

The association between CD157/BST1 polymorphisms and the susceptibility of Parkinson's disease: a meta-analysis

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Background: Different studies have provided some evidence for the association between BST1 polymorphisms and Parkinson's disease (PD). The extent to which these genetic effects are consistent across different populations is unknown.

Methods: A meta-analysis of PD case-control studies using a common set of three variants was conducted. Published reports were obtained from electronic databases including Pubmed, Embase, Chinese National Knowledge Infrastructure (CNKI) and Cochrane Library databases between August 2010 and January 2018.

Results: A total of 11 individual studies with 8,725 cases and 17,079 controls were included. The results showed statistically significant association between the dominant model of rs11931532 and PD risk in Asian populations ($P=0.006$, OR [95% CI]=1.22 [1.06–1.41]). Significant association was also detected between the allelic, dominant, and recessive models of rs4698412 and PD risk in Asian populations (allelic model: $P<0.00001$, OR [95% CI]=1.22 [1.16–1.29]; dominant model: $P<0.00001$, OR [95% CI]=1.35 [1.20–1.52]; recessive model: $P=0.0003$, OR [95% CI]=1.30 [1.13–1.50]). Nevertheless, the pooled analyses suggested that no significant association was uncovered between rs11724635 and PD risk ($P>0.05$).

Conclusion: The meta-analysis suggests that the rs11931532 and rs4698412, but not rs11724635 might be risk factors for PD in Asian populations.

Keywords: BST1, Parkinson's disease, polymorphisms, risk factor

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease that affects 1–2% of individuals aged ≥ 65 years.^{1,2} The progressive loss of the nigro-striatal dopaminergic neurons and presence of Lewy bodies were shown to be the most important histopathological features.^{3,4} Increasing evidence has supported that multiple genes, environmental factors including smoking, alcohol consumption, well water and pesticide use, as well as the interactions among these aspects, contributed to the etiology of PD.^{5–7} To date, genome-wide association (GWA) studies and familial PD cases studies have identified Alpha-synuclein (SNCA),⁸ Leucine rich repeat kinase 2 (LRRK2),⁹ Parkins (PARK3/9/10/11/15/16/17/18),^{10–15} HLA-DQB1,¹⁶ serine threonine kinase 39 (STK39),¹⁷ and bone marrow stromal cell antigen 1 (BST1)¹⁸ to be the susceptible loci for PD.

BST1, also referred to as CD157, is located on human chromosome 4 (4p15) and belongs to the NADase/ADP-ribosyl cyclase family, which is also a member of the CD38 gene family.^{6,19} Recent genetic analysis identified the CD157/BST1 gene

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as a susceptibility marker for PD. The genetic association between BST1 polymorphisms such as rs11931532, rs12645693, rs4698412, and rs4538475 and PD risk have been reported in several populations by GWA and case-control studies.^{8,20–24} Although numerous studies have demonstrated the association, inconsistency was presented for different allele frequencies among study populations, particularly in different ethnicity and geographical groups.^{10,15,25–28}

Meta-analysis is an effective tool to compensate the limitations by combining all publications and improve statistical power to obtain potential effects of an individual study with small or moderate sizes of subjects. The purpose of performing this meta-analysis is to reduce heterogeneity and summarize the published evidence on the prevalence of the BST1 polymorphisms among patients diagnosed with PD.

Materials and methods

Identification of eligible studies

This meta-analysis followed the Cochrane collaboration definition and PRISMA 2009 guidelines for meta-analysis and systematic review.²⁹ Literature were searched on electronic databases including Pubmed, Embase, Chinese National Knowledge Infrastructure (CNKI) databases, and the Cochrane Library databases with the following terms: bone marrow stromal cell antigen 1; BST1; CD157; polymorphism; single nucleotide polymorphism; SNP; and Parkinson's disease; PD. No language was limited. The search deadline for publications was June 1, 2018. Other potentially relevant studies were retrieved by cross-references.

Inclusion criteria: (1) case-control or cohort designed study; (2) refer to the association of BST1 polymorphisms and PD risk; (3) the genotype data in the studies were sufficient and available to extract; and (4) the distribution of genotypes in the control group were in Hardy-Weinberg equilibrium (HWE).

Exclusion criteria: (1) repeated studies, letters, dissertations, abstracts or reviews; and (2) publications that violated the inclusion criteria.

Data extraction

Two independent investigators (L.J. and L.L.) manually extracted the data. Any disagreements were resolved through discussion among the authors to achieve a consensus. Information on the first author, published year, ethnicity, number of cases and controls, genotyping methods, mean ages of

cases and controls, ratio of male:female, Hardy-Weinberg equilibrium (HWE) for control group, number of alleles and genotype, and SNPs were extracted, and are listed in Table 1. All discrepancies were resolved by a consensus achieved by J. M.L.

Quality assessment

All included studies were evaluated using the Newcastle-Ottawa Scale (NOS)³⁰ independently by L.L. and F.H. Any discrepancies in the assessment were resolved by the third author (L.T.). Adequacy of case definition, representative of the cases, selection of controls, definition of controls, comparability cases/controls, comparability cases/controls, same method of ascertainment, and non-response rate were taken into account and given a corresponding score. The quality scores ranged from 0–9. Only studies with a score of 6 or higher were included.

Statistical methods

All statistical analyses were performed using the STATA 12.0 software (StataCorp, College Station, TX, USA) and Revman 5 (Cochrane Collaboration, London, UK). The odds ratio (OR) and 95% confidence interval (95% CI) were calculated for evaluating the association between BST1 polymorphisms and PD risk. The pooled ORs were calculated using a genetic model of allelic, recessive, and dominant models. The statistical significance of the OR was determined using the *Z*-test. Variation and heterogeneity were evaluated using Cochran's *Q*-statistic. The random effect model was used when there was significant heterogeneity across studies ($I^2 > 50\%$ or $P < 0.05$), otherwise the fixed effect model was used in meta-analysis. Sources of heterogeneity were evaluated by stratification analysis of ethnicity. Sensitivity analysis was performed to assess the effects of individual study on pooled results and the stability of results. The publication bias was detected with Begg's test and Egger's test. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the studies

As shown in Figure 1, a total of 1,173 studies were identified through the initial search. After screening the titles and abstracts, 37 studies were excluded for being duplicated studies, and 1,085 studies were excluded for not being related to the genetic association between BST1 polymorphisms and PD risk. After reading the full articles, 35 studies were excluded for being reviews, letters, short

Table 1 Characteristics of included studies

Reference	Year	Ethnicity/ location	Case	Control	Genotyping methods	Age (mean ±SD), case/ control	Female %, case/ control	HWE	SNPs	NOS
Chang et al ²²	2011	Chinese	636	510	Massarray	55.83±11.18/ 52.44±14.01	40.6%/ 43.1%	<i>P</i> >0.05	rs11931532; rs4698412; rs11724635	7
Miyake et al ²⁸	2012	Japanese	229	357	TaqMan	68.4±8.7/ 66.6±8.5	61.6%/ 61.1%	<i>P</i> >0.05	rs11931532; rs11724635	8
Chang et al ²³	2015	Chinese	596	597	Agena Massarray	68.68±10.82/ 60.0±12.7	45.9%/ 54.4%	<i>P</i> >0.05	rs11724635	7
Cui et al ²⁶	2018	Chinese	168	196	Massarray	68.82±10.70/ 67.35±5.51	41.7%/ 45.4%	<i>P</i> >0.05	rs11931532; rs4698412	6
Tian ³¹	2012	Chinese	1,019	1,030	Sequencing	54.16±12.50/ 52.16±16.45	41.5%/ 47.6%	<i>P</i> >0.05	rs11931532; rs4698412	7
Satake et al [1] ²⁰	2011	Japanese	1,078	2,628	HumanHap550 array	NA	NA	<i>P</i> >0.05	rs11931532; rs4698412	6
Satake et al [2] ²⁰	2011	Japanese	988	2,521	HumanHap550 array	NA	NA	<i>P</i> >0.05	rs11931532; rs4698412	6
Tan et al ¹⁰	2010	Chinese	433	916	Massarray	NA	44%/40%	<i>P</i> >0.05	rs11931532; rs4698412	6
Simón- Sánchez et al ²⁵	2011	the Netherlands	772	2,024	Human660W- Quad array	57.5±12.0/ 53.75±13.4	39.9%/ 53.6%	<i>P</i> >0.05	rs11931532; rs4698412	8
Spencer et al ⁸	2011	UK	2,190	5,667	Human660- Quad array	NA	27.0%/NA	<i>P</i> >0.05	rs4698412	6
Xie ³²	2011	Chinese	744	743	Sequencing	53.05±10.9/ 52.34±12.1	36.7%/ 41.6%	<i>P</i> >0.05	rs4698412	6
Chen et al ²⁷	2014	Chinese	468	487	TaqMan	66.02±9.46/ 67.16±9.33	49.8%/ 66.5%	<i>P</i> >0.05	rs11724635	8

Abbreviations: HWE, Hardy-Weinberg equilibrium; SNP, single nucleotide polymorphism; NOS, Newcastle-Ottawa scale; NA, not available.

communications, or conference abstracts. In addition, five studies were excluded for unavailable data. Overall, a total of 11 studies were finally enrolled in the present meta-analysis.^{8,10,20,22,23,25–28,31,32} Among these studies, the study conducted by Satake et al²⁰ involved two different groups. We treated each group as an individual study. Therefore, there were 12 studies with 8,725 PD patients and 17,097 healthy controls in the present meta-analysis. Two studies were on Caucasians,^{8,25} the others were on Asians.^{10,20,22,23,26–28,31,32} A total of eight, nine, and three studies have reported the association between rs11931532, rs4698412, and rs11724635 and PD risk, respectively. The genetic distributions of the control groups in all studies were all consistent with the Hardy-Weinberg equilibrium (HWE). The Newcastle-Ottawa Scale (NOS) was used for quality assessment, and all of the studies achieved moderately high quality scores above 6 (Tables 1 and S1).

Results of meta-analysis

Significant association was observed between the dominant model (TT+CT/CC) of rs11931532 and PD risk (*P*=0.006, OR [95%CI]=1.22 [1.06–1.41]), but not in allelic (T/C) and recessive models (TT/CT+CC) of rs11931532 (allelic model: *P*=0.25, OR [95%CI]=1.24 [0.86–1.78]; recessive model: *P*=0.47, OR [95%CI]=1.05 [0.91–1.22]) (Table 2, Figure 2). Subgroup analysis stratified by ethnicity showed that the significant association between the dominant model (TT+CT/CC) of rs11931532 and PD risk can only be found in the Asian subgroup (*P*=0.01, OR [95%CI]=1.24 [1.05–1.47]), but not in the Caucasian subgroup (Table 2).

For rs4698412, significantly different distributions in cases and controls were detected between the allelic, dominant, and recessive models and PD risk (allelic model: *P*<0.0001, OR [95%CI]=1.16 [1.08–1.25]; dominant model: *P*<0.00001, OR [95%CI]=1.35 [1.20–1.52];

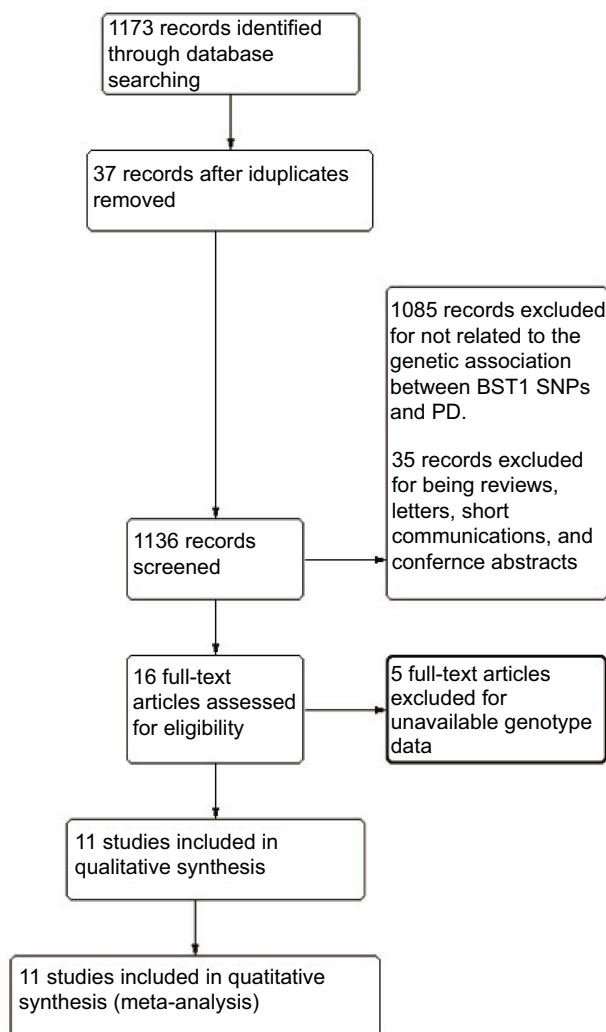


Figure 1 PRISMA flow chart of studies included and excluded.

recessive model; $P=0.0003$, OR [95%CI]=1.30 [1.13–1.50]) (Table 2, Figure 3). Subgroup analysis stratified by ethnicity showed that significant associations between the allelic, dominant, and recessive models of rs4698412 and PD risk can only be found in the Asian subgroup (allelic model: $P<0.00001$, OR [95%CI]=1.22 [1.16–1.29]; dominant model: $P<0.00001$, OR [95%CI]=1.35 [1.20–1.52]; recessive model; $P=0.0001$, OR [95%CI]=1.30 [1.13–1.50]), but not in the Caucasian subgroup ($P>0.05$) (Table 2).

No association was found between genetic models of rs11724635 and PD risk (Table 2, Figure 4). The subgroup analysis stratified by ethnicity was canceled for lack of sufficient data in the Caucasian group.

Heterogeneity

Significant heterogeneity were detected in the allelic model of rs11931532 ($P<0.00001$, $I^2=98%$) and the allelic model

of rs4698412 ($P=0.003$, $I^2=65%$). Therefore, subgroup analysis stratified by ethnicity was performed. Notably, the significant heterogeneity of the allelic model of rs11931532 was found in the Asian subgroup ($P<0.00001$, $I^2=98%$). The significant heterogeneity of the allelic model of rs4698412 disappeared in both Asian ($P=0.43$, $I^2=0%$) and Caucasian subgroups ($P=0.08$, $I^2=67%$) (Table 2). For the allelic model of rs11931532 in the Asian subgroup, this heterogeneity was contributed mainly by one positive study conducted by Satake et al⁶⁷. Removal of this study from meta-analysis gave 0% ($P=0.61$) heterogeneity.

Sensitive analysis and publication bias

Sensitivity analysis which excluded the influence of a single study on the overall risk estimate by excluding one study at a time was confirmed. The ORs were not significantly altered in genetic models of rs11931532, rs4698412, and rs11724635 in BST1 (Figure 5). Begg's test and Egger's test were used to evaluate publication bias. The P -value for Egger's linear regression test is shown in Figure 6. The results revealed that there was no obvious publication bias in overall analysis for BST1 rs11931532 ($p_{\text{egger}}=0.435$), rs4698412 ($p_{\text{egger}}=0.394$), and rs11724635 ($p_{\text{egger}}=0.649$) (Figure 6).

Discussion

In the present study, we have detected a significant association between the allelic, dominant, and recessive models of rs4698412, as well as the dominant model of rs11931532 and PD risk. To the best of our knowledge, this is the first study observing the genetic associations between BST1 rs4698412 and rs11931532 and PD risk using a meta-analysis.

CD157/BST-1 plays a variety of roles in humoral immune responses; neutrophil transmigration and hematopoietic stem cell support.^{33,34} BST-1 produces cyclic ADP-ribose, which is a second messenger that releases Ca^{2+} from intracellular Ca^{2+} stores. Ca^{2+} dyshomeostasis has been proposed a possible cause of selective vulnerability of dopaminergic neurons in PD.^{35,36} The rs11931532 and rs4698412 were located from intron 8 to 4.1 kb downstream of BST1 separately and may modify ADPribosylcyclase activity, thus leading to Ca^{2+} dyshomeostasis in dopaminergic neurons.^{20,37} There are an increasing number of new pathogenic variants located in introns. Recent evidence suggested that many disease-related intronic SNPs have been reported to be responsible for aberrant splice processes.^{38,39} Satake et al²⁰ have also suggested rs11931532 may modify ADPribosylcyclase activity, thus leading to Ca^{2+} dyshomeostasis

Table 2 The association between BST1 polymorphisms and Parkinson's disease

SNPs (minor allele)	Genetic model	Subgroup	Number of studies	Numbers		Test of association		Model	Test of heterogeneity	
				Case	Control	OR [95% CI]	P-value		P-value	I ² (%)
rs11931532 (T)	Allelic (T)	Total	8	10,646	20,364	1.24 [0.86–1.78]	0.25	R	<0.00001	98
		Asian	7	9,102	16,316	1.28 [0.86–1.88]	0.22	R	<0.00001	98
	Dominant (TT+CT/CC)	Caucasian	1	1,544	4,048	1.00 [0.71–1.41]	0.25	–	–	–
		Total	4	2,052	2,093	1.22 [1.06–1.41]	0.006	F	0.77	0
		Asian	4	2,052	2,093	1.22 [1.06–1.41]	0.006	F	0.77	0
		Caucasian	0	–	–	–	–	–	–	–
	Recessive (TT/CT+CC)	Total	4	2,052	2,093	1.05 [0.91–1.22]	0.47	F	0.31	17
		Asian	4	2,052	2,093	1.05 [0.91–1.22]	0.47	F	0.31	17
		Caucasian	0	–	–	–	–	–	–	–
		Total	4	2,052	2,093	1.05 [0.91–1.22]	0.47	F	0.31	17
rs4698412 (A)	Allelic (A)	Total	9	16,056	32,470	1.16 [1.08–1.25]	<0.0001	R	0.003	65
		Asian	7	10,132	17,008	1.22 [1.16–1.29]	<0.00001	F	0.43	0
	Dominant (AA+GA/GG)	Caucasian	2	5,924	15,382	1.03 [0.92–1.16]	0.62	R	0.08	67
		Total	4	2,576	2,479	1.35 [1.20–1.52]	<0.00001	F	0.67	0
		Asian	4	2,576	2,479	1.35 [1.20–1.52]	<0.00001	F	0.67	0
		Caucasian	0	–	–	–	–	–	–	–
	Recessive (AA/GA+GG)	Total	4	2,576	2,479	1.30 [1.13–1.50]	0.0003	F	0.44	0
		Asian	4	2,576	2,479	1.30 [1.13–1.50]	0.0003	F	0.44	0
		Caucasian	0	–	–	–	–	–	–	–
		Total	4	2,576	2,479	1.30 [1.13–1.50]	0.0003	F	0.44	0
rs11724635 (A)	Allelic (A)	Total	3	2,586	2,882	1.07 [0.96–1.20]	0.19	F	0.34	7
		Asian	3	2,586	2,882	1.07 [0.96–1.20]	0.19	F	0.34	7
	Dominant (AA+CA/CC)	Total	3	1,293	1,441	1.08 [0.92–1.27]	0.33	F	0.56	0
		Asian	3	1,293	1,441	1.08 [0.92–1.27]	0.33	F	0.56	0
		Total	3	1,293	1,441	1.12 [0.92–1.37]	0.25	F	0.42	0
	Recessive (AA/CA+AA)	Total	3	1,293	1,441	1.12 [0.92–1.37]	0.25	F	0.42	0
		Asian	3	1,293	1,441	1.12 [0.92–1.37]	0.25	F	0.42	0

Abbreviations: SNP, single nucleotide polymorphism; R, random model; F, fixed model; OR, odds ratios; CIs, confidence intervals.

in dopaminergic neurons in PD. Strong evidence of an association for the dominant model of rs11931532 and PD risk in Asian populations was found, which might indicate the dominant model of rs11931532 was a risk factor of PD in Asian populations.

The 3' UTR of genes were indicated to play an important role in regulating the expression of genes. Thus, the BST1 rs4698412 may increase the PD risk by changing the expression level of BST1 gene. Significant associations were found in GWAS studies and case-control stu-

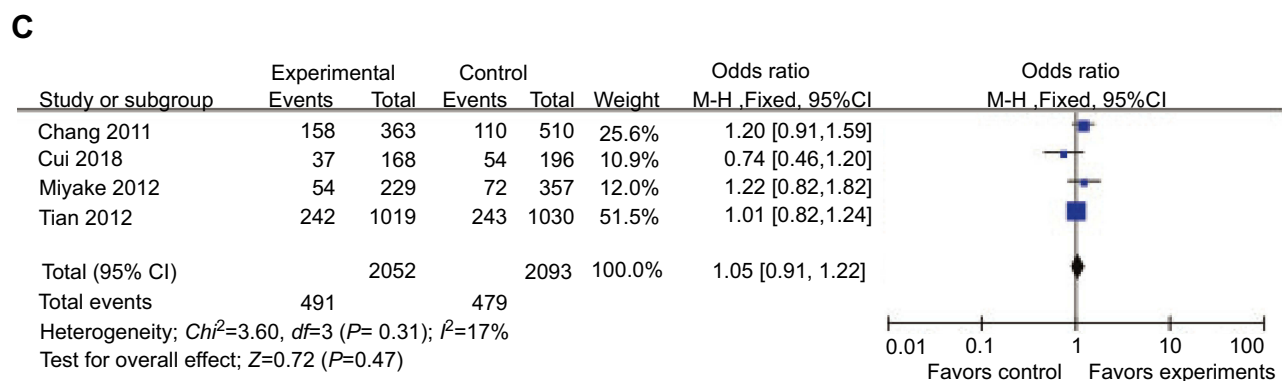
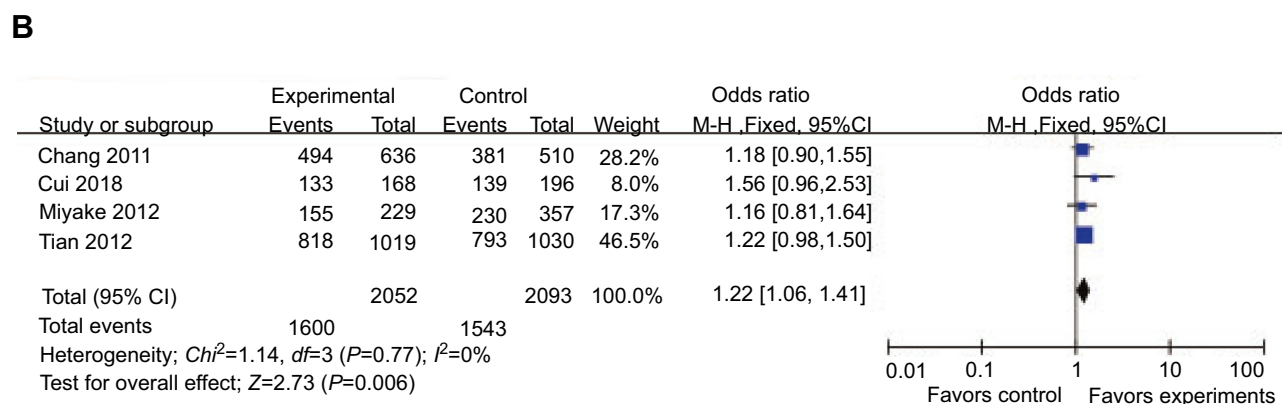
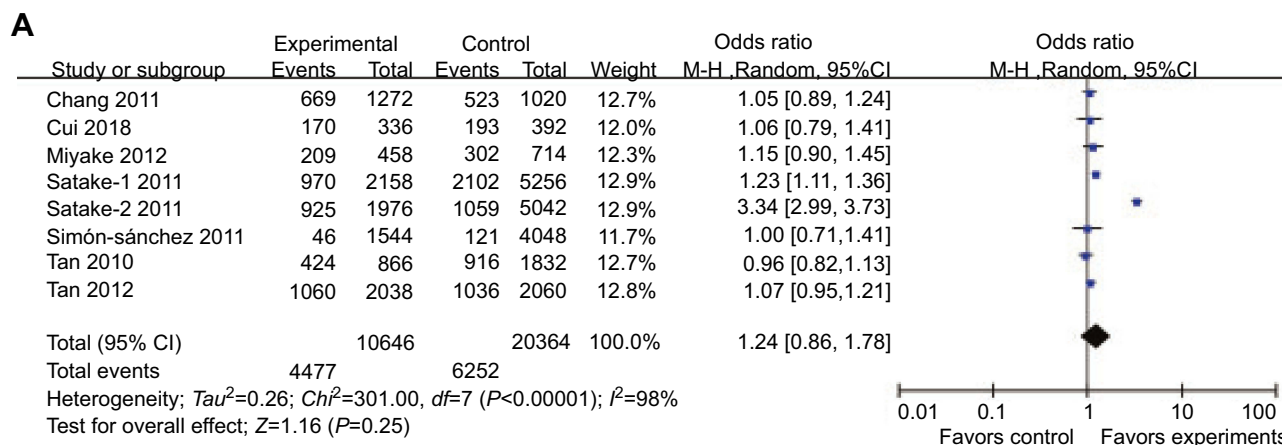


Figure 2 Forest plots of odds ratios for the association between BST1 rs11931532 and PD. (A) allelic model; (B) dominant model; (C) recessive model.
Abbreviation: PD, Parkinson's disease.

dies. However, negative results were reported by Tan et al¹⁰ and Chuang et al³⁴ in Chinese populations. The inconsistency of these researchers may be due to the different ethnicity, study design, sample size, and environmental factors. In our combined meta-analysis, we observed a significant association between BST1 rs4698412 and PD risk in Asian populations, but not in Caucasian populations, which may indicate the genetic

background influences the effect of BST1 rs4698412 to the PD risk. However, the sample size in the Caucasian population was relatively small. To identify the association between rs4698412 and PD risk in Caucasian populations, studies with a larger number of subjects from multiple ethnicity are necessary.

When investigating the rs11724635 with genetic models, no significant association with PD was found in the

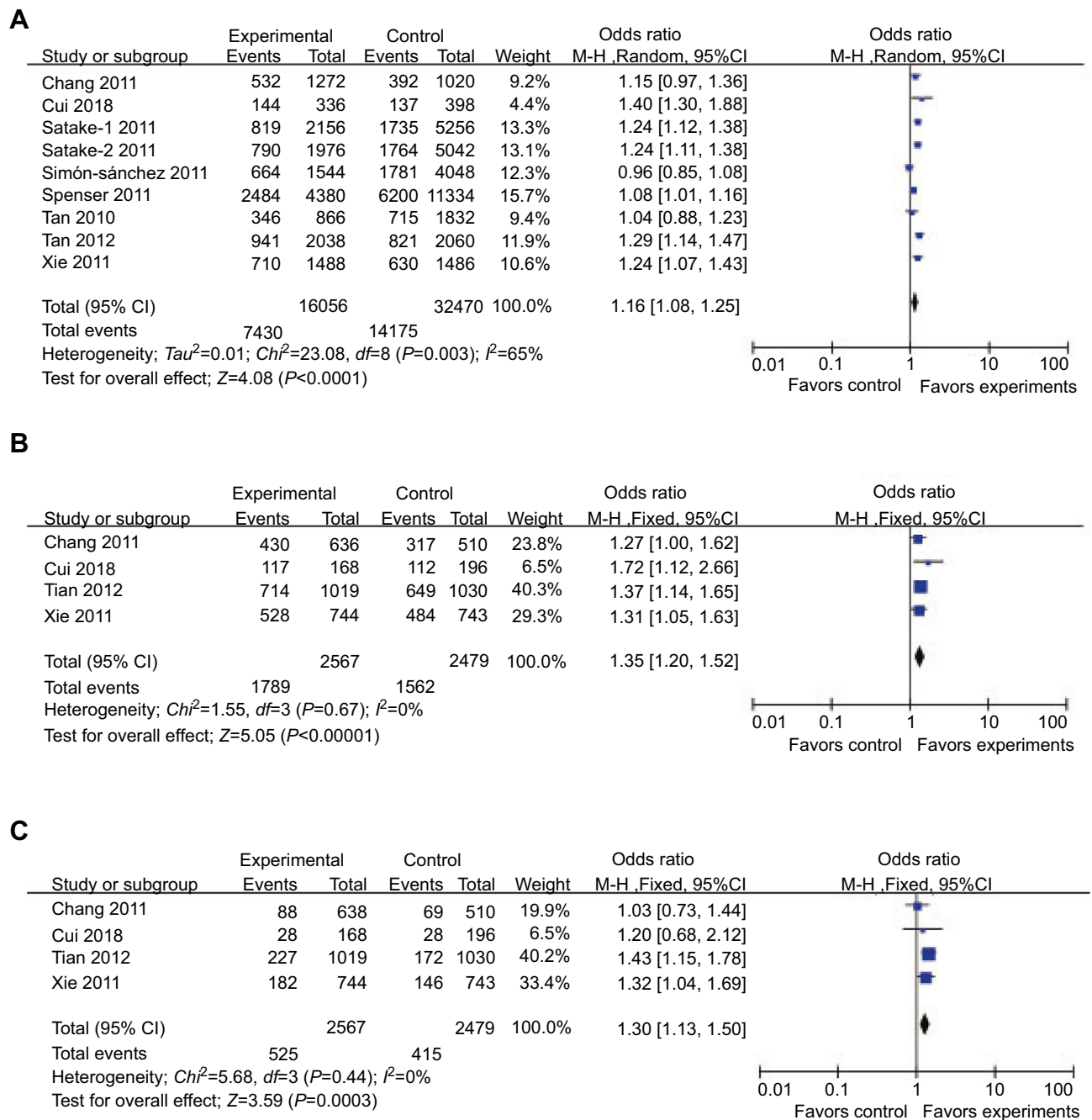


Figure 3 Forest plots of odds ratios for the association between BST1 rs4698412 and PD. (A) allelic model; (B) dominant model; (C) recessive model. **Abbreviation:** PD, Parkinson's disease.

overall and subgroup population-based analysis. A recent logistic regression analysis of data from a multi-center hospital-based case-control study in Japan found no relationship between BST1 rs11724635 and sporadic PD.²⁴ This negative result was replicated in subsequent studies in Chinese populations.^{23,26} However, a meta-analysis based on the GWAS studies has revealed that the BST1 rs11724635 was a strong susceptible factor for PD in US,

European, and Asian populations.²⁵ As there was no available data in the studies conducted by Saad et al²¹, Spencer et al⁸, and Simon-Sanchez et al²⁵, we had to exclude these three studies in the present study. In addition, we enrolled three other studies,^{23,26,28} and found no association between BST1 rs11724635 and PD risk, which brings us to the conclusion that the BST1 rs11724635 may not be a risk factor for PD.

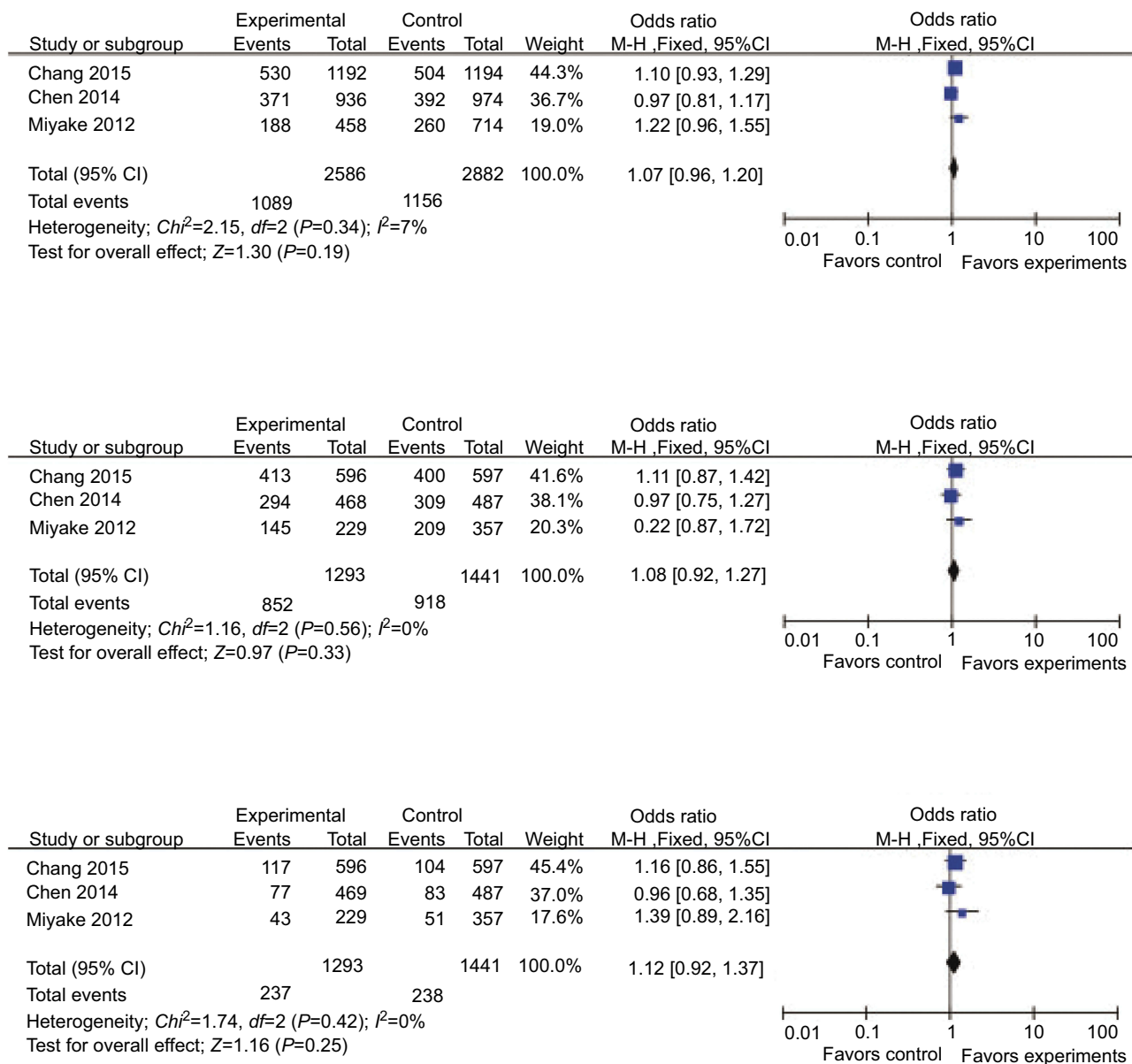


Figure 4 Forest plots of odds ratios for the association between BST1 rs11724635 and PD. (A) allelic model; (B) dominant model; (C) recessive model. **Abbreviation:** PD, Parkinson's disease.

Limitations should be taken into account. First, the polymorphisms included in the present meta-analysis were located in the 5' or 3' noncoding sequences of BST1 gene, and no polymorphism in the coding sequences was included. Although elements such as promoter, enhancer, or silencer were usually at untranslated region, which might be responsible for regulating gene expression, it still cannot be excluded that there are rare forms of mutation in the coding region. Further studies are required to include PD-associated polymorphisms in the coding sequences. Second, the number of subjects in the present study was relatively small, especially in the Caucasian subgroup, which may partly influence the result

of the association between the BST1 polymorphisms and PD in the Caucasian population. The lack of a significant association between SNP rs11724635 and sporadic PD is likely to be attributable to insufficient statistical power. Third, ethnic specific effect is an important consideration in meta-analysis. There were only two different ethnicities in the present study. A larger number of studies with more subjects of multiple ethnicities are necessary in the future.

Conclusions

Our meta-analysis suggests that the rs11931532 and rs4698412, but not rs11724635, might increase the risk

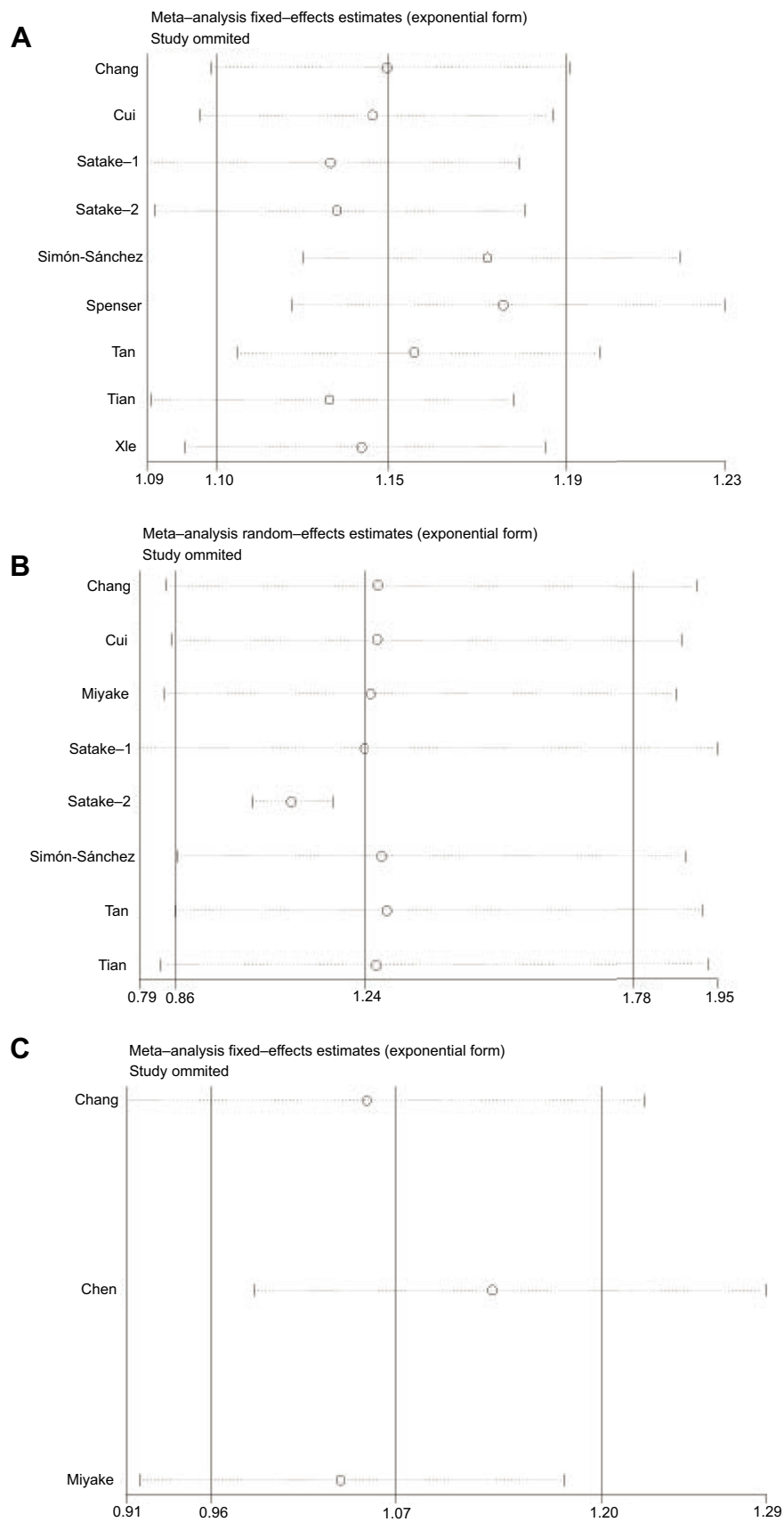
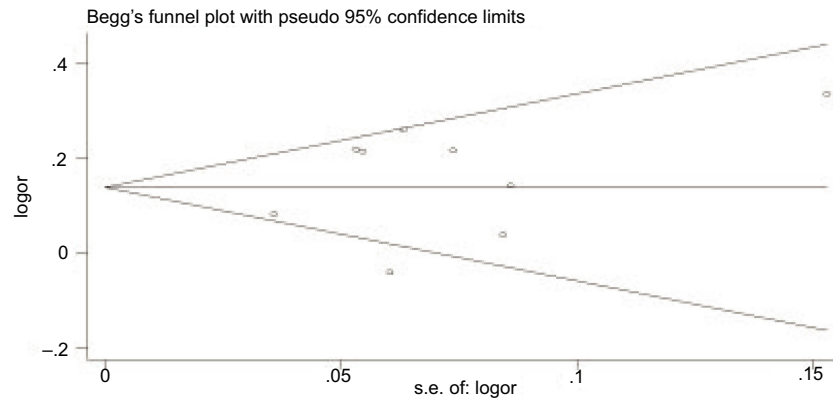


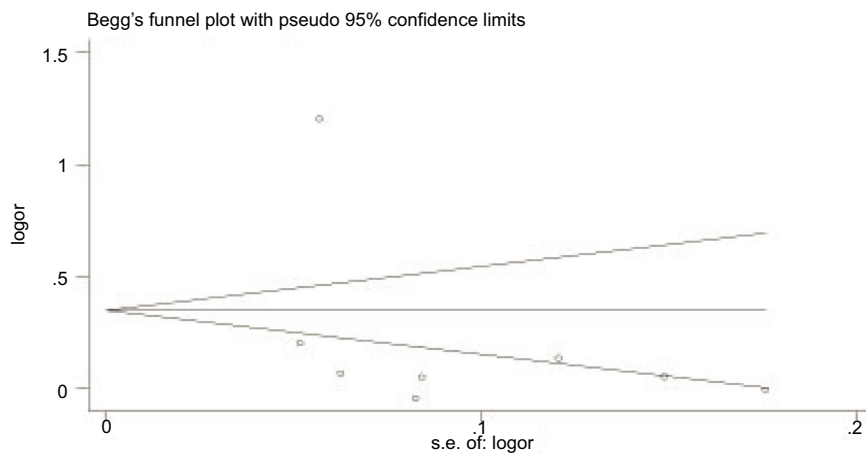
Figure 5 Sensitivity analyses between allelic models of BST1 rs11931532, rs4698412, rs11724635, and PD. **(A)** rs11931532; **(B)** rs4698412; **(C)** rs11724635. **Abbreviation:** PD, Parkinson's disease.

A



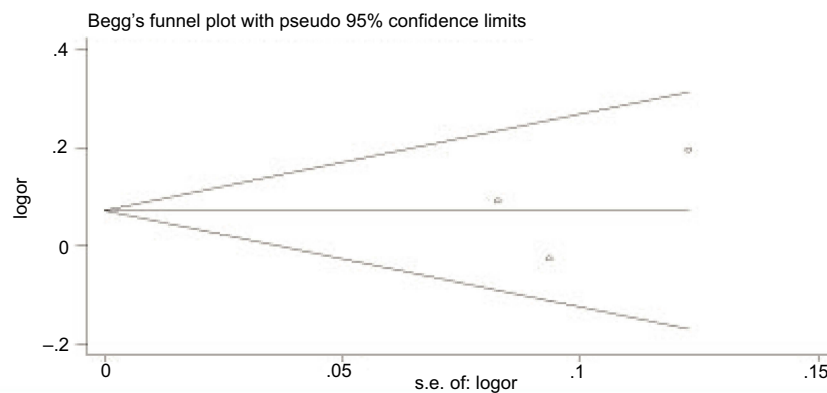
Std eff	Coef.	Std. Err	t	$P > t $	[95% confidence interval]	
Slope	.0579395	.102598	0.56	0.590	-.1846663	.3005452
Bias	1.412948	1.707726	0.83	0.435	-2.625183	5.451079

B



Std eff	Coef.	Std. Err	t	$P > t $	[95% confidence interval]	
Slope	.7691107	.4905801	1.57	0.168	-.4312956	1.969517
Bias	-5.906289	6.432422	-0.92	0.394	-21.64586	9.833282

C



Std eff	Coef.	Std. Err	t	$P > t $	[95% confidence interval]	
Slope	-.1962626	.4408354	-0.45	0.733	-5.797607	5.405082
Bias	2.834384	4.604102	0.62	0.649	-55.66628	61.33505

Figure 6 Publication bias of literatures for BST1 rs11931532, rs4698412, and rs11724635 were tested by Begg's funnel plot and Egger's test. (A) rs11931532; (B) rs4698412; (C) rs11724635.

Abbreviations: BST1, bone marrow stromal cell antigen 1.

of PD in Asian populations. However, more large-scale studies with a larger number of subjects are warranted to confirm these findings.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Methodological quality of the included studies according to the Newcastle-Ottawa scale

Reference	Year	Ethnicity/ location	Adequacy of case definition	Representative ness of the cases	Selection of controls	Definition of controls	Comparability cases/ controls	Ascertainment of exposure	Same method of ascertainment	Non- response rate	Total
Chang	2011	Chinese	*	*	*	NA	*	*	*	NA	7
Miyake	2012	Japanese	*	*	*	NA	*	*	*	*	8
Chang	2015	Chinese	*	*	*	NA	*	*	*	NA	7
Cui	2018	Chinese	*	*	*	NA	*	*	*	*	8
Tian	2012	Chinese	*	*	*	NA	*	*	*	NA	7
Satake	2011	Japanese	NA	NA	*	*	*	*	*	NA	6
Tan	2010	Chinese	NA	NA	*	*	*	*	*	NA	6
Simón-Sánchez	2011	the Netherlands	*	*	*	*	*	*	NA	*	8
Spencer	2011	UK	NA	NA	*	NA	*	*	*	*	6
Xie	2011	Chinese	NA	NA	*	*	*	*	NA	*	6
Chen	2014	Chinese	*	*	*	NA	*	*	*	*	8

Notes: This table identifies high quality choices with “an asterisk.” A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Abbreviations: *, Yes; NA, not applicable.

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