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Association of the HTR2C-759C/T polymorphism and antipsychotic-induced weight gain: a meta-analysis

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ABSTRACT

Background Antipsychotic-induced weight gain (AIWG) is a crucial factor for the medication cessation of patients with schizophrenia. Multiple studies have shown that the functional polymorphism -759 C/T (rs3813929) in the *HTR2C* promoter region could possibly be correlated with AIWG.

Aim To evaluate the genetic association of the HTR2C-759C/T polymorphism and AIWG in patients with schizophrenia with antipsychotic drugs (APDs) administration.

Methods Eligible studies were identified by searching the following databases: PubMed, Embase, Web of Science, China Nation Knowledge Infrastructure (CNKI), VIP, Wanfang Data, Chinese Biomedical Literature Database (CBM) and the Airiti Library. The quality of studies was evaluated based on the Newcastle-Ottawa Scale. The pooled OR and 95% CI were calculated for the dominant (CT/TT/T vs CC/C) mode, and subgroup analyses were performed based on ethnicity, antipsychotic medication and gender; all statistical analyses were performed using the statistical software STATA V.12.0.

Result A total of 17 studies with 3170 patients with schizophrenia were included in our meta-analysis. The result of the meta-analysis has shown that the association between the -759 C/T polymorphism and AIWG is statistically significant (OR 0.34, 95% CI: 0.20 to 0.57, z=4.11, p<0.001). The subgroup analyses revealed significant correlations between the -759 C/T polymorphism and AIWG in the Caucasian population (OR 0.33, 95% CI: 0.14 to 0.77, z=2.55, p=0.011), the Asian population (OR 0.31, 95% CI: 0.18 to 0.52, z=4.46, p<0.001), the patients with APDs administration (CT/TT/T vs CC/C: OR 0.63, 95% CI: 0.40 to 1.00, z=1.97, p=0.049) and the patients with atypical antipsychotic drug administration (CT/TT/T vs CC/C: OR 0.21, 95% CI: 0.09 to 0.47, z=3.83, p<0.001). The sensitivity analysis showed that the results were stable. Begg's test (after correction z=1.07, p=0.287) and Egger's test (t=−2.41, p=0.029) show that the included articles have no significant publication bias.

Conclusion There is a significant genetic association between *HTR2C*-759C/T and AIWG, and patients with T allele are less likely to have AIWG.

INTRODUCTION

Schizophrenia is a highly prevalent complex neuropsychiatric disease, and the pathophysiology is yet to be fully elucidated. Antipsychotic drugs (APDs) are the primary treatment methods for schizophrenia. Nevertheless, antipsychotic-induced weight gain (AIWG), a serious side effect, leads to increased risk for cardiovascular morbidity and social withdrawal and therefore is a crucial factor for the cessation of medication.[1 2]

The variability of AIWG among inter-racial and inter-individual along with the results of twin and adoption studies had suggested that the genetic factor plays an important role in AIWG. The gene of 5-hydroxytryptamine 2C receptor (5-HT2CR), *HTR2C*, is located at chromosome Xq23, and its expression product 5-HT2CR has a role in the mechanism of antipsychotic medication. Furthermore, atypical antipsychotic drugs (AAPs) that are prone to induce AIWG have a better affinity to 5-HT2CR than typical antipsychotic drugs (TAPs).[3] Numerous studies have consistently pinpointed that the changes of the serotonin system have a great effect on food and body weight regulation. High activity of 5-HT2CR decreases the appetite of mice, whereas the antagonists have an opposite effect. Furthermore, 5-HT2CR-deficient mice adopted an abnormal control of feeding behaviour, resulting in obesity and hyperglycaemias.[4–6] Taken together, previous genetic studies have found that a constellation of single-nucleotide polymorphisms in *HTR2C* is related to AIWG; the relationship between the -759 C/T (rs3813929) polymorphism and AIWG is an active field of research, but the results are controversial. Two earlier meta-analyses[7 8] ignored a number of studies in China; therefore, we performed a meta-analysis applying both English and Chinese databases to assess whether *HTR2C* -759 C/T is associated with AIWG.

374 articles published before Dec 31, 2018, were identified using a standard search strategy and other sources (see Method section):
— 3 from Chinese National Knowledge Infrastructure
— 44 from Wanfang Data
— 2 from VIP Data
— 6 from China Biology Medicine disc
— 0 from Airiti Library
— 160 from Web of Science
— 41 from PubMed
— 118 from Embase

↓

238 unduplicated studies

↓

34 full-text articles assessed for eligibility

→ **17 full-text articles excluded:**
– 16 data limited
– 1 data point based on the same sample
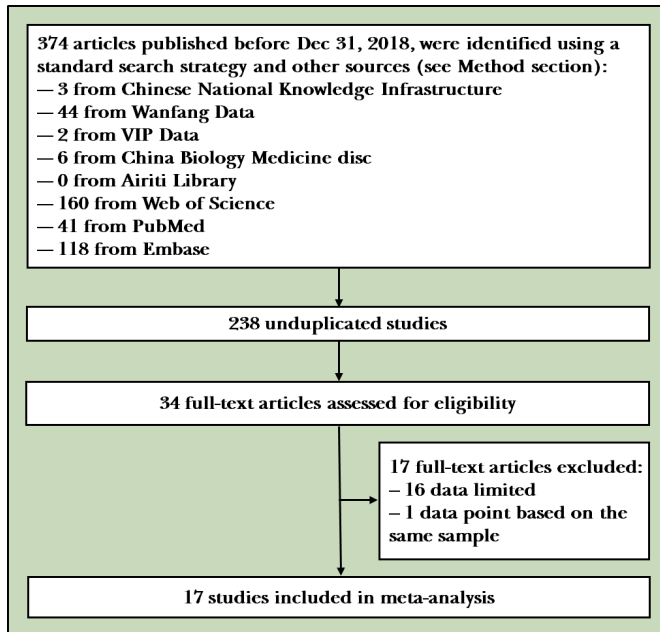
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17 studies included in meta-analysis

Figure 1 Flowchart of the search process

METHODS
Search strategy
A literature search of English (PubMed, Embase, Web of Science) and Chinese (China Nation Knowledge Infrastructure (CNKI), Wanfang Data, VIP, Chinese Biomedical Literature Database (CBM), the Airiti Library) databases was conducted for eligible articles published up until 31 December 2018, using key words "Weight gains", "schizophrenia", "polymorphism" and "HTR2C".

Inclusion and exclusion criteria
Studies were selected according to the following criteria presented using the acronym, *PICOS*: Participants (*P*): adult patients diagnosed with schizophrenia based on the Diagnostic and Statistical Manual of Disorder (DSM), International Statistical Classification of Diseases and Related Health Problems (ICD) or Chinese Classification of Mental Disorders (CCMD), while the *HTR2C*-759C/T (rs3813928) polymorphism was genotyped. Intervention (*I*): administration with antipsychotics. Comparison (*C*): patients with AIWG or not. Outcomes (*O*): the primary outcome included genotype frequencies, and the number or proportion of patients with weight gain in each genotype group. Study design (*S*): Case-control studies and cohort studies with meta-analysable data.

Studies were excluded according to the following criteria: (1) animal experiments; (2) patients enrolled had organic brain disease or were in medical conditions that could affect the weight (ie, hyperthyroidism, diabetes, etc); (3) studies with errors or incomplete data; (4) not published in Chinese or English languages; (5) only select the most complete study if a repeated publication or an overlapping sample existed.

Assessment of study quality and data extraction
According to the Newcastle-Ottawa Scale (NOS),[9] the quality of the included literature was evaluated based on three aspects: the selection of the research population (full score of 4), the comparability between groups (full score of 2) and the measurement of exposure factors (full score of 3), with a total score of 9 points.

The following data were extracted: study population characteristics (ie, country, population, gender, age, diagnosis), sample size, prior antipsychotic medication, type of antipsychotic medication, duration of treatment, definition of weight gain, conclusions and NOS score. Genotype or allele frequencies were calculated if not given directly in the articles.

Quality evaluation and data extraction were completed by two researchers (YC and Y-WW) independently. Inconsistent opinion was resolved by discussion or assistance from a third researcher (XYF).

Statistical methods
The presence of AIWG was analysed as a binary variable, which was defined by the original diagnostic definition applied in each study. The relationship between the *HTR2C* -759C/T polymorphism and AIWG in patients with schizophrenia was measured by using OR and 95% CI. In addition, multiple studies[10–21] demonstrated that the T allele has a dominant effect, indicating that it is more difficult for patients with the T allele (CT/TT/T) to suffer from AIWG than the homozygous wild type (CC/C). Therefore, we applied the dominant mode (CT/TT/T vs CC/C) to calculate ORs and 95% CI.

Heterogeneity was assessed using the χ^2 test–based Cochran Q test. The quantification of heterogeneity was evaluated using an I^2 index that approximately had values from 0% to 100%.

According to the Cochrane Handbook for Systematic Reviews of Interventions, if I^2 <40%, it can be considered that the heterogeneity of the included literature is not important; 30%–60% may be considered to have moderate heterogeneity; 50%–90% may be considered to have substantial heterogeneity; 75%–100% may have considerable heterogeneity. If p value >0.10 or I^2 <50%, the fixed-effect model (Mantel-Haenszel) was used to pool the data from included studies. Otherwise, the random-effect model (DerSimonian-Laird) was performed. We used Z test to assess the statistical significance of the pooled ORs. Meta-regression was performed to detect the source of heterogeneity.

Publication bias was detected by using Begg's funnel plot and Egger's regression test in the meta-analysis; a p value <0.01 indicates the existence of significant publication bias. Other than the tests for heterogeneity and publication bias, all analyses were two tailed, and the level of significance was set at 0.05.

All statistical analyses were performed using STATA V.12.0 (Stata, College Station, TX, USA).

Table 1 Characteristics of the eligible studies

Studies	Country	Ethnicity	Sample size	Male/female	Average age (SD)	Types of diagnosis	Prior antipsychotic medication	Type of antipsychotic medication	Duration of treatment	Definition of weight gain	Association	NOS score
Reynolds 2002[10]	China	Asian	123	61/62	26.6 (7.7)	SCZ (DSM-IV)	Yes	APDs	10 weeks	≥7% BMI change	T allele has a significant effect on weight (p<0.001)	7
Tsai 2002[39]	China	Asian	80	52/28	36.7 (8.4)	SCZ (DSM-IV)	NA	AAPs	4 months	≥7% BMI change	NS	7
Zhang 2002[11]	China	Asian	117	58/59	26(8)	First-episode SCZ (CCMD-II-R)	No	APDs	10 weeks	≥7% weight change	T allele has a significant protection effect on weight (p<0.001)	8
Theisen 2004[41]	Germany	Caucasian	97	57/40	22.1 (7.7)	SCZ (ICD-10)	Yes	AAPs	12 weeks	≥7% BMI change	NS	8
Ellingrod 2005[12]	USA	Caucasian	42	34/8	NA	SCZ (DSM-IV)	NA	AAPs	6 weeks	≥10% BMI change	T allele has a significant protection effect on weight (p=0.004)	7
Miller 2005[13]	USA	Caucasian	41	26/15	35.6 (9.7)	Treatment-resistant SCZ (DSM-IV)	Yes	AAPs	6 months	≥7% BMI change	T allele has a significant effect on weight (p=0.003)	8
Templeman 2005[14]	Spain	Caucasian	73	55/18	25.2 (0.78)	First-episode SCZ (DSM-IV)	No	APDs	9 months	7% BMI change	T allele has a significant protection effect on weight (p=0.01)	8
Ryu 2007[15]	Korea	Asian	84	39/45	30.1 (7.4)	First-episode SCZ (DSM-IV)	Mostly had	APDs	4 weeks	≥7% BMI change	T allele has a significant protection effect on weight (p=0.048)	7
Kuzman 2008[42]	Croatia	Caucasian	108	0/108	30.6 (11.5)	Acute-episode SCZ, SCA (DSM-IV)	Not taken or eluted	AAPs	4 months	≥7% weight gain	NS	8
Park 2008[40]	Korea	Asian	79	53/26	46.1 (12.1)	SCZ, SCA (DSM-IV)	Not taken olanzapine or clozapine	AAPs	≥3 months	≥7% weight gain	NS	8
Shao 2008[16]	China	Asian	170	60/110	23.1 (5.1)	First-episode SCZ (DSM-IV)	No	APDs	Varies	≥7% weight gain	T allele has a significant protection effect on weight (p<0.001)	8
Godlewska 2009[17]	Poland	Caucasian	107	53/54	29.3 (10)	SCZ (DSM-IV-TR)	Not taken AAPs	AAPs	6 weeks	≥10% BMI change	T allele has a significant protection effect on weight (p=0.002)	9
Opgen-Rhein 2009[18]	Germany	Caucasian	126	79/47	38.6 (12)	SCZ, SCA (DSM-IV)	Not taken AAPs	APDs	6 weeks	≥7% weight gain	T allele has a tendency of protection effect on weight (p=0.063)	8
Sicard 2010[7]	Germany and North America	Caucasian	201	138/63	35.9 (10.1)	SCZ, SCA (DSM-IV)	Yes	APDs	10 weeks	≥7% weight gain	NS	7

Continued

Table 1 Continued

Studies	Country	Ethnicity	Sample size	Male/female	Average age (SD)	Types of diagnosis	Prior antipsychotic medication	Type of antipsychotic medication	Duration of treatment	Definition of weight gain	Association	NOS score
Liu 2013[19]	China	Asian	181	92/89	30 (12)	SCZ (DSM)	No	AAPs	12 weeks	≥7% weight gain	T allele has a significant protection effect on weight (p=0.04)	9
Kang 2014[20]	Korea	Asian	113	81/32	39.5 (8.3)	SCZ (DSM-IV)	NA	AAPs	1 year	≥7% BMI change	T allele has a tendency of protection effect on weight (p=0.051)	8
Manuel 2017[21]	Argentina	Caucasian	48	0/48	34.48 (13.13)	SCZ, SCA (DSM-V-TR)	Not taken AAPs	AAPs	6 weeks	≥7% weight gain	T allele has a significant protection effect on weight (p=0.03)	8

AAP, atypical antipsychotic drug; APD, antipsychotic drug; BMI, body mass index; CCMD, Chinese Classification and Diagnostic Criteria of Mental Disorders; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of disease; NA, not available; NOS, Newcastle-Ottawa Scale; NS, not significant, the difference was not statistically significant; SCA, schizoaffective disorder; SCZ, schizophrenia.

RESULTS

Results of search

A total of 374 studies were found, including 319 studies from the English databases and 55 studies from the Chinese databases. After removing duplicated articles, 249 studies remained. Irrelevant studies were subsequently screened based on titles and abstracts and 34 remained. After reviewing full-text articles, 17 of the 34 studies were excluded. Among the 17 studies, 16 of them had incomplete data[22-37]; one of them employed a repeated sample.[38] In the end, 17 articles were included in this meta-analysis (figure 1).

Characteristics of eligible studies

In total, of the 17 studies included in this meta-analysis, 8 of them were studies of Asians[10 11 15 16 19 20 39 40] including 1696 patients, and 9 were Caucasian[7 12–14 17 18 21 41 42] including 1474 patients. Nine of the studies provide gender group data,[7 11 16 18–21 40 41] and seven of the nine studies provide data that could be used for calculating allele frequencies.[7 11 16 18 19 40 42] The NOS scores of the eligible studies were distributed between 7 and 9, indicating their relatively high quality. We divided patients into the ADP and AAP groups as different types of antipsychotic medication. The antipsychotic treatments administered in the ADP group consisted of typical antipsychotics (TAPs) or combined with AAPs; nevertheless, patients of the AAP group received monotherapy with AAPs. Details are shown in table 1.

Meta-analysis results

There is heterogeneity among the eligible studies (I^2=67.9%, p_h<0.001); therefore, a random-effect model was used to combine the data. The meta-analysis result showed that there is a significant correlation (CT/TT/T vs CC/C: OR 0.34, 95% CI: 0.20 to 0.57, z=4.11, p<0.001) between the HTR2C-759C/T polymorphism and AIWG in patients with schizophrenia; the patients with T allele on -759 C/T (CT/TT/T) are less likely to gain weight.

We then performed subgroup analyses to evaluate the effect of ethnicity, type of antipsychotic medication and gender. As for ethnicity, we found that patients with T allele are not prone to experience AIWG, whether they are Caucasian (CT/TT/T vs CC/C: OR 0.33, 95% CI: 0.14 to 0.77, z=2.55, p=0.011) or Asian (CT/TT/T vs CC/C: OR 0.31, 95% CI: 0.18 to 0.52, z=4.46, p<0.001). In addition, it is worth mentioning the heterogeneity results—the European population subgroup is highly heterogeneous (I^2=75.2%, p_h<0.001) while the heterogeneity of the Asian population is not significant (I^2=38%, p_h=0.127) (figure 2).

As for the type of antipsychotic medication, the patients were divided into the ADP and AAP groups, and the results showed that the -759 C/T polymorphism is significantly correlated with AIWG in both the population that received ADPs (CT/TT/T vs CC/C: OR 0.63, 95% CI: 0.40 to 1.00, z=1.97, p=0.049) and the population that received AAPs (CT/TT/T vs CC/C: OR 0.21, 95% CI:
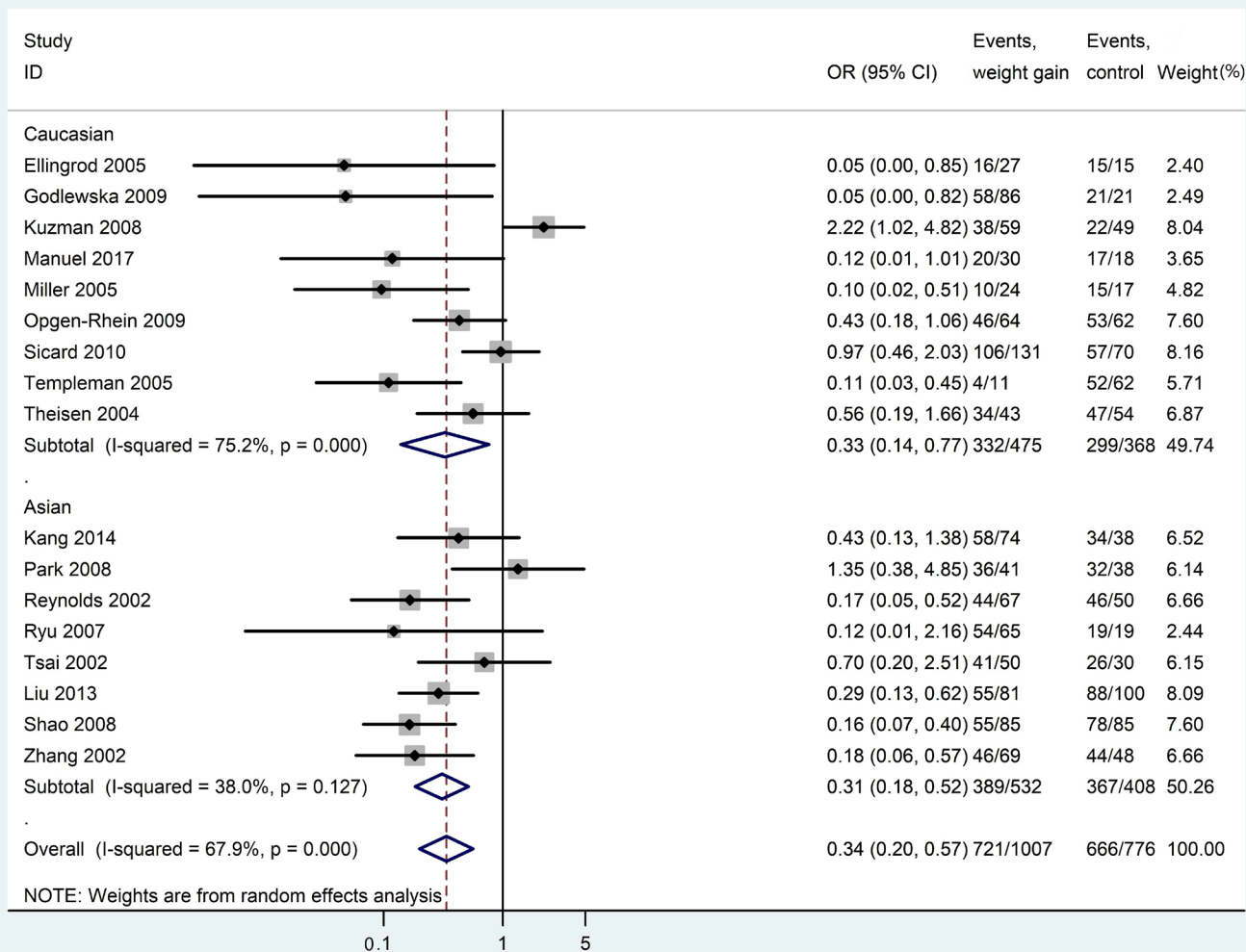
Figure 2 Meta-analysis forest plot of the genetic correlation of HTR2C-759C/T polymorphism and antipsychotic-induced weight gain (subgroup analysis based on ethnicity).

0.09 to 0.47, z=3.83, p<0.001). The results of the heterogeneity test suggested that the AAP subgroup population is highly heterogeneous (I^2=74.8%, p_h<0.001), whereas the ADP subgroup has insignificant heterogeneity (I^2=14.4%, pP_h=0.320) (figure 3).

It is noteworthy that *HTR2C* is located on chromosome X; of the included studies in this meta-analysis, nine studies provide gender group data and only seven studies provide data that could be used for calculating allele frequencies. The results demonstrated that the *HTR2C*-759C/T polymorphism is significantly correlated with AIWG in both the male and female populations. However, there was no statistical significance in the result of allele analysis. Details are shown in table 2.

Heterogeneity analysis and sensitivity analysis

The result of the heterogeneity test (I^2=67.9%, pP_h<0.001) has suggested that there is significant heterogeneity among the included studies. Meta-regression was performed to further explore the source of heterogeneity,

and potential confounding variables included population (Asia, America, Europe or mixed samples), type of antipsychotic medication (APDs or AAPs), publication year, sample size, definition of weight gain (7% increase in body weight/body mass index (BMI) or 10% increase in body weight/BMI) and NOS score. It is found that the American population (t=−1.88, p=0.079; corrected R^2=17.13%) and type of antipsychotic medication (t=−1.94, p=0.071; corrected R^2=17.69%) might be the main sources of heterogeneity, which can explain 17.13% and 17.69% of heterogeneity, respectively. Inserting each study to meta-regression, we found that the study of Kuzman *et al*[42] is the main source of heterogeneity (t=2.26, p=0.018; corrected R^2=47.45%), which can explain 47.75% of heterogeneity.

In terms of the sensitivity analysis, we conducted the analysis by excluding one included study at a time to determine the impact of each study on the combined effect size (figure 4). The result showed that the Kuzman 2008 study has a great effect on OR value and its 95% CI,
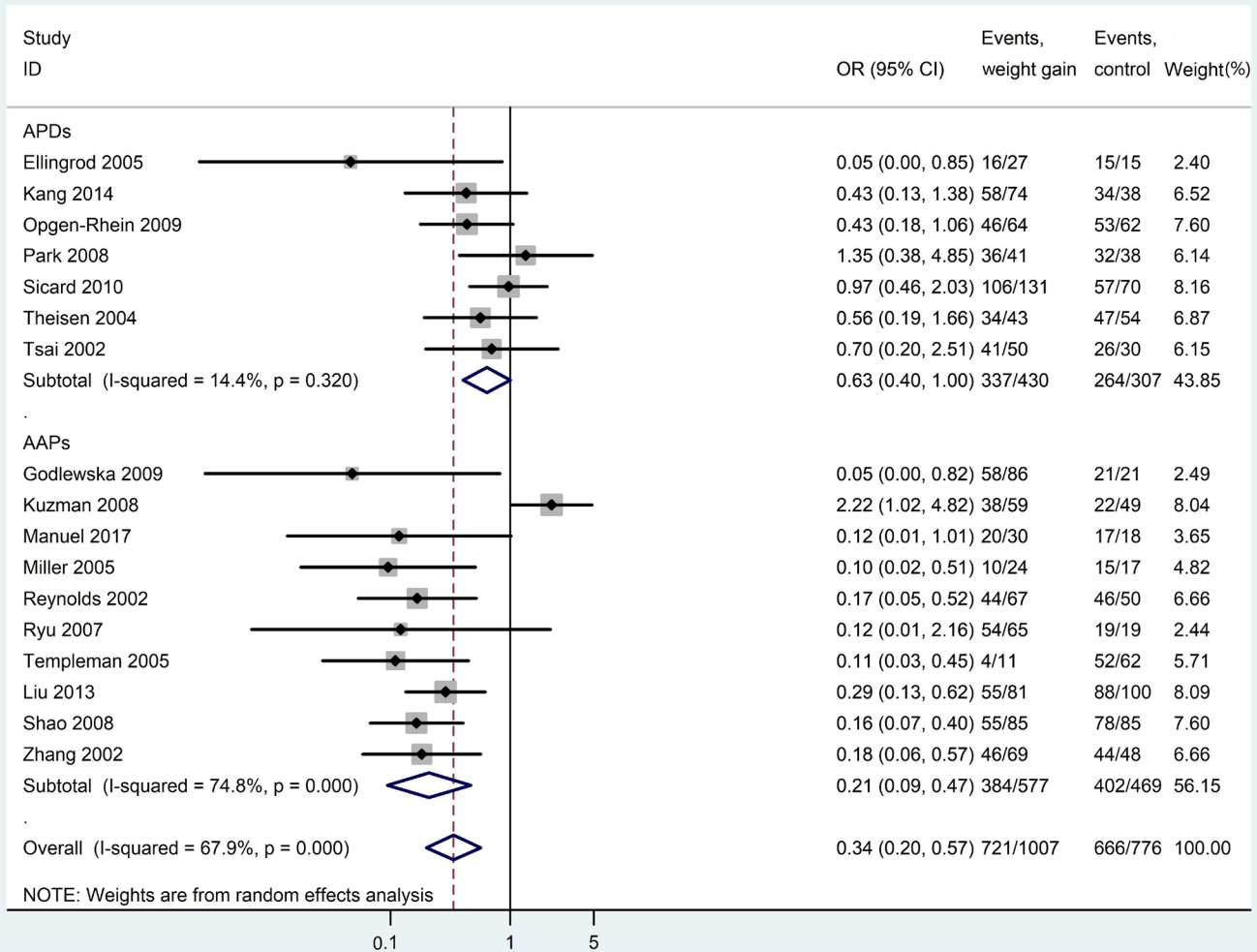
Figure 3 Meta-analysis forest plot of the genetic association between HTR2C-759C/T polymorphism and antipsychotic-induced weight gain (subgroup analysis based on the type of antipsychotic medication). AAP, atypical antipsychotic drug; APD, antipsychotic drug.

further validating that the Kuzman 2008 study was the main source of heterogeneity of this meta-analysis. However, this study had not affected the final direction of the results, so the results of this meta-analysis are relatively stable.

Publication bias
Publication bias is roughly determined by Begg's funnel plot (figure 5) and identified quantitatively by the combination of Begg's rank correlation test and Egger's

regression test. Begg's funnel plot showed that the distribution of each study is not completely symmetrical, suggesting the possibility of publication bias. The result

Figure 4 Sensitivity analysis.

Table 2 Results of allele analysis and the subgroup analysis based on gender

	Model	OR	95% CI	P value	I² (%)
Allele	T vs C	0.58	0.30 to 1.12	0.104	78.30
Male	T vs C	0.45	0.20 to 1.00	0.049	47.50
Female	CT/TT vs CC	0.34	0.14 to 0.80	0.013	73.60

Begg's funnel plot with pseudo 95% confidence limits
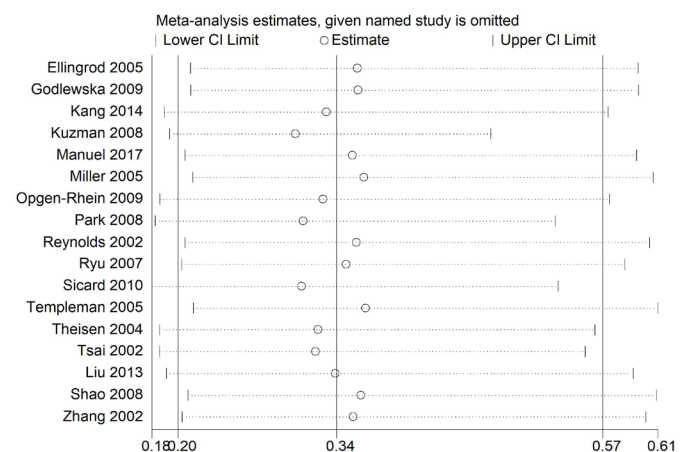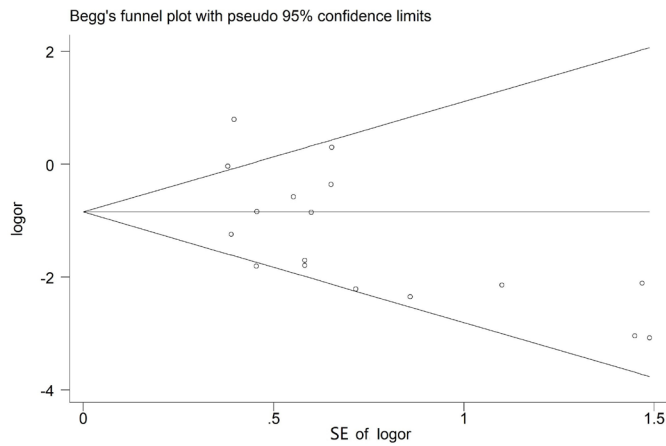

Figure 5 Begg's funnel plot.

of Begg's rank correlation test (z=1.07, p=0.284) and Egger's regression test (t=−2.41, p=0.029) suggested that publication bias was not significant in all eligible studies.

DISCUSSION
Main findings

The 5-HT2C receptor has played an important role in regulating the digestion function and the pharmacological mechanism of AAPs. A number of studies have found that the mutation of *HTR2C* is correlated with AIWG.[3–6] The -759 C/T polymorphism is located at the promoter region of *HTR2C* and associated with the ability to bind the transcription factor, affecting the expression of gene production.[21]

This article has unprecedentedly used the complete Chinese database and conducted analyses on the correlation between *HTR2C*-759C/T and AIWG by using evidence-based medicine methods.

A quality assessment of the included studies was performed according to the NOS, and the included studies have primarily lost points on the absence of an illustration of the pre-existence of metabolic diseases among the included patients before the experiment, and the confounding factors (such as type of antipsychotic medication) in the research process were not controlled. On average, the scores of the final included articles were within 7–9, indicating that the overall quality is high. Therefore, the results of this meta-analysis were relatively reliable. Among the 17 studies[7 10–21 39–42] included, 10 studies[10–17 19] showed that T allele had a significant weight protection effect, 2 studies[18 20] showed that T allele had a tendency of a weight protection effect, but 5 studies[7 39–42] showed that the difference was not statistically significant. The results of the meta-analysis showed that the HTR2C-759C/T polymorphism was significantly correlated with AIWG in schizophrenia, and the patients with T allele are less likely to have an increase in body weight compared with the homozygous wild type (CC/C) in the process of antipsychotic intake medication. Subgroup analyses suggested that the conclusion can be applied to all the groups, and the protective effect of T allele is more

significant in the AAP group than in the APD group, for the possible reason that AAPs are more likely to result in weight gain.[3] However, there was overlapping in the CIs of the two groups, indicating that there is no statistical significance despite the difference in tendency of the influence magnitude of the -759 C/T polymorphism on AIWG between the two groups.

Owing to the influence of chromosomes, hormones and different living habits, the occurrence and characteristics of metabolic-related diseases such as weight gain have gender differences.[43 44] Furthermore, the HTR2C gene is located on chromosome X; it is necessary to perform a subgroup analysis of gender stratification. Nevertheless, the provision of related data in the included studies is limited, the total sample size is relatively insufficient and the heterogeneity is high. Although the analyses results showed significant correlation between the HTR2C-759C/T polymorphism and AIWG in the male and female populations, and the T allele has a stronger protective effect on weight gain in the female population than the male population, the authenticity is still uncertain. For the possible association with few included data, the allele analysis had not shown significant results.

Generally, this meta-analysis has suggested that a significant association between the *HTR2C*-759C/T polymorphism and AIWG. The T allele of *HTR2C*-759C/T polymorphism has a protective effect on AIWG. Although the heterogeneity test showed that the included studies are of high heterogeneity, the sensitivity analysis and publication bias showed that the results of this study were relatively stable and have no significant publication bias.

Limitation

Our meta-analysis must be interpreted with some limitations. First, we use ORs for the estimation of effect size, only including the literature that provided the quantity or proportion of patients with a significant increase on weight or BMI in each genotype group, but not the literature that merely provided specific weight gain data. Although an OR is more clinically meaningful than the standard mean difference, it is undeniable that we have abandoned a lot of meaningful clinical data, resulting in a decrease in the number of included studies and a reduction in the effectiveness of the tests. Second, regarding the publication bias, the relevant results show that the publication bias is not significant, but it still exists, and some negative results may not have been published. In addition, the studies we have included were publicly published and the language is either Chinese or English. This may lead to the omission of relevant literature published in countries in which the native language is not Chinese or English, causing certain biases.

Implications

AIWG is a rigorous problem in the treatment of schizophrenia, and there is still not an effective way to reverse AIWG. In response to this situation, conducting genetic research on AIWG is of great significance for identifying

the high-risk population so as to guide them in drug selection. In addition, the eventual result direction aligns by comparing this article with the previous meta-analysis, suggesting a significant association between the *HTR2C*-759C/T polymorphism and AIWG and a protective effect of the T allele against AIWG. In comparison with the previous meta-analyses, this article supplements a lot of Chinese research, and the included studies were more comprehensive, with a larger total sample size and higher power of test.

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