TaqID	Yes	8
									C939T	Yes	8
									Ser311Cys	Yes	8
Xiao et al[76]	2013	China	Asians	120	100	PB	PCR	DSM-IV-TR	−141C Ins/Del	Yes	7
Comings et al[77]	1991	America	Caucasians	87	69	HB	PCR	DSM-III-R	TaqIA	Yes	7
Sanders et al[78]	1993	America	Caucasians	55	51	PB	PCR-RFLP	DSM-III-R + RDC	TaqIA	Yes	8
Campion et al[79]	1994	France	Caucasians	80	80	PB	PCR-RFLP	DSM-III-R	TaqIA	Yes	7
Itokawa et al[58]	1993	Japan	Asians	50	110	PB	PCR-RFLP	DSM-III-R	Ser311Cys	Yes	7
							SSCP analysis				
Nothen et al[34]	1993	German	Caucasians	60	60	PB	PCR	DSM-III-R	TaqIA	Yes	7
Arinami et al[9]	1994	Japan	Asians	156	300	HB	PCR	DSM-III-R	Ser311Cys	Yes	6
Asherson et al[59]	1994	England	Caucasians	112	64	PB	PCR	DSM-III-R	Ser311Cys	Yes	6
Gejman et al[61]	1994	America	Caucasians	106	113	HB	PCR-RFLP	DSM-III-R	Ser311Cys	Yes	7
Hattori et al[27]	1994	Japan	Asian	100	100	PB	PCR-RFLP	DSM-III-R	Ser311Cys	No	6
Nanko et al[60]	1994	Japan	Asian	100	100	PB	PCR	DSM-III-R	Ser311Cys	Yes	6
Nothen et al[34]	1993	German	Caucasians	179	138	PB	PCR	DSM-III-R	Ser311Cys	Yes	7
Shaikh et al[29]	1994	England	Caucasians	147	100	HB	PCR	DSM-III-R	Ser311Cys	No	5
Sobell et al[30]	1994	America	Caucasians	338	1,914	HB	–	–	Ser311Cys	Yes	5
Inada et al[80]	1999	Japan	Asian	234	94	PB	PCR	ICD-10	−141C Ins/Del	Yes	8
Serretti et al[81]	2000	Italy	Caucasians	366	267	HB	–	–	Ser311Cys	Yes	–
Itokawa et al[53]	2010	Japan	Asian	156	300	HB	SSCP	DSM-III-R	Ser311Cys	Yes	7
				291	579		PCR				
Li[82]	2014	China	Asian	915	421	PB	PCR-AFLP	ICD-10 + CCMD-II-R	TaqIA	Yes	7
							Sequenom				
							MassARRAY				
Fan et al[56]	1996	China	Asian	105	108	PB	PCR	ICD-10	Ser311Cys	Yes	7
Liu et al[33]	2012	China	Asian	317	310	PB	PCR	DSM-IV	TaqIA	Yes	7
Liu et al[83]	2009	China	Asian	128	124	PB	PCR-RFLP	CCMD-3	−141C Ins/Del	Yes	7
Luo[24]	2008	China	Asian	512	480	PB	PCR	DSM-IV	−141C Ins/Del	Yes	7
									Ser311Cys	No	6
									C957T	Yes	7
									C939T	Yes	7
									TaqIA	No	6
Shen et al[84]	2011	China	Asian	120	100	PB	PCR	DSM-IV	−141C Ins/Del	Yes	7
Zhang et al[85]	2003	China	Asian	67	77	PB	PCR	CCMD-II-R	TaqIA	Yes	6
Zheng[18]	2012	China	Asian	92	96	PB	PCR	–	C957T	Yes	6
									C939T	Yes	6
									Ser311Cys	Yes	6
Liang[86]	2005	China	Asian	101	105	PB	PCR	DSM-IV + CCMD-3	−141C Ins/Del	Yes	7

Abbreviations: AFLP, amplified fragment length polymorphism; CC, complication or comorbidity; CCMD, Chinese Classification of Mental Disorders; DSM, The Diagnostic and Statistical Manual of Mental Disorder; HB, hospital-based; PB, population-based; HWE, Hardy–Weinberg equilibrium; ICD-10, International Statistical Classification of Diseases and Related Health Problems – 10th version; PCR, polymerase chain reaction; RDC, Research Diagnostic Criteria; SNP, single-nucleotide polymorphisms; RFLP, restriction fragment length polymorphism.

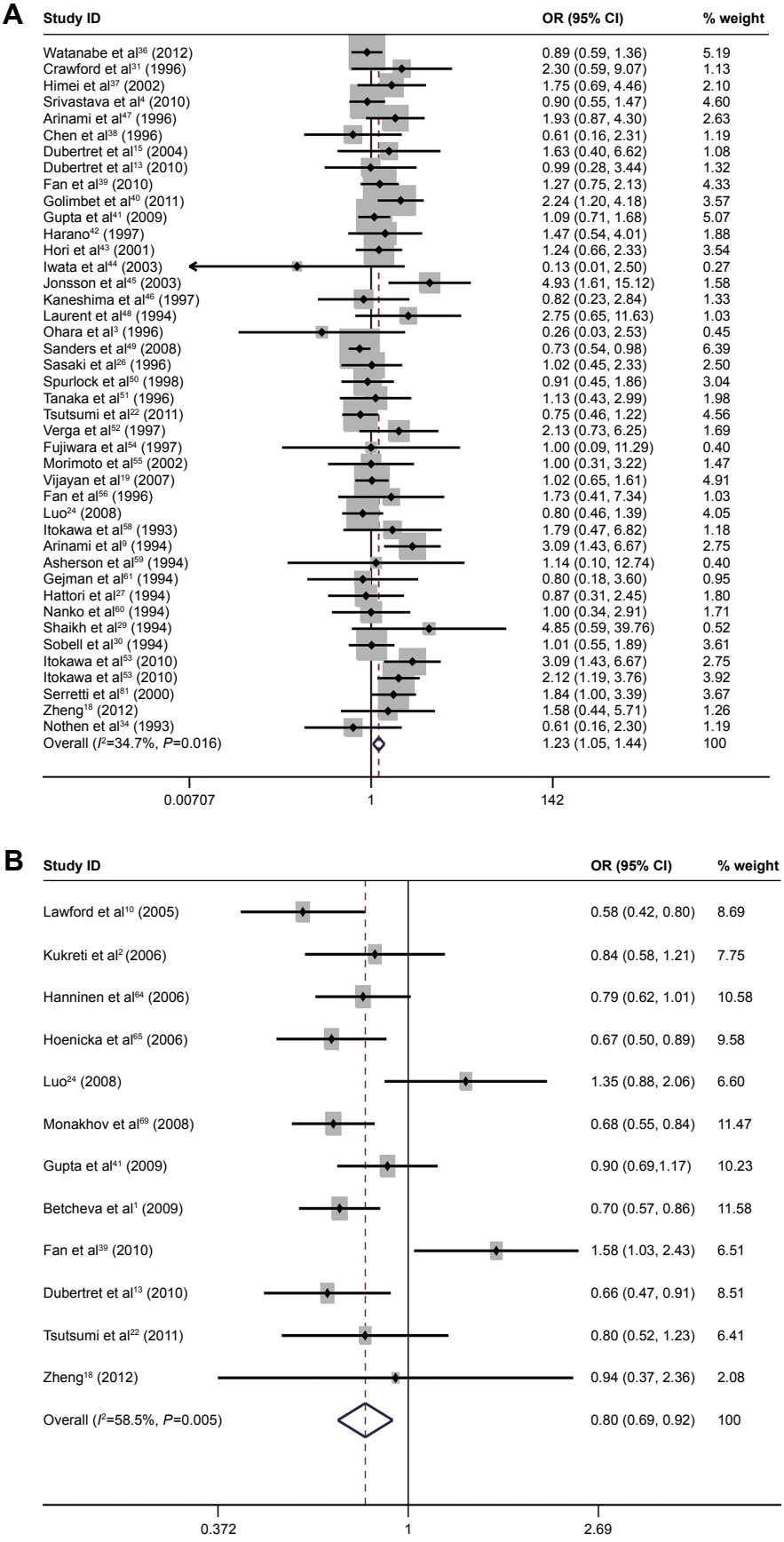

Figure 2 (*Continued*)

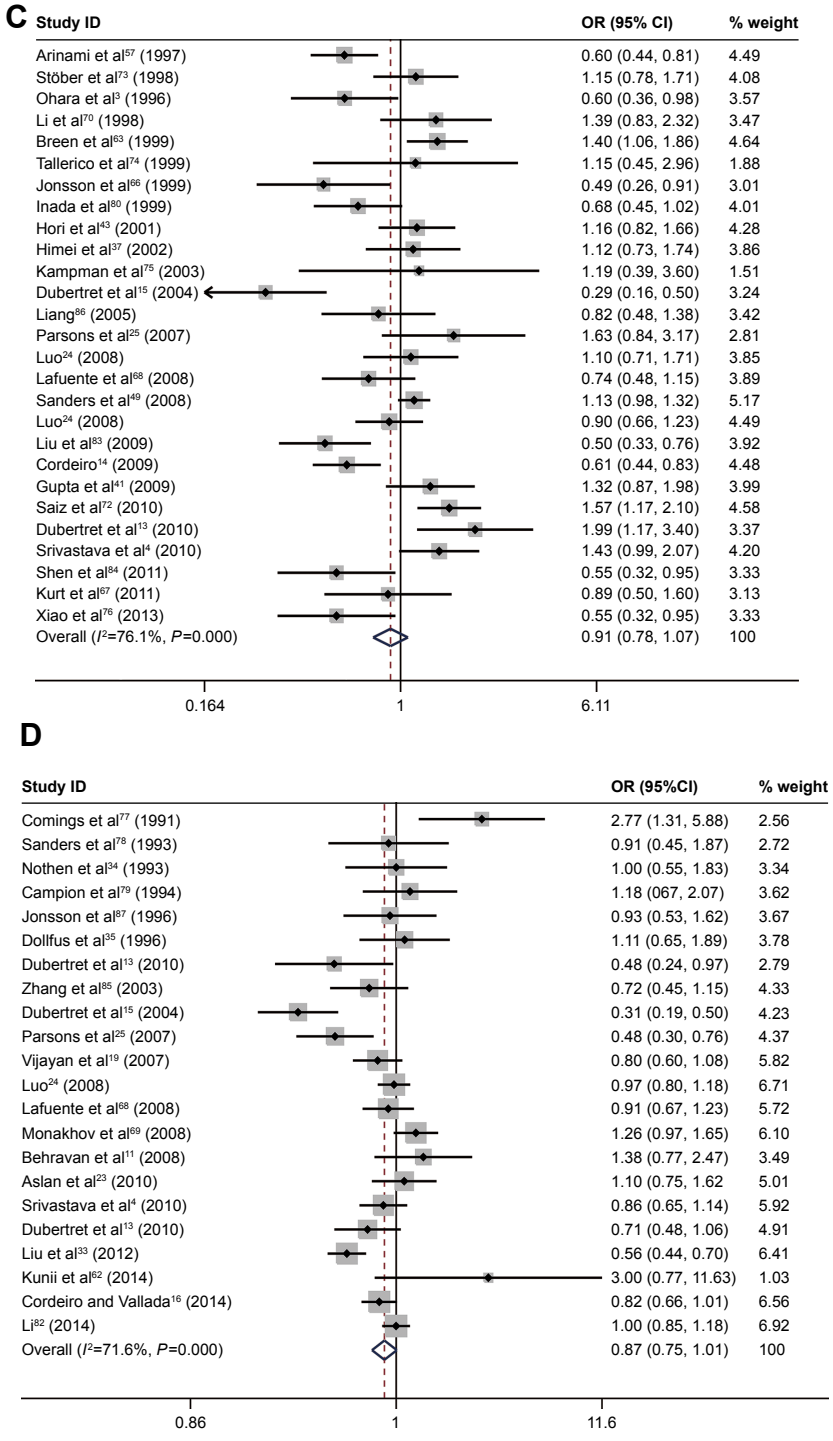

Figure 2 Calculated OR and 95% CI for the associations between *DRD2* gene polymorphism and schizophrenia risk.
Notes: (**A**) rs1801028; (**B**) rs6277; (**C**) rs1799732; (**D**) rs1800497. weights are from random effects analysis.
Abbreviations: CI, confidence interval; DRD2, dopamine D2 receptor; OR, odds ratio.

schizophrenia. There were four studies of the rs1800497 SNP that included controls that did not conform with HWE, but they did not influence the results.[11,23–25] In terms of publication bias, Egger's linear regression showed that the funnel plots were symmetrical (P=0.861).

Association between the other SNPs and schizophrenia risk

There was no evidence that the susceptibility to schizophrenia was associated with the rs6275 (T vs C, P=0.10, OR =0.92, 95% CI =0.83–1.02), rs1079597 (T vs C, P=0.12, OR =0.72, 95%

Table 2 Subgroup analysis of case–control studies on *DRD2* gene polymorphisms and schizophrenia risk

SNP	Subgroup type	Subgroup	N	*P*-value	OR	95% CI	I^2 (%)
rs1801028	Control sources	Population-based	31	0.99	1.00	0.88, 1.14	0
		Hospital-based	11	<0.01	1.91	1.39, 2.61	31
	Ethnicity	Caucasians	19	0.09	1.22	0.97, 1.54	41
		Asians	23	0.04	1.25	1.01, 1.55	31
rs6277	Ethnicity	Caucasians	8	<0.01	0.72	0.66, 0.79	0
		Asians	4	0.37	1.17	0.83, 1.64	46
rs1799732	Control sources	Population-based	24	0.36	0.92	0.78, 1.10	77
		Hospital-based	3	0.46	0.81	0.47, 1.41	71
	Ethnicity	Caucasians	15	0.33	1.11	0.90, 1.36	71
		Asians	11	0.004	0.76	0.63, 0.92	56
		Mixed	1	0.002	0.61	0.44, 0.83	–
rs1800497	Control sources	Population-based	20	0.02	0.84	0.72, 0.97	71
		Hospital-based	2	0.46	1.50	0.51, 4.47	86
	Ethnicity	Caucasians	16	0.24	0.88	0.72, 1.08	71
		Asians	5	0.29	0.85	0.63, 1.15	82
		Mixed	1	0.06	0.82	0.66, 1.01	–

Abbreviations: CI, confidence intervals; DRD2, dopamine D2 receptor; OR, odds ratios; SNP, single-nucleotide polymorphisms.

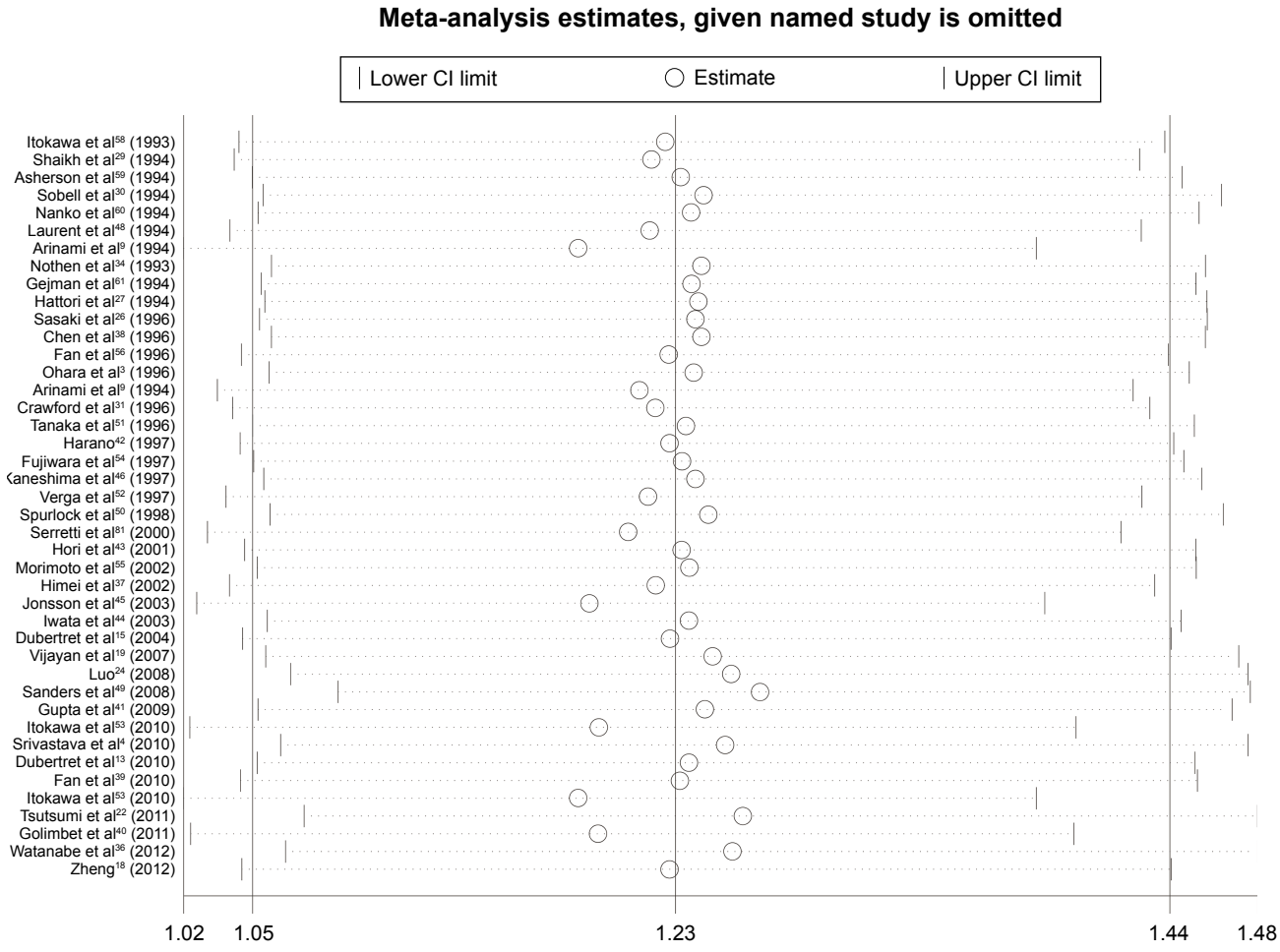

Figure 3 Sensitivity analysis via deletion of each individual study reflecting the relative influence of each individual dataset on the pooled ORs for the rs1801028.
Abbreviations: CI, confidence interval; OR, odds ratio.

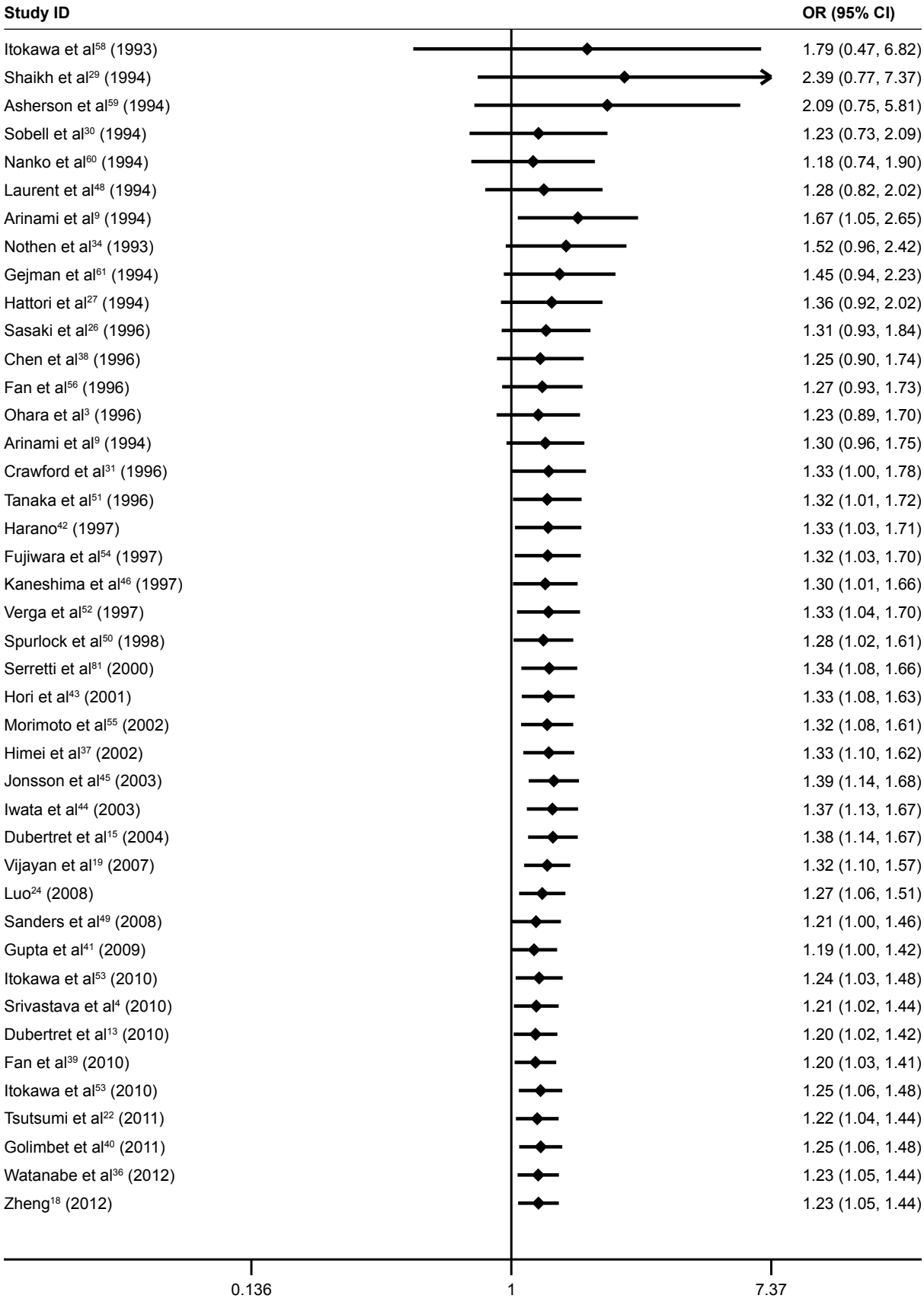

Figure 4 Cumulative meta-analyses according to publication year for the rs1801028.

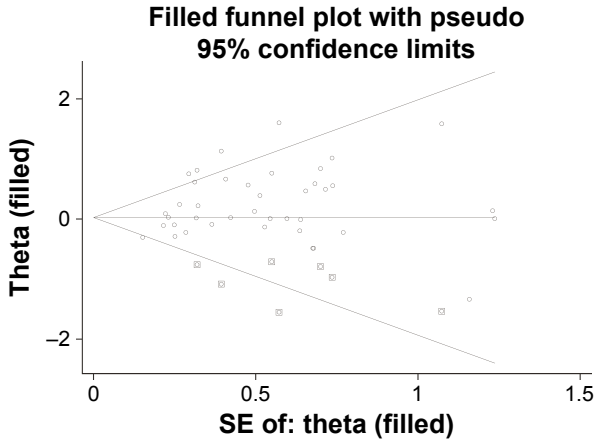

Figure 5 Trim-and-fill plot to correct publication bias for the rs1801028.
Abbreviation: SE, standard error.

CI =0.47–1.10), or rs1800498 (T vs C, *P*=0.52, OR =1.03, 95% CI =0.93–1.15) SNP. Sensitivity analysis indicated that no single study of the rs1800498 SNP qualitatively changed the pooled ORs. Removing the low-quality study[28] did not change the result.

Discussion

A comprehensive analysis about schizophrenia-associated genetic loci had been performed in a genome-wide association study.[32] Our meta-analysis results provide evidence that the rs1801028 and rs6277 SNPs are associated with the risk of schizophrenia. A subgroup analysis indicated that the rs1801028 SNP may increase the risk of schizophrenia in Asians and hospital-based controls, the rs6277 SNP may reduce the risk of schizophrenia in Caucasians, the rs1799732 SNP may reduce the risk of schizophrenia in Asians, and the rs1800497 SNP may reduce the risk of schizophrenia in population-based controls.

Yao et al performed a similar study of the associations between *DRD2* gene polymorphisms and schizophrenia risk.[12] That study used a genetic model, while our study used an allele contrast model since this made it possible to include the largest number of documents and the maximum sample sizes. Other advantages of the present study were 1) the inclusion of more published documents (including those written in Chinese), which increased the statistical power of our results, 2) more SNPs being investigated, and 3) the application of meta-regression and publication bias, nonparametric trim-and-fill, subgroup, sensitivity, cumulative, and fail-safe number analysis also being performed.

The results of the present study show that the rs1801028 SNP may increase the risk of schizophrenia in Asians and hospital-based controls. Yao et al reported the same result under the dominant model.[12] Different results may be obtained for different races due to differences in genetic backgrounds and living conditions.[33] Moreover, the results for the subgroup analysis based on hospital-based controls are not reliable because such controls may not be representative and samples of hospital-based controls are often too small, and so these results should be treated cautiously. The results for publication bias were significant, and these changed after being adjusted using the trim-and-fill method, which indicated that those results may not be very stable. This means that if new articles are published in the future, the results of a complete meta-analysis including all available data are very likely to change. The presence of significant publication bias was probably due to our meta-analysis including many small-sample studies. Yao et al found only slight publication bias, but this was not corrected using the trim-and-fill method.[12]

Twelve of the included documents related to the rs6277 SNP and the meta-analysis showed that this SNP may reduce the risk of schizophrenia in Caucasians; however, Yao et al did not study this SNP.[12] However, our included samples for this SNP were small and the cumulative analysis by publication year did not show a reliable trend. This means that the statistical power of the results may not have been high.

In our meta-analysis the rs1799732 SNP was not associated with schizophrenia risk, and Yao et al obtained the same result under the dominant model.[12] After performing subgroup analysis, the current meta-analysis indicated that the rs1799732 SNP might reduce the risk of schizophrenia in Asians. In contrast, Yao et al did not find any correlation between the rs1799732 SNP and schizophrenia risk in different races and different populations. The possible reasons for different conclusions being drawn based on the current and previous meta-analyses of the rs1799732 SNP are 1) more documents being included in the present study, especially the Chinese literature, because this is likely to have greatly increased the sample size for Asians, and 2) the use of different genetic models.

The previous meta-analyses did not explore the correlations between the rs1800497 SNP and schizophrenia risk in all populations. After performing subgroup analysis, the present study found that the rs1800497 SNP was associated with schizophrenia risk in population-based controls. In contrast, Yao et al found that the rs1800497 SNP may increase the risk of schizophrenia in Caucasians.[12] The possible reasons for the current and previous meta-analyses drawing different conclusions from their subgroup analyses of the rs1800497 SNP are 1) Yao et al applying the wrong allele or genotype distribution data of cases and controls regarding the study of Nothen et al;[34] 2) the smallness of the study sample of Yao et al; 3) that study not including Chinese studies; and

4) our use of different genetic models. These factors mean that the statistical power would have been higher for the present study.

It is important to note the limitations of our meta-analysis. 1) Meaningless or negative results might not be published, which would lead to some degree of publication bias. 2) Schizophrenia is a multifactorial disease, whereas the present study only considered the impact of the *DRD2* gene on schizophrenia risk, and also ignored the possible impacts of environmental factors, age, gender, lifestyle, and diagnosis standards.

In conclusion, this meta-analysis has shown that the rs1801028 SNP may be a risk factor for susceptibility to schizophrenia in Asians, the rs6277 SNP may be a protective factor for susceptibility to schizophrenia in Caucasians, and the rs1799732 SNP may be a protective factor for susceptibility to schizophrenia in Asians. However, the occurrence of schizophrenia represents the cumulative effect of multiple genes, and so only studying a single gene or single polymorphism is unlikely to be adequate. Future studies should pay more attention to the interactions within and between genes as well as within and between their polymorphisms in order to better explain the genetic mechanisms underlying mental illness.

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Author contributions

HRH and HHW performed literature research, data extraction, statistical analysis, and data interpretation. XCM contributed to the study concept and study design. LHY and FG contributed to make figures and tables. YJF and JGF were responsible for the quality control of data and algorithms. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Scale for quality assessment

Criteria	Score
Representativeness of cases	
Consecutive/randomly selected form case population with clearly defined sampling frame	2
Consecutive/randomly selected form case population without clearly defined sampling frame or with extensive	1
Not described	0
Definition of the DR	
Population- or health-based	2
Hospital-bases	1
Not described	0
Hardy–Weinberg equilibrium in controls	
Hardy–Weinberg equilibrium	2
Hardy–Weinberg disequilibrium	1
Genotyping examination	
Genotyping done under "blinded" condition	1
Unblinded done or not mentioned	0
Association assessment	
Assess association between genotypes and head and neck cancer with appropriate statistics and adjustment for confounders	2
Assess association between genotypes and head and neck cancer with appropriate statistics and without adjustment for confounders	1
Inappropriate statistics used	0