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LEPTIN -2548G/A GENE POLYMORPHISM IN ASSOCIATION WITH ANTIPSYCHOTIC-INDUCED WEIGHT GAIN: A META-ANALYSIS STUDY

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SUMMARY

Background: *The leptin -2548G/A (rs7799039) gene polymorphism has been implicated in susceptibility to antipsychotic-induced weight gain (AIWG), but study results are still controversial. The present meta-analysis was performed to investigate the relationship between the leptin -2548G/A gene polymorphism and AIWG.*

Methods: *Electronic databases were searched for eligible articles in English and Chinese and seven separate studies on the association of the leptin -2548G/A gene polymorphism with AIWG were analyzed.*

Results: *The meta-analysis involved 451 AIWG patients and 568 controls. The pooled odds ratio (OR) and their corresponding 95% confidence interval (CI) were calculated by a fixed or random effect. Overall, our meta-analysis suggests that the leptin -2548G/A gene polymorphism was not significantly associated with AIWG risk under various genetic models. But, in the subgroup analysis by ethnicity, significant association was found between leptin -2548A allele and the AIWG risk in Asian populations under additive, dominant, recessive, and homozygote genetic model. On the contrary, in European populations, the -2548A allele seemed to decrease the risk of AIWG when compared with the -2548G allele under various genetic models, even though they were not statistically significant.*

Conclusion: *Our meta-analysis suggests that the correlation between leptin -2548G/A gene polymorphism and AIWG risk has significant racial differences.*

Key words: *psychosis - schizophrenia - rs7799039 – genetics - AIWG - meta-analysis*

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INTRODUCTION

The prevalence of the schizophrenia is about one percent and has the potential for devastating emotional, physical, and mental consequences (Rummel-Kluge et al. 2010). So far, antipsychotic drugs are still the first-line of treatment for those with schizophrenia, schizoaffective disorders and other psychoses (Mueser & McGurk 2004). There are two classes of antipsychotic drugs used to be treated with either typical or atypical. Since extrapyramidal side effects and tardive dyskinesia are less common when taking atypical antipsychotics, the clinicians incline to select atypical antipsychotics as the first-line treatment for schizophrenia, and are gradually replacing typical antipsychotics. However, both typical and atypical antipsychotic drugs can induce substantial weight gain, which is particularly pronounced in patients treated with clozapine and olanzapine (Allison et al. 1999) and those treated with multiple antipsychotics (Sagud et al. 2013). Antipsychotic-induced weight gain (AIWG) can result in not only excessive weight gain, but also in metabolic sequelae, such as glucose dysregulation, dyslipidemia, and metabolic syndrome. Moreover, AIWG also adversely affects psychological well-being through poor self-esteem and social disadvantages, and finally decreases treatment adherence (Werneke et al. 2002, Weiden et al. 2004).

The exact mechanism of AIWG remains unknown and various parts of the endocrine system are presumably involved (Baptista 1999). Moreover, substantial interracial differences in drug-induced weight gain suggest that genetic factors may also be important (Lett et al. 2012). Over the past decade, a large number of studies have been conducted to investigate the relationship between gene variants and AIWG. Some candidate genes were found to be significantly associated with AIWG, including the 5-hydroxytryptamine 2C receptor gene (Reynolds et al. 2002), the cytochrome P450 2D6 gene (Ellingrod et al. 2002), the α2a-adrenergic receptor gene (Park et al. 2006), the synaptosomal-associated protein of 25 kDa (SNAP-25) gene (Muller et al. 2005), the G protein beta3 subunit gene (Wang et al. 2005), and the leptin gene (Templeman et al. 2005), the dopamine D2 receptor (Muller & Kennedy 2006). Moreover, recent study also highlights the potential importance of focusing on the leptin gene (Lett et al. 2012).

Leptin, a 16 kDa peptide, is a cytokine synthesized in white adipose tissue and plays an important role in regulating body weight. An increased level of exogenous leptin reduces appetite and increases energy metabolism by various regulatory mechanisms, such as stimulation of α-melanocyte-stimulating hormone release and inhibition of neuropeptide Y expression and agouti-related peptide (Schwartz et al. 2000). The serum leptin concentration is positively correlated with body

mass index (BMI) and percentage of body fat (Mantzoros 1999). Leptin deficiency can lead to extreme obesity, insulin resistance, cardiovascular complications, reproductive problems and bone formation deficiency in both mice and humans (Pelleymounter et al. 1995, Dubern & Clement 2012).

The leptin gene is located at chromosome 7q31.3, encodes a 3.5-kb cDNA and has three exons and two introns (Gong et al. 1996). Some single nucleotide polymorphisms (SNPs) of the leptin gene have been studied extensively. With regard to AIWG, many studies focused on the leptin genes with particular emphasis on a functional SNP in the promoter region, the -2548G/A polymorphism, and no other SNPs in leptin have yet been studied extensively about the relationship for AIWG, exception for one study by Srivastava et al (Srivastava et al. 2008). The −2548G/A polymorphism was first described by Mammès et al in 1998, and at that time it was wrongly designated as −2549C/A (Mammes et al. 1998). The -2548A allele was reported to lead to higher mRNA expression and increased leptin plasma levels (Hoffstedt et al. 2002). But, not all published studies have shown an association of rs7799039 with AIWG. Some studies indicated that -2548A allele might increase the risk of AIWG, while others thought that -2548G allele was the risk factor for AIWG (Brandl et al. 2012). Possible explanations for inconsistent findings include heterogeneity in terms of ethnicity, sex, age, illness characteristic, antipsychotic type, treatment duration, adjuvant treatments, adherence, etc. However, the most important influencing factors of study population in genetic association studies is the ethnicity of the patients. This is not only relevant because of different gene-environment interactions, but especially because genetic differences between these populations can be large. When looking at the prevalence of mutant alleles for various polymorphisms, these genetic differences between ethnic populations are clearly visible.

In consideration of these conflicting results, it cannot be concluded yet whether there is a significant association between the leptin -2548G/A gene polymorphism and AIWG and whether racial differences affect their relevance. Hence, the present meta-analysis, which involved 1019 subjects, was performed to derive a more precise estimate of the association between the leptin -2548G/A gene polymorphism and AIWG.

METHODS

Literature search and inclusion criteria

Computer-based searches of PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure, Wanfang data and China Biological Medicine Database were performed with restricting language in English and Chinese. while using key words relating to leptin (e.g. leptin OR LEP) in combination with words related to polymorphism (e.g. polymorphism OR mutation OR genetic OR genotype OR ‘‘single nucleotide polymorphism’’) and rs7799039 (e.g. rs7799039 OR 2548G OR 2548A OR G2548 OR A2548 OR 2548). The searches included all articles published before January 2014. Moreover, the reference lists in all relevant studies and review articles were also examined.

The inclusion criteria were as follows: 1) evaluation of the leptin -2548G/A gene polymorphism and AIWG risk, 2) schizophrenia, schizoaffective disorders and other psychoses diagnosis in accordance with the diagnosis requirements of the Chinese Classification and Diagnostic Criteria of Mental Disorders Second Edition Revision (CCMD-II-R) or Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV), 3) all patients received the antipsychotic medication, 4) the -2548G/A genotype frequencies of the leptin gene were provided, 5) AIWG had clear quantitative indicators: weight gain≥7% or body mass index (BMI)≥30kg/m2.

Data extraction

Two investigators independently reviewed all studies and extracted the data according to a standard protocol. Studies that did not meet the inclusion criteria, and provided little information or insufficient data were excluded. Table 1 lists the characteristics of the extracted data, including the name of the first author, publication date, region, number of genotypes, genotype, total number of cases and controls. The study regions comprised China, Netherlands, Britain, and Germany. China was classified into the Asian subgroup, and Netherlands, Britain, Germany into the European subgroup.

Statistical analysis

We systematically assessed the risk of different genotypes of the -2548G/A polymorphisms in AIWG under various genetic models, which included the additive (allele A versus allele G), the dominant (GA+AA versus GG), the recessive (AA versus GA+GG), the Homozygote (AA versus GG), and the heterozygote (GA versus GG) model. The association between the leptin -2548G/A gene polymorphism and AIWG risk was compared by the odds ratio (OR) and the corresponding 95% confidence interval (CI) between the AIWG and control groups. The heterogeneity assumption was checked by the Chi-square-based Q-test and significance was set at $p<0.05$. The inconsistency index I2 was also calculated to evaluate the variation caused by the heterogeneity. When heterogeneity was not significant (pheterogeneity≥0.05), the results were pooled using a fixed-effect model and the Mantel-Haenszel method. Otherwise, a random-effect model and the Dersimonian–Laird method were applied (Cochran 1968). Hardy-Weinberg Equilibrium (HWE) of the genotype distribution of controls was tested by a goodness-of-fit $\chi 2$ analysis using the DeFinetti program (available from http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) and $p<0.05$ indica-

ted a significant deviation for HWE. Funnel plots and Egger's test were used to examine the publication bias for reported associations and significance was also set at $p<0.05$ (Sterne & Egger 2001). Sensitivity analysis was conducted to assess potential influences of any one single study on the pooled effect size. Subgroup analysis stratified by ethnicity was performed to observe the effect of racial differences on the association of leptin -2548G/A gene polymorphism and AIWG. All analyses were performed by using the Review-manager 5.0.1 (Oxford, England) and the Stata version 12.0 (Stata Corporation, College Station, Texas, USA) softwares. All p-values were two-sided.

RESULTS

Studies and populations

89 articles were found based on the above searching criteria, among which seven articles were eligible based on the study selection criteria. 62 articles were excluded including reviews, editorials, and studies with insufficient detail on leptin -2548G/A gene polymorphism and AIWG by reading abstracts. Detailed evaluation on the full texts of the remaining 27 articles subsequently excluded 17 articles that failed to meet the inclusion criteria. Further assessment excluded 3 ineligible articles because of duplicate publications or deviate from HWE. Finally, 7 articles were included in the meta-analysis (Figure 1). The data of the seven included articles were obtained from 451 AIWG patients and 568 controls from four districts (Table 1). The OR differed among the seven studies: some of which indicated that the A allele increased AIWG risk, whereas the others reported that the G allele increased AIWG risk. Hence, a systematic analysis of the study results was performed to draw a reasonable conclusion.

Main analyses

The association between the leptin -2548G/A gene polymorphism and AIWG risk was investigated under the additive genetic model. Substantial heterogeneity among the studies ($I2=66\%$, $p= 0.012$) was found. The overall OR under a random effects model was 1.33 (95%CI=0.92 to 1.93), and was not significant ($p=0.127$). Then, an overall analysis under all other genetic models was performed. The results of meta-analysis also did not show a significant association under the dominant genetic model (OR=1.24, 95%CI=0.83 to 1.84, $p=0.294$), the recessive genetic model (OR=1.25, 95%CI=0.96 to 1.64, $p=0.103$), the homozygote genetic model (OR=1.32, 95%CI=0.84 to 2.08, $p=0.228$), and the heterozygote genetic model (OR=1.23, 95%CI=0.80 to 1.88, $p=0.339$). The results were shown in Table 2.

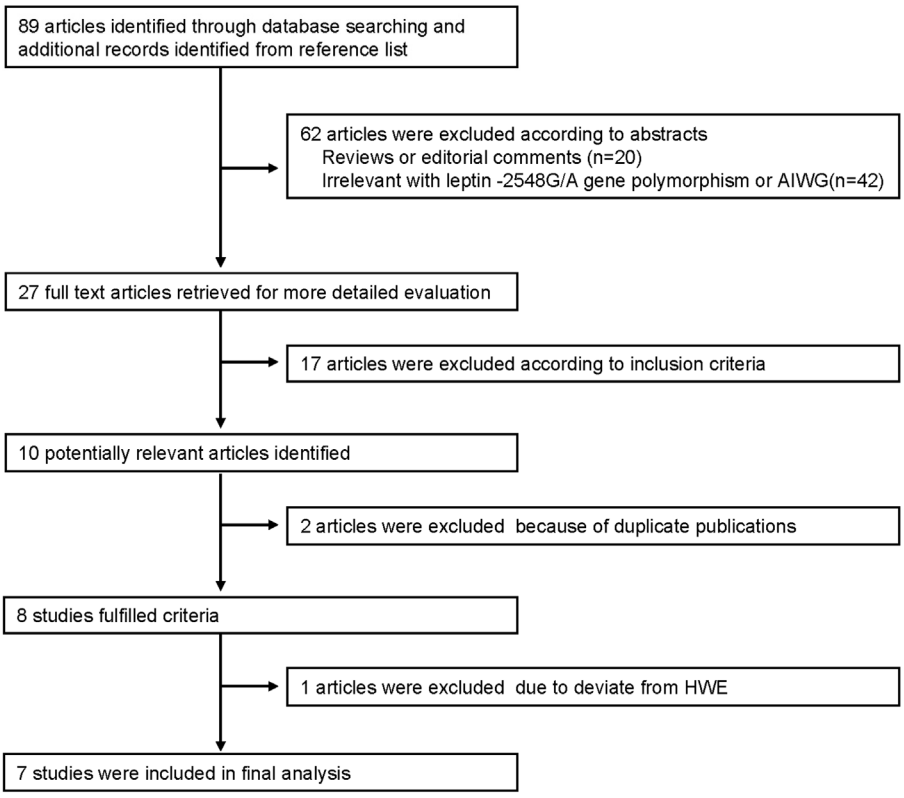

Figure 1. Flow diagram of articles selection process for leptin -2548G/A gene polymorphism and AIWG risk meta-analysis

Table 1. Characteristics of studies included for investigation of associations between leptin −2548G/A polymorphism and AIWG

Study details				AIWG (n) by total and genotype						Controls (n) by total and genotype						HWE (*p*)
Author (ref.)	Year	Ethnicity	Region	total	GG	AG	AA	G	A	total	GG	AG	AA	G	A	Controls
Zhang ZJ	2003	Asian	China	60	1	14	45	16	104	68	4	29	35	37	99	0.53
Yao PF	2008	Asian	China	86	11	33	42	55	117	95	13	34	48	60	130	0.09
Mou XD	2008	Asian	China	45	0	13	32	13	77	39	2	17	20	21	57	0.50
Yevtushenko	2008	European	Britain	52	-	42*	10	-	62	76	-	57*	19	-	95	>0.05
Gregoor	2009	European	Netherlands	61	18	31	12	67	55	139	33	73	33	139	139	0.55
Opgen-Rhein	2010	European	Germany	62	19	29	14	67	57	66	21	28	17	70	62	0.23
Wu RR	2011	Asian	China	85	1	29	55	31	139	85	10	31	44	51	119	0.22

Abbreviations: HWE: Hardy–Weinberg equilibrium; *: Combination of heterozygote and variant homozygote; >0.05: The authors stated that the distribution of leptin gene polymorphism did not deviate significantly from Hardy–Weinberg equilibrium

Table 2. Summary of meta-analysis for AIWG and the −2548G/A polymorphism in leptin gene under various genetic models

Genetic model	Pooled OR (95% *CI*)	p value	Number	AIWG size	Control size	$p_{heterogeneity}$	Statistic model
Additive genetic model	1.33 (0.92-1.93)	0.127	6	399	492	0.012	Random
Dominant genetic model	1.24 (0.83-1.84)	0.294	6	399	492	0.121	Fixed
Recessive genetic model	1.25 (0.96-1.64)	0.103	7	451	568	0.055	Fixed
Homozygote model	1.32 (0.84-2.08)	0.228	6	399	492	0.065	Fixed
Heterozygote model	1.23 (0.80-1.88)	0.339	6	399	492	0.323	Fixed

Abbreviations: CI: confidence interval; OR: odds ratio; Number: literature number; Additive genetic model: allele A versus allele G; Dominant genetic model: GA +AA versus GG; Recessive genetic model: AA versus GA+GG; Homozygote model: AA versus GG; Heterozygote model: GA versus GG

Table 3. Subgroup analysis for AIWG and the −2548G/A polymorphism in leptin gene under various genetic models

Subgroup	Genetic model	Pooled OR (95% *CI*)	p value	Number	AIWG size	control size	$p_{heterogeneity}$	Statistic model
Asian population	Additive genetic model	1.58 (1.20-2.07)	0.001	4	276	287	0.061	Fixed
	Dominant genetic model	2.20 (1.12-4.31)	0.022	4	276	287	0.133	Fixed
	Recessive genetic model	1.62 (1.15-2.26)	0.005	4	276	287	0.103	Fixed
	Homozygote model	2.37 (1.19-4.73)	0.014	4	276	287	0.082	Fixed
	Heterozygote model	2.03 (0.98-4.20)	0.057	4	276	287	0.309	Fixed
European population	Additive genetic model	0.88 (0.64-1.21)	0.430	2	123	205	0.636	Fixed
	Dominant genetic model	0.87 (0.53-1.44)	0.594	2	123	205	0.495	Fixed
	Recessive genetic model	0.78 (0.49-1.24)	0.296	3	175	281	0.964	Fixed
	Homozygote model	0.77 (0.41-1.46)	0.423	2	123	205	0.635	Fixed
	Heterozygote model	0.92 (0.54-1.57)	0.767	2	123	205	0.483	Fixed

Abbreviations: CI: confidence interval; OR: odds ratio; Number: literature number; Additive genetic model: allele A versus allele G; Dominant genetic model: GA +AA versus GG; Recessive genetic model: AA versus GA+GG; Homozygote model: AA versus GG; Heterozygote model: GA versus GG

In order to analyze characteristic-homogeneous groups, subgroup analyses were carried out according to ethnicity. Surprisingly, in addition to the heterozygote genetic model (OR=2.026, 95%CI=0.98 to 4.20, p=0.057), a significant association between the leptin -2548G/A gene polymorphism and AIWG risk was found in Asian population (China) under all other genetic models (Table 3). The heterogeneity between the invidual studies did not exist (p>0.05) which indicated that there was an intensively positive association between leptin -2548A allele and AIWG risk in Asian population. On the contrary, in European populations (Netherlands, Britain, and Germany), the -2548A allele seemed to decrease the risk of AIWG when compared with the -2548G allele under various genetic models, even though there were not statistically significant (Table 3).

Sensitivity analysis

Sensitivity analysis was conducted to assess the influence of any single study under the recessive genetic model. When removing one study at the time from the meta-analysis, there was no significant change in the pooled OR and associated p value (Figure 2).

Publication bias analysis

We used Egger's method to access the publication bias of -2548G/A polymorphism in the leptin gene and AIWG risk under the recessive genetic model. The funnel plot showed no apparent evidence of publication bias (Figure 3). There was also no significant difference in the Egger's test for the recessive genetic model, which suggested that the probability of publication bias was low in the current meta-analysis (T=0.11, p=0.917).

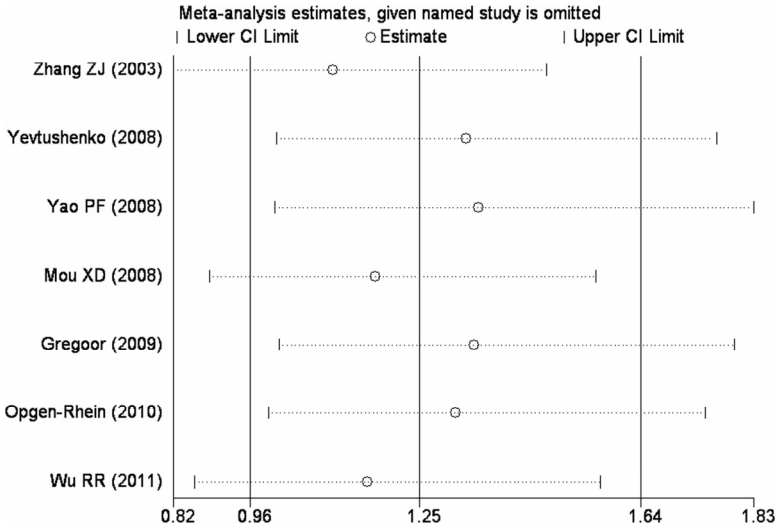

Figure 2. Sensitivity analysis for the meta-analysis under the recessive genetic model. Each circle represents a separate study

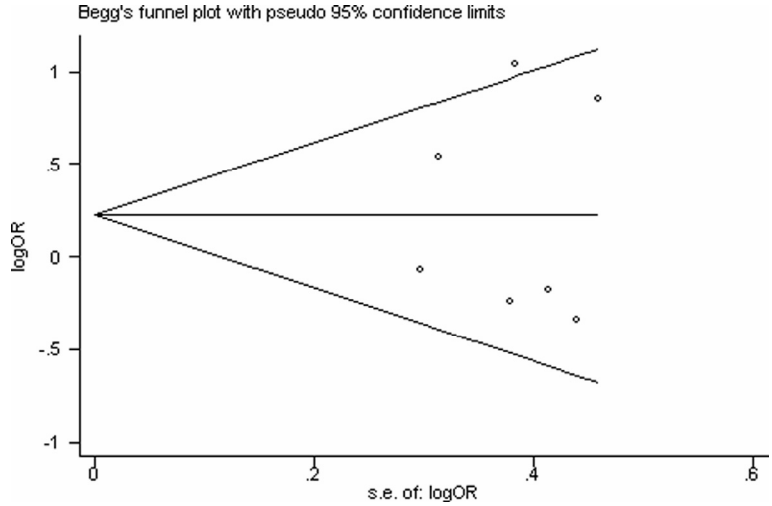

Figure 3. Begg's funnel plot for the meta-analysis under the recessive genetic model. The horizontal line in the middle represents the estimate of summary OR and the two slant sidelines show the confine of 95% *CI*. Each point represents a separate study

DISCUSSION

To our knowledge, this is the first meta-analysis study to evaluate the potential role of the leptin -2548G/A gene polymorphism in AIWG risk. In the present meta-analysis of 451 AIWG patients and 568 controls, the leptin -2548G/A gene polymorphism was not significantly associated with AIWG risk under various genetic models. However, in the subgroup analysis by ethnicity, a significant association was found under the additive genetic model (OR: 1.58), dominant genetic model (OR: 2.20), recessive genetic model (OR: 1.62), and the homozygote genetic model (OR: 2.37) in Asian population (China). In European populations (Netherlands, Britain, and Germany), the -2548A allele seemed to decrease the risk of AIWG when compared with the -2548G allele under various genetic models, even though there were not statistically significant. The present meta-analysis indicates that the correlation between leptin -2548G/A gene polymorphism and AIWG risk has significant racial differences.

Antipsychotic-induced weight gain (AIWG) is an undesirable somatic adverse effect of atypical antipsychotic medication. It negatively influences treatment adherence to antipsychotic medication and likely to contribute to hypertension, cardiovascular disease, dyslipidaemia and late-onset diabetes (Wirshing et al. 1998). Substantial weight gain may also adversely affect selfesteem, social functioning, and physical activity, and finally lead to the discontinuation of or noncompliance with atypical antipsychotics (Hugenholtz et al. 2005). Among the antipsychotics, olanzapine and clozapine may in particular induce profound weight gain (Allison et al. 1999). Most such weight gain occurs during the first 6–8weeks of therapy and reaches a plateau by the end of the 1st year of treatment (Nasrallah 2003).

Since the leptin system plays an important role in the regulation of food intake and energy homeostasis, leptin are particularly interesting candidate genes for AIWG.

A leptin gene variant, -2548G/A, has been associated with weight gain in several studies, but the direction of the allelic association is not clear. While half of the studies found an association with the A allele and weight gain or increased lipid / glucose measures (Calarge et al. 2009, Wu et al. 2011, Zhang et al. 2003, Mou et al. 2008), the other half of the studies reported significant results with the G allele (Gregoor et al. 2009, Yevtushenko et al. 2008). Meanwhile, some studies could not detect association of AIWG with the rs7799039 genotype (Opgen-Rhein et al. 2010, Perez-Iglesias et al. 2010, Yao et al. 2008).

Our meta-analysis suggests that racial differences may partly explain inconsistent results. But, in addition to ethnicity, there are many other possible explanations can be given. First of all, most studies have been conducted in relatively small sample size with an increased risk of a type I error with false positive findings. Second, the studies used different anti-psychotic drugs. Since the antipsychotic drugs have different pharmacologic profiles, there is bound to be a different modification of the gene-gene interactions that play a part in the etiology of weight gain resulting in ambiguous findings. In addition to single antipsychotic drugs, several studies even included multiple anti-psychotic drugs or allowed combinations of anti-psychotic drugs. Third, the patients took different duration of treatment. Since the period in which most antipsychotic-induced weight gain occurs endures for 3 months, it is possible that differences in weight gain between genotype groups are not maximal after 4-6 weeks. This could partly explain non-significant results in studies using a follow-up duration of 4-6 weeks. Fourth, choosing different endpoints for weight gain (weight gain≥7% or body mass index (BMI) ≥30kg/m^2) also partly explains the difference between study results, since the proportion of the population reaching clinically significant cutoff points is smaller than the proportion of the population with any increase in body weight. This makes it more difficult to find significant results between genotype groups when using cutoff points, especially when the impact of the genetic marker on weight gain is small.

Several limitations of this meta-analysis should be considered. First, our meta-analysis only focused on articles published in English and Chinese, with studies published in other languages systematically excluded. This may induce some publication bias in our meta-analysis, which may have affected the results of this meta-analysis. Second, the total sample size in our meta-analysis was relatively small, and since in-sufficient data, our further evaluation of potential inter-actions was limited (gene × gene, gene × environment etc.). Third, we were not able to obtain the original data, so we can not adjust the potential confounders for included seven studies (age, sex, BMI etc.), all of which could have influenced the relationship between the leptin -2548G/A gene polymorphism and risk of AIWG.

CONCLUSION

In summary, despite the limitations, our meta-analysis presents for the first time that the correlation between leptin -2548G/A gene polymorphism and AIWG risk has significant racial differences: the A allele of the leptin -2548G/A gene was a genetic risk factor for AIWG in Asian population, while a genetic protection factor in European populations. Well-designed studies with larger sample sizes and more details on participants' various characteristics are needed in order to provide precise evidence that would further confirm our findings.

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Conflict of interest: None to declare.

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