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Association between the resistin gene-420 C>G polymorphism and obesity: an updated meta-analysis

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Abstract. – OBJECTIVE: The aim of this study was to assess the relationship of the resistin gene (RETN)-420 C>G polymorphism and obesity susceptibility by conducting an updated meta-analysis.

MATERIALS AND METHODS: The electronic databases including PubMed, Medline, Embase, China National Knowledge Infrastructure, Chinese Wanfang Database, and Chinese VIP database were searched for relevant studies published before December 2013. The fixed effect model or random effects model was used based on the heterogeneity test results. The sensitivity analysis was performed in the allelic model and the dominant genetic model, respectively. Publication bias was assessed via funnel plot. The meta-analysis was performed using the software of RevMan 5.2.

RESULTS: Data were obtained from 10 included studies, involving 5,069 cases and 6,673 controls. The overall odds ratios (ORs) with its 95% confidence interval (CI) showed no association between RETN-420 C>G polymorphism and obesity in the allelic model (p = 0.09; OR = 1.10; 95% CI = 0.991.24), the dominant model (p = 0.09; OR = 1.16; 95% CI = 0.98-1.36), and the recessive model (p = 0.71; OR = 1.02; 95% CI = 0.90-1.16). Sensitivity analysis showed statistical differences of association analysis within the allelic model (p = 0.04; OR = 1.14; 95% CI = 1.01-1.28) and the dominant genetic model (p = 0.04; OR = 1.21; 95% CI = 1.01-1.45), when 1 study was omitted. No publication bias was observed.

CONCLUSIONS: The RETN-420 C>G polymorphism may be related to obesity with G allele as a risk factor.

Key Words:
Meta-analysis, Obesity, Polymorphism, RETN-420 C>G.

Introduction

Obesity is considered to be one of the major health problems all over the world nowadays[1]. Particularly, obesity is prevalent in pregnant women with severe adverse outcomes such as spontaneous miscarriage, metabolic dysregulation, and fetal congenital anomalies[2] and is associated with elevated level of pro-inflammatory cytokines in women undergoing procreation[3]. It is also reported that obesity is a risk factor for acute mountain sickness[4]. It is assumed that several genetic factors are likely to have a causal role in obesity[5]. Genome scanning and functional candidate approach indicate numerous gene polymorphisms are potentially associated with obesity[6]. Resistin (RETN) is a protein hormone secreted abundantly by adipocytes and immunocompetent cells[5], and it is also recognized as an obesity-related adipokine[7]. Recently, the effect of *RETN-420* C>G polymorphism on obesity has become a topic in medical field[8-10].

However, conflicting results of the relationship between *RETN-420* C>G polymorphism and obesity have been displayed in recent years. Some previous studies have proved that *RETN-420* C>G polymorphism has positive correlation with insulin sensitivity, body mass index (BMI), and obesity[11,12]. Furthermore, rs1862513, as one of the *RETN-420* C>G polymorphic sites, is located in the promoter region of *RETN*. It is reported to play a pivotal role in the production of insulin resistance (IR) and elevation of blood glucose level, and finally leads to obesity[12-15]. While the expression of *RETN-420* C>G polymorphism from obesity has been reported to be greatly reduced[16-18]. In addition, several analyses show that *RETN* has no association with obesity[19-22]. Therefore, the association of *RETN-420* C>G polymorphism and obesity susceptibility has not yet been fully clarified. A comprehensive retrospective analysis is necessary to determine the specific role of *RETN-420* C>G polymorphism in the risk of obesity.

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One previous meta-analysis of *RETN-420* C>G polymorphism on obesity, which includes 4 studies published before 2008, shows a negative conclusion[23]. In the present study, we aimed to verify the conclusion of the previous study and assess the relation of *RETN-420* C>G polymorphism with risk of obesity using an updated meta-analysis with 6 additionally included studies.

Materials and Methods

Study Search

Eligible studies were identified through PubMed, Medline, Embase, China National Knowledge Infrastructure, Chinese Wanfang Database, and Chinese VIP Database prior to December 2013. The searching keywords were polymorphism (genetic, variant), resistin (RETN), and obesity (obese). Publication languages were restricted to English and Chinese.

Inclusion and Exclusion Criteria

Studies included in this meta-analysis were required to meet the inclusion criteria as follows: (1) case-control studies; (2) case subjects were obese patients and control subjects were normal or medical individuals; (3) published studies which evaluated the relationship between *RETN-420* C>G polymorphism and obesity; (4) studies that measured the frequency of the genotype and allelic genes of subjects; (5) genotype distributions in controls fulfilled the Hardy-Weinberg equilibrium (HWE) criteria.

The reports, reviews, comments, and letters were excluded in this meta-analysis.

Data Extraction and Quality Assessment of Studies

Zheng-Lun Zhu and Qiu-Meng Yang independently extracted the data including the first author's name, published year, country, the standard definition of obesity, gender and age construction, and genotype distribution. Chen Li, Jun Chen and Min Xiang compared their results and any differences were resolved by a panel discussion with Ming-Min Chen, Min Yan and Zheng-Gang Zhu. The quality of included studies was analyzed based on a 10-point scoring sheet according to Clark et al[24]. Studies were considered as good with the score of 8-10, fair with the score of 5-7, and poor with the score less than 4[25].

Statistical Analysis

An overall meta-analysis of the association between *RETN-420* C>G polymorphism and obesity was constructed using the allelic model (G *vs.* C), the dominant genetic model (GG + GC *vs.* CC), and the recessive genetic model (GG *vs.* GC + CC). Meta-analysis of the data was conducted using RevMan version 5.2 software (Nordic Cochrane Center, Copenhagen, Denmark).

HWE test for each polymorphism was performed to confirm the quality of the included studies. A Bonferroni adjustment ($\alpha = 0.005$) was used to correct *p*-values for multiple testing. $P_{HWE} > 0.005$ was considered to be accorded with HWE. The heterogeneity was inspected by I^2 statistic and *Q*-test[26]. Effect sizes were odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). The pooled ORs and their corresponding 95% CIs were calculated by random effects model (Mantel-Haenszel method) if the heterogeneity was significant among studies ($p < 0.05$, $I^2 > 50\%$), otherwise, the fixed effect model (Mantel-Haenszel method) was used[27].

To ascertain if the results of our meta-analysis were strongly influenced by any single study, a sensitivity analysis was performed by a seriatim excluding individual study[28]. Funnel plots were created in order to assess publication bias by plotting individual study OR and the standard error of the log OR. In the absence of publication bias, plots should resemble a symmetrically inverted funnel.

Results

Study Inclusion and Characteristics

A flow diagram of the study of identification process was shown in Figure 1. A total of 219 potentially relevant studies were identified and screened for retrieval. We excluded 206 studies after reviewing the title or abstract. Among the remaining 13 studies, 3 studies were excluded due to duplicate publications. Finally, there were 10 studies[1,5,12,29-35] included in this meta-analysis with available data and gene distributions being in HWE ($p_{HWE} > 0.005$). The general characteristics and quality assessment of the included studies were summarized in Table I. Data of the included studies in the meta-analysis involved 11,742 subjects, consisting of 5,069 cases and 6,673 controls. Eight of the studies were written in English and 2 were in Chinese. The extracted data showed that the gender ratio

Table I. Characteristic of included studies on RETN -420 C>G polymorphism and obesity.

Author	Year	Country	Obesity definition	Obesity/control			Score	pHWE
				Male (%)	Age (years)	n		
Angeli CB	2011	Brazil	BMI ≥ 25 kg/m^2	47.5	44.18	143/223	7	0.4009
Beckers S	2008	Belgium	BMI ≥ 30 kg/m^2	0/0	38/40	541/235	8	0.5273
Boumaiza I	2012	Tunisia	BMI ≥ 30 kg/m^2	18.1/37.3	48.41/43.25	160/169	7	0.0052
Cauchi S	2008	France/Switzerland	BMI ≥ 30 kg/m^2	35.6/48.8	48.62/50.65	2864/4433	7	0.5231
Cieslak J	2011	Poland	BMI ≥ 25 kg/m^2	51.03/-	-	243/100	7	0.1531
El-Shal AS	2013	Egypt	BMI ≥ 30 kg/m^2	46.2/45.2	44.84/41.16	145/155	7	0.5244
Engert JC	2002	Canada	BMI ≥ 30 kg/m^2	-	-	468/1007	7	0.0385
Mattevi VS	2004	Brazil	BMI ≥ 25 kg/m^2	43.1/33.9	-	334/251	7	0.4919
Sun Z	2013	China	BMI ≥ 25 kg/m^2	53.8/53.3	45.6/40.5	130/60	5	0.6112
Zhao J	2007	China	BMI ≥ 25 kg/m^2	-	-	41/40	5	0.1444

Score, score of the quality assessment.
pHWE, *p*-value of Hardy-Weinberg equilibrium in the control groups.

and obesity definition were different in population came from different countries and races, but no obvious difference in age distribution. The genotype distributions of *RETN-420* C>G in controls fulfilled the HWE criterion in all of the included studies ($p_{HWE} > 0.005$). According to the quality assessment, the included studies with the score of 5-8 were considered to be high-quality for this meta-analysis.

Association Analysis of RETN-420 C>G Polymorphism and Obesity

The results of Q-test and I^2 statistic showed significant heterogeneity in the allelic model (p = 0.04, I^2 = 50%) and the dominant genetic model (p = 0.01, I^2 = 58%), so the random effects model was used to pool the data. While for the recessive genetic model, the fixed effects model was performed because heterogeneity was not observed (p = 0.18, I^2 = 30%).

The overall ORs showed no evidence of significant association between the *RETN-420* C>G polymorphism and obesity susceptibility in the allelic model (p = 0.09; OR = 1.10; 95% CI = 0.99-1.24, Figure 2A), the dominant genetic model (p = 0.09; OR = 1.16; 95% CI = 0.98-

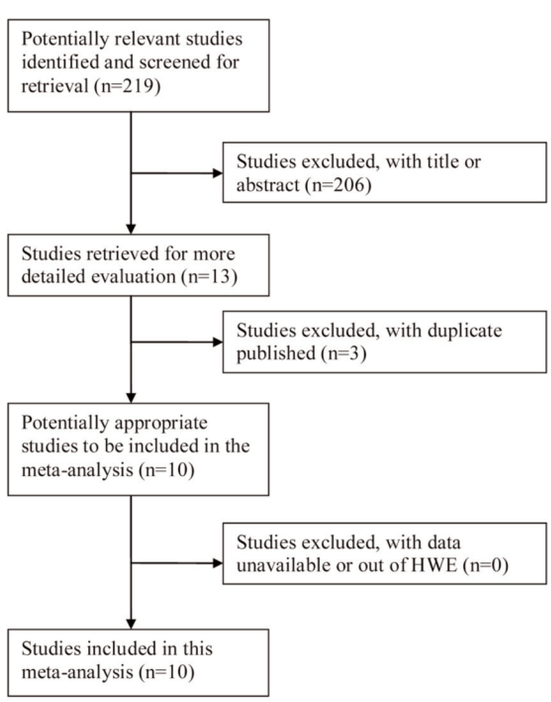

Figure 1. Selection process for included studies in the meta-analysis. HWE, Hardy-Weinberg equilibrium.

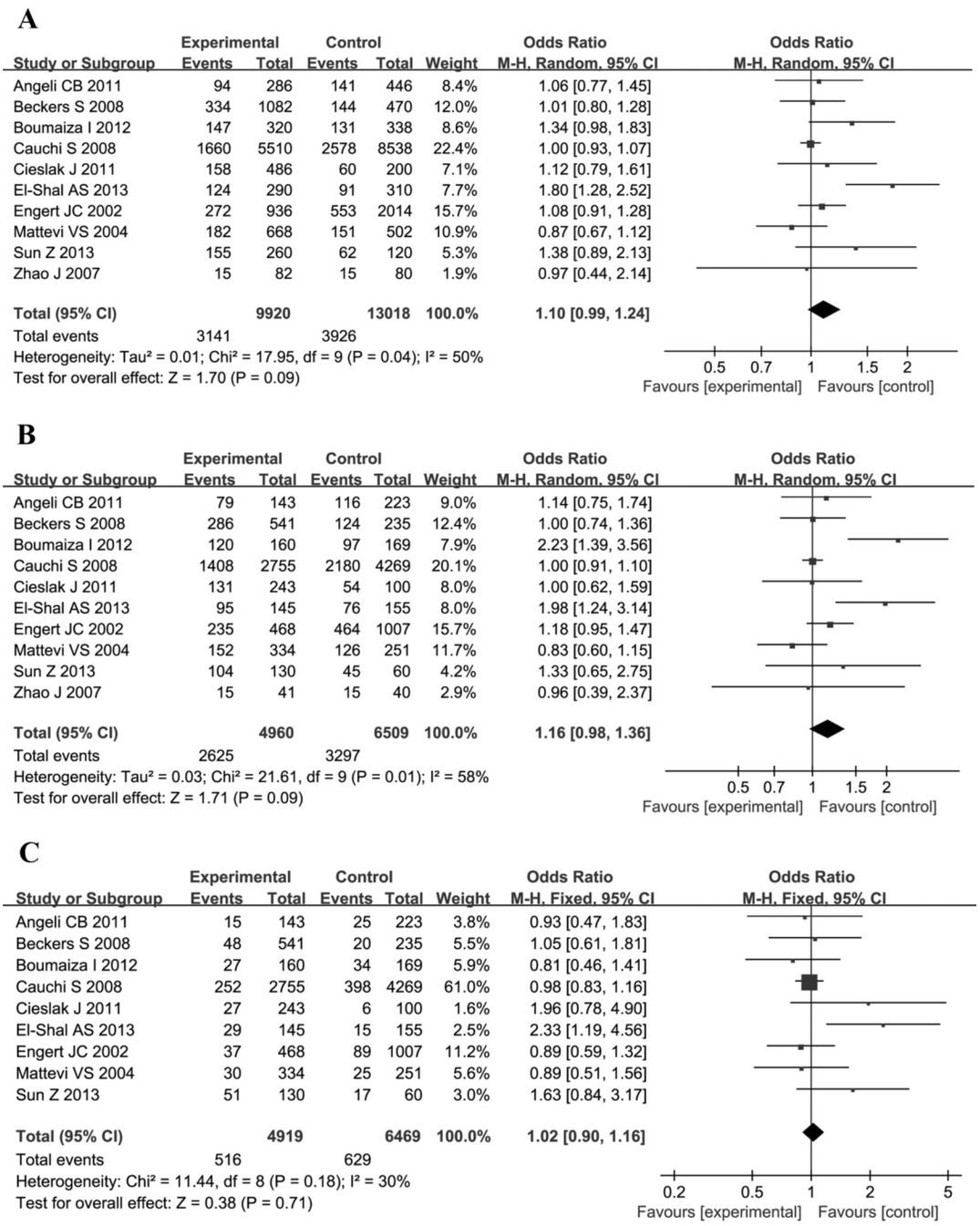

Figure 2. Association analysis of the RETN-420 C>G polymorphism and obesity. ***A***, Association analysis in allelic model. ***B***, Association analysis in dominant genetic model. ***C***, Association analysis in dominant genetic model. CI, confidence interval.

1.36, Figure 2B), and the recessive genetic model (p = 0.71; OR = 1.02; 95% CI = 0.90-1.16, Figure 2C).

Sensitivity Analysis

We performed a sensitivity analysis to evaluate the influence of each individual study on the above conclusion. When Mattevi et al[31] was omitted, the results showed a weak significance of the association between the *RETN-420* C>G polymorphism and obesity in the allelic model (p = 0.04; OR = 1.14; 95% CI = 1.01-1.28, Figure 3A) and the dominant genetic model (p = 0.04; OR = 1.21; 95% CI = 1.01-1.45, Figure 3B), respectively.

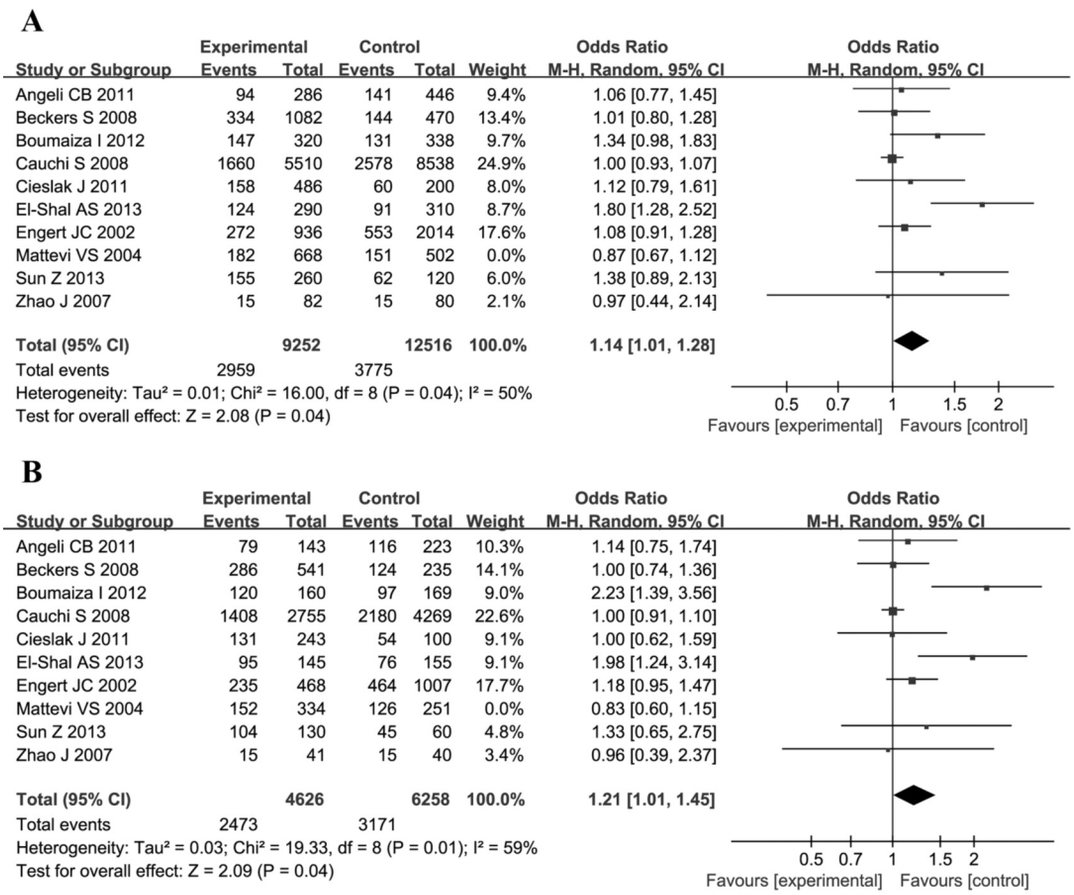

Figure 3. Sensitivity analysis of the RETN-420 C>G polymorphism and obesity. (A) Sensitivity analysis in allelic model. (B) Sensitivity analysis in dominant genetic model. CI, confidence interval.

Assessment of Publication Bias

As shown in Figure 4, no publication bias was observed due to the asymmetry in the funnel plot.

Discussion

Resistin, as an adipose tissue-specific secretory factor, has effects on glucose homeostasis that opposes insulin, and has a potential link with obesity[36]. In the present study, we systematically reviewed relevant studies to investigate the association between the *RETN-420* C>G polymorphism (rs1862513 was chose as a gene polymorphic site) and the risk of obesity. This updated meta-analysis involving 5,069 cases and 6,673 controls from 10 studies suggests that *RETN-420* C>G polymorphism may be associated with obesity susceptibility, and G allele of *RETN-420* C>G (rs1862513) may be a risk factor of obesity. We did not find any publication bias, which indicates the reliability of the pooled results.

Sensitivity analysis can evaluate the stability and reliability of meta-analysis when new meta-analyses are performed after excluding the studies with abnormal results[37]. In the present study,

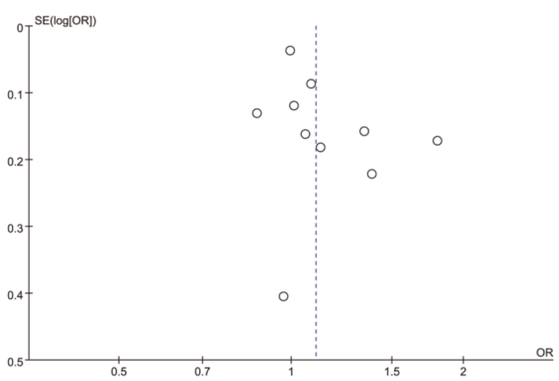

Figure 4. Funnel plot for evaluating the publication bias in allelic model. The symbol of "o" represents the individual studies. The summary estimate of the ORs of obesity for allelic model is represented by a vertical dashed line. OR, odds ratio.

the sensitivity analysis showed an undue influence as the results of the remained 9 studies were reversed after Mattevi et al[33] was omitted. The omitted study described a gender-specific association of-420 C>G polymorphism with BMI and waist circumference, but it was restricted to the premenopausal women. The genotype distribution of omitted study was influenced by stratification containing premenopausal women and postmenopausal women. Only age was included in the omitted study as a covariate. However, the evaluation of the interaction between genotypes and menopausal status seems impossible due to the high correlation between menopause and age. After omitting the study of Mattevi et al[33], the results of our meta-analysis suggest *RETN-420* C>G polymorphism may contribute to obesity susceptibility.

Interestingly, our results are contrary to the previous meta-analysis[23], which has indicated that the *RETN-420* C>G polymorphism is not related to the development of obesity. In the previous study, there were only 4 included studies describing *RETN-420* C>G polymorphism and obesity published up to 2008 in English. Additional case-control studies about *RETN-420* C>G polymorphism and obesity have been published during the succeeding 5 years. In comparison to the previous study, our meta-analysis includes 5 additionally relative studies published between 2011 and 2013 in both English and Chinese. Besides, 1 Chinese study published in 2007 is also included in our meta-analysis. Therefore, a larger sample size and enhanced statistical power can be represented. Moreover, an acceptable quality evaluation system is included in this meta-analysis, which powerfully results in minimization of potential bias.

Heterogeneity, representing a high degree of variability in accuracy estimates across studies, is usually a concern in meta-analysis[38]. After sensitivity analysis, there was still a strong evidence for heterogeneity in the allelic model and dominant genetic model. This result indicates that there is a greater variation among the results of studies than expected by chance. We speculate the heterogeneity might due to the difference of ethnic composition and location. Besides, the variables including gender, age, and criteria of the obesity definition are also significant as covariates in the meta-analysis. Another reason for heterogeneity might reside in the differences among these subjects in living habit, cultural exchange, and living condition.

Similarly, this work also has several limitations when interpreting these results. Firstly, the influence caused by concomitant variables, such as gender and age, were not considered during the meta-analysis due to the incomplete data of the included studies. Secondly, we just chose one gene polymorphic site (*RETN-420* C>G, rs1862513) to assess the relationship between the *RETN-420* C>G polymorphism and obesity susceptibility. The influence of other inheritance mutation site on the obesity is still confused. This may decrease the genetic effect on obesity. Thirdly, subgroup analysis was not constructed because of lacking studies and incomplete stratification information. In conclusion, the *RETN-420* C>G polymorphism appears to be related to obesity with G allele as a risk factor. However, it warrants further investigations on the association between *RETN-420* C>G polymorphism and obesity using large sample sizes in the future.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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